Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

A Daylong Clinical Summit Hosted in Partnership with Medical Oncology Association of Southern California (MOASC)

Saturday, May 15, 2021

10:30 AM – 6:30 PM ET

(7:30 AM – 3:30 PM Pacific Time)

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This program was recorded before the ASCO 2021 Annual Meeting.

Data from the abstracts presented at this meeting can be accessed at https://meetinglibrary.asco.org/results?meetingView=2021%20ASCO%20Annual%20Meeting.

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Agenda

Module 1 — Breast Cancer: *Drs O'Regan and Traina*

Module 2 — Multiple Myeloma: *Drs Anderson and Raje*

Module 3 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Moskowitz and Sharman*

Module 4 — Genitourinary Cancers: *Drs Bellmunt and Pal*

Module 5 — Gastrointestinal Cancers: *Drs Messersmith and O'Reilly*

Module 6 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Erba and Komrokji*

Module 7 — Lung Cancer: *Drs Camidge and Levy*

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Breast Cancer Faculty

Ruth O'Regan, MD
Chair, Department of Medicine
Charles A Dewey Professor of Medicine
University of Rochester
Rochester, New York

Tiffany A Traina, MD
Vice Chair, Oncology Care
Associate Attending Physician
Breast Medicine Service
Department of Medicine
Memorial Sloan Kettering Cancer Center
Associate Professor
Weill Cornell Medical College
New York, New York

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Commercial Support

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Dr Love — Disclosures

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Research To Practice CME and NCPD Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr O'Regan — Disclosures

Advisory Committee and Consulting Agreements	bioTheranostics Inc, Cyclacel Pharmaceuticals Inc, Lilly, MacroGenics Inc, Novartis, Pfizer Inc, Puma Biotechnology Inc, Seagen Inc
Data and Safety Monitoring Board/Committee	Immunomedics Inc

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Dr Traina — Disclosures

Consulting Agreements	Aduro Biotech, Advaxis Inc, AstraZeneca Pharmaceuticals LP, Athenex Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Exact Sciences Inc, Genentech, a member of the Roche Group, Halozyme Inc, Innocrin Pharmaceuticals Inc, Ionis Pharmaceuticals Inc, Merck, Pfizer Inc, Puma Biotechnology Inc, Samsung Bioepis, Seagen Inc
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Carrick Therapeutics, Daiichi Sankyo Inc, Eisai Inc, Genentech, a member of the Roche Group, Immunomedics Inc, Innocrin Pharmaceuticals Inc, Novartis, Pfizer Inc
Speakers Bureau	Genentech, a member of the Roche Group

Contributing Oncologists

Amanda Blackmon, DO, MS
Chief Fellow, Hematology/Oncology
University of California, Irvine
Irvine, California

Farshid Dayyani, MD, PhD
Professor of Clinical Medicine
Division of Hematology/Oncology
Department of Medicine
University of California, Irvine
UCI Health
Orange, California

Gigi Chen, MD
Diablo Valley Oncology and
Hematology Medical Group
Pleasant Hill, California

Michael Polintan Del Rosario, MD
Fellow Physician
Division of Hematology-Oncology
Department of Medicine
University of California, Irvine
Irvine, California

Mamta Choksi, MD
Florida Cancer Specialists and
Research Institute
New Port Richey, Florida

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

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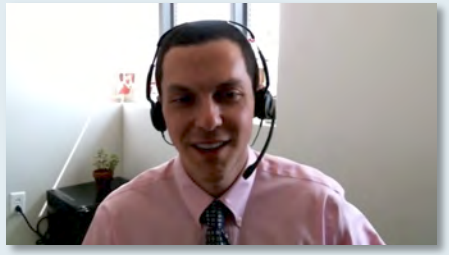
Contributing Oncologists

Rahul Gosain, MD
Division of Hematology and Oncology
Guthrie Corning Cancer Center
Corning, New York

Maen Hussein, MD
Florida Cancer Specialists and
Research Institute
The Villages, Florida

Ranju Gupta, MD
Attending Physician
Co-Director, Cardio-Oncology Program
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania



Jeremy Lorber, MD
Attending Hematologist-Oncologist
Tower Hematology Oncology
Cedars-Sinai Medical Center
Beverly Hills, California

Hatim Husain, MD
Physician, University of California San Diego
San Diego, California

Nataliya Mar, MD
Assistant Clinical Professor
Division of Hematology/Oncology
University of California, Irvine
Irvine, California

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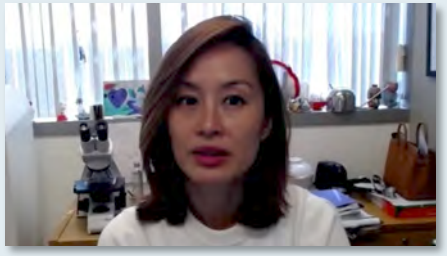
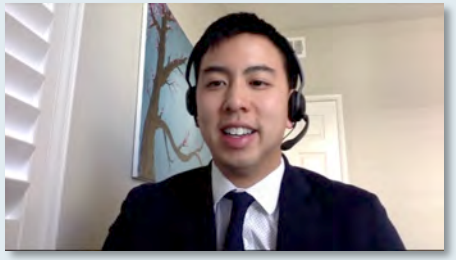
Contributing Oncologists

Mohamed K Mohamed, MD, PhD
Oncology Division Medical Director
Director of Thoracic Oncology
Hematologist/ Medical Oncologist
Cone Health Cancer Center
Greensboro, North Carolina

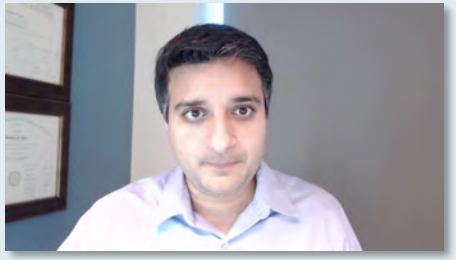


Helen H Moon, MD
Medical Oncologist
Southern California Permanente
Medical Group
Riverside, California

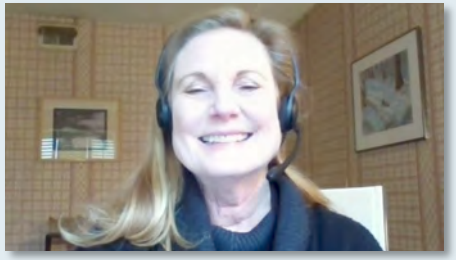
Neil Morganstein, MD
Hematology Oncology
Atlantic Health System
Summit, New Jersey



Anthony Nguyen, MD
Fellow, Loma Linda University Health
Loma Linda, California



Sandip Patel, MD
Associate Professor, Medical Oncology, UCSD
Leader, Experimental Therapeutics
Deputy Director, San Diego Center for
Precision Immunotherapy
San Diego, California



Andrea Stebel, MD
Newport Breast Care
Newport Beach, California

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Agenda

Module 1: ER-Positive, HER2-Negative Breast Cancer

- Dr Stebel: A 58-year-old woman with ER-positive, HER2-negative metastatic breast cancer
- *Key Recent Publications and Presentations*
- Dr Hussein: A 60-year-old woman with ER/PR-positive, HER2-negative, PIK3CA-positive metastatic breast cancer
- *Key Recent Publications and Presentations*

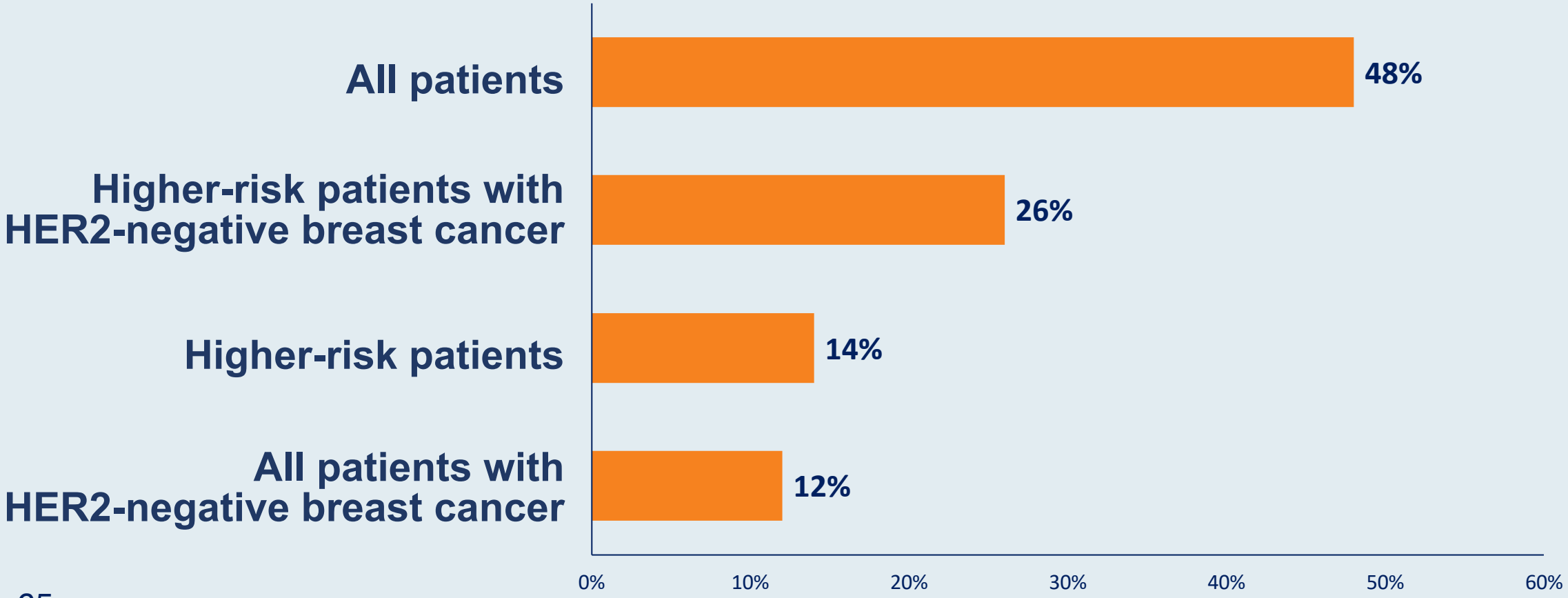
Module 2: HER2-Positive Breast Cancer

- Dr Stebel: A 35-year-old woman with a 3-cm weakly ER/PR-positive, HER2-positive node-negative breast cancer
- Dr Del Rosario: A 53-year-old woman with ER/PR-negative, HER2-positive metastatic inflammatory breast cancer
- *Key Recent Publications and Presentations*

Module 3: Triple-Negative Breast Cancer (TNBC)

- Dr Del Rosario: A 68-year-old woman with localized TNBC
- *Key Recent Publications and Presentations*
- Dr Del Rosario: A 70-year-old woman with metastatic TNBC
- *Key Recent Publications and Presentations*

If the findings of the OlympiA trial mirror what was seen in ovarian cancer in the SOLO-1 trial (hazard ratio for PFS of 0.33 but no OS data), which patients with localized breast cancer should undergo genomic evaluation at initial diagnosis?



N = 65

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Phase III OlympiA Trial of Adjuvant Olaparib for High-Risk HER2-Negative Localized Breast Cancer with a BRCA Mutation Crossed the Superiority Boundary for Invasive Disease-Free Survival

Press Release – February 17, 2021

"The OlympiA Phase III trial of [olaparib] will move to early primary analysis and reporting following a recommendation from the Independent Data Monitoring Committee (IDMC).

Based on the planned interim analysis, the IDMC concluded that the trial crossed the superiority boundary for its primary endpoint of invasive disease-free survival (iDFS) and demonstrated a sustainable, clinically relevant treatment effect for olaparib versus placebo for patients with germline BRCA-mutated (gBRCAm) high-risk human epidermal growth factor receptor 2 (HER2)-negative early breast cancer, and recommend primary analysis now take place.

In its communication, the IDMC did not raise any new safety concerns. The trial will continue to assess the key secondary endpoints of overall survival and distant disease-free survival."

https://www.astrazeneca.com/media-centre/press-releases/2021/olympia-trial-of-lynparza-idmc-recommend-early-analysis.html

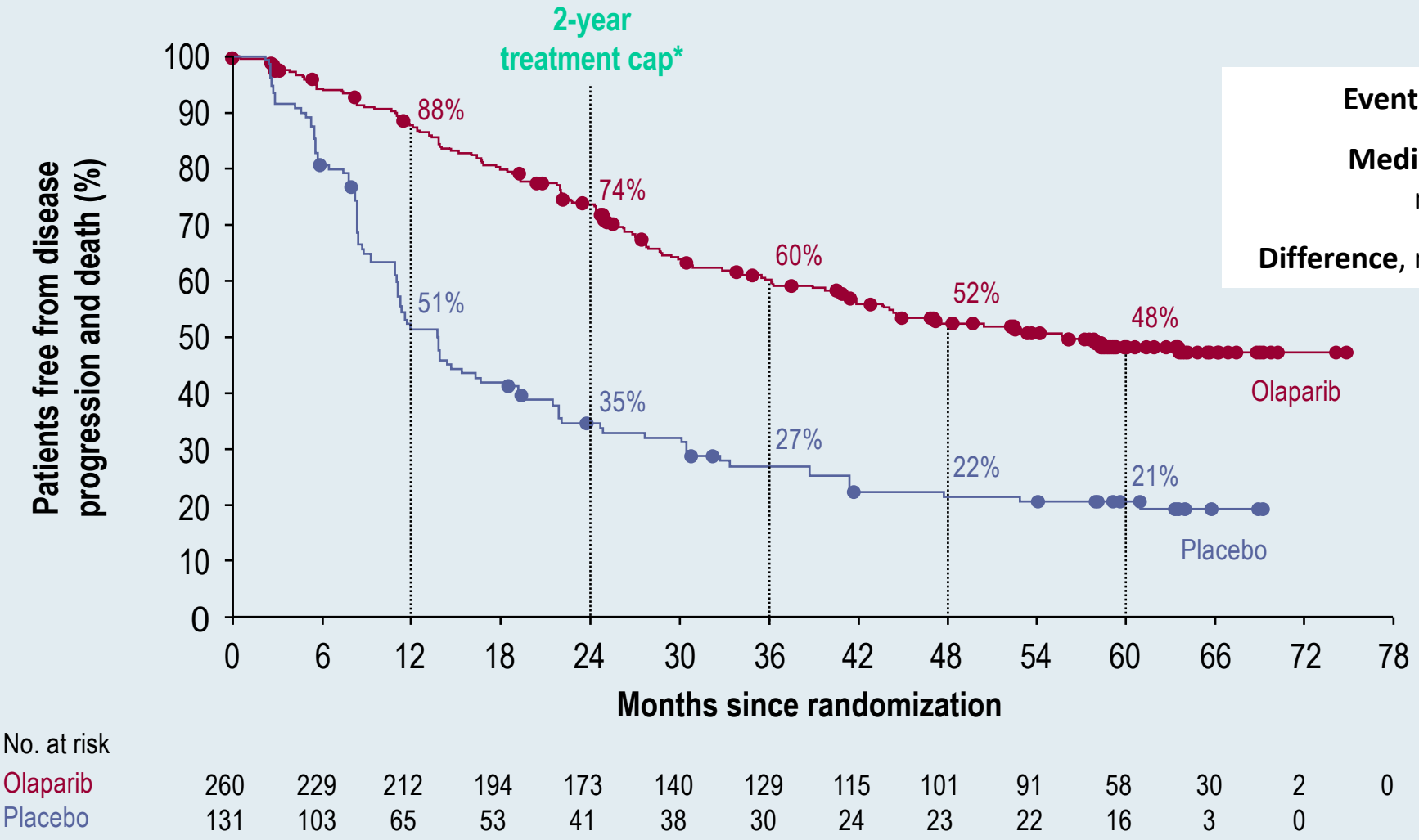
OlympiA: A Phase III, Multicenter, Randomized, Placebo-Controlled Trial of Adjuvant Olaparib After (Neo)Adjuvant Chemotherapy in Patients with Germline BRCA1/2 Mutations and High-Risk HER2-Negative Early Breast Cancer

Tutt A et al.

ASCO 2021;Abstract LBA1.

Sunday, June 6, 1:00 PM - 4:00 PM EDT

SOLO-1: Updated PFS (60 Months Follow-Up)



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	118 (45)	100 (76)
Median PFS, months	**56.0**	**13.8**
Difference, months	42.2	
	HR 0.33 (95% CI 0.25–0.43)	

Median treatment duration:
Olaparib, 24.6 months
Placebo†, 13.9 months

Banerjee S et al. ESMO 2020;Abstract 811MO.

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SOLO-1 Trial 5-Year Update: Safety Profile

n (%)	Olaparib (n=260)	Placebo (n=130)
Any AE	256 (98)	120 (92)
Grade ≥3 AE	103 (40)	25 (19)
Serious AE	55 (21)	17 (13)
AE leading to dose interruption	136 (52)	22 (17)
AE leading to dose reduction	75 (29)	4 (3)
AE leading to treatment discontinuation	30 (12)	4 (3)
MDS/AML	3 (1)	0 (0)
New primary malignancy	7 (3)	5 (4)

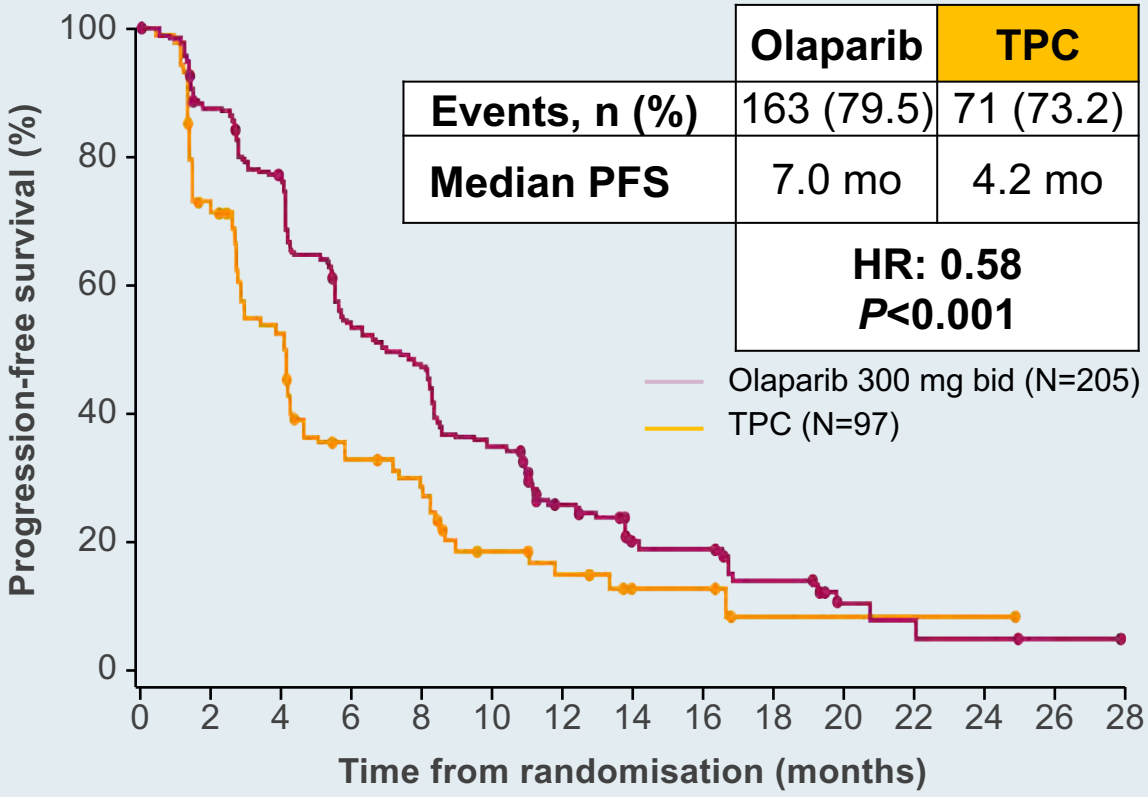
No additional cases of MDS/AML reported; incidence remained <1.5%

Follow-up for MDS/AML continued until death due to any cause

Banerjee S et al. ESMO 2020;Abstract 811MO.

Phase III Trials of PARP Inhibitors in gBRCA HER2-Negative Metastatic Breast Cancer

OlympiAD: Olaparib PFS[1,2]

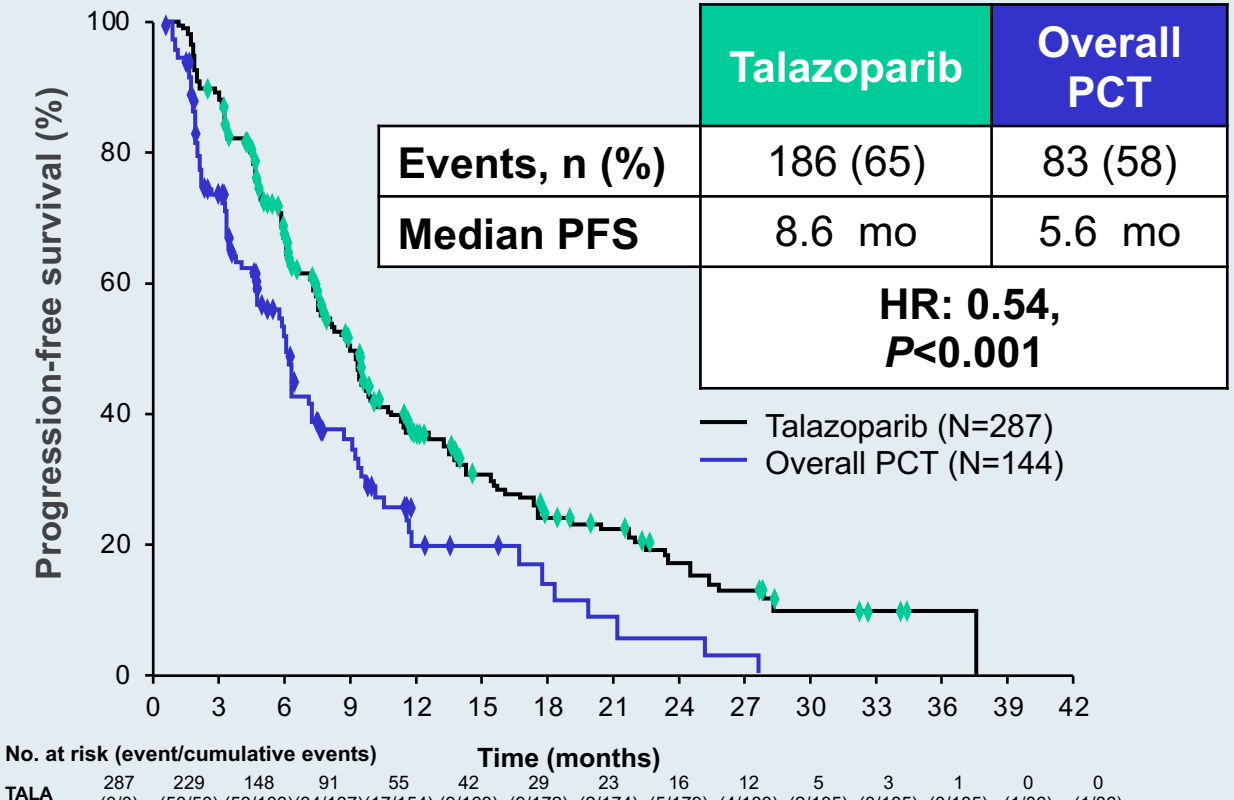


	Olaparib	TPC
Events, n (%)	163 (79.5)	71 (73.2)
Median PFS	7.0 mo	4.2 mo
	HR: 0.58 *P*<0.001	

Number at risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
TPC	97	88	83	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

EMBRACA: Talazoparib PFS[3]



	Talazoparib	Overall PCT
Events, n (%)	186 (65)	83 (58)
Median PFS	8.6 mo	5.6 mo
	HR: 0.54, *P*<0.001	

No. at risk (event/cumulative events)

TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/86)	0 (1/86)
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

1. Robson M, et al. *N Engl J Med* 2017;377:523-33; 2. Olaparib 150mg Film-Coated Tablets, SmPC. 2019;
3. Litton JK, et al. *N Engl J Med* 2018;379:753-63 (supplementary appendix)

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Agenda

Module 1: ER-Positive, HER2-Negative Breast Cancer

- Dr Stebel: A 58-year-old woman with ER-positive, HER2-negative metastatic breast cancer
- *Key Recent Publications and Presentations*
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- Dr Del Rosario: A 68-year-old woman with localized TNBC
- *Key Recent Publications and Presentations*
- Dr Del Rosario: A 70-year-old woman with metastatic TNBC
- *Key Recent Publications and Presentations*

Case Presentation – Dr Stebel: A 58-year-old woman with ER-positive, HER2-negative metastatic breast cancer

Dr Andrea Stebel

- 2009: ER/PR-positive, HER2-negative Stage IIIA left breast cancer s/p lumpectomy and ALND
- TC x 6 and RT → Tamoxifen x 9 years until 2019
  - No AI due to osteoporosis, zoledronic acid not tolerated
- Within 8 months of discontinuing tamoxifen: Left anterior cervical node (Strongly ER-positive, HER2-negative, PIK3CA-positive)
  - CT: Diffuse lymphadenopathy up to 11.8 cm and bony metastases
- Abemaciclib/fulvestrant + denosumab, with CR/nCR in nodes, stable disease in bone lesions

Questions

- If she presented today with a Stage IIIA tumor and 6 positive nodes, how would she be treated adjuvantly? Would there be a consideration of using a CDK4/6 inhibitor as part of adjuvant therapy?
- Would you use the Onco*type* DX® based on the RxPONDER data to see where her treatment should be, had she presented today?
- For her first-line therapy, would you have chosen a different CDK4/6 inhibitor or hormonal partner?

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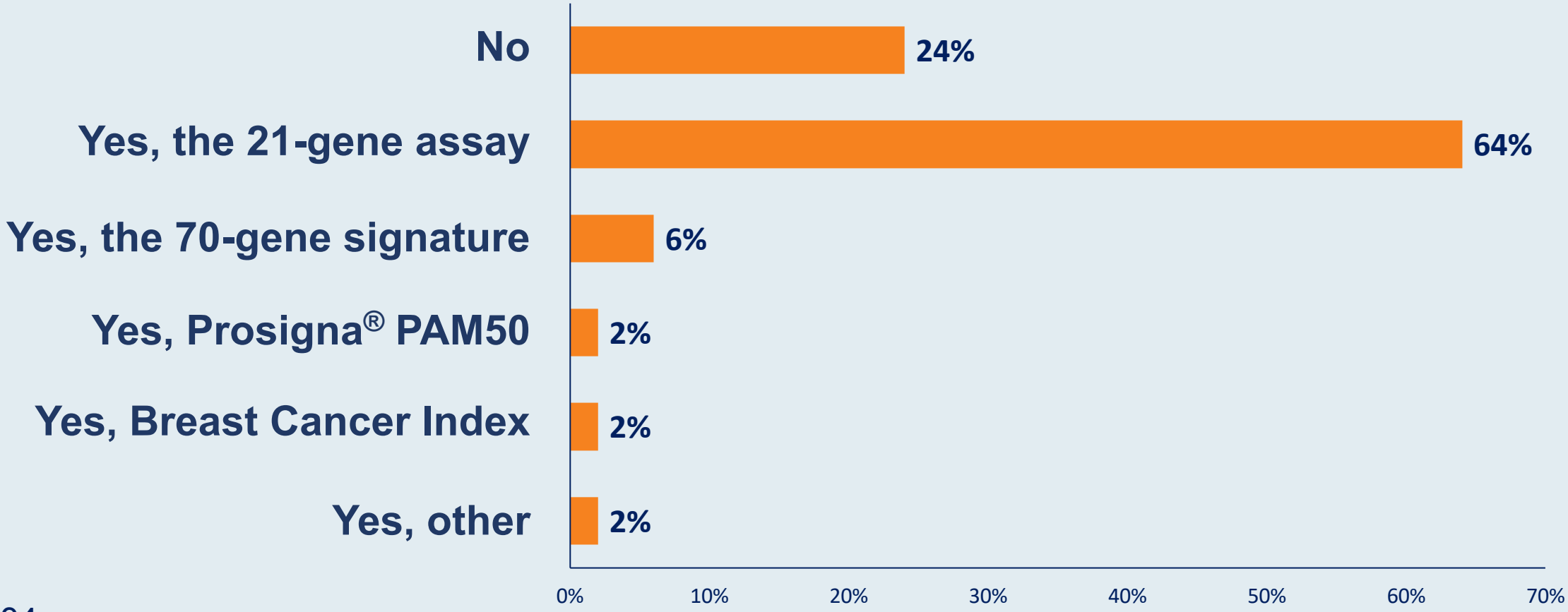
Key Recent Publications and Presentations

- Kalinsky K et al. **First Results from a Phase III Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy (ET) +/- Chemotherapy (CT) in Patients (pts) with 1-3 Positive Nodes, Hormone Receptor-Positive (HR+) and HER2-Negative (HER2-) Breast Cancer (BC) with Recurrence Score (RS) ≤25: SWOG S1007 (RxPonder).** San Antonio Breast Cancer Symposium 2020;Abstract GS3-00.
- Johnston SRD et al. **Abemaciclib Combined with Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE).** *J Clin Oncol* 2020;38(34):3987-98.
- Mayer EL et al. **Palbociclib with Adjuvant Endocrine Therapy in Early Breast Cancer (PALLAS): Interim Analysis of a Multicentre, Open-Label, Randomised, Phase 3 Study.** *Lancet Oncol* 2021;22:212-22.

A premenopausal woman presents with a 2.1-cm, Grade 2, ER/PR-positive, HER2-negative IDC with 2 positive sentinel lymph nodes. Would you order a genomic assay for this patient?



N = 104

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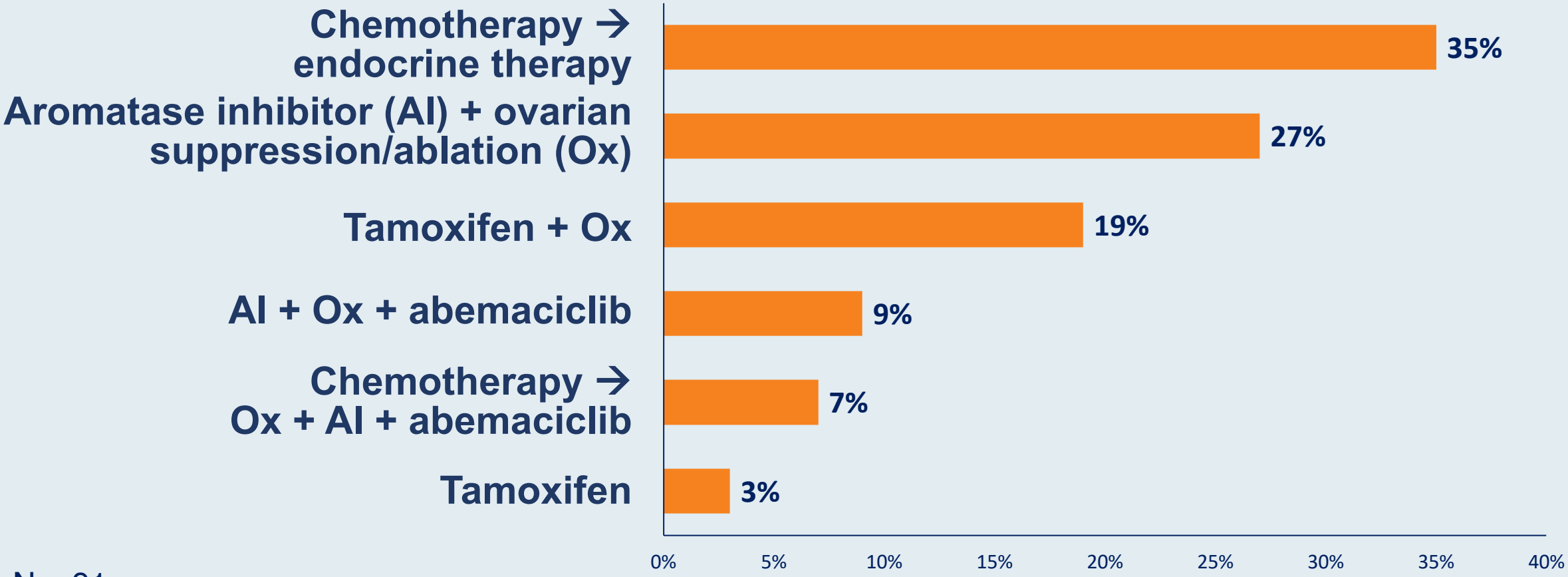
What adjuvant therapy would you generally recommend for a premenopausal woman with a 2.1-cm, Grade 2, ER/PR-positive, HER2-negative IDC with 2 positive sentinel nodes and a 21-gene Recurrence Score of 10?



N = 91

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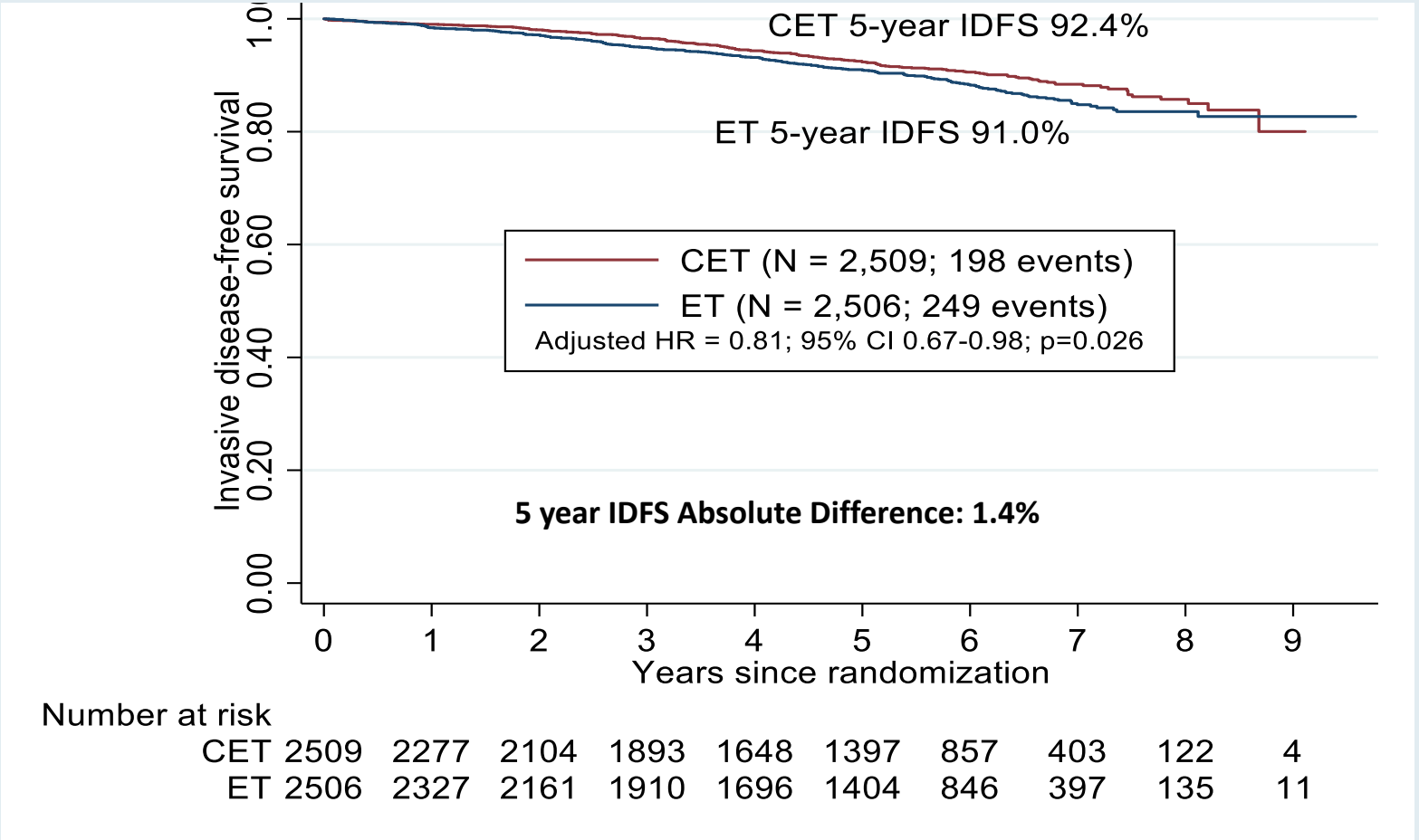
First Results from a Phase III Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy (ET) +/- Chemotherapy (CT) in Patients (pts) with 1-3 Positive Nodes, Hormone Receptor-Positive (HR+) and HER2-Negative (HER2-) Breast Cancer (BC) with Recurrence Score (RS) ≤25: SWOG S1007 (RxPonder)

Kalinsky K et al.

SABCS 2020;Abstract GS3-00.

RxPONDER: Invasive Disease-Free Survival (IDFS) in Overall Population by Treatment Arm



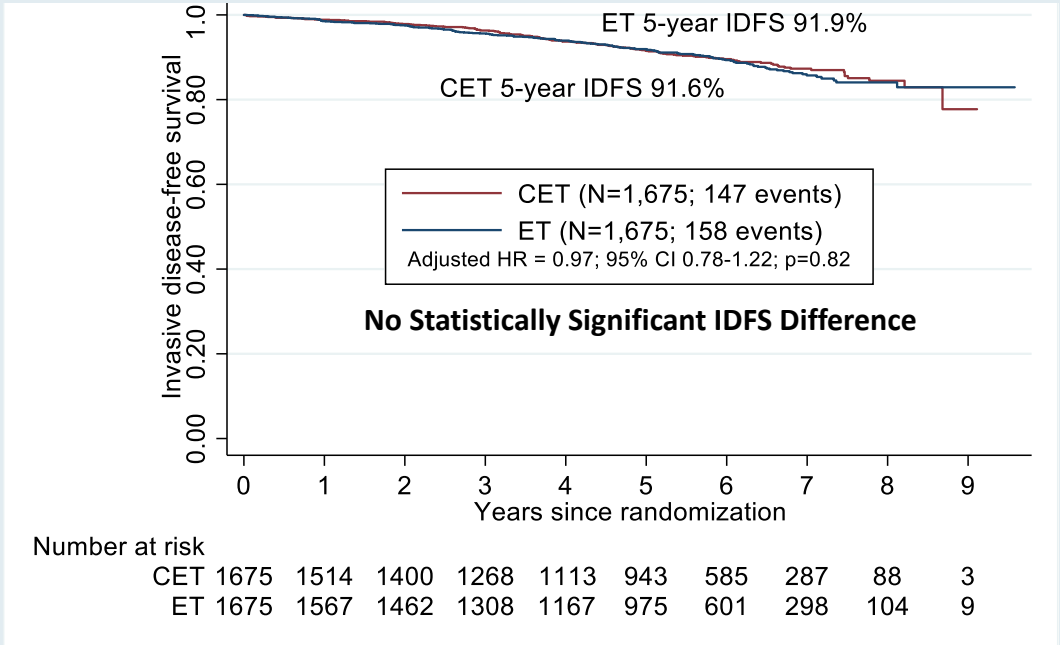
CET = Chemotherapy + Endocrine Therapy; ET = Endocrine Therapy Alone

447 observed IDFS events (54% of expected at final analysis) at a median follow-up of 5.1 years

Kalinsky K et al. SABCS 2020;Abstract GS3-00.

RxPONDER: IDFS Stratified by Menopausal Status

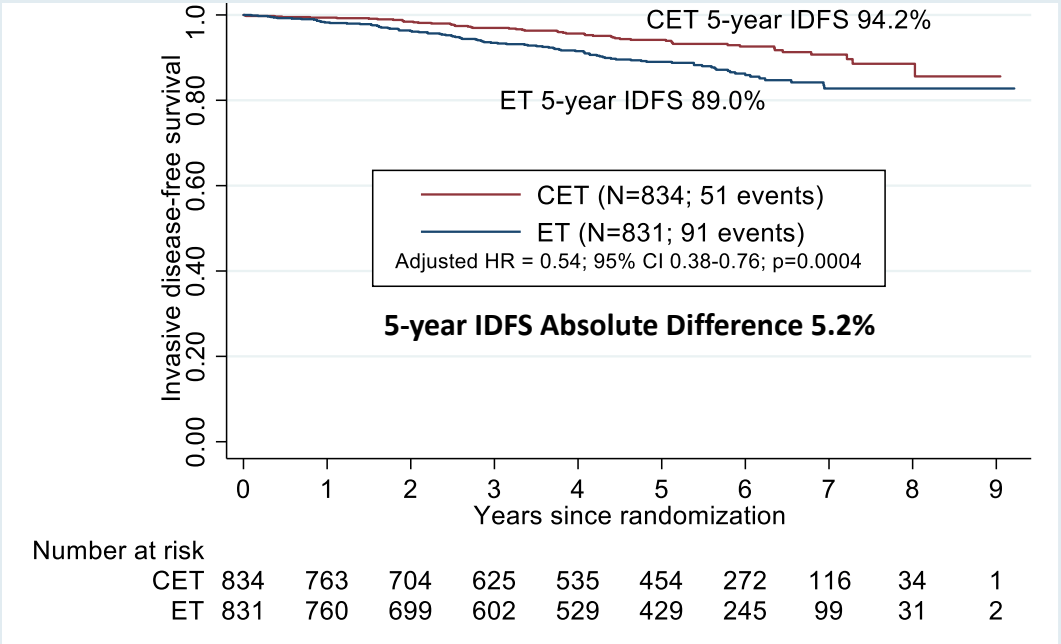
Postmenopausal



IDFS Event	CET	ET	Total (%)
Distant	39	44	83 (27%)
Local-Regional	10	14	24 (8%)
Contralateral	10	9	19 (6%)
Non-Breast Primary	44	47	91 (30%)
Recurrence Not Classified	9	7	16 (5%)
Death not due to Recurrence or Second Primary	35	37	72 (24%)

Absolute Difference in Distant Recurrence as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

Premenopausal



IDFS Event	CET	ET	Total (%)
Distant	26	50	76 (54%)
Local-Regional	8	17	25 (18%)
Contralateral	4	8	12 (8%)
Non-Breast Primary	10	10	20 (14%)
Recurrence Not Classified	1	1	2 (1%)
Death not due to Recurrence or Second Primary	2	5	7 (5%)

Absolute Difference in Distant Recurrence as 1st site: 2.9% (3.1% CET vs. 6.0% ET)

Kalinsky K et al. SABCS 2020;Abstract GS3-00.

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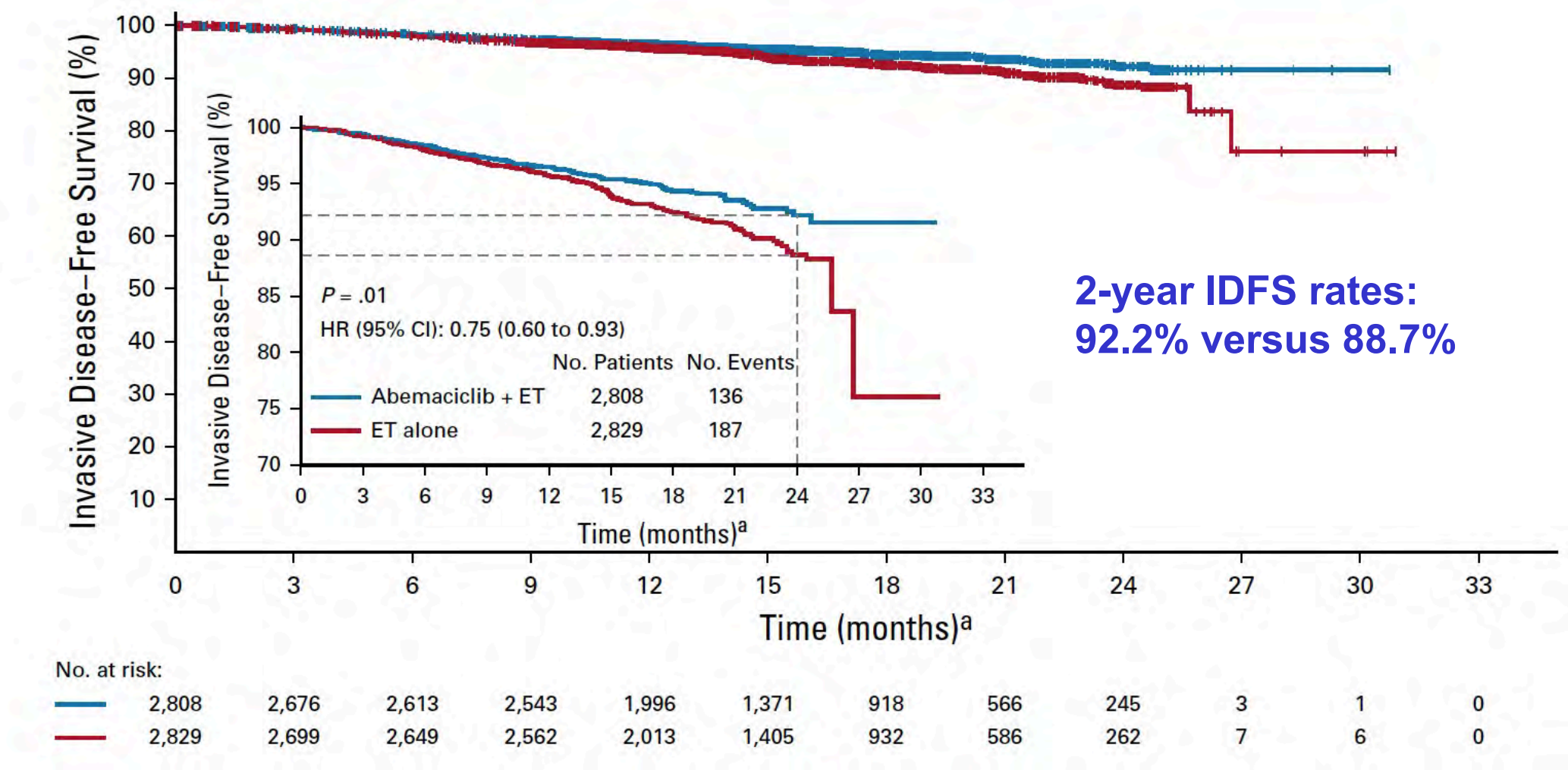
J Clin Oncol 2020;38(34):3987-98.

rapid communications

Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2−, Node-Positive, High-Risk, Early Breast Cancer (monarchE)

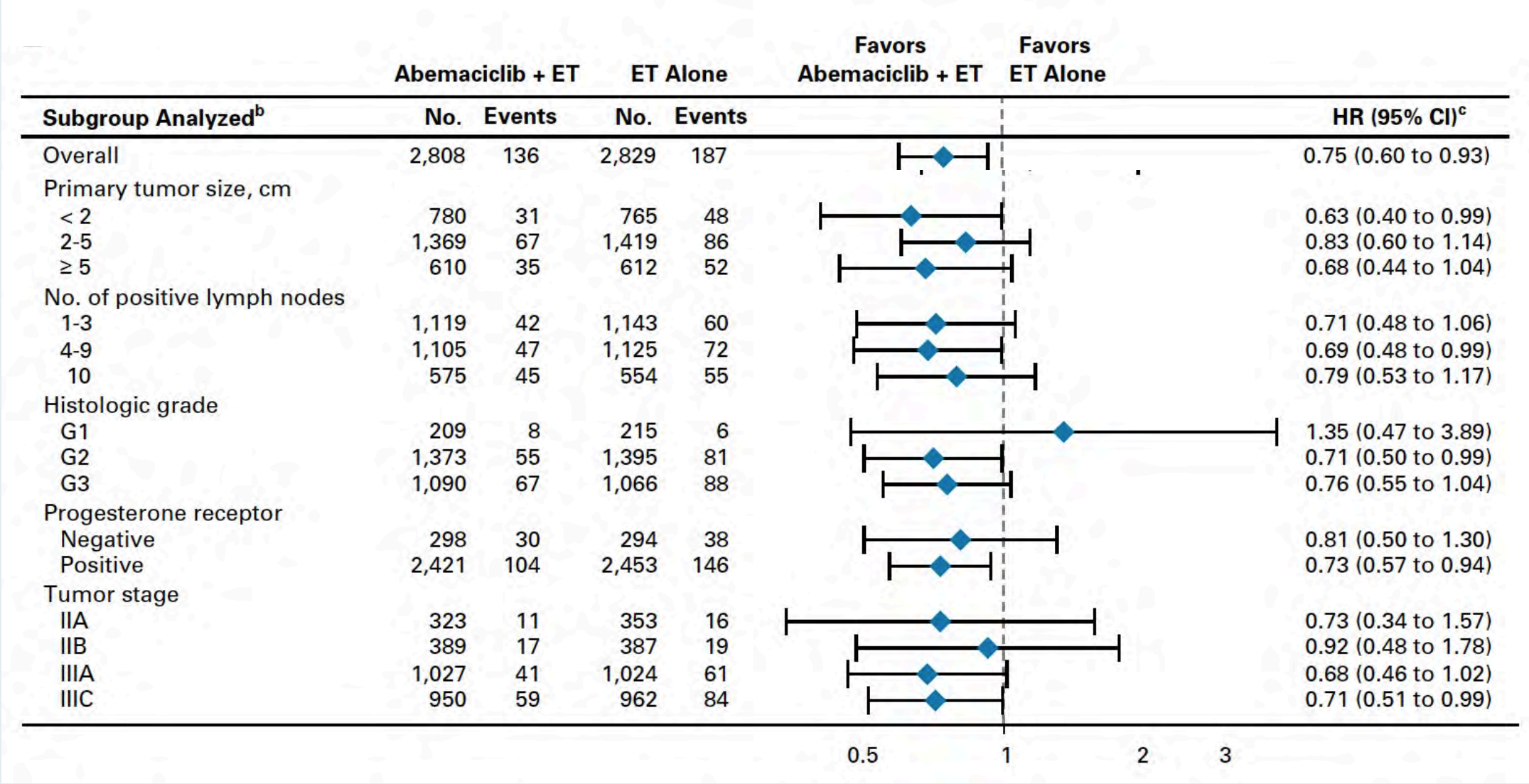
Stephen R. D. Johnston, MD, PhD[1]; Nadia Harbeck, MD, PhD[2]; Roberto Hegg, MD, PhD[3]; Masakazu Toi, MD, PhD[4]; Miguel Martin, MD, PhD[5]; Zhi Min Shao, MD[6]; Qing Yuan Zhang, MD, PhD[7]; Jorge Luis Martinez Rodriguez, MD[8]; Mario Campone, MD, PhD[9]; Erika Hamilton, MD[10]; Joohyuk Sohn, MD, PhD[11]; Valentina Guarneri, MD, PhD[12]; Morihito Okada, MD, PhD[13]; Frances Boyle, MD, MBBS, PhD[14]; Patrick Neven, MD, PhD[15]; Javier Cortés, MD, PhD[16]; Jens Huober, MD[17]; Andrew Wardley, MD, MBChB[18]; Sara M. Tolaney, MD, MPH[19]; Irfan Cicin, MD[20]; Ian C. Smith, MD[21,22]; Martin Frenzel, PhD[22]; Desirée Headley, MSc[22]; Ran Wei, PhD[22]; Belen San Antonio, PhD[22]; Maarten Hulstijn, PhD[22]; Joanne Cox, MD[22]; Joyce O'Shaughnessy, MD[23]; and Priya Rastogi, MD[24]; on behalf of the monarchE Committee Members and Investigators

monarchE: Invasive Disease-Free Survival (IDFS)



Johnston SRD et al. *J Clin Oncol* 2020;38(34):3987-98.

monarchE: IDFS Subgroups



Subgroup Analyzed[b]	Abemaciclib + ET No.	Abemaciclib + ET Events	ET Alone No.	ET Alone Events	HR (95% CI)[c]
Overall	2,808	136	2,829	187	0.75 (0.60 to 0.93)
Primary tumor size, cm					
< 2	780	31	765	48	0.63 (0.40 to 0.99)
2-5	1,369	67	1,419	86	0.83 (0.60 to 1.14)
≥ 5	610	35	612	52	0.68 (0.44 to 1.04)
No. of positive lymph nodes					
1-3	1,119	42	1,143	60	0.71 (0.48 to 1.06)
4-9	1,105	47	1,125	72	0.69 (0.48 to 0.99)
10	575	45	554	55	0.79 (0.53 to 1.17)
Histologic grade					
G1	209	8	215	6	1.35 (0.47 to 3.89)
G2	1,373	55	1,395	81	0.71 (0.50 to 0.99)
G3	1,090	67	1,066	88	0.76 (0.55 to 1.04)
Progesterone receptor					
Negative	298	30	294	38	0.81 (0.50 to 1.30)
Positive	2,421	104	2,453	146	0.73 (0.57 to 0.94)
Tumor stage					
IIA	323	11	353	16	0.73 (0.34 to 1.57)
IIB	389	17	387	19	0.92 (0.48 to 1.78)
IIIA	1,027	41	1,024	61	0.68 (0.46 to 1.02)
IIIC	950	59	962	84	0.71 (0.51 to 0.99)

Johnston SRD et al. *J Clin Oncol* 2020;38(34):3987-98.

RTP RESEARCH TO PRACTICE

monarchE: Treatment Duration and Adjustments

	Abemaciclib (n = 2,791)	Placebo (n = 2,800)
Median duration of ET	15 mo	15 mo
Median duration of abemaciclib	14 mo	—
Dose adjustments of abemaciclib due to AEs	68.1%	—
Discontinuation of abemaciblib due to AEs	16.6%	—
Discontinuation of ET and abemaciclib due to AEs	6.2%	6.2%
Discontinuation of ET due to AEs	—	0.8%

Johnston SRD et al. *J Clin Oncol* 2020;38(34):3987-98.

Articles

Lancet Oncol 2021;22:212-22

Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study

Erica L Mayer, Amylou C Dueck, Miguel Martin, Gabor Rubovszky, Harold J Burstein, Meritxell Bellet-Ezquerra, Kathy D Miller, Nicholas Zdenkowski, Eric P Winer, Georg Pfeiler, Matthew Goetz, Manuel Ruiz-Borrego, Daniel Anderson, Zbigniew Nowecki, Sibylle Loibl, Stacy Moulder, Alistair Ring, Florian Fitzal, Tiffany Traina, Arlene Chan, Hope S Rugo, Julie Lemieux, Fernando Henao, Alan Lyss, Silvia Antolin Novoa, Antonio C Wolff, Marcus Vetter, Daniel Egle, Patrick G Morris, Eleftherios P Mamounas, Miguel J Gil-Gil, Aleix Prat, Hannes Fohler, Otto Metzger Filho, Magdalena Schwarz, Carter DuFrane, Debora Fumagalli, Kathy Puyana Theall, Dongrui Ray Lu, Cynthia Huang Bartlett, Maria Koehler, Christian Fesl, Angela DeMichele, Michael Gnant**

Case Presentation – Dr Hussein: A 60-year-old woman with ER/PR-positive, HER2-negative, PIK3CA-positive metastatic breast cancer

Dr Maen Hussein

- 7/2015: Fulvestrant/anastrozole
- 10/2017: Palbociclib/letrozole
- 1/2020: Alpelisib/fulvestrant, with response x 6 months and good tolerability
  - Recurrent pleural effusion, SOB, rise in tumor markers
- 7/2020 and ongoing: Capecitabine, with stable disease

Questions

- What is your experience with alpelisib and its side effects? What kind of tricks do you use to manage the side effects?

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- André F et al. **Alpelisib plus Fulvestrant for PIK3CA-Mutated, Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-2-Negative Advanced Breast Cancer: Final Overall Survival Results from SOLAR-1.** *Ann Oncol* 2021;32(2):208-17.
- Rugo HS et al. **Alpelisib + Fulvestrant in Patients with PIK3CA-Mutated Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer Previously Treated with Cyclin-Dependent Kinase 4/6 Inhibitor + Aromatase Inhibitor: BYLieve Study Results.** ASCO 2020;Abstract 1006.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Alpelisib plus fulvestrant for *PIK3CA*-mutated, hormone receptor-positive, human epidermal growth factor receptor-2—negative advanced breast cancer: final overall survival results from SOLAR-1

F. André[1*], E. M. Ciruelos[2], D. Juric[3], S. Loibl[4], M. Campone[5], I. A. Mayer[6], G. Rubovszky[7], T. Yamashita[8], B. Kaufman[9], Y.-S. Lu[10], K. Inoue[11], Z. Pápai[12], M. Takahashi[13], F. Ghaznawi[14], D. Mills[15], M. Kaper[14], M. Miller[14], P. F. Conte[16], H. Iwata[17] & H. S. Rugo[18]

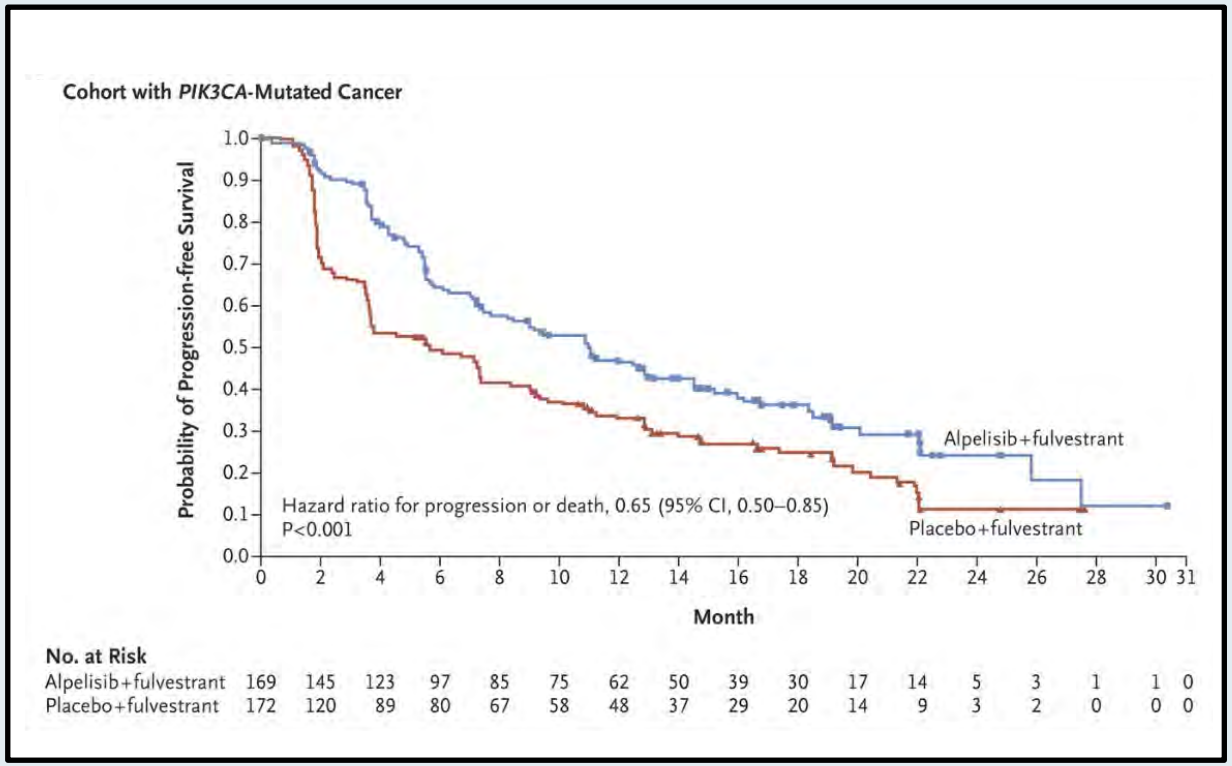
[1]Department of Medical Oncology, Institut Gustave Roussy, Villejuif and Paris Saclay University, Orsay, France; [2]Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; [3]Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, USA; [4]Department of Medicine and Research, German Breast Group, GBG Forschungs GmbH, Neu-Isenburg, Germany; [5]Medical Oncology, Institut de Cancerologie de l'Ouest, Saint-Herblain, Nantes Cedex, France; [6]Hematology/Oncology, Vanderbilt University, Nashville, USA; [7]Department of Medical Oncology and Clinical Pharmacology, National Institute of Oncology, Budapest, Hungary; [8]Department of Breast and Endocrine Surgery, Kanagawa Cancer Center, Yokohama, Japan; [9]Medical Oncology, Tel Aviv University, Sheba Medical Centre, Tel Hashomer, Israel; [10]Medical Oncology, National Taiwan University Hospital, Taipei, Taiwan; [11]Breast Surgery, Saitama Cancer Center, Saitama, Japan; [12]Medical Oncology, Hungarian Defence Forces Medical Centre, Budapest, Hungary; [13]Breast Surgery, NHO Hokkaido Cancer Center, Sapporo, Japan; [14]Novartis Pharmaceuticals Corporation, East Hanover, USA; [15]Novartis Pharma AG, Basel, Switzerland; [16]Medical Oncology, Universita di Padova and Oncologia Medica 2, Istituto Oncologico Veneto IRCCS, Padua, Italy; [17]Breast Oncology, Aichi Cancer Center Hospital, Aichi, Japan; [18]Breast Department, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, USA

Available online 25 November 2020

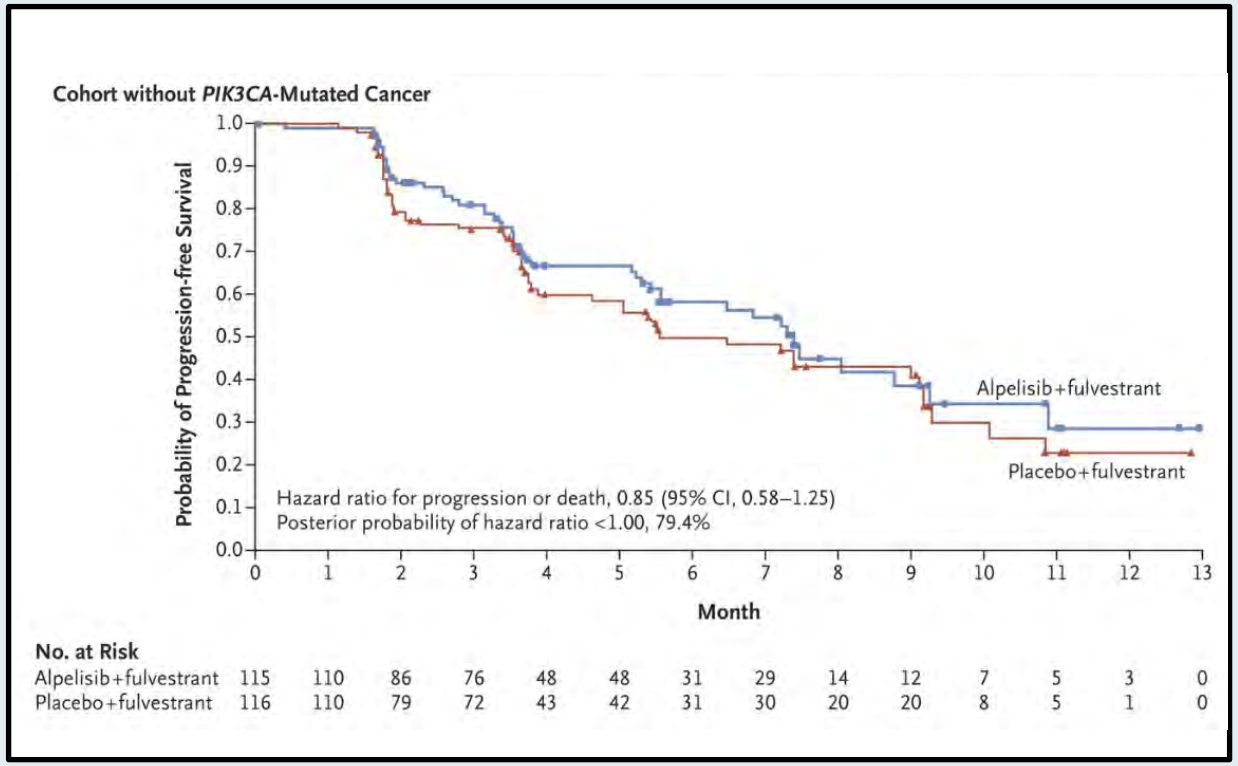
***Ann Oncol* 2021;32(2):208-17.**

SOLAR-1: PFS Outcomes by PIK3CA Mutation Status

PIK3CA mutated



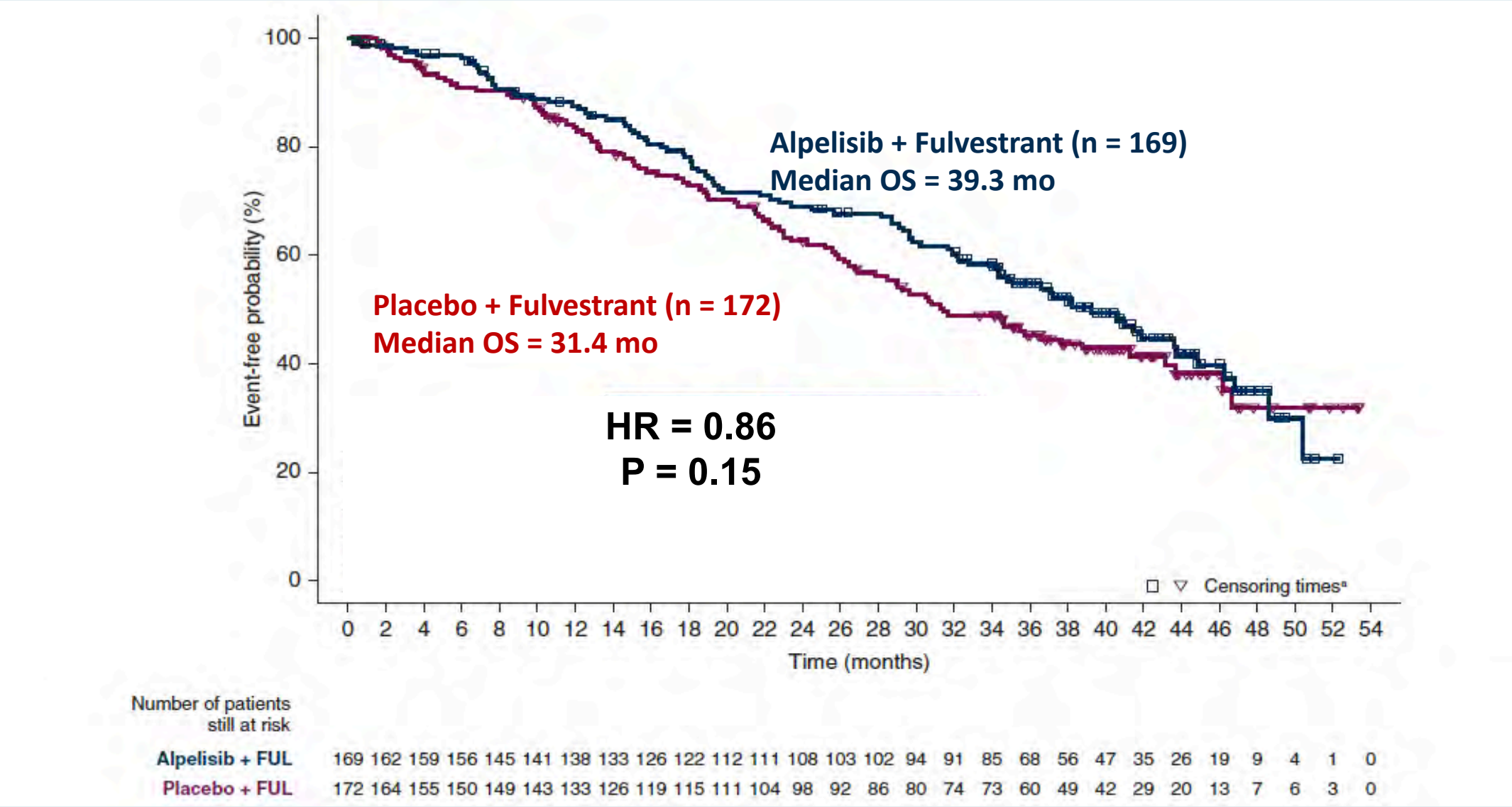
No PIK3CA mutation



André F et al. *N Engl J Med* 2019;380:1929-40.

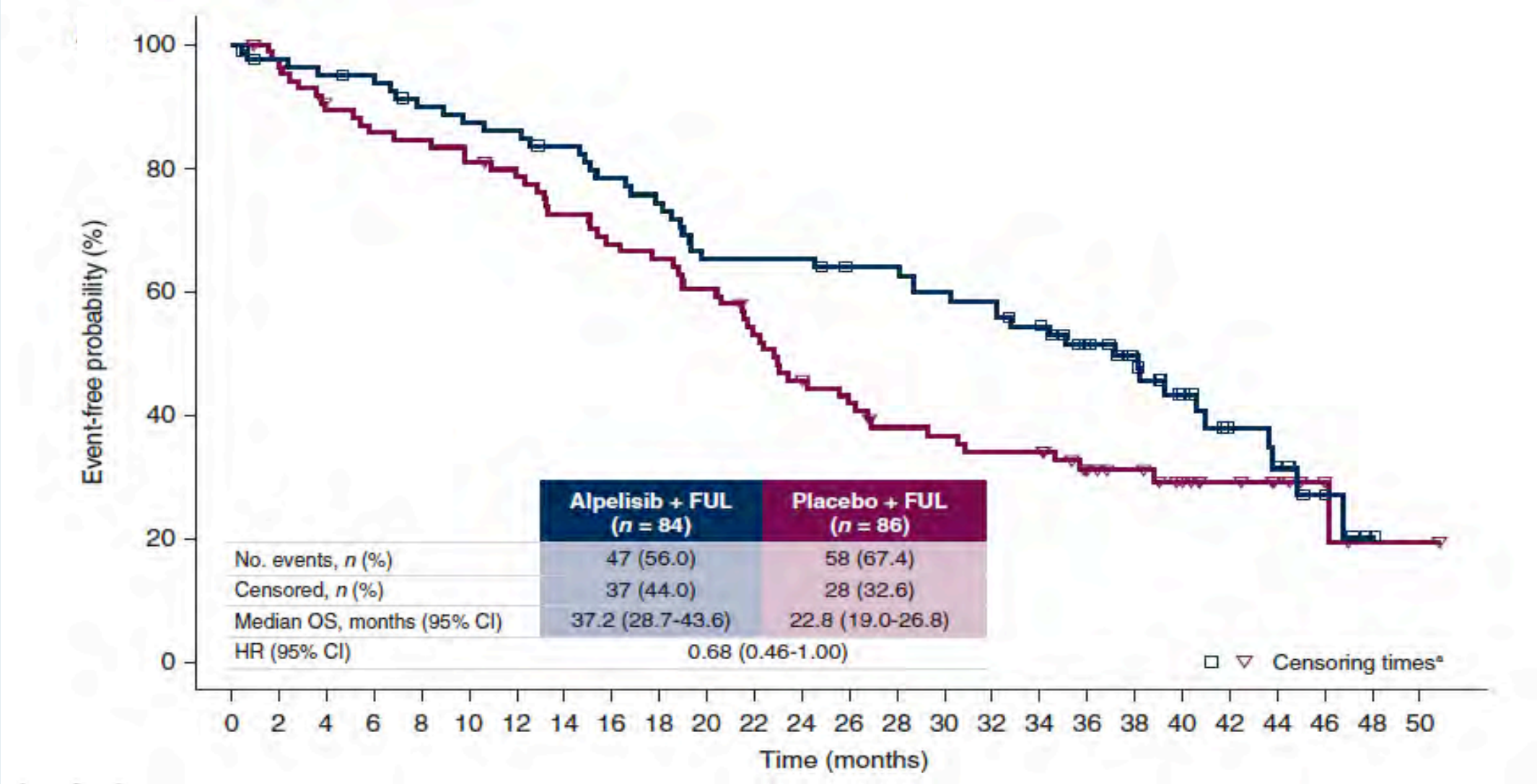
RTP RESEARCH TO PRACTICE

SOLAR-1: OS in Patients with Advanced BC with a PIK3CA Mutation



André F et al. *Ann Oncol* 2021;32(2):208-17.

SOLAR-1: OS in Patients with BC with PIK3CA Mutations and Lung/Liver Metastases



	Alpelisib + FUL (*n* = 84)	Placebo + FUL (*n* = 86)
No. events, *n* (%)	47 (56.0)	58 (67.4)
Censored, *n* (%)	37 (44.0)	28 (32.6)
Median OS, months (95% CI)	37.2 (28.7-43.6)	22.8 (19.0-26.8)
HR (95% CI)	0.68 (0.46-1.00)	

André F et al. *Ann Oncol* 2021;32(2):208-17.

SOLAR-1: Select Adverse Events in Overall Patient Population

Adverse Event	Alpelisib–Fulvestrant Group (N = 284)			Placebo–Fulvestrant Group (N = 287)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	282 (99.3)	183 (64.4)	33 (11.6)	264 (92.0)	87 (30.3)	15 (5.2)
Hyperglycemia	181 (63.7)	93 (32.7)	11 (3.9)	28 (9.8)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	19 (6.7)	0	45 (15.7)	1 (0.3)	0
Nausea	127 (44.7)	7 (2.5)	0	64 (22.3)	1 (0.3)	0
Decreased appetite	101 (35.6)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash	101 (35.6)	28 (9.9)	0	17 (5.9)	1 (0.3)	0

André F et al. *N Engl J Med* 2019;380:1929-40.

Alpelisib + Fulvestrant in Patients with *PIK3CA*-Mutated Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer Previously Treated with Cyclin-Dependent Kinase 4/6 Inhibitor + Aromatase Inhibitor: BYLieve Study Results

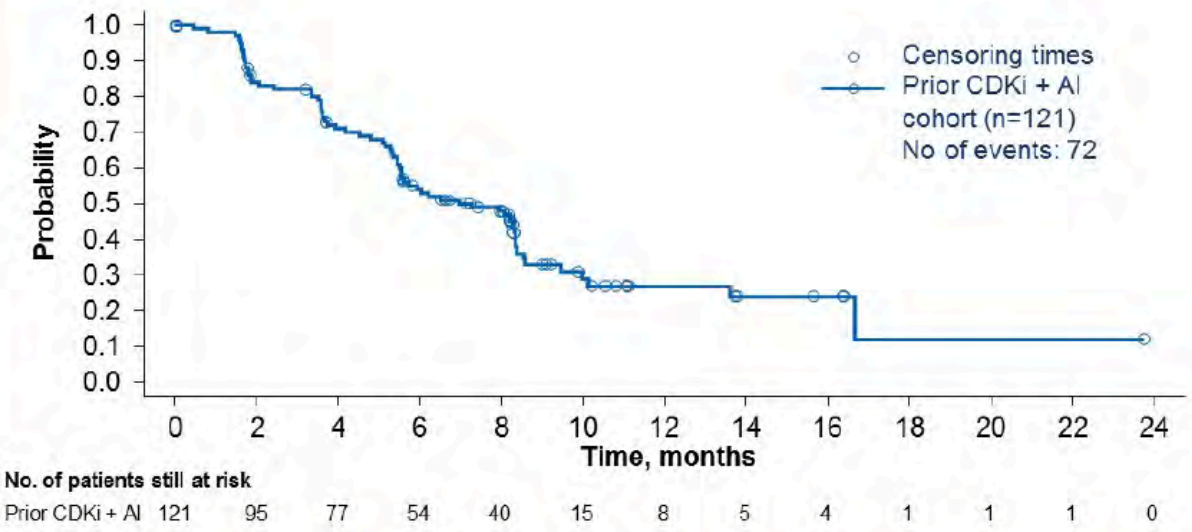
Rugo HS et al.

ASCO 2020;Abstract 1006.

BYLieve COHORT A: Primary Endpoint and PFS

Cohort A = Alpelisib + fulvestrant in patients who received CDK4/6i + AI as immediate prior treatment

Endpoint	Prior CDKi + AI (Cohort A) (n=121)
Primary endpoint: Patients who were alive without disease progression at 6 mo	**50.4%** (n=61; 95% CI, 41.2-59.6)
Secondary endpoint: Median PFS	**7.3 mo** [n=72 (59.5%) with event]; 95% CI, 5.6-8.3)

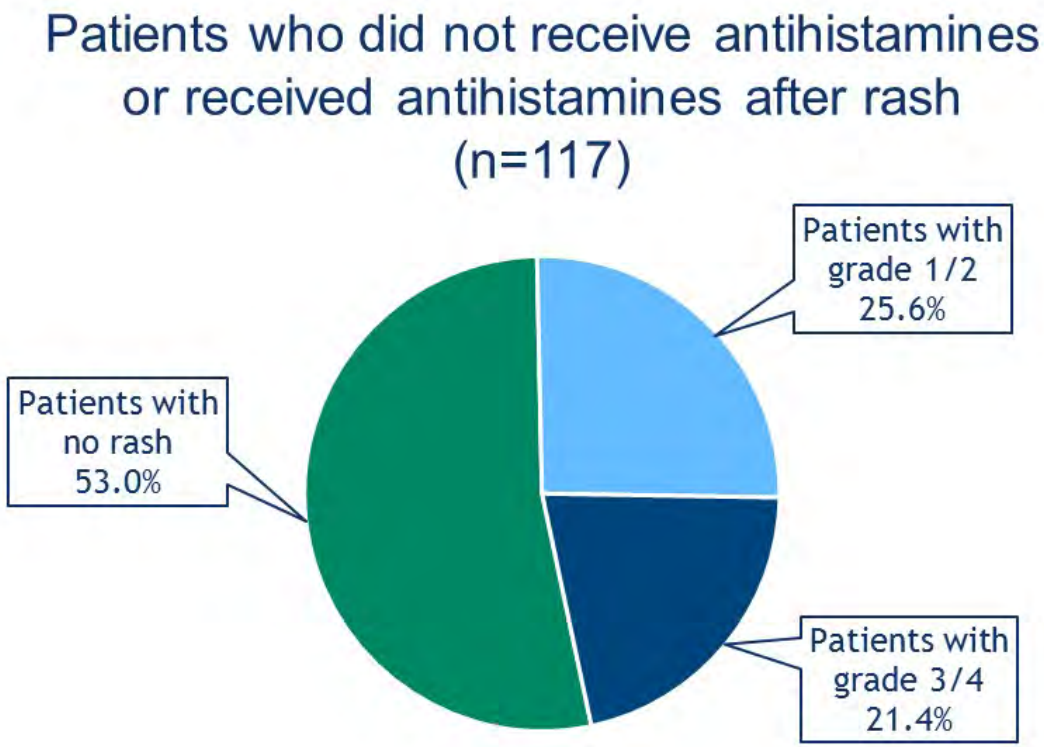


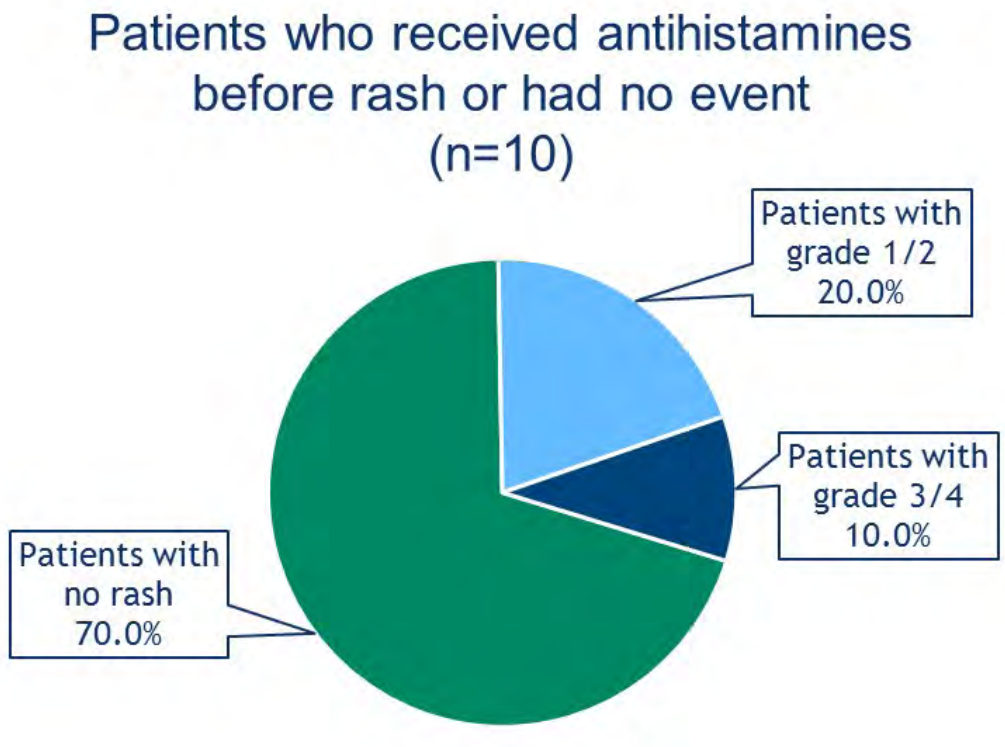
The primary endpoint for the prior CDKi + AI cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months

- In SOLAR-1, 44.4% of patients in the *PIK3CA*-mutant cohort with prior CDKi treated with alpelisib plus fulvestrant were alive without disease progression at 6 months

Rugo HS et al. ASCO 2020;Abstract 1006.

BYLieve: Incidence of Rash with and without Prophylactic Antihistamines





Rugo HS et al. ASCO 2020;Abstract 1006.

RTP RESEARCH TO PRACTICE

Results from VERONICA: A Randomized, Phase II Study of Second-/Third-Line Venetoclax (VEN) + Fulvestrant (F) versus F Alone in Estrogen Receptor (ER)-Positive, HER2-Negative, Locally Advanced, or Metastatic Breast Cancer (LA/MBC)

Lindeman GJ et al.
ASCO 2021;Abstract 1004.

Saturday, June 5, 1:30 PM - 4:30 PM EDT

Agenda

Module 1: ER-Positive, HER2-Negative Breast Cancer

- Dr Stebel: A 58-year-old woman with ER-positive, HER2-negative metastatic breast cancer
- *Key Recent Publications and Presentations*
- Dr Hussein: A 60-year-old woman with ER/PR-positive, HER2-negative, PIK3CA-positive metastatic breast cancer
- *Key Recent Publications and Presentations*

Module 2: HER2-Positive Breast Cancer

- Dr Stebel: A 35-year-old woman with a 3-cm weakly ER/PR-positive, HER2-positive node-negative breast cancer
- Dr Del Rosario: A 53-year-old woman with ER/PR-negative, HER2-positive metastatic inflammatory breast cancer
- *Key Recent Publications and Presentations*

Module 3: Triple-Negative Breast Cancer (TNBC)

- Dr Del Rosario: A 68-year-old woman with localized TNBC
- *Key Recent Publications and Presentations*
- Dr Del Rosario: A 70-year-old woman with metastatic TNBC
- *Key Recent Publications and Presentations*

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TO PRACTICE

Case Presentation – Dr Stebel: A 35-year-old woman with a 3-cm weakly ER/PR-positive, HER2-positive node-negative breast cancer

Dr Andrea Stebel

- 2019: 3-cm left breast mass → Biopsy: Weakly ER-positive, strongly PR-positive, HER2-positive IDC
- Neoadjuvant TCHP → Mastectomy, with no residual disease → HP to complete 1 year
  - No ovarian suppression administered
  - Difficulty tolerating chemotherapy, sought second opinion
- Patient is interested in preserving fertility
- Pathologist re-examined tissue blocks: ER (Allred 3 → 4), PR (Allred 7 → 1)

Questions

- Do we need to give all of these women, particularly those who have a negative axilla, neoadjuvant therapy?
- With her complete pathologic response, did she need to continue the HP for the rest of the year, again because of the negative axilla originally?
- When does one really consider extended adjuvant therapy with neratinib?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Del Rosario: A 53-year-old woman with ER/PR-negative, HER2-positive metastatic inflammatory breast cancer

Dr Michael Del Rosario

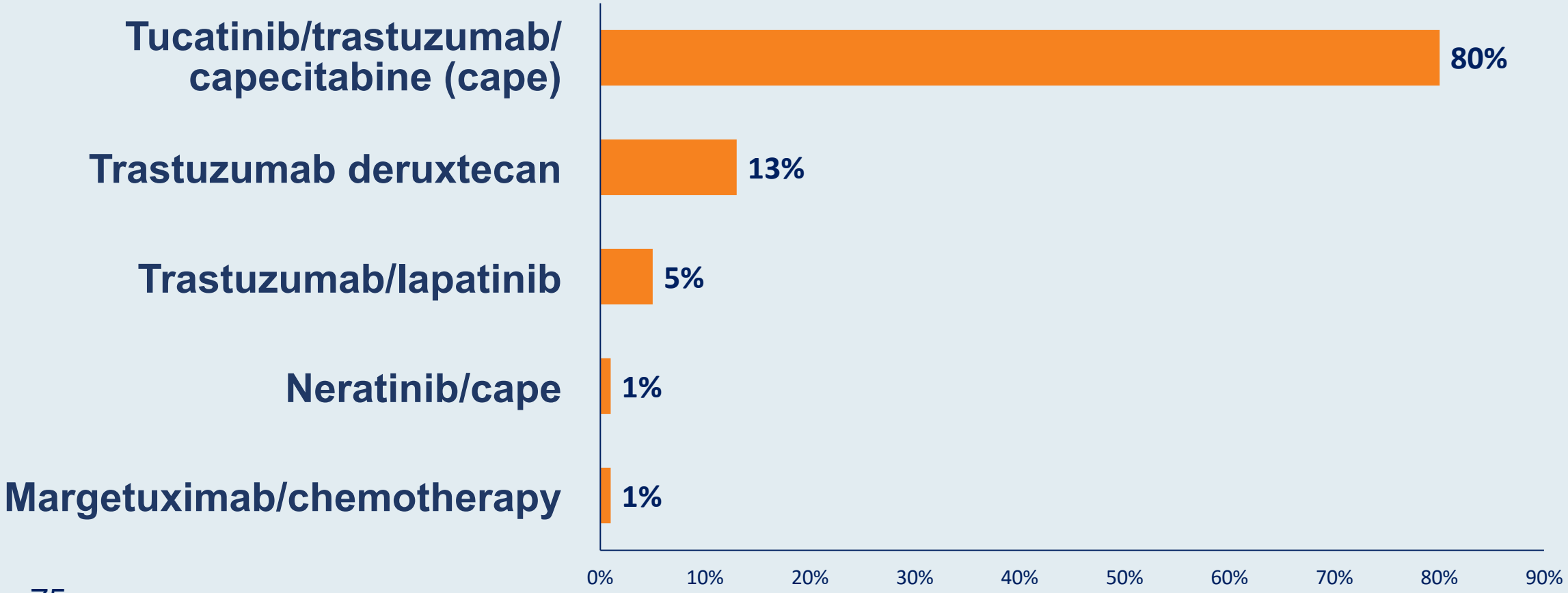
- Left-sided ER/PR-negative, HER2-positive T4dN1M1 metastatic, grade 3 inflammatory breast cancer, with liver and bone metastases
- Weekly paclitaxel/trastuzumab/pertuzumab → PD
- T-DM1

Questions

- In general, what is your preferred sequencing of treatments for HER2-positive metastatic breast cancer?
- For a patient with HER2-positive metastatic breast cancer, when would you consider using tucatinib and trastuzumab as a line of treatment with capecitabine?

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line THP and second-line T-DM1 but then experiences disease progression, including multiple brain metastases. What systemic treatment would you most likely recommend next?



N = 75

Survey of live webinar audience

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- Murthy RK et al. **Tucatinib, Trastuzumab and Capecitabine for HER2-Positive Metastatic Breast Cancer**. *N Engl J Med* 2020;382(7):597-609.
- Lin NU et al. **Intracranial Efficacy and Survival with Tucatinib plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer with Brain Metastases in the HER2CLIMB Trial.** *J Clin Oncol* 2020;38(23):2610-9.
- Modi S et al. **Trastuzumab Deruxtecan for Previously Treated HER2-Positive Metastatic Breast Cancer.** *N Engl J Med* 2020;382(7):610-21.
- Modi S et al. **Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients with HER2-Low-Expressing Advanced Breast Cancer: Results from a Phase Ib Study.** *J Clin Oncol* 2020;38(17):1887-96.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 13, 2020 VOL. 382 NO. 7

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

R.K. Murthy, S. Loi, A. Okines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.U. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S.S. Shachar, V. Müller, S. Braga, F.P. Duhoux, R. Greil, D. Cameron, L.A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Walker, W. Feng, and E.P. Winer

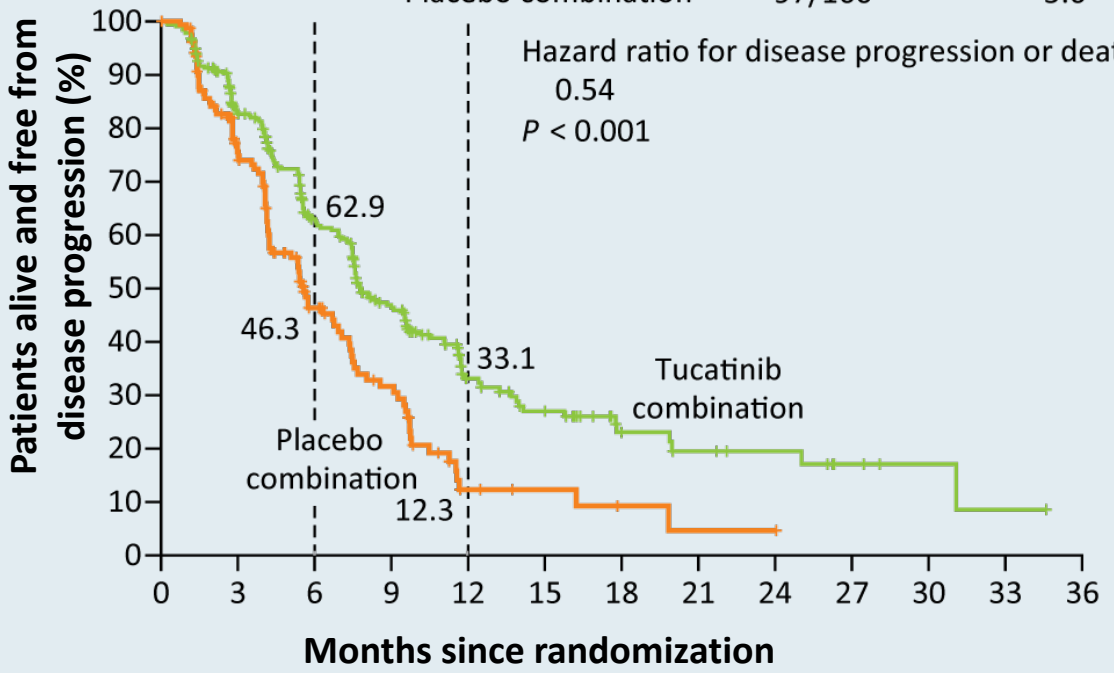
HER2CLIMB: Survival Outcomes

Among the patients with brain metastases:

- Median PFS = 7.6 mo (tucatinib) vs 5.4 mo (placebo)
  - HR = 0.48; $p < 0.001$
- 1-year PFS = 24.9% (tucatinib) vs 0% (placebo)

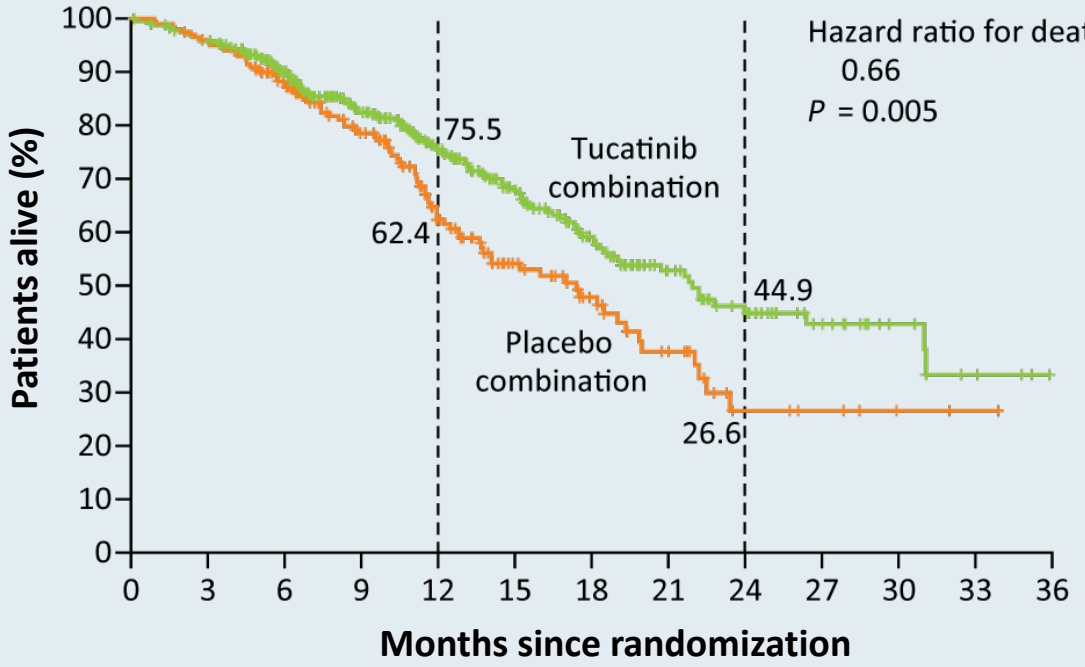
PFS

	No. of events/ No. of patients	Median duration *mo*
Tucatinib combination	178/320	7.8
Placebo combination	97/160	5.6



OS

	No. of deaths/ No. of patients	Median duration *mo*
Tucatinib combination	130/410	21.9
Placebo combination	85/202	17.4



Murthy R et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-01;
Murthy RK et al. *N Engl J Med* 2020;382(7):597-609.

RTP RESEARCH TO PRACTICE

HER2CLIMB: Safety Outcomes

Select AE	Tucatinib (n = 404)		Placebo (n = 197)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	99.3%	55.2%	97.0%	48.7%
Diarrhea	80.9%	12.9%	53.3%	8.6%
PPE syndrome	63.4%	13.1%	52.8%	9.1%
Nausea	58.4%	3.7%	43.7%	3.0%
Fatigue	45.0%	4.7%	43.1%	4.1%
Vomiting	35.9%	3.0%	25.4%	3.6%
Stomatitis	25.5%	2.5%	14.2%	0.5%
Increased AST	21.3%	4.5%	11.2%	0.5%
Increased ALT	20.0%	5.4%	6.6%	0.5%

Murthy R et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-01;
Murthy RK et al. *N Engl J Med* 2020;382(7):597-609.

rapid communications

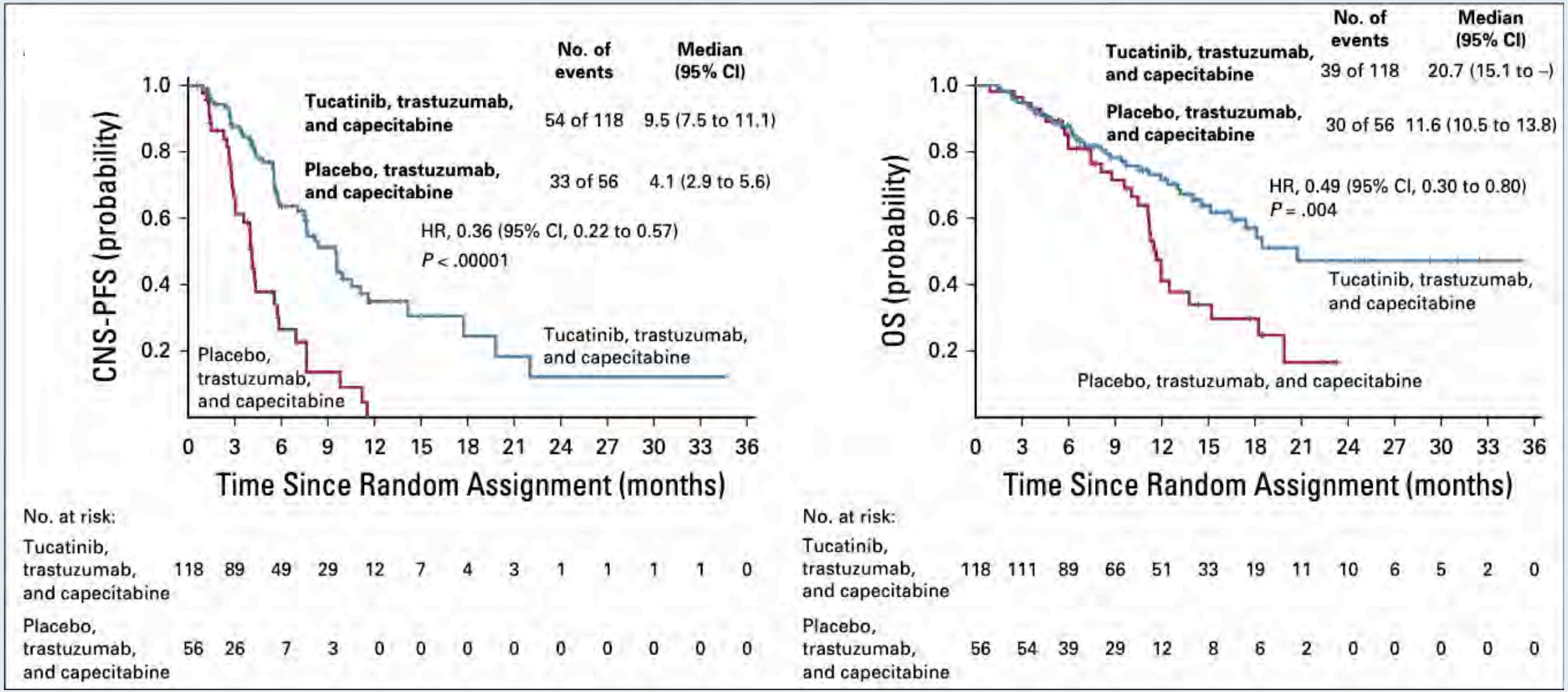
Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial

Nancy U. Lin, MD[1]; Virginia Borges, MMSc, MD[2]; Carey Anders, MD[3]; Rashmi K. Murthy, MD, MBE[4]; Elisavet Paplomata, MD[5]; Erika Hamilton, MD[6]; Sara Hurvitz, MD[7]; Sherene Loi, MD, PhD[8]; Alicia Okines, MBChB, MD[9]; Vandana Abramson, MD[10]; Philippe L. Bedard, MD[11]; Mafalda Oliveira, MD, PhD[12]; Volkmar Mueller, MD[13]; Amelia Zelnak, MD[14]; Michael P. DiGiovanna, MD, PhD[15]; Thomas Bachelot, MD[16]; A. Jo Chien, MD[17]; Ruth O'Regan, MD[5]; Andrew Wardley, MBChB, MSc, MD[18]; Alison Conlin, MD, MPH[19]; David Cameron, MD, MA[20]; Lisa Carey, MD[21]; Giuseppe Curigliano, MD, PhD[22]; Karen Gelmon, MD[23]; Sibylle Loibl, MD, PhD[24]; JoAl Mayor, PharmD[25]; Suzanne McGoldrick, MD, MPH[25]; Xuebei An, PhD[25]; and Eric P. Winer, MD[1]

J Clin Oncol 2020;38(23):2610-9.

RTP RESEARCH TO PRACTICE

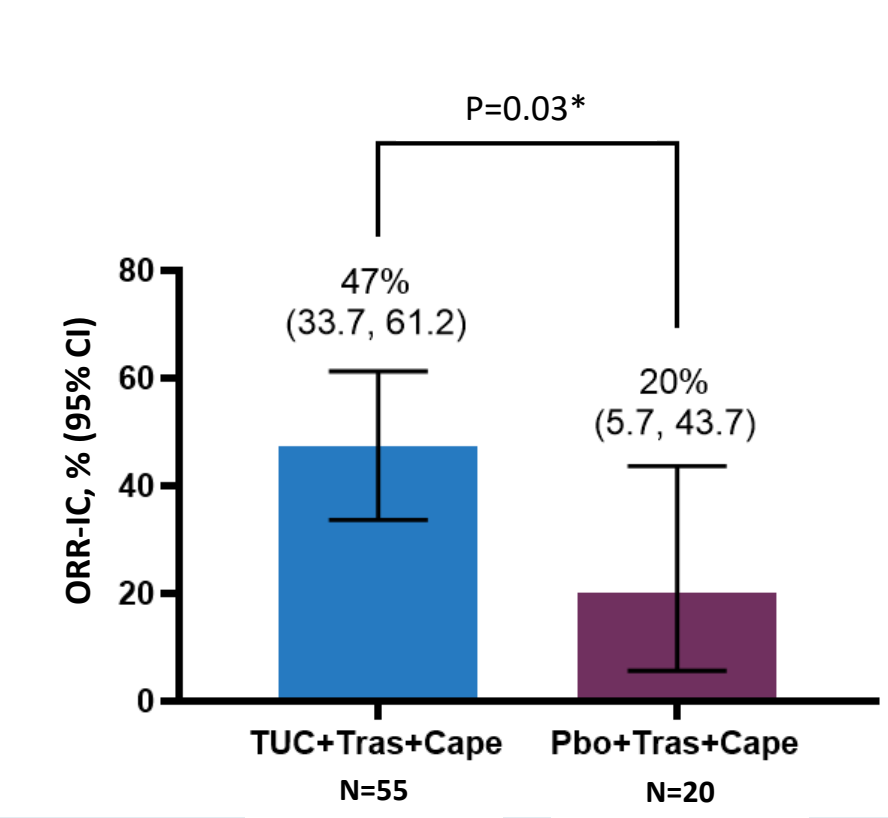
HER2CLIMB: CNS PFS and OS for Patients with Active Brain Metastases



Lin NU et al. *J Clin Oncol* 2020;38(23):2610-9.

HER2CLIMB: Intracranial Response Rate (ORR-IC) for Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

Confirmed Objective Response Rate (RECIST 1.1)



*Stratified Cochran-Mantel-Haenszel P value

Best Overall Intracranial Response[a], n (%)		
Complete Response (CR)	3 (5.5)	1 (5.0)
Partial Response (PR)	23 (41.8)	3 (15.0)
Stable Disease (SD)	24 (43.6)	16 (80.0)
Progressive Disease (PD)	2 (3.6)	0
Not Available[b]	3 (5.5)	0
Subjects with Objective Response of Confirmed CR or PR, n	26	4
Duration of Intracranial Response (DOR-IC)[e] (95% CI)[f], months	6.8 (5.5, 16.4)	3.0 (3.0, 10.3)

(a) Confirmed Best overall response assessed per RECIST 1.1. (b) Subjects with no post-baseline response assessments. (c) Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934). (d Cochran-Mantel-Haenszel test controlling for stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. (e) As estimated using Kaplan-Meier methods. (f) Calculated using the complementary log-log transformation method (Collett, 1994).

Courtesy of Carey K Anders, MD

The NEW ENGLAND JOURNAL of MEDICINE

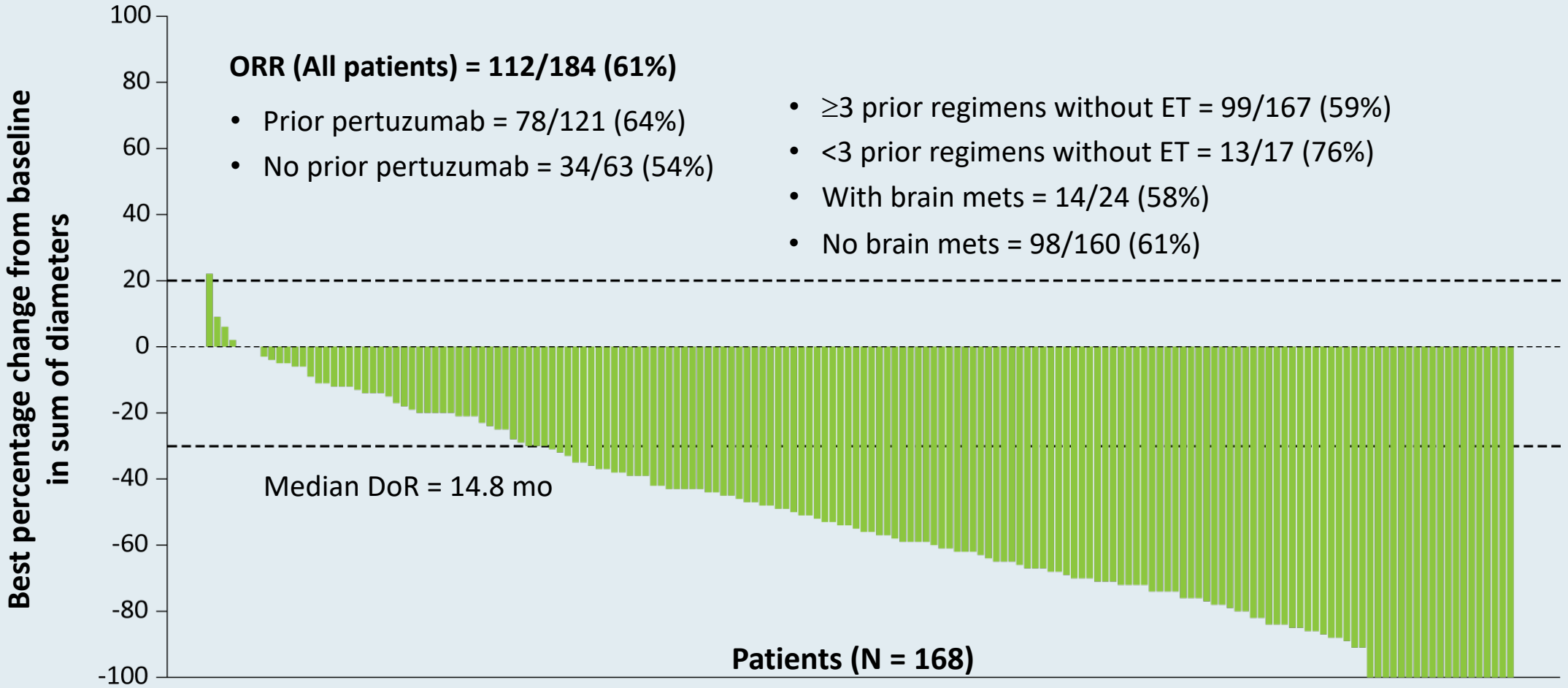
ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

N Engl J Med 2020;382(7):610-21.

DESTINY-Breast01: Response According to Tumor Size and Subgroup Analyses



Modi S et al. *N Engl J Med* 2020;382(7):610-21.

RTP RESEARCH TO PRACTICE

DESTINY-Breast01: Survival and Safety

- **Median duration of follow-up = 11.1 mo**
- **Median PFS = 16.4 mo**
- **Estimated 6-mo OS = 93.9%**
- **Estimated 12-mo OS = 86.2%**
- **Median OS not reached**

AEs of special interest (n = 184)	All grades	Grades 3/4
Interstitial lung disease	25 (13.6%)	1 (0.5%)
Prolonged QT interval	9 (4.9%)	2 (1.1%)
Infusion-related reaction	4 (2.2%)	0
Decreased left ventricular ejection fraction	3 (1.6%)	1 (0.5%)

- Most common Grade ≥3 AEs were decreased neutrophil count (21%), anemia (9%) and nausea (8%).

Modi S et al. *N Engl J Med* 2020;382(7):610-21.

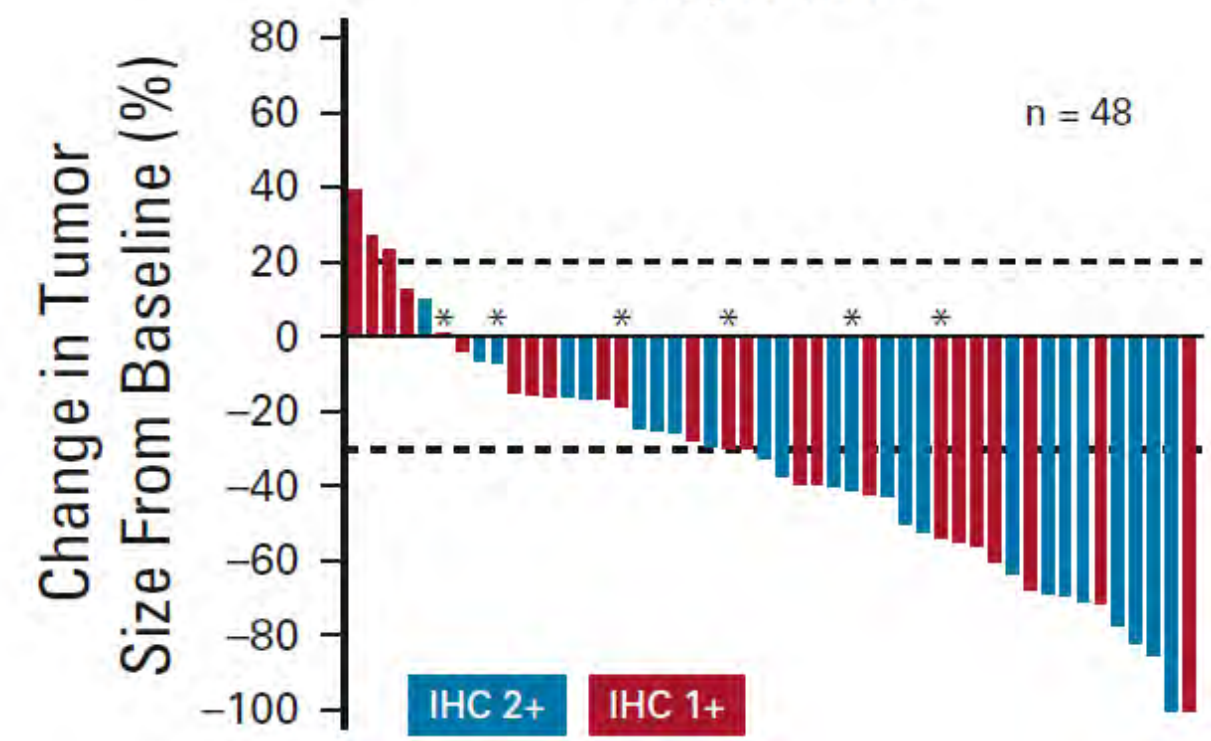
original reports

Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low–Expressing Advanced Breast Cancer: Results From a Phase Ib Study

Shanu Modi, MD[1]; Haeseong Park, MD, MPH[2]; Rashmi K. Murthy, MD, MBE[3]; Hiroji Iwata, PhD, MD[4]; Kenji Tamura, MD, PhD[5]; Junji Tsurutani, MD, PhD[6]; Alvaro Moreno-Aspitia, PhD[7]; Toshihiko Doi, MD, PhD[8]; Yasuaki Sagara, MD[9]; Charles Redfern, MD[10]; Ian E. Krop, MD, PhD[11]; Caleb Lee, MD, PhD[12]; Yoshihiko Fujisaki, MS[13]; Masahiro Sugihara, PhD[13]; Lin Zhang, MD, PhD[12]; Javad Shahidi, MD[12]; and Shunji Takahashi, MD[14]

J Clin Oncol 2020;38(17):1887-96.

Effect of Trastuzumab Deruxtecan in Heavily Pretreated* HER2-Low Metastatic Breast Cancer



Clinical activity (by independent review)

ORR		
	Overall	37%
	HER2 2+	39%
	HER2 1+	36%
	ER+	40% (N = 47)
	ER-	14% (N = 7)
PFS		
	Overall	11.1 months

* Median of 7.5 prior regimens

Modi et al. *J Clin Oncol* 2020;38(17):1887-96.

Courtesy of Ian E Krop, MD, PhD

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Trastuzumab plus Endocrine Therapy or Chemotherapy as First-Line Treatment for Metastatic Breast Cancer with Hormone Receptor-Positive and HER2-Positive: The SYSUCC-002 Randomized Clinical Trial

Yuan Z et al.
ASCO 2021;Abstract 1003.

Saturday, June 5, 1:30 PM - 4:30 PM EDT

FDA Approves Margetuximab for HER2-Positive mBC

Press Release – December 16, 2020

"On December 16, 2020, the Food and Drug Administration approved margetuximab-cmkb in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

Efficacy was evaluated in SOPHIA (NCT02492711), a randomized, multicenter, open-label trial of 536 patients with IHC 3+ or ISH-amplified HER2+ metastatic breast cancer who had received prior treatment with other anti-HER2 therapies. Patients were randomized (1:1) to margetuximab plus chemotherapy or trastuzumab plus chemotherapy. Randomization was stratified by chemotherapy choice (capecitabine, eribulin, gemcitabine, or vinorelbine), number of lines of therapy in the metastatic setting (≤ 2, > 2), and number of metastatic sites (≤ 2, > 2)."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-margetuximab-metastatic-her2-positive-breast-cancer

Research

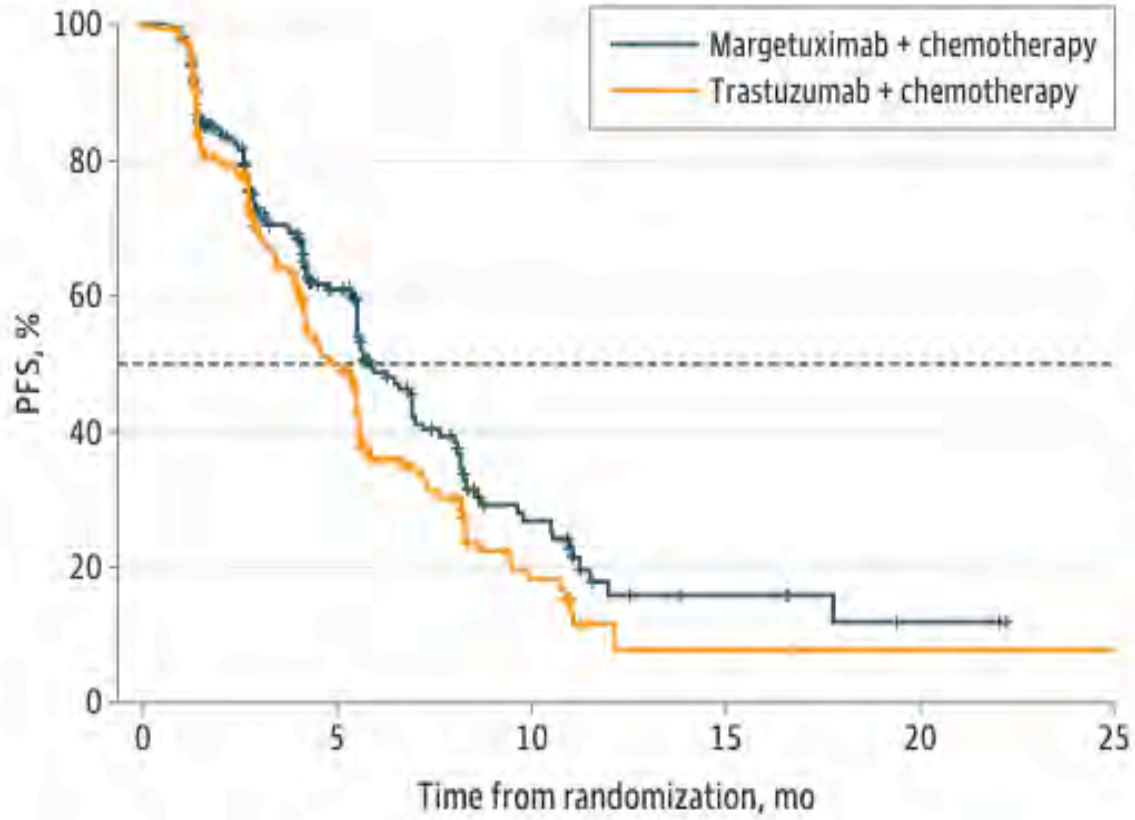
JAMA Oncology | Original Investigation

Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer
A Phase 3 Randomized Clinical Trial

Hope S. Rugo, MD; Seock-Ah Im, MD, PhD; Fatima Cardoso, MD; Javier Cortés, MD, PhD; Giuseppe Curigliano, MD, PhD; Antonino Musolino, MD, PhD, MSc; Mark D. Pegram, MD; Gail S. Wright, MD; Cristina Saura, MD, PhD; Santiago Escrivá-de-Romaní, MD; Michelino De Laurentiis, MD, PhD; Christelle Levy, MD; Ursa Brown-Glaberman, MD; Jean-Marc Ferrero, MD; Maaike de Boer, MD, PhD; Sung-Bae Kim, MD, PhD; Katarína Petráková, MD, PhD; Denise A. Yardley, MD; Orit Freedman, MD, MSc; Erik H. Jakobsen, MD; Bella Kaufman, MD; Rinat Yerushalmi, MD; Peter A. Fasching, MD; Jeffrey L. Nordstrom, PhD; Ezio Bonvini, MD; Scott Koenig, MD, PhD; Sutton Edlich, MS, PA; Shengyan Hong, PhD; Edwin P. Rock, MD, PhD; William J. Gradishar, MD; for the SOPHIA Study Group

JAMA Oncol 2021;[Online ahead of print].

SOPHIA: PFS by Central Blinded Analysis (ITT Population)

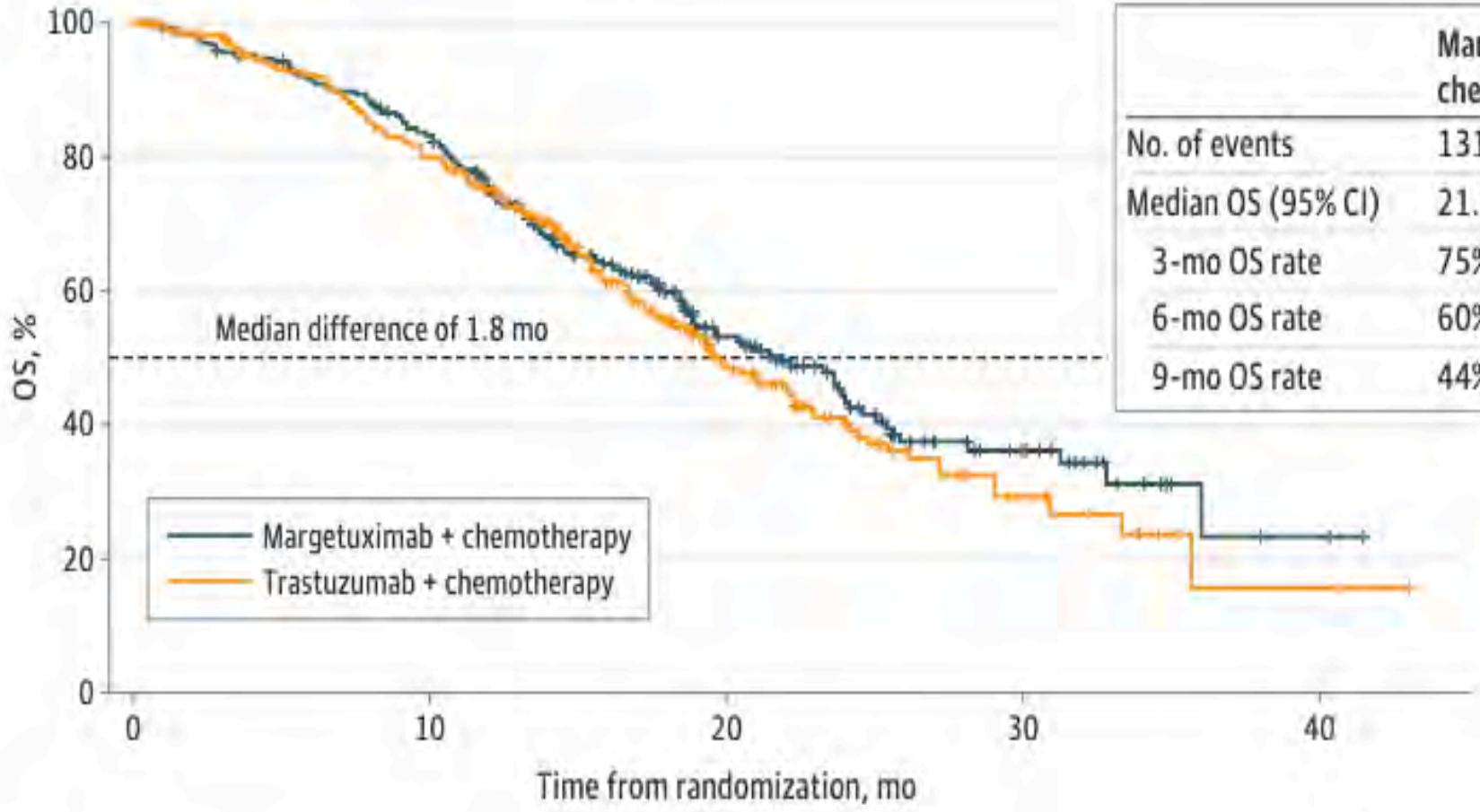


	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	130	135
Median PFS (95% CI)	5.8 mo (5.52-6.97)	4.9 mo (4.17-5.59)
3-mo PFS rate	72% (65%-77%)	70% (63%-76%)
6-mo PFS rate	48% (41%-56%)	36% (28%-44%)
9-mo PFS rate	30% (22%-38%)	22% (15%-30%)

HR by stratified Cox model, 0.76 (95% CI, 0.59-0.98)
Stratified log-rank *P* = .03
24% Risk reduction of disease progression[a]
Median follow-up, 2.8 mo

Rugo HS et al. *JAMA Oncol* 2021;[Online ahead of print].

SOPHIA: OS Analysis (ITT Population)



	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	131	139
Median OS (95% CI)	21.6 mo (18.86-24.05)	19.8 mo (17.54-22.28)
3-mo OS rate	75% (70%-80%)	75% (70%-80%)
6-mo OS rate	60% (53%-66%)	56% (49%-62%)
9-mo OS rate	44% (36%-51%)	40% (33%-48%)

HR by stratified Cox model, 0.89 (95% CI, 0.69-1.13)
Stratified log-rank $P = .33$
Median follow-up, 15.6 mo

Rugo HS et al. *JAMA Oncol* 2021;[Online ahead of print].

Agenda

Module 1: ER-Positive, HER2-Negative Breast Cancer

- Dr Stebel: A 58-year-old woman with ER-positive, HER2-negative metastatic breast cancer
- *Key Recent Publications and Presentations*
- Dr Hussein: A 60-year-old woman with ER/PR-positive, HER2-negative, PIK3CA-positive metastatic breast cancer
- *Key Recent Publications and Presentations*

Module 2: HER2-Positive Breast Cancer

- Dr Stebel: A 35-year-old woman with a 3-cm weakly ER/PR-positive, HER2-positive node-negative breast cancer
- Dr Del Rosario: A 53-year-old woman with ER/PR-negative, HER2-positive metastatic inflammatory breast cancer
- *Key Recent Publications and Presentations*

Module 3: Triple-Negative Breast Cancer (TNBC)

- Dr Del Rosario: A 68-year-old woman with localized TNBC
- *Key Recent Publications and Presentations*
- Dr Del Rosario: A 70-year-old woman with metastatic TNBC
- *Key Recent Publications and Presentations*

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Del Rosario: A 68-year-old woman with localized TNBC

Dr Michael Del Rosario

- Large, localized left TNBC, with axillary lymphadenopathy
- Plan: Neoadjuvant docetaxel/cyclophosphamide → BCS

Questions

- For a patient with large, localized triple-negative breast cancer, is immunotherapy a valid option in this setting? And if so, which immunotherapy agents can we use and would PD-L1 status be needed?
- For a patient with triple-negative localized breast cancer that received neoadjuvant chemotherapy and at the time of surgery had residual disease, what options do we have then? Would we consider immunotherapy or possibly capecitabine?

Key Recent Publications and Presentations

- Schmid P et al. **Pembrolizumab for Early Triple-Negative Breast Cancer.** *N Engl J Med* 2020;382(9):810-21.
- Mittendorf EA et al. **Neoadjuvant Atezolizumab in Combination with Sequential *Nab*-Paclitaxel and Anthracycline-Based Chemotherapy versus Placebo and Chemotherapy in Patients with Early-Stage Triple-Negative Breast Cancer (IMpassion031): A Randomised, Double-Blind, Phase 3 Trial.** *Lancet* 2020;396(10257):1090-100.

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Phase III KEYNOTE-522 Trial Meets Dual Primary Endpoint of Event-Free Survival for Patients with High-Risk Early-Stage TNBC

Press Release – May 13, 2021

"Positive results [were announced] from the pivotal neoadjuvant/adjuvant Phase 3 KEYNOTE-522 trial investigating pembrolizumab, an anti-PD-1 therapy, in combination with chemotherapy as pre-operative (neoadjuvant) treatment and then continuing as a single agent (adjuvant) treatment after surgery. KEYNOTE-522 met its dual primary endpoint of event-free survival (EFS) for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC).

Based on an interim analysis conducted by the independent Data Monitoring Committee (DMC), neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab as monotherapy showed a statistically significant and clinically meaningful improvement in EFS compared with neoadjuvant chemotherapy alone. As previously communicated, KEYNOTE-522 met its other dual primary endpoint of pathological complete response (pCR). The safety profile of pembrolizumab in this trial was consistent with that observed in previously reported studies; no new safety signals were identified."

https://finance.yahoo.com/news/merck-announces-phase-3-keynote-104500585.html

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

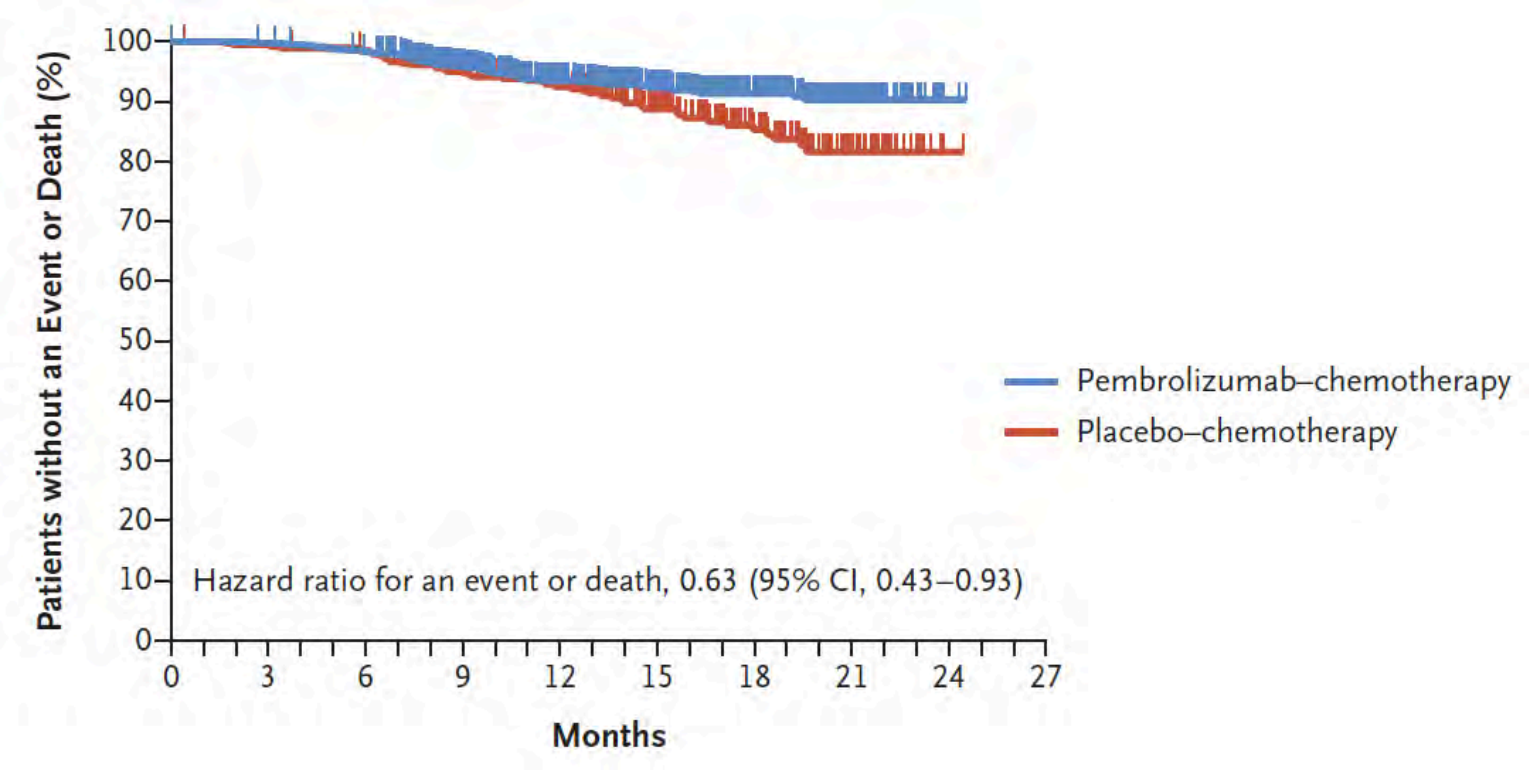
Pembrolizumab for Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, T. Foukakis, P.A. Fasching, F. Cardoso, M. Untch, L. Jia, V. Karantza, J. Zhao, G. Aktan, R. Dent, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

N Engl J Med 2020;382(9):810-21.

KEYNOTE-522 Primary Endpoints: pCR and EFS

Variable	Pembrolizumab + chemotherapy	Placebo + chemotherapy	Estimated Tx difference	*p*-value
Pathological stage ypT0/Tis ypN0	64.8%	51.2%	13.6%	< 0.001
Pathological stage ypT0 ypN0	59.9%	45.3%	14.5%	
Pathological stage ypT0/Tis	68.6%	53.7%	14.8%	



Schmid P et al. *N Engl J Med* 2020;382(9):810-21.

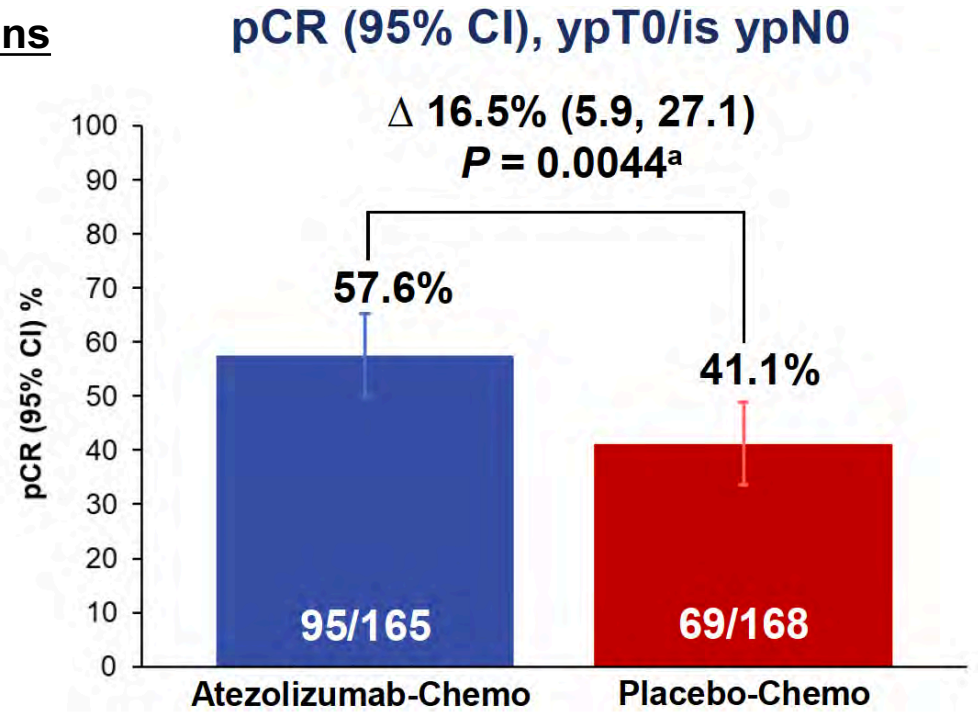
Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial

Elizabeth A Mittendorf, Hong Zhang, Carlos H Barrios, Shigehira Saji, Kyung Hae Jung, Roberto Hegg, Andreas Koehler, Joohyuk Sohn, Hiroji Iwata, Melinda L Telli, Cristiano Ferrario, Kevin Punie, Frédérique Penault-Llorca, Shilpen Patel, Anh Nguyen Duc, Mario Liste-Hermoso, Vidya Maiya, Luciana Molinero, Stephen Y Chui, Nadia Harbeck

***Lancet* 2020;396(10257):1090-100.**

IMpassion031 Primary Endpoints: pCR in ITT and PD-L1-Positive Tumors

ITT and PD-L1+ Populations



pCR, ypT0/Tis ypN0	Atezolizumab + chemotherapy	Placebo + chemotherapy	*p*-value
PD-L1 positive tumors (n = 77; 75)	68.8%	49.3%	0.021*
PD-L1 negative tumors (n = 88; 93)	47.7%	34.4%	Not reported

*Did not cross significance boundary of 0.0184.

Mittendorf EA et al. *Lancet* 2020;396(10257):1090-100; Harbeck N et al. ESMO 2020;Abstract LBA11.

Durvalumab Improves Long-Term Outcome in TNBC: Results from the Phase II Randomized GeparNUEVO Study Investigating Neodjuvant Durvalumab in Addition to an Anthracycline/Taxane Based Neoadjuvant Chemotherapy in Early Triple-Negative Breast Cancer (TNBC)

Loibl S et al.

ASCO 2021;Abstract 506.

Sunday, June 6, 8:00 AM - 11:00 AM EDT

Case Presentation – Dr Del Rosario: A 70-year-old woman with metastatic TNBC

Dr Michael Del Rosario

- Localized right TNBC s/p mastectomy → adjuvant paclitaxel
- Malignant pleural effusion, PD-L1-negative
- Has received multiple lines of chemotherapy, including carboplatin, gemcitabine, capecitabine, docetaxel
- Sacituzumab govitecan

Questions

- For a patient with triple-negative metastatic breast cancer that has recurred multiple times who is placed on sacituzumab govitecan, what adverse events should we monitor? Diarrhea, in particular?
- Would we even consider UGT1A1*28 allele prior to starting sacituzumab govitecan?
- In regard to the neutropenia, would we start GCSF on the get-go?

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- Bardia A et al. **Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer.** *N Engl J Med* 2021;384(16):1529-1541.

N Engl J Med 2021;384:1529-41.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

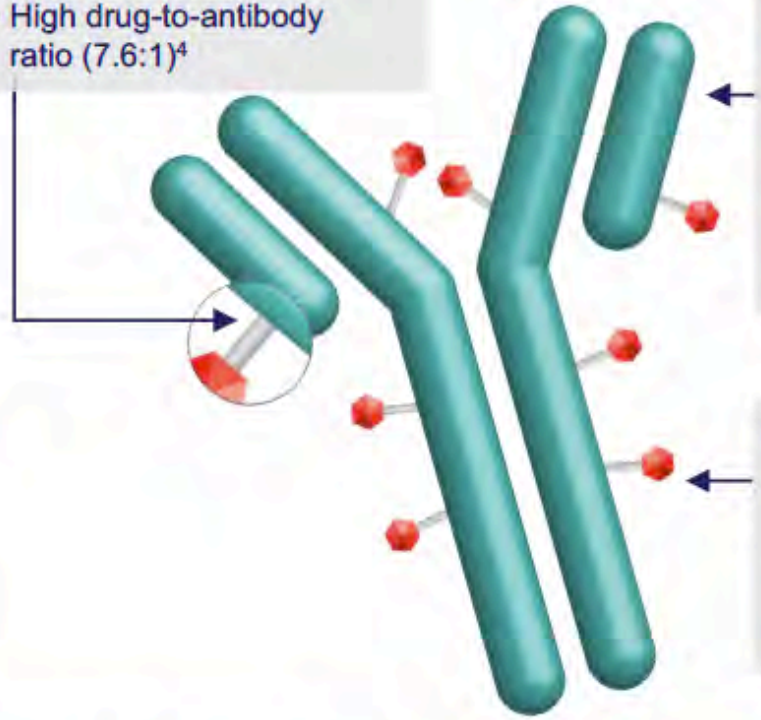
Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

A. Bardia, S.A. Hurvitz, S.M. Tolaney, D. Loirat, K. Punie, M. Oliveira, A. Brufsky, S.D. Sardesai, K. Kalinsky, A.B. Zelnak, R. Weaver, T. Traina, F. Dalenc, P. Aftimos, F. Lynce, S. Diab, J. Cortés, J. O'Shaughnessy, V. Diéras, C. Ferrario, P. Schmid, L.A. Carey, L. Gianni, M.J. Piccart, S. Loibl, D.M. Goldenberg, Q. Hong, M.S. Olivo, L.M. Itri, and H.S. Rugo, for the ASCENT Clinical Trial Investigators*

Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed ADC

- SG is distinct from other ADCs[1-4]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for SN-38 liberation from antibody
  - Hydrolysis of the linker also releases SN-38 extracellularly in the tumor microenvironment (bystander effect)
- Granted FDA accelerated approval for mTNBC[5]
- Landmark ASCENT study demonstrated a significant survival improvement of SG over chemotherapy, with a tolerable safety profile in pretreated mTNBC[6]
  - Median PFS of 5.6 vs 1.7 months (HR 0.41, *P*<0.0001)
  - Median OS of 12.1 vs 6.7 months (HR 0.48, *P*<0.0001)

Linker for SN-38
- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7.6:1)[4]



Humanized anti–Trop-2 antibody
- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

SN-38 payload
- SN-38 more potent than parent compound, irinotecan

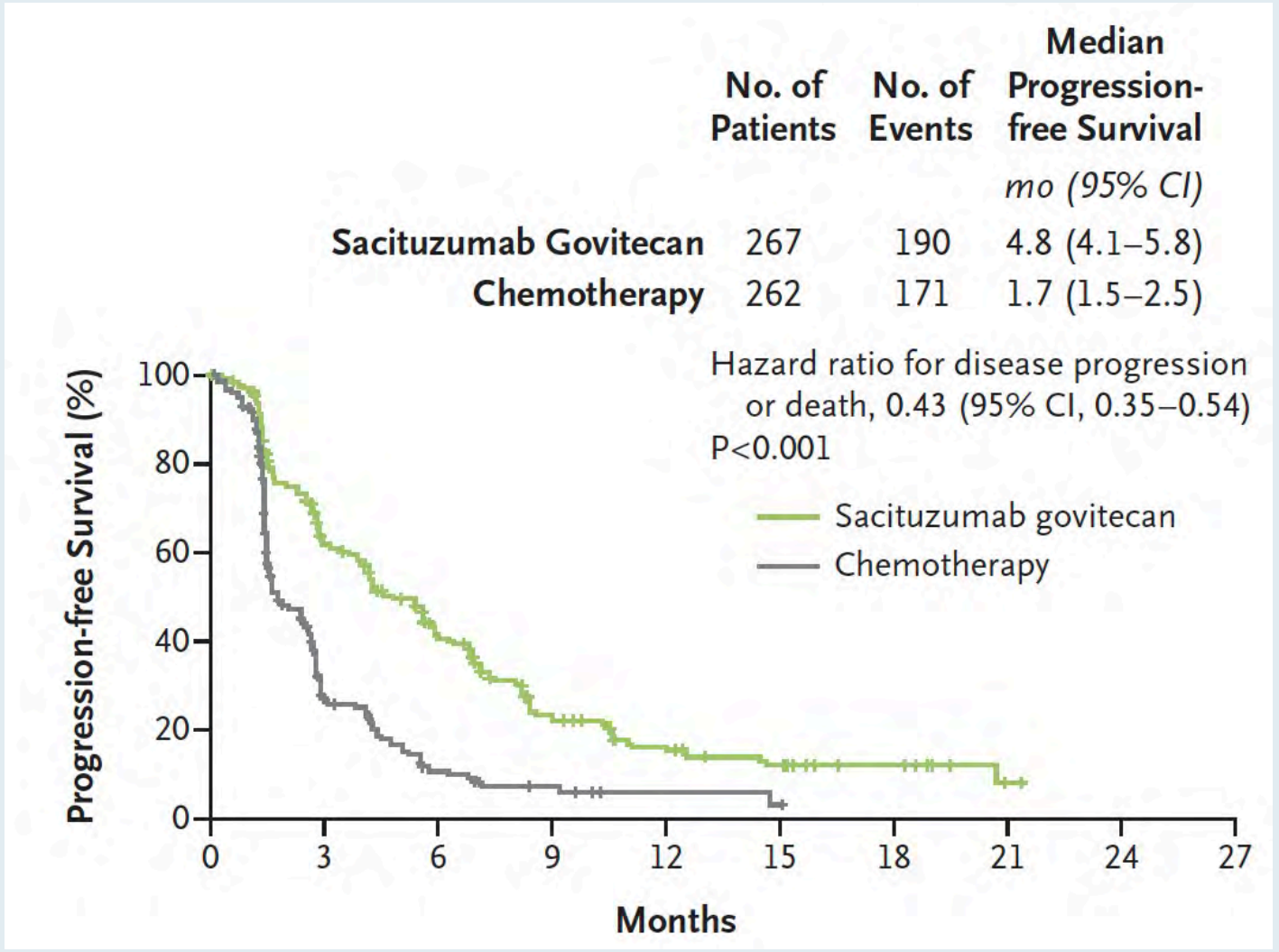
ADC, antibody-drug conjugate; FDA, US Food and Drug Administration; OS, overall survival; PFS, progression-free survival; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Goldenberg DM, et al. *Expert Opin Biol Ther*. 2020;20:871-885. 2. Nagayama A, et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 3. Cardillo TM, et al. *Bioconjugate Chem*. 2015;26:919-931. 4. Goldenberg DM, et al. *Oncotarget*. 2015;6:22496-224512. 5. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020. 6. Bardia A, et al. ESMO 2020. Abstract LBA17.

Hurvitz SA et al. SABCS 2020;Abstract GS3-06.

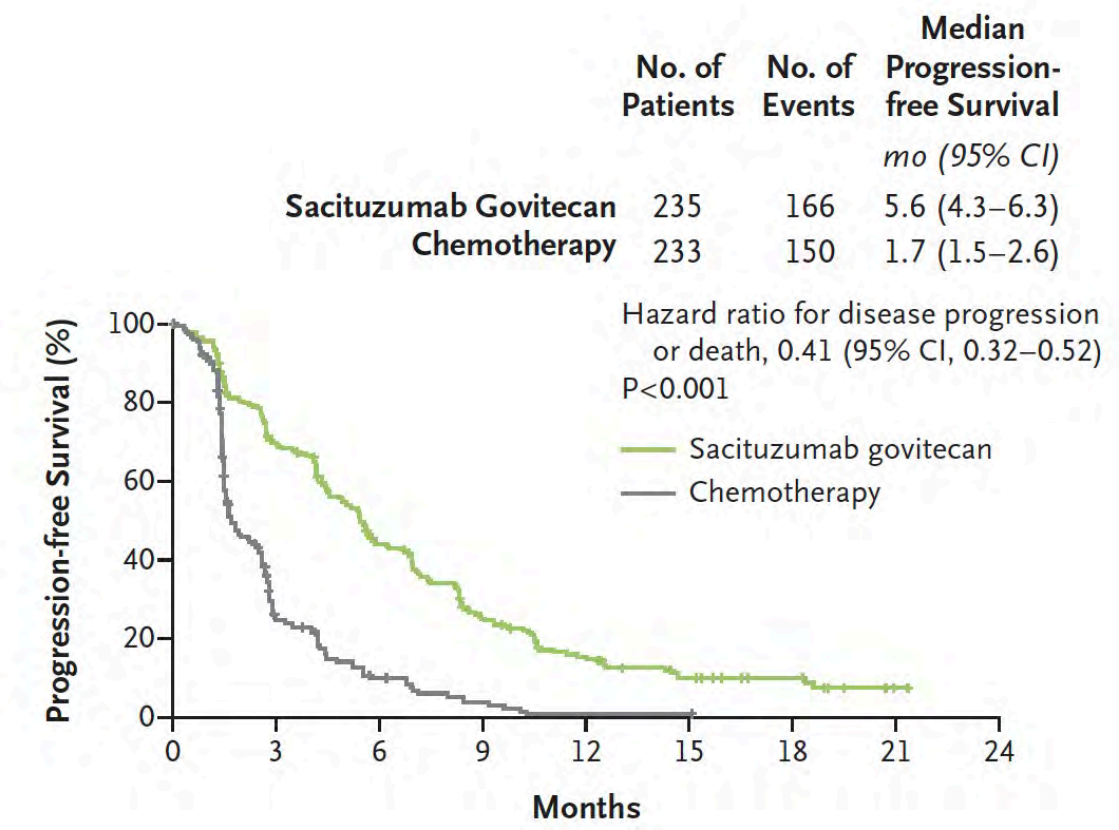
ASCENT: Progression-Free Survival (Overall Population)

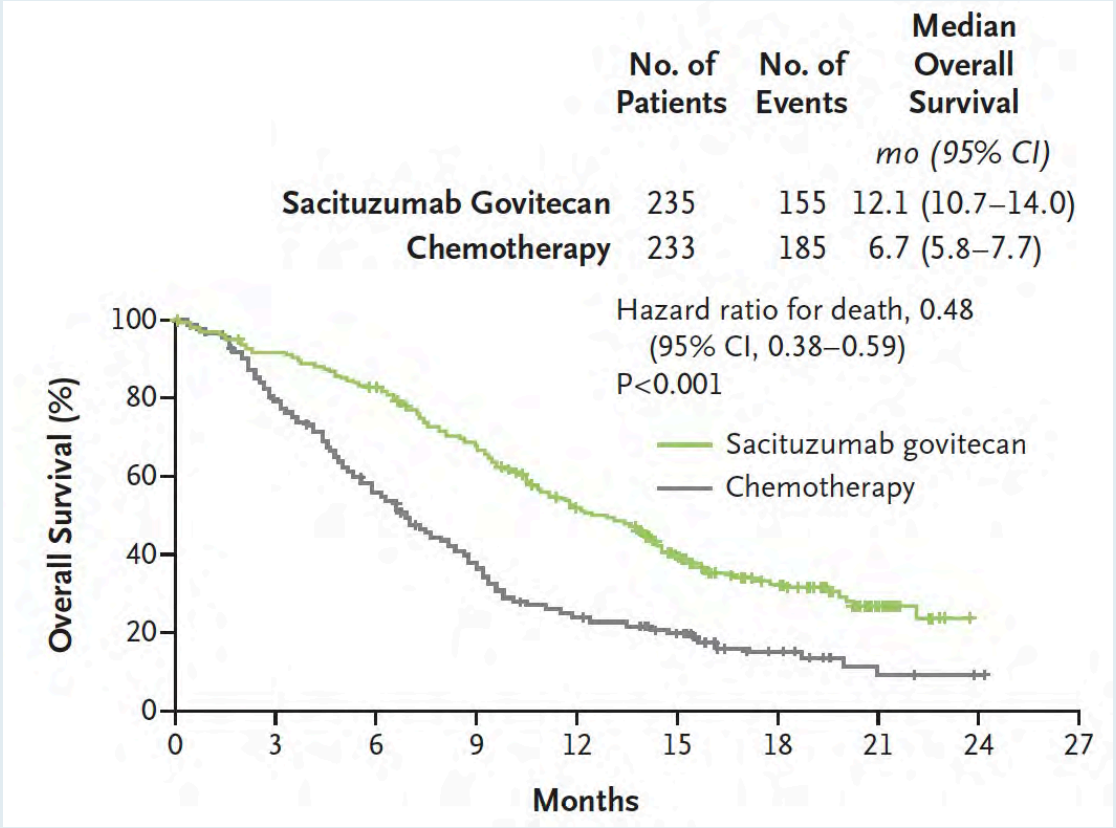
	No. of Patients	No. of Events	Median Progression-free Survival *mo (95% CI)*
Sacituzumab Govitecan	267	190	4.8 (4.1–5.8)
Chemotherapy	262	171	1.7 (1.5–2.5)



Bardia A et al. N Engl J Med 2021;384:1529-41.

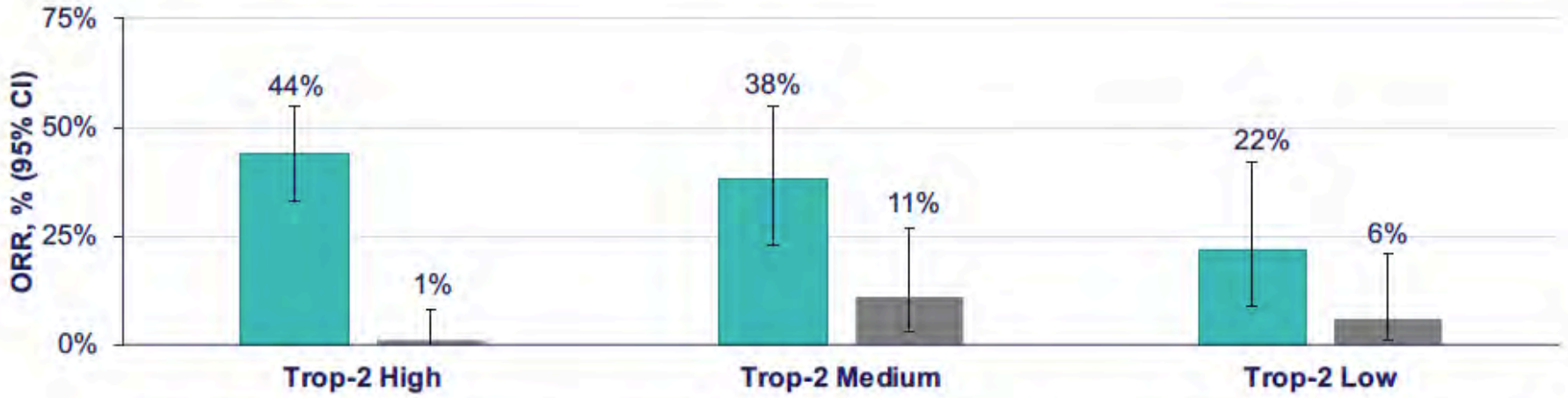
ASCENT: PFS and OS Among Patients without Brain Metastases





Bardia A et al. N Engl J Med 2021;384:1529-41.

ORR by Trop-2 Expression



	Trop-2 High H-score: 200-300 (n=157)		Trop-2 Medium H-score: 100-200 (n=74)		Trop-2 Low H-score: <100 (n=59)	
	SG (n=85)	TPC (n=72)	SG (n=39)	TPC (n=35)	SG (n=27)	TPC (n=32)
ORR—% (no.)	44% (37)	1% (1)	38% (15)	11% (4)	22% (6)	6% (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

Assessed in the brain metastases-negative population. ORR and PFS are assessed by BICR. Trop-2 expression determined in archival samples by validated immunohistochemistry assay and H-scoring.
BICR, blind independent central review; H-score, histochemical-score; ORR, objective response rate; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen-2.

Hurvitz SA et al. SABCS 2020;Abstract GS3-06.

Outcomes in Patients (pts) Aged ≥65 Years in the Phase 3 ASCENT Study of Sacituzumab Govitecan (SG) in Metastatic Triple-Negative Breast Cancer (mTNBC)

Kalinsky K et al.
ASCO 2021;Abstract 1011

Friday, June 4, 9:00 AM - 11:00 AM EDT

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

A Daylong Clinical Summit Hosted in Partnership with Medical Oncology Association of Southern California (MOASC)

Saturday, May 15, 2021

10:30 AM – 6:30 PM ET

(7:30 AM – 3:30 PM Pacific Time)

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This program was recorded before the ASCO 2021 Annual Meeting.

Data from the abstracts presented at this meeting can be accessed at https://meetinglibrary.asco.org/results?meetingView=2021%20ASCO%20Annual%20Meeting.

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Agenda

Module 1 — Breast Cancer: *Drs O'Regan and Traina*

Module 2 — Multiple Myeloma: *Drs Anderson and Raje*

Module 3 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Moskowitz and Sharman*

Module 4 — Genitourinary Cancers: *Drs Bellmunt and Pal*

Module 5 — Gastrointestinal Cancers: *Drs Messersmith and O'Reilly*

Module 6 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Erba and Komrokji*

Module 7 — Lung Cancer: *Drs Camidge and Levy*

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Multiple Myeloma Faculty

Kenneth C Anderson, MD
Director, Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Kraft Family Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Noopur Raje, MD
Director, Center for Multiple Myeloma
Massachusetts General Hospital Cancer Center
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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Commercial Support

This activity is supported by educational grants from AbbVie Inc, Astellas and Pfizer Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Blueprint Medicines, Daiichi Sankyo Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Incyte Corporation, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Lilly, Merck, Novartis, Oncopeptides, Sanofi Genzyme, Seagen Inc, and Taiho Oncology Inc.

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Eisai Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Turning Point Therapeutics Inc and Verastem Inc.

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Research To Practice CME and NCPD Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Anderson — Disclosures

Advisory Committee	Amgen Inc, AstraZeneca Pharmaceuticals LP, Janssen Biotech Inc, Pfizer Inc
Consulting Agreements	Mana Therapeutics, Precision BioSciences, Raqia Therapeutics Inc, WindMIL Therapeutics
Scientific Founder	C4 Therapeutics, OncoPep

Dr Raje — Disclosures

Consulting Agreements	Amgen Inc, bluebird bio, Celgene Corporation

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Contributing Oncologists

Amanda Blackmon, DO, MS
Chief Fellow, Hematology/Oncology
University of California, Irvine
Irvine, California

Farshid Dayyani, MD, PhD
Professor of Clinical Medicine
Division of Hematology/Oncology
Department of Medicine
University of California, Irvine
UCI Health
Orange, California

Gigi Chen, MD
Diablo Valley Oncology and
Hematology Medical Group
Pleasant Hill, California

Michael Polintan Del Rosario, MD
Fellow Physician
Division of Hematology-Oncology
Department of Medicine
University of California, Irvine
Irvine, California

Mamta Choksi, MD
Florida Cancer Specialists and
Research Institute
New Port Richey, Florida

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

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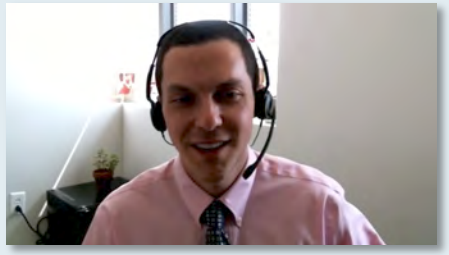
Contributing Oncologists

Rahul Gosain, MD
Division of Hematology and Oncology
Guthrie Corning Cancer Center
Corning, New York

Maen Hussein, MD
Florida Cancer Specialists and
Research Institute
The Villages, Florida

Ranju Gupta, MD
Attending Physician
Co-Director, Cardio-Oncology Program
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania



Jeremy Lorber, MD
Attending Hematologist-Oncologist
Tower Hematology Oncology
Cedars-Sinai Medical Center
Beverly Hills, California

Hatim Husain, MD
Physician, University of California San Diego
San Diego, California

Nataliya Mar, MD
Assistant Clinical Professor
Division of Hematology/Oncology
University of California, Irvine
Irvine, California

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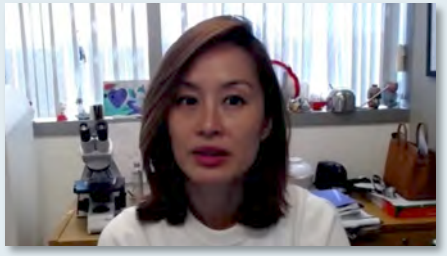
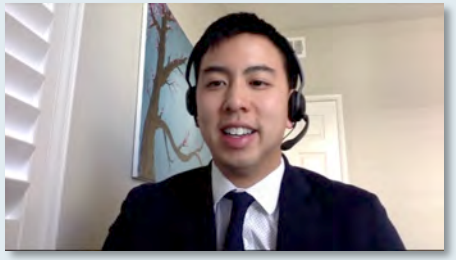
Contributing Oncologists

Mohamed K Mohamed, MD, PhD
Oncology Division Medical Director
Director of Thoracic Oncology
Hematologist/ Medical Oncologist
Cone Health Cancer Center
Greensboro, North Carolina

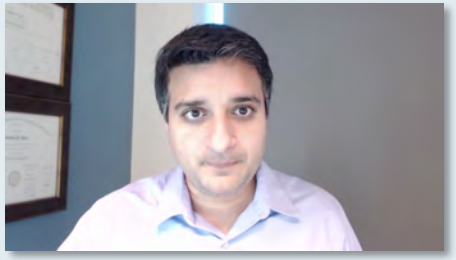


Helen H Moon, MD
Medical Oncologist
Southern California Permanente
Medical Group
Riverside, California

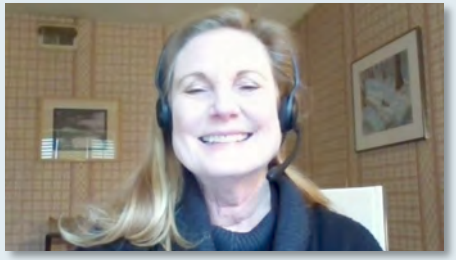
Neil Morganstein, MD
Hematology Oncology
Atlantic Health System
Summit, New Jersey



Anthony Nguyen, MD
Fellow, Loma Linda University Health
Loma Linda, California



Sandip Patel, MD
Associate Professor, Medical Oncology, UCSD
Leader, Experimental Therapeutics
Deputy Director, San Diego Center for
Precision Immunotherapy
San Diego, California



Andrea Stebel, MD
Newport Breast Care
Newport Beach, California

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Agenda

Module 1: Newly Diagnosed Multiple Myeloma

- Dr Chen: A 65-year-old man with newly diagnosed multiple myeloma
- Dr Lorber: A 78-year-old woman with newly diagnosed myeloma and a history of mycosis fungoides
- *Key Recent Publications and Presentations*

Module 2: Relapsed Multiple Myeloma

- Dr Favaro: An 82-year-old man with multiregimen-relapsed multiple myeloma
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- *Key Recent Publications and Presentations*
- Dr Lorber: A 75-year-old man with myeloma and disease progression on 5 lines of therapy
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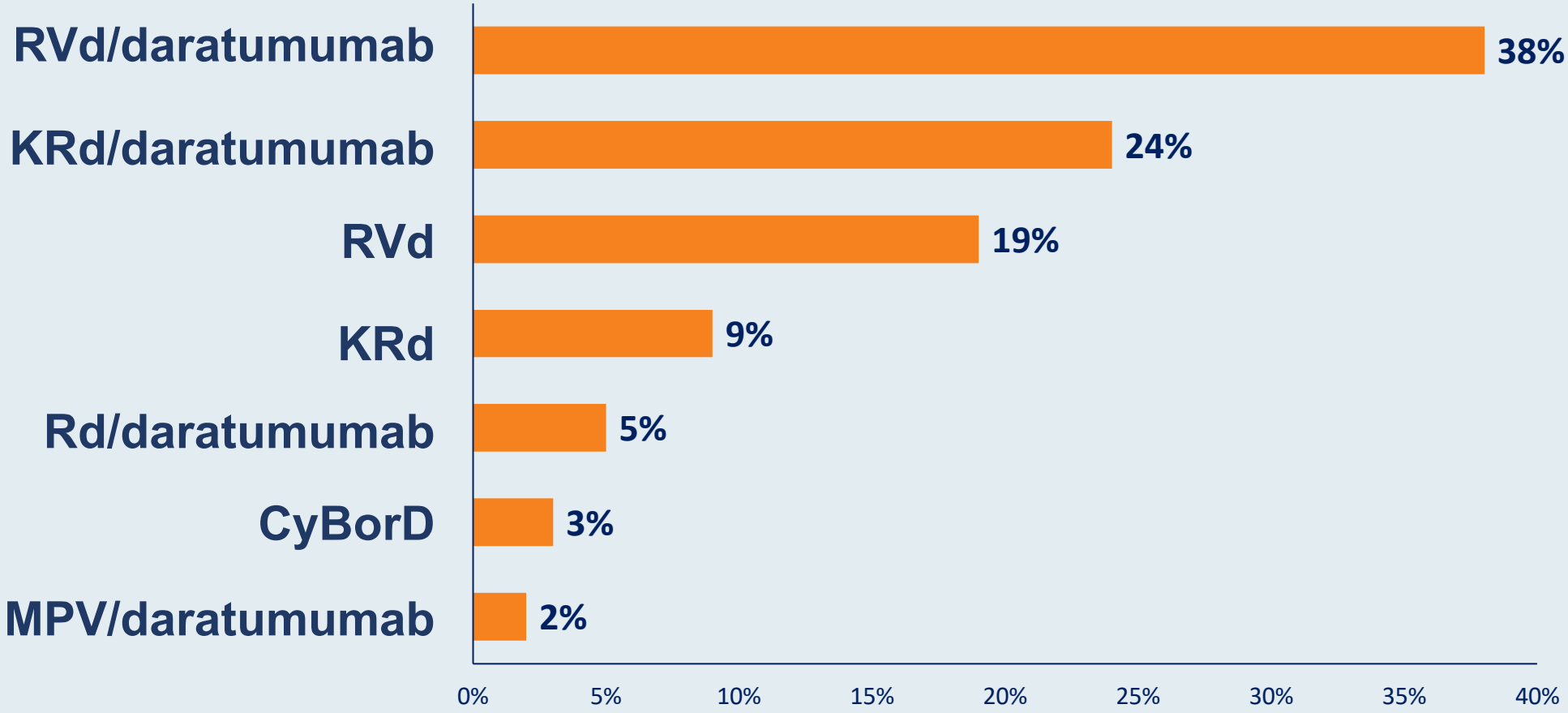
Regulatory and reimbursement issues aside, what is your preferred pretransplant induction regimen for a younger, otherwise healthy patient with MM and del(17p)?



N = 58

Survey of live webinar audience

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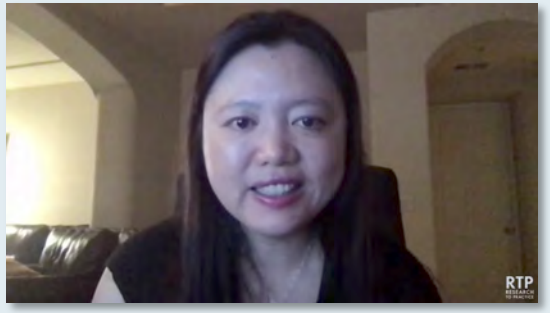
Case Presentation – Dr Chen: A 65-year-old man with newly diagnosed multiple myeloma



Dr Gigi Chen

- IgG kappa multiple myeloma
  - WBC: 4.5, Hgb: 11.7, Plt: 192, Total protein: 11.2,
  - SPEP: Monoclonal protein with M spike 4.6 g/dL
  - Bone marrow biopsy: 90% myeloma involvement
  - FISH: Negative
  - Cytogenetics: 5 cells with gains of chromosome 6, 9.15 and 3 marker with deletion of long arm of chromosome 6 and loss of chromosome 7, 18 and 21
  - PET/CT: Bone involvement and left ileum

Questions

- What would be the best induction treatment for him – RVD versus KRd, or a daratumumab-containing regimen?
- What is the role for consolidation therapy? How long should consolidation therapy be continued before maintenance therapy?
- What is the role of MRD monitoring in the setting of the multiple myeloma – before or after transplant? How do you monitor the MRD? Do you switch treatment based on MRD?

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Case Presentation – Dr Lorber: A 78-year-old woman with newly diagnosed myeloma and a history of mycosis fungoides

Dr Jeremy Lorber

- PMH: Well-controlled mycosis fungoides
- Presents with progressive bone pain and lytic lesions
- Diagnosed with lambda light chain multiple myeloma
- Karyotype: del 13q, loss of chromosomes X, 4, 10, 14, gain of 1q and abnormal copy of chromosome 6
- Treated with quadruplet regimen of daratumumab-RVD → VGPR
- Underwent ASCT successfully and currently on maintenance therapy

Questions

- What is the role of triplet versus quadruplet induction regimens, and of consolidative auto-SCT? What role does MRD play?
- Is there a role for quadruplet therapy in a patient who is not eligible for ASCT? For patients receiving triplet therapy, is there a role for DRd versus the VRd regimen?
- With the variety of novel agents on the horizon, will the role of ASCT shrink or remain, given that there are so many lines ahead of a patient even if they don't undergo a transplant?

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Key Recent Publications and Presentations

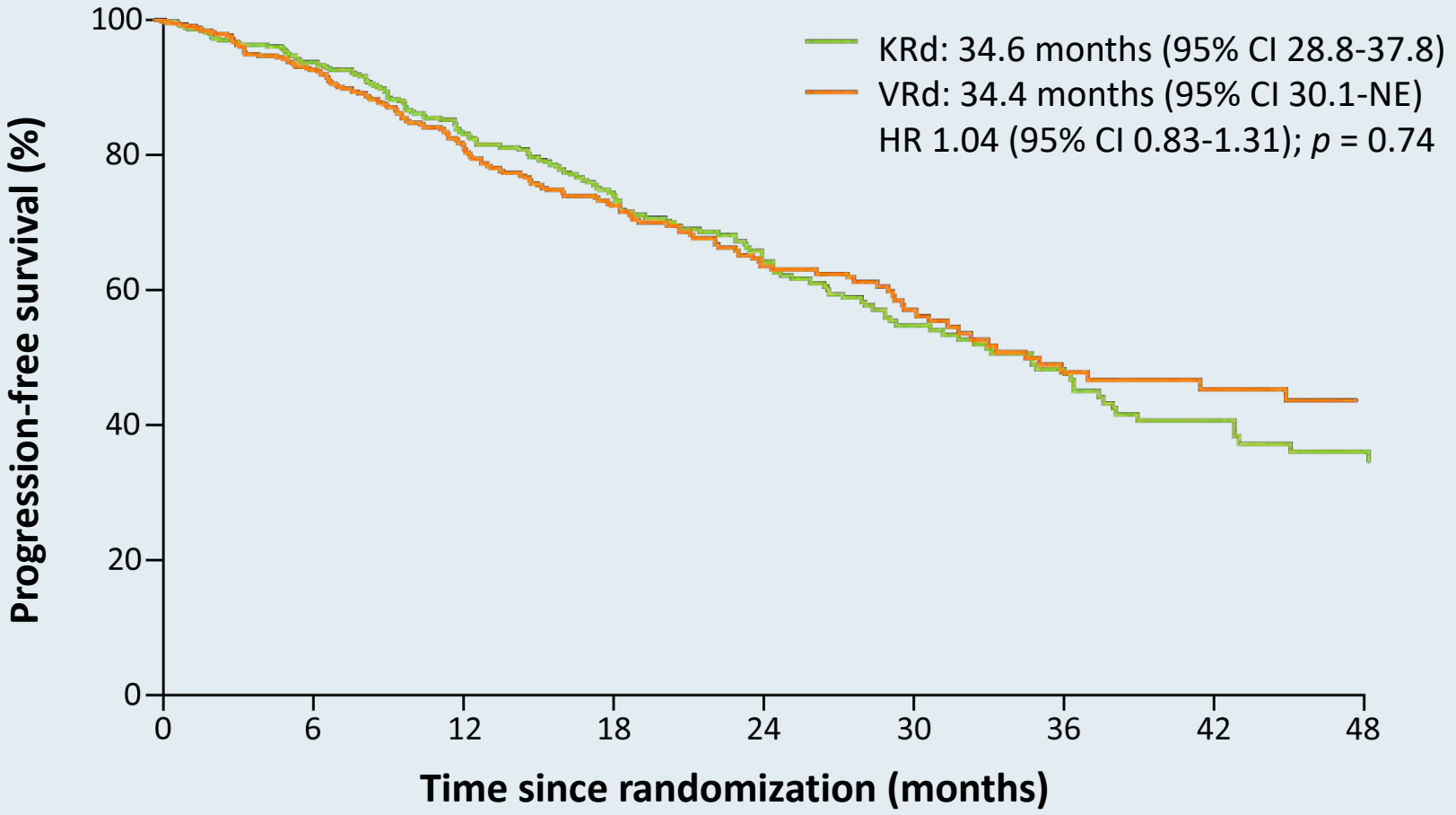
- Kumar SK et al. **Carfilzomib or Bortezomib in Combination with Lenalidomide and Dexamethasone for Patients with Newly Diagnosed Multiple Myeloma without Intention for Immediate Autologous Stem-Cell Transplantation (ENDURANCE): A Multicentre, Open-Label, Phase 3, Randomised, Controlled Trial.** *Lancet Oncol* 2020;21(10):1317-30.
- Kaufman JL et al. **Daratumumab (DARA) plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of Griffin After 12 Months of Maintenance Therapy.** ASH 2020;Abstract 549.
- Kumar SK et al. **Updated Analysis of Daratumumab plus Lenalidomide and Dexamethasone (D-Rd) versus Lenalidomide and Dexamethasone (Rd) in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma (NDMM): The Phase 3 Maia Study**. ASH 2020;Abstract 2276.
- Mateos MV et al. **Subcutaneous versus Intravenous Daratumumab in Patients with Relapsed or Refractory Multiple Myeloma (COLUMBA): A Multicentre, Open-Label, Non-Inferiority, Randomised, Phase 3 Trial.** *Lancet Haematol* 2020;7:e370-80.

Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial

Shaji K Kumar, Susanna J Jacobus, Adam D Cohen, Matthias Weiss, Natalie Callander, Avina K Singh, Terri L Parker, Alexander Menter, Xuezhong Yang, Benjamin Parsons, Pankaj Kumar, Prashant Kapoor, Aaron Rosenberg, Jeffrey A Zonder, Edward Faber Jr, Sagar Lonial, Kenneth C Anderson, Paul G Richardson, Robert Z Orlowski, Lynne I Wagner, S Vincent Rajkumar

***Lancet Oncol* 2020;21(10):1317-30**

ENDURANCE (E1A11): Primary PFS Endpoint (Second Interim Analysis)



- Median OS has not been reached in either group at median follow-up of 24 months; patients will continue on long-term follow-up for overall survival

Kumar SK et al. *Lancet Oncol* 2020;21(10):1317-30.

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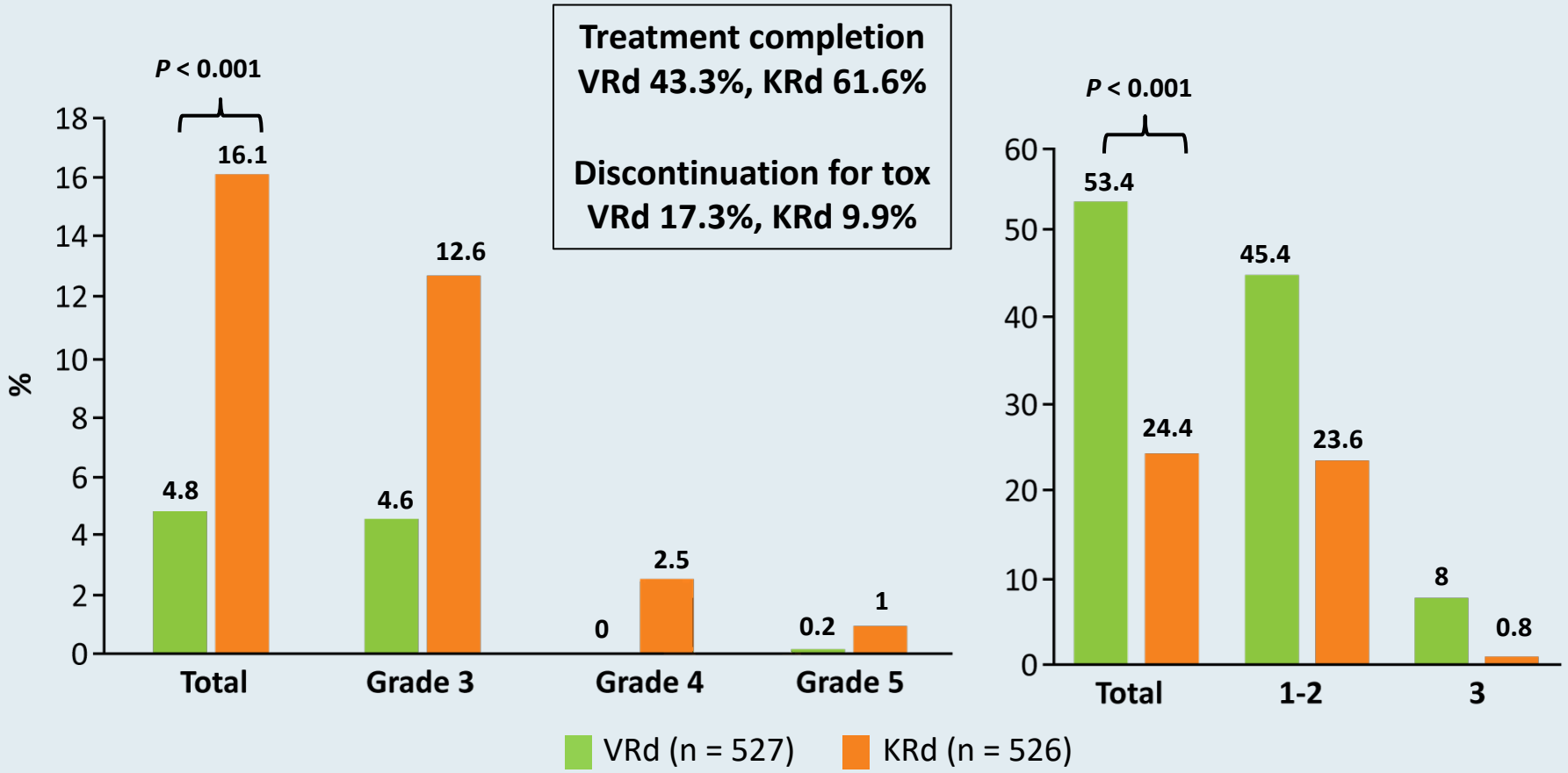
ENDURANCE (E1A11): Treatment-Emergent Adverse Events of Interest



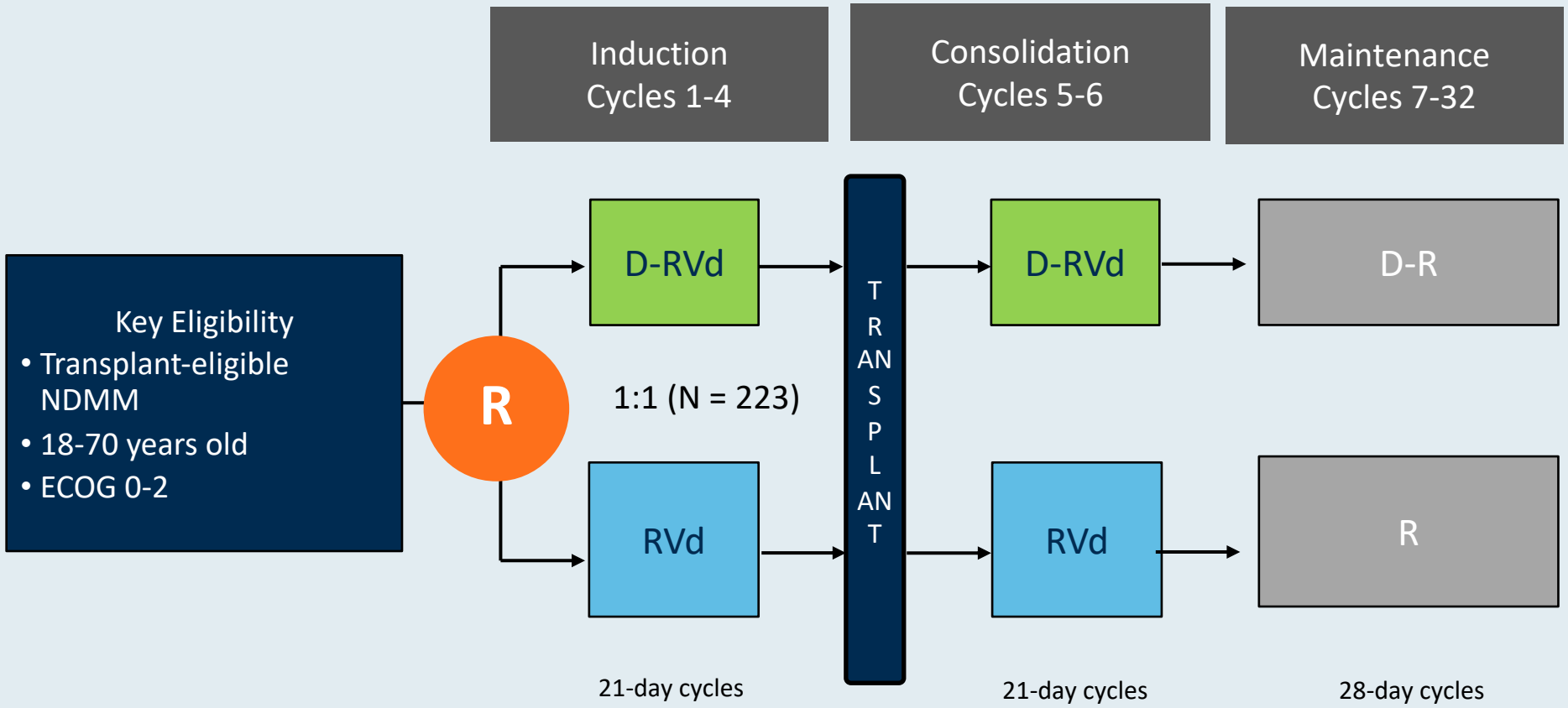
Berdeja JG. ASCO 2020 Discussant.

Daratumumab (DARA) plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of Griffin After 12 Months of Maintenance Therapy

Kaufman JL et al.

ASH 2020;Abstract 549.

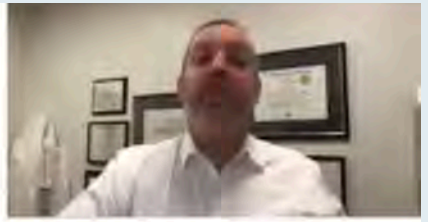
GRIFFIN Randomized Phase II Study Design

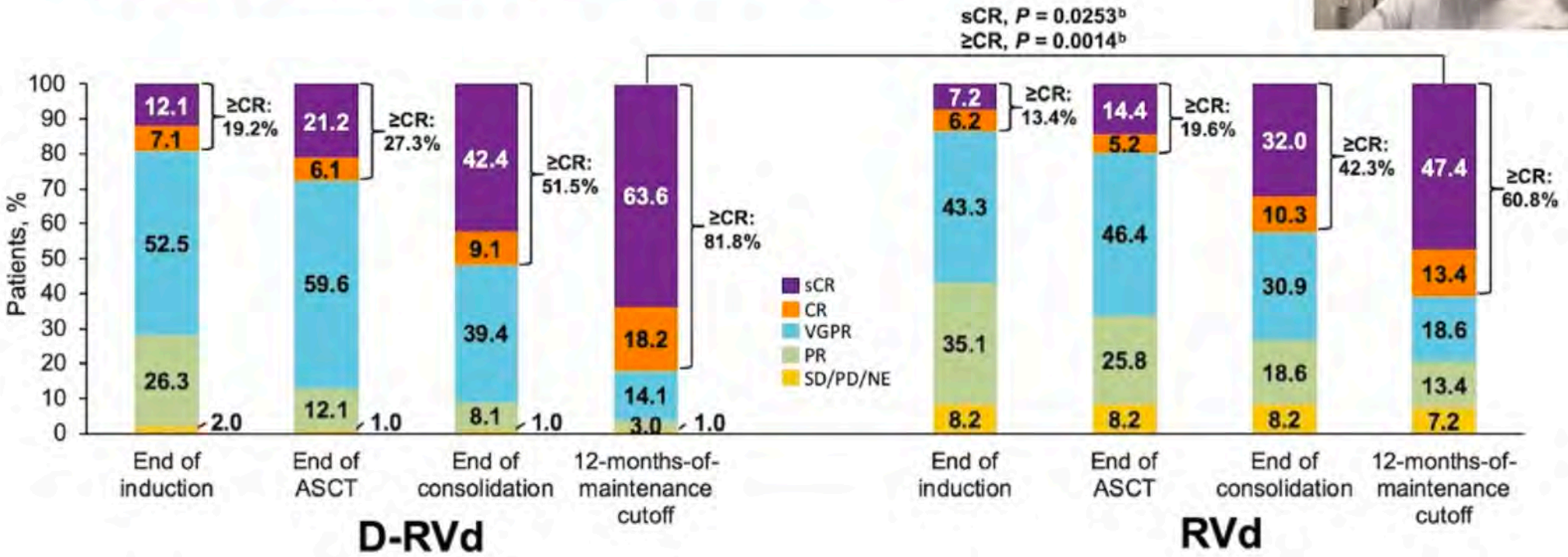


Primary endpoint: Stringent CR by end of consolidation

Voorhees P et al. IMW 2019;Abstract 906.
www.clinicaltrials.gov. Accessed January 23, 2020 (NCT02874742).

Responses Deepened over Time[a]





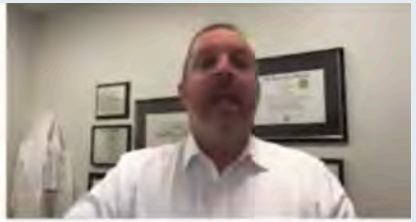
- *Results for end of induction, ASCT, and consolidation are based on a median follow up of 13.5 months at the primary analysis*
- *Median follow up at 12-months-of-maintenance therapy cutoff was 27.4 months*

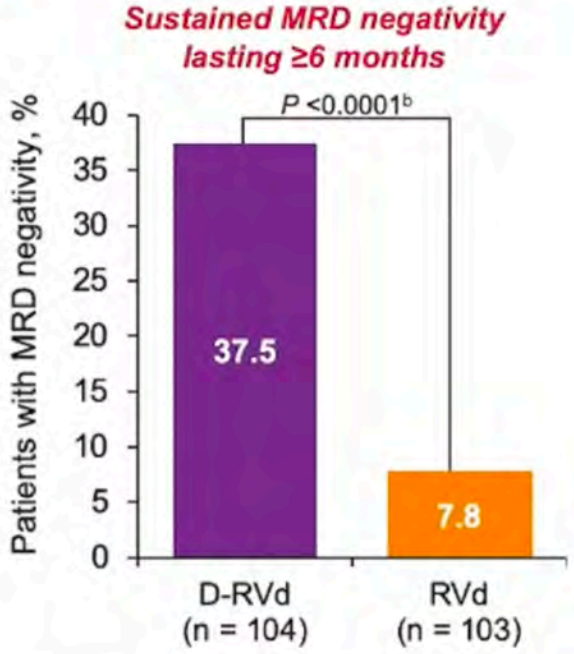
Response rates and depths were greater for D-RVd at all time points

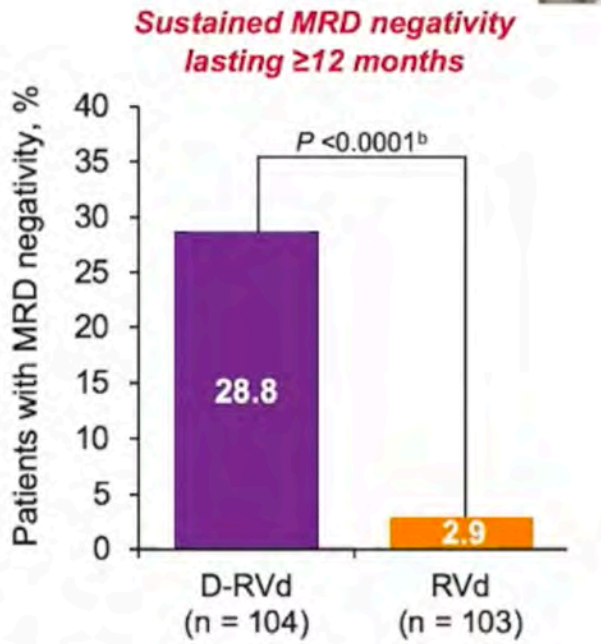
PR, partial response. SD/PD/NE, stable disease/progressive disease/not evaluable. [a]Data are shown for the response-evaluable population. [b]*P* values (2-sided) were calculated using the Cochran–Mantel–Haenszel chi-square test.

Kaufman JL et al. ASH 2020;Abstract 549.

Durable MRD (10^{-5}) Negativity[a] Lasting ≥6 and ≥12 Months







- *Among patients who achieved MRD negative (10^{-5}) status, sustained MRD negativity lasting ≥12 months was noted in 30/65 (46.2%) and 3/28 (10.7%) patients*

D-RVd improved rates of sustained MRD negativity versus RVd

[a]The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on the assessment of bone marrow aspirates by NGS in accordance with International Myeloma Working Group criteria. Median follow-up was 27.4 months, and MRD-negativity rates are among the ITT population. [b]*P* values were calculated using the Fisher's exact test.

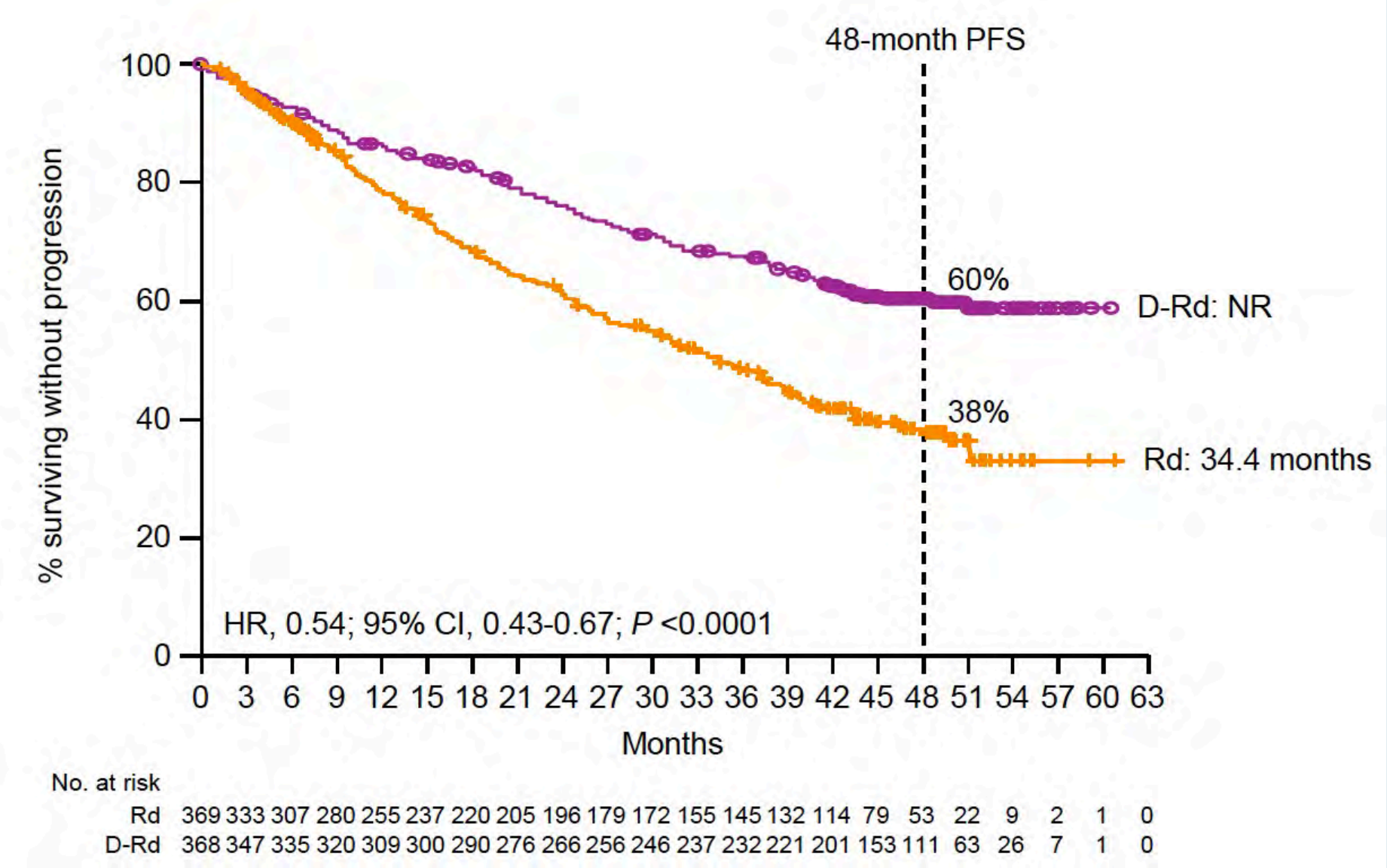
Kaufman JL et al. ASH 2020;Abstract 549.

Updated Analysis of Daratumumab plus Lenalidomide and Dexamethasone (D-Rd) versus Lenalidomide and Dexamethasone (Rd) in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma (NDMM): The Phase 3 Maia Study

Kumar SK et al.

ASH 2020;Abstract 2276.

MAIA: Updated PFS (Median Follow-Up 48 Months)



Kumar SK et al. ASH 2020;Abstract 2276.

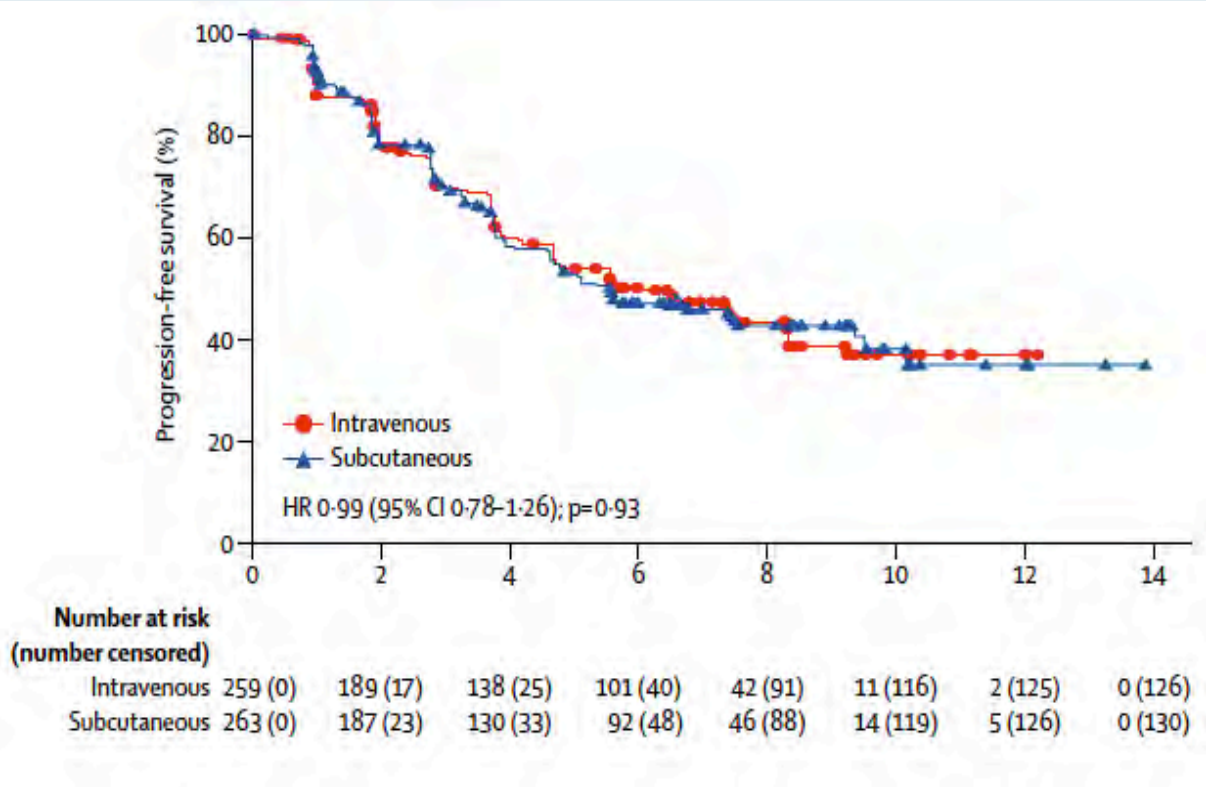
Lancet Haematol 2020;7:e370-80

Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial

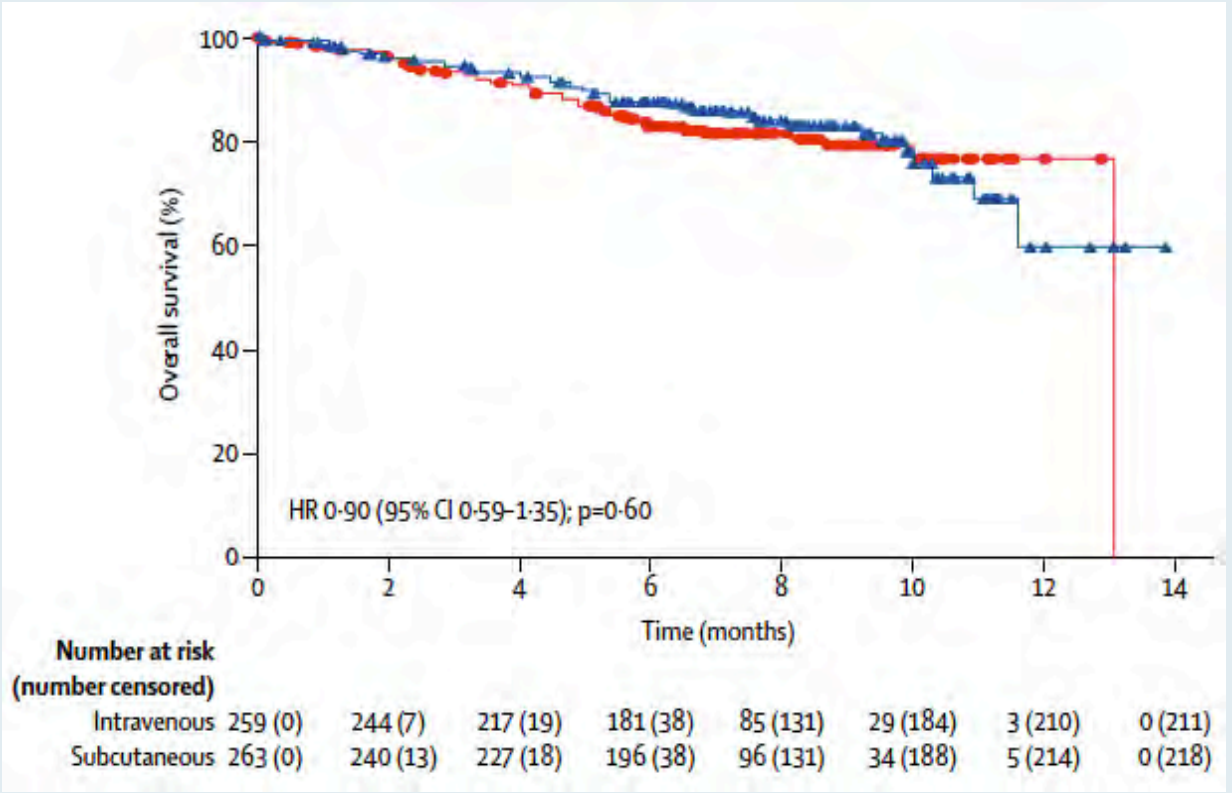
Maria-Victoria Mateos, Hareth Nahi, Wojciech Legiec, Sebastian Grosicki, Vladimir Vorobyev, Ivan Spicka, Vania Hungria, Sibirina Korenkova, Nizar Bahlis, Max Flogegard, Joan Bladé, Philippe Moreau, Martin Kaiser, Shinsuke Iida, Jacob Laubach, Hila Magen, Michele Cavo, Cyrille Hulin, Darrell White, Valerio De Stefano, Pamela L Clemens, Tara Masterson, Kristen Lantz, Lisa O'Rourke, Christoph Heuck, Xiang Qin, Dolly A Parasrampuria, Zhilong Yuan, Steven Xu, Ming Qi, Saad Z Usmani

COLUMBA: Subcutaneous versus Intravenous Daratumumab

Progression-Free Survival



Overall Survival



(Median follow-up 7.5 months)

Mateos MV et al. *Lancet Haematol* 2020;7(5):e370-80.

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Agenda

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- Dr Chen: A 65-year-old man with newly diagnosed multiple myeloma
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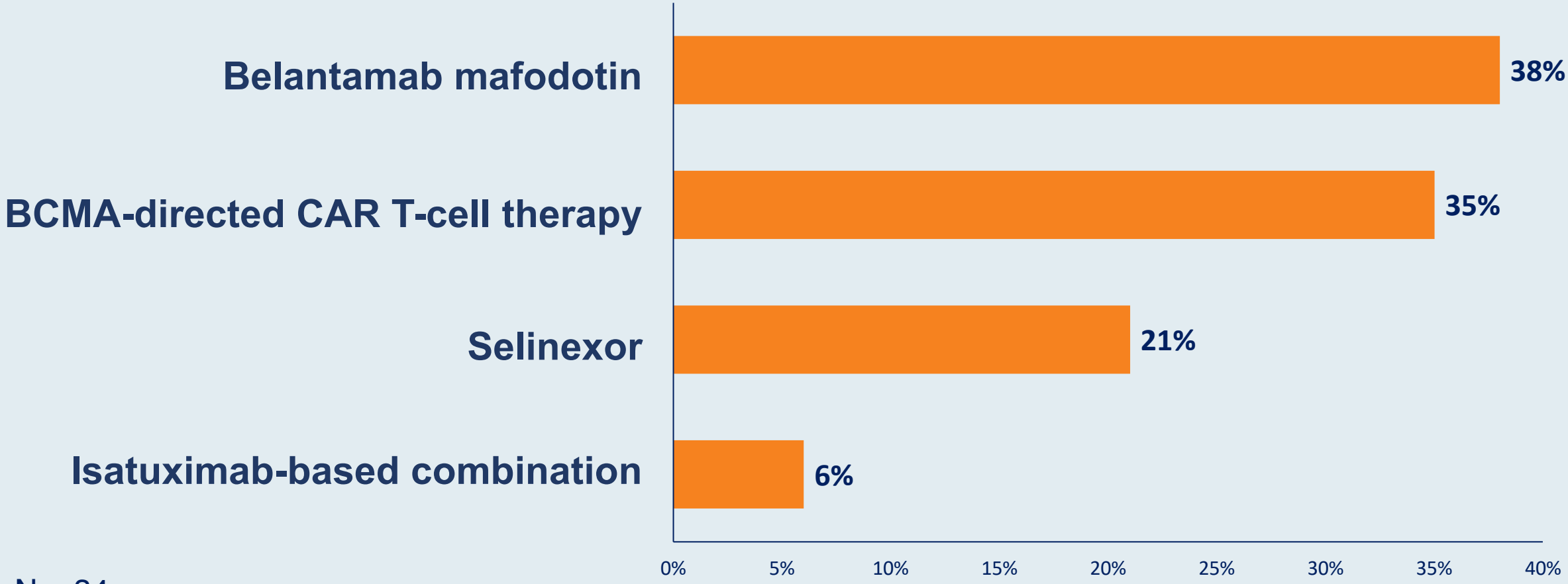
Which of the following strategies would you generally use first for a patient with relapsed MM who has experienced disease progression on multiple prior therapies, including daratumumab, proteasome inhibitors and IMiDs?



N = 34

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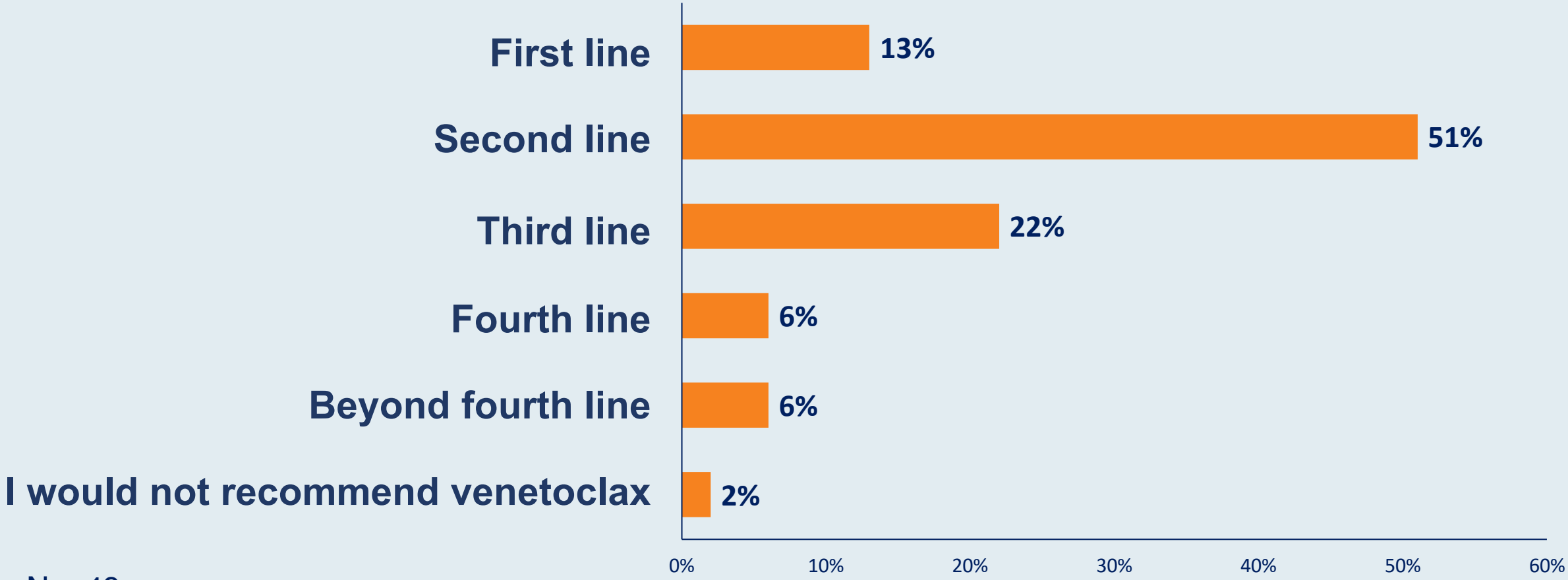
In what line of therapy, if any, do you generally use venetoclax either alone or in combination for a patient with t(11;14) MM?



N = 49

Survey of live webinar audience

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Case Presentation – Dr Favaro: An 82-year-old man with multiregimen-relapsed multiple myeloma

Dr Justin Favaro

- 2011: Presents with meningitis and simultaneously diagnosed with IgA kappa, t(11;14) multiple myeloma
- RVd → Autologous SCT → Maintenance lenalidomide → PD
- Carfilzomib/elotuzumab/daratumumab x 2 years
- 2019: Adenocarcinoma of the colon (pT4 pN2 PM1) → R hemicolectomy
  - Pembrolizumab x 1, with normal CEA and no other evidence of disease
- Venetoclax x 3 months → PD → Selinexor x 3 months → PD
- Bendamustine/bortezomib past 4 months, with decline in kappa light chain

Questions

- When secondary malignancies occur in the setting of multiple myeloma, what do you do? Is it better to treat surgically the secondary malignancy and then go back to treat the myeloma?
- Would it have been better to combine venetoclax with another agent, such as bortezomib or lenalidomide?
- Would a patient in their 80s with a slightly poor performance status be a candidate for CAR T-cell therapy?

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Case Presentation – Dr Del Rosario: A 54-year-old man with relapsed multiple myeloma who receives CAR T-cell therapy

Dr Michael Del Rosario

- 11/2017: High-risk IgG kappa multiple myeloma relapsing s/p KRd x 3 (PR) → ASCT
- Maintenance KRD not tolerated; maintenance ixazomib not tolerated; treatment held for 6 months
- Maintenance lenalidomide, with kappa light chain increasing
- 3/2019: Bone marrow biopsy – Relapsed disease
- Daratumumab → Carfilzomib/pomalidomide/dexamethasone
- 4/2020: BCMA-targeted CAR T-cell therapy
- 10/2020: Non-myeloablative haplo-matched peripheral blood stem cell transplant from daughter

Questions

- What are the indications for anti-BCMA CAR-T therapy for relapsed multiple myeloma? How do patients with myeloma fare on anti-BCMA CAR-T therapy compared to patients with relapsed lymphoma who receive the CD19 CAR-T therapy? Is there research on giving the CAR-T therapy sooner in the disease versus later? Any role for belantamab mafodotin after CAR-T therapy?
- What are the indications for belantamab mafodotin, and how do you manage the eye toxicities?
- How do you sequence new therapies such as selinexor, melflufen, or belantamab?

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Key Recent Publications and Presentations

- Munshi N et al. **Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma.** *N Engl J Med* 2021;384(8):705-16.
- Mailankody S et al. **Orvacabtagene Autoleucel (Orva-cel), a B-Cell Maturation Antigen (BCMA)-Directed CAR T Cell Therapy for Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Update of the Phase 1/2 EVOLVE Study (NCT03430011).** ASCO 2020;Abstract 8504.
- Berdeja JG et al. **Update of CARTITUDE-1: A Phase Ib/II Study of JNJ-4528, a B-Cell Maturation Antigen (BCMA)-Directed CAR-T-Cell Therapy, in Relapsed/Refractory Multiple Myeloma.** ASCO 2020;Abstract 8505.

FDA Approves Idecabtagene Vicleucel for Multiple Myeloma

Press Release – March 26, 2021

"On March 26, 2021, the FDA approved idecabtagene vicleucel for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. This is the first FDA-approved cell-based gene therapy for multiple myeloma.

Idecabtagene vicleucel is a BCMA-directed genetically modified autologous chimeric antigen receptor (CAR) T-cell therapy. Each dose is customized using a patient's own T-cells, which are collected and genetically modified, and infused back into the patient.

Efficacy was evaluated in 100 patients who received idecabtagene vicleucel in the dose range of 300 to 460 x 106 CAR-positive T cells. Efficacy was established based on overall response rate (ORR), complete response (CR) rate, and duration of response (DOR), as evaluated by an Independent Response committee using the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-idecabtagene-vicleucel-multiple-myeloma

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N Engl J Med 2021;384(8):705-16

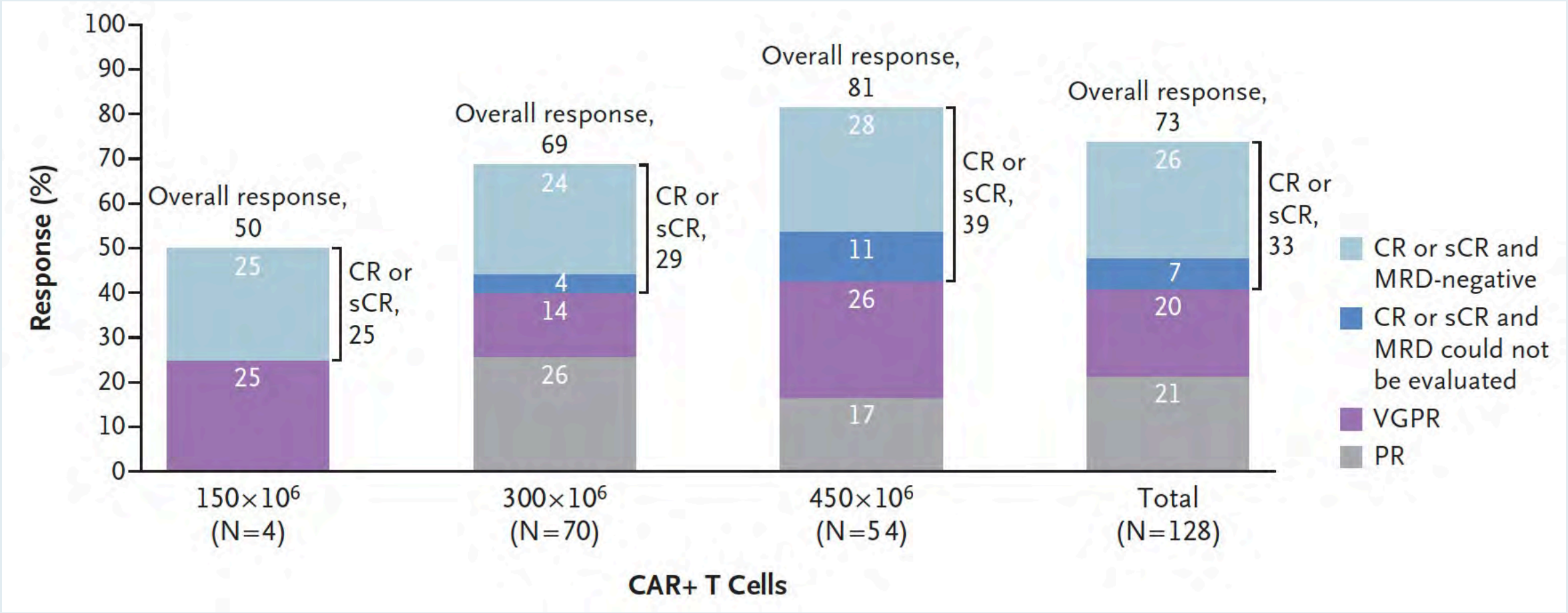
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

Nikhil C. Munshi, M.D., Larry D. Anderson, Jr., M.D., Ph.D., Nina Shah, M.D., Deepu Madduri, M.D., Jesús Berdeja, M.D., Sagar Lonial, M.D., Noopur Raje, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Albert Oriol, M.D., Philippe Moreau, M.D., Ibrahim Yakoub-Agha, M.D., Ph.D., Michel Delforge, M.D., Michele Cavo, M.D., Hermann Einsele, M.D., Hartmut Goldschmidt, M.D., Katja Weisel, M.D., Alessandro Rambaldi, M.D., Donna Reece, M.D., Fabio Petrocca, M.D., Monica Massaro, M.P.H., Jamie N. Connarn, Ph.D., Shari Kaiser, Ph.D., Payal Patel, Ph.D., Liping Huang, Ph.D., Timothy B. Campbell, M.D., Ph.D., Kristen Hege, M.D., and Jesús San-Miguel, M.D., Ph.D.

KarMMa: Tumor Response, Overall and According to Target Dose



Munshi NC et al. *N Engl J Med* 2021;384(8):705-16.

KarMMa: Select Adverse Events

	Any Grade	Grade 3 or 4
	no. of patients (%)	
Adverse event*		
Any	128 (100)	127 (99)
Hematologic		
Neutropenia	117 (91)	114 (89)
Anemia	89 (70)	77 (60)
Thrombocytopenia	81 (63)	67 (52)
Leukopenia	54 (42)	50 (39)
Lymphopenia	35 (27)	34 (27)
Febrile neutropenia	21 (16)	20 (16)
Cytokine release syndrome†	107 (84)	7 (5)
Neurotoxic effect‡	23 (18)	4 (3)

Munshi NC et al. *N Engl J Med* 2021;384(8):705-16.

Characteristics of Select BCMA CAR-T Studies in Multiple Myeloma

	KarMMa Idecabtagene vicleucel (n = 128)	EVOLVE Orvacabtagene autoleucel (n = 62)	CARTITUDE-1 Ciltacabtagene Autoleucel (n = 29)
Age	61 (33-78)	61 (33-77)	60 (50-75)
High-risk cytogenetics	35%	41%*	27%
Tumor burden in BM	>50% PC = 51	—	≥60% PC = 24
Extramedullary PCs	39%	23%	10%
Median prior line of therapy	6 (3-16)	6 (3-18)	5 (3-18)
Triple refractory	84%	94%	86%
Bridging therapy	88%	63%	79%

* Included +1q21

Approved 3/26/2021

Munshi NC et al. ASCO 2020; Abstract 8503 (KarMMA); Mailankody S et al. ASCO 2020; Abstract 8504. (EVOLVE)
Berdeja JG et al. ASCO 2020; Abstract 8505. (CARTITUDE-1); Patel K. ASCO 2020 Discussant

Safety of Select BCMA CAR-T Studies in Multiple Myeloma

	KarMMa	EVOLVE	CARTITUDE-1
ANC ≥G3	89%	90%	100%
plts ≥G3	52%	47%	69%
CRS: all, ≥G3	84%, 6%	89%, 3%	93%, 7%
Median time to CRS Median duration of CRS	1 (1-12) days 5 (1-63) days	2 (1-4) days 4 (1-10) days	7 (2-12) days 4 (2-64) days
ICANS: all, ≥G3	17%, 3%	13%, 3%	10%, 3%
Infections: all ≥G3	69%, NR	40%, 13%	NR, 19%
Tocilizumab use Steroid use Anakinra use	52% 15% 0	76% 52% 23%	79% 21% 21%

Approved 3/26/2021

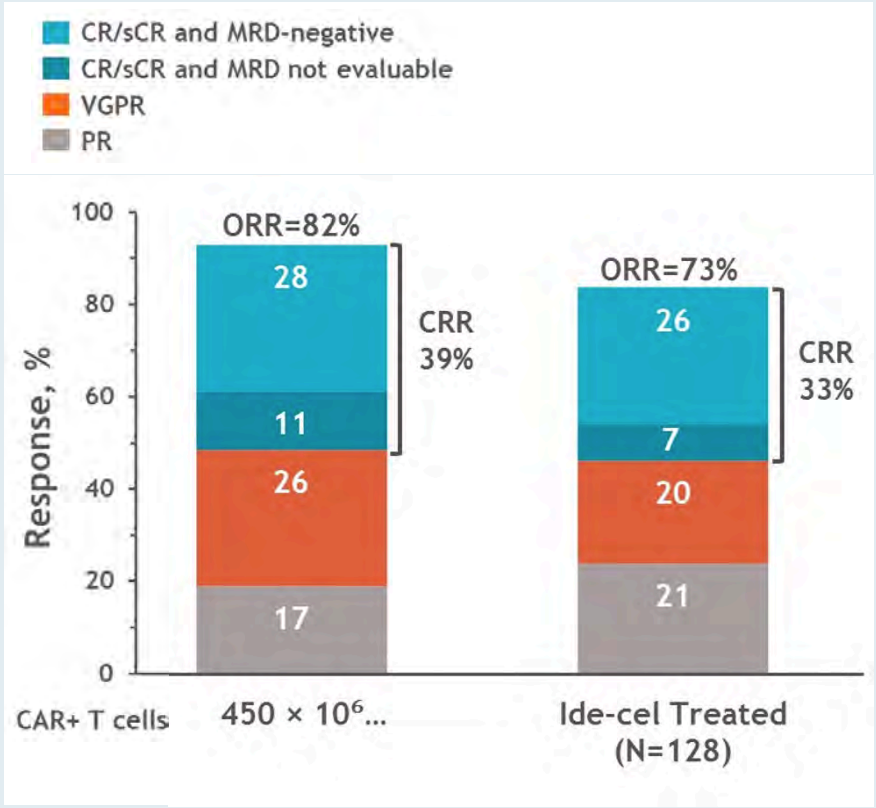
Munshi NC et al. ASCO 2020;Abstract 8503 (KarMMA); Mailankody S et al. ASCO 2020;Abstract 8504 (EVOLVE); Berdeja JG et al. ASCO 2020;Abstract 8505 (CARTITUDE-1); Patel K. ASCO 2020 Discussant.

RTP RESEARCH TO PRACTICE

Efficacy of Select BCMA CAR-T Studies in Multiple Myeloma

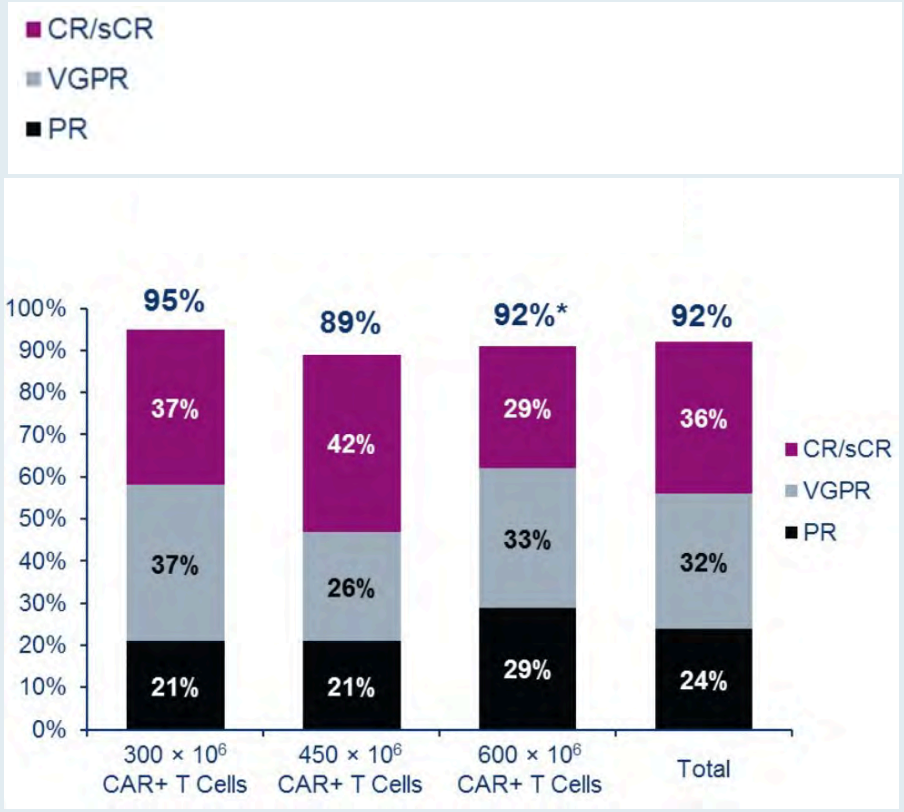
KarMMa

ORR: 73% | MRD-neg: 94%



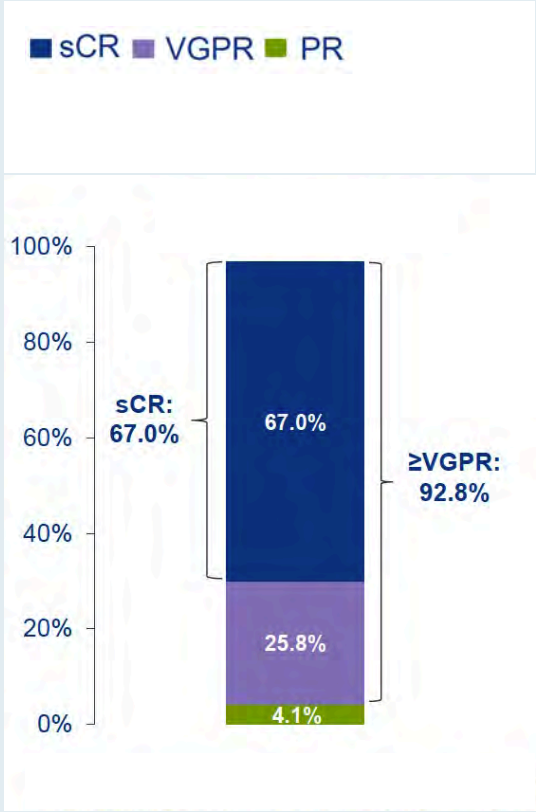
EVOLVE

ORR: 92% | MRD-neg: 84%



CARTITUDE-1

ORR: 97% | MRD-neg: 93%



Munshi NC et al. ASCO 2020;Abstract 8503. (KarMMA); Mailankody S et al. ASCO 2020;Abstract 8504. (EVOLVE): Madduri D et al. ASH 2020;Abstract 177. (CARTITUDE-1).

RTP RESEARCH TO PRACTICE

Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen (BCMA)-Directed Chimeric Antigen Receptor T-Cell (CAR-T) Therapy, in Relapsed/Refractory Multiple Myeloma (R/R MM): Updated Results from CARTITUDE-1

Usmani SZ et al.

ASCO 2021;Abstract 8005.

Tuesday, June 8, 8:00 AM - 11:00 AM EDT

Efficacy and Safety of Elranatamab (PF-06863135), a B-Cell Maturation Antigen (BCMA)-CD3 Bispecific Antibody, in Patients with Relapsed or Refractory Multiple Myeloma (MM)

Bahlis NJ et al.

ASCO 2021;Abstract 8006.

Tuesday, June 8, 8:00 AM - 11:00 AM EDT

Updated Phase 1 Results of Teclistamab, a B-Cell Maturation Antigen (BCMA) x CD3 Bispecific Antibody, in Relapsed/Refractory Multiple Myeloma (MM)

Krishnan AY et al.

ASCO 2021;Abstract 8007.

Tuesday, June 8, 8:00 AM - 11:00 AM EDT

Case Presentation – Dr Lorber: A 75-year-old man with myeloma and disease progression on 5 lines of therapy

Dr Jeremy Lorber

- Relatively fit man whose disease has progressed on 5 different therapies and ASCT
- Patient is interested in CAR-T therapy
- Other treatment options under consideration are melflufen and selinexor

Questions

- For patients with disease progression on earlier lines of therapy that include a CD38 agent, what would you recommend?
- Do you believe CAR-T therapy may be less effective after patients already receive an agent like belantamab? Should we avoid other non-CAR-T, BCMA-targeted therapies so that CAR T can be used later?

Key Recent Publications and Presentations

- Moreau P et al. **Isatuximab plus Carfilzomib and Dexamethasone vs Carfilzomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma (IKEMA): Interim Analysis of a Phase 3, Randomized, Open-Label Study**. EHA 2020;Abstract LB2603.
- Schjesvold FH et al. **Isatuximab plus Pomalidomide and Dexamethasone in Elderly Patients with Relapsed/Refractory Multiple Myeloma: ICARIA-MM Subgroup Analysis.** *Haematologica* 2021;106(4):1182-7.
- Grosicki S et al. **Once-Per-Week Selinexor, Bortezomib, and Dexamethasone versus Twice-Per-Week Bortezomib and Dexamethasone in Patients with Multiple Myeloma (BOSTON): A Randomised, Open-Label, Phase 3 Trial.** *Lancet* 2020;396(10262):1563-73.

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Key Recent Publications and Presentations

- Richardson PG et al. **Melflufen and Dexamethasone in Heavily Pretreated Relapsed and Refractory Multiple Myeloma.** *J Clin Oncol* 2021;39(7):757-67.
- Ocio E et al. **ANCHOR (OP-104): Melflufen plus Dexamethasone (dex) and Daratumumab (dara) or Bortezomib (BTZ) in Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to an IMiD and/or a Proteasome Inhibitor (PI) – Updated Efficacy and Safety.** ASH 2020;Abstract 417.
- Lonial S et al. **DREAMM-2: Single-Agent Belantamab Mafodotin (Belamaf) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) – 1-Year Outcomes By Prior Therapies.** ASH 2020;Abstract 1417.

FDA Approves Isatuximab-irfc for Multiple Myeloma

Press Release: March 31, 2021

"The Food and Drug Administration approved isatuximab-irfc (Sarclisa, sanofi-aventis U.S. LLC) in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy.

The efficacy and safety of isatuximab-irfc in combination with carfilzomib and dexamethasone was evaluated in IKEMA (NCT03275285), a multicenter, multinational, randomized, open-label, two-arm, phase 3 trial in patients with relapsed and/or refractory multiple myeloma who had received one to three prior lines of therapy. The trial randomized 302 patients (3:2) to receive isatuximab-irfc with carfilzomib and dexamethasone (Isa-Kd) or carfilzomib and dexamethasone (Kd).

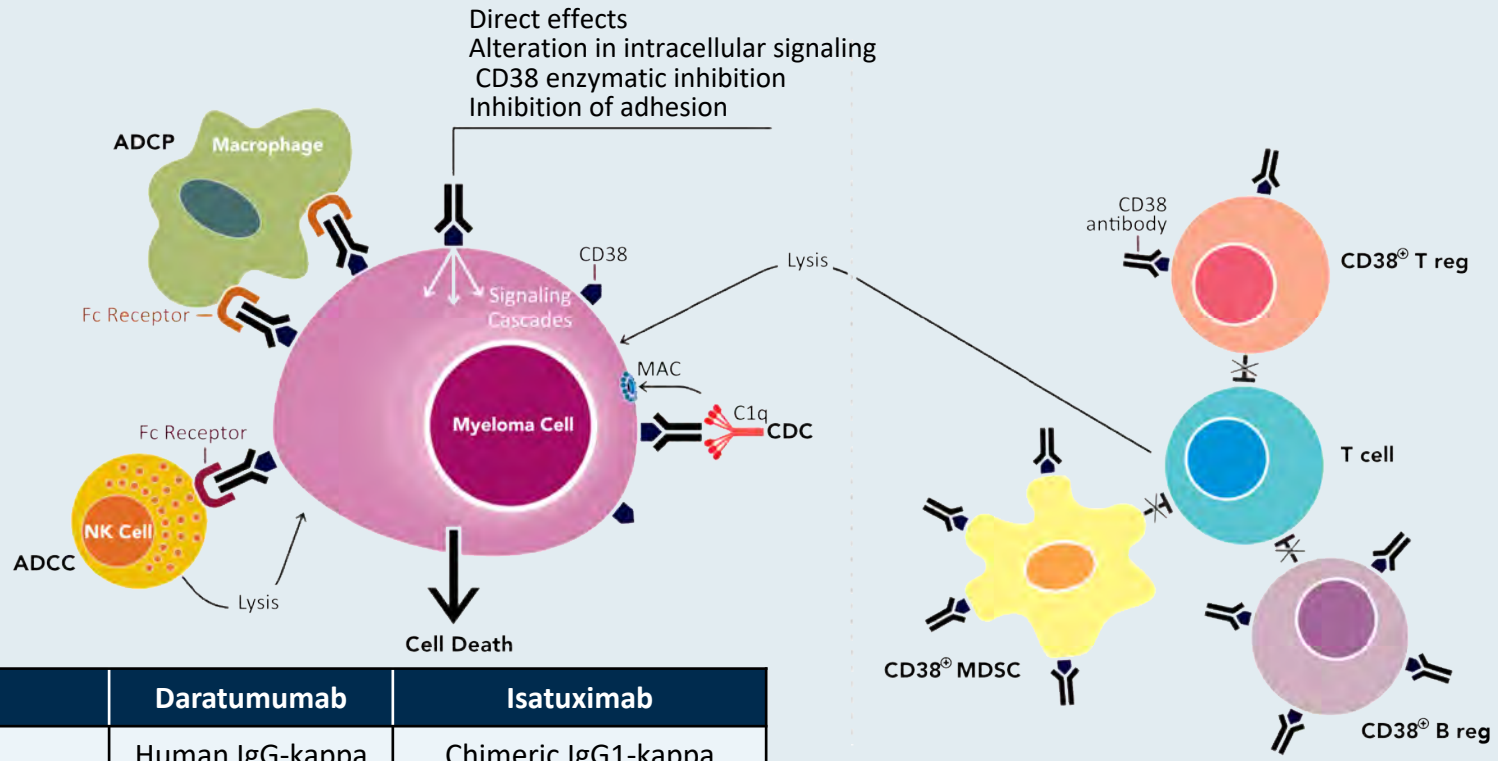
The main efficacy outcome measure was progression-free survival (PFS), assessed by an independent response committee based on central laboratory data for M-protein and central radiologic imaging review using International Myeloma Working Group criteria."

www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-isatuximab-irfc-multiple-myeloma

Anti-CD38 Antibodies: Mechanism of Action, Structural and Pharmacologic Similarities and Differences

Fc-dependent immune effector mechanisms and direct effects

Immunomodulatory effects



Mechanism of action	Daratumumab	Isatuximab
Origin, isotype	Human IgG-kappa	Chimeric IgG1-kappa
CDC	+++	+
ADCC	++	++
ADCP	+++	Not determined
PCD direct	—	++
PCD cross linking	+++	+++
Modulation ectoenzyme function	+	+++

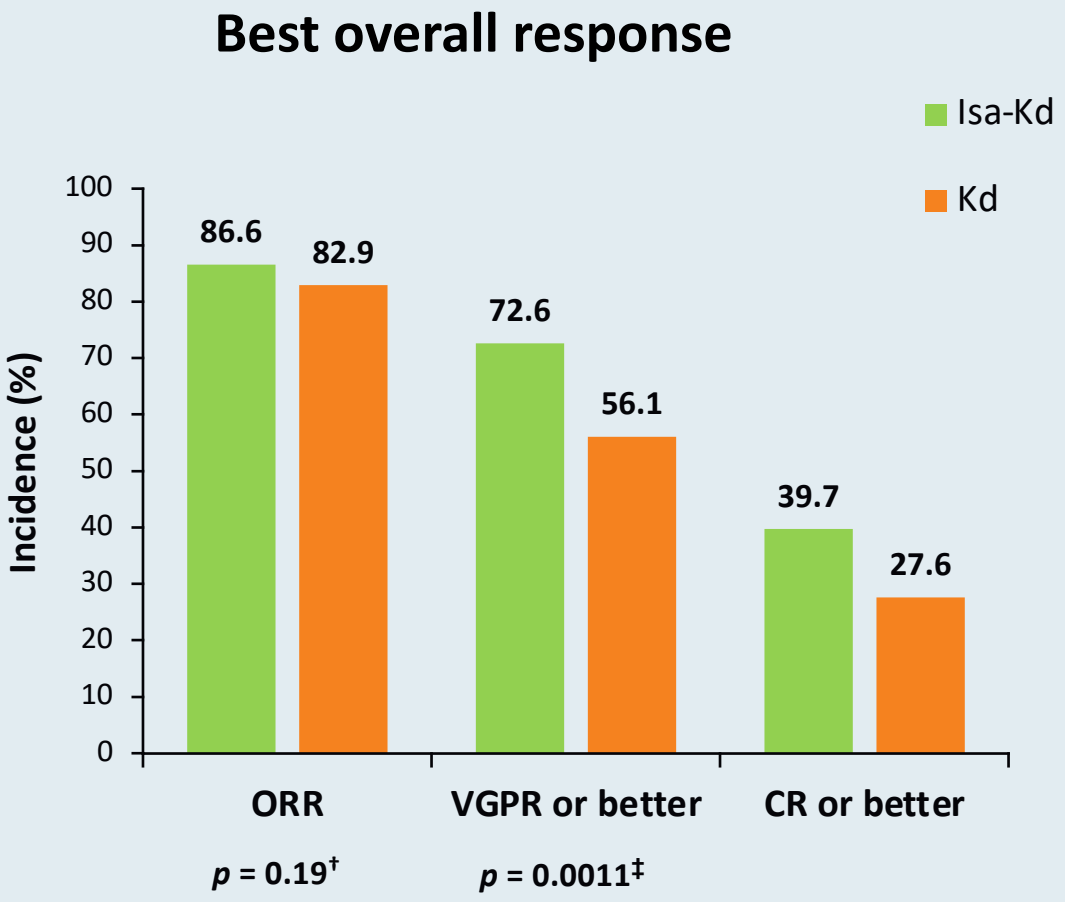
van de Donk NWCJ et al. *Blood* 2018;131(1):13-29.

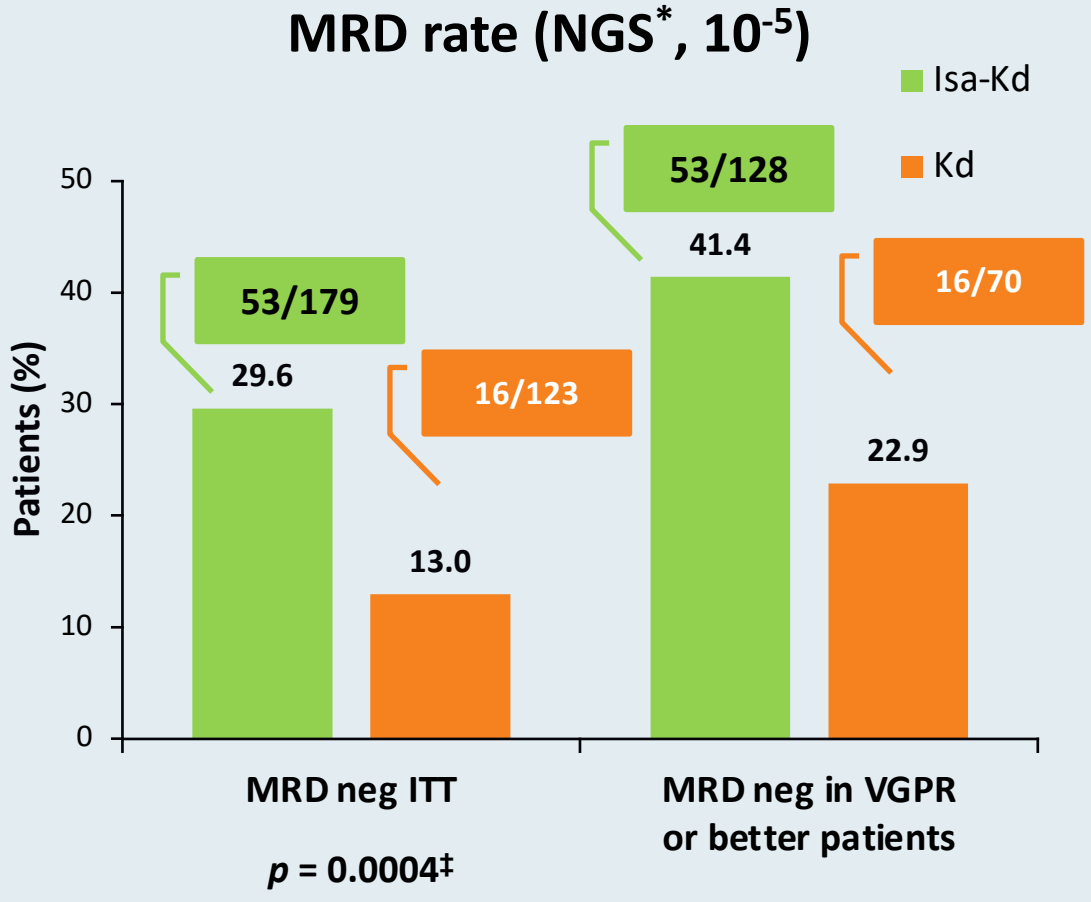
Isatuximab plus Carfilzomib and Dexamethasone vs Carfilzomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma (IKEMA): Interim Analysis of a Phase 3, Randomized, Open-Label Study

Moreau P et al.

EHA 2020;Abstract LB2603.

IKEMA – Isatuximab + Kd: Depth of Response





Moreau P et al. EHA 2020;Abstract LBA2603.

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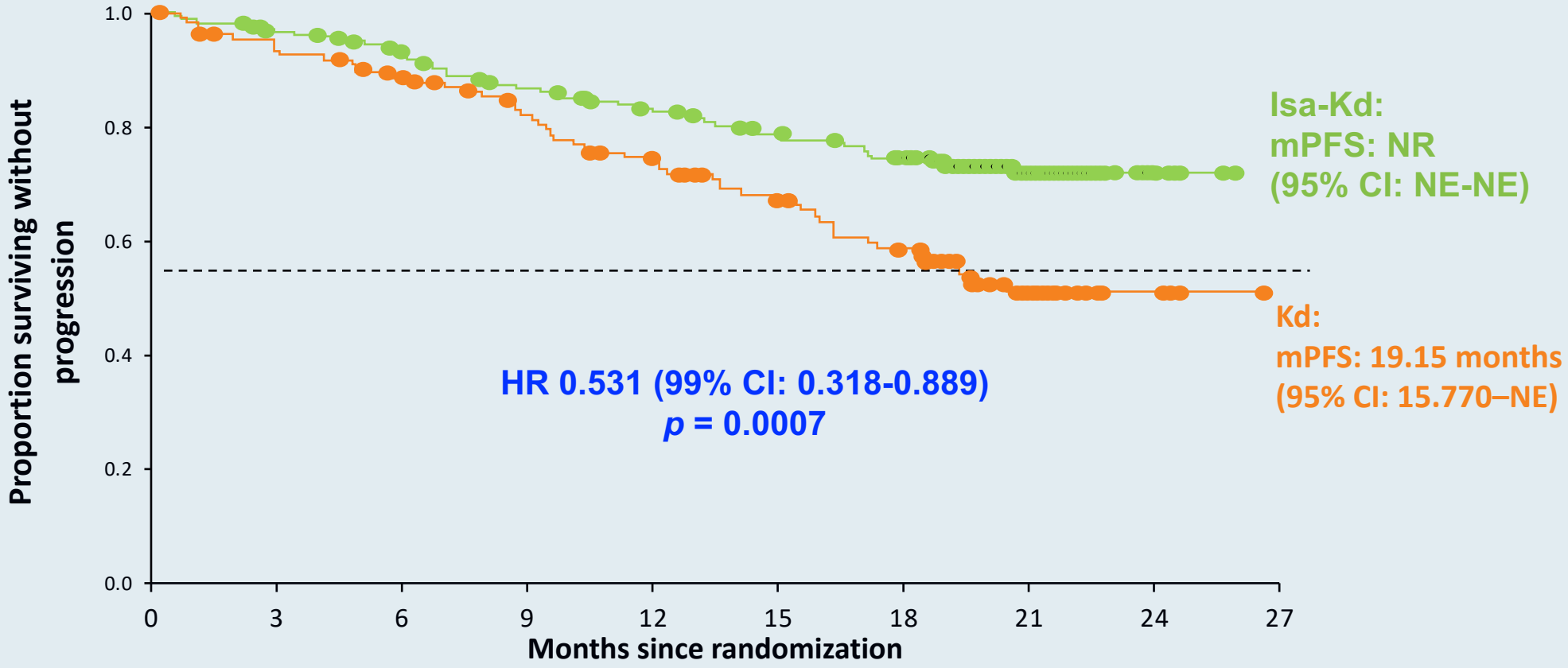
IKEMA: PFS

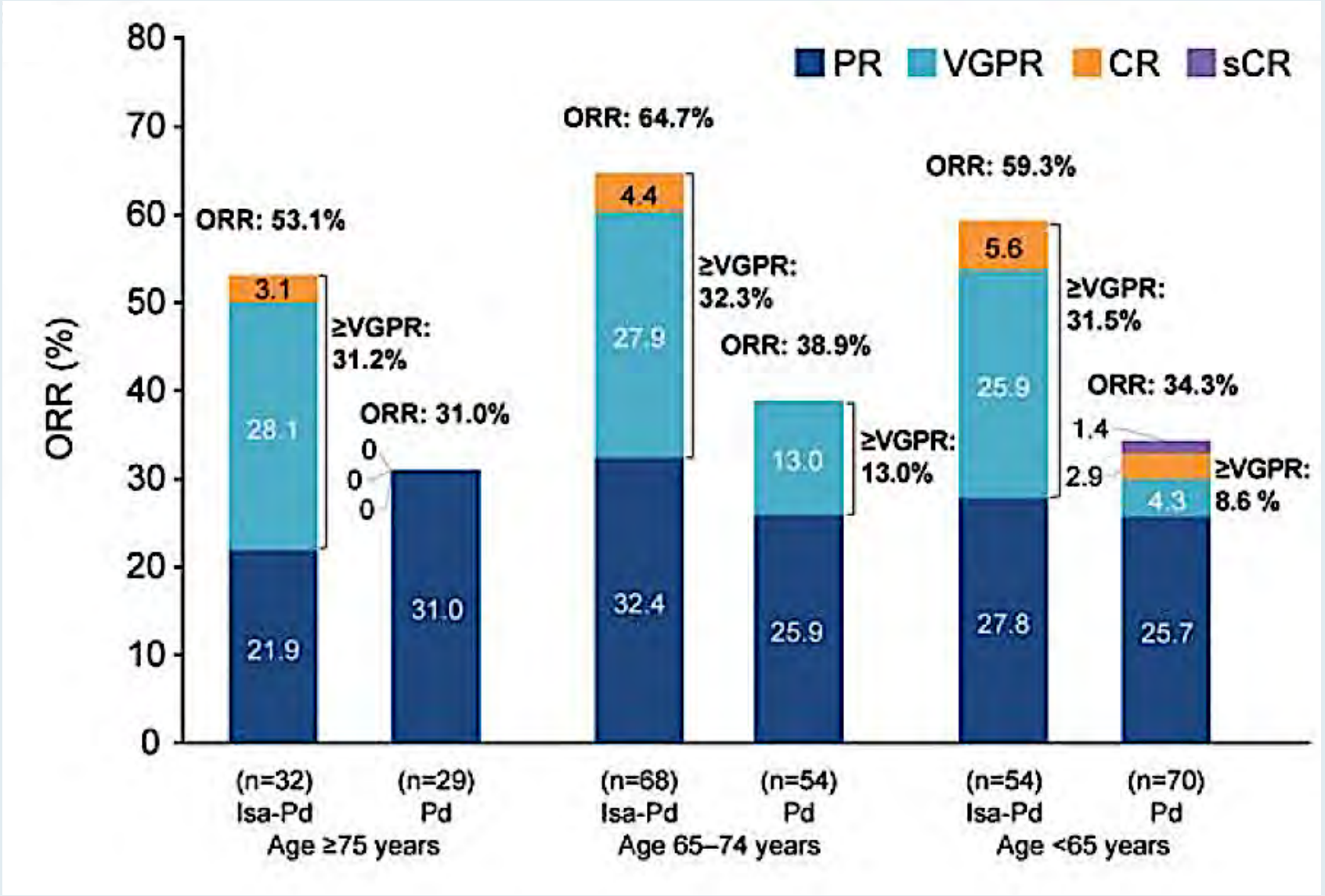


No. at risk										
Isa-Kd	179	164	151	136	124	110	100	36	5	0
Kd	123	108	99	85	72	61	50	19	6	0

One-sided *p*-value, level of significance <0.005

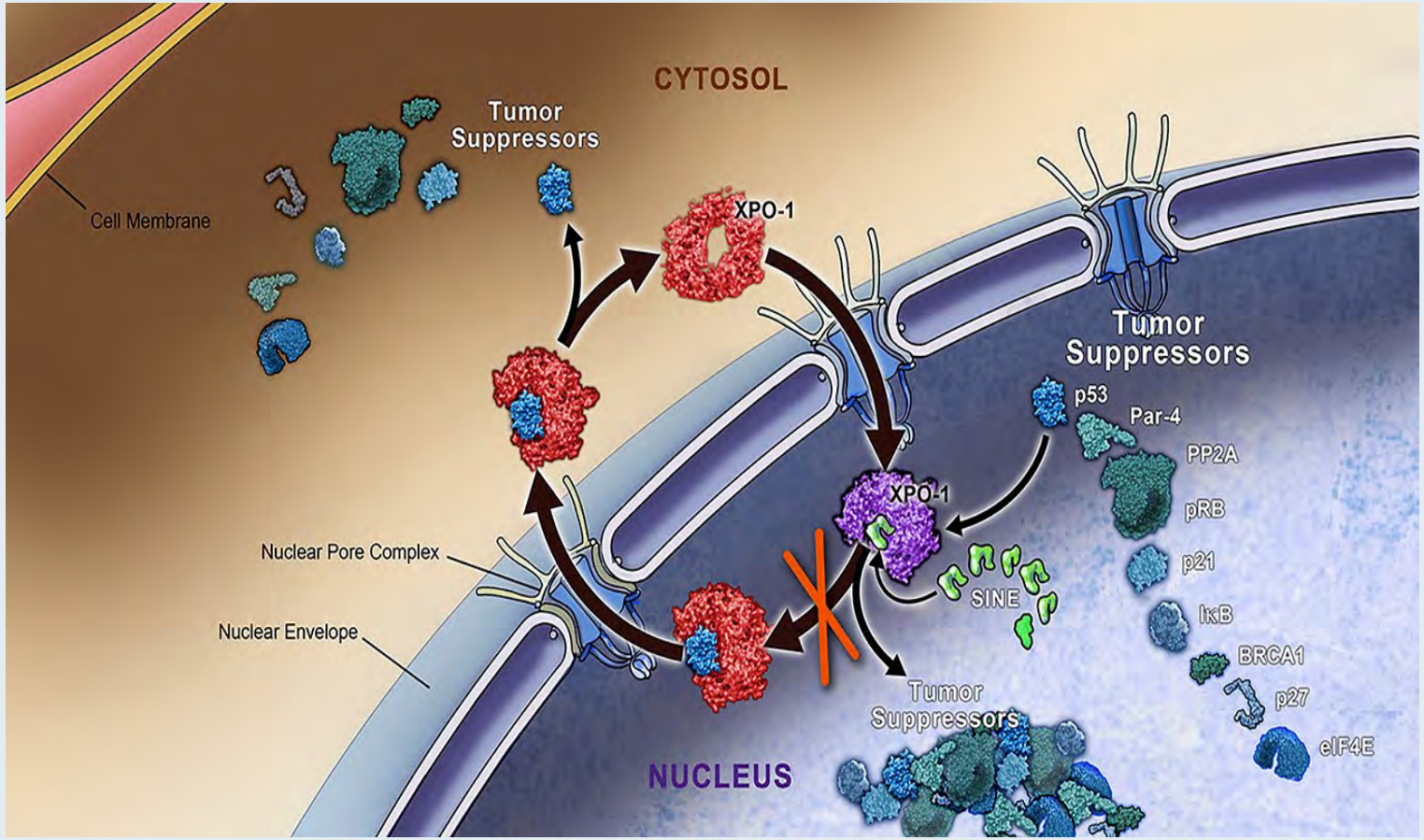
Moreau P et al. EHA 2020;Abstract LBA2603.

ICARIA-MM – Isatuximab + Pom/Dex: Response to Therapy by Patient Age Group



Schjesvold FH et al. *Haematologica* 2021;106(4):1182-87.

Selinexor Mechanism of Action



- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR) and eIF4E-bound oncoprotein mRNAs (c-myc, BCL2, BCL-xL and cyclins)
- XPO1 is overexpressed in MM and its levels often correlate with poor prognosis
- Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression.

Bahlis N et al. EHA 2016;Abstract P277.

RTP RESEARCH TO PRACTICE

FDA Approves Selinexor in Combination with Bortezomib and Dexamethasone for Refractory or Relapsed Multiple Myeloma

Press Release – December 18, 2020

"The Food and Drug Administration approved selinexor in combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

FDA granted selinexor accelerated approval in 2019 in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

Efficacy of selinexor in combination with bortezomib and dexamethasone was evaluated in the BOSTON Trial (KCP-330-023, NCT03110562), a randomized (1:1) open-label, multicenter, active comparator-controlled trial in patients with RRMM who had previously received at least one and at most three prior therapies."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-selinexor-refractory-or-relapsed-multiple-myeloma

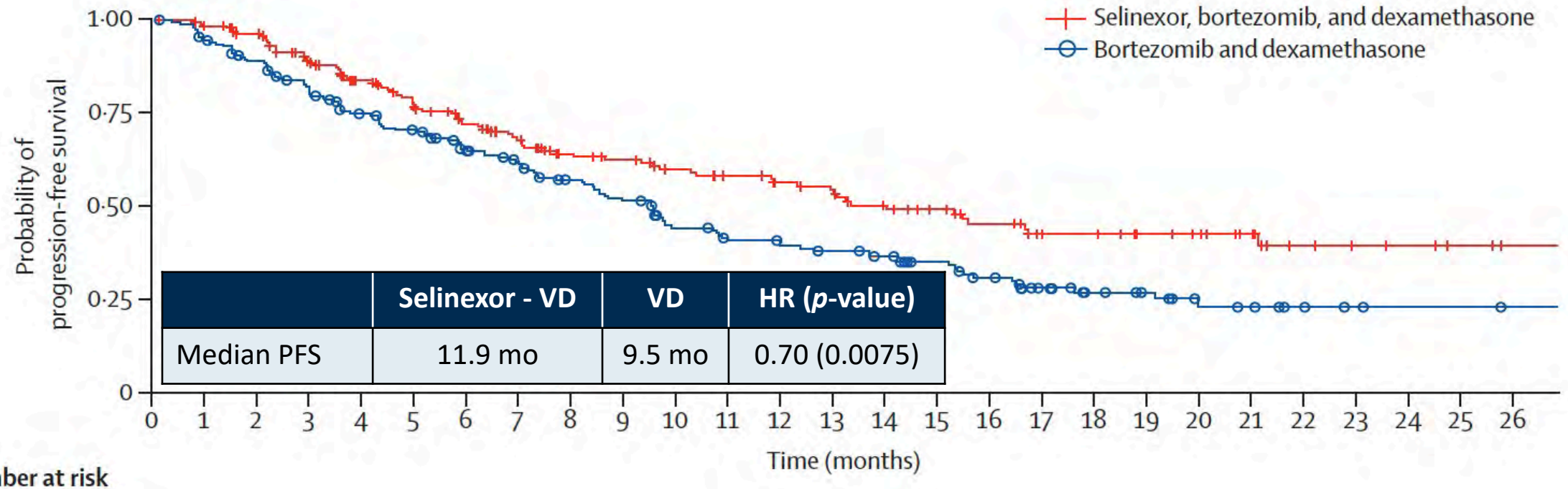
RTP RESEARCH TO PRACTICE

Lancet 2020;396:1563-73

Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial

Sebastian Grosicki, Maryana Simonova, Ivan Spicka, Ludek Pour, Iryrna Kriachok, Maria Gavriatopoulou, Halyna Pylypenko, Holger W Auner, Xavier Leleu, Vadim Doronin, Ganna Usenko, Nizar J Bahlis, Roman Hajek, Reuben Benjamin, Tuphan K Dolai, Dinesh K Sinha, Christopher P Venner, Mamta Garg, Mercedes Gironella, Artur Jurczyszyn, Pawel Robak, Monica Galli, Craig Wallington-Beddoe, Atanas Radinoff, Galina Salogub, Don A Stevens, Supratik Basu, Anna M Liberati, Hang Quach, Vesselina S Goranova-Marinova, Jelena Bila, Eirini Katodritou, Hanna Oliynyk, Sybiryna Korenkova, Jeevan Kumar, Sundar Jagannath, Phillipe Moreau, Moshe Levy, Darrell White, Moshe E Gatt, Thierry Facon, Maria V Mateos, Michele Cavo, Donna Reece, Larry D Anderson Jr, Jean-Richard Saint-Martin, Jacqueline Jeha, Anita A Joshi, Yi Chai, Lingling Li, Vishnuvardhan Peddagali, Melina Arazy, Jatin Shah, Sharon Shacham, Michael G Kauffman, Meletios A Dimopoulos, Paul G Richardson, Sosana Delimpasi**

BOSTON: Progression-Free Survival (ITT)



	Selinexor - VD	VD	HR (*p*-value)
Median PFS	11.9 mo	9.5 mo	0.70 (0.0075)

Number at risk (number censored)

Selinexor, bortezomib, and dexamethasone	195 (0)	187 (5)	175 (12)	152 (21)	135 (31)	117 (37)	106 (42)	89 (50)	79 (57)	76 (59)	69 (63)	64 (66)	57 (71)	51 (73)	45 (76)	41 (80)	35 (83)	27 (89)	26 (90)	22 (94)	19 (97)	14 (102)	9 (106)	7 (108)	6 (109)	4 (111)	2 (113)
Bortezomib and dexamethasone	207 (0)	187 (8)	175 (10)	152 (15)	138 (20)	127 (22)	111 (29)	100 (32)	90 (37)	81 (37)	66 (41)	59 (43)	56 (44)	53 (45)	49 (47)	42 (52)	35 (55)	26 (60)	20 (65)	16 (69)	10 (73)	8 (75)	5 (78)	4 (79)	3 (80)	3 (80)	2 (81)

Grosicki S et al. *Lancet* 2020;396(10262):1563-73.

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BOSTON: Select Adverse Events

Adverse event	Selinexor + Bort/dex (n = 195)		Bort/dex (n = 204)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Thrombocytopenia	60%	39%	27%	17%
Fatigue	42%	13%	18%	1%
Anemia	36%	16%	23%	10%
Peripheral neuropathy	32%	5%	47%	9%
Neutropenia	15%	9%	6%	3%

Grosicki S et al. *Lancet* 2020;396(10262):1563-73.

FDA Grants Accelerated Approval to Melphalan Flufenamide for Relapsed or Refractory Multiple Myeloma

Press Release: February 26, 2021

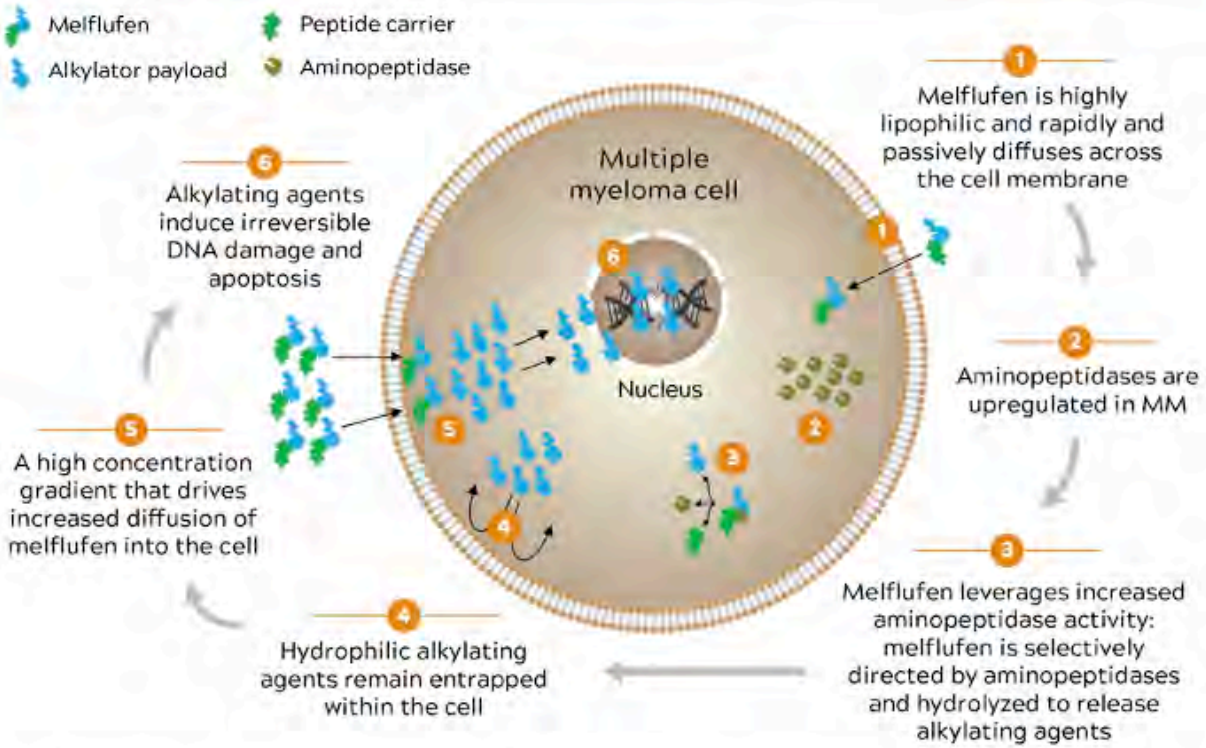
"The Food and Drug Administration granted accelerated approval to melphalan flufenamide in combination with dexamethasone for adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD-38 directed monoclonal antibody.

Efficacy was evaluated in HORIZON (NCT02963493), a multicenter, single-arm trial. Eligible patients were required to have relapsed refractory multiple myeloma. Patients received melphalan flufenamide 40 mg intravenously on day 1 and dexamethasone 40 mg orally (20 mg for patients ≥75 years of age) on day 1, 8, 15 and 22 of each 28-day cycle until disease progression or unacceptable toxicity."

www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-melphalan-flufenamide-relapsed-or-refractory-multiple-myeloma

Melphalan Flufenamide (Melflufen): Mechanism of Action

Melflufen is an investigational first-in-class peptide-drug conjugate (PDC) that **targets aminopeptidases and rapidly releases alkylating agents into tumor cells.**[1-5]



- In the pivotal phase 2 HORIZON study (OP-106), the activity of melflufen plus dexamethasone was further shown in heavily pretreated RRMM patients refractory to pomalidomide and/or anti-CD38 mAb therapy, with acceptable safety[6]
  - ORR was 29%; median PFS was 4.2 months, and median OS was 11.6 months
  - Grade 3/4 hematologic AEs were common (mainly neutropenia [79%], thrombocytopenia [76%], and anemia [71%]) but clinically manageable; nonhematologic AEs were infrequent

AE, adverse event; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-rate survival; RRMM, relapsed/refractory multiple myeloma.

Ocio E et al. ASH 2020;Abstract 417.

RTP RESEARCH TO PRACTICE

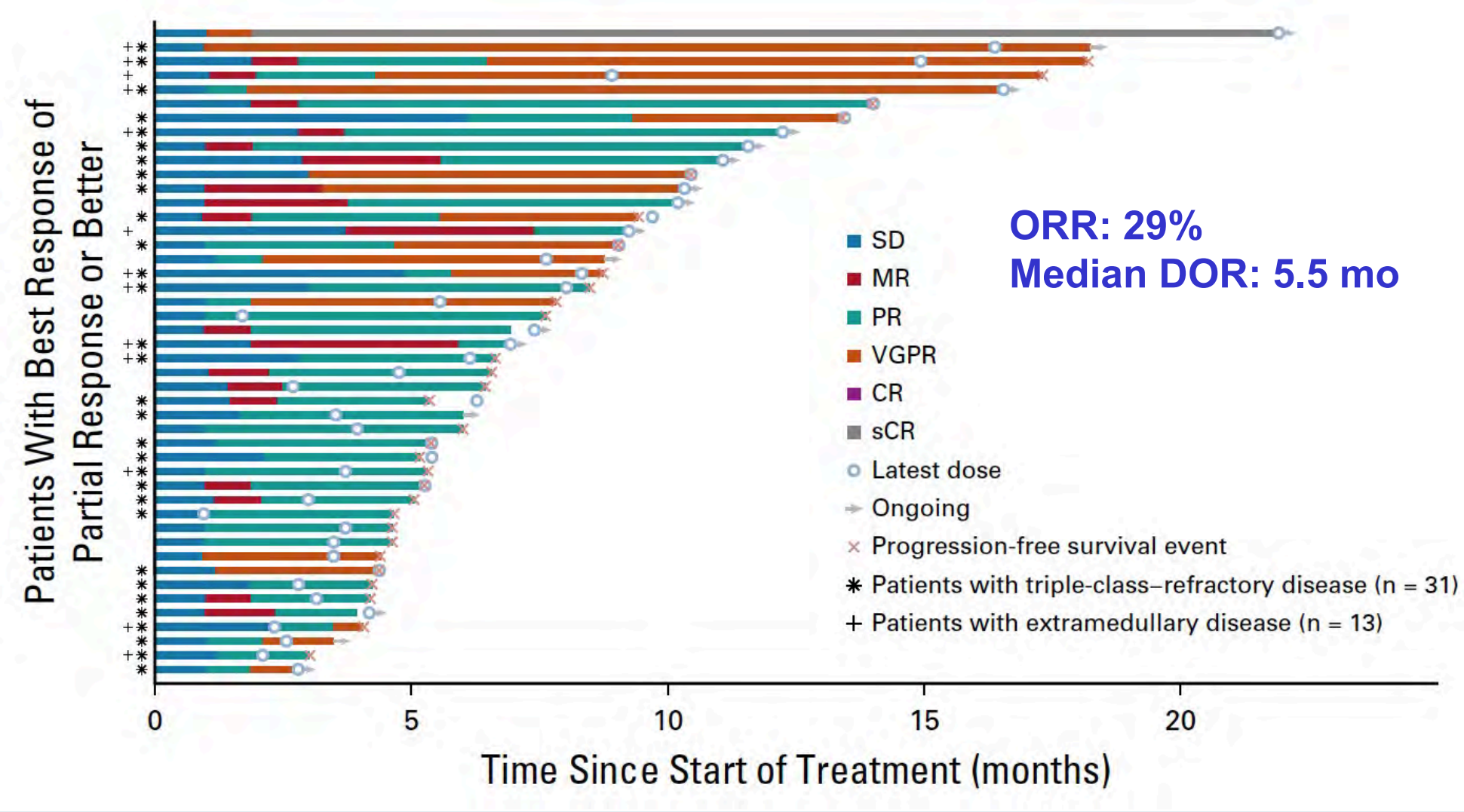
original reports

Melflufen and Dexamethasone in Heavily Pretreated Relapsed and Refractory Multiple Myeloma

Paul G. Richardson, MD[1]; Albert Oriol, MD[2]; Alessandra Larocca, MD, PhD[3]; Joan Bladé, MD, PhD[4]; Michele Cavo, MD[5]; Paula Rodriguez-Otero, MD, PhD[6]; Xavier Leleu, MD, PhD[7]; Omar Nadeem, MD[1]; John W. Hiemenz, MD[8]; Hani Hassoun, MD[9]; Cyrille Touzeau, MD, PhD[10,11,12]; Adrián Alegre, MD, PhD[13]; Agne Paner, MD[14]; Christopher Maisel, MD[15]; Amitabha Mazumder, MD[16]; Anastasios Raptis, MD[17]; Jan S. Moreb, MD[18]; Kenneth C. Anderson, MD[1]; Jacob P. Laubach, MD, MPP[1]; Sara Thuresson, MSc[19]; Marcus Thuresson, PhD[19]; Catriona Byrne, RN[19]; Johan Harmenberg, MD[19]; Nicolaas A. Bakker, MD, PhD[19]; and María-Victoria Mateos, MD, PhD[20]; on behalf of the HORIZON (OP-106) Investigators

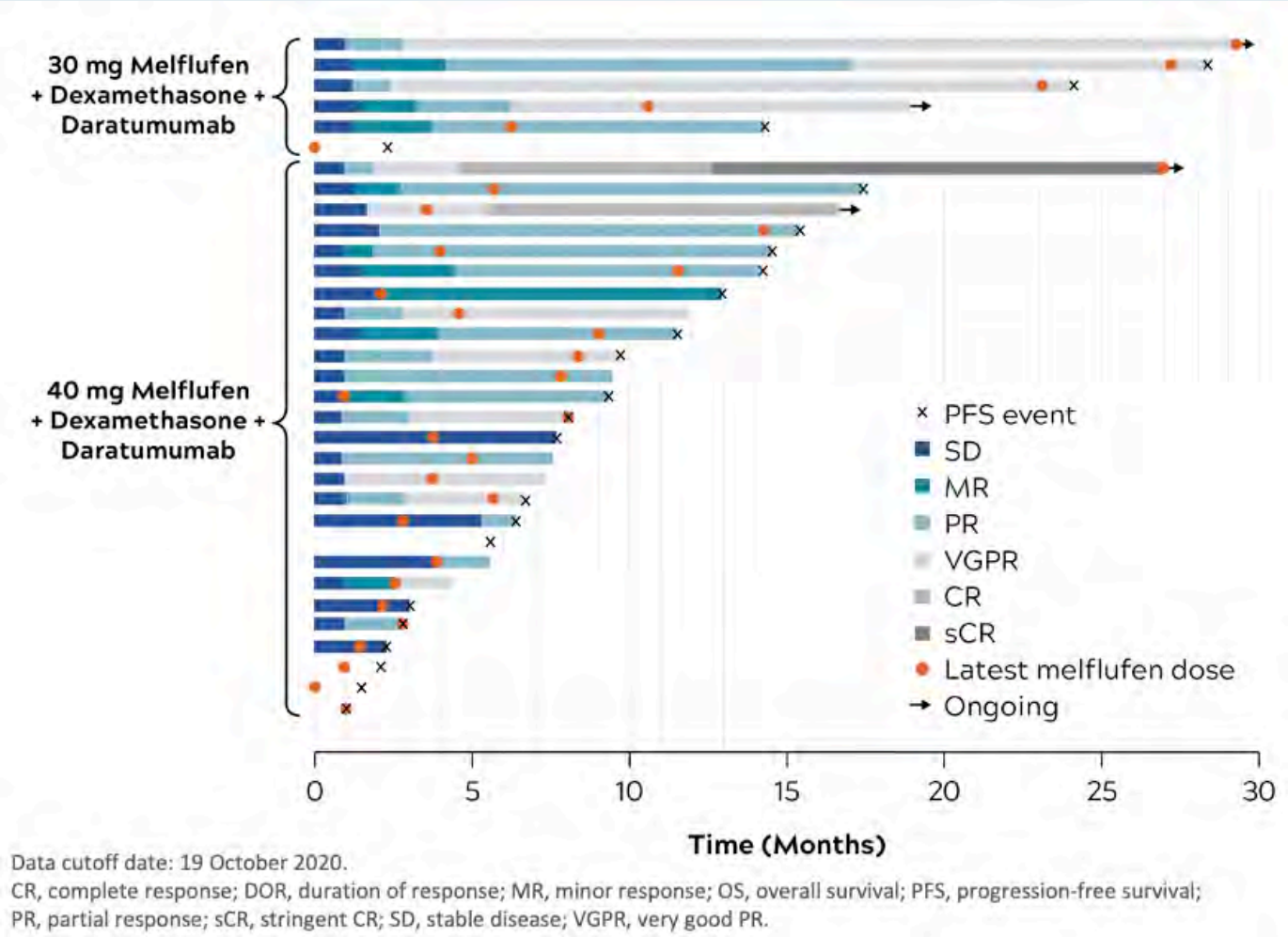
J Clin Oncol 2021;39(7):757-67.

HORIZON: Overall Response and Duration of Response with Melflufen



Richardson PG et al. *J Clin Oncol* 2021;39(7):757-67.

ANCHOR: Melflufen with Dexamethasone and Daratumumab



Data cutoff date: 19 October 2020.
CR, complete response; DOR, duration of response; MR, minor response; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good PR.

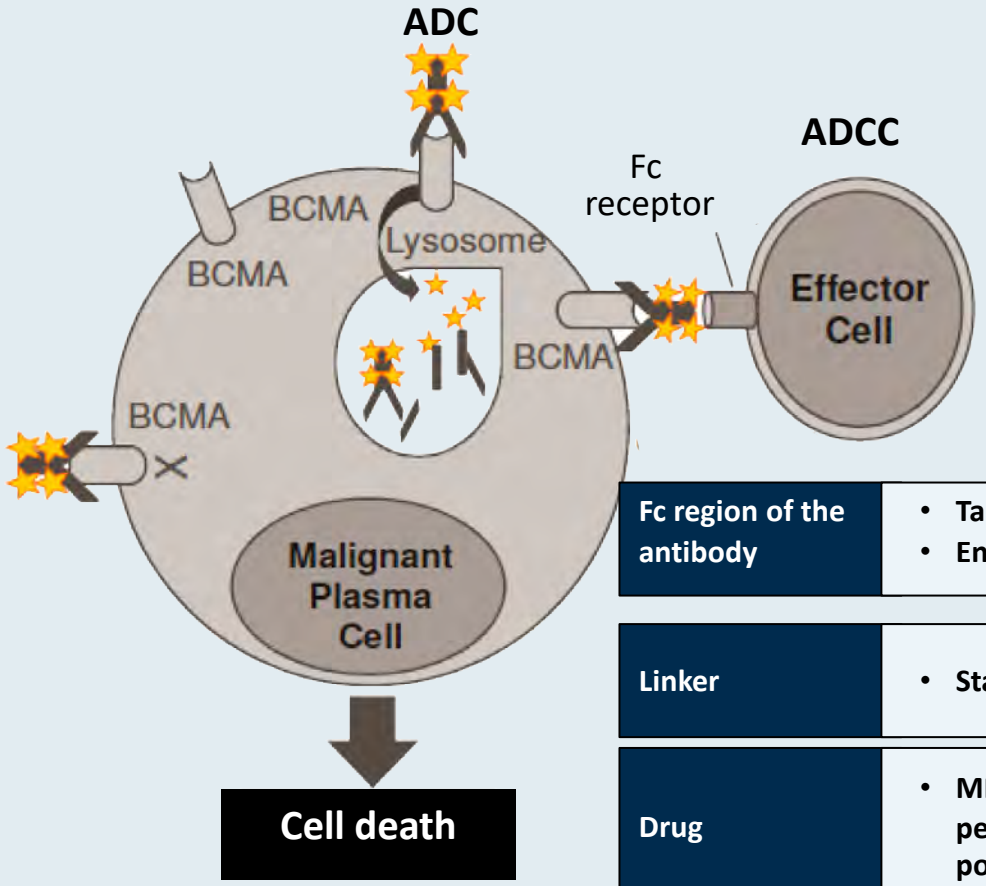
- No DLTs were observed at any dose
- 15 patients (45%) experienced SAEs, most commonly pneumonia (12%); influenza (9%); and parainfluenza virus infection, sepsis, urinary tract infection, and febrile neutropenia (6% each)[a]
  - 30 mg: 4 patients (67%)
  - 40 mg: 11 patients (41%)
- Four AEs with fatal outcomes
  - 30 mg: sepsis (unrelated to study treatment)
  - 40 mg: sepsis (possibly related to melflufen), and cardiac failure chronic and and general physical health deterioration (unrelated to study treatment)[b]

Ocio E et al. ASH 2020;Abstract 417.

RTP RESEARCH TO PRACTICE

Belamaf: Anti-BCMA Antibody-Drug Conjugate

- B-cell maturation factor (BCMA) expression is restricted to B cells at later stages of differentiation and is required for survival of plasma cells
- BCMA is broadly expressed at variable levels on malignant plasma cells
- Belantamab mafodotin is a humanized, afucosylated IgG1 anti-BCMA antibody conjugated to microtubule disrupting agent MMAF via a stable, protease-resistant maleimidocaproyl linker



Fc region of the antibody	• **Target specific** • **Enhanced ADCC**
Linker	• **Stable in circulation**
Drug	• **MMAF (non cell permeable, highly potent auristatin)**

Mechanisms of action:
- ADC mechanism
- ADCC mechanism
- Immunogenic cell death
- BCMA receptor signaling inhibition

Tai YT et al. *Blood* 2014;123(20):3128-38.

DREAMM-2: Single-Agent Belantamab Mafodotin (Belamaf) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM) – 1-Year Outcomes By Prior Therapies

Lonial S et al.

ASH 2020;Abstract 1417.

DREAMM-2 – Single-Agent Belantamab Mafodotin: Efficacy Outcomes

	Patients with 3-6 prior therapies (n = 47)	Patients with ≥7 prior therapies (n = 50)
ORR, % (97.5% CI)	34 (19.3-51.4)	30 (16.5-46.6)
Median DoR (95% CI estimates), months	11.0 (4.2-NR)	13.1 (4.0-NR)
Probability of DoR ≥6 months, % (95% CI estimates)	63 (31-83)	73 (44-89)
Median PFS (95% CI estimates), months	2.9 (1.5-5.7)	2.2 (1.2-3.6)
Probability of PFS at 6 months, % (95% CI estimates)	35 (20-50)	30 (17-43)

ORR = overall response rate; DoR = duration of response; NR = not reached; CI = confidence interval; PFS = progression-free survival

Lonial S et al. ASH 2020;Abstract 1417.

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

A Daylong Clinical Summit Hosted in Partnership with Medical Oncology Association of Southern California (MOASC)

Saturday, May 15, 2021

10:30 AM – 6:30 PM ET

(7:30 AM – 3:30 PM Pacific Time)

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This program was recorded before the ASCO 2021 Annual Meeting.

Data from the abstracts presented at this meeting can be accessed at https://meetinglibrary.asco.org/results?meetingView=2021%20ASCO%20Annual%20Meeting.

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Agenda

Module 1 — Breast Cancer: *Drs O'Regan and Traina*

Module 2 — Multiple Myeloma: *Drs Anderson and Raje*

Module 3 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Moskowitz and Sharman*

Module 4 — Genitourinary Cancers: *Drs Bellmunt and Pal*

Module 5 — Gastrointestinal Cancers: *Drs Messersmith and O'Reilly*

Module 6 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Erba and Komrokji*

Module 7 — Lung Cancer: *Drs Camidge and Levy*

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Chronic Lymphocytic Leukemia and Lymphomas Faculty

Craig Moskowitz, MD
Physician in Chief, Oncology Service Line
Sylvester Comprehensive Cancer Center
Professor of Medicine, Miller School of Medicine
University of Miami Health System
Miami, Florida

Jeff Sharman, MD
Medical Director of Hematology Research
US Oncology Network
Willamette Valley Cancer Institute and Research Center
Eugene, Oregon

Commercial Support

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Eisai Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Turning Point Therapeutics Inc and Verastem Inc.

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Research To Practice CME and NCPD Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Moskowitz — Disclosures

Contracted Research	ADC Therapeutics SA, AstraZeneca Pharmaceuticals LP, Incyte Corporation, Merck, Seagen Inc
Scientific Advisory Board	AstraZeneca Pharmaceuticals LP, Incyte Corporation, Merck, Molecular Templates, Seagen Inc, Takeda Oncology

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Dr Sharman — Disclosures

Advisory Committee, Consulting Agreements and Contracted Research	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Pharmacyclics LLC, an AbbVie Company, TG Therapeutics Inc

Contributing Oncologists

Amanda Blackmon, DO, MS
Chief Fellow, Hematology/Oncology
University of California, Irvine
Irvine, California

Farshid Dayyani, MD, PhD
Professor of Clinical Medicine
Division of Hematology/Oncology
Department of Medicine
University of California, Irvine
UCI Health
Orange, California

Gigi Chen, MD
Diablo Valley Oncology and
Hematology Medical Group
Pleasant Hill, California

Michael Polintan Del Rosario, MD
Fellow Physician
Division of Hematology-Oncology
Department of Medicine
University of California, Irvine
Irvine, California

Mamta Choksi, MD
Florida Cancer Specialists and
Research Institute
New Port Richey, Florida

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

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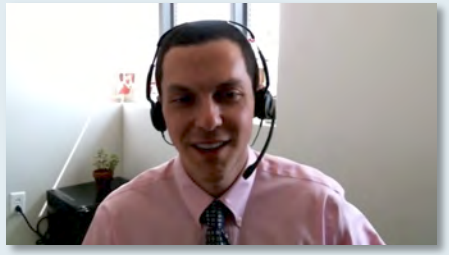
Contributing Oncologists

Rahul Gosain, MD
Division of Hematology and Oncology
Guthrie Corning Cancer Center
Corning, New York

Maen Hussein, MD
Florida Cancer Specialists and
Research Institute
The Villages, Florida

Ranju Gupta, MD
Attending Physician
Co-Director, Cardio-Oncology Program
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania



Jeremy Lorber, MD
Attending Hematologist-Oncologist
Tower Hematology Oncology
Cedars-Sinai Medical Center
Beverly Hills, California

Hatim Husain, MD
Physician, University of California San Diego
San Diego, California

Nataliya Mar, MD
Assistant Clinical Professor
Division of Hematology/Oncology
University of California, Irvine
Irvine, California

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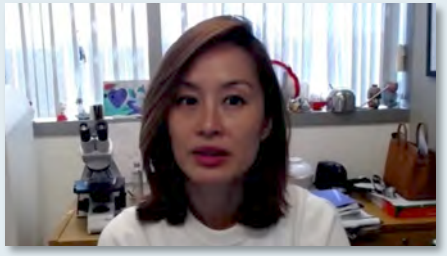
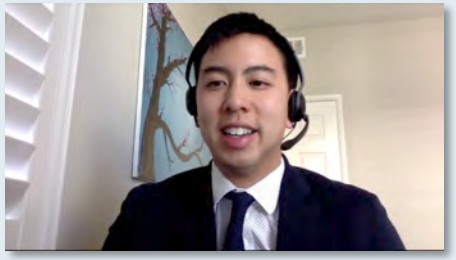
Contributing Oncologists

Mohamed K Mohamed, MD, PhD
Oncology Division Medical Director
Director of Thoracic Oncology
Hematologist/ Medical Oncologist
Cone Health Cancer Center
Greensboro, North Carolina

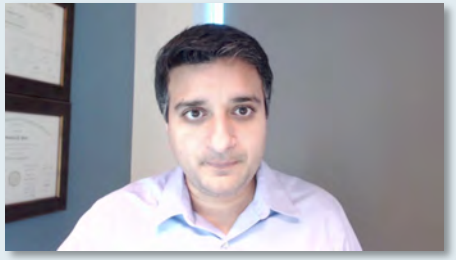


Helen H Moon, MD
Medical Oncologist
Southern California Permanente
Medical Group
Riverside, California

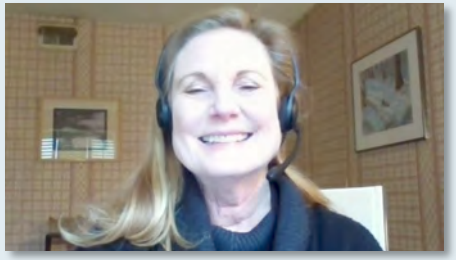
Neil Morganstein, MD
Hematology Oncology
Atlantic Health System
Summit, New Jersey



Anthony Nguyen, MD
Fellow, Loma Linda University Health
Loma Linda, California



Sandip Patel, MD
Associate Professor, Medical Oncology, UCSD
Leader, Experimental Therapeutics
Deputy Director, San Diego Center for
Precision Immunotherapy
San Diego, California



Andrea Stebel, MD
Newport Breast Care
Newport Beach, California

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Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)

- Dr Nguyen: A 75-year-old man with Stage IV gastric DLBCL
- *Key Recent Publications and Presentations*

Module 2: Hodgkin Lymphoma

- Dr Nguyen: A 26-year-old woman with classical Hodgkin lymphoma
- *Key Recent Publications and Presentations*

Module 3: Chronic Lymphocytic Leukemia (CLL)

- Dr Morganstein: A 75-year-old man with relapsed CLL
- Dr Chen: A 66-year-old woman with newly diagnosed CLL receives acalabrutinib
- *Key Recent Publications and Presentations*

Module 4: Follicular Lymphoma (FL)

- Dr Blackmon: A 50-year-old man with newly diagnosed Stage III, Grade I-II FL
- Dr Blackmon: A 37-year-old woman with multiregimen-relapsed FL
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Module 5: Mantle Cell Lymphoma (MCL)

- Dr Blackmon: A 50-year-old man with relapsed blastoid MCL
- *Key Recent Publications and Presentations*

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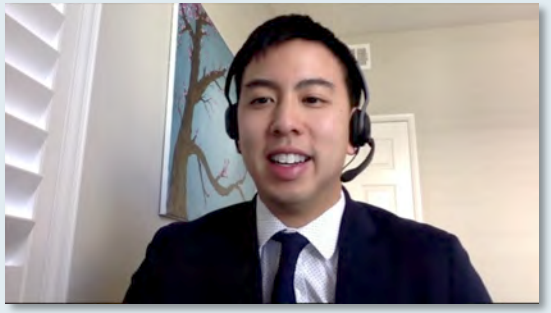
RTP RESEARCH TO PRACTICE

Case Presentation – Dr Nguyen: A 75-year-old man with Stage IV gastric DLBCL



Dr Anthony Nguyen

- PMH: HTN, DM, early-stage prostate cancer
- 3/2018: Diagnosed with Stage IV gastric DLBCL; double-expressor, MYC and Bcl-2 overexpression
- R-EPOCH x 6, with intrathecal methotrexate → CR
- 9/2020: B-symptoms, worsening cervical lymphadenopathy
  - PET: Gastric wall involvement Bcl-2+, MYC-negative, Bcl-6-negative
- R-GemOx x 6 → CR
- Referred for auto-SCT, being considered for CAR T-cell therapy

Questions

- What are your thoughts about doing an autotransplant versus CAR T-cell therapy in this 75-year-old man with an ECOG PS 0? How do you determine if a patient is a suitable candidate for CAR T-cell therapy?
- If this patient is deemed transplant-ineligible and CAR T-cell therapy-ineligible, would tafasitamab/lenalidomide be a therapy that you would consider, given that this patient has relapsed after the first, after R-EPOCH? Would tafasitamab/lenalidomide have been suitable instead of R-GemOx?

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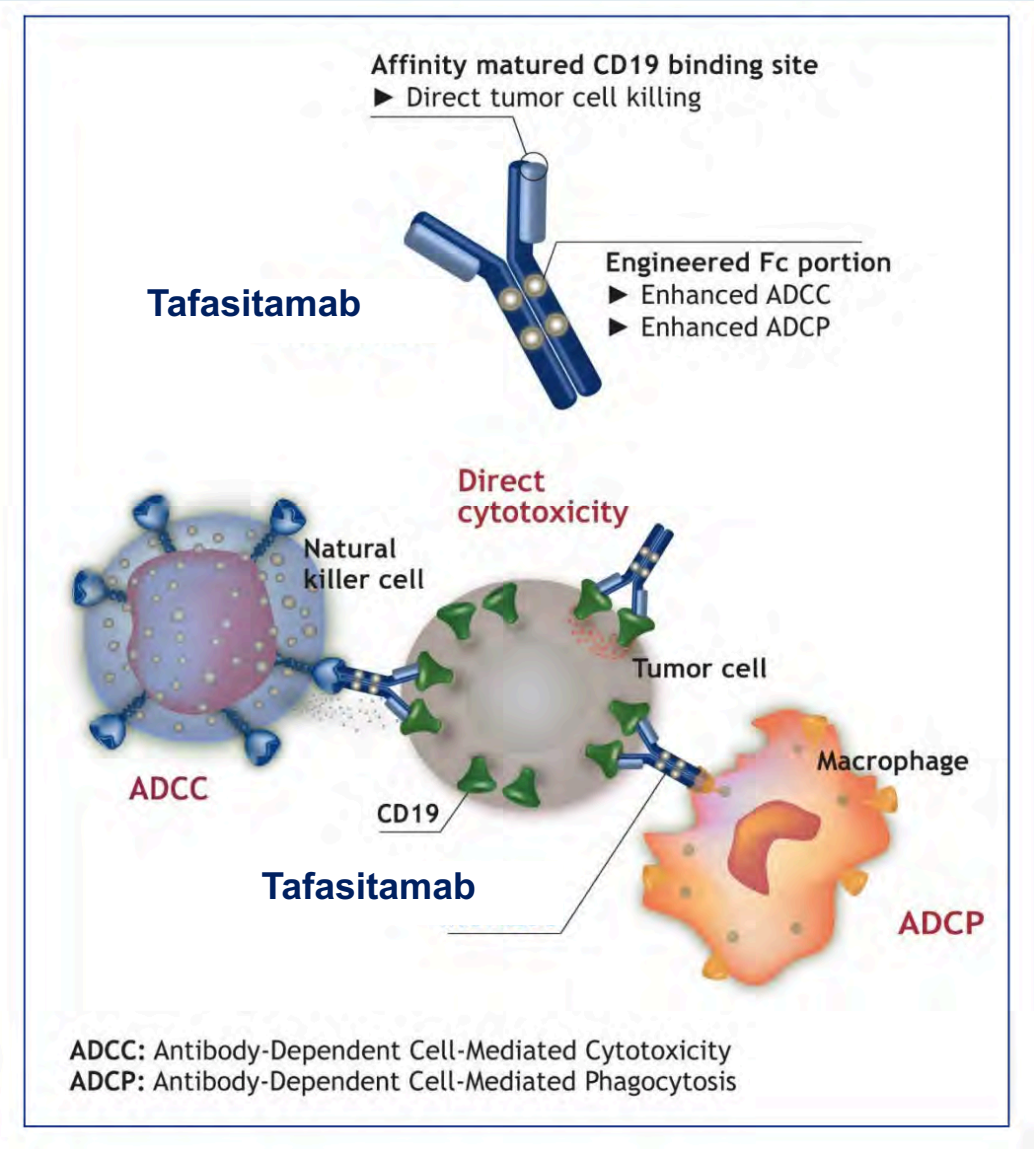
Key Recent Publications and Presentations

- Maddocks KJ et al. **Long-Term Subgroup Analyses from L-Mind, a Phase II Study of Tafasitamab (MOR208) Combined with Lenalidomide in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma.** ASH 2020;Abstract 3021.
- Belada D et al. **A Phase Ib, Open-Label, Randomized Study to Assess Safety and Preliminary Efficacy of Tafasitamab (MOR208) or Tafasitamab + Lenalidomide in Addition to R-CHOP in Patients with Newly Diagnosed Diffuse Large B-Cell Lymphoma: Analysis of the Safety Run-in Phase.** ASH 2020;Abstract 3028.
- Neelapa SS et al. **Interim Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) as First-Line Therapy in Patients (Pts) with High-Risk Large B Cell Lymphoma (LBCL).** ASH 2020;Abstract 405.
- Maloney DG et al. **Matching-Adjusted Indirect Comparison (MAIC) of Lisocabtagene Maraleucel (Liso-cel) vs Axicabtagene Ciloleucel (Axi-cel) and Tisagenlecleucel in Relapsed/Refractory (R/R) Large B-Cell Lymphoma (LBCL).** ASH 2020;Abstract 2116.

Tafasitamab (MOR208)



Lenalidomide enhances NK function with enhanced ADCC in vitro

Salles et al. *Lancet Onc* 2020.

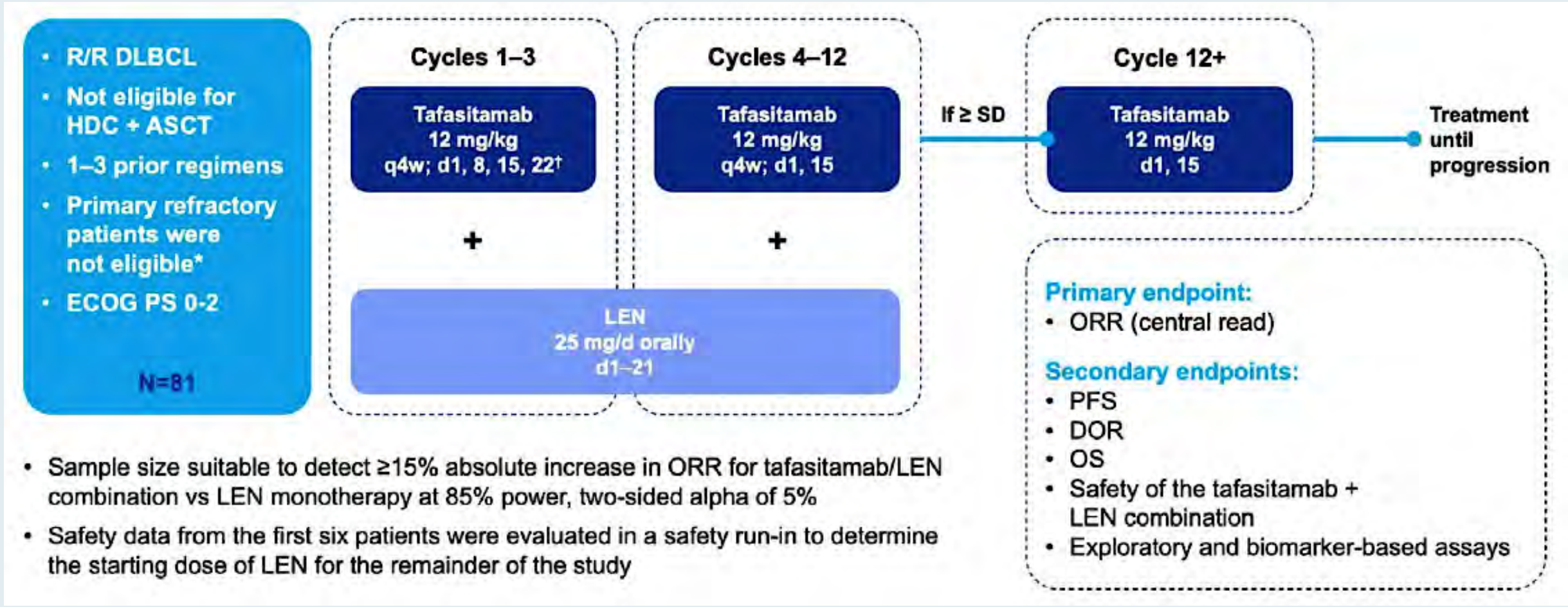
Courtesy of Ann S LaCasce, MD, MMSc

Long-Term Subgroup Analyses from L-Mind, a Phase II Study of Tafasitamab (MOR208) Combined with Lenalidomide in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Maddocks KJ et al.

ASH 2020;Abstract 3021.

L-MIND: Study Design



Maddocks KJ et al. ASH 2020;Abstract 3021.

L-MIND: Summary

Clinical endpoint	N = 80
ORR	57.5%
CR	40.0%
Median DOR	34.6 mo
24 mo DOR rate	71.3%
24 mo OS rate	57.2%

In the subgroup analysis, patients with CR as best objective response had better outcomes than those with PR:

- **Median DOR: NR vs 5.6**
- **24-month DOR rate: 86.4% vs 38.5%**
- **24-month OS rate: 90.6% vs 42.7%**

Maddocks KJ et al. ASH 2020;Abstract 3021.

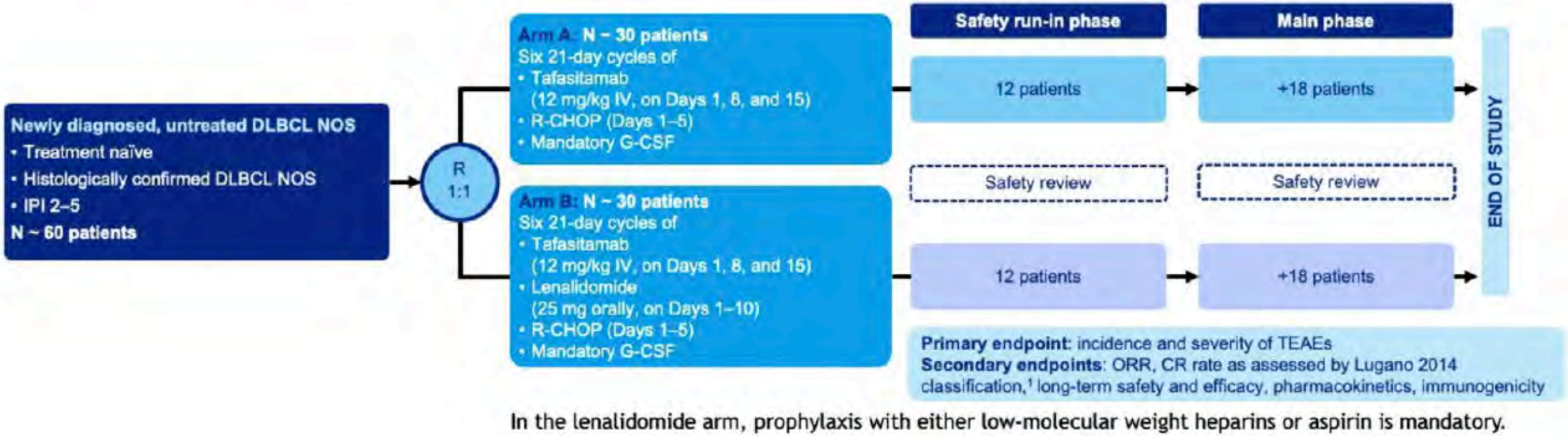
A Phase Ib, Open-Label, Randomized Study to Assess Safety and Preliminary Efficacy of Tafasitamab (MOR208) or Tafasitamab + Lenalidomide in Addition to R-CHOP in Patients with Newly Diagnosed Diffuse Large B-Cell Lymphoma: Analysis of the Safety Run-in Phase

Belada D et al.

ASH 2020;Abstract 3028.

First-MIND: Study Design

- An open-label, prospective, randomized, Phase Ib study designed to evaluate the safety and preliminary efficacy of tafasitamab or tafasitamab + lenalidomide in addition to R-CHOP in patients with newly diagnosed DLBCL



In the lenalidomide arm, prophylaxis with either low-molecular weight heparins or aspirin is mandatory.

Belada D et al. ASH 2020;Abstract 3028.

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First-MIND: Treatment Emergent Adverse Events

Overall summary by toxicity grade, n (%) [E]	Arm A: tafasitamab + R-CHOP (n=33)	Arm B: tafasitamab + lenalidomide + R-CHOP (n=33)	Total (N=66)
Patients with TEAEs and the total number of events	32* (97.0) [345]	33 (100) [443]	65 (98.5) [788]
Grade 1	26 (78.8) [140]	27 (81.8) [161]	53 (80.3) [301]
Grade 2	27 (81.8) [120]	28 (84.8) [135]	55 (83.3) [255]
Grade 3	21 (63.6) [48]	22 (66.7) [72]	43 (65.2) [120]
Grade 4	13 (39.4) [36]	19 (57.6) [75]	32 (48.5) [111]
Grade 5	1 (3.0) [1]	0	1 (1.5) [1]
Grade 3 or higher	23 (69.7) [85]	27 (81.8) [147]	50 (75.8) [232]

Overall summary of serious TEAEs, n (%) [E]	Arm A: tafasitamab + R-CHOP (n=33)	Arm B: tafasitamab + lenalidomide + R-CHOP (n=33)	Total (N=66)
Patients with serious TEAEs and the total number of events	13 (39.4) [28]	16 (48.5) [27]	29 (43.9) [55]

- Overall, 98.5% of patients experienced TEAEs; of these, 75.8% were grade 3 or higher
- Serious TEAEs were experienced by 29 patients in total (43.9%), 13 patients in arm A and 16 in arm B (39.4% vs 48.5%)
- No new safety signals were identified with either tafasitamab + R-CHOP or tafasitamab + lenalidomide + R-CHOP compared with previous Phase III studies with R-CHOP or R2-CHOP[1–3]

Belada D et al. ASH 2020;Abstract 3028.

RTP RESEARCH TO PRACTICE

FDA Grants Accelerated Approval to Loncastuximab Tesirine-lpyl for Large B-cell Lymphoma

Press Release – April 23, 2021

"On April 23, 2021, the Food and Drug Administration granted accelerated approval to loncastuximab tesirine-lpyl, a CD19-directed antibody and alkylating agent conjugate, for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.

Approval was based on LOTIS-2 (NCT03589469), an open-label, single-arm trial in 145 adult patients with relapsed or refractory DLBCL or high-grade B-cell lymphoma after at least two prior systemic regimens.

The ORR was 48.3% (95% CI: 39.9, 56.7) with a complete response rate of 24.1% (95% CI: 17.4, 31.9). After a median follow-up of 7.3 months, median response duration was 10.3 months (95% CI: 6.9, NE)."

https://www.fda.gov/drugs/fda-grants-accelerated-approval-loncastuximab-tesirine-lpyl-large-b-cell-lymphoma

RTP RESEARCH TO PRACTICE

FDA Approves Lisocabtagene Maraleucel for Relapsed or Refractory Large B-cell Lymphoma

Press Release – February 5, 2021

"The Food and Drug Administration approved lisocabtagene maraleucel for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.

Efficacy was evaluated in TRANSCEND (NCT02631044), a single-arm, open label, multicenter trial that evaluated lisocabtagene maraleucel, preceded by lymphodepleting chemotherapy, in adults with R/R large B-cell lymphoma after at least two lines of therapy.

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-lisocabtagene-maraleucel-relapsed-or-refractory-large-b-cell-lymphoma

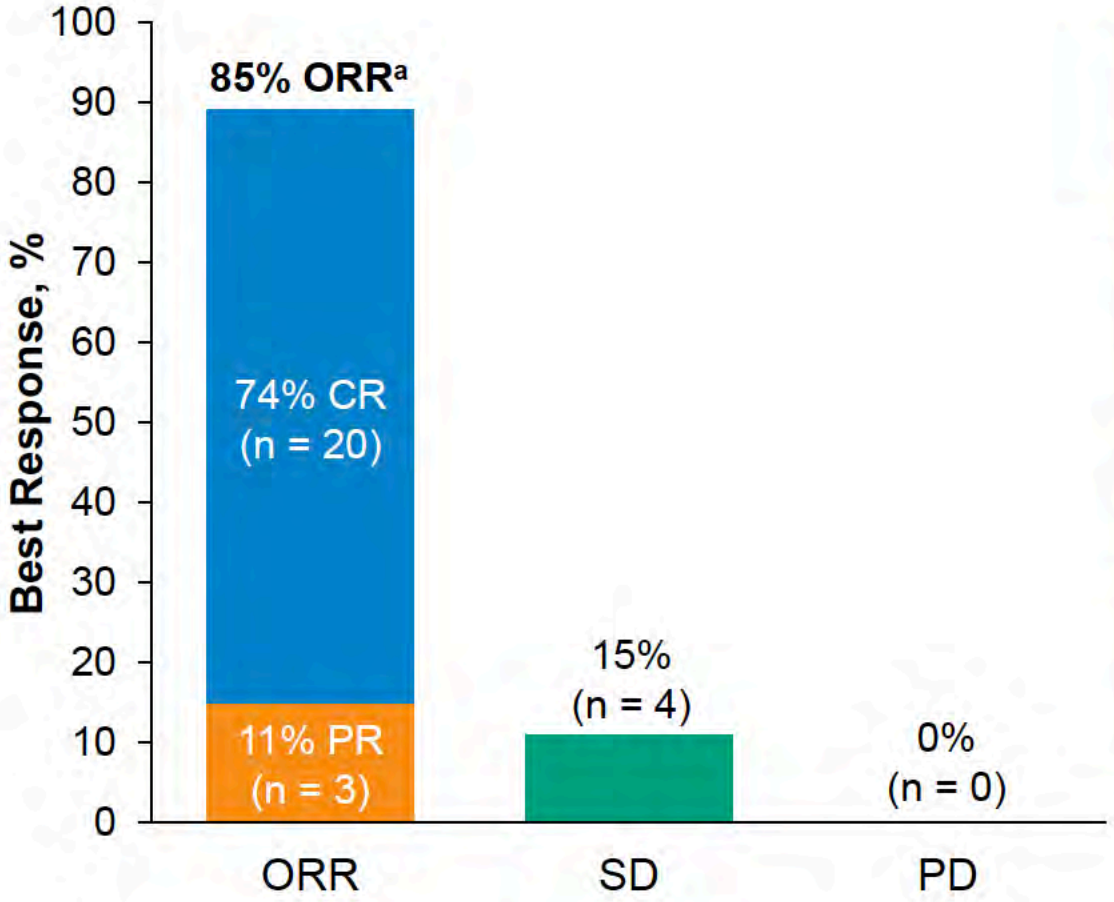
RTP RESEARCH TO PRACTICE

Interim Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) as First-Line Therapy in Patients (Pts) With High-Risk Large B Cell Lymphoma (LBCL)

Neelapu SS et al.

ASH 2020;Abstract 405.

ZUMA-12: Response Rates



	Response Evaluable N = 27[b]
Median follow-up (range), months	9.3 (0.9 – 18.0)
Patients with ≥ 6-month follow-up, n (%)	19 (70)
Patients with ongoing response as of data cutoff	19 (70)
Median time to response (range), months	
Initial objective response	1.0 (0.9 – 3.1)
CR	1.0 (0.9 – 6.4)
Patients converted from PR / SD to CR, n (%)	5 (19)
PR to CR	4 (15)
SD to CR	1 (4)

Neelapu SS et al. *ASH* 2020;Abstract 405.

Matching-Adjusted Indirect Comparison (MAIC) of Lisocabtagene Maraleucel (Liso-cel) vs Axicabtagene Ciloleucel (Axi-cel) and Tisagenlecleucel in Relapsed/Refractory (R/R) Large B-Cell Lymphoma (LBCL)

Maloney DG et al.

ASH 2020;Abstract 2116.

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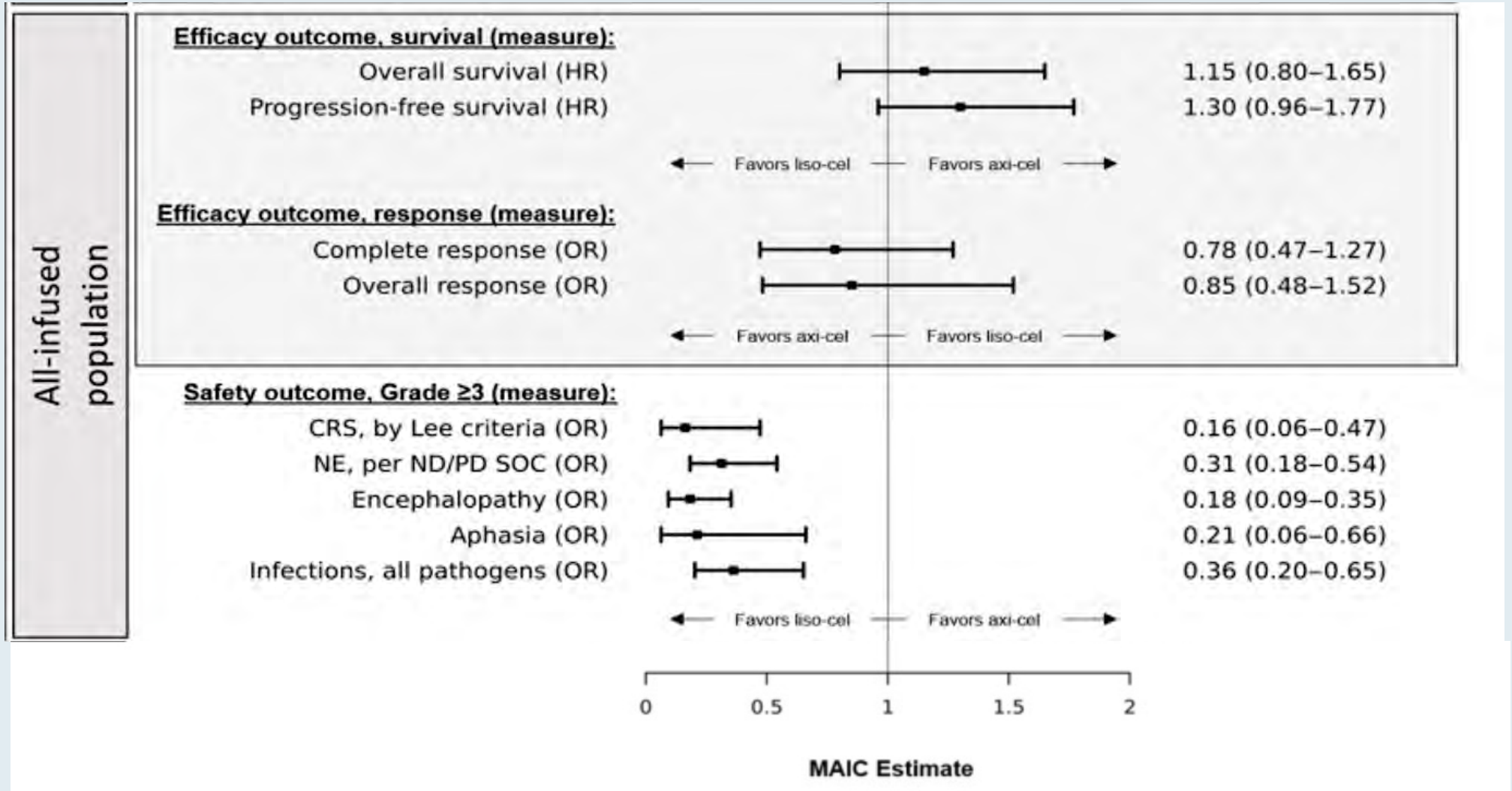
Matching-Adjusted Indirect Comparison of Liso-cel versus Axi-cel



Maloney DG et al. ASH 2020;Abstract 2116.

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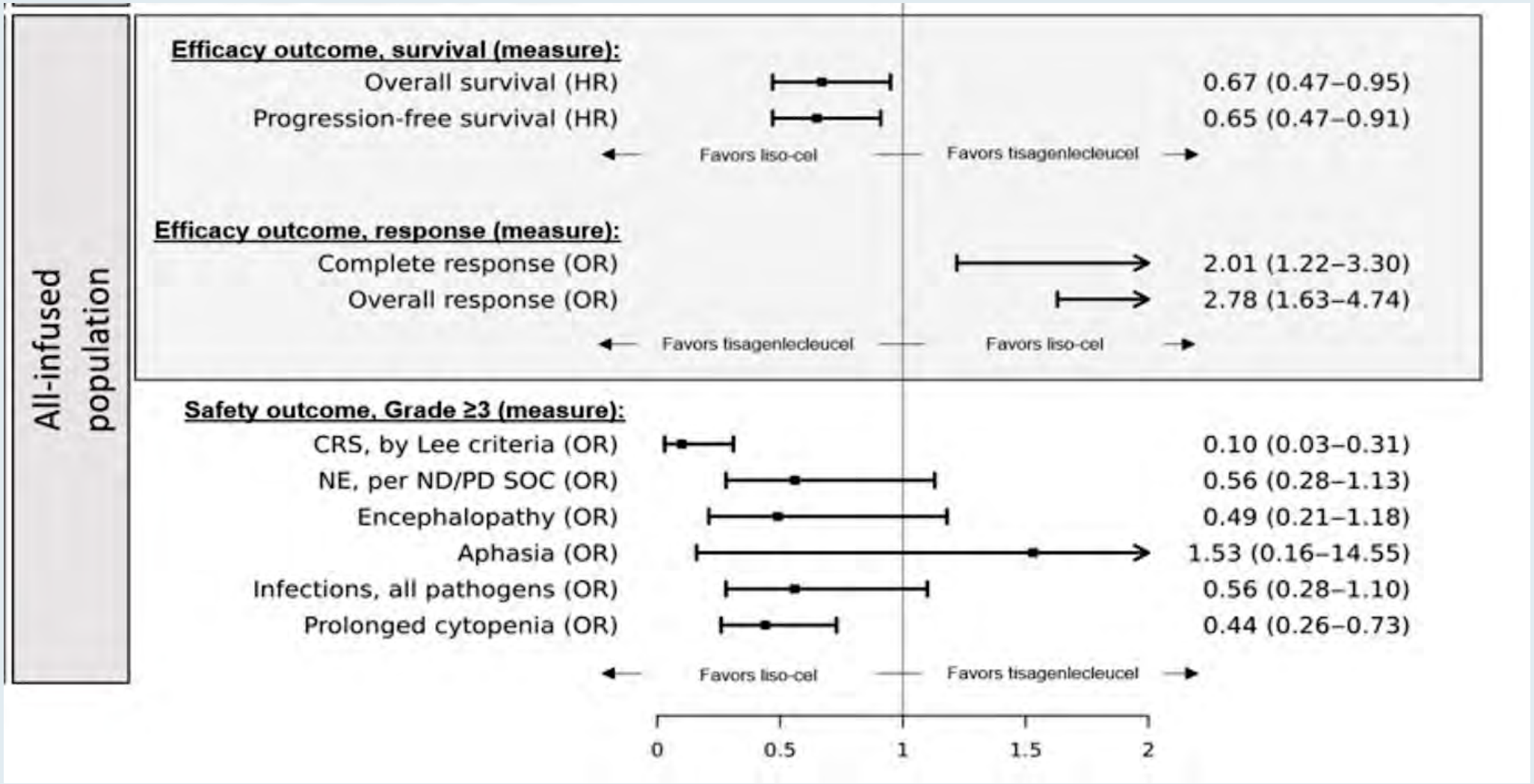

Maloney DG et al. ASH 2020;Abstract 2116.

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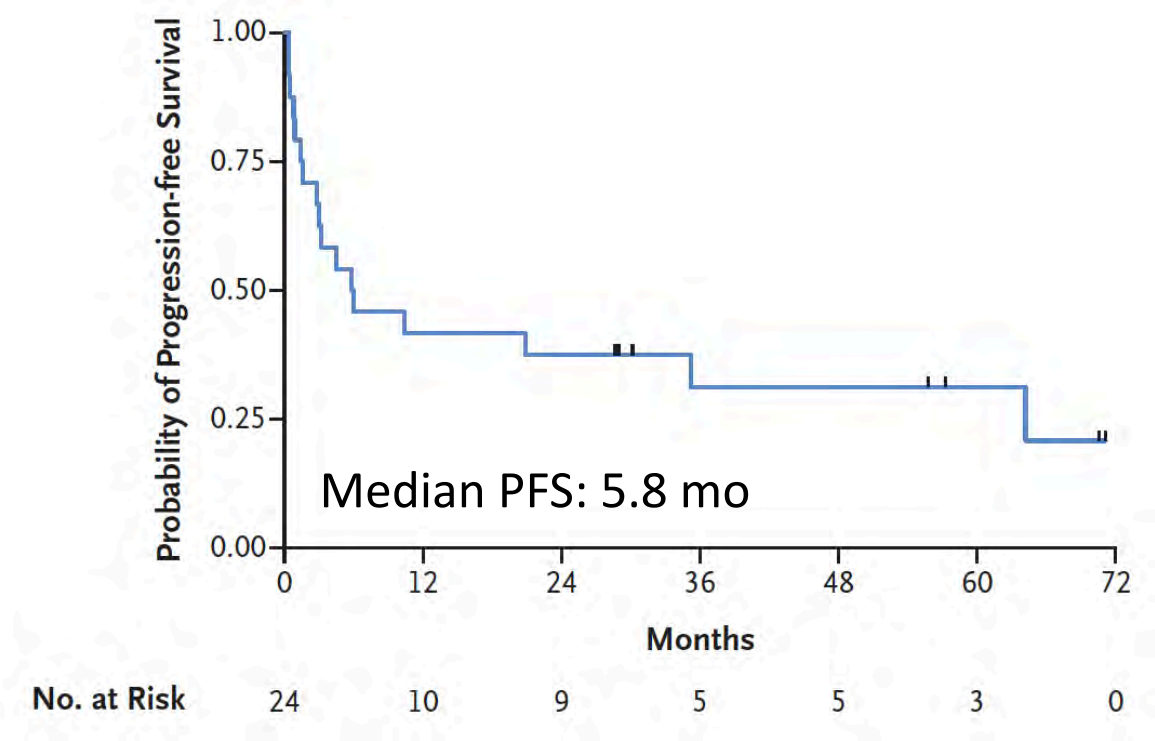
Five-Year Outcomes for Refractory B-Cell Lymphomas with CAR T-Cell Therapy Tisagenlecleucel

DLBCL



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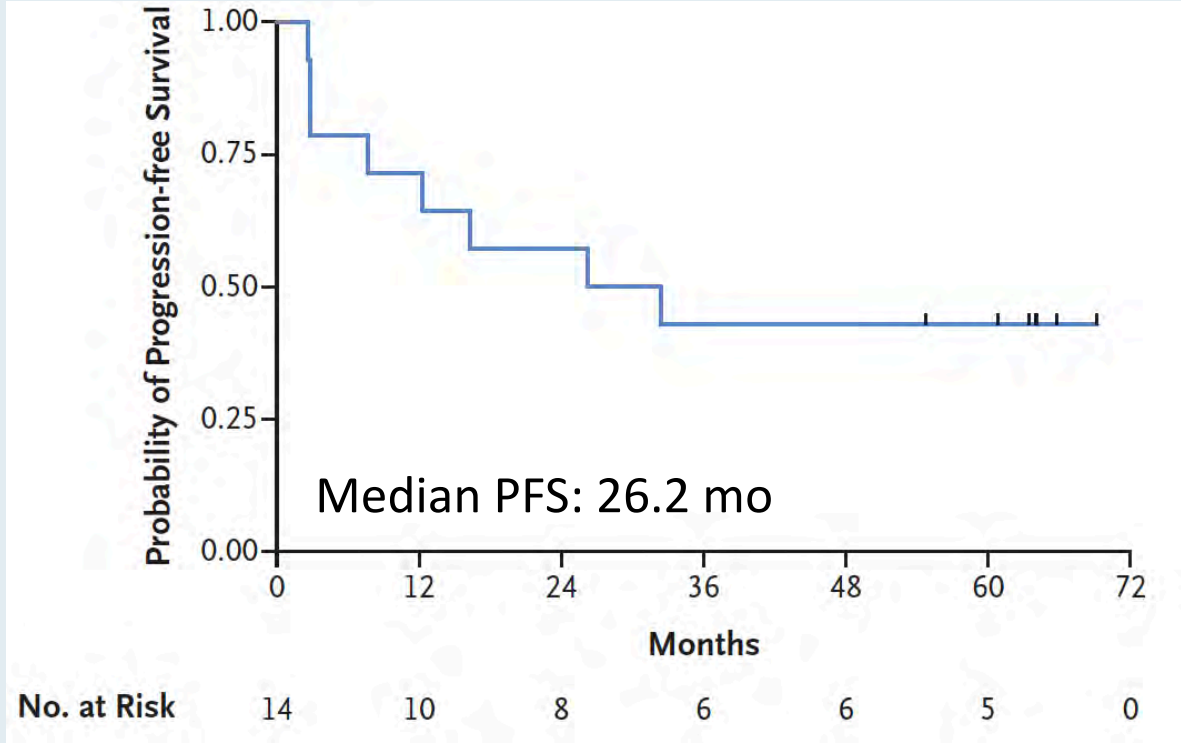

Chong EA et al. *N Engl J Med* 2021;384(7):673-4.

RTP RESEARCH TO PRACTICE

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Module 4: Follicular Lymphoma (FL)

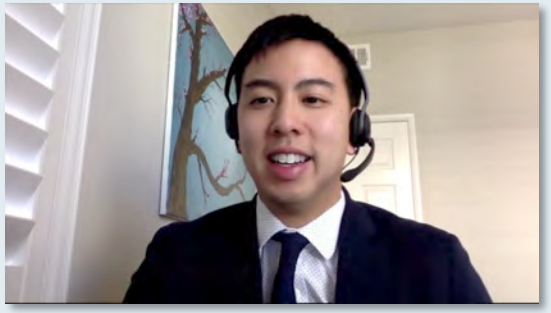
- Dr Blackmon: A 50-year-old man with newly diagnosed Stage III, Grade I-II FL
- Dr Blackmon: A 37-year-old woman with multiregimen-relapsed FL
- *Key Recent Publications and Presentations*

Module 5: Mantle Cell Lymphoma (MCL)

- Dr Blackmon: A 50-year-old man with relapsed blastoid MCL
- *Key Recent Publications and Presentations*

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Nguyen: A 26-year-old woman with classical Hodgkin lymphoma



Dr Anthony Nguyen

- Presents with enlarging neck mass, profound anemia, double-vision, headache
  - PET/CT: Diffuse cervical, intrathoracic, and intrabdominal adenopathy; hepatosplenomegaly and diffuse bone marrow involvement
  - MRI: 1.4-cm avidly enhancing pituitary mass (prolactinoma)
  - Biopsy of axillary node: Classical Hodgkin lymphoma
- AVD + brentuximab vedotin x 6
  - End of treatment PET: Deauville 2 and 3, except of anterior mediastinum → Biopsy: Thymus
- Currently, patient is pregnant and undergoing surveillance every 6 months

Questions

- For a younger patient, would you consider using BV plus AVD, or ABVD?
- Is there any data on the fertility rates for BV plus AVD versus ABVD?

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Key Recent Publications and Presentations

- Straus DJ et al. **Brentuximab Vedotin with Chemotherapy for Patients with Previously Untreated, Stage III/IV Classical Hodgkin Lymphoma: 5-Year Update of the ECHELON-1 Study.** ASH 2020;Abstract 2973.
- Kumar A et al. **Brentuximab Vedotin Combined with Chemotherapy in Patients with Newly Diagnosed Early-Stage, Unfavorable-Risk Hodgkin Lymphoma.** *J Clin Oncol* 2021;[Online ahead of print].
- Yasenchak CA et al. **Frontline Brentuximab Vedotin as Monotherapy or in Combination for Older Hodgkin Lymphoma Patients.** ASH 2020;Abstract 471.
- Kuruvilla J et al. **Pembrolizumab versus Brentuximab Vedotin in Relapsed or Refractory Classical Hodgkin Lymphoma (KEYNOTE-204): An Interim Analysis of a Multicentre, Randomised, Open-Label, Phase 3 Study.** *Lancet Oncol* 2021;22(4):512-24.
- Herrera AF et al. **Consolidation with Nivolumab and Brentuximab Vedotin After Autologous Hematopoietic Cell Transplantation in Patients with High-Risk Hodgkin Lymphoma.** ASH 2020;Abstract 472.

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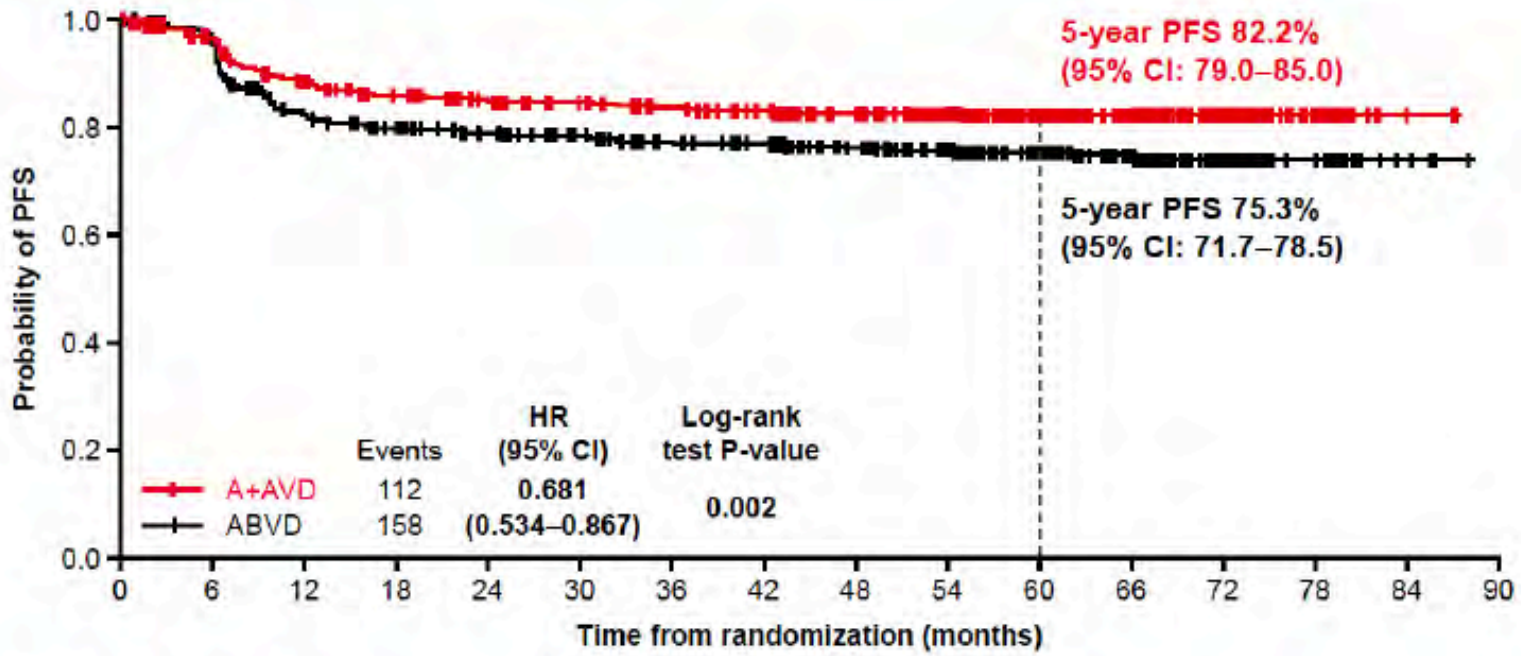
Brentuximab Vedotin with Chemotherapy for Patients with Previously Untreated, Stage III/IV Classical Hodgkin Lymphoma: 5-Year Update of the ECHELON-1 Study

Straus DJ et al.

ASH 2020;Abstract 2973.

ECHELON-1: PFS per investigator at 5 years' follow-up*



Number of patients at risk

A+AVD	664	620	562	535	518	505	492	474	446	414	333	201	102	38	2	0
ABVD	670	613	521	500	478	456	432	423	397	360	292	179	73	22	4	0

- As of the 5-year follow-up, the prespecified number of events required to trigger an OS analysis have not been reached.
- OS was a prespecified key secondary endpoint.

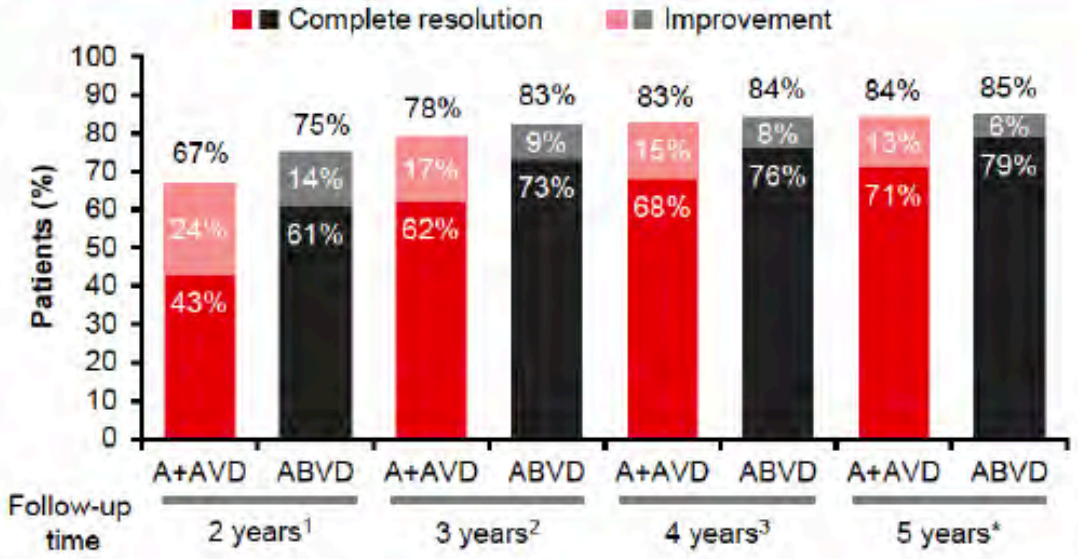
*September 14, 2020 data cut-off.

Straus DJ et al. ASH 2020;Abstract 2973.

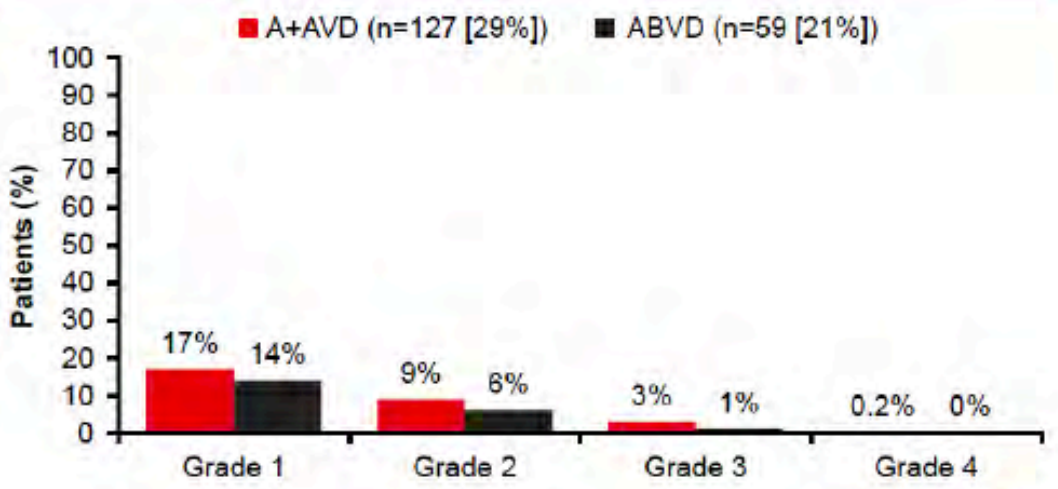
ECHELON-1: PN resolution and improvement

- At the primary analysis, 442 and 286 patients in A+AVD and ABVD arms, respectively, had experienced PN.

Patients with complete resolution or improvement of PN over time (%)*



Patients with ongoing PN by grade at last follow-up†



Resolution was defined as event outcome of "resolved" or "resolved with sequelae"; Improvement was defined as "improved by ≥1 grade from worst grade as of the latest assessment"; *Percentages rounded to nearest integer; †Median follow-up 236.9 weeks (range: 0–344); Assessment of ongoing PN with maximum severity of grade 3/4 was confounded in 12 of the 15 A+AVD patients by death prior to resolution (n=3), loss to follow-up (n=4), and withdrawal from study (n=5); Among the ABVD patients with grade 3 PN, two were lost to follow-up and two died prior to resolution of PN.

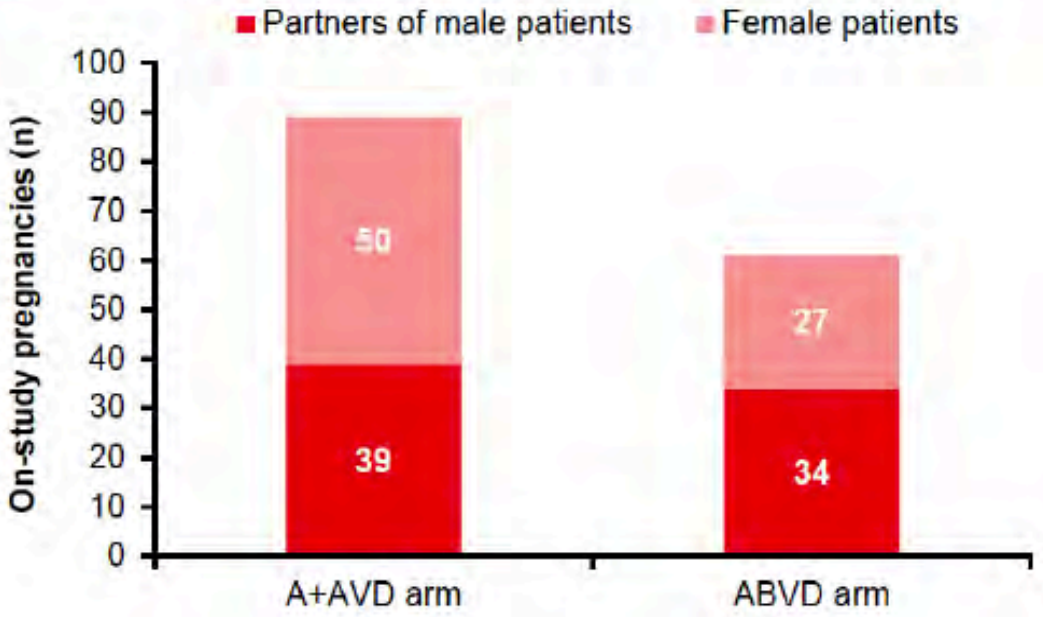
1. Connors JM, et al. N Engl J Med 2018;378:331–44;
2. Straus DJ, et al. Blood 2020;135:735–42;
3. Bartlett NL, et al. Blood 2019;134 (Suppl. 1):4026.

Straus DJ et al. ASH 2020;Abstract 2973.

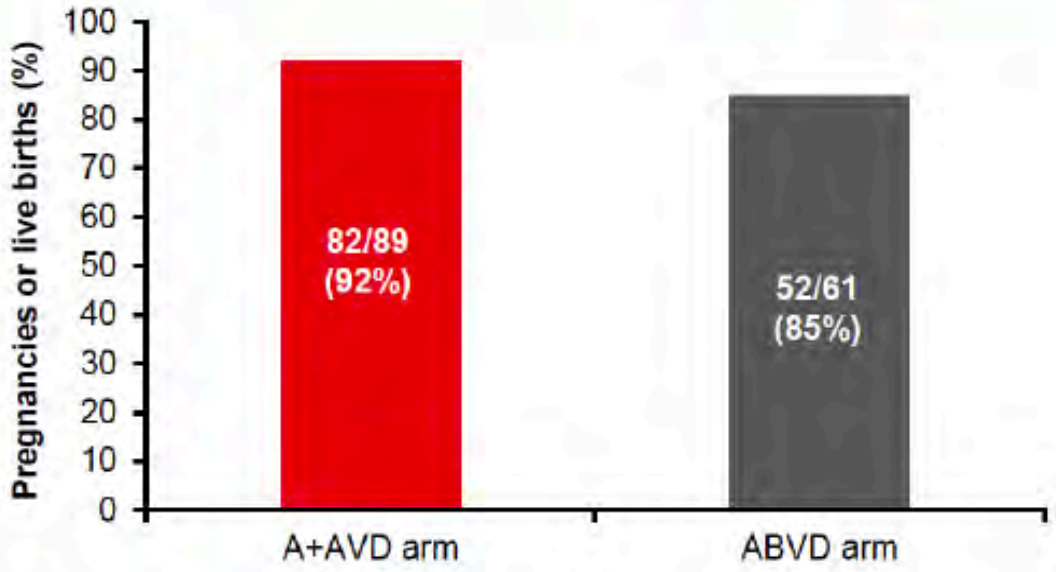
ECHELON-1: Pregnancies

- A total of 150 pregnancies were reported among study participants and their partners.

On-study pregnancies in patients or their partners



Ongoing pregnancies or live births



Straus DJ et al. ASH 2020;Abstract 2973.

original reports

Brentuximab Vedotin Combined With Chemotherapy in Patients With Newly Diagnosed Early-Stage, Unfavorable-Risk Hodgkin Lymphoma

Anita Kumar, MD[1]; Carla Casulo, MD[2]; Ranjana H. Advani, MD[3]; Elizabeth Budde, MD[4]; Paul M. Barr, MD[2]; Connie L. Batlevi, MD, PhD[1]; Philip Caron, MD[1]; Louis S. Constine, MD[2]; Savita V. Dandapani, MD[4]; Esther Drill, MD[1]; Pamela Drullinsky, MD[1]; Jonathan W. Friedberg, MD[2]; Clare Grieve, BA[1]; Audrey Hamilton, MD[1]; Paul A. Hamlin, MD[1]; Richard T. Hoppe, MD[3]; Steven M. Horwitz, MD[1]; Ashlee Joseph, BA[1]; Niloufer Khan, MD[1]; Leana Laraque, BA[1]; Matthew J. Matasar, MD[1]; Alison J. Moskowitz, MD[1]; Ariela Noy, MD[1]; Maria Lia Palomba, MD[1]; Heiko Schöder, MD[1]; David J. Straus, MD[1]; Shreya Vemuri, BA[1]; Joanna Yang, MD[5]; Anas Younes, MD[6]; Andrew D. Zelenetz, MD, PhD[1]; Joachim Yahalom, MD[1]; and Craig H. Moskowitz, MD[7]

J Clin Oncol 2021;[Online ahead of print].

Multicenter Pilot Study of BV + AVD with or without Consolidative Radiation Therapy for Early-Stage, Unfavorable-Risk HL

- Patients who achieved a negative end of therapy (EOT) PET-4 scan after 4 cycles of BV + AVD were studied with de-escalating radiation dose and field

Clinical endpoint	Cohort 1 30-Gy ISRT (n = 29)	Cohort 2 20-Gy ISRT (n = 29)	Cohort 3 30-Gy CVRT (n = 29)	Cohort 4 No radiation (n = 29)	All patients (n = 114)
EOT CR rate	27 (93%)	29 (100%)	27 (93%)	28 (97%)	111 (96%)
2-year PFS rate	93.1%	96.6%	89.7%	96.6%	94%

"BV + AVD x four cycles is a highly active and well-tolerated treatment program for ES, unfavorable-risk Hodgkin lymphoma, including bulky disease. The efficacy of BV + AVD supports the safe reduction or elimination of consolidative radiation among PET-4–negative patients."

Kumar A et al. *J Clin Oncol* 2021;[Online ahead of print].

Frontline Brentuximab Vedotin as Monotherapy or in Combination for Older Hodgkin Lymphoma Patients

Yasenchak CA et al.
ASH 2020;Abstract 471.

Best Responses per Investigator – Efficacy Evaluable Set

Efficacy Evaluable Set	Part A BV mono N=25	Part B BV+DTIC N=19	Part C BV+benda N=17	Part D BV+nivo N=19
ORR, n (%)	**23 (92)**	**19 (100)**	**17 (100)**	**18 (95)**
Best overall response				
Complete response	18 (72)	13 (68)	15 (88)	15 (79)
Partial response	5 (20)	6 (32)	2 (12)	3 (16)
Stable disease	2 (8)	0	0	1 (5)
Progressive disease	0	0	0	0
Duration of response, n	23	19	17	18
Median (min, max)	9.1 (2.8, 81.4+)	45.4 (0.0+, 67.3)	39.0 (0.0+, 56.8+)	NR (1.4+, 27.5+)

Patients who were not efficacy-evaluable included:

- Patients with no post-baseline response assessment due to deaths (n=3) and patient withdrawal (non-AE related, n=2) on or before the first scheduled post-baseline scan at Cycle 2
- One patient lost to follow-up
- One patient who was not an eligible cHL subtype (nodular lymphocyte-predominant HL) but still achieved partial response after receiving BV

Yasenchak CA et al. ASH 2020;Abstract 471.

Summary

Treatment options for older adults with cHL that may not be considered for conventional combination therapy:

- **BV monotherapy**
  - Active regimen in elderly population
    - Median 78 years of age
    - Median follow up of 54.5 months
    - ORR 92% (95% CI: 74%, 99%)
    - Median OS >6 years
  - Notable activity and tolerability in cHL patients unable to tolerate a multi-agent regimen
- **BV combination treatments**
  - BV+nivo and BV+DTIC
    - Promising activity (ORR 95%-100%)
    - Favorable safety profile in older adults with previously untreated cHL
  - BV+benda associated with multiple acute toxicities
  - Additional long-term follow-up is ongoing

Yasenchak CA et al. ASH 2020;Abstract 471.

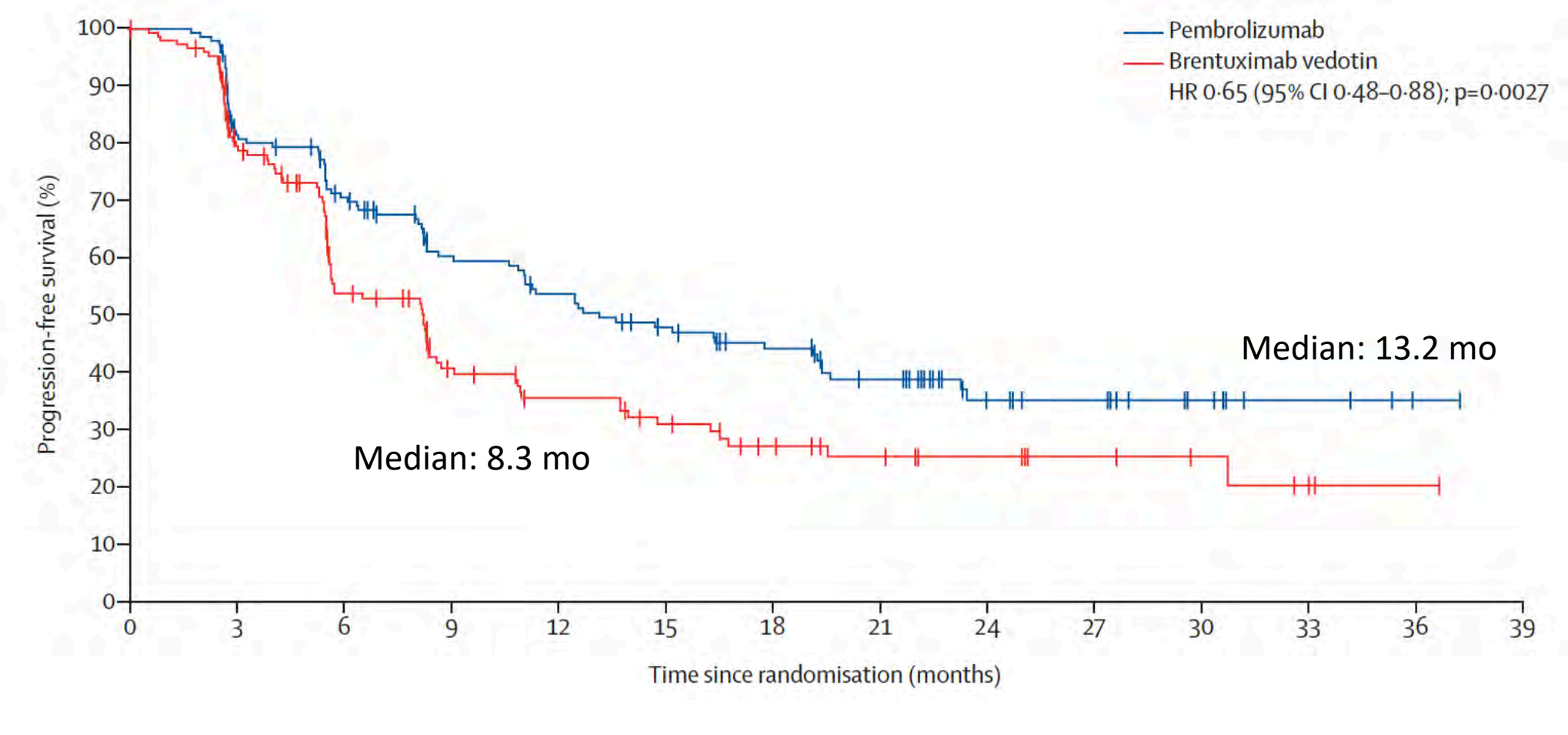
Articles

Lancet Oncol 2021;22(4):512-24.

Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study

*John Kuruvilla, Radhakrishnan Ramchandren, Armando Santoro, Ewa Paszkiewicz-Kozik, Robin Gasiorowski, Nathalie A Johnson, Laura Maria Fogliatto, Iara Goncalves, Jose S R de Oliveira, Valeria Buccheri, Guilherme F Perini, Neta Goldschmidt, Iryna Kriachok, Michael Dickinson, Mieczyslaw Komarnicki, Andrew McDonald, Muhit Ozcan, Naohiro Sekiguchi, Ying Zhu, Akash Nahar, Patricia Marinello, Pier Luigi Zinzani, on behalf of the KEYNOTE-204 investigators**

KEYNOTE-204: PFS Primary Endpoint



Kuruvilla J et al. *Lancet Oncol* 2021;22(4):512-24.

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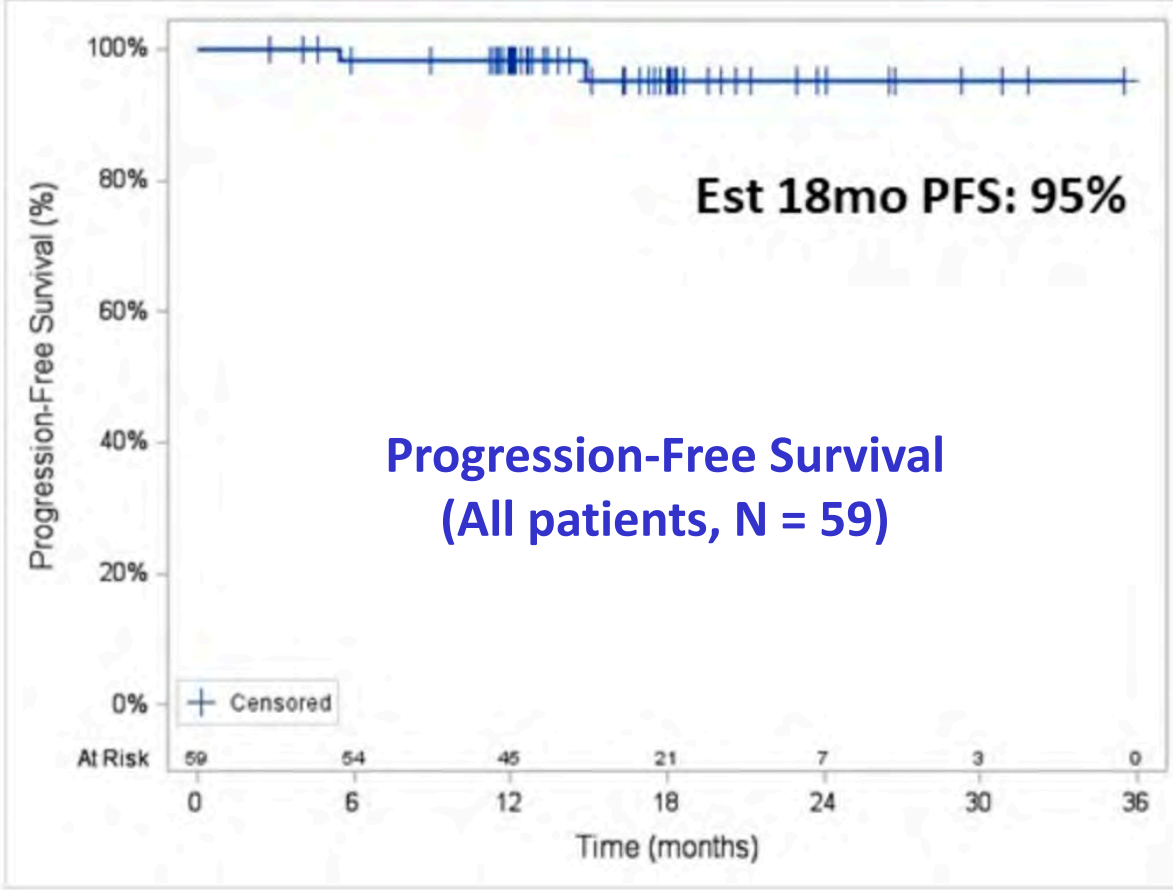
Consolidation with Nivolumab and Brentuximab Vedotin After Autologous Hematopoietic Cell Transplantation in Patients with High-Risk Hodgkin Lymphoma

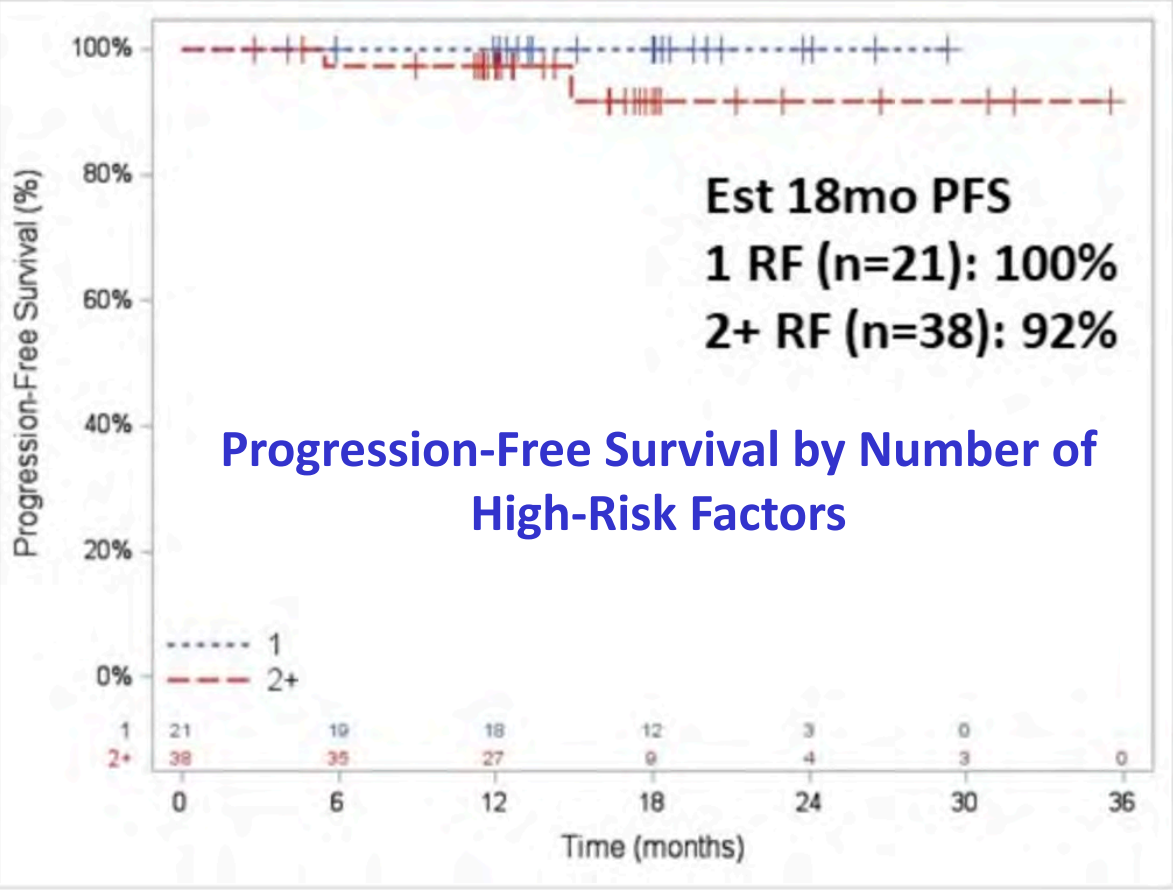
Herrera AF et al.

ASH 2020;Abstract 472.

Consolidation with Nivolumab and Brentuximab Vedotin After ASCT: Progression-Free Survival



Progression-Free Survival (All patients, N = 59)



Progression-Free Survival by Number of High-Risk Factors

Herrera AF et al. ASH 2020;Abstract 472.

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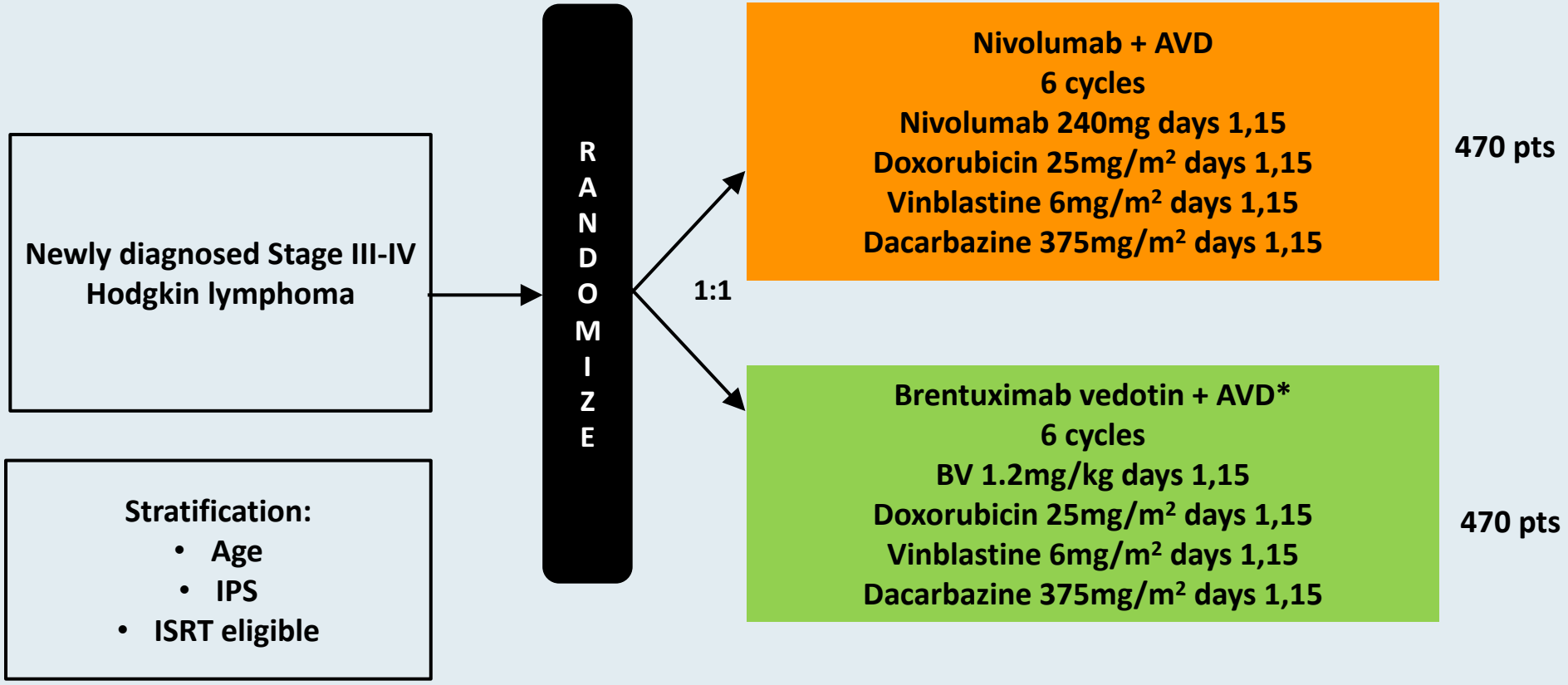
Summary Conclusions

- BV+Nivo consolidation for 8 cycles after AHCT in patients with high-risk R/R HL is a promising approach
  - 92% 19-month PFS in all pts
  - 19-month PFS was 96% in pts with 2 risk factors, 83% with 3+ risk factors
  - 51% with prior BV exposure, 42% with prior anti-PD1 exposure
- BV+Nivo consolidation was tolerable, but associated with more irAE than in pre-AHCT setting (27% requiring steroids)
  - Neuropathy (51%) and neutropenia (42%) were common, no febrile neutropenia
- Based on these results, BV+Nivo consolidation after AHCT should be evaluated further

Herrera AF et al. ASH 2020;Abstract 472.

SWOG-1826: Ongoing Phase III Trial of Nivolumab or Brentuximab Vedotin with Combination Chemotherapy for Newly Diagnosed Stage III-IV Classical HL



* **G-CSF is mandatory in BV-AVD arm**, optional in N-AVD

Courtesy of Craig Moskowitz, MD.

Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)

- Dr Nguyen: A 75-year-old man with Stage IV gastric DLBCL
- *Key Recent Publications and Presentations*

Module 2: Hodgkin Lymphoma

- Dr Nguyen: A 26-year-old woman with classical Hodgkin lymphoma
- *Key Recent Publications and Presentations*

Module 3: Chronic Lymphocytic Leukemia (CLL)

- Dr Morganstein: A 75-year-old man with relapsed CLL
- Dr Chen: A 66-year-old woman with newly diagnosed CLL receives acalabrutinib
- *Key Recent Publications and Presentations*

Module 4: Follicular Lymphoma (FL)

- Dr Blackmon: A 50-year-old man with newly diagnosed Stage III, Grade I-II FL
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Module 5: Mantle Cell Lymphoma (MCL)

- Dr Blackmon: A 50-year-old man with relapsed blastoid MCL
- *Key Recent Publications and Presentations*

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Morganstein: A 75-year-old man with relapsed CLL

Dr Neil Morganstein

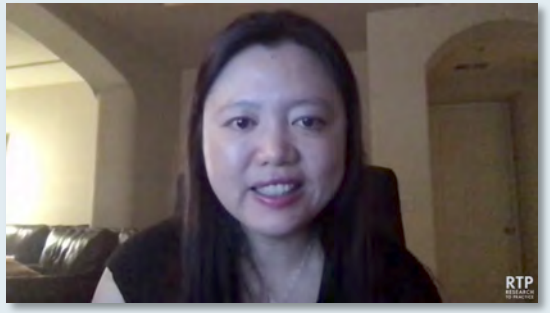
- 2009: Diagnosed with CLL, s/p FR chemotherapy with response x years
- Bendamustine/rituximab, with discontinuation of rituximab due to severe, persistent reactions
- Ibrutinib, with amazing response x 2 years
  - Atrial fibrillation with continued treatment; severe, debilitating shingles → ibrutinib discontinuation
- Off treatment x 6 months → acalabrutinib
  - Severe anemia requiring transfusions (no evidence of hemolysis)
  - Platelets drop, WBC >400K → hospitalized
- Venetoclax, with TLS despite rasburicase prophylaxis; renal failure not requiring dialysis
  - Venetoclax titrated up to 400 mg → severe, symptomatic neutropenia
  - Venetoclax held, dose reduced to 200 mg → lymphocytes rose → dose increased to 300 mg

Question

- Looking forward to when this patient has disease progression, what treatment would you recommend next for him given his age?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Chen: A 66-year-old woman with newly diagnosed CLL receives acalabrutinib



Dr Gigi Chen

- March 2012: Diagnosed with CLL → 1 cycle of FCR → switched to BR x 5 cycles due to FCR side effects
- 2020: Patient presents with new lymphadenopathy in neck and is experiencing night sweats
  - PET/CT: Recurrent CLL with hypermetabolic lymphadenopathy seen in the neck, chest, abdomen, and pelvis
  - Bone marrow biopsy: CLL/FL
  - FISH: Trisomy 12
- Acalabrutinib therapy initiated

Questions

- How do you select the best treatment for a patient such as this with higher-risk CLL? If this patient had presented today instead of in 2012, would the best initial treatment still be FCR?
- What is the role of MRD testing?

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Key Recent Publications and Presentations

- Brown JR et al. **Efficacy and Safety of Zanubrutinib in Patients with Treatment-Naïve (TN) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) with del(17p): Follow-Up Results from Arm C of the SEQUOIA (BGB-3111-304) Trial.** ASH 2020;Abstract 1306.
- Mato AR et al. **Pirtobrutinib in Relapsed or Refractory B-Cell Malignancies (BRUIN): A Phase 1/2 Study**. *Lancet* 2021;397(10277):892-901.
- Al-Sawaf O et al**. Venetoclax plus Obinutuzumab versus Chlorambucil plus Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukaemia (CLL14): Follow-Up Results from a Multicentre, Open-Label, Randomised, Phase 3 Trial.** *Lancet Oncol* 2020;21(9):1188-200.
- Kater AP et al. **Five-Year Analysis of Murano Study Demonstrates Enduring Undetectable Minimal Residual Disease (uMRD) in a Subset of Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Patients (Pts) Following Fixed-Duration Venetoclax-Rituximab (VenR) Therapy (Tx).** ASH 2020;Abstract 125.
- Weirda WG et al. **Ibrutinib (Ibr) plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): 1-Year Disease-Free Survival (DFS) Results from the MRD Cohort of the Phase 2 CAPTIVATE Study Trial.** ASH 2020;Abstract 123.

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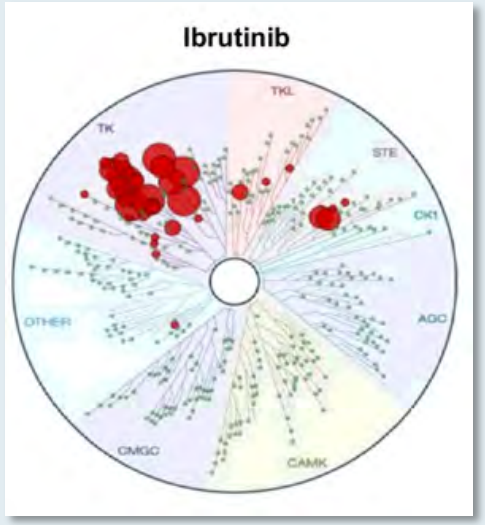
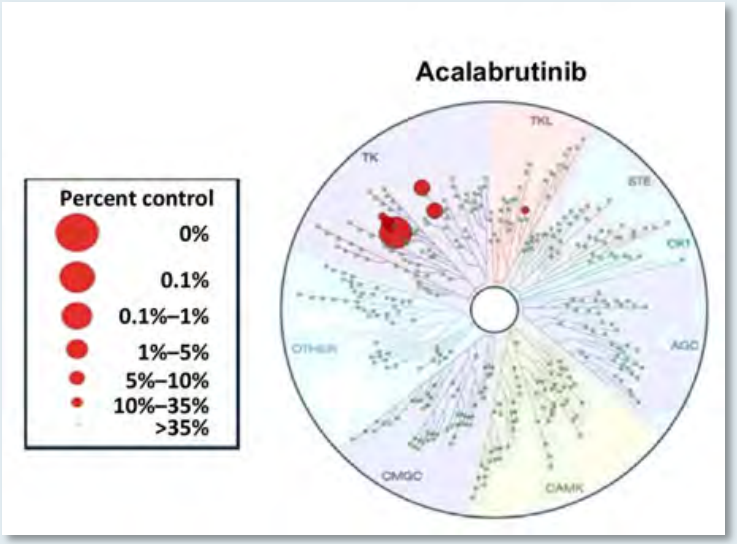
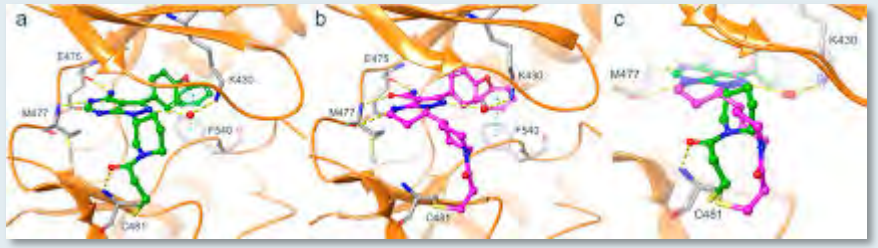
Overview of BTK Inhibitors in CLL

Irreversible



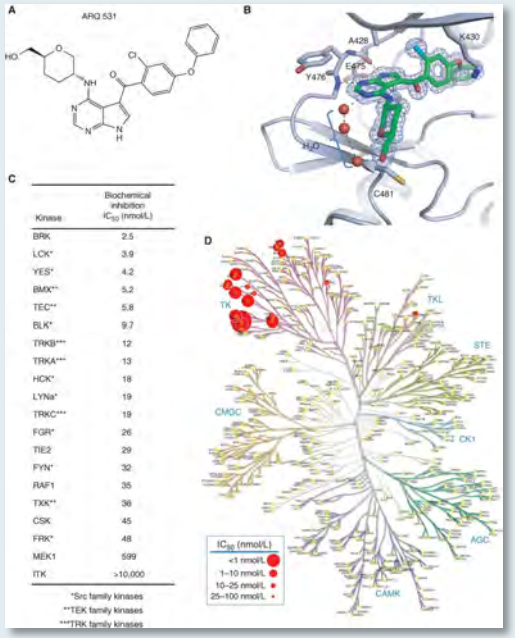


Zanubrutinib

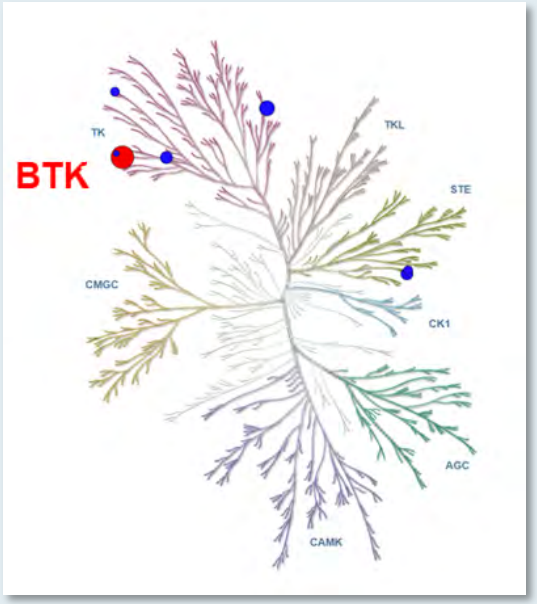


Reversible

ARQ-531 (MK-1026)



Pirtobrutinib (LOXO-305)



Courtesy of Matthew S Davids, MD, MMSc

RTP RESEARCH TO PRACTICE

ELEVATE-RR Trial Meets Primary and Secondary Endpoints

Press Release: January 25, 2021

Positive high-level results from the ELEVATE-RR Phase III trial showed that acalabrutinib met the primary endpoint demonstrating non-inferior progression-free survival (PFS) for adults with previously treated, high-risk chronic lymphocytic leukemia (CLL) compared to ibrutinib.

The trial also met a key secondary endpoint for safety, showing patients treated with acalabrutinib had statistically significantly lower incidence of atrial fibrillation compared to patients treated with ibrutinib. Further hierarchical testing revealed no difference for Grade 3 or higher infections or Richter's transformation. There was a descriptive trend for numerically favorable overall survival. Overall, the safety and tolerability of acalabrutinib were consistent with the profile seen in the broader acalabrutinib clinical development program.

ELEVATE-RR is the first Phase III trial to compare two Bruton's tyrosine kinase (BTK) inhibitors in patients with CLL, the most common type of leukemia in adults. Patients diagnosed with high-risk CLL may experience rapid worsening of their disease, requiring treatment.

The ELEVATE-RR data will be presented at a forthcoming medical meeting and shared with health authorities.

https://www.astrazeneca.com/media-centre/press-releases/2021/calquence-met-primary-endpoint-against-ibrutinib.html

First Results of a Head-to-Head Trial of Acalabrutinib versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia

Byrd JC et al.
ASCO 2021;Abstract 7500.

Monday, June 7, 11:30 AM - 2:30 PM EDT

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Zanubrutinib Demonstrates Superior ORR and Reduced Rates of Atrial Fibrillation or Flutter in Head-to-Head Trial Against Ibrutinib for CLL

Press Release: April 28, 2021

"Positive results from a planned interim analysis of the Phase 3 ALPINE trial comparing zanubrutinib against ibrutinib in adults with relapsed or refractory CLL or SLL.

Zanubrutinib met the primary endpoint of the trial, demonstrating non-inferiority in objective response rate (ORR) by both investigator and independent review committee (IRC) assessments ($p < 0.0001$). The interim analysis from this fully-enrolled, ongoing trial is based on 415 of 652 patients followed for a minimum of 12 months.

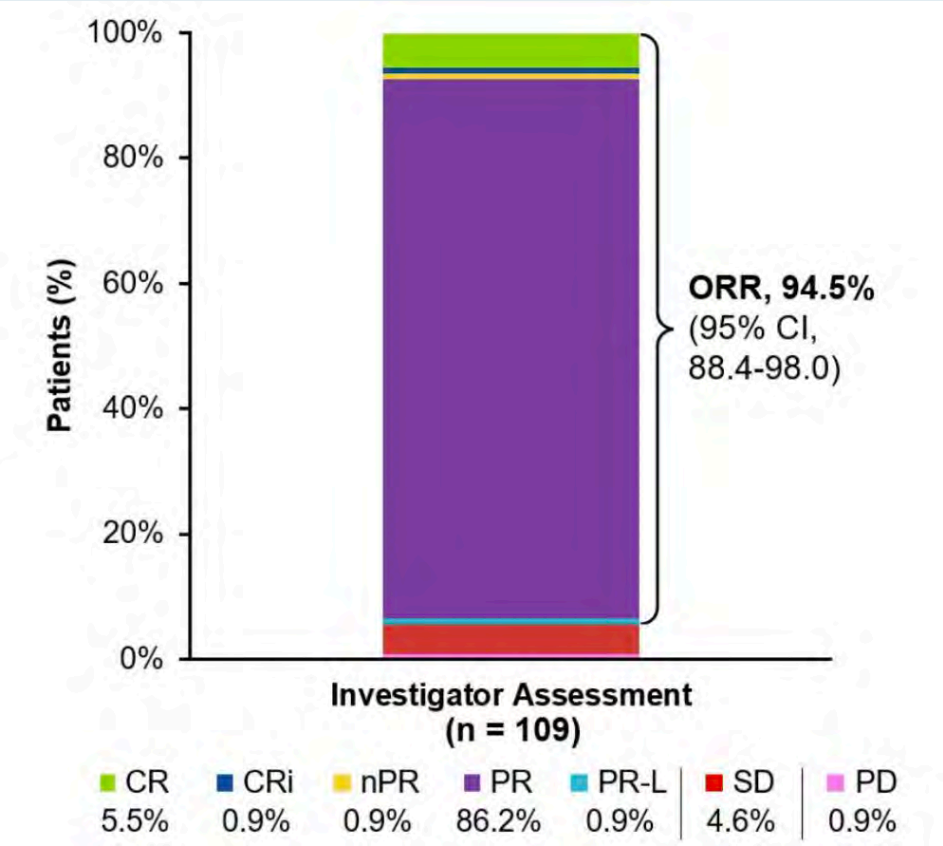
The trial also met a pre-specified secondary endpoint related to safety. Compared to ibrutinib, zanubrutinib demonstrated a statistically significant lower risk of atrial fibrillation or flutter…"

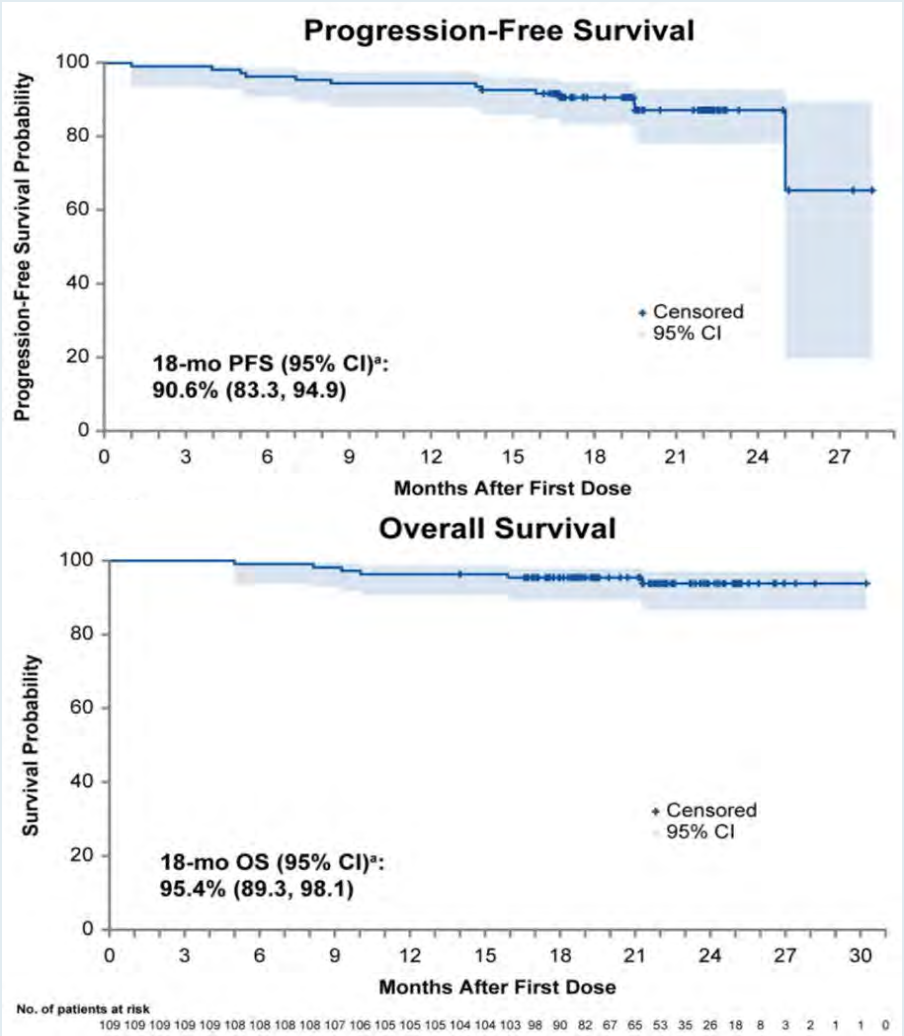
https://www.businesswire.com/news/home/20210428005360/en/BRUKINSA%C2%AE-Zanubrutinib-Demonstrates-Superior-Objective-Response-Rate-by-Investigator-Assessment-and-Reduced-Rates-of-Atrial-Fibrillation-or-Flutter-at-Interim-Analysis-in-Head-to-Head-Trial-Against-Ibrutinib-in-Chronic-Lymphocytic-Leukemia

RTP RESEARCH TO PRACTICE

Results From Arm C of the Phase 3 SEQUOIA Trial of Zanubrutinib for Patients With TN del(17p) CLL/SLL: Efficacy

Best Overall Response





Median follow-up: 21.9 months (range, 5.0-30.2)

.

Brown JR, et al. ASH 2020. Abstract 1306.

Courtesy of Matthew S Davids, MD, MMSc

RTP RESEARCH TO PRACTICE

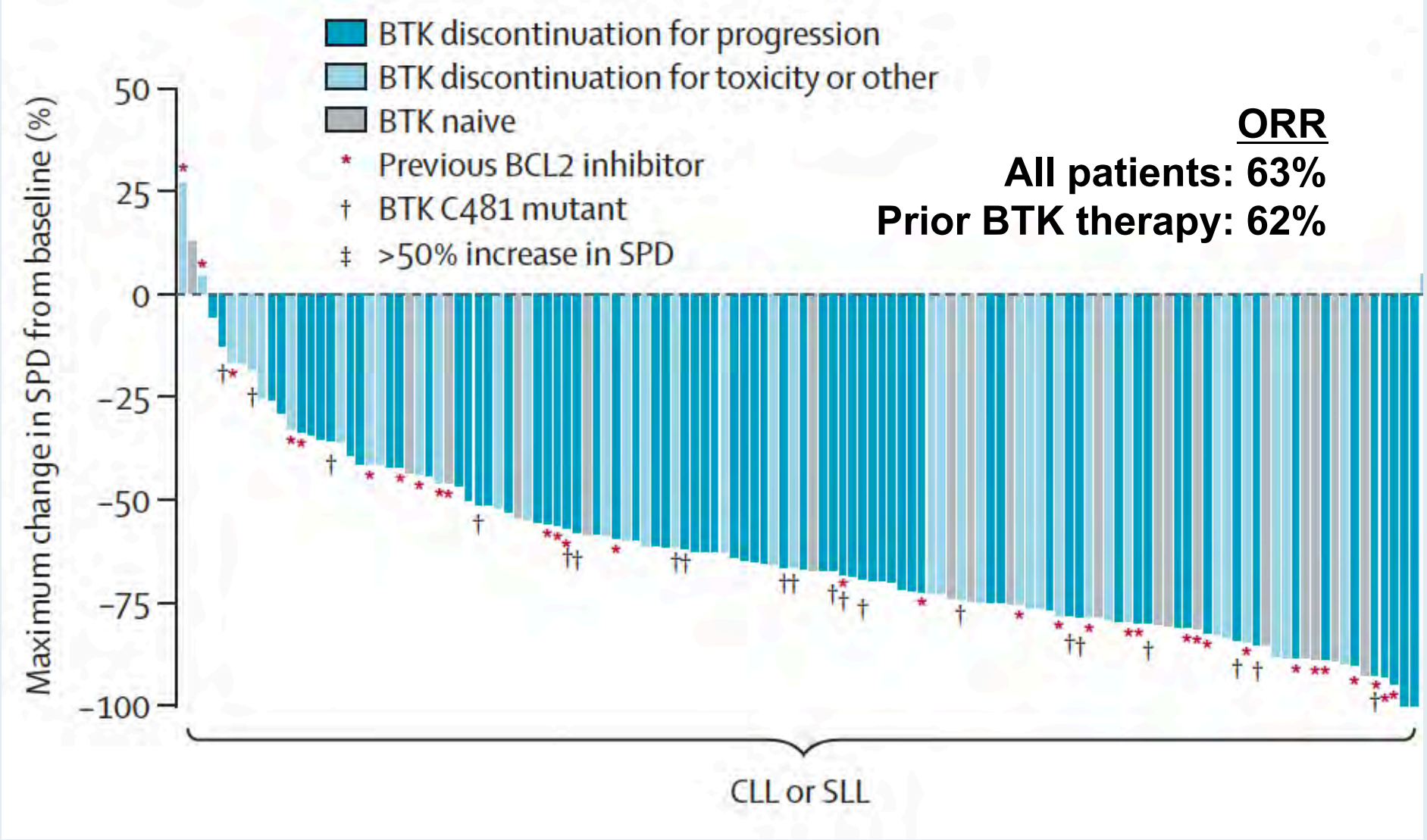
Articles

Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study

Anthony R Mato, Nirav N Shah, Wojciech Jurczak, Chan Y Cheah, John M Pagel, Jennifer A Woyach, Bita Fakhri, Toby A Eyre, Nicole Lamanna, Manish R Patel, Alvaro Alencar, Ewa Lech-Maranda, William G Wierda, Catherine C Coombs, James N Gerson, Paolo Ghia, Steven Le Gouill, David John Lewis, Suchitra Sundaram, Jonathon B Cohen, Ian W Flinn, Constantine S Tam, Minal A Barve, Bryone Kuss, Justin Taylor, Omar Abdel-Wahab, Stephen J Schuster, M Lia Palomba, Katharine L Lewis, Lindsey E Roeker, Matthew S Davids, Xuan Ni Tan, Timothy S Fenske, Johan Wallin, Donald E Tsai, Nora C Ku, Edward Zhu, Jessica Chen, Ming Yin, Binoj Nair, Kevin Ebata, Narasimha Marella, Jennifer R Brown, Michael Wang

Lancet 2021;397(10277):892-901.

BRUIN: Change in Tumor Burden from Baseline with Pirtobrutinib (LOXO-305) in Evaluable Patients with CLL or SLL



Mato AR et al. *Lancet* 2021;397(10277):892-901.

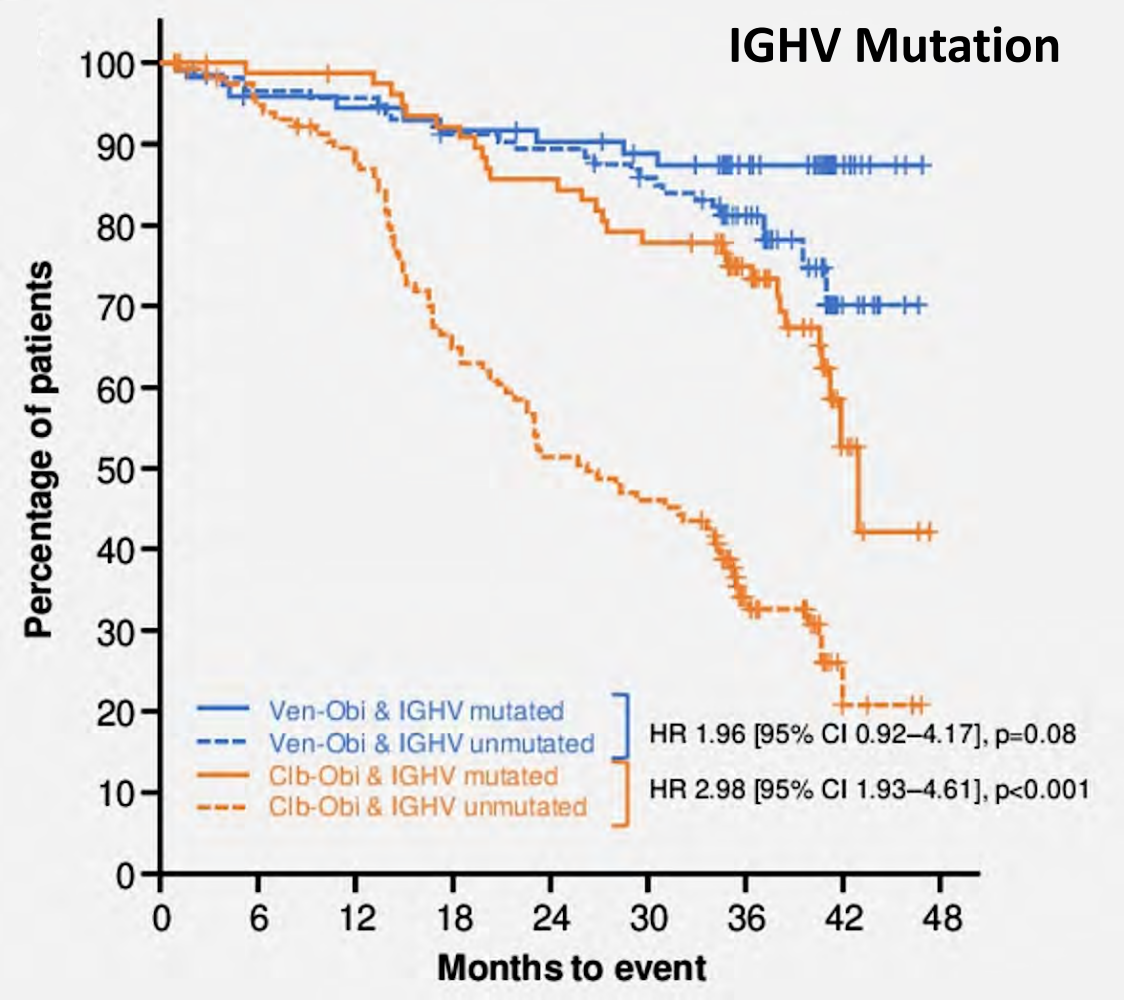
Articles

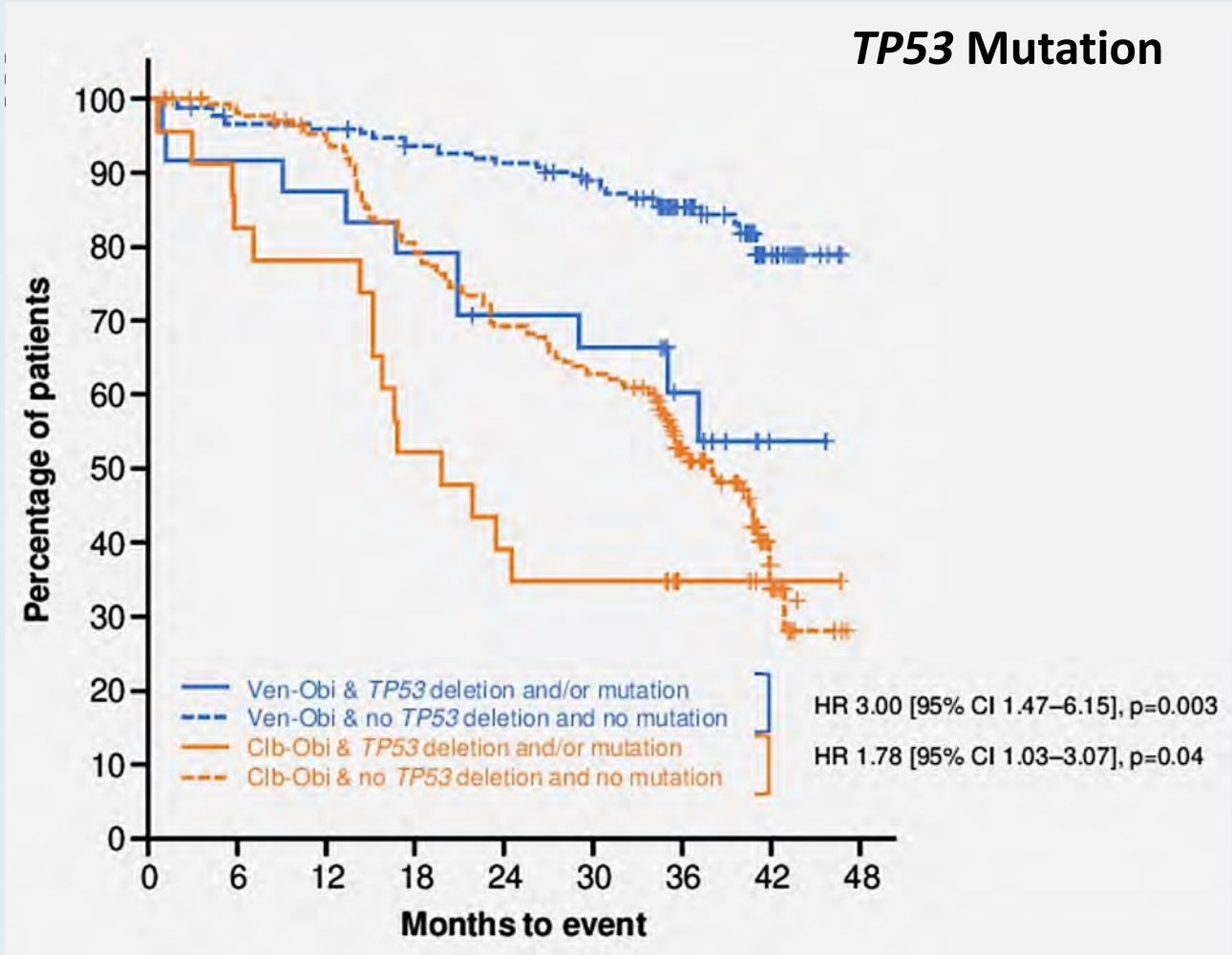
Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial

Othman Al-Sawaf, Can Zhang, Maneesh Tandon, Arijit Sinha, Anna-Maria Fink, Sandra Robrecht, Olga Samoylova, Anna M Liberati, Javier Pinilla-Ibarz, Stephen Opat, Liliya Sivcheva, Katell Le Dû, Laura M Fogliatto, Carsten U Niemann, Robert Weinkove, Sue Robinson, Thomas J Kipps, Eugen Tausch, William Schary, Matthias Ritgen, Clemens-Martin Wendtner, Karl-Anton Kreuzer, Barbara Eichhorst, Stephan Stilgenbauer, Michael Hallek, Kirsten Fischer**

Lancet Oncol 2020;21(9):1188-200.

CLL14: PFS by IGHV and TP53 Mutation Status

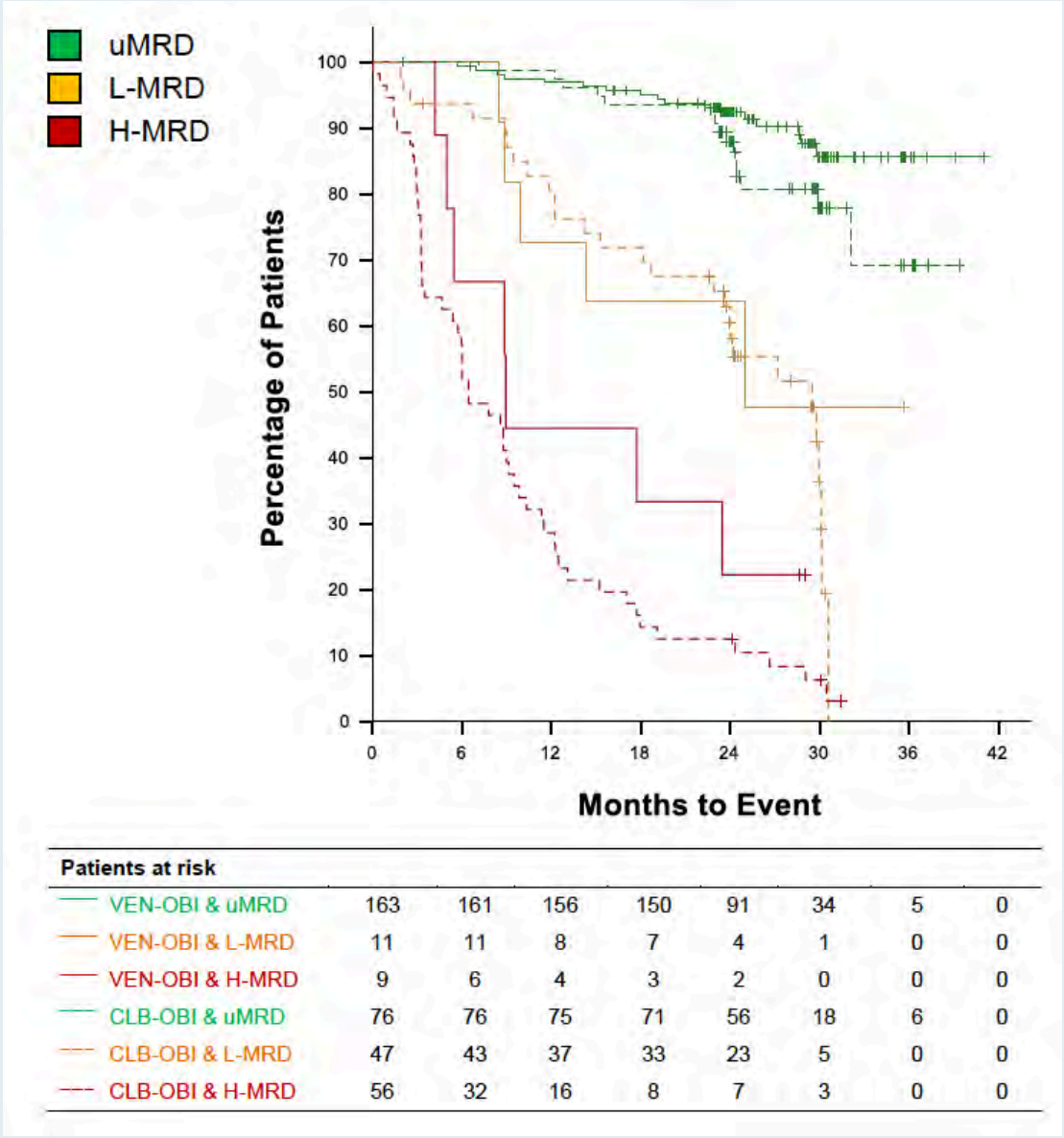




Al-Sawaf O et al. *Lancet Oncol* 2020;21(9):1188-200.

RTP RESEARCH TO PRACTICE

CLL14: Landmark Analysis from End of Therapy PFS by MRD Group



Patients at risk								
VEN-OBI & uMRD	163	161	156	150	91	34	5	0
VEN-OBI & L-MRD	11	11	8	7	4	1	0	0
VEN-OBI & H-MRD	9	6	4	3	2	0	0	0
CLB-OBI & uMRD	76	76	75	71	56	18	6	0
CLB-OBI & L-MRD	47	43	37	33	23	5	0	0
CLB-OBI & H-MRD	56	32	16	8	7	3	0	0

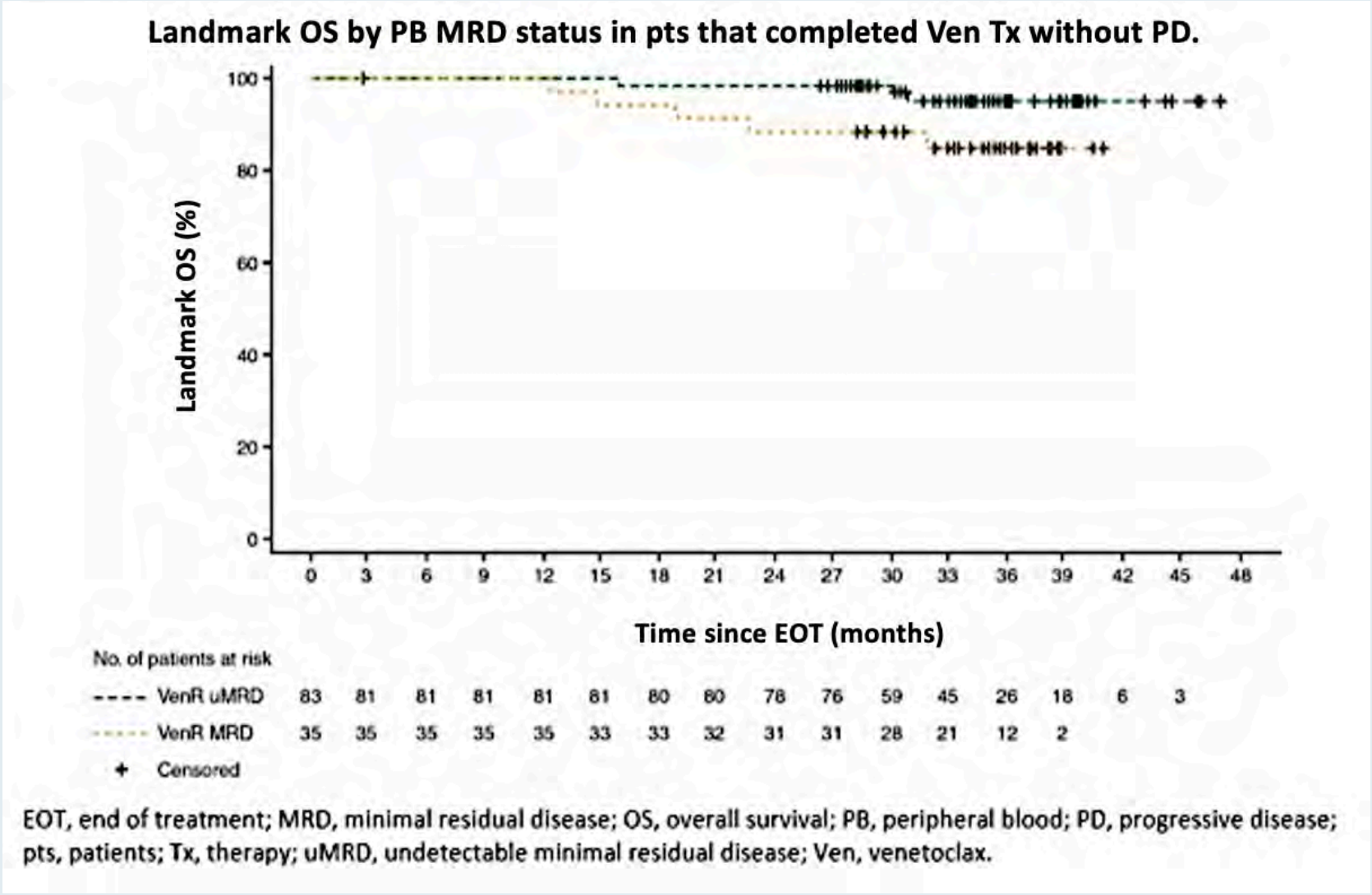
Al-Sawaf O et al. *Lancet Oncol* 2020;21(9):1188-200.

Five-Year Analysis of Murano Study Demonstrates Enduring Undetectable Minimal Residual Disease (uMRD) in a Subset of Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Patients (Pts) Following Fixed-Duration Venetoclax-Rituximab (VenR) Therapy (Tx)

Kater AP et al.

ASH 2020;Abstract 125.

MURANO: 5-Year Follow-Up of Venetoclax/Rituximab (Ven/R) in R/R CLL



EOT, end of treatment; MRD, minimal residual disease; OS, overall survival; PB, peripheral blood; PD, progressive disease; pts, patients; Tx, therapy; uMRD, undetectable minimal residual disease; Ven, venetoclax.

- Median PFS for VenR: 53.6 mo
- 5 year OS rate: 82%
- Of 83 patients with uMRD at end of therapy, 38.5% remained uMRD
- 25 months was the average time from MRD conversion to requirement for therapy

Kater AP et al. ASH 2020;Abstract 125.

RTP RESEARCH TO PRACTICE

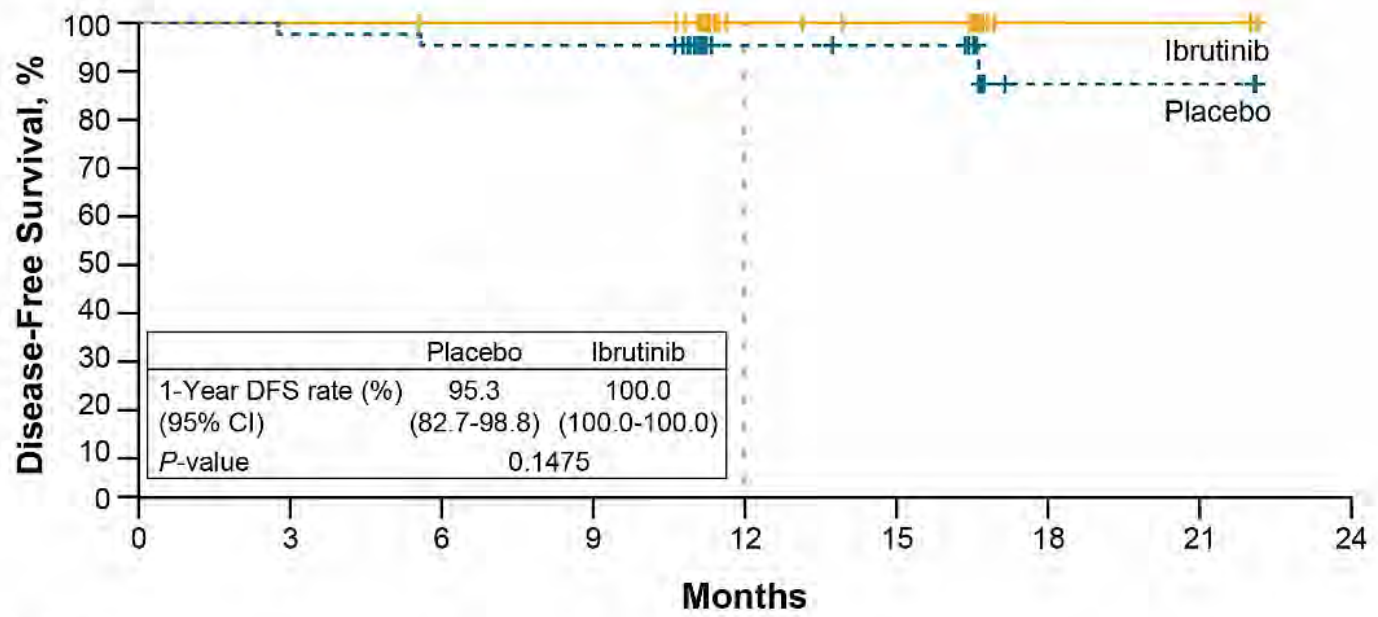
Ibrutinib (Ibr) plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): 1-Year Disease-Free Survival (DFS) Results from the MRD Cohort of the Phase 2 CAPTIVATE Study Trial

Wierda WG et al.

ASH 2020;Abstract 123.

CAPTIVATE Phase II Trial of First-Line Ibrutinib with Venetoclax for CLL: 1-Year DFS Results from the MRD Cohort

Figure. DFS by Randomized Treatment Arm in Confirmed uMRD Group[a]



Patients at Risk

Placebo	43	42	41	41	22	21	3	3	0
Ibrutinib	43	43	42	42	25	23	5	5	0

[a]The 3 DFS events in placebo arm were disease progression in 2 patients and MRD relapse in 1 patient.

<u>30 month PFS Rate:</u>

Confirmed uMRD:

- 95.3% placebo
- 100% ibrutinib

Without confirmed uMRD:

- 95.2% ibrutinib
- 96.7% ibr/ven

AEs were primarily grade 1/2 and mostly occurred in early cycles of Ibr + Ven, with modest differences by randomized treatment arm.

Wierda WG et al. ASH 2020;Abstract 123.

RTP RESEARCH TO PRACTICE

Fixed-Duration (FD) First-Line Treatment (tx) with Ibrutinib (I) plus Venetoclax (V) for Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): Primary Analysis of the FD Cohort of the Phase 2 Captivate Study

Ghia P et al.

ASCO 2021;Abstract 7501.

Monday, June 7, 11:30 AM - 2:30 PM EDT

Agenda

Module 1: Diffuse Large B-Cell Lymphoma (DLBCL)

- Dr Nguyen: A 75-year-old man with Stage IV gastric DLBCL
- *Key Recent Publications and Presentations*

Module 2: Hodgkin Lymphoma

- Dr Nguyen: A 26-year-old woman with classical Hodgkin lymphoma
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- Dr Morganstein: A 75-year-old man with relapsed CLL
- Dr Chen: A 66-year-old woman with newly diagnosed CLL receives acalabrutinib
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Module 4: Follicular Lymphoma (FL)

- Dr Blackmon: A 50-year-old man with newly diagnosed Stage III, Grade I-II FL
- Dr Blackmon: A 37-year-old woman with multiregimen-relapsed FL
- *Key Recent Publications and Presentations*

Module 5: Mantle Cell Lymphoma (MCL)

- Dr Blackmon: A 50-year-old man with relapsed blastoid MCL
- *Key Recent Publications and Presentations*

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Blackmon: A 50-year-old man with newly diagnosed Stage III, Grade I-II FL

Dr Amanda Blackmon

- 2018: Presented with diffuse adenopathy and diagnosed with Stage III, Grade I-II FL
  - Observed until fatigue worsened and patient desired treatment
  - Discussion of R-chemotherapy and lenalidomide/rituximab (R^2) as treatment options
- R^2 → rituximab maintenance
- Patient remains in CR 2.5 years after completing maintenance therapy
- Agammaglobulinemia and COVID-19 vaccine

Questions

- What is your opinion regarding R-chemotherapy and R^2 as front-line treatment options?
- Does the extent of this patient's disease have any influence on which regimen you would choose?

Case Presentation – Dr Blackmon: A 37-year-old woman with multiregimen-relapsed FL

Dr Amanda Blackmon

- 2013: Diagnosed with Grade I-II, Stage IV FL with marrow involvement; B-symptoms at diagnosis
  - R-CHOP x 4 cycles with 4-year remission
- 2017: Biopsy-confirmed relapse → BR with response for 6 months
- 2018: Biopsy-confirmed relapse → R^2, progressed within 6 months
- Copanlisib administered with response for about 1 year, but complicated by mucositis, HSV, and fungemia
- Tazemetostat initiated; patient is EZH2 mutation-negative

Questions

- Is testing for EZH2 mutation necessary before administering tazemetostat? Since tazemetostas has activity in patients with wildtype disease, is testing even necessary? Can you test on peripheral blood or do you need to rebiopsy?
- Given the patient's young age, should we be considering treatment with a BiTE or CAR-T therapy? What is the role of transplant?

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- Salles G et al. **Analyzing Efficacy Outcomes from the Phase 2 Study of Single-Agent Tazemetostat as Third-Line Therapy in Patients with Relapsed or Refractory Follicular Lymphoma to Identify Predictors of Response.** ASH 2020;Abstract 2047.
- Jacobson CA et al. **Primary Analysis of Zuma-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL).** ASH 2020;Abstract 700.
- Fowler NH et al. **Efficacy and Safety of Tisagenlecleucel in Adult Patients with Relapsed/Refractory Follicular Lymphoma: Interim Analysis of the Phase 2 Elara Trial.** ASH 2020;Abstract 1149.

FDA Grants Accelerated Approval to Umbralisib for Marginal Zone Lymphoma and Follicular Lymphoma

Press Release: February 5, 2021

The Food and Drug Administration granted accelerated approval to umbralisib, a kinase inhibitor including PI3K-delta and casein kinase CK1-epsilon, for the following indications:

- Adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen
- Adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy.

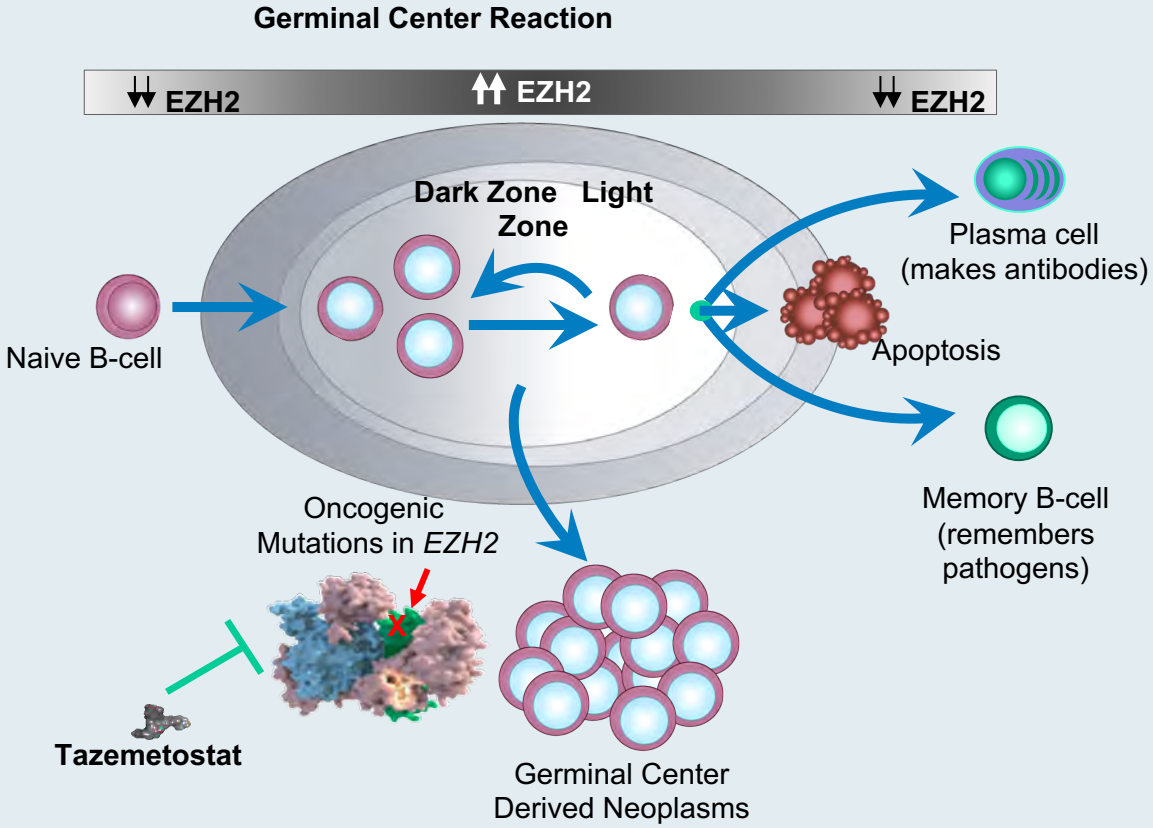
Approval was based on two single-arm cohorts of an open-label, multi-center, multi-cohort trial, UTX-TGR-205 (NCT02793583), in 69 patients with MZL who received at least one prior therapy, including an anti-CD20 containing regimen, and in 117 patients with FL after at least 2 prior systemic therapies. Patients received umbralisib 800 mg orally once daily until disease progression or unacceptable toxicity.

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-umbralisib-marginal-zone-lymphoma-and-follicular-lymphoma?utm_medium=email&utm_source=govdelivery

RTP RESEARCH TO PRACTICE

Follicular Lymphoma and EZH2

- *EZH2* an epigenetic regulator of gene expression and cell fate decisions[1]
- *EZH2* is required for normal B-cell biology and germinal center formation[2]
  - Oncogenic mutations in *EZH2* suppress exit from germinal state and "lock" B cells in this state thereby transforming into a cancer[2]
- *EZH2* biology relevant in both mutant (MT) and wild-type (WT) *EZH2* FL
  - ~20% of patients with FL also have *EZH2* gain of function mutations[3]



Tazemetostat, a selective, oral inhibitor of EZH2 has shown antitumor activity in non-Hodgkin's lymphoma patients with either MT or WT EZH2[4,5]

1. Gan L, et al. *Biomark Res*. 2018;6(1):10; 2. Béguelin W, et al. *Cancer Cell*. 2013;23(5)677-692.
3. Bödör C, et al. *Blood*. 2013;122:3165-3168. 4. Italiano A, et al. *Lancet Oncol*. 2018;19(5):649-59;
5. Morschhauser F, et al. *Hematol Oncol*. 2017 Jun;35:24-5.

Courtesy of John P Leonard, MD

Analyzing Efficacy Outcomes from the Phase 2 Study of Single-Agent Tazemetostat As Third-Line Therapy in Patients with Relapsed or Refractory Follicular Lymphoma to Identify Predictors of Response

Salles G et al.

ASH 2020;Abstract 2047.

Phase 2 Efficacy Outcomes

Efficacy Outcome[a]	Combined WT and MT *EZH2* (N=99)	WT *EZH2* (n=54)[1]	MT *EZH2* (n=45)[1]
ORR, % (95% CI)	51 (40–61)	35 (23-49)	69 (53-82)
Median DOR, months (95% CI)	11 (7–19)	13 (6-NE)	11 (7-NE)
Median PFS, months (95% CI)	12 (8–15)	11 (4-15)	14 (11-22)
Median OS, months (95% CI)	NR (38–NE)	NR	NR

- The DOR was consistent between WT and MT *EZH2* groups[1]
- Consistent ORRs were also observed across high-risk subgroups, such as patients with POD24, double-refractory disease, and refractoriness to rituximab therapy, regardless of mutation status[1]

[a]ORR, DOR, and PFS are based on IRC assessments.

1. Morschhauser F, et al. *Lancet Oncology*; 2020;21(11):1433-42.

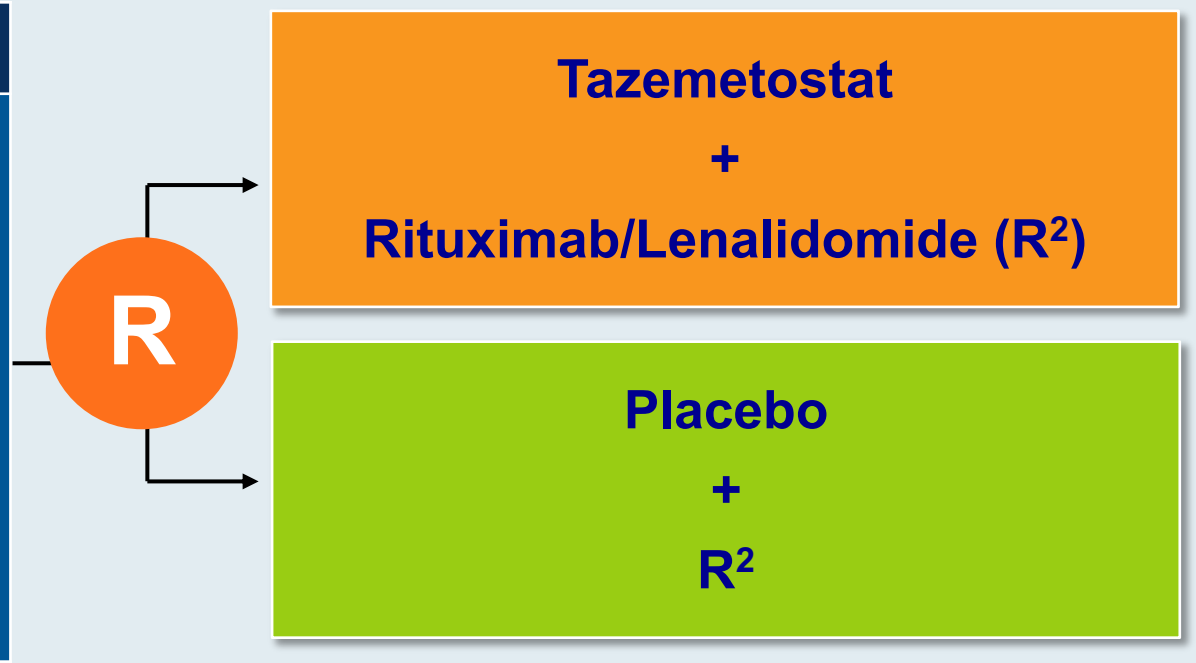
CI, confidence interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EZH2, enhancer of zeste homolog 2; IRC, independent radiology committee; MT, mutant; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; MT, mutant; NE, not evaluable; NR, not reached; PFS, progression-free survival; WT, wild type.

Salles G et al. ASH 2020;Abstract 2047.

Ongoing Phase Ib/III Trial of Tazemetostat + Len/Rituximab in R/R FL

Target accrual (N = 518)

- Grade I to IIIA FL
- At least 1 prior line of therapy
- No prior EZH2 inhibitor
- No prior lenalidomide for FL



- **Primary endpoint:**
  - **Stage 1: RP3D of tazemetostat in combination with R^2**
  - **Stage 2: PFS**

Batlevi CL et al. ASH 2020; Abstract 2052; Clinicaltrials.gov; NCT04224493 (Accessed January 2021).

FDA Grants Accelerated Approval to Axicabtagene Ciloleucel for Relapsed or Refractory Follicular Lymphoma

Press Release – March 5, 2021

"The Food and Drug Administration granted accelerated approval to axicabtagene ciloleucel for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Approval in FL was based on a single-arm, open-label, multicenter trial (ZUMA-5; NCT03105336) that evaluated axicabtagene ciloleucel, a CD19-directed chimeric antigen receptor (CAR) T cell therapy, in adult patients with relapsed or refractory FL after two or more lines of systemic therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. Following lymphodepleting chemotherapy, axicabtagene ciloleucel was administered as a single intravenous infusion.

The main efficacy measures were objective response rate (ORR) and duration of response (DOR) as determined by an independent review committee. Among 81 patients in the primary efficacy analysis, the ORR was 91% with a complete remission (CR) rate of 60% and a median time-to-response of 1 month. The median DOR was not reached, and the 1-year rate of continued remission was 76.2%. For all leukapheresed patients in this trial (n=123), the ORR was 89% with a CR rate of 62%."

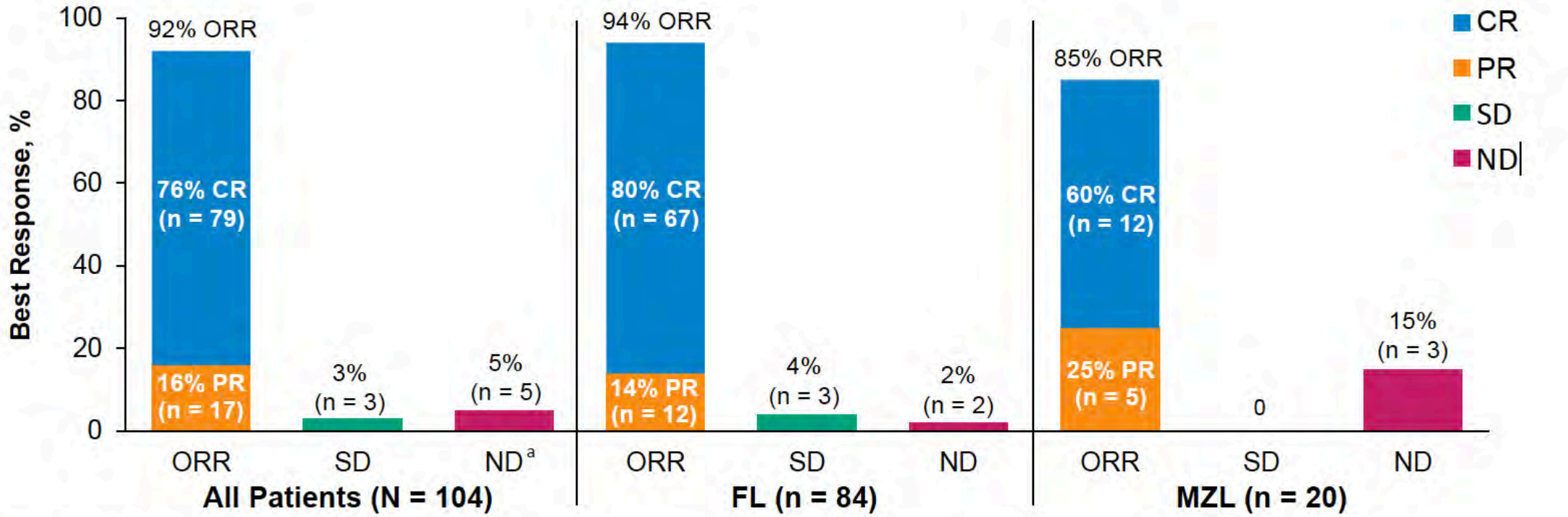
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-axicabtagene-ciloleucel-relapsed-or-refractory-follicular-lymphoma

Primary Analysis of Zuma-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL)

Jacobson CA et al.

ASH 2020;Abstract 700.

ZUMA-5 Primary Endpoint: ORR by IRRC Assessment



- The median time to first response was 1 month (range, 0.8 – 3.1)
- Among the 25 patients with FL who initially had a PR, 13 (52%) subsequently converted to a CR after a median of 2.2 months (range, 1.9 – 11.2)

Jacobson CA et al. ASH 2020;Abstract 700.

Efficacy and Safety of Tisagenlecleucel in Adult Patients with Relapsed/Refractory Follicular Lymphoma: Interim Analysis of the Phase 2 Elara Trial

Fowler NH et al.

ASH 2020;Abstract 1149.

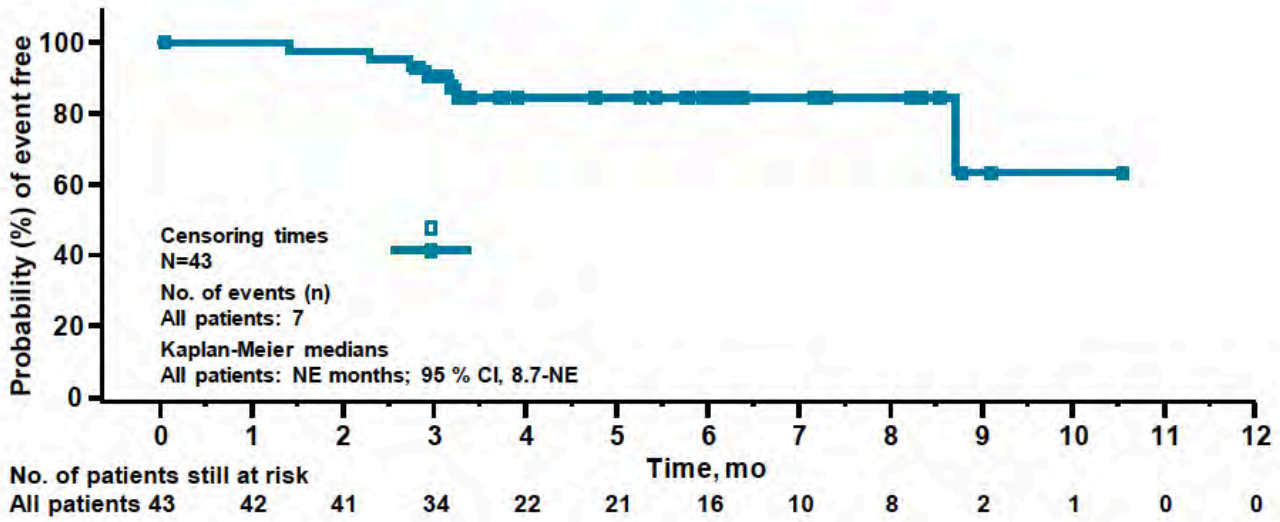
ELARA Interim Analysis: Primary CR Endpoint

Best Overall Response Rate

Response Rate, %	Patients Evaluable for Efficacy[a] (n=52)
CR	65.4[a]
PR	17.3
ORR (CR + PR)	82.7

- Investigator-assessed CR rate was 67.3%[b] (ORR 88.5%)
- ORR was consistent across subgroups, including prior SCT, disease status, and high-risk features

At 10 Months Median Follow-up for Efficacy, Median DOR Not Reached



- Median follow-up for efficacy (n=52): 9.9 months (6.0-15.6)
- Probability for a responding patient to remain in response ≥6 months was 84.4%
- 8 of 18 PRs (44%) converted to CRs; all but 1 occurred between Month 3 and Month 6
- Median time to next antilymphoma treatment was not reached
- 69% (36/52) had ongoing responses at the time of data cutoff

Fowler NH et al. ASH 2020;Abstract 1149.

ELARA: Overall Safety Profile

Adverse Events, n (%)	Treated Patients N=97
Any AE (all grade)	92 (94.8)
AEs suspected to be drug-related	71 (73.2)
Any SAE	37 (38.1)
Suspected to be drug-related	26 (26.8)
Any grade 3/4 AE	68 (70.1)
Suspected to be drug-related	37 (38.1)
Death	3 (3.1)
Deaths due to study indication	3 (3.1)
Deaths within 30 days post infusion	0

	Treated Patients N=97	
AESI (within 8 weeks of infusion)	**All grades, %**	**Grade ≥3, %**
Cytokine release syndrome[a]	48.5	0
Serious neurological adverse reactions	9.3	1.0
Infections	18.6	4.1
Tumor lysis syndrome	1.0	0
Prolonged depletion of B cells/ agammaglobulinemia	9.3	0
Hematologic disorders including cytopenias		
Neutropenia[b,c]	28.9	24.7
Anemia[b]	22.7	12.4
Thrombocytopenia[b]	15.5	8.2

- Median onset of neurological events was 8.5 (4-190[d]) days
- Only 1 case of serious ICANS within the first 8 weeks
- CRS median onset was 4.0 (1-14) days

- **All neurological and CRS events resolved with appropriate management**

Fowler NH et al. ASH 2020;Abstract 1149.

Efficacy and Safety of Tisagenlecleucel (Tisa-cel) in Adult Patients (Pts) with Relapsed/Refractory Follicular Lymphoma (R/R FL): Primary Analysis of the Phase 2 Elara Trial

Schuster SJ et al.

ASCO 2021;Abstract 7508.

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- *Key Recent Publications and Presentations*

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Blackmon: A 50-year-old man with relapsed blastoid MCL

Dr Amanda Blackmon

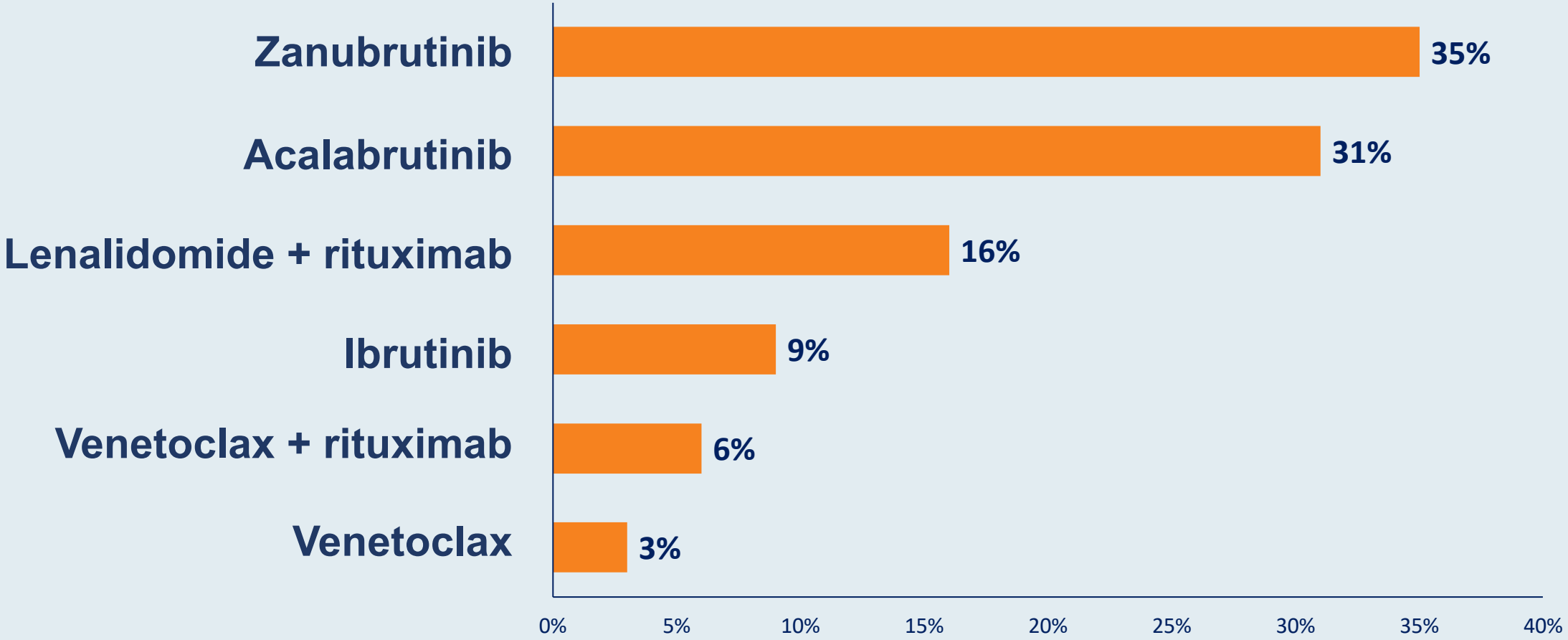
- Diagnosed with blastoid MCL → NORDIC regimen with molecular CR
- Autologous HSCT → rituximab maintenance
- Disease relapse 15 months later
- Ibrutinib administered but stopped after 3 weeks due to severe mucositis
- Lisocabtagene maraleucel on clinical trial → refractory 30-day PET with progression
- Acalabrutinib → CR → allogeneic HSCT

Questions

- Should acalabrutinib be given as maintenance in this patient who does not have any treatment options left should he relapse?
- Are late responses being seen after CAR T therapy in mantle cell lymphoma? This patient went into a remission about 2 months after his CAR T and we're attributing this to acalabrutinib, but he did receive the CAR T.

RTP RESEARCH TO PRACTICE

A 78-year-old patient with MCL initially treated with BR followed by 2 years of maintenance rituximab experiences disease relapse 3 years later. The patient is otherwise healthy. What would you recommend?



N = 32

Survey of live webinar audience

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- Song Y et al. **Treatment of Patients with Relapsed or Refractory Mantle-Cell Lymphoma with Zanubrutinib, a Selective Inhibitor of Bruton's Tyrosine Kinase.** *Clin Cancer Res* 2020;26(16):4216-24.
- Mato AR et al. **Pirtobrutinib in Relapsed or Refractory B-Cell Malignancies (BRUIN): A Phase 1/2 Study**. *Lancet* 2021;397(10277):892-901.
- Eyre T et al. **Efficacy of Venetoclax Monotherapy in Patients with Relapsed, Refractory Mantle Cell Lymphoma Post BTK Inhibition Therapy**. EHA 2018;Abstract S855.
- Wang M et al. **KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma.** *N Engl J Med* 2020;382:1331-42.

RTP RESEARCH TO PRACTICE

Efficacy of Zanubrutinib for MCL

Study	Evaluable patients	ORR, CR	Median DoR	Median PFS
Phase I/II (NCT02343120)	N = 48 R/R = 37 TN = 11	87%, 31% 87%, 30% 88%, 38%	16.2 mo (all) 14.7 mo 14.7 mo	15.4 mo
Phase II (NCT03206970)	N = 86 R/R	84%, 69%	19.5 mo	22.1 mo

Song Y et al. ICML 2019;Abstract 015; Tam CS et al. ICML 2019;Abstract 191;
Tam CS. *Clin Advances in Hem Oncol* 2019;17(1):32-34; Song Y et al. *Clin Cancer Res* 2020;26(16):4216-24.

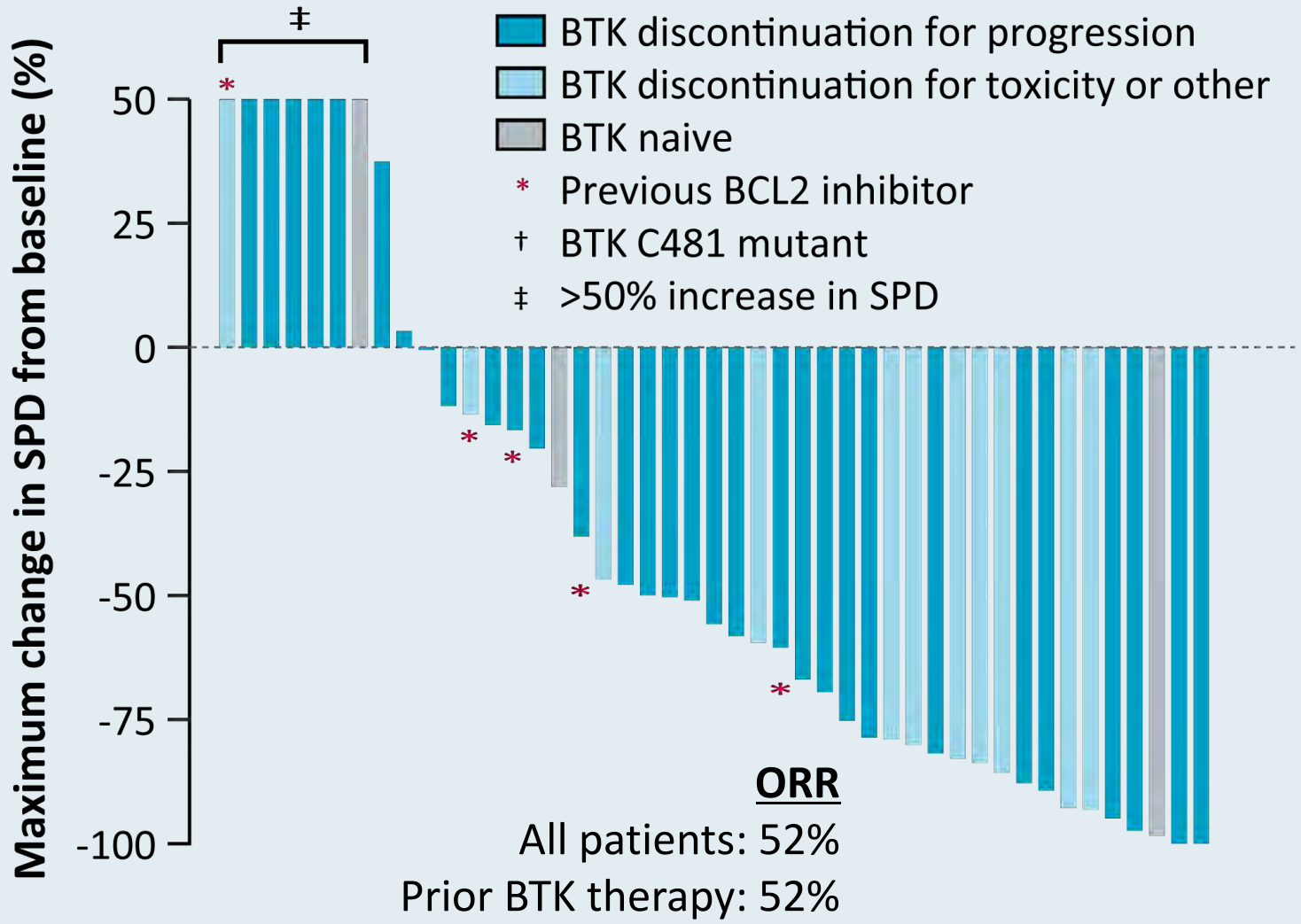
Articles

Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study

Anthony R Mato, Nirav N Shah, Wojciech Jurczak, Chan Y Cheah, John M Pagel, Jennifer A Woyach, Bita Fakhri, Toby A Eyre, Nicole Lamanna, Manish R Patel, Alvaro Alencar, Ewa Lech-Maranda, William G Wierda, Catherine C Coombs, James N Gerson, Paolo Ghia, Steven Le Gouill, David John Lewis, Suchitra Sundaram, Jonathon B Cohen, Ian W Flinn, Constantine S Tam, Minal A Barve, Bryone Kuss, Justin Taylor, Omar Abdel-Wahab, Stephen J Schuster, M Lia Palomba, Katharine L Lewis, Lindsey E Roeker, Matthew S Davids, Xuan Ni Tan, Timothy S Fenske, Johan Wallin, Donald E Tsai, Nora C Ku, Edward Zhu, Jessica Chen, Ming Yin, Binoj Nair, Kevin Ebata, Narasimha Marella, Jennifer R Brown, Michael Wang

Lancet 2021;397(10277):892-901.

BRUIN: Change in Tumor Burden from Baseline with Pirtobrutinib (LOXO-305) in Evaluable Patients with MCL



Mato AR et al. *Lancet* 2021;397(10277):892-901.

RTP RESEARCH TO PRACTICE

Venetoclax Monotherapy for BTK Inhibitor-Resistant MCL: Results Summary

Clinical endpoint	Venetoclax (N = 20)
Overall response rate (ORR) Complete response rate	60% 20%
ORR (prior response to BTKi) ORR (primary resistance to BTKi)	72.7% 44.4%
Median PFS	2.6 mo
Median OS	4.3 mo

No cases of clinical TLS were observed.

Eyre T et al. EHA 2018;Abstract S855.

The Combination of Venetoclax, Lenalidomide, and Rituximab in Patients with Newly Diagnosed Mantle Cell Lymphoma Induces High Response Rates and MRD Undetectability

Phillips TJ et al.
ASCO 2021;Abstract 7505.

Monday, June 7, 11:30 AM - 2:30 PM EDT

The NEW ENGLAND JOURNAL of MEDICINE

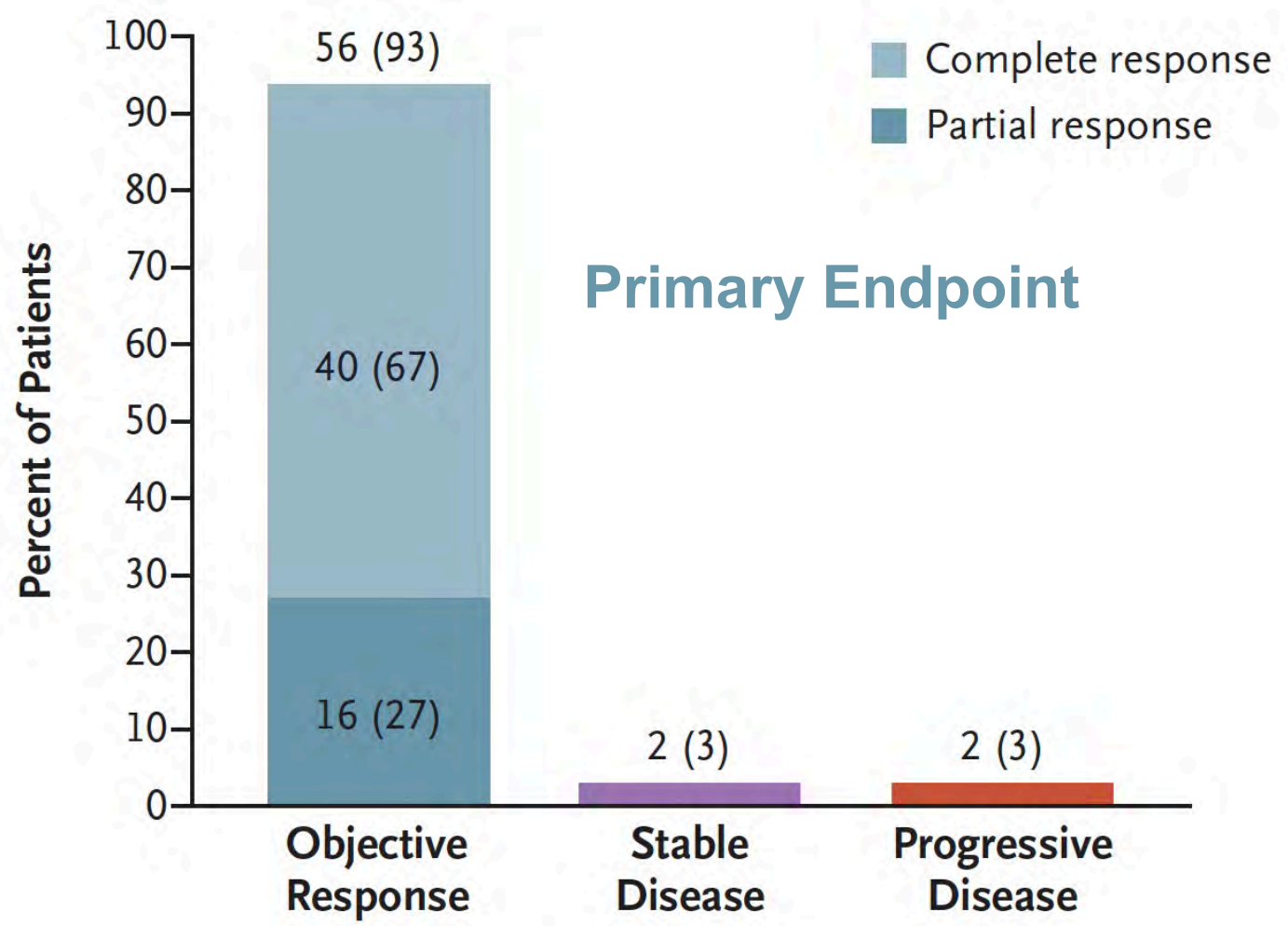
ORIGINAL ARTICLE

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan

N Engl J Med 2020;382:1331-42.

ZUMA-2: Objective Response (IRR), Survival and Key Toxicities



Estimated 12-month survival rate	
Median PFS	61%
Median OS	83%

Key toxicities		
	Grade 1-2	Grade 3-4
Cytokine release syndrome	76%	15%
Neurologic events	32%	31%
Cytopenias	—	94%
Infections	23%	32%

Wang M et al. *N Engl J Med* 2020;382(14):1331-42.

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

A Daylong Clinical Summit Hosted in Partnership with Medical Oncology Association of Southern California (MOASC)

Saturday, May 15, 2021

10:30 AM – 6:30 PM ET

(7:30 AM – 3:30 PM Pacific Time)

RTP RESEARCH TO PRACTICE

This program was recorded before the ASCO 2021 Annual Meeting.

Data from the abstracts presented at this meeting can be accessed at https://meetinglibrary.asco.org/results?meetingView=2021%20ASCO%20Annual%20Meeting.

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Agenda

Module 1 — Breast Cancer: *Drs O'Regan and Traina*

Module 2 — Multiple Myeloma: *Drs Anderson and Raje*

Module 3 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Moskowitz and Sharman*

Module 4 — Genitourinary Cancers: *Drs Bellmunt and Pal*

Module 5 — Gastrointestinal Cancers: *Drs Messersmith and O'Reilly*

Module 6 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Erba and Komrokji*

Module 7 — Lung Cancer: *Drs Camidge and Levy*

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Genitourinary Cancers Faculty

Joaquim Bellmunt, MD, PhD
Director, Bladder Cancer Program
Beth Israel Deaconess Medical Center
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Sumanta Kumar Pal, MD
Clinical Professor, Department of Medical Oncology and Therapeutics Research
City of Hope Comprehensive Cancer Center
Duarte, California

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Commercial Support

This activity is supported by educational grants from AbbVie Inc, Astellas and Pfizer Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Blueprint Medicines, Daiichi Sankyo Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Incyte Corporation, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Lilly, Merck, Novartis, Oncopeptides, Sanofi Genzyme, Seagen Inc, and Taiho Oncology Inc.

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Eisai Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Turning Point Therapeutics Inc and Verastem Inc.

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Research To Practice CME and NCPD Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Messersmith — Disclosures

Contracted Research	ALX Oncology, BeiGene Ltd, Bristol-Myers Squibb Company, Exelixis Inc, Experimental Drug Development Centre (Singapore), Immunomedics Inc, Pfizer Inc, Mitsubishi Tanabe Pharma America
Data and Safety Monitoring Board/Committee	Five Prime Therapeutics Inc, QED Therapeutics, Zymeworks

Dr O'Reilly — Disclosures

Consulting Agreements	Agios Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Autem Medical, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Berry Genomics, Celgene Corporation, CytomX Therapeutics, Debiopharm Group, Eisai Inc, Exelixis Inc, Flatiron Health, Genentech, a member of the Roche Group, Gilead Sciences Inc, HelioHealth, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, MiNA Therapeutics, Polaris Group, QED Therapeutics, RedHill Biopharma Ltd, Silenseed Ltd, SillaJen, Sobi, TheraBionic, twoXAR, Vector Pharma, Yiviva
Contracted Research	*Acta Biológica*, Agios Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Berry Genomics, Bristol-Myers Squibb Company, CASI Pharmaceuticals Inc, Celgene Corporation, Exelixis Inc, Genentech, a member of the Roche Group, Halozyme Inc, Incyte Corporation, MabVax Therapeutics, Puma Biotechnology Inc, QED Therapeutics, SillaJen, Yiviva

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Contributing Oncologists

Amanda Blackmon, DO, MS
Chief Fellow, Hematology/Oncology
University of California, Irvine
Irvine, California

Farshid Dayyani, MD, PhD
Professor of Clinical Medicine
Division of Hematology/Oncology
Department of Medicine
University of California, Irvine
UCI Health
Orange, California

Gigi Chen, MD
Diablo Valley Oncology and
Hematology Medical Group
Pleasant Hill, California

Michael Polintan Del Rosario, MD
Fellow Physician
Division of Hematology-Oncology
Department of Medicine
University of California, Irvine
Irvine, California

Mamta Choksi, MD
Florida Cancer Specialists and
Research Institute
New Port Richey, Florida

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

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RESEARCH
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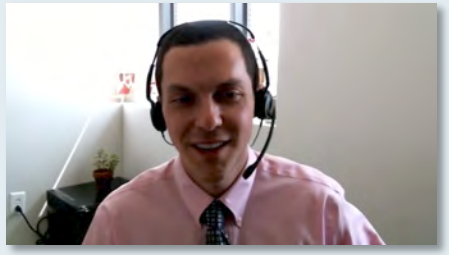
Contributing Oncologists

Rahul Gosain, MD
Division of Hematology and Oncology
Guthrie Corning Cancer Center
Corning, New York

Maen Hussein, MD
Florida Cancer Specialists and
Research Institute
The Villages, Florida

Ranju Gupta, MD
Attending Physician
Co-Director, Cardio-Oncology Program
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania



Jeremy Lorber, MD
Attending Hematologist-Oncologist
Tower Hematology Oncology
Cedars-Sinai Medical Center
Beverly Hills, California

Hatim Husain, MD
Physician, University of California San Diego
San Diego, California

Nataliya Mar, MD
Assistant Clinical Professor
Division of Hematology/Oncology
University of California, Irvine
Irvine, California

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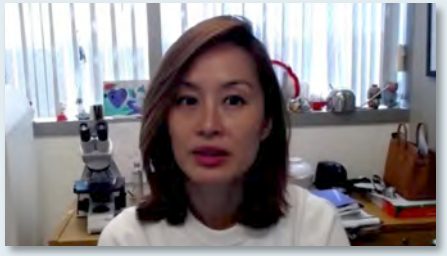
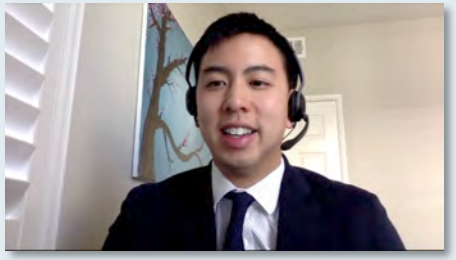
Contributing Oncologists

Mohamed K Mohamed, MD, PhD
Oncology Division Medical Director
Director of Thoracic Oncology
Hematologist/ Medical Oncologist
Cone Health Cancer Center
Greensboro, North Carolina

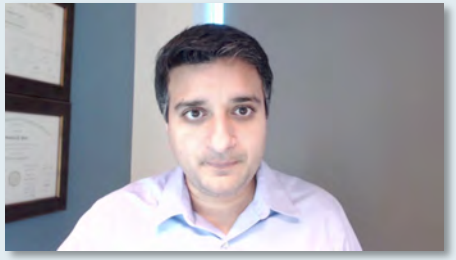


Helen H Moon, MD
Medical Oncologist
Southern California Permanente
Medical Group
Riverside, California

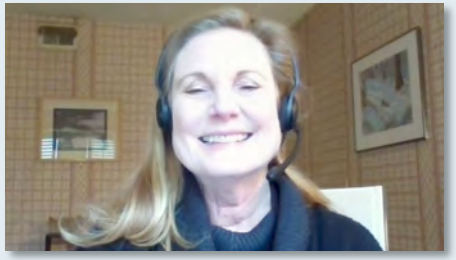
Neil Morganstein, MD
Hematology Oncology
Atlantic Health System
Summit, New Jersey



Anthony Nguyen, MD
Fellow, Loma Linda University Health
Loma Linda, California



Sandip Patel, MD
Associate Professor, Medical Oncology, UCSD
Leader, Experimental Therapeutics
Deputy Director, San Diego Center for
Precision Immunotherapy
San Diego, California



Andrea Stebel, MD
Newport Breast Care
Newport Beach, California

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Agenda

Module 1: Prostate Cancer

- Dr Nguyen: An 86-year-old man with a biochemical recurrence after local therapy
- *Key Recent Publications and Presentations*
- Dr Moon: A 65-year-old man with metastatic castration-resistant prostate cancer and a gBRCA2 mutation
- *Key Recent Publications and Presentations*

Module 2: Urothelial Bladder Cancer (UBC)

- Dr Moon: An 82-year-old man with metastatic UBC
- *Key Recent Publications and Presentations*
- Dr Gosain: A 65-year-old woman with metastatic UBC
- *Key Recent Publications and Presentations*

Module 3: Renal Cell Carcinoma (RCC)

- Dr Lorber: A 77-year-old man with de novo metastatic clear cell RCC treated with ipilimumab/nivolumab
- Dr Moon: A 43-year-old woman with metastatic RCC
- *Key Recent Publications and Presentations*

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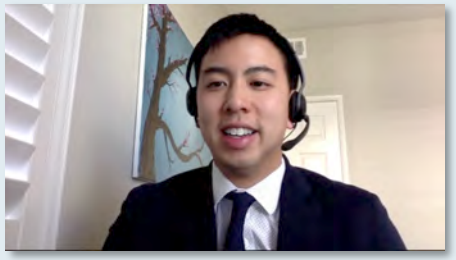
- *Key Recent Publications and Presentations*

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Nguyen: An 86-year-old man with a biochemical recurrence after local therapy



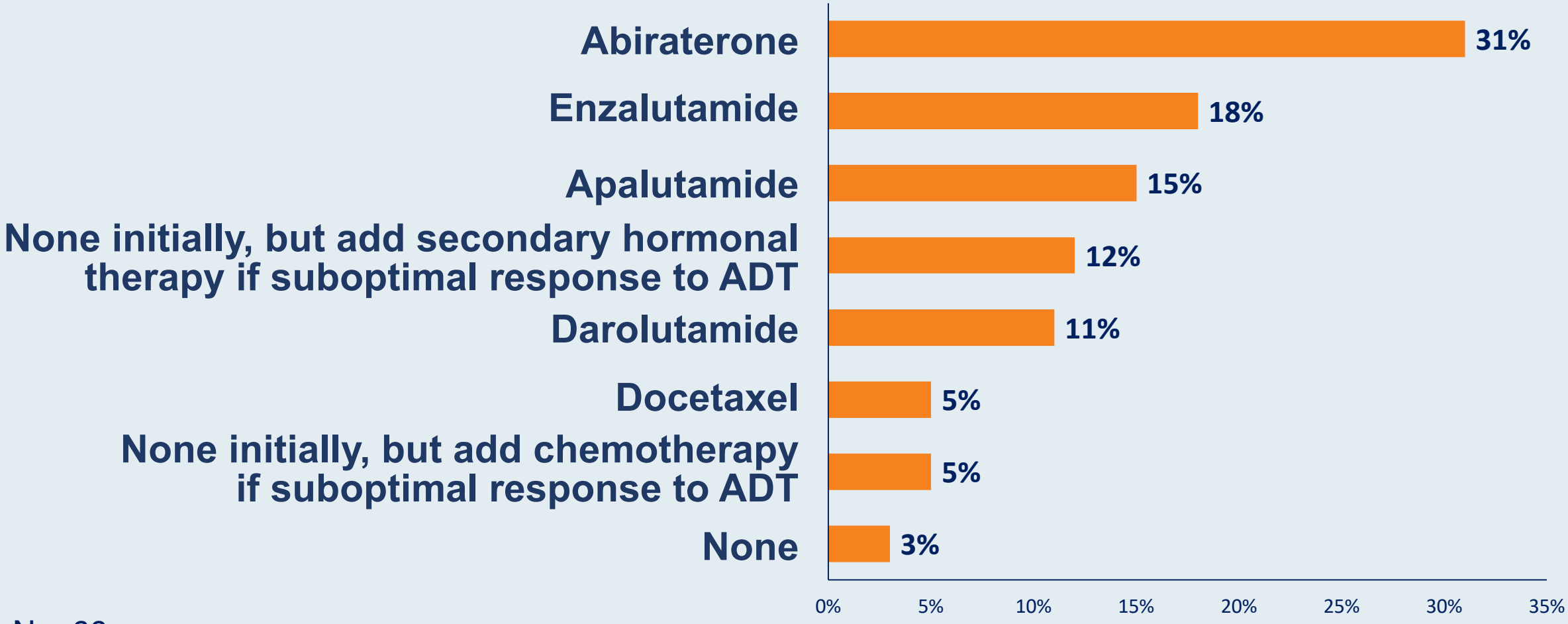
Dr Anthony Nguyen

- PMH: HTN, atrial fibrillation well controlled, osteoporosis
- Diagnosed with Gleason 3 + 3 = 6, Stage II prostate cancer, s/p proton therapy and RT
- Three years later: PSA increasing slowly x 1 year then increased rapidly from 2.8 to 76 over 2 years
  - CT/bone scan: No metastatic disease
  - MRI: Inguinal lymphadenopathy suspicious for metastatic disease
- Every-3-month leuprolide, with downtrending PSA

Questions

- For this elderly man, with an ECOG PS of 0, would you consider adding abiraterone, enzalutamide or apalutamide, or would you wait until his disease progresses or his PSA rises again?
- In younger patients with lymph node involvement, who are motivated, would you consider using docetaxel up front even though they may not have a high burden of disease?

Regulatory and reimbursement issues aside, what systemic therapy would you typically add to ADT for an 80-year-old patient who presents with prostate cancer and 3 asymptomatic bone metastases?



N = 66

Survey of live webinar audience

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- Shore ND et al. **Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer.** *N Engl J Med* 2020;382(23):2187-96.
- Fizazi K et al; ARAMIS Investigators. **Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide**. *N Engl J Med* 2020;383(11):1040-9.
- Sternberg CN et al; PROSPER Investigators. **Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer**. *N Engl J Med* 2020;382(23):2197-206.
- Smith MR et al. **Apalutamide and Overall Survival in Prostate Cancer.** *Eur Urol* 2021;79(1):150-8.
- Armstrong AJ et al. **ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer.** *J Clin Oncol* 2019;37(32):2974-86.
- Chi KN et al; TITAN Investigators. **Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer.** *N Engl J Med* 2019;381(1):13-24.

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TO PRACTICE

Key Recent Publications and Presentations

- Chi KN et al. **Final Analysis Results from TITAN: A Phase III Study of Apalutamide (APA) versus Placebo (PBO) in Patients (pts) with Metastatic Castration-Sensitive Prostate Cancer (mCSPC) Receiving Androgen Deprivation Therapy (ADT).** Genitourinary Cancers Symposium 2021;Abstract 11.

- Davis ID et al; ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group. **Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer.** *N Engl J Med* 2019;381(2):121-31.

- Agarwal N et al. **Cabozantinib in Combination with Atezolizumab in Patients with mCRPC: Results of Cohort 6 of the COSMIC-021 Study.** ASCO 2020;Abstract 5564.

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FDA Approves Relugolix for Advanced Prostate Cancer

Press Release: December 18, 2020

"On December 18, 2020, the U.S. Food and Drug Administration approved the first oral gonadotropin-releasing hormone (GnRH) receptor antagonist, relugolix, for adult patients with advanced prostate cancer.

Efficacy was evaluated in HERO (NCT03085095), a randomized, open label trial in men requiring at least one year of androgen deprivation therapy with either prostate cancer recurrence following radiation or surgery or newly diagnosed castration-sensitive advanced prostate cancer.

Patients (N=934) were randomized (2:1) to receive relugolix 360 mg oral loading dose on the first day, followed by daily oral doses of 120 mg, or leuprolide acetate 22.5 mg injection subcutaneously every 3 months for 48 weeks."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-relugolix-advanced-prostate-cancer

RTP RESEARCH TO PRACTICE

HERO Phase III Trial: Results Comparing Relugolix, an Oral GnRH Receptor Antagonist, versus Leuprolide Acetate for Advanced Prostate Cancer[1]

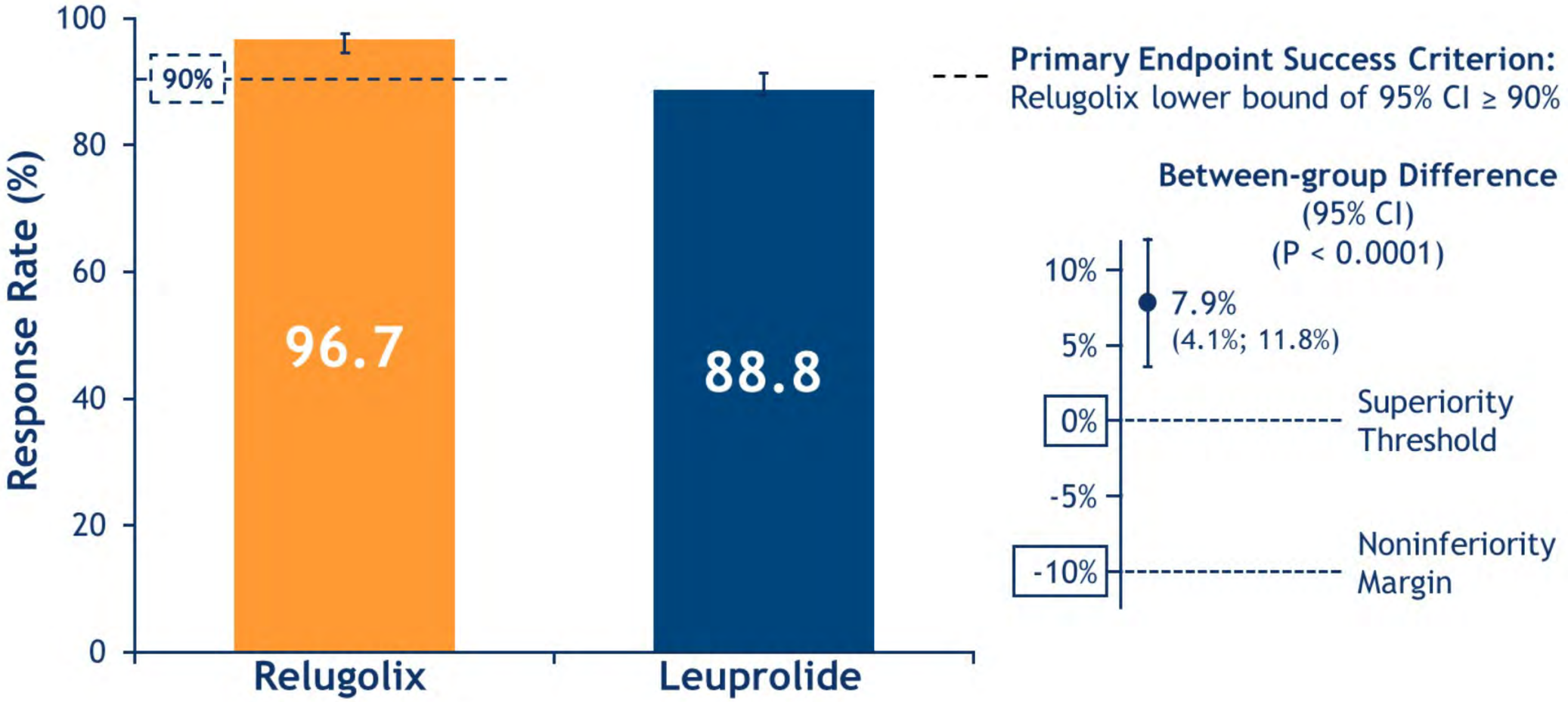
Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer[2]

[1] Shore N et al.
ASCO 2020;Abstract 5602.

[2] Shore ND et al.
N Engl J Med 2020;382(23):2187-96.

RTP RESEARCH TO PRACTICE

HERO: Primary Endpoint – Sustained Castration
Key Secondary Endpoint – Noninferiority to Leuprolide



Shore N et al. ASCO 2020;Abstract 5602; Shore ND et al. *N Engl J Med* 2020;382(23):2187-96.

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2020;383:1040-9.

ORIGINAL ARTICLE

Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide

K. Fizazi, N. Shore, T.L. Tammela, A. Ulys, E. Vjaters, S. Polyakov, M. Jievaltas, M. Luz, B. Alekseev, I. Kuss, M.-A. Le Berre, O. Petrenciuc, A. Snapir, T. Sarapohja, and M.R. Smith, for the ARAMIS Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2020;382(23):2197-206.

ORIGINAL ARTICLE

Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer

Cora N. Sternberg, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Neal D. Shore, M.D., Ugo De Giorgi, M.D., Ph.D., David F. Penson, M.D., M.P.H., Ubirajara Ferreira, M.D., Ph.D., Eleni Efstathiou, M.D., Ph.D., Katarzyna Madziarska, M.D., Ph.D., Michael P. Kolinsky, M.D., Daniel I. G. Cubero, M.D., Ph.D., Bettina Noerby, M.D., Fabian Zohren, M.D., Ph.D., Xun Lin, Ph.D., Katharina Modelska, M.D., Ph.D., Jennifer Sugg, M.S., Joyce Steinberg, M.D., and Maha Hussain, M.D., for the PROSPER Investigators*

European Association of Urology

Eur J Cancer 2020;[Online ahead of print].

Prostate Cancer

Apalutamide and Overall Survival in Prostate Cancer

Matthew R. Smith[a,], Fred Saad[b], Simon Chowdhury[c], Stéphane Oudard[d], Boris A. Hadaschik[e], Julie N. Graff[f], David Olmos[g], Paul N. Mainwaring[h], Ji Youl Lee[i], Hiroji Uemura[j], Peter De Porre[k], Andressa A. Smith[l], Sabine D. Brookman-May[m,n], Susan Li[l], Ke Zhang[o], Brendan Rooney[p], Angela Lopez-Gitlitz[m], Eric J. Small[q]*

Survival: Darolutamide, Enzalutamide, Apalutamide

	ARAMIS[1]	PROSPER[2]	SPARTAN[3]
Antiandrogen	Darolutamide	Enzalutamide	Apalutamide
Median follow-up	49 mo	47 mo	52 mo
Median OS	Not estimated	57 vs 56 mo	74 vs 60 mo
OS hazard ratio	0.69	0.73	0.78

[1] Fizazi K et al; ARAMIS Investigators. *N Engl J Med* 2020;383:1040-9.
[2] Sternberg CN et al; PROSPER Investigators. *N Engl J Med* 2020;382(23):2197-206.
[3] Smith MR et al; *Eur Urol* 2020;79(1):150-8.

FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer

Press Release: December 1, 2020

"The US Food and Drug Administration approved Gallium 68 PSMA-11 (Ga 68 PSMA-11) – the first drug for positron emission tomography (PET) imaging of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer.

Ga 68 PSMA-11 is indicated for patients with suspected prostate cancer metastasis (when cancer cells spread from the place where they first formed to another part of the body) who are potentially curable by surgery or radiation therapy. Ga 68 PSMA-11 is also indicated for patients with suspected prostate cancer recurrence based on elevated serum prostate-specific antigen (PSA) levels. Ga 68 PSMA-11 is a radioactive diagnostic agent that is administered in the form of an intravenous injection.

Once administered via injection, Ga 68 PSMA-11 binds to PSMA, which is an important pharmacologic target for prostate cancer imaging because prostate cancer cells usually contain elevated levels of the antigen. As a radioactive drug that emits positrons, Ga 68 PSMA-11 can be imaged by PET to indicate the presence of PSMA-positive prostate cancer lesions in the tissues of the body."

https://www.fda.gov/news-events/press-announcements/fda-approves-first-psma-targeted-pet-imaging-drug-men-prostate-cancer#:~:text=Today%2C%20the%20U.S.%20Food%20and,in%20men%20with%20prostate%20cancer

RTP RESEARCH TO PRACTICE

Recent FDA Approvals of Next-Generation Antiandrogens in Metastatic Hormone-Sensitive Prostate Cancer

Agent	Approval date	Pivotal study
Enzalutamide	December 16, 2019	ARCHES
Apalutamide	September 17, 2019	TITAN

https://www.fda.gov/drugs/resources-information-approved-drugs/

RTP RESEARCH TO PRACTICE

Survival Analyses for ARCHES and TITAN: ADT + Enzalutamide or Apalutamide in Metastatic HSPC

	ARCHES (N = 1,150)		TITAN (N = 1,052)	
Characteristics	• 2/3rd high volume • 17% prior docetaxel • 25% prior RP/XRT		• 2/3rd high volume • 10% prior docetaxel • 17% prior RP/XRT	
	ADT + enzalutamide (n = 574)	**ADT (n = 576)**	**ADT + apalutamide (n = 955)**	**ADT (n = 554)**
Radiographic PFS	NR	19.0 mo	NR	22.1 mo
	HR (overall): 0.39 • HR (prior docetaxel): 0.52 • HR (high volume): 0.43 • HR (low volume): 0.25		**HR (overall): 0.48** • HR (prior docetaxel): 0.47 • HR (high volume): 0.53 • HR (low volume): 0.36	
Overall survival	NR	NR	NR	NR
	HR: 0.81 (immature)		**HR (overall): 0.67** • HR (prior docetaxel): 1.27 • HR (high volume): 0.68 • HR (low volume): 0.67	

NR = not reached

Armstrong AJ et al. *J Clin Oncol* 2019;37(32):2974-86. Chi KN et al. *N Engl J Med* 2019;381(1):13-24.

Abstract #11

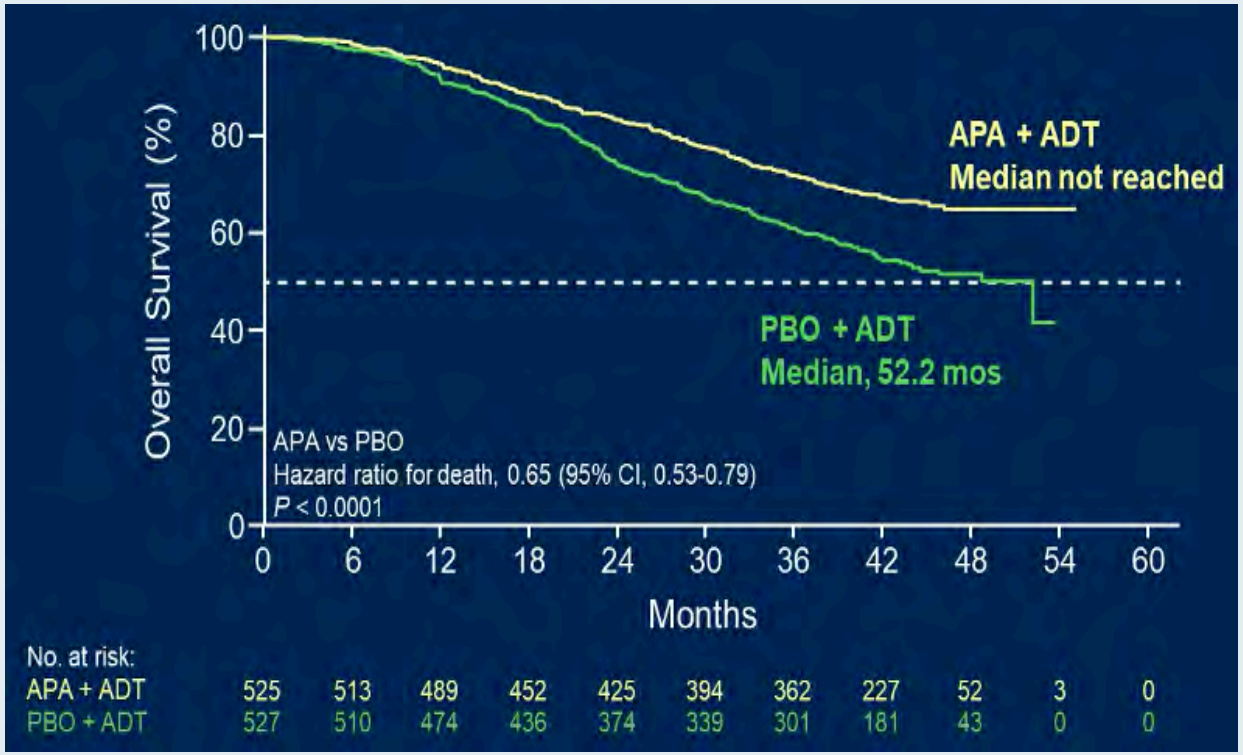
Final Analysis Results From TITAN: A Phase 3 Study of Apalutamide vs Placebo in Patients With Metastatic Castration-Sensitive Prostate Cancer Receiving Androgen Deprivation Therapy

Kim N. Chi,[1] Simon Chowdhury,[2] Anders Bjartell,[3] Byung Ha Chung,[4] Andrea J. Pereira de Santana Gomes,[5] Robert Given,[6] Álvaro Juárez Soto,[7] Axel S. Merseburger,[8] Mustafa Özgüroğlu,[9] Hirotsugu Uemura,[10] Dingwei Ye,[11] Spyros Triantos,[12] Sabine Brookman-May,[12,13] Suneel Mundle,[14] Sharon A. McCarthy,[14] Julie S. Larsen,[15] Weili Sun,[15] Katherine Bevans,[16] Ke Zhang,[17] Nibedita Bandyopadhyay,[14] Neeraj Agarwal,[18] for the TITAN Investigators

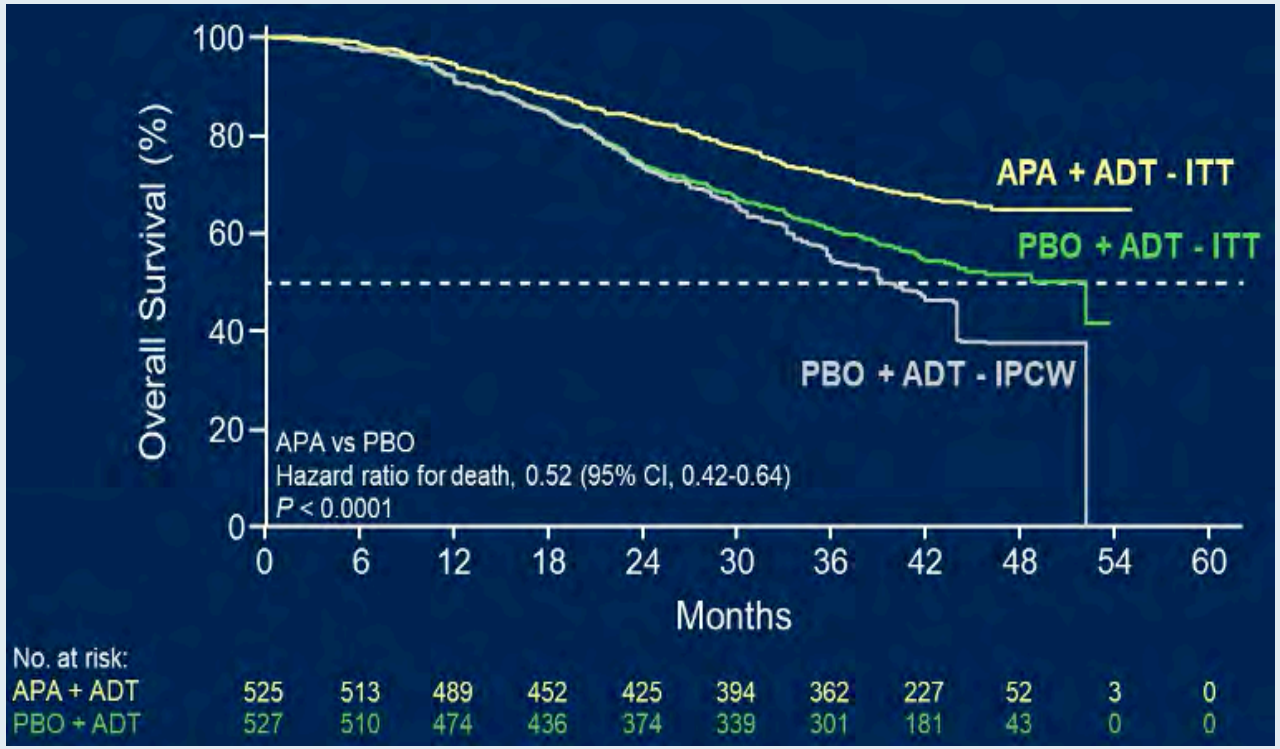
[1]BC Cancer and Vancouver Prostate Centre, Vancouver, BC, Canada; [2]Guy's, King's, and St. Thomas' Hospitals, and Sarah Cannon Research Institute, London, UK; [3]Skåne University Hospital, Lund University, Malmö, Sweden; [4]Yonsei University College of Medicine and Gangnam Severance Hospital, Seoul, South Korea; [5]Liga Norte Riograndense Contra O Cancer, Natal, Brazil; [6]Urology of Virginia, Eastern Virginia Medical School, Norfolk, VA; [7]Hospital Universitario de Jerez de la Frontera, Cadiz, Spain; [8]University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; [9]Istanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey; [10]Kindai University Faculty of Medicine, Osaka, Japan; [11]Fudan University Shanghai Cancer Center, Shanghai, China; [12]Janssen Research & Development, Spring House, PA; [13]Ludwig-Maximilians-University (LMU), Munich, Germany; [14]Janssen Research & Development, Raritan, NJ; [15]Janssen Research & Development, Los Angeles, CA; [16]Janssen Research & Development, Horsham, PA; [17]Janssen Research & Development, San Diego, CA; [18]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

TITAN – Final Analysis: Overall Survival

OS (Co-primary endpoint)
Median follow-up: 44.0 months



OS with adjustment for ~40% crossover from PBO



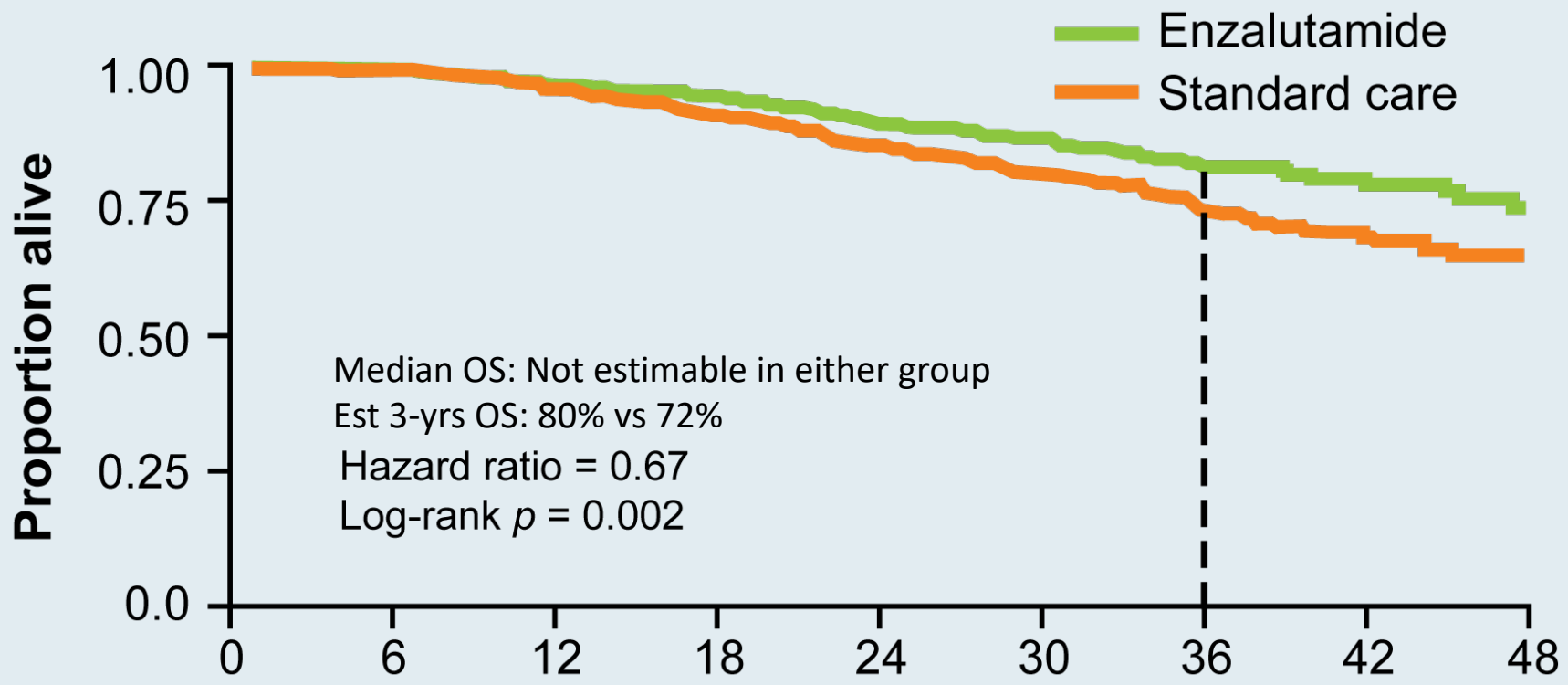
Chi KN et al. Genitourinary Cancers Symposium 2021;Abstract 11.

RTP RESEARCH TO PRACTICE

ENZAMET: ADT + Enzalutamide or Standard Nonsteroidal Antiandrogen — Primary Endpoint Overall Survival

A Mixed Bag

- High and Low Volume
- *De novo* vs Metach
- Concurrent Docetaxel
- Many Permutations



Number at risk

Standard care	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45

Davis ID et al. *N Engl J Med* 2019;381(2):121-31.

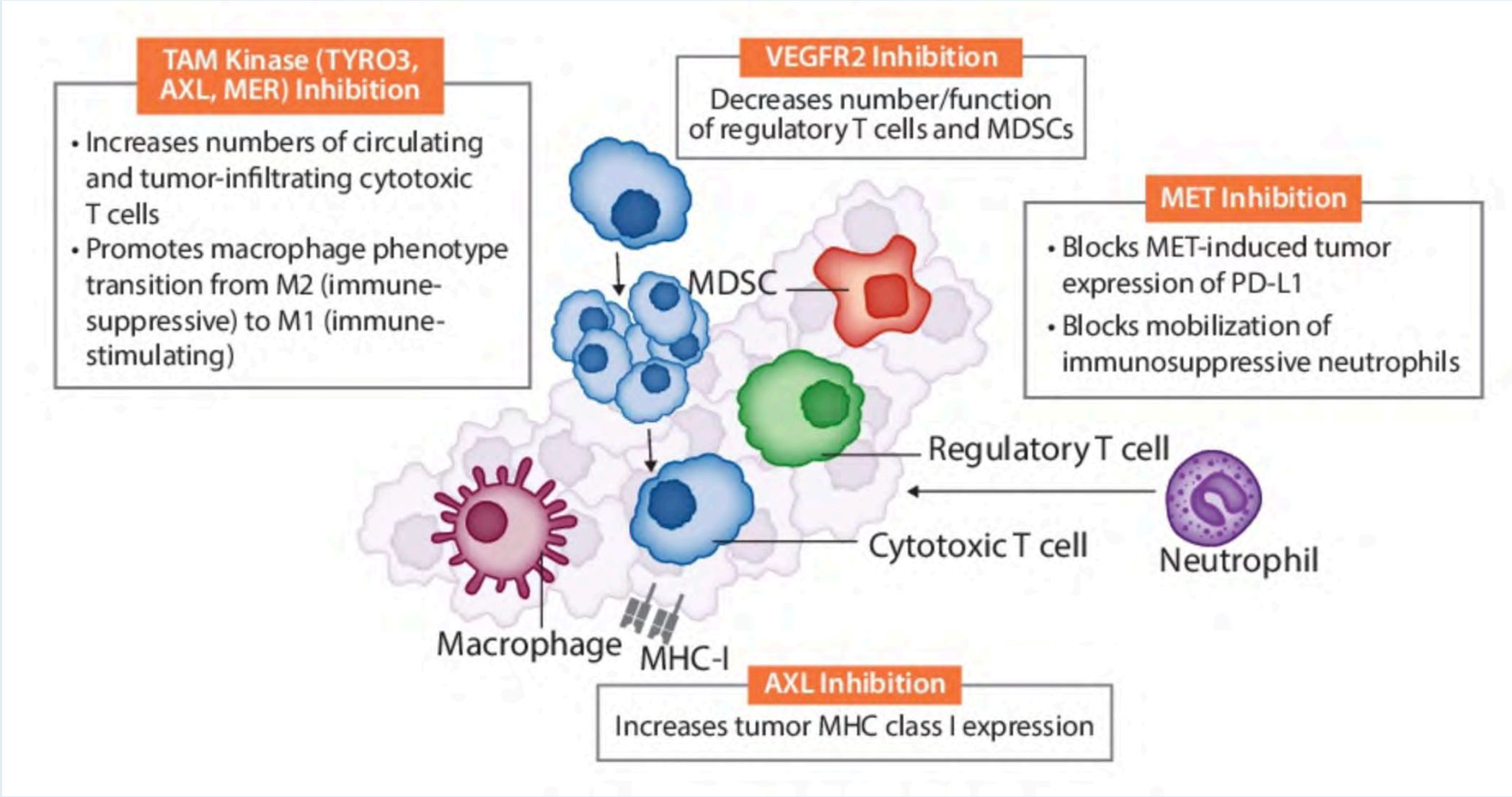
RTP RESEARCH TO PRACTICE

Cabozantinib in Combination with Atezolizumab in Patients with mCRPC: Results of Cohort 6 of the COSMIC-021 Study

Agarwal N et al.

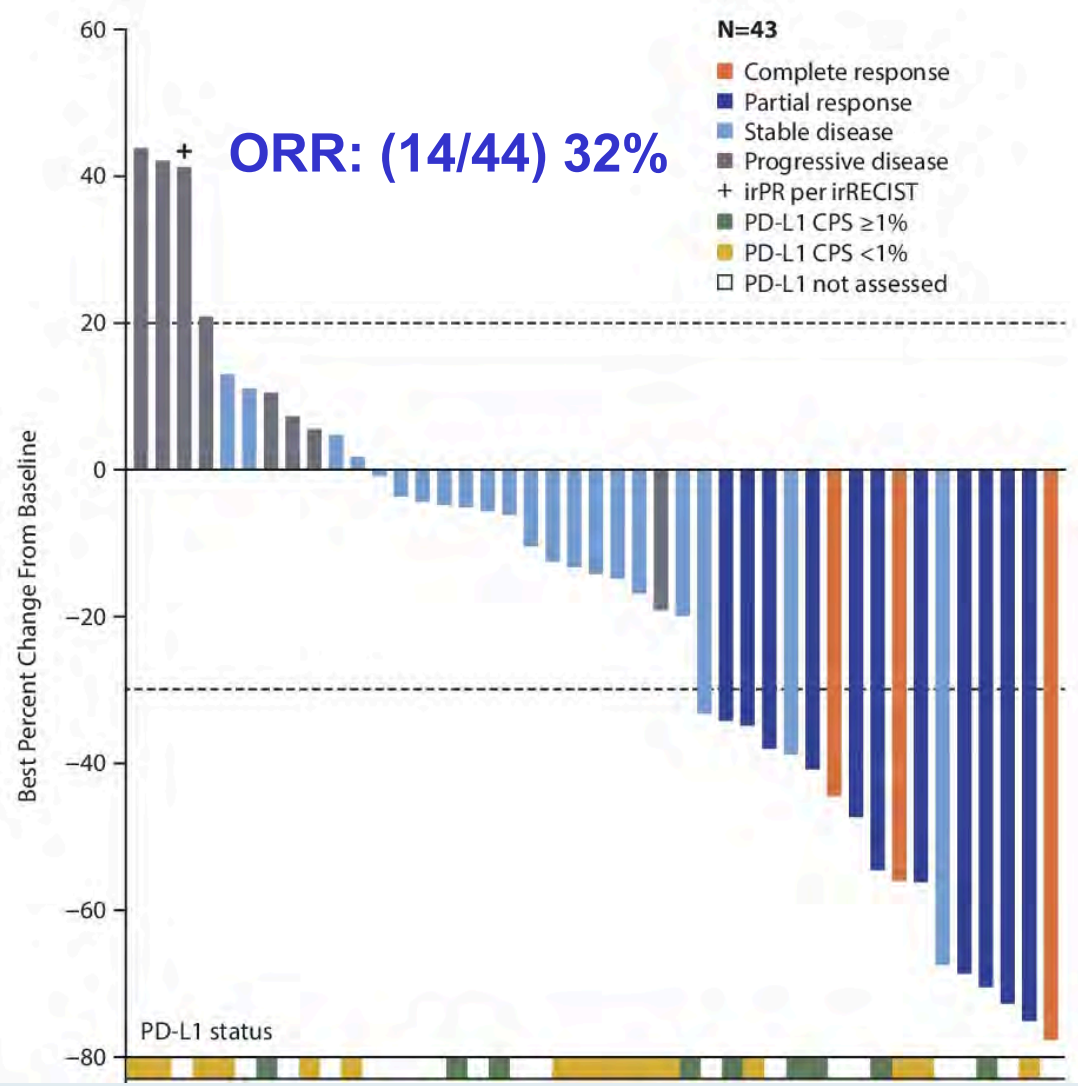
ASCO 2020;Abstract 5564.

Cabozantinib Targets Pathways Associated with Tumor Immune Suppression



Agarwal N et al. ASCO 2020;Abstract 5564.

COSMIC-021 Primary Endpoint: Investigator-Assessed ORR with Cabozantinib/Atezolizumab in mCRPC

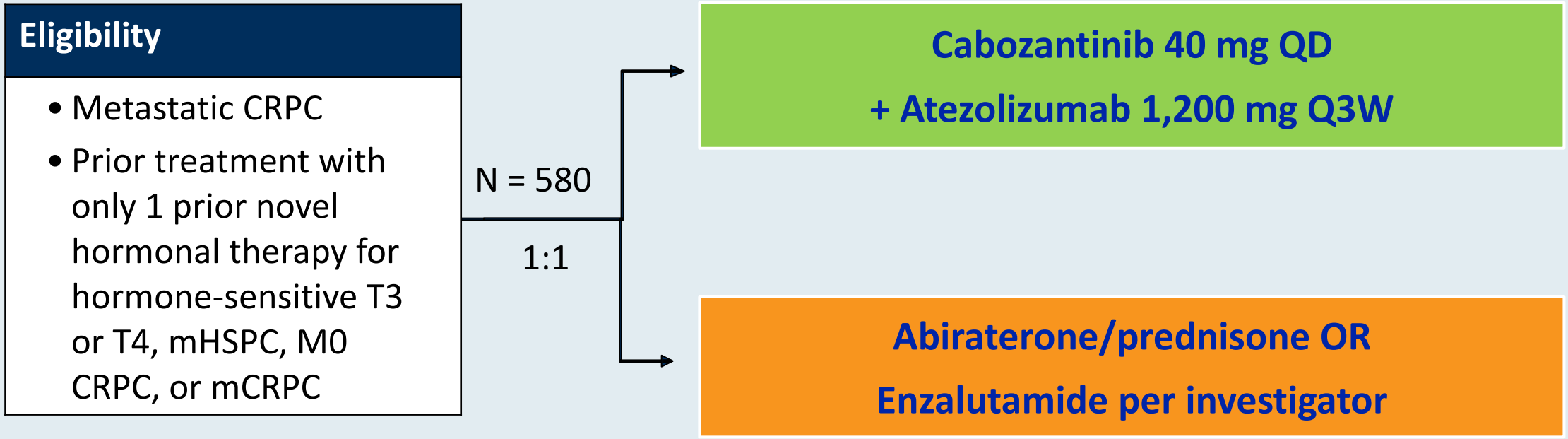


	CRPC Cohort (N=44)		
	Any Grade	Grade 3	Grade 4
Any AE, n (%)	42 (95)	26 (59)	1 (2.3)*
Fatigue	22 (50)	3 (6.8)	0
Diarrhea	20 (45)	3 (6.8)	0
Nausea	20 (45)	0	0
Decreased appetite	17 (39)	0	0
Dysgeusia	15 (34)	0	0
PPE	14 (32)	1 (2.3)	0
Vomiting	11 (25)	1 (2.3)	0
AST increased	9 (20)	2 (4.5)	0
White blood cell count decreased	7 (16)	2 (4.5)	0
Stomatitis	7 (16)	1 (2.3)	0
Dry mouth	7 (16)	0	0
Dysphonia	7 (16)	0	0
Headache	7 (16)	0	0
Weight decreased	7 (16)	0	0
Pulmonary embolism	6 (14)	5 (11)	0
Arthralgia	6 (14)	1 (2.3)	0
Hypertension	6 (14)	1 (2.3)	0
Platelet count decreased	6 (14)	0	0
Rash maculo-papular	6 (14)	0	0
Hyponatremia	5 (11)	3 (6.8)	0
ALT increased	5 (11)	2 (4.5)	0
Neutrophil count decreased	5 (11)	2 (4.5)	0
Abdominal pain	5 (11)	1 (2.3)	0
Hypophosphatemia	5 (11)	1 (2.3)	0
Oral pain	5 (11)	0	0

Agarwal N et al. ASCO 2020;Abstract 5564.

RTP RESEARCH TO PRACTICE

CONTACT-02 Phase III Study Schema



Coprimary endpoints: Duration of PFS and OS

Clinicaltrials.gov, Accessed October 2020 (NCT04446117)

Case Presentation – Dr Moon: A 65-year-old man with metastatic castration-resistant prostate cancer and a germline BRCA2 mutation

Dr Helen Moon

- Strong family history of cancer
- Prostate cancer with bone metastases
- Leuprolide and abiraterone, with response for 12-14 months
- PSA rising
- Olaparib, with objective response, PSA decline by 50% and normalization of alkaline phosphatase
  - 1 dose held due to white blood cell counts

Question

- Am I denying patients with other mutations beyond BRCA1 and BRCA2 the opportunity for PARP inhibitor treatment?

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- de Bono J et al. **Olaparib for Metastatic Castration-Resistant Prostate Cancer.** *N Engl J Med* 2020;382(22):2091-102.

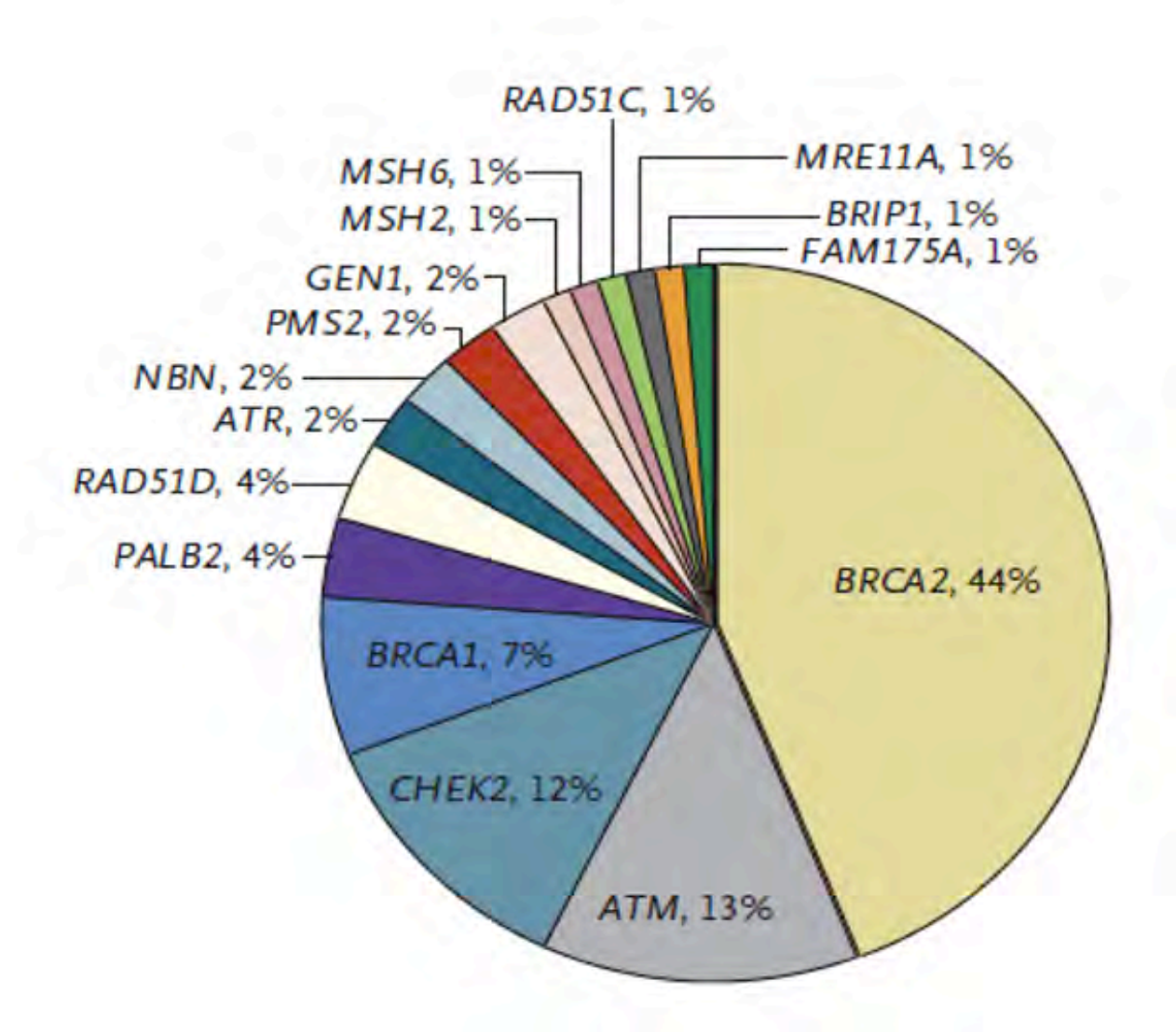
- Hussain M et al; PROfound Trial Investigators. **Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer.** *N Engl J Med* 2020;383(24):2345-57.

- Abida W et al; TRITON2 investigators. **Rucaparib in Men with Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration.** *J Clin Oncol* 2020;38(32):3763-72.

- Hofman MS et al; TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group. **177Lu]Lu-PSMA-617 versus Cabazitaxel in Patients with Metastatic Castration-Resistant Prostate Cancer (TheraP): A Randomised, Open-Label, Phase 2 Trial.** *Lancet* 2021;397(10276):797-804.

RTP
RESEARCH
TO PRACTICE

Inherited DNA Repair Gene Mutations in Men with mPC



- Multicenter study of 692 men
- Deleterious mutations were found in 82 men (11.8%) in 16 genes
- Observed rate exceeded that associated with localized prostate cancer (4.6%) and general population without cancer (2.7%)

Courtesy of Matthew Smith, MD, PhD.

RTP RESEARCH TO PRACTICE

Recent FDA Approvals of PARP Inhibitors for mCRPC

PARP inhibitor	Approval date	Pivotal study
Olaparib	May 19, 2020	PROfound
Rucaparib	May 15, 2020	TRITON2

https://www.fda.gov/drugs/resources-information-approved-drugs/

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

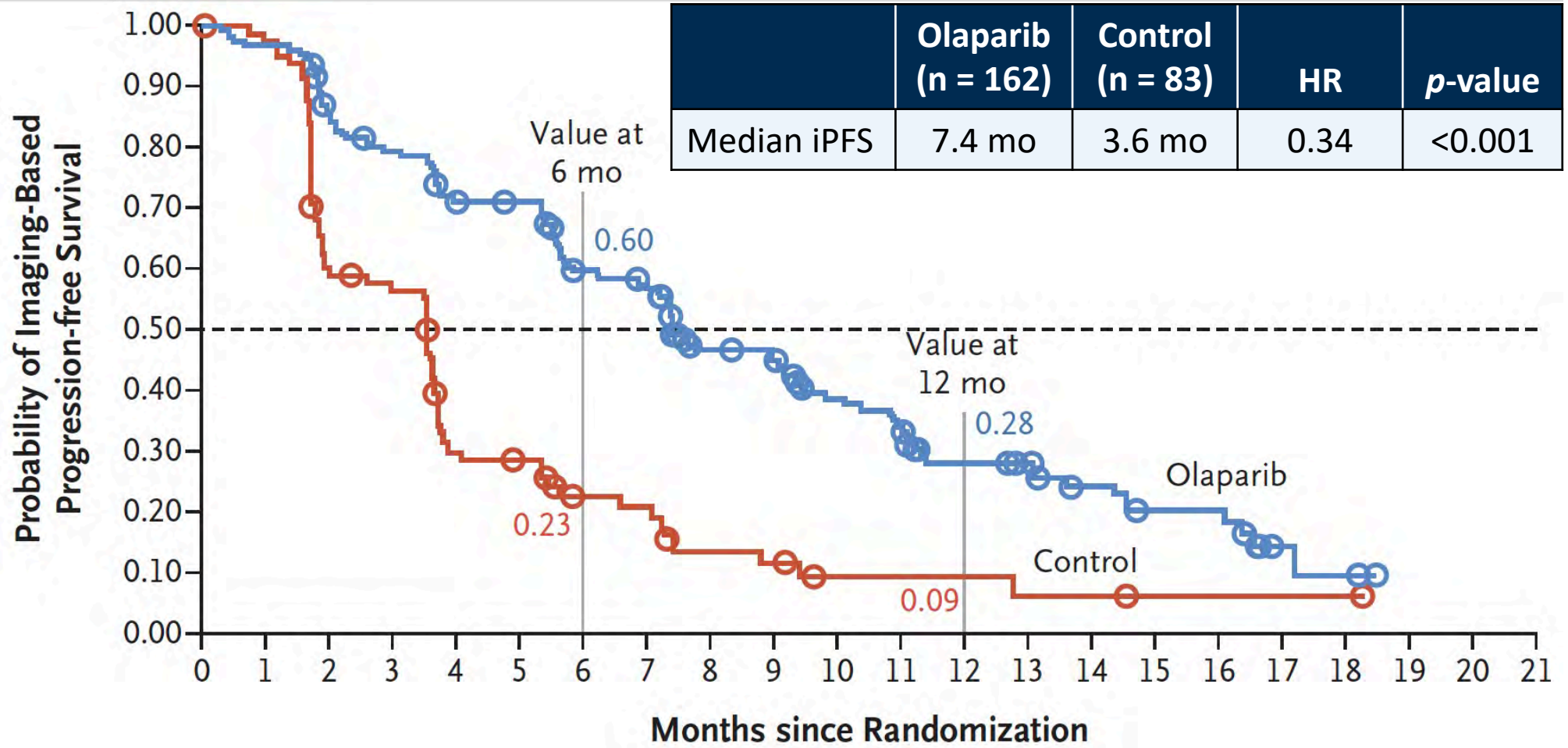
Olaparib for Metastatic Castration-Resistant Prostate Cancer

J. de Bono, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, N. Mehra, C. Goessl, J. Kang, J. Burgents, W. Wu, A. Kohlmann, C.A. Adelman, and M. Hussain

***N Engl J Med* 2020;382:2091-102.**

PROfound Primary Endpoint: Imaging-Based PFS with Olaparib for Patients with mCRPC Who Had at Least 1 Alteration in BRCA1, BRCA2 or ATM (Cohort A)

	Olaparib (n = 162)	Control (n = 83)	HR	*p*-value
Median iPFS	7.4 mo	3.6 mo	0.34	<0.001



de Bono J et al; PROfound investigators. *N Engl J Med* 2020;382(22):2091-102.

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

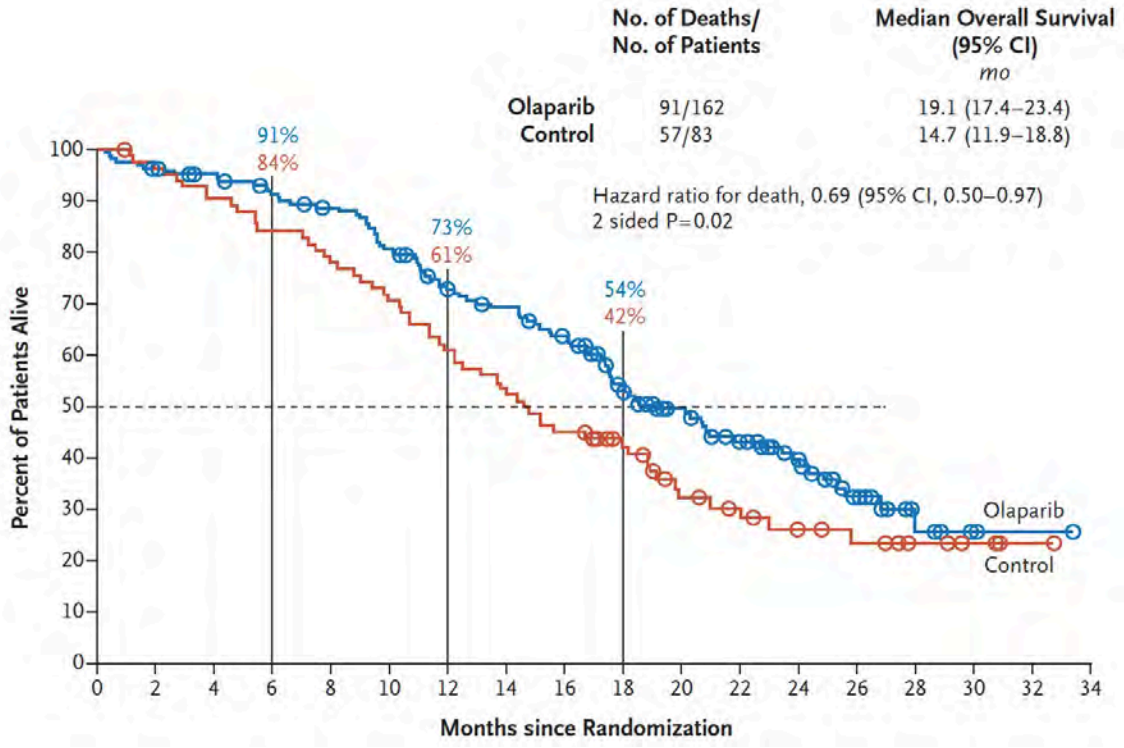
Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

M. Hussain, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, G. Roubaud, M. Özgüroğlu, J. Kang, J. Burgents, C. Gresty, C. Corcoran, C.A. Adelman, and J. de Bono, for the PROfound Trial Investigators*

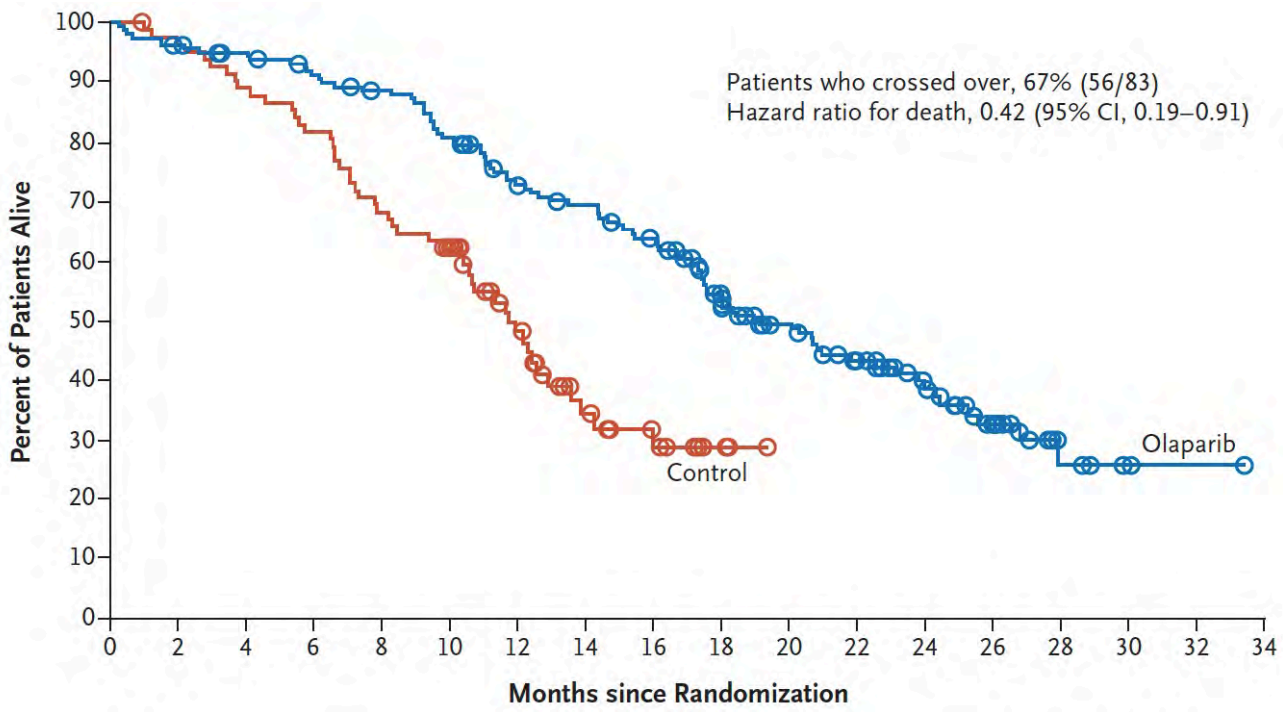
***N Engl J Med* 2020;383(24):2345-57.**

PROfound: Overall Survival with Olaparib for Patients with mCRPC Who Had at Least 1 Alteration in BRCA1, BRCA2 or ATM (Cohort A)

Overall survival



Cross-over adjusted overall survival



Hussain M et al; PROfound investigators. *N Engl J Med* 2020;383(24):2345-57.

rapid communications

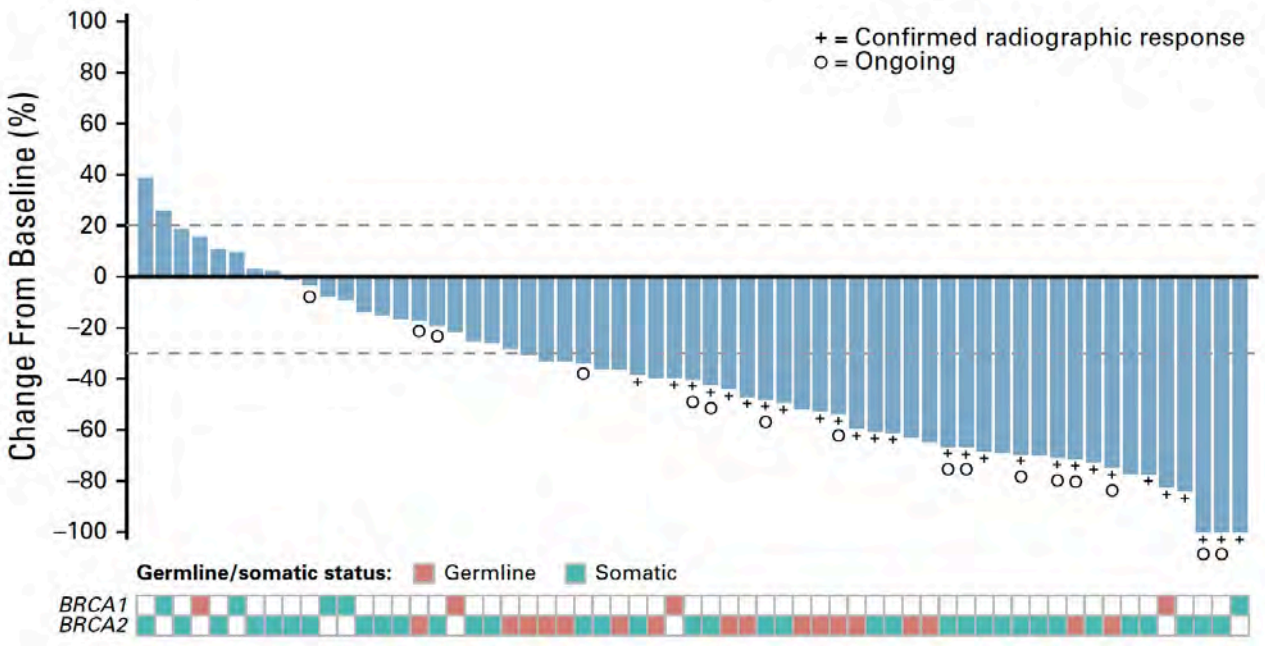
Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration

Wassim Abida, MD, PhD[1]; Akash Patnaik, MD, PhD, MMSc[2]; David Campbell, MBBS[3]; Jeremy Shapiro, MBBS[4]; Alan H. Bryce, MD[5]; Ray McDermott, MD, PhD, MBA[6]; Brieuc Sautois, MD, PhD[7]; Nicholas J. Vogelzang, MD[8]; Richard M. Bambury, MD[9]; Eric Voog, MD[10]; Jingsong Zhang, MD, PhD[11]; Josep M. Piulats, MD[12]; Charles J. Ryan, MD[13]; Axel S. Merseburger, PhD[14]; Gedske Daugaard, DMSc[15]; Axel Heidenreich, MD[16]; Karim Fizazi, MD, PhD[17]; Celestia S. Higano, MD[18]; Laurence E. Krieger, MBChB[19]; Cora N. Sternberg, MD[20]; Simon P. Watkins, PhD[21]; Darrin Despain, MStat[22]; Andrew D. Simmons, PhD[23]; Andrea Loehr, PhD[23]; Melanie Dowson, BA[24]; Tony Golsorkhi, MD[25]; and Simon Chowdhury, MD, PhD[26,27]; on behalf of the TRITON2 investigators

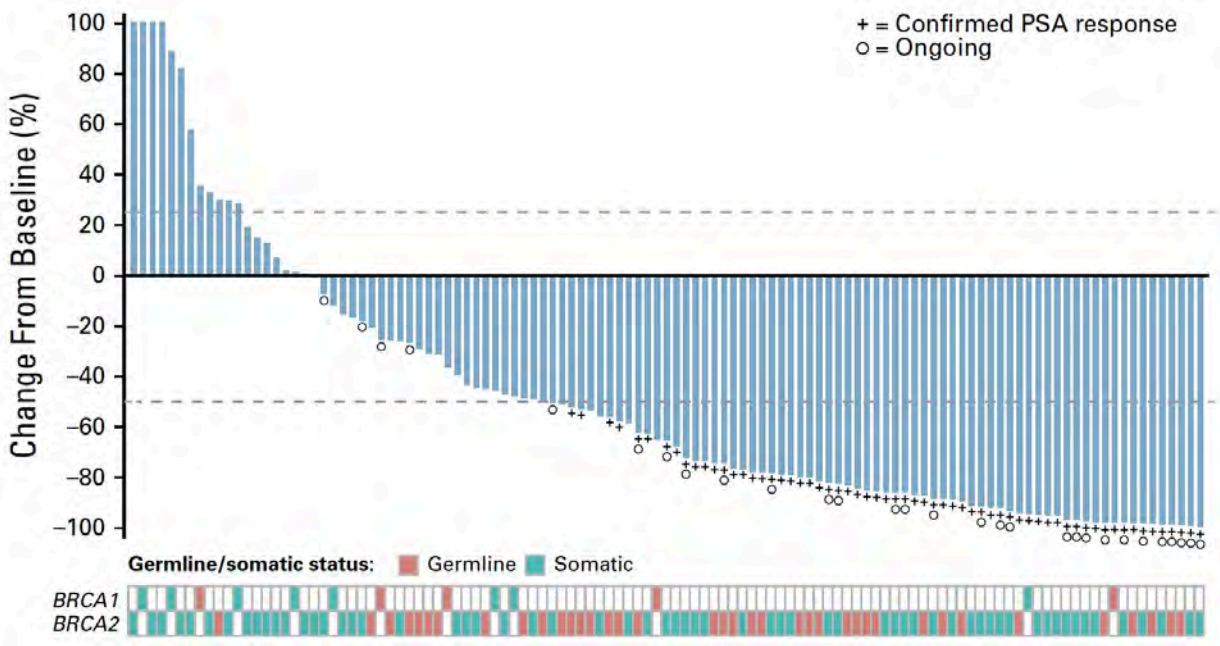
J Clin Oncol 2020;38(22):3763-72.

TRITON2: Response to Rucaparib in Patients with mCRPC Harboring a BRCA1 or BRCA2 Gene Alteration

ORR per independent radiology review: 43.5%

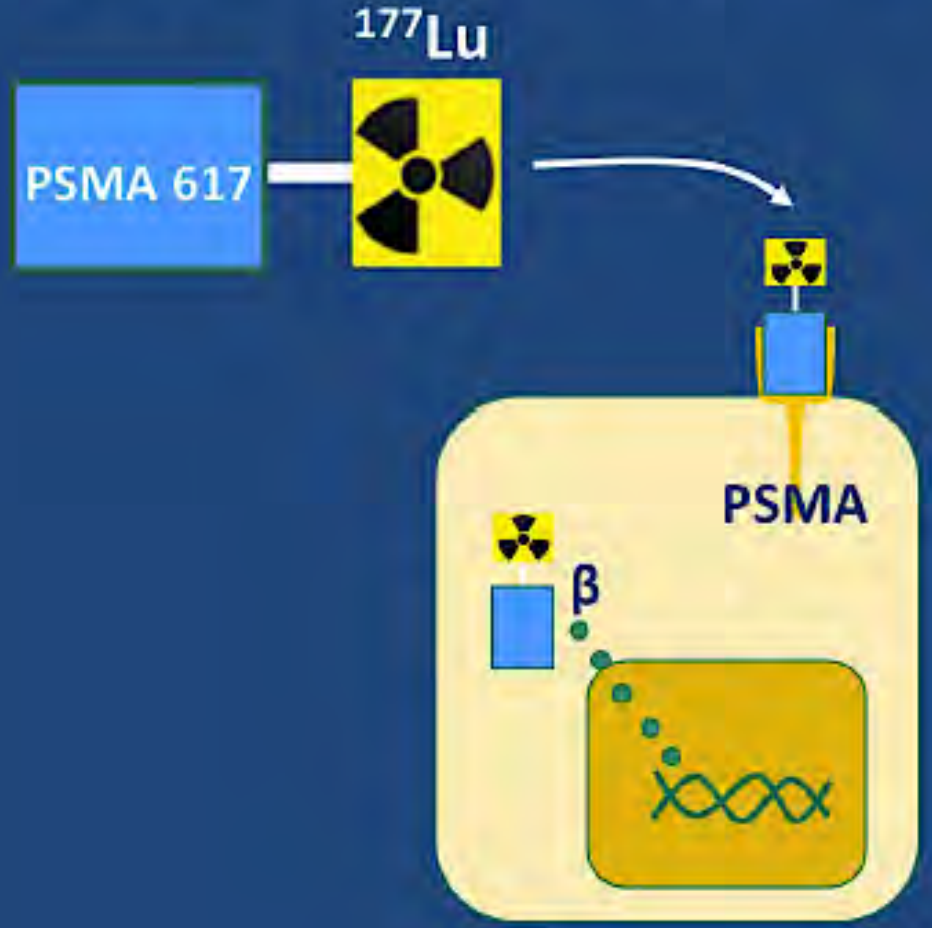


Confirmed PSA response rate: 54.8%



Abida W et al. TRITON2 investigators. *J Clin Oncol* 2020;38(32):3763-72.

^{177}Lu-PSMA-617 is a small molecule RLT targeting PSMA



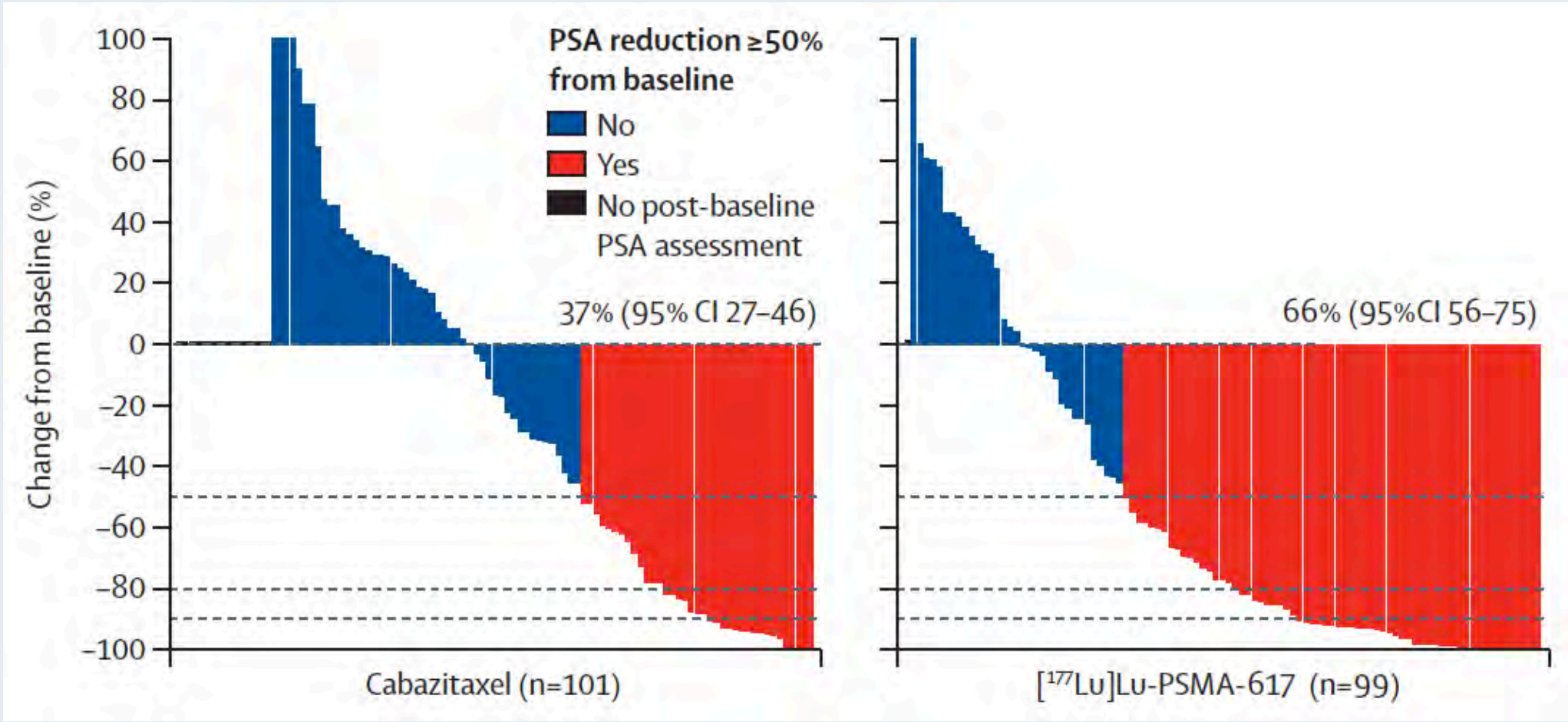
Hofman S et al. ASCO 2020;Abstract 5500.

Lancet 2021;397:797-804.

[^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

Michael S Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony M Joshua, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Siobhan Ng, Roslyn J Francis, Craig Gedye, Natalie K Rutherford, Andrew Weickhardt , Andrew M Scott, Sze-Ting Lee, Edmond M Kwan, Arun A Azad, Shakher Ramdave, Andrew D Redfern, William Macdonald, Alex Guminski, Edward Hsiao, Wei Chua, Peter Lin, Alison Y Zhang, Margaret M McJannett, Martin R Stockler, John A Violet, Scott G Williams, Andrew J Martin, Ian D Davis, for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†*

TheraP: Primary Endpoint — PSA Response ≥50%



Hofman MS et al. *Lancet* 2021;397(10276):797-804.

Positive Results Announced from the Phase III VISION Trial of Radioligand Therapy ^{177}Lu-PSMA-617 for Advanced Prostate Cancer

Press Release: Mar 23, 2021

"The Phase III VISION study [is] evaluating the efficacy and safety of ^{177}Lu-PSMA-617, a targeted radioligand therapy in patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) compared to best standard of care alone.

The trial met both primary endpoints of overall survival and radiographic progression-free survival… The safety profile was consistent with data reported in previous clinical studies.

Results from the VISION trial will be presented at an upcoming medical meeting and included in US and EU regulatory submissions."

https://www.novartis.com/news/media-releases/novartis-announces-positive-result-phase-iii-study-radioligand-therapy-177lu-psma-617-patients-advanced-prostate-cancer

RTP RESEARCH TO PRACTICE

Phase III Study of Lutetium-177-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer (VISION)

Morris MJ et al.
ASCO 2021;Abstract LBA4.

Plenary Session: Sunday, June 6, 1:00 PM - 4:00 PM EDT

Agenda

Module 1: Prostate Cancer

- Dr Nguyen: An 86-year-old man with a biochemical recurrence after local therapy
- *Key Recent Publications and Presentations*
- Dr Moon: A 65-year-old man with metastatic castration-resistant prostate cancer and a gBRCA2 mutation
- *Key Recent Publications and Presentations*

Module 2: Urothelial Bladder Cancer (UBC)

- Dr Moon: An 82-year-old man with metastatic UBC
- *Key Recent Publications and Presentations*
- Dr Gosain: A 65-year-old woman with metastatic UBC
- *Key Recent Publications and Presentations*

Module 3: Renal Cell Carcinoma (RCC)

- Dr Lorber: A 77-year-old man with de novo metastatic clear cell RCC treated with ipilimumab/nivolumab
- Dr Moon: A 43-year-old woman with metastatic RCC
- *Key Recent Publications and Presentations*

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Moon: An 82-year-old man with metastatic urothelial bladder cancer

Dr Helen Moon

- PMH: DM, HTN, peripheral neuropathy, overweight with limited mobility, creatinine clearance 45-55%
- Non-muscle-invasive bladder cancer past 3-5 years, sporadically treated with TURBT and BCG therapy
- Recently, CT urogram: Significant retroperitoneal lymph nodes, with squamous dedifferentiation
- Enrolled on a clinical trial of first-line enfortumab vedotin

Questions

- With an ECOG PS 1-2 and creatinine clearance of 45-55%, what treatment regimen would you recommend?

Key Recent Publications and Presentations

- Balar AV et al. **Pembrolizumab for the Treatment of Patients with High-Risk (HR) Non-Muscle-Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guérin: Extended Follow-Up of KEYNOTE-057 Cohort A.** Genitourinary Cancers Symposium 2021;Abstract 451.

- Bajorin DF et al. **First Results from the Phase 3 CheckMate 274 Trial of Adjuvant Nivolumab vs Placebo in Patients Who Underwent Radical Surgery for High-Risk Muscle-Invasive Urothelial Carcinoma (MIUC).** Genitourinary Cancers Symposium 2021;Abstract 391.

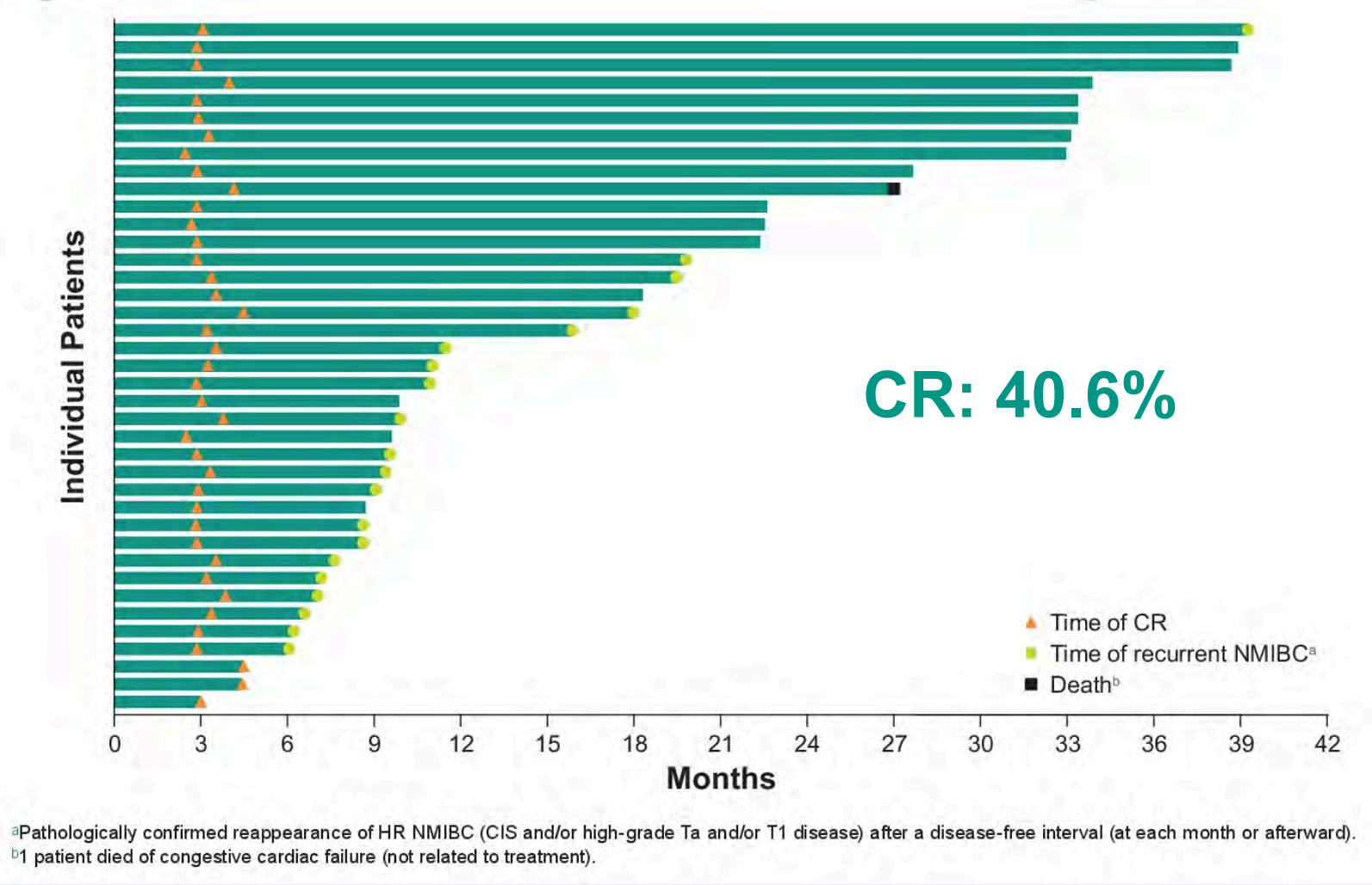
- Powles T et al. **Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma.** *N Engl J Med* 2020;383(13):1218-30.

Pembrolizumab for the Treatment of Patients with High-Risk (HR) Non-Muscle-Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guérin: Extended Follow-Up of KEYNOTE-057 Cohort A

Balar AV et al.

Genitourinary Cancers Symposium 2021;Abstract 451.

Extended Follow-Up of KEYNOTE-057: Response, Time to Response and Recurrence of HR NMIBC in Patients Who Experienced a CR



[a]Pathologically confirmed reappearance of HR NMIBC (CIS and/or high-grade Ta and/or T1 disease) after a disease-free interval (at each month or afterward).
[b]1 patient died of congestive cardiac failure (not related to treatment).

Balar AV et al. Genitourinary Cancers Symposium 2021;Abstract 451.

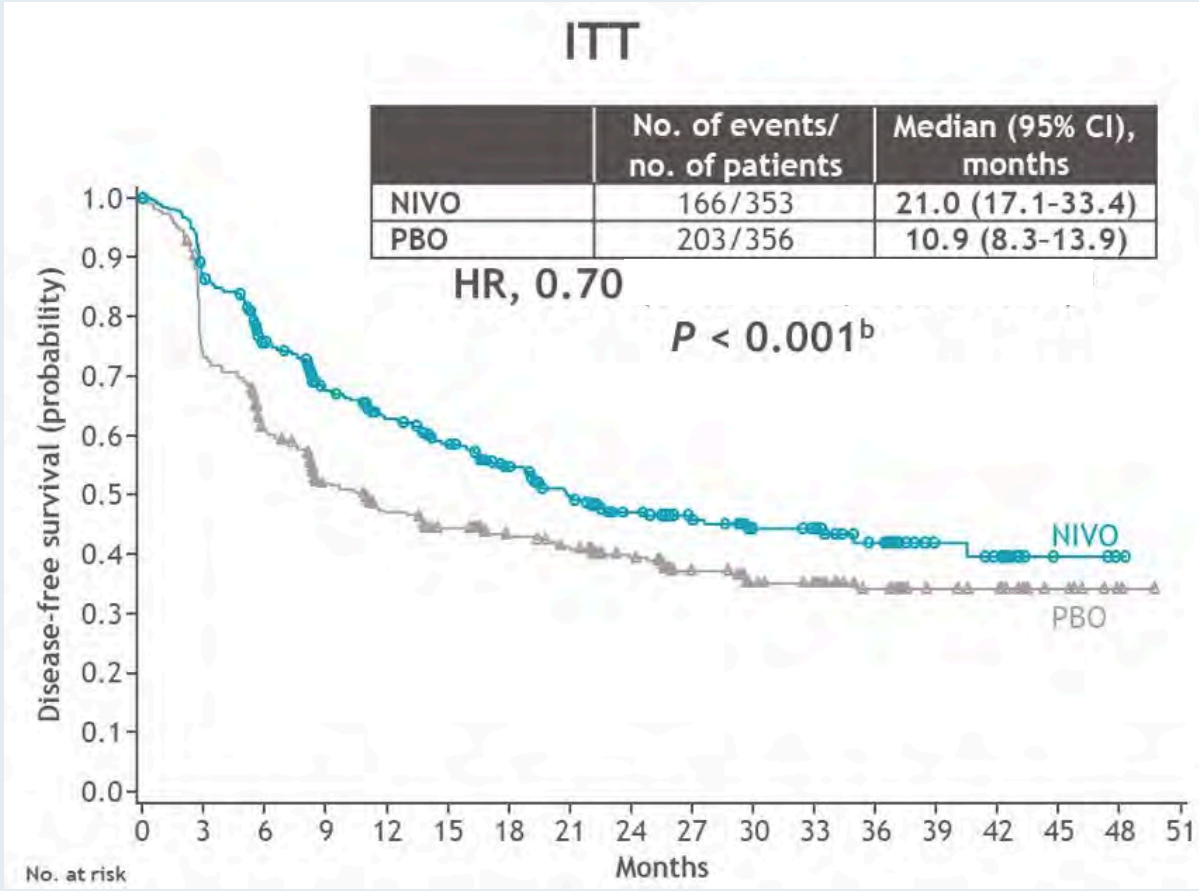
RTP RESEARCH TO PRACTICE

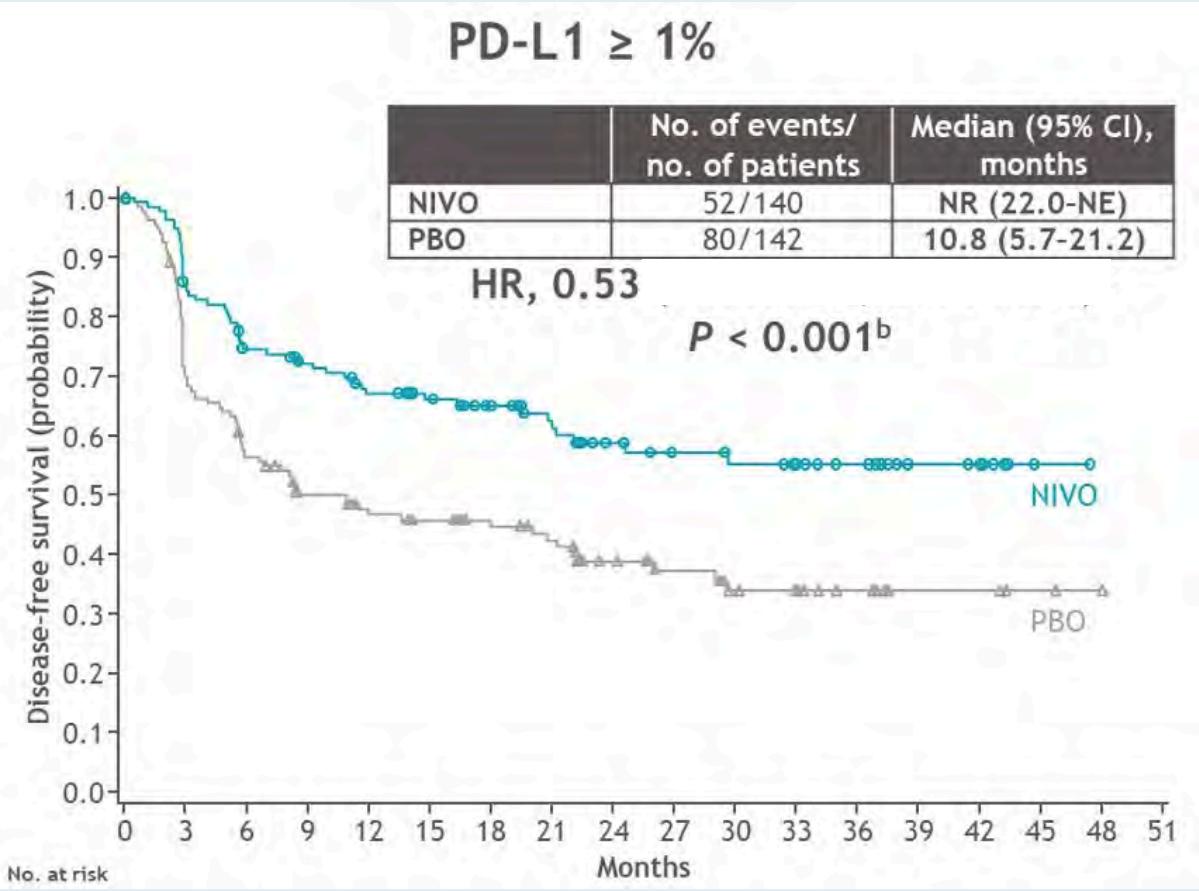
First Results from the Phase 3 CheckMate 274 Trial of Adjuvant Nivolumab vs Placebo in Patients Who Underwent Radical Surgery for High-Risk Muscle-Invasive Urothelial Carcinoma (MIUC)

Bajorin DF et al.

Genitourinary Cancers Symposium 2021;Abstract 391.

CheckMate 274: Disease-Free Survival in the ITT and PD-L1 ≥1% Populations





Bajorin DF et al. Genitourinary Cancers Symposium 2021;Abstract 391.

RTP RESEARCH TO PRACTICE

N Engl J Med 2020;383:1218-30.

The NEW ENGLAND JOURNAL of MEDICINE

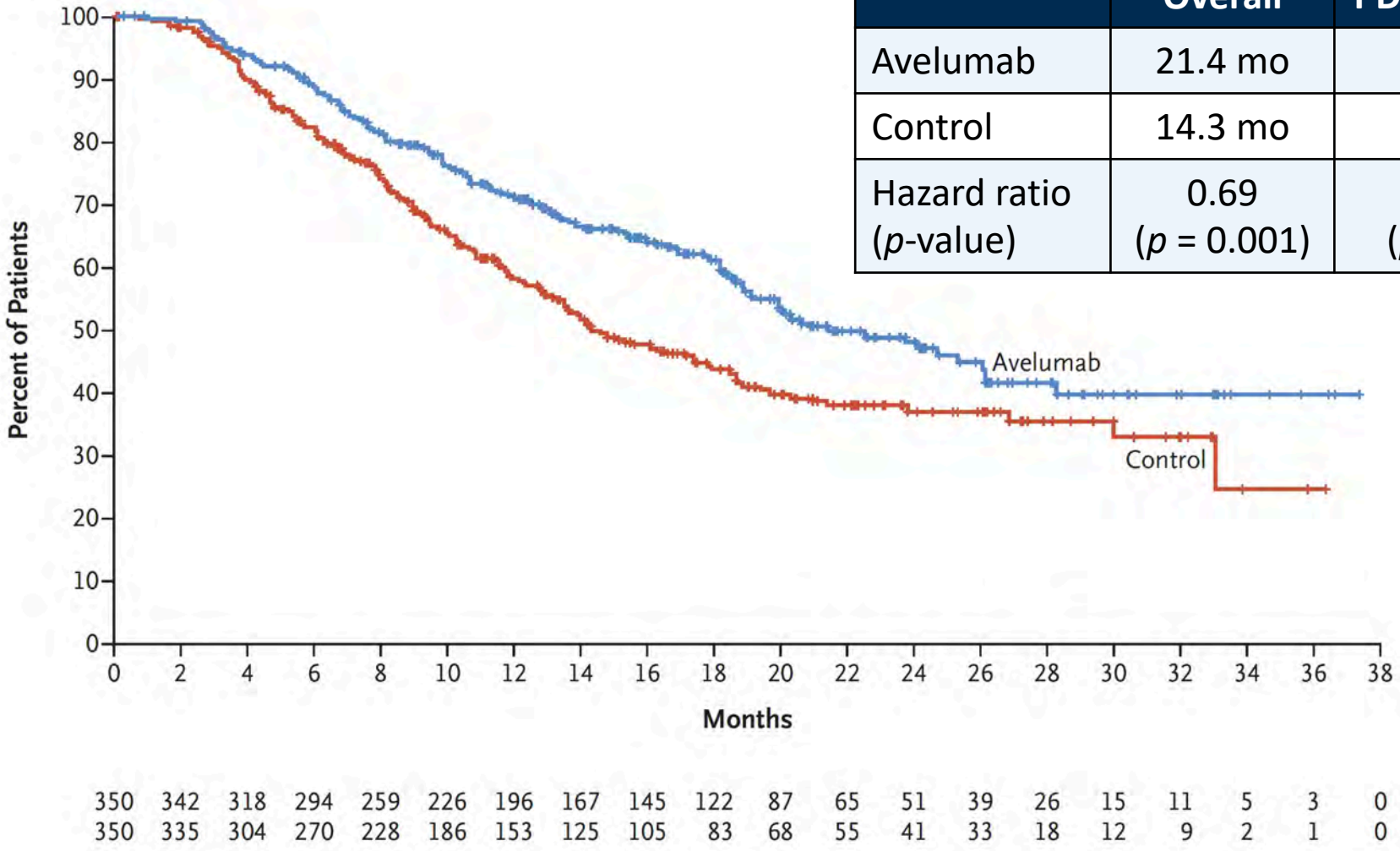
ORIGINAL ARTICLE

Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma

T. Powles, S.H. Park, E. Voog, C. Caserta, B.P. Valderrama, H. Gurney, H. Kalofonos, S. Radulović, W. Demey, A. Ullén, Y. Loriot, S.S. Sridhar, N. Tsuchiya, E. Kopyltsov, C.N. Sternberg, J. Bellmunt, J.B. Aragon-Ching, D.P. Petrylak, R. Laliberte, J. Wang, B. Huang, C. Davis, C. Fowst, N. Costa, J.A. Blake-Haskins, A. di Pietro, and P. Grivas

JAVELIN Bladder 100 Primary Endpoint: Overall Survival

	Overall	PD-L1-positive
Avelumab	21.4 mo	NE
Control	14.3 mo	17.1 mo
Hazard ratio (*p*-value)	0.69 ($p = 0.001$)	0.56 ($p < 0.001$)



Powles T et al. *N Engl J Med* 2020;383:1218-30.

RTP RESEARCH TO PRACTICE

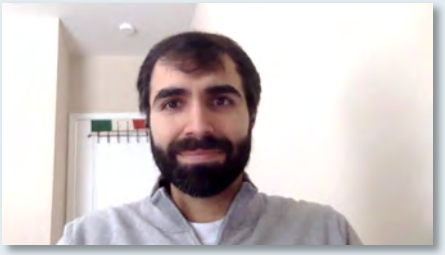
FDA-Approved Immune Checkpoint Inhibitors for UBC

Agent	Indication
Avelumab	• Maintenance treatment after first-line platinum-containing chemotherapy • Previously platinum-treated locally advanced or metastatic UBC
Pembrolizumab	• BCG-unresponsive, high-risk NMIBC in patients ineligible for or electing not to undergo cystectomy • Locally advanced or metastatic cisplatin-ineligible UBC, PD-L1 CPS ≥10 • Ineligible for any platinum-containing therapy, regardless of PD-L1 status
Durvalumab	*FDA indication voluntarily withdrawn (2/22/2021)*
Nivolumab	• Previously platinum-treated locally advanced or metastatic UBC
Atezolizumab	• Locally advanced or metastatic cisplatin-ineligible UBC, PD-L1 IC ≥5% • Ineligible for any platinum-containing therapy, regardless of PD-L1 status

NMIBC = non-muscle-invasive bladder cancer

https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications

Case Presentation – Dr Gosain: A 65-year-old woman with metastatic urothelial bladder cancer



Dr Rahul Gosain

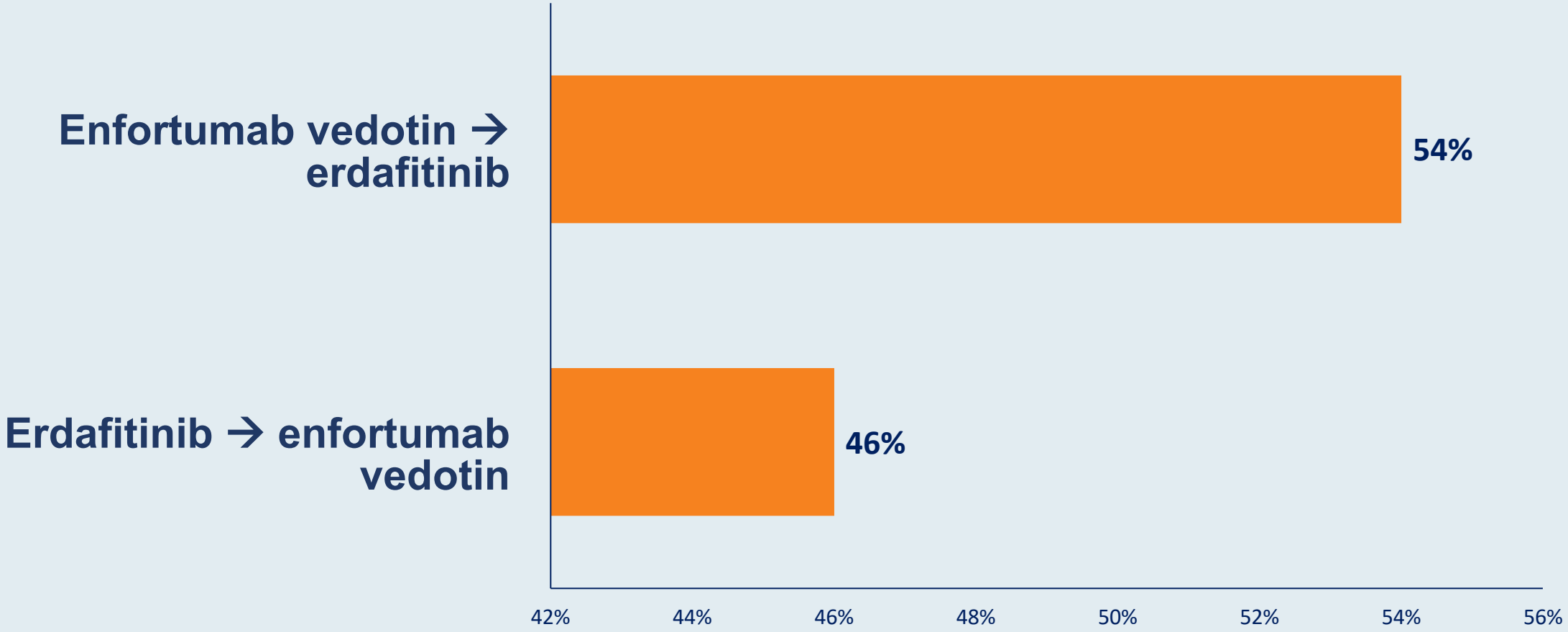
- 2018: Non-muscle-invasive urothelial carcinoma s/p TURBT → lost to follow-up
- 8/2020: Presents with fatigue, worsening pain
  - Workup: Iron deficiency, bladder mass, multiple bone lesions
  - Urology workup: Large fungating bladder mass (biopsy) with bleeding c/w high-grade UCC
- Palliative RT to bladder
- Split-dose cisplatin (GFR: 50) + gemcitabine → Worsening renal function → Carboplatin/gemcitabine x 4
- New pulmonary and bone lesions → Pembrolizumab
- Liquid biopsy: MSS, MTB 3 mut/Mb; FGFR3, ATM and CDK12 mutations

Questions

- In light of her FGFR mutation, if their disease progresses, would you consider erdafitinib, or enfortumab vedotin?
- Given her low TMB score, MSS and the FGFR mutation, would you have considered erdafitinib for second line versus immunotherapy? If considering immunotherapy, what would you recommend?
- What side effects need to be watched for with erdatifinib and enfortumab vedotin, and how do you manage them? With enfortumab, could you expand a little on the data for the skin toxicity?

RTP RESEARCH TO PRACTICE

How would you generally sequence enfortumab vedotin and erdafitinib for a patient with metastatic UBC who is eligible to receive both agents?



N = 63

Survey of live webinar audience

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- Powles T et al. **Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma.** *N Engl J Med* 2021;384(12):1125-35.

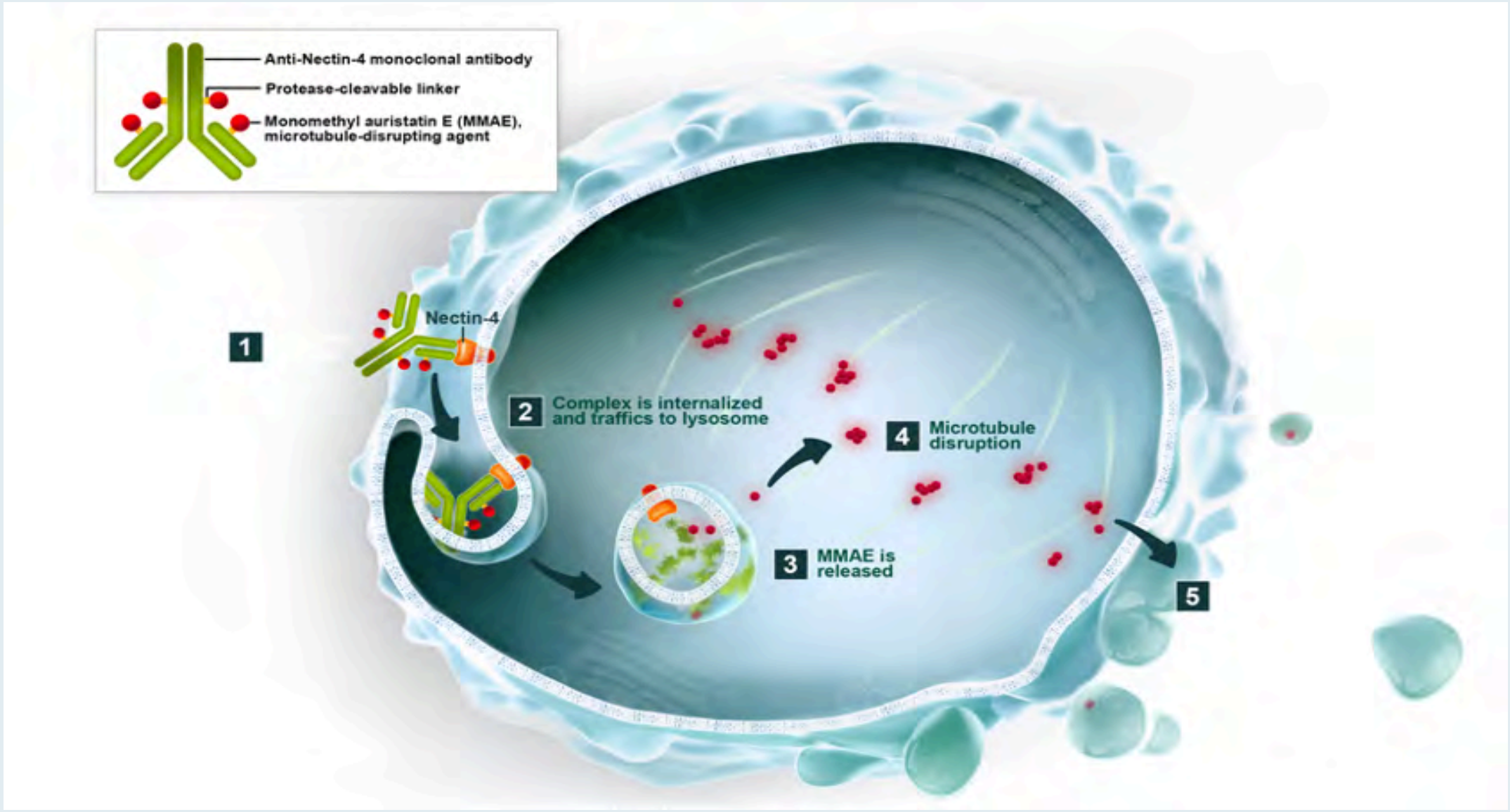
- Balar AV et al. **EV-201 Cohort 2: Enfortumab Vedotin in Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Cancer Who Received Prior PD-1/PD-L1 Inhibitors.** Genitourinary Cancers Symposium 2021;Abstract 394.

- Rosenberg JE et al. **Study EV-103: Durability Results of Enfortumab Vedotin plus Pembrolizumab for Locally Advanced or Metastatic Urothelial Carcinoma.** ASCO 2020;Abstract 5044.

- Siefker-Radtke AO et al. **Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma (mUC): Long-Term Outcomes in BLC2001.** ASCO 2020;Abstract 5015.

- Tagawa ST et al. **TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors.** *J Clin Oncol* 2021;[Online ahead of print].

Enfortumab Vedotin: Nectin-4 Targeted Therapy



Courtesy of Jonathan Rosenberg, MD

RTP RESEARCH TO PRACTICE

Priority Review Granted to 2 Applications of Enfortumab Vedotin for Metastatic Urothelial Carcinoma

Press Release – April 19, 2021

"Two supplemental biologics license applications for enfortumab vedotin have been accepted by the FDA and granted priority review for the treatment of locally advanced or metastatic urothelial carcinoma"

The first application seeks to convert the current accelerated approval in the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a PD-1/PD-L1 inhibitor and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting to a full approval based on results of the phase 3 EV-301 trial (NCT03474107).

The second application is based on results of the pivotal cohort 2 of the phase 2 EV-201 trial (NCT03219333) and seeks to expand the current indication to include patients who've previously been treated with a PD-1/PD-L1 inhibitor but are not eligible for cisplatin. The target action date for both applications is August 17, 2021."

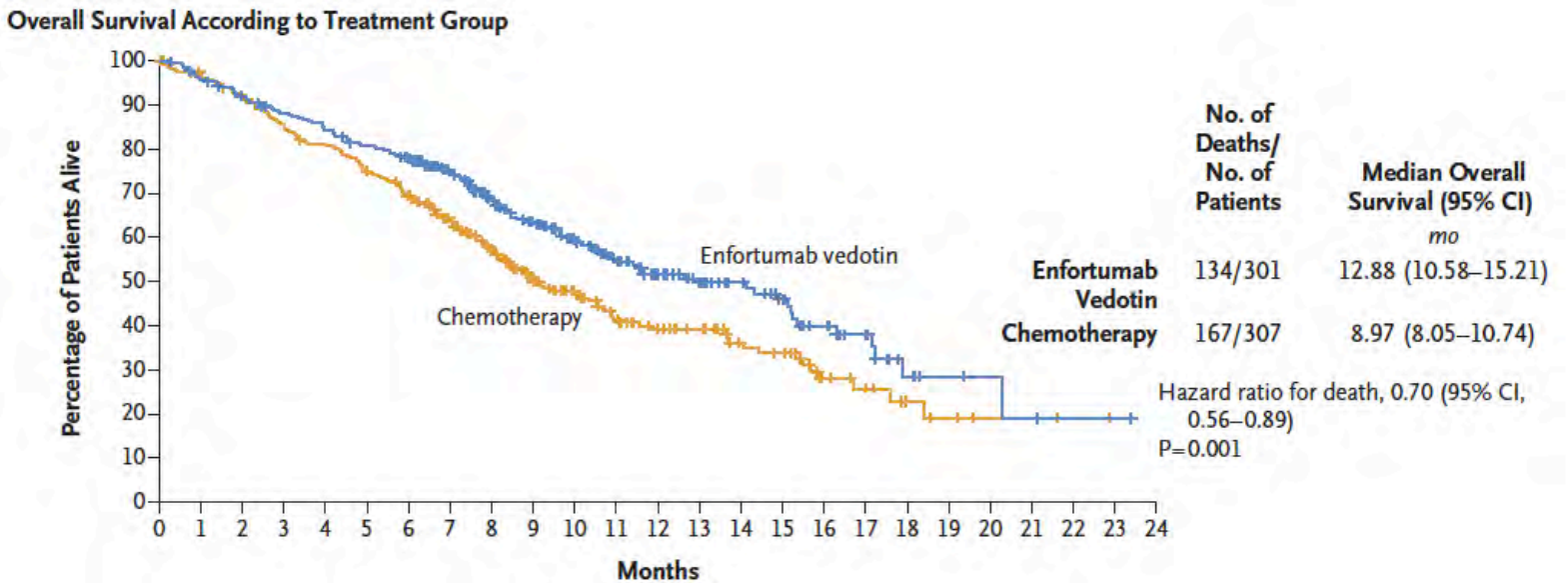
ORIGINAL ARTICLE

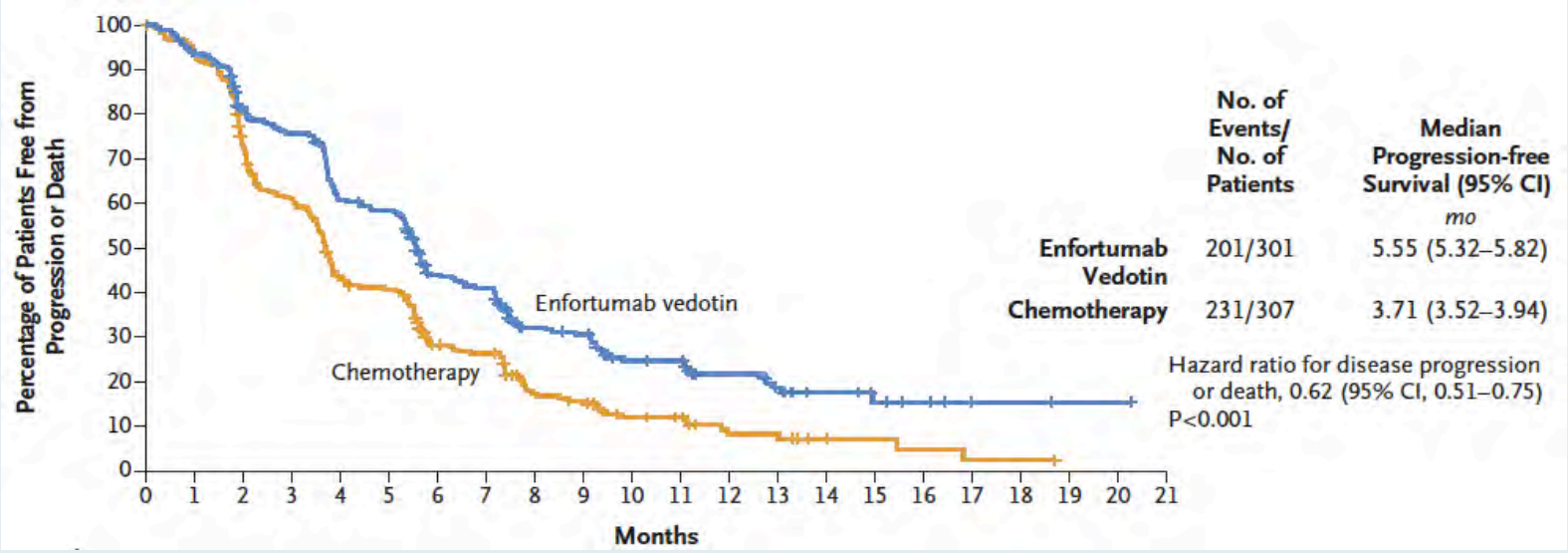
Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

Thomas Powles, M.D., Jonathan E. Rosenberg, M.D., Guru P. Sonpavde, M.D., Yohann Loriot, M.D., Ph.D., Ignacio Durán, M.D., Ph.D., Jae-Lyun Lee, M.D., Ph.D., Nobuaki Matsubara, M.D., Christof Vulsteke, M.D., Ph.D., Daniel Castellano, M.D., Chunzhang Wu, Ph.D., Mary Campbell, M.D., Maria Matsangou, M.B., Ch.B., M.D., and Daniel P. Petrylak, M.D.

N Engl J Med 2021;384(12):1125-35.

EV-301: Survival and Response Analyses





	EV (n = 301)	Chemo (n = 307)
ORR	40.6%	17.9%
DCR	71.9%	53.4%

Incidence of treatment-related adverse events was similar in the two groups:

- 93.9% versus 91.8%

Incidence of events of grade 3 or higher was also similar in the two groups:

- 51.4% versus 49.8%

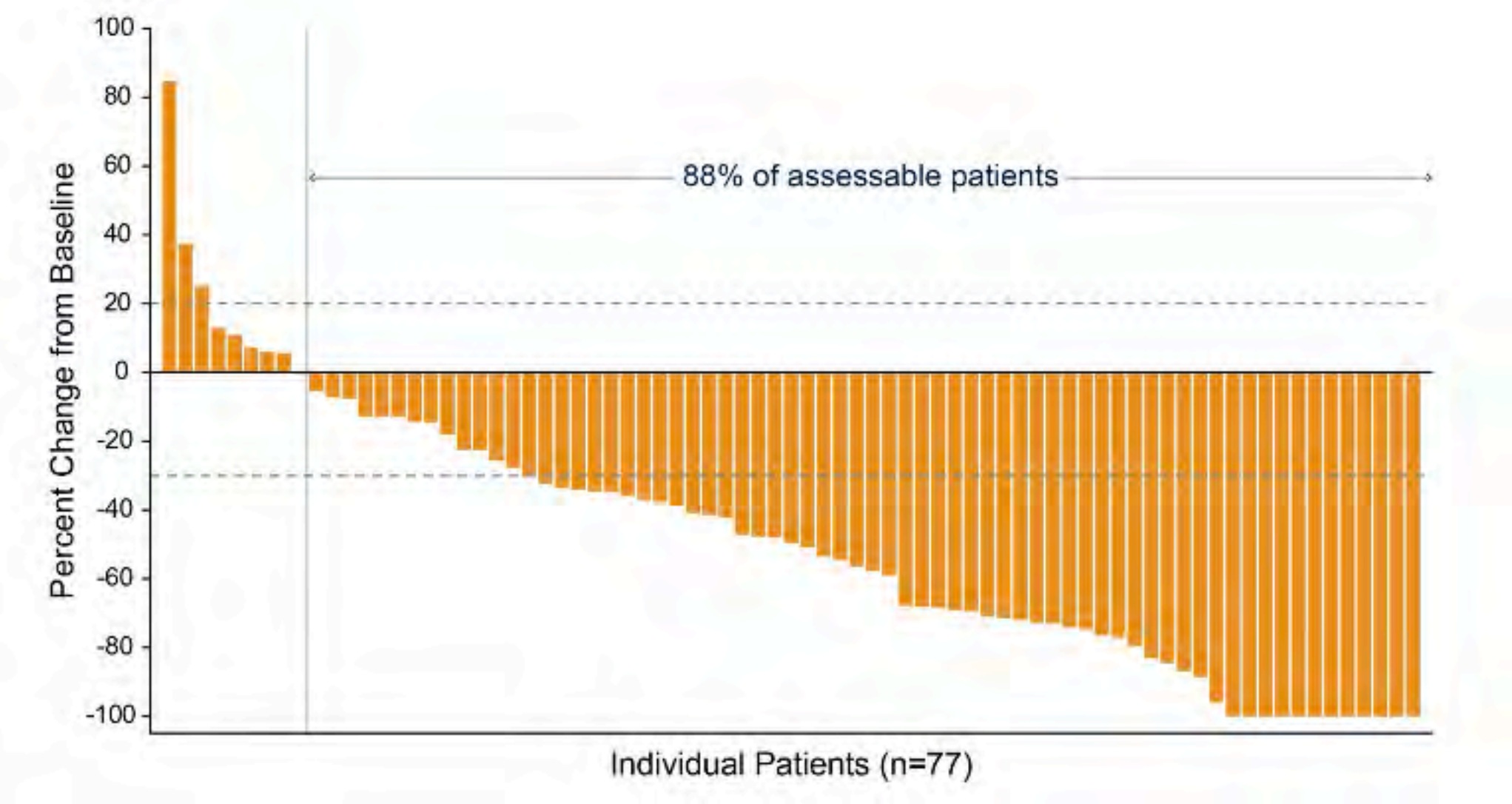
Powles T et al. *N Engl J Med* 2021;384(12):1125-35.

EV-201 Cohort 2: Enfortumab Vedotin in Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Cancer Who Received Prior PD-1/PD-L1 Inhibitors

Balar AV et al.

Genitourinary Cancers Symposium 2021;Abstract 394.

EV-201 Cohort 2: Change in Tumor Measurements per BICR



Balar AV et al. Genitourinary Cancers Symposium 2021;Abstract 394.

RTP RESEARCH TO PRACTICE

EV-201 Cohort 2: Response and Survival Analyses

Efficacy endpoints	(N = 91)
Confirmed ORR per BICR	52%
CR	20%
Median DOR	10.9 mo
Median PFS	5.8 mo
Median OS	14.7 mo

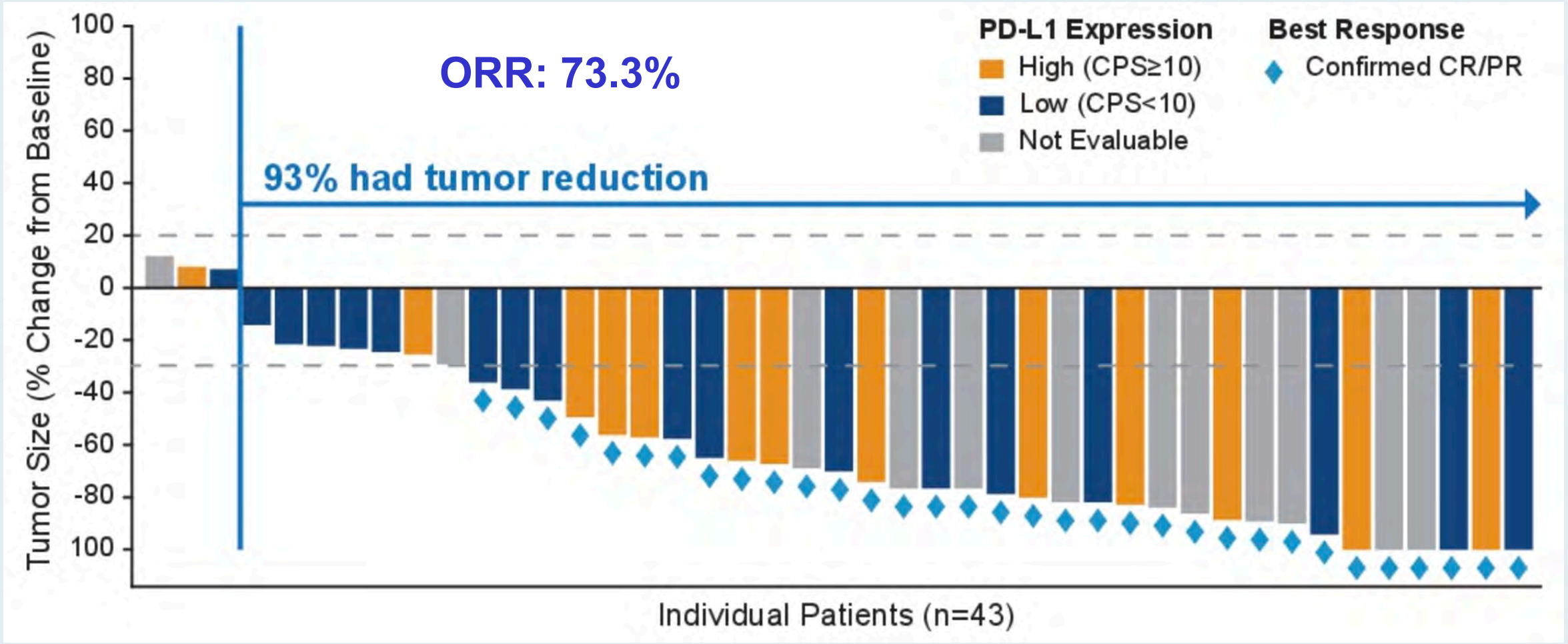
Balar AV et al. Genitourinary Cancers Symposium 2021;Abstract 394.

Study EV-103: Durability Results of Enfortumab Vedotin plus Pembrolizumab for Locally Advanced or Metastatic Urothelial Carcinoma

Rosenberg JE et al.

ASCO 2020;Abstract 5044.

EV-103: Response to Enfortumab Vedotin with Pembrolizumab in the First-Line Setting

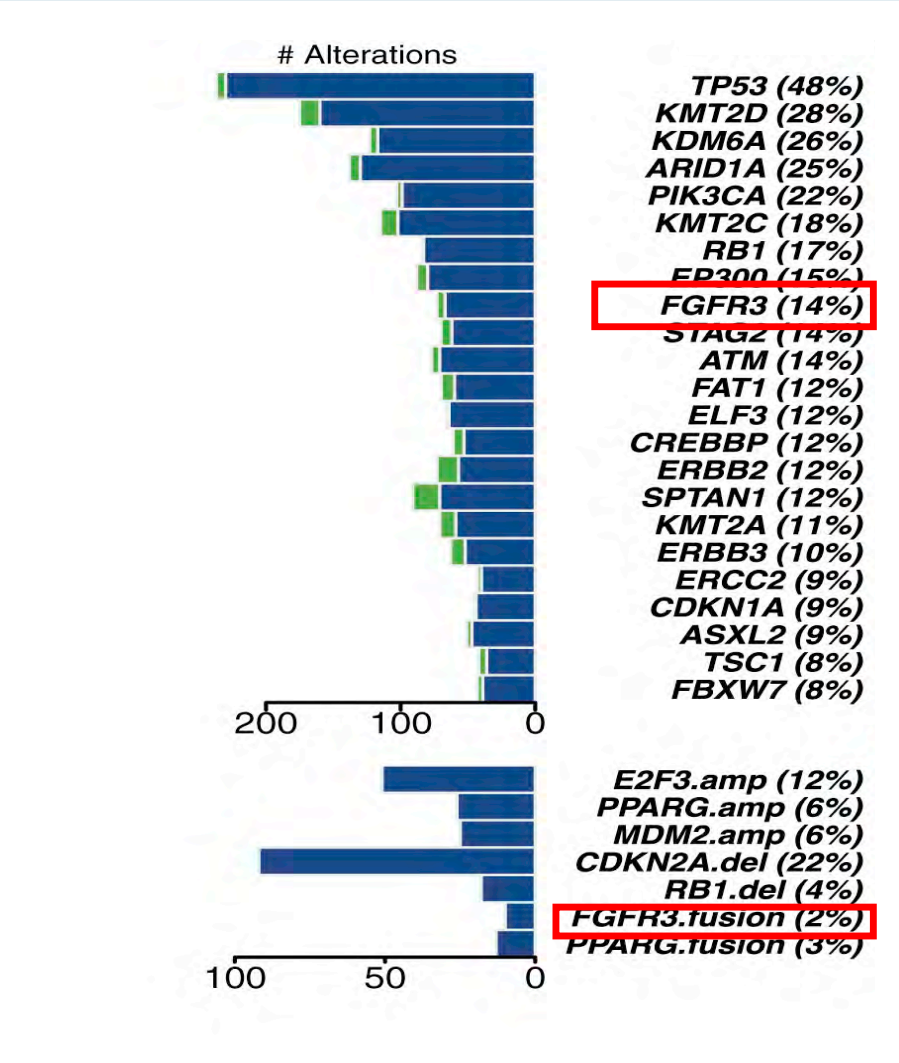


Rosenberg JE et al. ASCO 2020;Abstract 5044.

RTP RESEARCH TO PRACTICE

FGFR3 Genomic Alterations in Muscle-Invasive Bladder Cancer

Genomics of MIBC: TCGA



- In muscle-invasive disease, *FGFR3* mutations in ~20% of tumors, but protein and/or gene overexpression in ~50%.
- Activating mutations of *FGFR3* in ~75% of low-grade papillary bladder tumors.
- FGFR3-TACC3 fusions enriched in young, Asian, non-smokers, upper tract tumors (invasive, high grade)
- Preclinical evidence for activity of FGFR inhibitors in selected cells with FGFR alterations

Courtesy of Guru Sonpavde, MD

Robertson AG et al. *Cell* 2017;171(3):540-56; Cappellen D et al. *Nat Genet* 1999;23:18-20; Nassar A et al. *JCO Precis Oncol* 2018; Gust KM et al. *Mol Cancer Ther* 2013;12:1245-54; Grünewald S et al. *Int J Cancer* 2019; Sfakianos JP Eur Urol 2015;68(6):970-7.

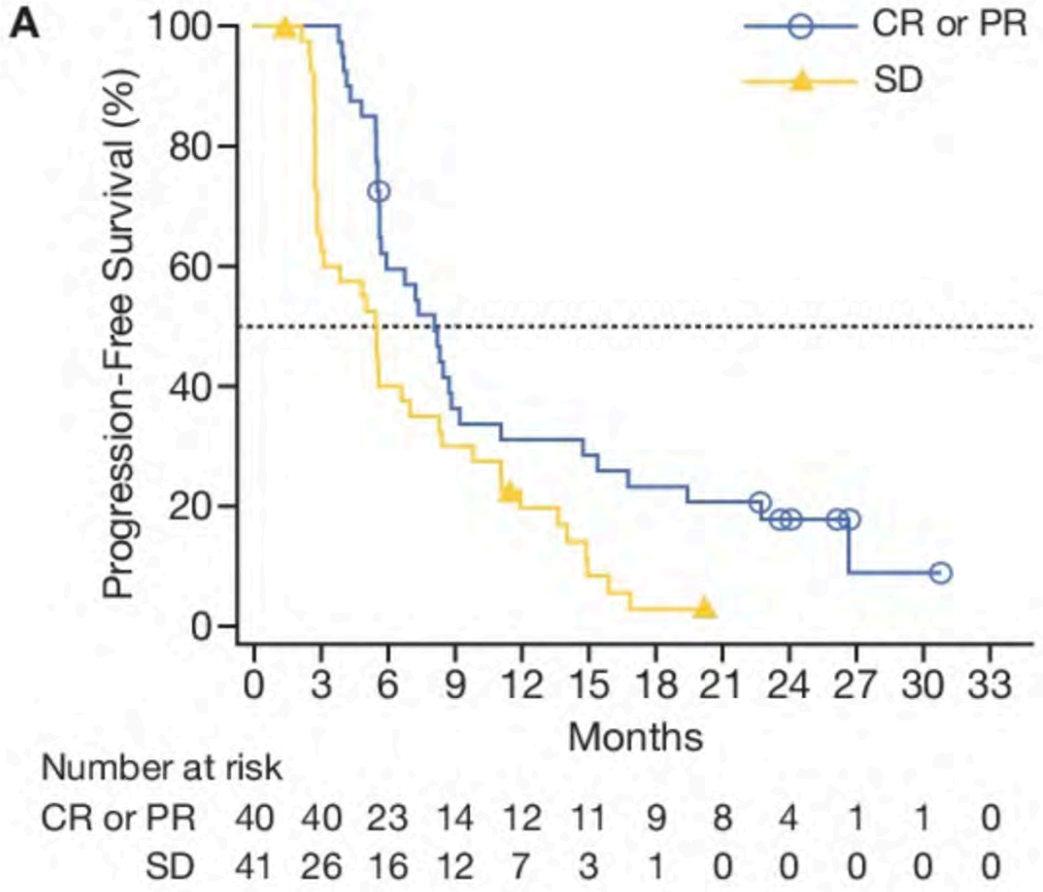
Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma (mUC): Long-Term Outcomes in BLC2001

Siefker-Radtke AO et al.

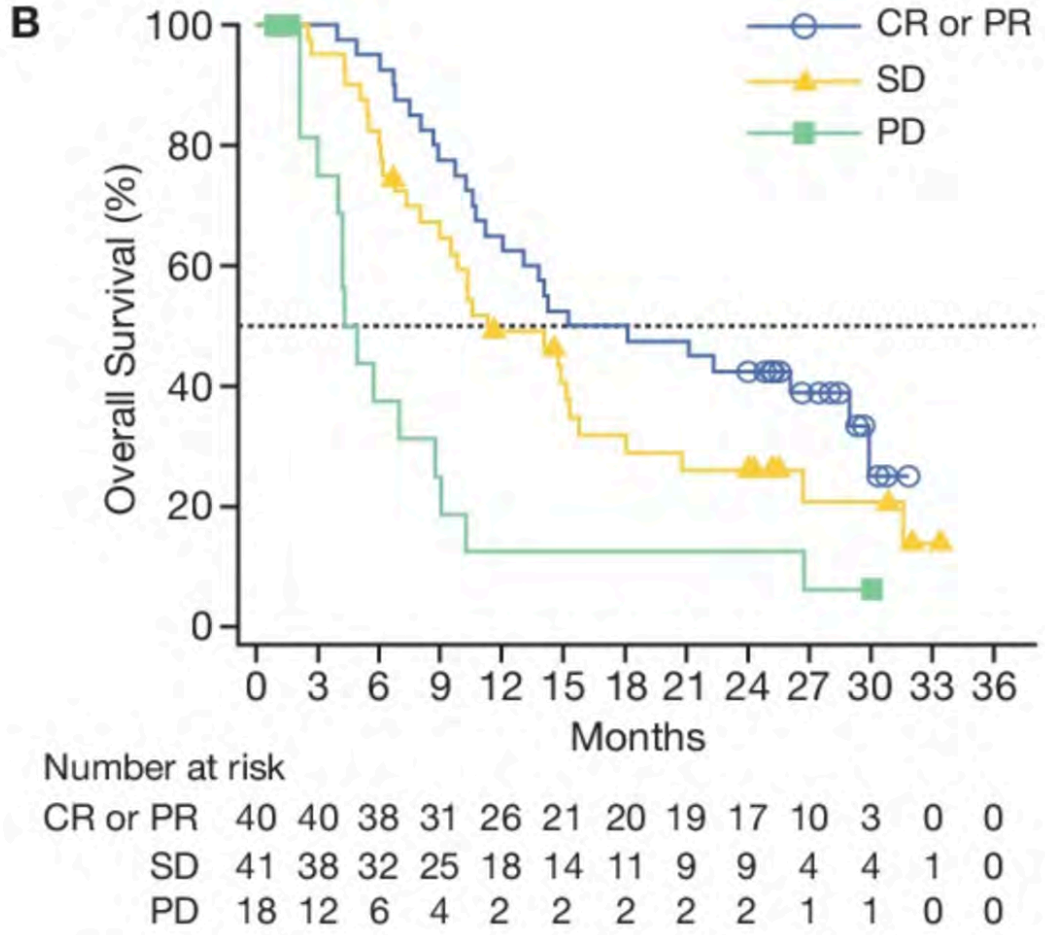
ASCO 2020;Abstract 5015.

BLC2001: Survival

Median PFS: 5.5 months



Median OS: 11.3 months



Siefker-Radtke AO et al. ASCO 2020;Abstract 5015.

RTP RESEARCH TO PRACTICE

Are FGFR3 Alterations Associated with Resistance to PD-1/PD-L1 Blockade in Large Clinical Trial Cohorts?

18% mFGFR

Objective Response Rate

Wild type	**21% (95% CI: 16%, 27%)**
Mutant	**24% (95% CI: 14%, 39%)**

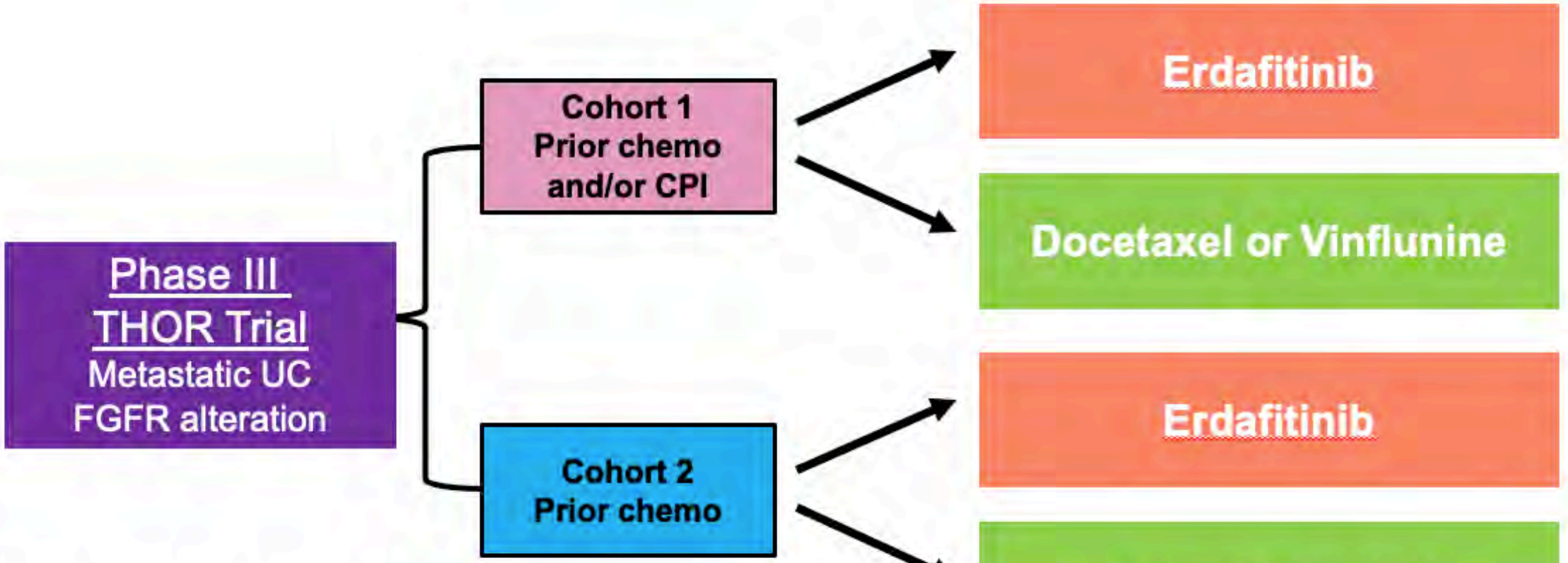
11% mFGFR

Wild type	**21% (95% CI: 15%, 29%)**
Mutant	**21% (95% CI: 15%, 29%)**

Wang, European Urology, 2019

Courtesy of Matthew Galsky, MD.

Ongoing Phase III THOR Trial Design



Primary endpoint: Overall survival
Secondary endpoints include progression-free survival, response, safety, change in disease severity and quality of life

FDA Grants Accelerated Approval to Sacituzumab Govitecan for Advanced Urothelial Cancer

Press Release – April 13, 2021

"The Food and Drug Administration granted accelerated approval to sacituzumab govitecan for patients with locally advanced or metastatic urothelial cancer (mUC) who previously received a platinum-containing chemotherapy and either a programmed death receptor-1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor.

Efficacy and safety were evaluated in TROPHY (IMMU-132-06; NCT03547973), a single-arm, multicenter trial that enrolled 112 patients with locally advanced or mUC who received prior treatment with a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor. Patients received sacituzumab govitecan, 10 mg/kg intravenously, on days 1 and 8 of a 21-day treatment cycle."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sacituzumab-govitecan-advanced-urothelial-cancer

RTP RESEARCH TO PRACTICE

TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors

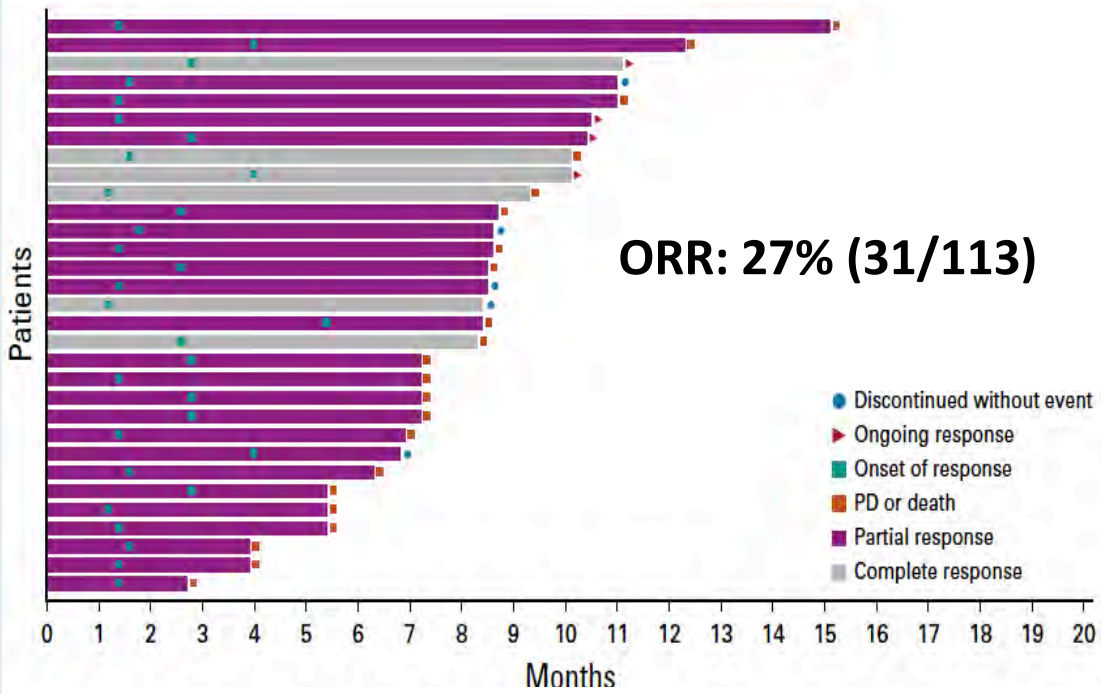
Scott T. Tagawa, MD, MS[1]; Arjun V. Balar, MD[2]; Daniel P. Petrylak, MD[3]; Arash Rezazadeh Kalebasty, MD[4]; Yohann Loriot, MD, PhD[5]; Aude Fléchon, MD, PhD[6]; Rohit K. Jain, MD[7]; Neeraj Agarwal, MD[8]; Manojkumar Bupathi, MD, MS[9]; Philippe Barthelemy, MD, PhD[10]; Philippe Beuzeboc, MD, PhD[11]; Phillip Palmbos, MD, PhD[12]; Christos E. Kyriakopoulos, MD[13]; Damien Pouessel, MD, PhD[14]; Cora N. Sternberg, MD[1]; Quan Hong, MD[15]; Trishna Goswami, MD[15]; Loretta M. Itri, MD[15]; and Petros Grivas, MD, PhD[16]

J Clin Oncol 2021;[Online ahead of print].

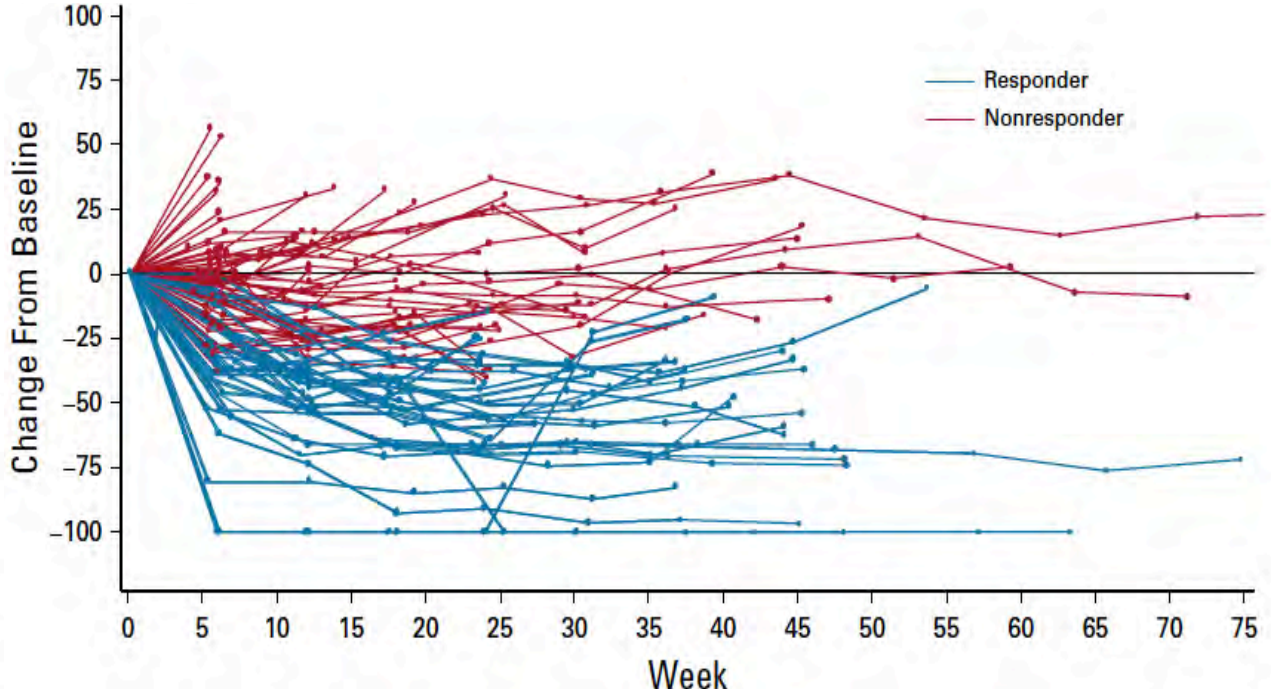
TROPHY-U-01 (Cohort 1): ORR, Duration of Response and Survival

Median DOR: 7.2 mo

Median time to onset of response: 1.6 mo



ORR: 27% (31/113)



Median PFS: 5.4 mo

Median OS: 10.9 mo

Tagawa ST et al. *J Clin Oncol* 2021;[Online ahead of print]; Loriot Y et al. ESMO 2020;Abstract LBA24.

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Prostate Cancer

- Dr Nguyen: An 86-year-old man with a biochemical recurrence after local therapy
- *Key Recent Publications and Presentations*
- Dr Moon: A 65-year-old man with metastatic castration-resistant prostate cancer and a gBRCA2 mutation
- *Key Recent Publications and Presentations*

Module 2: Urothelial Bladder Cancer (UBC)

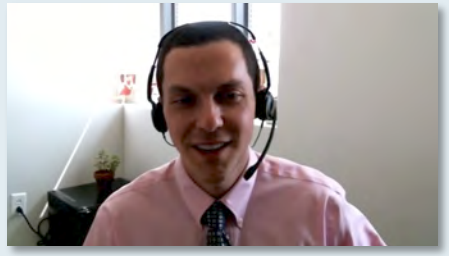
- Dr Moon: An 82-year-old man with metastatic UBC
- *Key Recent Publications and Presentations*
- Dr Gosain: A 65-year-old woman with metastatic UBC
- *Key Recent Publications and Presentations*

Module 3: Renal Cell Carcinoma (RCC)

- Dr Lorber: A 77-year-old man with de novo metastatic clear cell RCC treated with ipilimumab/nivolumab
- Dr Moon: A 43-year-old woman with metastatic RCC
- *Key Recent Publications and Presentations*

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Lorber: A 77-year-old man with de novo metastatic clear cell RCC treated with ipilimumab/nivolumab



Dr Jeremy Lorber

- PMH: No underlying health issues
- Presented with *de novo* metastatic clear cell RCC with asymptomatic lung metastasis and symptoms of only mild flank pain
- Ipilimumab/nivolumab with partial response lasting 20 months

Questions

- Given prolonged response to checkpoint inhibitor therapy, would it be reasonable to reintroduce ipilimumab? If not, what would be your preferred second-line treatment for this patient?
- How do you distinguish between the TKIs? Is the toxicity profile worse or different amongst the TKIs?
- Is cabozantinib better not used in first line since at least it preserves a later-line therapy whereas one is less likely to use something like axitinib in later line?
- What role, if any, is there for nephrectomy in a patient like this man?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Moon: A 43-year-old woman with metastatic RCC

Dr Helen Moon

- Presents with a cough, and lung metastases are identified from an 11-cm RCC primary
- Ipilimumab/nivolumab x 3
  - Last held due to “terrible” colitis, which resolved with steroids
- Maintenance nivolumab x 1.5 years, with near CR

Question

- Would you have selected a double-immunotherapy regimen versus one of the currently available TKI/immunotherapy combinations?

Key Recent Publications and Presentations

- Powles T et al. **Pembrolizumab plus Axitinib versus Sunitinib Monotherapy as First-Line Treatment of Advanced Renal Cell Carcinoma (KEYNOTE-426): Extended Follow-Up from a Randomised, Open-Label, Phase 3 Trial.** *Lancet Oncol* 2020;21(12):1563-73.

- Choueiri TK et al. **Updated Efficacy Results from the JAVELIN Renal 101 Trial: First-Line Avelumab plus Axitinib versus Sunitinib in Patients with Advanced Renal Cell Carcinoma.** *Ann Oncol* 2020;31(8):1030-39.

- Choueiri TK et al; CheckMate 9ER Investigators. **Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma.** *N Engl J Med* 2021;384(9):829-41.

- Motzer R et al; CLEAR Trial Investigators. **Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma.** *N Engl J Med* 2021;384(14):1289-300.

- Pal SK et al. **A Comparison of Sunitinib with Cabozantinib, Crizotinib, and Savolitinib for Treatment of Advanced Papillary Renal Cell Carcinoma: A Randomised, Open-Label, Phase 2 Trial.** *Lancet* 2021;397(10275):695-703.

Pembrolizumab versus Placebo as Post-Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase III KEYNOTE-564 Study

Choueiri TK et al.
ASCO 2021;Abstract LBA5.

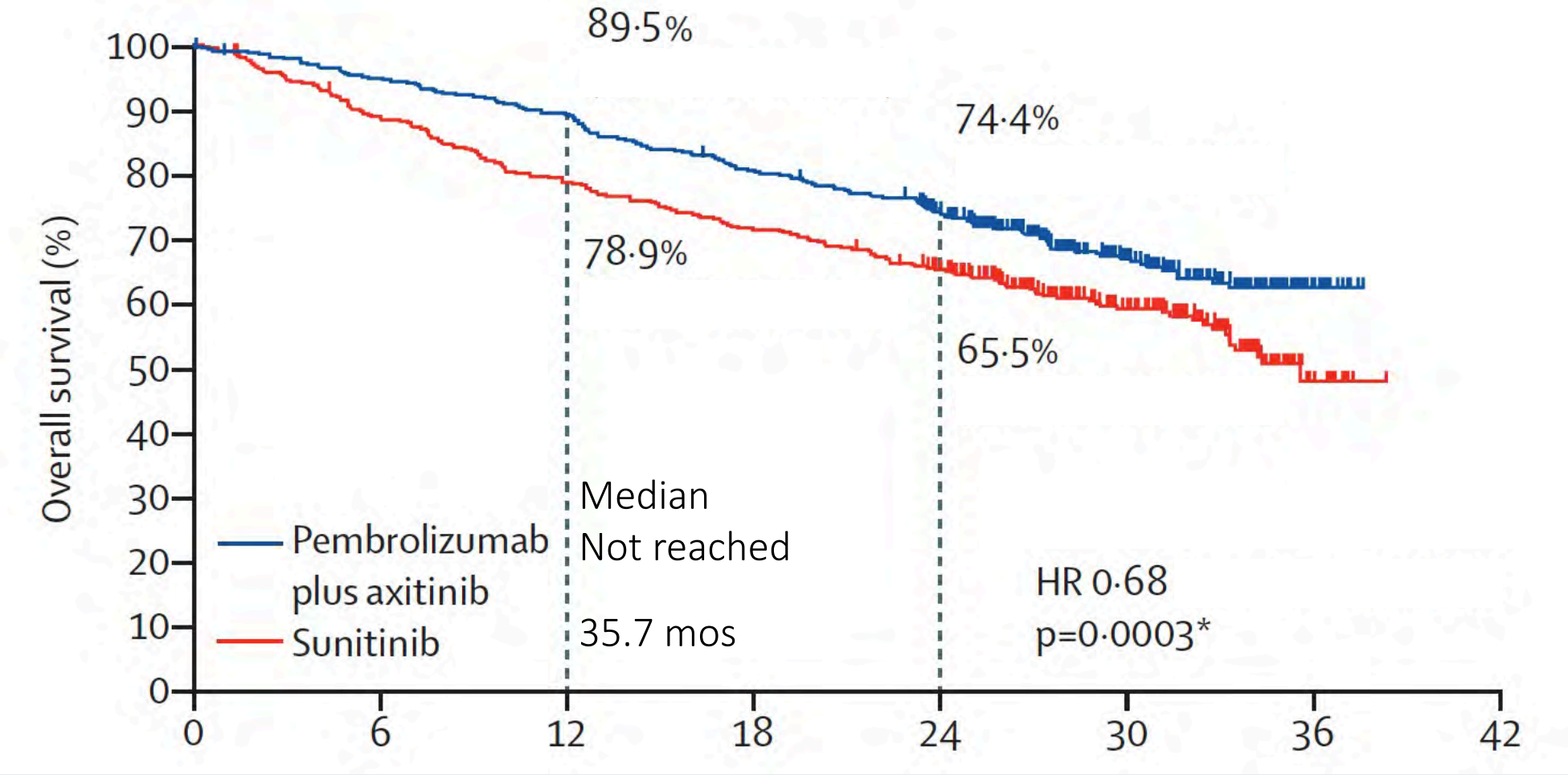
Plenary Session: Sunday, June 6, 1:00 PM - 4:00 PM EDT

Lancet Oncol 2020;21:1563-73.

Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial

Thomas Powles, Elizabeth R Plimack, Denis Soulières, Tom Waddell, Viktor Stus, Rustem Gafanov, Dmitry Nosov, Frédéric Pouliot, Bohuslav Melichar, Ihor Vynnychenko, Sergio J Azevedo, Delphine Borchiellini, Raymond S McDermott, Jens Bedke, Satoshi Tamada, Lina Yin, Mei Chen, L Rhoda Molife, Michael B Atkins, Brian I Rini

KEYNOTE-426: Overall Survival with Extended Follow-Up



Powles T et al. *Lancet Oncol* 2020;21:1563-73.

RTP RESEARCH TO PRACTICE

Ann Oncol 2020;31(8):1030-9.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma

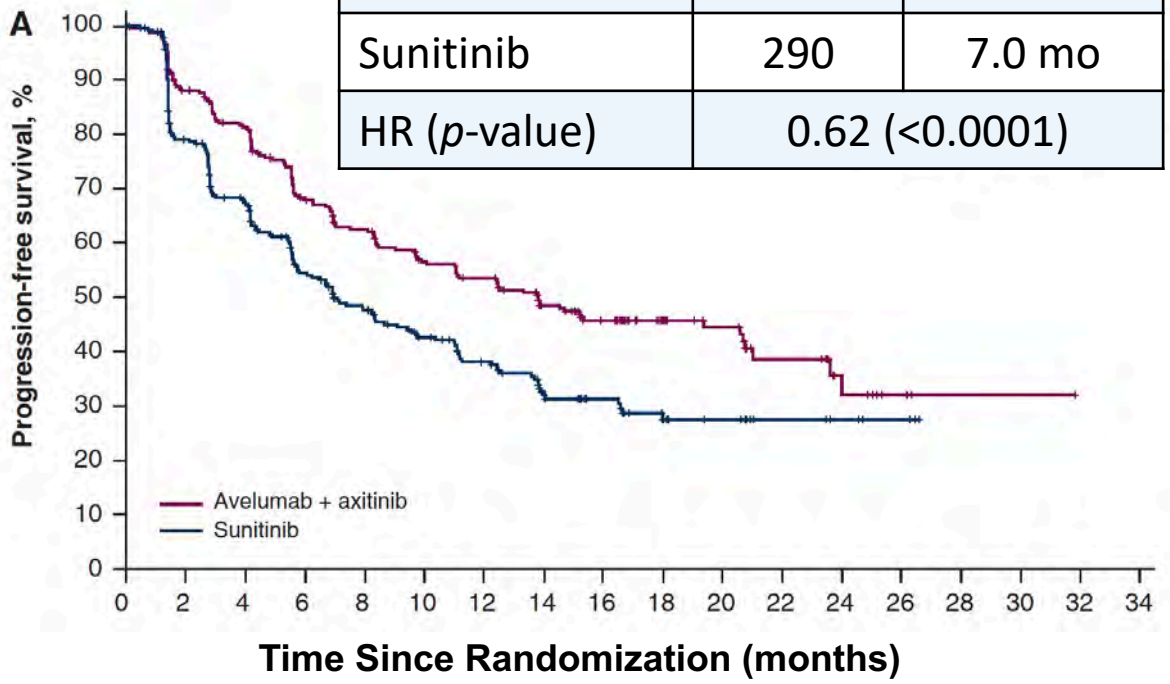
T. K. Choueiri[1*], R. J. Motzer[2], B. I. Rini[3†], J. Haanen[4], M. T. Campbell[5], B. Venugopal[6], C. Kollmannsberger[7], G. Gravis-Mescam[8], M. Uemura[9], J. L. Lee[10], M.-O. Grimm[11], H. Gurney[12], M. Schmidinger[13], J. Larkin[14], M. B. Atkins[15], S. K. Pal[16], J. Wang[17], M. Mariani[18], S. Krishnaswami[19], P. Cislo[20], A. Chudnovsky[21], C. Fowst[18], B. Huang[19], A. di Pietro[22] & L. Albiges[23]

RTP RESEARCH TO PRACTICE

JAVELIN Renal 101: PFS in the PD-L1+ and Overall Populations

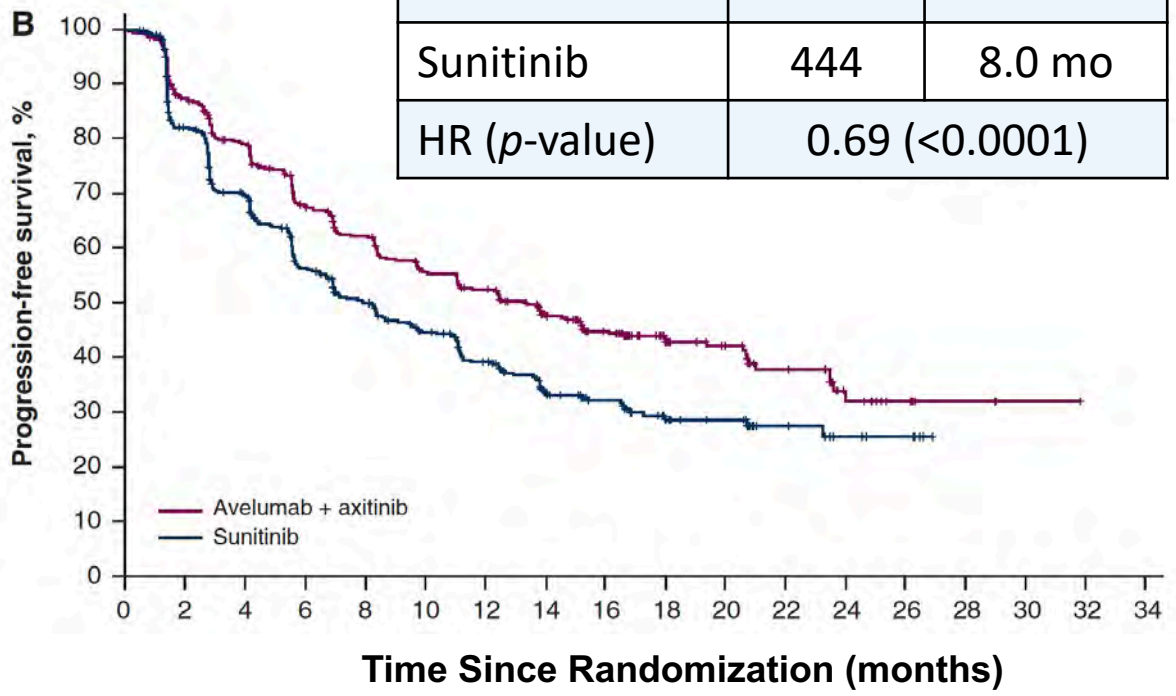
PD-L1 ≥ 1% Population

	N	mPFS
Avelumab + Axitinib	270	13.8 mo
Sunitinib	290	7.0 mo
HR (*p*-value)	0.62 (<0.0001)	



Overall Population

	N	mPFS
Avelumab + Axitinib	442	13.3 mo
Sunitinib	444	8.0 mo
HR (*p*-value)	0.69 (<0.0001)	



Choueiri TK et al. *Ann Oncol* 2020;31(8):1030-9.

RTP RESEARCH TO PRACTICE

FDA Approves Nivolumab with Cabozantinib for Advanced RCC

Press Release: January 22, 2021

"On January 22, 2021, the Food and Drug Administration approved the combination of nivolumab and cabozantinib as first-line treatment for patients with advanced renal cell carcinoma (RCC).

Efficacy was evaluated in CHECKMATE-9ER (NCT03141177), a randomized, open-label trial in patients with previously untreated advanced RCC. Patients were randomized to receive either nivolumab 240 mg over 30 minutes every 2 weeks in combination with cabozantinib 40 mg orally once daily (n=323) or sunitinib 50 mg orally daily for the first 4 weeks of a 6-week cycle (4 weeks on treatment followed by 2 weeks off) (n=328)."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-nivolumab-plus-cabozantinib-advanced-renal-cell-carcinoma

RTP RESEARCH TO PRACTICE

ORIGINAL ARTICLE

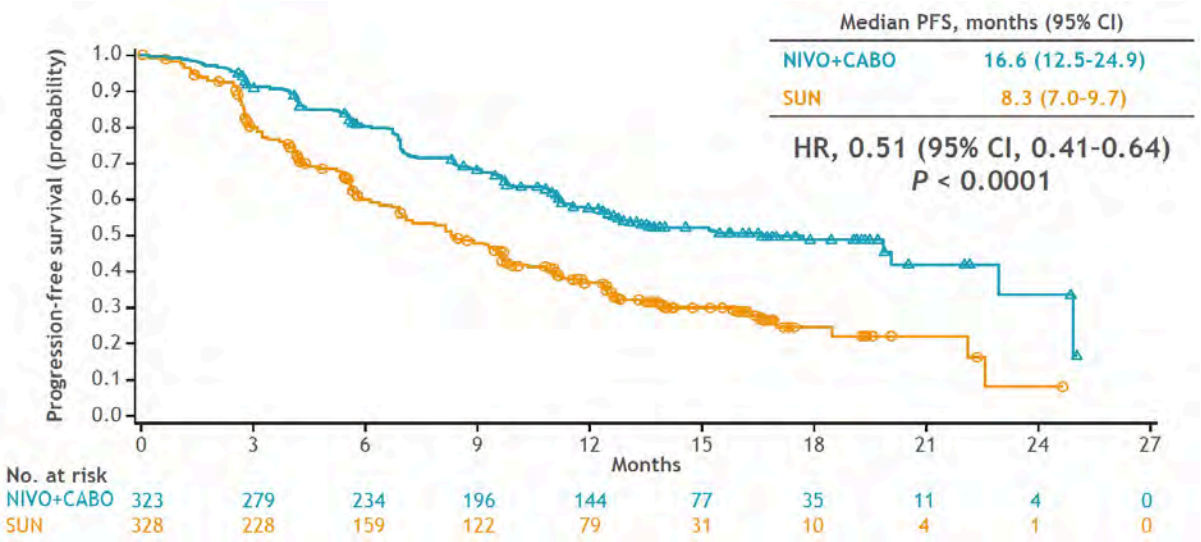
Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma

T.K. Choueiri, T. Powles, M. Burotto, B. Escudier, M.T. Bourlon, B. Zurawski, V.M. Oyervides Juárez, J.J. Hsieh, U. Basso, A.Y. Shah, C. Suárez, A. Hamzaj, J.C. Goh, C. Barrios, M. Richardet, C. Porta, R. Kowalyszyn, J.P. Feregrino, J. Żołnierek, D. Pook, E.R. Kessler, Y. Tomita, R. Mizuno, J. Bedke, J. Zhang, M.A. Maurer, B. Simsek, F. Ejzykowicz, G.M. Schwab, A.B. Apolo, and R.J. Motzer, for the CheckMate 9ER Investigators*

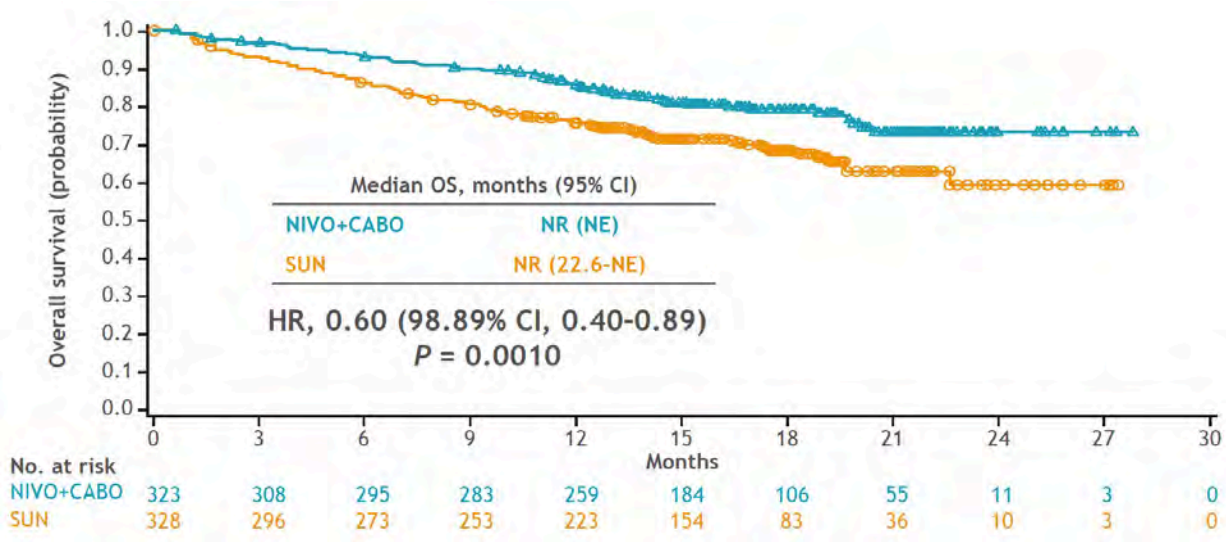
N Engl J Med 2021;384(9):829-41.

CheckMate 9ER Survival Analyses: Nivolumab/Cabozantinib for Previously Untreated Advanced RCC

Progression-free survival per BICR



Overall survival



Choueiri TK et al. *N Engl J Med* 2021;384(9):829-41; ESMO 2020;Abstract 696O.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma

R. Motzer, B. Alekseev, S.-Y. Rha, C. Porta, M. Eto, T. Powles, V. Grünwald, T.E. Hutson, E. Kopyltsov, M.J. Méndez-Vidal, V. Kozlov, A. Alyasova, S.-H. Hong, A. Kapoor, T. Alonso Gordoa, J.R. Merchan, E. Winquist, P. Maroto, J.C. Goh, M. Kim, H. Gurney, V. Patel, A. Peer, G. Procopio, T. Takagi, B. Melichar, F. Rolland, U. De Giorgi, S. Wong, J. Bedke, M. Schmidinger, C.E. Dutcus, A.D. Smith, L. Dutta, K. Mody, R.F. Perini, D. Xing, and T.K. Choueiri, for the CLEAR Trial Investigators*

N Engl J Med 2021;384(14):1289-1300.

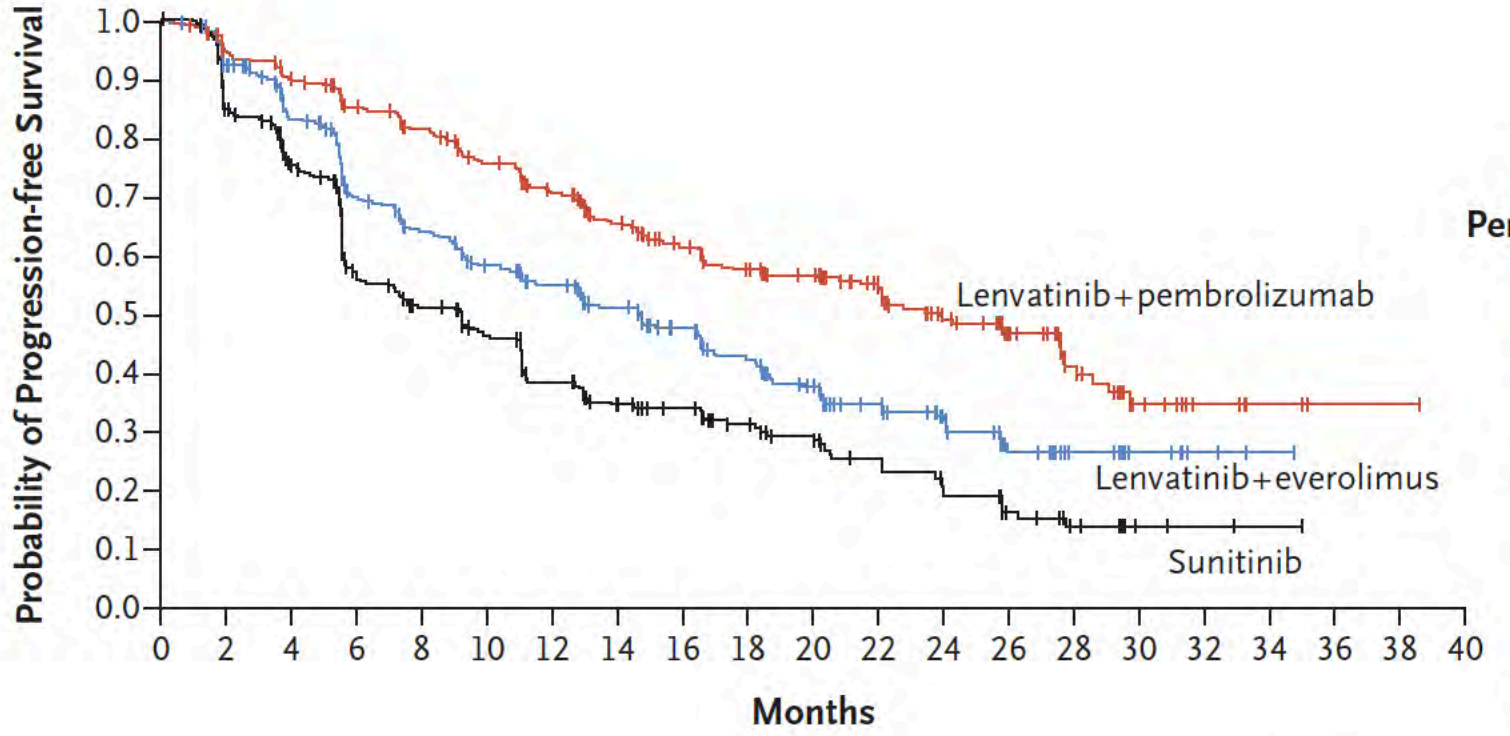
EDITORIAL

A Step Ahead in Metastatic Renal Cell Carcinoma

Alain Ravaud, M.D., Ph.D.

N Engl J Med 2021;384(14):1360-61.

CLEAR: Progression-Free Survival



No. at Risk

Lenvatinib+pembrolizumab	355	321	300	276	259	235	213	186	160	136	126	106	80	56	30	14	6	3	1	1	0
Lenvatinib+everolimus	357	305	259	207	185	163	149	125	105	85	70	53	37	20	13	7	3	1	0		
Sunitinib	357	262	218	145	124	107	85	69	62	49	42	32	25	16	9	3	2	1	0		

Median Progression-free Survival (95% CI)

	mo
Lenvatinib+ Pembrolizumab	23.9 (20.8–27.7)
Lenvatinib+ Everolimus	14.7 (11.1–16.7)
Sunitinib	9.2 (6.0–11.0)

Hazard ratio for disease progression or death (lenvatinib+ pembrolizumab vs. sunitinib), 0.39 (95% CI, 0.32–0.49); P<0.001

Hazard ratio for disease progression or death (lenvatinib+ everolimus vs. sunitinib), 0.65 (95% CI, 0.53–0.80); P<0.001

Motzer R et al. *N Engl J Med* 2021;384(14):1289-1300.

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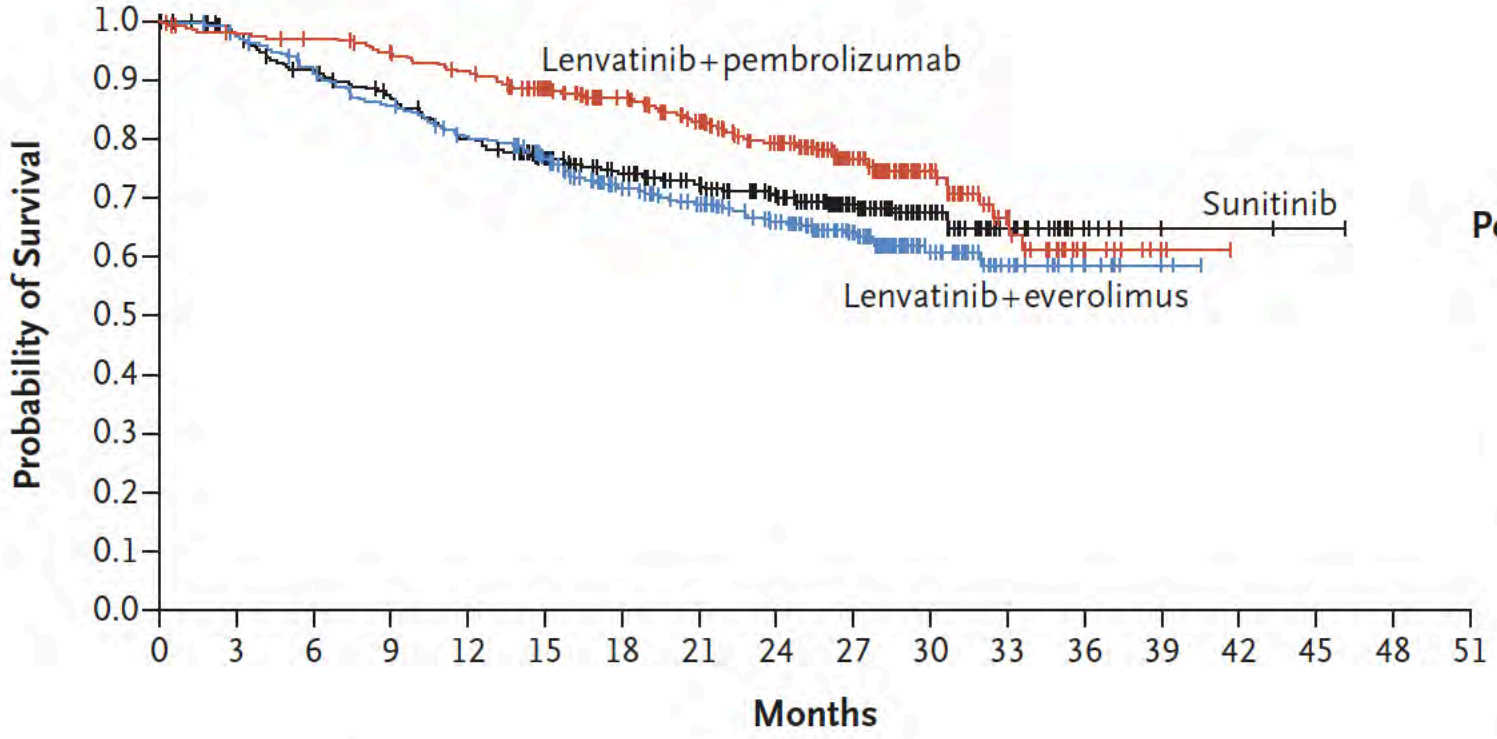
CLEAR: Overall Survival



Median Overall Survival (95% CI)	*mo*
Lenvatinib+ Pembrolizumab	NR (33.6–NE)
Lenvatinib+ Everolimus	NR (NE–NE)
Sunitinib	NR (NE–NE)

Hazard ratio for death (lenvatinib+ pembrolizumab vs. sunitinib), 0.66 (95% CI, 0.49–0.88); P=0.005

Hazard ratio for death (lenvatinib+ everolimus vs. sunitinib), 1.15 (95% CI, 0.88–1.50); P=0.30

No. at Risk

Lenvatinib+pembrolizumab	355	342	338	327	313	280	253	222	188	129	66	26	10	2	0		
Lenvatinib+everolimus	357	346	321	299	277	246	205	183	154	109	46	22	8	2	0		
Sunitinib	357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0

Motzer R et al. *N Engl J Med* 2021;384(14):1289-1300.

A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial

Sumanta K Pal, Catherine Tangen, Ian M Thompson Jr, Naomi Balzer-Haas, Daniel J George, Daniel Y C Heng, Brian Shuch, Mark Stein, Maria Tretiakova, Peter Humphrey, Adebowale Adeniran, Vivek Narayan, Georg A Bjarnason, Ulka Vaishampayan, Ajjai Alva, Tian Zhang, Scott Cole, Melissa Plets, John Wright, Primo N Lara Jr

***Lancet* 2021;397(10275):695-703.**

EDITORIAL

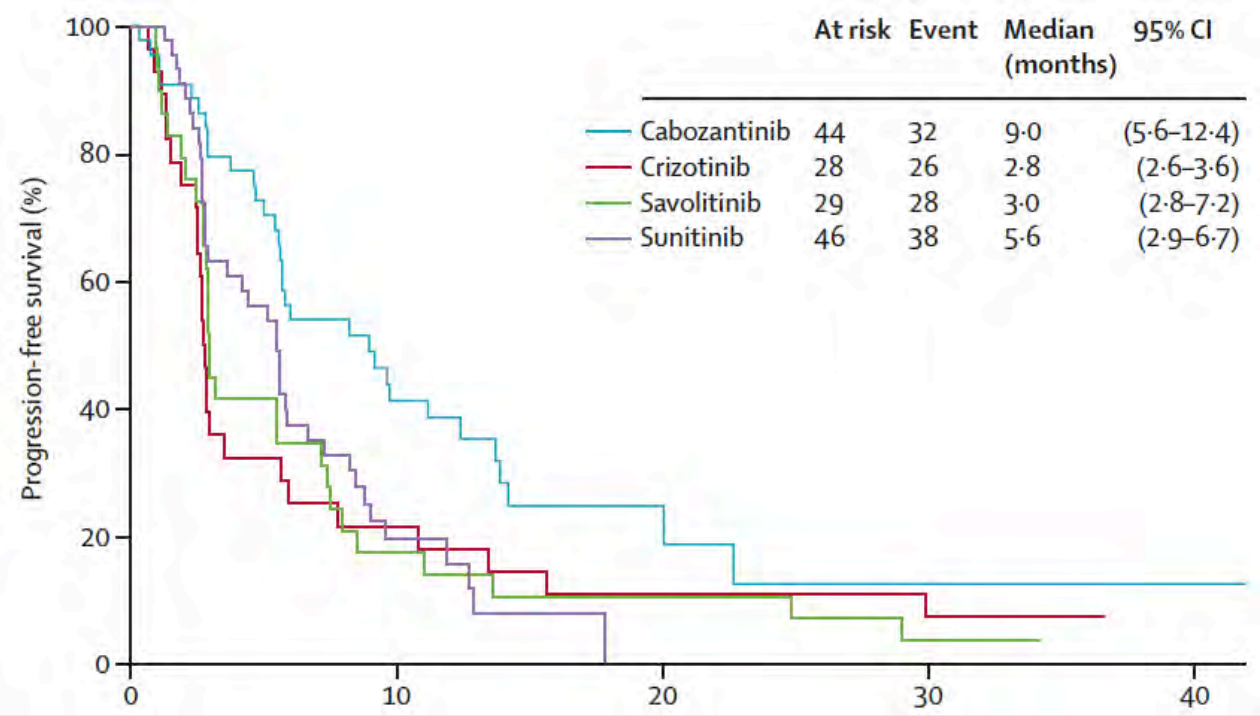
Cabozantinib: a new first-line option for papillary renal cell carcinoma?

**Delphine Borchiellini, Philippe Barthélémy*

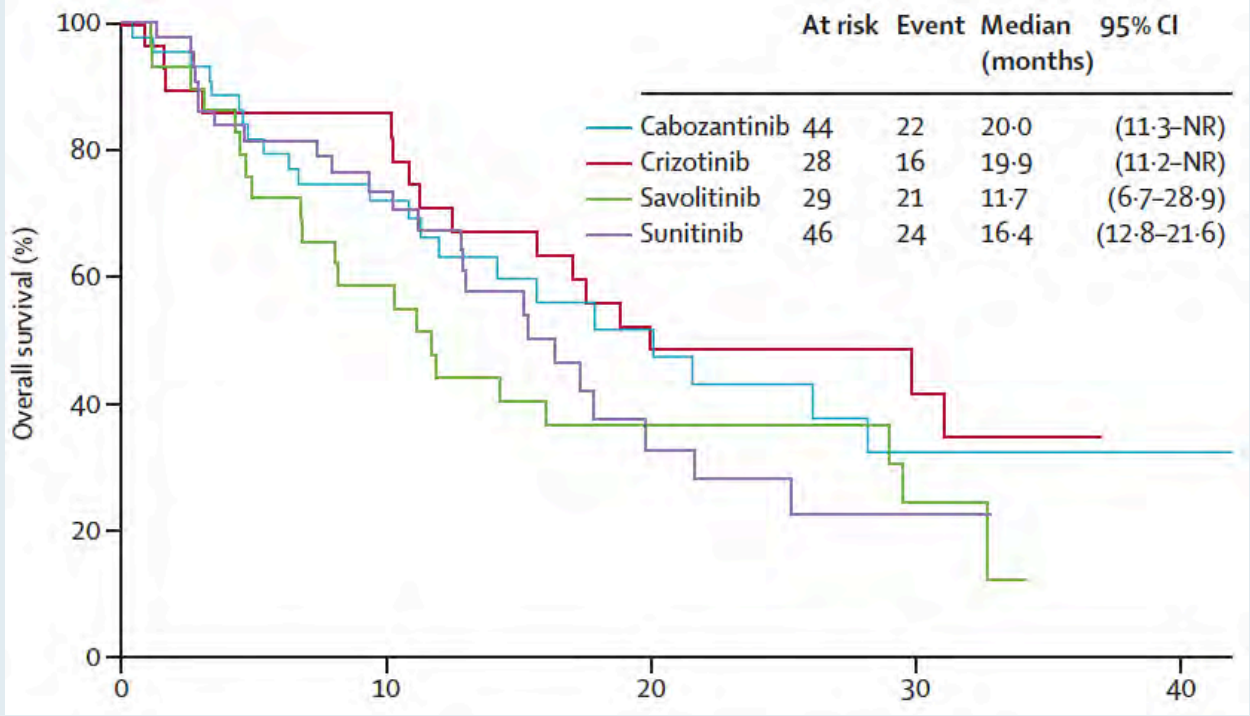
***Lancet* 2021;397(10275):645-47.**

Sunitinib with Cabozantinib, Crizotinib, and Savolitinib for Treatment of Advanced Papillary RCC

Progression-free survival



Overall survival



Pal SK et al. *Lancet* 2021;397(10275):695-703.

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rapid communications

Salvage Ipilimumab and Nivolumab in Patients With Metastatic Renal Cell Carcinoma After Prior Immune Checkpoint Inhibitors

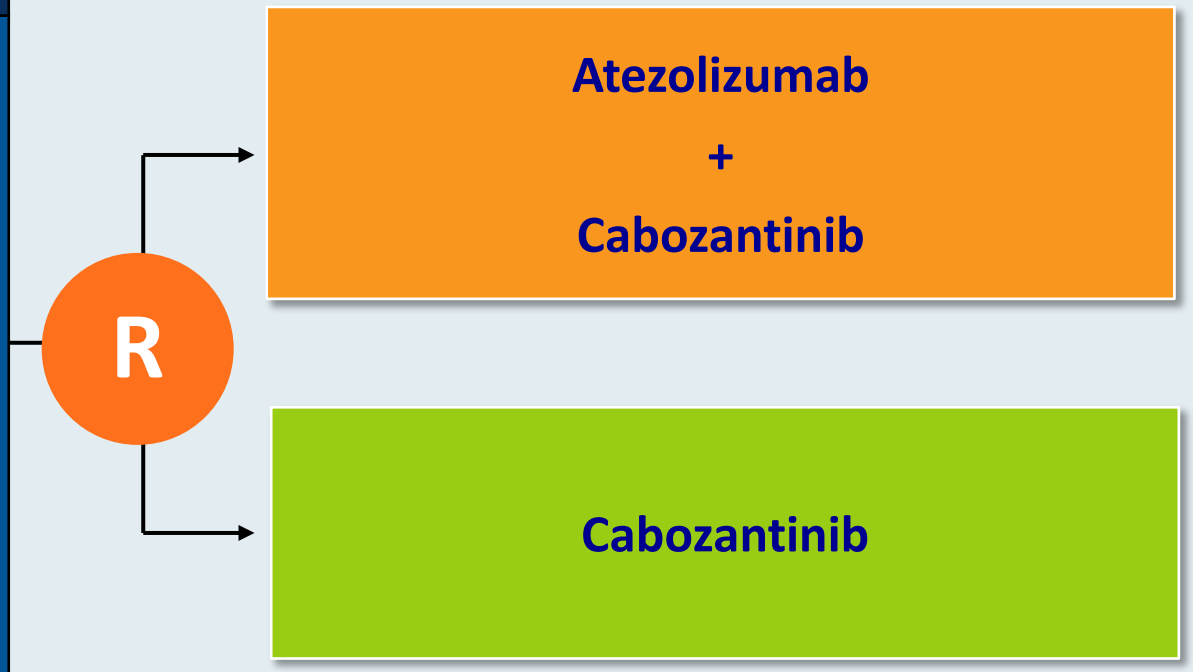
Anita Gul, MD[1]; Tyler F. Stewart, MD[2,3]; Charlene M. Mantia, MD[4]; Neil J. Shah, MD[5]; Emily Stern Gatof, MD[4]; Ying Long, PharmD[2]; Kimberly D. Allman, MSN, CNP[1]; Moshe C. Ornstein, MD, MA[1]; Hans J. Hammers, MD, PhD[6]; David F. McDermott, MD[4]; Michael B. Atkins, MD[5]; Michael Hurwitz, MD, PhD[2]; and Brian I. Rini, MD[1]

J Clin Oncol 2020;38:3088-94.

Ongoing Phase III CONTACT-03 Trial Design

Eligibility (N = 500)

- Inoperable, locally advanced or metastatic RCC
- After radiographic tumor progression during or after ICI
- Karnofsky PS ≥70
- Not more than 1 prior ICI regimen
- Not more than 2 prior lines for advanced disease



Primary endpoints: PFS and OS

Secondary endpoints include Objective Response, Duration of Response

Clinicaltrials.gov; NCT02811861 (Accessed February 2021).

FDA Approves Tivozanib for Relapsed or Refractory Advanced Renal Cell Carcinoma

Press Release: March 10, 2021

"The Food and Drug Administration approved tivozanib, a kinase inhibitor, for adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.

Efficacy was evaluated in TIVO-3 (NCT02627963), a randomized (1:1), open-label, multicenter trial of tivozanib versus sorafenib in patients with relapsed or refractory advanced RCC who received two or three prior systemic treatments, including at least one VEGFR kinase inhibitor other than sorafenib or tivozanib. Patients were randomized to either tivozanib 1.34 mg orally once daily for 21 consecutive days every 28 days or sorafenib 400 mg orally twice a day continuously, until disease progression or unacceptable toxicity.

The main efficacy outcome measure was progression-free survival (PFS), assessed by a blinded independent radiology review committee. Other efficacy endpoints were overall survival (OS) and objective response rate (ORR).

Median PFS was 5.6 months in the tivozanib arm (n=175) compared with 3.9 months for those treated with sorafenib (HR 0.73; p=0.016). Median OS was 16.4 and 19.2 months, for the tivozanib and sorafenib arms, respectively (HR 0.97). The ORR was 18% for the tivozanib arm and 8% for the sorafenib arm."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-tivozanib-relapsed-or-refractory-advanced-renal-cell-carcinoma

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

A Daylong Clinical Summit Hosted in Partnership with Medical Oncology Association of Southern California (MOASC)

Saturday, May 15, 2021

10:30 AM – 6:30 PM ET

(7:30 AM – 3:30 PM Pacific Time)

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This program was recorded before the ASCO 2021 Annual Meeting.

Data from the abstracts presented at this meeting can be accessed at https://meetinglibrary.asco.org/results?meetingView=2021%20ASCO%20Annual%20Meeting.

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Agenda

Module 1 — Breast Cancer: *Drs O'Regan and Traina*

Module 2 — Multiple Myeloma: *Drs Anderson and Raje*

Module 3 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Moskowitz and Sharman*

Module 4 — Genitourinary Cancers: *Drs Bellmunt and Pal*

Module 5 — Gastrointestinal Cancers: *Drs Messersmith and O'Reilly*

Module 6 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Erba and Komrokji*

Module 7 — Lung Cancer: *Drs Camidge and Levy*

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Gastrointestinal Cancers Faculty

Wells A Messersmith, MD
Professor and Head, Division of Medical Oncology
Associate Director for Translational Research
University of Colorado Cancer Center
Aurora, Colorado

Eileen M O'Reilly, MD
Winthrop Rockefeller Endowed Chair in Medical Oncology
Section Head, Hepatopancreaticobiliary and Neuroendocrine Cancers
Co-Director, Medical Initiatives
David M Rubenstein Center for Pancreatic Cancer Research
Attending Physician, Member
Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Cornell Medical College
New York, New York

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Commercial Support

This activity is supported by educational grants from AbbVie Inc, Astellas and Pfizer Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Blueprint Medicines, Daiichi Sankyo Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Incyte Corporation, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Lilly, Merck, Novartis, Oncopeptides, Sanofi Genzyme, Seagen Inc, and Taiho Oncology Inc.

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Eisai Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Turning Point Therapeutics Inc and Verastem Inc.

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Research To Practice CME and NCPD Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Messersmith — Disclosures

Contracted Research	ALX Oncology, BeiGene Ltd, Bristol-Myers Squibb Company, Exelixis Inc, Experimental Drug Development Centre (Singapore), Immunomedics Inc, Pfizer Inc, Mitsubishi Tanabe Pharma America
Data and Safety Monitoring Board/Committee	Five Prime Therapeutics Inc, QED Therapeutics, Zymeworks

Dr O'Reilly — Disclosures

Consulting Agreements	Agios Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Autem Medical, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Berry Genomics, Celgene Corporation, CytomX Therapeutics, Debiopharm Group, Eisai Inc, Exelixis Inc, Flatiron Health, Genentech, a member of the Roche Group, Gilead Sciences Inc, HelioHealth, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, MiNA Therapeutics, Polaris Group, QED Therapeutics, RedHill Biopharma Ltd, Silenseed Ltd, SillaJen, Sobi, TheraBionic, twoXAR, Vector Pharma, Yiviva
Contracted Research	*Acta Biológica*, Agios Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Berry Genomics, Bristol-Myers Squibb Company, CASI Pharmaceuticals Inc, Celgene Corporation, Exelixis Inc, Genentech, a member of the Roche Group, Halozyme Inc, Incyte Corporation, MabVax Therapeutics, Puma Biotechnology Inc, QED Therapeutics, SillaJen, Yiviva

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Contributing Oncologists

Amanda Blackmon, DO, MS
Chief Fellow, Hematology/Oncology
University of California, Irvine
Irvine, California

Farshid Dayyani, MD, PhD
Professor of Clinical Medicine
Division of Hematology/Oncology
Department of Medicine
University of California, Irvine
UCI Health
Orange, California

Gigi Chen, MD
Diablo Valley Oncology and
Hematology Medical Group
Pleasant Hill, California

Michael Polintan Del Rosario, MD
Fellow Physician
Division of Hematology-Oncology
Department of Medicine
University of California, Irvine
Irvine, California

Mamta Choksi, MD
Florida Cancer Specialists and
Research Institute
New Port Richey, Florida

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

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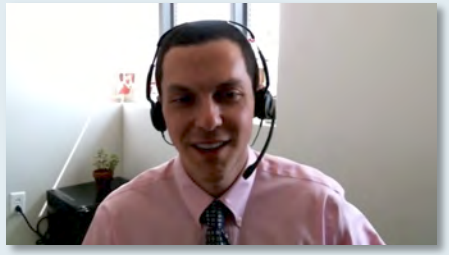
Contributing Oncologists

Rahul Gosain, MD
Division of Hematology and Oncology
Guthrie Corning Cancer Center
Corning, New York

Maen Hussein, MD
Florida Cancer Specialists and
Research Institute
The Villages, Florida

Ranju Gupta, MD
Attending Physician
Co-Director, Cardio-Oncology Program
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania



Jeremy Lorber, MD
Attending Hematologist-Oncologist
Tower Hematology Oncology
Cedars-Sinai Medical Center
Beverly Hills, California

Hatim Husain, MD
Physician, University of California San Diego
San Diego, California

Nataliya Mar, MD
Assistant Clinical Professor
Division of Hematology/Oncology
University of California, Irvine
Irvine, California

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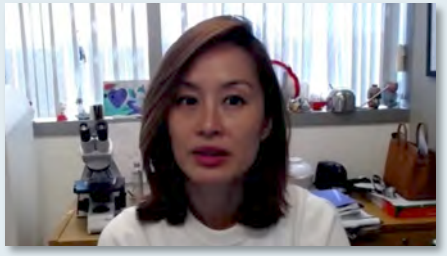
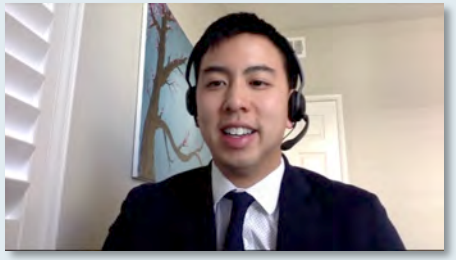
Contributing Oncologists

Mohamed K Mohamed, MD, PhD
Oncology Division Medical Director
Director of Thoracic Oncology
Hematologist/ Medical Oncologist
Cone Health Cancer Center
Greensboro, North Carolina

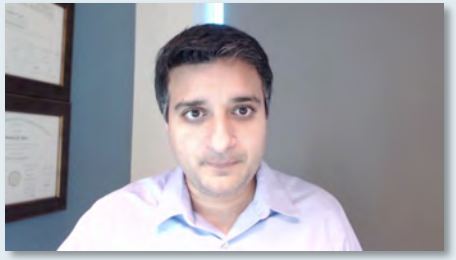


Helen H Moon, MD
Medical Oncologist
Southern California Permanente
Medical Group
Riverside, California

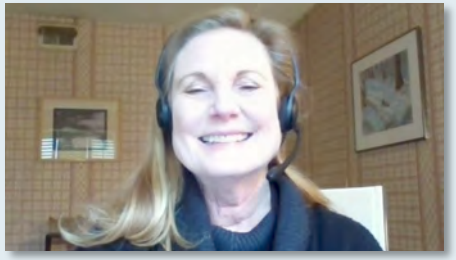
Neil Morganstein, MD
Hematology Oncology
Atlantic Health System
Summit, New Jersey



Anthony Nguyen, MD
Fellow, Loma Linda University Health
Loma Linda, California



Sandip Patel, MD
Associate Professor, Medical Oncology, UCSD
Leader, Experimental Therapeutics
Deputy Director, San Diego Center for
Precision Immunotherapy
San Diego, California



Andrea Stebel, MD
Newport Breast Care
Newport Beach, California

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Agenda

Module 1: Colorectal Cancer

- Dr Lorber: A 74-year-old woman with MSI-high mCRC – BRAF V600E mutation
- *Key Recent Publications and Presentations*
- Dr Dayyani: A 60-year-old woman with MSS mCRC – TMB 35.4 mut/Mb, KRAS G12D mutation
- *Key Recent Publications and Presentations*

Module 2: Gastric, Gastroesophageal and Esophageal Cancers

- Dr Dayyani: A 60-year-old man with relapsed MSS esophageal squamous cell cancer – PD-L1 CPS 15
- *Key Recent Publications and Presentations*
- Dr Del Rosario: A 49-year-old woman with HER2-positive metastatic gastric adenocarcinoma – PD-L1 CPS 5
- *Key Recent Publications and Presentations*

Module 3: Hepatocellular Cancer (HCC)

- Dr Dayyani: A 59-year-old man with advanced HCC
- Dr Lorber: An 80-year-old woman with unresectable advanced HCC
- *Key Recent Publications and Presentations*

Module 4: Pancreatic Adenocarcinoma

- Dr Chen: An 80-year-old woman with localized pancreatic cancer
- Dr Dayyani: A 79-year-old woman with pancreatic cancer and a germline BRCA2 mutation
- *Key Recent Publications and Presentations*

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Case Presentation – Dr Lorber: A 74-year-old woman with MSI-high mCRC – BRAF V600E mutation

Dr Jeremy Lorber

- Diagnosed with cecal adenocarcinoma on colonoscopy (prompted by screening stool DNA test).
  - Asymptomatic
  - Staging CT scan: pericecal adenopathy and three liver metastases, measuring 1-3 cm
- Genetic analyses: loss of MLH-1 and PMS-2 expression and a BRAF V600E mutation
- Pembrolizumab therapy → CT scan at 3 months showed complete resolution of liver metastases and pericecal adenopathy
- Combined hemicolectomy and metastasectomy → pCR
- Pembrolizumab therapy continued

Questions

- Now that she's had a great response and resection and no evidence of disease, is there an optimal duration of therapy after surgery?
- What is the role of ctDNA testing, if any, or other assessments?

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Key Recent Publications and Presentations

- André T et al. **Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer.** *N Engl J Med* 2020;383(23):2207-18.
- Tabernero J et al. **Encorafenib plus Cetuximab as a New Standard of Care for Previously Treated BRAF V600E-Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study.** *J Clin Oncol* 2021;39(4):273-84.
- Siena S et al. **Trastuzumab Deruxtecan (DS-8201) in Patients with HER2-Expressing Metastatic Colorectal Cancer (DESTINY-CRC01): A Multicentre, Open-Label, Phase 2 Trial.** *Lancet Oncol* 2021; Online ahead of print.

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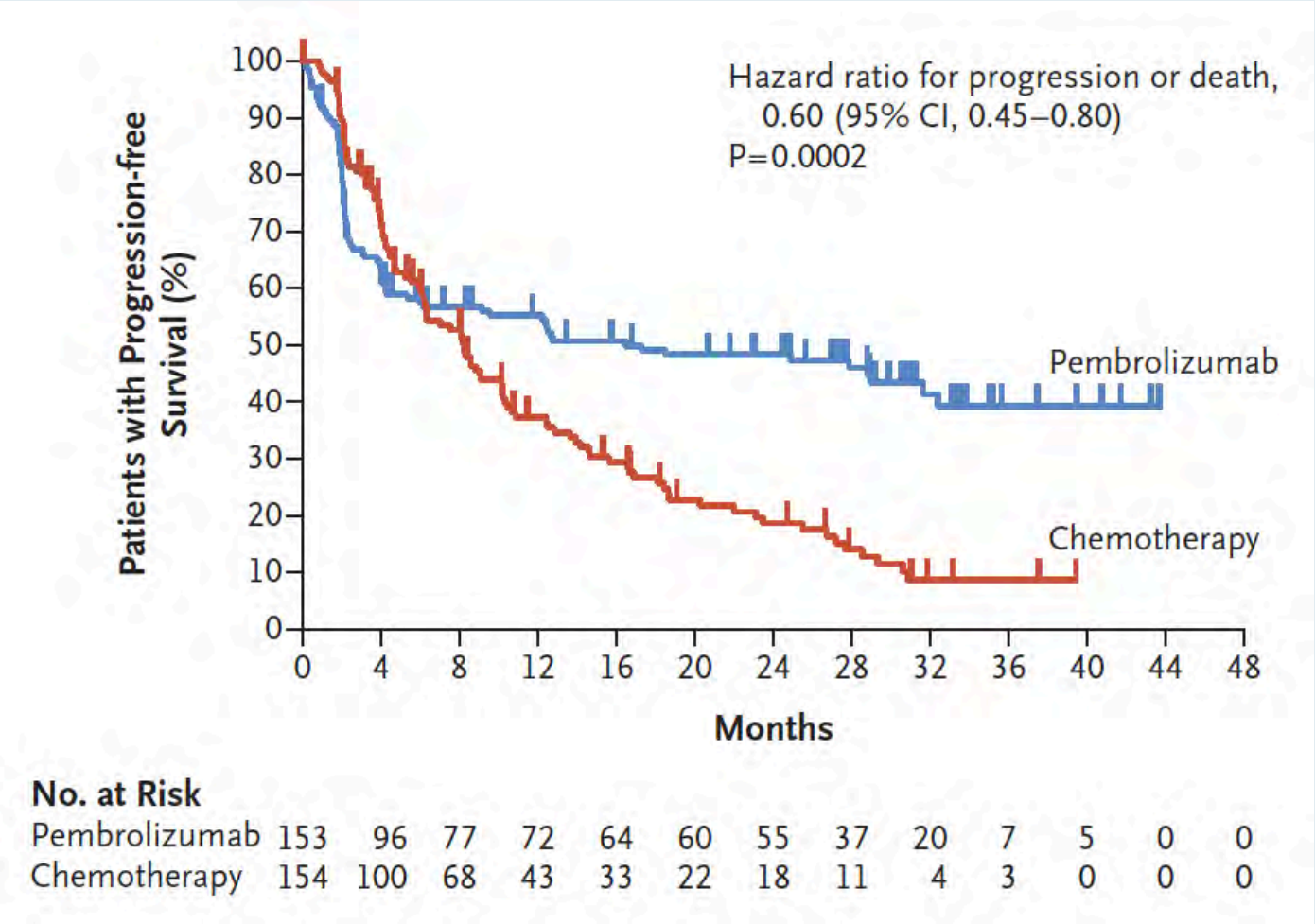
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*

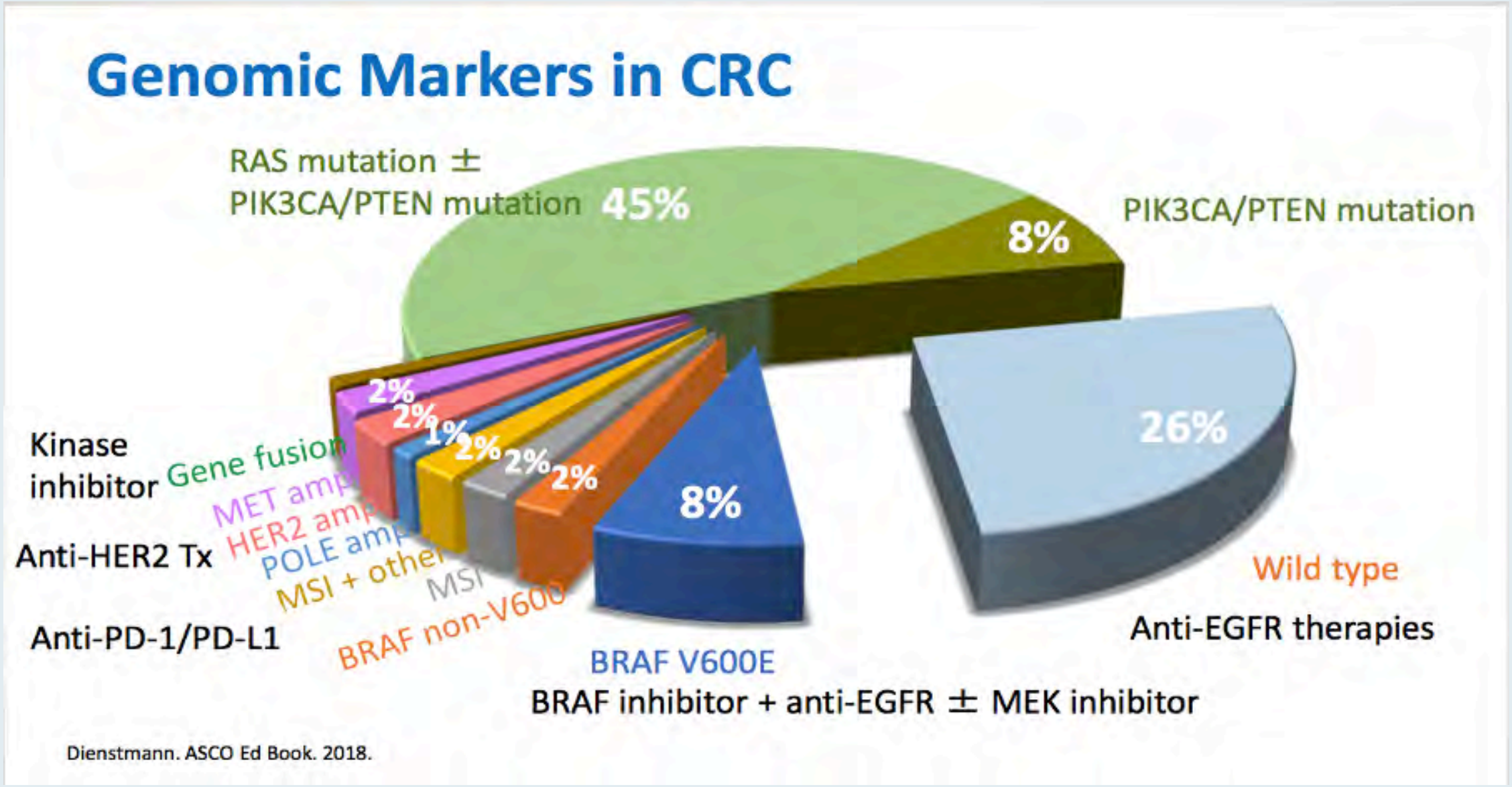
KEYNOTE-177: Primary Survival Endpoints



At the time of data cutoff, data on overall survival were still evolving.

André T et al. *N Engl J Med* 2020;383(23):2207-18.

Genomic Markers in CRC



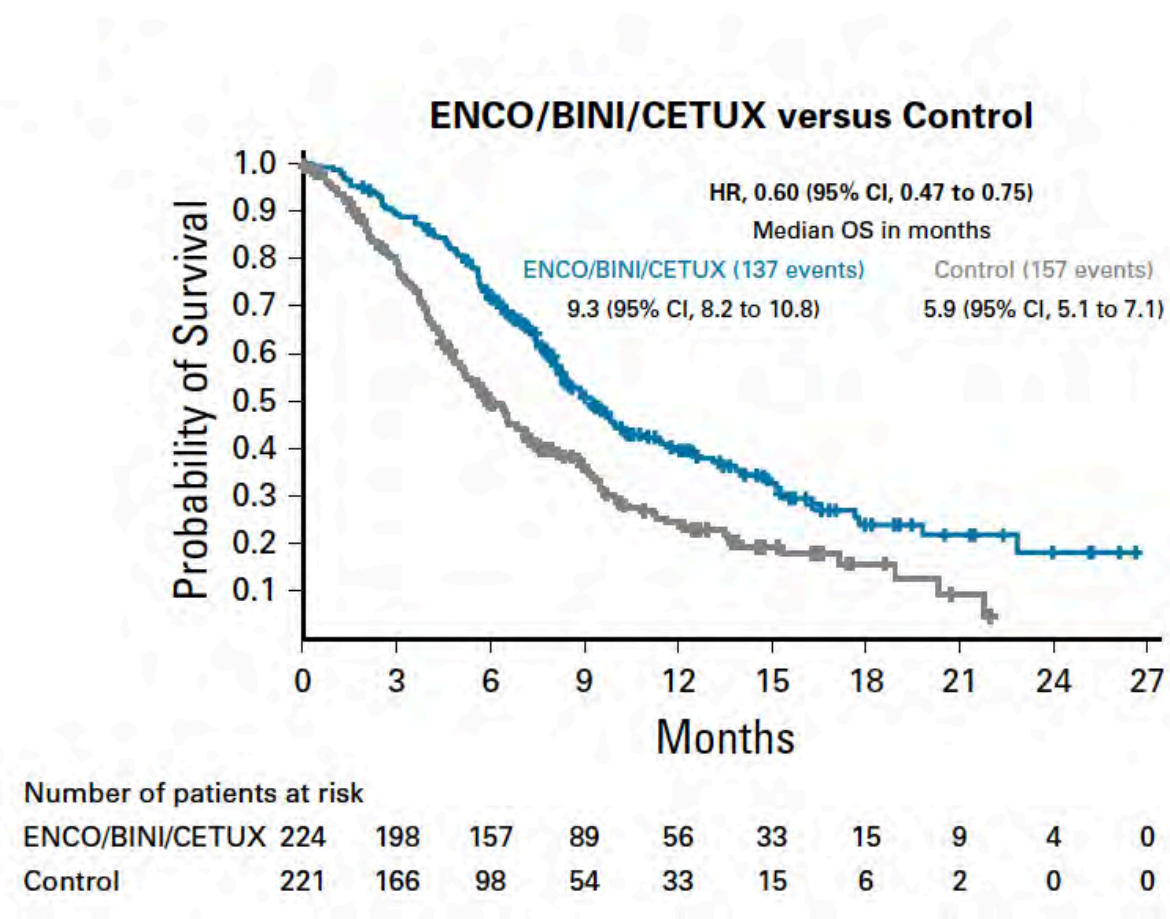
rapid communications

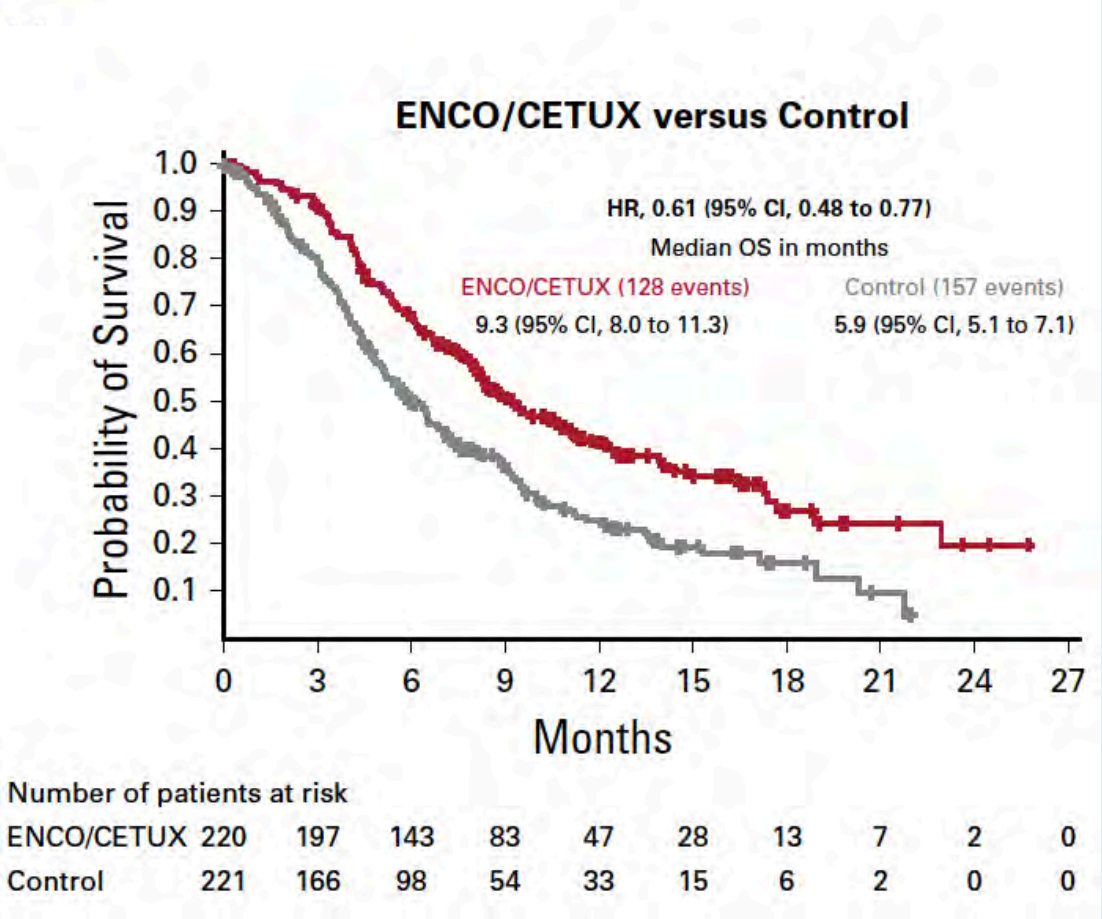
Encorafenib Plus Cetuximab as a New Standard of Care for Previously Treated *BRAF* V600E–Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study

Josep Tabernero, MD, PhD[1]; Axel Grothey, MD[2]; Eric Van Cutsem, MD, PhD[3]; Rona Yaeger, MD[4]; Harpreet Wasan, MD[5]; Takayuki Yoshino, MD, PhD[6]; Jayesh Desai, MBBS[7]; Fortunato Ciardiello, MD, PhD[8]; Fotios Loupakis, MD, PhD[9]; Yong Sang Hong, MD, PhD[10]; Neeltje Steeghs, MD, PhD[11]; Tormod Kyrre Guren, MD, PhD[12]; Hendrik-Tobias Arkenau, MD, PhD[13]; Pilar Garcia-Alfonso, MD[14]; Elena Elez, MD, PhD[1]; Ashwin Gollerkeri, MD[15]; Kati Maharry, PhD[15]; Janna Christy-Bittel, MSN[15]; and Scott Kopetz, MD, PhD[16]

J Clin Oncol 2021;39(4):273-84.

BEACON: Overall Survival Results





Tabanero J et al. *J Clin Oncol* 2021;39(4):273-84.

RTP RESEARCH TO PRACTICE

Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial

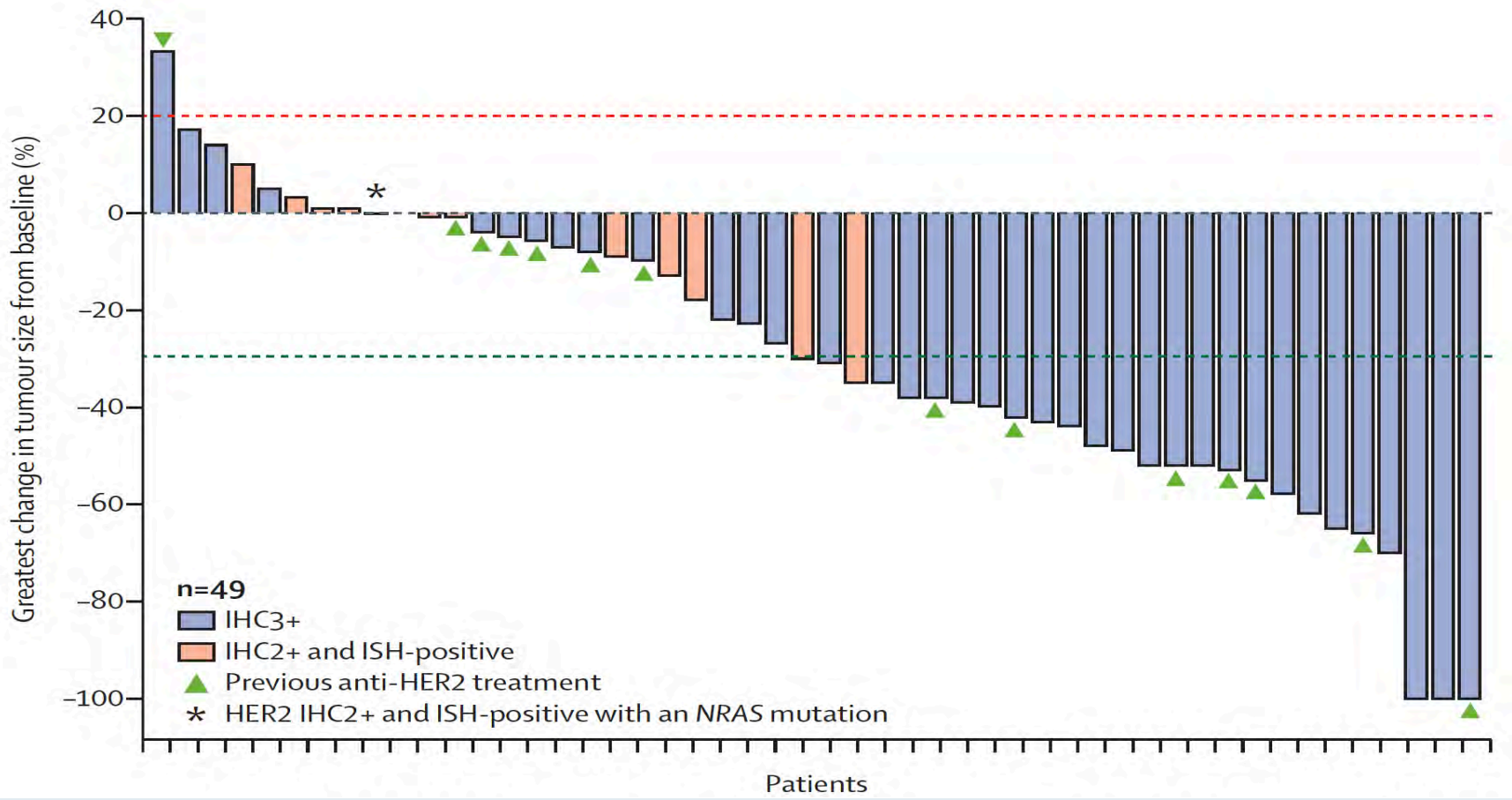
Salvatore Siena, Maria Di Bartolomeo, Kanwal Raghav, Toshiki Masuishi, Fotios Loupakis, Hisato Kawakami, Kensei Yamaguchi, Tomohiro Nishina, Marwan Fakih, Elena Elez, Javier Rodriguez, Fortunato Ciardiello, Yoshito Komatsu, Taito Esaki, Ki Chung, Zev Wainberg, Andrea Sartore-Bianchi, Kapil Saxena, Eriko Yamamoto, Emarjola Bako, Yasuyuki Okuda, Javad Shahidi, Axel Grothey, Takayuki Yoshino, on behalf of the DESTINY-CRC01 investigators

***Lancet Oncol* 2021;[Online ahead of print].**

DESTINY-CRC01: Response

Best Change in Tumor Size

ORR: 45.3%



Siena S et al. *Lancet Oncol* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

DESTINY-CRC01: AEs of Special Interest

	All Patients (N = 78)					
Preferred Term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial Lung Disease	0	2 (2.6)	1 (1.3)	0	2 (2.6)	5 (6.4)

Among the 5 total events:

- Median time to investigator-reported onset was 80 days (range, 22-132)
- 5 of 5 patients with grade ≥ 2 ILD received corticosteroids
- 2 patients recovered, 1 did not recover (later died due to disease progression), and 2 died
- In the 2 fatal cases, onset was from 40-126 days, both received steroids as part of treatment, and death occurred 6-18 days after diagnosis

Protocol recommendations: Monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is suspected

Siena S et al. ASCO 2020;Abstract 4000.

Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients (pts) with HER2-Expressing Metastatic Colorectal Cancer (mCRC): Final Results from a Phase 2, Multicenter, Open-Label Study (DESTINY-CRC01)

Yoshino T et al.

ASCO 2021;Abstract 3505.

Monday, June 7, 1:15 PM - 4:15 PM EDT

Case Presentation – Dr Dayyani: A 60-year-old woman with MSS mCRC – TMB 35.4 mut/Mb, KRAS G12D mutation

Dr Farshid Dayyani

- Diagnosed in Iran at age 45 with rectal cancer, s/p chemoradiation therapy and surgery → FOLFOX x 6
- 9/2017: Moved to US, recurrence with lung and abdominal lymph node metastases
- Capecitabine/bevacizumab, with mixed response → CAPOX/bevacizumab (severe oxaliplatin reaction)
- FOLFIRI, with nausea and frequent ER visits → Maintenance 5-FU/LV and dose-reduced bevacizumab → PD
- Regorafenib 80 mg daily, with poor tolerability
- NGS: MSS, KRAS G12D, TMB 35.4 mut/Mb
- Discussed treatment with single-agent pembrolizumab

Questions

- What are your views on the clinical data available with third-line single-agent regorafenib and third-line TAS-102 plus bevacizumab? How would you prefer to sequence these treatments?
- Is it reasonable in a patient with KRAS mutation G12D, microsatellite stable to try pembrolizumab due to the high TMB score?

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- Van Cutsem E et al. **Trifluridine/Tipiracil plus Bevacizumab in Patients with Untreated Metastatic Colorectal Cancer Ineligible for Intensive Therapy: The Randomized TASCO1 Study.** *Ann Oncol* 2020;31(9):1160-8.
- Pfeiffer P et al. **TAS-102 with or without Bevacizumab in Patients with Chemorefractory Metastatic Colorectal Cancer: An Investigator-Initiated, Open-Label, Randomised, Phase 2 Trial.** *Lancet Oncol* 2020;21(3):412-20.

Ann Oncol 2020;31(9):1160-8.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

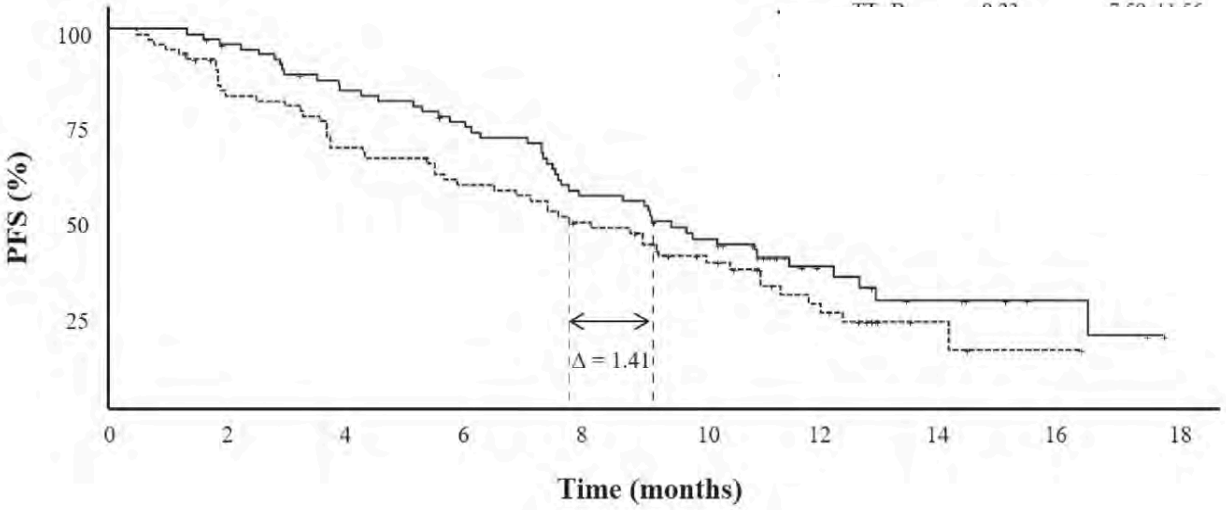
Trifluridine/tipiracil plus bevacizumab in patients with untreated metastatic colorectal cancer ineligible for intensive therapy: the randomized TASCO1 study☆

E. Van Cutsem[1*], I. Danielewicz[2], M. P. Saunders[3], P. Pfeiffer[4], G. Argilés[5], C. Borg[6], R. Glynne-Jones[7], C. J. A. Punt[8], A. J. Van de Wouw[9], M. Fedyanin[10], D. Stroyakovskiy[11], H. Kroening[12], P. Garcia-Alfonso[13], H. Wasan[14], A. Falcone[15], A. Kanehisa[16], A. Egorov[16], P. Aubel[16], N. Amellal[16] & V. Moiseenko[17]

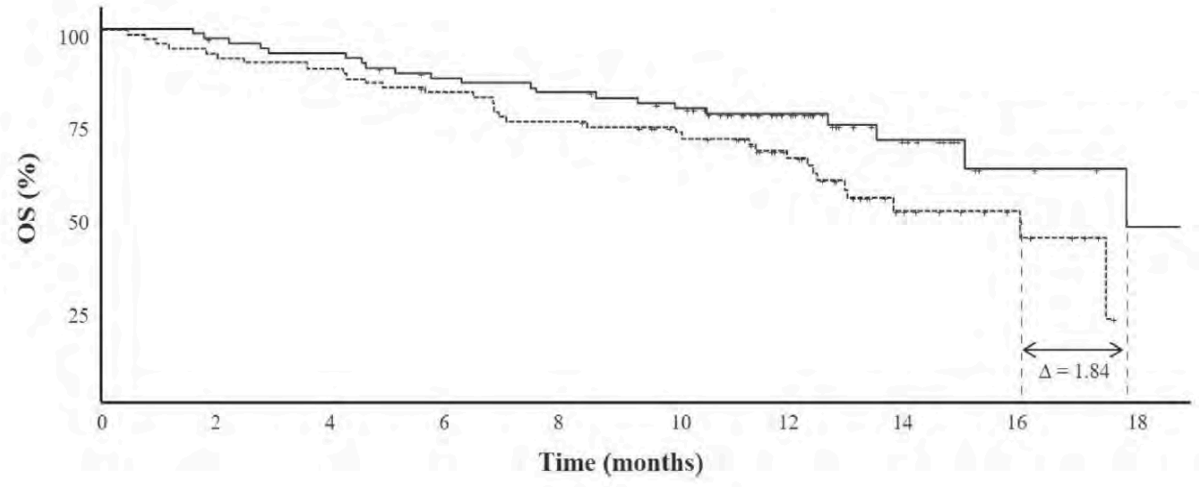
RTP RESEARCH TO PRACTICE

TASCO1: TAS-102 with Bevacizumab for Untreated mCRC Ineligible for Intensive Therapy

	Cape/Bev (n = 76)	TAS-102/Bev (n = 77)
mPFS	7.8 mo	9.2 mo
	HR: 0.71	



	Cape/Bev (n = 76)	TAS-102/Bev (n = 77)
mOS	16.2 mo	18.0 mo
	HR: 0.56	



Van Cutsem E et al. *Ann Oncol* 2020;31(9):1160-8.

RTP RESEARCH TO PRACTICE

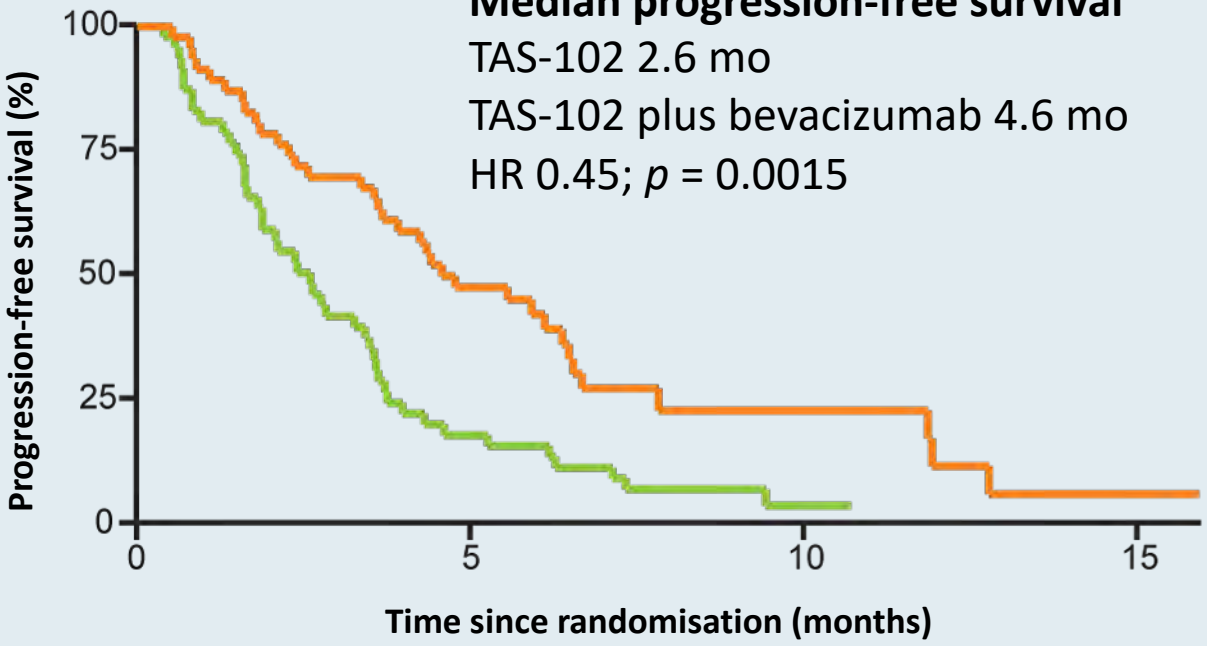
TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial

Per Pfeiffer, Mette Yilmaz, Sören Möller, Daniela Zitnjak, Merete Krogh, Lone Nørgård Petersen, Laurids Østergaard Poulsen, Stine Braendegaard Winther, Karina Gravgaard Thomsen, Camilla Qvortrup

Lancet Oncol 2020; 21: 412–20

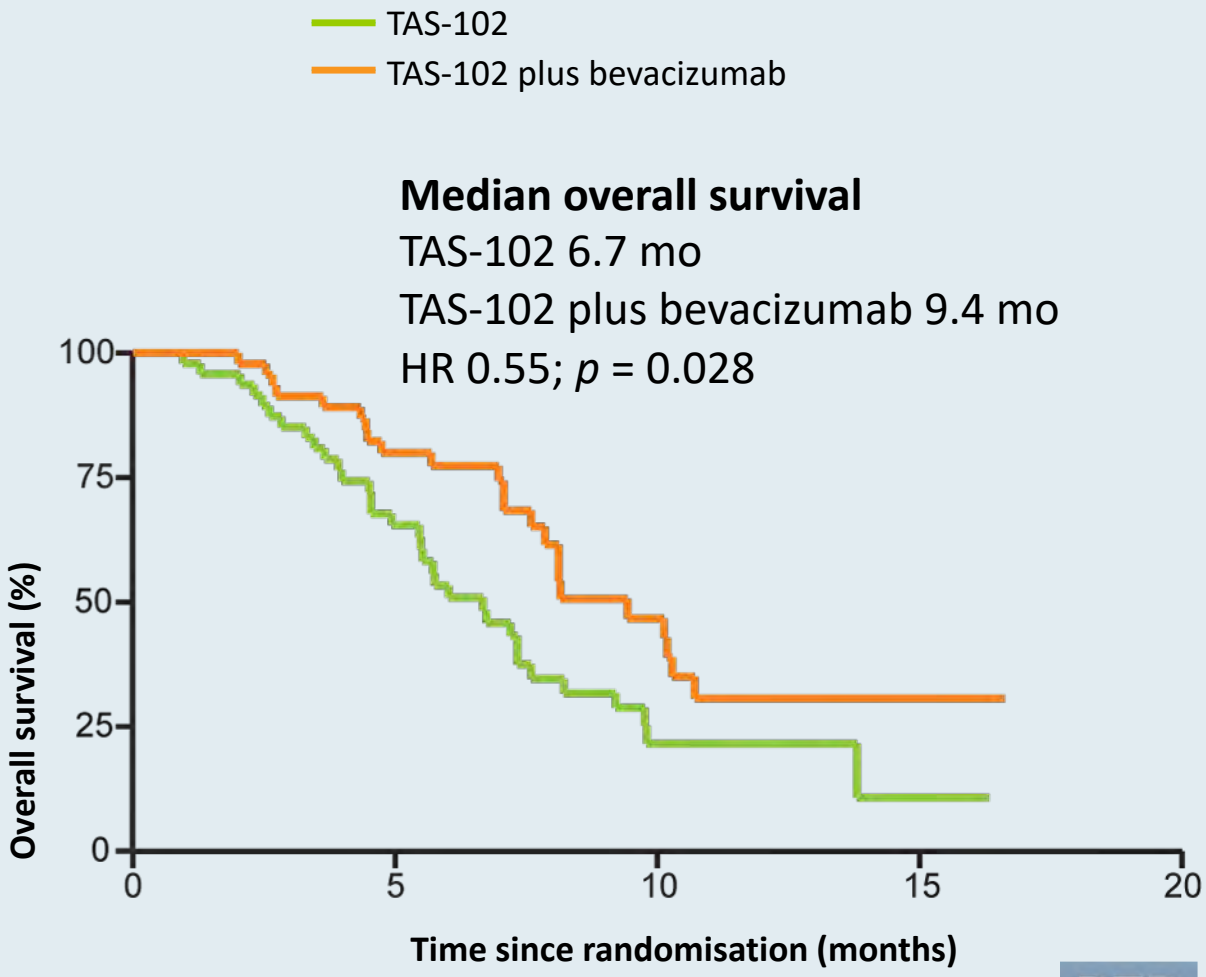
TAS-102 with or without Bevacizumab: Efficacy Results

Median progression-free survival
TAS-102 2.6 mo
TAS-102 plus bevacizumab 4.6 mo
HR 0.45; *p* = 0.0015



Disease control rate:

- TAS-102/Bev = 67%
- TAS-102 = 51%



Median overall survival
TAS-102 6.7 mo
TAS-102 plus bevacizumab 9.4 mo
HR 0.55; *p* = 0.028

Pfeiffer P et al. *Lancet Oncol* 2020;21(3):412-20.

The TRUSTY Study: A Randomized Phase 2/3 Study of Trifluridine/Tipiracil plus Bevacizumab versus Irinotecan and Fluoropyrimidine plus Bevacizumab as Second-Line Treatment in Patients with Metastatic Colorectal Cancer

Kuboki Y et al.
ASCO 2021;Abstract 3507.

Monday, June 7, 1:15 PM - 4:15 PM EDT

Agenda

Module 1: Colorectal Cancer

- Dr Lorber: A 74-year-old woman with MSI-high mCRC – BRAF V600E mutation
- *Key Recent Publications and Presentations*
- Dr Dayyani: A 60-year-old woman with MSS mCRC – TMB 35.4 mut/Mb, KRAS G12D mutation
- *Key Recent Publications and Presentations*

Module 2: Gastric, Gastroesophageal and Esophageal Cancers

- Dr Dayyani: A 60-year-old man with relapsed MSS esophageal squamous cell cancer – PD-L1 CPS 15
- *Key Recent Publications and Presentations*
- Dr Del Rosario: A 49-year-old woman with HER2-positive metastatic gastric adenocarcinoma – PD-L1 CPS 5
- *Key Recent Publications and Presentations*

Module 3: Hepatocellular Cancer (HCC)

- Dr Dayyani: A 59-year-old man with advanced HCC
- Dr Lorber: An 80-year-old woman with unresectable advanced HCC
- *Key Recent Publications and Presentations*

Module 4: Pancreatic Adenocarcinoma

- Dr Chen: An 80-year-old woman with localized pancreatic cancer
- Dr Dayyani: A 79-year-old woman with pancreatic cancer and a germline BRCA2 mutation
- *Key Recent Publications and Presentations*

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Dayyani: A 60-year-old man with relapsed MSS esophageal squamous cell cancer – PD-L1 CPS 15

Dr Farshid Dayyani

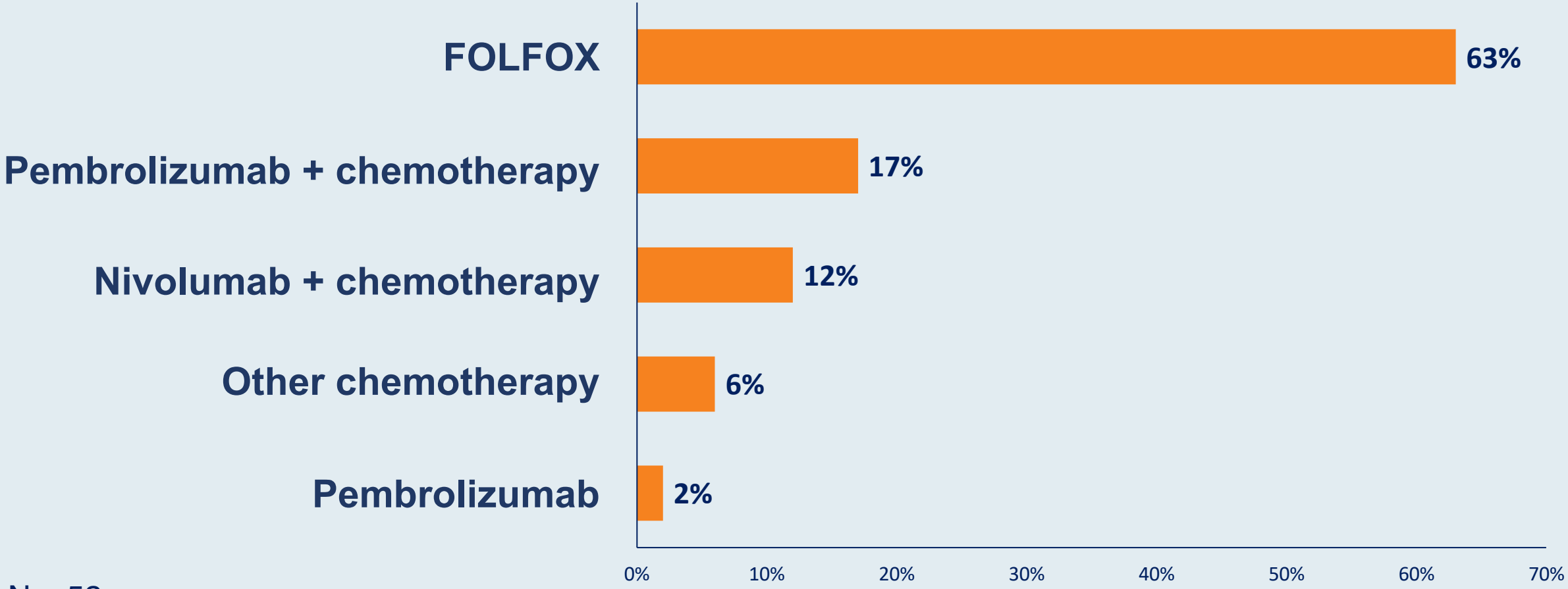
- Long history of swallowing difficulties, with multiple EGDs and biopsies significant for inflammation and ulcers but no malignancy
- 10/2017: Severe pain in swallowing and constant esophageal spasms
- 11/2017: Admitted to UCI, underwent EGD/EUS, with biopsy significant for esophageal SCC
- FOLFOX x 6 → Concurrent chemoRT with carboplatin/paclitaxel
- 9/2018: Laparoscopic and thorascopic esophagectomy (ypTis ypN0)
- Remains NED on surveillance but last clinic visit in 11/2020 due to COVID-19
- Recurrent disease, with pleural effusion, dysphagia, ascites, anorexia, hypercalcemia
- Testing: PD-L1 CPS 15, MSS

Questions

- Would you treat with single-agent pembrolizumab, paclitaxel, or a combination?

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what is your usual initial treatment for a 65-year-old patient with MSS adenocarcinoma of the esophagus with a PD-L1 CPS of 0?



N = 52

Survey of live webinar audience

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- Kelly RJ et al. **Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer.** *N Engl J Med* 2021;384(13):1191-203.
- Kato K et al. **Pembrolizumab plus Chemotherapy versus Chemotherapy as First-Line Therapy in Patients with Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study.** ESMO 2020;Abstract LBA8_PR.
- Moehler M et al. **Nivolumab plus Chemotherapy versus Chemotherapy as First-Line Treatment for Advanced Gastric Cancer/Gastroesophageal Junction Cancer/Esophageal Adenocarcinoma: First Results of the CheckMate 649 Study.** ESMO 2020;Abstract LBA6.

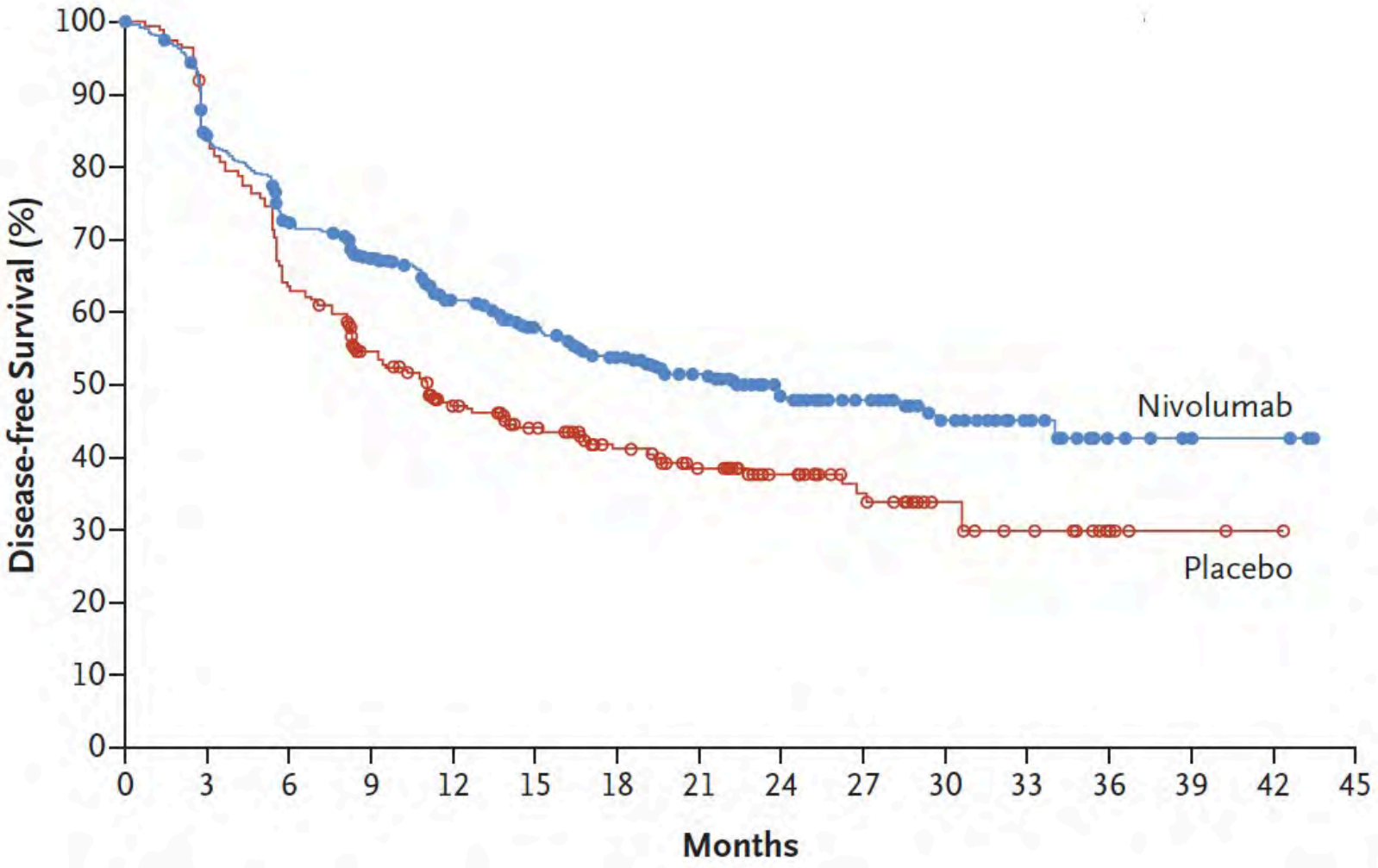
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 1, 2021 VOL. 384 NO. 13

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

R.J. Kelly, J.A. Ajani, J. Kuzdzal, T. Zander, E. Van Cutsem, G. Piessen, G. Mendez, J. Feliciano, S. Motoyama, A. Lièvre, H. Uronis, E. Elimova, C. Grootscholten, K. Geboes, S. Zafar, S. Snow, A.H. Ko, K. Feeney, M. Schenker, P. Kocon, J. Zhang, L. Zhu, M. Lei, P. Singh, K. Kondo, J.M. Cleary, and M. Moehler, for the CheckMate 577 Investigators*

CheckMate-577: Disease-Free Survival in the Overall Population



	No. of Patients	Median Disease-free Survival *mo (95% CI)*
Nivolumab	532	22.4 (16.6–34.0)
Placebo	262	11.0 (8.3–14.3)

Hazard ratio for disease recurrence or death, 0.69 (96.4% CI, 0.56–0.86)
P<0.001

Kelly RJ et al. *N Engl J Med* 2021;384(13):1191-203.

Adjuvant Nivolumab (NIVO) in Resected Esophageal or Gastroesophageal Junction Cancer (EC/GEJC) Following Neoadjuvant Chemoradiotherapy (CRT): Expanded Efficacy and Safety Analyses from CheckMate 577

Kelly RJ et al.
ASCO 2021;Abstract 4003.

Saturday, June 5, 1:45 PM - 4:45 PM EDT

Multicenter, Randomized Phase II Study of Neoadjuvant Pembrolizumab plus Chemotherapy and Chemoradiotherapy in Esophageal Adenocarcinoma (EAC)

Shah MA et al.
ASCO 2021;Abstract 4005.

Saturday, June 5, 1:45 PM - 4:45 PM EDT

Checkpoint Inhibitor Approvals in Gastric, GEJ and Esophageal Cancers

Regimen	Location	Histology	Setting	PD-L1
Pembrolizumab 7/30/2019	Esophageal, GEJ	Squamous	• Recurrent locally advanced or metastatic • Not amenable to surgical resection or definitive chemoradiation • After ≥1 prior lines of systemic therapy	CPS ≥10
Nivolumab 6/10/2020	Esophageal	Squamous	• Unresectable advanced, recurrent or metastatic • After prior fluoropyrimidine- and platinum-based chemotherapy	Not required
Pembrolizumab + cisplatin/5-FU 3/22/2021	Esophageal, GEJ	Adenocarcinoma and squamous	• Recurrent locally advanced or metastatic • Not amenable to surgical resection or definitive chemoradiation	Not required
Nivolumab + mFOLFOX6 or CAPOX 4/16/2021	Gastric, GEJ, esophageal	Adenocarcinoma	• Advanced or metastatic gastric, GEJ or esophageal adenocarcinoma	Not required
Pembrolizumab + trastuzumab + chemotherapy 5/5/2021	Gastric, GEJ	Adenocarcinoma	• First-line treatment for locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma	Not required

FDA Approves Pembrolizumab in Combination with Chemotherapy for Esophageal or GEJ Carcinoma

Press Release – March 22, 2021

"On March 22, 2021, the Food and Drug Administration approved pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for patients with metastatic or locally advanced esophageal or gastroesophageal (GEJ) (tumors with epicenter 1 to 5 centimeters above the gastroesophageal junction) carcinoma who are not candidates for surgical resection or definitive chemoradiation.

Efficacy was evaluated in KEYNOTE-590 (NCT03189719), a multicenter, randomized, placebo-controlled trial that enrolled 749 patients with metastatic or locally advanced esophageal or gastroesophageal junction carcinoma who were not candidates for surgical resection or definitive chemoradiation.

The recommended pembrolizumab dose for esophageal cancer is 200 mg every 3 weeks or 400 mg every 6 weeks."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-esophageal-or-gej-carcinoma?utm_medium=email&utm_source=govdelivery

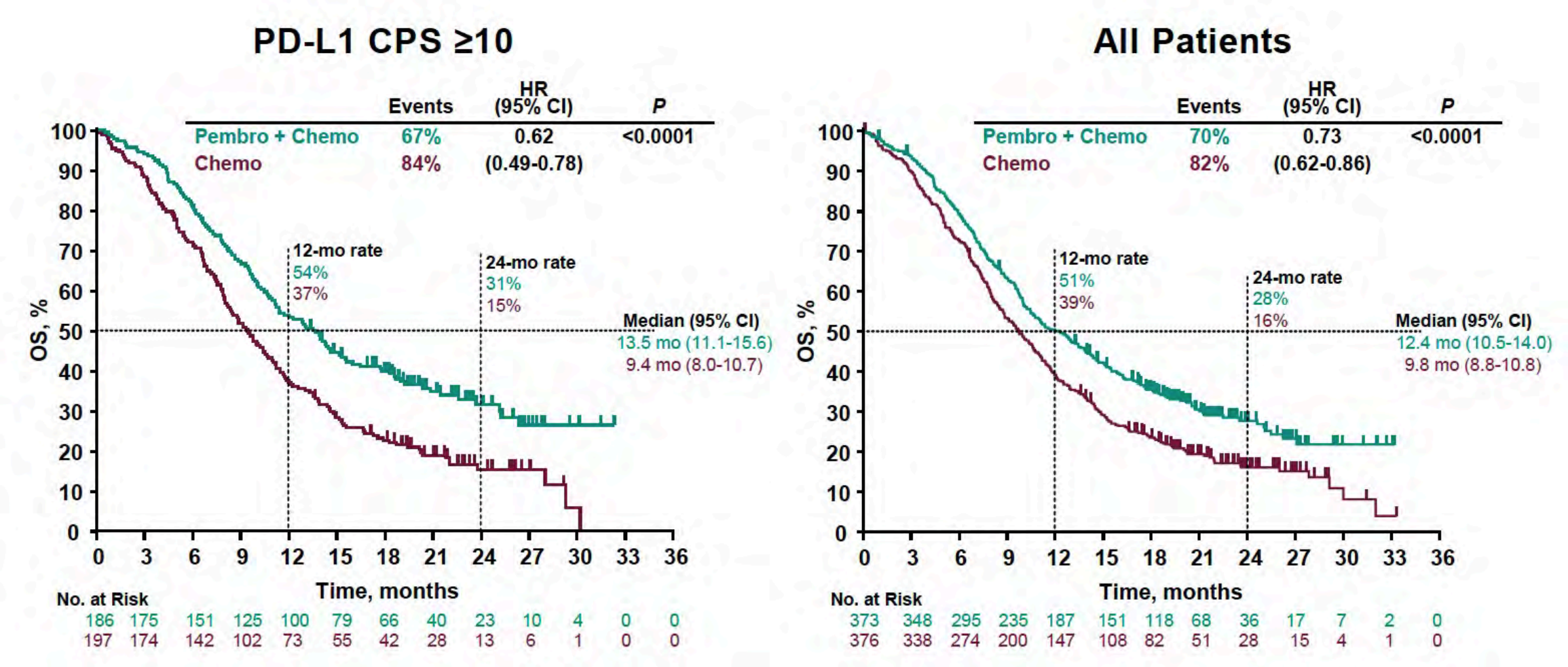
RTP RESEARCH TO PRACTICE

Pembrolizumab plus Chemotherapy versus Chemotherapy as First-Line Therapy in Patients with Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study

Kato K et al.

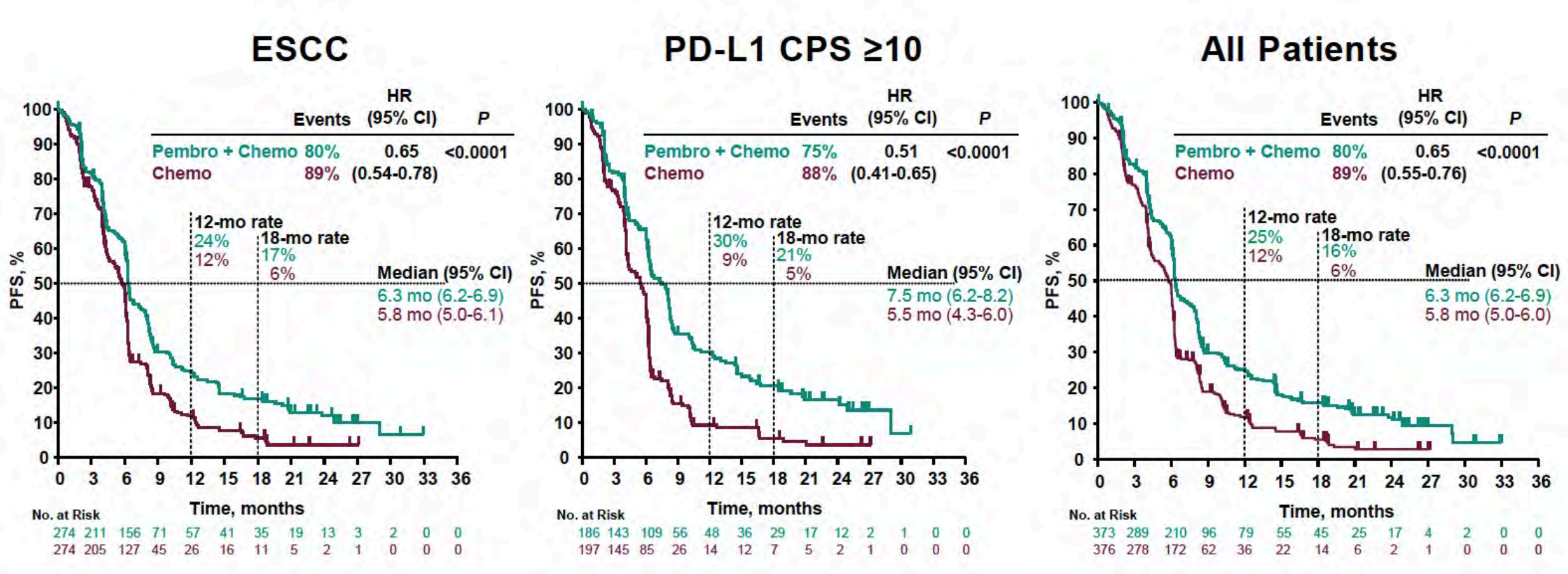
ESMO 2020;Abstract LBA8_PR.

KEYNOTE-590: Overall Survival



Kato K et al. ESMO 2020;Abstract LBA8_PR.

KEYNOTE-590: Progression-Free Survival



Kato K et al. ESMO 2020;Abstract LBA8_PR.

RTP RESEARCH TO PRACTICE

FDA Approves Nivolumab with Chemotherapy for Front-Line Advanced Gastric Cancer

Press Release – April 16, 2021

"The FDA approved nivolumab in combination with certain types of chemotherapy for the frontline treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma, making it the first approved immunotherapy for this patient population.

The agency based the approval on data from the randomized, multicenter, open-label phase 3 CheckMate-649 trial, designed to evaluate nivolumab – a monoclonal antibody that inhibits tumor growth by enhancing T-cell function – plus chemotherapy in 1,581 patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma. Of the 789 patients treated in the nivolumab arm, median overall survival was 13.8 months, compared with 11.6 months for patients who received chemotherapy alone."

https://www.cancernetwork.com/view/fda-approves-nivolumab-plus-chemo-for-frontline-advanced-gastric-cancer?utm_source=sfmc&utm_medium=email&utm_campaign=4.16.21_CN_Breaking&eKey=Z2tlbGx5QHJlc2VhcmNodG9wcmFjdGljZS5jb20=

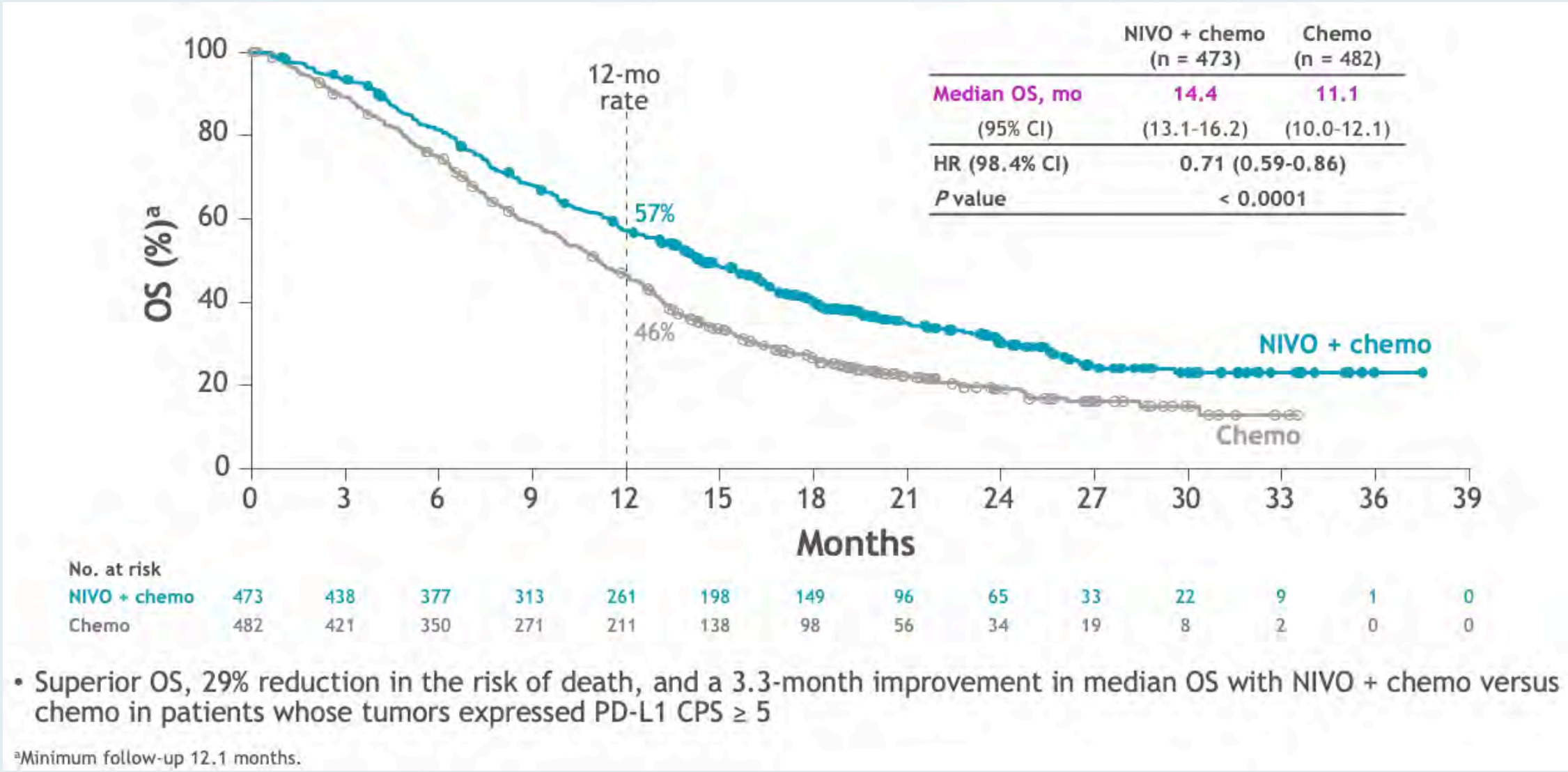
RTP RESEARCH TO PRACTICE

Nivolumab plus Chemotherapy versus Chemotherapy as First-Line Treatment for Advanced Gastric Cancer/Gastroesophageal Junction Cancer/Esophageal Adenocarcinoma: First Results of the CheckMate 649 Study

Moehler M et al.

ESMO 2020;Abstract LBA6.

CheckMate 649: Dual Primary Endpoint – OS (PD-L1 CPS ≥5)



- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

[a]Minimum follow-up 12.1 months.

Moehler M et al. ESMO 2020;Abstract LBA6.

First-Line (1L) Nivolumab (NIVO) plus Chemotherapy (Chemo) versus Chemo in Advanced Gastric Cancer/Gastroesophageal Junction Cancer/Esophageal Adenocarcinoma (GC/GEJC/EAC): Expanded Efficacy and Safety Data from CheckMate 649

Moehler MH et al.
ASCO 2021;Abstract 4002.

Saturday, June 5, 1:45 PM - 4:45 PM EDT

Nivolumab (NIVO) plus Ipilimumab (IPI) or NIVO plus Chemotherapy (Chemo) versus Chemo as First-Line (1L) Treatment for Advanced Esophageal Squamous Cell Carcinoma (ESCC): First Results of the CheckMate 648 Study

Chau I et al.
ASCO 2021;Abstract LBA4001.

Saturday, June 5, 1:45 PM - 4:45 PM EDT

Case Presentation – Dr Del Rosario: A 49-year-old woman with HER2-positive metastatic gastric adenocarcinoma – PD-L1 CPS 5

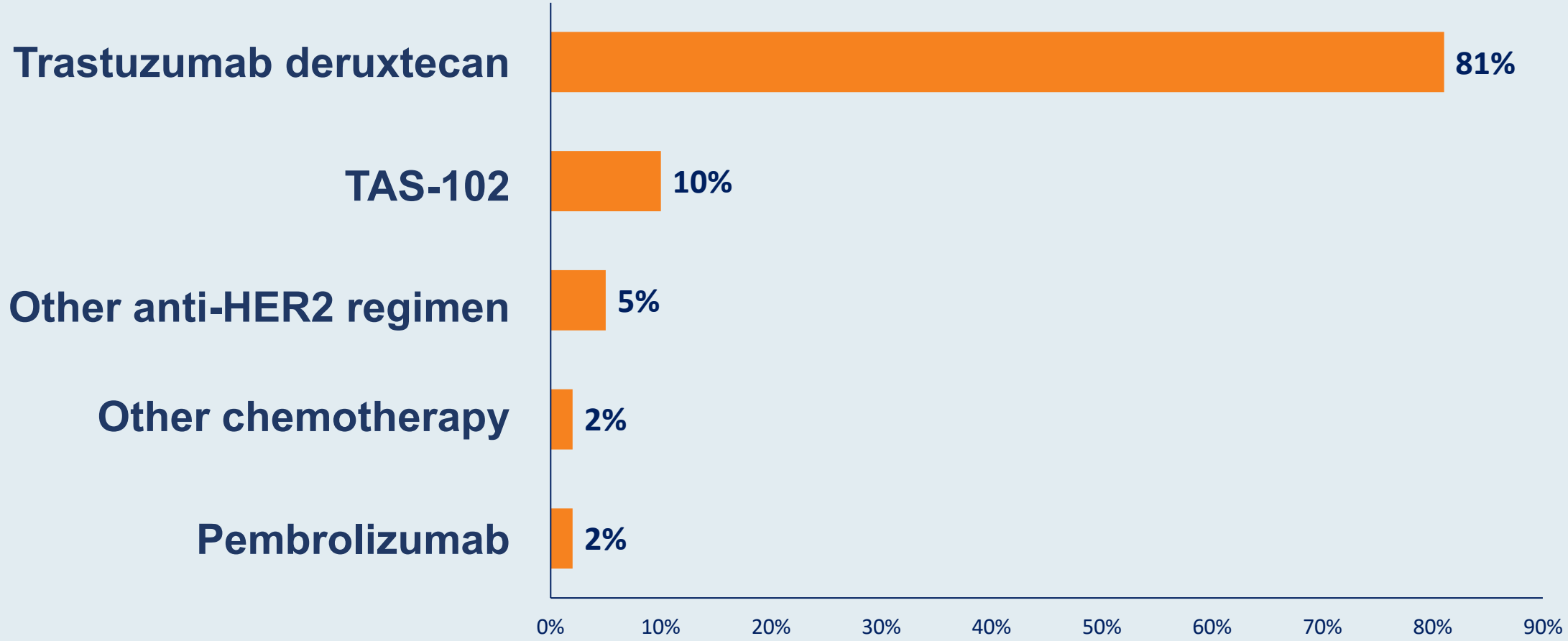
Dr Michael Del Rosario

- HER2-positive, MMR proficient, metastatic gastric adenocarcinoma, PD-L1 CPS: 5, ECOG PS: 1
- FOLFOX/trastuzumab

Questions

- Upon disease progression is immunotherapy still an option in light of her PD-L1 CPS of 5?
- Does HER2 status need to be confirmed upon disease progression? What treatment would you recommend if the tumor remains HER2-positive? If the tumor is now HER2-negative?
- With trastuzumab deruxtecan, which side effects should we monitor for in patients? How should we monitor for ILD?

Regulatory and reimbursement issues aside, what third-line treatment would you recommend for a younger patient (PS 0) with metastatic HER2-positive, MSS gastric cancer (CPS <1) with progression on FOLFOX/trastuzumab and then paclitaxel/ramucirumab?



N = 59

Survey of live webinar audience

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- Shitara K et al. **Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer.** *N Engl J Med* 2020;382(25):2419-30.
- Dayyani F et al. **A Phase Ib Multicenter Study of Trifluridine/Tipiracil (FTD/TPI) in Combination with Irinotecan (IRI) in Patients with Advanced Recurrent or Unresectable Gastric and Gastroesophageal Adenocarcinoma (aGEC) After at Least One Line of Treatment with a Fluoropyrimidine and Platinum Containing Regimen.** Gastrointestinal Cancers Symposium 2021;Abstract TPS251.
- Hara H et al. **A Phase I/II Trial of Trifluridine/Tipiracil in Combination with Irinotecan in Patients with Advanced Gastric Cancer Refractory to Fluoropyrimidine, Platinum, and Taxane.** Gastrointestinal Cancers Symposium 2021;Abstract 210.

FDA Approves Trastuzumab Deruxtecan for HER2-Positive Gastric Adenocarcinomas

Press Release – January 15, 2021

"On January 15, 2021, the Food and Drug Administration approved fam-trastuzumab deruxtecan-nxki for adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

Efficacy was evaluated in a multicenter, open-label, randomized trial (DESTINY-Gastric01, NCT03329690) in patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens, including trastuzumab, a fluoropyrimidine- and a platinum-containing chemotherapy. A total of 188 patients were randomized (2:1) to receive fam-trastuzumab deruxtecan-nxki 6.4 mg/kg intravenously every 3 weeks or physician's choice of either irinotecan or paclitaxel monotherapy."

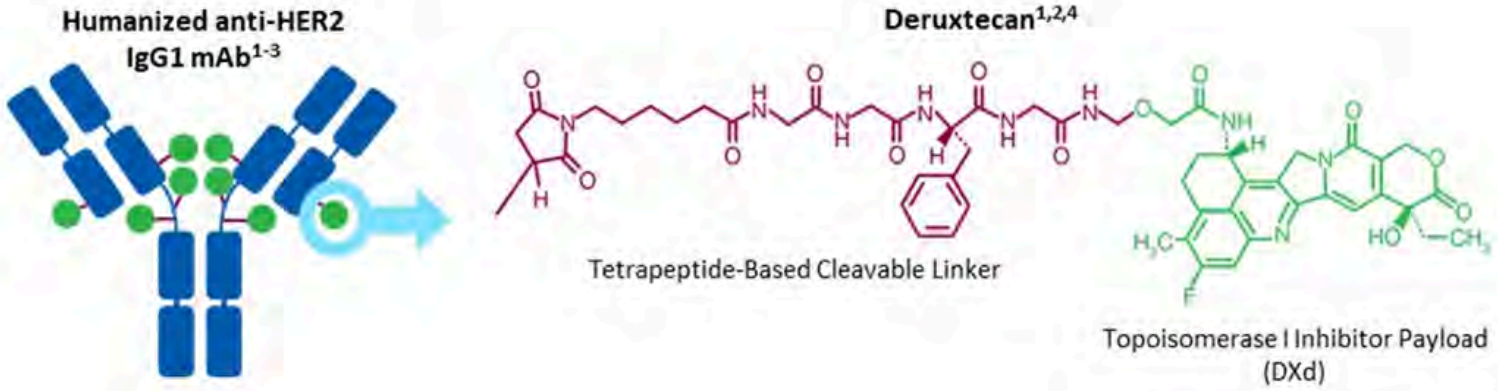
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-fam-trastuzumab-deruxtecan-nxki-her2-positive-gastric-adenocarcinomas

RTP RESEARCH TO PRACTICE

Trastuzumab Deruxtecan (T-DXd) Is a Novel Antibody-Drug Conjugate Designed to Deliver an Antitumor Effect

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



- T-DXd is being clinically evaluated across a number of HER2-expressing or mutated cancers, including breast cancer, CRC, non-small cell lung cancer, and others

Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

Siena S et al. ASCO 2020;Abstract 4000.

The NEW ENGLAND JOURNAL of MEDICINE

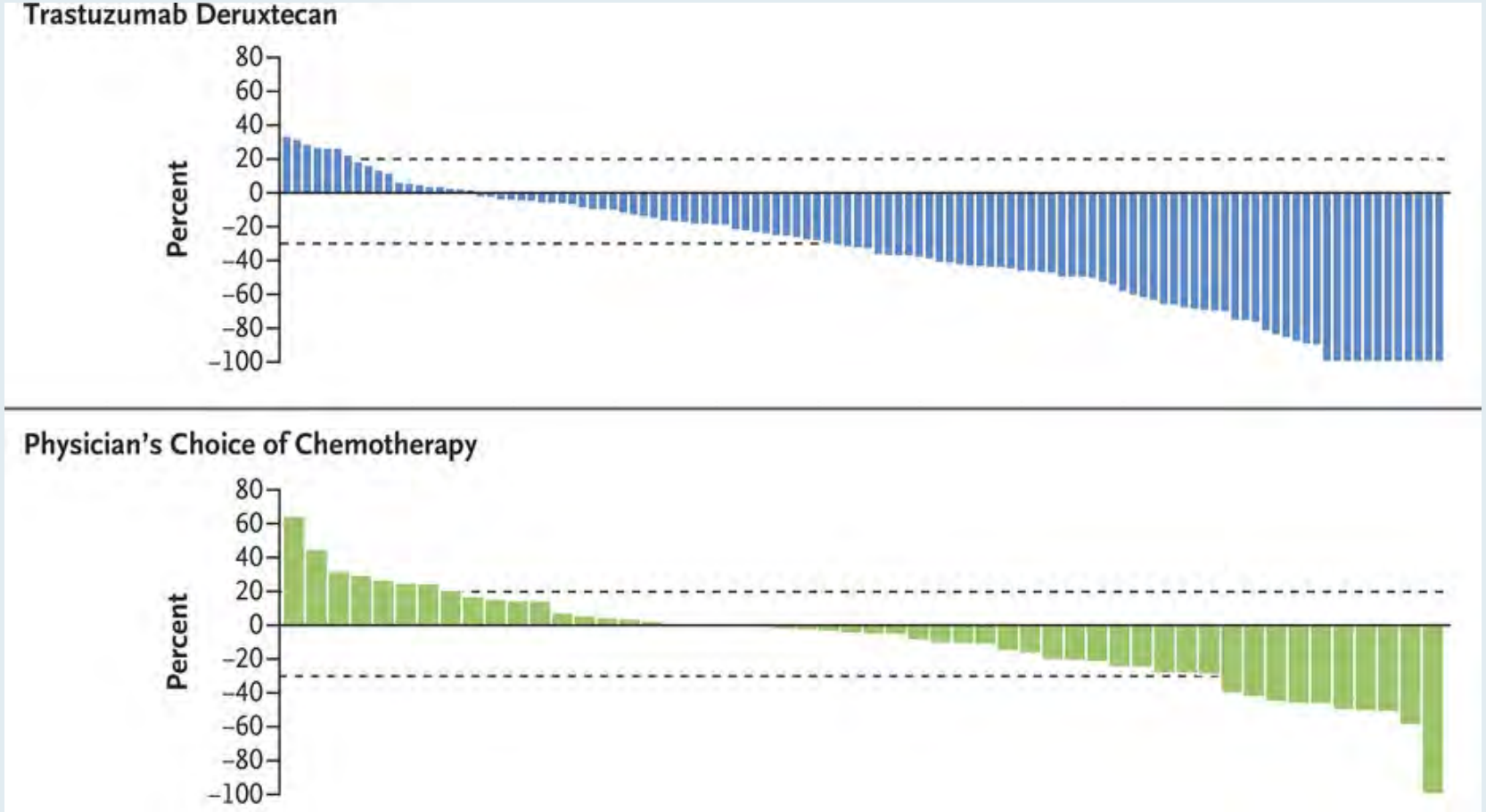
ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

K. Shitara, Y.-J. Bang, S. Iwasa, N. Sugimoto, M.-H. Ryu, D. Sakai, H.-C. Chung, H. Kawakami, H. Yabusaki, J. Lee, K. Saito, Y. Kawaguchi, T. Kamio, A. Kojima, M. Sugihara, and K. Yamaguchi, for the DESTINY-Gastric01 Investigators*

N Engl J Med 2020;382(25):2419-30

DESTINY-Gastric01: Trastuzumab Deruxtecan for Previously Treated HER2-Positive Gastric Cancer

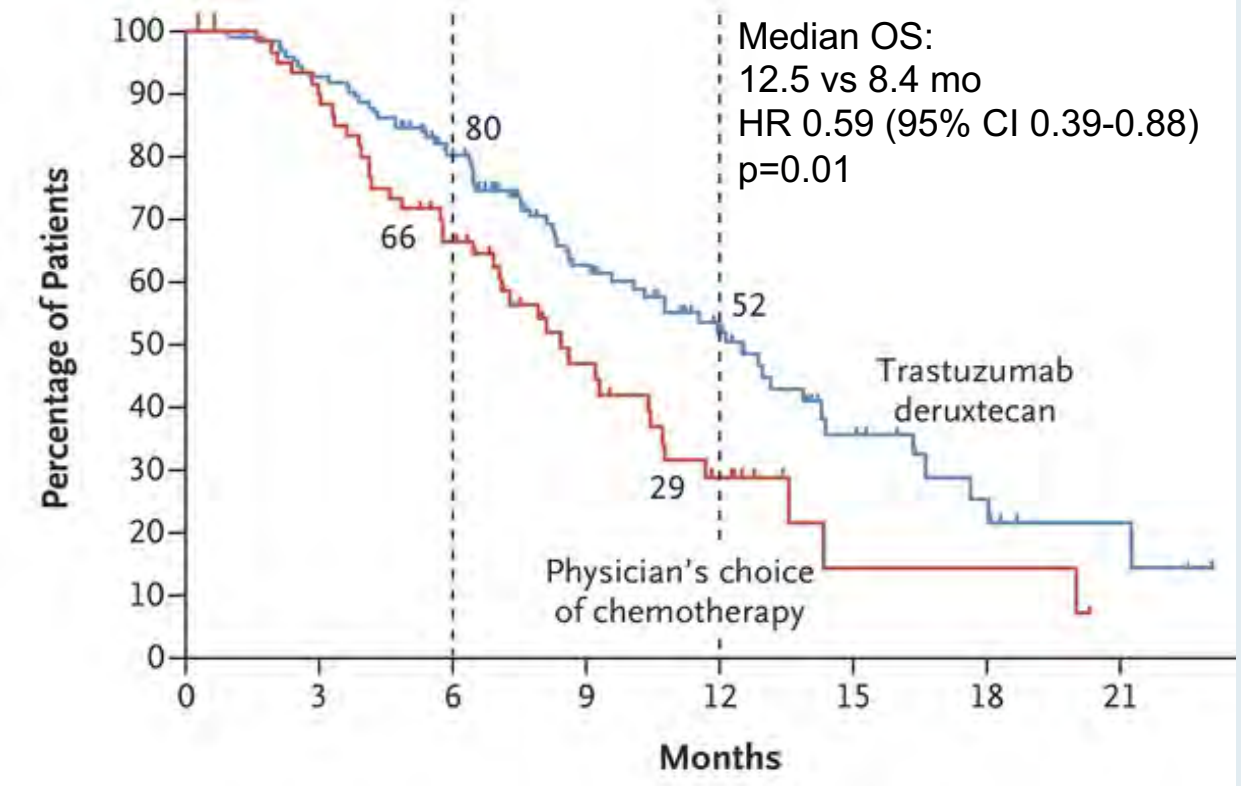


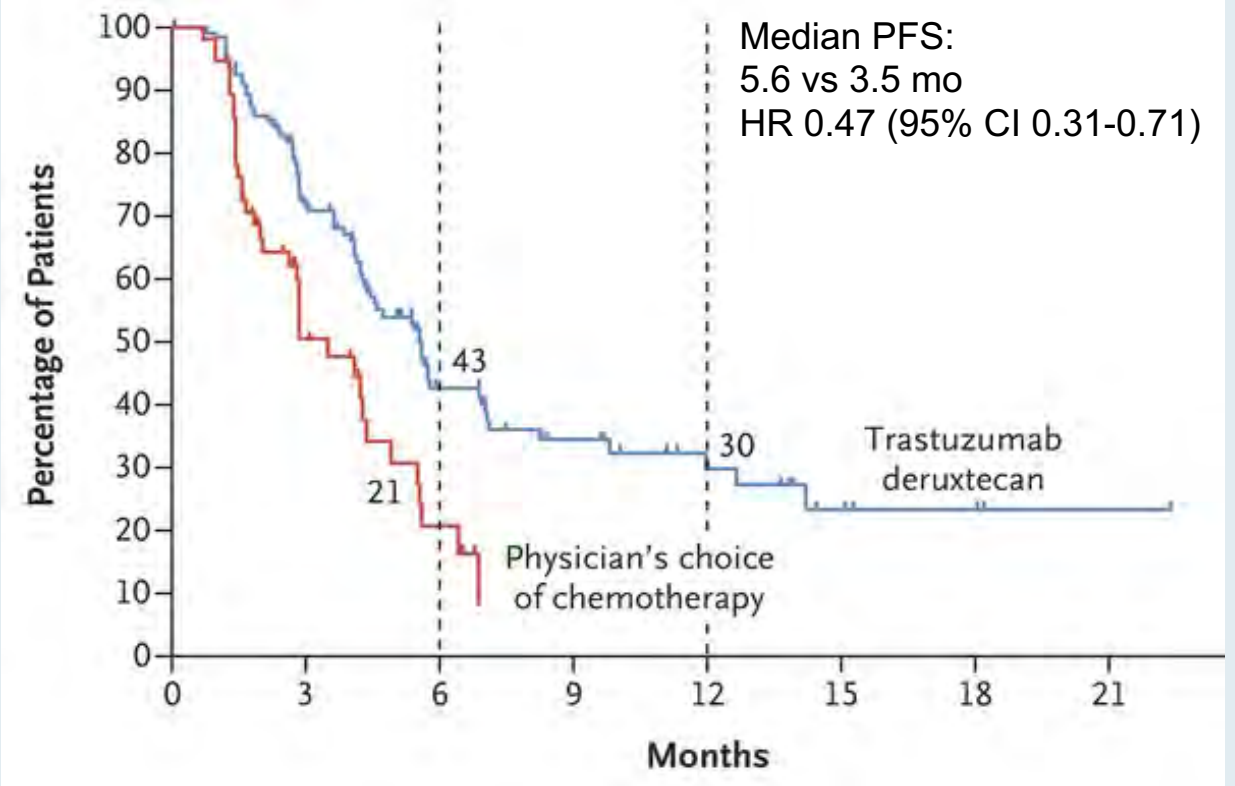
	T-DXd (n = 119)	PC (n = 56)
ORR	**51%**	**14%**
Confirmed ORR	**43%**	**12%**
CR	8%	0%
PR	34%	12%

Shitara K et al. *N Engl J Med* 2020;382(25):2419-30.

RTP RESEARCH TO PRACTICE

DESTINY-Gastric01: Survival Results





Shitara K et al. *N Engl J Med* 2020;382(25):2419-30.

DESTINY-Gastric01: AEs of Special Interest – Interstitial Lung Disease

	T-DXd (n = 125)					
Preferred Term, n	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total, n (%)
Interstitial Lung Disease	3	6	2	1	0	12 (9.6)

- Drug-related ILD/pneumonitis as determined by an independent adjudication committee was only observed in patients receiving T-DXd
- Among the 12 total events, the median time to investigator-reported first onset was 84.5 days (range, 36-638 days)

Recommendations: It is important to monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is confirmed.

Yamaguchi K et al. ESMO World GI Congress 2020;Abstract O-11.

Ongoing Phase III Trial of Trastuzumab Deruxtecan for HER2-Positive Gastric Cancer

Trial (NCT#)	Phase	Target (N)	Setting	Treatment arms
DESTINY-Gastric04 (NCT04704934)	III	490	Metastatic and/or unresectable gastric or GEJ adenocarcinoma; Progression on or after trastuzumab-based regimen	• Trastuzumab deruxtecan • Ramucirumab + paclitaxel

Clinicaltrials.gov; Accessed February 2021.

FDA Grants Accelerated Approval to Pembrolizumab with Trastuzumab and Chemotherapy as First-Line Therapy for HER2-Positive Gastric Cancer

Press Release – May 5, 2021

"On May 5, 2021, the Food and Drug Administration granted accelerated approval to pembrolizumab in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Approval was based on the prespecified interim analysis of the first 264 patients of the ongoing KEYNOTE-811 (NCT03615326) trial, a multicenter, randomized, double-blind, placebo-controlled trial in patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who had not previously received systemic therapy for metastatic disease. Patients were randomized (1:1) to receive pembrolizumab 200 mg or placebo every 3 weeks, in combination with trastuzumab and either fluorouracil plus cisplatin or capecitabine plus oxaliplatin.

The main efficacy measure for this analysis was overall response rate (ORR) assessed by blinded independent review committee. The ORR was 74% in the pembrolizumab arm and 52% in the placebo arm (one-sided p-value< 0.0001, statistically significant). The median duration of response (DoR) was 10.6 months for patients treated with pembrolizumab and 9.5 months for those in the placebo arm."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-pembrolizumab-her2-positive-gastric-cancer

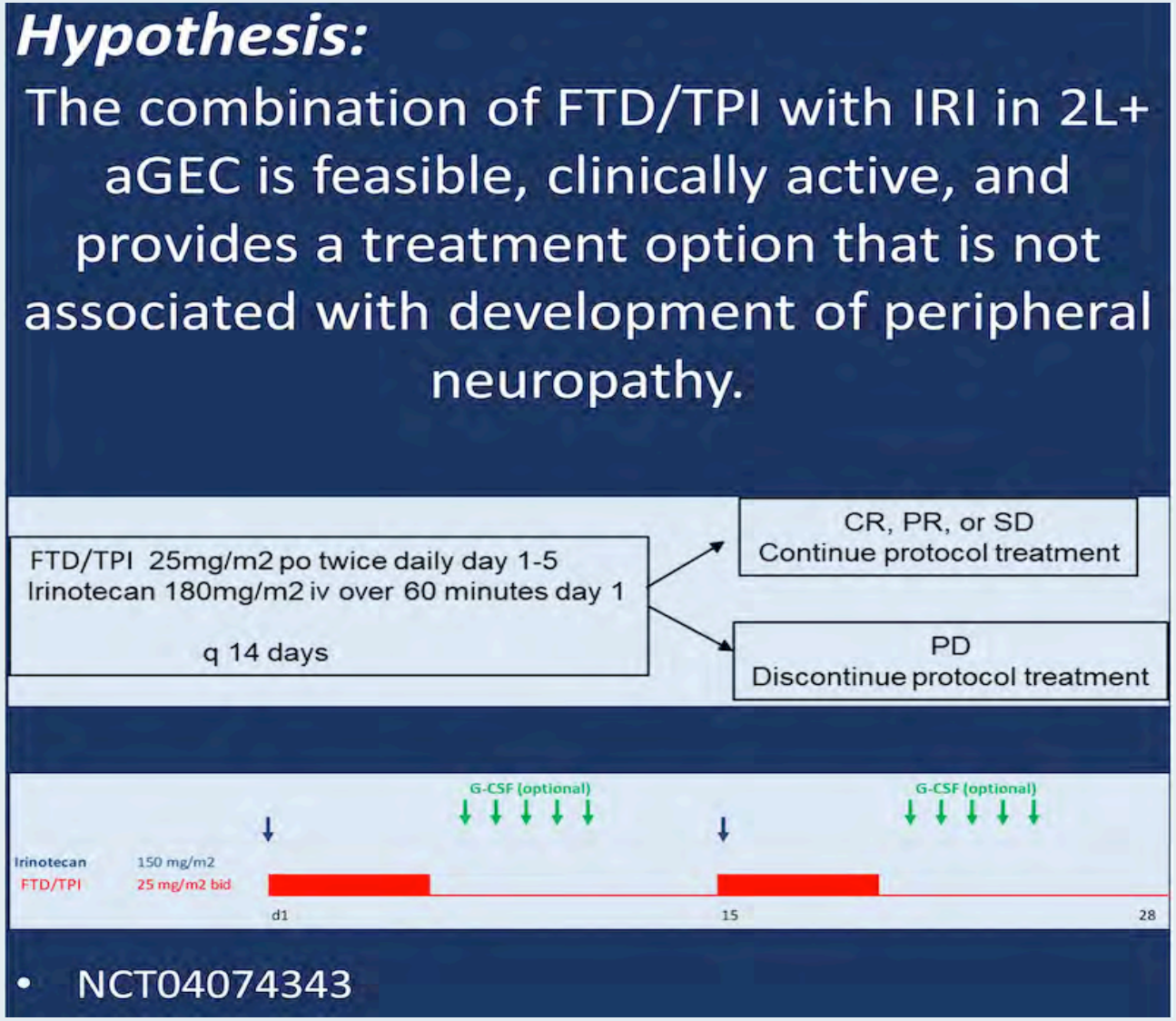
RTP RESEARCH TO PRACTICE

A Phase Ib Multicenter Study of Trifluridine/Tipiracil (FTD/TPI) in Combination with Irinotecan (IRI) in Patients with Advanced Recurrent or Unresectable Gastric and Gastroesophageal Adenocarcinoma (aGEC) After at Least One Line of Treatment with a Fluoropyrimidine and Platinum Containing Regimen

Dayyani F et al.

Gastrointestinal Cancers Symposium 2021;Abstract TPS251.

TAS-102 in Combination with Irinotecan: Ongoing Phase Ib Study Design and Objectives



Current Enrollment (n = 20)

Primary Objective:

- Regimen feasibility and efficacy estimate

Secondary Objectives:

- Overall survival
- Overall response rate
- Adverse events

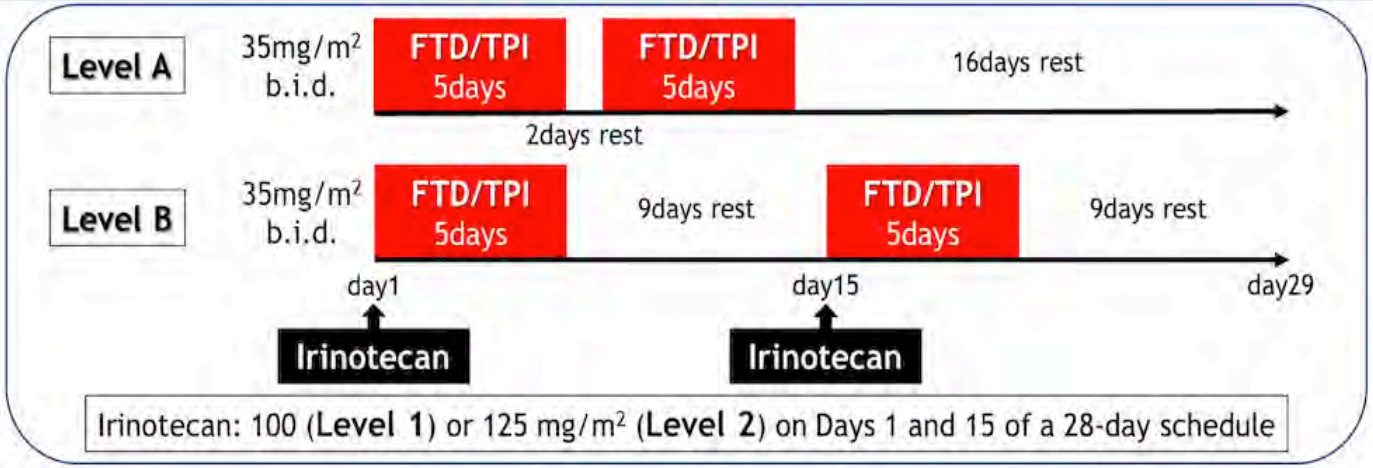
Dayyani F et al. Gastrointestinal Cancers Symposium 2021;Abstract TPS251.

A Phase I/II Trial of Trifluridine/Tipiracil in Combination with Irinotecan in Patients with Advanced Gastric Cancer Refractory to Fluoropyrimidine, Platinum, and Taxane

Hara H et al.

Gastrointestinal Cancers Symposium 2021;Abstract 210.

TAS-102 in Combination with Irinotecan: Results from a Phase I/II Study



	Level 1A (N = 2) N (%)	Level 1B (N = 3) N (%)	Level 2B (N = 6) N (%)	Total (N = 11) N (%)
CR	0 (0.0)	0 (0.0)	0 (0.0)	0
PR	0 (0.0)	0 (0.0)	1 (16.7)	1 (9.1)
SD	1 (50.0)	2 (66.7)	4 (66.7)	7 (63.6)
PD	1 (50.0)	1 (33.3)	1 (16.7)	3 (27.3)
NE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ORR (%) [95% CI]	0.0 [0.0- 84.1]	0.0 [0.0-70.8]	16.7 [0.4-64.1]	9.1 [0.2-41.3]
DCR (%) [95% CI]	50.0 [1.3-98.7]	66.6 [9.4-99.2]	83.3 [35.9-99.6]	72.7 [39.0-94.0]

	Level 1A (N=2)		Level 1B (N=3)		Level 2B (N=6)	
	All N (%)	≥G3 N (%)	All N (%)	≥G3 N (%)	All N (%)	≥G3 N (%)
Hematologic						
Neutropenia	2 (100.0)	2 (100.0)	3 (100.0)	2 (66.7)	6 (100.0)	6 (100.0)
WBC decreased	2 (100.0)	1 (50.0)	3 (100.0)	1 (33.3)	5 (83.3)	4 (66.7)
Anemia	2 (100.0)	2 (100.0)	2 (66.7)	1 (33.3)	3 (50.0)	2 (33.3)
Plt count decreased	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	4 (66.7)	1 (16.7)
Lymphocyte count decreased	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	2 (33.3)	1 (16.7)
Febrile neutropenia	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)
Non-hematologic						
Appetite loss	1 (50.0)	0 (0.0)	2 (66.7)	0 (0.0)	5 (83.3)	0 (0.0)
Diarrhea	1 (50.0)	0 (0.0)	2 (66.7)	0 (0.0)	2 (33.3)	0 (0.0)
Constipation	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	0 (0.0)

The RP2D of FTD/TPI in combination with irinotecan was determined to be Level 1B although further investigation to explore optimal regimen is needed.

Hara H et al. Gastrointestinal Cancers Symposium 2021;Abstract 210.

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Colorectal Cancer

- Dr Lorber: A 74-year-old woman with MSI-high mCRC – BRAF V600E mutation
- *Key Recent Publications and Presentations*
- Dr Dayyani: A 60-year-old woman with MSS mCRC – TMB 35.4 mut/Mb, KRAS G12D mutation
- *Key Recent Publications and Presentations*

Module 2: Gastric, Gastroesophageal and Esophageal Cancers

- Dr Dayyani: A 60-year-old man with relapsed MSS esophageal squamous cell cancer – PD-L1 CPS 15
- *Key Recent Publications and Presentations*
- Dr Del Rosario: A 49-year-old woman with HER2-positive metastatic gastric adenocarcinoma – PD-L1 CPS 5
- *Key Recent Publications and Presentations*

Module 3: Hepatocellular Cancer (HCC)

- Dr Dayyani: A 59-year-old man with advanced HCC
- Dr Lorber: An 80-year-old woman with unresectable advanced HCC
- *Key Recent Publications and Presentations*

Module 4: Pancreatic Adenocarcinoma

- Dr Chen: An 80-year-old woman with localized pancreatic cancer
- Dr Dayyani: A 79-year-old woman with pancreatic cancer and a germline BRCA2 mutation
- *Key Recent Publications and Presentations*

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Case Presentation – Dr Dayyani: A 59-year-old man with advanced HCC

Dr Farshid Dayyani

- PMH: Treated Hepatitis C, cirrhosis, esophageal varices, UGIB (2012) and liver lesions consistent with HCC
- 10/2016: Presents with abdominal pain and thought to have hemoperitoneum from HCC rupture
  - Ascites, elevated bilirubin
- 11/2016 imaging: Viable tumor in segment 4
- 12/2016: TACE, with PR → 1/2017: Repeat TACE
- 3/2018 CT abdomen: Numerous larger lesions
- 9/2018: Enrolled on IMbrave 150 and received atezolizumab/bevacizumab → SD x 12 months
  - Proteinuria after 16 cycles; bevacizumab held
- 2/2020: Came off trial due to recurrent grade 3 proteinuria with bevacizumab

Questions

- For a patient who had atezolizumab/bevacizumab but didn't tolerate it, he's technically TKI naïve. Do I switch him to a TKI given the fact that he had proteinuria? Or, do we continue on one of the approved checkpoint inhibitors?

Case Presentation – Dr Lorber: An 80-year-old woman with unresectable advanced HCC

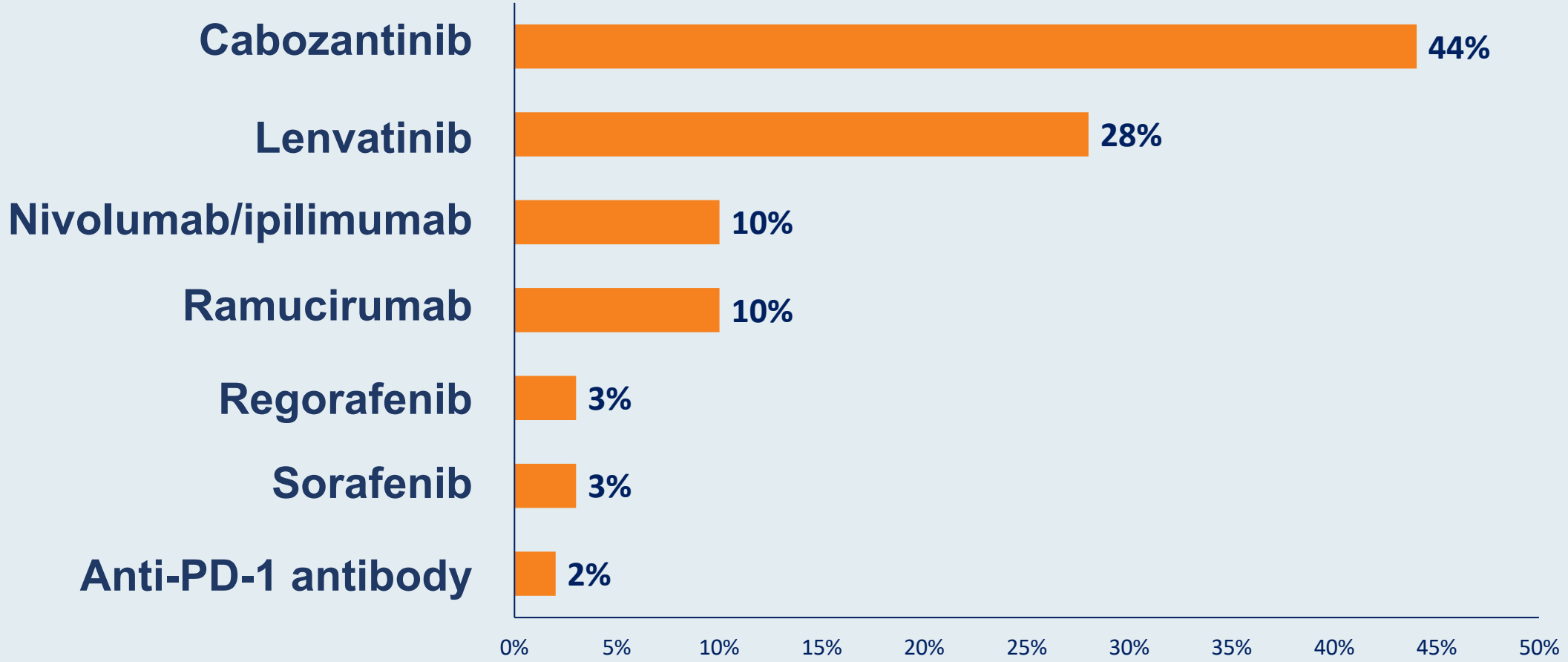
Dr Jeremy Lorber

- Diagnosed with unresectable HCC after presenting with right upper quadrant pain, pleural effusion, and weight loss
- Imaging reveals a 15-cm primary liver tumor and smaller satellite nodules
- Atezolizumab/bevacizumab with initial response and then stable disease for 9 months before experiencing symptomatic progression
- Lenvatinib initiated but discontinued due to issues with stomatitis, nausea, and skin ulcerations
- Currently receiving treatment with dose-reduced cabozantinib and tolerating treatment well

Questions

- With atezolizumab with bevacizumab approved in the first line, where does that leave the other available therapies? Which treatment is best to use second line?
- Is there a way to distinguish between atezolizumab/bevacizumab and nivolumab/ipilimumab as first-line therapy options?

What would be your second-line therapy for a 65-year-old patient with HCC, a Child-Pugh A score and PS 0 who received first-line atezolizumab/bevacizumab and experienced disease progression after 18 months (AFP 2,500 ng/mL)?



N = 58

Survey of live webinar audience

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- Finn RS et al. **IMbrave150: Updated Overall Survival (OS) Data from a Global, Randomized, Open-Label Phase III Study of Atezolizumab (atezo) + Bevacizumab (bev) versus Sorafenib (sor) in Patients (pts) with Unresectable Hepatocellular Carcinoma (HCC).** Gastrointestinal Cancers Symposium 2021;Abstract 267.
- Ren Z et al. **Sintilimab plus Bevacizumab Biosimilar vs Sorafenib as First-Line Treatment for Advanced Hepatocellular Carcinoma (ORIENT-32).** ESMO Asia 2020;Abstract LBA2.
- El-Khoueiry AB et al. **Nivolumab (NIVO) plus Ipilimumab (IPI) Combination Therapy in Patients (Pts) with Advanced Hepatocellular Carcinoma (aHCC): Long-Term Results from CheckMate 040.** Gastrointestinal Cancers Symposium 2021;Abstract 269.

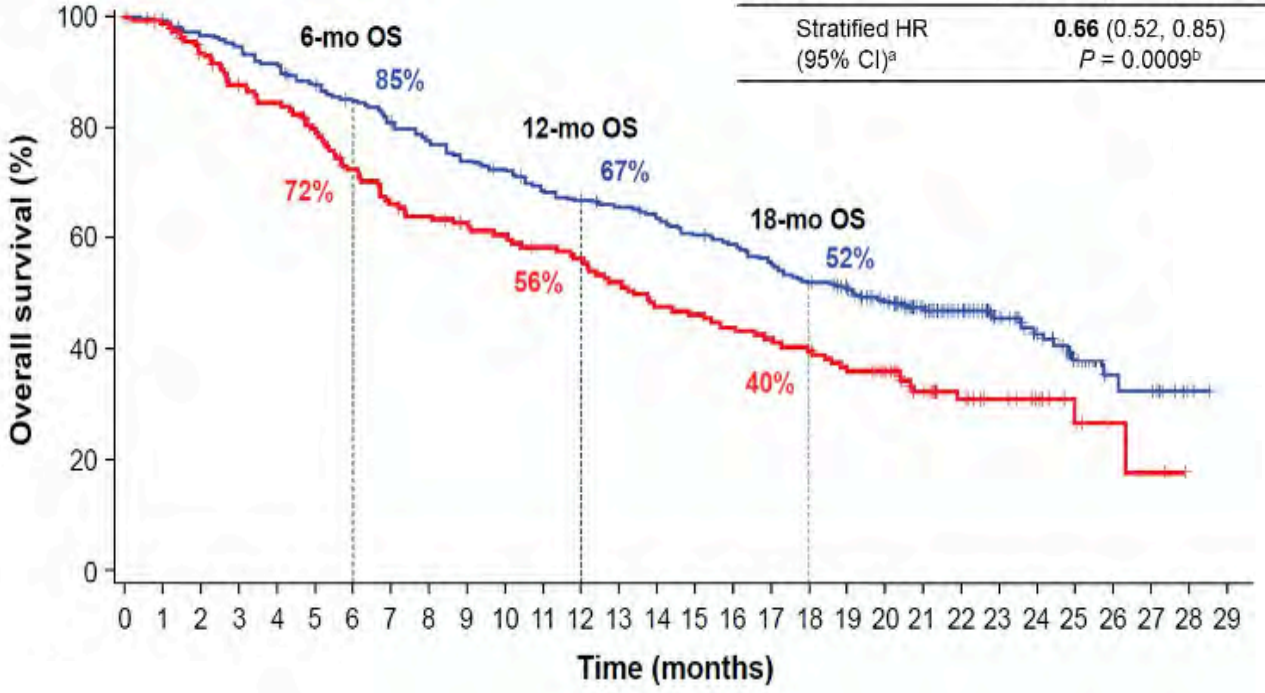
IMbrave150: Updated Overall Survival (OS) Data from a Global, Randomized, Open-Label Phase III Study of Atezolizumab (atezo) + Bevacizumab (bev) versus Sorafenib (sor) in Patients (pts) with Unresectable Hepatocellular Carcinoma (HCC)

Finn RS et al.

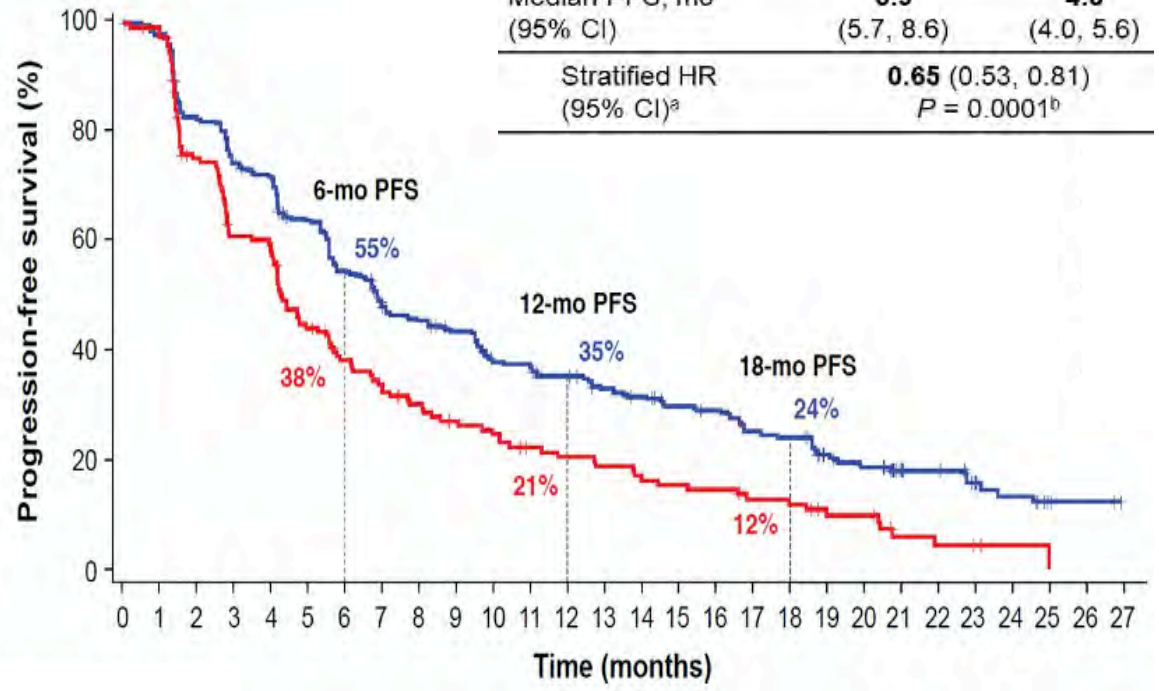
Gastrointestinal Cancers Symposium 2021;Abstract 267.

IMbrave150: Updated OS and PFS (Median Follow-Up 15.6 Months)

Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	



Updated PFS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
PFS events, n (%)	257 (76)	130 (79)
Median PFS, mo (95% CI)	**6.9** (5.7, 8.6)	**4.3** (4.0, 5.6)
Stratified HR (95% CI)[a]	**0.65** (0.53, 0.81) *P* = 0.0001[b]	



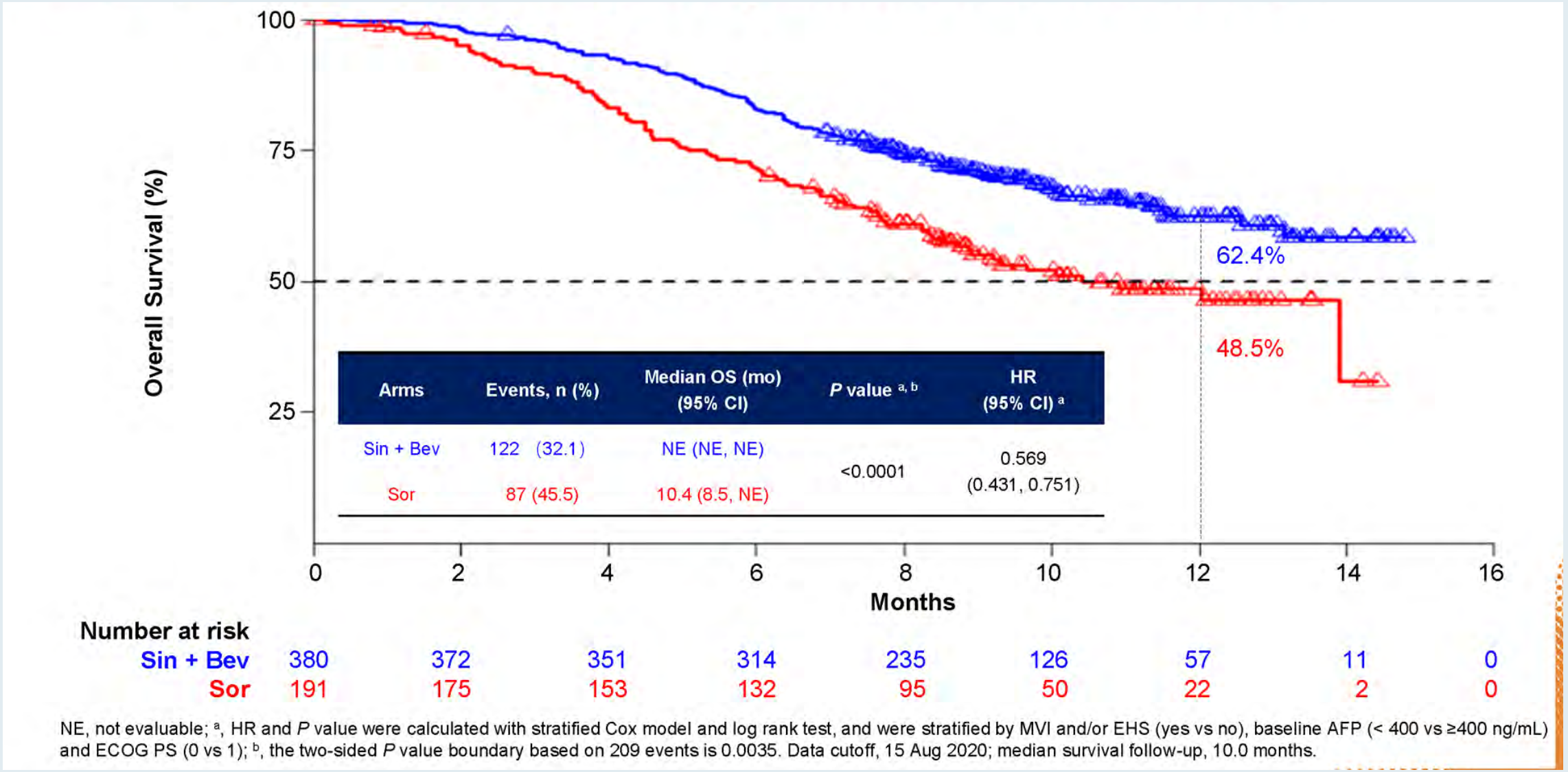
Finn RS et al. Gastrointestinal Cancers Symposium 2021;Abstract 267.

RTP RESEARCH TO PRACTICE

Sintilimab plus Bevacizumab Biosimilar vs Sorafenib as First-Line Treatment for Advanced Hepatocellular Carcinoma (ORIENT-32)

Ren Z et al. ESMO Asia 2020;Abstract LBA2.

ORIENT-32 Coprimary Endpoint: Overall Survival

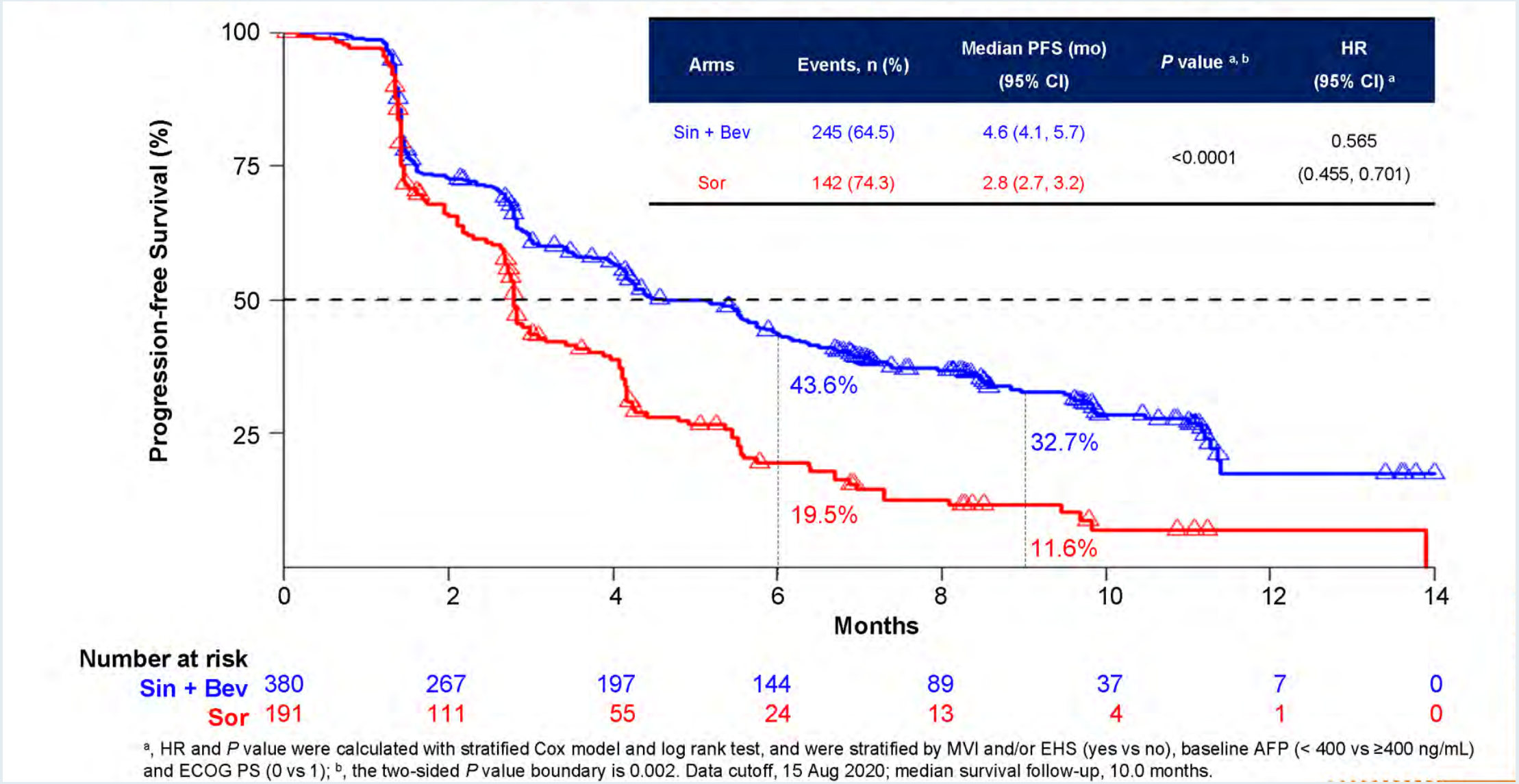


NE, not evaluable; [a], HR and *P* value were calculated with stratified Cox model and log rank test, and were stratified by MVI and/or EHS (yes vs no), baseline AFP (< 400 vs ≥400 ng/mL) and ECOG PS (0 vs 1); [b], the two-sided *P* value boundary based on 209 events is 0.0035. Data cutoff, 15 Aug 2020; median survival follow-up, 10.0 months.

The superior OS benefit with sintilimab plus bev biosimilar was generally consistent across all subgroups

Ren Z et al. ESMO Asia 2020;Abstract LBA2.

ORIENT-32 Coprimary Endpoint: Progression-Free Survival



[a], HR and *P* value were calculated with stratified Cox model and log rank test, and were stratified by MVI and/or EHS (yes vs no), baseline AFP (< 400 vs ≥400 ng/mL) and ECOG PS (0 vs 1); [b], the two-sided *P* value boundary is 0.002. Data cutoff, 15 Aug 2020; median survival follow-up, 10.0 months.

The superior PFS benefit with sintilimab plus bev biosimilar was generally consistent across all subgroups

Ren Z et al. ESMO Asia 2020;Abstract LBA2.

RTP RESEARCH TO PRACTICE

FDA Grants Accelerated Approval to Nivolumab and Ipilimumab Combination for HCC

Press Release – March 10, 2020

"On March 10, 2020, the Food and Drug Administration granted accelerated approval to the combination of nivolumab and ipilimumab for patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Efficacy of the combination was investigated in Cohort 4 of CHECKMATE-040, (NCT01658878) a multicenter, multiple cohort, open-label trial conducted in patients with HCC who progressed on or were intolerant to sorafenib. A total of 49 patients received nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for four doses, followed by single-agent nivolumab 240 mg every 2 weeks until disease progression or unacceptable toxicity.

The main efficacy outcome measures were overall response rate and duration of response as determined by blinded independent central review (BICR) using RECIST v1.1. ORR was 33% (n=16; 95% CI: 20, 48), with 4 complete responses and 12 partial responses. Response duration ranged from 4.6 to 30.5+ months, with 31% of responses lasting at least 24 months."

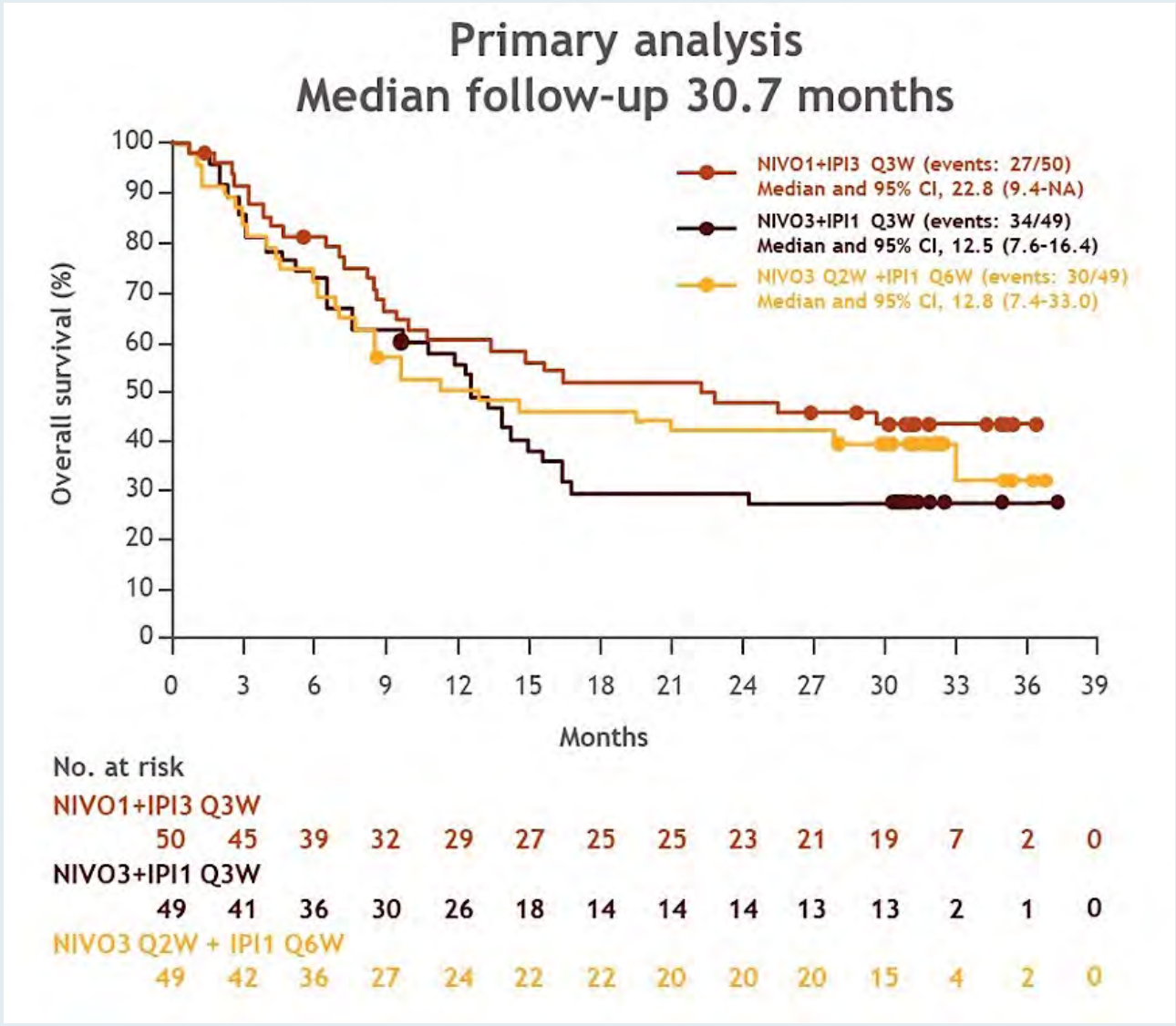
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-and-ipilimumab-combination-hepatocellular-carcinoma

Nivolumab (NIVO) plus Ipilimumab (IPI) Combination Therapy in Patients (Pts) with Advanced Hepatocellular Carcinoma (aHCC): Long-Term Results from CheckMate 040

El-Khoueiry AB et al.

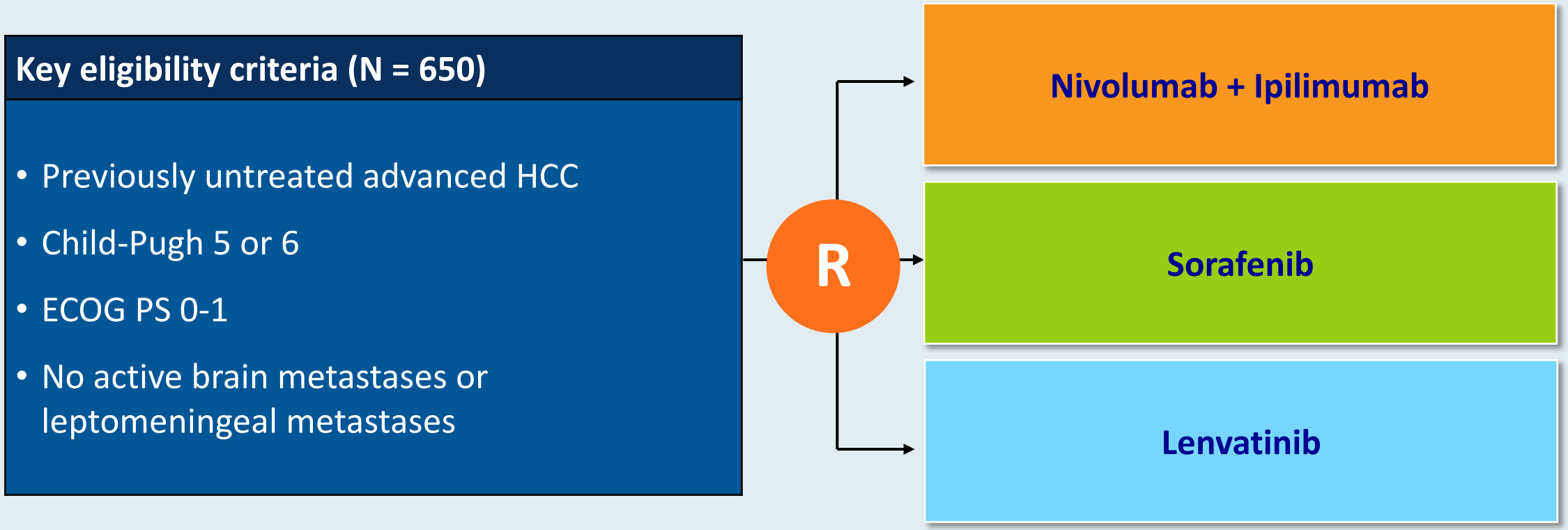
Gastrointestinal Cancers Symposium 2021;Abstract 269.

CheckMate 040: Updated Overall Survival with Ipilimumab/Nivolumab



El-Khoueiry AB et al. Gastrointestinal Cancers Symposium 2021;Abstract 269.

Ongoing Phase III CheckMate 9DW Trial Design



Primary endpoint: Overall survival

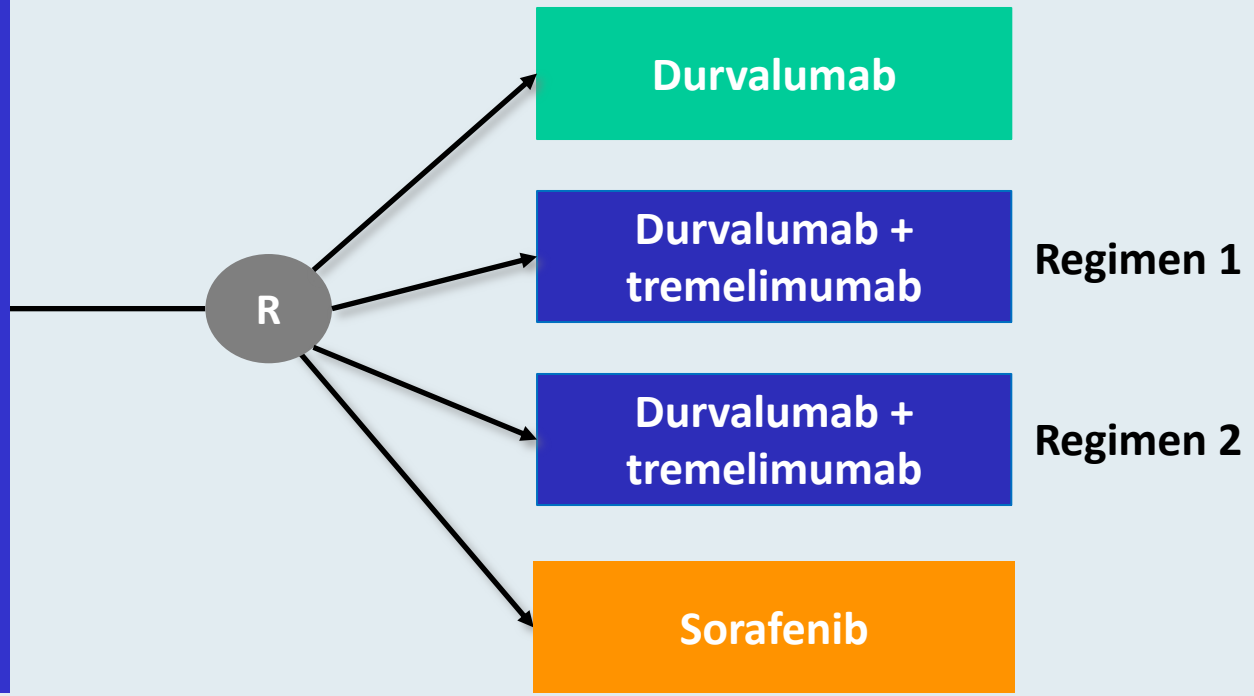
Secondary endpoints: ORR, DoR and time to symptom deterioration

Clinicaltrials.gov/NCT04039607 (Accessed February 2021).

Ongoing Phase III HIMALAYA Trial Design

Key eligibility criteria (N = 1,504)

- Unresectable advanced HCC not eligible for LRTs
- BCLC stage B or C
- Child–Pugh A
- No prior systemic therapy



- Primary endpoint: OS
- Other endpoints: TTP, PFS, ORR, DCR, DoR, and QoL

Clinicaltrials.gov/NCT03298451 (Accessed February 2021).

Agenda

Module 1: Colorectal Cancer

- Dr Lorber: A 74-year-old woman with MSI-high mCRC – BRAF V600E mutation
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- Dr Dayyani: A 60-year-old woman with MSS mCRC – TMB 35.4 mut/Mb, KRAS G12D mutation
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- Dr Lorber: An 80-year-old woman with unresectable advanced HCC
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Module 4: Pancreatic Adenocarcinoma

- Dr Chen: An 80-year-old woman with localized pancreatic cancer
- Dr Dayyani: A 79-year-old woman with pancreatic cancer and a germline BRCA2 mutation
- *Key Recent Publications and Presentations*

Case Presentation – Dr Chen: An 80-year-old woman with localized pancreatic cancer

Dr Gigi Chen

- Previously healthy woman presented with jaundice, elevated LFT and 10-pound weight loss; ultrasound showed pancreatic head mass, biliary dilatation, distended GB with sludge.
- Workup showed 22-mm hypoenhancing pancreatic head/uncinate process lesion and no additional sites of disease
- Germline genetic testing: negative
- Gemcitabine/*nab*-paclitaxel cycle 1 completed

Questions

- What is the benefit of neoadjuvant therapy followed by surgery versus up-front surgery followed by adjuvant chemotherapy? How would you sequence treatment for older patients?
- Which regimen would you generally recommend as neoadjuvant chemotherapy? Would it be FOLFIRINOX or gemcitabine/*nab*-paclitaxel?
- Would you recommend surgery or radiation for this patient after her neoadjuvant chemotherapy?
- If her tumor is found to have a somatic BRCA mutation or be HRD-positive, is there any data for PARP maintenance for early-stage patients?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Dayyani: A 79-year-old woman with pancreatic cancer and a germline BRCA2 mutation

Dr Farshid Dayyani

- PMH: HTN, breast cancer with BRCA2 mutation, s/p surgery in the 1990s, hypothyroidism
- Early 2019: Severe lower back pain treated with steroid injections
- 6/2019 CT: 5 x 4 x 3-cm mass in the head of the pancreas
- Cytology: Adenocarcinoma
- FOLFOX x 8, with response, Grade 2 neuropathy
- Maintenance with olaparib 300 mg BID (dose reduced due to diarrhea) → SBRT
- 7/2020: Subtotal distal pancreatectomy with splenectomy and intraoperative RT
  - pT1a pN0

Questions

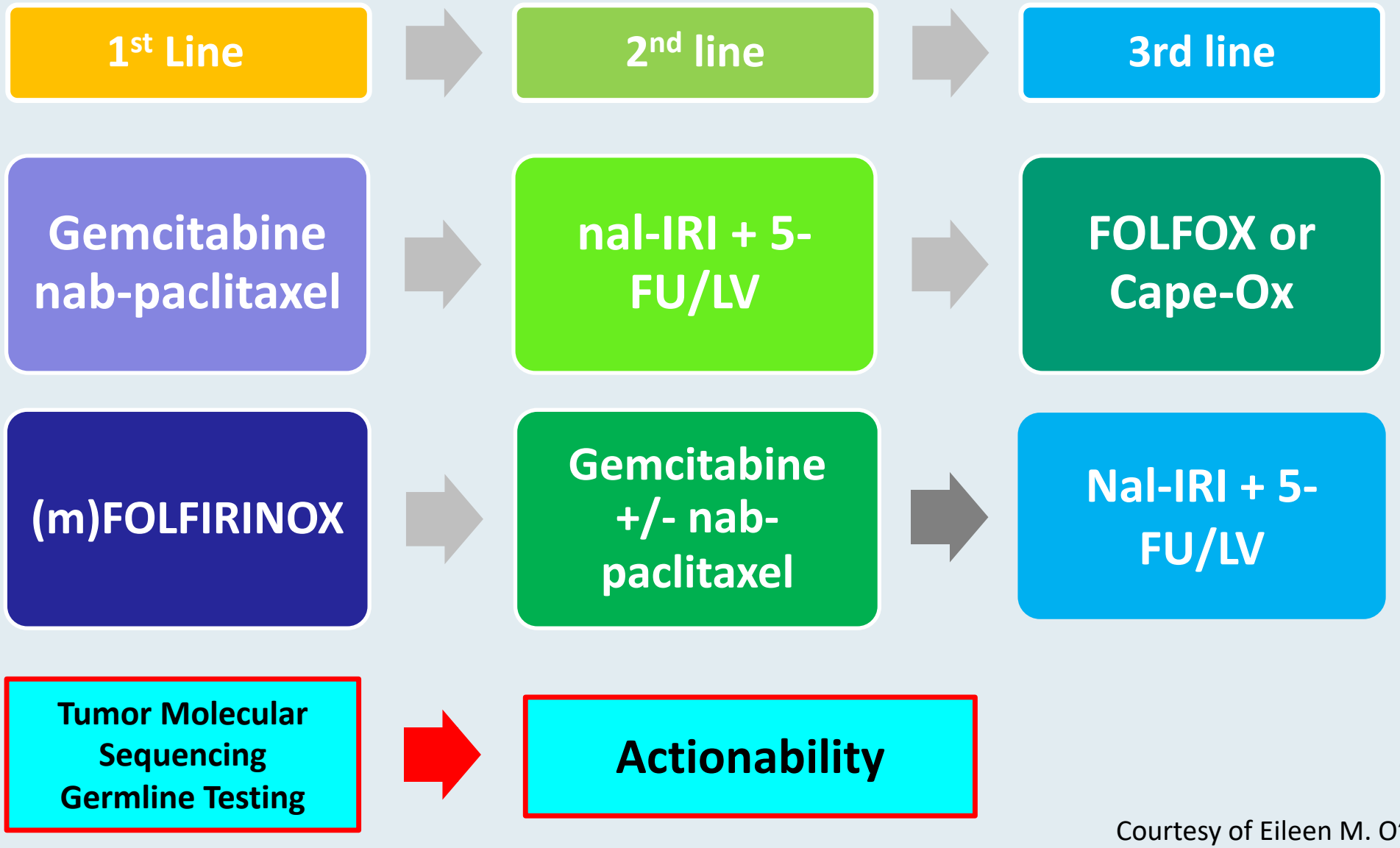
- Do you think there might be additional benefit of trying to further achieve a cytoreduction by PARP inhibition that might then enable a better resection, or R0 resection, for a patient?
- Is there a known synergy between radiation and PARP inhibitor therapy?

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- Kindler HL et al. **Maintenance Olaparib in Patients Aged ≥65 Years with a Germline BRCA Mutation and Metastatic Pancreatic Cancer: Phase III POLO Trial.** ESMO 2020;Abstract SO-3.
- Golan T et al. **Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer.** *N Engl J Med* 2019;381(4):317-27.
- Golan T et al. **Olaparib as Maintenance Treatment Following First-Line Platinum-Based Chemotherapy (PBC) in Patients with a Germline BRCA Mutation and Metastatic Pancreatic Cancer: Phase III POLO Trial.** ASCO 2019;Abstract LBA4.

Therapeutic Approach: Advanced PDAC 2020



Courtesy of Eileen M. O'Reilly, MD

Maintenance Olaparib in Patients Aged ≥65 Years with a Germline BRCA Mutation and Metastatic Pancreatic Cancer: Phase III POLO Trial[1]

Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer[2]

Olaparib as Maintenance Treatment Following First-Line Platinum-Based Chemotherapy (PBC) in Patients with a Germline BRCA Mutation and Metastatic Pancreatic Cancer: Phase III POLO Trial[3]

[1] Kindler HL et al.
ESMO 2020;Abstract SO-3.

[2] Golan T et al.
N Engl J Med 2019;381(4):317-27.

[3] Kindler HL et al.
ASCO 2019;Abstract LBA4.

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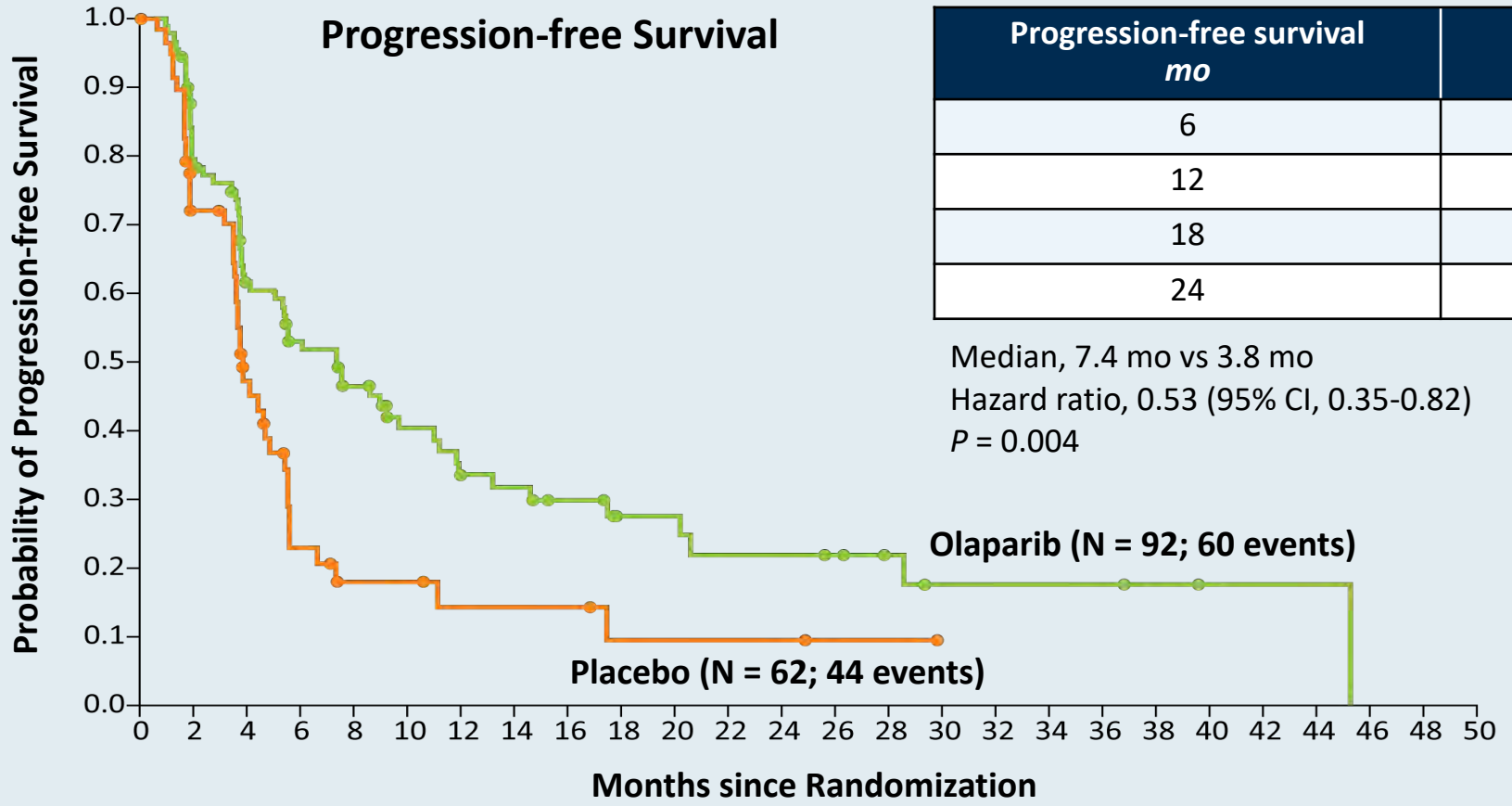
POLO: A Phase III Trial of Maintenance Olaparib for Metastatic Pancreatic Cancer with BRCA Mutation



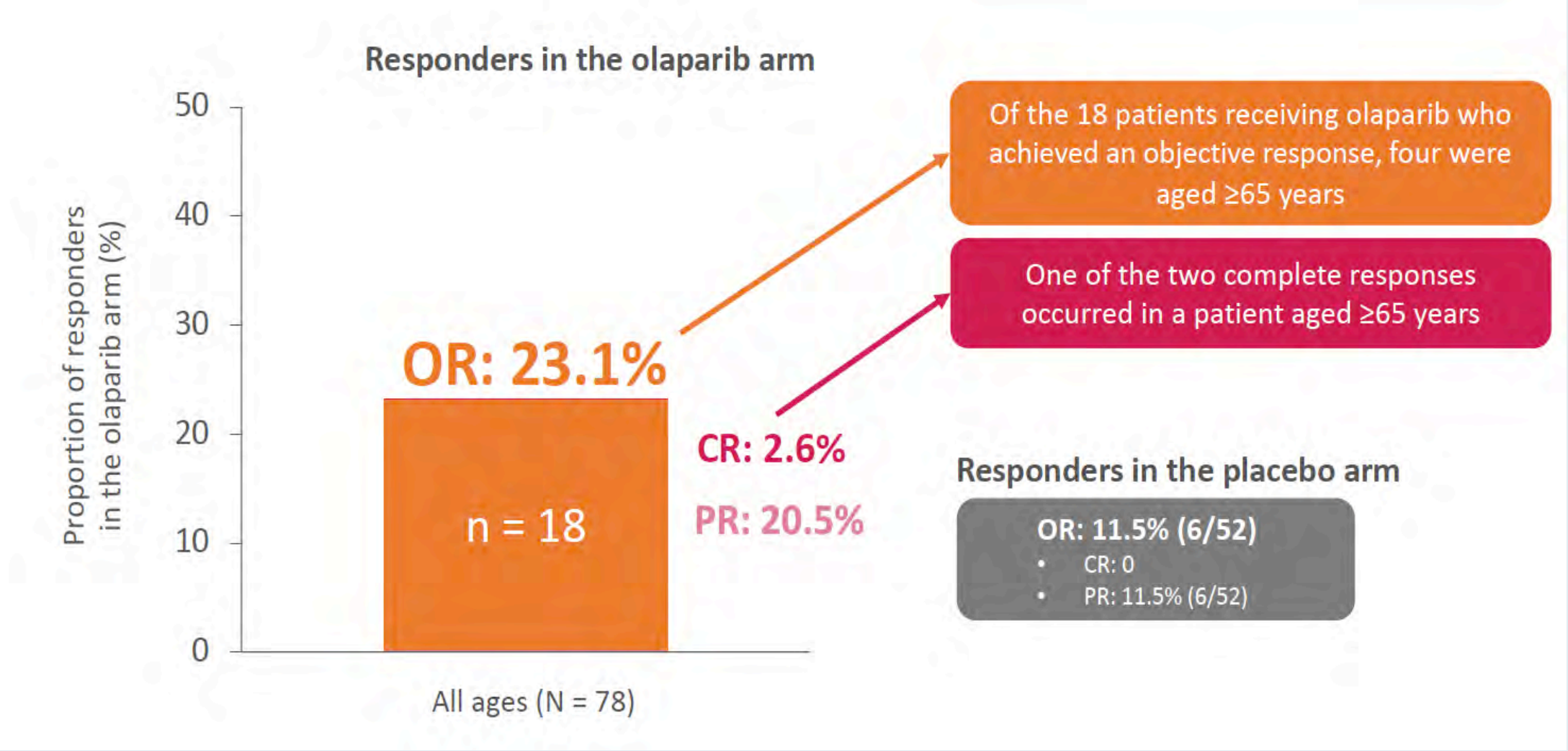
Progression-free survival *mo*	Olaparib group	Placebo group
6	53.0%	23%
12	33.7%	14.5%
18	27.6%	9.6%
24	22.1%	9.6%

Median, 7.4 mo vs 3.8 mo
Hazard ratio, 0.53 (95% CI, 0.35-0.82)
P = 0.004

- An interim analysis of overall survival showed no difference between olaparib and placebo (median 18.9 mo vs 18.1 mo, HR 0.91, *p* = 0.68)
- The adverse-effect profile of maintenance olaparib was similar to that observed in other tumor types

Kindler HL et al. ESMO 2020;Abstract SO-3; Golan T et al. *N Engl J Med* 2019;381(4):317-27; Kindler HL et al. ASCO 2019;Abstract LBA4.

POLO: Patients Receiving Olaparib with an Objective Response (CR or PR)



Kindler HL et al. ESMO 2020;Abstract SO-3.

Select Ongoing Trials of Olaparib in PAD

Trial (NCT#)	Phase	Target (N)	Setting	Treatment arms
SWOG-S2001 (NCT04548752)	II	88	Metastatic PAD; Germline BRCA1/2 mutation-positive; Received 1L platinum-based chemotherapy	• Olaparib + pembrolizumab • Olaparib
STUDY00019211 (NCT04005690)	I	14	Resectable, borderline resectable, locally advanced or metastatic PAD; Untreated or previously treated	• Cobimetinib • Olaparib

Clinicaltrials.gov; Accessed February 2021.

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

A Daylong Clinical Summit Hosted in Partnership with Medical Oncology Association of Southern California (MOASC)

Saturday, May 15, 2021

10:30 AM – 6:30 PM ET

(7:30 AM – 3:30 PM Pacific Time)

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This program was recorded before the ASCO 2021 Annual Meeting.

Data from the abstracts presented at this meeting can be accessed at https://meetinglibrary.asco.org/results?meetingView=2021%20ASCO%20Annual%20Meeting.

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Agenda

Module 1 — Breast Cancer: *Drs O'Regan and Traina*

Module 2 — Multiple Myeloma: *Drs Anderson and Raje*

Module 3 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Moskowitz and Sharman*

Module 4 — Genitourinary Cancers: *Drs Bellmunt and Pal*

Module 5 — Gastrointestinal Cancers: *Drs Messersmith and O'Reilly*

Module 6 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Erba and Komrokji*

Module 7 — Lung Cancer: *Drs Camidge and Levy*

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Acute Myeloid Leukemia and Myelodysplastic Syndromes Faculty

Harry Paul Erba, MD, PhD
Director, Leukemia Program
Instructor in the Department of Medicine
Member of the Duke Cancer Institute
Duke University School of Medicine
Durham, North Carolina

Rami Komrokji, MD
Senior Member and Section Head for Leukemia and MDS
Vice Chair, Department of Malignant Hematology
Moffitt Cancer Center
Professor of Oncologic Sciences
Morsani College of Medicine, University of South Florida
Tampa, Florida

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Commercial Support

This activity is supported by educational grants from AbbVie Inc, Astellas and Pfizer Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Blueprint Medicines, Daiichi Sankyo Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Incyte Corporation, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Lilly, Merck, Novartis, Oncopeptides, Sanofi Genzyme, Seagen Inc, and Taiho Oncology Inc.

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Eisai Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Turning Point Therapeutics Inc and Verastem Inc.

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Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Erba — Disclosures

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Contracted Research	AbbVie Inc, Agios Pharmaceuticals Inc, ALX Oncology, Amgen Inc, Daiichi Sankyo Inc, FORMA Therapeutics, Forty Seven Inc, Gilead Sciences Inc, GlycoMimetics Inc, ImmunoGen Inc, Jazz Pharmaceuticals Inc, MacroGenics Inc, Novartis, PTC Therapeutics
Independent Review Committee (IRC)	AbbVie Inc
Speakers Bureau	AbbVie Inc, Agios Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Incyte Corporation, Jazz Pharmaceuticals Inc, Novartis

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Dr Komrokji — Disclosures

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Speakers Bureau	AbbVie Inc, Agios Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Jazz Pharmaceuticals Inc

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Contributing Oncologists

Amanda Blackmon, DO, MS
Chief Fellow, Hematology/Oncology
University of California, Irvine
Irvine, California

Farshid Dayyani, MD, PhD
Professor of Clinical Medicine
Division of Hematology/Oncology
Department of Medicine
University of California, Irvine
UCI Health
Orange, California

Gigi Chen, MD
Diablo Valley Oncology and
Hematology Medical Group
Pleasant Hill, California

Michael Polintan Del Rosario, MD
Fellow Physician
Division of Hematology-Oncology
Department of Medicine
University of California, Irvine
Irvine, California

Mamta Choksi, MD
Florida Cancer Specialists and
Research Institute
New Port Richey, Florida

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

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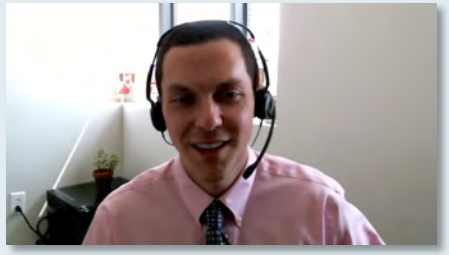
RESEARCH
TO PRACTICE

Contributing Oncologists

Rahul Gosain, MD
Division of Hematology and Oncology
Guthrie Corning Cancer Center
Corning, New York

Maen Hussein, MD
Florida Cancer Specialists and
Research Institute
The Villages, Florida

Ranju Gupta, MD
Attending Physician
Co-Director, Cardio-Oncology Program
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania



Jeremy Lorber, MD
Attending Hematologist-Oncologist
Tower Hematology Oncology
Cedars-Sinai Medical Center
Beverly Hills, California

Hatim Husain, MD
Physician, University of California San Diego
San Diego, California

Nataliya Mar, MD
Assistant Clinical Professor
Division of Hematology/Oncology
University of California, Irvine
Irvine, California

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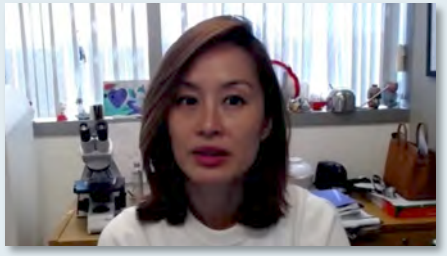
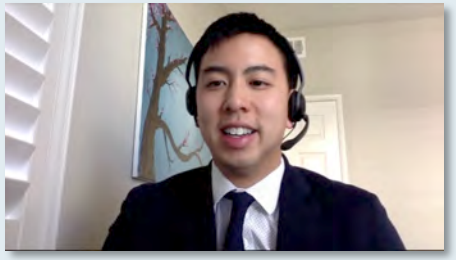
Contributing Oncologists

Mohamed K Mohamed, MD, PhD
Oncology Division Medical Director
Director of Thoracic Oncology
Hematologist/ Medical Oncologist
Cone Health Cancer Center
Greensboro, North Carolina

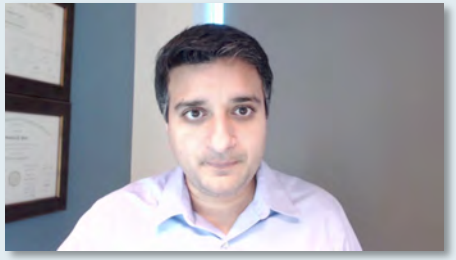


Helen H Moon, MD
Medical Oncologist
Southern California Permanente
Medical Group
Riverside, California

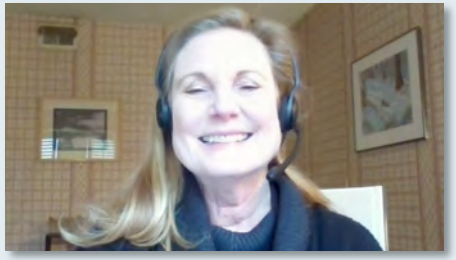
Neil Morganstein, MD
Hematology Oncology
Atlantic Health System
Summit, New Jersey



Anthony Nguyen, MD
Fellow, Loma Linda University Health
Loma Linda, California



Sandip Patel, MD
Associate Professor, Medical Oncology, UCSD
Leader, Experimental Therapeutics
Deputy Director, San Diego Center for
Precision Immunotherapy
San Diego, California



Andrea Stebel, MD
Newport Breast Care
Newport Beach, California

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Agenda

Module 1: Myelodysplastic Syndromes (MDS)

- Dr Lorber: A 73-year-old man with MDS, ring sideroblasts and multilineage dysplasia
- *Key Recent Publications and Presentations*

Module 2: Newly Diagnosed Acute Myeloid Leukemia (AML)

- Dr Blackmon: A 40-year-old woman with newly diagnosed AML and a FLT3-TKD mutation
- *Key Recent Publications and Presentations*
- Dr Husain: A frail 85-year-old man with AML who received decitabine/venetoclax
- *Key Recent Publications and Presentations*

Module 3: Secondary AML

- Dr Husain: A 65-year-old man who develops AML while receiving therapy for metastatic NSCLC
- Dr Lorber: A 74-year-old otherwise healthy man with atrial fibrillation develops AML secondary to MDS
- *Key Recent Publications and Presentations*

Agenda

Module 1: Myelodysplastic Syndromes (MDS)

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Case Presentation – Dr Lorber: A 73-year-old man with MDS, ring sideroblasts and multilineage dysplasia

Dr Jeremy Lorber

- Presented with months of progressive fatigue
- Pancytopenia – WBC: 4.0, Hgb: 8.3, PLT: 59K
- Bone marrow c/w MDS RS-MLD, blasts 3%, deletion 5q, monosomy 7, trisomy 8, loss of 17
- FISH: monosomy 5, deletion 7q, deletion 17p
- NGS: variant of TP53
- Decitabine, with complete normalization of counts
  - Referral for allogeneic SCT (not a candidate due to TP53)

Questions

- When his disease progresses, what would be the best treatment option for him in light of his high-risk MDS?
- What are the most promising agents in the pipeline for MDS? Is there a role for treating patients with MDS — either up front or at progression — with the addition of venetoclax, similar to an AML patient?

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Key Recent Publications and Presentations

- Garcia-Manero G et al. **Oral Cedazuridine/Decitabine for MDS and CMML: A Phase 2 Pharmacokinetic/Pharmacodynamic Randomized Crossover Study.** *Blood* 2020;136(6):674-83.
- Garcia-Manero G et al. **Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross-Over Phase 3 Study (ASCERTAIN) of an Oral Hypomethylating Agent ASTX727 (Cedazuridine/Decitabine) Compared to IV Decitabine.** ASH 2019;Abstract 846.
- Fenaux P et al. **Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes.** *N Engl J Med* 2020;382(2):140-51.
- Sallman D et al. **Tolerability and Efficacy of the First-in-Class Anti-CD47 Antibody Magrolimab Combined with Azacitidine in MDS and AML Patients: Phase Ib Results.** ASCO 2020;Abstract 7507.
- Ball BJ et al. **Venetoclax and Hypomethylating Agents (HMAs) Induce High Response Rates in MDS, Including Patients After HMA Therapy Failure.** *Blood Adv* 2020;4(13):2866-70.

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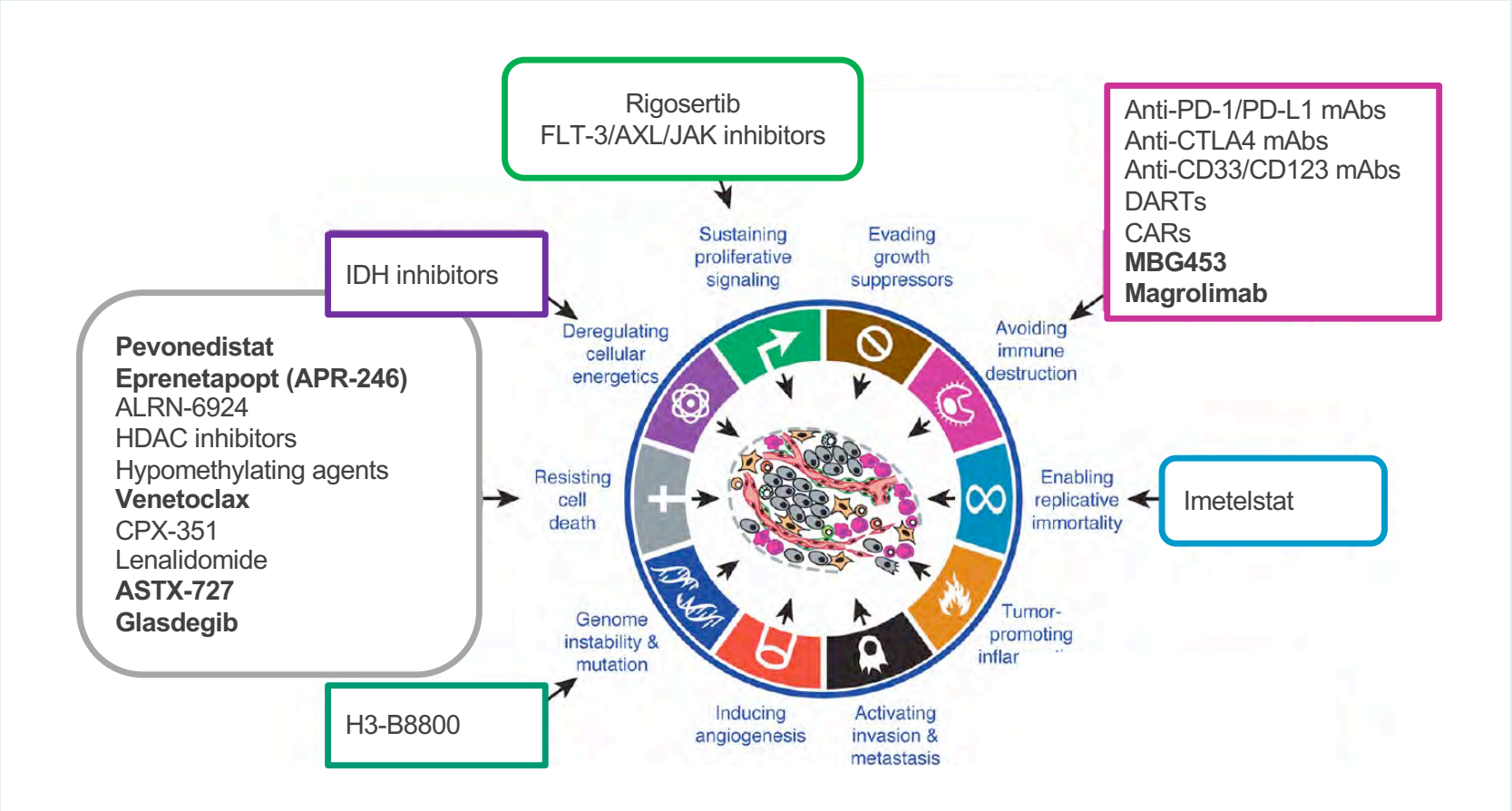
Treating MDS | Disease Biology



Courtesy of Mikkael A Sekeres, MD, MS

Figure adapted from Hanahan D, Weinberg RA. *Cell* 2011;144:646–74

BH3, bcl homology domain 3; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DARTs, dual affinity retargeting agents; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; mAb, monoclonal antibody; PARP, poly adenosine diphosphate ribose polymerase; VEGF, vascular endothelial growth factor

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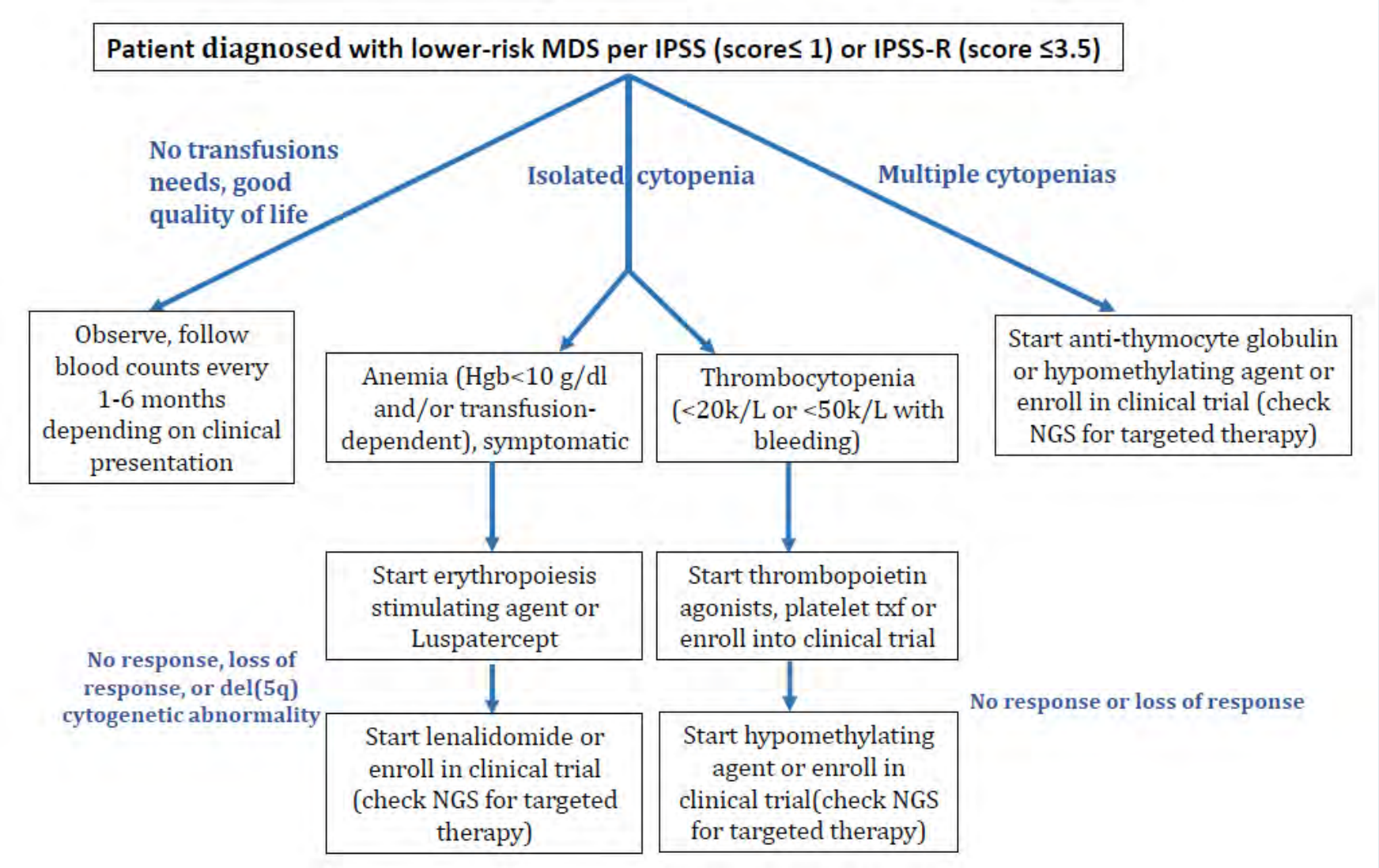
Treating MDS | Lower-Risk Disease



Sekeres and Patel Hematology (ASH Educ Book) 2019.

Courtesy of Mikkael A Sekeres, MD, MS

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blood

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study

Guillermo Garcia-Manero,[1] Elizabeth A. Griffiths,[2] David P. Steensma,[3] Gail J. Roboz,[4] Richard Wells,[5] James McCloskey II,[6] Olatoyosi Odenike,[7] Amy E. DeZern,[8] Karen Yee,[9] Lambert Busque,[10] Casey O'Connell,[11] Laura C. Michaelis,[12] Joseph Brandwein,[13] Hagop Kantarjian,[1] Aram Oganesian,[14] Mohammad Azab,[14] and Michael R. Savona[15]

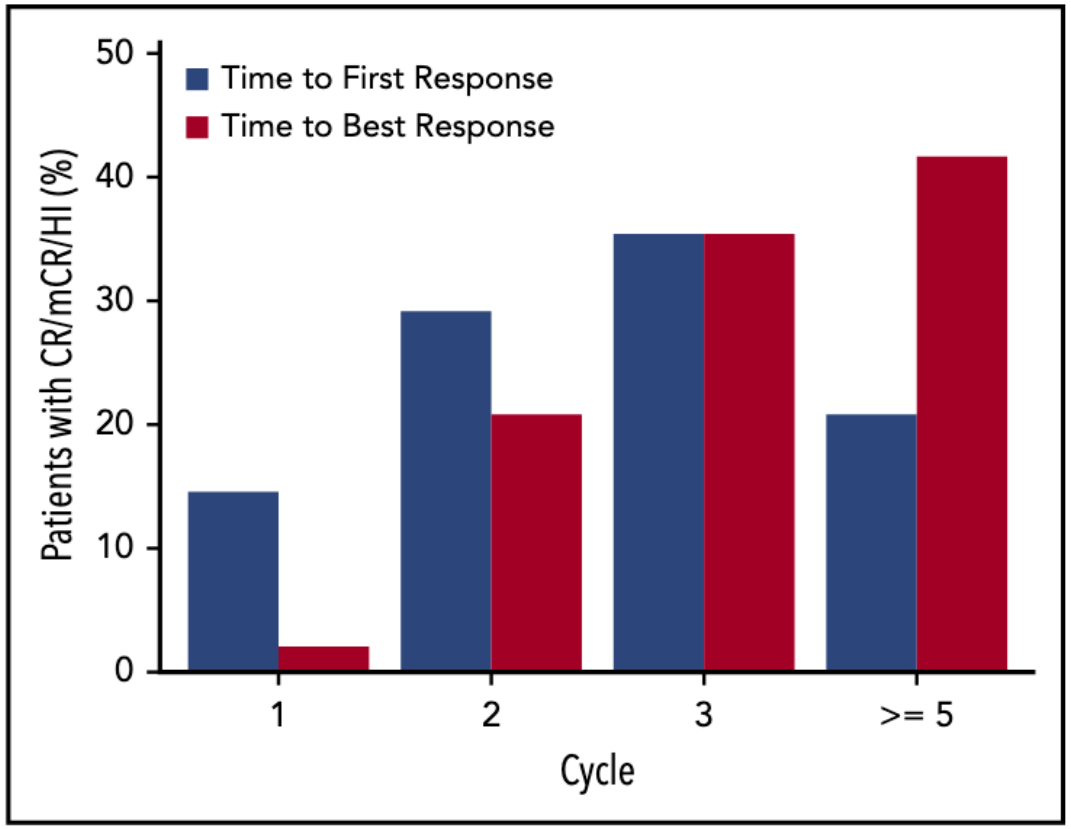
Blood 2020;136(6):674-83.

ASTX727-01-B: Response Summary

Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13-32
PR	0	
mCR	18 (22)	14-33
mCR with HI	6 (7)	3-16
HI	13 (16)	9-26
HI-E	8 (10)	4-19
HI-N	2 (2)	0-9
HI-P	11 (14)	7-23
Overall response* (CR + PR + mCR + HI)	48 (60)	48-71
No response	32 (40)	29-52

CR, complete response; HI, hematologic improvement; HI-E, erythroid response; HI-N, neutrophil response; HI-P, platelet response; mCR, marrow complete response; PR, partial response.

*Patients are counted only once with their best response as per the table hierarchy.



Garcia-Manero G et al. *Blood* 2020;136(6):674-83.

ASTX727-01-B: Adverse Events

Preferred term, n (%)	IV decitabine cycle 1 or 2 (n = 75)	Oral cedazuridine/ decitabine cycle 1 or 2 (n =78)	All oral cedazuridine/ decitabine cycles (n = 78)
Patients with grade ≥3 TEAEs	44 (59)	45 (58)	65 (83)
Most common grade ≥3 TEAEs (≥10% of patients)			
Neutropenia	20 (27)	16 (21)	36 (46)
Thrombocytopenia	21 (28)	18 (23)	30 (38)
Febrile neutropenia	12 (16)	9 (12)	23 (29)
Leukopenia	8 (11)	7 (9)	19 (24)
Anemia	9 (12)	9 (12)	17 (22)
Pneumonia	5 (7)	7 (9)	10 (13)
Sepsis	1 (1)	4 (5)	8 (10)

Garcia-Manero G et al. *Blood* 2020;136(6):674-83.

Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross-Over Phase 3 Study (ASCERTAIN) of an Oral Hypomethylating Agent ASTX727 (Cedazuridine/Decitabine) Compared to IV Decitabine

Garcia-Manero G et al.

ASH 2019;Abstract 846.

ASCERTAIN: Primary Endpoint of Total 5-Day Decitabine AUC Equivalence

Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC		Oral ASTX727		Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
		N	Geo. LSM	N	Geo. LSM		
Primary Analysis	Paired[1]	123	864.9	123	855.7	98.9 (92.7, 105.6)	31.7

[1] Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All Sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

Garcia-Manero G et al. *ASH* 2019;Abstract .

ASCERTAIN: Preliminary Response in MDS/CMML

	Evaluable Patients[1] N=101 n (%)
Complete response (CR)	12 (11.9%)
Partial response (PR)	0
Marrow CR (mCR)	46 (45.5%)
mCR with hematologic improvement	14 (13.9%)
Hematologic improvement (HI)	7 (5.3%)
HI-erythroid	2 (2.0%)
HI-neutrophils	1 (1.0%)
HI-platelet	6 (5.9%)
Overall response (CR + PR + mCR + HI)	65 (64.4%)
Stable disease	28 (27.7%)
Progressive disease	8 (7.9%)

[1] Due to short median follow up (~ 5 months) at data cutoff, 32 patients could not be evaluated for response by the Central IRC. Response was assessed by IWG 2006 criteria

Garcia-Manero G et al. *ASH* 2019;Abstract .

The NEW ENGLAND JOURNAL of MEDICINE

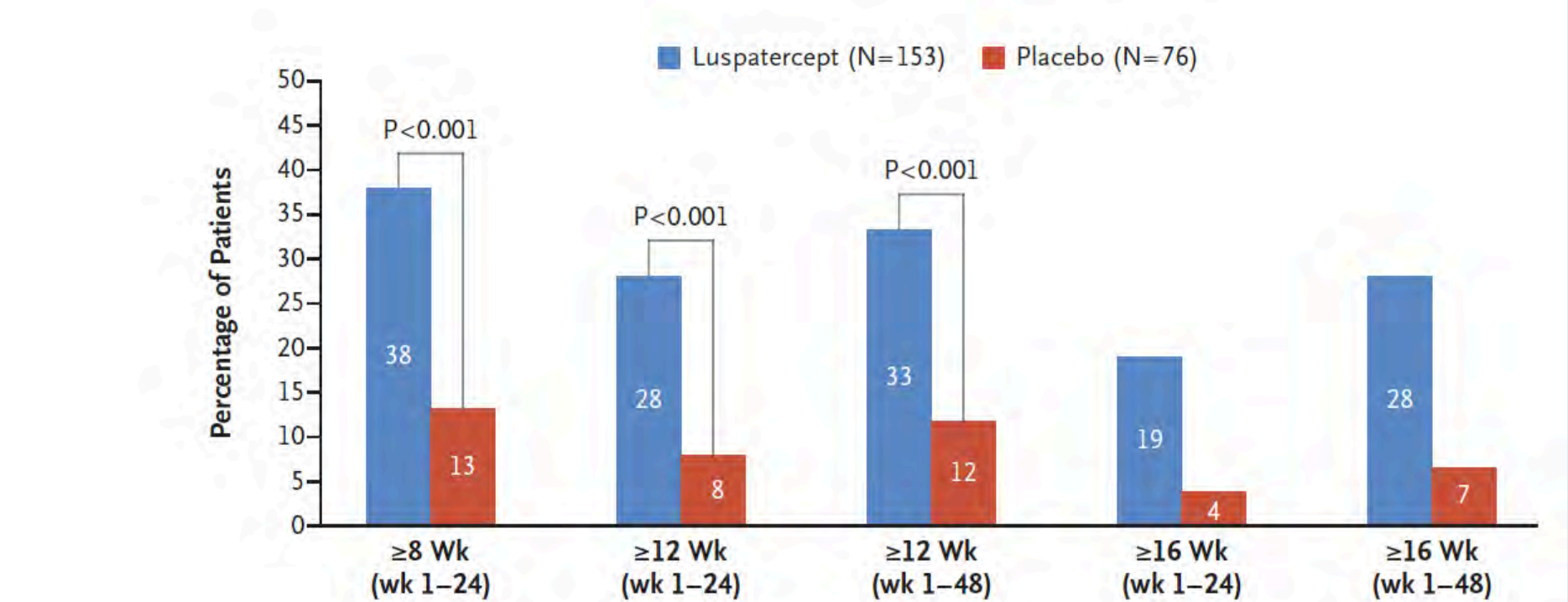
ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

P. Fenaux, U. Platzbecker, G.J. Mufti, G. Garcia-Manero, R. Buckstein, V. Santini, M. Díez-Campelo, C. Finelli, M. Cazzola, O. Ilhan, M.A. Sekeres, J.F. Falantes, B. Arrizabalaga, F. Salvi, V. Giai, P. Vyas, D. Bowen, D. Selleslag, A.E. DeZern, J.G. Jurcic, U. Germing, K.S. Götze, B. Quesnel, O. Beyne-Rauzy, T. Cluzeau, M.-T. Voso, D. Mazure, E. Vellenga, P.L. Greenberg, E. Hellström-Lindberg, A.M. Zeidan, L. Adès, A. Verma, M.R. Savona, A. Laadem, A. Benzohra, J. Zhang, A. Rampersad, D.R. Dunshee, P.G. Linde, M.L. Sherman, R.S. Komrokji, and A.F. List

***N Engl J Med* 2020;382(2):140-51.**

MEDALIST: Independence from Red-Cell Transfusion in Phase II Trial of Luspatercept



No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

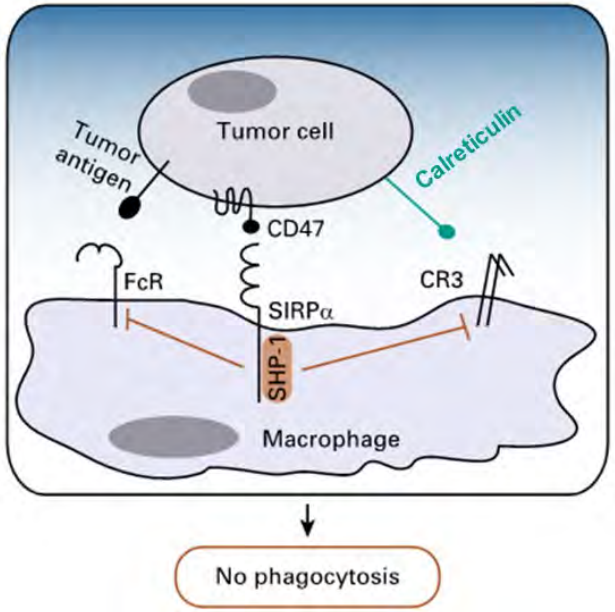
Fenaux P et al. *N Engl J Med* 2020;382:140-51.

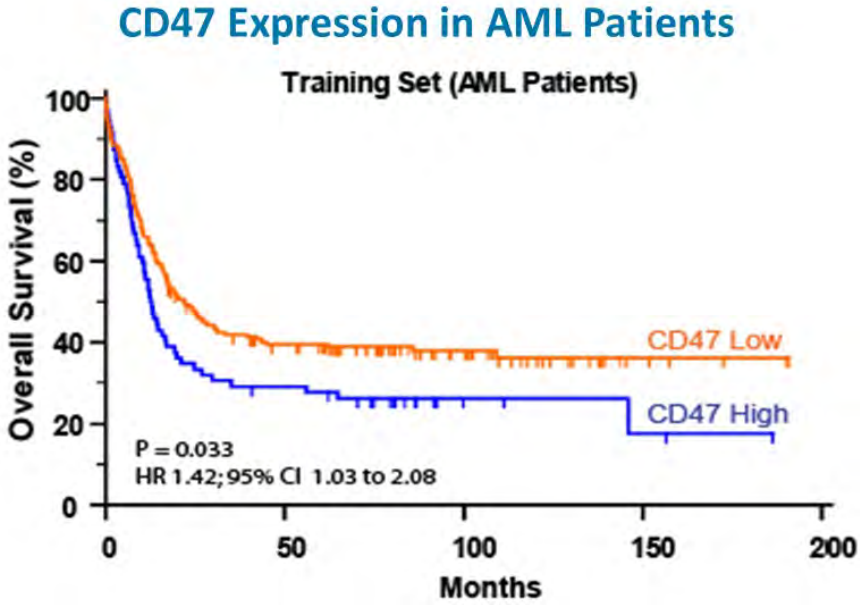
Tolerability and Efficacy of the First-in-Class Anti-CD47 Antibody Magrolimab Combined with Azacitidine in MDS and AML Patients: Phase Ib Results

Sallman D et al.

ASCO 2020;Abstract 7507.

CD47 Is a Major Macrophage Immune Checkpoint and 'Do Not Eat Me' Signal in Myeloid Malignancies Including MDS and AML





- CD47 is a "do not eat me" signal on cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in AML patients

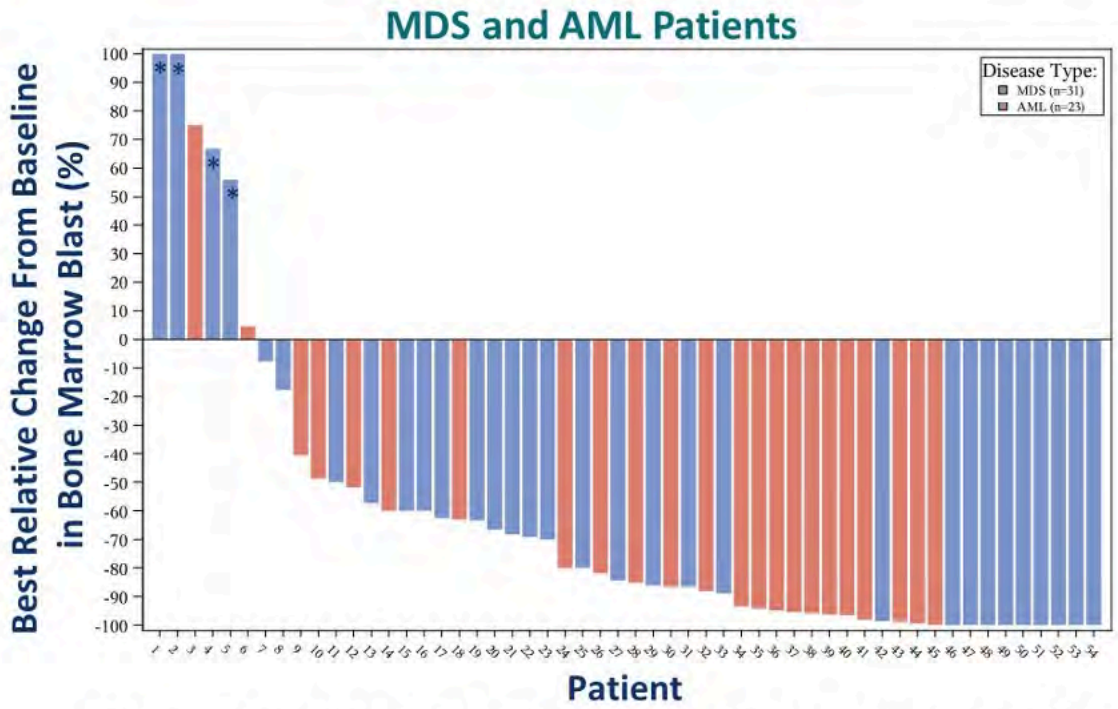
Figure at left adapted from Veillette A, Tang Z. *J Clin Onc.* 2019;37(12)1012-1014, and Chao MP, et al. *Current Opin Immunol.* 2012; 24(2):225-232.
Figure at right adapted from Majeti R, et al. *Cell.* 2009;138(2):286-299.

Sallman D et al. ASCO 2020;Abstract 7507.

Magrolimab with Azacitidine Induces High Response Rates in MDS and AML

Best Overall Response	1L MDS N=33	1L AML N=25
ORR	30 (91%)	16 (64%)
CR	14 (42%)	10 (40%)
CRi	NA	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	NA
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML patients (1 AE, 2 early withdrawal).



Four patients not shown due to missing values; <5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

- Magrolimab + AZA induces a 91% ORR (42% CR) in MDS and 64% ORR (56% CR/CRi) in AML
- Responses deepened over time with a 56% 6-month CR rate in MDS patients (assessed in all patients 6 months after initial treatment)
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 6-17%[1,2])

1. Azacitidine USPI. 2. Fenaux P, et al. *Lancet Oncol.* 2009 ;10(3):223-232.

Sallman D et al. ASCO 2020;Abstract 7507.

STIMULUS REPORT

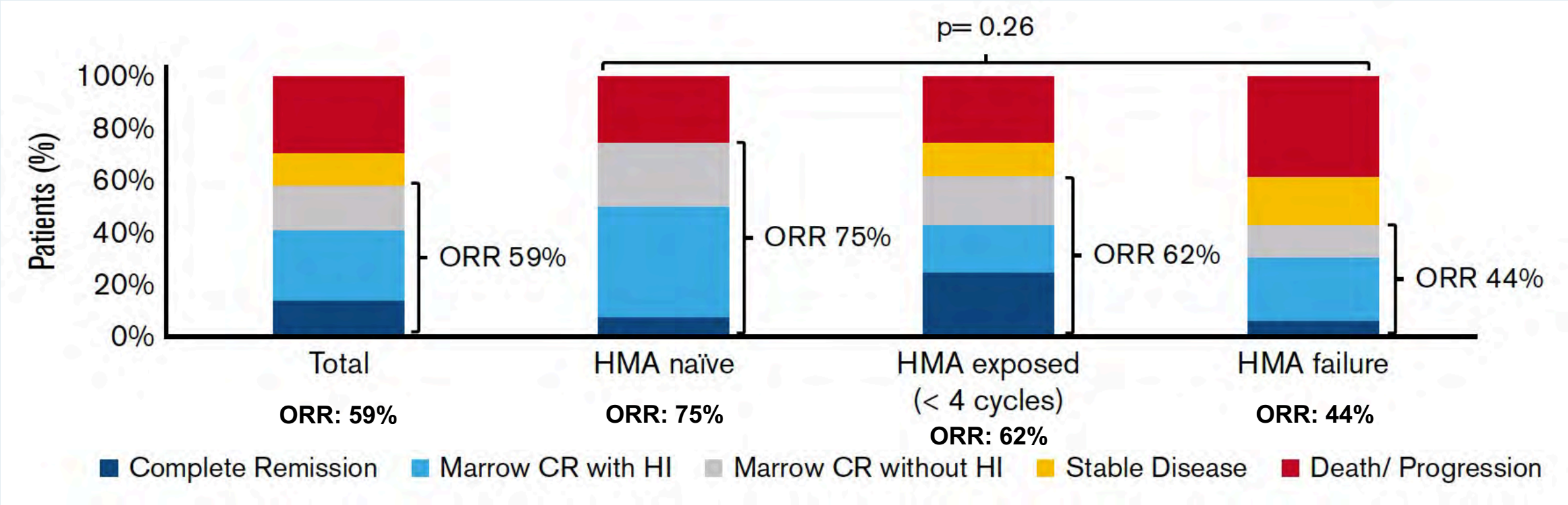
blood advances

Venetoclax and hypomethylating agents (HMAs) induce high response rates in MDS, including patients after HMA therapy failure

Brian J. Ball,[1] Christopher A. Famulare,[2] Eytan M. Stein,[1] Martin S. Tallman,[1] Andriy Derkach,[3] Mikhail Roshal,[1] Saar I. Gill,[4] Benjamin M. Manning,[4] Jamie Koprivnikar,[5] James McCloskey,[5] Rebecca Testi,[5] Thomas Prebet,[6] Najla H. Al Ali,[7] Eric Padron,[7] David A. Sallman,[7] Rami S. Komrokji,[7,*] and Aaron D. Goldberg[1,*]

Blood Adv 2020;4(13):2866-70

Responses in Patients with MDS Receiving Venetoclax with a Hypomethylating Agent



Median OS: 19.5 months

Median OS with HMA failure: 11.4 months

Ball BJ et al. *Blood Adv* 2020;4(13):2866-70.

Agenda

Module 1: Myelodysplastic Syndromes (MDS)

- Dr Lorber: A 73-year-old man with MDS, ring sideroblasts and multilineage dysplasia
- *Key Recent Publications and Presentations*

Module 2: Newly Diagnosed Acute Myeloid Leukemia (AML)

- Dr Blackmon: A 40-year-old woman with newly diagnosed AML and a FLT3-TKD mutation
- *Key Recent Publications and Presentations*
- Dr Husain: A frail 85-year-old man with AML who received decitabine/venetoclax
- *Key Recent Publications and Presentations*

Module 3: Secondary AML

- Dr Husain: A 65-year-old man who develops AML while receiving therapy for metastatic NSCLC
- Dr Lorber: A 74-year-old otherwise healthy man with atrial fibrillation develops AML secondary to MDS
- *Key Recent Publications and Presentations*

Case Presentation – Dr Blackmon: A 40-year-old woman with newly diagnosed AML and a FLT3-TKD mutation

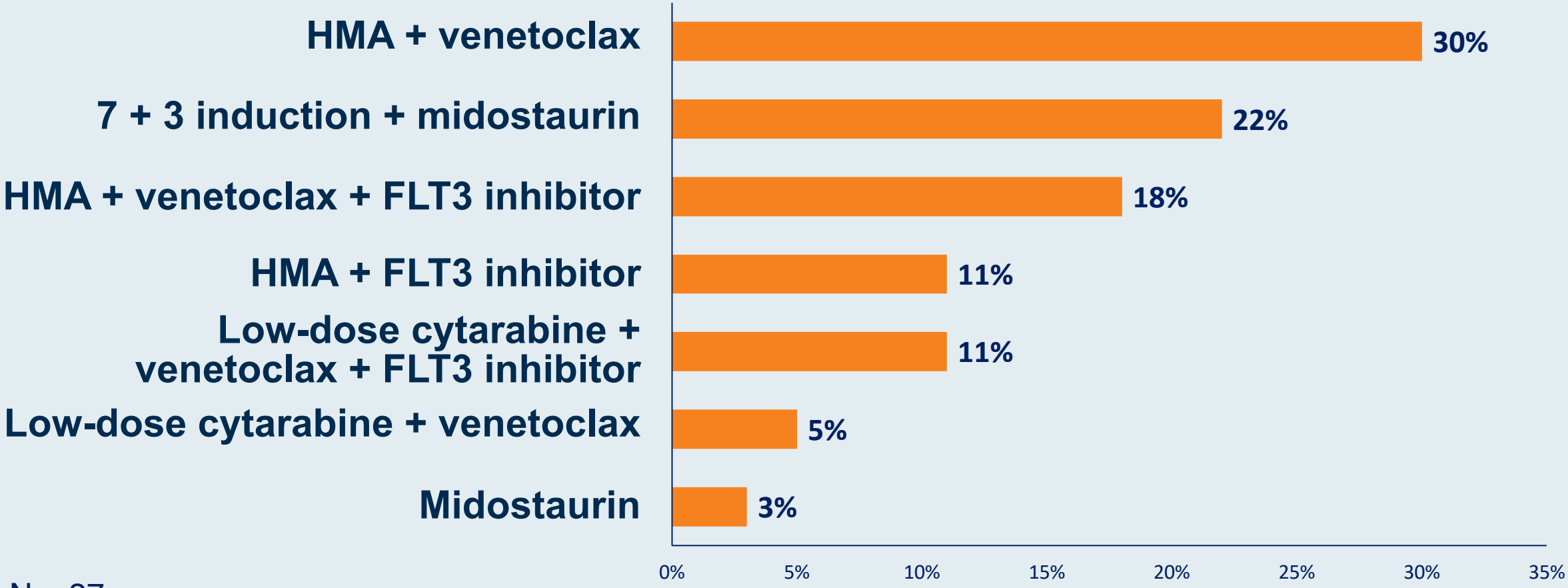
Dr Amanda Blackmon

- Presented with bruising and found to have pancytopenia and AML
- Bone marrow biopsy: FLT3-TKD mutation
- 7 + 3 induction therapy and midostaurin → CR

Questions

- Should we transplant this patient population?
- As more information becomes available regarding mutations and cytogenetics, will we have an updated risk stratification system?
- Is gilteritinib being used in front-line treatment? Is low FLT3-ITD an indication not to transplant a patient?
- If this patient were elderly with AML and a FLT3 mutation, what front-line approach for treatment would you recommend – Azacitidine/venetoclax plus a FLT3 inhibitor, or just a hypomethylating agent and FLT3 inhibitor?
- In elderly patients who have cytopenias from their AML, do you dose reduce the venetoclax? Would you decrease the number of days of the hypomethylating agent? Do you choose decitabine or azacitidine at the time of diagnosis?

What would you recommend as first-line therapy to a 78-year-old patient (PS 0) who presents with intermediate-risk AML with a FLT3-ITD mutation?



N = 37

Survey of live webinar audience

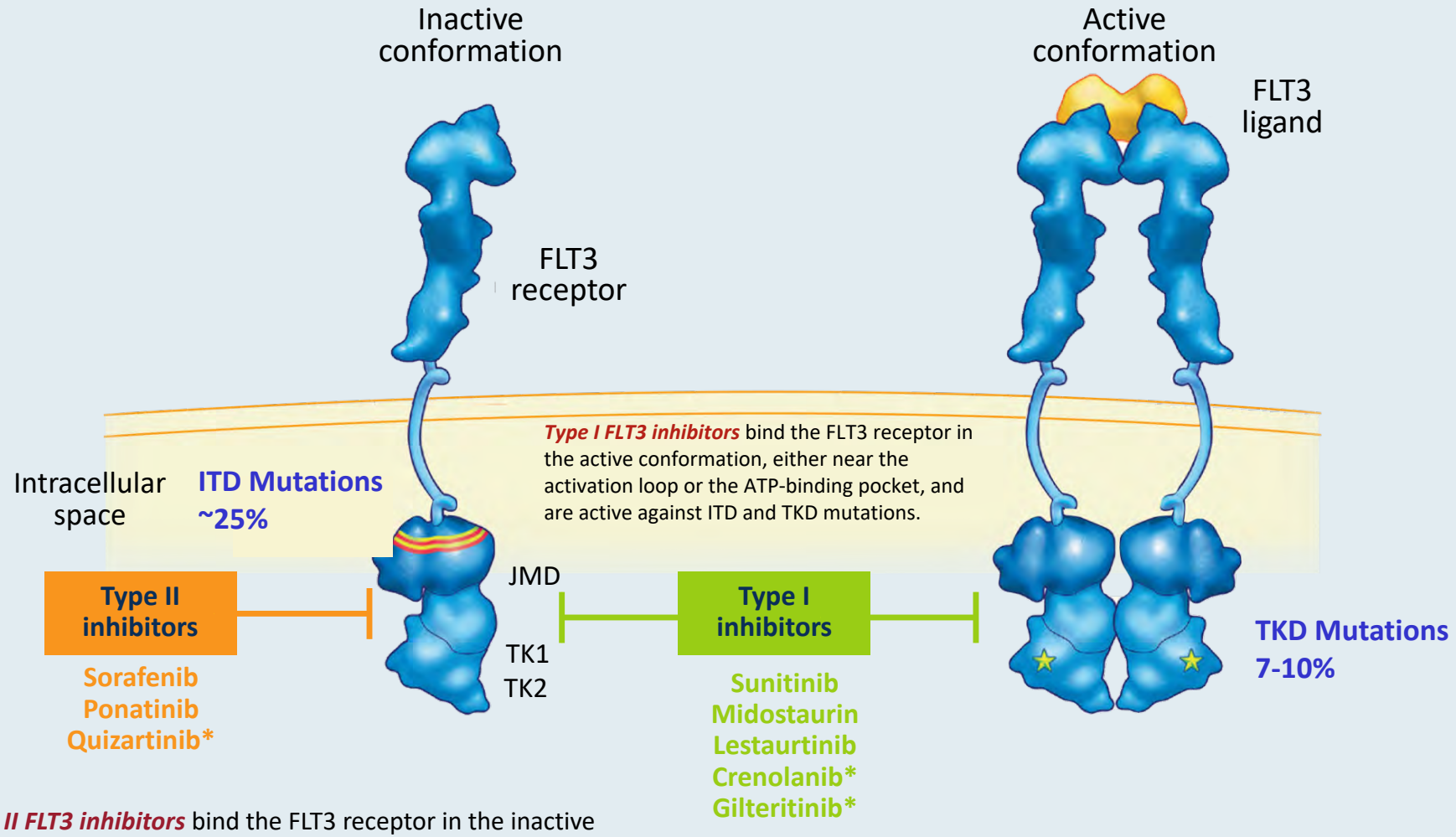
RTP RESEARCH TO PRACTICE

Key Recent Presentations and Publications

- Perl AE et al. **Long-Term Survivors and Gilteritinib Safety Beyond One Year in *FLT3*-Mutated R/R AML: ADMIRAL Trial Follow-Up.** ASCO 2020;Abstract 7514.
- Stein EM et al. **Enasidenib Monotherapy Is Effective in Older Patients with Newly Diagnosed IDH2 Mutated Acute Myeloid Leukemia and Addition of Azacitidine Rescues Enasidenib Monotherapy Failures: A Phase 2/IB Study of the Beat AML Master Trial.** ASH 2020;Abstract 636.
- DiNardo CD et al. **Mutant Isocitrate Dehydrogenase 1 Inhibitor Ivosidenib in Combination with Azacitidine for Newly Diagnosed Acute Myeloid Leukemia.** *J Clin Oncol* 2021;39(1):57-65.

RTP RESEARCH TO PRACTICE

FLT3 Mutations (ITD and TKD) Occur in Approximately 30% to 35% of Patients with AML



Type II FLT3 inhibitors bind the FLT3 receptor in the inactive conformation in a region adjacent to the ATP-binding domain.

* Second-generation FLT3 inhibitors

Daver N et al. *Leukemia* 2019;33:299-312.

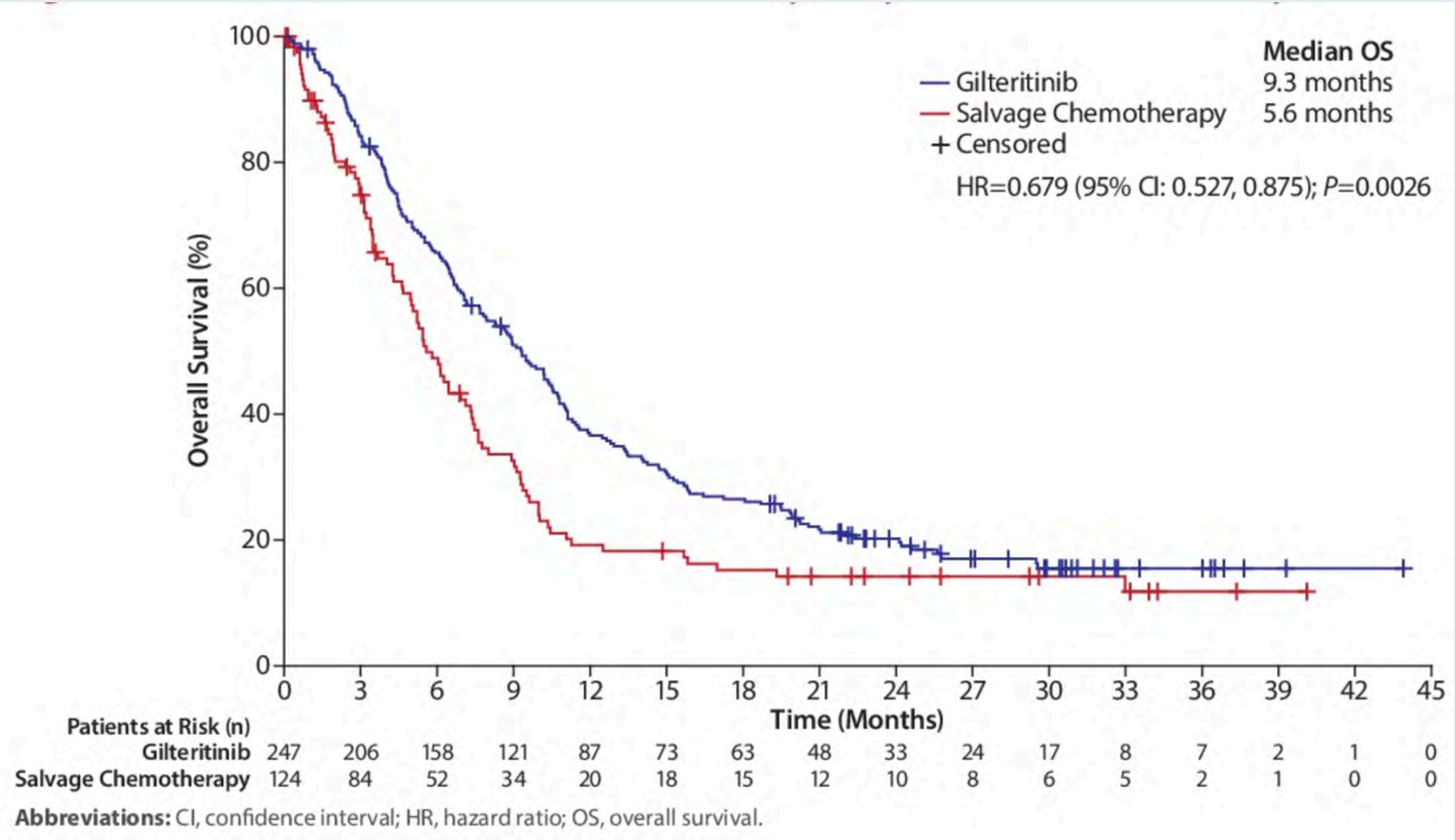
RTP RESEARCH TO PRACTICE

Long-Term Survivors and Gilteritinib Safety Beyond One Year in *FLT3*-Mutated R/R AML: ADMIRAL Trial Follow-Up

Perl AE et al.

ASCO 2020;Abstract 7514

ADMIRAL: Overall Survival at 1 Year After the Primary Analysis



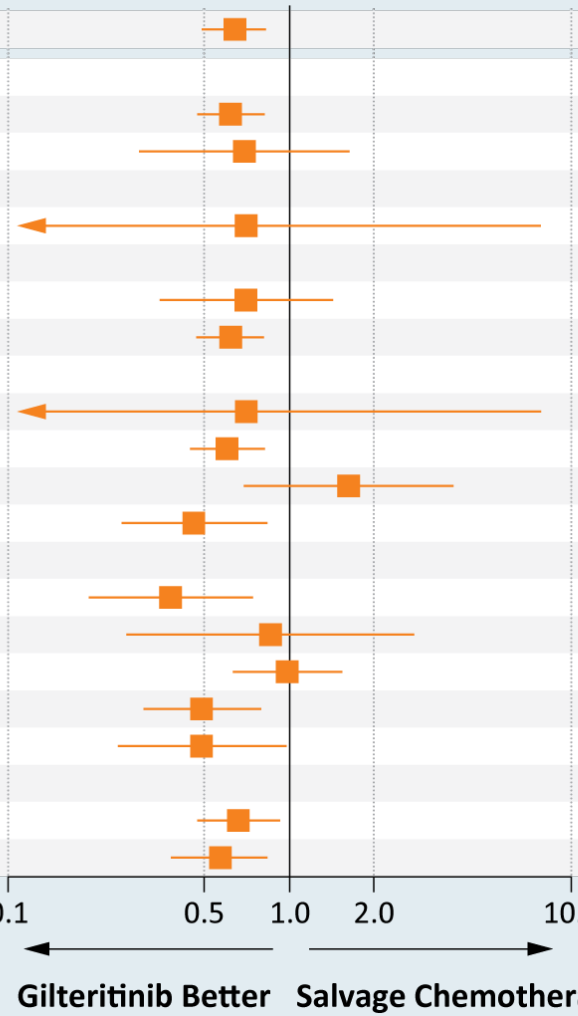
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Perl AE et al. ASCO 2020;Abstract 7514.

RTP RESEARCH TO PRACTICE

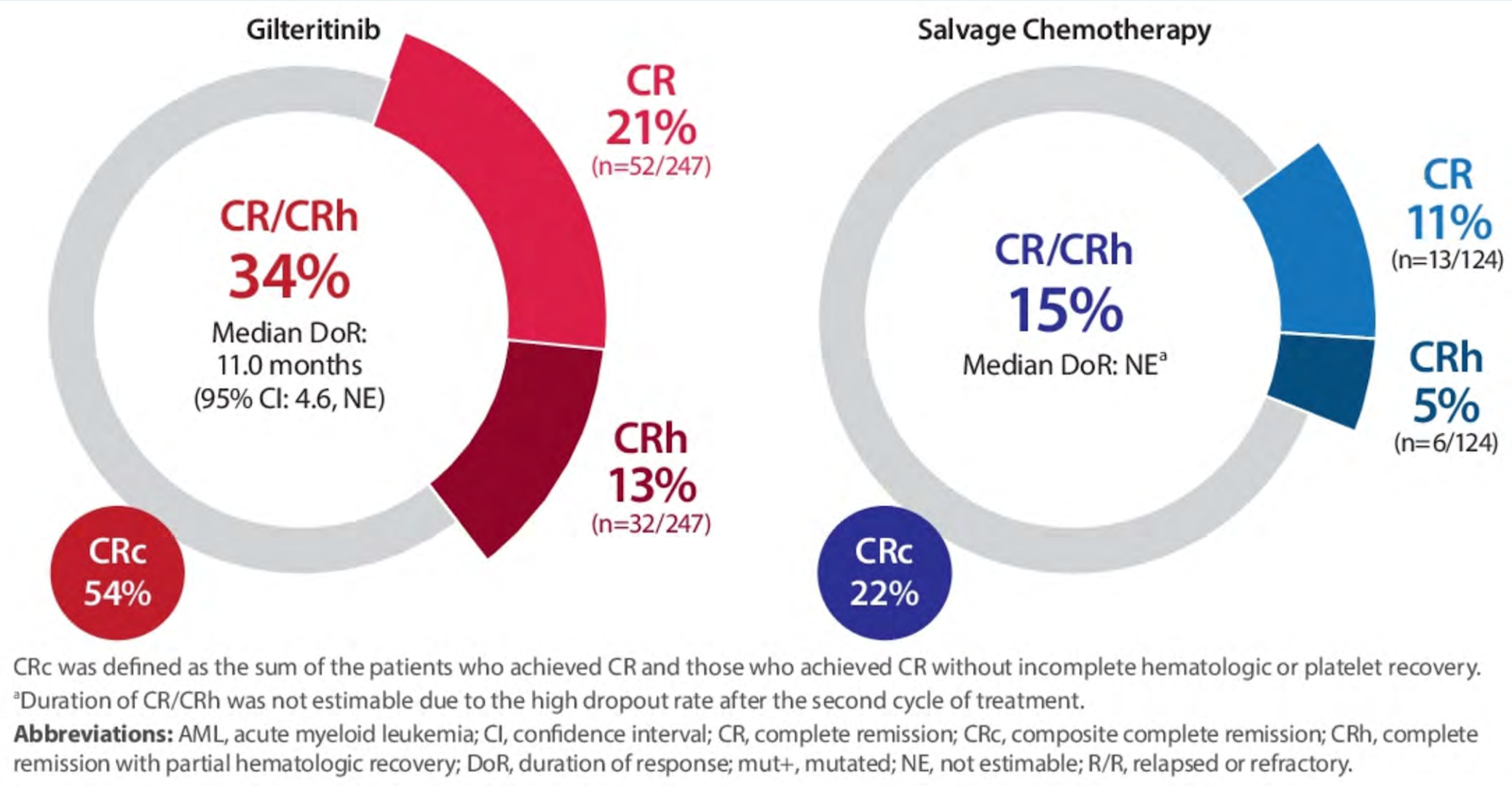
ADMIRAL: Subgroup Analysis of Overall Survival

Subgroup	Gilteritinib	Salvage Chemotherapy	Hazard Ratio for Death
	no. of events/total no. of patients		
All patients	171/247	90/124	0.64
FLT3 mutation type			
FLT3 ITD alone	145/215	81/113	0.62
FLT3 TKD alone	16/21	8/10	0.69
FLT3 ITD and FLT3 TKD	6/7	0	NE
Other	4/4	1/1	0.70
Previous use of FLT3 inhibitor			
Yes	26/32	11/14	0.70
No	145/215	79/110	0.62
Cytogenetic risk status			
Favorable	3/4	1/1	0.70
Intermediate	119/182	63/89	0.60
Unfavorable	22/26	7/11	1.63
Unknown	27/35	19/23	0.46
Response to first-line therapy per IRT			
Relapse ≤6 mo after allogeneic HSCT	24/31	16/17	0.38
Relapse >6 mo after allogeneic HSCT	10/17	4/8	0.86
Primary refractory disease without HSCT	70/98	28/48	0.99
Relapse ≤6 mo after composite complete remission and no HSCT	47/67	28/34	0.49
Relapse >6 mo after composite complete remission and no HSCT	20/34	14/17	0.49
Preselected chemotherapy per IRT			
High intensity	96/149	52/75	0.66
Low intensity	75/98	38/49	0.56



Perl AE et al. *N Engl J Med* 2019;381:1728-40.

ADMIRAL: Response Rates



CRc was defined as the sum of the patients who achieved CR and those who achieved CR without incomplete hematologic or platelet recovery.

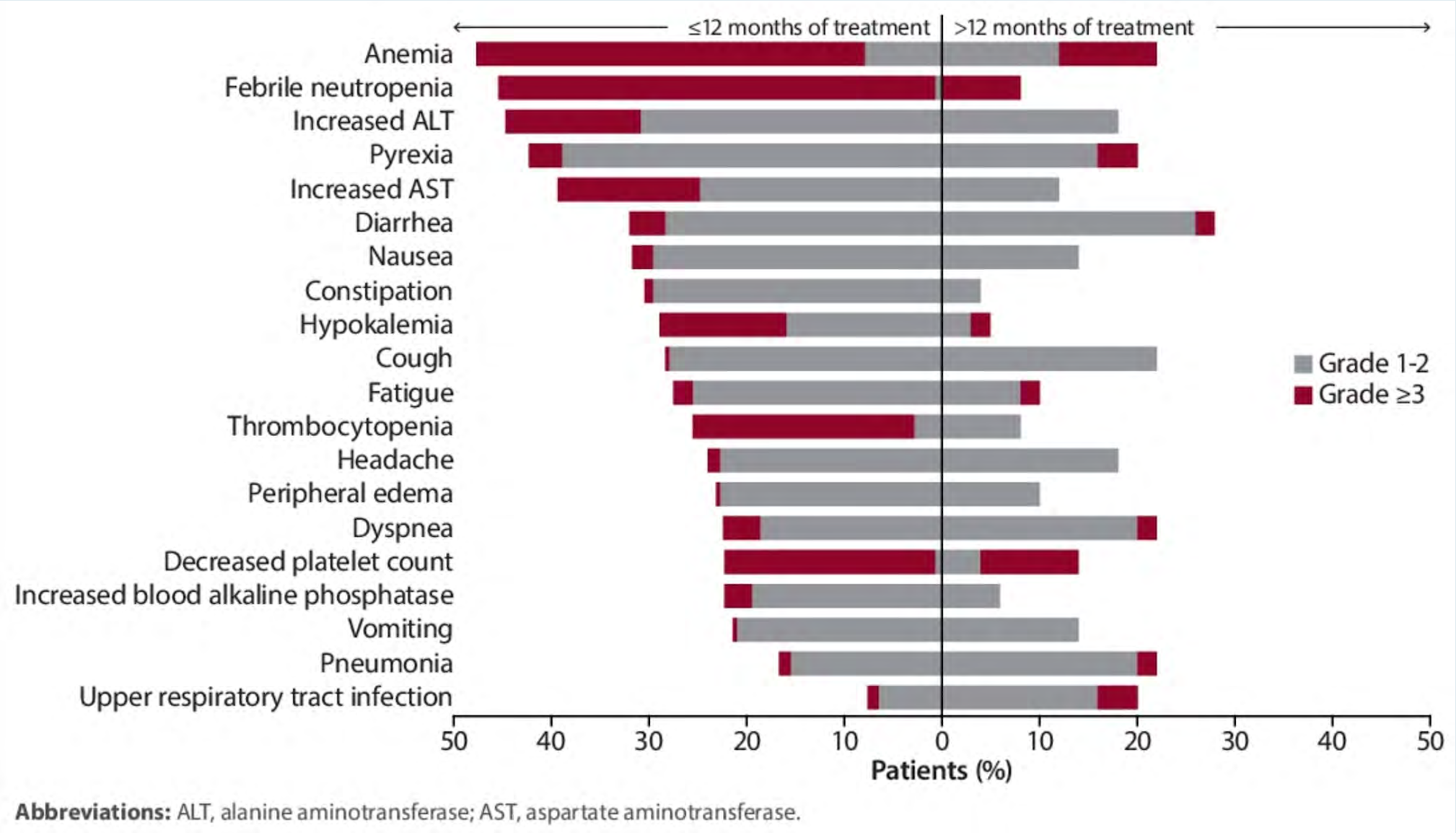
[a]Duration of CR/CRh was not estimable due to the high dropout rate after the second cycle of treatment.

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; DoR, duration of response; mut+, mutated; NE, not estimable; R/R, relapsed or refractory.

Perl AE et al. ASCO 2020;Abstract 7514.

RTP RESEARCH TO PRACTICE

ADMIRAL: Adverse Events Occurring in ≥20% of Patients Receiving Gilteritinib



Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Perl AE et al. ASCO 2020;Abstract 7514.

RTP RESEARCH TO PRACTICE

ADMIRAL: Adverse Events Leading to Death

AEs Leading to Death[a,b], n (%)		≤12 Months of Treatment (n=246)	>12 Months of Treatment (n=50)
Cardiac disorders	Cardiac arrest	4 (1.6)	0
	Pericardial effusion	2 (0.8)	0
Infections and infestations	Septic shock	7 (2.8)	0
	Sepsis	5 (2.0)	0
	Lung infection	4 (1.6)	0
	Pneumonia	3 (1.2)	0
Gastrointestinal disorders	Large intestinal perforation	2 (0.8)	0
Nervous system disorders	Cerebral hemorrhage	2 (0.8)	0
Respiratory, thoracic, and mediastinal disorders	Respiratory failure	2 (0.8)	0

[a]Patients may have had more than one fatal AE; [b]Excludes deaths stemming from AML progression or relapse.
Abbreviation: AE, adverse event.

Perl AE et al. ASCO 2020;Abstract 7514.

RTP RESEARCH TO PRACTICE

Phase 1 First-in-Human Study of Irreversible FLT3 Inhibitor FF-10101-01 in Relapsed or Refractory Acute Myeloid Leukemia

Levis MJ et al.
ASCO 2021;Abstract 7008.

Friday, June 4, 2:30 PM - 5:30 PM EDT

Phase III LACEWING Trial Fails to Meet Primary Endpoint of OS in Newly Diagnosed AML with FLT3 Mutation

Press Release – December 21, 2020

"The phase 3 LACEWING trial of the FMS-like tyrosine kinase 3 (FLT3) inhibitor gilteritinib plus azacitidine versus azacitidine alone in patients with newly diagnosed *FLT3* mutation-positive acute myeloid leukemia (AML) who were ineligible for intensive induction chemotherapy did not meet its primary end point of overall survival (OS) at a planned interim analysis, according to the developer of the agent.

Based on these results, an independent data monitoring committee recommended the study be terminated for futility, citing that the results are unlikely to demonstrate a statistically significant increase in OS. [The developer of the agent has] indicated it has since halted enrollment in the trial and is reviewing the results for other action as needed."

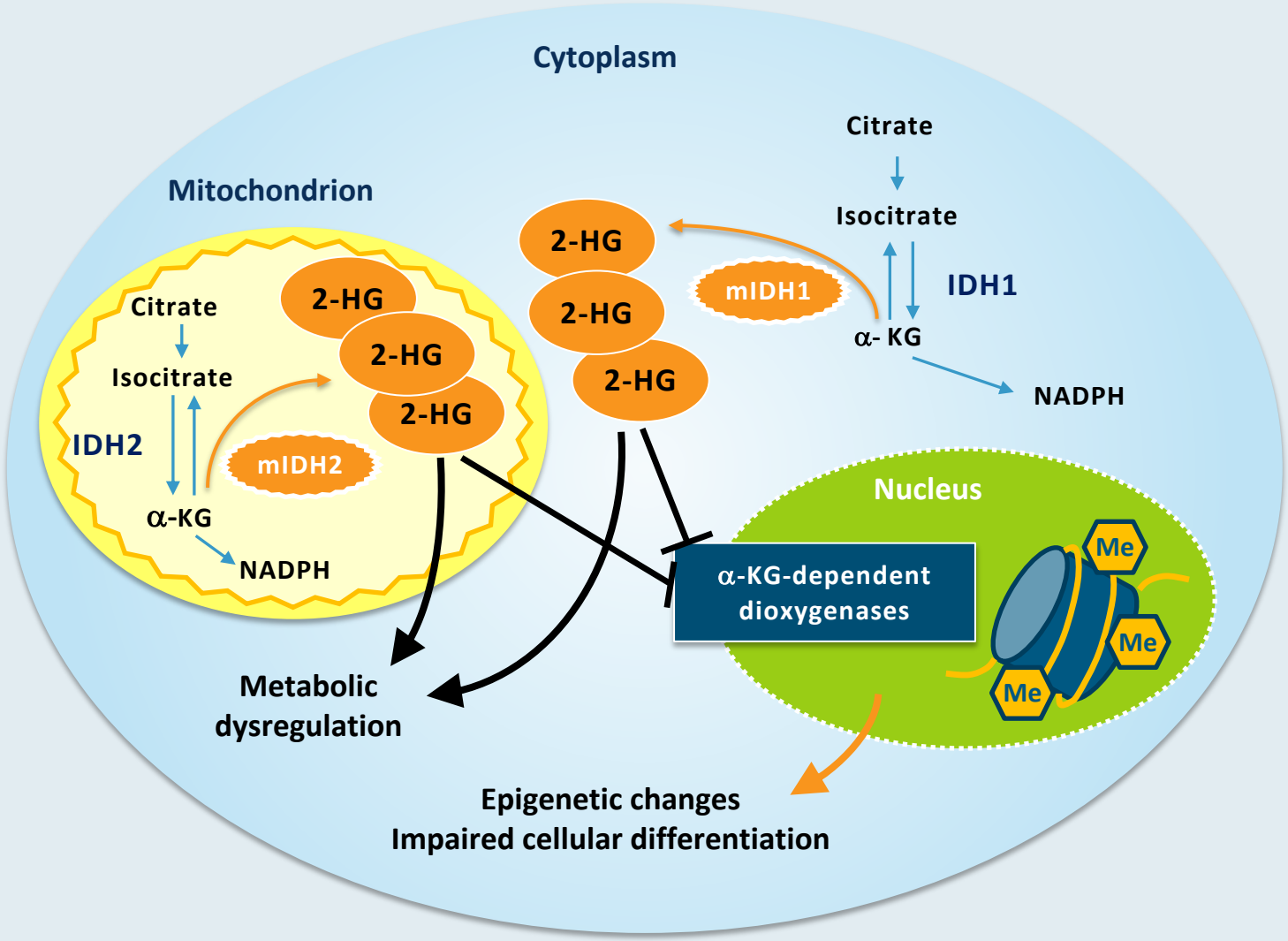
https://www.cancernetwork.com/view/phase-3-lacewing-trial-fails-to-meet-primary-end-point-of-os-in-newly-diagnosed-flt3-aml

RTP RESEARCH TO PRACTICE

IDH1 and IDH2 Mutations in AML

IDH mutations occur in ~20% of AML

- Frequency: 6%-16% IDH1 and 8%-18% IDH2
- Majority (85%) with diploid or +8 cytogenetics
- ↑ prevalence with ↑ patient age
- Prognostic effect in AML remains controversial
- IDH1 and IDH2 mutations may have different effects on prognosis



Buege MJ et al. *Cancers* 2018;10:187; Chou WC et al. *Leukemia* 2011;25(2):246-53; Dang L et al. *Trends Mol Med* 2010;16(9):387-97. Döhner H et al. *N Engl J Med* 2015;373(12):1136-52; Bullinger L et al. *J Clin Oncol* 2017;35(9):934-46; Patel JP et al. *N Engl J Med* 2012;366(2):1079-89. Medeiros BC et al. *Leukemia* 2017;31:272-81.

Enasidenib Monotherapy is Effective in Older Patients with Newly Diagnosed IDH2 Mutated Acute Myeloid Leukemia and Addition of Azacitidine Rescues Enasidenib Monotherapy Failures: A Phase 2/1B Study of the BEAT AML Master Trial

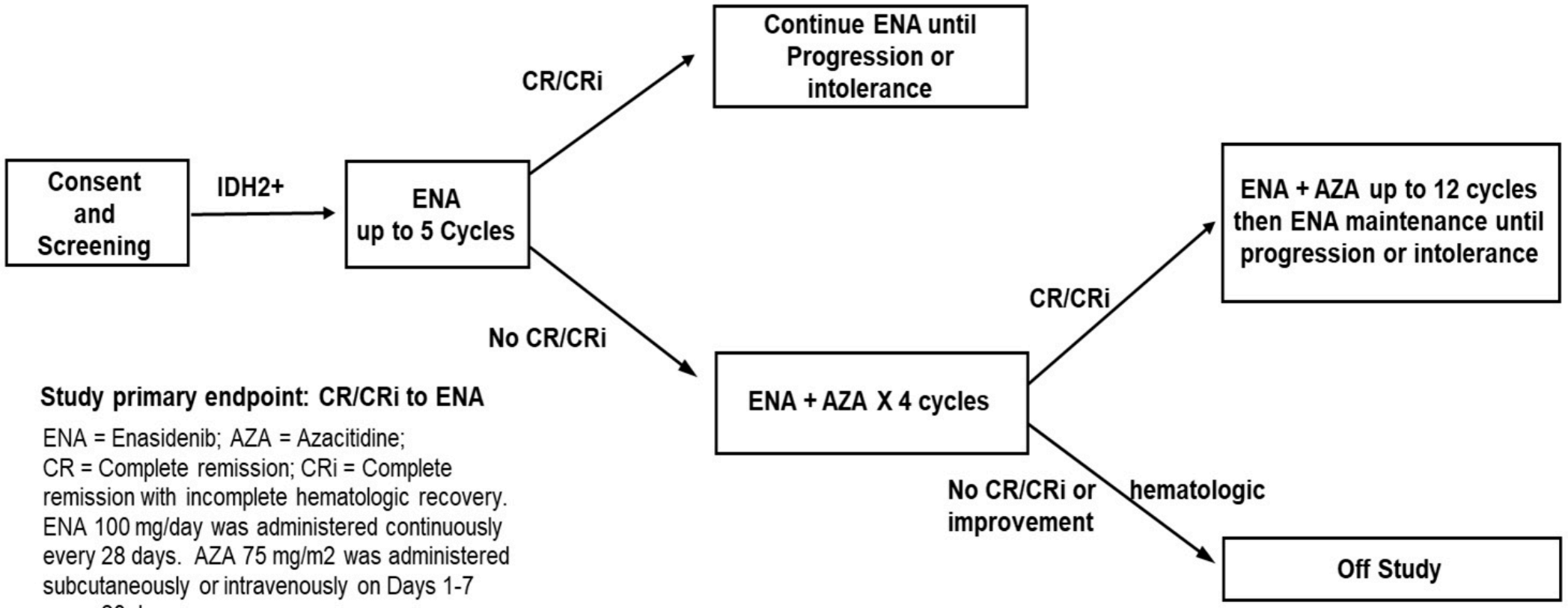
Stein EM et al.

ASH 2020;Abstract 636

LEUKEMIA & LYMPHOMA SOCIETY®

RTP RESEARCH TO PRACTICE

Beat AML S3 Study Design and Objectives



Study primary endpoint: CR/CRi to ENA

ENA = Enasidenib; AZA = Azacitidine;
CR = Complete remission; CRi = Complete remission with incomplete hematologic recovery.
ENA 100 mg/day was administered continuously every 28 days. AZA 75 mg/m2 was administered subcutaneously or intravenously on Days 1-7 every 28 days.

Response to Enasidenib Monotherapy for Newly Diagnosed AML and Efficacy of Azacitidine After Failure of Enasidenib

	Enasidenib (n = 60)	Azacitidine added after no response to enasidenib (n = 17)
Overall response rate	50%	47%
CR/CRi rate	47%	41%
Median overall survival	24.4 mo	8.9 mo

Stein EM et al. ASH 2020;Abstract 636.

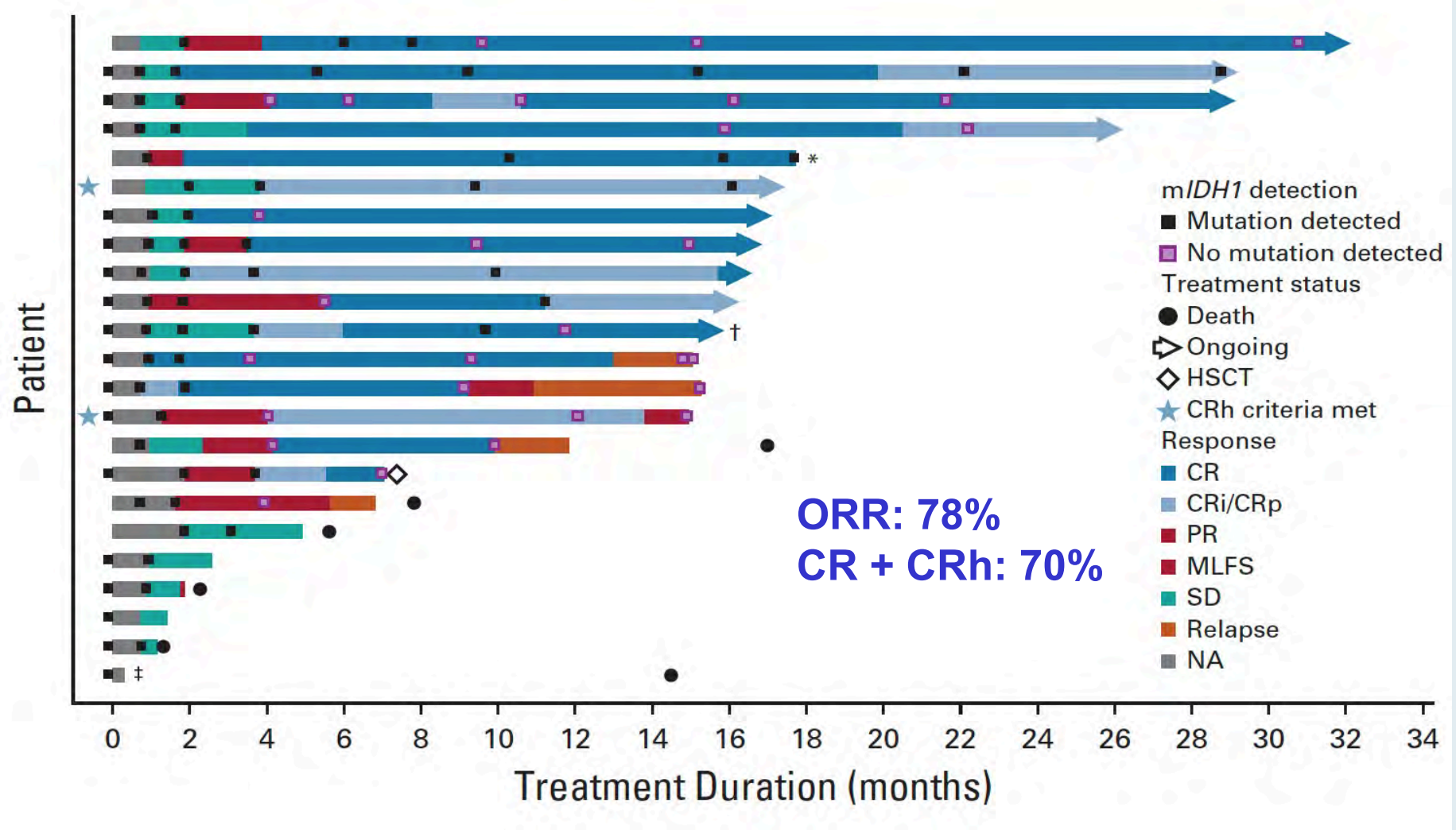
original reports

Mutant Isocitrate Dehydrogenase 1 Inhibitor Ivosidenib in Combination With Azacitidine for Newly Diagnosed Acute Myeloid Leukemia

Courtney D. DiNardo, MD[1]; Anthony S. Stein, MD[2]; Eytan M. Stein, MD[3]; Amir T. Fathi, MD[4]; Olga Frankfurt, MD[5]; Andre C. Schuh, MD[6]; Hartmut Döhner, MD[7]; Giovanni Martinelli, MD[8]; Prapti A. Patel, MD[9]; Emmanuel Raffoux, MD[10]; Peter Tan, MBBS[11]; Amer M. Zeidan, MBBS[12]; Stéphane de Botton, MD, PhD[13]; Hagop M. Kantarjian, MD[1]; Richard M. Stone, MD[14]; Mark G. Frattini, MD, PhD[15]; Frederik Lersch, RN[16]; Jing Gong, PhD[15]; Diego A. Gianolio, PhD[17]; Vickie Zhang, PhD[17]; Aleksandra Franovic, PhD[18]; Bin Fan, PhD[17]; Meredith Goldwasser, ScD[17]; Scott Daigle, MS[17]; Sung Choe, PhD[17]; Bin Wu, PhD[17]; Thomas Winkler, MD[17]; and Paresh Vyas, MD, PhD[19]

J Clin Oncol 2021;39(1):57-65.

Treatment Duration, Response Over Time and IDH1 Mutation Status



DiNardo CD et al. *J Clin Oncol* 2021;39(1):57-65.

IDH Differentiation Syndrome (IDH-DS)

- **Potentially fatal complication of effective leukemia treatment**
  - First described in patients with APL treated with ATRA
- **Signs and symptoms of DS are not specific**
  - Fever, edema, weight gain, leukocytosis, rash, hypotension, renal dysfunction, and pleural and pericardial effusions
  - A rising leukocyte count, comprising increasing neutrophils with a parallel decrease in leukemic blasts
- **Median time to onset:** ~30 days (range: 5-340 days)
- **Frequency:** 5-6% Grade 3 or higher
  - Frequent dose interruptions but not associated with treatment discontinuation
- **Treatment**
  - Corticosteroids for IDH-DS
  - Hydroxyurea for leukocytosis, which frequently accompanies IDH-DS
  - Hyperuricemia agents for tumor lysis syndrome, which may co-occur

Stein EM et al. *Blood* 2017;130(6):722-31; Stein EM et al. *Blood* 2019;133(7):676-87;
DiNardo CD et al. *N Engl J Med* 2018;378:2386-98; Birendra KC, DiNardo CD. *Clin Lymphoma Myeloma Leuk* 2016;16(8):460-5.

Frequency of Signs and Symptoms Consistent with IDH-DS

Sign or symptom	Patients with IDH-DS (N = 33)
Dyspnea	28 (85%)
Unexplained fever (body temp of 38.0°C for 2 d)	26 (79%)
Pulmonary infiltrates	24 (73%)
Hypoxia	19 (58%)
Acute kidney injury	14 (42%)
Pleural effusion	14 (42%)
Bone pain or arthralgia	9 (27%)
Lymphadenopathy	8 (24%)
Rash	8 (24%)
Disseminated intravascular coagulopathy	7 (21%)
Edema or weight gain of >5 kg from screening	7 (21%)
Pericardial effusion	5 (15%)

Fathi A et al. *JAMA Oncol* 2018;4(8):1106-10.

Case Presentation – Dr Husain: A frail 85-year-old man with AML who received decitabine/venetoclax

Dr Hatim Husain

- PMH: Prostate cancer, s/p RT 8 years ago
- 2019: MDS, anemia requiring epoetin alfa
- 12/2020: Presents with worsening leukocytosis, with circulating blasts
- 1/2021 BMB: AML
- Decitabine/venetoclax

Questions

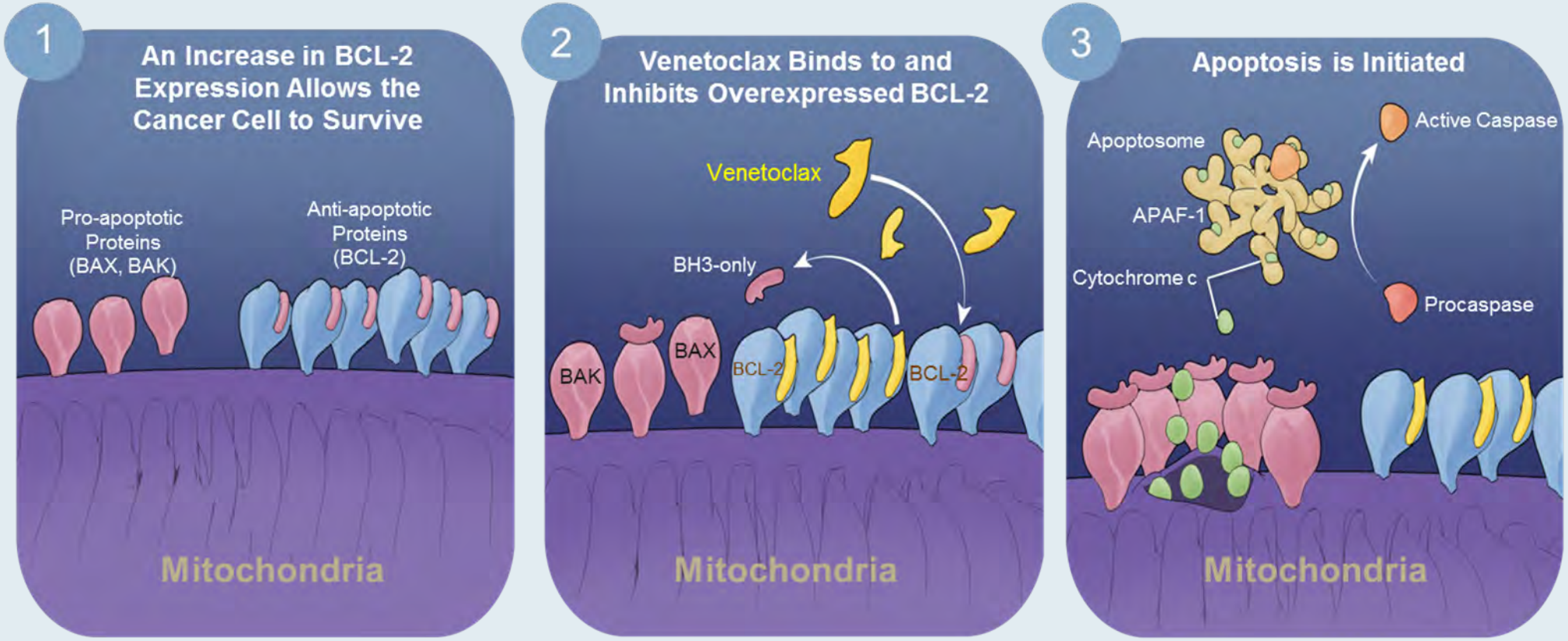
- What treatment would you recommend at disease progression?
- Would you discuss luspatercept and how that might have been useful in this patient?
- What are your thoughts about the oral hypomethylating agents?

RTP
RESEARCH
TO PRACTICE

Key Recent Publications and Presentations

- DiNardo CD et al. **Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia.** *N Engl J Med* 2020;383(7):617-29.
- Wei AH et al. **Venetoclax plus LDAC for Newly Diagnosed AML Ineligible for Intensive Chemotherapy: A Phase 3 Randomized Placebo-Controlled Trial.** *Blood* 2020;135(24):2137-45.
- Wei AH et al. **Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission.** *N Engl J Med* 2020;383(26):2526-37.

Venetoclax Mechanism of Action



- Cancer cells increase the expression of anti-apoptotic proteins to offset the increase in pro-apoptotic proteins, tipping the balance toward cell survival
- The large # of pro-apoptotic proteins bound and sequestered by Bcl-2 in AML make them “primed” for death

Kumar et al. *Proc ASCO* 2015;Abstract 8576.

N Engl J Med 2020;383:617-29.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 13, 2020 VOL. 383 NO. 7

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

C.D. DiNardo, B.A. Jonas, V. Pullarkat, M.J. Thirman, J.S. Garcia, A.H. Wei, M. Konopleva, H. Döhner, A. Letai, P. Fenaux, E. Koller, V. Havelange, B. Leber, J. Esteve, J. Wang, V. Pejsa, R. Hájek, K. Porkka, Á. Illés, D. Lavie, R.M. Lemoli, K. Yamamoto, S.-S. Yoon, J.-H. Jang, S.-P. Yeh, M. Turgut, W.-J. Hong, Y. Zhou, J. Potluri, and K.W. Pratz

VIALE-A Study Design

(NCT02993523)

Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ❖ ≥75 years of age
  - ❖ 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤65% or FEV_1 ≤65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Randomization 2:1
N = 433*

Treatment

Venetoclax + Azacitidine
(n = 286)
Venetoclax 400 mg PO, daily, days 1–28 +
Azacitidine 75 mg/m² SC /IV days 1–7

Placebo + Azacitidine
(n = 145)
Placebo daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

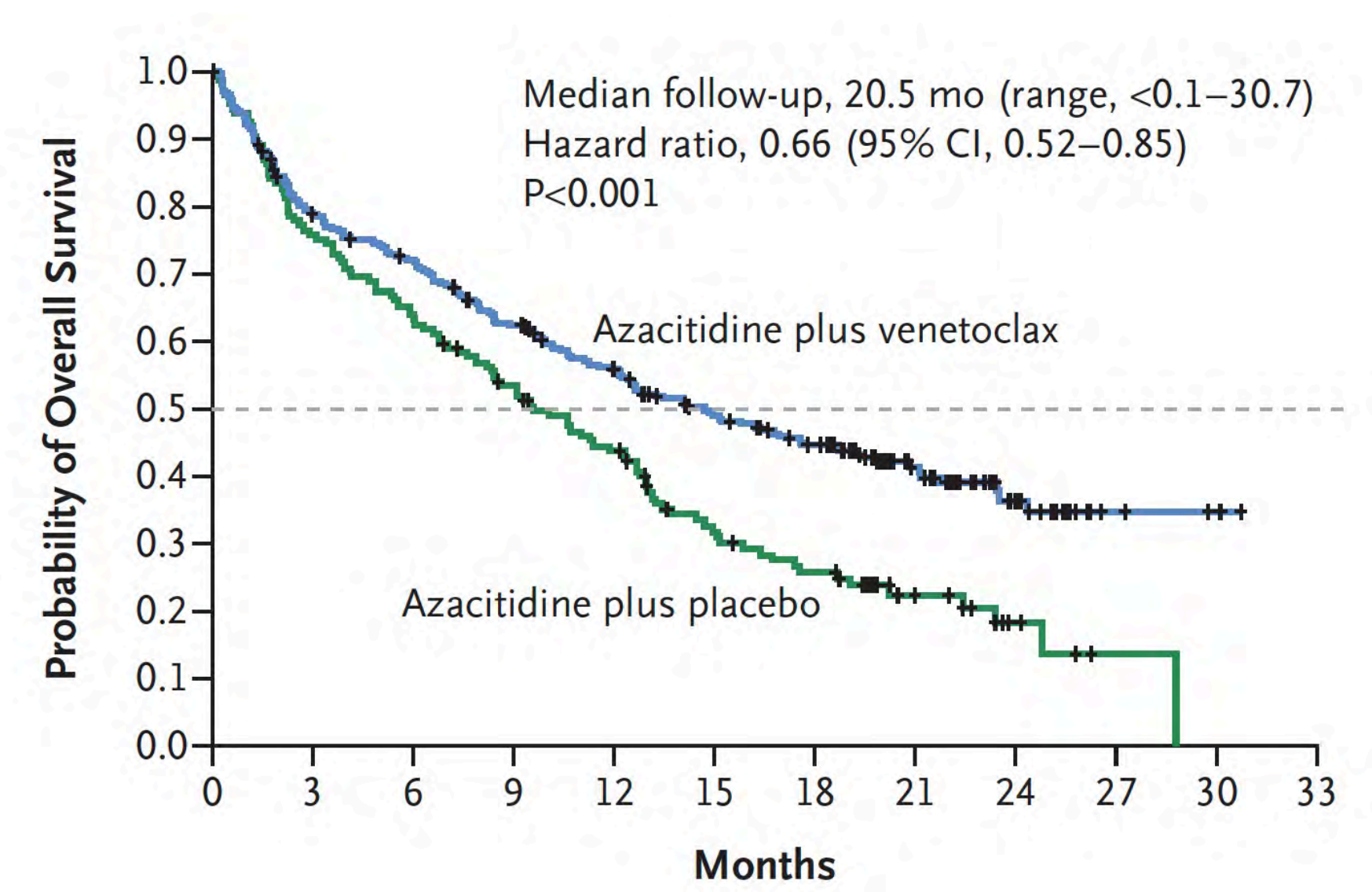
Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors	Age (<75 vs. ≥75 years); Cytogenetic risk (intermediate, poor); region
Venetoclax dosing ramp-up	**Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg **Cycle 2** Day 1-28: 400 mg

DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

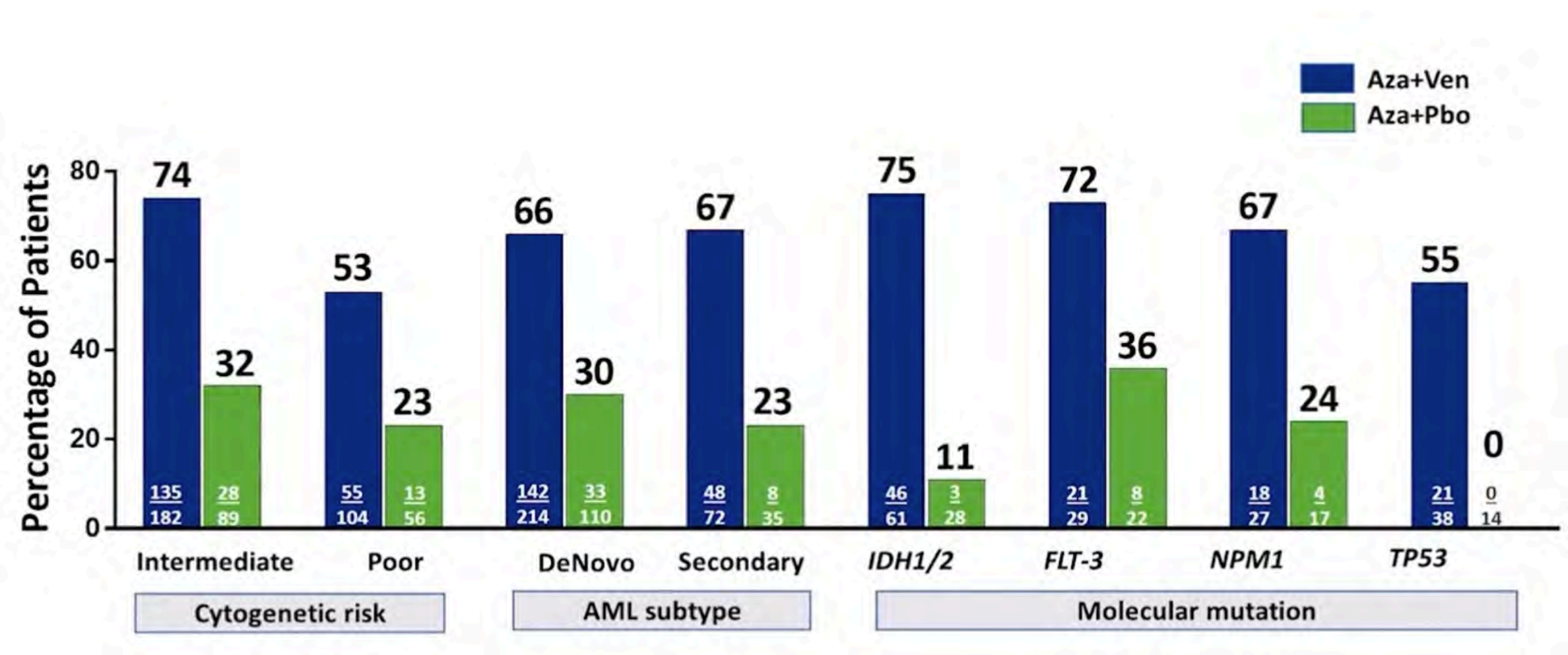
VIALE-A: Overall Survival (N = 431)



DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

RTP RESEARCH TO PRACTICE

VIALE-A: Response Rates (CR + CRi) Subgroups



DiNardo C et al. EHA 2020;Abstract LB2601.

blood

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial

Andrew H. Wei,[1,2] Pau Montesinos,[3,4] Vladimir Ivanov,[5] Courtney D. DiNardo,[6] Jan Novak,[7,8] Kamel Laribi,[9] Inho Kim,[10] Don A. Stevens,[11] Walter Fiedler,[12] Maria Pagoni,[13] Olga Samoilova,[14] Yu Hu,[15] Achilles Anagnostopoulos,[16] Julie Bergeron,[17] Jing-Zhou Hou,[18] Vidhya Murthy,[19] Takahiro Yamauchi,[20] Andrew McDonald,[21] Brenda Chyla,[22] Sathej Gopalakrishnan,[22] Qi Jiang,[22] Wellington Mendes,[22] John Hayslip,[22] and Panayiotis Panayiotidis[23]

Blood 2020;135(24):2137-45.

VIALE-C Phase 3 Study Design

- Randomized 2:1, double-blind, placebo-controlled trial

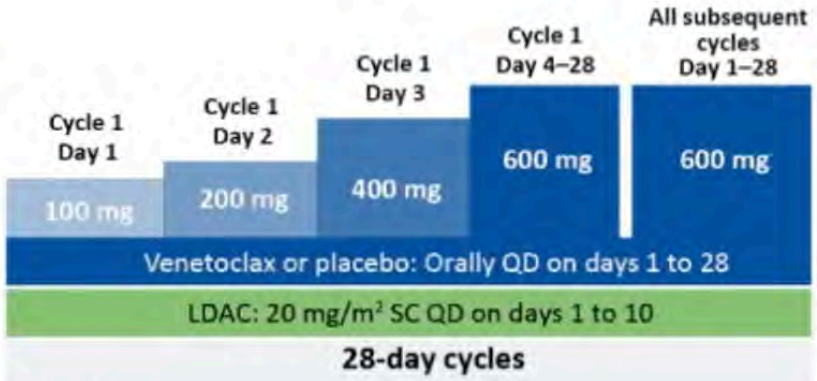
2:1 Randomization via IRT
N=211

- Venetoclax + LDAC (n=143)
- Placebo + LDAC (n=68)

Patients could continue receiving treatment until progression or until study treatment discontinuation criteria were met

Patients remained on study for OS assessment and follow-up, even if they initiated additional lines of treatment

Stratification factors
- AML status (secondary vs de novo)
- Age (18 to <75 vs ≥75)
- Region (US, EU, China, Japan, ROW)



Primary endpoint: overall survival

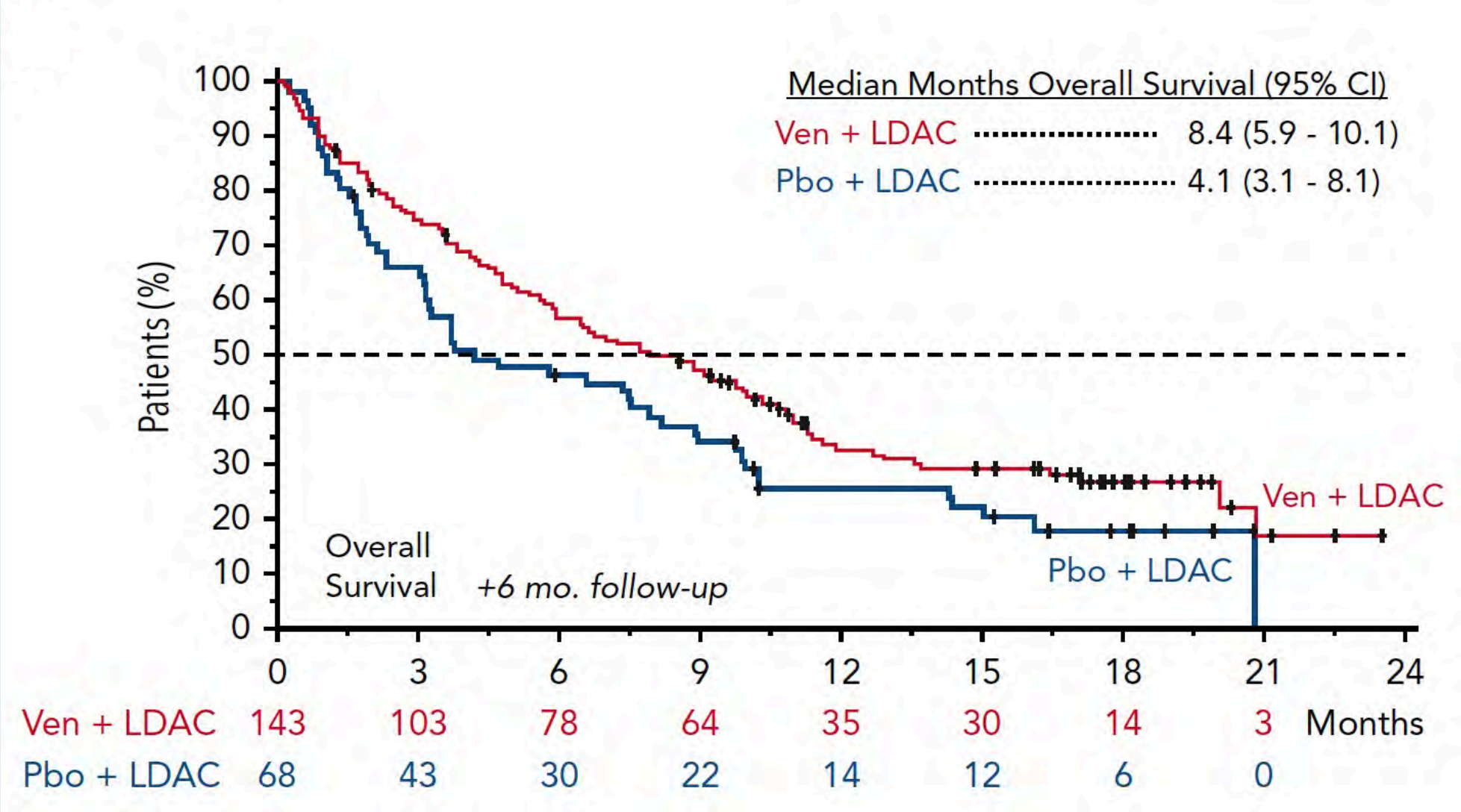
Secondary endpoints
- CR, CRh, and CRi (modified IWG criteria[1])
- Rate of transfusion independence
- EFS
- MRD

Progressive disease was defined per ELN recommendations.[2]

AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete blood count recovery; EFS, event-free survival; ELN, European LeukemiaNet; IRT, Interactive Response Technology; IWG, International Working Group; LDAC, low-dose cytarabine; MRD, minimal residual disease; OS, overall survival; QD, once a day; ROW, rest of world; SC, subcutaneous.

1. Cheson BD, et al. *J Clin Oncol.* 2003;21:4642-4649; 2. Döhner H, et al. *Blood.* 2017;129:424-447.

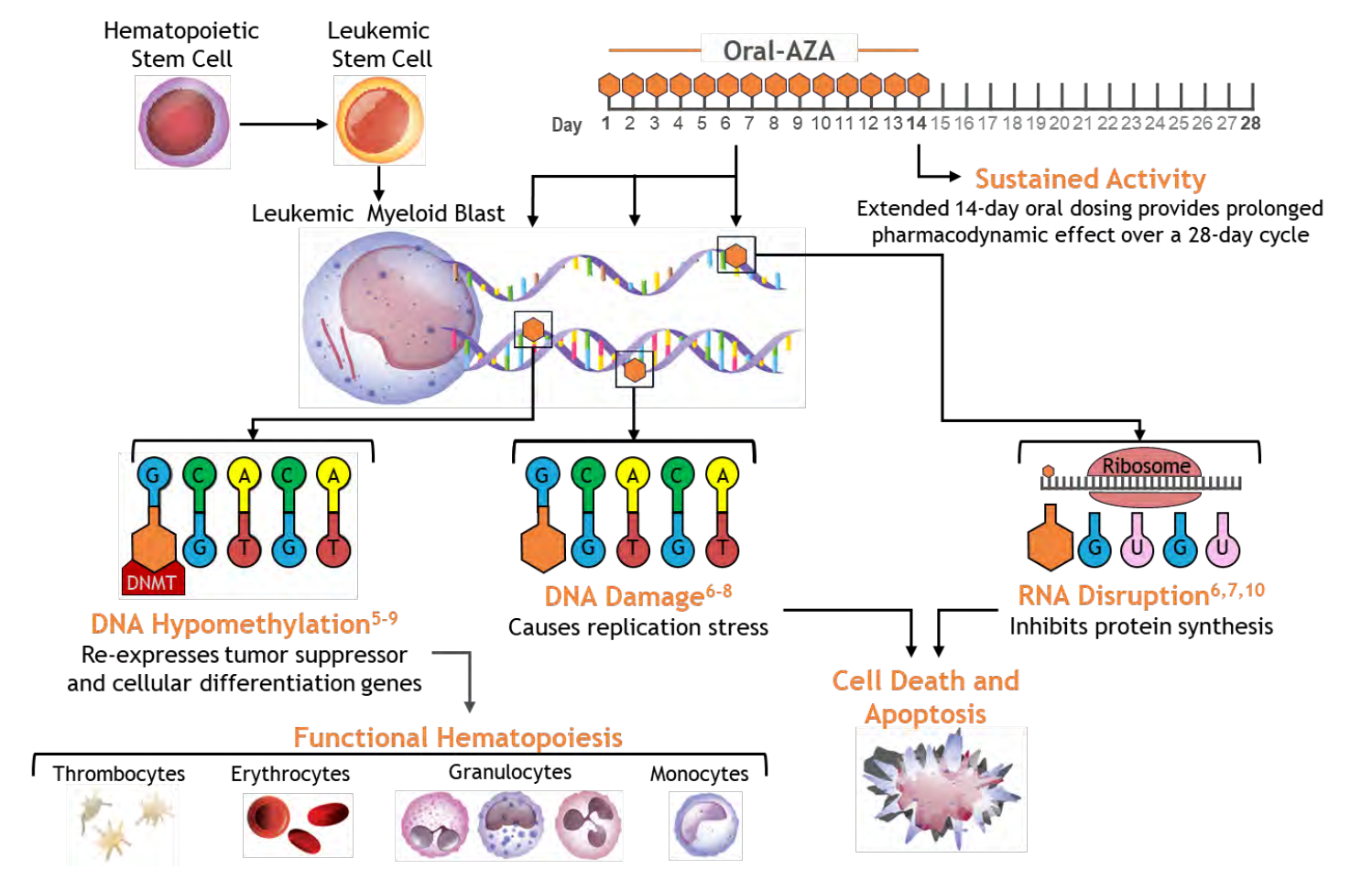
VIALE-C: Overall Survival



Wei AH et al. *Blood* 2020;135(24):2137-45.

Oral Azacitidine (CC-486)

- Oral HMA with a distinct PK/PD profile from injectable AZA; the two are not bioequivalent[1,2]
- Approved in the United States for continued Tx of adult pts with AML in first CR/CRi post-IC and not able to complete intensive curative therapy (eg, HSCT)[3]
  - Oral dosing allows for extended drug exposure during each Tx cycle to prolong AZA activity[1,2]



1. Garcia-Manero et al. *J Clin Oncol*. 2011;29(18):2521–7. 2. Laille et al. *PLoS One*. 2015;10(8):e0135520. 3. ONUREG® (azacitidine) tablets [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Rev. 9/2020. 4. Savona et al. *Am J Hematol*. 2018;93(10):1199–206. 5. Stresemann et al. *Mol Cancer Ther*. 2008;7:2998–3005. 6. Hollenbach et al. *PLoS One*. 2010;5(2):e9001. 7. Scott LJ. *Drugs*. 2016;76(8):889–900. 8. Stresemann C, Lyko F. *Int J Cancer*. 2008;123(1):8–13. 9. Aimiuwu et al. *Blood*. 2012;119(22):5229–38.

AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; PD, pharmacodynamic; PK, pharmacokinetic; pts, patients; Tx, treatment.

Courtesy of Richard M Stone, MD

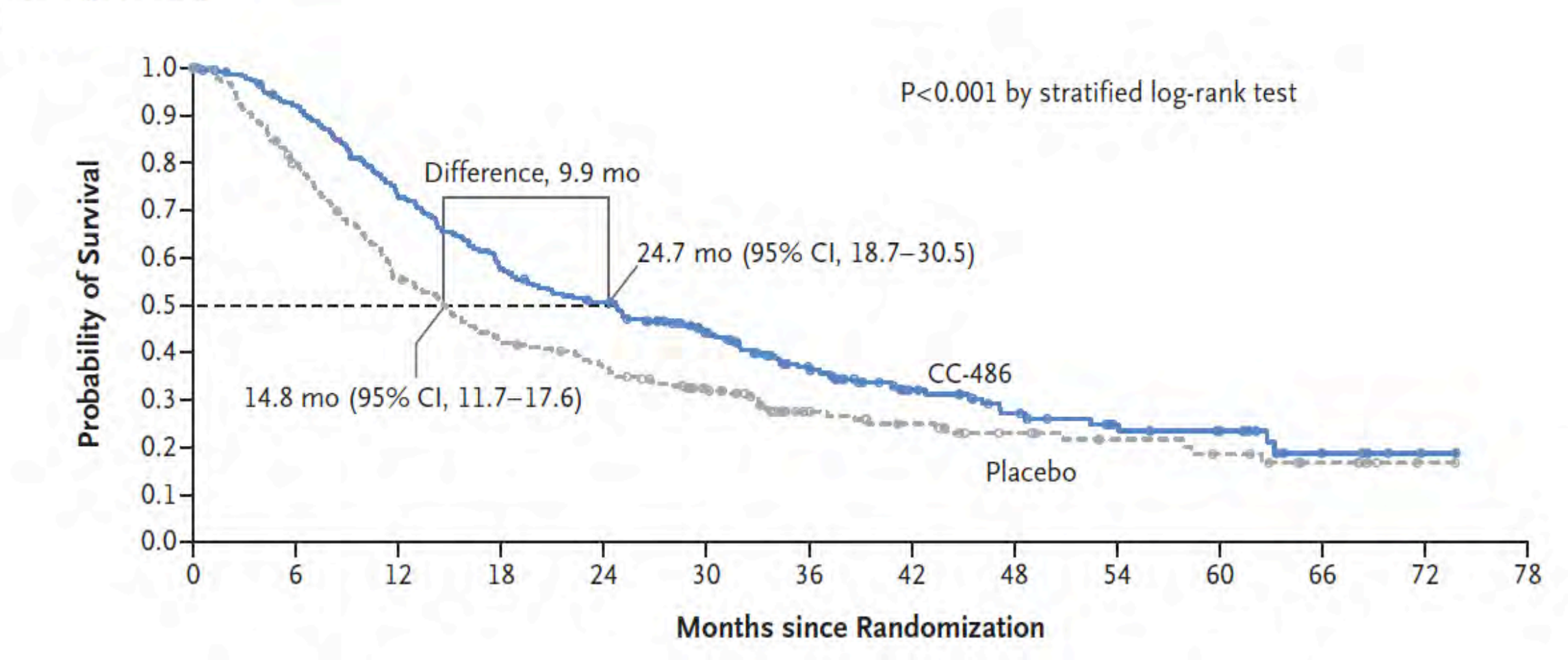
ORIGINAL ARTICLE

Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission

A.H. Wei, H. Döhner, C. Pocock, P. Montesinos, B. Afanasyev,* H. Dombret, F. Ravandi, H. Sayar, J.-H. Jang, K. Porkka, D. Selleslag, I. Sandhu, M. Turgut, V. Giai, Y. Ofran, M. Kizil Çakar, A. Botelho de Sousa, J. Rybka, C. Frairia, L. Borin, G. Beltrami, J. Čermák, G.J. Ossenkoppele, I. La Torre, B. Skikne, K. Kumar, Q. Dong, C.L. Beach, and G.J. Roboz, for the QUAZAR AML-001 Trial Investigators†

N Engl J Med 2020;383:2526-37.

QUAZAR AML-001: Overall Survival



Wei AH et al. *N Engl J Med* 2020;383:2526-37.

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Myelodysplastic Syndromes (MDS)

- Dr Lorber: A 73-year-old man with MDS, ring sideroblasts and multilineage dysplasia
- *Key Recent Publications and Presentations*

Module 2: Newly Diagnosed Acute Myeloid Leukemia (AML)

- Dr Blackmon: A 40-year-old woman with newly diagnosed AML and a FLT3-TKD mutation
- *Key Recent Publications and Presentations*
- Dr Husain: A frail 85-year-old man with AML who received decitabine/venetoclax
- *Key Recent Publications and Presentations*

Module 3: Secondary AML

- Dr Husain: A 65-year-old man who develops AML while receiving therapy for metastatic NSCLC
- Dr Lorber: A 74-year-old otherwise healthy man with atrial fibrillation develops AML secondary to MDS
- *Key Recent Publications and Presentations*

Case Presentation – Dr Husain: A 65-year-old man who develops AML while receiving therapy for metastatic NSCLC

Dr Hatim Husain

- PMH: Stage IIIC adenocarcinoma of the lung, s/p cisplatin/etoposide/RT
- Intrathoracic disease progressing 3 months after completing RT
- Carboplatin/pemetrexed/pembrolizumab → Pemetrexed/pembrolizumab, with PD
- Docetaxel/ramucirumab
  - After 3 months: WBC 106, HB 6.3, Plt 112
- BMB: AML, monosomy 7 with no clinically significant somatic mutations via NGS
- Best supportive care with hydroxyurea, transfusions and pain control

Questions

- What are the new options for treatment-related AML, and are there genomic characteristics that can better help us understand the therapeutic strategies?
- Would you discuss what is known about CPX-351 in terms of its pros and cons and applicability to this case?

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Case Presentation – Dr Lorber: A 74-year-old otherwise healthy man with atrial fibrillation develops AML secondary to MDS

Dr Jeremy Lorber

- PMH: diagnosed with MDS with trilineage dyspoesis, del13q, and U2AF1 mutation; baseline atrial fibrillation
- Initially responded to ESA but transformed to AML within 5 months
- Liposomal daunorubicin/cytarabine, with CR → Consolidation daunorubicin/cytarabine x 1
- Plan for possible bone marrow transplant
- Recurred with cutaneous manifestation of AML

Questions

- What is the most appropriate regimen given his age? Is liposomal daunorubicin and cytarabine "worth" the toxicity compared to HMA + venetoclax?
- With venetoclax, are the initial cytopenias from the disease or the drug? How do you manage the cytopenias – dose reduction, hold the drug or change cycle duration?

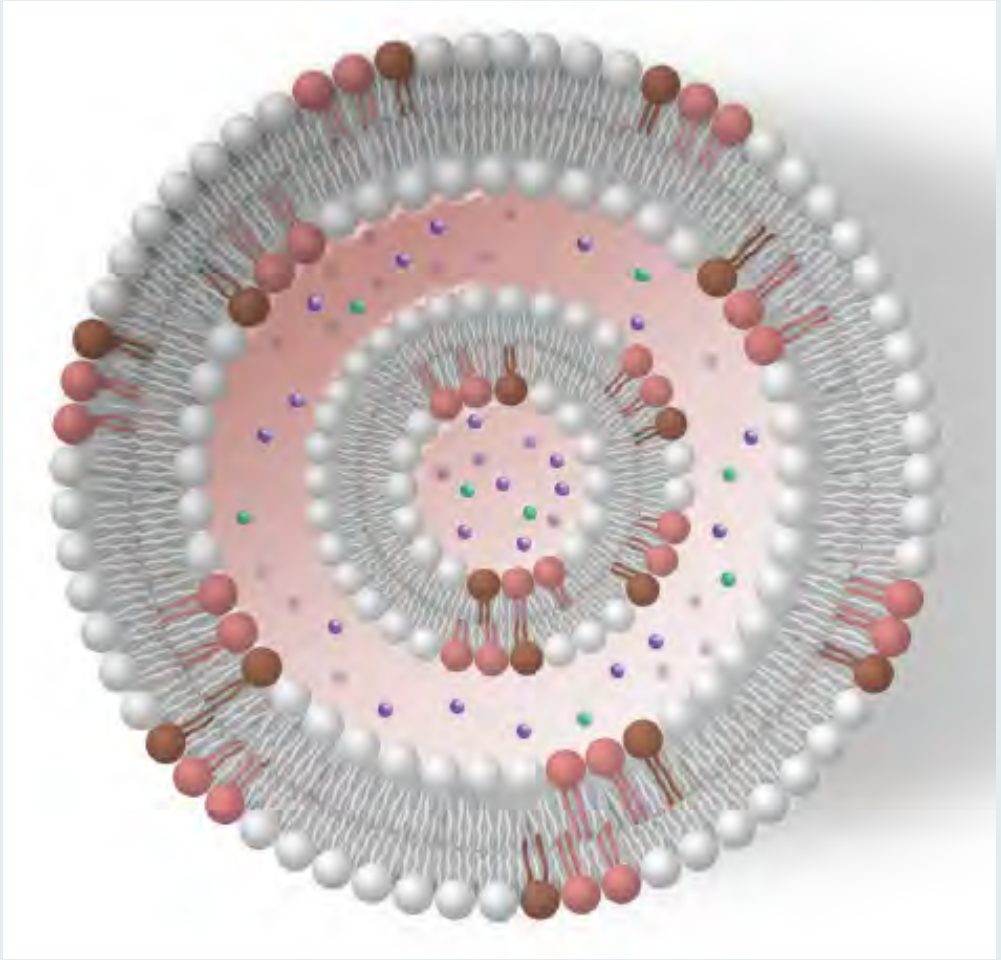
RTP RESEARCH TO PRACTICE

Key Recent Presentations

- Lancet JE et al. **Five-Year Final Results of a Phase 3 Study of CPX-351 versus 7 + 3 in Older Adults with Newly Diagnosed High-Risk/Secondary Acute Myeloid Leukemia (AML): Outcomes by Age Subgroup and Among Responders.** ASH 2020;Abstract 635.
- Kadia TM et al. **Phase II Study of CPX-351 plus Venetoclax in Patients with Acute Myeloid Leukemia (AML).** ASH 2020;Abstract 28.
- Ramos Perez JM et al. **Liposomal Cytarabine and Daunorubicin (CPX-351) in Combination with Gemtuzumab Ozogamicin (GO) in Relapsed Refractory (R/R) Patients with Acute Myeloid Leukemia (AML) and Post-Hypomethylating Agent (Post-HMA) Failure High-Risk Myelodysplastic Syndrome (HR-MDS).** ASH 2020;Abstract 987.

CPX-351

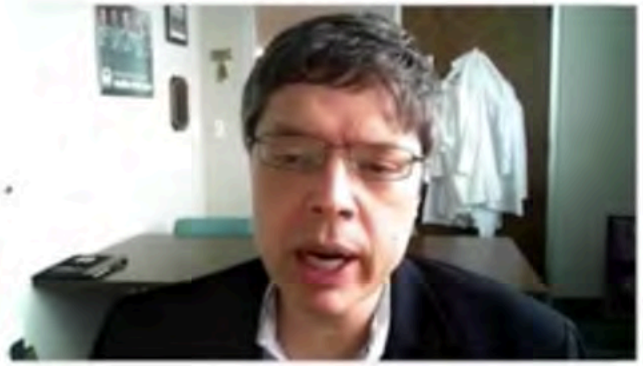
- CPX-351 is a liposomal co-formulation of cytarabine and daunorubicin designed to achieve synergistic antileukemia activity
  - 5:1 molar ratio of cytarabine:daunorubicin provides synergistic leukemia cell killing *in vitro*[1]
  - In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days[2]
  - Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]



1. Tardi P et al. *Leuk Res.* 2009;33(1):129-139. 2. Feldman EJ et al. *J Clin Oncol.* 2011;29(8):979-985;
3. Lim WS et al. *Leuk Res.* 2010;34(9):1245-1223.

ASH 2020;Abstract 635.

Five-year Final Results of a Phase 3 Study of CPX-351 Versus 7+3 in Older Adults with Newly Diagnosed High-risk/Secondary Acute Myeloid Leukemia (AML): Outcomes by Age Subgroup and Among Responders



Presenter: Jeffrey E. Lancet

H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

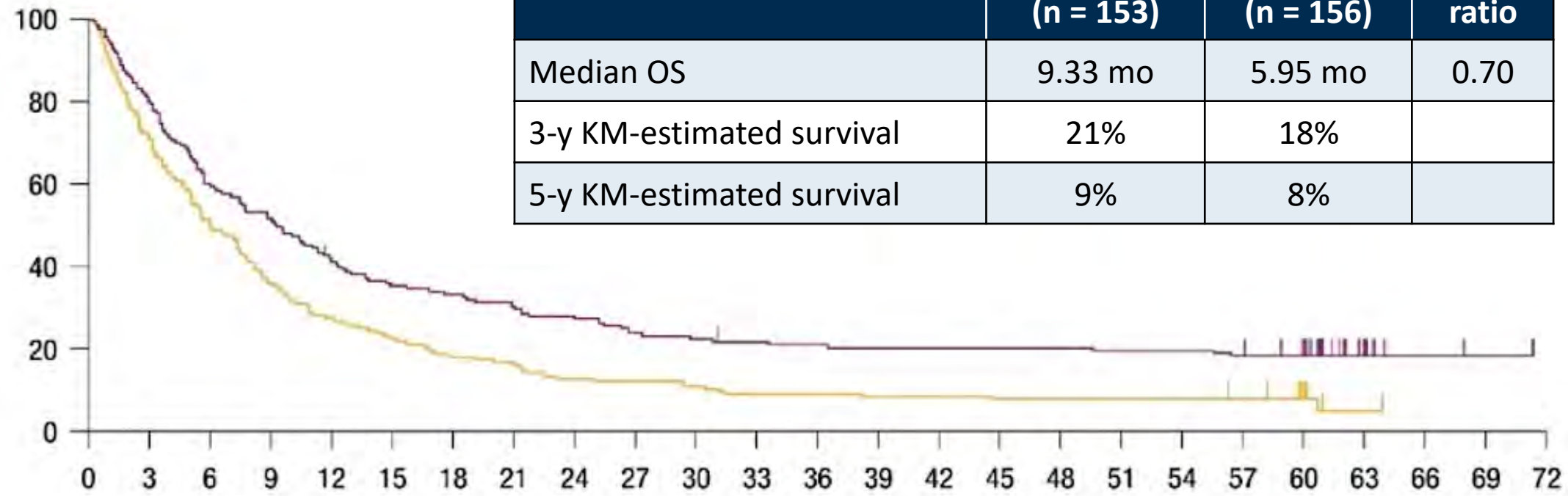
Jeffrey E. Lancet,[1] Geoffrey L. Uy,[2] Laura F. Newell,[3] Tara L. Lin,[4] Donna Hogge,[5] Scott R. Solomon,[6] Gary J. Schiller,[7] Matthew J. Wieduwilt,[8] Daniel H. Ryan,[9] Stefan Faderl,[10] Yu-Lin Chang,[10] Jorge E. Cortes[11,12]

[1]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [2]Washington University School of Medicine, St. Louis, MO, USA; [3]Oregon Health & Science University, Portland, OR, USA; [4]University of Kansas Medical Center, Kansas City, KS, USA; [5]Leukemia/BMT Program of British Columbia, Vancouver, BC, Canada; [6]Leukemia Program, Northside Hospital Cancer Center Institute, Atlanta, GA, USA; [7]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [8]University of California – San Diego Moores Cancer Center, La Jolla, CA, USA; [9]University of Rochester, Rochester, NY, USA; [10]Jazz Pharmaceuticals, Palo Alto, CA, USA; [11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]Georgia Cancer Center, Augusta University, Augusta, GA, USA.

62nd ASH Annual Meeting & Exposition; December 5-8, 2020

Five-Year Final Overall Survival Results with CPX-351 versus 7 + 3 for Older Patients with Newly Diagnosed High-Risk or Secondary AML

	CPX-351 (n = 153)	7 + 3 (n = 156)	Hazard ratio
Median OS	9.33 mo	5.95 mo	0.70
3-y KM-estimated survival	21%	18%	
5-y KM-estimated survival	9%	8%	

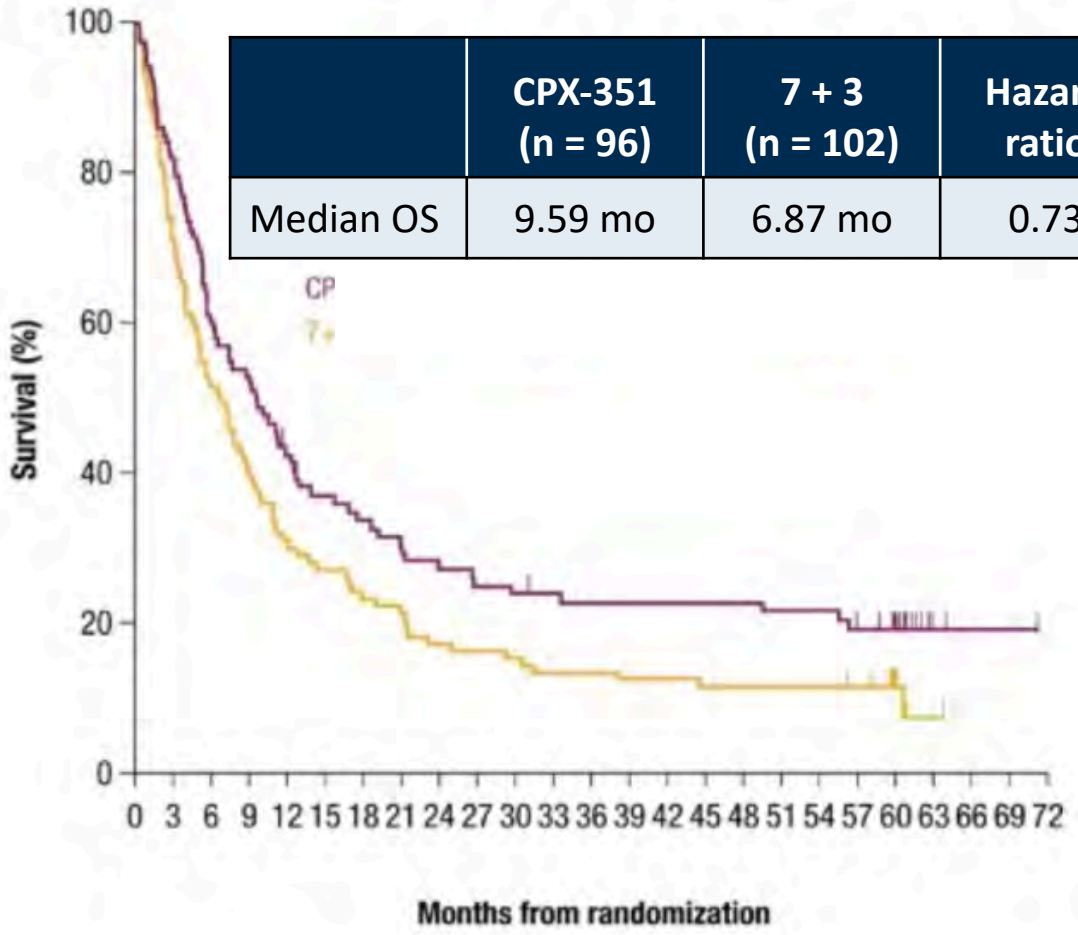


Lancet JE et al. ASH 2020;Abstract 635.

Overall Survival Results by Age

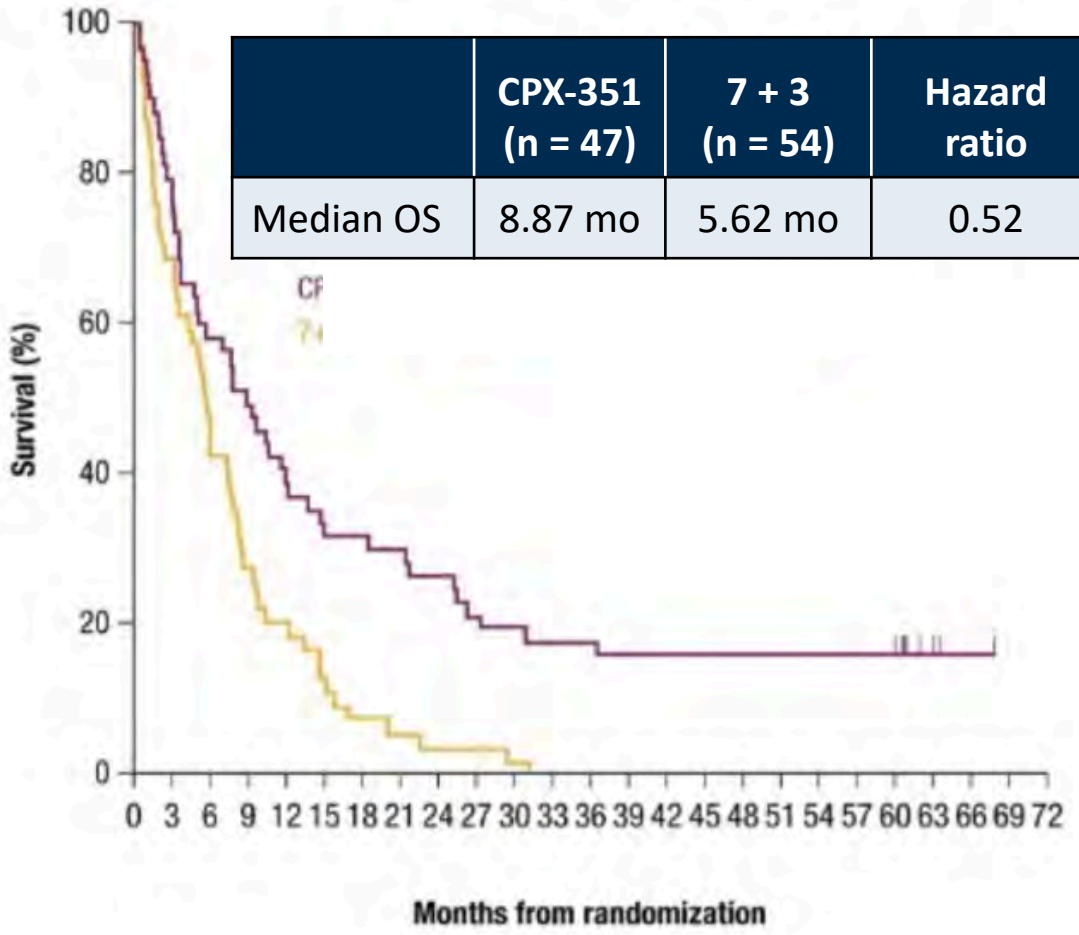
Ages 60 to 69 Years

	CPX-351 (n = 96)	7 + 3 (n = 102)	Hazard ratio
Median OS	9.59 mo	6.87 mo	0.73



Ages 70 to 75 Years

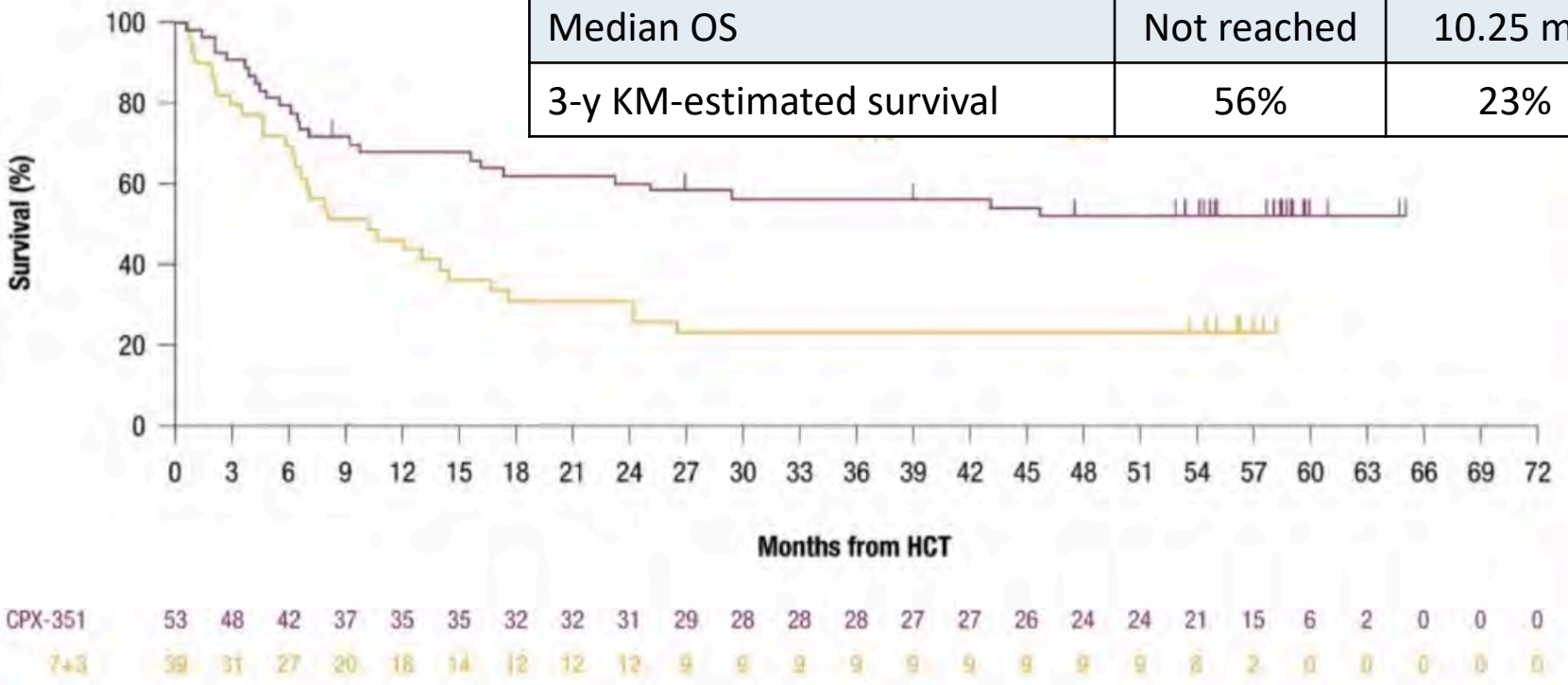
	CPX-351 (n = 47)	7 + 3 (n = 54)	Hazard ratio
Median OS	8.87 mo	5.62 mo	0.52

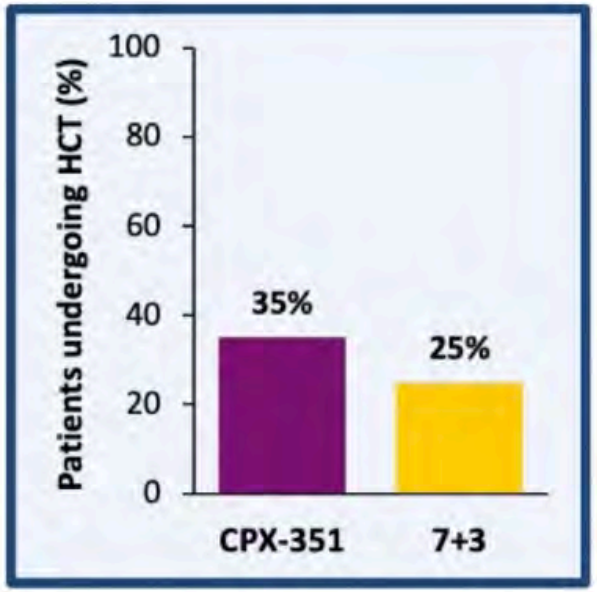


Lancet JE et al. ASH 2020;Abstract 635.

Overall Survival Landmarked from the HCT Date

	CPX-351 (n = 153)	7 + 3 (n = 156)	Hazard ratio
Median OS	Not reached	10.25 mo	0.51
3-y KM-estimated survival	56%	23%	





- **Kaplan-Meier–estimated survival rate landmarked from the date of HCT was >50% at 3 and 5 years for patients treated with CPX-351**

Lancet JE et al. ASH 2020;Abstract 635.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Abstract # 28

Phase II Study of CPX-351 Plus Venetoclax in Patients with Acute Myeloid Leukemia (AML)

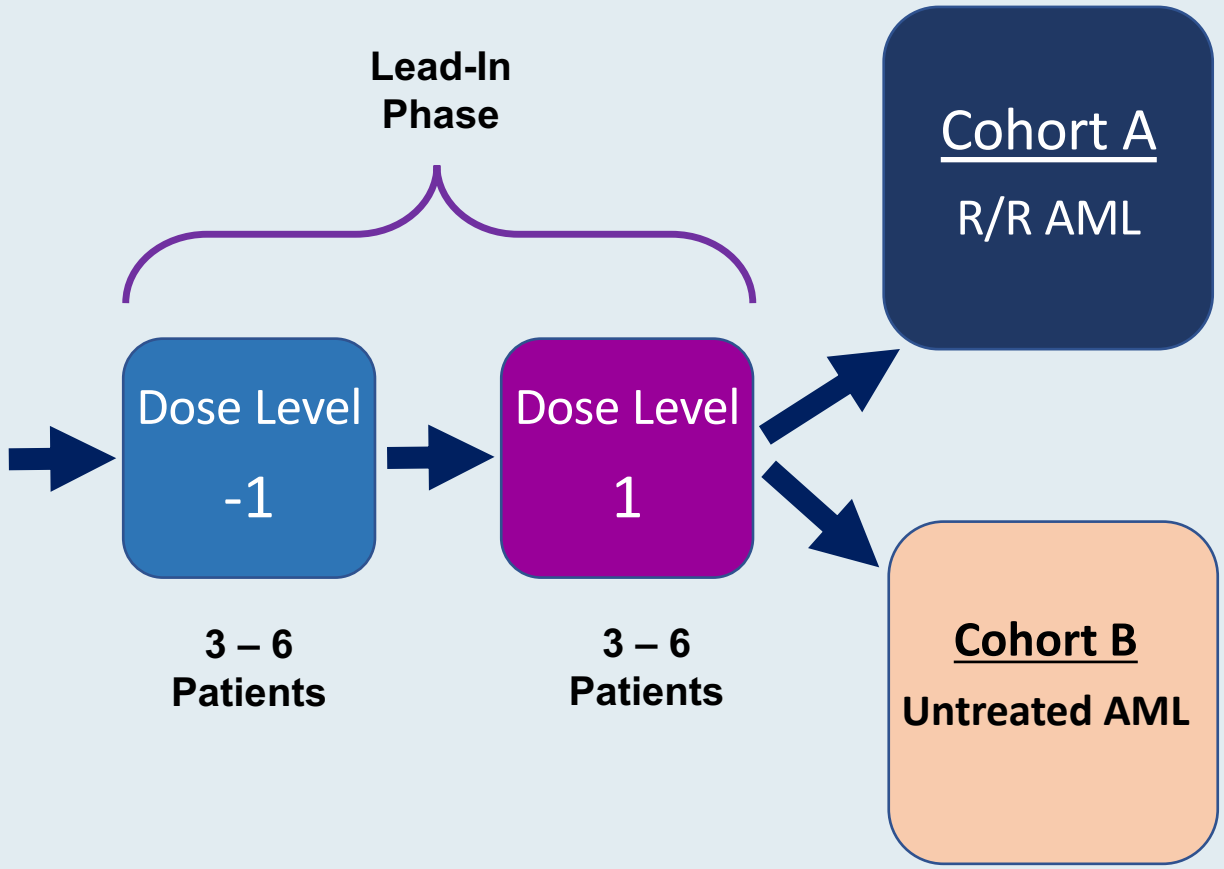
Tapan M. Kadia, Gautam Borthakur, Koichi Takahashi, Courtney Dinardo, Naval Daver, Naveen Pemmaraju, Elias Jabbour, Nitin Jain, Nicholas Short, Wei Qiao, Lade Adewale, Caitlin Rausch, Sherry Pierce, Yesid Alvarado, Amin Alousi, Uday Popat, Issa Khouri, Guillermo Garcia-Manero, Marina Konopleva, Jorge Cortes, Farhad Ravandi, and Hagop Kantarjian.

CPX-351 + Venetoclax in AML

Study Design

Patient Selection

- **Lead in phase:** Patients ≥ 18 years of age with relapsed and/or refractory AML will be eligible.
- **Cohort A (R/R AML):** Patients ≥ 18 years of age with R/R AML.
- **Cohort B (de novo AML):** Patients ≥ **18 to 65** years of age. Patients in this cohort must have received no prior therapy for AML.
- Adequate organ function:
  - Bilirubin ≤ 2mg/dL, AST / ALT ≤ 3 x ULN or ≤ 5 x ULN if related to leukemic involvement
  - creatinine ≤ 1.5 x ULN
  - known cardiac ejection fraction of ≥45% within the past 3 months
- ECOG performance status of ≤ 2.
- Prior Venetoclax allowed in R/R cohorts.



Kadia TM et al. ASH 2020;Abstract 28.

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CPX351 + Venetoclax in AML

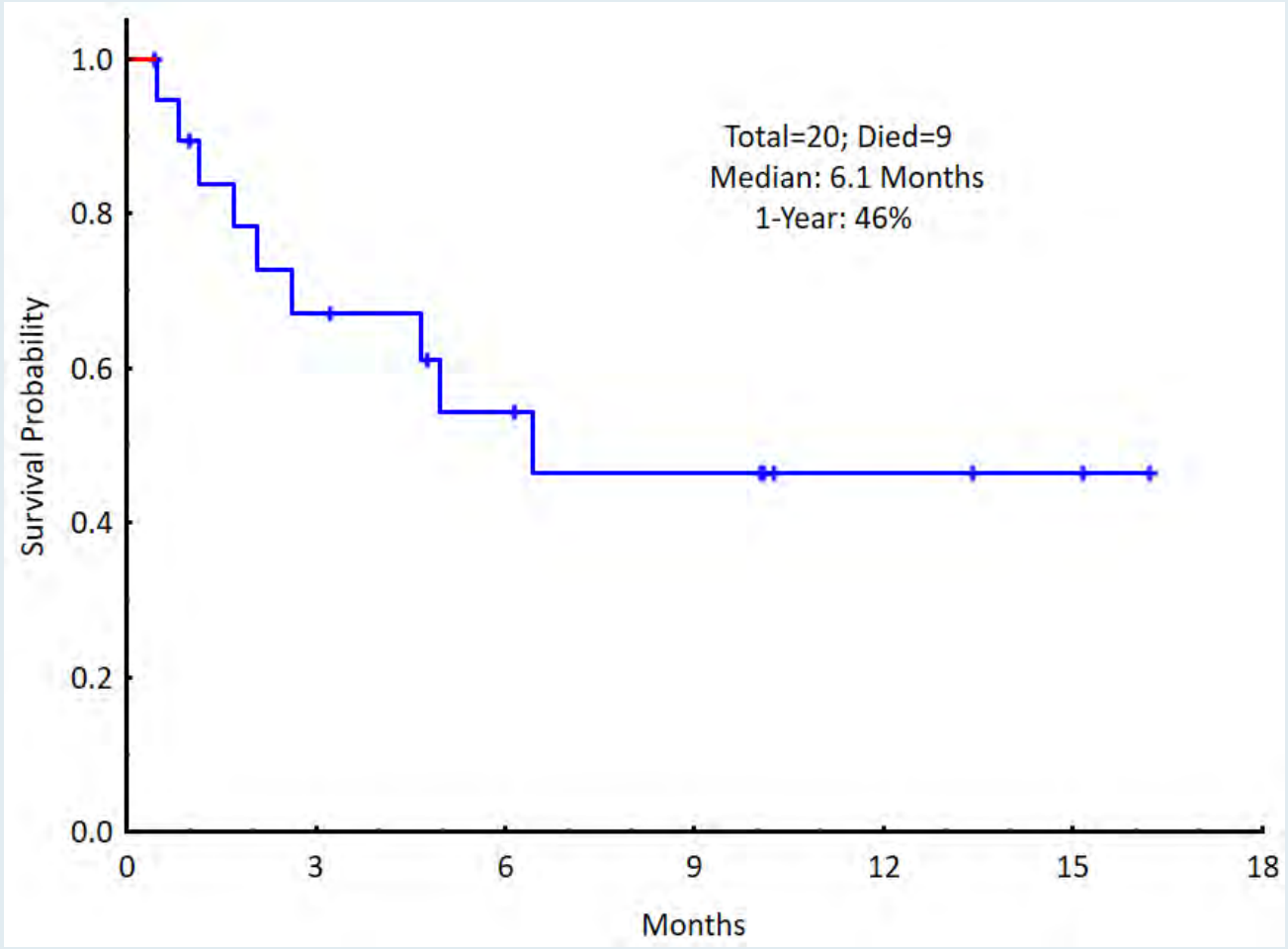
Responses

Response / Outcome	N	%
Evaluable for Response	18	90
CR	1	6
CRi	6	33
MLFS	1	6
ORR	8	44
Died ≤ 4 weeks	2	10
Died ≤ 8 weeks	4	20
Median # of cycles given [Range]	1 [1 – 2]	
Median # of cycles to response	1 [1 – 2]	
No. of Responding Pts Receiving SCT	7	88
Median time to count recover (days)	41 [23 – 60]	

Kadia TM et al. ASH 2020;Abstract 28.

CPX-351 + Venetoclax in AML

Overall Survival



Kadia TM et al. ASH 2020;Abstract 28.

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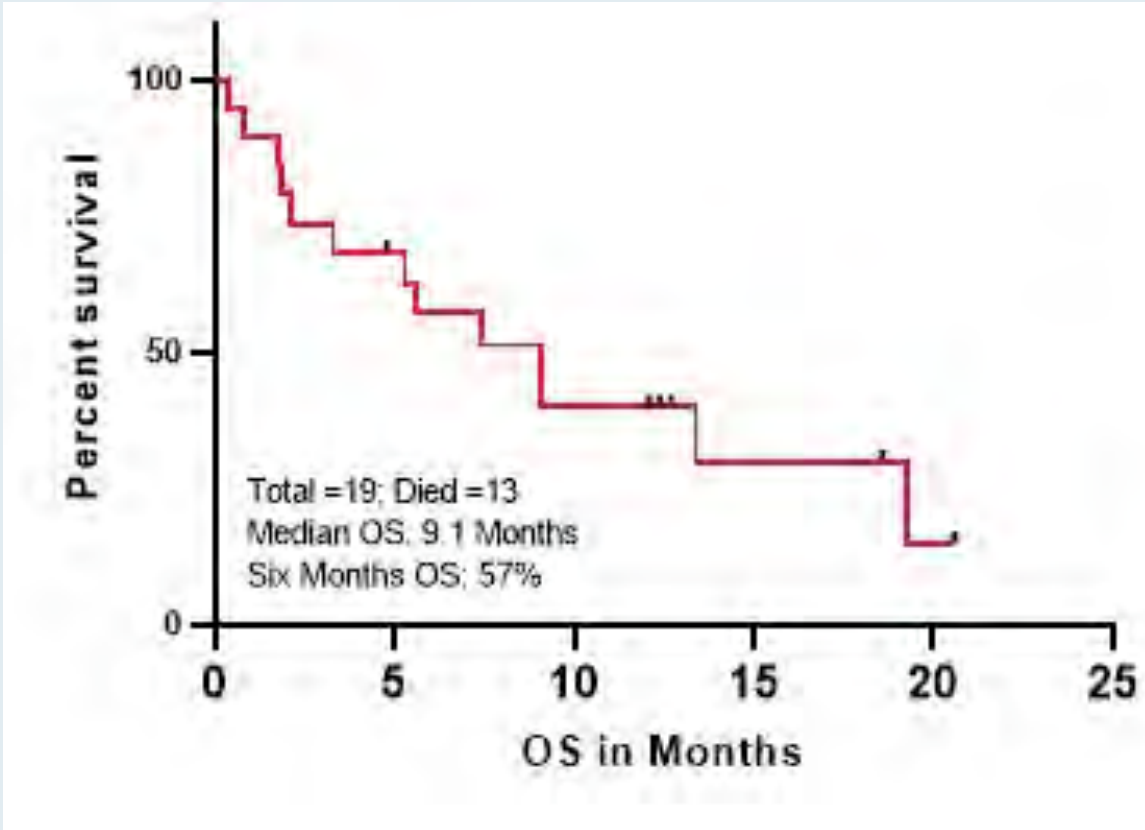
Liposomal Cytarabine and Daunorubicin (CPX-351) in Combination with Gemtuzumab Ozogamicin (GO) in Relapsed Refractory (R/R) Patients with Acute Myeloid Leukemia (AML) and Post-Hypomethylating Agent (Post-HMA) Failure High-Risk Myelodysplastic Syndrome (HR-MDS)

Ramos Perez JM et al.

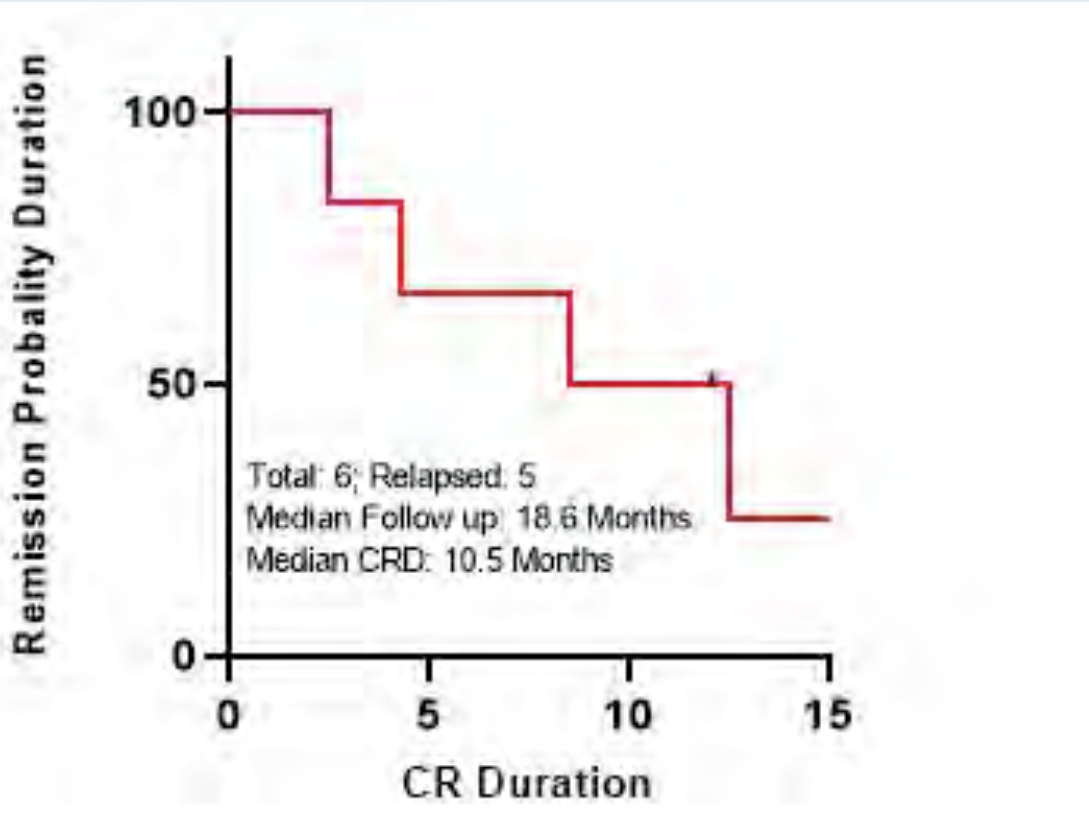
ASH 2020;Abstract 987.

CPX-351 in Combination with Gemtuzumab Ozogamicin in Relapsed/Refractory AML

Overall Survival



Complete Remission Duration



Ramos Perez JM et al. ASH 2020;Abstract 987.

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Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

A Daylong Clinical Summit Hosted in Partnership with Medical Oncology Association of Southern California (MOASC)

Saturday, May 15, 2021

10:30 AM – 6:30 PM ET

(7:30 AM – 3:30 PM Pacific Time)

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This program was recorded before the ASCO 2021 Annual Meeting.

Data from the abstracts presented at this meeting can be accessed at https://meetinglibrary.asco.org/results?meetingView=2021%20ASCO%20Annual%20Meeting.

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Agenda

Module 1 — Breast Cancer: *Drs O'Regan and Traina*

Module 2 — Multiple Myeloma: *Drs Anderson and Raje*

Module 3 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Moskowitz and Sharman*

Module 4 — Genitourinary Cancers: *Drs Bellmunt and Pal*

Module 5 — Gastrointestinal Cancers: *Drs Messersmith and O'Reilly*

Module 6 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Erba and Komrokji*

Module 7 — Lung Cancer: *Drs Camidge and Levy*

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Dr Love — Disclosures

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Research To Practice CME and NCPD Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Lung Cancer Faculty

D Ross Camidge, MD, PhD
Professor of Medicine/Oncology
Joyce Zeff Chair in Lung Cancer Research
Director of Thoracic Oncology
University of Colorado, Anschutz Medical Campus
Denver, Colorado

Benjamin Levy, MD
Associate Professor
Johns Hopkins School of Medicine
Clinical Director
Medical Director, Thoracic Oncology Program
Johns Hopkins Sidney Kimmel Cancer Center at Sibley Memorial
Washington, DC

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Dr Camidge — Disclosures

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Eisai Inc, EMD Serono Inc, GlaxoSmithKline, Helsinn Healthcare SA, Janssen Biotech Inc, Lilly, Mersana Therapeutics, OnKure, Pfizer Inc, Qilu Pharmaceutical Co Ltd, Roche Laboratories Inc, Sanofi Genzyme, Seagen Inc, Takeda Oncology, Turning Point Therapeutics
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP, Bio-Thera Solutions
ILD Adjudication Committee	Daiichi Sankyo Inc
Scientific Advisory Board	Amgen Inc, Anchiano Therapeutics, Apollomics Inc, Elevation Oncology, Kestrel, Nuvalent

Dr Levy — Disclosures

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Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Calithera Biosciences, Daiichi Sankyo Inc, Genentech, a member of the Roche Group

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Contributing Oncologists

Amanda Blackmon, DO, MS
Chief Fellow, Hematology/Oncology
University of California, Irvine
Irvine, California

Farshid Dayyani, MD, PhD
Professor of Clinical Medicine
Division of Hematology/Oncology
Department of Medicine
University of California, Irvine
UCI Health
Orange, California

Gigi Chen, MD
Diablo Valley Oncology and
Hematology Medical Group
Pleasant Hill, California

Michael Polintan Del Rosario, MD
Fellow Physician
Division of Hematology-Oncology
Department of Medicine
University of California, Irvine
Irvine, California

Mamta Choksi, MD
Florida Cancer Specialists and
Research Institute
New Port Richey, Florida

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

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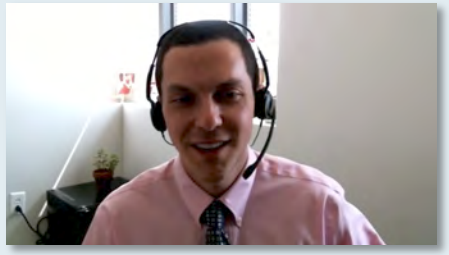
Contributing Oncologists

Rahul Gosain, MD
Division of Hematology and Oncology
Guthrie Corning Cancer Center
Corning, New York

Maen Hussein, MD
Florida Cancer Specialists and
Research Institute
The Villages, Florida

Ranju Gupta, MD
Attending Physician
Co-Director, Cardio-Oncology Program
LVPG Hematology Oncology Associates
Lehigh Valley Health Network
Bethlehem, Pennsylvania



Jeremy Lorber, MD
Attending Hematologist-Oncologist
Tower Hematology Oncology
Cedars-Sinai Medical Center
Beverly Hills, California

Hatim Husain, MD
Physician, University of California San Diego
San Diego, California

Nataliya Mar, MD
Assistant Clinical Professor
Division of Hematology/Oncology
University of California, Irvine
Irvine, California

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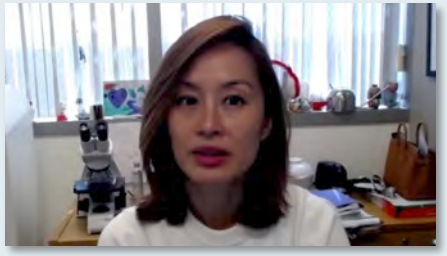
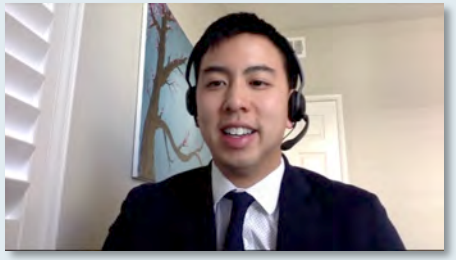
Contributing Oncologists

Mohamed K Mohamed, MD, PhD
Oncology Division Medical Director
Director of Thoracic Oncology
Hematologist/ Medical Oncologist
Cone Health Cancer Center
Greensboro, North Carolina

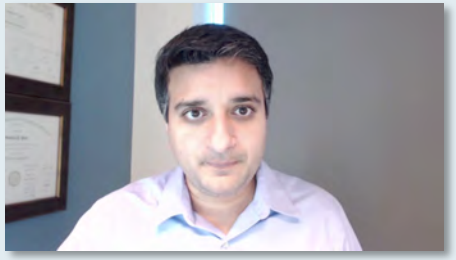


Helen H Moon, MD
Medical Oncologist
Southern California Permanente
Medical Group
Riverside, California

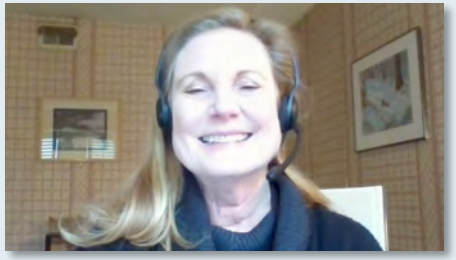
Neil Morganstein, MD
Hematology Oncology
Atlantic Health System
Summit, New Jersey



Anthony Nguyen, MD
Fellow, Loma Linda University Health
Loma Linda, California



Sandip Patel, MD
Associate Professor, Medical Oncology, UCSD
Leader, Experimental Therapeutics
Deputy Director, San Diego Center for
Precision Immunotherapy
San Diego, California



Andrea Stebel, MD
Newport Breast Care
Newport Beach, California

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Agenda

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- Dr Patel: A 57-year-old woman with locally advanced NSCLC
- *Key Recent Publications and Presentations*

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- Dr Patel: A 63-year-old man with extensive-stage SCLC
- *Key Recent Publications and Presentations*

RTP RESEARCH TO PRACTICE

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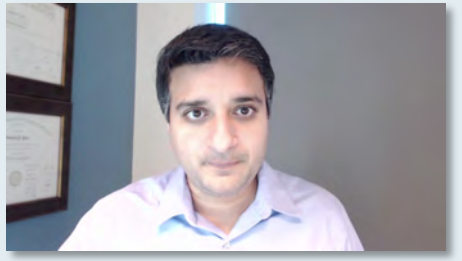
RTP RESEARCH TO PRACTICE

Case Presentation – Dr Patel: A 57-year-old woman with locally advanced NSCLC



Dr Sandip Patel

- Diagnosed with Stage III NSCLC
- Concurrent chemoradiation therapy → Consolidation durvalumab x 1 year
  - Surveillance scans normal past 6 months
- Six months after her last dose of immunotherapy, she presents to the ER with sudden onset blood sugar of 650, creatinine of 4, anti-bet islet antibodies; diabetic ketoacidosis (DKA)
  - Insulin initiated

Questions

- For a patient like this woman who presents to the ER with DKA but has a response to their cancer, how would you manage her now that she is on a stable insulin regimen?
- When do you typically start durvalumab after completion of radiation therapy?

Key Recent Publications and Presentations

- Faivre-Finn C et al. **Four-Year Survival with Durvalumab After Chemoradiotherapy in Stage III NSCLC — An Update from the PACIFIC Trial.** *J Thorac Oncol* 2021;16(5):860-67.
- Saito et al. **Real-World Survey of Pneumonitis/Radiation Pneumonitis Among Patients with Locally Advanced Non-Small Cell Lung Cancer Treated with Chemoradiotherapy After Durvalumab Approval: A Multicenter Retrospective Cohort Study (HOPE-005/CRIMSON).** ASCO 2020;Abstract 9039.
- Thomas T et al. **Evaluation of the Incidence of Pneumonitis in United States Veterans with Non-Small Cell Lung Cancer Receiving Durvalumab Following Chemoradiation.** ASCO 2020;Abstract 9034.
- Reck M et al. **Pembrolizumab plus Platinum Chemotherapy and Radiotherapy in Unresectable, Locally Advanced, Stage III NSCLC (KEYNOTE-799).** IASLC WCLC 2020;Abstract 0A02.03.

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J Thorac Oncol 2021;16(5):860-67.

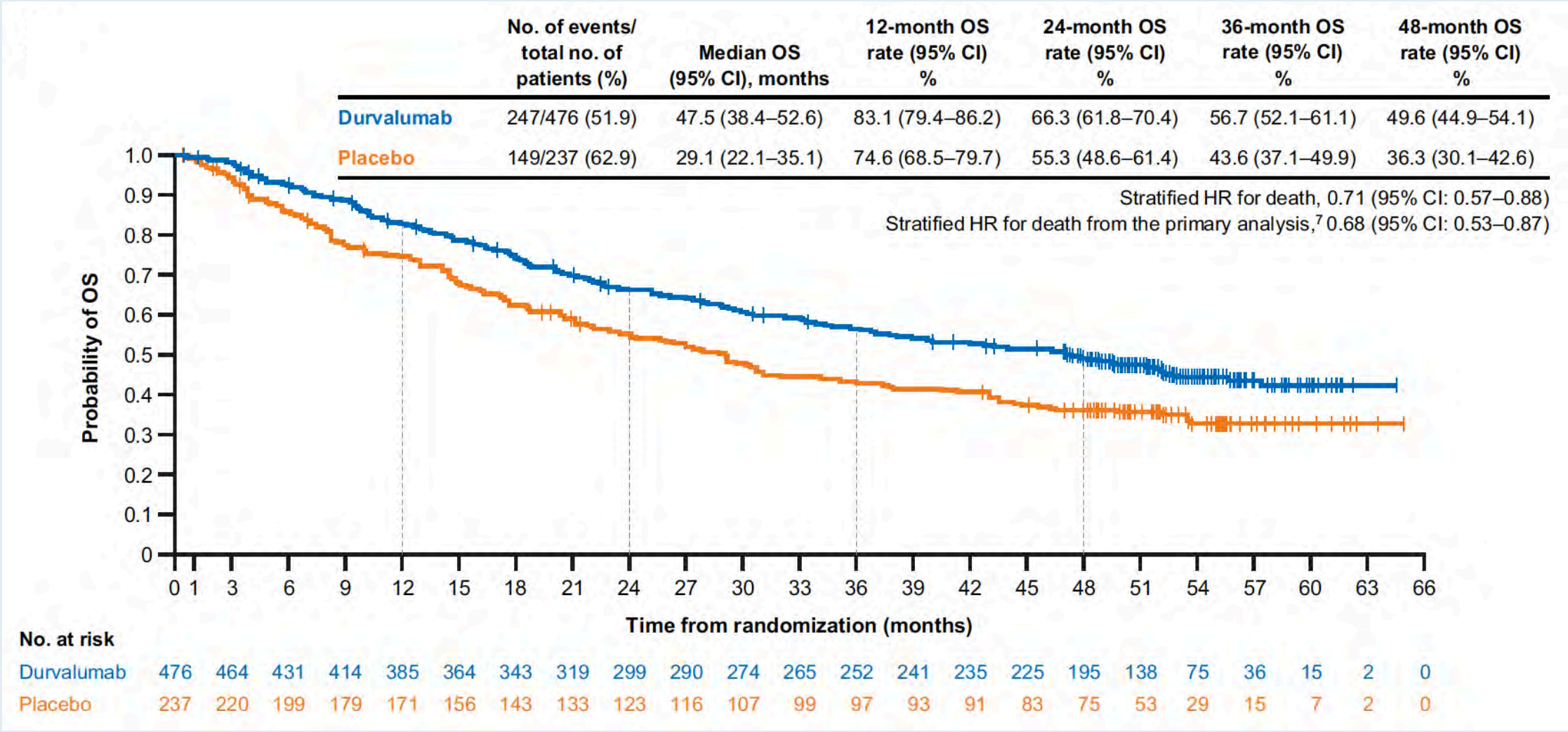
BRIEF REPORT

Four-Year Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC—an Update From the PACIFIC Trial

Corinne Faivre-Finn, MD, PhD,[a,b,*] David Vicente, MD,[c] Takayasu Kurata, MD,[d] David Planchard, MD, PhD,[e] Luis Paz-Ares, MD, PhD,[f,g] Johan F. Vansteenkiste, MD, PhD,[h] David R. Spigel, MD,[i] Marina C. Garassino, MD,[j] Martin Reck, MD, PhD,[k] Suresh Senan, PhD,[l] Jarushka Naidoo, MBBCH, MHS,[m,n] Andreas Rimner, MD,[o] Yi-Long Wu, MD,[p] Jhanelle E. Gray, MD,[q] Mustafa Özgüroğlu, MD,[r] Ki H. Lee, MD,[s] Byoung C. Cho, MD, PhD,[t] Terufumi Kato, MD,[u] Maike de Wit, MD, PhD,[v] Michael Newton, PharmD,[w] Lu Wang, PhD,[w] Piruntha Thiyagarajah, MD,[x] Scott J. Antonia, MD, PhD[q]

PACIFIC: 4-Year Overall Survival – Intent-To-Treat Population

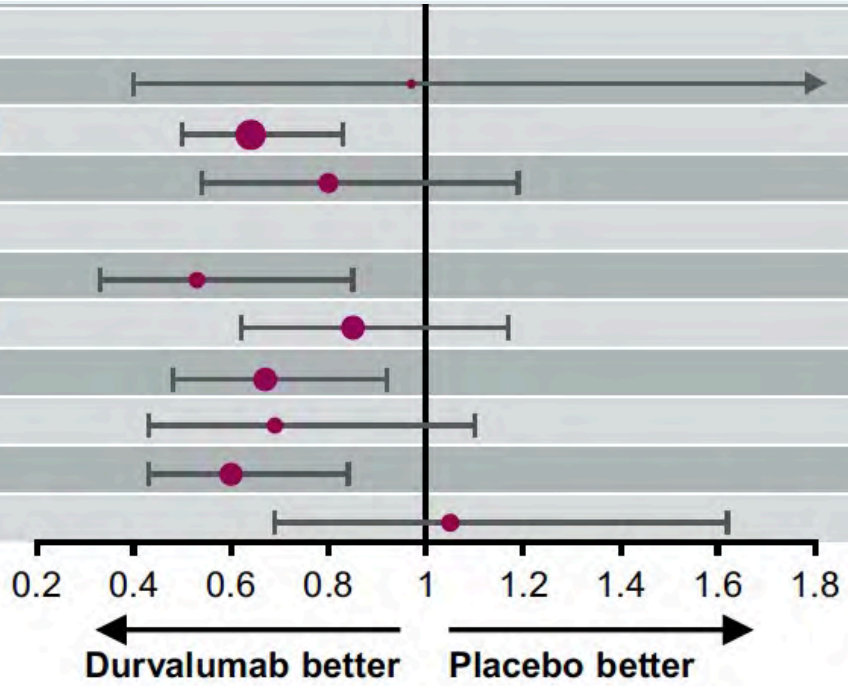
	No. of events/ total no. of patients (%)	Median OS (95% CI), months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %	48-month OS rate (95% CI) %
Durvalumab	247/476 (51.9)	47.5 (38.4–52.6)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	56.7 (52.1–61.1)	49.6 (44.9–54.1)
Placebo	149/237 (62.9)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.6 (37.1–49.9)	36.3 (30.1–42.6)



Faivre-Finn C et al. *J Thorac Oncol* 2021;16(5):860-67.

PACIFIC: 4-Year Overall Survival by EGFR and PD-L1 Status

	No. of events / No. of patients (%)		Unstratified HR (95% CI)
	Durvalumab	Placebo	
***EGFR* mutation**			
Positive	17/29 (58.6%)	7/14 (50.0%)	0.97 (0.40–2.33)
Negative	156/317 (49.2%)	105/165 (63.6%)	0.64 (0.50–0.83)
Unknown	74/130 (56.9%)	37/58 (63.8%)	0.80 (0.54–1.19)
PD-L1 status			
≥25%	50/115 (43.5%)	26/44 (59.1%)	0.53 (0.33–0.85)
<25%	102/187 (54.5%)	62/105 (59.0%)	0.85 (0.62–1.17)
Unknown	95/174 (54.6%)	61/88 (69.3%)	0.67 (0.48–0.92)
1–24% (post hoc analysis)	47/97 (48.5%)	28/47 (59.6%)	0.69 (0.43–1.10)
≥1% (post hoc analysis)	97/212 (45.8%)	54/91 (59.3%)	0.60 (0.43–0.84)
<1% (post hoc analysis)	55/90 (61.1%)	34/58 (58.6%)	1.05 (0.69–1.62)



Faivre-Finn C et al. *J Thorac Oncol* 2021;16(5):860-67.

Real-World Rates of Pneumonitis After Consolidation Durvalumab

Real-World Survey of Pneumonitis/Radiation Pneumonitis in LA-NSCLC After Approval of Durvalumab: HOPE-005/CRIMSON Retrospective Cohort Study

- >80% developed pneumonitis
- More than half of them were asymptomatic, but 5% needed HOT and 1.5% developed fatal pneumonitis
- V20 was an independent risk factor for symptomatic pneumonitis (Grade ≥2)
- With careful consideration, durvalumab rechallenge could be an option after corticosteroid therapy for pneumonitis

Incidence of Pneumonitis in US Veterans with NSCLC Receiving Durvalumab After Chemoradiation Therapy

- In this real-world cohort, clinically significant pneumonitis was
  - More frequent compared to clinical trial reports
    - Asymptomatic infiltrates on imaging: 39.8%
    - Clinically significant pneumonitis: 21.1%
      - Grade 2 (7.3%), Grade 3 (11.4%), Grade 4 (1.6%), Grade 5 (0.8%)
  - Not associated with increased risk of death

Saito et al. ASCO 2020;Abstract 9039. Thomas T et al. ASCO 2020;Abstract 9034.

RTP RESEARCH TO PRACTICE

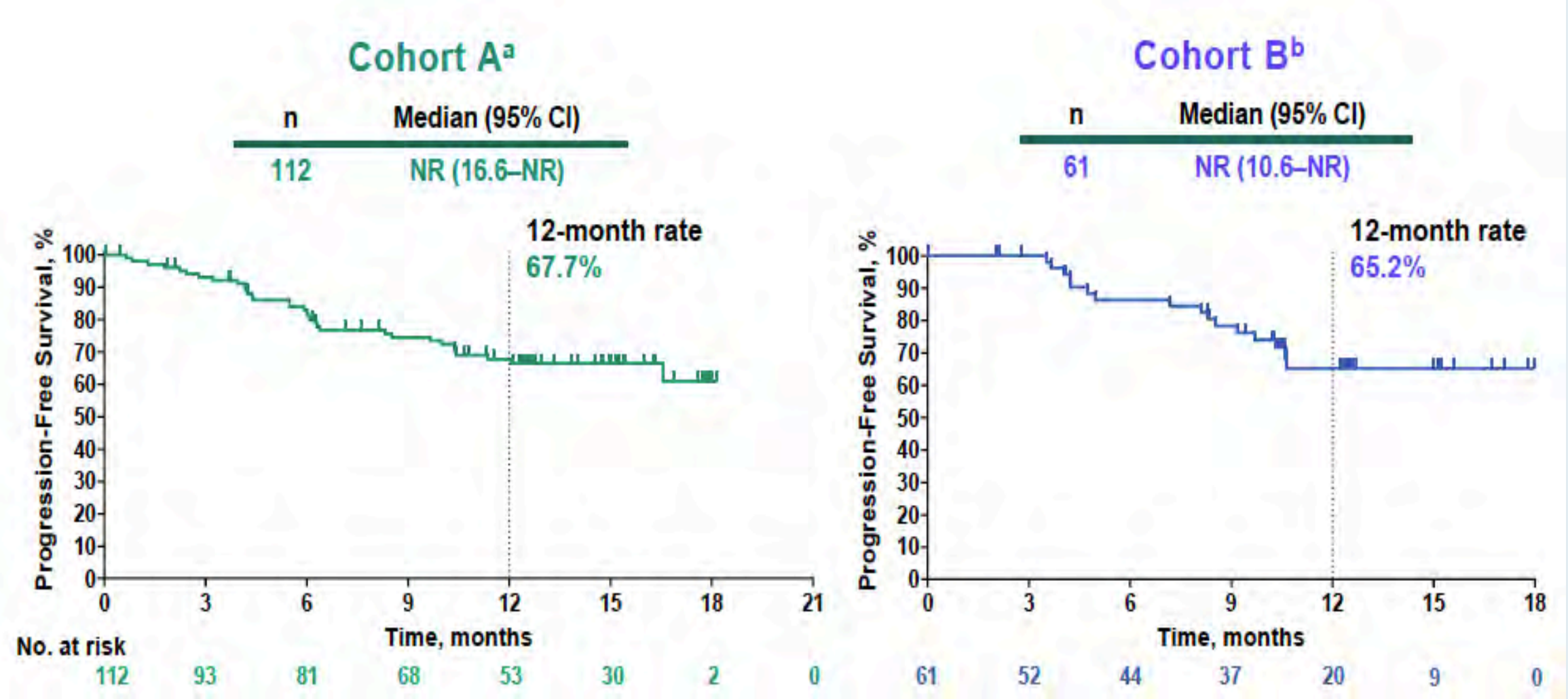
IASLC/WCLC 2020;Abstract 0A02.03.

Pembrolizumab Plus Platinum Chemotherapy and Radiotherapy in Unresectable, Locally Advanced, Stage III NSCLC: KEYNOTE-799

M. Reck,[1] K.H. Lee,[2] N. Frost,[3] D.M. Kowalski,[4] V. Breder,[5] T. Pollock,[6] N. Reguart,[7] B. Houghton,[8] X. Quantin,[9] S.M. Keller,[10] H. Liu,[10] B. Piperdi,[10] S.K. Jabbour[11]

[1]LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [2]Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, South Korea; [3]Department of Infectious Diseases and Respiratory Medicine, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; [4]The Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [5]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [6]Southwestern Regional Medical Center, Inc., Cancer Treatment Centers of America, Tulsa, OK, USA; [7]Hospital Clínic de Barcelona, Barcelona, Spain; [8]Mid North Coast Cancer Institute, Port Macquarie Base Hospital, Port Macquarie, NSW, Australia; [9]Department of Medical Oncology, Montpellier Cancer Institute, Montpellier, France; [10]Merck & Co., Inc., Kenilworth, NJ, USA; [11]Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ, USA

KEYNOTE-799: Progression-Free Survival



Reck M et al. IASLC/WCLC 2020;Abstract 0A02.03.

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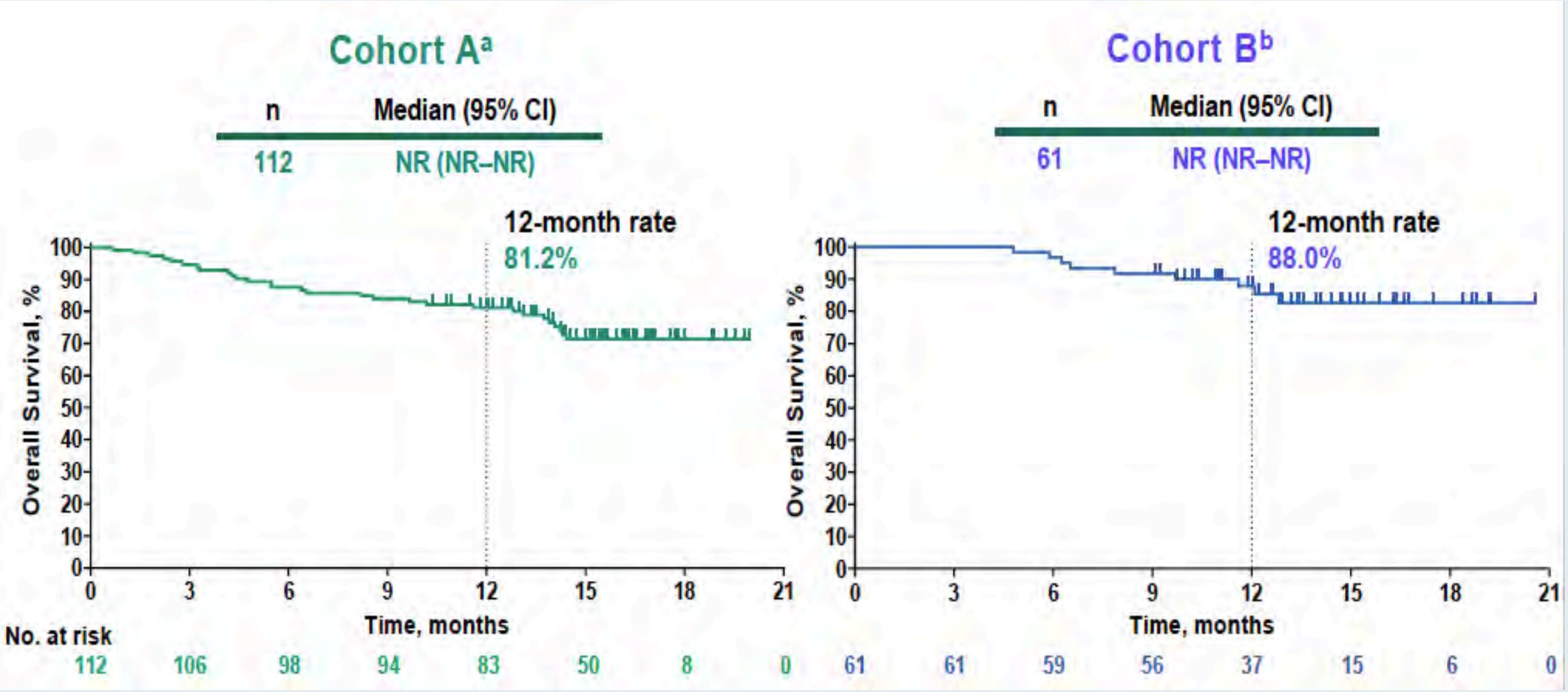
KEYNOTE-799: Overall Survival



Reck M et al. IASLC/WCLC 2020;Abstract 0A02.03.

Pivotal Phase III IMpower010 Trial Demonstrates DFS Improvement with Adjuvant Atezolizumab for Resectable Early-Stage Lung Cancer

Press Release — March 22, 2021

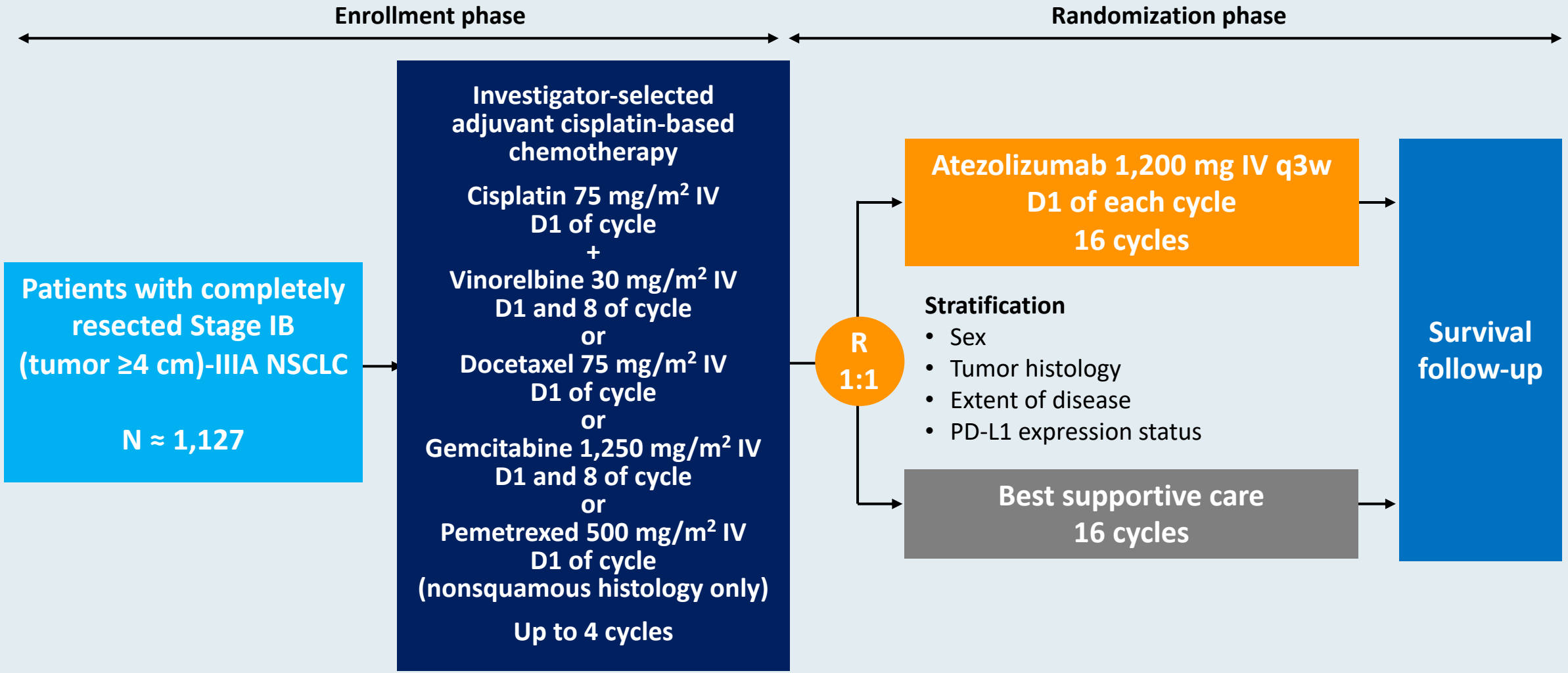
"Today [it was] announced that the Phase III IMpower010 study evaluating atezolizumab, compared with best supportive care (BSC), met its primary endpoint of disease-free survival (DFS) at the interim analysis. Atezolizumab showed a statistically significant improvement in DFS as adjuvant therapy following surgery and chemotherapy in all randomized Stage II-IIIA populations with non-small cell lung cancer (NSCLC). The magnitude of DFS benefit was particularly pronounced in the PD-L1-positive population.

Follow-up will continue with planned analyses of DFS in the overall intent-to-treat (ITT) population, which at the time of analysis did not cross the threshold, and overall survival (OS) data, which were immature at the time of interim analysis. Safety for atezolizumab was consistent with its known safety profile and no new safety signals were identified. Results from the IMpower010 study will be presented at an upcoming medical meeting and submitted to health authorities globally, including the US Food and Drug Administration and the European Medicines Agency."

https://www.businesswire.com/news/home/20210321005036/en/

RTP RESEARCH TO PRACTICE

IMpower010: Phase III Trial Design



Primary endpoint: Disease-free survival (DFS)

Secondary endpoints include overall survival, 3- and 5-year DFS rates, safety and tolerability

Wakelee HA et al. ASCO 2017;Abstract TPS8576.

IMpower010: Primary Results of a Phase III Global Study of Atezolizumab versus Best Supportive Care After Adjuvant Chemotherapy in Resected Stage IB-IIIA Non-Small Cell Lung Cancer (NSCLC)

Wakelee HA et al.
ASCO 2021;Abstract 8500.

Saturday, June 5, 1:30 PM - 4:30 PM EDT

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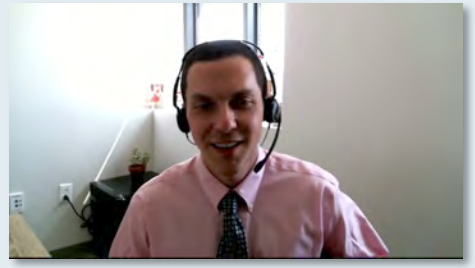
RTP RESEARCH TO PRACTICE

Case Presentation – Dr Lorber: A 66-year-old man with metastatic adenocarcinoma of the lung – PD-L1 60%, TMB 14 mut/Mb



Dr Jeremy Lorber

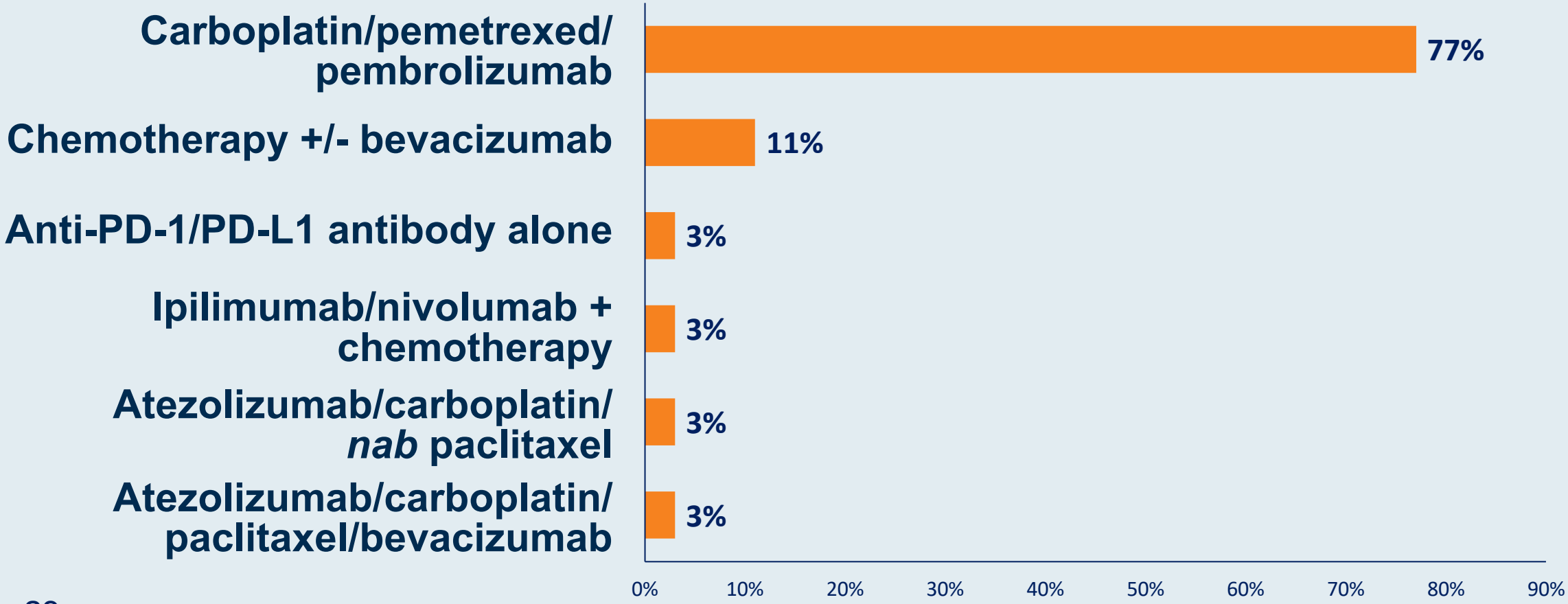
- Presented with highly symptomatic malignant pleural and pericardial effusion
- Lung mass biopsy: consistent with non-small cell adenocarcinoma
  - PD-L1 60%, TMB 14 mut/Mb
  - No driver mutations
- Pembrolizumab with a near complete response lasting 28 months
- Developed progression of lung mass and a single vertebral metastasis
- RT to vertebra metastasis, added carboplatin/pemetrexed to pembrolizumab

Questions

- Given his prolonged response to checkpoint inhibitor therapy, should it continue to be included as part of his second-line therapy?

RTP RESEARCH TO PRACTICE

Which first-line treatment regimen would you recommend for a 65-year-old patient with metastatic nonsquamous lung cancer, no identified targetable mutations and a PD-L1 TPS of 0%?



N = 29

Survey of live webinar audience

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations*

- Ramalingam SS et al. **Nivolumab + Ipilimumab versus Platinum-Doublet Chemotherapy as First-Line Treatment for Advanced Non-Small Cell Lung Cancer: Three-Year Update from CheckMate 227 Part 1**. ASCO 2020;Abstract 9500.
- Paz-Ares L et al. **First-Line Nivolumab plus Ipilimumab Combined with Two Cycles of Chemotherapy in Patients with Non-Small-Cell Lung Cancer (CheckMate 9LA): An International, Randomised, Open-Label, Phase 3 Trial.** *Lancet Oncol* 2021;22(2):198-211.
- Boyer M et al. **Pembrolizumab plus Ipilimumab or Placebo for Metastatic Non-Small-Cell Lung Cancer with PD-L1 Tumor Proportion Score ≥ 50%: Randomized, Double-Blind Phase III KEYNOTE-598 Study.** *J Clin Oncol* 2021;[Online ahead of print].
- Sezer A et al. **Cemiplimab Monotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer with PD-L1 of at Least 50%: A Multicentre, Open-Label, Global, Phase 3, Randomised, Controlled Trial**. *Lancet* 2021;397(10274):592-604.

***Summarized in table format**

RTP RESEARCH TO PRACTICE

FDA-Approved Immunotherapy Combination Options for First-Line Therapy

Combination regimen	FDA approval	Pivotal study	Histologic type	HR (OS)
Pembrolizumab + Platinum and pemetrexed[1]	8/20/18	KEYNOTE-189	Nonsquamous	0.49
Pembrolizumab + Carboplatin, paclitaxel or *nab* paclitaxel[2]	10/30/18	KEYNOTE-407	Squamous	0.64
Atezolizumab + Carboplatin and paclitaxel and bevacizumab[3]	12/6/18	IMpower150	Nonsquamous	0.78
Atezolizumab + Carboplatin and *nab* paclitaxel[4]	12/3/19	IMpower130	Nonsquamous	0.79
Nivolumab + Ipilimumab[5]	5/15/20	CheckMate-227	PD-L1 TPS ≥1, EGFR and/or ALK wt	0.62
Nivolumab + Ipilimumab and chemotherapy[6]	5/26/20	CheckMate-9LA	EGFR and/or ALK wt	0.69

[1] Gandhi. *NEJM* 2018. [2] Paz-Ares.*NEJM* 2018. [3] Socinski *NEJM* 2018. [4] West. *Lancet Oncol* 2019. [5] Hellmann. *N Engl J Med* 2019. [6] Reck. ASCO 2020;Ab 9501.

FDA-Approved Immunotherapy Monotherapy Options for First-Line Therapy (continued)

Monotherapy	FDA approval	Pivotal study	Histologic type	HR (OS)
Pembrolizumab[1,2]	4/11/19 10/24/16	KEYNOTE-042 KEYNOTE-024	PD-L1 TPS ≥1%	0.63
Atezolizumab[3]	5/18/20	IMpower110	PD-L1 TPS ≥50, EGFR and/or ALK wt	0.59
Cemiplimab[4]	2/22/2021	EMPOWER-Lung 1 (Study 1624)	PD-L1 TPS ≥50, EGFR and/or ALK and/or ROS1 wt	0.57

[1] Mok. *Lancet* 2019. [2] Reck. *J Clin Oncol* 2019. [3] Spigel. ESMO 2019;Ab LBA78. [4] Sezer. *Lancet* 2021.

FDA Approves Cemiplimab-rwlc Monotherapy for NSCLC with High PD-L1 Expression

Press Release – February 22, 2021

"The Food and Drug Administration approved cemiplimab-rwlc for the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) (locally advanced who are not candidates for surgical resection or definitive chemoradiation or metastatic) whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] > 50%) as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations.

Efficacy was evaluated in Study 1624 (NCT03088540), a multi-center, randomized, open-label trial in 710 patients with locally advanced NSCLC who were not candidates for surgical resection or definitive chemoradiation or with metastatic NSCLC. Patients were randomized (1:1) to receive cemiplimab-rwlc 350 mg intravenously every 3 weeks for up to 108 weeks or a platinum-based chemotherapy. The main efficacy outcome measures were overall survival (OS) and progression-free survival (PFS) per blinded independent central review (BICR)."

www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-cemiplimab-rwlc-non-small-cell-lung-cancer-high-pd-l1-expression

Durvalumab and Tremelimumab with Chemotherapy Demonstrate Overall Survival Benefit in POSEIDON Trial for First-Line Stage IV NSCLC

Press Release — May 7, 2021

"Positive high-level results from the final analysis of POSEIDON showed the combination of durvalumab, tremelimumab and chemotherapy demonstrated a statistically significant and clinically meaningful overall survival (OS) benefit versus chemotherapy alone. This immunotherapy combination also demonstrated a statistically significant improvement in progression-free survival (PFS) versus chemotherapy alone, as previously reported in October 2019. Patients in this arm were treated with a short course of tremelimumab, an anti-CTLA4 antibody, over a 16-week period in addition to durvalumab and standard chemotherapy.

The durvalumab plus chemotherapy arm demonstrated a statistically significant improvement in PFS versus chemotherapy in the previous analysis, but the OS trend observed in this analysis did not achieve statistical significance. Patients in the control arm were treated with up to six cycles of chemotherapy, while those in the experimental arms were treated with up to four cycles.

Each combination demonstrated an acceptable safety profile, and no new safety signals were identified. The combination with tremelimumab delivered a broadly similar safety profile to the durvalumab and chemotherapy combination and did not lead to an increased discontinuation of treatment."

https://www.astrazeneca.com/media-centre/press-releases/2021/imfinzi-and-tremelimumab-showed-survival-in-poseidon.html

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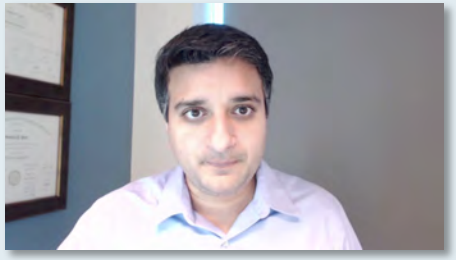
Case Presentation – Dr Patel: A 47-year-old woman with metastatic adenocarcinoma of the lung and asymptomatic brain metastases – EGFR exon 19 mutation



Dr Sandip Patel

- Newly diagnosed metastatic lung adenocarcinoma
  - >50 brain metastases but is asymptomatic
- Biopsy: Insufficient tissue for next-generation, PD-L1 50%
- Sent cfDNA for testing: EGFR exon 19 mutation
- Osimertinib
  - MRI after 1 month: Two remaining metastases, which were decreased in size

Questions

- For a patient who's asymptomatic but with 2 to 3 CNS metastases, what is your preferred strategy for managing those brain metastases?
- What is your preferred management of some of the chronic side effects associated with EGFR TKIs, such as the paronychia, dermatitis and diarrhea?

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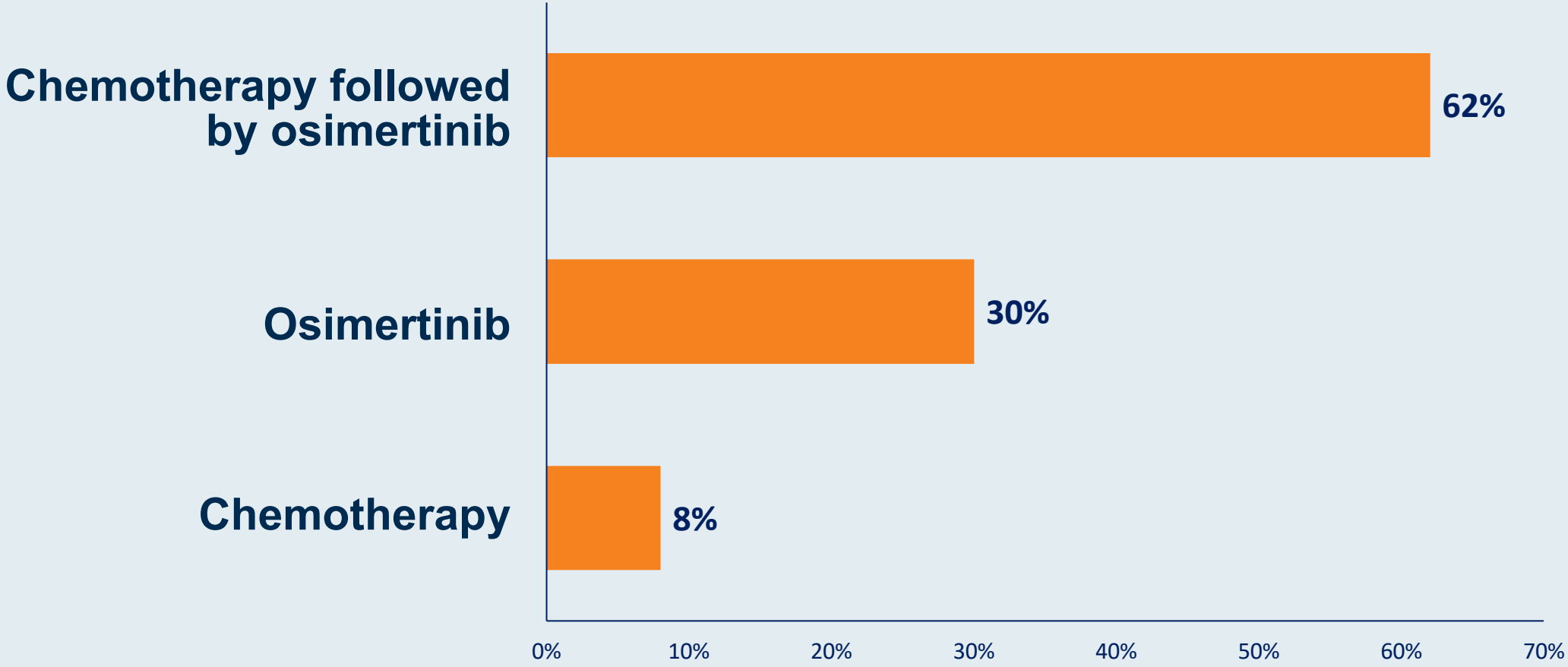
Regulatory and reimbursement issues aside, which adjuvant systemic therapy would you generally recommend for a patient with Stage IIB nonsquamous NSCLC and an EGFR exon 19 deletion?



N = 74

Survey of live webinar audience

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Key Recent Publications and Presentations

- Wu YL et al. **Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer.** *N Engl J Med* 2020;383(18):1711-23.
- Soria JC et al. **Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer.** *N Engl J Med* 2018;378(2):113-25.
- Yang JCH et al. **Osimertinib in Patients with Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer and Leptomeningeal Metastases: The BLOOM Study.** *J Clin Oncol* 2020;38(6):538-47.
- Sabari JK et al. **Amivantamab in Post-platinum EGFR Exon 20 Insertion Mutant Non-Small Cell Lung Cancer.** IASCL WCLC 2020;Abstract OA04.04.
- Smit EF et al. **Trastuzumab Deruxtecan in HER2-Mutated Metastatic Non-Small Cell Lung Cancer (NSCLC): Interim Results of DESTINY-Lung01.** WCLC 2021;Abstract MA11.03.
- Nakagawa K et al. **Trastuzumab Deruxtecan in HER2-Overexpressing Metastatic Non-Small Cell Lung Cancer (NSCLC): Interim Results of DESTINY-Lung01.** WCLC 2021;Abstract OA04.05.

FDA Approves Osimertinib as Adjuvant Therapy for NSCLC with EGFR Mutations

Press Release — December 18, 2020

- The FDA approved osimertinib as adjuvant therapy after tumor resection in patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- Efficacy was demonstrated in the randomized, double-blind, placebo-controlled ADAURA trial for patients with EGFR exon 19 deletions or exon 21 L858R mutation-positive NSCLC who had complete tumor resection, with or without prior adjuvant chemotherapy.
- Eligible patients with resectable tumors (stage IB – IIIA) were required to have predominantly non-squamous histology and EGFR exon 19 deletions or exon 21 L858R mutations identified prospectively from tumor tissue in a central laboratory EGFR Mutation Test.

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-osimertinib-adjuvant-therapy-non-small-cell-lung-cancer-egfr-mutations

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The NEW ENGLAND JOURNAL of MEDICINE

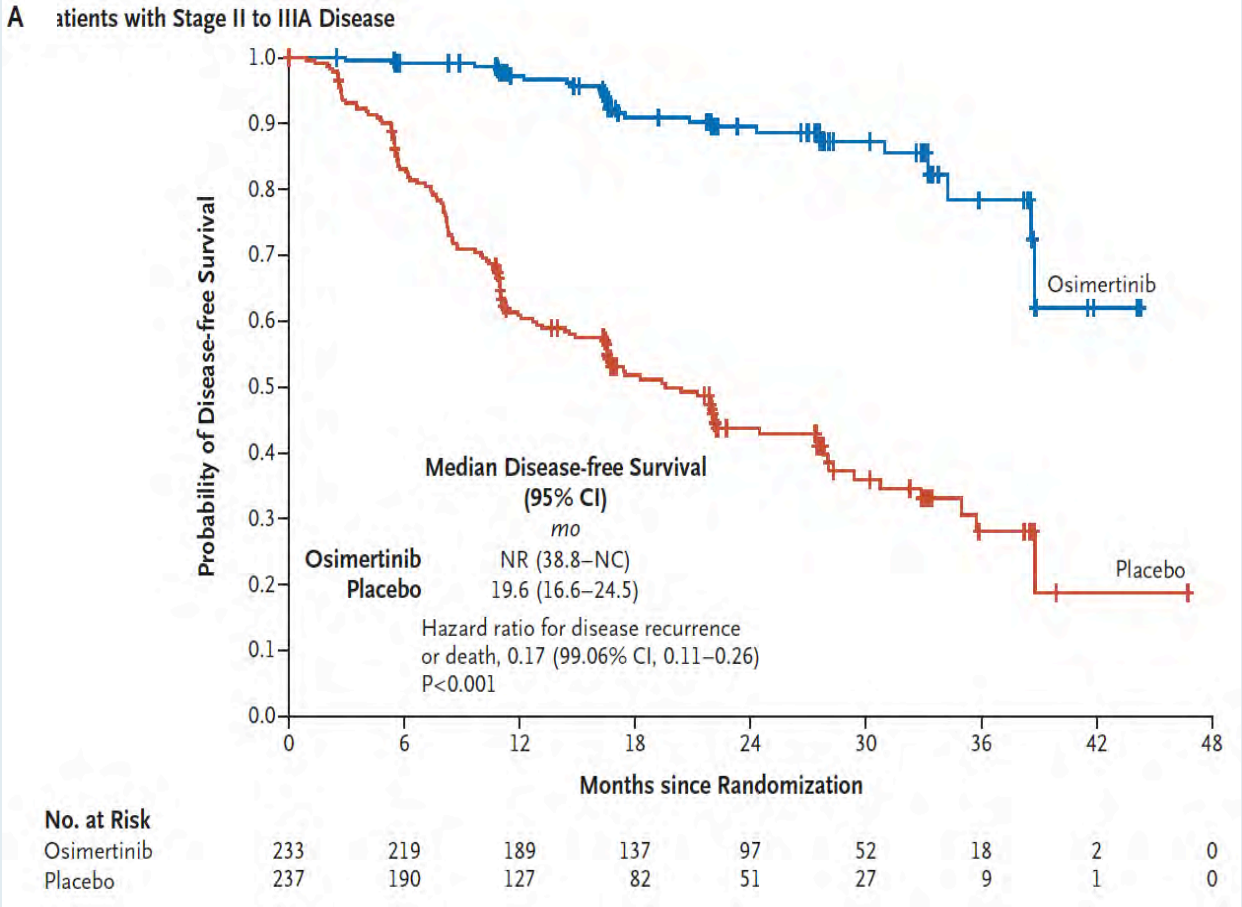
ORIGINAL ARTICLE

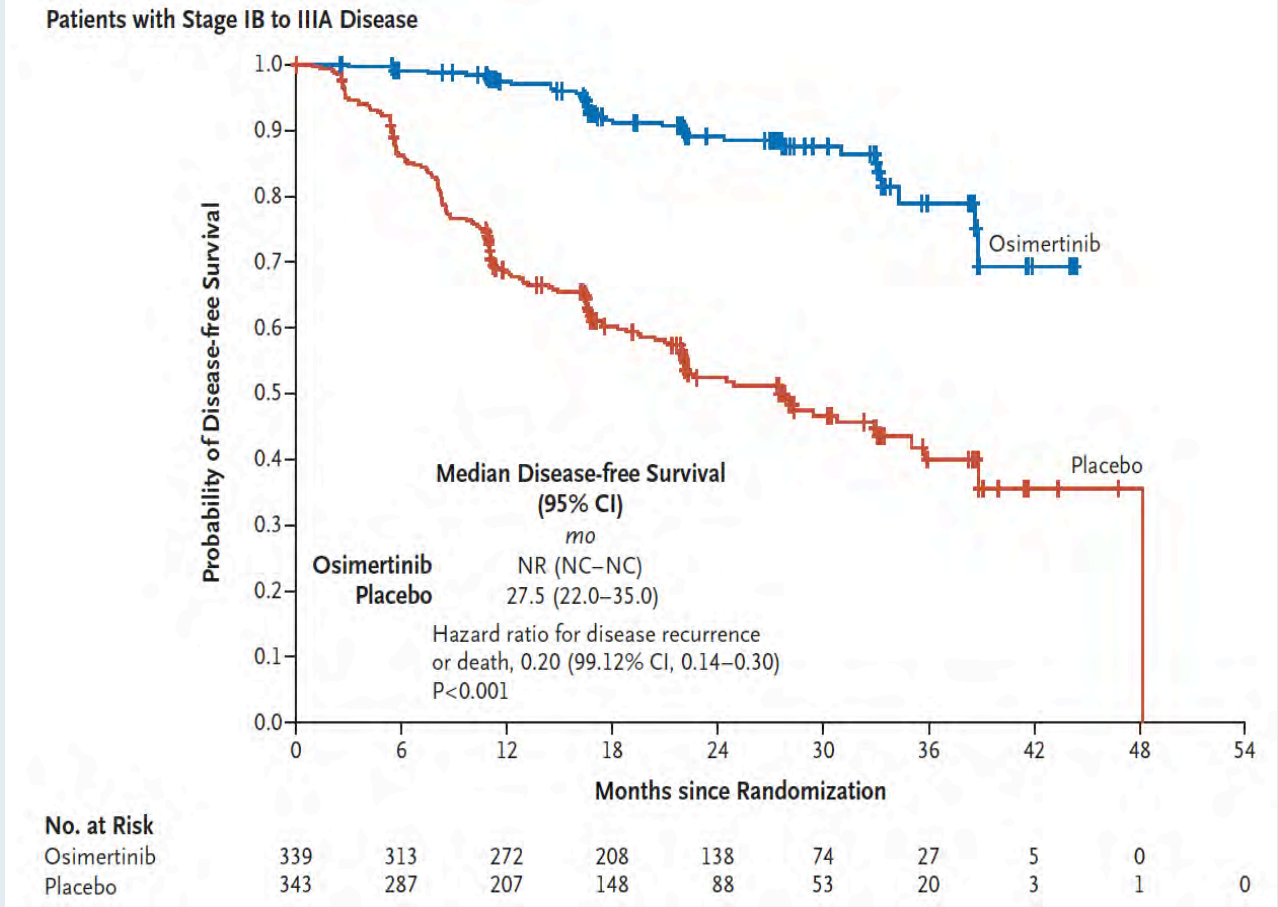
Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., Kye-Young Lee, M.D., Ph.D., Charuwan Akewanlop, M.D., Chong-Jen Yu, M.D., Ph.D., Filippo de Marinis, M.D., Laura Bonanno, M.D., Manuel Domine, M.D., Ph.D., Frances A. Shepherd, M.D., Lingmin Zeng, Ph.D., Rachel Hodge, M.Sc., Ajlan Atasoy, M.D., Yuri Rukazenkov, M.D., Ph.D., and Roy S. Herbst, M.D., Ph.D.,

N Engl J Med 2020;383)18):1711-23.

ADAURA: Disease-Free Survival by Stage





Wu YL et al. *N Engl J Med* 2020;383(18):1711-23.

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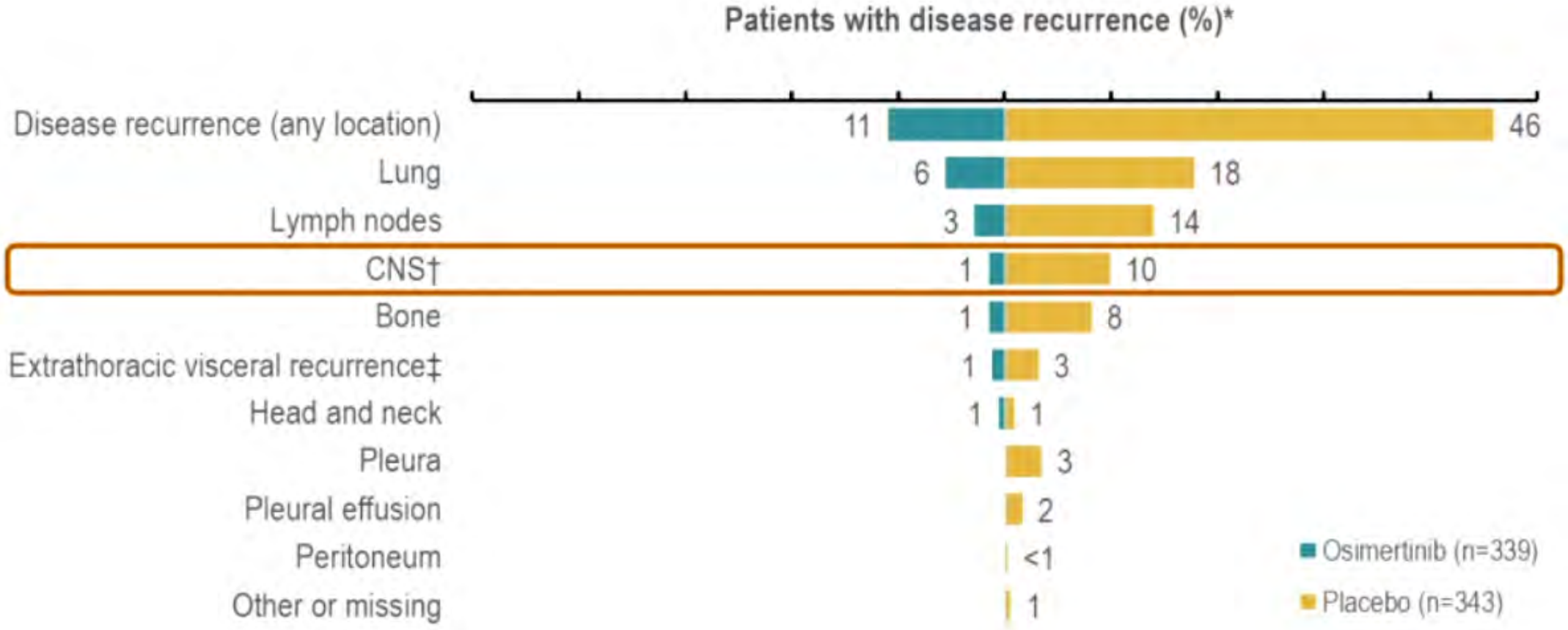
ADAURA: Sites of Disease Recurrence



Tsuboi M et al. ESMO 2020;Abstract LBA1.

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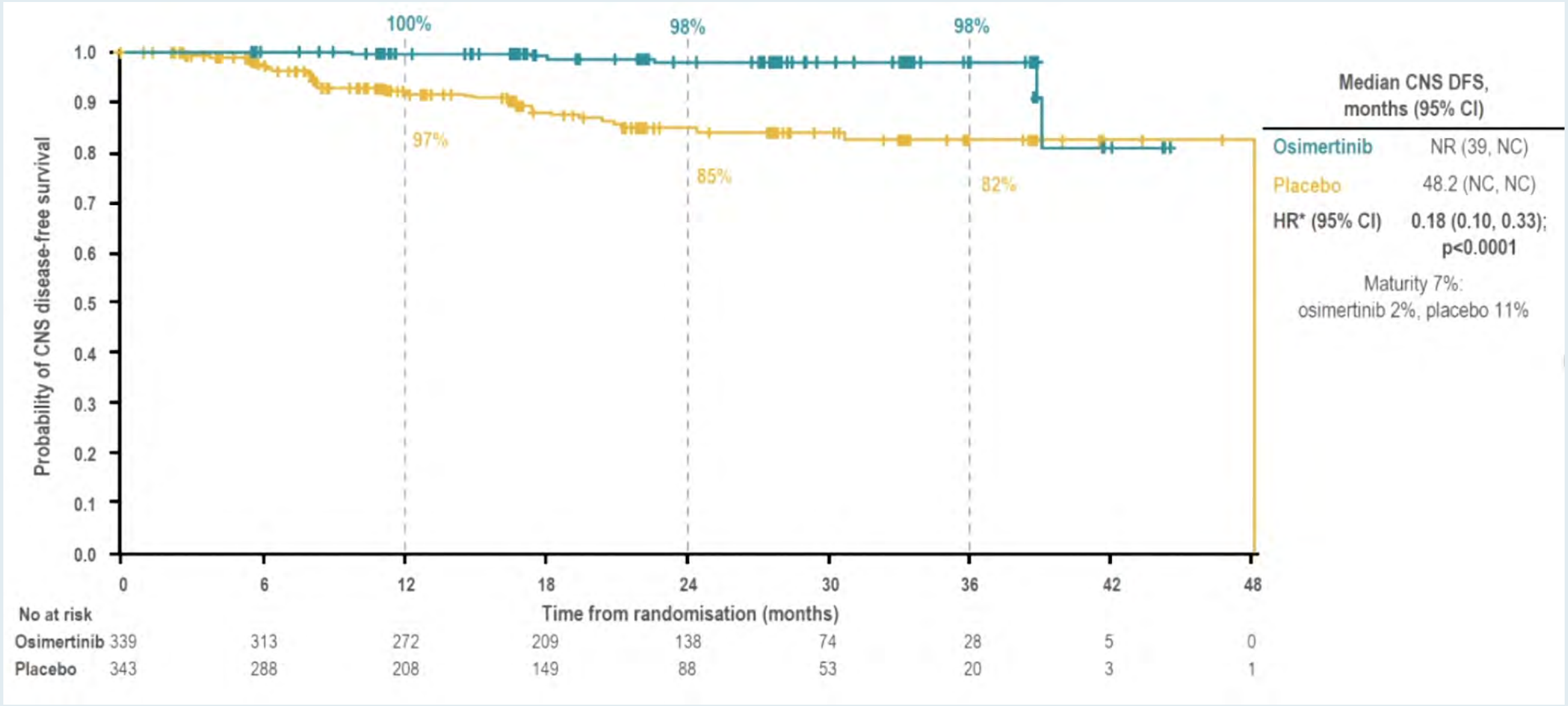
ADAURA: CNS DFS Events

- Overall, 45 patients (osimertinib n=6, placebo n=39) had CNS DFS events

	Overall population	
Patients, n (%)	**Osimertinib n=339**	**Placebo n=343**
CNS DFS events:	6 (2%)	39 (11%)
CNS recurrence	4 (1%)	33 (10%)
Death	2 (1%)	6 (2%)

Tsuboi M et al. ESMO 2020;Abstract LBA1.

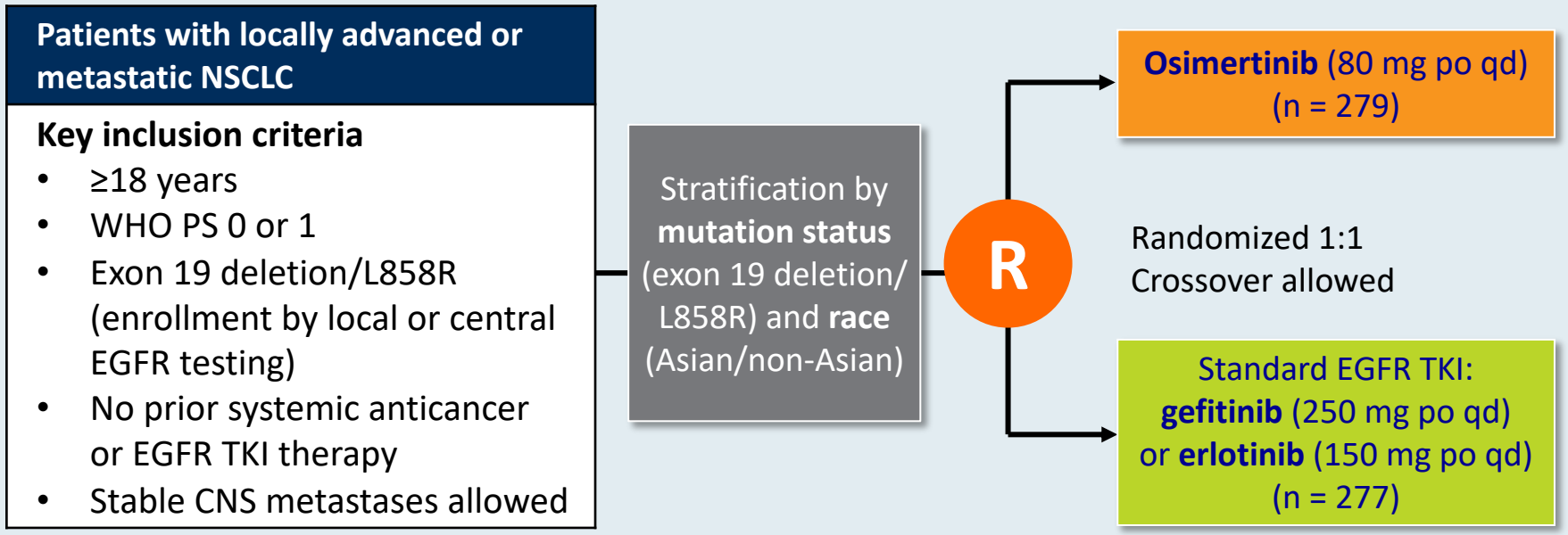
ADAURA: CNS DFS in Overall Population



Tsuboi M et al. ESMO 2020;Abstract LBA1.

RTP RESEARCH TO PRACTICE

FLAURA: A Phase III Study of Osimertinib versus Gefitinib or Erlotinib as First-Line Treatment for Advanced NSCLC with EGFR Tumor Mutation



Primary endpoint: Progression-free survival (PFS) based on investigator assessment (per RECIST 1.1)
Key secondary endpoints: Objective response rate, overall survival and quality of life

NSCLC= non-small cell lung cancer; TKI = tyrosine kinase inhibitor

www.clinicaltrials.gov. March 2020; Soria JC et al. *N Engl J Med* 2018;378(2):113-25.

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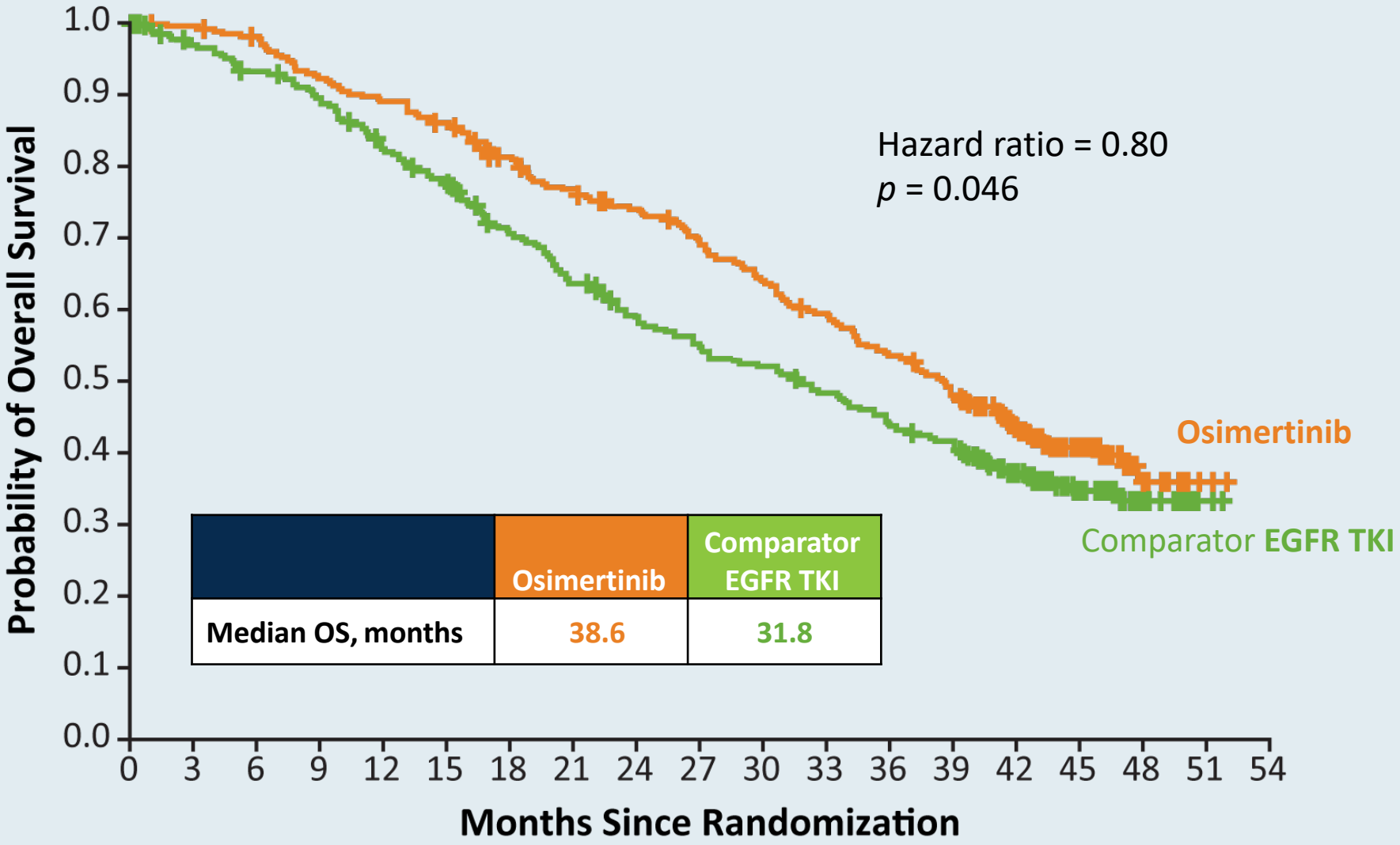
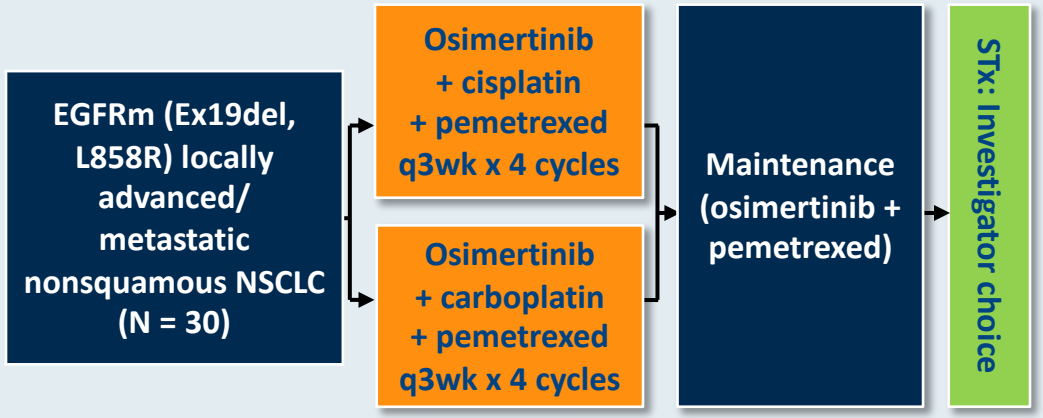
FLAURA: Final Overall Survival Analysis



Ramalingam SS et al. *N Engl J Med* 2020;382(1):41-50.

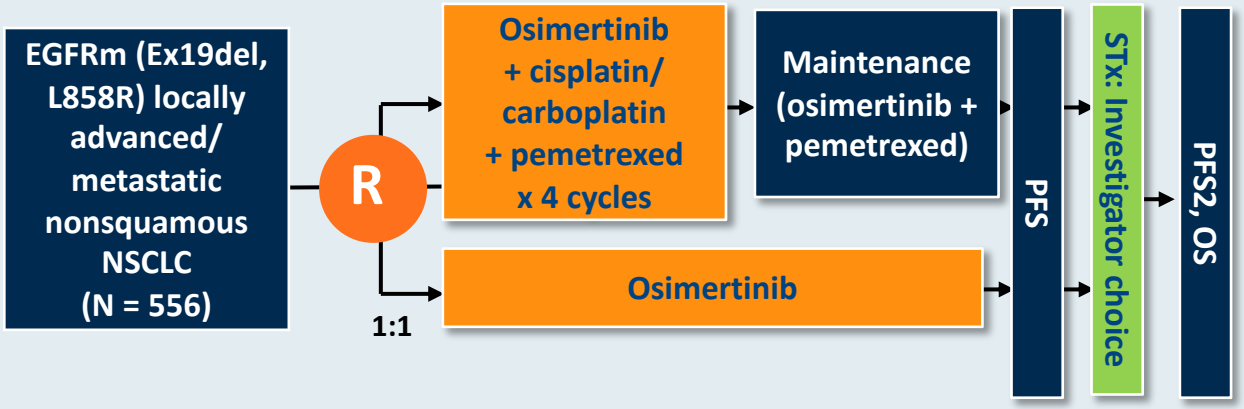
FLAURA2 Study Design: Safety Run-In and Randomization Phases

Study design: Safety run-in phase



- Osimertinib dose is 80 mg daily during induction and maintenance
- Selection of cisplatin or carboplatin is the investigator's choice
- Safety parameters are primary endpoints

Study design: Randomization phase



- Osimertinib given at a dose of 80 mg daily during induction and maintenance
- Osimertinib dose can be reduced to 40 mg daily for management of AEs; chemotherapy dose interruption/reduction is to be prioritized over osimertinib reduction/interruption
- Randomization will be stratified by race (Asian versus non-Asian), WHO PS (0 vs 1) and tissue EGFR mutation test at enrollment
- Involvement planned for approximately 248 sites in 27 countries

EGFR = epidermal growth factor receptor; EGFRm = EGFR mutation; Ex19del = exon 19 deletion; STx = subsequent treatment; PFS2 = time from randomization to second disease progression or death on a subsequent treatment; OS = overall survival; WHO = World Health Organization

Jänne PA et al. IASLC 2019;Abstract OA07.01.

rapid communications

Osimertinib in Patients With Epidermal Growth Factor Receptor Mutation–Positive Non–Small-Cell Lung Cancer and Leptomeningeal Metastases: The BLOOM Study

James C.H. Yang, MD, PhD[1]; Sang-We Kim, MD, PhD[2]; Dong-Wan Kim, MD, PhD[3]; Jong-Seok Lee, MD, PhD[4]; Byoung Chul Cho, MD, PhD[5]; Jin-Seok Ahn, MD, PhD[6]; Dae H. Lee, MD, PhD[2]; Tae Min Kim, MD[3]; Jonathan W. Goldman, MD[7]; Ronald B. Natale, MD[8]; Andrew P. Brown, MSc, MPhil[9]; Barbara Collins, PhD[9]; Juliann Chmielecki, PhD[10]; Karthick Vishwanathan, PhD[1,10]; Ariadna Mendoza-Naranjo, PhD[9]; and Myung-Ju Ahn, MD, PhD[6]

J Clin Oncol 2020;38(6):538-47.

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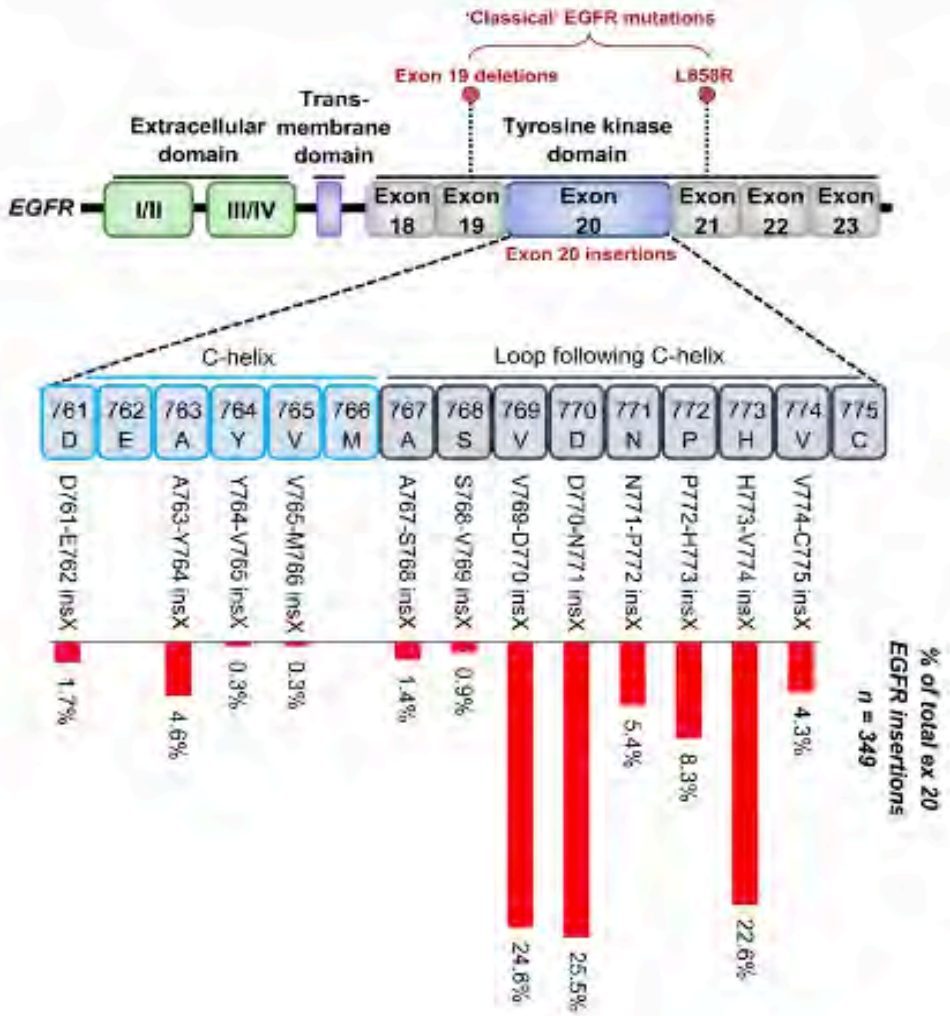
BLOOM: Osimertinib in Patients with NSCLC with an EGFR Mutation and Leptomeningeal Metastases (LM)

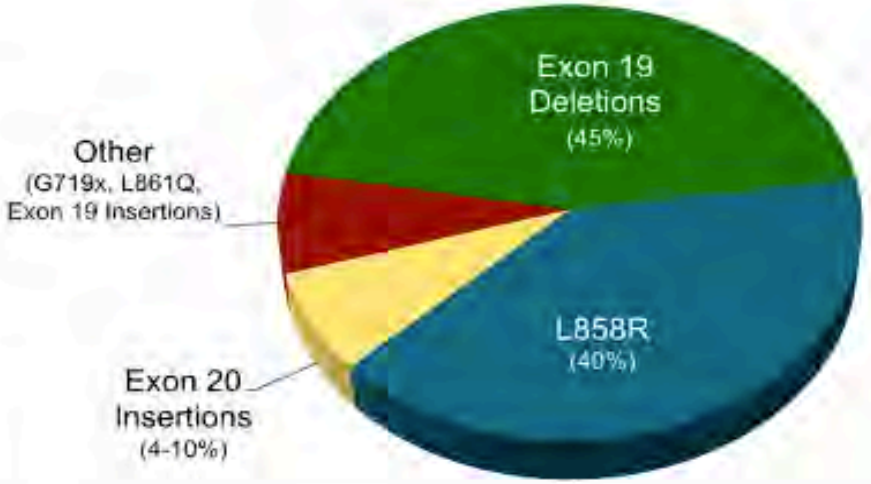
Patients with cytologically confirmed LM received osimertinib 160 mg once daily.

	Leptomeningeal metastases (N = 37)
ORR by BICR	62%
Complete response	32%
Partial response	30%
Stable disease ≥ 6 weeks	32%
Progression	3%
Not evaluable	3%
Median DoR	15.2 months

Yang JCH et al. *J Clin Oncol* 2020;38(6):538-47.

Frequency of EGFR Exon 20 Mutations





Exon 20 NSCLC: US and China				
		Exon 20 Frequency	Total Number of NSCLC Patients/year	
United States	EGFR HER2	2.1% 1.5%	3.6%	7700
China	EGFR HER2	2.4% 3.9%	6.3%	41100

Courtesy of Zosia Piotrowska, MD.

Emerging Targeted Therapies for EGFR Exon 20 Mutations

Drug	MOA	N	ORR	mPFS	Major toxicities	Discont due to toxicities	FDA Status re Exon 20
Poziotinib[1,2]	TKI	115	15%	4.2 mo	Diarrhea Rash	12%	Fast track designation March 2021
Mobocertinib[3,4]	TKI	28	43%	7.3 mo	Diarrhea Rash Nausea	14%	Breakthrough therapy designation April 2020
Amivantamab[5,6]	EGFR/MET Ab	39	36%	8.3 mo	Rash Infusion reaction Paronychia	6%	Breakthrough therapy designation March 2020
Osimertinib[7]	TKI	17	24%	9.6 mo	Diarrhea Rash Platelets	6%	No indication in Exon 20
CLN-081[8]	TKI	22	35%	NR	Rash Stomatitis	0%	Investigational

1. Le X. AACR 2020, 2. Socinski M. ESMO 2020; 3. Riely G. ESMO 2020; 4. Zhou C. IASLC 2020; 5. Park K. ASCO 2020; 6. Sabari JK. IASLC 2020; 7. Piotrowska Z. ASCO 2020; 8. Piotrowska Z. ESMO 2020.

IASLC | 2020 World Conference on Lung Cancer Singapore
wclc2020.IASLC.com | #WCLC20
CONQUERING THORACIC CANCERS WORLDWIDE

Amivantamab in Post-platinum EGFR Exon 20 Insertion Mutant Non-small Cell Lung Cancer

Joshua K. Sabari[1], Catherine A. Shu[2], Keunchil Park[3], Natasha B. Leighl[4], Paul Mitchell[5], Sang-We Kim[6], Jong-Seok Lee[7], Dong-Wan Kim[8], Santiago Viteri[9], Alexander I. Spira[10], Ji-Youn Han[11], José Trigo[12], Chee Khoon Lee[13], Ki Hyeong Lee[14], Nicolas Girard[15], Tsung-Ying Yang[16], Koichi Goto[17], Rachel E. Sanborn[18], James Chih-Hsin Yang[19], Joshua C. Curtin[20], John Xie[20], Amy Roshak[20], Meena Thayu[20], Roland E. Knoblauch[20], Byoung Chul Cho[21]

IASLC/WCLC 2020;Abstract OA04.04

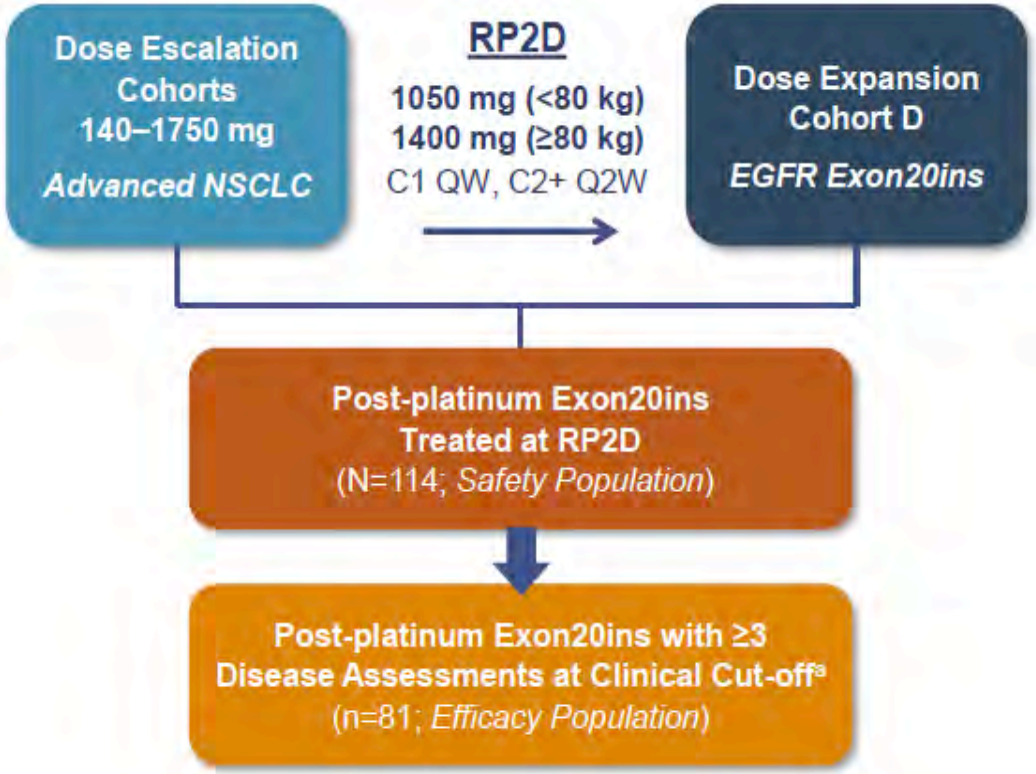
CHRYSALIS Study Design: Postplatinum Exon 20 Insertion Population

Key Objectives

- Dose escalation: Establish RP2D
- Dose expansion: Assess safety and efficacy at RP2D

Key Eligibility Criteria for Post-platinum Population

- Metastatic/unresectable NSCLC
- EGFR Exon20ins mutation
- Progressed on platinum-based chemotherapy



Efficacy End Points

Primary

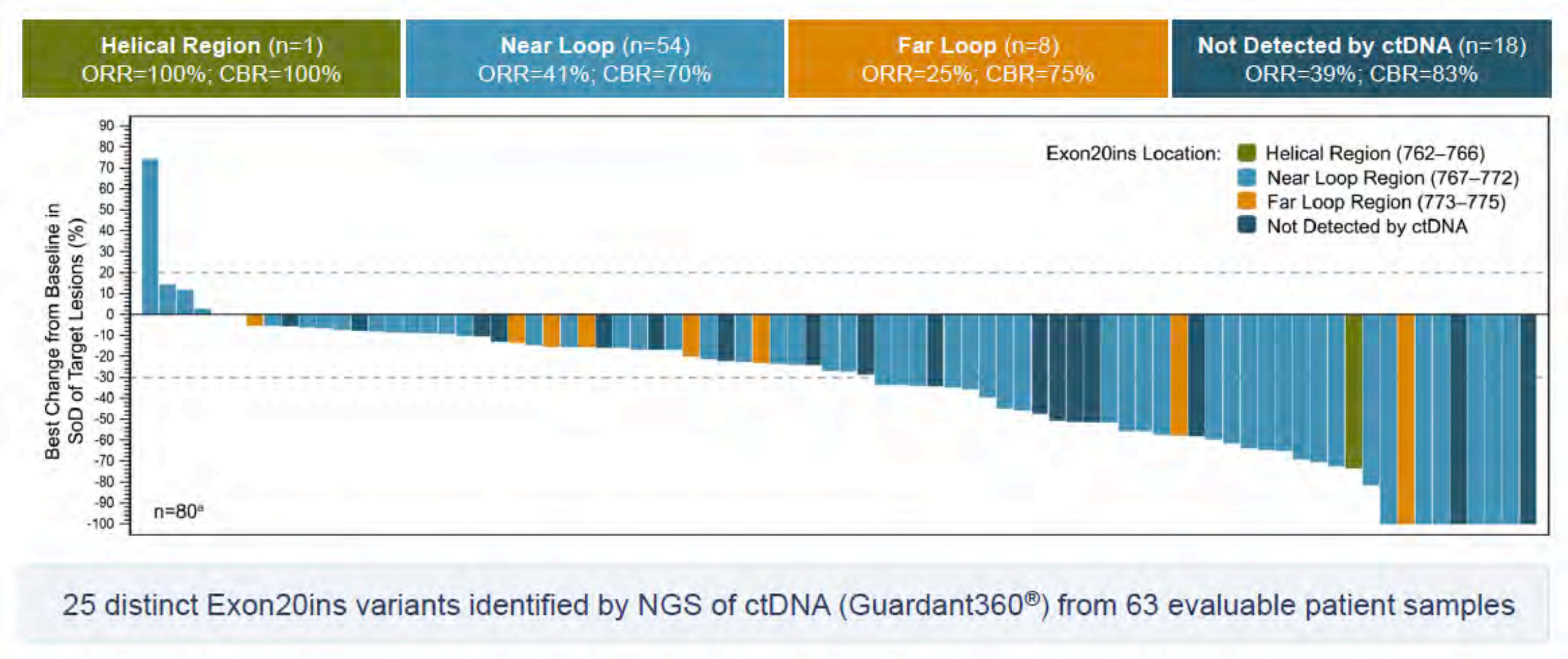
- Overall response rate per RECIST v1.1

Key Secondary

- Clinical benefit rate
- Duration of response
- Progression-free survival
- Overall survival

Sabari JK et al. IASLC WCLC 2020;Abstract OA04.04.

CHRYSALIS: Best ORR by Insertion Region of Exon 20



Sabari JK et al. IASLC WCLC 2020;Abstract OA04.04.

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Amivantamab in Combination with Lazertinib for the Treatment of Osimertinib-Relapsed, Chemotherapy-Naïve EGFR Mutant (EGFRm) Non-Small Cell Lung Cancer (NSCLC) and Potential Biomarkers for Response

Bauml J et al.
ASCO 2021;Abstract 9006.

Saturday, June 5, 1:30 PM - 4:30 PM EDT

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Trastuzumab Deruxtecan in HER2-Mutated Metastatic Non-Small Cell Lung Cancer (NSCLC): Interim Results of DESTINY-Lung01[1]

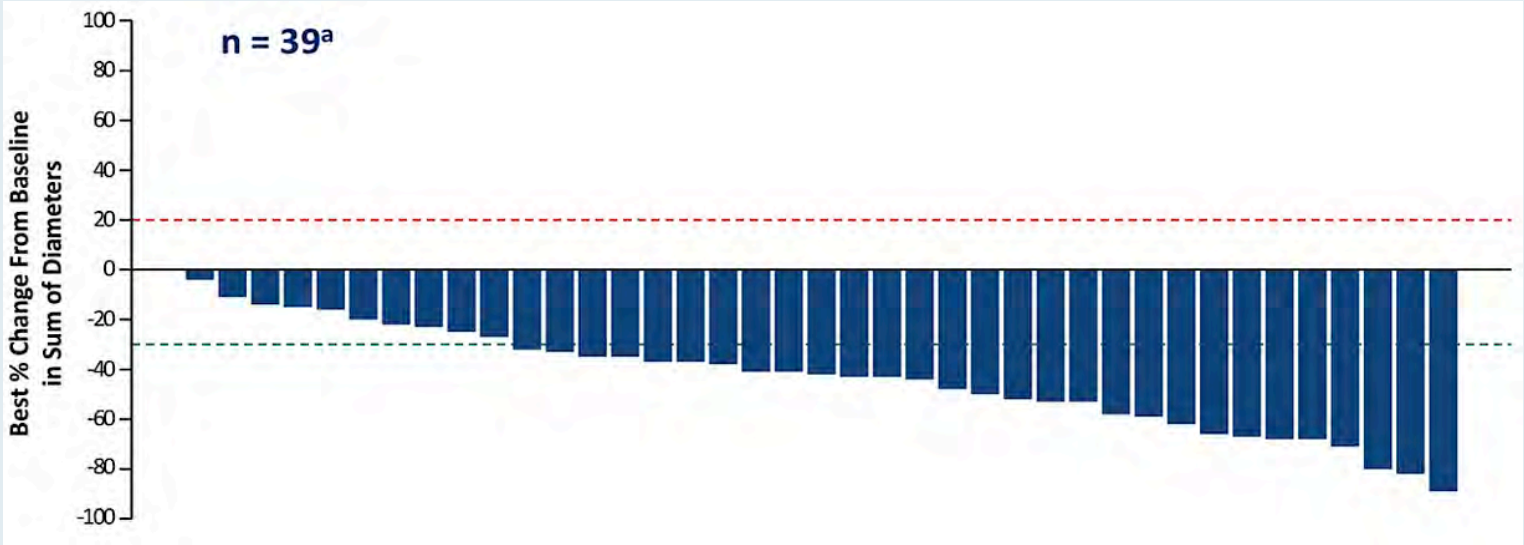
Trastuzumab Deruxtecan in HER2-Overexpressing Metastatic Non-Small Cell Lung Cancer (NSCLC): Interim Results of DESTINY-Lung01[2]

[1] Smit EF et al.
WCLC 2021;Abstract MA11.03.

[2] Nakagawa K et al.
WCLC 2021;Abstract OA04.05.

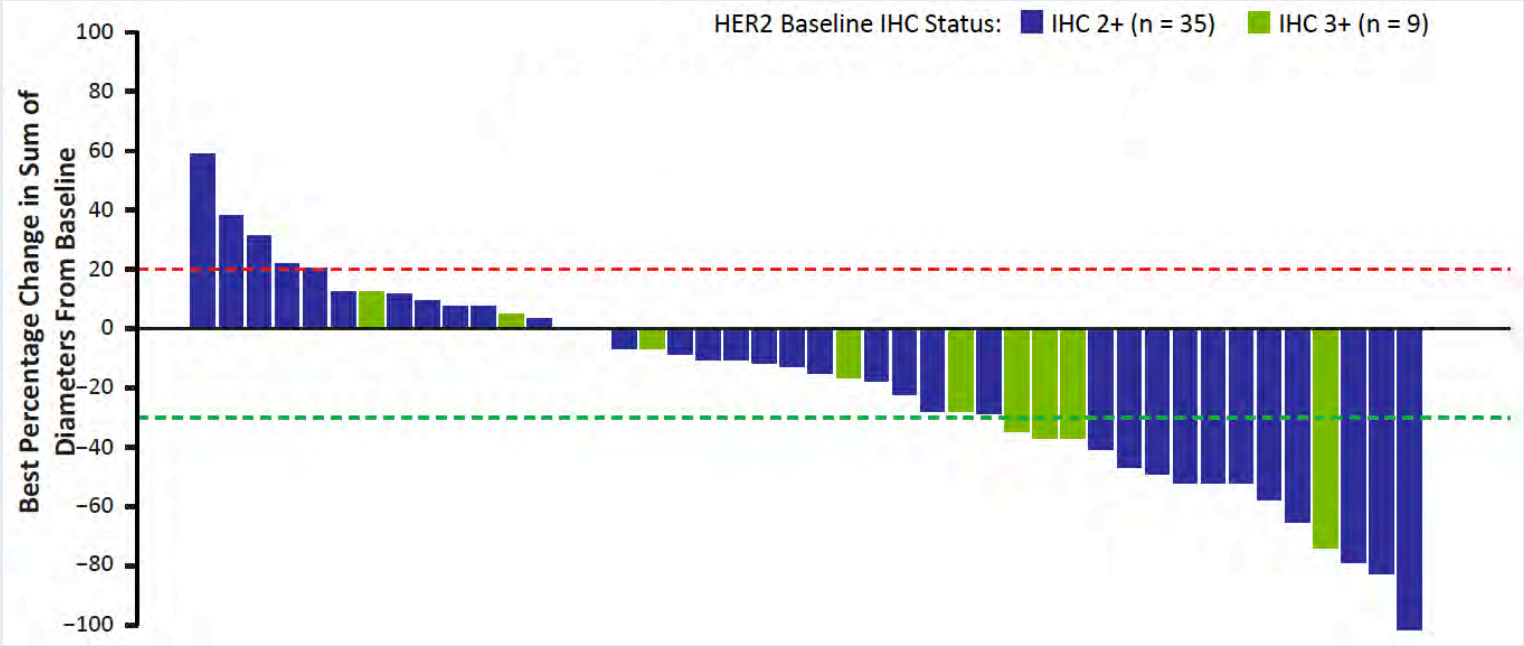
DESTINY-Lung01: Best Percentage Change in Tumor Size with T-DXd for HER2-Mutated versus Overexpressing NSCLC

Mutant



Confirmed ORR = 61.9%
DCR = 90.5%
Median DoR = not reached
Median PFS = 14.0 months

Overexpressing



Confirmed ORR = 24.5%
DCR = 69.4%
Median DoR = 6.0 months
Median PFS = 5.4 months

Smit EF et al. WCLC 2021;Abstract MA11.03; Nakagawa K et al. WCLC 2021;Abstract OA04.05.

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DESTINY-Lung01: AEs of Special Interest – Interstitial Lung Disease

Mutant

	All Patients (N = 42)					
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial lung disease	0	5 (11.9)	0	0	0	5 (11.9)

Overexpressing

All Patients (N = 49)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/Total
Adjudicated drug-related ILD	2 (4.1%)	3 (6.1%)	0	0	3 (6.1%)	8 (16.3%)

Smit EF et al. WCLC 2021;Abstract MA11.03; Nakagawa K et al. WCLC 2021;Abstract OA04.05.

Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor-Resistant, *EGFR*-Mutated (*EGFR*m) Non-Small Cell Lung Cancer (NSCLC)

Janne PA et al.
ASCO 2021;Abstract 9007.

Saturday, June 5, 1:30 PM - 4:30 PM EDT

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Agenda

Module 1 : Localized or Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

- Dr Patel: A 57-year-old woman with locally advanced NSCLC
- *Key Recent Publications and Presentations*

Module 2: Newly Diagnosed NSCLC with No Actionable Mutation

- Dr Lorber: A 66-year-old man with metastatic adenocarcinoma of the lung – PD-L1 60%, TMB 14 mut/Mb
- *Key Recent Publications and Presentations*

Module 3: NSCLC with an EGFR Tumor Mutation

- Dr Patel: A 47-year-old woman with metastatic adenocarcinoma of the lung and asymptomatic brain metastases – EGFR exon 19 mutation
- *Key Recent Publications and Presentations*

Module 4: Metastatic NSCLC Harboring Other Mutations

- Dr Gupta: A 61-year-old man with metastatic adenocarcinoma of the lung with a RET fusion
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations
- Dr Chen: A 59-year-old woman with metastatic adenocarcinoma of the lung with a ROS1 fusion
- Dr Morganstein: A 62-year-old man with metastatic adenocarcinoma of the lung with a BRAF V600E mutation
- *Key Recent Publications and Presentations*

Module 5: Extensive-Stage Small Cell Lung Cancer (SCLC)

- Dr Patel: A 63-year-old man with extensive-stage SCLC
- *Key Recent Publications and Presentations*

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Case Presentation – Dr Gupta: A 61-year-old man with metastatic adenocarcinoma of the lung with a RET fusion – PD-L1 0%, TMB 3 mut/Mb

Dr Ranju Gupta

- 1/2019: Diagnosed with Stage IV adenocarcinoma of the lung
  - 15-year smoking history
- Carboplatin/pemetrexed/pembrolizumab → developed severe autoimmune enteritis after cycle 1 requiring hospitalization and high-dose steroids
- 9/2020: PD → selpercatinib 160 mg dose → uncontrolled high BP, swelling in legs, drowsiness
  - Dose reductions down to 40 mg did not lead to lowering of BP
- 12/2020: Ramucirumab with docetaxel initiated

Questions

- How do you manage the pedal edema and drowsiness? Is it common?
- What is your experience with pralsetinib in terms of toxicities?

Case Presentation – Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%

Dr Mohamed Mohamed

- Never smoker presents with bilateral flank pain and 5-month history of weight loss and fatigue
- Workup reveals Stage IV poorly differentiated adenocarcinoma of the lung; lung obstructions and 2 small, subcentimeter lesions in brain detected
- Molecular analyses: MET exon 14 skipping mutation, MET amplification
- PD-L1: 95%
- Palliative RT to the lung; SRS to the brain
- Capmatinib initiated

Questions

- If she didn't need to receive RT due to the lung obstructions, should I have initiated treatment with targeted therapy alone? Does capmatinib work on brain lesions by itself?
- With a PD-L1 of 95%, should she have been considered for immunotherapy, or should targeted therapy precede that as first-line therapy?
- Are mutations in MET regarded in the same way as mutations in EGFR and ALK in terms of immune therapy? Or are they regarded like BRAF mutations in that you could use immune therapy?

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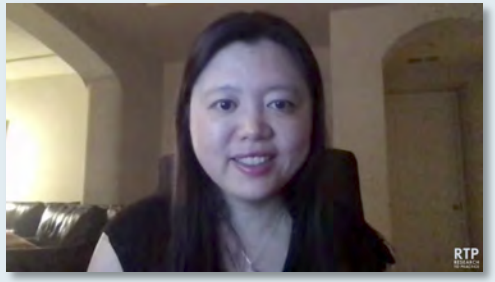
Case Presentation – Dr Chen: A 59-year-old woman with metastatic adenocarcinoma of the lung with a ROS1 fusion and severe rheumatoid arthritis



Dr Gigi Chen

- Never smoker presents with persistent cough
- RLL lung mass, mediastinal adenopathy and multiple bone lesions; MRI brain: Negative
- CT-guided biopsy: Adenocarcinoma, CD 74 ROS1 fusion
- Crizotinib and denosumab x 9 months → Headache → MRI brain: 3-mm parietal lobe and 2-mm frontal lobe lesions
- Systemic disease is well controlled

Questions

- What is the next step in her treatment?
- Would it be best to change to a different TKI versus chemotherapy in this patient who has had brain progression only? What would be the best choices in terms of the TKIs?

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Case Presentation – Dr Morganstein: A 62-year-old man with metastatic adenocarcinoma of the lung with a BRAF V600E mutation – PD-L1 TPS 80%

Dr Neil Morganstein

- Heavy smoker presents with shortness of breath
- Workup reveals lung adenocarcinoma with metastases to the liver and bone
- PD-L1 TPS: 80%
- Carboplatin/paclitaxel/pembrolizumab initiated (pembrolizumab not given due to renal insufficiency)
- Molecular analysis results returned after treatment initiated → BRAF V600E mutation

Questions

- In patients with BRAF V600E mutations, is BRAF-targeted therapy recommended in the first line?
- How imperative is it to have molecular study results before initiating therapy?
- Is BRAF considered a classic driver mutation? Should I be concerned about the efficacy of immunotherapies in patients whose tumors harbor BRAF mutations?
- How would you characterize the type of clinical response that I may expect from BRAF-targeted therapies? What is the standard-of-care for BRAF-directed therapy – dabrafenib/trametinib?

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Key Recent Publications and Presentations

- Xia B et al. **How to Select the Best Upfront Therapy for Metastatic Disease? Focus on *ALK*-Rearranged Non-Small Cell Lung Cancer (NSCLC).** *Transl Lung Cancer Res* 2020;9(6):2521-34.
- Shaw AT et al. **First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer.** *N Engl J Med* 2020;383(21):2018-29.
- Gainor JT et al. **Registrational Dataset from the Phase 1/2 ARROW Trial of Pralsetinib (BLU-667) in Patients with Advanced RET Fusion+ Non-Small Cell Lung Cancer (NSCLC).** ASCO 2020;Abstract 9515.
- Wolf J et al. **Capmatinib in MET Exon 14-Mutated or MET-Amplified Non-Small-Cell Lung Cancer.** *N Engl J Med* 2020;383(10):944-57.
- Paik PK et al. **Tepotinib in Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations.** *N Engl J Med* 2020;383(10):931-43.

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RESEARCH TO PRACTICE

Activity of ALK TKIs in the First-Line Setting for Advanced NSCLC with ALK Rearrangement

ALK TKI	Median PFS	ORR	Intracranial response
Crizotinib	10.9 mo	74%	NA
Ceritinib	16.6 mo	72.5%	72.7%
Alectinib	34.8 mo	82.9%	82.9%
Brigatinib	29.4 mo	71%	78%
Lorlatinib	Not reached	90%	66.7%
Ensartinib	26.2 mo	80%	64.3%

Xia B et al. *Transl Lung Cancer Res* 2020;9(6):2521-253.

RTP RESEARCH TO PRACTICE

Common and Unique Adverse Effects of ALK TKIs

ALK TKI	Most common adverse effects
Crizotinib	Vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy
Ceritinib	Diarrhea, nausea, vomiting, fatigue, abdominal pain, decreased appetite, and weight loss
Alectinib	Constipation, fatigue, edema, myalgia and anemia
Brigatinib	Diarrhea, fatigue, nausea, rash , cough, myalgia, headache, hypertension, vomiting, and dyspnea
Lorlatinib	Hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, weight gain, cognitive effects, fatigue, dyspnea, arthralgia, diarrhea
Ensartinib	Rash, nausea, pruritis, and vomiting

Crizotinib PI, rev 1/2021; Ceritinib PI, rev 3/2019; Alectinib PI, rev 1/2021; Brigatinib PI, rev 5/2020; Lorlatinib PI, rev 3/2021
Xia B et al. *Transl Lung Cancer Res* 2020;9(6):2521-253; Gristina V et al. *Pharmaceuticals* 2020;13:474.

FDA Expands Lorlatinib Approval to Front-Line Treatment of Metastatic NSCLC with ALK Fusion

Press Release – March 3, 2021

"The Food and Drug Administration granted regular approval to lorlatinib for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive, detected by an FDA-approved test. The FDA also approved the Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems, Inc) as a companion diagnostic for lorlatinib.

Lorlatinib received accelerated approval in November 2018 for the second- or third-line treatment of ALK-positive metastatic NSCLC.

This current approval is based on data from Study B7461006 (NCT03052608), a randomized, multicenter, open-label, active-controlled trial conducted in 296 patients with ALK-positive metastatic NSCLC who had not received prior systemic therapy for metastatic disease. Patients were required to have ALK-positive tumors detected by the VENTANA ALK (D5F3) CDx assay. Patients were randomized 1:1 to receive lorlatinib 100 mg orally once daily (n=149) or crizotinib 250 mg orally twice daily (n=147). Study B7461006 demonstrated an improvement in progression-free survival (PFS) as assessed by blinded independent central review (BICR), with a hazard ratio of 0.28 (95% CI: 0.19, 0.41; p<0.0001)."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-lorlatinib-metastatic-alk-positive-nsclc?utm_medium=email&utm_source=govdelivery

RTP RESEARCH TO PRACTICE

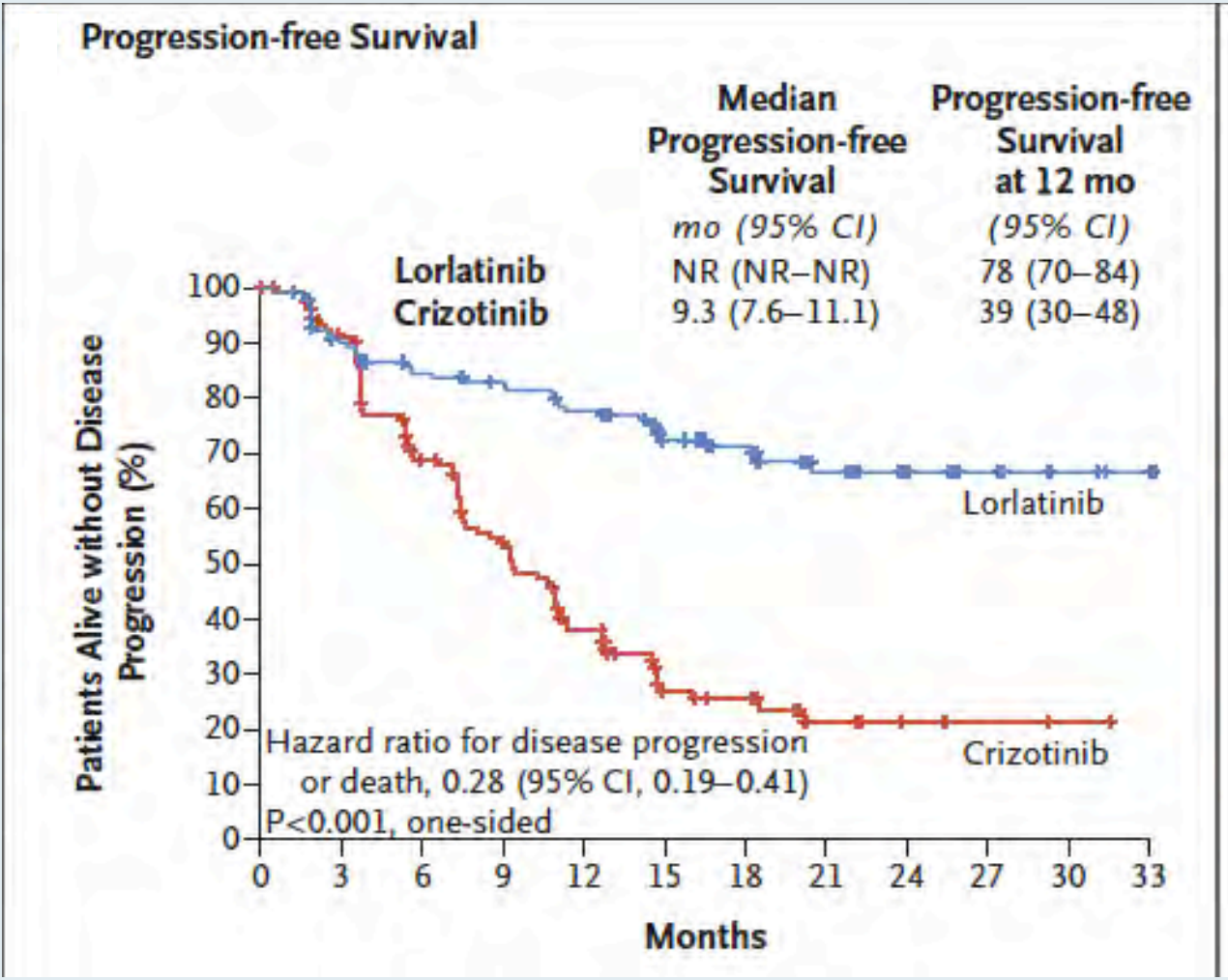
The NEW ENGLAND JOURNAL of MEDICINE

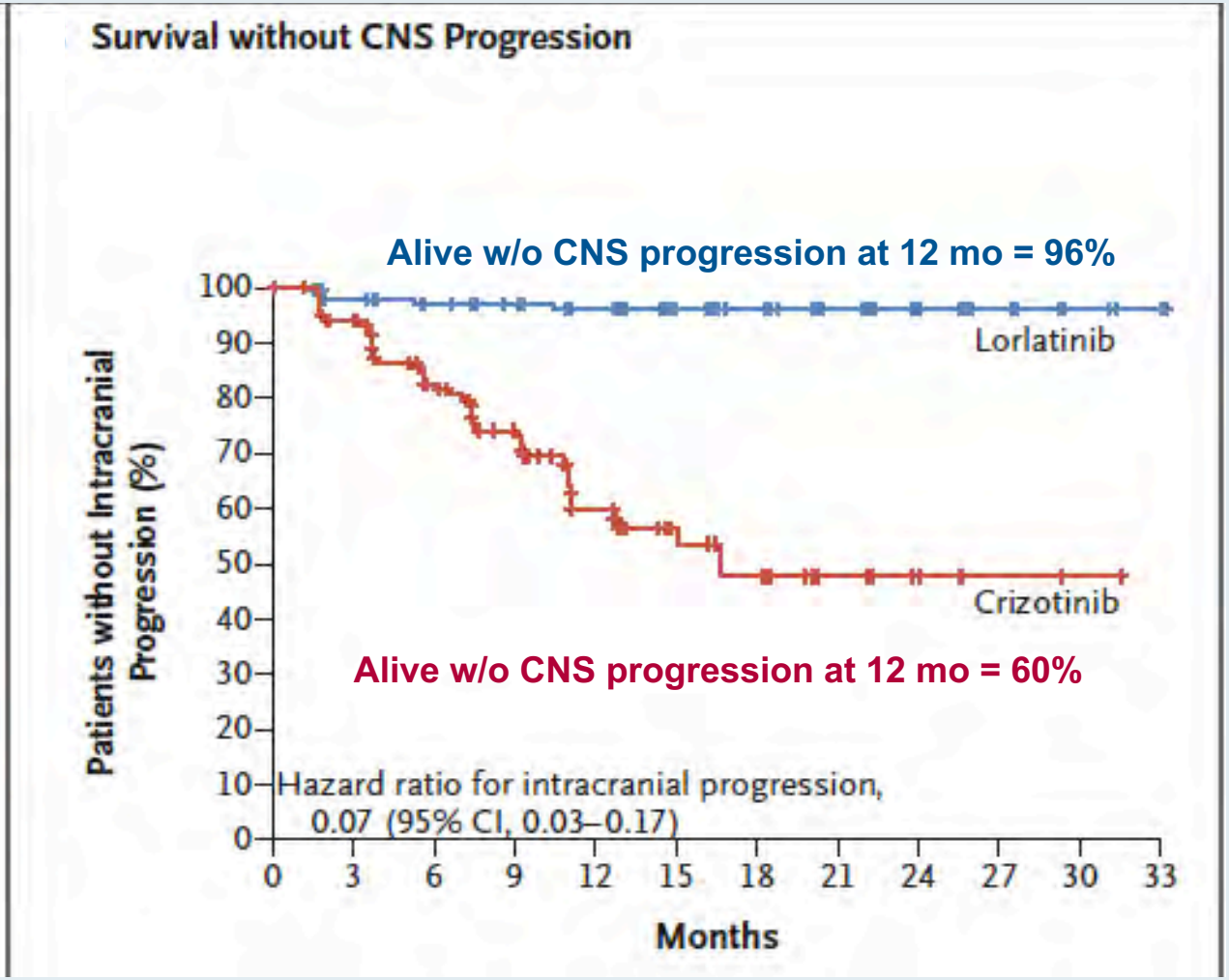
ORIGINAL ARTICLE

First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Todd M. Bauer, M.D., Filippo de Marinis, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Geoffrey Liu, M.D., Julien Mazieres, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Tony Mok, M.D., Anna Polli, B.Sc., Holger Thurm, M.D., Anna M. Calella, Ph.D., Gerson Peltz, M.D., M.P.H., and Benjamin J. Solomon, M.B., B.S., Ph.D., for the CROWN Trial Investigators*

CROWN: PFS and Survival without Intracranial Progression



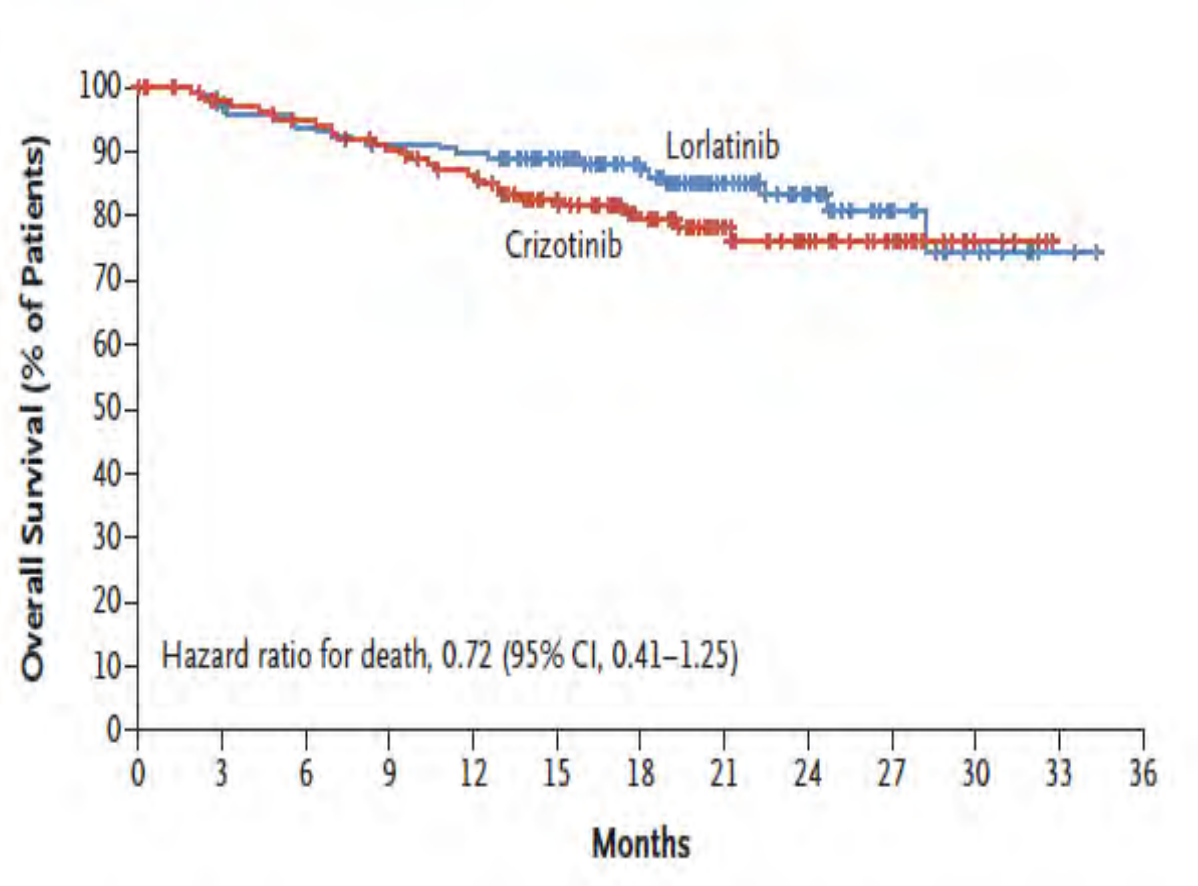


Shaw AT et al. *N Engl J Med* 2020;383(21):2018-29.

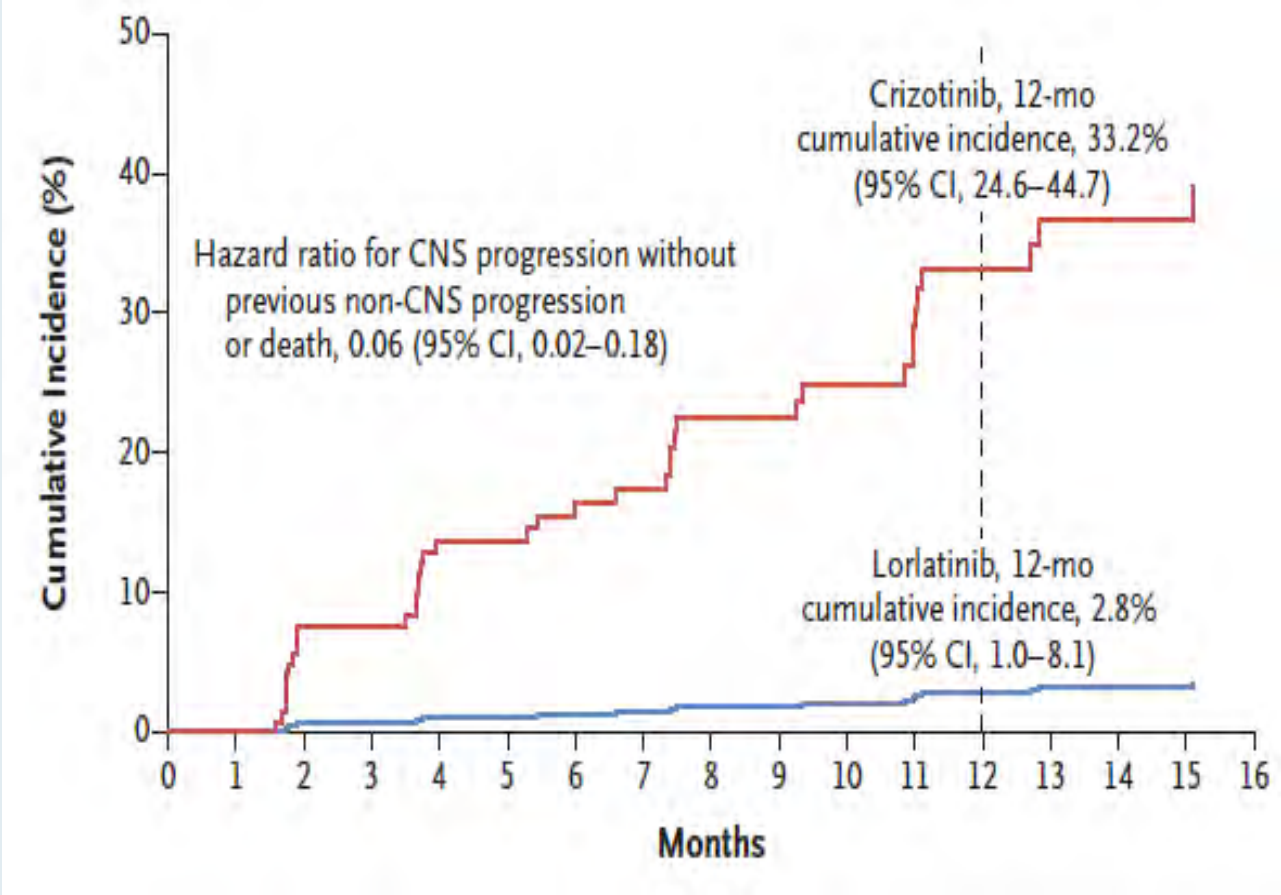
RTP RESEARCH TO PRACTICE

CROWN: OS and Cumulative Incidence of CNS Progression

Overall Survival



Cumulative Incidence of CNS Progression as First Event



Shaw AT et al. *N Engl J Med* 2020;383(21):2018-29.

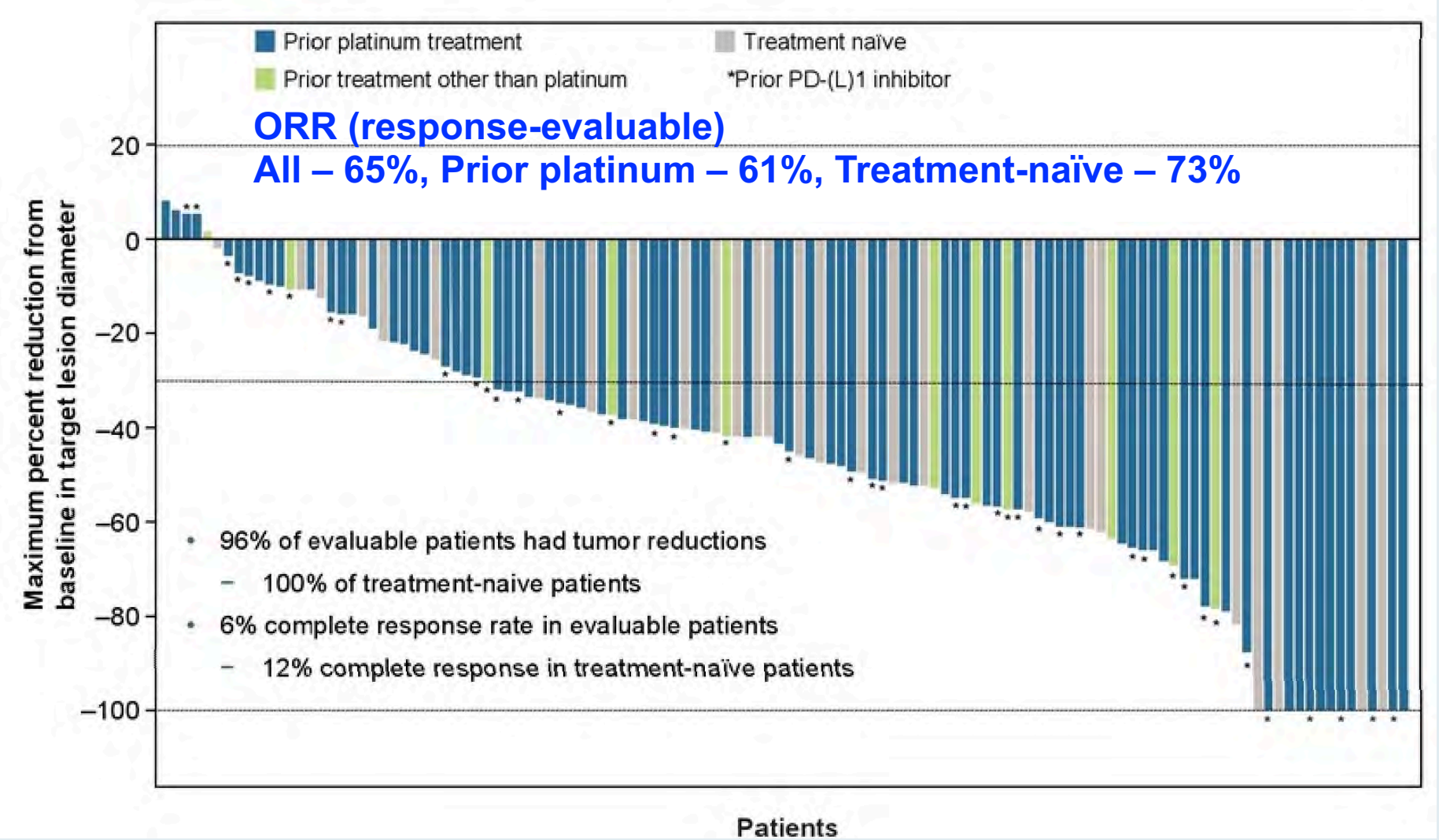
RTP RESEARCH TO PRACTICE

Registrational Dataset from the Phase 1/2 ARROW Trial of Pralsetinib (BLU-667) in Patients with Advanced RET Fusion+ Non-Small Cell Lung Cancer (NSCLC)

Gainor JT et al.

ASCO 2020;Abstract 9515.

ARROW Primary Endpoint: Response to Pralsetinib



Gainor JF et al. ASCO 2020;Abstract 9515.

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

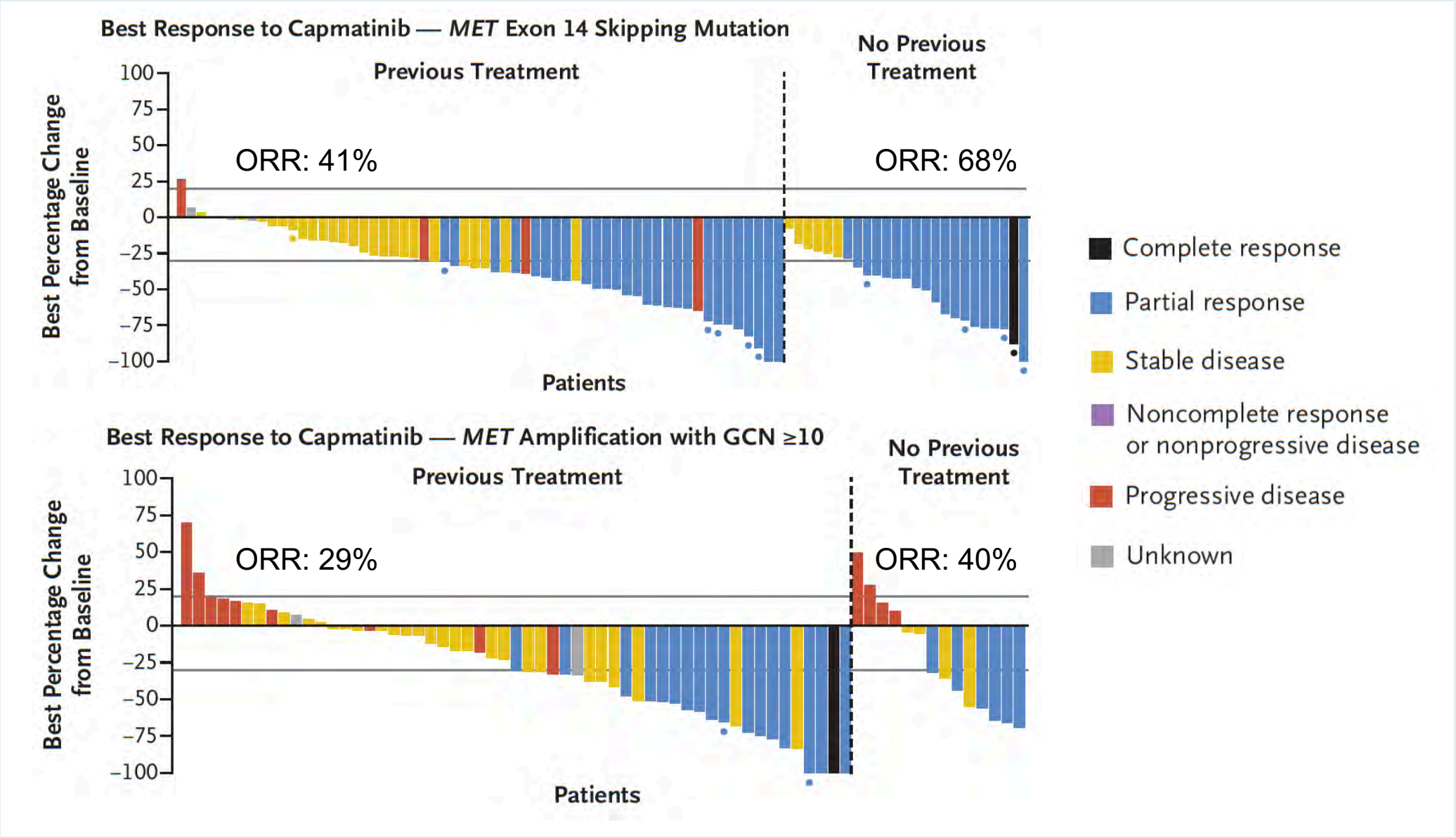
Capmatinib in *MET* Exon 14–Mutated or *MET*-Amplified Non–Small-Cell Lung Cancer

J. Wolf, T. Seto, J.-Y. Han, N. Reguart, E.B. Garon, H.J.M. Groen, D.S.W. Tan, T. Hida, M. de Jonge, S.V. Orlov, E.F. Smit, P.-J. Souquet, J. Vansteenkiste, M. Hochmair, E. Felip, M. Nishio, M. Thomas, K. Ohashi, R. Toyozawa, T.R. Overbeck, F. de Marinis, T.-M. Kim, E. Laack, A. Robeva, S. Le Mouhaer, M. Waldron-Lynch, B. Sankaran, O.A. Balbin, X. Cui, M. Giovannini, M. Akimov, and R.S. Heist, for the GEOMETRY mono-1 Investigators*

ABSTRACT

N Engl J Med 2020;383(10):944-57.

Capmatinib: Response Rate and Change from Baseline in Tumor Burden



Wolf J et al. *N Engl J Med* 2020;383(10):944-57.

FDA Grants Accelerated Approval to Tepotinib for Metastatic Non-Small Cell Lung Cancer

Press Release — February 03, 2021

"On February 3, 2021, the Food and Drug Administration granted accelerated approval to tepotinib for adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.

Efficacy was demonstrated in the VISION trial (NCT02864992), a multicenter, non-randomized, open-label, multicohort study enrolling 152 patients with advanced or metastatic NSCLC with MET exon 14 skipping alterations. Patients received tepotinib 450 mg orally once daily until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-tepotinib-metastatic-non-small-cell-lung-cancer

The NEW ENGLAND JOURNAL of MEDICINE

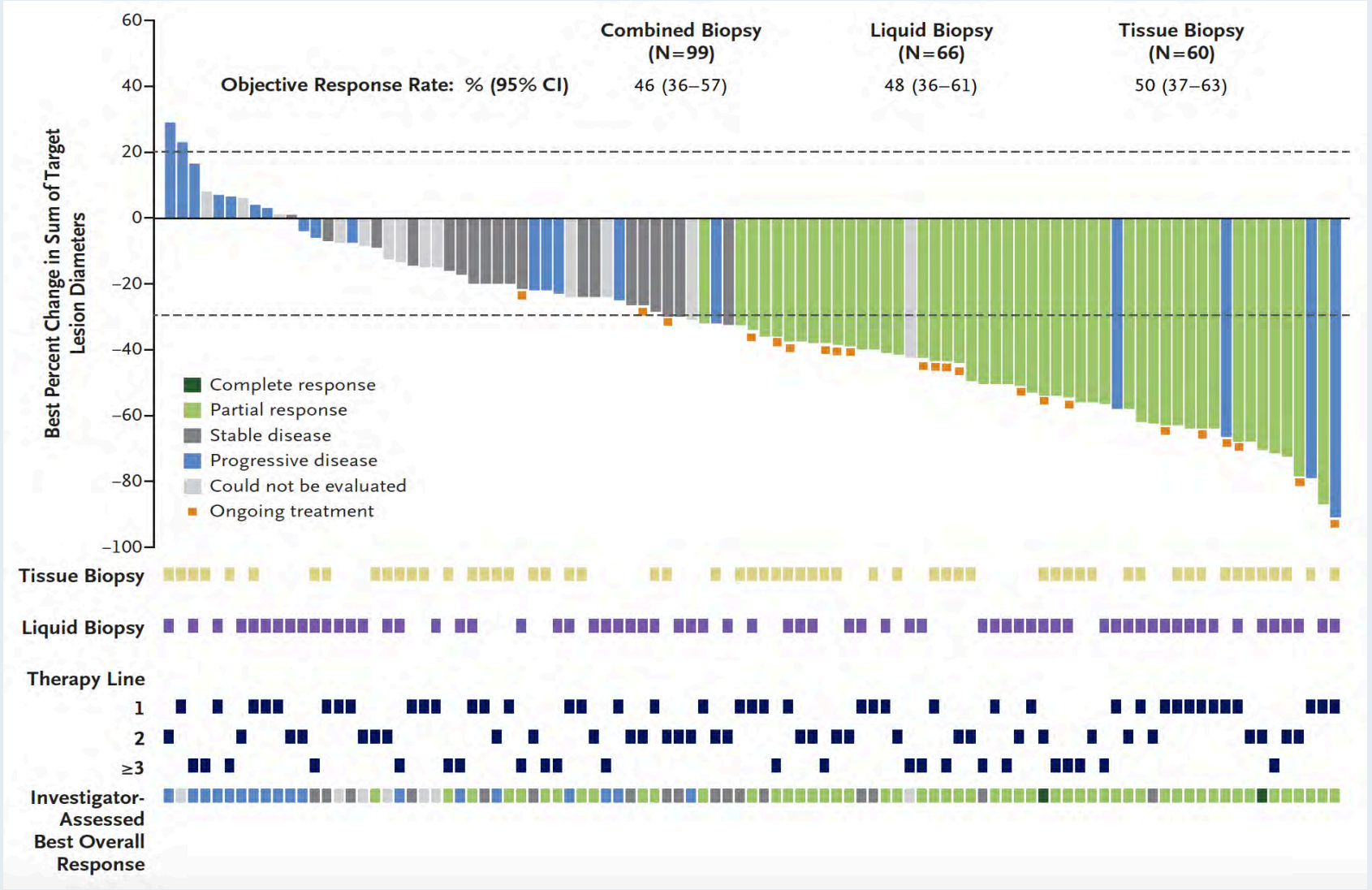
ORIGINAL ARTICLE

Tepotinib in Non–Small-Cell Lung Cancer with *MET* Exon 14 Skipping Mutations

P.K. Paik, E. Felip, R. Veillon, H. Sakai, A.B. Cortot, M.C. Garassino, J. Mazieres, S. Viteri, H. Senellart, J. Van Meerbeeck, J. Raskin, N. Reinmuth, P. Conte, D. Kowalski, B.C. Cho, J.D. Patel, L. Horn, F. Griesinger, J.-Y. Han, Y.-C. Kim, G.-C. Chang, C.-L. Tsai, J.C.-H. Yang, Y.-M. Chen, E.F. Smit, A.J. van der Wekken, T. Kato, D. Juraeva, C. Stroh, R. Bruns, J. Straub, A. Johne, J. Scheele, J.V. Heymach, and X. Le

N Engl J Med 2020;383(10):931-43.

VISION Trial of Tepotinib: Response Rate and Change from Baseline in Tumor Burden



Paik PK et al. *N Engl J Med* 2020;383(10):931-43.

Agenda

Module 1 : Localized or Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

- Dr Patel: A 57-year-old woman with locally advanced NSCLC
- *Key Recent Publications and Presentations*

Module 2: Newly Diagnosed NSCLC with No Actionable Mutation

- Dr Lorber: A 66-year-old man with metastatic adenocarcinoma of the lung – PD-L1 60%, TMB 14 mut/Mb
- *Key Recent Publications and Presentations*

Module 3: NSCLC with an EGFR Tumor Mutation

- Dr Patel: A 47-year-old woman with metastatic adenocarcinoma of the lung and asymptomatic brain metastases – EGFR exon 19 mutation
- *Key Recent Publications and Presentations*

Module 4: Metastatic NSCLC Harboring Other Mutations

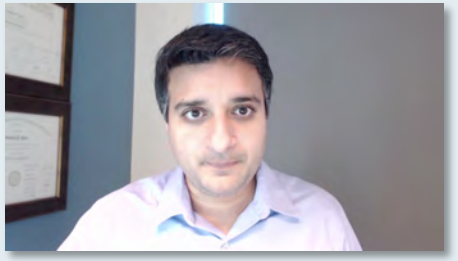
- Dr Gupta: A 61-year-old man with metastatic adenocarcinoma of the lung with a RET fusion
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations
- Dr Chen: A 59-year-old woman with metastatic adenocarcinoma of the lung with a ROS1 fusion
- Dr Morganstein: A 62-year-old man with metastatic adenocarcinoma of the lung with a BRAF V600E mutation
- *Key Recent Publications and Presentations*

Module 5: Extensive-Stage Small Cell Lung Cancer (SCLC)

- Dr Patel: A 63-year-old man with extensive-stage SCLC
- *Key Recent Publications and Presentations*

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Patel: A 63-year-old man with extensive-stage SCLC



Dr Sandip Patel

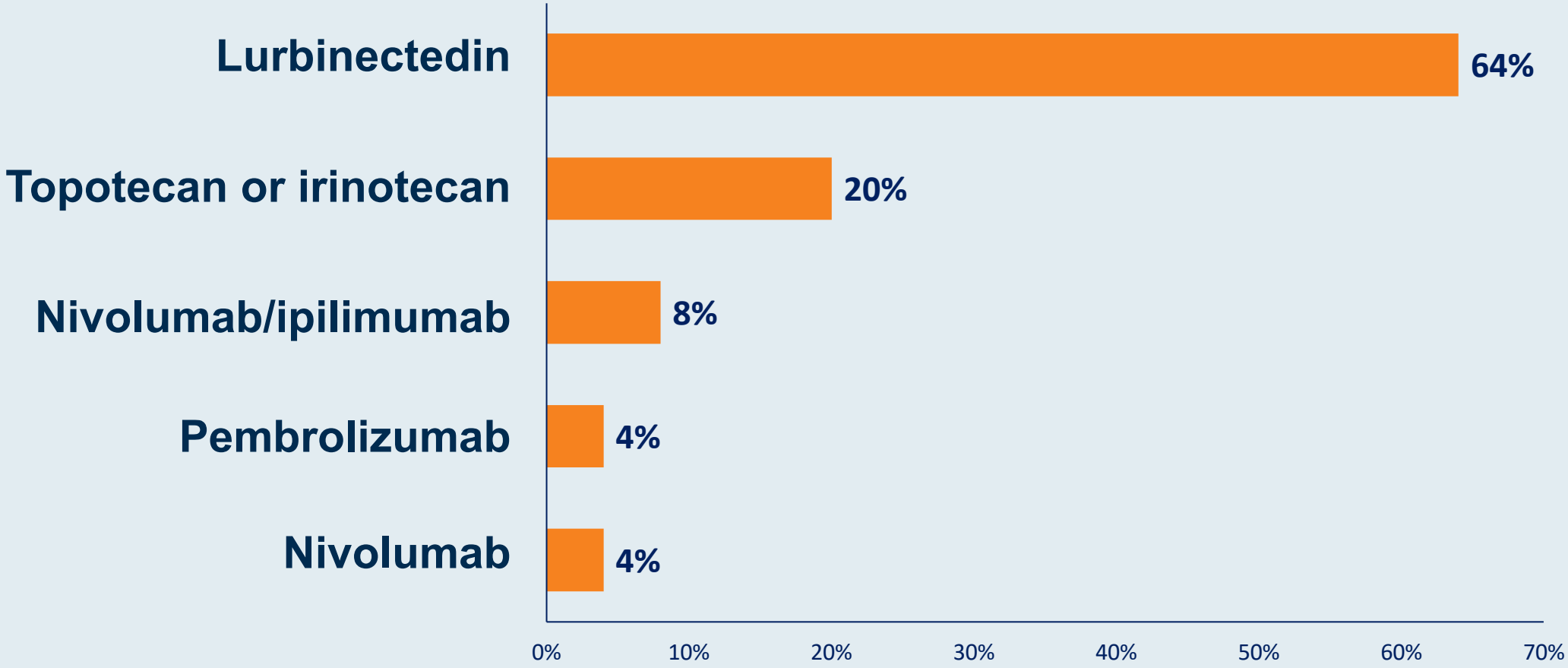
- Diagnosed with ES-SCLC
- Induction carboplatin/etoposide/PD-L1 inhibitor x 4 cycles, with response in lung and liver → Maintenance immunotherapy
  - Diarrhea 5 times/day
  - C diff-negative
  - TB and viral hepatitis testing: Negative
  - Prednisone, with improvement but couldn't get below 20 mg → infliximab, with resolution of diarrhea
- Resumed anti-PD-L1 therapy

Questions

- What would you recommend for this patient to try to improve his outcome?

RTP RESEARCH TO PRACTICE

What is your preferred second-line treatment for a patient with extensive-stage small cell lung cancer and disease progression on chemotherapy/atezolizumab?



N = 49

Survey of live webinar audience

RTP RESEARCH TO PRACTICE

Key Recent Publications and Presentations

- Liu SV et al. **Updated Overall Survival and PD-L1 Subgroup Analysis of Patients with Extensive-Stage Small-Cell Lung Cancer Treated with Atezolizumab, Carboplatin, and Etoposide (IMpower133).** *J Clin Oncol* 2021;39(6):619-30.
- Reck M et al. **IMpower133: Exploratory Analysis of Maintenance Therapy in Patients with Extensive-Stage Small Cell Lung Cancer.** IASLC WCLC 2020;Abstract 0A11.06.
- Goldman JW et al. **Durvalumab, with or without Tremelimumab, plus Platinum-Etoposide versus Platinum-Etoposide Alone in First-Line Treatment of Extensive-Stage Small-Cell Lung Cancer (CASPIAN): Updated Results from a Randomised, Controlled, Open-Label, Phase 3 Trial.** *Lancet Oncol* 2021;22(1):51-65.
- Trigo J et al. **Lurbinectedin as Second-Line Treatment for Patients with Small-Cell Lung Cancer: A Single-Arm, Open-Label, Phase 2 Basket Trial.** *Lancet Oncol* 2020;21(5):645-54.

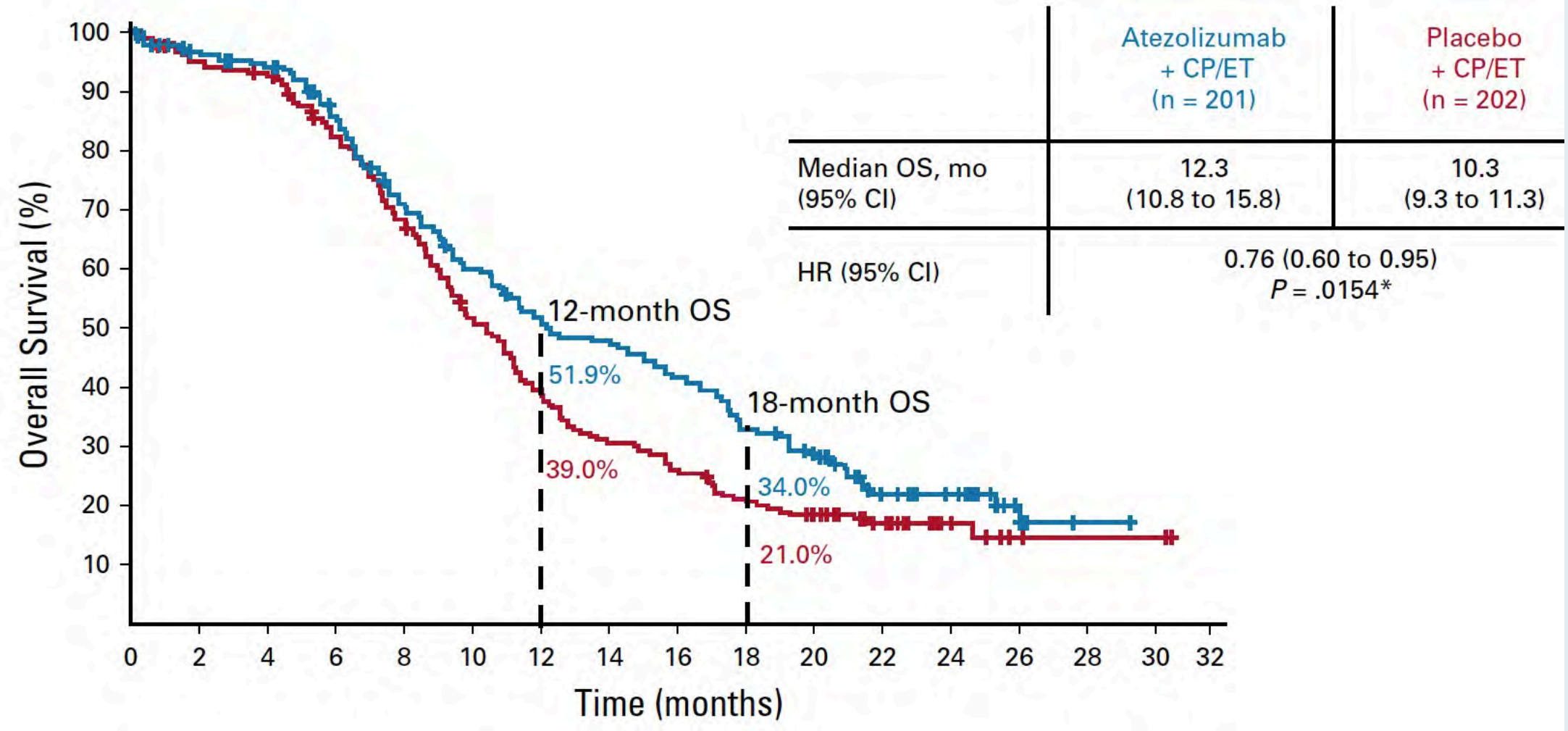
original reports

Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133)

Stephen V. Liu, MD[1]; Martin Reck, MD, PhD[2]; Aaron S. Mansfield, MD[3]; Tony Mok, MD[4]; Arnaud Scherpereel, MD, PhD[5]; Niels Reinmuth, MD, PhD[6]; Marina Chiara Garassino, MD[7]; Javier De Castro Carpeno, MD[8]; Raffaele Califano, MD[9]; Makoto Nishio, MD[10]; Francisco Orlandi, MD[11]; Jorge Alatorre-Alexander, MD[12]; Ticiana Leal, MD[13]; Ying Cheng, MD[14]; Jong-Seok Lee, MD[15]; Sivuonthanh Lam, PharmD[16]; Mark McCleland, PhD[16]; Yu Deng, PhD[16]; See Phan, MD[16]; and Leora Horn, MD[17]

J Clin Oncol 2021;39(6):619-30.

IMpower133: Updated Overall Survival



	Atezolizumab + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mo (95% CI)	12.3 (10.8 to 15.8)	10.3 (9.3 to 11.3)
HR (95% CI)	0.76 (0.60 to 0.95) *P* = .0154*	

Liu SV et al. *J Clin Oncol* 2021;39(6):619-30.

IASLC 2020 World Conference on Lung Cancer Singapore
wclc2020.IASLC.com | #WCLC20
CONQUERING THORACIC CANCERS WORLDWIDE

IASLC/WCLC 2020;Abstract 0A11.06

IMpower133: exploratory analysis of maintenance therapy in patients with extensive-stage small cell lung cancer

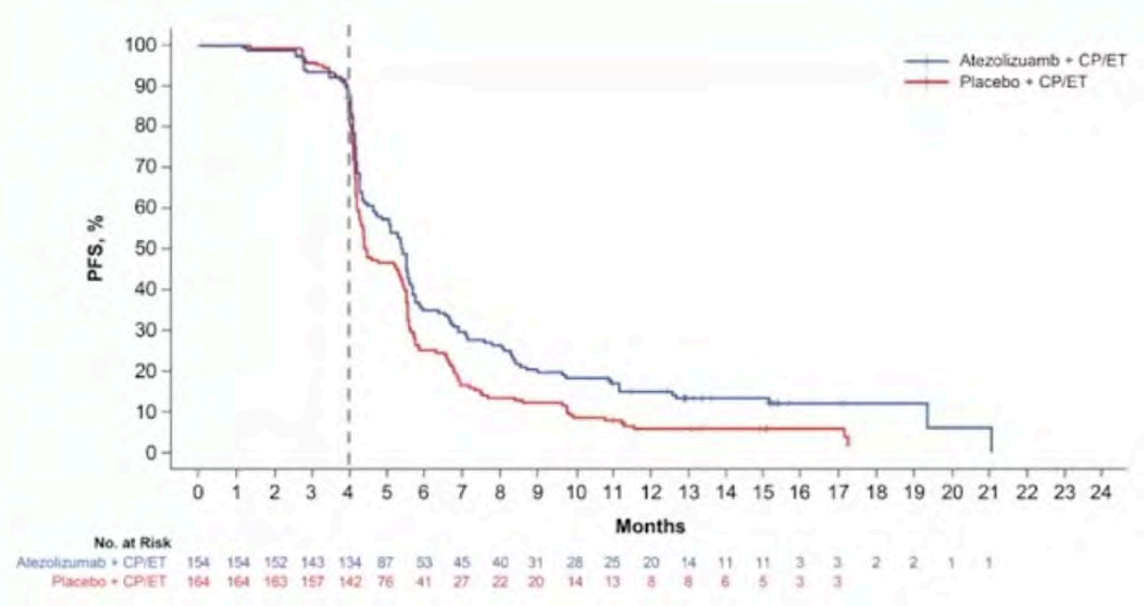
Martin Reck,[1] Leora Horn,[2] Tony S. K. Mok,[3] Aaron S. Mansfield,[4] Richard De Boer,[5] Gyorgy Losonczy,[6] Shunichi Sugawara,[7] Rafal Dziadziuszko,[8] Maciej Krzakowski,[9] Alexey Smolin,[10] Maximilian Hochmair,[11] Marina Garassino,[12] Gilberto Castro,[13] Helge Bischoff,[14] Andres Cardona,[15] Stefanie Morris,[15] Stephen V. Liu[16]

[1] Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany; [2] Vanderbilt University Medical Center, Nashville, TN, USA; [3] The Chinese University of Hong Kong, Hong Kong; [4] Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA; [5] Peter MacCallum Cancer Centre, Melbourne, Australia; [6] Semmelweis Egyetem ÁOK, Budapest, Hungary; [7] Sendai Kousei Hospital, Sendai, Japan; [8] Medical University of Gdansk, Gdansk, Poland; [9] Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [10] Burdenko Main Military Hospital, Moscow, Russia; [11] Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Vienna North Hospital – Klinik Floridsdorf, Vienna, Austria; [12] Thoracic Oncology Unit, Instituto Nazionale dei Tumori, Milan, Italy; [13] Instituto de Cancer do Estado de São Paulo, Hospital das Clínicas da FMUSP, São Paulo, Brazil; [14] Thoraxklinik Heidelberg gGmbH – Universität Heidelberg, Heidelberg, Germany; [15] F. Hoffmann-La Roche Ltd, Basel, Switzerland; [16] Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA

Presented by: Dr Martin Reck

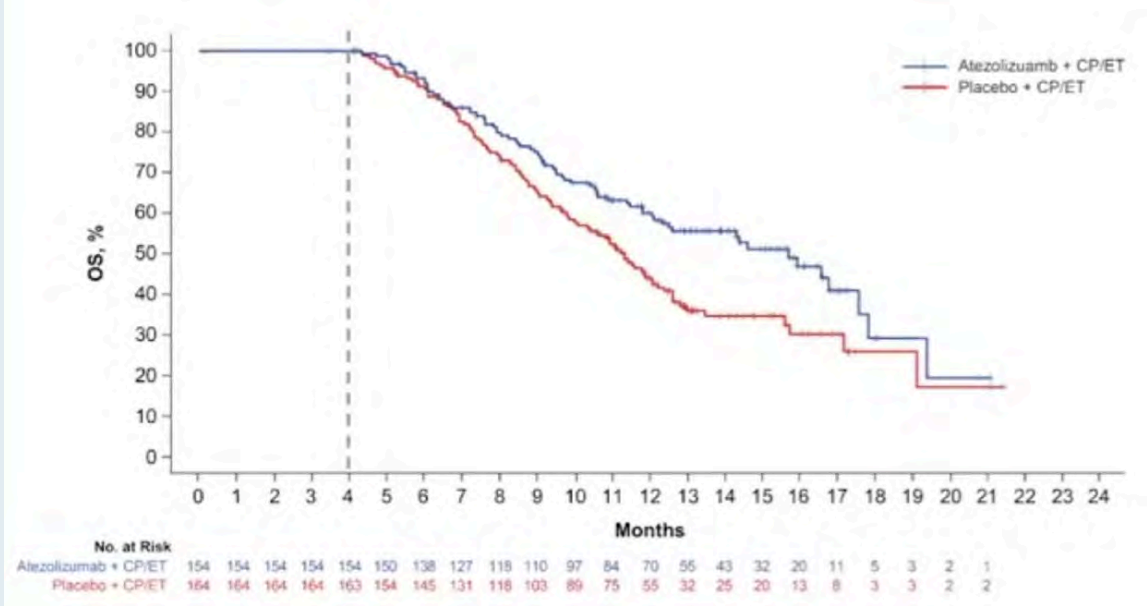
IMpower133: Survival Outcomes in the Maintenance Population

Progression-free survival (PFS)



Median PFS	Atezolizumab	Placebo	HR
From start of maintenance	2.6 mo	1.8 mo	0.64
From randomization	5.5 mo	4.5 mo	Not reported

Overall survival (OS)



Median PFS	Atezolizumab	Placebo	HR
From start of maintenance	12.5 mo	8.4 mo	0.59
From randomization	15.7 mo	11.3 mo	Not reported

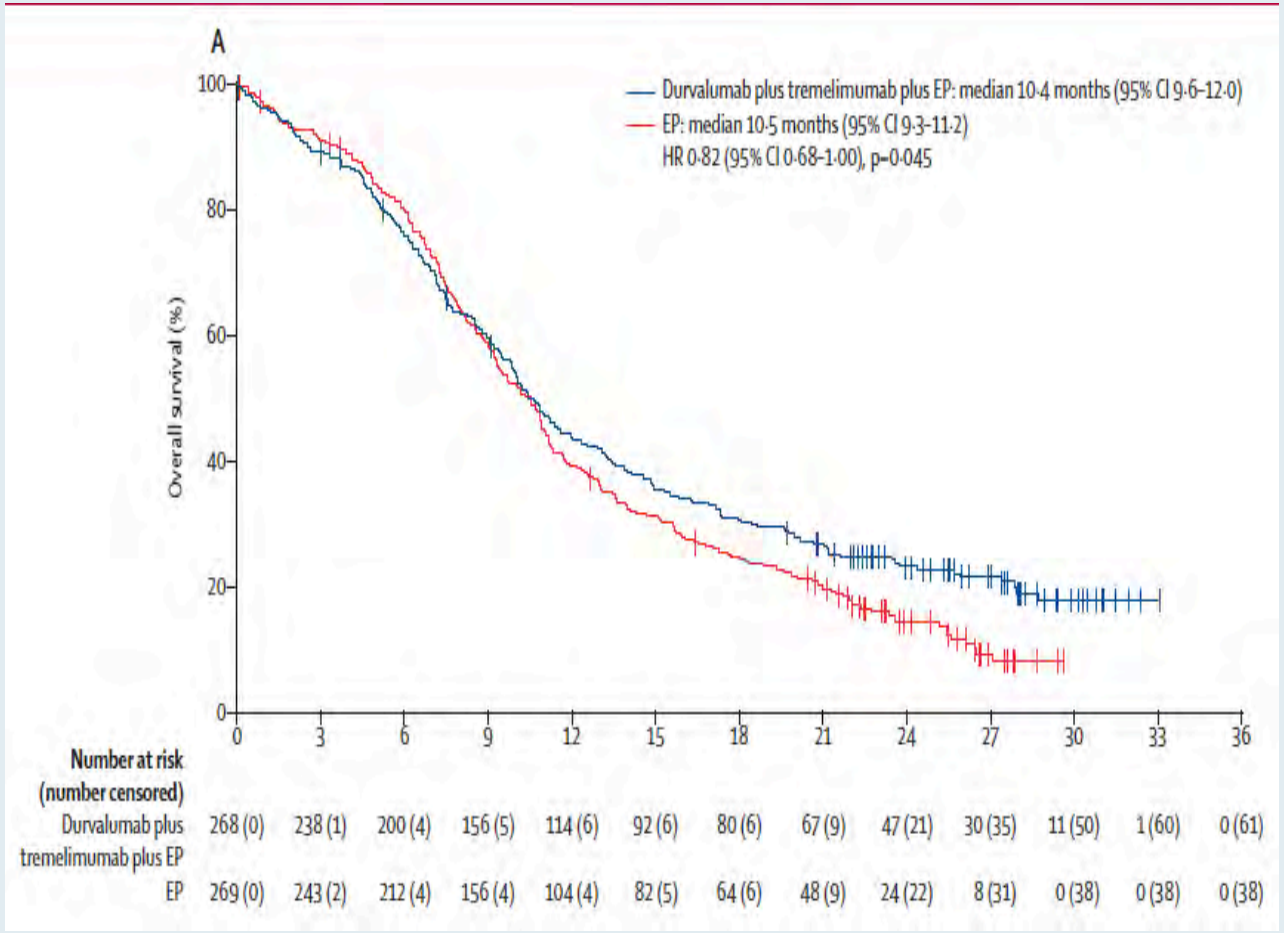
Reck M et al. IASLC/WCLC 2020;Abstract 0A11.06.

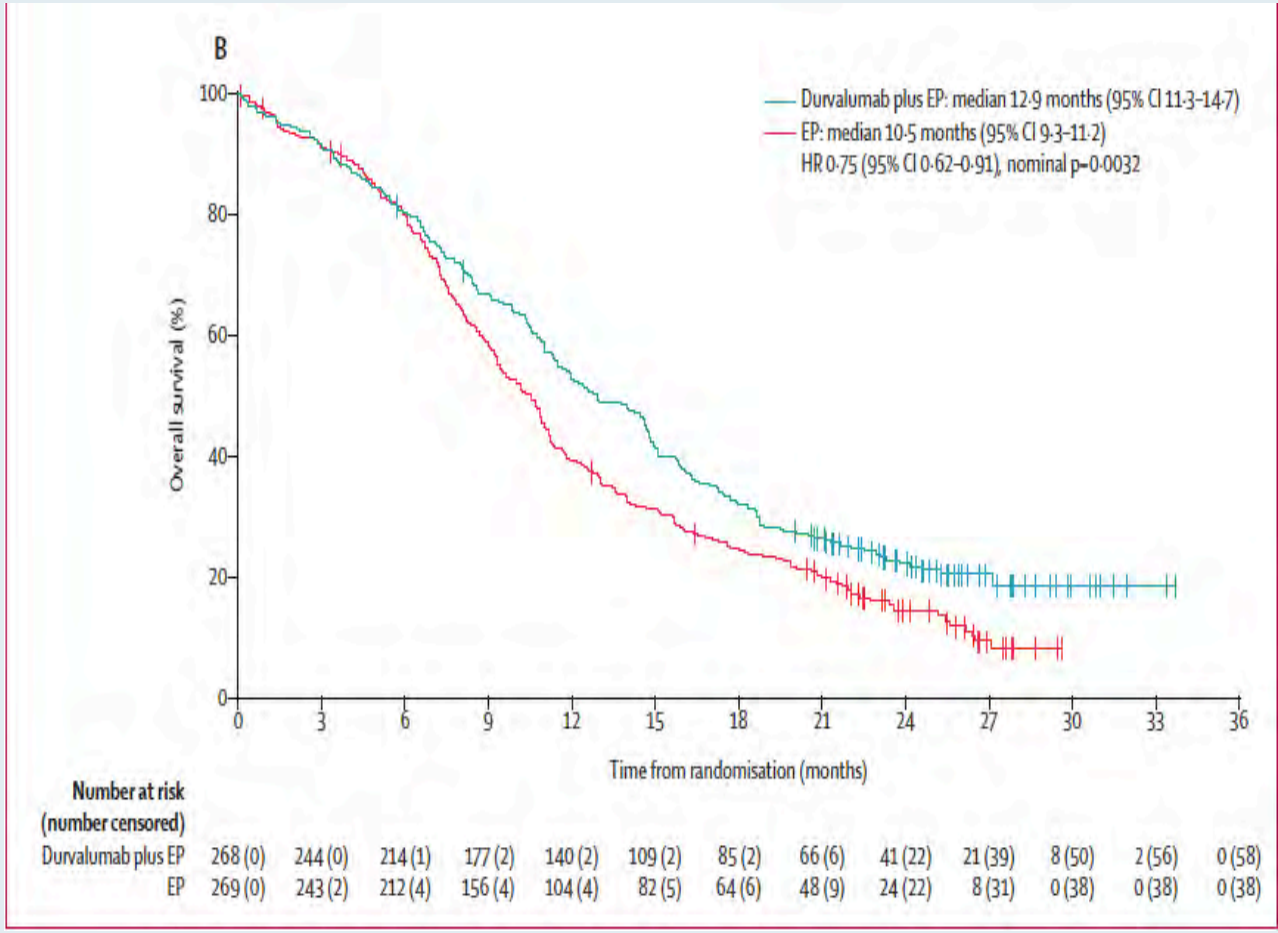
RTP RESEARCH TO PRACTICE

Durvalumab, with or without tremelimumab, plus platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial

*Jonathan W Goldman, Mikhail Dvorkin, Yuanbin Chen, Niels Reinmuth, Katsuyuki Hotta, Dmytro Trukhin, Galina Statsenko, Maximilian J Hochmair, Mustafa Özgüroğlu, Jun Ho Ji, Marina Chiara Garassino, Oleksandr Voitko, Artem Poltoratskiy, Santiago Ponce, Francesco Verderame, Libor Havel, Igor Bondarenko, Andrzej Każarnowicz, György Losonczy, Nikolay V Conev, Jon Armstrong, Natalie Byrne, Piruntha Thiyagarajah, Haiyi Jiang, Luis Paz-Ares, for the CASPIAN investigators**

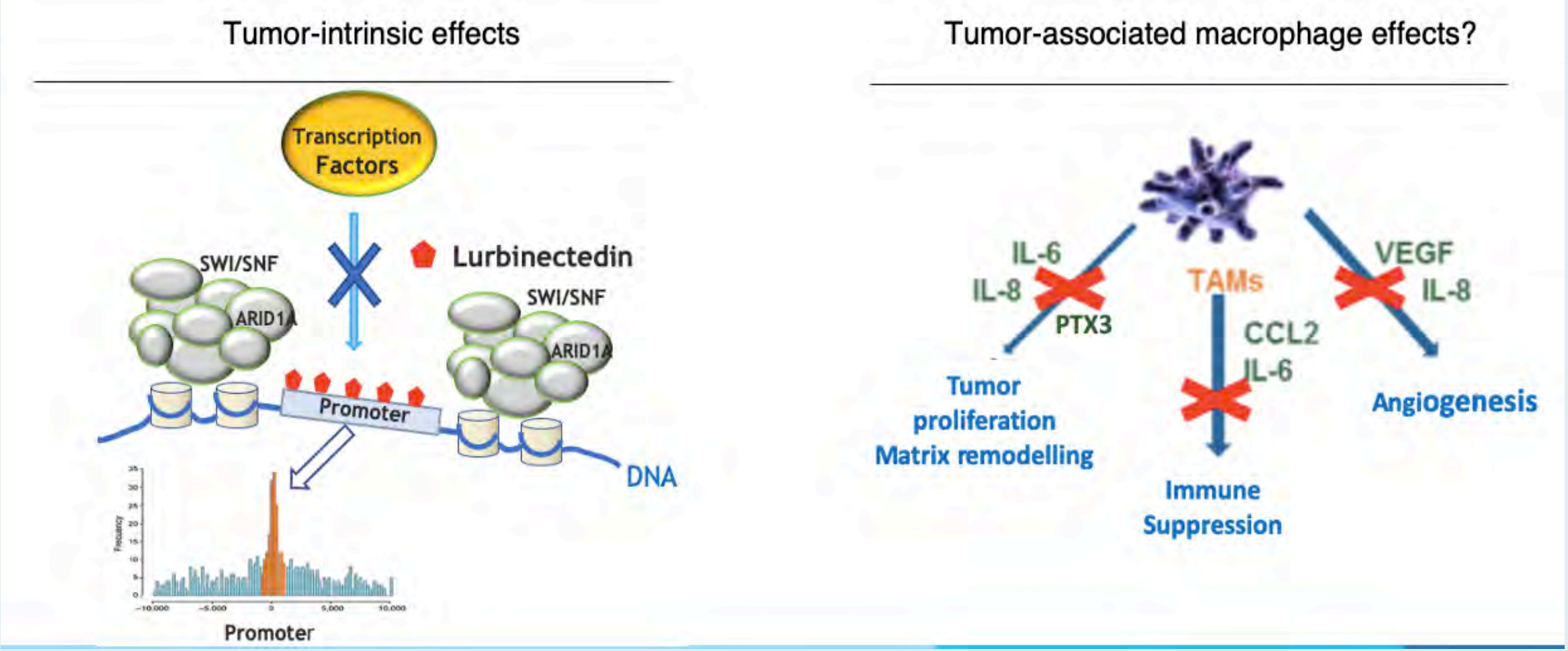
CASPIAN: Updated OS Analyses in ITT Population





Goldman JW et al. *Lancet Oncol* 2021;22(1):51-65.

Lurbinectedin: A Selective Inhibitor of Oncogenic Transcription



How does it work?

- **Alkylator**
- **Minor groove DNA binder**

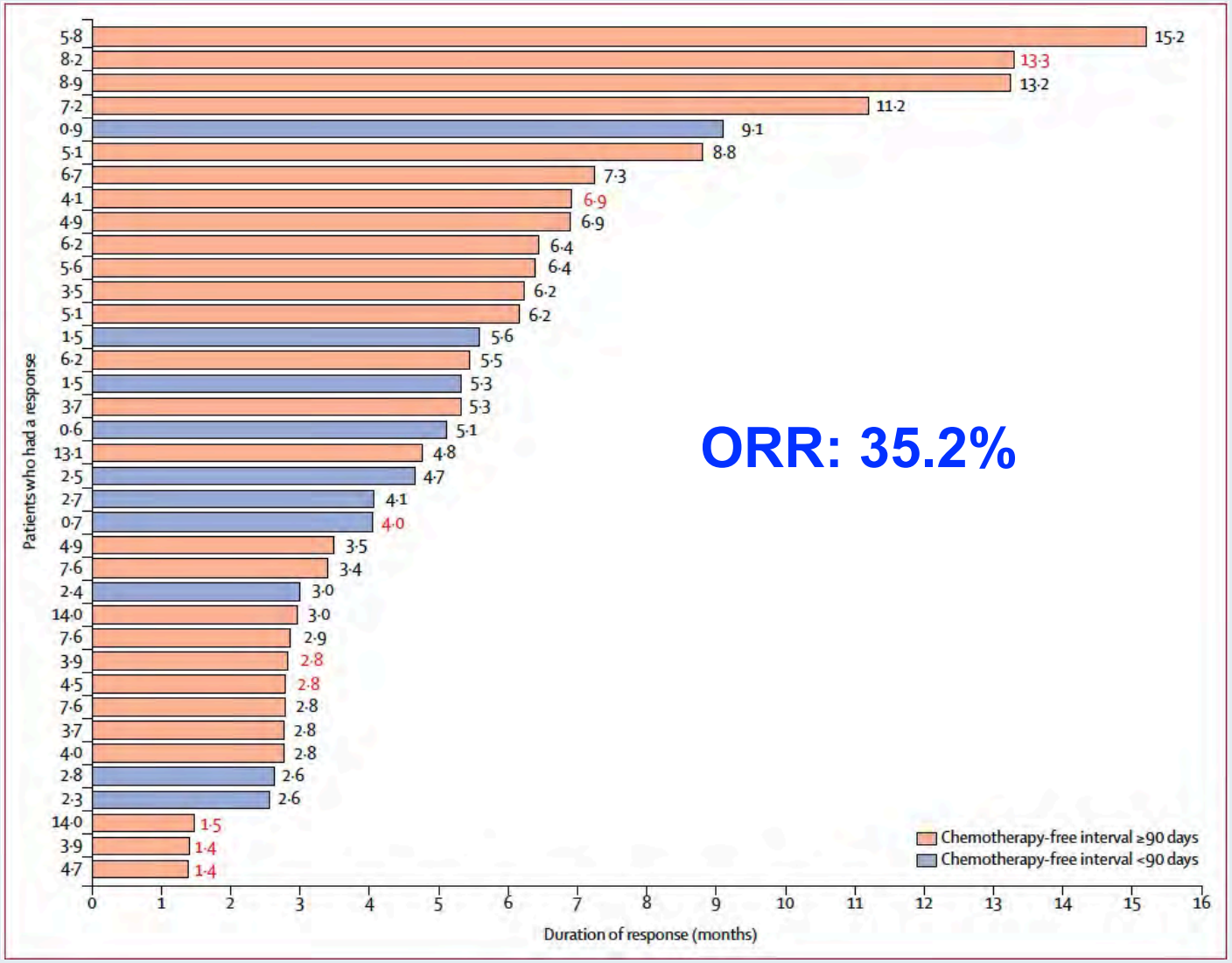
Paz-Ares LG et al. ASCO 2019;Abstract 8506.

Lancet Oncol 2020;21:645-54.

Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial

José Trigo, Vivek Subbiah*, Benjamin Besse, Victor Moreno, Rafael López, María Angeles Sala, Solange Peters, Santiago Ponce, Cristian Fernández, Vicente Alfaro, Javier Gómez, Carmen Kahatt, Ali Zeaiter, Khalil Zaman, Valentina Boni, Jennifer Arrondeau, Maite Martínez, Jean-Pierre Delord, Ahmad Awada, Rebecca Kristeleit, Maria Eugenia Olmedo, Luciano Wannesson, Javier Valdivia, María Jesús Rubio, Antonio Anton, John Sarantopoulos, Sant P Chawla, Joaquín Mosquera-Martinez, Manolo D'Arcangelo, Armando Santoro, Victor M Villalobos, Jacob Sands, Luis Paz-Ares*

Rate and Duration of Response with Lurbinectedin as Second-Line Therapy for SCLC



Trigo J et al. *Lancet Oncol* 2020;21(5):645-54.

ATLANTIS Trial Did Not Meet the Prespecified Criteria of Significance for the Primary Endpoint of Overall Survival

Press Release — December 03, 2020

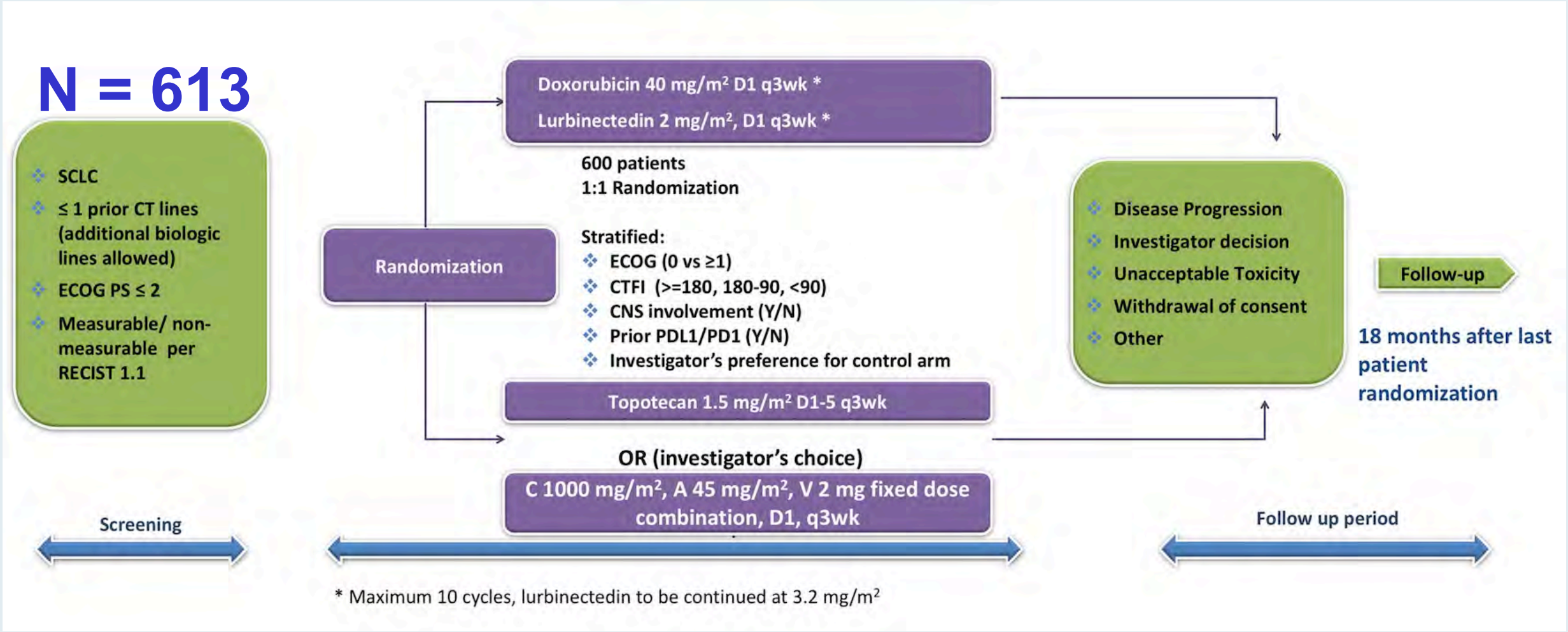
"Results from the ATLANTIS Phase 3 multicenter, randomized, controlled study evaluating lurbinectedin in combination with doxorubicin versus physician's choice of topotecan or cyclophosphamide/doxorubicin/vincristine (CAV) for adult patients with SCLC whose disease progressed following one prior platinum-containing line. Patients received lurbinectedin at 2.0 mg/m^2 in the combination arm, which is lower than the FDA approved dose of lurbinectedin at 3.2 mg/m^2.

The study did not meet the pre-specified criteria of significance for the primary endpoint of overall survival (OS) in the intent-to-treat (ITT) population comparing lurbinectedin in combination with doxorubicin to the control arm, though there was no adverse effect on OS with the experimental arm. Based on the study design, no additional hypotheses were formally tested. Importantly, key secondary and subgroup analyses favored the lurbinectedin combination arm. Lurbinectedin monotherapy was not tested in ATLANTIS.

The safety data in this study was consistent with the known safety profile of lurbinectedin monotherapy with no new safety signals observed."

https://investor.jazzpharma.com/news-releases/news-release-details/jazz-pharmaceuticals-and-pharmamar-announce-results-atlantis

ATLANTIS: Phase III Trial Design



Clinicaltrials.gov (NCT02566993); Accessed February 2021; Farago AF et al. ASCO 2018;Abstract TPS8587.