

# **Current Concepts and Recent Advances in Oncology**

## ***A Daylong Clinical Summit Hosted in Partnership with Florida Cancer Specialists***

**Saturday, October 24, 2020  
8:30 AM – 4:30 PM ET**

### **Faculty**

**Arjun Balar, MD  
Johanna Bendell, MD  
Axel Grothey, MD  
Brad S Kahl, MD  
Shaji K Kumar, MD**

**Kathleen Moore, MD  
Loretta Nastoupil, MD  
William K Oh, MD  
David M O'Malley, MD  
Robert Z Orlowski, MD, PhD**

**Gregory J Riely, MD, PhD  
Hope S Rugo, MD  
David R Spigel, MD  
Sara M Tolaney, MD, MPH**

### **Moderator**

**Neil Love, MD**

# Agenda

**Module 1 — Lung Cancer:** *Drs Riely and Spigel*

**Module 2 — Multiple Myeloma:** *Drs Kumar and Orlowski*

**Module 3 — Chronic Lymphocytic Leukemia and Lymphomas:**  
*Drs Kahl and Nastoupil*

**Module 4 — Gastrointestinal Cancers:** *Drs Bendell and Grothey*

**Module 5 — Genitourinary Cancers:** *Drs Balar and Oh*

**Module 6 — Gynecologic Cancers:** *Drs Moore and O'Malley*

**Module 7 — Breast Cancer:** *Drs Rugo and Tolaney*

# Lung Cancer Faculty



**Gregory J Riely, MD, PhD**  
Associate Attending  
Memorial Sloan Kettering Cancer Center  
New York, New York



**David R Spigel, MD**  
Chief Scientific Officer  
Program Director, Lung Cancer Research  
Sarah Cannon Research Institute  
Nashville, Tennessee

# Dr Riely — Disclosures

|   |   |
|---|---|
| <b>Advisory Committee and Consulting Agreements</b> | Daiichi Sankyo Inc, Takeda Oncology   |
| <b>Contracted Research</b>                          | Merck, Mirati Therapeutics, Novartis, Pfizer Inc, Roche Laboratories Inc, Takeda Oncology |

# Dr Spigel — Disclosures

|                              |  |
|------------------------------|--|
| <b>Consulting Agreements</b> | Aptitude Health, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Celgene Corporation, Dracen Pharmaceuticals, EMD Serono Inc, Evelo Biosciences Inc, Genentech, a member of the Roche Group, GlaxoSmithKline, Iksuda Therapeutics, Illumina, Merck, Molecular Templates, Nektar, Novartis, Pfizer Inc, PharmaMar, Roche Laboratories Inc, Seagen Inc, Takeda Pharmaceutical Company Limited, Triptych Health Partners, TRM Oncology  |
| <b>Contracted Research</b>   | Aeglea BioTherapeutics, Astellas, AstraZeneca Pharmaceuticals LP, BIND Therapeutics Inc, Bristol-Myers Squibb Company, Celgene Corporation, Celldex Therapeutics, Clovis Oncology, Daiichi Sankyo Inc, Eisai Inc, EMD Serono Inc, G1 Therapeutics, Genentech, a member of the Roche Group, Grail Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, ImmunoGen Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, Lilly, Merck, Molecular Partners, Nektar, Neon Therapeutics, Novartis, Takeda Oncology, Transgene, UT Southwestern Medical Center |

# We Encourage Clinicians in Practice to Submit Questions

The image shows a Zoom meeting interface. At the top, there is a gallery view of six participants. The main area is a white slide with the text: "You may submit questions using the Zoom Chat option below". A large red arrow points downwards from this text. On the right side, there is a "Participants (10)" list with names and initials: John Smith (JS), Mary Major (MM), Richard Miles (RM), John Noakes (JN), and Alice Suarez (AS). Below the list is a "Zoom Group Chat" window showing a message from "Me to Everyone" at 12:49 PM. The bottom toolbar includes icons for "Join Audio", "Start Video", "Invite", "Participants", "Share", "Chat", "Record", "Leave Meeting", "Mute Me", and "Raise Hand".

Feel free to submit questions now before the program begins and throughout the program.

# FCS Contributing Oncologists



**Mamta Choksi, MD**  
New Port Richey, Florida



**Zanetta S Lamar, MD**  
Naples, Florida



**Uday Dandamudi, MD**  
New Port Richey, Florida



**Vikas Malhotra, MD**  
Spring Hill, Florida



**Lowell L Hart, MD**  
Fort Myers, Florida



**Shachar Peles, MD**  
Lake Worth, Florida



**Maen Hussein, MD**  
Tavares, Florida



**Syed F Zafar, MD**  
Fort Myers, Florida

# Agenda

## **Module 1: Newly Diagnosed Non-Small Cell Lung Cancer (NSCLC) without Actionable Tumor Mutations**

- Dr Peles: 80-year-old woman with MDS/AML and metastatic NSCLC; PD-L1 95%
- Dr Choksi: 76-year-old man with metastatic NSCLC, single-agent pembrolizumab

## **Module 2: Extensive-Stage Small Cell Lung Cancer (SCLC)**

- Dr Hart: 75-year-old man with extensive-stage SCLC

## **Module 3: Locally Advanced NSCLC**

- Dr Zafar: 63-year-old man, never smoker with Stage IIIB NSCLC; EGFR L858R mutation

## **Module 4: NSCLC with an EGFR Exon 19 Deletion Mutation**

- Dr Lamar: 81-year-old man with NSCLC, pleural effusion and EGFR exon 19 mutation

## **Module 5: Second-Line Therapy After Chemoimmunotherapy**

- Dr Hussein: 76-year-old woman with metastatic NSCLC and MET exon 14, IDH2, PD-L1+

## **Module 6: Metastatic NSCLC with an ALK Rearrangement**

- Dr Dandamudi: 68-year-old woman with NSCLC; pleural effusion; ALK rearrangement

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# Case Presentation – Dr Peles: An 80-year-old woman with high-risk MDS/AML and metastatic adenocarcinoma of the lung – PD-L1 95%



**Dr Schachar Peles**

- High-risk MDS/AML receiving azacitidine/venetoclax
  - Cytopenia, admitted with pneumonia
- 2/2019 PET/CT: Lung and liver hypermetabolic activity
- 2/2019 liver biopsy: Metastatic poorly differentiated adenocarcinoma consistent with pulmonary primary (CK7, TTF-1-positive)
  - PD-L1: 95%; EGFR, ALK, MET, RET wildtype
- 3/2019: Pembrolizumab, with complete remission

# What first-line treatment would you likely recommend for a 76-year-old man with nonsquamous NSCLC and widespread, symptomatic bone metastases with a PD-L1 TPS of 50%?

- a. Chemotherapy +/- bevacizumab
- b. Anti-PD-1/PD-L1 antibody alone
- c. Carboplatin/pemetrexed/pembrolizumab
- d. Atezolizumab/carboplatin/*nab* paclitaxel
- e. Atezolizumab/carboplatin/paclitaxel/bevacizumab
- f. Ipilimumab/nivolumab
- g. Ipilimumab/nivolumab + chemotherapy
- h. Other

# Case Presentation – Dr Choksi: A 76-year-old man with widespread bony metastatic NSCLC



**Dr Mamta Choksi**

- 9/2019: Spinal compression fracture → kyphoplasty
- 12/2019: MRI, PET/CT: Diffuse osseous metastatic disease, hypermetabolic left lung nodule, mediastinal nodes, paraortic and pelvic lymph nodes and mass in the spleen
- Repeat kyphoplasty and palliative RT
- PD-L1: High expression, 2+, 50%
- Initiated single-agent pembrolizumab due to poor performance status
  - 2/2020: Added carboplatin/pemetrexed
    - Significant fatigue, weakness and GERD-like symptoms
- 5/2020: Maintenance pemetrexed/pembrolizumab with improvement
- 9/2020: Maintenance pembrolizumab

## Questions

- What is your recommendation for second-line treatment if he is not eligible for a clinical trial?
- What is your current preference for first-line therapy for a patient with widely metastatic bony disease and a poor performance status?

# FDA Approves Nivolumab with Ipilimumab for First-Line Metastatic NSCLC with PD-L1 Tumor Expression $\geq 1\%$

Press Release — May 15, 2020

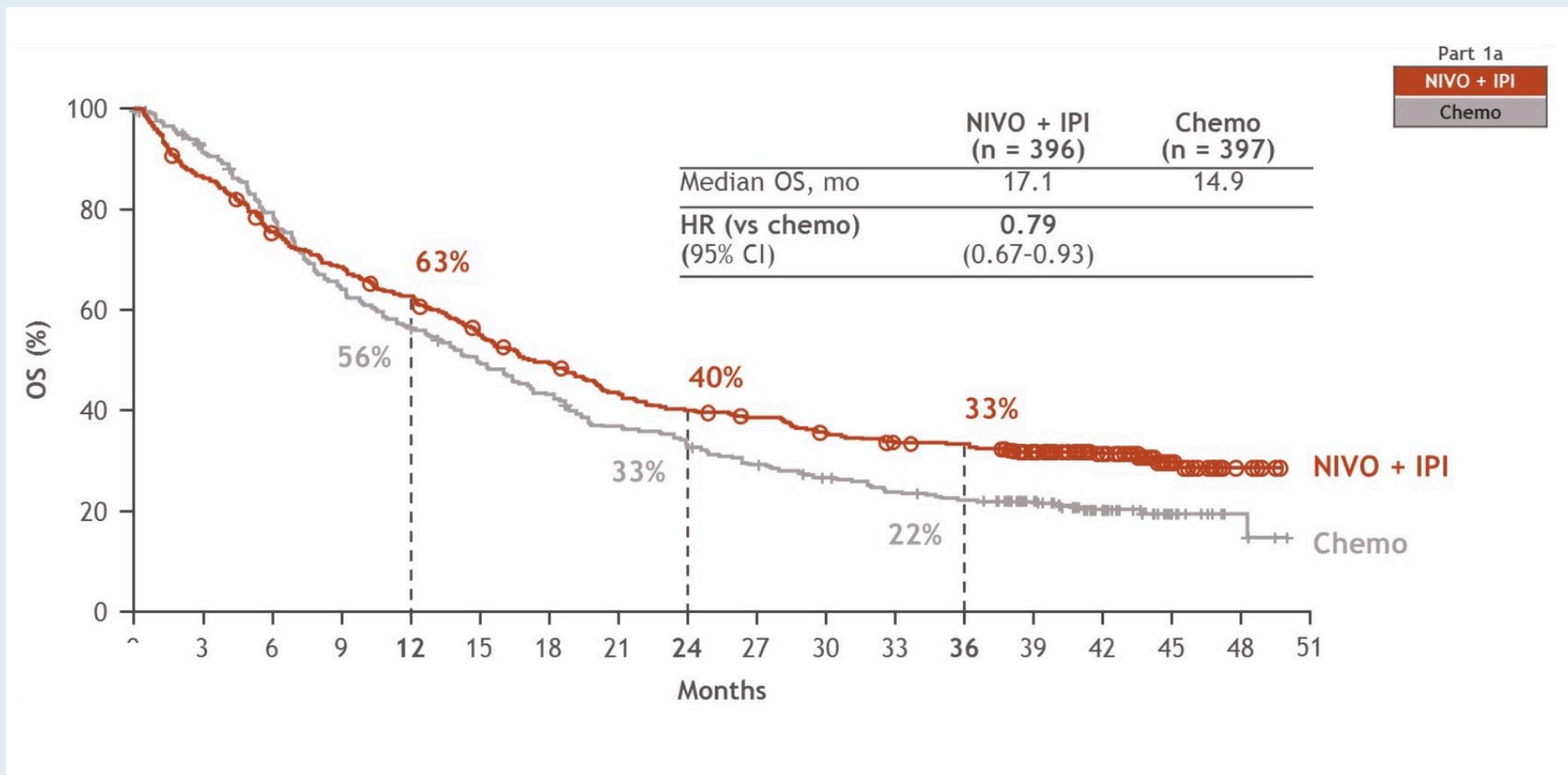
“The Food and Drug Administration approved the combination of nivolumab plus ipilimumab as first-line treatment for patients with metastatic non-small cell lung cancer whose tumors express PD-L1( $\geq 1\%$ ), as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

Efficacy was investigated in CHECKMATE-227 (NCT02477826), a randomized, open-label, multi-part trial in patients with metastatic or recurrent NSCLC and no prior anticancer therapy. In Part 1a of the trial, 793 patients with PD-L1 tumor expression  $\geq 1\%$  were randomized to receive either the combination of nivolumab plus with ipilimumab (n=396) or platinum-doublet chemotherapy (n=397).”

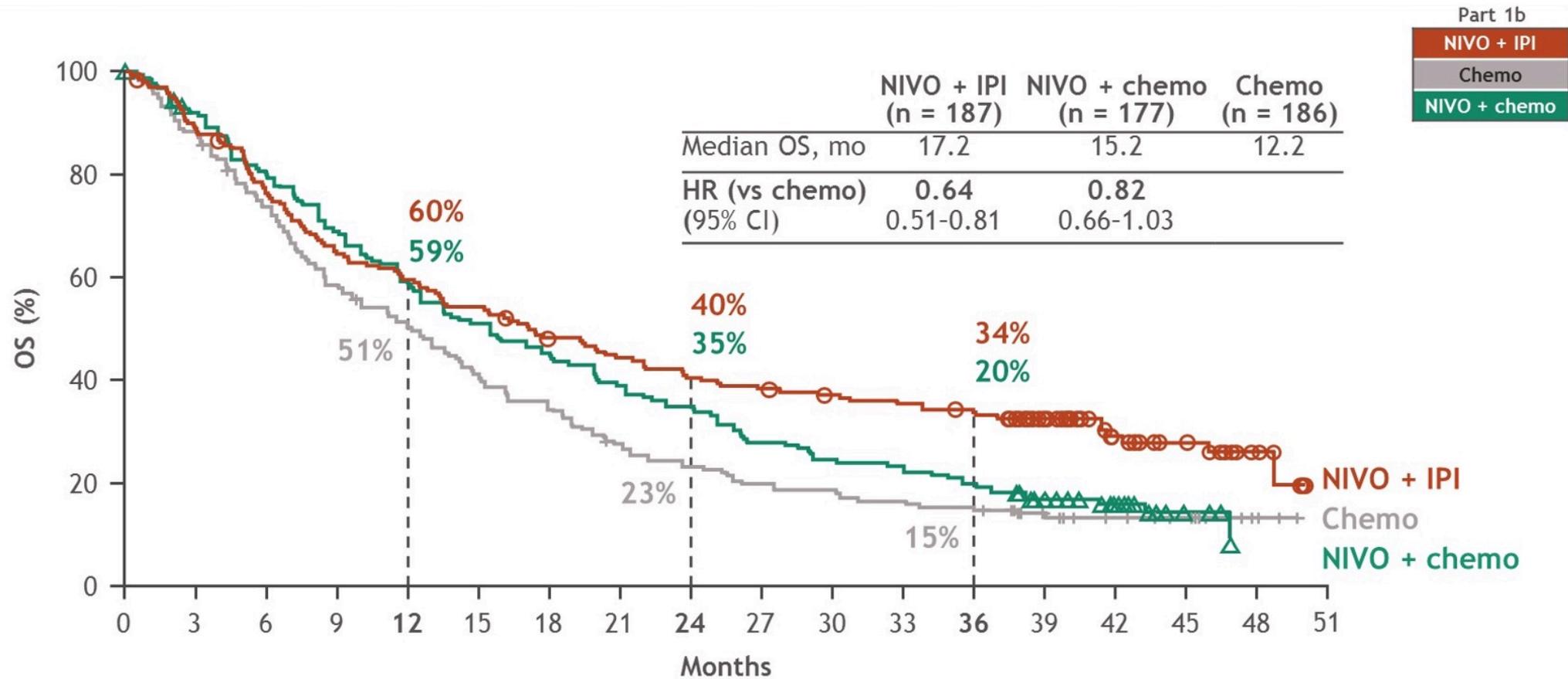
# **Nivolumab + Ipilimumab versus Platinum-Doublet Chemotherapy as First-Line Treatment for Advanced Non-Small Cell Lung Cancer: Three-Year Update from CheckMate 227 Part 1**

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%)



# Landmark Analysis of OS by Response Status at 6 Months with PD-L1 $\geq 1\%$ (IPI + Nivo vs Chemo)

|                 | Ipi + Nivo (n = 295) versus Chemo (n = 306) |             |             |             |
|-----------------|---|-------------|-------------|-------------|
| Response status | Response at 6 mo                            | 1-y OS rate | 2-y OS rate | 3-y OS rate |
| CR or PR        | 39% vs 25%                                  | 90% vs 73%  | 76% vs 51%  | 70% vs 39%  |
| SD              | 14% vs 18%                                  | 69% vs 54%  | 45% vs 38%  | 34% vs 33%  |
| PD              | 46% vs 58%                                  | 44% vs 47%  | 22% vs 25%  | 19% vs 17%  |

# FDA Approves Nivolumab with Ipilimumab and Chemotherapy for First-Line Treatment of Metastatic NSCLC

Press Release — May 26, 2020

“The Food and Drug Administration approved the combination of nivolumab plus ipilimumab and 2 cycles of platinum-doublet chemotherapy as first-line treatment for patients with metastatic or recurrent non-small cell lung cancer (NSCLC), with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

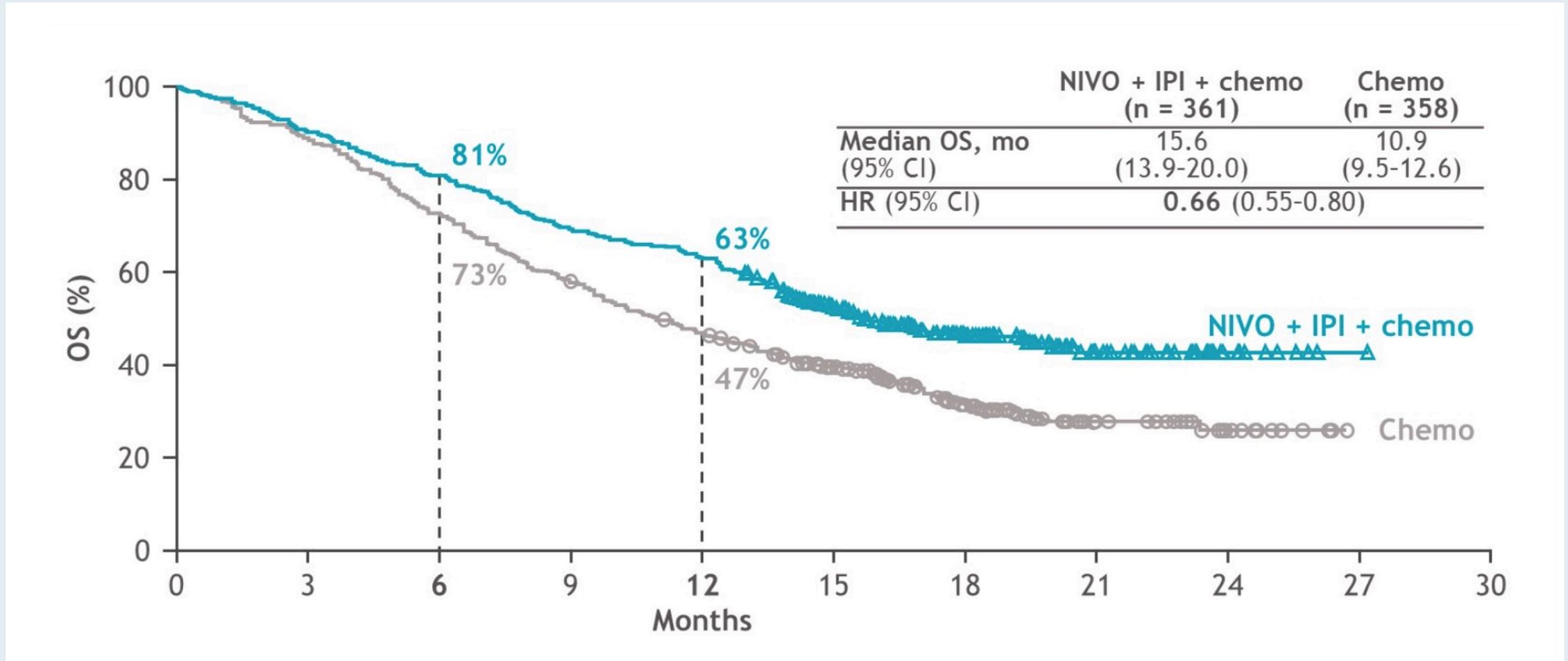
Efficacy was investigated in CHECKMATE-9LA (NCT03215706), a randomized, open-label trial in patients with metastatic or recurrent NSCLC. Patients were randomized to receive either the combination of nivolumab plus ipilimumab and 2 cycles of platinum-doublet chemotherapy (n=361) or platinum-doublet chemotherapy for 4 cycles (n=358).”

# **Nivolumab (NIVO) + Ipilimumab (IPI) + 2 Cycles of Platinum-Doublet Chemotherapy (Chemo) vs 4 Cycles Chemo as First-Line (1L) Treatment (tx) for Stage IV/Recurrent Non-Small Cell Lung Cancer (NSCLC): CheckMate 9LA**

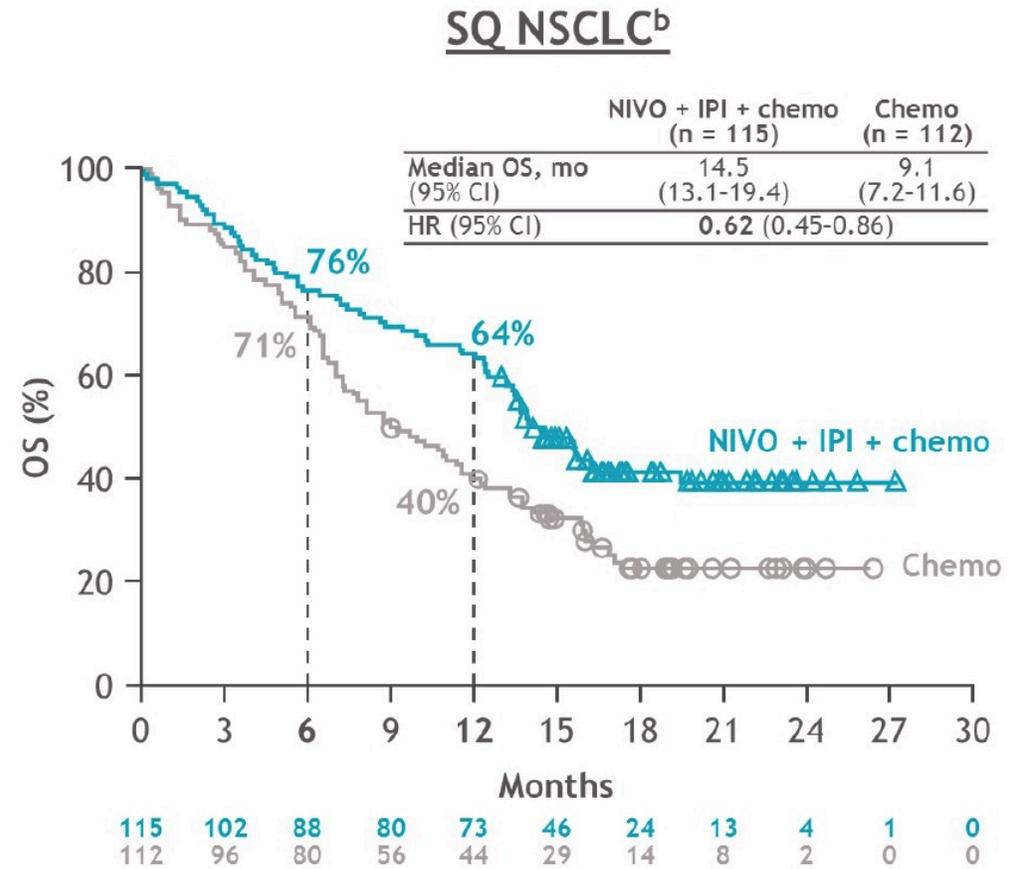
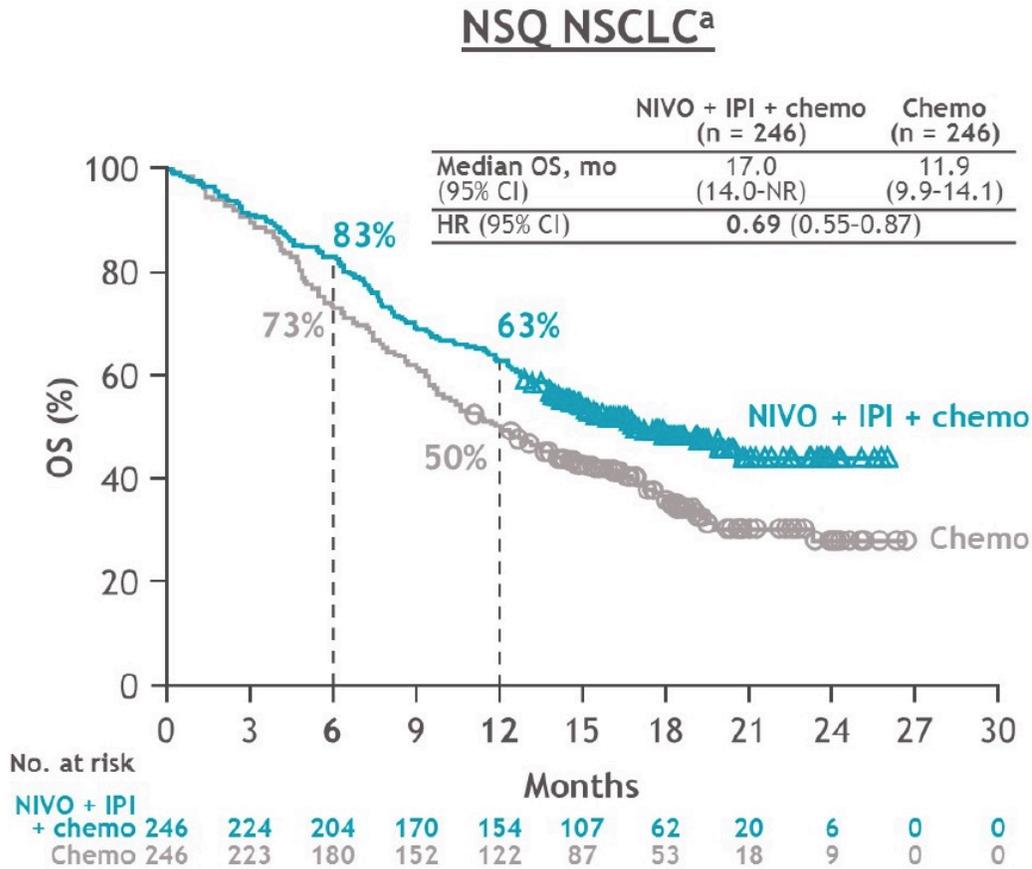
Reck M et al.

ASCO 2020;Abstract 9501.

# CheckMate 9LA: Updated OS



# CheckMate 9LA: Updated OS by Histology



# **Nivolumab (NIVO) plus Ipilimumab (IPI) with Two Cycles of Chemotherapy (Chemo) in First-Line Metastatic Non-Small Cell Lung Cancer (NSCLC): CheckMate 568 Part 2**

Gainor JF et al.

ASCO 2020;Abstract 9560.

# FDA-Approved Immunotherapy Options for the First-Line Treatment of Metastatic NSCLC

| Combination regimen  | FDA approval        | Pivotal study              | Histologic type                                   | HR (OS) |
|--|---------------------|----------------------------|---|---------|
| Pembrolizumab +<br>Platinum and pemetrexed <sup>1</sup>                          | 8/20/18             | KEYNOTE-189                | Nonsquamous                                       | 0.49    |
| Pembrolizumab +<br>Carboplatin, paclitaxel or <i>nab</i> paclitaxel <sup>2</sup> | 10/30/18            | KEYNOTE-407                | Squamous  | 0.64    |
| Atezolizumab +<br>Carboplatin and paclitaxel and bevacizumab <sup>3</sup>        | 12/6/18             | IMpower150                 | Nonsquamous                                       | 0.78    |
| Atezolizumab +<br>Carboplatin and <i>nab</i> paclitaxel <sup>4</sup>             | 12/3/19             | IMpower130                 | Nonsquamous                                       | 0.79    |
| Nivolumab +<br>Ipilimumab <sup>5</sup>   | 5/15/20             | CheckMate-227              | PD-L1 TPS $\geq$ 1,<br>EGFR and/or ALK <i>wt</i>  | 0.62    |
| Nivolumab +<br>Ipilimumab and chemotherapy <sup>6</sup>                          | 5/26/20             | CheckMate-9LA              | EGFR and/or ALK <i>wt</i>                         | 0.69    |
| Monotherapy  | FDA approval        | Pivotal study              | Histologic type                                   | HR (OS) |
| Pembrolizumab <sup>7,8</sup>   | 4/11/19<br>10/24/16 | KEYNOTE-042<br>KEYNOTE-024 | PD-L1 TPS $\geq$ 1%                               | 0.63    |
| Atezolizumab <sup>9</sup>  | 5/18/20             | IMpower110                 | PD-L1 TPS $\geq$ 50,<br>EGFR and/or ALK <i>wt</i> | 0.59    |

<sup>1</sup> Gandhi L et al. *NEJM* 2018;378(22):2078-92. <sup>2</sup> Paz-Ares L et al. *NEJM* 2018;379(21):2040-51.

<sup>3</sup> Socinski MA et al. *NEJM* 2018;378(24):2288-301. <sup>4</sup> West H et al. *Lancet Oncol* 2019;20(7):924-37.

<sup>5</sup> Hellmann MD et al. *N Engl J Med* 2019;381(21):2020-31. <sup>6</sup> Reck M et al. ASCO 2020;Abstract 9501.

<sup>7</sup> Mok TSK et al. *Lancet* 2019;393(10183):1819-30. <sup>8</sup> Reck M et al. *J Clin Oncol* 2019;37(7):537-46.

<sup>9</sup> Spigel DR et al. ESMO 2019;Abstract LBA78

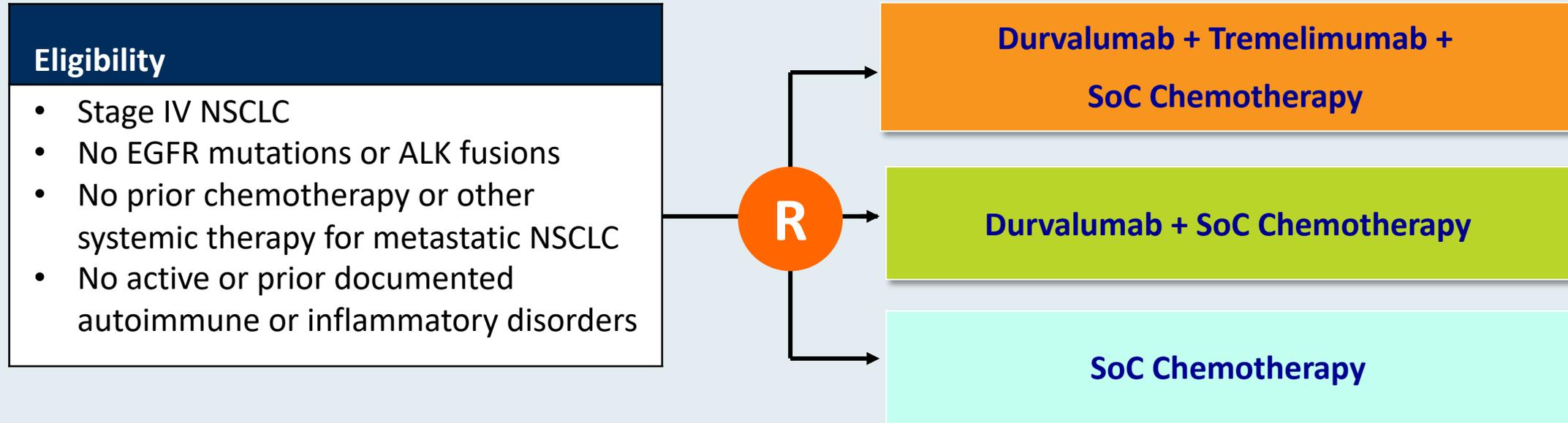
# Durvalumab and Durvalumab with Tremelimumab Delayed Disease Progression in Phase III POSEIDON Trial for First-Line Treatment of Stage IV NSCLC

Press Release – October 28, 2019

“Positive progression-free survival (PFS) results [*were announced*] for durvalumab and tremelimumab, an anti-CTLA4 antibody, when added to chemotherapy, from the Phase III POSEIDON trial in previously-untreated Stage IV (metastatic) non-small cell lung cancer (NSCLC).

The trial met a primary endpoint by showing a statistically significant and clinically meaningful improvement in the final PFS analysis in patients treated with the combination of durvalumab and a broad choice of five standard-of-care platinum-based chemotherapy options vs. chemotherapy alone. The triple combination of durvalumab plus tremelimumab and chemotherapy also demonstrated a statistically significant and clinically meaningful PFS improvement vs. chemotherapy alone as a key secondary endpoint. The safety and tolerability of durvalumab was consistent with its known safety profile. The triple combination delivered a broadly similar safety profile to the durvalumab and chemotherapy combination and did not result in increased discontinuation of therapy.”

# POSEIDON Phase III Study Schema



**Primary endpoints:** Progression-free survival (BICR) and Overall Survival

**SoC Chemotherapy:** Nab paclitaxel + carboplatin (squamous or nonsquamous), Gemcitabine + cisplatin or carboplatin (squamous only), Pemetrexed + cisplatin or carboplatin (nonsquamous only)

# Agenda

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- Dr Peles: 80-year-old woman with MDS/AML and metastatic NSCLC; PD-L1 95%
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- Dr Dandamudi: 68-year-old woman with NSCLC; pleural effusion; ALK rearrangement

# Case Presentation – Dr Hart: A 75-year-old man with extensive-stage SCLC



**Dr Lowell Hart**

- Fall 2019: Limited-stage SCLC
- 2/2020: Completes carboplatin/VP16 and radiation therapy
- 5/2020: Completes prophylactic brain radiation therapy, with plans to enroll in trial of durvalumab +/- tremelimumab
- PET: New liver metastases → topotecan (poorly tolerated)
- Switched to nivolumab/ipilimumab → PD after several cycles in 9/2020
- 10/2020: Lurbinectedin

## Questions

- What are the pluses and minus of lurbinectedin?
- If a patient has extensive-stage disease and gets chemotherapy and a checkpoint inhibitor first line, what would then be their second line of therapy?
- Is lurbinectedin a good enough drug to move up and take the place of topotecan in the second-line setting?
- Since we know the minority of patients with limited-stage SCLC are cured with chemotherapy and radiation therapy, should we try to give them a checkpoint inhibitor immediately after radiation therapy? For extensive-stage SCLC, which is the checkpoint inhibitor of choice? Are there differences in toxicity or activity?

# What is your preferred checkpoint inhibitor to combine with chemotherapy as first-line treatment for extensive-stage small cell lung cancer?

- a. None
- b. Durvalumab
- c. Atezolizumab
- d. No preference — coin flip
- e. Other

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

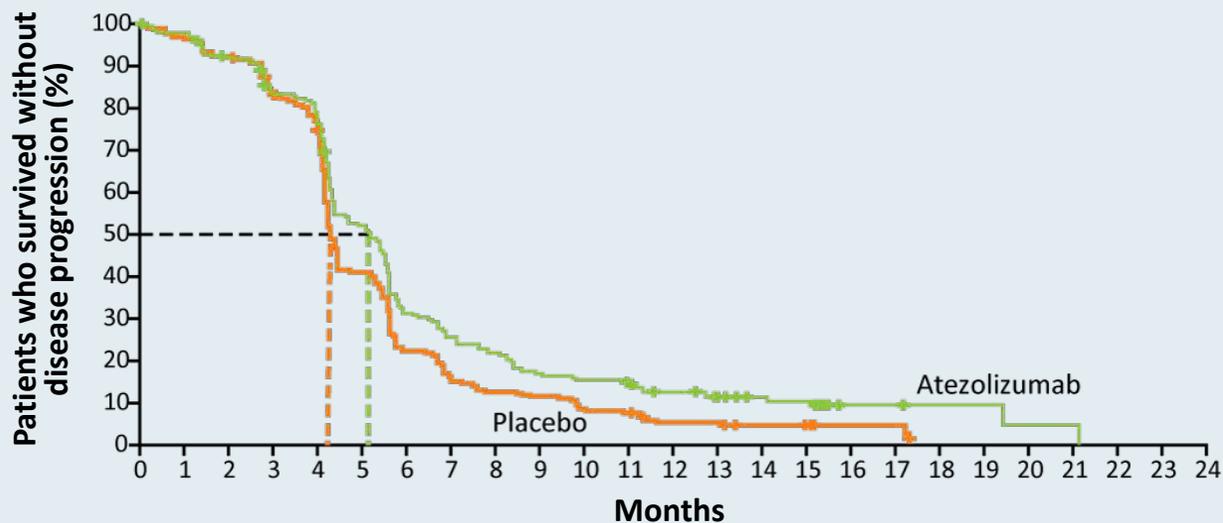
# First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

L. Horn, A.S. Mansfield, A. Szczesna, L. Havel, M. Krzakowski, M.J. Hochmair,  
F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, M. Reck, T. Mok, S. Lam,  
D.S. Shames, J. Liu, B. Ding, A. Lopez-Chavez, F. Kabbinavar, W. Lin, A. Sandler,  
and S.V. Liu, for the IMpower133 Study Group\*

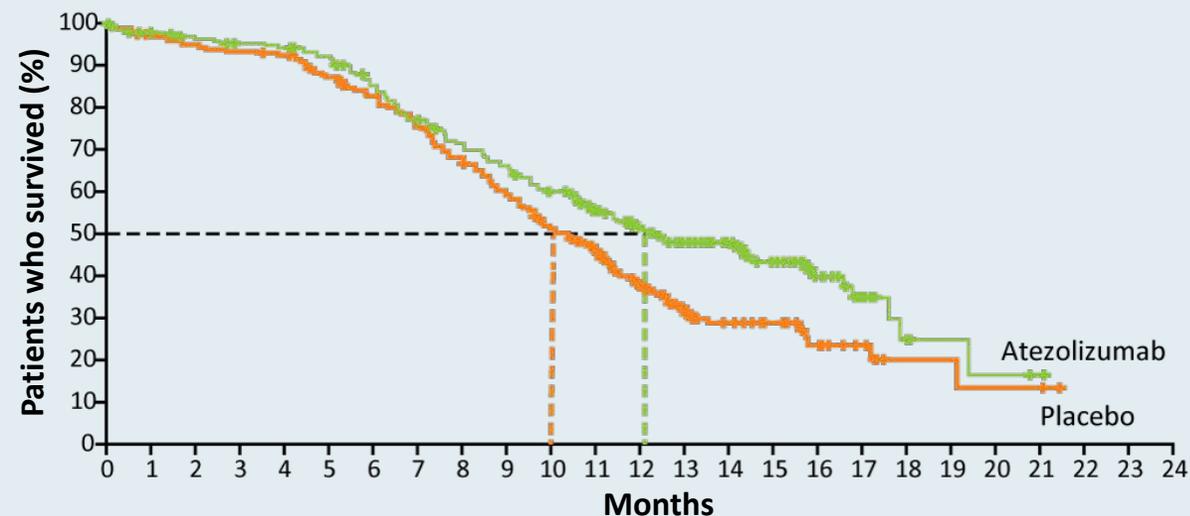
*N Engl J Med* 2018;379(23):2220-9.

# IMpower133: Survival Outcomes

## Progression-free survival (PFS)



## Overall survival (OS)



|              | Median PFS | 12-mo PFS | HR   | <i>p</i> -value |
|--------------|------------|-----------|------|-----------------|
| Atezolizumab | 5.2 mo     | 12.6%     | 0.77 | 0.02            |
| Placebo      | 4.3 mo     | 5.4%      |      |                 |

|              | Median OS | 12-mo OS | HR   | <i>p</i> -value |
|--------------|-----------|----------|------|-----------------|
| Atezolizumab | 12.3 mo   | 51.7%    | 0.70 | 0.007           |
| Placebo      | 10.3 mo   | 38.2%    |      |                 |

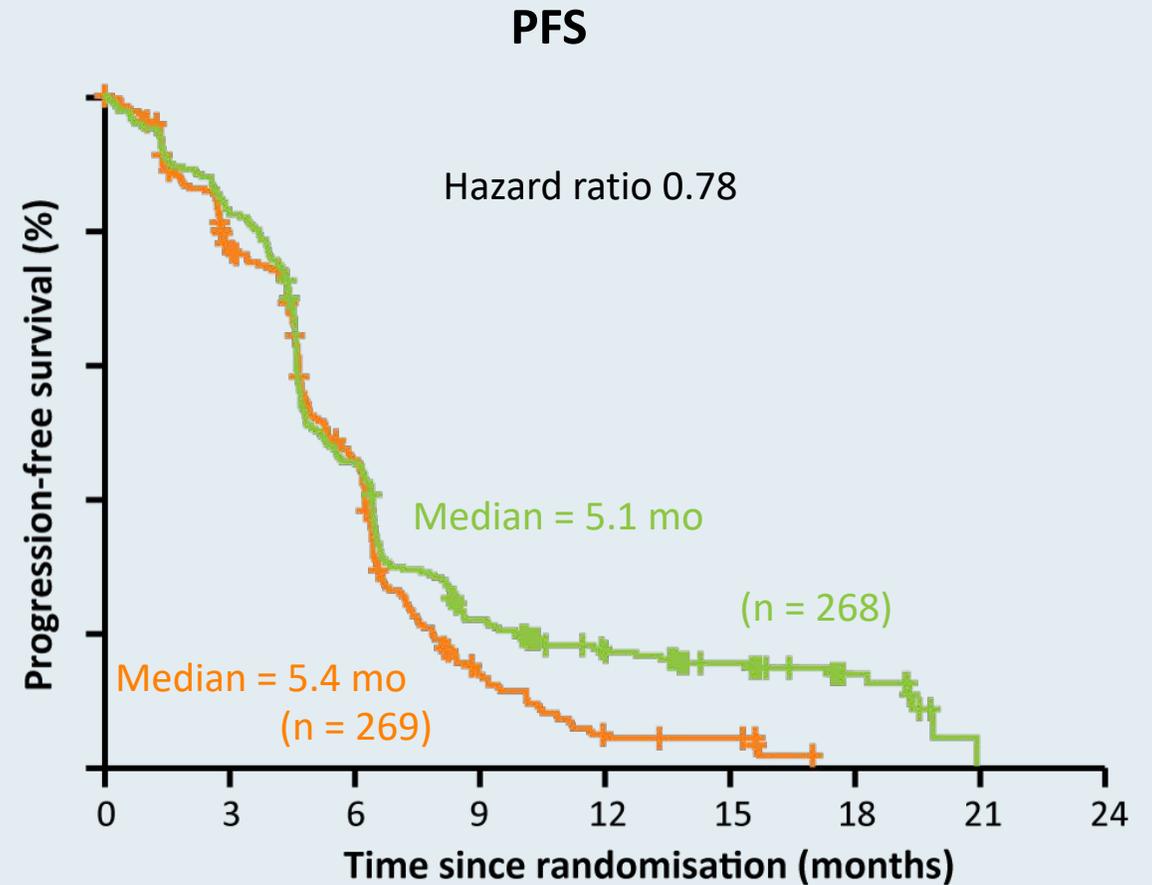
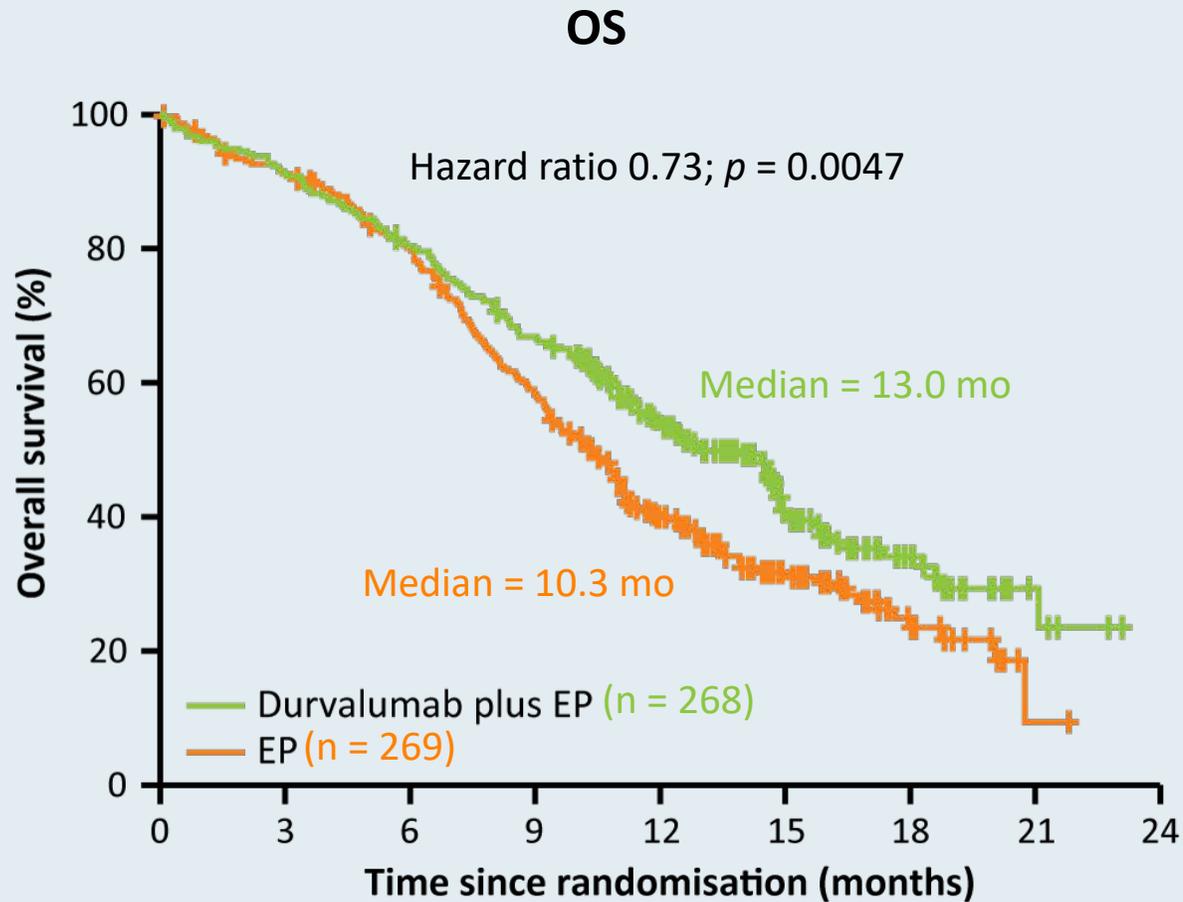
- The safety profile of atezolizumab + carboplatin and etoposide was consistent with the previously reported safety profile of the individual agents; no new findings were observed.

# Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial

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

*Lancet 2019;394(10212):1929-39.*

# CASPIAN: Survival Analyses in ITT Population



# Accelerated Approval of Lurbinectedin for Metastatic SCLC

Press Release – June 15, 2020

“On June 15, 2020, the Food and Drug Administration granted accelerated approval to lurbinectedin for adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy.

Efficacy was demonstrated in the PM1183-B-005-14 trial (Study B-005; NCT02454972), a multicenter open-label, multi-cohort study enrolling 105 patients with metastatic SCLC who had disease progression on or after platinum-based chemotherapy. Patients received lurbinectedin 3.2 mg/m<sup>2</sup> by intravenous infusion every 21 days until disease progression or unacceptable toxicity.

The recommended lurbinectedin dose is 3.2 mg/m<sup>2</sup> every 21 days.”

***Lancet Oncol 2020; 21: 645–54***

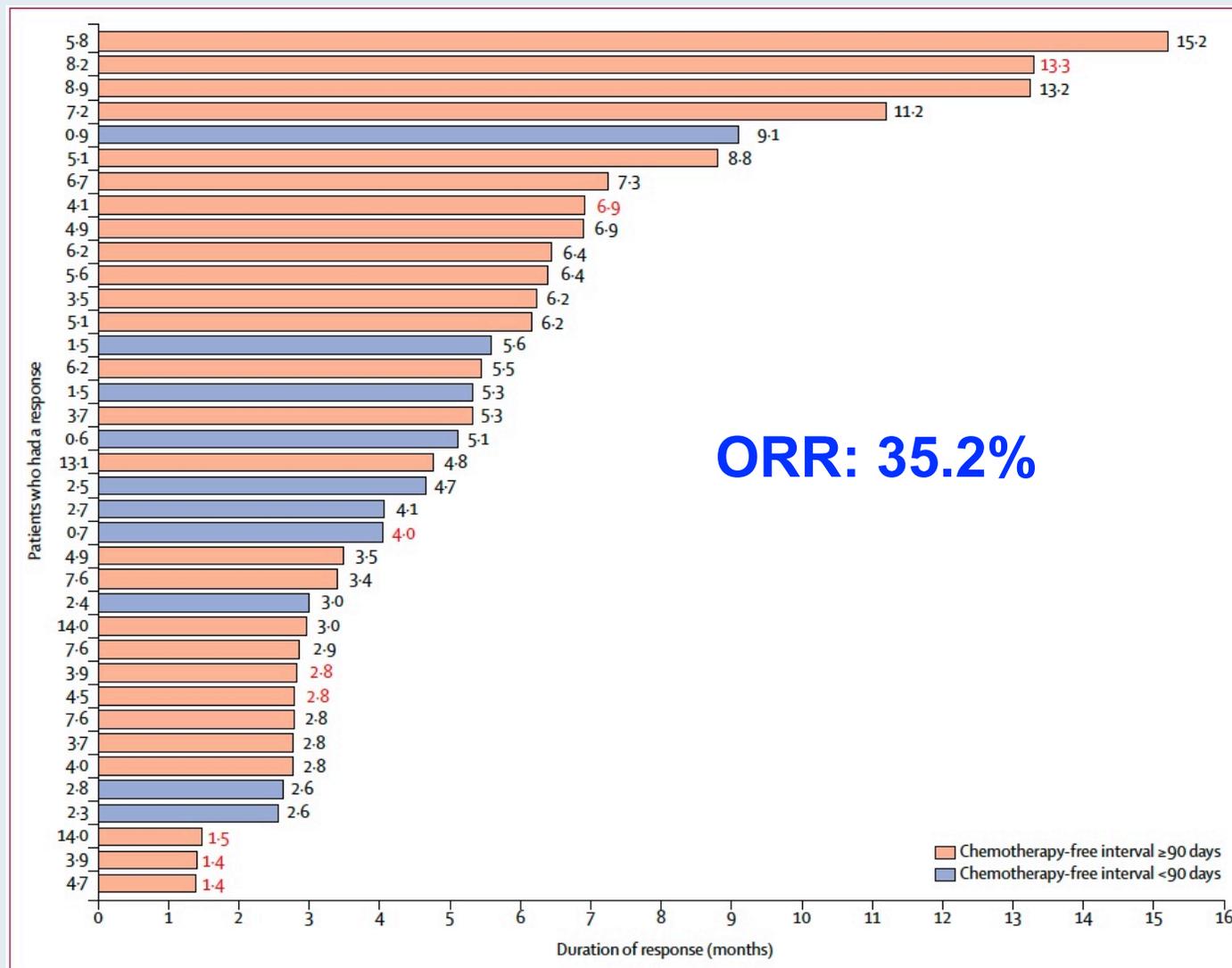
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# **Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial**



*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 in SCLC



# Agenda

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## **Module 6: Metastatic NSCLC with an ALK Rearrangement**

- Dr Dandamudi: 68-year-old woman with NSCLC; pleural effusion; ALK rearrangement

# What would you most likely recommend as consolidation treatment for a patient with locally advanced NSCLC who has completed chemoradiation therapy and is found to have an EGFR activating mutation?

- a. Durvalumab
- b. Osimertinib
- c. Durvalumab + osimertinib
- d. Durvalumab followed by osimertinib
- e. Other

# Case Presentation – Dr Zafar: A 63-year-old man, never smoker with metastatic adenocarcinoma of the lung – EGFR L858R mutation



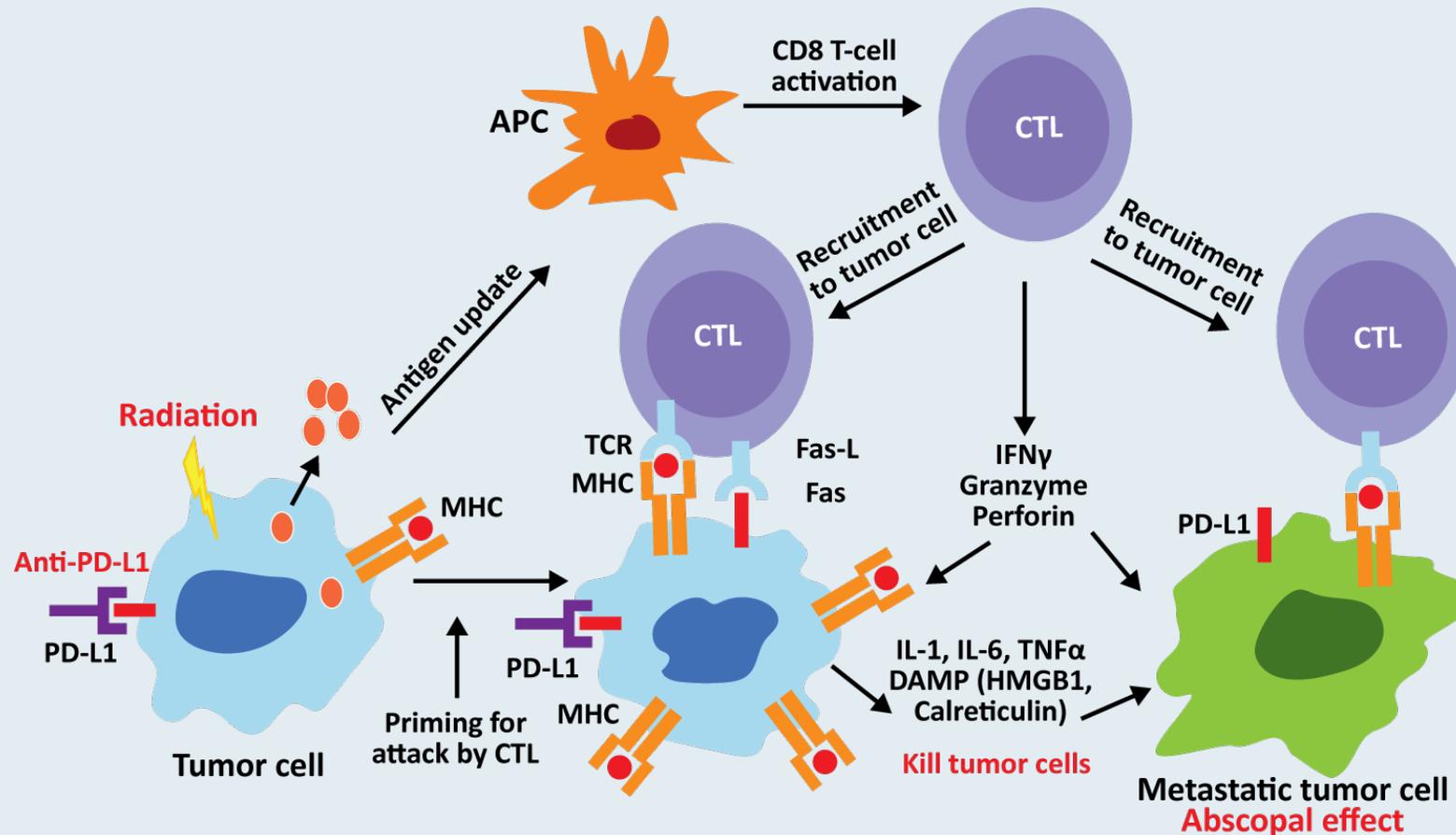
Dr Syed Zafar

- Stage IIIB lung adenocarcinoma
  - NGS: EGFR L858R mutation
- Concurrent chemoradiation therapy → Durvalumab x 1 year
- 2 months later: Seizure, vertigo
  - MRI brain: Left front (2.5 x 2.5 cm), left cerebellar (2 x 1.5 cm) + vasogenic edema
  - Systemic CT/PET: Negative

## Question

- After radiation therapy, should I observe and treat upon disease progression, or start osimertinib now?

# Rationale for Immune Checkpoint Inhibitors After Chemoradiation Therapy for Locally Advanced NSCLC



- Chemoradiation therapy may increase neoantigen production, which promotes T-cell infiltration
- Immune checkpoint inhibitors prevent PD-1/PD-L1 proteins from interfering with cytotoxic T-cell response

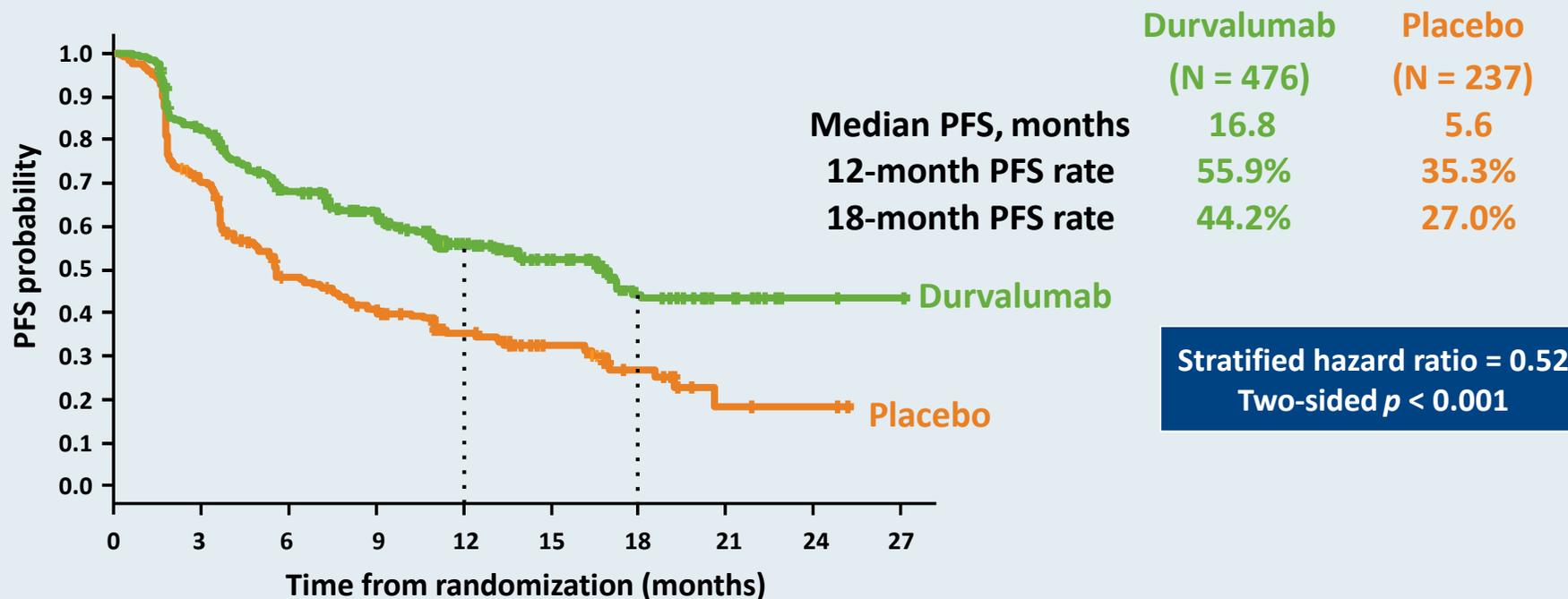
ORIGINAL ARTICLE

# Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Kurata, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hirt, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Faivre-Finn, M. Reck, J. Vansteenkiste, D.R. Spigel, C. Wadsworth, G. Melillo, M. Taboada, P.A. Dennis, and M. Özgüroğlu,  
for the PACIFIC Investigators\*

*N Engl J Med* 2018;379(24):2342-50.

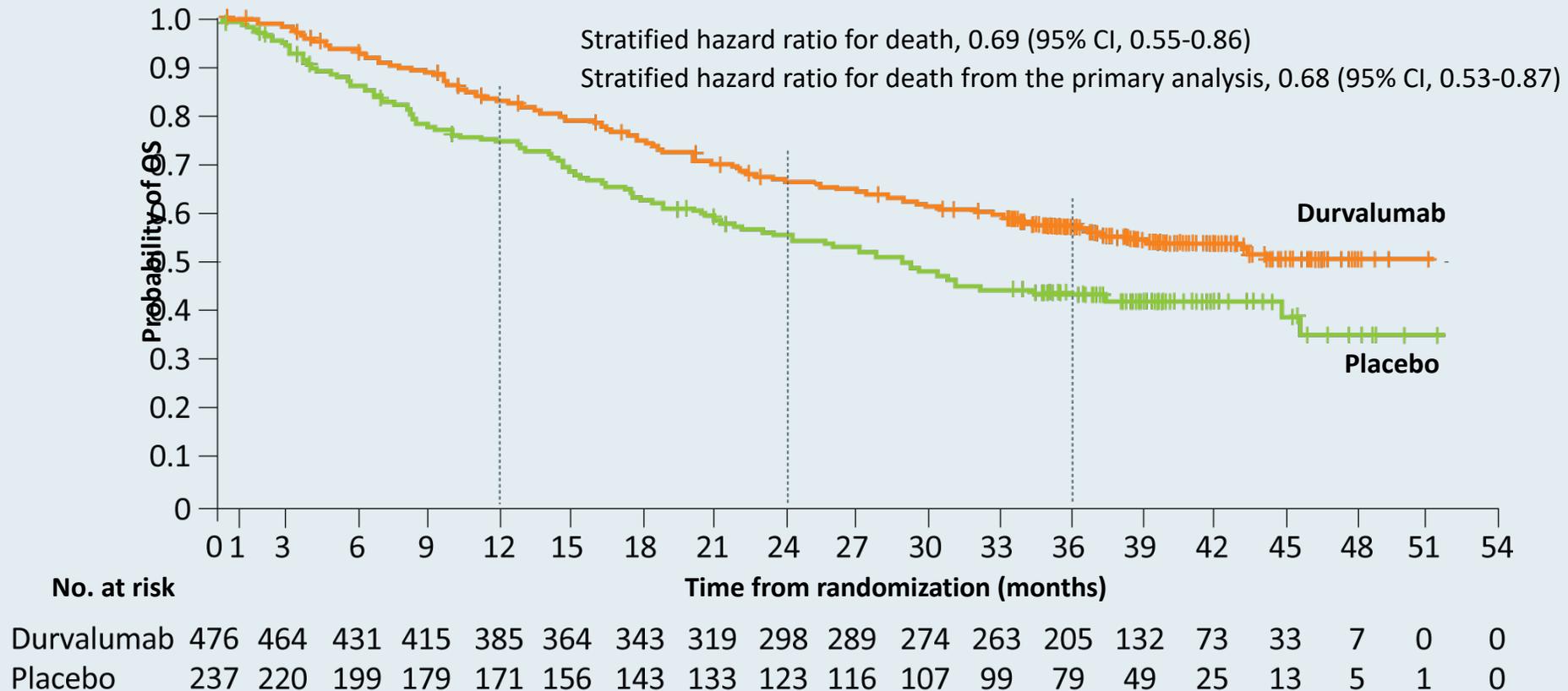
# PACIFIC: PFS by Blinded Independent Central Review in the Intention-to-Treat Population (Primary Endpoint)



- No new safety signals were observed, and the most common Grade 3 or 4 adverse event associated with durvalumab compared to placebo was pneumonia (4.4% and 3.8%, respectively).
- OS data were immature at the time of this analysis.

# PACIFIC: 3-Year Overall Survival Analysis in the Intention-to-Treat Population

|            | No. of events/<br>total no. of<br>patients (%) | Median OS<br>(95% CI)<br>months | 12-month OS<br>rate (95% CI)<br>% | 24-month OS<br>rate (95% CI)<br>% | 36-month OS<br>rate (95% CI)<br>% |
|------------|--|---------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Durvalumab | 210/476 (44.1)                                 | NR (38.4-NR)                    | 83.1 (79.4-86.2)                  | 66.3 (61.8-70.4)                  | 57.0 (52.3-61.4)                  |
| Placebo    | 134/237 (56.5)                                 | 29.1 (22.1-35.1)                | 74.6 (68.5-79.7)                  | 55.3 (48.6-61.4)                  | 43.5 (37.0-49.9)                  |



# 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  $\geq 2$ )
- 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

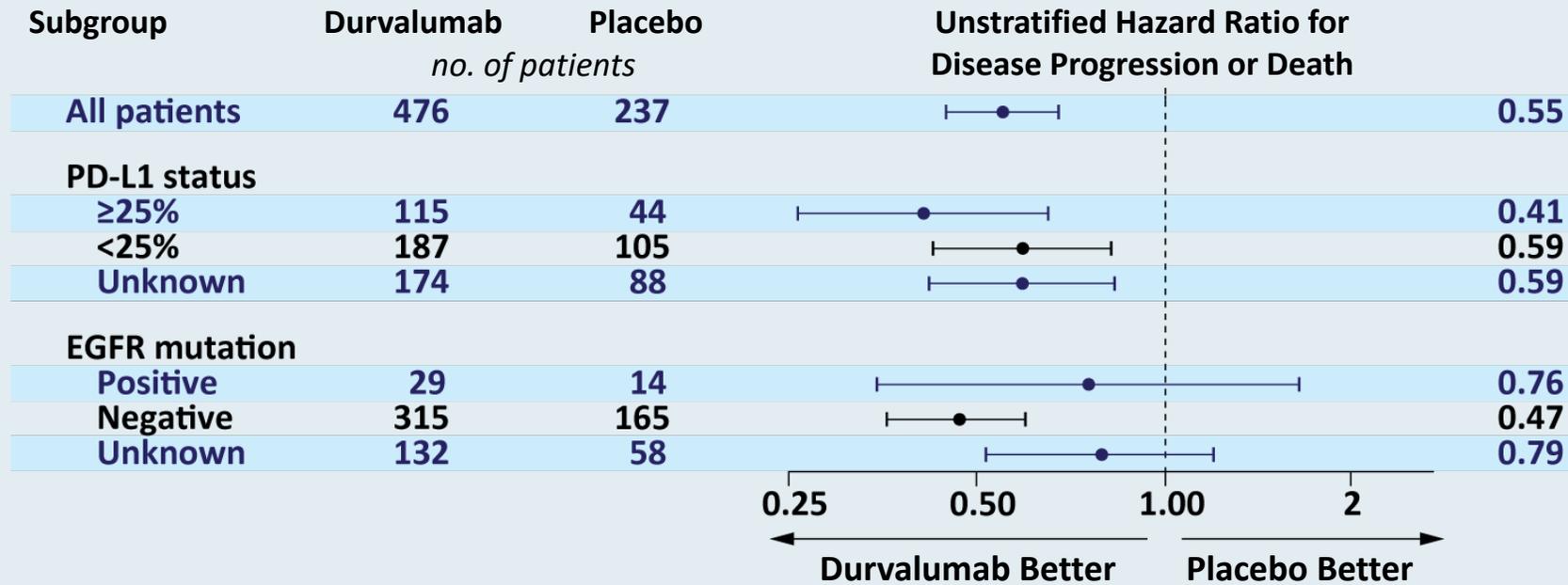
# Multi-Institutional Study of Pneumonitis After Durvalumab and Chemoradiation Therapy: Impact on Survival

- N = 36 patients with NSCLC (89% Stage III) treated according to the PACIFIC paradigm
- Grade  $\geq 2$  pneumonitis:
  - 3 months after treatment, 26%
  - 6 months after treatment, 29%
- Median time to development of pneumonitis after completion of radiation therapy: 71 days (range 29-270)
- Development of pneumonitis did not affect survival outcomes

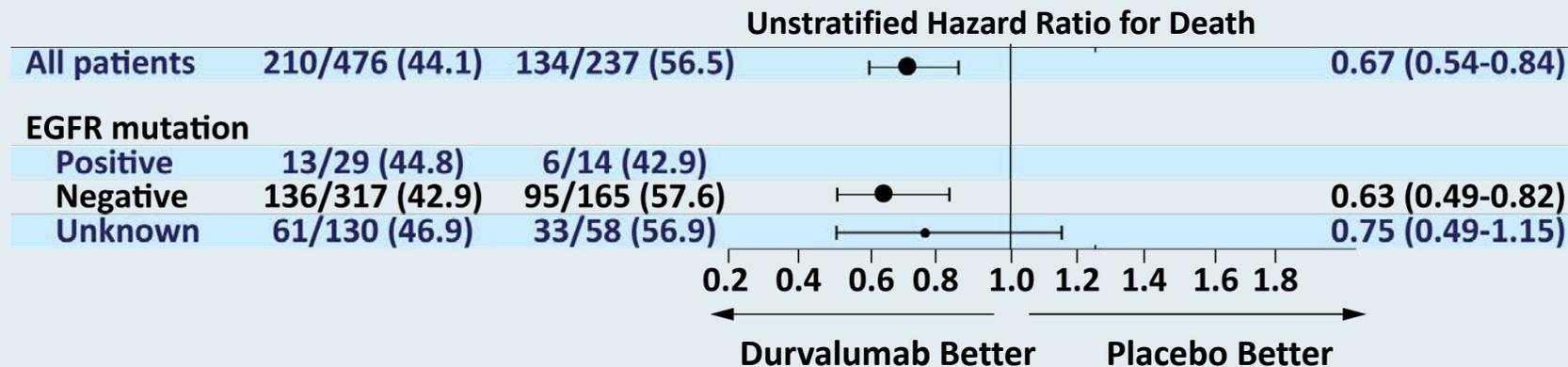
|                 | Pneumonitis | No pneumonitis | <i>p</i> -value |
|-----------------|-------------|----------------|-----------------|
| PFS at 9 months | 70%         | 66%            | 0.94            |
| OS at 12 months | 100%        | 83.3%          | 0.32            |

# PACIFIC: Outcomes by EGFR Status

## Progression-free Survival

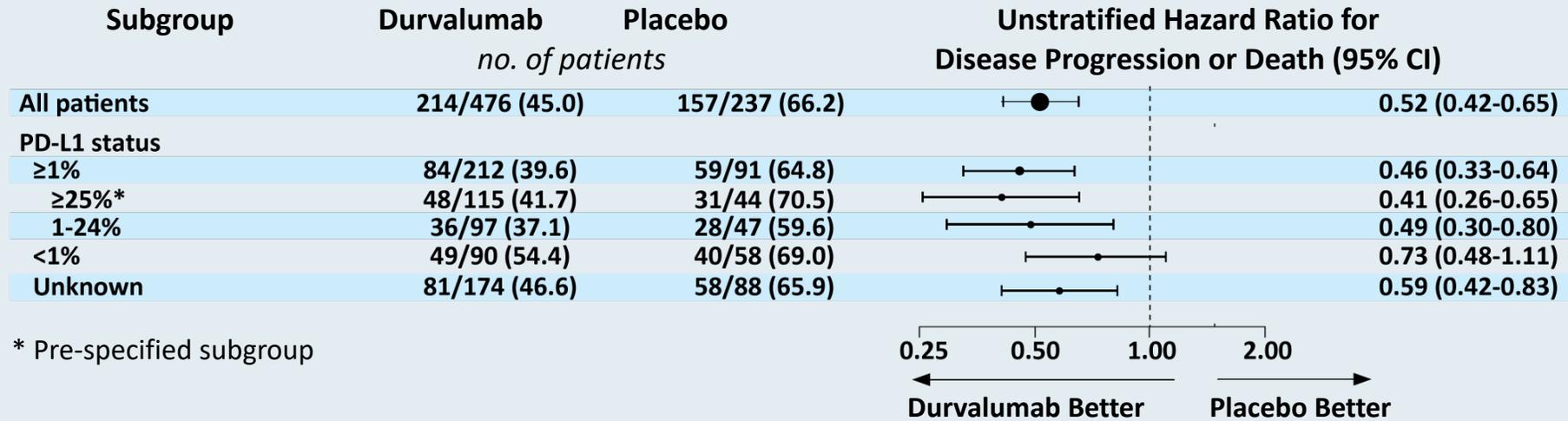


## Overall Survival

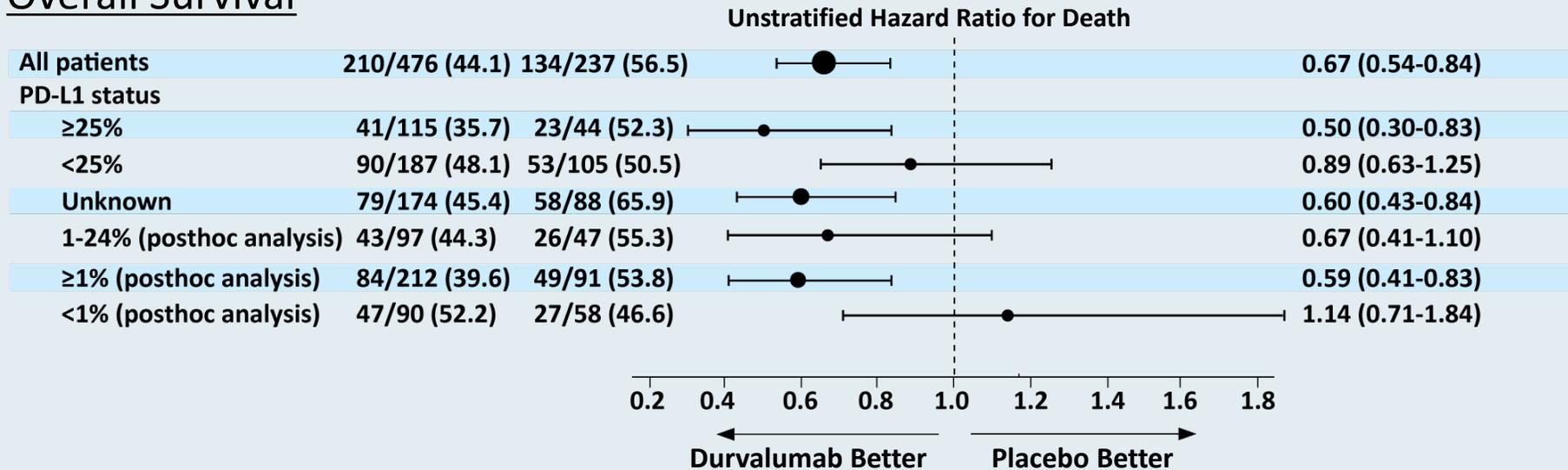


# PACIFIC: Outcomes by PD-L1 Status

## Progression-free Survival



## Overall Survival



# Phase II Study of Pembrolizumab (Pembro) plus Platinum Doublet Chemotherapy and Radiotherapy as First-Line Therapy for Unresectable, Locally Advanced Stage III NSCLC: KEYNOTE-799

Jabbour SK et al.

ASCO 2020;Abstract 9008.

# KEYNOTE-799 Phase II Study Schema

## Study Design

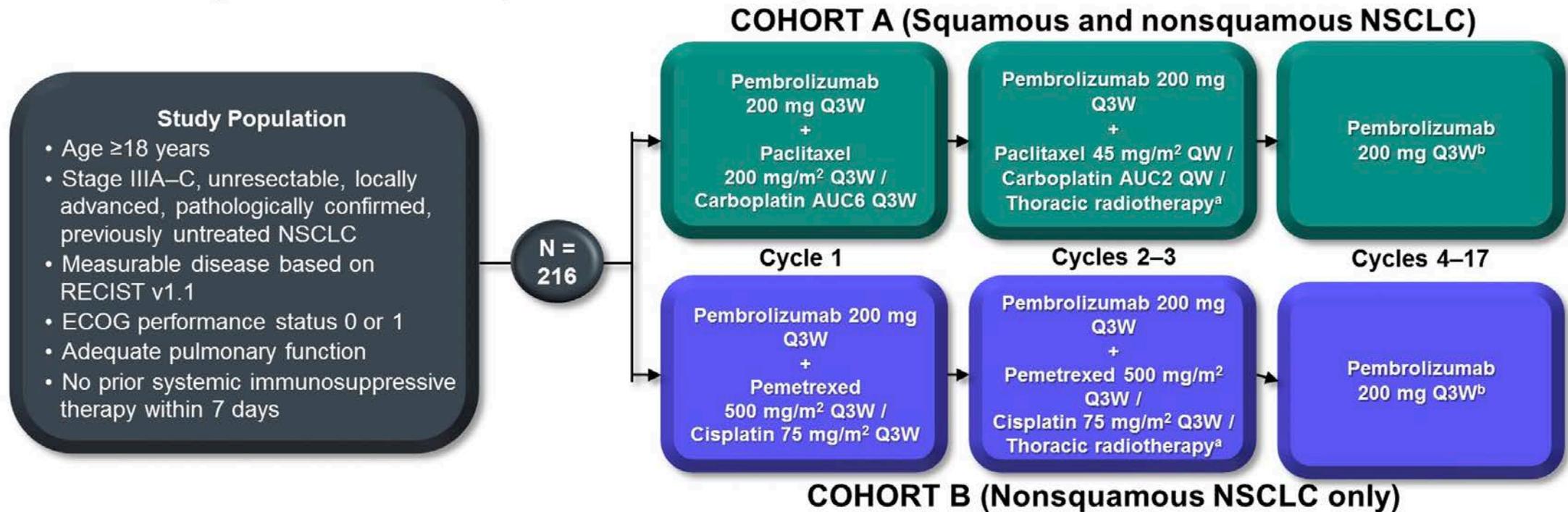
- Nonrandomized, open-label study
- Choice of chemotherapy per investigator
- Nonsquamous NSCLC patients eligible for cohort A or B
- Squamous NSCLC patients eligible for cohort A only
- Cohort A fully accrued at data cutoff; cohort B is still accruing

## Primary Objectives

- ORR per RECIST version 1.1 by BICR
- Percentage of patients who develop grade  $\geq 3$  pneumonitis

## Secondary Objectives

- PFS, OS, safety



<sup>a</sup>60 Gy in 30 daily 2-Gy fractions.

<sup>b</sup>Treatment will continue until cycle 17 is completed or until documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, or study withdrawal. Pembrolizumab therapy will be discontinued permanently in patients who develop grade  $\geq 3$  or recurrent grade 2 pneumonitis.

## KEYNOTE-799 Primary Endpoint: ORR

|   | Cohort A<br>(N = 112) | Cohort B<br>(N = 53)  |
|---|-----------------------|-----------------------|
| ORR, n (%) [90% CI]                                   | 75 (67.0) [58.9–74.3] | 30 (56.6) [44.4–68.2] |
| CR  | 3 (2.7)               | 2 (3.8)               |
| PR  | 72 (64.3)             | 28 (52.8)             |
| SD, n (%)   | 23 (20.5)             | 18 (34.0)             |
| PD, n (%)   | 1 (0.9)               | 0                     |
| Not evaluable, n (%)                                  | 3 (2.7)               | 0                     |
| No assessment, n (%)                                  | 10 (8.9)              | 5 (9.4)               |
| Duration of response, median (range), <sup>a</sup> mo | NR (1.6+ to 10.5+)    | NR (1.7+ to 10.5+)    |
| Response duration ≥6 mo, <sup>a</sup> n (%)           | 30 (91.1)             | 9 (100)               |
| 6-mo PFS rate, <sup>a</sup> %                         | 81.4                  | 85.2                  |
| 6-mo OS rate, <sup>a</sup> %                          | 87.2                  | 94.8                  |

# **A Phase I Safety and Feasibility Study of Neoadjuvant Chemoradiation plus Pembrolizumab Followed by Consolidation Pembrolizumab in Resectable Stage IIIA Non-Small Cell Lung Cancer**

Lemmon C et al.

ASCO 2020;Abstract 9009.

## Select Ongoing Phase III Studies of Immune Checkpoint Inhibitor Therapy for Locally Advanced NSCLC

| Trial identifier             | N   | Setting   | Treatment arms   |
|------------------------------|-----|---|--|
| PACIFIC-2<br>(NCT03519971)   | 328 | Unresectable, Stage III                                   | <ul style="list-style-type: none"> <li>Durvalumab + platinum-based chemotherapy/RT</li> <li>Placebo + platinum-based chemotherapy/RT</li> </ul>  |
| KEYNOTE-671<br>(NCT03425643) | 786 | Resectable, Stage II, IIIA or IIIB, Neoadjuvant/ adjuvant | <ul style="list-style-type: none"> <li>Platinum-doublet chemotherapy + placebo</li> <li>Platinum-doublet chemotherapy + pembrolizumab</li> </ul> |
| NCT04092283                  | 660 | Unresectable, Stage III                                   | <ul style="list-style-type: none"> <li>Durvalumab + chemotherapy/RT → durvalumab</li> <li>Chemotherapy/RT → durvalumab</li> </ul>                |

# Agenda

## **Module 1: Newly Diagnosed Non-Small Cell Lung Cancer (NSCLC) without Actionable Tumor Mutations**

- Dr Peles: 80-year-old woman with MDS/AML and metastatic NSCLC; PD-L1 95%
- Dr Choksi: 76-year-old man with metastatic NSCLC, single-agent pembrolizumab

## **Module 2: Extensive-Stage Small Cell Lung Cancer (SCLC)**

- Dr Hart: 75-year-old man with extensive-stage SCLC

## **Module 3: Locally Advanced NSCLC**

- Dr Zafar: 63-year-old man, never smoker with Stage IIIB NSCLC; EGFR L858R mutation

## **Module 4: NSCLC with an EGFR Exon 19 Deletion Mutation**

- Dr Lamar: 81-year-old man with NSCLC, pleural effusion and EGFR exon 19 mutation

## **Module 5: Second-Line Therapy After Chemoimmunotherapy**

- Dr Hussein: 76-year-old woman with metastatic NSCLC and MET exon 14, IDH2, PD-L1+

## **Module 6: Metastatic NSCLC with an ALK Rearrangement**

- Dr Dandamudi: 68-year-old woman with NSCLC; pleural effusion; ALK rearrangement

# Case Presentation – Dr Lamar: An 81-year-old man with very symptomatic, large pleural effusion – EGFR exon 19 mutation



Dr Zanetta Lamar

- Presents with large, right pleural effusion, with displacement of the mediastinum
- Thoracentesis: Adenocarcinoma
- TALC pleurodesis, with right pleural biopsy
- Liquid biopsy, NGS: EGFR exon 19 mutation, PD-L1 TPS: 20%; ALK, RET, ROS1 and BRAF wildtype

## Questions

- Would you consider chemotherapy to potentially improve his outcome while waiting for him to receive osimertinib?
- Do you approach treatment differently for patients with EGFR exon 19 versus exon 21 mutations?

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

- a. Chemotherapy
- b. Osimertinib
- c. Chemotherapy followed by osimertinib
- d. Other

# FDA Grants Priority Review to Osimertinib for Adjuvant Treatment of Early-Stage NSCLC with EGFR Mutation

Press Release – October 20, 2020

“The FDA has accepted and granted priority review to the supplemental new drug application (sNDA) for osimertinib for the adjuvant treatment of patients with early-stage *EGFR*-mutated (EGFRm) non-small cell lung cancer (NSCLC) after complete tumor resection with curative intent.

The sNDA was based on data observed in the phase 3 ADAURA trial, which showed osimertinib, a third-generation, irreversible EGFR-TKI, demonstrated a statistically significant and clinically meaningful improvement in disease-free survival (DFS) in the study’s primary analysis population of patients with stage II and IIIA EGFRm NSCLC, as well as in the overall trial population of patients with stage IB-IIIa disease, which is a key secondary end point.

The results from the ADAURA trial were presented during the plenary session of the American Society of Clinical Oncology ASCO20 Virtual Scientific Program in May 2020 and were also recently published in *The New England Journal of Medicine*.”

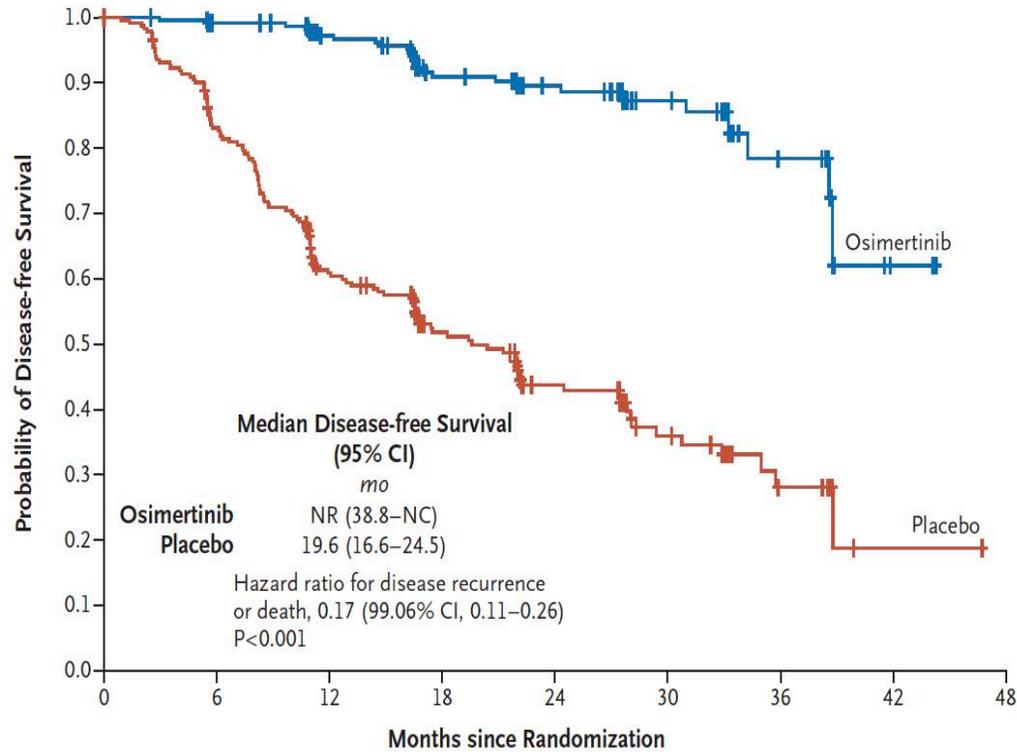
ORIGINAL ARTICLE

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

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

# ADAURA: Disease-Free Survival by Stage

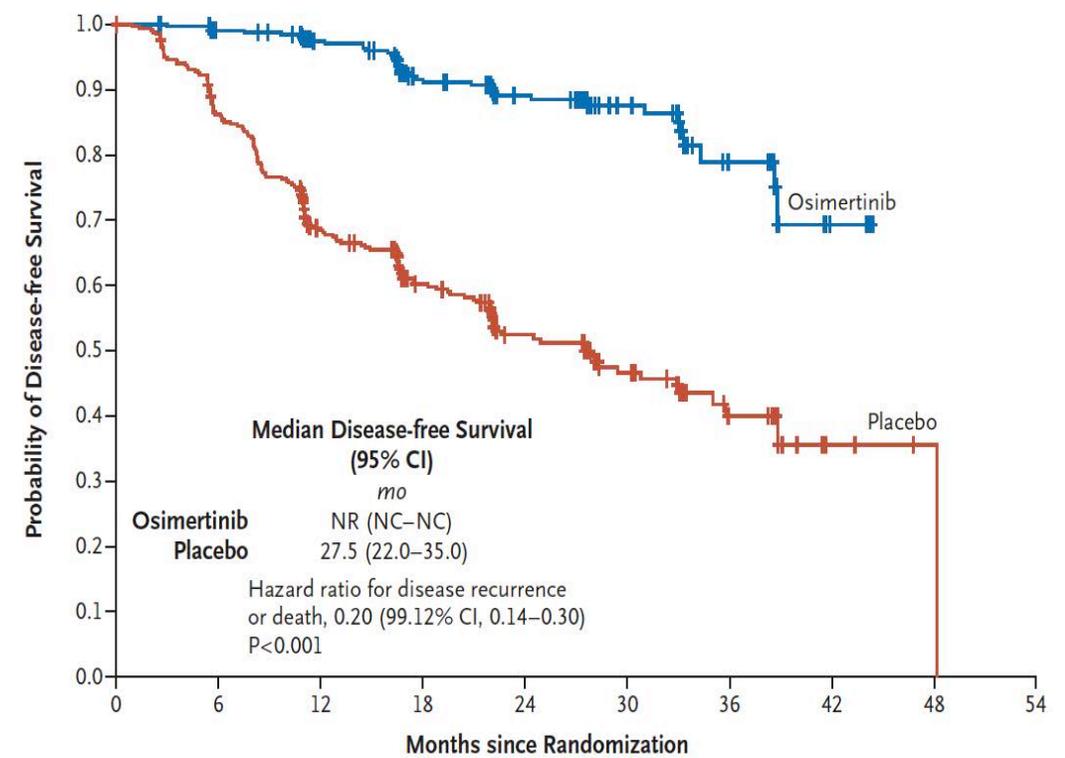
Patients with Stage II to IIIA Disease



No. at Risk

|             |     |     |     |     |    |    |    |   |   |
|-------------|-----|-----|-----|-----|----|----|----|---|---|
| Osimertinib | 233 | 219 | 189 | 137 | 97 | 52 | 18 | 2 | 0 |
| Placebo     | 237 | 190 | 127 | 82  | 51 | 27 | 9  | 1 | 0 |

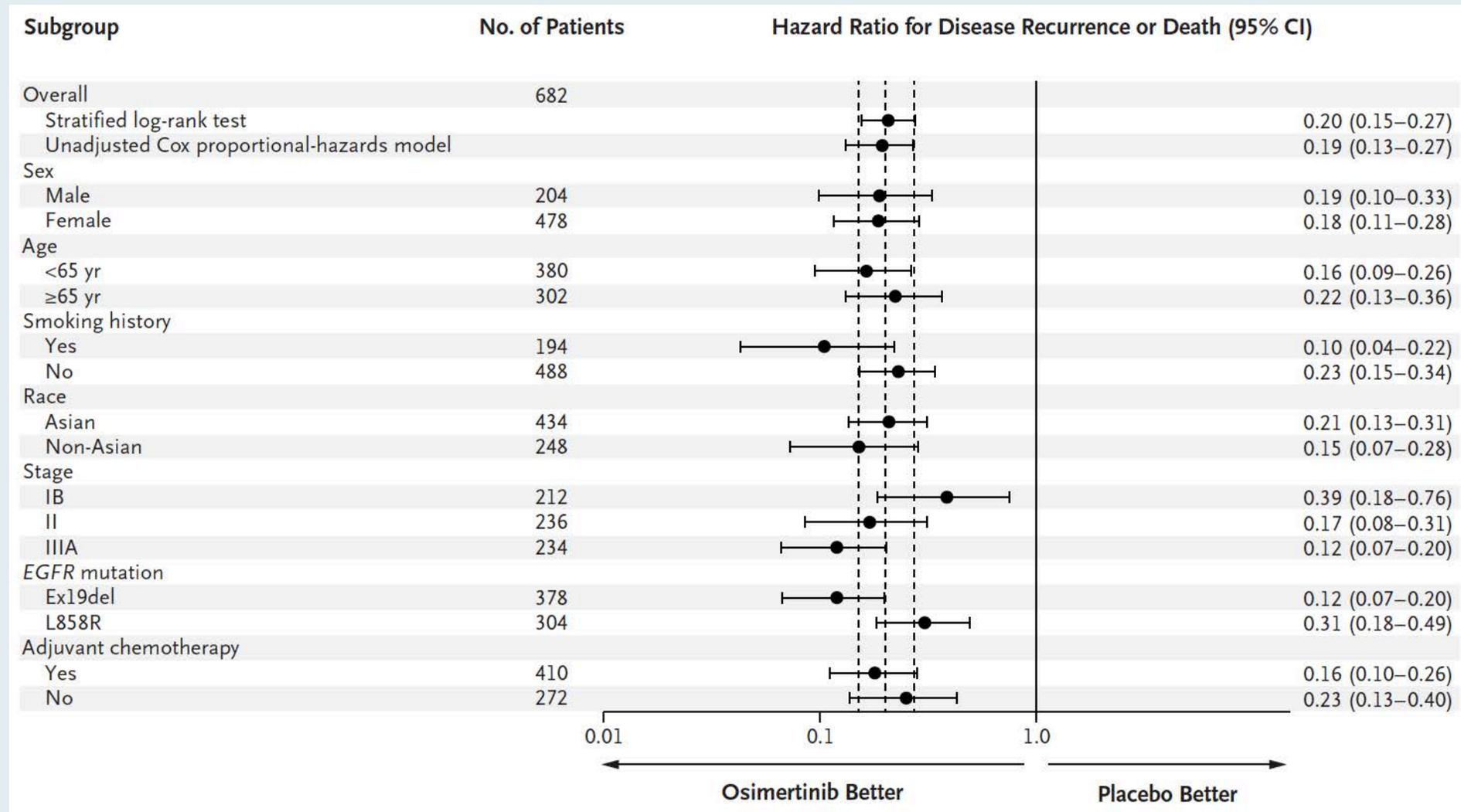
Patients with Stage IB to IIIA Disease



No. at Risk

|             |     |     |     |     |     |    |    |   |   |   |
|-------------|-----|-----|-----|-----|-----|----|----|---|---|---|
| Osimertinib | 339 | 313 | 272 | 208 | 138 | 74 | 27 | 5 | 0 |   |
| Placebo     | 343 | 287 | 207 | 148 | 88  | 53 | 20 | 3 | 1 | 0 |

# ADAURA: Subgroup Analysis of Disease-Free Survival

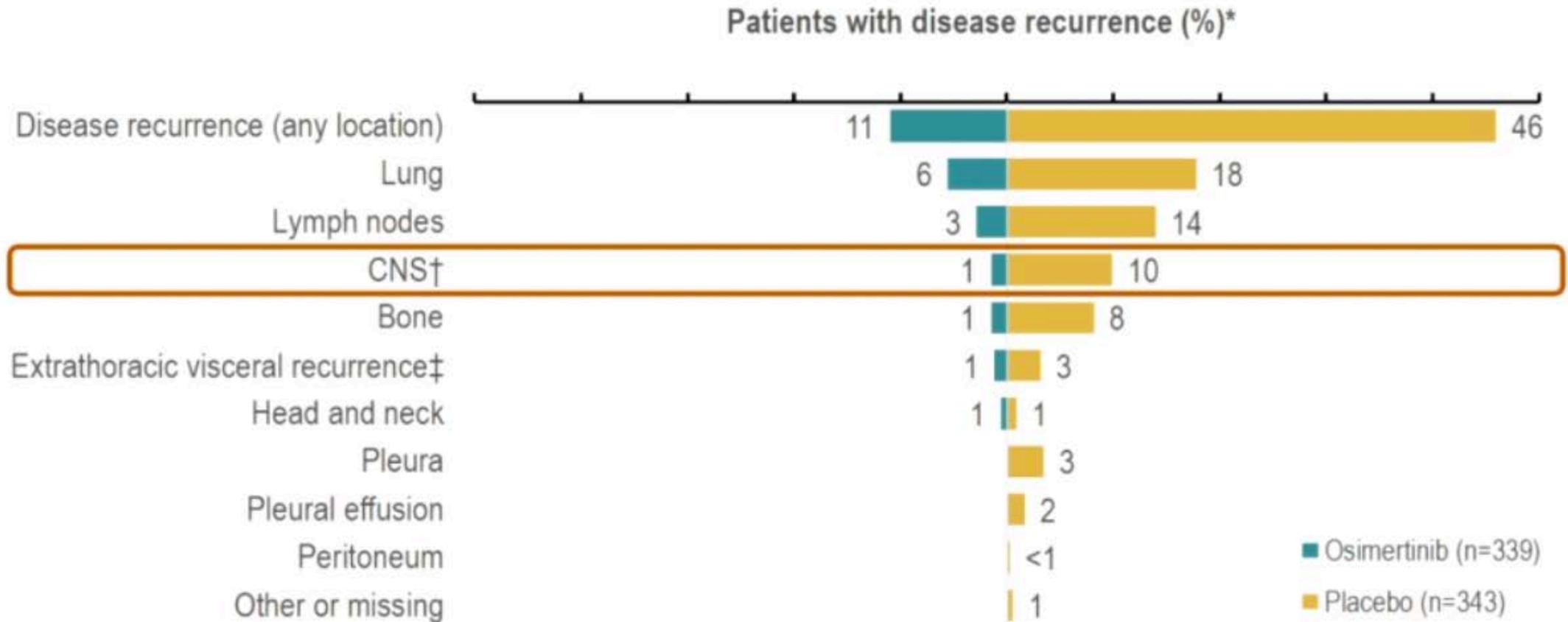


# **Osimertinib Adjuvant Therapy in Patients (pts) with Resected EGFR Mutated (EGFRm) NSCLC (ADAURA): Central Nervous System (CNS) Disease Recurrence**

Tsuboi M et al.

ESMO 2020;Abstract LBA1.

# ADAURA: Sites of Disease Recurrence

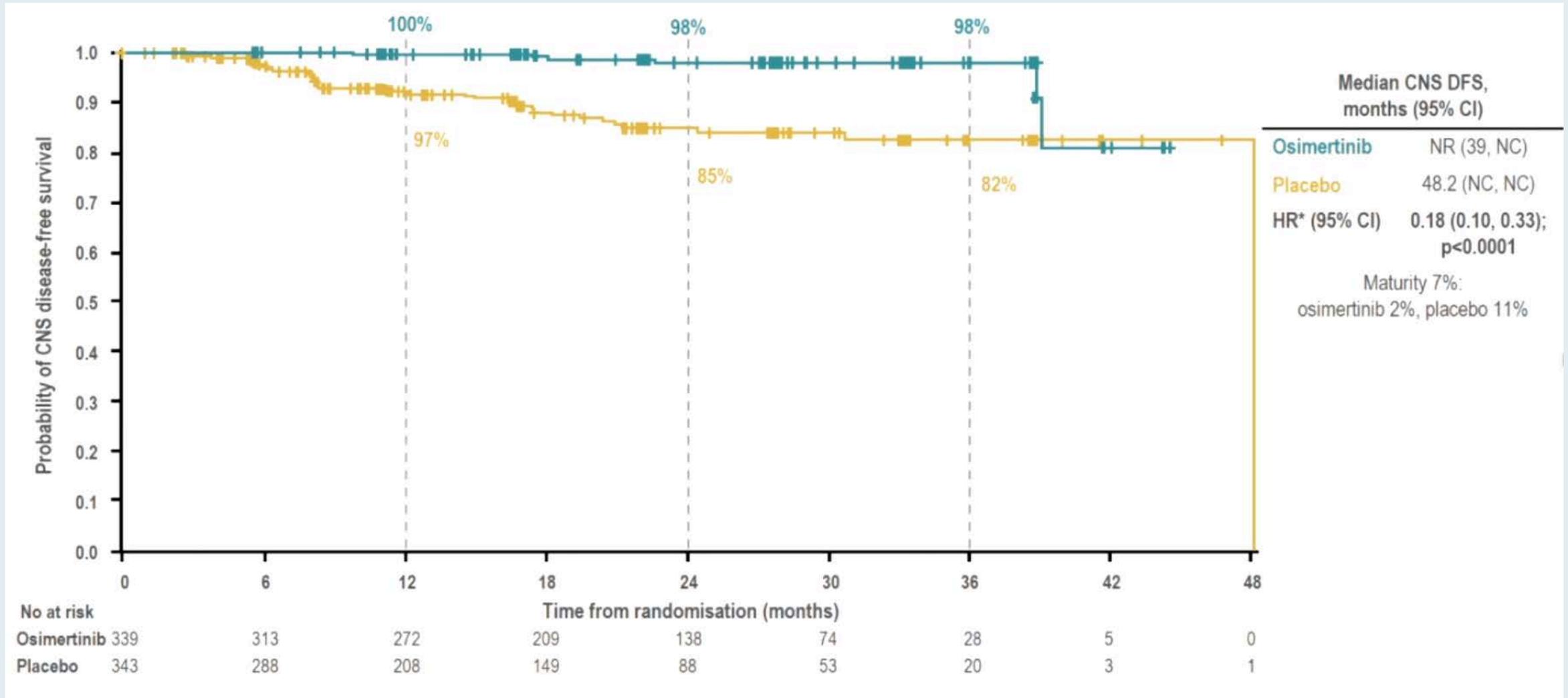


## ADAURA: CNS DFS Events

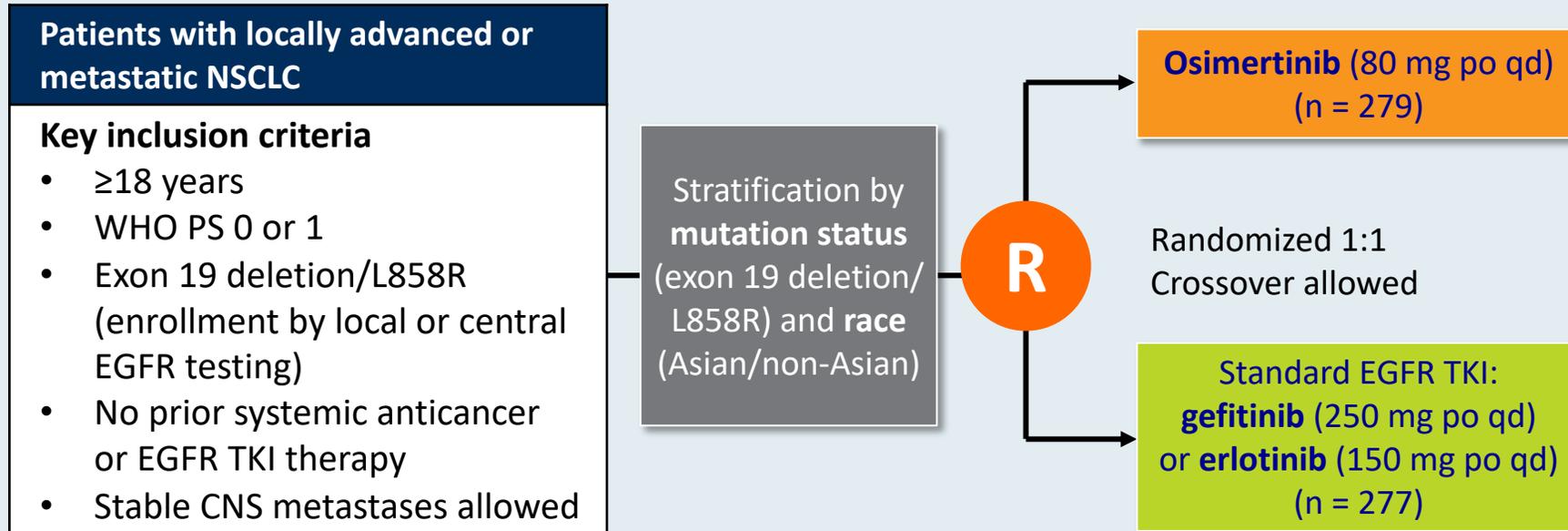
- Overall, 45 patients (osimertinib n=6, placebo n=39) had CNS DFS events

| Patients, n (%) | Overall population    |                  |
|-----------------|-----------------------|------------------|
|                 | Osimeertinib<br>n=339 | Placebo<br>n=343 |
| CNS DFS events: | 6 (2%)                | 39 (11%)         |
| CNS recurrence  | 4 (1%)                | 33 (10%)         |
| Death           | 2 (1%)                | 6 (2%)           |

# 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



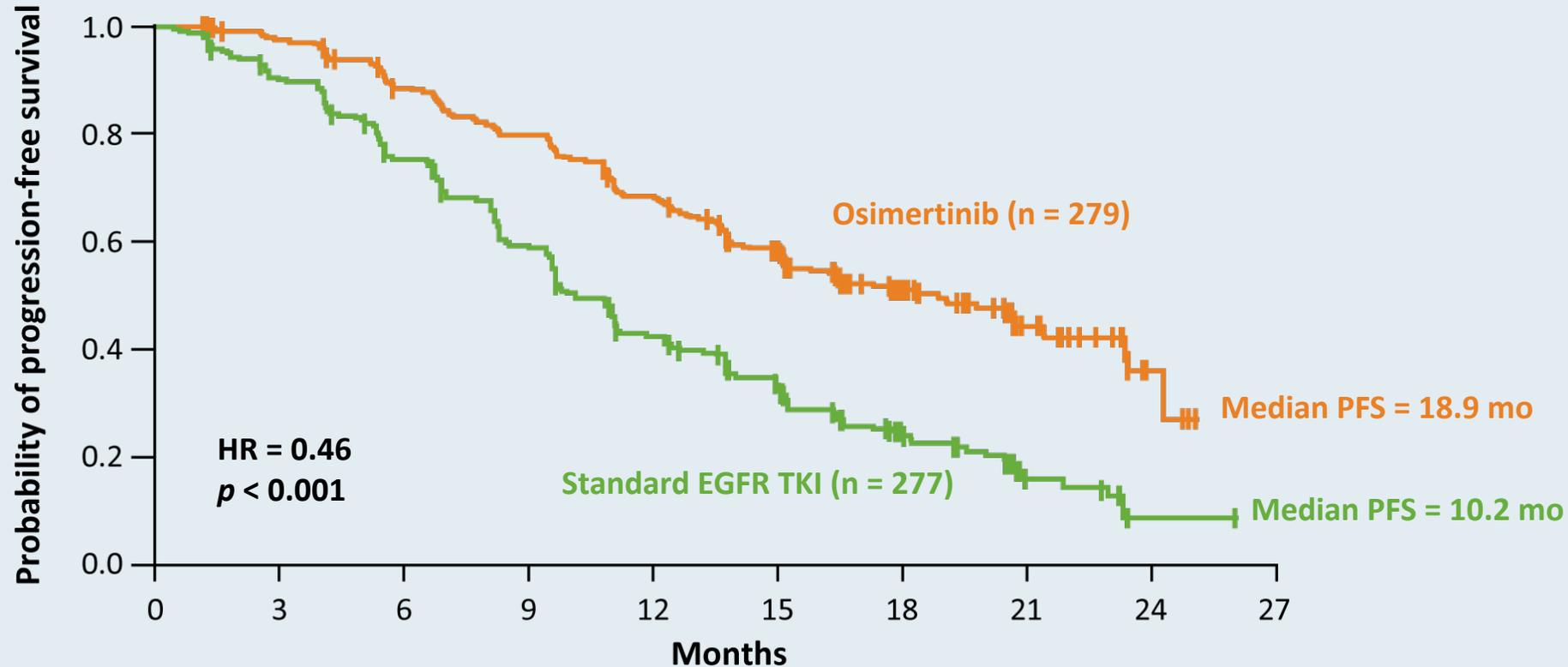
**Primary endpoint:** Progression-free survival (PFS) based on investigator assessment (per RECIST 1.1)

**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)<sup>1</sup>

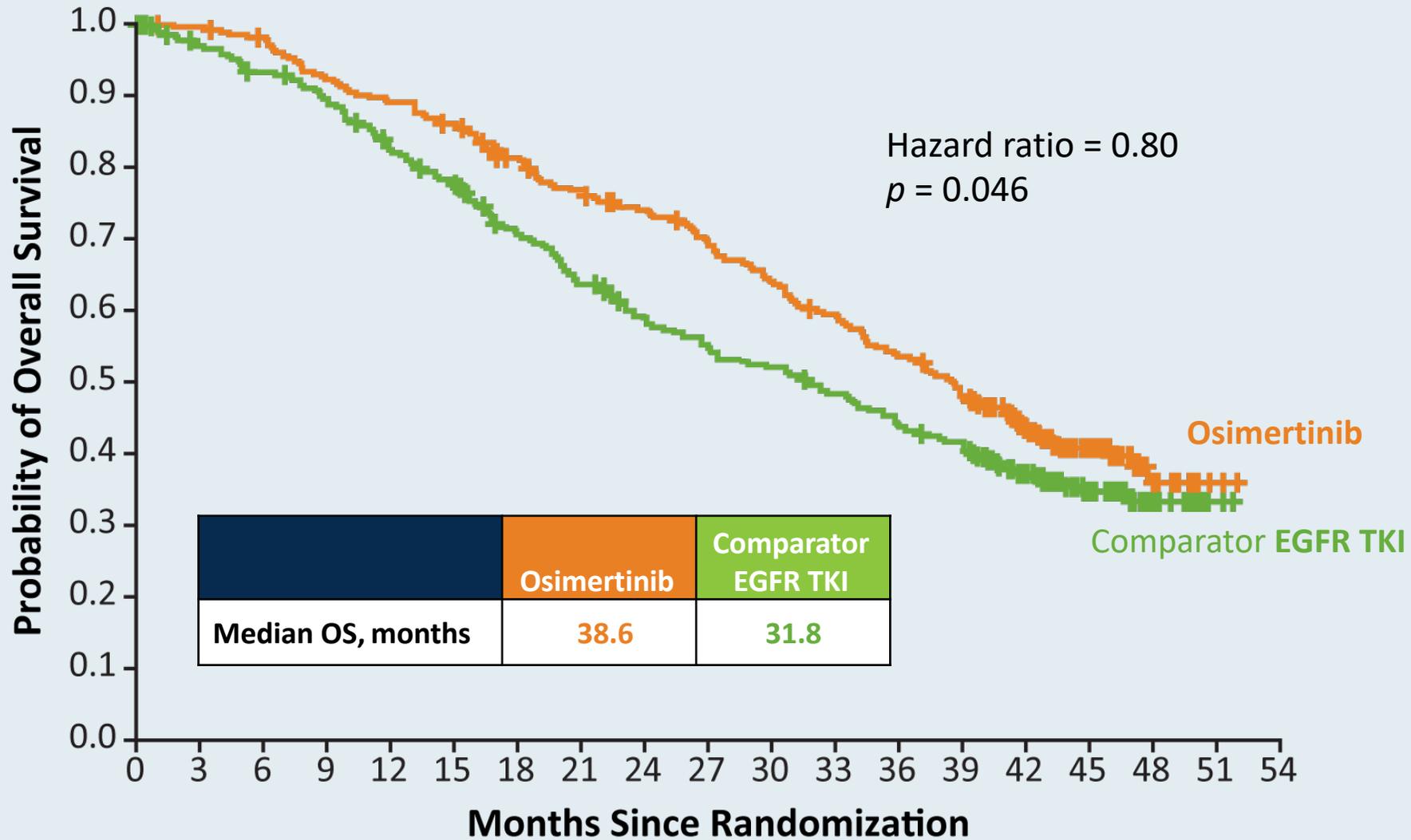


Interim overall survival (data immature), HR = 0.63,  $p = 0.007$ <sup>1,2</sup>

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

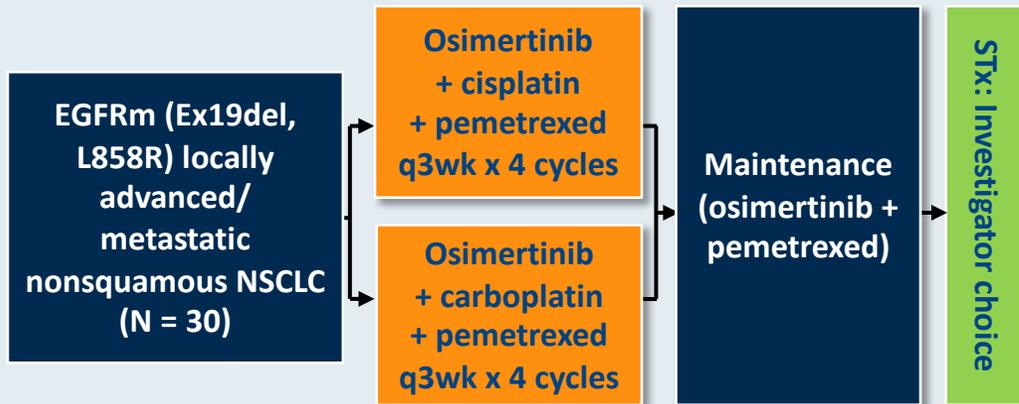
<sup>2</sup> Planchard D et al. *ELCC* 2018;Abstract 1280.

# FLAURA: Final Overall Survival Analysis



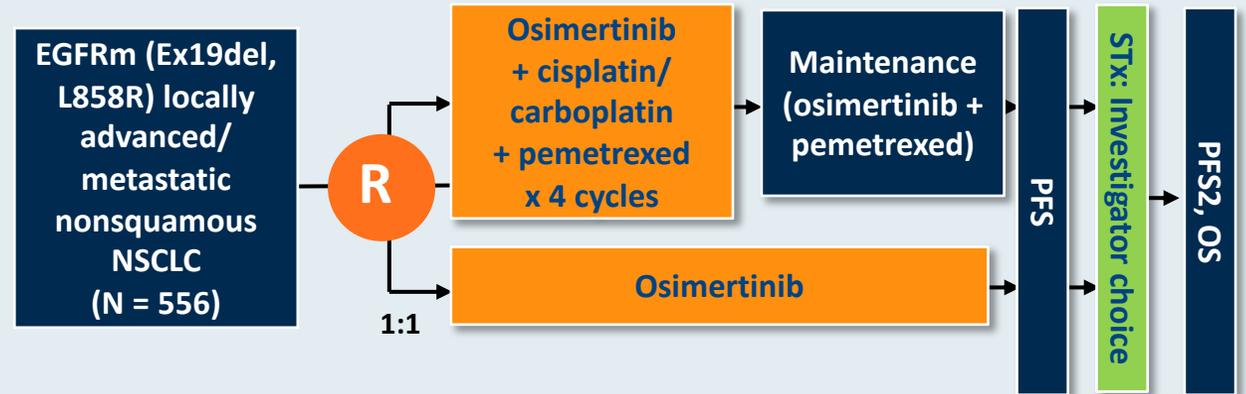
# FLAURA2 Study Design: Safety Run-In and Randomization Phases

## 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

# FDA Approves Ramucirumab plus Erlotinib for First-Line NSCLC

Press Release – May 29, 2020

“The Food and Drug Administration approved ramucirumab in combination with erlotinib for first-line treatment of metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.

Efficacy was evaluated in RELAY (NCT02411448), a multinational, randomized, double-blind, placebo-controlled, multicenter study in patients with previously untreated metastatic NSCLC whose tumors have EGFR exon 19 deletion or exon 21 (L858R) substitution mutations. A total of 449 patients were randomized (1:1) to receive either ramucirumab 10 mg/kg or placebo every 2 weeks as an intravenous infusion, in combination with erlotinib 150 mg orally once daily, until disease progression or unacceptable toxicity.”

*Lancet Oncol 2019; 20: 1655–69*

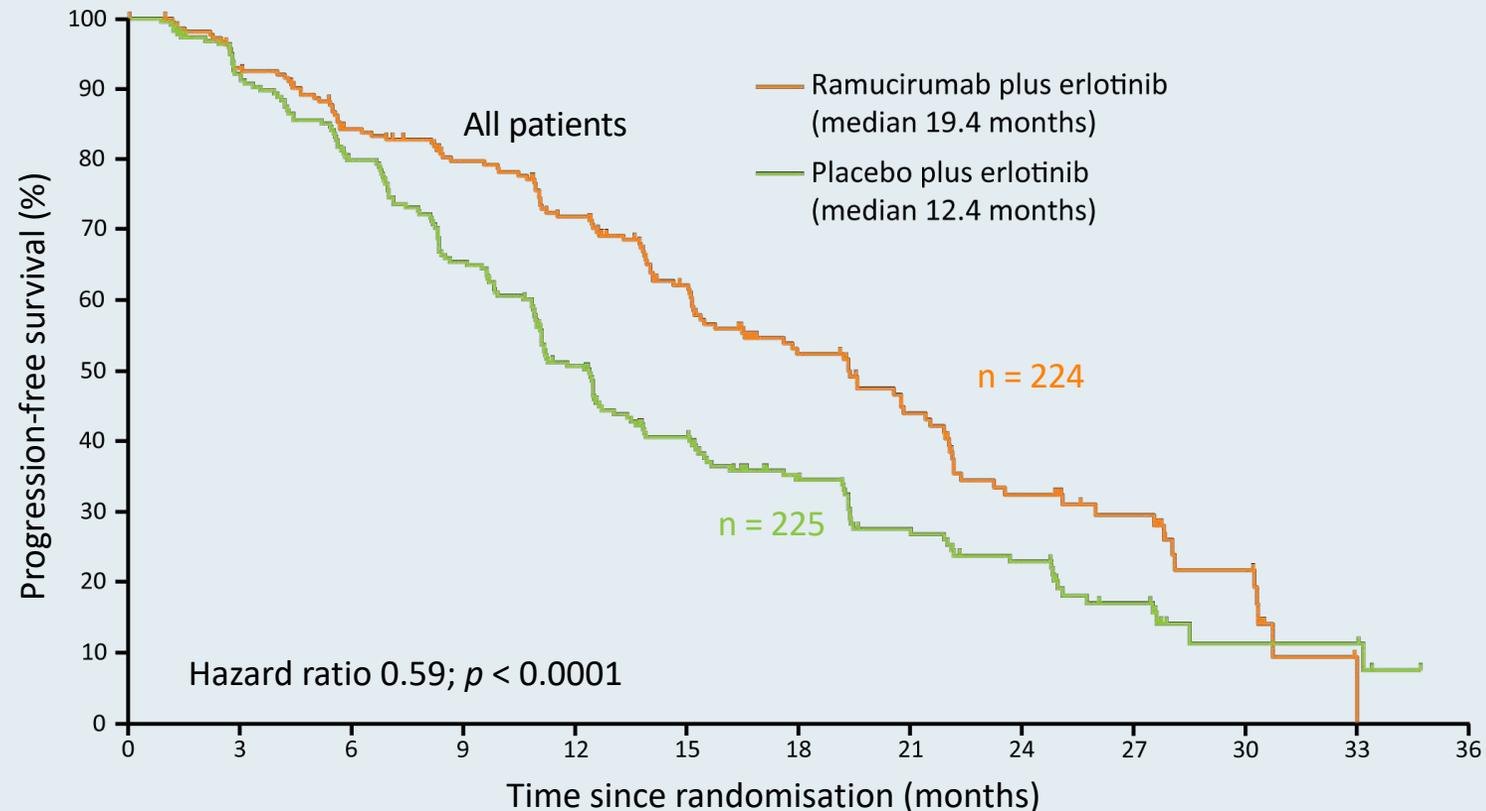
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**Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial**



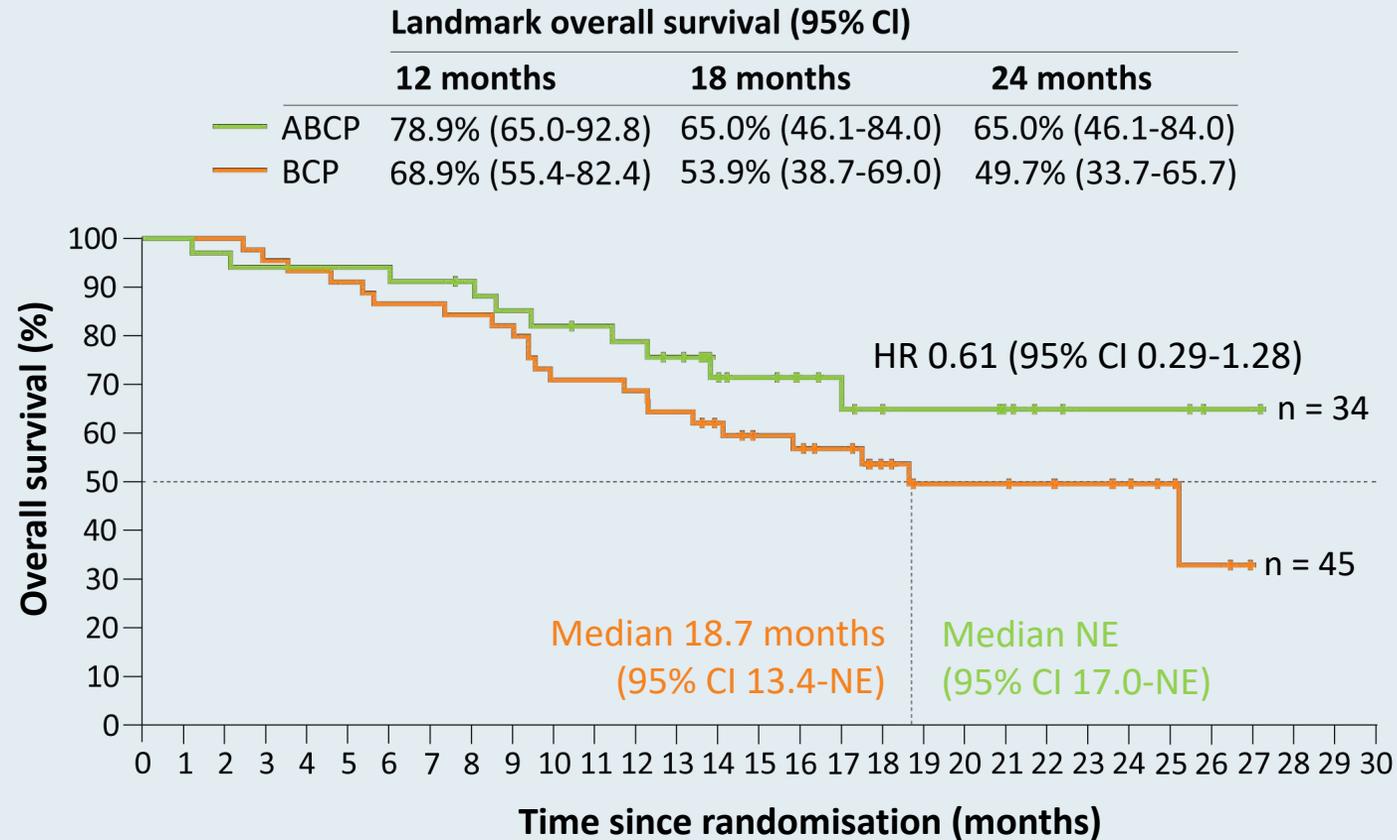
*Kazuhiko Nakagawa, Edward B Garon, Takashi Seto, Makoto Nishio, Santiago Ponce Aix, Luis Paz-Ares, Chao-Hua Chiu, Keunchil Park, Silvia Novello, Ernest Nadal, Fumio Imamura, Kiyotaka Yoh, Jin-Yuan Shih, Kwok Hung Au, Denis Moro-Sibilot, Sotaro Enatsu, Annamaria Zimmermann, Bente Frimodt-Moller, Carla Visseren-Grul, Martin Reck, for the RELAY Study Investigators\**

# RELAY: A Phase III Trial of Ramucirumab with Erlotinib for Untreated Advanced NSCLC with an EGFR Tumor Mutation



- Subgroup analysis of median PFS (ramucirumab/erlotinib vs placebo/erlotinib)
  - Patients with baseline EGFR exon19 deletion mutation: 19.6 mo vs 12.5 mo (HR = 0.65;  $p = 0.0098$ )
  - Patients with baseline EGFR L858R mutation: 19.4 mo vs 11.2 mo (HR = 0.62;  $p = 0.0060$ )

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



Median OS: ABCP versus BCP in patients with sensitizing EGFR mutations:  
NE vs 17.5 mo; HR 0.31

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

# Agenda

## **Module 1: Newly Diagnosed Non-Small Cell Lung Cancer (NSCLC) without Actionable Tumor Mutations**

- Dr Peles: 80-year-old woman with MDS/AML and metastatic NSCLC; PD-L1 95%
- Dr Choksi: 76-year-old man with metastatic NSCLC, single-agent pembrolizumab

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## **Module 4: NSCLC with an EGFR Exon 19 Deletion Mutation**

- Dr Lamar: 81-year-old man with NSCLC, pleural effusion and EGFR exon 19 mutation

## **Module 5: Second-Line Therapy After Chemoimmunotherapy**

- Dr Hussein: 76-year-old woman with metastatic NSCLC and MET exon 14, IDH2, PD-L1+

## **Module 6: Metastatic NSCLC with an ALK Rearrangement**

- Dr Dandamudi: 68-year-old woman with NSCLC; pleural effusion; ALK rearrangement

# Case Presentation – Dr Hussein: A 76-year-old woman with metastatic adenocarcinoma of the lung – MET exon 14 skipping mutation, IDH2 mutation, PD-L1+



**Dr Maen Hussein**

- Stage IV adenocarcinoma of the lung, with bone metastases
- EGFR, ALK, ROS1 wildtype
- PD-L1 low positive, MET exon 14 skipping mutation, IDH2 R140Q mutation
- 6/2019 – 9/2019: LUN 396 trial of durvalumab + SoC chemotherapy
- 10/2019 – 3/2020: LUN 396 maintenance therapy → PD
- 4/2020 – 8/2020: LUN 402 trial of sitravatinib + nivolumab → PD
- 9/2020 – present: APL-101 (C-MET inhibitor)

## Questions

- Would you have used a cMET inhibitor knowing that she has a mutation from the beginning? Or, is that a good sequence – to go with clinical trials and save the cMET inhibitor until later?
- With the MET inhibitors, is it important to know whether there is a mutation versus expression level? For the MET exon 14 skipping mutation, is it important to know what type of mutation? Do we have MET inhibitor that can cover all? Do we have some MET inhibitors that are specific?

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

Press Release — May 6, 2020

“On May 6, 2020, the Food and Drug Administration granted accelerated approval to capmatinib for adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test.

The FDA also approved the FoundationOne CDx assay as a companion diagnostic for capmatinib.

Efficacy was demonstrated in the GEOMETRY mono-1 trial (NCT02414139), a multicenter, non-randomized, open-label, multicohort study enrolling 97 patients with metastatic NSCLC with confirmed MET exon 14 skipping.

The recommended capmatinib dose is 400 mg orally twice daily with or without food.”

ORIGINAL ARTICLE

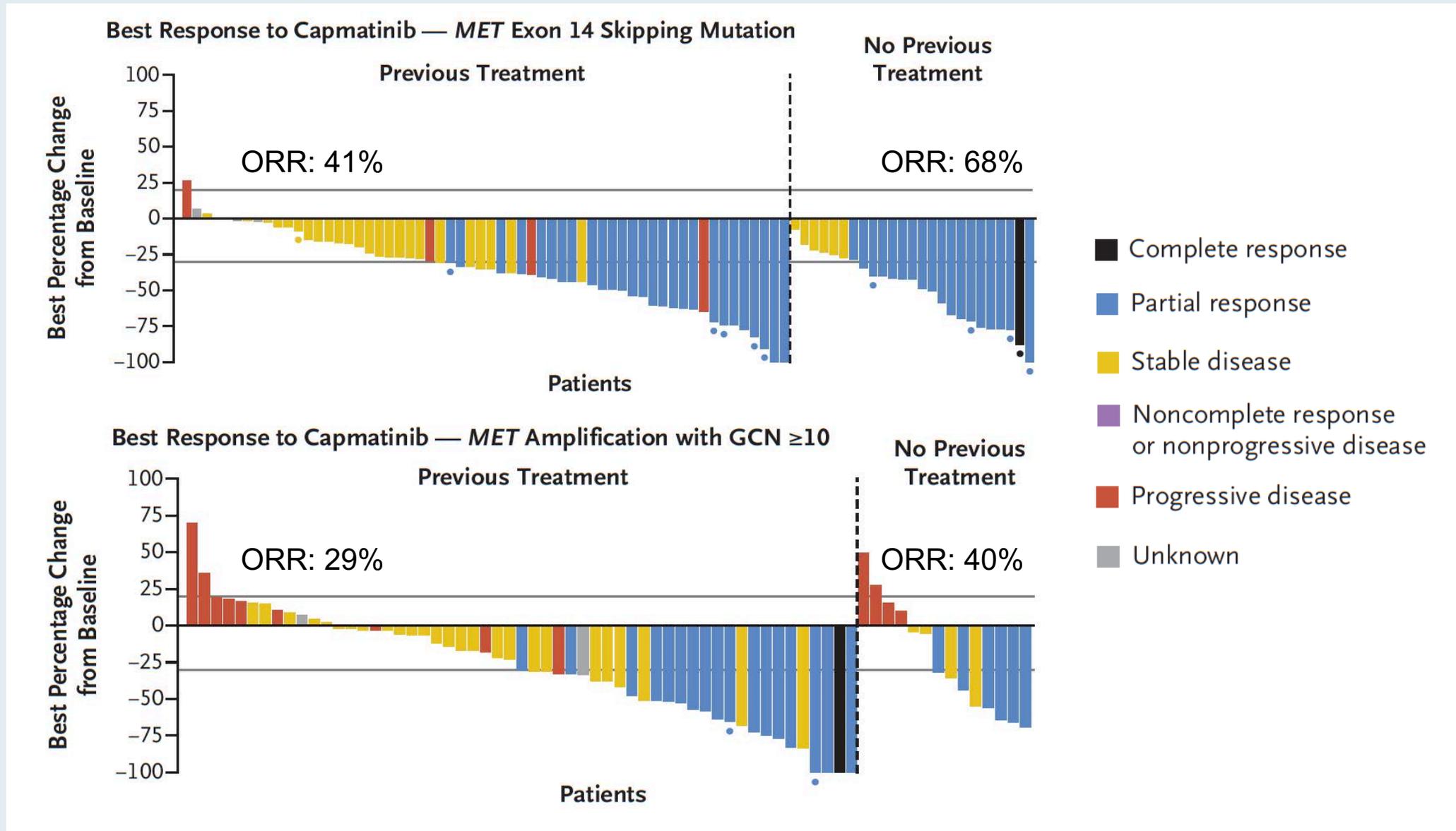
# Capmatinib in *MET* Exon 14–Mutated or *MET*-Amplified Non–Small-Cell Lung Cancer

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

ABSTRACT

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

# Capmatinib: Response Rate and Change from Baseline in Tumor Burden



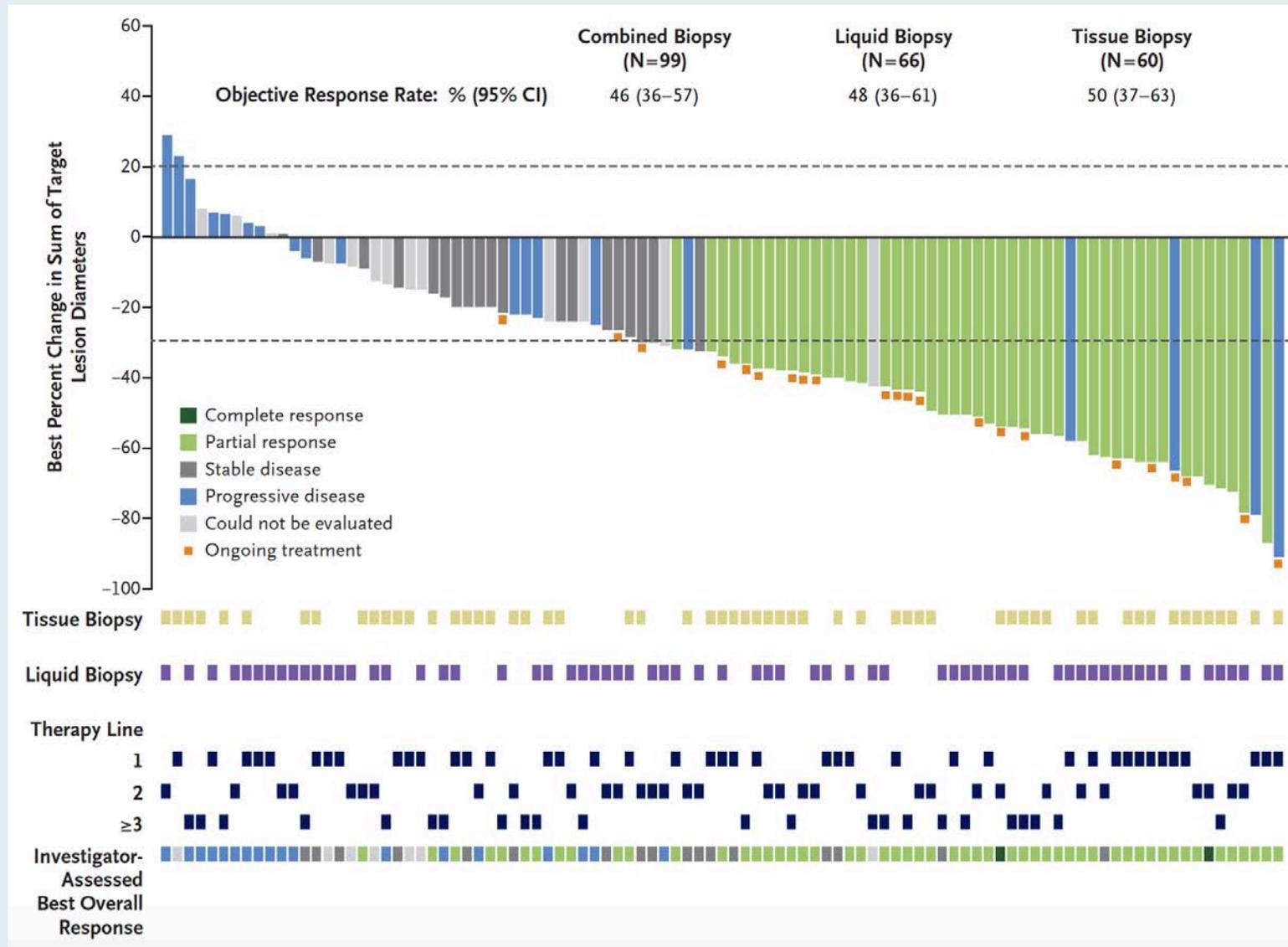
ORIGINAL ARTICLE

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

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

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

# Tepotinib: Response Rate and Change from Baseline in Tumor Burden



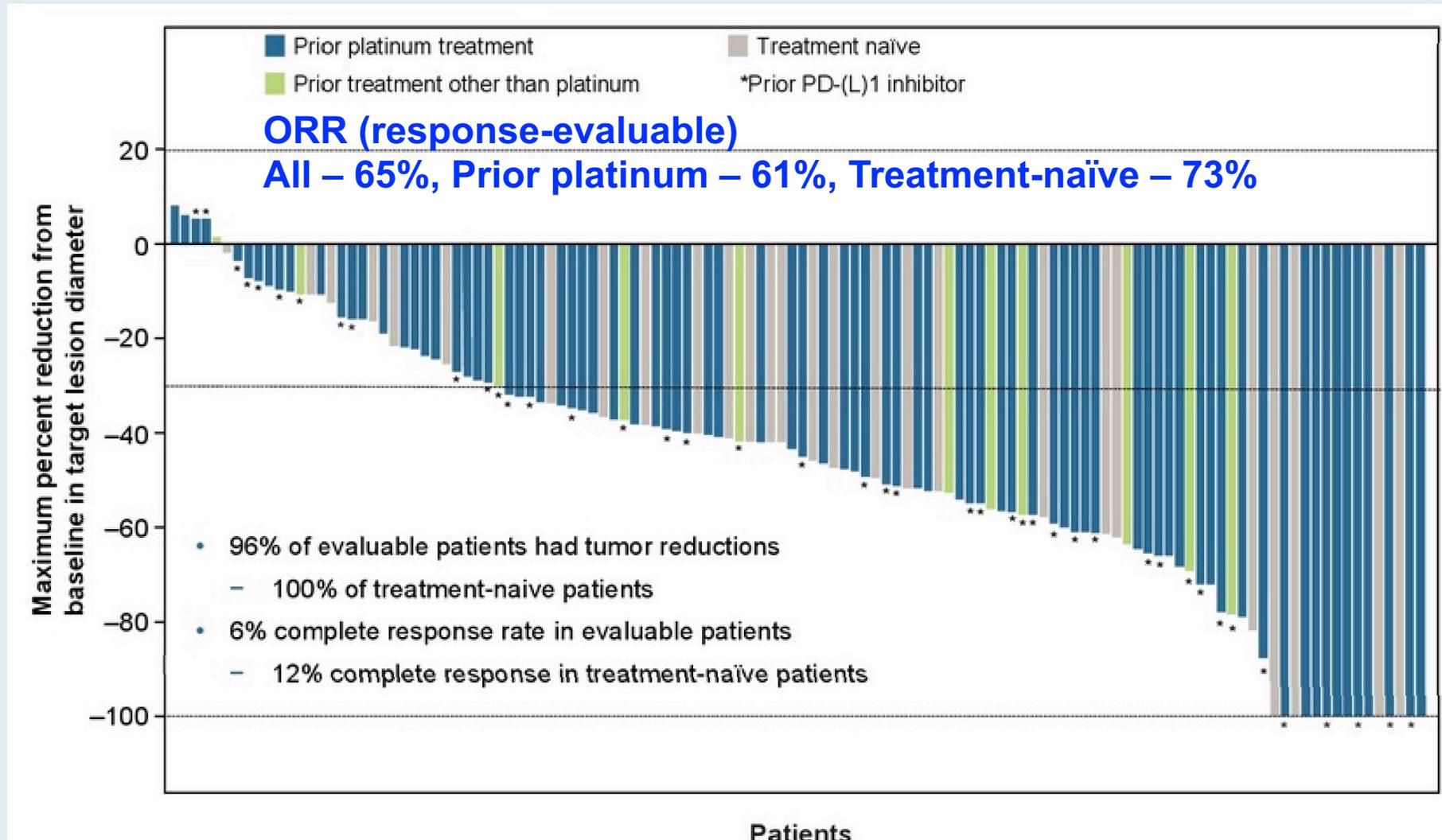
# FDA Grants Approval of Pralsetinib for the Treatment of Metastatic NSCLC with RET Fusion

Press Release – September 7, 2020

“The Food and Drug Administration has approved pralsetinib for the treatment of adults with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test. This indication was approved under the FDA’s Accelerated Approval programme, based on data from the phase I/II ARROW study. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. Pralsetinib is a once-daily, oral precision therapy designed to selectively target RET alterations, including fusions and mutations.

The approval is based on the results from the phase I/II ARROW study, in which pralsetinib produced durable clinical responses in people with RET fusion-positive NSCLC with or without prior therapy, and regardless of RET fusion partner or central nervous system involvement. Pralsetinib demonstrated an overall response rate (ORR) of 57% ... and complete response (CR) rate of 5.7% in the 87 people with NSCLC previously treated with platinum-based chemotherapy. In the 27 people with treatment-naïve NSCLC, the ORR was 70%, with an 11% CR rate.”

# ARROW Primary Endpoint: Response to Pralsetinib



# FDA Approves Selpercatinib for Lung and Thyroid Cancer with RET Gene Mutations or Fusions

Press Release — May 8, 2020

“On May 8, 2020, the Food and Drug Administration granted accelerated approval to selpercatinib for the following indications:

- Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC);
- Adult and pediatric patients  $\geq 12$  years of age with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy;
- Adult and pediatric patients  $\geq 12$  years of age with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

Efficacy was investigated in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001) in patients whose tumors had RET alterations.”

# Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients with HER2-Mutated Metastatic Non-Small Cell Lung Cancer (NSCLC): Interim Results of DESTINY-Lung01

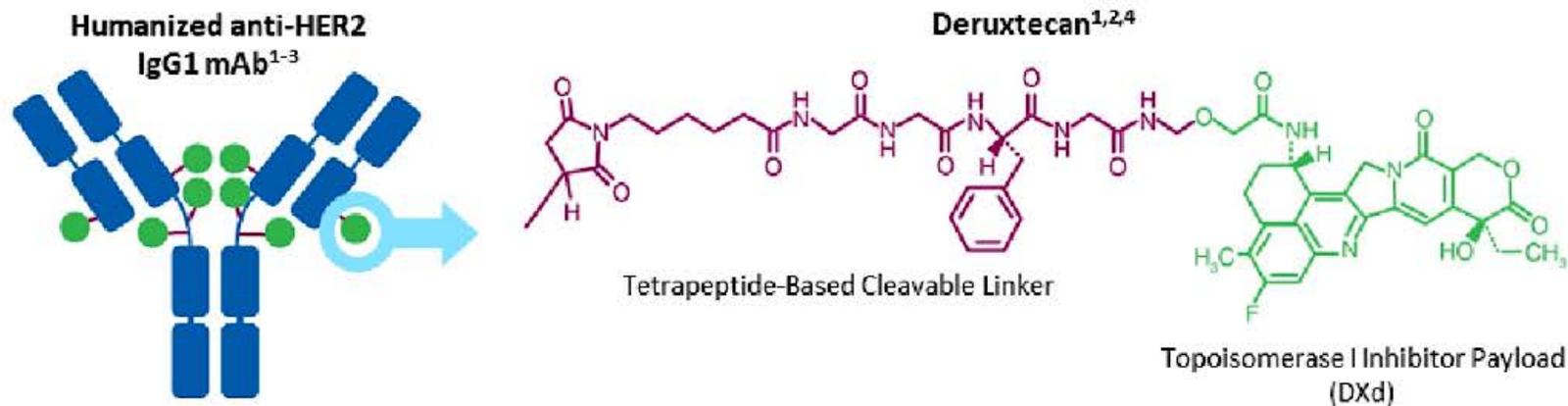
Smit EF et al.

ASCO 2020;Abstract 9504.

# Antibody-Drug Conjugate Trastuzumab Deruxtecan

## T-DXd is an ADC with 3 components:

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



Payload mechanism of action:  
topoisomerase I inhibitor

High potency of payload

High drug to antibody ratio  $\approx 8$

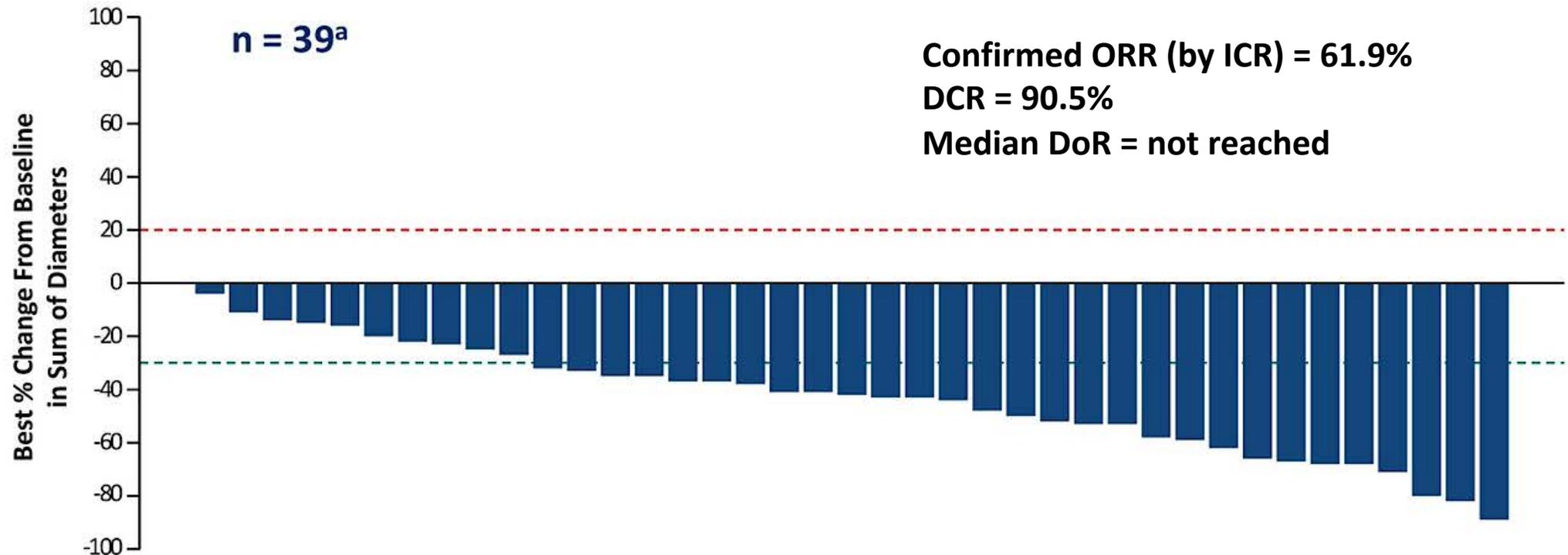
Payload with short systemic half-life

Stable linker-payload

Tumor-selective cleavable linker

Membrane-permeable payload

# DESTINY-Lung01: Efficacy

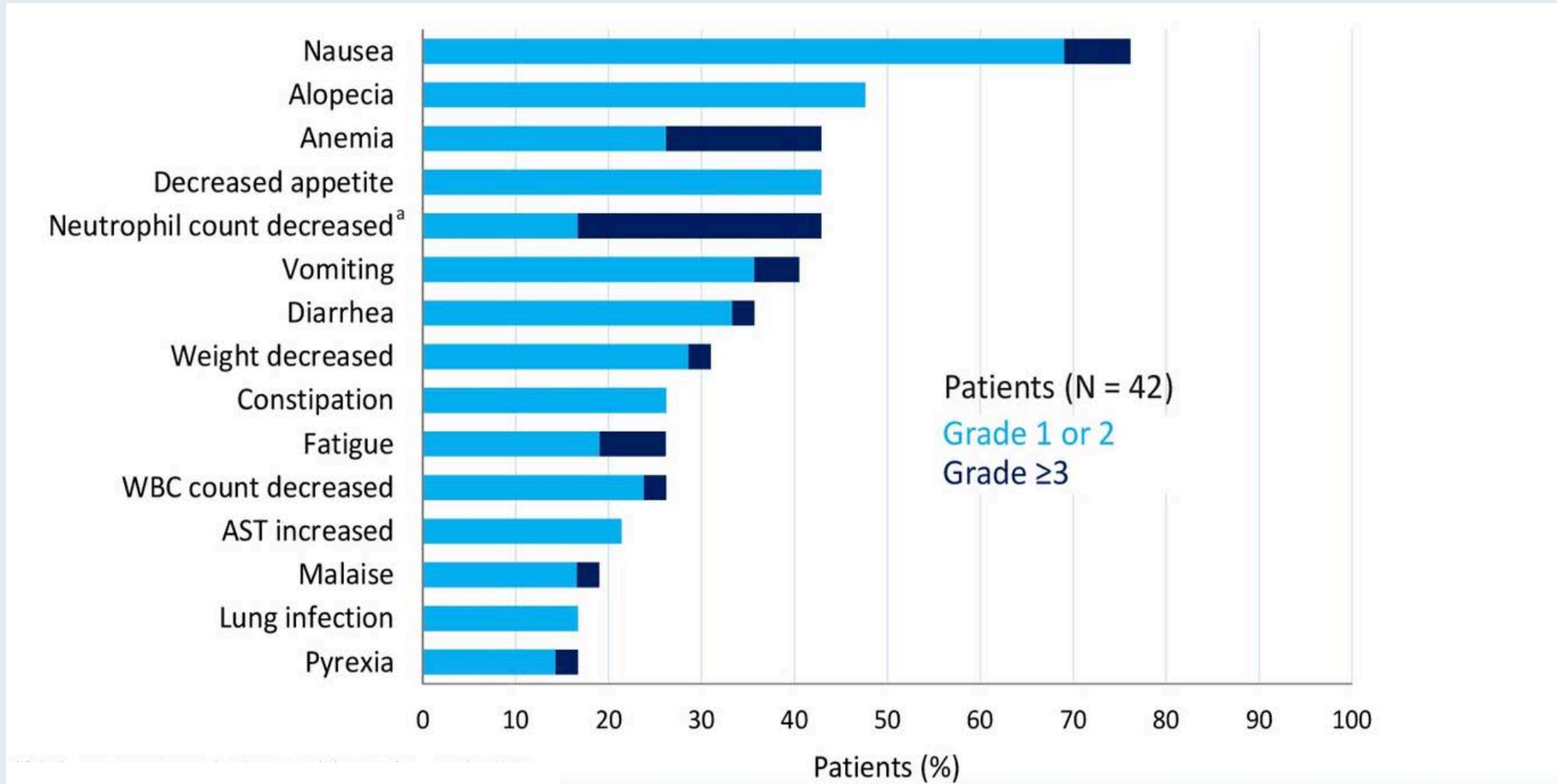


Based on independent central review. Baseline is last measurement taken before enrollment. Shown is best (minimum) percent change from baseline in the sum of diameters for all target lesions.

<sup>a</sup>One patient was missing a baseline assessment and 2 additional patients were missing post-baseline assessments.

- Median PFS = 14.0 months

# DESTINY-Lung01: Treatment-Emergent AEs



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

| All Patients (N = 42)     |                |          |         |         |         |                 |
|---------------------------|----------------|----------|---------|---------|---------|-----------------|
| n (%)                     | Grade 1        | Grade 2  | Grade 3 | Grade 4 | Grade 5 | Any Grade/Total |
| Interstitial lung disease | 0 <sup>a</sup> | 5 (11.9) | 0       | 0       | 0       | 5 (11.9)        |

- Median time to onset of investigator-reported ILD was at 86 days (range, 41-255 days)
- 4 patients had drug withdrawn and 1 had drug interrupted
- All patients received steroid treatment
- 2 patients recovered, 1 recovered with sequelae, 1 was recovering, and 1 had not recovered by data-cutoff
- No grade 5 ILD was observed in this cohort

# Agenda

## **Module 1: Newly Diagnosed Non-Small Cell Lung Cancer (NSCLC) without Actionable Tumor Mutations**

- Dr Peles: 80-year-old woman with MDS/AML and metastatic NSCLC; PD-L1 95%
- Dr Choksi: 76-year-old man with metastatic NSCLC, single-agent pembrolizumab

## **Module 2: Extensive-Stage Small Cell Lung Cancer (SCLC)**

- Dr Hart: 75-year-old man with extensive-stage SCLC

## **Module 3: Locally Advanced NSCLC**

- Dr Zafar: 63-year-old man, never smoker with Stage IIIB NSCLC; EGFR L858R mutation

## **Module 4: NSCLC with an EGFR Exon 19 Deletion Mutation**

- Dr Lamar: 81-year-old man with NSCLC, pleural effusion and EGFR exon 19 mutation

## **Module 5: Second-Line Therapy After Chemoimmunotherapy**

- Dr Hussein: 76-year-old woman with metastatic NSCLC and MET exon 14, IDH2, PD-L1+

## **Module 6: Metastatic NSCLC with an ALK Rearrangement**

- Dr Dandamudi: 68-year-old woman with NSCLC; pleural effusion; ALK rearrangement

# Case Presentation – Dr Dandamudi: A 68-year-old woman with adenocarcinoma of the lung and pleural effusion – ALK rearrangement



Dr Uday Dandamudi

- 8/2016: Presents to ER with large pleural effusion with atelectasis
  - Thoracentesis: 2.4 liters removed, positive for malignant cell
  - Rapid re-accumulation of fluids requiring VATS, pleural biopsy and pleurodesis: Positive for adenocarcinoma
- MRI: Negative for metastatic disease
- 9/2016: Crizotinib discontinued due to elevated LFTs (10 x ULN)
- 1/2017: Alectinib, intolerant with nonspecific symptoms dose reduced to 300 mg BID 10/2017
- 8/2020 surveillance scans: PD
  - Testing: ALK rearrangement, I1171N mutation
  - Switched to lorlatinib, but patient expresses concern about cognitive impairment listed in the PI

## Question

- In light of the patient's expressed concern about possible cognitive impairment with lorlatinib, what would you do – switch to brigatinib?

*Ann Oncol* 2020 May 11; Epub ahead of print



**ORIGINAL ARTICLE**

**Updated overall survival and final progression-free survival data for patients with treatment-naive advanced *ALK*-positive non-small-cell lung cancer in the ALEX study**

T. Mok<sup>1</sup>, D. R. Camidge<sup>2</sup>, S. M. Gadgeel<sup>3</sup>, R. Rosell<sup>4</sup>, R. Dziadziuszko<sup>5</sup>, D.-W. Kim<sup>6</sup>, M. Pérol<sup>7</sup>, S.-H. I. Ou<sup>8</sup>, J. S. Ahn<sup>9</sup>, A. T. Shaw<sup>10†</sup>, W. Bordogna<sup>11</sup>, V. Smoljanović<sup>11</sup>, M. Hilton<sup>11</sup>, T. Ruf<sup>11</sup>, J. Noé<sup>11</sup> & S. Peters<sup>12\*</sup>

# FDA Approves Brigatinib for ALK-Positive Metastatic NSCLC

Press Release – May 22, 2020

“The Food and Drug Administration approved brigatinib for adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.

Today, the FDA also approved the Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular, Inc.) as a companion diagnostic for brigatinib.

Efficacy was investigated in ALTA 1L (NCT02737501), a randomized (1:1), open-label, multicenter trial in adult patients with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy. The trial required patients to have an ALK rearrangement based on a local standard of care testing. The trial randomized 275 patients to receive brigatinib 180 mg orally once daily with a 7-day lead-in at 90 mg once daily (n=137) or crizotinib 250 mg orally twice daily (n=138). A subset of the clinical samples was retrospectively tested with the Vysis ALK Break Apart FISH Probe Kit. Of the enrolled patients, 239 had positive results using the Vysis diagnostic test (central results were negative for 20 patients and unavailable for 16 patients).”

# Brigatinib Versus Crizotinib in Advanced ALK Inhibitor–Naive ALK-Positive Non–Small Cell Lung Cancer: Second Interim Analysis of the Phase III ALTA-1L Trial



D. Ross Camidge, MD, PhD<sup>1</sup>; Hye Ryun Kim, MD, PhD<sup>2</sup>; Myung-Ju Ahn, MD, PhD<sup>3</sup>; James C. H. Yang, MD, PhD<sup>4</sup>; Ji-Youn Han, MD, PhD<sup>5</sup>; Maximilian J. Hochmair, MD<sup>6</sup>; Ki Hyeong Lee, MD, PhD<sup>7</sup>; Angelo Delmonte, MD, PhD<sup>8</sup>; Maria Rosario García Campelo, MD<sup>9</sup>; Dong-Wan Kim, MD<sup>10</sup>; Frank Griesinger, MD<sup>11</sup>; Enriqueta Felip, MD, PhD<sup>12</sup>; Raffaele Califano, MD<sup>13</sup>; Alexander Spira, MD<sup>14</sup>; Scott N. Gettinger, MD<sup>15</sup>; Marcello Tiseo, MD<sup>16</sup>; Huamao M. Lin, PhD<sup>17</sup>; Neeraj Gupta, PhD, FCP<sup>17</sup>; Michael J. Hanley, PharmD, PhD<sup>17</sup>; Quanhong Ni, MS<sup>17</sup>; Pingkuan Zhang, MD<sup>17</sup>; and Sanjay Popat, BSc, PhD, FRCP<sup>18,19</sup>

*J Clin Oncol* 2020;[Epub ahead of print]

# Lorlatinib vs Crizotinib in the First-Line Treatment of Patients (pts) with Advanced ALK-Positive Non-Small Cell Lung Cancer (NSCLC): Results of the Phase 3 CROWN Study

Solomon B et al.

ESMO 2020;Abstract LBA2. Presidential Symposium

# Phase III Randomized Study of Ensartinib vs Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive NSCLC Patients: eXalt3

Horn L et al.

WCLC 2020;Abstract 2. Presidential Symposium

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

# **Current Concepts and Recent Advances in Oncology**

## ***A Daylong Clinical Summit Hosted in Partnership with Florida Cancer Specialists***

**Saturday, October 24, 2020  
8:30 AM – 4:30 PM ET**

### **Faculty**

**Arjun Balar, MD  
Johanna Bendell, MD  
Axel Grothey, MD  
Brad S Kahl, MD  
Shaji K Kumar, MD**

**Kathleen Moore, MD  
Loretta Nastoupil, MD  
William K Oh, MD  
David M O'Malley, MD  
Robert Z Orlowski, MD, PhD**

**Gregory J Riely, MD, PhD  
Hope S Rugo, MD  
David R Spigel, MD  
Sara M Tolaney, MD, MPH**

### **Moderator**

**Neil Love, MD**

# Agenda

**Module 1 — Lung Cancer:** *Drs Riely and Spigel*

**Module 2 — Multiple Myeloma:** *Drs Kumar and Orłowski*

**Module 3 — Chronic Lymphocytic Leukemia and Lymphomas:**  
*Drs Kahl and Nastoupil*

**Module 4 — Gastrointestinal Cancers:** *Drs Bendell and Grothey*

**Module 5 — Genitourinary Cancers:** *Drs Balar and Oh*

**Module 6 — Gynecologic Cancers:** *Drs Moore and O'Malley*

**Module 7 — Breast Cancer:** *Drs Rugo and Tolaney*

# Multiple Myeloma Faculty



**Shaji K Kumar, MD**  
Mark and Judy Mullins Professor of  
Hematological Malignancies  
Consultant, Division of Hematology  
Professor of Medicine  
Mayo Clinic  
Rochester, Minnesota



**Robert Z Orlowski, MD, PhD**  
Florence Maude Thomas Cancer  
Research Professor  
Department of Lymphoma and Myeloma  
Professor, Department of  
Experimental Therapeutics  
Director, Myeloma Section  
Division of Cancer Medicine  
The University of Texas  
MD Anderson Cancer Center  
Houston, Texas

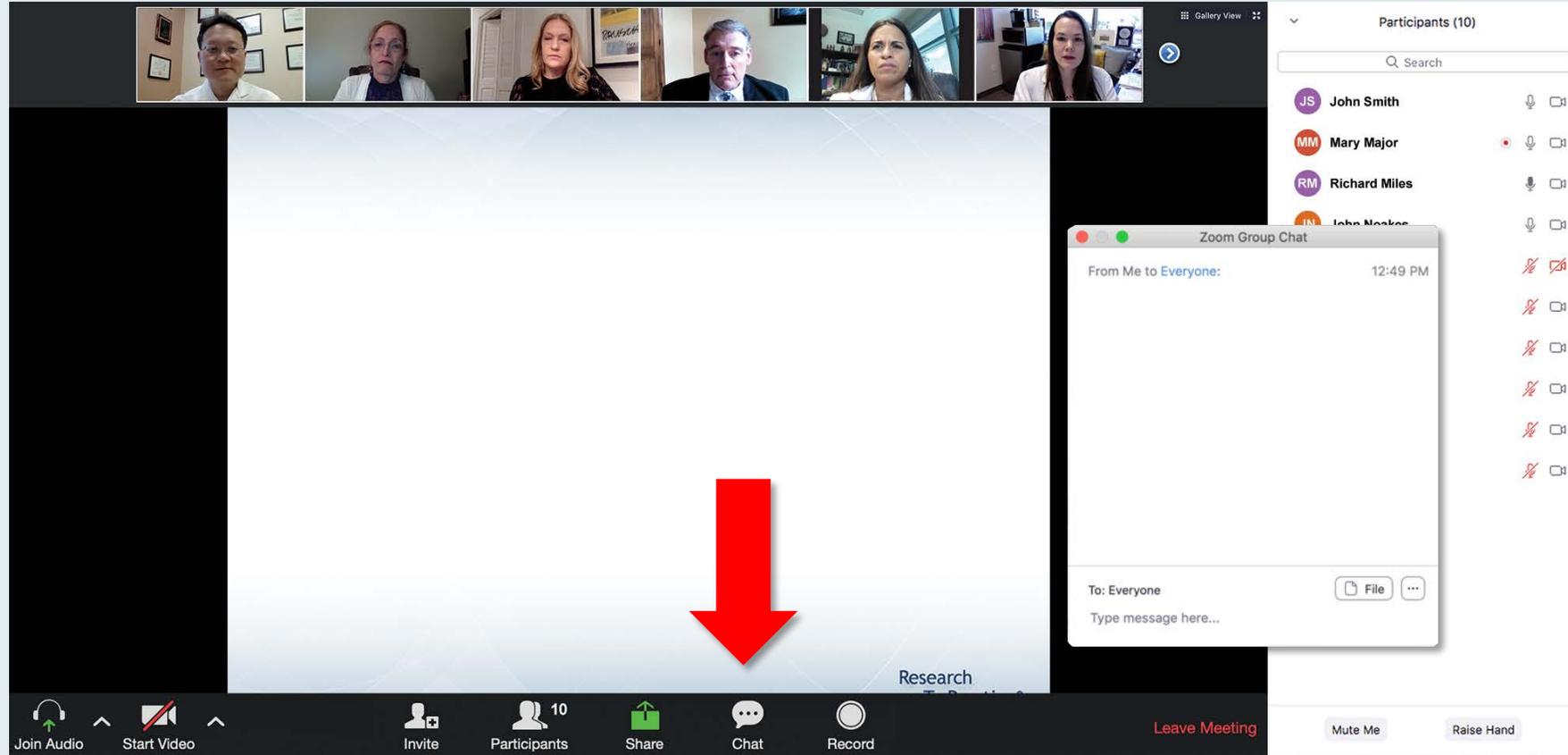
## Dr Kumar — Disclosures

|                              |   |
|------------------------------|---|
| <b>Advisory Committee</b>    | AbbVie Inc, Celgene Corporation, Genentech, a member of the Roche Group, Janssen Biotech Inc, Takeda Oncology   |
| <b>Consulting Agreements</b> | AbbVie Inc, Amgen Inc, Celgene Corporation, CellerBio Inc, GeneCentrix Inc, Genentech, a member of the Roche Group, Janssen Biotech Inc, Molecular Partners, Oncocept, Takeda Oncology  |
| <b>Contracted Research</b>   | AbbVie Inc, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, CARsgen Therapeutics, Celgene Corporation, Genentech, a member of the Roche Group, Janssen Biotech Inc, Kite, A Gilead Company, Merck, Novartis, Takeda Oncology, TeneoBio |

## Dr Orlowski — Disclosures

|                             |   |
|-----------------------------|---|
| <b>Advisory Committee</b>   | Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, EcoR1 Capital LLC, FORMA Therapeutics, Genzyme Corporation, GlaxoSmithKline, Ionis Pharmaceuticals Inc, Janssen Biotech Inc, Juno Therapeutics, a Celgene Company, Kite, A Gilead Company, Legend Biotech, Molecular Partners, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Servier, Takeda Pharmaceuticals North America Inc |
| <b>Consulting Agreement</b> | STATinMED   |
| <b>Contracted Research</b>  | BioTheryX Inc, CARsgen Therapeutics, Celgene Corporation, Exelixis Inc, Janssen Biotech Inc, Sanofi Genzyme, Takeda Pharmaceuticals North America Inc   |
| <b>Ownership Interest</b>   | Asyilia Therapeutics Inc (founder, patents, equity)   |

# We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

# FCS Contributing Oncologists



**Mamta Choksi, MD**  
New Port Richey, Florida



**Zanetta S Lamar, MD**  
Naples, Florida



**Uday Dandamudi, MD**  
New Port Richey, Florida



**Vikas Malhotra, MD**  
Spring Hill, Florida



**Lowell L Hart, MD**  
Fort Myers, Florida



**Shachar Peles, MD**  
Lake Worth, Florida



**Maen Hussein, MD**  
Tavares, Florida



**Syed F Zafar, MD**  
Fort Myers, Florida

# Multiple Myeloma

## Management of Newly Diagnosed Multiple Myeloma

- Dr Zafar: A 53-year-old man with high-risk lambda light chain disease

## Relapsed/Refractory Multiple Myeloma

- Dr Lamar: A 68-year-old woman with relapsed multiple myeloma
- Dr Hart: A 70-year-old man with relapsed multiple myeloma

## Novel Treatment Approaches for Multiple Myeloma

- Dr Zafar: A 67-year-old man with high-risk IgA multiple myeloma
- Dr Peles: A 75-year-old woman with high-risk smoldering myeloma

# Multiple Myeloma

## Management of Newly Diagnosed Multiple Myeloma

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## Novel Treatment Approaches for Multiple Myeloma

- Dr Zafar: A 67-year-old man with high-risk IgA multiple myeloma
- Dr Peles: A 75-year-old woman with high-risk smoldering myeloma

# Case Presentation – Dr Zafar: A 53-year-old man with high-risk lambda light chain disease



Dr Syed Zafar

- 7/2020: Acute renal failure, creatinine 6.98, nephrotic range proteinuria > 6 gm
  - Diagnosis: Light chain nephropathy, lambda restricted
- Bone marrow biopsy: 80% clonal plasma cells
- FISH: t(4;14), gain of 1q, del13, IgH gene rearrangement
- Labs: Hg 8.7, serum lambda 23,000 mg/L
- Urgently initiated cyclophosphamide/bortezomib/dexamethasone (CyBorD)
  - Post-Cycle 1 – Creatinine 2.6

## Question

- What are your thoughts about adding daratumumab to CyBorD?

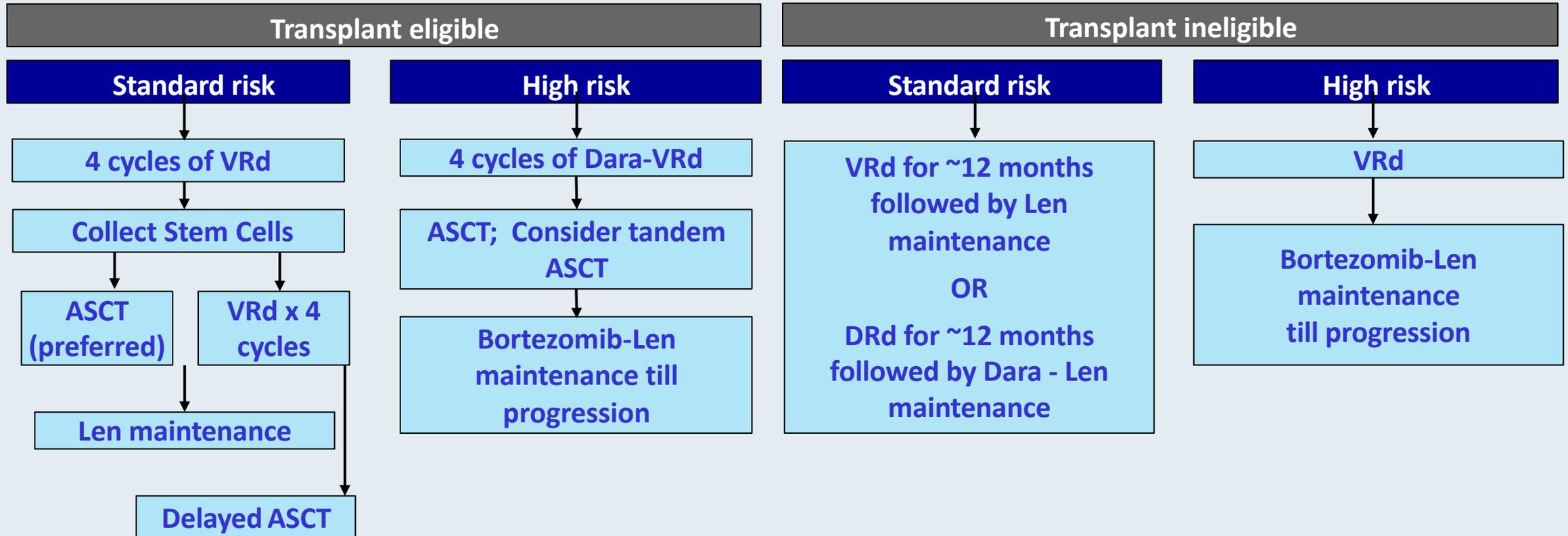
## Currently, what is your usual pretransplant induction regimen for a 65-year-old patient with MM and no high-risk features?

- a. RVD
- b. KRd
- c. MPV/daratumumab
- d. Rd/daratumumab
- e. VTd/daratumumab
- f. RVD/daratumumab
- g. KRd/daratumumab
- h. Other

# Regulatory and reimbursement issues aside, what is your preferred induction regimen for an 85-year-old patient with del(17p) MM?

- a. Rd
- b. RVD
- c. RVD lite
- d. KRd
- e. MPV/daratumumab
- f. Rd/daratumumab
- g. VTd/daratumumab
- h. Other

# Approach to Newly Diagnosed MM



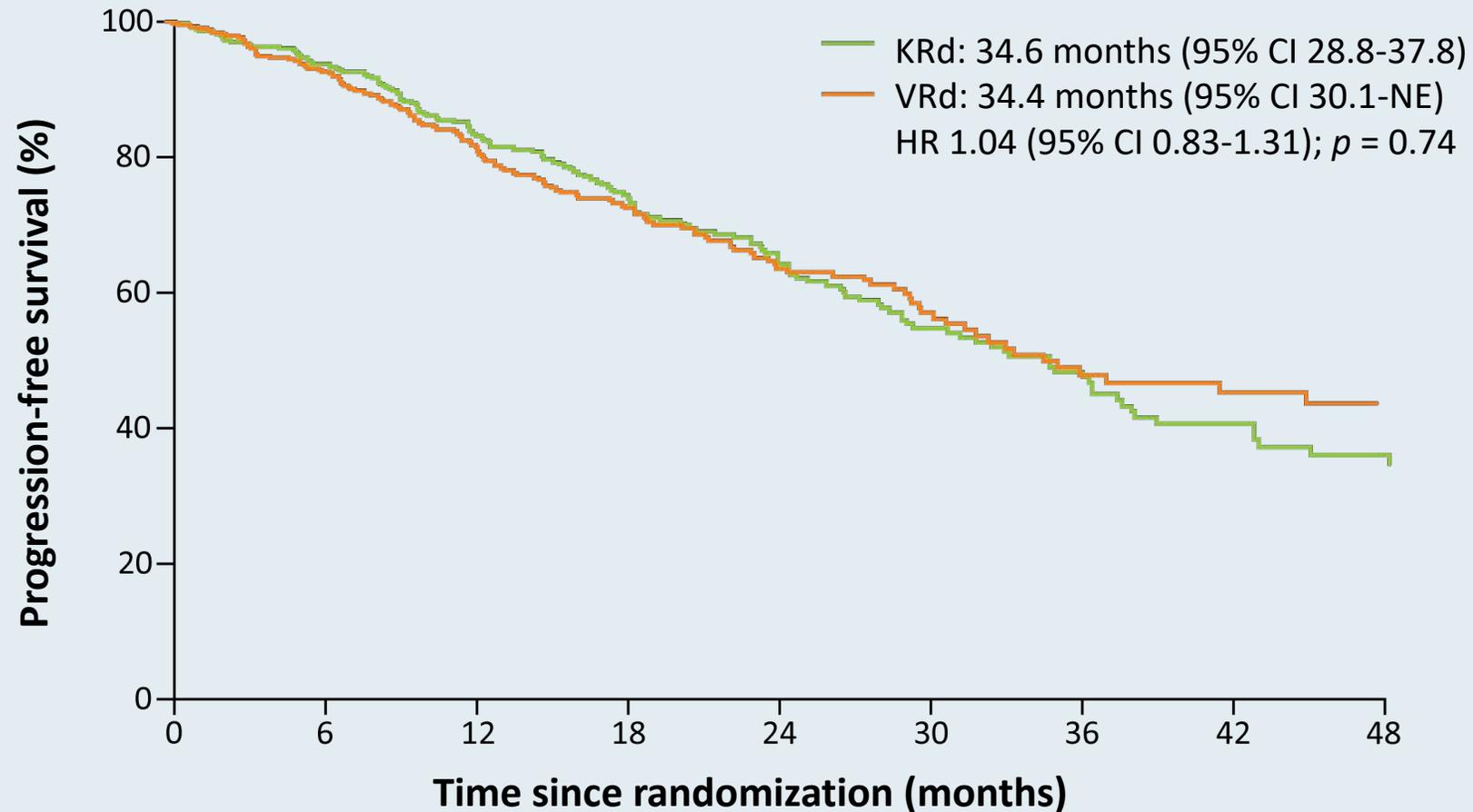


# Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial

*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*

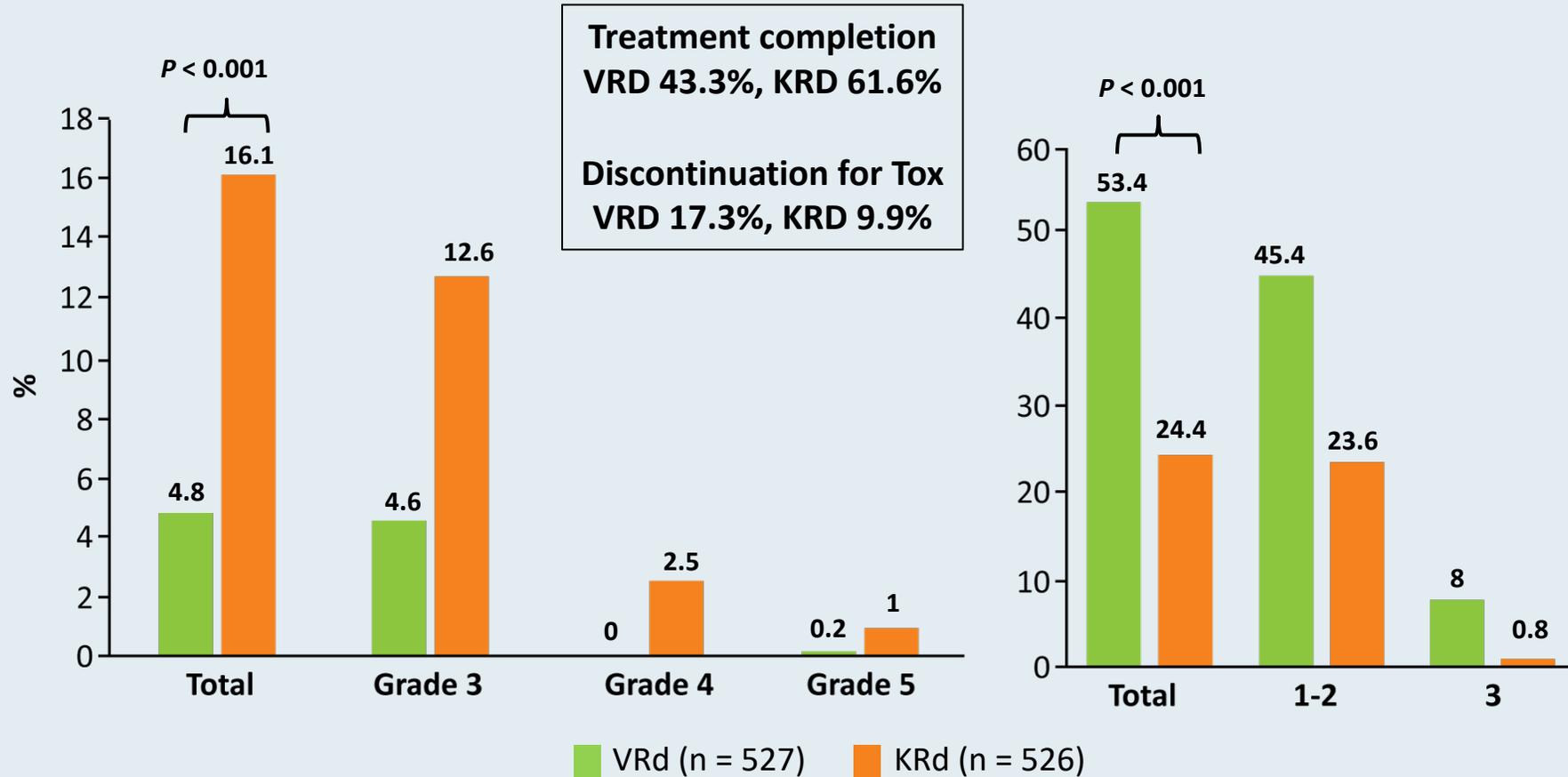
***Lancet Oncol 2020;21(10):1317-30***

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



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

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



Cardiac, pulmonary and renal

Peripheral neuropathy\*

\* Grades 1-2 not required reporting

ORIGINAL ARTICLE

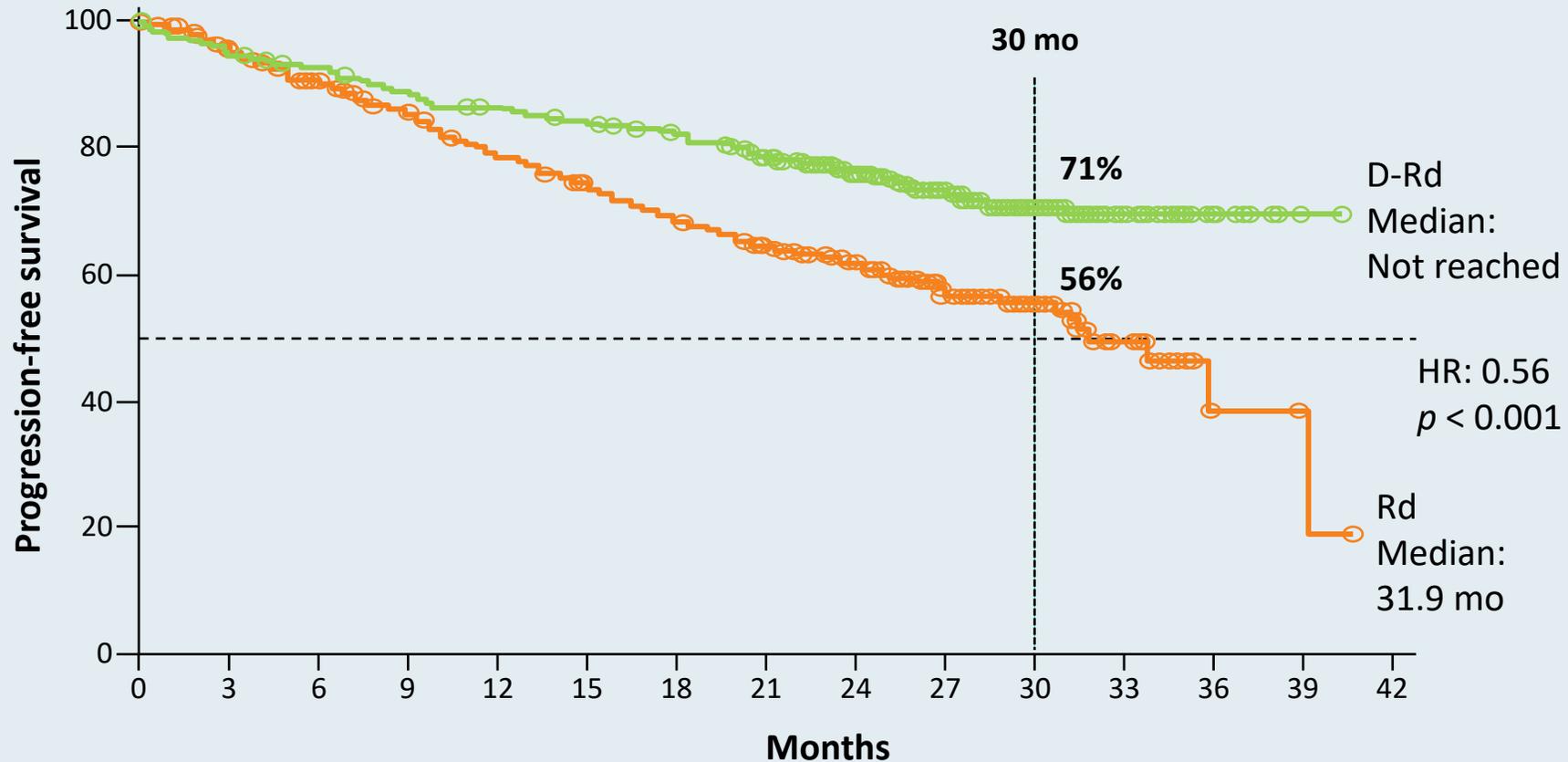
# Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma

T. Facon, S. Kumar, T. Plesner, R.Z. Orlowski, P. Moreau, N. Bahlis, S. Basu, H. Nahi, C. Hulin, H. Quach, H. Goldschmidt, M. O'Dwyer, A. Perrot, C.P. Venner, K. Weisel, J.R. Mace, N. Raje, M. Attal, M. Tiab, M. Macro, L. Frenzel, X. Leleu, T. Ahmadi, C. Chiu, J. Wang, R. Van Rampelbergh, C.M. Uhlar, R. Kobos, M. Qi, and S.Z. Usmani, for the MAIA Trial Investigators\*

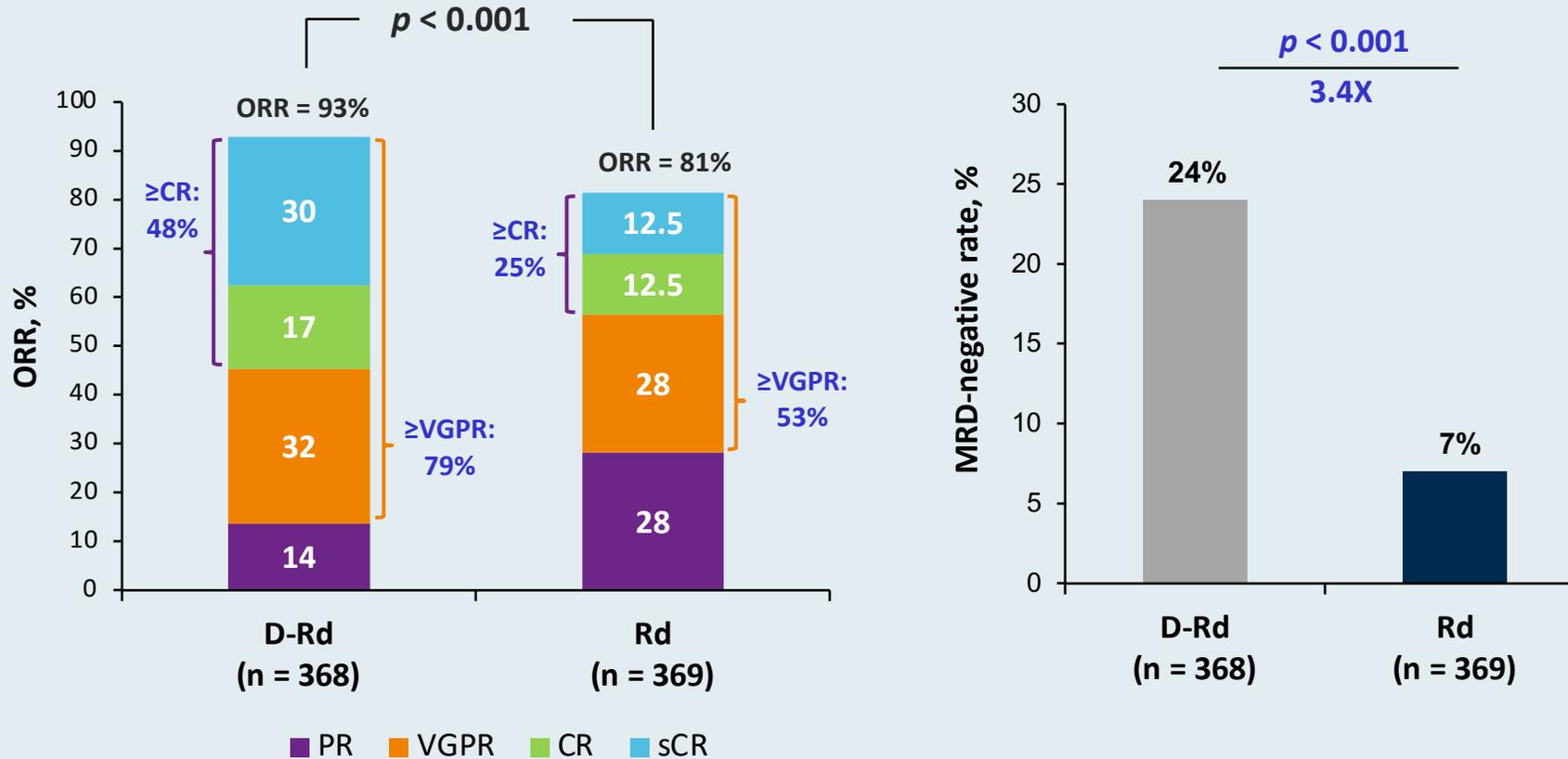
*N Engl J Med* 2019;380(22):2104-15.

# MAIA Primary Endpoint: Progression-Free Survival

## NDMM Transplant Ineligible



# MAIA: Overall Response Rate and MRD (NGS; $10^{-5}$ Sensitivity Threshold) Rate

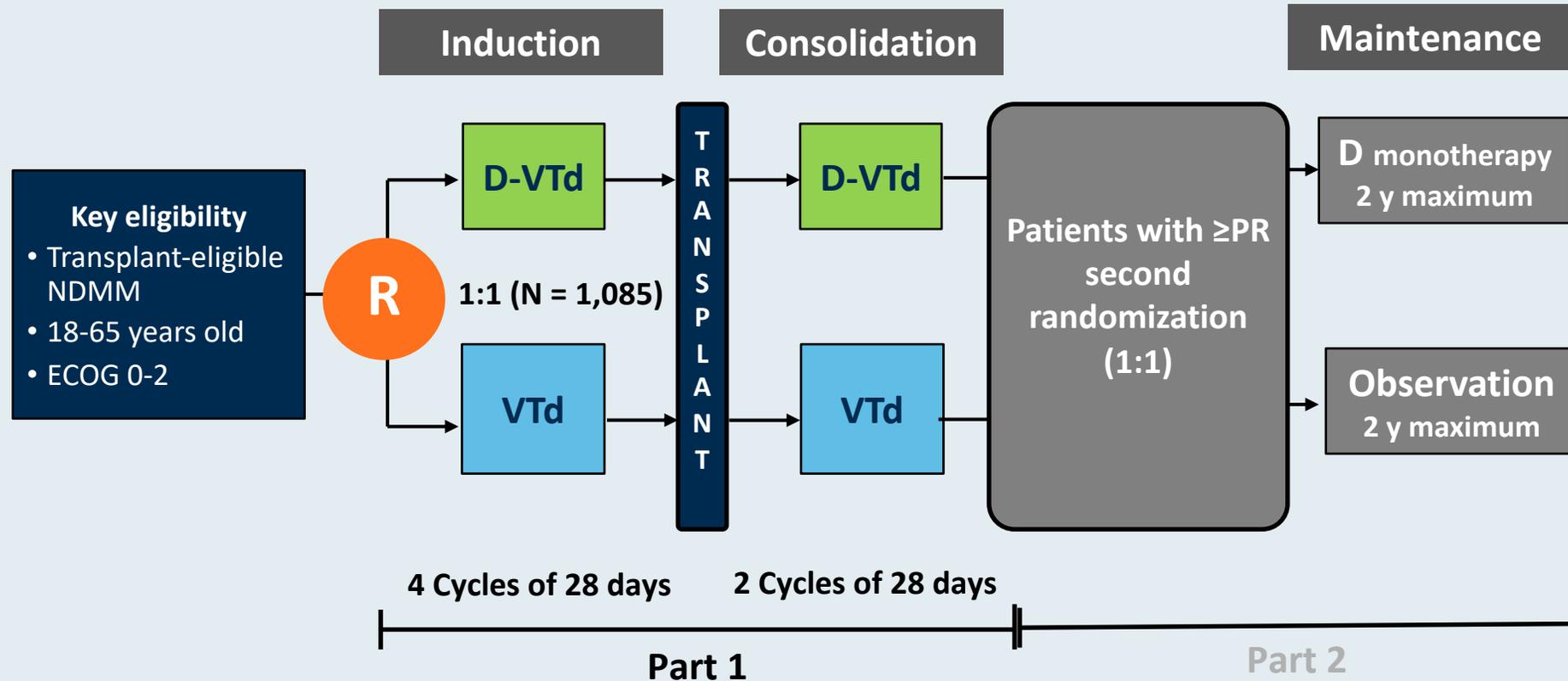


# **Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study**

*Philippe Moreau, Michel Attal, Cyrille Hulin, Bertrand Arnulf, Karim Belhadj, Lotfi Benboubker, Marie C Béné, Annemiek Broijl, Hélène Caillon, Denis Caillot, Jill Corre, Michel Delforge, Thomas Dejoie, Chantal Doyen, Thierry Facon, Cécile Sonntag, Jean Fontan, Laurent Garderet, Kon-Siong Jie, Lionel Karlin, Frédérique Kuhnowski, Jérôme Lambert, Xavier Leleu, Pascal Lenain, Margaret Macro, Claire Mathiot, Frédérique Orsini-Piocelle, Aurore Perrot, Anne-Marie Stoppa, Niels W C J van de Donk, Soraya Wuilleme, Sonja Zweegman, Brigitte Kolb, Cyrille Touzeau, Murielle Roussel, Mourad Tiab, Jean-Pierre Marolleau, Nathalie Meuleman, Marie-Christiane Vekemans, Matthijs Westerman, Saskia K Klein, Mark-David Levin, Jean Paul Femand, Martine Escoffre-Barbe, Jean-Richard Eveillard, Reda Garidi, Tahamtan Ahmadi, Sen Zhuang, Christopher Chiu, Lixia Pei, Carla de Boer, Elena Smith, William Deraedt, Tobias Kampfenkel, Jordan Schechter, Jessica Vermeulen, Hervé Avet-Loiseau, Pieter Sonneveld*

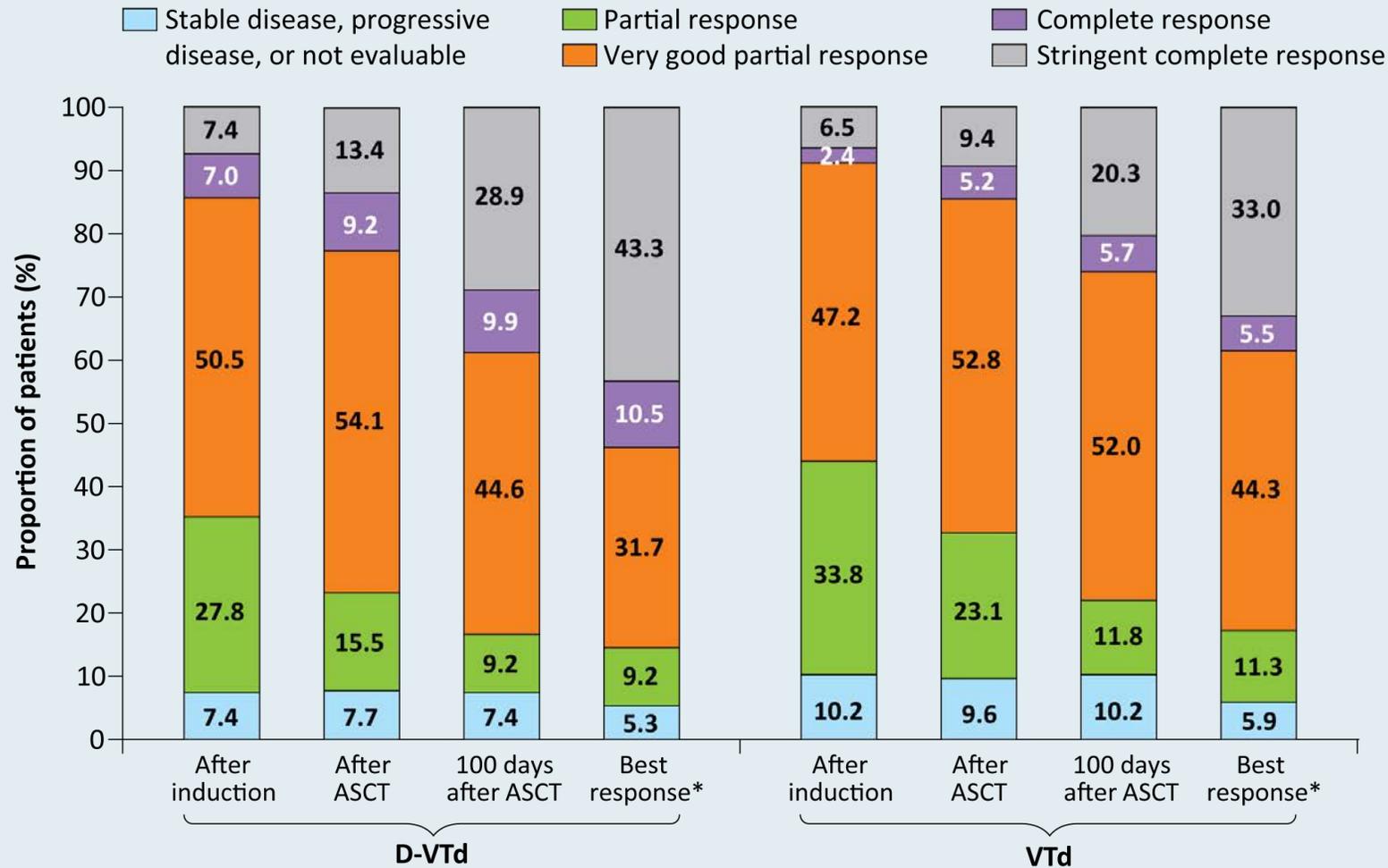
*Lancet* 2019;394:29-38.

# CASSIOPEIA Phase III Study Design



**Primary endpoint:** Postconsolidation stringent CR

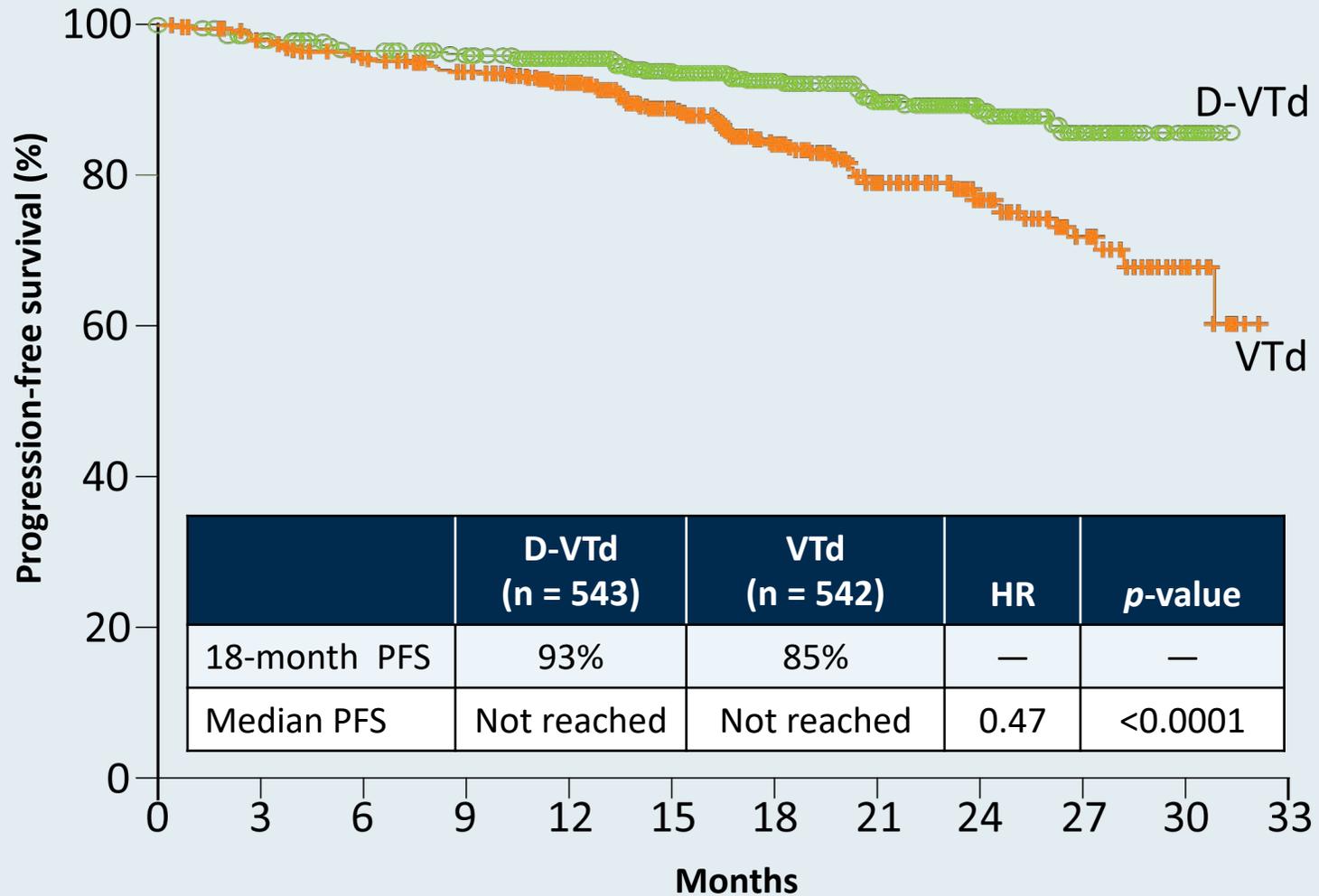
# CASSIOPEIA Primary Endpoint: Postconsolidation Stringent Complete Response (sCR)



**sCR 100 days after ASCT: 28.9% vs 20.3%, OR: 1.60,  $p = 0.001$**

\* At clinical cutoff (June 19, 2018) for the primary analysis of part 1 and regardless of second randomisation (post-hoc analysis)

# CASSIOPEIA: Progression-Free Survival (ITT)





## Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial

*Maria-Victoria Mateos, Michele Cavo, Joan Blade, Meletios A Dimopoulos, Kenshi Suzuki, Andrzej Jakubowiak, Stefan Knop, Chantal Doyen, Paulo Lucio, Zsolt Nagy, Ludek Pour, Mark Cook, Sebastian Grosicki, Andre Crepaldi, Anna Marina Liberati, Philip Campbell, Tatiana Shelekhova, Sung-Soo Yoon, Genadi Iosava, Tomoaki Fujisaki, Mamta Garg, Maria Krevvata, Ying Chen, Jianping Wang, Anupa Kudva, Jon Ukropec, Susan Wroblewski, Ming Qi, Rachel Kobos, Jesus San-Miguel*

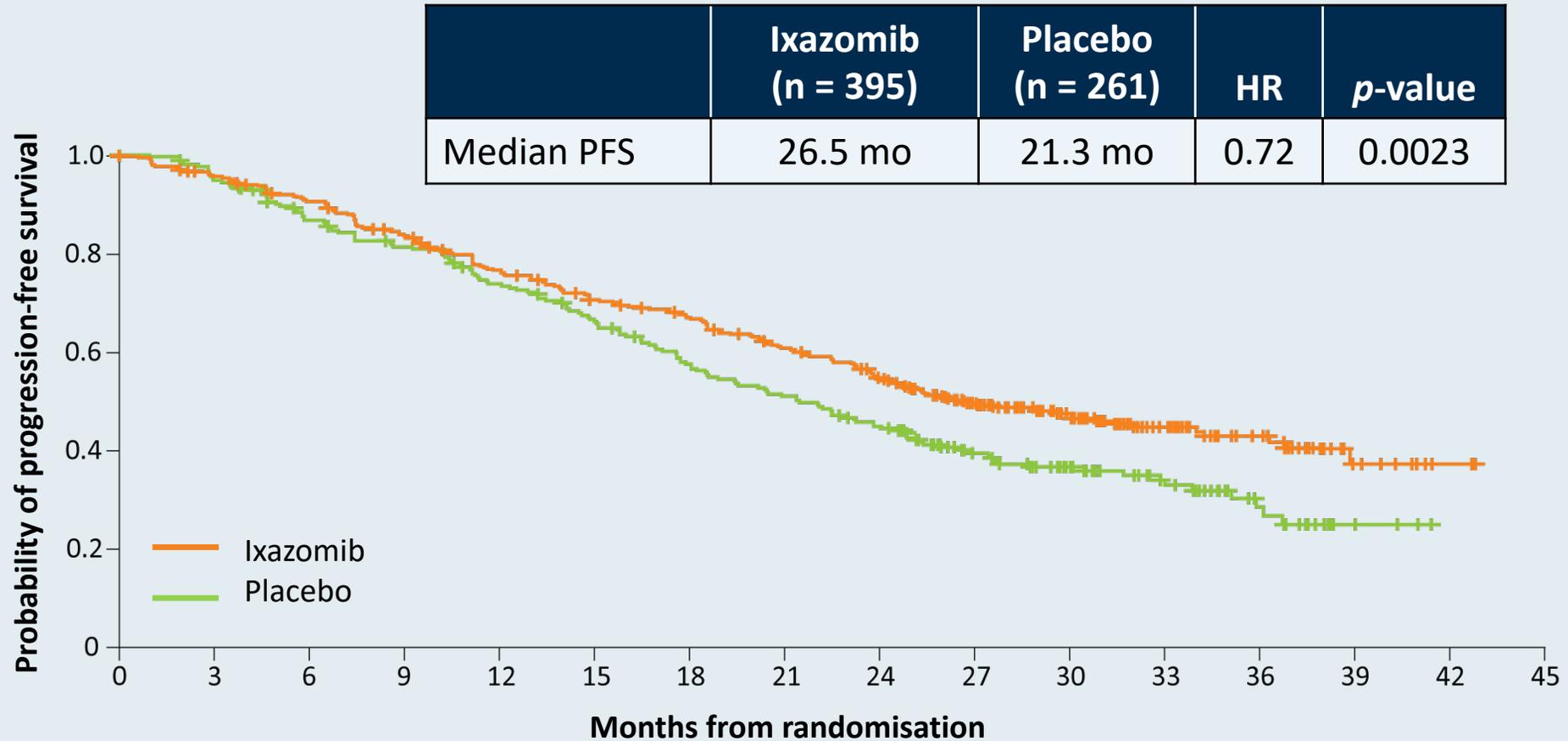
*Lancet* 2020;395(10218):132-41.

# Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial

*Meletios A Dimopoulos, Francesca Gay, Fredrik Schjesvold, Meral Beksac, Roman Hajek, Katja Christina Weisel, Hartmut Goldschmidt, Vladimir Maisnar, Philippe Moreau, Chang Ki Min, Agnieszka Pluta, Wee-Joo Chng, Martin Kaiser, Sonja Zweegman, Maria-Victoria Mateos, Andrew Spencer, Shinsuke Iida, Gareth Morgan, Kaveri Suryanarayan, Zhaoyang Teng, Tomas Skacel, Antonio Palumbo, Ajeeta B Dash, Neeraj Gupta, Richard Labotka, S Vincent Rajkumar, on behalf of the TOURMALINE-MM3 study group\**

*Lancet* 2019;393(10168):253-64.

# TOURMALINE-MM3 Primary Endpoint: Progression-Free Survival (ITT)

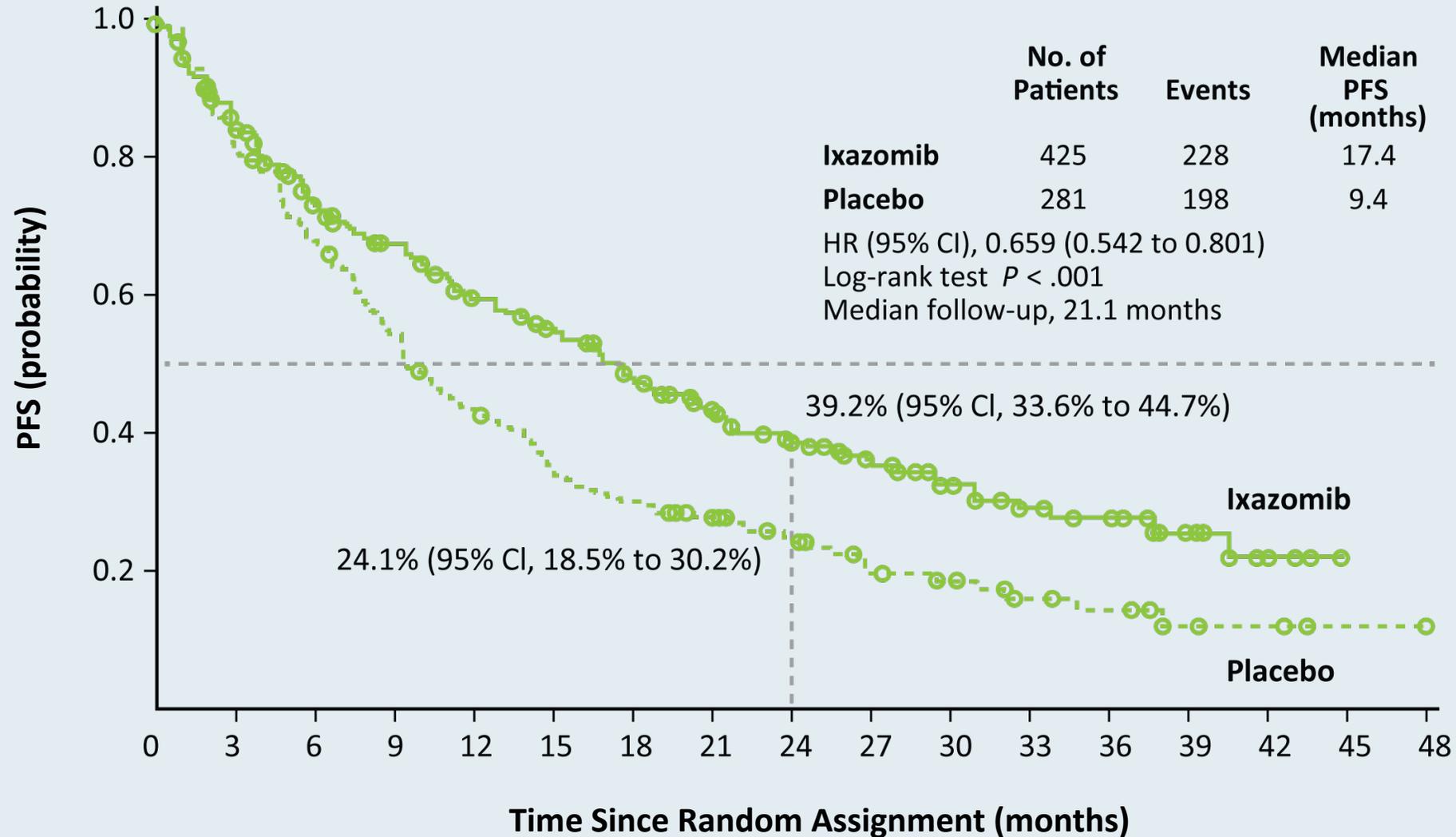


# **Ixazomib as Postinduction Maintenance for Patients With Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 Trial**

Meletios A. Dimopoulos, MD<sup>1</sup>; Ivan Špička, MD<sup>2</sup>; Hang Quach, MD<sup>3</sup>; Albert Oriol, MD<sup>4</sup>; Roman Hájek, MD<sup>5</sup>; Mamta Garg, MD<sup>6</sup>; Meral Beksac, MD<sup>7</sup>; Sara Bringhen, MD<sup>8</sup>; Eirini Katodritou, MD<sup>9</sup>; Wee-Joo Chng, MD<sup>10</sup>; Xavier Leleu, MD<sup>11</sup>; Shinsuke Iida, MD<sup>12</sup>; María-Victoria Mateos, MD<sup>13</sup>; Gareth Morgan, MD<sup>14</sup>; Alexander Vorog, MD<sup>15</sup>; Richard Labotka, MD<sup>15</sup>; Bingxia Wang, PhD<sup>15</sup>; Antonio Palumbo, MD<sup>15</sup>; and Sagar Lonial, MD<sup>16</sup>; on behalf of the TOURMALINE-MM4 study group

*J Clin Oncol* 2020;[Online ahead of print].

# TOURMALINE-MM4 Primary Endpoint: Progression-Free Survival



# Phase III TOURMALINE-MM2 Trial of Ixazomib with Lenalidomide and Dexamethasone Fails to Meet Primary PFS Endpoint

Press Release – September 9, 2020

“The study found the addition of ixazomib to lenalidomide and dexamethasone resulted in a 13.5 month increase in median progression-free survival (PFS) (35.3 months in the ixazomib arm, compared to 21.8 months in the placebo arm; hazard ratio [HR] 0.830;  $p=0.073$ ). The trial did not meet the threshold for statistical significance and the primary endpoint of PFS was not met.

The data were presented at the virtual scientific meeting of the Society of Hematologic Oncology (SOHO).”

# Multiple Myeloma

## Management of Newly Diagnosed Multiple Myeloma

- Dr Zafar: A 53-year-old man with high-risk lambda light chain disease

## Relapsed/Refractory Multiple Myeloma

- Dr Lamar: A 68-year-old woman with relapsed multiple myeloma
- Dr Hart: A 70-year-old man with relapsed multiple myeloma

## Novel Treatment Approaches for Multiple Myeloma

- Dr Zafar: A 67-year-old man with high-risk IgA multiple myeloma
- Dr Peles: A 75-year-old woman with high-risk smoldering myeloma

# Case Presentation – Dr Lamar: A 68-year-old woman with relapsed multiple myeloma



Dr Zanetta Lamar

- 1997: Diagnosed with lambda light chain myeloma
  - Stage IV kidney disease and severe heart disease
  - VAD x 3 cycles → tandem transplant (no maintenance due to complications from multi-organ failure)
- 7/2020: Presents with worsening renal failure and anemia
  - Labs showed a lambda light level of 3863 and bone marrow biopsy showed 80% involvement.
- CyBorD x 2 cycles → normalization of lambda light chains
- Repeat bone marrow biopsy with MRD testing is planned

## Questions

- Would you consider testing for MRD to determine when to go forward with maintenance therapy?
- Do you ever consider use of IVIG in patients with multiple myeloma, particularly during this COVID and flu season?

# Case Presentation – Dr Hart: A 70-year-old man with relapsed multiple myeloma



**Dr Lowell Hart**

- Presented with anemia; bone marrow biopsy showed 80% cellularity lambda restricted plasma cell neoplasm; skeletal survey had lytic lesions
- 2/2013: RVD → ASCT → maintenance rituximab (developed rash and DVT)
- 1/2014: Bortezomib/dexamethasone
- 4/2019: Progression → daratumumab/pomalidomide/dexamethasone
- 8/2019: Fatigue worsened and pomalidomide stopped
- 4/2020: New lesions in T-spine with pain
- 5/2020: Carfilzomib/dexamethasone with zoledronic acid → stable disease

## Questions

- What would be your approach for this patient if he progresses on carfilzomib/dexamethasone?
- What about newer agents such as selinexor? What toxicities are associated with this agent?
- What is the role of autotransplant in light of upcoming CAR T-cell therapy and bi-specific antibodies?

# Selecting the Optimal Regimen

**Lenalidomide refractory,  
Bortezomib sensitive**

***Bortezomib based***

**Dara-Bortezomib-Dex**

**Selinexor-Bortezomib-Dex**

**Elotuzumab-Bortezomib-Dex**

**Panobinostat-Bortezomib-Dex**

***Pomalidomide based***

**Pomalidomide-Bortezomib-Dex**

**Elo-Pom Dex**

**Bortezomib refractory,  
Lenalidomide sensitive**

***Carfilzomib based***

**Carfilzomib-Lenalidomide-Dex**

***IMiD based***

**Elotuzumab-Lenalidomide-Dex**

**Lenalidomide AND Bortezomib  
refractory**

***Carfilzomib based***

**Carfilzomib-Dara-Dex**

**Carfilzomib-Isatuximab-Dex**

**Carfilzomib-Pom Dex**

***MoAb based***

**Dara-Pom-Dex**

**Isa-Pom Dex**

***Other***

**Selinexor**

# FDA Approves Carfilzomib and Daratumumab with Dexamethasone for Multiple Myeloma

Press Release – August 20, 2020

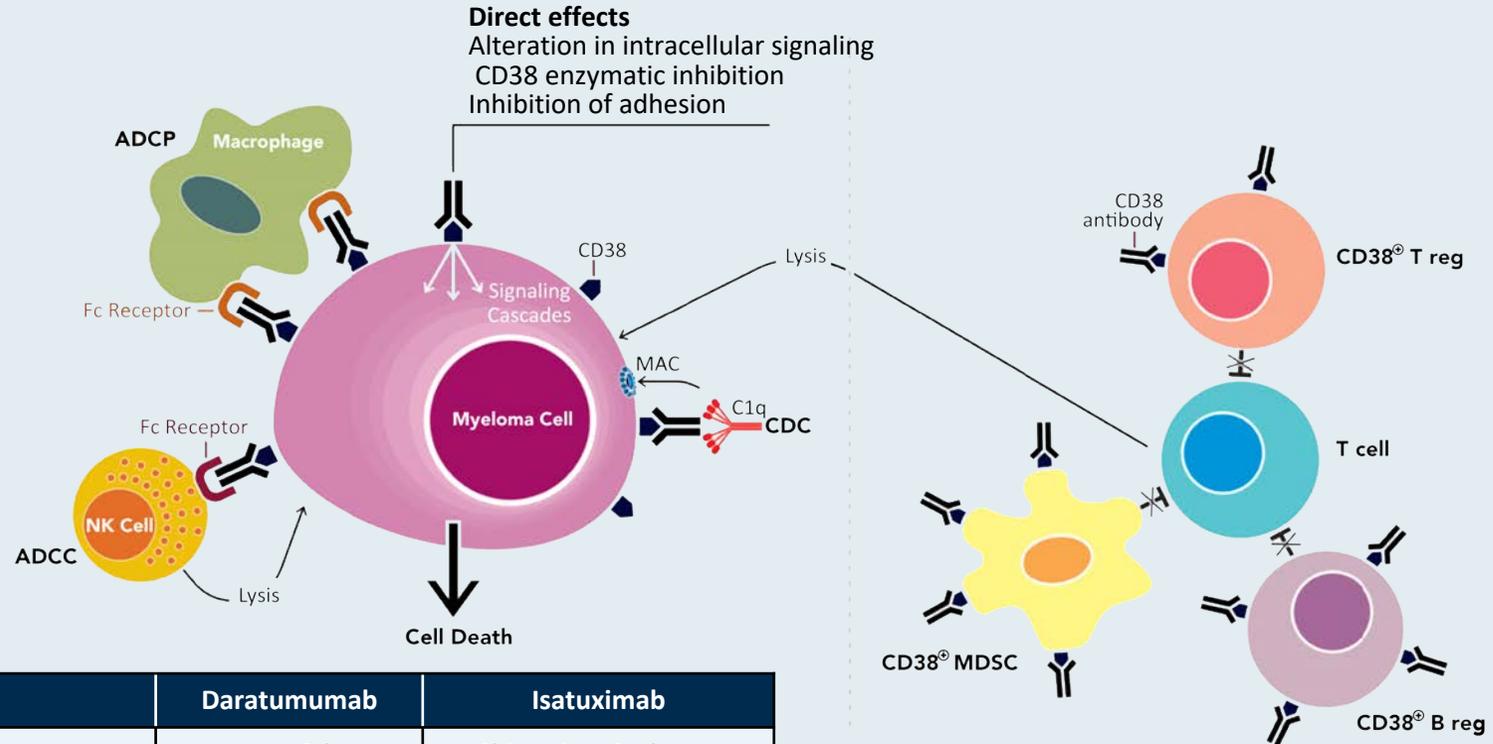
“On August 20, 2020, the Food and Drug Administration approved carfilzomib and daratumumab in combination with dexamethasone for adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

The efficacy of carfilzomib and daratumumab with dexamethasone was evaluated in two clinical trials, CANDOR and EQUULEUS.”

# 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 | +               | +++                 |

# FDA Approves New Therapy for Patients with Previously Treated Multiple Myeloma

Press Release – March 02, 2020

“Today, the US Food and Drug Administration approved isatuximab-irfc, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

The FDA approved isatuximab-irfc based on the results of a clinical trial involving 307 patients with relapsed and refractory multiple myeloma who had received at least two prior therapies, including lenalidomide and a proteasome inhibitor.

Patients who received isatuximab-irfc in combination with pomalidomide and low-dose dexamethasone showed improvement in PFS with a 40% reduction in the risk of disease progression or death compared to patients who received pomalidomide and dexamethasone. These patients also had an overall response rate of 60.4%. In comparison, the patients who only received pomalidomide and low-dose dexamethasone had an overall response rate of 35.3%.”

<https://www.fda.gov/news-events/press-announcements/fda-approves-new-therapy-patients-previously-treated-multiple-myeloma>

# ICARIA-MM: Efficacy Summary of Isatuximab Plus Pomalidomide/Low-dose Dexamethasone

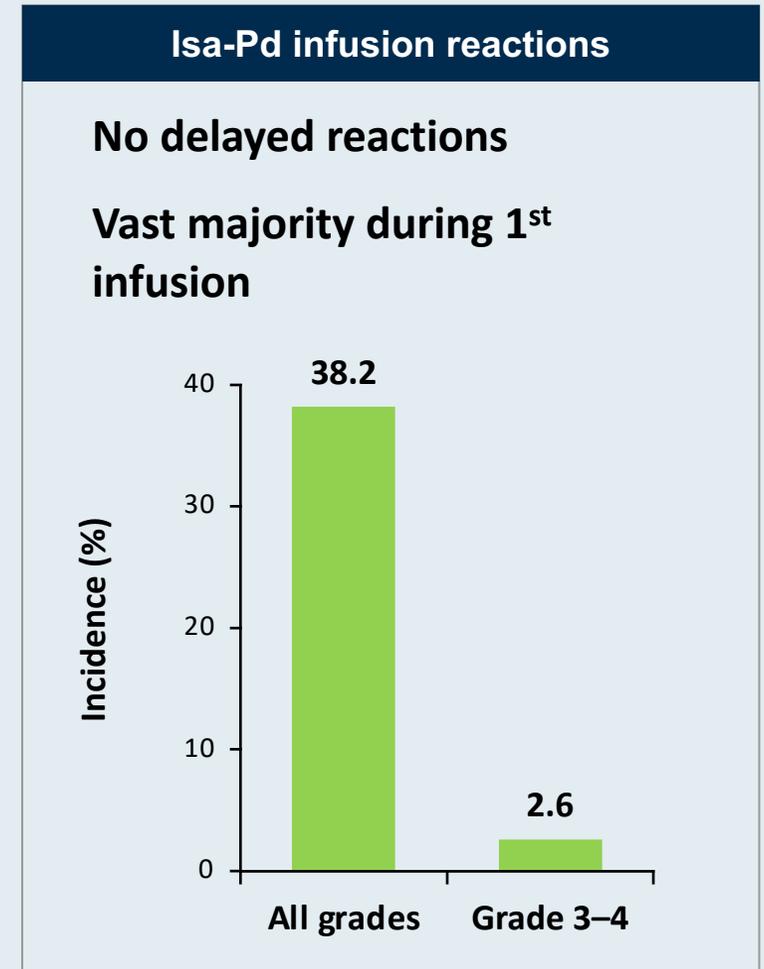
| Prior treatments                 | Isatuximab + pom/dex<br>(n = 154) | Pom/dex<br>(n = 153) |
|----------------------------------|-----------------------------------|----------------------|
| Median # prior therapies (range) | 3 (2-4)                           | 3 (2-4)              |
| Prior proteasome inhibitors      | 100%                              | 100%                 |
| Prior lenalidomide               | 100%                              | 100%                 |

| Efficacy         | Isatuximab + pom/dex<br>(n = 154) | Pom/dex<br>(n = 153) | Hazard or odds<br>ratio | p-value |
|------------------|-----------------------------------|----------------------|-------------------------|---------|
| Median PFS (ITT) | 11.5 mo                           | 6.5 mo               | 0.596                   | 0.001   |
| Median OS        | Not reached                       | Not reached          | 0.687                   | 0.063   |
| ORR              | 60%                               | 35%                  | 2.795                   | <0.0001 |
| ≥VGPR            | 32%                               | 9%                   | 5.026                   | <0.0001 |

# ICARIA-MM: Treatment-Emergent Adverse Events

| TEAE         | Isa-Pd (n = 152) |          | Pd (n = 149) |          |
|--------------|------------------|----------|--------------|----------|
|              | All grades       | Grade ≥3 | All grades   | Grade ≥3 |
| URTI         | 28.3             | 3.3      | 17.4         | 0.7      |
| Diarrhea     | 25.7             | 2.0      | 19.5         | 0.7      |
| Bronchitis   | 23.7             | 3.3      | 8.7          | 0.7      |
| Pneumonia    | 20.4             | 16.4     | 17.4         | 14.7     |
| Fatigue      | 17.1             | 3.9      | 21.5         | 0        |
| Back pain    | 16.4             | 2.0      | 14.8         | 1.3      |
| Constipation | 15.8             | 0        | 17.4         | 0        |
| Asthenia     | 15.1             | 3.3      | 18.1         | 2.7      |
| Dyspnea      | 15.1             | 3.9      | 10.1         | 1.3      |
| Nausea       | 15.1             | 0        | 9.4          | 0        |

- **URTI = upper respiratory tract infection**



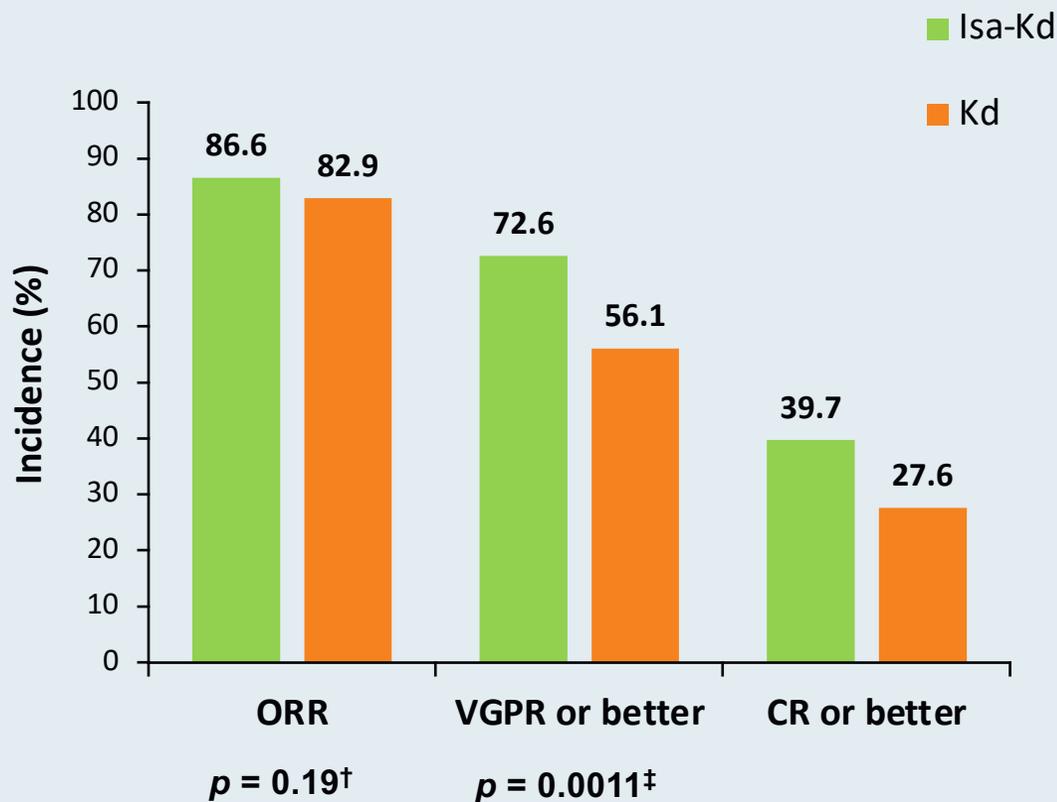
# Isatuximab plus Carfilzomib and Dexamethasone vs Carfilzomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma (IKEMA): Interim Analysis of a Phase 3, Randomized, Open-label Study

Moreau P et al.

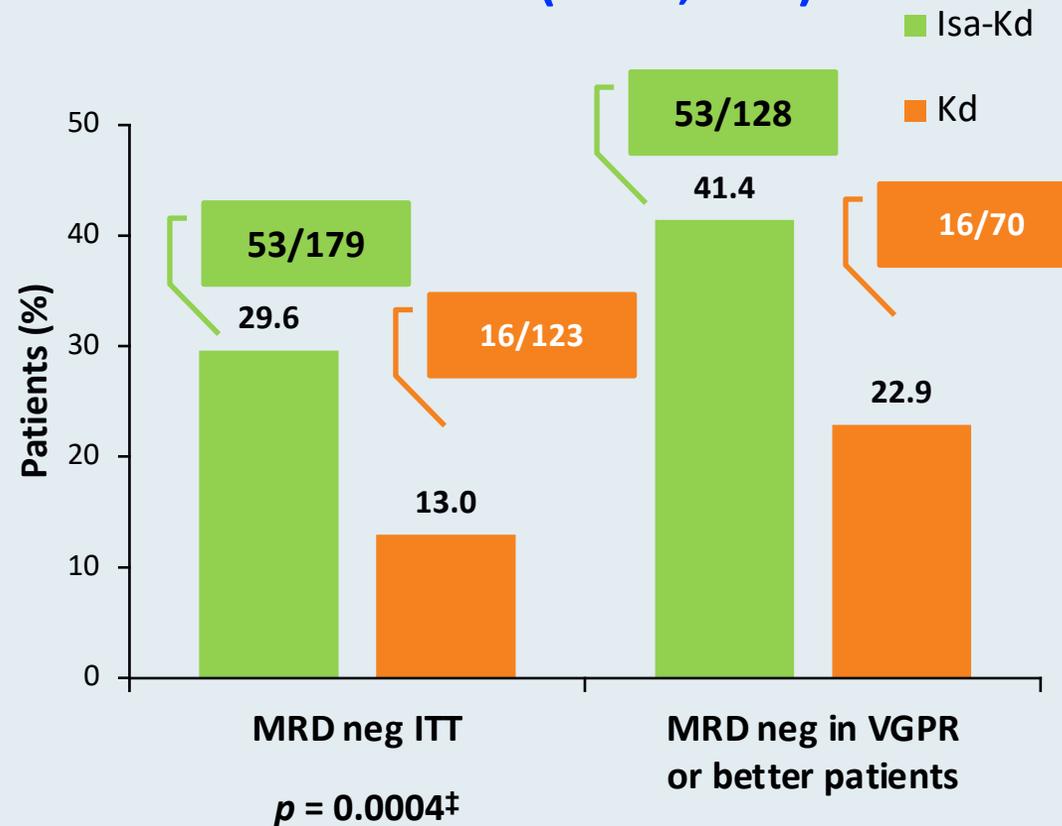
EHA 2020;Abstract LBA2603.

# IKEMA: Depth of response

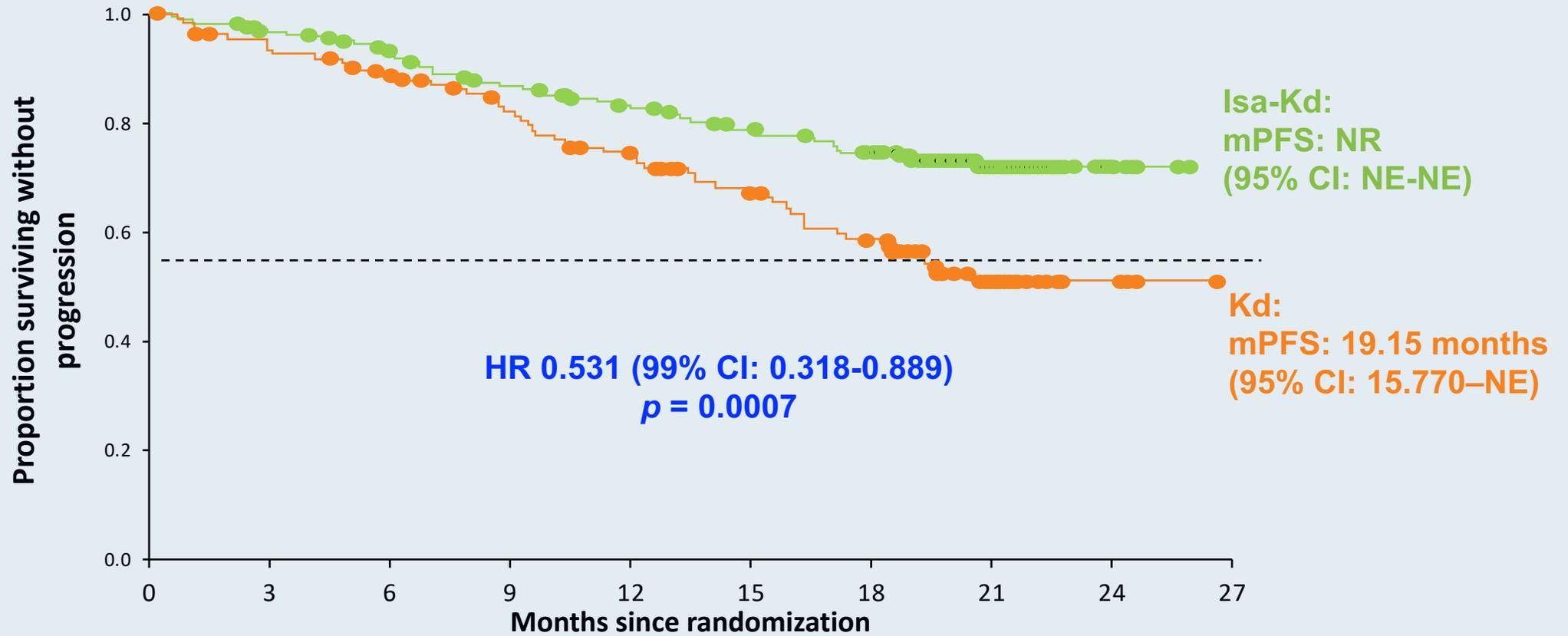
## Best overall response



## MRD rate (NGS\*, $10^{-5}$ )



# IKEMA: PFS



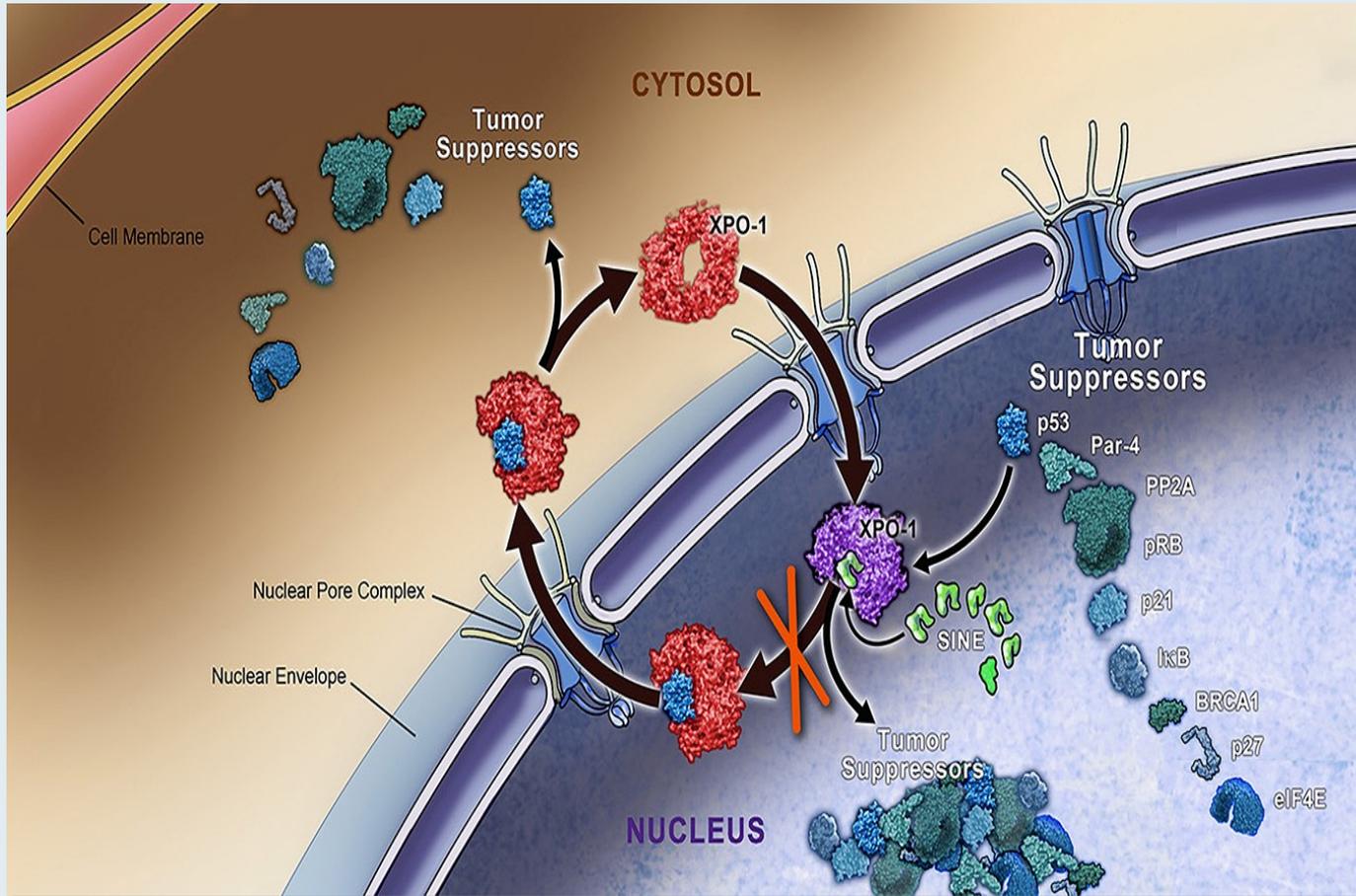
| No. at risk | 0   | 3   | 6   | 9   | 12  | 15  | 18  | 21 | 24 | 27 |
|-------------|-----|-----|-----|-----|-----|-----|-----|----|----|----|
| Isa-Kd      | 179 | 164 | 151 | 136 | 124 | 110 | 100 | 36 | 5  | 0  |
| Kd          | 123 | 108 | 99  | 85  | 72  | 61  | 50  | 19 | 6  | 0  |

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

**Which of the following would you generally use first in a patient with relapsed MM who has experienced disease progression on multiple prior therapies?**

- a. Selinexor
- b. Belantamab mafodotin
- c. I wouldn't use either

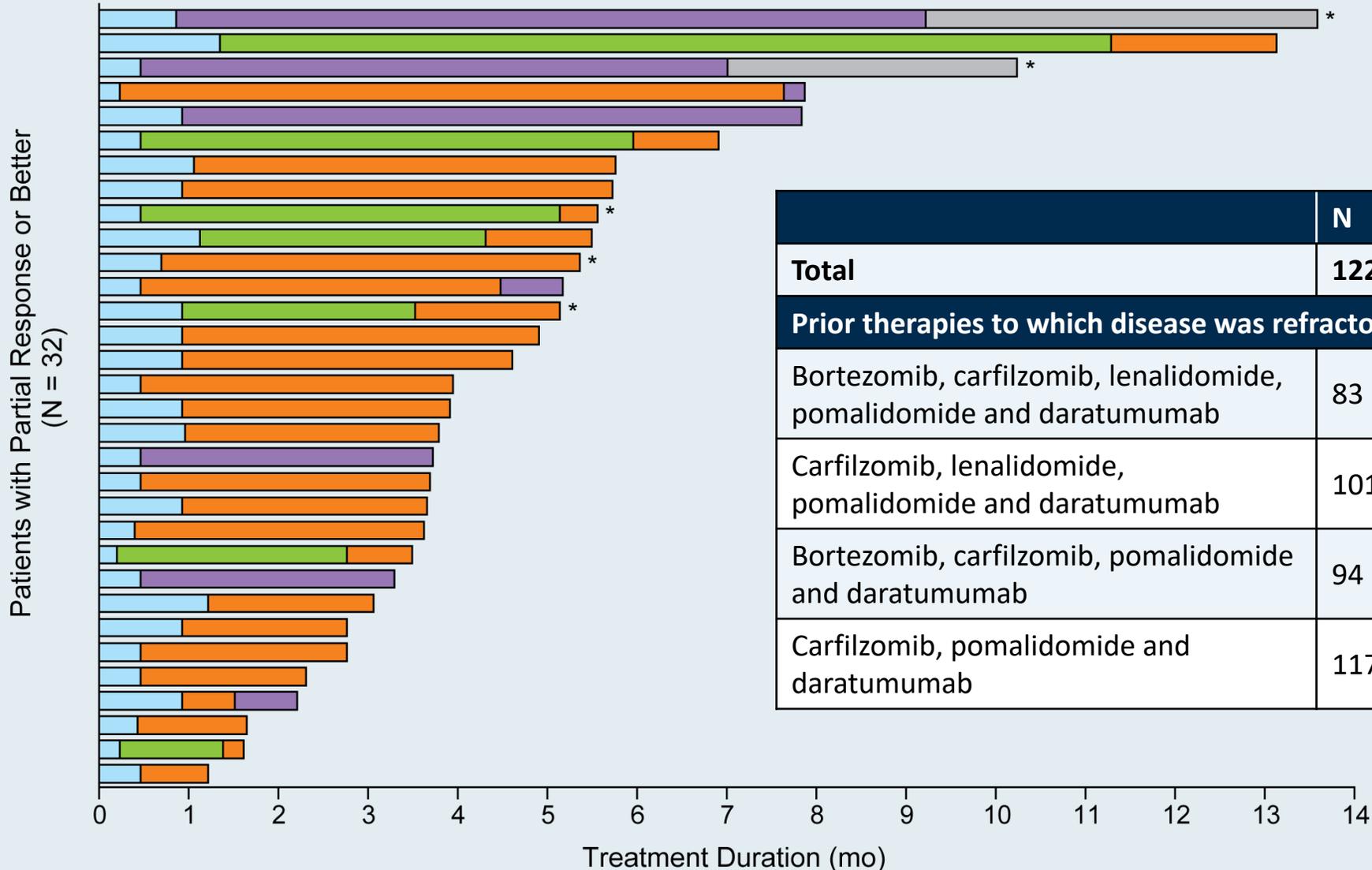
# Selinexor Mechanism of Action



- 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.

# STORM: Duration and Rate of Response

■ No response yet   
 ■ Minimal response   
 ■ Partial response   
 ■ Very good partial response   
 ■ Stringent complete response



|   | N          | ≥ PR            | ≥ MR            |
|---|------------|-----------------|-----------------|
| <b>Total</b>  | <b>122</b> | <b>32 (26%)</b> | <b>48 (39%)</b> |
| <b>Prior therapies to which disease was refractory</b>              |            |                 |                 |
| Bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab | 83         | 21 (25%)        | 31 (37%)        |
| Carfilzomib, lenalidomide, pomalidomide and daratumumab             | 101        | 26 (26%)        | 37 (37%)        |
| Bortezomib, carfilzomib, pomalidomide and daratumumab               | 94         | 25 (27%)        | 36 (38%)        |
| Carfilzomib, pomalidomide and daratumumab                           | 117        | 31 (26%)        | 45 (38%)        |

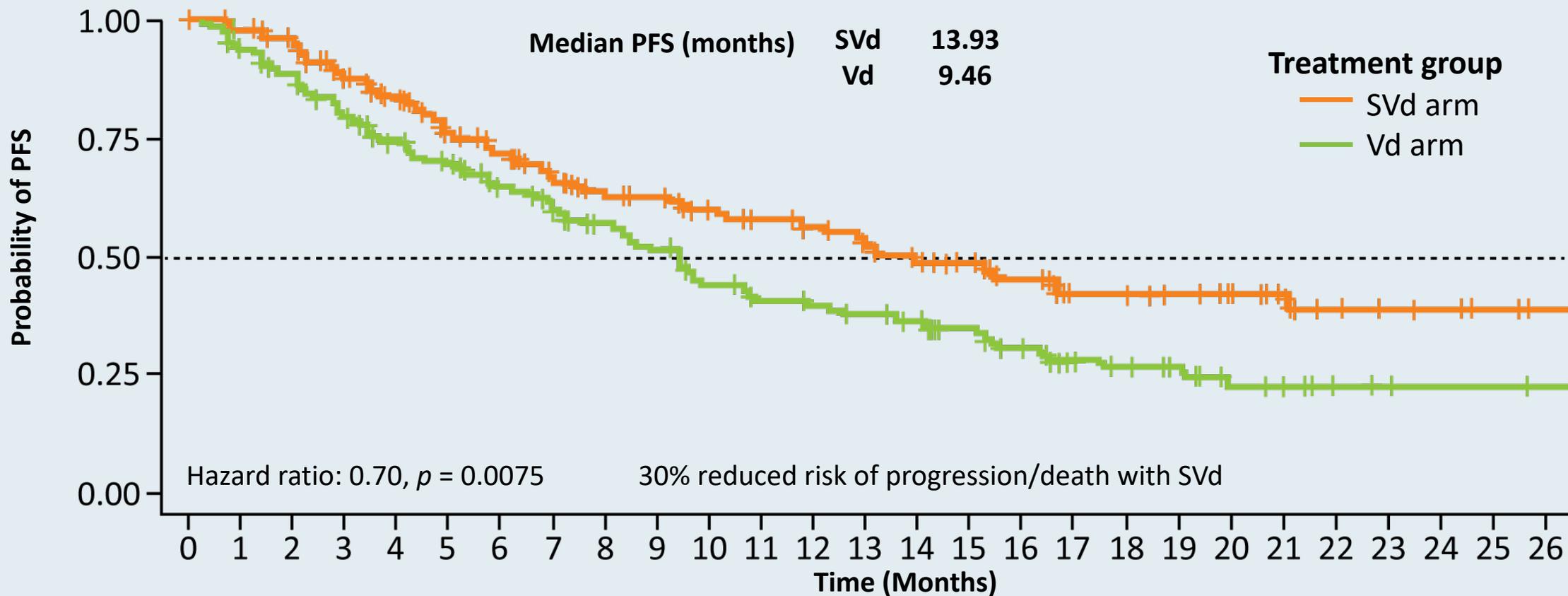
# Safety Profile of Selinexor/Dexamethasone

| Adverse events (n = 123)                              | Grade 1-2 | Grade 3 | Grade 4 |
|---|-----------|---------|---------|
| <b>Hematologic adverse events</b>                     |           |         |         |
| Thrombocytopenia                                      | 15%       | 25%     | 33%     |
| Anemia  | 24%       | 43%     | 1%      |
| Neutropenia   | 19%       | 18%     | 3%      |
| <b>Nonhematologic adverse events</b>                  |           |         |         |
| Fatigue   | 48%       | 25%     | 0       |
| Nausea  | 62%       | 10%     | 0       |
| Hyponatremia  | 15%       | 21%     | 1%      |
| Patients with ≥1 serious treatment emergent AE (TEAE) |           |         | 63.4%   |
| Pneumonia   |           |         | 11.4%   |
| Sepsis  |           |         | 8.9%    |
| Treatment discontinuation due to TEAE                 |           |         | 18%     |
| AE-related dose modification or interruption          |           |         | 80%     |

**Weekly Selinexor, Bortezomib, and Dexamethasone (SVd) versus Twice Weekly Bortezomib and Dexamethasone (Vd) in Patients with Multiple Myeloma (MM) After One to Three Prior Therapies: Initial Results of the Phase III BOSTON Study**

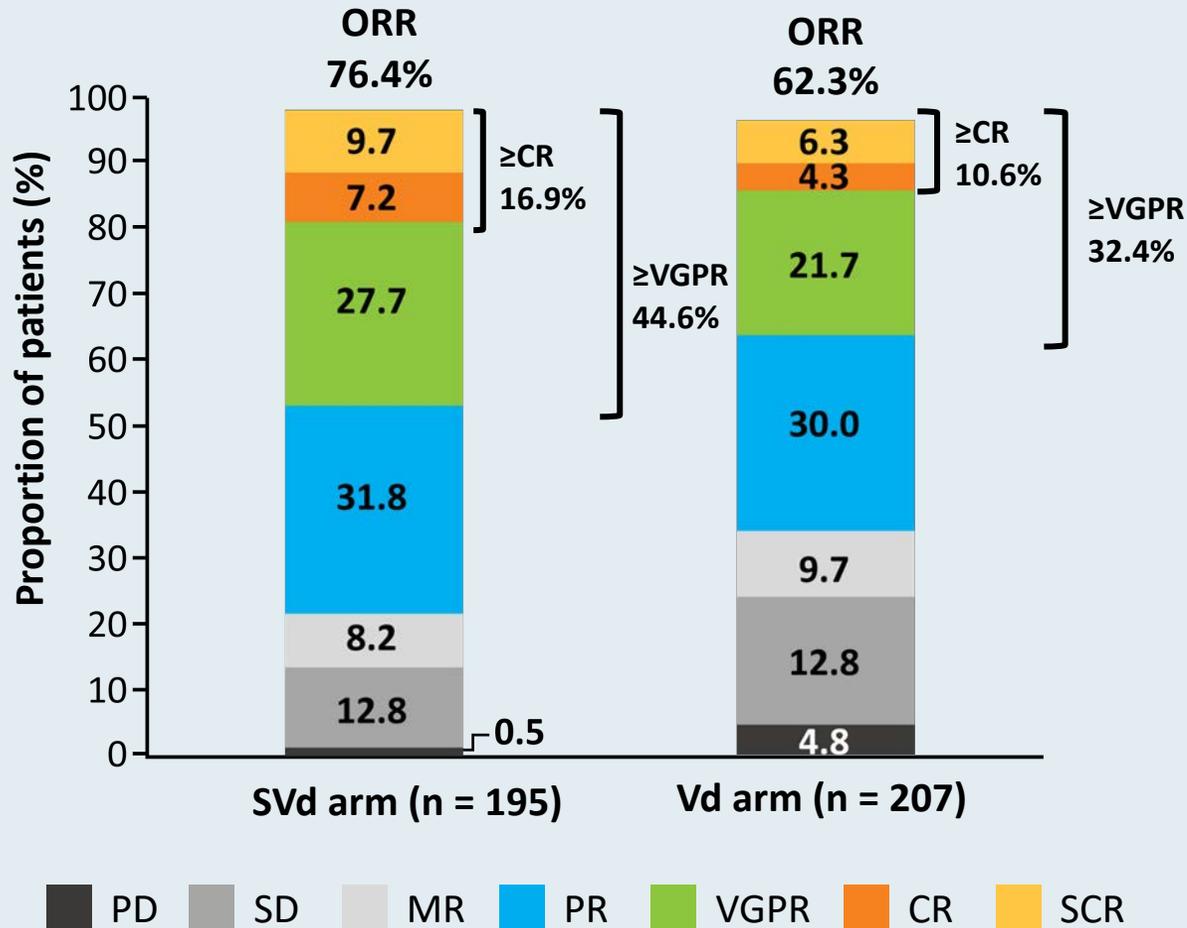
Dimopoulos MA et al.  
ASCO 2020;Abstract 8501.

# BOSTON Trial: PFS



|                |     |     |     |     |     |     |     |     |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |   |   |   |   |
|----------------|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|---|---|---|---|
| <b>SVd Arm</b> | 195 | 187 | 175 | 152 | 135 | 117 | 106 | 89  | 79 | 76 | 69 | 64 | 57 | 51 | 45 | 41 | 35 | 27 | 26 | 22 | 19 | 14 | 9 | 7 | 6 | 4 | 2 |
| <b>Vd Arm</b>  | 207 | 187 | 175 | 152 | 138 | 127 | 111 | 100 | 90 | 81 | 66 | 59 | 56 | 53 | 49 | 42 | 35 | 26 | 20 | 16 | 10 | 8  | 5 | 4 | 3 | 3 | 2 |

# BOSTON Trial: Response



## Longer duration of response with SVd

|                                      | SVd arm (n = 149) | Vd arm (n = 129) |
|--------------------------------------|-------------------|------------------|
| Median time to response (months)     | 1.1               | 1.4              |
| Median duration of response (months) | 20.3              | 12.9             |

**Fewer patients with progressive disease: SVd (n = 1, 0.5%) vs Vd (n = 10, 4.8%)**

# FDA Granted Accelerated Approval to Belantamab Mafodotin-blmf for Multiple Myeloma

Press Release – August 5, 2020

“The Food and Drug Administration granted accelerated approval to belantamab mafodotin-blmf for adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

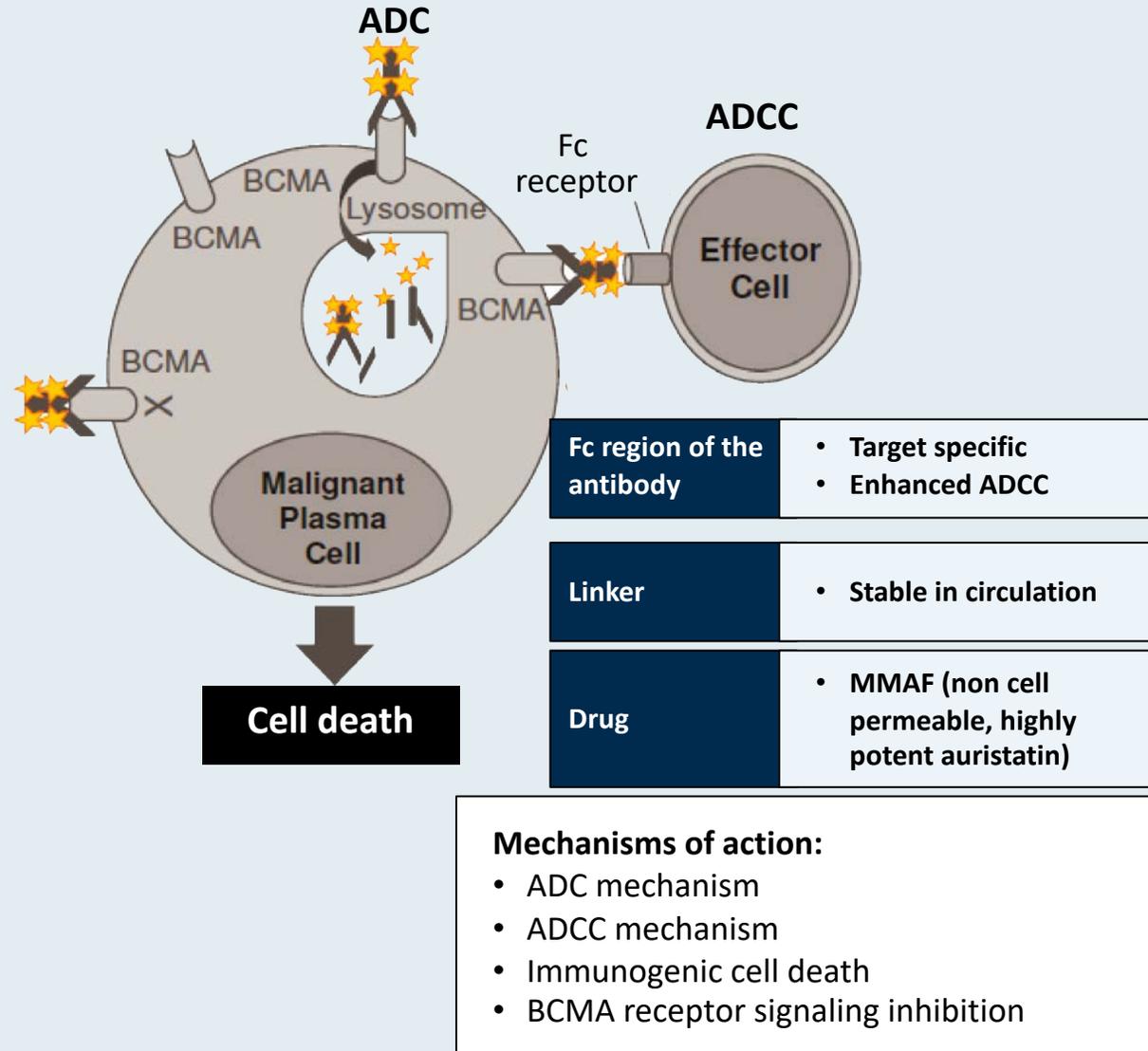
Belantamab mafodotin-blmf was evaluated in DREAMM-2 (NCT 03525678), an open-label, multicenter trial. Patients received either belantamab mafodotin-blmf, 2.5 mg/kg or 3.4 mg/kg intravenously, once every 3 weeks until disease progression or unacceptable toxicity.

Efficacy was based on overall response rate (ORR) and response duration, as evaluated by an independent review committee using the International Myeloma Working Group uniform response criteria. The ORR was 31%. Seventy-three percent of responders had response durations  $\geq 6$  months. These results were observed in patients receiving the recommended dose of 2.5 mg/kg.

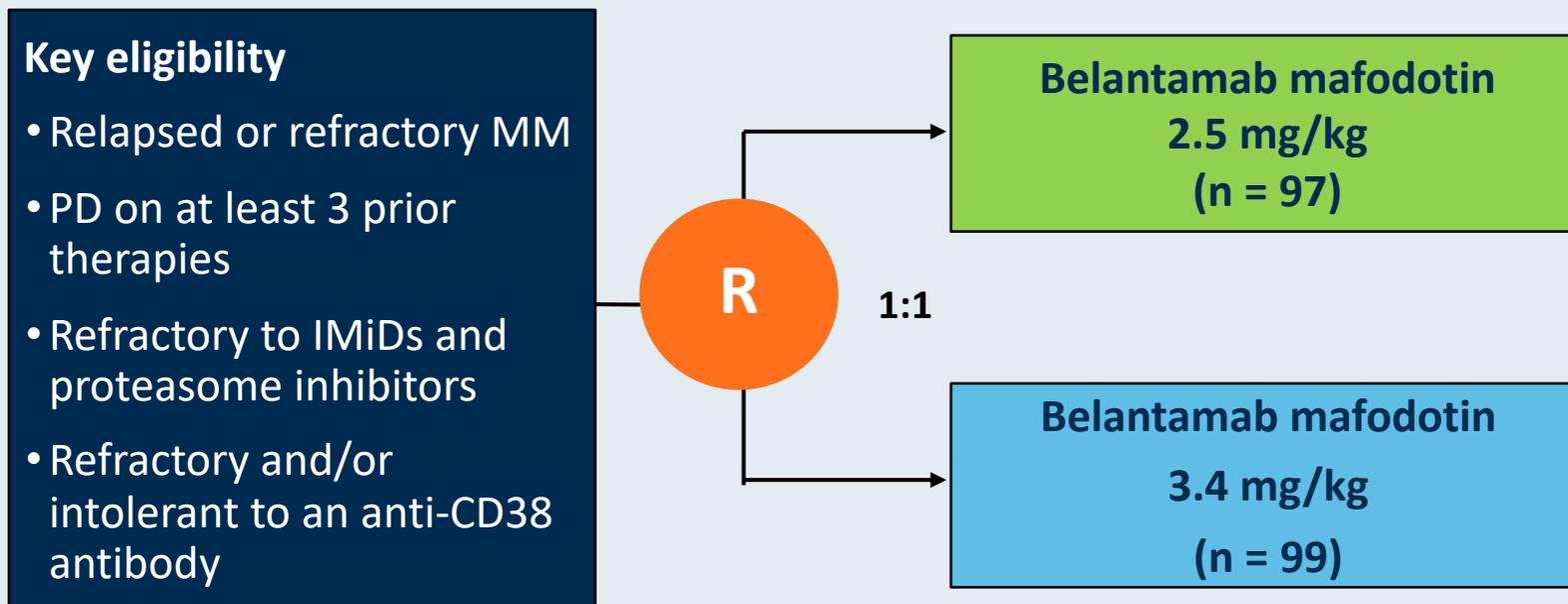
The prescribing information includes a Boxed Warning stating belantamab mafodotin-blmf causes changes in the corneal epithelium resulting in alterations in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes. Ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms should be conducted.”

# Belantamab Mafodotin: 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



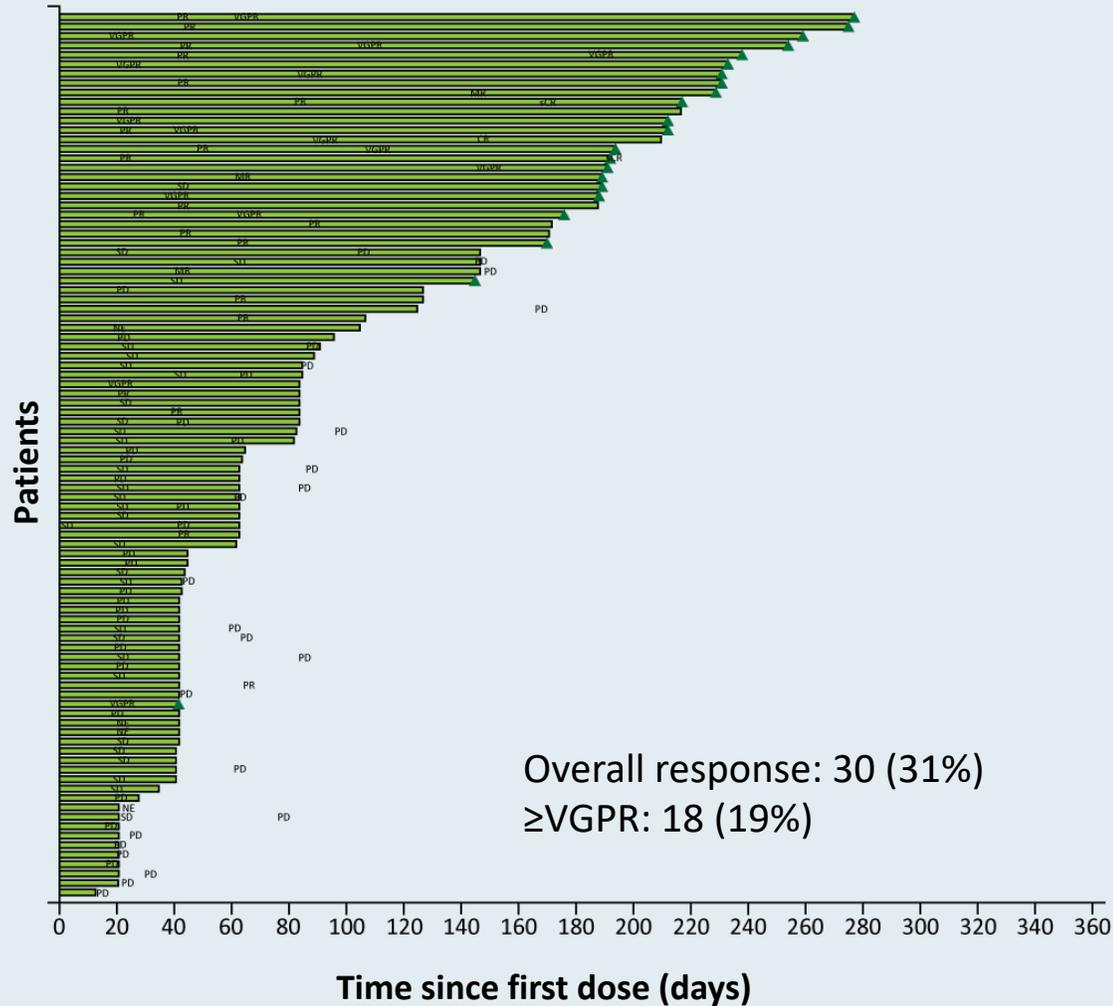
# DREAMM-2 Randomized Phase II Study Design



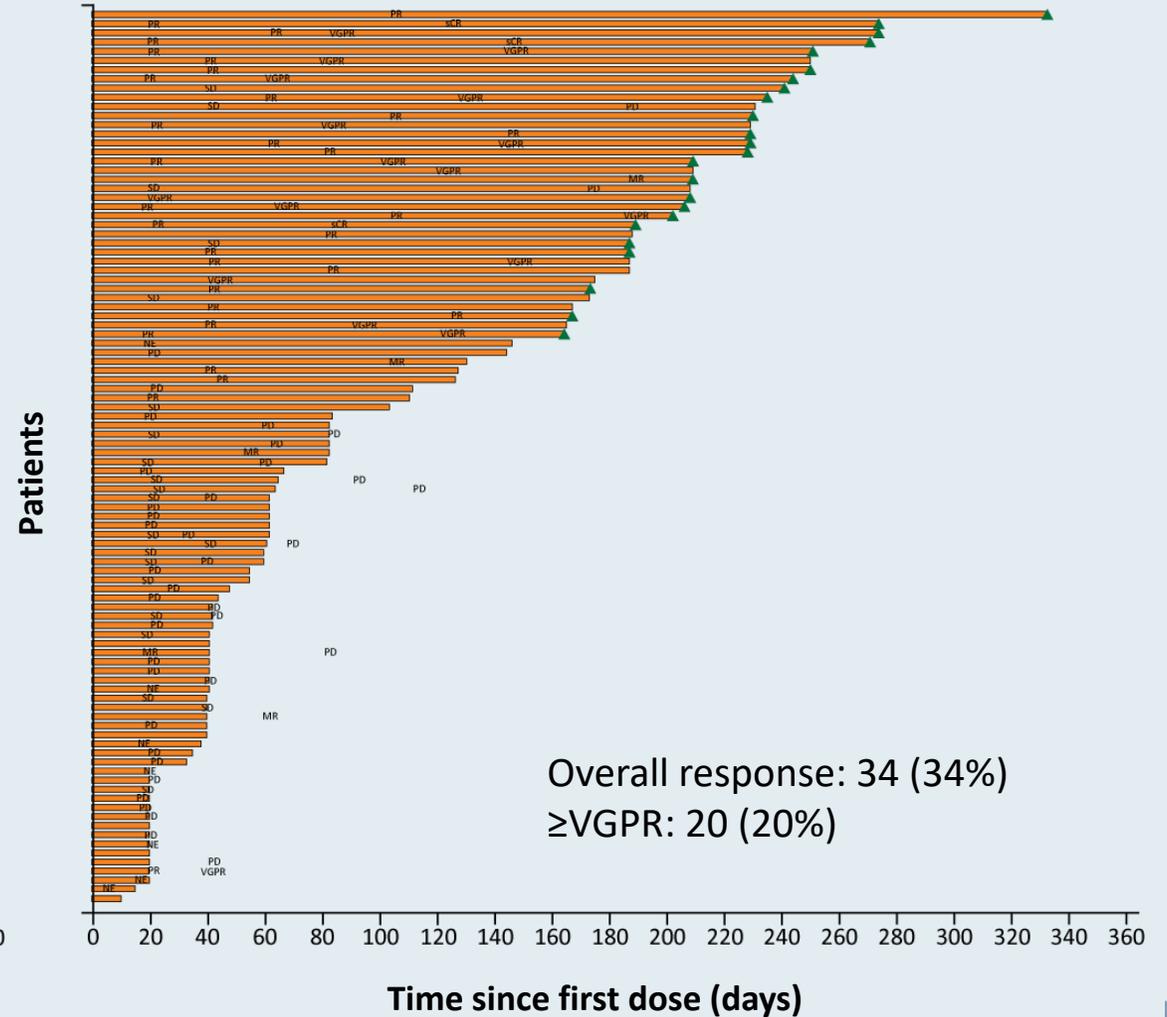
**Primary endpoint:** Overall response in the intent-to-treat population as determined by an independent review committee

# DREAMM-2: Response and Duration of Response

2.5 mg/kg



3.4 mg/kg



## DREAMM-2: Select Adverse Events (AEs)

| <b>AEs of special interest, any grade</b> | <b>Belantamab mafodotin<br/>2.5 mg/kg<br/>(n = 95)</b> | <b>Belantamab mafodotin<br/>3.4 mg/kg<br/>(n = 99)</b> |
|---|--|--|
| Thrombocytopenia                          | 35%  | 59%  |
| Infusion-related reactions                | 21%  | 16%  |
| Corneal events                            | 71%  | 75%  |
| <b>Drug-related serious AEs</b>           |  |  |
| Infusion-related reactions                | 3%   | 2%   |
| Pyrexia                                   | 6%   | 5%   |
| Sepsis                                    | 2%   | 2%   |
| Pneumonia                                 | 4%   | 12%  |

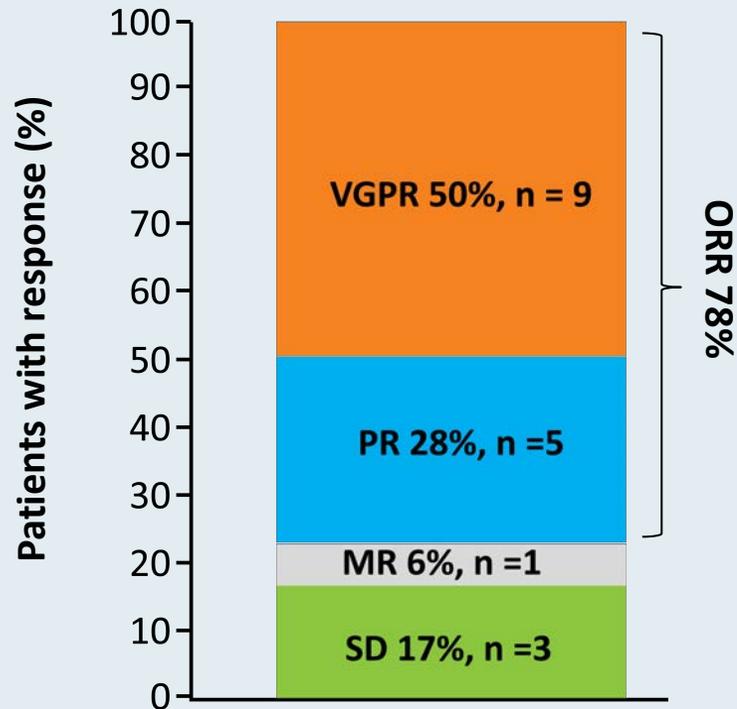
# **DREAMM-6: Safety and Tolerability of Belantamab Mafodotin in Combination with Bortezomib/Dexamethasone in Relapsed/Refractory Multiple Myeloma (RRMM)**

Nooka AK et al.

ASCO 2020;Abstract 8502.

# DREAMM-6 Arm B: Investigator-Assessed Best Confirmed Response

Belamaf 2.5 mg/kg SINGLE + BorDex (n = 18) [Part 1 + Part 2] preliminary best confirmed response data



In patients with  $\geq 1$  prior line of therapy, B-Vd treatment an **ORR of 78%** (95% CI 52.4-93.6)

**CBR** was 83% (95% CI 58.6-96.4)

All patients had an **evaluable response**

**50%** of patients experienced **VGPR**

**DoR** is not yet reached

In patients with  $\geq 1$  prior line of therapy, Vd treatment demonstrated an **ORR of 50%-63%**<sup>1-3</sup>

\* Investigator-assessed best confirmed response (International Myeloma Working Group 2016 criteria). No patients had stringent complete response (sCR), complete response (CR), or progressive disease. B-Vd = belamaf/ bortezomib/desamethasone; BCR = Clinical Benefit Rate (sCR + CR + VGPR + PR + MR). CI = confidence interval based on exact method; MR = minimal response; OR = overall response rate (sCR + CR + VGPR + PR); PR = partial response; SD = stable disease; Vd = bortezomib/dexamethasone; VGPR = very good partial response.

1. Palumbo A, et al. *N Engl J Med* 2016;375:754-66; 2. San Miguel F, et al. *Lancet Oncol.* 2014;15(11):1195-206; 3. Richardson P, et al. *Lancet Oncol.* 2019;20(6):781-94.

# Multiple Myeloma

## Management of Newly Diagnosed Multiple Myeloma

- Dr Zafar: A 53-year-old man with high-risk lambda light chain disease

## Relapsed/Refractory Multiple Myeloma

- Dr Lamar: A 68-year-old woman with relapsed multiple myeloma
- Dr Hart: A 70-year-old man with relapsed multiple myeloma

## Novel Treatment Approaches for Multiple Myeloma

- Dr Zafar: A 67-year-old man with high-risk IgA multiple myeloma
- Dr Peles: A 75-year-old woman with high-risk smoldering myeloma

# Case Presentation – Dr Zafar: A 67-year-old man with high-risk IgA multiple myeloma



Dr Syed Zafar

- 8/2017: Diagnosed with IgA multiple myeloma, with t(4:14), gain 1q, trisomy 9, 11, 15
  - Osteolytic lesion involving right humeral head → palliative RT
- 10/2017 – 1/2018: Lenalidomide/bortezomib/dexamethasone, with CR → ASCT, with MRD
- 6/2018 – 5/2019: Maintenance lenalidomide/ixazomib/dexamethasone → Lenalidomide → PD
- 6/2019 – 11/2019: Daratumumab/pomalidomide/dexamethasone → PD
- 1/2020: MM115 trial with antibody-drug conjugate (ADC) against BCMA (CC99712), with CR
  - Study drug held for 1 month due to sensory neuropathy
  - 4/2020: Continued CR, but treatment stopped due to persistent Grade 3 sensory neuropathy
  - 9/2020: Still in CR

## Questions

- How do we select patients for ADCs now that they're available? Who would we expect to benefit from ADC therapy? How do we monitor and mitigate toxicities?
- If this patient has disease progression, what would be the next treatment – CAR T-cell therapy, CELMoDs, or Selinexor?

# Case Presentation – Dr Peles: A 75-year-old woman with high-risk smoldering myeloma



**Dr Shachar Peles**

- IgG lambda M spike 2.3g/dL, lambda 250, kappa 17.22, kappa/lambda 0.07
- Hb 12.0, normal renal function, normal calcium
- Bone marrow: Monoclonal lambda restricted plasma cells, ~20-30% cellularity
- Karyotype: 46, XX [20]
- FISH: Deletion 13q (whole arm deletion)/monosomy 13; monosomy 9 (-9)
- PET: No bone lesions

## Questions

- What would be your approach for this patient? Would you favor observation or treatment?
- How frequently do you monitor patients who are being observed? How often do you repeat bone imaging or bone marrow biopsies?

**The risk of cytokine release syndrome and neurotoxicity with BCMA-targeted CAR T-cell therapy in relapsed MM is generally less than that with the CD19-targeted agents used in lymphoma.**

- a. Agree
- b. Disagree
- c. I don't know

# Idecabtagene Vicleucel (Ide-cel; bb2121), a BCMA-Targeted CAR T-Cell Therapy, in Patients with Relapsed and Refractory Multiple Myeloma (RRMM): Initial KarMMa Results

Munshi NC et al.

ASCO 2020;Abstract 8503.

# **Update of CARTITUDE-1: A Phase Ib/II Study of JNJ-4528, a B-Cell Maturation Antigen (BCMA) Directed CAR-T-Cell Therapy, in Relapsed/Refractory Multiple Myeloma**

Berdeja JG et al.

ASCO 2020;Abstract 8505.

# Orvacabtagene Autoleucel (Orva-cel), a B-Cell Maturation Antigen (BCMA)-Directed CAR T Cell Therapy for Patients (pts) with Relapsed/Refractory Multiple Myeloma (RRMM): Update of the Phase 1/2 EVOLVE Study (NCT03430011)

Mailankody S et al.

ASCO 2020;Abstract 8504.

# ASCO 2020: 3 BCMA CAR-T Studies

## Characteristics Summary

|                              | KarMMA: idecabtagene vicleucel<br>(n = 128) | EVOLVE: orvacabtagene autoleucel<br>(n = 62)    | CARTITUDE-1: JNJ-4528<br>(n = 29)  |
|------------------------------|---|---|--|
| Age                          | 61 (33-78)                                  | 61 (33-77)                                      | 60 (50-75)   |
| High risk cytogenetics, %    | 35  | 41*   | 27   |
| Tumor burden in BM, %        | >50% PC = 51                                | —   | ≥60% PC = 24   |
| Extramedullary PCs, %        | 39  | 23  | 10   |
| Median prior line of therapy | 6 (3-16)                                    | 6 (3-18)  | 5 (3-18)   |
| Triple refractory, %         | 84  | 94  | 86   |
| Bridging therapy, %          | 88  | 63  | 79   |
| Unique properties            | Human BCMA,<br>4-1BB, CD3z                  | Modified spacer,<br>CD4: CD8 enriched<br>for CM | Median cell dose<br>0.72x10 <sup>6</sup> cells/kg<br>2 BCMA single chain<br>antibodies |

\* Included +1q21

# ASCO 2020: 3 BCMA CAR-T Studies

## Safety

|                                  | KarMMa               | EVOLVE              | CARTITUDE-1          |
|----------------------------------|----------------------|---------------------|----------------------|
| ANC $\geq$ G3, % $\downarrow$    | 89                   | 90                  | 100                  |
| plts $\geq$ G3, % $\downarrow$   | 52                   | 47                  | 69                   |
| CRS: all, $\geq$ G3, %           | 84, 6                | 89, 3               | 93, 7                |
| Med. time to CRS, duration, days | 1 (1-12)<br>5 (1-63) | 2 (1-4)<br>4 (1-10) | 7 (2-12)<br>4 (2-64) |
| ICANS: all, $\geq$ G3, %         | 17, 3                | 13, 3               | 10, 3                |
| HLH/MAS, %                       | —                    | 5                   | ? 7 (lfts)           |
| Infections: all, $\geq$ G3 %     | 69, —                | 40, 13              | —, 19                |
| Toci/steroid/<br>anakinra use, % | 52/15/0              | 76/52/23            | 79/21/21             |

? This was not listed at MAS/HLH, I am just speculating  $\rightarrow$   
could this have been early MAS

## Efficacy

|  | KarMMa<br>(n = 128) | EVOLVE<br>(n = 62) | CARTITUDE-1<br>(n = 29) |
|--|---------------------|--------------------|-------------------------|
| ORR, %                                       | 73 (66-81)          | 92                 | 100                     |
| sCR/CR, %                                    | 33                  | 36                 | 86                      |
| MRD neg $\geq 10^{-5}$ , %<br>(of evaluable) | 94                  | 84                 | 81                      |
| PFS, DoR, months                             | 8.8/10.7            | NR*                | NR**                    |
| Screened Apheresed<br>Treated                | 150<br>140<br>128   | —                  | 35<br>35<br>29          |

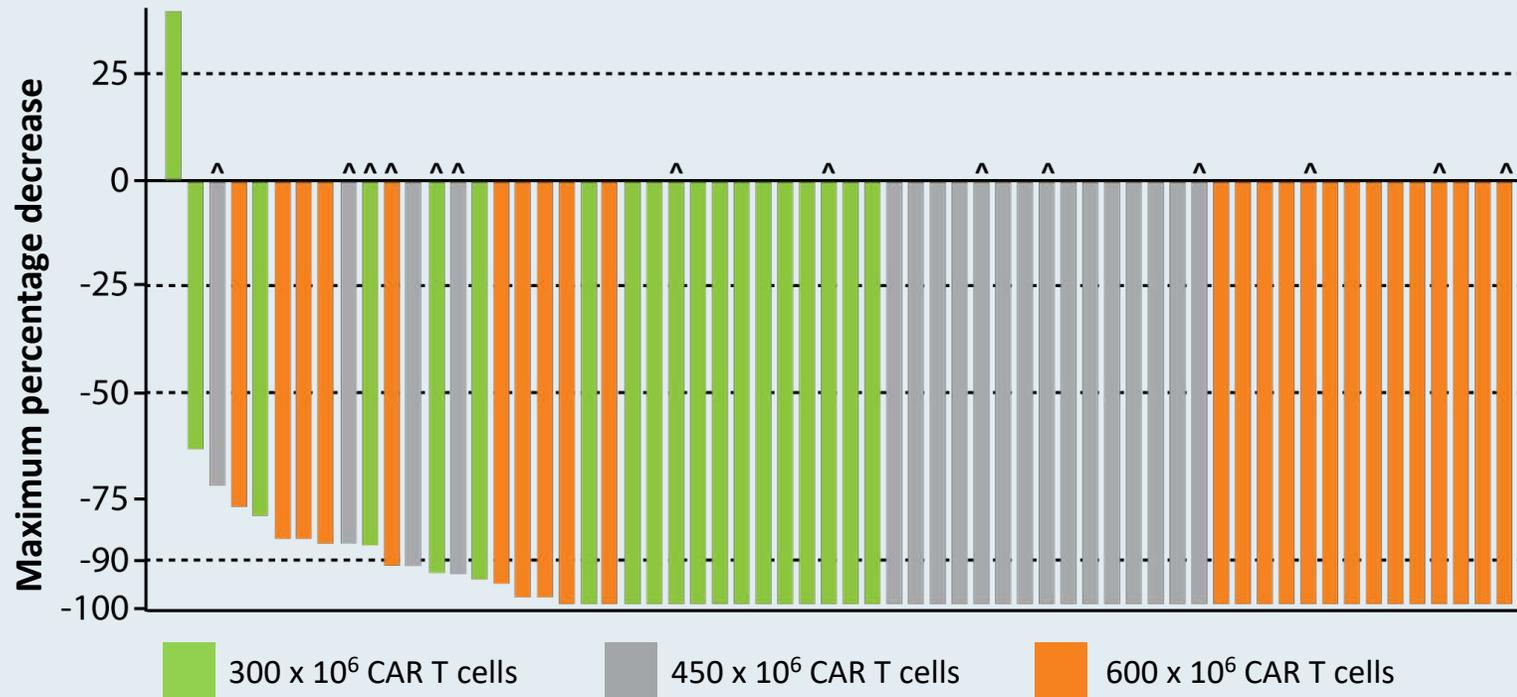
\* 300 x 10<sup>6</sup> cell dose cohort (lowest) = PFS 9.3 months,  
other med F/U = 8.8 and 2.3 month

\*\* 9 mo PFS = 86%

# EVOLVE BCMA CAR-T Study

Look at that waterfall!

EVOLVE: Deep tumor burden reduction across dose levels



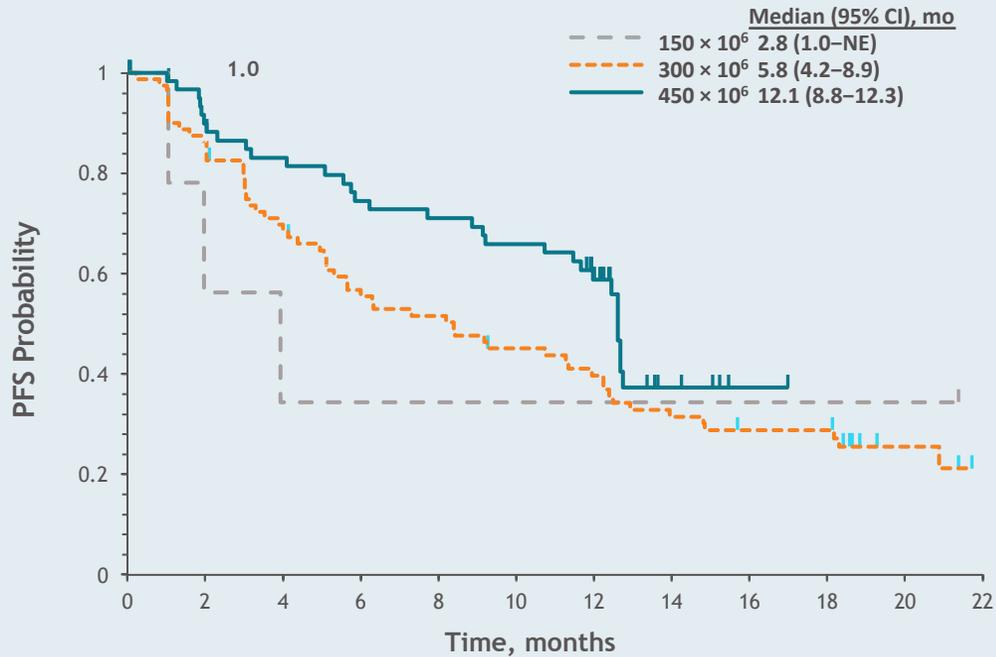
Serological responses\* were observed in all patients treated at 450 x 10<sup>6</sup> and 600 x 10<sup>6</sup> DLs

\* Involved serum or urine paraprotein, free light chains. ^ Patient with baseline extramedullary plasmacytoma.

# Idecabtagene Vicleucel BCMA CAR-T Study

## Progression-free survival with single-cell infusion!

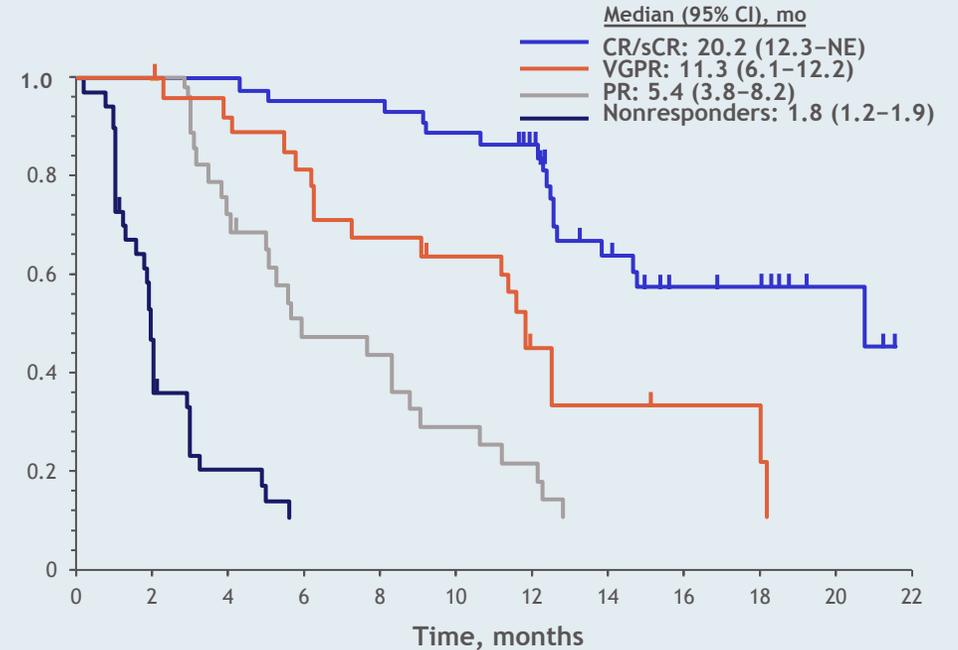
PFS by Target Dose



| At risk, N            | 0  | 2  | 4  | 6  | 8  | 10 | 12 | 14 | 16 | 18 | 20 | 22 |
|-----------------------|----|----|----|----|----|----|----|----|----|----|----|----|
| 150 × 10 <sup>6</sup> | 4  | 2  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 0  |
| 300 × 10 <sup>6</sup> | 70 | 56 | 42 | 33 | 29 | 24 | 17 | 14 | 11 | 7  | 2  | 0  |
| 450 × 10 <sup>6</sup> | 54 | 44 | 40 | 36 | 34 | 31 | 17 | 4  | 1  | 0  | 0  | 0  |

- PFS increased with higher target dose; median PFS was 12 mo at 450 × 10<sup>6</sup> CAR+ T cells

PFS by Best Response



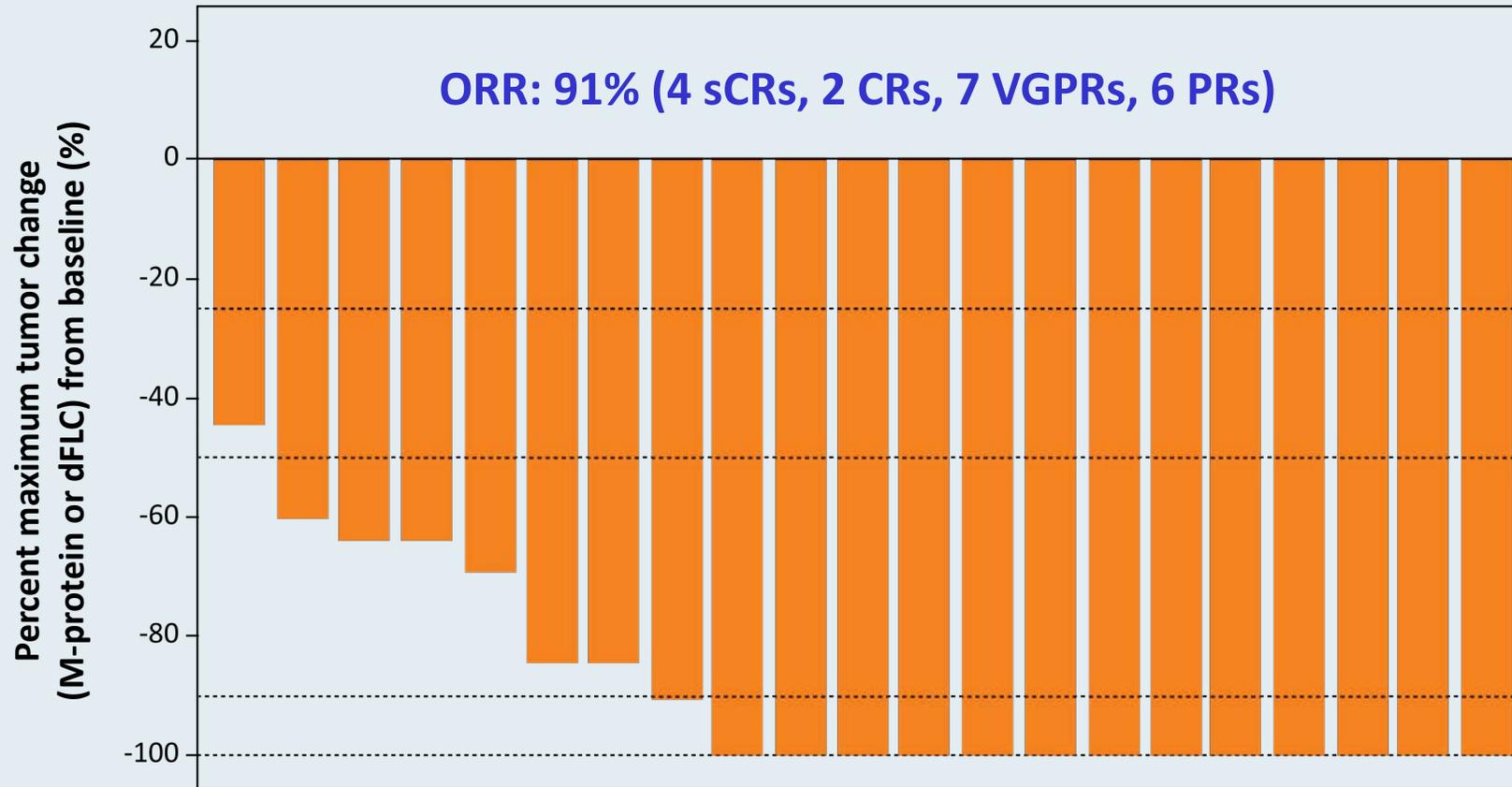
|               |    |    |    |    |    |    |    |    |    |   |   |   |
|---------------|----|----|----|----|----|----|----|----|----|---|---|---|
| CR/sCR        | 42 | 42 | 42 | 40 | 39 | 37 | 26 | 16 | 11 | 8 | 4 | 0 |
| VGPR          | 25 | 25 | 22 | 20 | 16 | 14 | 8  | 3  | 2  | 0 | 0 | 0 |
| PR            | 27 | 16 | 10 | 9  | 5  | 1  | 0  | 0  | 0  | 0 | 0 | 0 |
| Nonresponders | 34 | 8  | 83 | 70 | 64 | 56 | 35 | 19 | 13 | 8 | 4 | 0 |

- PFS increased by depth of response; median PFS was 20 mo in patients with CR/sCR

# CARTITUDE-1: A Phase Ib/II Study of JNJ-4528 in R/R MM

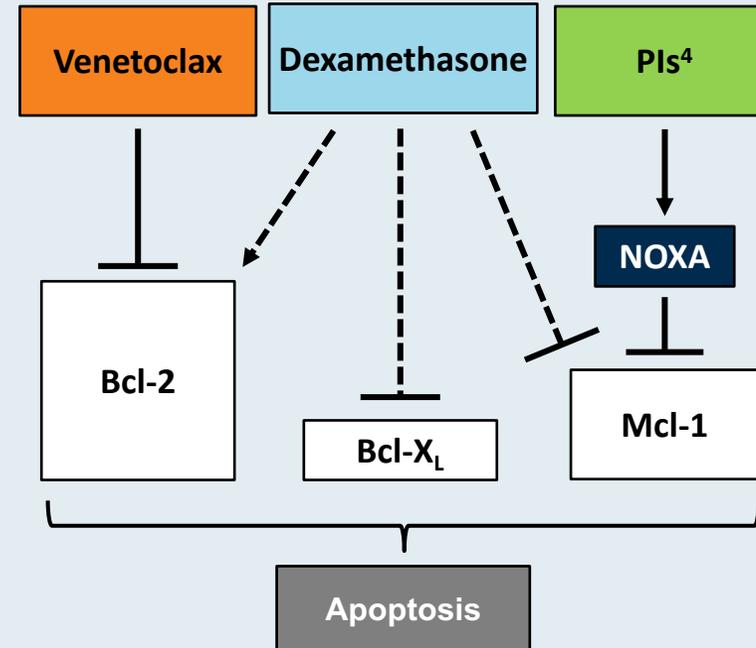
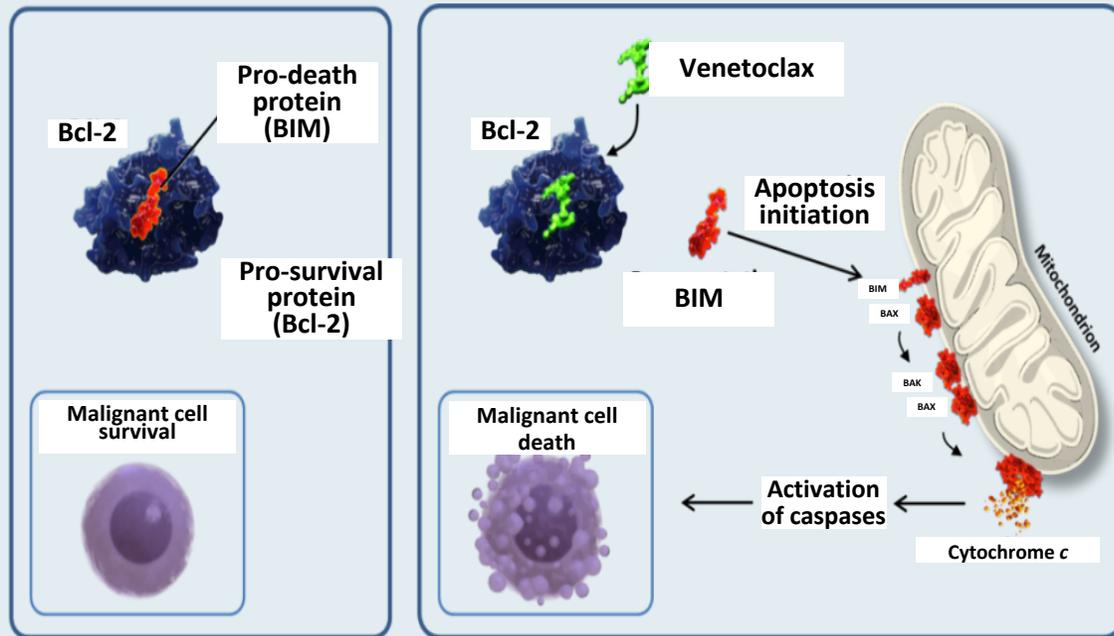
Median prior lines of treatment: 5 (range: 3-16)

Maximum Reduction in Tumor Burden from Baseline in Response-Evaluable Patients (n = 21)



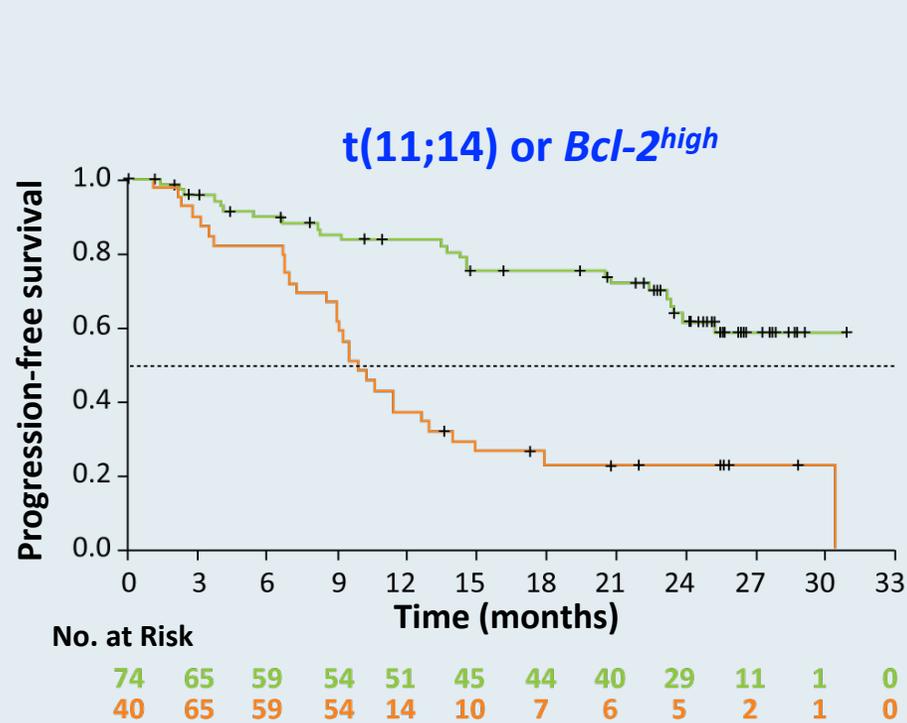
# Rationale for Targeting Bcl-2 in MM

- Pro-survival proteins Bcl-2, Mcl-1 and Bcl-X<sub>L</sub> promote MM cell survival<sup>1</sup>
- Venetoclax is a highly selective, potent, oral Bcl-2 inhibitor<sup>2</sup>
- Dexamethasone is a glucocorticoid that can indirectly promote Bcl-2 dependency in MM cells<sup>3</sup>

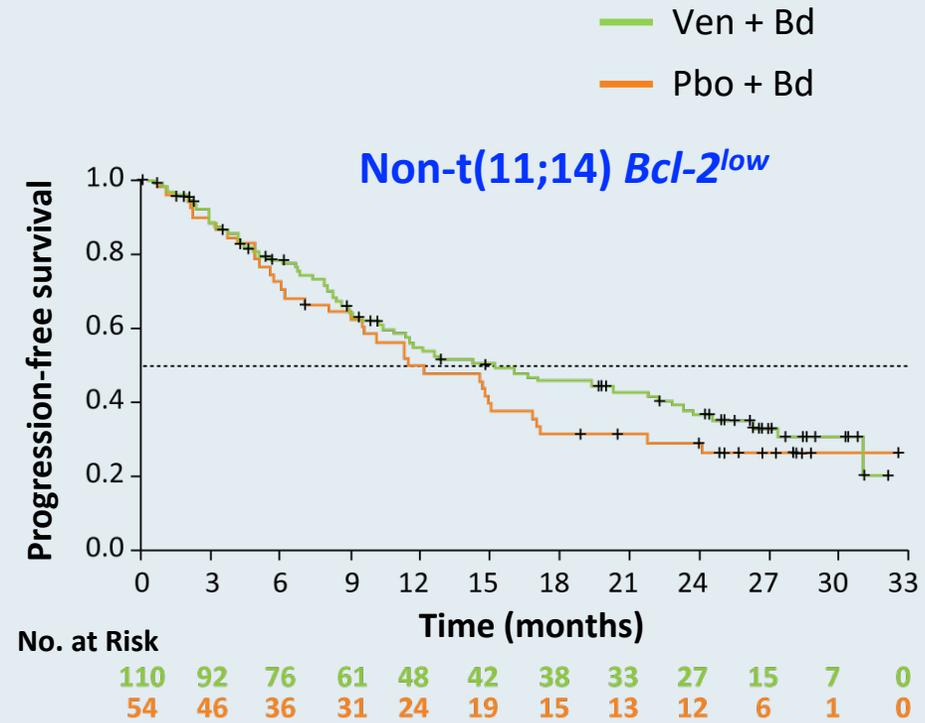


<sup>1</sup> Touzeau C et al. *Leukemia* 2018;32(9):1899-907; <sup>2</sup> Souers AJ et al. *Nat Med* 2013; 19(2):202-8; <sup>3</sup> Matulis SM et al. *Leukemia* 2016;30(5):1086-93; <sup>4</sup> Ponder KG et al. *Cancer Biol Ther* 2016;17(7):769-77.

# BELLINI: PFS in t(11;14) and Bcl-2 Subsets



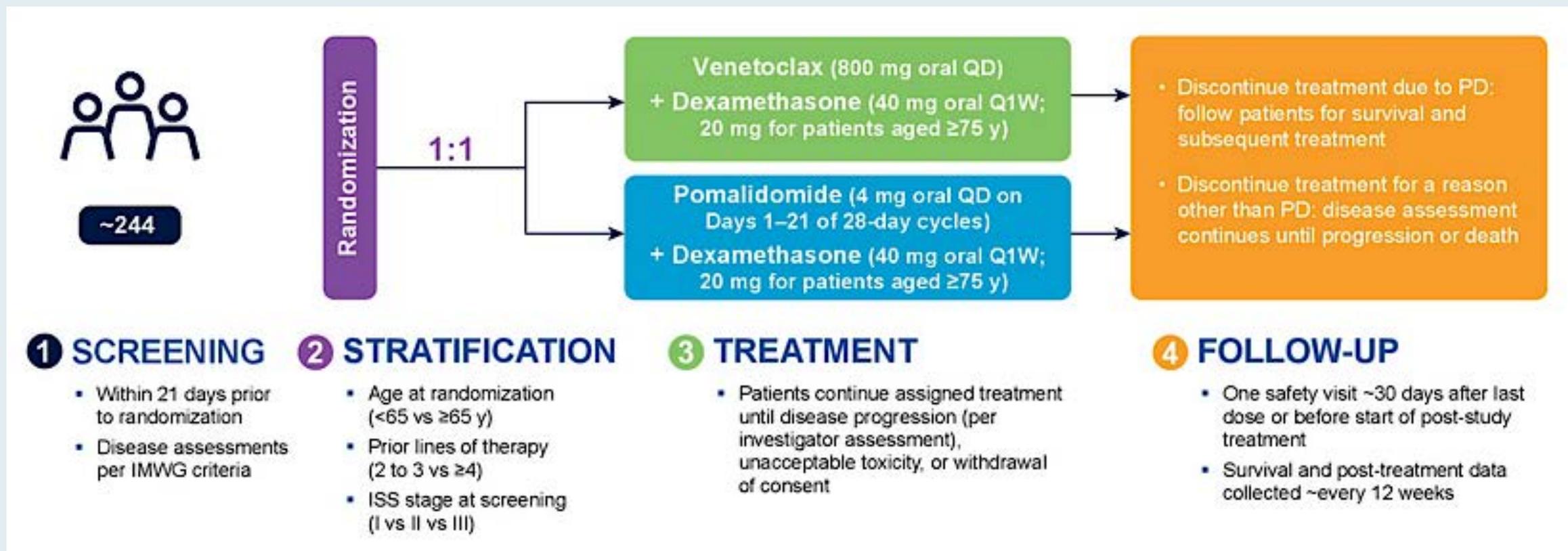
| PFS            | Ven + Bd    | Pbo + Bd |
|----------------|-------------|----------|
| Median, months | Not reached | 9.9      |
| HR (95% CI)    | 0.30        |          |
| p-value        | <0.001      |          |



| PFS            | Ven + Bd | Pbo + Bd |
|----------------|----------|----------|
| Median, months | 15.3     | 11.5     |
| HR (95% CI)    | 0.85     |          |
| p-value        | 0.451    |          |

High Bcl-2 gene expression was determined by qPCR.

# CANOVA: A Phase III Trial of Venetoclax or Pomalidomide in Combination with Dexamethasone in Patients with t(11;14)-Positive Relapsed/Refractory Multiple Myeloma



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

***We are taking a short break!***

**The program will resume at 10:45 AM ET**

***Up Next...***

**Drs Brad Kahl and Loretta Nastoupil  
discuss the management of  
chronic lymphocytic leukemia and lymphomas**

# **Current Concepts and Recent Advances in Oncology**

## ***A Daylong Clinical Summit Hosted in Partnership with Florida Cancer Specialists***

**Saturday, October 24, 2020  
8:30 AM – 4:30 PM ET**

### **Faculty**

**Arjun Balar, MD  
Johanna Bendell, MD  
Axel Grothey, MD  
Brad S Kahl, MD  
Shaji K Kumar, MD**

**Kathleen Moore, MD  
Loretta Nastoupil, MD  
William K Oh, MD  
David M O'Malley, MD  
Robert Z Orlowski, MD, PhD**

**Gregory J Riely, MD, PhD  
Hope S Rugo, MD  
David R Spigel, MD  
Sara M Tolaney, MD, MPH**

### **Moderator**

**Neil Love, MD**

# Agenda

**Module 1 — Lung Cancer:** *Drs Riely and Spigel*

**Module 2 — Multiple Myeloma:** *Drs Kumar and Orlowski*

**Module 3 — Chronic Lymphocytic Leukemia and Lymphomas:**  
*Drs Kahl and Nastoupil*

**Module 4 — Gastrointestinal Cancers:** *Drs Bendell and Grothey*

**Module 5 — Genitourinary Cancers:** *Drs Balar and Oh*

**Module 6 — Gynecologic Cancers:** *Drs Moore and O'Malley*

**Module 7 — Breast Cancer:** *Drs Rugo and Tolaney*

# Chronic Lymphocytic Leukemia and Lymphomas Faculty



**Brad S Kahl, MD**  
Professor of Medicine  
Washington University School of Medicine  
Director, Lymphoma Program  
Siteman Cancer Center  
St Louis, Missouri



**Loretta Nastoupil, MD**  
Associate Professor  
Department of Lymphoma/Myeloma  
The University of Texas  
MD Anderson Cancer Center  
Houston, Texas

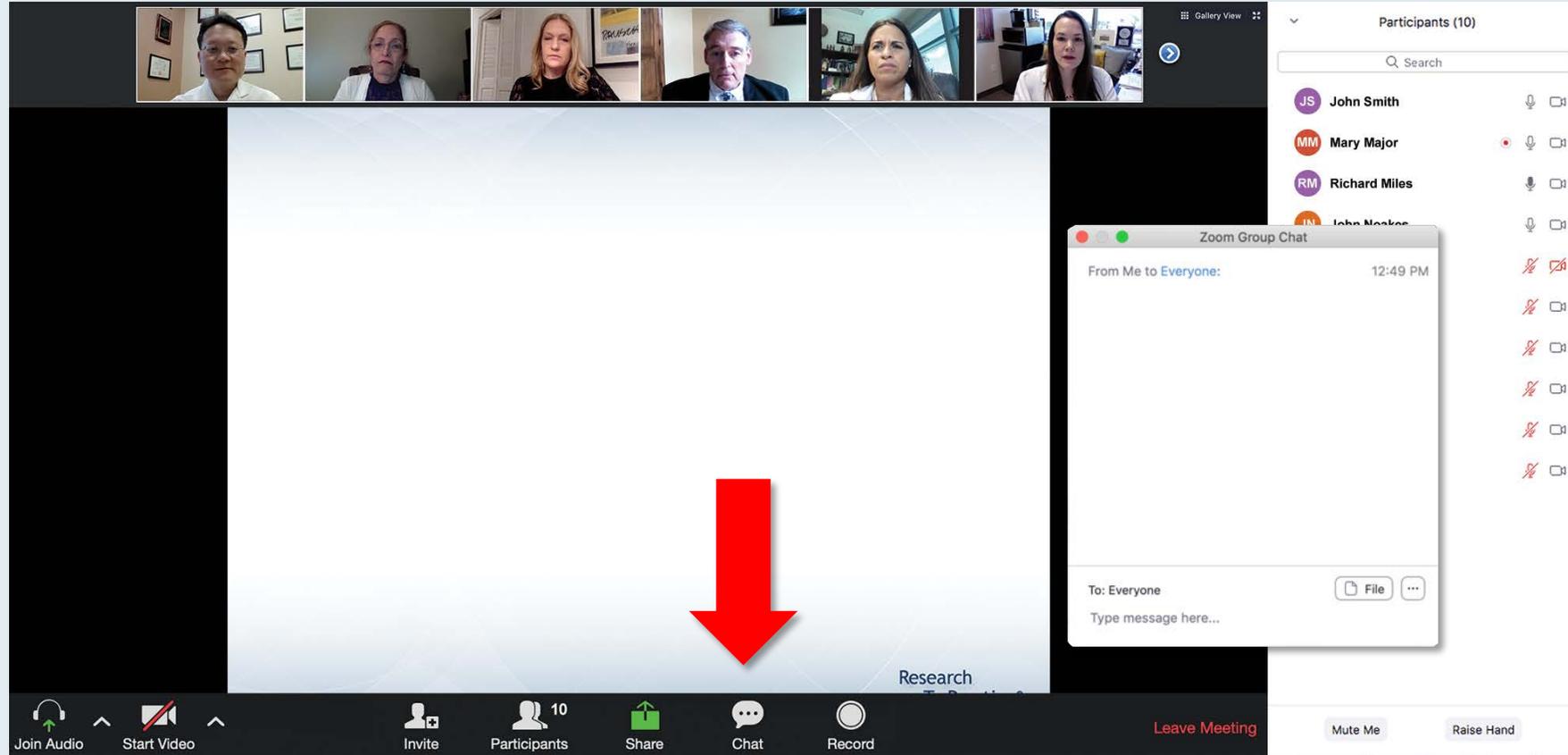
# Dr Kahl — Disclosures

|   |  |
|---|--|
| <b>Advisory Committee</b>               | AstraZeneca Pharmaceuticals LP   |
| <b>Consulting Agreements</b>            | AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Genentech, a member of the Roche Group, Pharmacyclics LLC, an AbbVie Company, Roche Laboratories Inc, TG Therapeutics Inc |
| <b>Contracted Research</b>              | Acerta Pharma — A member of the AstraZeneca Group, BeiGene, Celgene Corporation, Genentech, a member of the Roche Group  |
| <b>Data and Safety Monitoring Board</b> | Celgene Corporation  |

## Dr Nastoupil — Disclosures

|   |   |
|---|---|
| <b>Advisory Committee</b>                         | Bayer HealthCare Pharmaceuticals, Celgene Corporation, Gamida Cell, Genentech, a member of the Roche Group, Janssen Biotech Inc, Kite, A Gilead Company, Novartis, Pfizer Inc |
| <b>Contracted Research</b>                        | Celgene Corporation, Epizyme Inc, Genentech, a member of the Roche Group, Janssen Biotech Inc, Merck, Novartis, Pfizer Inc  |
| <b>Data and Safety Monitoring Board/Committee</b> | Denovo Biopharma  |

# We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

# FCS Contributing Oncologists



**Mamta Choksi, MD**  
New Port Richey, Florida



**Zanetta S Lamar, MD**  
Naples, Florida



**Uday Dandamudi, MD**  
New Port Richey, Florida



**Vikas Malhotra, MD**  
Spring Hill, Florida



**Lowell L Hart, MD**  
Fort Myers, Florida



**Shachar Peles, MD**  
Lake Worth, Florida



**Maen Hussein, MD**  
Tavares, Florida



**Syed F Zafar, MD**  
Fort Myers, Florida

# Agenda

## Module 1: Chronic Lymphocytic Leukemia (CLL)

- Dr Malhotra: A 79-year-old man with CLL – trisomy 12, unmutated IgVH
- Dr Peles: A 45-year-old man with favorable-risk CLL

## Module 2: Follicular Lymphoma

- Dr Zafar: A 78-year-old woman with follicular lymphoma

## Module 3: Diffuse Large B-Cell Lymphoma (DLBCL)

- Dr Hart: A 58-year-old man with relapsed DLBCL

## Module 4: Mantle Cell Lymphoma (MCL)

- Dr Malhotra: A healthy, active 73-year-old man with MCL
- Dr Peles: A 73-year-old woman with MCL

## Module 5: Hodgkin Lymphoma

- Dr Choksi: A 75-year-old woman with recurrent Hodgkin lymphoma

# Case Presentation – Dr Malhotra: A 79-year-old man with CLL – trisomy 12, unmutated IgVH



Dr Vikas Malhotra

- 2018: Diagnosed with CLL, trisomy 12, unmutated IgVH
- 4/2020: Progressive adenopathy, fatigue, night sweats
  - CBC: WBC 71K, 90% lymphocytes
- Acalabrutinib 100 mg BID
- Recent CBC: Normal; Adenopathy resolved

## Questions

- How do you choose first-line therapy – with either ibrutinib, acalabrutinib or venetoclax combinations?
- How would you treat a patient who has had disease progression on both a BTK inhibitor and venetoclax? Are there any encouraging clinical trials in this setting?

# Case Presentation – Dr Peles: A 45-year-old man with favorable-risk CLL



Dr Shachar Peles

- Presents with night sweats, right neck adenopathy, LUQ pain, early satiety, 10-lb weight loss, and dyspnea with exertion
- WBC: 204K, with 92% lymphocytes, Hb 8.3, Plt 61, LDH and Haptoglobin normal
- Massive splenomegaly (32-cm), generalized adenopathy
- FLOW: CD5/CD23+ mature B lymphocytes
- FISH: 13q14 deletion, no Del17p, IgVH mutated

## Questions

- What is the ideal front-line treatment for this patient – FCR? Before administering FCR, do you check for p53 mutation by NGS, or do you rely upon FISH for del17p?
- Instead of FCR, would you administer a BTK inhibitor, and if so, do you prefer acalabrutinib or ibrutinib? Would you combine one of these with an anti-CD20 monoclonal antibody, and do you prefer rituximab or obinutuzumab?
- What are your thoughts about venetoclax and obinutuzumab?

# What is your usual preferred initial regimen for a 60-year-old patient with CLL with mutated IGHV and no del(17p) or TP53 mutation who requires treatment?

- a. FCR
- b. Ibrutinib
- c. Ibrutinib + rituximab
- d. Ibrutinib + obinutuzumab
- e. Acalabrutinib
- f. Acalabrutinib + obinutuzumab
- g. Venetoclax + obinutuzumab
- h. Other

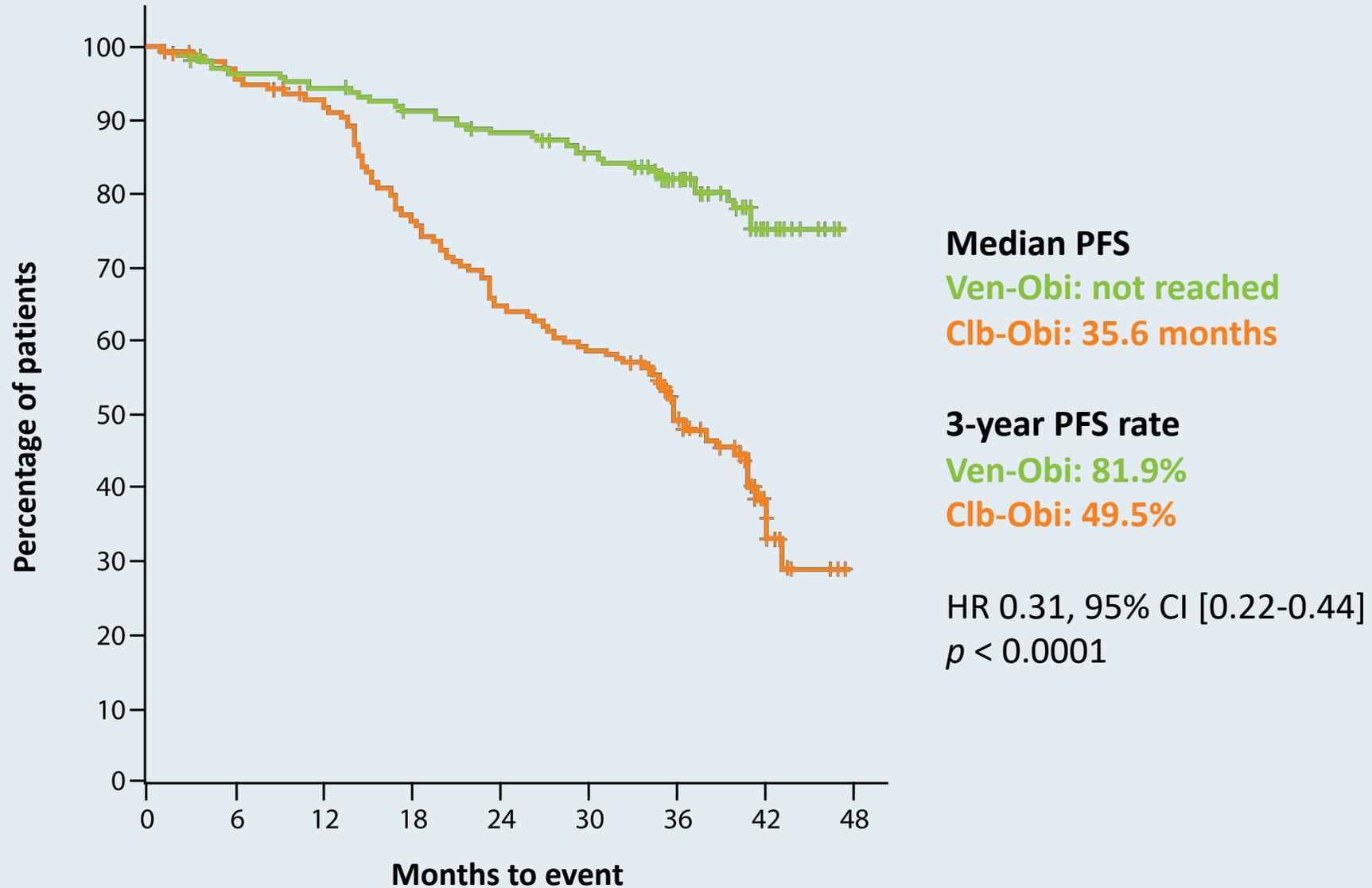


## Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial

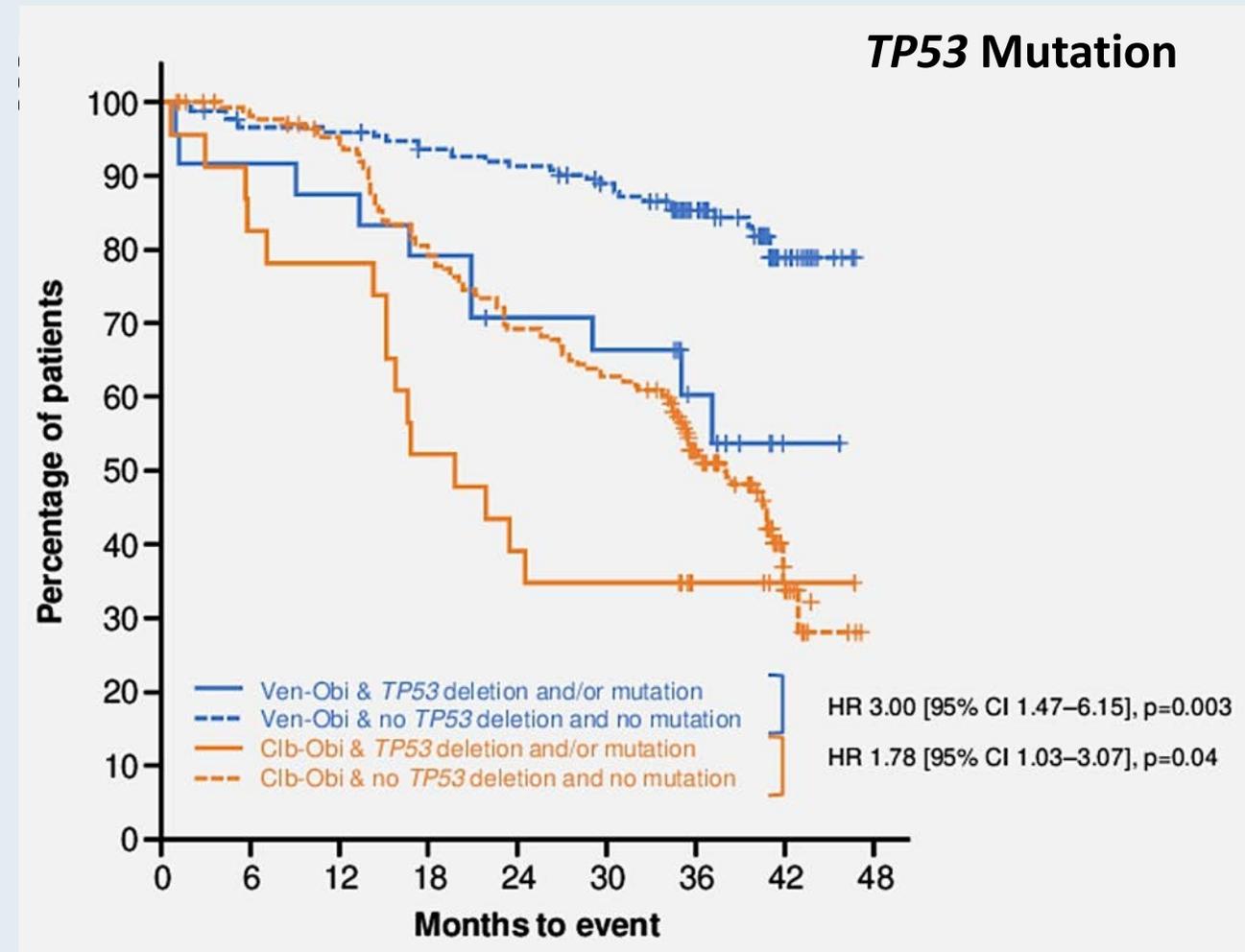
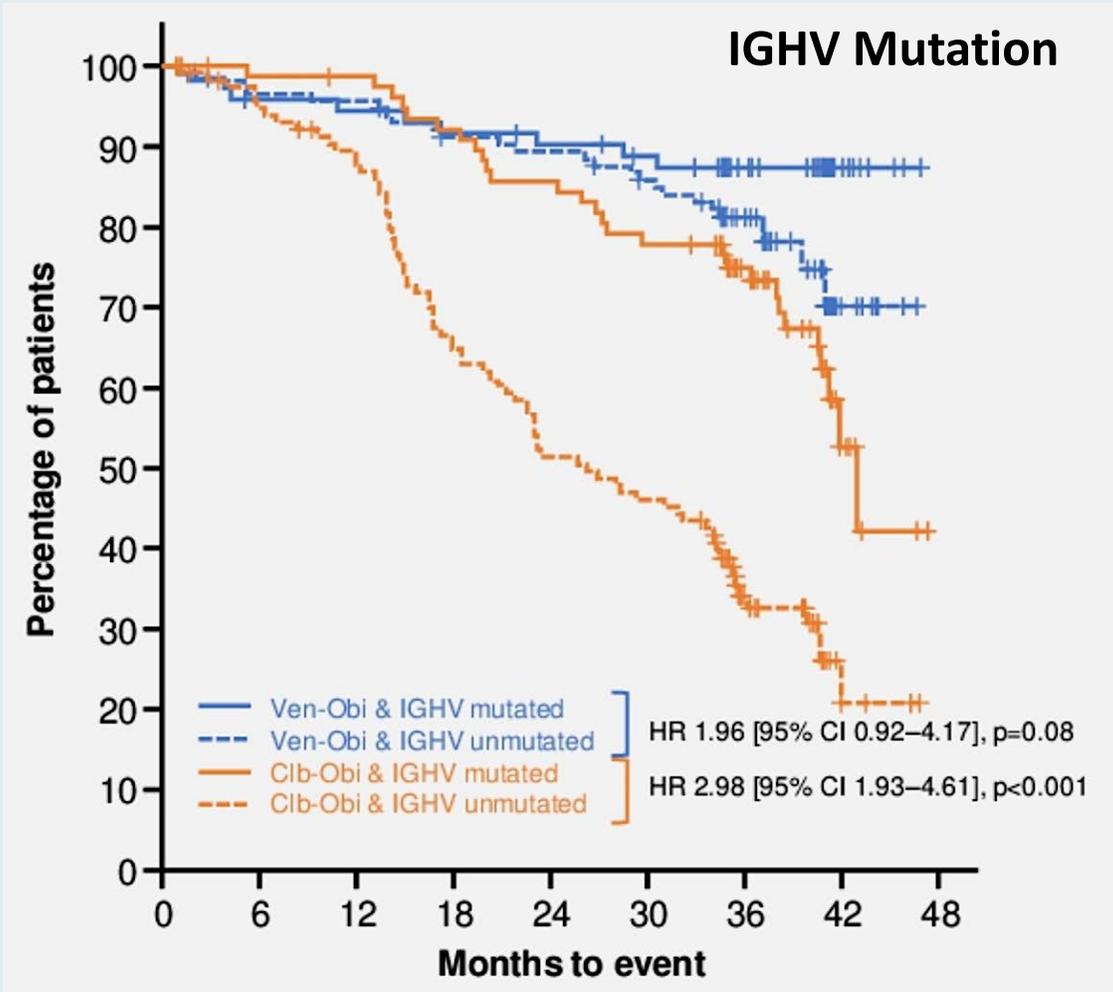
*Othman Al-Sawaf, Can Zhang, Maneesh Tandon, Arijit Sinha, Anna-Maria Fink, Sandra Robrecht, Olga Samoylova, Anna M Liberati, Javier Pinilla-Ibarz, Stephen Opat, Liliya Sivcheva, Katell Le Dû, Laura M Fogliatto, Carsten U Niemann, Robert Weinkove, Sue Robinson, Thomas J Kipps, Eugen Tausch, William Schary,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

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

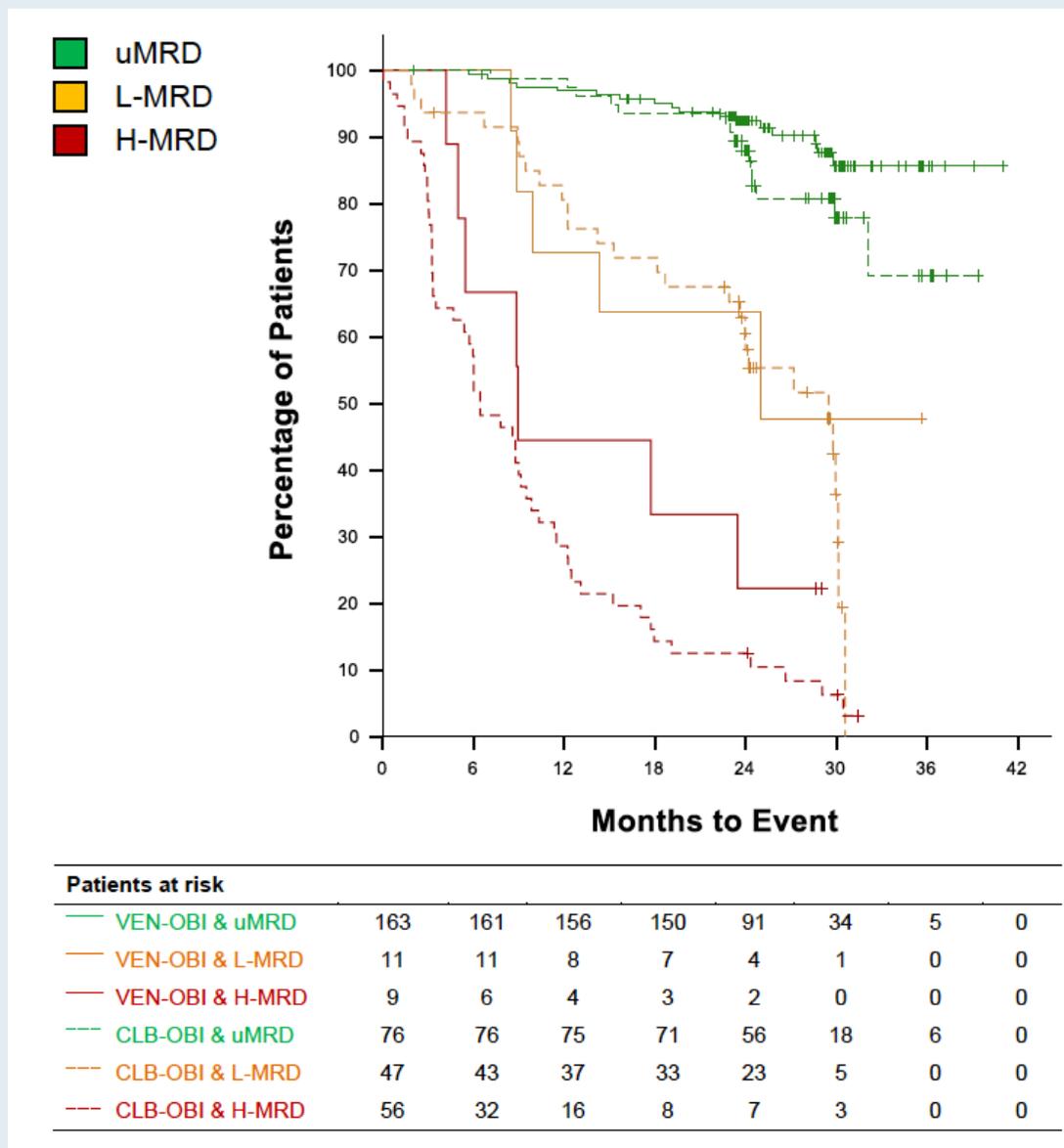
# CLL14: Updated 3-Year PFS



# CLL14: PFS by IGHV and TP53 Mutation Status



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



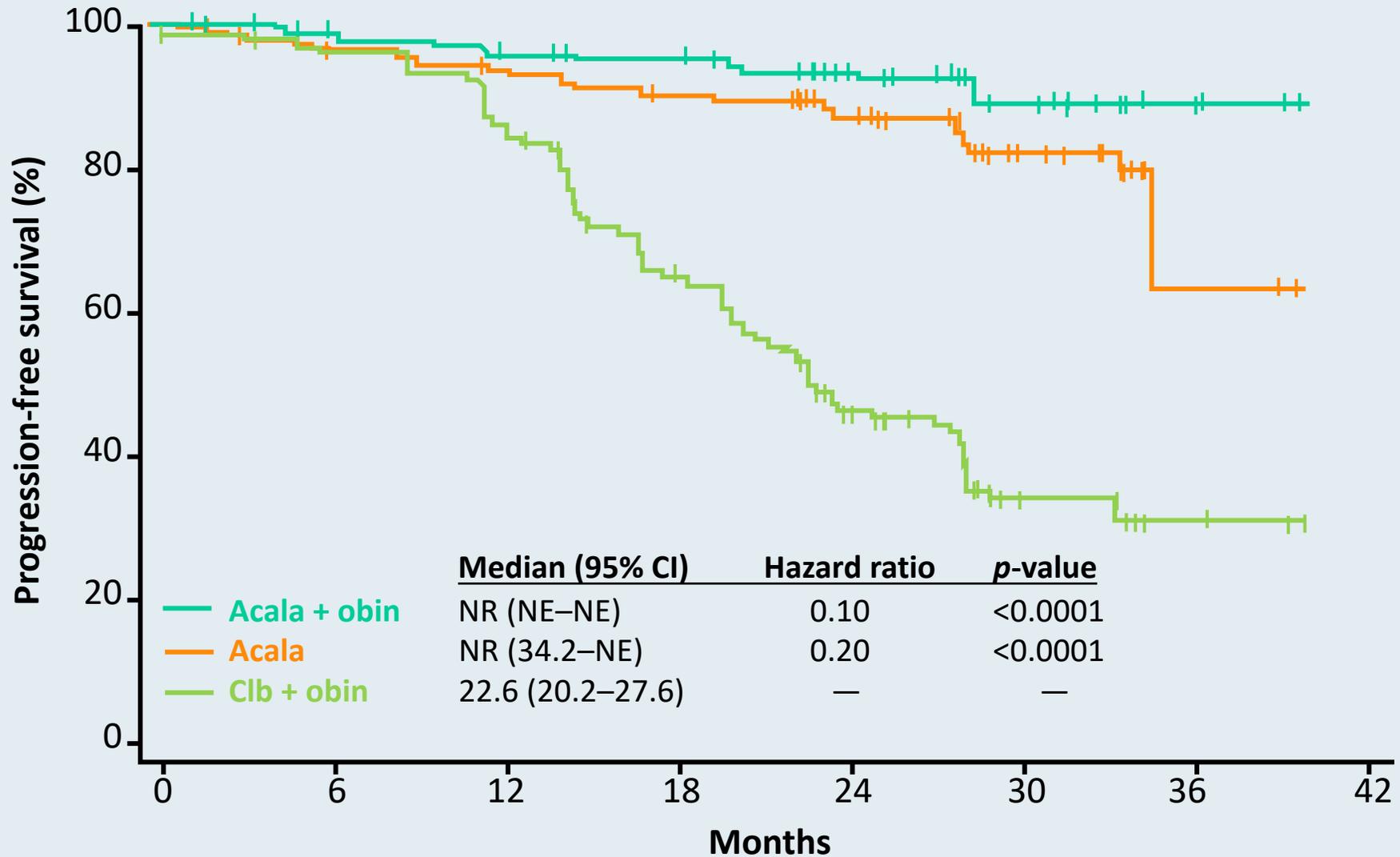


## **Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE-TN): a randomised, controlled, phase 3 trial**

*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 Munugalavadla, Priti Patel, Min Hui Wang, Sofia Wong, John C Byrd*

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

# ELEVATE-TN: PFS (IRC)



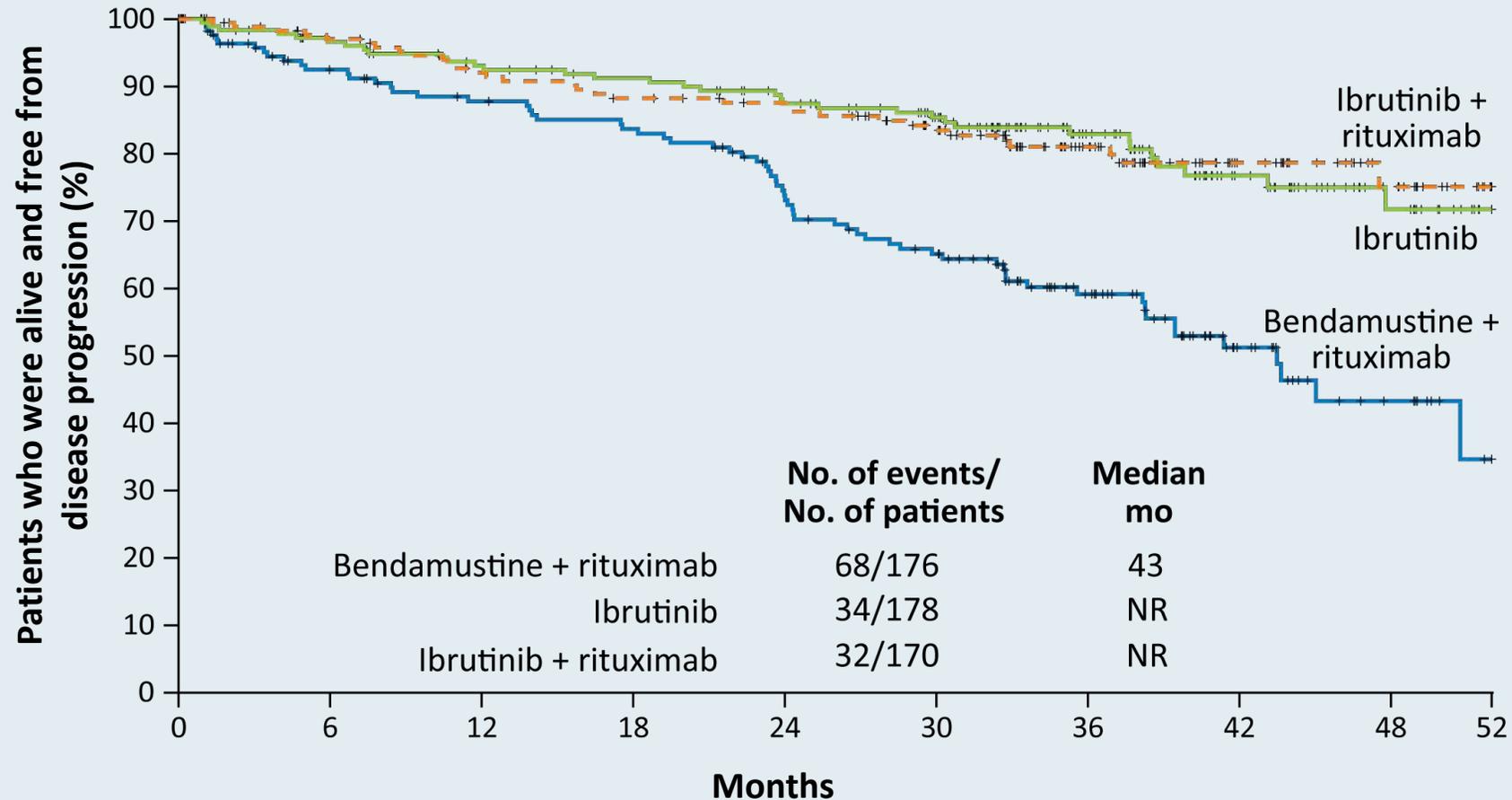
ORIGINAL ARTICLE

# Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL

J.A. Woyach, A.S. Ruppert, N.A. Heerema, W. Zhao, A.M. Booth, W. Ding, N.L. Bartlett, D.M. Brander, P.M. Barr, K.A. Rogers, S.A. Parikh, S. Coutre, A. Hurria,\* J.R. Brown, G. Lozanski, J.S. Blachly, H.G. Ozer, B. Major-Elechi, B. Fruth, S. Nattam, R.A. Larson, H. Erba, M. Litzow, C. Owen, C. Kuzma, J.S. Abramson, R.F. Little, S.E. Smith, R.M. Stone, S.J. Mandrekar, and J.C. Byrd

*N Engl J Med* 2018;379(26):2517-28.

# Alliance A041202: Efficacy with Ibrutinib Alone or in Combination with Rituximab Compared to Bendamustine/Rituximab



# FDA Approval of Ibrutinib with Rituximab for Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Press Release – April 21, 2020

“The Food and Drug Administration expanded the indication of ibrutinib to include its combination with rituximab for the initial treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

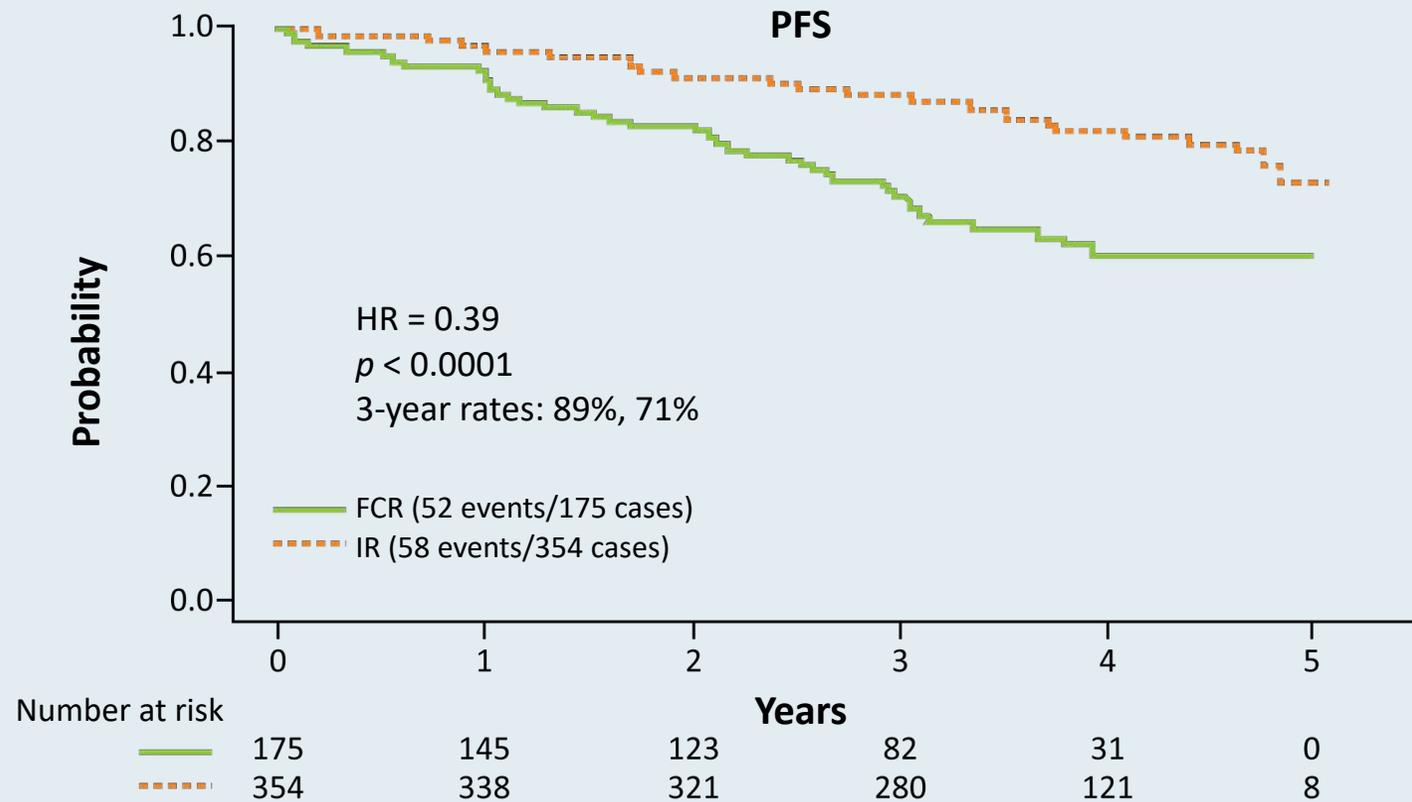
Approval was based on the E1912 trial (NCT02048813), a 2:1 randomized, multicenter, open-label, actively controlled trial of ibrutinib with rituximab compared to fludarabine, cyclophosphamide, and rituximab (FCR) in 529 adult patients 70 years or younger with previously untreated CLL or SLL requiring systemic therapy. Patients with 17p deletion were excluded. Ibrutinib was administered at 420 mg daily until disease progression or unacceptable toxicity.”

# 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  $\geq 3$  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.



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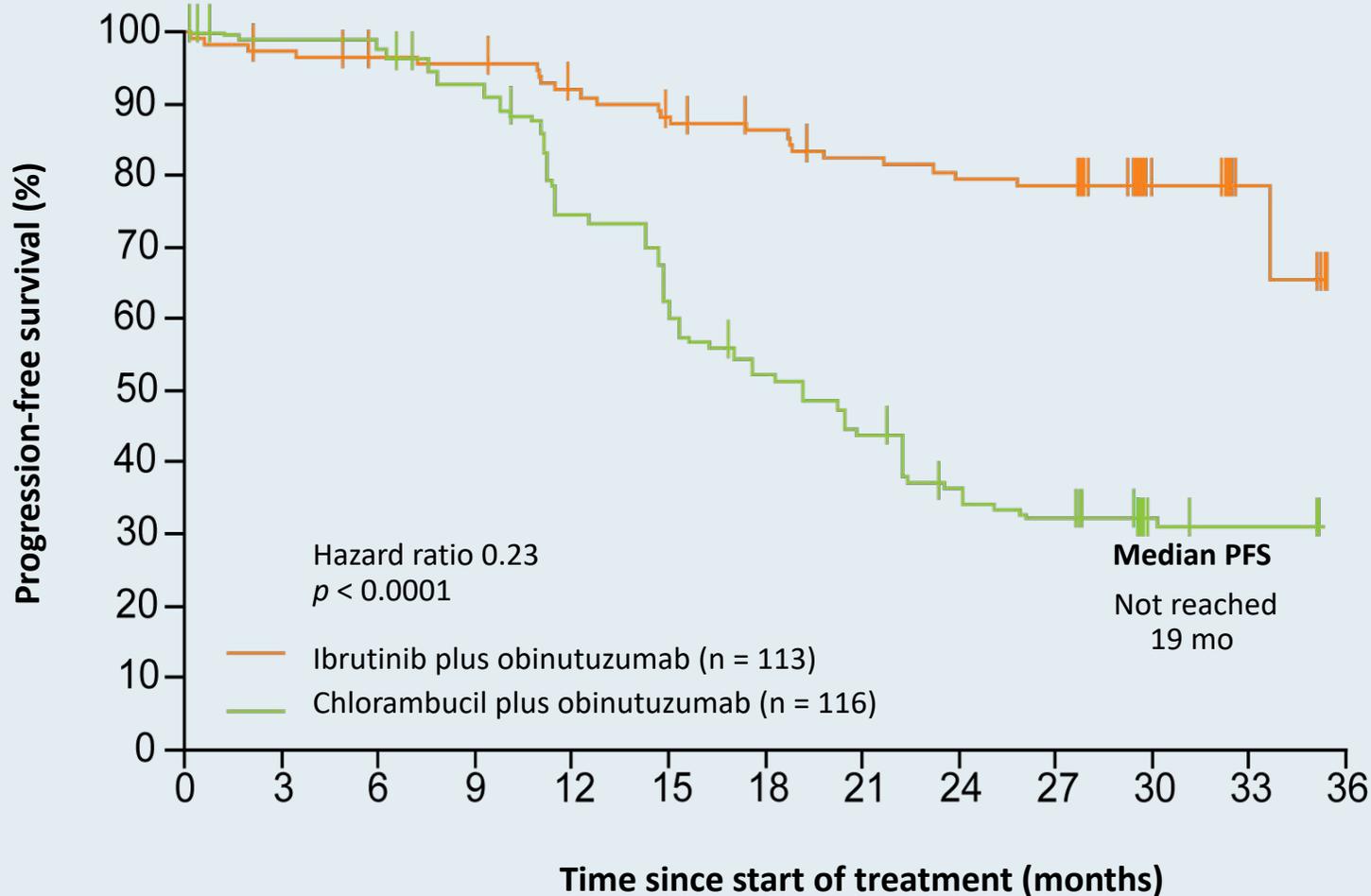
# Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial



*Carol Moreno, Richard Greil, Fatih Demirkan, Alessandra Tedeschi, Bertrand Anz, Loree Larratt, Martin Simkovic, Olga Samoilova, Jan Novak, Dina Ben-Yehuda, Vladimir Strugov, Devinder Gill, John G Gribben, Emily Hsu, Chih-Jian Lih, Cathy Zhou, Fong Clow, Danelle F James, Lori Styles, Ian W Flinn*

*Lancet Oncol* 2019;20(1):43-56.

# iLLUMINATE: A Phase III Trial of Ibrutinib and Obinutuzumab as First-Line Therapy for CLL



## Most common Grade 3 or 4 AEs

- Neutropenia
- Thrombocytopenia

## Serious AEs

- Ibrutinib/obinutuzumab: 58%
- Chlorambucil/obinutuzumab: 35%

# Agenda

## **Module 1: Chronic Lymphocytic Leukemia (CLL)**

- Dr Malhotra: A 79-year-old man with CLL – trisomy 12, unmutated IgVH
- Dr Peles: A 45-year-old man with favorable-risk CLL

## **Module 2: Follicular Lymphoma**

- Dr Zafar: A 78-year-old woman with follicular lymphoma

## **Module 3: Diffuse Large B-Cell Lymphoma**

- Dr Hart: A 58-year-old man with relapsed DLBCL

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- Dr Peles: A 73-year-old woman with MCL

## **Module 5: Hodgkin Lymphoma**

- Dr Choksi: A 75-year-old woman with recurrent Hodgkin lymphoma

# Case Presentation – Dr Zafar: A 78-year-old woman with follicular lymphoma



Dr Syed Zafar

- PMH: Parkinson's disease, DM, CAD
- 2015: Thrombocytopenia, lymphadenopathy. Bone marrow biopsy: Grade 1, Stage IV FL
- Rituximab x 4, with CR → maintenance rituximab
- 2019: Relapse with B symptoms, lymphadenopathy above and below diaphragm
  - Excisional biopsy: Grade 3A follicular lymphoma
- Ibritumomab tiuxetan, with CR
- 2020: Relapsed disease, with lymphadenopathy, osseous lesions, B symptoms
  - Repeat excisional biopsy: Grade 1-2 FL
  - NGS: EZH2 and other mutations (see report)

## Questions

- What would be the most appropriate treatment for her now – tazemetostat, PIK3A inhibitors, lenalidomide/rituximab?

# Case Presentation – Dr Zafar: A 78-year-old woman – NGS



Dr Syed Zafar

## Genomic Findings

*For a complete list of the genes assayed, please refer to the Appendix.*

**EZH2** Y646S

**IGH** IGH-BCL2 rearrangement, IGH-13p12 rearrangement

**MLL2** C1408\*, Q2576\*

**MUTYH** G382D

2 Therapies with Clinical Benefit

12 Clinical Trials

0 Therapies with Lack of Response

### BIOMARKER FINDINGS

**Microsatellite status** - MS-Stable

**Tumor Mutational Burden** - 7 Muts/Mb

### GENOMIC FINDINGS

**EZH2** - Y646S

2 Trials *see p. 7*

**IGH** - IGH-BCL2 rearrangement, IGH-13p12 rearrangement

### ACTIONABILITY

No therapies or clinical trials. *see Biomarker Findings section*

No therapies or clinical trials. *see Biomarker Findings section*

THERAPIES WITH CLINICAL BENEFIT  
(IN PATIENT'S TUMOR TYPE)

Tazemetostat

2A

none

THERAPIES WITH CLINICAL BENEFIT  
(IN OTHER TUMOR TYPE)

none

Venetoclax

**Regulatory and reimbursement issues aside, what would be your most likely second-line treatment for a 78-year-old patient with FL who experiences disease progression after completing treatment with BR 14 months ago?**

- a. Rituximab/lenalidomide
- b. Rituximab (R) or obinutuzumab (O) alone
- c. R-chemotherapy
- d. O-chemotherapy
- e. Idelalisib
- f. Copanlisib
- g. Duvelisib
- h. Other

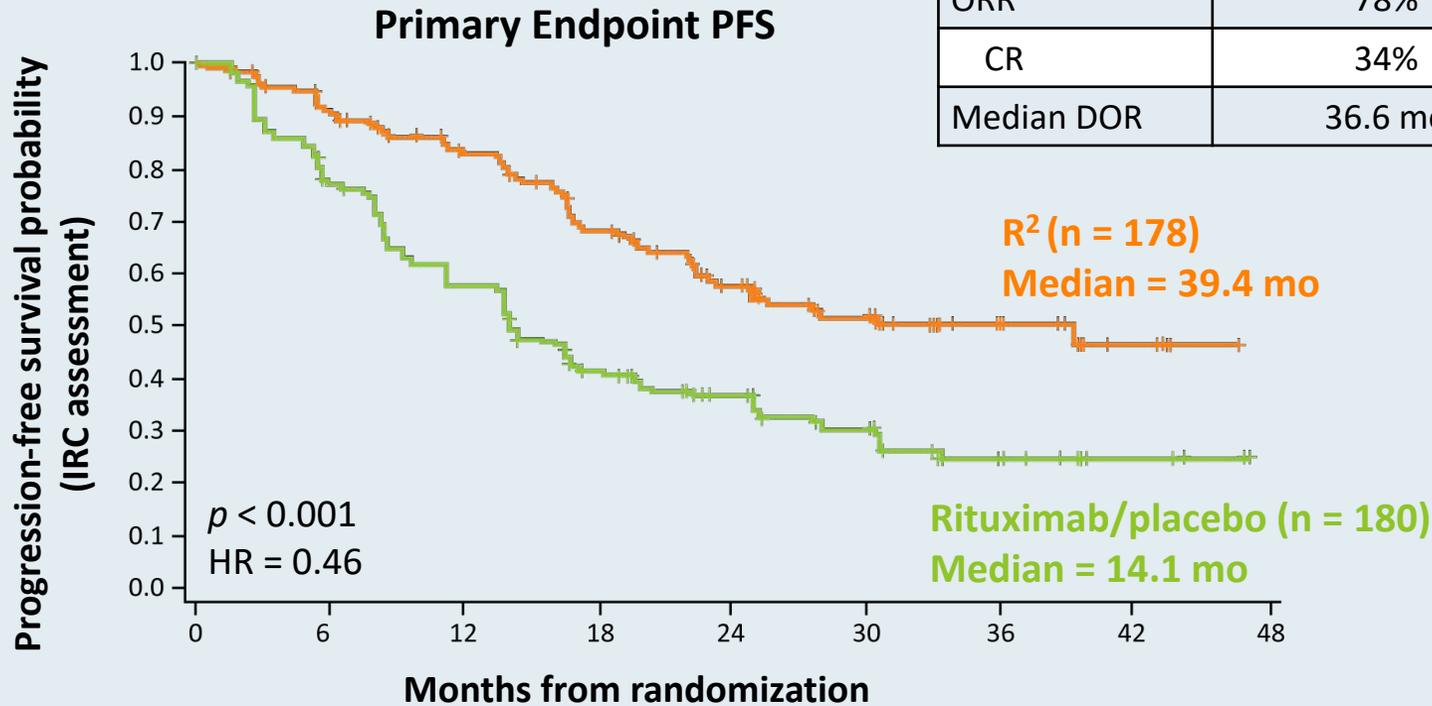
# **AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma**



John P. Leonard, MD<sup>1</sup>; Marek Trneny, MD<sup>2</sup>; Koji Izutsu, MD<sup>3</sup>; Nathan H. Fowler, MD<sup>4</sup>; Xiaonan Hong, MD<sup>5</sup>; Jun Zhu, PhD<sup>6</sup>; Huilai Zhang, MD<sup>7</sup>; Fritz Offner, MD, PhD<sup>8</sup>; Adriana Scheliga, MD<sup>9</sup>; Grzegorz S. Nowakowski, MD<sup>10</sup>; Antonio Pinto, MD<sup>11</sup>; Francesca Re, MD<sup>12</sup>; Laura Maria Fogliatto, MD, PhD<sup>13</sup>; Phillip Scheinberg, MD<sup>14</sup>; Ian W. Flinn, MD, PhD<sup>15</sup>; Claudia Moreira, MD<sup>16</sup>; José Cabeçadas, MD<sup>17</sup>; David Liu, MD, PhD<sup>18</sup>; Stacey Kalambakas, MD<sup>18</sup>; Pierre Fustier, PhD<sup>19</sup>; Chengqing Wu, PhD<sup>18</sup>; and John G. Gribben, MD, DSc<sup>20</sup>; for the AUGMENT Trial Investigators

***J Clin Oncol 2019;37:1188-99***

# AUGMENT: R<sup>2</sup> versus Rituximab/Placebo for R/R FL or Marginal Zone Lymphoma



| By IRC     | R <sup>2</sup> (n = 178) | R/placebo (n = 180) |
|------------|--------------------------|---------------------|
| ORR*       | 78%                      | 53%                 |
| CR         | 34%                      | 18%                 |
| Median DOR | 36.6 mo                  | 21.7 mo             |

\*  $p < 0.001$

- Grade 3 or 4 treatment-emergent adverse events: 69% with R<sup>2</sup> versus 32% with R/placebo
  - Neutropenia: 50% with R<sup>2</sup> versus 13% with R/placebo
  - Leukopenia: 7% with R<sup>2</sup> versus 2% with R/placebo

# FDA Granted Accelerated Approval to Tazemetostat for Follicular Lymphoma

Press Release – June 18, 2020

- The Food and Drug Administration granted accelerated approval to tazemetostat, an EZH2 inhibitor, for adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies, and for adult patients with R/R FL who have no satisfactory alternative treatment options.
- Today, the FDA also approved the cobas EZH2 Mutation Test as a companion diagnostic for tazemetostat.
- Approval was based on two open-label, single-arm cohorts (Cohort 4 - EZH2 mutated FL and Cohort 5 - EZH2 wild-type FL) of a multi-center trial (Study E7438-G000-101, NCT01897571) in patients with histologically confirmed FL after at least 2 prior systemic therapies. EZH2 mutations were identified prospectively using formalin-fixed, paraffin-embedded tumor samples, which were centrally tested using the cobas<sup>®</sup> EZH2 Mutation Test. Patients received tazemetostat 800 mg orally twice daily until confirmed disease progression or unacceptable toxicity.

# Phase II Multicenter Study of Tazemetostat, an EZH2 Inhibitor, in R/R Follicular Lymphoma

| Endpoint                | EZH2 MT cohort              |                         | EZH2 WT cohort              |                         |
|-------------------------|-----------------------------|-------------------------|-----------------------------|-------------------------|
|                         | Response-evaluable (n = 43) | POD24 subgroup (n = 17) | Response-evaluable (n = 53) | POD24 subgroup (n = 30) |
| Objective response rate | 77%                         | 65%                     | 34%                         | 30%                     |
| Complete response       | 7%                          | 6%                      | 6%                          | 0                       |
| Stable disease          | 23%                         | 35%                     | 30%                         | 27%                     |
| Median PFS              | 11.1 mo                     | 13.8 mo                 | 5.7 mo                      | 5.6 mo                  |
| Median DoR              | 8.3 mo                      | 8.2 mo                  | 13.0 mo                     | 7.3 mo                  |

# Phase II ELARA Trial Meets Primary Endpoint; Tisagenlecleucel Receives FDA Regenerative Medicine Advanced Therapy Designation in R/R Follicular Lymphoma

Press Release – August 4, 2020

“The interim analysis of the global phase 2 ELARA trial of tisagenlecleucel found that the study met its primary end point of complete response rate (CRR), as assessed by independent review committee, in patients with relapsed or refractory follicular lymphoma. Moreover, no new safety signals were observed with tisagenlecleucel.

The single-arm, multicenter, open-label, phase 2 ELARA trial is evaluating the safety and efficacy of tisagenlecleucel in adult patients with relapsed or refractory follicular lymphoma. The international trial has enrolled participants from over 30 sites across 12 countries.

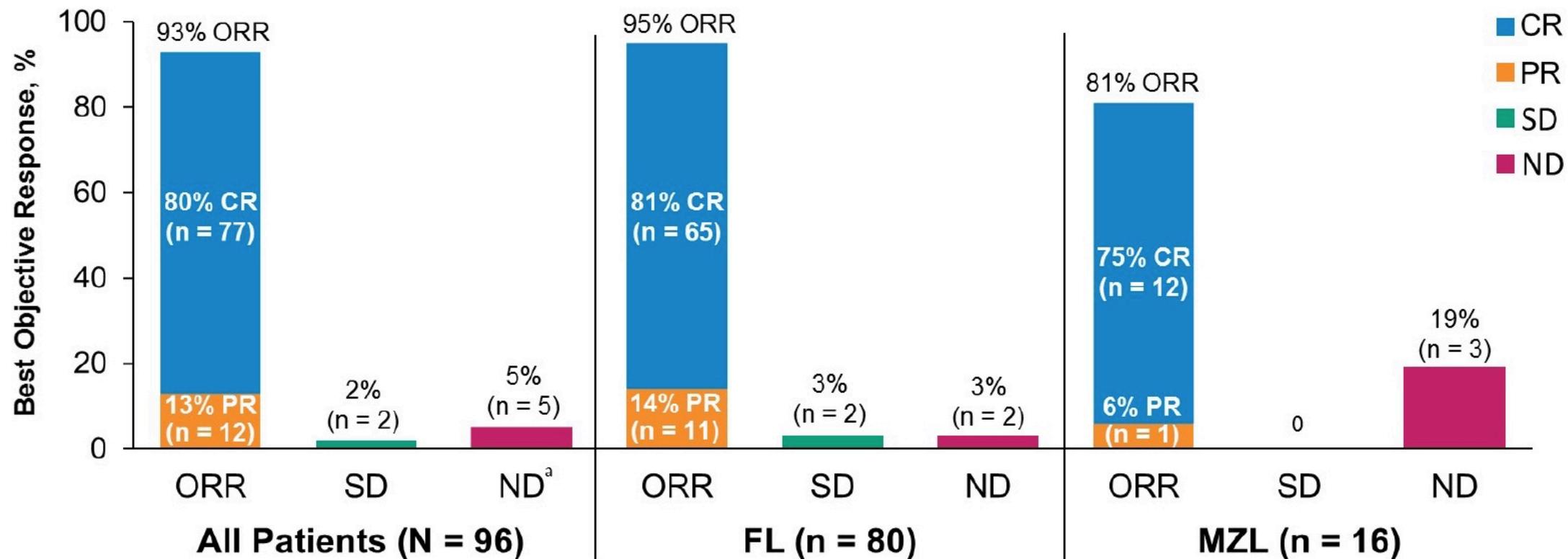
Notably, the FDA granted regenerative medicine advanced therapy (RMAT) designation to tisagenlecleucel for this indication in the second quarter of 2020 based on preliminary results observed in the ELARA trial.”

# Interim Analysis of ZUMA-5: A Phase II Study of Axicabtagene Ciloleucel (axi-cel) in Patients (pts) with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (R/R iNHL)

Jacobson CA et al.

ASCO 2020;Abstract 8008.

## ZUMA-5 Primary Endpoint: ORR by IRRC Assessment



- The median time to first response was 1 month (range, 0.8 – 3.1)

# Agenda

## Module 1: Chronic Lymphocytic Leukemia (CLL)

- Dr Malhotra: A 79-year-old man with CLL – trisomy 12, unmutated IgVH
- Dr Peles: A 45-year-old man with favorable-risk CLL

## Module 2: Follicular Lymphoma

- Dr Zafar: A 78-year-old woman with follicular lymphoma

## Module 3: Diffuse Large B-Cell Lymphoma

- Dr Hart: A 58-year-old man with relapsed DLBCL

## Module 4: Mantle Cell Lymphoma

- Dr Malhotra: A healthy, active 73-year-old man with MCL
- Dr Peles: A 73-year-old woman with MCL

## Module 5: Hodgkin Lymphoma

- Dr Choksi: A 75-year-old woman with recurrent Hodgkin lymphoma

# Case Presentation – Dr Hart: A 58-year-old man with relapsed DLBCL



**Dr Lowell Hart**

- Presented with Stage III, non-GCB subtype DLBCL
- R-CHOP, with complete response but relapsed 4 months later
- ICE → ASCT → PD
- CAR T-cell therapy, with objective response
  - No CRS, mild neurologic side effects
- One year later, no disease progression on PET

## Questions

- Is the safety and efficacy data with CAR T-cell therapy good enough yet that we can consider using it ahead of ASCT in the relapsed setting?
- Do you think CAR T-cell therapy will be more widely available 5 years from now? And where is the technology heading – will we see “off-the-shelf” CAR T products in use?

# Regulatory and reimbursement issues aside, which would you recommend first for a patient with DLBCL with disease progression after first-line R-CHOP?

- a. Additional chemotherapy → ASCT
- b. CAR T-cell therapy

## Pivotal CAR-T Studies in DLBCL: Summary of Efficacy

|                    | <b>ZUMA-1<br/>Axicabtagene<br/>ciloleucel</b> | <b>JULIET<br/>Tisagenlecleucel</b> | <b>TRANSCEND NHL 001<br/>Lisocabtagene<br/>maraleucel</b> |
|--------------------|---|------------------------------------|---|
| Evaluable patients | 101   | 93                                 | 102 (core: 73)  |
| Median follow-up   | 15.4 mo                                       | 19.3 mo                            | 12 mo   |
| Best ORR           | 83%   | 52%                                | 75%   |
| CR                 | 58%   | 40%                                | 55%   |
| 6-mo ORR           | 41%   | 33%                                | 47%   |
| 12-mo OS           | 59%   | 49%                                | 63%   |

Locke F et al; ZUMA-1 Investigators. *Lancet Oncol* 2019;20(1):31-42. Schuster SJ et al; JULIET Investigators. *N Engl J Med* 2019;380(1):45-56. Abramson JS et al; TRANSCEND NHL 001 Investigators. ASCO 2018;Abstract 7505.

# TRANSCEND NHL 001: Pivotal Efficacy and Safety Results with Long-Term Follow-Up

| <b>Clinical endpoint</b>        | <b>Evaluable patients<br/>(n = 255)</b> |
|---------------------------------|---|
| ORR for patients with R/R DLBCL | 73%                                     |
| CR                              | 53%                                     |
| DoR all patients                | 13.3 mo                                 |
| DoR in patients with CR         | Not reached                             |
| Median PFS                      | 6.8 mo                                  |
| Median OS                       | 19.9 mo                                 |
| <b>Adverse events, Grade ≥3</b> | <b>Evaluable patients<br/>(n = 268)</b> |
| Cytokine release syndrome       | 2%                                      |
| Neurologic events               | 10%                                     |

## Pivotal CAR-T Studies in DLBCL: Select Toxicities

|                          | ZUMA-1<br>Axicabtagene<br>ciloleucel | JULIET<br>Tisagenlecleucel | TRANSCEND NHL 001<br>Lisocabtagene<br>maraleucel |
|--------------------------|--------------------------------------|----------------------------|--|
| All grades CRS           | 93%                                  | 58%                        | 37%  |
| Grade ≥3 CRS             | 13%                                  | 23%                        | 1%   |
| All grades neurotoxicity | 64%                                  | 21%                        | 23%  |
| Grade ≥3 neurotoxicity   | 28%                                  | 12%                        | 13%  |
| Tocilizumab use          | 43%                                  | 15%                        | 17%  |
| Steroid treatment        | 27%                                  | 11%                        | 21%  |

Locke FL et al; ZUMA-1 Investigators. *Lancet Oncol* 2019;20(1):31-42; Neelapu SS et al. *N Engl J Med* 2017;377:2531-44; Schuster SJ et al; JULIET Investigators. *N Engl J Med* 2019;380(1):45-56; Abramson JS et al; TRANSCEND NHL 001 Investigators. ASCO 2018;Abstract 7505; Abramson JS et al. ASCO 2019 Education Book.

# FDA Approves Selinexor for Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Press Release – June 22, 2020

“The Food and Drug Administration granted accelerated approval to selinexor for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.

Approval was based on SADAL (KCP-330-009; NCT02227251), a multicenter, single-arm, open-label trial in patients with DLBCL after 2 to 5 systemic regimens. Patients received selinexor 60 mg orally on days 1 and 3 of each week.”

*Lancet Haematol* 2020;7: e511–22

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# Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial

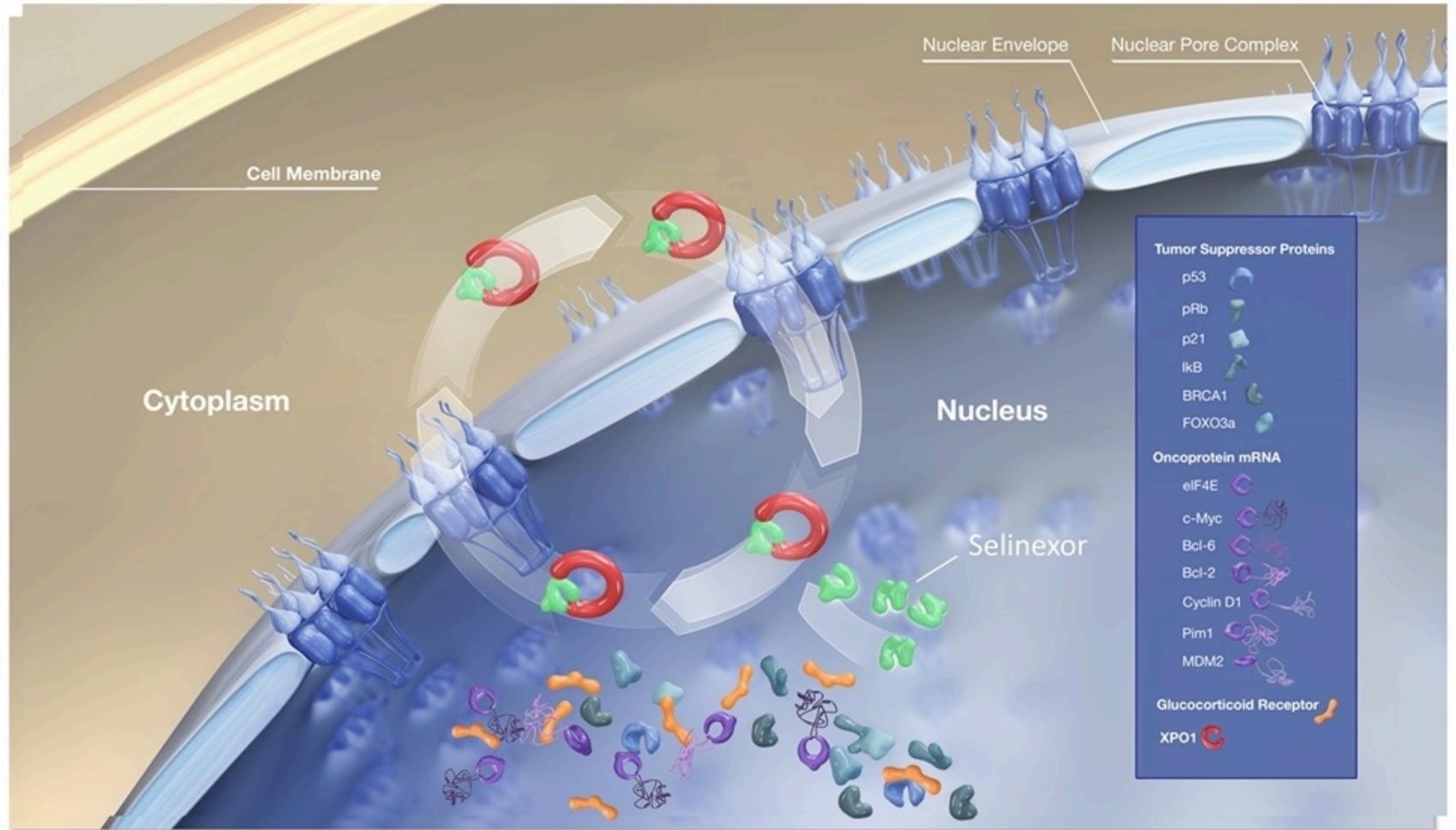


*Nagesh Kalakonda\*, Marie Maerevoet\*, Federica Cavallo, George Follows, Andre Goy, Joost S P Vermaat, Olivier Casasnovas, Nada Hamad, Josée M Zijlstra, Sameer Bakhshi, Reda Bouabdallah, Sylvain Choquet, Ronit Gurion, Brian Hill, Ulrich Jaeger, Juan Manuel Sancho, Michael Schuster, Catherine Thieblemont, Fátima De la Cruz, Miklos Egyed, Sourav Mishra, Fritz Offner, Theodoros P Vassilakopoulos, Krzysztof Warzocha, Daniel McCarthy, Xiwen Ma, Kelly Corona, Jean-Richard Saint-Martin, Hua Chang, Yosef Landesman, Anita Joshi, Hongwei Wang, Jatin Shah, Sharon Shacham, Michael Kauffman, Eric Van Den Neste, Miguel A Canales*

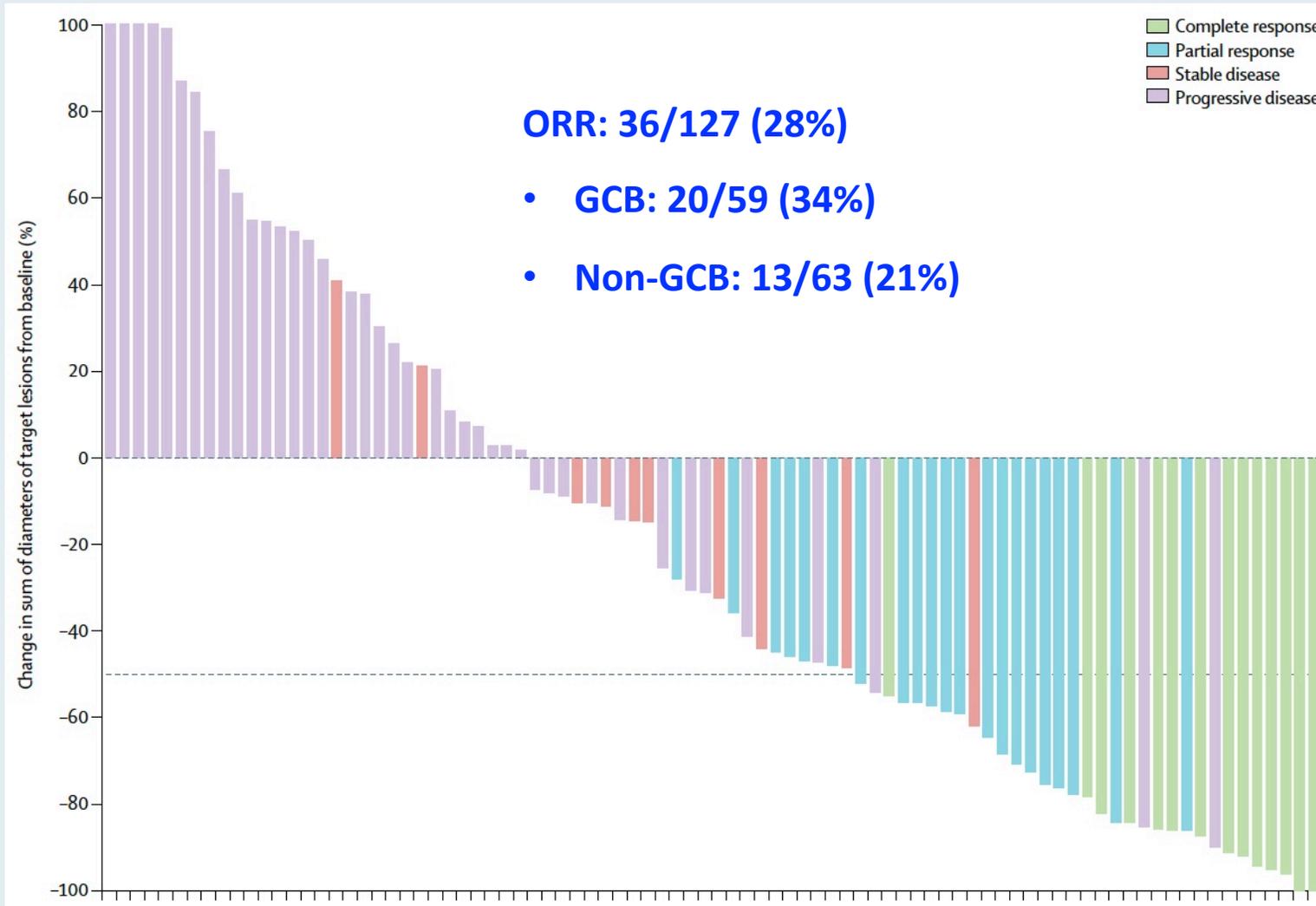
# Selinexor/SINE Mechanism of Action: Inhibition of XPO1

Inhibition of XPO1 impacts tumor cells via 3 core mechanisms

1. Increases nuclear levels and activation of tumor suppressor proteins
2. Traps oncoprotein mRNA in the nucleus leading to reduced oncoprotein levels
3. Retains activated glucocorticoid receptor in the nucleus



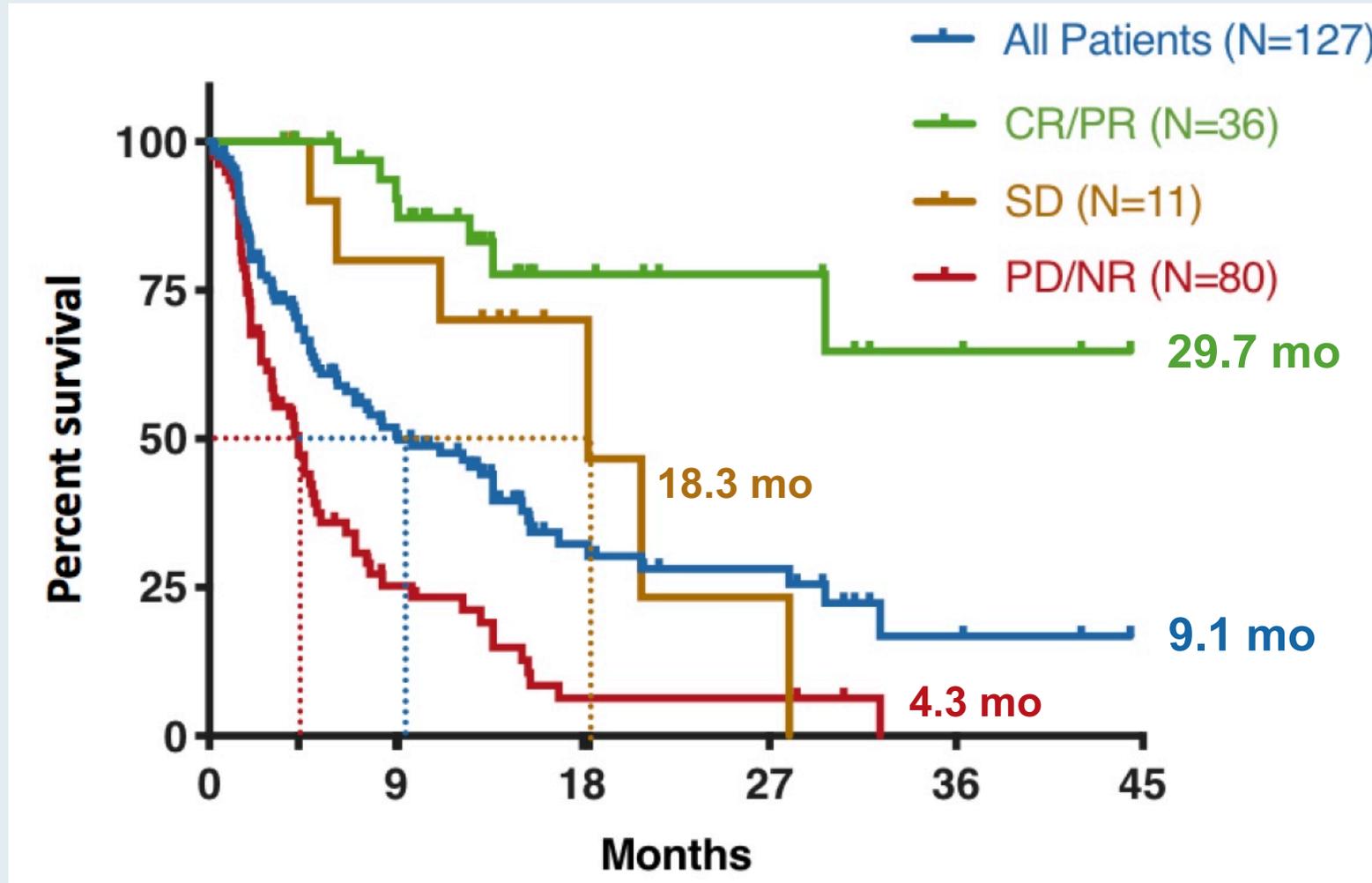
# SADAL: Selinexor in R/R DLBCL – Response and Change in Tumor Burden



Median PFS: 2.6 months

Median DoR: 9.3 months

# SADAL: Selinexor in R/R DLBCL – Overall Survival by Response



# FDA Grants Accelerated Approval to Tafasitamab-cxix for Diffuse Large B-Cell Lymphoma

Press Release – July 31, 2020

“The Food and Drug Administration granted accelerated approval to tafasitamab-cxix, a CD19-directed cytolytic antibody, indicated in combination with lenalidomide for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant.

The efficacy of tafasitamab-cxix with lenalidomide was evaluated in L-MIND (NCT02399085), an open label, multicenter single-arm trial in 81 patients. Patients received tafasitamab-cxix 12 mg/kg intravenously with lenalidomide (25 mg orally on days 1 to 21 of each 28-day cycle) for maximum of 12 cycles, followed by tafasitamab-cxix as monotherapy.”

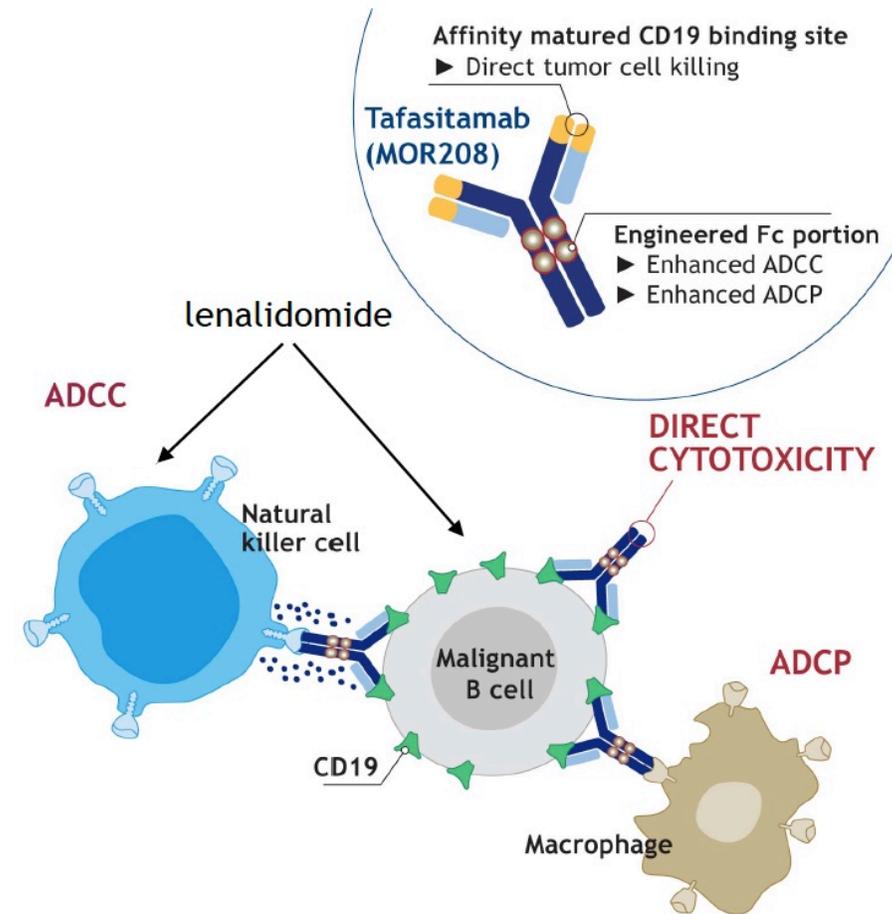
# Tafasitamab Mechanism of Action and Rationale for Combining with Lenalidomide

## Tafasitamab

- Fc-enhanced to improve effector function
- Mediates direct cell death
- Encouraging single agent activity in r/r DLBCL & iNHL patients

## Lenalidomide

- Activation and expansion of immune cells
- Mediates direct cell death
- Well studied as anti-lymphoma agent, alone or in combination



ADCC: Antibody-Dependent Cell-Mediated Cytotoxicity  
ADCP: Antibody-Dependent Cell-Mediated Phagocytosis

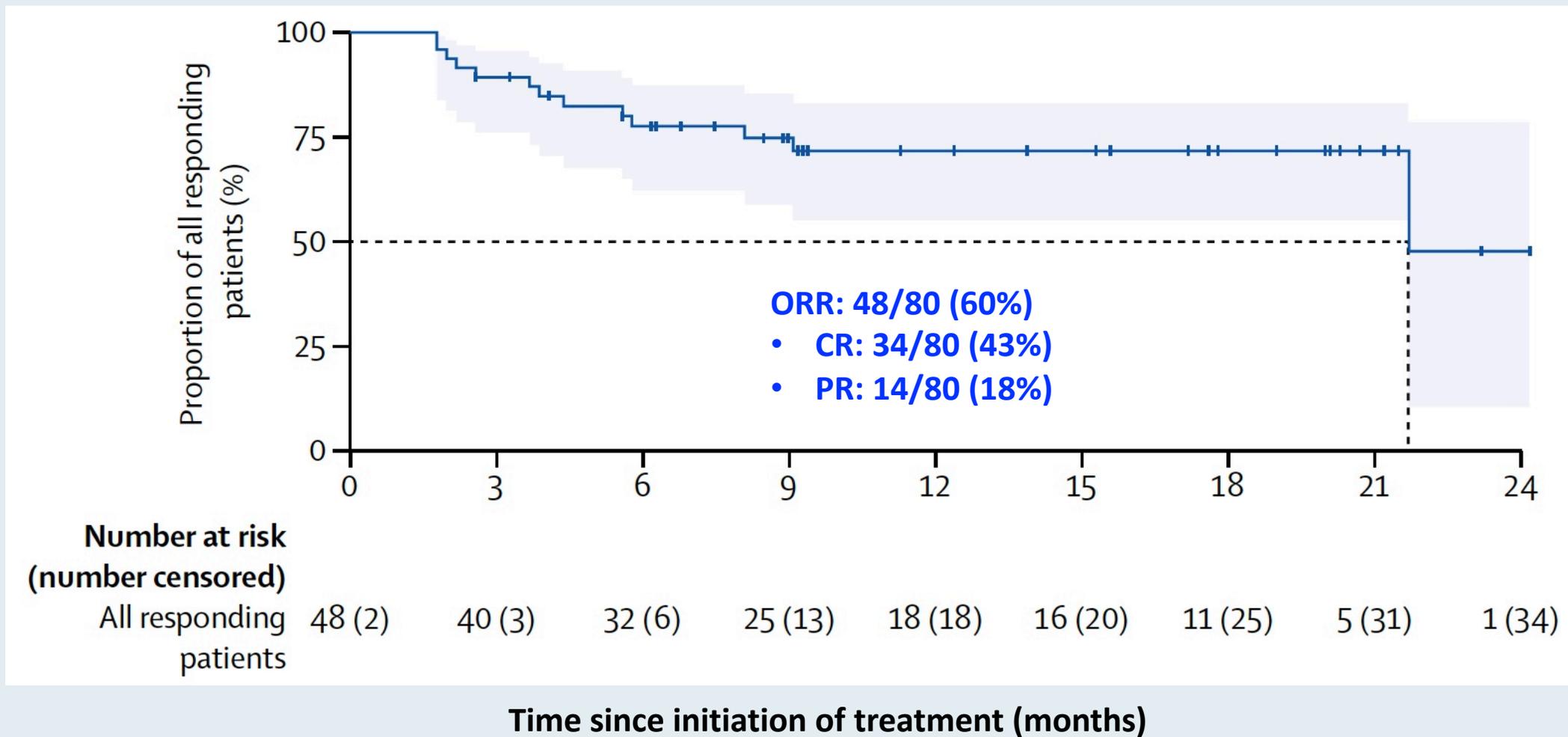


# Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study

*Gilles Salles\*, Johannes Duell\*, Eva González Barca, Olivier Tournilhac, Wojciech Jurczak, Anna Marina Liberati, Zsolt Nagy, Aleš Obr, Gianluca Gaidano, Marc André, Nagesh Kalakonda, Martin Dreyling, Johannes Weirather, Maren Dirnberger-Hertweck, Sumeet Ambarkhane, Günter Fingerle-Rowson, Kami Maddocks*

***Lancet Oncol 2020;21:978-88***

# L-MIND: Tafasitamab plus Lenalidomide in R/R DLBCL – Proportion of Patients with an Objective Response



# Polatumumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

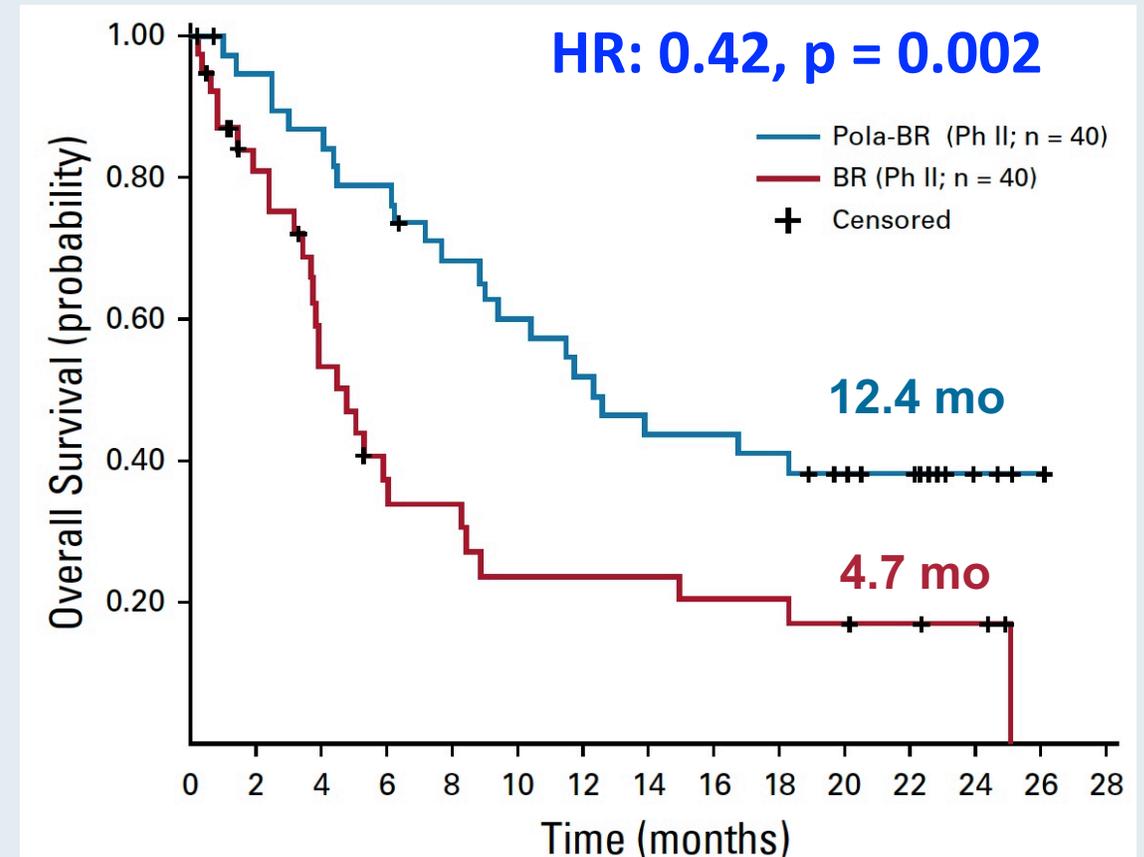
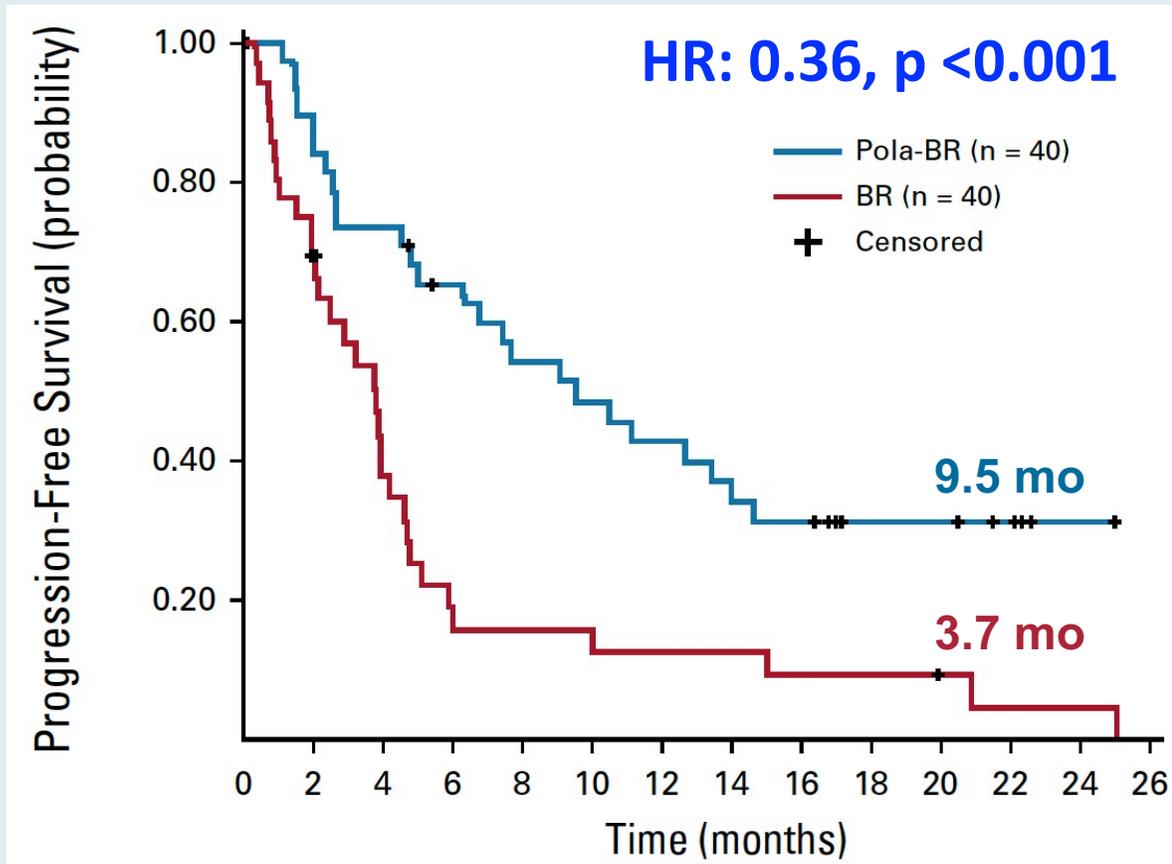


Laurie H. Sehn, MD, MPH<sup>1</sup>; Alex F. Herrera, MD<sup>2</sup>; Christopher R. Flowers, MD, MSc<sup>3</sup>; Manali K. Kamdar, MD, MBBS<sup>4</sup>; Andrew McMillan, PhD<sup>5</sup>; Mark Hertzberg, MBBS, PhD<sup>6</sup>; Sarit Assouline, MDCM, MSc<sup>7</sup>; Tae Min Kim, MD<sup>8</sup>; Won Seog Kim, MD, PhD<sup>9</sup>; Muhit Ozcan, MD<sup>10</sup>; Jamie Hirata, PharmD<sup>11</sup>; Elicia Penuel, PhD<sup>11</sup>; Joseph N. Paulson, PhD<sup>11</sup>; Ji Cheng, PhD<sup>12</sup>; Grace Ku, MD<sup>11</sup>; and Matthew J. Matasar, MD<sup>13</sup>

*J Clin Oncol* 2020;38:155-65

# Bendamustine/Rituximab +/- Polatuzumab Vedotin in R/R DLBCL — Response and Survival Analyses

Primary Endpoint: IRC-assessed CR rate: 40% vs 17.5%



# Agenda

## Module 1: Chronic Lymphocytic Leukemia (CLL)

- Dr Malhotra: A 79-year-old man with CLL – trisomy 12, unmutated IgVH
- Dr Peles: A 45-year-old man with favorable-risk CLL

## Module 2: Follicular Lymphoma

- Dr Zafar: A 78-year-old woman with follicular lymphoma

## Module 3: Diffuse Large B-Cell Lymphoma

- Dr Hart: A 58-year-old man with relapsed DLBCL

## Module 4: Mantle Cell Lymphoma

- Dr Malhotra: A healthy, active 73-year-old man with MCL
- Dr Peles: A 73-year-old woman with MCL

## Module 5: Hodgkin Lymphoma

- Dr Choksi: A 75-year-old woman with recurrent Hodgkin lymphoma

# Case Presentation – Dr Malhotra: A healthy, active 73-year-old man with MCL



Dr Vikas Malhotra

- 2/2019: Presents with LUQ pain, WBC: 30K
  - Work up: Splenomegaly, monoclonal B-cell population in peripheral blood,
  - Bone marrow: MCL, t(11;14), p53 mutation
- Lenalidomide/rituximab → lenalidomide, with CR

## Questions

- Which upfront treatment would you have chosen in this setting – lenalidomide/rituximab or bendamustine/rituximab?
- Would you have considered adding a BTK inhibitor to lenalidomide/rituximab?
- Are there any clinical trials that you would have considered?

# Case Presentation – Dr Peles: A 73-year-old woman with MCL



Dr Shachar Peles

- Presents with complaints of fatigue and abdominal/groin discomfort
- CT: Adenopathy in neck, chest, abdomen and pelvis; right inguinal mass 4.1 x 2.7 cm
- Axillary nodal biopsy and workup: MCL, t(11;14), WBC 9.8K, LDH 174, PS 1
- Clinical trial of bendamustine/rituximab → acalabrutinib or placebo, with CR after 6 cycles
  - Persistent nausea, despite dose reductions and completion of BR
  - Discontinued study drug, continued maintenance rituximab

## Questions

- What is your preferred first-line treatment for MCL – BR, R-CHOP, R-hyperCVAD or some other intensive regimen if younger?
- What are your thoughts about maintenance rituximab, and are there regimens where you would or would not recommend it?
- What are your thoughts about high-dose chemotherapy and ASCT in MCL?
- Are there patients for whom you don't recommend any therapy? How do you decide?
- What about BTK inhibitors in MCL – is there a frontline role, or should we reserve for relapsed disease?

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

- a. Ibrutinib
- b. Acalabrutinib
- c. Zanubrutinib
- d. Lenalidomide + rituximab
- e. Bortezomib + rituximab
- f. Other

## Novel Approaches for R/R MCL

| Agent                  | N   | Response Rate | mDOR             |
|------------------------|-----|---------------|------------------|
| Bortezomib             | 155 | 33%           | 9.2 months       |
| Temsirolimus           | 54  | 22%           | 7.1 months       |
| Lenalidomide           | 134 | 28%           | 16.6 months      |
| Lenalidomide-rituximab | 52  | 57%           | 18.9 months      |
| Ibrutinib              | 111 | 68%           | 17.5 months      |
| Acalabrutinib          | 124 | 81%           | 72% at 12 months |
| Zanubrutinib           | 86  | 84%           | 75% at 12 months |
| Venetoclax             | 28  | 75%           | 12 months        |
| Ibrutinib-venetoclax   | 24  | 71% (all CR)  | 80% at 12 months |

**Toxicity Profiles: Least to Most (my personal opinion)**

**Venetoclax < Acalabrutinib = Zanubrutinib < Ibrutinib < Lenalidomide < R<sup>2</sup> < Bortezomib < Temsirolimus**

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

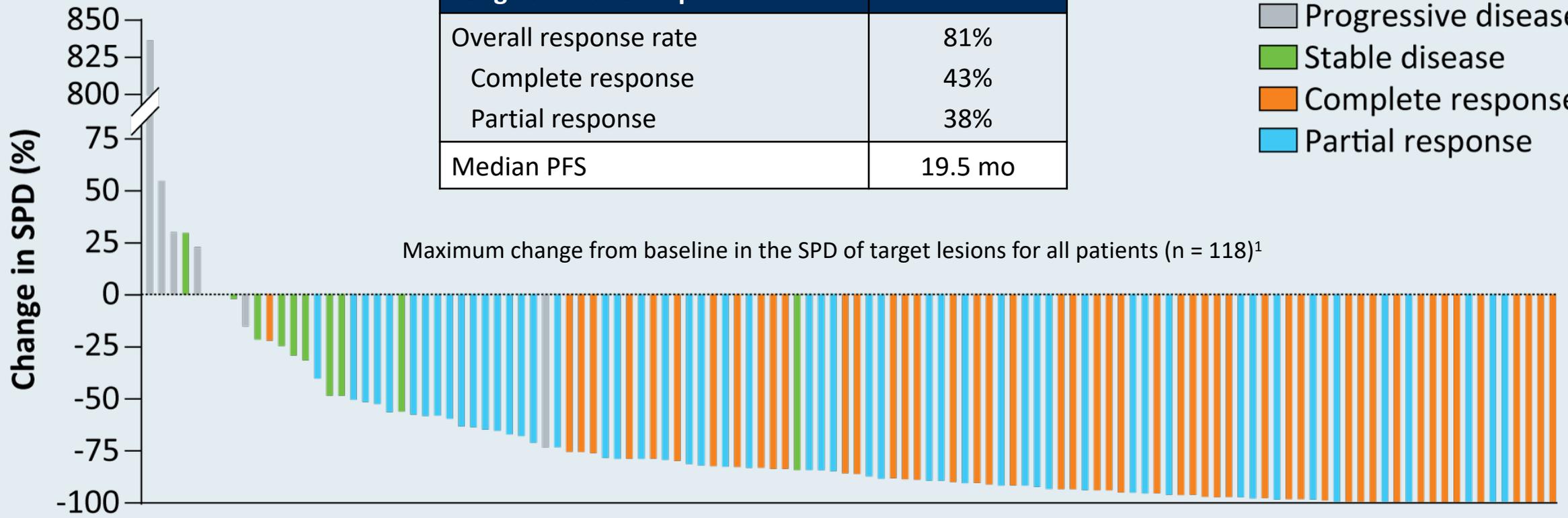
(Phase II PCYC-1104 and SPARK and Phase III RAY Studies)

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

# ACE-LY-004 Phase II Trial of Acalabrutinib in Relapsed/Refractory MCL: Response and Long-Term Follow-Up Results

| Long-term follow-up >24 mo <sup>2</sup> | N = 124 |
|---|---------|
| Overall response rate                   | 81%     |
| Complete response                       | 43%     |
| Partial response                        | 38%     |
| Median PFS                              | 19.5 mo |

- Progressive disease
- Stable disease
- Complete response
- Partial response



<sup>1</sup> Wang M et al. *Lancet* 2018;391(10121):659-67; <sup>2</sup> Wang M et al. ASH 2018;Abstract 2876.

# FDA Approves Zanubrutinib for Relapsed/Refractory MCL

Press Release – November 15, 2019

"The US Food and Drug Administration granted accelerated approval to zanubrutinib capsules for the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy.

A single-arm clinical trial of zanubrutinib included 86 patients with mantle cell lymphoma who had received at least one prior treatment. In the trial, 84% of patients had tumor shrinkage with a median duration of response of 19.5 months. This trial was supported by an additional single-arm trial that included 32 patients, in which 84% of patients had tumor shrinkage with a median duration of response of 18.5 months."

## Efficacy of Zanubrutinib for MCL

| Study                       | Evaluable patients            | ORR, CR                          | Median DoR                          | Median PFS |
|-----------------------------|-------------------------------|----------------------------------|-------------------------------------|------------|
| Phase I/II<br>(NCT02343120) | N = 48<br>R/R = 37<br>TN = 11 | 87%, 31%<br>87%, 30%<br>88%, 38% | 16.2 mo (all)<br>14.7 mo<br>14.7 mo | 15.4 mo    |
| Phase II<br>(NCT03206970)   | N = 86 R/R                    | 85%, 77%                         | 14.0 mo                             | 16.7 mo    |

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

| Clinical endpoint                | Venetoclax<br>(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.

## AIM: A Phase II Trial of Ibrutinib/Venetoclax for MCL (Median 2 Prior Therapies)

| Primary endpoint                       | Without PET<br>(n = 24)    | With PET<br>(n = 24) |
|--|----------------------------|----------------------|
| CR at 16 weeks                         | 10 (42%)                   | 15 (62%)             |
| <b>Best response</b>                   |                            |                      |
| CR                                     | 16 (67%)                   | 17 (71%)             |
| <b>Best response, total population</b> | <b>With flow cytometry</b> | <b>With ASO-PCR</b>  |
| MRD negative                           | 16 (67%)                   | 9 (38%)              |
| MRD not negative                       | 8 (33%)                    | 15 (62%)             |

- Updated analysis with median 37.5 mo of follow-up:
  - Median PFS = 29 months and median OS = 32 months
  - Median DOR and TTP had not been reached and were estimated to be 74% and 60% at 30 months, respectively.

# OAsis Phase I/II Trial of Ibrutinib, Venetoclax and Obinutuzumab in Newly Diagnosed MCL (N = 15)

| <b>CR/CRu after cycle 6</b> | <b>MRD-negative after cycle 6</b> | <b>1-y PFS rate</b> | <b>1-y OS rate</b> |
|-----------------------------|-----------------------------------|---------------------|--------------------|
| 80%                         | 100%                              | 93.3%               | 100%               |

| <b>Grade III-IV adverse events</b> | <b>Serious adverse events</b> | <b>Grade III-IV neutropenia</b> | <b>ALT/AST increase</b> |
|------------------------------------|-------------------------------|---------------------------------|-------------------------|
| 55% (8/15)                         | 7% (1/15)                     | 20% (3/15)                      | 14% (2/15)              |

# FDA Approves Brexucabtagene Autoleucel for Relapsed or Refractory Mantle Cell Lymphoma

Press Release – July 24, 2020

The Food and Drug Administration granted accelerated approval to brexucabtagene autoleucel, a CD19-directed genetically modified autologous T cell immunotherapy, for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

Approval was based on ZUMA-2 (NCT02601313), an open-label, multicenter, single-arm trial of 74 patients with relapsed or refractory MCL who had previously received anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor. Patients received a single infusion of brexucabtagene autoleucel following completion of lymphodepleting chemotherapy. The primary efficacy outcome measure was objective response rate (ORR) per Lugano [2014] criteria as assessed by an independent review committee.

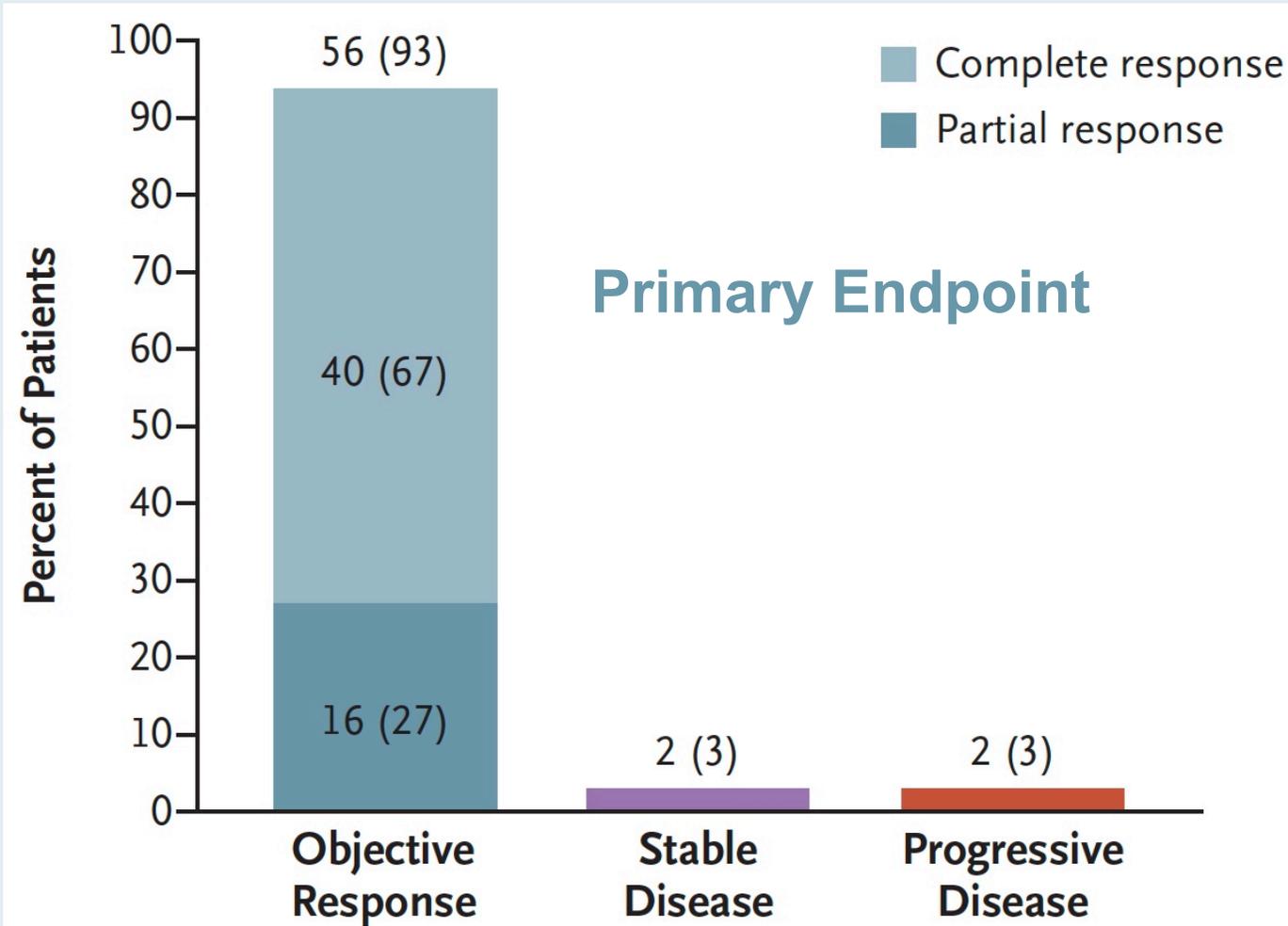
ORIGINAL ARTICLE

# 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%       |

## Select Ongoing Studies of CAR T-Cell Therapy in MCL

| Study identifier      | Phase | N  | Setting | Protocol treatment               |
|-----------------------|-------|----|---------|----------------------------------|
| NCT04484012           | II    | 36 | R/R MCL | Acalabrutinib + CD19 CAR T cells |
| TARMAC<br>NCT04234061 | II    | 20 | R/R MCL | Ibrutinib + tisagenlecleucel     |

# Agenda

## **Module 1: Chronic Lymphocytic Leukemia (CLL)**

- Dr Malhotra: A 79-year-old man with CLL – trisomy 12, unmutated IgVH
- Dr Peles: A 45-year-old man with favorable-risk CLL

## **Module 2: Follicular Lymphoma**

- Dr Zafar: A 78-year-old woman with follicular lymphoma

## **Module 3: Diffuse Large B-Cell Lymphoma**

- Dr Hart: A 58-year-old man with relapsed DLBCL

## **Module 4: Mantle Cell Lymphoma**

- Dr Malhotra: A healthy, active 73-year-old man with MCL
- Dr Peles: A 73-year-old woman with MCL

## **Module 5: Hodgkin Lymphoma**

- Dr Choksi: A 75-year-old woman with recurrent Hodgkin lymphoma

# Case Presentation – Dr Choksi: A 75-year-old woman with recurrent Hodgkin lymphoma



**Dr Mamta Choksi**

- PMH: NHL involving upper eyelid and lacrimal duct treated with RT (2000), ITP treated with IVIG, Parkinson's disease
- 12/2017: Hospitalized after a fall, lymphadenopathy
  - Workup: Classical Hodgkin lymphoma, with LAN, bony metastatic disease
- 1/2018 – 6/2018: AVD, with response after 3 cycles, NED
- 8/2018 Restaging: PD
- 9/2018 – present: Nivolumab 240 mg every 2 weeks
  - Diabetes, significant response, NED

## Questions

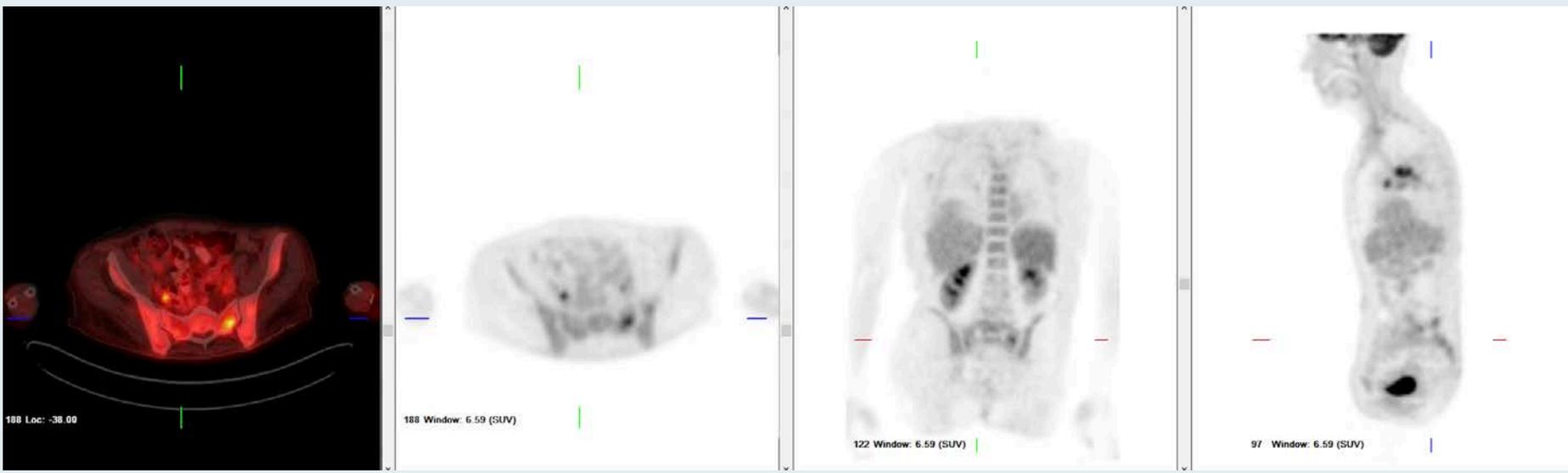
- Should I stop the nivolumab at some point and monitor her clinically?
- For elderly patients with Parkinson's disease, have you used brentuximab vedotin, and if so, have you observed additional neurotoxicity?
- If this patient presented today, what would be your choice for first-line and then second-line therapy?

# Case Presentation – Dr Choksi: A 75-year-old woman with recurrent Hodgkin lymphoma (continued)

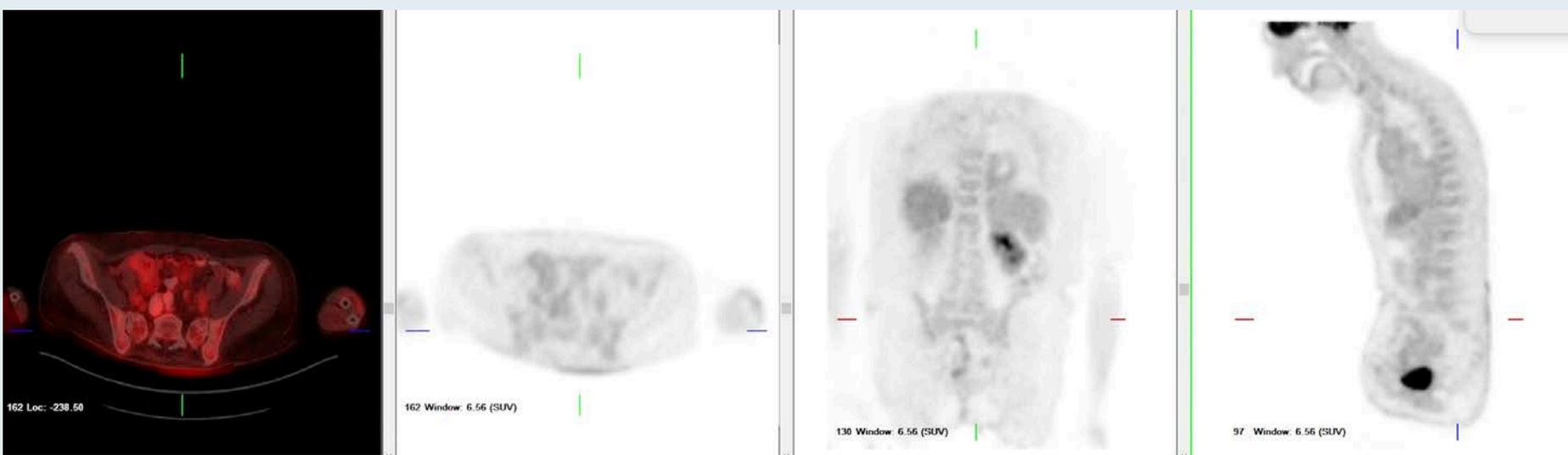


Dr Mamta Choksi

Before Nivolumab



After Nivolumab



**An 85-year-old frail patient with advanced-stage symptomatic HL is not a candidate for aggressive chemotherapy but is seeking active treatment. Regulatory and reimbursement issues aside, what would you recommend?**

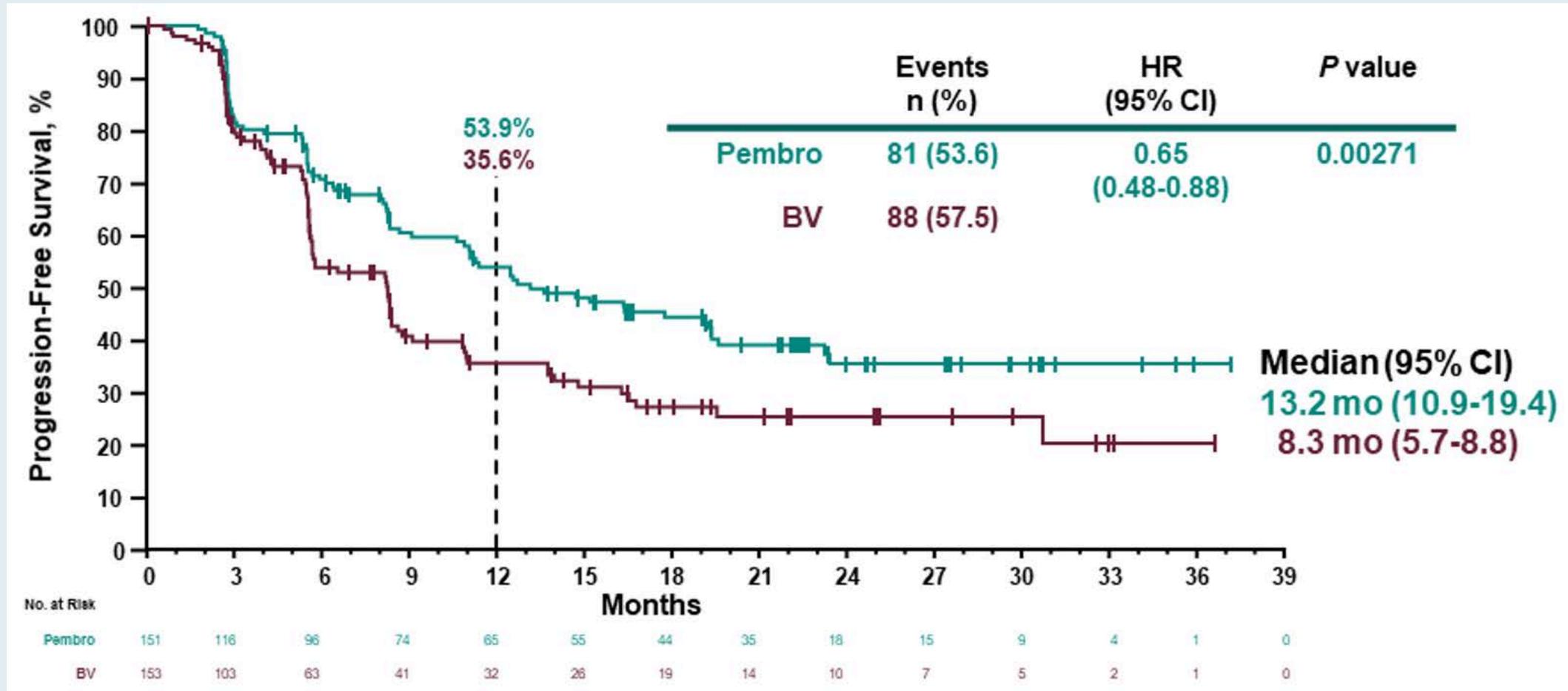
- a. Brentuximab vedotin
- b. Brentuximab vedotin + anti-PD-1/PD-L1 antibody
- c. Anti-PD-1/PD-L1 antibody
- d. Brentuximab vedotin/DTIC
- e. Other

# **KEYNOTE-204: Randomized, Open-label, Phase 3 Study of Pembrolizumab versus Brentuximab Vedotin in Relapsed or Refractory Classical Hodgkin Lymphoma**

Kuruvilla J et al.

ASCO 2020;Abstract 8005.

# KEYNOTE-204: PFS Primary Endpoint

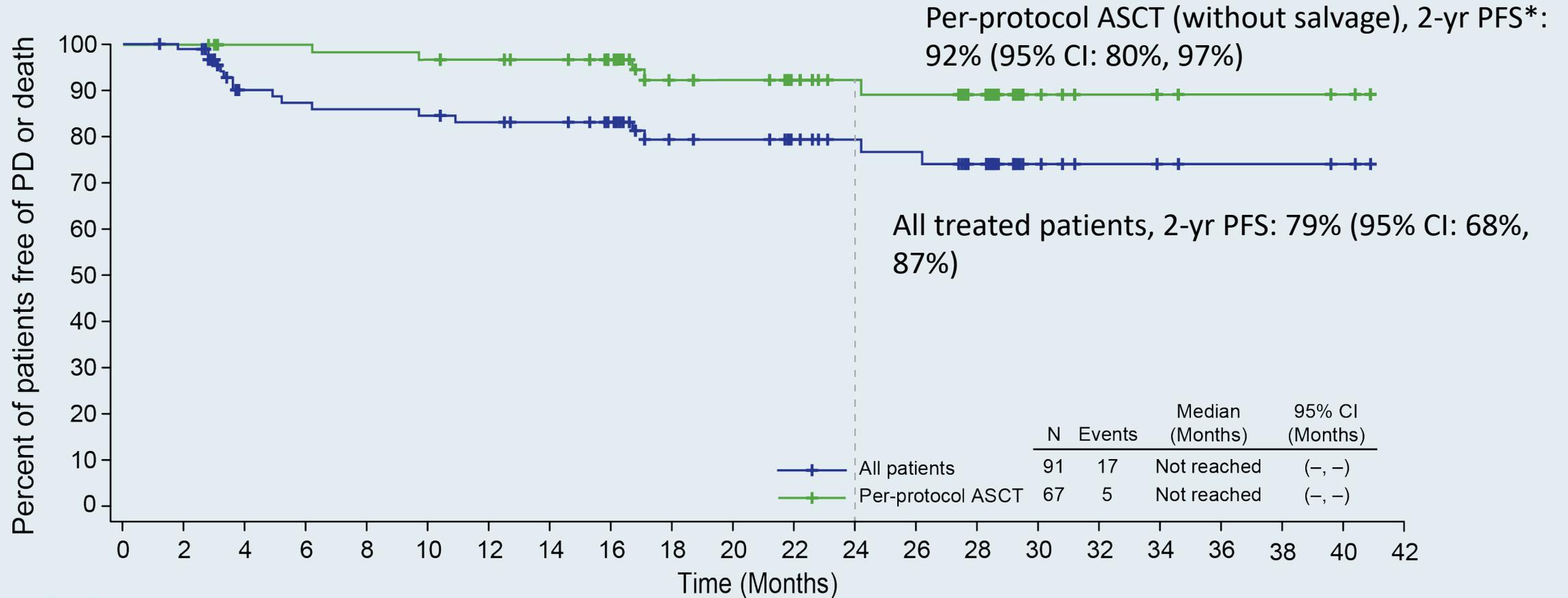


# 2-Year Follow-Up Results from the Phase 1–2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma

Moskowitz A et al.

ASH 2019;Abstract 238.

# PFS for All Treated Patients versus Patients Who Received Per-Protocol ASCT (without Salvage)



### N at Risk (Events)

|                   |       |       |       |        |        |        |        |        |        |        |        |        |        |        |        |       |       |       |       |       |       |       |
|-------------------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|-------|-------|-------|-------|-------|-------|-------|
| All patients      | 91(0) | 89(1) | 65(8) | 63(10) | 62(11) | 61(12) | 58(13) | 56(13) | 51(13) | 39(15) | 38(15) | 34(15) | 30(15) | 29(16) | 24(17) | 8(17) | 5(17) | 4(17) | 3(17) | 3(17) | 2(17) | 0(17) |
| Per-protocol ASCT | 67(0) | 67(0) | 61(0) | 61(0)  | 60(1)  | 59(2)  | 57(2)  | 55(2)  | 50(2)  | 38(4)  | 37(4)  | 33(4)  | 29(4)  | 28(5)  | 24(5)  | 8(5)  | 5(5)  | 4(5)  | 3(5)  | 3(5)  | 2(5)  | 0(5)  |

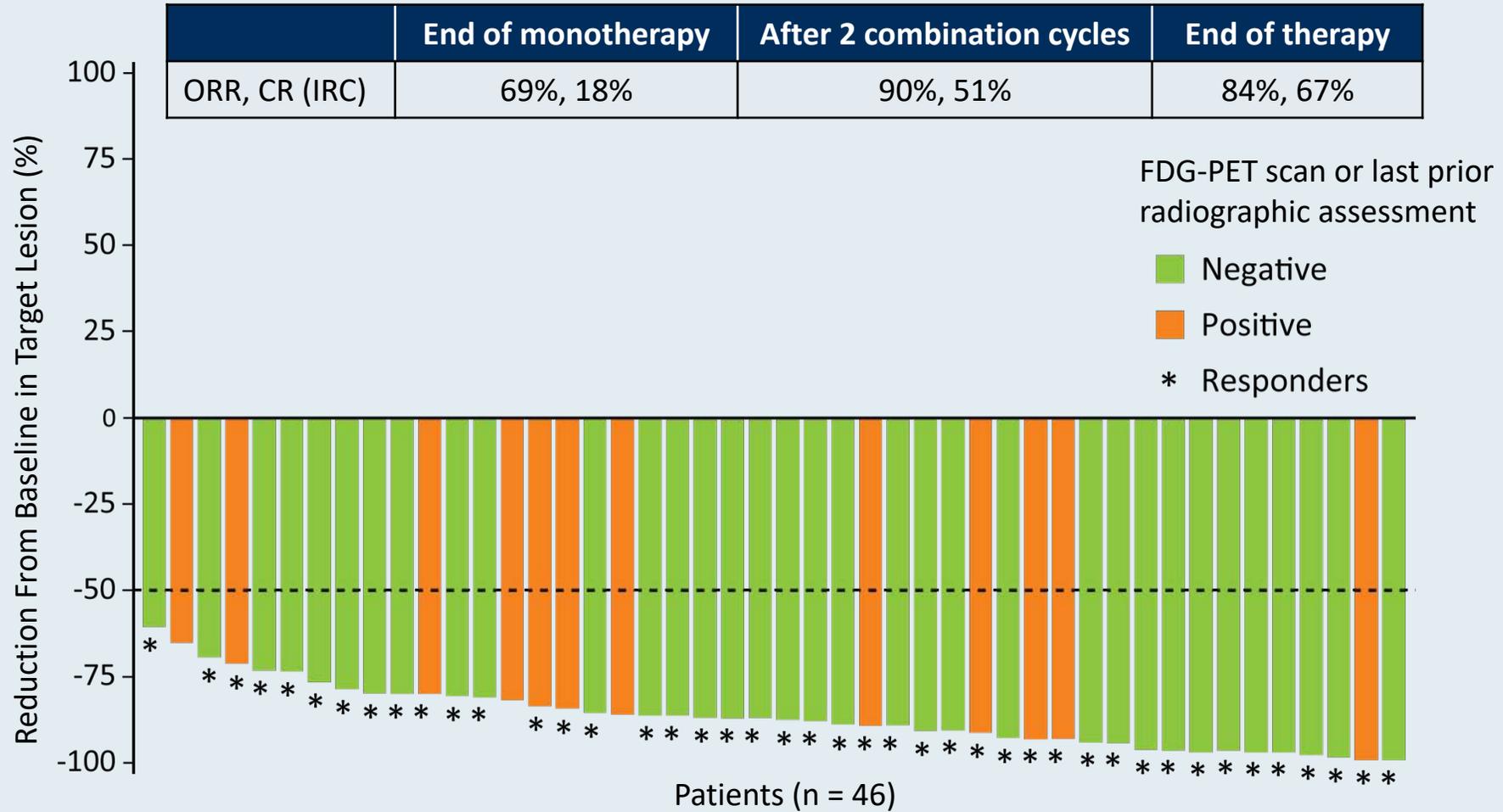
# Nivolumab for Newly Diagnosed Advanced-Stage Classic Hodgkin Lymphoma: Safety and Efficacy in the Phase II CheckMate 205 Study



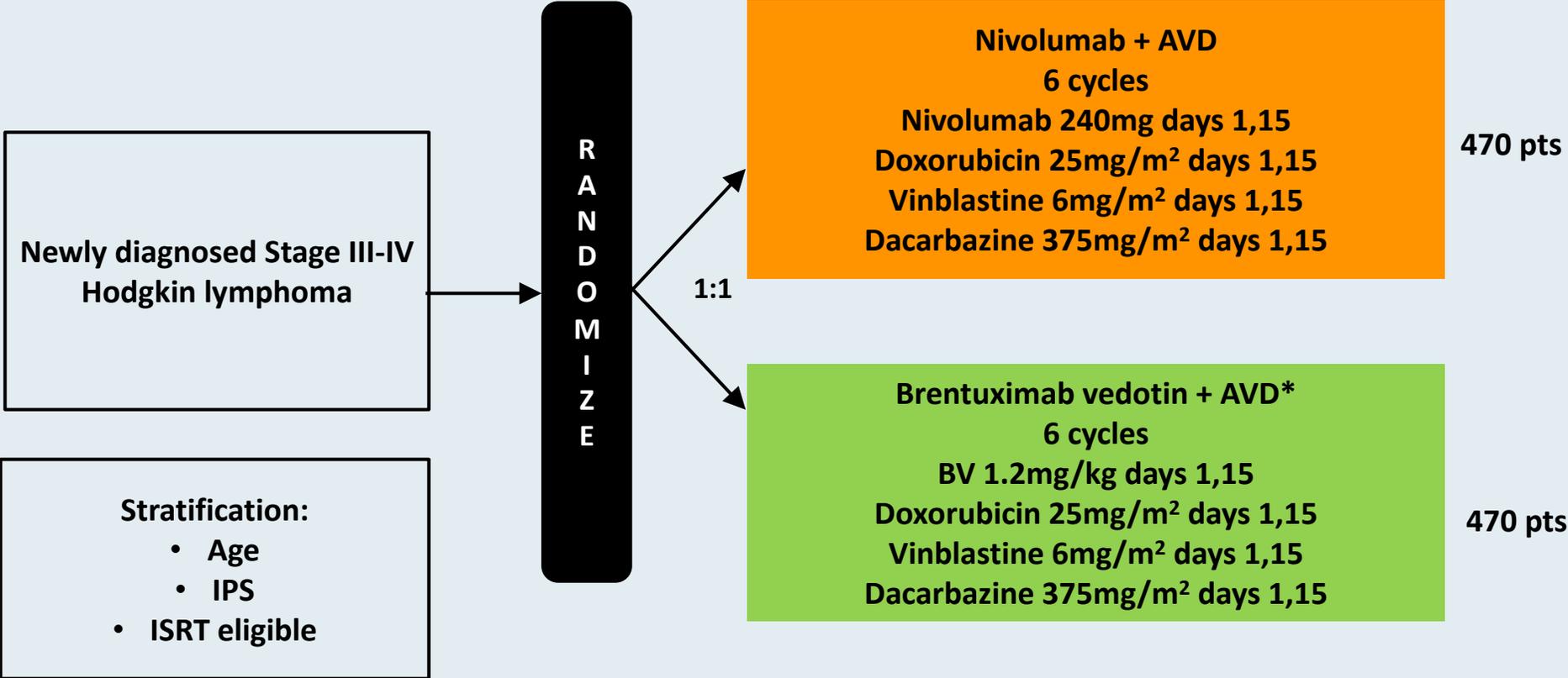
Radhakrishnan Ramchandren, MD<sup>1,2</sup>; Eva Domingo-Domènech, MD<sup>3</sup>; Antonio Rueda, MD, PhD<sup>4</sup>; Marek Trněný, MD<sup>5</sup>; Tatyana A. Feldman, MD<sup>6</sup>; Hun Ju Lee, MD<sup>7</sup>; Mariano Provencio, MD, PhD<sup>8</sup>; Christian Sillaber, MD<sup>9</sup>; Jonathon B. Cohen, MD, MS<sup>10</sup>; Kerry J. Savage, MD<sup>11</sup>; Wolfgang Willenbacher, MD<sup>12,13</sup>; Azra H. Ligon, PhD<sup>14</sup>; Jing Ouyang, PhD<sup>15</sup>; Robert Redd, MD<sup>15</sup>; Scott J. Rodig, MD<sup>14,15</sup>; Margaret A. Shipp, MD<sup>15</sup>; Mariana Sacchi, MD<sup>16</sup>; Anne Sumbul, MS<sup>16</sup>; Philippe Armand, MD, PhD<sup>15</sup>; and Stephen M. Ansell, MD, PhD<sup>17</sup>

*J Clin Oncol* 2019;37(23):1997-2007.

# CheckMate 205 (Cohort D): Nivolumab for Newly Diagnosed Advanced-Stage Classical HL



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

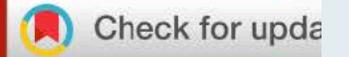


\* G-CSF is mandatory in BV-AVD arm, optional in N-AVD



blood®

Regular Article



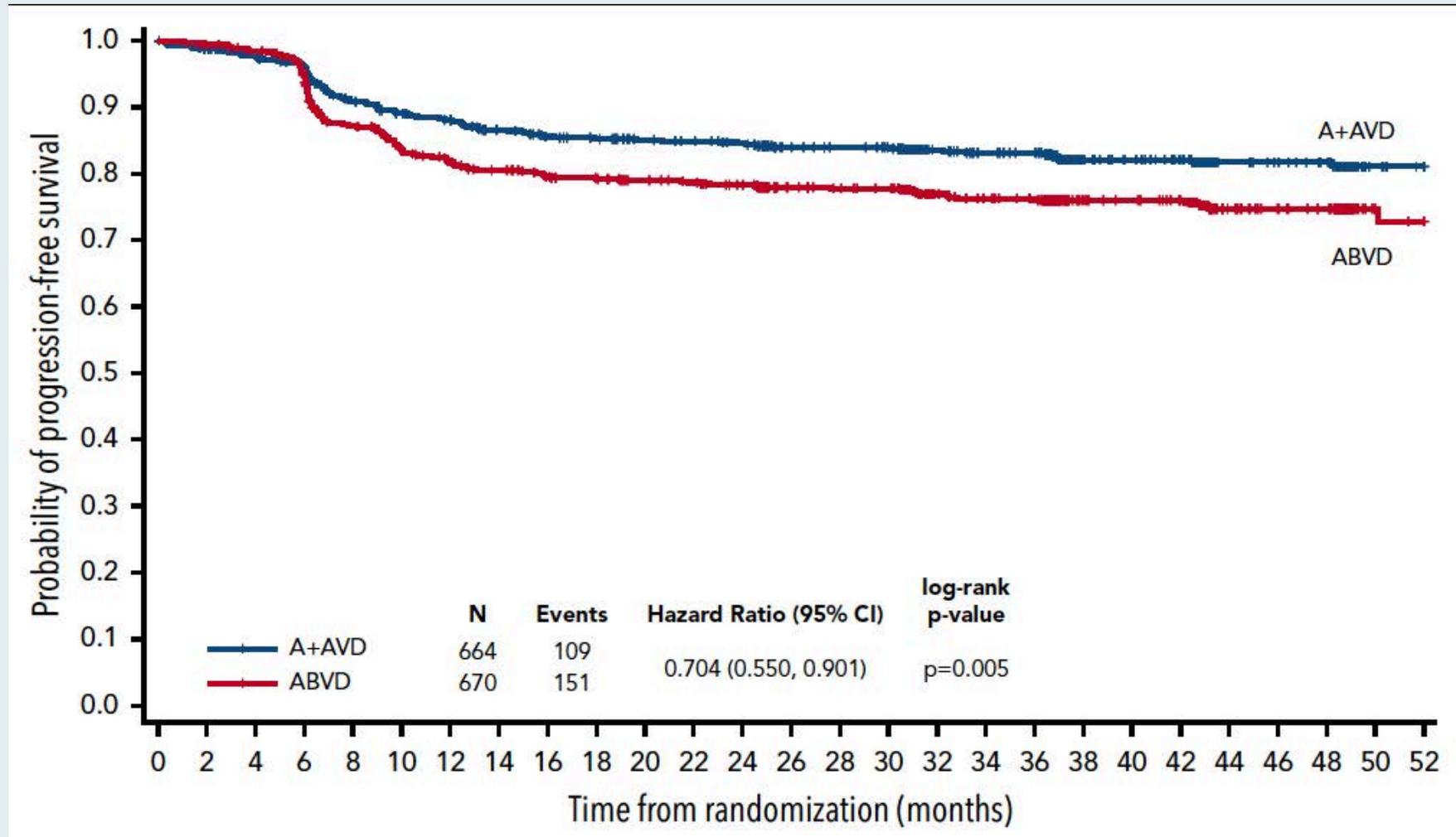
**CLINICAL TRIALS AND OBSERVATIONS**

# Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study

David J. Straus,<sup>1</sup> Monika Długosz-Danecka,<sup>2</sup> Sergey Alekseev,<sup>3</sup> Árpád Illés,<sup>4</sup> Marco Picardi,<sup>5</sup> Ewa Lech-Maranda,<sup>6</sup> Tatyana Feldman,<sup>7</sup> Piotr Smolewski,<sup>8</sup> Kerry J. Savage,<sup>9,10</sup> Nancy L. Bartlett,<sup>11</sup> Jan Walewski,<sup>12</sup> Radhakrishnan Ramchandren,<sup>13</sup> Pier Luigi Zinzani,<sup>14</sup> Martin Hutchings,<sup>15</sup> Joseph M. Connors,<sup>9,10</sup> John Radford,<sup>16,17</sup> Javier Munoz,<sup>18</sup> Won Seog Kim,<sup>19</sup> Ranjana Advani,<sup>20</sup> Stephen M. Ansell,<sup>21</sup> Anas Younes,<sup>1</sup> Harry Miao,<sup>22</sup> Rachael Liu,<sup>22</sup> Keenan Fenton,<sup>23</sup> Andres Forero-Torres,<sup>23</sup> and Andrea Gallamini<sup>24</sup>

*Blood* 2020;135(10):735-42.

# ECHELON-1: PFS Per Investigator at 3 Years



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

# **Current Concepts and Recent Advances in Oncology**

## ***A Daylong Clinical Summit Hosted in Partnership with Florida Cancer Specialists***

**Saturday, October 24, 2020  
8:30 AM – 4:30 PM ET**

### **Faculty**

**Arjun Balar, MD  
Johanna Bendell, MD  
Axel Grothey, MD  
Brad S Kahl, MD  
Shaji K Kumar, MD**

**Kathleen Moore, MD  
Loretta Nastoupil, MD  
William K Oh, MD  
David M O'Malley, MD  
Robert Z Orlowski, MD, PhD**

**Gregory J Riely, MD, PhD  
Hope S Rugo, MD  
David R Spigel, MD  
Sara M Tolaney, MD, MPH**

### **Moderator**

**Neil Love, MD**

# Agenda

**Module 1 — Lung Cancer:** *Drs Riely and Spigel*

**Module 2 — Multiple Myeloma:** *Drs Kumar and Orłowski*

**Module 3 — Chronic Lymphocytic Leukemia and Lymphomas:**  
*Drs Kahl and Nastoupil*

**Module 4 — Gastrointestinal Cancers:** *Drs Bendell and Grothey*

**Module 5 — Genitourinary Cancers:** *Drs Balar and Oh*

**Module 6 — Gynecologic Cancers:** *Drs Moore and O'Malley*

**Module 7 — Breast Cancer:** *Drs Rugo and Tolaney*

# Gastrointestinal Cancers Faculty



**Johanna Bendell, MD**

Chief Development Officer  
Director, Drug Development Unit Nashville  
Sarah Cannon Research Institute  
Tennessee Oncology  
Nashville, Tennessee



**Axel Grothey, MD**

Director, GI Cancer Research  
West Cancer Center and Research Institute  
Chair, OneOncology Research Network  
OneOncology  
Germantown, Tennessee

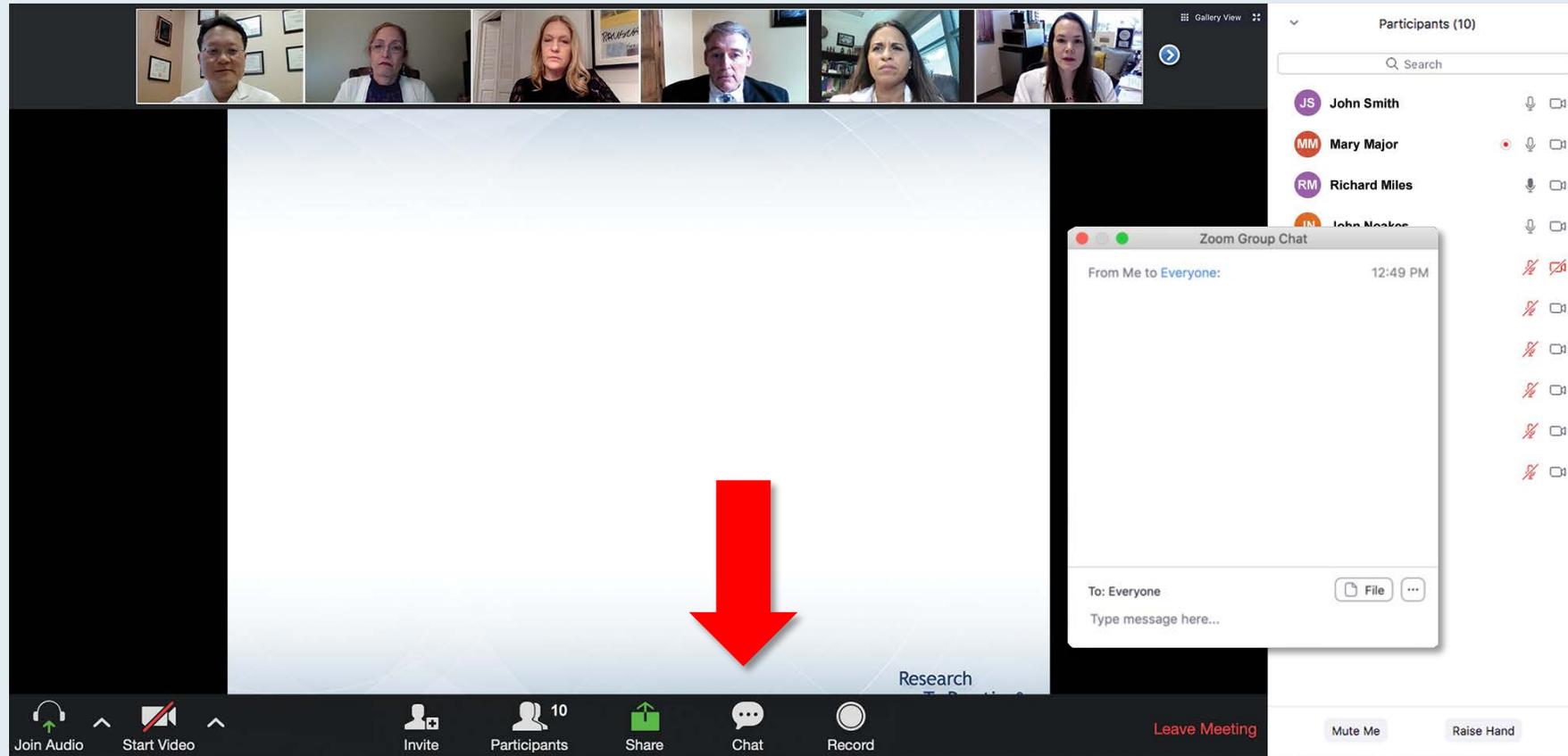
# Dr Bendell — Disclosures

|   |  |
|---|--|
| <p><b>Advisory Committee and Consulting Agreements (To Institution)</b></p> | <p>Agios Pharmaceuticals Inc, Amgen Inc, Apexigen, Arch Oncology, ARMO BioSciences, Array BioPharma Inc, a subsidiary of Kyn Therapeutics, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene, Bicycle Therapeutics, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Continuum Clinical, Cyteir Therapeutics, Daiichi Sankyo Inc, Evelo Biosciences Inc, Five Prime Therapeutics Inc, FORMA Therapeutics, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Incyte Corporation, Innate Pharma, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, Leap Therapeutics Inc, Lilly, MacroGenics Inc, Merck, Merrimack Pharmaceuticals Inc, Moderna Inc, Molecular Partners, Novartis, OncoGenex Pharmaceuticals Inc, OncoMed Pharmaceuticals Inc, Pfizer Inc, PhoenixBio, Piper Biotech, Prelude Therapeutics, Relay Therapeutics, Samsung Bioepis, Sanofi Genzyme, Seagen Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Tanabe Research Laboratories, TG Therapeutics Inc, Tizona Therapeutics Inc, Torque Therapeutics, Translational Drug Development</p>  |
| <p><b>Research Funding to Institution</b></p>                               | <p>AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, ADC Therapeutics SA, Agios Pharmaceuticals Inc, Amgen Inc, Apexigen, Arch Oncology, Arcus Biosciences, ARMO BioSciences, Array BioPharma Inc, a subsidiary of Kyn Therapeutics, Arrys Therapeutics, a wholly owned subsidiary of Kyn Therapeutics, AstraZeneca Pharmaceuticals LP, AtlasMedx Inc, Bayer HealthCare Pharmaceuticals, Beigene, Bellicum Pharmaceuticals Inc, Bicycle Therapeutics, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, CALGB, Calithera Biosciences, Celgene Corporation, Celldex Therapeutics, Cyteir Therapeutics, CytomX Therapeutics, Daiichi Sankyo Inc, eFFECTOR Therapeutics Inc, Eisai Inc, EMD Serono Inc, Evelo Biosciences, Five Prime Therapeutics Inc, FORMA Therapeutics, Forty Seven Inc, Foundation Medicine, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Gossamer Bio, Harpoon Therapeutics, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Incyte Corporation, Innate Pharma, Ipsen Biopharmaceuticals Inc, Jacobio Pharmaceuticals Co Ltd, Kolltan Pharmaceutical Inc, Leap Therapeutics Inc, Lilly, MacroGenics Inc, MEI Pharma, Merck, Merrimack Pharmaceuticals Inc, Mersana Therapeutics, Merus BV, Morphotek Inc, Nektar, NGM Biopharmaceuticals, Novartis, Novocure, Numab Therapeutics, OncoGenex Pharmaceuticals Inc, Oncologie, OncoMed Pharmaceuticals Inc, Onyx Pharmaceuticals, an Amgen subsidiary, Pfizer Inc, Pieris Pharmaceuticals Inc, Prelude Therapeutics, Relay Therapeutics, Revolution Medicines, Rgenix, Sanofi Genzyme, Scholar Rock, Seagen Inc, Shattuck Labs, Sierra Oncology, Stemcentrx, Sumitomo Dainippon Pharma Oncology Inc, SynDevRx Inc, Synthorx, Taiho Oncology Inc, Takeda Oncology, Tarveda Therapeutics, Tempest Therapeutics Inc, TG Therapeutics Inc, TRACON Pharmaceuticals Inc, Tyrogenex Inc, Unum Therapeutics, Vyriad, Zymeworks</p> |

# Dr Grothey — Disclosures

|   |  |
|---|--|
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| <b>Data and Safety Monitoring Board/Committee</b> | Regeneron Pharmaceuticals Inc  |

# We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

# FCS Contributing Oncologists



**Mamta Choksi, MD**  
New Port Richey, Florida



**Zanetta S Lamar, MD**  
Naples, Florida



**Uday Dandamudi, MD**  
New Port Richey, Florida



**Vikas Malhotra, MD**  
Spring Hill, Florida



**Lowell L Hart, MD**  
Fort Myers, Florida



**Shachar Peles, MD**  
Lake Worth, Florida



**Maen Hussein, MD**  
Tavares, Florida



**Syed F Zafar, MD**  
Fort Myers, Florida

# Agenda

## **Module 1: Metastatic Colorectal Cancer (mCRC)**

- Dr Choksi: A 65-year-old man with recurrent colon cancer, RAS mutation-positive
- Dr Hart: A 59-year-old man with mCRC – KRAS wild type, COVID-19 infection
- Dr Zafar: A 77-year-old woman with mCRC – BRAF V600E mutation, MSI-H, TMB 42 mut/Mb

## **Module 2: Gastric Cancer (GC)**

- Dr Malhotra: A 52-year-old woman with HER2-negative metastatic GC – PD-L1-positive, MSS

## **Module 3: Hepatocellular Carcinoma (HCC)**

- Dr Hussein: A 67-year-old man with recurrent metastatic HCC

## **Module 4: Pancreatic Adenocarcinoma (PAD)**

- Dr Lamar: A 90-year-old man with locally advanced PAD

## **Module 5: Advanced Cholangiocarcinoma with an Activating FGFR2 Rearrangement**

- Dr Hussein: A 66-year-old woman with intrahepatic cholangiocarcinoma

# Agenda

## Module 1: Metastatic Colorectal Cancer (mCRC)

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# Case Presentation – Dr Choksi: A 65-year-old man with recurrent colon cancer, RAS mutation-positive



**Dr Mamta T Choksi**

- 2/2011: Diagnosed with mucinous adenocarcinoma arising from right side of colon, T3N1bMX, stage IIIB colon carcinoma
  - Resection → adjuvant FOLFOX4 x 12, developed peripheral neuropathy
- 9/2011: PD in aortocaval LN, KRAS wildtype → FOLFIRI + cetuximab → maintenance cetuximab
- 12/2013: PD with retroperitoneal lymphadenopathy → FOLFIRI + ziv-aflibercept → observation
- 6/2016: PD with retroperitoneal lymphadenopathy
  - Diagnostic laparoscopy and retroperitoneal LN biopsy consistent with colon primary
  - RAS mutation positive
- 10/2016: 5-FU/LV + bevacizumab → NED since 3/2018
- 12/2018: Maintenance bevacizumab initiated (dose decreased by 50% since 1/2019)

## Questions

- How often do you see discrepancy in RAS mutation status over time?
- What are your thoughts about this histology of mucinous adenocarcinoma and response from the different treatment options?

# Case Presentation – Dr Hart: A 59-year-old man with metastatic colorectal cancer, KRAS wild type, COVID-19 infection



**Dr Lowell Hart**

- 2/2015: Presented with non-obstructing rectosigmoid mass and liver metastases
- Capecitabine-XRT to primary → FOLFOX/bevacizumab → maintenance bevacizumab/5-FU
- 5/2016: PD in liver → FOLFIRI/panitumumab
- 3/2017 – 6/2017: Transarterial radioembolization to R liver → Yttrium-90 → continued FOLFIRI/panitumumab
- 8/2018 – 8/2019: Switched to capecitabine per patient preference → PD
- Stereotactic XRT to liver and continued capecitabine; bevacizumab added in 10/2019
- 2/2020: PD in lung → Phase 1 clinical trial of PD1 inhibitor + SMAC mimetic → SD after 2 cycles, iron deficiency anemia due to bleeding ulcer → discontinued trial
- 6/2020: TAS-102 → COVID hospitalization, off drug from late June 2020 until 8/2020
- Currently resumed TAS-102, scan pending

## Questions

- For a patient with KRAS wildtype colorectal cancer who progresses on FOLFOX/bevacizumab, is it best to switch out the antibody and the chemotherapy?
- Are there any risks resuming TAS-102 therapy in this patient?

# Case Presentation – Dr Zafar: A 77-year-old woman with metastatic colorectal cancer – BRAF V600E mutation, MSI-H, TMB 42 mut/Mb



Dr Syed Zafar

- 7/2018: Ascending colon mass, multiple hepatic metastases
- NGS: BRAF V600E, BRCA2 and other mutations, MSI-H, TMB: 42 muts/Mb (see results)
- Genetic testing ATM VUS (see results)
- FOLFOX/bevacizumab, with PR → Maintenance 5FU/bevacizumab → PD 12 months later
  - Ablation of residual hepatic metastases x 2
- Pembrolizumab x 6 months → PD
- Ipilimumab/nivolumab x 6 months → PD
- Encorafenib/cetuximab (BEACON CRC regimen), with PR
  - Multiple keratoacanthomas, severe lichenoid keratosis → dose reduced encorafenib, but ongoing cutaneous effects
  - Patient discontinued treatment
- Currently, multiple hepatic and osseous metastases, deteriorating LFTs

## Question

- Will we be evaluating BRAF inhibitors combined with immunotherapy?

# Case Presentation – Dr Zafar: A 77-year-old woman – NGS



Dr Syed Zafar

## KRAS/NRAS

wildtype (codons 12, 13, 59, 61, 117, & 146 in exons 2, 3, & 4)

## Panitumumab

### OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapy. Please refer to the *professional services* section for additional information.

*Microsatellite status* MSI-High §

*Tumor Mutational Burden* 42 Muts/Mb §

AKT1 W80R

APC T1556fs\*3

APC D156fs\*14

BCOR C1329fs\*45

BRAF V600E

BRCA2 N863fs\*18

CTCF T69fs\*8

DNMT3A W297\*

FBXW7 R465C

FLCN H429fs\*39

MSH3 K383fs\*32

NOTCH1 P2415del

NOTCH3 R1895C

PTCH1 A239fs\*13

SMAD4 D415fs\*20

SMAD4 R361H

SMARCB1 T72fs\*13

SOX9 Q208\*

SUFU P24fs\*72

WHSC1 (MMSET) E1344fs\*91

# Case Presentation – Dr Zafar: A 77-year-old woman – Genetic testing



Dr Syed Zafar

-

**GENETIC RESULT: NEGATIVE - NO CLINICALLY SIGNIFICANT MUTATION IDENTIFIED**

Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

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**BREAST CANCER RISKSCORE™: REMAINING LIFETIME RISK 10.5%**

See riskScore™ Interpretation Section for more information.

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**CLINICAL HISTORY ANALYSIS: NO ADDITIONAL MANAGEMENT GUIDELINES IDENTIFIED BASED ON THE CLINICAL HISTORY PROVIDED**

Other clinical factors may influence individualized management. This analysis may be incomplete if details about cancer diagnoses, ages, family relationships or other factors were omitted or ambiguous.

**ADDITIONAL FINDINGS: VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED**

| GENE | VARIANT(S) OF UNCERTAIN SIGNIFICANCE | INTERPRETATION  |
|------|--------------------------------------|---|
| ATM  | c.2942G>A (p.Arg981His)              | <b>UNCERTAIN CLINICAL SIGNIFICANCE</b><br>There are currently insufficient data to determine if these variants cause increased cancer risk. |

**Regulatory and reimbursement issues aside, what would you generally recommend for a young patient with RAS wild-type, BRAF wild-type, MSS, left-sided mCRC who responded to then progressed on FOLFOX/bevacizumab?**

- a. FOLFIRI
- b. FOLFIRI/bevacizumab
- c. FOLFIRI/EGFR antibody
- d. Regorafenib
- e. TAS-102
- f. TAS-102/bevacizumab
- g. Other

# Have you or would you use TAS-102 in combination with bevacizumab outside of a clinical trial setting for a patient with mCRC?

- a. I have
- b. I have not but would for the right patient
- c. I have not and would not



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

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

*Lancet Oncol 2020; 21: 412–20*

# TAS-102 with Bevacizumab for Chemorefractory mCRC

- Randomized study with N = 93 patients with chemorefractory mCRC

|            | TAS-102/ bevacizumab<br>(n = 46) | TAS-102<br>(n = 47) | HR   | p-value |
|------------|----------------------------------|---------------------|------|---------|
| Median PFS | 4.6 mo                           | 2.6 mo              | 0.45 | 0.0015  |
| Median OS  | 9.4 mo                           | 6.7 mo              | 0.55 | 0.028   |

- Adverse events were as expected
- Grade 3 or 4 neutropenia (TAS-102/bev vs TAS-102): 67% vs 38% ( $p < 0.05$ )
- Serious adverse events (TAS-102/bev vs TAS-102): 19 patients vs 21 patients

# Comparison of Phase III Trials of Regorafenib and TAS-102 in mCRC

| Agent           | Regorafenib                  |                       |                              |                      | TAS-102                                     |                       |                              |                       |
|-----------------|------------------------------|-----------------------|------------------------------|----------------------|---|-----------------------|------------------------------|-----------------------|
| Trial           | CORRECT <sup>1</sup>         |                       | CONCUR <sup>2</sup>          |                      | RECOURSE <sup>3</sup>                       |                       | TERRA <sup>4</sup>           |                       |
| Prior biologics | 100% BEV<br>100% EGFR mAbs   |                       | 60%                          |                      | 100% BEV<br>53% EGFR mAbs<br>18% Prior REGO |                       | 20% BEV<br>18% EGFR mAbs     |                       |
|                 | REGO<br>(n = 505)            | BSC + PL<br>(n = 255) | REGO<br>(n = 136)            | BSC + PL<br>(n = 68) | TAS-102<br>(n = 534)                        | BSC + PL<br>(n = 266) | TAS-102<br>(n = 271)         | BSC + PL<br>(n = 135) |
| Prior lines     |                              |                       |                              |                      |   |                       |                              |                       |
| ≤2              | 27%                          | 25%                   | 35%                          | 35%                  | 18%   | 17%                   | 23%                          | 19%                   |
| 3               | 25%                          | 28%                   | 24%                          | 25%                  | 22%   | 20%                   | 27%                          | 27%                   |
| ≥4              | 49%                          | 47%                   | 38%                          | 40%                  | 60%   | 63%                   | 50%                          | 55%                   |
| Median OS, mo   | 6.4                          | 5.0                   | 8.8                          | 6.3                  | 7.1   | 5.3                   | 7.8                          | 7.1                   |
|                 | <b>HR: 0.77</b><br>P = .0052 |                       | <b>HR: 0.55</b><br>P = .0002 |                      | <b>HR: 0.68</b><br>P <.0001                 |                       | <b>HR: 0.79</b><br>P = .0035 |                       |
| Median PFS, mo  | 1.9                          | 1.7                   | 3.2                          | 1.7                  | 2.0   | 1.7                   | 2.0                          | 1.8                   |
|                 | HR: 0.49<br>P <.0001         |                       | HR: 0.31<br>P <.0001         |                      | HR: 0.48<br>P <.0001                        |                       | HR: 0.43<br>P <.0001         |                       |
| RR, %           | 1.0                          | 0.4                   | 4.4                          | 0                    | 1.6   | 0.4                   | 1.1                          | 0                     |

1. Grothey A, et al. *Lancet*. 2013;381:303-312; 2. Li J, et al. *Lancet Oncol*. 2015;16:619-629; 3. Mayer RJ, et al. *N Engl J Med*. 2015;372:1909-1919; 4. Kim TW, et al. ESMO 2016. Abstract 465PD.

Courtesy of Axel Grothey, MD

# FDA Approves Pembrolizumab as First-Line Treatment for Patients with Unresectable or Metastatic MSI-H or dMMR CRC

Press Release – June 29, 2020

“On June 29, 2020, the Food and Drug Administration approved pembrolizumab for the first-line treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer.

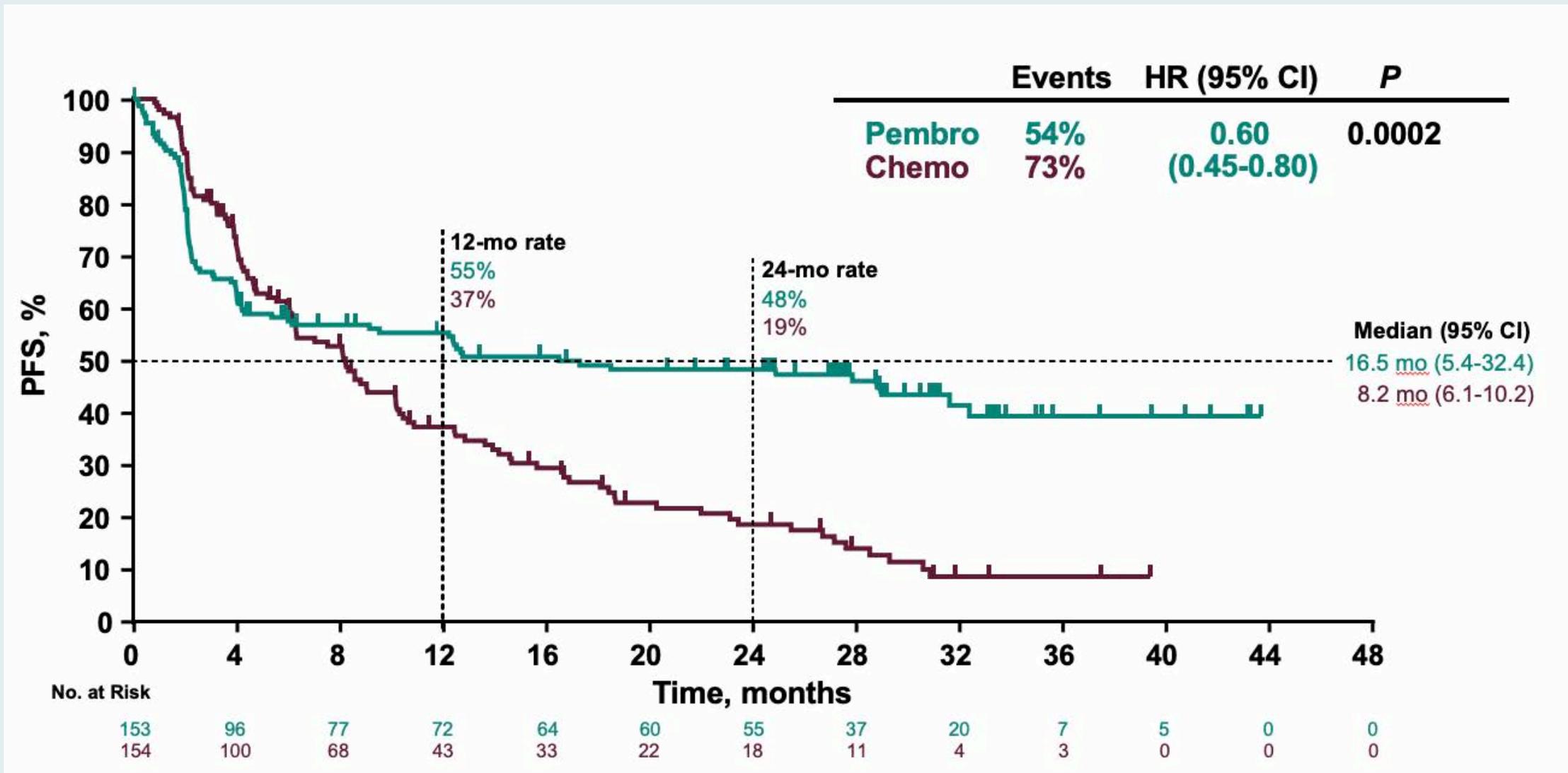
Approval was based on KEYNOTE-177 (NCT02563002), a multicenter, international, open-label, active-controlled, randomized trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR colorectal cancer. Determination of MSI or MMR tumor status was made locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients were randomized (1:1) to receive pembrolizumab 200 mg intravenously every 3 weeks or investigator’s choice of mFOLFOX6/FOLFIRI  $\pm$  bevacizumab or cetuximab given intravenously every 2 weeks. Patients randomized to chemotherapy were offered pembrolizumab at the time of disease progression.”

# **Pembrolizumab versus Chemotherapy for Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer: The Phase 3 KEYNOTE-177 Study**

Andre T et al.

ASCO 2020;Abstract LBA4.

# KEYNOTE-177: Progression-Free Survival Analysis



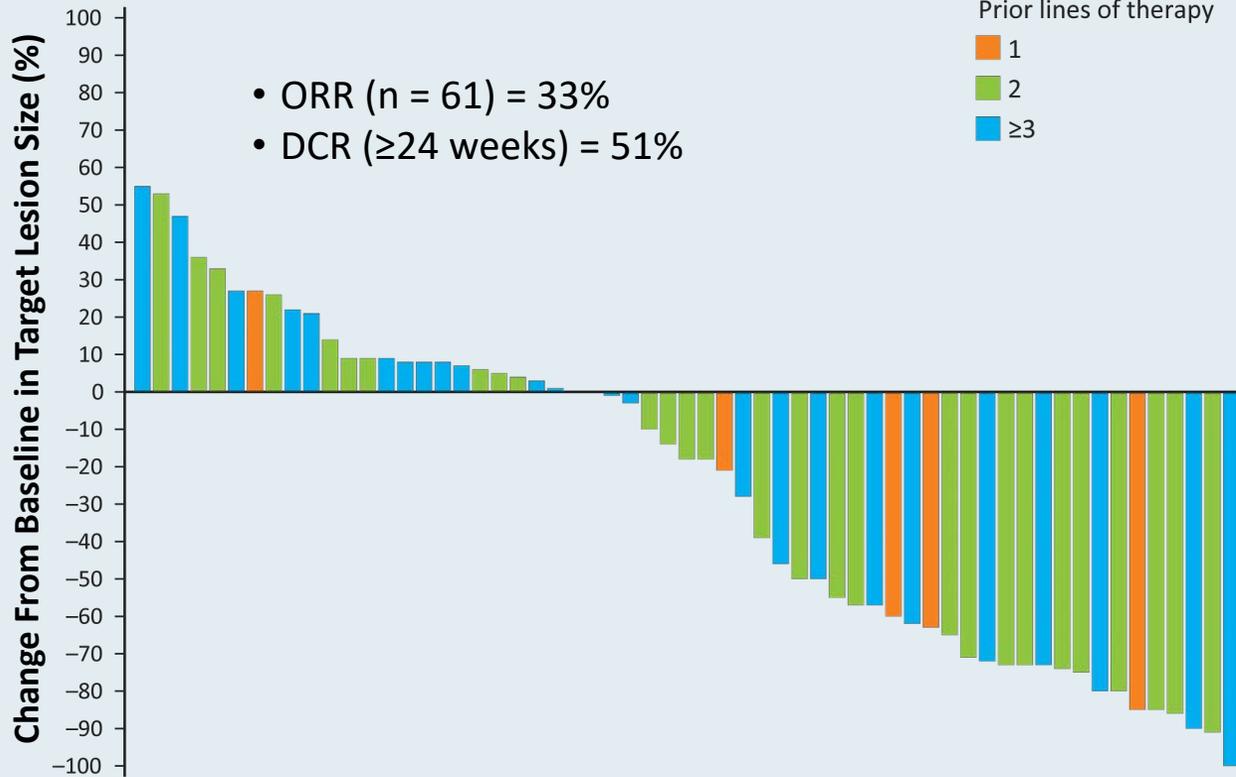
# Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164.

Le DT et al.

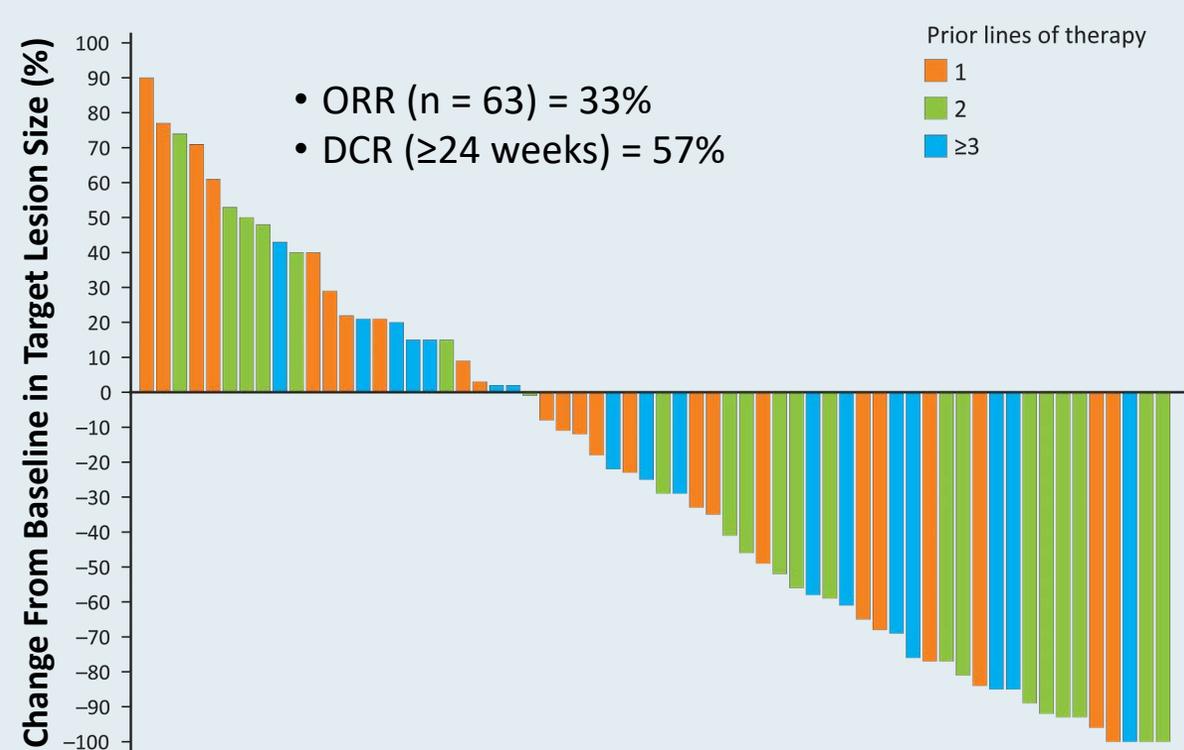
*J Clin Oncol* 2020;38(1):11-19.

# KEYNOTE-164: Pembrolizumab in Previously Treated dMMR/MSI-H mCRC

Cohort A:  $\geq 2$  prior lines of standard therapy



Cohort B:  $\geq 1$  prior line of systematic therapy



## Select Grade 3/4 immune-mediated AEs:

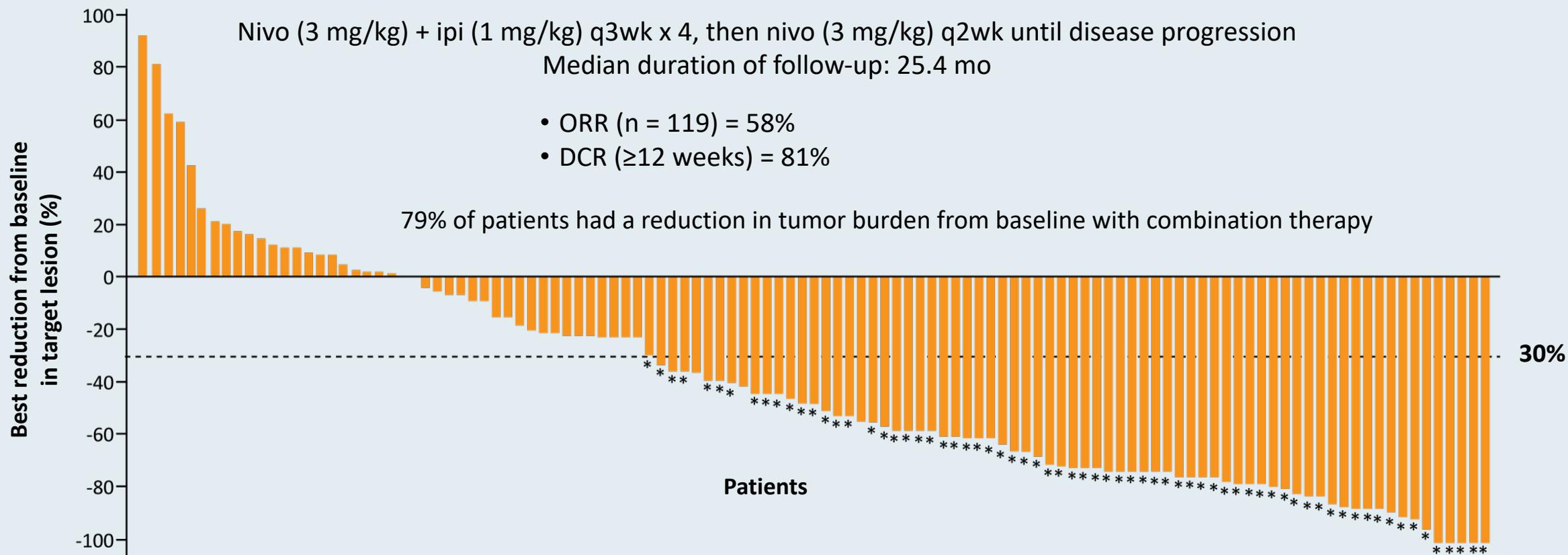
- Cohort A: Pancreatitis (3%), hepatitis (2%), pneumonitis (2%), severe skin toxicity (2%)
- Cohort B: Colitis (2%), pneumonitis (2%)

# **Nivolumab (NIVO) + Low-Dose Ipilimumab (IPI) in Previously Treated Patients (pts) with Microsatellite Instability-High/Mismatch Repair-Deficient (MSI-H/dMMR) Metastatic Colorectal Cancer (mCRC): Long-Term Follow-Up**

Overman MJ al.

Gastrointestinal Cancers Symposium 2019;Abstract 635.

# CheckMate 142: Long-Term Follow-Up of Nivolumab + Low-Dose Ipilimumab in Previously Treated dMMR/MSI-H mCRC



Patients had target lesion at baseline and at least 1 on-treatment tumor assessment.

\* Confirmed response per investigator assessment

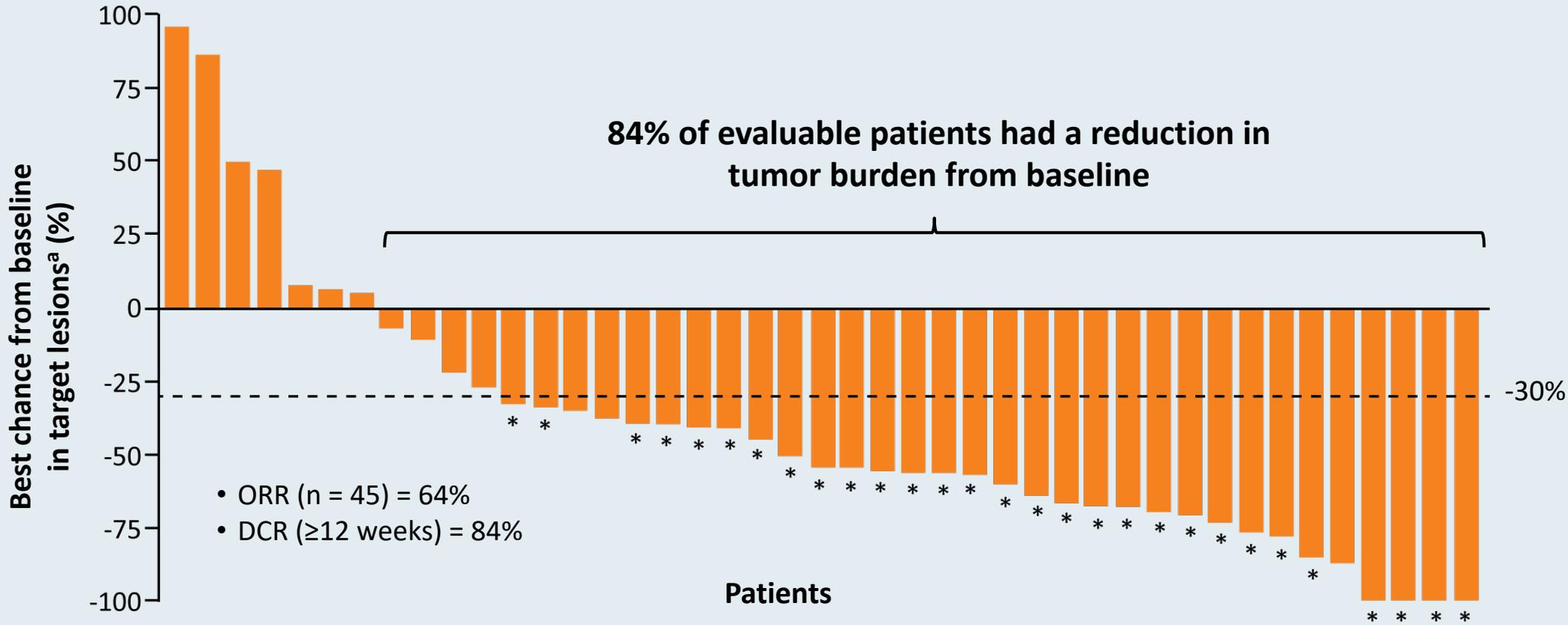
- Select Grade 3/4 treatment-related AEs:
  - Elevated AST (8%), diarrhea (3%), pruritus (2%), fatigue (2%)

# **Nivolumab plus Low-Dose Ipilimumab as First-Line Therapy in Microsatellite Instability-High/DNA Mismatch Repair Deficient Metastatic Colorectal Cancer: Clinical Update**

Lenz HJ al.

Gastrointestinal Cancers Symposium 2020;Abstract 11.

# CheckMate 142: Nivolumab with Low-Dose Ipilimumab as First-Line Therapy for dMMR/MSI-H mCRC



# FDA Approves Encorafenib in Combination with Cetuximab for mCRC with a BRAF V600E Mutation

Press Release – April 8, 2020

“On April 8, 2020, the Food and Drug Administration approved encorafenib in combination with cetuximab for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, detected by an FDA-approved test, after prior therapy.

Efficacy was evaluated in a randomized, active-controlled, open-label, multicenter trial (BEACON CRC; NCT02928224). Eligible patients were required to have BRAF V600E mutation-positive metastatic CRC with disease progression after one or two prior regimens.

Median OS was 8.4 months in the encorafenib and cetuximab arm compared to 5.4 months in the control arm (HR 0.60;  $p=0.0003$ ). Median PFS was 4.2 months in the encorafenib and cetuximab arm compared to 1.5 months in the control arm (HR 0.40;  $p<0.0001$ ).

The recommended encorafenib dose is 300 mg orally once daily in combination with cetuximab.”

# **A Phase II, Multicenter, Open-Label Study of Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients (pts) with HER2-Expressing Metastatic Colorectal Cancer (mCRC): DESTINY-CRC01**

Siena S et al.

ASCO 2020;Abstract 4000.

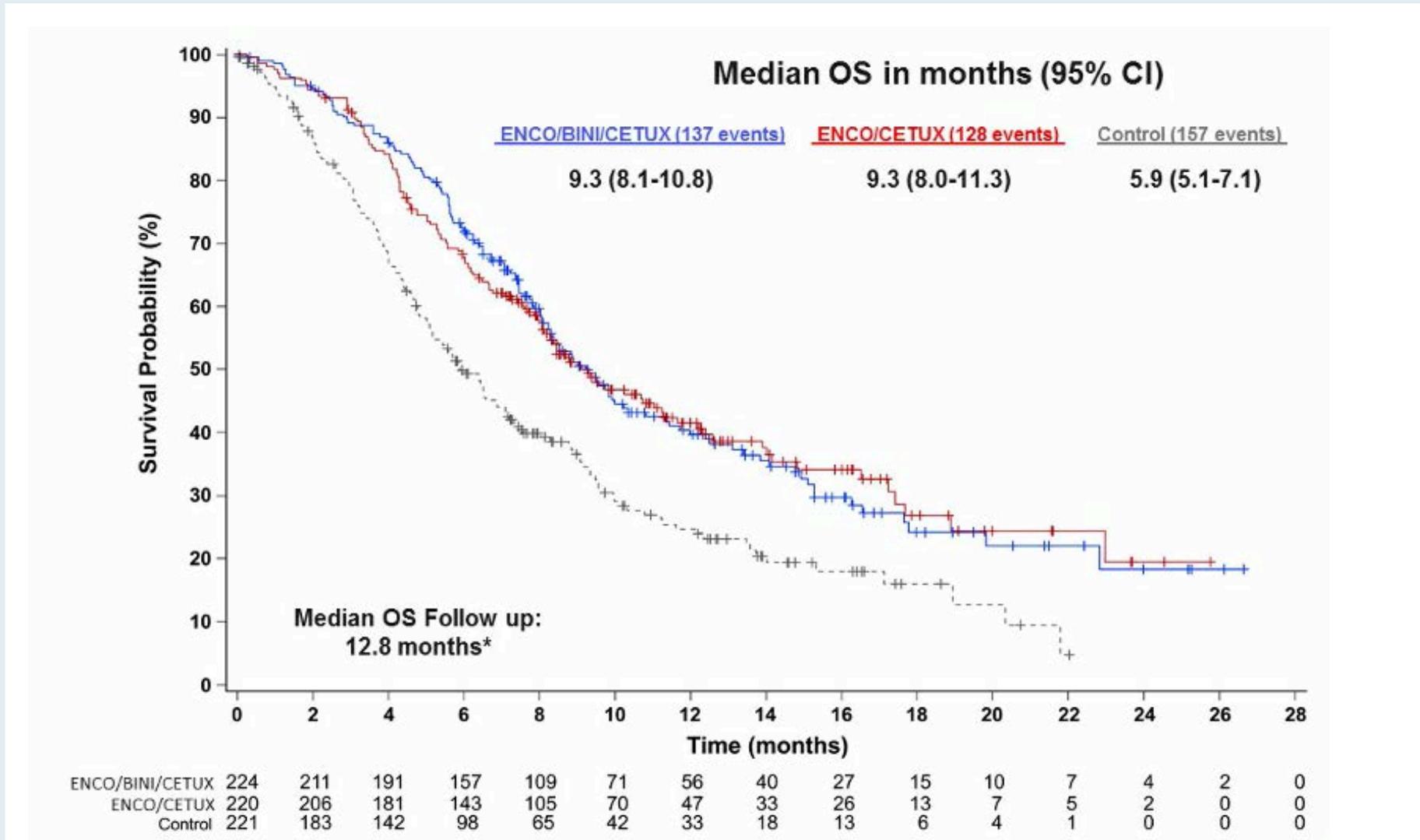


# **Encorafenib plus Cetuximab with or without Binimetinib for BRAF V600E Metastatic Colorectal Cancer: Updated Survival Results from a Randomized, Three-Arm, Phase III Study versus Choice of Either Irinotecan or FOLFIRI plus Cetuximab (BEACON CRC)**

Kopetz S et al.

ASCO 2020;Abstract 4001.

# BEACON CRC: Updated Overall Survival Analysis



# Agenda

## Module 1: Metastatic Colorectal Cancer (mCRC)

- Dr Choksi: A 65-year-old man with recurrent colon cancer, RAS mutation-positive
- Dr Hart: A 59-year-old man with mCRC – KRAS wild type, COVID-19 infection
- Dr Zafar: A 77-year-old woman with mCRC – BRAF V600E mutation, MSI-H, TMB 42 mut/Mb

## Module 2: Gastric Cancer (GC)

- Dr Malhotra: A 52-year-old woman with HER2-negative metastatic GC – PD-L1-positive, MSS

## Module 3: Hepatocellular Carcinoma (HCC)

- Dr Hussein: A 67-year-old man with recurrent metastatic HCC

## Module 4: Pancreatic Adenocarcinoma (PAD)

- Dr Lamar: A 90-year-old man with locally advanced PAD

## Module 5: Advanced Cholangiocarcinoma with an Activating FGFR2 Rearrangement

- Dr Hussein: A 66-year-old woman with intrahepatic cholangiocarcinoma

# Case Presentation – Dr Malhotra: A 52-year-old woman with HER2-negative metastatic gastric cancer, PD-L1-positive, MSS



**Dr Vikas Malhotra**

- Presented with anemia; workup showed large fungating, ulcerating mass in pyloric channel and lesions in liver; biopsy confirms poorly differentiated adenocarcinoma
- HER2-negative, PD-L1-positive, MSS
- 10/2019: Capecitabine/oxaliplatin with PR for 3 months
- 1/2020: PD → pembrolizumab
- Continues on pembrolizumab with good response

## Question

- Could you review the available data with pembrolizumab combined with chemotherapy in gastric cancer?

**A 65-year-old patient with locally advanced MSS gastric cancer responds to carboplatin/paclitaxel and radiation therapy but then develops recurrent disease 3 months later. CPS = 10. Regulatory and reimbursement issues aside, what treatment would you recommend?**

- a. FOLFOX
- b. Other chemotherapy
- c. Pembrolizumab
- d. Nivolumab
- e. Nivolumab + chemotherapy
- f. Other

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

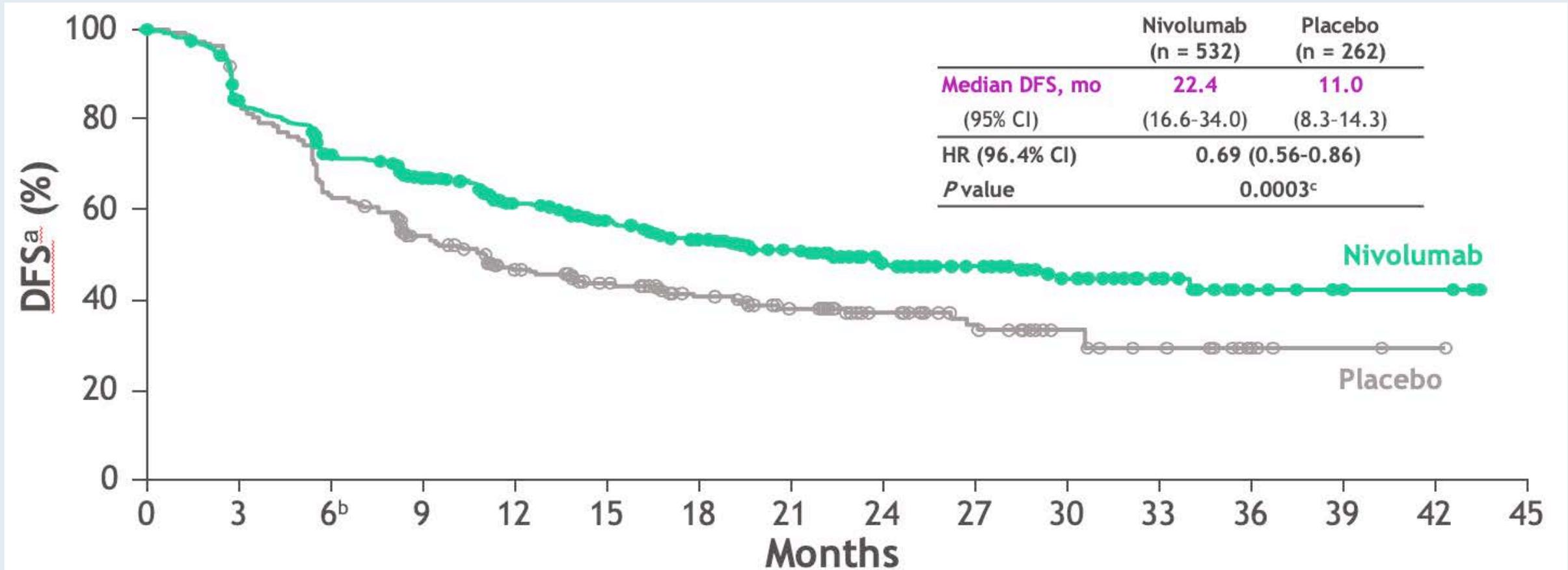
- a. TAS-102
- b. Other chemotherapy
- c. Pembrolizumab
- d. Nivolumab
- e. Trastuzumab deruxtecan
- f. Palliative care
- g. Other

# Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer Following Neoadjuvant Chemoradiation Therapy: First Results of the CheckMate 577 Study

Kelly RJ et al.

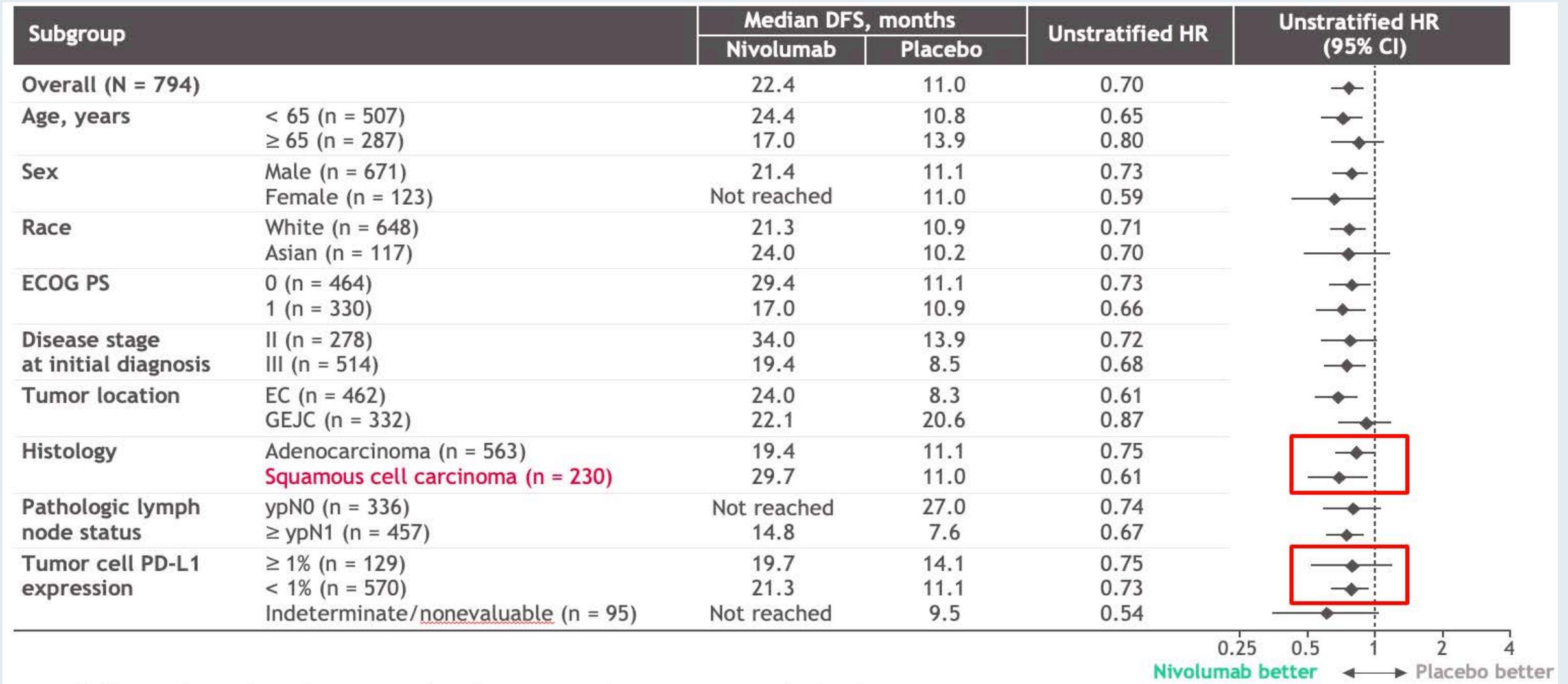
ESMO 2020;Abstract LBA9.

# CheckMate 577: Disease-Free Survival



<sup>a</sup> Per investigator assessment; <sup>b</sup>6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; <sup>c</sup>The boundary for statistical significance at the pre-specified interim analysis required the *P* value to be less than 0.036.

# CheckMate 577: Disease-Free Survival – Subgroup Analysis

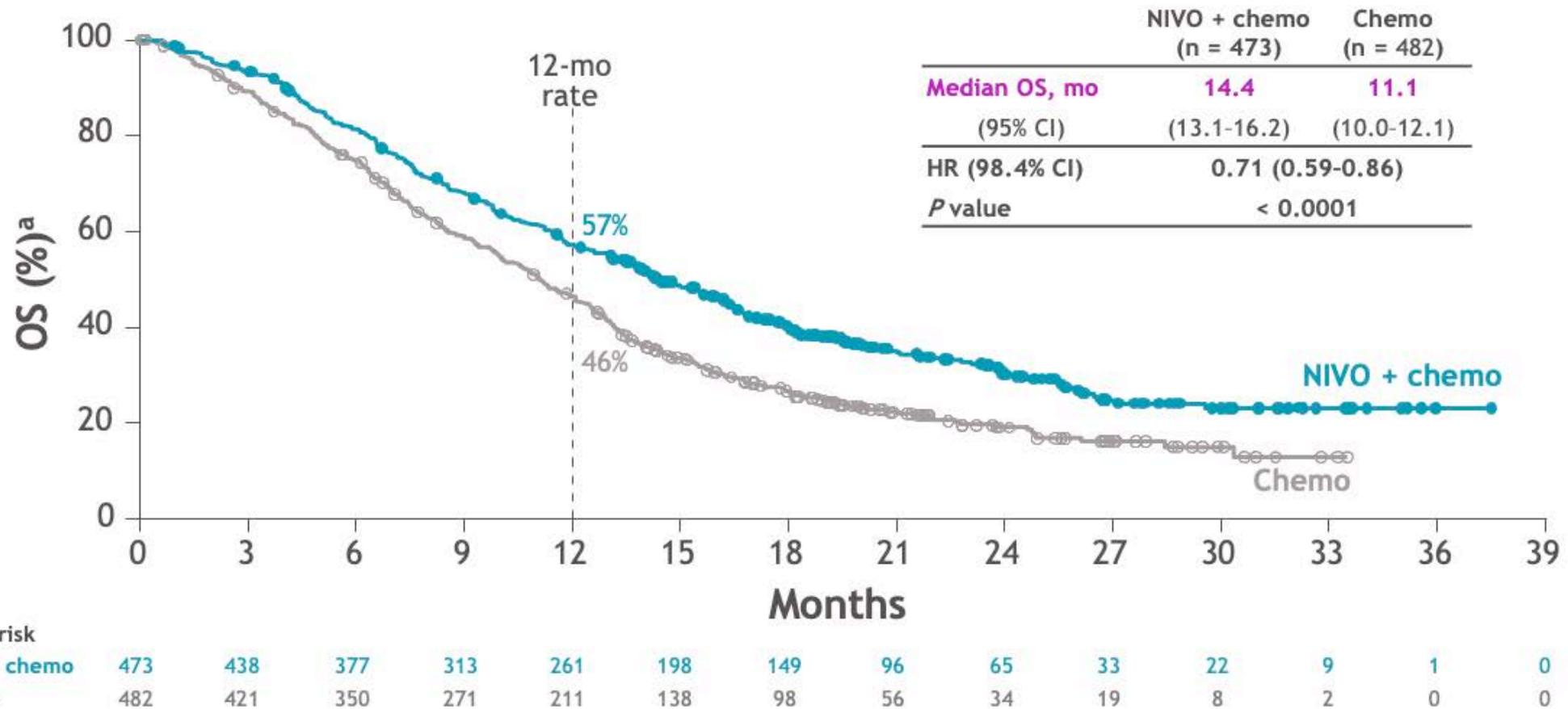


# **Nivolumab plus Chemotherapy versus Chemotherapy as First-Line Treatment for Advanced Gastric Cancer/Gastroesophageal Junction Cancer/Esophageal Adenocarcinoma: First Results of the CheckMate 649 Study**

Moehler M et al.

ESMO 2020;Abstract LBA6.

# CheckMate 649: Dual Primary Endpoint – OS (PD-L1 CPS $\geq 5$ )



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

<sup>a</sup>Minimum follow-up 12.1 months.

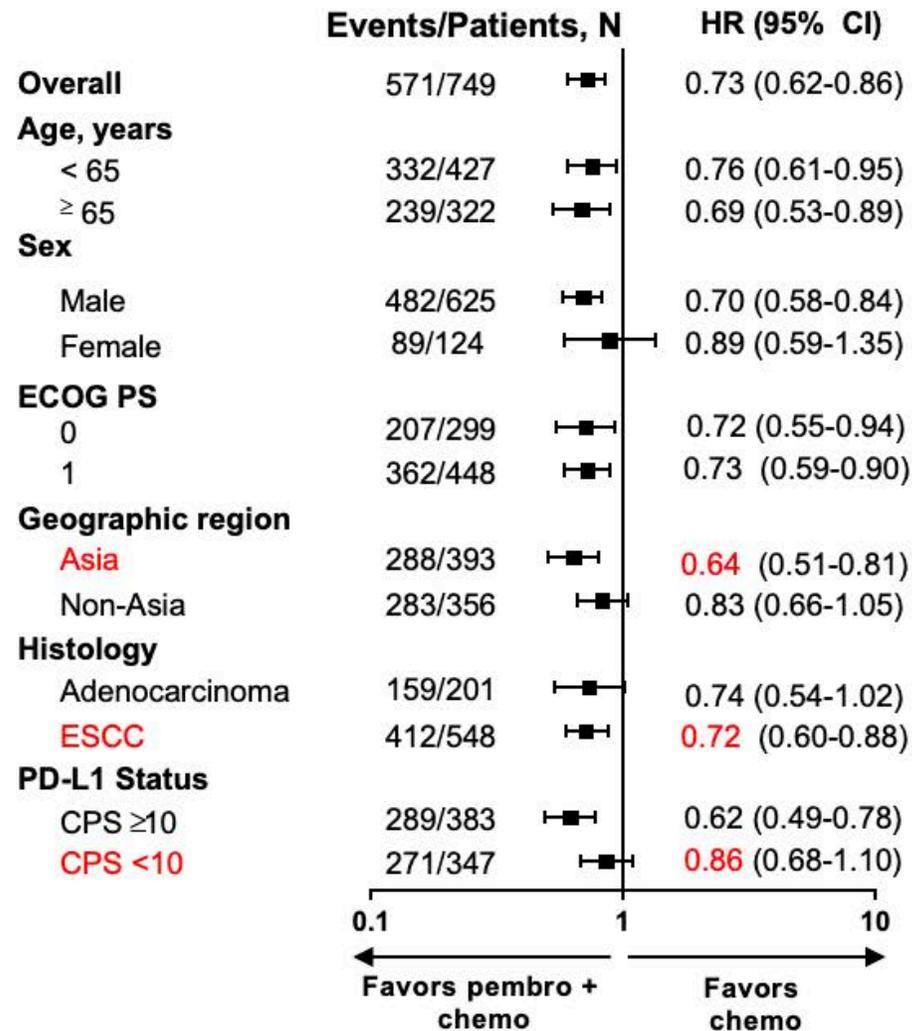
# **Pembrolizumab plus Chemotherapy versus Chemotherapy as First-Line Therapy in Patients with Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study**

Kato K et al.

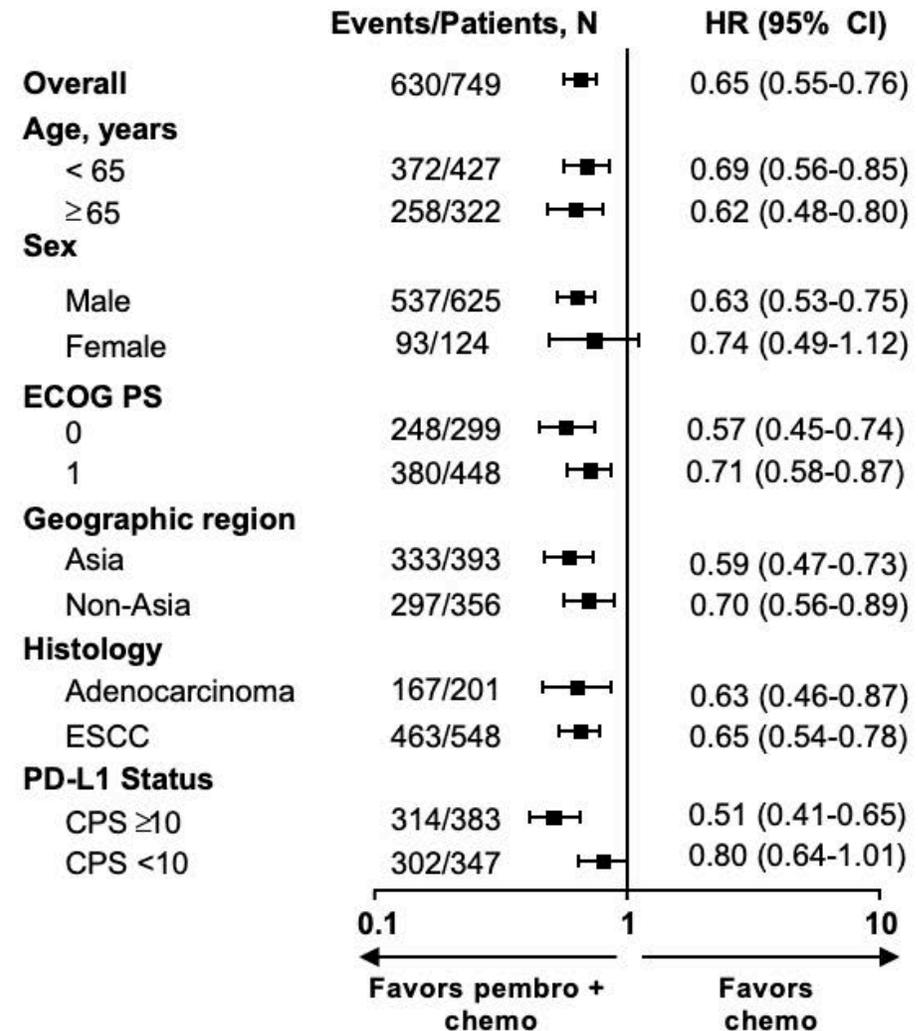
ESMO 2020;Abstract LBA8.

# KEYNOTE-590: Survival in Key Subgroups

## Overall Survival



## Progression-free Survival

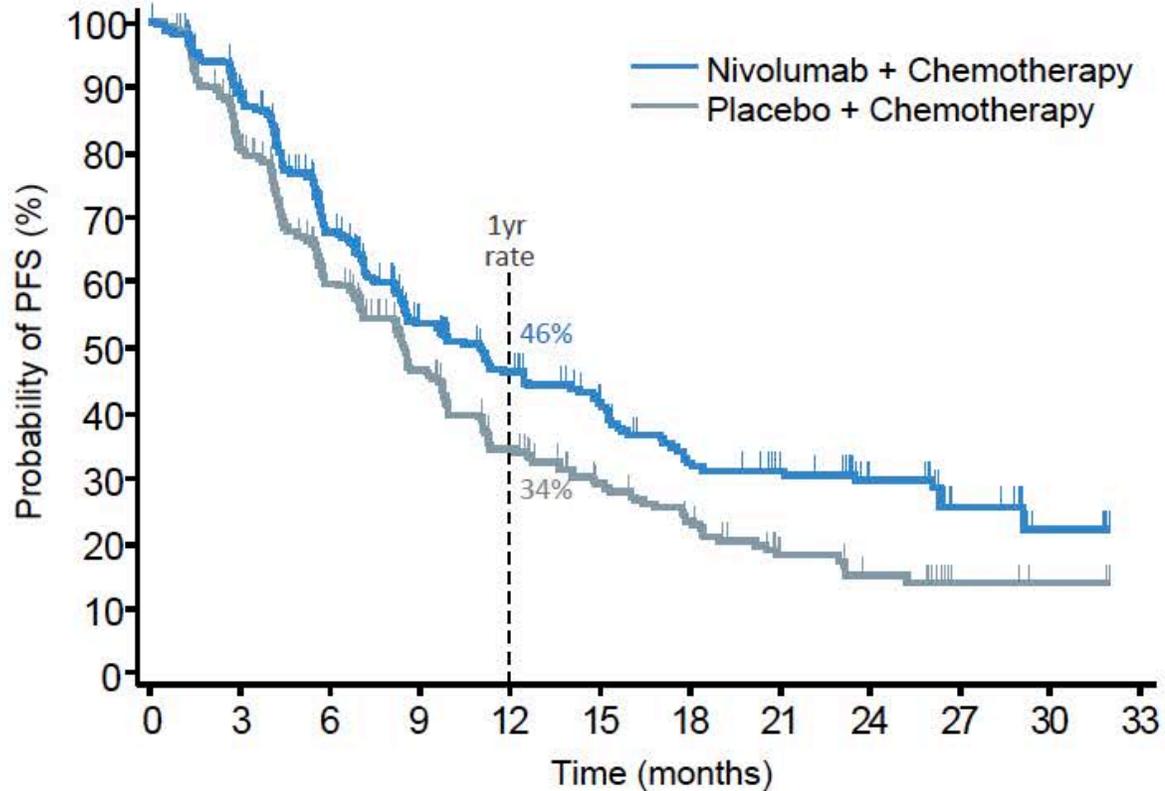


# **Nivolumab plus Chemotherapy versus Chemotherapy Alone in Patients with Previously Untreated Advanced or Recurrent Gastric/ Gastroesophageal Junction (G/GEJ) Cancer: ATTRACTION-4 (ONO-4538-37) Study**

Boku N et al.

ESMO 2020;Abstract LBA7.

# ATTRACTION-4: Survival (Final Analysis)



|                                | Nivolumab +<br>Chemotherapy<br>N = 362 | Placebo +<br>Chemotherapy<br>N = 362 |
|--------------------------------|--|--------------------------------------|
| Median PFS, months<br>(95% CI) | 10.94<br>(8.44-14.03)                  | 8.41<br>(7.03-9.69)                  |
| Hazard ratio<br>(95% CI)       | 0.70<br>(0.57 – 0.86)                  |                                      |
| <i>P</i> value                 | 0.0005                                 |                                      |
| 1yr PFS rate (%)               | 46.1                                   | 34.3                                 |

|                            | Nivolumab + chemotherapy<br>N = 362 | Placebo + chemotherapy<br>N = 362 |
|----------------------------|-------------------------------------|-----------------------------------|
| Median OS, months (95% CI) | 17.45 (15.67-20.83)                 | 17.15 (15.18-19.65)               |
| Hazard ratio (95% CI)      | 0.90 (0.75 – 1.08)                  |                                   |
| <i>P</i> value             | 0.257                               |                                   |

# FDA Grants Breakthrough Therapy Designation for Trastuzumab Deruxtecan for HER2-Positive Gastric or GEJ Adenocarcinoma

Press Release – May 11, 2020

“Trastuzumab deruxtecan has been granted Breakthrough Therapy Designation (BTD) in the US for the treatment of patients with HER2-positive unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma who have received two or more prior regimens including trastuzumab. The FDA granted BTD based on data from the registrational Phase II DESTINY-Gastric01 trial and data from the Phase I trial published in *The Lancet Oncology*<sup>5,6</sup>. In DESTINY-Gastric01, patients treated with trastuzumab deruxtecan demonstrated a statistically significant and clinically meaningful improvement in ORR, the primary endpoint, and OS, a key secondary endpoint, versus patients treated with investigator’s choice of chemotherapy (irinotecan or paclitaxel monotherapy).

The overall safety and tolerability profile in DESTINY-Gastric01 was consistent with that seen in the Phase I trial. The most common adverse events were haematologic and gastrointestinal including neutrophil count decrease, anaemia, nausea and decreased appetite. There were cases of drug-related interstitial lung disease (ILD) and pneumonitis, the majority of which were Grade 1 and 2, with two Grade 3 and one Grade 4. No ILD-related deaths (Grade 5) occurred in patients with gastric cancer in the Phase I trial or in the Phase II DESTINY-Gastric01 trial.”

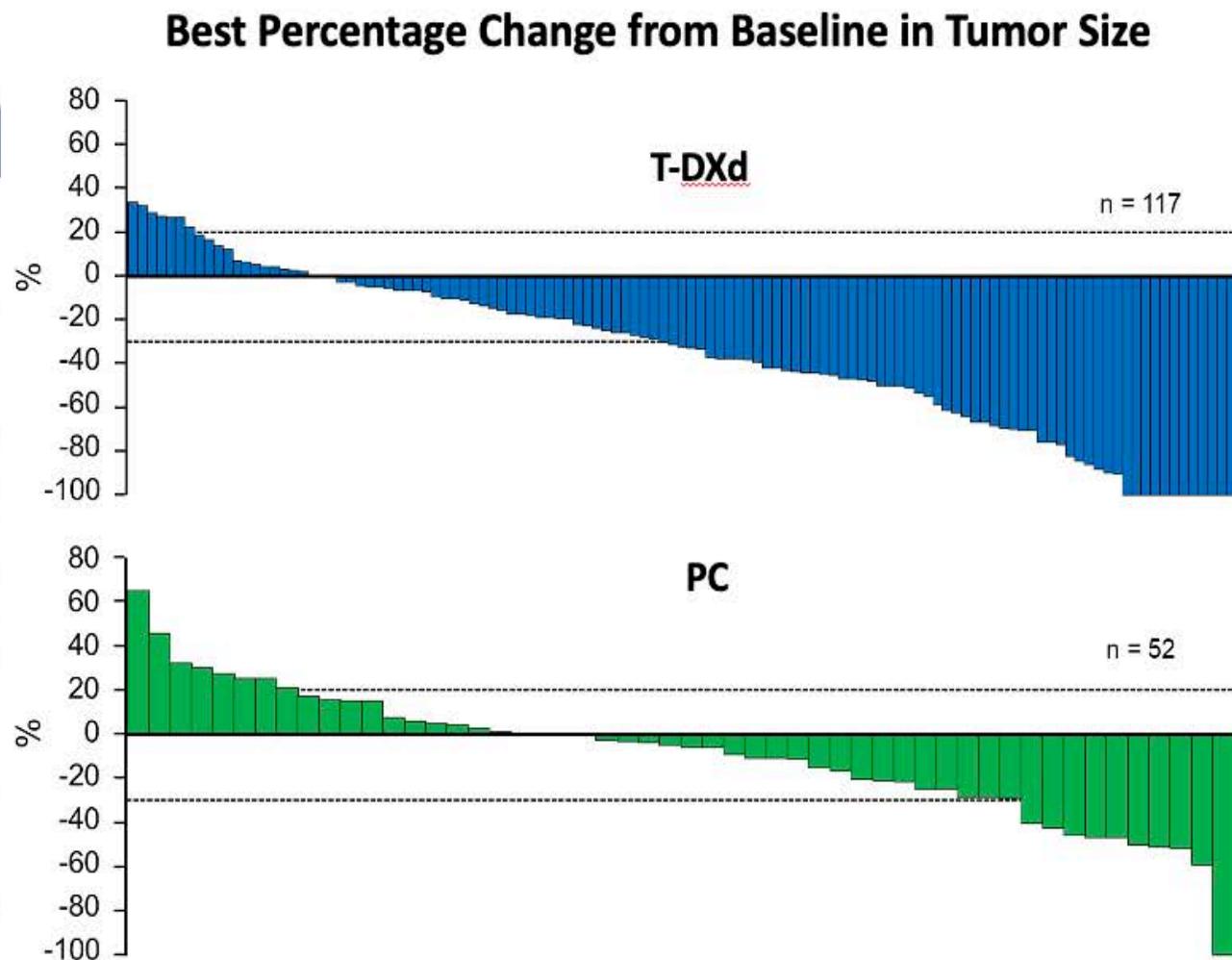
# **Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients (pts) with HER2-Positive Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma: A Randomized, Phase 2, Multicenter, Open-Label Study (DESTINY-Gastric01)**

Yamaguchi K et al.

ESMO World GI Congress 2020;Abstract O-11.

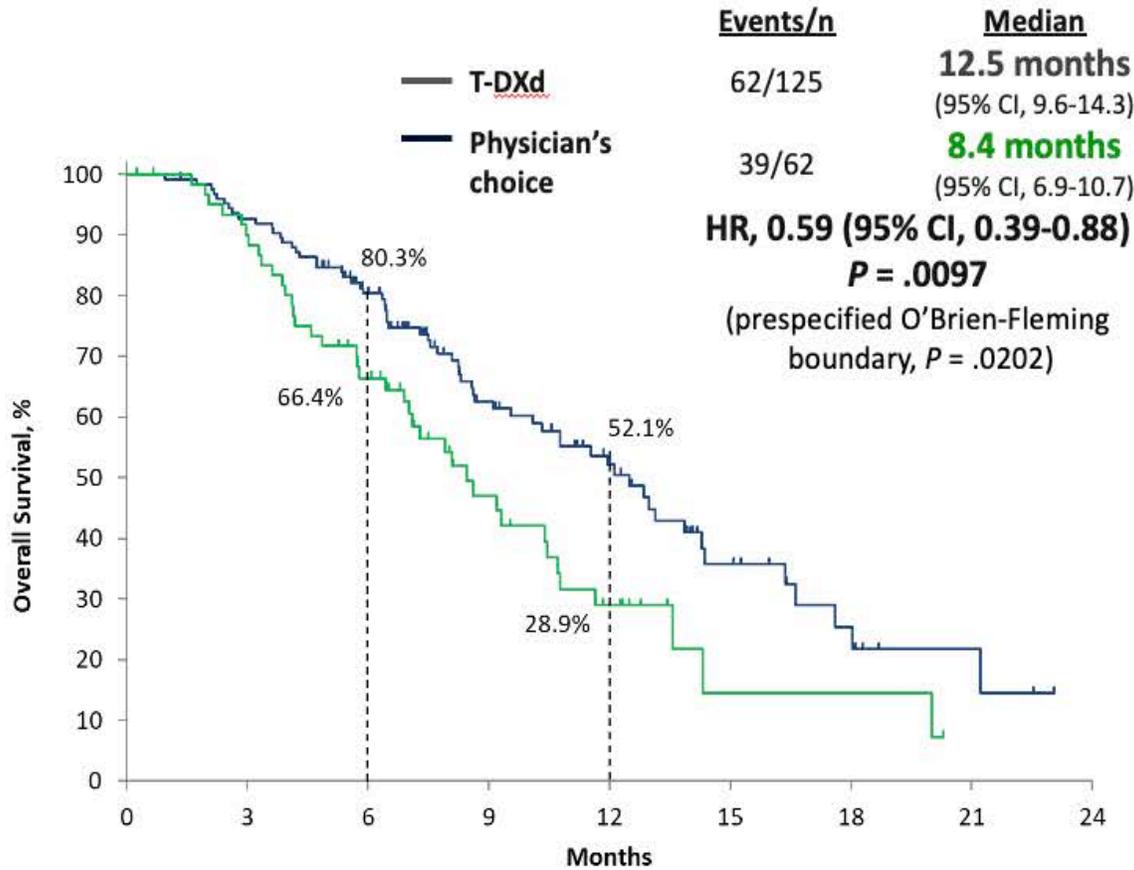
# DESTINY-Gastric01: Objective Response Rate (Primary Endpoint)

|                                       | <b>T-DXd (n = 119)</b>                                       | <b>PC (n = 56)</b>                         |
|---------------------------------------|--|--|
| <b>ORR by ICR (CR + PR)</b>           | <b>51.3% (n = 61)</b><br>95% CI, 41.9-60.5; <i>P</i> < .0001 | <b>14.3% (n = 8)</b><br>95% CI, 6.4-26.2   |
| <b>Confirmed ORR by ICR (CR + PR)</b> | <b>42.9% (n = 51)</b><br>95% CI, 33.8-52.3                   | <b>12.5% (n = 7)</b><br>95% CI, 5.2-24.1   |
| CR                                    | 8.4% (n = 10)  | 0  |
| PR                                    | 34.5% (n = 41)   | 12.5% (n = 7)                              |
| SD                                    | 42.9% (n = 51)   | 50.0% (n = 28)                             |
| PD                                    | 11.8% (n = 14)   | 30.4% (n = 17)                             |
| Not evaluable                         | 2.5% (n = 3)   | 7.1% (n = 4)                               |
| <b>Confirmed DCR (CR + PR + SD)</b>   | <b>85.7% (n = 102)</b><br>95% CI, 78.1-91.5                  | <b>62.5% (n = 35)</b><br>95% CI, 48.5-75.1 |
| <b>Median confirmed DOR</b>           | <b>11.3 months</b><br>95% CI, 5.6-NE                         | <b>3.9 months</b><br>95% CI, 3.0-4.9       |

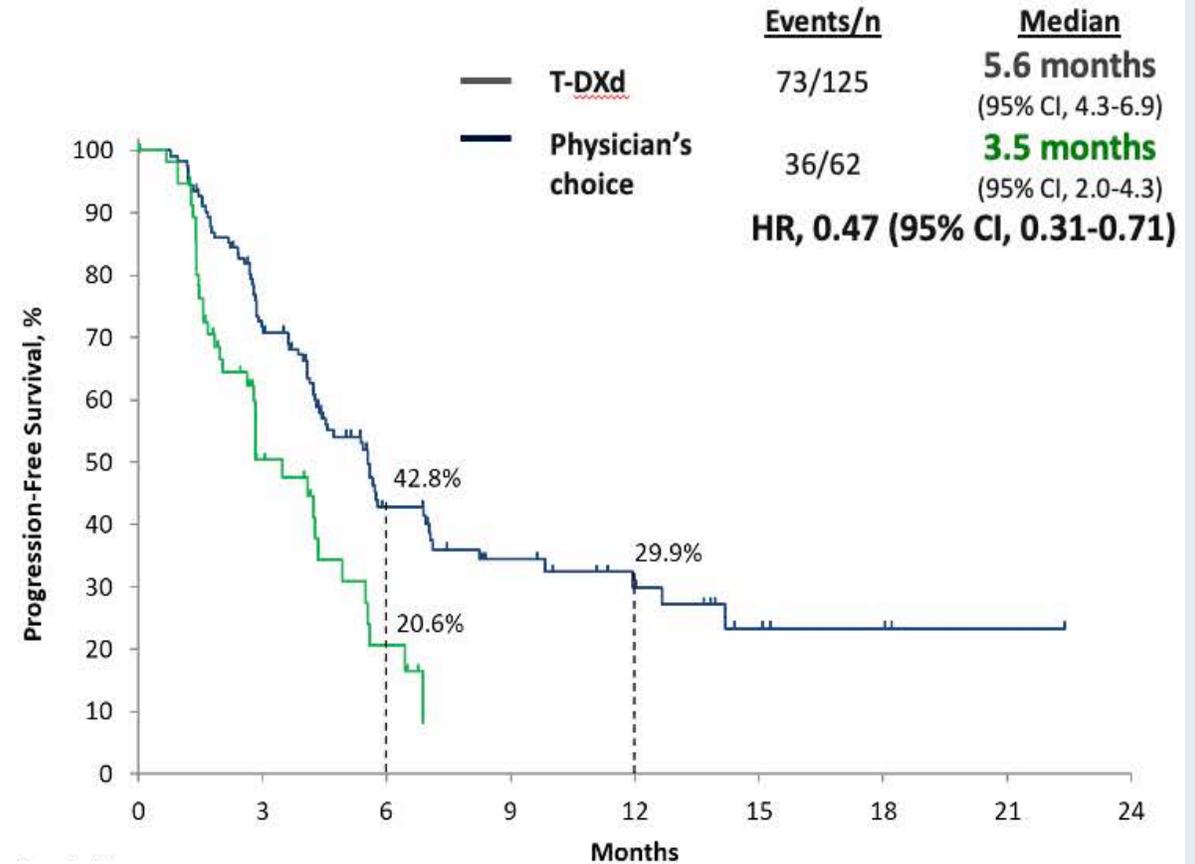


# DESTINY-Gastric01: Survival

## Overall Survival



## Progression-Free Survival



# Agenda

## **Module 1: Metastatic Colorectal Cancer (mCRC)**

- Dr Choksi: A 65-year-old man with recurrent colon cancer, RAS mutation-positive
- Dr Hart: A 59-year-old man with mCRC – KRAS wild type, COVID-19 infection
- Dr Zafar: A 77-year-old woman with mCRC – BRAF V600E mutation, MSI-H, TMB 42 mut/Mb

## **Module 2: Gastric Cancer (GC)**

- Dr Malhotra: A 52-year-old woman with HER2-negative metastatic GC – PD-L1-positive, MSS

## **Module 3: Hepatocellular Carcinoma (HCC)**

- Dr Hussein: A 67-year-old man with recurrent metastatic HCC

## **Module 4: Pancreatic Adenocarcinoma (PAD)**

- Dr Lamar: A 90-year-old man with locally advanced PAD

## **Module 5: Advanced Cholangiocarcinoma with an Activating FGFR2 Rearrangement**

- Dr Hussein: A 66-year-old woman with intrahepatic cholangiocarcinoma

# Case Presentation – Dr Hussein: A 67-year-old man with recurrent metastatic HCC



**Dr Maen Hussein**

- Past medical history of hepatitis and liver cirrhosis
- Initial diagnosis of localized HCC, clear cell features
  - Local therapy → recurrence in liver with peritoneal disease
- 5/2020: Atezolizumab + bevacizumab x 4 cycles → PD on imaging, patient doing well clinically
- 8/2020: Lenvatinib → hypertension, mouth sores, jaundice → lenvatinib discontinued

## Questions

- Would you have kept the patient on atezolizumab/bevacizumab given that progression was noted on imaging but the patient was doing well clinically?
- What therapy would you offer next to this patient? Is it reasonable to return to immunotherapy since the patient responded well clinically?
- Would cabozantinib be an option for this patient as 3<sup>rd</sup>-line therapy? Other TKIs?

**Regulatory and reimbursement issues aside, what would be your most likely second-line systemic therapy for a 65-year-old patient with HCC, a Child-Pugh A score and a PS of 0 who received first-line atezolizumab/bevacizumab with minimal toxicity and then experienced disease progression after 18 months (AFP = 2,500)?**

- a. Lenvatinib
- b. Regorafenib
- c. Ramucirumab
- d. Cabozantinib
- e. Sorafenib
- f. Anti-PD-1 antibody monotherapy
- g. Nivolumab/ipilimumab
- h. Other

# FDA Approves First-Line Atezolizumab with Bevacizumab for Unresectable or Metastatic HCC

Press Release – May 29, 2020

“On May 29, 2020, the Food and Drug Administration approved atezolizumab in combination with bevacizumab for patients with unresectable or metastatic hepatocellular carcinoma who have not received prior systemic therapy.

Efficacy was investigated in IMbrave150 (NCT03434379), a multicenter, international, open-label, randomized trial in patients with locally advanced unresectable or metastatic hepatocellular carcinoma who had not received prior systemic therapy. A total of 501 patients were randomized (2:1) to receive either atezolizumab 1200 mg as an intravenous infusion (IV) followed by bevacizumab 15 mg/kg IV on the same day, every 3 weeks, or sorafenib orally twice daily.”

ORIGINAL ARTICLE

# Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Richard S. Finn, M.D., Shukui Qin, M.D., Masafumi Ikeda, M.D., Peter R. Galle, M.D.,  
Michel Ducreux, M.D., Tae-You Kim, M.D., Masatoshi Kudo, M.D.,  
Valeriy Breder, M.D., Philippe Merle, M.D., Ahmed O. Kaseb, M.D., Daneng Li, M.D.,  
Wendy Verret, Ph.D., Derek-Zhen Xu, M.D., Sairy Hernandez, Ph.D., Juan Liu, Ph.D.,  
Chen Huang, M.D., Sohail Mulla, Ph.D., Yulei Wang, Ph.D., Ho Yeong Lim, M.D.,  
Andrew X. Zhu, M.D., Ph.D., and Ann-Lii Cheng, M.D.,  
for the IMbrave150 Investigators\*

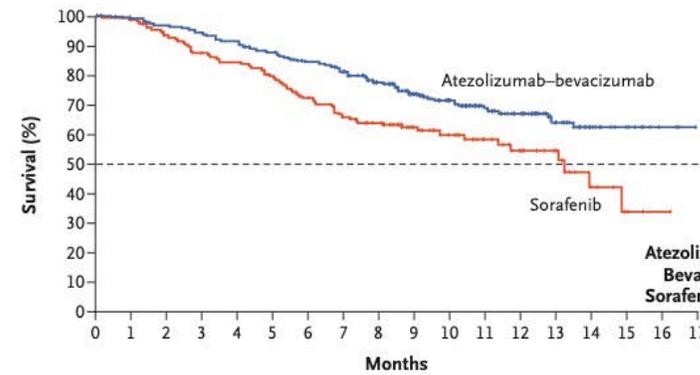
N Engl J Med 2020;382:1894-905.

# IMbrave150: Patient Characteristics and Survival

**Table 1. Patient Characteristics at Baseline.\***

| Variable   | Atezolizumab–Bevacizumab (N=336) | Sorafenib (N=165) |
|--|----------------------------------|-------------------|
| Median age (IQR) — yr  | 64 (56–71)                       | 66 (59–71)        |
| Male sex — no. (%)   | 277 (82)                         | 137 (83)          |
| Geographic region — no. (%)  |                                  |                   |
| Asia, excluding Japan  | 133 (40)                         | 68 (41)           |
| Rest of the world†   | 203 (60)                         | 97 (59)           |
| ECOG performance status score — no. (%)‡                                   |                                  |                   |
| 0  | 209 (62)                         | 103 (62)          |
| 1  | 127 (38)                         | 62 (38)           |
| Child–Pugh classification — no./total no. (%)§                             |                                  |                   |
| A5   | 239/333 (72)                     | 121/165 (73)      |
| A6   | 94/333 (28)                      | 44/165 (27)       |
| Barcelona Clinic liver cancer stage — no. (%)¶                             |                                  |                   |
| A  | 8 (2)                            | 6 (4)             |
| B  | 52 (15)                          | 26 (16)           |
| C  | 276 (82)                         | 133 (81)          |
| Alpha-fetoprotein ≥400 ng per milliliter — no. (%)                         | 126 (38)                         | 61 (37)           |
| Presence of macrovascular invasion, extrahepatic spread, or both — no. (%) | 258 (77)                         | 120 (73)          |
| Macrovascular invasion   | 129 (38)                         | 71 (43)           |
| Extrahepatic spread  | 212 (63)                         | 93 (56)           |
| Varices — no. (%)  |                                  |                   |
| Present at baseline  | 88 (26)                          | 43 (26)           |
| Treated at baseline  | 36 (11)                          | 23 (14)           |
| Cause of hepatocellular carcinoma — no. (%)                                |                                  |                   |
| Hepatitis B  | 164 (49)                         | 76 (46)           |
| Hepatitis C  | 72 (21)                          | 36 (22)           |
| Nonviral   | 100 (30)                         | 53 (32)           |
| Prior local therapy for hepatocellular carcinoma — no. (%)                 | 161 (48)                         | 85 (52)           |

**A Overall Survival**



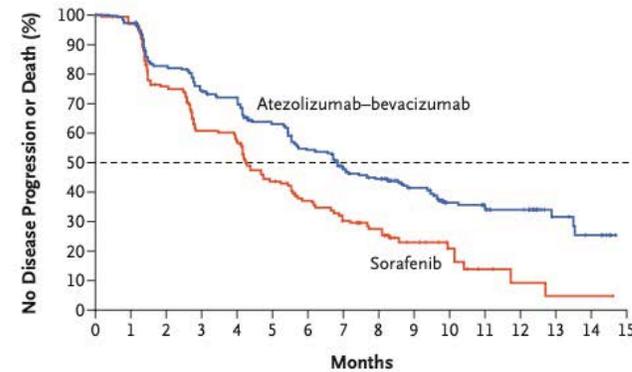
| No. of Events/<br>No. of Patients (%)  | Median Overall Survival (95% CI) mo | Overall Survival at 6 Mo % |
|--|-------------------------------------|----------------------------|
| Atezolizumab–Bevacizumab 96/336 (28.6) | NE                                  | 84.8                       |
| Sorafenib 65/165 (39.4)                | 13.2 (10.4–NE)                      | 72.2                       |

Stratified hazard ratio for death, 0.58 (95% CI, 0.42–0.79)  
P<0.001

**No. at Risk**

|                          |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |    |   |    |
|--------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|---|----|
| Atezolizumab–bevacizumab | 336 | 329 | 320 | 312 | 302 | 288 | 275 | 255 | 222 | 165 | 118 | 87 | 64 | 40 | 20 | 11 | 3 | NE |
| Sorafenib                | 165 | 157 | 143 | 132 | 127 | 118 | 105 | 94  | 86  | 60  | 45  | 33 | 24 | 16 | 7  | 3  | 1 | NE |

**B Survival without Disease Progression**



| No. of Events/<br>No. of Patients (%)   | Median Progression-free Survival (95% CI) mo | Progression-free Survival at 6 Mo % |
|---|--|-------------------------------------|
| Atezolizumab–Bevacizumab 197/336 (58.6) | 6.8 (5.7–8.3)                                | 54.5                                |
| Sorafenib 109/165 (66.1)                | 4.3 (4.0–5.6)                                | 37.2                                |

Stratified hazard ratio for progression or death, 0.59 (95% CI, 0.47–0.76)  
P<0.001

**No. at Risk**

|                          |     |     |     |     |     |     |     |     |     |    |    |    |    |    |   |    |
|--------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|---|----|
| Atezolizumab–bevacizumab | 336 | 322 | 270 | 243 | 232 | 201 | 169 | 137 | 120 | 74 | 50 | 46 | 34 | 11 | 7 | NE |
| Sorafenib                | 165 | 148 | 109 | 84  | 80  | 57  | 44  | 34  | 27  | 15 | 9  | 4  | 2  | 1  | 1 | NE |

# KEYNOTE-524: Phase Ib Study of Lenvatinib + Pembrolizumab for Patients with Unresectable HCC

**Lenvatinib 12 or 8 mg daily orally (based on body weight) + pembrolizumab 200 mg IV on Day 1 (21-day cycle)**

## DLT Evaluation (Part 1)

- n = 6
- Patients ineligible for other therapies
- Tolerability evaluated by DLTs during cycle 1

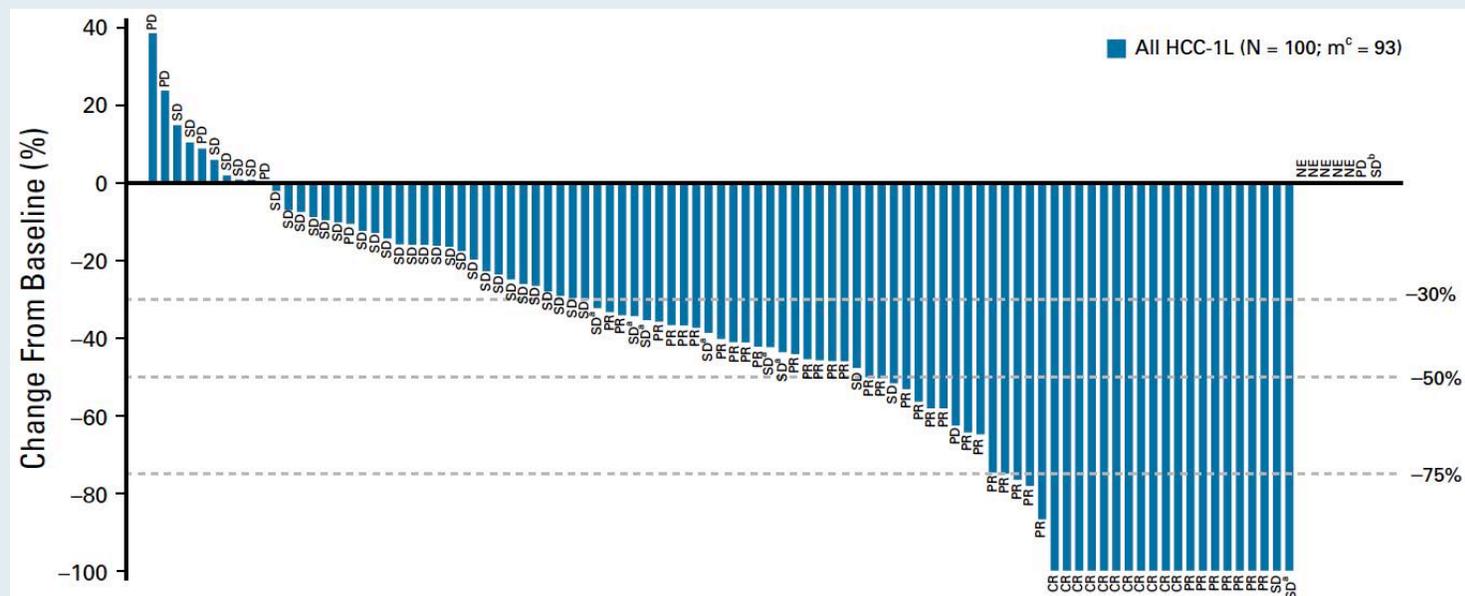
## Expansion (Part 2)

- n = 98
- No prior systemic therapy for uHCC

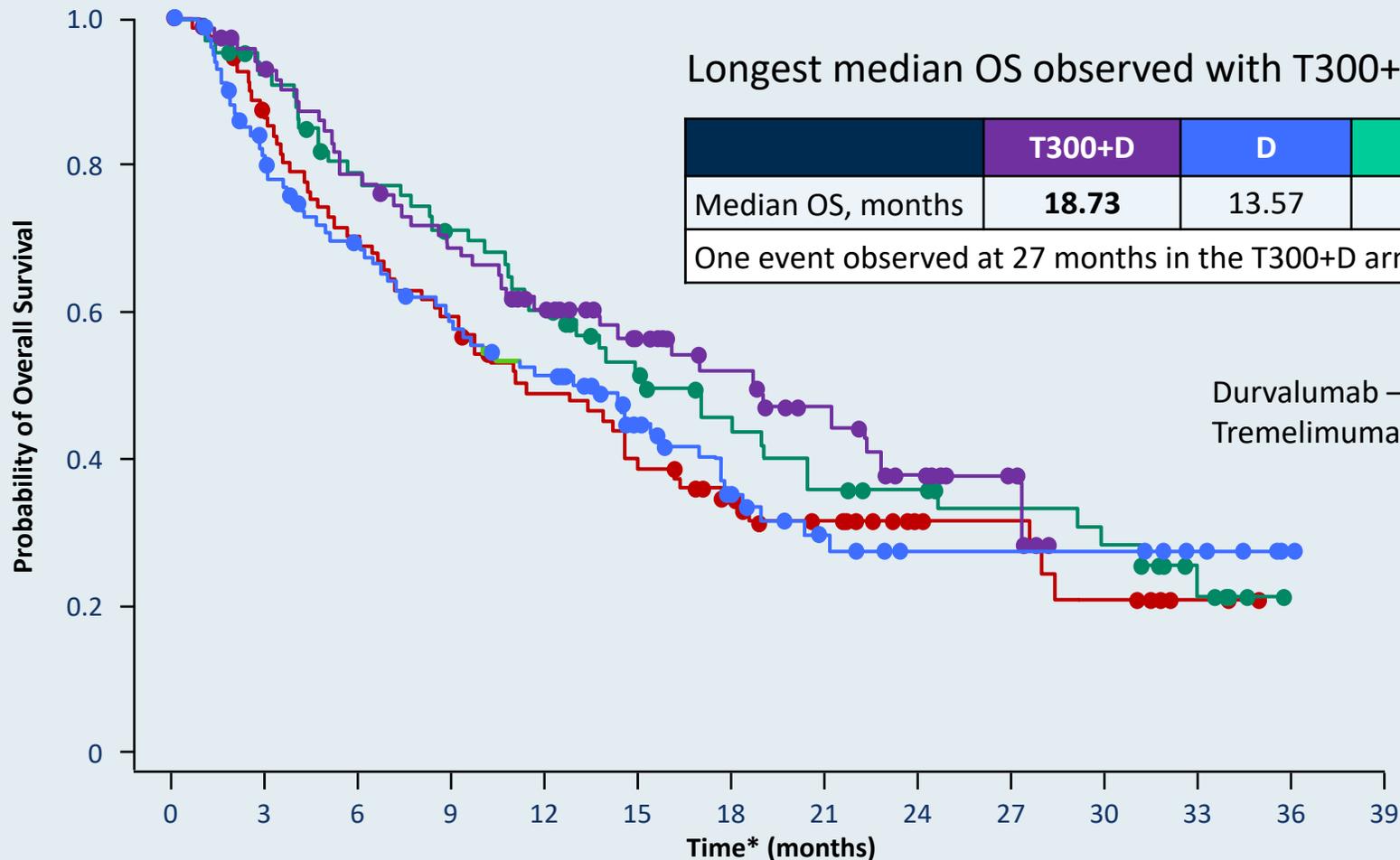
## Key Eligibility Criteria

- uHCC
- BCLC Stage B (not applicable for TACE) or C
- Child–Pugh class A
- ECOG performance status 0–1
- At least 1 measurable target lesion according to mRECIST

Response Rate: mRECIST



# Study 22: Durvalumab with or without Tremelimumab in Checkpoint Inhibitor-Naïve Advanced HCC



| Number of patients at risk | T300+D | D  | T  | T75+D | 75 | 90 | 105 | 120 | 135 | 150 | 165 | 180 | 195 | 210 | 225 | 240 | 255 | 270 | 285 | 300 | 315 | 330 | 345 | 360 |
|----------------------------|--------|----|----|-------|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| T300+D                     | 75     | 67 | 56 | 48    | 39 | 30 | 22  | 16  | 10  | 5   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| D                          | 104    | 78 | 65 | 54    | 46 | 31 | 20  | 14  | 8   | 8   | 8   | 5   | 1   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| T                          | 69     | 62 | 51 | 45    | 38 | 29 | 23  | 18  | 16  | 13  | 11  | 5   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |
| T75+D                      | 84     | 69 | 56 | 48    | 38 | 30 | 23  | 17  | 10  | 9   | 6   | 2   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   | 0   |

\*Time from randomization (Part 2A, 3) or first dose (Part 2B)

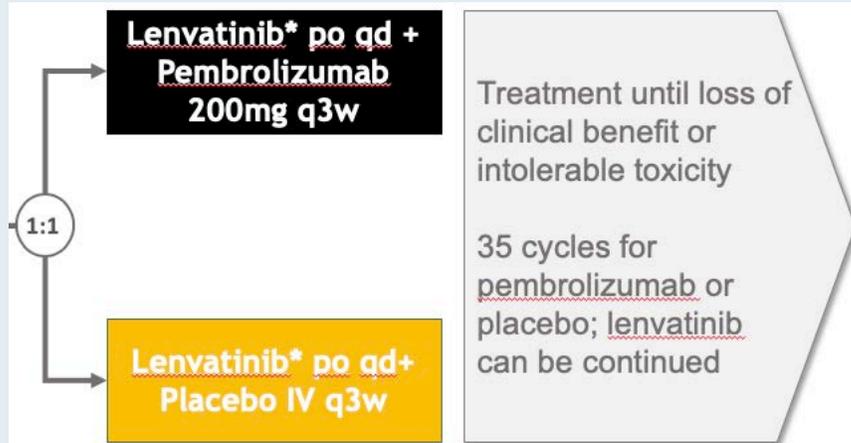
CI, confidence interval; D, durvalumab; OS, overall survival; T, tremelimumab



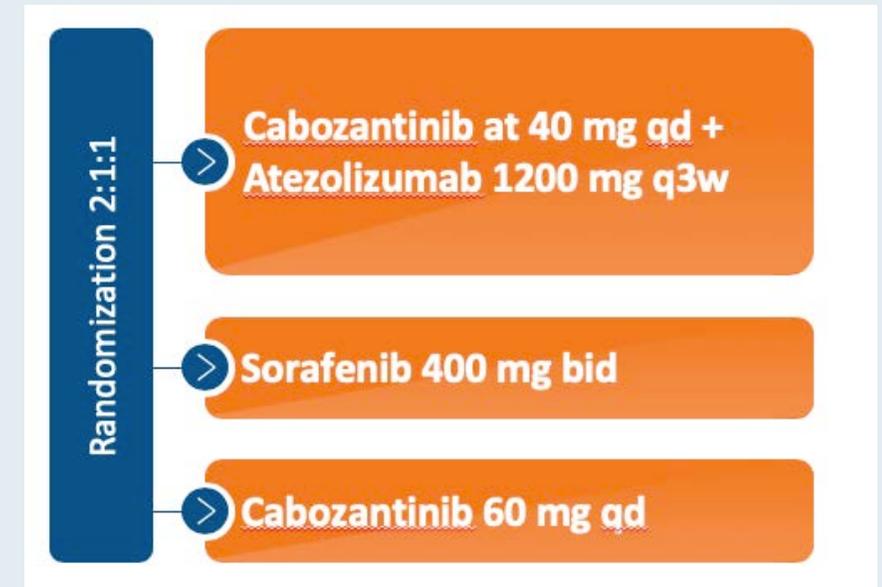
Courtesy of Alan P. Venook, M.D., FASCO

# Key Ongoing Phase III Trials of Checkpoint Inhibitor-Based Therapies for HCC

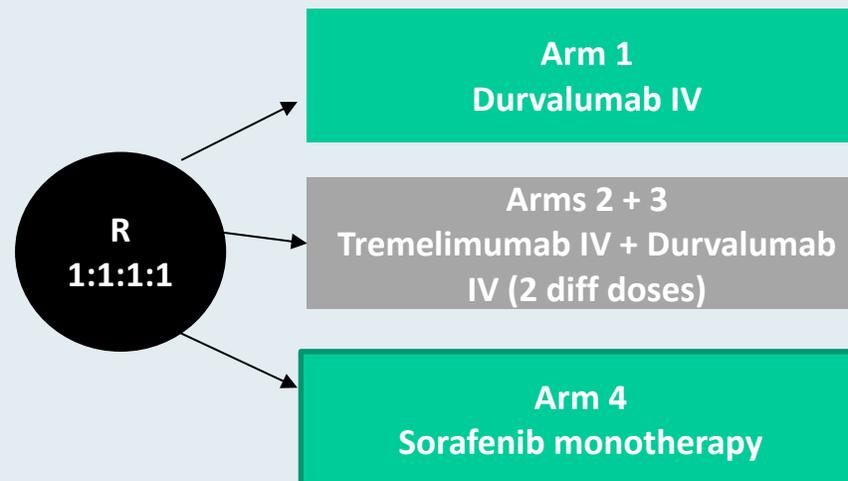
## LEAP-002 Trial



## COSMIC-312 Trial



## HIMALAYA Trial



Courtesy of Alan P. Venook, M.D., FASCO

# FDA Grants Accelerated Approval to Nivolumab and Ipilimumab Combination for HCC

Press Release – March 10, 2020

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

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

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

## CheckMate 040: Efficacy

|                                      | <b>NIVO1+IPI3 Q3 wk<br/>N = 50</b> | <b>NIVO3+IPI1 Q3 wk<br/>N = 49</b> | <b>NIVO3 Q 2 wk/<br/>IPI1 Q 6 wk<br/>N = 49</b> |
|--------------------------------------|------------------------------------|------------------------------------|---|
| Objective response rate (%)          | 32                                 | 31                                 | 31  |
| Median duration of response (months) | 17.5                               | 22.2                               | 16.6  |
| Median OS (months)                   | 23.0                               | 12.0                               | 13.0  |

# Agenda

## **Module 1: Metastatic Colorectal Cancer (mCRC)**

- Dr Choksi: A 65-year-old man with recurrent colon cancer, RAS mutation-positive
- Dr Hart: A 59-year-old man with mCRC – KRAS wild type, COVID-19 infection
- Dr Zafar: A 77-year-old woman with mCRC – BRAF V600E mutation, MSI-H, TMB 42 mut/Mb

## **Module 2: Gastric Cancer (GC)**

- Dr Malhotra: A 52-year-old woman with HER2-negative metastatic GC – PD-L1-positive, MSS

## **Module 3: Hepatocellular Carcinoma (HCC)**

- Dr Hussein: A 67-year-old man with recurrent metastatic HCC

## **Module 4: Pancreatic Adenocarcinoma (PAD)**

- Dr Lamar: A 90-year-old man with locally advanced PAD

## **Module 5: Advanced Cholangiocarcinoma with an Activating FGFR2 Rearrangement**

- Dr Hussein: A 66-year-old woman with intrahepatic cholangiocarcinoma

# Case Presentation – Dr Lamar: A 90-year-old man with locally advanced pancreatic cancer



Dr Zanetta Lamar

- Presented with locally advanced pancreatic cancer
- Gemcitabine/*nab* paclitaxel x 3 cycles → SD with improvement in CA19-9
- Evaluated for surgery and radiation

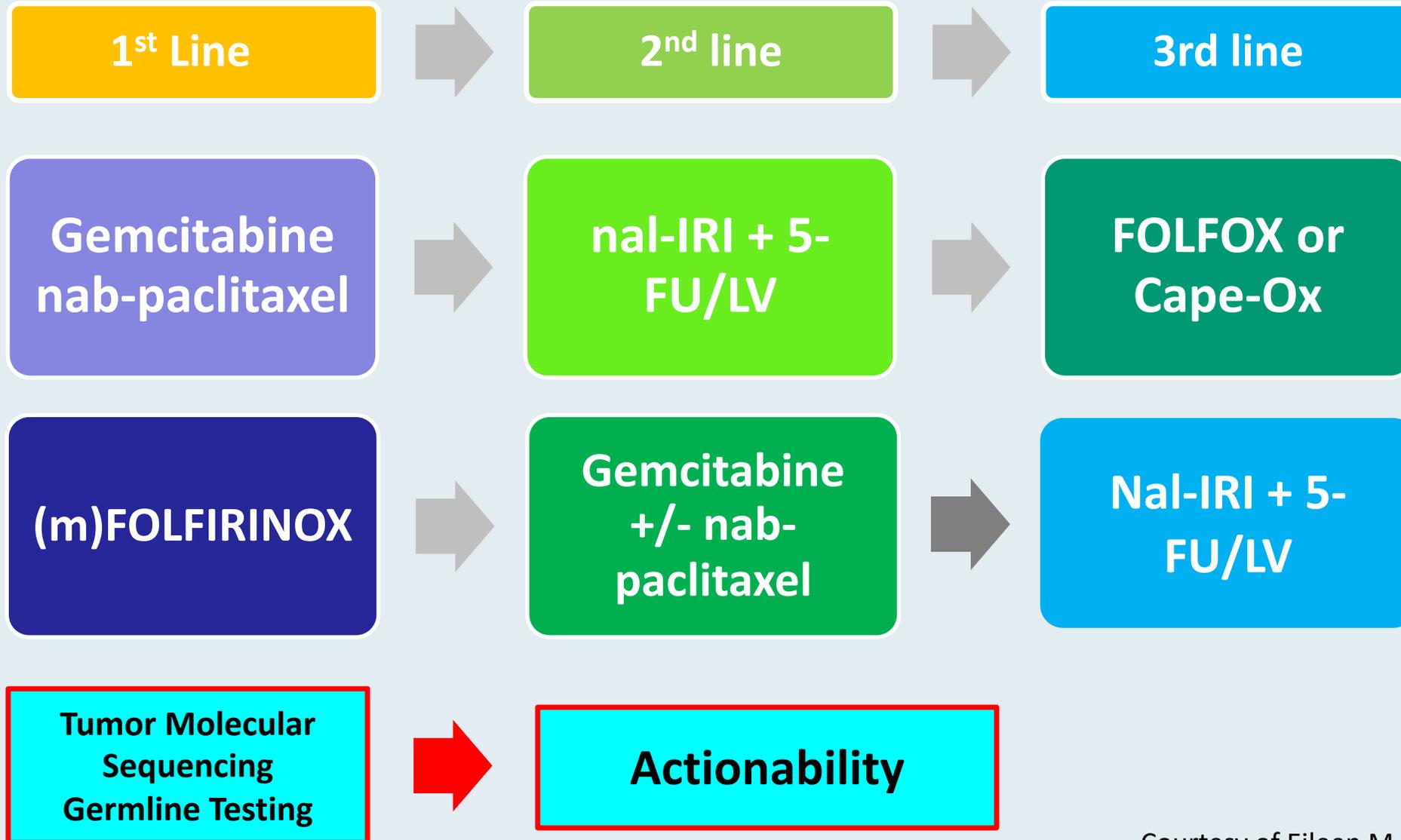
## Questions

- How do you determine which neoadjuvant chemotherapy regimen to use? Do age, performance status, or disease factors play a role in your choice?

# What is your usual neoadjuvant systemic therapy recommendation for a 78-year-old patient with borderline resectable pancreatic cancer?

- a. Gemcitabine/*nab* paclitaxel
- b. FOLFIRINOX
- c. Modified FOLFIRINOX
- d. Other

# Therapeutic Approach: Advanced PDAC 2020



Courtesy of Eileen M. O'Reilly, MD

# FDA Approves Olaparib as First-Line Maintenance for Metastatic Pancreatic Cancer with a Germline BRCA Mutation

Press Release – December 27, 2019

“The Food and Drug Administration approved olaparib for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated metastatic pancreatic adenocarcinoma, as detected by an FDA-approved test, whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

The FDA also approved the BRCAAnalysis CDx test as a companion diagnostic for the selection of patients with pancreatic cancer for treatment with olaparib based upon the identification of deleterious or suspected deleterious germline mutations in BRCA1 or BRCA2 genes.”

# Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer<sup>1</sup>

## Olaparib as Maintenance Treatment Following First-Line Platinum-Based Chemotherapy (PBC) in Patients with a Germline BRCA Mutation and Metastatic Pancreatic Cancer: Phase III POLO Trial<sup>2</sup>

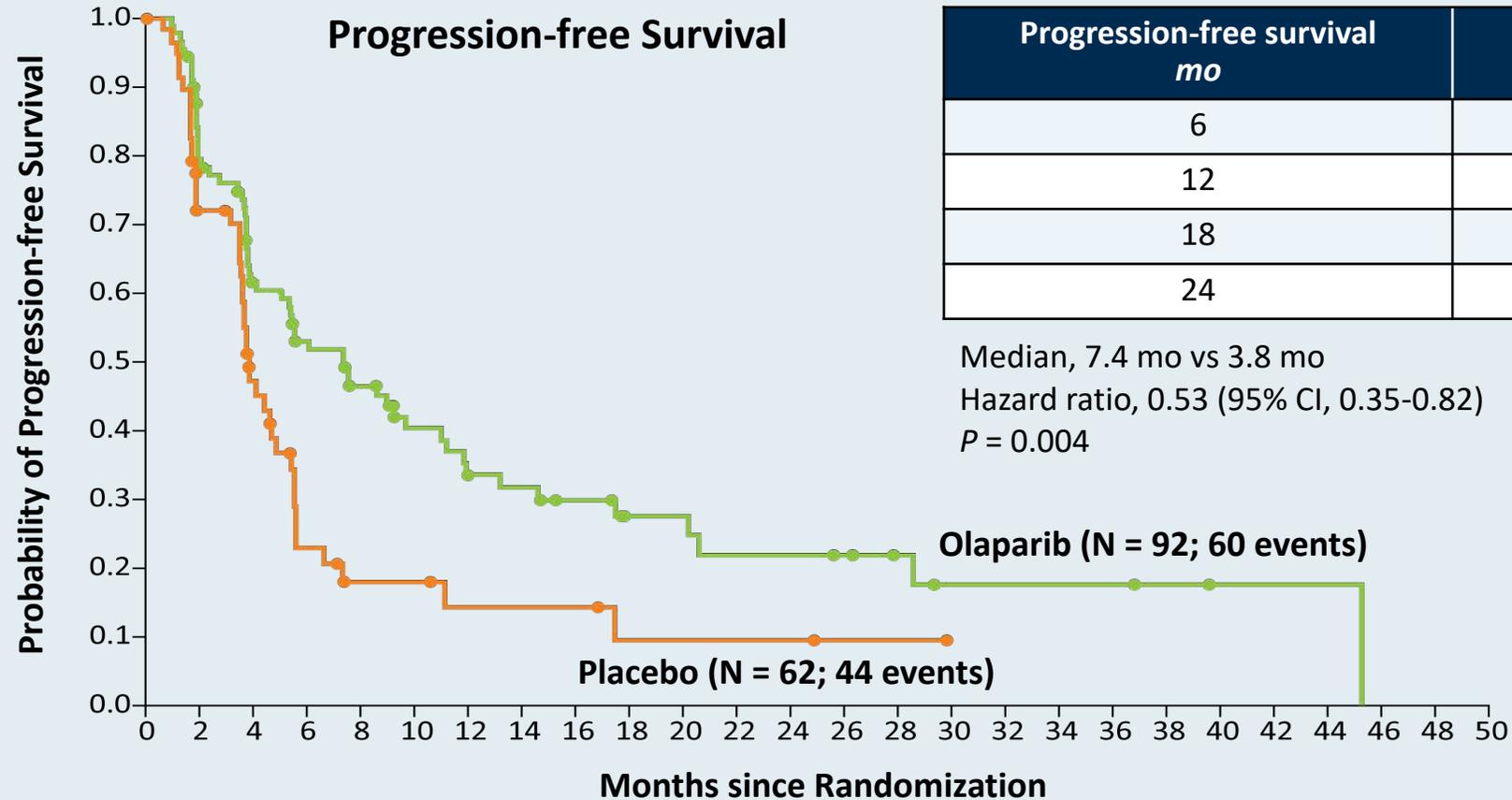
<sup>1</sup> Golan T et al.

*N Engl J Med* 2019;381(4):317-27.

<sup>2</sup> Kindler HL et al.

ASCO 2019;Abstract LBA4.

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



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

# Agenda

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## **Module 5: Advanced Cholangiocarcinoma with an Activating FGFR2 Rearrangement**

- Dr Hussein: A 66-year-old woman with intrahepatic cholangiocarcinoma

# Case Presentation – Dr Hussein: A 66-year-old woman with intrahepatic cholangiocarcinoma



**Dr Maen Hussein**

- Fall 2018: Diagnosed with Stage IV intrahepatic cholangiocarcinoma
- NGS: MSS, MMR proficient, PD-L1 negative, TMB 9 muts/Mb, HER2 negative, BRCA1/2 wildtype, NTRRK1/2/3 not detected, IDH2 negative
- 11/2018 – 1/2019: Cisplatin/gemcitabine, with cis-related toxicity
- 2/2019 – 3/2020: Switched to oxaliplatin/gemcitabine → PD
- 3/2020 – Ongoing: Capecitabine, with continued response (good QoL)

## Questions

- Maintaining quality of life is important to her, so what is the next step for this patient?
- Would you repeat NGS liquid biopsies at least, or get another tissue biopsy if she has progression in one of her lesions?
- What treatment would you recommend if her disease progresses on capecitabine?
- Is a TMB 9 muts/MB enough to consider immunotherapy, with her MMS, PD-L1-negative status?
- What are your thoughts about IDH mutations and the role of IDH inhibitors in cholangiocarcinoma?
- What are your thoughts about the FGFR2 inhibitors in cholangiocarcinoma?

# FDA Grants Accelerated Approval to Pemigatinib for Cholangiocarcinoma with an FGFR2 Rearrangement or Fusion

## Press Release – April 17, 2020

“On April 17, 2020, the Food and Drug Administration granted accelerated approval to pemigatinib for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test. The FDA also approved the FoundationOne® CDX as a companion diagnostic for patient selection.

Efficacy was investigated in FIGHT-202 (NCT02924376), a multicenter open-label single-arm trial, in 107 patients with locally advanced unresectable or metastatic cholangiocarcinoma whose disease had progressed on or after at least one prior therapy and had an FGFR2 gene fusion or rearrangement. Among the 107 patients, the ORR was 36%, including 3 complete responses.

The most common adverse reactions to pemigatinib (incidence  $\geq 20\%$ ) were hyperphosphatemia, alopecia, diarrhea, nail toxicity, fatigue, dysgeusia, nausea, constipation, stomatitis, dry eye, dry mouth, decreased appetite, vomiting, arthralgia, abdominal pain, hypophosphatemia, back pain, and dry skin. Ocular toxicity and hyperphosphatemia are important risks of pemigatinib.”

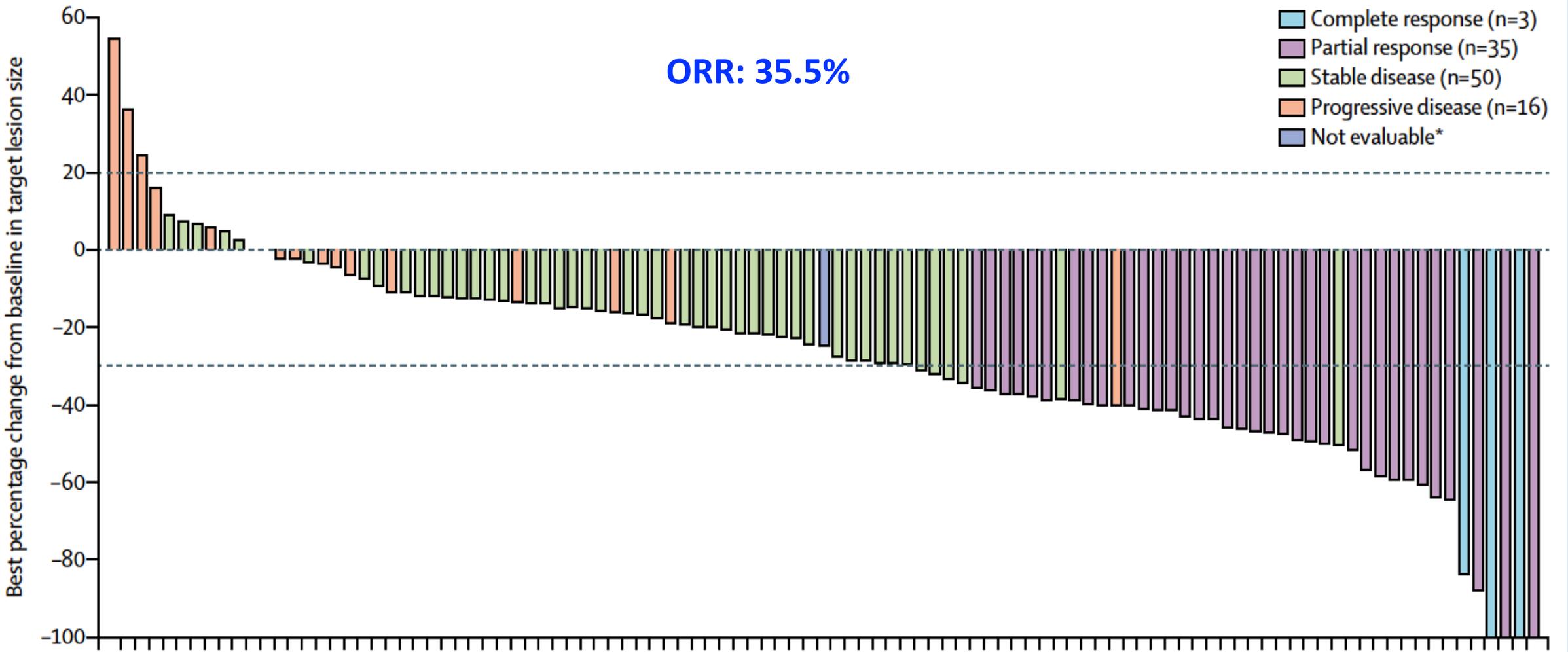
# Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study



*Ghassan K Abou-Alfa, Vaibhav Sahai, Antoine Hollebecque, Gina Vaccaro, Davide Melisi, Raed Al-Rajabi, Andrew S Paulson, Mitesh J Borad, David Gallinson, Adrian G Murphy, Do-Youn Oh, Efrat Dotan, Daniel V Catenacci, Eric Van Cutsem, Tao Ji, Christine F Lihou, Huiling Zhen, Luis Féliz, Arndt Vogel*

***Lancet Oncol 2020; 21: 671–84***

# FIGHT-202: Response



Abou-Alfa GK et al. *Lancet Oncol* 2020;21:671-84.

# FIGHT-202: Select Treatment-Related Adverse Events

|                                   | Grade 1-2 | Grade 3 | Grade 4 |
|-----------------------------------|-----------|---------|---------|
| Hyperphosphataemia                | 81 (55%)  | 0       | 0       |
| Alopecia                          | 67 (46%)  | 0       | 0       |
| Dysgeusia                         | 55 (38%)  | 0       | 0       |
| Diarrhoea                         | 49 (34%)  | 4 (3%)  | 0       |
| Fatigue                           | 45 (31%)  | 2 (1%)  | 0       |
| Stomatitis                        | 39 (27%)  | 8 (5%)  | 0       |
| Dry mouth                         | 42 (29%)  | 0       | 0       |
| Nausea                            | 34 (23%)  | 2 (1%)  | 0       |
| Decreased appetite                | 34 (23%)  | 1 (1%)  | 0       |
| Dry eye                           | 30 (21%)  | 1 (1%)  | 0       |
| Dry skin                          | 22 (15%)  | 1 (1%)  | 0       |
| Arthralgia                        | 16 (11%)  | 6 (4%)  | 0       |
| Palmar-plantar erythrodysesthesia | 16 (11%)  | 6 (4%)  | 0       |
| Constipation                      | 20 (14%)  | 0       | 0       |
| Hypophosphataemia                 | 8 (5%)    | 10 (7%) | 0       |
| Pain in extremity                 | 15 (10%)  | 0       | 0       |

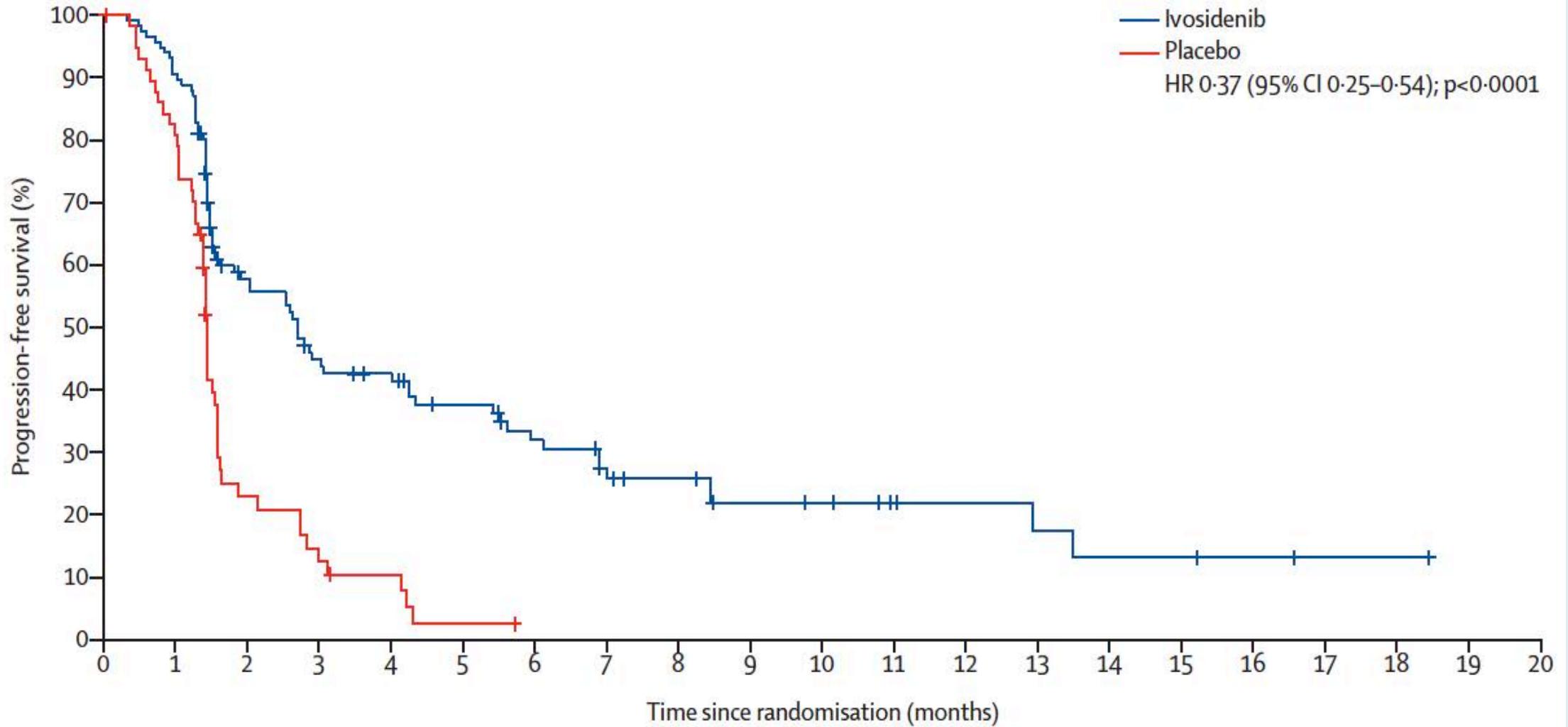


# Ivosidenib in *IDH1*-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study

Ghassan K Abou-Alfa\*, Teresa Macarulla, Milind M Javle, Robin K Kelley, Sam J Lubner, Jorge Adeva, James M Cleary, Daniel V Catenacci, Mitesh J Borad, John Bridgewater, William P Harris, Adrian G Murphy, Do-Youn Oh, Jonathan Whisenant, Maeve A Lowery, Lipika Goyal, Rachna T Shroff, Anthony B El-Khoueiry, Bin Fan, Bin Wu, Christina X Chamberlain, Liewen Jiang, Camelia Gliser, Shuchi S Pandya, Juan W Valle, Andrew X Zhu\*

***Lancet Oncol* 2020; 21: 796–807**

# ClarIDHy: Progression-Free Survival



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

***We are taking a 30-minute lunch break!***

**The program will resume at 1:15 PM ET**

***Up Next...***

**Drs Arjun Balar and William Oh discuss the  
management of genitourinary cancers**