

Module 1: Lung Cancer

Relevant Recent Data Sets

First-line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) without a Targetable Mutation

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

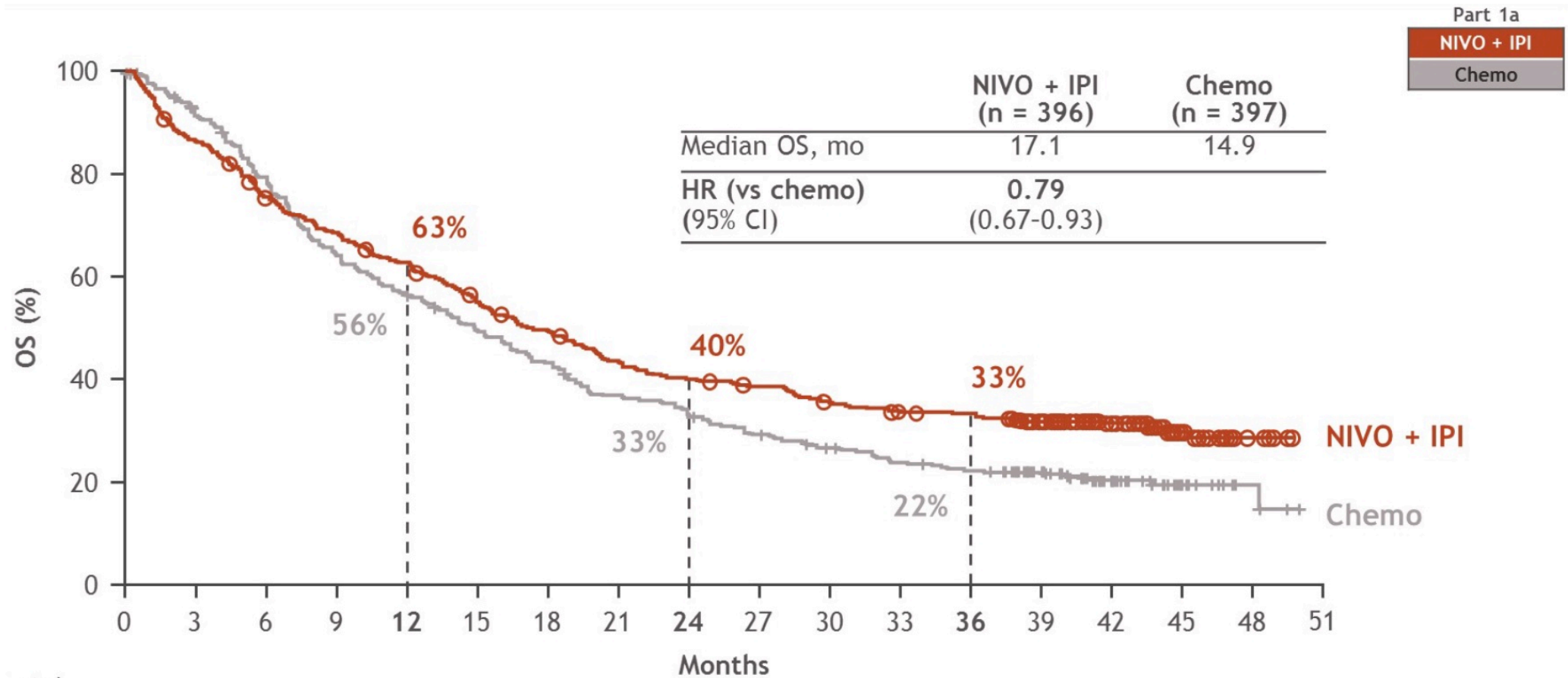
| Monotherapy | FDA approval | Pivotal study | Histologic type | HR (OS) |
|------------------------------|---------------------|--------------------------------|---|---------|
| Pembrolizumab ^{1,2} | 4/11/19 10/24/16 | KEYNOTE-042 KEYNOTE-024 | PD-L1 TPS ≥1% | 0.63 |
| Atezolizumab ³ | 5/18/20 | IMpower110 | 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.

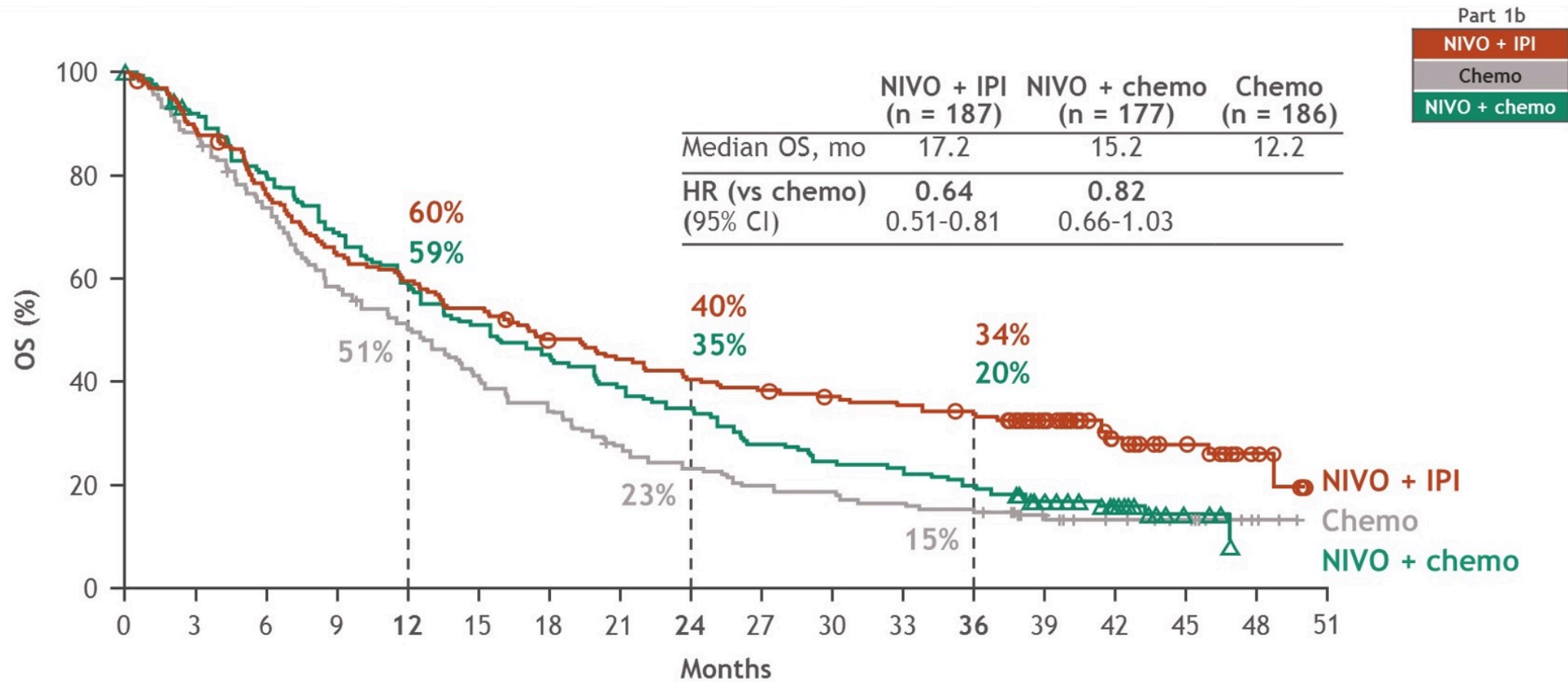
Nivolumab + Ipilimumab versus Platinum-Doublet Chemotherapy as First-Line Treatment for Advanced Non-Small Cell Lung Cancer: Three-Year Update from CheckMate 227 Part 1

Ramalingam SS et al.
ASCO 2020;Abstract 9500.

Three-Year Update: OS with IPI + Nivo vs Chemo (PD-L1 $\geq 1\%$)



Three-Year Update: OS with IPI + Nivo vs Chemo vs Nivo + Chemo (PD-L1 <1%)



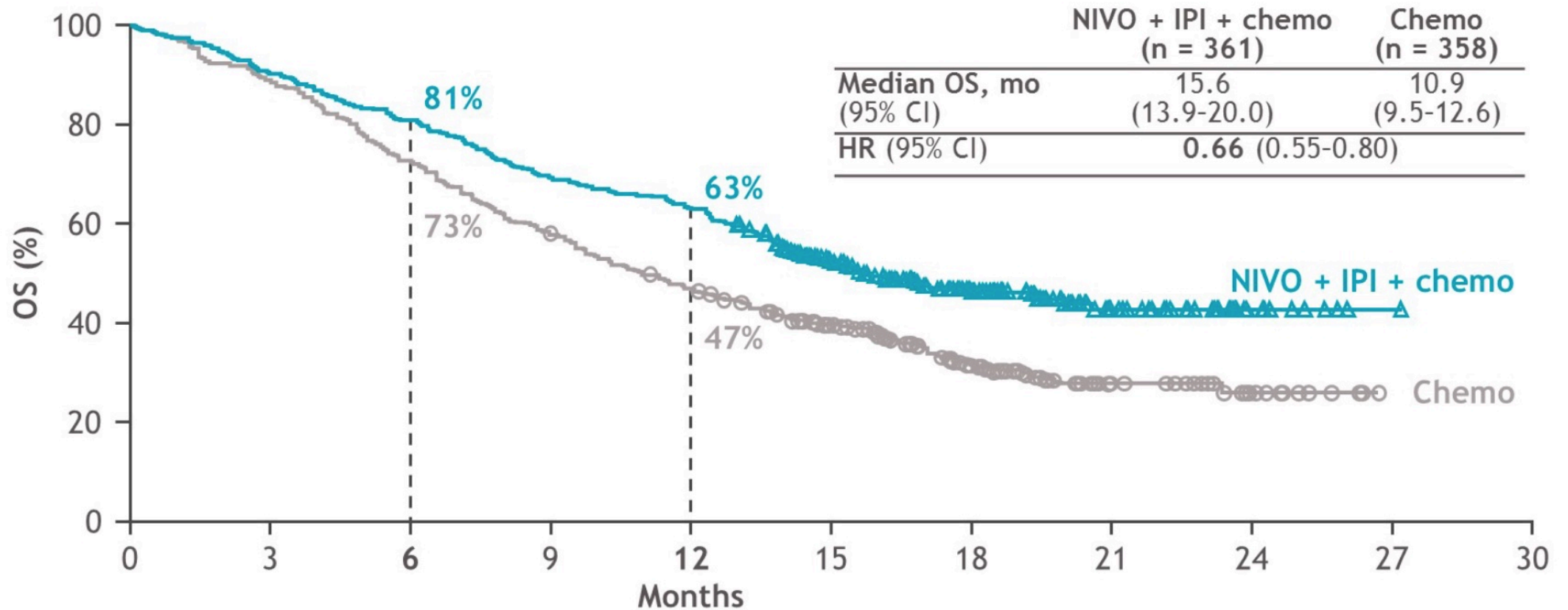
Lancet Oncol 2021;22(2):198-211.



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

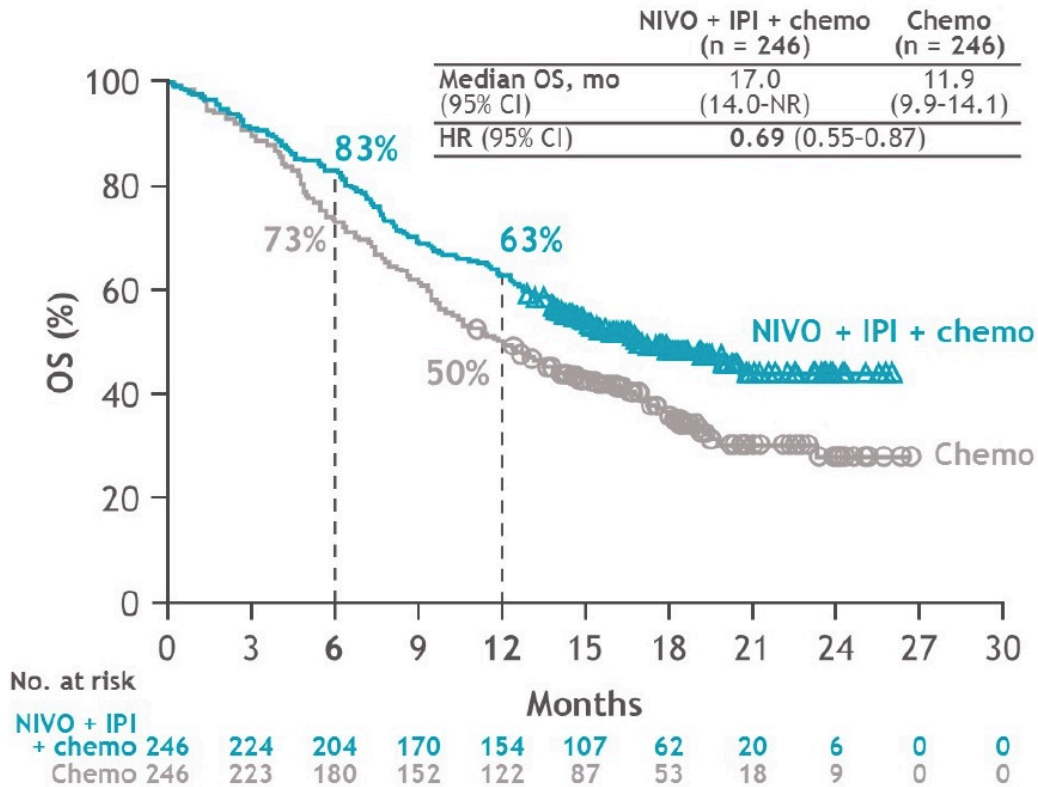
Luis Paz-Ares, Tudor-Eliade Ciuleanu, Manuel Cobo, Michael Schenker, Bogdan Zurawski, Juliana Menezes, Eduardo Richardet, Jaafar Bennouna, Enriqueta Felip, Oscar Juan-Vidal, Aurelia Alexandru, Hiroshi Sakai, Alejo Lingua, Pamela Salman, Pierre-Jean Souquet, Pedro De Marchi, Claudio Martin, Maurice Pérol, Arnaud Scherpereel, Shun Lu, Thomas John, David P Carbone, Stephanie Meadows-Shropshire, Shruti Agrawal, Abderrahim Oukessou, Jinchun Yan, Martin Reck

CheckMate 9LA: Updated OS

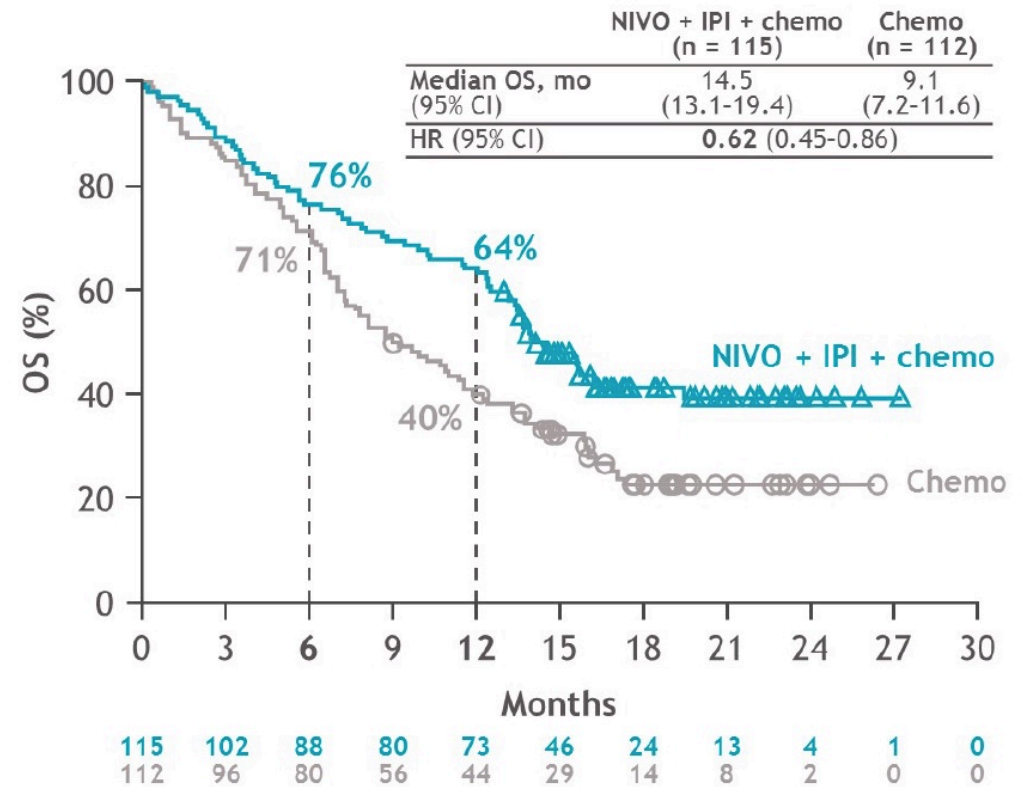


CheckMate 9LA: Updated OS by Histology

NSQ NSCLC^a



SQ NSCLC^b



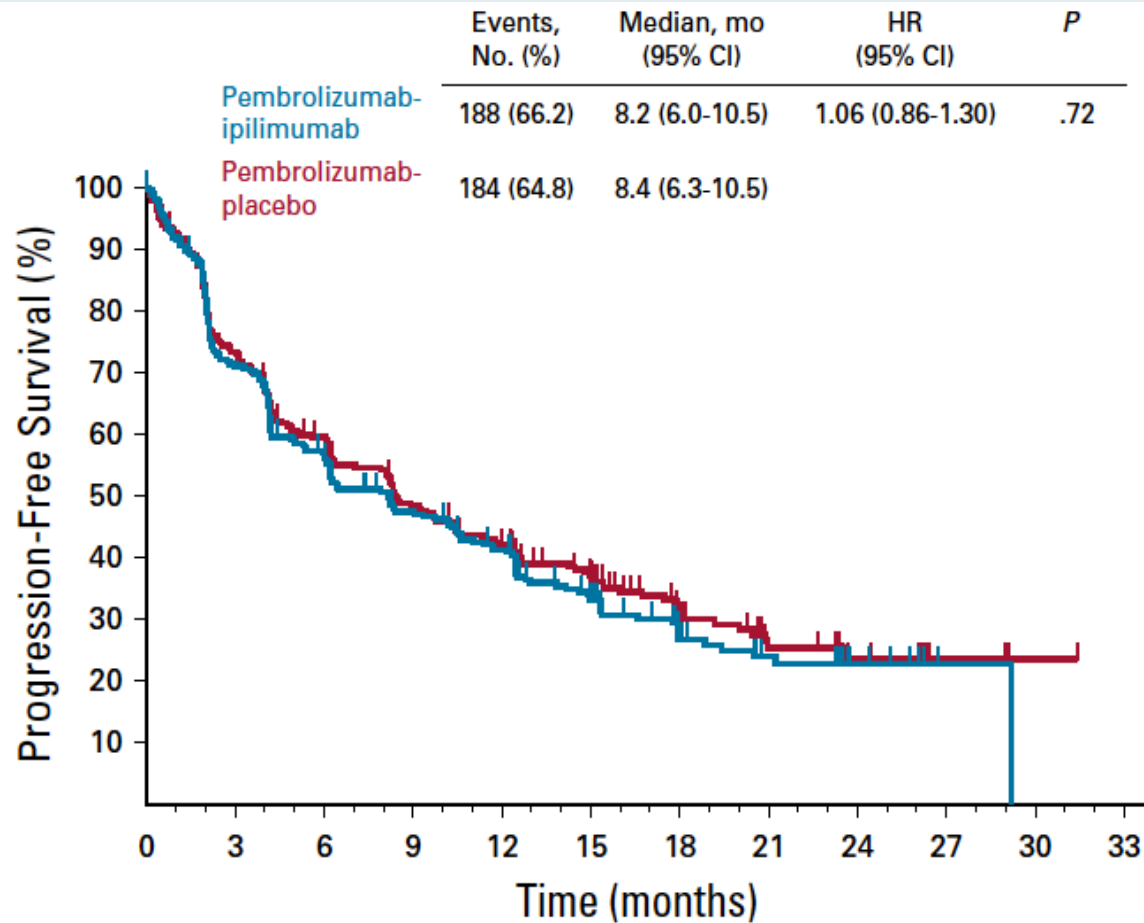
Pembrolizumab Plus Ipilimumab or Placebo for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score $\geq 50\%$: Randomized, Double-Blind Phase III KEYNOTE-598 Study

Michael Boyer, MBBS, PhD¹; Mehmet A. N. Şendur, MD²; Delvys Rodríguez-Abreu, MD³; Keunchil Park, MD, PhD⁴; Dae Ho Lee, MD, PhD⁵; Irfan Çiçin, MD⁶; Perran Fulden Yumuk, MD⁷; Francisco J. Orlandi, MD⁸; Ticiana A. Leal, MD⁹; Olivier Molinier, MD¹⁰; Nopadol Soparattanapaisam, MD¹¹; Adrian Langleben, MD¹²; Raffaele Califano, MD¹³; Balazs Medgyasszay, MD¹⁴; Te-Chun Hsia, MD¹⁵; Gregory A. Otterson, MD¹⁶; Lu Xu, PhD¹⁷; Bilal Piperdi, MD¹⁷; Ayman Samkari, MD¹⁷; and Martin Reck, MD, PhD¹⁸ for the KEYNOTE-598 Investigators

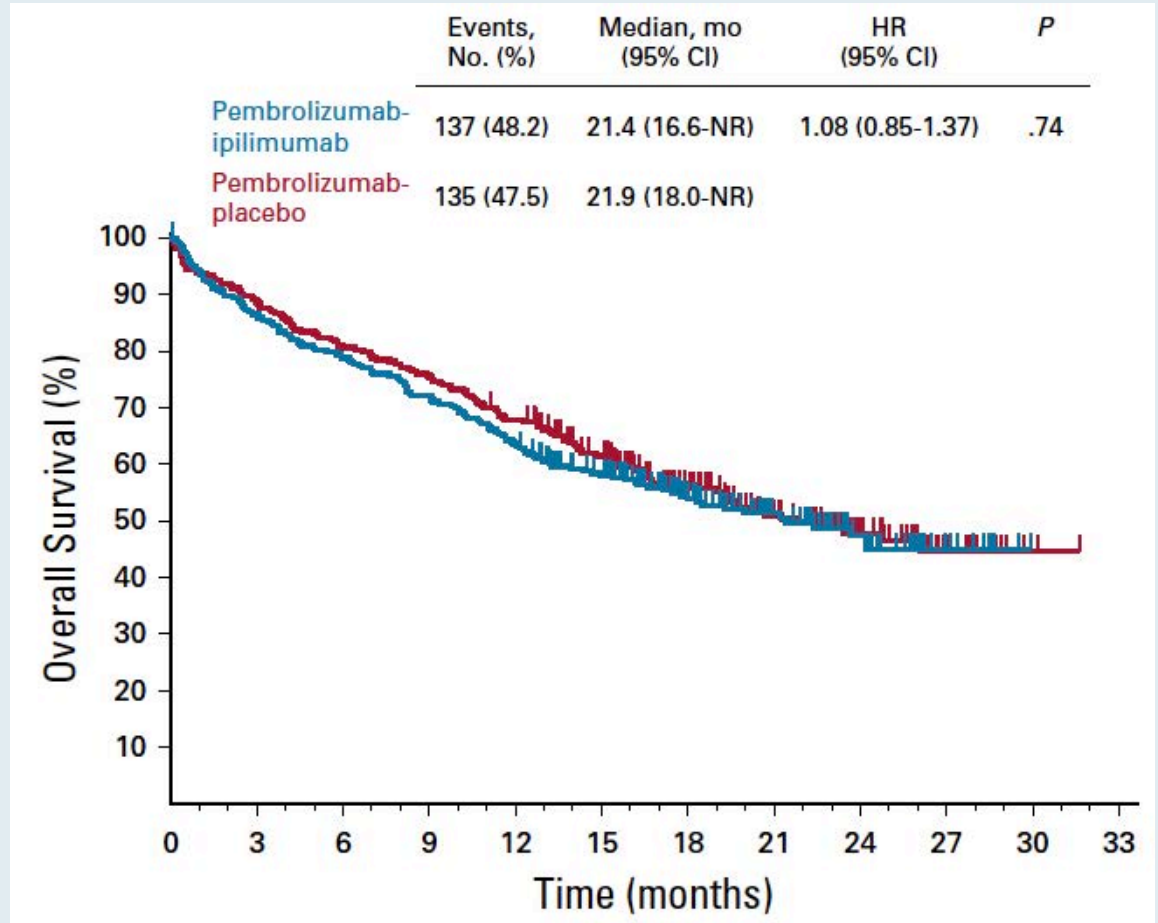
Boyer M et al. *J Clin Oncol* 2021;[Online ahead of print].

KEYNOTE-598: Survival

Progression-free survival (PFS)



Overall survival (OS)



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).”

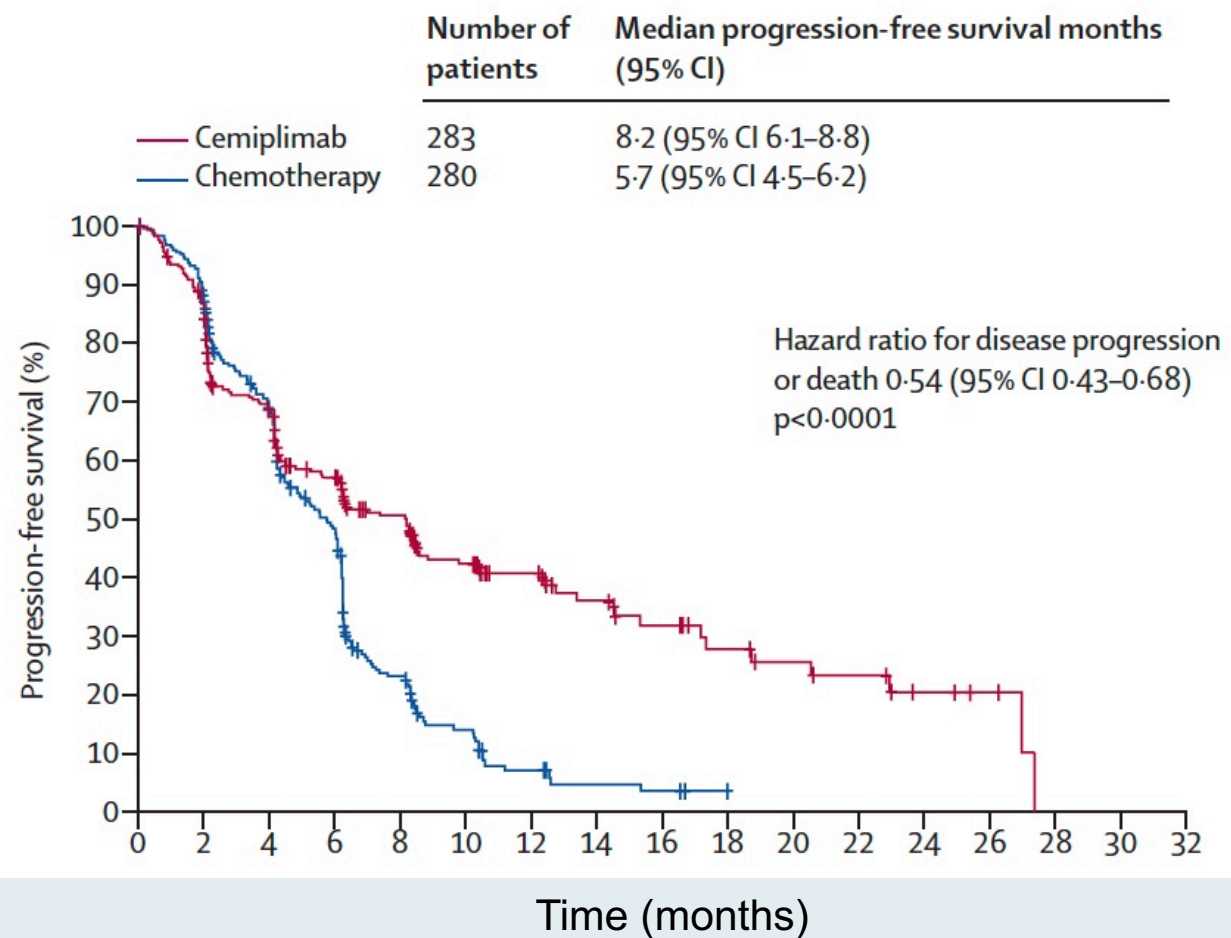
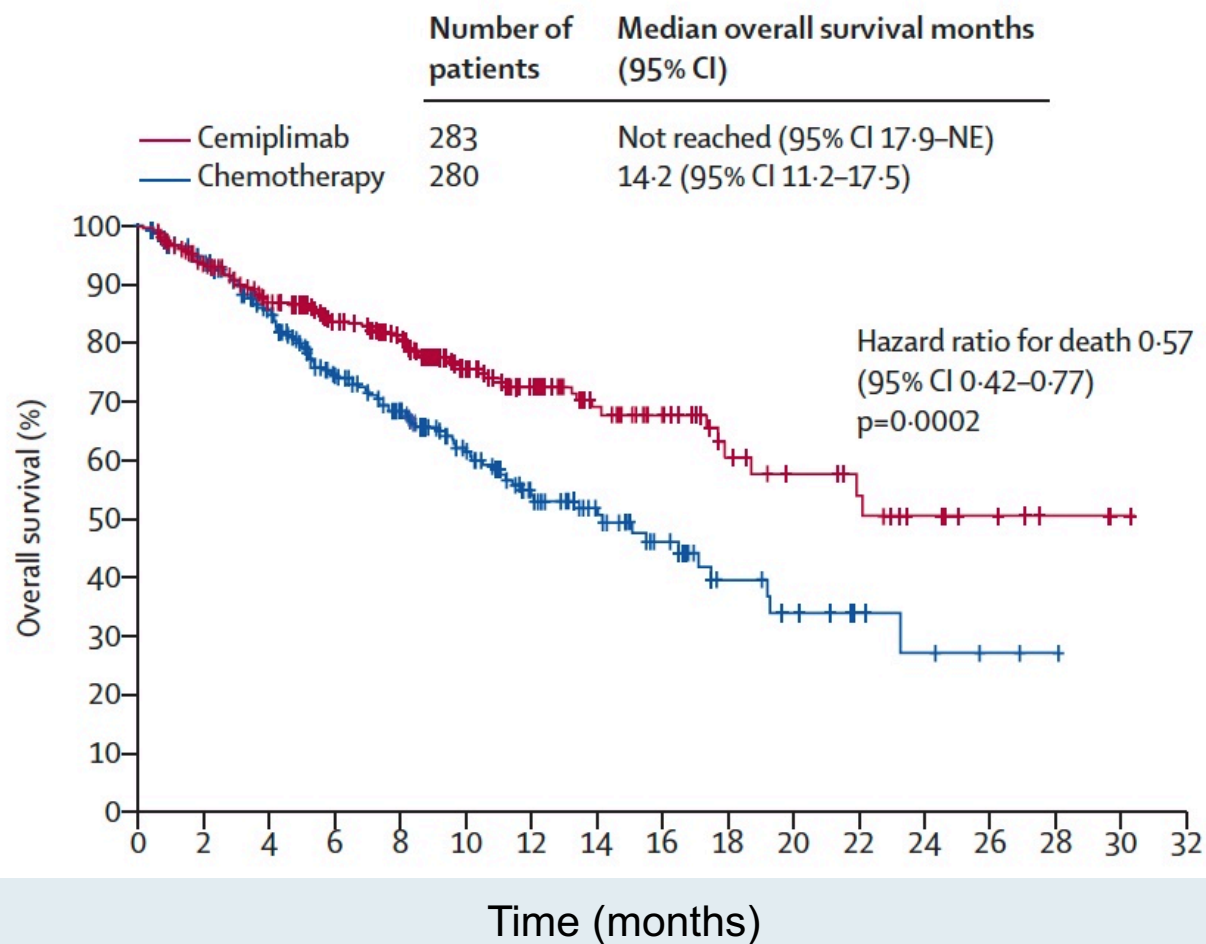
Lancet 2021;397(10274):592-604.



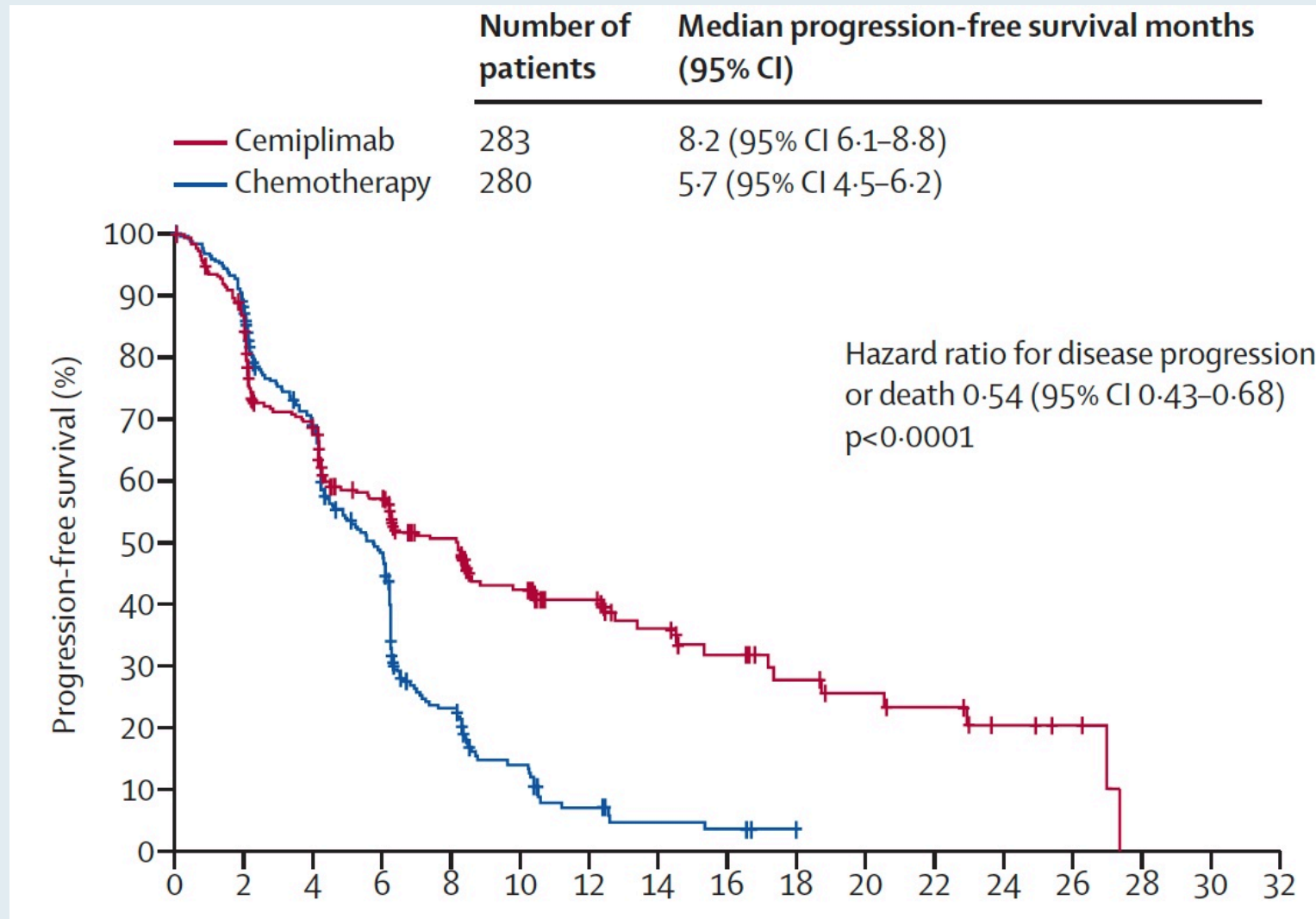
Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial

Ahmet Sezer, Saadettin Kilickap, Mahmut Gümüþ, Igor Bondarenko, Mustafa Özgüroğlu, Miranda Gogishvili, Hacı M Turk, Irfan Cicin, Dmitry Bentsion, Oleg Gladkov, Philip Clingan, Virote Sriuranpong, Naiyer Rizvi, Bo Gao, Siyu Li, Sue Lee, Kristina McGuire, Chieh-I Chen, Tamta Makharadze, Semra Paydas, Marina Nechaeva, Frank Seebach, David M Weinreich, George D Yancopoulos, Giuseppe Gullo, Israel Lowy, Petra Rietschel

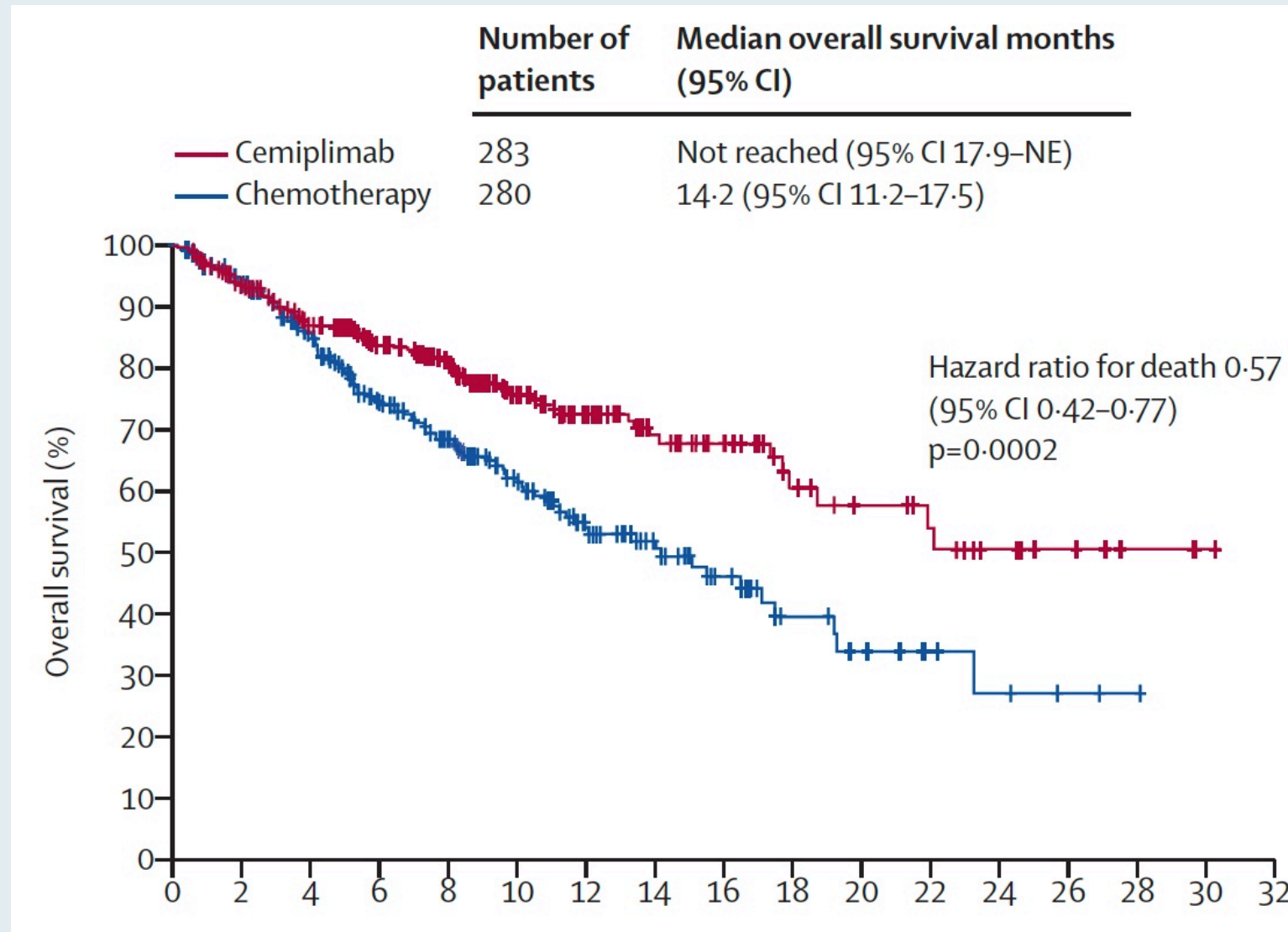
EMPOWER-Lung 1: Overall and Progression-Free Survival with First-Line Cemiplimab versus Chemotherapy



EMPOWER-Lung 1: Progression-Free Survival in the PD-L1 $\geq 50\%$ Population



EMPOWER-Lung 1: Overall Survival in the PD-L1 $\geq 50\%$ Population



Metastatic NSCLC Harboring Targetable Mutations other than EGFR, ALK or ROS1

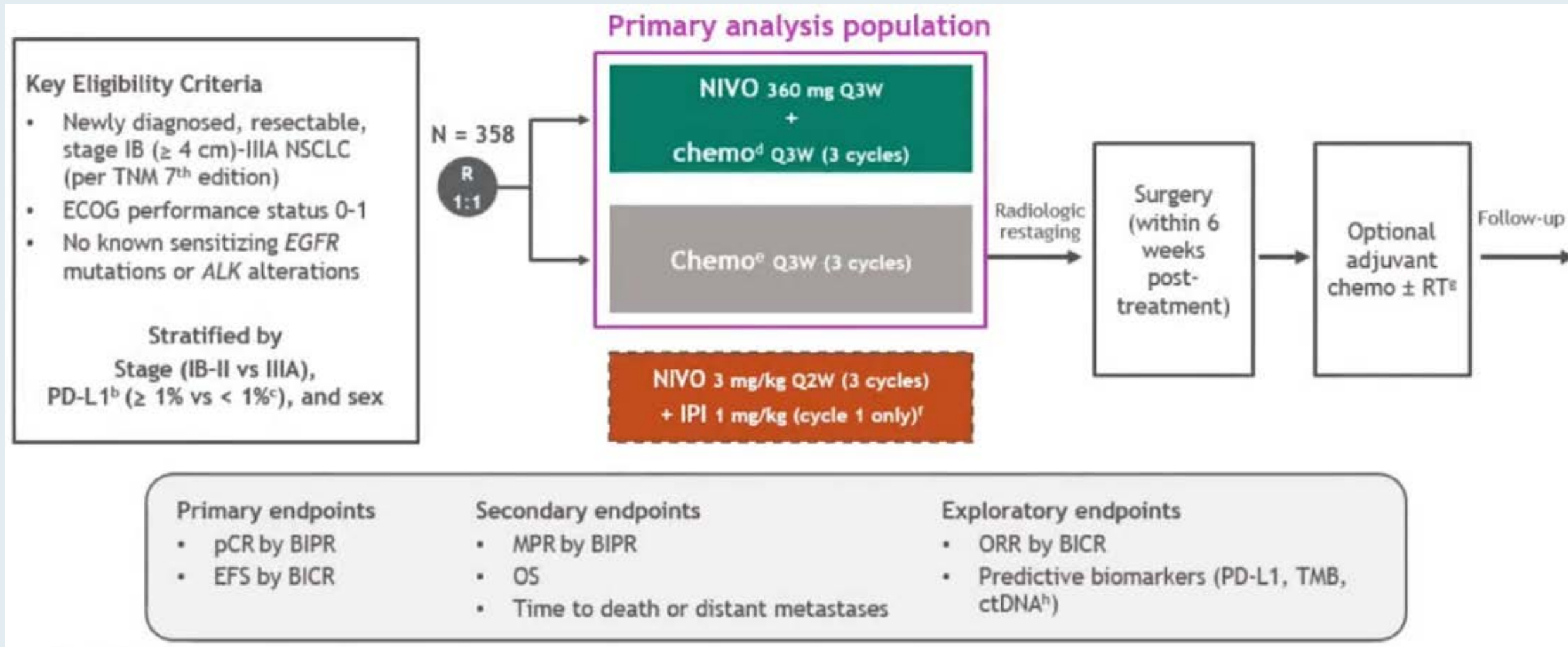
Immunotherapy Consolidation after Chemoradiation Therapy for Localized or Locally Advanced NSCLC

Nivolumab + platinum-doublet chemotherapy vs chemotherapy as neoadjuvant treatment for resectable (IB-IIIA) non-small cell lung cancer in the phase 3 CheckMate 816 trial

Patrick M. Forde,¹ Jonathan Spicer,² Shun Lu,³ Mariano Provencio,⁴
Tetsuya Mitsudomi,⁵ Mark M. Awad,⁶ Enriqueta Felip,⁷ Stephen Broderick,¹
Julie Brahmer,¹ Scott J. Swanson,⁶ Keith Kerr,⁸ Changli Wang,⁹ Gene B. Saylor,¹⁰
Fumihiko Tanaka,¹¹ Hiroyuki Ito,¹² Ke-Neng Chen,¹³ Cecile Dorange,¹⁴ Junliang Cai,¹⁴
Joseph Fiore,¹⁴ Nicolas Girard¹⁵

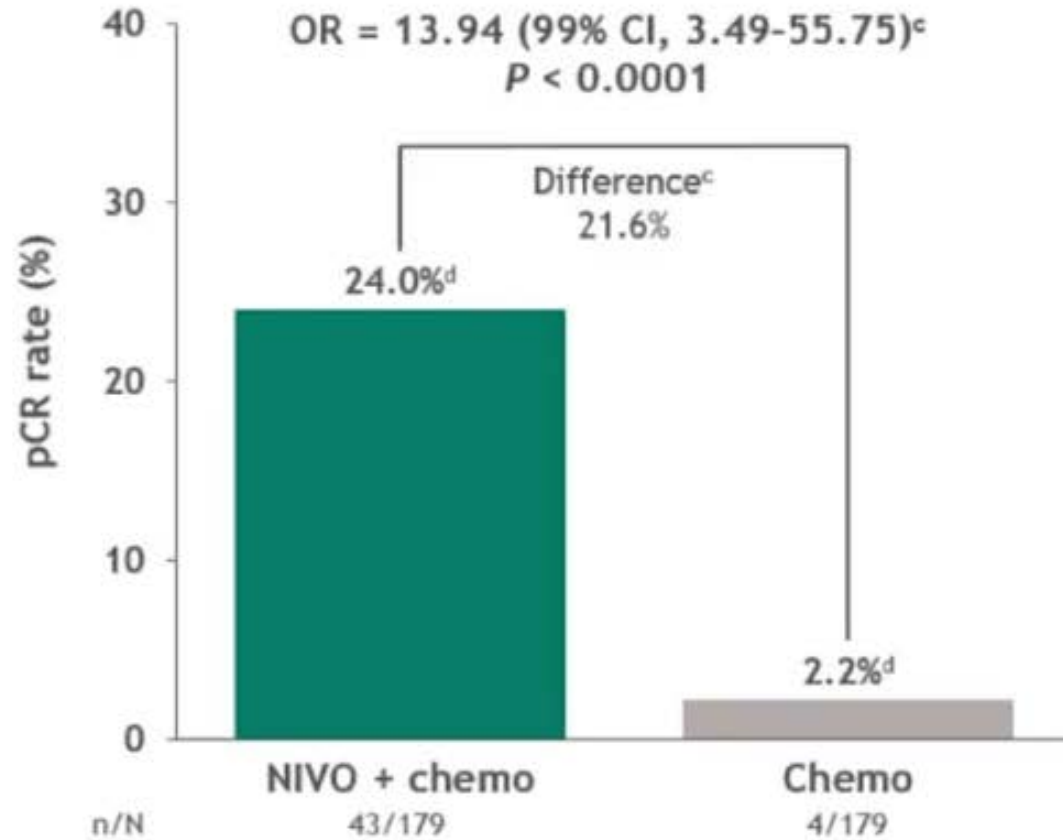
¹Johns Hopkins Kimmel Cancer Center, Baltimore, MD, USA; ²McGill University Health Center, Montreal, Québec, Canada; ³Shanghai Chest Hospital, Shanghai, China; ⁴Hospital Universitario Puerta de Hierro, Madrid, Spain; ⁵Kindai University Faculty of Medicine, Ohno-Higashi, Osaka-Sayama, Japan; ⁶Dana-Farber Cancer Institute, Boston, MA, USA; ⁷Vall d'Hebron Institute of Oncology, Barcelona, Spain; ⁸Aberdeen Royal Infirmary, Aberdeen, UK; ⁹Tianjin Lung Cancer Center, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; ¹⁰Charleston Oncology, Charleston, SC, USA; ¹¹University of Occupational and Environmental Health, Kitakyushu, Japan; ¹²Kanagawa Cancer Center, Yokohama, Japan; ¹³Peking University School of Oncology, Beijing Cancer Hospital, Beijing, China; ¹⁴Bristol Myers Squibb, Princeton, NJ, USA; ¹⁵Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France

Phase III CheckMate 816 Trial Design

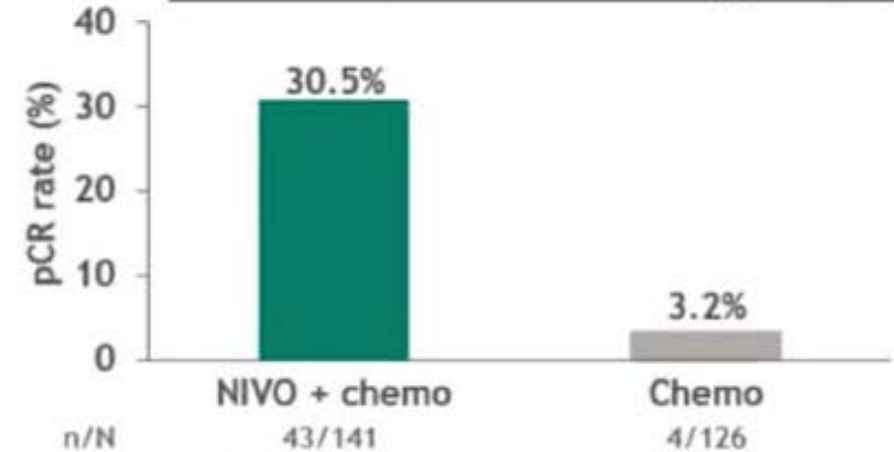


CheckMate 816: pCR Rate with Neoadjuvant Nivolumab (Primary Endpoint)

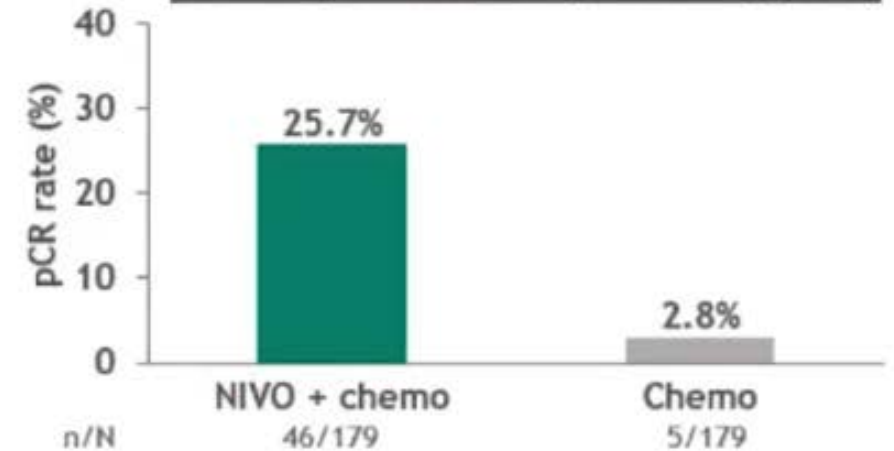
Primary endpoint: ITT (ypT0N0)^b



Patients with resection^e (ypT0N0)



Primary tumor only in ITT (ypT0)

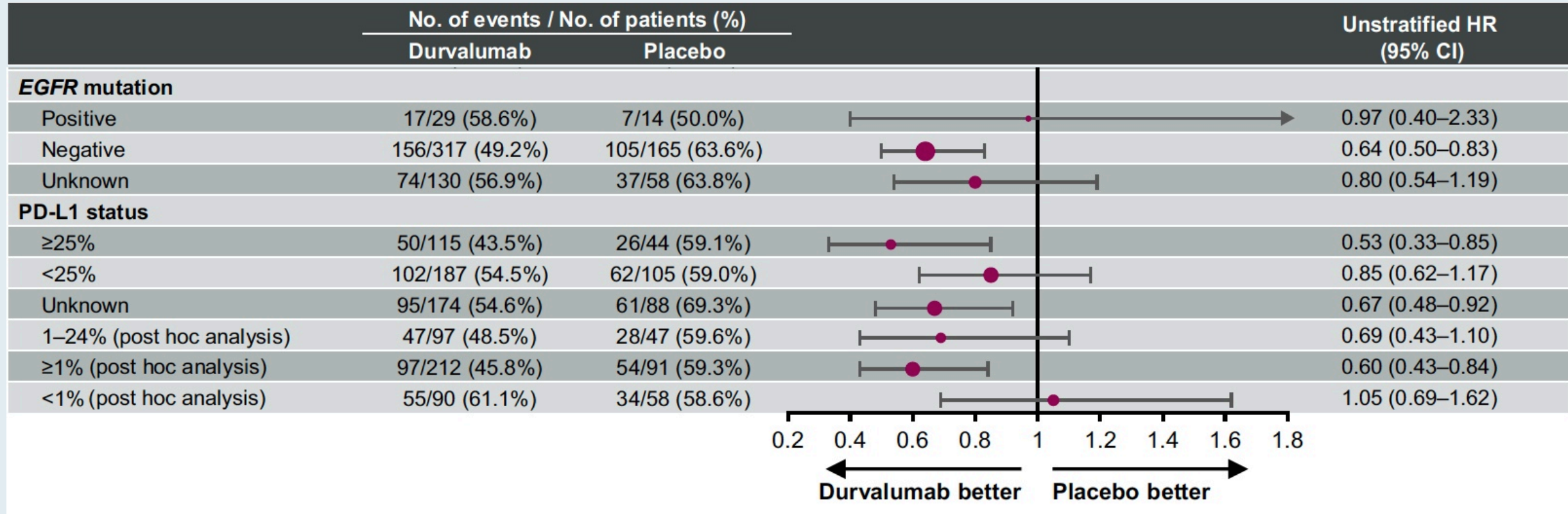


• pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4-29.0)

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

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

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



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

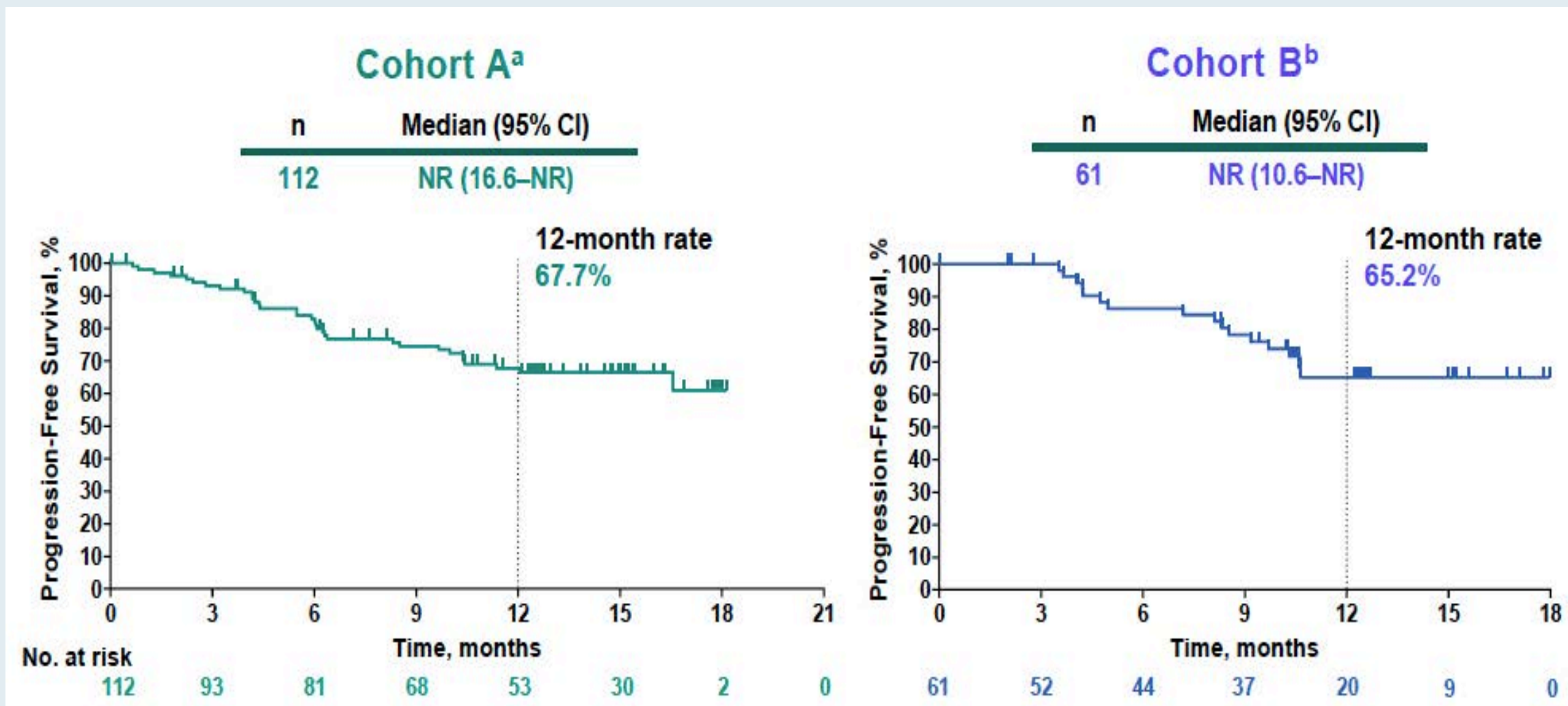
- In this real-world cohort, clinically significant pneumonitis was
 - More frequent compared to clinical trial reports
 - Asymptomatic infiltrates on imaging: 39.8%
 - Clinically significant pneumonitis: 21.1%
 - Grade 2 (7.3%), Grade 3 (11.4%), Grade 4 (1.6%), Grade 5 (0.8%)
 - Not associated with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

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

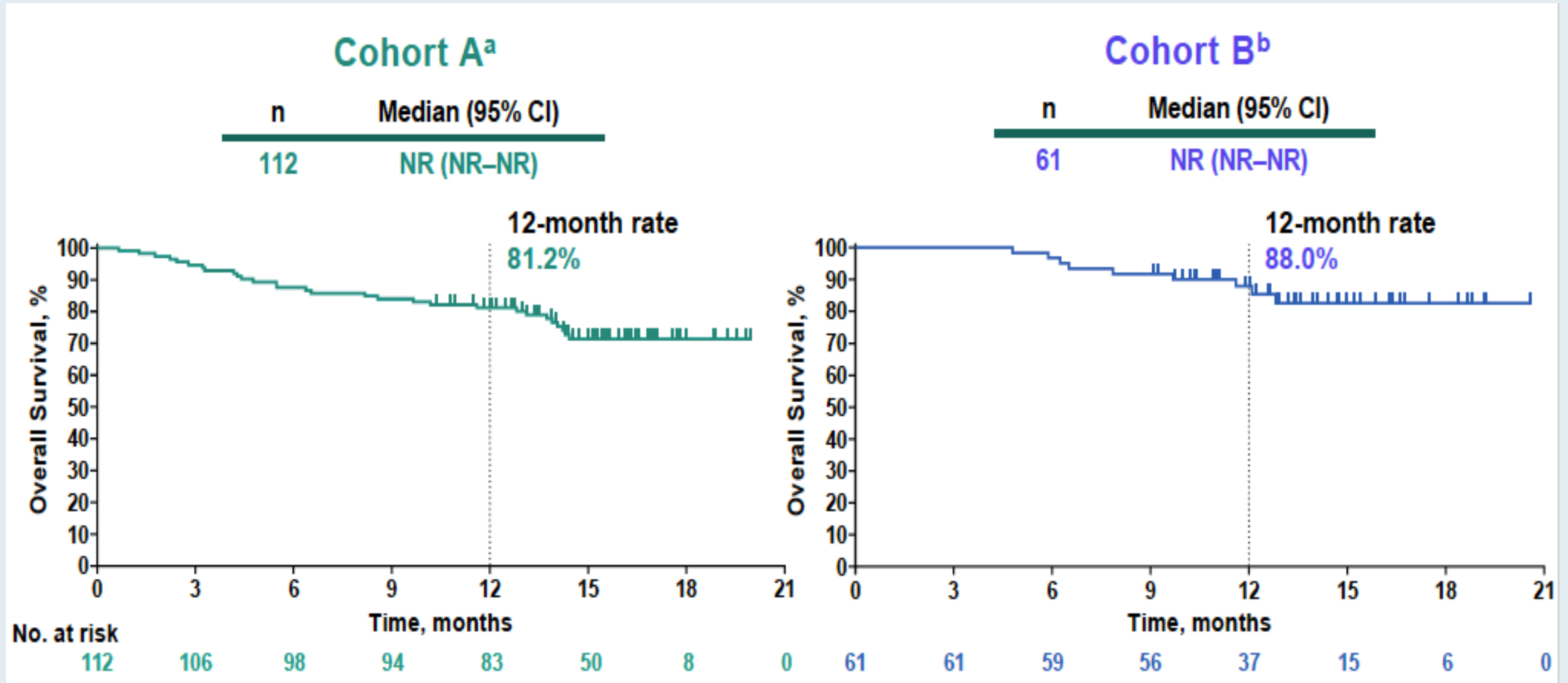
M. Reck,¹ K.H. Lee,² N. Frost,³ D.M. Kowalski,⁴ V. Breder,⁵ T. Pollock,⁶ N. Reguart,⁷ B. Houghton,⁸ X. Quantin,⁹ S.M. Keller,¹⁰ H. Liu,¹⁰ B. Piperdi,¹⁰ S.K. Jabbour¹¹

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

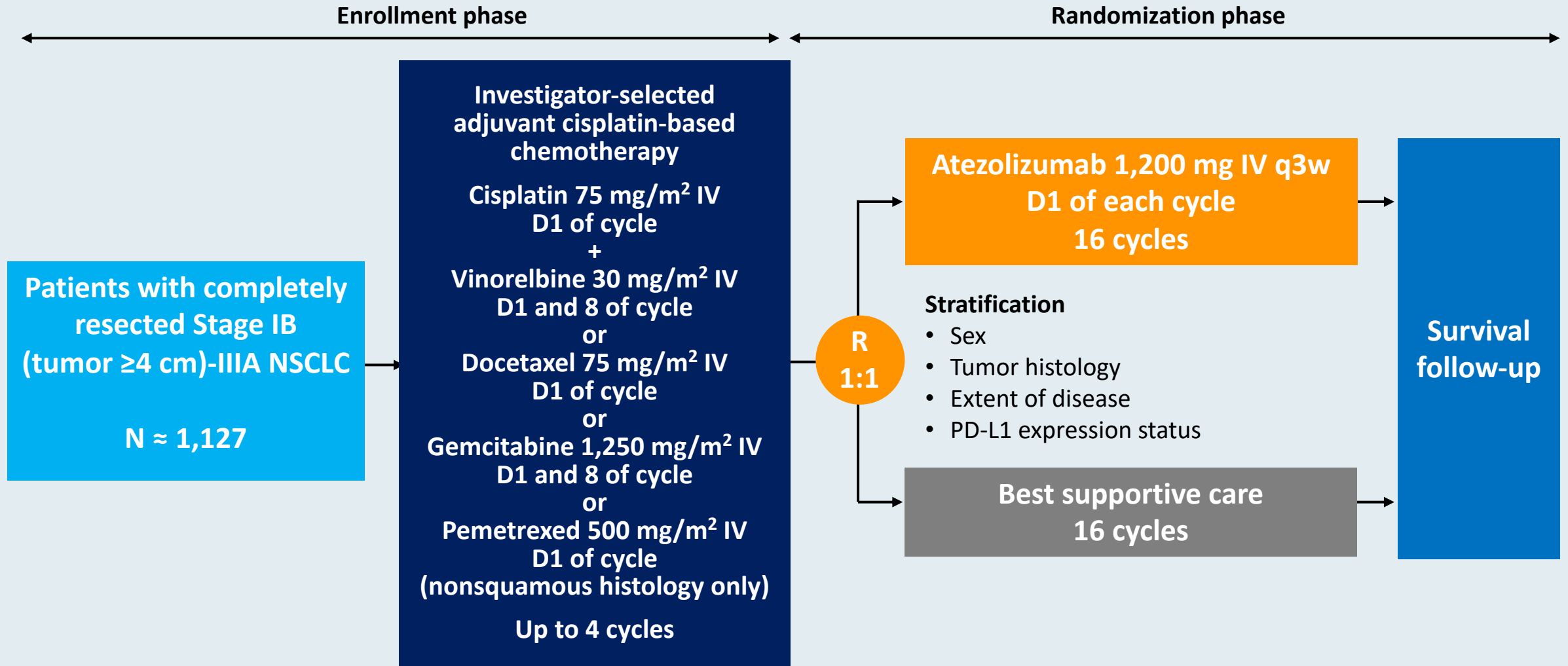
KEYNOTE-799: Progression-Free Survival



KEYNOTE-799: Overall Survival



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

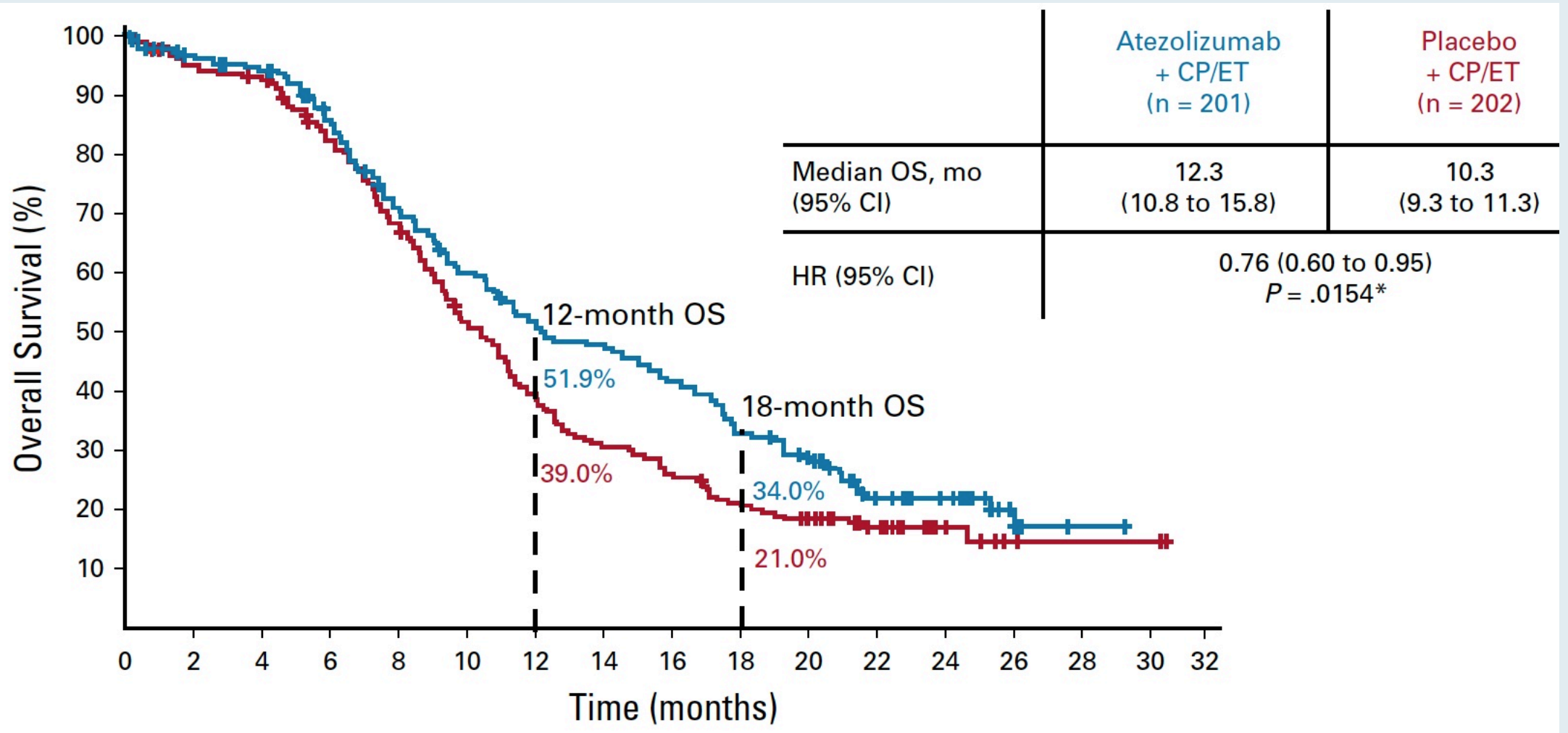
Extensive-Stage Small Cell Lung Cancer

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, MD¹; Martin Reck, MD, PhD²; Aaron S. Mansfield, MD³; Tony Mok, MD⁴; Arnaud Scherpereel, MD, PhD⁵; Niels Reinmuth, MD, PhD⁶; Marina Chiara Garassino, MD⁷; Javier De Castro Carpeno, MD⁸; Raffaele Califano, MD⁹; Makoto Nishio, MD¹⁰; Francisco Orlandi, MD¹¹; Jorge Alatorre-Alexander, MD¹²; Ticiana Leal, MD¹³; Ying Cheng, MD¹⁴; Jong-Seok Lee, MD¹⁵; Sivuonthanh Lam, PharmD¹⁶; Mark McClelland, PhD¹⁶; Yu Deng, PhD¹⁶; See Phan, MD¹⁶; and Leora Horn, MD¹⁷

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

IMpower133: Updated Overall Survival





IASLC/WCLC 2020;Abstract 0A11.06

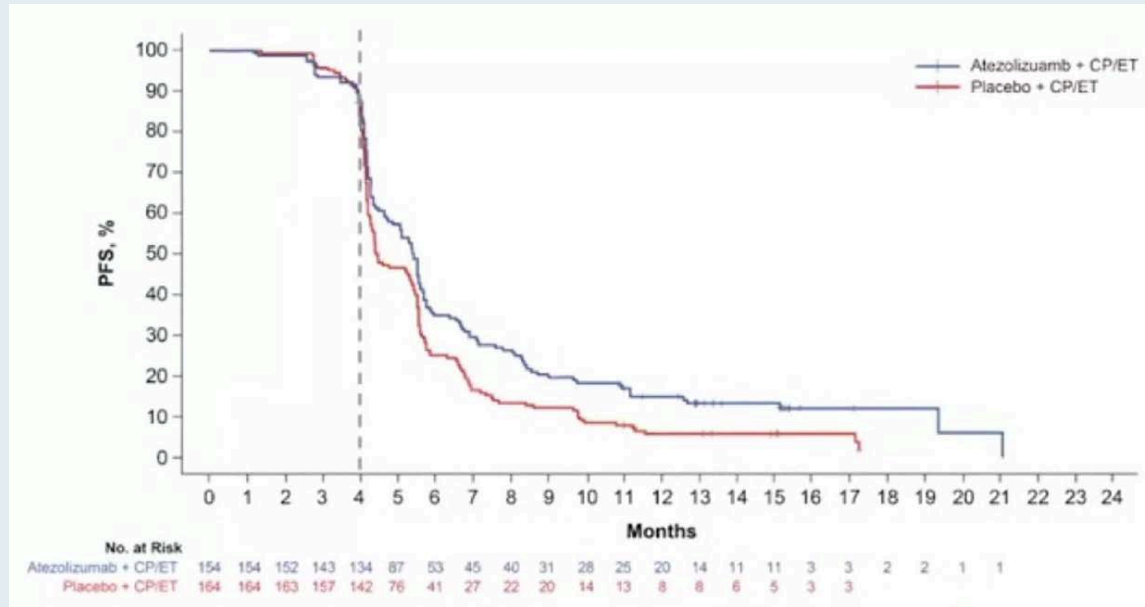
IMpower133: exploratory analysis of maintenance therapy in patients with extensive-stage small cell lung cancer

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. Liu¹⁶

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 Skłodowska-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, Istituto 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

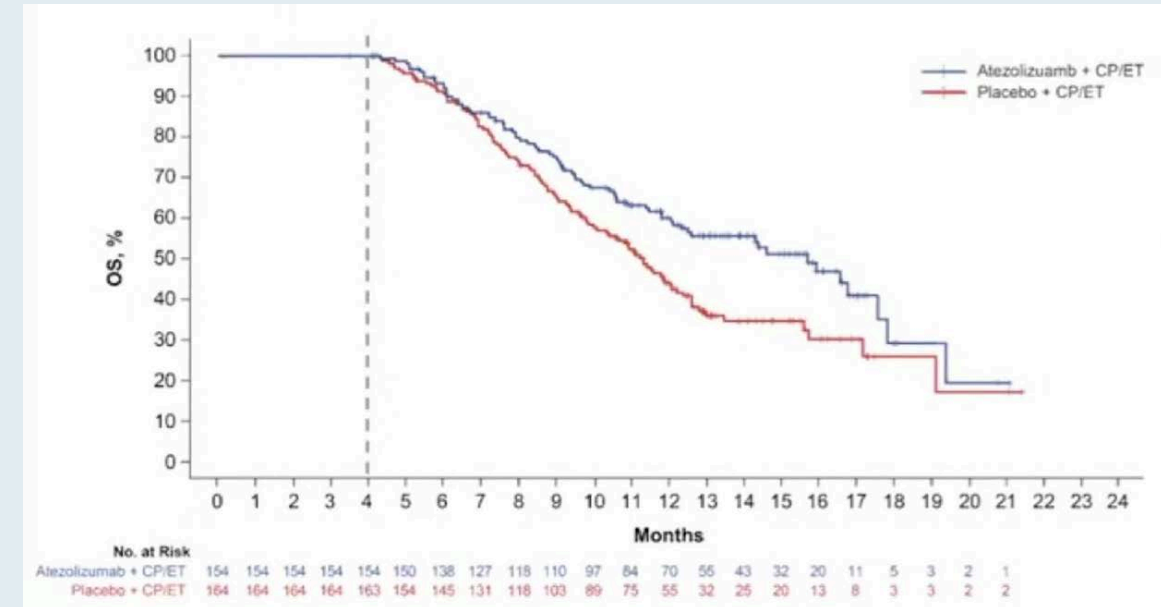
IMpower133: Survival Outcomes in the Maintenance Population

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)



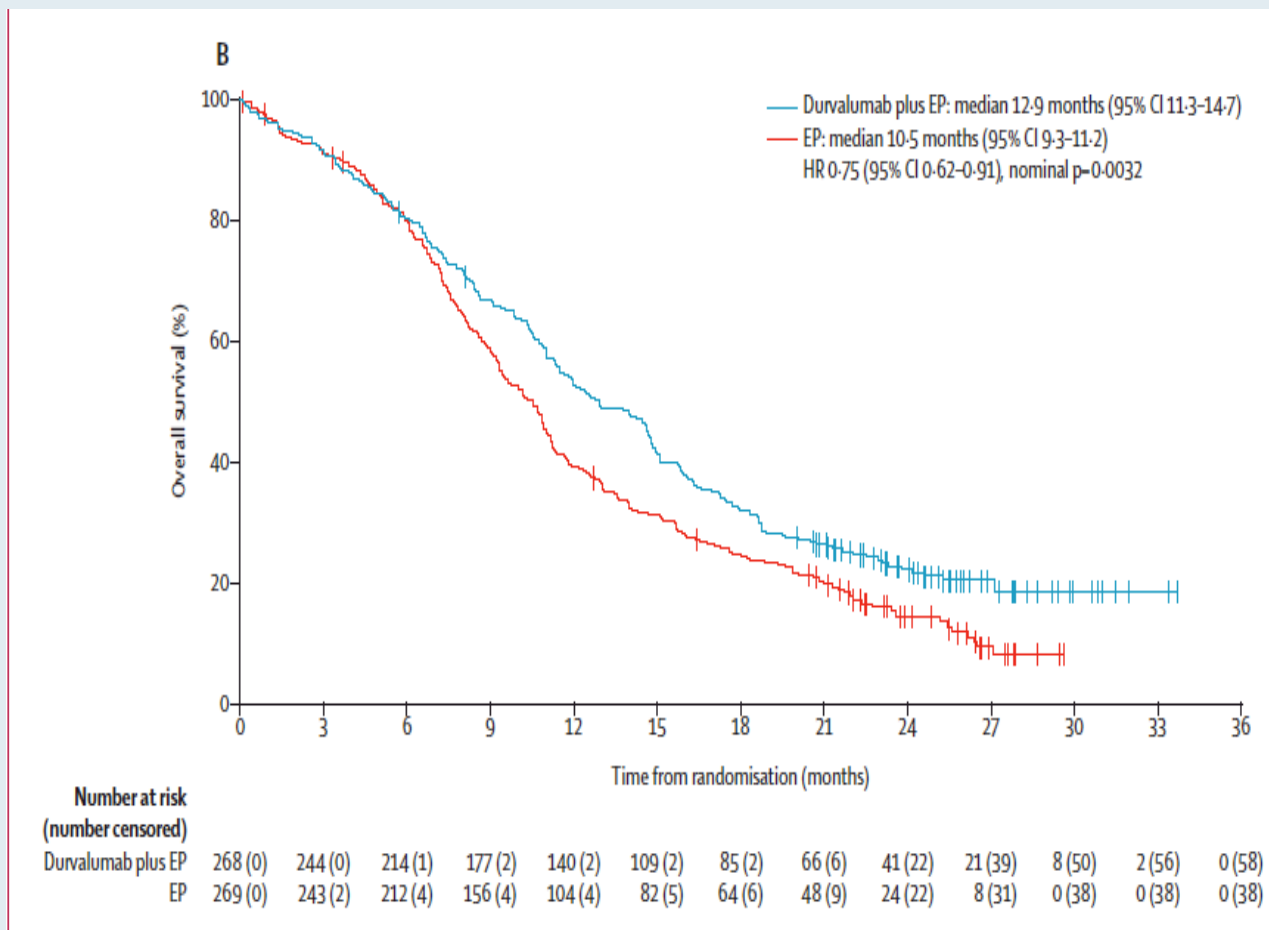
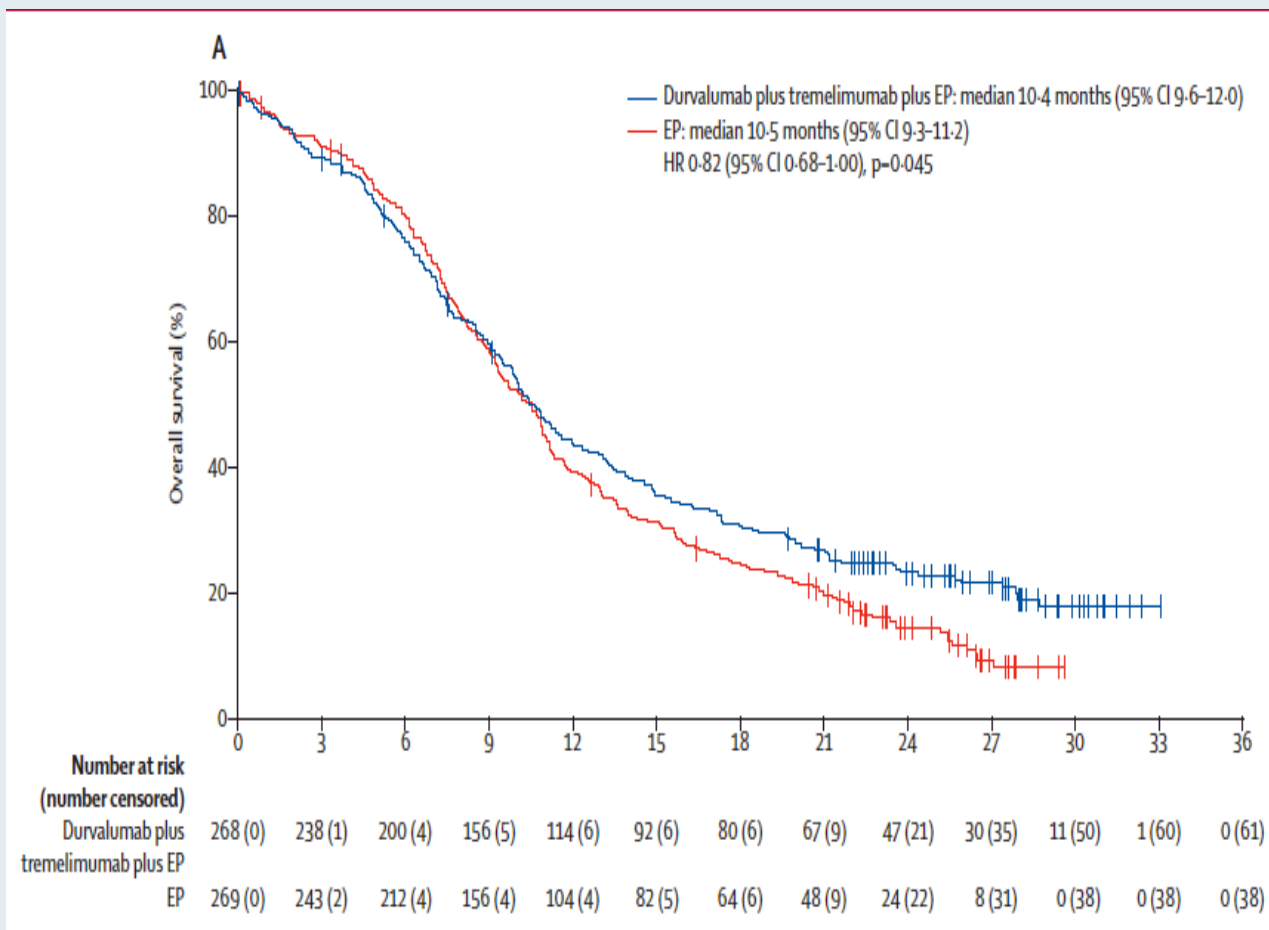
| Median PFS | Atezolizumab | Placebo | HR |
|---------------------------|--------------|---------|--------------|
| From start of maintenance | 12.5 mo | 8.4 mo | 0.59 |
| From randomization | 15.7 mo | 11.3 mo | Not reported |



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

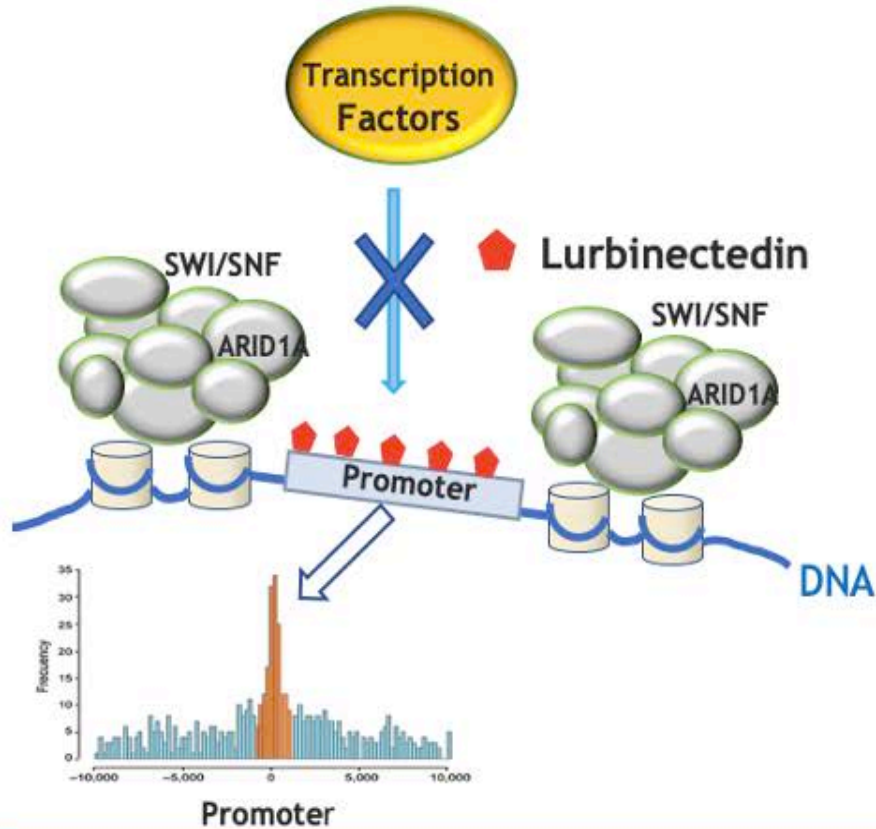
*Jonathan W Goldman, Mikhail Dvorkin, Yuanbin Chen, Niels Reinmuth, Katsuyuki Hotta, Dmytro Trukhin, Galina Statsenko, Maximilian J Hochmair, Mustafa Özgüroğlu, Jun Ho Ji, Marina Chiara Garassino, Oleksandr Voitko, Artem Poltoratskiy, Santiago Ponce, Francesco Verderame, Libor Havel, Igor Bondarenko,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

CASPIAN: Updated OS Analyses in ITT Population

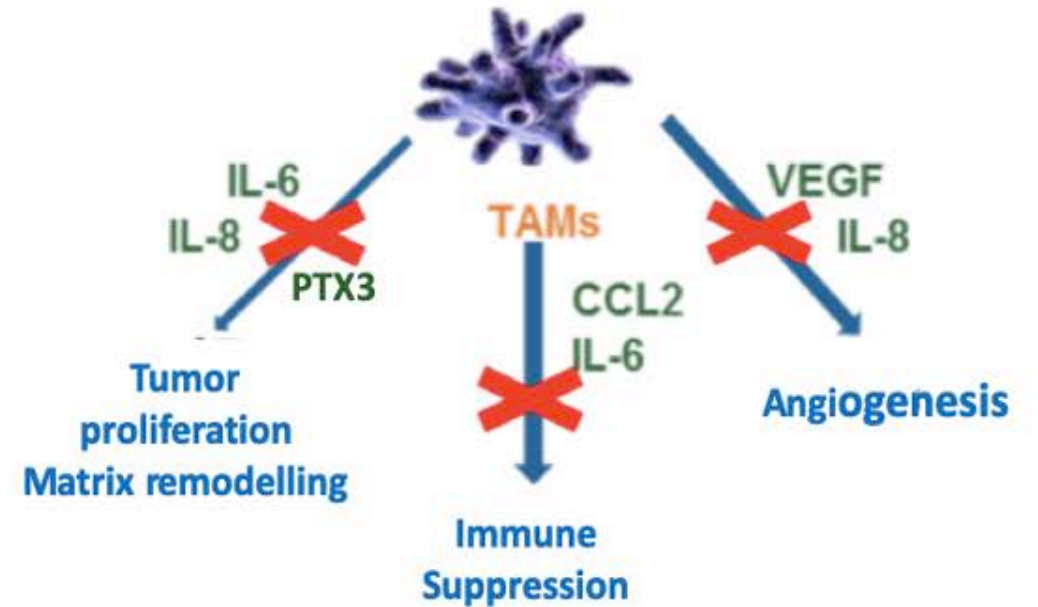


Lurbinectedin: A Selective Inhibitor of Oncogenic Transcription

Tumor-intrinsic effects



Tumor-associated macrophage effects?



How does it work?

- Alkylator
- Minor groove DNA binder

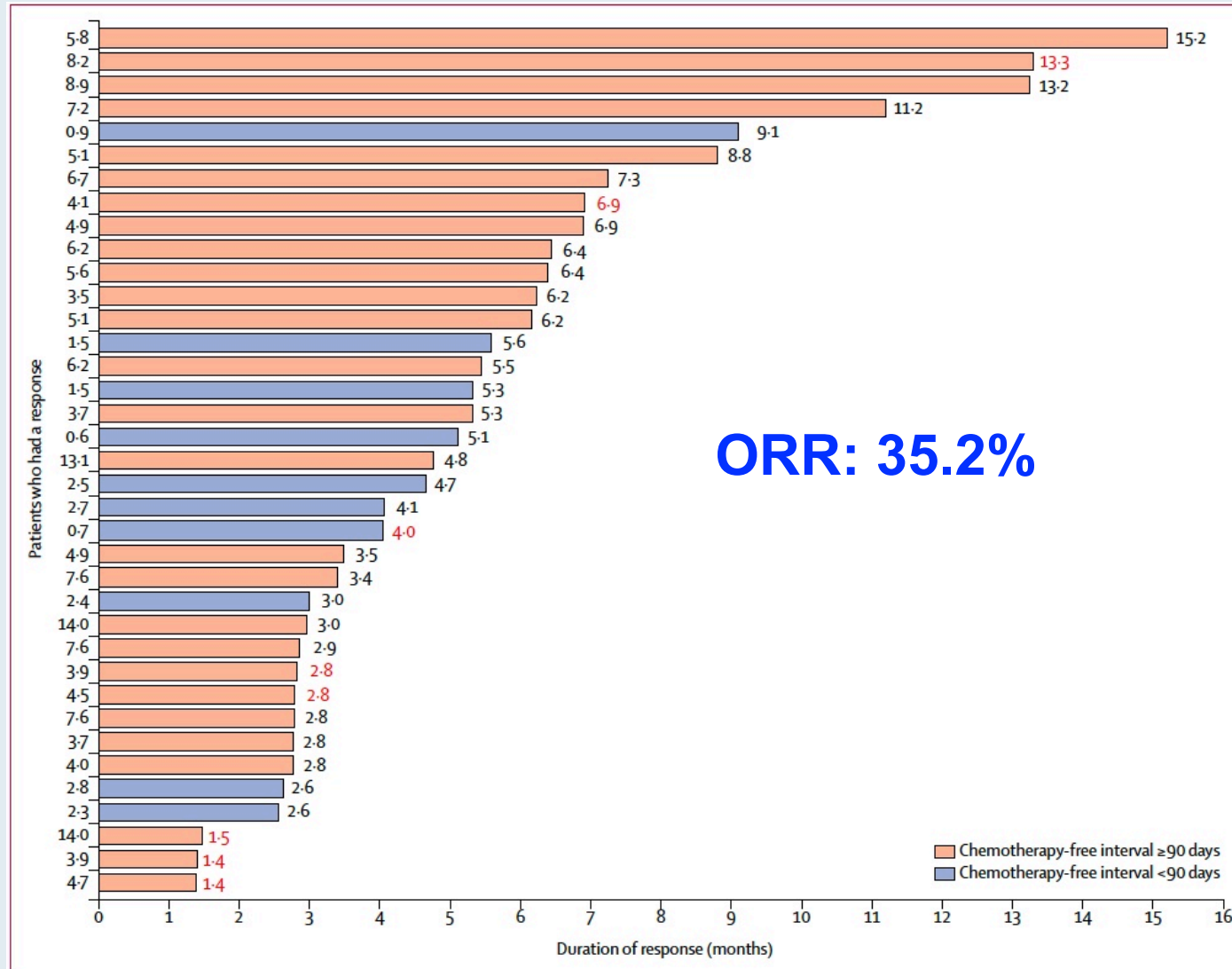
Lancet Oncol 2020;21:645-54.

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



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

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



Use of Targeted Treatment in NSCLC

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.

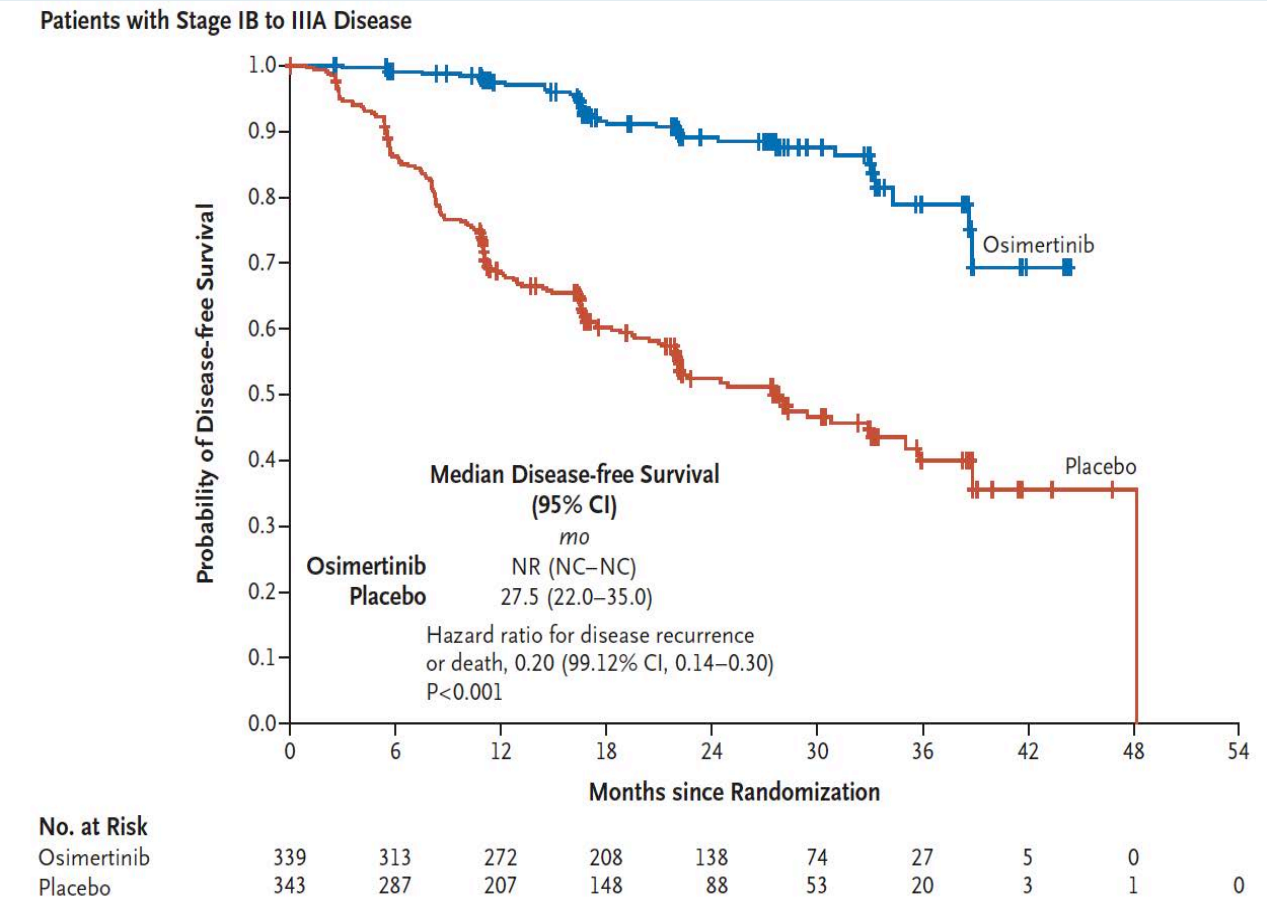
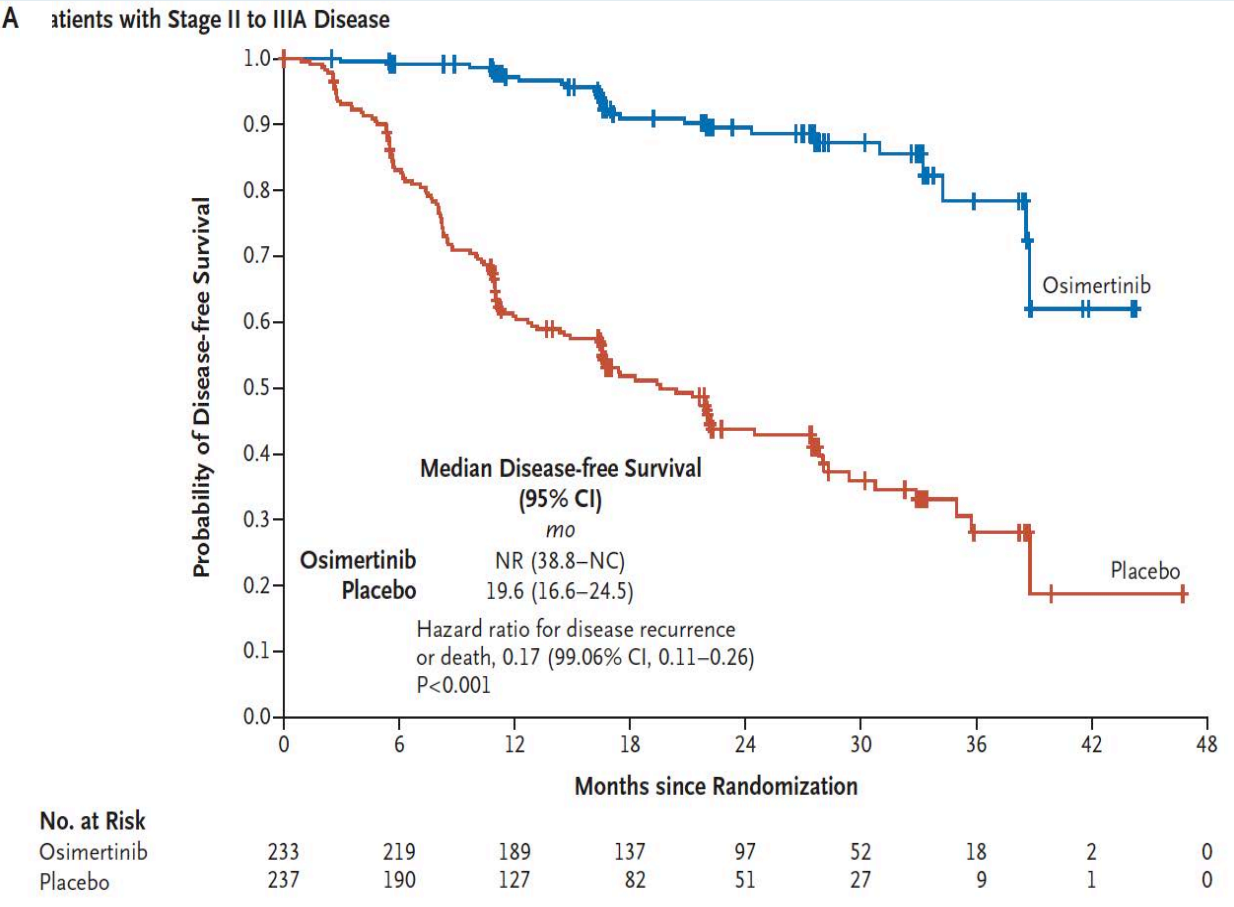
ORIGINAL ARTICLE

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

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

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

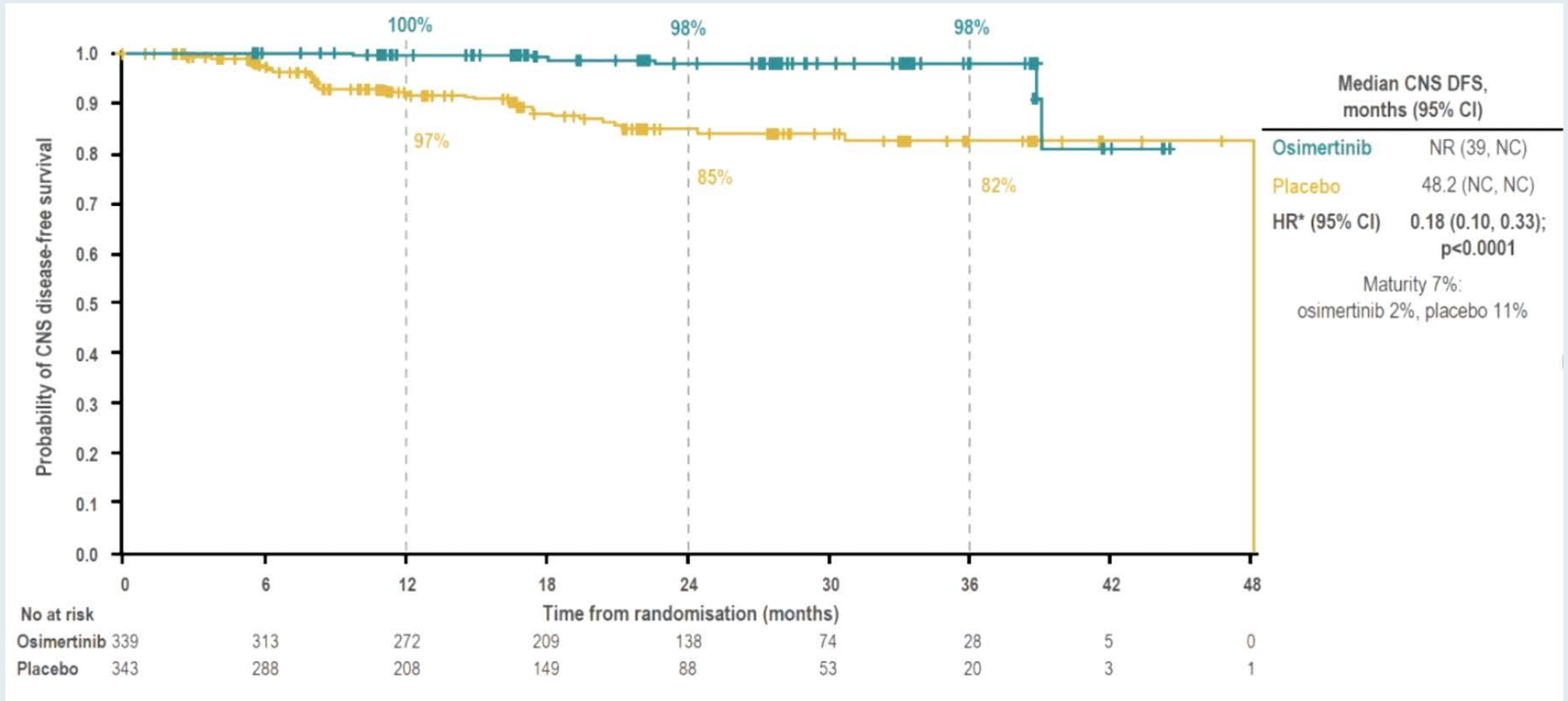
ADAURA: Disease-Free Survival by Stage



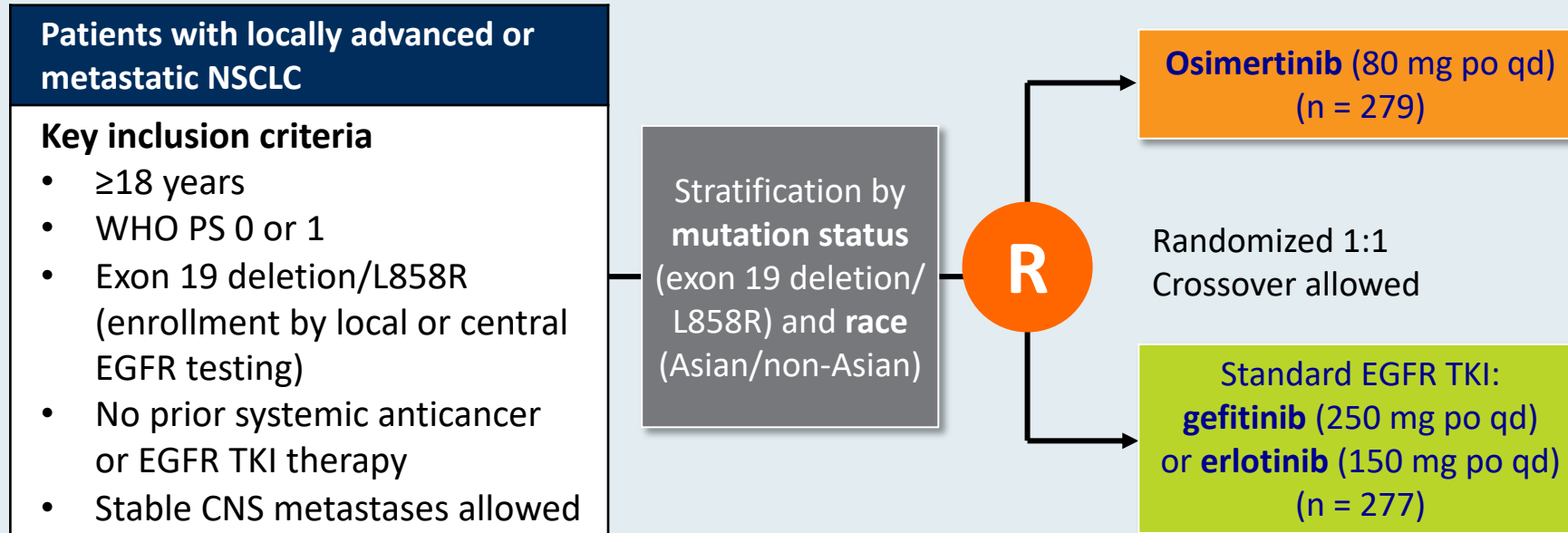
ADAURA: Sites of Disease Recurrence



ADAURA: CNS DFS in Overall Population



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



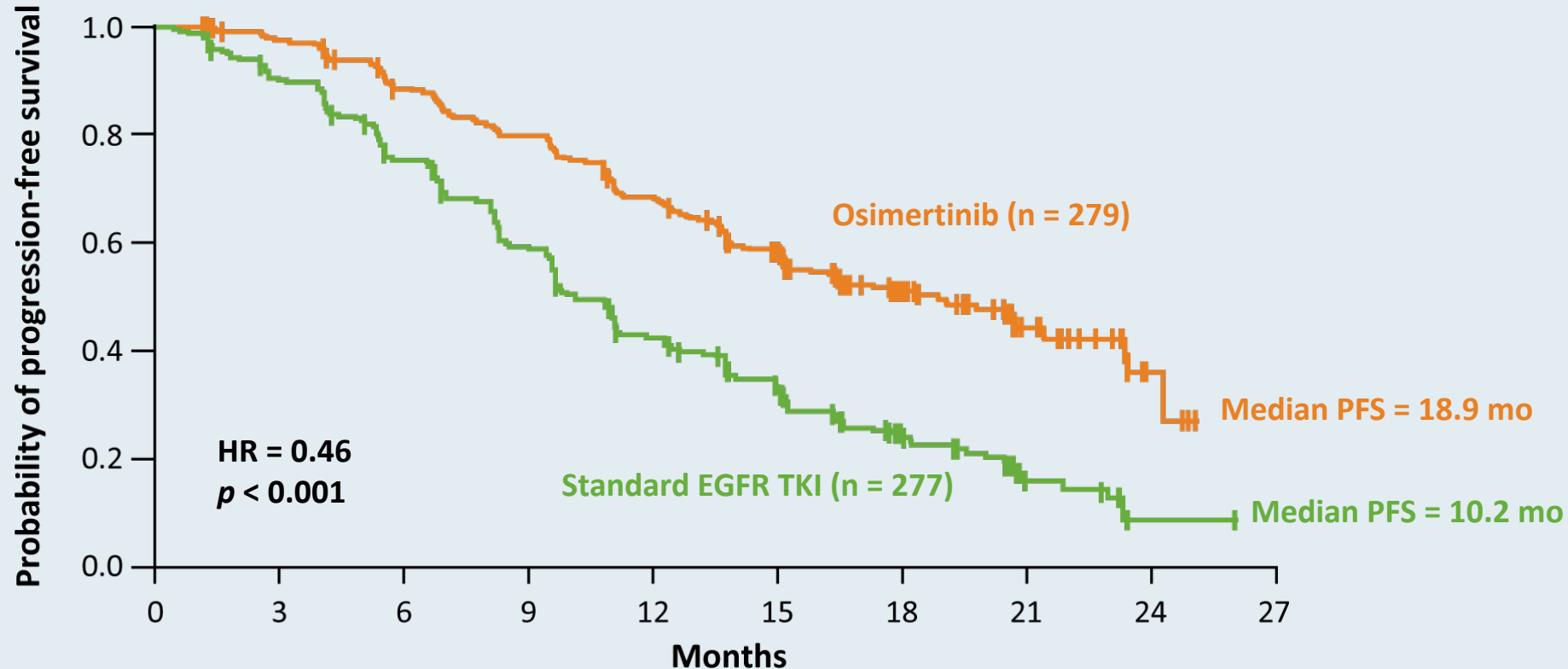
Primary endpoint: Progression-free survival (PFS) based on investigator assessment (per RECIST 1.1)

Key secondary endpoints: Objective response rate, overall survival and quality of life

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

FLAURA: PFS with Osimertinib for Patients with NSCLC and EGFR Tumor Mutations

FLAURA primary endpoint: PFS for patients with EGFR exon 19 del or L858R mutation (full analysis set)¹



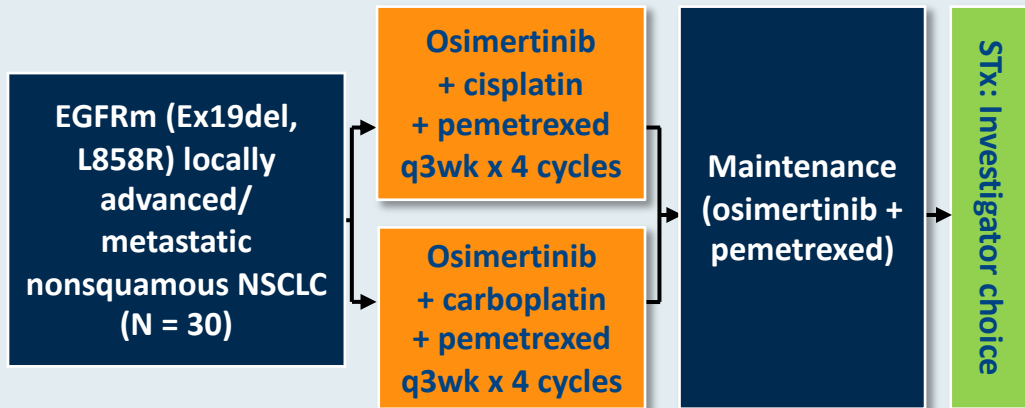
Interim overall survival (data immature), HR = 0.63, $p = 0.007^{1,2}$

¹ Soria JC et al. *N Engl J Med* 2018;378(2):113-25.

² Planchard D et al. ELCC 2018;Abstract 128O.

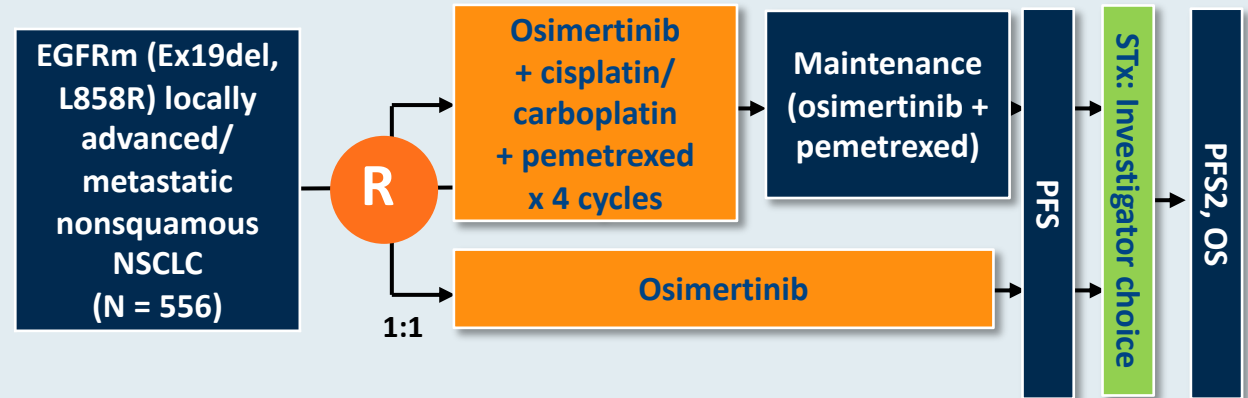
FLAURA2 Study Design: Safety Run-In and Randomization Phases

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

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, PhD¹; Sang-We Kim, MD, PhD²; Dong-Wan Kim, MD, PhD³; Jong-Seok Lee, MD, PhD⁴; Byoung Chul Cho, MD, PhD⁵; Jin-Seok Ahn, MD, PhD⁶; Dae H. Lee, MD, PhD²; Tae Min Kim, MD³; Jonathan W. Goldman, MD⁷; Ronald B. Natale, MD⁸; Andrew P. Brown, MSc, MPhil⁹; Barbara Collins, PhD⁹; Juliann Chmielecki, PhD¹⁰; Karthick Vishwanathan, PhD^{1,10}; Ariadna Mendoza-Naranjo, PhD⁹; and Myung-Ju Ahn, MD, PhD⁶

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

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 \geq 6 weeks | 32% |
| Progression | 3% |
| Not evaluable | 3% |
| Median DoR | 15.2 months |

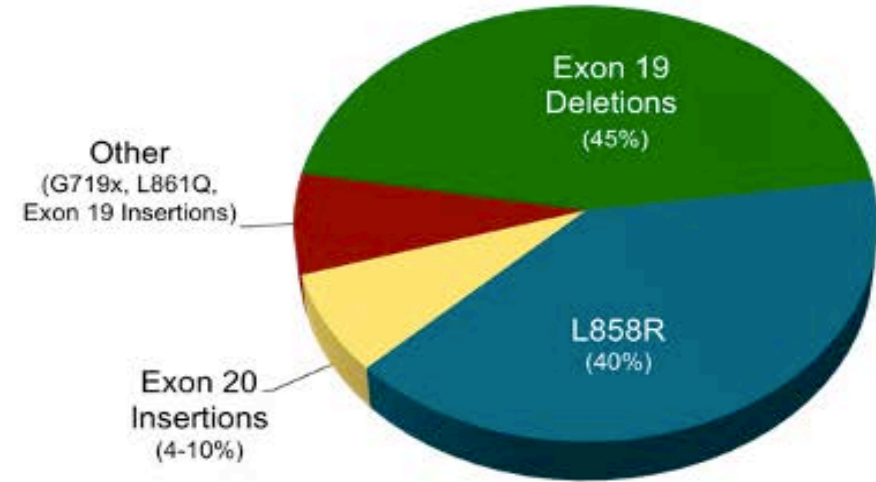
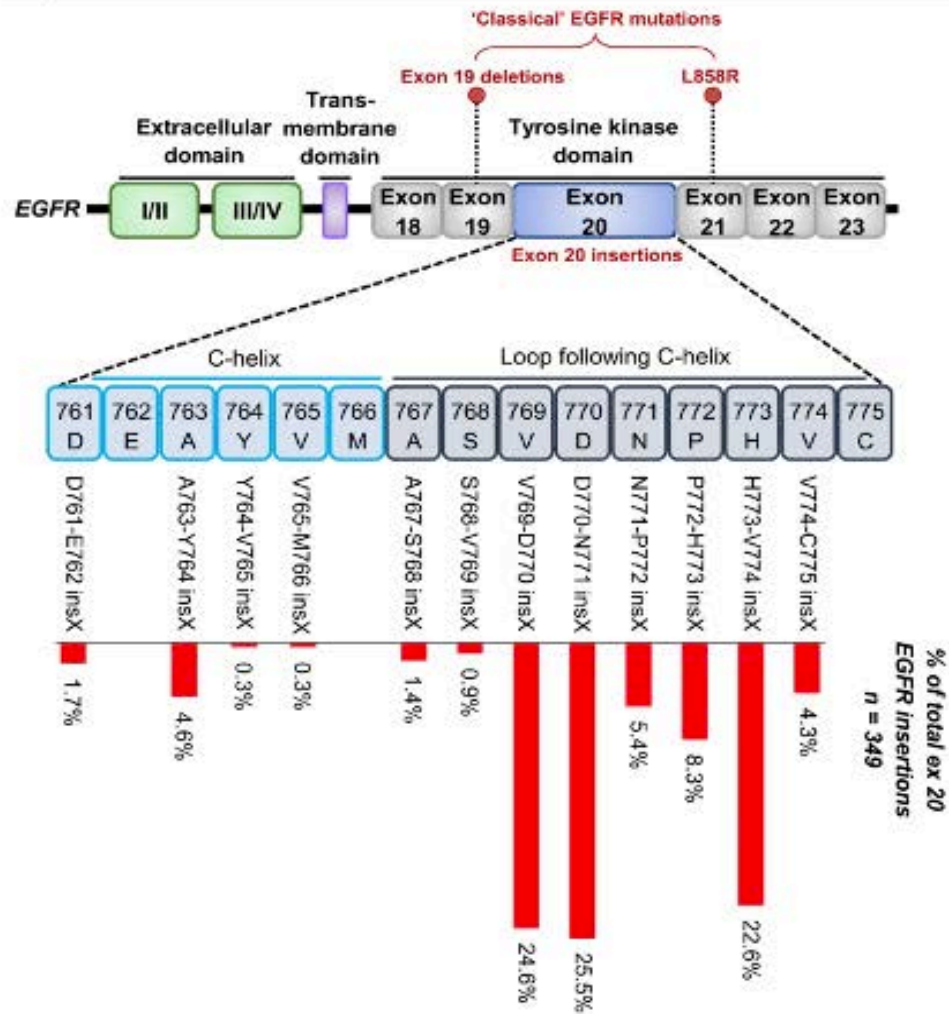
Amivantamab in Combination with Lazertinib for the Treatment of Osimertinib-Relapsed, Chemotherapy-Naïve EGFR Mutant (EGFRm) Non-Small Cell Lung Cancer (NSCLC) and Potential Biomarkers for Response

Bauml J et al.

ASCO 2021;Abstract 9006.

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

Frequency of EGFR Exon 20 Mutations



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

Courtesy of Zosia Piotrowska, MD.

Emerging Targeted Therapies for EGFR Exon 20 Mutations

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

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

IASLC/WCLC 2020;Abstract OA04.03

Mobocertinib in NSCLC With *EGFR* Exon 20 Insertions: Results From EXCLAIM and Platinum-Pretreated Patient Populations

Caicun Zhou
Shanghai Pulmonary Hospital
Shanghai, China

Caicun Zhou, Shanghai Pulmonary Hospital, China



2020 World Conference
on Lung Cancer Singapore

JANUARY 28-31, 2021 | WORLDWIDE VIRTUAL EVENT

RTP
RESEARCH
TO PRACTICE

Design and Patient Cohorts in Phases I/II and EXCLAIM

Phase 1 Dose Escalation: 3+3 Design (Advanced non–small cell lung cancer; ECOG PS <2) (Prior Platinum: n=6)

Phase 2 Expansion: Mobocertinib 160 mg QD

Phase 2: Primary endpoint: ORR by RECIST v1.1
Secondary endpoints: Safety, tolerability, PK, efficacy

Cohort 1
(Prior Platinum: n=22)
Refractory *EGFR* exon 20 insertion;
no active, measurable CNS metastases^a

Cohort 2
Refractory *HER2* exon 20 insertion or point mutation;
no active, measurable CNS metastases^a

Cohort 3
Refractory *EGFR* or *HER2* exon 20 insertions or point mutations with measurable, active CNS metastases

Cohort 4
Treatment naive or refractory Other *EGFR* mutations: +/- T790M, uncommon *EGFR*

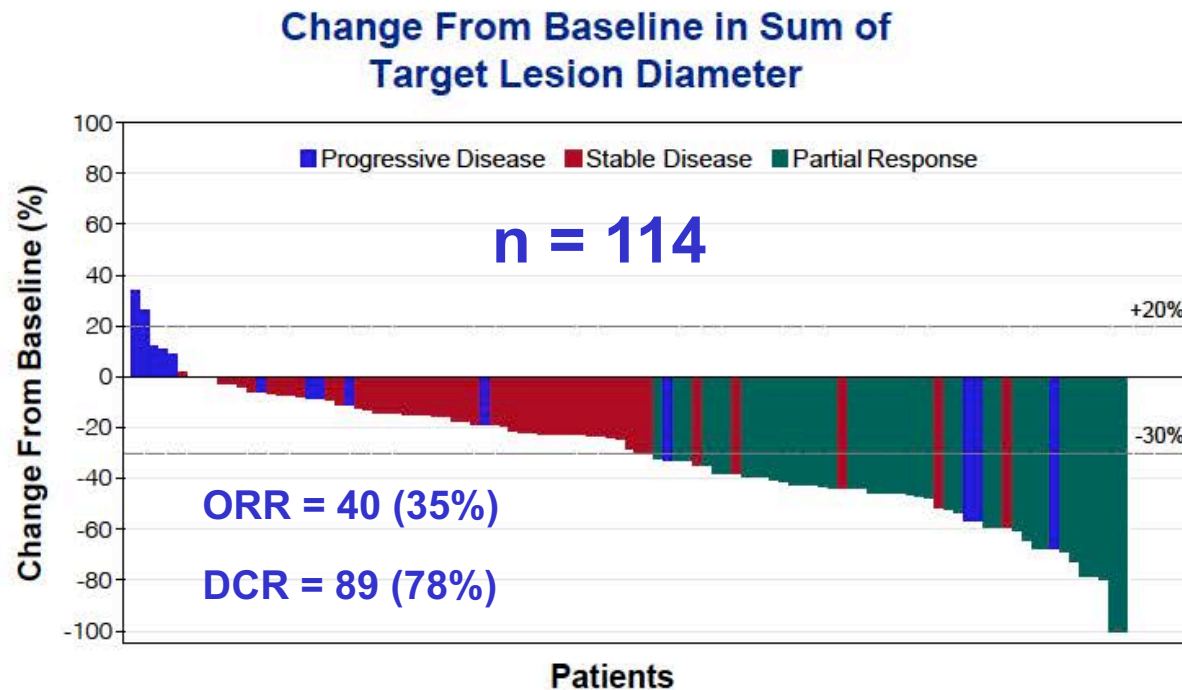
Cohort 5
Refractory *EGFR* exon 20 insertion with prior response to *EGFR* TKI

Cohort 6
Treatment naive *EGFR* exon 20 insertions

Cohort 7
Refractory other tumor types (non-NSCLC) with *EGFR/HER2* mutations

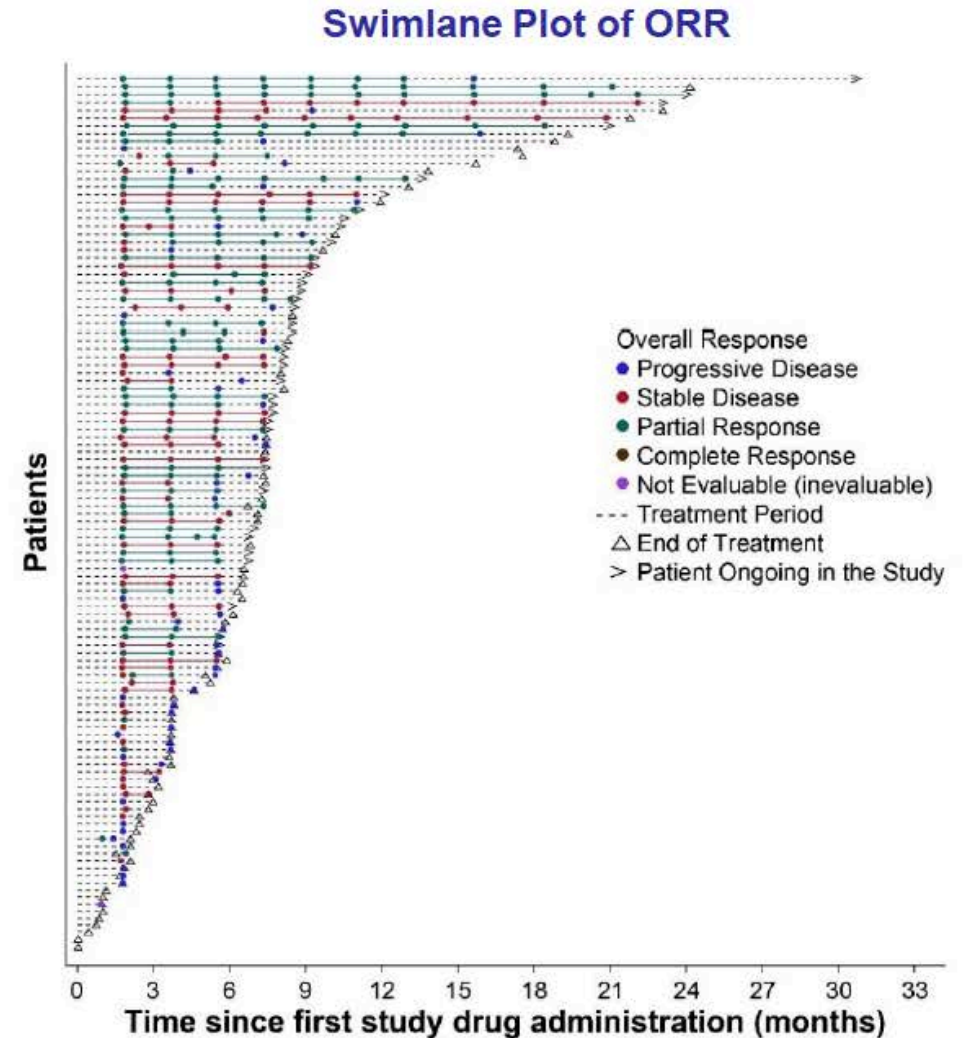
EXCLAIM
Extension Cohort
(N=96; Prior Platinum: n=86) Previously treated patients
EGFR exon 20 insertions

Mobocertinib Resulted in Reductions in Target Lesion Volume among Patients Who Previously Received Platinum-Containing Therapy

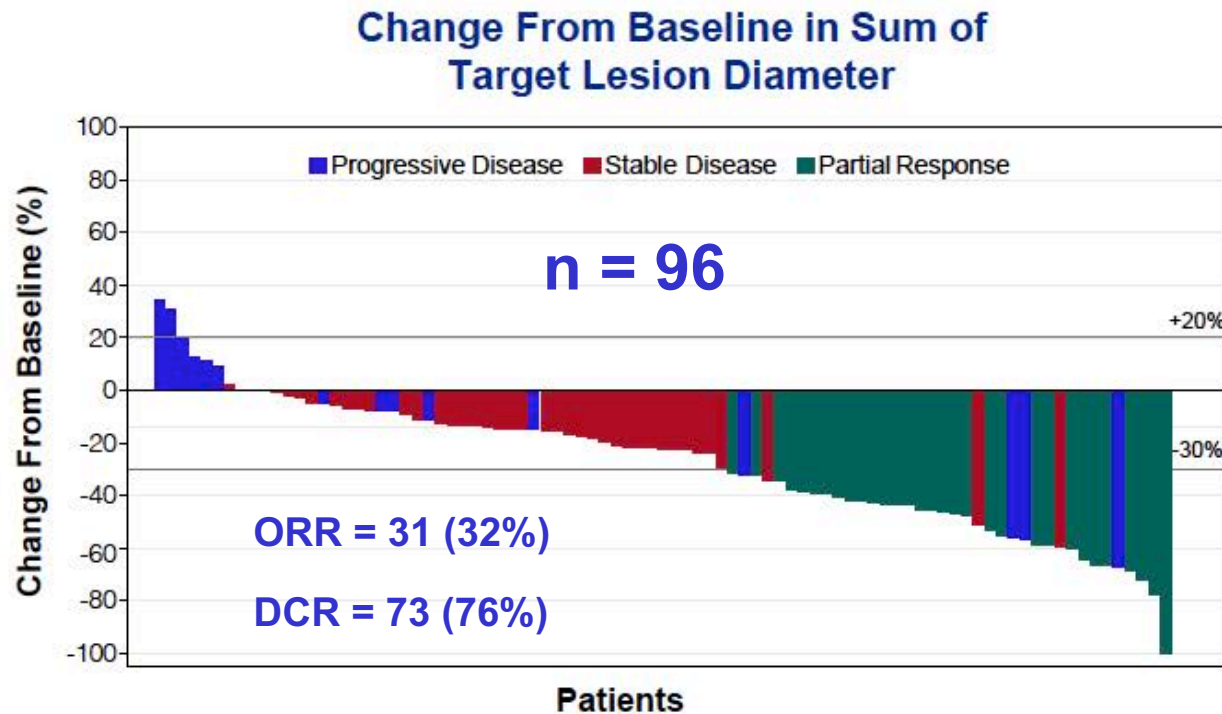


- 94 patients (82%) had a reduction from baseline in the sum of target lesion diameter

ORR, objective response rate; PPP, platinum-pretreated patients

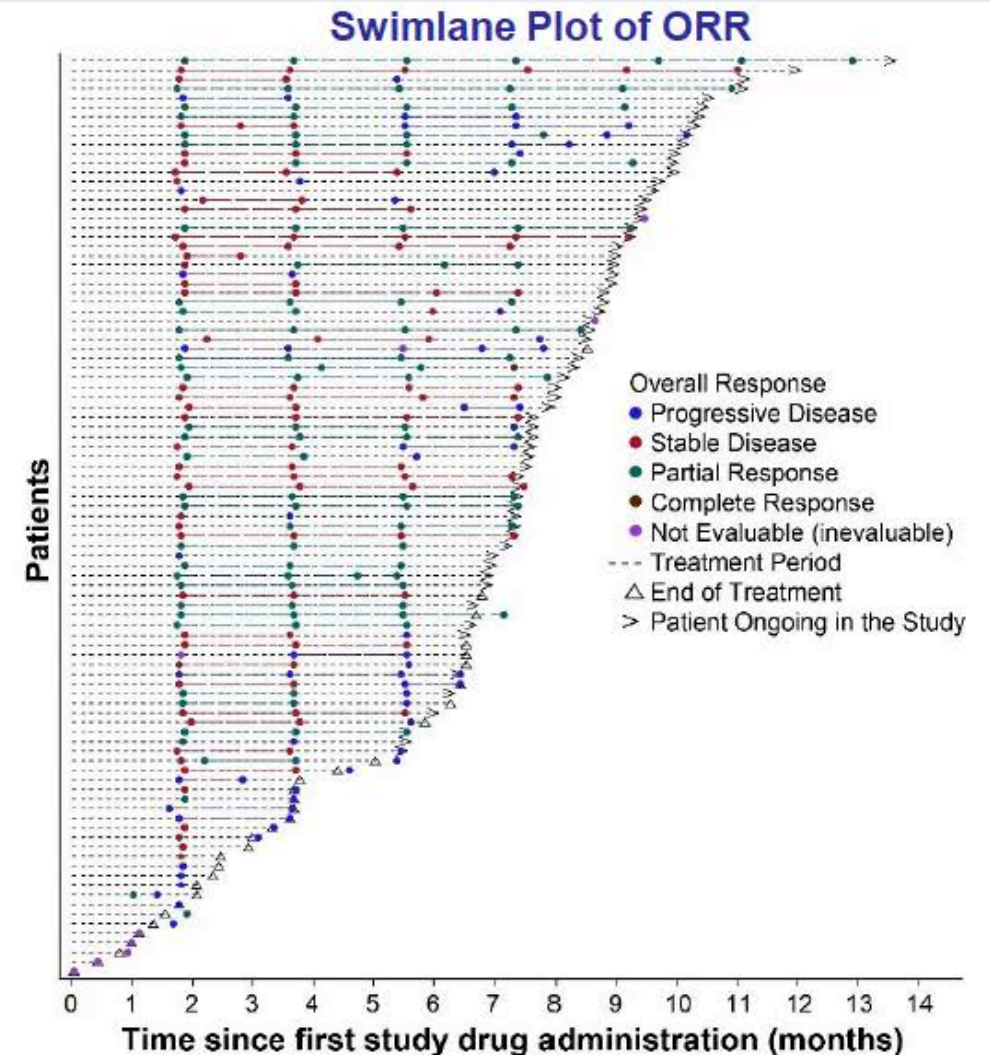


Mobocertinib Resulted in Reductions in Target Lesion Volume in EXCLAIM Cohort



- 77 patients (80%) had a reduction from baseline in the sum of target lesion diameter

ORR, objective response rate





2020 World Conference
on Lung Cancer Singapore

wclc2020.IASLC.com | #WCLC20

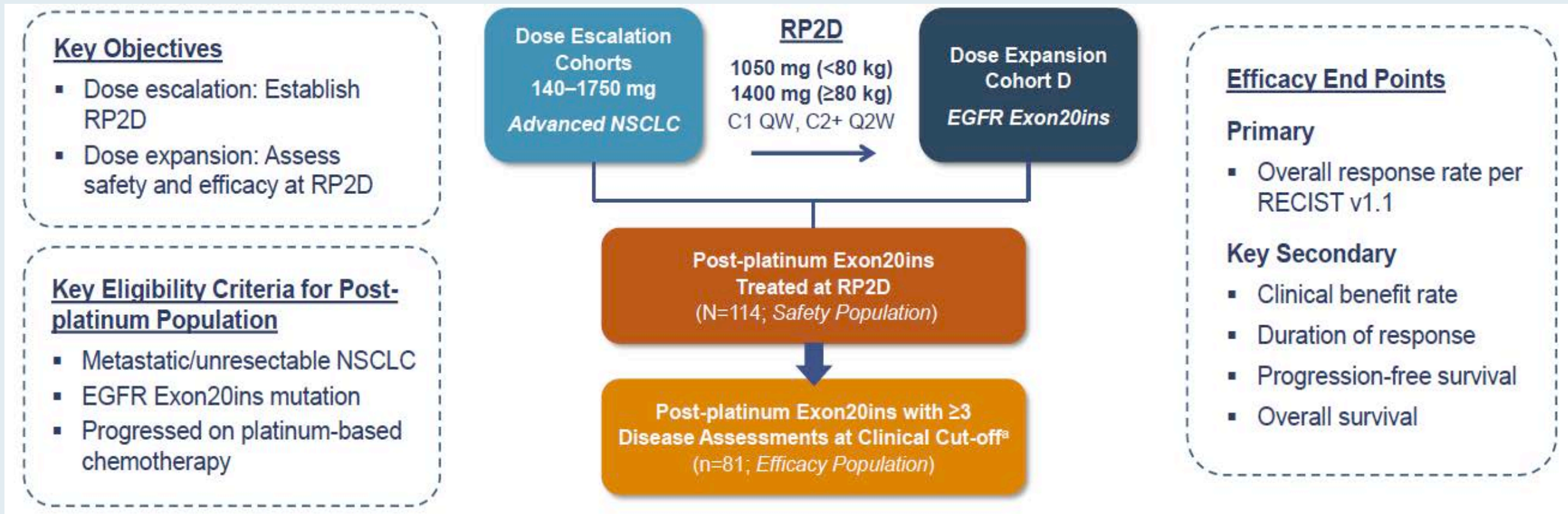
CONQUERING THORACIC CANCERS WORLDWIDE

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

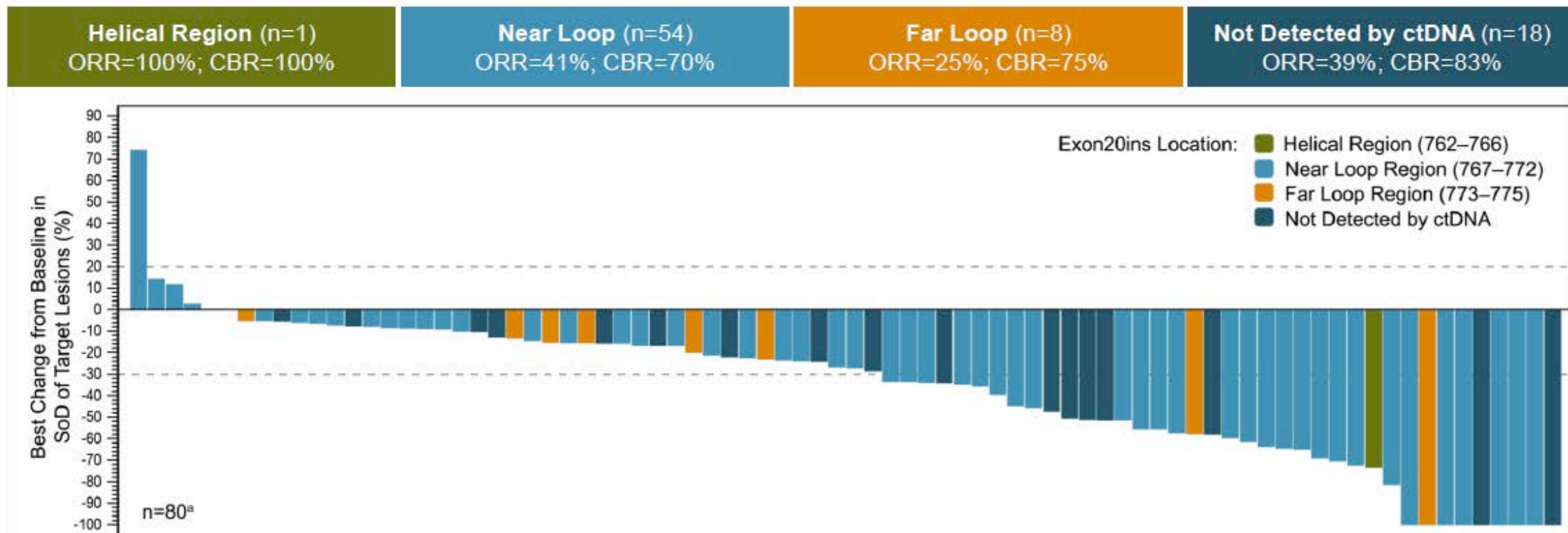
Joshua K. Sabari¹, Catherine A. Shu², Keunchil Park³, Natasha B. Leigh⁴, Paul Mitchell⁵, Sang-We Kim⁶, Jong-Seok Lee⁷, Dong-Wan Kim⁸, Santiago Viteri⁹, Alexander I. Spira¹⁰, Ji-Youn Han¹¹, José Trigo¹², Chee Khoon Lee¹³, Ki Hyeong Lee¹⁴, Nicolas Girard¹⁵, Tsung-Ying Yang¹⁶, Koichi Goto¹⁷, Rachel E. Sanborn¹⁸, James Chih-Hsin Yang¹⁹, Joshua C. Curtin²⁰, John Xie²⁰, Amy Roshak²⁰, Meena Thayu²⁰, Roland E. Knoblauch²⁰, Byoung Chul Cho²¹

IASLC/WCLC 2020;Abstract OA04.04

CHRYSLIS Study Design: Post-Platinum Exon 20 Insertion Population



CHRYSLIS: Best ORR by Insertion Region of Exon 20



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

IMpower150: Updated Efficacy Analysis in Patients with EGFR Mutations

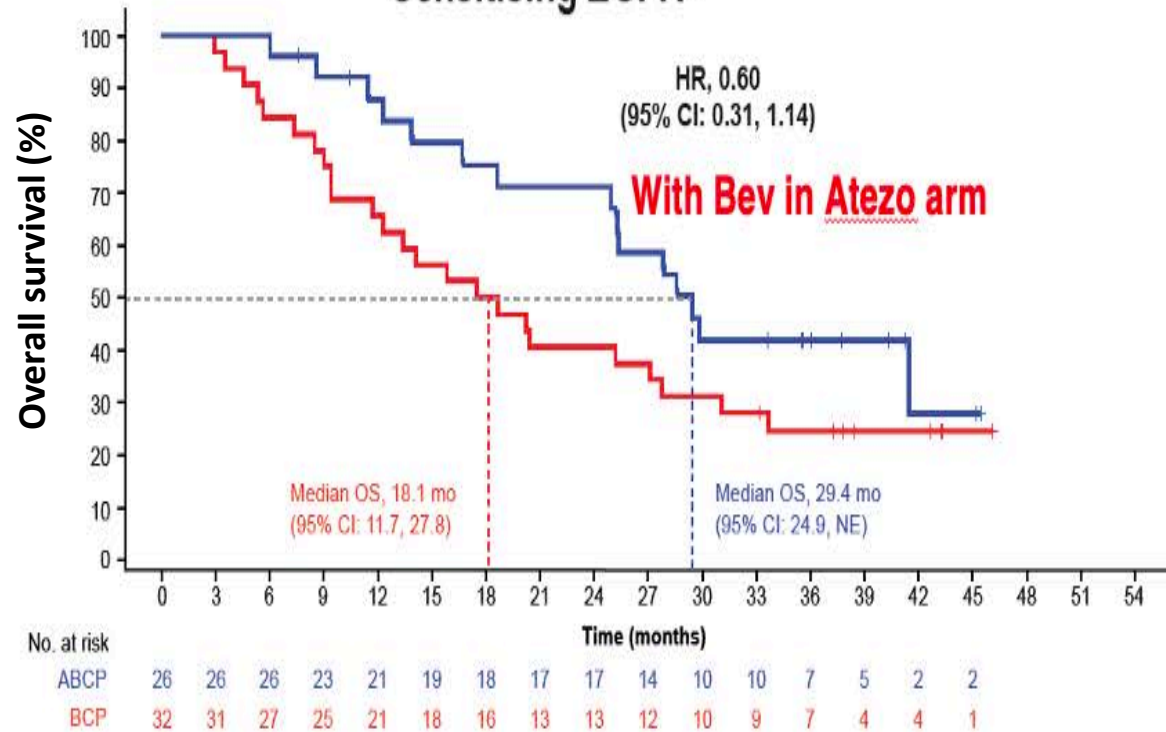
Reck M et al.

ESMO 2020;Abstract 1293P.

IMpower150 Trial: OS Benefit of First-Line Atezolizumab for Patients with Metastatic NSCLC with EGFR Tumor Mutations

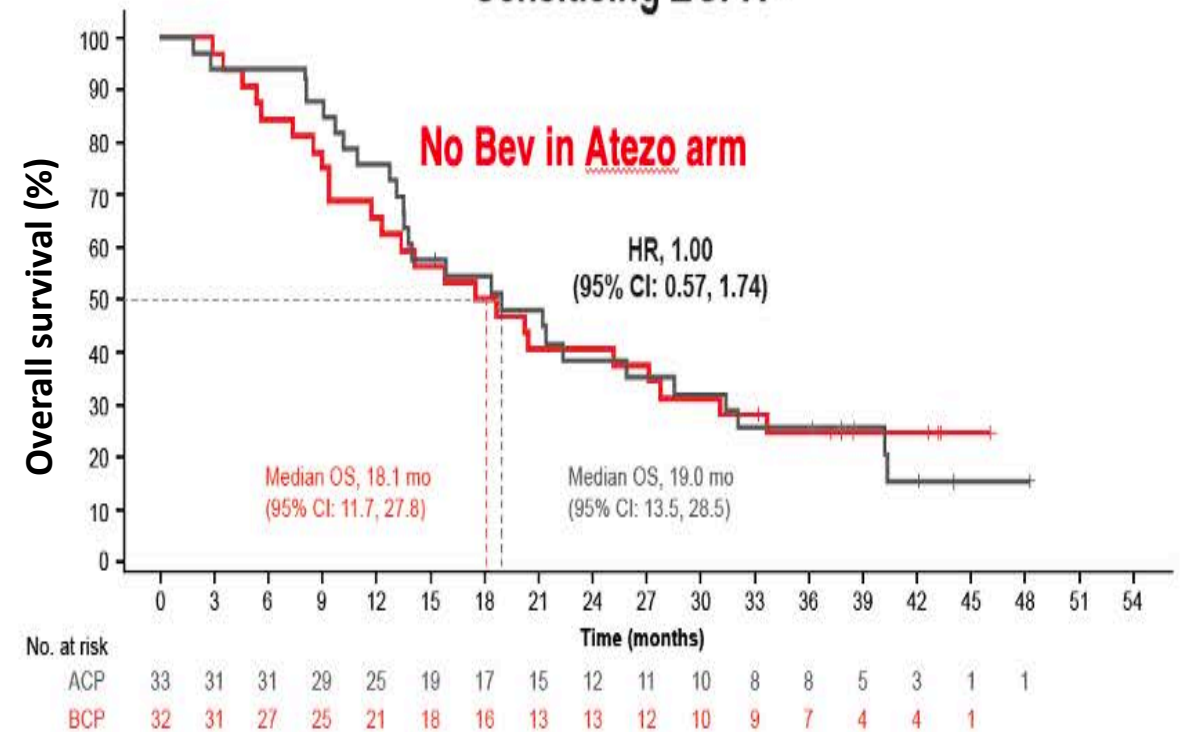
ABCP vs BCP (13% of ITT)

Sensitising EGFR+



ACP vs BCP

Sensitising EGFR+



ABCP = atezolizumab + bevacizumab/carboplatin/paclitaxel; BCP = bevacizumab/carboplatin/paclitaxel

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% |

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 |

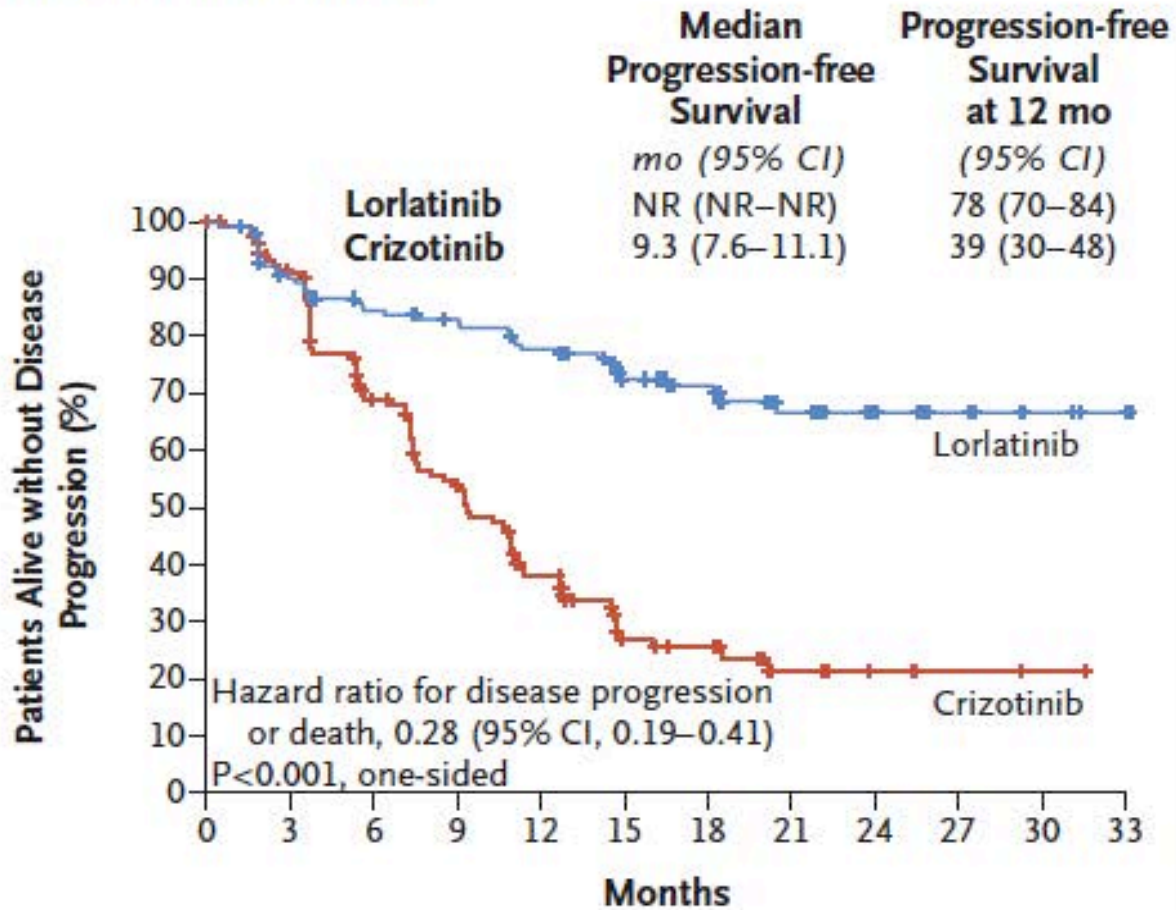
ORIGINAL ARTICLE

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

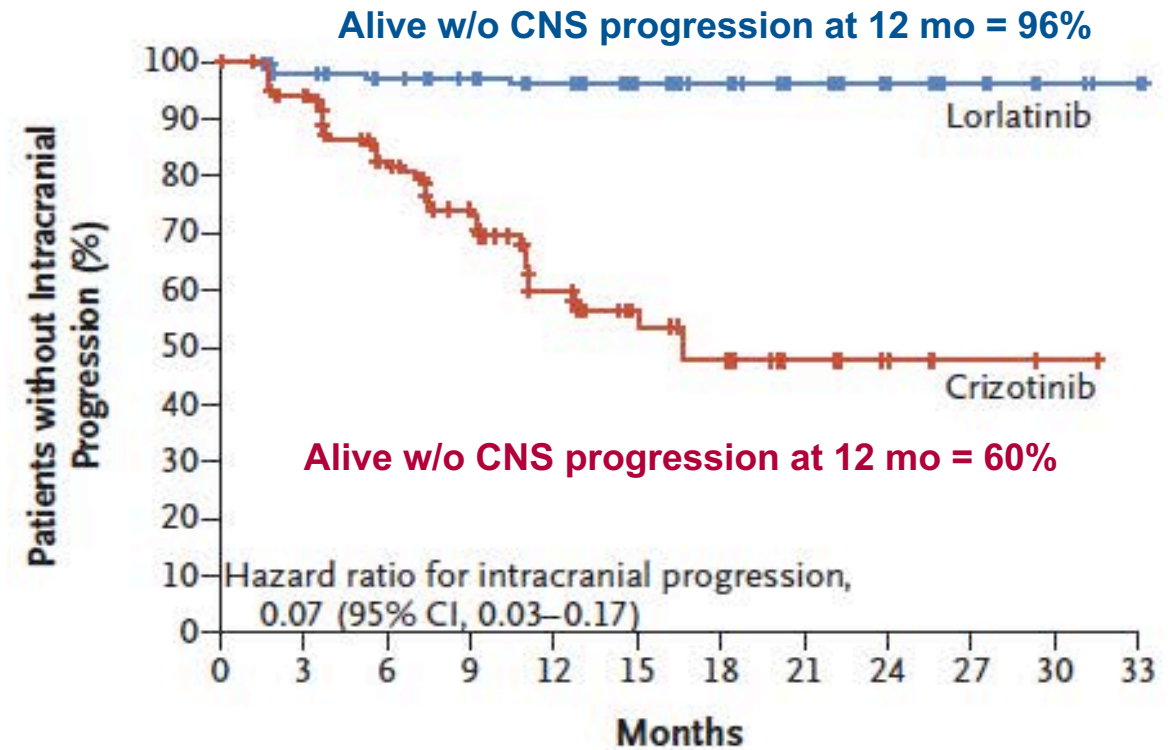
Alice T. Shaw, M.D., Ph.D., Todd M. Bauer, M.D., Filippo de Marinis, M.D., Ph.D.,
Enriqueta Felip, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Geoffrey Liu, M.D.,
Julien Mazieres, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Tony Mok, M.D.,
Anna Polli, B.Sc., Holger Thurm, M.D., Anna M. Calella, Ph.D.,
Gerson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

CROWN: PFS and Survival without Intracranial Progression

Progression-free Survival

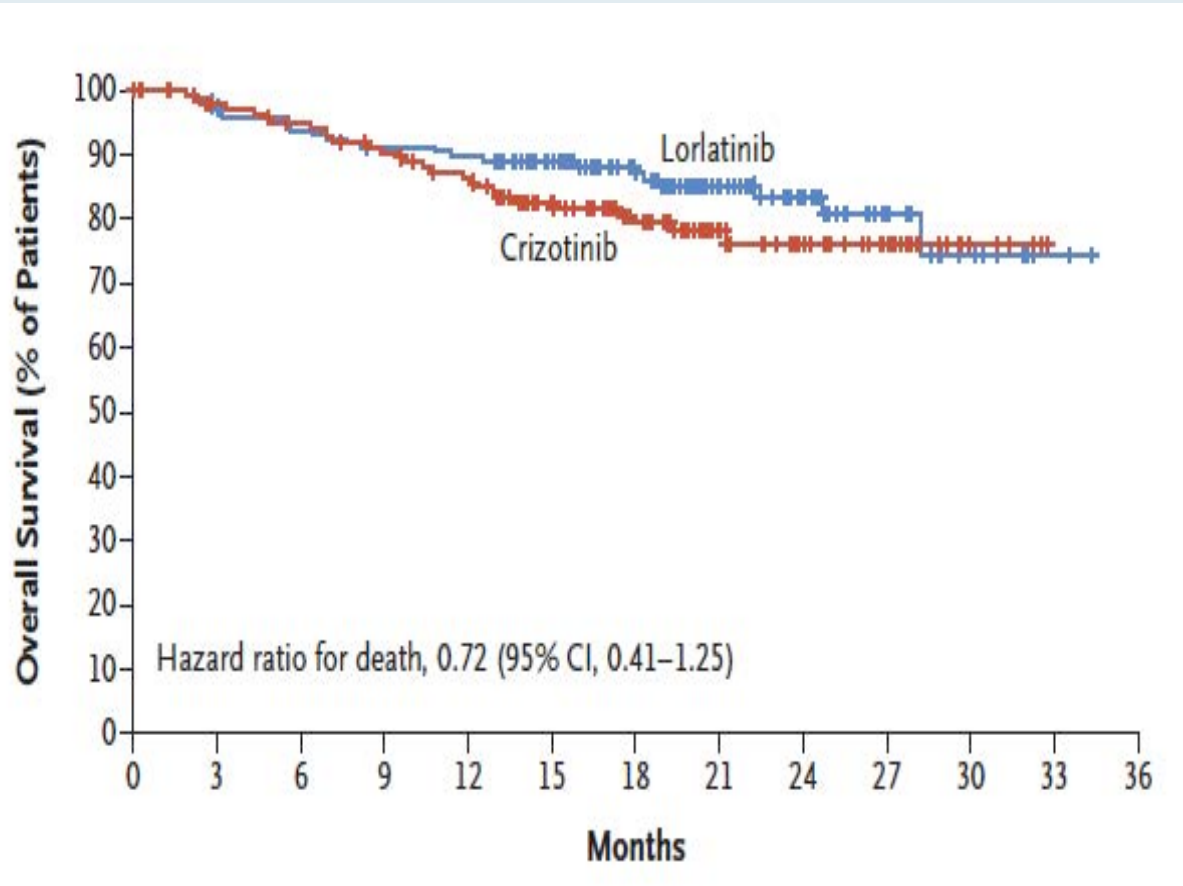


Survival without CNS Progression

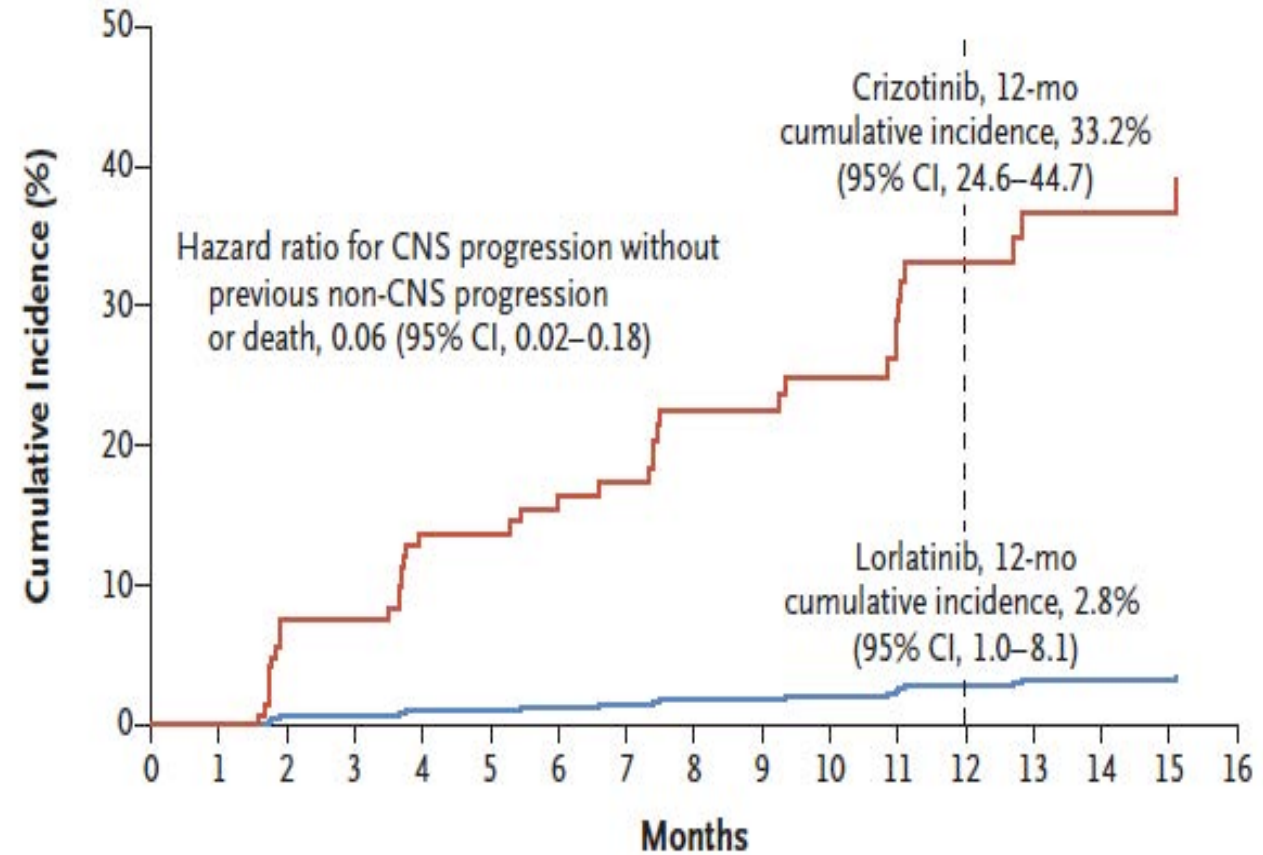


CROWN: OS and Cumulative Incidence of CNS Progression

Overall Survival



Cumulative Incidence of CNS Progression as First Event



Module 2: Genitourinary Cancers

Relevant Recent Data Sets

Renal Cell Carcinoma

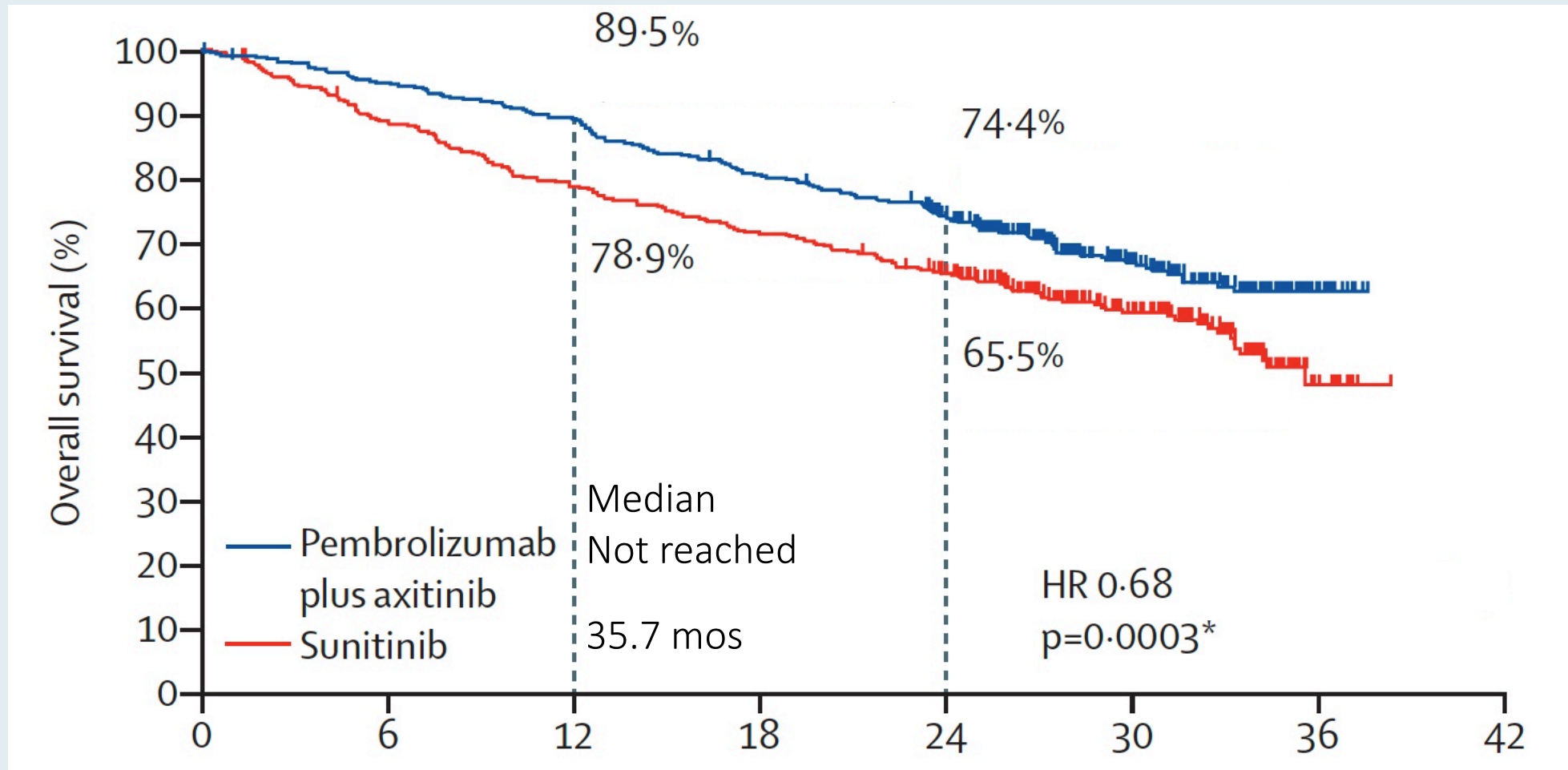
Lancet Oncol 2020;21:1563-73.

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



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

KEYNOTE-426: Overall Survival with Extended Follow-Up



ORIGINAL ARTICLE

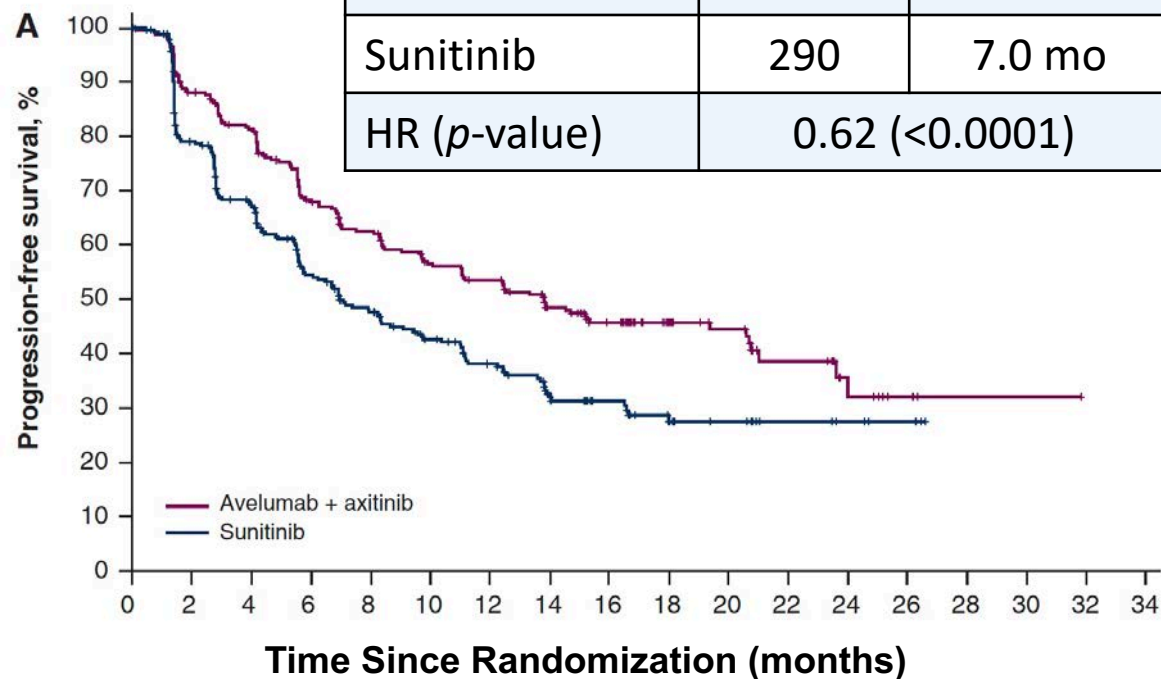
Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma

T. K. Choueiri^{1*}, R. J. Motzer², B. I. Rini^{3†}, J. Haanen⁴, M. T. Campbell⁵, B. Venugopal⁶, C. Kollmannsberger⁷, G. Gravis-Mescam⁸, M. Uemura⁹, J. L. Lee¹⁰, M.-O. Grimm¹¹, H. Gurney¹², M. Schmidinger¹³, J. Larkin¹⁴, M. B. Atkins¹⁵, S. K. Pal¹⁶, J. Wang¹⁷, M. Mariani¹⁸, S. Krishnaswami¹⁹, P. Cislo²⁰, A. Chudnovsky²¹, C. Fowst¹⁸, B. Huang¹⁹, A. di Pietro²² & L. Albiges²³

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

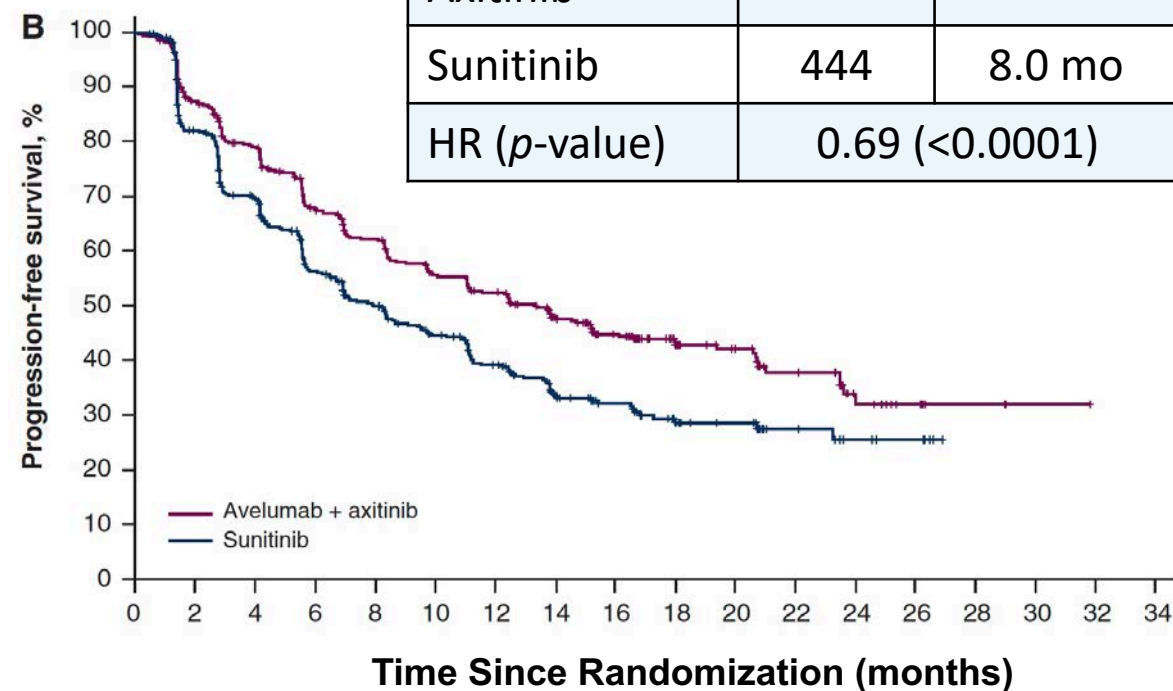
PD-L1 $\geq 1\%$ Population

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



Overall Population

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



FDA Approves Nivolumab with Cabozantinib for Advanced RCC

Press Release: January 22, 2021

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

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

ORIGINAL ARTICLE

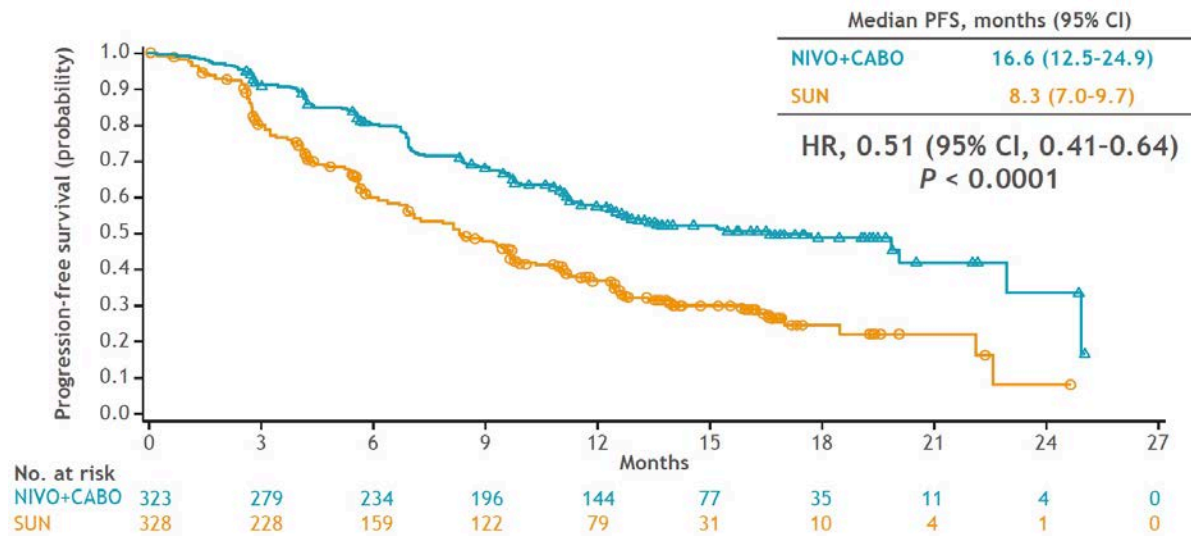
Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma

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

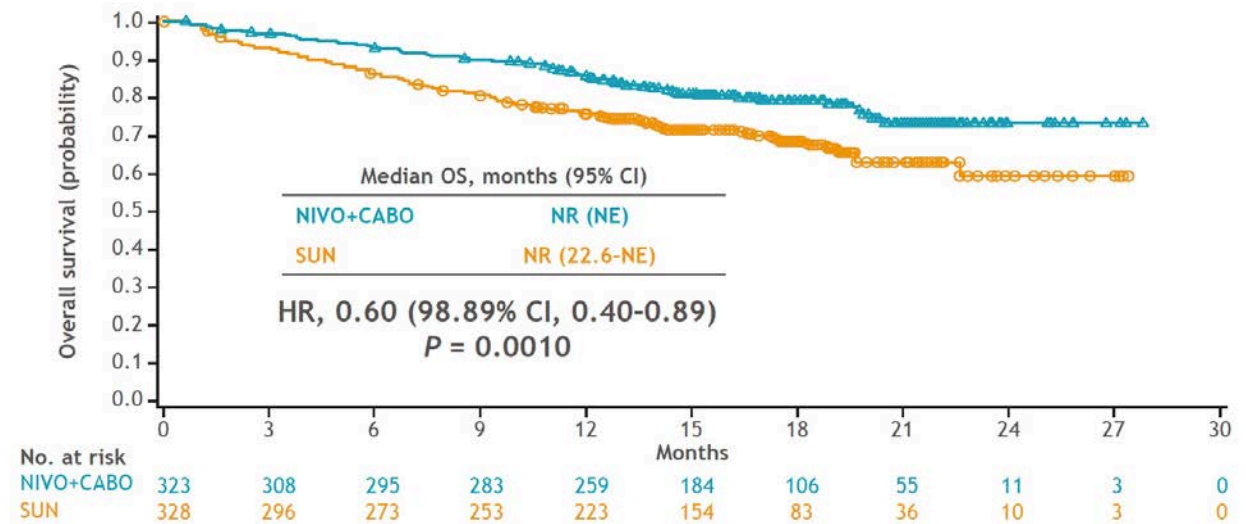
N Engl J Med 2021;384(9):829-41.

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

Progression-free survival per BICR



Overall survival



ORIGINAL ARTICLE

Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma

R. Motzer, B. Alekseev, S.-Y. Rha, C. Porta, M. Eto, T. Powles, V. Grünwald, T.E. Hutson, E. Kopyltsov, M.J. Méndez-Vidal, V. Kozlov, A. Alyasova, S.-H. Hong, A. Kapoor, T. Alonso Gordo, J.R. Merchan, E. Winqvist, P. Maroto, J.C. Goh, M. Kim, H. Gurney, V. Patel, A. Peer, G. Procopio, T. Takagi, B. Melichar, F. Rolland, U. De Giorgi, S. Wong, J. Bedke, M. Schmidinger, C.E. Dutcus, A.D. Smith, L. Dutta, K. Mody, R.F. Perini, D. Xing, and T.K. Choueiri, for the CLEAR Trial Investigators*

N Engl J Med 2021;384(14):1289-1300.

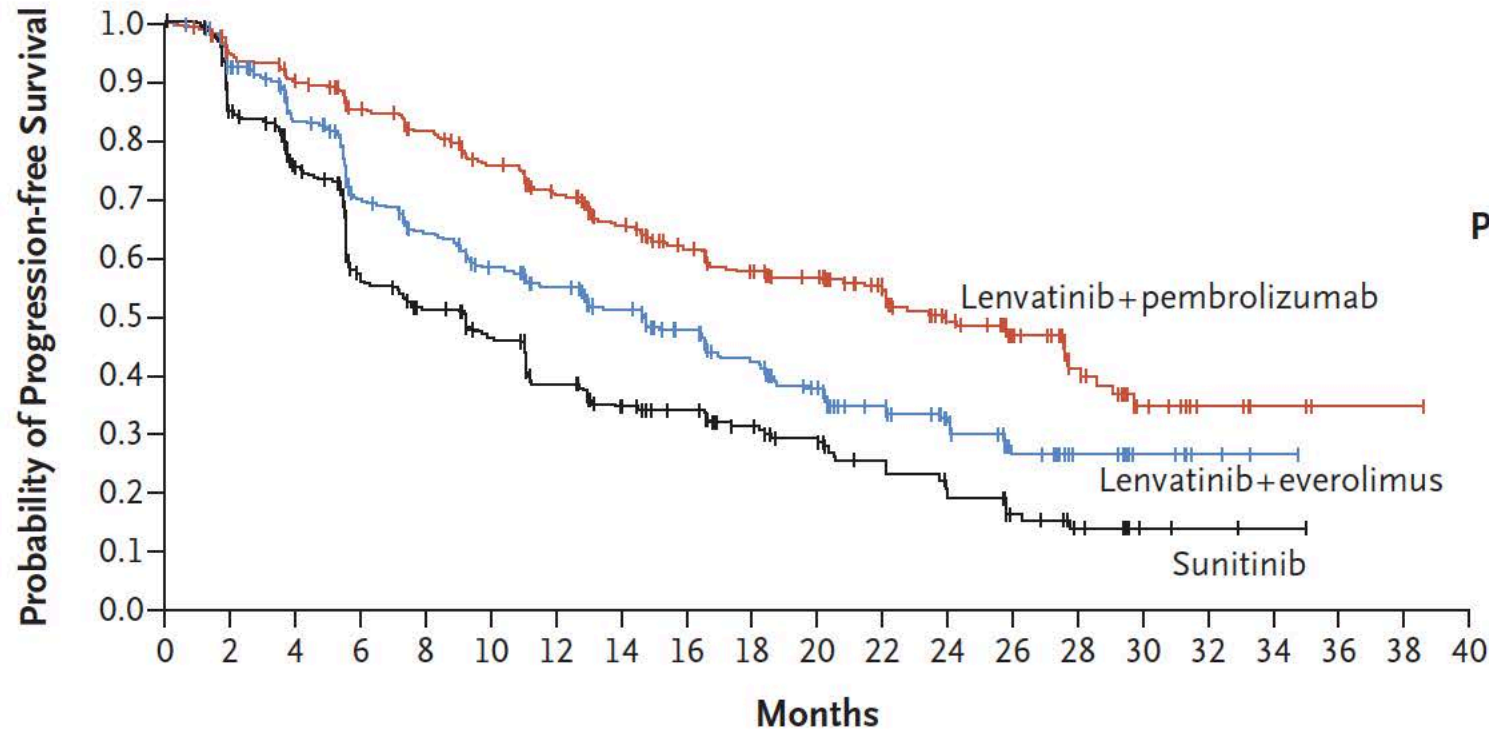
EDITORIAL

A Step Ahead in Metastatic Renal Cell Carcinoma

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

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

CLEAR: Progression-Free Survival



No. at Risk

| | | | | | | | | | | | | | | | | | | | | | |
|--------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|---|---|---|---|---|
| Lenvatinib+pembrolizumab | 355 | 321 | 300 | 276 | 259 | 235 | 213 | 186 | 160 | 136 | 126 | 106 | 80 | 56 | 30 | 14 | 6 | 3 | 1 | 1 | 0 |
| Lenvatinib+everolimus | 357 | 305 | 259 | 207 | 185 | 163 | 149 | 125 | 105 | 85 | 70 | 53 | 37 | 20 | 13 | 7 | 3 | 1 | 0 | | |
| Sunitinib | 357 | 262 | 218 | 145 | 124 | 107 | 85 | 69 | 62 | 49 | 42 | 32 | 25 | 16 | 9 | 3 | 2 | 1 | 0 | | |

Median Progression-free Survival (95% CI)

mo

Lenvatinib+ Pembrolizumab 23.9 (20.8–27.7)

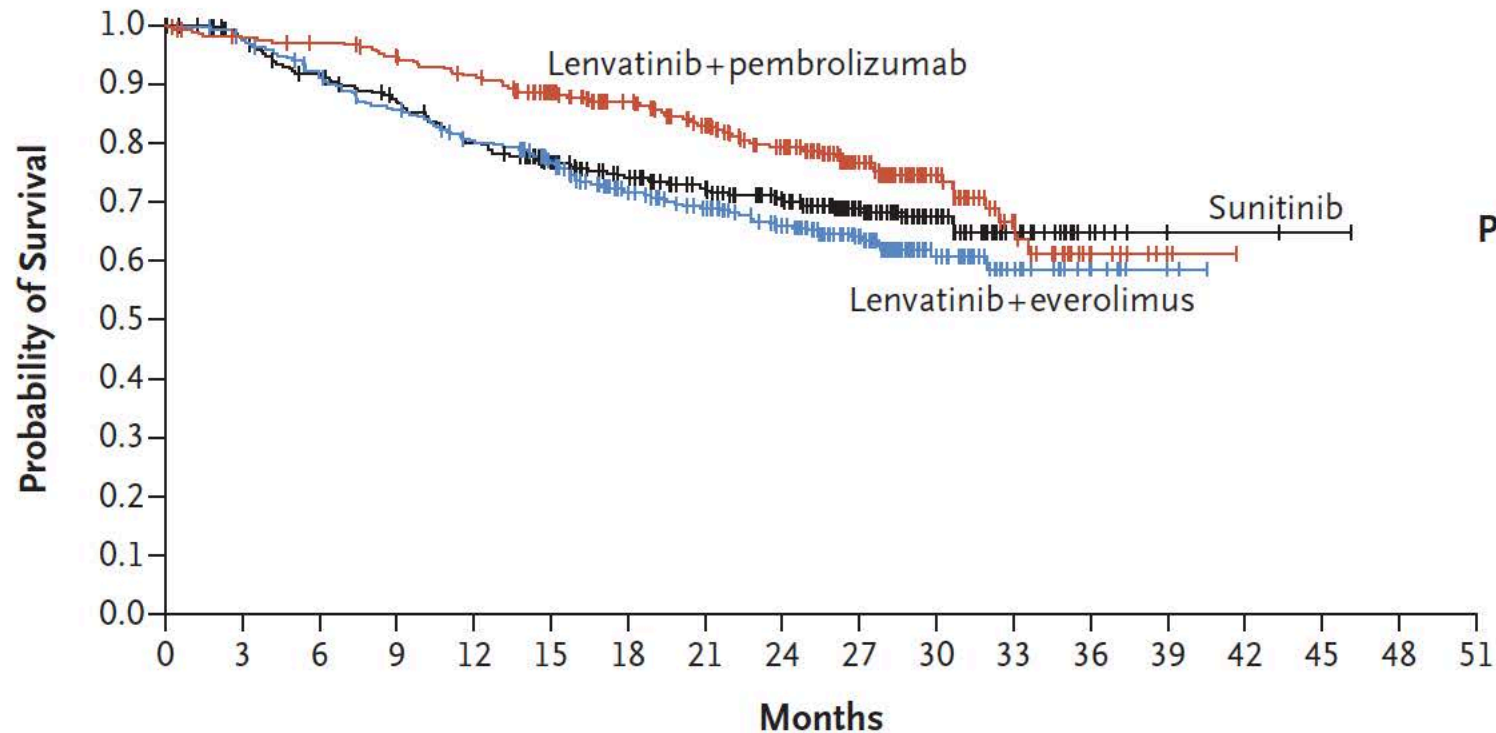
Lenvatinib+ Everolimus 14.7 (11.1–16.7)

Sunitinib 9.2 (6.0–11.0)

Hazard ratio for disease progression or death (lenvatinib+ pembrolizumab vs. sunitinib), 0.39 (95% CI, 0.32–0.49); $P < 0.001$

Hazard ratio for disease progression or death (lenvatinib+ everolimus vs. sunitinib), 0.65 (95% CI, 0.53–0.80); $P < 0.001$

CLEAR: Overall Survival



No. at Risk

| | | | | | | | | | | | | | | | | | |
|--------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|---|---|---|---|
| Lenvatinib+pembrolizumab | 355 | 342 | 338 | 327 | 313 | 280 | 253 | 222 | 188 | 129 | 66 | 26 | 10 | 2 | 0 | | |
| Lenvatinib+everolimus | 357 | 346 | 321 | 299 | 277 | 246 | 205 | 183 | 154 | 109 | 46 | 22 | 8 | 2 | 0 | | |
| Sunitinib | 357 | 332 | 307 | 289 | 264 | 236 | 207 | 186 | 160 | 112 | 60 | 25 | 7 | 2 | 2 | 1 | 0 |

Median Overall Survival (95% CI)

mo

| | |
|---------------------------|--------------|
| Lenvatinib+ Pembrolizumab | NR (33.6–NE) |
| Lenvatinib+ Everolimus | NR (NE–NE) |
| Sunitinib | NR (NE–NE) |

Hazard ratio for death (lenvatinib+ pembrolizumab vs. sunitinib),
0.66 (95% CI, 0.49–0.88);
P=0.005

Hazard ratio for death (lenvatinib+ everolimus vs. sunitinib),
1.15 (95% CI, 0.88–1.50);
P=0.30

A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial

Sumanta K Pal, Catherine Tangen, Ian M Thompson Jr, Naomi Balzer-Haas, Daniel J George, Daniel Y C Heng, Brian Shuch, Mark Stein, Maria Tretiakova, Peter Humphrey, Adebowale Adeniran, Vivek Narayan, Georg A Bjarnason, Ulka Vaishampayan, Ajai Alva, Tian Zhang, Scott Cole, Melissa Plets, John Wright, Primo N Lara Jr

Lancet 2021;397(10275):695-703.

EDITORIAL

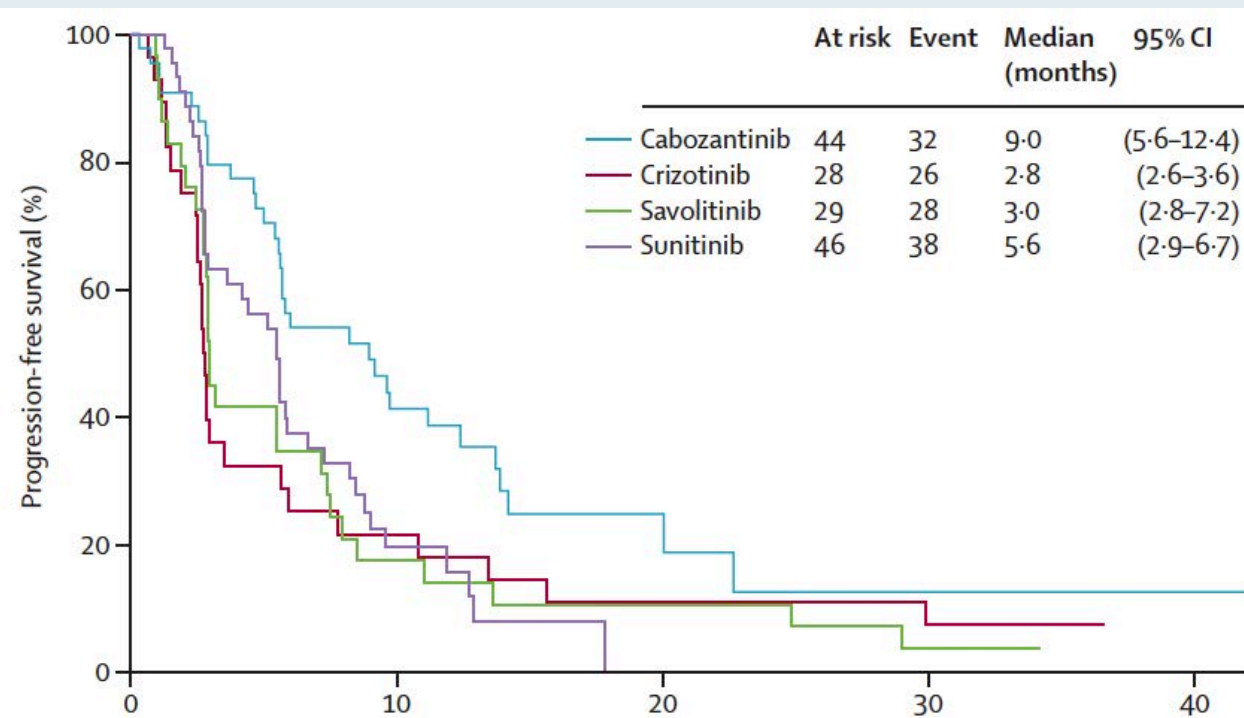
Cabozantinib: a new first-line option for papillary renal cell carcinoma?

**Delphine Borchellini, Philippe Barthélémy*

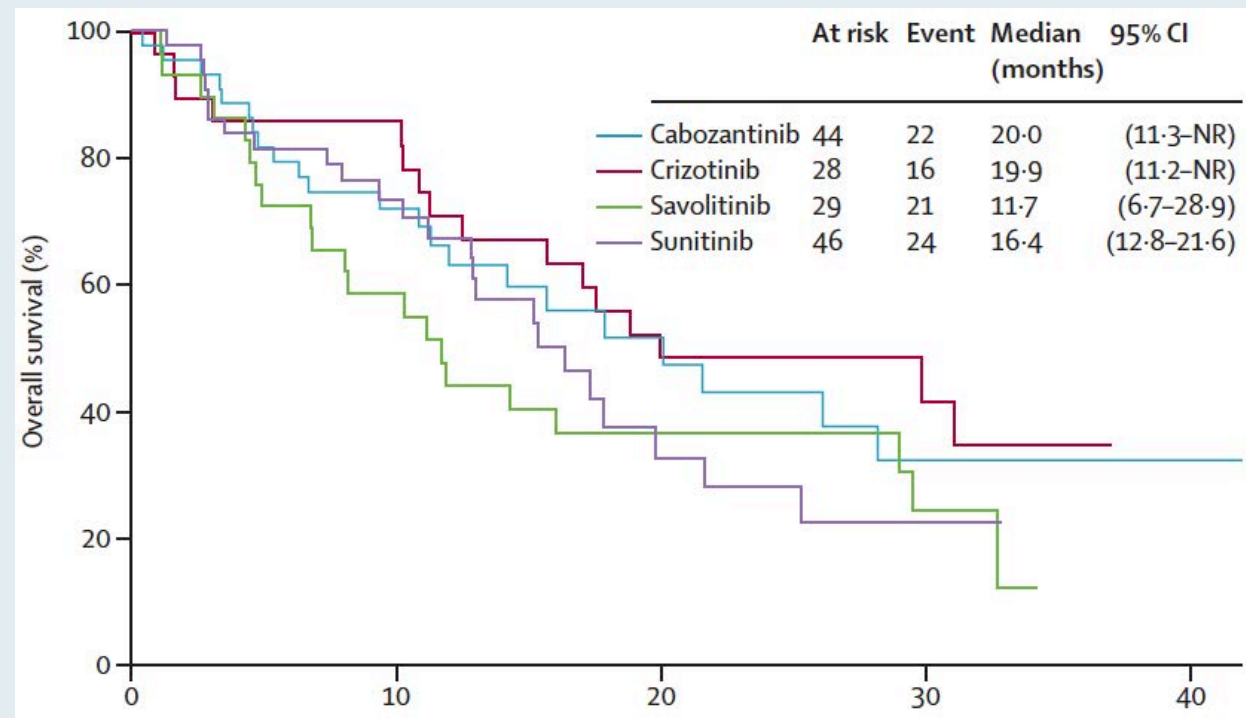
Lancet 2021;397(10275):645-47.

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

Progression-free survival



Overall survival



Salvage Ipilimumab and Nivolumab in Patients With Metastatic Renal Cell Carcinoma After Prior Immune Checkpoint Inhibitors

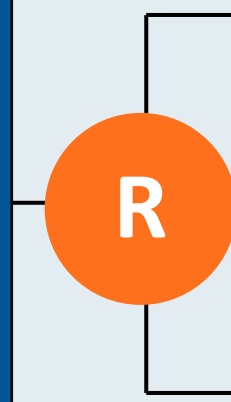
Anita Gul, MD¹; Tyler F. Stewart, MD^{2,3}; Charlene M. Mantia, MD⁴; Neil J. Shah, MD⁵; Emily Stern Gatof, MD⁴; Ying Long, PharmD²; Kimberly D. Allman, MSN, CNP¹; Moshe C. Ornstein, MD, MA¹; Hans J. Hammers, MD, PhD⁶; David F. McDermott, MD⁴; Michael B. Atkins, MD⁵; Michael Hurwitz, MD, PhD²; and Brian I. Rini, MD¹

J Clin Oncol 2020;38:3088-94.

Ongoing Phase III CONTACT-03 Trial Design

Eligibility (N = 500)

- Inoperable, locally advanced or metastatic RCC
- After radiographic tumor progression during or after ICI
- Karnofsky PS ≥ 70
- Not more than 1 prior ICI regimen
- Not more than 2 prior lines for advanced disease



**Atezolizumab
+
Cabozantinib**

Cabozantinib

Primary endpoints: PFS and OS

Secondary endpoints include Objective Response, Duration of Response

FDA Approves Tivozanib for Relapsed or Refractory Advanced Renal Cell Carcinoma

Press Release: March 10, 2021

“The Food and Drug Administration approved tivozanib, a kinase inhibitor, for adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.

Efficacy was evaluated in TIVO-3 (NCT02627963), a randomized (1:1), open-label, multicenter trial of tivozanib versus sorafenib in patients with relapsed or refractory advanced RCC who received two or three prior systemic treatments, including at least one VEGFR kinase inhibitor other than sorafenib or tivozanib. Patients were randomized to either tivozanib 1.34 mg orally once daily for 21 consecutive days every 28 days or sorafenib 400 mg orally twice a day continuously, until disease progression or unacceptable toxicity.

The main efficacy outcome measure was progression-free survival (PFS), assessed by a blinded independent radiology review committee. Other efficacy endpoints were overall survival (OS) and objective response rate (ORR).

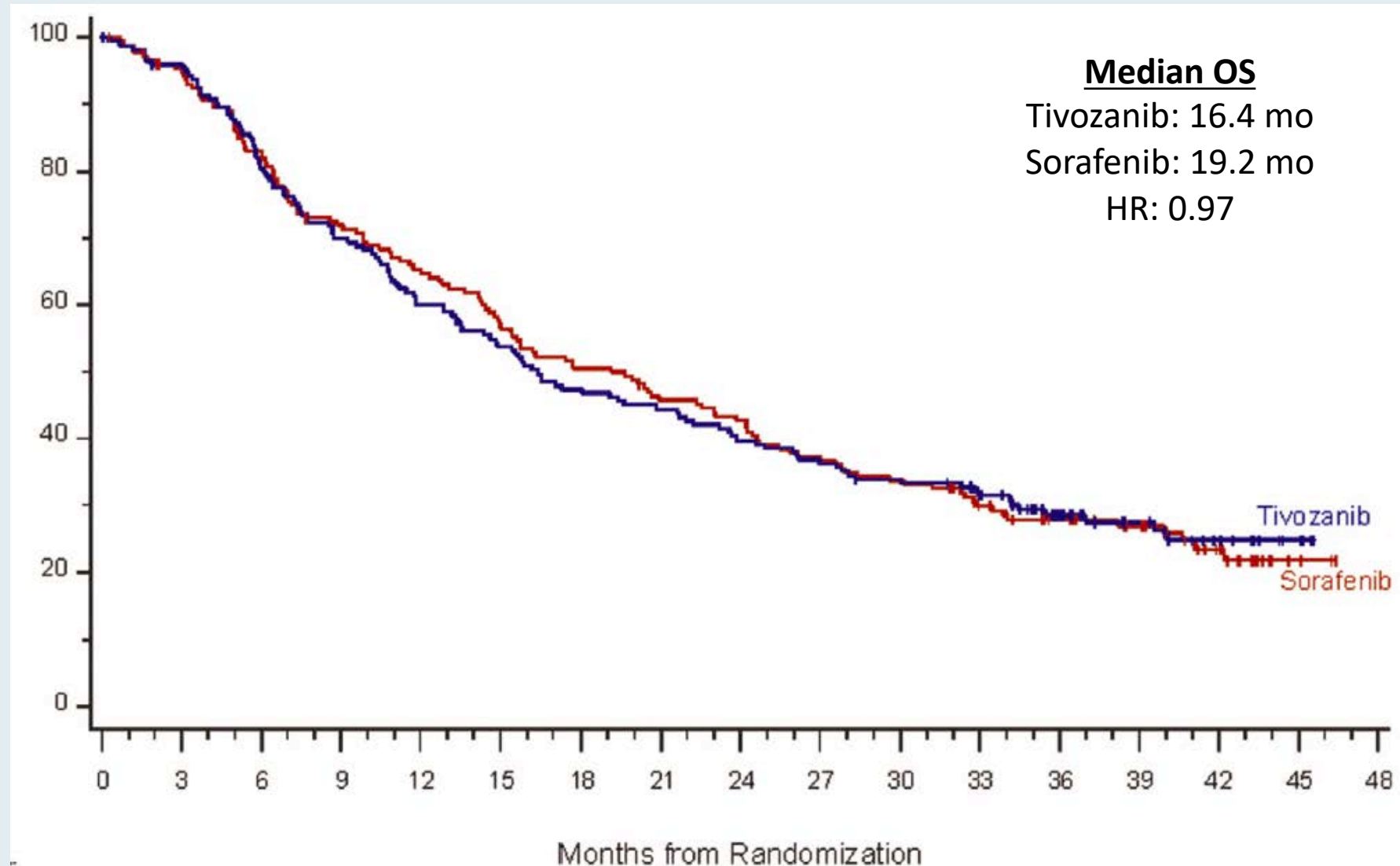
Median PFS was 5.6 months in the tivozanib arm (n=175) compared with 3.9 months for those treated with sorafenib (HR 0.73; p=0.016). Median OS was 16.4 and 19.2 months, for the tivozanib and sorafenib arms, respectively (HR 0.97). The ORR was 18% for the tivozanib arm and 8% for the sorafenib arm.”

Final Overall Survival Results from a Phase 3 Study to Compare Tivozanib to Sorafenib as Third- or Fourth-line Therapy in Subjects with Metastatic Renal Cell Carcinoma

Sumanta K. Pal^a, Bernard J. Escudier^b, Michael B. Atkins^c, Thomas E. Hutson^d, Camillo Porta^e, Elena Verzoni^f, Michael N. Needle^g, Daniel Powers^g, David F. McDermott^h, Brian I. Rini^{i,}*

Eur Urol 2020;78(6):783-85.

TIVO-3: Final Overall Survival Analysis



Median PFS²
Tivozanib: 5.6 mo
Sorafenib: 3.9 mo
HR: 0.73, p = 0.016

¹ Pal SK et al. *Eur Urol* 2020;78(6):783-85; ² Rini BI et al. *Lancet Oncol* 2020;21:95-104.

Prostate Cancer

HERO Phase III Trial: Results Comparing Relugolix, an Oral GnRH Receptor Antagonist, versus Leuprolide Acetate for Advanced Prostate Cancer¹

Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer²

¹ Shore N et al.

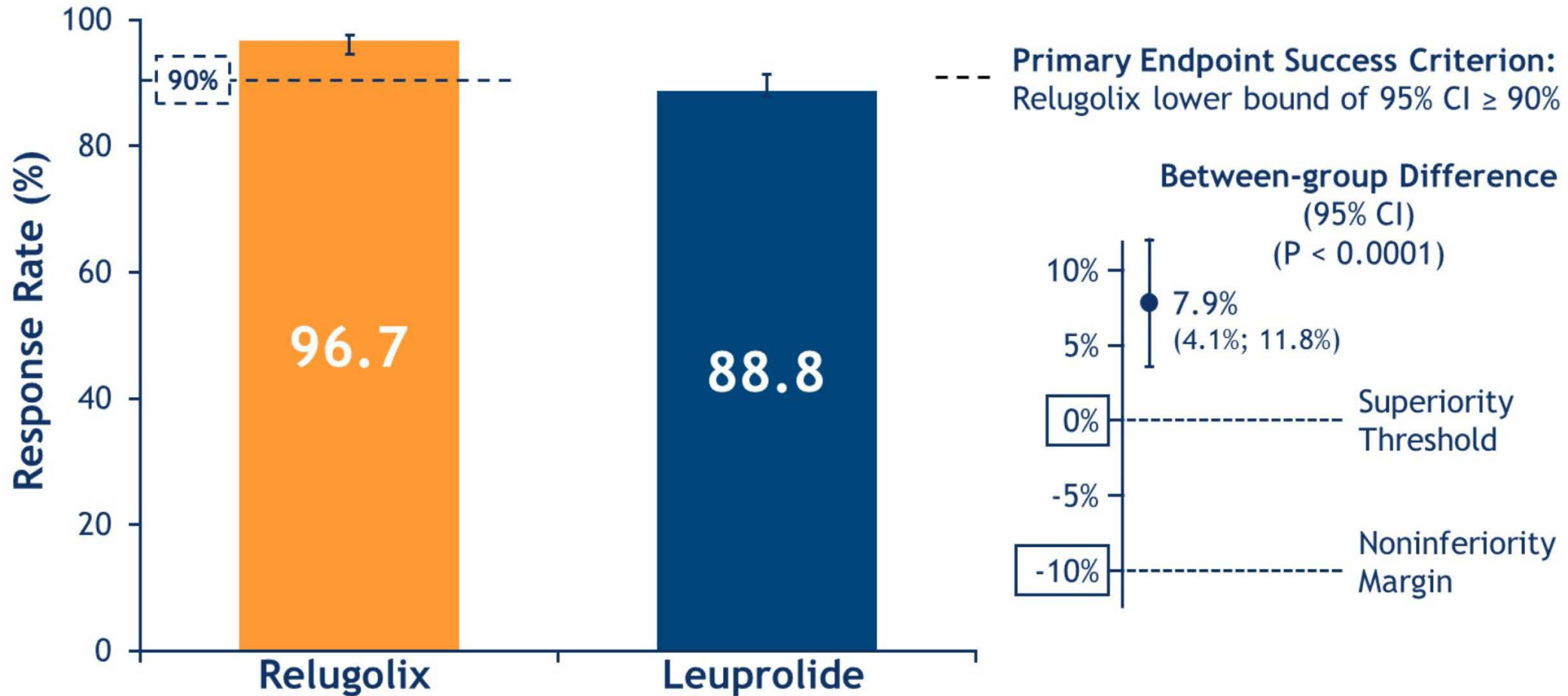
ASCO 2020;Abstract 5602.

² Shore ND et al.

N Engl J Med 2020;382(23):2187-96.

HERO: Primary Endpoint – Sustained Castration

Key Secondary Endpoint – Noninferiority to Leuprolide



The NEW ENGLAND JOURNAL of MEDICINE

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

ORIGINAL ARTICLE

Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide

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

The NEW ENGLAND JOURNAL of MEDICINE

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

ORIGINAL ARTICLE

Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer

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



European Association of Urology

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

Prostate Cancer

Apalutamide and Overall Survival in Prostate Cancer

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

Survival: Darolutamide, Enzalutamide, Apalutamide

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

¹ Fizazi K et al; ARAMIS Investigators. *N Engl J Med* 2020;383:1040-9.

² Sternberg CN et al; PROSPER Investigators. *N Engl J Med* 2020;382(23):2197-206.

³ Smith MR et al; SPARTAN Investigators. *Eur Urol* 2020;[Online ahead of print].

Comparison of Toxicities: Darolutamide, Enzalutamide, Apalutamide

| Toxicity | ARAMIS | | PROSPER | | SPARTAN | |
|-------------------|--------------|---------|--------------|---------|-------------|---------|
| | Darolutamide | Placebo | Enzalutamide | Placebo | Apalutamide | Placebo |
| Fatigue/asthenia | 16% | 11% | 33% | 14% | 30% | 21% |
| Falling | 4% | 5% | 11% | 4% | 16% | 9% |
| Dizziness | 5% | 4% | 10% | 4% | 9% | 6% |
| Mental impairment | 1% | 2% | 5% | 2% | 5% | 3% |

Sternberg CN et al; PROSPER Investigators. *N Engl J Med* 2020;382(23):2197-206.

Fizazi K et al; ARAMIS Investigators. *N Engl J Med* 2020;383:1040-9.

Small EJ et al; SPARTAN Investigators. ASCO 2020;Abstract 5516.

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

Press Release: December 1, 2020

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

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

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

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

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

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

| | ARCHES (N = 1,150) | | TITAN (N = 1,052) | |
|------------------|---|------------------|---|------------------|
| Characteristics | <ul style="list-style-type: none"> 2/3rd high volume 17% prior docetaxel 25% prior RP/XRT | | <ul style="list-style-type: none"> 2/3rd high volume 10% prior docetaxel 17% prior RP/XRT | |
| | ADT + enzalutamide (n = 574) | ADT (n = 576) | ADT + apalutamide (n = 955) | ADT (n = 554) |
| Radiographic PFS | NR | 19.0 mo | NR | 22.1 mo |
| | HR (overall): 0.39 <ul style="list-style-type: none"> HR (prior docetaxel): 0.52 HR (high volume): 0.43 HR (low volume): 0.25 | | HR (overall): 0.48 <ul style="list-style-type: none"> HR (prior docetaxel): 0.47 HR (high volume): 0.53 HR (low volume): 0.36 | |
| Overall survival | NR | NR | NR | NR |
| | HR: 0.81 (immature) | | HR (overall): 0.67 <ul style="list-style-type: none"> HR (prior docetaxel): 1.27 HR (high volume): 0.68 HR (low volume): 0.67 | |

NR = not reached

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

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

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



TITAN – Final Analysis: Overall Survival

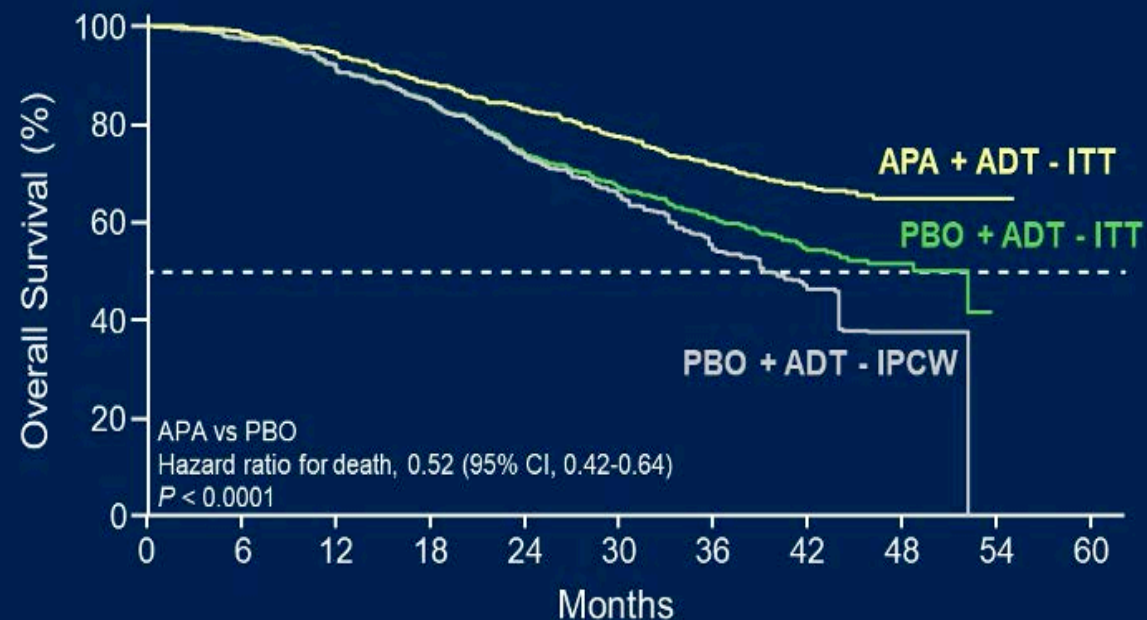
OS (Co-primary endpoint)
Median follow-up: 44.0 months



No. at risk:

| | | | | | | | | | | | |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|----|---|---|
| APA + ADT | 525 | 513 | 489 | 452 | 425 | 394 | 362 | 227 | 52 | 3 | 0 |
| PBO + ADT | 527 | 510 | 474 | 436 | 374 | 339 | 301 | 181 | 43 | 0 | 0 |

OS with adjustment for ~40%
crossover from PBO



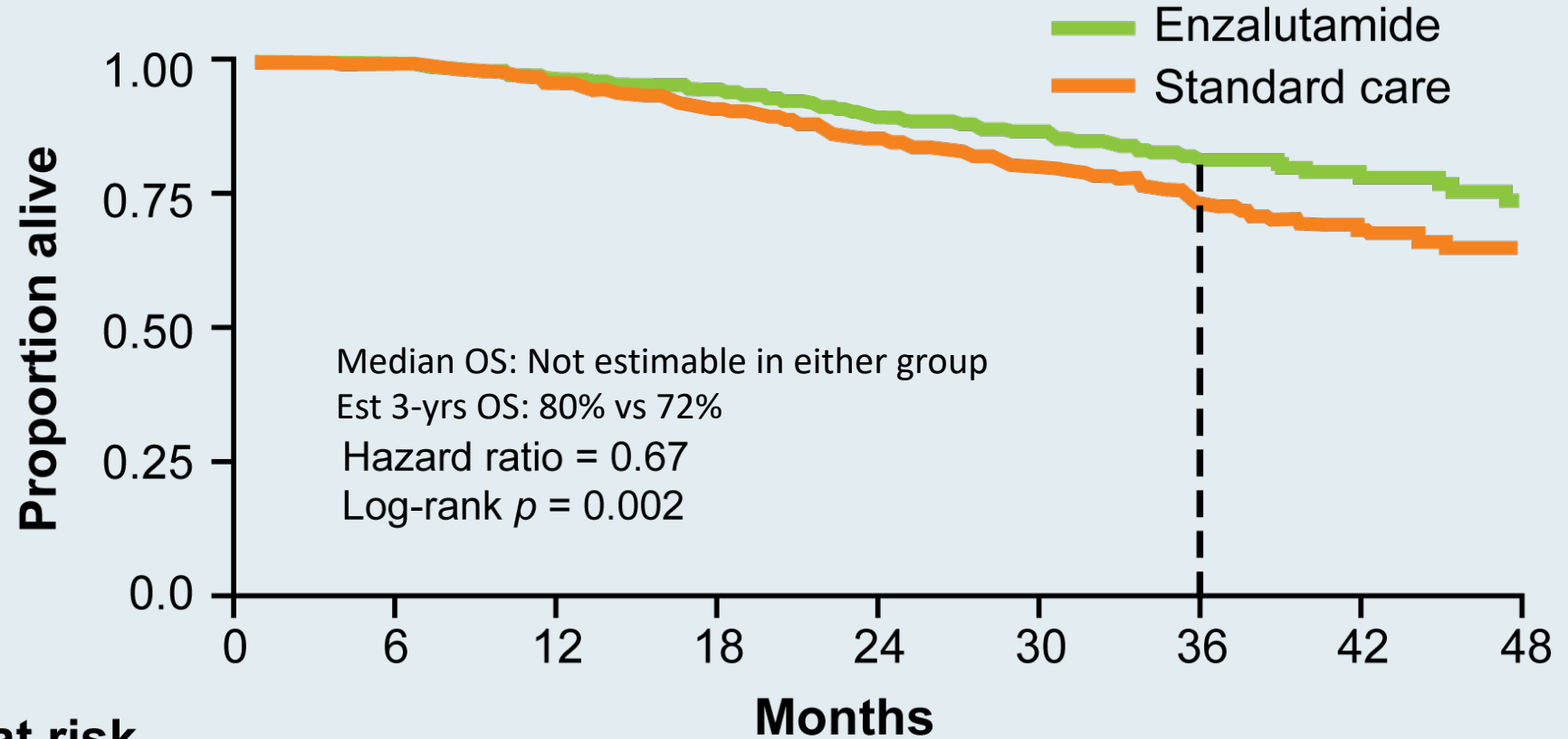
No. at risk:

| | | | | | | | | | | | |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|----|---|---|
| APA + ADT | 525 | 513 | 489 | 452 | 425 | 394 | 362 | 227 | 52 | 3 | 0 |
| PBO + ADT | 527 | 510 | 474 | 436 | 374 | 339 | 301 | 181 | 43 | 0 | 0 |

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

A Mixed Bag

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



Number at risk

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

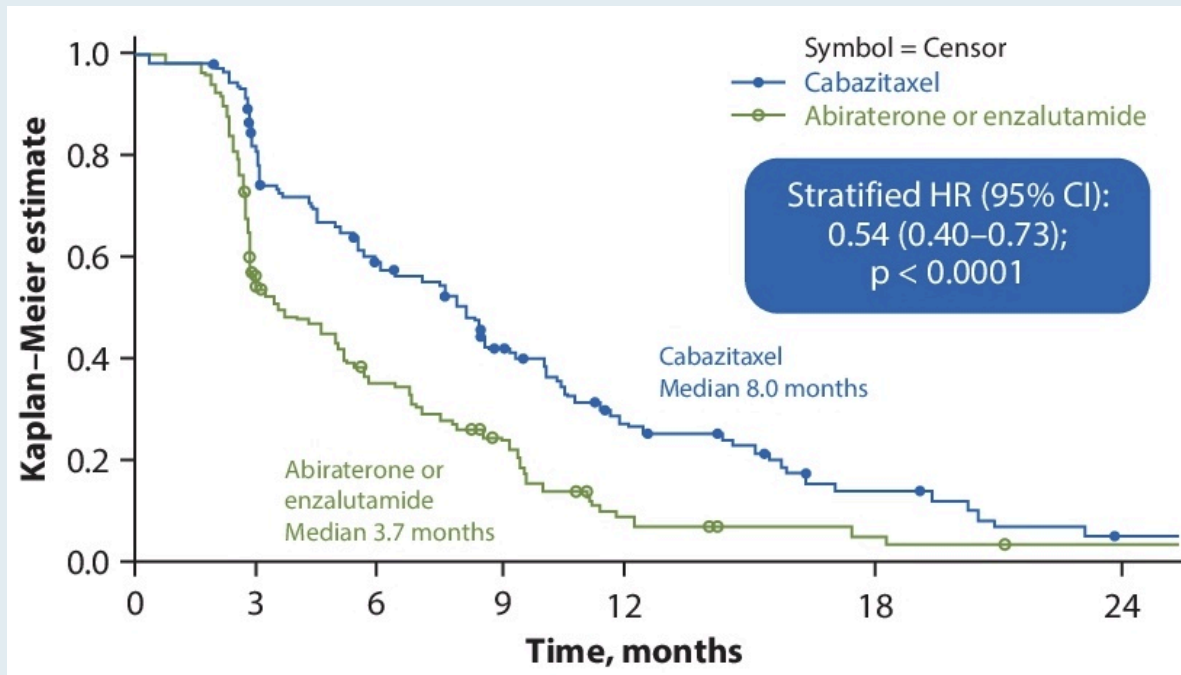
CARD: Overall Survival Analysis of Patients with Metastatic Castration-Resistant Prostate Cancer Receiving Cabazitaxel vs Abiraterone or Enzalutamide

Tombal B et al.

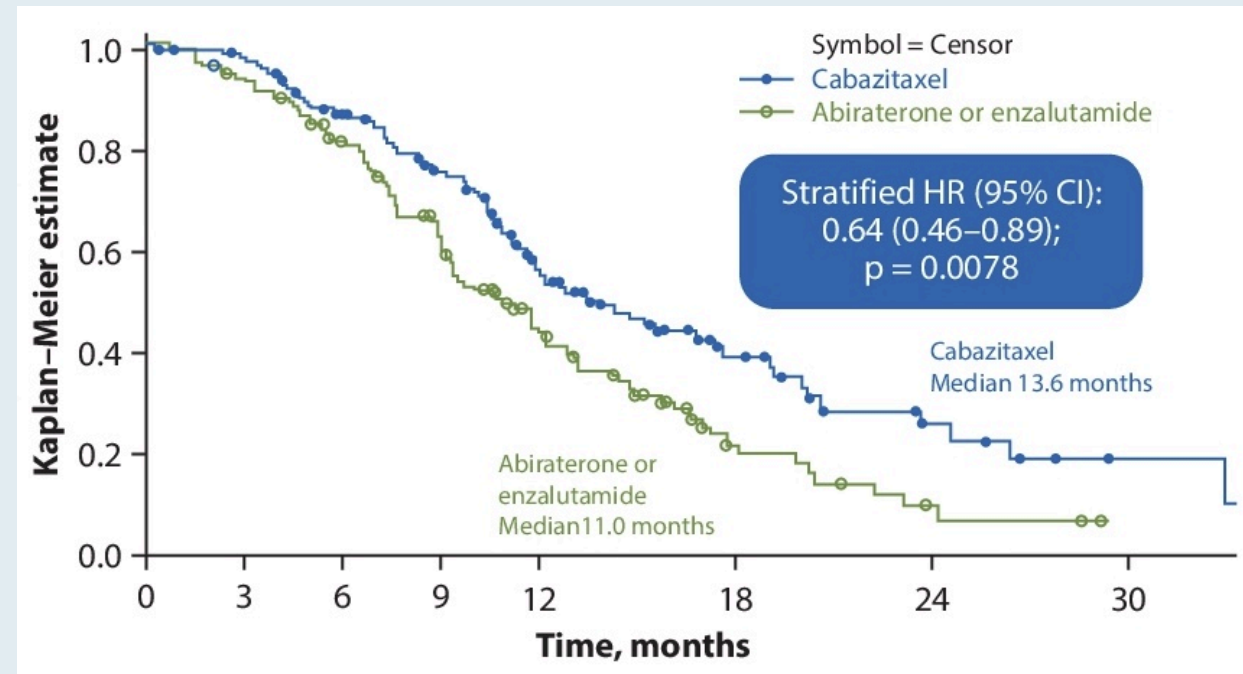
ASCO 2020;Abstract 5569.

CARD Study of Cabazitaxel: Survival Analyses

rPFS (primary endpoint)



OS (key secondary endpoint)

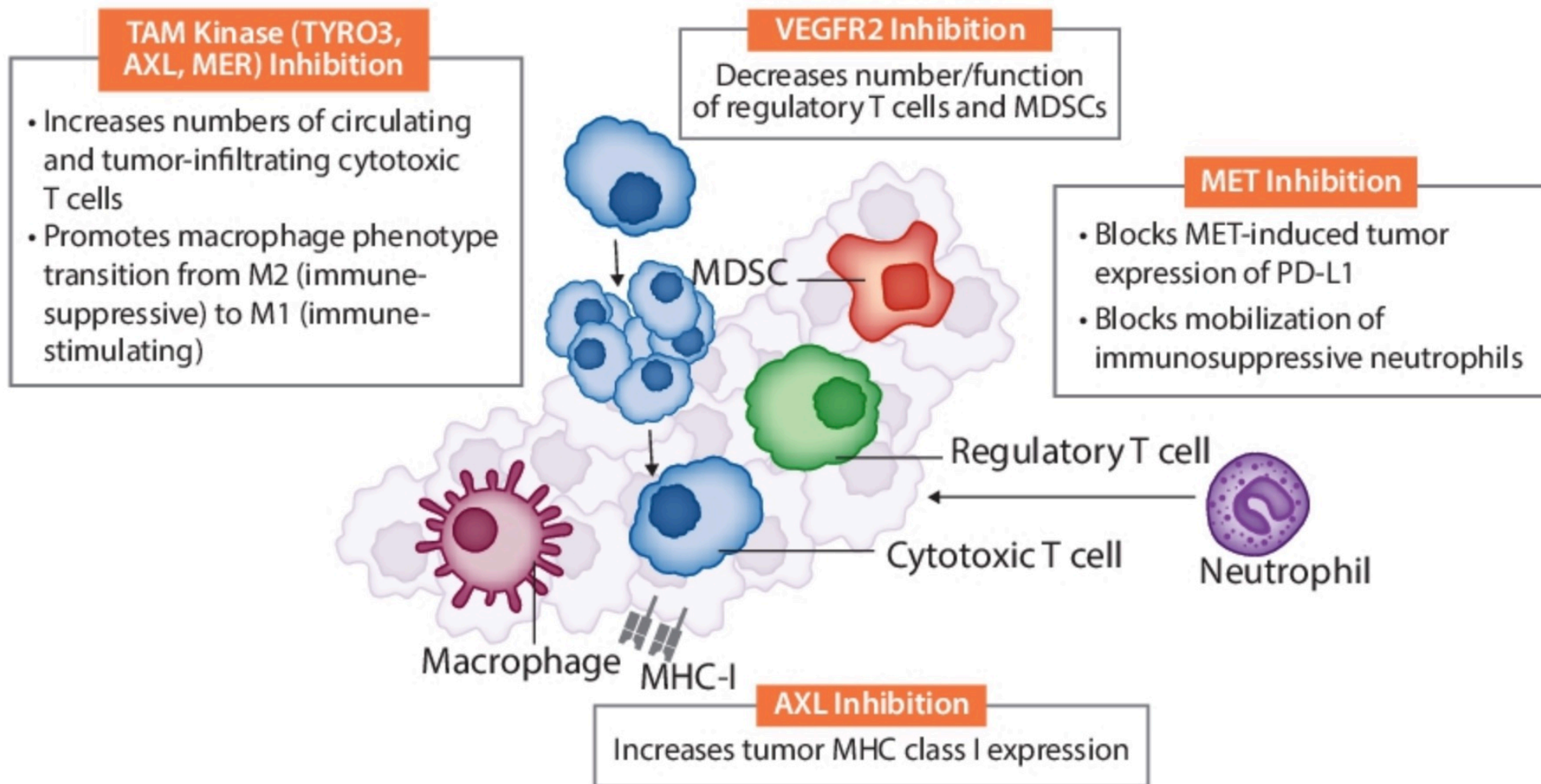


Cabozantinib in Combination with Atezolizumab in Patients with mCRPC: Results of Cohort 6 of the COSMIC-021 Study

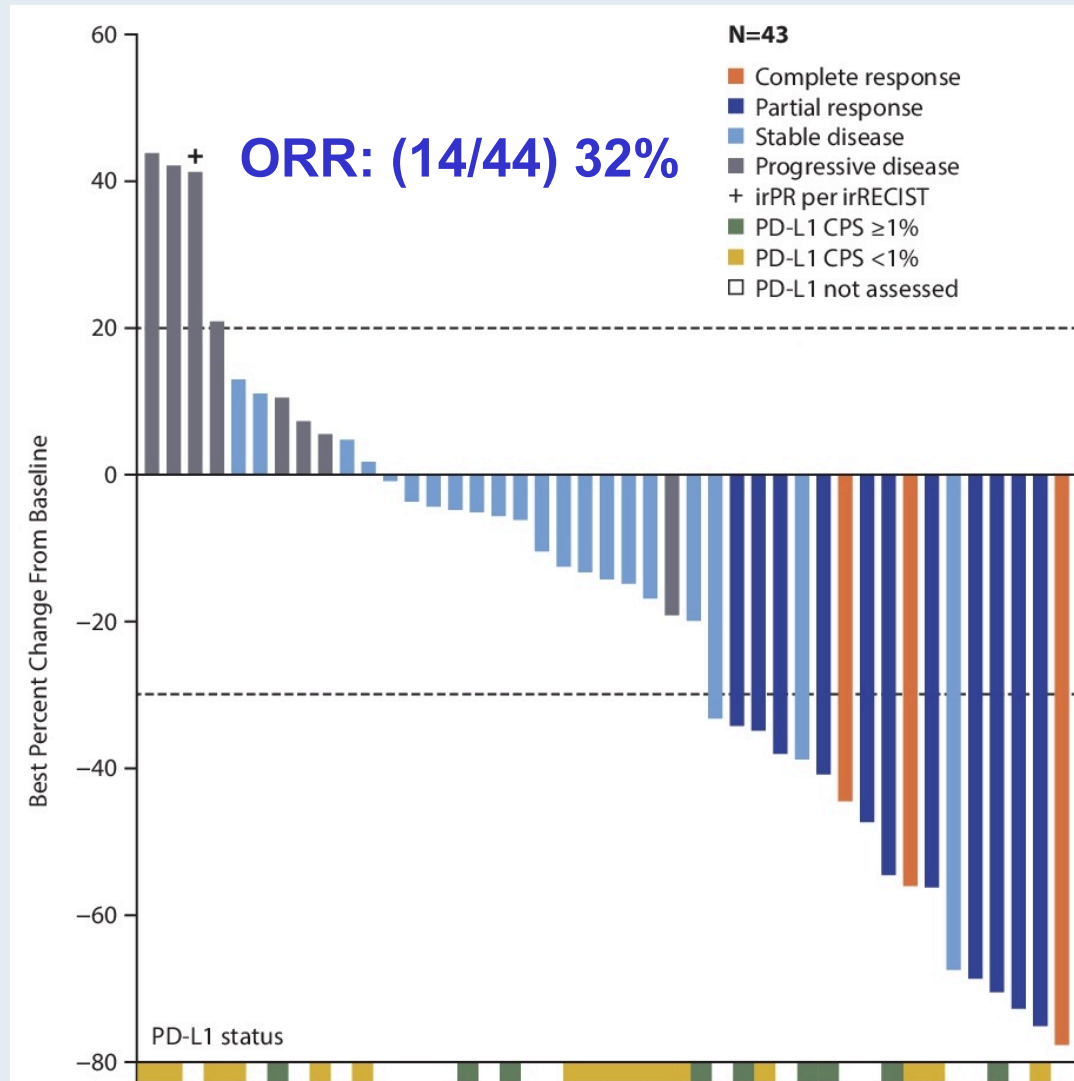
Agarwal N et al.

ASCO 2020;Abstract 5564.

Cabozantinib Targets Pathways Associated with Tumor Immune Suppression

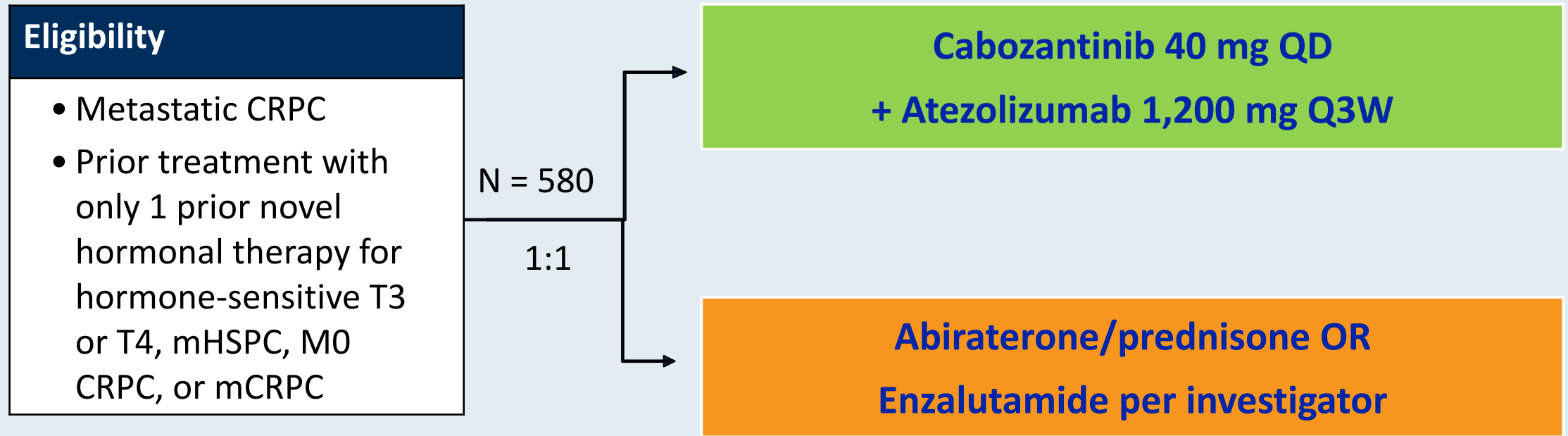


COSMIC-021 Primary Endpoint: Investigator-Assessed ORR with Cabozantinib/Atezolizumab in mCRPC



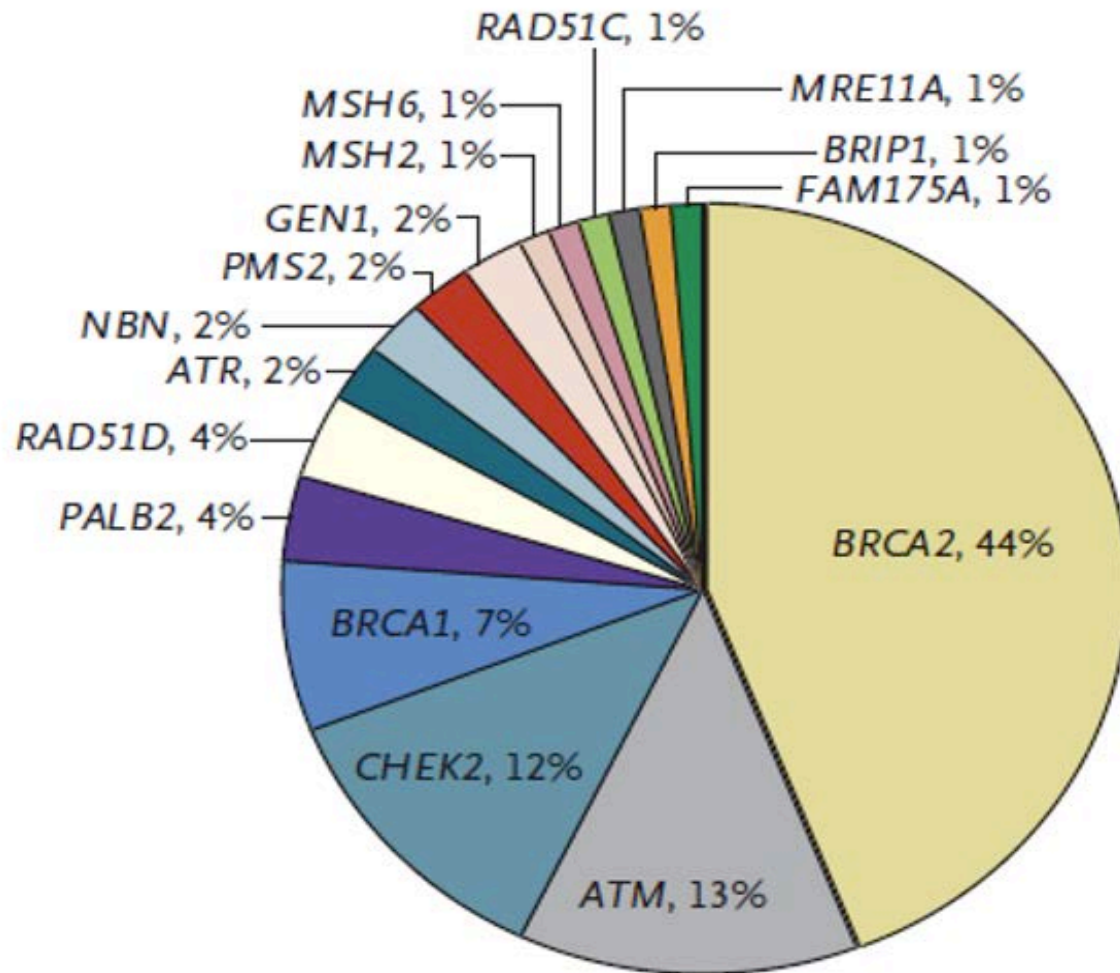
| | CRPC Cohort (N=44) | | |
|----------------------------------|--------------------|---------|----------|
| | Any Grade | Grade 3 | Grade 4 |
| Any AE, n (%) | 42 (95) | 26 (59) | 1 (2.3)* |
| Fatigue | 22 (50) | 3 (6.8) | 0 |
| Diarrhea | 20 (45) | 3 (6.8) | 0 |
| Nausea | 20 (45) | 0 | 0 |
| Decreased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

CONTACT-02 Phase III Study Schema



Coprimary endpoints: Duration of PFS and OS

Inherited DNA Repair Gene Mutations in Men with mPC



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

Recent FDA Approvals of PARP Inhibitors for mCRPC

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

ORIGINAL ARTICLE

Olaparib for Metastatic Castration-Resistant Prostate Cancer

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

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

ORIGINAL ARTICLE

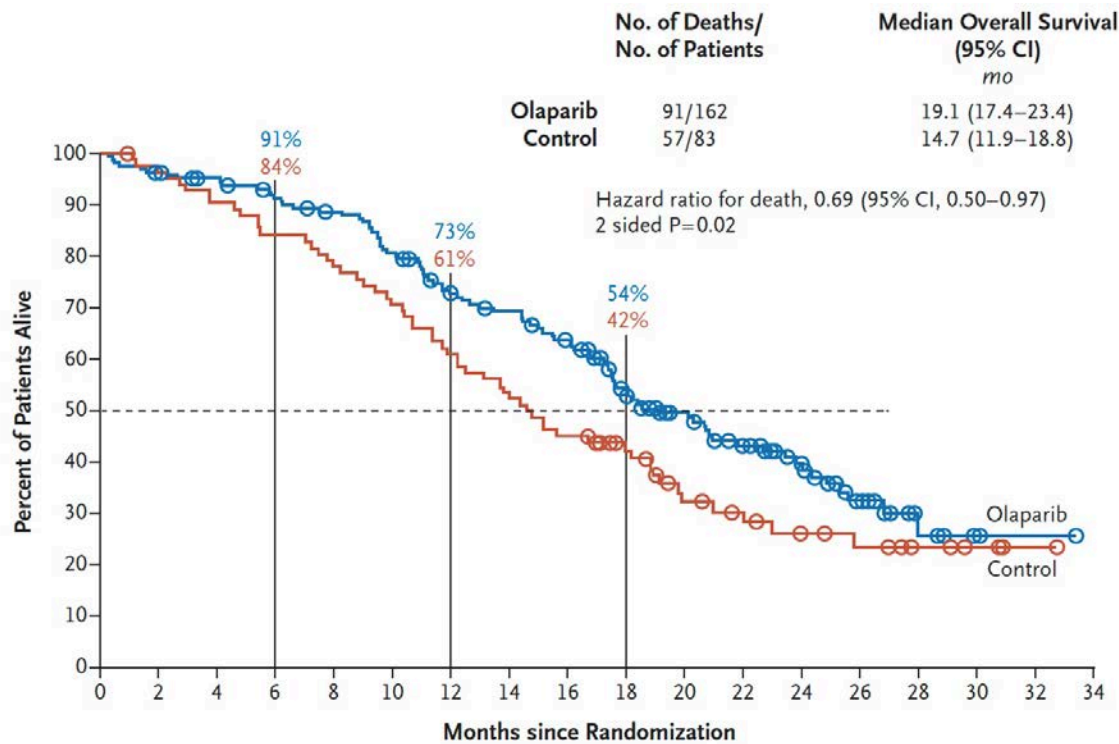
Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

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

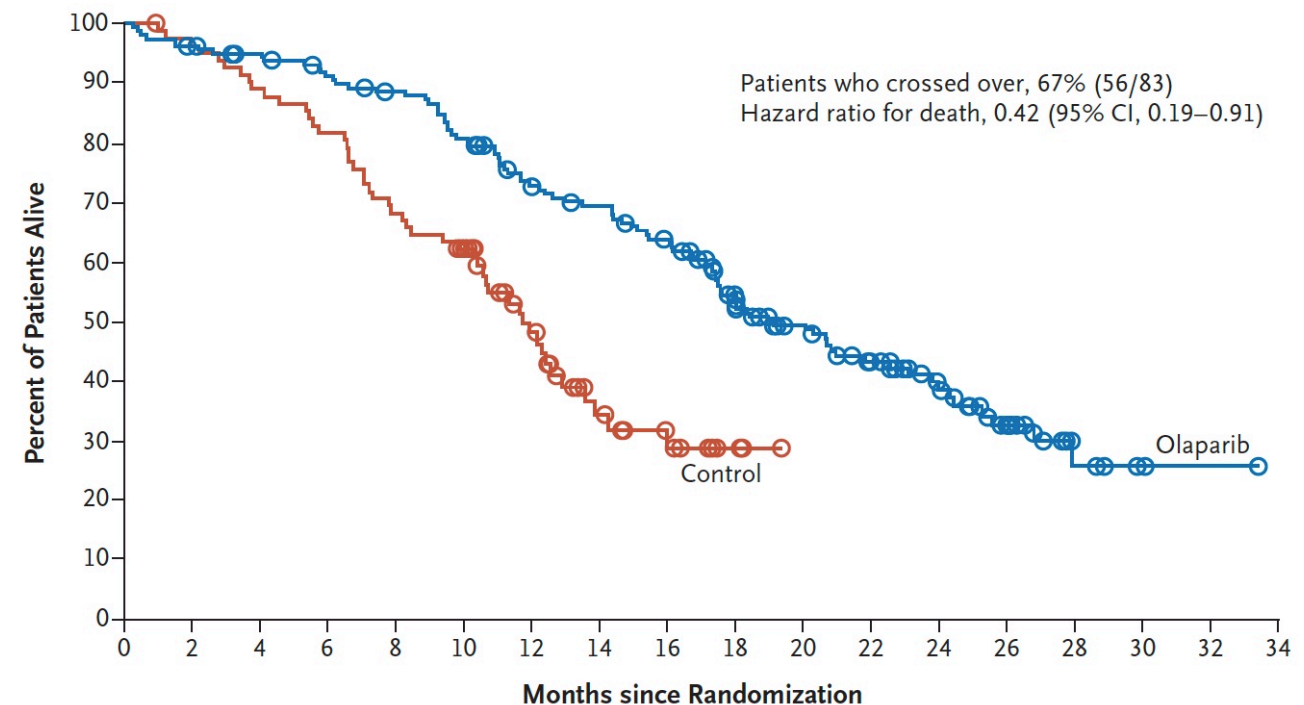
***N Engl J Med* 2020;383(24):2345-57.**

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

Overall survival



Cross-over adjusted overall survival

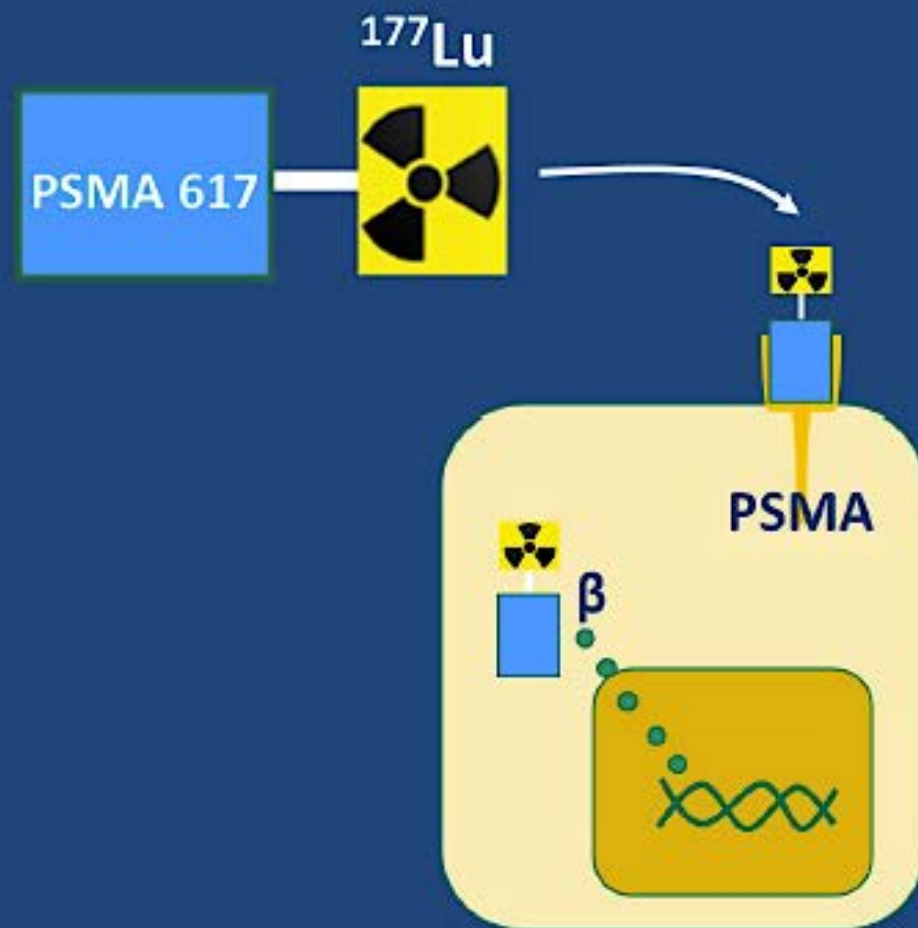


Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration

Wassim Abida, MD, PhD¹; Akash Patnaik, MD, PhD, MMSc²; David Campbell, MBBS³; Jeremy Shapiro, MBBS⁴; Alan H. Bryce, MD⁵; Ray McDermott, MD, PhD, MBA⁶; Brieuc Sautois, MD, PhD⁷; Nicholas J. Vogelzang, MD⁸; Richard M. Bambury, MD⁹; Eric Voog, MD¹⁰; Jingsong Zhang, MD, PhD¹¹; Josep M. Piulats, MD¹²; Charles J. Ryan, MD¹³; Axel S. Merseburger, PhD¹⁴; Gedske Daugaard, DMSc¹⁵; Axel Heidenreich, MD¹⁶; Karim Fizazi, MD, PhD¹⁷; Celestia S. Higano, MD¹⁸; Laurence E. Krieger, MBChB¹⁹; Cora N. Sternberg, MD²⁰; Simon P. Watkins, PhD²¹; Darrin Despain, MStat²²; Andrew D. Simmons, PhD²³; Andrea Loehr, PhD²³; Melanie Dowson, BA²⁴; Tony Golsorkhi, MD²⁵; and Simon Chowdhury, MD, PhD^{26,27}; on behalf of the TRITON2 investigators

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

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



***Lancet* 2021;397:797-804.**

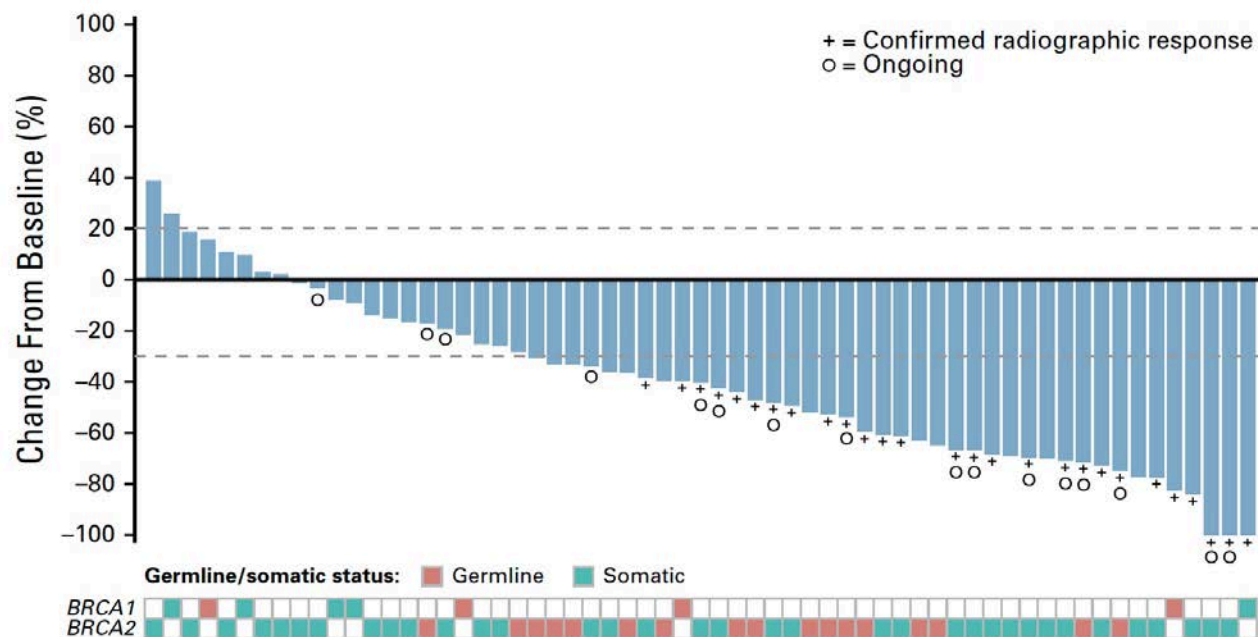
[¹⁷⁷Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial



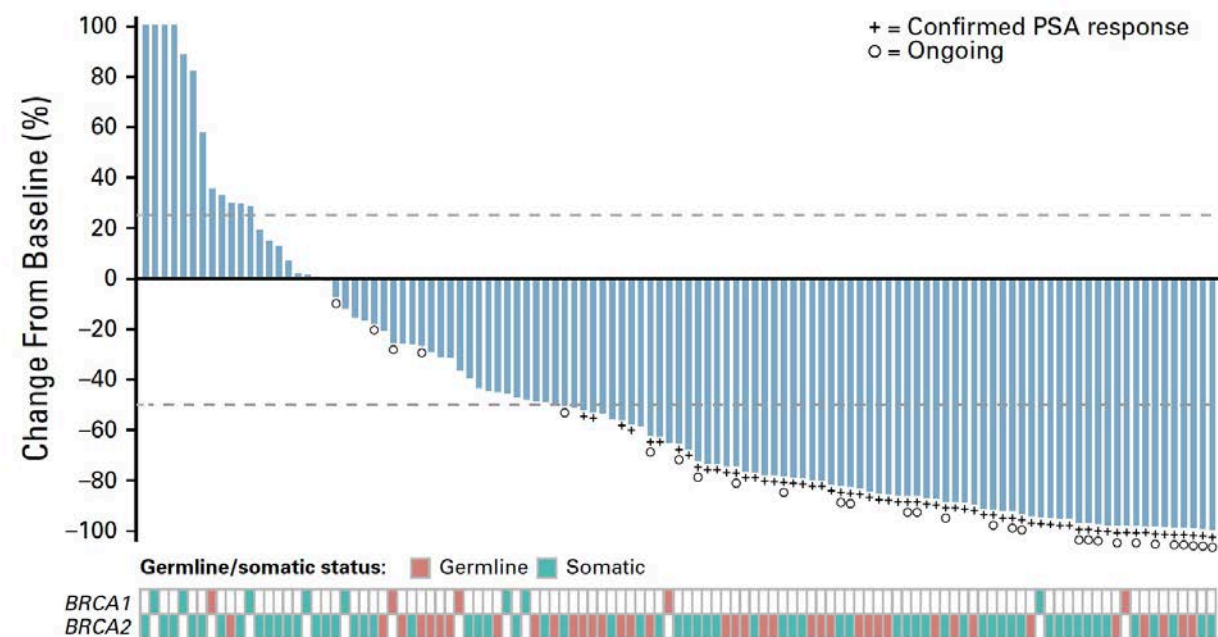
Michael S Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony M Joshua, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Siobhan Ng, Roslyn J Francis, Craig Gedy, Natalie K Rutherford, Andrew Weickhardt, Andrew M Scott, Sze-Ting Lee, Edmond M Kwan, Arun A Azad, Shakher Ramdave,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

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

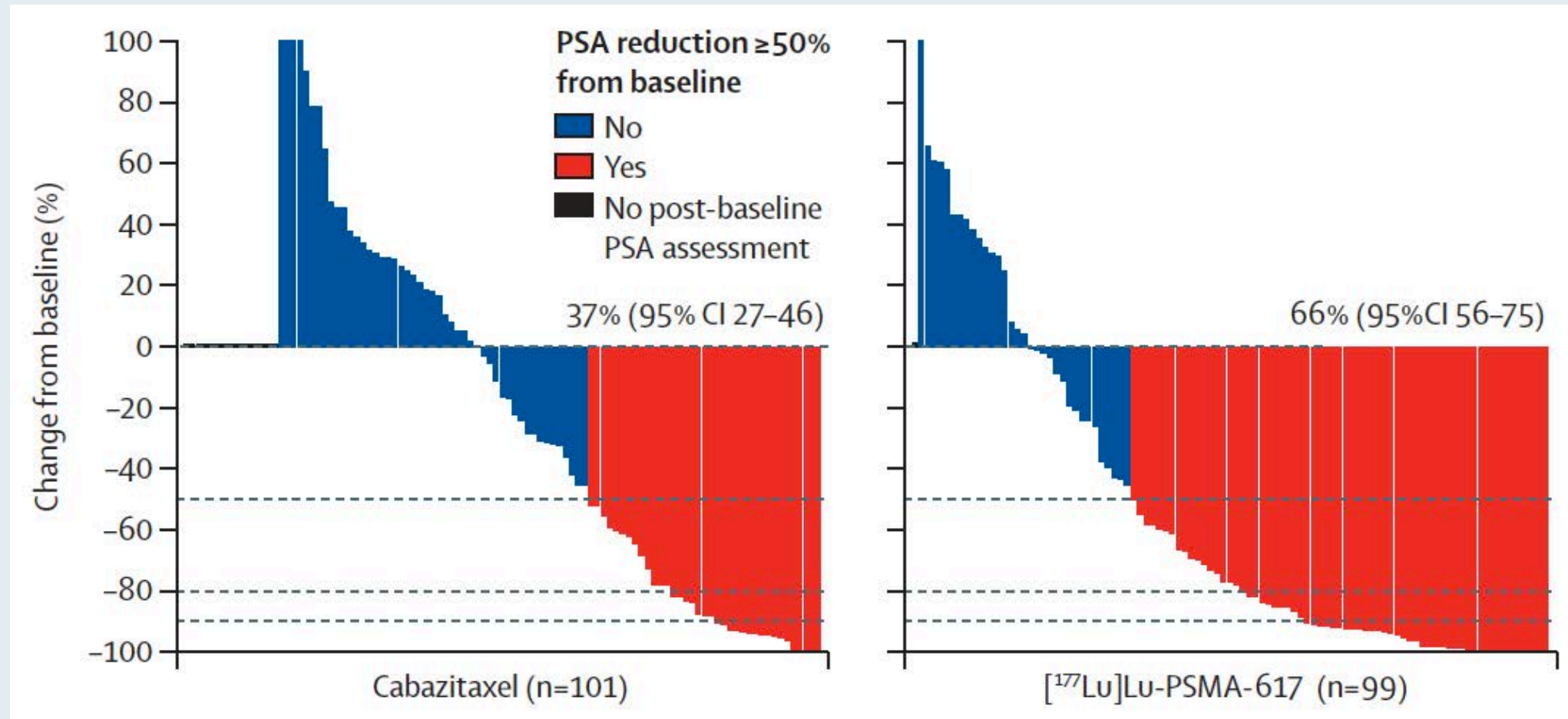
ORR per independent radiology review: 43.5%



Confirmed PSA response rate: 54.8%



TheraP: Primary Endpoint — PSA Response $\geq 50\%$



TheraP: Select Adverse Events

| Event | ¹⁷⁷ Lu-PSMA-617 (n = 98) | | Cabazitaxel (n = 85) | |
|------------------|-------------------------------------|-----------|----------------------|-----------|
| | Grade 1/2 | Grade 3/4 | Grade 1/2 | Grade 3/4 |
| Pain | 61% | 11% | 61% | 5% |
| Thrombocytopenia | 18% | 11% | 5% | 0 |
| Anemia | 19% | 8% | 13% | 8% |
| Neutropenia | 7% | 4% | 5% | 13% |

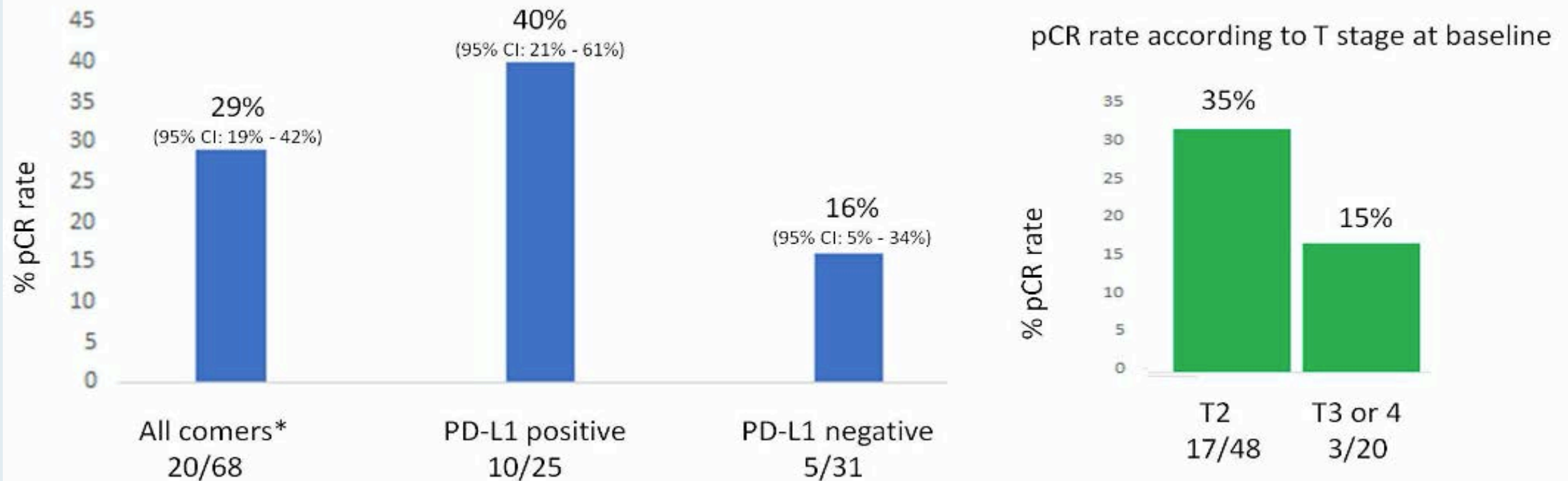
Urothelial Bladder Cancer

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

Balar AV et al.

Genitourinary Cancers Symposium 2021;Abstract 451.

ABACUS Phase II Trial of Neoadjuvant Atezolizumab for Muscle-Invasive Bladder Cancer: pCR Rate for Evaluable Patients



ORIGINAL ARTICLE

Does the administration of preoperative pembrolizumab lead to sustained remission post-cystectomy? First survival outcomes from the PURE-01 study[☆]

M. Bandini¹, E. A. Gibb², A. Gallina¹, D. Raggi³, L. Marandino³, M. Bianchi¹, J. S. Ross^{4,5}, M. Colecchia³, G. Gandaglia¹, N. Fossati¹, F. Pederzoli¹, R. Lucianò⁶, R. Colombo¹, A. Salonia¹, A. Briganti¹, F. Montorsi¹ & A. Necchi^{3*}

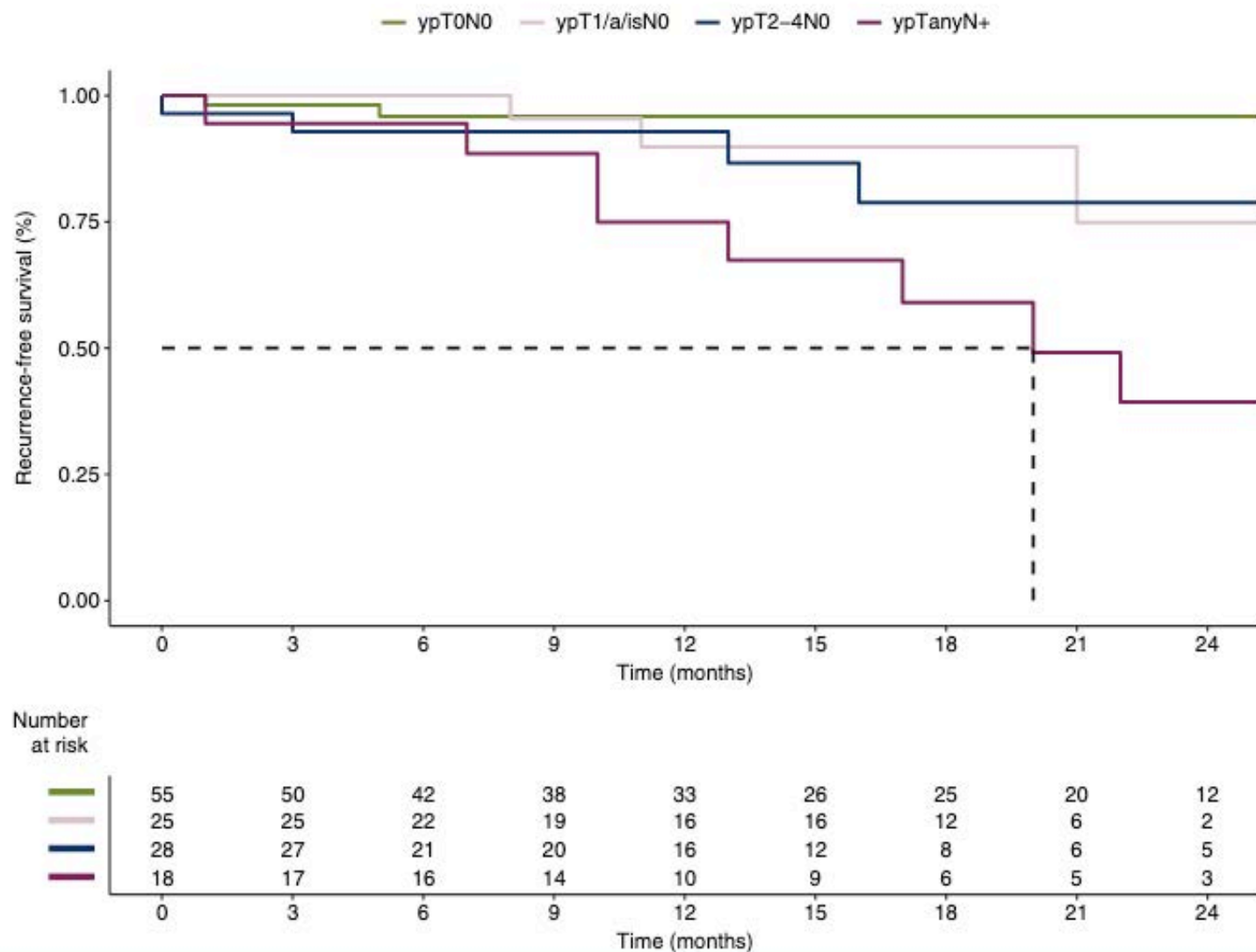
¹Urological Research Institute (URI), Unit of Urology, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; ²Decipher Biosciences Inc., Vancouver, Canada; ³Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; ⁴Foundation Medicine Inc., Cambridge; ⁵Upstate Medical University, Syracuse, United States; ⁶Department of Pathology, IRCCS Ospedale San Raffaele, Milan, Italy



Available online 23 September 2020

PURE-01: Recurrence-Free Survival (RFS) by ypTypN Stage

B



| RFS | 12-mo | 24-mo |
|-------------------------------------|-------|-------|
| Overall (n = 126) | 90.5% | 78.3% |
| ypT0ypN0 (n = 55) | 95.9% | 95.9% |
| ypT _{1/a/is} ypN0 (n = 25) | 89.8% | 74.9% |
| ypT2-4 ypN0 (n = 28) | 92.9% | 78.8% |
| ypTanyN+ (n = 18) | 74.9% | 39.3% |

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

Bajorin DF et al.

Genitourinary Cancers Symposium 2021;Abstract 391.

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

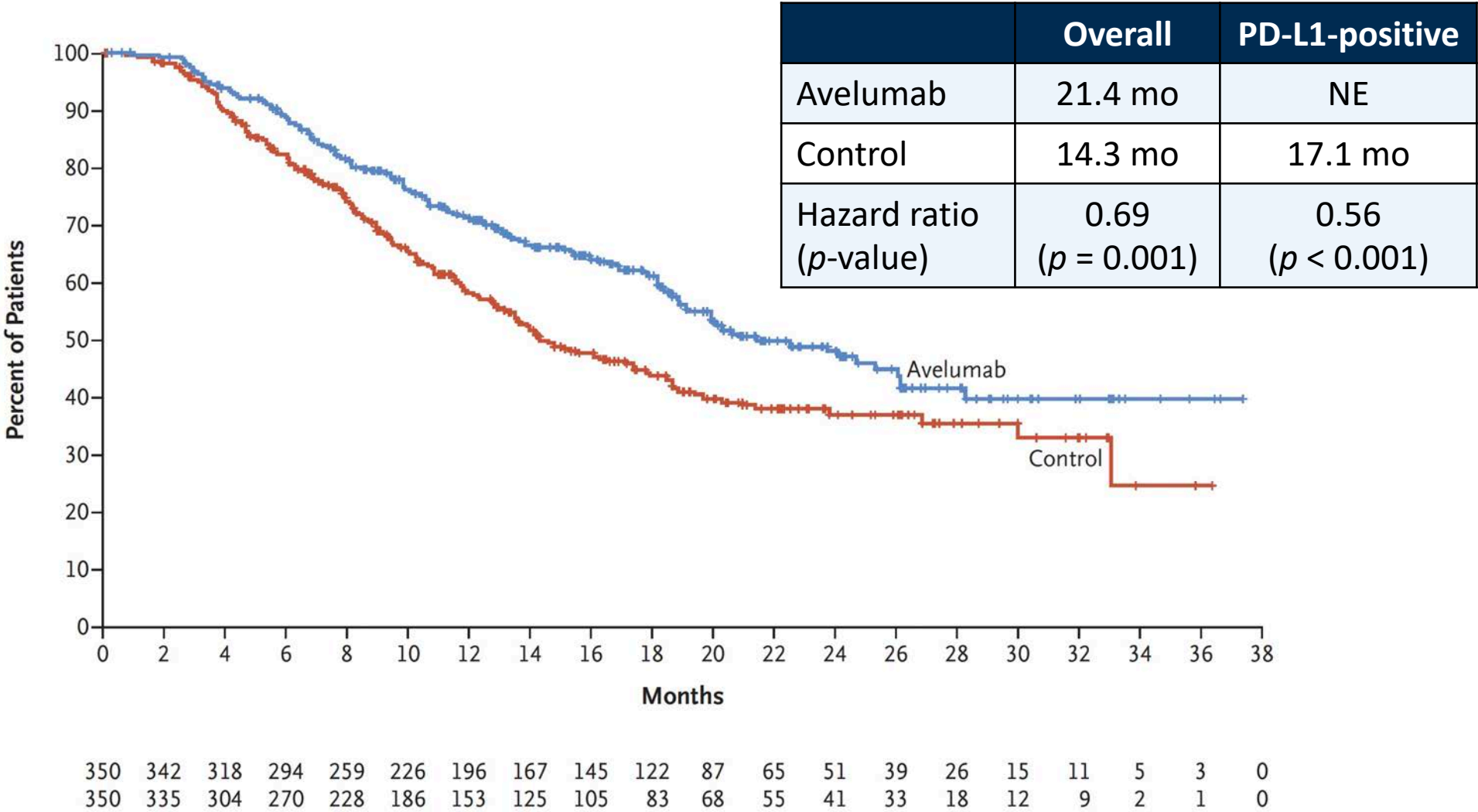
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma

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

JAVELIN Bladder 100 Primary Endpoint: Overall Survival



FDA-Approved Immune Checkpoint Inhibitors for UBC

| Agent | Indication |
|---------------|---|
| Avelumab | <ul style="list-style-type: none">• Maintenance treatment after first-line platinum-containing chemotherapy• Previously platinum-treated locally advanced or metastatic UBC |
| Pembrolizumab | <ul style="list-style-type: none">• BCG-unresponsive, high-risk NMIBC in patients ineligible for or electing not to undergo cystectomy• Locally advanced or metastatic cisplatin-ineligible UBC, PD-L1 CPS ≥ 10• Ineligible for any platinum-containing therapy, regardless of PD-L1 status |
| Durvalumab | <i>FDA indication voluntarily withdrawn (2/22/2021)</i> |
| Nivolumab | <ul style="list-style-type: none">• Previously platinum-treated locally advanced or metastatic UBC |
| Atezolizumab | <ul style="list-style-type: none">• Locally advanced or metastatic cisplatin-ineligible UBC, PD-L1 IC $\geq 5\%$• Ineligible for any platinum-containing therapy, regardless of PD-L1 status |

NMIBC = non-muscle-invasive bladder cancer

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

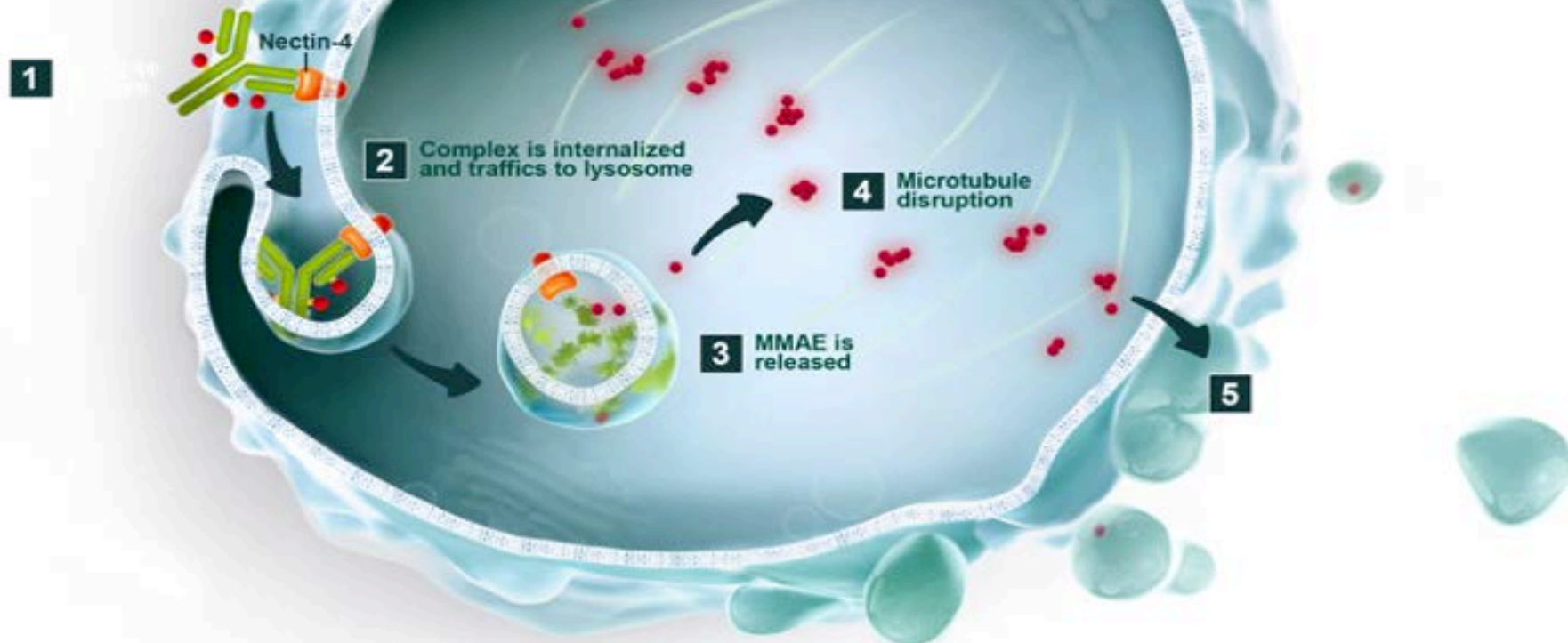
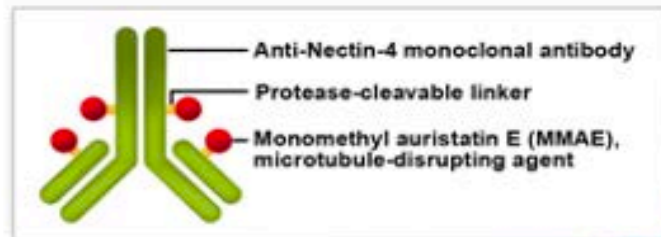
Press Release – April 19, 2021

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

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

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

Enfortumab Vedotin: Nectin-4 Targeted Therapy



Courtesy of Jonathan Rosenberg, MD

ORIGINAL ARTICLE

Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma

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

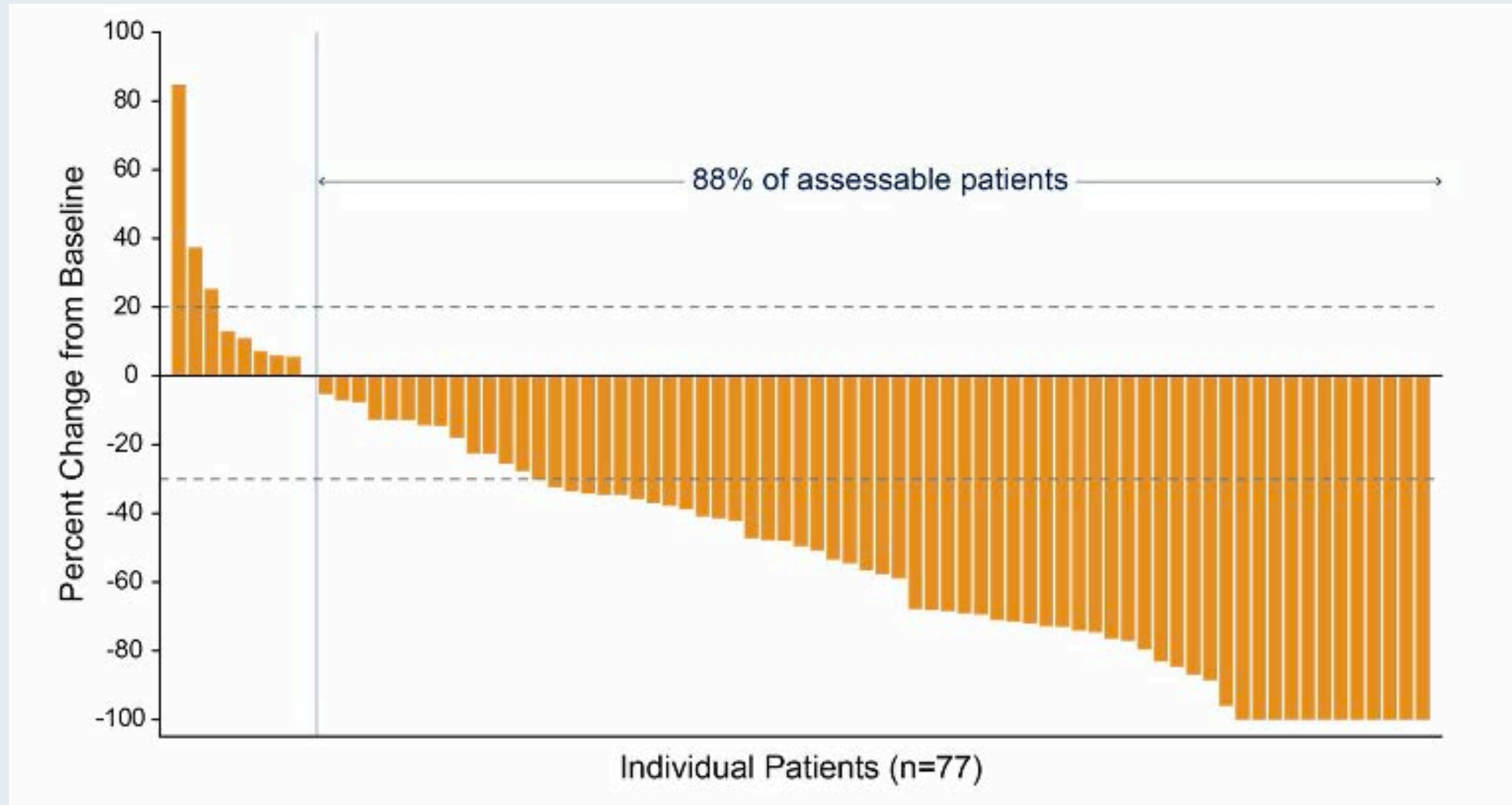
N Engl J Med 2021;384(12):1125-35.

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

Balar AV et al.

Genitourinary Cancers Symposium 2021;Abstract 394.

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



EV-201 Cohort 2: Response and Survival Analyses

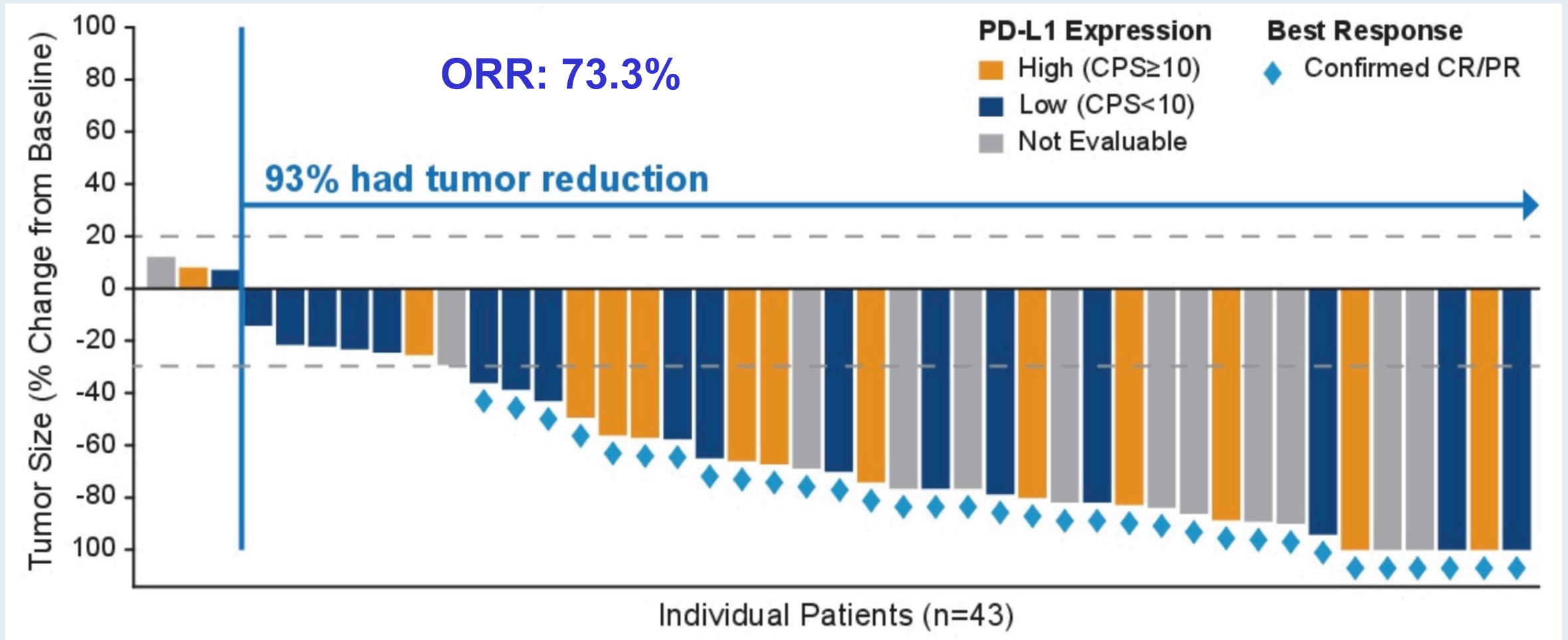
| Efficacy endpoints (N = 91) | |
|-----------------------------|---------|
| Confirmed ORR per BICR | 52% |
| CR | 20% |
| Median DOR | 10.9 mo |
| Median PFS | 5.8 mo |
| Median OS | 14.7 mo |

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

Rosenberg JE et al.

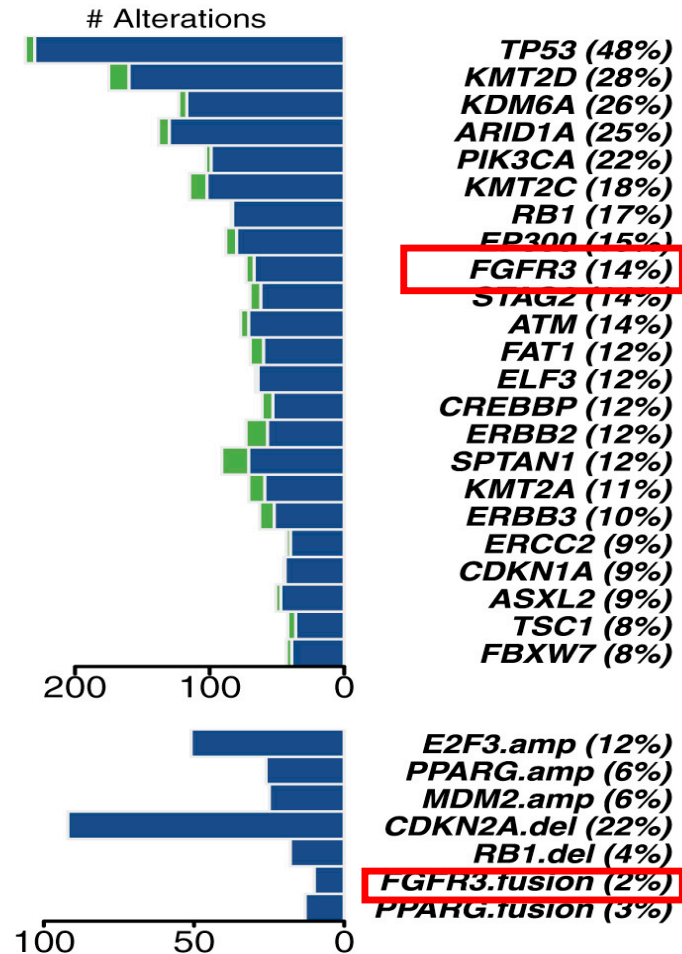
ASCO 2020;Abstract 5044.

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



FGFR3 Genomic Alterations in Muscle-Invasive Bladder Cancer

Genomics of MIBC: TCGA



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

Courtesy of Guru Sonpavde, MD

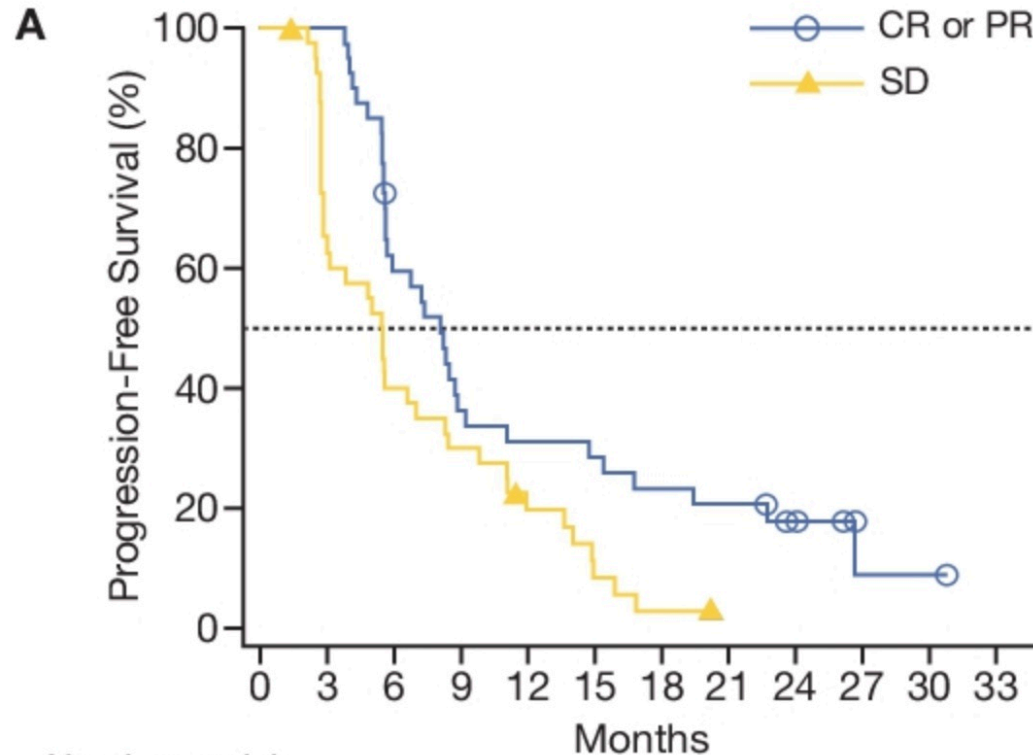
Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma (mUC): Long-Term Outcomes in BLC2001

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

BLC2001: Survival

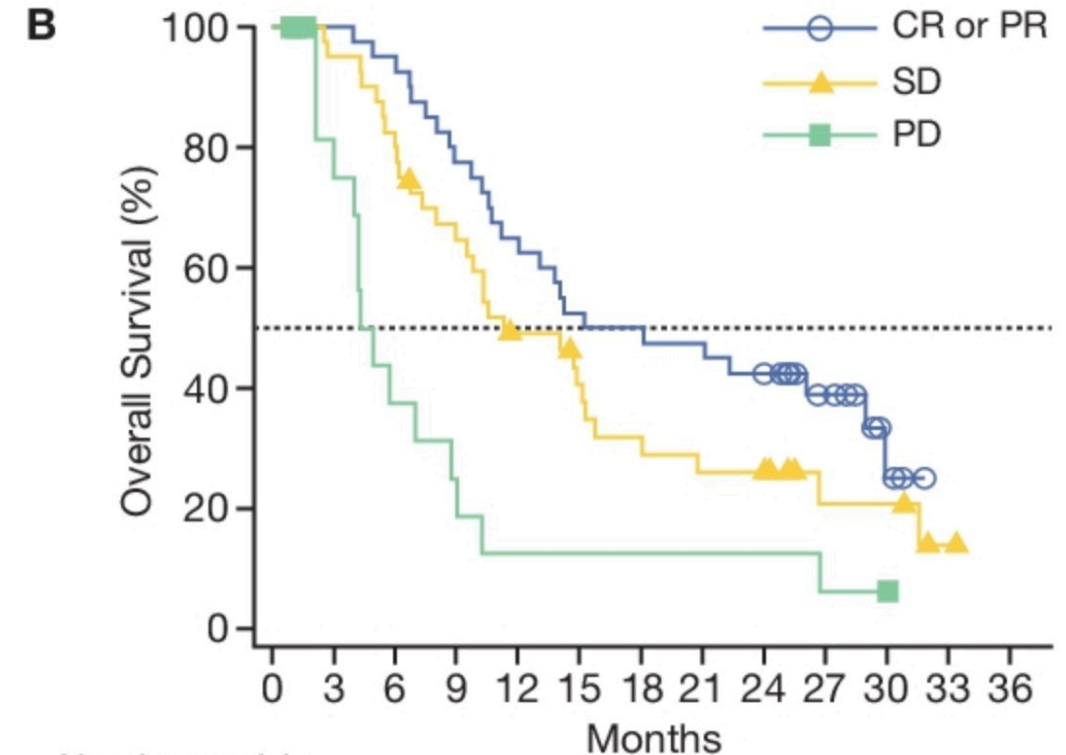
Median PFS: 5.5 months

Median OS: 11.3 months



Number at risk

| | | | | | | | | | | | | |
|----------|----|----|----|----|----|----|---|---|---|---|---|---|
| CR or PR | 40 | 40 | 23 | 14 | 12 | 11 | 9 | 8 | 4 | 1 | 1 | 0 |
| SD | 41 | 26 | 16 | 12 | 7 | 3 | 1 | 0 | 0 | 0 | 0 | 0 |



Number at risk

| | | | | | | | | | | | | | |
|----------|----|----|----|----|----|----|----|----|----|----|---|---|---|
| CR or PR | 40 | 40 | 38 | 31 | 26 | 21 | 20 | 19 | 17 | 10 | 3 | 0 | 0 |
| SD | 41 | 38 | 32 | 25 | 18 | 14 | 11 | 9 | 9 | 4 | 4 | 1 | 0 |
| PD | 18 | 12 | 6 | 4 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 0 | 0 |

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

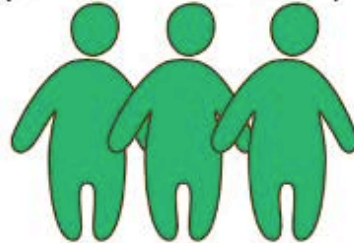
Phase 2
(IMvigor 210)



N = 274

18% mFGFR

Phase 2
(Checkmate 275)



N = 139

11% mFGFR

Objective Response Rate

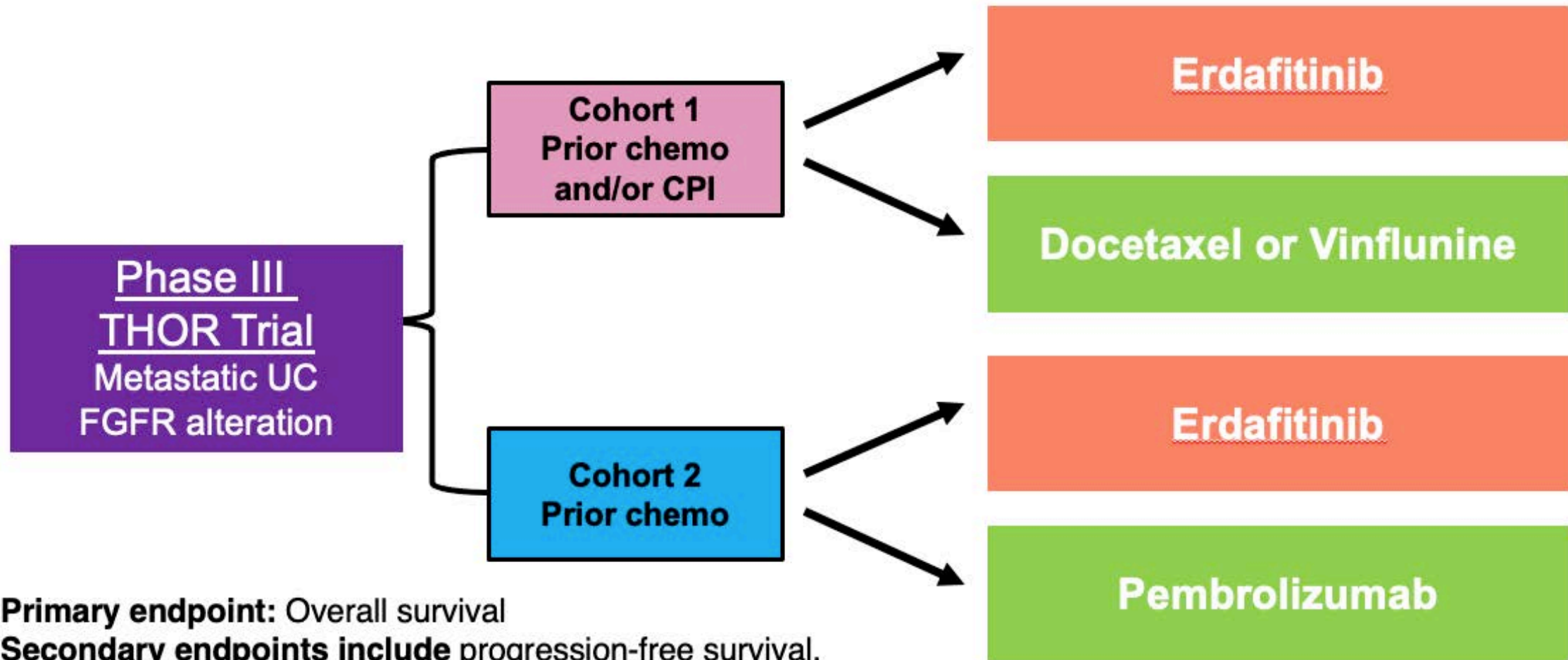
| | |
|------------------|-------------------------------|
| Wild type | 21% (95% CI: 16%, 27%) |
| Mutant | 24% (95% CI: 14%, 39%) |

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

Wang, *European Urology*, 2019

Courtesy of Matthew Galsky, MD.

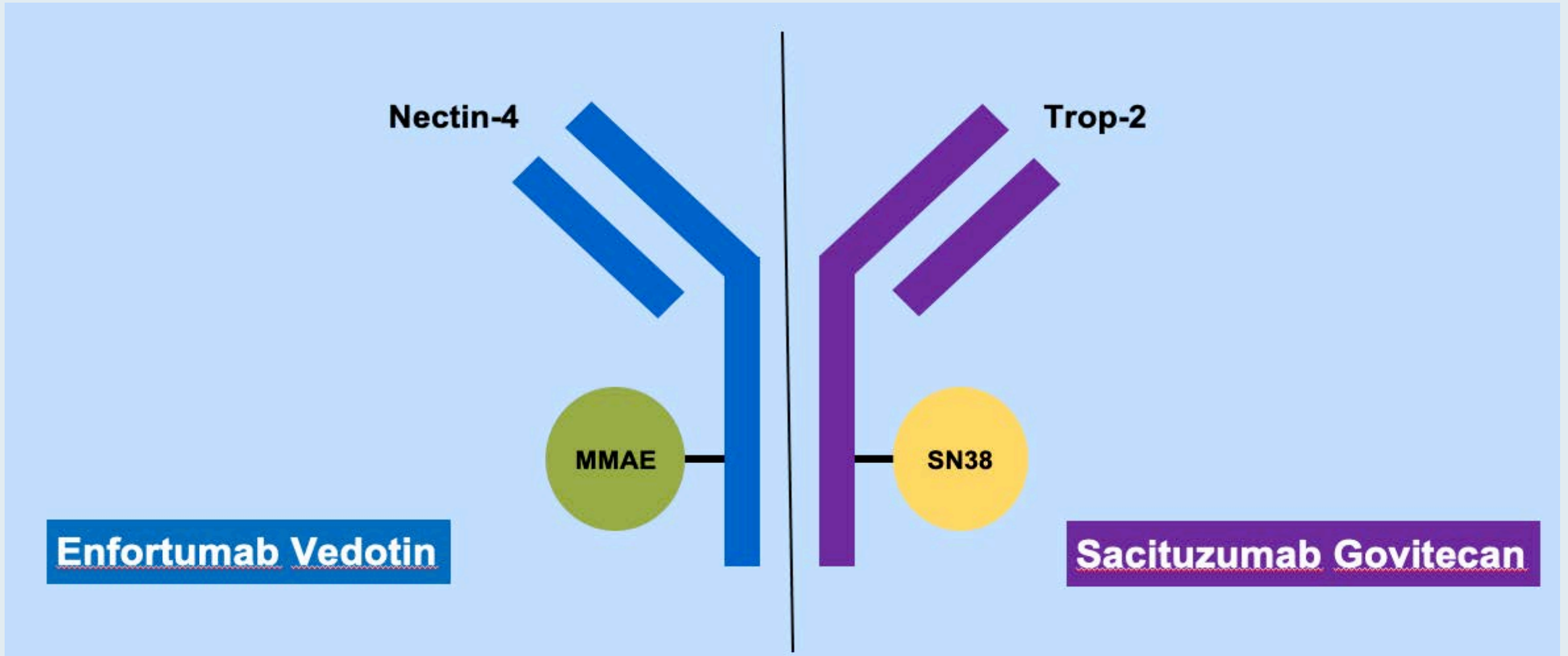
Ongoing Phase III THOR Trial Design



Primary endpoint: Overall survival

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

Antibody-Drug Conjugates in UBC



Courtesy of Matthew Galsky, MD.

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

Scott T. Tagawa, MD, MS¹; Arjun V. Balar, MD²; Daniel P. Petrylak, MD³; Arash Rezazadeh Kalebasty, MD⁴; Yohann Loriot, MD, PhD⁵; Aude Fléchon, MD, PhD⁶; Rohit K. Jain, MD⁷; Neeraj Agarwal, MD⁸; Manojkumar Bupathi, MD, MS⁹; Philippe Barthelemy, MD, PhD¹⁰; Philippe Beuzeboc, MD, PhD¹¹; Phillip Palmbos, MD, PhD¹²; Christos E. Kyriakopoulos, MD¹³; Damien Pouessel, MD, PhD¹⁴; Cora N. Sternberg, MD¹; Quan Hong, MD¹⁵; Trishna Goswami, MD¹⁵; Loretta M. Itri, MD¹⁵; and Petros Grivas, MD, PhD¹⁶

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

Module 3: Chronic Lymphocytic Leukemia and Lymphomas

Relevant Recent Data Sets

Hodgkin Lymphoma

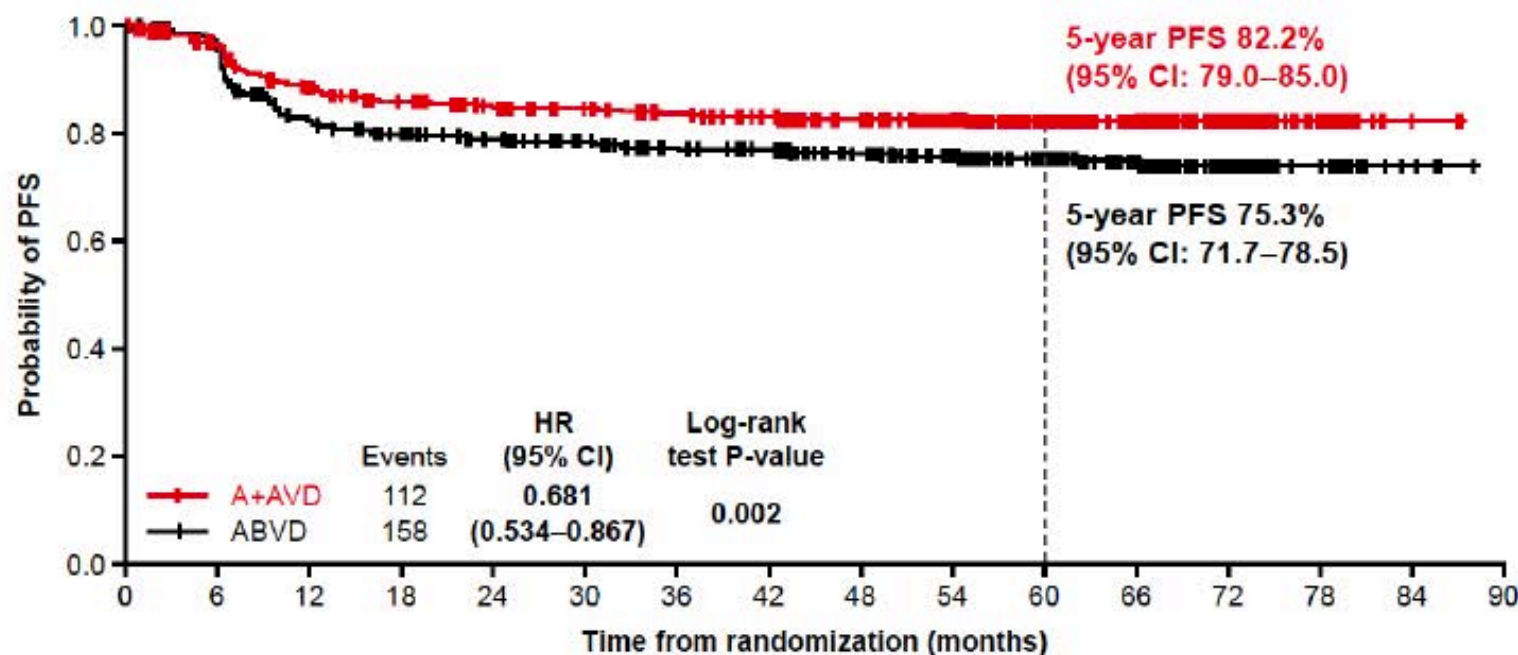
Brentuximab Vedotin with Chemotherapy for Patients with Previously Untreated, Stage III/IV Classical Hodgkin Lymphoma: 5-Year Update of the ECHELON-1 Study

Straus DJ et al.

ASH 2020;Abstract 2973.



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



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

Number of patients at risk

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

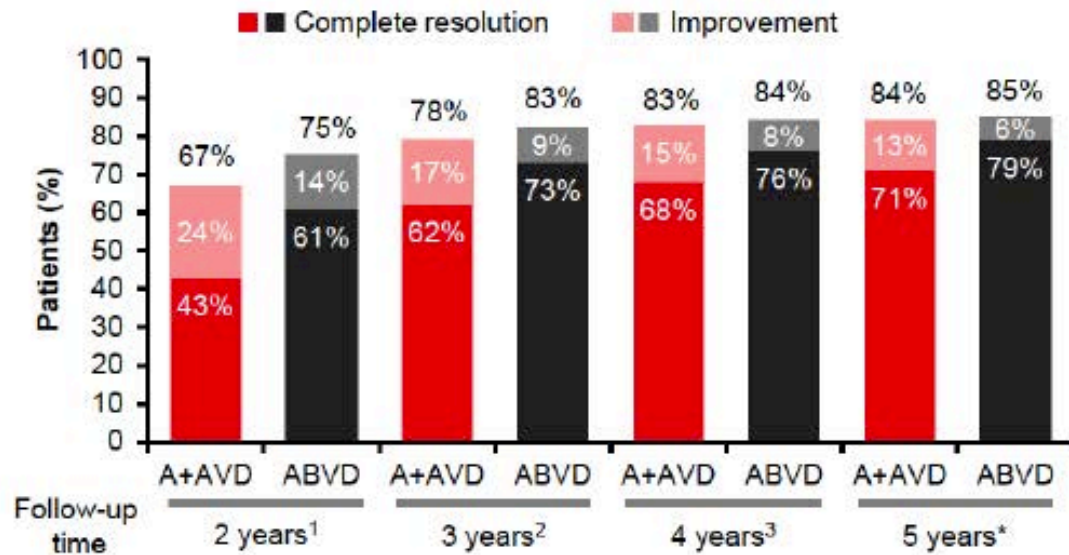
*September 14, 2020 data cut-off.



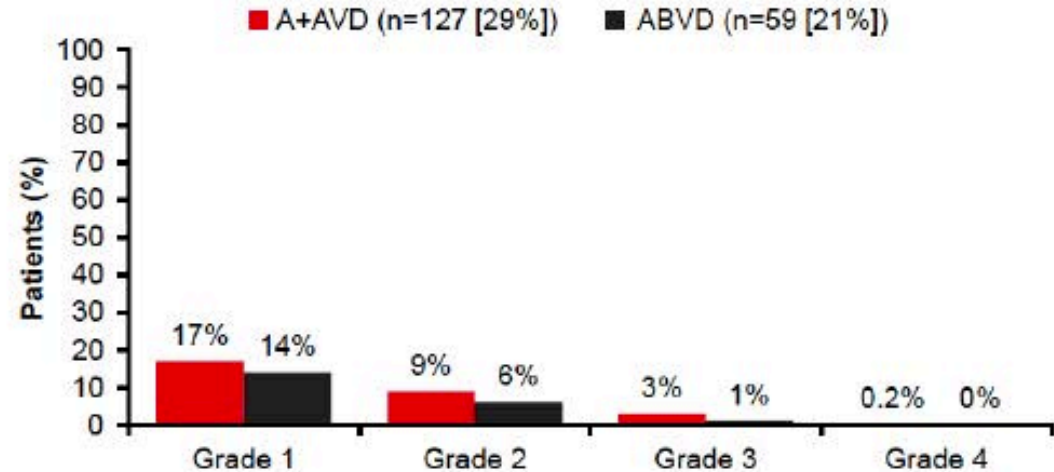
ECHELON-1: PN resolution and improvement

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

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

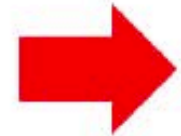


Patients with ongoing PN by grade at last follow-up[†]



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

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

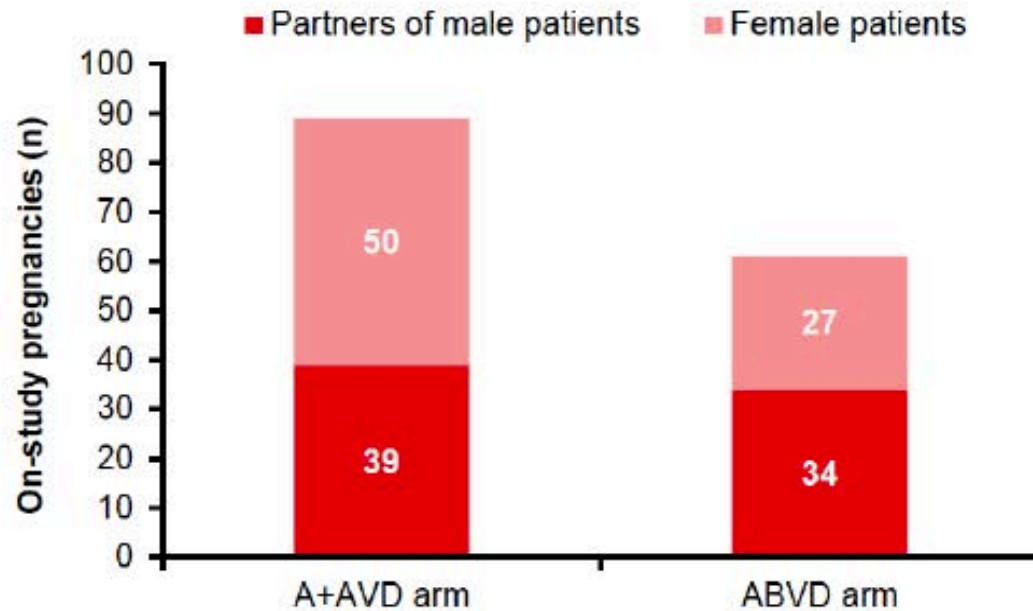




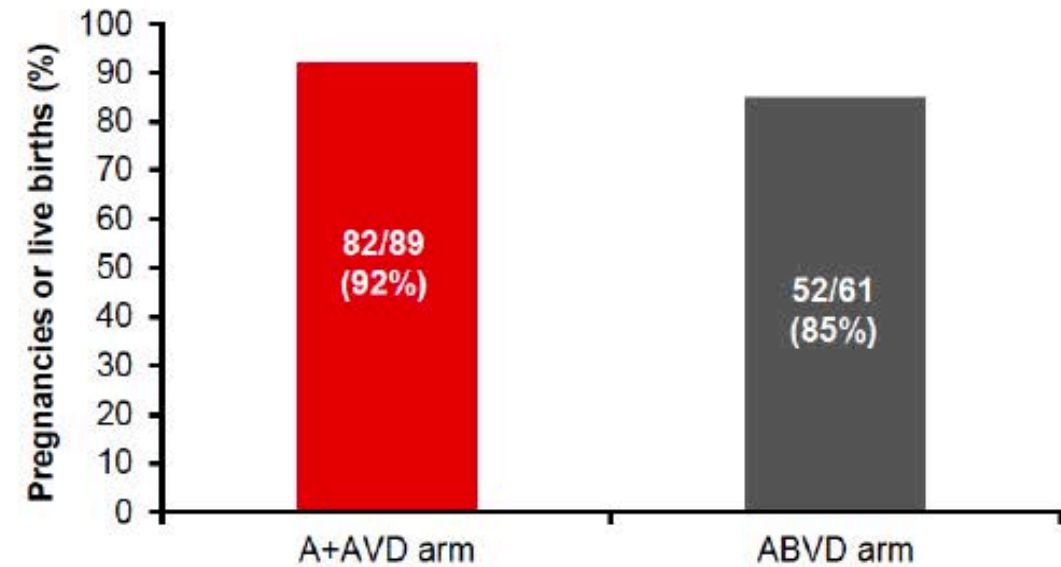
ECHELON-1: Pregnancies

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

On-study pregnancies in patients or their partners



Ongoing pregnancies or live births



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

Anita Kumar, MD¹; Carla Casulo, MD²; Ranjana H. Advani, MD³; Elizabeth Budde, MD⁴; Paul M. Barr, MD²; Connie L. Batlevi, MD, PhD¹; Philip Caron, MD¹; Louis S. Constine, MD²; Savita V. Dandapani, MD⁴; Esther Drill, MD¹; Pamela Drullinsky, MD¹; Jonathan W. Friedberg, MD²; Clare Grieve, BA¹; Audrey Hamilton, MD¹; Paul A. Hamlin, MD¹; Richard T. Hoppe, MD³; Steven M. Horwitz, MD¹; Ashlee Joseph, BA¹; Niloufer Khan, MD¹; Leana Laraque, BA¹; Matthew J. Matasar, MD¹; Alison J. Moskowitz, MD¹; Ariela Noy, MD¹; Maria Lia Palomba, MD¹; Heiko Schöder, MD¹; David J. Straus, MD¹; Shreya Vemuri, BA¹; Joanna Yang, MD⁵; Anas Younes, MD⁶; Andrew D. Zelenetz, MD, PhD¹; Joachim Yahalom, MD¹; and Craig H. Moskowitz, MD⁷

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

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

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

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

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

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

Yasenchak CA et al.
ASH 2020;Abstract 471.

Best Responses per Investigator – Efficacy Evaluable Set

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

Patients who were not efficacy-evaluable included:

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

Summary

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

- **BV monotherapy**

- Active regimen in elderly population
 - Median 78 years of age
 - Median follow up of 54.5 months
 - ORR 92% (95% CI: 74%, 99%)
 - Median OS >6 years
- Notable activity and tolerability in cHL patients unable to tolerate a multi-agent regimen

- **BV combination treatments**

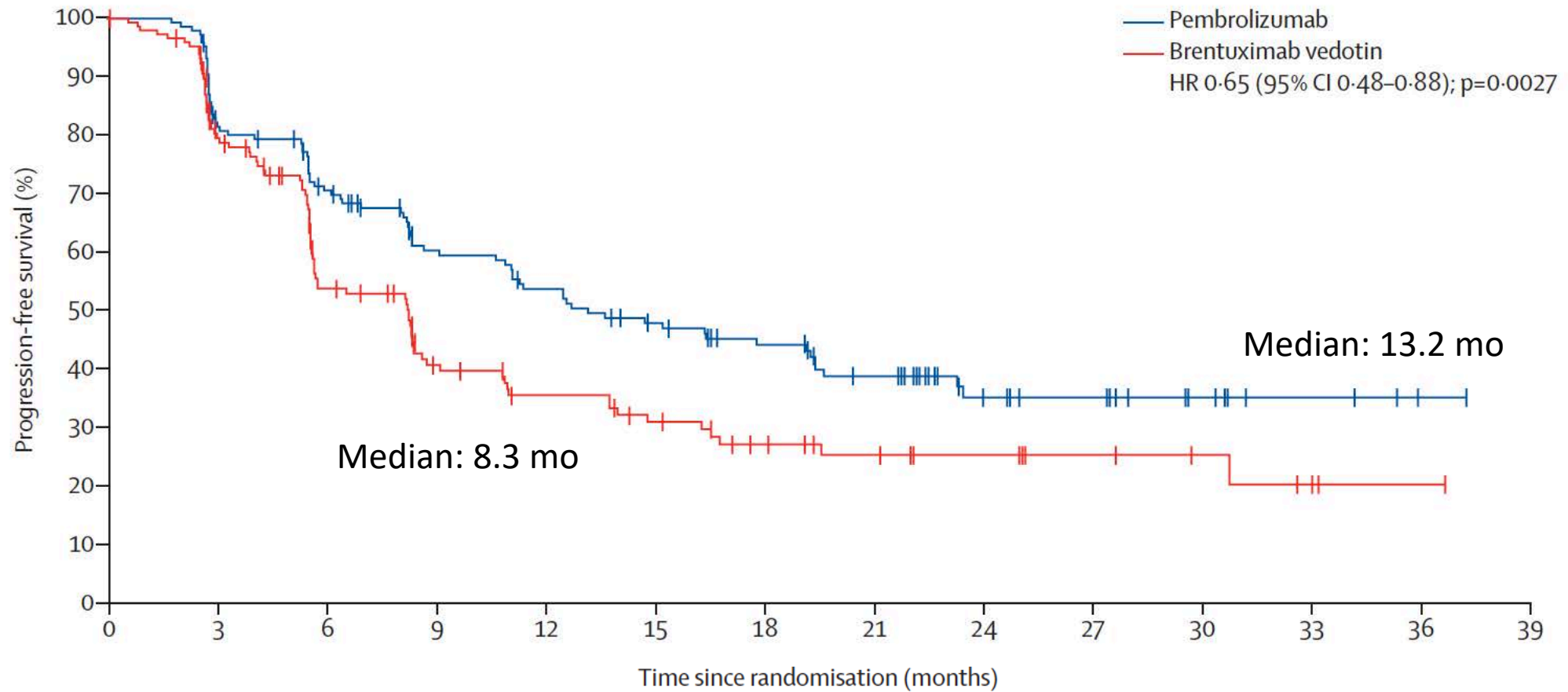
- BV+nivo and BV+DTIC
 - Promising activity (ORR 95%-100%)
 - Favorable safety profile in older adults with previously untreated cHL
- BV+benda associated with multiple acute toxicities
- Additional long-term follow-up is ongoing



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

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

KEYNOTE-204: PFS Primary Endpoint

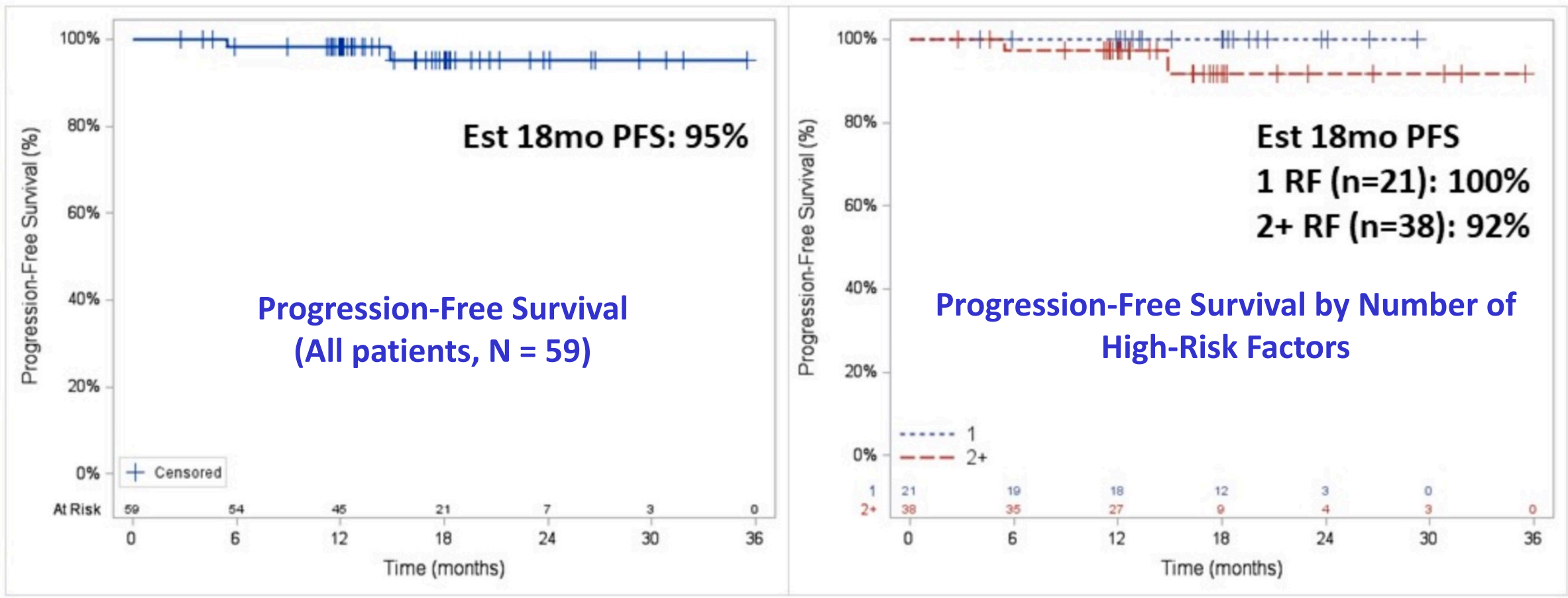


Consolidation with Nivolumab and Brentuximab Vedotin After Autologous Hematopoietic Cell Transplantation in Patients with High-Risk Hodgkin Lymphoma

Herrera AF et al.

ASH 2020;Abstract 472.

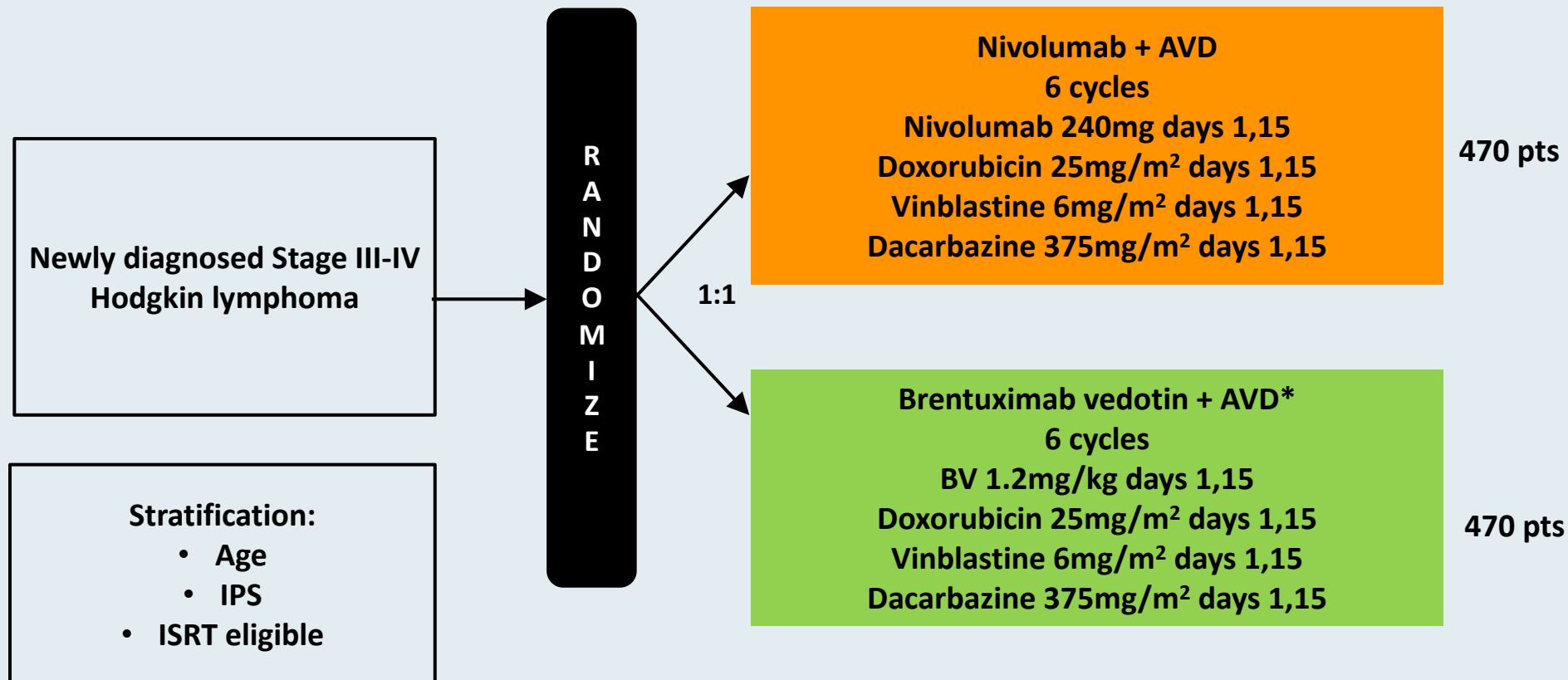
Consolidation with Nivolumab and Brentuximab Vedotin After ASCT: Progression-Free Survival



Summary Conclusions

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

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



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

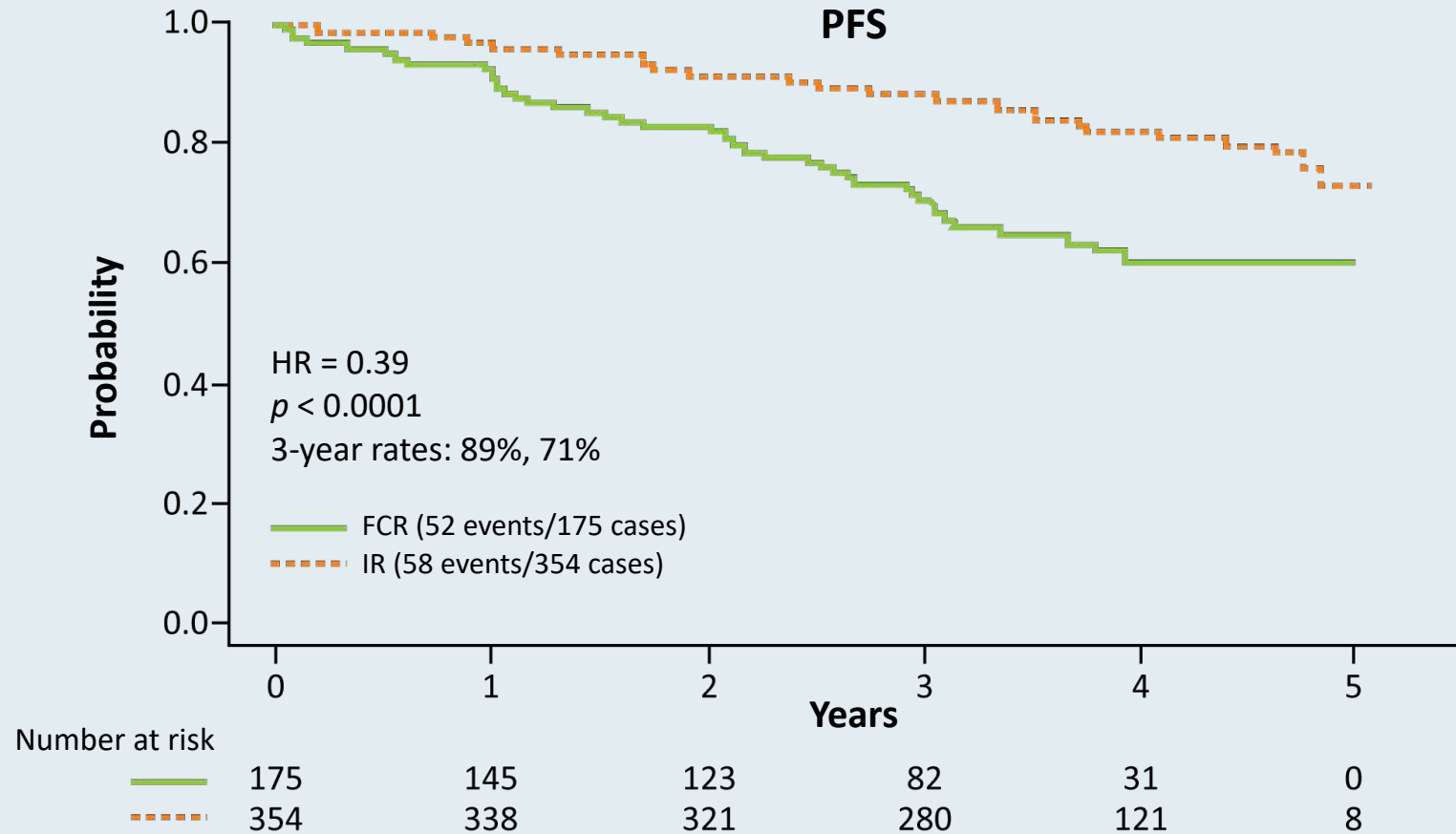
Chronic Lymphocytic Leukemia (CLL)

Ibrutinib and Rituximab Provides Superior Clinical Outcome Compared to FCR in Younger Patients with Chronic Lymphocytic Leukemia (CLL): Extended Follow-Up from the E1912 Trial.

Shanafelt TD et al.

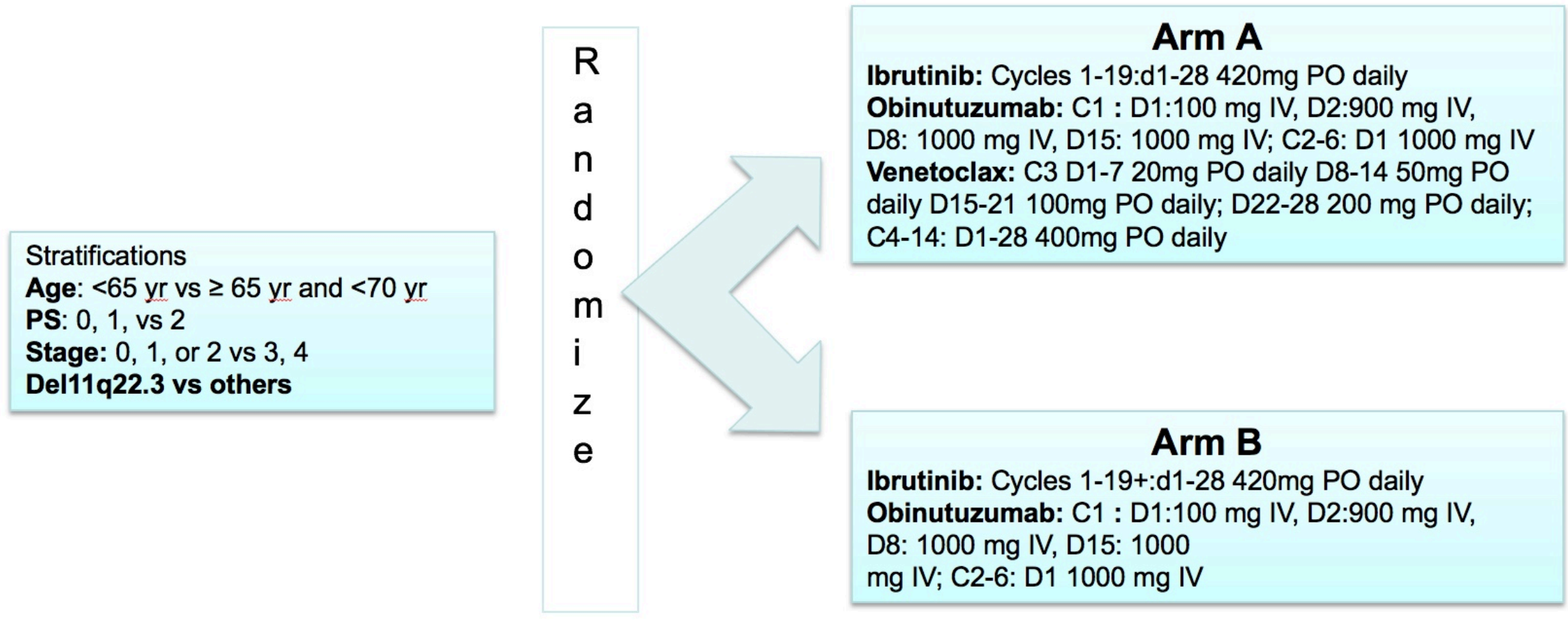
ASH 2019;Abstract 33.

ECOG-ACRIN E1912 Extended Follow-Up: Up-Front IR Compared to FCR for Younger Patients with CLL



- Grade ≥ 3 treatment-related AEs were reported in 70% of patients receiving IR and 80% of patients receiving FCR (odds ratio = 0.56; $p = 0.013$).
- Among the 95 patients who discontinued ibrutinib, the most common cause was AE or complication.

Phase III EA9161 Schema



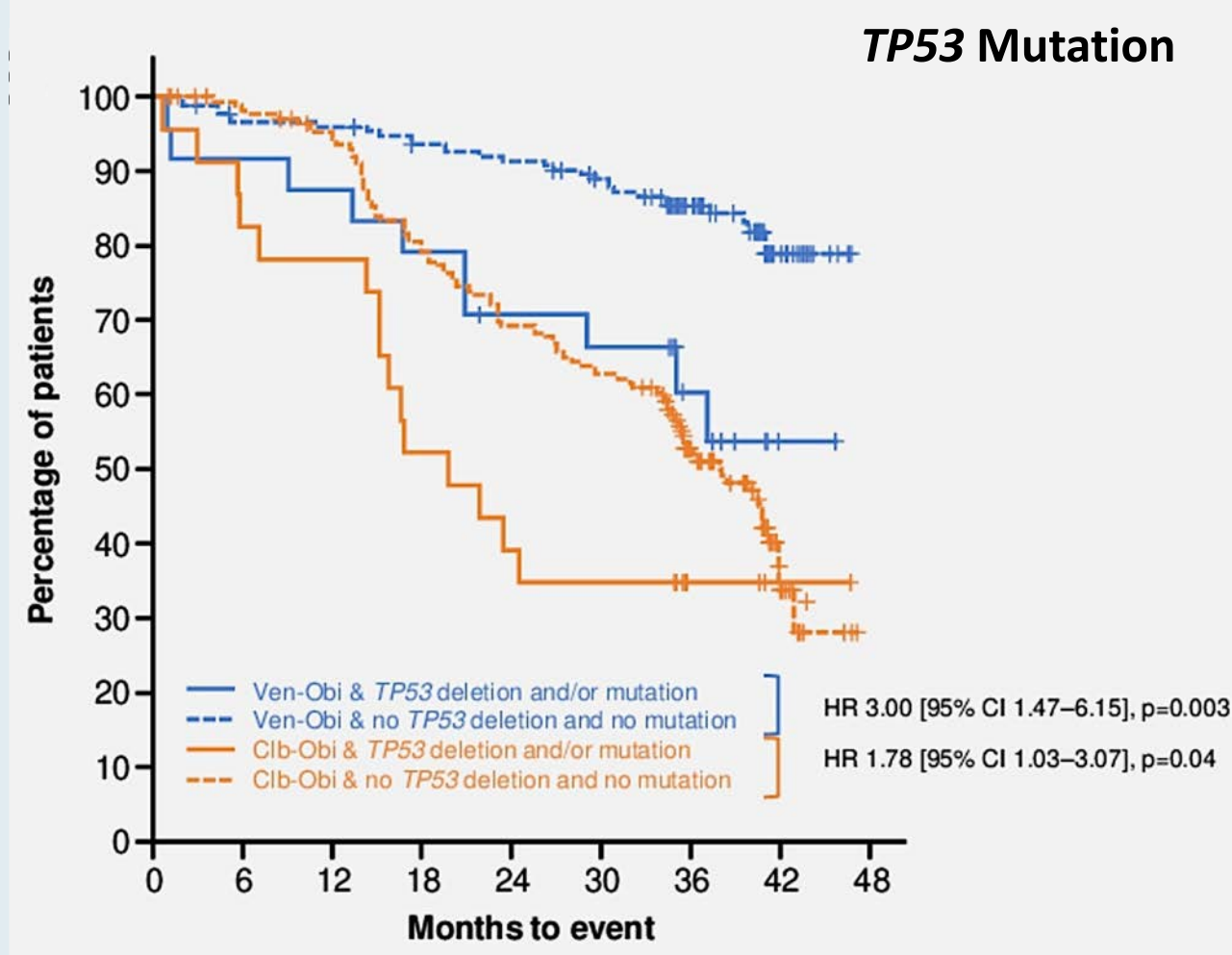
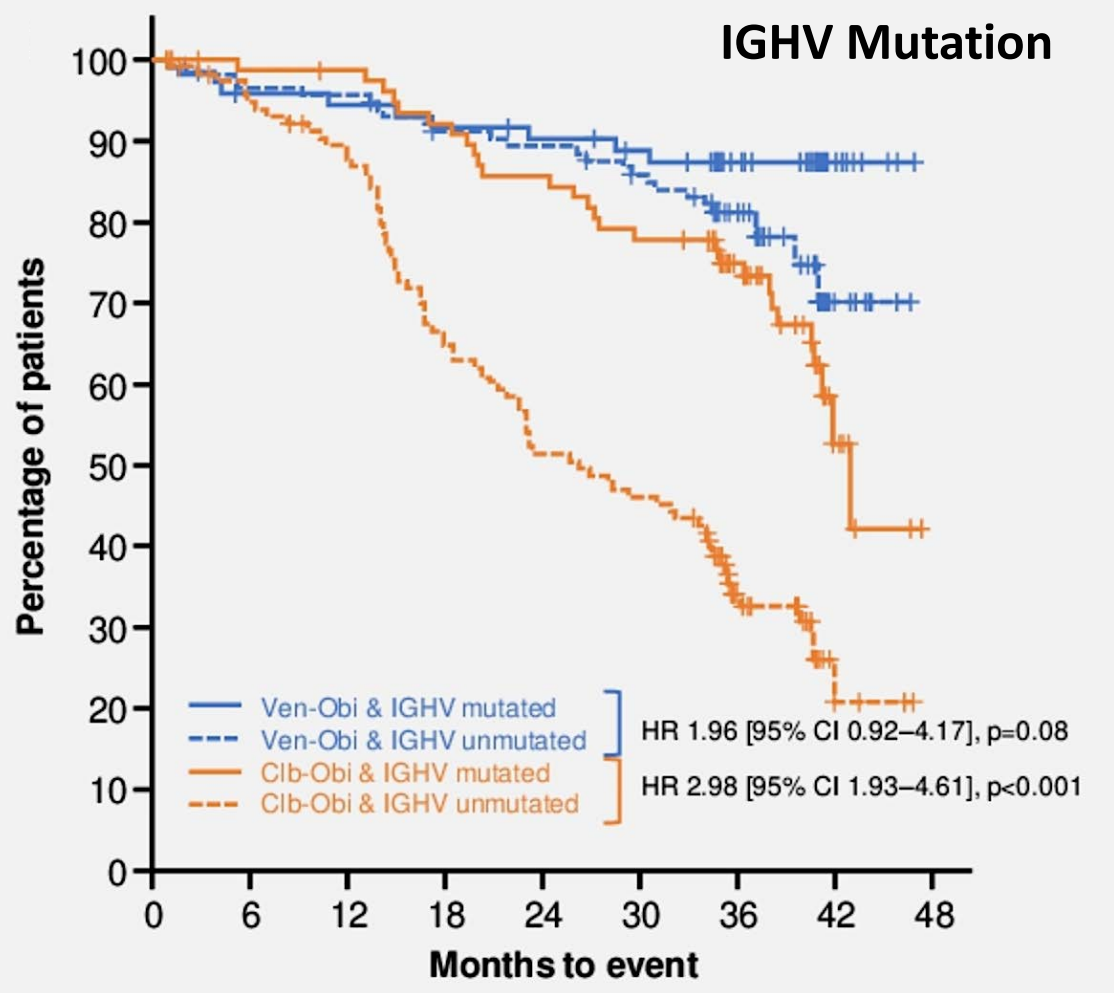


Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial

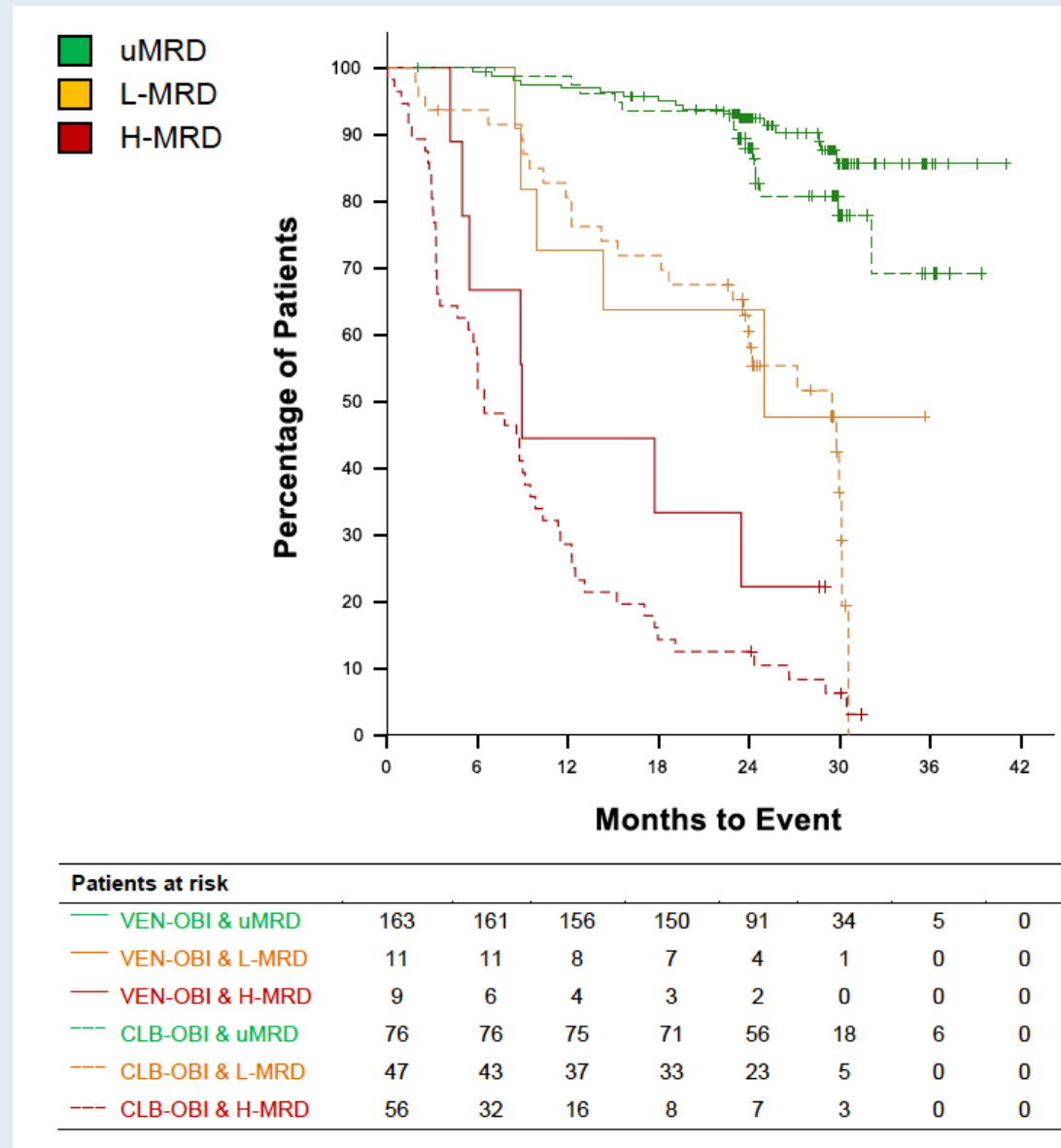
Othman Al-Sawaf, Can Zhang, Maneesh Tandon, Arijit Sinha, Anna-Maria Fink, Sandra Robrecht, Olga Samoylova, Anna M Liberati, Javier Pinilla-Ibarz, Stephen Opat, Liliya Sivcheva, Katell Le Dû, Laura M Fogliatto, Carsten U Niemann, Robert Weinkove, Sue Robinson, Thomas J Kipps, Eugen Tausch, William Schary,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

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

CLL14: PFS by IGHV and TP53 Mutation Status



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



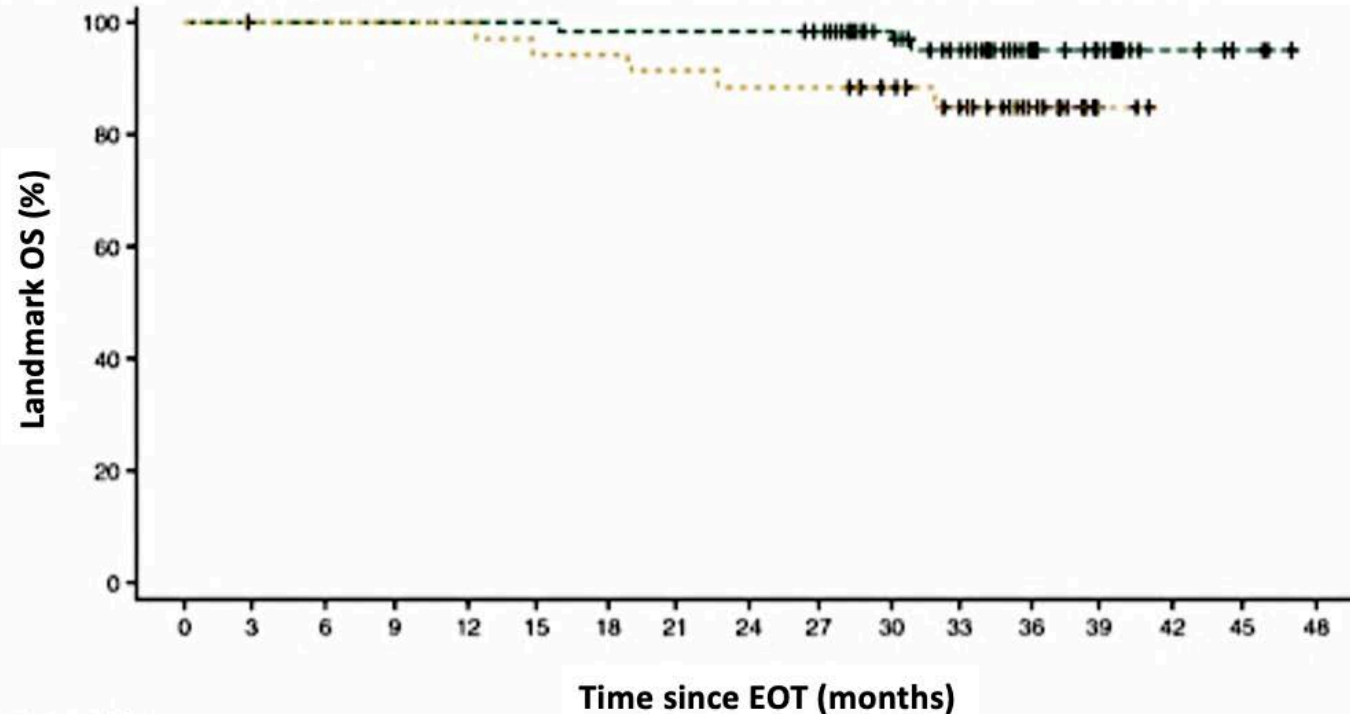
Five-Year Analysis of Murano Study Demonstrates Enduring Undetectable Minimal Residual Disease (uMRD) in a Subset of Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Patients (Pts) Following Fixed-Duration Venetoclax-Rituximab (VenR) Therapy (Tx)

Kater AP et al.

ASH 2020;Abstract 125.

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

Landmark OS by PB MRD status in pts that completed Ven Tx without PD.



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

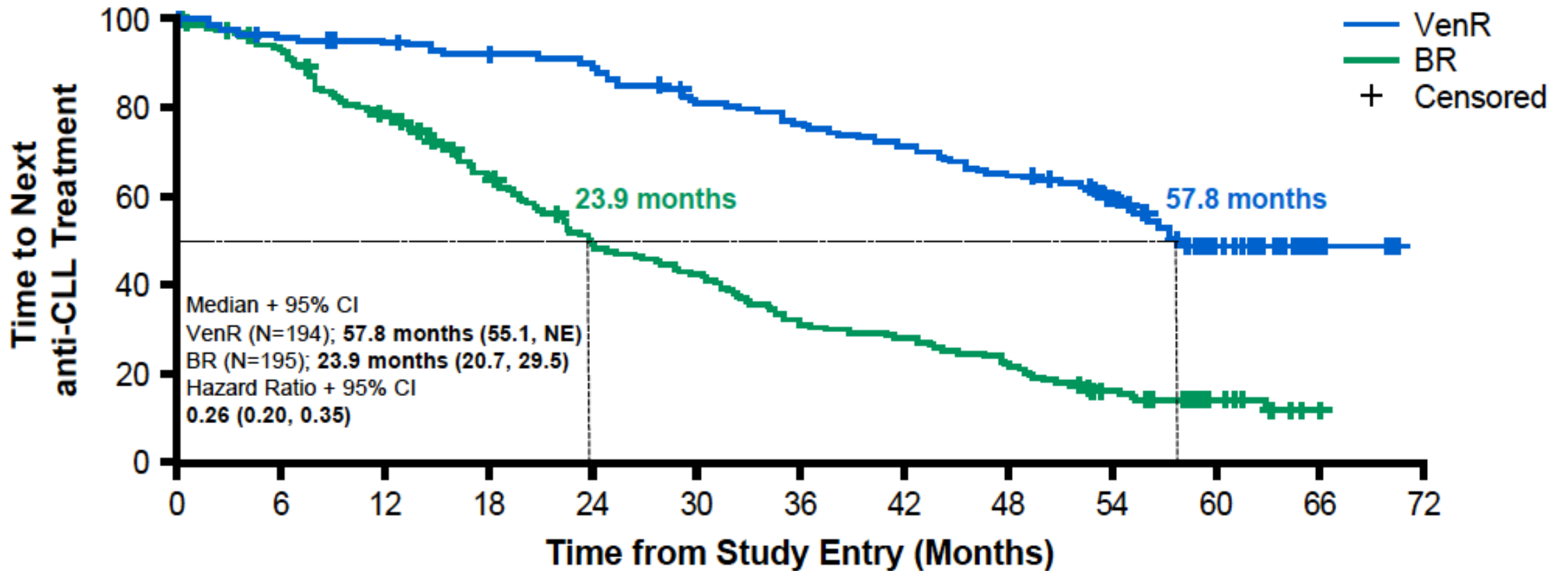
EOT, end of treatment; MRD, minimal residual disease; OS, overall survival; PB, peripheral blood; PD, progressive disease; pts, patients; Tx, therapy; uMRD, undetectable minimal residual disease; Ven, venetoclax.

Efficacy of Subsequent Novel Targeted Therapies, Including Repeated Venetoclax-Rituximab (VenR), in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Previously Treated with Fixed-Duration VenR in the MURANO Study

Harrup R et al.

ASH 2020;Abstract 3139.

MURANO: TTNT with VenR versus BR



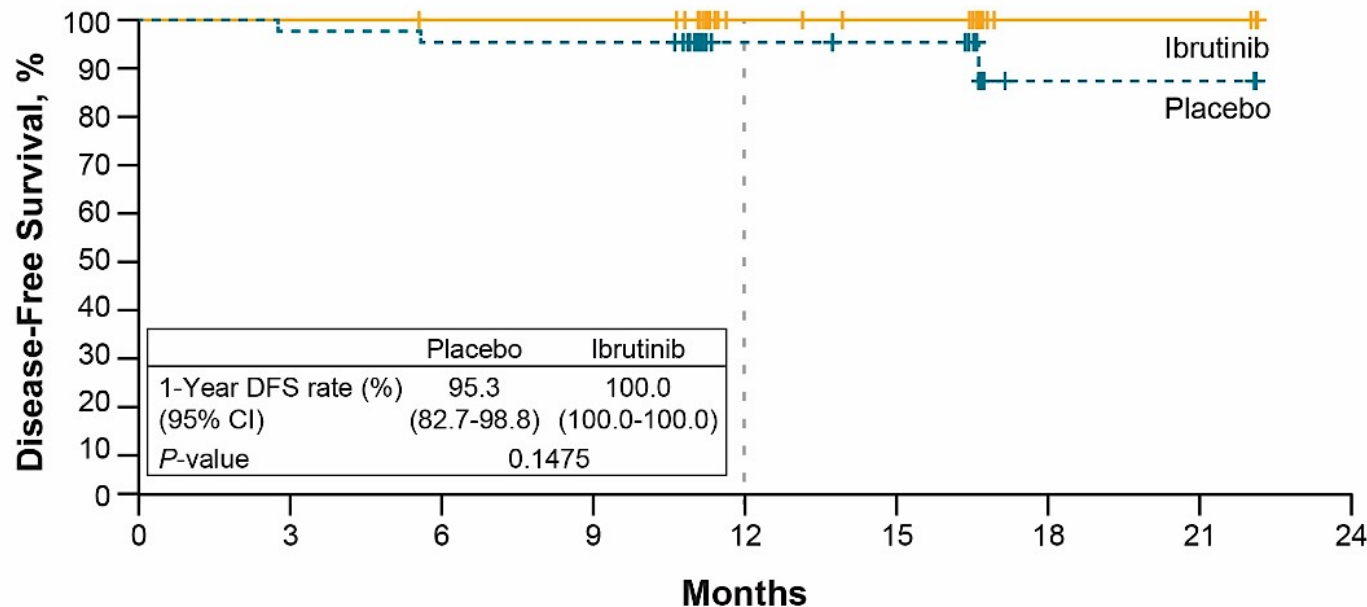
Ibrutinib (Ibr) plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): 1-Year Disease-Free Survival (DFS) Results from the MRD Cohort of the Phase 2 CAPTIVATE Study Trial

Wierda WG et al.

ASH 2020;Abstract 123.

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

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



Patients at Risk

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

^aThe 3 DFS events in placebo arm were disease progression in 2 patients and MRD relapse in 1 patient.

30 month PFS Rate:

Confirmed uMRD:

- 95.3% placebo
- 100% ibrutinib

Without confirmed uMRD:

- 95.2% ibrutinib
- 96.7% ibr/ven

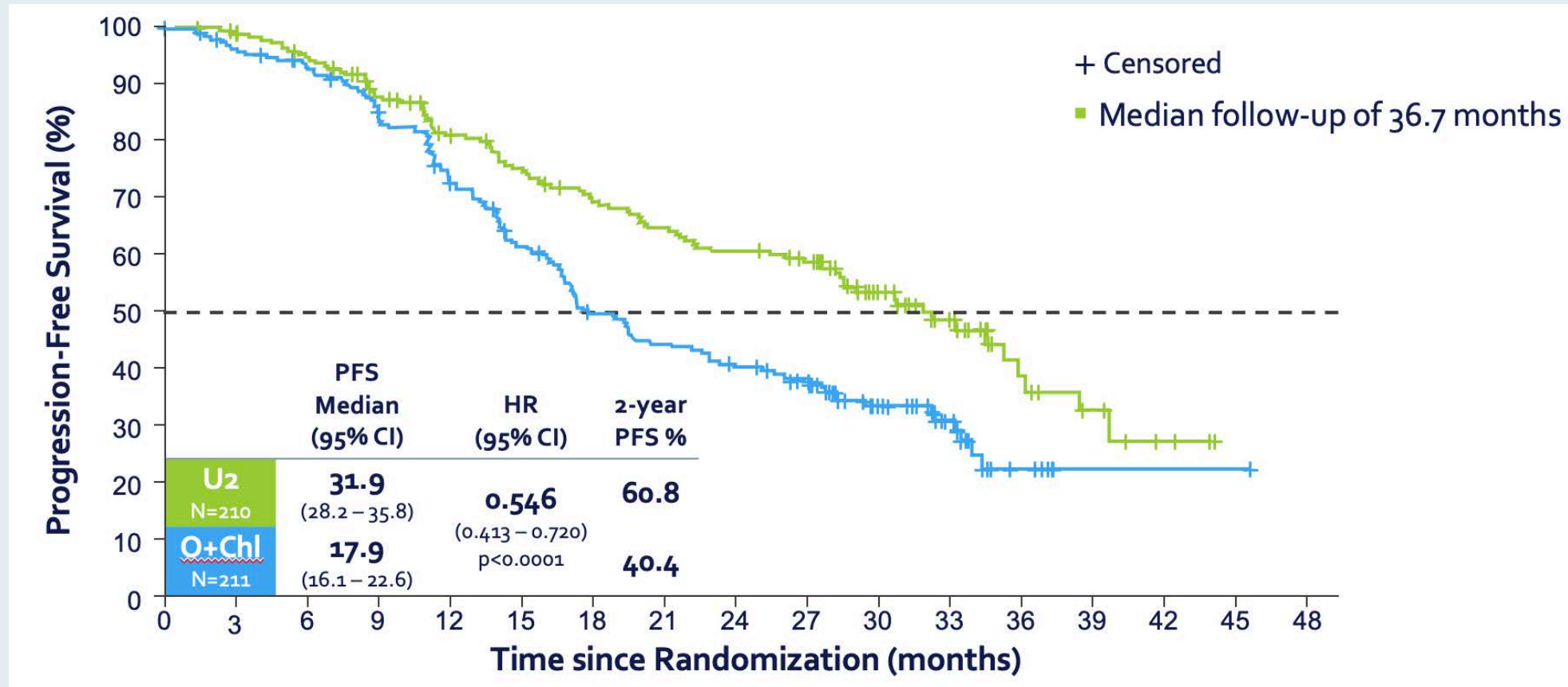
AEs were primarily grade 1/2 and mostly occurred in early cycles of Ibr + Ven, with modest differences by randomized treatment arm.

Umbralisib plus Ublituximab (U2) Is Superior to Obinutuzumab plus Chlorambucil (O+Chl) in Patients with Treatment Naïve (TN) and Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL): Results from the Phase 3 Unity-CLL Study

Gribben JG et al.

ASH 2020;Abstract 542.

UNITY-CLL Phase III Trial of Umbralisib with Ublituximab (U2) versus Obinutuzumab with Chlorambucil in CLL



- PFS in treatment-naïve patients (U2 vs O+Chl): 38.5 vs 26.1 mo
- PFS in R/R patients (U2 vs O+Chl): 19.5 vs 12.9 mo
- Grade 3+ colitis in 3.4%, transaminitis Grade 3+ in 8.3%, Grade 3+ pneumonitis in 2.9%



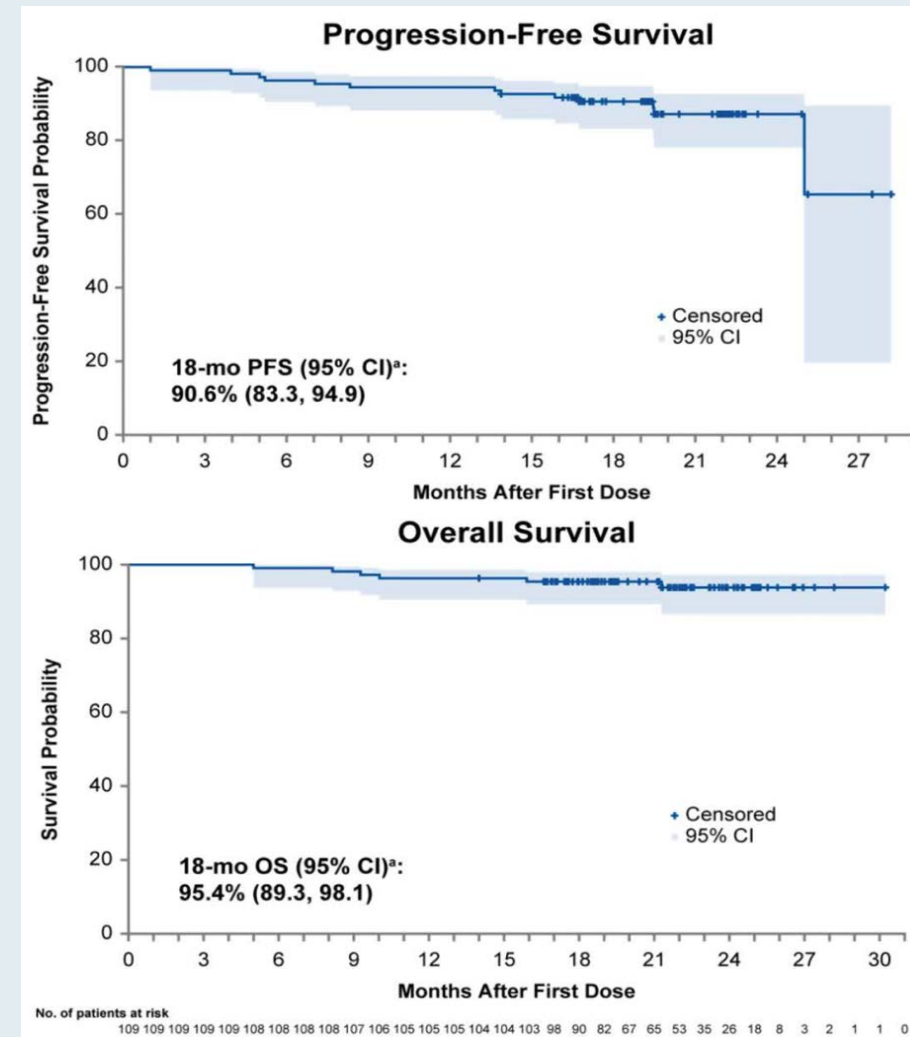
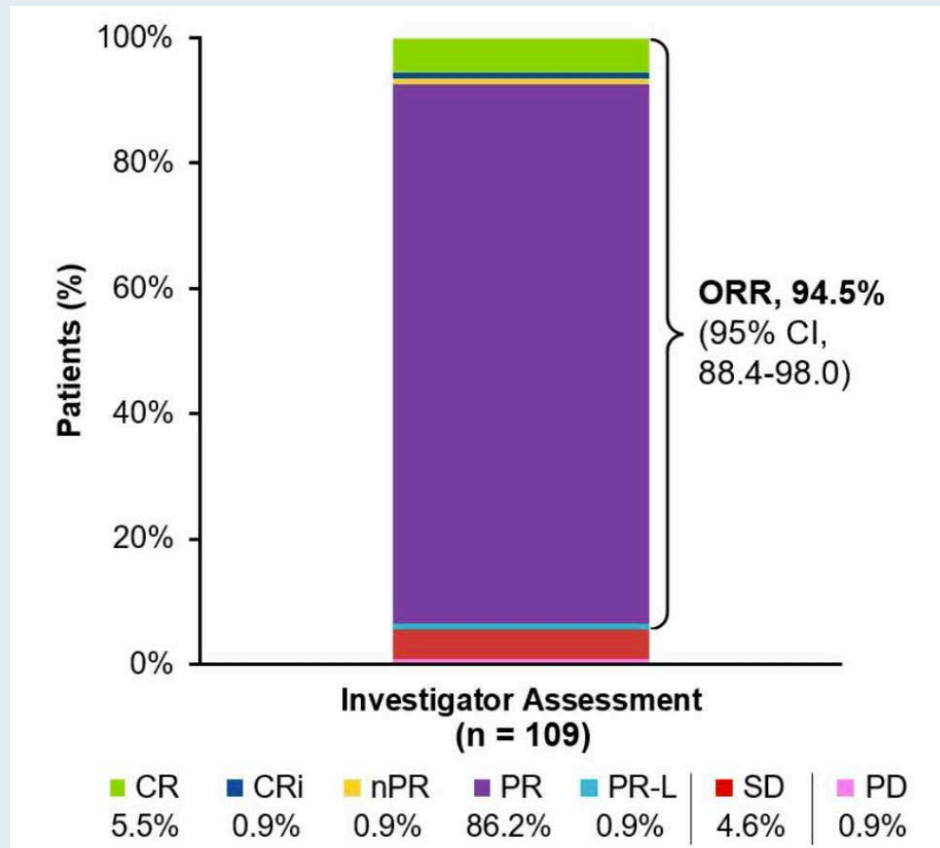
Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE-TN): a randomised, controlled, phase 3 trial

Jeff P Sharman, Miklos Egyed, Wojciech Jurczak, Alan Skarbnik, John M Pagel, Ian W Flinn, Manali Kamdar, Talha Munir, Renata Walewska, Gillian Corbett, Laura Maria Fogliatto, Yair Herishanu, Versha Banerji, Steven Coutre, George Follows, Patricia Walker, Karin Karlsson, Paolo Ghia, Ann Janssens, Florence Cymbalista, Jennifer A Woyach, Gilles Salles, William G Wierda, Raquel Izumi, Veerendra Munuglavada, Priti Patel, Min Hui Wang, Sofia Wong, John C Byrd

Lancet 2020;395(10232):1278-91.

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

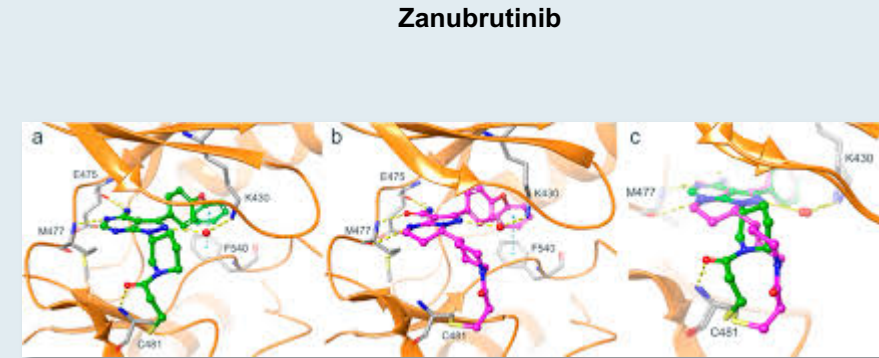
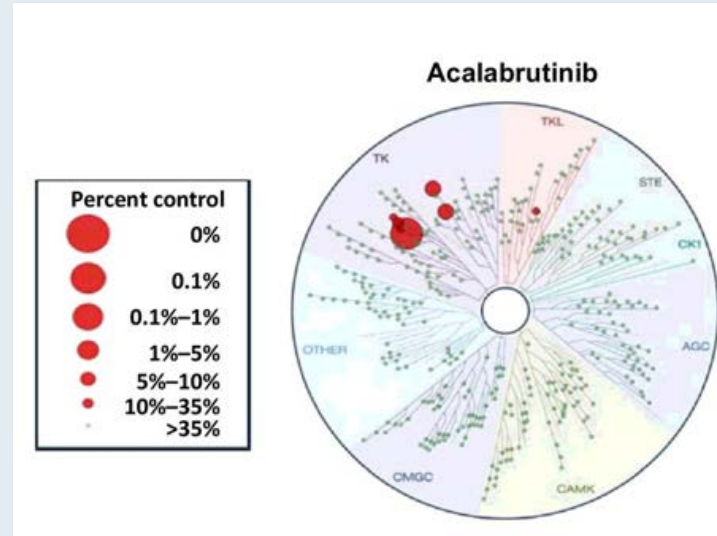
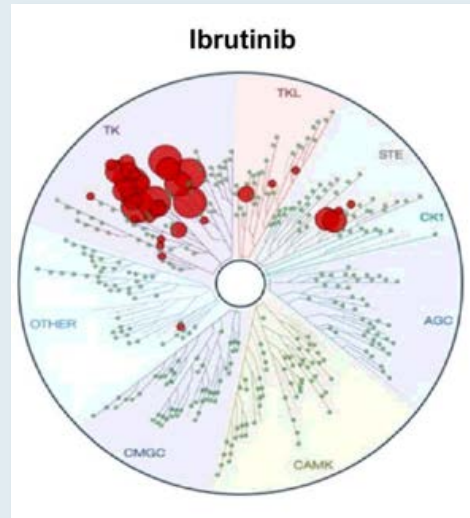
Best Overall Response



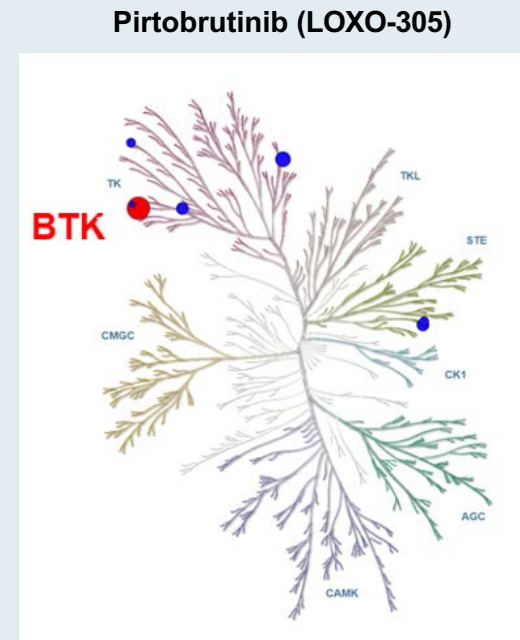
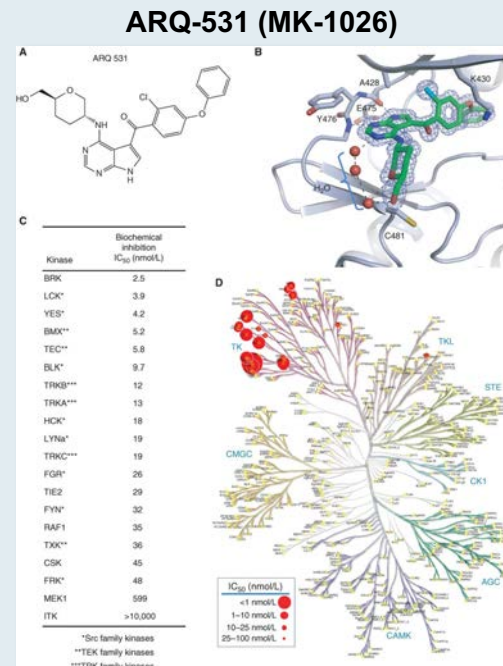
Median follow-up: 21.9 months (range, 5.0-30.2)

Overview of BTK Inhibitors in CLL

Irreversible



Reversible



Courtesy of Matthew S Davids, MD, MMSc

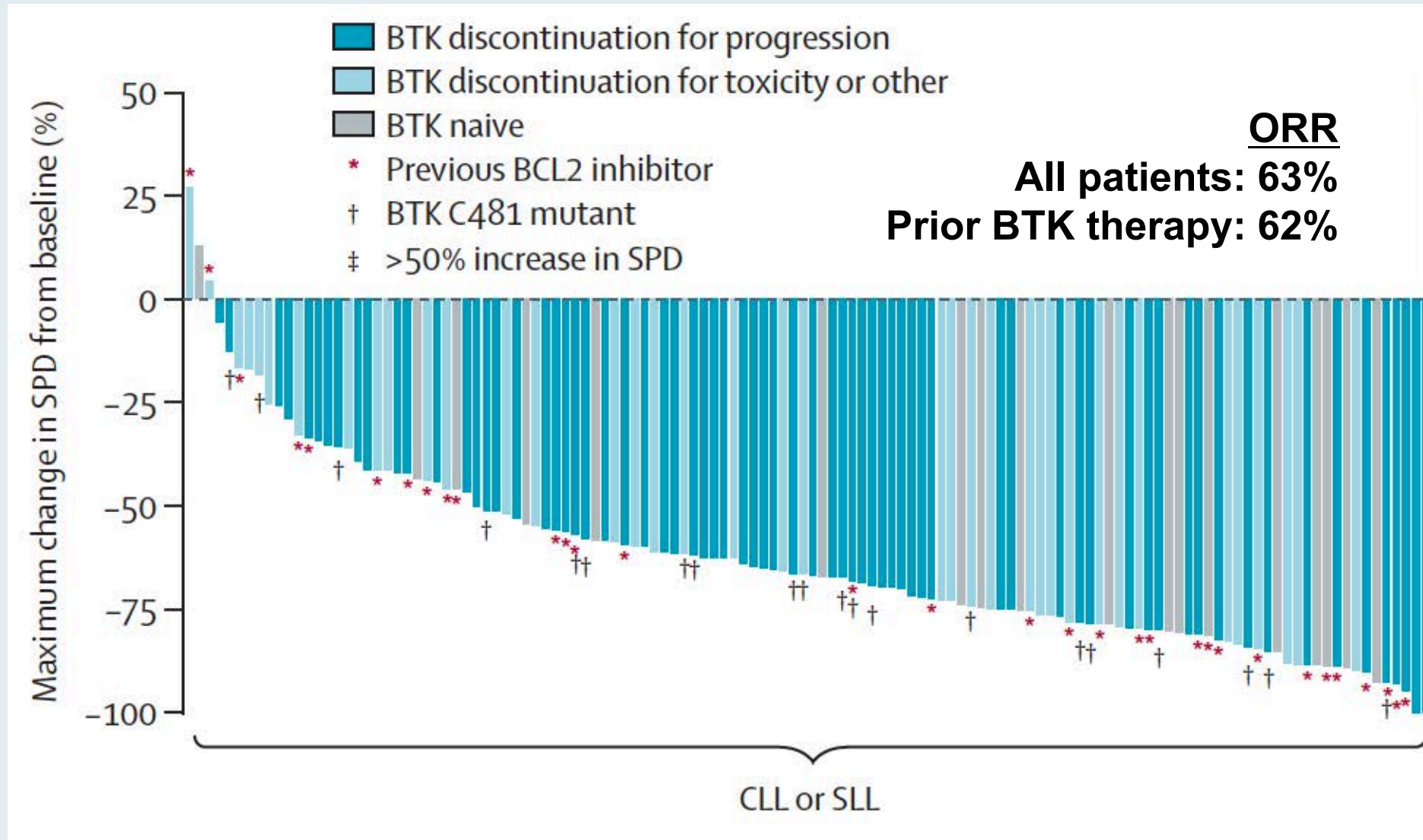


Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study

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

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

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

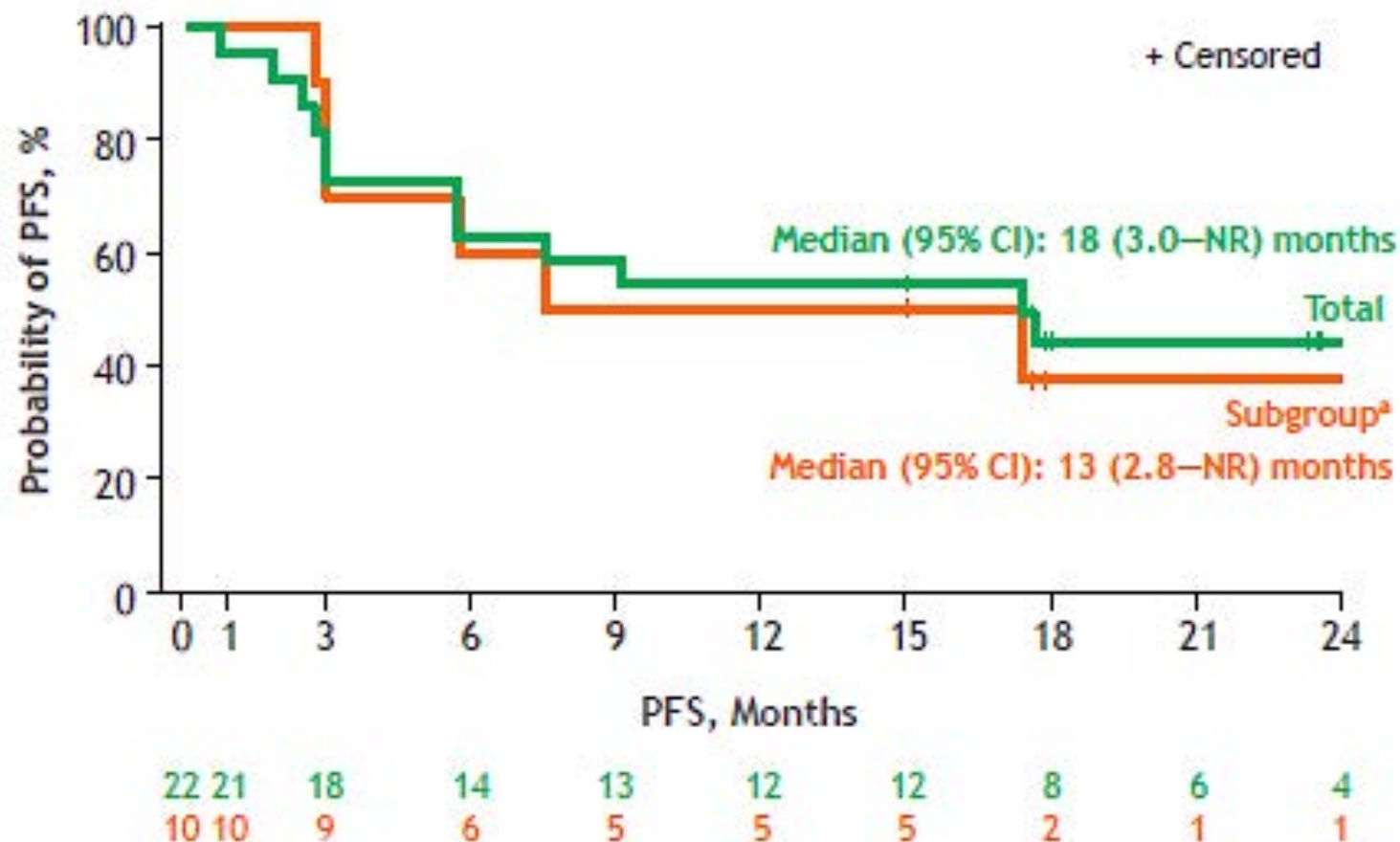


Updated Follow-Up of Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Treated with Lisocabtagene Maraleucel in the Phase 1 Monotherapy Cohort of Transcend CLL 004, Including High-Risk and Ibrutinib-Treated Patients

Siddiqi T et al.

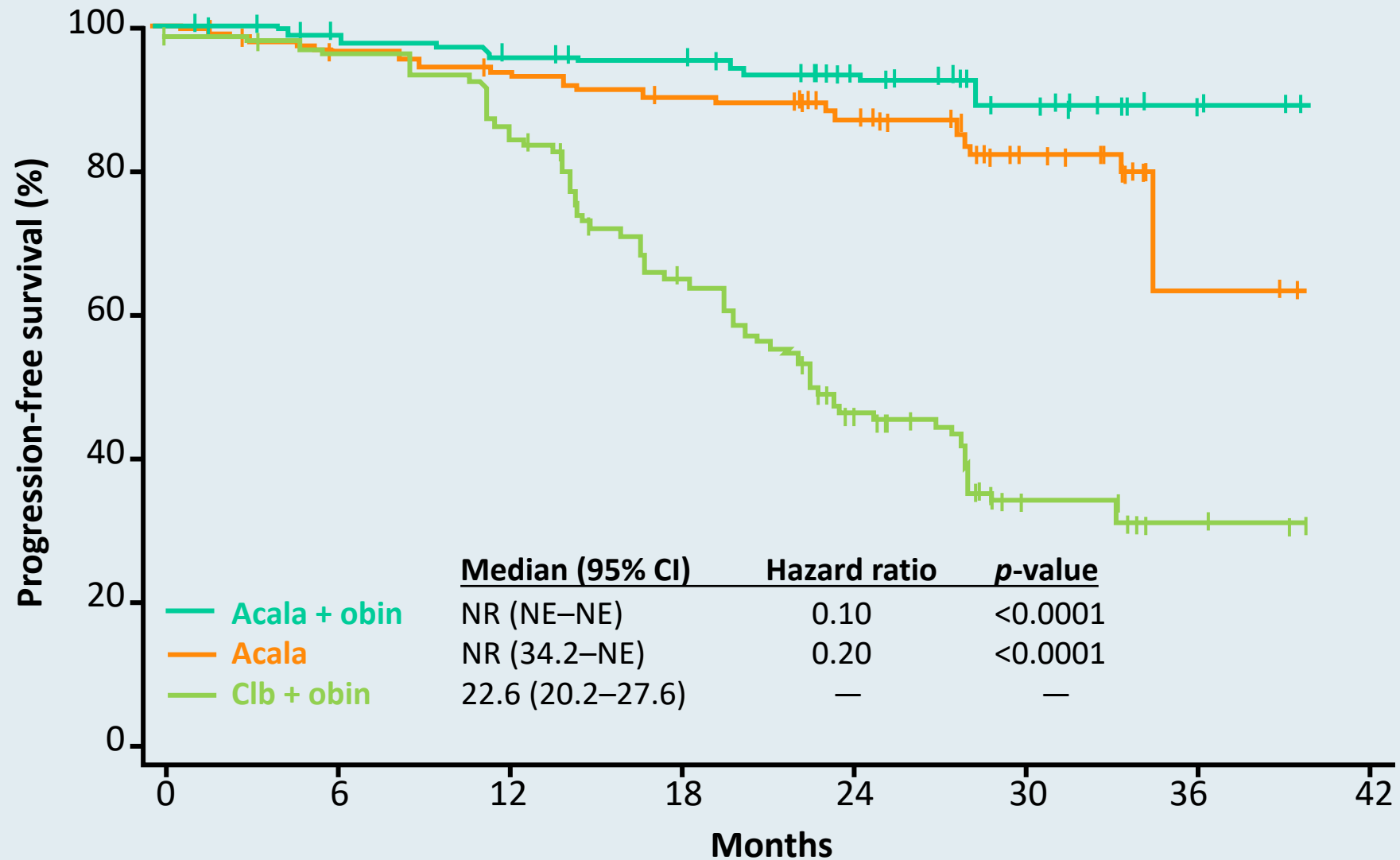
ASH 2020;Abstract 546.

TRANSCEND CLL 04: Liso-cel Monotherapy Cohort



- ORR/CR = 82%/68%
- Median PFS 13 mo and DOR 50% at 12 mo
- Gr 3 CRS= 9% and NE 22% (No Grade 4/5)
- 4 of 6 progressions due to RT

ELEVATE-TN: PFS (IRC)



Mantle Cell Lymphoma (MCL)

Pooled Analysis of Ibrutinib for R/R MCL: Median 41 Months Follow-Up

(Phase II PCYC-1104 and SPARK and Phase III RAY Studies)

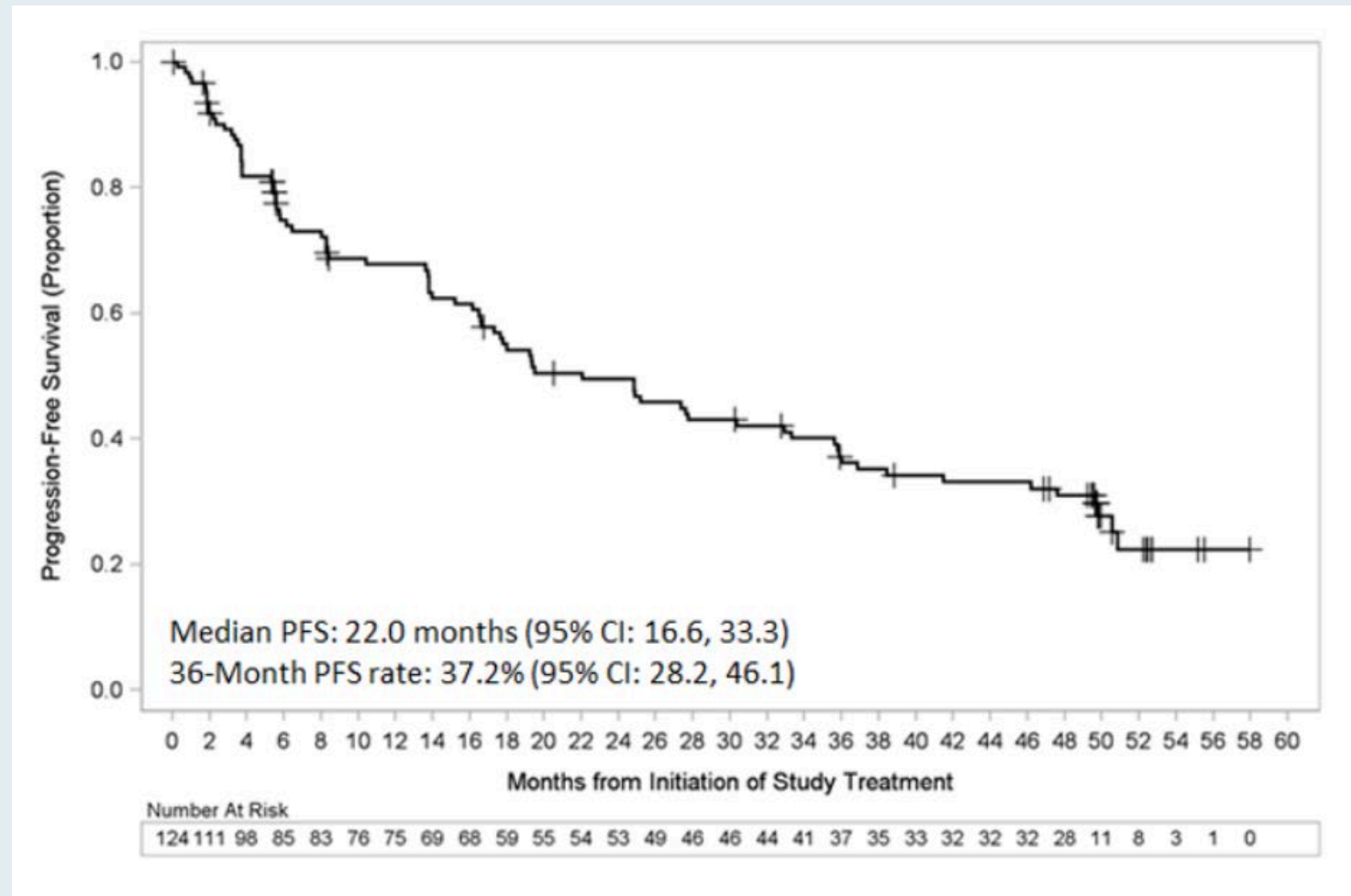
| Endpoint | Overall (N = 370) | Prior lines of therapy | |
|---|------------------------|------------------------|------------------------|
| | | 1 (n = 99) | >1 (n = 271) |
| Median PFS | 12.5 mo | 25.4 mo | 10.3 mo |
| Median PFS by best response CR (n = 102) PR (n = 156) | 67.7 mo 12.6 mo | 68.5 mo 24.2 mo | 67.7 mo 10.5 mo |
| Median OS | 26.7 mo | 61.6 mo | 22.5 mo |
| Median OS by best response CR (n = 102) PR (n = 156) | Not reached 23.6 mo | Not reached 36.0 mo | Not reached 22.6 mo |
| ORR, CR | 70%, 28% | 78%, 37% | 67%, 24% |

Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Long-Term Efficacy and Safety Results from a Phase 2 Study

Wang M et al.

ASH 2020;Abstract 2040.

ACE-LY-004 Long-Term Follow-Up: Progression-Free Survival



The adverse event profile was largely unchanged with an additional year of follow-up.

Efficacy of Zanubrutinib for MCL

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

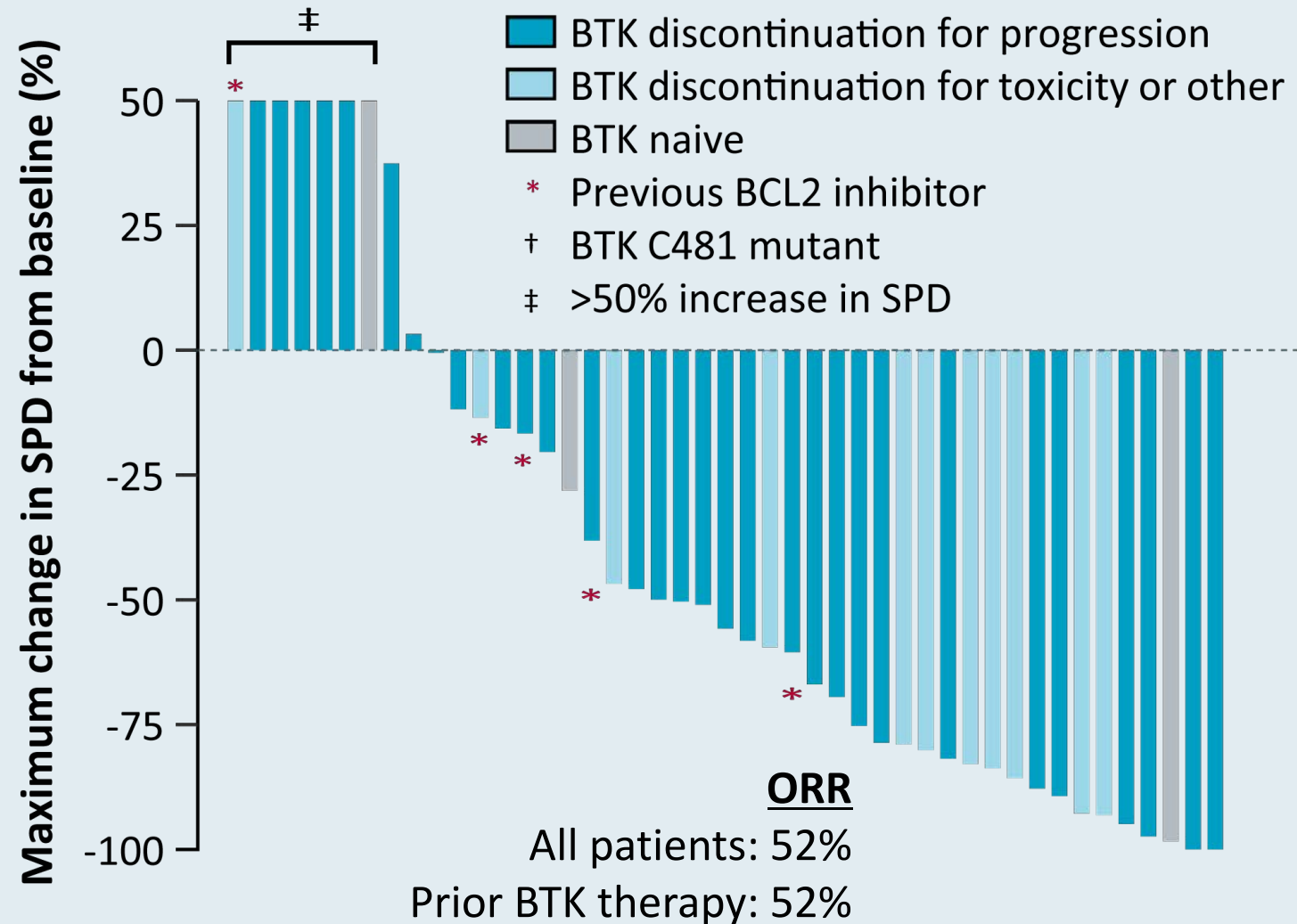


Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study

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

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

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



Venetoclax Monotherapy for BTK Inhibitor-Resistant MCL: Results Summary

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

No cases of clinical TLS were observed.

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

Phillips TJ et al.

ASCO 2021;Abstract 7505.

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

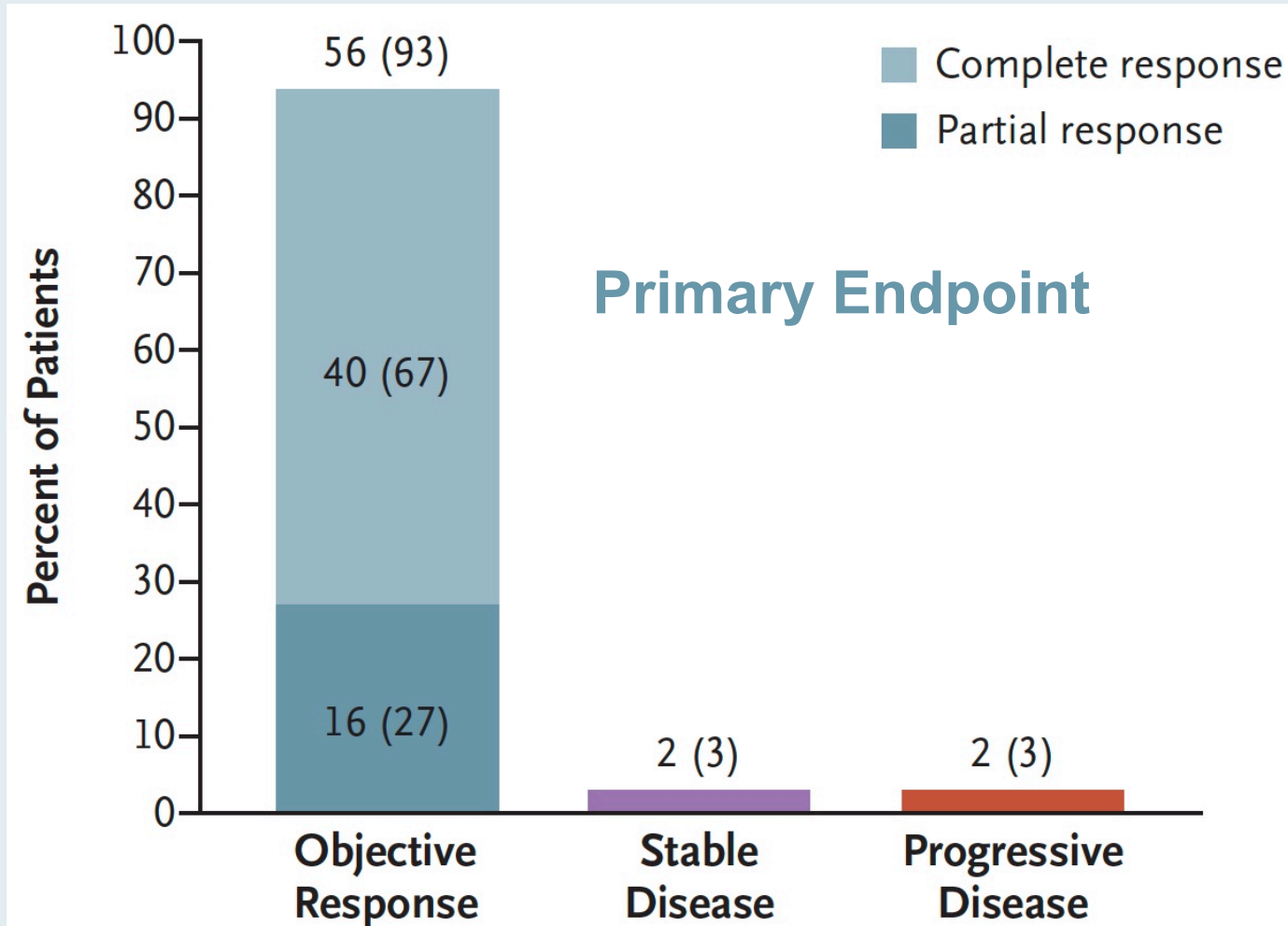
ORIGINAL ARTICLE

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

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

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

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

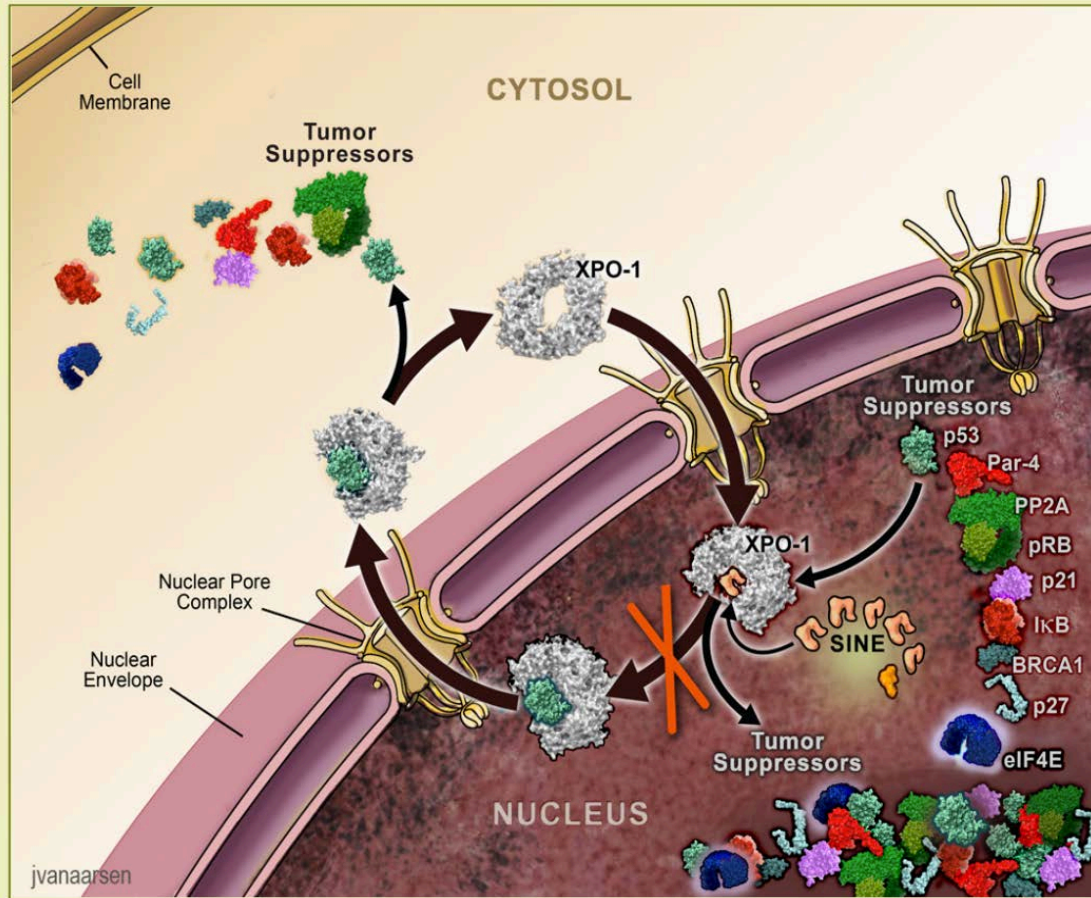


| Estimated 12-month survival rate | |
|----------------------------------|-----|
| Median PFS | 61% |
| Median OS | 83% |

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

Diffuse Large B-Cell Lymphoma (DLBCL)

Selinexor has a novel mechanism of action: XPO-1 inhibitor



XPO1 over-expressed in DLBCL and correlates with poor prognosis

Induces nuclear accumulation of tumor suppressors including p53, p73, IκB and FOXO

Decreases production of oncoproteins including c-MYC, BCL2, BCL6 and BCL-XL

Kalakonda. *Lancet Heme* 2020.

Courtesy of Ann S LaCasce, MD, MMSc

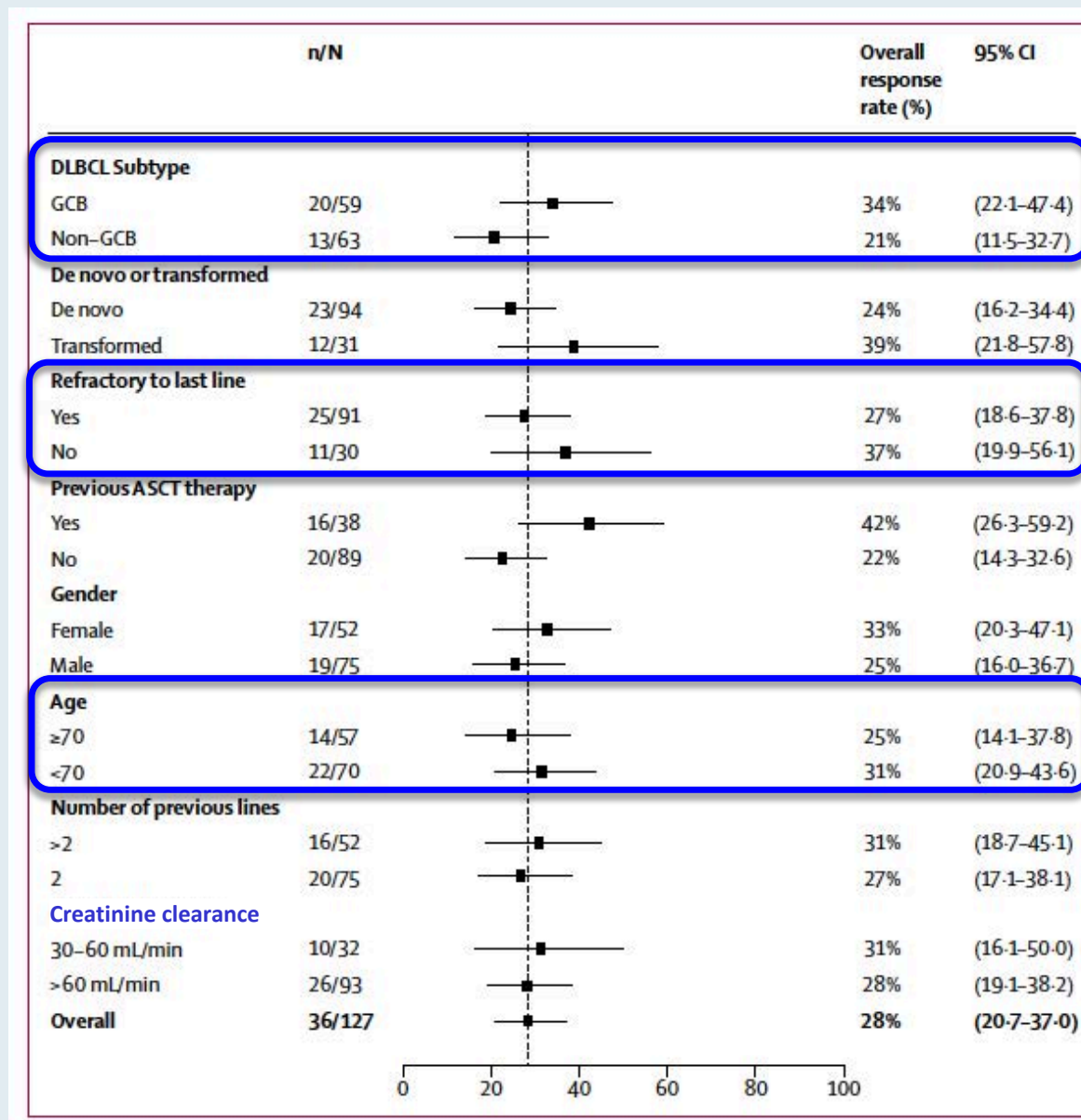
SADAL: Phase II Trial of Selinexor Monotherapy in R/R DLBCL

Patient characteristics:

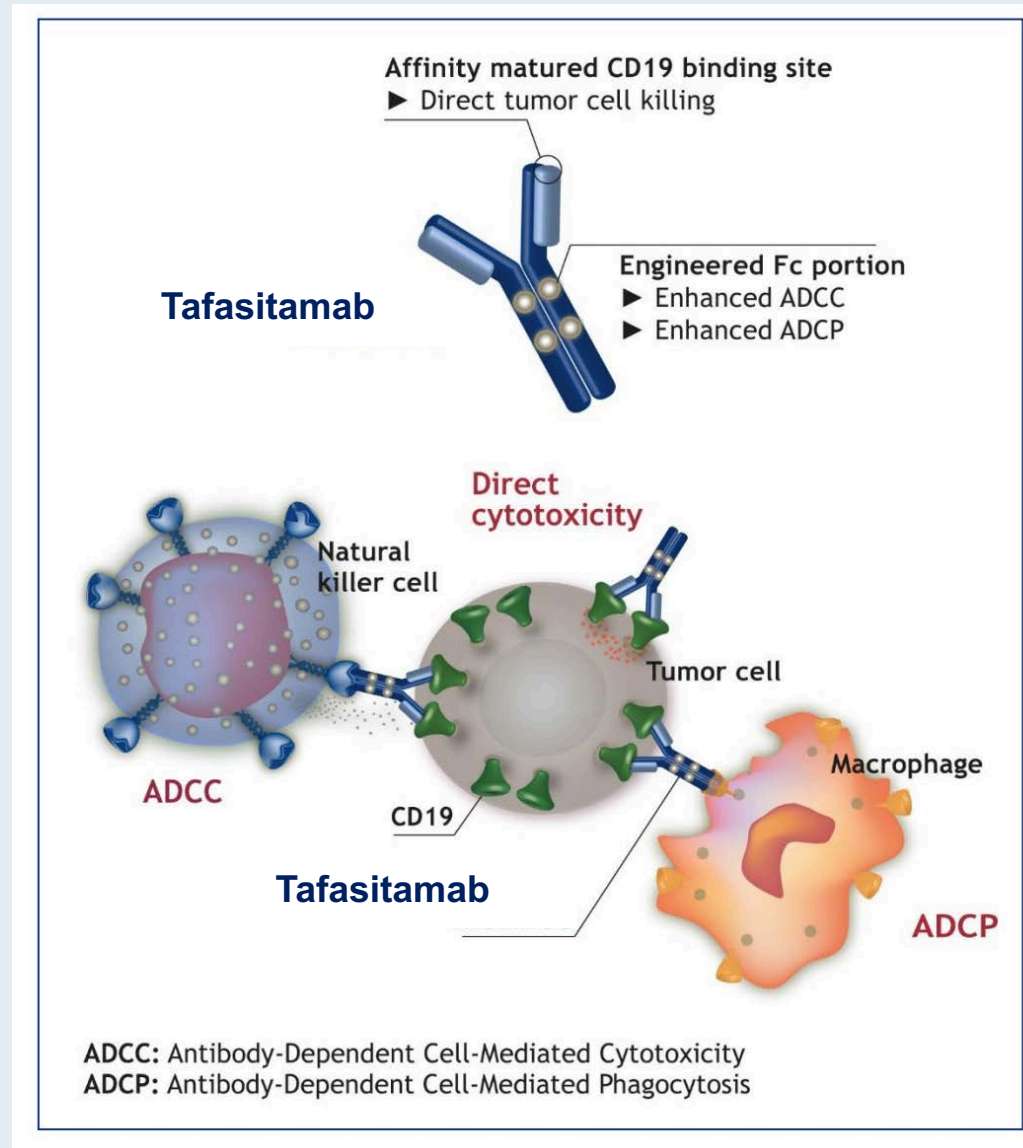
N=127 with med age 67y
45% of pts ≥ 70 y
72% refractory to last regimen

Results:

ORR 28%
CR 12%
Med DR 9.3m
--med DR for CR pts 23m
--med DR for PR pts 4.4m
No impact of COO



Tafasitamab (MOR208)



Lenalidomide enhances
NK function with
enhanced ADCC in vitro

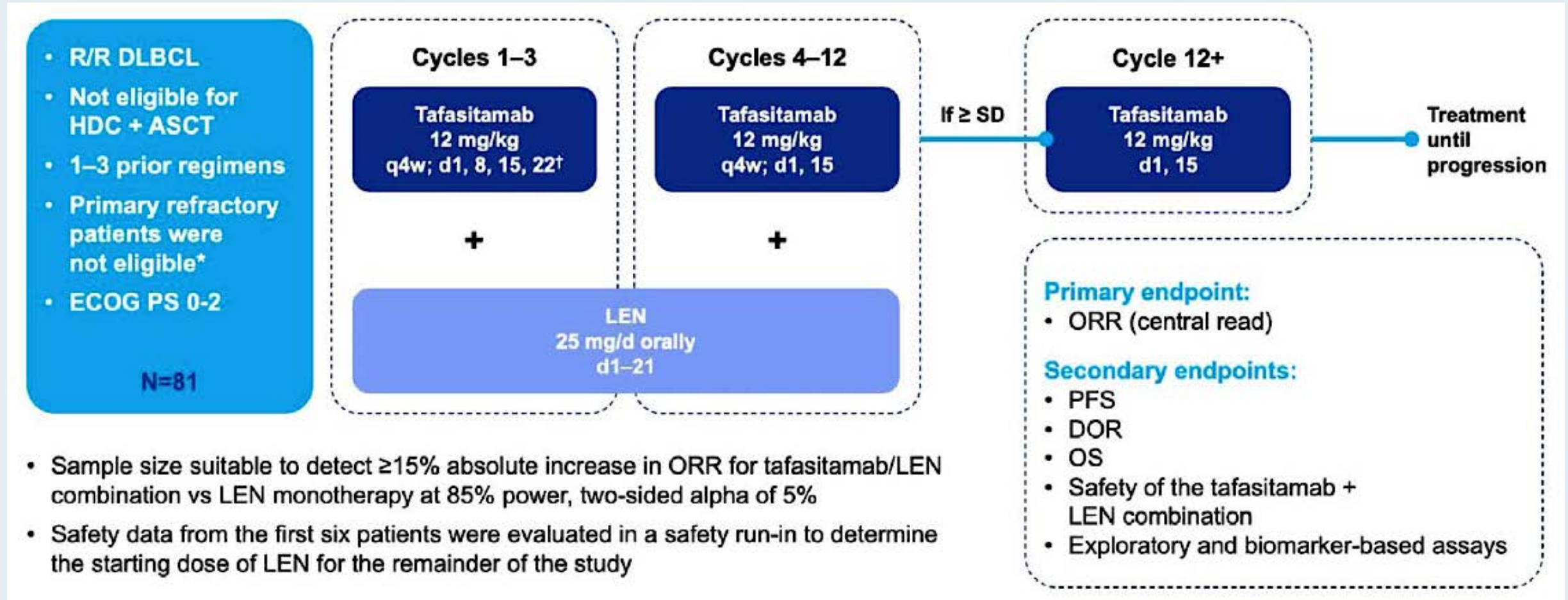
Salles et al. *Lancet Onc* 2020.

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

Maddocks KJ et al.

ASH 2020;Abstract 3021.

L-MIND: Study Design



L-MIND: Summary

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

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

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

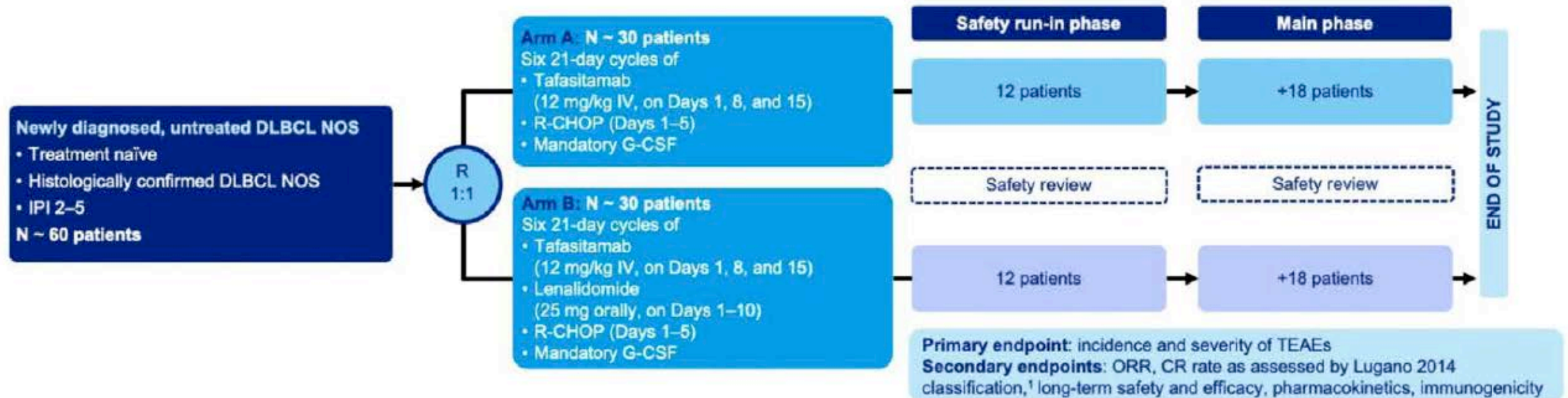
A Phase Ib, Open-Label, Randomized Study to Assess Safety and Preliminary Efficacy of Tafasitamab (MOR208) or Tafasitamab + Lenalidomide in Addition to R-CHOP in Patients with Newly Diagnosed Diffuse Large B-Cell Lymphoma: Analysis of the Safety Run-in Phase

Belada D et al.

ASH 2020;Abstract 3028.

First-MIND: Study Design

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



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

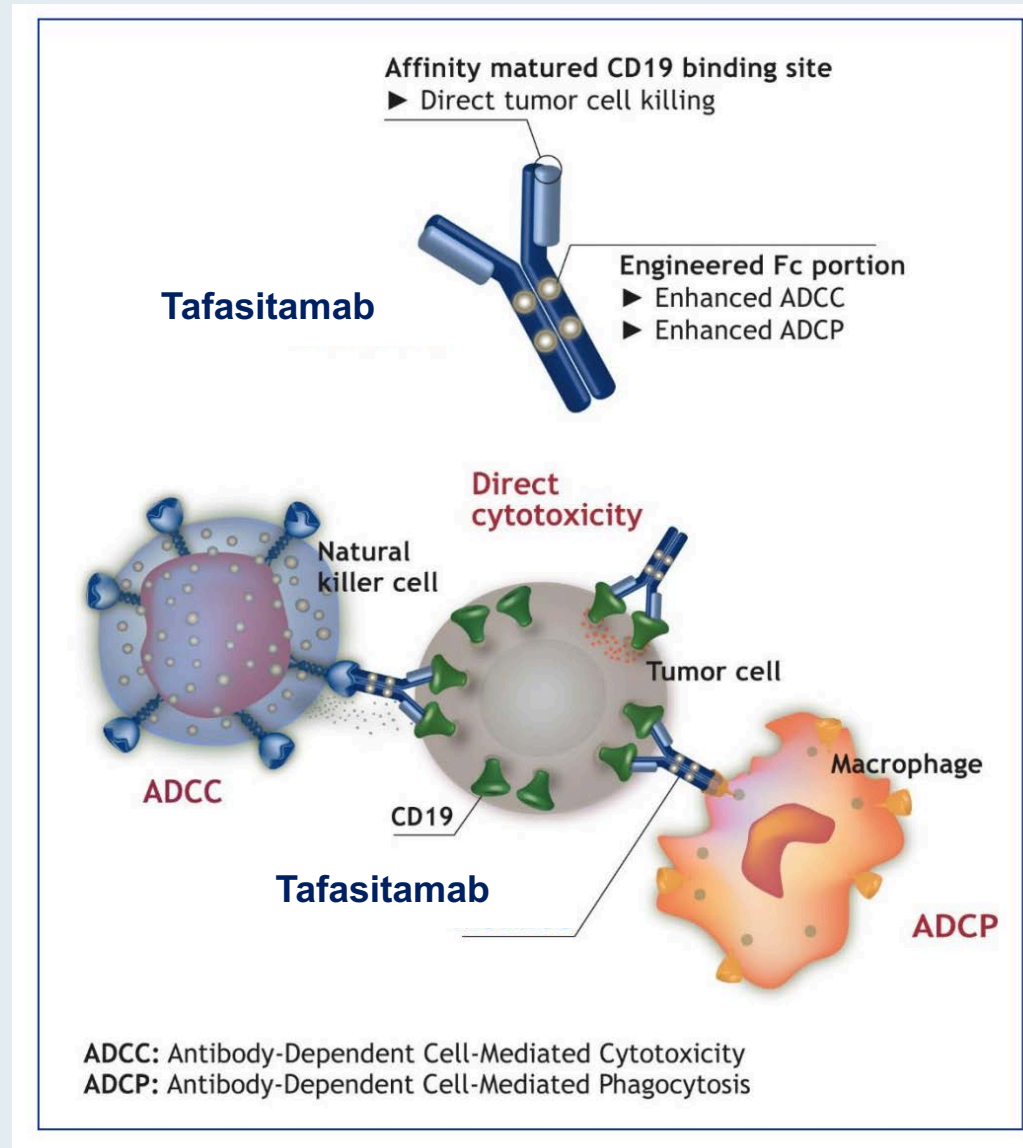
First-MIND: Treatment Emergent Adverse Events

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

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

- Overall, 98.5% of patients experienced TEAEs; of these, 75.8% were grade 3 or higher
- Serious TEAEs were experienced by 29 patients in total (43.9%), 13 patients in arm A and 16 in arm B (39.4% vs 48.5%)
- No new safety signals were identified with either tafasitamab + R-CHOP or tafasitamab + lenalidomide + R-CHOP compared with previous Phase III studies with R-CHOP or R2-CHOP¹⁻³

Tafasitamab (MOR208)



Lenalidomide enhances
NK function with
enhanced ADCC in vitro

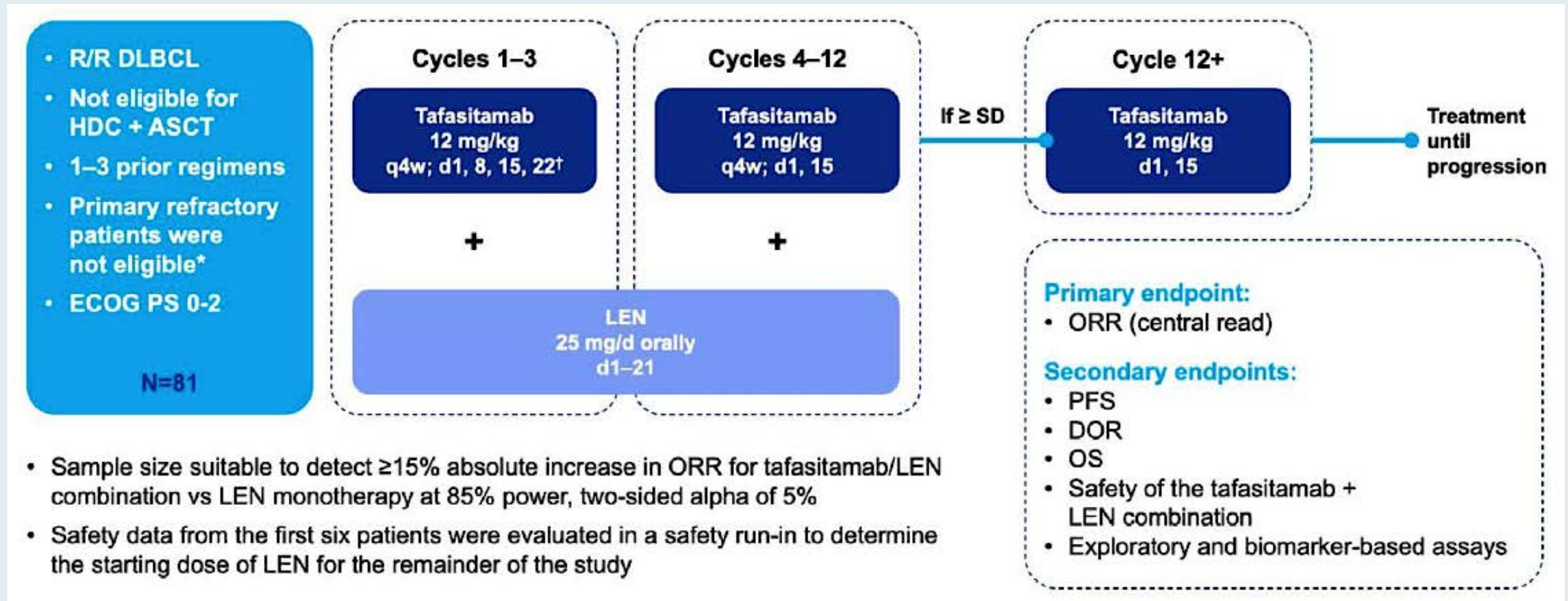
Salles et al. *Lancet Onc* 2020.

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

Maddocks KJ et al.

ASH 2020;Abstract 3021.

L-MIND: Study Design



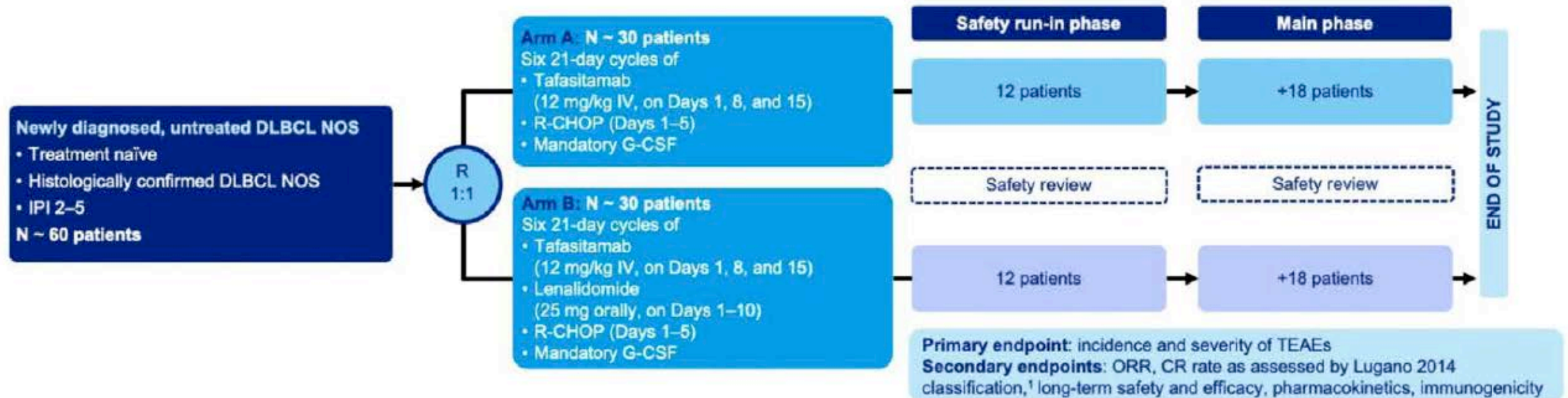
A Phase Ib, Open-Label, Randomized Study to Assess Safety and Preliminary Efficacy of Tafasitamab (MOR208) or Tafasitamab + Lenalidomide in Addition to R-CHOP in Patients with Newly Diagnosed Diffuse Large B-Cell Lymphoma: Analysis of the Safety Run-in Phase

Belada D et al.

ASH 2020;Abstract 3028.

First-MIND: Study Design

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



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

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- Serious TEAEs were experienced by 29 patients in total (43.9%), 13 patients in arm A and 16 in arm B (39.4% vs 48.5%)
- No new safety signals were identified with either tafasitamab + R-CHOP or tafasitamab + lenalidomide + R-CHOP compared with previous Phase III studies with R-CHOP or R2-CHOP¹⁻³

Polatuzumab Vedotin plus Venetoclax with Rituximab in Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Primary Efficacy Analysis of a Phase Ib/II Study

Gritti G et al.

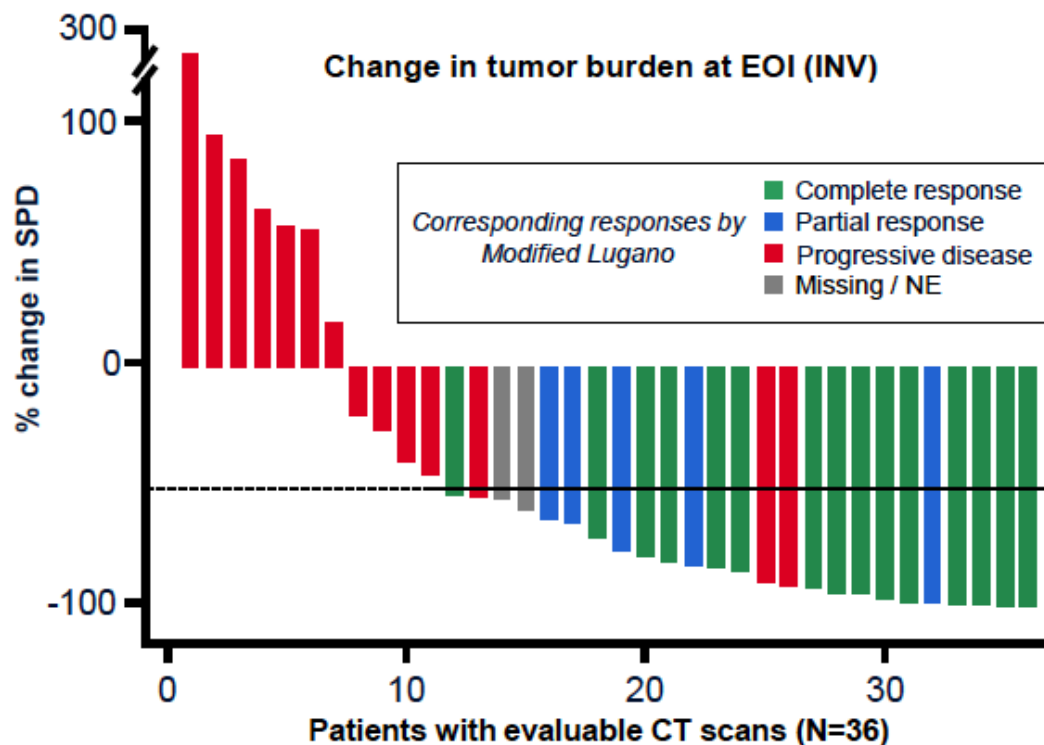
ASH 2020;Abstract 599.

Polatuzumab Vedotin with Venetoclax and Rituximab for Relapsed DLBCL: Efficacy Summary

| Response at EOI, n (%) [*] | INV N=48 | IRC N=48 |
|--|-------------|----------------|
| Objective response | 20 (42) | 14 (29) |
| Complete response | 15 (31) | 14 (29) |
| Partial response | 5 (10) | 0 |
| Stable disease | 0 | 5 (10) |
| Disease progression | 23 (48) | 12 (25) |
| Missing / NE | 5 (10) | 17 (35) |
| INV N=48 | | |
| Best objective response[†] | 31 (65) | |
| Complete response | 18 (38) | |
| Partial response | 13 (27) | |

^{*}Responses reported according to Modified Lugano criteria

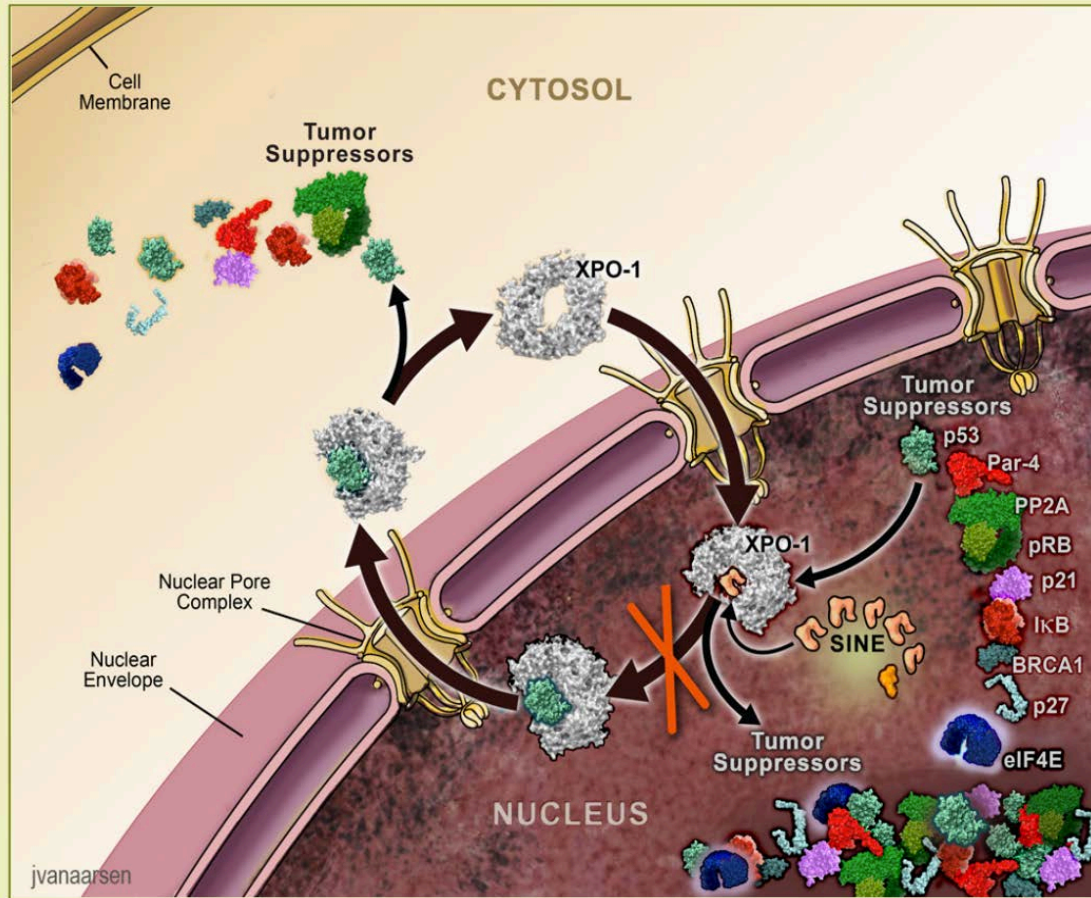
[†]Based on composite result: Modified Lugano > Lugano PET-CT > Lugano CT only
CT, computed tomography; INV, investigator-assessed; NE, not evaluable
SPD, sum of the product of diameters



- CR rate by IRC at EOI was 29% (by Modified Lugano)
- Best objective response on study was 65%
- Most patients achieved >50% reduction in SPD at EOI

CCOD: 30 Jan 2020

Selinexor has a novel mechanism of action: XPO-1 inhibitor



XPO1 over-expressed in DLBCL and correlates with poor prognosis

Induces nuclear accumulation of tumor suppressors including p53, p73, IκB and FOXO

Decreases production of oncoproteins including c-MYC, BCL2, BCL6 and BCL-XL

Kalakonda. *Lancet Heme* 2020.

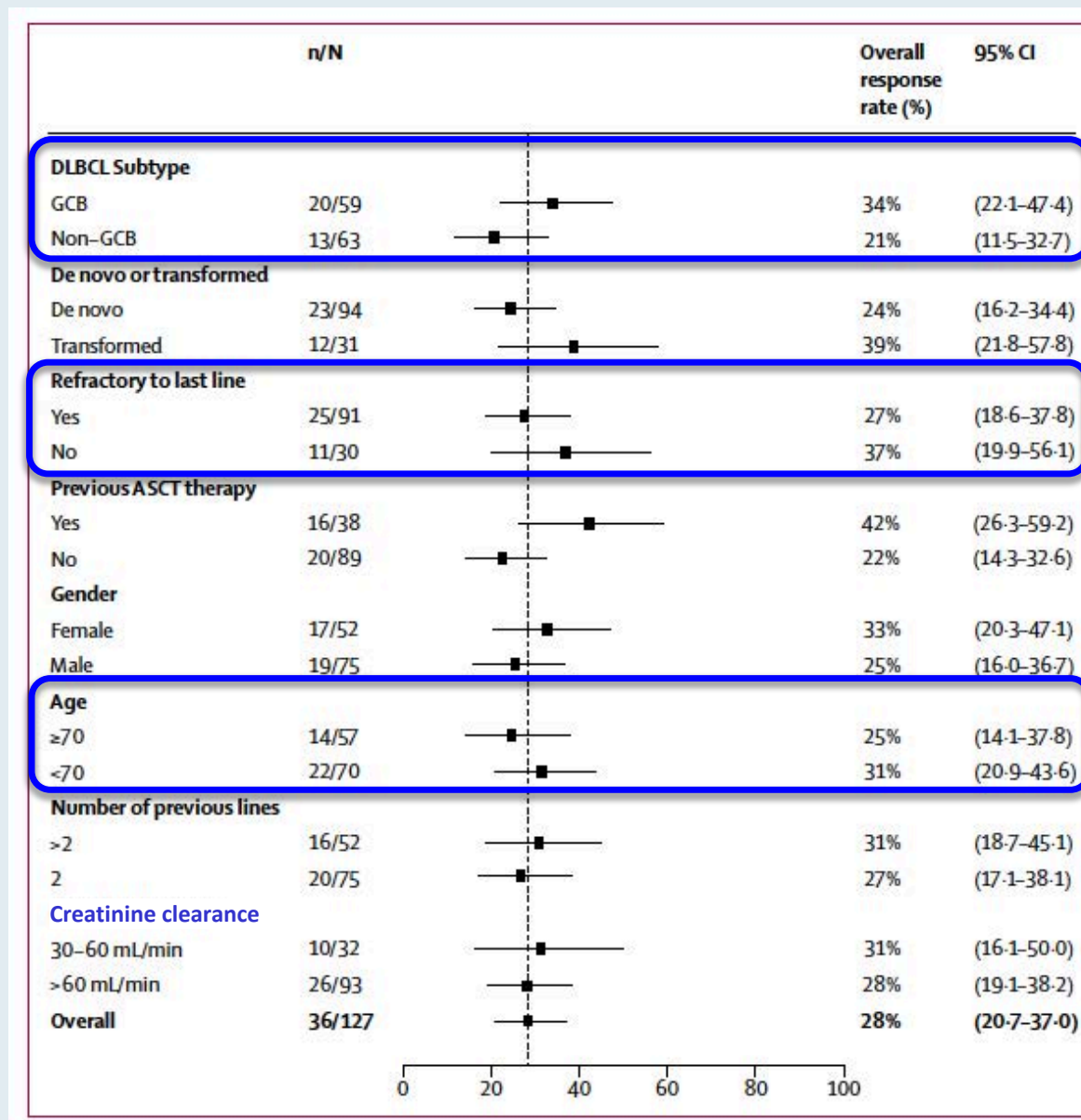
SADAL: Phase II Trial of Selinexor Monotherapy in R/R DLBCL

Patient characteristics:

N=127 with med age 67y
45% of pts ≥ 70 y
72% refractory to last regimen

Results:

ORR 28%
CR 12%
Med DR 9.3m
--med DR for CR pts 23m
--med DR for PR pts 4.4m
No impact of COO



Lancet Oncol 2021;[Online ahead of print].

Articles

Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial



Paolo F Caimi, Weiyun Ai, Juan Pablo Alderuccio, Kirit M Ardeshta, Mehdi Hamadani, Brian Hess, Brad S Kahl, John Radford, Melhem Solh, Anastasios Stathis, Pier Luigi Zinzani, Karin Havenith, Jay Feingold, Shui He, Yajuan Qin, David Ungar, Xiaoyan Zhang, Carmelo Carlo-Stella

LOTIS-2: Response Rates and Safety Summary

| Clinical endpoint | N = 145 |
|-------------------|---------|
| ORR | 48.3% |
| CR | 24.0% |
| PR | 24.0% |
| Stable disease | 15.0% |

The most common grade 3 or higher treatment-emergent adverse events were:

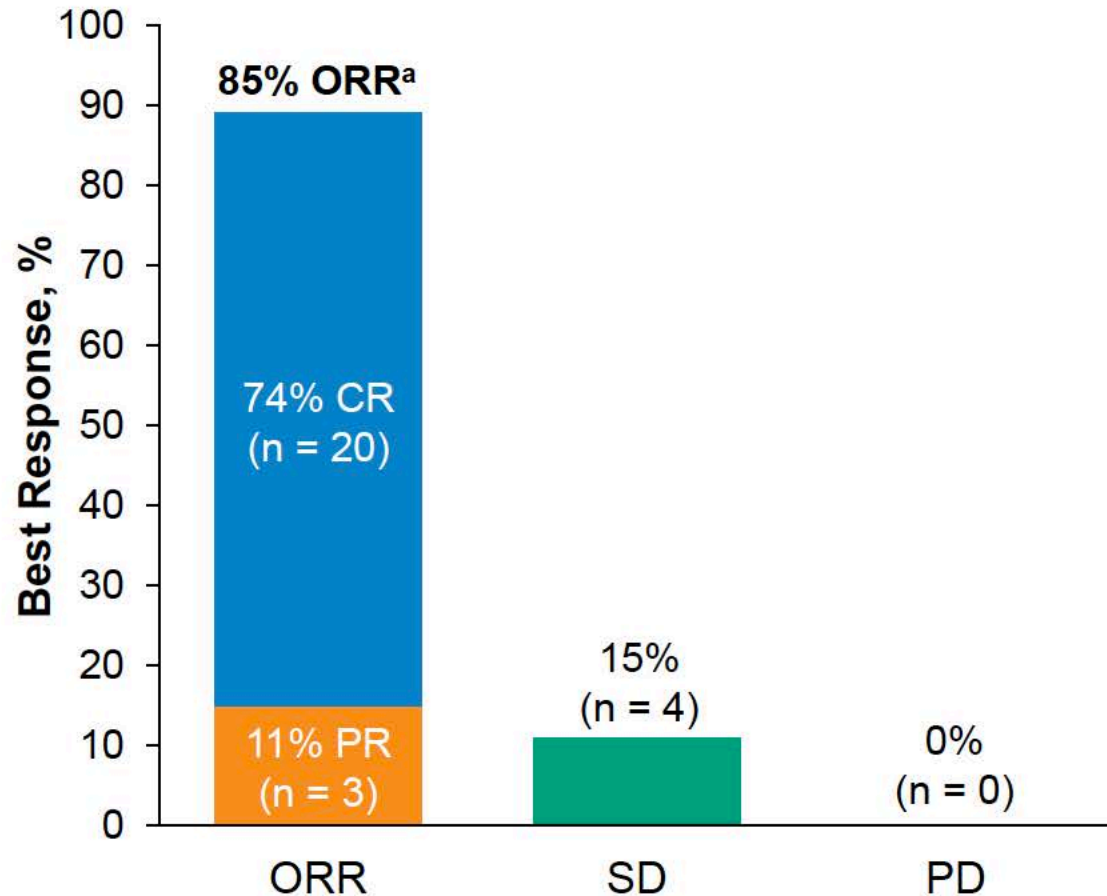
- **Neutropenia 26%**
- **Thrombocytopenia 18%**
- **Increased gamma-glutamyltransferase 17%**

Serious adverse events were reported in 57 (39%) of 145 patients

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

Neelapu SS et al.
ASH 2020;Abstract 405.

ZUMA-12: Response Rates



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

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

Press Release – February 5, 2021

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

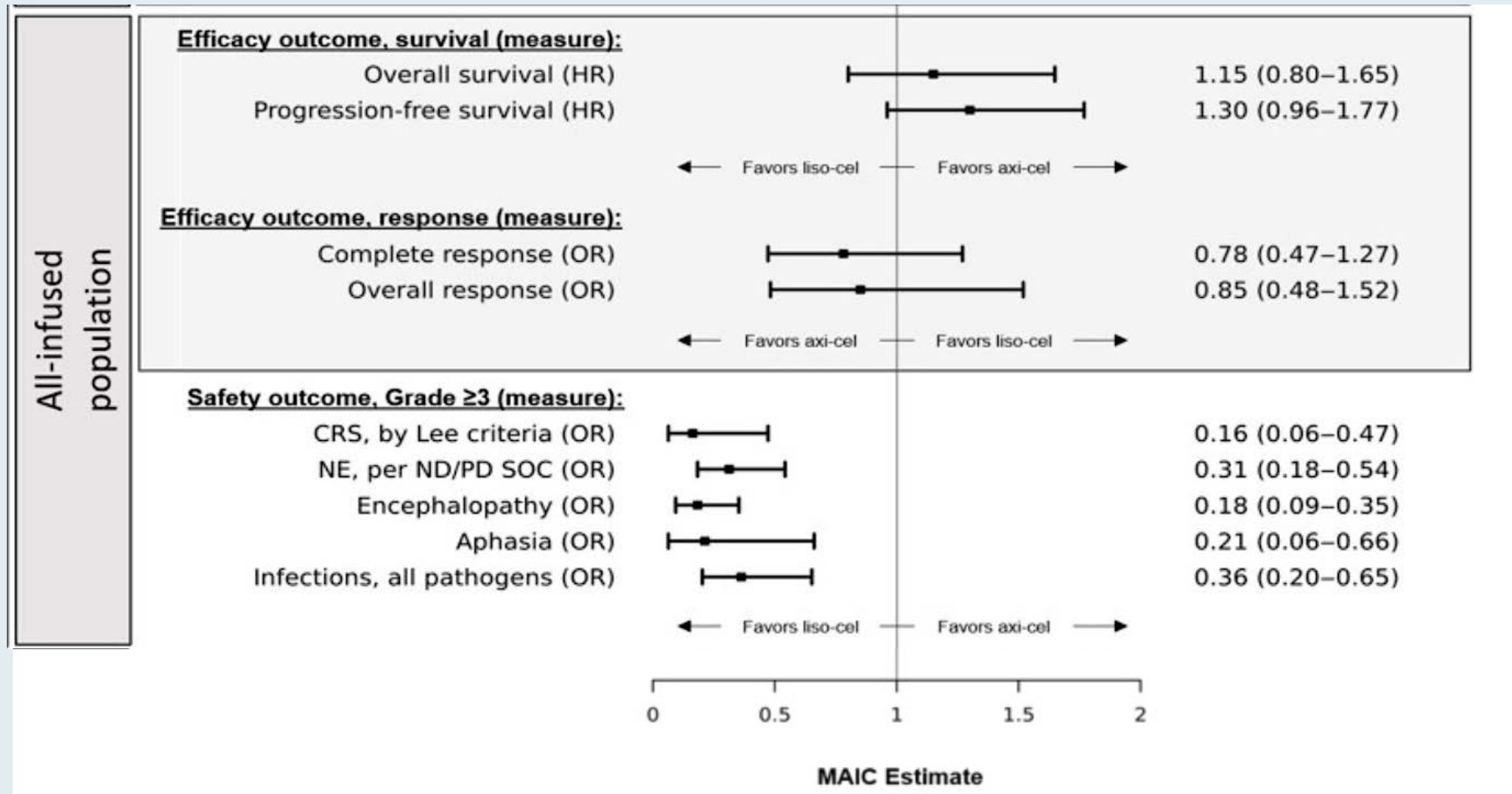
Efficacy was evaluated in TRANSCEND (NCT02631044), a single-arm, open label, multicenter trial that evaluated lisocabtagene maraleucel, preceded by lymphodepleting chemotherapy, in adults with R/R large B-cell lymphoma after at least two lines of therapy.

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

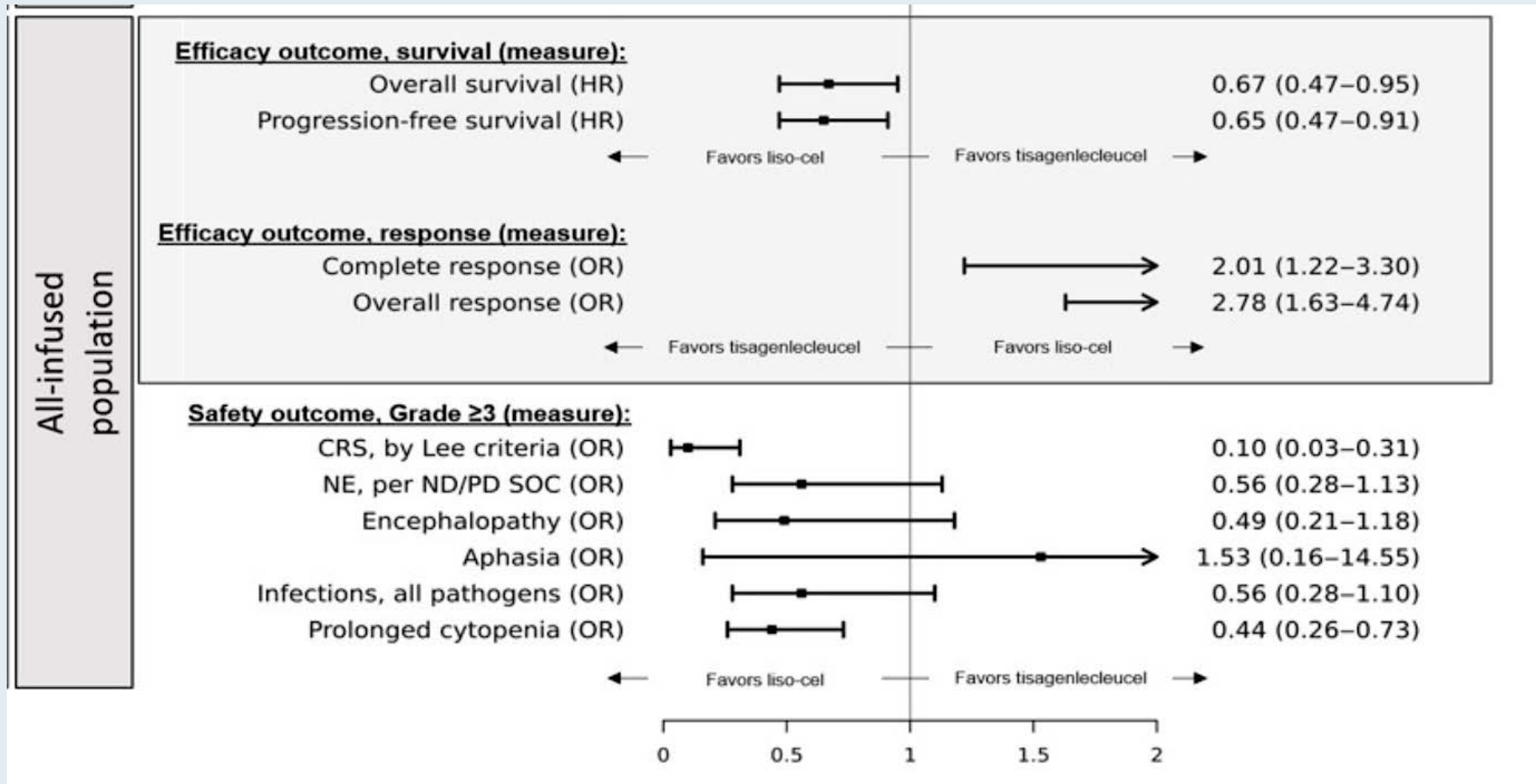
Maloney DG et al.

ASH 2020;Abstract 2116.

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

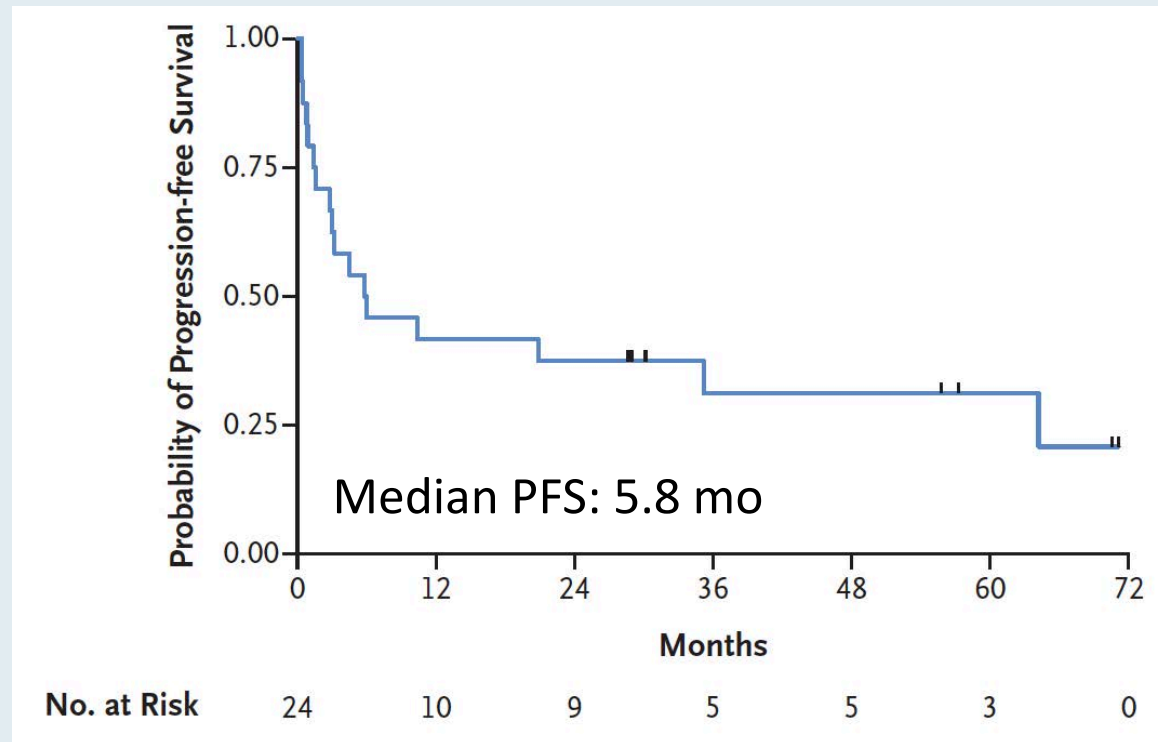


Matching-Adjusted Indirect Comparison of Liso-cel versus Tisagenlecleucel

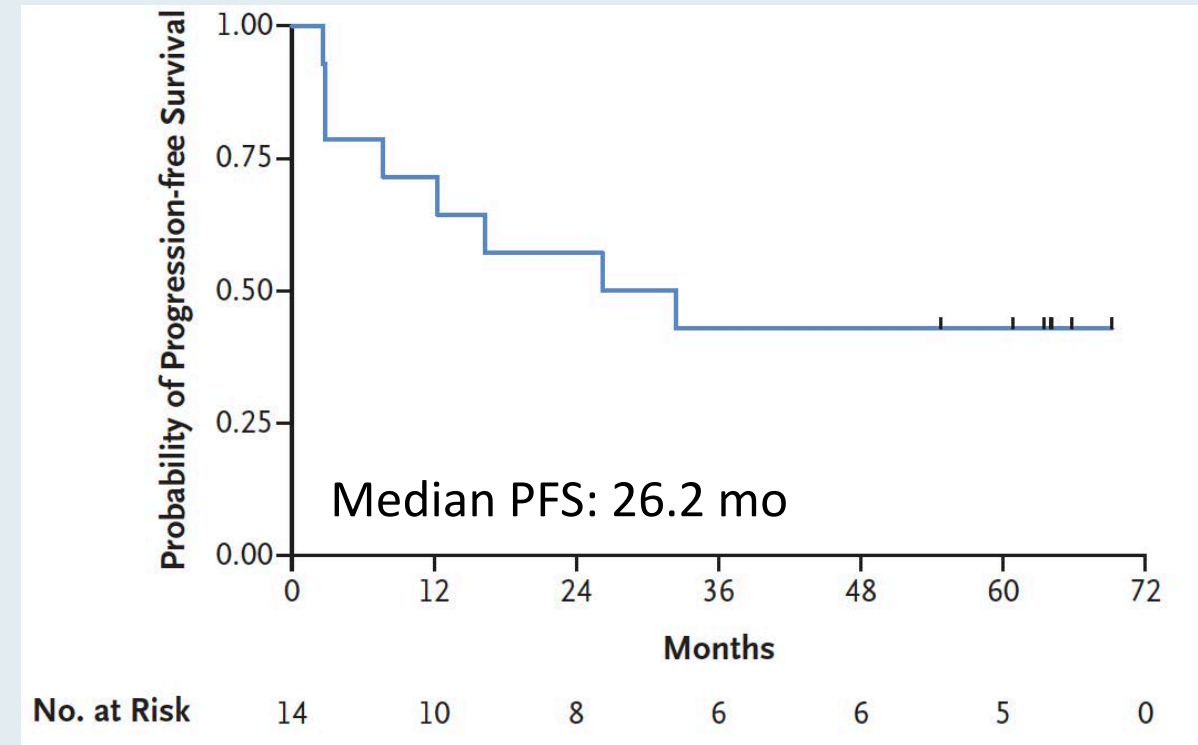


Five-Year Outcomes for Refractory B-Cell Lymphomas with CAR T-Cell Therapy Tisagenlecleucel

DLBCL



FL



Follicular Lymphoma (FL)

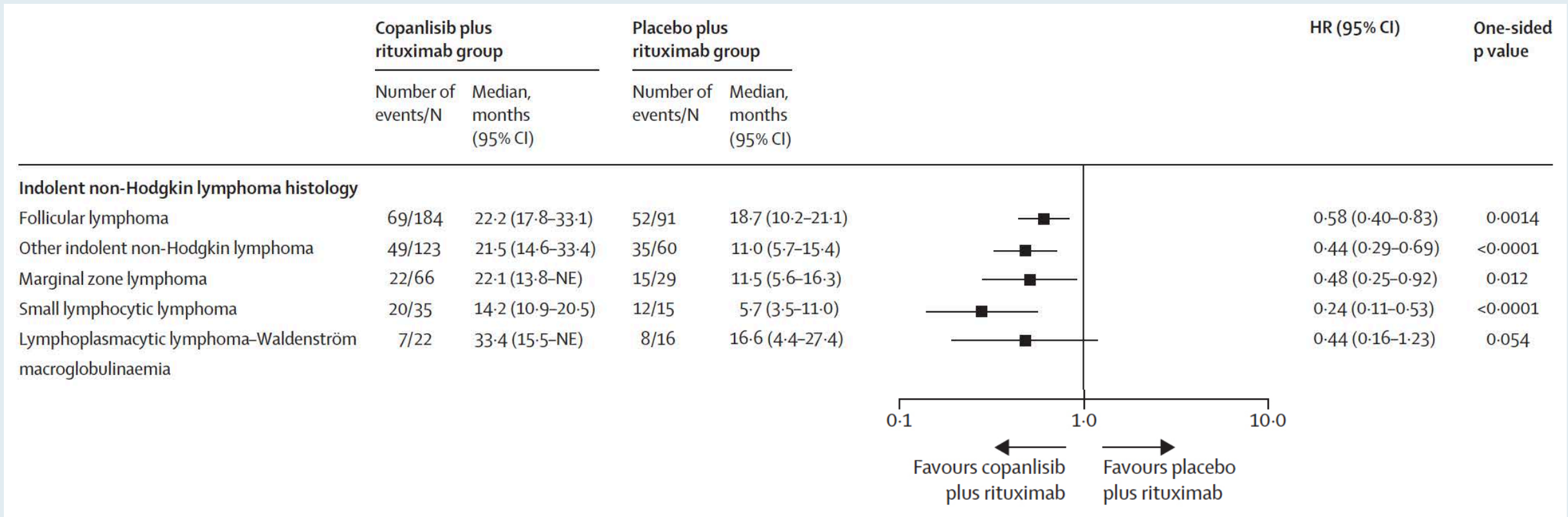


Copanlisib plus rituximab versus placebo plus rituximab in patients with relapsed indolent non-Hodgkin lymphoma (CHRONOS-3): a double-blind, randomised, placebo-controlled, phase 3 trial

Matthew J Matasar, Marcelo Capra, Muhit Özcan, Fangfang Lv, Wei Li, Eduardo Yañez, Katya Sapunarova, Tongyu Lin, Jie Jin, Wojciech Jurczak, Aryan Hamed, Ming-Chung Wang, Ross Baker, Igor Bondarenko, Qingyuan Zhang, Jifeng Feng, Klaus Geissler, Mihaela Lazaroiu, Guray Saydam, Árpád Szomor, Krimo Bouabdallah, Rinat Galiulin, Toshiki Uchida, Lidia Mongay Soler, Anjun Cao, Florian Hiemeyer, Aruna Mehra, Barrett H Childs, Yuankai Shi, Pier Luigi Zinzani

Lancet Oncol 2021;22(5):678-89.

CHRONOS-3 Trial: Progression-Free Survival by Subgroup



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

Press Release: February 5, 2021

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

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

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

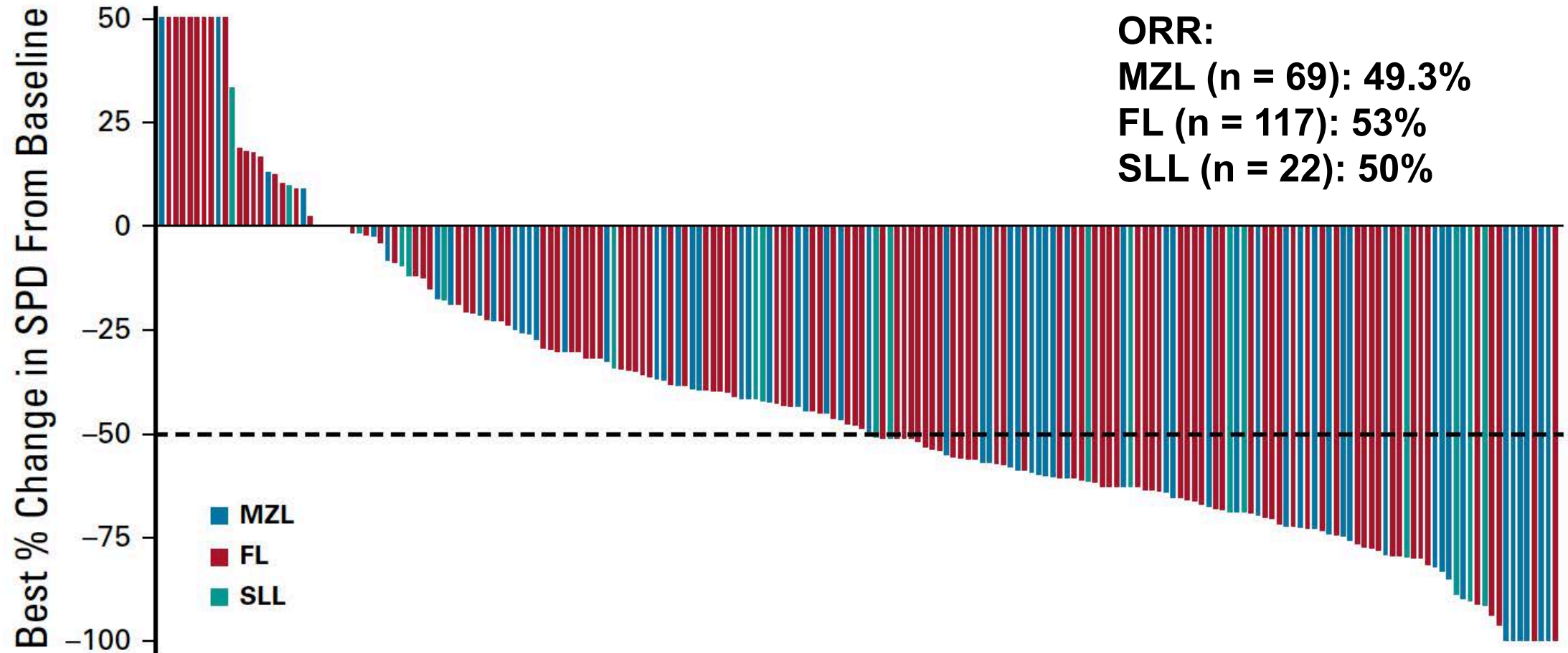
Umbralisib, a Dual PI3K δ /CK1 ϵ Inhibitor in Patients With Relapsed or Refractory Indolent Lymphoma

Nathan H. Fowler, MD¹; Felipe Samaniego, MD¹; Wojciech Jurczak, MD, PhD²; Nilanjan Ghosh, MD, PhD³; Enrico Derenzini, MD^{4,5}; James A. Reeves, MD⁶; Wanda Knopińska-Postuszny, MD⁷; Chan Y. Cheah, DMSc⁸; Tycel Phillips, MD⁹; Ewa Lech-Maranda, MD, PhD¹⁰; Bruce D. Cheson, MD¹¹; Paolo F. Caimi, MD¹²; Sebastian Grosicki, MD, PhD¹³; Lori A. Leslie, MD¹⁴; Julio C. Chavez, MD¹⁵; Gustavo Fonseca, MD¹⁶; Sunil Babu, MD¹⁷; Daniel J. Hodson, MD¹⁸; Spencer H. Shao, MD¹⁹; John M. Burke, MD²⁰; Jeff P. Sharman, MD²¹; Jennie Y. Law, MD²²; John M. Pagel, MD, PhD²³; Hari P. Miskin, MSc²⁴; Peter Sportelli, BS²⁴; Owen A. O'Connor, MD, PhD^{24,25}; Michael S. Weiss, JD²⁴; and Pier Luigi Zinzani, MD, PhD^{26,27}

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

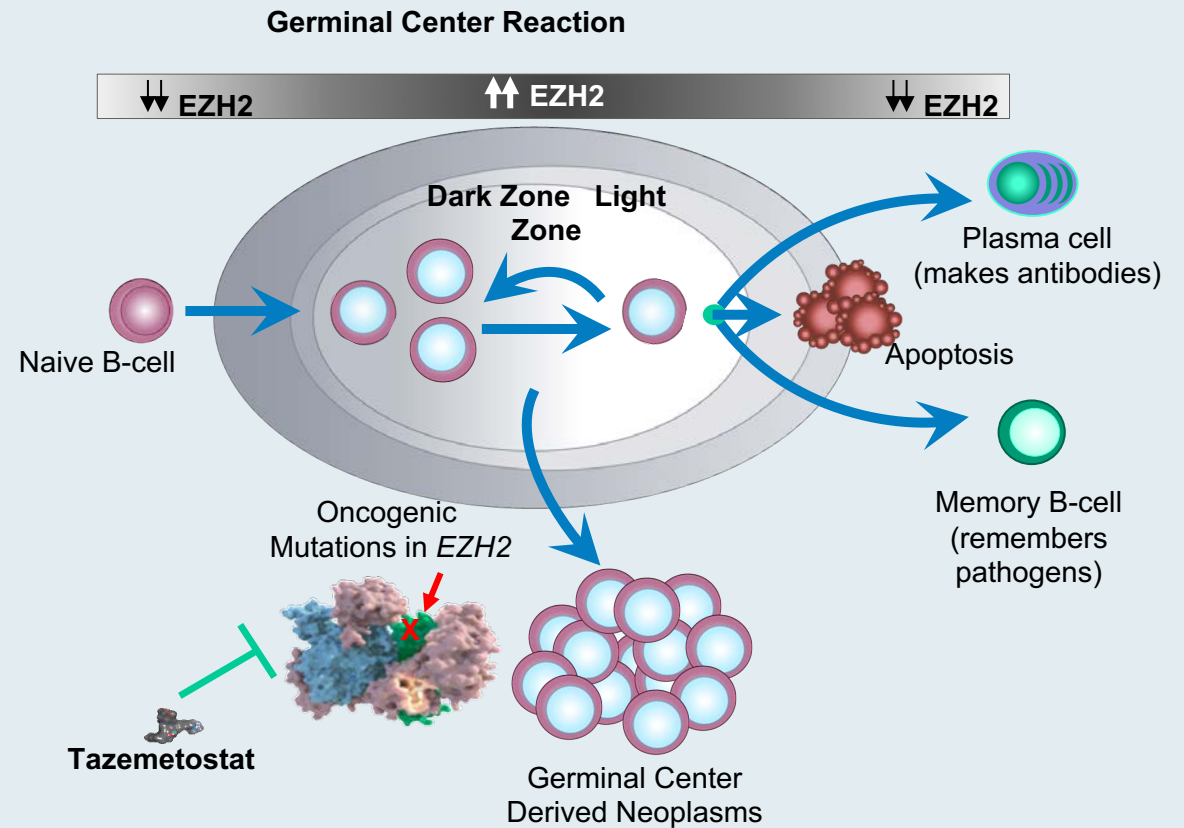
Phase IIb Trial of Umbralisib in Relapsed/Refractory Indolent Lymphoma

ORR:
MZL (n = 69): 49.3%
FL (n = 117): 53%
SLL (n = 22): 50%



Follicular Lymphoma and EZH2

- *EZH2* an epigenetic regulator of gene expression and cell fate decisions¹
- *EZH2* is required for normal B-cell biology and germinal center formation²
 - Oncogenic mutations in *EZH2* suppress exit from germinal state and “lock” B cells in this state thereby transforming into a cancer²
- *EZH2* biology relevant in both mutant (MT) and wild-type (WT) *EZH2* FL
 - ~20% of patients with FL also have *EZH2* gain of function mutations³



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

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

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

Salles G et al.

ASH 2020;Abstract 2047.

Phase 2 Efficacy Outcomes

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

- The DOR was consistent between WT and MT *EZH2* groups¹
- Consistent ORRs were also observed across high-risk subgroups, such as patients with POD24, double-refractory disease, and refractoriness to rituximab therapy, regardless of mutation status¹

^aORR, DOR, and PFS are based on IRC assessments.

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

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




American Society of Hematology

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

Target accrual (N = 518)

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

R



**Tazemetostat
+
Rituximab/Lenalidomide (R²)**

**Placebo
+
R²**

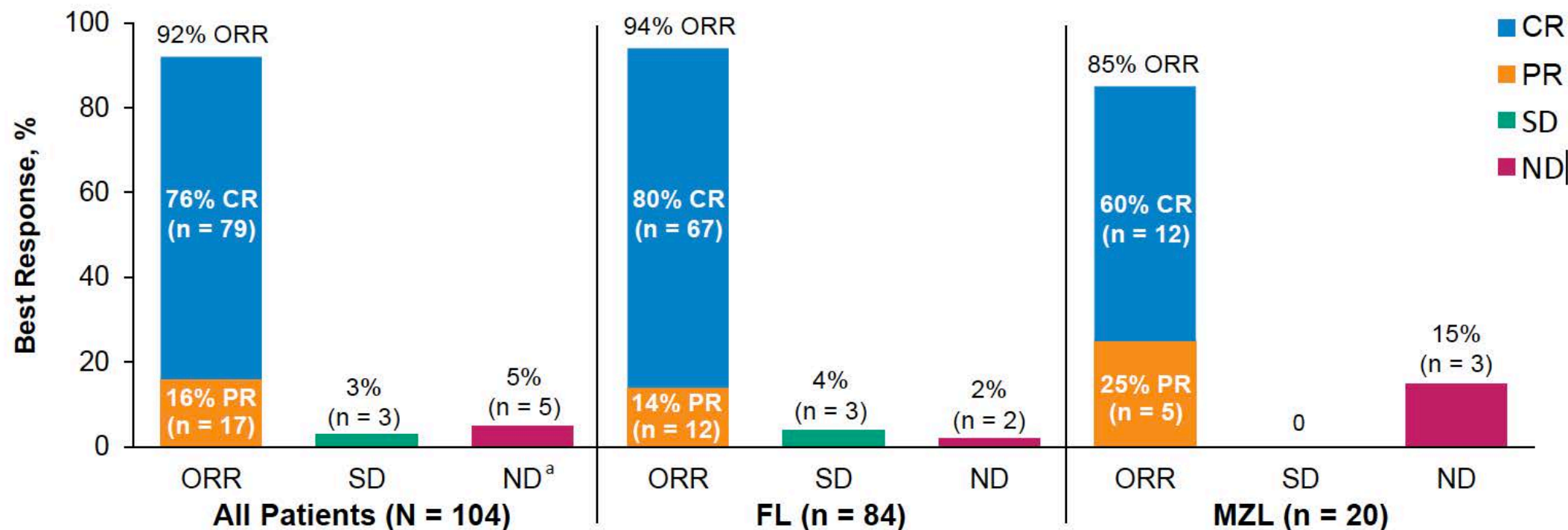
- **Primary endpoint:**
 - **Stage 1: RP3D of tazemetostat in combination with R²**
 - **Stage 2: PFS**

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

Jacobson CA et al.

ASH 2020;Abstract 700.

ZUMA-5 Primary Endpoint: ORR by IRRC Assessment



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

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

Fowler NH et al.

ASH 2020;Abstract 1149.

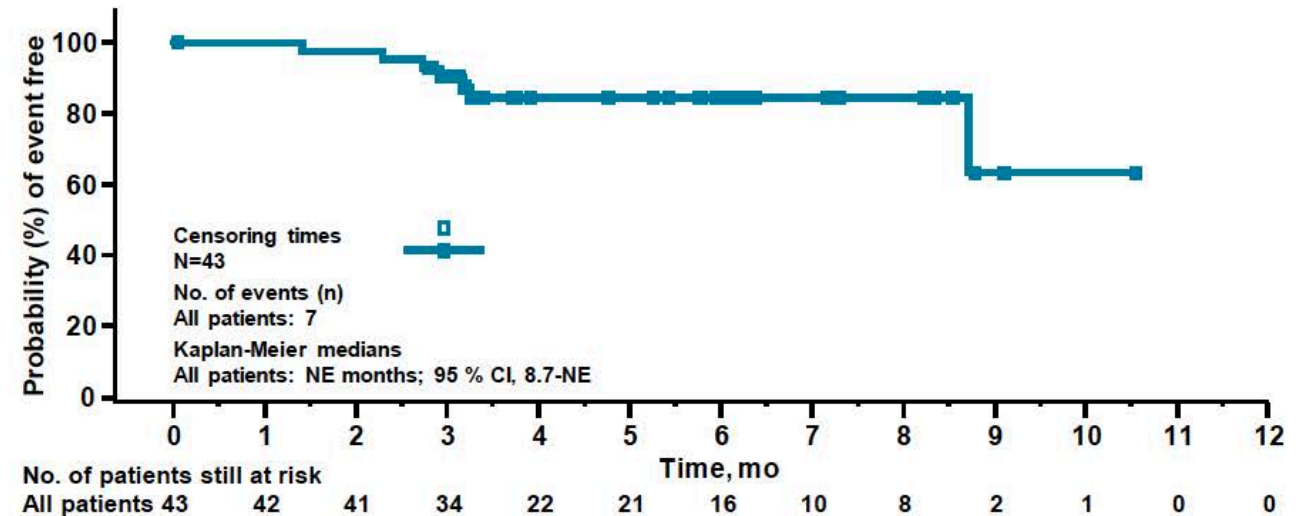
ELARA Interim Analysis: Primary CR Endpoint

Best Overall Response Rate

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

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

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



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

ELARA: Overall Safety Profile

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

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

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

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

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

Schuster SJ et al.

ASCO 2021;Abstract 7508.

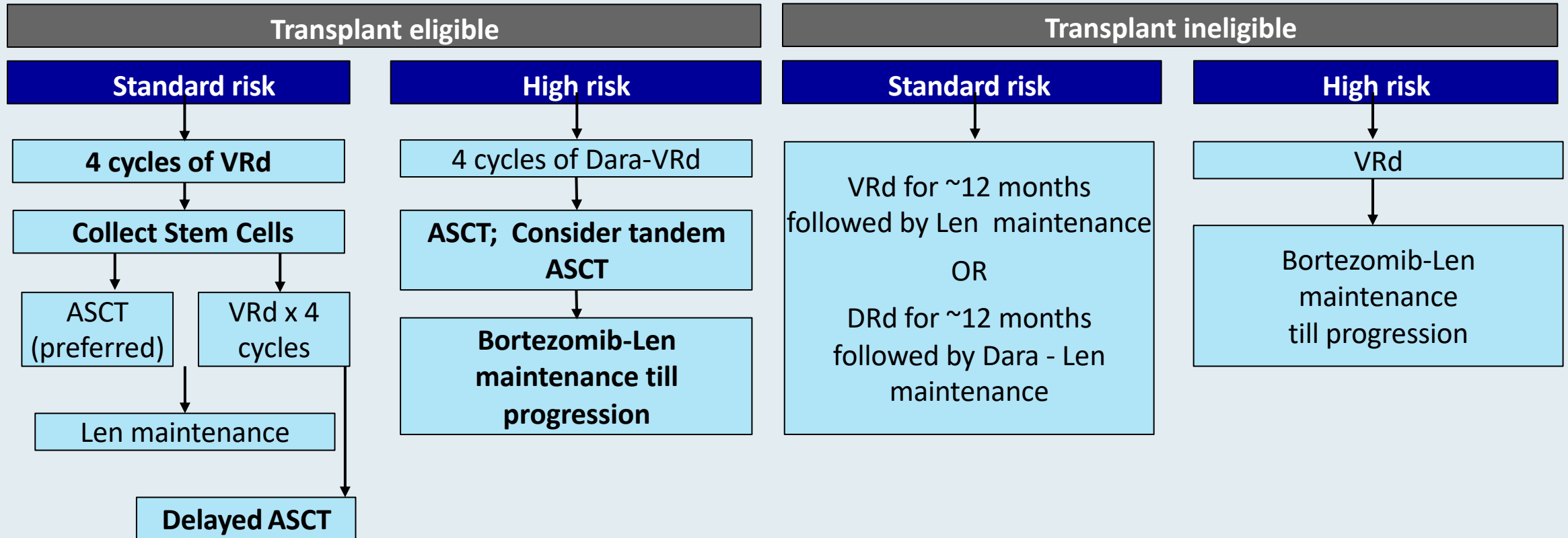
Monday, June 7, 11:30 AM - 2:30 PM EDT

Module 4: Multiple Myeloma

Relevant Recent Data Sets

Newly Diagnosed Multiple Myeloma

Approach to Newly Diagnosed MM



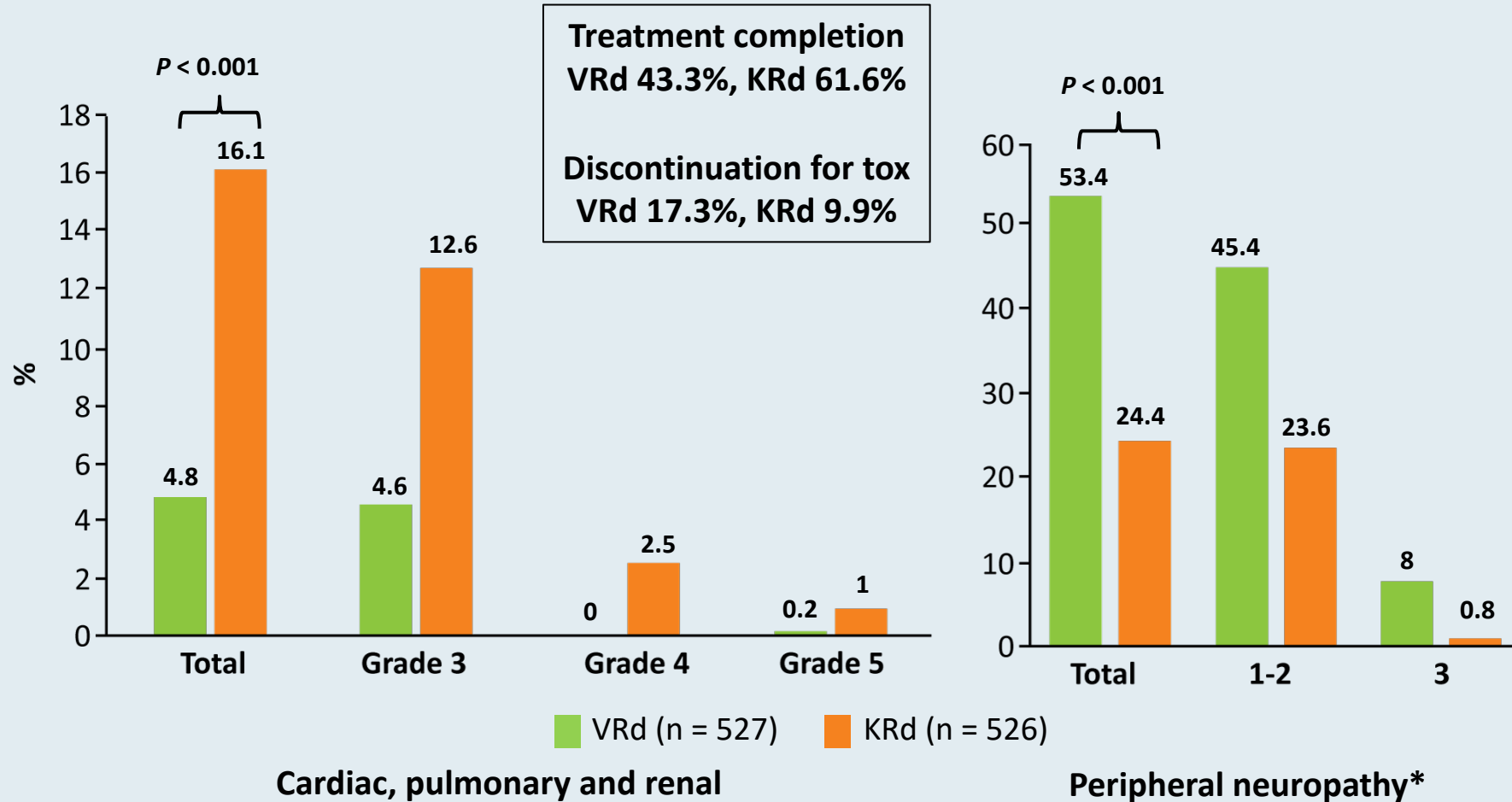


Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial

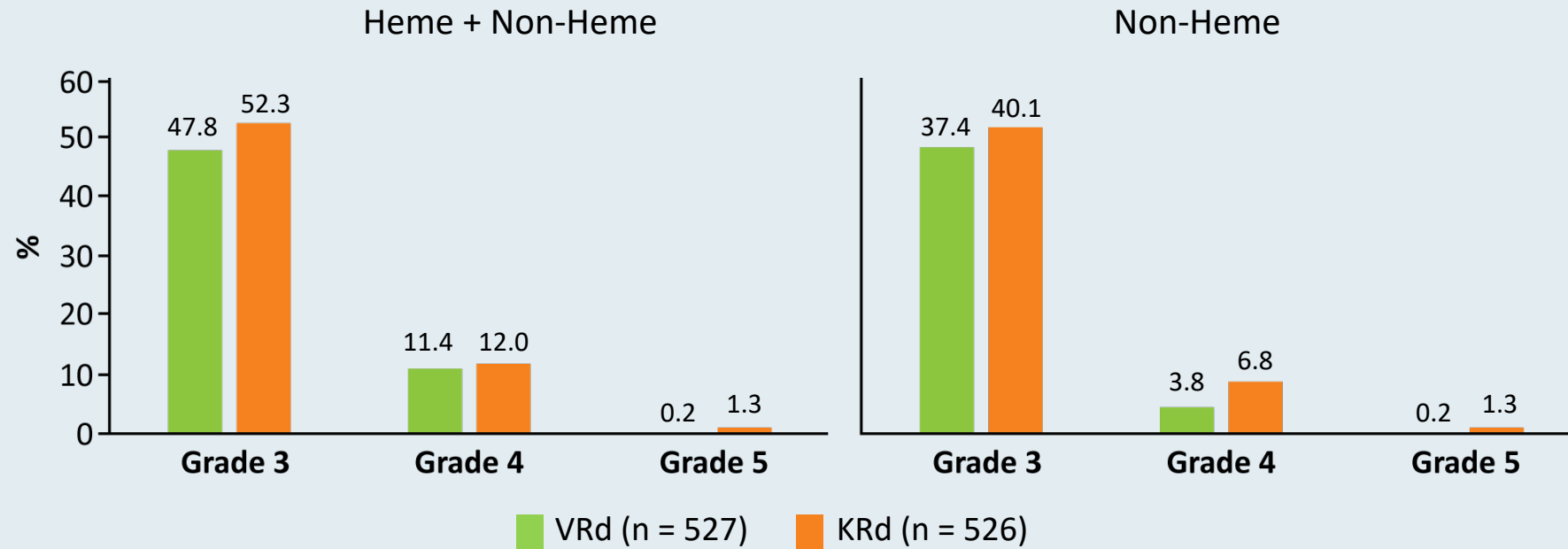
Shaji K Kumar, Susanna J Jacobus, Adam D Cohen, Matthias Weiss, Natalie Callander, Avina K Singh, Terri L Parker, Alexander Menter, Xuezhong Yang, Benjamin Parsons, Pankaj Kumar, Prashant Kapoor, Aaron Rosenberg, Jeffrey A Zonder, Edward Faber Jr, Sagar Lonial, Kenneth C Anderson, Paul G Richardson,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

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

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



ENDURANCE (E1A11): Treatment-Related AEs



| Step 1 treated patients | VRd (n = 527) N (%) | KRd (n = 526) N (%) | Diff KRd-VRd | Chi-sq p-value |
|-------------------------|---------------------------|---------------------------|-----------------|-------------------|
| Grades 3-5 | 313 (59.4) | 345 (65.6) | 6.2 | 0.038 |
| (95% CI) | (55.1-63.6) | (61.3-69.6) | | |
| Grades 4-5 | 61 (11.6) | 70 (13.3) | 1.7 | 0.394 |
| (95% CI) | (9.0-14.6) | (10.5-16.5) | | |

| Step 1 treated patients | VRd (n = 527) N (%) | KRd (n = 526) N (%) | Diff KRd-VRd | Chi-sq p-value |
|-------------------------|---------------------------|---------------------------|-----------------|-------------------|
| Grades 3-5 | 254 (48.3) | 254 (48.3) | 6.9 | 0.024 |
| (95% CI) | (37.1- 45.7) | (44.0-52.6) | | |
| Grades 4-5 | 21 (4.0) | 43 (8.2) | 4.2 | 0.004 |
| (95% CI) | (2.5-6.1) | (6.0-10.9) | | |

Upfront Autologous Stem Cell Transplantation (ASCT) versus Carfilzomib-Cyclophosphamide- Dexamethasone (KCd) Consolidation with K Maintenance in Transplant-Eligible, Newly Diagnosed (NDTE) Multiple Myeloma (MM)

Yong K et al.

ASCO 2021;Abstract 8000.

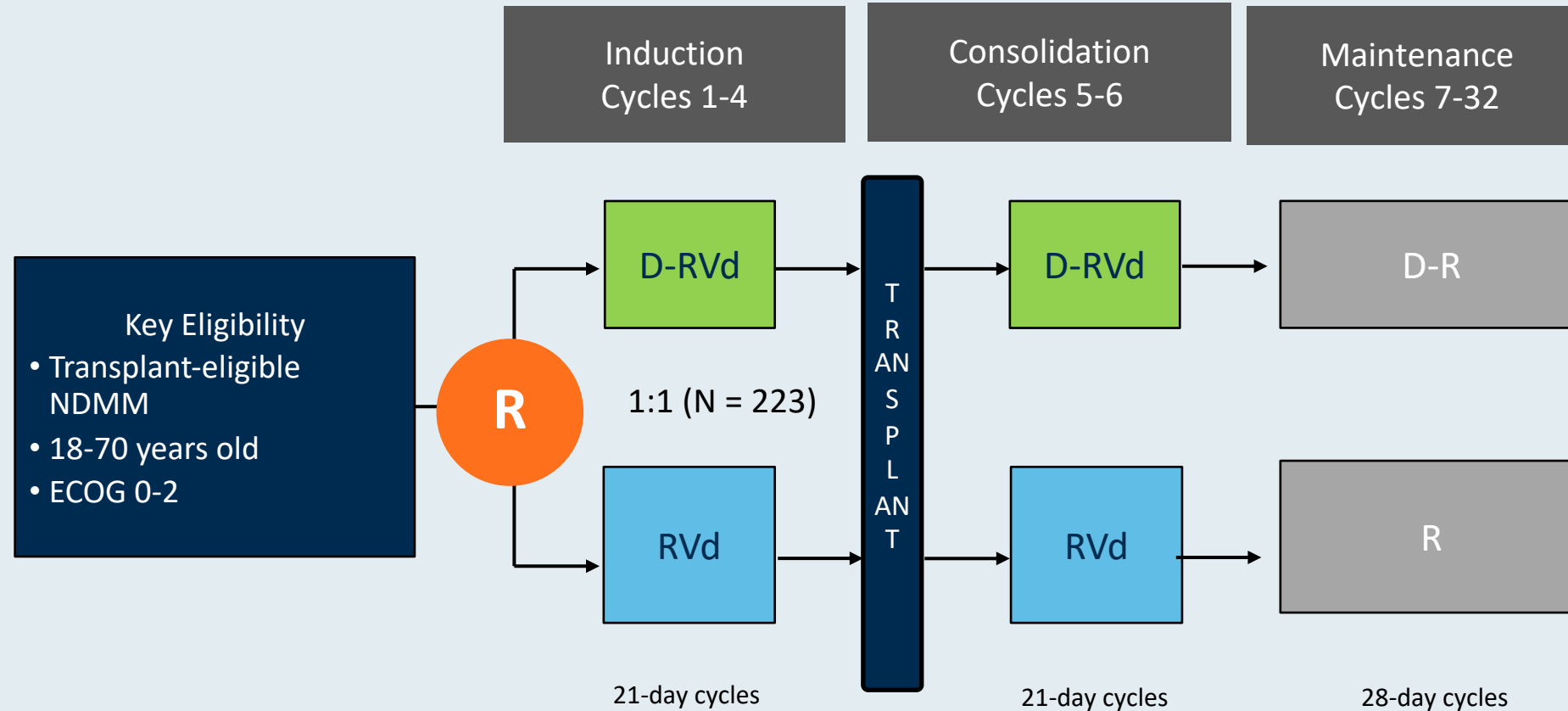
Tuesday, June 8, 8:00 AM - 11:00 AM EDT

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

Kaufman JL et al.

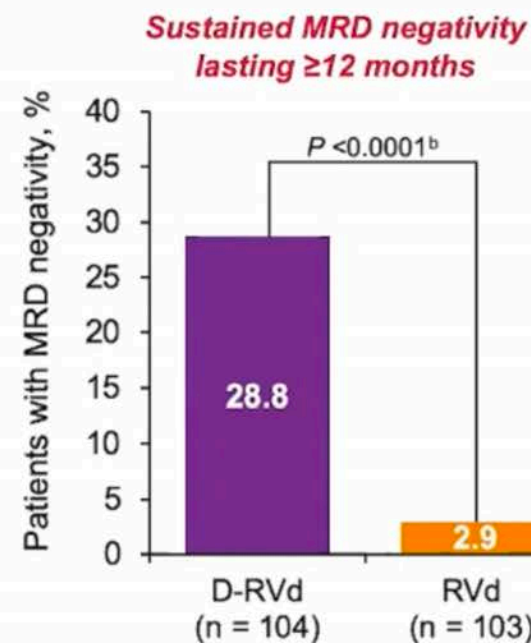
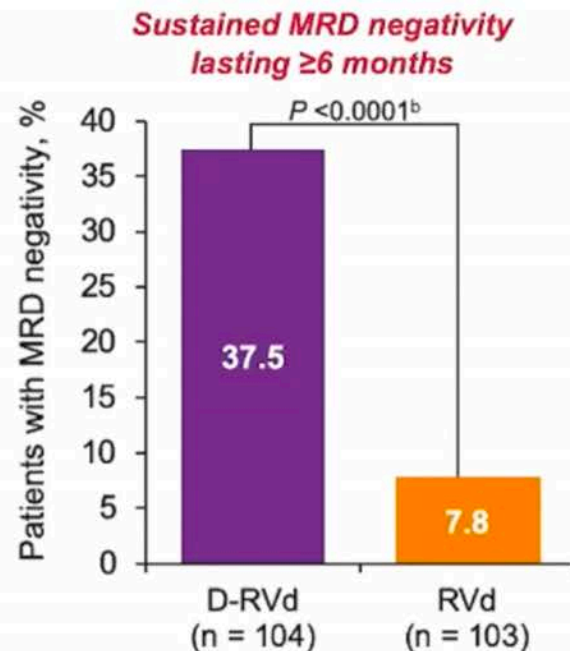
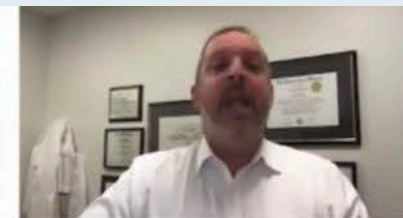
ASH 2020;Abstract 549.

GRIFFIN Randomized Phase II Study Design



Primary endpoint: Stringent CR by end of consolidation

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



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

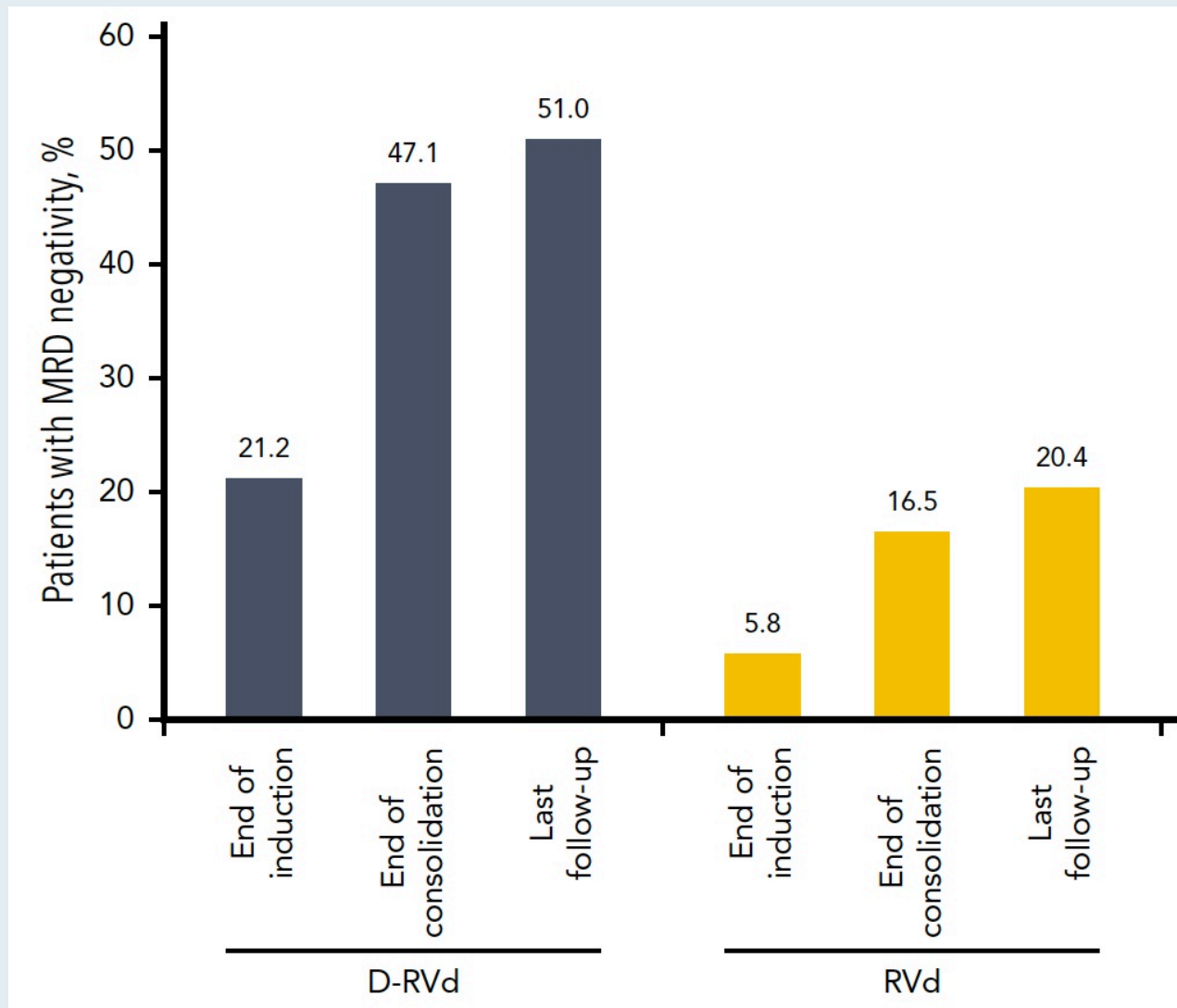
D-RVd improved rates of sustained MRD negativity versus RVd

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



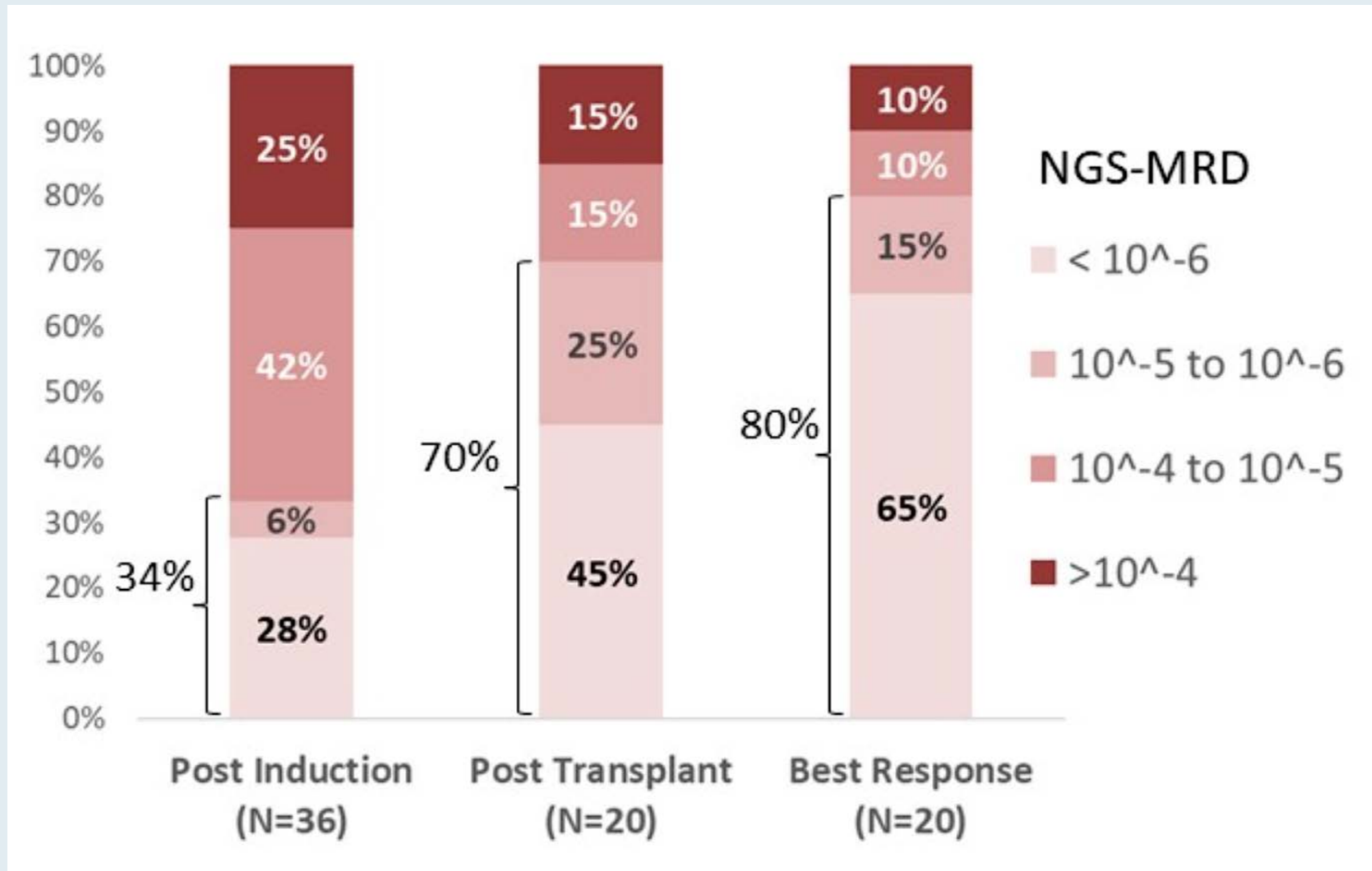
American Society of Hematology

GRIFFIN: Summary of Response Rates and MRD Negativity (10^{-5}) Rates Over Time



- MRD negativity (10^{-5}) rates in the intent-to-treat population by the end of induction therapy, end of consolidation and last follow-up
- All MRD data are from the analysis with a median follow-up of 22.1 months
- MRD was evaluated at baseline, first evidence of suspected CR or sCR, at the end of induction and consolidation, and after 12 and 24 months of maintenance, regardless of response (per protocol amendment 2)

MASTER: MRD-Negative Remissions

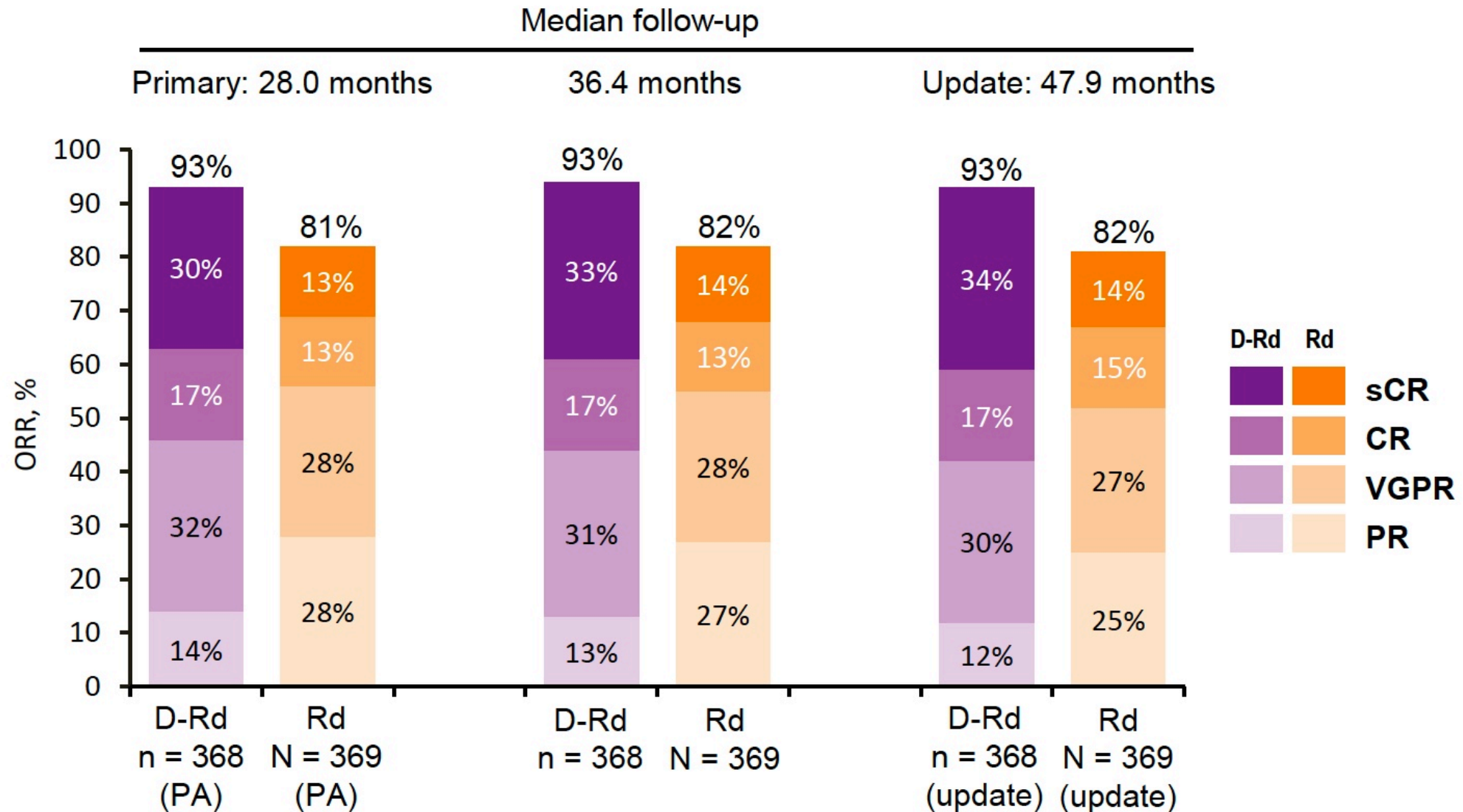


Updated Analysis of Daratumumab plus Lenalidomide and Dexamethasone (D-Rd) versus Lenalidomide and Dexamethasone (Rd) in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma (NDMM): The Phase 3 Maia Study

Kumar SK et al.

ASH 2020;Abstract 2276.

MAIA: Updated Response



MAIA: Updated Overall Response

| | D-Rd (n = 368) | Rd (n = 369) | <i>p</i> -value |
|-------|-------------------|-----------------|-----------------|
| ORR | 93% | 82% | <0.0001 |
| sCR | 34% | 14% | <0.0001 |
| CR | 17% | 15% | — |
| VGPR | 30% | 27% | — |
| PR | 12% | 25% | — |
| ≥VGPR | 81% | 57% | <0.0001 |
| ≥CR | 51% | 30% | <0.0001 |

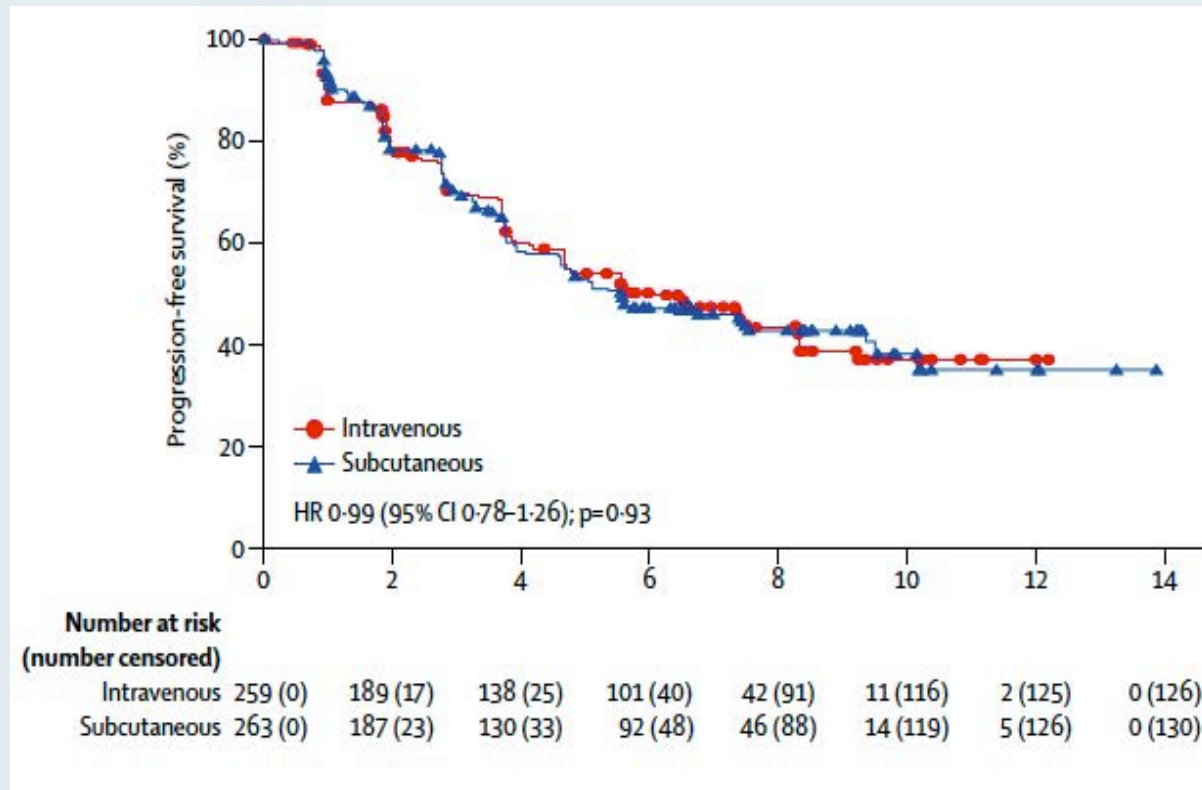


Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial

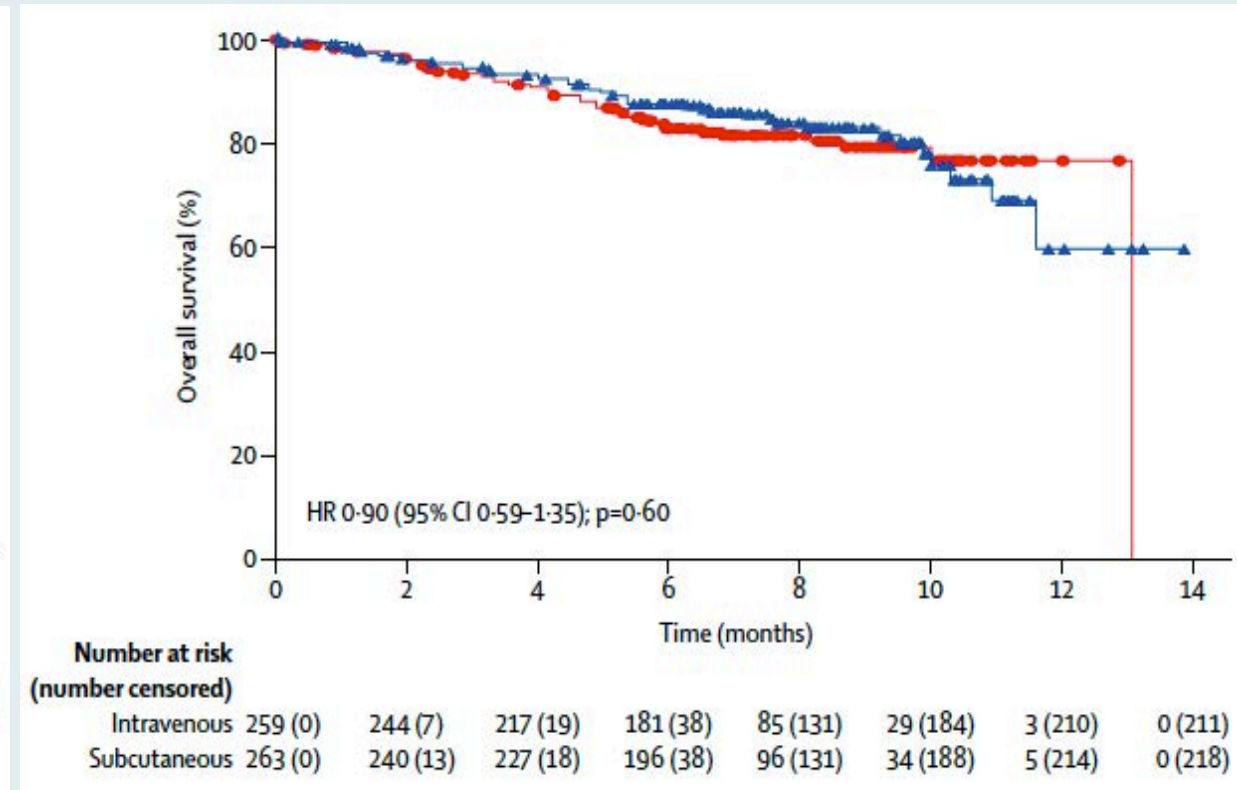
Maria-Victoria Mateos, Hareth Nahi, Wojciech Legiec, Sebastian Grosicki, Vladimir Vorobyev, Ivan Spicka, Vania Hungria, Sibirina Korenkova, Nizar Bahlis, Max Flogegard, Joan Bladé, Philippe Moreau, Martin Kaiser, Shinsuke Iida, Jacob Laubach, Hila Magen, Michele Cavo, Cyrille Hulin, Darrell White, Valerio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

COLUMBA: Subcutaneous versus Intravenous Daratumumab

Progression-Free Survival



Overall Survival



(Median follow-up 7.5 months)

Efficacy of Daratumumab in the Treatment of Multiple Myeloma with High-Risk Cytogenetics: Meta-analysis of Randomized Phase III Trials

Giri S et al.

ASCO 2020;Abstract 8540.

Impact of Daratumumab on PFS Among Patients with Multiple Myeloma and High-Risk Cytogenetics [t(4;14), t(14;16) or del(17p)]

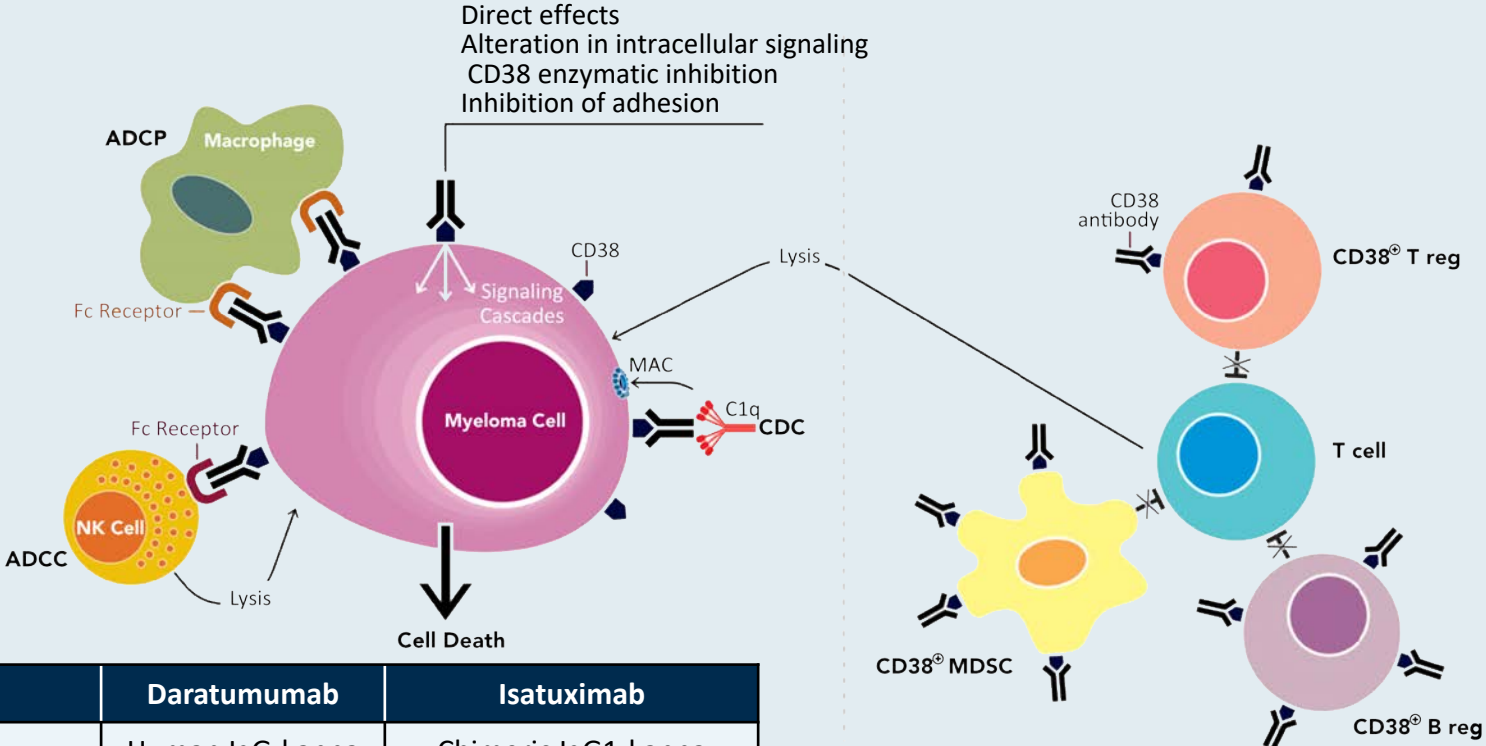
| Study | Intervention | Control | Hazard ratio | <i>p</i> -value |
|----------------------------------|--------------|---------|--------------|------------------|
| ALCYONE | DaraVMP | VMP | 0.78 | 0.42 |
| MAIA | DaraRD | RD | 0.57 | 0.06 |
| CASSIOPEIA | DaraVTD | VTD | 0.67 | 0.23 |
| <i>Pooled effect size</i> | | | 0.67 | 0.025 |
| CASTOR | DaraVD | VD | 0.41 | 0.01 |
| POLLUX | DaraRD | RD | 0.37 | 0.01 |
| CANDOR | DaraKD | KD | 0.58 | 0.11 |
| <i>Pooled effect size</i> | | | 0.45 | <0.001 |

Relapsed Multiple Myeloma

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

Fc-dependent immune effector mechanisms and direct effects

Immunomodulatory effects



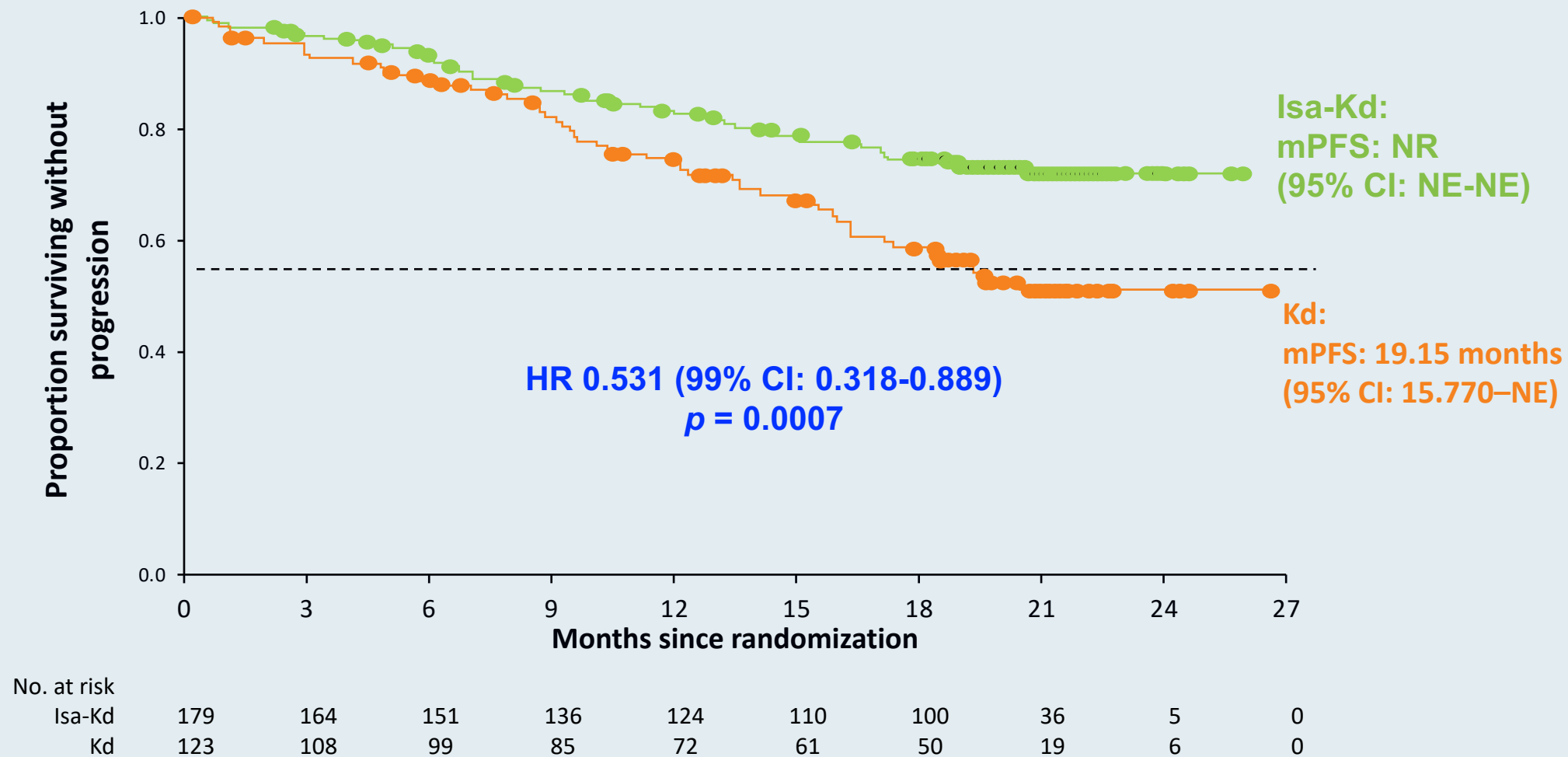
| Mechanism of action | Daratumumab | Isatuximab |
|--------------------------------|-----------------|---------------------|
| Origin, isotype | Human IgG-kappa | Chimeric IgG1-kappa |
| CDC | +++ | + |
| ADCC | ++ | ++ |
| ADCP | +++ | Not determined |
| PCD direct | — | ++ |
| PCD cross linking |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

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

Moreau P et al.

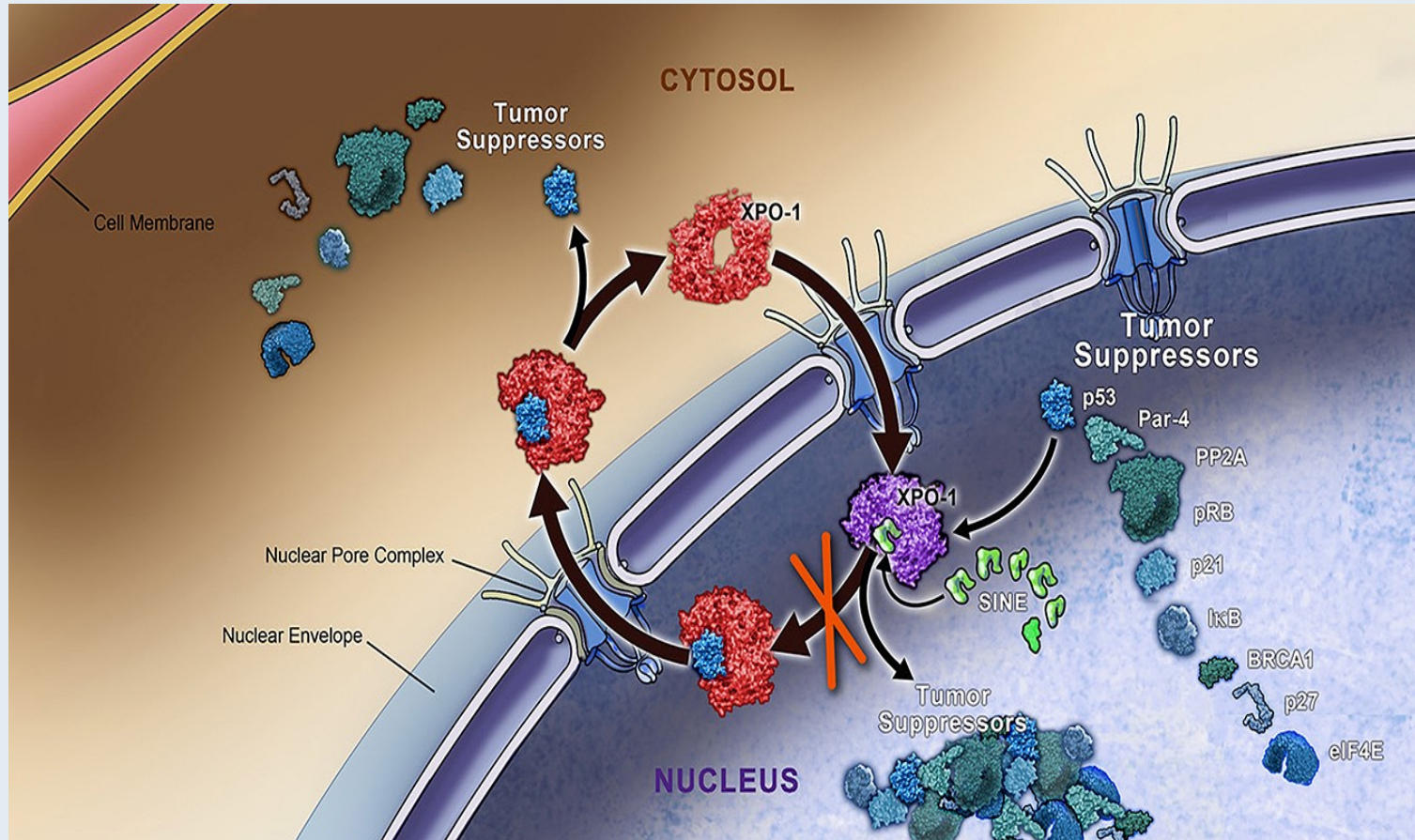
EHA 2020;Abstract LB2603.

IKEMA: PFS



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

Selinexor Mechanism of Action



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

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



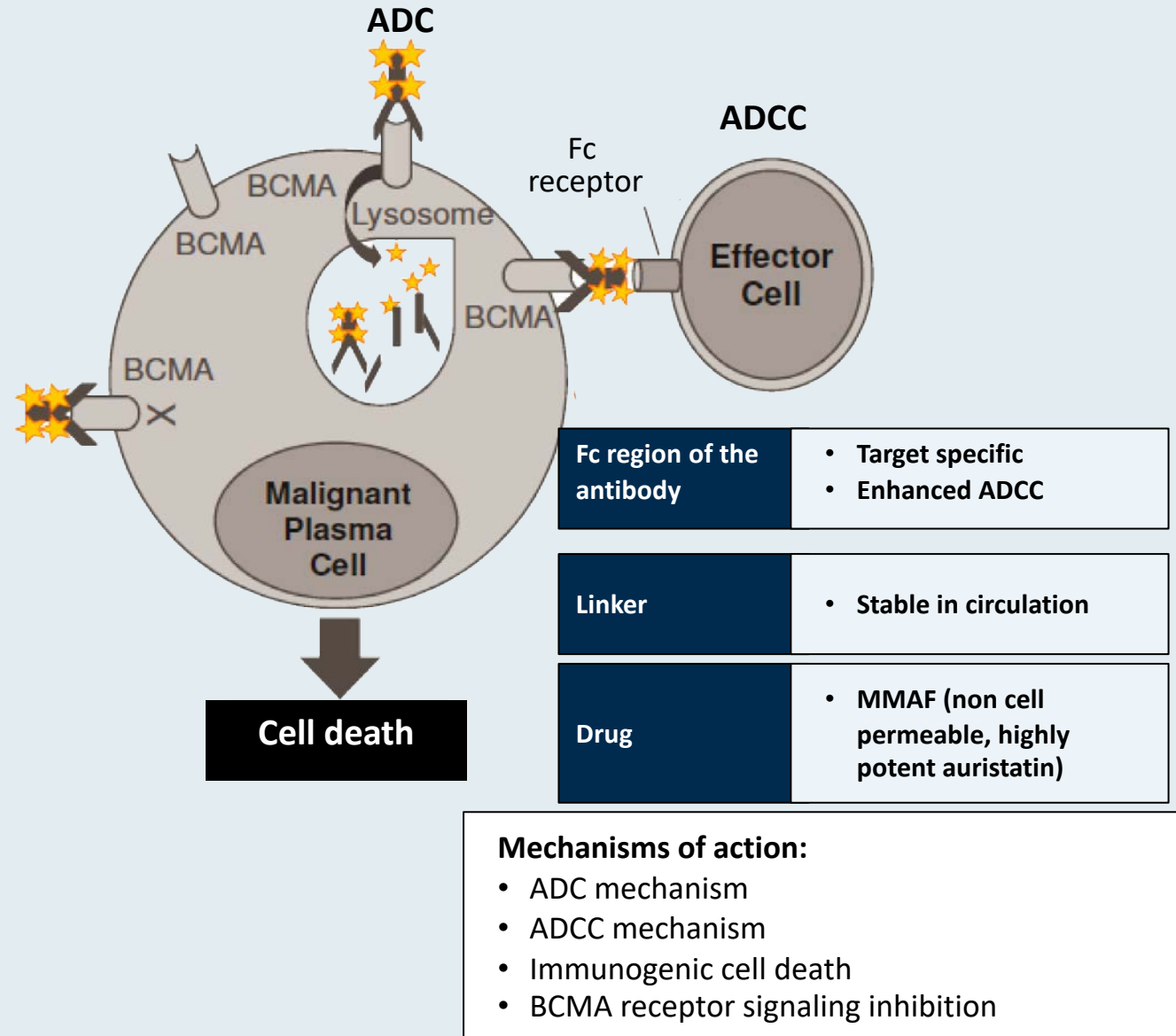
Sebastian Grosicki, Maryana Simonova, Ivan Spicka, Ludek Pour, Iryna Kriachok, Maria Gavriatopoulou, Halyna Pylypenko, Holger W Auner, Xavier Lelev, Vadim Doronin, Ganna Usenko, Nizar J Bahlis, Roman Hajek, Reuben Benjamin, Tuphan K Dolai, Dinesh K Sinha, Christopher P Venner, Mamta Garg, Mercedes Gironella,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

BOSTON: Select Adverse Events

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

Belamaf: Anti-BCMA Antibody-Drug Conjugate

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



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

Lonial S et al.

ASH 2020;Abstract 1417.

DREAMM-6: Safety, Tolerability and Clinical Activity of Belantamab Mafodotin (Belamaf) in Combination with Bortezomib/Dexamethasone (BorDex) in Relapsed/Refractory Multiple Myeloma (RRMM)

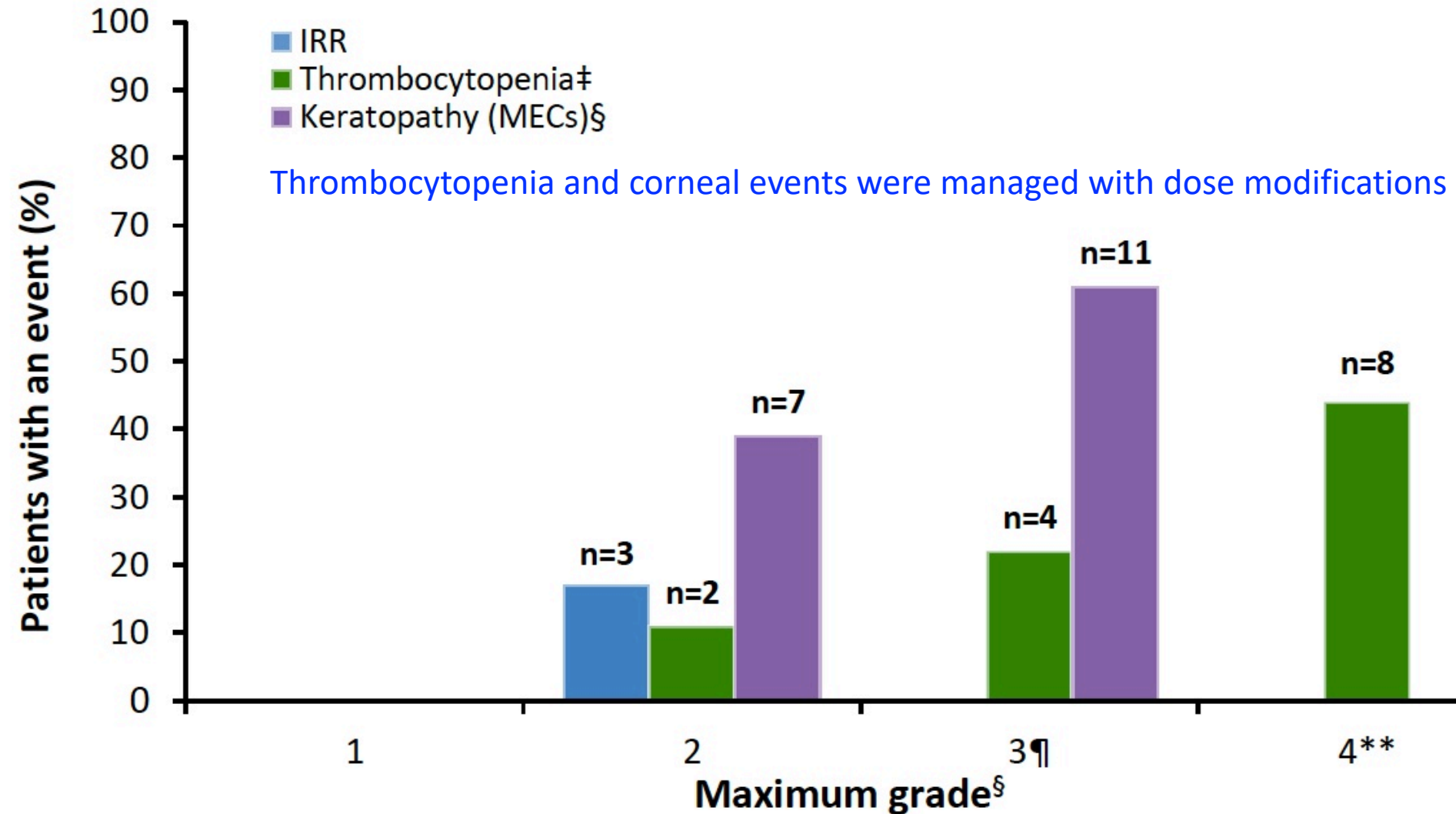
Popat R et al.

ASH 2020;Abstract 1419.

DREAMM-6: Overview of Adverse Events

| Patients with AE, n (%) | Belantamab mafodotin 2.5 mg/kg single + Vd (N = 18) |
|---|--|
| AEs related to study treatment | 18 (100) |
| Grade 3/4 AE | 16 (89) |
| AEs leading to permanent discontinuation of a study treatment | 5 (28) |
| AEs leading to permanent discontinuation of belamaf | 0 |
| AEs leading to dose reductions | 13 (72) |
| Corneal events | 7 (39) |
| Thrombocytopenia | 6 (33) |
| AEs leading to dose interruption/delay | 18 (100) |
| Corneal events | 15 (83) |
| Thrombocytopenia | 7 (39) |
| Any SAE | 12 (67) |
| Fatal SAE | 0 |
| SAEs related to study treatment | 5 (28) |

DREAMM-6: Adverse Events of Special Interest



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

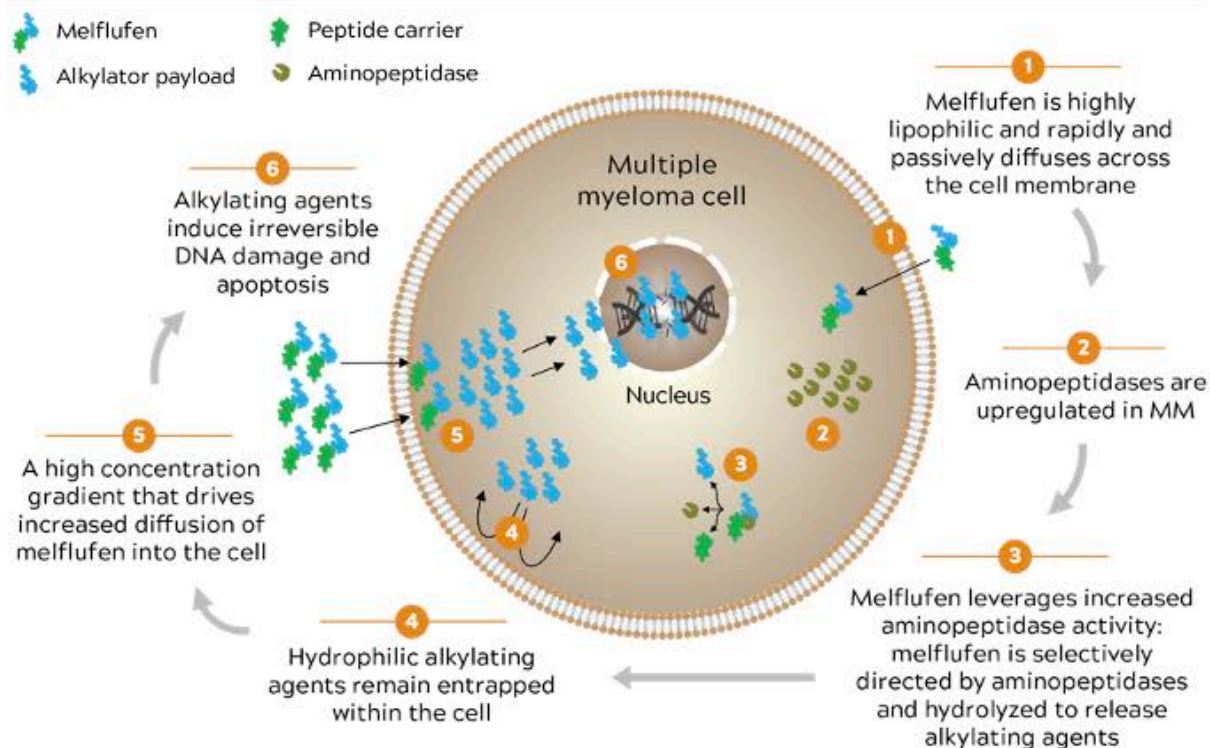
Press Release: February 26, 2021

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

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

Melphalan Flufenamide (Melflufen): Mechanism of Action

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



- In the pivotal phase 2 HORIZON study (OP-106), the activity of melflufen plus dexamethasone was further shown in heavily pretreated RRMM patients refractory to pomalidomide and/or anti-CD38 mAb therapy, with acceptable safety⁶
 - ORR was 29%; median PFS was 4.2 months, and median OS was 11.6 months
 - Grade 3/4 hematologic AEs were common (mainly neutropenia [79%], thrombocytopenia [76%], and anemia [71%]) but clinically manageable; nonhematologic AEs were infrequent

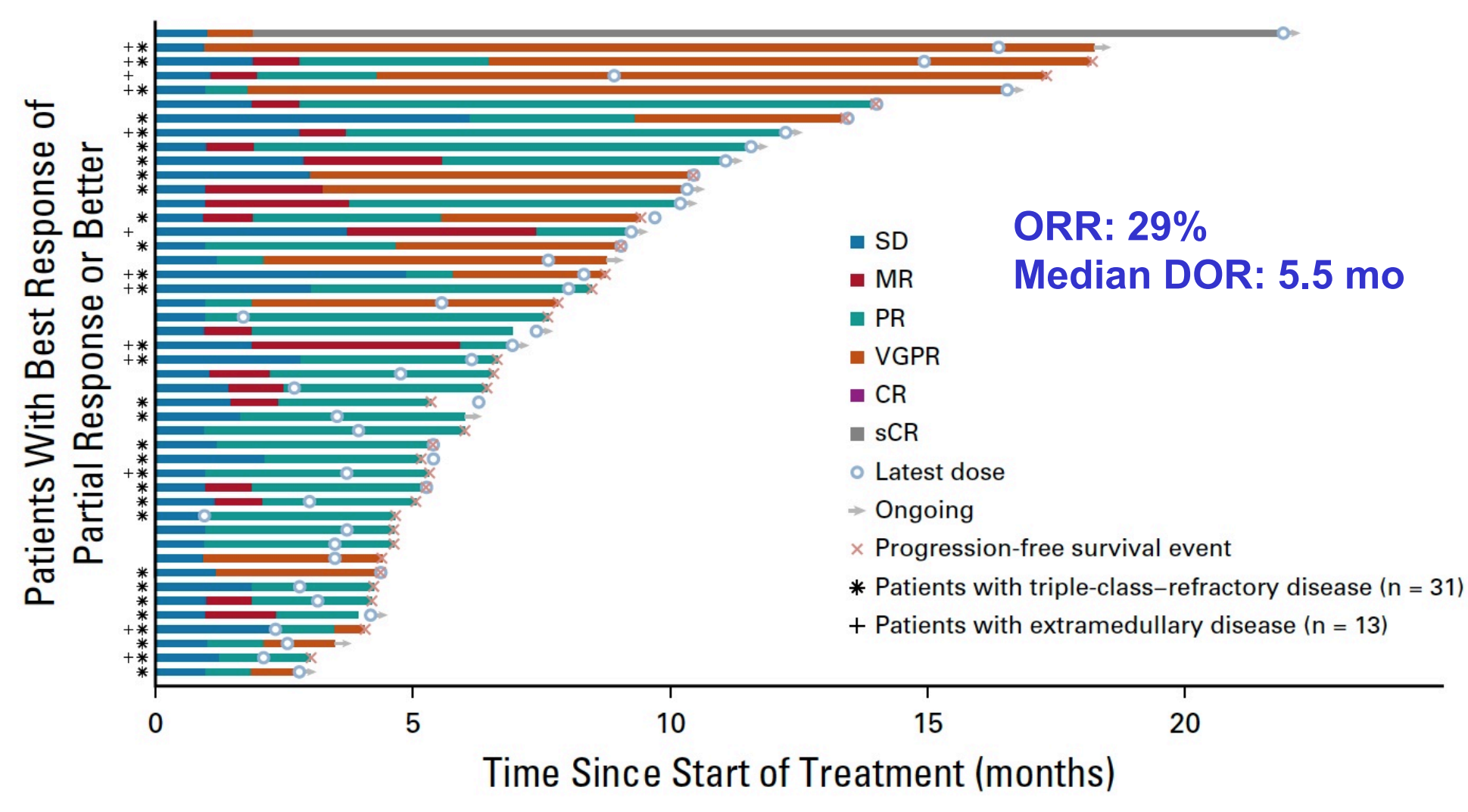
AE, adverse event; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-rate survival; RRMM, relapsed/refractory multiple myeloma.

Melflufen and Dexamethasone in Heavily Pretreated Relapsed and Refractory Multiple Myeloma

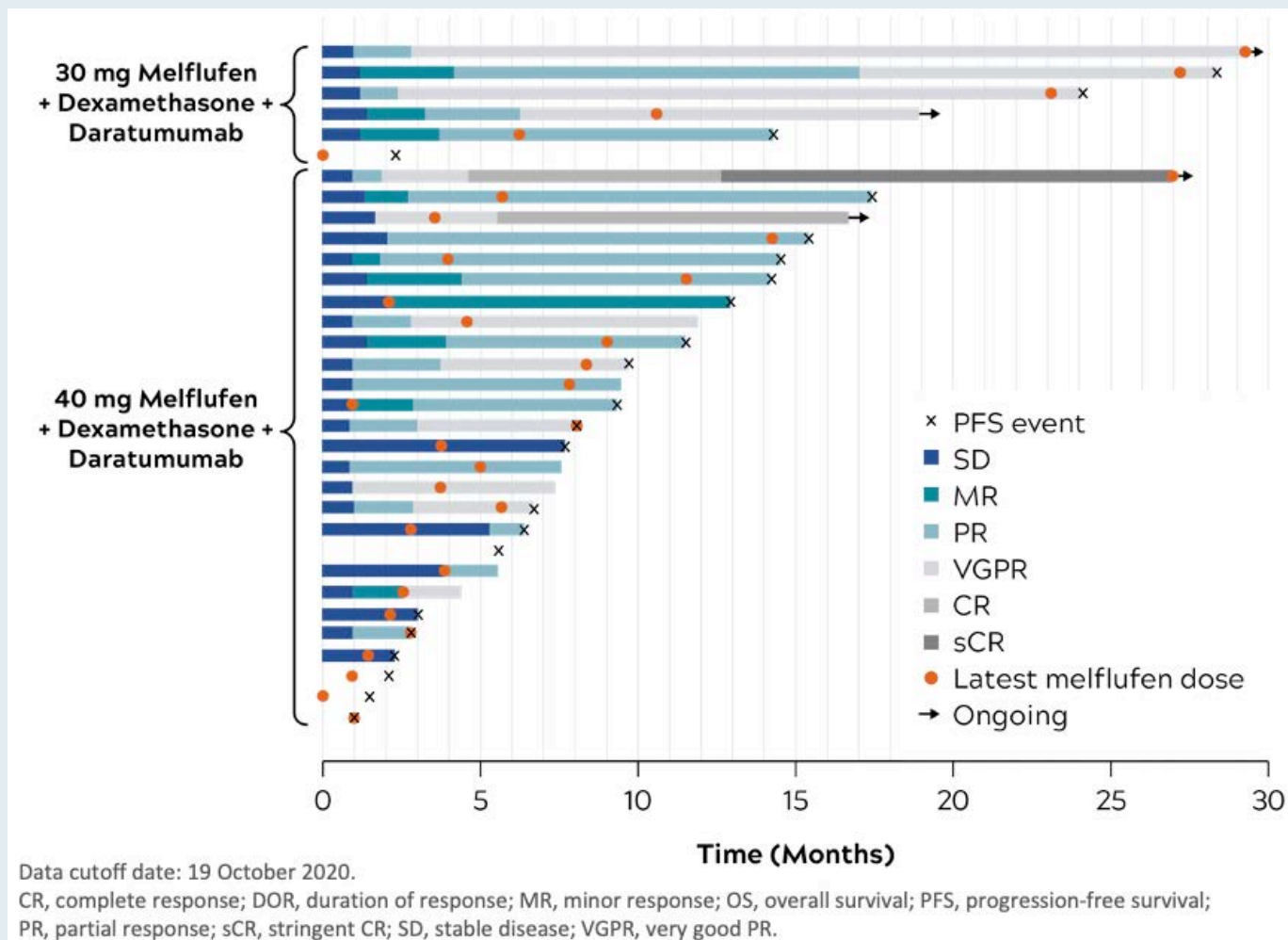
Paul G. Richardson, MD¹; Albert Oriol, MD²; Alessandra Larocca, MD, PhD³; Joan Bladé, MD, PhD⁴; Michele Cavo, MD⁵; Paula Rodriguez-Otero, MD, PhD⁶; Xavier Leleu, MD, PhD⁷; Omar Nadeem, MD¹; John W. Hiemenz, MD⁸; Hani Hassoun, MD⁹; Cyrille Touzeau, MD, PhD^{10,11,12}; Adrián Alegre, MD, PhD¹³; Agne Paner, MD¹⁴; Christopher Maisel, MD¹⁵; Amitabha Mazumder, MD¹⁶; Anastasios Raptis, MD¹⁷; Jan S. Moreb, MD¹⁸; Kenneth C. Anderson, MD¹; Jacob P. Laubach, MD, MPP¹; Sara Thuresson, MSc¹⁹; Marcus Thuresson, PhD¹⁹; Catriona Byrne, RN¹⁹; Johan Harmenberg, MD¹⁹; Nicolaas A. Bakker, MD, PhD¹⁹; and María-Victoria Mateos, MD, PhD²⁰; on behalf of the HORIZON (OP-106) Investigators

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

HORIZON: Overall Response and Duration of Response with Melflufen



ANCHOR: Melflufen with Dexamethasone and Daratumumab



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

ORIGINAL ARTICLE

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

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

KarMMa: Select Adverse Events

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

Characteristics of Select BCMA CAR-T Studies in Multiple Myeloma

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






Approved 3/26/2021

* Included +1q21

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

Safety of Select BCMA CAR-T Studies in Multiple Myeloma

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


Approved 3/26/2021

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

Module 5: Breast Cancer

Relevant Recent Data Sets

HER2-Positive Breast Cancer

FDA-Approved Agents for Early-Stage HER2-Positive BC

| Agent | Setting | Pivotal trial(s) | Regimens | Year approved |
|-------------|---|--|--|---------------|
| Trastuzumab | Adjuvant HER2+ EBC, first line | NSABP-31 N9831 BCIRG 006 HERA | AC-T-placebo vs AC-T-H AC-T vs AC-H vs AC-T-H ACT vs ACT-H vs TC-H Observation vs trastuzumab | 2006 |
| Pertuzumab | Neoadjuvant HER2+, EBC | NeoSphere | TD vs PTD vs PT vs PD | 2013 |
| Pertuzumab | Adjuvant HER2+, EBC | APHINITY | Chemotherapy plus trastuzumab plus pertuzumab vs placebo | 2017 |
| Neratinib | Extended adjuvant treatment of HER2+ EBC | ExteNET | Placebo vs neratinib | 2017 |
| T-DM1 | Adjuvant HER2+ EBC with residual disease after neoadjuvant taxane and trastuzumab based treatment | KATHERINE | Trastuzumab vs T-DM1 | 2019 |

AC-H = doxorubicin, cyclophosphamide, and trastuzumab; AC-T, doxorubicin, cyclophosphamide, and paclitaxel; AC-T-H, doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab; H, trastuzumab; PD, pertuzumab and docetaxel; PT, trastuzumab and pertuzumab; PTD, pertuzumab, trastuzumab, and docetaxel; TC, docetaxel and cyclophosphamide; TC-H, docetaxel, cyclophosphamide, and trastuzumab; TD, trastuzumab and docetaxel; THP, docetaxel, trastuzumab, and pertuzumab

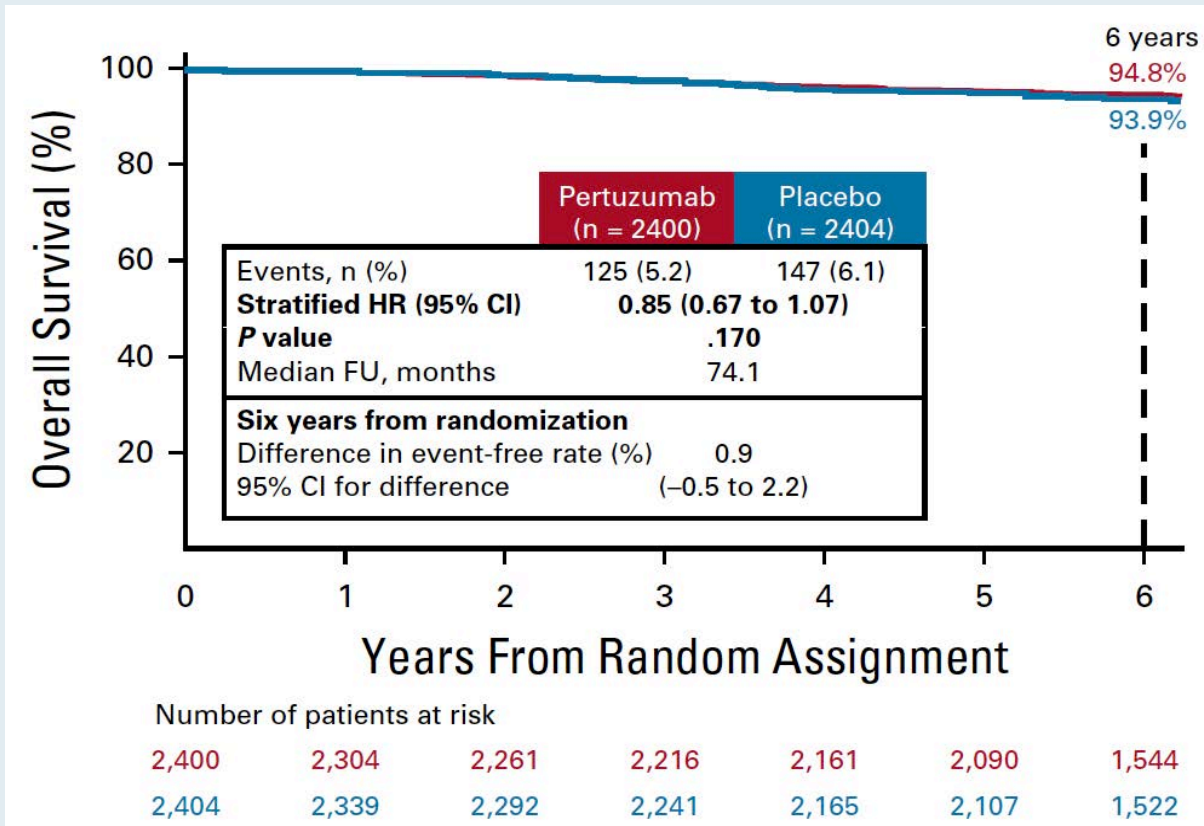
Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up

Martine Piccart, MD, PhD¹; Marion Procter, PhD²; Debora Fumagalli, MD, PhD³; Evandro de Azambuja, MD, PhD¹; Emma Clark, MSc⁴; Michael S. Ewer, MD, JD, PhD⁵; Eleonora Restuccia, MD⁶; Guy Jerusalem, MD, PhD⁷; Susan Dent, BSc, MD⁸; Linda Reaby, AM, PhD^{9,10}; Hervé Bonnefoi, MD¹¹; Ian Krop, MD, PhD¹²; Tsang-Wu Liu, MD¹³; Tadeusz Pieńkowski, MD, PhD¹⁴; Masakazu Toi, MD, PhD¹⁵; Nicholas Wilcken, PhD^{16,17}; Michael Andersson, MD, DMSci^{19,18}; Young-Hyuck Im, MD, PhD¹⁹; Ling Ming Tseng, MD²⁰; Hans-Joachim Lueck, MD²¹; Marco Colleoni, MD²²; Estefania Monturus, PhD⁶; Mihaela Sicoe, MSc³; Sébastien Guillaume, MSc¹; José Bines, MD, PhD²³; Richard D. Gelber, PhD²⁴; Giuseppe Viale, MD²⁵; and Christoph Thomssen, MD²⁶ for the APHINITY Steering Committee and Investigators

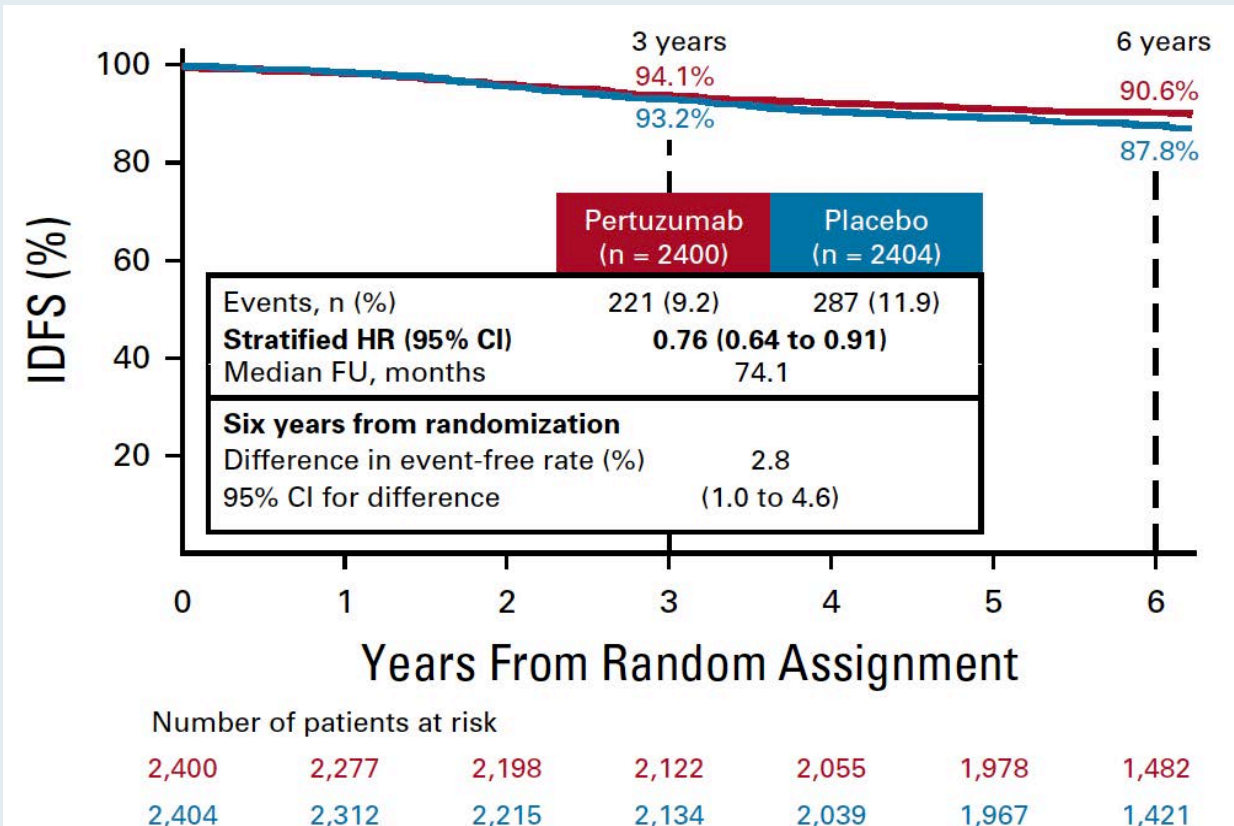
J Clin Oncol 2021;[Online ahead of print].

APHINITY: 6-Year Follow-Up

Overall Survival

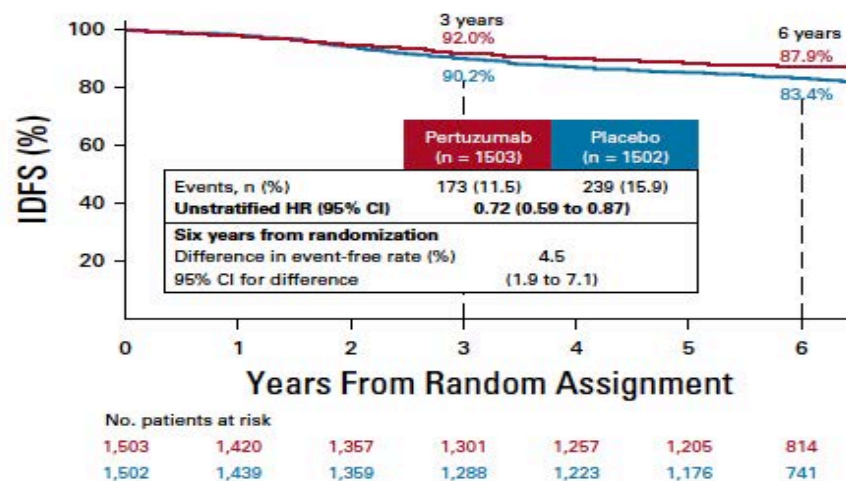


Invasive Disease-Free Survival

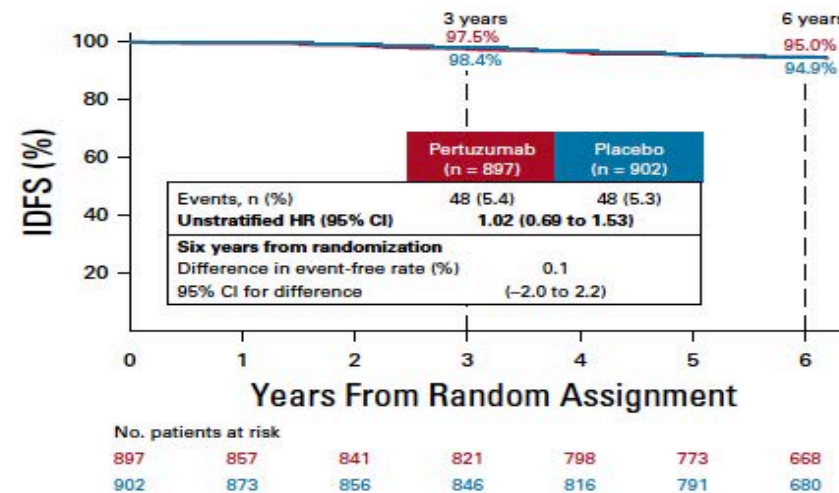


APHINITY: 6-Year IDFS by Subgroup

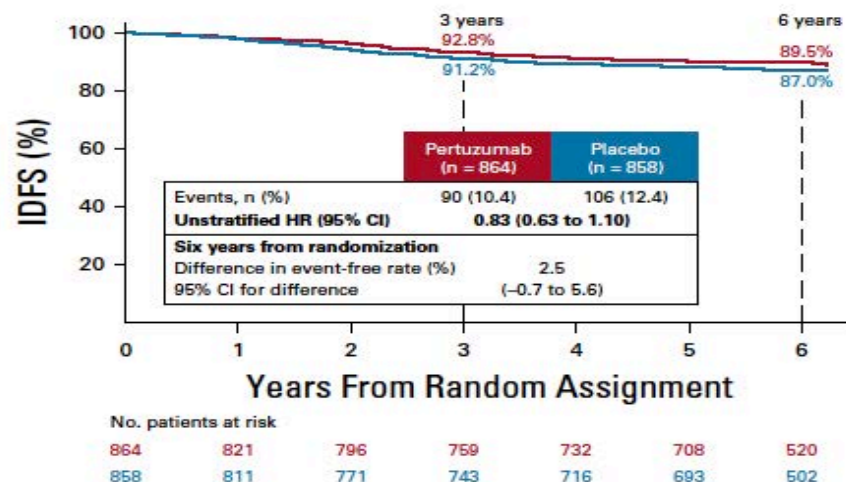
Node-positive cohort



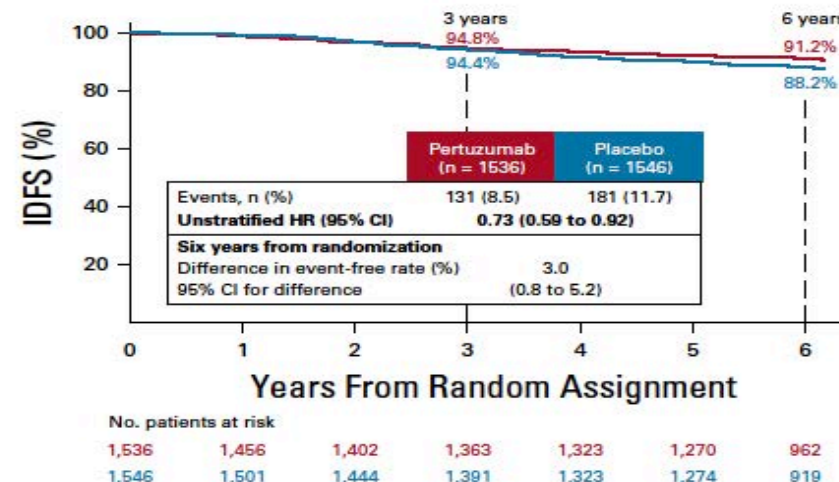
Node-negative cohort



HR-negative cohort



HR-positive cohort



Original Study

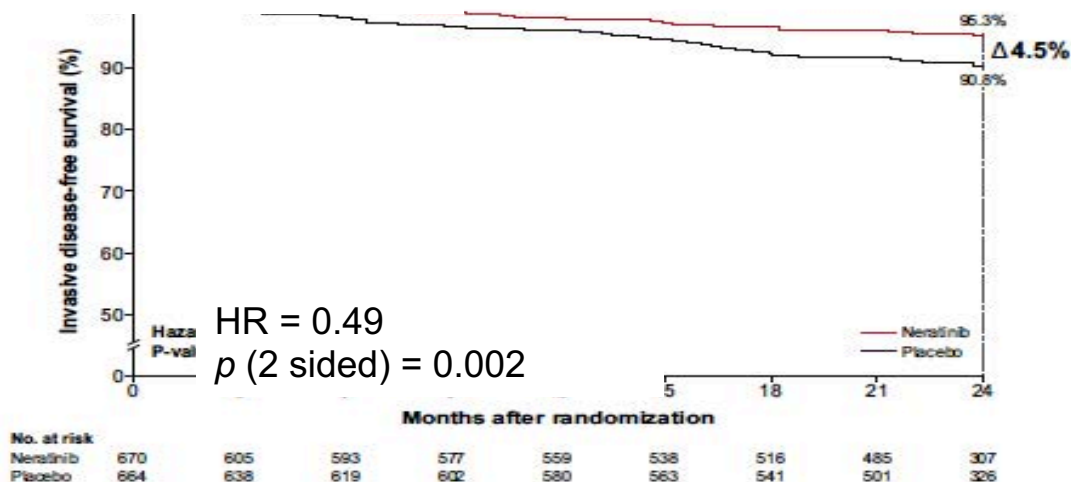
Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial

Arlene Chan,¹ Beverly Moy,² Janine Mansi,³ Bent Ejlersen,⁴ Frankie Ann Holmes,⁵
Stephen Chia,⁶ Hiroji Iwata,⁷ Michael Gnant,⁸ Sibylle Loibl,⁹ Carlos H. Barrios,¹⁰
Isil Somali,¹¹ Snezhana Smichkoska,¹² Noelia Martinez,¹³ Mirta Garcia Alonso,¹⁴
John S. Link,¹⁵ Ingrid A. Mayer,¹⁶ Søren Cold,¹⁷ Serafin Morales Murillo,¹⁸
Francis Senecal,¹⁹ Kenichi Inoue,²⁰ Manuel Ruiz-Borrego,²¹ Rina Hui,²²
Neelima Denduluri,²³ Debra Patt,²⁴ Hope S. Rugo,²⁵ Stephen R.D. Johnston,²⁶
Richard Bryce,²⁷ Bo Zhang,²⁷ Feng Xu,²⁷ Alvin Wong,²⁷ Miguel Martin,²⁸ for the
ExteNET Study Group

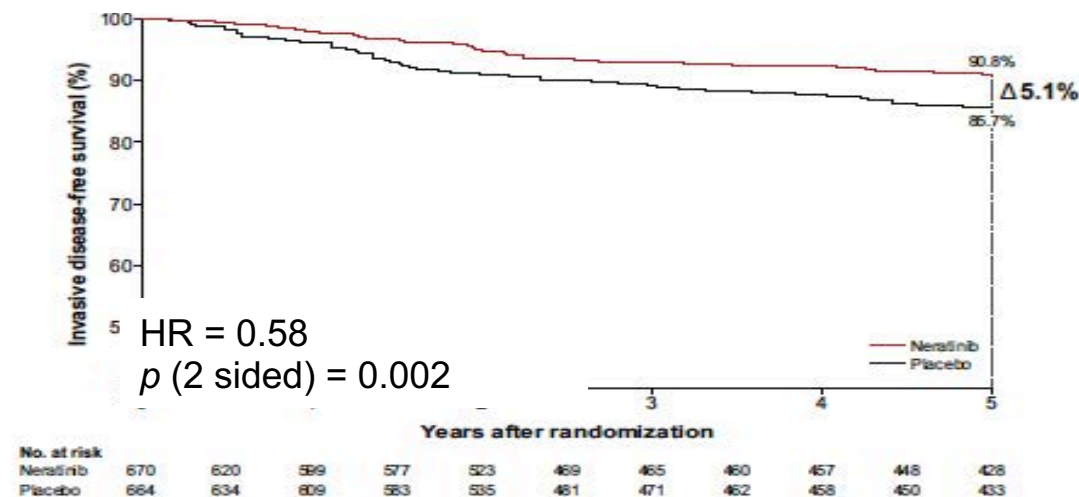
Clin Breast Cancer 2021;21(1):80-91.e.7.

ExteNET: Final Efficacy Results in HR+ Population (n = 1,334)

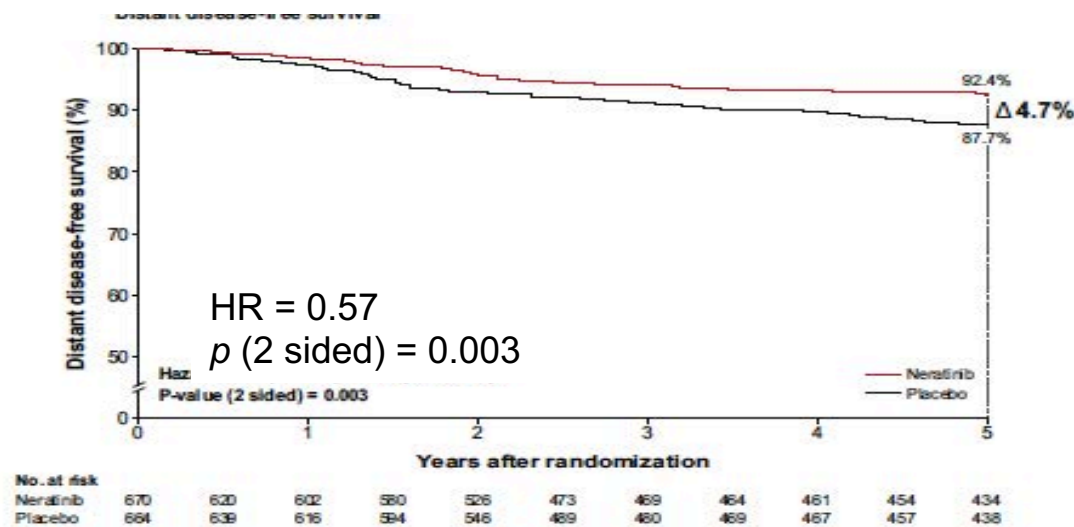
IDFS at 2 Years



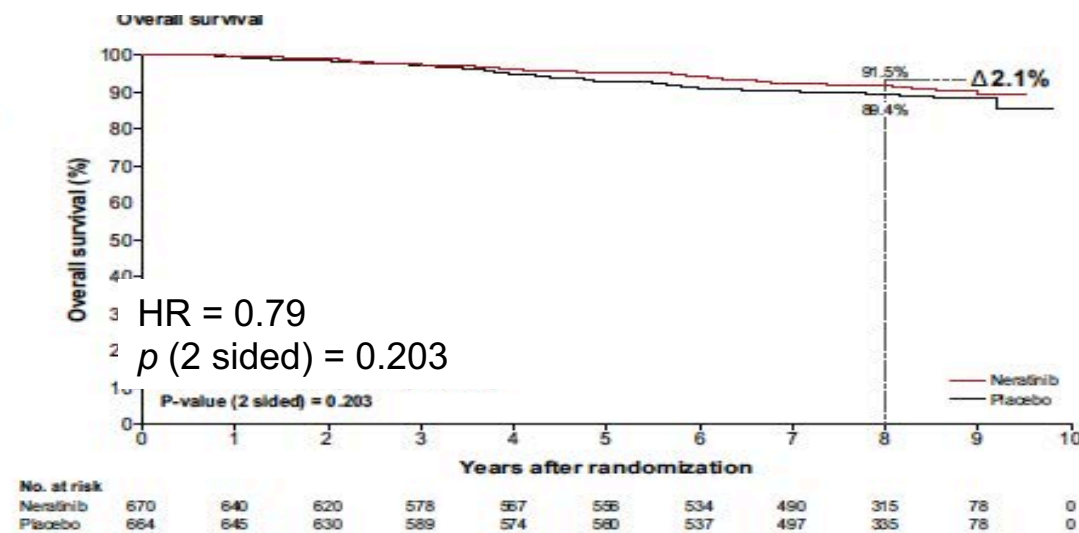
IDFS at 5 Years



Distant DFS at 5 Years



OS



CONTROL Trial: Strategies to Improve Neratinib Tolerability

Background: Neratinib is approved for extended adjuvant therapy in HER2-positive BC

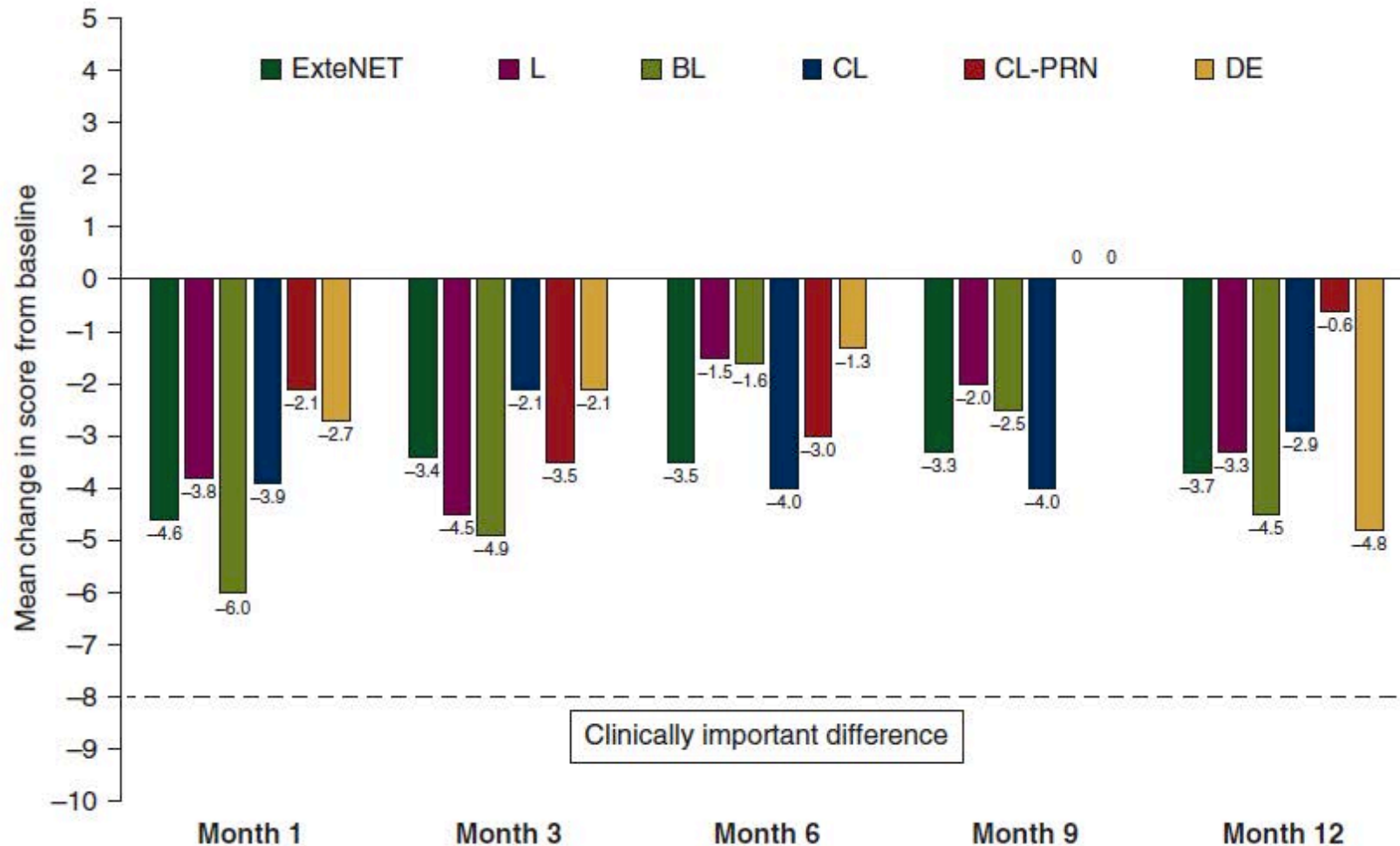
- Neratinib poorly tolerated in ExteNET
 - Discontinuation rate: 17%
 - Grade 3 diarrhea: 40%

Objective: Improve GI tolerability of neratinib

Methods: Sequential single arm interventions in patients treated with adjuvant therapy

- Cohort 1 (L): Loperamide (n = 137)
- Cohort 2 (BL): Budesonide + loperamide (n = 64)
- Cohort 3 (CL or CL-PRN): Colestipol + loperamide (n = 136) or colestipol + as needed loperamide (n = 104)
- Cohort 4 (DE): Neratinib dose escalation; ongoing (n = 60)

CONTROL: Mean Change in Functional Assessment of Cancer Therapy*



*A higher score indicates better quality of life.

Select Ongoing Phase III Trials in HER2-Positive Localized BC

| Trial name (NCT#) | N | Setting | Treatment arms | Estimated primary completion date |
|-----------------------------------|-------|--|---|-----------------------------------|
| DESTINY-Breast05 (NCT04622319) | 1,600 | High-risk with residual invasive BC following neoadjuvant therapy | <ul style="list-style-type: none"> Trastuzumab deruxtecan T-DM1 | December 2025 |
| CompassHER2RD (NCT04457596) | 1,031 | HR-negative disease in breast and/or lymph nodes; T1-4, N0-3 dx at presentation and residual invasive disease postoperatively | <ul style="list-style-type: none"> T-DM1 Tucatinib + T-DM1 | January 2028 |

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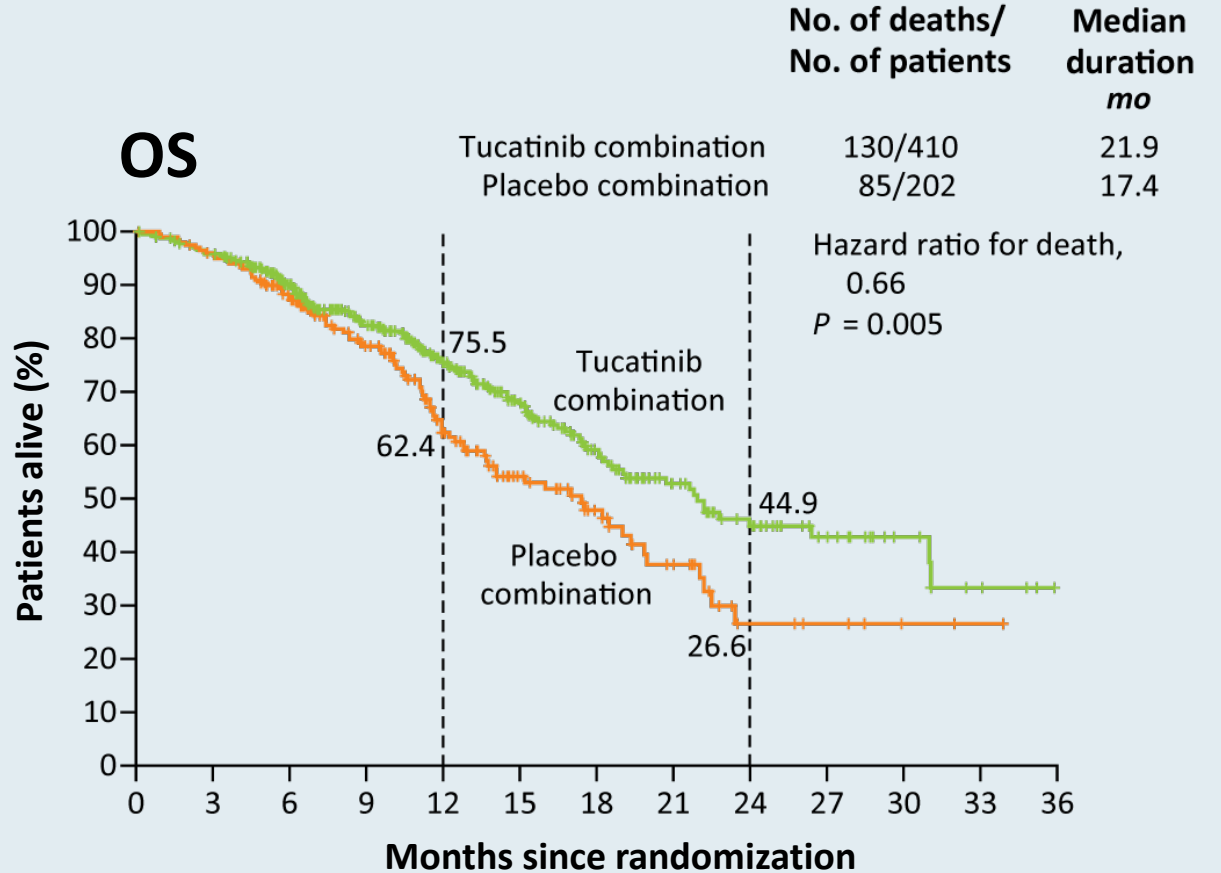
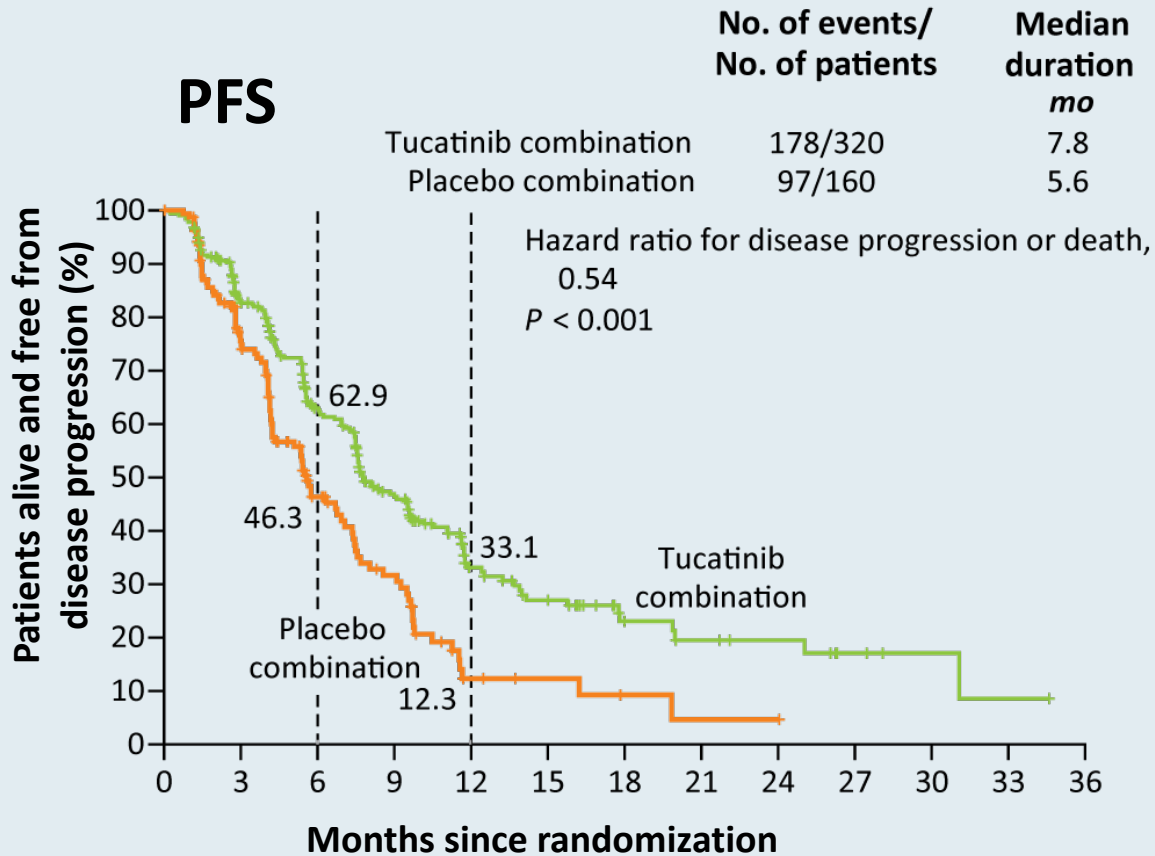
Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

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

HER2CLIMB: Survival Outcomes

Among the patients with brain metastases:

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



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

HER2CLIMB: Safety Outcomes

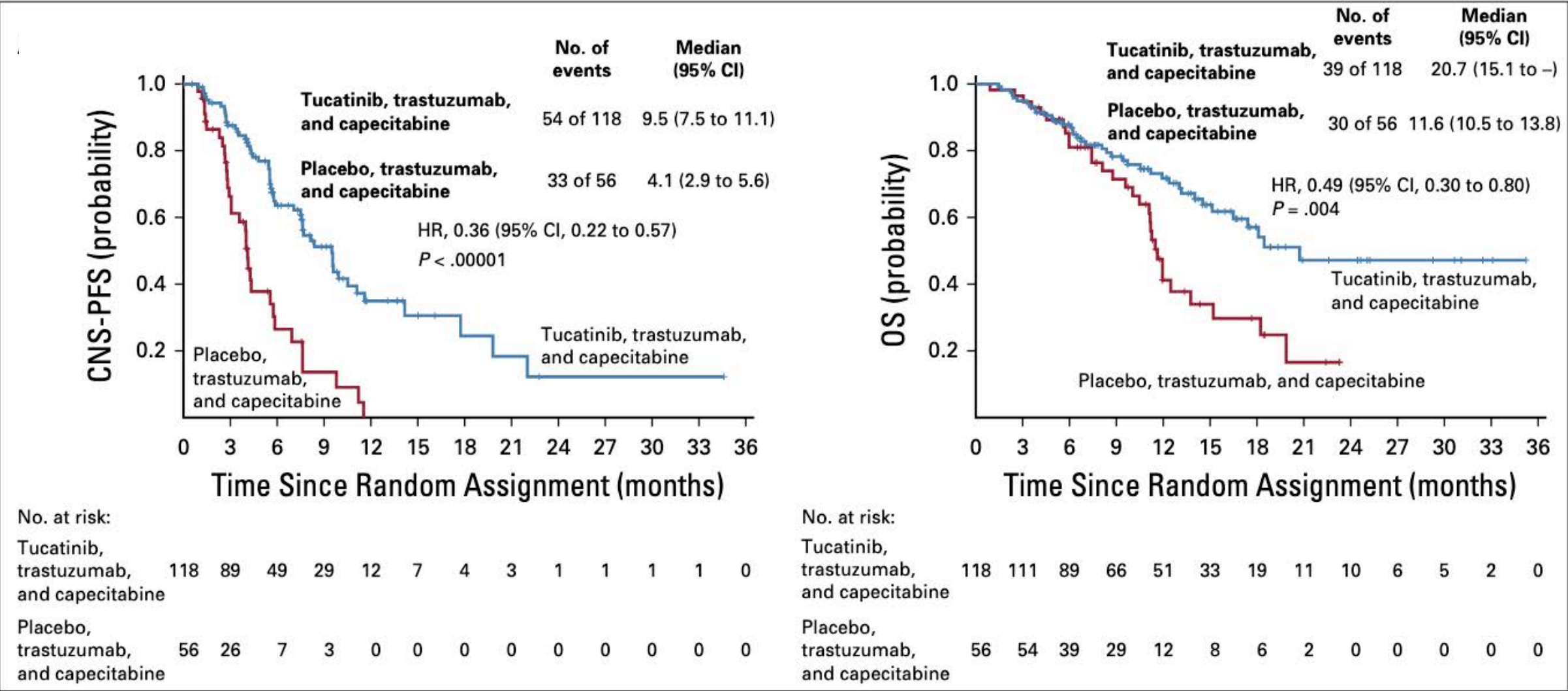
| Select AE | Tucatinib (n = 404) | | Placebo (n = 197) | |
|---------------|---------------------|----------|-------------------|----------|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Any | 99.3% | 55.2% | 97.0% | 48.7% |
| Diarrhea | 80.9% | 12.9% | 53.3% | 8.6% |
| PPE syndrome | 63.4% |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

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

Nancy U. Lin, MD¹; Virginia Borges, MMSc, MD²; Carey Anders, MD³; Rashmi K. Murthy, MD, MBE⁴; Elisavet Paplomata, MD⁵; Erika Hamilton, MD⁶; Sara Hurvitz, MD⁷; Sherene Loi, MD, PhD⁸; Alicia Okines, MBChB, MD⁹; Vandana Abramson, MD¹⁰; Philippe L. Bedard, MD¹¹; Mafalda Oliveira, MD, PhD¹²; Volkmar Mueller, MD¹³; Amelia Zelnak, MD¹⁴; Michael P. DiGiovanna, MD, PhD¹⁵; Thomas Bachelot, MD¹⁶; A. Jo Chien, MD¹⁷; Ruth O'Regan, MD⁵; Andrew Wardley, MBChB, MSc, MD¹⁸; Alison Conlin, MD, MPH¹⁹; David Cameron, MD, MA²⁰; Lisa Carey, MD²¹; Giuseppe Curigliano, MD, PhD²²; Karen Gelmon, MD²³; Sibylle Loibl, MD, PhD²⁴; JoAl Mayor, PharmD²⁵; Suzanne McGoldrick, MD, MPH²⁵; Xuebei An, PhD²⁵; and Eric P. Winer, MD¹

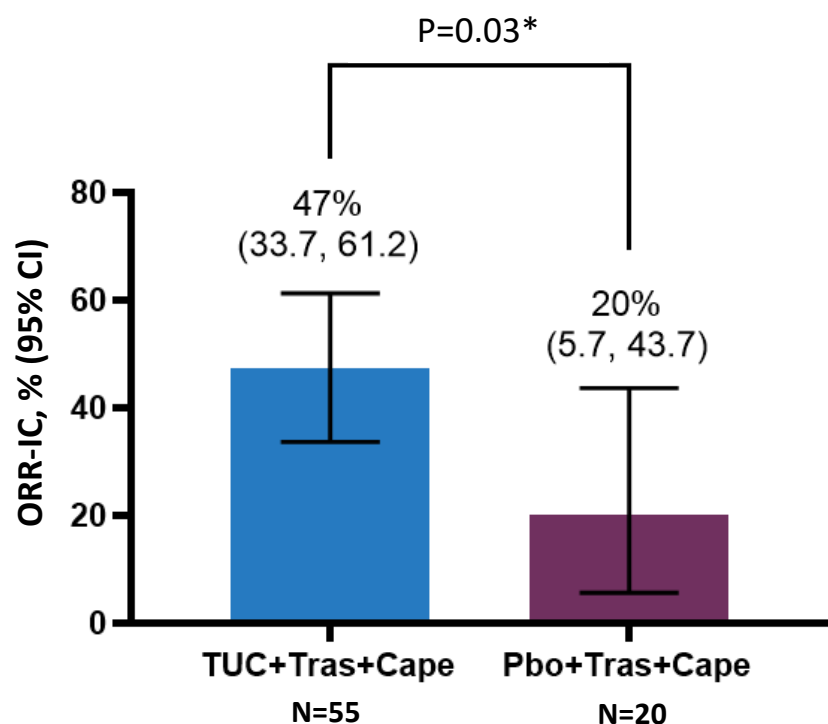
J Clin Oncol 2020;38(23):2610-9.

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



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

Confirmed Objective Response Rate (RECIST 1.1)



*Stratified Cochran-Mantel-Haenszel P value

Courtesy of Carey K Anders, MD

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

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

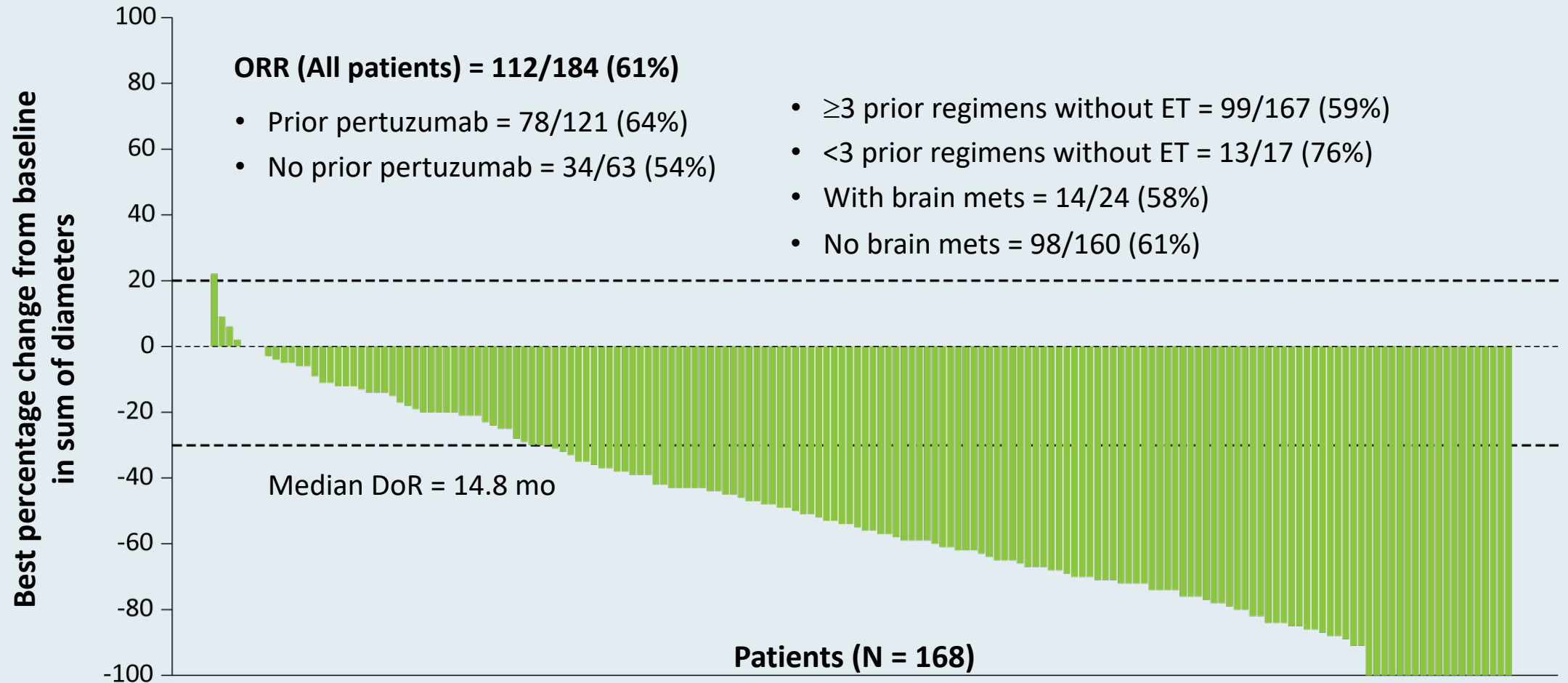
ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

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

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

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



DESTINY-Breast01: Survival and Safety

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

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

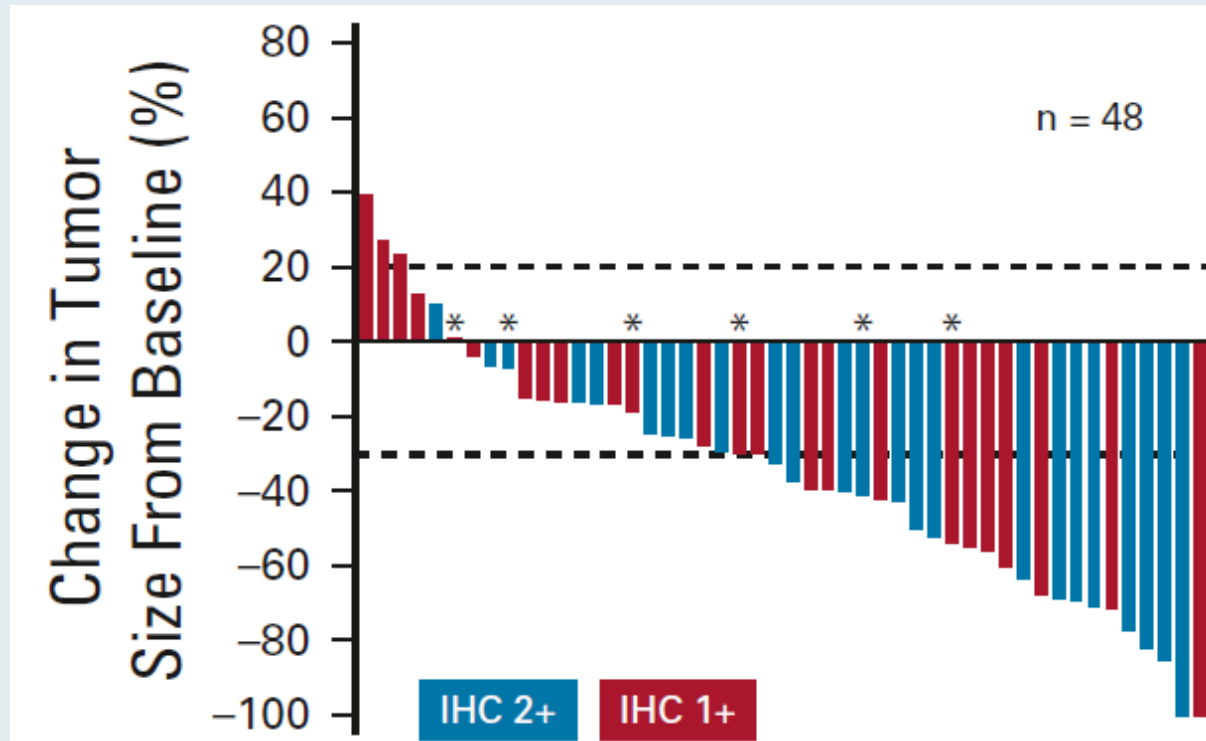
- Most common Grade ≥ 3 AEs were decreased neutrophil count (21%), anemia (9%) and nausea (8%).

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

Shanu Modi, MD¹; Haeseong Park, MD, MPH²; Rashmi K. Murthy, MD, MBE³; Hiroji Iwata, PhD, MD⁴; Kenji Tamura, MD, PhD⁵; Junji Tsurutani, MD, PhD⁶; Alvaro Moreno-Aspitia, PhD⁷; Toshihiko Doi, MD, PhD⁸; Yasuaki Sagara, MD⁹; Charles Redfern, MD¹⁰; Ian E. Krop, MD, PhD¹¹; Caleb Lee, MD, PhD¹²; Yoshihiko Fujisaki, MS¹³; Masahiro Sugihara, PhD¹³; Lin Zhang, MD, PhD¹²; Javad Shahidi, MD¹²; and Shunji Takahashi, MD¹⁴

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

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



Clinical activity (by independent review)

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

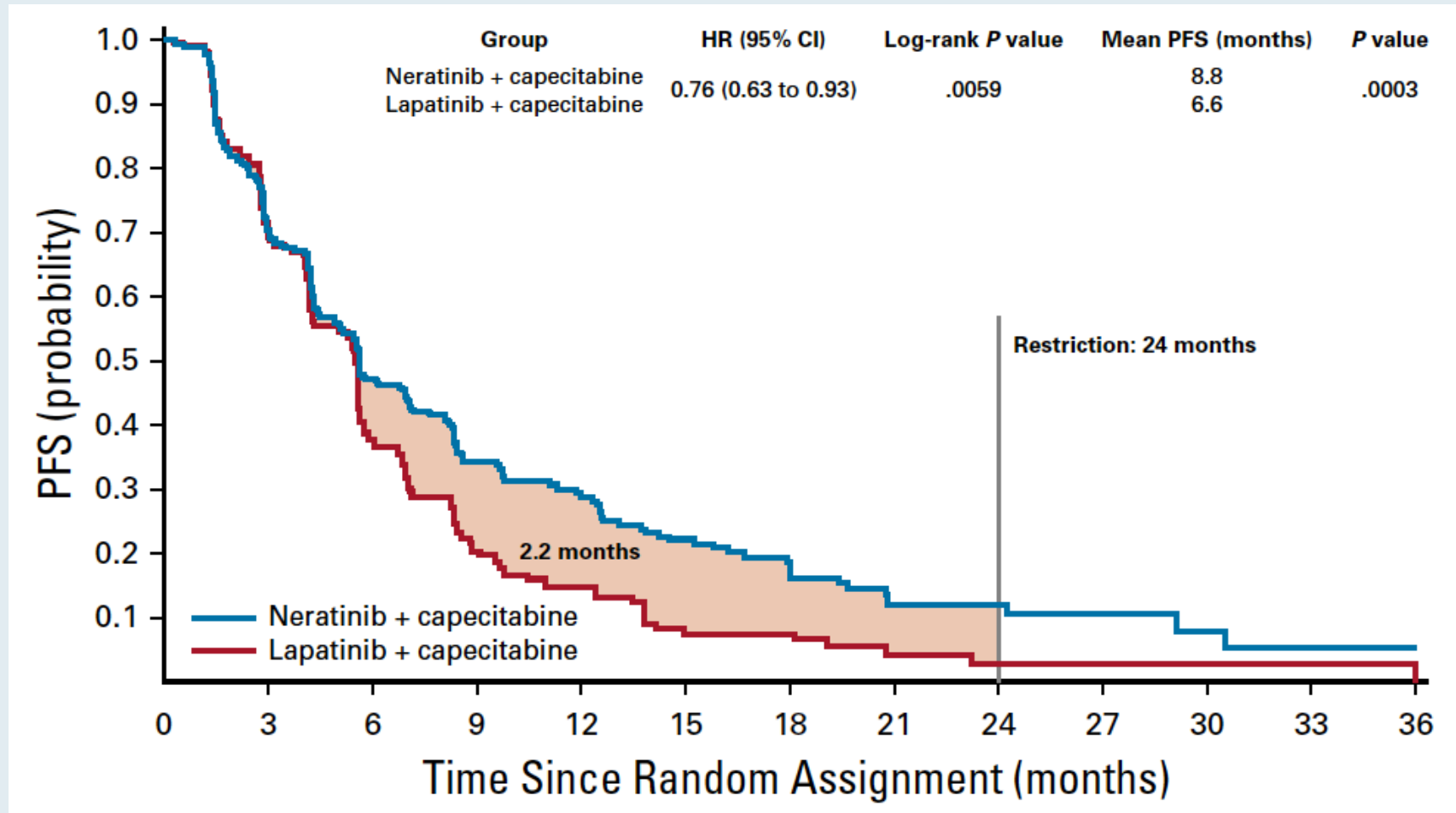
* Median of 7.5 prior regimens

Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial

Cristina Saura, MD¹; Mafalda Oliveira, MD, PhD¹; Yin-Hsun Feng, MD, PhD²; Ming-Shen Dai, MD, PhD²; Shang-Wen Chen, MD²; Sara A. Hurvitz, MD³; Sung-Bae Kim, MD, PhD⁴; Beverly Moy, MD, PhD⁵; Suzette Delaloge, MD, MSc⁶; William Gradishar, MD⁷; Norikazu Masuda, MD, PhD⁸; Marketa Palacova, MD⁹; Maureen E. Trudeau, MD¹⁰; Johanna Mattson, MD, PhD¹¹; Yoon Sim Yap, MBBS¹²; Ming-Feng Hou, MD¹³; Michelino De Laurentiis, MD, PhD¹⁴; Yu-Min Yeh, MD¹⁵; Hong-Tai Chang, MD¹⁶; Thomas Yau, MBBS, MD¹⁷; Hans Wildiers, MD, PhD^{18,19}; Barbara Haley, MD²⁰; Daniele Fagnani, MD²¹; Yen-Shen Lu, MD, PhD²²; John Crown, MBBCh, MD²³; Johnson Lin, MD²⁴; Masato Takahashi, MD, PhD²⁵; Toshimi Takano, MD²⁶; Miki Yamaguchi, MD, PhD²⁷; Takaaki Fujii, MD, PhD²⁸; Bin Yao, MS²⁹; Judith Bechuk, ScD²⁹; Kiana Keyvanjah, PharmD²⁹; Richard Bryce, MBChB²⁹; and Adam Brufsky, MD, PhD³⁰; for the NALA Investigators

J Clin Oncol 2020;38(27):3138-49.

NALA Trial – Centrally Confirmed Coprimary Endpoints: PFS and OS



- Although a numerical difference with neratinib + capecitabine was observed for OS, it did not meet statistical significance (HR 0.88, $p = 0.2086$)



Research

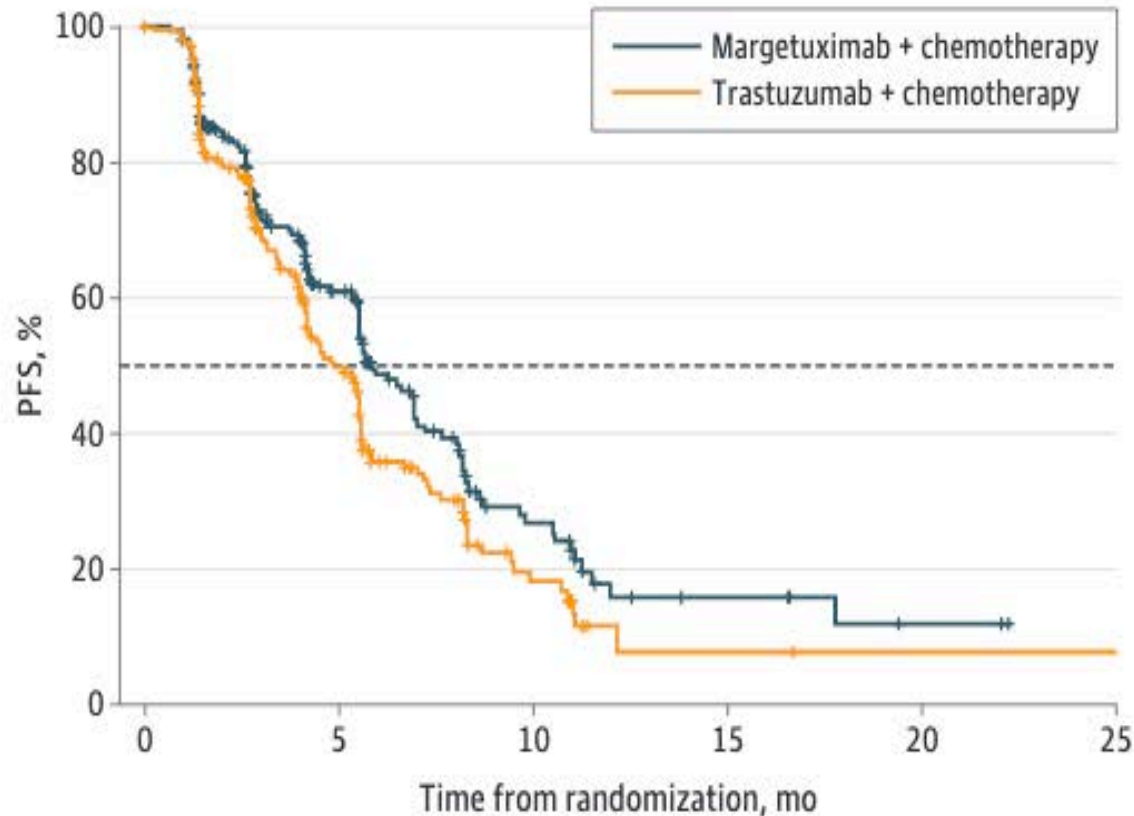
JAMA Oncology | **Original Investigation**

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

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

JAMA Oncol 2021;[Online ahead of print].

SOPHIA: PFS by Central Blinded Analysis (ITT Population)



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

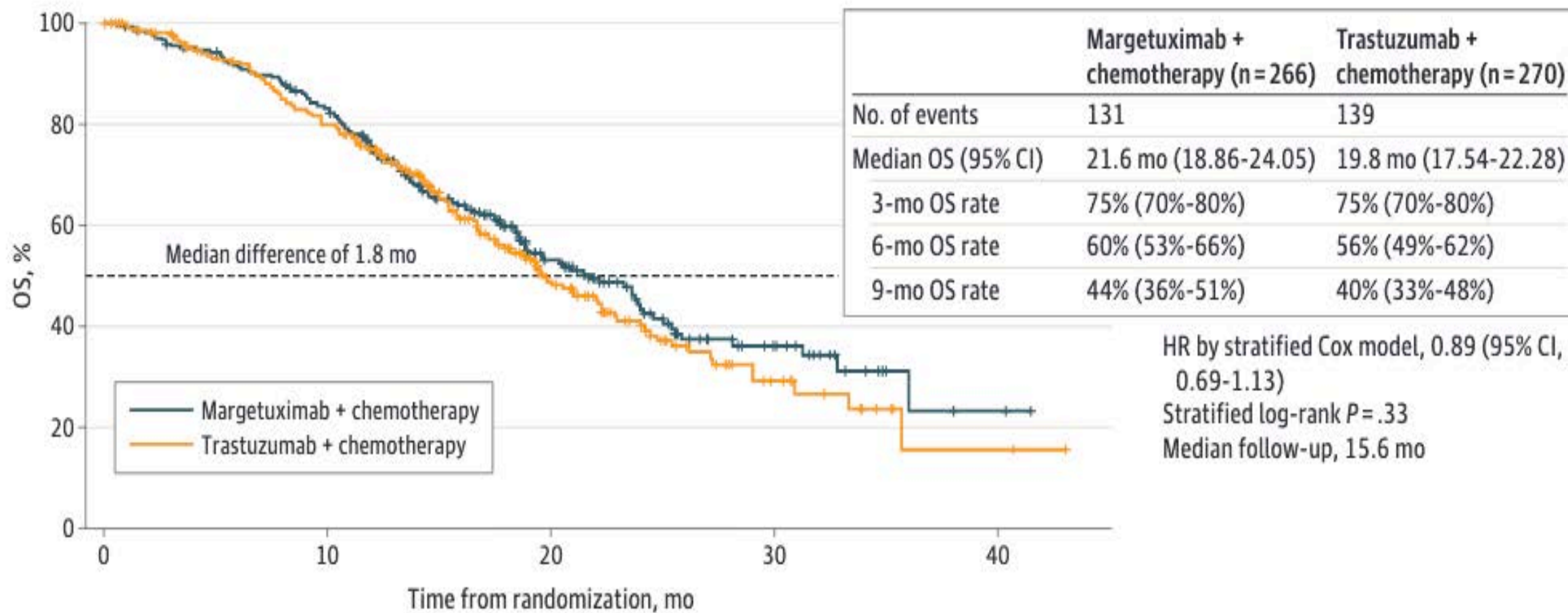
HR by stratified Cox model, 0.76 (95% CI, 0.59-0.98)

Stratified log-rank $P = .03$

24% Risk reduction of disease progression^a

Median follow-up, 2.8 mo

SOPHIA: OS Analysis (ITT Population)



FDA Approves Margetuximab for HER2-Positive mBC

Press Release – December 16, 2020

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

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

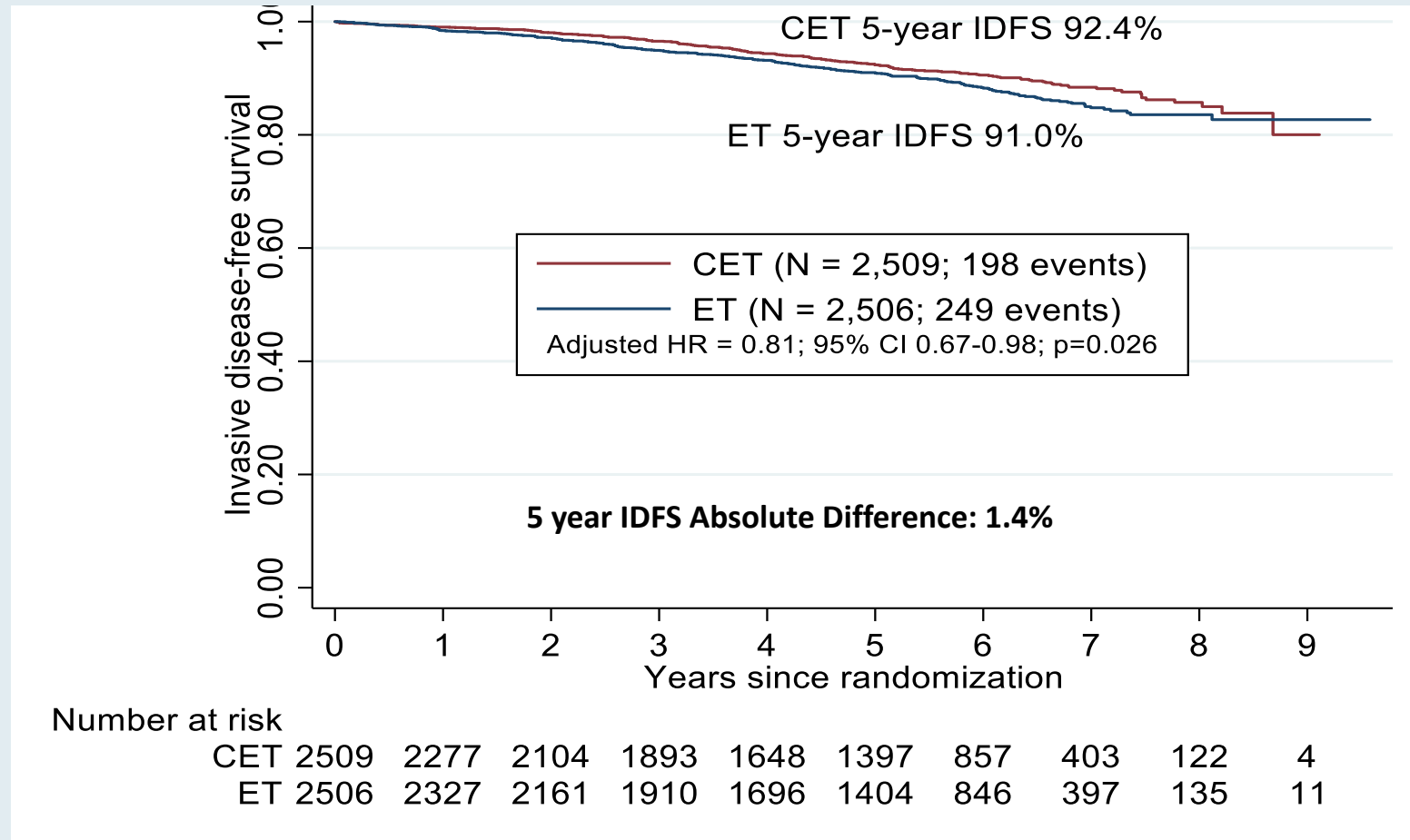
ER-Positive, HER2-Negative Breast Cancer

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

Kalinsky K et al.

SABCS 2020;Abstract GS3-00.

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



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

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

Endocrine Therapy Alone in Patients with Intermediate or High-Risk Luminal Early Breast Cancer (0-3 lymph nodes), Recurrence Score <26 and Ki67 Response after Preoperative Endocrine Therapy: First Efficacy Results from the ADAPT HR+/HER2- Trial

Harbeck N et al.

SABCS 2020;Abstract GS4-04.

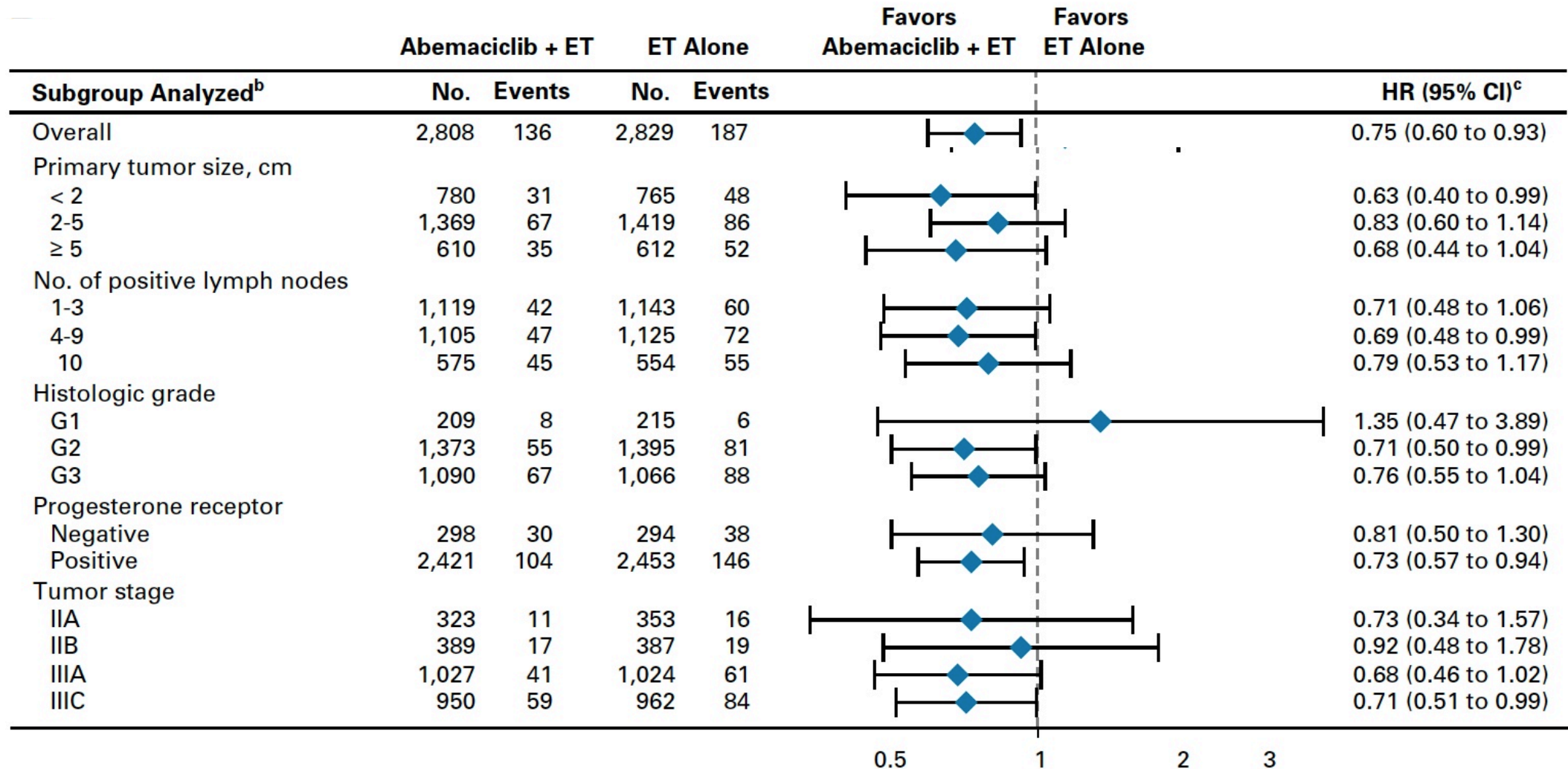
J Clin Oncol 2020;38(34):3987-98.

© rapid communications

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

Stephen R. D. Johnston, MD, PhD¹; Nadia Harbeck, MD, PhD²; Roberto Hegg, MD, PhD³; Masakazu Toi, MD, PhD⁴; Miguel Martin, MD, PhD⁵; Zhi Min Shao, MD⁶; Qing Yuan Zhang, MD, PhD⁷; Jorge Luis Martinez Rodriguez, MD⁸; Mario Campone, MD, PhD⁹; Erika Hamilton, MD¹⁰; Joohyuk Sohn, MD, PhD¹¹; Valentina Guarneri, MD, PhD¹²; Morihito Okada, MD, PhD¹³; Frances Boyle, MD, MBBS, PhD¹⁴; Patrick Neven, MD, PhD¹⁵; Javier Cortés, MD, PhD¹⁶; Jens Huober, MD¹⁷; Andrew Wardley, MD, MBChB¹⁸; Sara M. Tolaney, MD, MPH¹⁹; Irfan Cicin, MD²⁰; Ian C. Smith, MD^{21,22}; Martin Frenzel, PhD²²; Desirée Headley, MSc²²; Ran Wei, PhD²²; Belen San Antonio, PhD²²; Maarten Hulstijn, PhD²²; Joanne Cox, MD²²; Joyce O'Shaughnessy, MD²³; and Priya Rastogi, MD²⁴; on behalf of the monarchE Committee Members and Investigators

monarchE: IDFS Subgroups



monarchE: Treatment Duration and Adjustments

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



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

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

Randomized Trials of Endocrine Therapy +/- CDK4/6 Inhibition

| Line | Trial | Schema | PFS HR compared to endocrine alone | OS HR compared to endocrine alone |
|-------------|--------------------------------|--|------------------------------------|-----------------------------------|
| First line | PALOMA-1 | Letrozole ± palbociclib | 0.49 | 0.897 |
| | PALOMA-2 | Letrozole ± palbociclib | 0.58 | NR |
| | MONALEESA-2 | Letrozole ± ribociclib | 0.56 | 0.75 |
| | MONALEESA-3 | Fulvestrant ± ribociclib | 0.55 | 0.72 |
| | MONALEESA-7 (premenopausal) | Goserelin + AI or tamoxifen ± ribociclib | 0.55 | 0.71 |
| | MONARCH 3 | Letrozole or anastrozole, ± abemaciclib | 0.54 | NR |
| Second line | PALOMA-3 | Fulvestrant ± palbociclib | 0.46 | 0.75 |
| | MONARCH 2 | Fulvestrant ± abemaciclib | 0.55 | 0.757 |

Key AEs with CDK4/6 Inhibitors: Monitoring and Prevention

| Diarrhea | Hepatobiliary Toxicity | QT Prolongation | Neutropenia | VTE | ILD/ Pneumonitis |
|--|--|--|---|--|---|
| Abemaciclib (more) Palbociclib Ribociclib | Abemaciclib Ribociclib | Ribociclib | Abemaciclib (less) Palbociclib Ribociclib | Abemaciclib | Abemaciclib Palbociclib Ribociclib |
| Antidiarrheal therapy Increase oral hydration Notify HCP | LFTs before starting tx, Q2W x 2 mos, then: <ul style="list-style-type: none"> ▪ <i>abemaciclib</i>, as indicated ▪ <i>ribociclib</i>, at start of cycle x 4 cycles | EKG before cycle 1, Day 14 of cycle 1, start of cycle 2, then as indicated Electrolytes at start of cycle x 6 cycles, then as indicated | CBC before starting tx, then: <ul style="list-style-type: none"> ▪ <i>abemaciclib</i>, Q2W x 2 mos, QM x 2 mos, then as indicated ▪ <i>palbociclib</i>, Days 1 and 15 of cycles 1-2, then as indicated ▪ <i>ribociclib</i>, Q2W x 2 cycles, start of next 4 cycles, then as indicated | Monitor for signs and symptoms of thrombosis or pulmonary embolism | Monitor for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea) |

ORIGINAL ARTICLE

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

F. André^{1*}, E. M. Ciruelos², D. Juric³, S. Loibl⁴, M. Campone⁵, I. A. Mayer⁶, G. Rubovszky⁷, T. Yamashita⁸, B. Kaufman⁹, Y.-S. Lu¹⁰, K. Inoue¹¹, Z. Pápai¹², M. Takahashi¹³, F. Ghaznawi¹⁴, D. Mills¹⁵, M. Kaper¹⁴, M. Miller¹⁴, P. F. Conte¹⁶, H. Iwata¹⁷ & H. S. Rugo¹⁸

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

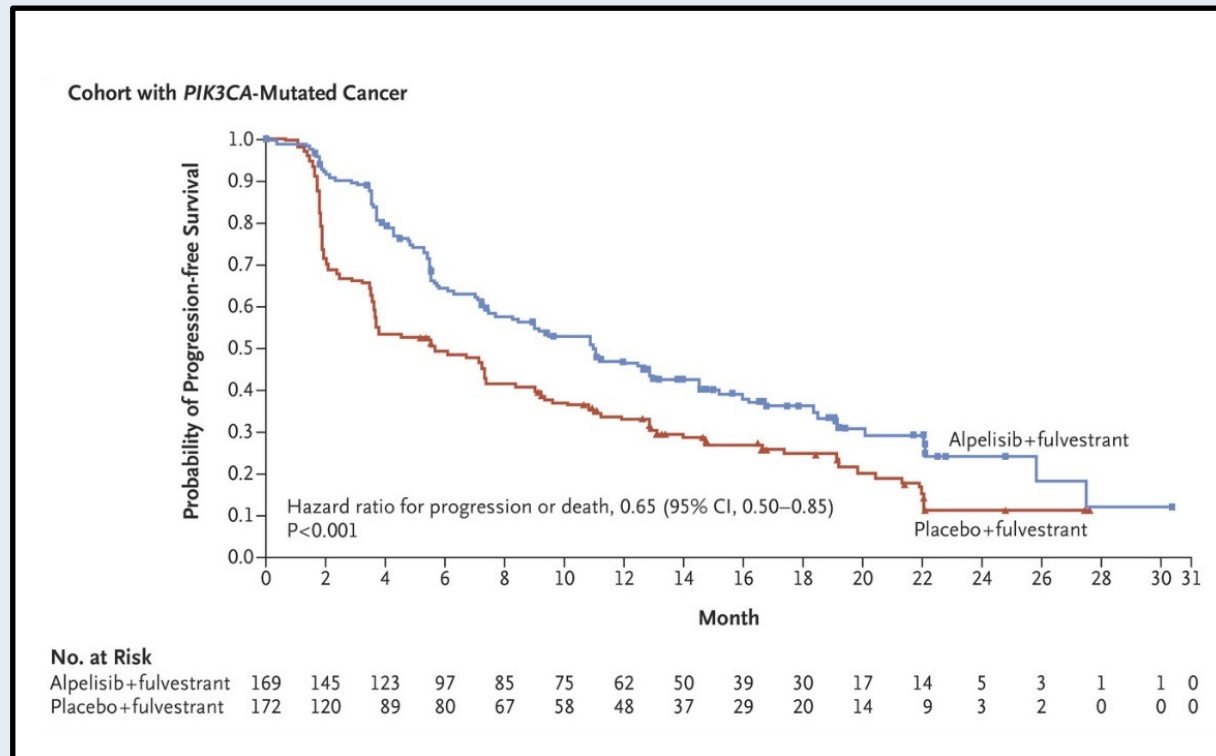


Available online 25 November 2020

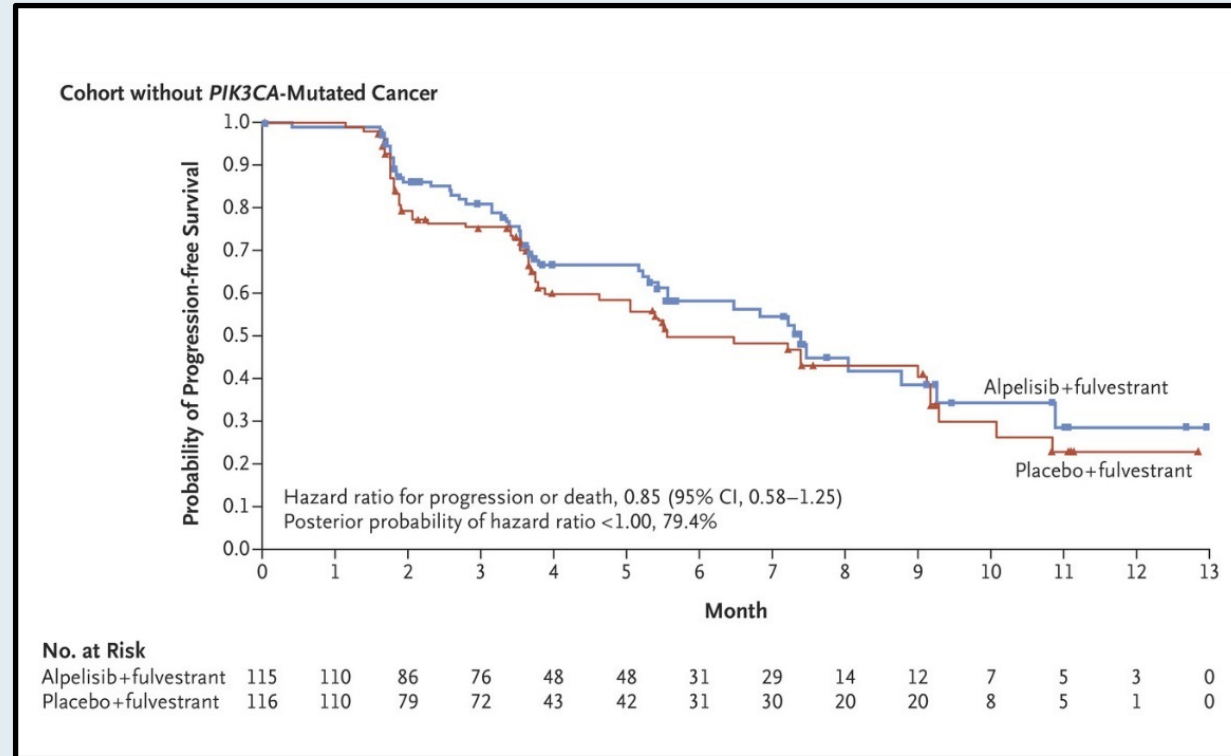
***Ann Oncol* 2021;32(2):208-17.**

SOLAR-1: PFS Outcomes by PIK3CA Mutation Status

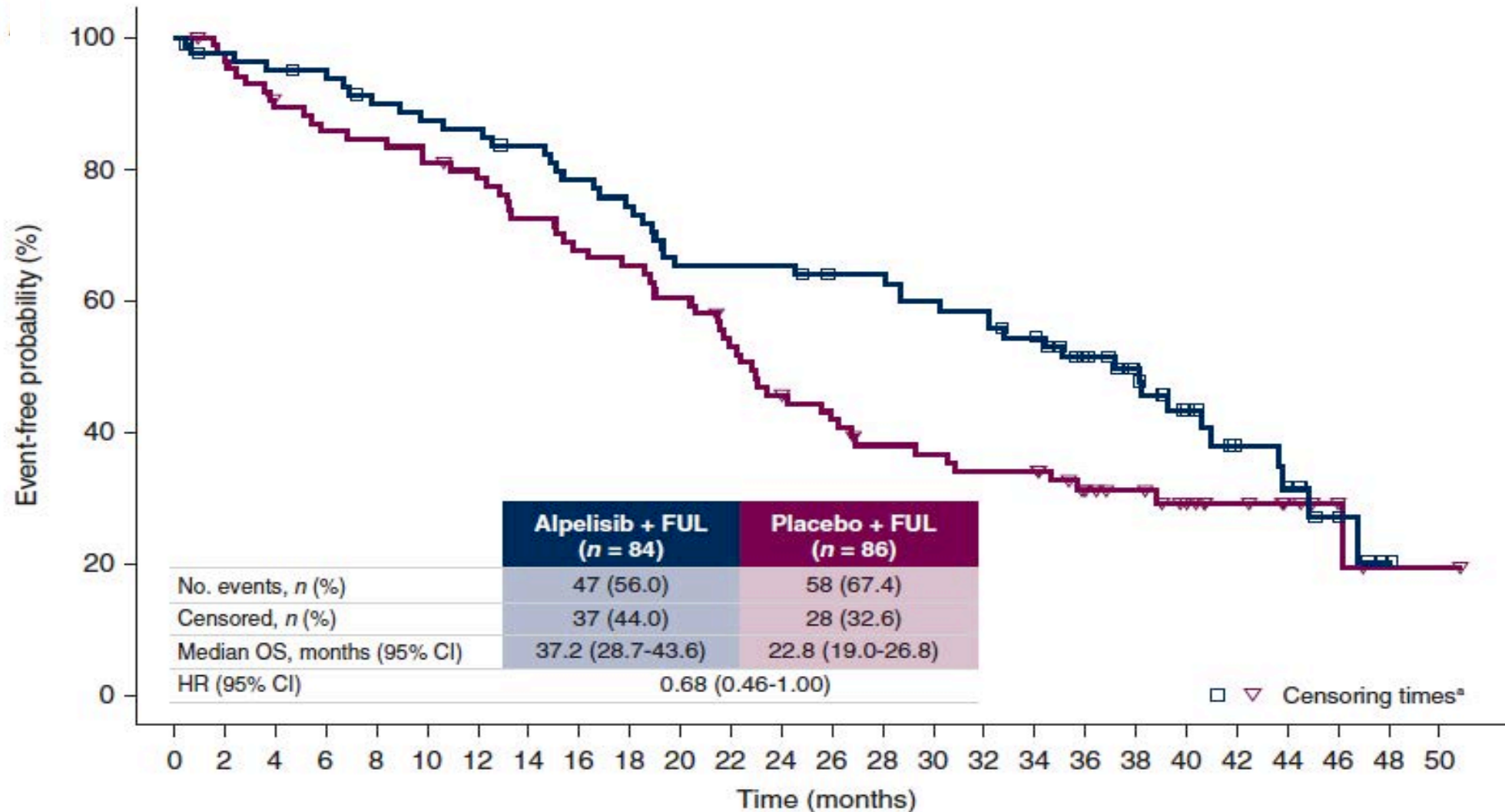
PIK3CA mutated



No PIK3CA mutation



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



SOLAR-1: Select Adverse Events in Overall Patient Population

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

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

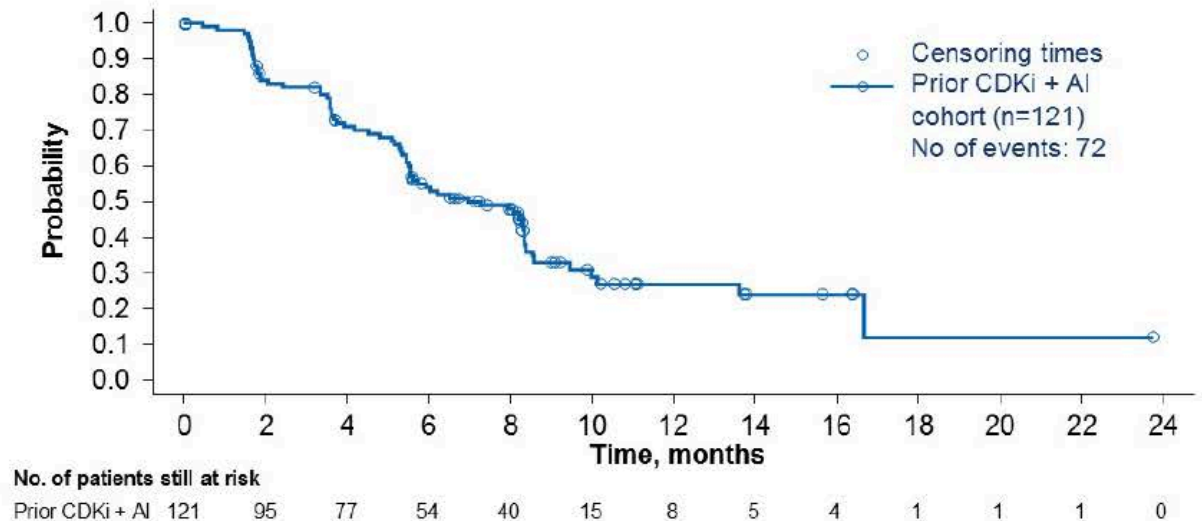
Rugo HS et al.

ASCO 2020;Abstract 1006.

BYLieve COHORT A: Primary Endpoint and PFS

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

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

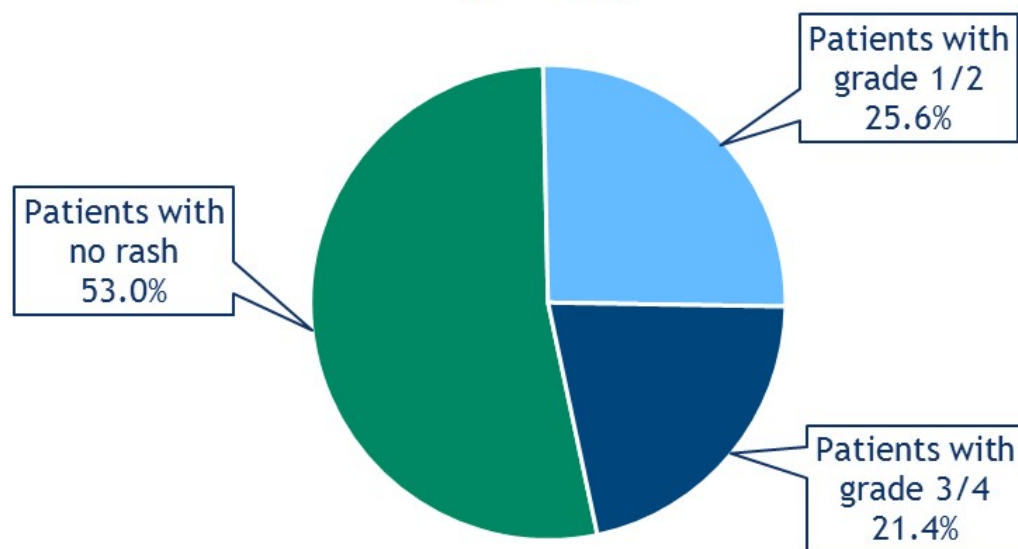


The primary endpoint for the prior CDKi + AI cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months

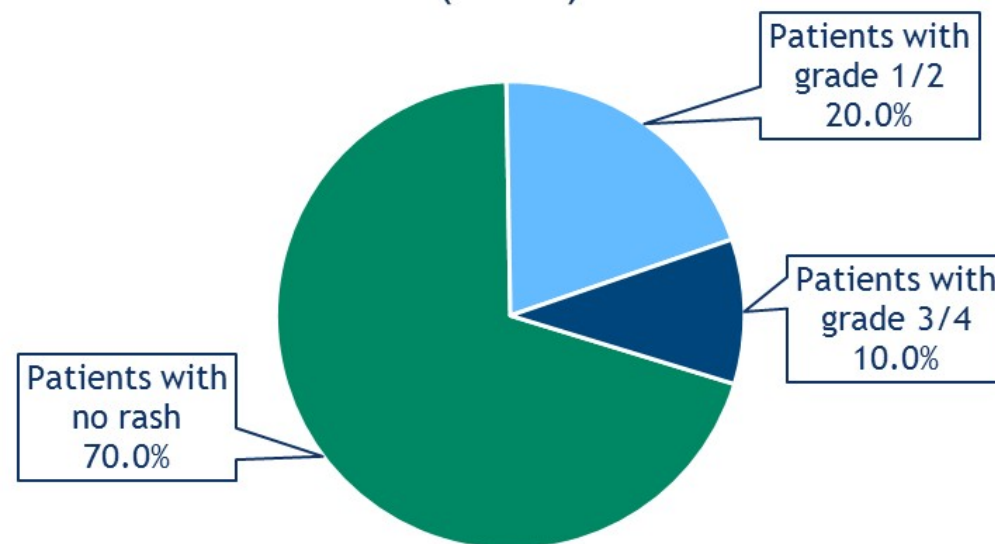
- In SOLAR-1, 44.4% of patients in the *PIK3CA*-mutant cohort with prior CDKi treated with alpelisib plus fulvestrant were alive without disease progression at 6 months

BYLieve: Incidence of Rash with and without Prophylactic Antihistamines

Patients who did not receive antihistamines
or received antihistamines after rash
(n=117)



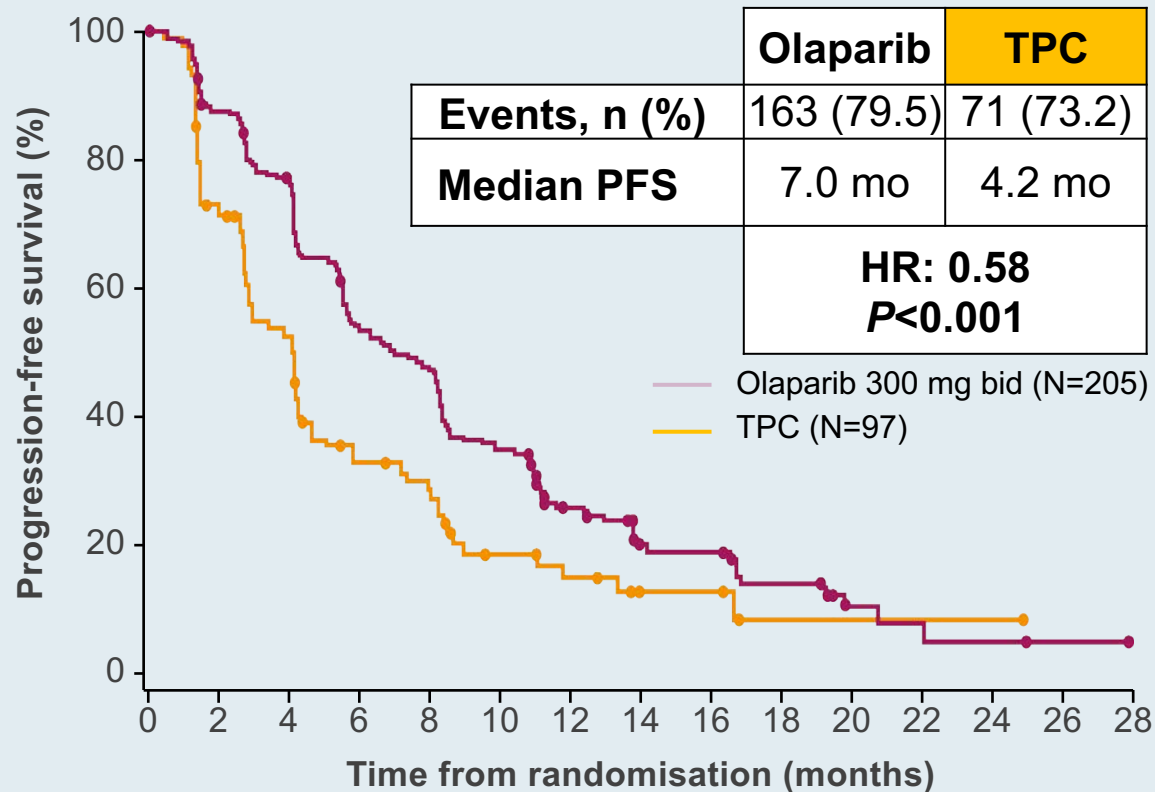
Patients who received antihistamines
before rash or had no event
(n=10)



Triple-Negative Breast Cancer

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

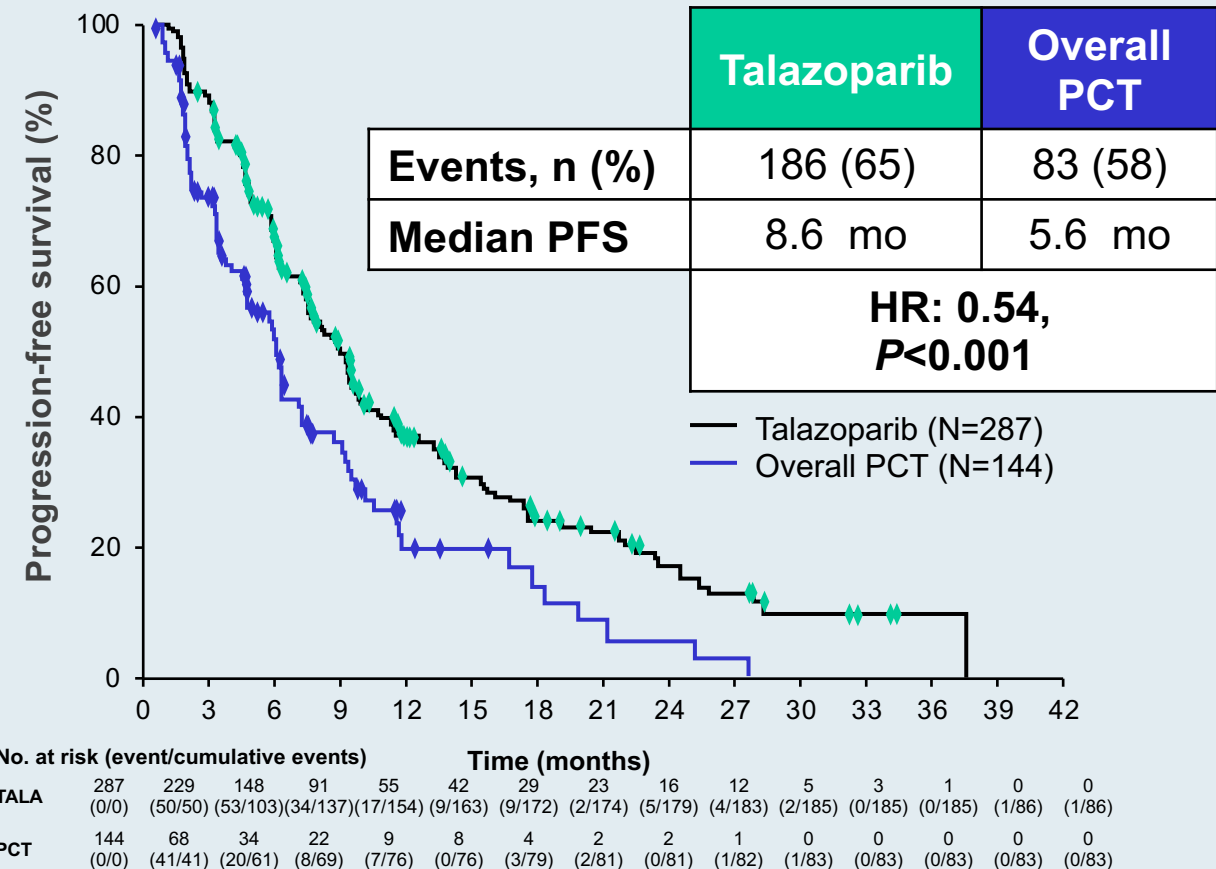
OlympiAD: Olaparib PFS^{1,2}



Number at risk

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

EMBRACA: Talazoparib PFS³



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

ORIGINAL ARTICLE

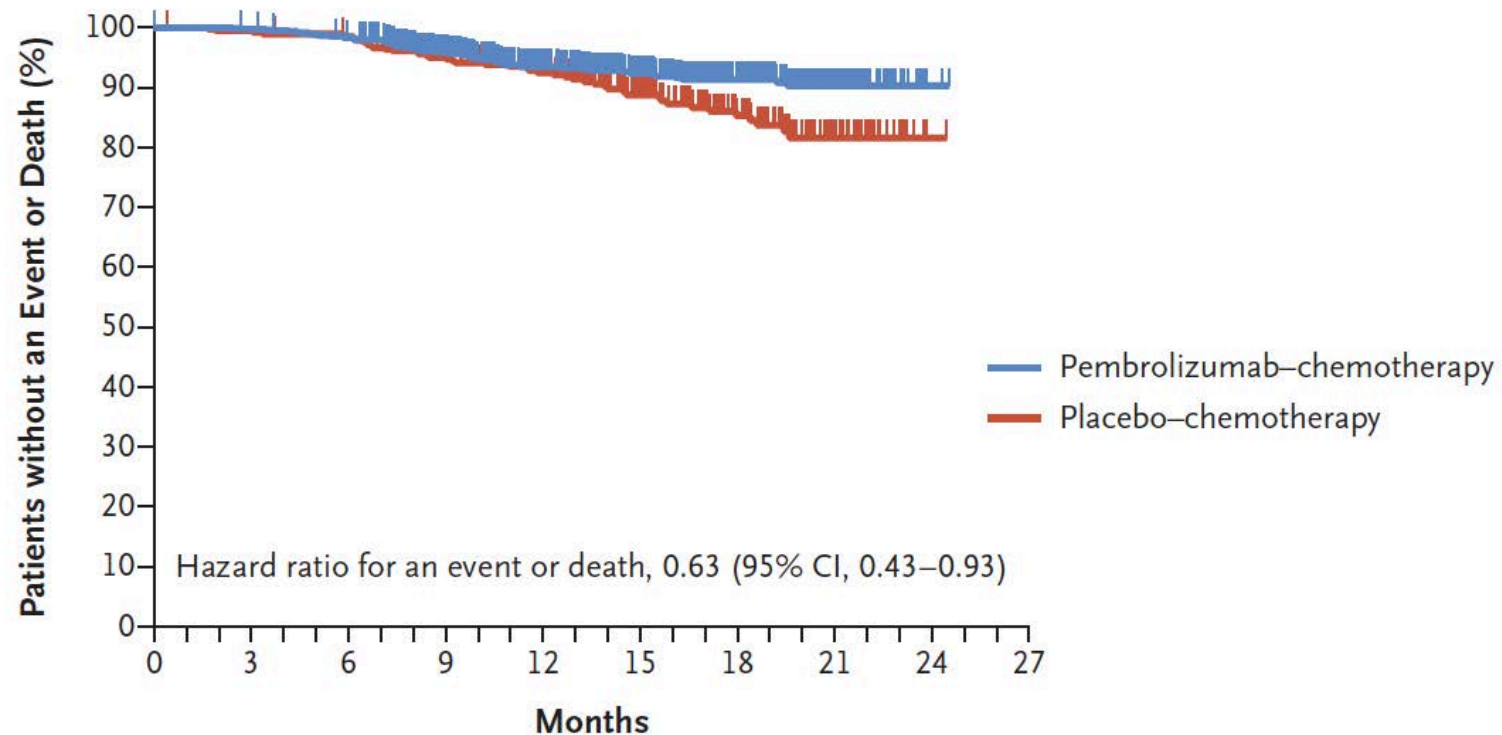
Pembrolizumab for Early Triple-Negative Breast Cancer

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

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

KEYNOTE-522 Primary Endpoints: pCR and EFS

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





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

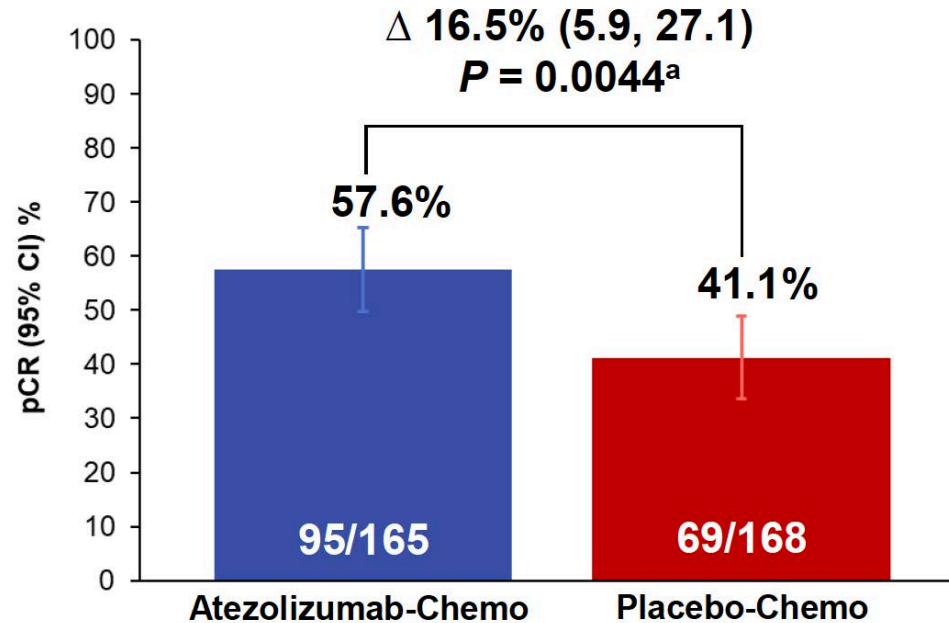
Elizabeth A Mittendorf, Hong Zhang, Carlos H Barrios, Shigehira Saji, Kyung Hae Jung, Roberto Hegg, Andreas Koehler, Joohyuk Sohn, Hiroji Iwata, Melinda L Telli, Cristiano Ferrario, Kevin Punie, Frédérique Penault-Llorca, Shilpen Patel, Anh Nguyen Duc, Mario Liste-Hermoso, Vidya Maiya, Luciana Molinero,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

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

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

ITT and PD-L1+ Populations

pCR (95% CI), ypT0/is ypN0



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

*Did not cross significance boundary of 0.0184.

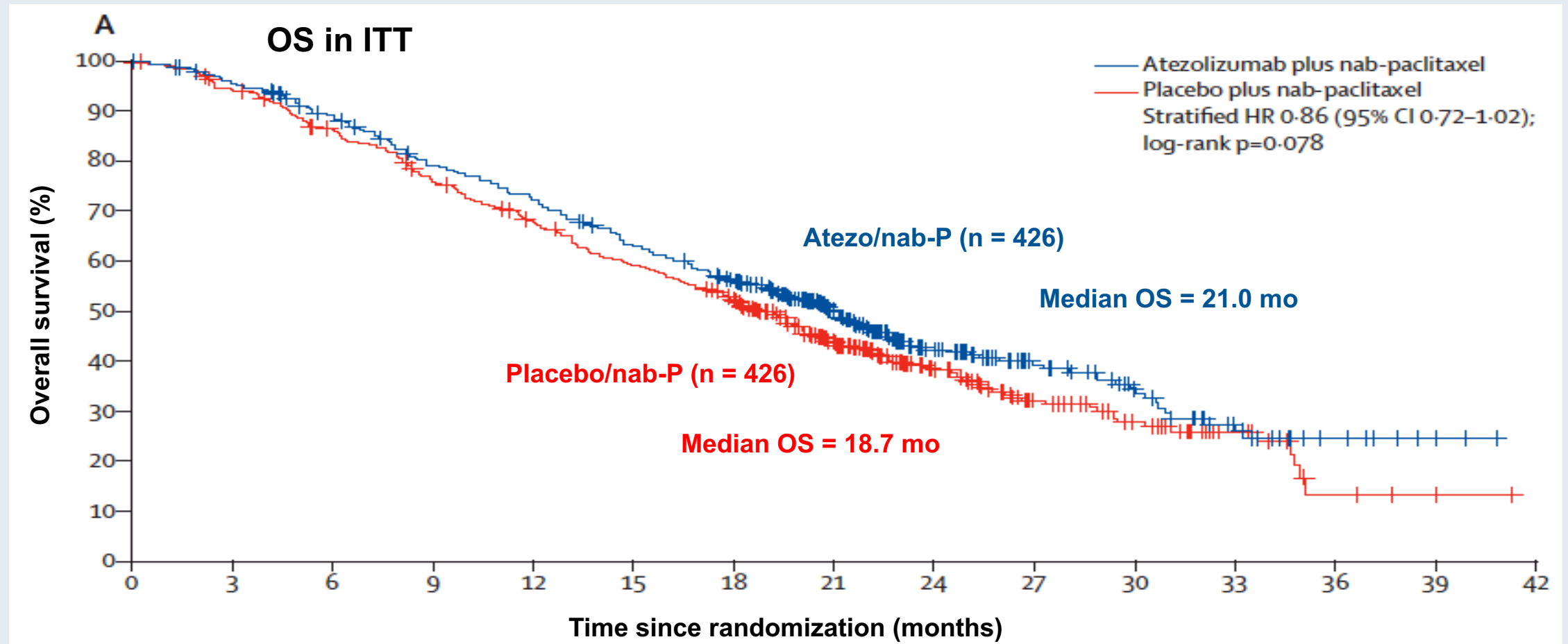


Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial

Peter Schmid, Hope S Rugo*, Sylvia Adams, Andreas Schneeweiss, Carlos H Barrios, Hiroji Iwata, Véronique Diéras, Volkmar Henschel, Luciana Molinero, Stephen Y Chui, Vidya Maiya, Amreen Husain, Eric P Winer, Sherene Loi, Leisha A Emens, for the IMpassion130 Investigators†*

Lancet Oncol 2020;21(1):44-59.

IMpassion130: OS in the ITT and PD-L1-Positive Population



- Median OS in PD-L1-positive patients: 25.0 mo (atezo) vs 18.0 mo (placebo)
 - HR = 0.71 (95% CI 0.54 – 0.94)

Atezolizumab and *Nab*-Paclitaxel in Advanced Triple-Negative Breast Cancer: Biomarker Evaluation of the IMpassion130 Study

Emens LA et al.

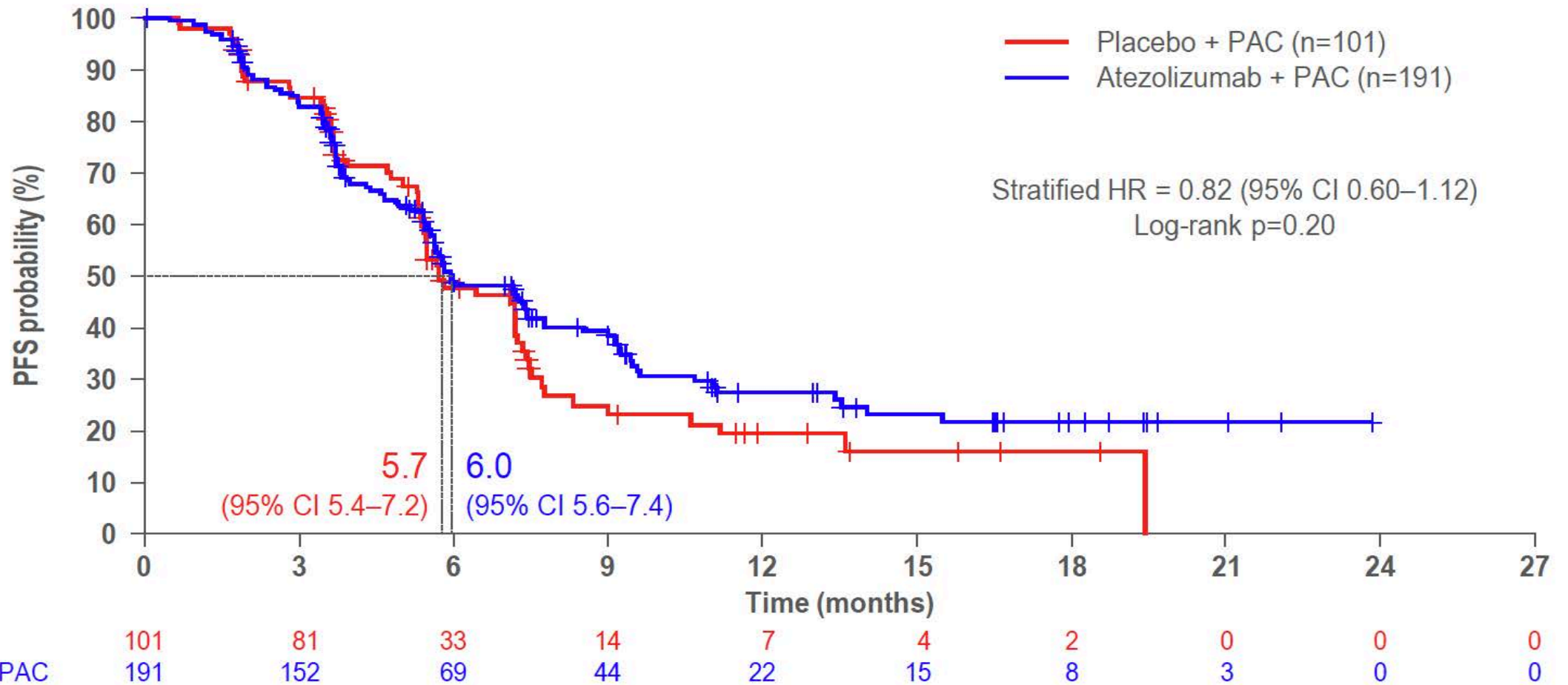
J Natl Cancer Inst 2021;[Online ahead of print].

Primary Results from IMpassion131, a Double-Blind Placebo-Controlled Randomised Phase 3 Trial of First-Line Paclitaxel (PAC) +/- Atezolizumab (Atezo) for Unresectable Locally Advanced/Metastatic Triple-Negative Breast Cancer (mTNBC)

Miles D et al.

ESMO 2020;Abstract LBA15.

IMpassion131: PFS in the PD-L1-Positive Population





Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial

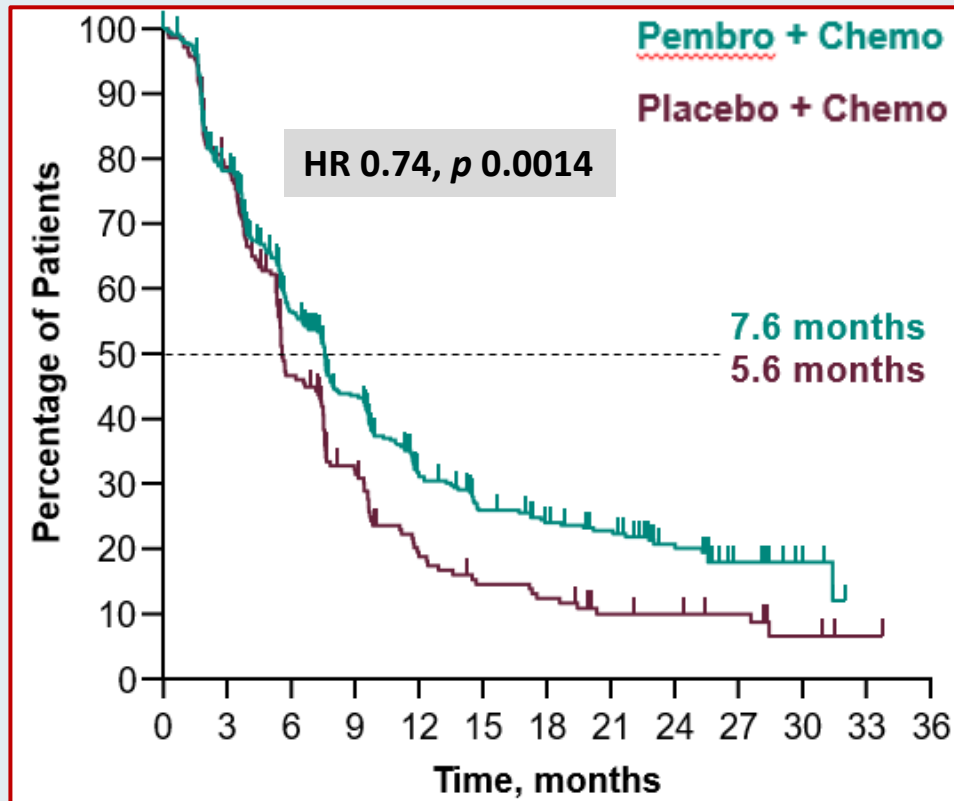


Javier Cortes, David W Cescon, Hope S Rugo, Zbigniew Nowecki, Seock-Ah Im, Mastura Md Yusof, Carlos Gallardo, Oleg Lipatov, Carlos H Barrios, Esther Holgado, Hiroji Iwata, Norikazu Masuda, Marco Torregroza Otero, Erhan Gokmen, Sherene Loi, Zifang Guo, Jing Zhao, Gursel Aktan, Vassiliki Karantza, Peter Schmid, for the KEYNOTE-355 Investigators*

***Lancet* 2020;396(10265):1817-28.**

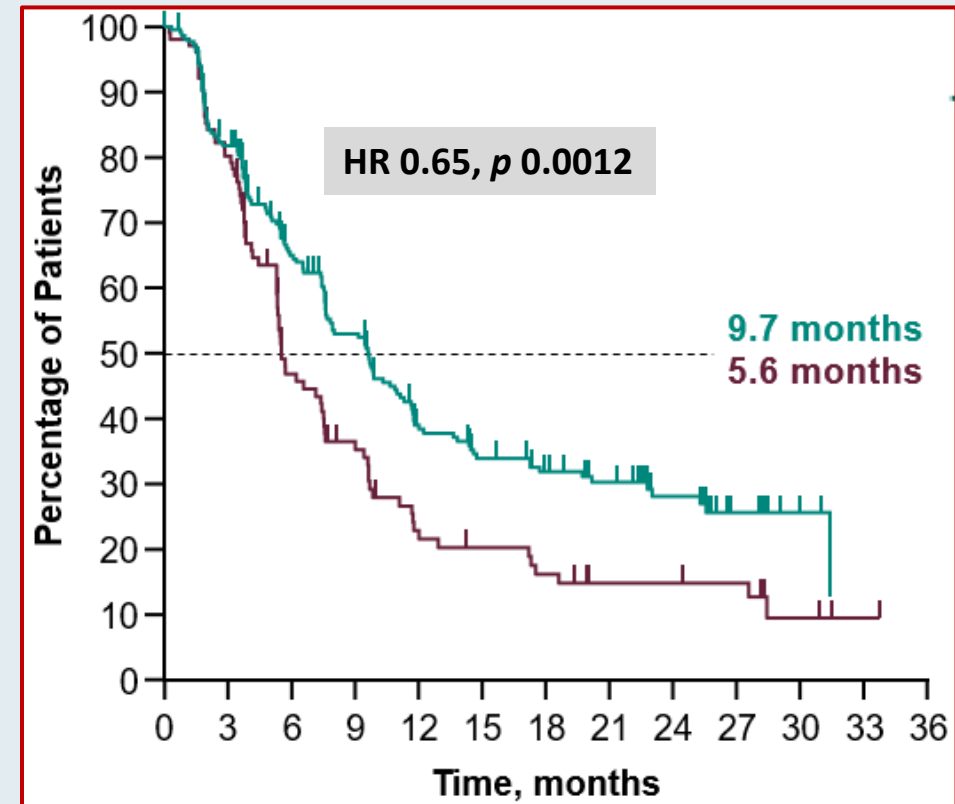
KEYNOTE-355: PFS for Patients with PD-L1-Positive Tumors

PD-L1 CPS ≥ 1



Prespecified p value boundary of 0.00111 not met

PD-L1 CPS ≥ 10



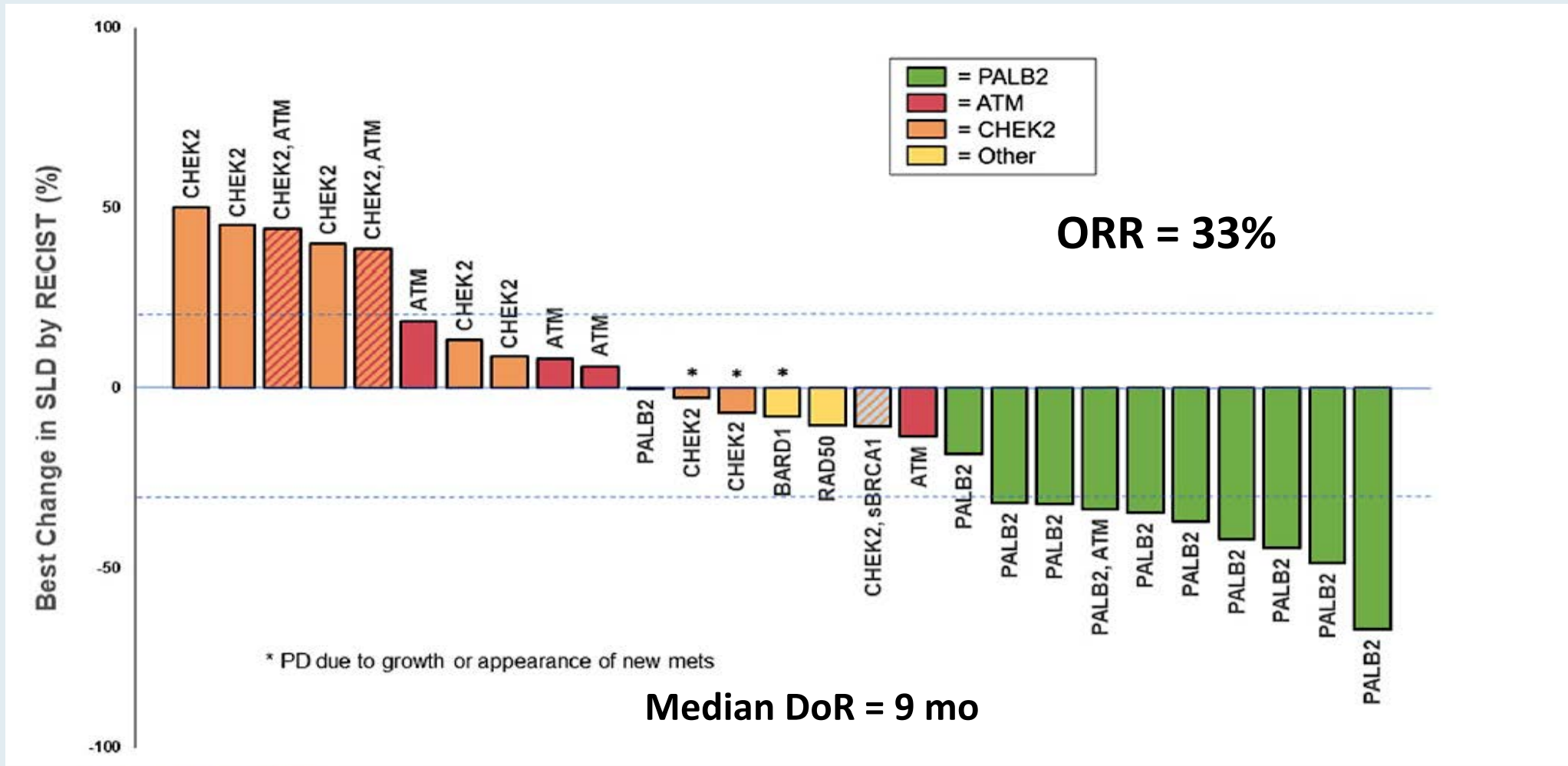
Prespecified p value boundary of 0.00411 met

TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes

Nadine M. Tung, MD^{1,2}; Mark E. Robson, MD³; Steffen Ventz, PhD⁴; Cesar A. Santa-Maria, MD, MSCI⁵; Rita Nanda, MD⁶; Paul K. Marcom, MD⁷; Payal D. Shah, MD⁸; Tarah J. Ballinger, MD⁹; Eddy S. Yang, MD, PhD¹⁰; Shaveta Vinayak, MD, MS¹¹; Michelle Melisko, MD¹²; Adam Brufsky, MD, PhD¹³; Michelle DeMeo, BS⁴; Colby Jenkins, MS¹; Susan Domchek, MD⁸; Alan D'Andrea, MD^{2,4}; Nancy U. Lin, MD^{2,4}; Melissa E. Hughes, MS⁴; Lisa A. Carey, MD¹⁴; Nick Wagle, MD^{2,4}; Gerburg M. Wulf, MD, PhD^{1,2}; Ian E. Krop, MD, PhD^{2,4}; Antonio C. Wolff, MD⁵; Eric P. Winer, MD^{2,4}; and Judy E. Garber, MD, MPH^{2,4}

J Clin Oncol 2020;38(36):4274-82.

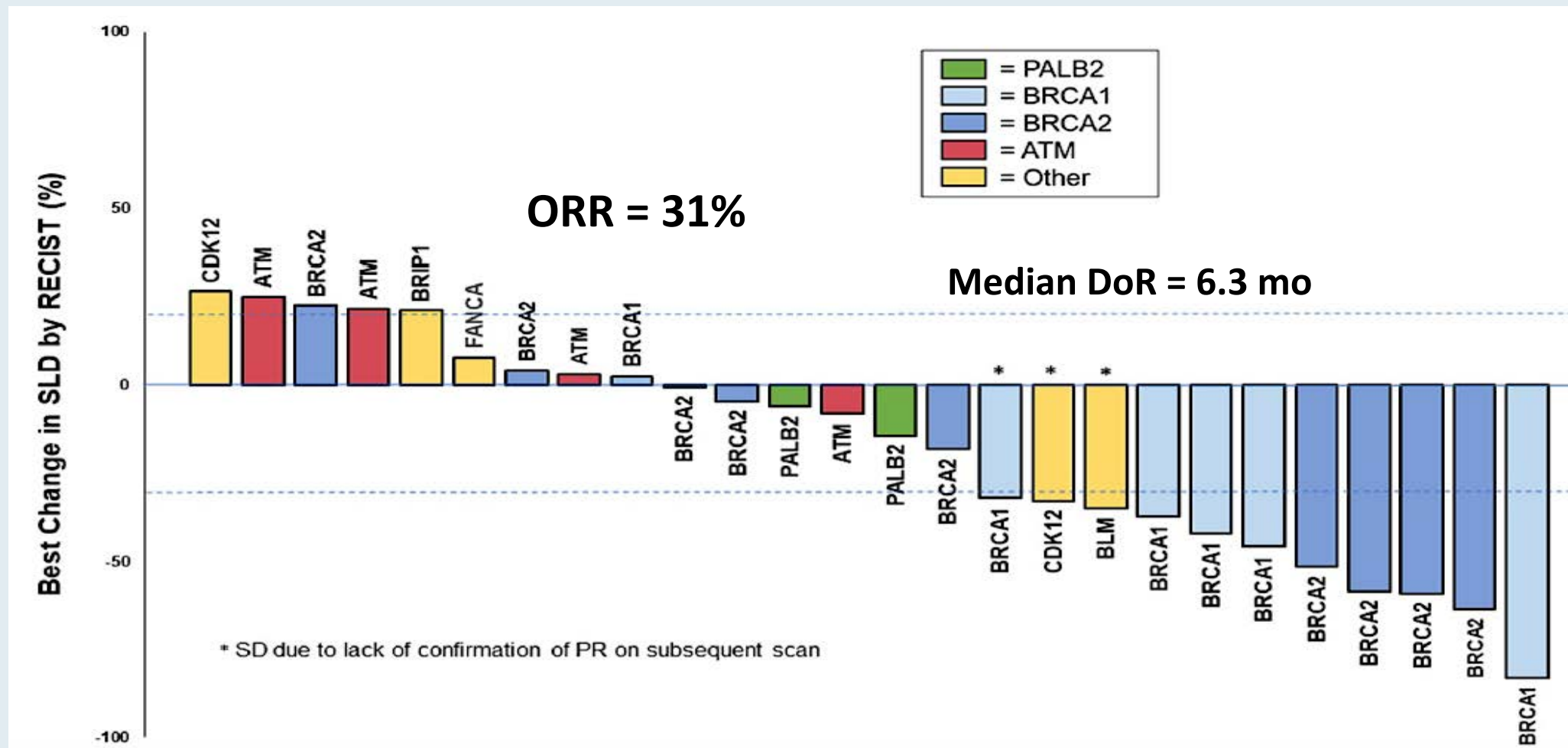
TBCRC 048: Best Overall Responses in Cohort 1 (Germline)



Median PFS = 4.5 mo

Median time to onset of response = 12.1 weeks

TBCRC 048: Best Overall Responses in Cohort 2 (Somatic)



Median PFS = 4.1 mo

Median time to onset of response = 10.3 weeks

TBCRC 048: Responses for 5 Most Common Genes

| <i>PALB2</i> N=13 | <i>sBRCA1/2</i> N=17[^] | <i>ATM & CHEK2^{**}</i> N=17 |
|---|---|---|
| Germline: 9/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr Somatic: 0/2 – both SD* (limited assessments) | 8/16 PR (50%) | 0/13 germline 0/4 somatic |

15 patients remain on study

* 1 sPALB2- lost to follow-up after 1st tumor assessment with skin and tumor marker response

[^] includes patient from Cohort 1 with sBRCA1 and gCHEK2

^{**} Not included: patient with both gCHEK2 & sBRCA1; patient with gATM and gPALB2

N Engl J Med 2021;384:1529-41

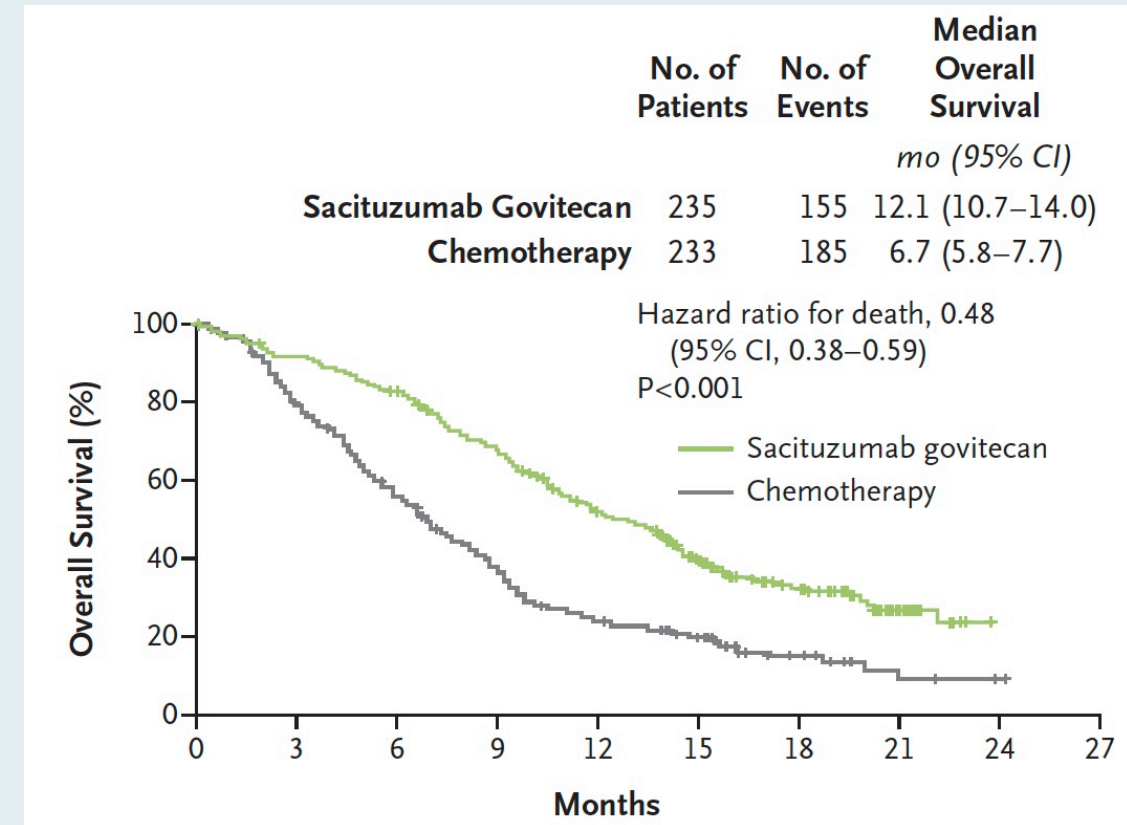
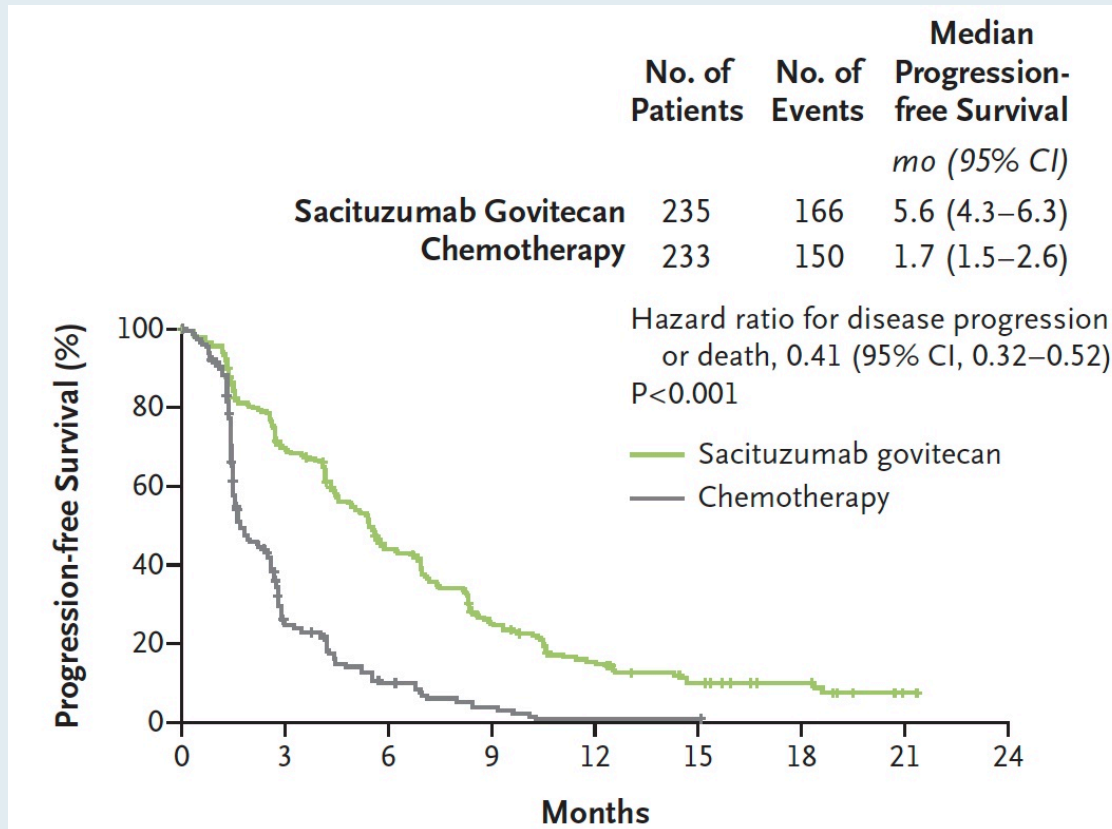
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ORIGINAL ARTICLE

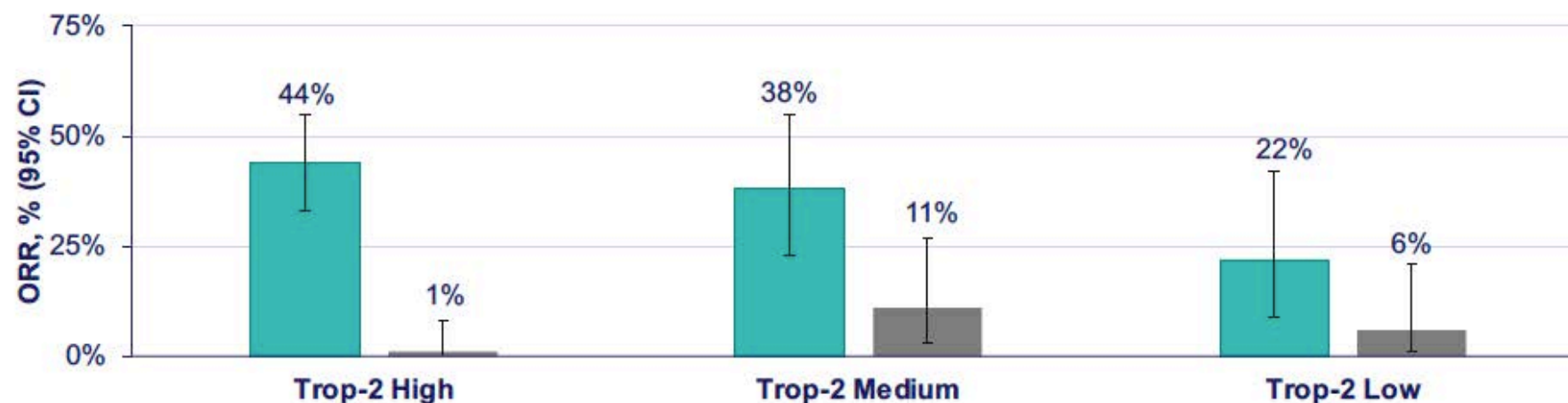
Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

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

ASCENT: PFS and OS Among Patients without Brain Metastases



ORR by Trop-2 Expression



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

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

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