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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Gastrointestinal Cancers Faculty

Wells A Messersmith, MD
Professor and Head, Division of Medical Oncology
Associate Director for Translational Research
University of Colorado Cancer Center
Aurora, Colorado

Eileen M O'Reilly, MD
Winthrop Rockefeller Endowed Chair in Medical Oncology
Section Head, Hepatopancreaticobiliary and Neuroendocrine Cancers
Co-Director, Medical Initiatives
David M Rubenstein Center for Pancreatic Cancer Research
Attending Physician, Member
Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Cornell Medical College
New York, New York

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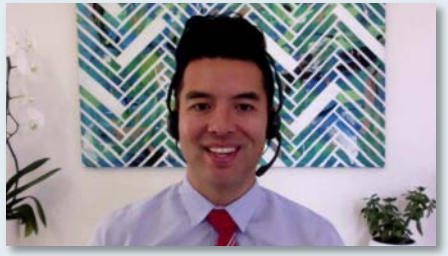
Contributing Oncologists

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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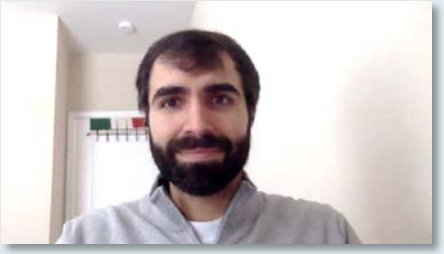
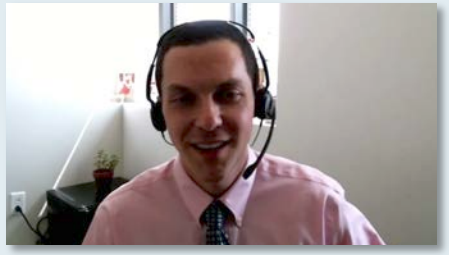
Contributing Oncologists



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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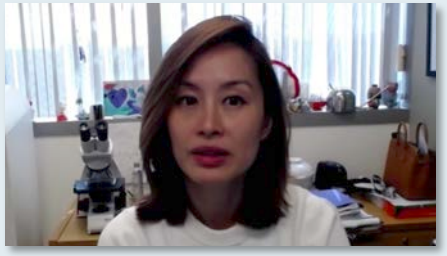
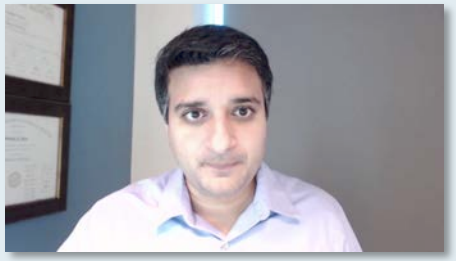
Contributing Oncologists

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: Colorectal Cancer

- Dr Lorber: A 74-year-old woman with MSI-high mCRC – BRAF V600E mutation
- *Key Recent Publications and Presentations*
- Dr Dayyani: A 60-year-old woman with MSS mCRC – TMB 35.4 mut/Mb, KRAS G12D mutation
- *Key Recent Publications and Presentations*

Module 2: Gastric, Gastroesophageal and Esophageal Cancers

- Dr Dayyani: A 60-year-old man with relapsed MSS esophageal squamous cell cancer – PD-L1 CPS 15
- *Key Recent Publications and Presentations*
- Dr Del Rosario: A 49-year-old woman with HER2-positive metastatic gastric adenocarcinoma – PD-L1 CPS 5
- *Key Recent Publications and Presentations*

Module 3: Hepatocellular Cancer (HCC)

- Dr Dayyani: A 59-year-old man with advanced HCC
- Dr Lorber: An 80-year-old woman with unresectable advanced HCC
- *Key Recent Publications and Presentations*

Module 4: Pancreatic Adenocarcinoma

- Dr Chen: An 80-year-old woman with localized pancreatic cancer
- Dr Dayyani: A 79-year-old woman with pancreatic cancer and a germline BRCA2 mutation
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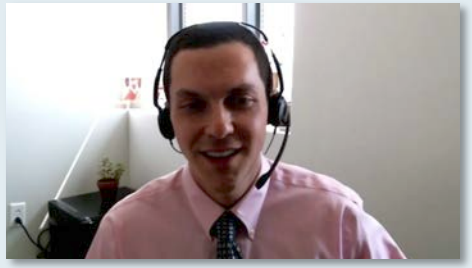
Case Presentation – Dr Lorber: A 74-year-old woman with MSI-high mCRC – BRAF V600E mutation



Dr Jeremy Lorber

- Diagnosed with cecal adenocarcinoma on colonoscopy (prompted by screening stool DNA test).
  - Asymptomatic
  - Staging CT scan: pericecal adenopathy and three liver metastases, measuring 1-3 cm
- Genetic analyses: loss of MLH-1 and PMS-2 expression and a BRAF V600E mutation
- Pembrolizumab therapy → CT scan at 3 months showed complete resolution of liver metastases and pericecal adenopathy
- Combined hemicolectomy and metastasectomy → pCR
- Pembrolizumab therapy continued

Questions

- Now that she's had a great response and resection and no evidence of disease, is there an optimal duration of therapy after surgery?
- What is the role of ctDNA testing, if any, or other assessments?

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Key Recent Publications and Presentations

- André T et al. **Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer.** *N Engl J Med* 2020;383(23):2207-18.
- Tabernero J et al. **Encorafenib plus Cetuximab as a New Standard of Care for Previously Treated BRAF V600E-Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study.** *J Clin Oncol* 2021;39(4):273-84.
- Siena S et al. **Trastuzumab Deruxtecan (DS-8201) in Patients with HER2-Expressing Metastatic Colorectal Cancer (DESTINY-CRC01): A Multicentre, Open-Label, Phase 2 Trial.** *Lancet Oncol* 2021; Online ahead of print.

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*

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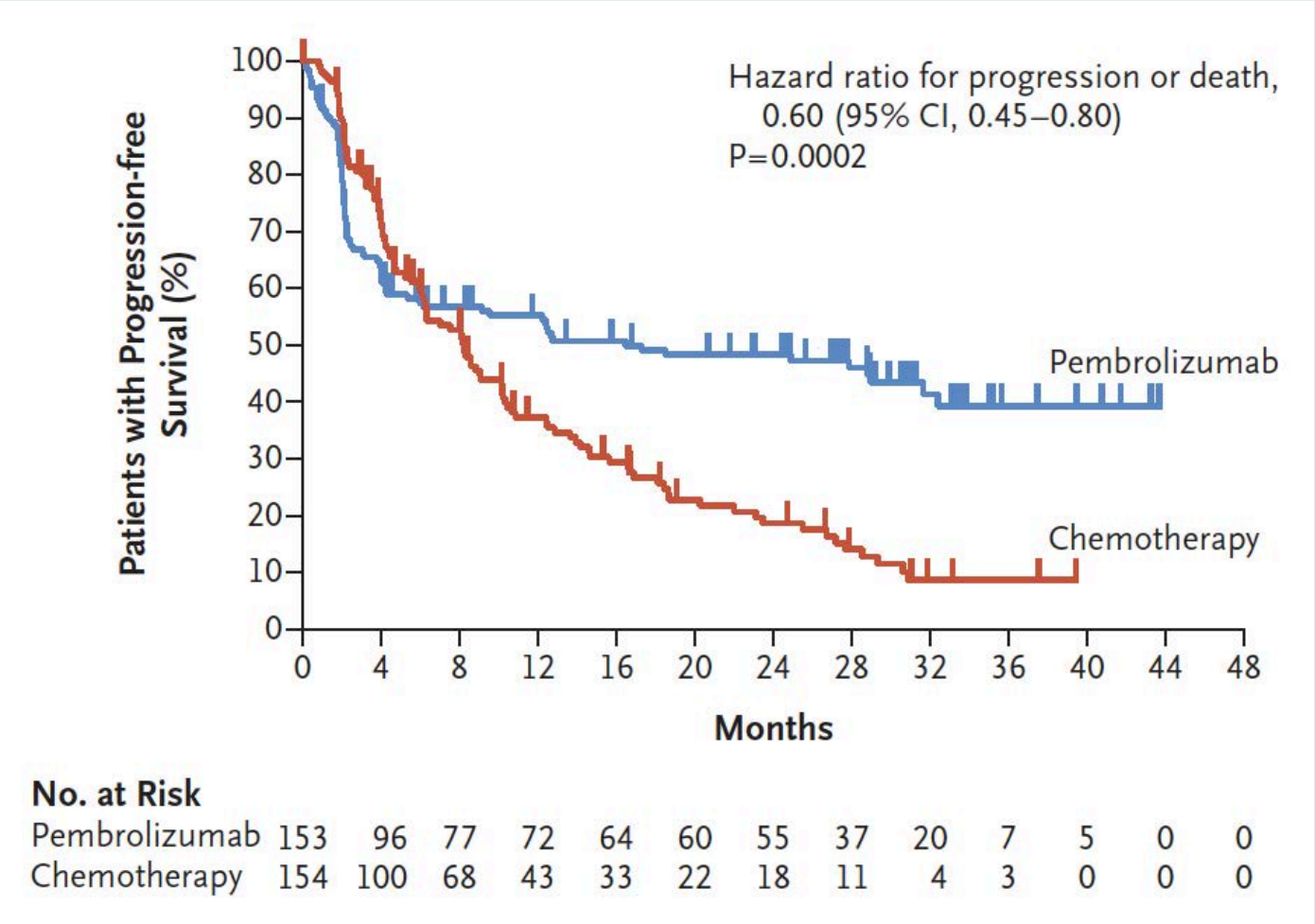
KEYNOTE-177: Primary Survival Endpoints



At the time of data cutoff, data on overall survival were still evolving.

André T et al. *N Engl J Med* 2020;383(23):2207-18.

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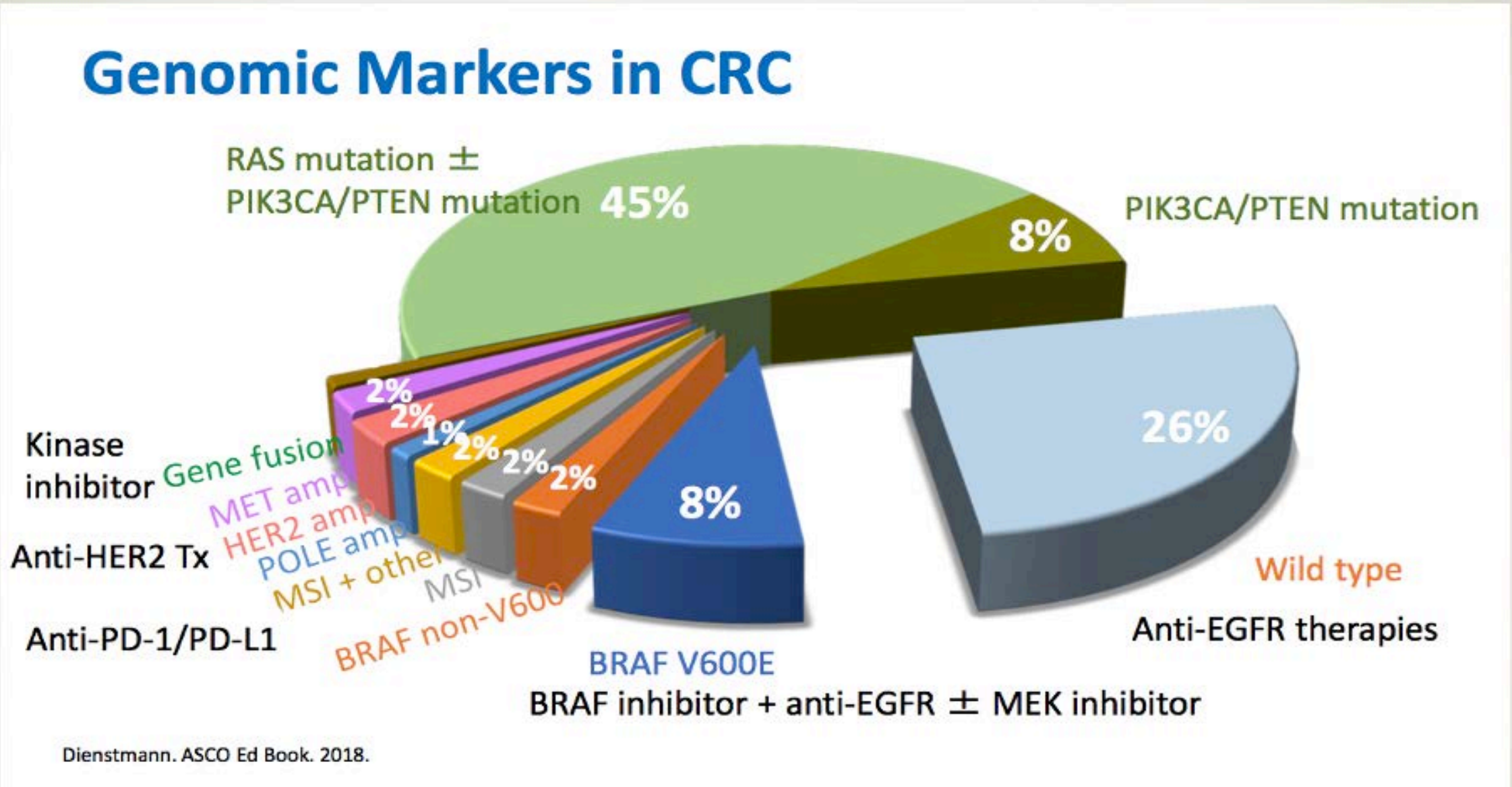
Genomic Markers in CRC



Dienstmann. ASCO Ed Book. 2018.

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rapid communications

Encorafenib Plus Cetuximab as a New Standard of Care for Previously Treated *BRAF* V600E–Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study

Josep Tabernero, MD, PhD[1]; Axel Grothey, MD[2]; Eric Van Cutsem, MD, PhD[3]; Rona Yaeger, MD[4]; Harpreet Wasan, MD[5]; Takayuki Yoshino, MD, PhD[6]; Jayesh Desai, MBBS[7]; Fortunato Ciardiello, MD, PhD[8]; Fotios Loupakis, MD, PhD[9]; Yong Sang Hong, MD, PhD[10]; Neeltje Steeghs, MD, PhD[11]; Tormod Kyrre Guren, MD, PhD[12]; Hendrik-Tobias Arkenau, MD, PhD[13]; Pilar Garcia-Alfonso, MD[14]; Elena Elez, MD, PhD[1]; Ashwin Gollerkeri, MD[15]; Kati Maharry, PhD[15]; Janna Christy-Bittel, MSN[15]; and Scott Kopetz, MD, PhD[16]

J Clin Oncol 2021;39(4):273-84.

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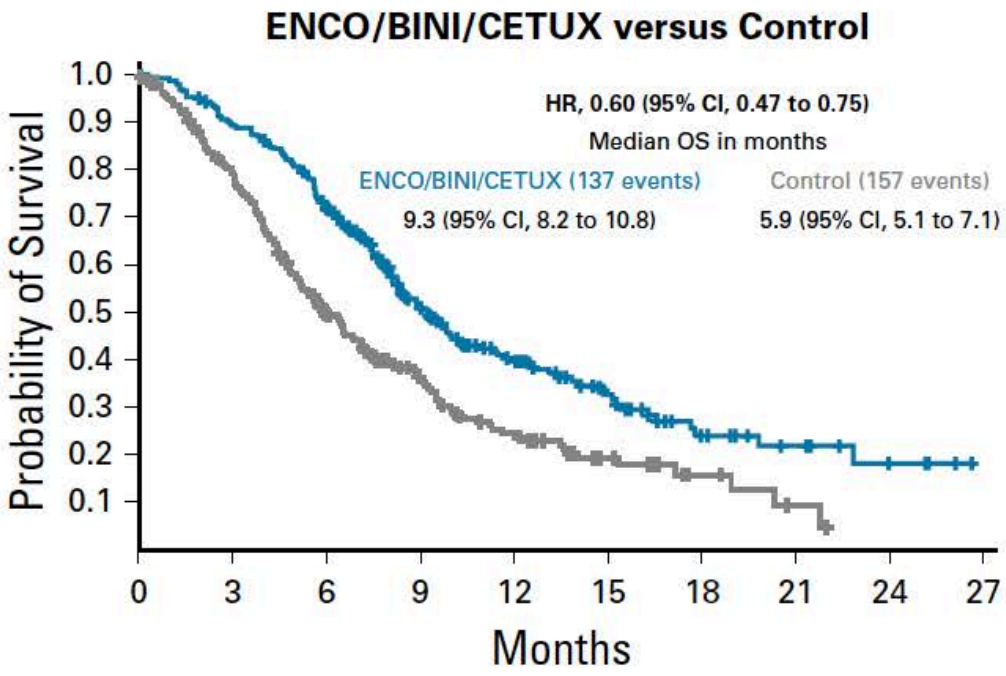
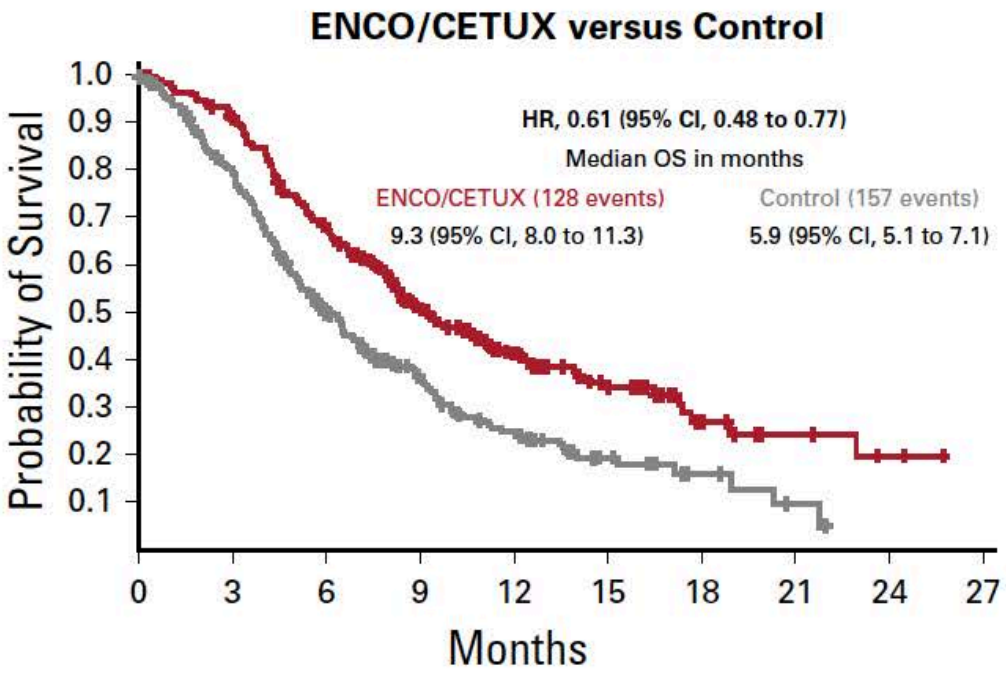
BEACON: Overall Survival Results



Number of patients at risk

ENCO/BINI/CETUX	224	198	157	89	56	33	15	9	4	0
Control	221	166	98	54	33	15	6	2	0	0



Number of patients at risk

ENCO/CETUX	220	197	143	83	47	28	13	7	2	0
Control	221	166	98	54	33	15	6	2	0	0

Tabanero J et al. *J Clin Oncol* 2021;39(4):273-84.

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Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial

Salvatore Siena, Maria Di Bartolomeo, Kanwal Raghav, Toshiki Masuishi, Fotios Loupakis, Hisato Kawakami, Kensei Yamaguchi, Tomohiro Nishina, Marwan Fakih, Elena Elez, Javier Rodriguez, Fortunato Ciardiello, Yoshito Komatsu, Taito Esaki, Ki Chung, Zev Wainberg, Andrea Sartore-Bianchi, Kapil Saxena, Eriko Yamamoto, Emarjola Bako, Yasuyuki Okuda, Javad Shahidi, Axel Grothey, Takayuki Yoshino, on behalf of the DESTINY-CRC01 investigators

***Lancet Oncol* 2021;[Online ahead of print].**

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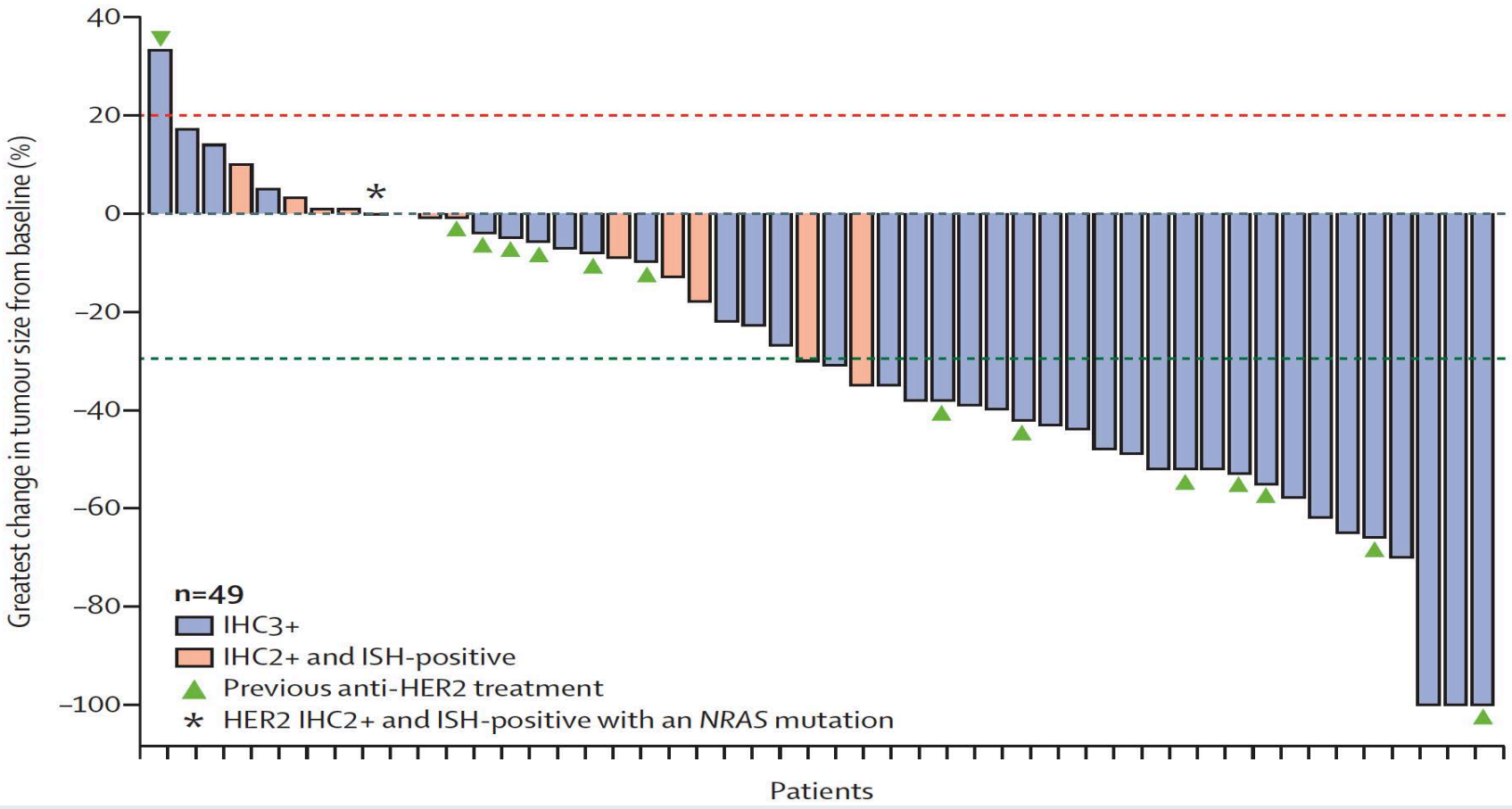
DESTINY-CRC01: Response

Best Change in Tumor Size

ORR: 45.3%



Siena S et al. *Lancet Oncol* 2021;[Online ahead of print].

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DESTINY-CRC01: AEs of Special Interest

	All Patients (N = 78)					
Preferred Term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial Lung Disease	0	2 (2.6)	1 (1.3)	0	2 (2.6)	5 (6.4)

Among the 5 total events:

- Median time to investigator-reported onset was 80 days (range, 22-132)
- 5 of 5 patients with grade ≥ 2 ILD received corticosteroids
- 2 patients recovered, 1 did not recover (later died due to disease progression), and 2 died
- In the 2 fatal cases, onset was from 40-126 days, both received steroids as part of treatment, and death occurred 6-18 days after diagnosis

Protocol recommendations: Monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is suspected

Siena S et al. ASCO 2020;Abstract 4000.

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Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients (pts) with HER2-Expressing Metastatic Colorectal Cancer (mCRC): Final Results from a Phase 2, Multicenter, Open-Label Study (DESTINY-CRC01)

Yoshino T et al.
ASCO 2021;Abstract 3505.

Monday, June 7, 1:15 PM - 4:15 PM EDT

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Case Presentation – Dr Dayyani: A 60-year-old woman with MSS mCRC – TMB 35.4 mut/Mb, KRAS G12D mutation

Dr Farshid Dayyani

- Diagnosed in Iran at age 45 with rectal cancer, s/p chemoradiation therapy and surgery → FOLFOX x 6
- 9/2017: Moved to US, recurrence with lung and abdominal lymph node metastases
- Capecitabine/bevacizumab, with mixed response → CAPOX/bevacizumab (severe oxaliplatin reaction)
- FOLFIRI, with nausea and frequent ER visits → Maintenance 5-FU/LV and dose-reduced bevacizumab → PD
- Regorafenib 80 mg daily, with poor tolerability
- NGS: MSS, KRAS G12D, TMB 35.4 mut/Mb
- Discussed treatment with single-agent pembrolizumab

Questions

- What are your views on the clinical data available with third-line single-agent regorafenib and third-line TAS-102 plus bevacizumab? How would you prefer to sequence these treatments?
- Is it reasonable in a patient with KRAS mutation G12D, microsatellite stable to try pembrolizumab due to the high TMB score?

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Key Recent Publications and Presentations

- Van Cutsem E et al. **Trifluridine/Tipiracil plus Bevacizumab in Patients with Untreated Metastatic Colorectal Cancer Ineligible for Intensive Therapy: The Randomized TASCO1 Study.** *Ann Oncol* 2020;31(9):1160-8.
- Pfeiffer P et al. **TAS-102 with or without Bevacizumab in Patients with Chemorefractory Metastatic Colorectal Cancer: An Investigator-Initiated, Open-Label, Randomised, Phase 2 Trial.** *Lancet Oncol* 2020;21(3):412-20.

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Ann Oncol 2020;31(9):1160-8.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Trifluridine/tipiracil plus bevacizumab in patients with untreated metastatic colorectal cancer ineligible for intensive therapy: the randomized TASCO1 study☆

E. Van Cutsem[1*], I. Danielewicz[2], M. P. Saunders[3], P. Pfeiffer[4], G. Argilés[5], C. Borg[6], R. Glynne-Jones[7], C. J. A. Punt[8], A. J. Van de Wouw[9], M. Fedyanin[10], D. Stroyakovskiy[11], H. Kroening[12], P. Garcia-Alfonso[13], H. Wasan[14], A. Falcone[15], A. Kanehisa[16], A. Egorov[16], P. Aubel[16], N. Amellal[16] & V. Moiseenko[17]

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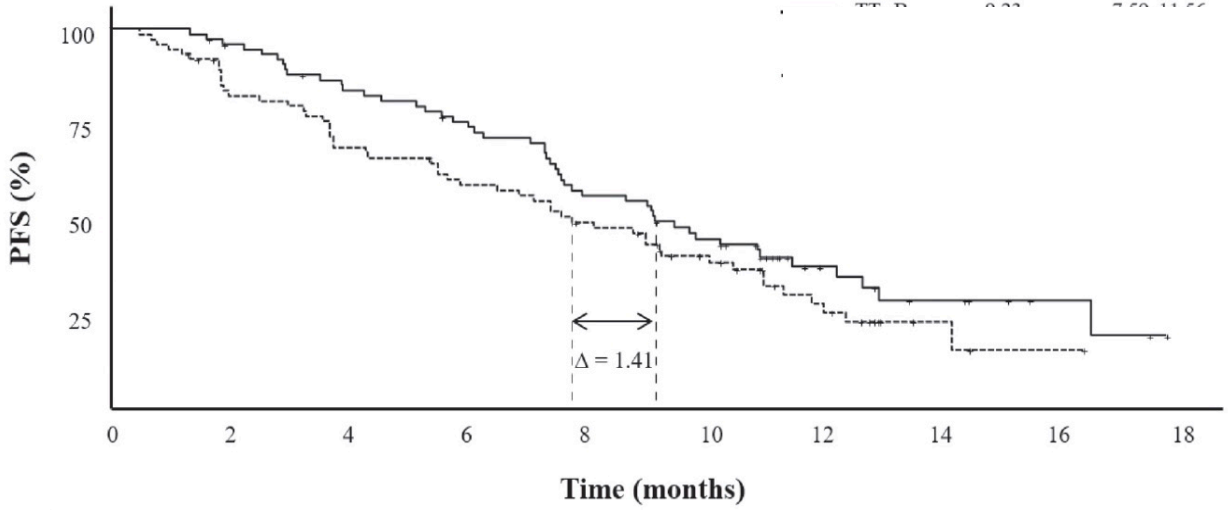
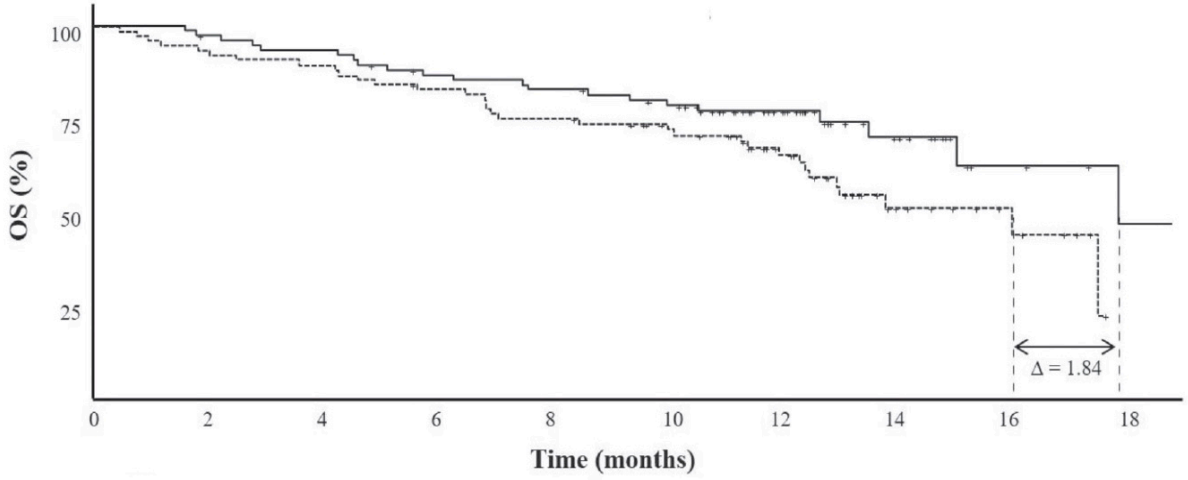
TASCO1: TAS-102 with Bevacizumab for Untreated mCRC Ineligible for Intensive Therapy

	Cape/Bev (n = 76)	TAS-102/Bev (n = 77)
mPFS	7.8 mo	9.2 mo
	HR: 0.71	



	Cape/Bev (n = 76)	TAS-102/Bev (n = 77)
mOS	16.2 mo	18.0 mo
	HR: 0.56	



Van Cutsem E et al. *Ann Oncol* 2020;31(9):1160-8.

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TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial

Per Pfeiffer, Mette Yilmaz, Sören Möller, Daniela Zitnjak, Merete Krogh, Lone Nørgård Petersen, Laurids Østergaard Poulsen, Stine Braendegaard Winther, Karina Gravgaard Thomsen, Camilla Qvortrup

Lancet Oncol 2020; 21: 412–20

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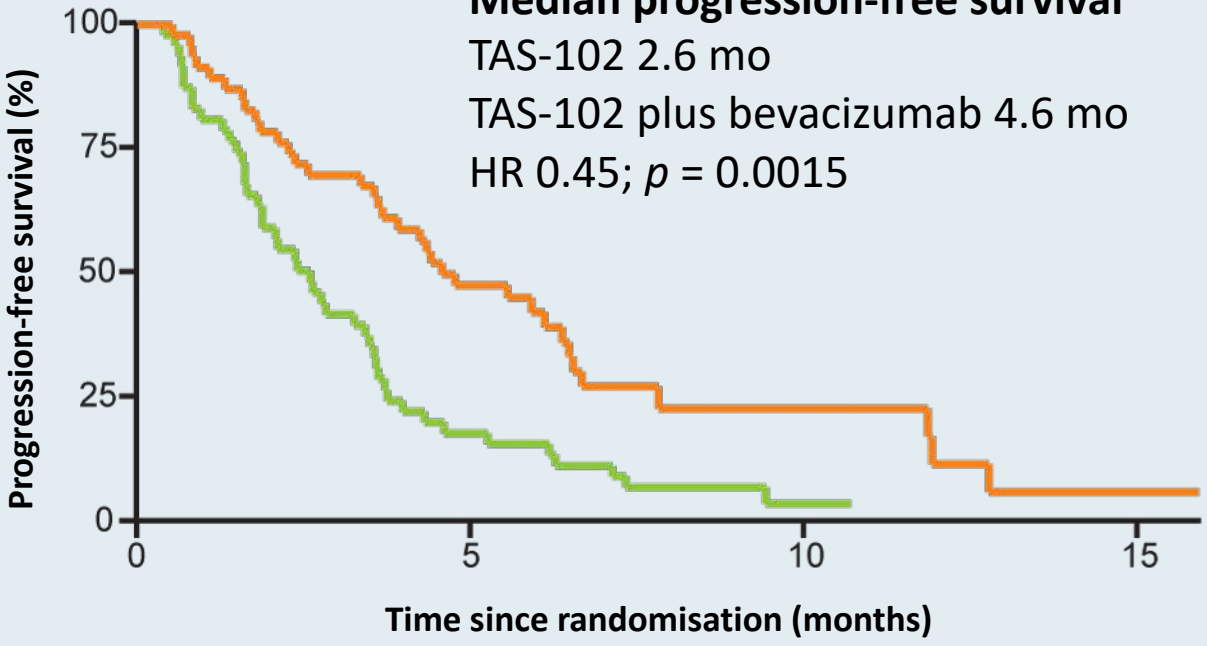
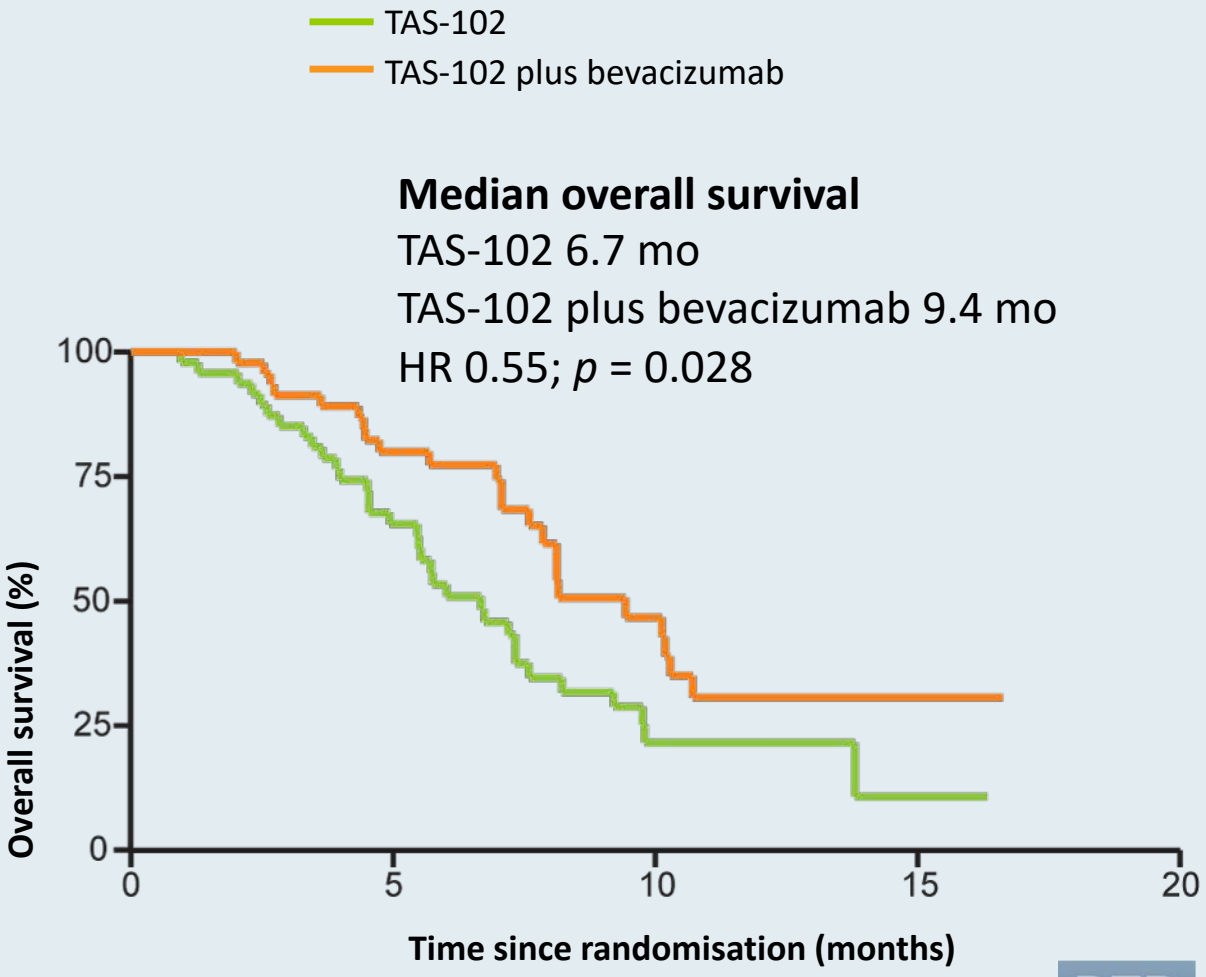
TAS-102 with or without Bevacizumab: Efficacy Results





Disease control rate:

- TAS-102/Bev = 67%
- TAS-102 = 51%

Pfeiffer P et al. *Lancet Oncol* 2020;21(3):412-20.

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The TRUSTY Study: A Randomized Phase 2/3 Study of Trifluridine/Tipiracil plus Bevacizumab versus Irinotecan and Fluoropyrimidine plus Bevacizumab as Second-Line Treatment in Patients with Metastatic Colorectal Cancer

Kuboki Y et al.
ASCO 2021;Abstract 3507.

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Module 1: Colorectal Cancer

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- Dr Dayyani: A 60-year-old woman with MSS mCRC – TMB 35.4 mut/Mb, KRAS G12D mutation
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- Dr Chen: An 80-year-old woman with localized pancreatic cancer
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Case Presentation – Dr Dayyani: A 60-year-old man with relapsed MSS esophageal squamous cell cancer – PD-L1 CPS 15

Dr Farshid Dayyani

- Long history of swallowing difficulties, with multiple EGDs and biopsies significant for inflammation and ulcers but no malignancy
- 10/2017: Severe pain in swallowing and constant esophageal spasms
- 11/2017: Admitted to UCI, underwent EGD/EUS, with biopsy significant for esophageal SCC
- FOLFOX x 6 → Concurrent chemoRT with carboplatin/paclitaxel
- 9/2018: Laparoscopic and thorascopic esophagectomy (ypTis ypN0)
- Remains NED on surveillance but last clinic visit in 11/2020 due to COVID-19
- Recurrent disease, with pleural effusion, dysphagia, ascites, anorexia, hypercalcemia
- Testing: PD-L1 CPS 15, MSS

Questions

- Would you treat with single-agent pembrolizumab, paclitaxel, or a combination?

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Regulatory and reimbursement issues aside, what is your usual initial treatment for a 65-year-old patient with MSS adenocarcinoma of the esophagus with a PD-L1 CPS of 0?

1. FOLFOX
2. Other chemotherapy
3. Pembrolizumab
4. Pembrolizumab + chemotherapy
5. Nivolumab
6. Nivolumab + chemotherapy
7. Other

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Key Recent Publications and Presentations

- Kelly RJ et al. **Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer.** *N Engl J Med* 2021;384(13):1191-203.
- Kato K et al. **Pembrolizumab plus Chemotherapy versus Chemotherapy as First-Line Therapy in Patients with Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study.** ESMO 2020;Abstract LBA8_PR.
- Moehler M et al. **Nivolumab plus Chemotherapy versus Chemotherapy as First-Line Treatment for Advanced Gastric Cancer/Gastroesophageal Junction Cancer/Esophageal Adenocarcinoma: First Results of the CheckMate 649 Study.** ESMO 2020;Abstract LBA6.

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 1, 2021 VOL. 384 NO. 13

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

R.J. Kelly, J.A. Ajani, J. Kuzdzal, T. Zander, E. Van Cutsem, G. Piessen, G. Mendez, J. Feliciano, S. Motoyama, A. Lièvre, H. Uronis, E. Elimova, C. Grootscholten, K. Geboes, S. Zafar, S. Snow, A.H. Ko, K. Feeney, M. Schenker, P. Kocon, J. Zhang, L. Zhu, M. Lei, P. Singh, K. Kondo, J.M. Cleary, and M. Moehler, for the CheckMate 577 Investigators*

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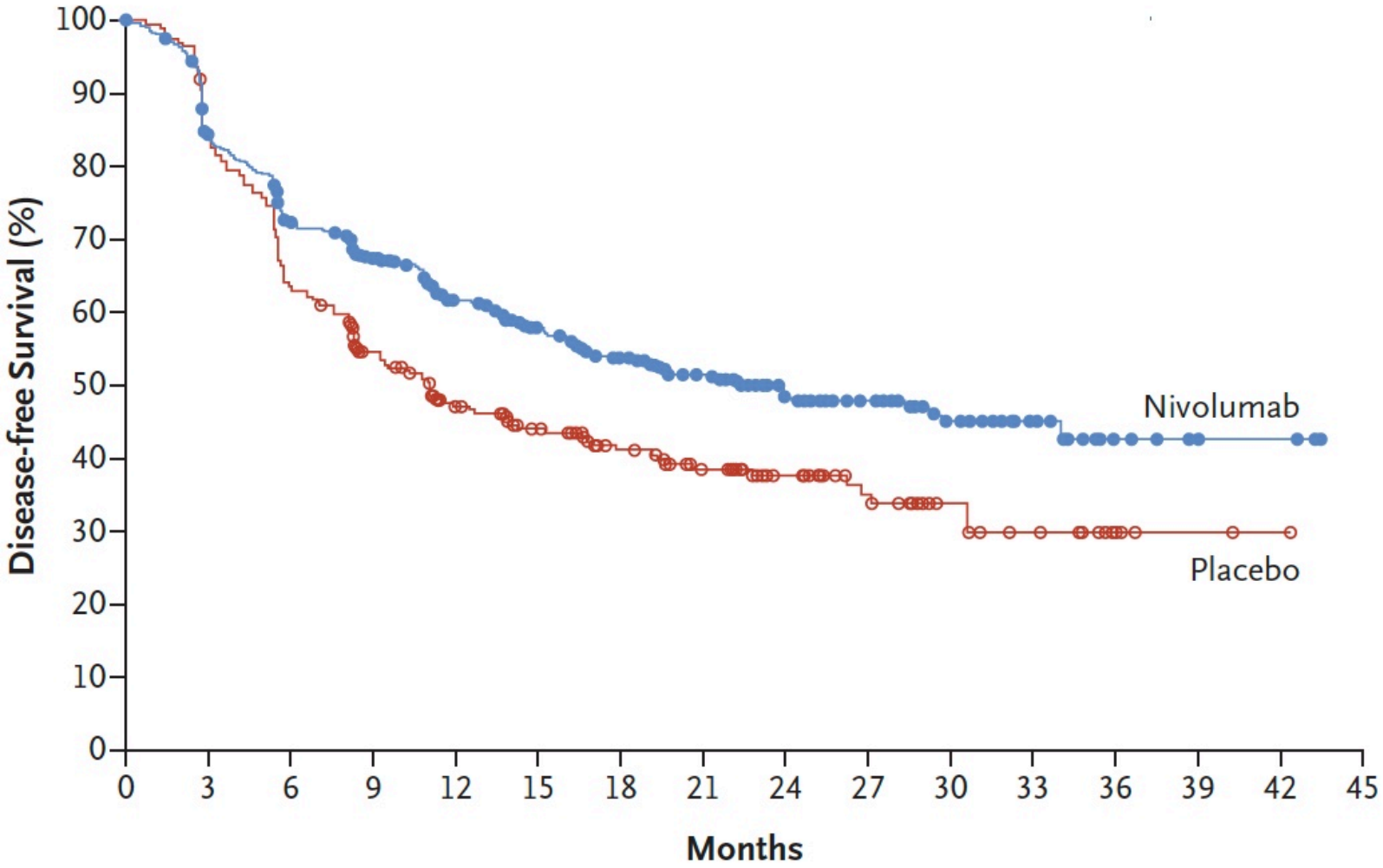
CheckMate-577: Disease-Free Survival in the Overall Population



	No. of Patients	Median Disease-free Survival
		mo (95% CI)
Nivolumab	532	22.4 (16.6–34.0)
Placebo	262	11.0 (8.3–14.3)

Hazard ratio for disease recurrence or death, 0.69 (96.4% CI, 0.56–0.86)
P<0.001

Kelly RJ et al. *N Engl J Med* 2021;384(13):1191-203.

RTP RESEARCH TO PRACTICE

Adjuvant Nivolumab (NIVO) in Resected Esophageal or Gastroesophageal Junction Cancer (EC/GEJC) Following Neoadjuvant Chemoradiotherapy (CRT): Expanded Efficacy and Safety Analyses from CheckMate 577

Kelly RJ et al.
ASCO 2021;Abstract 4003.

Saturday, June 5, 1:45 PM - 4:45 PM EDT

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Multicenter, Randomized Phase II Study of Neoadjuvant Pembrolizumab plus Chemotherapy and Chemoradiotherapy in Esophageal Adenocarcinoma (EAC)

Shah MA et al.
ASCO 2021;Abstract 4005.

Saturday, June 5, 1:45 PM - 4:45 PM EDT

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Checkpoint Inhibitor Approvals in Gastric, GEJ and Esophageal Cancers

Regimen	Location	Histology	Setting	PD-L1
Pembrolizumab 7/30/2019	Esophageal, GEJ	Squamous	• Recurrent locally advanced or metastatic • Not amenable to surgical resection or definitive chemoradiation • After ≥1 prior lines of systemic therapy	CPS ≥10
Nivolumab 6/10/2020	Esophageal	Squamous	• Unresectable advanced, recurrent or metastatic • After prior fluoropyrimidine- and platinum-based chemotherapy	Not required
Pembrolizumab + cisplatin/5-FU 3/22/2021	Esophageal, GEJ	Adenocarcinoma and squamous	• Recurrent locally advanced or metastatic • Not amenable to surgical resection or definitive chemoradiation	Not required
Nivolumab + mFOLFOX6 or CAPOX 4/16/2021	Gastric, GEJ, esophageal	Adenocarcinoma	• Advanced or metastatic gastric, GEJ or esophageal adenocarcinoma	Not required
Pembrolizumab + trastuzumab + chemotherapy 5/5/2021	Gastric, GEJ	Adenocarcinoma	• First-line treatment for locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma	Not required

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FDA Approves Pembrolizumab in Combination with Chemotherapy for Esophageal or GEJ Carcinoma

Press Release – March 22, 2021

"On March 22, 2021, the Food and Drug Administration approved pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for patients with metastatic or locally advanced esophageal or gastroesophageal (GEJ) (tumors with epicenter 1 to 5 centimeters above the gastroesophageal junction) carcinoma who are not candidates for surgical resection or definitive chemoradiation.

Efficacy was evaluated in KEYNOTE-590 (NCT03189719), a multicenter, randomized, placebo-controlled trial that enrolled 749 patients with metastatic or locally advanced esophageal or gastroesophageal junction carcinoma who were not candidates for surgical resection or definitive chemoradiation.

The recommended pembrolizumab dose for esophageal cancer is 200 mg every 3 weeks or 400 mg every 6 weeks."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-esophageal-or-gej-carcinoma?utm_medium=email&utm_source=govdelivery

RTP RESEARCH TO PRACTICE

Pembrolizumab plus Chemotherapy versus Chemotherapy as First-Line Therapy in Patients with Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study

Kato K et al.

ESMO 2020;Abstract LBA8_PR.

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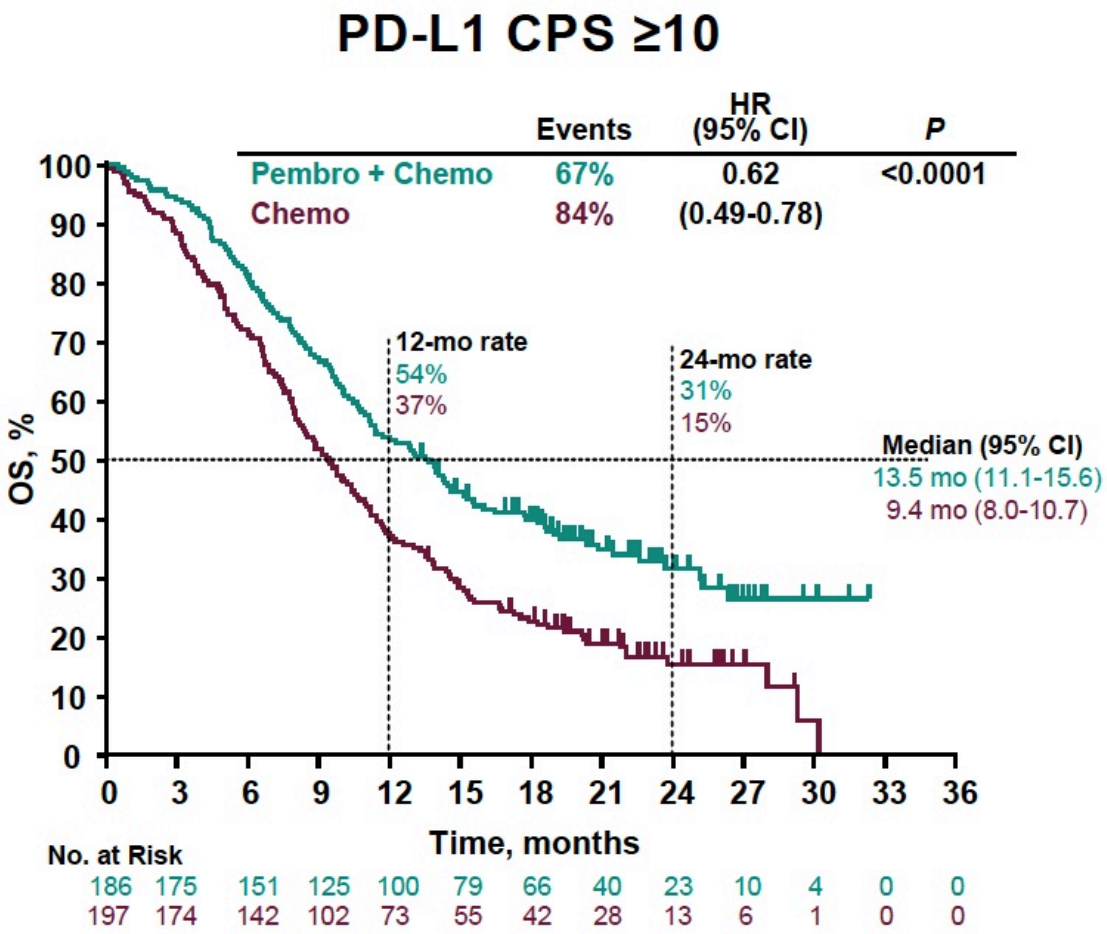
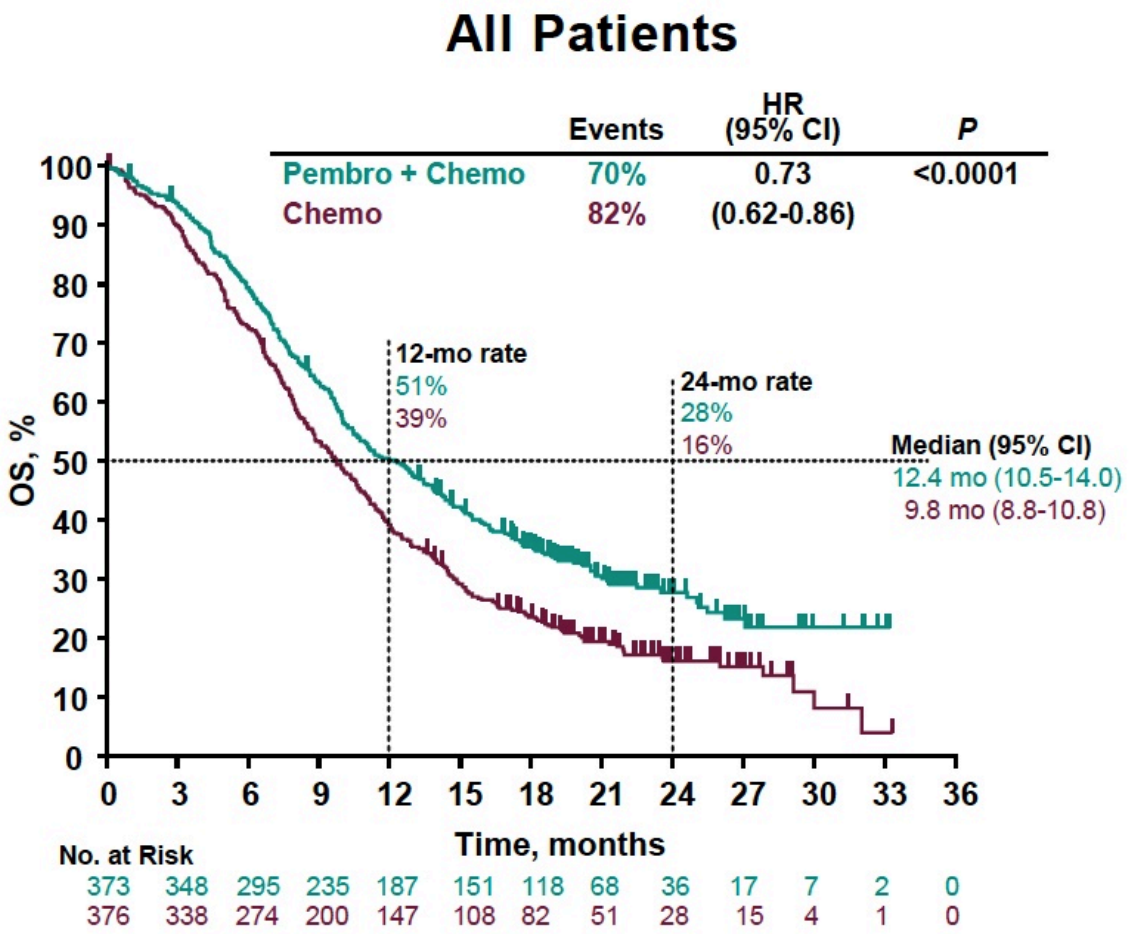
KEYNOTE-590: Overall Survival





Kato K et al. ESMO 2020;Abstract LBA8_PR.

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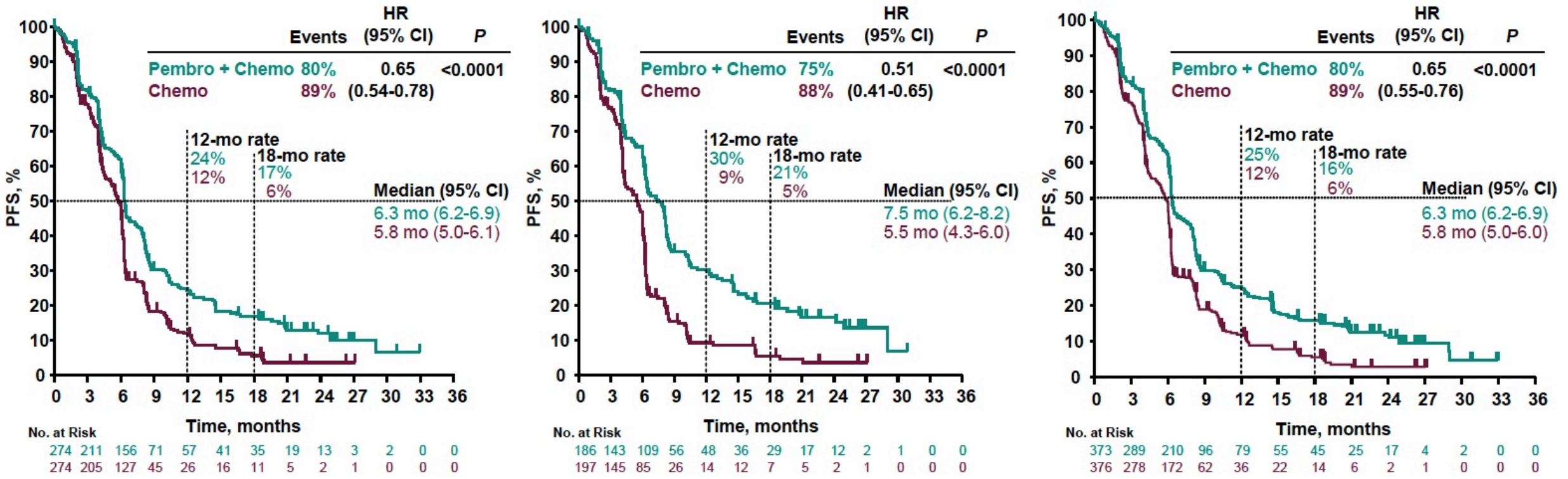
KEYNOTE-590: Progression-Free Survival



Kato K et al. ESMO 2020;Abstract LBA8_PR.

RTP RESEARCH TO PRACTICE

FDA Approves Nivolumab with Chemotherapy for Front-Line Advanced Gastric Cancer

Press Release – April 16, 2021

"The FDA approved nivolumab in combination with certain types of chemotherapy for the frontline treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma, making it the first approved immunotherapy for this patient population.

The agency based the approval on data from the randomized, multicenter, open-label phase 3 CheckMate-649 trial, designed to evaluate nivolumab – a monoclonal antibody that inhibits tumor growth by enhancing T-cell function – plus chemotherapy in 1,581 patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma. Of the 789 patients treated in the nivolumab arm, median overall survival was 13.8 months, compared with 11.6 months for patients who received chemotherapy alone."

https://www.cancernetwork.com/view/fda-approves-nivolumab-plus-chemo-for-frontline-advanced-gastric-cancer?utm_source=sfmc&utm_medium=email&utm_campaign=4.16.21_CN_Breaking&eKey=Z2tlbGx5QHJlc2VhcmNodG9wcmFjdGljZS5jb20=

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Nivolumab plus Chemotherapy versus Chemotherapy as First-Line Treatment for Advanced Gastric Cancer/Gastroesophageal Junction Cancer/Esophageal Adenocarcinoma: First Results of the CheckMate 649 Study

Moehler M et al.

ESMO 2020;Abstract LBA6.

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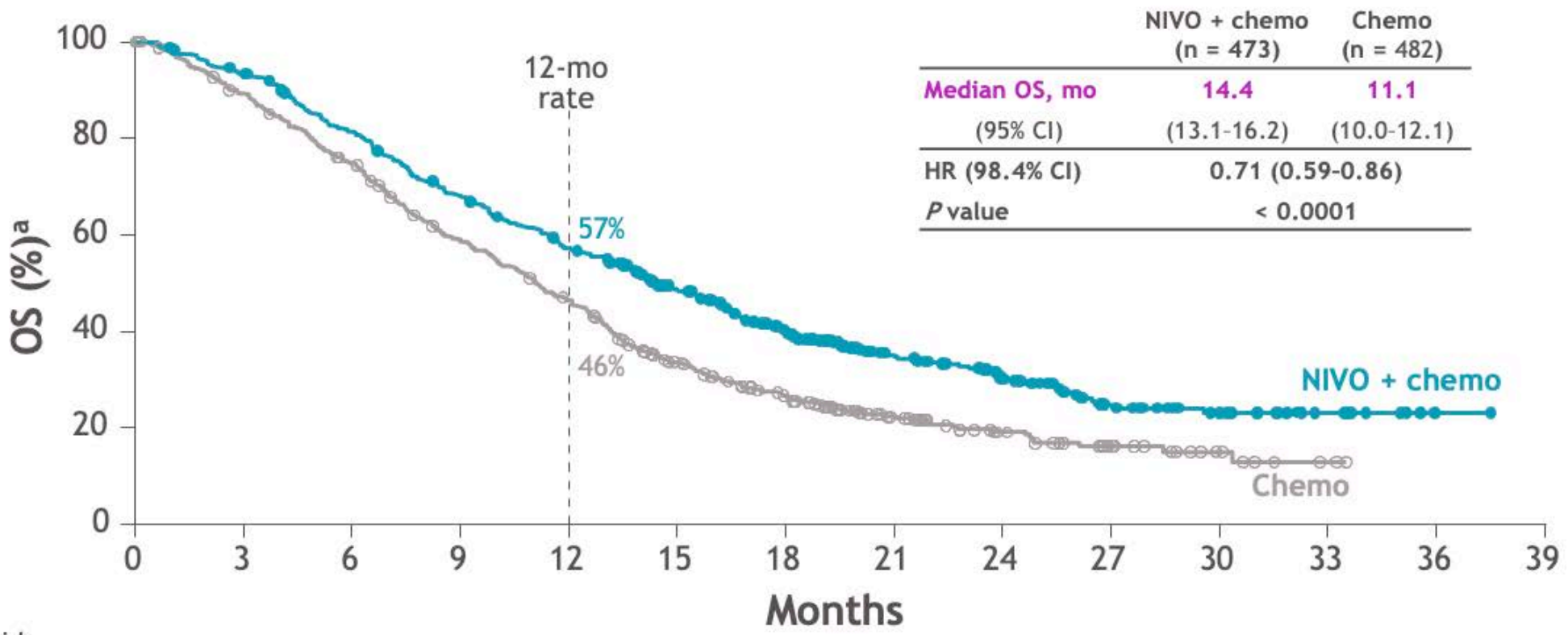
CheckMate 649: Dual Primary Endpoint – OS (PD-L1 CPS ≥5)



	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P value	< 0.0001	

No. at risk														
NIVO + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

[a]Minimum follow-up 12.1 months.

Moehler M et al. ESMO 2020;Abstract LBA6.

RTP RESEARCH TO PRACTICE

First-Line (1L) Nivolumab (NIVO) plus Chemotherapy (Chemo) versus Chemo in Advanced Gastric Cancer/Gastroesophageal Junction Cancer/Esophageal Adenocarcinoma (GC/GEJC/EAC): Expanded Efficacy and Safety Data from CheckMate 649

Moehler MH et al.
ASCO 2021;Abstract 4002.

Saturday, June 5, 1:45 PM - 4:45 PM EDT

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Nivolumab (NIVO) plus Ipilimumab (IPI) or NIVO plus Chemotherapy (Chemo) versus Chemo as First-Line (1L) Treatment for Advanced Esophageal Squamous Cell Carcinoma (ESCC): First Results of the CheckMate 648 Study

Chau I et al.
ASCO 2021;Abstract LBA4001.

Saturday, June 5, 1:45 PM - 4:45 PM EDT

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Case Presentation – Dr Del Rosario: A 49-year-old woman with HER2-positive metastatic gastric adenocarcinoma – PD-L1 CPS 5

Dr Michael Del Rosario

- HER2-positive, MMR proficient, metastatic gastric adenocarcinoma, PD-L1 CPS: 5, ECOG PS: 1
- FOLFOX/trastuzumab

Questions

- Upon disease progression is immunotherapy still an option in light of her PD-L1 CPS of 5?
- Does HER2 status need to be confirmed upon disease progression? What treatment would you recommend if the tumor remains HER2-positive? If the tumor is now HER2-negative?
- With trastuzumab deruxtecan, which side effects should we monitor for in patients? How should we monitor for ILD?

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Regulatory and reimbursement issues aside, what third-line treatment would you recommend for a younger patient (PS 0) with metastatic HER2-positive, MSS gastric cancer (CPS <1) with progression on FOLFOX/trastuzumab and then paclitaxel/ramucirumab?

1. TAS-102
2. Other chemotherapy
3. Pembrolizumab
4. Nivolumab
5. Trastuzumab deruxtecan
6. Other anti-HER2 regimen
7. Palliative care
8. Other

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Key Recent Publications and Presentations

- Shitara K et al. **Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer.** *N Engl J Med* 2020;382(25):2419-30.
- Dayyani F et al. **A Phase Ib Multicenter Study of Trifluridine/Tipiracil (FTD/TPI) in Combination with Irinotecan (IRI) in Patients with Advanced Recurrent or Unresectable Gastric and Gastroesophageal Adenocarcinoma (aGEC) After at Least One Line of Treatment with a Fluoropyrimidine and Platinum Containing Regimen.** Gastrointestinal Cancers Symposium 2021;Abstract TPS251.
- Hara H et al. **A Phase I/II Trial of Trifluridine/Tipiracil in Combination with Irinotecan in Patients with Advanced Gastric Cancer Refractory to Fluoropyrimidine, Platinum, and Taxane.** Gastrointestinal Cancers Symposium 2021;Abstract 210.

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FDA Approves Trastuzumab Deruxtecan for HER2-Positive Gastric Adenocarcinomas

Press Release – January 15, 2021

"On January 15, 2021, the Food and Drug Administration approved fam-trastuzumab deruxtecan-nxki for adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

Efficacy was evaluated in a multicenter, open-label, randomized trial (DESTINY-Gastric01, NCT03329690) in patients with HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma who had progressed on at least two prior regimens, including trastuzumab, a fluoropyrimidine- and a platinum-containing chemotherapy. A total of 188 patients were randomized (2:1) to receive fam-trastuzumab deruxtecan-nxki 6.4 mg/kg intravenously every 3 weeks or physician's choice of either irinotecan or paclitaxel monotherapy."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-fam-trastuzumab-deruxtecan-nxki-her2-positive-gastric-adenocarcinomas

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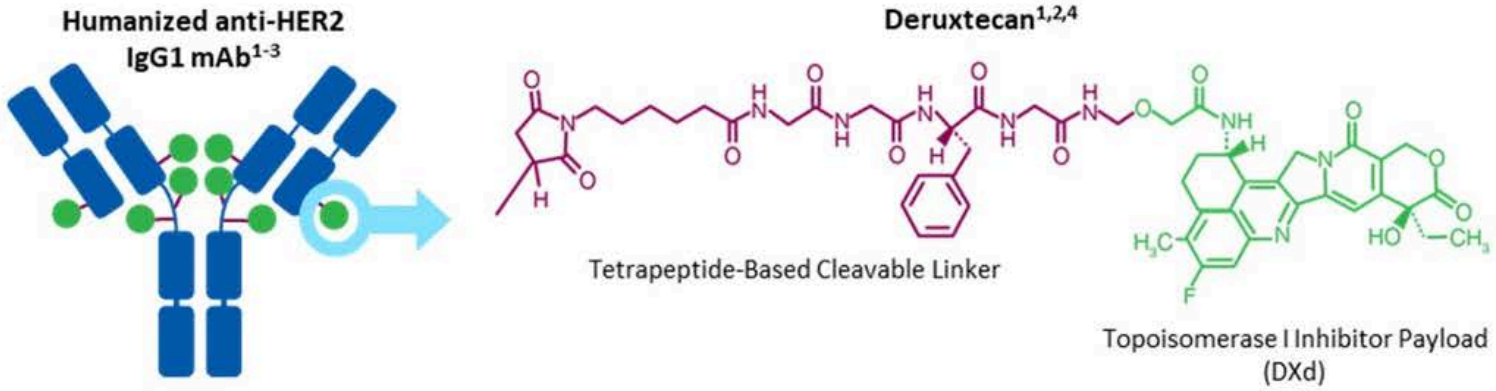
Trastuzumab Deruxtecan (T-DXd) Is a Novel Antibody-Drug Conjugate Designed to Deliver an Antitumor Effect

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



- T-DXd is being clinically evaluated across a number of HER2-expressing or mutated cancers, including breast cancer, CRC, non-small cell lung cancer, and others

Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

Siena S et al. ASCO 2020;Abstract 4000.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

K. Shitara, Y.-J. Bang, S. Iwasa, N. Sugimoto, M.-H. Ryu, D. Sakai, H.-C. Chung, H. Kawakami, H. Yabusaki, J. Lee, K. Saito, Y. Kawaguchi, T. Kamio, A. Kojima, M. Sugihara, and K. Yamaguchi, for the DESTINY-Gastric01 Investigators*

N Engl J Med 2020;382(25):2419-30

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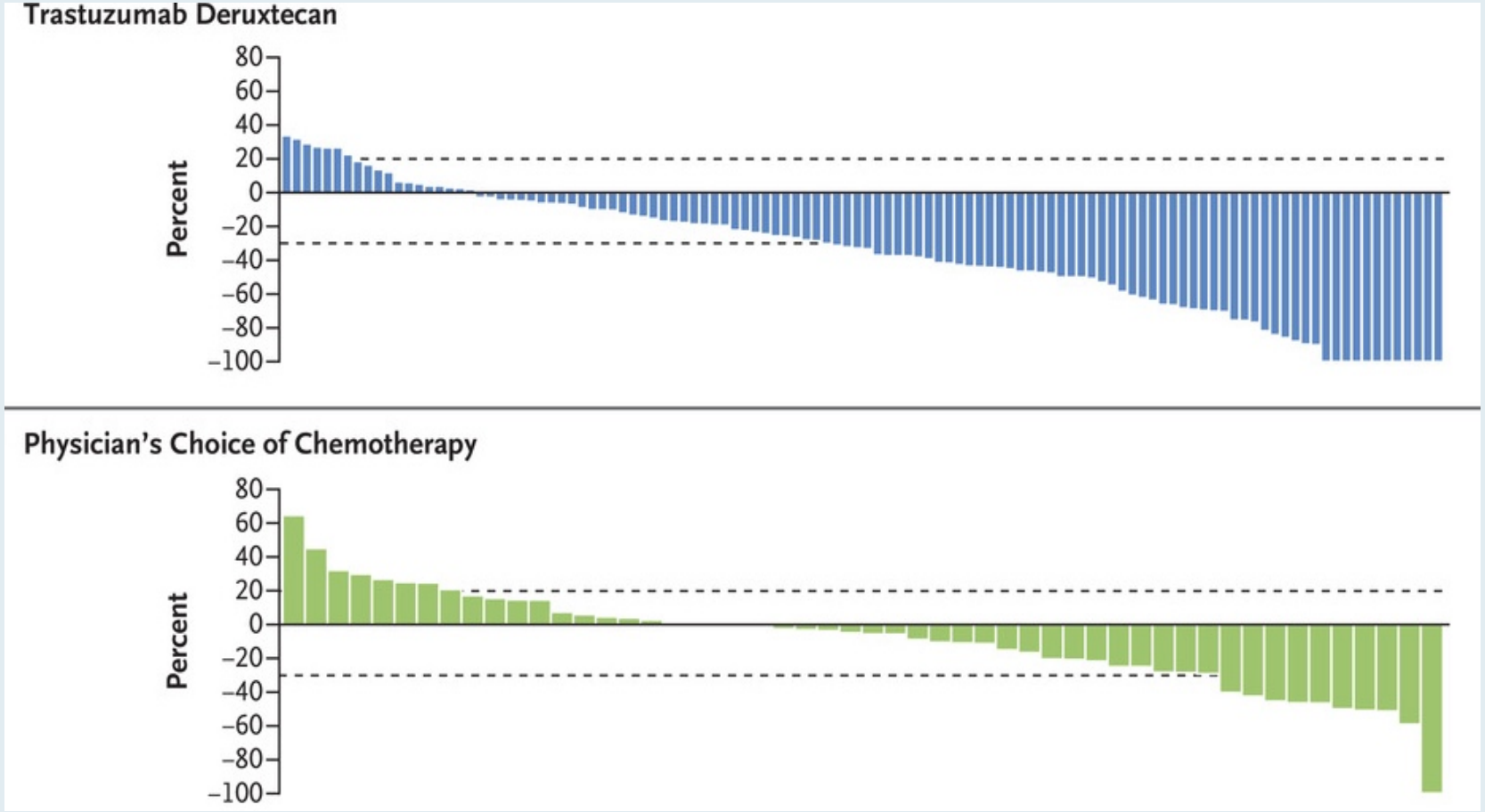
DESTINY-Gastric01: Trastuzumab Deruxtecan for Previously Treated HER2-Positive Gastric Cancer



	T-DXd (n = 119)	PC (n = 56)
ORR	**51%**	**14%**
Confirmed ORR	**43%**	**12%**
CR	8%	0%
PR	34%	12%

Shitara K et al. *N Engl J Med* 2020;382(25):2419-30.

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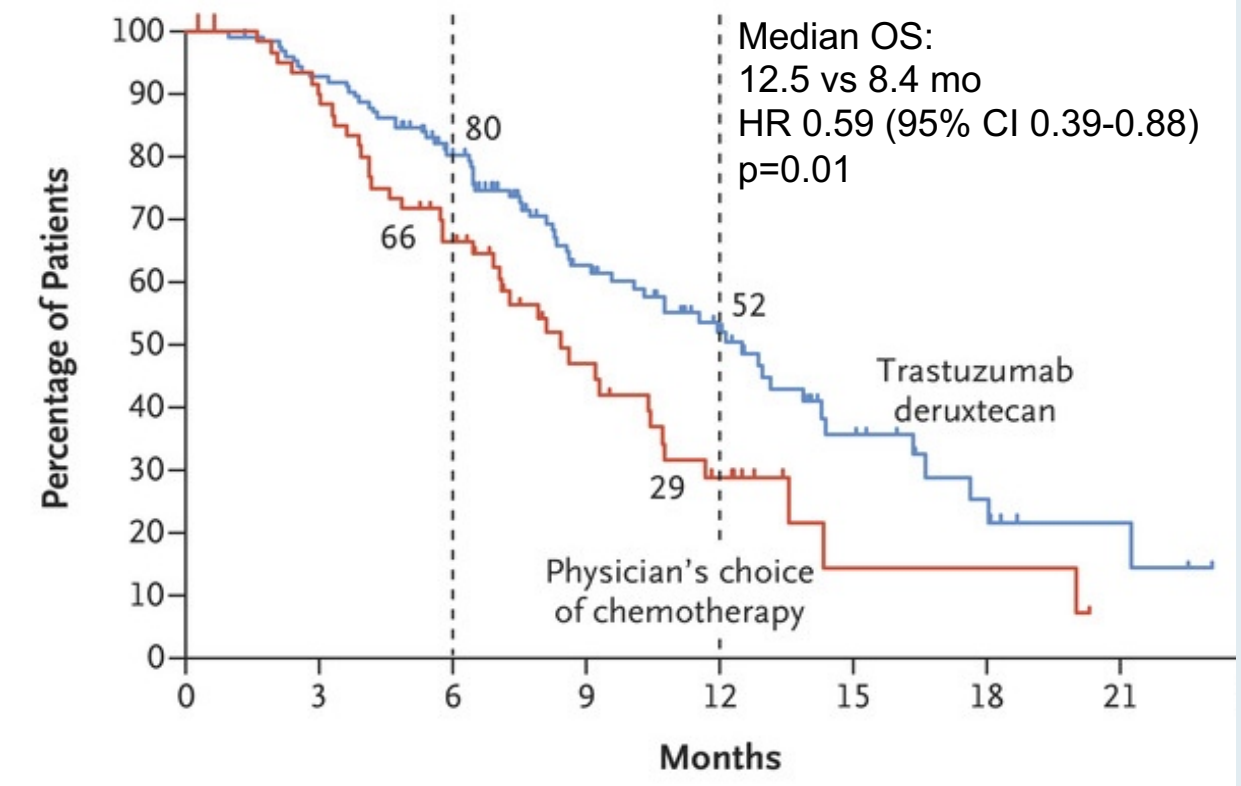
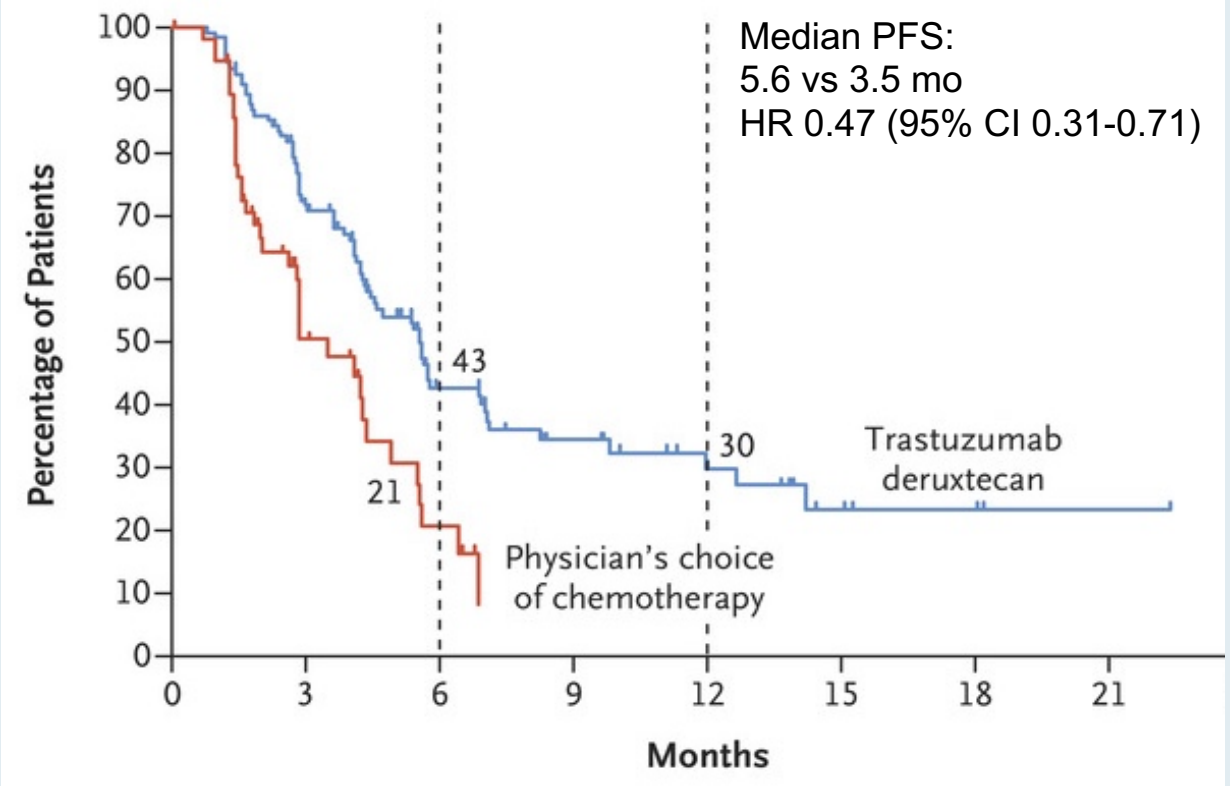
DESTINY-Gastric01: Survival Results





Shitara K et al. *N Engl J Med* 2020;382(25):2419-30.

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DESTINY-Gastric01: AEs of Special Interest – Interstitial Lung Disease

	T-DXd (n = 125)					
Preferred Term, n	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total, n (%)
Interstitial Lung Disease	3	6	2	1	0	12 (9.6)

- Drug-related ILD/pneumonitis as determined by an independent adjudication committee was only observed in patients receiving T-DXd
- Among the 12 total events, the median time to investigator-reported first onset was 84.5 days (range, 36-638 days)

Recommendations: It is important to monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is confirmed.

Yamaguchi K et al. ESMO World GI Congress 2020;Abstract O-11.

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Ongoing Phase III Trial of Trastuzumab Deruxtecan for HER2-Positive Gastric Cancer

Trial (NCT#)	Phase	Target (N)	Setting	Treatment arms
DESTINY-Gastric04 (NCT04704934)	III	490	Metastatic and/or unresectable gastric or GEJ adenocarcinoma; Progression on or after trastuzumab-based regimen	• Trastuzumab deruxtecan • Ramucirumab + paclitaxel

Clinicaltrials.gov; Accessed February 2021.

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FDA Grants Accelerated Approval to Pembrolizumab with Trastuzumab and Chemotherapy as First-Line Therapy for HER2-Positive Gastric Cancer

Press Release – May 5, 2021

"On May 5, 2021, the Food and Drug Administration granted accelerated approval to pembrolizumab in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Approval was based on the prespecified interim analysis of the first 264 patients of the ongoing KEYNOTE-811 (NCT03615326) trial, a multicenter, randomized, double-blind, placebo-controlled trial in patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who had not previously received systemic therapy for metastatic disease. Patients were randomized (1:1) to receive pembrolizumab 200 mg or placebo every 3 weeks, in combination with trastuzumab and either fluorouracil plus cisplatin or capecitabine plus oxaliplatin.

The main efficacy measure for this analysis was overall response rate (ORR) assessed by blinded independent review committee. The ORR was 74% in the pembrolizumab arm and 52% in the placebo arm (one-sided p-value< 0.0001, statistically significant). The median duration of response (DoR) was 10.6 months for patients treated with pembrolizumab and 9.5 months for those in the placebo arm."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-pembrolizumab-her2-positive-gastric-cancer

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A Phase Ib Multicenter Study of Trifluridine/Tipiracil (FTD/TPI) in Combination with Irinotecan (IRI) in Patients with Advanced Recurrent or Unresectable Gastric and Gastroesophageal Adenocarcinoma (aGEC) After at Least One Line of Treatment with a Fluoropyrimidine and Platinum Containing Regimen

Dayyani F et al.

Gastrointestinal Cancers Symposium 2021;Abstract TPS251.

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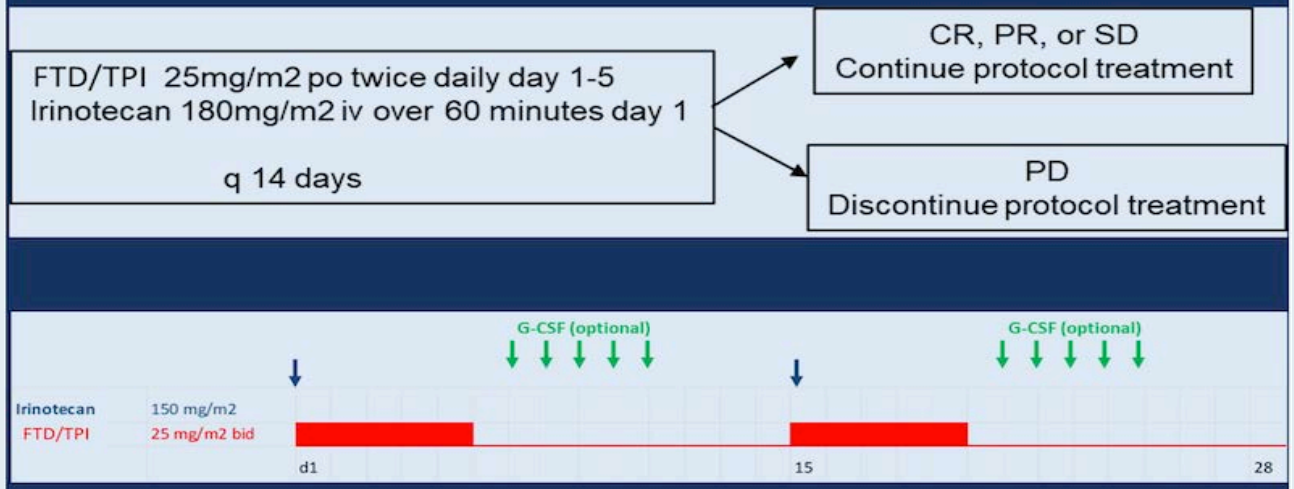
TAS-102 in Combination with Irinotecan: Ongoing Phase Ib Study Design and Objectives

Hypothesis:

The combination of FTD/TPI with IRI in 2L+ aGEC is feasible, clinically active, and provides a treatment option that is not associated with development of peripheral neuropathy.



- NCT04074343

Current Enrollment (n = 20)

Primary Objective:

- Regimen feasibility and efficacy estimate

Secondary Objectives:

- Overall survival
- Overall response rate
- Adverse events

Dayyani F et al. Gastrointestinal Cancers Symposium 2021;Abstract TPS251.

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A Phase I/II Trial of Trifluridine/Tipiracil in Combination with Irinotecan in Patients with Advanced Gastric Cancer Refractory to Fluoropyrimidine, Platinum, and Taxane

Hara H et al.

Gastrointestinal Cancers Symposium 2021;Abstract 210.

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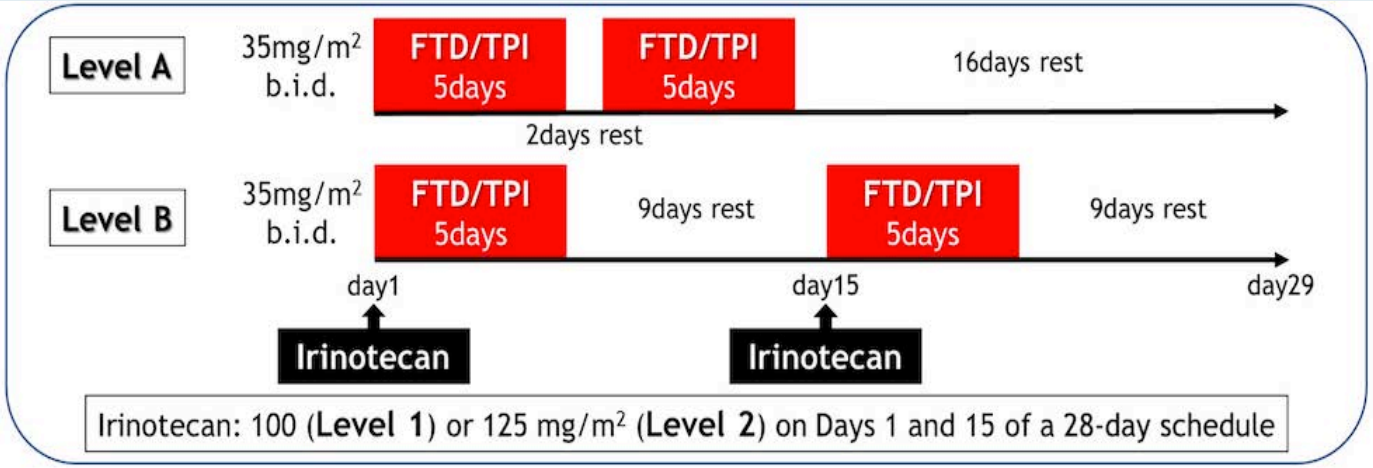
TAS-102 in Combination with Irinotecan: Results from a Phase I/II Study



	Level 1A (N = 2) N (%)	Level 1B (N = 3) N (%)	Level 2B (N = 6) N (%)	Total (N = 11) N (%)
CR	0 (0.0)	0 (0.0)	0 (0.0)	0
PR	0 (0.0)	0 (0.0)	1 (16.7)	1 (9.1)
SD	1 (50.0)	2 (66.7)	4 (66.7)	7 (63.6)
PD	1 (50.0)	1 (33.3)	1 (16.7)	3 (27.3)
NE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ORR (%) [95% CI]	0.0 [0.0- 84.1]	0.0 [0.0-70.8]	16.7 [0.4-64.1]	9.1 [0.2-41.3]
DCR (%) [95% CI]	50.0 [1.3-98.7]	66.6 [9.4-99.2]	83.3 [35.9-99.6]	72.7 [39.0-94.0]

	Level 1A (N=2)		Level 1B (N=3)		Level 2B (N=6)	
	All N (%)	≥G3 N (%)	All N (%)	≥G3 N (%)	All N (%)	≥G3 N (%)
Hematologic						
Neutropenia	2 (100.0)	2 (100.0)	3 (100.0)	2 (66.7)	6 (100.0)	6 (100.0)
WBC decreased	2 (100.0)	1 (50.0)	3 (100.0)	1 (33.3)	5 (83.3)	4 (66.7)
Anemia	2 (100.0)	2 (100.0)	2 (66.7)	1 (33.3)	3 (50.0)	2 (33.3)
Plt count decreased	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	4 (66.7)	1 (16.7)
Lymphocyte count decreased	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	2 (33.3)	1 (16.7)
Febrile neutropenia	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)
Non-hematologic						
Appetite loss	1 (50.0)	0 (0.0)	2 (66.7)	0 (0.0)	5 (83.3)	0 (0.0)
Diarrhea	1 (50.0)	0 (0.0)	2 (66.7)	0 (0.0)	2 (33.3)	0 (0.0)
Constipation	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	0 (0.0)

The RP2D of FTD/TPI in combination with irinotecan was determined to be Level 1B although further investigation to explore optimal regimen is needed.

Hara H et al. Gastrointestinal Cancers Symposium 2021;Abstract 210.

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Agenda

Module 1: Colorectal Cancer

- Dr Lorber: A 74-year-old woman with MSI-high mCRC – BRAF V600E mutation
- *Key Recent Publications and Presentations*
- Dr Dayyani: A 60-year-old woman with MSS mCRC – TMB 35.4 mut/Mb, KRAS G12D mutation
- *Key Recent Publications and Presentations*

Module 2: Gastric, Gastroesophageal and Esophageal Cancers

- Dr Dayyani: A 60-year-old man with relapsed MSS esophageal squamous cell cancer – PD-L1 CPS 15
- *Key Recent Publications and Presentations*
- Dr Del Rosario: A 49-year-old woman with HER2-positive metastatic gastric adenocarcinoma – PD-L1 CPS 5
- *Key Recent Publications and Presentations*

Module 3: Hepatocellular Cancer (HCC)

- Dr Dayyani: A 59-year-old man with advanced HCC
- Dr Lorber: An 80-year-old woman with unresectable advanced HCC
- *Key Recent Publications and Presentations*

Module 4: Pancreatic Adenocarcinoma

- Dr Chen: An 80-year-old woman with localized pancreatic cancer
- Dr Dayyani: A 79-year-old woman with pancreatic cancer and a germline BRCA2 mutation
- *Key Recent Publications and Presentations*

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Case Presentation – Dr Dayyani: A 59-year-old man with advanced HCC

Dr Farshid Dayyani

- PMH: Treated Hepatitis C, cirrhosis, esophageal varices, UGIB (2012) and liver lesions consistent with HCC
- 10/2016: Presents with abdominal pain and thought to have hemoperitoneum from HCC rupture
  - Ascites, elevated bilirubin
- 11/2016 imaging: Viable tumor in segment 4
- 12/2016: TACE, with PR → 1/2017: Repeat TACE
- 3/2018 CT abdomen: Numerous larger lesions
- 9/2018: Enrolled on IMbrave 150 and received atezolizumab/bevacizumab → SD x 12 months
  - Proteinuria after 16 cycles; bevacizumab held
- 2/2020: Came off trial due to recurrent grade 3 proteinuria with bevacizumab

Questions

- For a patient who had atezolizumab/bevacizumab but didn't tolerate it, he's technically TKI naïve. Do I switch him to a TKI given the fact that he had proteinuria? Or, do we continue on one of the approved checkpoint inhibitors?

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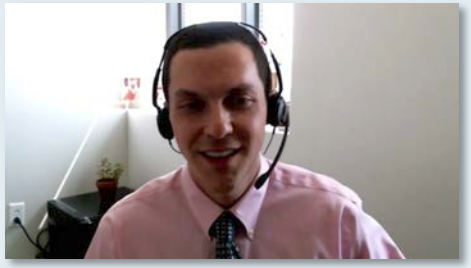
Case Presentation – Dr Lorber: An 80-year-old woman with unresectable advanced HCC



Dr Jeremy Lorber

- Diagnosed with unresectable HCC after presenting with right upper quadrant pain, pleural effusion, and weight loss
- Imaging reveals a 15-cm primary liver tumor and smaller satellite nodules
- Atezolizumab/bevacizumab with initial response and then stable disease for 9 months before experiencing symptomatic progression
- Lenvatinib initiated but discontinued due to issues with stomatitis, nausea, and skin ulcerations
- Currently receiving treatment with dose-reduced cabozantinib and tolerating treatment well

Questions

- With atezolizumab with bevacizumab approved in the first line, where does that leave the other available therapies? Which treatment is best to use second line?
- Is there a way to distinguish between atezolizumab/bevacizumab and nivolumab/ipilimumab as first-line therapy options?

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What would be your second-line therapy for a 65-year-old patient with HCC, a Child-Pugh A score and PS 0 who received first-line atezolizumab/bevacizumab and experienced disease progression after 18 months (AFP 2,500 ng/mL)?

1. Cabozantinib
2. Lenvatinib
3. Anti-PD-1 antibody
4. Nivolumab/ipilimumab
5. Ramucirumab
6. Regorafenib
7. Sorafenib
8. Other

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Key Recent Publications and Presentations

- Finn RS et al. **IMbrave150: Updated Overall Survival (OS) Data from a Global, Randomized, Open-Label Phase III Study of Atezolizumab (atezo) + Bevacizumab (bev) versus Sorafenib (sor) in Patients (pts) with Unresectable Hepatocellular Carcinoma (HCC).** Gastrointestinal Cancers Symposium 2021;Abstract 267.
- Ren Z et al. **Sintilimab plus Bevacizumab Biosimilar vs Sorafenib as First-Line Treatment for Advanced Hepatocellular Carcinoma (ORIENT-32).** ESMO Asia 2020;Abstract LBA2.
- El-Khoueiry AB et al. **Nivolumab (NIVO) plus Ipilimumab (IPI) Combination Therapy in Patients (Pts) with Advanced Hepatocellular Carcinoma (aHCC): Long-Term Results from CheckMate 040.** Gastrointestinal Cancers Symposium 2021;Abstract 269.

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IMbrave150: Updated Overall Survival (OS) Data from a Global, Randomized, Open-Label Phase III Study of Atezolizumab (atezo) + Bevacizumab (bev) versus Sorafenib (sor) in Patients (pts) with Unresectable Hepatocellular Carcinoma (HCC)

Finn RS et al.

Gastrointestinal Cancers Symposium 2021;Abstract 267.

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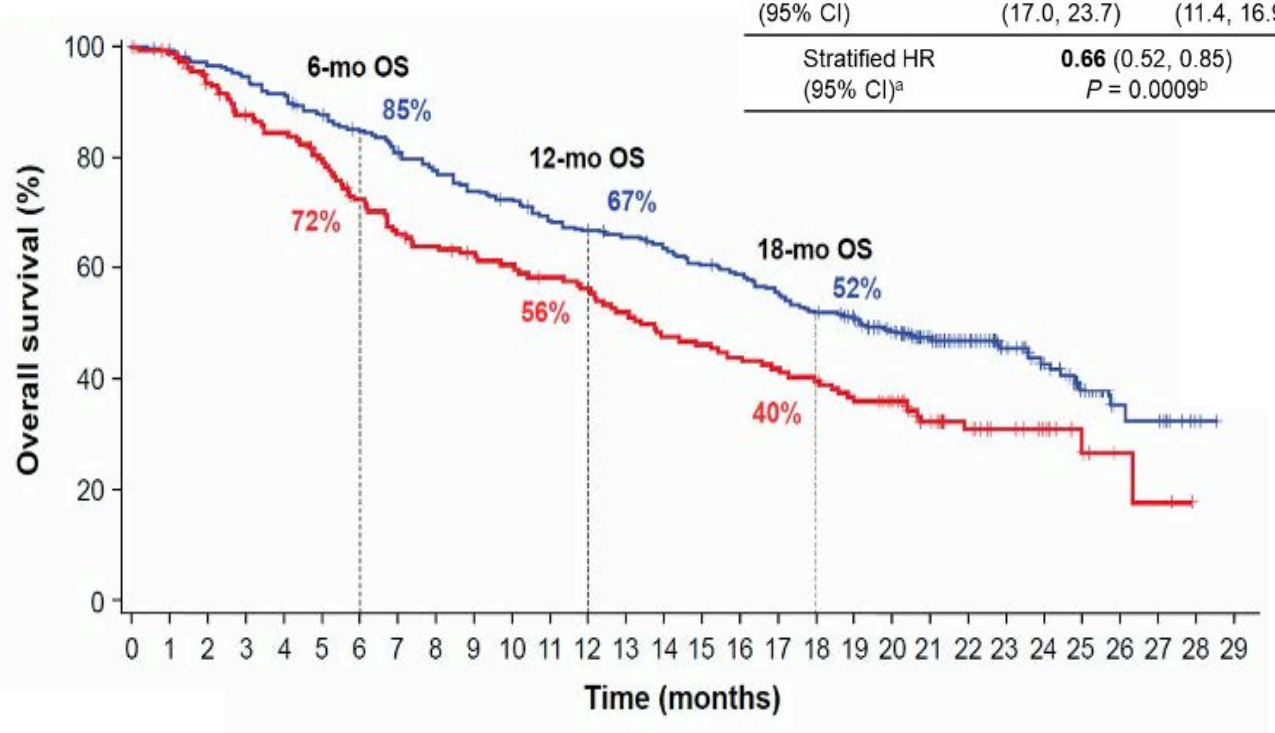
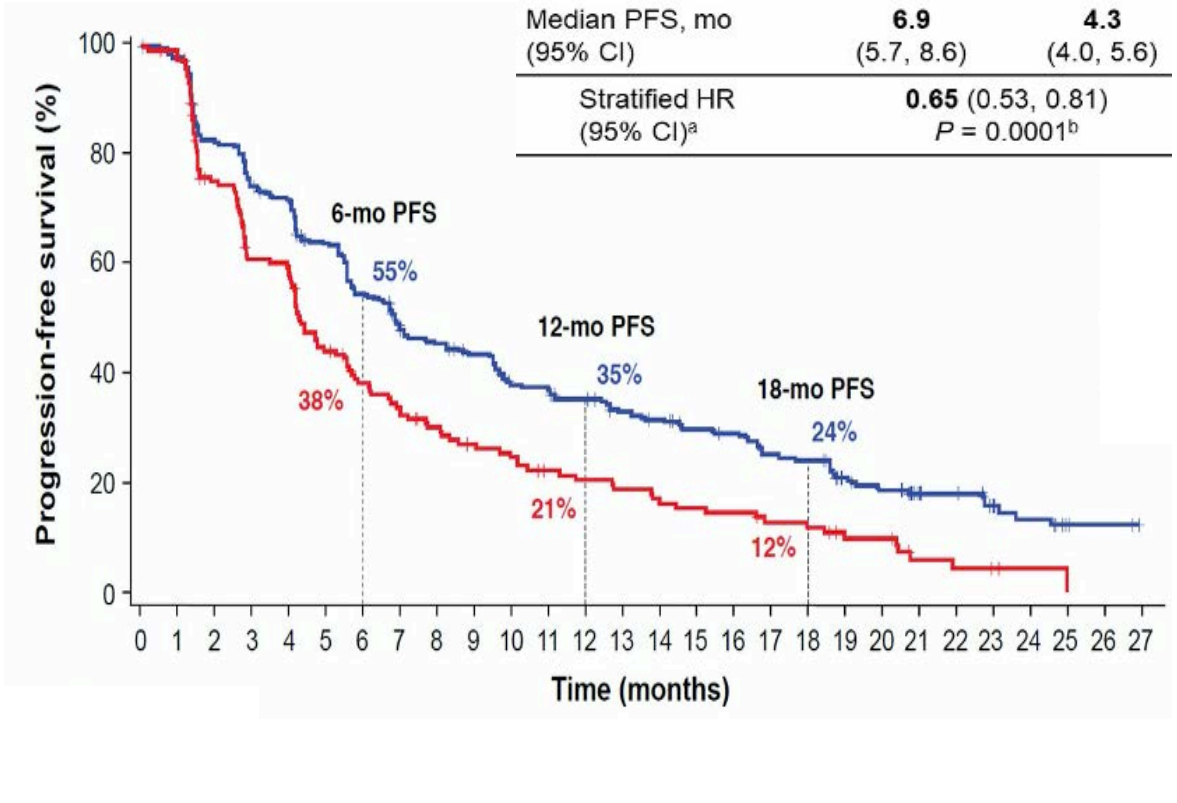
IMbrave150: Updated OS and PFS (Median Follow-Up 15.6 Months)

Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) $P = 0.0009^b$	



Updated PFS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
PFS events, n (%)	257 (76)	130 (79)
Median PFS, mo (95% CI)	**6.9** (5.7, 8.6)	**4.3** (4.0, 5.6)
Stratified HR (95% CI)[a]	**0.65** (0.53, 0.81) $P = 0.0001^b$	



Finn RS et al. Gastrointestinal Cancers Symposium 2021;Abstract 267.

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Sintilimab plus Bevacizumab Biosimilar vs Sorafenib as First-Line Treatment for Advanced Hepatocellular Carcinoma (ORIENT-32)

Ren Z et al. ESMO Asia 2020;Abstract LBA2.

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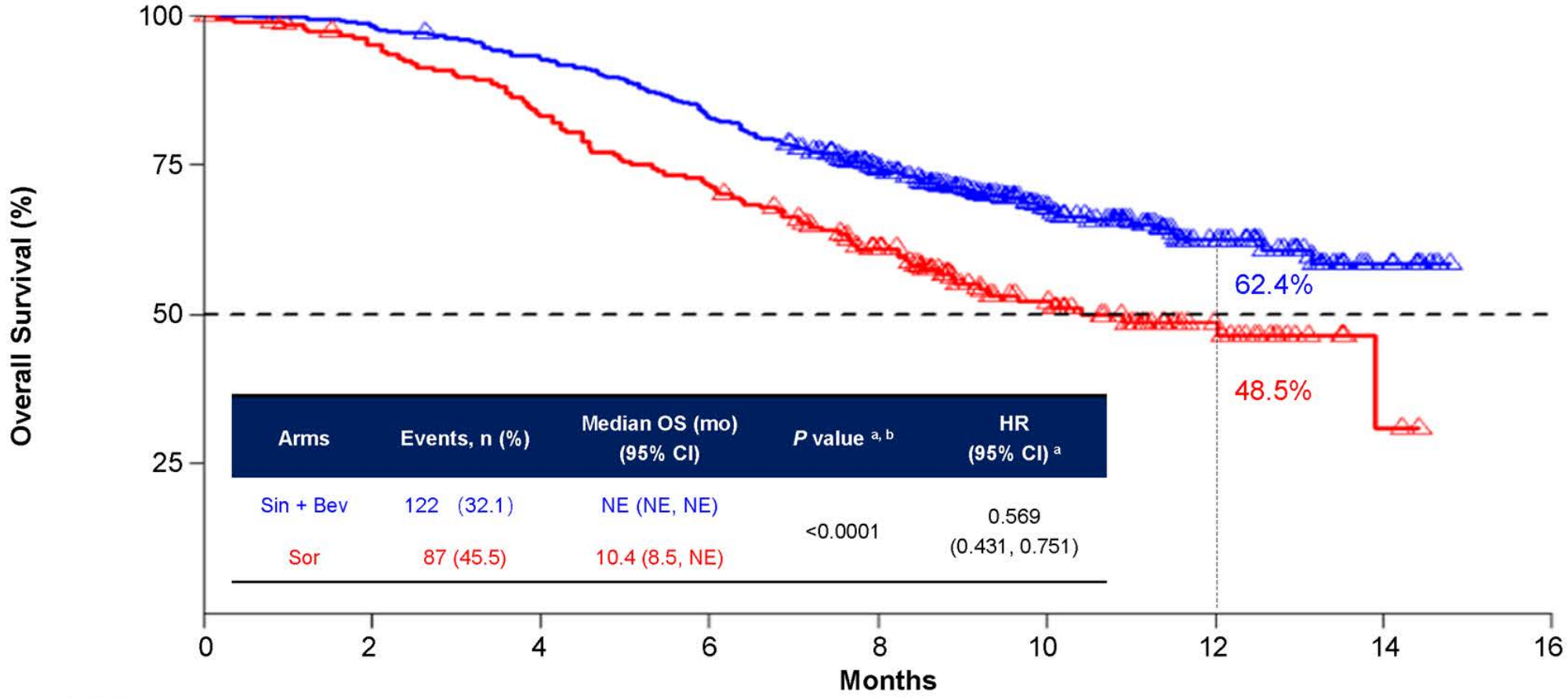
ORIENT-32 Coprimary Endpoint: Overall Survival



Arms	Events, n (%)	Median OS (mo) (95% CI)	*P* value [a, b]	HR (95% CI) [a]
Sin + Bev	122 (32.1)	NE (NE, NE)	<0.0001	0.569 (0.431, 0.751)
Sor	87 (45.5)	10.4 (8.5, NE)		

Number at risk									
Sin + Bev	380	372	351	314	235	126	57	11	0
Sor	191	175	153	132	95	50	22	2	0

NE, not evaluable; [a], HR and *P* value were calculated with stratified Cox model and log rank test, and were stratified by MVI and/or EHS (yes vs no), baseline AFP (< 400 vs ≥400 ng/mL) and ECOG PS (0 vs 1); [b], the two-sided *P* value boundary based on 209 events is 0.0035. Data cutoff, 15 Aug 2020; median survival follow-up, 10.0 months.

The superior OS benefit with sintilimab plus bev biosimilar was generally consistent across all subgroups

Ren Z et al. ESMO Asia 2020;Abstract LBA2.

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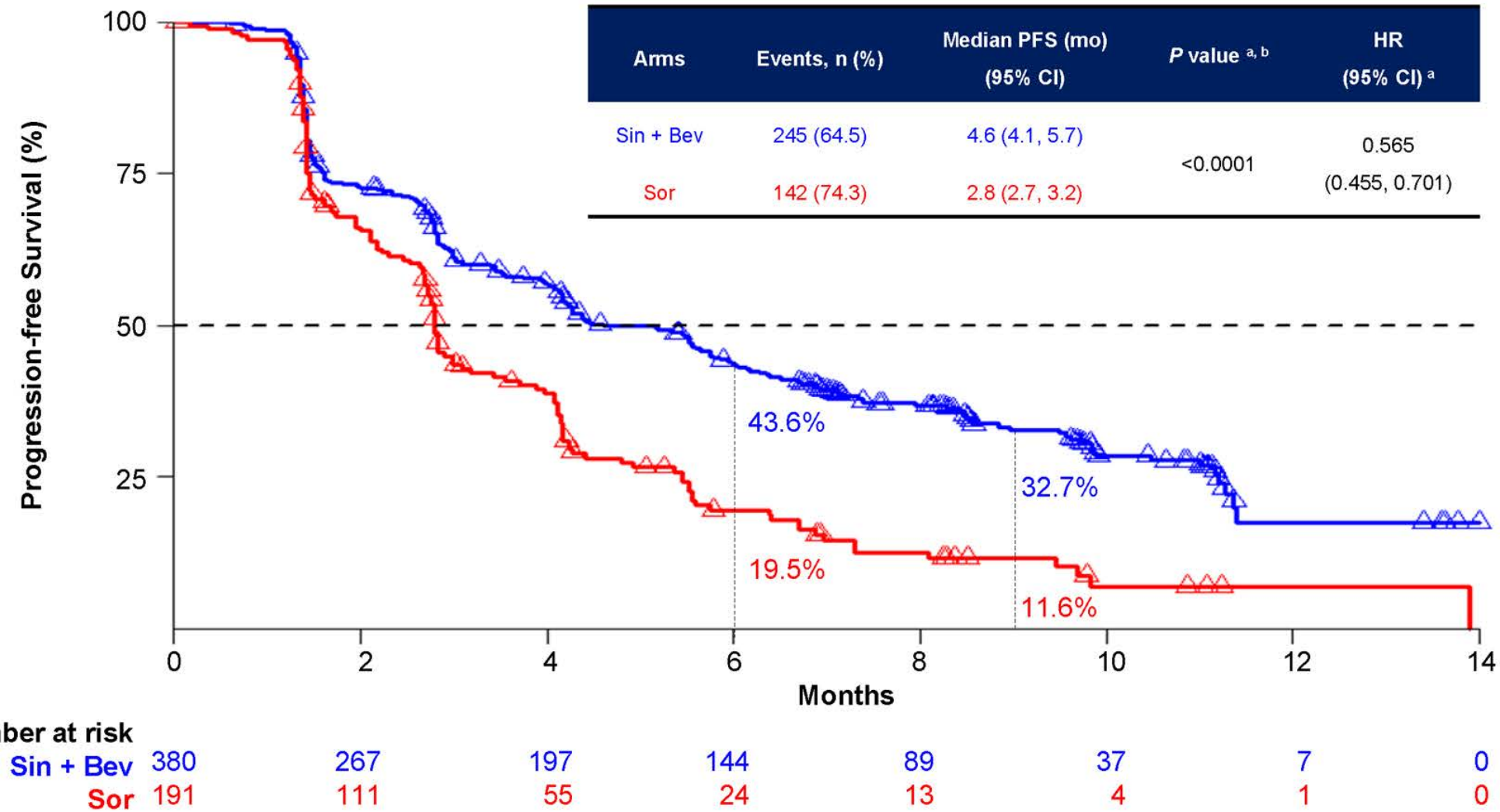
ORIENT-32 Coprimary Endpoint: Progression-Free Survival



Arms	Events, n (%)	Median PFS (mo) (95% CI)	*P* value [a, b]	HR (95% CI) [a]
Sin + Bev	245 (64.5)	4.6 (4.1, 5.7)	<0.0001	0.565 (0.455, 0.701)
Sor	142 (74.3)	2.8 (2.7, 3.2)		

[a], HR and *P* value were calculated with stratified Cox model and log rank test, and were stratified by MVI and/or EHS (yes vs no), baseline AFP (< 400 vs ≥400 ng/mL) and ECOG PS (0 vs 1); [b], the two-sided *P* value boundary is 0.002. Data cutoff, 15 Aug 2020; median survival follow-up, 10.0 months.

The superior PFS benefit with sintilimab plus bev biosimilar was generally consistent across all subgroups

Ren Z et al. ESMO Asia 2020;Abstract LBA2.

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FDA Grants Accelerated Approval to Nivolumab and Ipilimumab Combination for HCC

Press Release – March 10, 2020

"On March 10, 2020, the Food and Drug Administration granted accelerated approval to the combination of nivolumab and ipilimumab for patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Efficacy of the combination was investigated in Cohort 4 of CHECKMATE-040, (NCT01658878) a multicenter, multiple cohort, open-label trial conducted in patients with HCC who progressed on or were intolerant to sorafenib. A total of 49 patients received nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for four doses, followed by single-agent nivolumab 240 mg every 2 weeks until disease progression or unacceptable toxicity.

The main efficacy outcome measures were overall response rate and duration of response as determined by blinded independent central review (BICR) using RECIST v1.1. ORR was 33% (n=16; 95% CI: 20, 48), with 4 complete responses and 12 partial responses. Response duration ranged from 4.6 to 30.5+ months, with 31% of responses lasting at least 24 months."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-and-ipilimumab-combination-hepatocellular-carcinoma

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Nivolumab (NIVO) plus Ipilimumab (IPI) Combination Therapy in Patients (Pts) with Advanced Hepatocellular Carcinoma (aHCC): Long-Term Results from CheckMate 040

El-Khoueiry AB et al.

Gastrointestinal Cancers Symposium 2021;Abstract 269.

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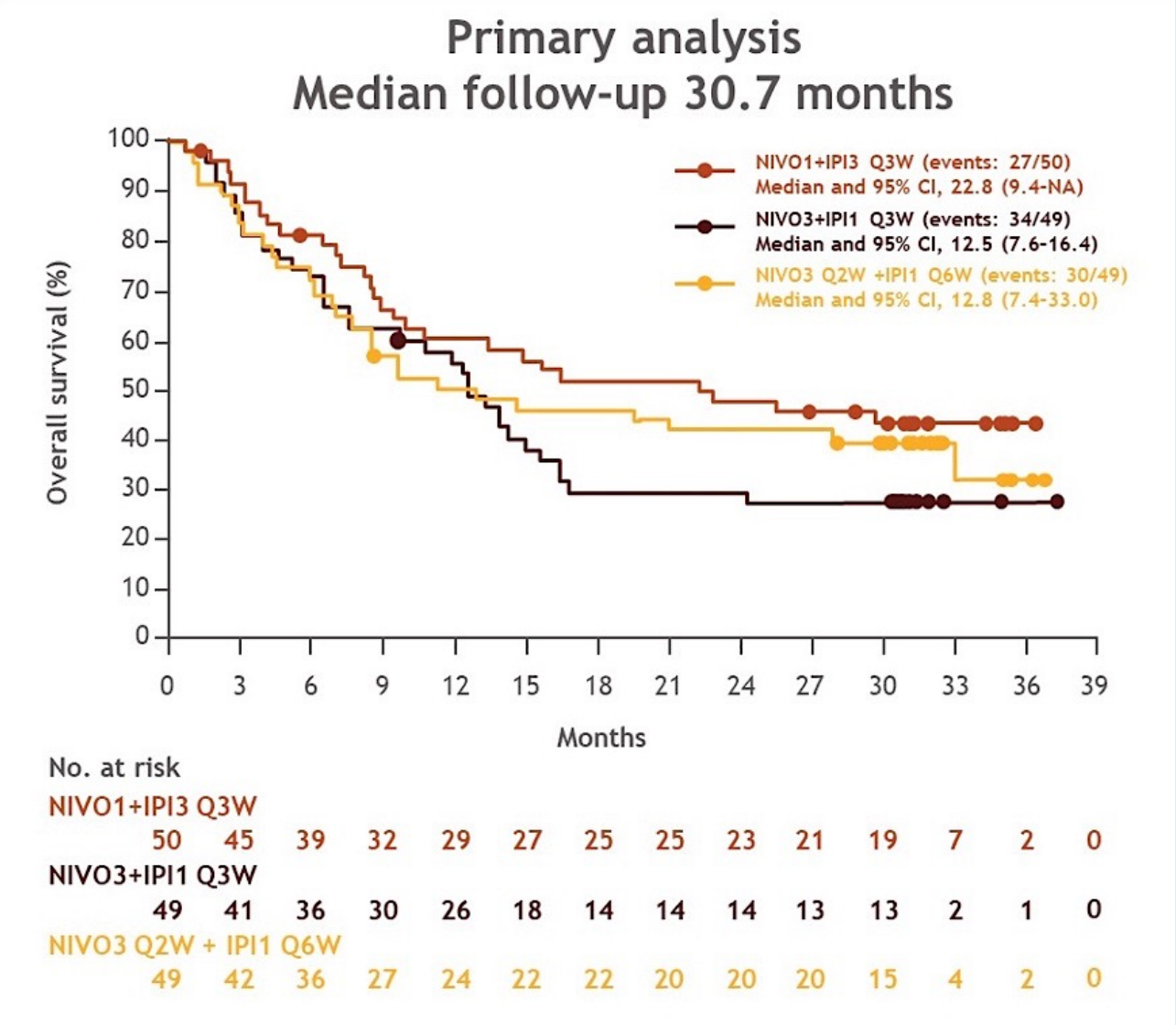
CheckMate 040: Updated Overall Survival with Ipilimumab/Nivolumab



El-Khoueiry AB et al. Gastrointestinal Cancers Symposium 2021;Abstract 269.

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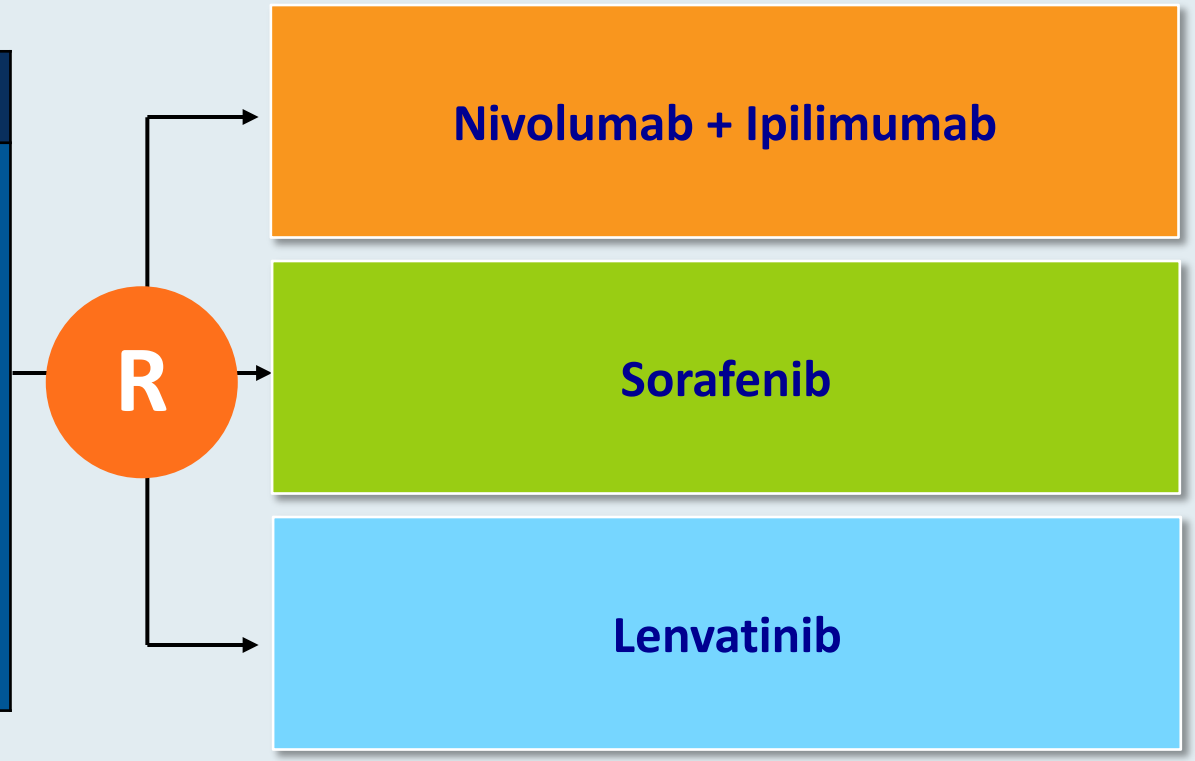
Ongoing Phase III CheckMate 9DW Trial Design

Key eligibility criteria (N = 650)

- Previously untreated advanced HCC
- Child-Pugh 5 or 6
- ECOG PS 0-1
- No active brain metastases or leptomeningeal metastases



Primary endpoint: Overall survival

Secondary endpoints: ORR, DoR and time to symptom deterioration

Clinicaltrials.gov/NCT04039607 (Accessed February 2021).

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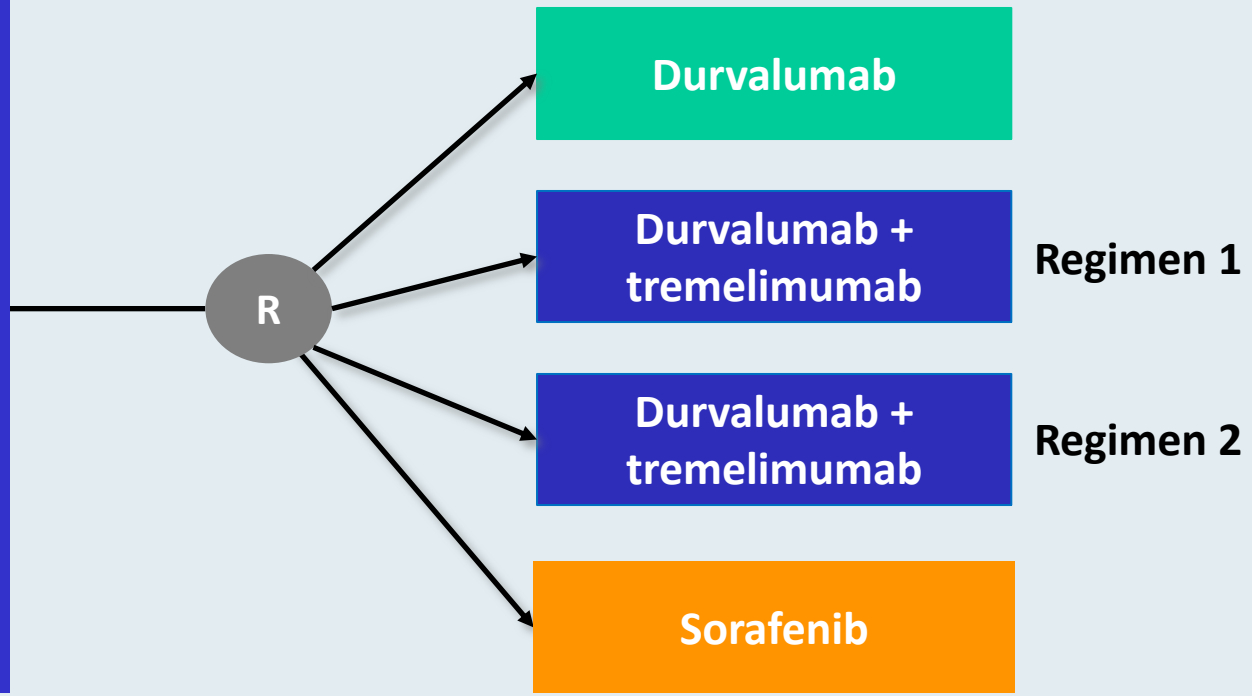
Ongoing Phase III HIMALAYA Trial Design

<u>Key eligibility criteria (N = 1,504)</u>

- Unresectable advanced HCC not eligible for LRTs
- BCLC stage B or C
- Child–Pugh A
- No prior systemic therapy



- **Primary endpoint: OS**
- **Other endpoints: TTP, PFS, ORR, DCR, DoR, and QoL**

Clinicaltrials.gov/NCT03298451 (Accessed February 2021).

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Agenda

Module 1: Colorectal Cancer

- Dr Lorber: A 74-year-old woman with MSI-high mCRC – BRAF V600E mutation
- *Key Recent Publications and Presentations*
- Dr Dayyani: A 60-year-old woman with MSS mCRC – TMB 35.4 mut/Mb, KRAS G12D mutation
- *Key Recent Publications and Presentations*

Module 2: Gastric, Gastroesophageal and Esophageal Cancers

- Dr Dayyani: A 60-year-old man with relapsed MSS esophageal squamous cell cancer – PD-L1 CPS 15
- *Key Recent Publications and Presentations*
- Dr Del Rosario: A 49-year-old woman with HER2-positive metastatic gastric adenocarcinoma – PD-L1 CPS 5
- *Key Recent Publications and Presentations*

Module 3: Hepatocellular Cancer (HCC)

- Dr Dayyani: A 59-year-old man with advanced HCC
- Dr Lorber: An 80-year-old woman with unresectable advanced HCC
- *Key Recent Publications and Presentations*

Module 4: Pancreatic Adenocarcinoma

- Dr Chen: An 80-year-old woman with localized pancreatic cancer
- Dr Dayyani: A 79-year-old woman with pancreatic cancer and a germline BRCA2 mutation
- *Key Recent Publications and Presentations*

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Case Presentation – Dr Chen: An 80-year-old woman with localized pancreatic cancer

Dr Gigi Chen

- Previously healthy woman presented with jaundice, elevated LFT and 10-pound weight loss; ultrasound showed pancreatic head mass, biliary dilatation, distended GB with sludge.
- Workup showed 22-mm hypoenhancing pancreatic head/uncinate process lesion and no additional sites of disease
- Germline genetic testing: negative
- Gemcitabine/*nab*-paclitaxel cycle 1 completed

Questions

- What is the benefit of neoadjuvant therapy followed by surgery versus up-front surgery followed by adjuvant chemotherapy? How would you sequence treatment for older patients?
- Which regimen would you generally recommend as neoadjuvant chemotherapy? Would it be FOLFIRINOX or gemcitabine/*nab*-paclitaxel?
- Would you recommend surgery or radiation for this patient after her neoadjuvant chemotherapy?
- If her tumor is found to have a somatic BRCA mutation or be HRD-positive, is there any data for PARP maintenance for early-stage patients?

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Case Presentation – Dr Dayyani: A 79-year-old woman with pancreatic cancer and a germline BRCA2 mutation

Dr Farshid Dayyani

- PMH: HTN, breast cancer with BRCA2 mutation, s/p surgery in the 1990s, hypothyroidism
- Early 2019: Severe lower back pain treated with steroid injections
- 6/2019 CT: 5 x 4 x 3-cm mass in the head of the pancreas
- Cytology: Adenocarcinoma
- FOLFOX x 8, with response, Grade 2 neuropathy
- Maintenance with olaparib 300 mg BID (dose reduced due to diarrhea) → SBRT
- 7/2020: Subtotal distal pancreatectomy with splenectomy and intraoperative RT
  - pT1a pN0

Questions

- Do you think there might be additional benefit of trying to further achieve a cytoreduction by PARP inhibition that might then enable a better resection, or R0 resection, for a patient?
- Is there a known synergy between radiation and PARP inhibitor therapy?

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Key Recent Publications and Presentations

- Kindler HL et al. **Maintenance Olaparib in Patients Aged ≥65 Years with a Germline BRCA Mutation and Metastatic Pancreatic Cancer: Phase III POLO Trial.** ESMO 2020;Abstract SO-3.
- Golan T et al. **Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer.** *N Engl J Med* 2019;381(4):317-27.
- Golan T et al. **Olaparib as Maintenance Treatment Following First-Line Platinum-Based Chemotherapy (PBC) in Patients with a Germline BRCA Mutation and Metastatic Pancreatic Cancer: Phase III POLO Trial.** ASCO 2019;Abstract LBA4.

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Therapeutic Approach: Advanced PDAC 2020

1st Line	2nd line	3rd line
Gemcitabine nab-paclitaxel	nal-IRI + 5-FU/LV	FOLFOX or Cape-Ox
(m)FOLFIRINOX	Gemcitabine +/- nab-paclitaxel	Nal-IRI + 5-FU/LV

Tumor Molecular Sequencing
Germline Testing

→ **Actionability**

Courtesy of Eileen M. O'Reilly, MD

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Maintenance Olaparib in Patients Aged ≥65 Years with a Germline BRCA Mutation and Metastatic Pancreatic Cancer: Phase III POLO Trial[1]

Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer[2]

Olaparib as Maintenance Treatment Following First-Line Platinum-Based Chemotherapy (PBC) in Patients with a Germline BRCA Mutation and Metastatic Pancreatic Cancer: Phase III POLO Trial[3]

[1] Kindler HL et al.
ESMO 2020;Abstract SO-3.

[2] Golan T et al.
N Engl J Med 2019;381(4):317-27.

[3] Kindler HL et al.
ASCO 2019;Abstract LBA4.

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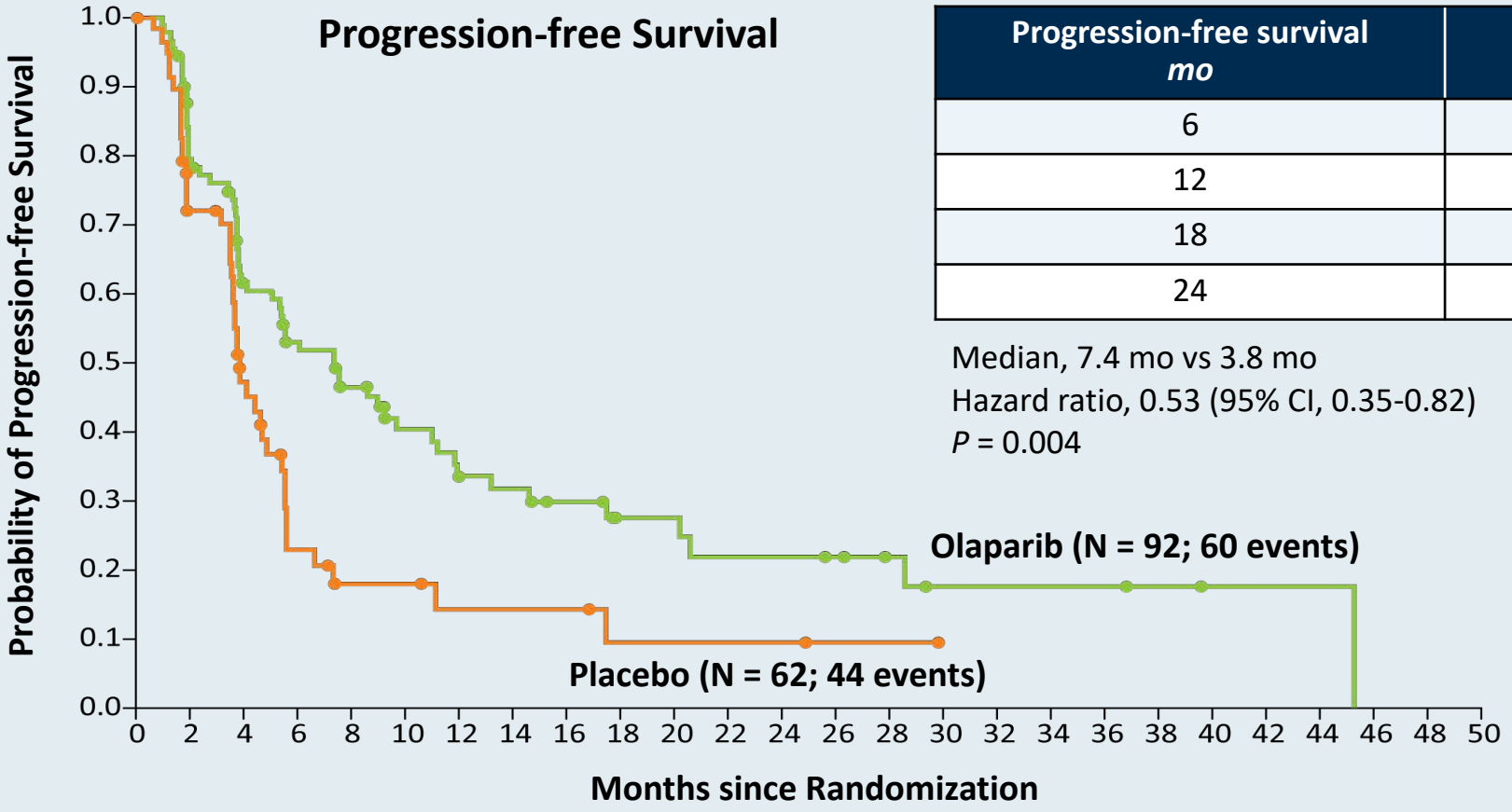
POLO: A Phase III Trial of Maintenance Olaparib for Metastatic Pancreatic Cancer with BRCA Mutation



Progression-free survival *mo*	Olaparib group	Placebo group
6	53.0%	23%
12	33.7%	14.5%
18	27.6%	9.6%
24	22.1%	9.6%

Median, 7.4 mo vs 3.8 mo
Hazard ratio, 0.53 (95% CI, 0.35-0.82)
P = 0.004

- An interim analysis of overall survival showed no difference between olaparib and placebo (median 18.9 mo vs 18.1 mo, HR 0.91, *p* = 0.68)
- The adverse-effect profile of maintenance olaparib was similar to that observed in other tumor types

Kindler HL et al. ESMO 2020;Abstract SO-3; Golan T et al. *N Engl J Med* 2019;381(4):317-27; Kindler HL et al. ASCO 2019;Abstract LBA4.

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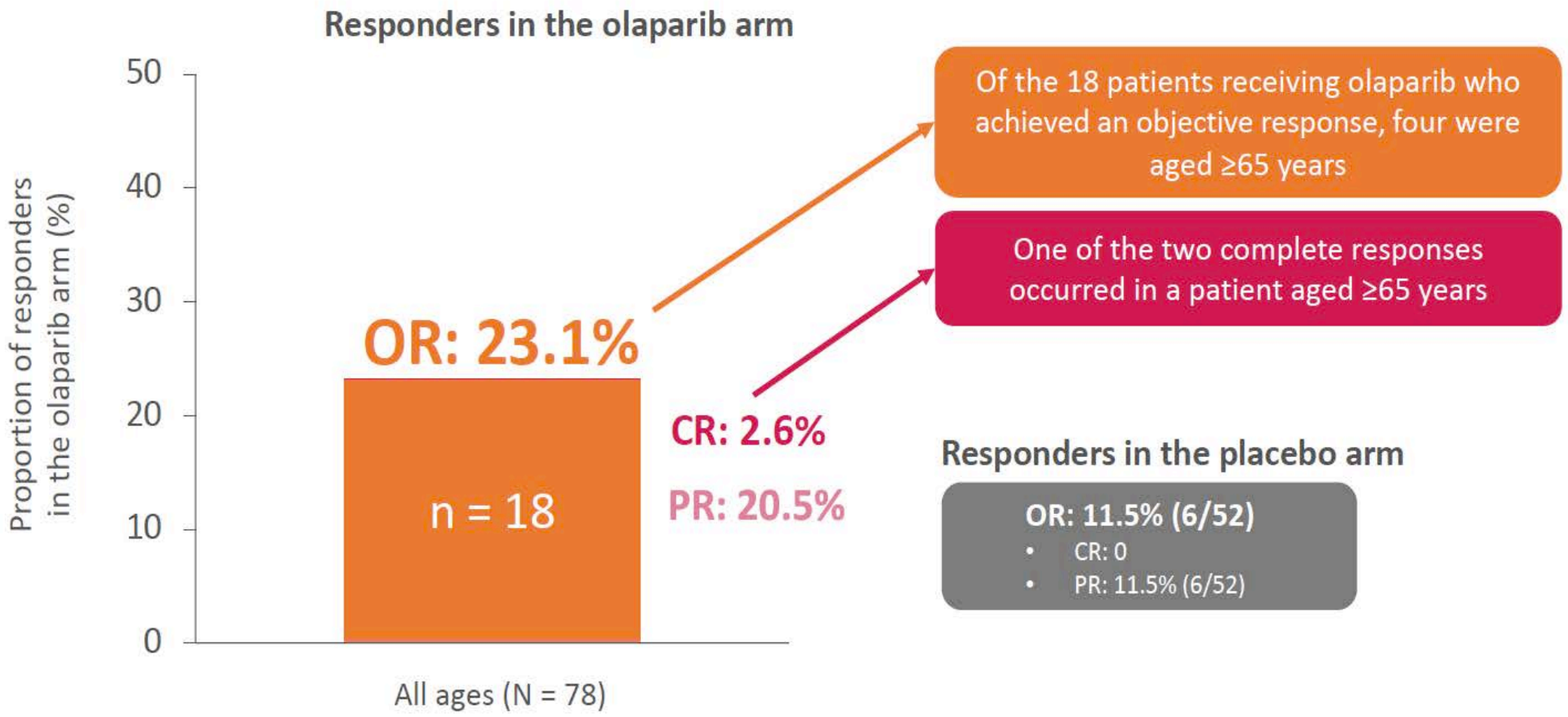
POLO: Patients Receiving Olaparib with an Objective Response (CR or PR)



Kindler HL et al. ESMO 2020;Abstract SO-3.

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Select Ongoing Trials of Olaparib in PAD

Trial (NCT#)	Phase	Target (N)	Setting	Treatment arms
SWOG-S2001 (NCT04548752)	II	88	Metastatic PAD; Germline BRCA1/2 mutation-positive; Received 1L platinum-based chemotherapy	• Olaparib + pembrolizumab • Olaparib
STUDY00019211 (NCT04005690)	I	14	Resectable, borderline resectable, locally advanced or metastatic PAD; Untreated or previously treated	• Cobimetinib • Olaparib

Clinicaltrials.gov; Accessed February 2021.

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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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Acute Myeloid Leukemia and Myelodysplastic Syndromes Faculty

Harry Paul Erba, MD, PhD
Director, Leukemia Program
Instructor in the Department of Medicine
Member of the Duke Cancer Institute
Duke University School of Medicine
Durham, North Carolina

Rami Komrokji, MD
Senior Member and Section Head for Leukemia and MDS
Vice Chair, Department of Malignant Hematology
Moffitt Cancer Center
Professor of Oncologic Sciences
Morsani College of Medicine, University of South Florida
Tampa, Florida

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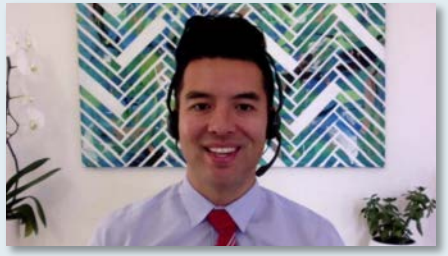
Contributing Oncologists

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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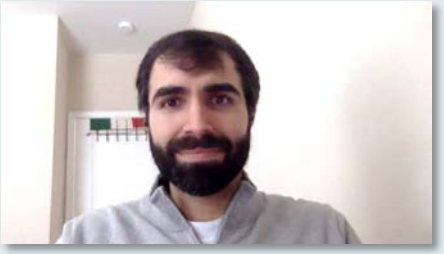
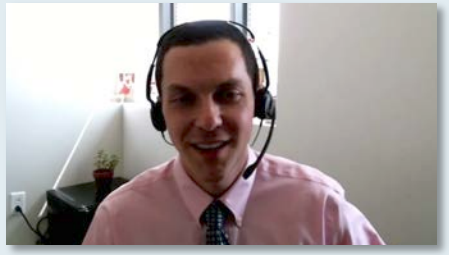
Contributing Oncologists



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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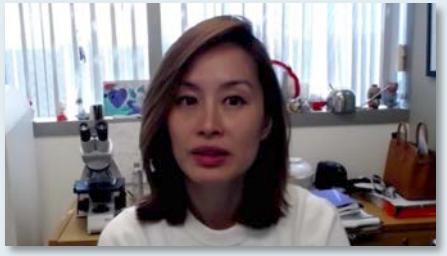
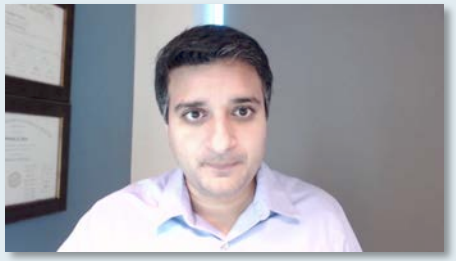
Contributing Oncologists

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: Myelodysplastic Syndromes (MDS)

- Dr Lorber: A 73-year-old man with MDS, ring sideroblasts and multilineage dysplasia
- *Key Recent Publications and Presentations*

Module 2: Newly Diagnosed Acute Myeloid Leukemia (AML)

- Dr Blackmon: A 40-year-old woman with newly diagnosed AML and a FLT3-TKD mutation
- *Key Recent Publications and Presentations*
- Dr Husain: A frail 85-year-old man with AML who received decitabine/venetoclax
- *Key Recent Publications and Presentations*

Module 3: Secondary AML

- Dr Husain: A 65-year-old man who develops AML while receiving therapy for metastatic NSCLC
- Dr Lorber: A 74-year-old otherwise healthy man with atrial fibrillation develops AML secondary to MDS
- *Key Recent Publications and Presentations*

Module 4: Relapsed/Refractory AML

- Dr Blackmon: A 46-year-old man with refractory AML and complex cytogenetics

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Agenda

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Case Presentation – Dr Lorber: A 73-year-old man with MDS, ring sideroblasts and multilineage dysplasia

Dr Jeremy Lorber

- Presented with months of progressive fatigue
- Pancytopenia – WBC: 4.0, Hgb: 8.3, PLT: 59K
- Bone marrow c/w MDS RS-MLD, blasts 3%, deletion 5q, monosomy 7, trisomy 8, loss of 17
- FISH: monosomy 5, deletion 7q, deletion 17p
- NGS: variant of TP53
- Decitabine, with complete normalization of counts
  - Referral for allogeneic SCT (not a candidate due to TP53)

Questions

- When his disease progresses, what would be the best treatment option for him in light of his high-risk MDS?
- What are the most promising agents in the pipeline for MDS? Is there a role for treating patients with MDS — either up front or at progression — with the addition of venetoclax, similar to an AML patient?

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Key Recent Publications and Presentations

- Garcia-Manero G et al. **Oral Cedazuridine/Decitabine for MDS and CMML: A Phase 2 Pharmacokinetic/Pharmacodynamic Randomized Crossover Study.** *Blood* 2020;136(6):674-83.
- Garcia-Manero G et al. **Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross-Over Phase 3 Study (ASCERTAIN) of an Oral Hypomethylating Agent ASTX727 (Cedazuridine/Decitabine) Compared to IV Decitabine.** ASH 2019;Abstract 846.
- Fenaux P et al. **Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes.** *N Engl J Med* 2020;382(2):140-51.
- Sallman D et al. **Tolerability and Efficacy of the First-in-Class Anti-CD47 Antibody Magrolimab Combined with Azacitidine in MDS and AML Patients: Phase Ib Results.** ASCO 2020;Abstract 7507.
- Ball BJ et al. **Venetoclax and Hypomethylating Agents (HMAs) Induce High Response Rates in MDS, Including Patients After HMA Therapy Failure.** *Blood Adv* 2020;4(13):2866-70.

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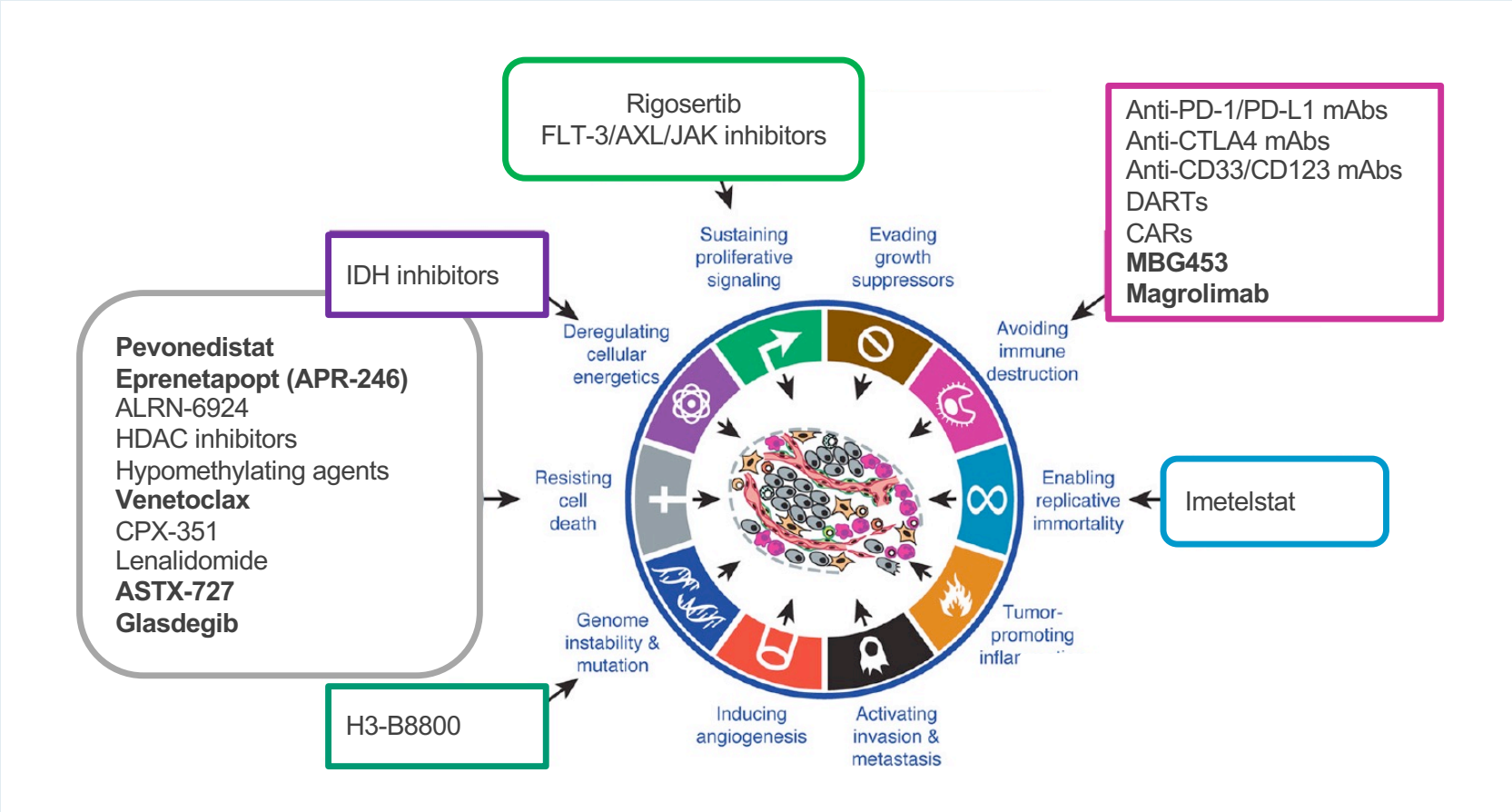
RESEARCH
TO PRACTICE

Treating MDS | Disease Biology



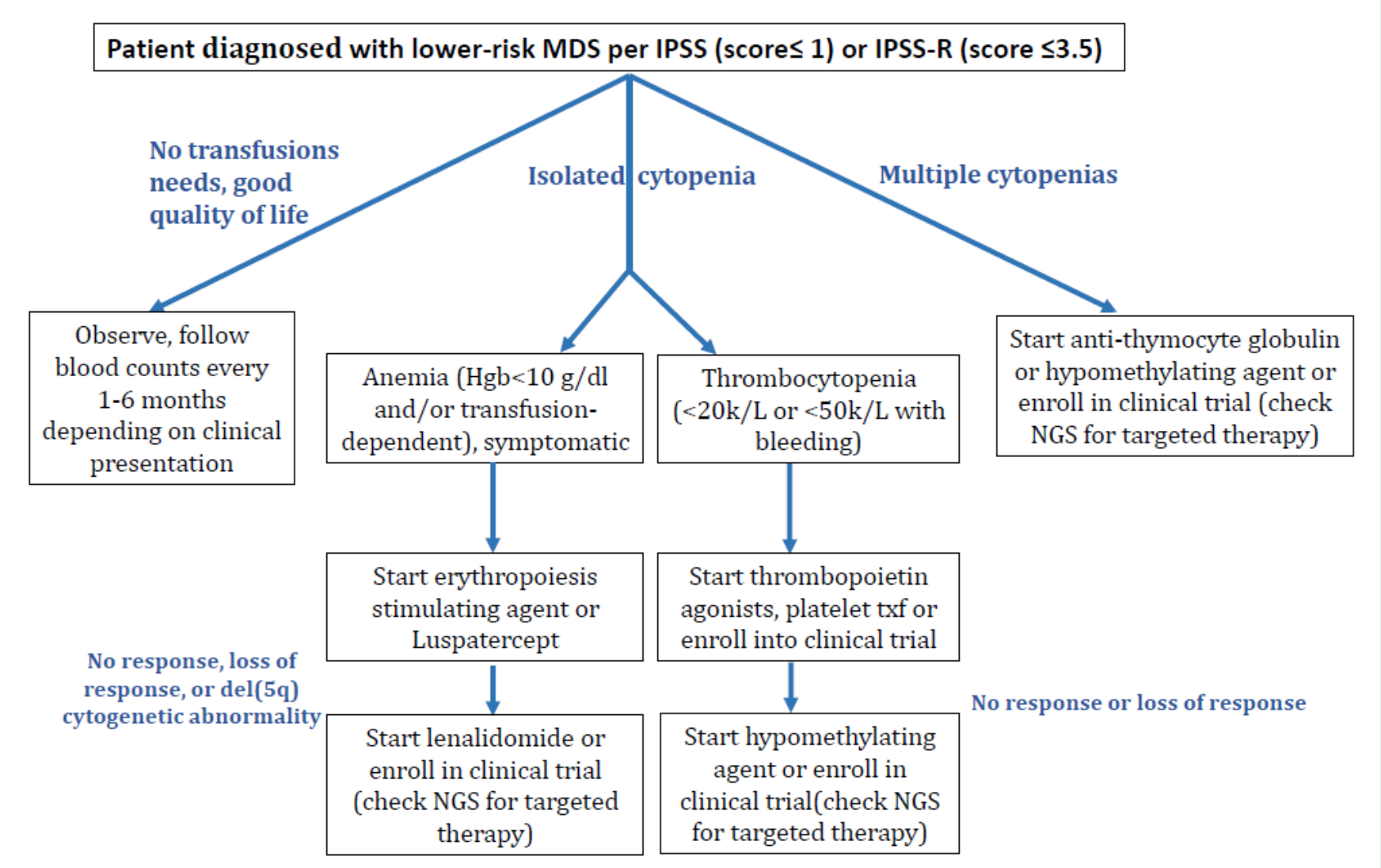
Courtesy of Mikkael A Sekeres, MD, MS

Figure adapted from Hanahan D, Weinberg RA. *Cell* 2011;144:646–74

BH3, bcl homology domain 3; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DARTs, dual affinity retargeting agents; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; mAb, monoclonal antibody; PARP, poly adenosine diphosphate ribose polymerase; VEGF, vascular endothelial growth factor

RTP RESEARCH TO PRACTICE

Treating MDS | Lower-Risk Disease



Sekeres and Patel Hematology (ASH Educ Book) 2019.

Courtesy of Mikkael A Sekeres, MD, MS

RTP RESEARCH TO PRACTICE

blood®
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study

Guillermo Garcia-Manero,[1] Elizabeth A. Griffiths,[2] David P. Steensma,[3] Gail J. Roboz,[4] Richard Wells,[5] James McCloskey II,[6] Olatoyosi Odenike,[7] Amy E. DeZern,[8] Karen Yee,[9] Lambert Busque,[10] Casey O'Connell,[11] Laura C. Michaelis,[12] Joseph Brandwein,[13] Hagop Kantarjian,[1] Aram Oganesian,[14] Mohammad Azab,[14] and Michael R. Savona[15]

Blood 2020;136(6):674-83.

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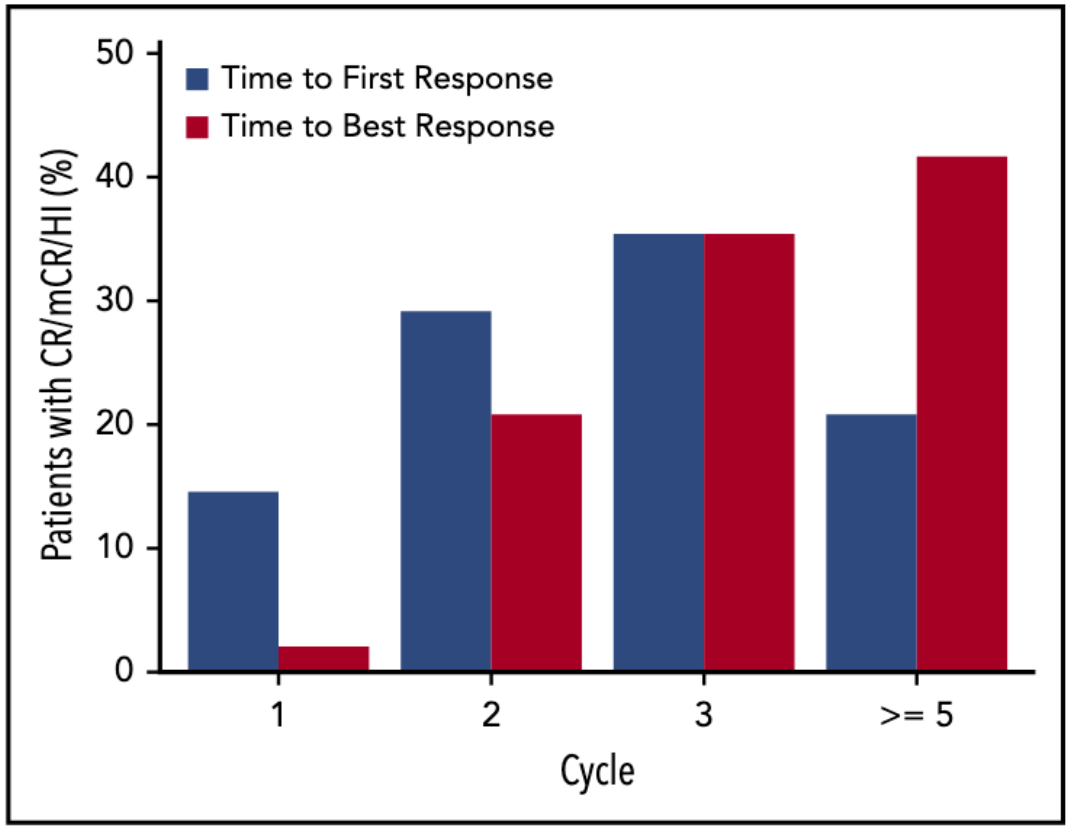
ASTX727-01-B: Response Summary

Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13-32
PR	0	
mCR	18 (22)	14-33
mCR with HI	6 (7)	3-16
HI	13 (16)	9-26
HI-E	8 (10)	4-19
HI-N	2 (2)	0-9
HI-P	11 (14)	7-23
Overall response* (CR + PR + mCR + HI)	48 (60)	48-71
No response	32 (40)	29-52

CR, complete response; HI, hematologic improvement; HI-E, erythroid response; HI-N, neutrophil response; HI-P, platelet response; mCR, marrow complete response; PR, partial response.

*Patients are counted only once with their best response as per the table hierarchy.



Garcia-Manero G et al. *Blood* 2020;136(6):674-83.

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ASTX727-01-B: Adverse Events

Preferred term, n (%)	IV decitabine cycle 1 or 2 (n = 75)	Oral cedazuridine/ decitabine cycle 1 or 2 (n =78)	All oral cedazuridine/ decitabine cycles (n = 78)
Patients with grade ≥3 TEAEs	44 (59)	45 (58)	65 (83)
Most common grade ≥3 TEAEs (≥10% of patients)			
Neutropenia	20 (27)	16 (21)	36 (46)
Thrombocytopenia	21 (28)	18 (23)	30 (38)
Febrile neutropenia	12 (16)	9 (12)	23 (29)
Leukopenia	8 (11)	7 (9)	19 (24)
Anemia	9 (12)	9 (12)	17 (22)
Pneumonia	5 (7)	7 (9)	10 (13)
Sepsis	1 (1)	4 (5)	8 (10)

Garcia-Manero G et al. *Blood* 2020;136(6):674-83.

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Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross-Over Phase 3 Study (ASCERTAIN) of an Oral Hypomethylating Agent ASTX727 (Cedazuridine/Decitabine) Compared to IV Decitabine

Garcia-Manero G et al.

ASH 2019;Abstract 846.

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ASCERTAIN: Primary Endpoint of Total 5-Day Decitabine AUC Equivalence

Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC		Oral ASTX727		Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
		N	Geo. LSM	N	Geo. LSM		
Primary Analysis	Paired[1]	123	864.9	123	855.7	98.9 (92.7, 105.6)	31.7

[1] Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All Sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

Garcia-Manero G et al. *ASH* 2019;Abstract .

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ASCERTAIN: Preliminary Response in MDS/CMML

	Evaluable Patients[1] N=101 n (%)
Complete response (CR)	12 (11.9%)
Partial response (PR)	0
Marrow CR (mCR)	46 (45.5%)
mCR with hematologic improvement	14 (13.9%)
Hematologic improvement (HI)	7 (5.3%)
HI-erythroid	2 (2.0%)
HI-neutrophils	1 (1.0%)
HI-platelet	6 (5.9%)
Overall response (CR + PR + mCR + HI)	65 (64.4%)
Stable disease	28 (27.7%)
Progressive disease	8 (7.9%)

[1] Due to short median follow up (~ 5 months) at data cutoff, 32 patients could not be evaluated for response by the Central IRC. Response was assessed by IWG 2006 criteria

Garcia-Manero G et al. *ASH* 2019;Abstract .

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

P. Fenaux, U. Platzbecker, G.J. Mufti, G. Garcia-Manero, R. Buckstein, V. Santini, M. Díez-Campelo, C. Finelli, M. Cazzola, O. Ilhan, M.A. Sekeres, J.F. Falantes, B. Arrizabalaga, F. Salvi, V. Giai, P. Vyas, D. Bowen, D. Selleslag, A.E. DeZern, J.G. Jurcic, U. Germing, K.S. Götze, B. Quesnel, O. Beyne-Rauzy, T. Cluzeau, M.-T. Voso, D. Mazure, E. Vellenga, P.L. Greenberg, E. Hellström-Lindberg, A.M. Zeidan, L. Adès, A. Verma, M.R. Savona, A. Laadem, A. Benzohra, J. Zhang, A. Rampersad, D.R. Dunshee, P.G. Linde, M.L. Sherman, R.S. Komrokji, and A.F. List

***N Engl J Med* 2020;382(2):140-51.**

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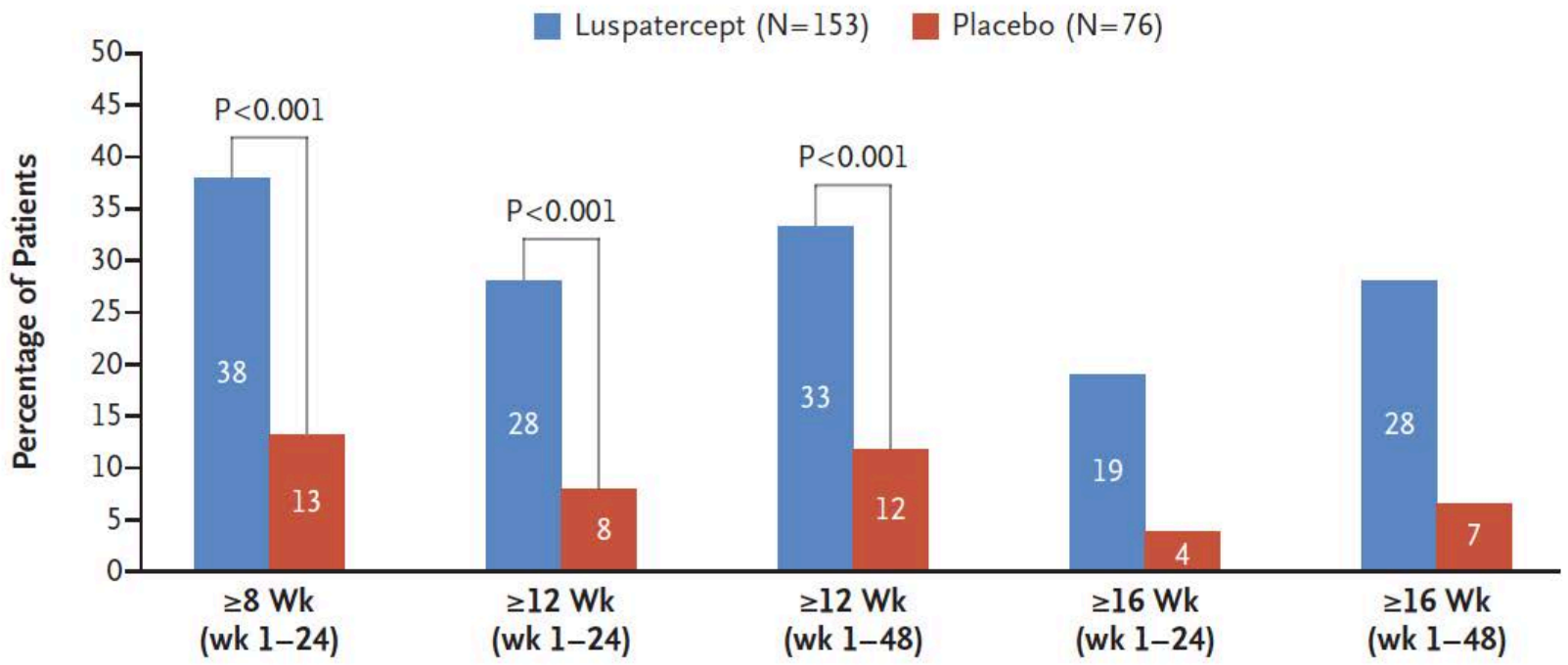
MEDALIST: Independence from Red-Cell Transfusion in Phase II Trial of Luspatercept



No. of Patients with Response (% [95% CI])					
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

Fenaux P et al. *N Engl J Med* 2020;382:140-51.

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Tolerability and Efficacy of the First-in-Class Anti-CD47 Antibody Magrolimab Combined with Azacitidine in MDS and AML Patients: Phase Ib Results

Sallman D et al.

ASCO 2020;Abstract 7507.

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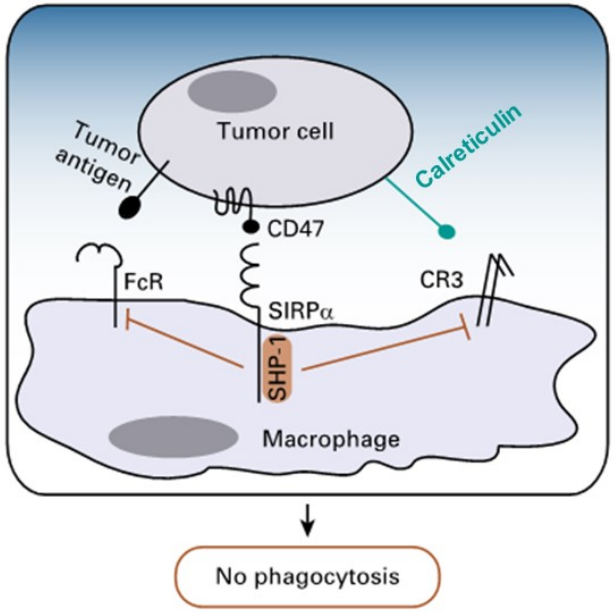
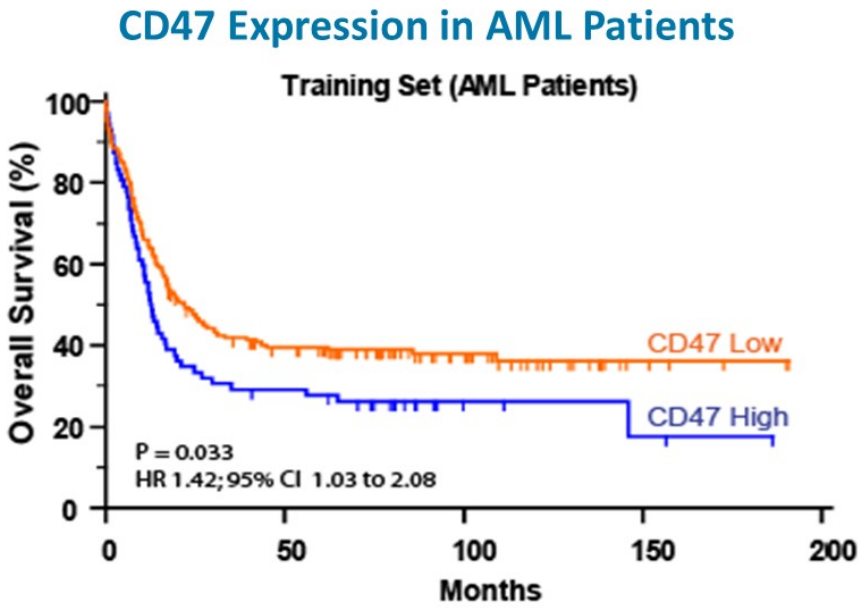
CD47 Is a Major Macrophage Immune Checkpoint and 'Do Not Eat Me' Signal in Myeloid Malignancies Including MDS and AML





- CD47 is a "do not eat me" signal on cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in AML patients

Figure at left adapted from Veillette A, Tang Z. *J Clin Onc*. 2019;37(12)1012-1014, and Chao MP, et al. *Current Opin Immunol*. 2012; 24(2):225-232.
Figure at right adapted from Majeti R, et al. *Cell*. 2009;138(2):286-299.

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Sallman D et al. ASCO 2020;Abstract 7507.

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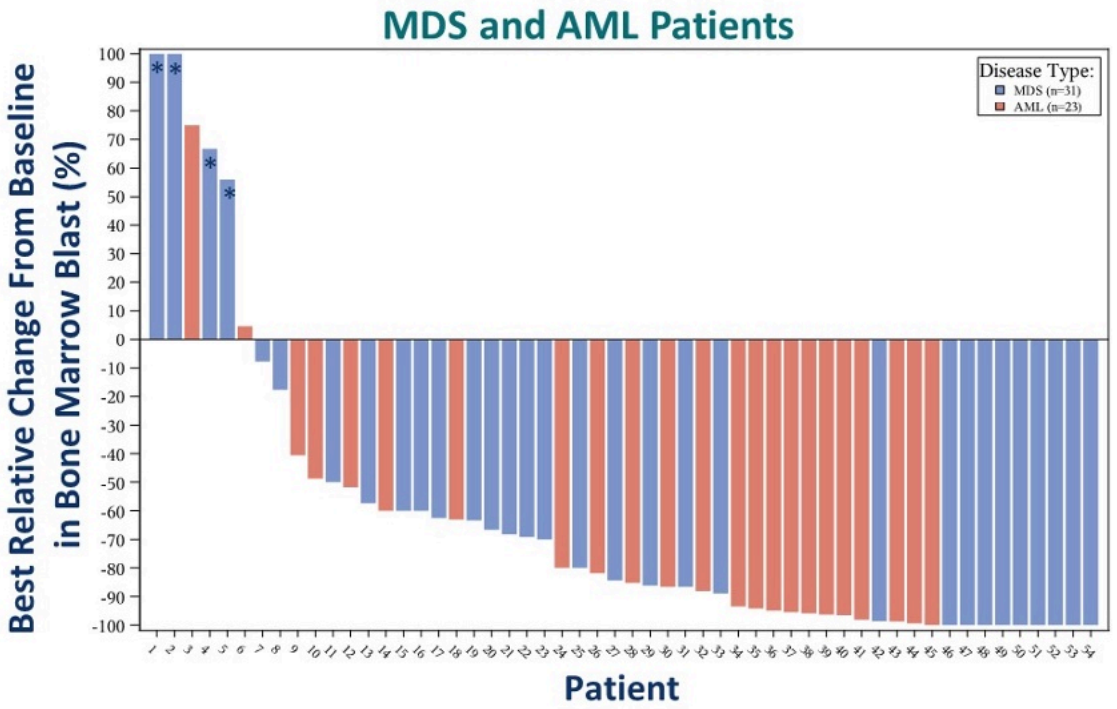
Magrolimab with Azacitidine Induces High Response Rates in MDS and AML

Best Overall Response	1L MDS N=33	1L AML N=25
ORR	30 (91%)	16 (64%)
CR	14 (42%)	10 (40%)
CRi	NA	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	NA
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML patients (1 AE, 2 early withdrawal).



Four patients not shown due to missing values; <5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

- Magrolimab + AZA induces a 91% ORR (42% CR) in MDS and 64% ORR (56% CR/CRi) in AML
- Responses deepened over time with a 56% 6-month CR rate in MDS patients (assessed in all patients 6 months after initial treatment)
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 6-17%[1,2])

1. Azacitidine USPI. 2. Fenaux P, et al. *Lancet Oncol.* 2009 ;10(3):223-232.

Sallman D et al. ASCO 2020;Abstract 7507.

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STIMULUS REPORT

blood advances

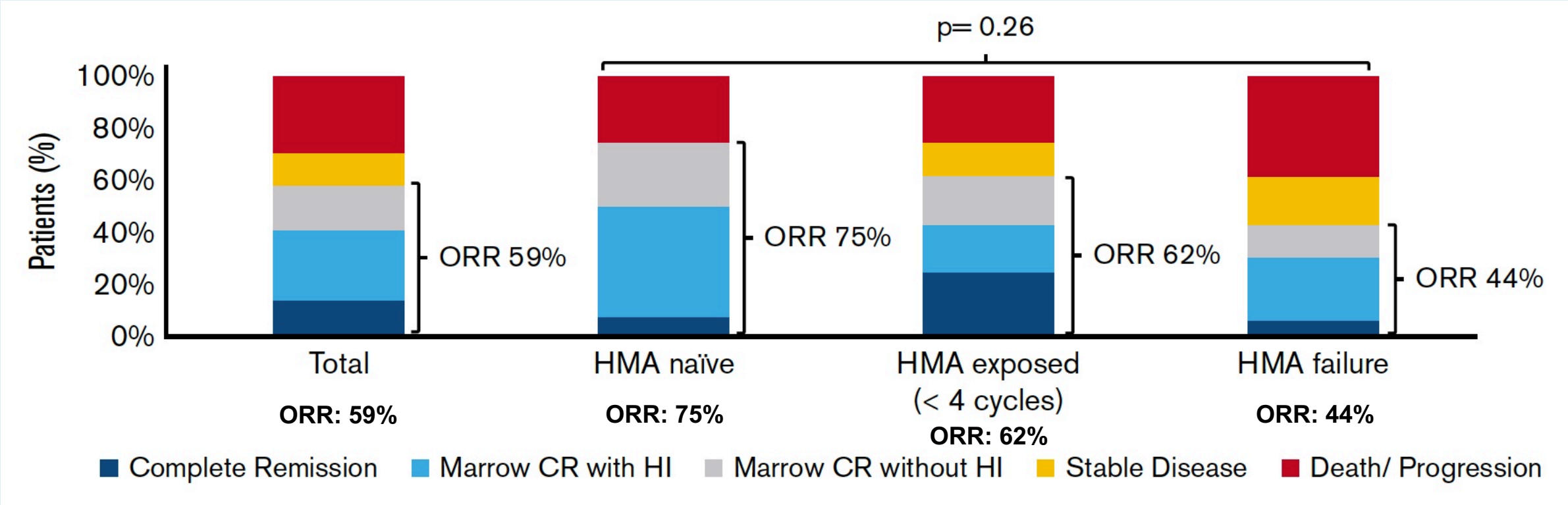
Venetoclax and hypomethylating agents (HMAs) induce high response rates in MDS, including patients after HMA therapy failure

Brian J. Ball,[1] Christopher A. Famulare,[2] Eytan M. Stein,[1] Martin S. Tallman,[1] Andriy Derkach,[3] Mikhail Roshal,[1] Saar I. Gill,[4] Benjamin M. Manning,[4] Jamie Koprivnikar,[5] James McCloskey,[5] Rebecca Testi,[5] Thomas Prebet,[6] Najla H. Al Ali,[7] Eric Padron,[7] David A. Sallman,[7] Rami S. Komrokji,[7,*] and Aaron D. Goldberg[1,*]

Blood Adv 2020;4(13):2866-70

RTP RESEARCH TO PRACTICE

Responses in Patients with MDS Receiving Venetoclax with a Hypomethylating Agent



Median OS: 19.5 months

Median OS with HMA failure: 11.4 months

Ball BJ et al. *Blood Adv* 2020;4(13):2866-70.

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Agenda

Module 1: Myelodysplastic Syndromes (MDS)

- Dr Lorber: A 73-year-old man with MDS, ring sideroblasts and multilineage dysplasia
- *Key Recent Publications and Presentations*

Module 2: Newly Diagnosed Acute Myeloid Leukemia (AML)

- Dr Blackmon: A 40-year-old woman with newly diagnosed AML and a FLT3-TKD mutation
- *Key Recent Publications and Presentations*
- Dr Husain: A frail 85-year-old man with AML who received decitabine/venetoclax
- *Key Recent Publications and Presentations*

Module 3: Secondary AML

- Dr Husain: A 65-year-old man who develops AML while receiving therapy for metastatic NSCLC
- Dr Lorber: A 74-year-old otherwise healthy man with atrial fibrillation develops AML secondary to MDS
- *Key Recent Publications and Presentations*

Module 4: Relapsed/Refractory AML

- Dr Blackmon: A 46-year-old man with refractory AML and complex cytogenetics

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Case Presentation – Dr Blackmon: A 40-year-old woman with newly diagnosed AML and a FLT3-TKD mutation

Dr Amanda Blackmon

- Presented with bruising and found to have pancytopenia and AML
- Bone marrow biopsy: FLT3-TKD mutation
- 7 + 3 induction therapy and midostaurin → CR

Questions

- Should we transplant this patient population?
- As more information becomes available regarding mutations and cytogenetics, will we have an updated risk stratification system?
- Is gilteritinib being used in front-line treatment? Is low FLT3-ITD an indication not to transplant a patient?
- If this patient were elderly with AML and a FLT3 mutation, what front-line approach for treatment would you recommend – Azacitidine/venetoclax plus a FLT3 inhibitor, or just a hypomethylating agent and FLT3 inhibitor?
- In elderly patients who have cytopenias from their AML, do you dose reduce the venetoclax? Would you decrease the number of days of the hypomethylating agent? Do you choose decitabine or azacitidine at the time of diagnosis?

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What would you recommend as first-line therapy to a 78-year-old patient (PS 0) who presents with intermediate-risk AML with a FLT3-ITD mutation?

1. Midostaurin
2. 7 + 3 induction + midostaurin
3. HMA + FLT3 inhibitor
4. HMA + venetoclax
5. HMA + venetoclax + FLT3 inhibitor
6. Low-dose cytarabine + venetoclax
7. Low-dose cytarabine + venetoclax + FLT3 inhibitor
8. Gilteritinib
9. Other

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Key Recent Presentations and Publications

- Perl AE et al. **Long-Term Survivors and Gilteritinib Safety Beyond One Year in *FLT3*-Mutated R/R AML: ADMIRAL Trial Follow-Up.** ASCO 2020;Abstract 7514.
- Stein EM et al. **Enasidenib Monotherapy Is Effective in Older Patients with Newly Diagnosed IDH2 Mutated Acute Myeloid Leukemia and Addition of Azacitidine Rescues Enasidenib Monotherapy Failures: A Phase 2/IB Study of the Beat AML Master Trial.** ASH 2020;Abstract 636.
- DiNardo CD et al. **Mutant Isocitrate Dehydrogenase 1 Inhibitor Ivosidenib in Combination with Azacitidine for Newly Diagnosed Acute Myeloid Leukemia.** *J Clin Oncol* 2021;39(1):57-65.

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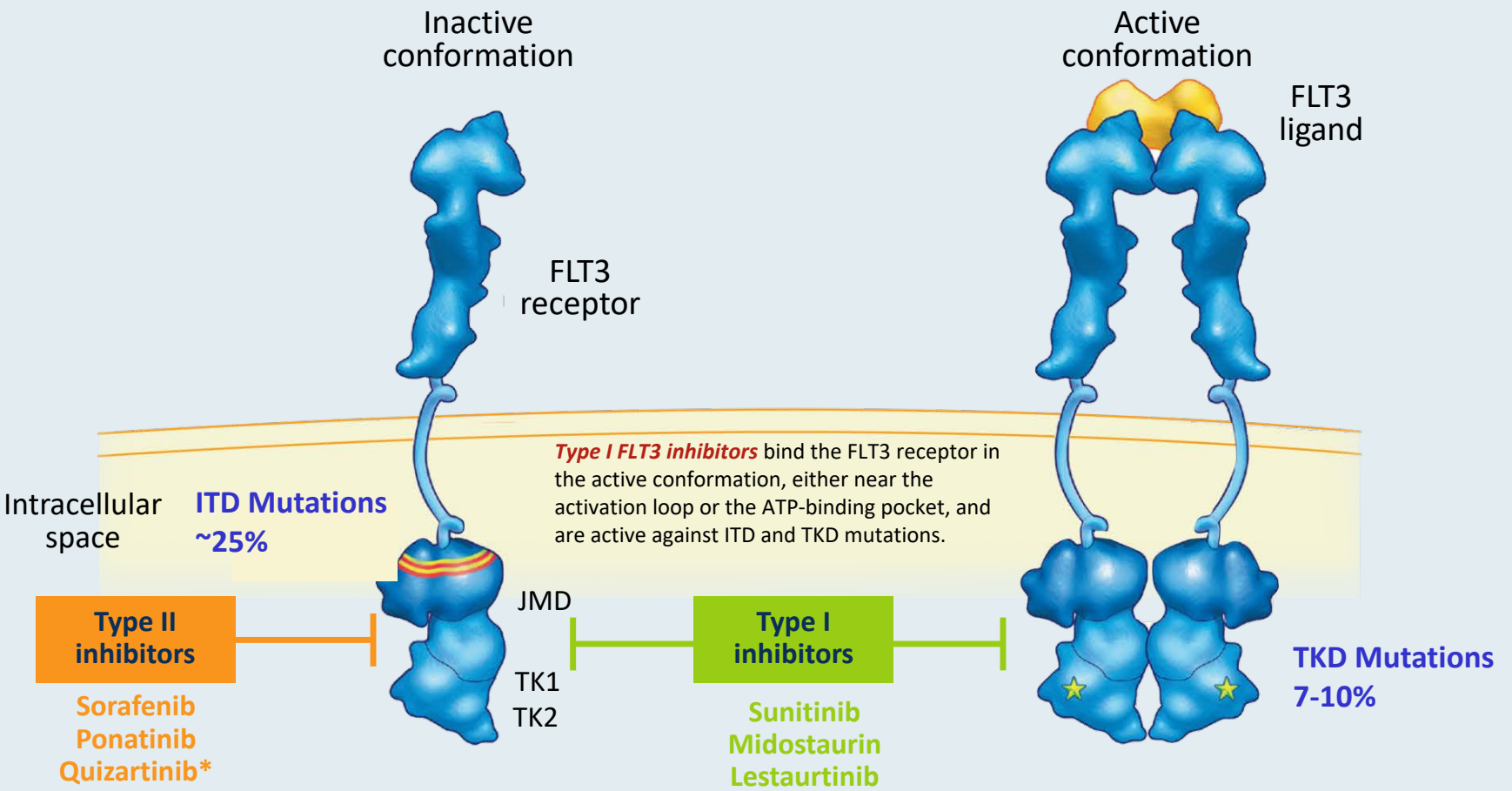
TO PRACTICE

FLT3 Mutations (ITD and TKD) Occur in Approximately 30% to 35% of Patients with AML



Type II FLT3 inhibitors bind the FLT3 receptor in the inactive conformation in a region adjacent to the ATP-binding domain.

* Second-generation FLT3 inhibitors

Daver N et al. *Leukemia* 2019;33:299-312.

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Long-Term Survivors and Gilteritinib Safety Beyond One Year in *FLT3*-Mutated R/R AML: ADMIRAL Trial Follow-Up

Perl AE et al.

ASCO 2020;Abstract 7514

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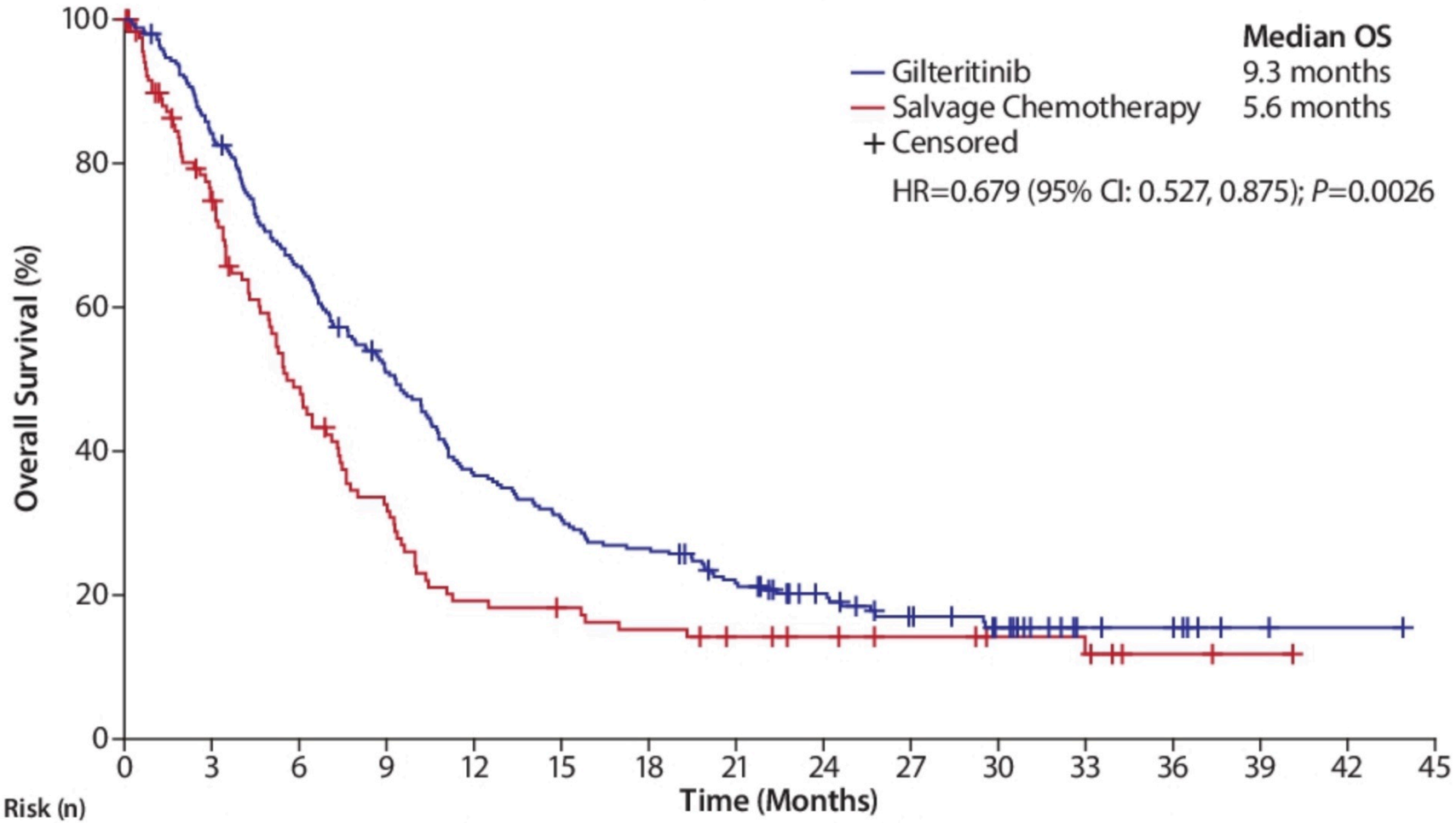
ADMIRAL: Overall Survival at 1 Year After the Primary Analysis



Patients at Risk (n)															
Gilteritinib	247	206	158	121	87	73	63	48	33	24	17	8	7	2	1	0
Salvage Chemotherapy	124	84	52	34	20	18	15	12	10	8	6	5	2	1	0	0

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Perl AE et al. ASCO 2020;Abstract 7514.

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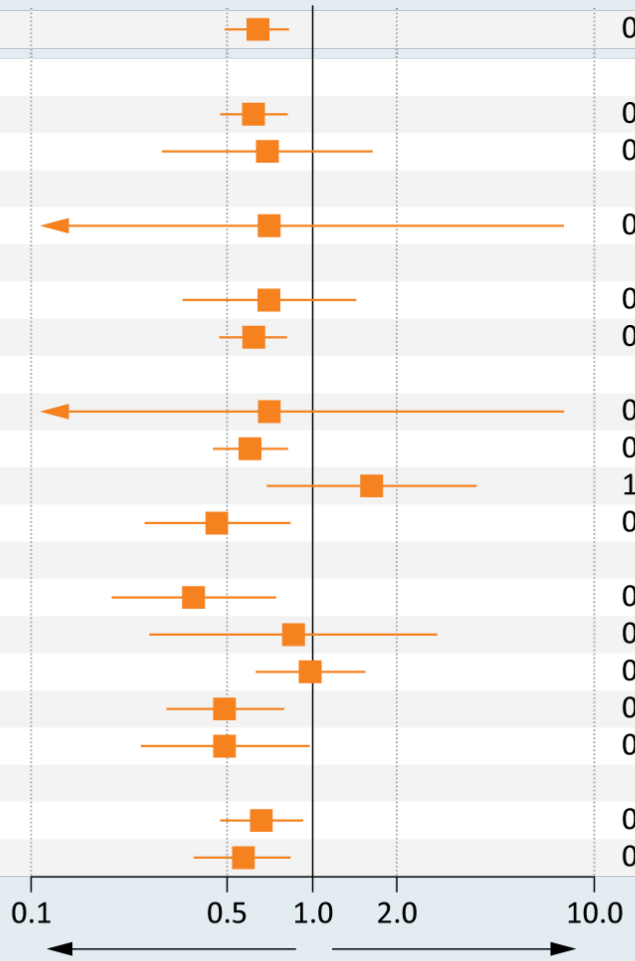
ADMIRAL: Subgroup Analysis of Overall Survival

Subgroup	Gilteritinib	Salvage Chemotherapy	Hazard Ratio for Death
	no. of events/total no. of patients		
All patients	171/247	90/124	0.64
FLT3 mutation type			
FLT3 ITD alone	145/215	81/113	0.62
FLT3 TKD alone	16/21	8/10	0.69
FLT3 ITD and FLT3 TKD	6/7	0	NE
Other	4/4	1/1	0.70
Previous use of FLT3 inhibitor			
Yes	26/32	11/14	0.70
No	145/215	79/110	0.62
Cytogenetic risk status			
Favorable	3/4	1/1	0.70
Intermediate	119/182	63/89	0.60
Unfavorable	22/26	7/11	1.63
Unknown	27/35	19/23	0.46
Response to first-line therapy per IRT			
Relapse ≤6 mo after allogeneic HSCT	24/31	16/17	0.38
Relapse >6 mo after allogeneic HSCT	10/17	4/8	0.86
Primary refractory disease without HSCT	70/98	28/48	0.99
Relapse ≤6 mo after composite complete remission and no HSCT	47/67	28/34	0.49
Relapse >6 mo after composite complete remission and no HSCT	20/34	14/17	0.49
Preselected chemotherapy per IRT			
High intensity	96/149	52/75	0.66
Low intensity	75/98	38/49	0.56



Perl AE et al. *N Engl J Med* 2019;381:1728-40.

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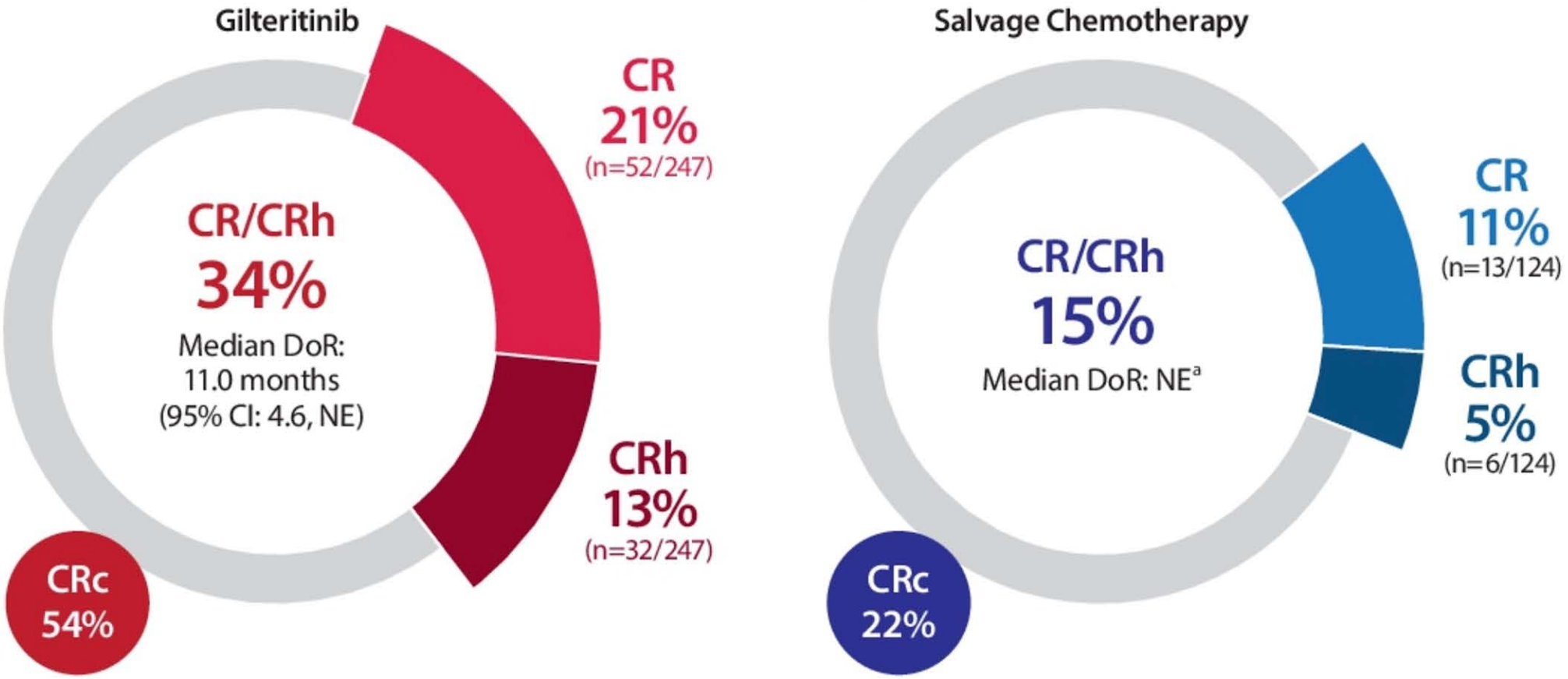
ADMIRAL: Response Rates



CRc was defined as the sum of the patients who achieved CR and those who achieved CR without incomplete hematologic or platelet recovery.

[a]Duration of CR/CRh was not estimable due to the high dropout rate after the second cycle of treatment.

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; DoR, duration of response; mut+, mutated; NE, not estimable; R/R, relapsed or refractory.

Perl AE et al. ASCO 2020;Abstract 7514.

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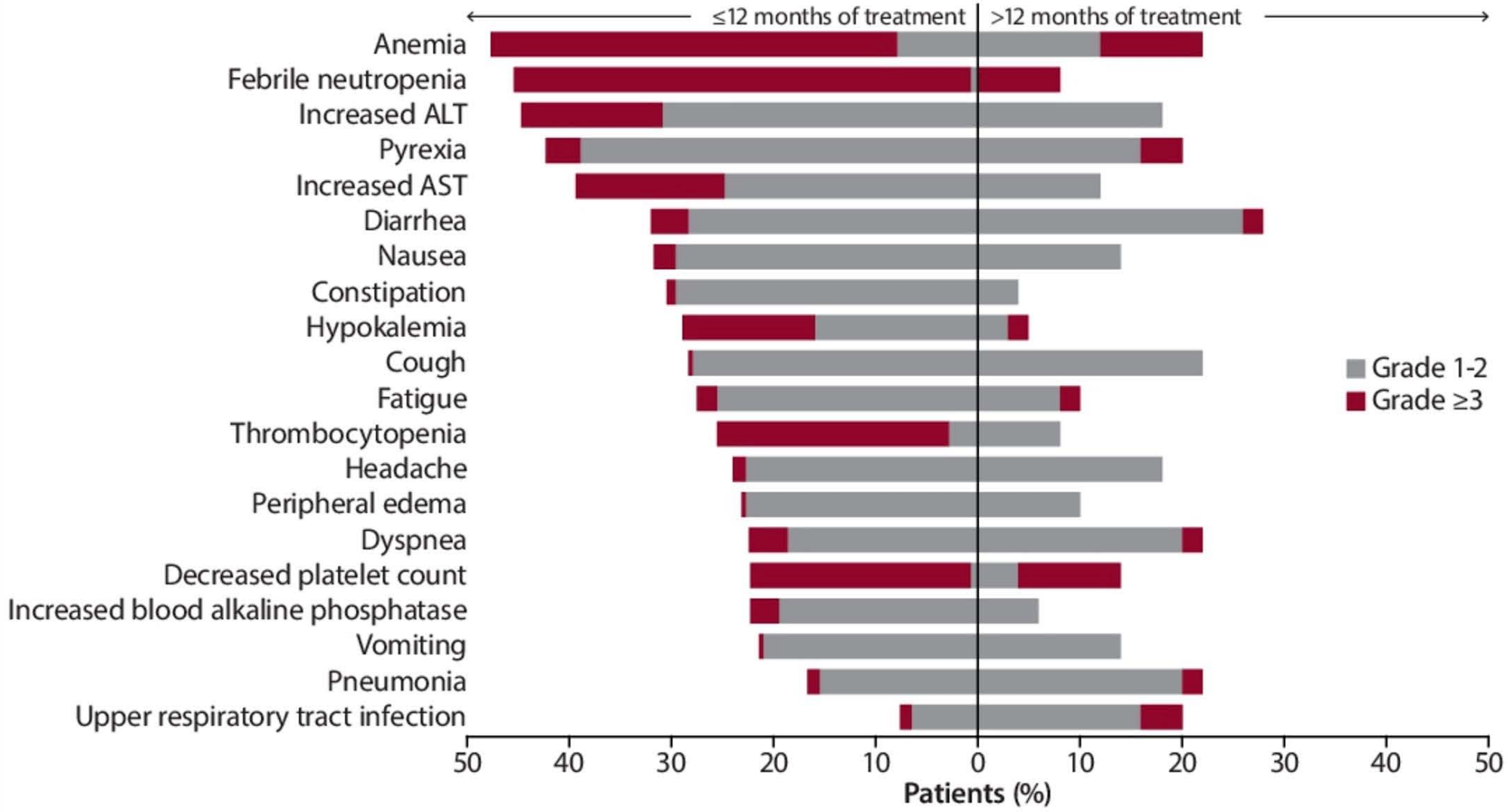
ADMIRAL: Adverse Events Occurring in ≥20% of Patients Receiving Gilteritinib



Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Perl AE et al. ASCO 2020;Abstract 7514.

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ADMIRAL: Adverse Events Leading to Death

AEs Leading to Death[a,b], n (%)		≤12 Months of Treatment (n=246)	>12 Months of Treatment (n=50)
Cardiac disorders	Cardiac arrest	4 (1.6)	0
	Pericardial effusion	2 (0.8)	0
Infections and infestations	Septic shock	7 (2.8)	0
	Sepsis	5 (2.0)	0
	Lung infection	4 (1.6)	0
	Pneumonia	3 (1.2)	0
Gastrointestinal disorders	Large intestinal perforation	2 (0.8)	0
Nervous system disorders	Cerebral hemorrhage	2 (0.8)	0
Respiratory, thoracic, and mediastinal disorders	Respiratory failure	2 (0.8)	0

[a]Patients may have had more than one fatal AE; [b]Excludes deaths stemming from AML progression or relapse.
Abbreviation: AE, adverse event.

Perl AE et al. ASCO 2020;Abstract 7514.

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Phase 1 First-in-Human Study of Irreversible FLT3 Inhibitor FF-10101-01 in Relapsed or Refractory Acute Myeloid Leukemia

Levis MJ et al.
ASCO 2021;Abstract 7008.

Friday, June 4, 2:30 PM - 5:30 PM EDT

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Phase III LACEWING Trial Fails to Meet Primary Endpoint of OS in Newly Diagnosed AML with FLT3 Mutation

Press Release – December 21, 2020

"The phase 3 LACEWING trial of the FMS-like tyrosine kinase 3 (FLT3) inhibitor gilteritinib plus azacitidine versus azacitidine alone in patients with newly diagnosed *FLT3* mutation-positive acute myeloid leukemia (AML) who were ineligible for intensive induction chemotherapy did not meet its primary end point of overall survival (OS) at a planned interim analysis, according to the developer of the agent.

Based on these results, an independent data monitoring committee recommended the study be terminated for futility, citing that the results are unlikely to demonstrate a statistically significant increase in OS. [The developer of the agent has] indicated it has since halted enrollment in the trial and is reviewing the results for other action as needed."

https://www.cancernetwork.com/view/phase-3-lacewing-trial-fails-to-meet-primary-end-point-of-os-in-newly-diagnosed-flt3-aml

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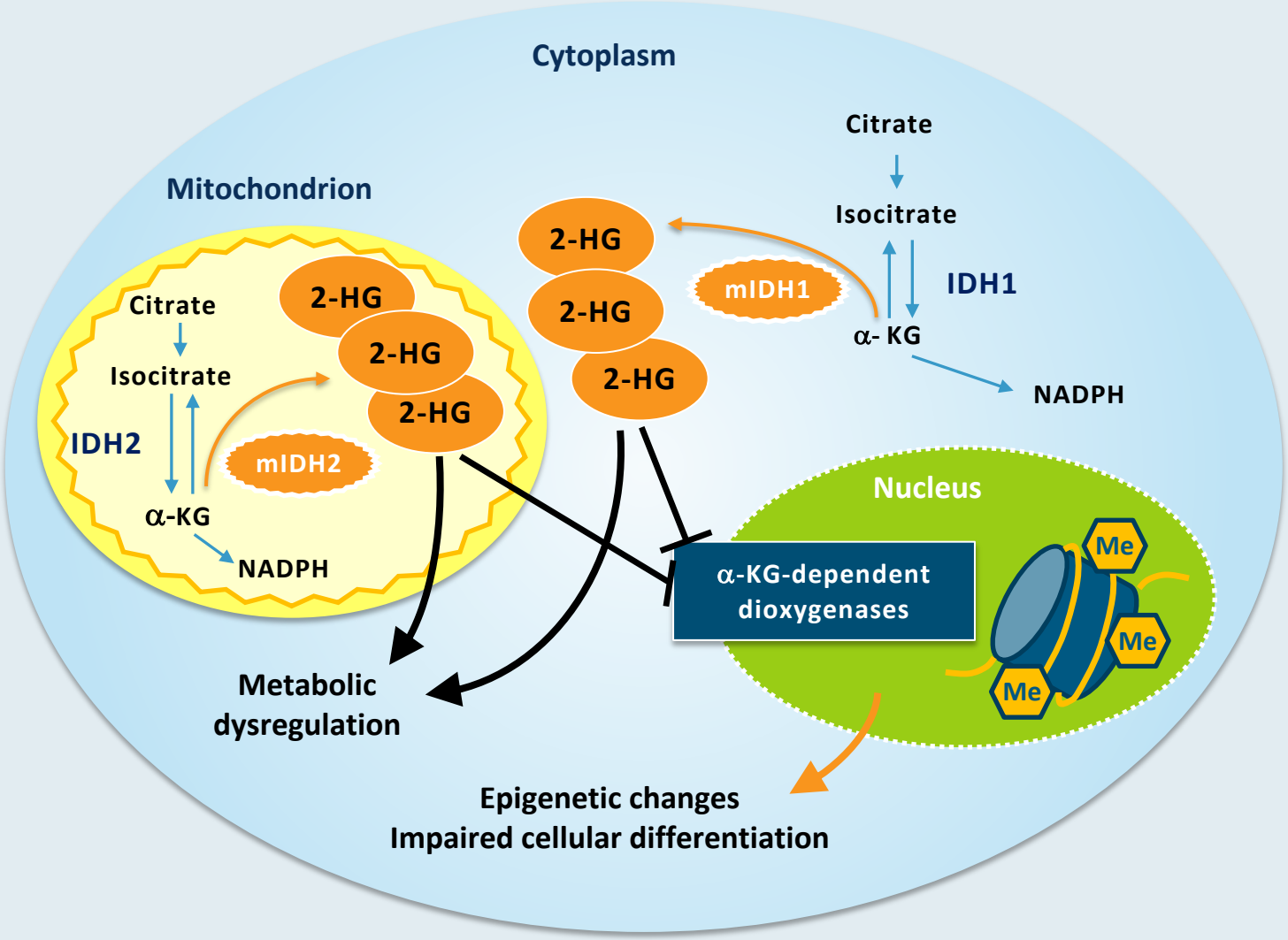
IDH1 and IDH2 Mutations in AML

IDH mutations occur in ~20% of AML

- **Frequency: 6%-16% IDH1 and 8%-18% IDH2**
- **Majority (85%) with diploid or +8 cytogenetics**
- **↑ prevalence with ↑ patient age**
- **Prognostic effect in AML remains controversial**
- **IDH1 and IDH2 mutations may have different effects on prognosis**



Buege MJ et al. *Cancers* 2018;10:187; Chou WC et al. *Leukemia* 2011;25(2):246-53; Dang L et al. *Trends Mol Med* 2010;16(9):387-97. Döhner H et al. *N Engl J Med* 2015;373(12):1136-52; Bullinger L et al. *J Clin Oncol* 2017;35(9):934-46; Patel JP et al. *N Engl J Med* 2012;366(2):1079-89. Medeiros BC et al. *Leukemia* 2017;31:272-81.

RTP RESEARCH TO PRACTICE

Enasidenib Monotherapy is Effective in Older Patients with Newly Diagnosed IDH2 Mutated Acute Myeloid Leukemia and Addition of Azacitidine Rescues Enasidenib Monotherapy Failures: A Phase 2/1B Study of the BEAT AML Master Trial

Stein EM et al.
ASH 2020;Abstract 636

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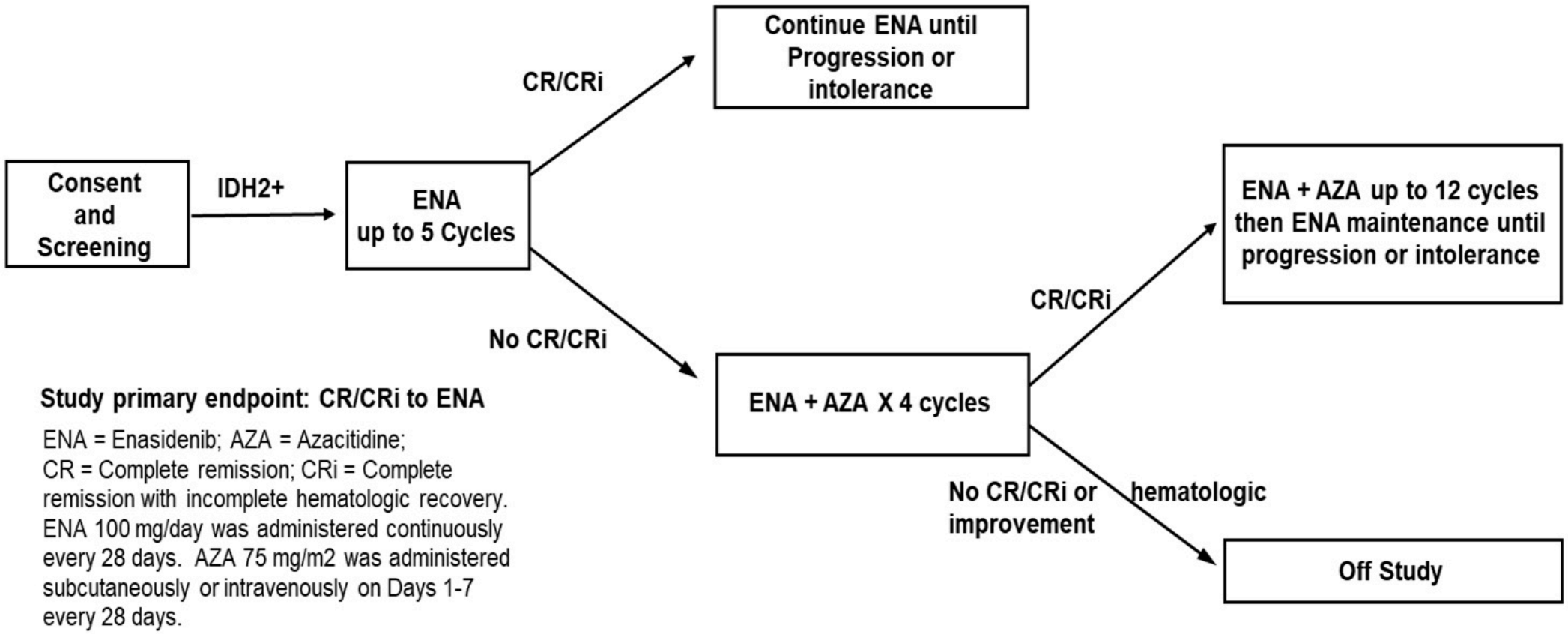
RTP RESEARCH TO PRACTICE

Beat AML S3 Study Design and Objectives



Study primary endpoint: CR/CRi to ENA

ENA = Enasidenib; AZA = Azacitidine;
CR = Complete remission; CRi = Complete remission with incomplete hematologic recovery.
ENA 100 mg/day was administered continuously every 28 days. AZA 75 mg/m2 was administered subcutaneously or intravenously on Days 1-7 every 28 days.

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Response to Enasidenib Monotherapy for Newly Diagnosed AML and Efficacy of Azacitidine After Failure of Enasidenib

	Enasidenib (n = 60)	Azacitidine added after no response to enasidenib (n = 17)
Overall response rate	50%	47%
CR/CRi rate	47%	41%
Median overall survival	24.4 mo	8.9 mo

Stein EM et al. ASH 2020;Abstract 636.

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original reports

Mutant Isocitrate Dehydrogenase 1 Inhibitor Ivosidenib in Combination With Azacitidine for Newly Diagnosed Acute Myeloid Leukemia

Courtney D. DiNardo, MD[1]; Anthony S. Stein, MD[2]; Eytan M. Stein, MD[3]; Amir T. Fathi, MD[4]; Olga Frankfurt, MD[5]; Andre C. Schuh, MD[6]; Hartmut Döhner, MD[7]; Giovanni Martinelli, MD[8]; Prapti A. Patel, MD[9]; Emmanuel Raffoux, MD[10]; Peter Tan, MBBS[11]; Amer M. Zeidan, MBBS[12]; Stéphane de Botton, MD, PhD[13]; Hagop M. Kantarjian, MD[1]; Richard M. Stone, MD[14]; Mark G. Frattini, MD, PhD[15]; Frederik Lersch, RN[16]; Jing Gong, PhD[15]; Diego A. Gianolio, PhD[17]; Vickie Zhang, PhD[17]; Aleksandra Franovic, PhD[18]; Bin Fan, PhD[17]; Meredith Goldwasser, ScD[17]; Scott Daigle, MS[17]; Sung Choe, PhD[17]; Bin Wu, PhD[17]; Thomas Winkler, MD[17]; and Paresh Vyas, MD, PhD[19]

J Clin Oncol 2021;39(1):57-65.

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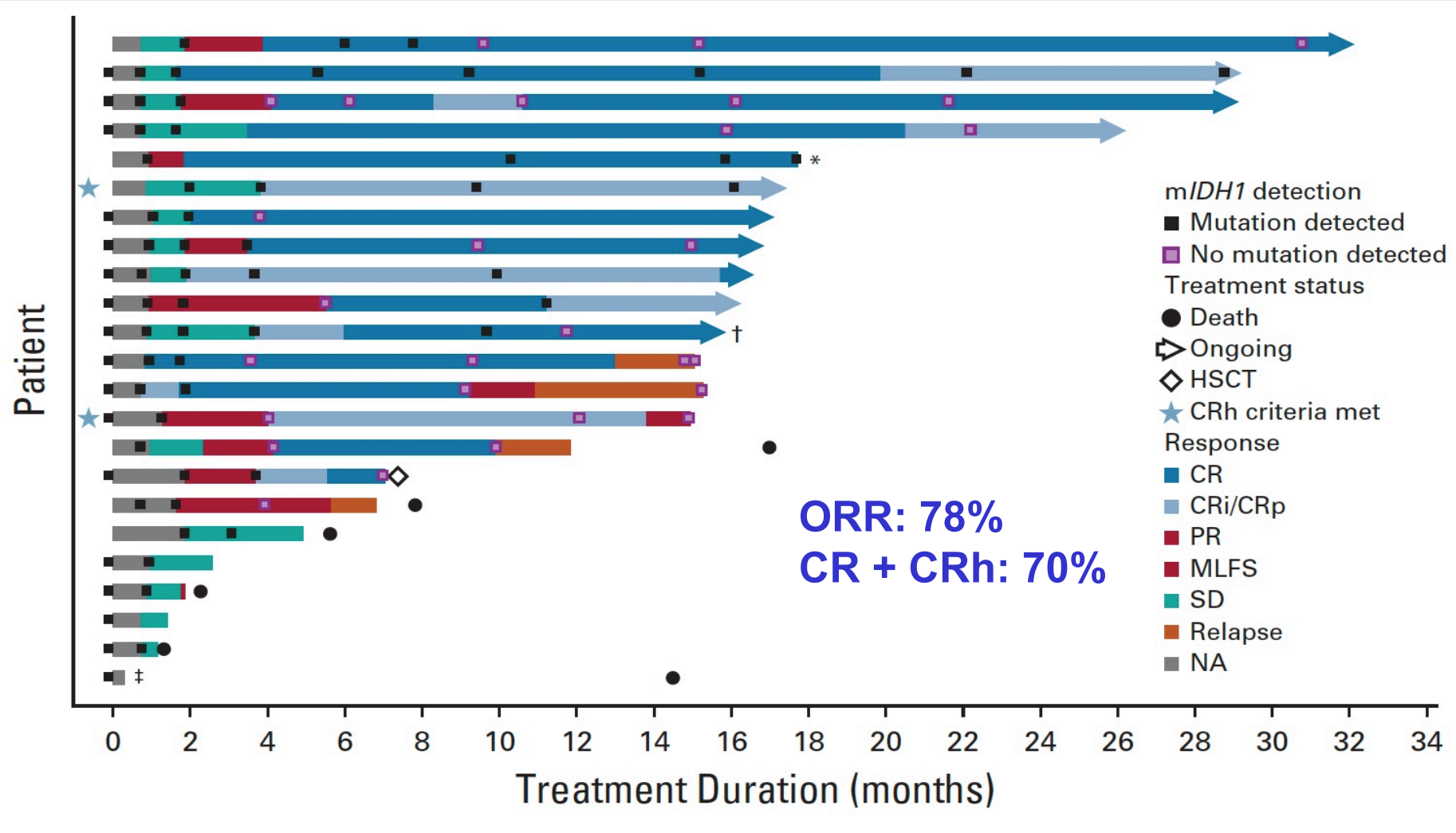
Treatment Duration, Response Over Time and IDH1 Mutation Status



DiNardo CD et al. *J Clin Oncol* 2021;39(1):57-65.

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IDH Differentiation Syndrome (IDH-DS)

- **Potentially fatal complication of effective leukemia treatment**
  - First described in patients with APL treated with ATRA
- **Signs and symptoms of DS are not specific**
  - Fever, edema, weight gain, leukocytosis, rash, hypotension, renal dysfunction, and pleural and pericardial effusions
  - A rising leukocyte count, comprising increasing neutrophils with a parallel decrease in leukemic blasts
- **Median time to onset:** ~30 days (range: 5-340 days)
- **Frequency:** 5-6% Grade 3 or higher
  - Frequent dose interruptions but not associated with treatment discontinuation
- **Treatment**
  - Corticosteroids for IDH-DS
  - Hydroxyurea for leukocytosis, which frequently accompanies IDH-DS
  - Hyperuricemia agents for tumor lysis syndrome, which may co-occur

Stein EM et al. *Blood* 2017;130(6):722-31; Stein EM et al. *Blood* 2019;133(7):676-87;
DiNardo CD et al. *N Engl J Med* 2018;378:2386-98; Birendra KC, DiNardo CD. *Clin Lymphoma Myeloma Leuk* 2016;16(8):460-5.

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Frequency of Signs and Symptoms Consistent with IDH-DS

Sign or symptom	Patients with IDH-DS (N = 33)
Dyspnea	28 (85%)
Unexplained fever (body temp of 38.0°C for 2 d)	26 (79%)
Pulmonary infiltrates	24 (73%)
Hypoxia	19 (58%)
Acute kidney injury	14 (42%)
Pleural effusion	14 (42%)
Bone pain or arthralgia	9 (27%)
Lymphadenopathy	8 (24%)
Rash	8 (24%)
Disseminated intravascular coagulopathy	7 (21%)
Edema or weight gain of >5 kg from screening	7 (21%)
Pericardial effusion	5 (15%)

Fathi A et al. *JAMA Oncol* 2018;4(8):1106-10.

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Case Presentation – Dr Husain: A frail 85-year-old man with AML who received decitabine/venetoclax

Dr Hatim Husain

- PMH: Prostate cancer, s/p RT 8 years ago
- 2019: MDS, anemia requiring epoetin alfa
- 12/2020: Presents with worsening leukocytosis, with circulating blasts
- 1/2021 BMB: AML
- Decitabine/venetoclax

Questions

- What treatment would you recommend at disease progression?
- Would you discuss luspatercept and how that might have been useful in this patient?
- What are your thoughts about the oral hypomethylating agents?

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Key Recent Publications and Presentations

- DiNardo CD et al. **Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia.** *N Engl J Med* 2020;383(7):617-29.
- Wei AH et al. **Venetoclax plus LDAC for Newly Diagnosed AML Ineligible for Intensive Chemotherapy: A Phase 3 Randomized Placebo-Controlled Trial.** *Blood* 2020;135(24):2137-45.
- Wei AH et al. **Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission.** *N Engl J Med* 2020;383(26):2526-37.

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What initial treatment would you recommend for a 65-year-old man with AML with a PS of 1 and pancytopenia, 35% marrow myeloblasts, a complex karyotype and a TP53 mutation?

1. 7 + 3 induction
2. Azacitidine
3. Decitabine
4. Azacitidine + venetoclax
5. Decitabine + venetoclax
6. Low-dose cytarabine + venetoclax
7. Other

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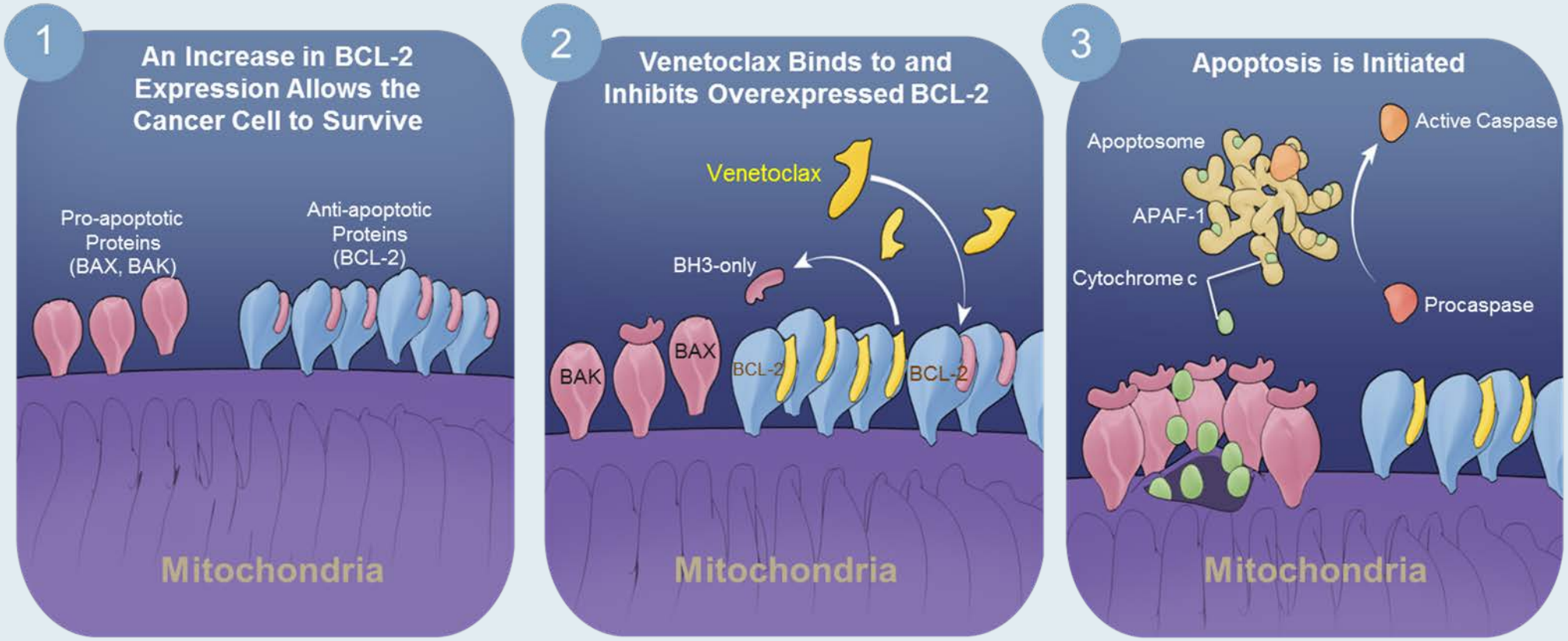
Venetoclax Mechanism of Action



- Cancer cells increase the expression of anti-apoptotic proteins to offset the increase in pro-apoptotic proteins, tipping the balance toward cell survival
- The large # of pro-apoptotic proteins bound and sequestered by Bcl-2 in AML make them “primed” for death

Kumar et al. *Proc ASCO* 2015;Abstract 8576.

RTP RESEARCH TO PRACTICE

N Engl J Med 2020;383:617-29.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 13, 2020 VOL. 383 NO. 7

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

C.D. DiNardo, B.A. Jonas, V. Pullarkat, M.J. Thirman, J.S. Garcia, A.H. Wei, M. Konopleva, H. Döhner, A. Letai, P. Fenaux, E. Koller, V. Havelange, B. Leber, J. Esteve, J. Wang, V. Pejsa, R. Hájek, K. Porkka, Á. Illés, D. Lavie, R.M. Lemoli, K. Yamamoto, S.-S. Yoon, J.-H. Jang, S.-P. Yeh, M. Turgut, W.-J. Hong, Y. Zhou, J. Potluri, and K.W. Pratz

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VIALE-A Study Design

(NCT02993523)

Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤65% or FEV_1 ≤65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Randomization 2:1
N = 433*

Treatment

Venetoclax + Azacitidine
(n = 286)
Venetoclax 400 mg PO, daily, days 1–28 + Azacitidine 75 mg/m² SC /IV days 1–7

Placebo + Azacitidine
(n = 145)
Placebo daily, days 1–28 + Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors	Age (<75 vs. ≥75 years); Cytogenetic risk (intermediate, poor); region
Venetoclax dosing ramp-up	**Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg **Cycle 2** Day 1-28: 400 mg

DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

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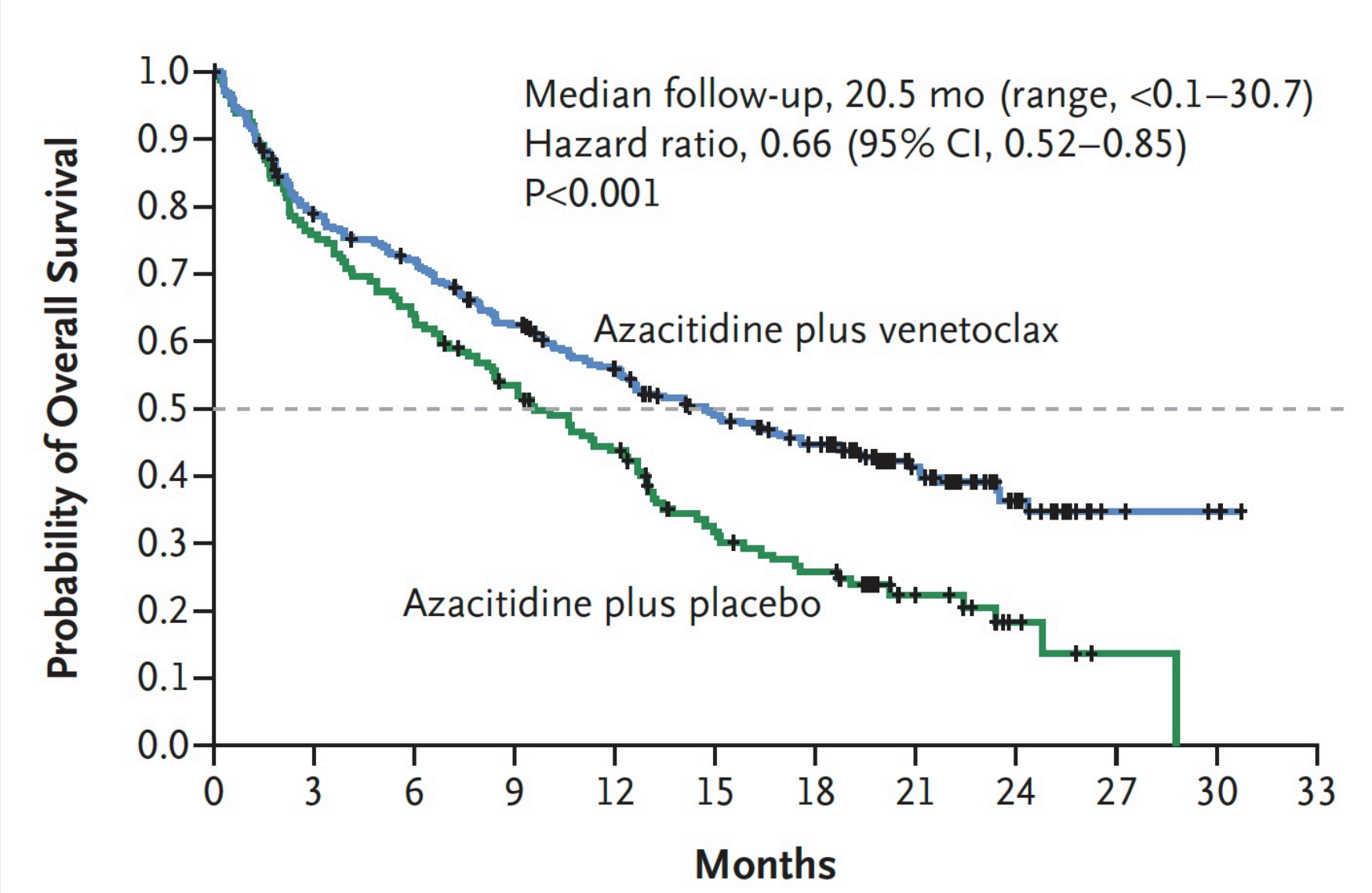
VIALE-A: Overall Survival (N = 431)



DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

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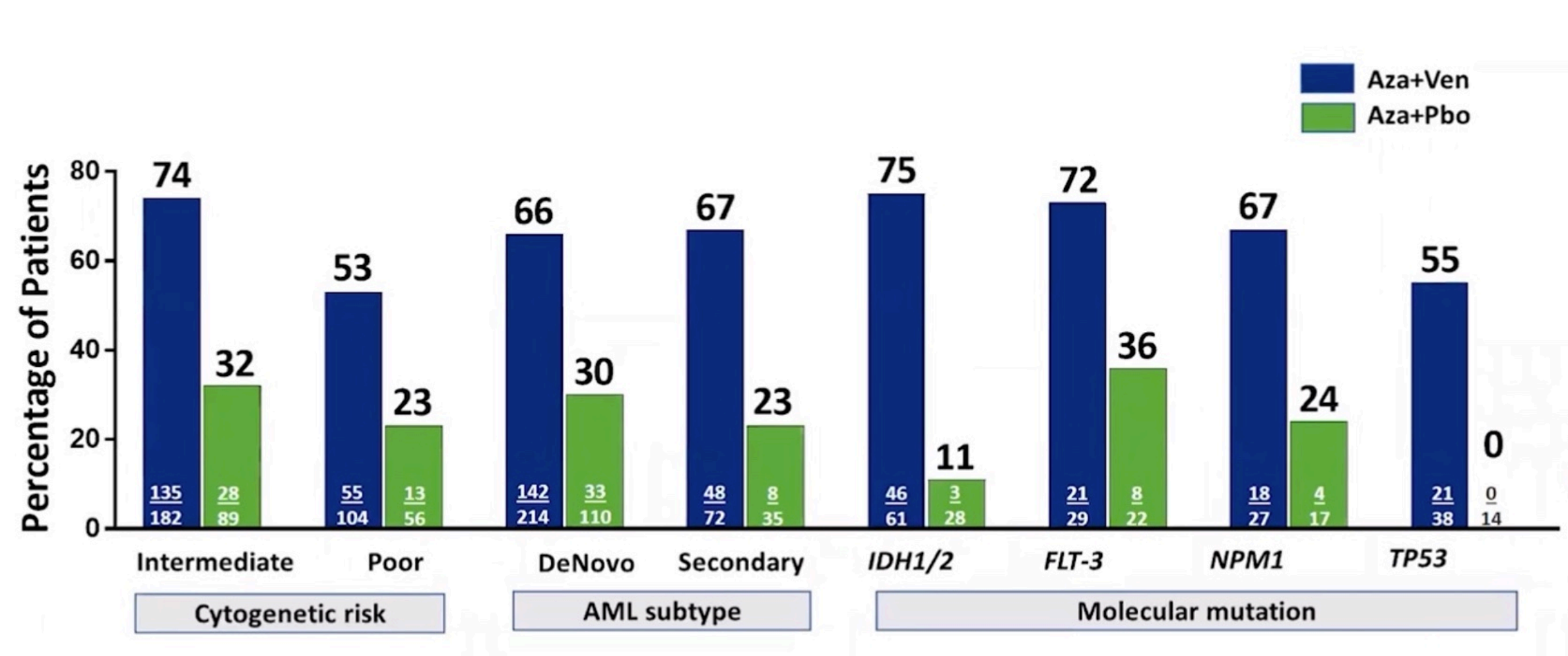
VIALE-A: Response Rates (CR + CRi) Subgroups



DiNardo C et al. EHA 2020;Abstract LB2601.

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AMERICAN SOCIETY OF HEMATOLOGY®
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial

Andrew H. Wei,[1,2] Pau Montesinos,[3,4] Vladimir Ivanov,[5] Courtney D. DiNardo,[6] Jan Novak,[7,8] Kamel Laribi,[9] Inho Kim,[10] Don A. Stevens,[11] Walter Fiedler,[12] Maria Pagoni,[13] Olga Samoilova,[14] Yu Hu,[15] Achilles Anagnostopoulos,[16] Julie Bergeron,[17] Jing-Zhou Hou,[18] Vidhya Murthy,[19] Takahiro Yamauchi,[20] Andrew McDonald,[21] Brenda Chyla,[22] Sathej Gopalakrishnan,[22] Qi Jiang,[22] Wellington Mendes,[22] John Hayslip,[22] and Panayiotis Panayiotidis[23]

Blood 2020;135(24):2137-45.

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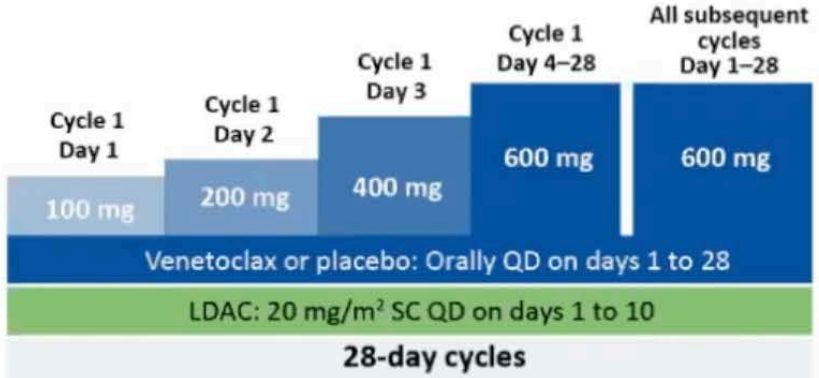
VIALE-C Phase 3 Study Design

- Randomized 2:1, double-blind, placebo-controlled trial

Stratification factors

- AML status (secondary vs de novo)
- Age (18 to <75 vs ≥75)
- Region (US, EU, China, Japan, ROW)



Primary endpoint: overall survival

Secondary endpoints

- CR, CRh, and CRi (modified IWG criteria[1])
- Rate of transfusion independence
- EFS
- MRD

Progressive disease was defined per ELN recommendations.[2]

AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete blood count recovery; EFS, event-free survival; ELN, European LeukemiaNet; IRT, Interactive Response Technology; IWG, International Working Group; LDAC, low-dose cytarabine; MRD, minimal residual disease; OS, overall survival; QD, once a day; ROW, rest of world; SC, subcutaneous.

1. Cheson BD, et al. *J Clin Oncol.* 2003;21:4642-4649; 2. Döhner H, et al. *Blood.* 2017;129:424-447.

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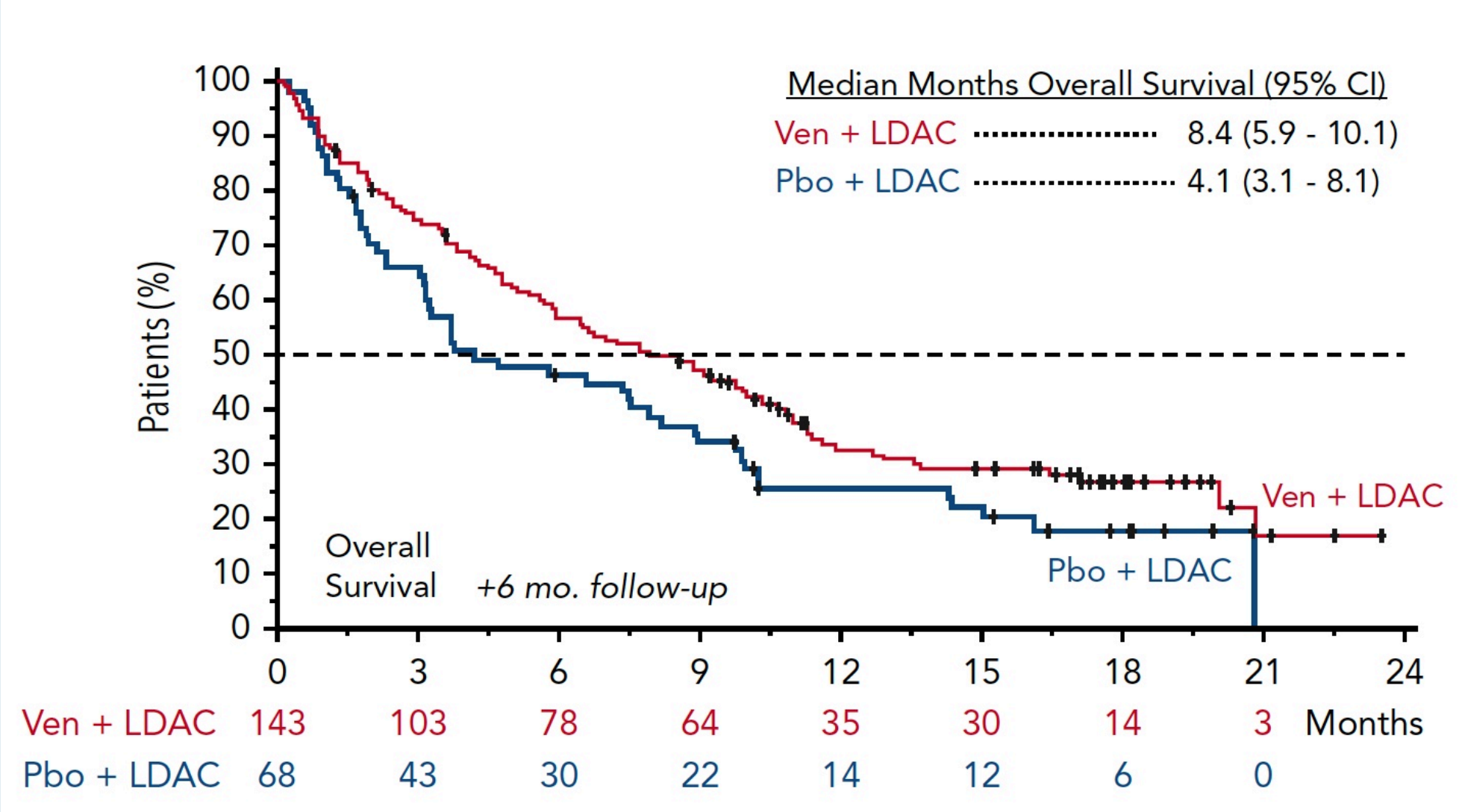
VIALE-C: Overall Survival



Wei AH et al. *Blood* 2020;135(24):2137-45.

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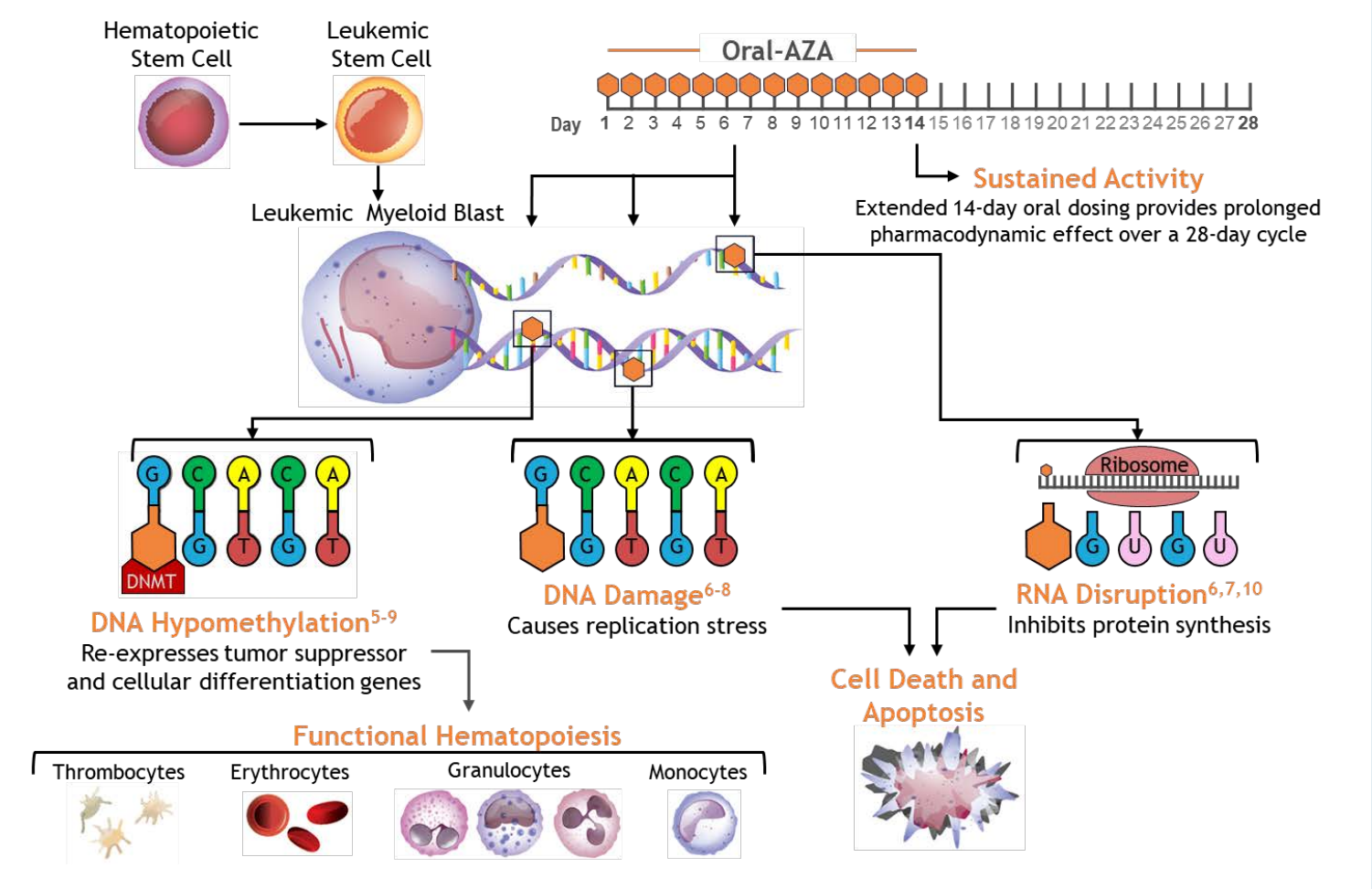
Oral Azacitidine (CC-486)

- Oral HMA with a distinct PK/PD profile from injectable AZA; the two are not bioequivalent[1,2]
- Approved in the United States for continued Tx of adult pts with AML in first CR/CRi post-IC and not able to complete intensive curative therapy (eg, HSCT)[3]
  - Oral dosing allows for extended drug exposure during each Tx cycle to prolong AZA activity[1,2]



1. Garcia-Manero et al. *J Clin Oncol*. 2011;29(18):2521–7. 2. Laille et al. *PLoS One*. 2015;10(8):e0135520. 3. ONUREG® (azacitidine) tablets [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Rev. 9/2020. 4. Savona et al. *Am J Hematol*. 2018;93(10):1199–206. 5. Stresemann et al. *Mol Cancer Ther*. 2008;7:2998–3005. 6. Hollenbach et al. *PLoS One*. 2010;5(2):e9001. 7. Scott LJ. *Drugs*. 2016;76(8):889–900. 8. Stresemann C, Lyko F. *Int J Cancer*. 2008;123(1):8–13. 9. Aimiuwu et al. *Blood*. 2012;119(22):5229–38.

AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; PD, pharmacodynamic; PK, pharmacokinetic; pts, patients; Tx, treatment.

Courtesy of Richard M Stone, MD

RTP RESEARCH TO PRACTICE

ORIGINAL ARTICLE

Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission

A.H. Wei, H. Döhner, C. Pocock, P. Montesinos, B. Afanasyev,* H. Dombret, F. Ravandi, H. Sayar, J.-H. Jang, K. Porkka, D. Selleslag, I. Sandhu, M. Turgut, V. Giai, Y. Ofran, M. Kizil Çakar, A. Botelho de Sousa, J. Rybka, C. Frairia, L. Borin, G. Beltrami, J. Čermák, G.J. Ossenkoppele, I. La Torre, B. Skikne, K. Kumar, Q. Dong, C.L. Beach, and G.J. Roboz, for the QUAZAR AML-001 Trial Investigators†

N Engl J Med 2020;383:2526-37.

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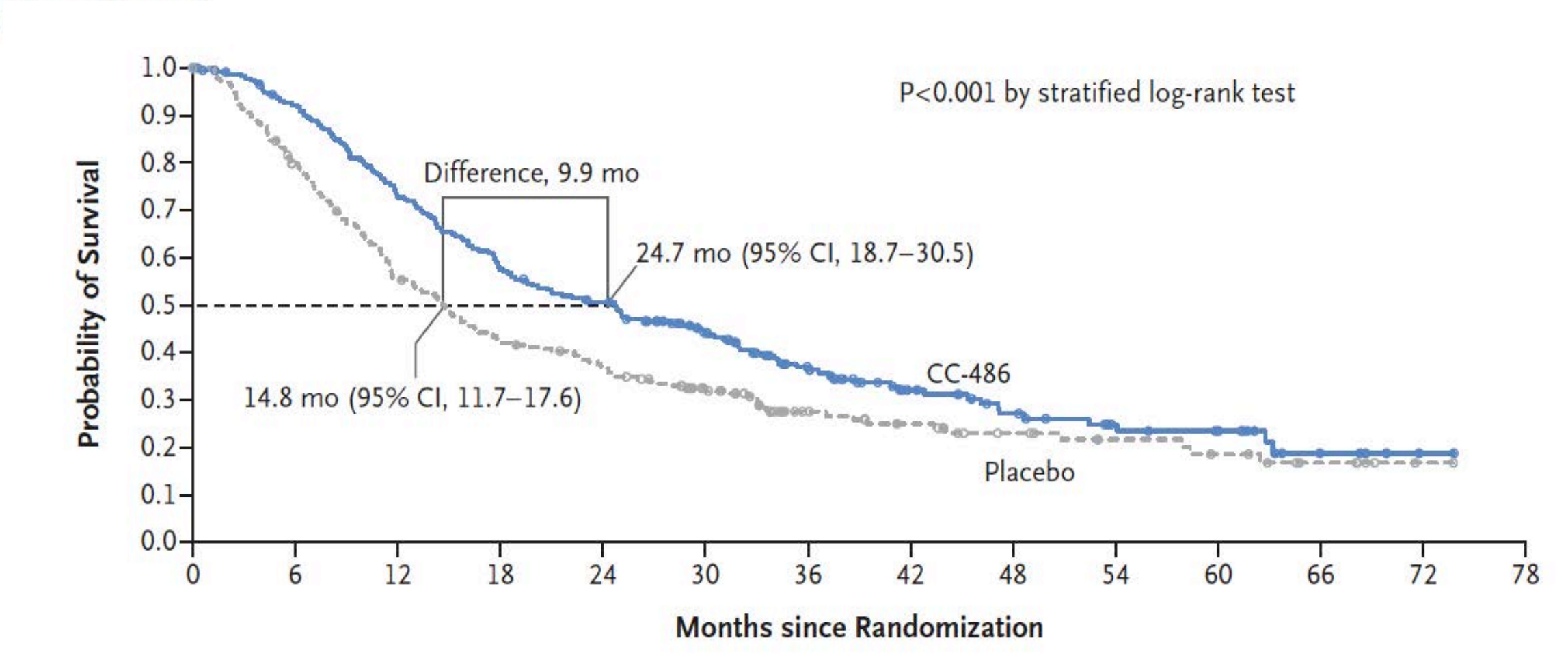
QUAZAR AML-001: Overall Survival



Wei AH et al. *N Engl J Med* 2020;383:2526-37.

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Agenda

Module 1: Myelodysplastic Syndromes (MDS)

- Dr Lorber: A 73-year-old man with MDS, ring sideroblasts and multilineage dysplasia
- *Key Recent Publications and Presentations*

Module 2: Newly Diagnosed Acute Myeloid Leukemia (AML)

- Dr Blackmon: A 40-year-old woman with newly diagnosed AML and a FLT3-TKD mutation
- *Key Recent Publications and Presentations*
- Dr Husain: A frail 85-year-old man with AML who received decitabine/venetoclax
- *Key Recent Publications and Presentations*

Module 3: Secondary AML

- Dr Husain: A 65-year-old man who develops AML while receiving therapy for metastatic NSCLC
- Dr Lorber: A 74-year-old otherwise healthy man with atrial fibrillation develops AML secondary to MDS
- *Key Recent Publications and Presentations*

Module 4: Relapsed/Refractory AML

- Dr Blackmon: A 46-year-old man with refractory AML and complex cytogenetics

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Case Presentation – Dr Husain: A 65-year-old man who develops AML while receiving therapy for metastatic NSCLC

Dr Hatim Husain

- PMH: Stage IIIC adenocarcinoma of the lung, s/p cisplatin/etoposide/RT
- Intrathoracic disease progressing 3 months after completing RT
- Carboplatin/pemetrexed/pembrolizumab → Pemetrexed/pembrolizumab, with PD
- Docetaxel/ramucirumab
  - After 3 months: WBC 106, HB 6.3, Plt 112
- BMB: AML, monosomy 7 with no clinically significant somatic mutations via NGS
- Best supportive care with hydroxyurea, transfusions and pain control

Questions

- What are the new options for treatment-related AML, and are there genomic characteristics that can better help us understand the therapeutic strategies?
- Would you discuss what is known about CPX-351 in terms of its pros and cons and applicability to this case?

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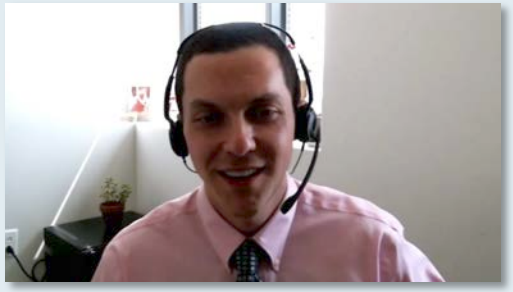
Case Presentation – Dr Lorber: A 74-year-old otherwise healthy man with atrial fibrillation develops AML secondary to MDS



Dr Jeremy Lorber

- PMH: diagnosed with MDS with trilineage dyspoesis, del13q, and U2AF1 mutation; baseline atrial fibrillation
- Initially responded to ESA but transformed to AML within 5 months
- Liposomal daunorubicin/cytarabine, with CR → Consolidation daunorubicin/cytarabine x 1
- Plan for possible bone marrow transplant
- Recurred with cutaneous manifestation of AML

Questions

- What is the most appropriate regimen given his age? Is liposomal daunorubicin and cytarabine "worth" the toxicity compared to HMA + venetoclax?
- With venetoclax, are the initial cytopenias from the disease or the drug? How do you manage the cytopenias – dose reduction, hold the drug or change cycle duration?

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Key Recent Presentations

- Lancet JE et al. **Five-Year Final Results of a Phase 3 Study of CPX-351 versus 7 + 3 in Older Adults with Newly Diagnosed High-Risk/Secondary Acute Myeloid Leukemia (AML): Outcomes by Age Subgroup and Among Responders.** ASH 2020;Abstract 635.
- Kadia TM et al. **Phase II Study of CPX-351 plus Venetoclax in Patients with Acute Myeloid Leukemia (AML).** ASH 2020;Abstract 28.
- Ramos Perez JM et al. **Liposomal Cytarabine and Daunorubicin (CPX-351) in Combination with Gemtuzumab Ozogamicin (GO) in Relapsed Refractory (R/R) Patients with Acute Myeloid Leukemia (AML) and Post-Hypomethylating Agent (Post-HMA) Failure High-Risk Myelodysplastic Syndrome (HR-MDS).** ASH 2020;Abstract 987.

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What initial treatment would you recommend for a 64-year-old woman with a history of breast cancer, for which she received adjuvant chemotherapy, who now presents with bone marrow findings consistent with therapy-related AML?

1. 7 + 3 induction
2. CPX-351
3. Decitabine
4. Decitabine + venetoclax
5. Azacitidine + venetoclax
6. Low-dose cytarabine + venetoclax
7. Other

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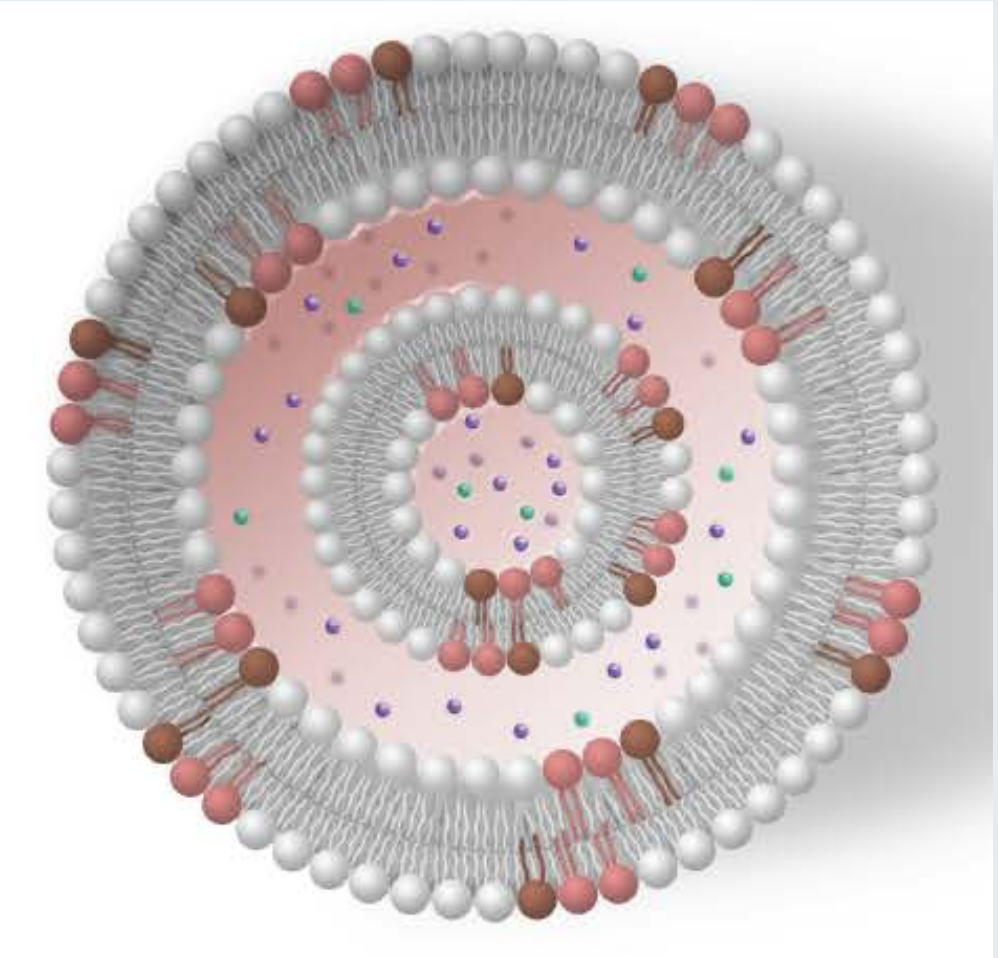
CPX-351

- CPX-351 is a liposomal co-formulation of cytarabine and daunorubicin designed to achieve synergistic antileukemia activity
  - 5:1 molar ratio of cytarabine:daunorubicin provides synergistic leukemia cell killing *in vitro*[1]
  - In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days[2]
  - Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]



1. Tardi P et al. *Leuk Res.* 2009;33(1):129-139. 2. Feldman EJ et al. *J Clin Oncol.* 2011;29(8):979-985;
3. Lim WS et al. *Leuk Res.* 2010;34(9):1245-1223.

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TO PRACTICE

ASH 2020;Abstract 635.

Five-year Final Results of a Phase 3 Study of CPX-351 Versus 7+3 in Older Adults with Newly Diagnosed High-risk/Secondary Acute Myeloid Leukemia (AML): Outcomes by Age Subgroup and Among Responders

Presenter: Jeffrey E. Lancet

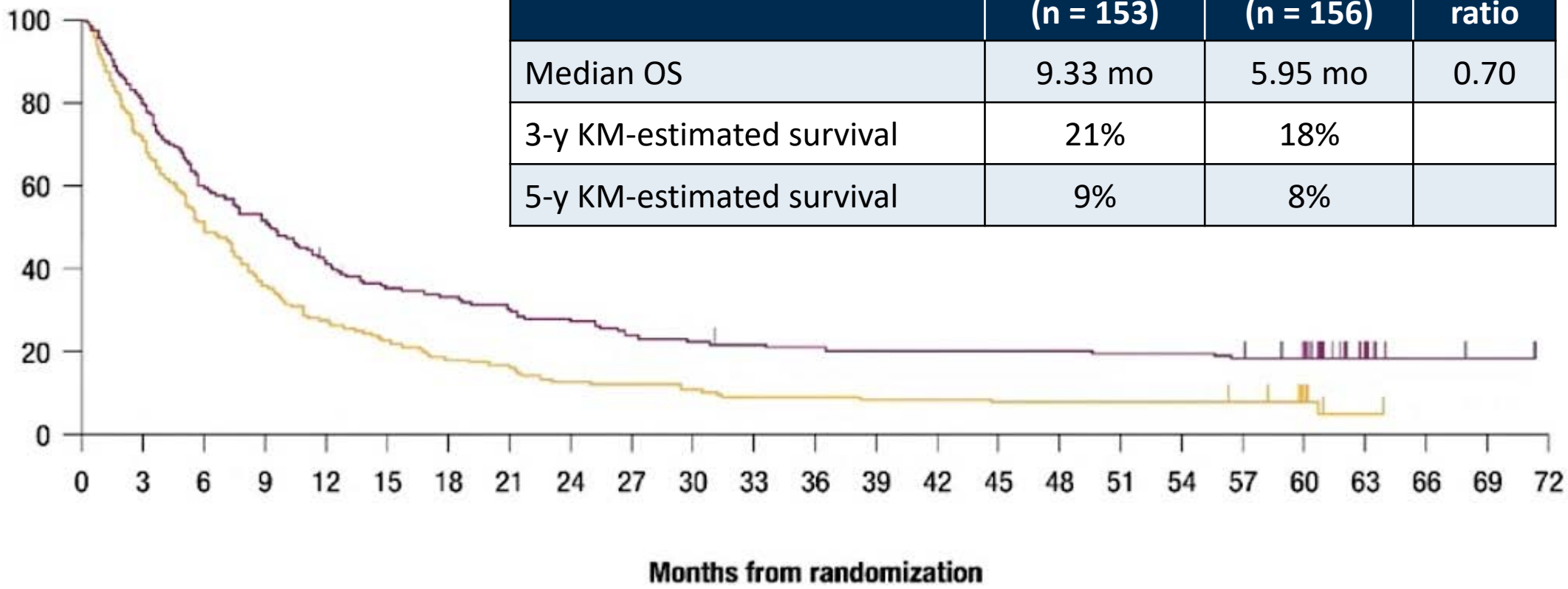
H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Jeffrey E. Lancet,[1] Geoffrey L. Uy,[2] Laura F. Newell,[3] Tara L. Lin,[4] Donna Hogge,[5] Scott R. Solomon,[6] Gary J. Schiller,[7] Matthew J. Wieduwilt,[8] Daniel H. Ryan,[9] Stefan Faderl,[10] Yu-Lin Chang,[10] Jorge E. Cortes[11,12]

[1]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [2]Washington University School of Medicine, St. Louis, MO, USA; [3]Oregon Health & Science University, Portland, OR, USA; [4]University of Kansas Medical Center, Kansas City, KS, USA; [5]Leukemia/BMT Program of British Columbia, Vancouver, BC, Canada; [6]Leukemia Program, Northside Hospital Cancer Center Institute, Atlanta, GA, USA; [7]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [8]University of California – San Diego Moores Cancer Center, La Jolla, CA, USA; [9]University of Rochester, Rochester, NY, USA; [10]Jazz Pharmaceuticals, Palo Alto, CA, USA; [11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]Georgia Cancer Center, Augusta University, Augusta, GA, USA.

62nd ASH Annual Meeting & Exposition; December 5-8, 2020

Five-Year Final Overall Survival Results with CPX-351 versus 7 + 3 for Older Patients with Newly Diagnosed High-Risk or Secondary AML



	CPX-351 (n = 153)	7 + 3 (n = 156)	Hazard ratio
Median OS	9.33 mo	5.95 mo	0.70
3-y KM-estimated survival	21%	18%	
5-y KM-estimated survival	9%	8%	

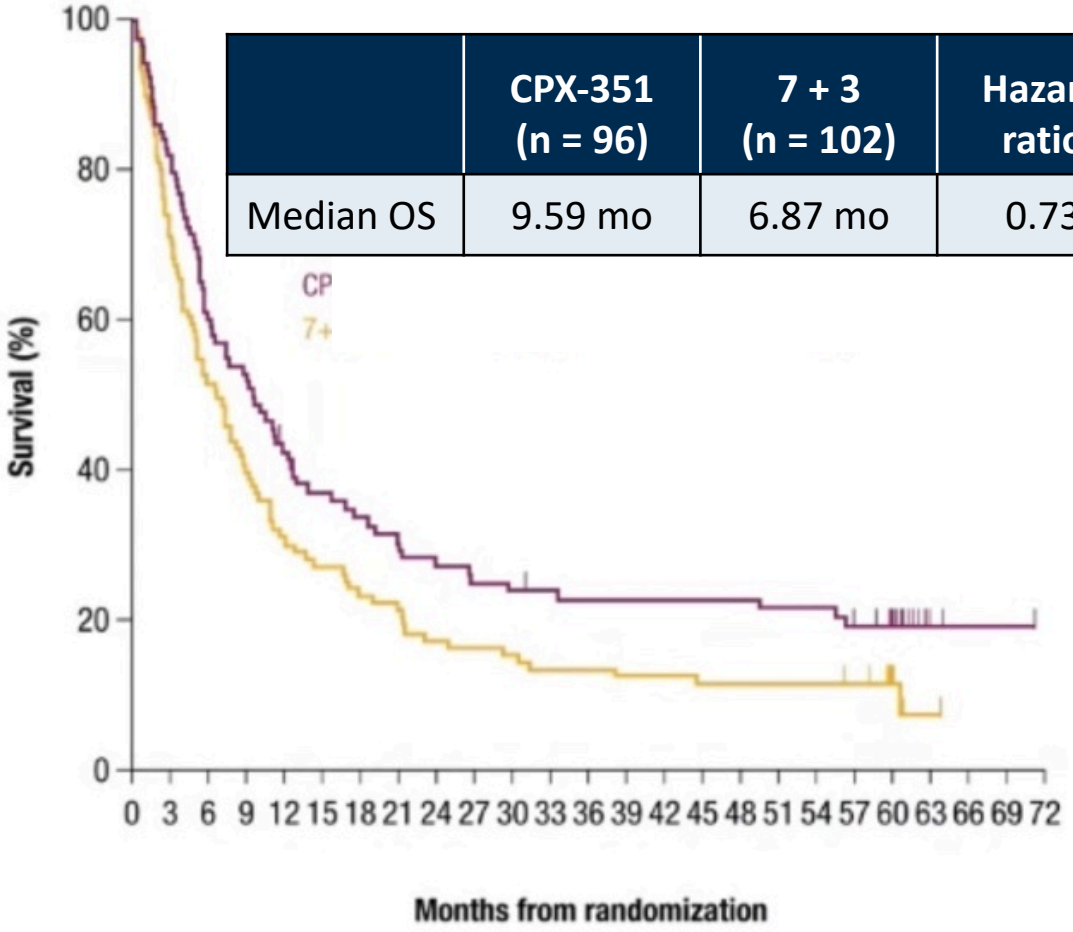
Lancet JE et al. ASH 2020;Abstract 635.

RTP RESEARCH TO PRACTICE

Overall Survival Results by Age

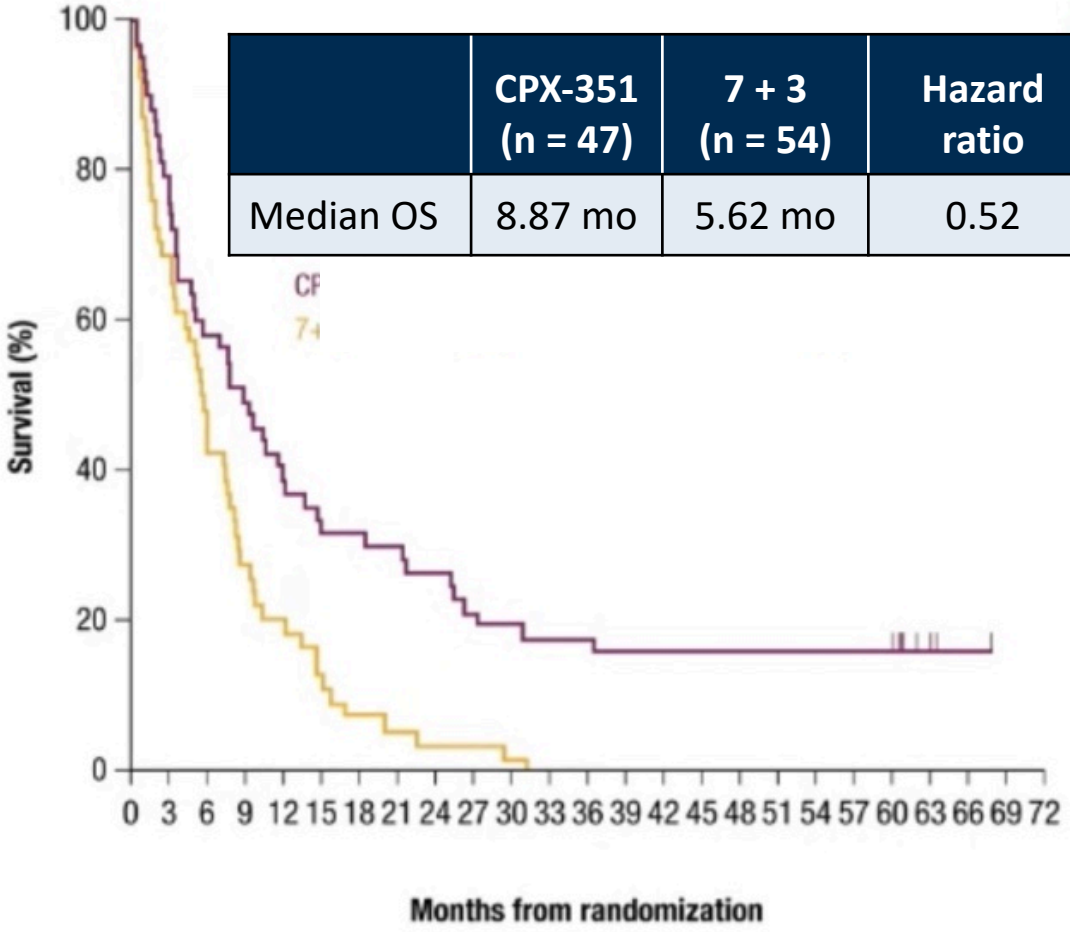
Ages 60 to 69 Years

	CPX-351 (n = 96)	7 + 3 (n = 102)	Hazard ratio
Median OS	9.59 mo	6.87 mo	0.73



Ages 70 to 75 Years

	CPX-351 (n = 47)	7 + 3 (n = 54)	Hazard ratio
Median OS	8.87 mo	5.62 mo	0.52



Lancet JE et al. ASH 2020;Abstract 635.

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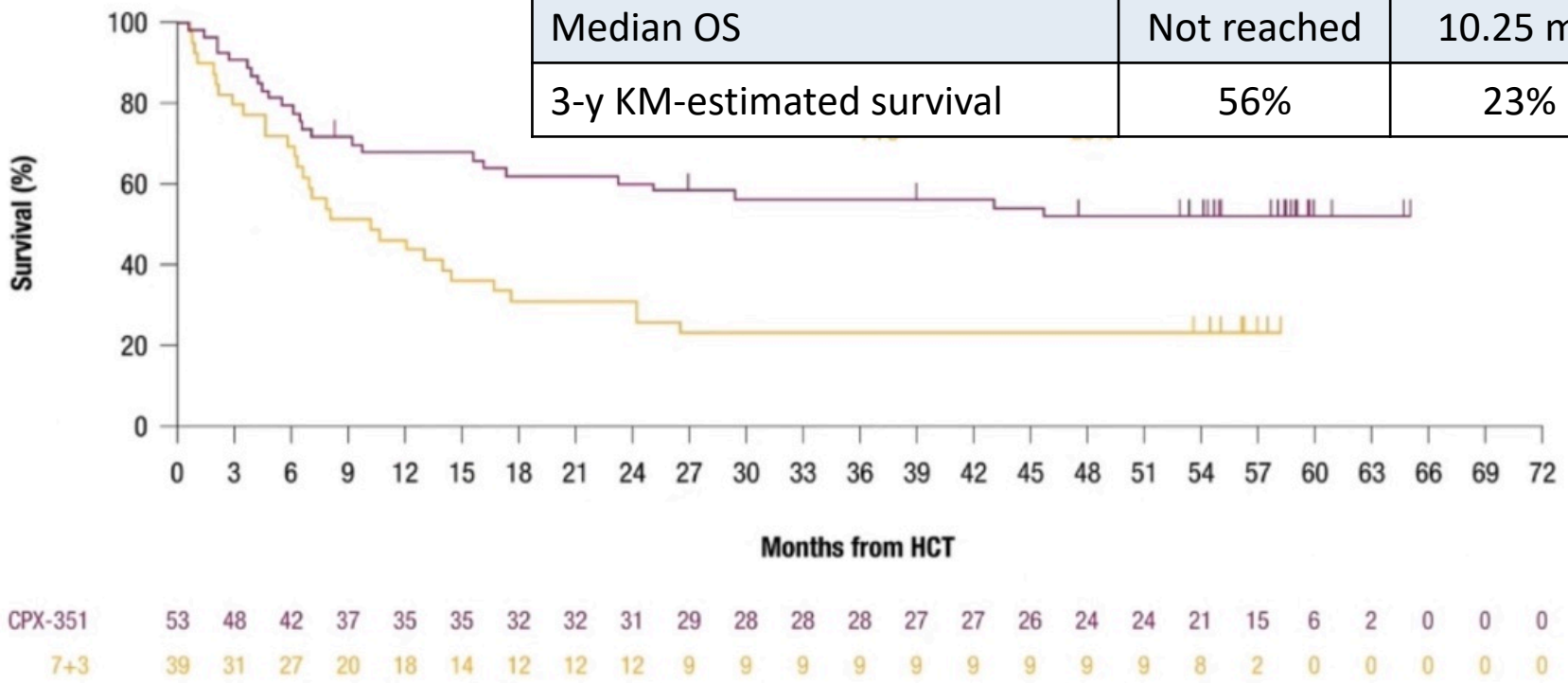
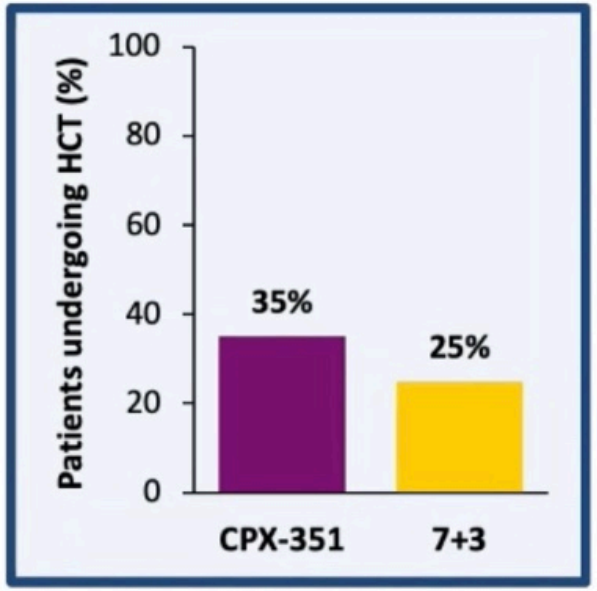
Overall Survival Landmarked from the HCT Date

	CPX-351 (n = 153)	7 + 3 (n = 156)	Hazard ratio
Median OS	Not reached	10.25 mo	0.51
3-y KM-estimated survival	56%	23%	





- **Kaplan-Meier–estimated survival rate landmarked from the date of HCT was >50% at 3 and 5 years for patients treated with CPX-351**

Lancet JE et al. ASH 2020;Abstract 635.

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Abstract # 28

Phase II Study of CPX-351 Plus Venetoclax in Patients with Acute Myeloid Leukemia (AML)

Tapan M. Kadia, Gautam Borthakur, Koichi Takahashi, Courtney Dinardo, Naval Daver, Naveen Pemmaraju, Elias Jabbour, Nitin Jain, Nicholas Short, Wei Qiao, Lade Adewale, Caitlin Rausch, Sherry Pierce, Yesid Alvarado, Amin Alousi, Uday Popat, Issa Khouri, Guillermo Garcia-Manero, Marina Konopleva, Jorge Cortes, Farhad Ravandi, and Hagop Kantarjian.

58:13

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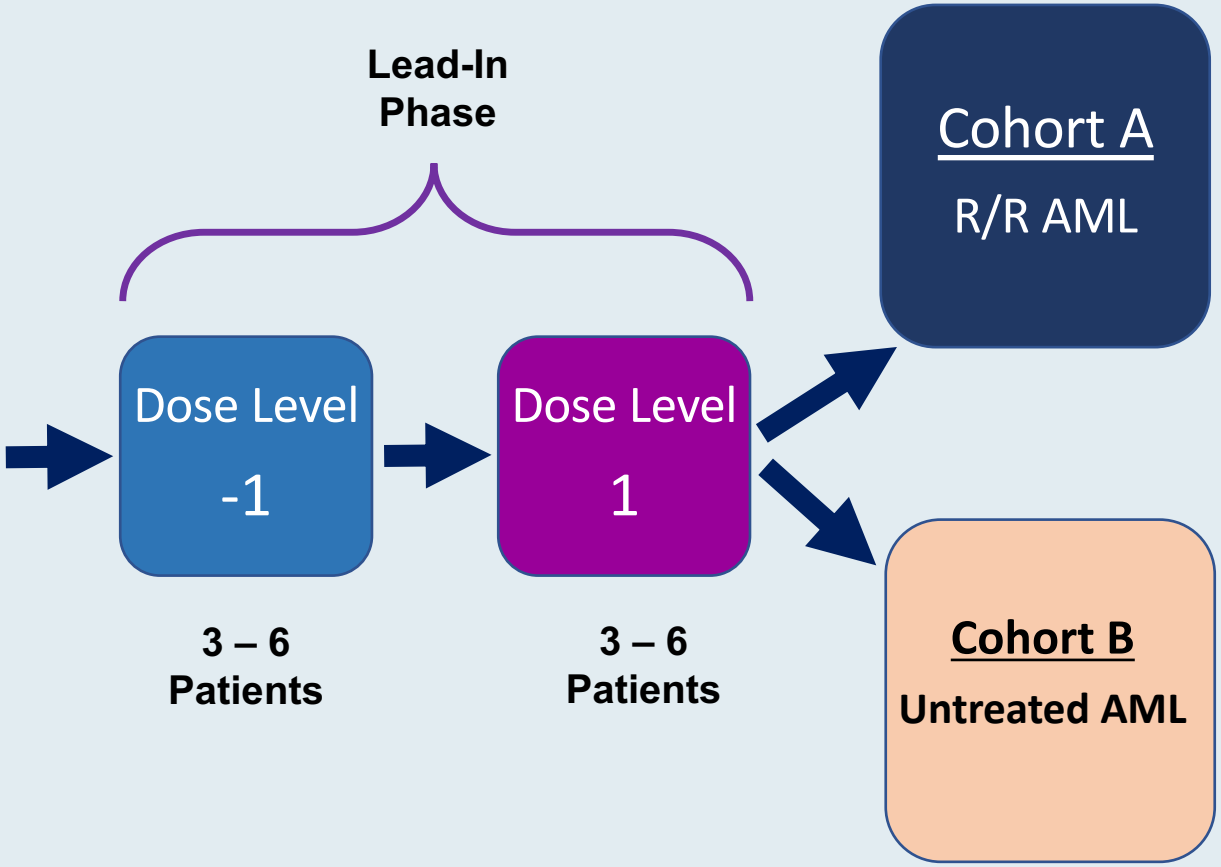
CPX-351 + Venetoclax in AML

Study Design

Patient Selection

- **Lead in phase:** Patients ≥ 18 years of age with relapsed and/or refractory AML will be eligible.
- **Cohort A (R/R AML):** Patients ≥ 18 years of age with R/R AML.
- **Cohort B (de novo AML):** Patients ≥ **18 to 65** years of age. Patients in this cohort must have received no prior therapy for AML.
- Adequate organ function:
  - Bilirubin ≤ 2mg/dL, AST / ALT ≤ 3 x ULN or ≤ 5 x ULN if related to leukemic involvement
  - creatinine ≤ 1.5 x ULN
  - known cardiac ejection fraction of ≥45% within the past 3 months
- ECOG performance status of ≤ 2.
- Prior Venetoclax allowed in R/R cohorts.



Kadia TM et al. ASH 2020;Abstract 28.

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CPX351 + Venetoclax in AML

Responses

Response / Outcome	N	%
Evaluable for Response	18	90
CR	1	6
CRi	6	33
MLFS	1	6
ORR	8	44
Died ≤ 4 weeks	2	10
Died ≤ 8 weeks	4	20
Median # of cycles given [Range]	1 [1 – 2]	
Median # of cycles to response	1 [1 – 2]	
No. of Responding Pts Receiving SCT	7	88
Median time to count recover (days)	41 [23 – 60]	

Kadia TM et al. ASH 2020;Abstract 28.

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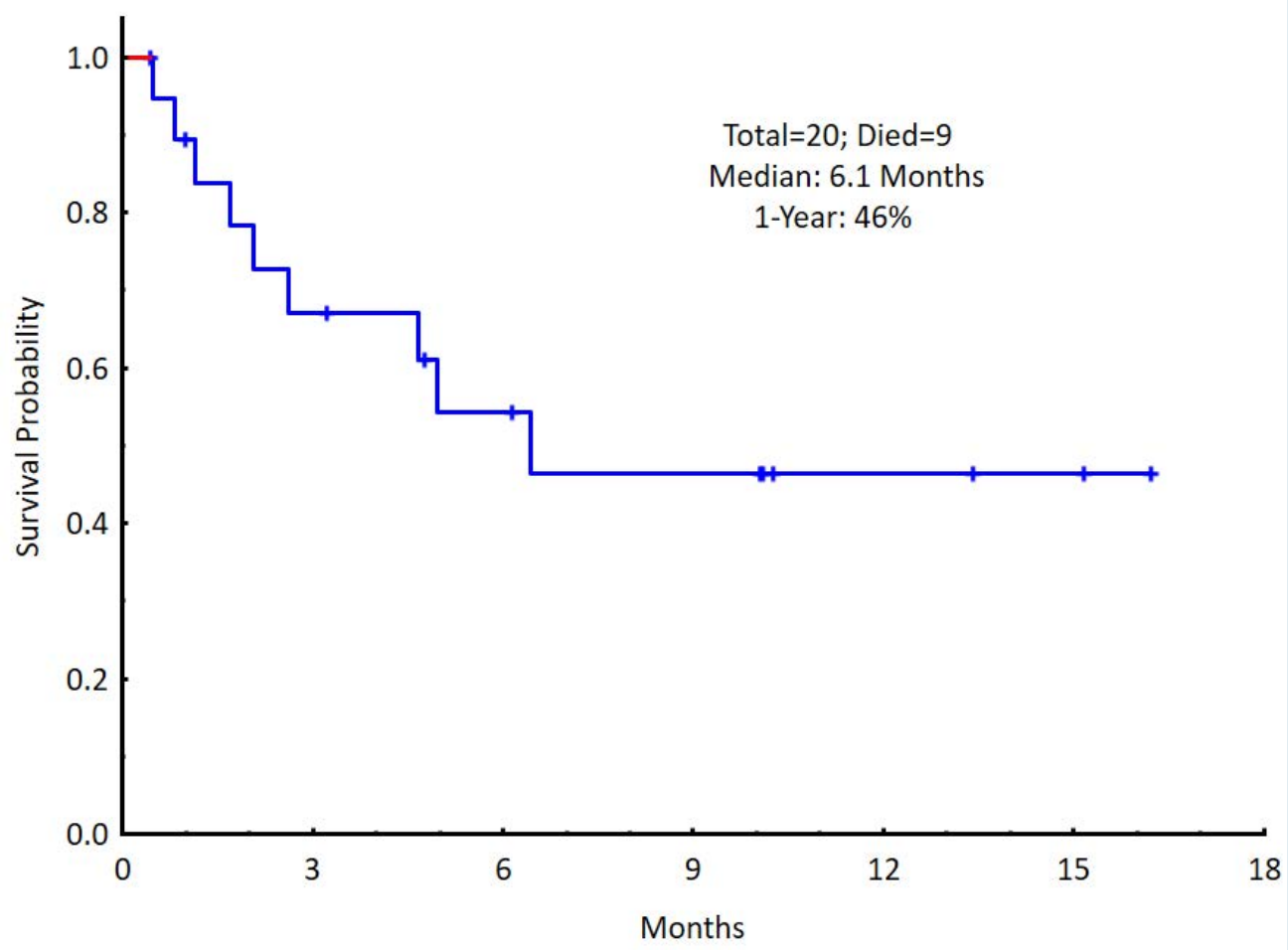
CPX-351 + Venetoclax in AML

Overall Survival



Kadia TM et al. ASH 2020;Abstract 28.

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Liposomal Cytarabine and Daunorubicin (CPX-351) in Combination with Gemtuzumab Ozogamicin (GO) in Relapsed Refractory (R/R) Patients with Acute Myeloid Leukemia (AML) and Post-Hypomethylating Agent (Post-HMA) Failure High-Risk Myelodysplastic Syndrome (HR-MDS)

Ramos Perez JM et al.

ASH 2020;Abstract 987.

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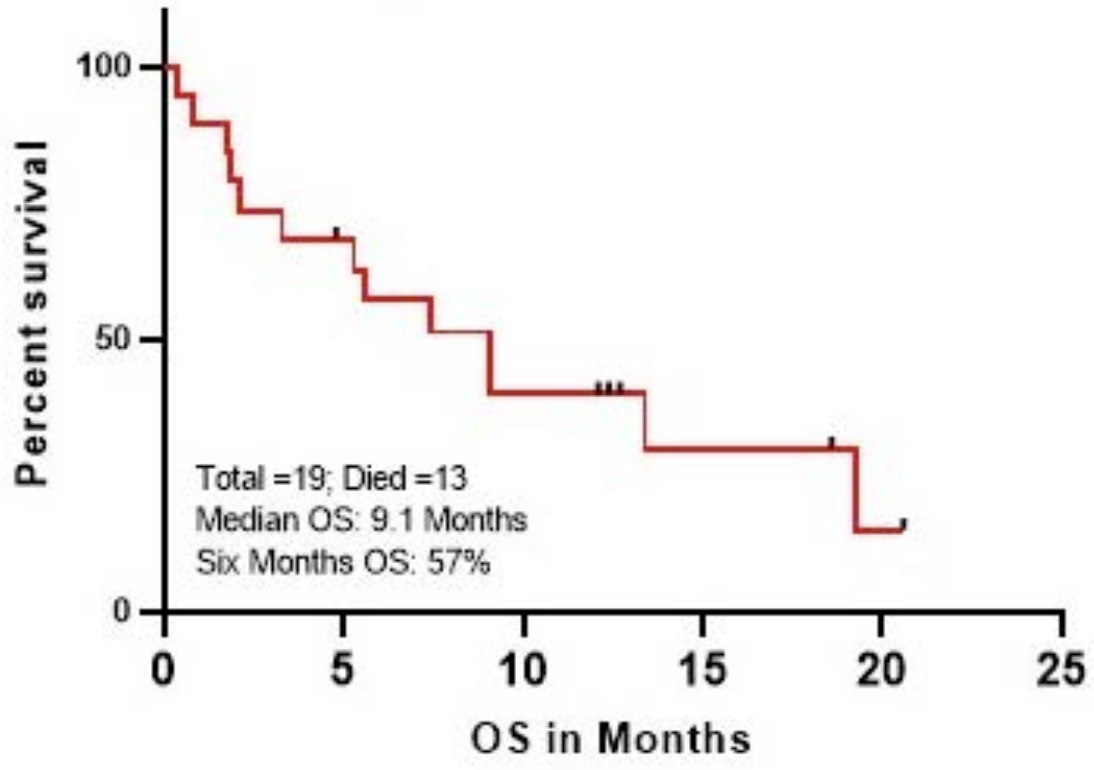
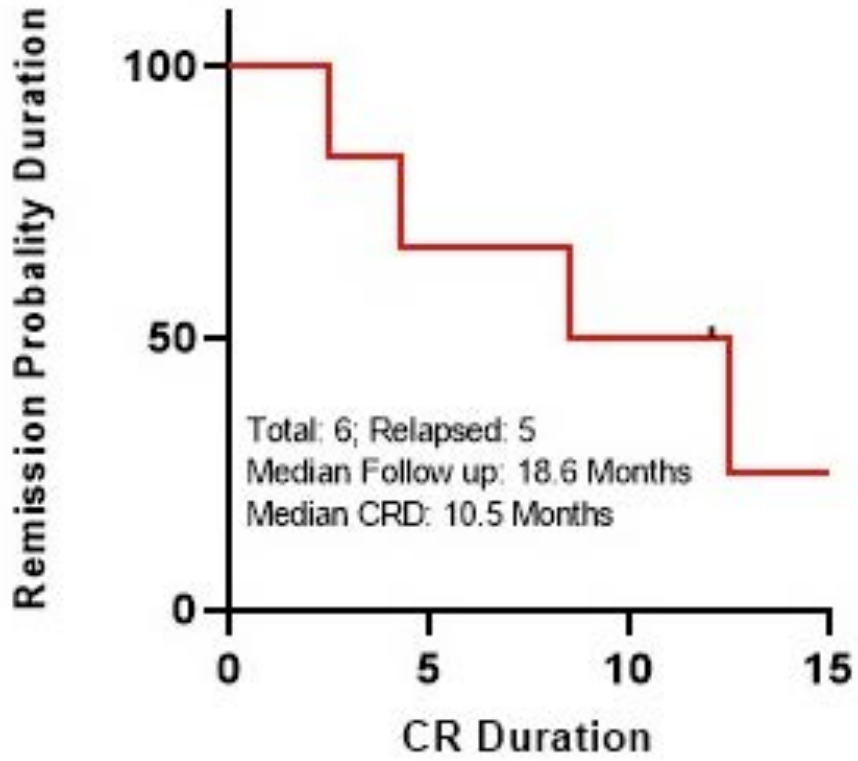
CPX-351 in Combination with Gemtuzumab Ozogamicin in Relapsed/Refractory AML

Overall Survival



Complete Remission Duration



Ramos Perez JM et al. ASH 2020;Abstract 987.

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Agenda

Module 1: Myelodysplastic Syndromes (MDS)

- Dr Lorber: A 73-year-old man with MDS, ring sideroblasts and multilineage dysplasia
- *Key Recent Publications and Presentations*

Module 2: Newly Diagnosed Acute Myeloid Leukemia (AML)

- Dr Blackmon: A 40-year-old woman with newly diagnosed AML and a FLT3-TKD mutation
- *Key Recent Publications and Presentations*
- Dr Husain: A frail 85-year-old man with AML who received decitabine/venetoclax
- *Key Recent Publications and Presentations*

Module 3: Secondary AML

- Dr Husain: A 65-year-old man who develops AML while receiving therapy for metastatic NSCLC
- Dr Lorber: A 74-year-old otherwise healthy man with atrial fibrillation develops AML secondary to MDS
- *Key Recent Publications and Presentations*

Module 4: Relapsed/Refractory AML

- Dr Blackmon: A 46-year-old man with refractory AML and complex cytogenetics

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Case Presentation – Dr Blackmon: A 46-year-old man with refractory AML and complex cytogenetics

Dr Amanda Blackmon

- Diagnosed with AML with complex cytogenetics:
  - Inv3, t(3;8), -7 and t(9/22), with p190 BCR-ABL and SF3B1 mutations
- 7 + 3 induction therapy with addition of dasatinib → did not achieve remission
- Decitabine/venetoclax x 2 cycles → 20-30% blasts on marrow
- BCR-ABL resistance panel does not pick up a mutation

Questions

- What salvage regimen would you recommend for this patient?
- What is the significance of the p190 BCR-ABL mutation?
- If this was a CML blast crisis, is 7 + 3 induction therapy sufficient or should G-CLAM be considered?

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We are taking a short break!

The program will resume at 5:35 PM ET

Up Next…

Drs Benjamin Levy and Ross Camidge discuss the management of lung cancer

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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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Lung Cancer Faculty

D Ross Camidge, MD, PhD
Professor of Medicine/Oncology
Joyce Zeff Chair in Lung Cancer Research
Director of Thoracic Oncology
University of Colorado, Anschutz Medical Campus
Denver, Colorado

Benjamin Levy, MD
Associate Professor
Johns Hopkins School of Medicine
Clinical Director
Medical Director, Thoracic Oncology Program
Johns Hopkins Sidney Kimmel Cancer Center
at Sibley Memorial
Washington, DC

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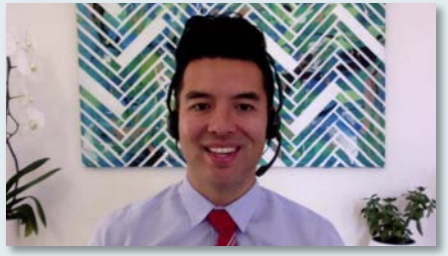
Contributing Oncologists

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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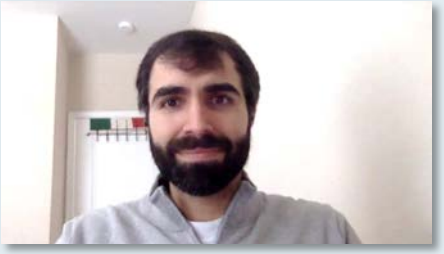
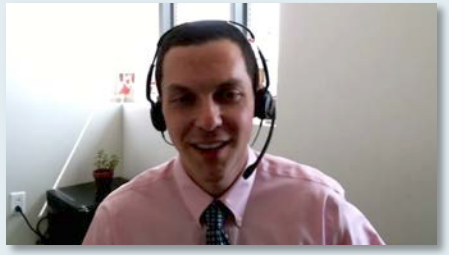
Contributing Oncologists



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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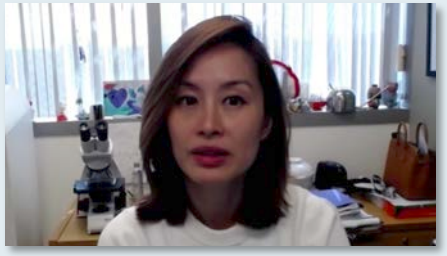
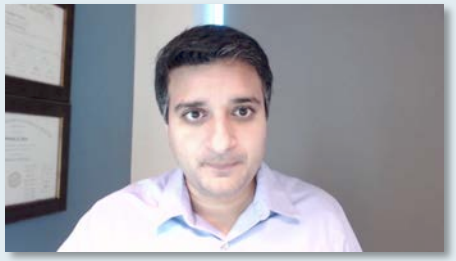
Contributing Oncologists

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 : Localized or Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

- Dr Patel: A 57-year-old woman with locally advanced NSCLC
- *Key Recent Publications and Presentations*

Module 2: Newly Diagnosed NSCLC with No Actionable Mutation

- Dr Lorber: A 66-year-old man with metastatic adenocarcinoma of the lung – PD-L1 60%, TMB 14 mut/Mb
- *Key Recent Publications and Presentations*

Module 3: NSCLC with an EGFR Tumor Mutation

- Dr Patel: A 47-year-old woman with metastatic adenocarcinoma of the lung and asymptomatic brain metastases – EGFR exon 19 mutation
- *Key Recent Publications and Presentations*

Module 4: Metastatic NSCLC Harboring Other Mutations

- Dr Gupta: A 61-year-old man with metastatic adenocarcinoma of the lung with a RET fusion
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations
- Dr Chen: A 59-year-old woman with metastatic adenocarcinoma of the lung with a ROS1 fusion
- Dr Morganstein: A 62-year-old man with metastatic adenocarcinoma of the lung with a BRAF V600E mutation
- *Key Recent Publications and Presentations*

Module 5: Extensive-Stage Small Cell Lung Cancer (SCLC)

- Dr Patel: A 63-year-old man with extensive-stage SCLC
- *Key Recent Publications and Presentations*

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Agenda

Module 1 : Localized or Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

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Module 5: Extensive-Stage Small Cell Lung Cancer (SCLC)

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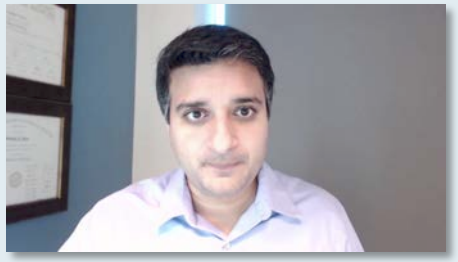
Case Presentation – Dr Patel: A 57-year-old woman with locally advanced NSCLC



Dr Sandip Patel

- Diagnosed with Stage III NSCLC
- Concurrent chemoradiation therapy → Consolidation durvalumab x 1 year
  - Surveillance scans normal past 6 months
- Six months after her last dose of immunotherapy, she presents to the ER with sudden onset blood sugar of 650, creatinine of 4, anti-bet islet antibodies; diabetic ketoacidosis (DKA)
  - Insulin initiated

Questions

- For a patient like this woman who presents to the ER with DKA but has a response to their cancer, how would you manage her now that she is on a stable insulin regimen?
- When do you typically start durvalumab after completion of radiation therapy?

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Key Recent Publications and Presentations

- Faivre-Finn C et al. **Four-Year Survival with Durvalumab After Chemoradiotherapy in Stage III NSCLC — An Update from the PACIFIC Trial.** *J Thorac Oncol* 2021;16(5):860-67.
- Saito et al. **Real-World Survey of Pneumonitis/Radiation Pneumonitis Among Patients with Locally Advanced Non-Small Cell Lung Cancer Treated with Chemoradiotherapy After Durvalumab Approval: A Multicenter Retrospective Cohort Study (HOPE-005/CRIMSON).** ASCO 2020;Abstract 9039.
- Thomas T et al. **Evaluation of the Incidence of Pneumonitis in United States Veterans with Non-Small Cell Lung Cancer Receiving Durvalumab Following Chemoradiation.** ASCO 2020;Abstract 9034.
- Reck M et al. **Pembrolizumab plus Platinum Chemotherapy and Radiotherapy in Unresectable, Locally Advanced, Stage III NSCLC (KEYNOTE-799).** IASLC WCLC 2020;Abstract 0A02.03.

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J Thorac Oncol 2021;16(5):860-67.

IASLC

BRIEF REPORT

Four-Year Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC—an Update From the PACIFIC Trial

Corinne Faivre-Finn, MD, PhD,[a,b,*] David Vicente, MD,[c] Takayasu Kurata, MD,[d]
David Planchard, MD, PhD,[e] Luis Paz-Ares, MD, PhD,[f,g]
Johan F. Vansteenkiste, MD, PhD,[h] David R. Spigel, MD,[i] Marina C. Garassino, MD,[j]
Martin Reck, MD, PhD,[k] Suresh Senan, PhD,[l] Jarushka Naidoo, MBBCH, MHS,[m,n]
Andreas Rimner, MD,[o] Yi-Long Wu, MD,[p] Jhanelle E. Gray, MD,[q]
Mustafa Özgüroğlu, MD,[r] Ki H. Lee, MD,[s] Byoung C. Cho, MD, PhD,[t]
Terufumi Kato, MD,[u] Maike de Wit, MD, PhD,[v] Michael Newton, PharmD,[w]
Lu Wang, PhD,[w] Piruntha Thiyagarajah, MD,[x] Scott J. Antonia, MD, PhD[q]

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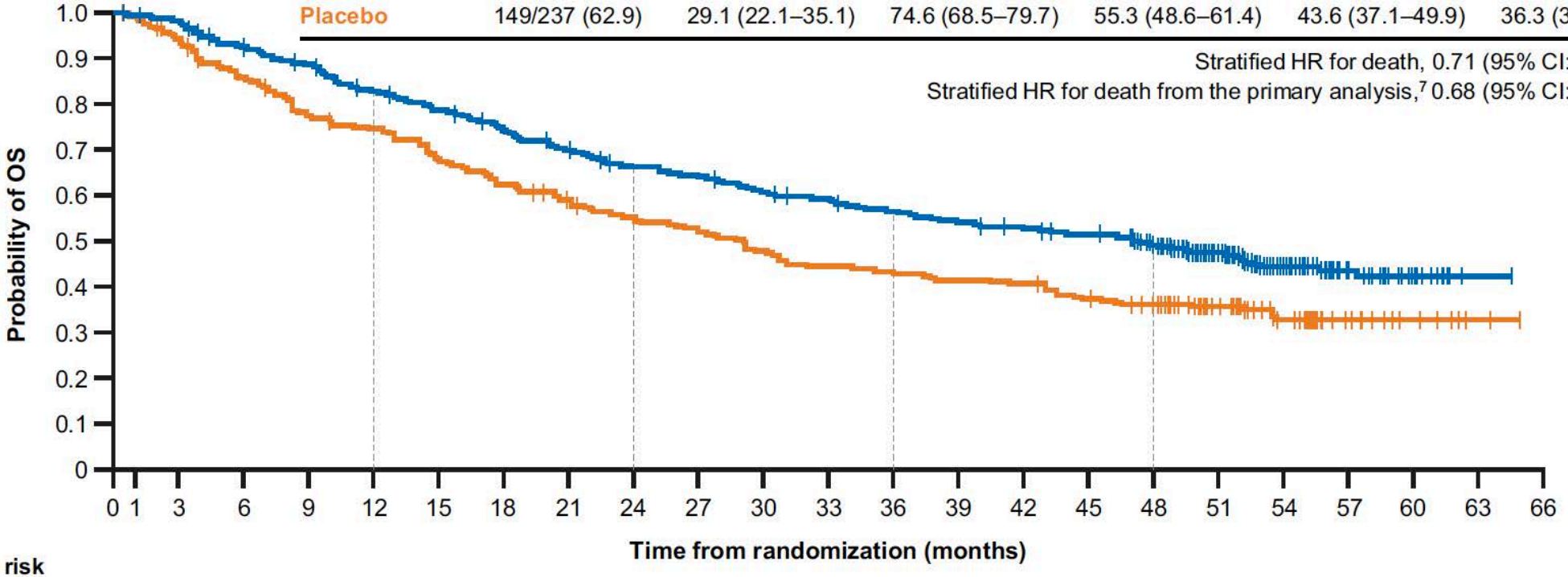
PACIFIC: 4-Year Overall Survival – Intent-To-Treat Population

	No. of events/ total no. of patients (%)	Median OS (95% CI), months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %	48-month OS rate (95% CI) %
Durvalumab	247/476 (51.9)	47.5 (38.4–52.6)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	56.7 (52.1–61.1)	49.6 (44.9–54.1)
Placebo	149/237 (62.9)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.6 (37.1–49.9)	36.3 (30.1–42.6)

Stratified HR for death, 0.71 (95% CI: 0.57–0.88)
Stratified HR for death from the primary analysis,[7] 0.68 (95% CI: 0.53–0.87)



No. at risk																						
Durvalumab	476	464	431	414	385	364	343	319	299	290	274	265	252	241	235	225	195	138	75	36	15	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	75	53	29	15	7	2	0

Faivre-Finn C et al. *J Thorac Oncol* 2021;16(5):860-67.

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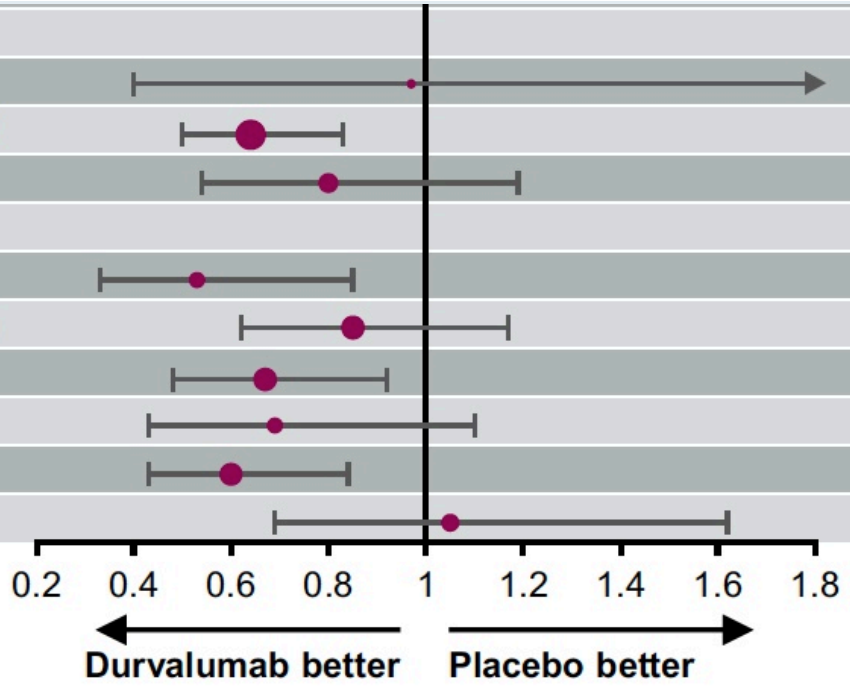
PACIFIC: 4-Year Overall Survival by EGFR and PD-L1 Status

	No. of events / No. of patients (%)		Unstratified HR (95% CI)
	Durvalumab	Placebo	
***EGFR* mutation**			
Positive	17/29 (58.6%)	7/14 (50.0%)	0.97 (0.40–2.33)
Negative	156/317 (49.2%)	105/165 (63.6%)	0.64 (0.50–0.83)
Unknown	74/130 (56.9%)	37/58 (63.8%)	0.80 (0.54–1.19)
PD-L1 status			
≥25%	50/115 (43.5%)	26/44 (59.1%)	0.53 (0.33–0.85)
<25%	102/187 (54.5%)	62/105 (59.0%)	0.85 (0.62–1.17)
Unknown	95/174 (54.6%)	61/88 (69.3%)	0.67 (0.48–0.92)
1–24% (post hoc analysis)	47/97 (48.5%)	28/47 (59.6%)	0.69 (0.43–1.10)
≥1% (post hoc analysis)	97/212 (45.8%)	54/91 (59.3%)	0.60 (0.43–0.84)
<1% (post hoc analysis)	55/90 (61.1%)	34/58 (58.6%)	1.05 (0.69–1.62)



Faivre-Finn C et al. *J Thorac Oncol* 2021;16(5):860-67.

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Real-World Rates of Pneumonitis After Consolidation Durvalumab

Real-World Survey of Pneumonitis/Radiation Pneumonitis in LA-NSCLC After Approval of Durvalumab: HOPE-005/CRIMSON Retrospective Cohort Study

- >80% developed pneumonitis
- More than half of them were asymptomatic, but 5% needed HOT and 1.5% developed fatal pneumonitis
- V20 was an independent risk factor for symptomatic pneumonitis (Grade ≥2)
- With careful consideration, durvalumab rechallenge could be an option after corticosteroid therapy for pneumonitis

Incidence of Pneumonitis in US Veterans with NSCLC Receiving Durvalumab After Chemoradiation Therapy

- In this real-world cohort, clinically significant pneumonitis was
  - More frequent compared to clinical trial reports
    - Asymptomatic infiltrates on imaging: 39.8%
    - Clinically significant pneumonitis: 21.1%
      - Grade 2 (7.3%), Grade 3 (11.4%), Grade 4 (1.6%), Grade 5 (0.8%)
  - Not associated with increased risk of death

Saito et al. ASCO 2020;Abstract 9039. Thomas T et al. ASCO 2020;Abstract 9034.

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IASLC/WCLC 2020;Abstract 0A02.03.

Pembrolizumab Plus Platinum Chemotherapy and Radiotherapy in Unresectable, Locally Advanced, Stage III NSCLC: KEYNOTE-799

M. Reck,[1] K.H. Lee,[2] N. Frost,[3] D.M. Kowalski,[4] V. Breder,[5] T. Pollock,[6] N. Reguart,[7] B. Houghton,[8] X. Quantin,[9] S.M. Keller,[10] H. Liu,[10] B. Piperdi,[10] S.K. Jabbour[11]

[1]LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [2]Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, South Korea; [3]Department of Infectious Diseases and Respiratory Medicine, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; [4]The Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [5]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [6]Southwestern Regional Medical Center, Inc., Cancer Treatment Centers of America, Tulsa, OK, USA; [7]Hospital Clínic de Barcelona, Barcelona, Spain; [8]Mid North Coast Cancer Institute, Port Macquarie Base Hospital, Port Macquarie, NSW, Australia; [9]Department of Medical Oncology, Montpellier Cancer Institute, Montpellier, France; [10]Merck & Co., Inc., Kenilworth, NJ, USA; [11]Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ, USA

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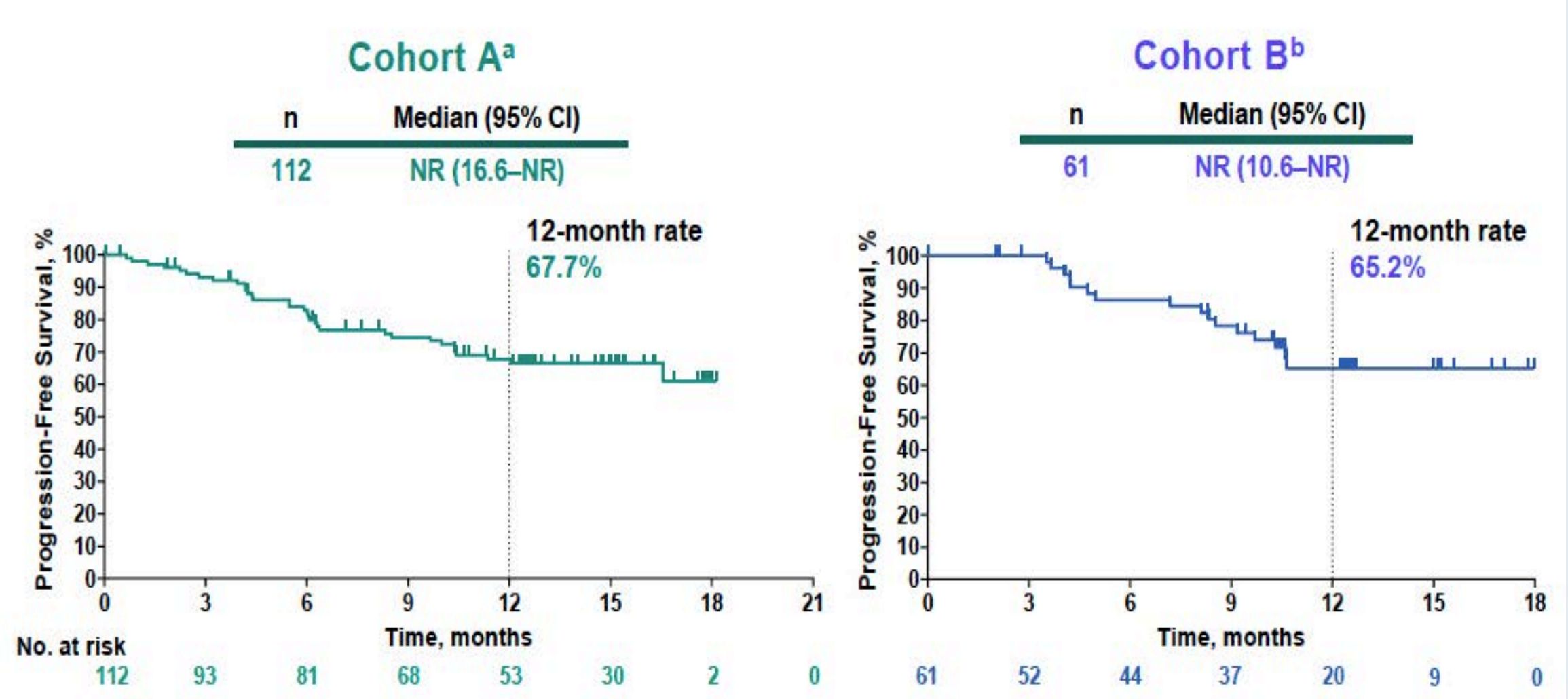
KEYNOTE-799: Progression-Free Survival



Reck M et al. IASLC/WCLC 2020;Abstract 0A02.03.

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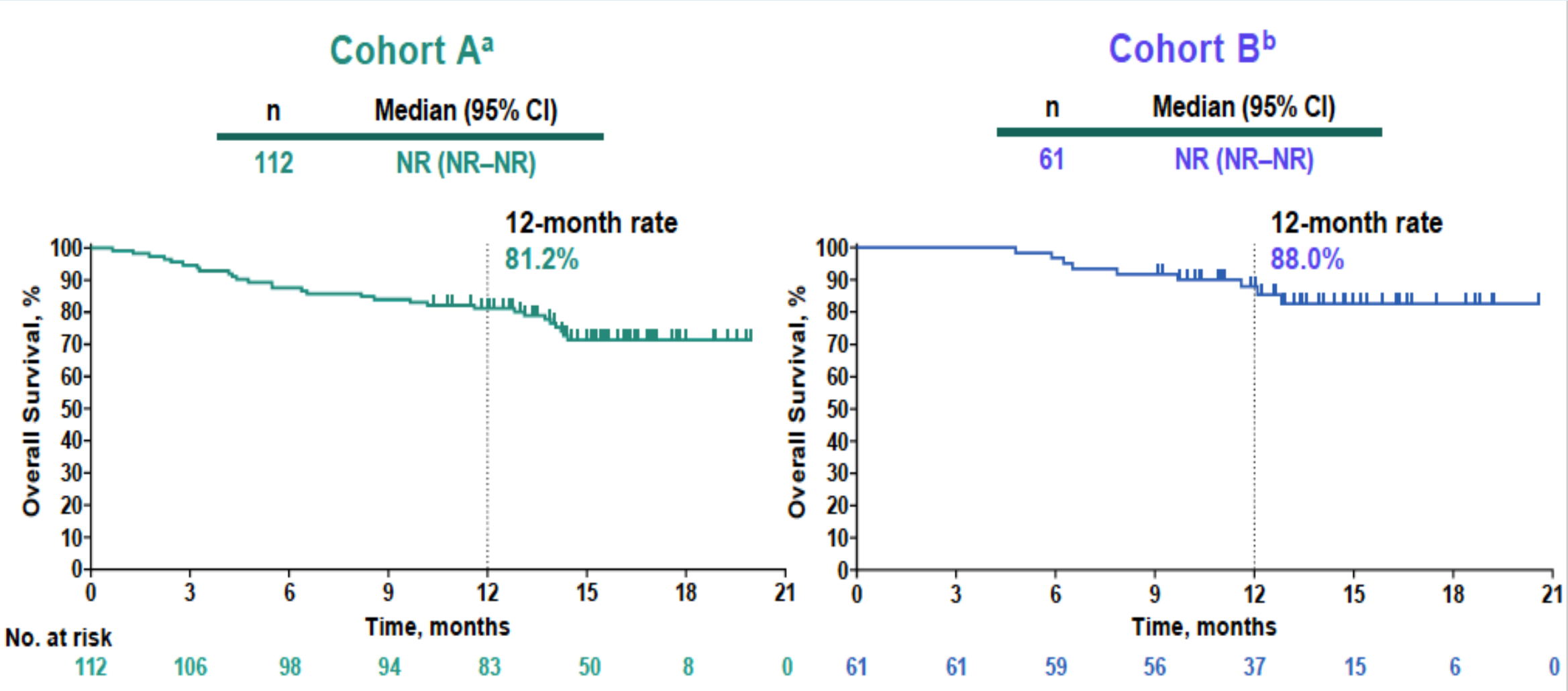
KEYNOTE-799: Overall Survival



Reck M et al. IASLC/WCLC 2020;Abstract 0A02.03.

RTP RESEARCH TO PRACTICE

Pivotal Phase III IMpower010 Trial Demonstrates DFS Improvement with Adjuvant Atezolizumab for Resectable Early-Stage Lung Cancer

Press Release — March 22, 2021

"Today [it was] announced that the Phase III IMpower010 study evaluating atezolizumab, compared with best supportive care (BSC), met its primary endpoint of disease-free survival (DFS) at the interim analysis. Atezolizumab showed a statistically significant improvement in DFS as adjuvant therapy following surgery and chemotherapy in all randomized Stage II-IIIA populations with non-small cell lung cancer (NSCLC). The magnitude of DFS benefit was particularly pronounced in the PD-L1-positive population.

Follow-up will continue with planned analyses of DFS in the overall intent-to-treat (ITT) population, which at the time of analysis did not cross the threshold, and overall survival (OS) data, which were immature at the time of interim analysis. Safety for atezolizumab was consistent with its known safety profile and no new safety signals were identified. Results from the IMpower010 study will be presented at an upcoming medical meeting and submitted to health authorities globally, including the US Food and Drug Administration and the European Medicines Agency."

https://www.businesswire.com/news/home/20210321005036/en/

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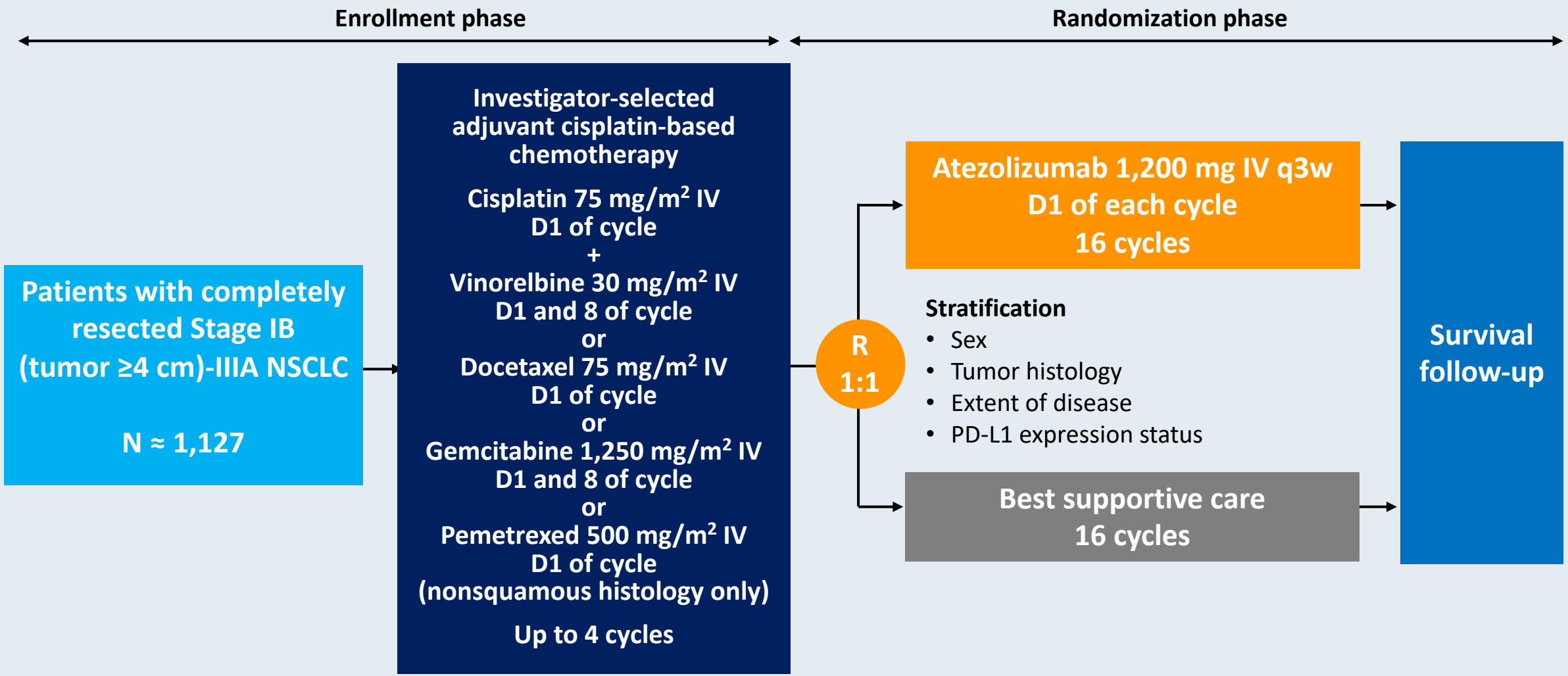
IMpower010: Phase III Trial Design



Primary endpoint: Disease-free survival (DFS)

Secondary endpoints include overall survival, 3- and 5-year DFS rates, safety and tolerability

Wakelee HA et al. ASCO 2017;Abstract TPS8576.

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IMpower010: Primary Results of a Phase III Global Study of Atezolizumab versus Best Supportive Care After Adjuvant Chemotherapy in Resected Stage IB-IIIA Non-Small Cell Lung Cancer (NSCLC)

Wakelee HA et al.
ASCO 2021;Abstract 8500.

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

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Agenda

Module 1 : Localized or Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

- Dr Patel: A 57-year-old woman with locally advanced NSCLC
- *Key Recent Publications and Presentations*

Module 2: Newly Diagnosed NSCLC with No Actionable Mutation

- Dr Lorber: A 66-year-old man with metastatic adenocarcinoma of the lung – PD-L1 60%, TMB 14 mut/Mb
- *Key Recent Publications and Presentations*

Module 3: NSCLC with an EGFR Tumor Mutation

- Dr Patel: A 47-year-old woman with metastatic adenocarcinoma of the lung and asymptomatic brain metastases – EGFR exon 19 mutation
- *Key Recent Publications and Presentations*

Module 4: Metastatic NSCLC Harboring Other Mutations

- Dr Gupta: A 61-year-old man with metastatic adenocarcinoma of the lung with a RET fusion
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations
- Dr Chen: A 59-year-old woman with metastatic adenocarcinoma of the lung with a ROS1 fusion
- Dr Morganstein: A 62-year-old man with metastatic adenocarcinoma of the lung with a BRAF V600E mutation
- *Key Recent Publications and Presentations*

Module 5: Extensive-Stage Small Cell Lung Cancer (SCLC)

- Dr Patel: A 63-year-old man with extensive-stage SCLC
- *Key Recent Publications and Presentations*

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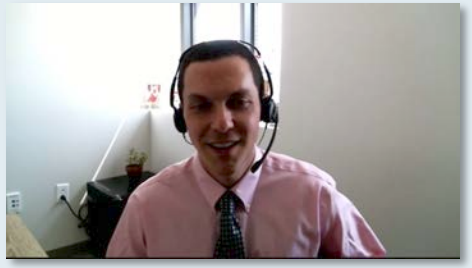
Case Presentation – Dr Lorber: A 66-year-old man with metastatic adenocarcinoma of the lung – PD-L1 60%, TMB 14 mut/Mb



Dr Jeremy Lorber

- Presented with highly symptomatic malignant pleural and pericardial effusion
- Lung mass biopsy: consistent with non-small cell adenocarcinoma
  - PD-L1 60%, TMB 14 mut/Mb
  - No driver mutations
- Pembrolizumab with a near complete response lasting 28 months
- Developed progression of lung mass and a single vertebral metastasis
- RT to vertebra metastasis, added carboplatin/pemetrexed to pembrolizumab

Questions

- Given his prolonged response to checkpoint inhibitor therapy, should it continue to be included as part of his second-line therapy?

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Which first-line treatment regimen would you recommend for a 65-year-old patient with metastatic nonsquamous lung cancer, no identified targetable mutations and a PD-L1 TPS of 0%?

1. Chemotherapy +/- bevacizumab
2. Anti-PD-1/PD-L1 antibody alone
3. Carboplatin/pemetrexed/pembrolizumab
4. Atezolizumab/carboplatin/*nab* paclitaxel
5. Atezolizumab/carboplatin/paclitaxel/bevacizumab
6. Ipilimumab/nivolumab
7. Ipilimumab/nivolumab + chemotherapy
8. Other

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Key Recent Publications and Presentations*

- Ramalingam SS et al. **Nivolumab + Ipilimumab versus Platinum-Doublet Chemotherapy as First-Line Treatment for Advanced Non-Small Cell Lung Cancer: Three-Year Update from CheckMate 227 Part 1**. ASCO 2020;Abstract 9500.
- Paz-Ares L et al. **First-Line Nivolumab plus Ipilimumab Combined with Two Cycles of Chemotherapy in Patients with Non-Small-Cell Lung Cancer (CheckMate 9LA): An International, Randomised, Open-Label, Phase 3 Trial.** *Lancet Oncol* 2021;22(2):198-211.
- Boyer M et al. **Pembrolizumab plus Ipilimumab or Placebo for Metastatic Non-Small-Cell Lung Cancer with PD-L1 Tumor Proportion Score ≥ 50%: Randomized, Double-Blind Phase III KEYNOTE-598 Study.** *J Clin Oncol* 2021;[Online ahead of print].
- Sezer A et al. **Cemiplimab Monotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer with PD-L1 of at Least 50%: A Multicentre, Open-Label, Global, Phase 3, Randomised, Controlled Trial**. *Lancet* 2021;397(10274):592-604.

*Summarized in table format

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FDA-Approved Immunotherapy Combination Options for First-Line Therapy

Combination regimen	FDA approval	Pivotal study	Histologic type	HR (OS)
Pembrolizumab + Platinum and pemetrexed[1]	8/20/18	KEYNOTE-189	Nonsquamous	0.49
Pembrolizumab + Carboplatin, paclitaxel or *nab* paclitaxel[2]	10/30/18	KEYNOTE-407	Squamous	0.64
Atezolizumab + Carboplatin and paclitaxel and bevacizumab[3]	12/6/18	IMpower150	Nonsquamous	0.78
Atezolizumab + Carboplatin and *nab* paclitaxel[4]	12/3/19	IMpower130	Nonsquamous	0.79
Nivolumab + Ipilimumab[5]	5/15/20	CheckMate-227	PD-L1 TPS ≥1, EGFR and/or ALK wt	0.62
Nivolumab + Ipilimumab and chemotherapy[6]	5/26/20	CheckMate-9LA	EGFR and/or ALK wt	0.69

[1] Gandhi. *NEJM* 2018. [2] Paz-Ares.*NEJM* 2018. [3] Socinski *NEJM* 2018. [4] West. *Lancet Oncol* 2019. [5] Hellmann. *N Engl J Med* 2019. [6] Reck. ASCO 2020;Ab 9501.

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FDA-Approved Immunotherapy Monotherapy Options for First-Line Therapy (continued)

Monotherapy	FDA approval	Pivotal study	Histologic type	HR (OS)
Pembrolizumab[1,2]	4/11/19 10/24/16	KEYNOTE-042 KEYNOTE-024	PD-L1 TPS ≥1%	0.63
Atezolizumab[3]	5/18/20	IMpower110	PD-L1 TPS ≥50, EGFR and/or ALK wt	0.59
Cemiplimab[4]	2/22/2021	EMPOWER-Lung 1 (Study 1624)	PD-L1 TPS ≥50, EGFR and/or ALK and/or ROS1 wt	0.57

[1] Mok. *Lancet* 2019. [2] Reck. *J Clin Oncol* 2019. [3] Spigel. ESMO 2019;Ab LBA78. [4] Sezer. *Lancet* 2021.

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FDA Approves Cemiplimab-rwlc Monotherapy for NSCLC with High PD-L1 Expression

Press Release – February 22, 2021

"The Food and Drug Administration approved cemiplimab-rwlc for the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) (locally advanced who are not candidates for surgical resection or definitive chemoradiation or metastatic) whose tumors have high PD-L1 expression (Tumor Proportion Score [TPS] > 50%) as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations.

Efficacy was evaluated in Study 1624 (NCT03088540), a multi-center, randomized, open-label trial in 710 patients with locally advanced NSCLC who were not candidates for surgical resection or definitive chemoradiation or with metastatic NSCLC. Patients were randomized (1:1) to receive cemiplimab-rwlc 350 mg intravenously every 3 weeks for up to 108 weeks or a platinum-based chemotherapy. The main efficacy outcome measures were overall survival (OS) and progression-free survival (PFS) per blinded independent central review (BICR)."

www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-cemiplimab-rwlc-non-small-cell-lung-cancer-high-pd-l1-expression

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Durvalumab and Tremelimumab with Chemotherapy Demonstrate Overall Survival Benefit in POSEIDON Trial for First-Line Stage IV NSCLC

Press Release — May 7, 2021

"Positive high-level results from the final analysis of POSEIDON showed the combination of durvalumab, tremelimumab and chemotherapy demonstrated a statistically significant and clinically meaningful overall survival (OS) benefit versus chemotherapy alone. This immunotherapy combination also demonstrated a statistically significant improvement in progression-free survival (PFS) versus chemotherapy alone, as previously reported in October 2019. Patients in this arm were treated with a short course of tremelimumab, an anti-CTLA4 antibody, over a 16-week period in addition to durvalumab and standard chemotherapy.

The durvalumab plus chemotherapy arm demonstrated a statistically significant improvement in PFS versus chemotherapy in the previous analysis, but the OS trend observed in this analysis did not achieve statistical significance. Patients in the control arm were treated with up to six cycles of chemotherapy, while those in the experimental arms were treated with up to four cycles.

Each combination demonstrated an acceptable safety profile, and no new safety signals were identified. The combination with tremelimumab delivered a broadly similar safety profile to the durvalumab and chemotherapy combination and did not lead to an increased discontinuation of treatment."

https://www.astrazeneca.com/media-centre/press-releases/2021/imfinzi-and-tremelimumab-showed-survival-in-poseidon.html

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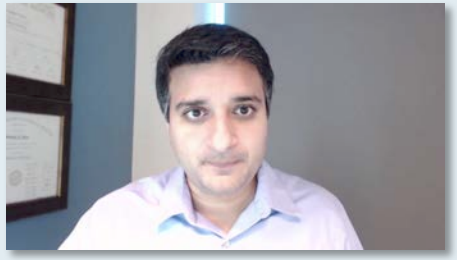
Case Presentation – Dr Patel: A 47-year-old woman with metastatic adenocarcinoma of the lung and asymptomatic brain metastases – EGFR exon 19 mutation



Dr Sandip Patel

- Newly diagnosed metastatic lung adenocarcinoma
  - >50 brain metastases but is asymptomatic
- Biopsy: Insufficient tissue for next-generation, PD-L1 50%
- Sent cfDNA for testing: EGFR exon 19 mutation
- Osimertinib
  - MRI after 1 month: Two remaining metastases, which were decreased in size

Questions

- For a patient who's asymptomatic but with 2 to 3 CNS metastases, what is your preferred strategy for managing those brain metastases?
- What is your preferred management of some of the chronic side effects associated with EGFR TKIs, such as the paronychia, dermatitis and diarrhea?

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Regulatory and reimbursement issues aside, which adjuvant systemic therapy would you generally recommend for a patient with Stage IIB nonsquamous NSCLC and an EGFR exon 19 deletion?

1. Chemotherapy
2. Osimertinib
3. Chemotherapy followed by osimertinib
4. Other

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Key Recent Publications and Presentations

- Wu YL et al. **Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer.** *N Engl J Med* 2020;383(18):1711-23.
- Soria JC et al. **Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer.** *N Engl J Med* 2018;378(2):113-25.
- Yang JCH et al. **Osimertinib in Patients with Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer and Leptomeningeal Metastases: The BLOOM Study.** *J Clin Oncol* 2020;38(6):538-47.
- Sabari JK et al. **Amivantamab in Post-platinum EGFR Exon 20 Insertion Mutant Non-Small Cell Lung Cancer.** IASCL WCLC 2020;Abstract OA04.04.
- Smit EF et al. **Trastuzumab Deruxtecan in HER2-Mutated Metastatic Non-Small Cell Lung Cancer (NSCLC): Interim Results of DESTINY-Lung01.** WCLC 2021;Abstract MA11.03.
- Nakagawa K et al. **Trastuzumab Deruxtecan in HER2-Overexpressing Metastatic Non-Small Cell Lung Cancer (NSCLC): Interim Results of DESTINY-Lung01.** WCLC 2021;Abstract OA04.05.

RTP RESEARCH TO PRACTICE

FDA Approves Osimertinib as Adjuvant Therapy for NSCLC with EGFR Mutations

Press Release — December 18, 2020

- The FDA approved osimertinib as adjuvant therapy after tumor resection in patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- Efficacy was demonstrated in the randomized, double-blind, placebo-controlled ADAURA trial for patients with EGFR exon 19 deletions or exon 21 L858R mutation-positive NSCLC who had complete tumor resection, with or without prior adjuvant chemotherapy.
- Eligible patients with resectable tumors (stage IB – IIIA) were required to have predominantly non-squamous histology and EGFR exon 19 deletions or exon 21 L858R mutations identified prospectively from tumor tissue in a central laboratory EGFR Mutation Test.

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-osimertinib-adjuvant-therapy-non-small-cell-lung-cancer-egfr-mutations

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

Yi-Long Wu, M.D., Masahiro Tsuboi, M.D., Jie He, M.D., Thomas John, Ph.D., Christian Grohe, M.D., Margarita Majem, M.D., Jonathan W. Goldman, M.D., Konstantin Laktionov, Ph.D., Sang-We Kim, M.D., Ph.D., Terufumi Kato, M.D., Huu-Vinh Vu, M.D., Ph.D., Shun Lu, M.D., Kye-Young Lee, M.D., Ph.D., Charuwan Akewanlop, M.D., Chong-Jen Yu, M.D., Ph.D., Filippo de Marinis, M.D., Laura Bonanno, M.D., Manuel Domine, M.D., Ph.D., Frances A. Shepherd, M.D., Lingmin Zeng, Ph.D., Rachel Hodge, M.Sc., Ajlan Atasoy, M.D., Yuri Rukazenkov, M.D., Ph.D., and Roy S. Herbst, M.D., Ph.D.,

N Engl J Med 2020;383)18):1711-23.

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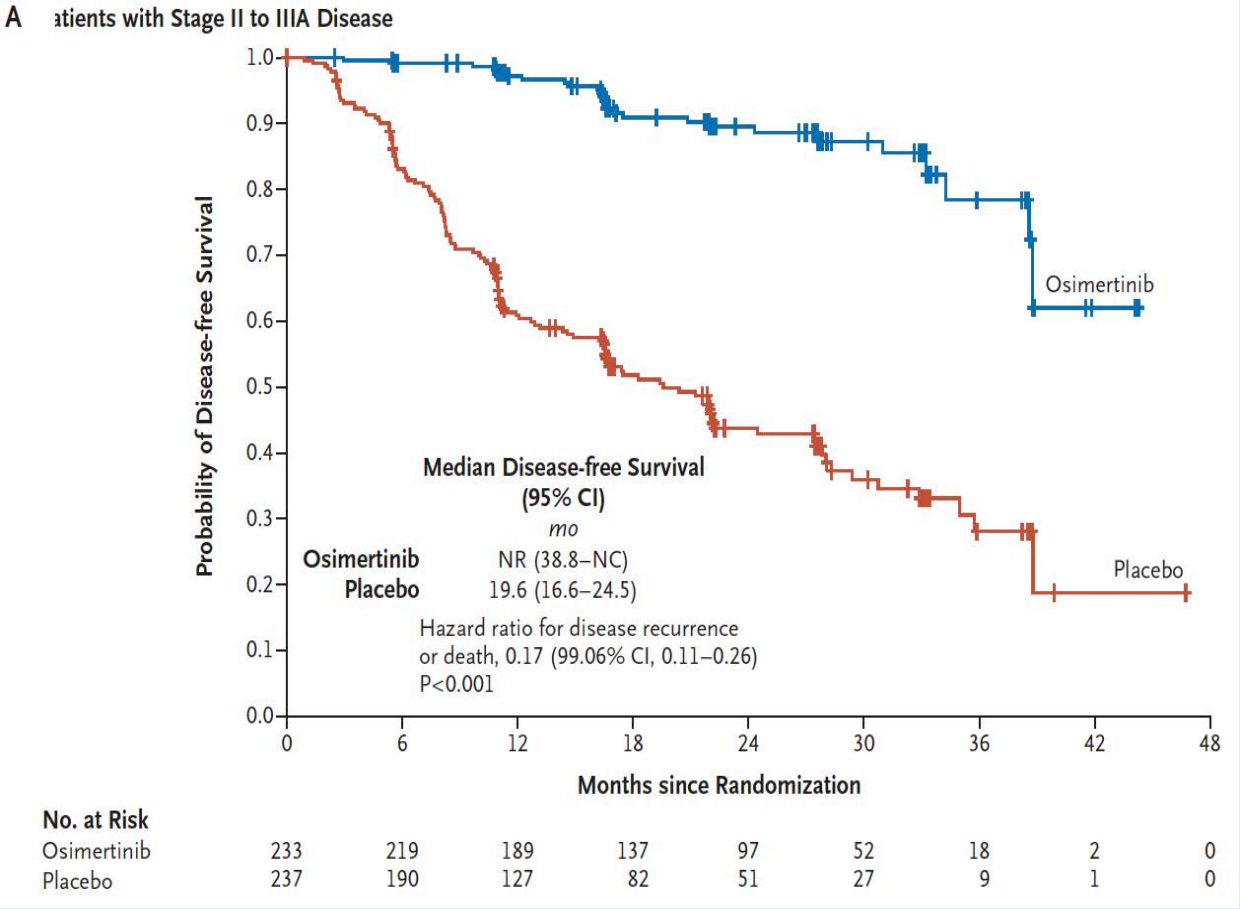
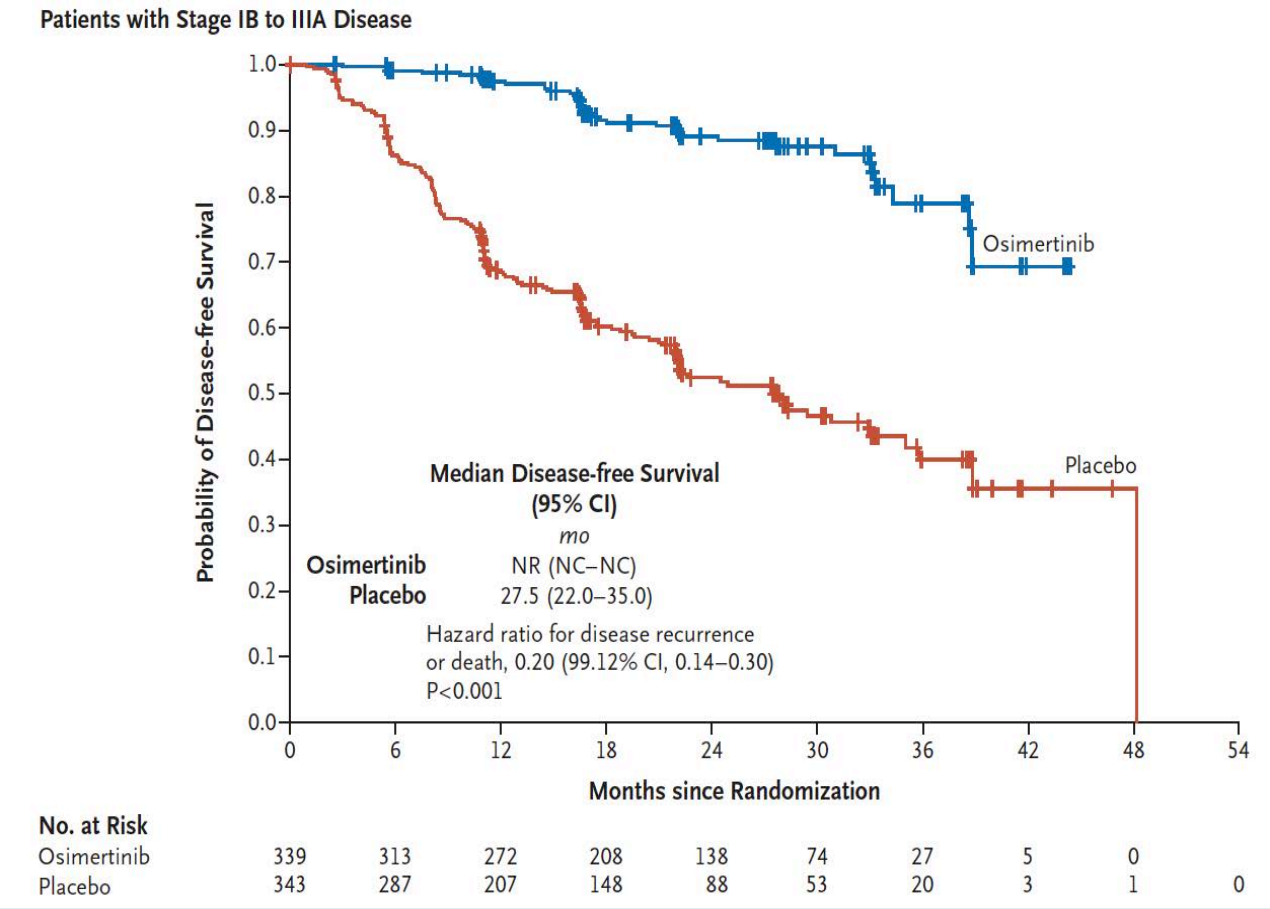
ADAURA: Disease-Free Survival by Stage





Wu YL et al. *N Engl J Med* 2020;383(18):1711-23.

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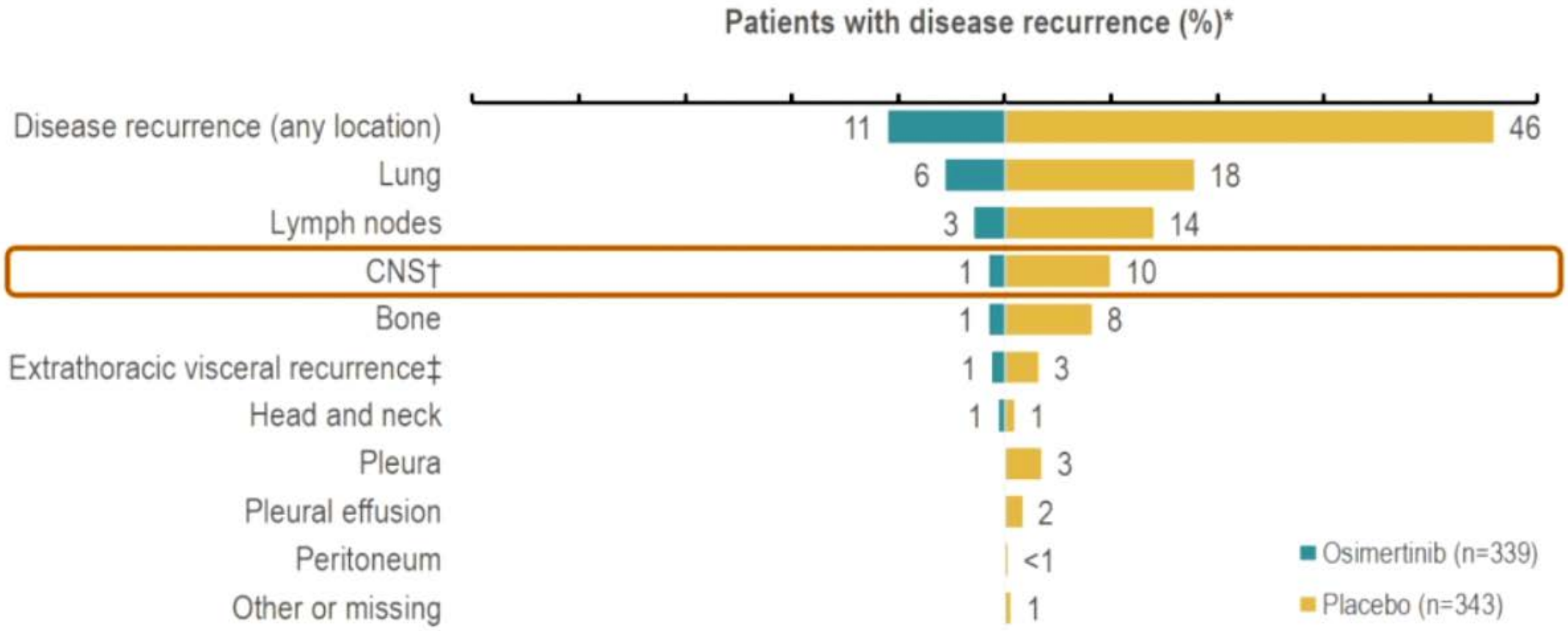
ADAURA: Sites of Disease Recurrence



Tsuboi M et al. ESMO 2020;Abstract LBA1.

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ADAURA: CNS DFS Events

- Overall, 45 patients (osimertinib n=6, placebo n=39) had CNS DFS events

	Overall population	
Patients, n (%)	**Osimertinib n=339**	**Placebo n=343**
CNS DFS events:	6 (2%)	39 (11%)
CNS recurrence	4 (1%)	33 (10%)
Death	2 (1%)	6 (2%)

Tsuboi M et al. ESMO 2020;Abstract LBA1.

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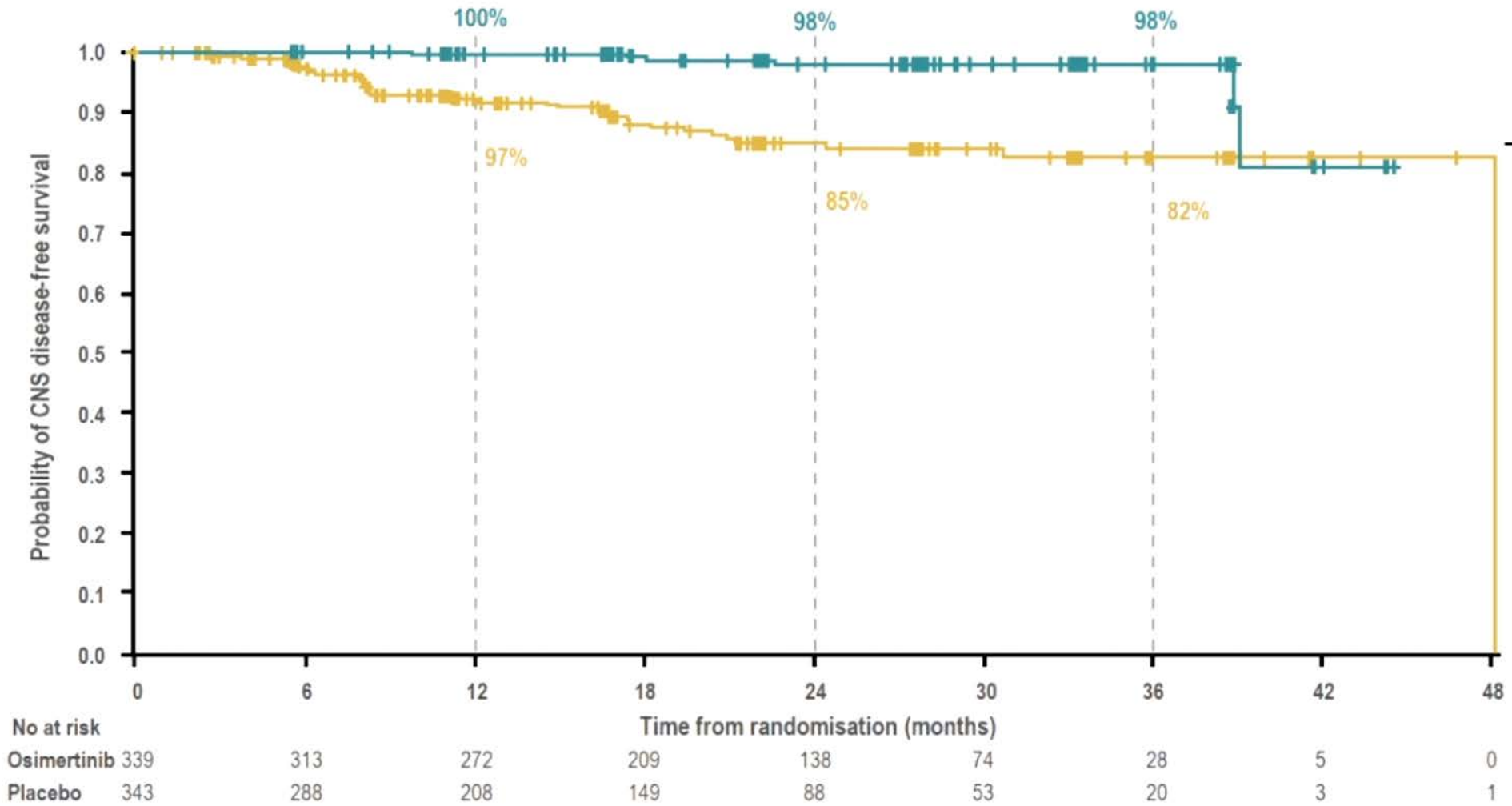
ADAURA: CNS DFS in Overall Population



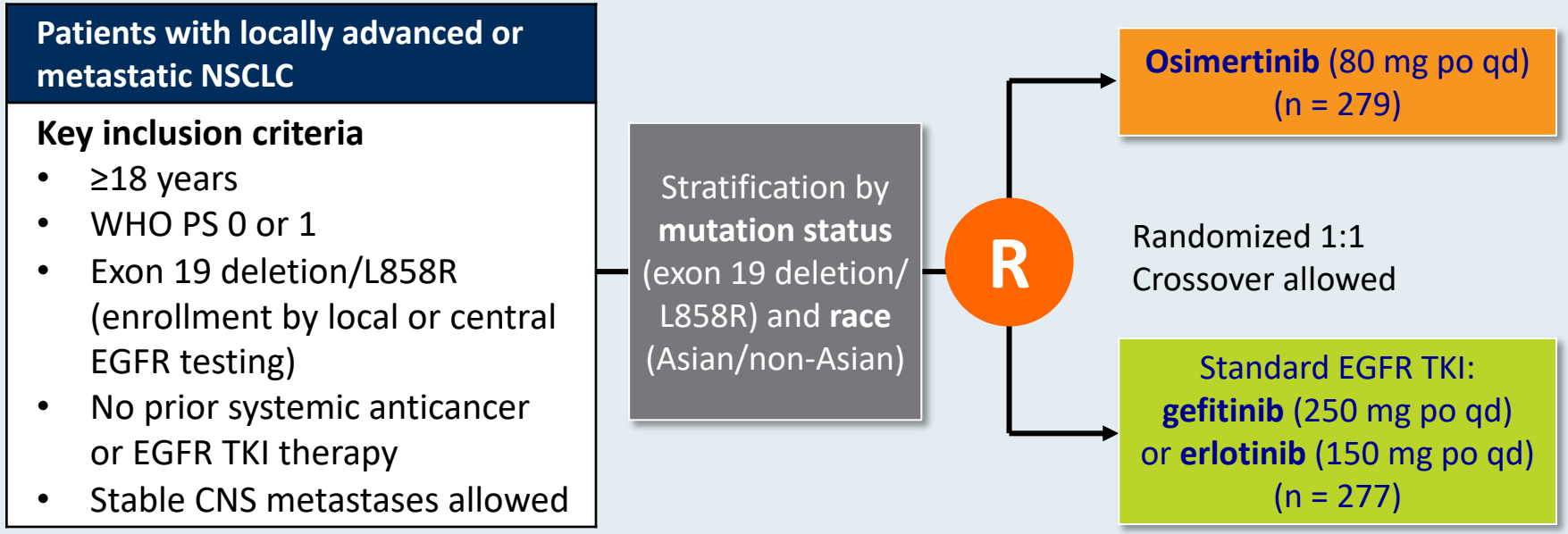
Median CNS DFS, months (95% CI)	
Osimertinib	NR (39, NC)
Placebo	48.2 (NC, NC)
HR* (95% CI)	0.18 (0.10, 0.33); p<0.0001

Maturity 7%:
osimertinib 2%, placebo 11%

Tsuboi M et al. ESMO 2020;Abstract LBA1.

RTP RESEARCH TO PRACTICE

FLAURA: A Phase III Study of Osimertinib versus Gefitinib or Erlotinib as First-Line Treatment for Advanced NSCLC with EGFR Tumor Mutation



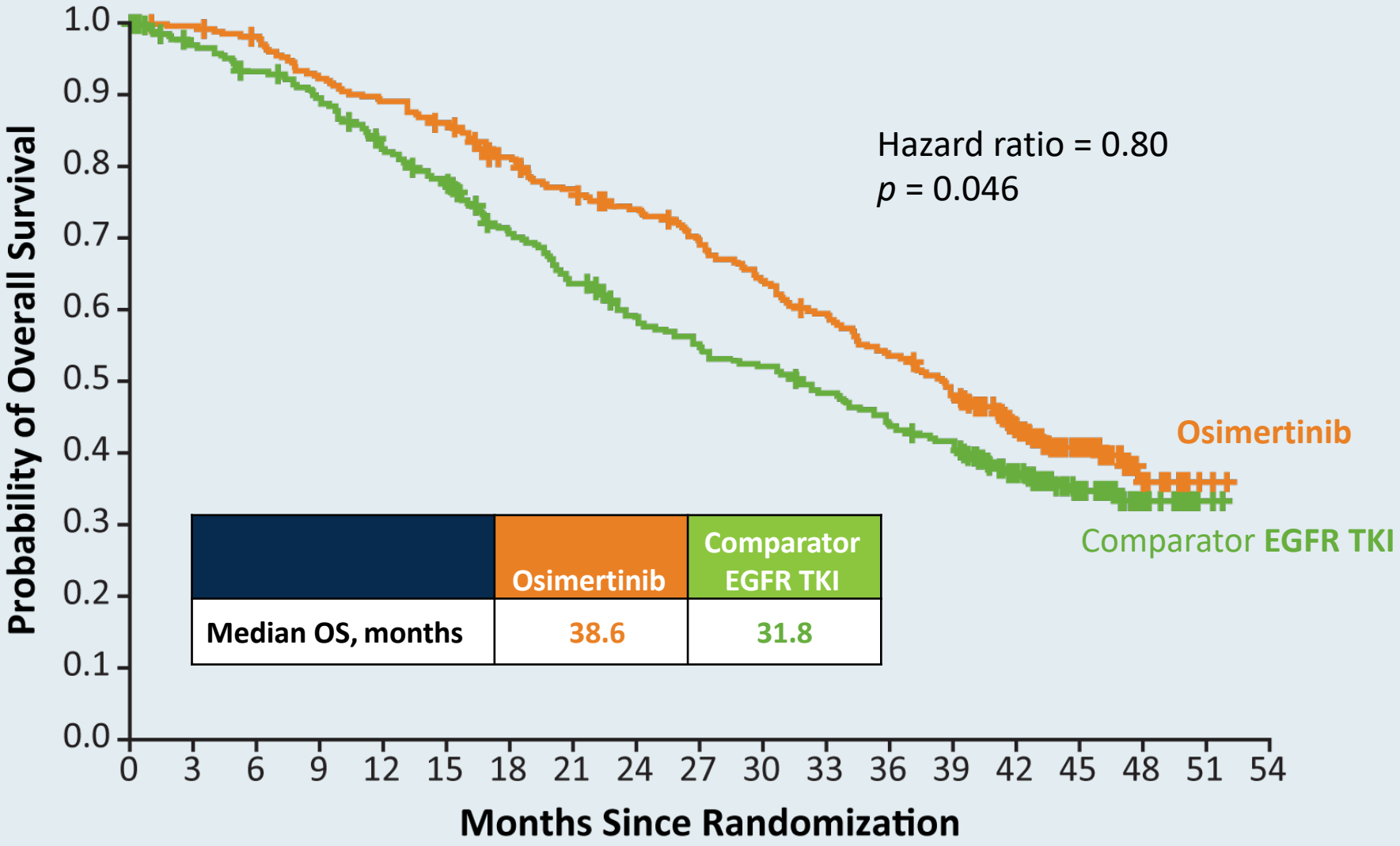
Primary endpoint: Progression-free survival (PFS) based on investigator assessment (per RECIST 1.1)
Key secondary endpoints: Objective response rate, overall survival and quality of life

NSCLC= non-small cell lung cancer; TKI = tyrosine kinase inhibitor

www.clinicaltrials.gov. March 2020; Soria JC et al. *N Engl J Med* 2018;378(2):113-25.

RTP RESEARCH TO PRACTICE

FLAURA: Final Overall Survival Analysis



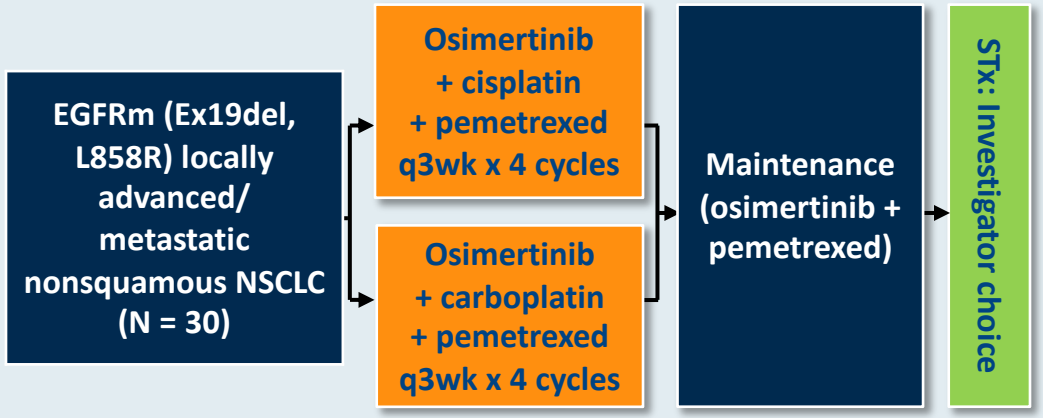
	Osimertinib	Comparator EGFR TKI
Median OS, months	38.6	31.8

Ramalingam SS et al. *N Engl J Med* 2020;382(1):41-50.

RTP RESEARCH TO PRACTICE

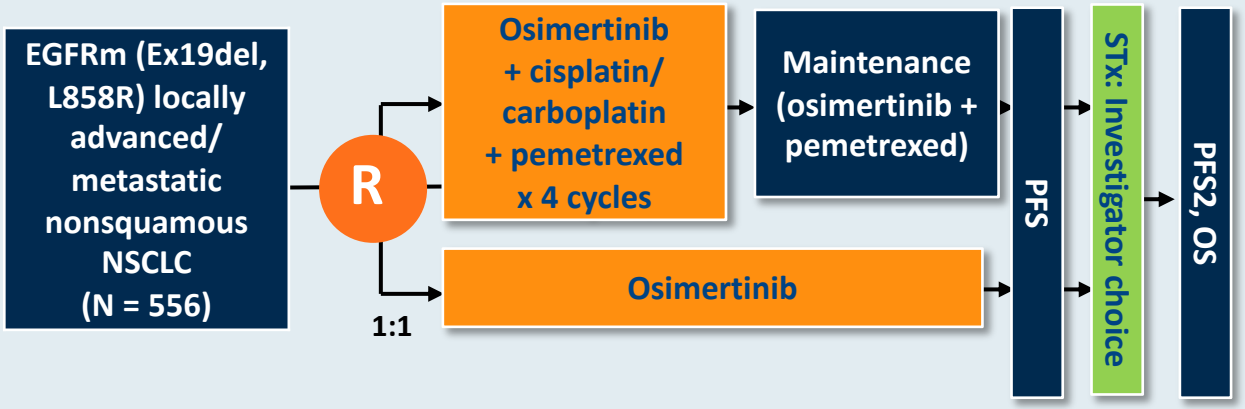
FLAURA2 Study Design: Safety Run-In and Randomization Phases

Study design: Safety run-in phase



- Osimertinib dose is 80 mg daily during induction and maintenance
- Selection of cisplatin or carboplatin is the investigator's choice
- Safety parameters are primary endpoints

Study design: Randomization phase



- Osimertinib given at a dose of 80 mg daily during induction and maintenance
- Osimertinib dose can be reduced to 40 mg daily for management of AEs; chemotherapy dose interruption/reduction is to be prioritized over osimertinib reduction/interruption
- Randomization will be stratified by race (Asian versus non-Asian), WHO PS (0 vs 1) and tissue EGFR mutation test at enrollment
- Involvement planned for approximately 248 sites in 27 countries

EGFR = epidermal growth factor receptor; EGFRm = EGFR mutation; Ex19del = exon 19 deletion; STx = subsequent treatment; PFS2 = time from randomization to second disease progression or death on a subsequent treatment; OS = overall survival; WHO = World Health Organization

Jänne PA et al. IASLC 2019;Abstract OA07.01.

RTP RESEARCH TO PRACTICE

rapid communications

Osimertinib in Patients With Epidermal Growth Factor Receptor Mutation–Positive Non–Small-Cell Lung Cancer and Leptomeningeal Metastases: The BLOOM Study

James C.H. Yang, MD, PhD[1]; Sang-We Kim, MD, PhD[2]; Dong-Wan Kim, MD, PhD[3]; Jong-Seok Lee, MD, PhD[4]; Byoung Chul Cho, MD, PhD[5]; Jin-Seok Ahn, MD, PhD[6]; Dae H. Lee, MD, PhD[2]; Tae Min Kim, MD[3]; Jonathan W. Goldman, MD[7]; Ronald B. Natale, MD[8]; Andrew P. Brown, MSc, MPhil[9]; Barbara Collins, PhD[9]; Juliann Chmielecki, PhD[10]; Karthick Vishwanathan, PhD[1,10]; Ariadna Mendoza-Naranjo, PhD[9]; and Myung-Ju Ahn, MD, PhD[6]

J Clin Oncol 2020;38(6):538-47.

RTP RESEARCH TO PRACTICE

BLOOM: Osimertinib in Patients with NSCLC with an EGFR Mutation and Leptomeningeal Metastases (LM)

Patients with cytologically confirmed LM received osimertinib 160 mg once daily.

	Leptomeningeal metastases (N = 37)
ORR by BICR	62%
Complete response	32%
Partial response	30%
Stable disease ≥ 6 weeks	32%
Progression	3%
Not evaluable	3%
Median DoR	15.2 months

Yang JCH et al. *J Clin Oncol* 2020;38(6):538-47.

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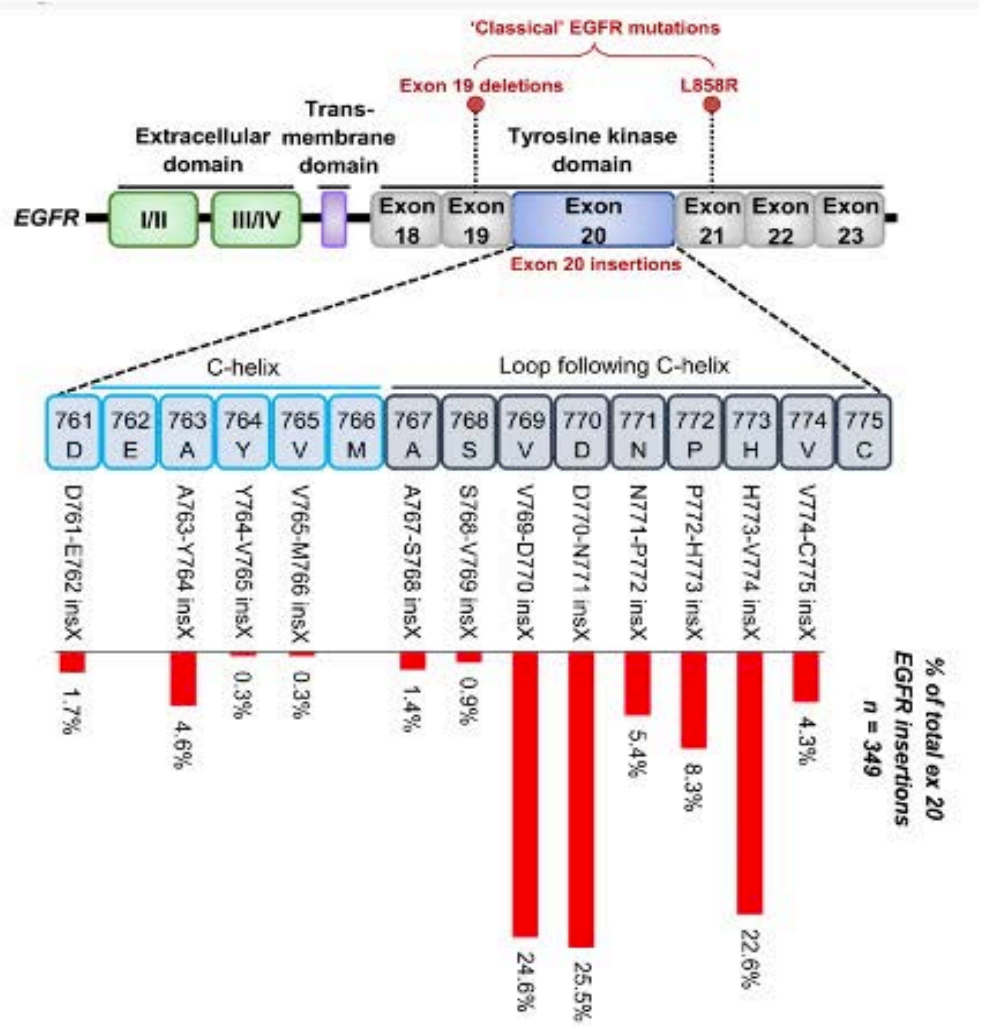
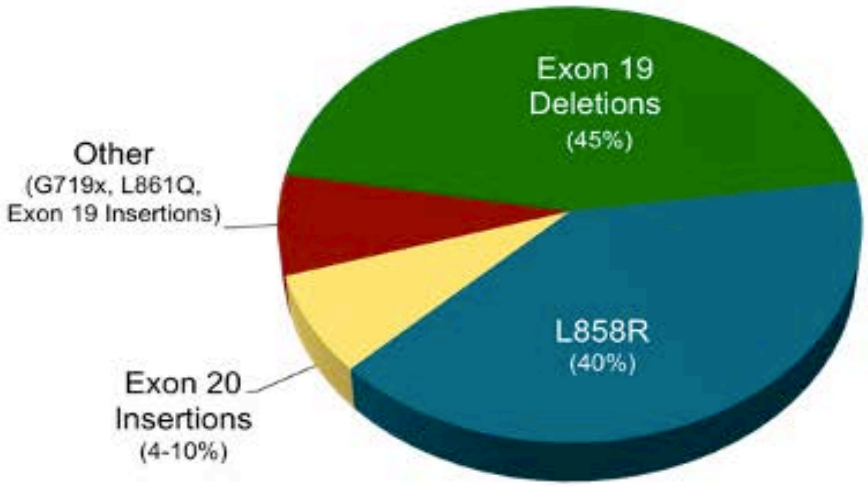
Frequency of EGFR Exon 20 Mutations





Exon 20 NSCLC: US and China				
		Exon 20 Frequency	Total Number of NSCLC Patients/year	
United States	EGFR HER2	2.1% 1.5%	3.6%	7700
China	EGFR HER2	2.4% 3.9%	6.3%	41100

Courtesy of Zosia Piotrowska, MD.

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Emerging Targeted Therapies for EGFR Exon 20 Mutations

Drug	MOA	N	ORR	mPFS	Major toxicities	Discont due to toxicities	FDA Status re Exon 20
Poziotinib[1,2]	TKI	115	15%	4.2 mo	Diarrhea Rash	12%	Fast track designation March 2021
Mobocertinib[3,4]	TKI	28	43%	7.3 mo	Diarrhea Rash Nausea	14%	Breakthrough therapy designation April 2020
Amivantamab[5,6]	EGFR/MET Ab	39	36%	8.3 mo	Rash Infusion reaction Paronychia	6%	Breakthrough therapy designation March 2020
Osimertinib[7]	TKI	17	24%	9.6 mo	Diarrhea Rash Platelets	6%	No indication in Exon 20
CLN-081[8]	TKI	22	35%	NR	Rash Stomatitis	0%	Investigational

1. Le X. AACR 2020, 2. Socinski M. ESMO 2020; 3. Riely G. ESMO 2020; 4. Zhou C. IASLC 2020; 5. Park K. ASCO 2020; 6. Sabari JK. IASLC 2020; 7. Piotrowska Z. ASCO 2020; 8. Piotrowska Z. ESMO 2020.

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IASLC
2020 World Conference on Lung Cancer Singapore
wclc2020.IASLC.com | #WCLC20
CONQUERING THORACIC CANCERS WORLDWIDE

Amivantamab in Post-platinum EGFR Exon 20 Insertion Mutant Non-small Cell Lung Cancer

Joshua K. Sabari[1], Catherine A. Shu[2], Keunchil Park[3], Natasha B. Leighl[4], Paul Mitchell[5], Sang-We Kim[6], Jong-Seok Lee[7], Dong-Wan Kim[8], Santiago Viteri[9], Alexander I. Spira[10], Ji-Youn Han[11], José Trigo[12], Chee Khoon Lee[13], Ki Hyeong Lee[14], Nicolas Girard[15], Tsung-Ying Yang[16], Koichi Goto[17], Rachel E. Sanborn[18], James Chih-Hsin Yang[19], Joshua C. Curtin[20], John Xie[20], Amy Roshak[20], Meena Thayu[20], Roland E. Knoblauch[20], Byoung Chul Cho[21]

IASLC/WCLC 2020;Abstract OA04.04

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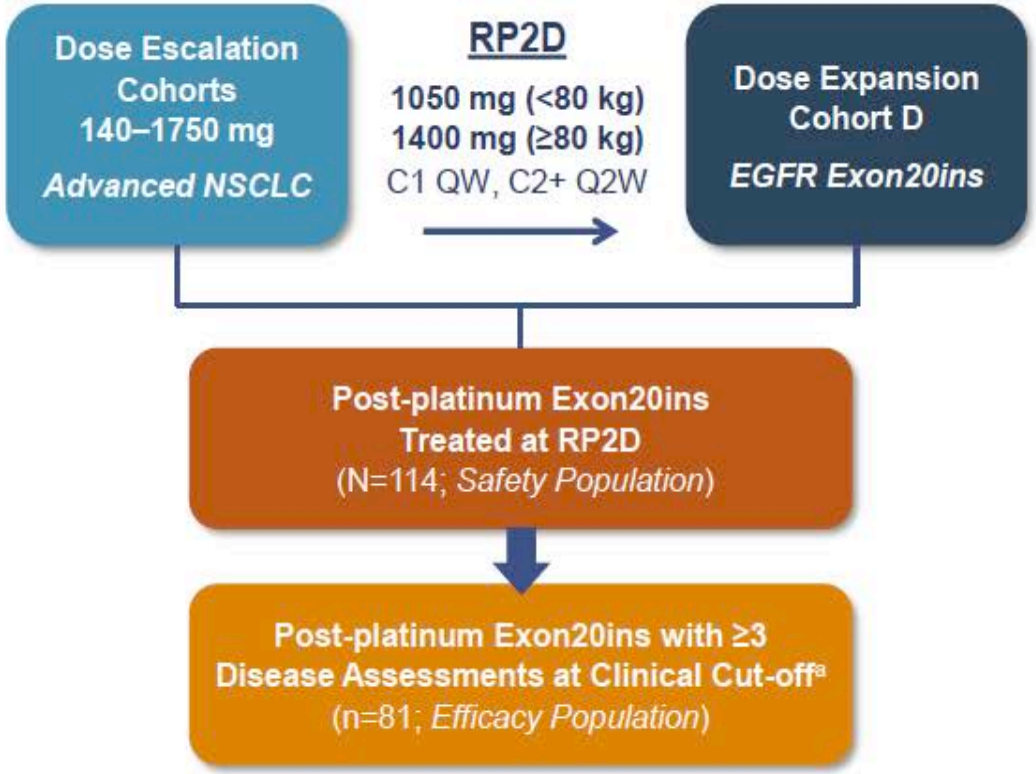
CHRYSALIS Study Design: Postplatinum Exon 20 Insertion Population

Key Objectives

- Dose escalation: Establish RP2D
- Dose expansion: Assess safety and efficacy at RP2D

Key Eligibility Criteria for Post-platinum Population

- Metastatic/unresectable NSCLC
- EGFR Exon20ins mutation
- Progressed on platinum-based chemotherapy



Efficacy End Points

Primary

- Overall response rate per RECIST v1.1

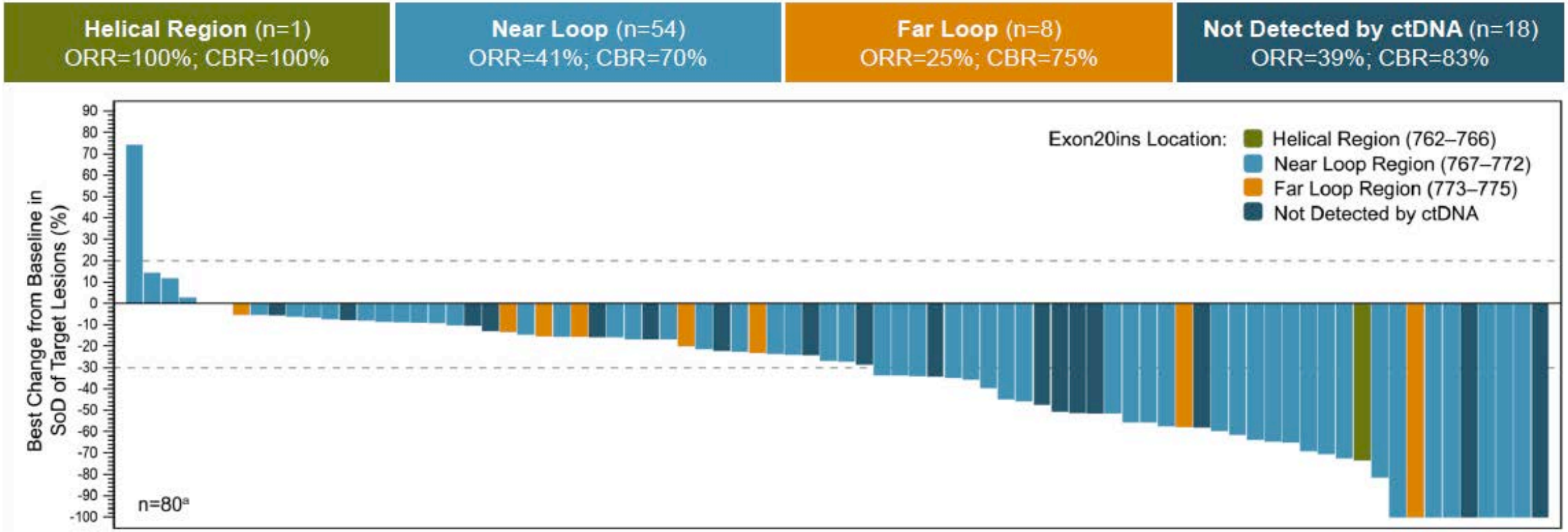
Key Secondary

- Clinical benefit rate
- Duration of response
- Progression-free survival
- Overall survival

Sabari JK et al. IASLC WCLC 2020;Abstract OA04.04.

RTP RESEARCH TO PRACTICE

CHRYSALIS: Best ORR by Insertion Region of Exon 20



25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

Sabari JK et al. IASLC WCLC 2020;Abstract OA04.04.

RTP RESEARCH TO PRACTICE

Amivantamab in Combination with Lazertinib for the Treatment of Osimertinib-Relapsed, Chemotherapy-Naïve EGFR Mutant (EGFRm) Non-Small Cell Lung Cancer (NSCLC) and Potential Biomarkers for Response

Bauml J et al.
ASCO 2021;Abstract 9006.

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

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RESEARCH
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Trastuzumab Deruxtecan in HER2-Mutated Metastatic Non-Small Cell Lung Cancer (NSCLC): Interim Results of DESTINY-Lung01[1]

Trastuzumab Deruxtecan in HER2-Overexpressing Metastatic Non-Small Cell Lung Cancer (NSCLC): Interim Results of DESTINY-Lung01[2]

[1] Smit EF et al.
WCLC 2021;Abstract MA11.03.

[2] Nakagawa K et al.
WCLC 2021;Abstract OA04.05.

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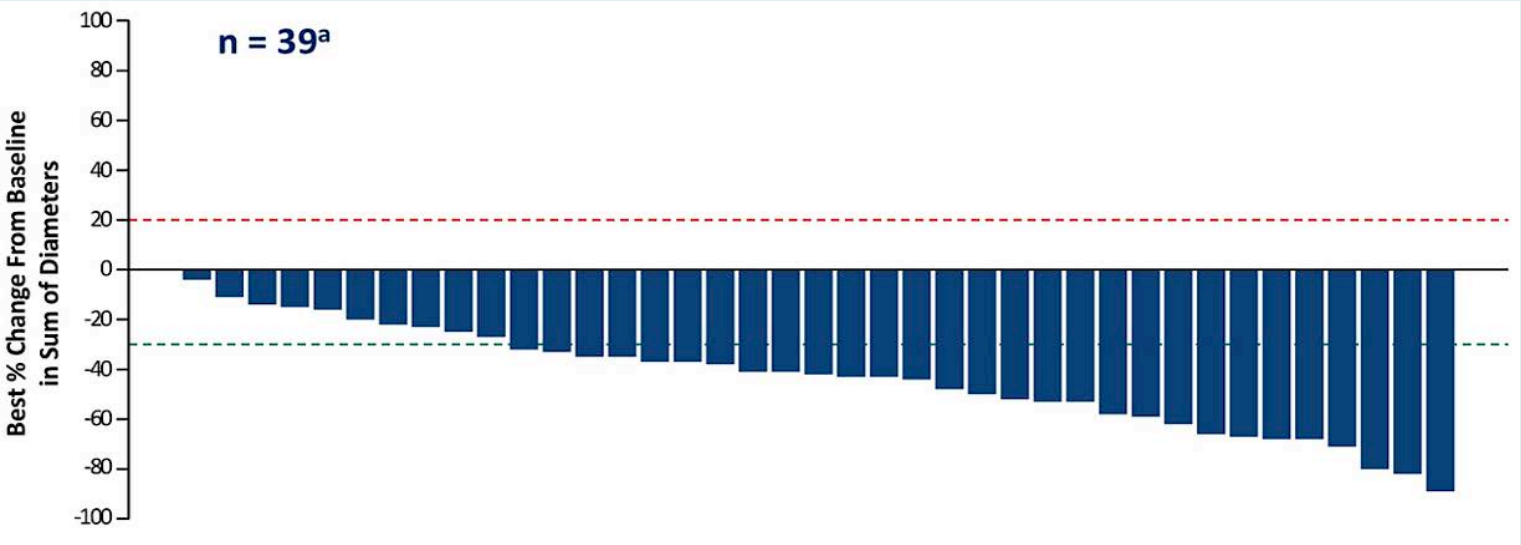
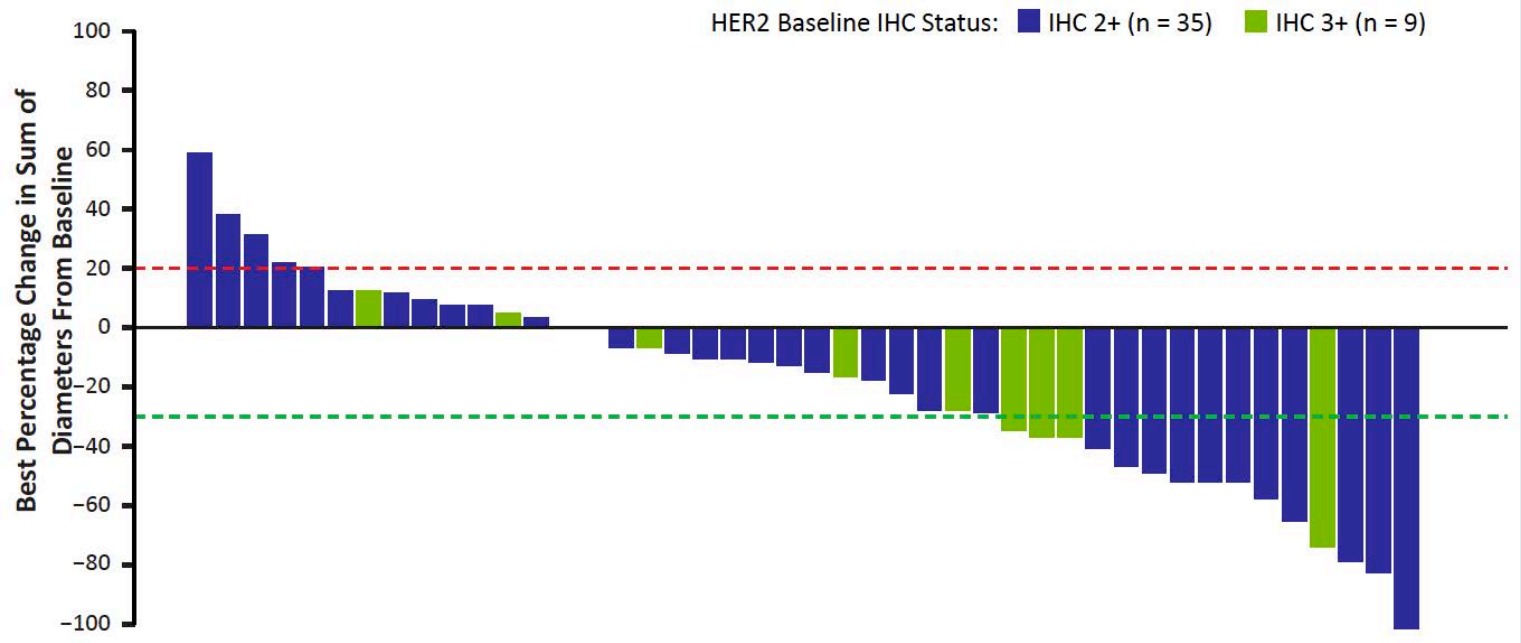
DESTINY-Lung01: Best Percentage Change in Tumor Size with T-DXd for HER2-Mutated versus Overexpressing NSCLC

Mutant



Confirmed ORR = 61.9%
DCR = 90.5%
Median DoR = not reached
Median PFS = 14.0 months

Overexpressing



Confirmed ORR = 24.5%
DCR = 69.4%
Median DoR = 6.0 months
Median PFS = 5.4 months

Smit EF et al. WCLC 2021;Abstract MA11.03; Nakagawa K et al. WCLC 2021;Abstract OA04.05.

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DESTINY-Lung01: AEs of Special Interest – Interstitial Lung Disease

Mutant

	All Patients (N = 42)					
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial lung disease	0	5 (11.9)	0	0	0	5 (11.9)

Overexpressing

All Patients (N = 49)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/Total
Adjudicated drug-related ILD	2 (4.1%)	3 (6.1%)	0	0	3 (6.1%)	8 (16.3%)

Smit EF et al. WCLC 2021;Abstract MA11.03; Nakagawa K et al. WCLC 2021;Abstract OA04.05.

RTP RESEARCH TO PRACTICE

Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor-Resistant, *EGFR*-Mutated (*EGFR*m) Non-Small Cell Lung Cancer (NSCLC)

Janne PA et al.

ASCO 2021;Abstract 9007.

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

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TO PRACTICE

Agenda

Module 1 : Localized or Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

- Dr Patel: A 57-year-old woman with locally advanced NSCLC
- *Key Recent Publications and Presentations*

Module 2: Newly Diagnosed NSCLC with No Actionable Mutation

- Dr Lorber: A 66-year-old man with metastatic adenocarcinoma of the lung – PD-L1 60%, TMB 14 mut/Mb
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Module 3: NSCLC with an EGFR Tumor Mutation

- Dr Patel: A 47-year-old woman with metastatic adenocarcinoma of the lung and asymptomatic brain metastases – EGFR exon 19 mutation
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Module 4: Metastatic NSCLC Harboring Other Mutations

- Dr Gupta: A 61-year-old man with metastatic adenocarcinoma of the lung with a RET fusion
- Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations
- Dr Chen: A 59-year-old woman with metastatic adenocarcinoma of the lung with a ROS1 fusion
- Dr Morganstein: A 62-year-old man with metastatic adenocarcinoma of the lung with a BRAF V600E mutation
- *Key Recent Publications and Presentations*

Module 5: Extensive-Stage Small Cell Lung Cancer (SCLC)

- Dr Patel: A 63-year-old man with extensive-stage SCLC
- *Key Recent Publications and Presentations*

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Case Presentation – Dr Gupta: A 61-year-old man with metastatic adenocarcinoma of the lung with a RET fusion – PD-L1 0%, TMB 3 mut/Mb

Dr Ranju Gupta

- 1/2019: Diagnosed with Stage IV adenocarcinoma of the lung
  - 15-year smoking history
- Carboplatin/pemetrexed/pembrolizumab → developed severe autoimmune enteritis after cycle 1 requiring hospitalization and high-dose steroids
- 9/2020: PD → selpercatinib 160 mg dose → uncontrolled high BP, swelling in legs, drowsiness
  - Dose reductions down to 40 mg did not lead to lowering of BP
- 12/2020: Ramucirumab with docetaxel initiated

Questions

- How do you manage the pedal edema and drowsiness? Is it common?
- What is your experience with pralsetinib in terms of toxicities?

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Case Presentation – Dr Mohamed: A 71-year-old woman with metastatic adenocarcinoma of the lung with MET exon 14 skipping and MET amplification mutations – PD-L1 TPS 95%

Dr Mohamed Mohamed

- Never smoker presents with bilateral flank pain and 5-month history of weight loss and fatigue
- Workup reveals Stage IV poorly differentiated adenocarcinoma of the lung; lung obstructions and 2 small, subcentimeter lesions in brain detected
- Molecular analyses: MET exon 14 skipping mutation, MET amplification
- PD-L1: 95%
- Palliative RT to the lung; SRS to the brain
- Capmatinib initiated

Questions

- If she didn't need to receive RT due to the lung obstructions, should I have initiated treatment with targeted therapy alone? Does capmatinib work on brain lesions by itself?
- With a PD-L1 of 95%, should she have been considered for immunotherapy, or should targeted therapy precede that as first-line therapy?
- Are mutations in MET regarded in the same way as mutations in EGFR and ALK in terms of immune therapy? Or are they regarded like BRAF mutations in that you could use immune therapy?

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Case Presentation – Dr Chen: A 59-year-old woman with metastatic adenocarcinoma of the lung with a ROS1 fusion and severe rheumatoid arthritis

Dr Gigi Chen

- Never smoker presents with persistent cough
- RLL lung mass, mediastinal adenopathy and multiple bone lesions; MRI brain: Negative
- CT-guided biopsy: Adenocarcinoma, CD 74 ROS1 fusion
- Crizotinib and denosumab x 9 months → Headache → MRI brain: 3-mm parietal lobe and 2-mm frontal lobe lesions
- Systemic disease is well controlled

Questions

- What is the next step in her treatment?
- Would it be best to change to a different TKI versus chemotherapy in this patient who has had brain progression only? What would be the best choices in terms of the TKIs?

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Case Presentation – Dr Morganstein: A 62-year-old man with metastatic adenocarcinoma of the lung with a BRAF V600E mutation – PD-L1 TPS 80%

Dr Neil Morganstein

- Heavy smoker presents with shortness of breath
- Workup reveals lung adenocarcinoma with metastases to the liver and bone
- PD-L1 TPS: 80%
- Carboplatin/paclitaxel/pembrolizumab initiated (pembrolizumab not given due to renal insufficiency)
- Molecular analysis results returned after treatment initiated → BRAF V600E mutation

Questions

- In patients with BRAF V600E mutations, is BRAF-targeted therapy recommended in the first line?
- How imperative is it to have molecular study results before initiating therapy?
- Is BRAF considered a classic driver mutation? Should I be concerned about the efficacy of immunotherapies in patients whose tumors harbor BRAF mutations?
- How would you characterize the type of clinical response that I may expect from BRAF-targeted therapies? What is the standard-of-care for BRAF-directed therapy – dabrafenib/trametinib?

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Key Recent Publications and Presentations

- Xia B et al. **How to Select the Best Upfront Therapy for Metastatic Disease? Focus on *ALK*-Rearranged Non-Small Cell Lung Cancer (NSCLC).** *Transl Lung Cancer Res* 2020;9(6):2521-34.
- Shaw AT et al. **First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer.** *N Engl J Med* 2020;383(21):2018-29.
- Gainor JT et al. **Registrational Dataset from the Phase 1/2 ARROW Trial of Pralsetinib (BLU-667) in Patients with Advanced RET Fusion+ Non-Small Cell Lung Cancer (NSCLC).** ASCO 2020;Abstract 9515.
- Wolf J et al. **Capmatinib in MET Exon 14-Mutated or MET-Amplified Non-Small-Cell Lung Cancer.** *N Engl J Med* 2020;383(10):944-57.
- Paik PK et al. **Tepotinib in Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations.** *N Engl J Med* 2020;383(10):931-43.

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Activity of ALK TKIs in the First-Line Setting for Advanced NSCLC with ALK Rearrangement

ALK TKI	Median PFS	ORR	Intracranial response
Crizotinib	10.9 mo	74%	NA
Ceritinib	16.6 mo	72.5%	72.7%
Alectinib	34.8 mo	82.9%	82.9%
Brigatinib	29.4 mo	71%	78%
Lorlatinib	Not reached	90%	66.7%
Ensartinib	26.2 mo	80%	64.3%

Xia B et al. *Transl Lung Cancer Res* 2020;9(6):2521-253.

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Common and Unique Adverse Effects of ALK TKIs

ALK TKI	Most common adverse effects
Crizotinib	Vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy
Ceritinib	Diarrhea, nausea, vomiting, fatigue, abdominal pain, decreased appetite, and weight loss
Alectinib	Constipation, fatigue, edema, myalgia and anemia
Brigatinib	Diarrhea, fatigue, nausea, rash , cough, myalgia, headache, hypertension, vomiting, and dyspnea
Lorlatinib	Hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, weight gain, cognitive effects, fatigue, dyspnea, arthralgia, diarrhea
Ensartinib	Rash, nausea, pruritis, and vomiting

Crizotinib PI, rev 1/2021; Ceritinib PI, rev 3/2019; Alectinib PI, rev 1/2021; Brigatinib PI, rev 5/2020; Lorlatinib PI, rev 3/2021
Xia B et al. *Transl Lung Cancer Res* 2020;9(6):2521-253; Gristina V et al. *Pharmaceuticals* 2020;13:474.

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FDA Expands Lorlatinib Approval to Front-Line Treatment of Metastatic NSCLC with ALK Fusion

Press Release – March 3, 2021

"The Food and Drug Administration granted regular approval to lorlatinib for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive, detected by an FDA-approved test. The FDA also approved the Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems, Inc) as a companion diagnostic for lorlatinib.

Lorlatinib received accelerated approval in November 2018 for the second- or third-line treatment of ALK-positive metastatic NSCLC.

This current approval is based on data from Study B7461006 (NCT03052608), a randomized, multicenter, open-label, active-controlled trial conducted in 296 patients with ALK-positive metastatic NSCLC who had not received prior systemic therapy for metastatic disease. Patients were required to have ALK-positive tumors detected by the VENTANA ALK (D5F3) CDx assay. Patients were randomized 1:1 to receive lorlatinib 100 mg orally once daily (n=149) or crizotinib 250 mg orally twice daily (n=147). Study B7461006 demonstrated an improvement in progression-free survival (PFS) as assessed by blinded independent central review (BICR), with a hazard ratio of 0.28 (95% CI: 0.19, 0.41; p<0.0001)."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-lorlatinib-metastatic-alk-positive-nsclc?utm_medium=email&utm_source=govdelivery

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Todd M. Bauer, M.D., Filippo de Marinis, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Geoffrey Liu, M.D., Julien Mazieres, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Tony Mok, M.D., Anna Polli, B.Sc., Holger Thurm, M.D., Anna M. Calella, Ph.D., Gerson Peltz, M.D., M.P.H., and Benjamin J. Solomon, M.B., B.S., Ph.D., for the CROWN Trial Investigators*

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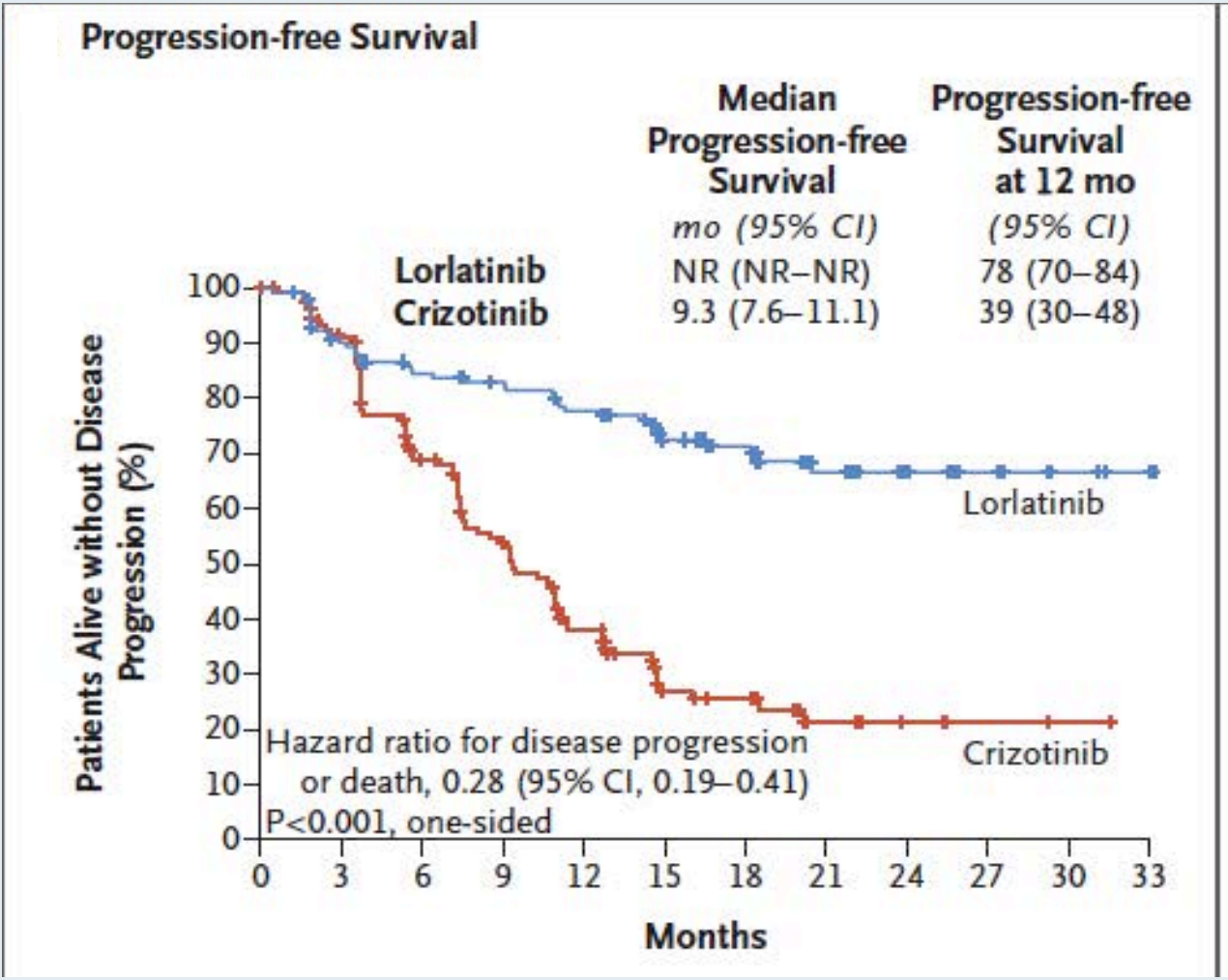
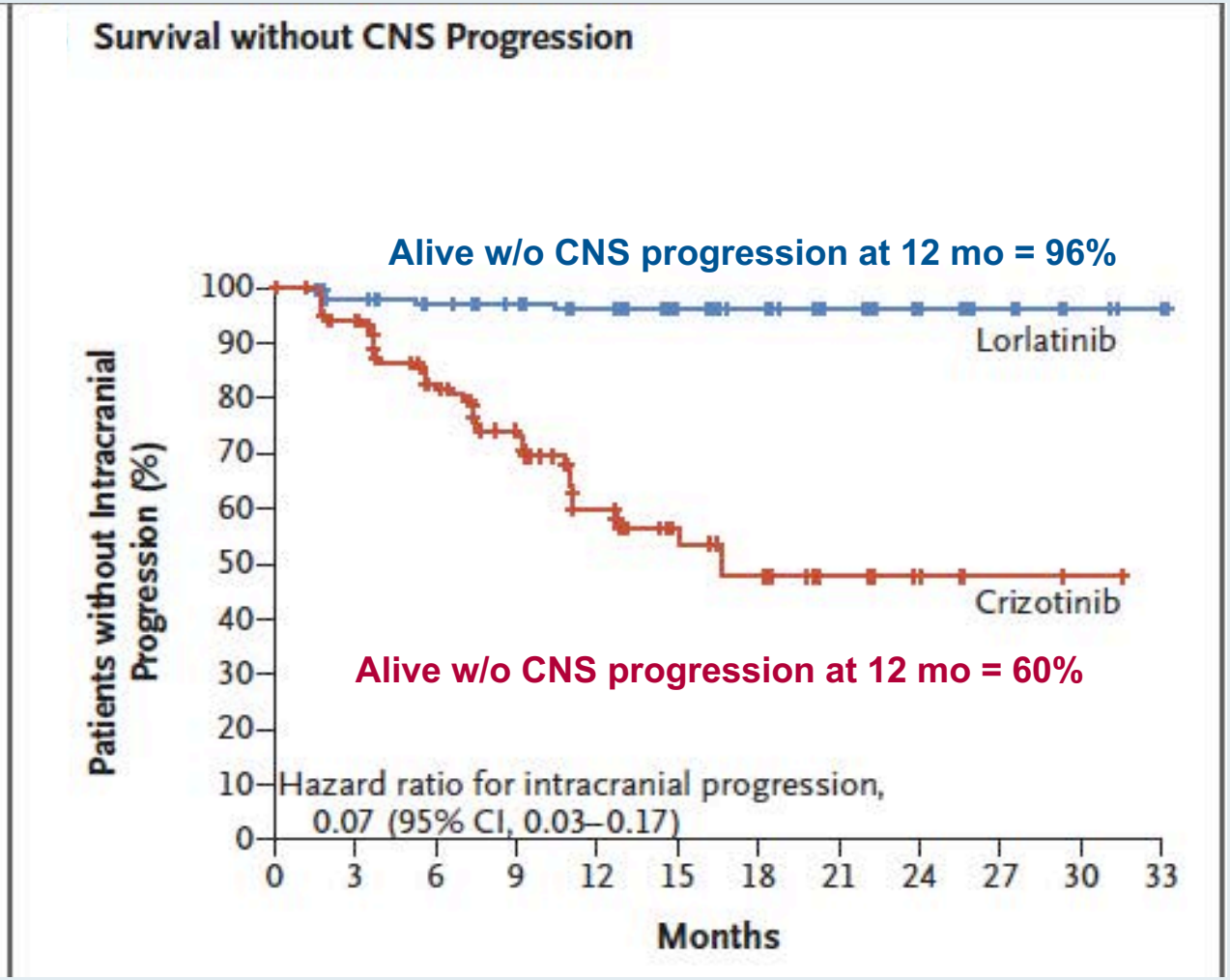
CROWN: PFS and Survival without Intracranial Progression





Shaw AT et al. *N Engl J Med* 2020;383(21):2018-29.

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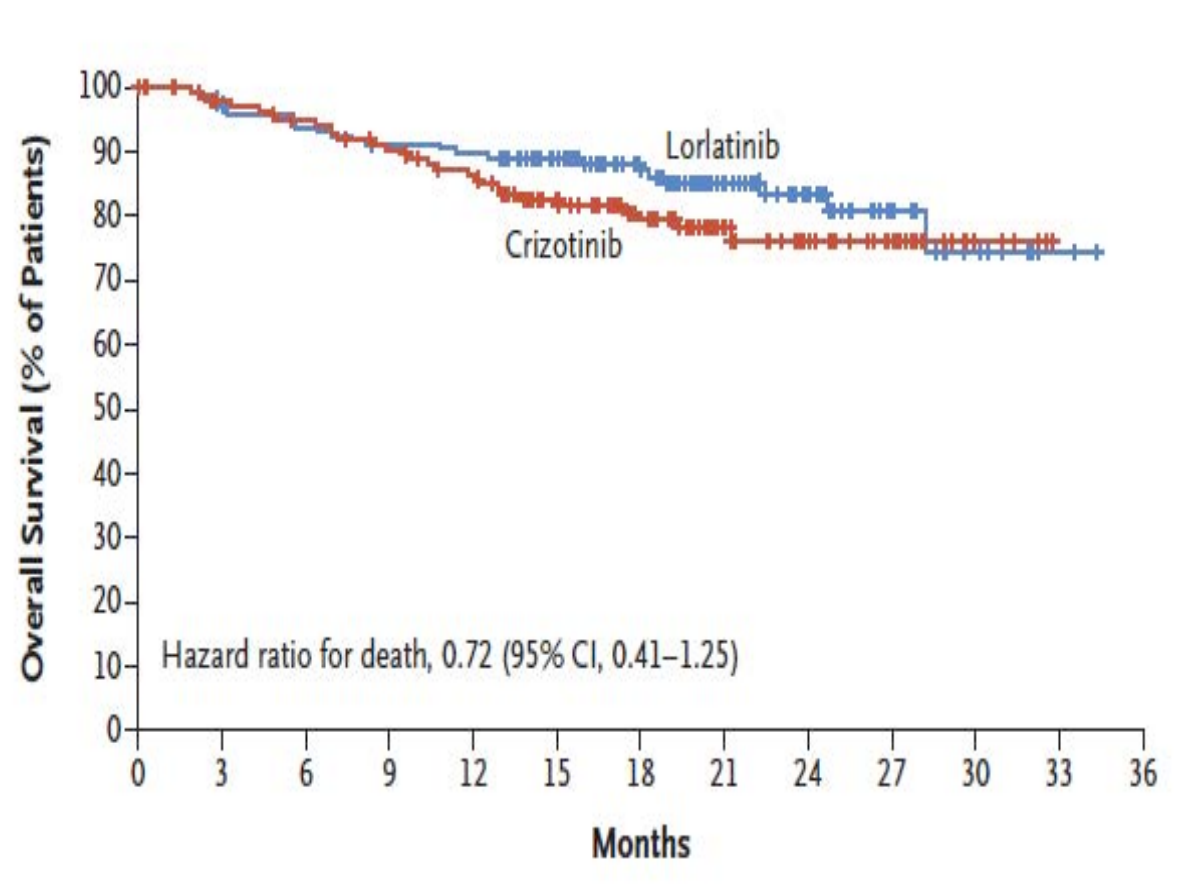
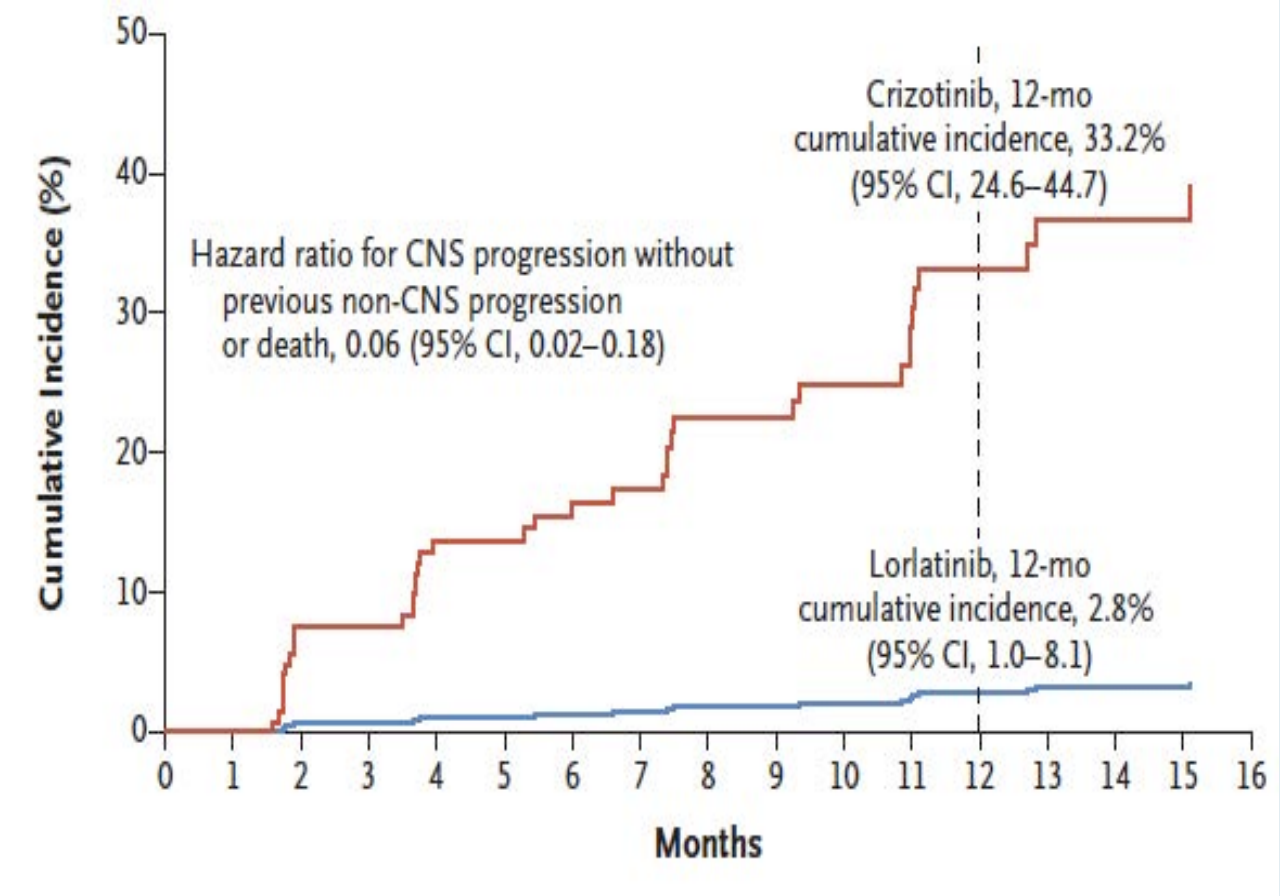
CROWN: OS and Cumulative Incidence of CNS Progression

Overall Survival



Cumulative Incidence of CNS Progression as First Event



Shaw AT et al. *N Engl J Med* 2020;383(21):2018-29.

RTP RESEARCH TO PRACTICE

Registrational Dataset from the Phase 1/2 ARROW Trial of Pralsetinib (BLU-667) in Patients with Advanced RET Fusion+ Non-Small Cell Lung Cancer (NSCLC)

Gainor JT et al.

ASCO 2020;Abstract 9515.

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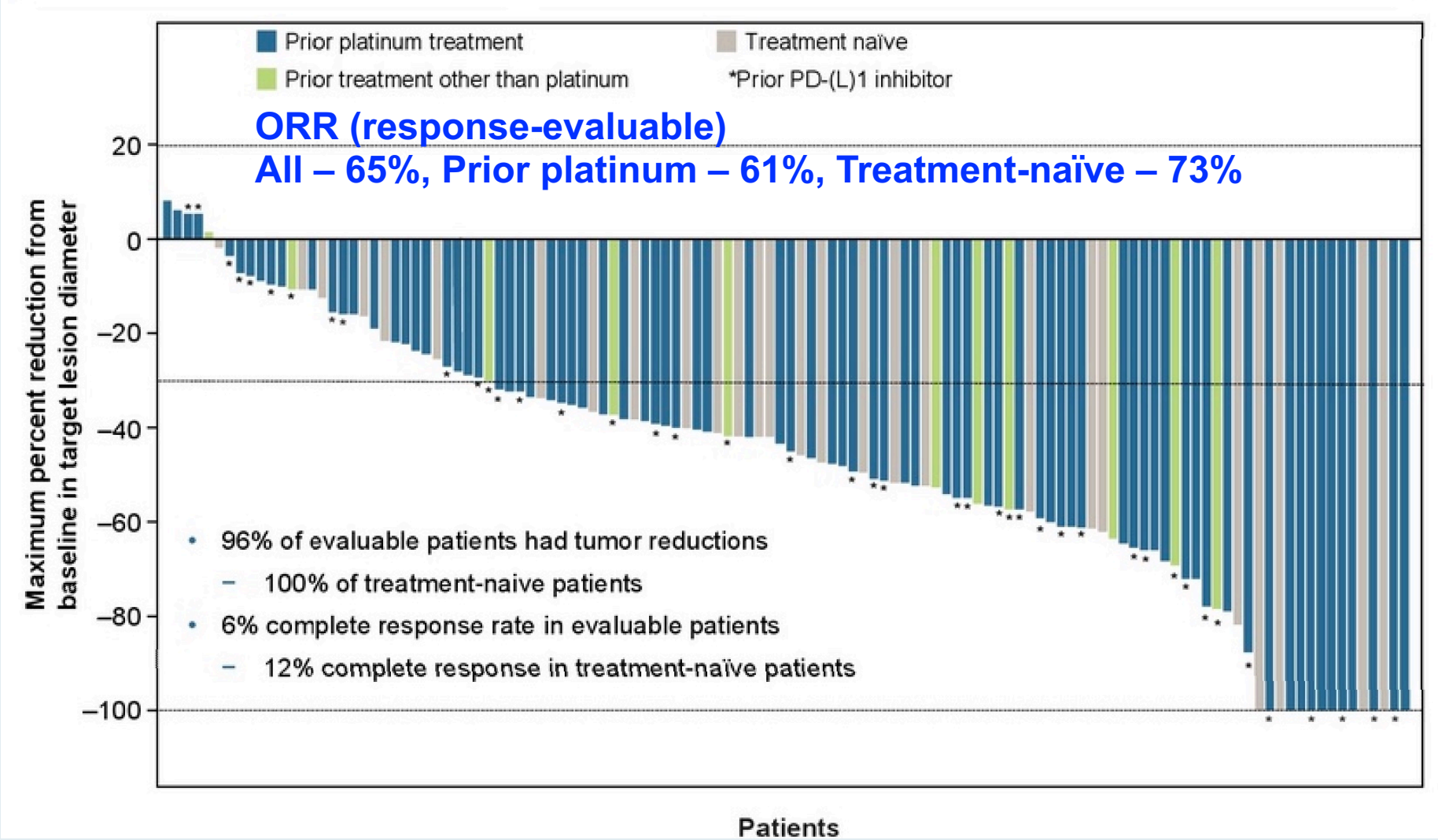
ARROW Primary Endpoint: Response to Pralsetinib



Gainor JF et al. ASCO 2020;Abstract 9515.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Capmatinib in *MET* Exon 14–Mutated or *MET*-Amplified Non–Small-Cell Lung Cancer

J. Wolf, T. Seto, J.-Y. Han, N. Reguart, E.B. Garon, H.J.M. Groen, D.S.W. Tan, T. Hida, M. de Jonge, S.V. Orlov, E.F. Smit, P.-J. Souquet, J. Vansteenkiste, M. Hochmair, E. Felip, M. Nishio, M. Thomas, K. Ohashi, R. Toyozawa, T.R. Overbeck, F. de Marinis, T.-M. Kim, E. Laack, A. Robeva, S. Le Mouhaer, M. Waldron-Lynch, B. Sankaran, O.A. Balbin, X. Cui, M. Giovannini, M. Akimov, and R.S. Heist, for the GEOMETRY mono-1 Investigators*

ABSTRACT

N Engl J Med 2020;383(10):944-57.

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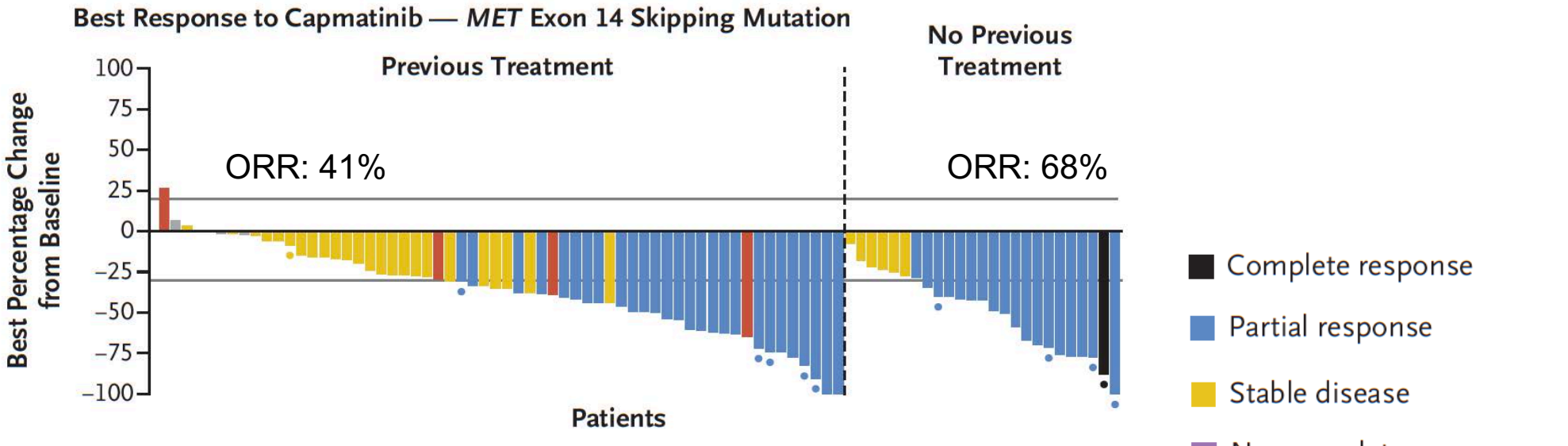
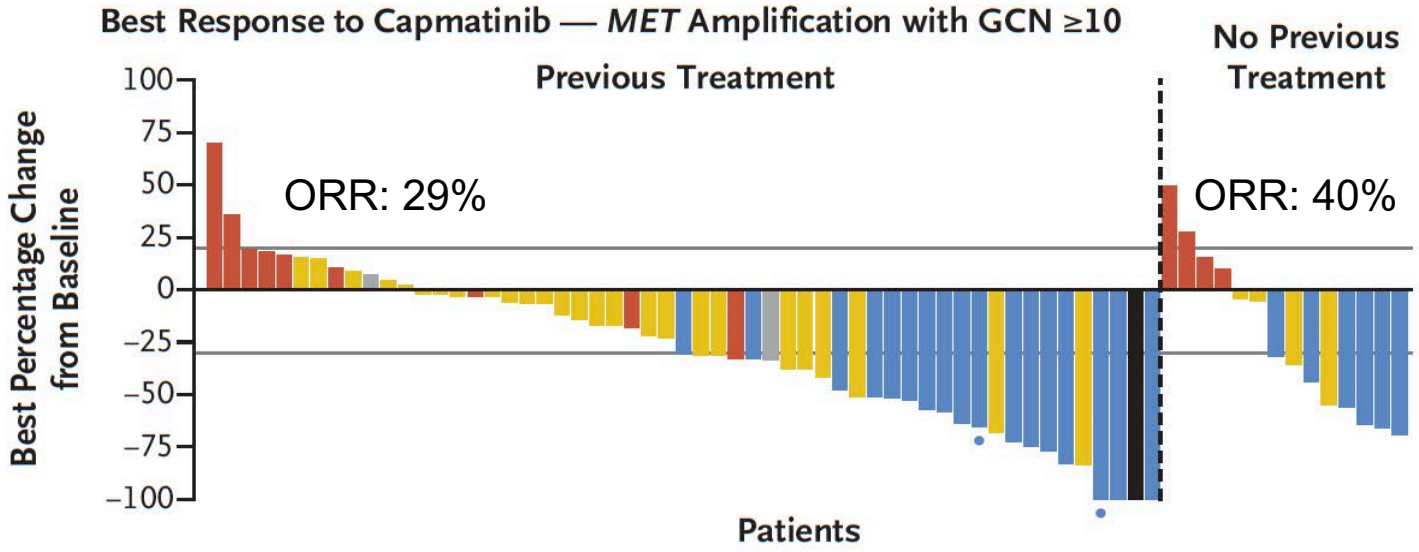
Capmatinib: Response Rate and Change from Baseline in Tumor Burden





- Complete response
- Partial response
- Stable disease
- Noncomplete response or nonprogressive disease
- Progressive disease
- Unknown

Wolf J et al. *N Engl J Med* 2020;383(10):944-57.

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FDA Grants Accelerated Approval to Tepotinib for Metastatic Non-Small Cell Lung Cancer

Press Release — February 03, 2021

"On February 3, 2021, the Food and Drug Administration granted accelerated approval to tepotinib for adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.

Efficacy was demonstrated in the VISION trial (NCT02864992), a multicenter, non-randomized, open-label, multicohort study enrolling 152 patients with advanced or metastatic NSCLC with MET exon 14 skipping alterations. Patients received tepotinib 450 mg orally once daily until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-tepotinib-metastatic-non-small-cell-lung-cancer

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RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tepotinib in Non–Small-Cell Lung Cancer with *MET* Exon 14 Skipping Mutations

P.K. Paik, E. Felip, R. Veillon, H. Sakai, A.B. Cortot, M.C. Garassino, J. Mazieres, S. Viteri, H. Senellart, J. Van Meerbeeck, J. Raskin, N. Reinmuth, P. Conte, D. Kowalski, B.C. Cho, J.D. Patel, L. Horn, F. Griesinger, J.-Y. Han, Y.-C. Kim, G.-C. Chang, C.-L. Tsai, J.C.-H. Yang, Y.-M. Chen, E.F. Smit, A.J. van der Wekken, T. Kato, D. Juraeva, C. Stroh, R. Bruns, J. Straub, A. Johne, J. Scheele, J.V. Heymach, and X. Le

N Engl J Med 2020;383(10):931-43.

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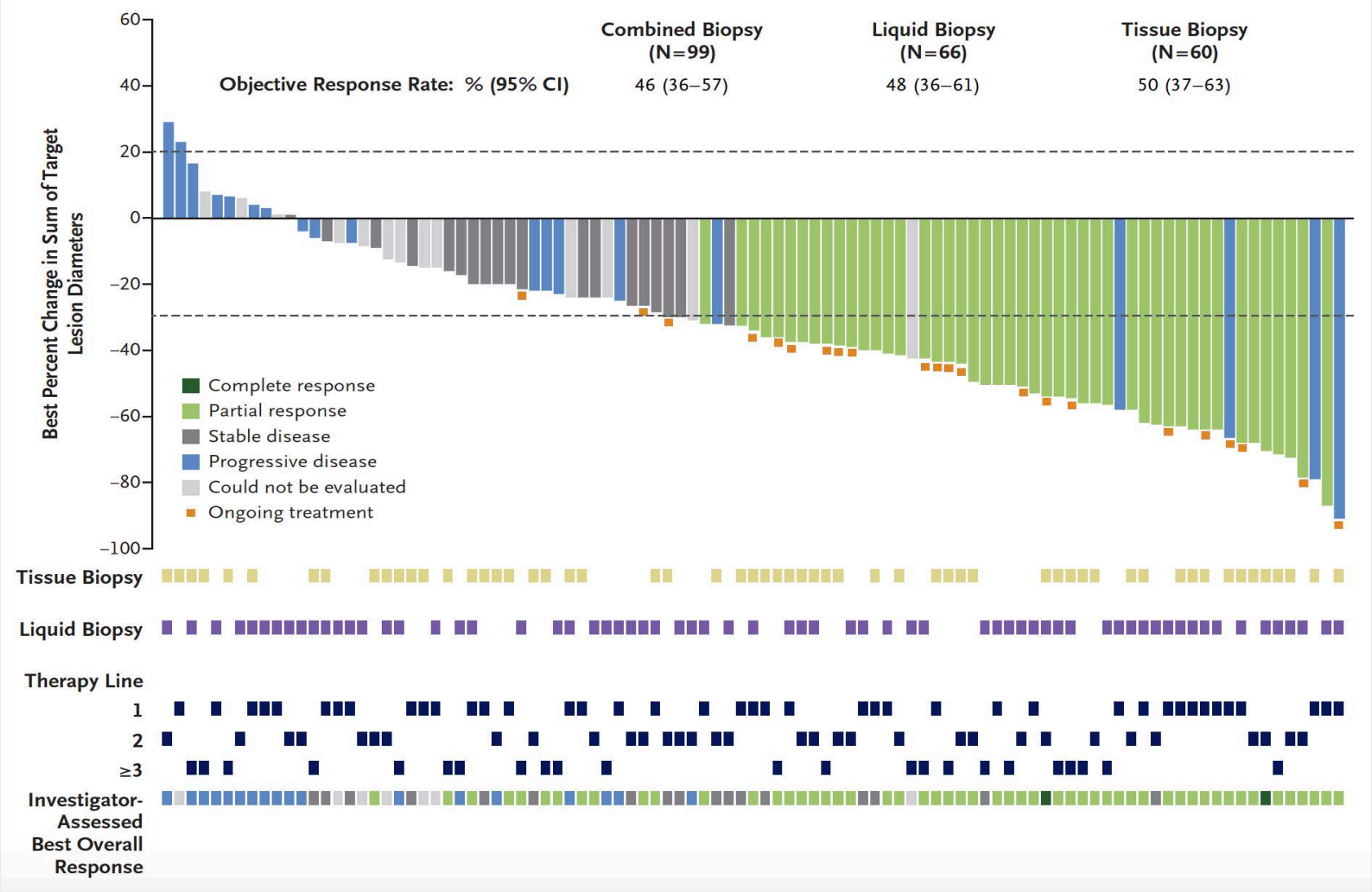
VISION Trial of Tepotinib: Response Rate and Change from Baseline in Tumor Burden



Paik PK et al. *N Engl J Med* 2020;383(10):931-43.

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Agenda

Module 1 : Localized or Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

- Dr Patel: A 57-year-old woman with locally advanced NSCLC
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Module 5: Extensive-Stage Small Cell Lung Cancer (SCLC)

- Dr Patel: A 63-year-old man with extensive-stage SCLC
- *Key Recent Publications and Presentations*

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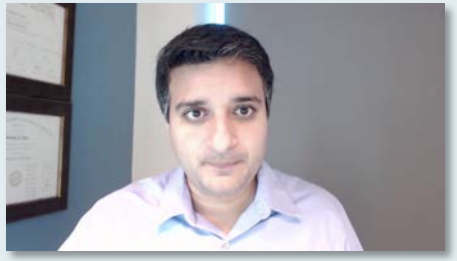
Case Presentation – Dr Patel: A 63-year-old man with extensive-stage SCLC



Dr Sandip Patel

- Diagnosed with ES-SCLC
- Induction carboplatin/etoposide/PD-L1 inhibitor x 4 cycles, with response in lung and liver → Maintenance immunotherapy
  - Diarrhea 5 times/day
  - C diff-negative
  - TB and viral hepatitis testing: Negative
  - Prednisone, with improvement but couldn't get below 20 mg → infliximab, with resolution of diarrhea
- Resumed anti-PD-L1 therapy

Questions

- What would you recommend for this patient to try to improve his outcome?

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What is your preferred second-line treatment for a patient with extensive-stage small cell lung cancer and disease progression on chemotherapy/atezolizumab?

1. Topotecan or irinotecan
2. Lurbinectedin
3. Nivolumab/ipilimumab
4. Pembrolizumab
5. Nivolumab
6. Other

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Key Recent Publications and Presentations

- Liu SV et al. **Updated Overall Survival and PD-L1 Subgroup Analysis of Patients with Extensive-Stage Small-Cell Lung Cancer Treated with Atezolizumab, Carboplatin, and Etoposide (IMpower133).** *J Clin Oncol* 2021;39(6):619-30.
- Reck M et al. **IMpower133: Exploratory Analysis of Maintenance Therapy in Patients with Extensive-Stage Small Cell Lung Cancer.** IASLC WCLC 2020;Abstract 0A11.06.
- Goldman JW et al. **Durvalumab, with or without Tremelimumab, plus Platinum-Etoposide versus Platinum-Etoposide Alone in First-Line Treatment of Extensive-Stage Small-Cell Lung Cancer (CASPIAN): Updated Results from a Randomised, Controlled, Open-Label, Phase 3 Trial.** *Lancet Oncol* 2021;22(1):51-65.
- Trigo J et al. **Lurbinectedin as Second-Line Treatment for Patients with Small-Cell Lung Cancer: A Single-Arm, Open-Label, Phase 2 Basket Trial.** *Lancet Oncol* 2020;21(5):645-54.

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original reports

Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133)

Stephen V. Liu, MD[1]; Martin Reck, MD, PhD[2]; Aaron S. Mansfield, MD[3]; Tony Mok, MD[4]; Arnaud Scherpereel, MD, PhD[5]; Niels Reinmuth, MD, PhD[6]; Marina Chiara Garassino, MD[7]; Javier De Castro Carpeno, MD[8]; Raffaele Califano, MD[9]; Makoto Nishio, MD[10]; Francisco Orlandi, MD[11]; Jorge Alatorre-Alexander, MD[12]; Ticiana Leal, MD[13]; Ying Cheng, MD[14]; Jong-Seok Lee, MD[15]; Sivuonthanh Lam, PharmD[16]; Mark McCleland, PhD[16]; Yu Deng, PhD[16]; See Phan, MD[16]; and Leora Horn, MD[17]

J Clin Oncol 2021;39(6):619-30.

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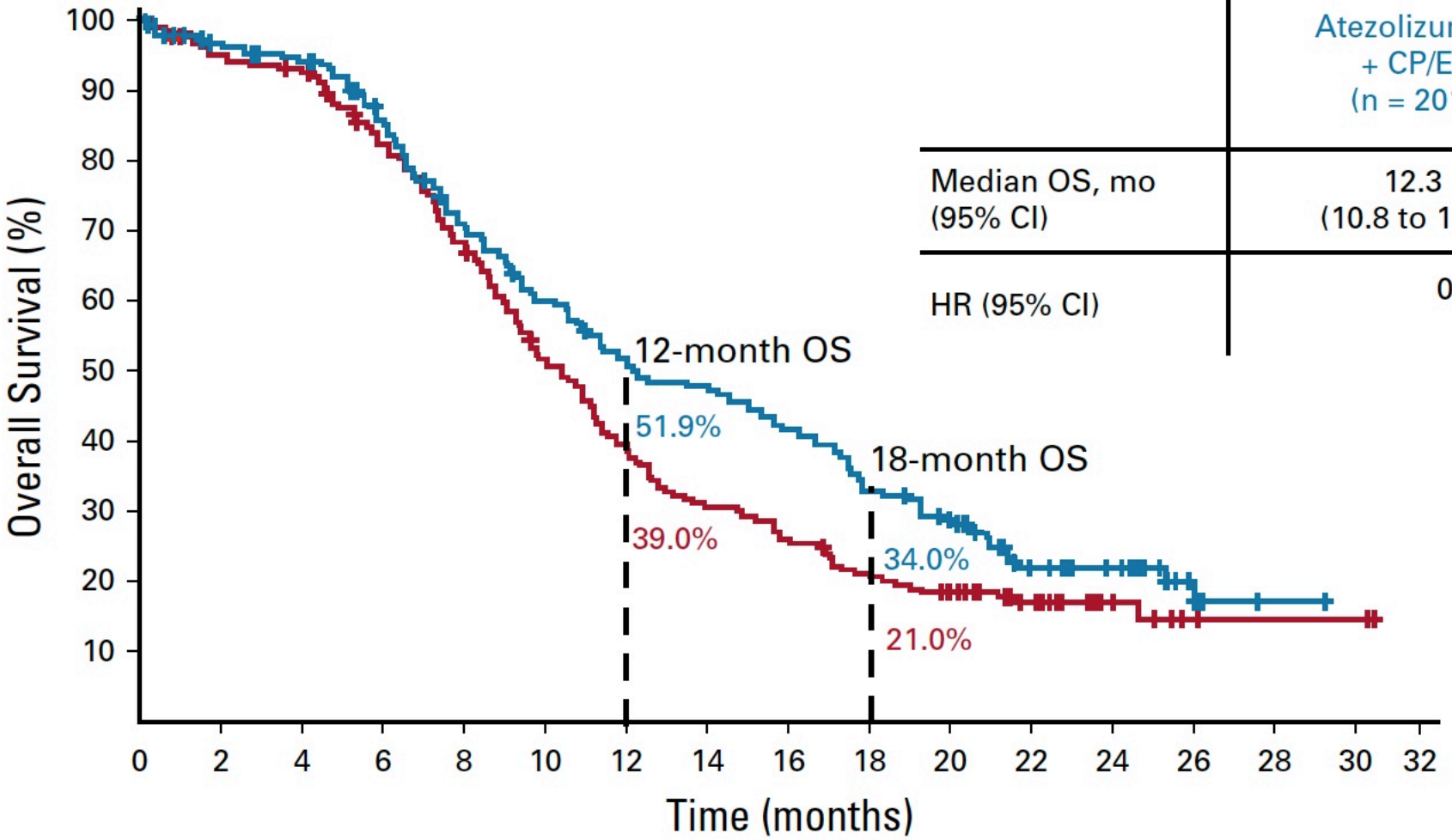
IMpower133: Updated Overall Survival



	Atezolizumab + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mo (95% CI)	12.3 (10.8 to 15.8)	10.3 (9.3 to 11.3)
HR (95% CI)	0.76 (0.60 to 0.95) *P* = .0154*	

Liu SV et al. *J Clin Oncol* 2021;39(6):619-30.

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IASLC

2020 World Conference on Lung Cancer Singapore

wclc2020.IASLC.com | #WCLC20

CONQUERING THORACIC CANCERS WORLDWIDE

IASLC/WCLC 2020;Abstract 0A11.06

IMpower133: exploratory analysis of maintenance therapy in patients with extensive-stage small cell lung cancer

Martin Reck,[1] Leora Horn,[2] Tony S. K. Mok,[3] Aaron S. Mansfield,[4] Richard De Boer,[5] Gyorgy Losonczy,[6] Shunichi Sugawara,[7] Rafal Dziadziuszko,[8] Maciej Krzakowski,[9] Alexey Smolin,[10] Maximilian Hochmair,[11] Marina Garassino,[12] Gilberto Castro,[13] Helge Bischoff,[14] Andres Cardona,[15] Stefanie Morris,[15] Stephen V. Liu[16]

[1] Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany; [2] Vanderbilt University Medical Center, Nashville, TN, USA; [3] The Chinese University of Hong Kong, Hong Kong; [4] Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA; [5] Peter MacCallum Cancer Centre, Melbourne, Australia; [6] Semmelweis Egyetem ÁOK, Budapest, Hungary; [7] Sendai Kousei Hospital, Sendai, Japan; [8] Medical University of Gdansk, Gdansk, Poland; [9] Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [10] Burdenko Main Military Hospital, Moscow, Russia; [11] Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Vienna North Hospital – Klinik Floridsdorf, Vienna, Austria; [12] Thoracic Oncology Unit, Instituto Nazionale dei Tumori, Milan, Italy; [13] Instituto de Cancer do Estado de São Paulo, Hospital das Clínicas da FMUSP, São Paulo, Brazil; [14] Thoraxklinik Heidelberg gGmbH – Universität Heidelberg, Heidelberg, Germany; [15] F. Hoffmann-La Roche Ltd, Basel, Switzerland; [16] Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA

Presented by: Dr Martin Reck

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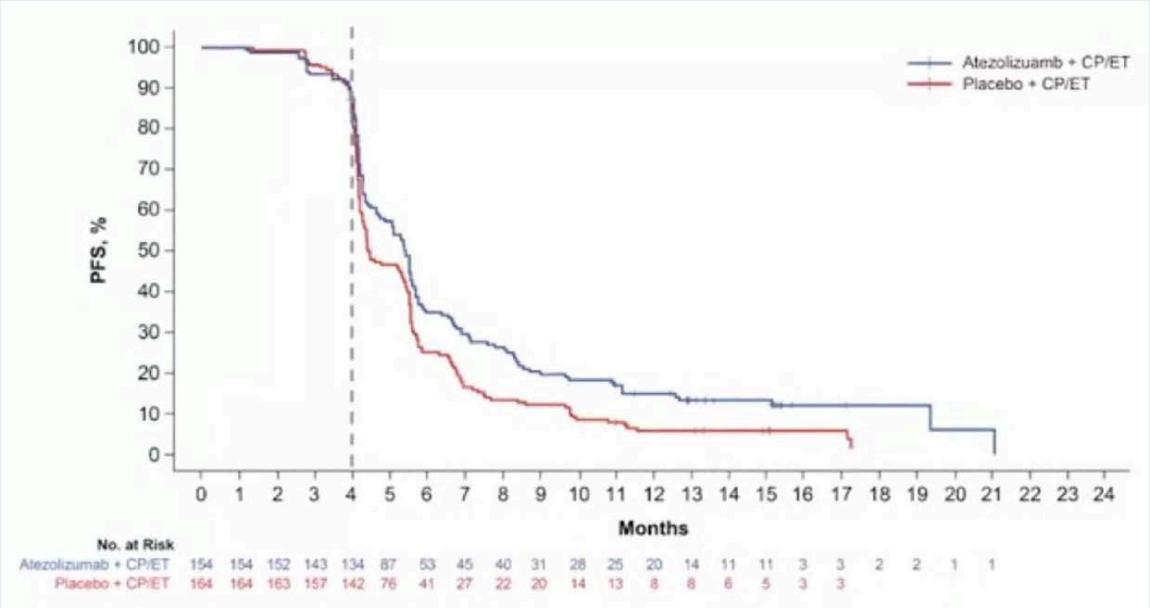
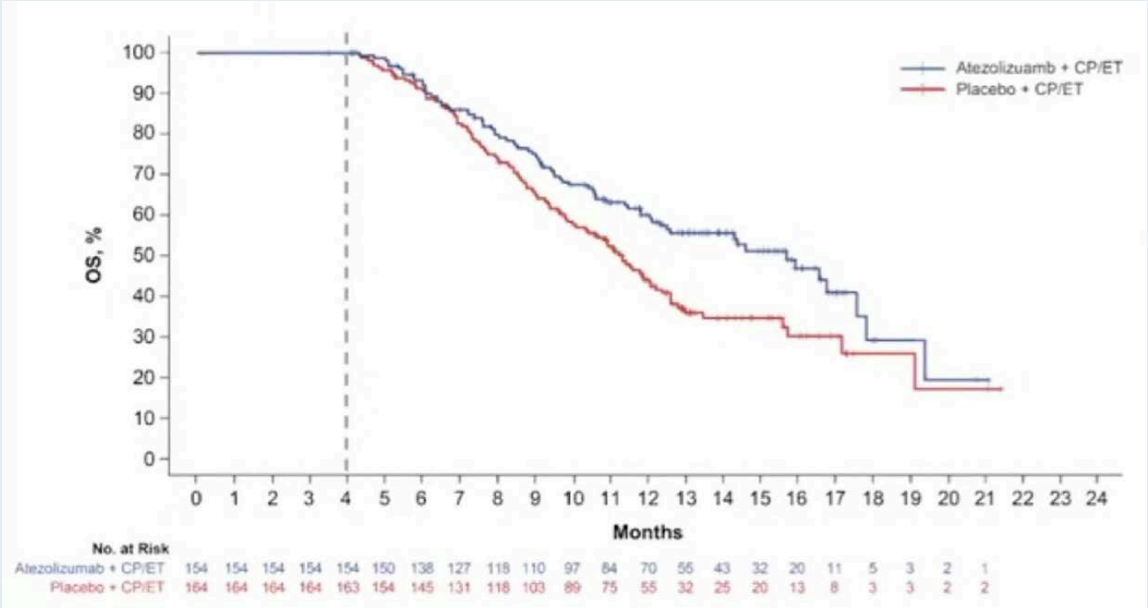
IMpower133: Survival Outcomes in the Maintenance Population

Progression-free survival (PFS)



Median PFS	Atezolizumab	Placebo	HR
From start of maintenance	2.6 mo	1.8 mo	0.64
From randomization	5.5 mo	4.5 mo	Not reported

Overall survival (OS)



Median PFS	Atezolizumab	Placebo	HR
From start of maintenance	12.5 mo	8.4 mo	0.59
From randomization	15.7 mo	11.3 mo	Not reported

Reck M et al. IASLC/WCLC 2020;Abstract 0A11.06.

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Durvalumab, with or without tremelimumab, plus platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial

*Jonathan W Goldman, Mikhail Dvorkin, Yuanbin Chen, Niels Reinmuth, Katsuyuki Hotta, Dmytro Trukhin, Galina Statsenko, Maximilian J Hochmair, Mustafa Özgüroğlu, Jun Ho Ji, Marina Chiara Garassino, Oleksandr Voitko, Artem Poltoratskiy, Santiago Ponce, Francesco Verderame, Libor Havel, Igor Bondarenko, Andrzej Każarnowicz, György Losonczy, Nikolay V Conev, Jon Armstrong, Natalie Byrne, Piruntha Thiyagarajah, Haiyi Jiang, Luis Paz-Ares, for the CASPIAN investigators**

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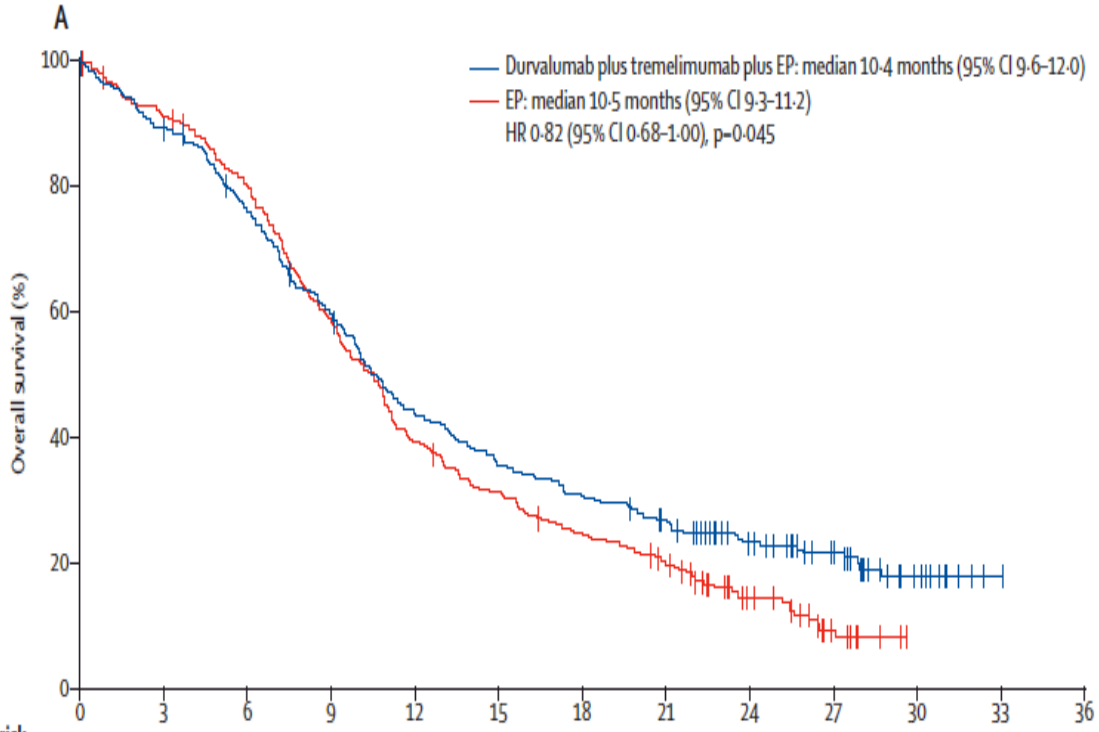
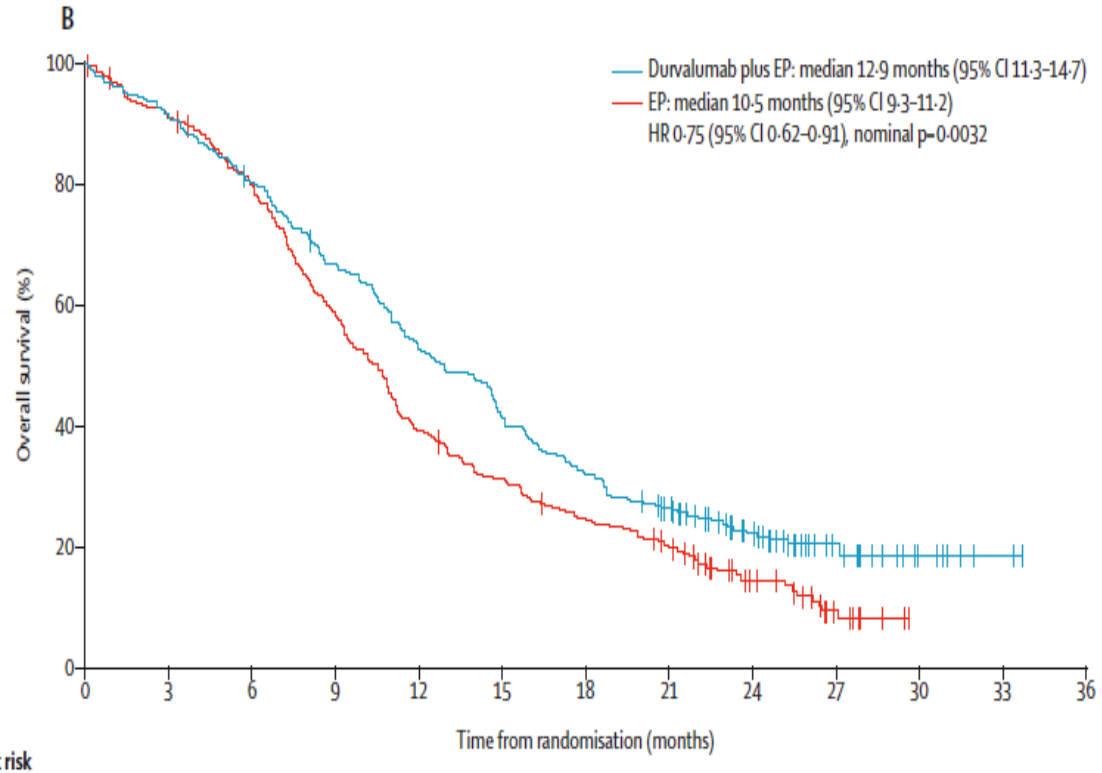
CASPIAN: Updated OS Analyses in ITT Population



Number at risk (number censored)													
Durvalumab plus tremelimumab plus EP	268 (0)	238 (1)	200 (4)	156 (5)	114 (6)	92 (6)	80 (6)	67 (9)	47 (21)	30 (35)	11 (50)	1 (60)	0 (61)
EP	269 (0)	243 (2)	212 (4)	156 (4)	104 (4)	82 (5)	64 (6)	48 (9)	24 (22)	8 (31)	0 (38)	0 (38)	0 (38)



Number at risk (number censored)													
Durvalumab plus EP	268 (0)	244 (0)	214 (1)	177 (2)	140 (2)	109 (2)	85 (2)	66 (6)	41 (22)	21 (39)	8 (50)	2 (56)	0 (58)
EP	269 (0)	243 (2)	212 (4)	156 (4)	104 (4)	82 (5)	64 (6)	48 (9)	24 (22)	8 (31)	0 (38)	0 (38)	0 (38)

Goldman JW et al. *Lancet Oncol* 2021;22(1):51-65.

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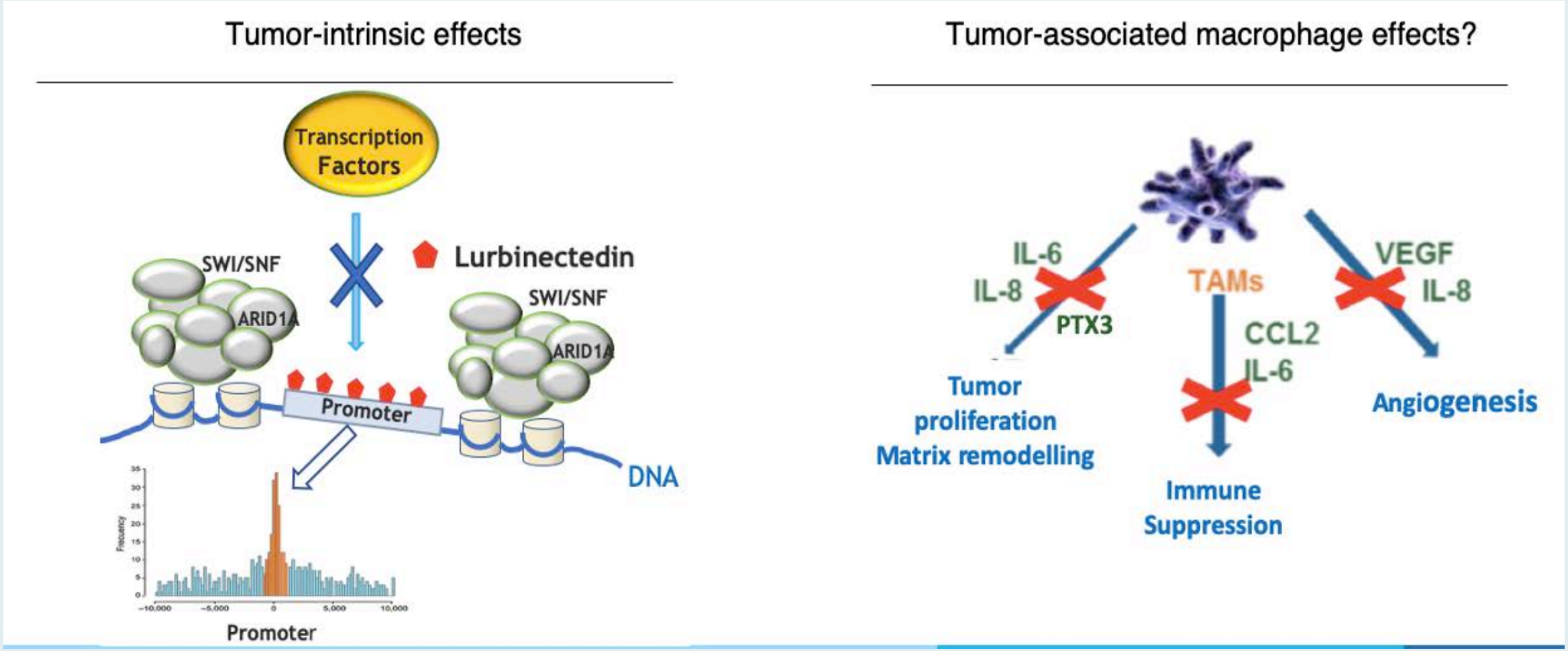
Lurbinectedin: A Selective Inhibitor of Oncogenic Transcription



How does it work?

- **Alkylator**
- **Minor groove DNA binder**

Paz-Ares LG et al. ASCO 2019;Abstract 8506.

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Lancet Oncol 2020;21:645-54.

Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial

José Trigo, Vivek Subbiah*, Benjamin Besse, Victor Moreno, Rafael López, María Angeles Sala, Solange Peters, Santiago Ponce, Cristian Fernández, Vicente Alfaro, Javier Gómez, Carmen Kahatt, Ali Zeaiter, Khalil Zaman, Valentina Boni, Jennifer Arrondeau, Maite Martínez, Jean-Pierre Delord, Ahmad Awada, Rebecca Kristeleit, Maria Eugenia Olmedo, Luciano Wannesson, Javier Valdivia, María Jesús Rubio, Antonio Anton, John Sarantopoulos, Sant P Chawla, Joaquín Mosquera-Martinez, Manolo D'Arcangelo, Armando Santoro, Victor M Villalobos, Jacob Sands, Luis Paz-Ares*

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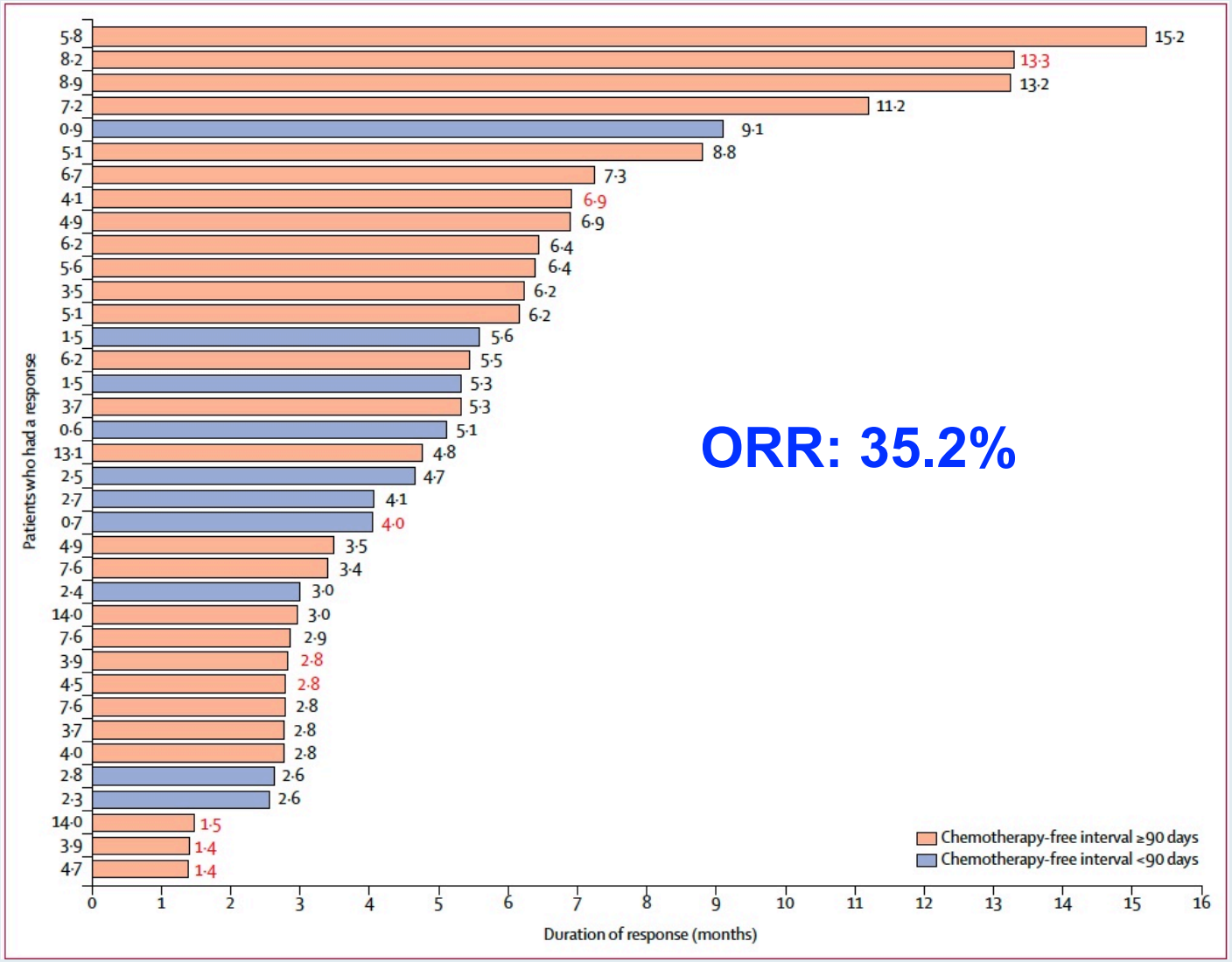
Rate and Duration of Response with Lurbinectedin as Second-Line Therapy for SCLC



Trigo J et al. *Lancet Oncol* 2020;21(5):645-54.

RTP RESEARCH TO PRACTICE

ATLANTIS Trial Did Not Meet the Prespecified Criteria of Significance for the Primary Endpoint of Overall Survival

Press Release — December 03, 2020

"Results from the ATLANTIS Phase 3 multicenter, randomized, controlled study evaluating lurbinectedin in combination with doxorubicin versus physician's choice of topotecan or cyclophosphamide/doxorubicin/vincristine (CAV) for adult patients with SCLC whose disease progressed following one prior platinum-containing line. Patients received lurbinectedin at 2.0 mg/m^2 in the combination arm, which is lower than the FDA approved dose of lurbinectedin at 3.2 mg/m^2.

The study did not meet the pre-specified criteria of significance for the primary endpoint of overall survival (OS) in the intent-to-treat (ITT) population comparing lurbinectedin in combination with doxorubicin to the control arm, though there was no adverse effect on OS with the experimental arm. Based on the study design, no additional hypotheses were formally tested. Importantly, key secondary and subgroup analyses favored the lurbinectedin combination arm. Lurbinectedin monotherapy was not tested in ATLANTIS.

The safety data in this study was consistent with the known safety profile of lurbinectedin monotherapy with no new safety signals observed."

https://investor.jazzpharma.com/news-releases/news-release-details/jazz-pharmaceuticals-and-pharmamar-announce-results-atlantis

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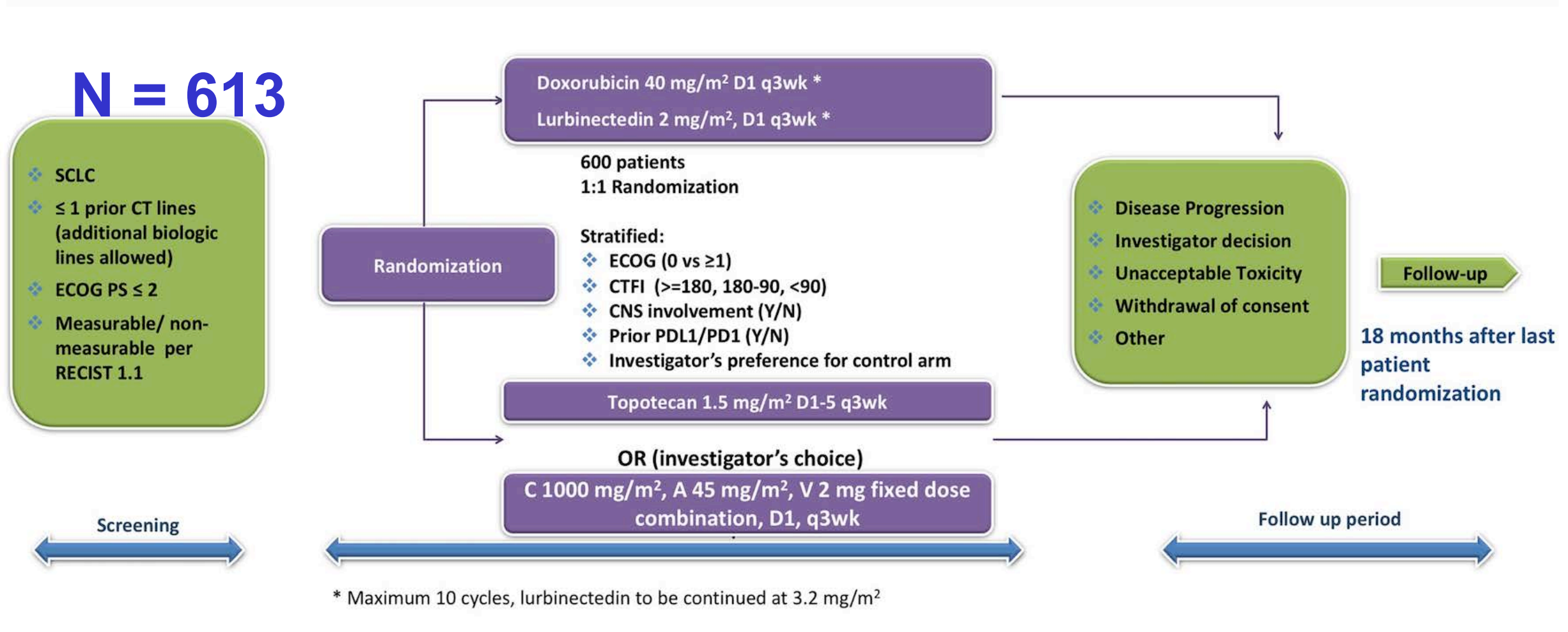
ATLANTIS: Phase III Trial Design



Clinicaltrials.gov (NCT02566993); Accessed February 2021; Farago AF et al. ASCO 2018;Abstract TPS8587.

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Thank you for joining us!

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

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