# 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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# Up for Debate: Oncology Investigators Provide Their Take on Current Controversies in Patient Care

*A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists*

**Saturday, May 22, 2021**
**10:15 AM – 4:15 PM ET**

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# Saturday, May 22, 2021

**10:15 AM — Lung Cancer**
John V Heymach, Stephen V Liu

**11:30 AM — Genitourinary Cancers**
Maha Hussain, Elizabeth R Plimack

**12:45 PM — Chronic Lymphocytic Leukemia and Lymphomas**
Jonathan W Friedberg, Laurie H Sehn

**2:00 PM — Multiple Myeloma**
Irene M Ghobrial, Sagar Lonial

**3:15 PM — Breast Cancer**
Virginia Kaklamani, Nancy U Lin

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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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# 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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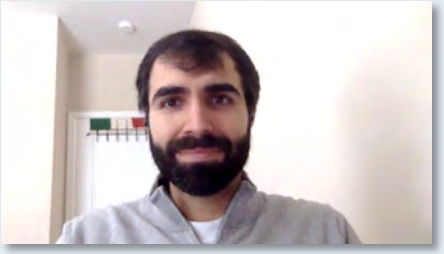
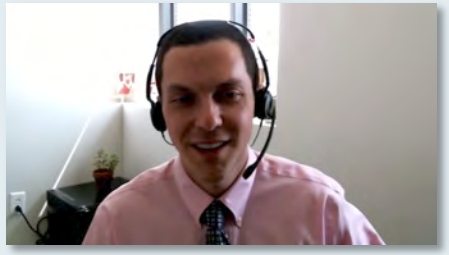
# Contributing Oncologists



**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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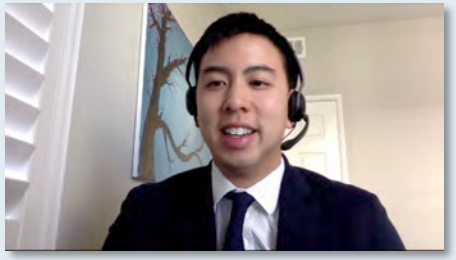
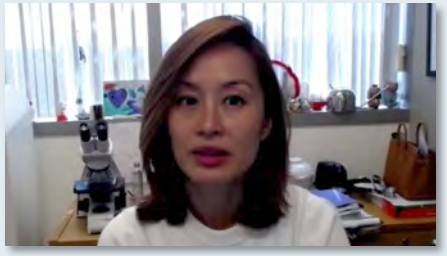
# Contributing Oncologists

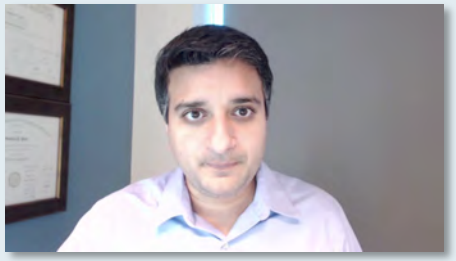
**Mohamed K Mohamed, MD, PhD**
Oncology Division Medical Director
Director of Thoracic Oncology
Hematologist/ Medical Oncologist
Cone Health Cancer Center
Greensboro, North Carolina



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

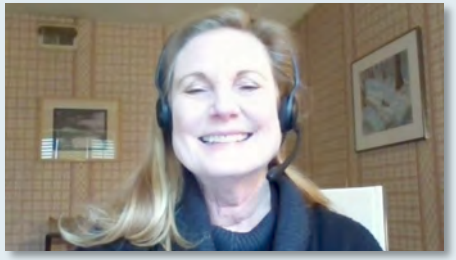


**Helen H Moon, MD**
Medical Oncologist
Southern California Permanente
Medical Group
Riverside, California



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

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



**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*

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## 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?

1. All patients
2. All patients with HER2-negative breast cancer
3. Higher-risk patients
4. Higher-risk patients with HER2-negative breast cancer
5. None
6. Other

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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

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# 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**

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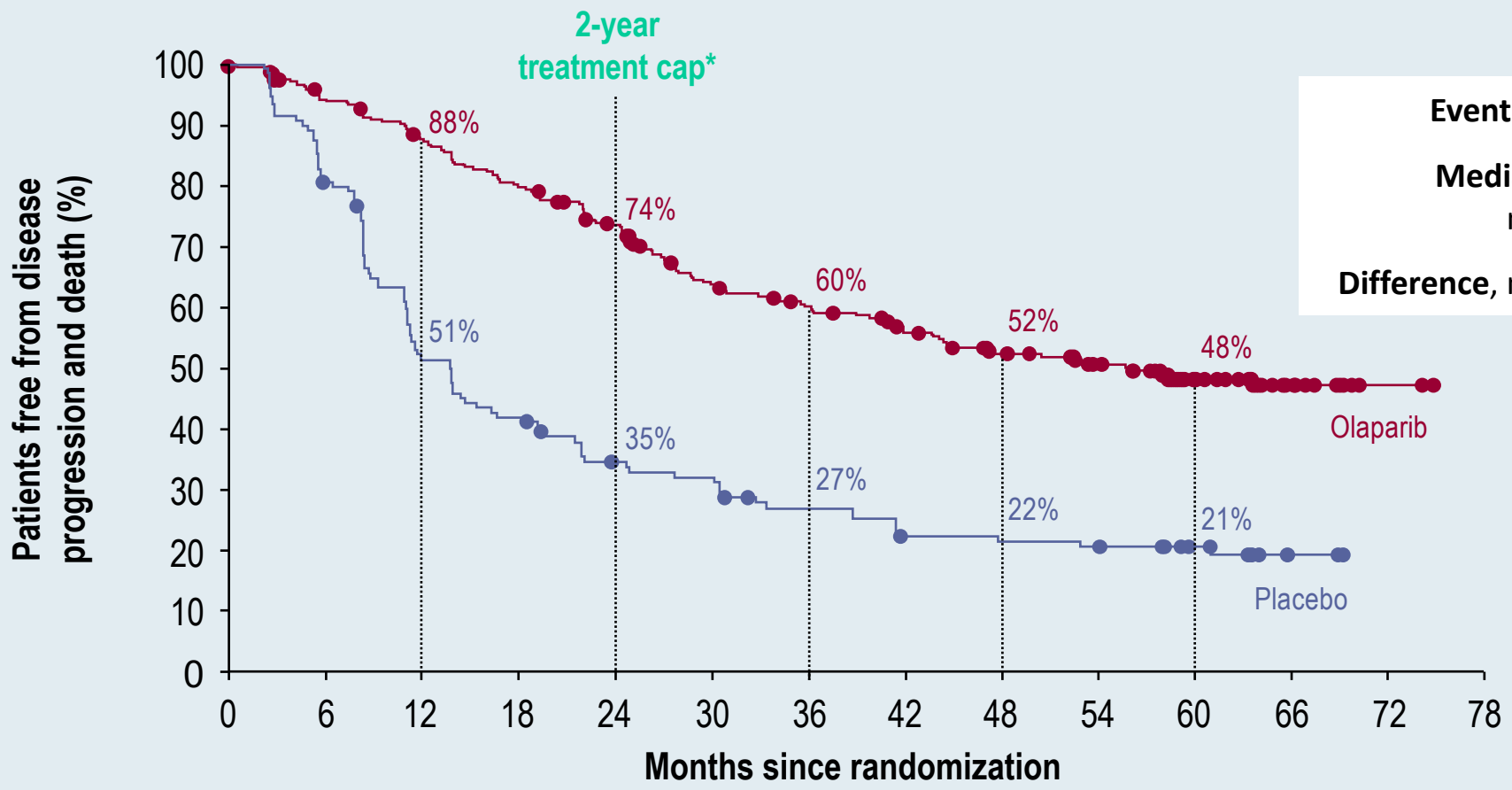
# SOLO-1: Updated PFS (60 Months Follow-Up)




No. at risk

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Olaparib | 260 | 229 | 212 | 194 | 173 | 140 | 129 | 115 | 101 | 91 | 58 | 30 | 2 | 0 |
| Placebo | 131 | 103 | 65 | 53 | 41 | 38 | 30 | 24 | 23 | 22 | 16 | 3 | 0 | |

| | 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.

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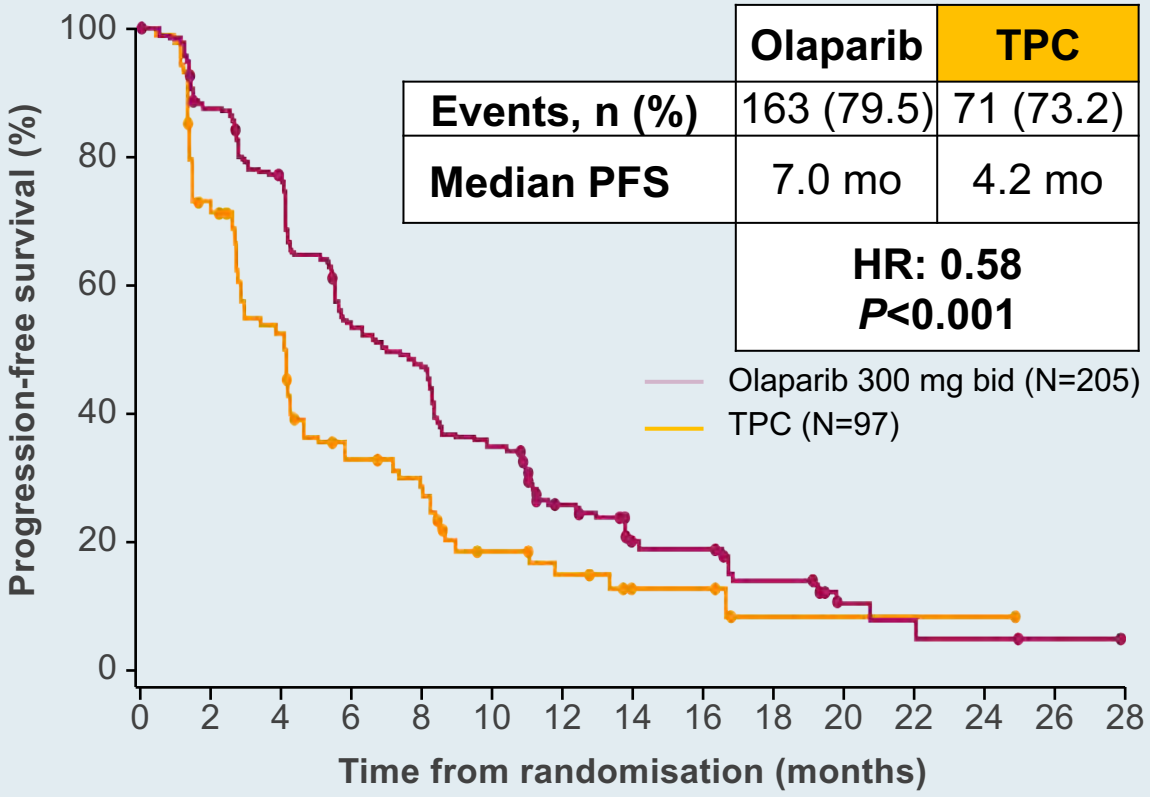
# Phase III Trials of PARP Inhibitors in gBRCA HER2-Negative Metastatic Breast Cancer

## OlympiAD: Olaparib PFS[1,2]

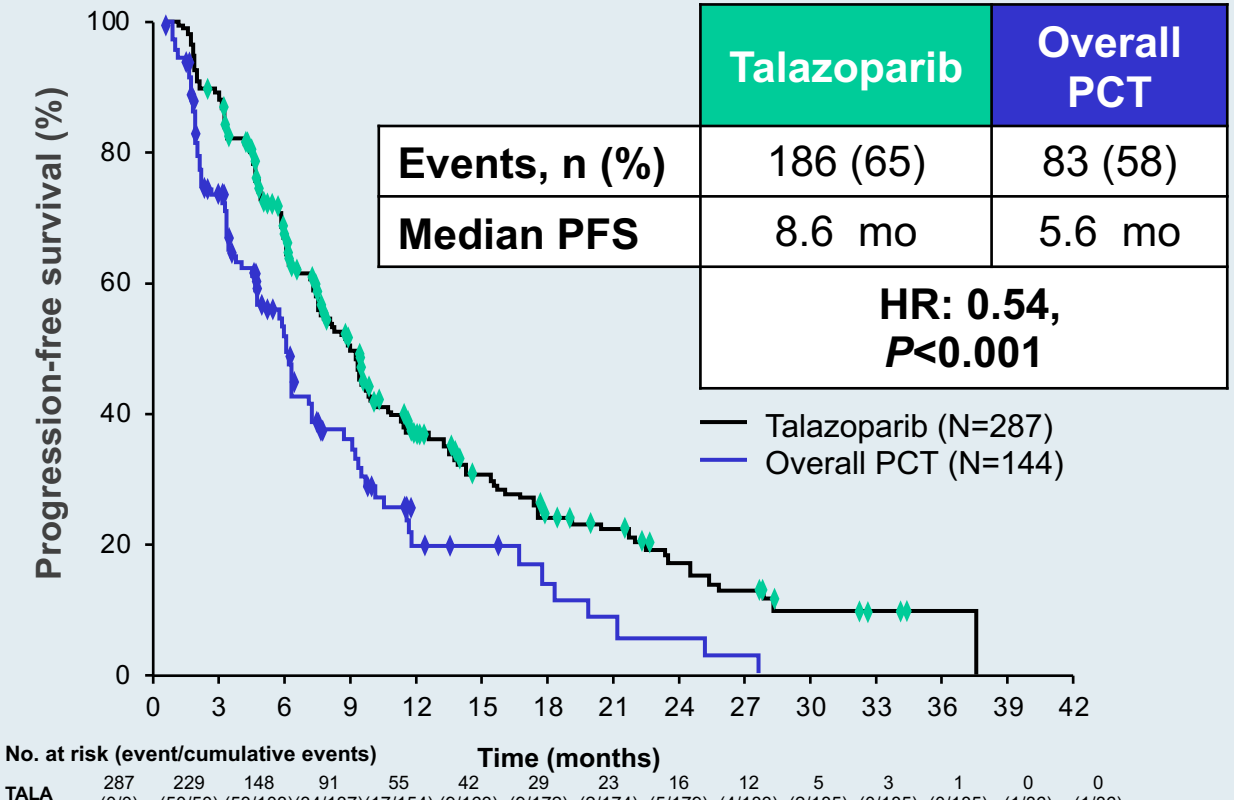



| | Olaparib | TPC |
|---|---|---|
| Events, n (%) | 163 (79.5) | 71 (73.2) |
| Median PFS | 7.0 mo | 4.2 mo |
| | HR: 0.58 *P*<0.001 | |

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

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

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# 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.

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## 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?

1. No
2. Yes, the 21-gene assay
3. Yes, the 70-gene signature
4. Yes, Prosigna PAM50
5. Yes, Breast Cancer Index
6. Yes, other

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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?

1. Tamoxifen
2. Tamoxifen + ovarian suppression/ablation (Ox)
3. Aromatase inhibitor (AI) + Ox
4. AI + Ox + abemaciclib
5. Chemotherapy → endocrine therapy
6. Chemotherapy → Ox + AI + abemaciclib
7. Other

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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.

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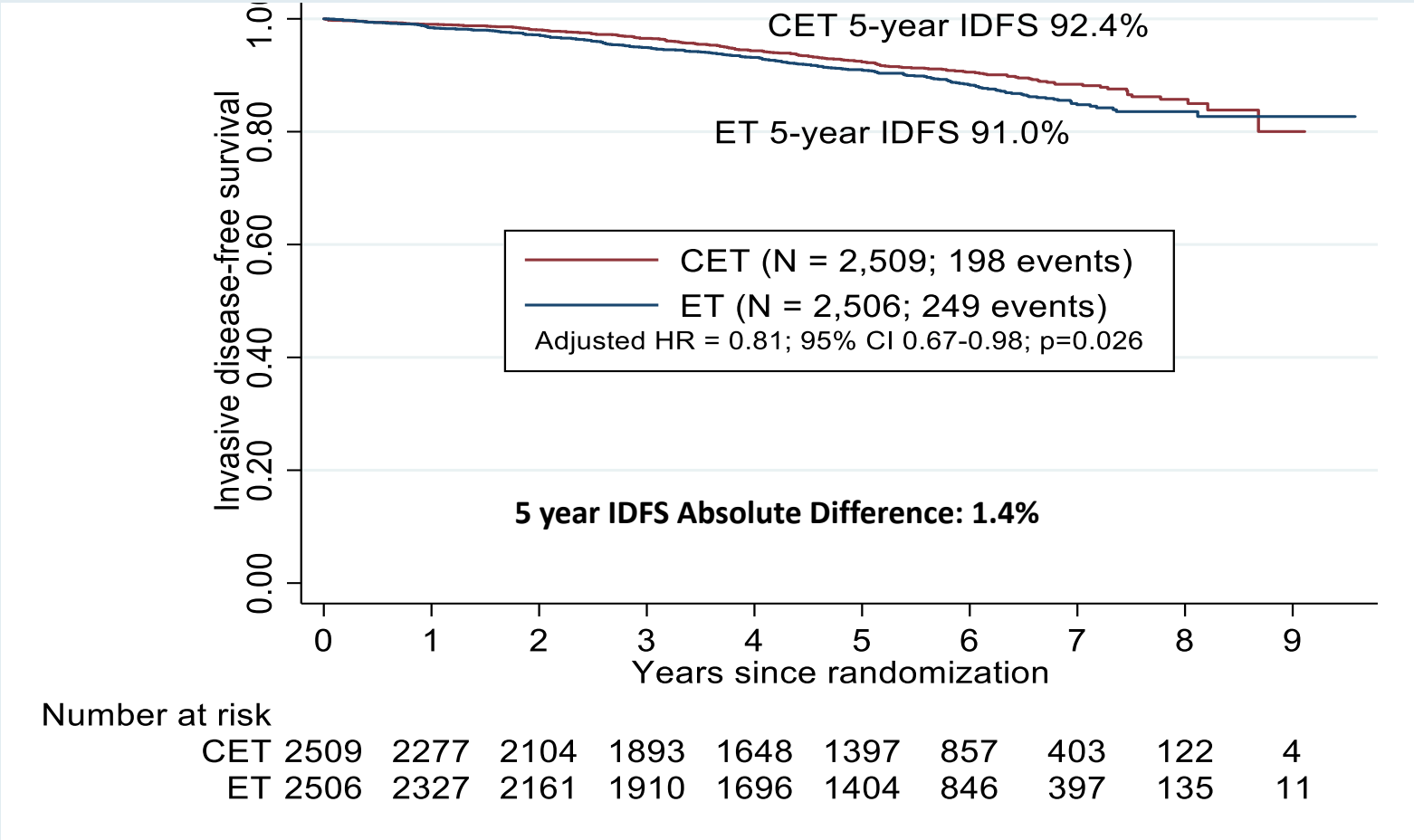
# RxPONDER: Invasive Disease-Free Survival (IDFS) in Overall Population by Treatment Arm




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.

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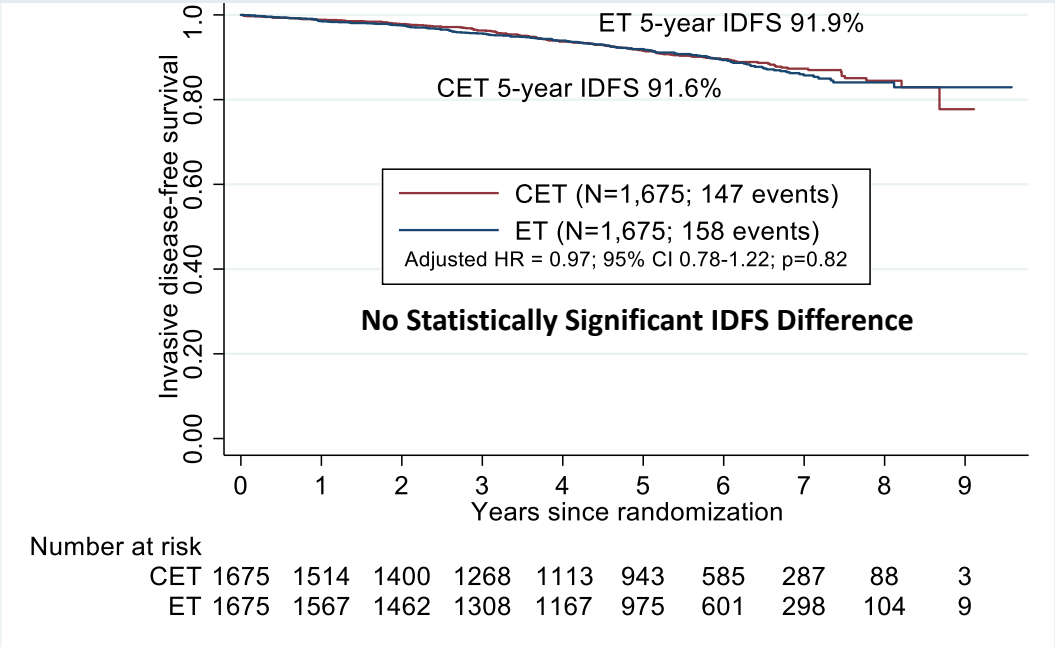
# RxPONDER: IDFS Stratified by Menopausal Status

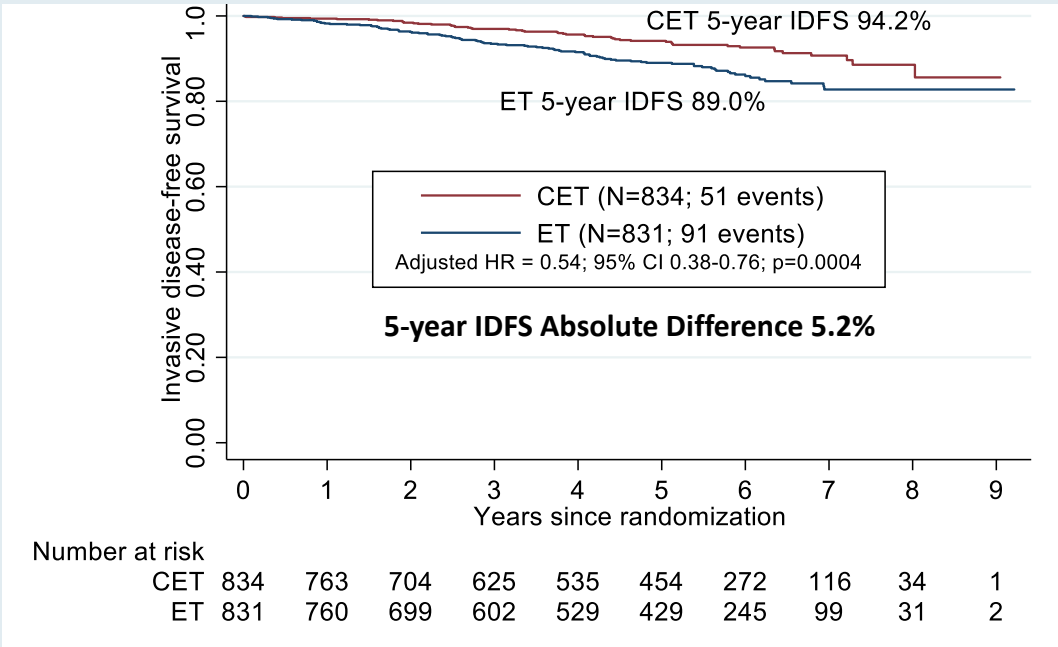
## Postmenopausal




| 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

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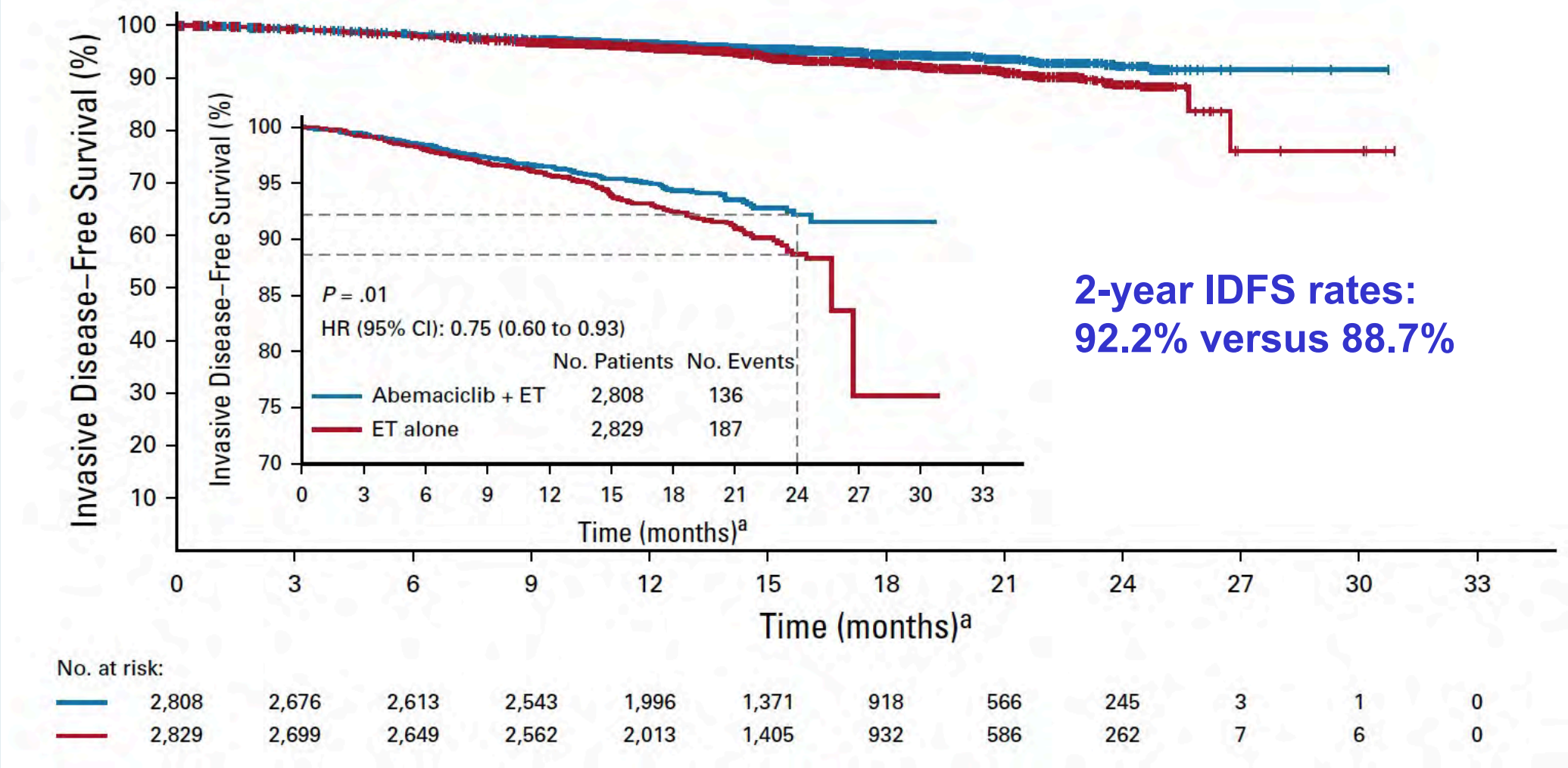
# monarchE: Invasive Disease-Free Survival (IDFS)




**2-year IDFS rates:**
**92.2% versus 88.7%**

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

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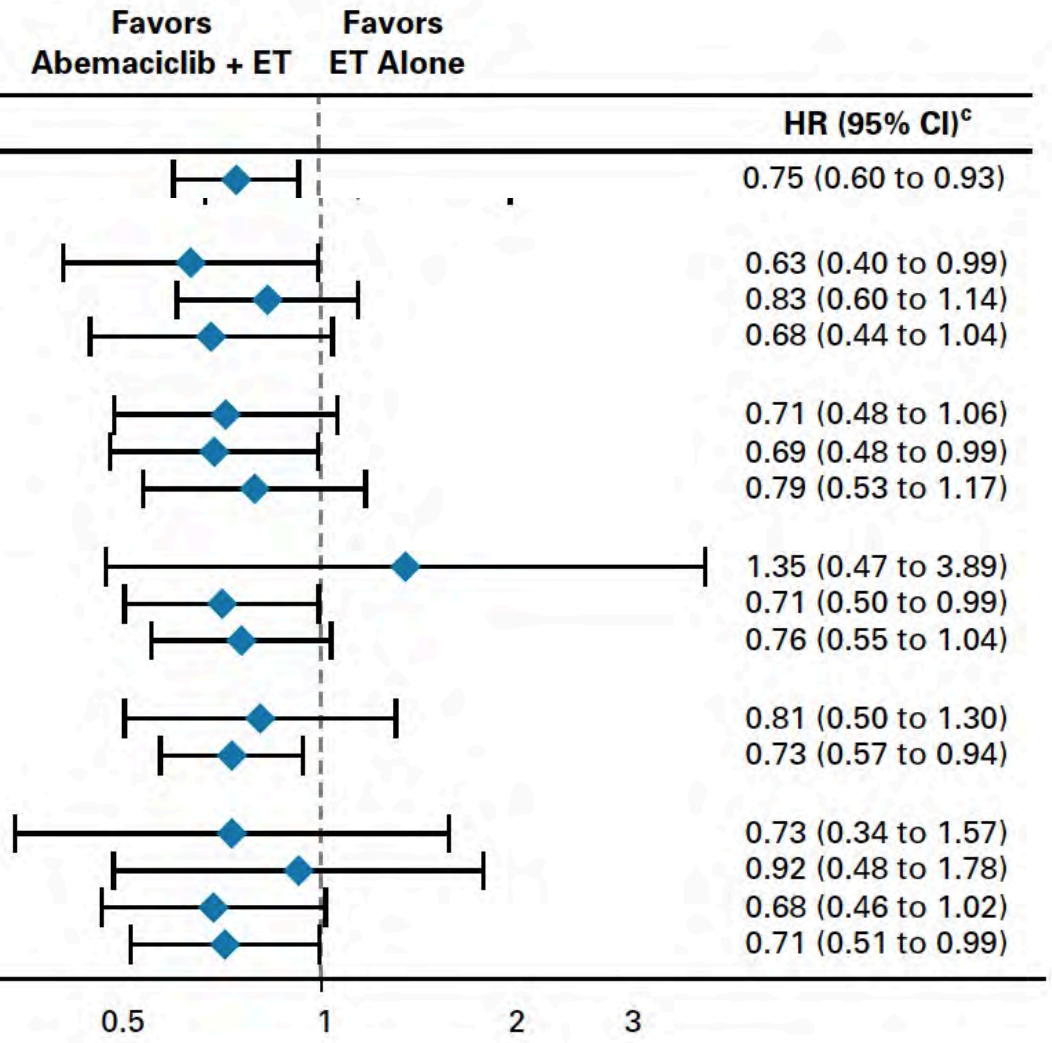
# monarchE: IDFS Subgroups

| 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.

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# 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.

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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*

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# 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?

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# 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.


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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.

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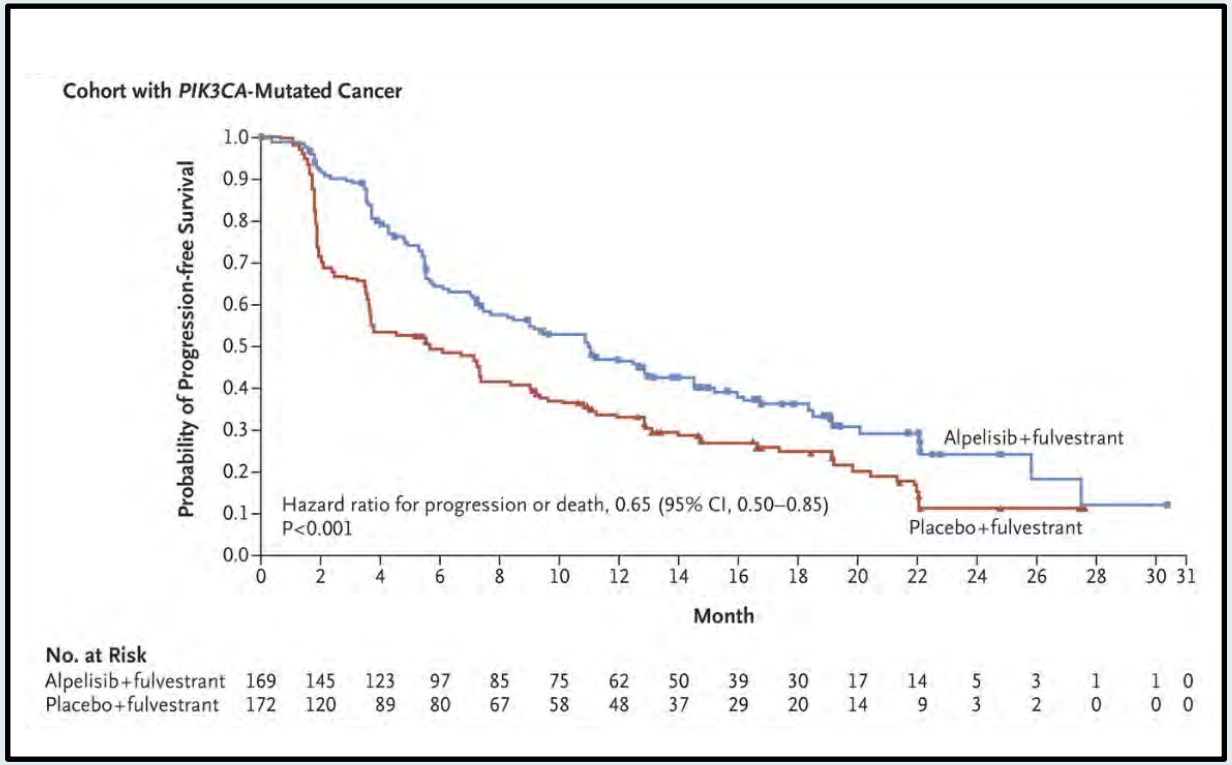
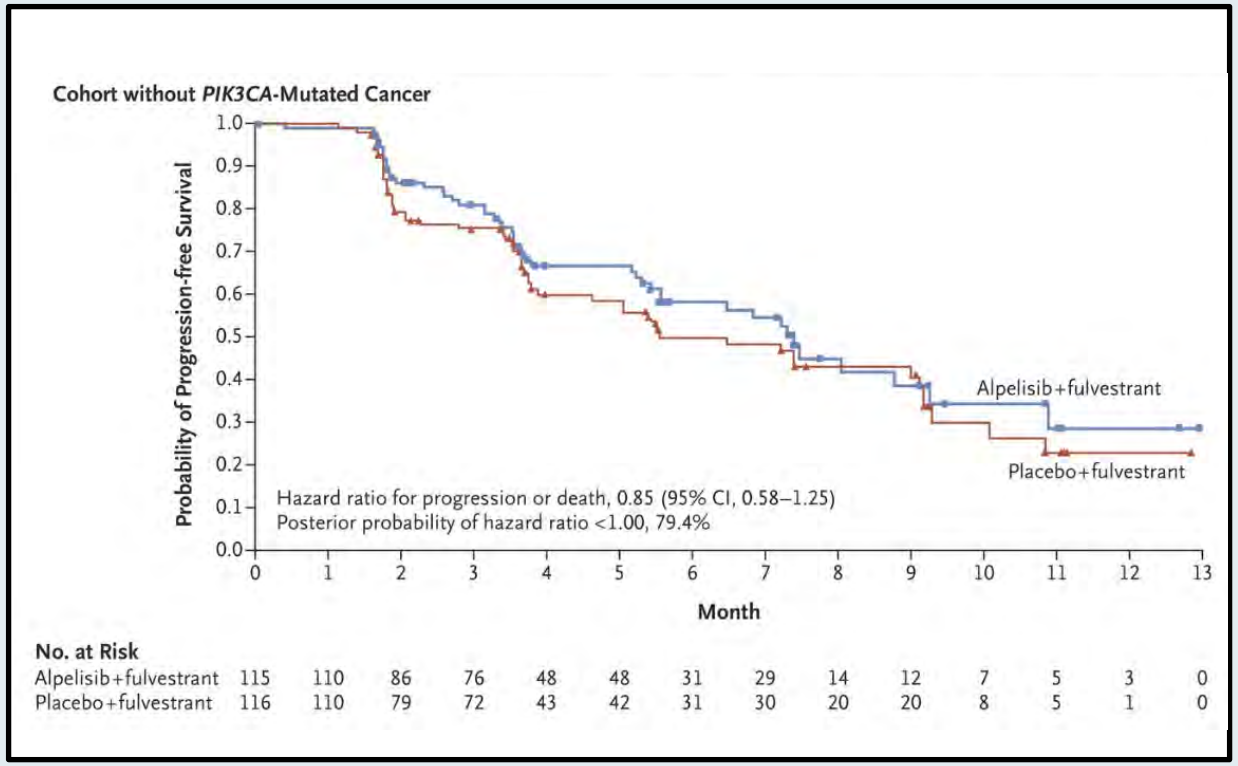
# SOLAR-1: PFS Outcomes by PIK3CA Mutation Status

## PIK3CA mutated




## No PIK3CA mutation




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

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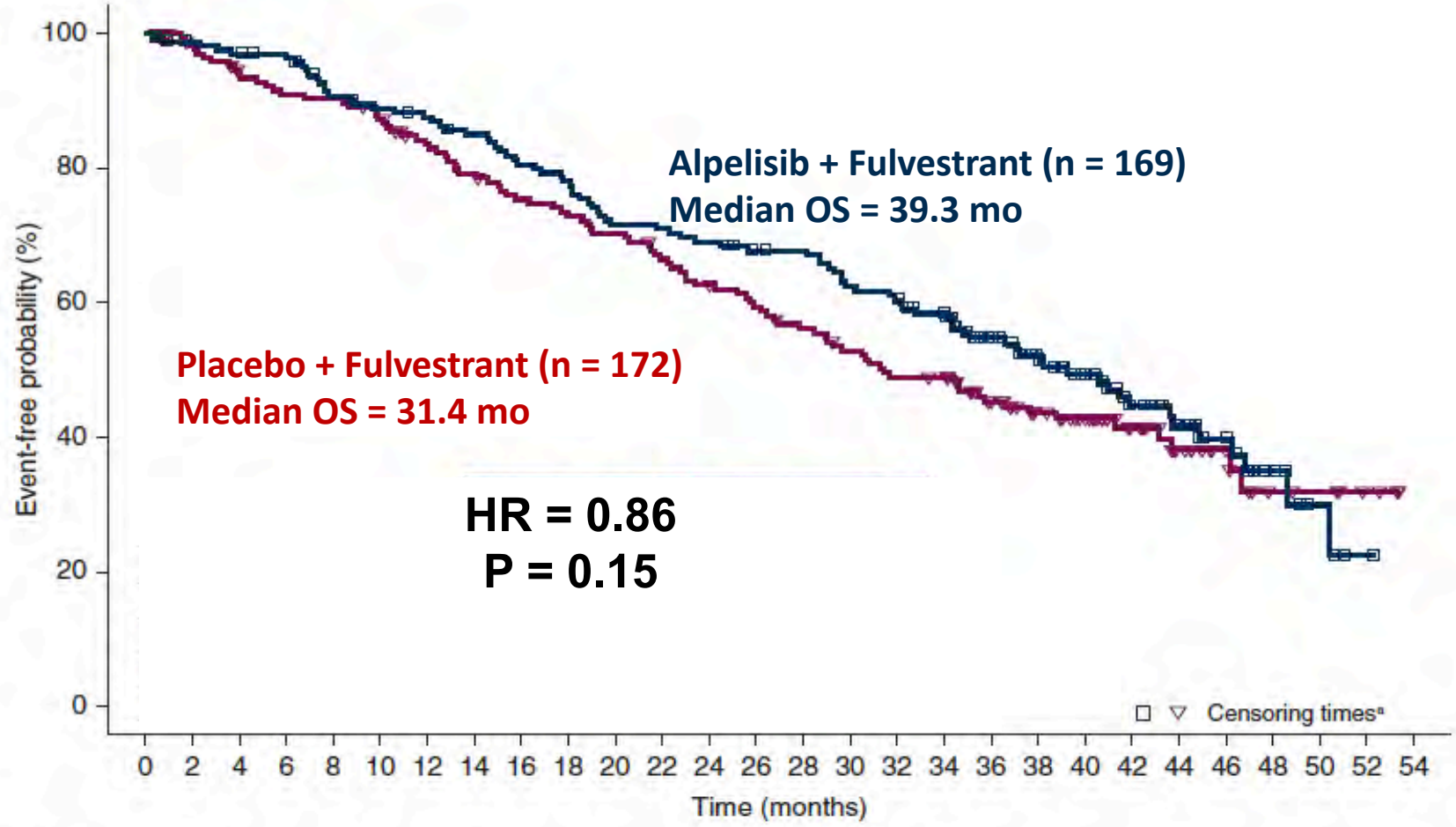
# SOLAR-1: OS in Patients with Advanced BC with a PIK3CA Mutation




Number of patients still at risk

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alpelisib + FUL | 169 | 162 | 159 | 156 | 145 | 141 | 138 | 133 | 126 | 122 | 112 | 111 | 108 | 103 | 102 | 94 | 91 | 85 | 68 | 56 | 47 | 35 | 26 | 19 | 9 | 4 | 1 | 0 |
| Placebo + FUL | 172 | 164 | 155 | 150 | 149 | 143 | 133 | 126 | 119 | 115 | 111 | 104 | 98 | 92 | 86 | 80 | 74 | 73 | 60 | 49 | 42 | 29 | 20 | 13 | 7 | 6 | 3 | 0 |

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

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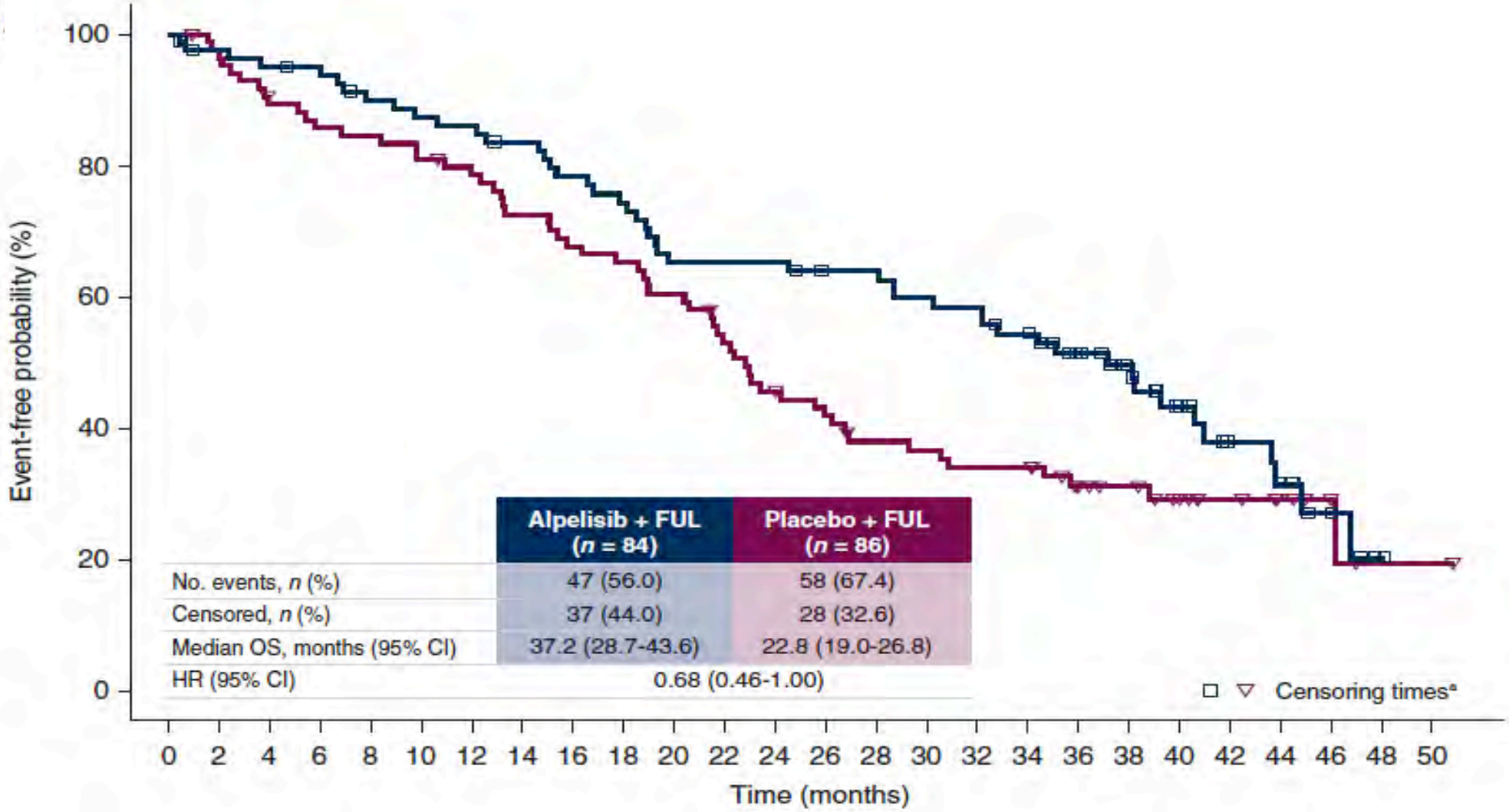
# SOLAR-1: OS in Patients with BC with PIK3CA Mutations and Lung/Liver Metastases




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

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# 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.

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# 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.

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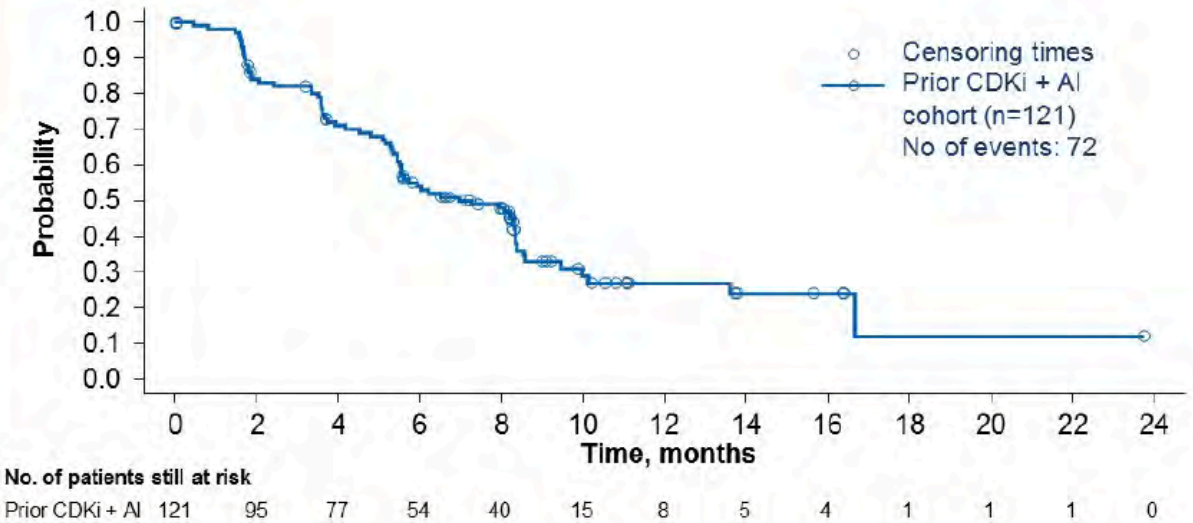
# BYLieve COHORT A: Primary Endpoint and PFS

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.

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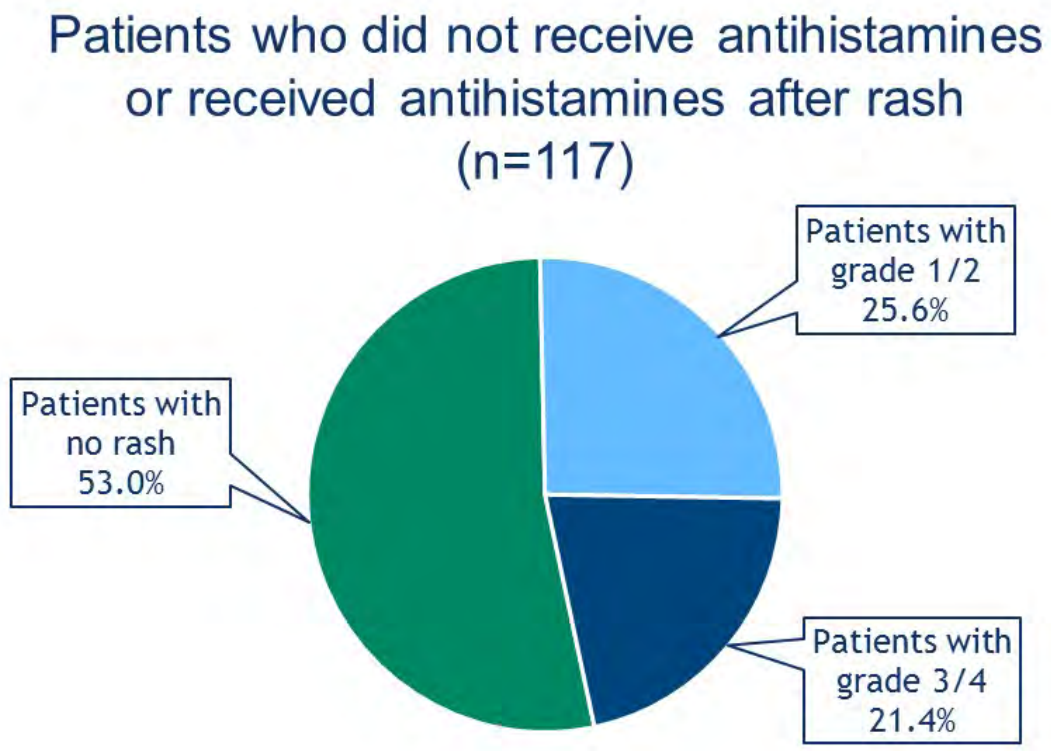
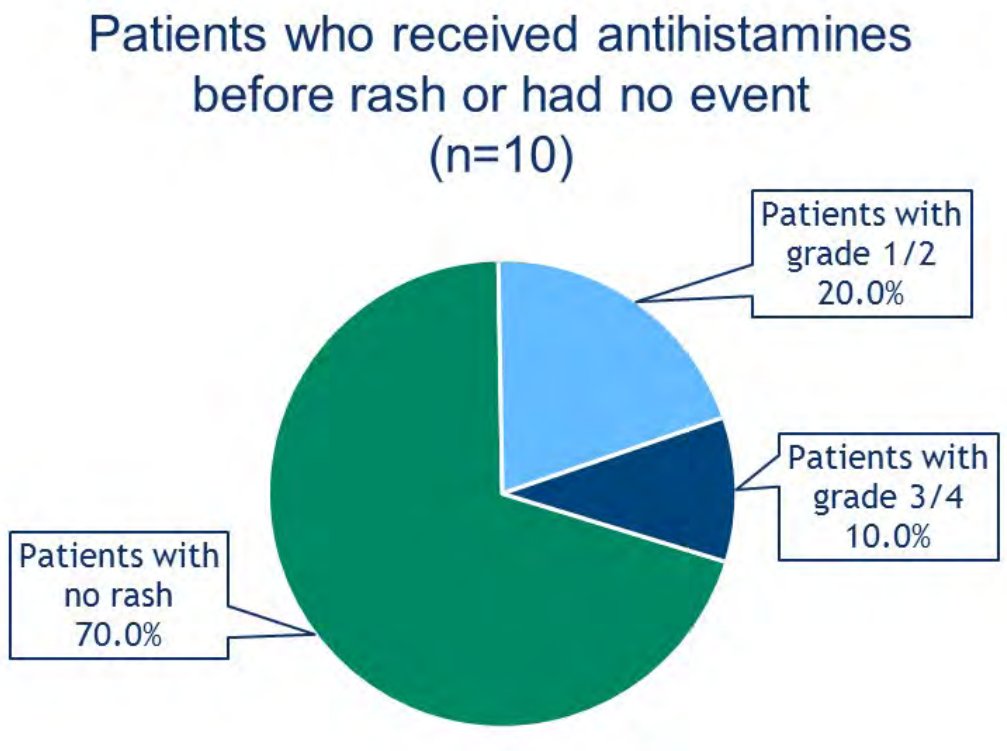
# BYLieve: Incidence of Rash with and without Prophylactic Antihistamines




Rugo HS et al. ASCO 2020;Abstract 1006.

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# 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**

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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*

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# 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?

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# 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?

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## 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?

1. Trastuzumab/lapatinib
2. Neratinib/capecitabine (cape)
3. Tucatinib/trastuzumab/cape
4. Trastuzumab deruxtecan
5. Margetuximab/chemotherapy
6. Other

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# 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.

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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

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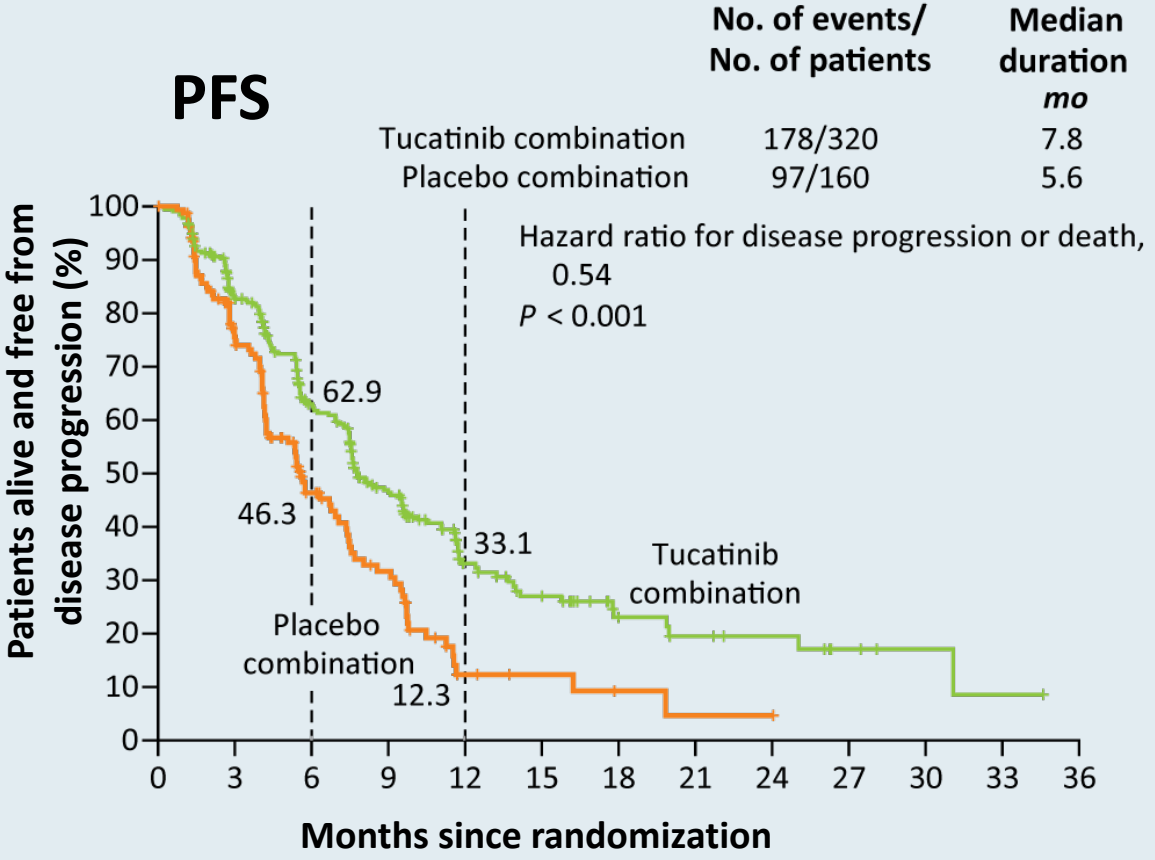
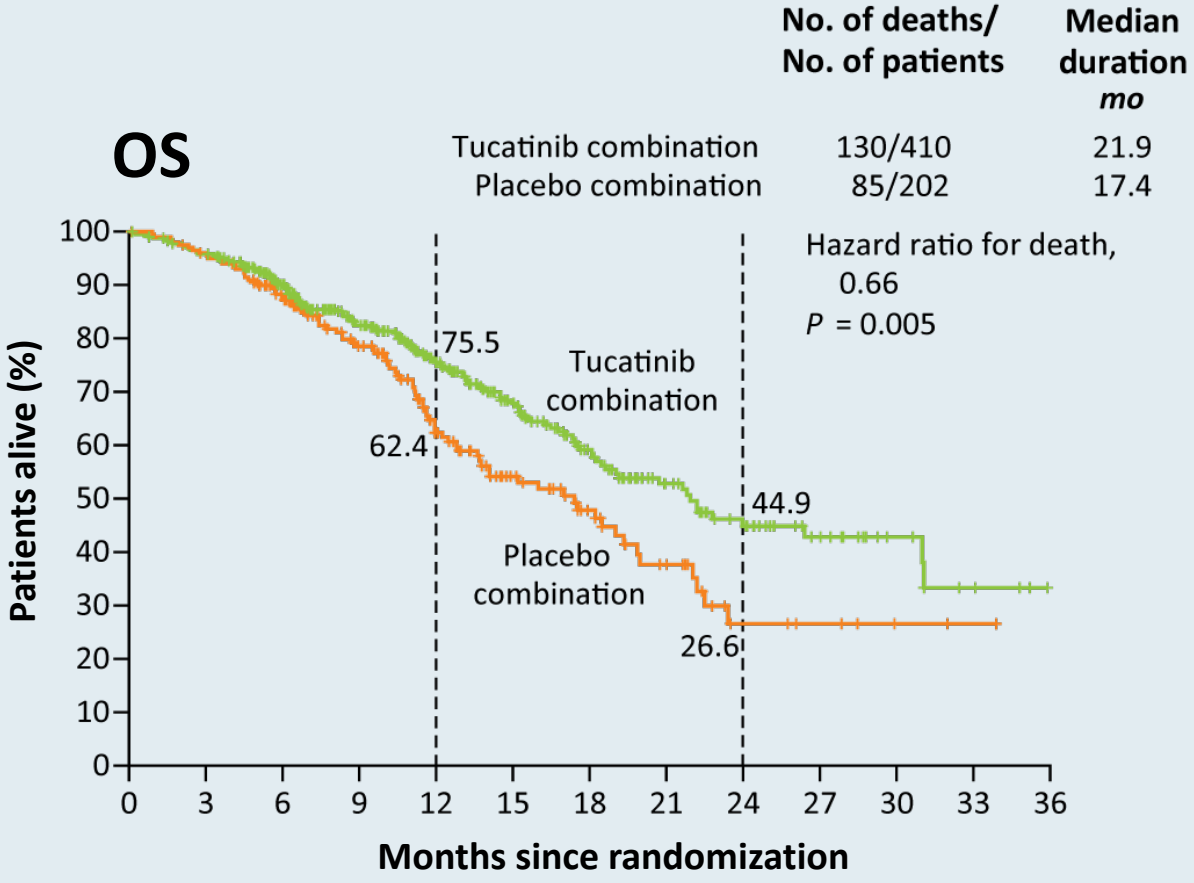
# HER2CLIMB: Survival Outcomes

**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)




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.

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# 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.

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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.

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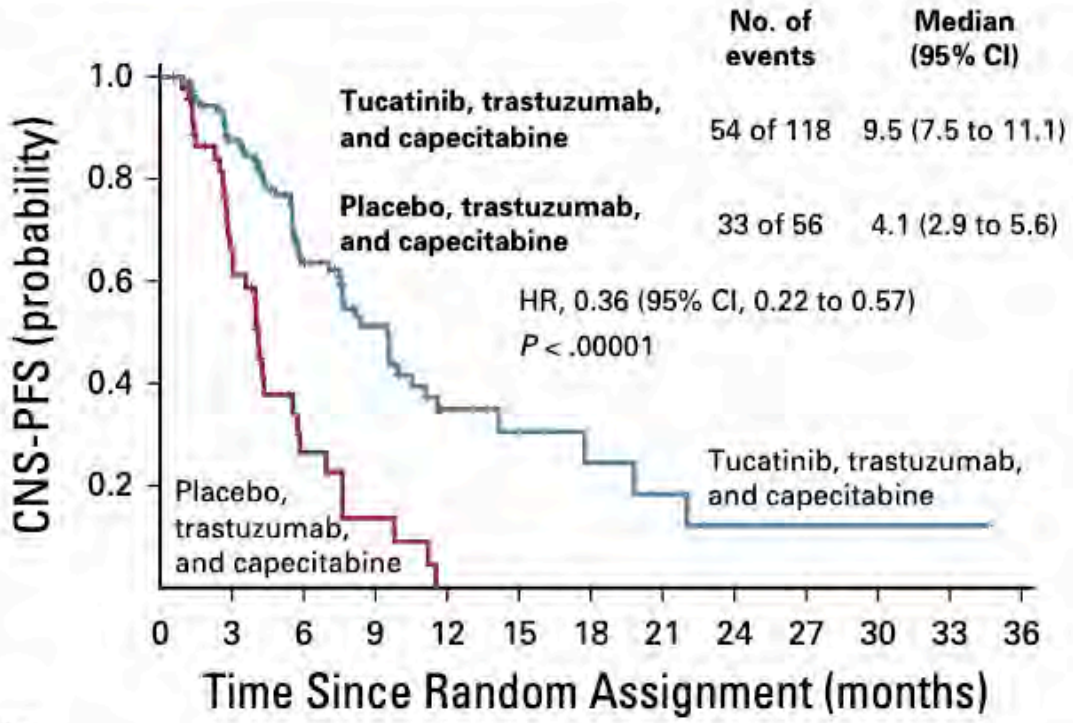
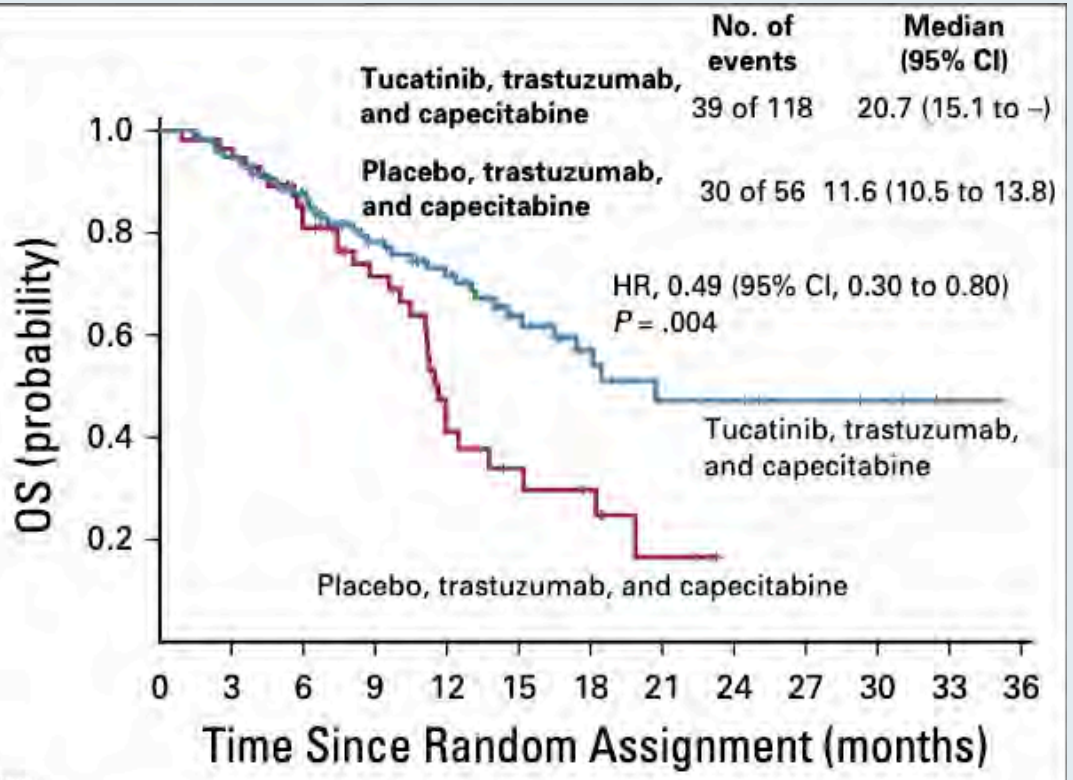
# HER2CLIMB: CNS PFS and OS for Patients with Active Brain Metastases




No. at risk:

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tucatinib, trastuzumab, and capecitabine | 118 | 89 | 49 | 29 | 12 | 7 | 4 | 3 | 1 | 1 | 1 | 1 | 0 |
| Placebo, trastuzumab, and capecitabine | 56 | 26 | 7 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |




No. at risk:

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tucatinib, trastuzumab, and capecitabine | 118 | 111 | 89 | 66 | 51 | 33 | 19 | 11 | 10 | 6 | 5 | 2 | 0 |
| Placebo, trastuzumab, and capecitabine | 56 | 54 | 39 | 29 | 12 | 8 | 6 | 2 | 0 | 0 | 0 | 0 | 0 |

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

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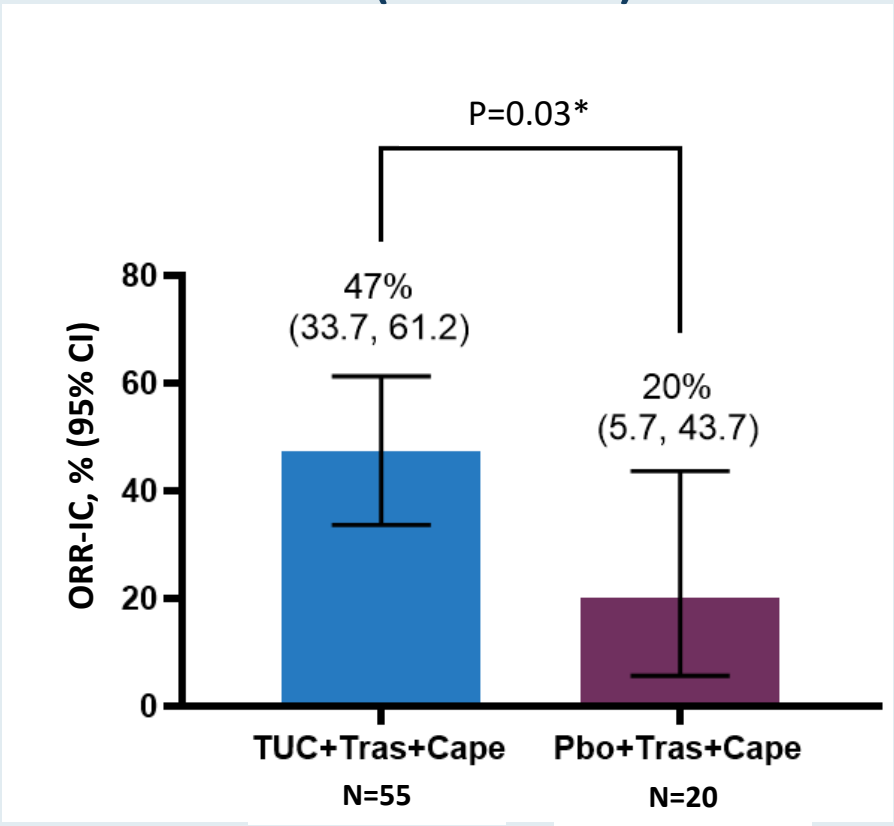
# HER2CLIMB: Intracranial Response Rate (ORR-IC) for Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

## 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

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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.

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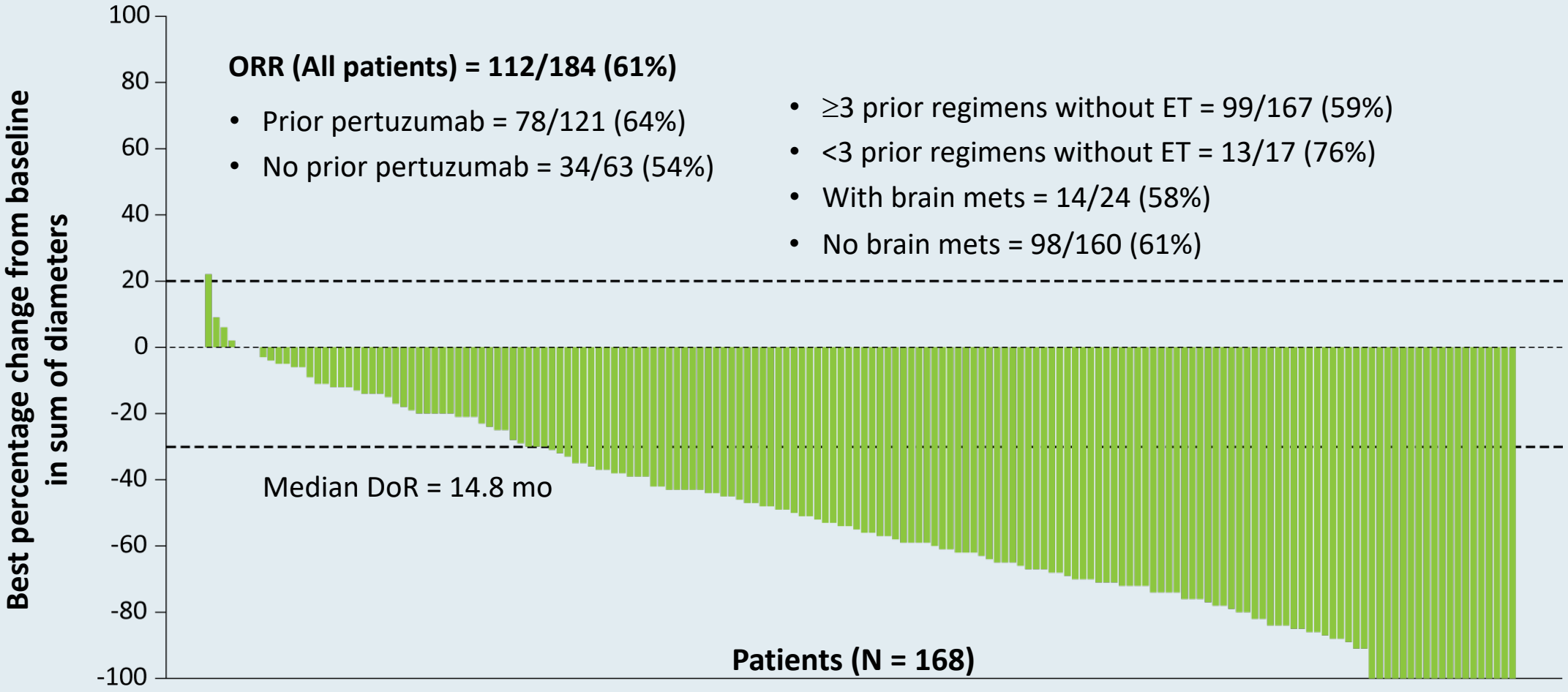
# DESTINY-Breast01: Response According to Tumor Size and Subgroup Analyses




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

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# 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.

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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.

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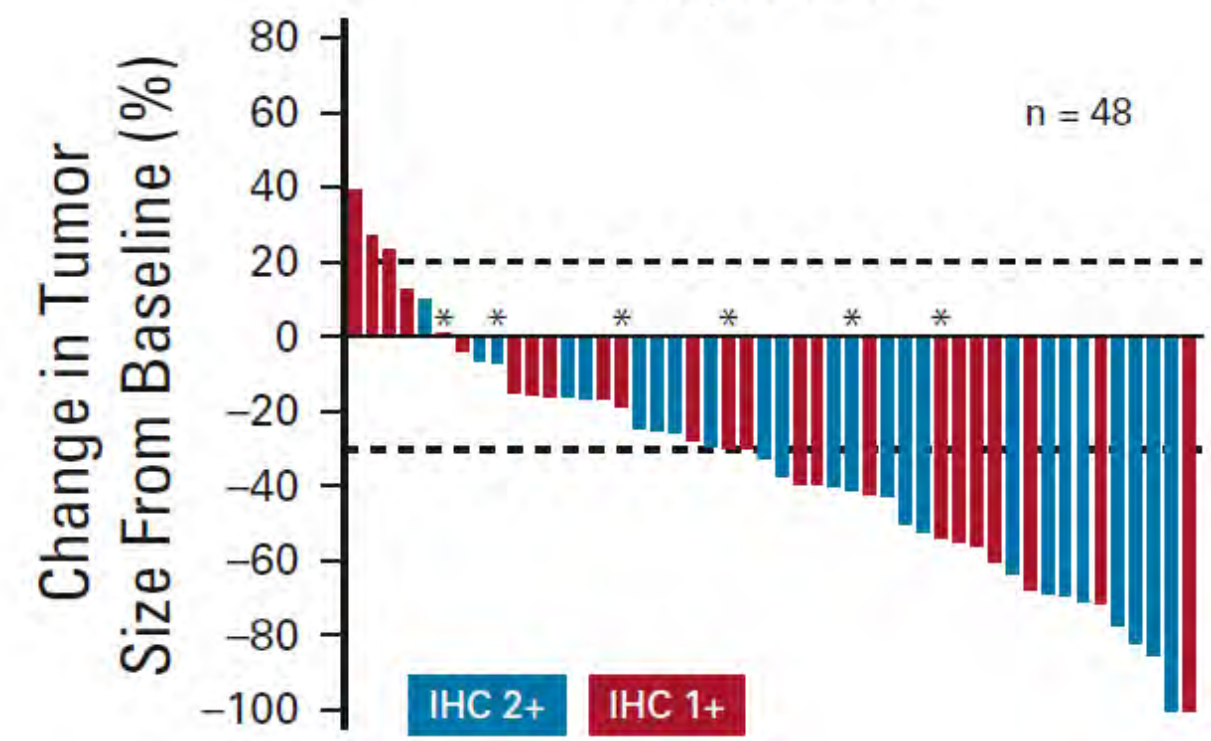
# Effect of Trastuzumab Deruxtecan in Heavily Pretreated* HER2-Low Metastatic Breast Cancer




**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

RTP RESEARCH TO PRACTICE

# 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**

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TO PRACTICE

# 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

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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].

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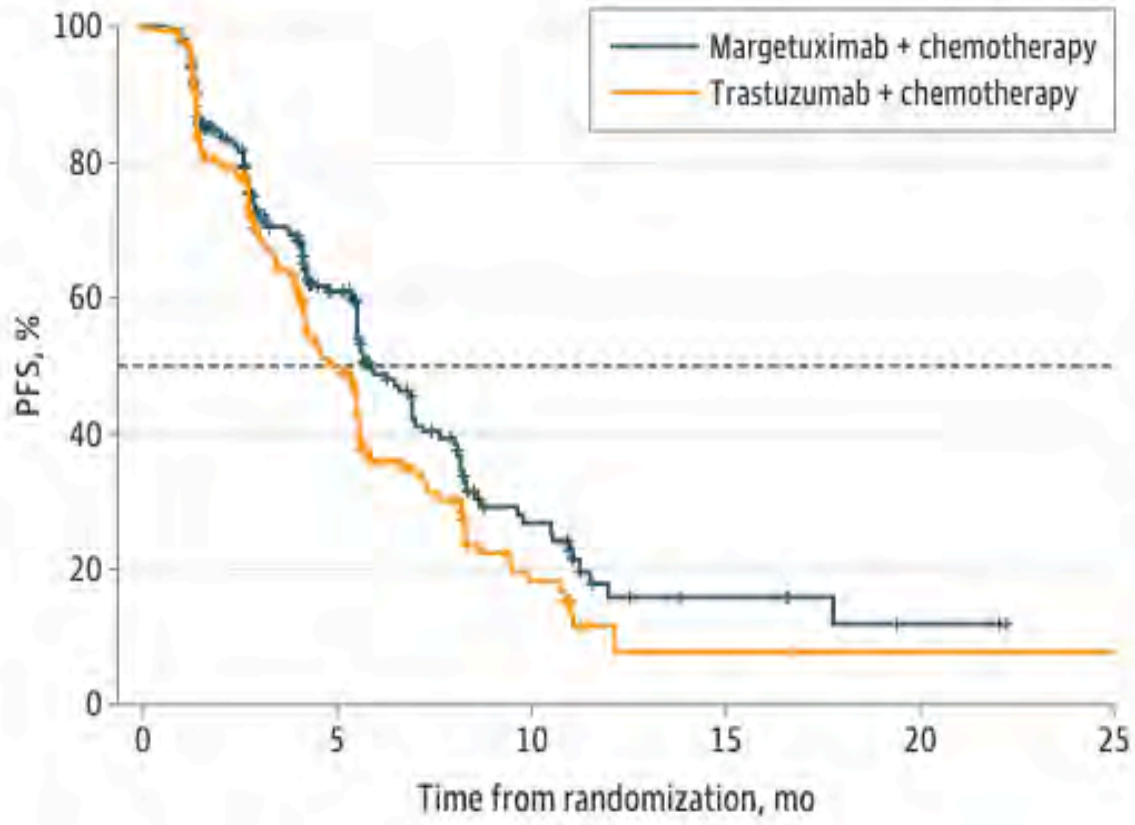
# SOPHIA: PFS by Central Blinded Analysis (ITT Population)




| | 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].

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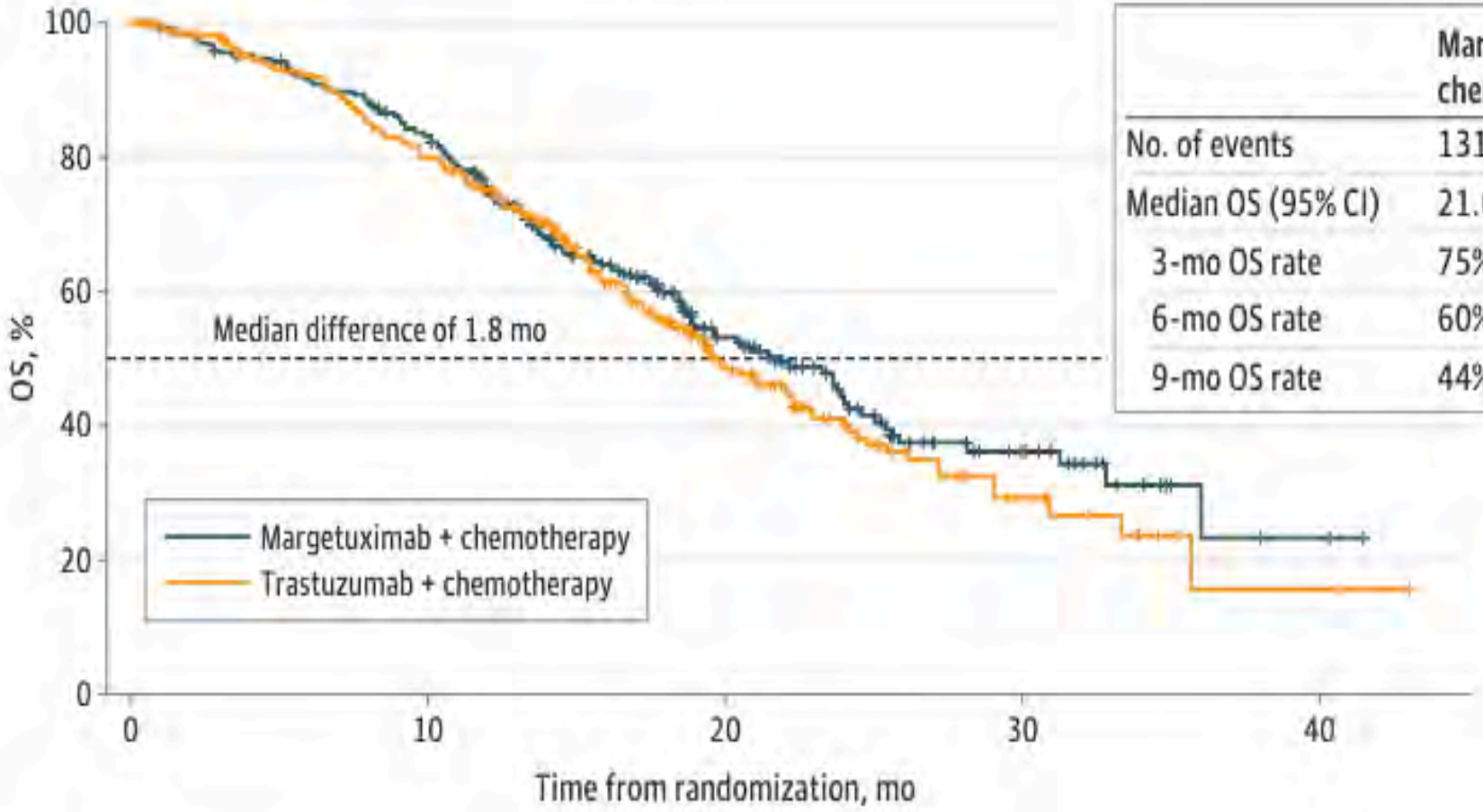
# SOPHIA: OS Analysis (ITT Population)




| | 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].

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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*

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# 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?

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# 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

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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.

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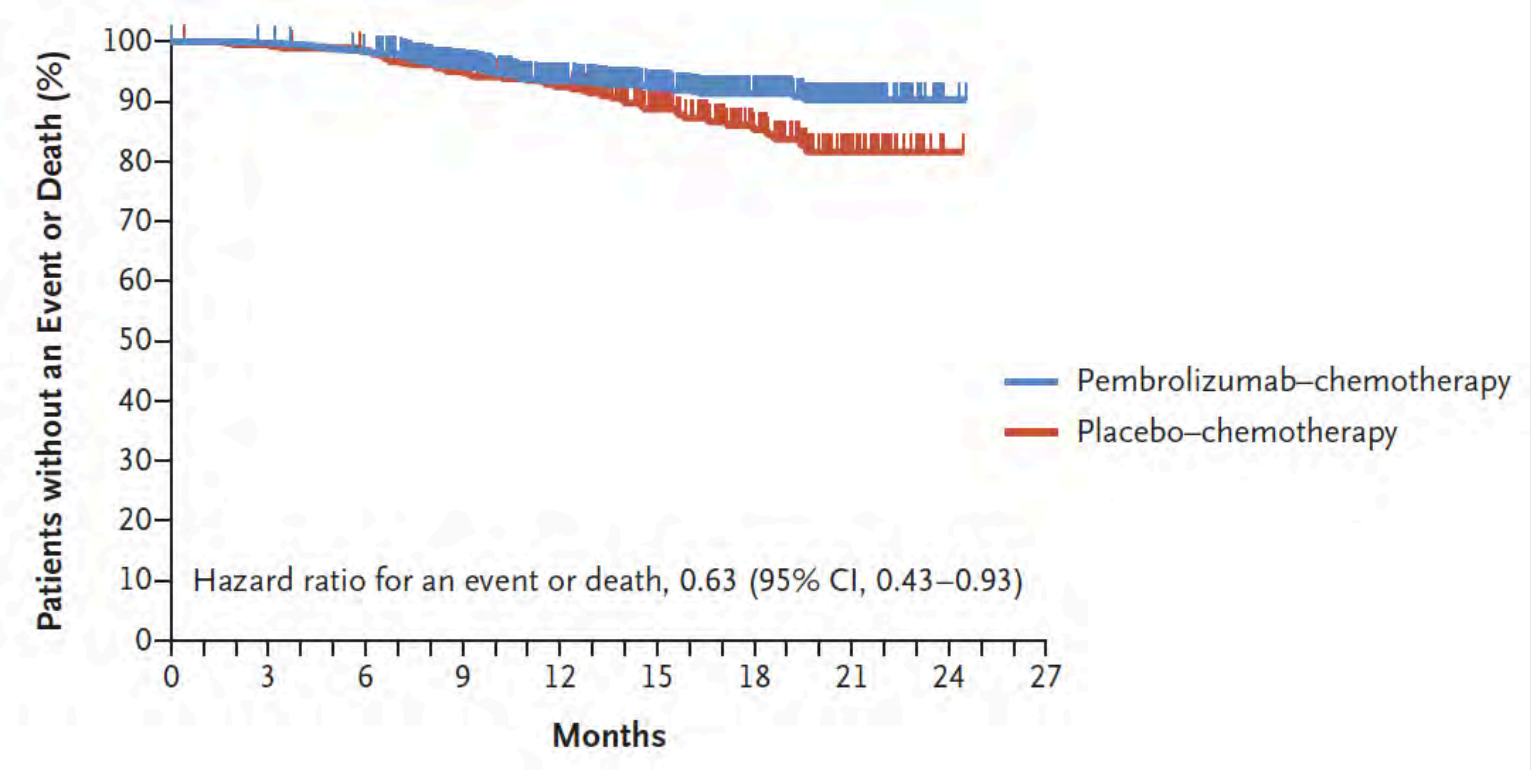
# KEYNOTE-522 Primary Endpoints: pCR and EFS

| 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.

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# 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.

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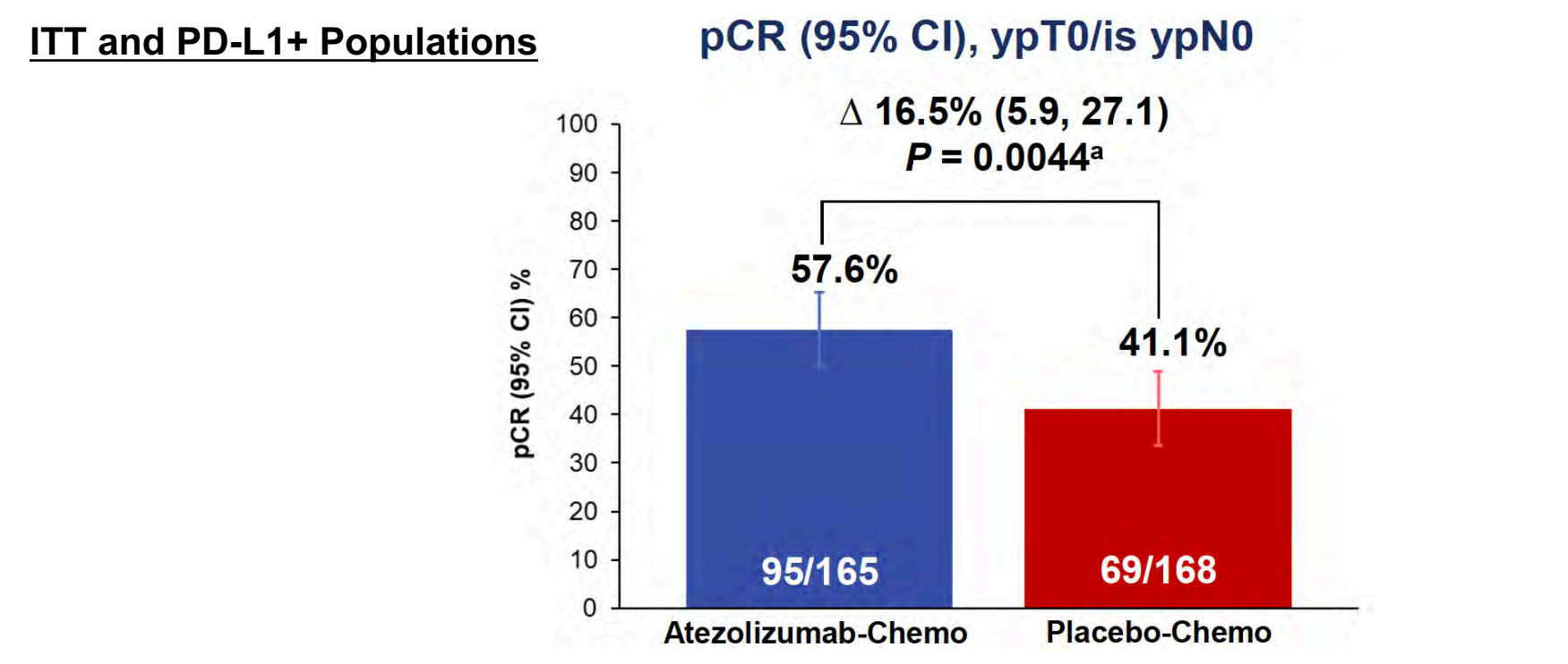
# IMpassion031 Primary Endpoints: pCR in ITT and PD-L1-Positive Tumors




| 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.

RTP RESEARCH TO PRACTICE

# 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**

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# 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?

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# 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.

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*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*

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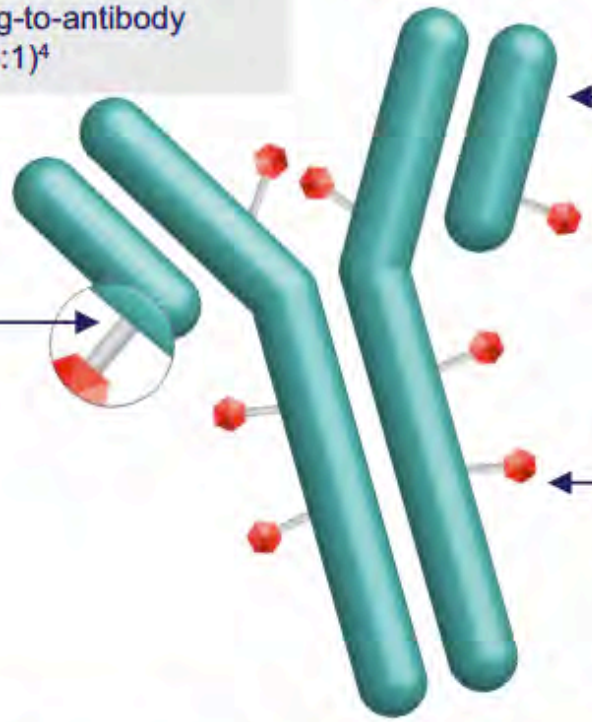
# Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed ADC

- 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.



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

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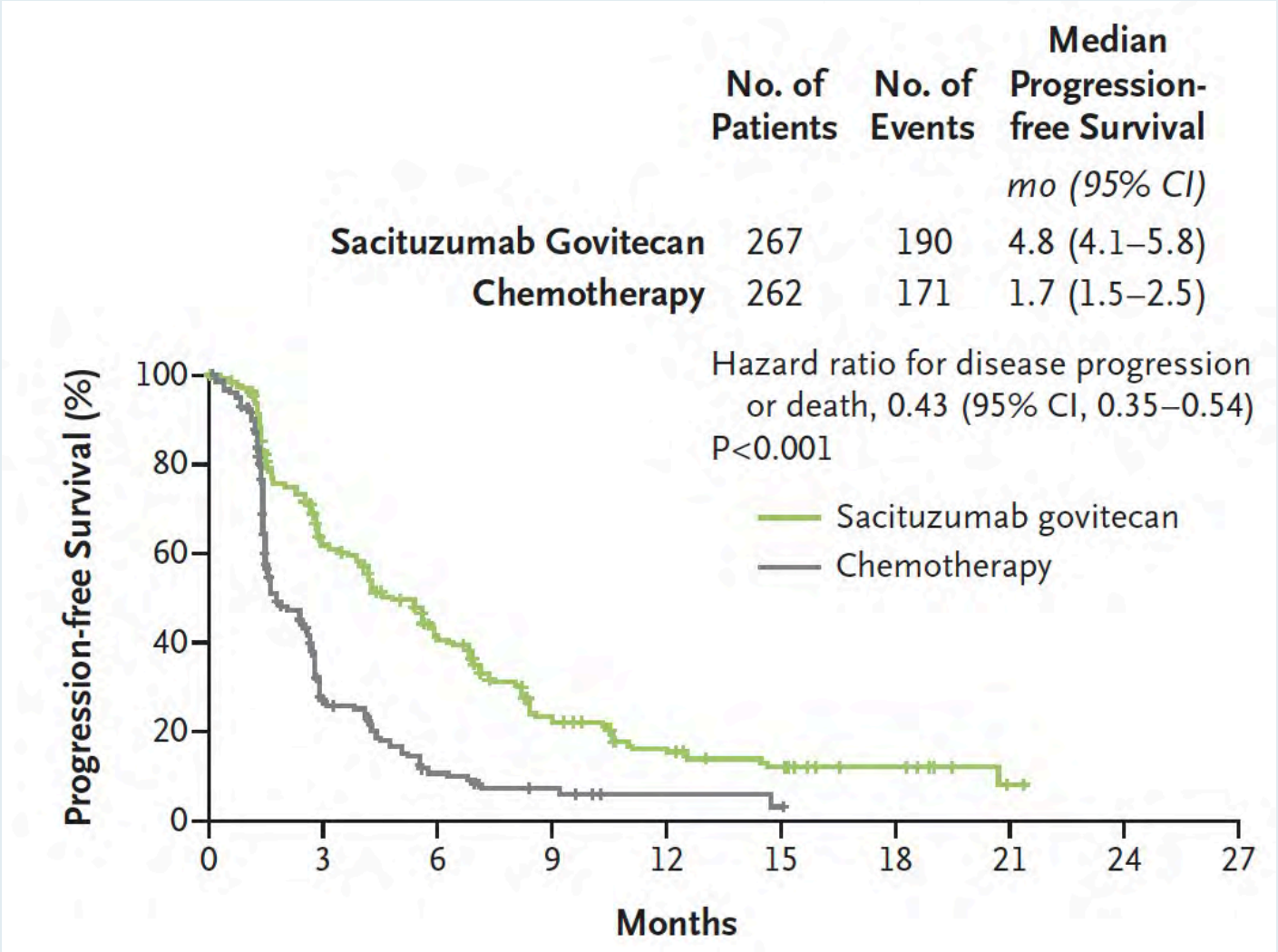
# ASCENT: Progression-Free Survival (Overall Population)




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

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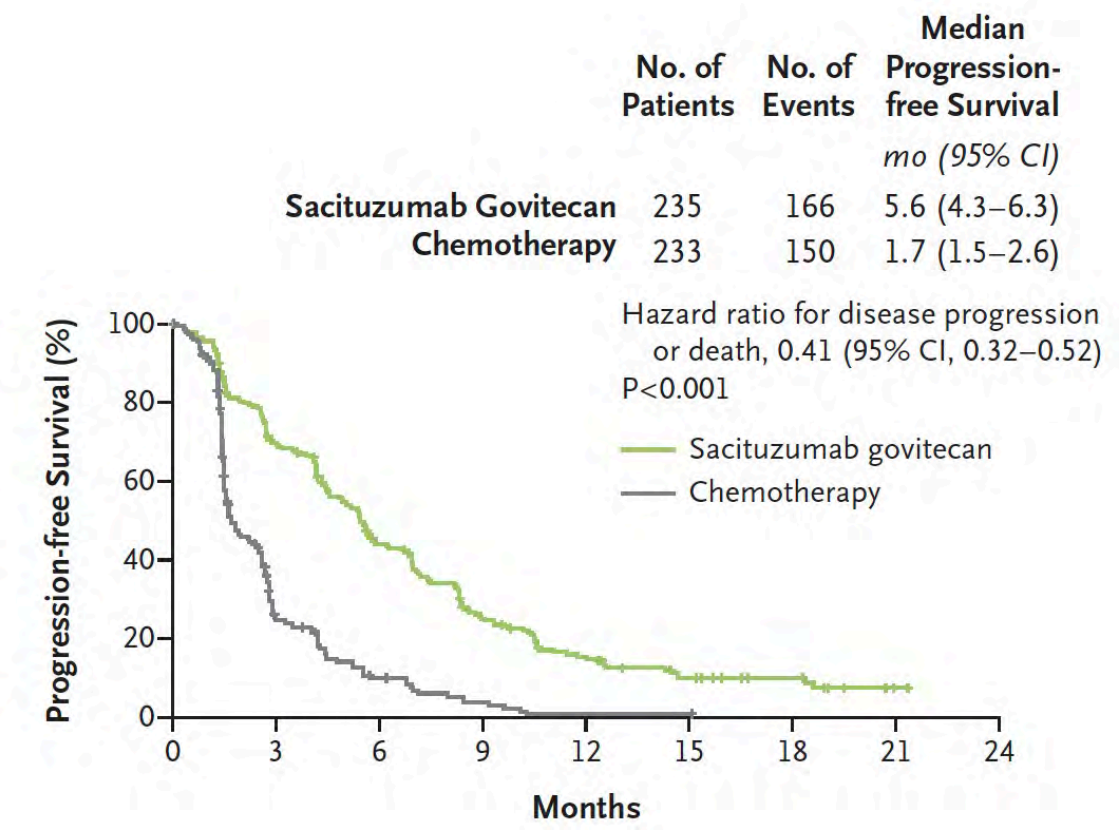
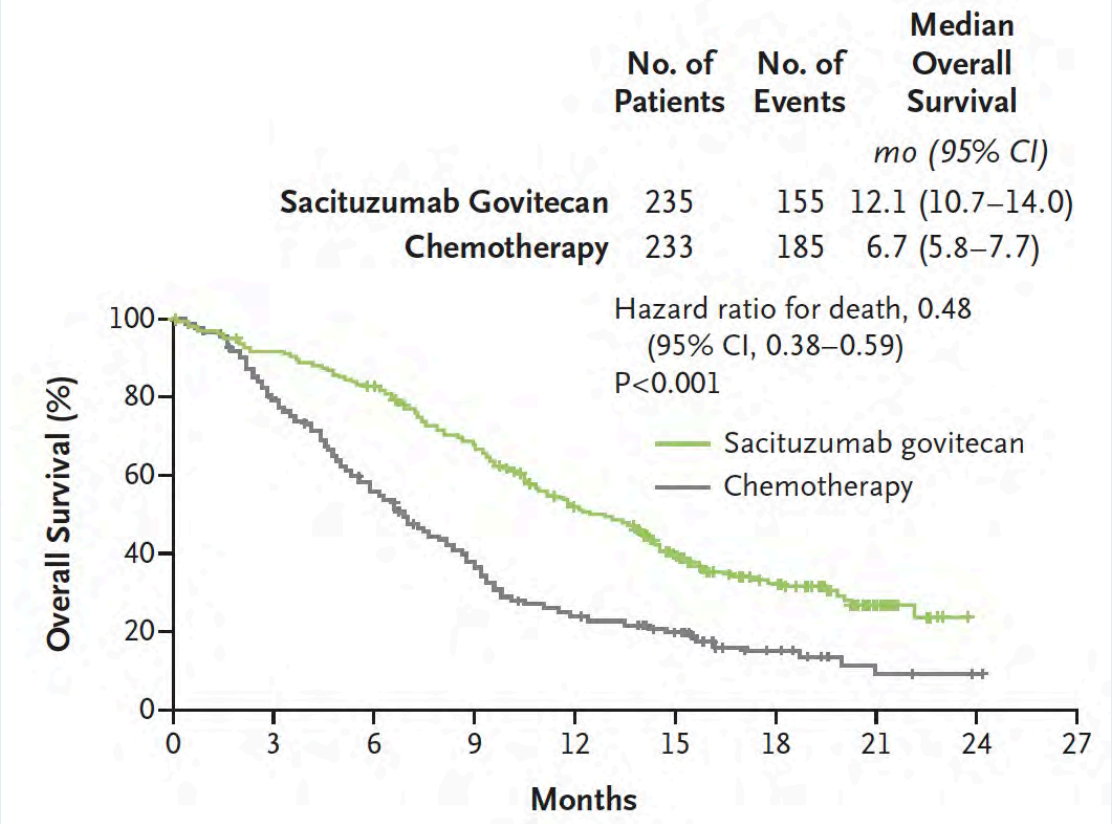
# ASCENT: PFS and OS Among Patients without Brain Metastases




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

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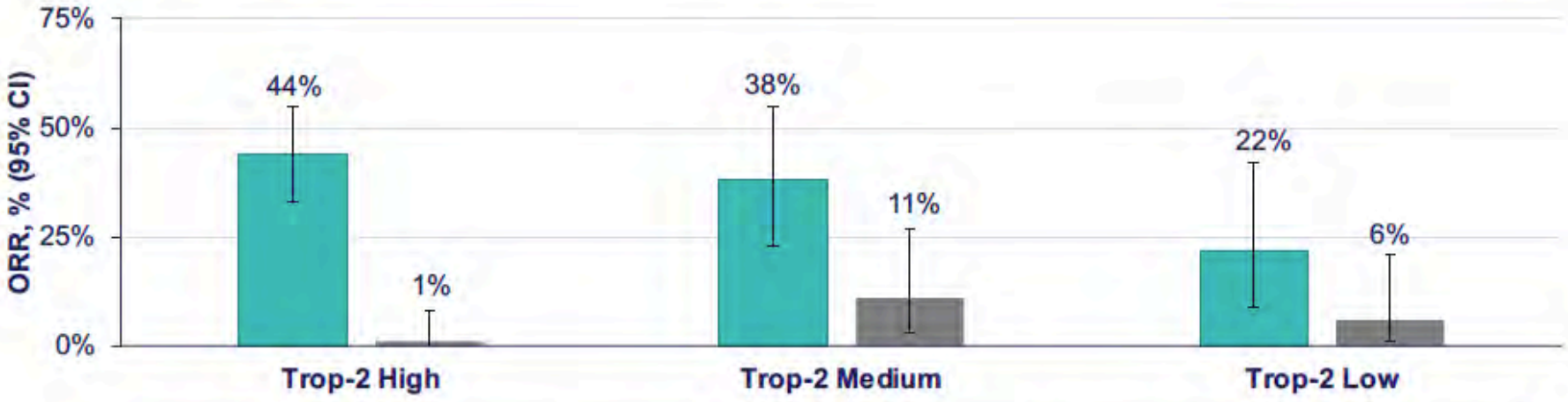
ASCENT

# 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.



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

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# 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**

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***CME, MOC and NCPD credit information will be emailed to each participant within 5 business days.***

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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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# Up for Debate: Oncology Investigators Provide Their Take on Current Controversies in Patient Care

*A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists*

**Saturday, May 22, 2021**
**10:15 AM – 4:15 PM ET**

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# Saturday, May 22, 2021

**10:15 AM — Lung Cancer**
John V Heymach, Stephen V Liu

**11:30 AM — Genitourinary Cancers**
Maha Hussain, Elizabeth R Plimack

**12:45 PM — Chronic Lymphocytic Leukemia and Lymphomas**
Jonathan W Friedberg, Laurie H Sehn

**2:00 PM — Multiple Myeloma**
Irene M Ghobrial, Sagar Lonial

**3:15 PM — Breast Cancer**
Virginia Kaklamani, Nancy U Lin

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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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# 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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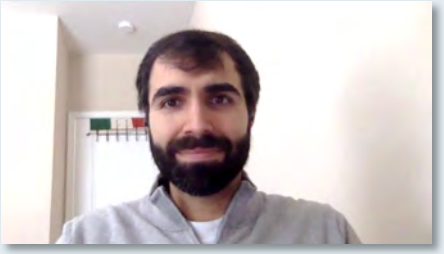
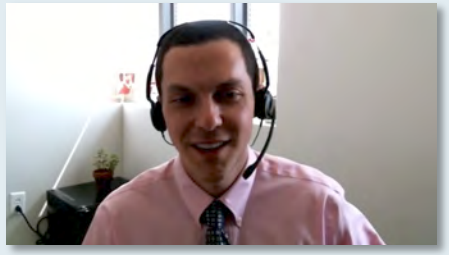
# Contributing Oncologists



**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
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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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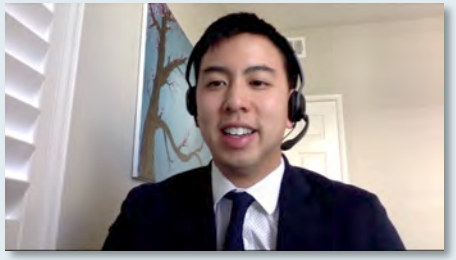
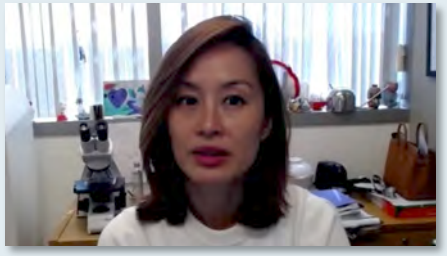
# Contributing Oncologists

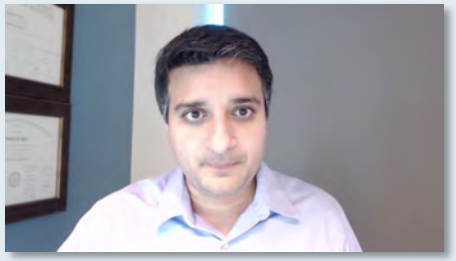
**Mohamed K Mohamed, MD, PhD**
Oncology Division Medical Director
Director of Thoracic Oncology
Hematologist/ Medical Oncologist
Cone Health Cancer Center
Greensboro, North Carolina



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

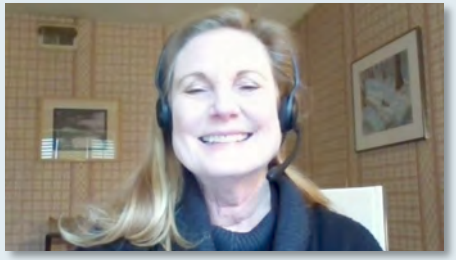


**Helen H Moon, MD**
Medical Oncologist
Southern California Permanente
Medical Group
Riverside, California



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

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



**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
- Dr Del Rosario: A 54-year-old man with relapsed multiple myeloma who receives CAR T-cell therapy
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- Dr Lorber: A 75-year-old man with myeloma and disease progression on 5 lines of therapy
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## Module 3: Amyloid Light Chain (AL) Amyloidosis

- Dr Chen: A 65-year-old man with AL amyloidosis and renal failure
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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)?

1. RVd
2. KRd
3. CyBorD
4. Rd/daratumumab
5. RVd/daratumumab
6. KRd/daratumumab
7. MPV/daratumumab
8. Other

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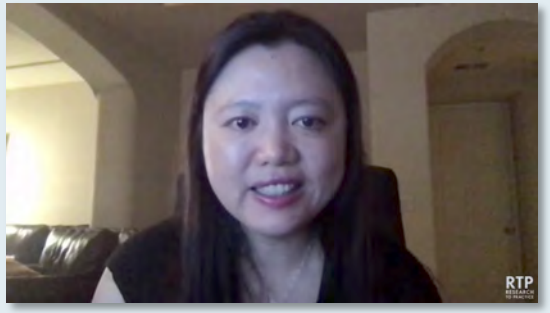
# Case Presentation – Dr Chen: A 65-year-old man with newly diagnosed multiple myeloma




**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.

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# 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**

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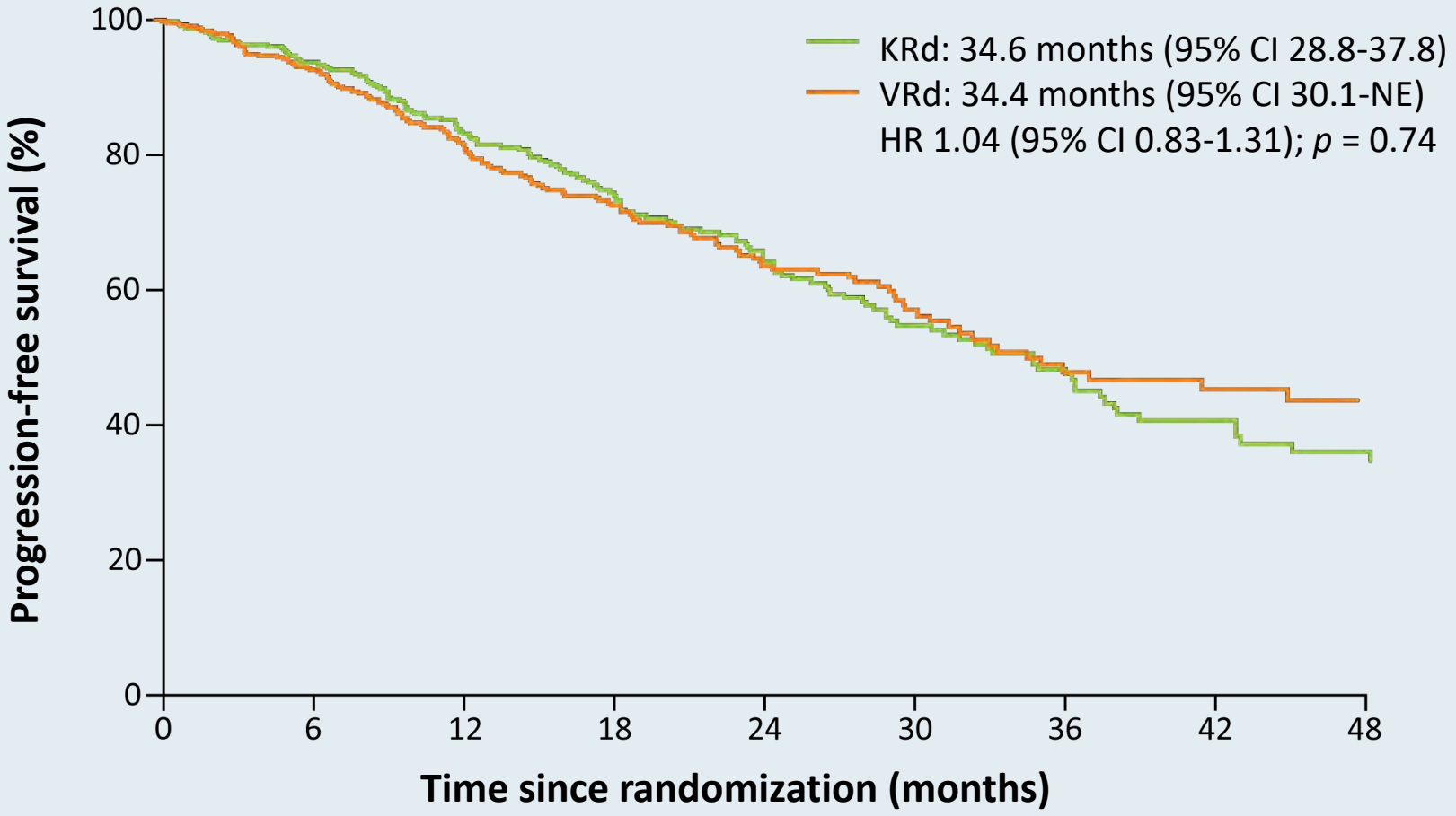
# ENDURANCE (E1A11): Primary PFS Endpoint (Second Interim Analysis)




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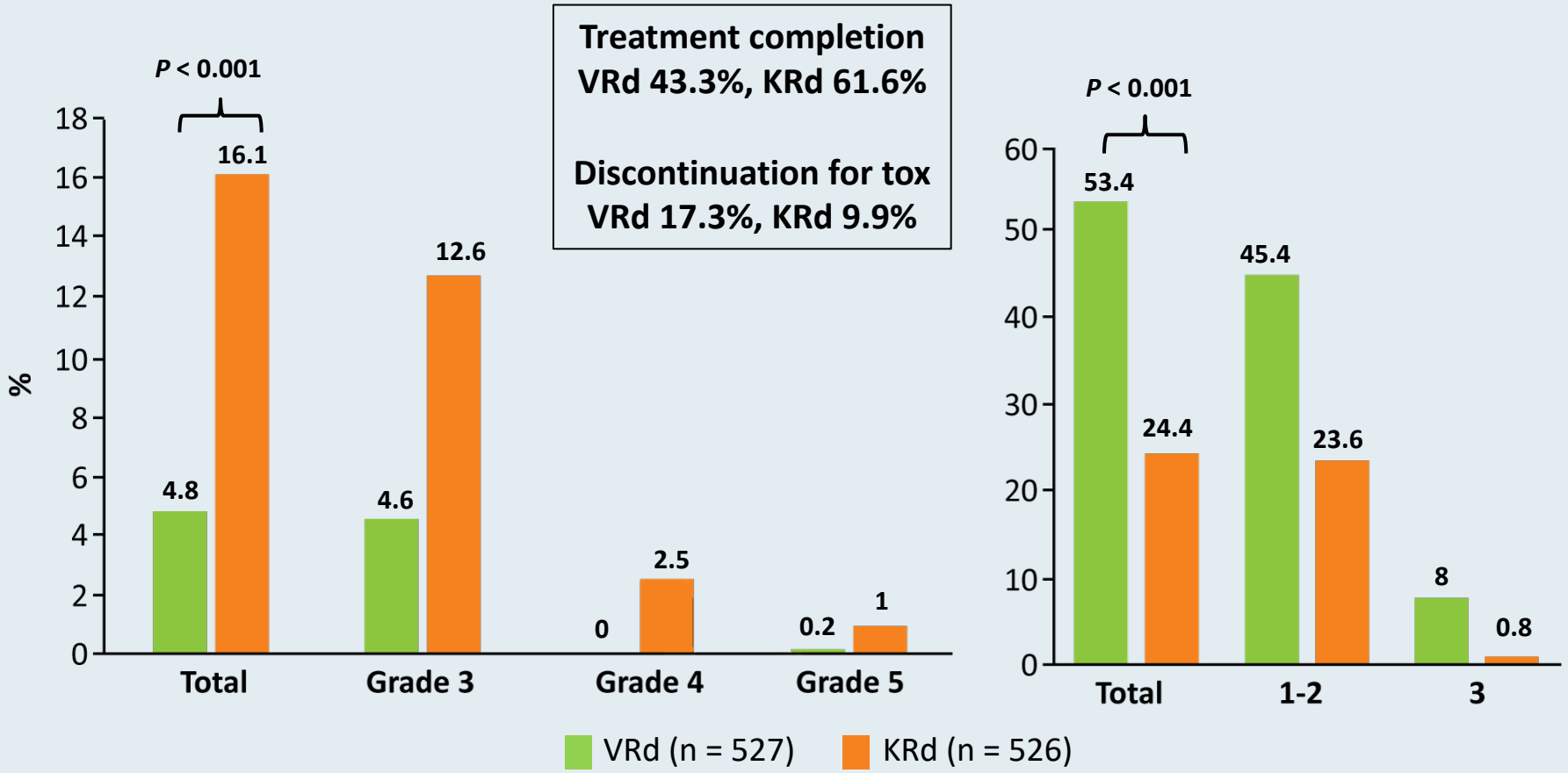
# ENDURANCE (E1A11): Treatment-Emergent Adverse Events of Interest




**Cardiac, pulmonary and renal**

**Peripheral neuropathy***

* Grades 1-2 not required reporting

Berdeja JG. ASCO 2020 Discussant.

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# 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.

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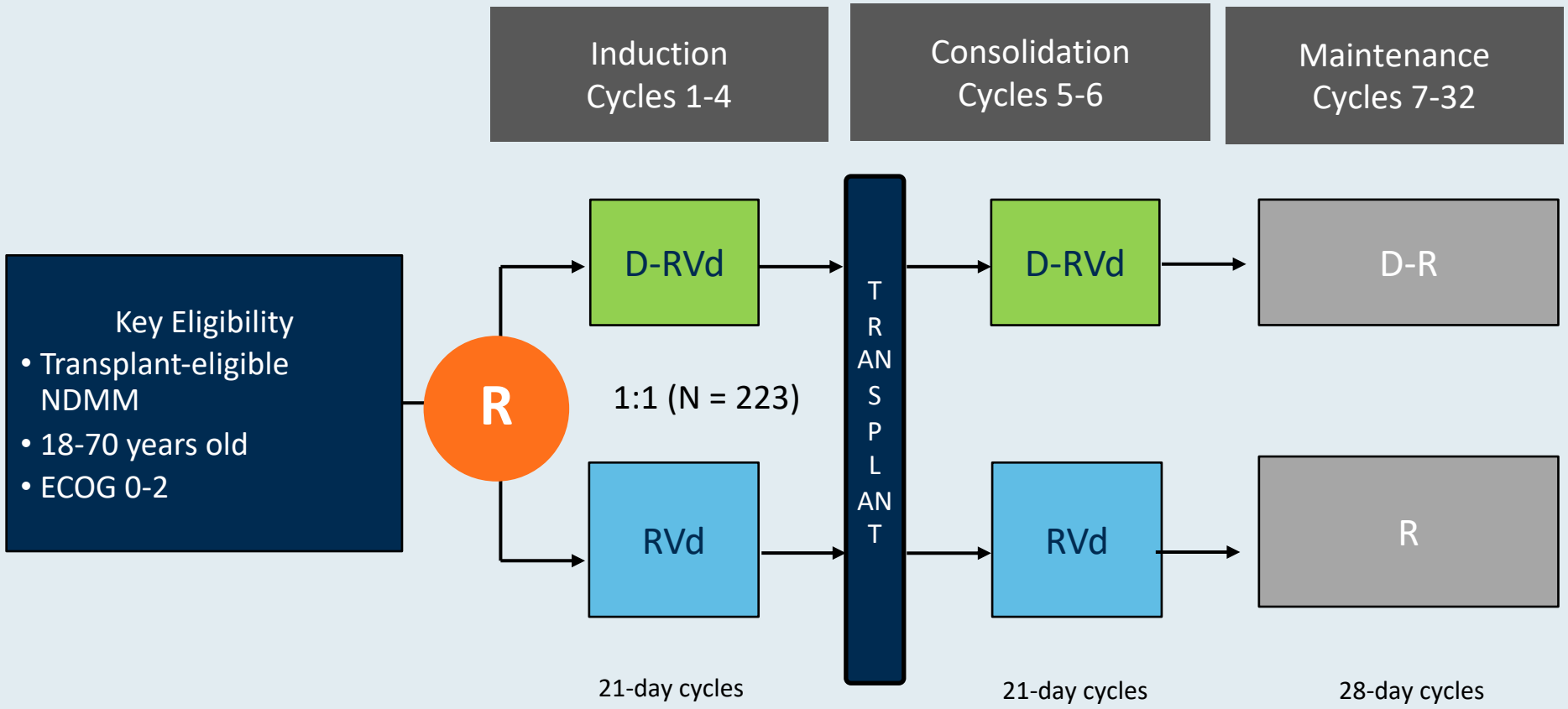
# GRIFFIN Randomized Phase II Study Design




Primary endpoint: Stringent CR by end of consolidation

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

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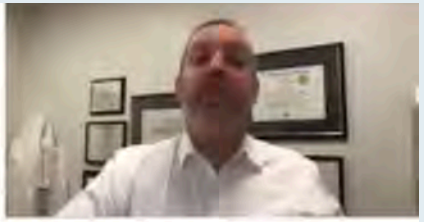
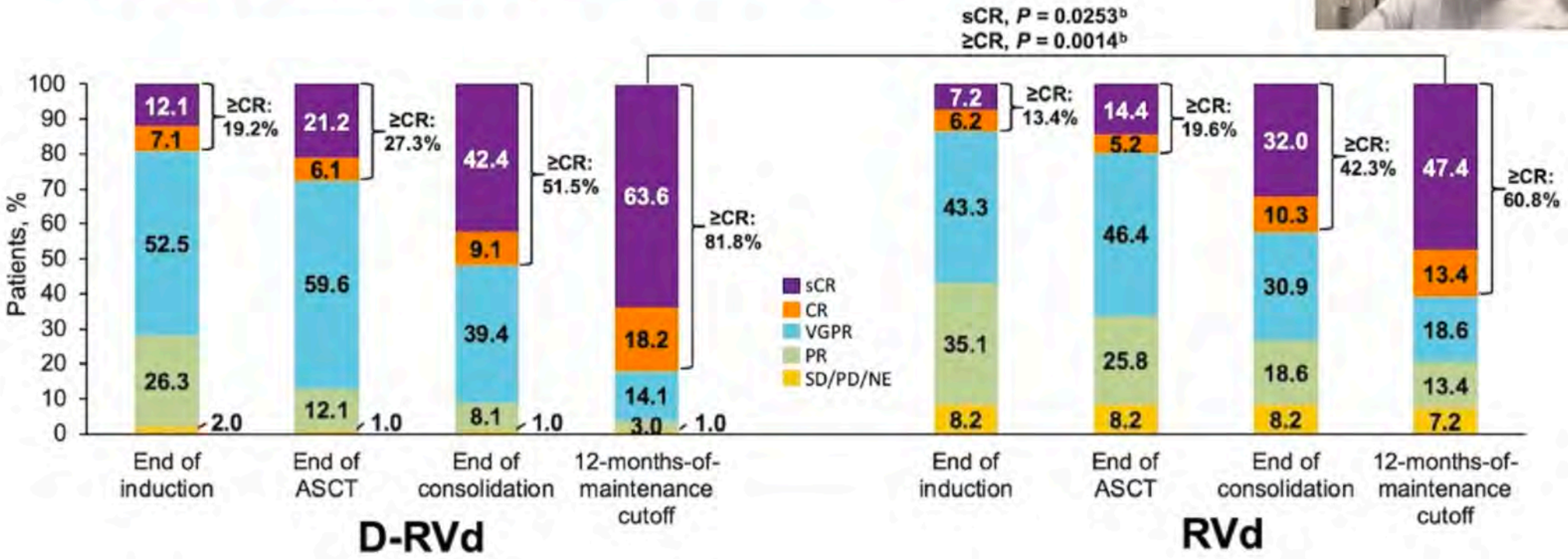
# Responses Deepened over Time[a]






- *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.

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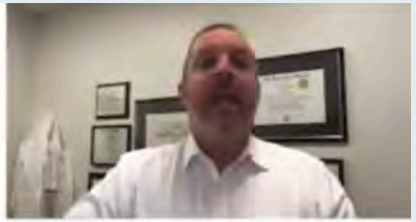
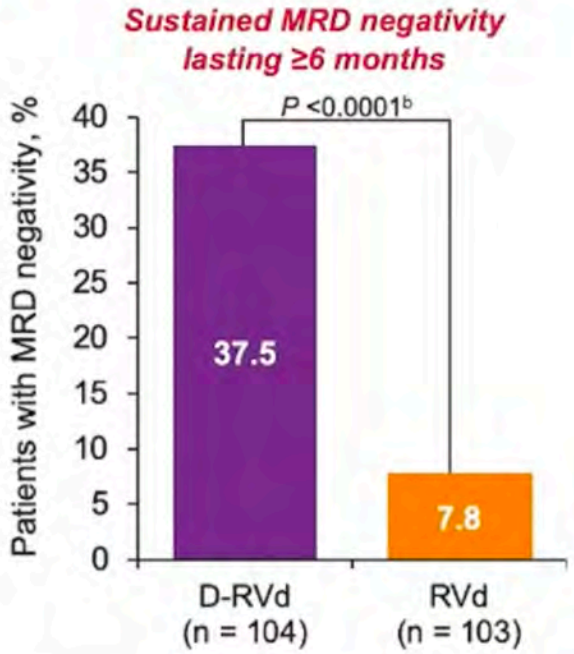
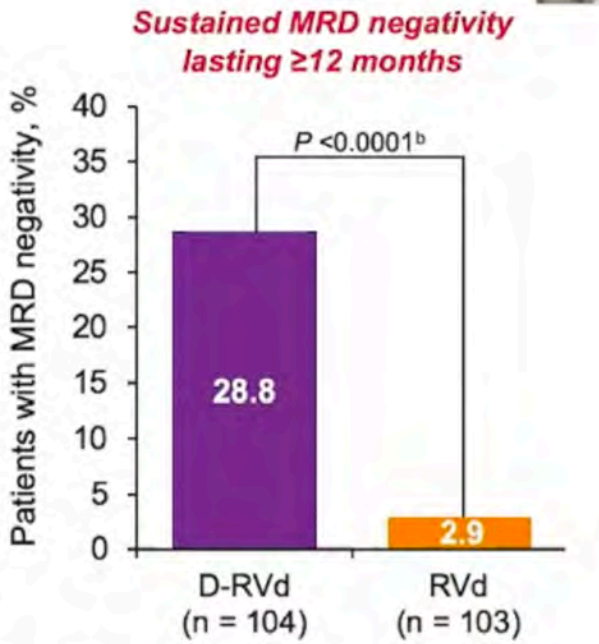
# Durable MRD ($10^{-5}$) Negativity[a] Lasting ≥6 and ≥12 Months






- *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.

American Society *of* Hematology



Kaufman JL et al. ASH 2020;Abstract 549.

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# 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.

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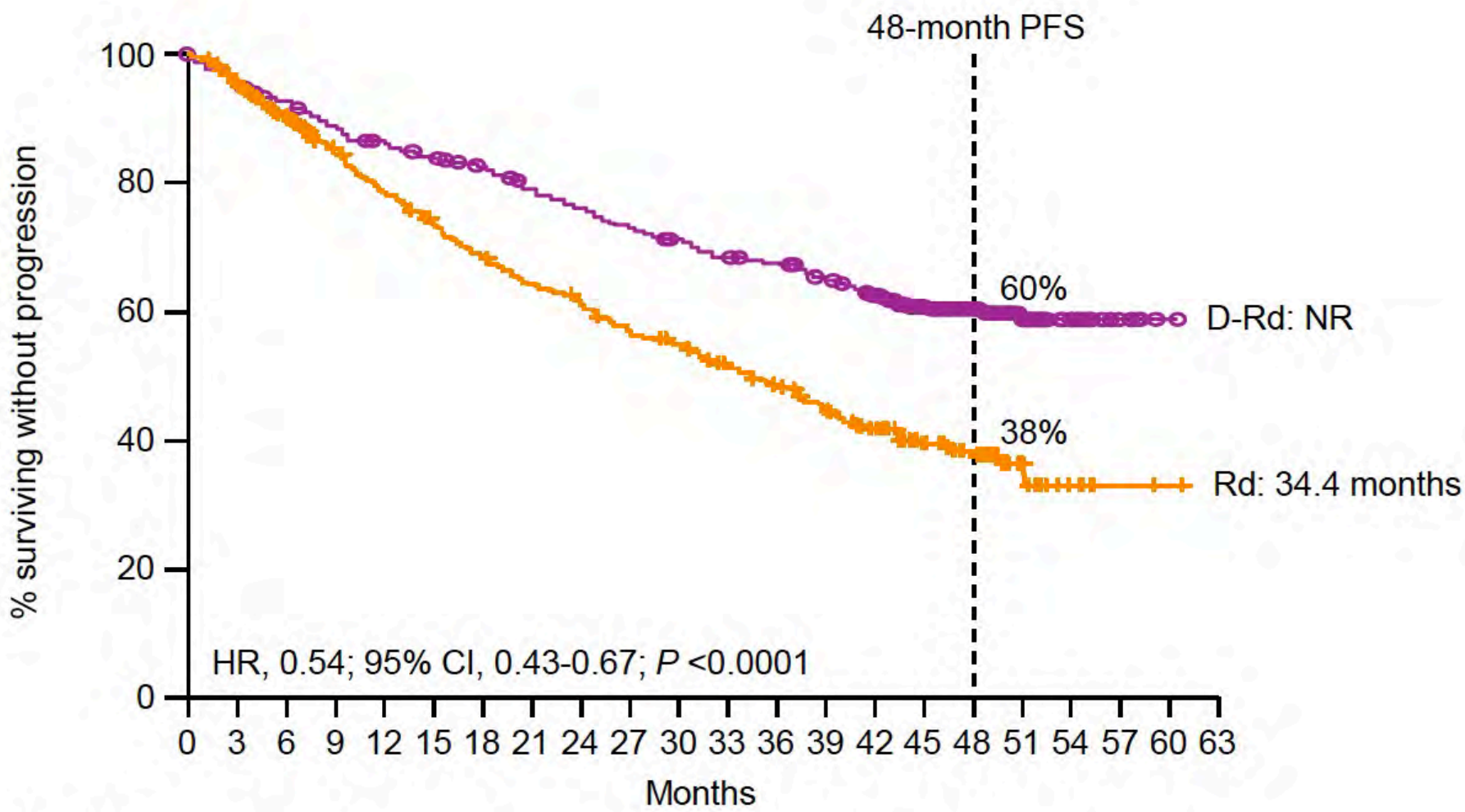
# MAIA: Updated PFS (Median Follow-Up 48 Months)




Kumar SK et al. ASH 2020;Abstract 2276.

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*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*

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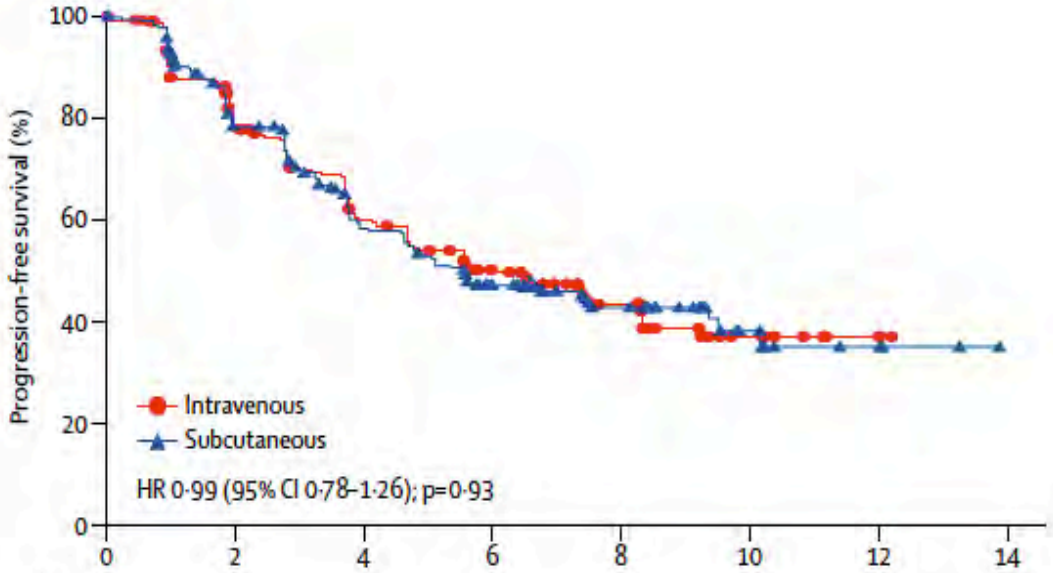
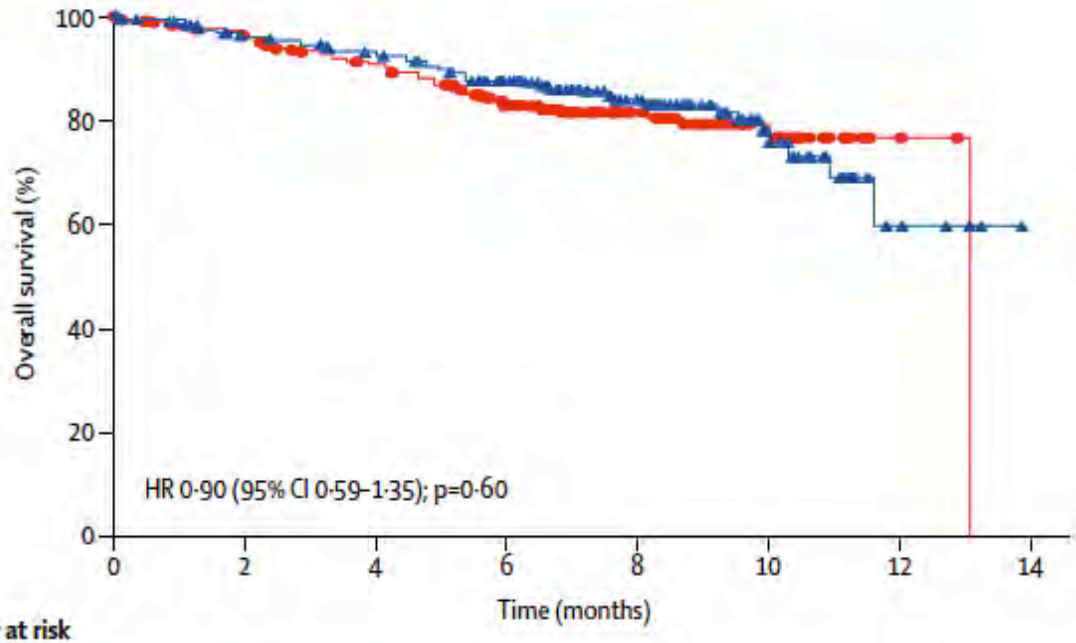
# COLUMBA: Subcutaneous versus Intravenous Daratumumab

## Progression-Free Survival




| Number at risk (number censored) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Intravenous | 259 (0) | 189 (17) | 138 (25) | 101 (40) | 42 (91) | 11 (116) | 2 (125) | 0 (126) |
| Subcutaneous | 263 (0) | 187 (23) | 130 (33) | 92 (48) | 46 (88) | 14 (119) | 5 (126) | 0 (130) |

## Overall Survival




| Number at risk (number censored) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Intravenous | 259 (0) | 244 (7) | 217 (19) | 181 (38) | 85 (131) | 29 (184) | 3 (210) | 0 (211) |
| Subcutaneous | 263 (0) | 240 (13) | 227 (18) | 196 (38) | 96 (131) | 34 (188) | 5 (214) | 0 (218) |

**(Median follow-up 7.5 months)**

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

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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?

1. Isatuximab-based combination
2. Selinexor
3. Belantamab mafodotin
4. Melflufen
5. BCMA-directed CAR T-cell therapy
6. Venetoclax
7. I would not recommend any of these

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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?

1. First line
2. Second line
3. Third line
4. Fourth line
5. Beyond fourth line
6. I would not recommend venetoclax

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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.

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# 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.

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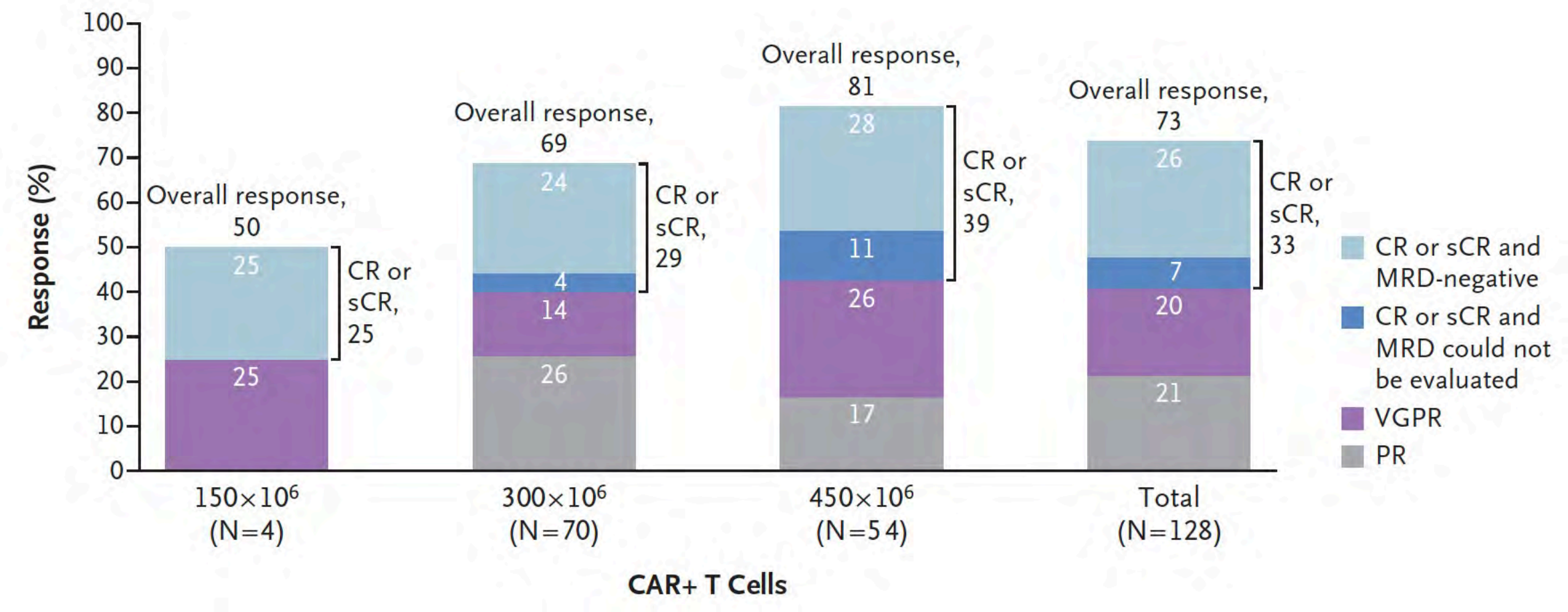
# KarMMa: Tumor Response, Overall and According to Target Dose




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

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# 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.

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# Characteristics of Select BCMA CAR-T Studies in Multiple Myeloma

| | KarMMa<br>Idecabtagene vicleucel<br>(n = 128) | EVOLVE<br>Orvacabtagene autoleucel<br>(n = 62) | CARTITUDE-1<br>Ciltacabtagene Autoleucel<br>(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

RTP RESEARCH TO PRACTICE

# 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<br>Median duration of CRS | 1 (1-12) days<br>5 (1-63) days | 2 (1-4) days<br>4 (1-10) days | 7 (2-12) days<br>4 (2-64) days |
| ICANS: all, ≥G3 | 17%, 3% | 13%, 3% | 10%, 3% |
| Infections: all ≥G3 | 69%, NR | 40%, 13% | NR, 19% |
| Tocilizumab use<br>Steroid use<br>Anakinra use | 52%<br>15%<br>0 | 76%<br>52%<br>23% | 79%<br>21%<br>21% |

**Approved 3/26/2021**

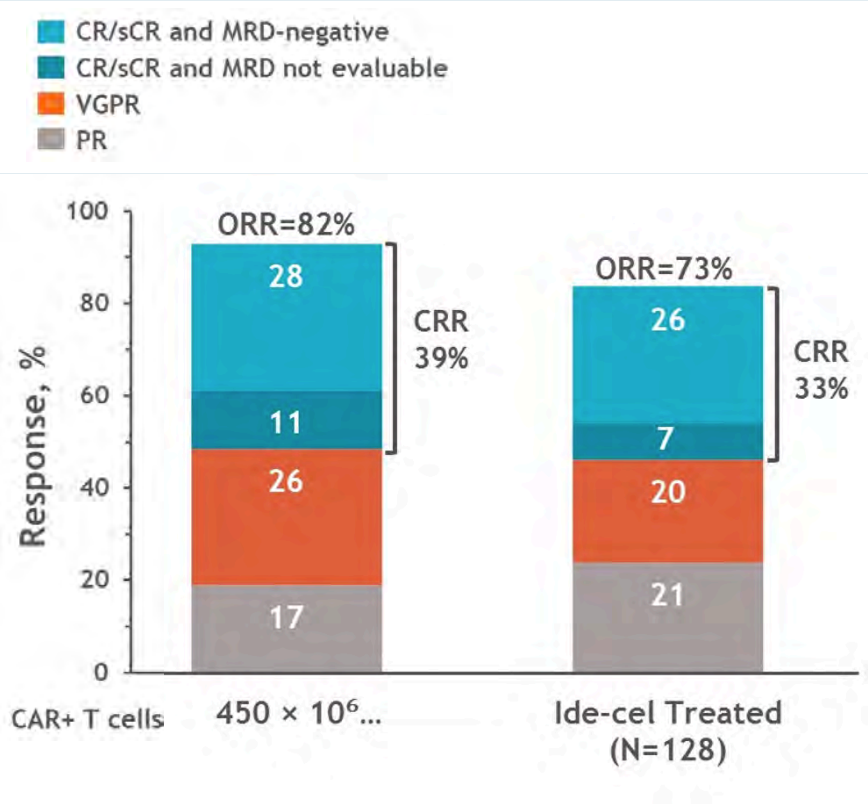
Munshi NC et al. ASCO 2020;Abstract 8503 (KarMMA); Mailankody S et al. ASCO 2020;Abstract 8504 (EVOLVE); Berdeja JG et al. ASCO 2020;Abstract 8505 (CARTITUDE-1); Patel K. ASCO 2020 Discussant.

RTP RESEARCH TO PRACTICE

# Efficacy of Select BCMA CAR-T Studies in Multiple Myeloma

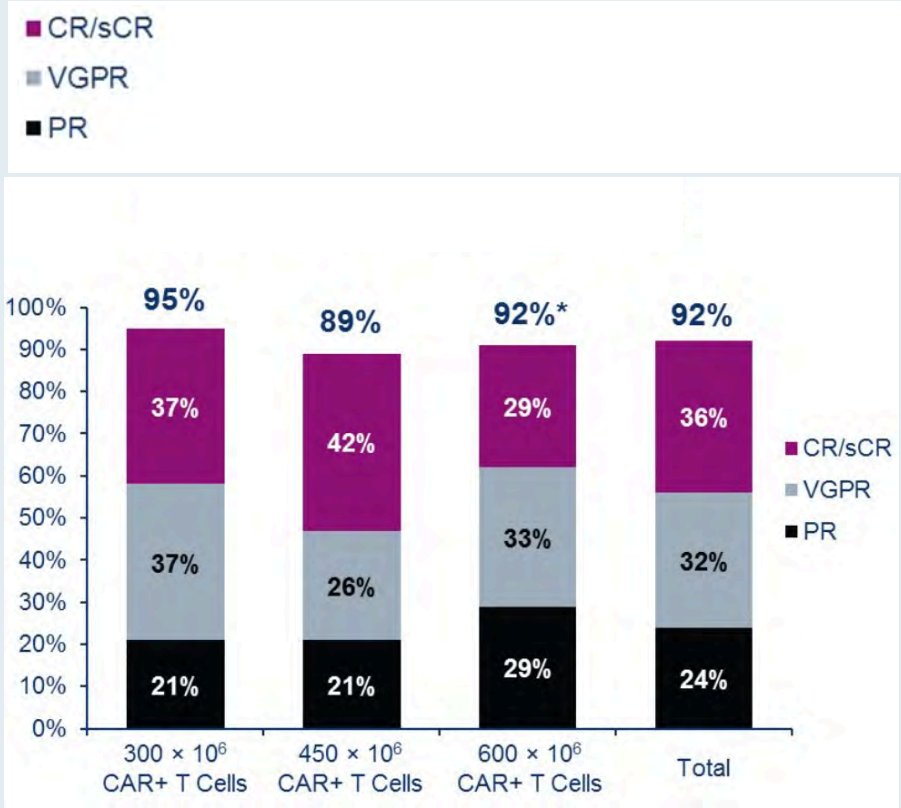
## KarMMa

**ORR: 73% | MRD-neg: 94%**



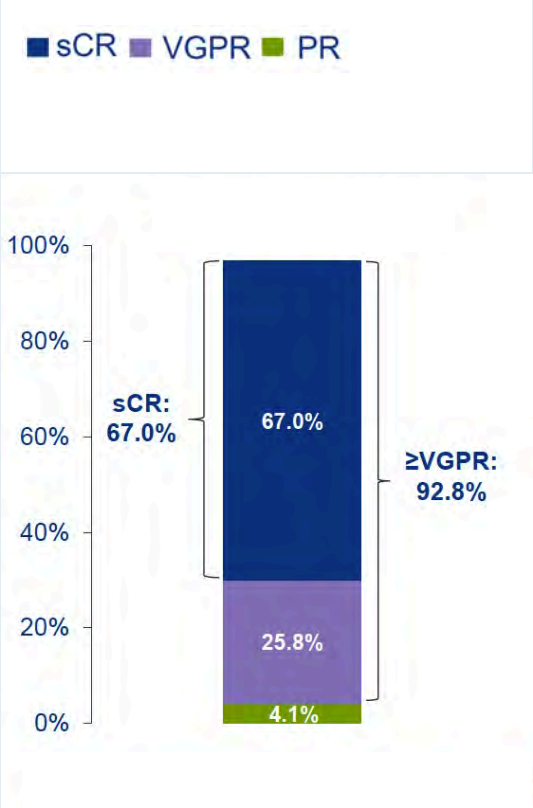

## EVOLVE

**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**

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TO PRACTICE

# 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**

RTP
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TO PRACTICE

# 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**

RTP
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TO PRACTICE

# 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?

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# 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.

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RESEARCH
TO PRACTICE

# 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

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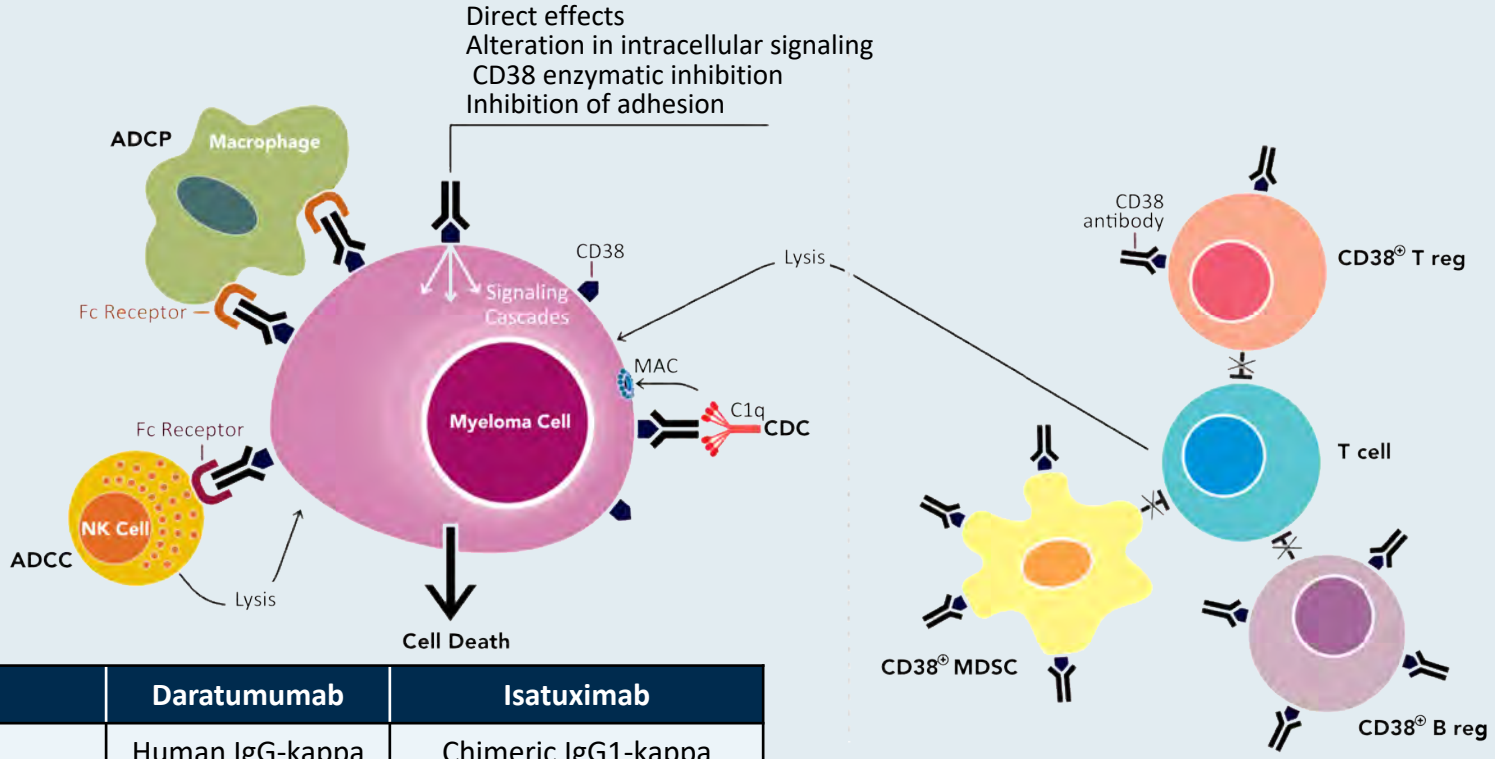
# Anti-CD38 Antibodies: Mechanism of Action, Structural and Pharmacologic Similarities and Differences

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.

RTP RESEARCH TO PRACTICE

# 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.

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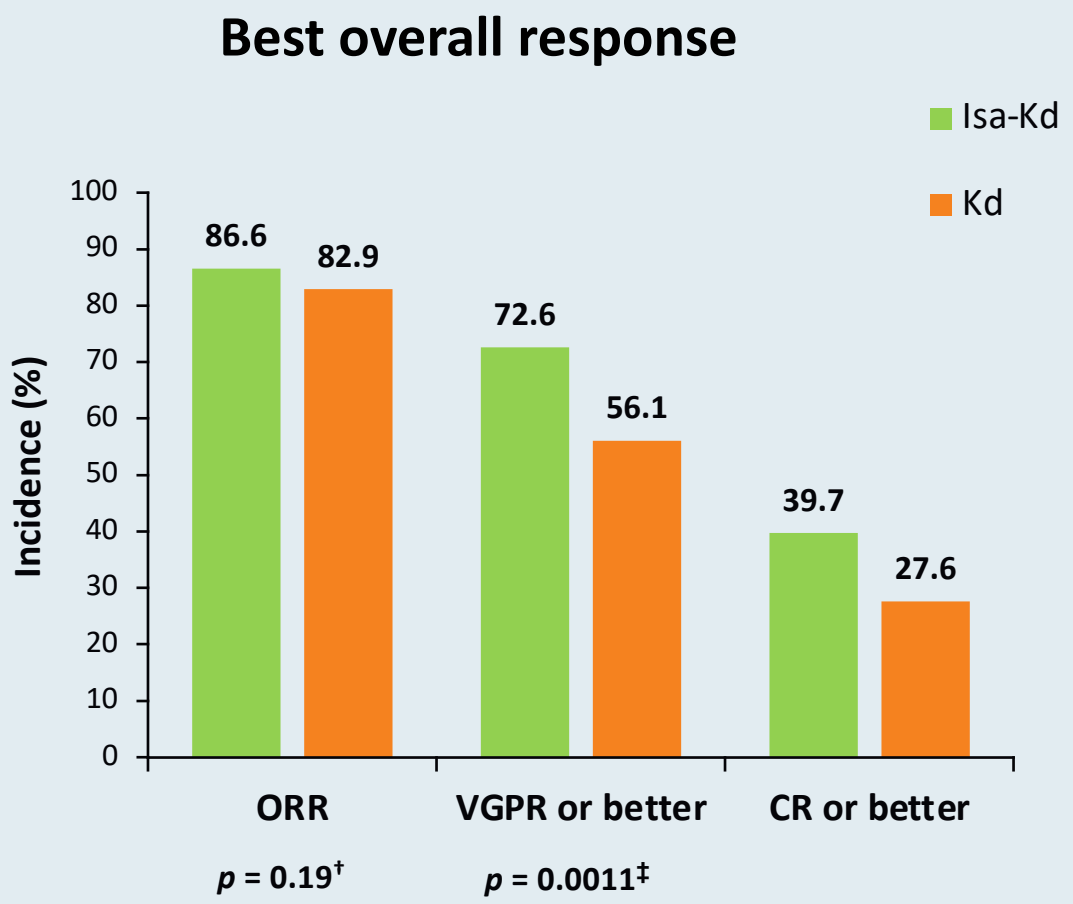
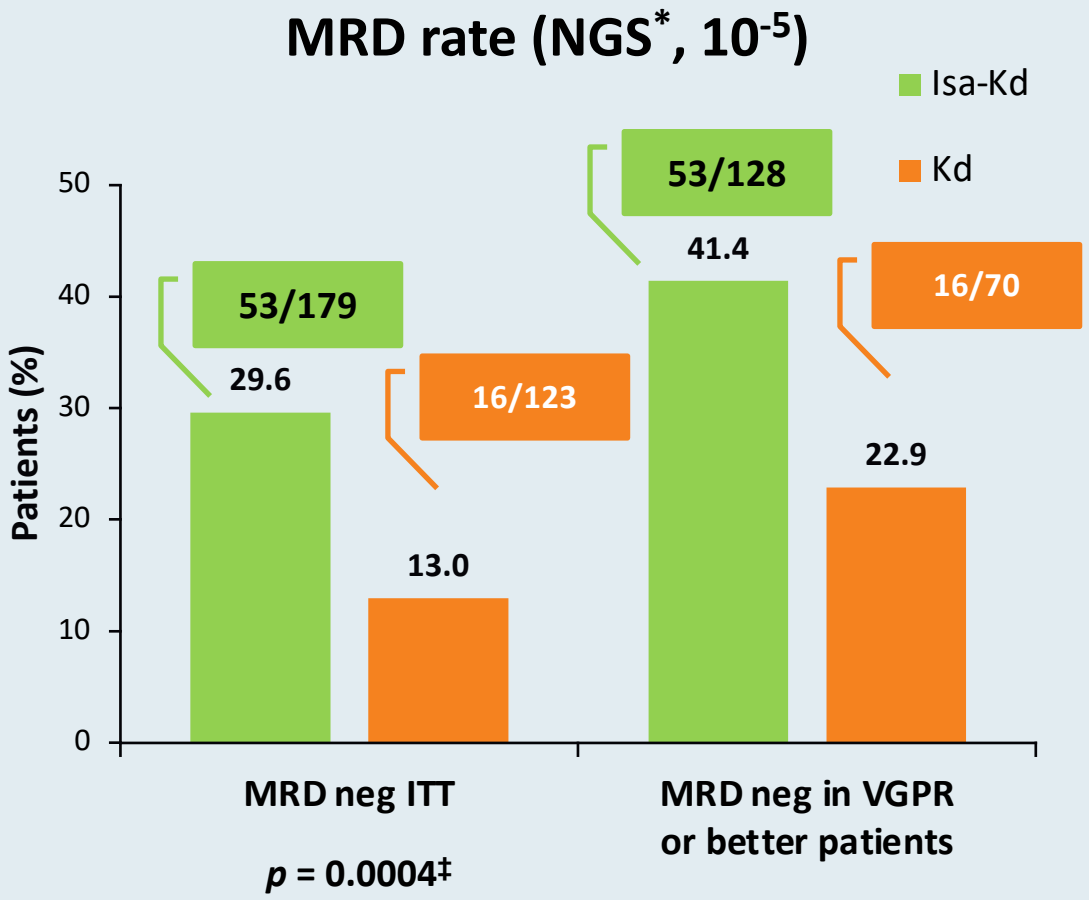
# IKEMA – Isatuximab + Kd: Depth of Response




Moreau P et al. EHA 2020;Abstract LBA2603.

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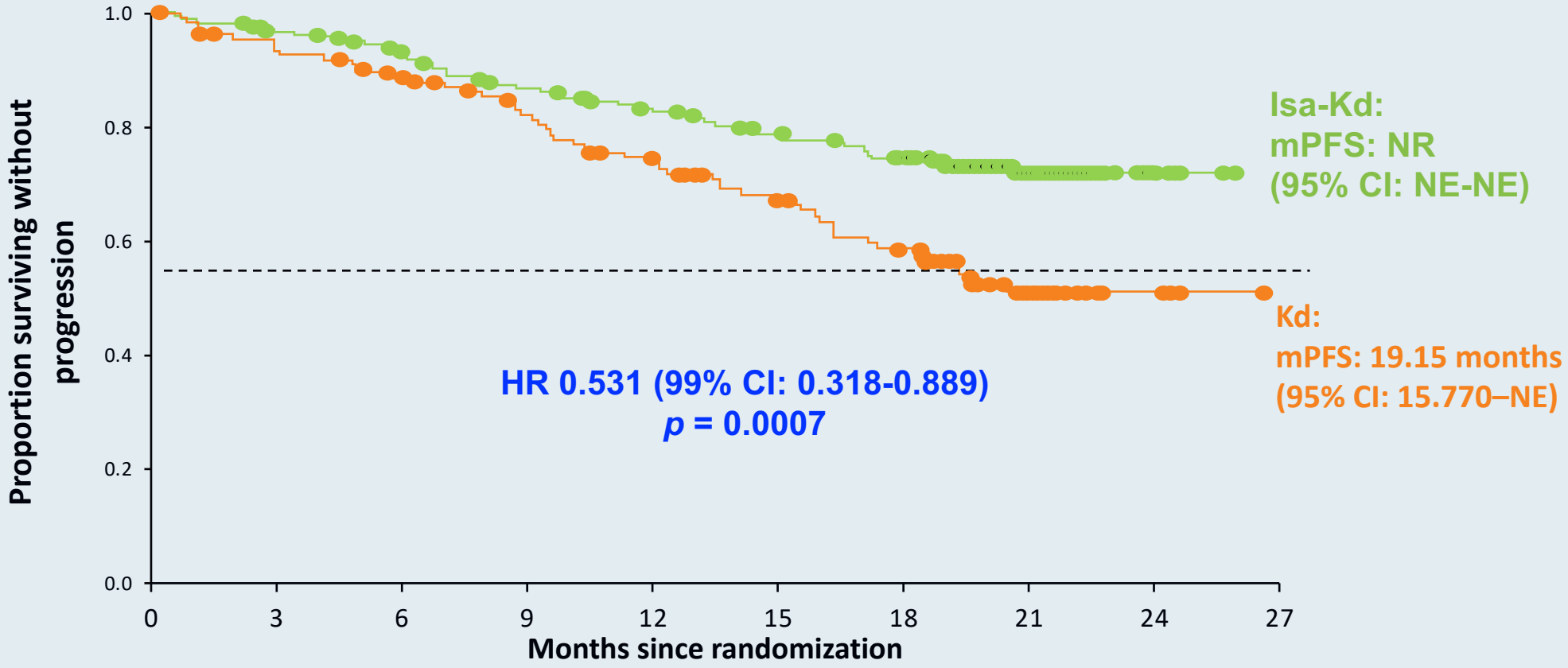
# IKEMA: PFS




| 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.

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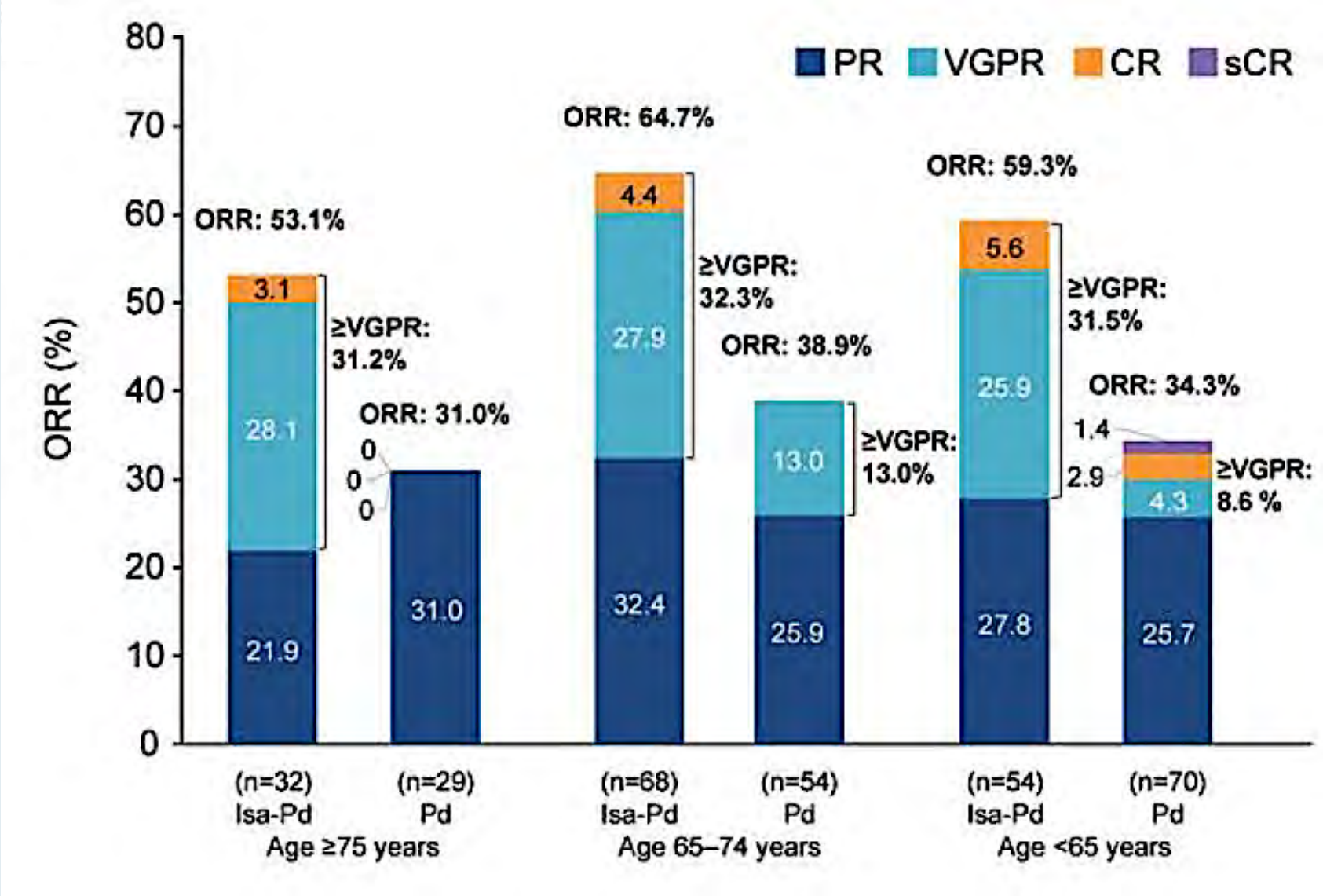
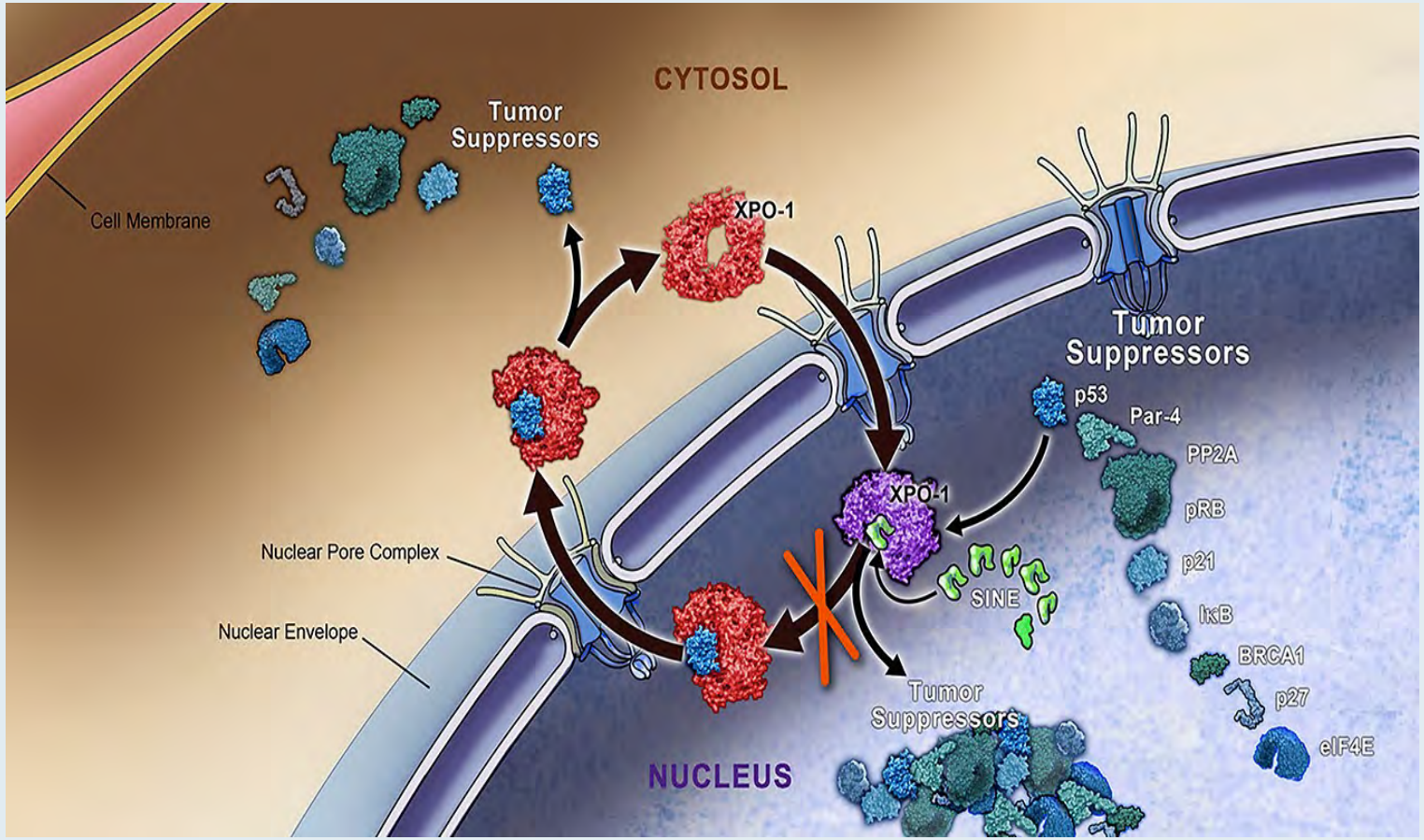
# ICARIA-MM – Isatuximab + Pom/Dex: Response to Therapy by Patient Age Group




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

RTP RESEARCH TO PRACTICE

# 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

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*Lancet* 2020;396:1563-73

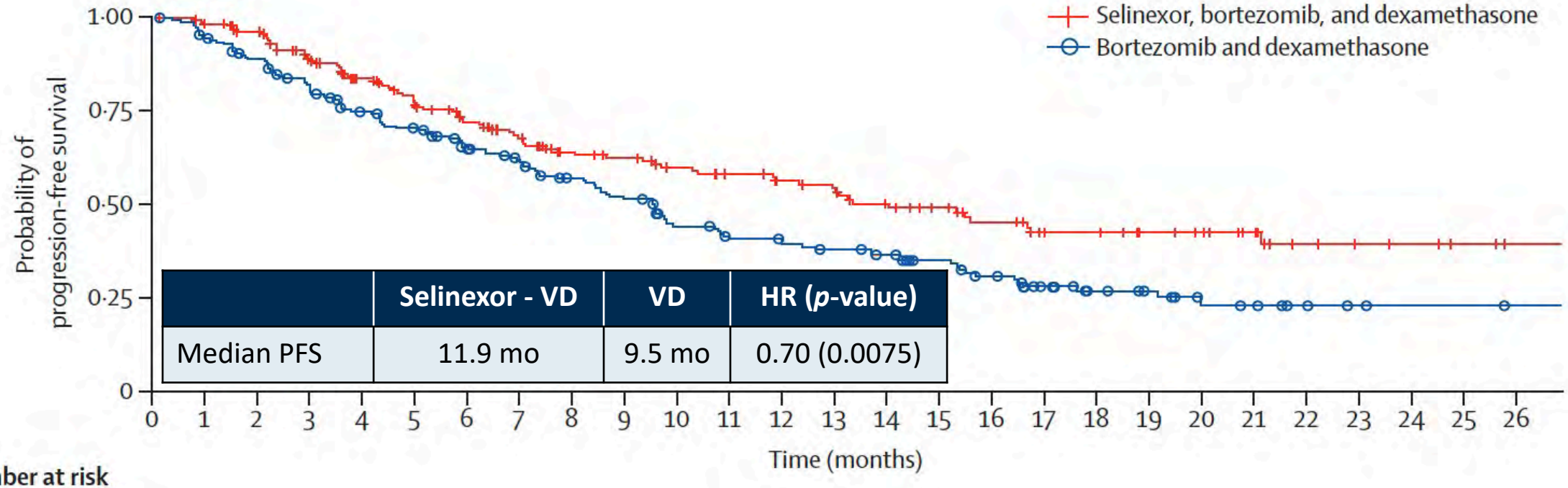
Articles

# 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**

RTP RESEARCH TO PRACTICE

# 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.

RTP RESEARCH TO PRACTICE

# 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.

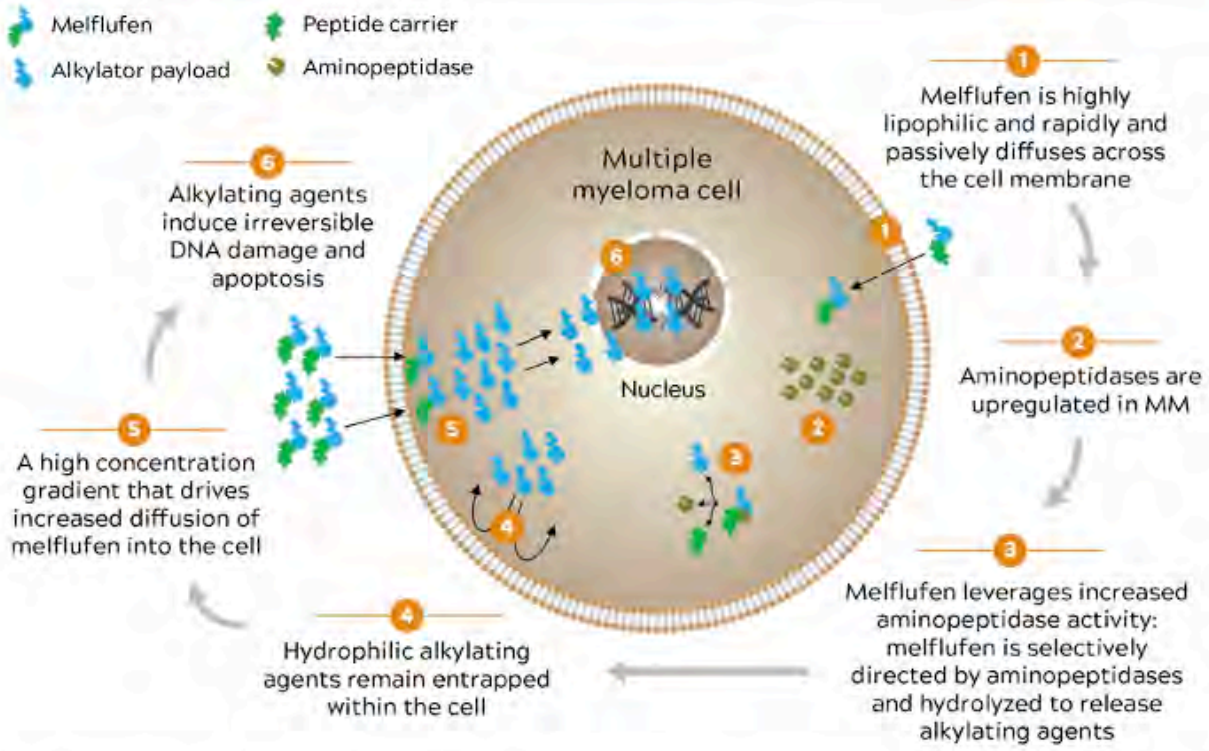
Efficacy was evaluated in HORIZON (NCT02963493), a multicenter, single-arm trial. Eligible patients were required to have relapsed refractory multiple myeloma. Patients received melphalan flufenamide 40 mg intravenously on day 1 and dexamethasone 40 mg orally (20 mg for patients ≥75 years of age) on 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

RTP RESEARCH TO PRACTICE

# 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.

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original reports

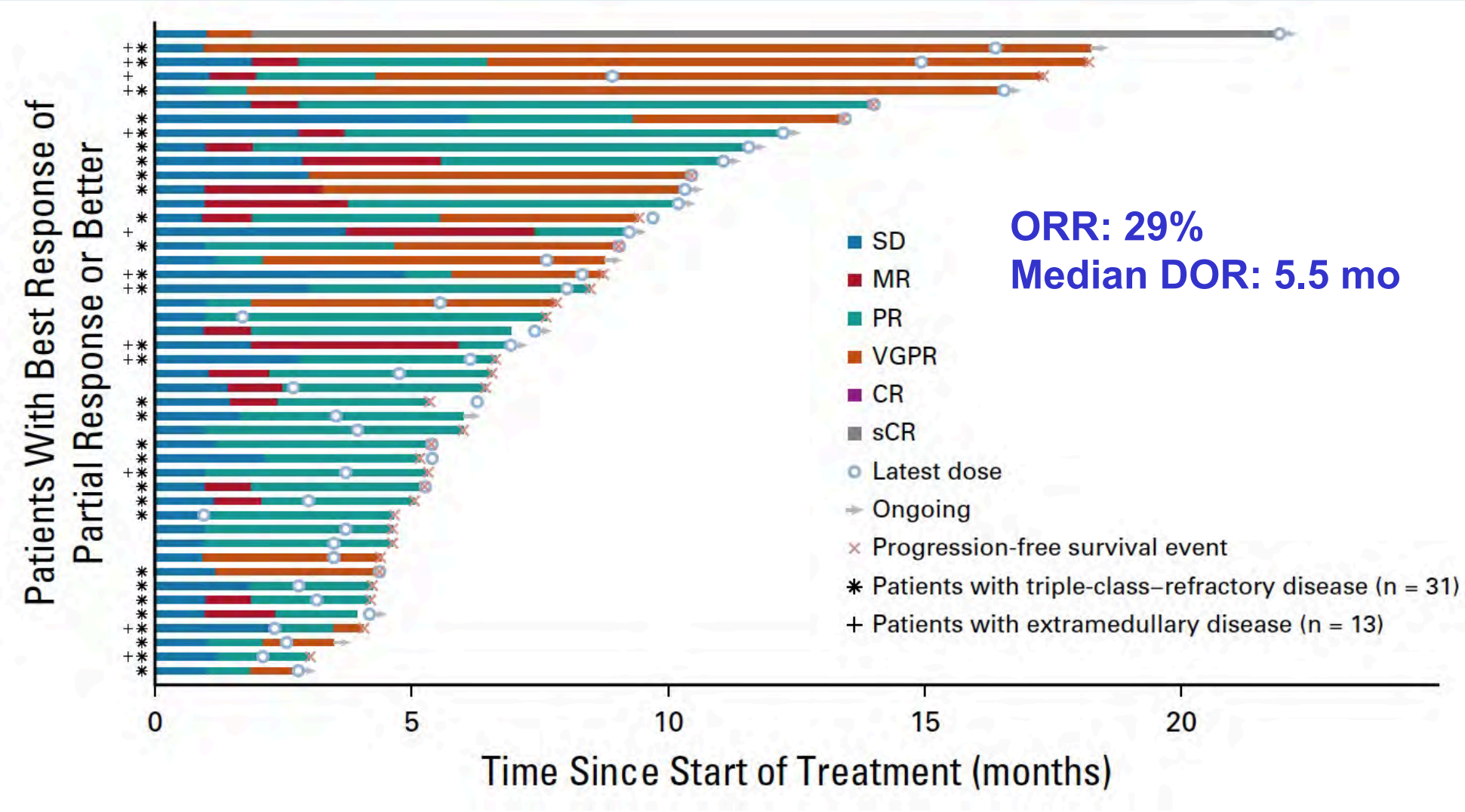
# Melflufen and Dexamethasone in Heavily Pretreated Relapsed and Refractory Multiple Myeloma

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.

RTP RESEARCH TO PRACTICE

# HORIZON: Overall Response and Duration of Response with Melflufen




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

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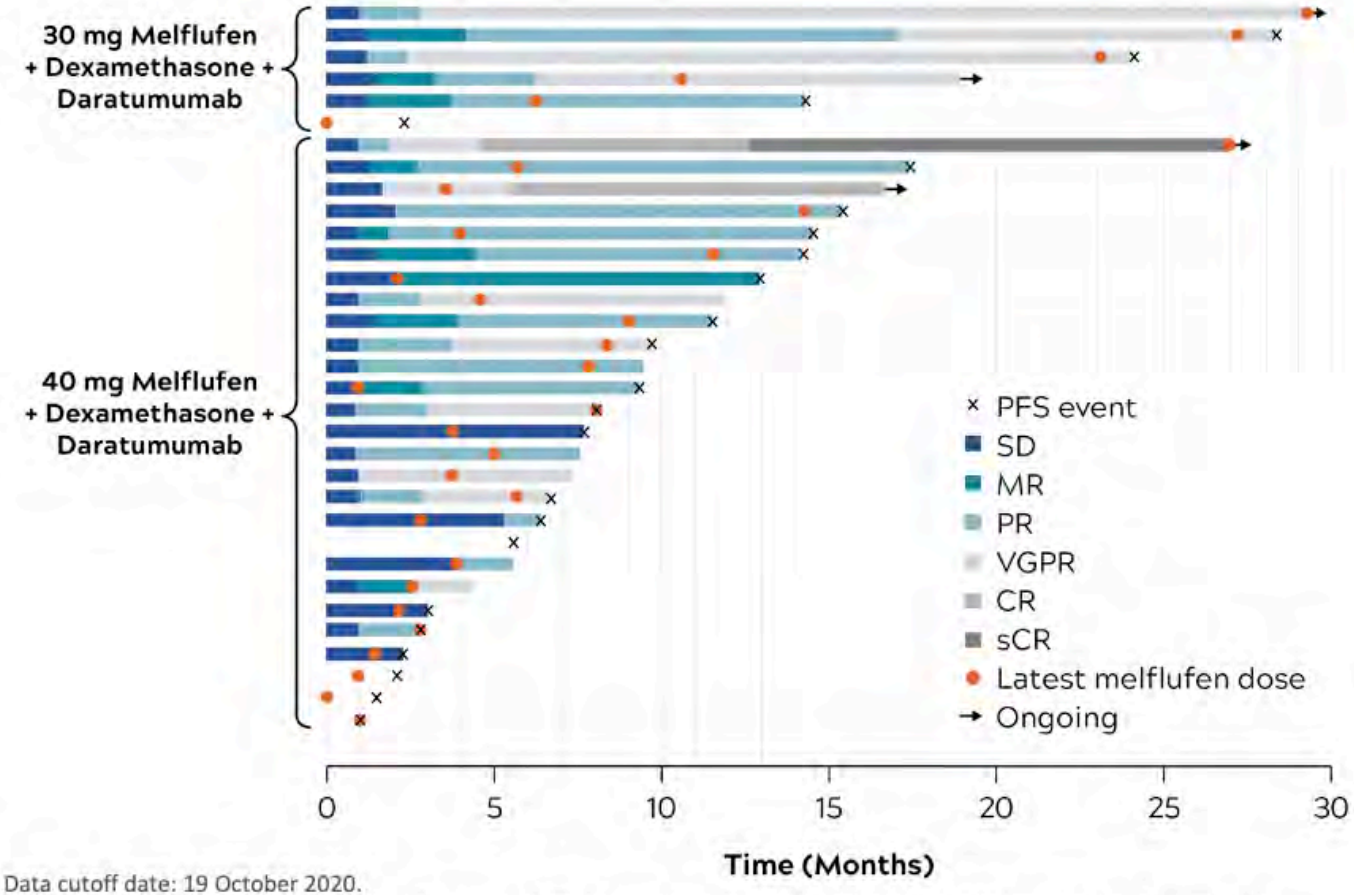
# ANCHOR: Melflufen with Dexamethasone and Daratumumab




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.

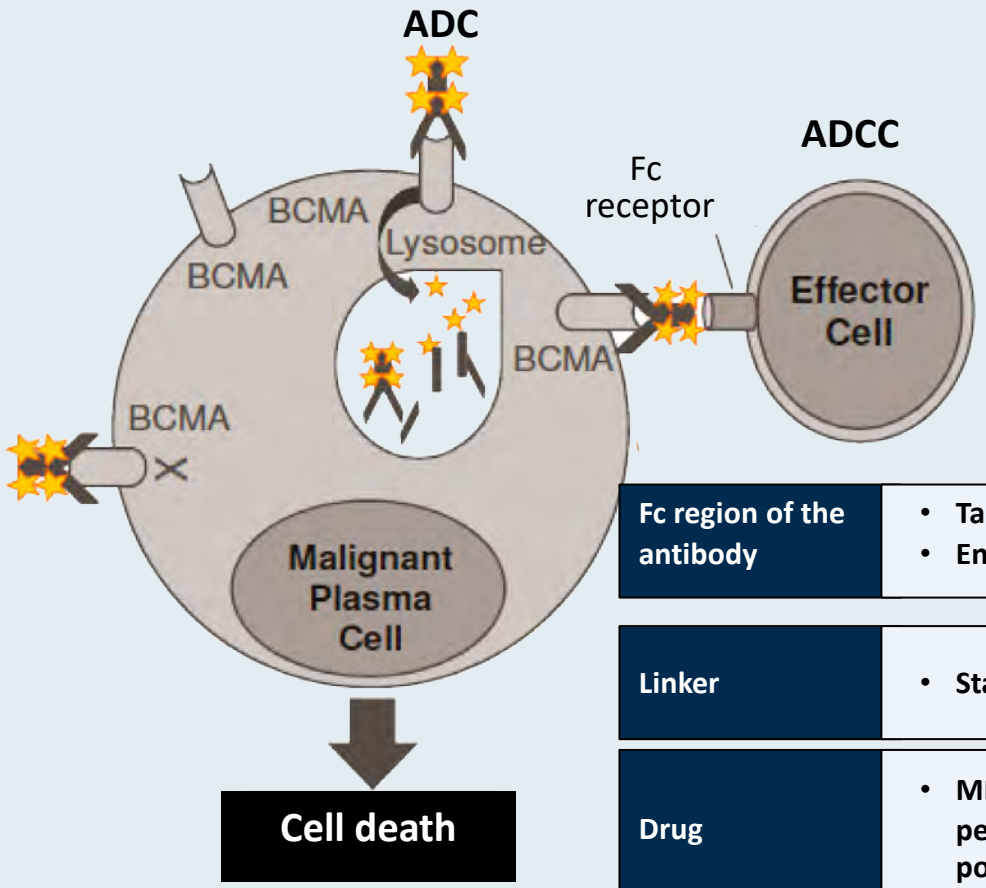
- No DLTs were observed at any dose
- 15 patients (45%) experienced SAEs, most commonly pneumonia (12%); influenza (9%); and parainfluenza virus infection, sepsis, urinary tract infection, and febrile neutropenia (6% each)[a]
  - 30 mg: 4 patients (67%)
  - 40 mg: 11 patients (41%)
- Four AEs with fatal 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**<br>• **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.

RTP RESEARCH TO PRACTICE

# 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.

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# 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.

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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
- Dr Del Rosario: A 54-year-old man with relapsed multiple myeloma who receives CAR T-cell therapy
- *Key Recent Publications and Presentations*
- Dr Lorber: A 75-year-old man with myeloma and disease progression on 5 lines of therapy
- *Key Recent Publications and Presentations*

## Module 3: Amyloid Light Chain (AL) Amyloidosis

- Dr Chen: A 65-year-old man with AL amyloidosis and renal failure
- *Key Recent Publications and Presentations*

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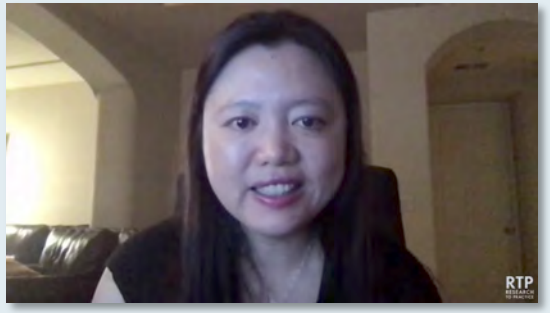
TO PRACTICE

# Case Presentation – Dr Chen: A 65-year-old man with AL amyloidosis and renal failure




**Dr Gigi Chen**

- Initially presented with bilateral edema and weight gain
  - Proteinuria 4+, creatinine 2.3, 24-hour urine protein evaluation: 9.4 g
- Renal biopsy: renal amyloidosis, lambda restricted
- Bone marrow biopsy: 15% – 20% consistent with plasma cell myeloma
- FISH: t(11;14)
- PET: moderate ascites, no bone lesions
- Peritoneal dialysis
- Plan to initiate treatment with a daratumumab-based regimen

**Questions**

- What would be the best treatment for this patient with amyloidosis and renal failure, who is on dialysis?

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# Key Recent Publications and Presentations

- Palladini G et al. **Daratumumab plus CyBorD for Patients with Newly Diagnosed AL Amyloidosis: Safety Run-In Results of ANDROMEDA.** *Blood* 2020;136(1):71-80.

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*Blood* 2020;136(1):71-80.

blood

Regular Article

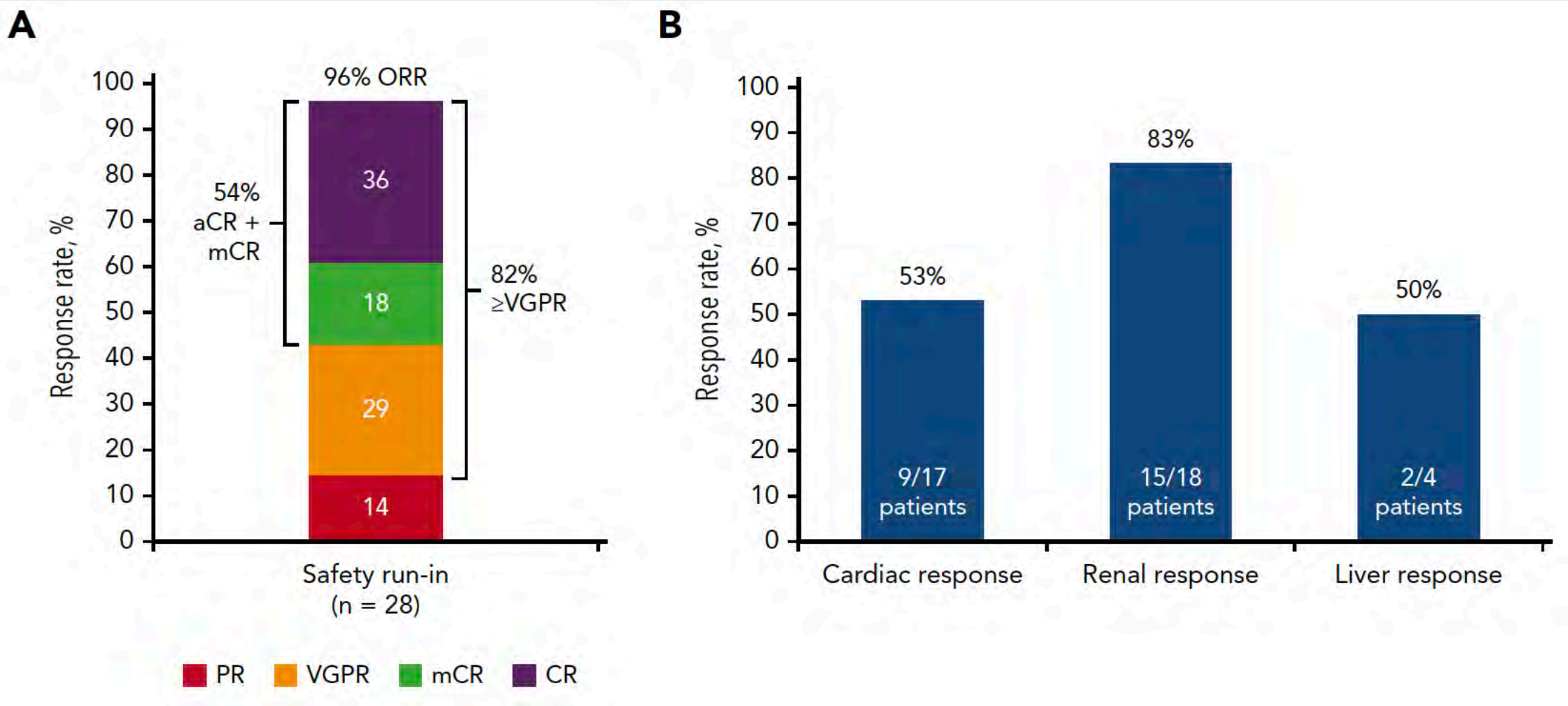
CLINICAL TRIALS AND OBSERVATIONS

# Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA

Giovanni Palladini,[1,2] Efstathios Kastritis,[3] Mathew S. Maurer,[4] Jeffrey Zonder,[5] Monique C. Minnema,[6] Ashutosh D. Wechalekar,[7] Arnaud Jaccard,[8] Hans C. Lee,[9] Naresh Bumma,[10] Jonathan L. Kaufman,[11] Eva Medvedova,[12] Tibor Kovacsovics,[13] Michael Rosenzweig,[14] Vaishali Sanchorawala,[15] Xiang Qin,[16] Sandra Y. Vasey,[16] Brendan M. Weiss,[16] Jessica Vermeulen,[17] Giampaolo Merlini,[1,2] and Raymond L. Comenzo[18]

RTP RESEARCH TO PRACTICE

# ANDROMEDA: Summary of Overall Best Hematologic and Organ Responses




Palladini G et al. *Blood* 2020;136(1):71-80.

RTP RESEARCH TO PRACTICE

# FDA Grants Accelerated Approval to Subcutaneous Daratumumab for Newly Diagnosed Light Chain Amyloidosis

## Press Release – January 15, 2021

"On January 15, 2021, the Food and Drug Administration granted accelerated approval to subcutaneous daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone for newly diagnosed light chain (AL) amyloidosis.

Efficacy was evaluated in ANDROMEDA (NCT03201965), an open-label, randomized, active-controlled trial in 388 patients with newly diagnosed AL amyloidosis with measurable disease and at least one affected organ according to consensus criteria. Patients were randomized to receive bortezomib, cyclophosphamide, and dexamethasone (VCd arm) or with subcutaneous daratumumab (D-VCd arm).

The hematologic complete response (HemCR) rate based on established consensus response criteria as evaluated by an independent review committee was 42.1% for the D-VCd arm and 13.5% for the VCd arm (odds ratio=4.8; 95% CI: 2.9, 8.1; $p<0.0001$)."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-darzalex-faspro-newly-diagnosed-light-chain-amyloidosis

RTP RESEARCH TO PRACTICE

# Subcutaneous Daratumumab + Bortezomib, Cyclophosphamide, and Dexamethasone (VCd) in Patients with Newly Diagnosed Light Chain (AL) Amyloidosis: Updated Results from the Phase 3 ANDROMEDA Study

Kastritis E et al.

ASCO 2021;Abstract 8003.

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

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# Reduction in Absolute Involved Free Light Chain and Difference between Involved and Uninvolved Free Light Chain Is Associated with Prolonged Major Organ Deterioration Progression-Free Survival in Patients with Newly Diagnosed AL Amyloidosis Receiving Bortezomib, Cyclophosphamide, and Dexamethasone with or without Daratumumab: Results from Andromeda

Comenzo RL et al.

ASH 2020;Abstract 552.

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***CME, MOC and NCPD credit information will be emailed to each participant within 5 business days.***

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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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# Up for Debate: Oncology Investigators Provide Their Take on Current Controversies in Patient Care

*A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists*

**Saturday, May 22, 2021**
**10:15 AM – 4:15 PM ET**

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# Saturday, May 22, 2021

**10:15 AM — Lung Cancer**
John V Heymach, Stephen V Liu

**11:30 AM — Genitourinary Cancers**
Maha Hussain, Elizabeth R Plimack

**12:45 PM — Chronic Lymphocytic Leukemia and Lymphomas**
Jonathan W Friedberg, Laurie H Sehn

**2:00 PM — Multiple Myeloma**
Irene M Ghobrial, Sagar Lonial

**3:15 PM — Breast Cancer**
Virginia Kaklamani, Nancy U Lin

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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

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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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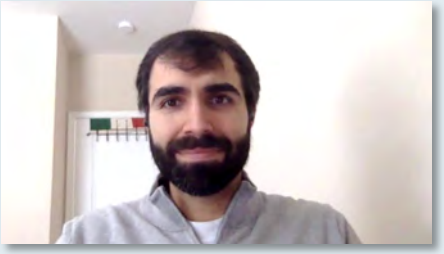
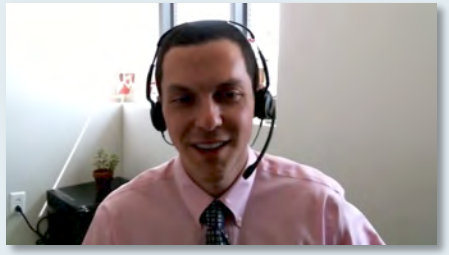
# Contributing Oncologists



**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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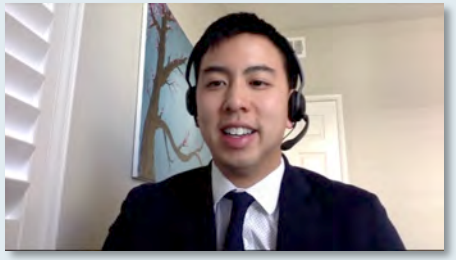
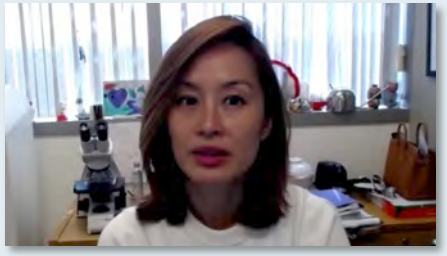
# Contributing Oncologists

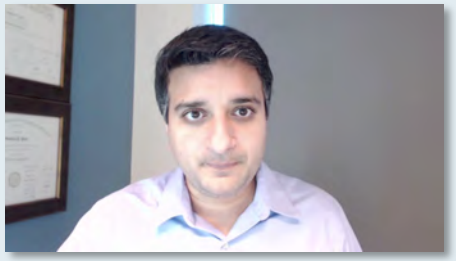
**Mohamed K Mohamed, MD, PhD**
Oncology Division Medical Director
Director of Thoracic Oncology
Hematologist/ Medical Oncologist
Cone Health Cancer Center
Greensboro, North Carolina



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

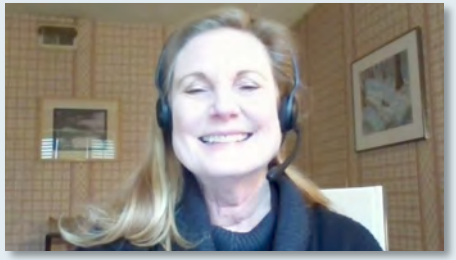


**Helen H Moon, MD**
Medical Oncologist
Southern California Permanente
Medical Group
Riverside, California



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

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



**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
- *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*

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# Agenda

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

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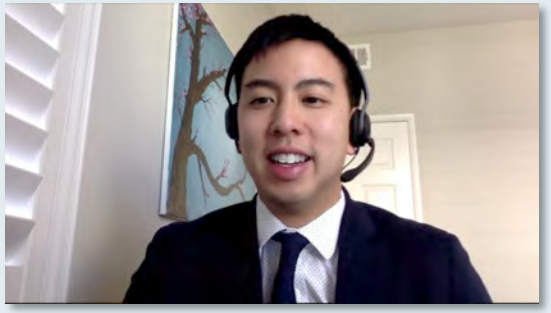
# Case Presentation – Dr Nguyen: A 75-year-old man with Stage IV gastric DLBCL



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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## Which treatment would you generally recommend first for a patient with DLBCL who experiences disease progression on front-line R-CHOP and is not eligible for high-dose therapy?

1. Polatuzumab vedotin/BR
2. Tafasitamab/lenalidomide
3. Lenalidomide
4. Lenalidomide/rituximab
5. Selinexor
6. CAR T-cell therapy
7. Loncastuximab tesirine
8. I don’t know

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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.

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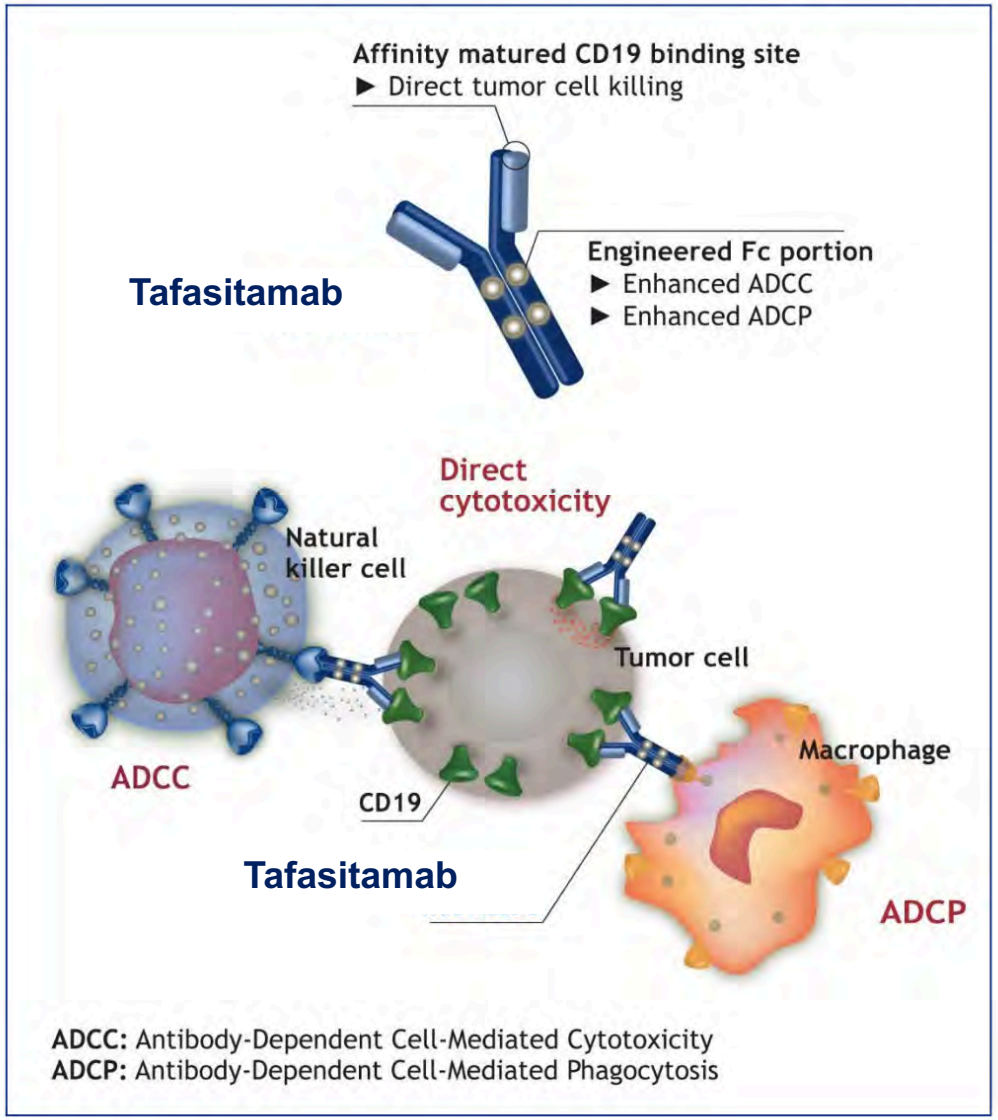
# Tafasitamab (MOR208)




**Lenalidomide enhances NK function with enhanced ADCC in vitro**

Salles et al. *Lancet Onc* 2020.

Courtesy of Ann S LaCasce, MD, MMSc

RTP RESEARCH TO PRACTICE

# 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.

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# L-MIND: Study Design

- R/R DLBCL
- Not eligible for HDC + ASCT
- 1–3 prior regimens
- Primary refractory patients were not eligible*
- ECOG PS 0-2

N=81

**Cycles 1–3**

Tafasitamab 12 mg/kg q4w; d1, 8, 15, 22†

+

LEN 25 mg/d orally d1–21

**Cycles 4–12**

Tafasitamab 12 mg/kg q4w; d1, 15

+

LEN 25 mg/d orally d1–21

If ≥ SD

**Cycle 12+**

Tafasitamab 12 mg/kg d1, 15

Treatment until progression

**Primary endpoint:**
- ORR (central read)

**Secondary endpoints:**
- PFS
- DOR
- OS
- Safety of the tafasitamab + LEN combination
- Exploratory and biomarker-based assays

- Sample size suitable to detect ≥15% absolute increase in ORR for tafasitamab/LEN combination vs LEN monotherapy at 85% power, two-sided alpha of 5%
- Safety data from the first six patients were evaluated in a safety run-in to determine the starting dose of LEN for the remainder of the study

Maddocks KJ et al. ASH 2020;Abstract 3021.

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# 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.

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# 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.

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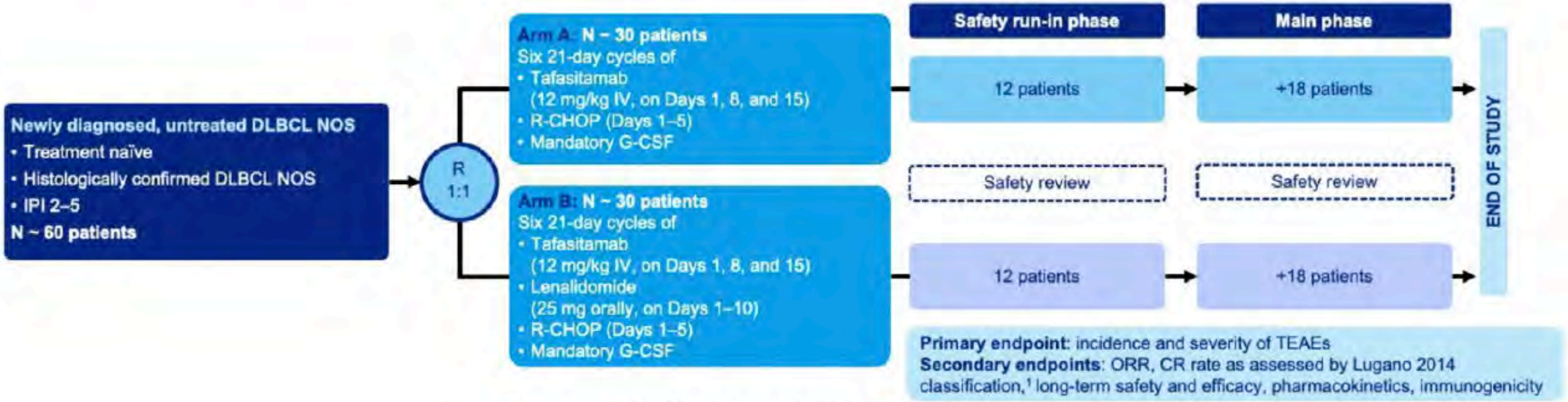
# First-MIND: Study Design

- 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.

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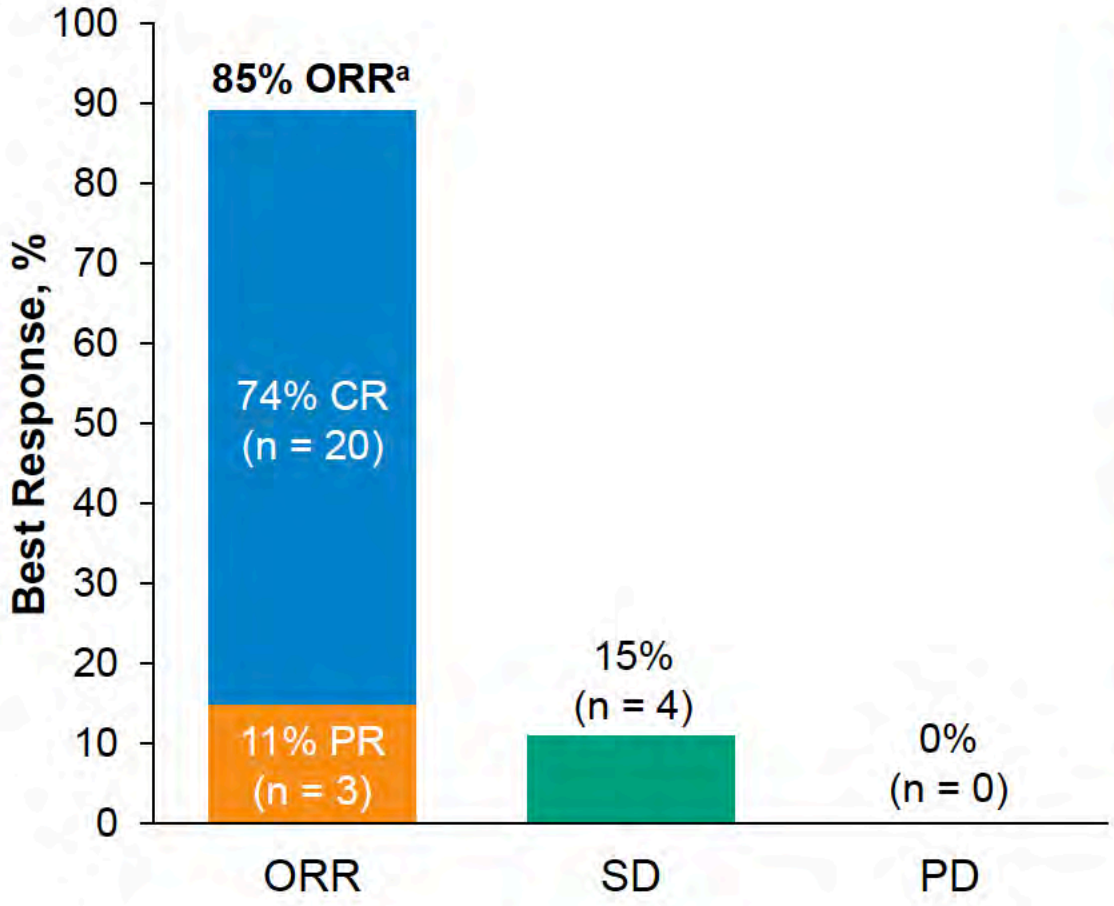
# ZUMA-12: Response Rates




| | 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.

RTP RESEARCH TO PRACTICE

# 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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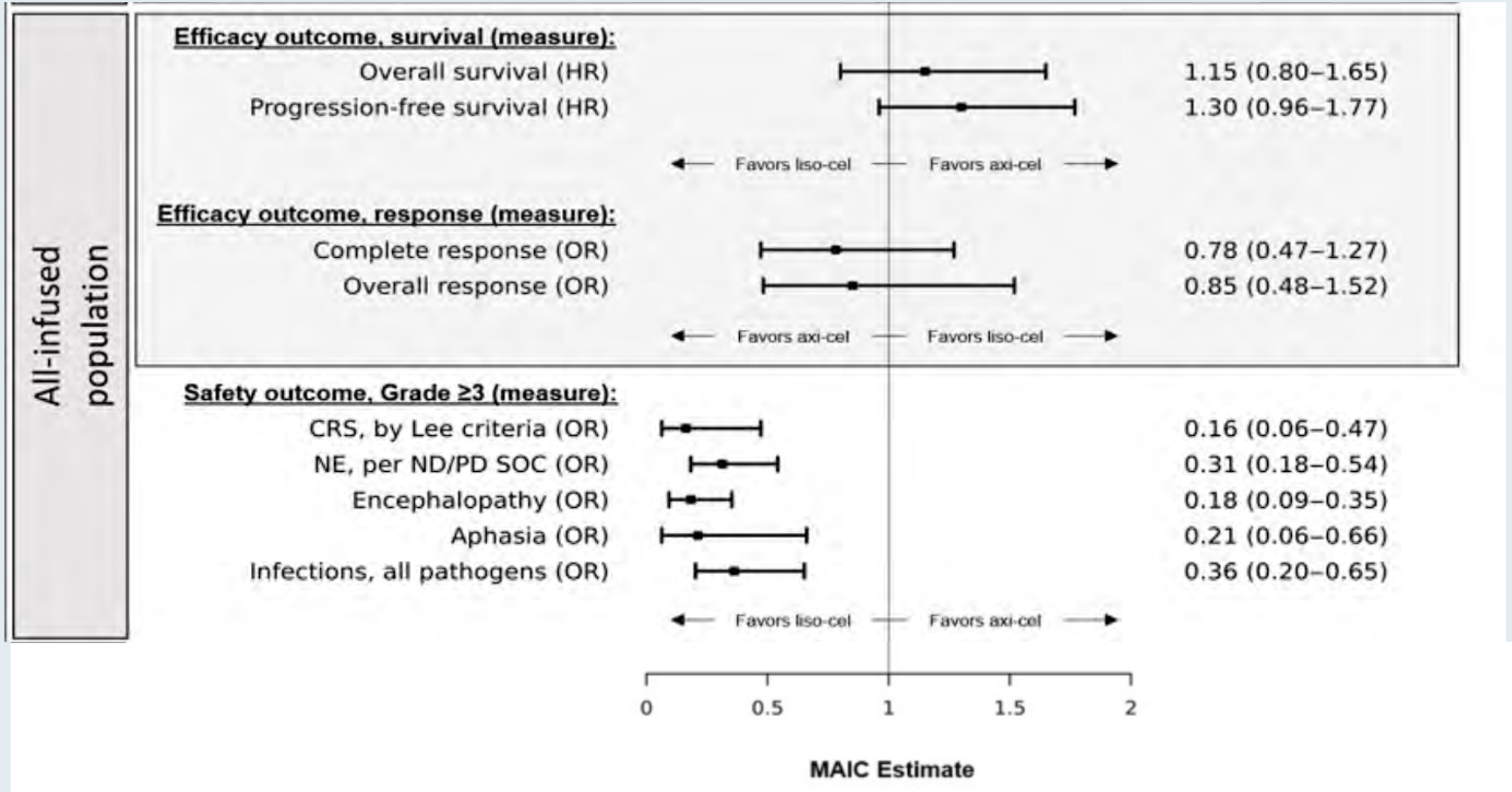
TO PRACTICE

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




Maloney DG et al. ASH 2020;Abstract 2116.

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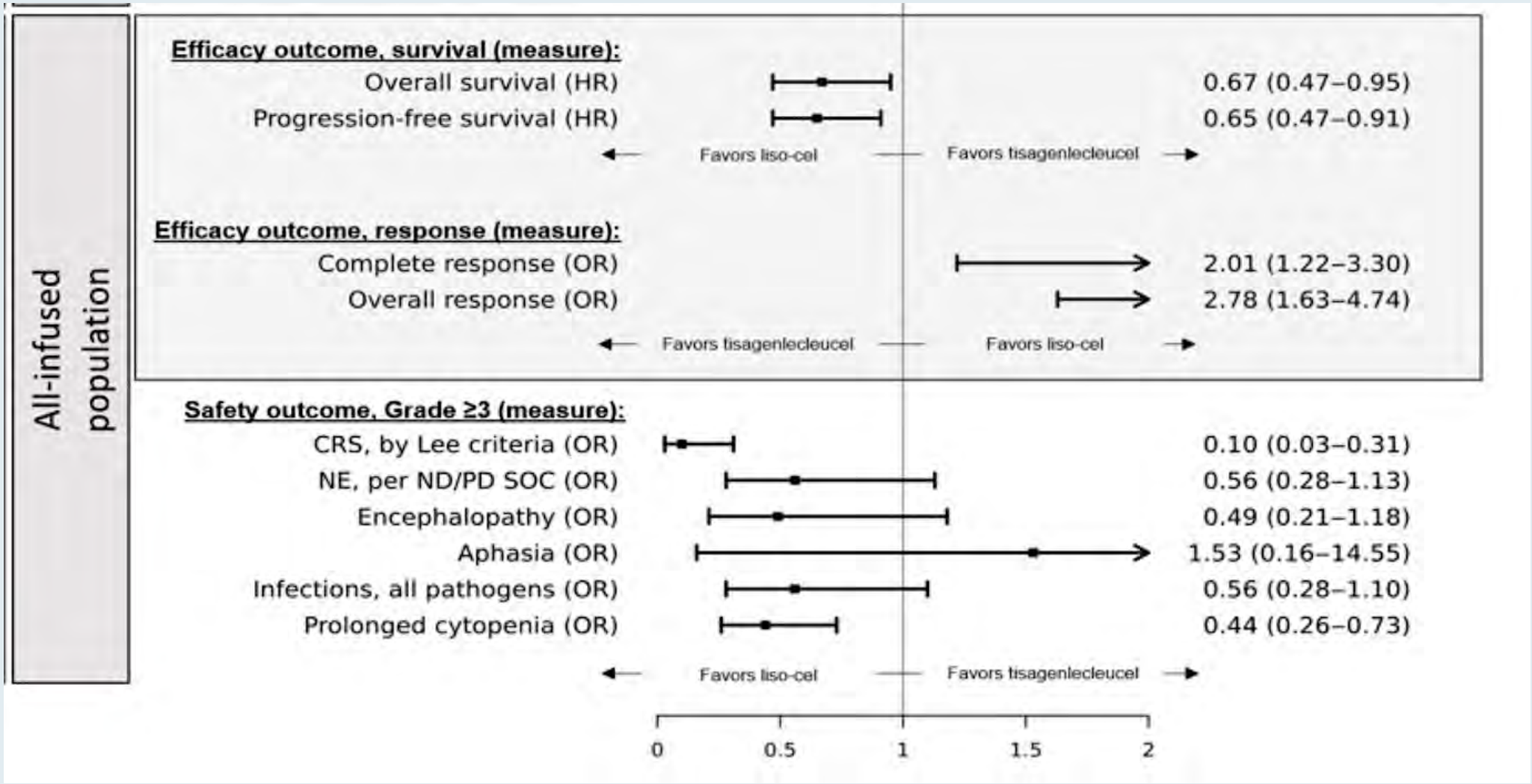
# Matching-Adjusted Indirect Comparison of Liso-cel versus Tisagenlecleucel




Maloney DG et al. ASH 2020;Abstract 2116.

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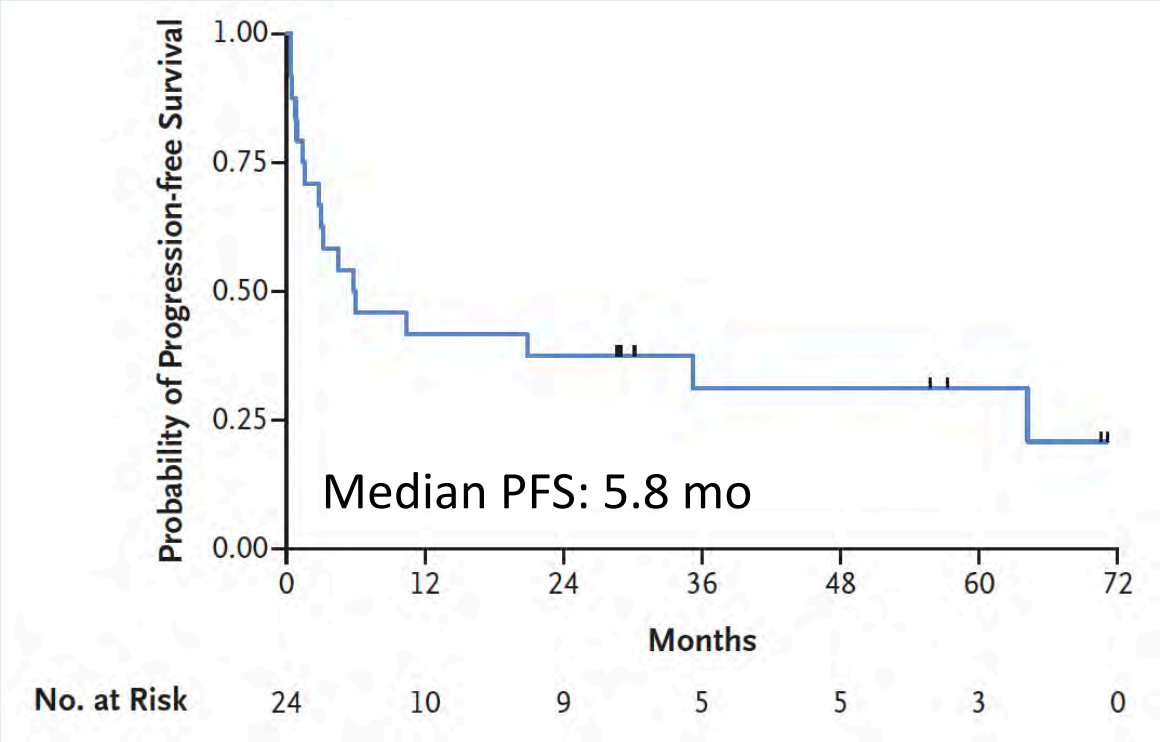
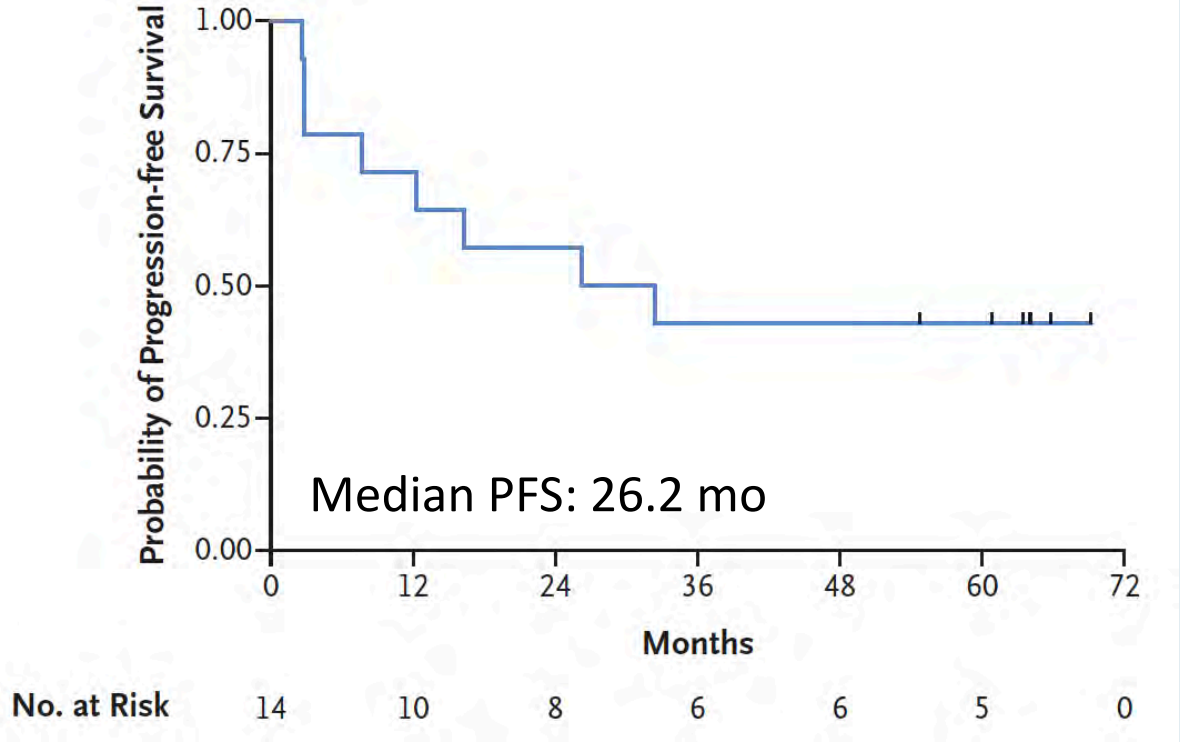
# Five-Year Outcomes for Refractory B-Cell Lymphomas with CAR T-Cell Therapy Tisagenlecleucel

## DLBCL




## FL




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

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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
- *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*

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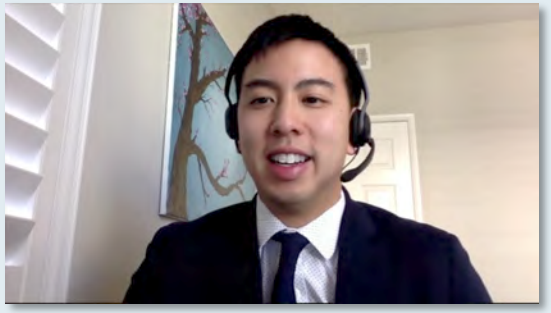
# Case Presentation – Dr Nguyen: A 26-year-old woman with classical Hodgkin lymphoma



**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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## What initial treatment would you recommend for a 26-year-old patient with classical HL with profound anemia, diffuse adenopathy, hepatosplenomegaly and diffuse bone marrow involvement?

1. ABVD
2. PET-adapted ABVD
3. Brentuximab vedotin + AVD
4. AVD
5. Other chemotherapy
6. Other

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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.

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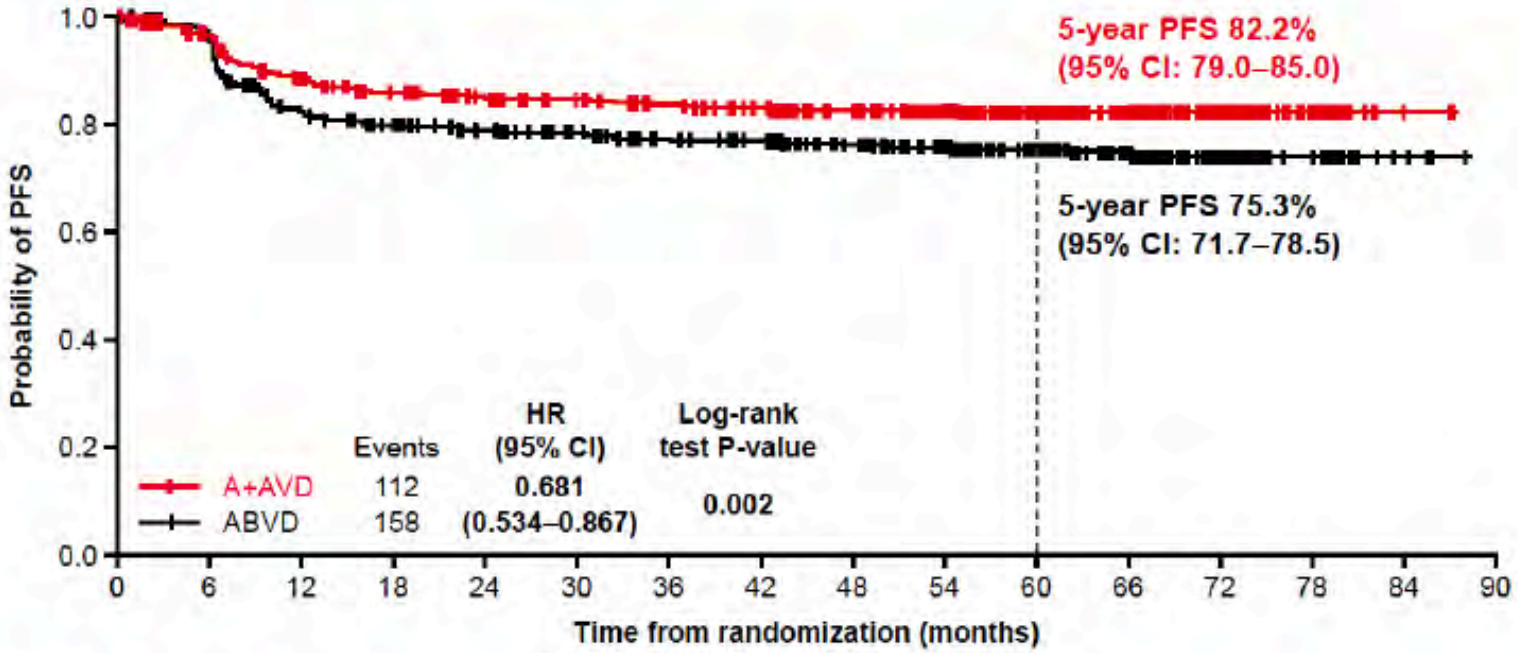
# ECHELON-1: PFS per investigator at 5 years' follow-up*




**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.

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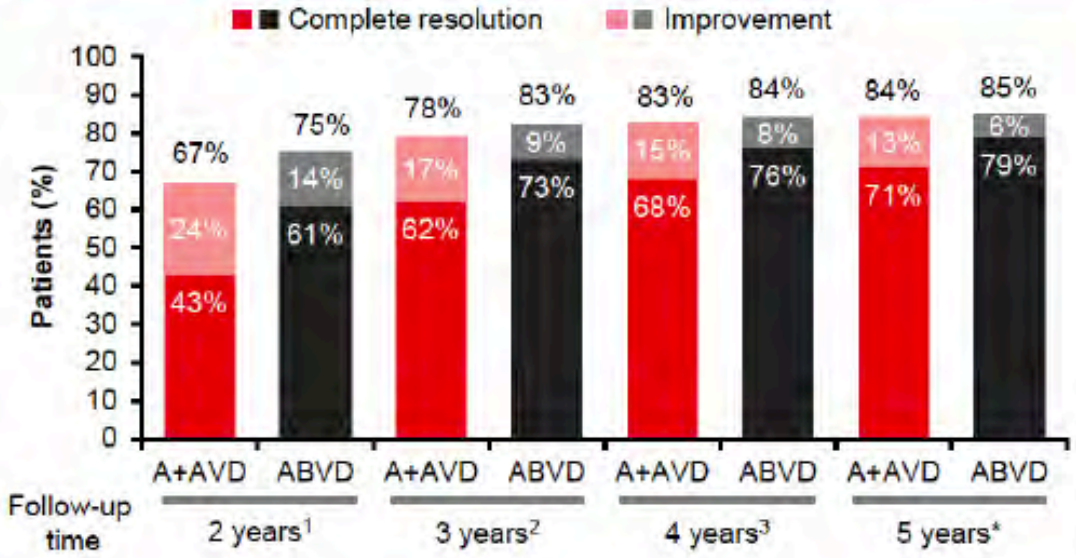
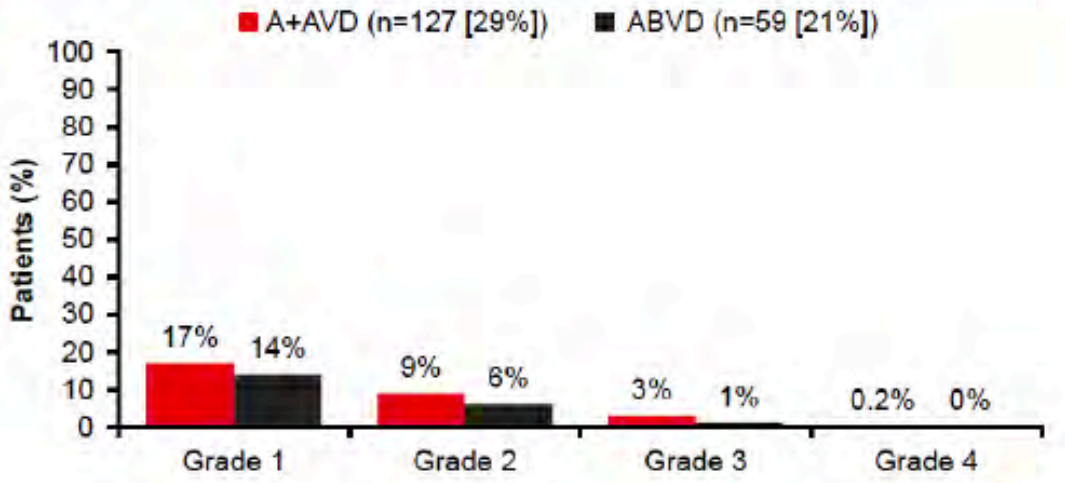
# ECHELON-1: PN resolution and improvement

- 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.

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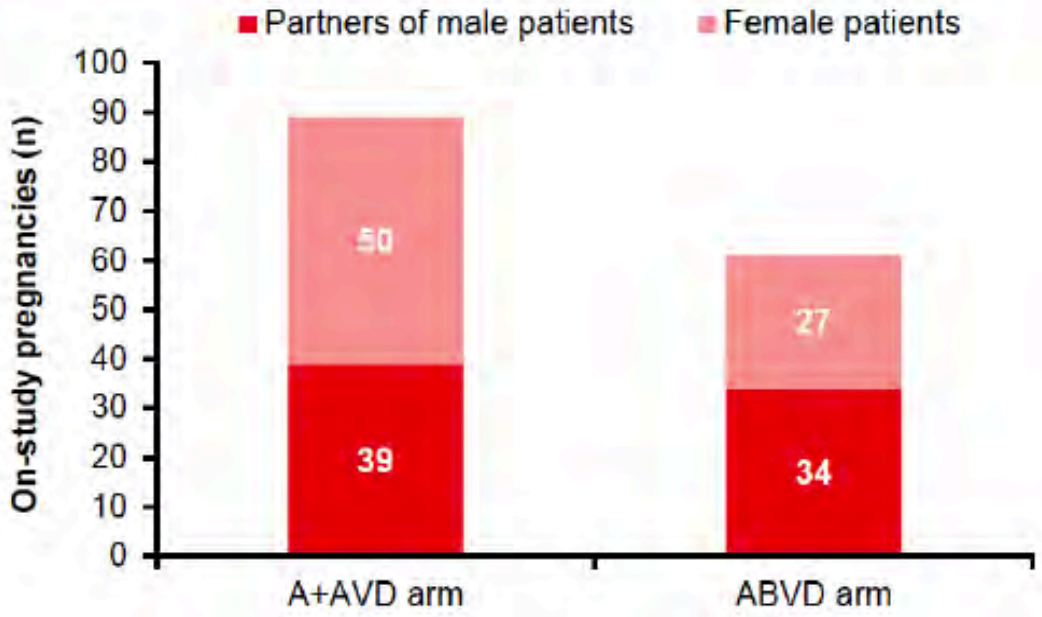
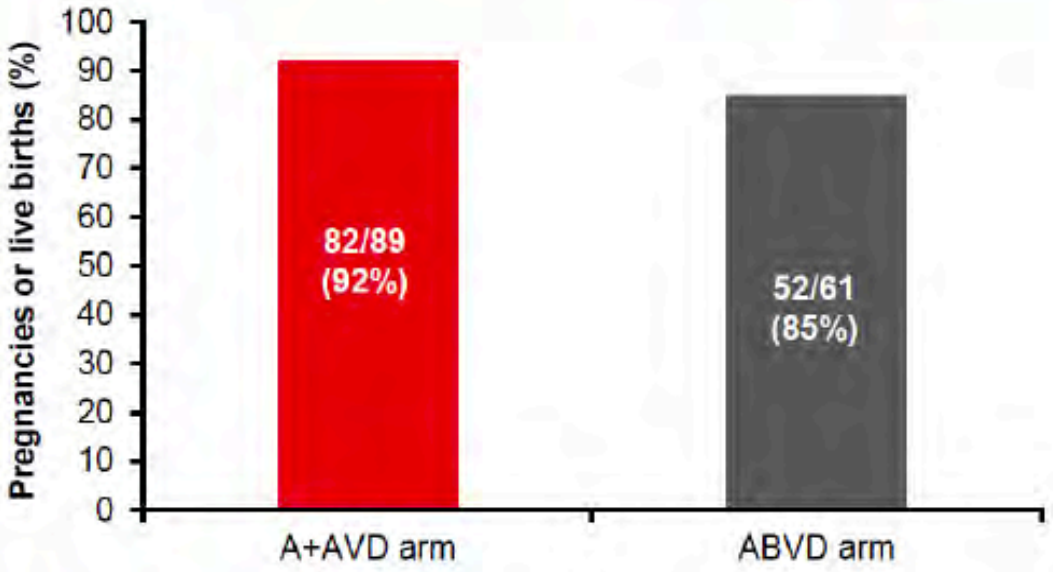
# ECHELON-1: Pregnancies

- 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.

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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].

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# 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].

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

Yasenchak CA et al.
ASH 2020;Abstract 471.

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# 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.

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# 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.

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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**

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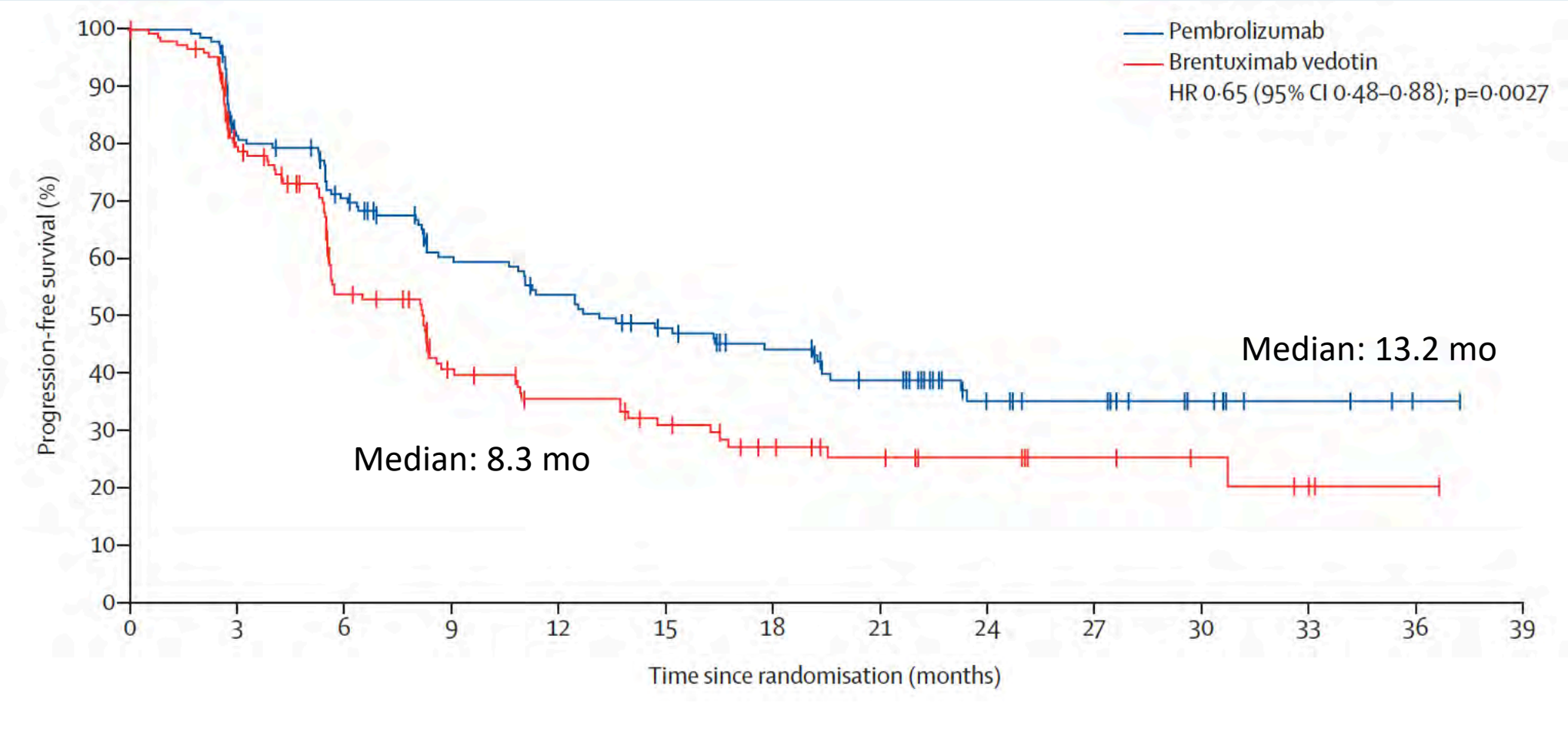
# KEYNOTE-204: PFS Primary Endpoint




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.

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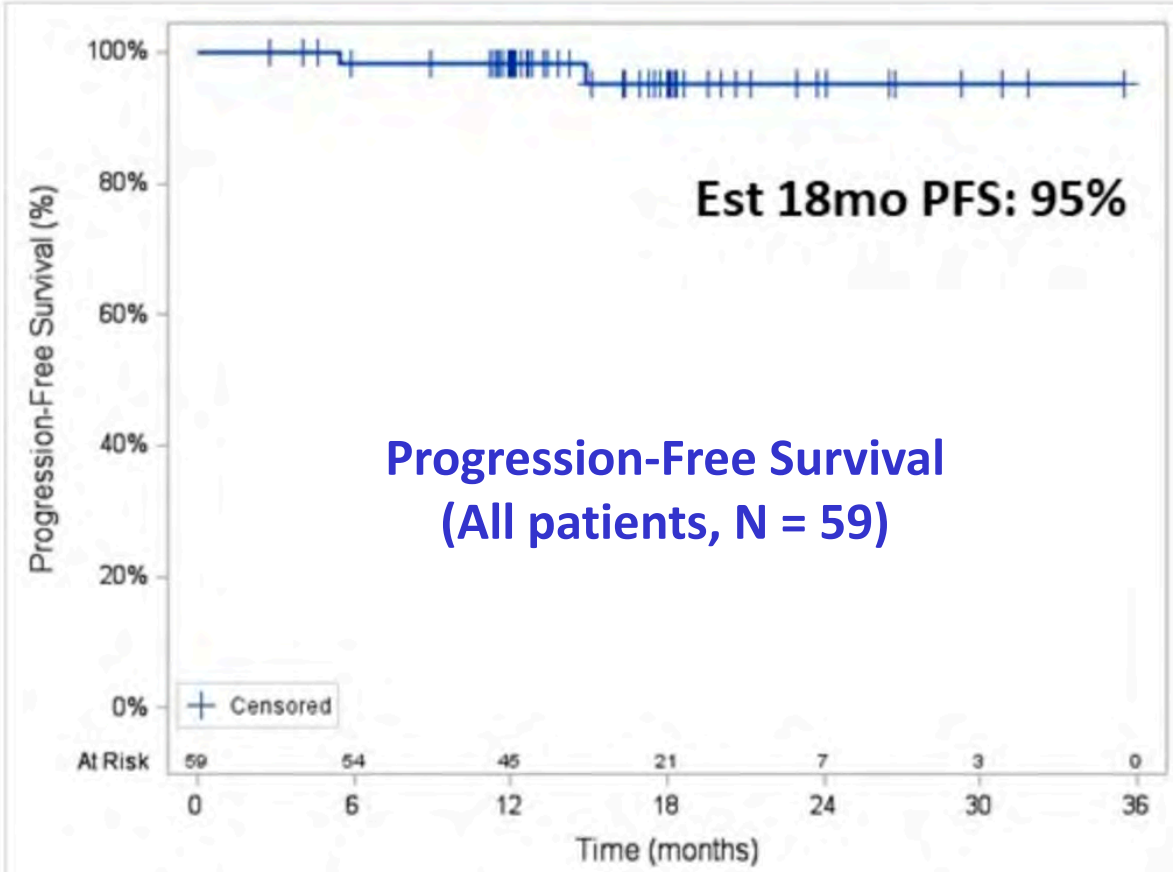
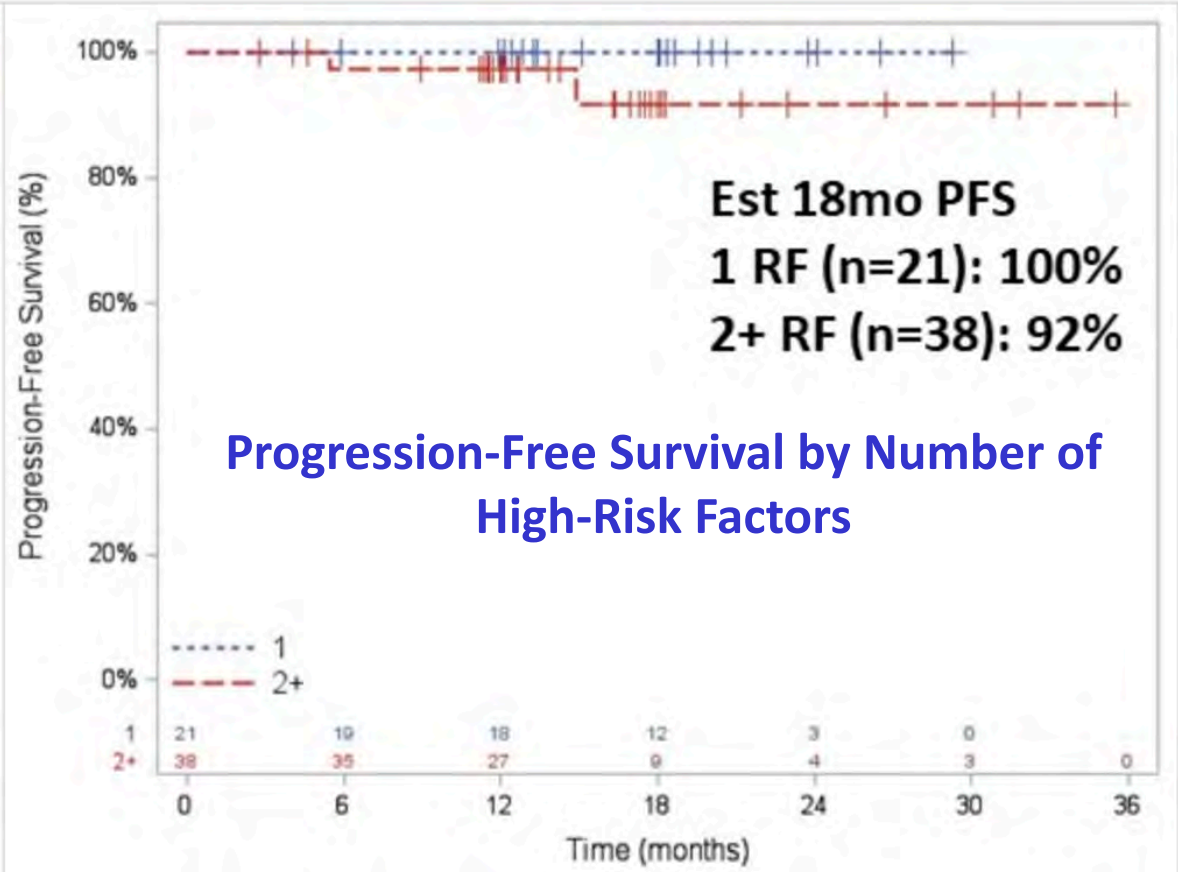
# Consolidation with Nivolumab and Brentuximab Vedotin After ASCT: Progression-Free Survival




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.

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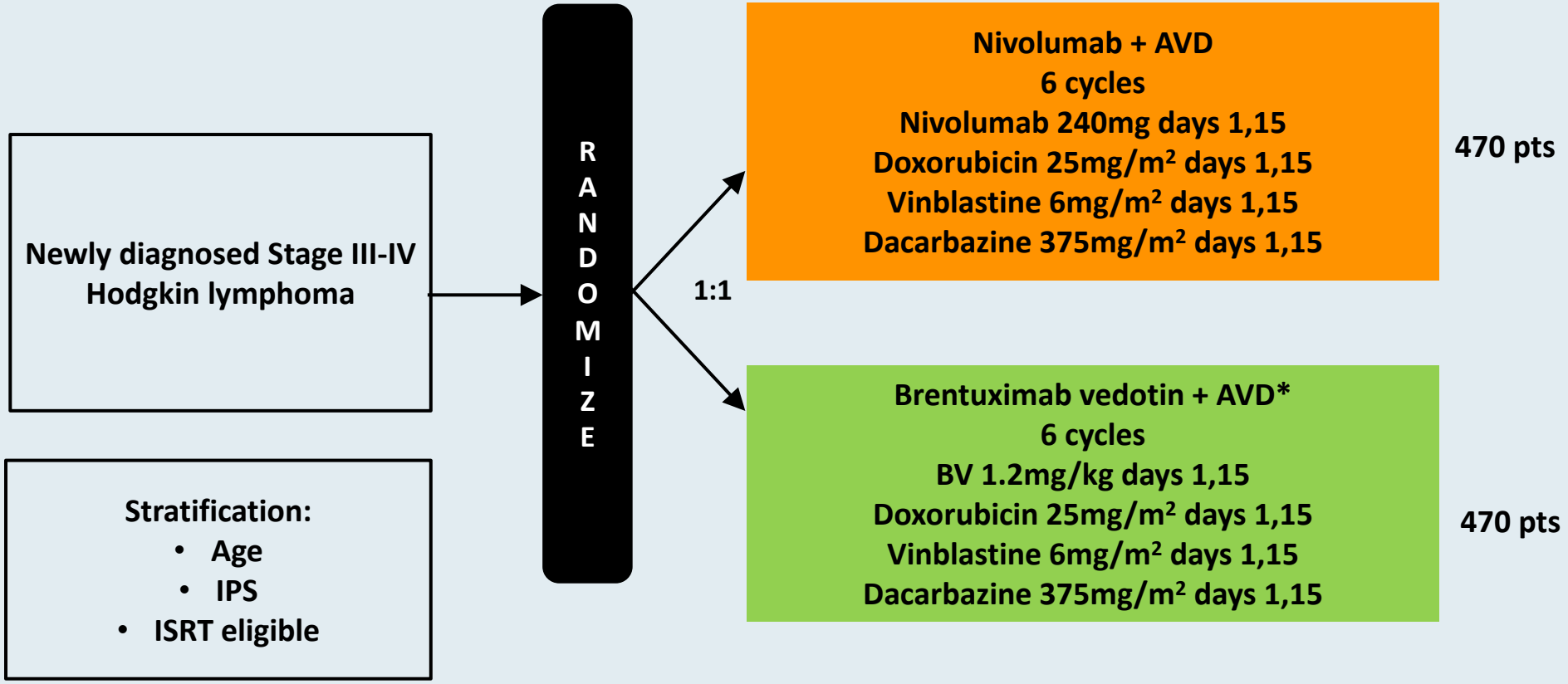
# SWOG-1826: Ongoing Phase III Trial of Nivolumab or Brentuximab Vedotin with Combination Chemotherapy for Newly Diagnosed Stage III-IV Classical HL




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

Courtesy of Craig Moskowitz, MD.

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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*

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

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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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# 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?

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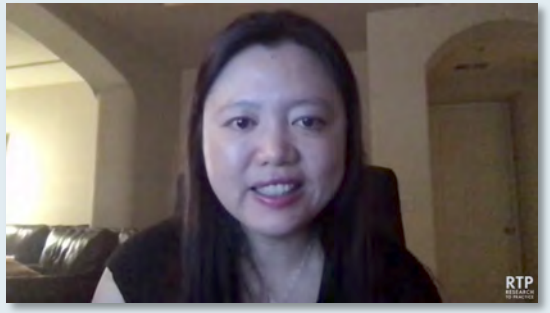
# Case Presentation – Dr Chen: A 66-year-old woman with newly diagnosed CLL receives acalabrutinib




**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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## What is your usual preferred initial regimen for a 75-year-old patient with IGHV-unmutated CLL without del(17p) or TP53 mutation who requires treatment?

1. BR
2. Ibrutinib
3. Ibrutinib + rituximab
4. Acalabrutinib
5. Acalabrutinib + obinutuzumab
6. Venetoclax + obinutuzumab
7. Other

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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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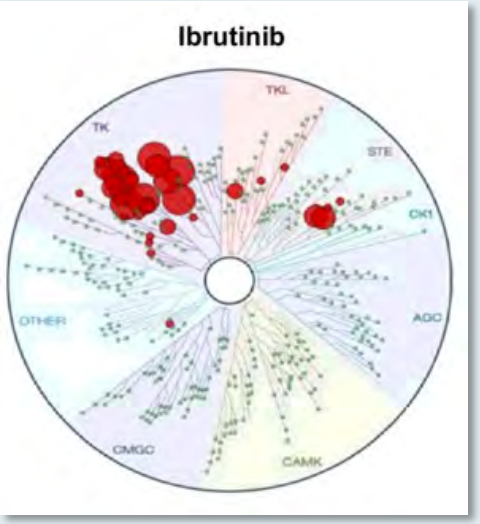
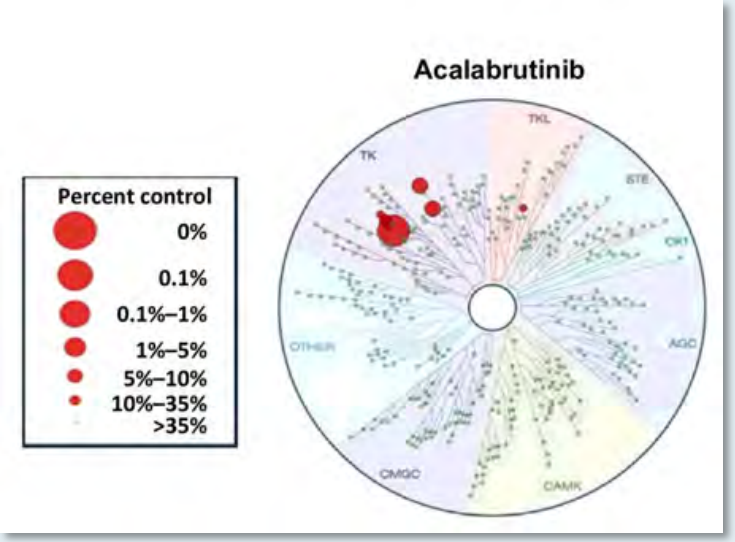
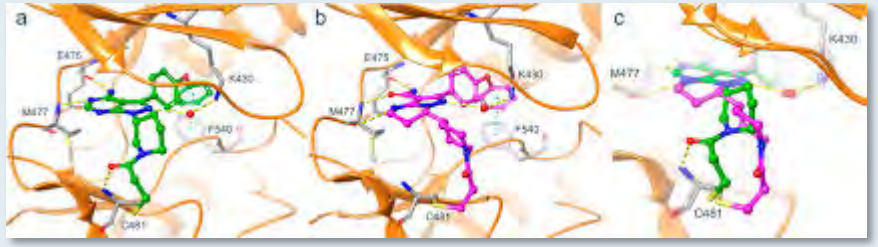
# Overview of BTK Inhibitors in CLL

## Irreversible



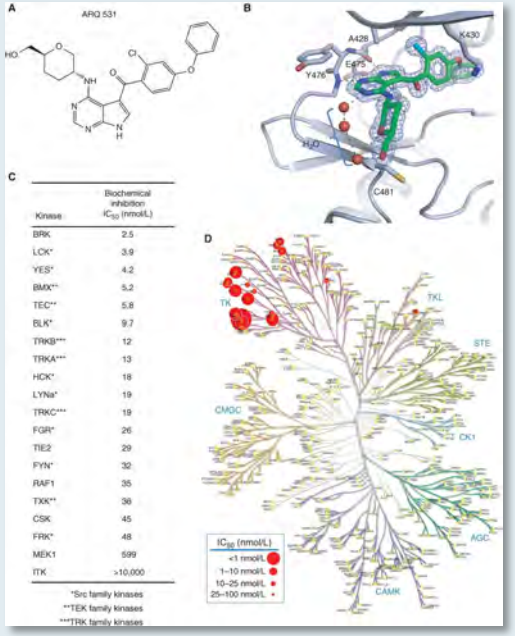




Zanubrutinib

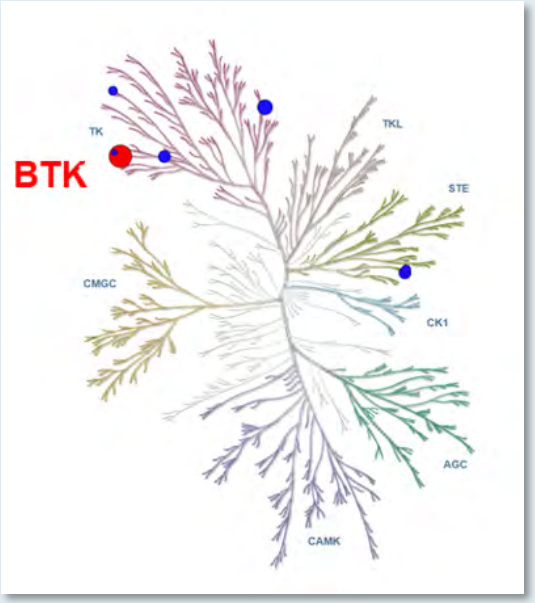



## Reversible

ARQ-531 (MK-1026)




Pirtobrutinib (LOXO-305)




Courtesy of Matthew S Davids, MD, MMSc

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# 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

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TO PRACTICE

# 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**

RTP
RESEARCH
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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

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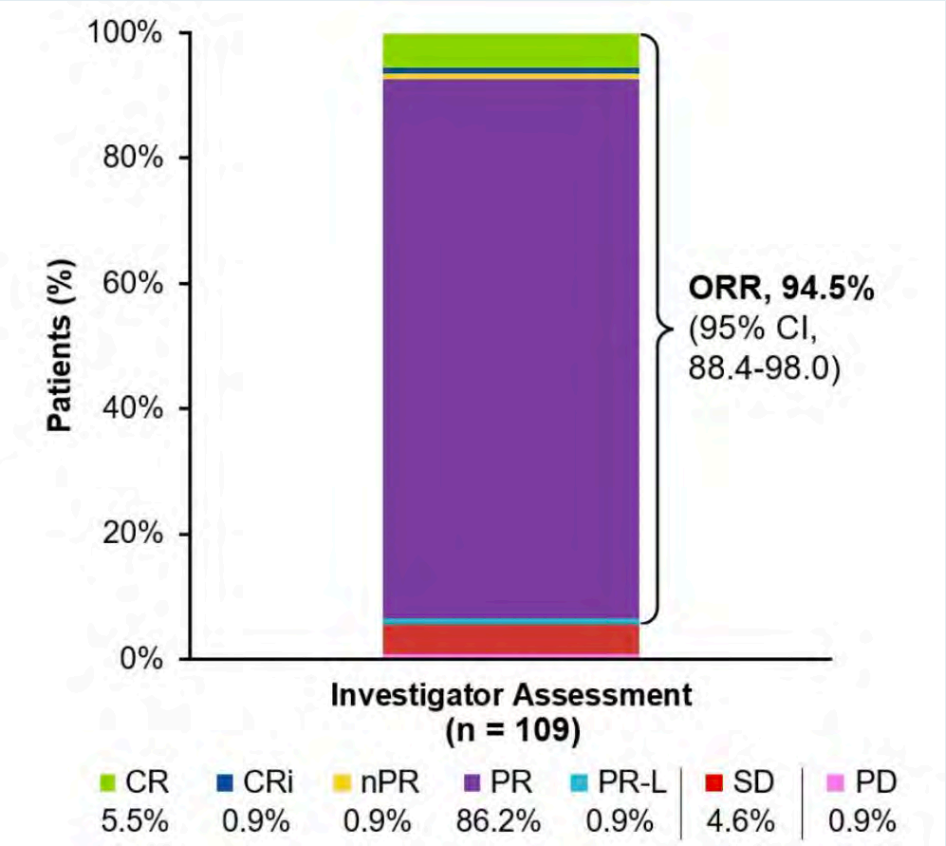
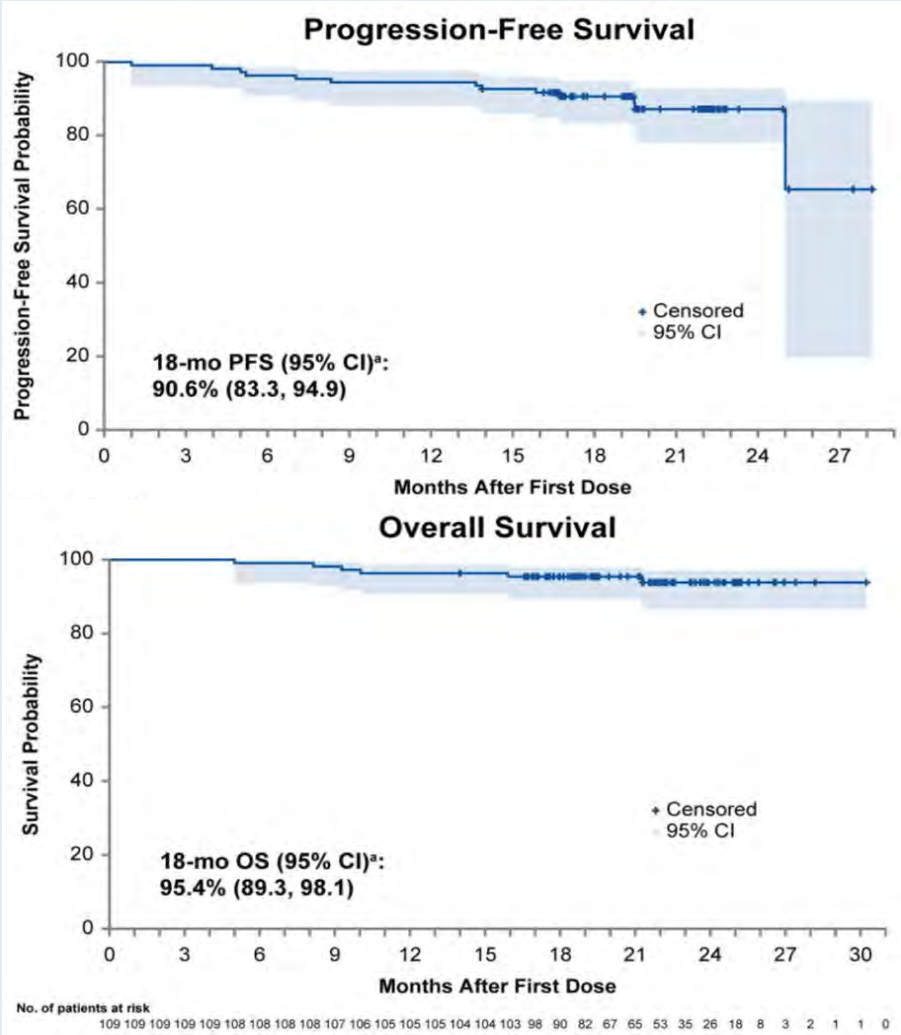
RESEARCH TO PRACTICE

# 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)

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

Courtesy of Matthew S Davids, MD, MMSc

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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.

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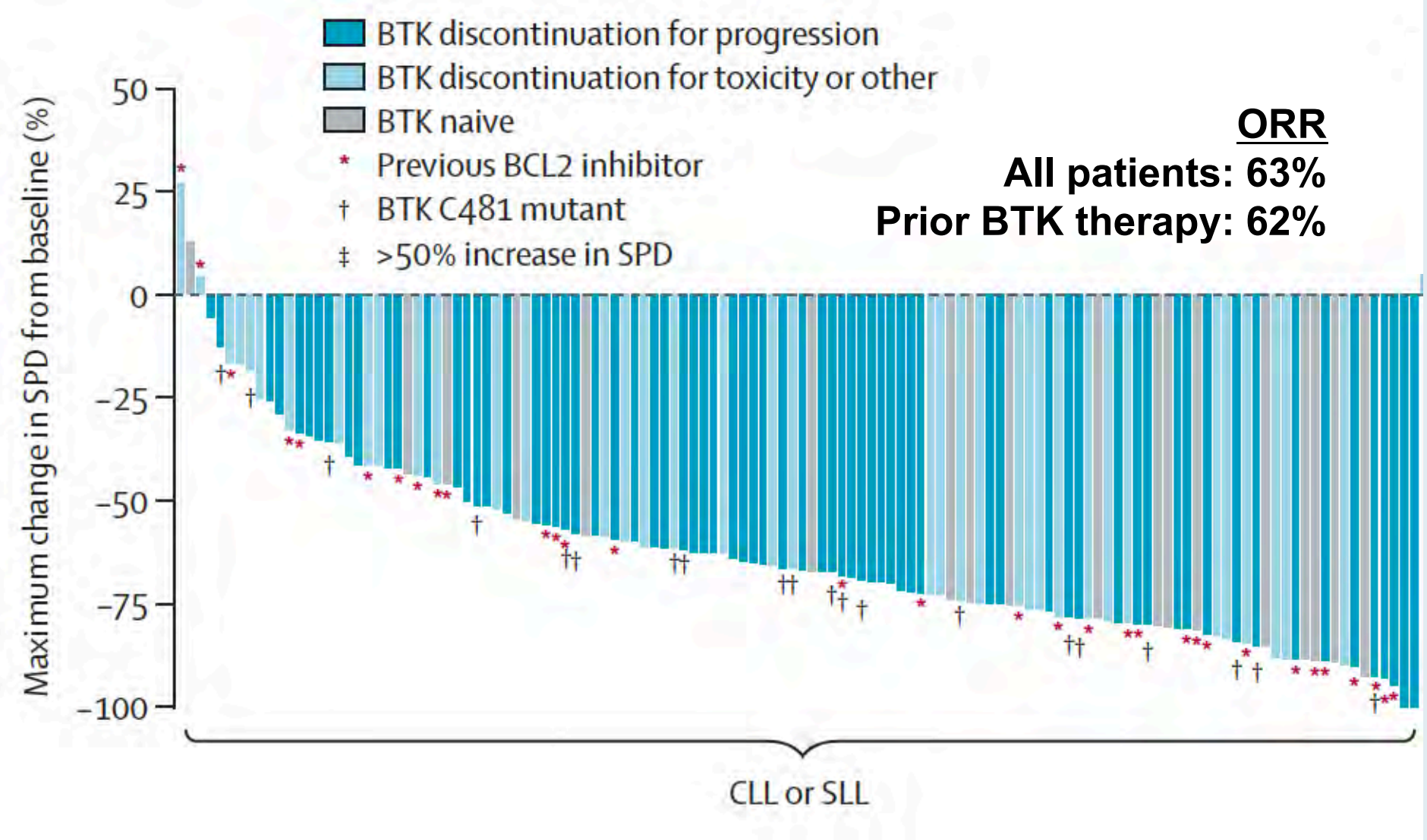
# BRUIN: Change in Tumor Burden from Baseline with Pirtobrutinib (LOXO-305) in Evaluable Patients with CLL or SLL




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

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Articles

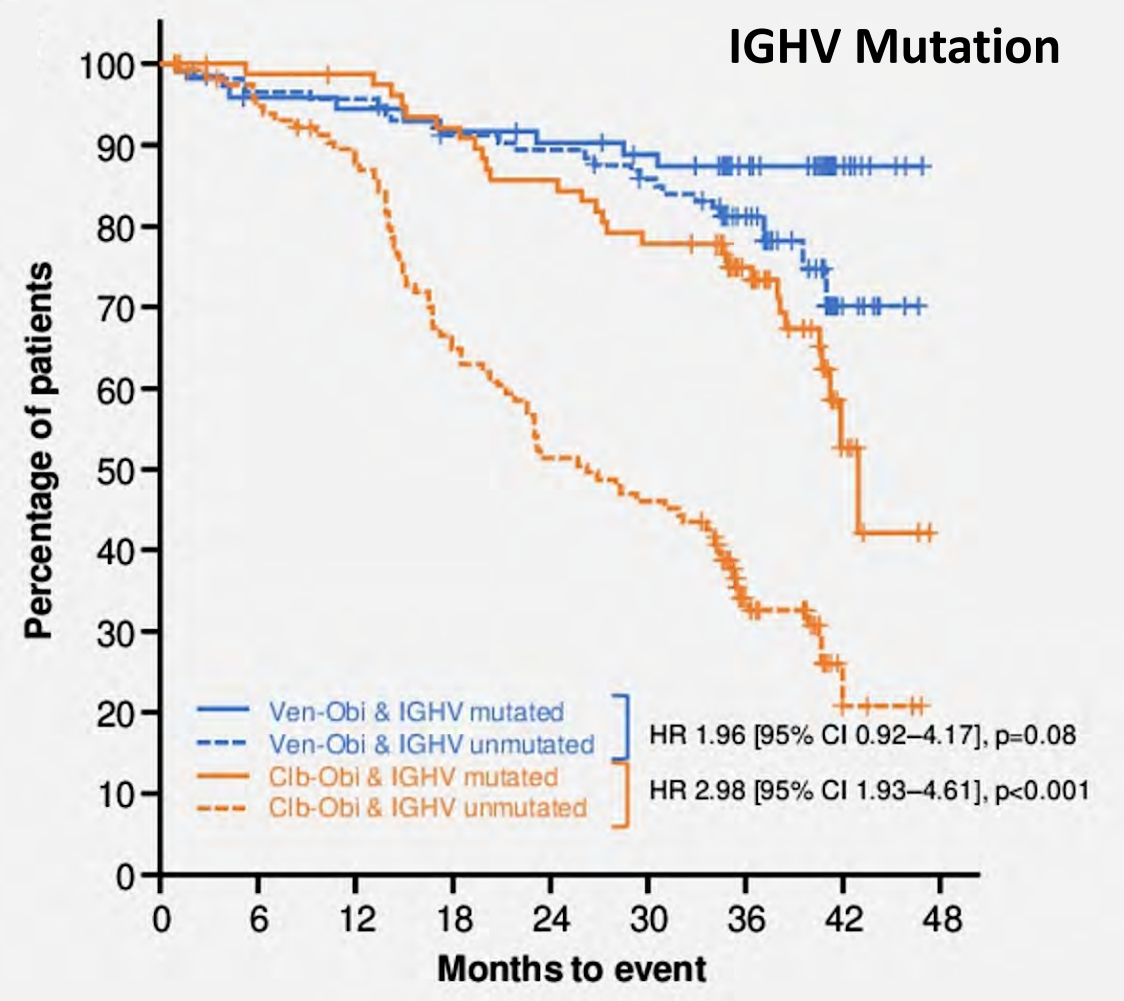
# Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial

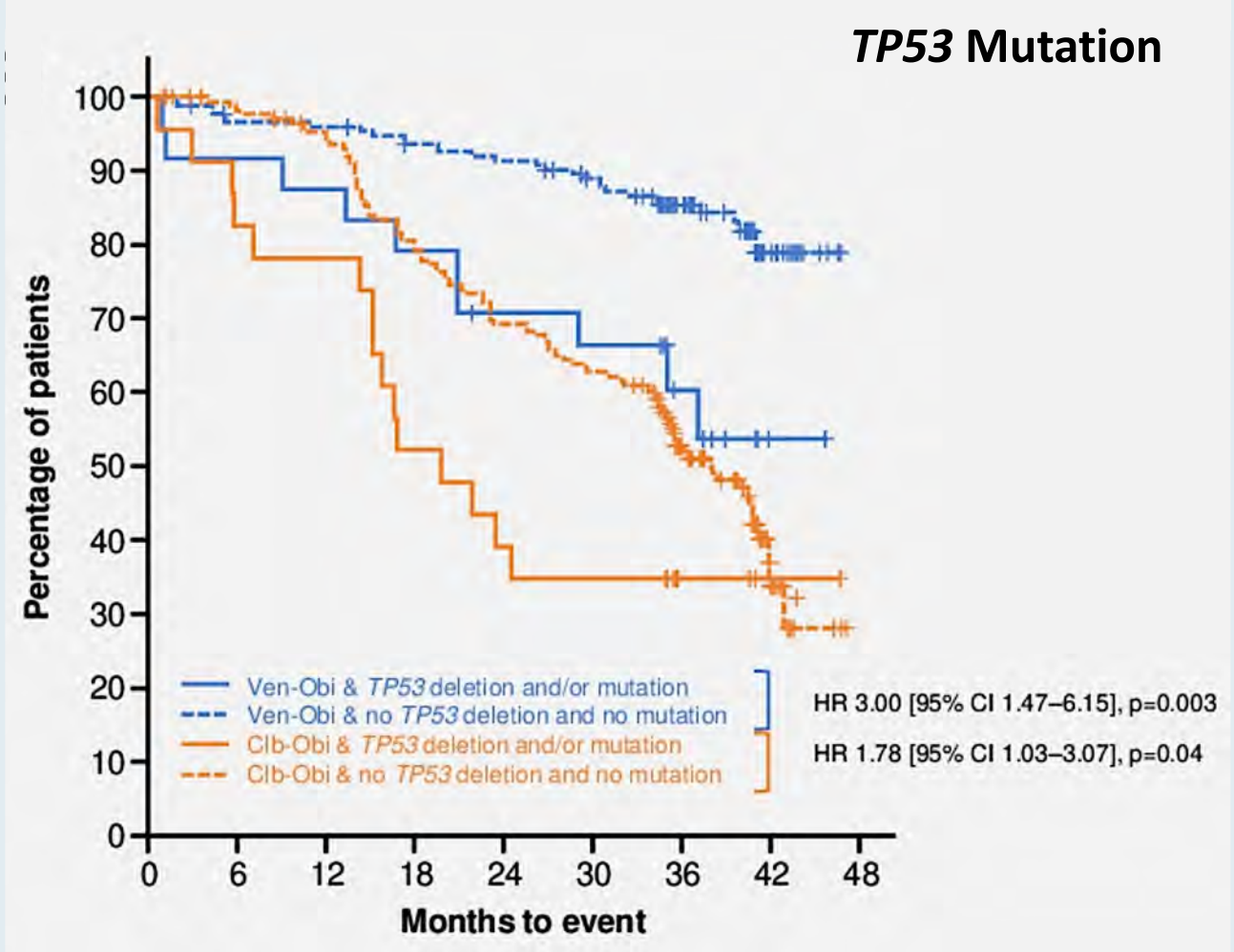
*Othman Al-Sawaf, Can Zhang, Maneesh Tandon, Arijit Sinha, Anna-Maria Fink, Sandra Robrecht, Olga Samoylova, Anna M Liberati, Javier Pinilla-Ibarz, Stephen Opat, Liliya Sivcheva, Katell Le Dû, Laura M Fogliatto, Carsten U Niemann, Robert Weinkove, Sue Robinson, Thomas J Kipps, Eugen Tausch, William Schary,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

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

RTP RESEARCH TO PRACTICE

# CLL14: PFS by IGHV and TP53 Mutation Status




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

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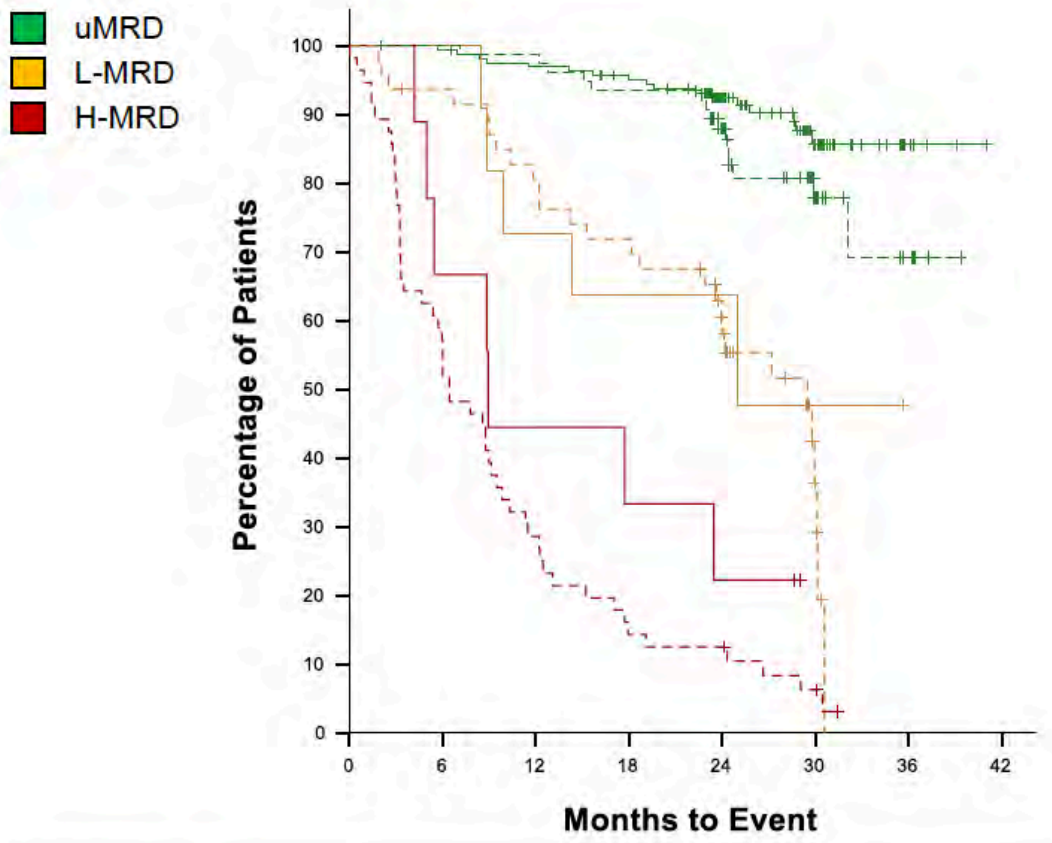
# CLL14: Landmark Analysis from End of Therapy PFS by MRD Group




| 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.

RTP RESEARCH TO PRACTICE

# 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.

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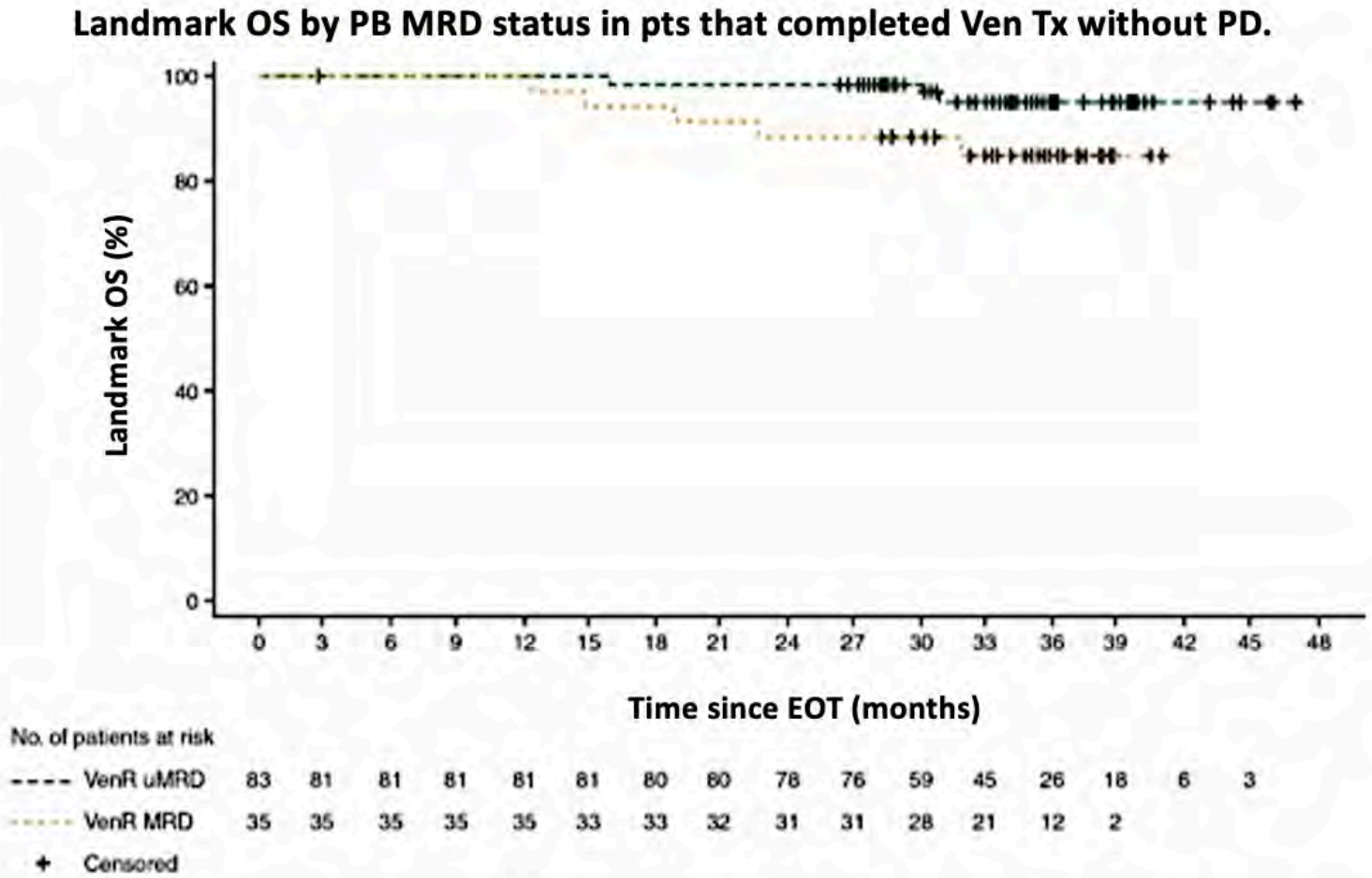
# MURANO: 5-Year Follow-Up of Venetoclax/Rituximab (Ven/R) in R/R CLL




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.

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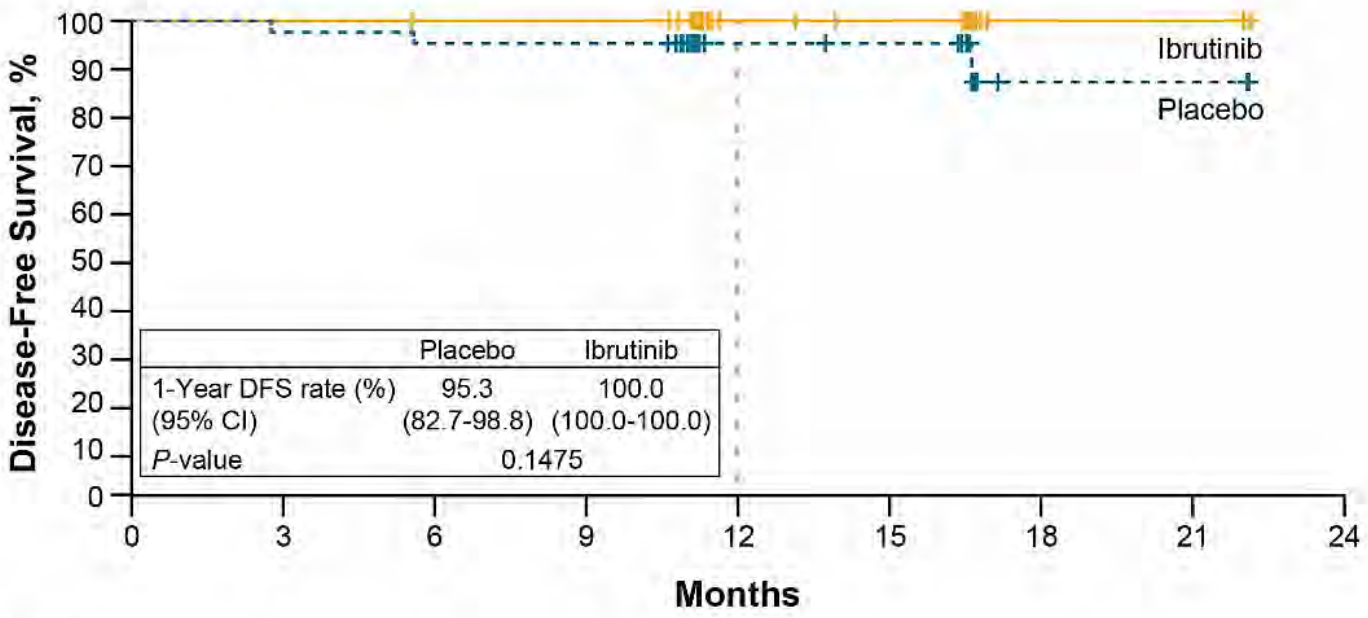
TO PRACTICE

# 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.

**30 month PFS Rate:**

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**

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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
- *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*

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# 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?

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# 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?

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## What is your usual third-line treatment for a patient with FL with an EZH2 mutation who received first-line BR, second-line lenalidomide/rituximab and then develops disease progression?

1. Idelalisib
2. Copanlisib
3. Duvelisib
4. Umbralisib
5. Tazemetostat
6. R-CHOP
7. Obinutuzumab +/- chemotherapy
8. Other

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# 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.

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# 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

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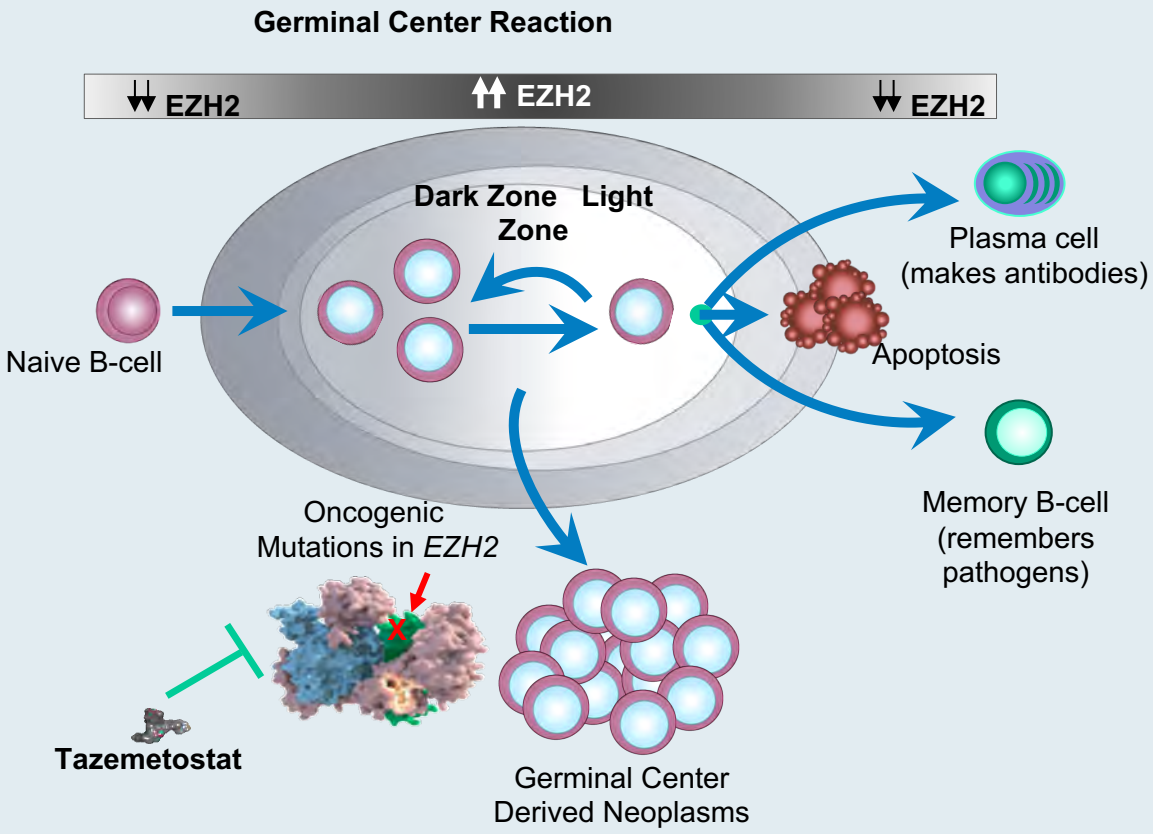
# Follicular Lymphoma and EZH2

- *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

RTP RESEARCH TO PRACTICE

# 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.

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# 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.

American Society *of* Hematology

Salles G et al. ASH 2020;Abstract 2047.

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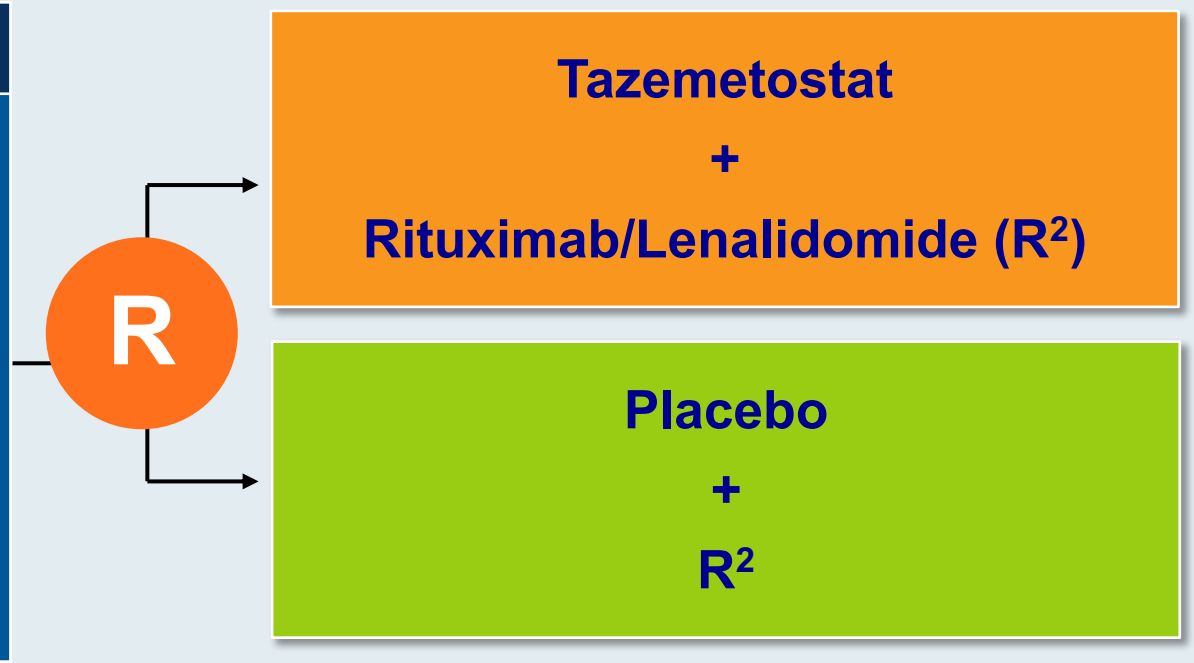
# Ongoing Phase Ib/III Trial of Tazemetostat + Len/Rituximab in R/R FL

**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).

RTP RESEARCH TO PRACTICE

# 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

RTP RESEARCH TO PRACTICE

# 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.

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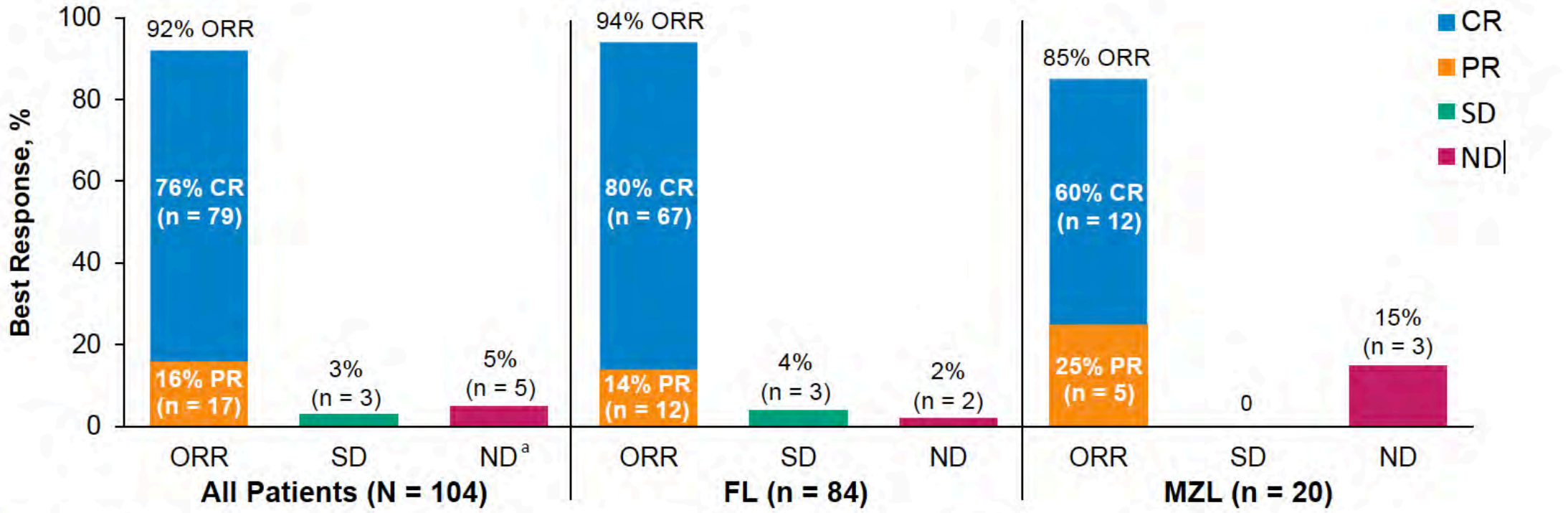
# ZUMA-5 Primary Endpoint: ORR by IRRC Assessment




- 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.

RTP RESEARCH TO PRACTICE

# 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.

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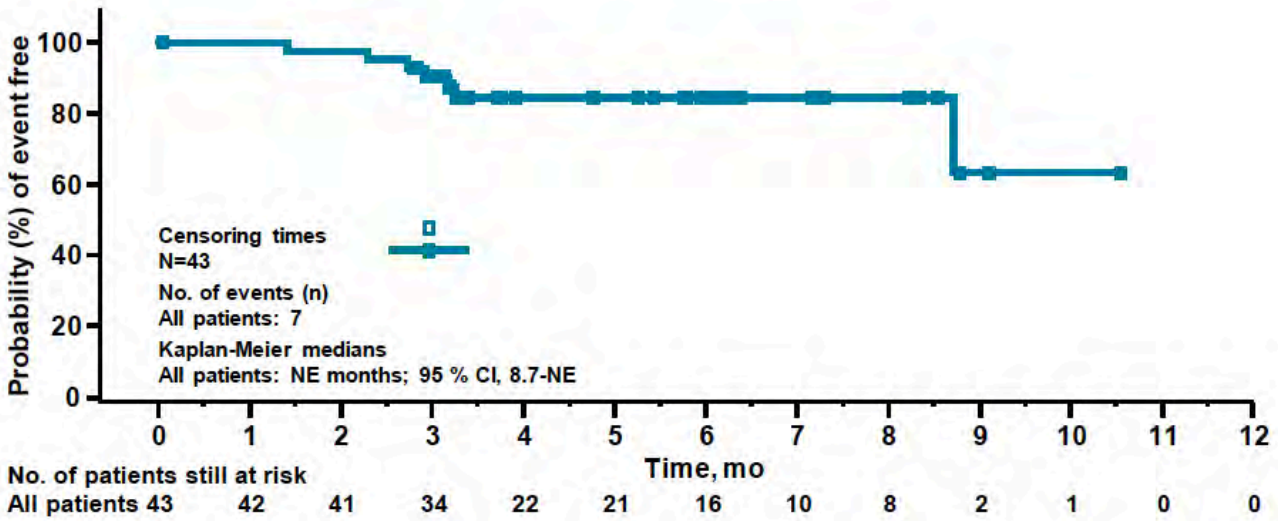
# ELARA Interim Analysis: Primary CR Endpoint

## 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.

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# 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.

RTP RESEARCH TO PRACTICE

# 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.

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

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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
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- 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
- *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*

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# 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.

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## 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?

1. Ibrutinib
2. Acalabrutinib
3. Zanubrutinib
4. Lenalidomide
5. Lenalidomide + rituximab
6. Venetoclax
7. Venetoclax + rituximab
8. Other

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# 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.


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# Efficacy of Zanubrutinib for MCL

| Study | Evaluable patients | ORR, CR | Median DoR | Median PFS |
|---|---|---|---|---|
| Phase I/II (NCT02343120) | N = 48<br>R/R = 37<br>TN = 11 | 87%, 31%<br>87%, 30%<br>88%, 38% | 16.2 mo (all)<br>14.7 mo<br>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.

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Articles

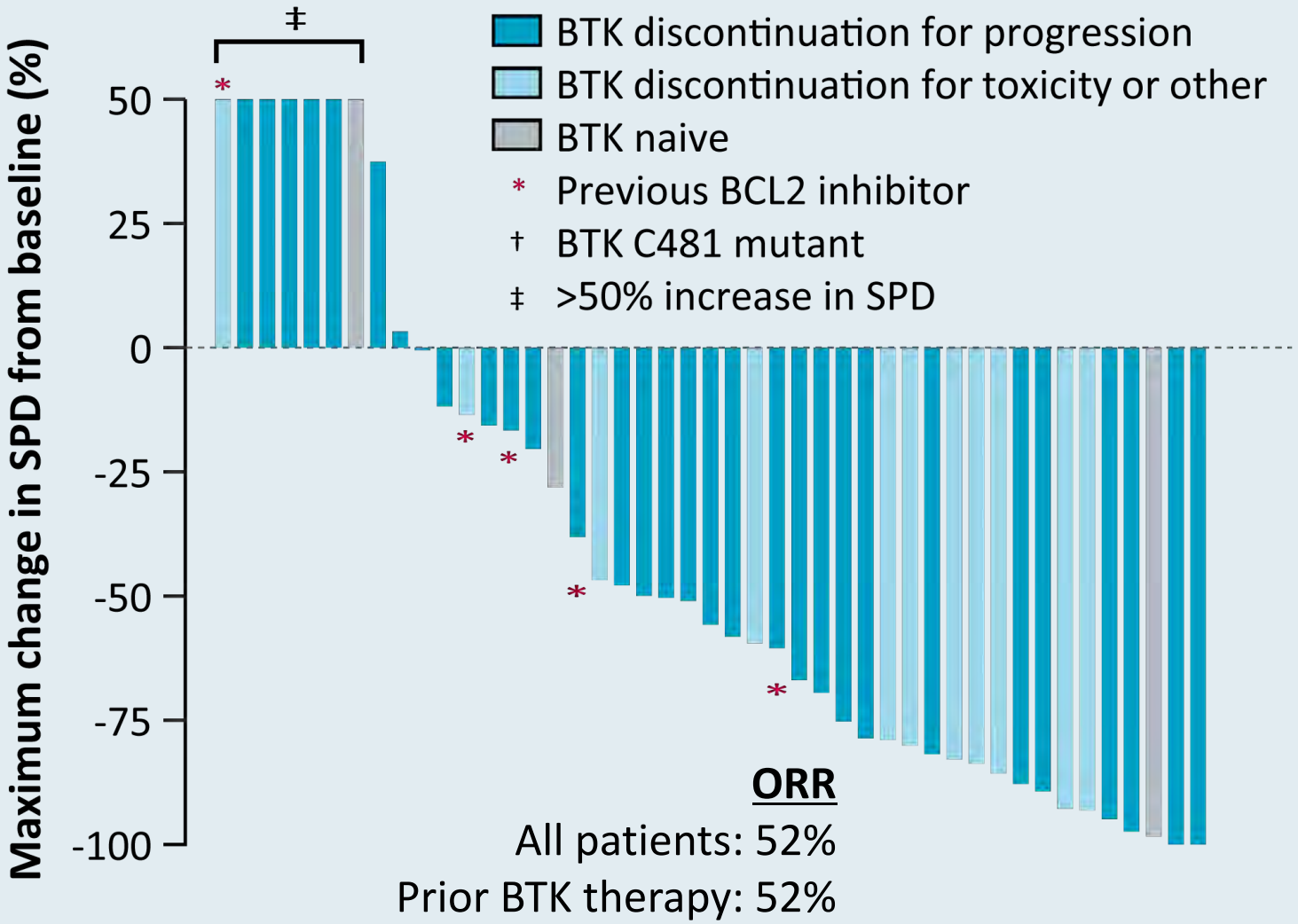
# Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study

*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.

RTP RESEARCH TO PRACTICE

# 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.

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# Venetoclax Monotherapy for BTK Inhibitor-Resistant MCL: Results Summary

| Clinical endpoint | Venetoclax (N = 20) |
|---|---|
| Overall response rate (ORR) | 60% |
| Complete response rate | 20% |
| ORR (prior response to BTKi) | 72.7% |
| ORR (primary resistance to BTKi) | 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.

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# 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**

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TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

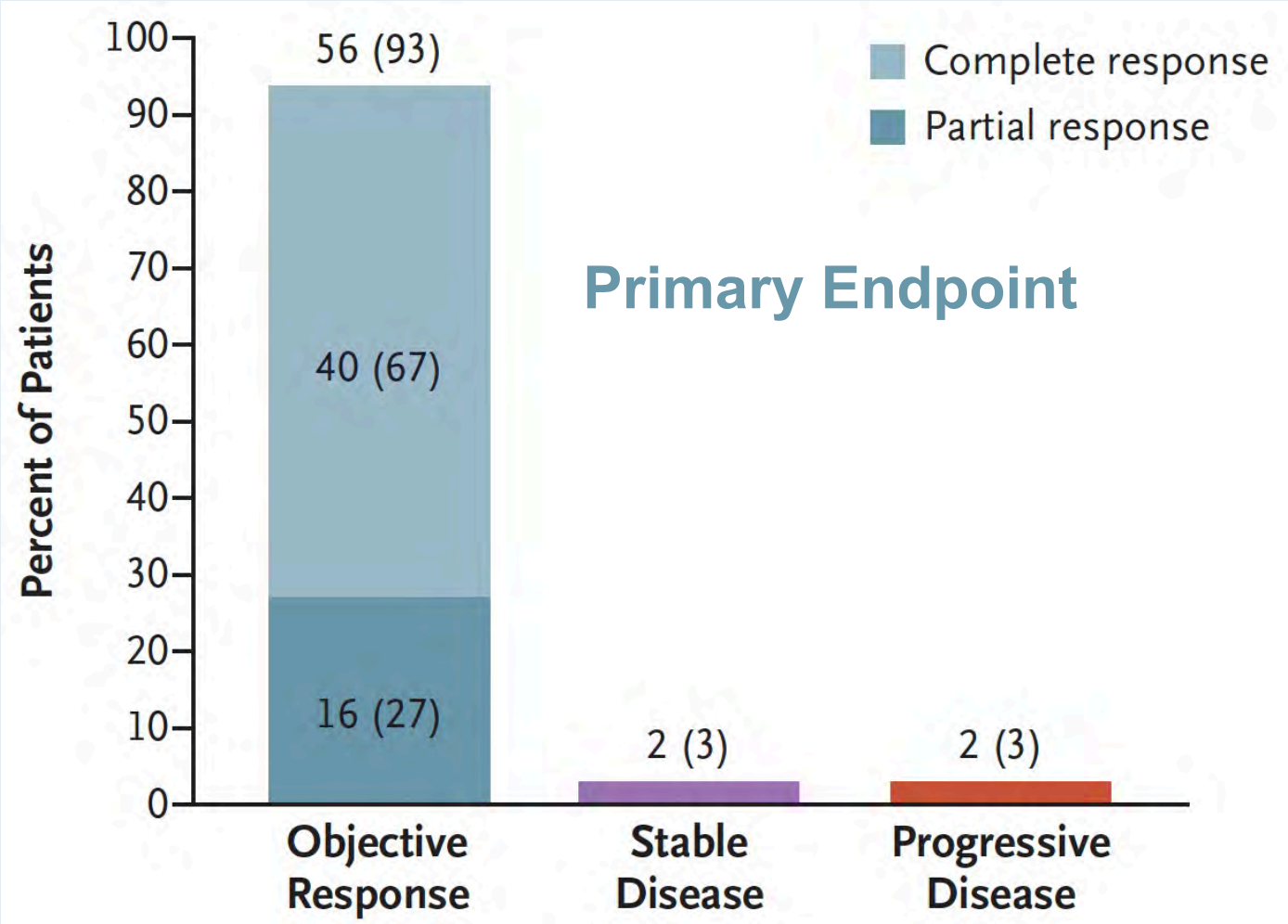
# KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

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.

RTP RESEARCH TO PRACTICE

# 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.

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***CME, MOC and NCPD credit information will be emailed to each participant within 5 business days.***

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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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# Up for Debate: Oncology Investigators Provide Their Take on Current Controversies in Patient Care

*A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists*

**Saturday, May 22, 2021**
**10:15 AM – 4:15 PM ET**

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# Saturday, May 22, 2021

**10:15 AM — Lung Cancer**
John V Heymach, Stephen V Liu

**11:30 AM — Genitourinary Cancers**
Maha Hussain, Elizabeth R Plimack

**12:45 PM — Chronic Lymphocytic Leukemia and Lymphomas**
Jonathan W Friedberg, Laurie H Sehn

**2:00 PM — Multiple Myeloma**
Irene M Ghobrial, Sagar Lonial

**3:15 PM — Breast Cancer**
Virginia Kaklamani, Nancy U Lin

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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
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# Contributing Oncologists

**Amanda Blackmon, DO, MS**
Chief Fellow, Hematology/Oncology
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**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
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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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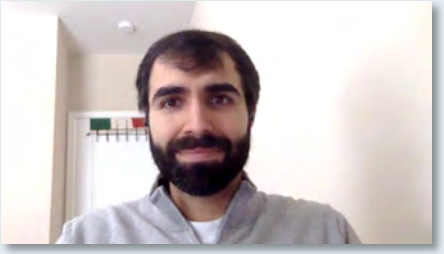
# Contributing Oncologists



**Rahul Gosain, MD**
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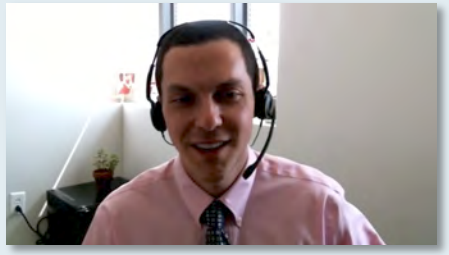
Corning, New York

**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**
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Tower Hematology Oncology
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**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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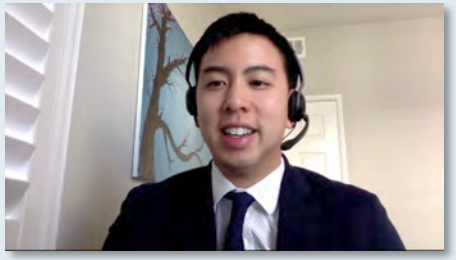
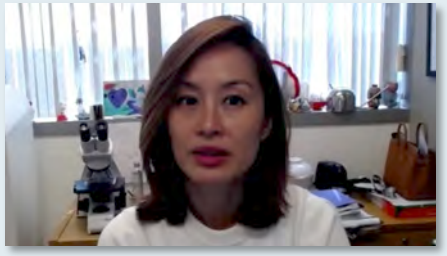
# Contributing Oncologists

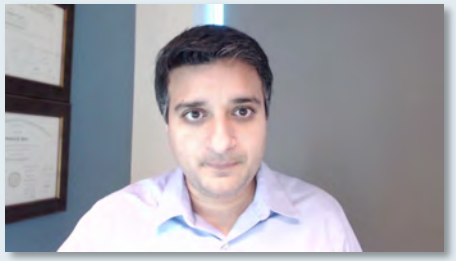
**Mohamed K Mohamed, MD, PhD**
Oncology Division Medical Director
Director of Thoracic Oncology
Hematologist/ Medical Oncologist
Cone Health Cancer Center
Greensboro, North Carolina



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

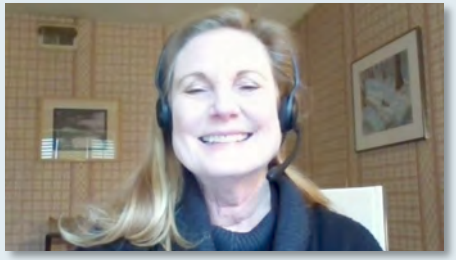


**Helen H Moon, MD**
Medical Oncologist
Southern California Permanente
Medical Group
Riverside, California



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

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



**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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# Agenda

## Module 1: Prostate Cancer

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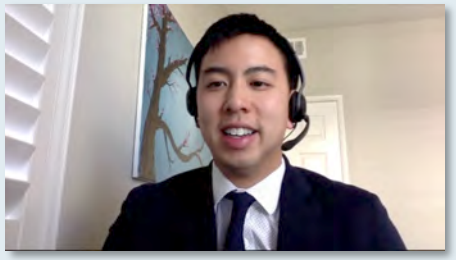
# Case Presentation – Dr Nguyen: An 86-year-old man with a biochemical recurrence after local therapy



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?

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## 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?

1. Abiraterone
2. Apalutamide
3. Enzalutamide
4. Darolutamide
5. Docetaxel
6. None initially, but add secondary hormonal therapy if suboptimal response to ADT
7. None initially, but add chemotherapy if suboptimal response to ADT
8. None

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# 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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# 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

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# 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.

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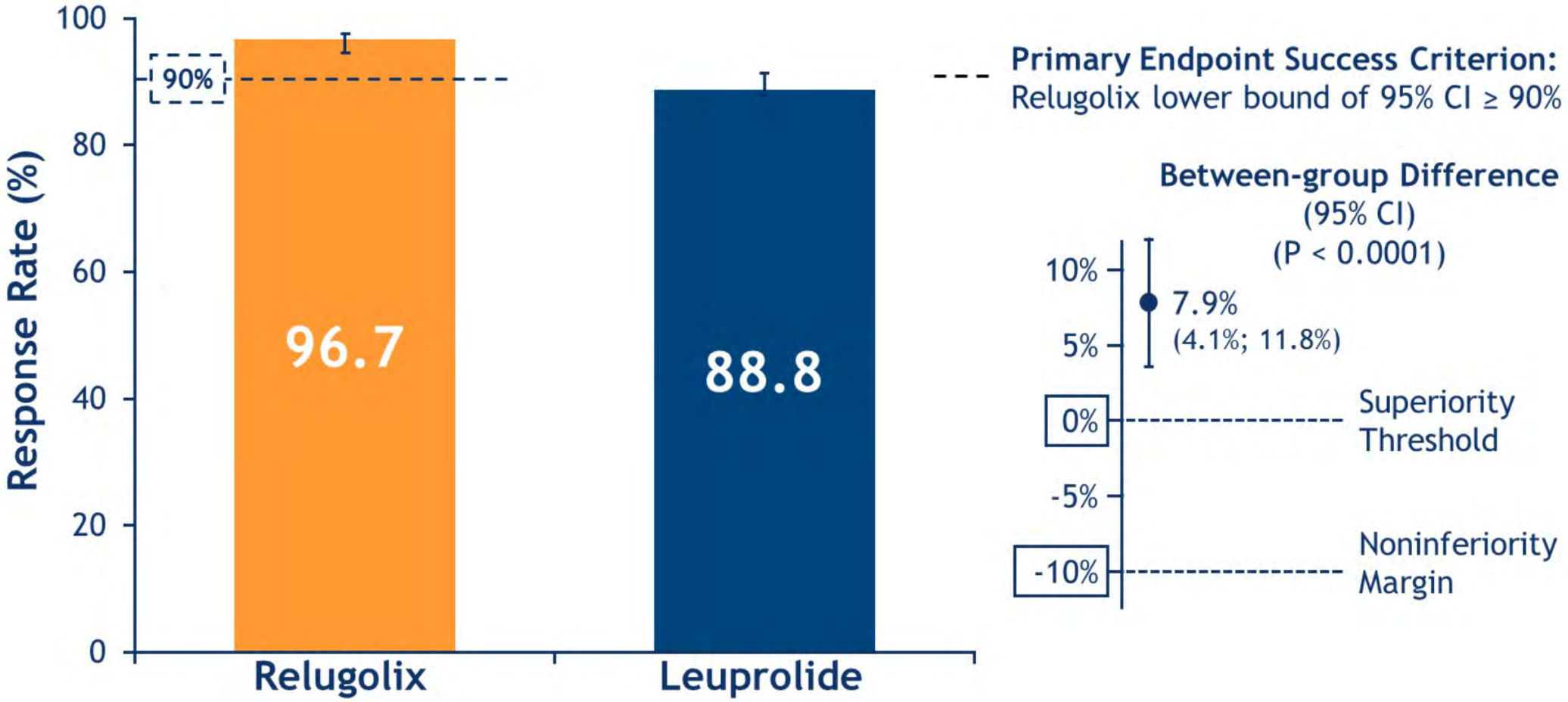
# HERO: Primary Endpoint – Sustained Castration
# Key Secondary Endpoint – Noninferiority to Leuprolide




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

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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]*

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# 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.


RTP RESEARCH TO PRACTICE

# 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<br>• 17% prior docetaxel<br>• 25% prior RP/XRT | | • 2/3rd high volume<br>• 10% prior docetaxel<br>• 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**<br>• HR (prior docetaxel): 0.52<br>• HR (high volume): 0.43<br>• HR (low volume): 0.25 | | **HR (overall): 0.48**<br>• HR (prior docetaxel): 0.47<br>• HR (high volume): 0.53<br>• HR (low volume): 0.36 | |
| Overall survival | NR | NR | NR | NR |
| | **HR: 0.81 (immature)** | | **HR (overall): 0.67**<br>• HR (prior docetaxel): 1.27<br>• HR (high volume): 0.68<br>• 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.

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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

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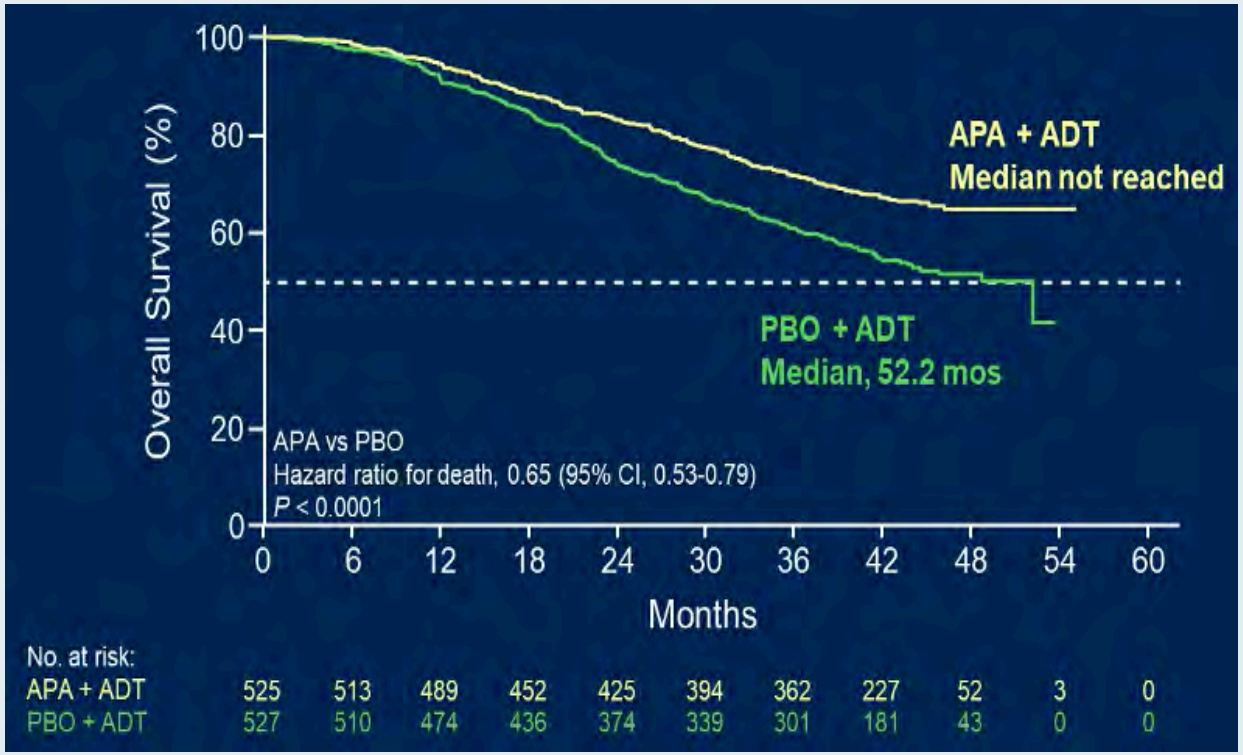
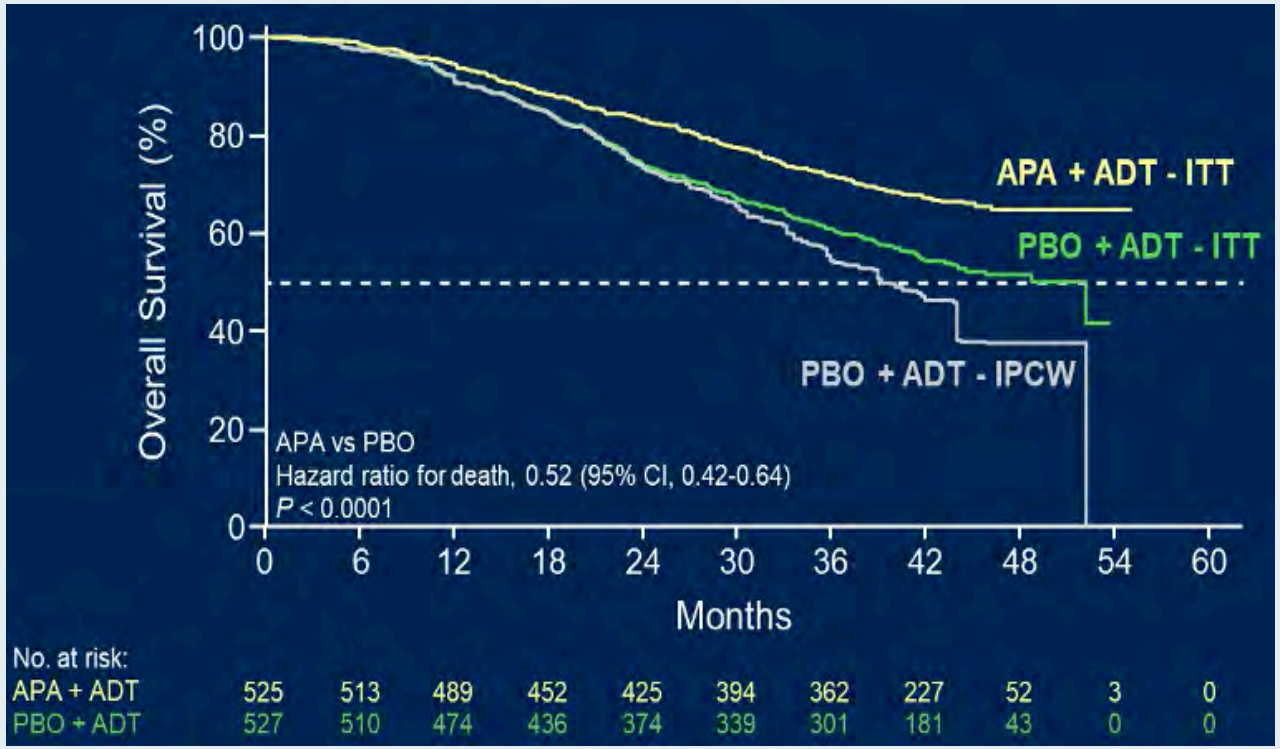
# TITAN – Final Analysis: Overall Survival

**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.

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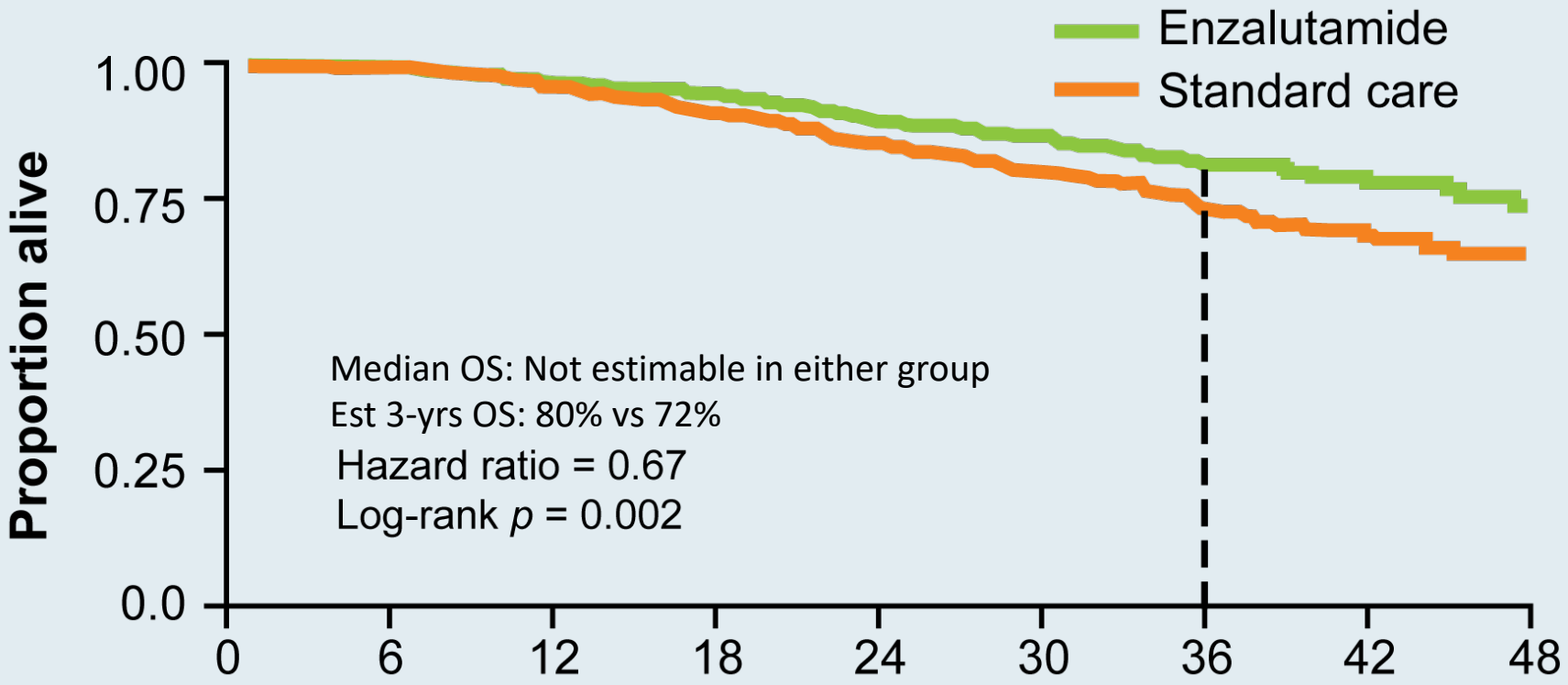
# ENZAMET: ADT + Enzalutamide or Standard Nonsteroidal Antiandrogen — Primary Endpoint Overall Survival

**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.

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# 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.

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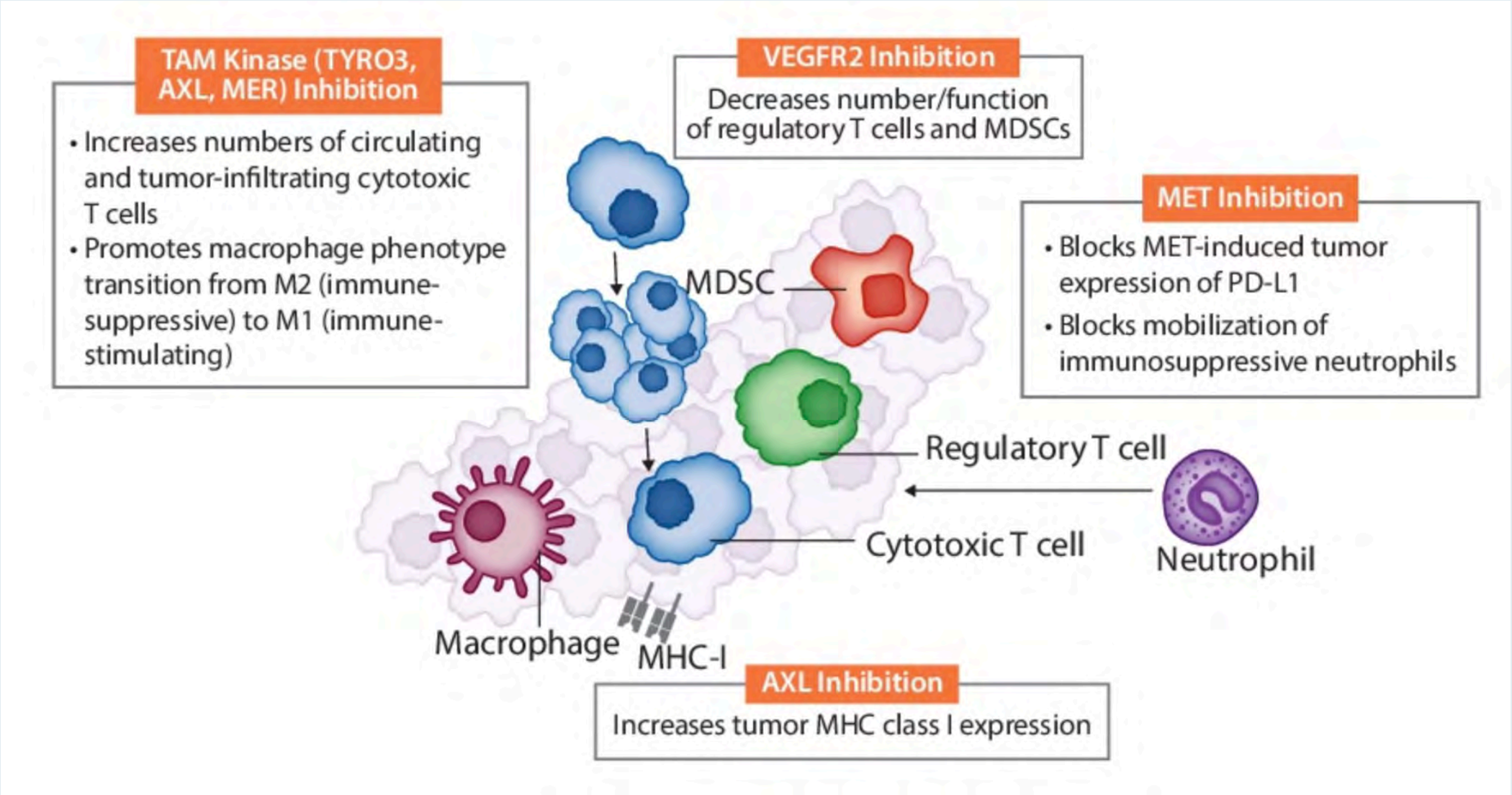
# Cabozantinib Targets Pathways Associated with Tumor Immune Suppression




Agarwal N et al. ASCO 2020;Abstract 5564.

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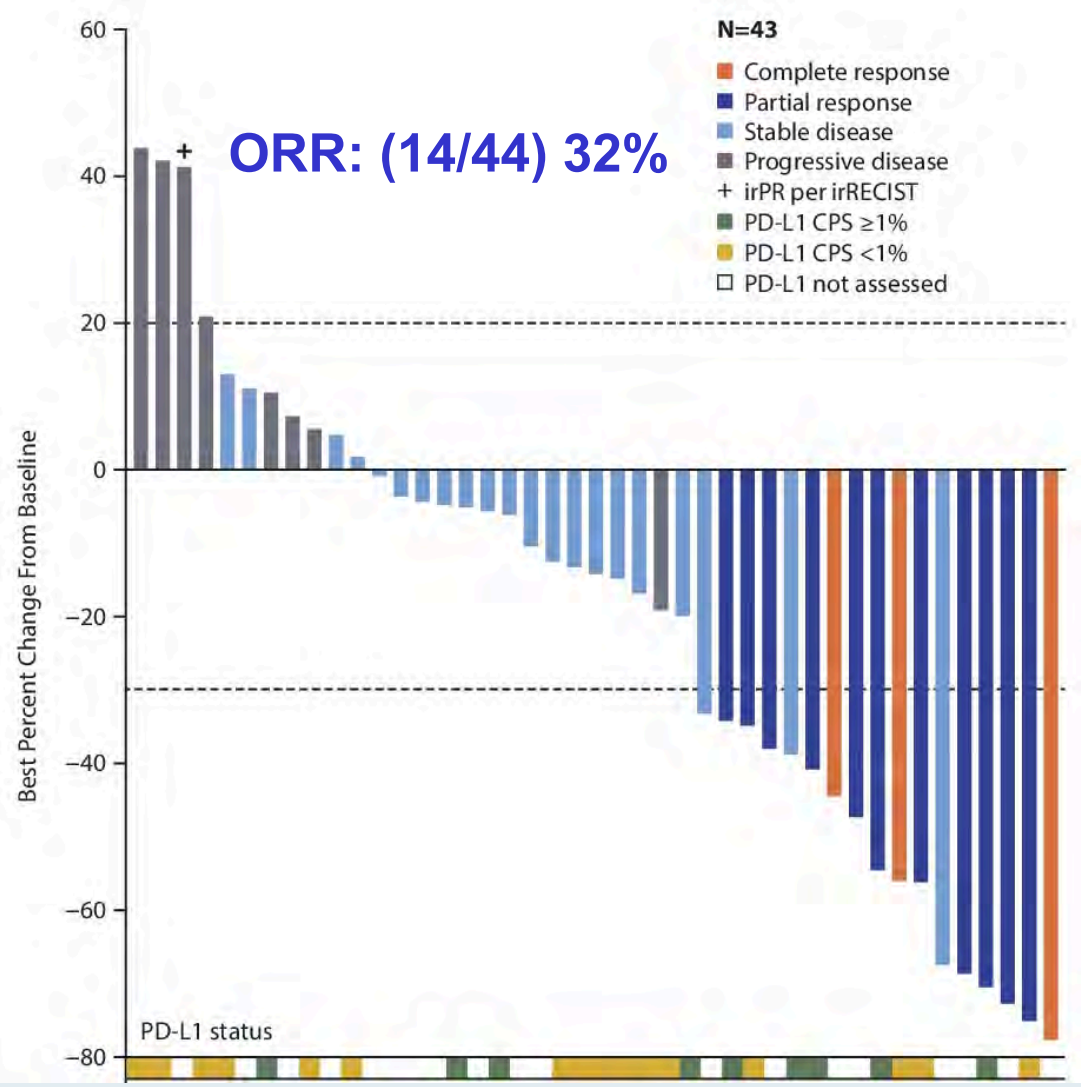
# COSMIC-021 Primary Endpoint: Investigator-Assessed ORR with Cabozantinib/Atezolizumab in mCRPC




| | 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.

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# CONTACT-02 Phase III Study Schema

**Eligibility**

- Metastatic CRPC
- Prior treatment with only 1 prior novel hormonal therapy for hormone-sensitive T3 or T4, mHSPC, M0 CRPC, or mCRPC

N = 580

1:1

**Cabozantinib 40 mg QD**
**+ Atezolizumab 1,200 mg Q3W**

**Abiraterone/prednisone OR**
**Enzalutamide per investigator**

**Coprimary endpoints: Duration of PFS and OS**

Clinicaltrials.gov, Accessed October 2020 (NCT04446117)

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# 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?

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# 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.


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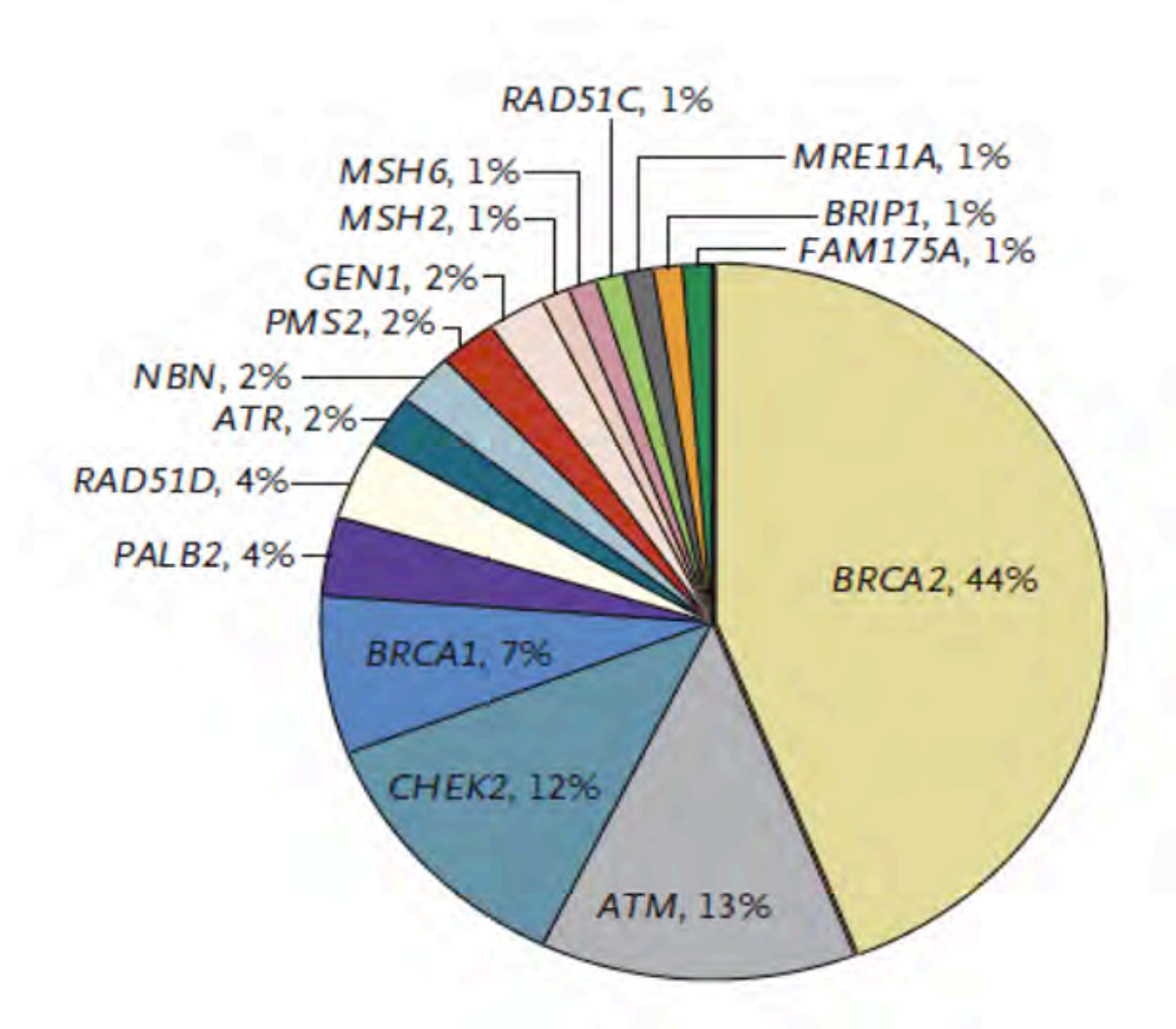
# Inherited DNA Repair Gene Mutations in Men with mPC




- 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.

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# 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/

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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.**

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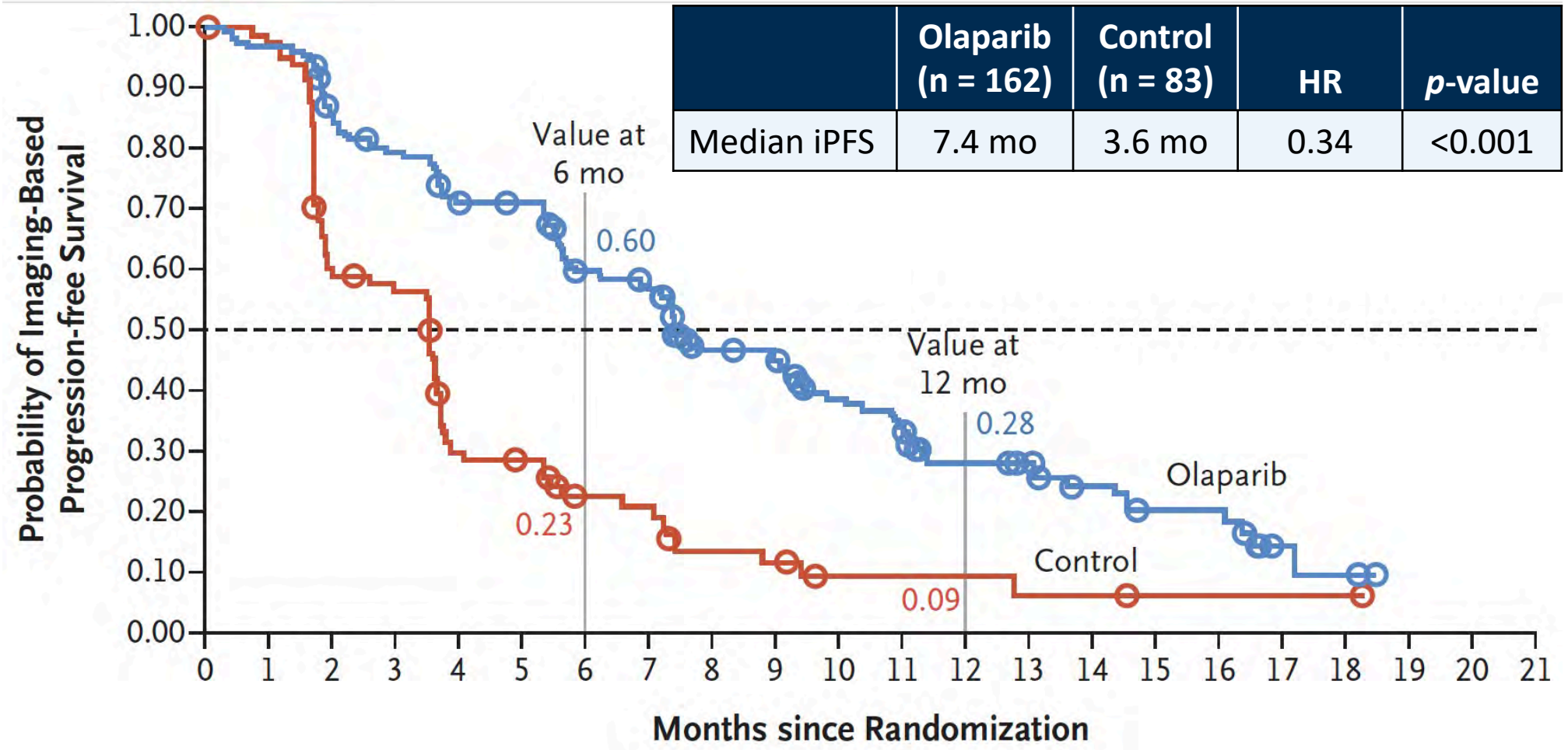
# PROfound Primary Endpoint: Imaging-Based PFS with Olaparib for Patients with mCRPC Who Had at Least 1 Alteration in BRCA1, BRCA2 or ATM (Cohort A)




| | 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.

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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.**

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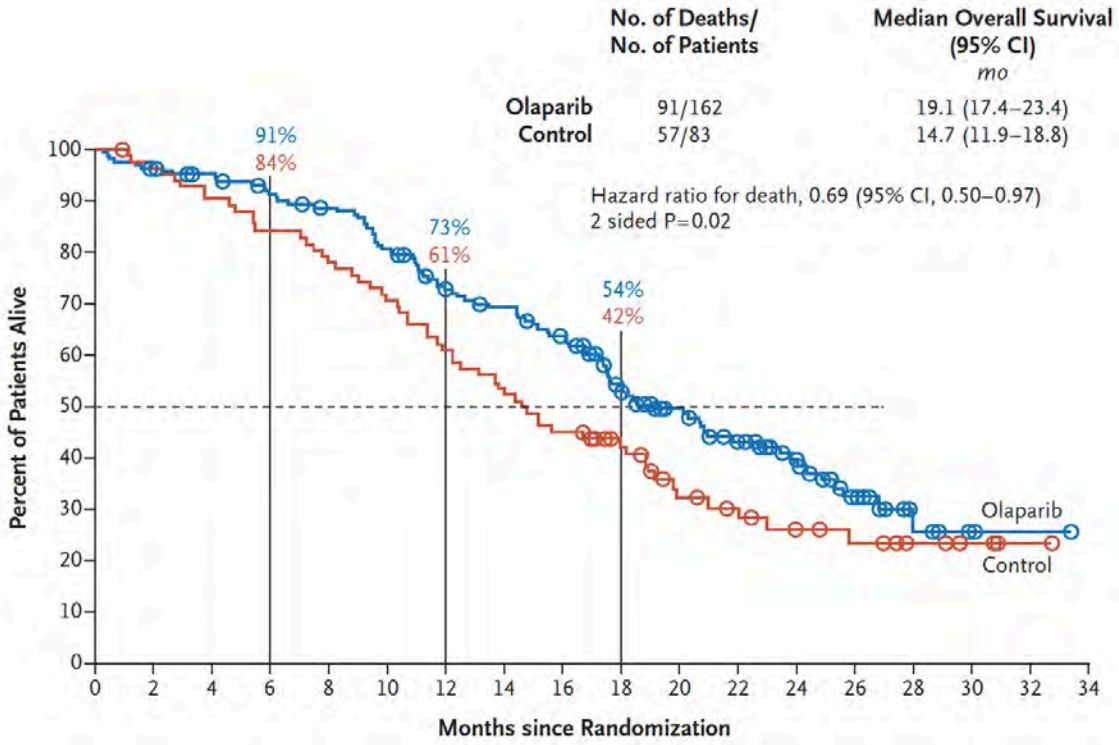
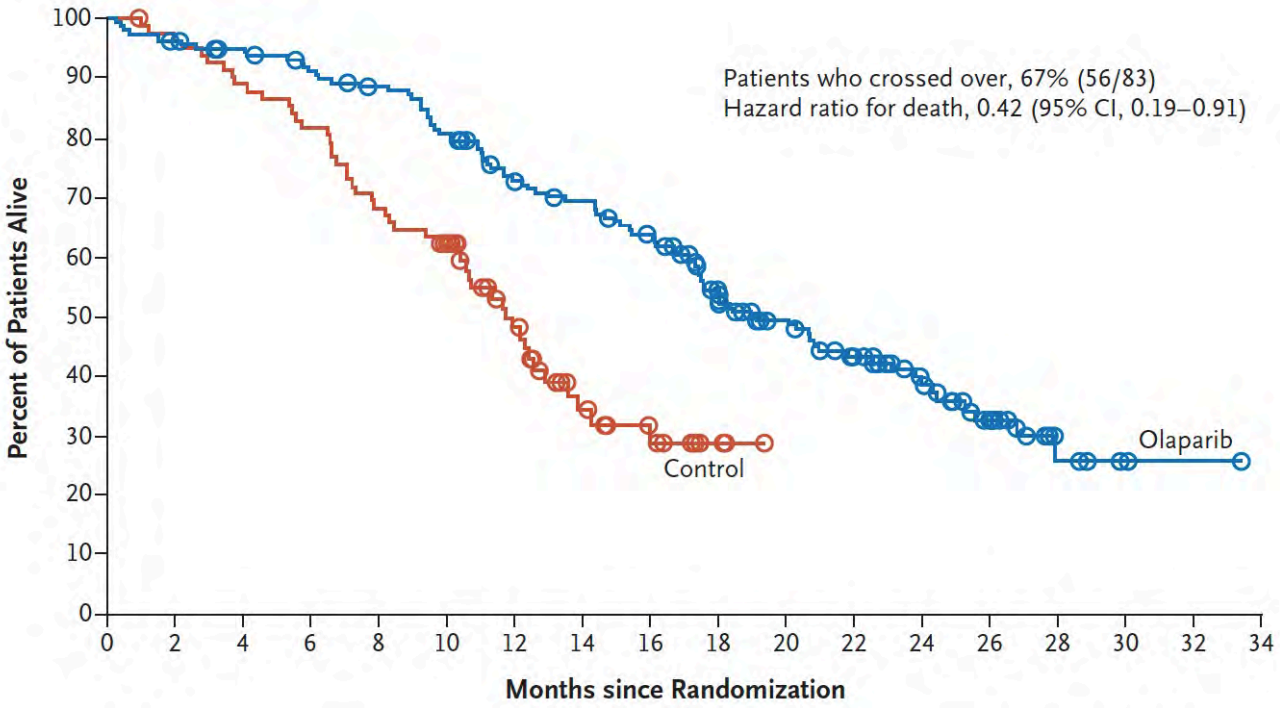
# PROfound: Overall Survival with Olaparib for Patients with mCRPC Who Had at Least 1 Alteration in BRCA1, BRCA2 or ATM (Cohort A)

## Overall survival




## Cross-over adjusted overall survival




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

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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.

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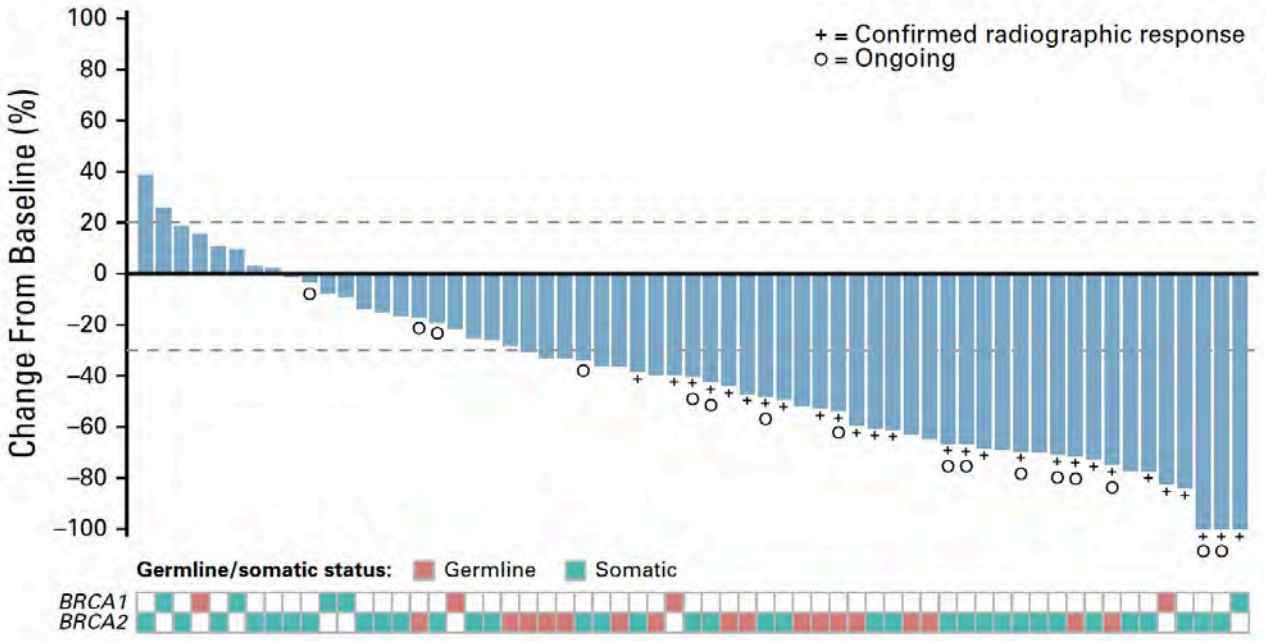
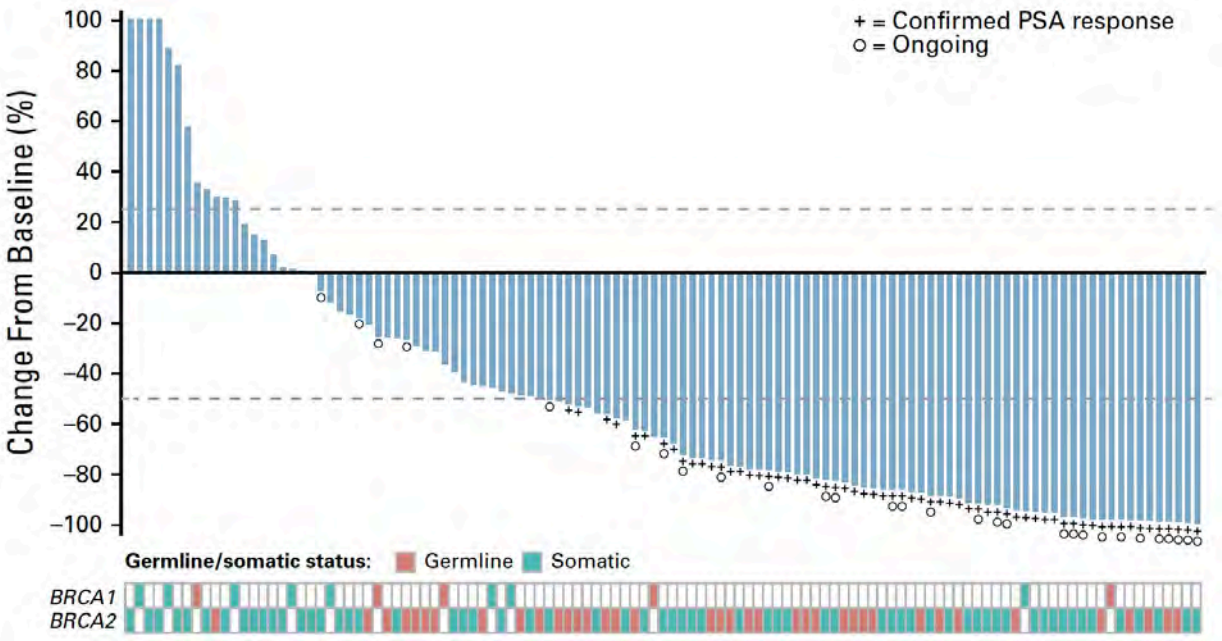
# TRITON2: Response to Rucaparib in Patients with mCRPC Harboring a BRCA1 or BRCA2 Gene Alteration

## 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.

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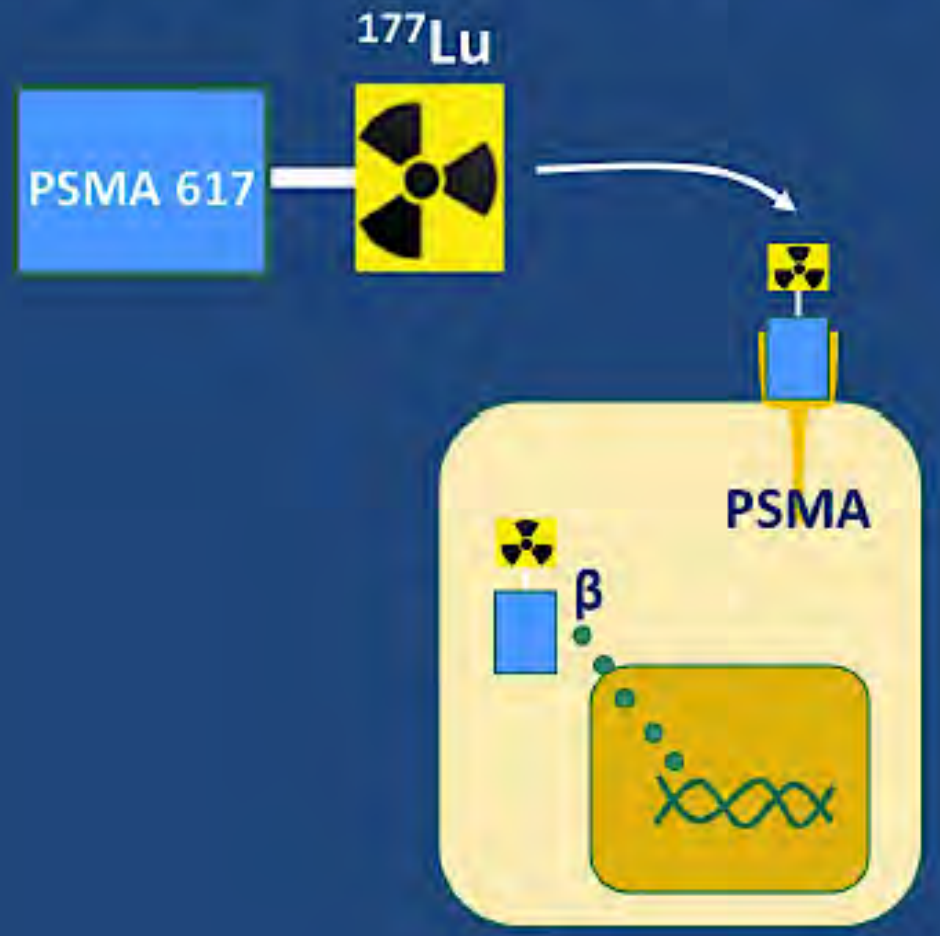
# $^{177}$Lu-PSMA-617 is a small molecule RLT targeting PSMA




Hofman S et al. ASCO 2020;Abstract 5500.

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*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†*

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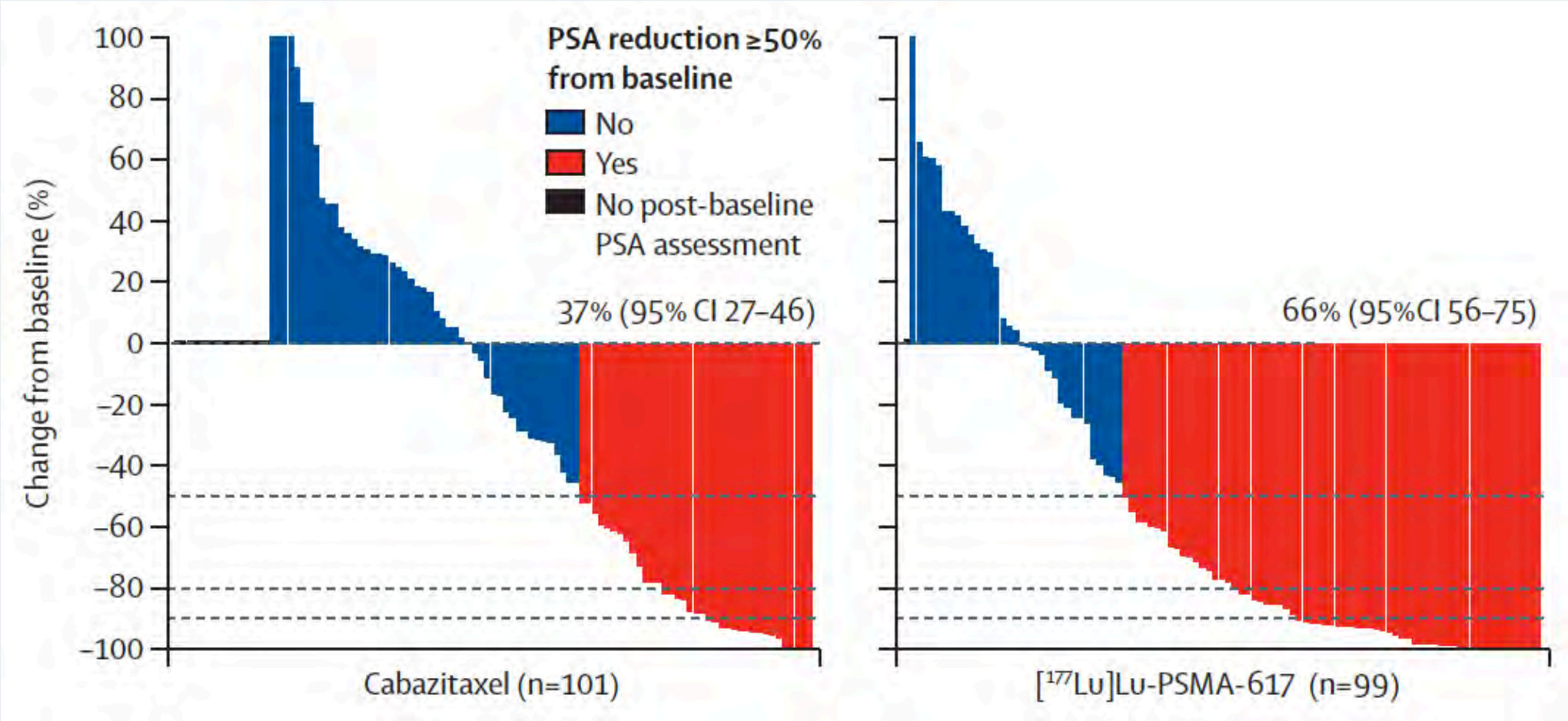
# TheraP: Primary Endpoint — PSA Response ≥50%




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

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# 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

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# 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**

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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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# 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?

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# 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.


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# 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.

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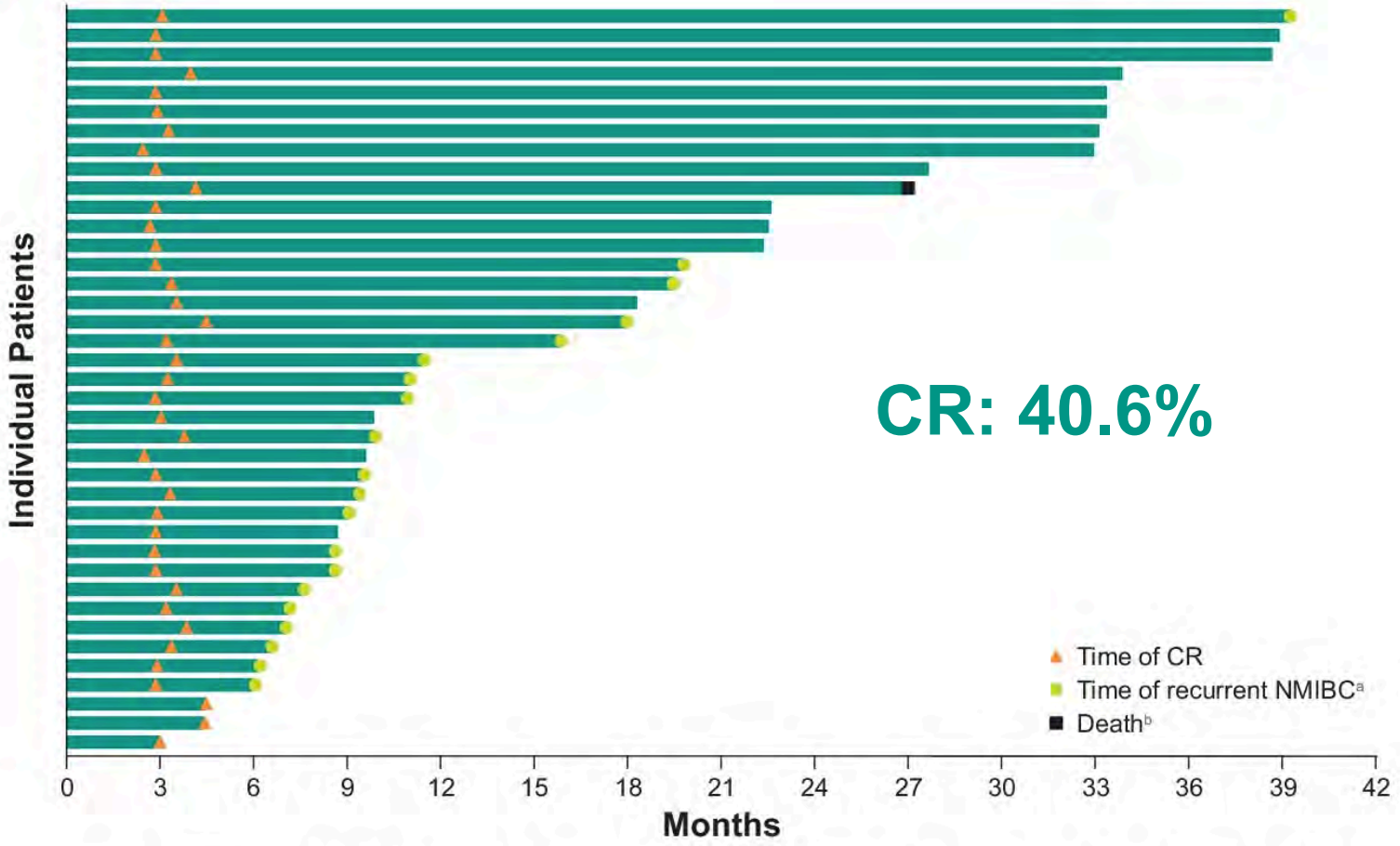
# Extended Follow-Up of KEYNOTE-057: Response, Time to Response and Recurrence of HR NMIBC in Patients Who Experienced a CR




[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.

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# 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.

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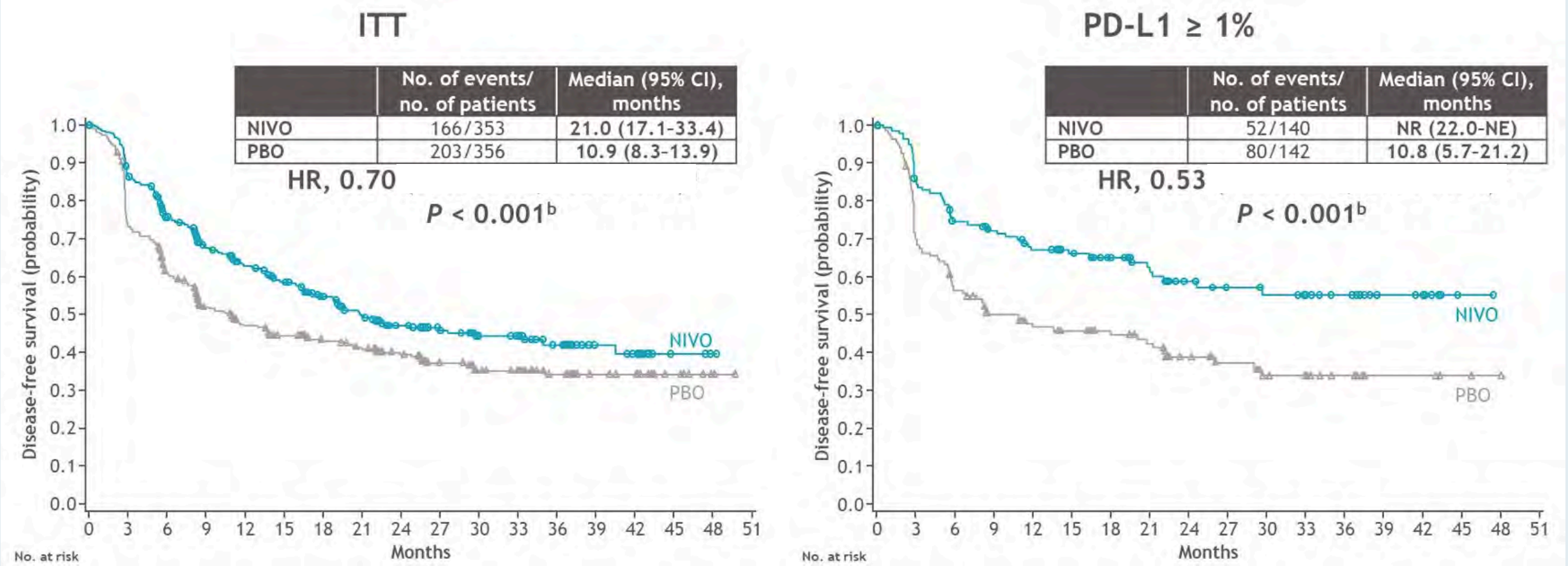
# CheckMate 274: Disease-Free Survival in the ITT and PD-L1 ≥1% Populations




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

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*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

RTP
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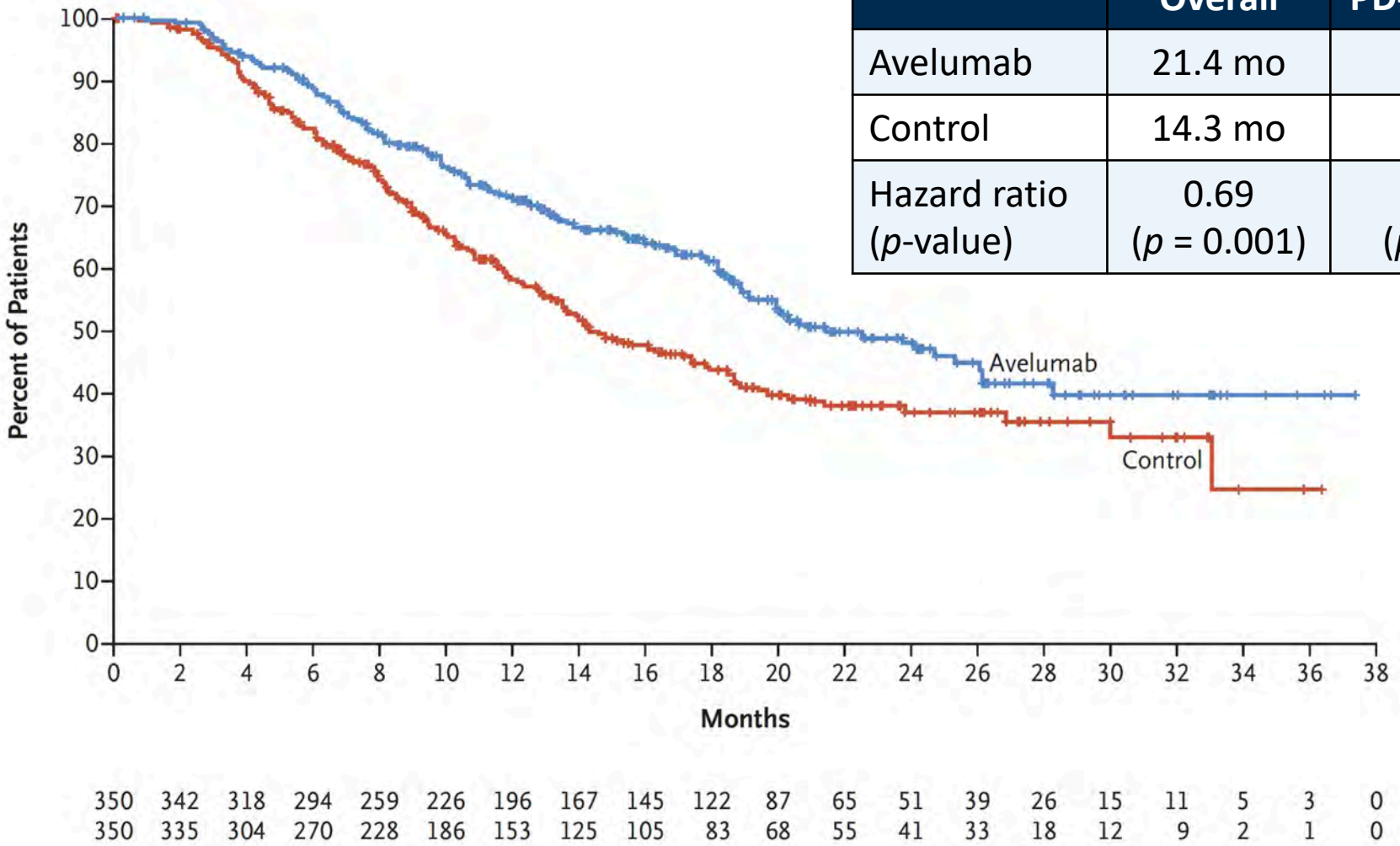
# JAVELIN Bladder 100 Primary Endpoint: Overall Survival




| | 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<br>• Previously platinum-treated locally advanced or metastatic UBC |
| Pembrolizumab | • BCG-unresponsive, high-risk NMIBC in patients ineligible for or electing not to undergo cystectomy<br>• Locally advanced or metastatic cisplatin-ineligible UBC, PD-L1 CPS ≥10<br>• 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%<br>• 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

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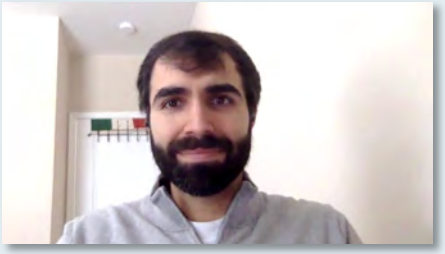
# Case Presentation – Dr Gosain: A 65-year-old woman with metastatic urothelial bladder cancer



**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?

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

1. Enfortumab vedotin → erdafitinib
2. Erdafitinib → enfortumab vedotin

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# 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].

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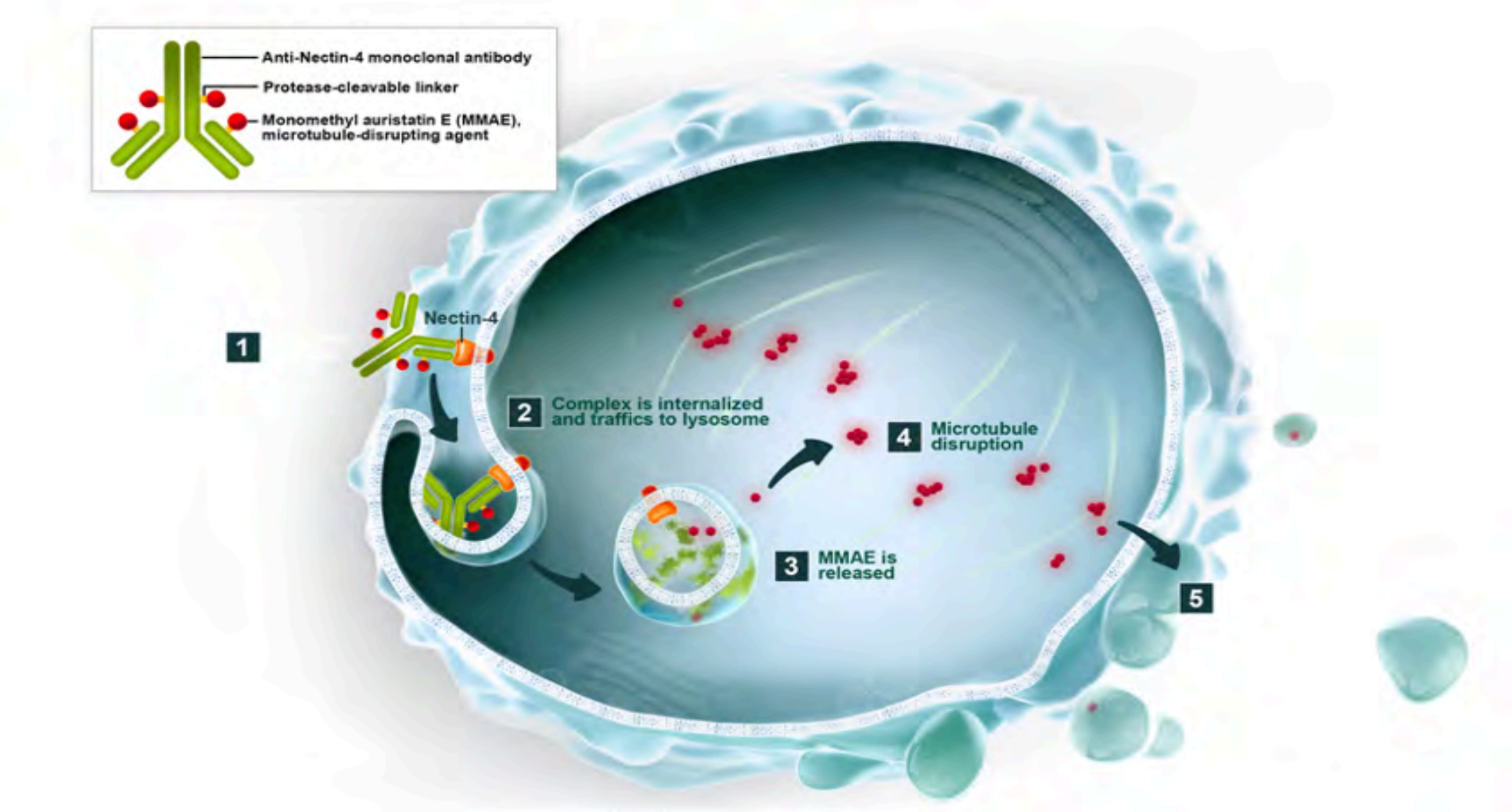
# Enfortumab Vedotin: Nectin-4 Targeted Therapy




Courtesy of Jonathan Rosenberg, MD

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# 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.

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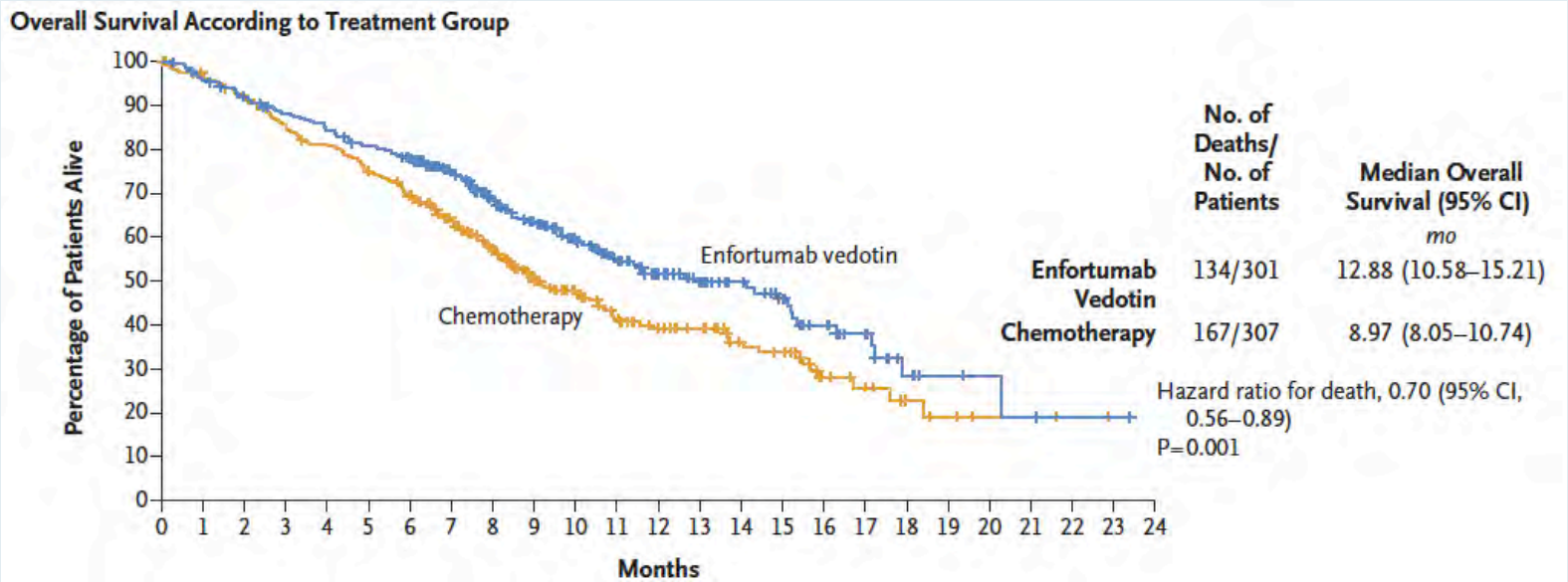
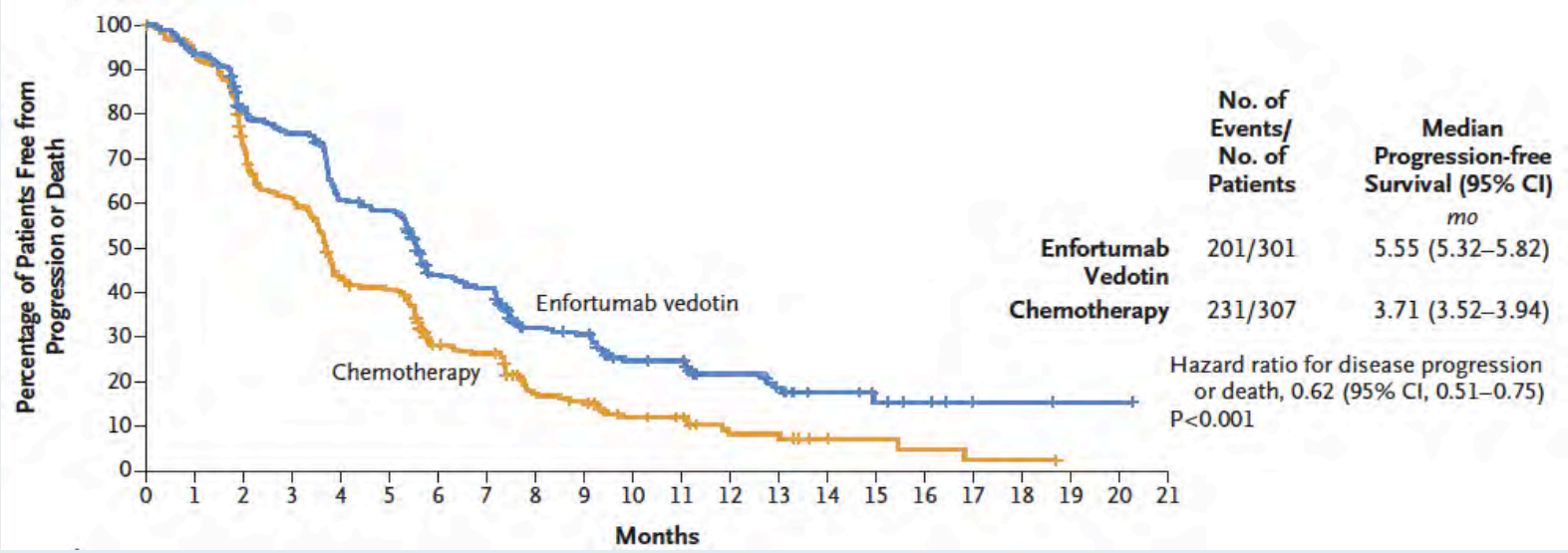
# EV-301: Survival and Response Analyses




| | 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.

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# 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.

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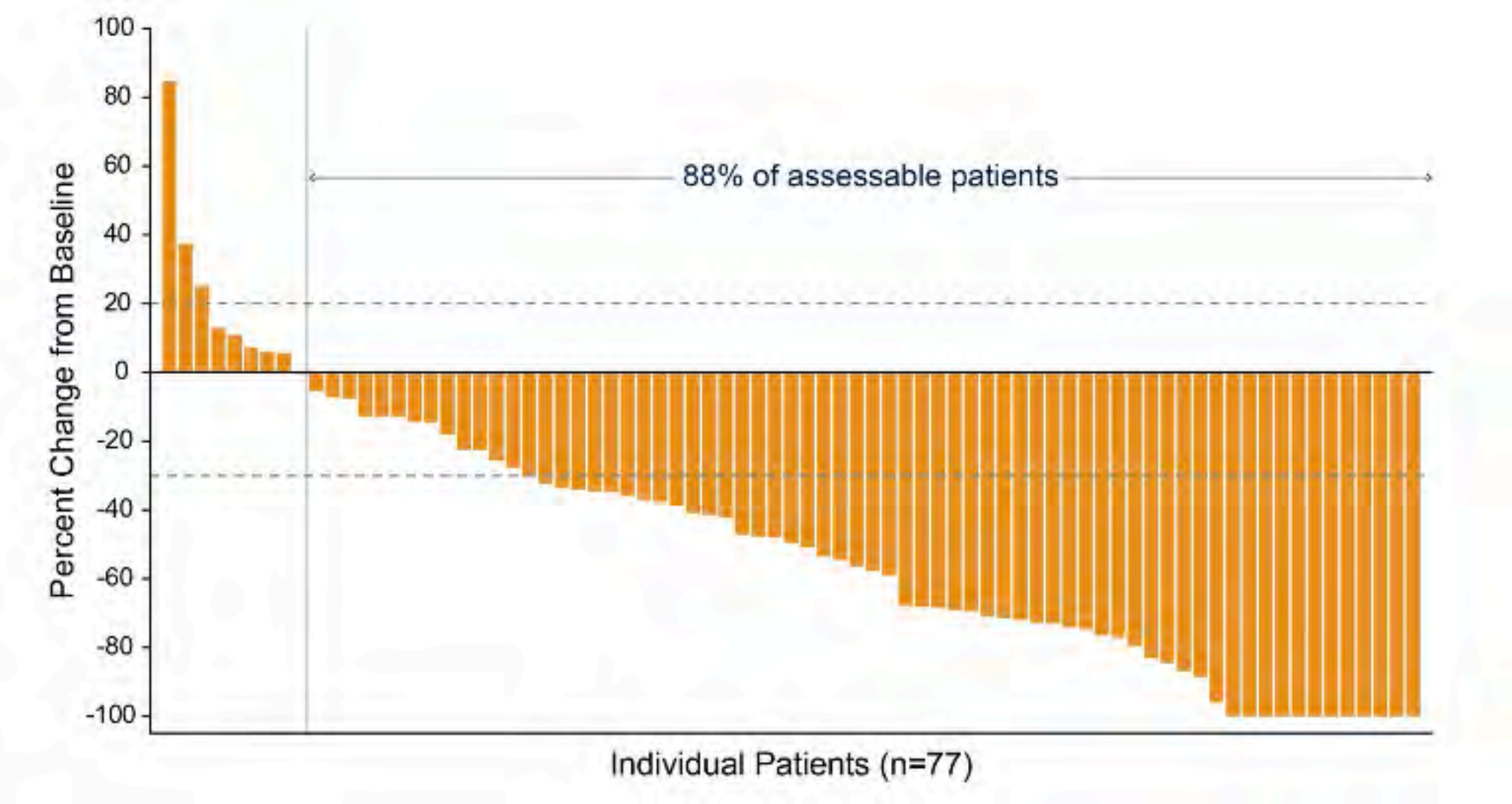
# EV-201 Cohort 2: Change in Tumor Measurements per BICR




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

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# 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.

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# 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.

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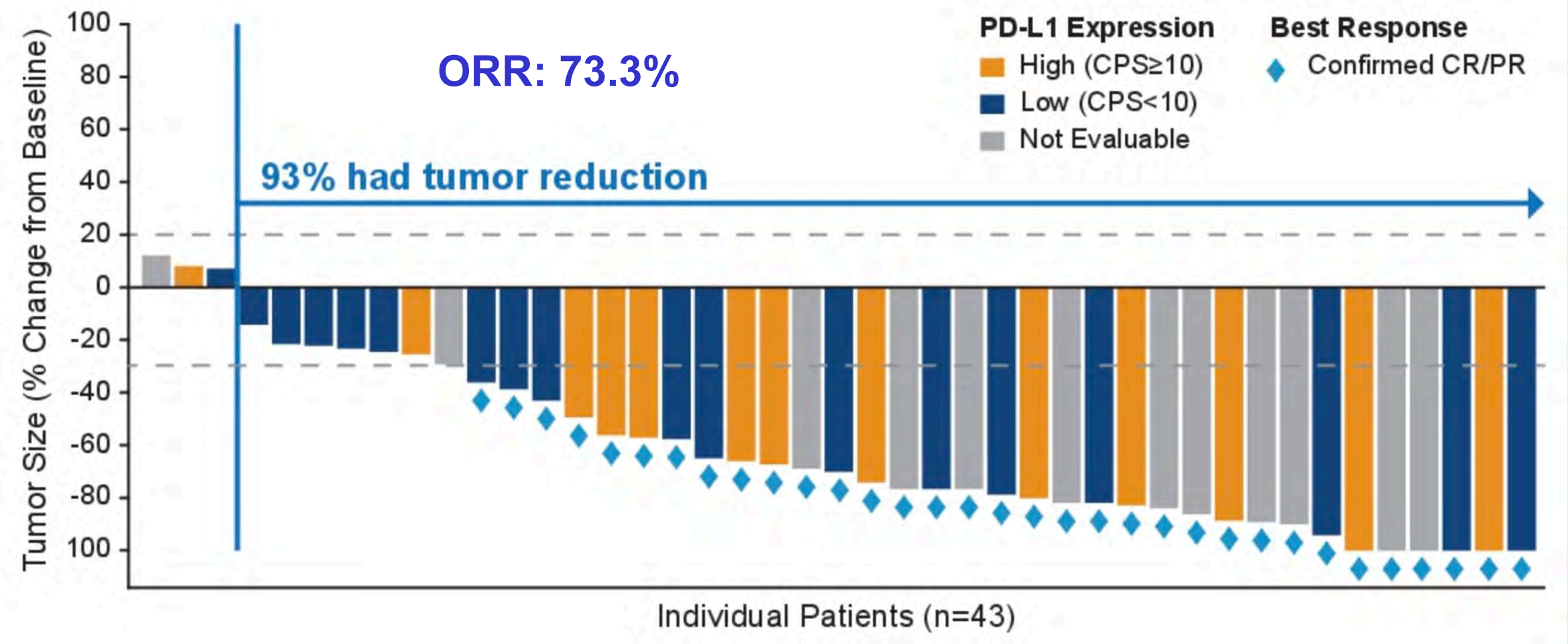
# EV-103: Response to Enfortumab Vedotin with Pembrolizumab in the First-Line Setting




Rosenberg JE et al. ASCO 2020;Abstract 5044.

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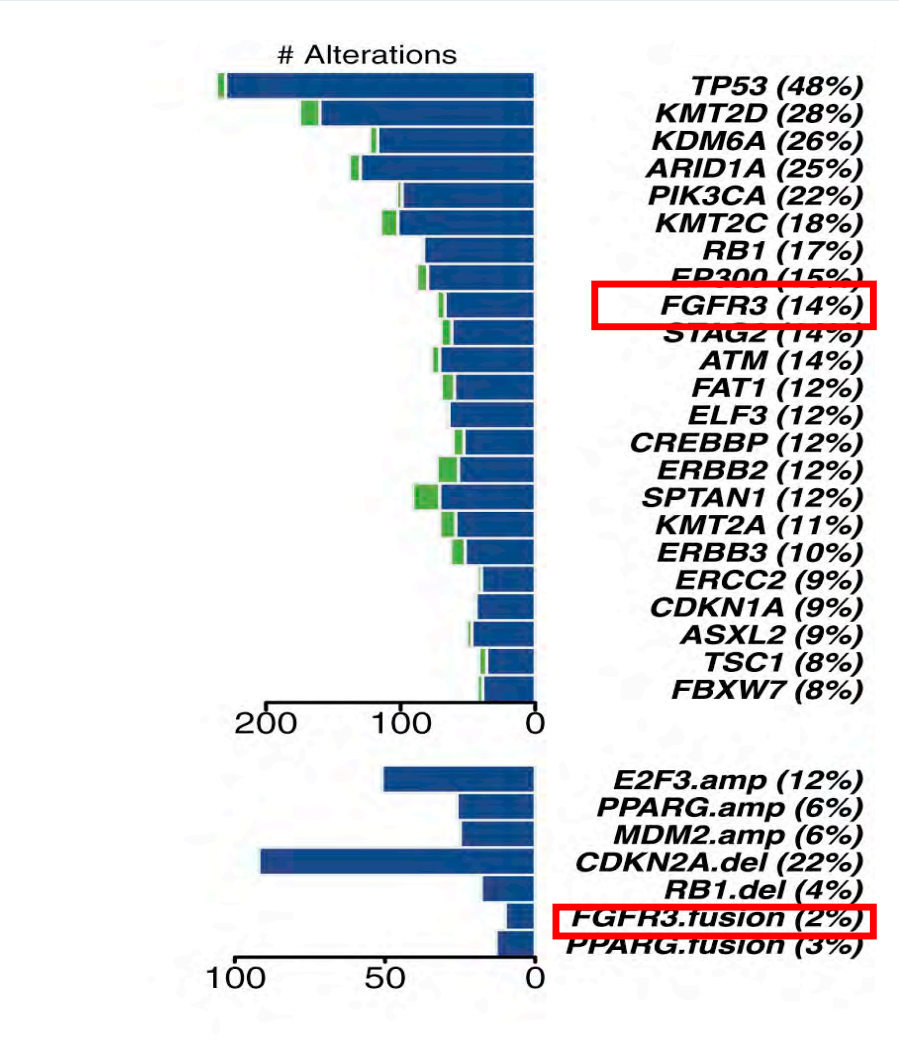
# FGFR3 Genomic Alterations in Muscle-Invasive Bladder Cancer

**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.

RTP RESEARCH TO PRACTICE

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

Siefker-Radtke AO et al.

ASCO 2020;Abstract 5015.

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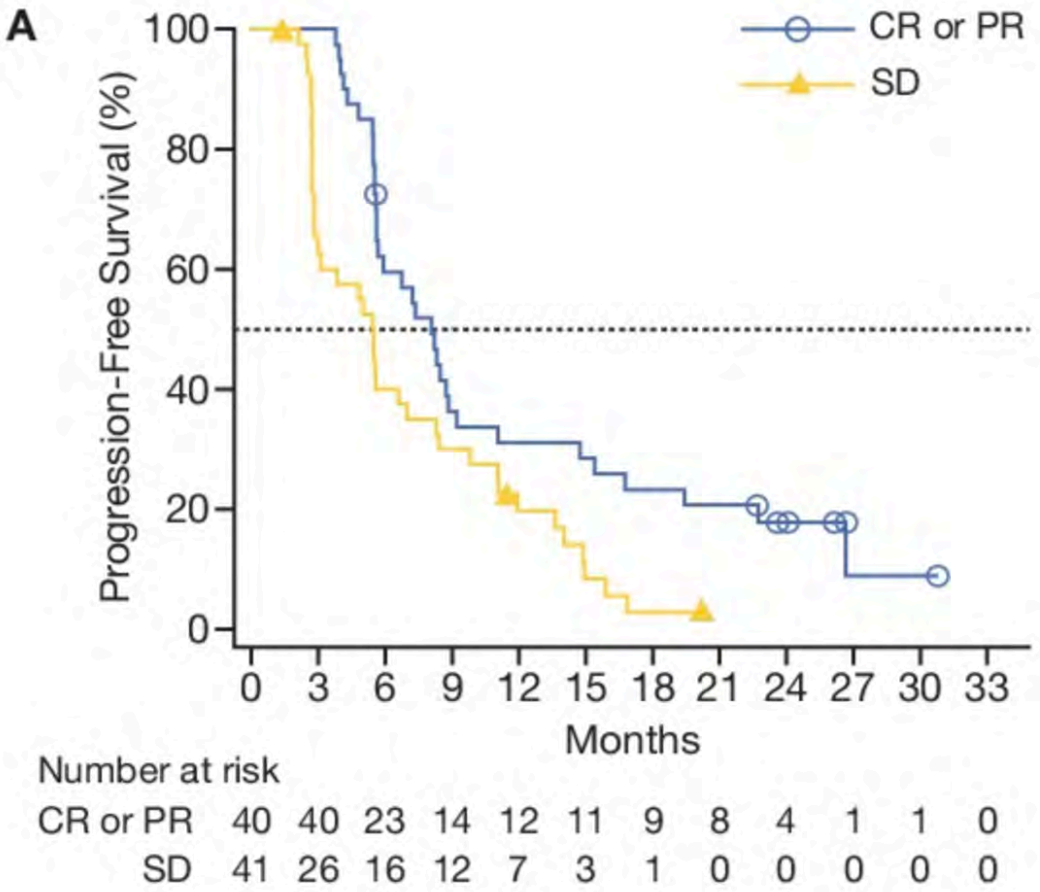
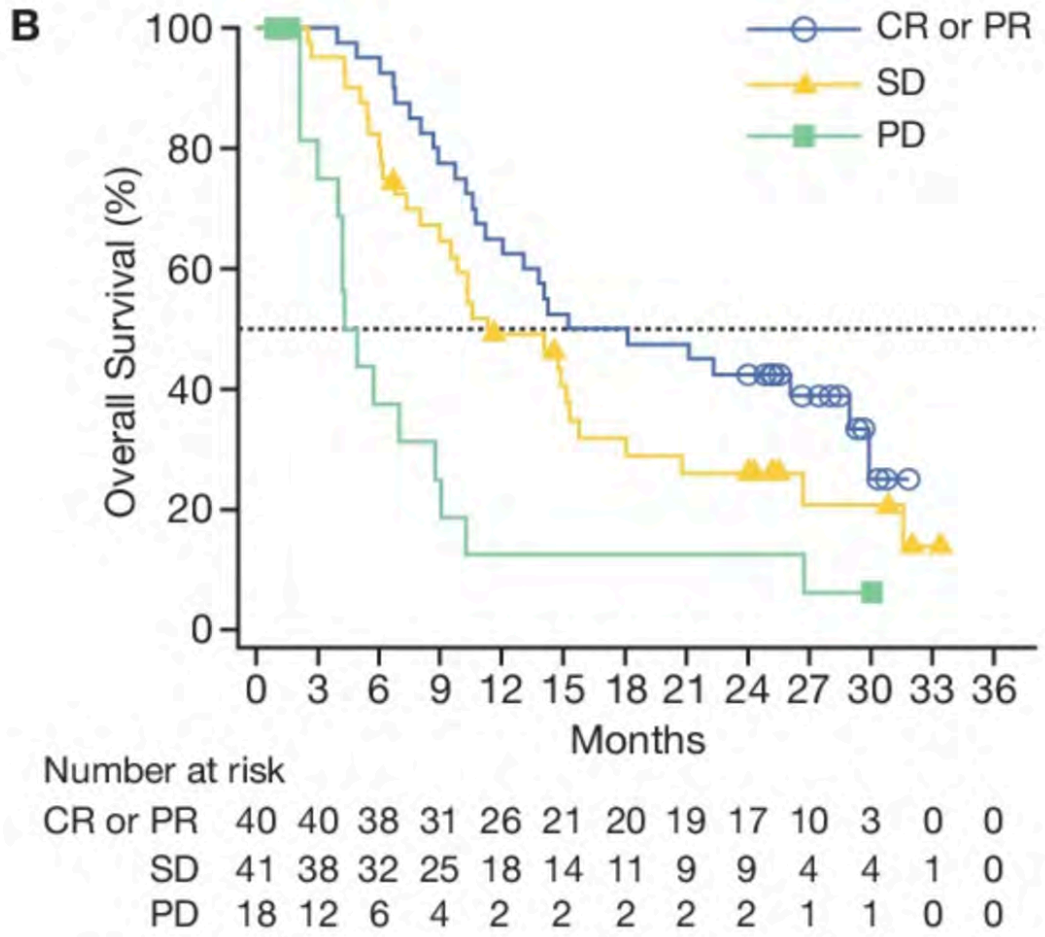
# BLC2001: Survival

**Median PFS: 5.5 months**




**Median OS: 11.3 months**




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

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

Phase 2
(IMvigor 210)

N = 274

*18% mFGFR*

Phase 2
(*Checkmate 275*)

N = 139

*11% mFGFR*

**Objective Response Rate**

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

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

*Wang, European Urology, 2019*

Courtesy of Matthew Galsky, MD.

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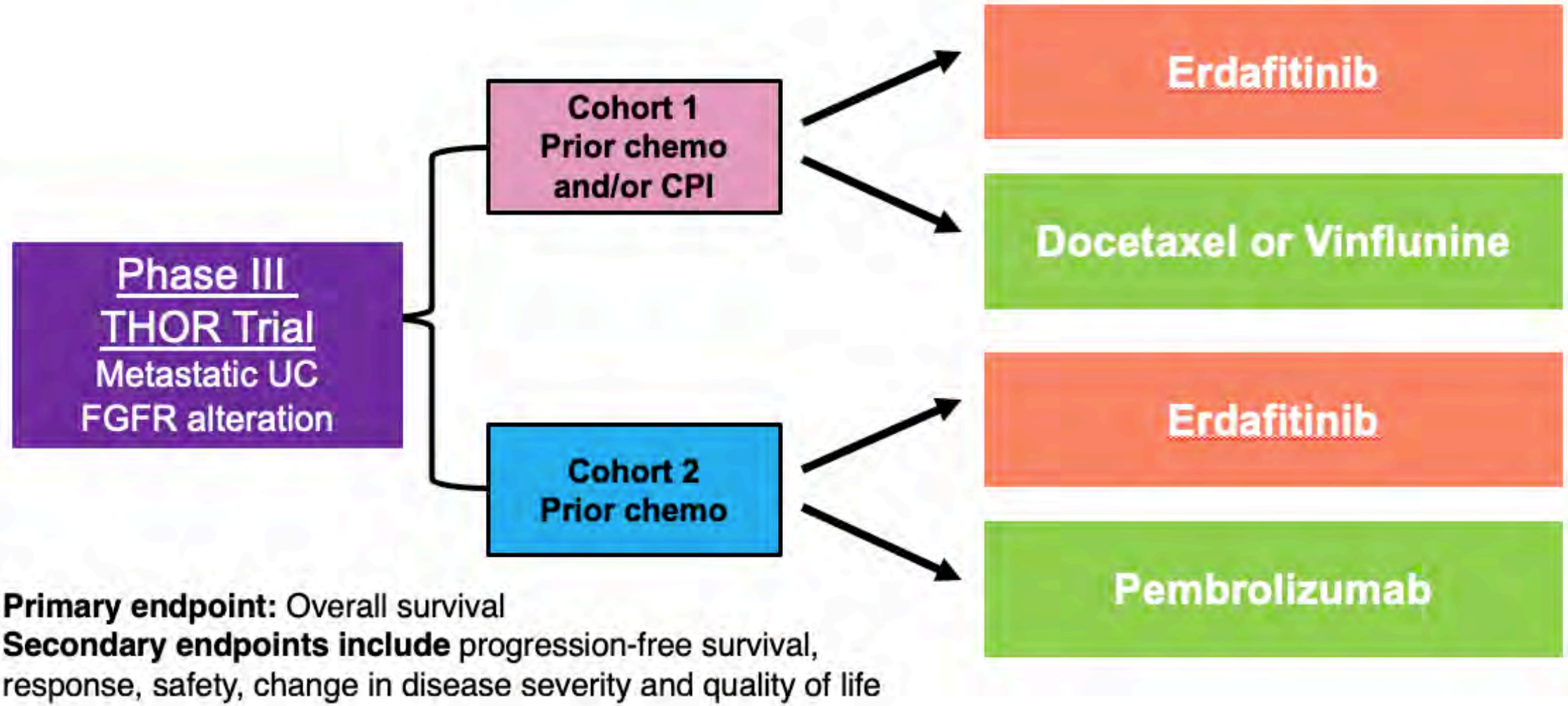
# Ongoing Phase III THOR Trial Design




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

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# 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

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# 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].

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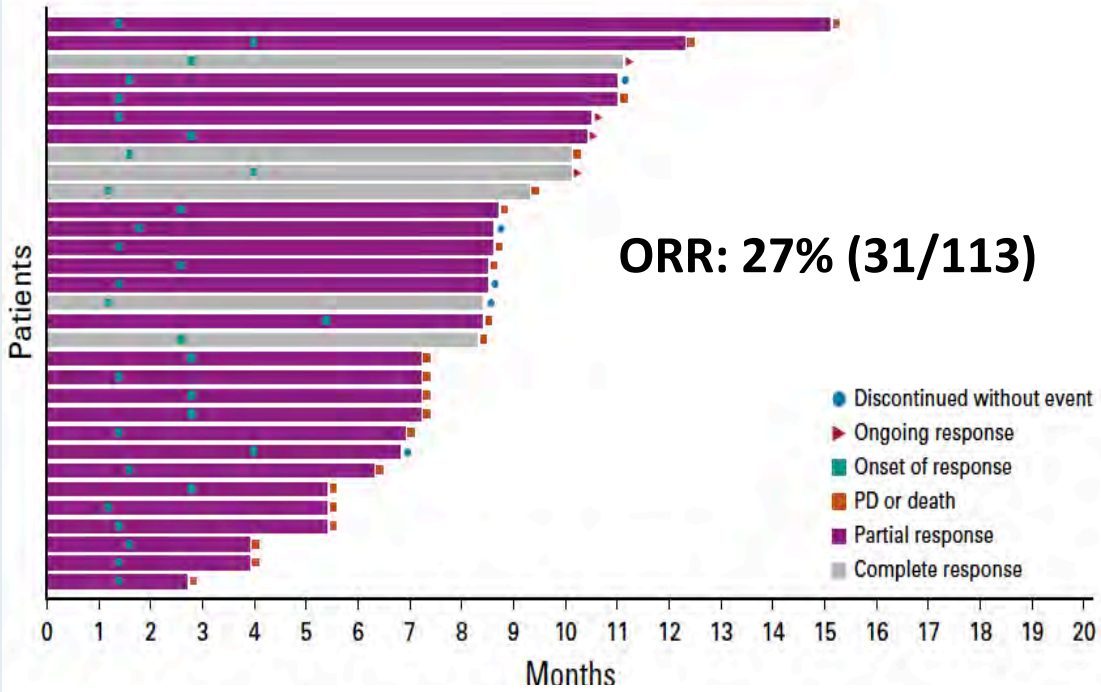
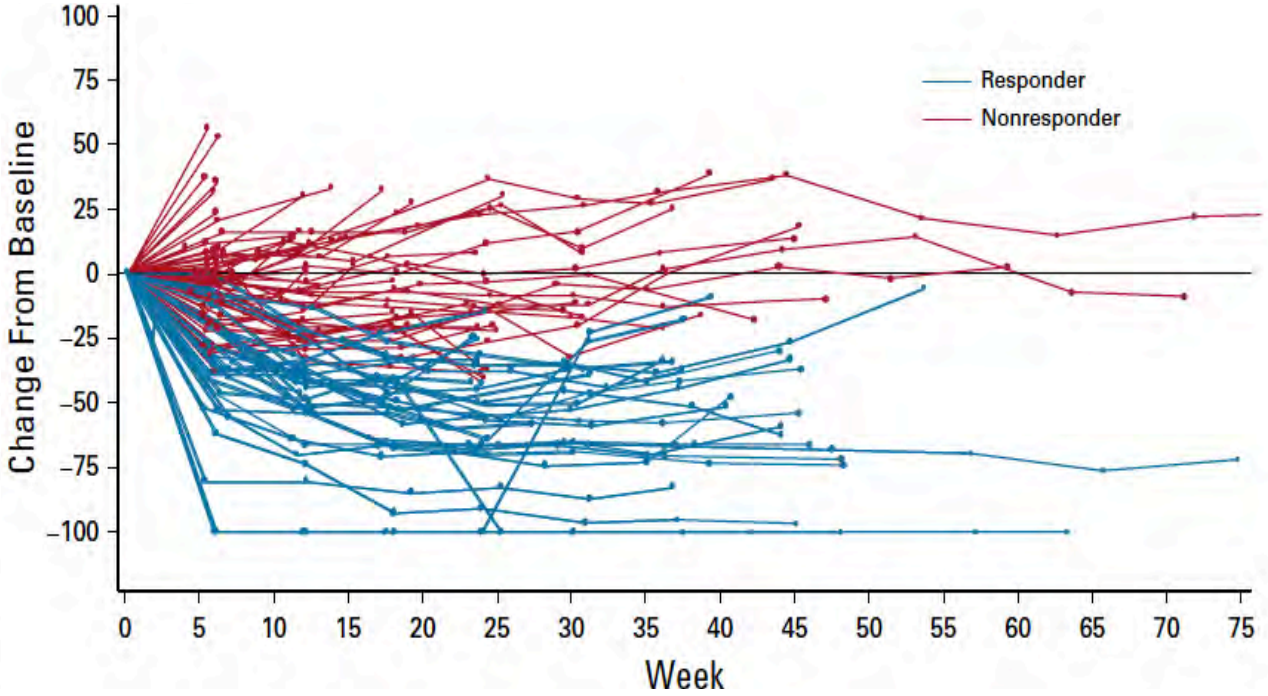
# TROPHY-U-01 (Cohort 1): ORR, Duration of Response and Survival

**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.

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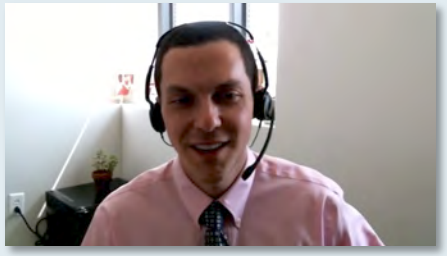
# Case Presentation – Dr Lorber: A 77-year-old man with de novo metastatic clear cell RCC treated with ipilimumab/nivolumab



**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?

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# 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?

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## Regulatory and reimbursement issues aside, which first-line therapy would you recommend for a 65-year-old patient with a history of nephrectomy for clear cell RCC who on routine follow-up 3 years later is found to have asymptomatic bone metastases (PS 0)?

1. Nivolumab/ipilimumab
2. Avelumab/axitinib
3. Pembrolizumab/axitinib
4. Nivolumab/cabozantinib
5. Pembrolizumab/lenvatinib
6. TKI monotherapy
7. Anti-PD-1/PD-L1 monotherapy
8. Other

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## What is your usual second-line treatment for a patient with metastatic clear cell RCC who responds to first-line pembrolizumab/axitinib but then experiences disease progression?

1. Sunitinib
2. Pazopanib
3. Cabozantinib
4. Nivolumab/ipilimumab
5. Other

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# 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.


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# 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**

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*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*

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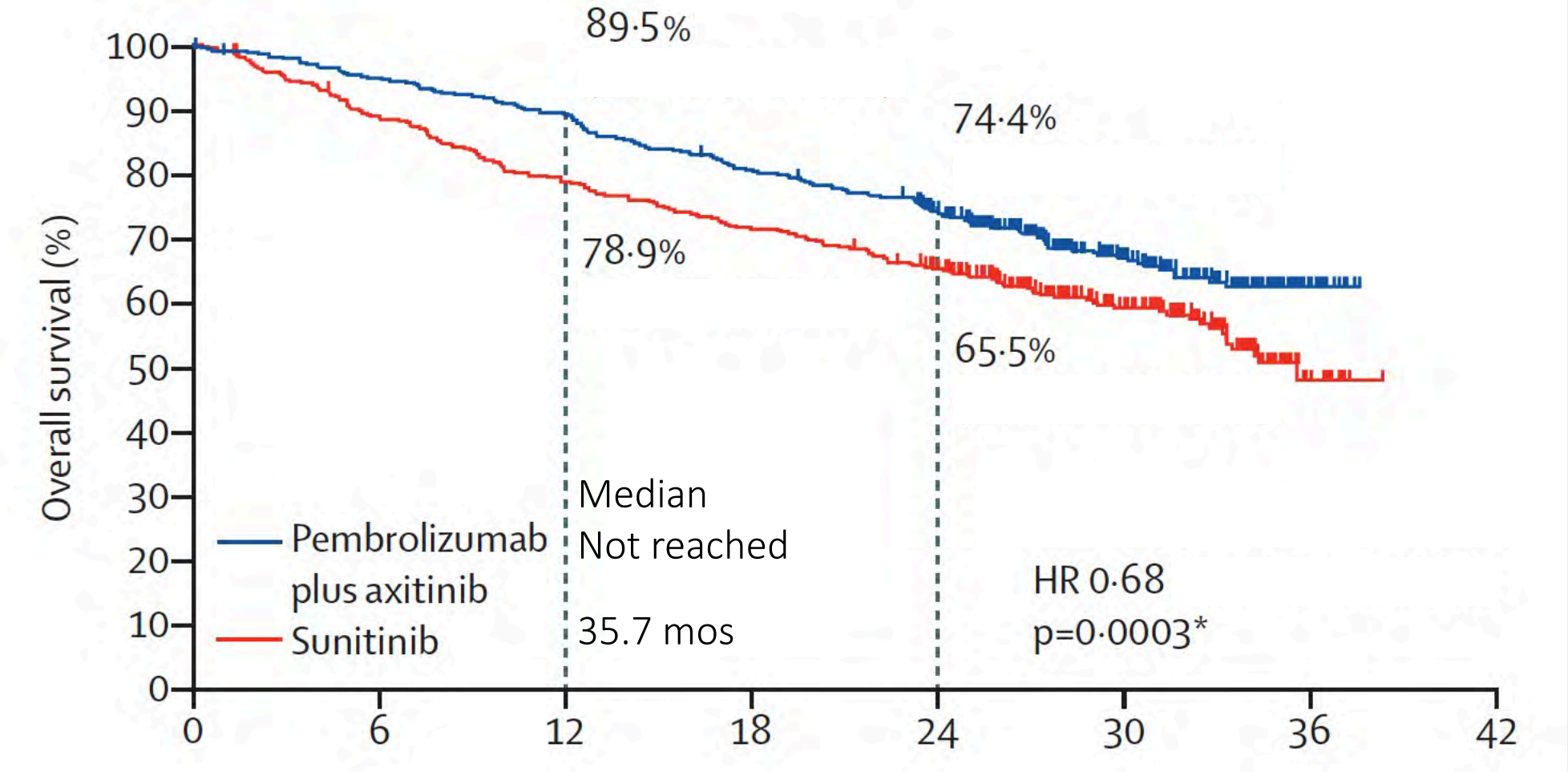
# KEYNOTE-426: Overall Survival with Extended Follow-Up




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

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*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]

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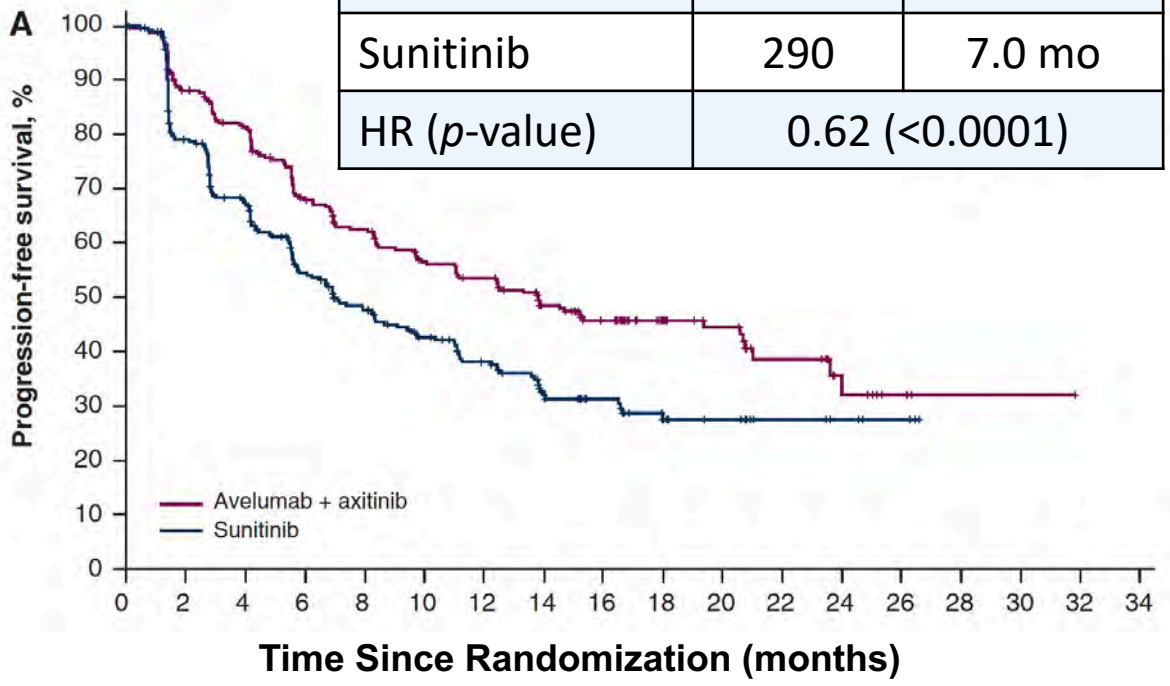
# JAVELIN Renal 101: PFS in the PD-L1+ and Overall Populations

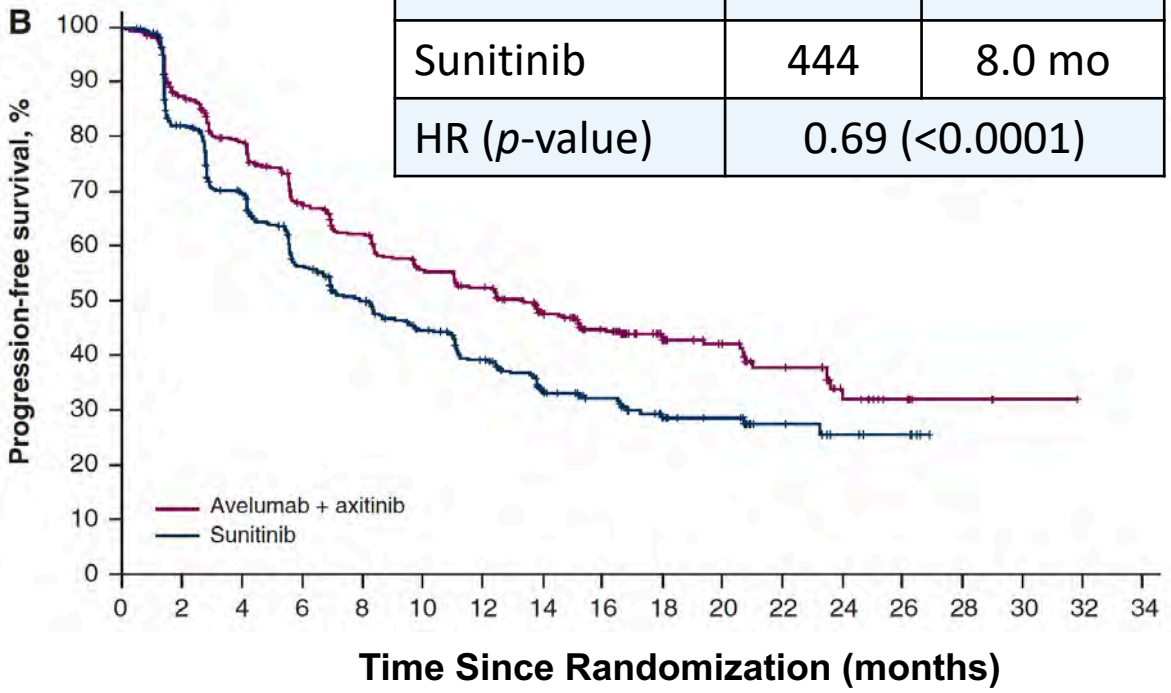
## PD-L1 ≥ 1% Population

| | 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.

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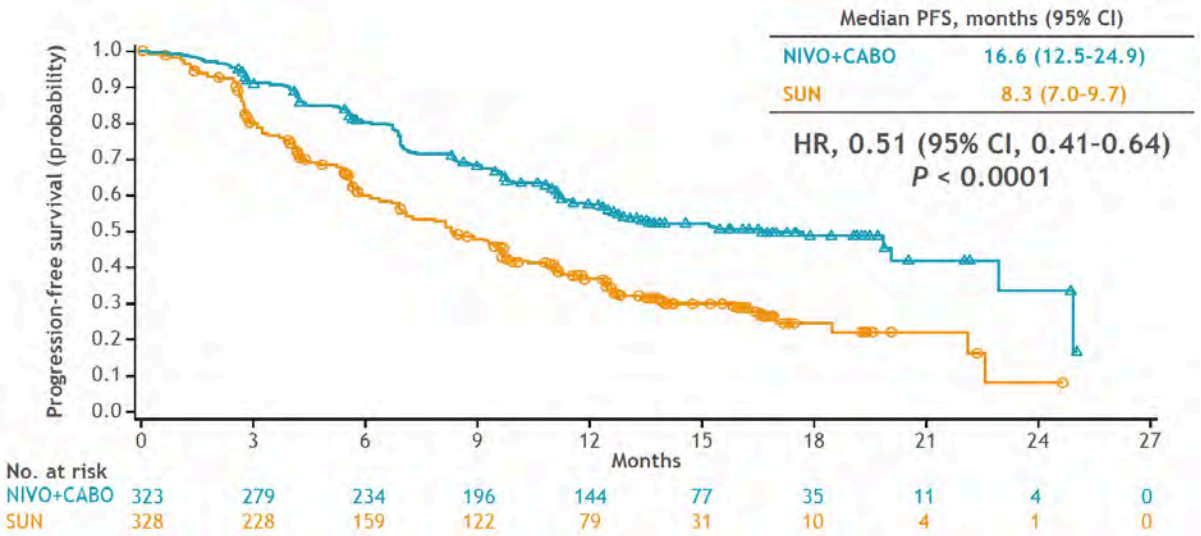
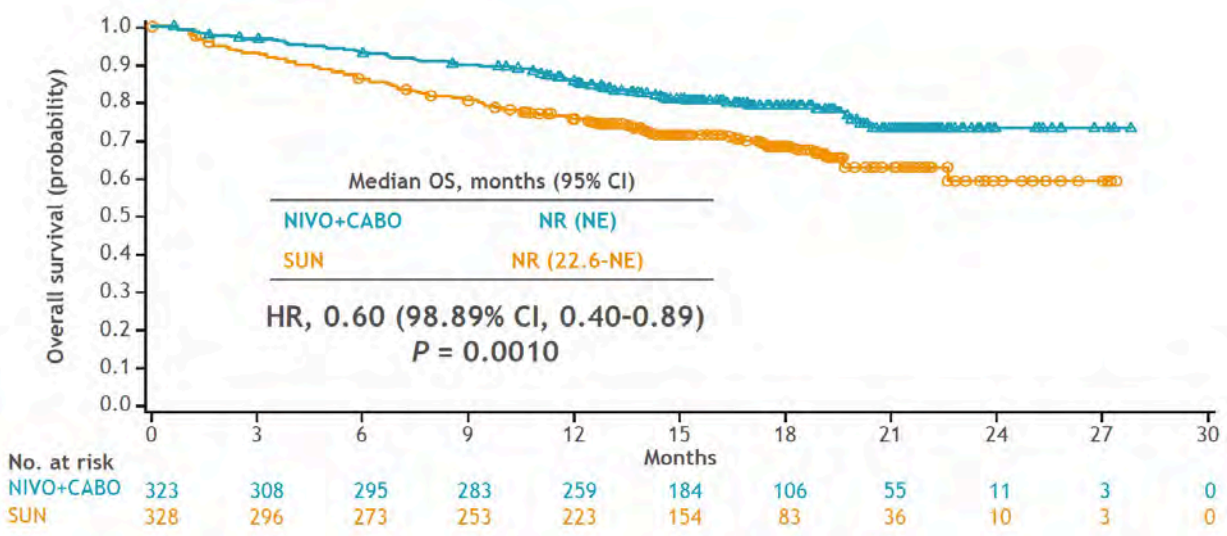
# CheckMate 9ER Survival Analyses: Nivolumab/Cabozantinib for Previously Untreated Advanced RCC

## 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

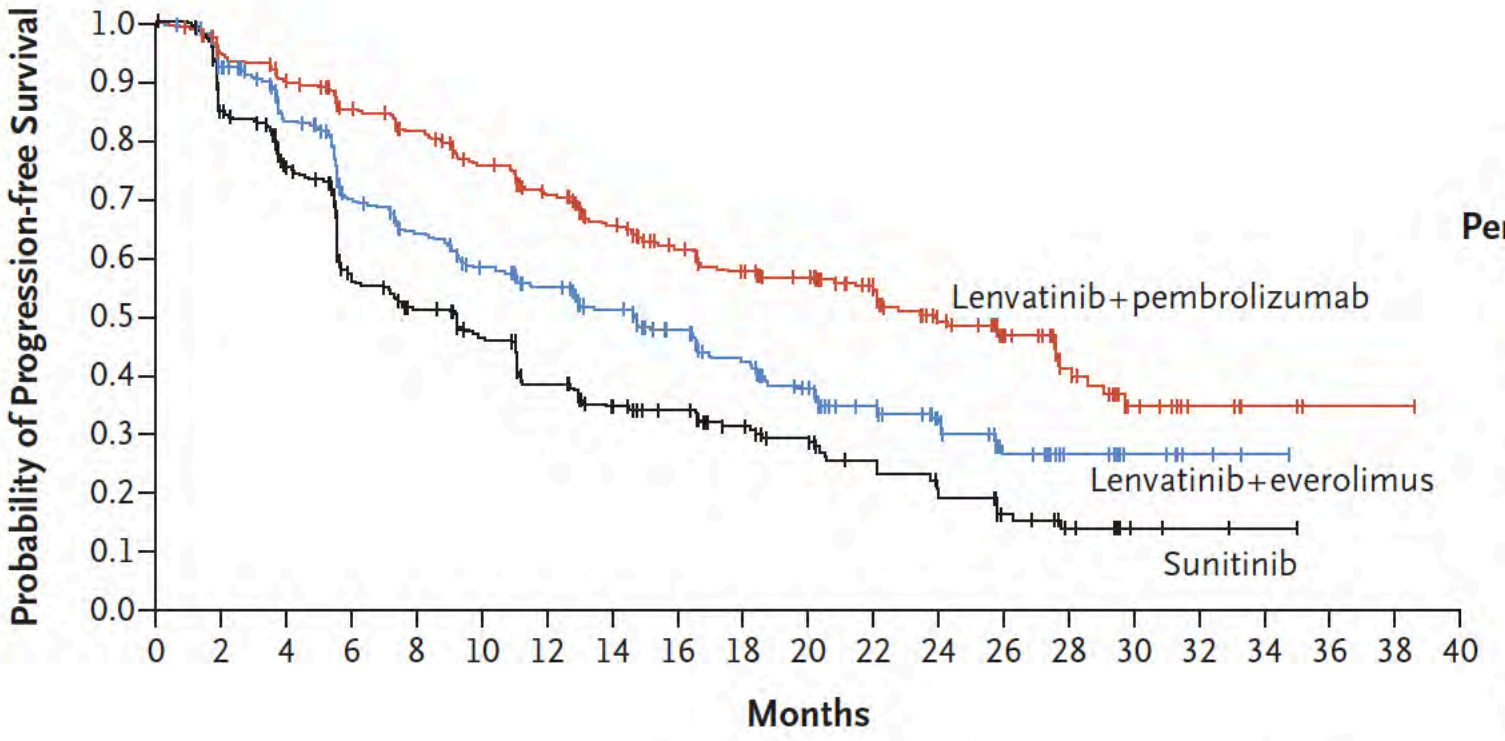
# A Step Ahead in Metastatic Renal Cell Carcinoma

Alain Ravaud, M.D., Ph.D.

*N Engl J Med* 2021;384(14):1360-61.

RTP RESEARCH TO PRACTICE

# CLEAR: Progression-Free Survival




| | 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

**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 | | |

Motzer R et al. *N Engl J Med* 2021;384(14):1289-1300.

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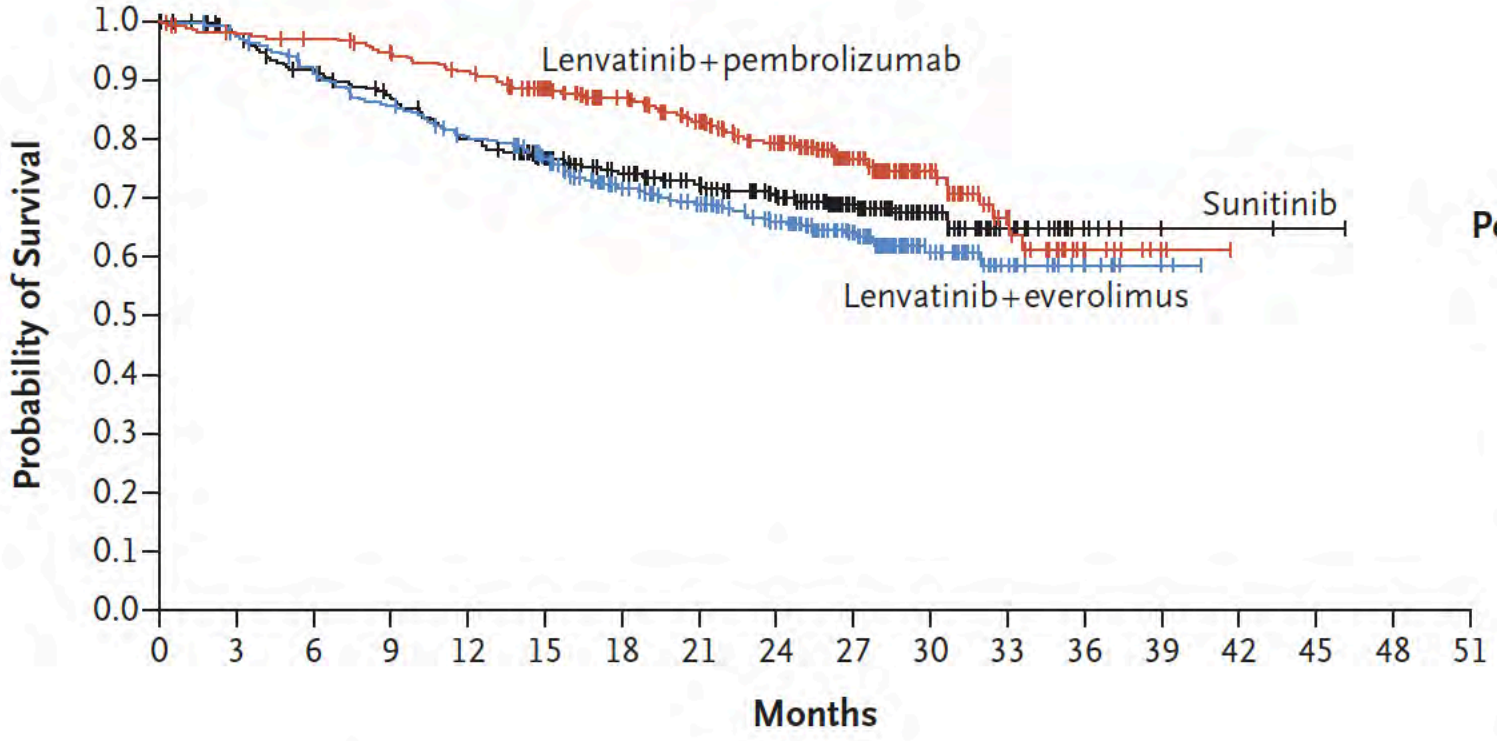
# CLEAR: Overall Survival




| | 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.

RTP RESEARCH TO PRACTICE

# 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.**

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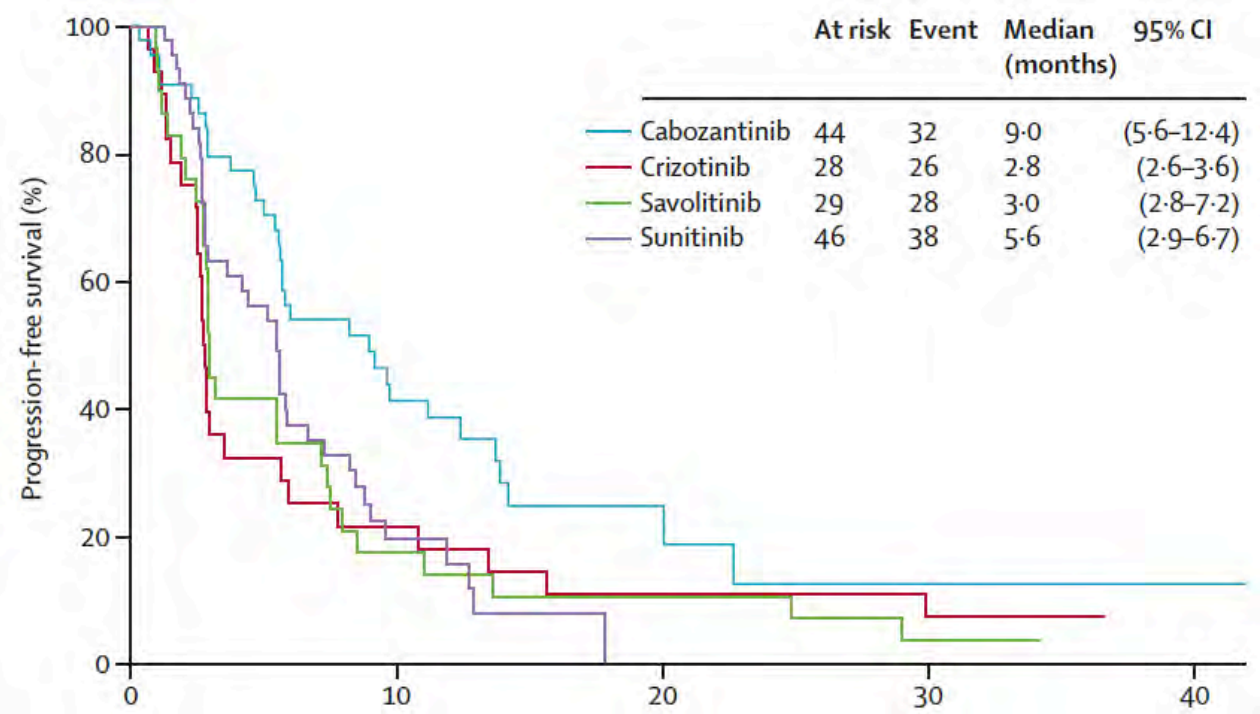
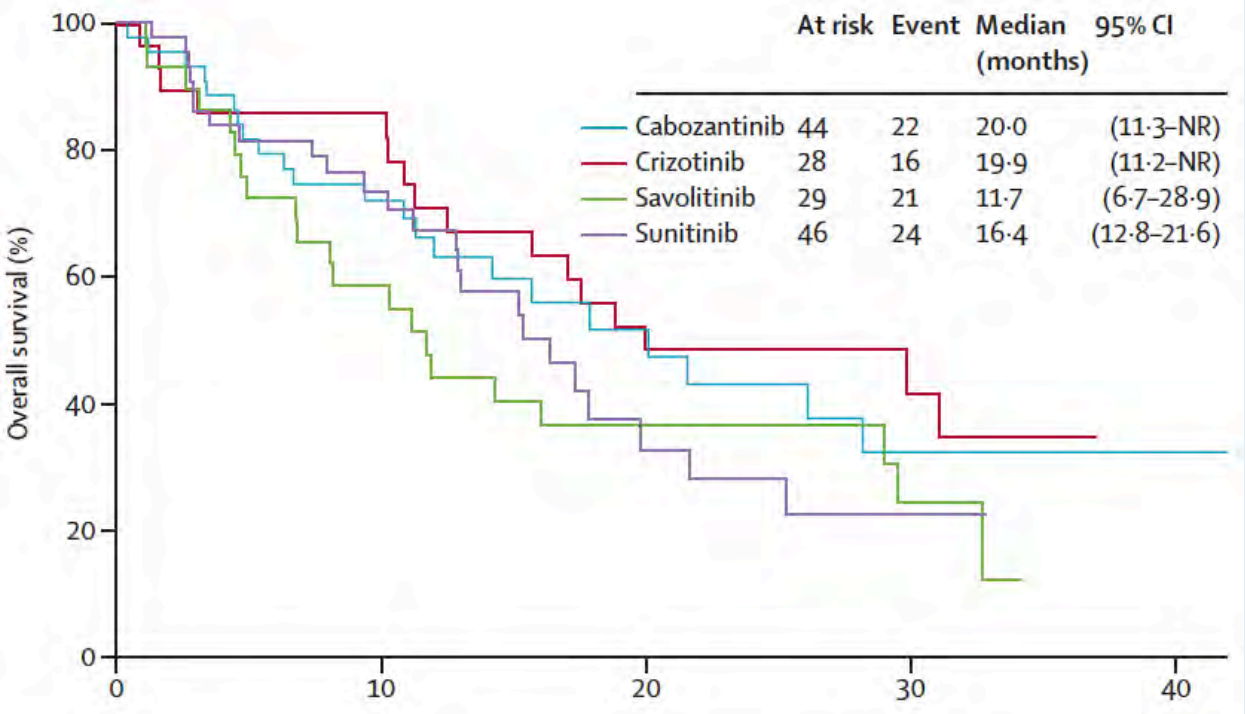
# Sunitinib with Cabozantinib, Crizotinib, and Savolitinib for Treatment of Advanced Papillary RCC

## 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.

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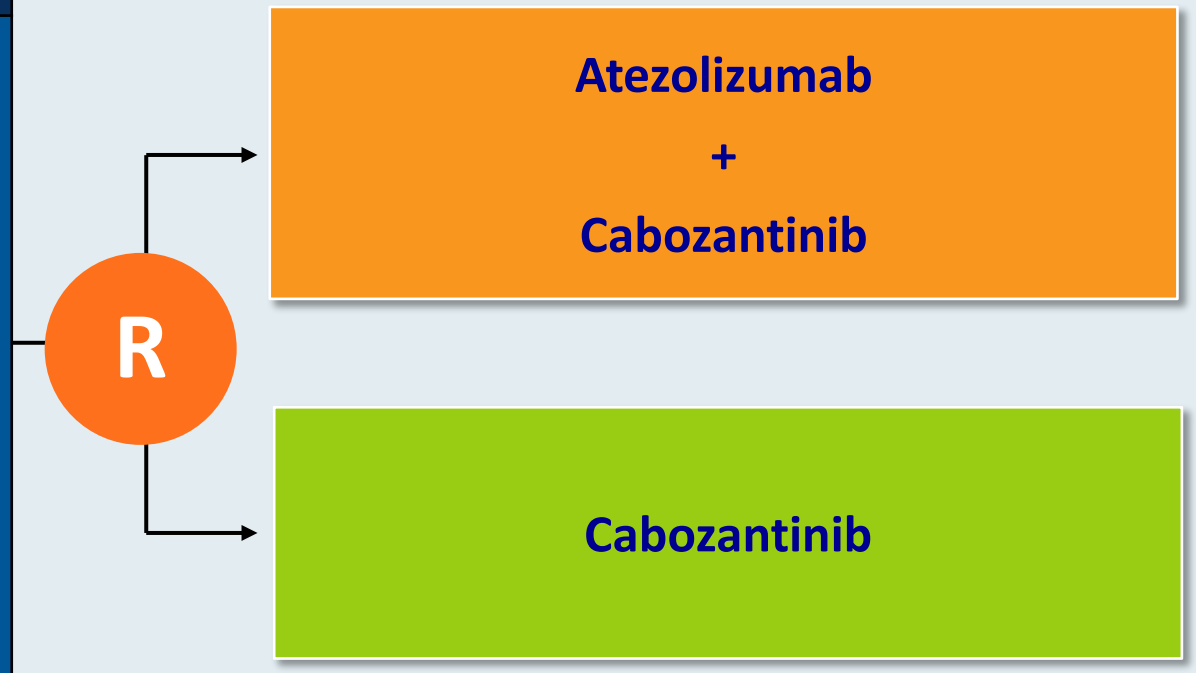
# Ongoing Phase III CONTACT-03 Trial Design

**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).

RTP RESEARCH TO PRACTICE

# 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

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***CME, MOC and NCPD credit information will be emailed to each participant within 5 business days.***

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# *We are taking a short break!*

**The program will resume at 3:15 PM ET**

# *Up Next…*

**Drs Wells Messersmith and Eileen O'Reilly discuss the management of gastrointestinal cancers**

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