

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

**A Daylong Clinical Summit Hosted in Partnership with
North Carolina Oncology Association (NCOA) and
South Carolina Oncology Society (SCOS)**

Saturday, February 13, 2021

8:30 AM – 4:30 PM ET

FACULTY

Courtney D DiNardo, MD, MSCE

Robert Dreicer, MD, MS

Justin F Gainor, MD

Sara Hurvitz, MD

Ian E Krop, MD, PhD

John M Pagel, MD, PhD

Alexander Perl, MD

Daniel P Petrylak, MD

Philip A Philip, MD, PhD, FRCP

Paul G Richardson, MD

Mitchell R Smith, MD, PhD

Eric Van Cutsem, MD, PhD

Peter Voorhees, MD

Heather Wakelee, MD

MODERATOR

Neil Love, MD

Saturday, February 13, 2021

**8:30 AM — Chronic Lymphocytic
Leukemia and Lymphomas**

John Pagel, Mitchell Smith

9:30 AM — Multiple Myeloma

Paul Richardson, Peter Voorhees

10:45 AM — Genitourinary Cancers

Robert Dreicer, Daniel Petrylak

11:45 AM — Lung Cancer

Justin Gainor, Heather Wakelee

Saturday, February 13, 2021

1:15 PM — Gastrointestinal Cancers

Philip Philip, Eric Van Cutsem

2:15 PM — Breast Cancer

Sara Hurvitz, Ian Krop

**3:30 PM — Acute Myeloid Leukemia
and Myelodysplastic Syndromes**

Courtney DiNardo, Alexander Perl

Agenda

Module 1 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Pagel and Smith*

Module 2 — Multiple Myeloma: *Drs Richardson and Voorhees*

Module 3 — Genitourinary Cancers: *Drs Dreicer and Petrylak*

Module 4 — Lung Cancer: *Drs Gainor and Wakelee*

Module 5 — Gastrointestinal Cancers: *Dr Philip and Prof Van Cutsem*

Module 6 — Breast Cancer: *Drs Hurvitz and Krop*

Module 7 — Acute Myeloid Leukemia and Myelodysplastic Syndromes:
Drs DiNardo and Perl

Commercial Support

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

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies Corporation, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Guardant Health, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seagen Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Teva Oncology, Tokai Pharmaceuticals Inc and Verastem Inc.

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

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

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George Washington University
Washington, DC

Dr Pagel — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, BeiGene, Epizyme Inc, Gilead Sciences Inc, MorphoSys, Seagen Inc
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Dr Smith — Disclosures

Advisory Committee	Pharmacyclics LLC, an AbbVie Company
Contracted Research	Karyopharm Therapeutics
Speakers Bureau	Acrotech Biopharma, AstraZeneca Pharmaceuticals LP

Multiple Myeloma Faculty



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RJ Corman Professor of Medicine
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Dr Voorhees — Disclosures

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Data and Safety Monitoring Board/Committee	Bristol-Myers Squibb Company

Genitourinary Cancers Faculty



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Data and Safety Monitoring Board/Committee	Hinova Pharmaceuticals Inc, Merck

Dr Petrylak — Disclosures

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Contracted Research	Advanced Accelerator Applications, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BioXcel Therapeutics Inc, Bristol-Myers Squibb Company, Clovis Oncology, Eisai Inc, Endocyte Inc, Genentech, a member of the Roche Group, Innocrin Pharmaceuticals Inc, Lilly, Medivation Inc, a Pfizer Company, Merck, Mirati Therapeutics, Novartis, Pfizer Inc, Progenics Pharmaceuticals Inc, Replimune, Roche Laboratories Inc, Sanofi Genzyme, Seagen Inc
Ownership Interest	Bellicum Pharmaceuticals Inc (sold 7/2020), Tyme Inc (sold 10/2019)

Lung Cancer Faculty



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Dr Gainor — Disclosures

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Employment (Immediate Family Member)	Ironwood Pharmaceuticals

Dr Wakelee — Disclosures

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Research Funding to Institution	ACEA Biosciences Inc, Arrys Therapeutics, a wholly owned subsidiary of Kyn Therapeutics, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Exelixis Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Merck, Novartis, Pharmacyclics LLC, an AbbVie Company, Seagen Inc, Xcovery

Gastrointestinal Cancers Faculty



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Dr Philip — Disclosures

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Consulting Agreements	Blueprint Medicines, Erytech, SynCore Biotechnology Co Ltd, TriSalus Life Sciences
Contracted Research	Astellas, Bayer HealthCare Pharmaceuticals, BeiGene, Bristol-Myers Squibb Company, Celgene Corporation, Five Prime Therapeutics Inc, Forty Seven Inc, Incyte Corporation, Karyopharm Therapeutics, Merck, Merus BV, Novartis, Novocure, QED Therapeutics, Rafael Pharmaceuticals Inc, SynCore Biotechnology Co Ltd, Taiho Oncology Inc, Tyme Inc
Data and Safety Monitoring Board/Committee	ASLAN Pharmaceuticals, Blueprint Medicines, Erytech
Speakers Bureau	Advanced Accelerator Applications, Celgene Corporation, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Novartis

Prof Van Cutsem — Disclosures

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Dr Hurvitz — Disclosures

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Stocks (Spouse)	IDEAL IMPLANT, ROMTech

Dr Krop — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, MacroGenics Inc
Contracted Research	Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Pfizer Inc, Taiho Oncology Inc
Data and Safety Monitoring Board/Committee	Merck, Novartis

Acute Myeloid Leukemia and Myelodysplastic Syndromes Faculty



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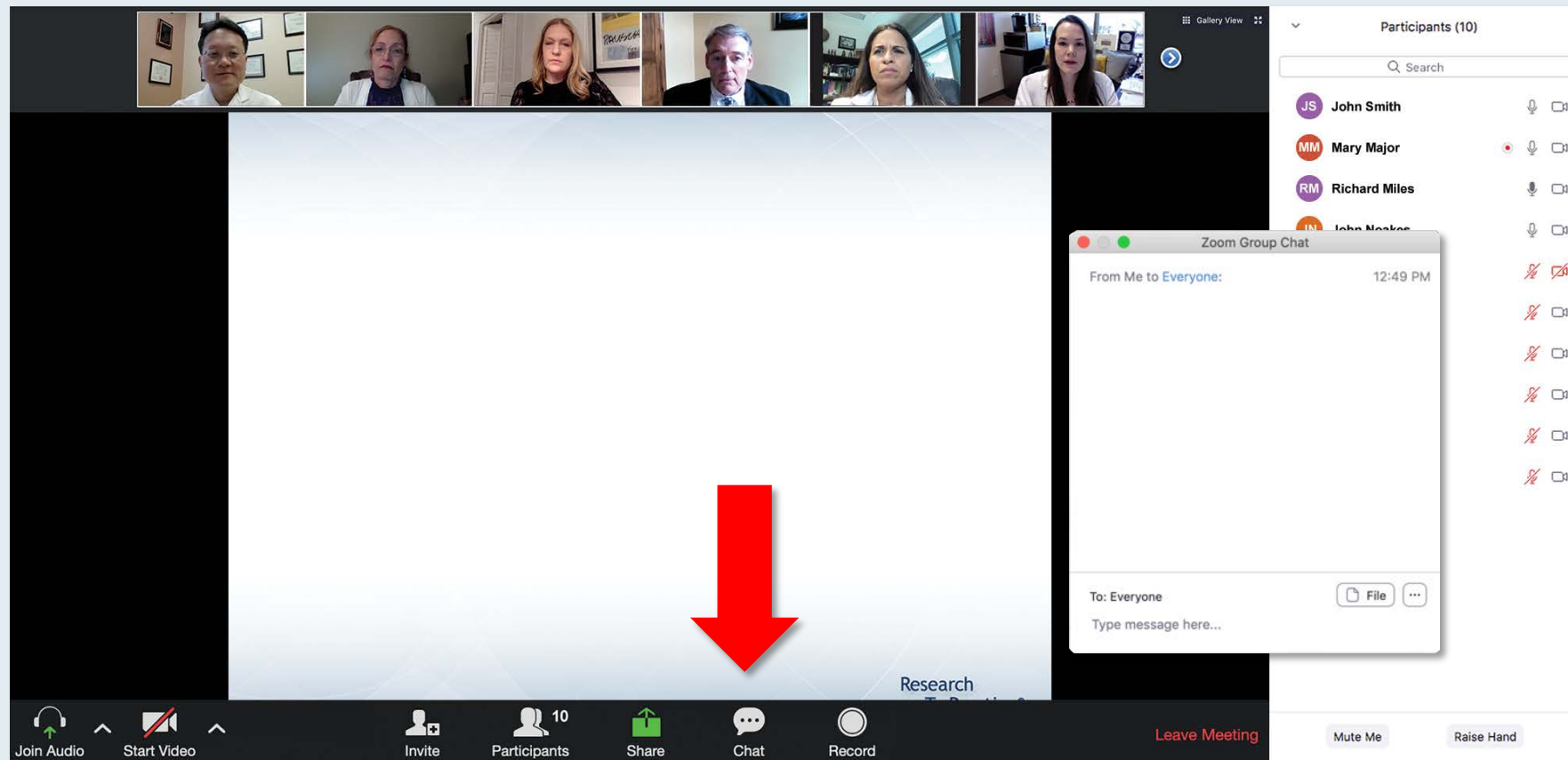
Dr DiNardo — Disclosures

Advisory Committee	Foghorn Therapeutics, Gilead Sciences Inc, Immune-Onc Therapeutics Inc, Novartis, Takeda Oncology
Consulting Agreements	AbbVie Inc, Agios Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genentech, a member of the Roche Group
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Dr Perl — Disclosures

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Contracted Research (All Monies to Institution)	AbbVie Inc, Actinium Pharmaceuticals Inc, Astellas, Daiichi Sankyo Inc, FUJIFILM Pharmaceuticals USA Inc
Data and Safety Monitoring Board/Committee	Beat AML LLC, Leukemia & Lymphoma Society

We Encourage Clinicians in Practice to Submit Questions



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

ONCOLOGY TODAY

WITH DR NEIL LOVE



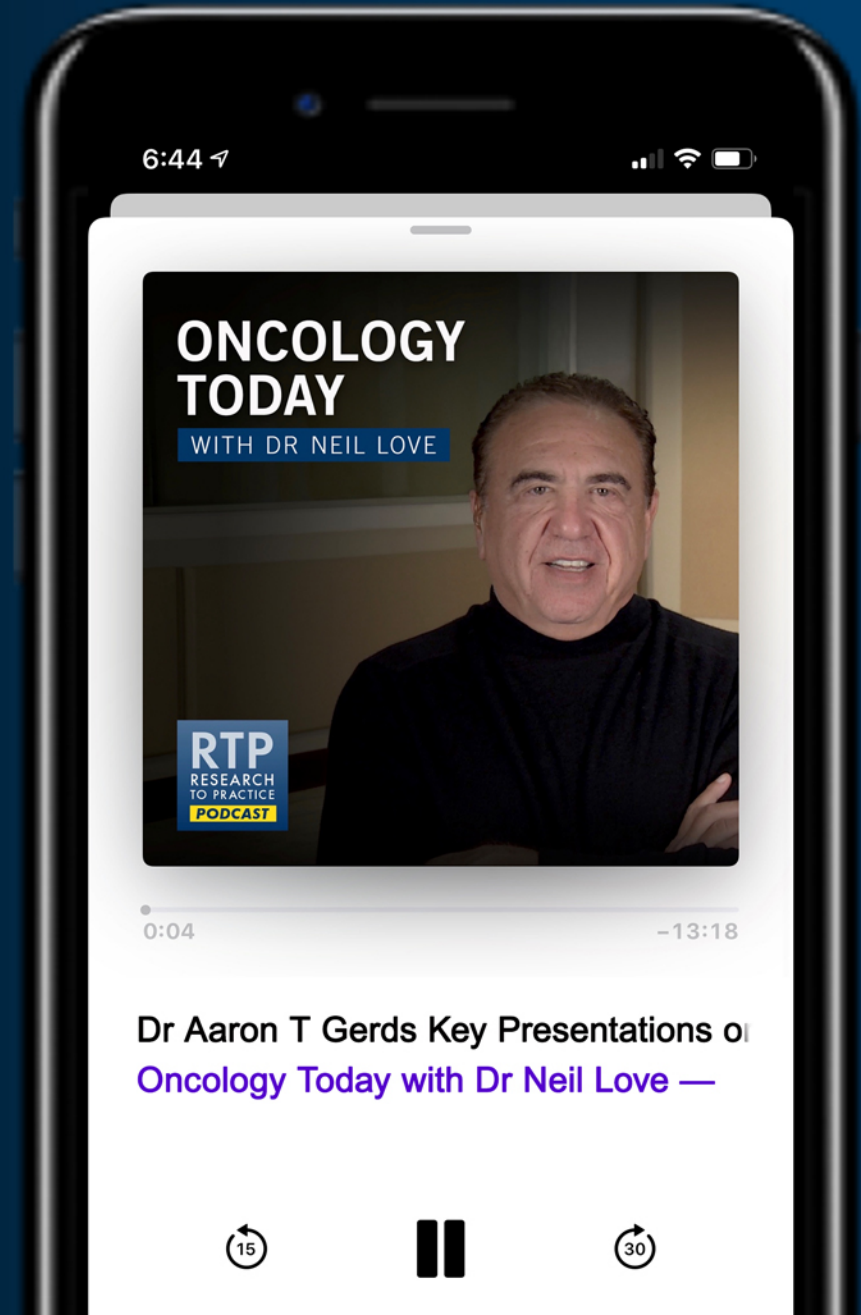
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Contributing Oncologists



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Associate Program Director –
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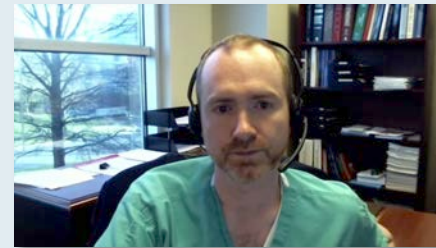
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Greenville, North Carolina



Richard Zelkowitz, MD
Regional Director of the Breast Program
Hematology and Oncology
Hartford HealthCare Cancer Institute
Bridgeport, Connecticut

Meet The Professor
**Optimizing the Selection and Sequencing
of Therapy for Patients with Advanced
Gastrointestinal Cancers**

**Tuesday, February 16, 2021
12:00 PM – 1:00 PM ET**

Faculty

Axel Grothey, MD

Moderator

Neil Love, MD

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

**Wednesday, February 17, 2021
12:00 PM – 1:00 PM ET**

Faculty

Eric Jonasch, MD

Moderator

Neil Love, MD

What Clinicians Want to Know: Understanding the Factors Affecting the Optimal Diagnosis and Management of Ovarian Cancer

**Thursday, February 18, 2021
5:00 PM – 6:00 PM ET**

Faculty

Michael J Birrer, MD, PhD

Kathleen Moore, MD

David M O'Malley, MD

Moderator

Neil Love, MD

Meet The Professor

Management of Multiple Myeloma

**Friday, February 19, 2021
12:30 PM – 1:30 PM ET**

Faculty

A Keith Stewart, MB, ChB

Moderator

Neil Love, MD



Targeted Therapy in NSCLC

- KRAS G12C inhibitor AMG 510 for wild-type tumors with KRAS mutation
- EGFR lung resistance, including in those with CNS metastases
- Toxicity of TKIs after immune checkpoint inhibitors
- EGFR exon 20 mutations: TAA-788, asciminib
- ALK rearrangement: alectinib, brigance, lorlatinib
- ROS1 rearrangement: entrectinib
- NTRK gene fusion: larotrectinib, entrectinib
- RET fusion: selpercatinib, pralsetinib
- MET exon 14 mutation: capmatinib, tepotinib

Targeted The

- KRAS G12C in
- EGFR tumor m
- Toxicity of TKIs
- EGFR exon 20
- ALK rearrange
- ROS1 rearrang
- NTRK gene fus
- RET fusions: S
- MET exon 14





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Targeted Th

- KRAS G12C
- EGFR tumor
- Toxicity of TKI
- EGFR exon 20
- ALK rearrange
- ROS1 rearrang
- NTRK gene fu
- RET fusion
- MET exon 14



Revenue Checkpoint Initiatives

- Audit: Review with transparency and accountability to stakeholders. Introduce controls for programmatic sales.
- Revenue: Introduce new compensation for sales in 2022.
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- Revenue: Introduce new compensation for sales in 2022.



- MET exon 14 mutations: Capmatinib, tepotinib





- Sequential treatment
- Consolidation durvalumab after crv
- First-line treatment for metastatic N
- Immune toxicity of checkpoint inhibi
- Duration of treatment in patients for
- Response progression?











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Current Concepts and Recent Advances in Oncology

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Alexander Perl, MD

Daniel P Petrylak, MD

Philip A Philip, MD, PhD, FRCP

Paul G Richardson, MD

Mitchell R Smith, MD, PhD

Eric Van Cutsem, MD, PhD

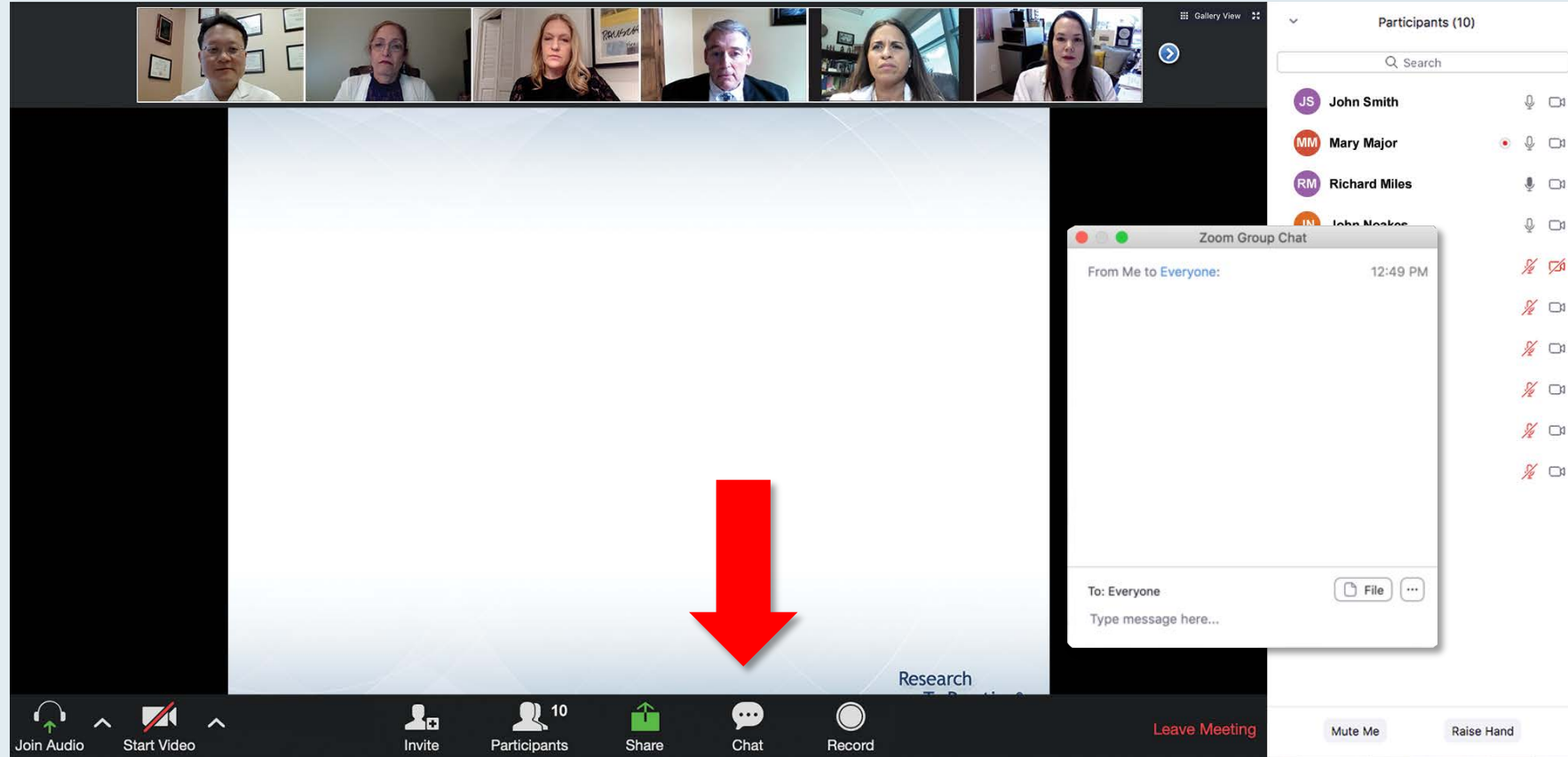
Peter Voorhees, MD

Heather Wakelee, MD

MODERATOR

Neil Love, MD

We Encourage Clinicians in Practice to Submit Questions



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

Agenda

Module 1 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Pagel and Smith*

Module 2 — Multiple Myeloma: *Drs Richardson and Voorhees*

Module 3 — Genitourinary Cancers: *Drs Dreicer and Petrylak*

Module 4 — Lung Cancer: *Drs Gainor and Wakelee*

Module 5 — Gastrointestinal Cancers: *Dr Philip and Prof Van Cutsem*

Module 6 — Breast Cancer: *Drs Hurvitz and Krop*

Module 7 — Acute Myeloid Leukemia and Myelodysplastic Syndromes:
Drs DiNardo and Perl

Chronic Lymphocytic Leukemia and Lymphomas Faculty



John M Pagel, MD, PhD

Chief of Hematologic Malignancies Program
Center for Blood Disorders and Stem Cell
Transplantation
Swedish Cancer Institute
Seattle, Washington



Mitchell R Smith, MD, PhD

Clinical Professor of Medicine
George Washington University
Washington, DC

The patients I saw today...

82	M	Chronic myeloid leukemia - Newly diagnosed, Sokal intermediate risk, I recommended dasatinib
42	F	Breast Cancer - Stage III TNBC s/p adjuvant DD AC-T
89	M	Acute Myeloid Leukemia - Venetoclax/azacytidine
38	F	Colorectal Cancer - Metastatic colon cancer on FOLFOX/bevacizumab
76	M	Hepatocellular carcinoma – Nivolumab
71	F	Diffuse Large B Cell Lymphoma - Completed R-CHOP
84	M	Multiple myeloma - Bortezomib/Dex
59	M	Multiple myeloma or other plasma cell dyscrasias – Maintenance Carfilzomib/Dex
62	M	Multiple myeloma - Relapsed/ Refractory- Carfilzomib/Cyclophosphamide/Dex

72	F	Breast Cancer – Anastrozole
54	F	Breast Cancer – Tamoxifen
35	M	Benign Hematology - Enoxaparin for DVT
32	F	Benign Hematology - DSVT on warfarin
40	F	Benign Hematology - Iron def anemia on oral iron
42	F	T-Cell Lymphoma - T-Cell LGL on weekly Methotrexate
68	M	Diffuse Large B Cell Lymphoma - Primary CNS lymphoma s/p HD- Methotrexate/Rituximab
57	F	Melanoma - IPI/ Nivo
62	M	Renal Cell Carcinoma - Ipi/ Nivo
62	M	Lung Cancer - Consolidative Durvalumab after chemoRT
92	M	Prostate cancer - Enzalutamide/ Leuprolide/Denosumab

Contributing Oncologists



Daniel R Carrizosa, MD, MS
Atrium Health Levine Cancer Institute
Associate Program Director –
Hematology/Oncology Fellowship
Medical Director: Diversity/Disparities and
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Section Head: Head and Neck Division
Member: Head and Neck and Thoracic Sections
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Mamta Choksi, MD
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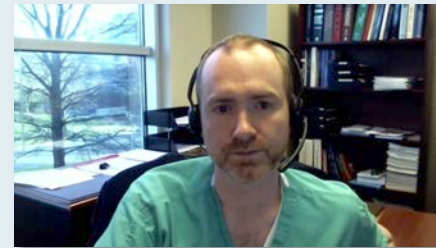
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Zanetta S Lamar, MD
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Charlotte, North Carolina



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Greenville, North Carolina



Richard Zelkowitz, MD
Regional Director of the Breast Program
Hematology and Oncology
Hartford HealthCare Cancer Institute
Bridgeport, Connecticut

Agenda

Module 1: Chronic Lymphocytic Leukemia (CLL)

- Case Presentation – Dr Deutsch: A 65-year-old man with relapsed CLL – del(11q)
- Case Presentation – Dr Lamar: An asymptomatic 81-year-old man with newly diagnosed CLL

Module 2: Follicular Lymphoma

- Dr Favaro: A 61-year-old man with low volume of relapsed FL

Module 3: Mantle Cell Lymphoma (MCL)

- Dr Deutsch: A 62-year-old man with relapsed MCL

Module 4: Diffuse Large B-Cell Lymphoma (DLBCL)

- Dr Favaro: A moderately frail 74-year-old woman with Stage III DLBCL

Module 5: Hodgkin Lymphoma

- Dr Mohamed: A 26-year-old woman with classical Hodgkin lymphoma
- Dr Mohamed: A 55-year-old man with late-stage Hodgkin lymphoma

Case Presentation – Dr Deutsch: A 65-year-old man with relapsed CLL – del(11q)



Dr Margaret Deutsch

- 2014: Diagnosed with del(11q) CLL
- Obinutuzumab/chlorambucil x 6
- 9/2017: Progressive disease → Ibrutinib (dose-reduced from 420 mg to 280 mg qd due to myalgias)
- 6/2019: Ibrutinib discontinued due to diffuse ground glass changes with significant dyspnea
- Currently, Increasing white cell count, lymphocytosis, minimal lymphadenopathy

Questions

- Is pulmonary toxicity common with ibrutinib?
- What would be the best therapy for this patient now, who lives a considerable distance away and liked the oral therapy?

Case Presentation – Dr Lamar: An asymptomatic 81-year-old man with newly diagnosed CLL



Dr Zanetta Lamar

- December 2019: Presents with elevated white blood cell count found on routine blood work
- Flow cytometry: CD5+, CD23+, CD38-, ZAP70-, IGHV mutated
- FISH: del17p negative
- CT scan shows splenomegaly, 17 cm
- Observation recommended; Second opinion at academic center recommended treatment
- ***Obinutuzumab/venetoclax***

Questions

- How do you make treatment decisions for these patients – convenience, side effects? Are there differences with the newer-generation BTK inhibitors in terms of side effects?
- Do you ever incorporate MRD testing into your treatment algorithm for patients with CLL? If so, how do you incorporate MRD testing? If not, how do you envision that we will use MRD testing in the future?

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

1. FCR (fludarabine/cyclophosphamide/rituximab)
2. BR (bendamustine/rituximab)
3. Ibrutinib
4. Ibrutinib + rituximab
5. Acalabrutinib
6. Acalabrutinib + obinutuzumab
7. Venetoclax + obinutuzumab
8. Other

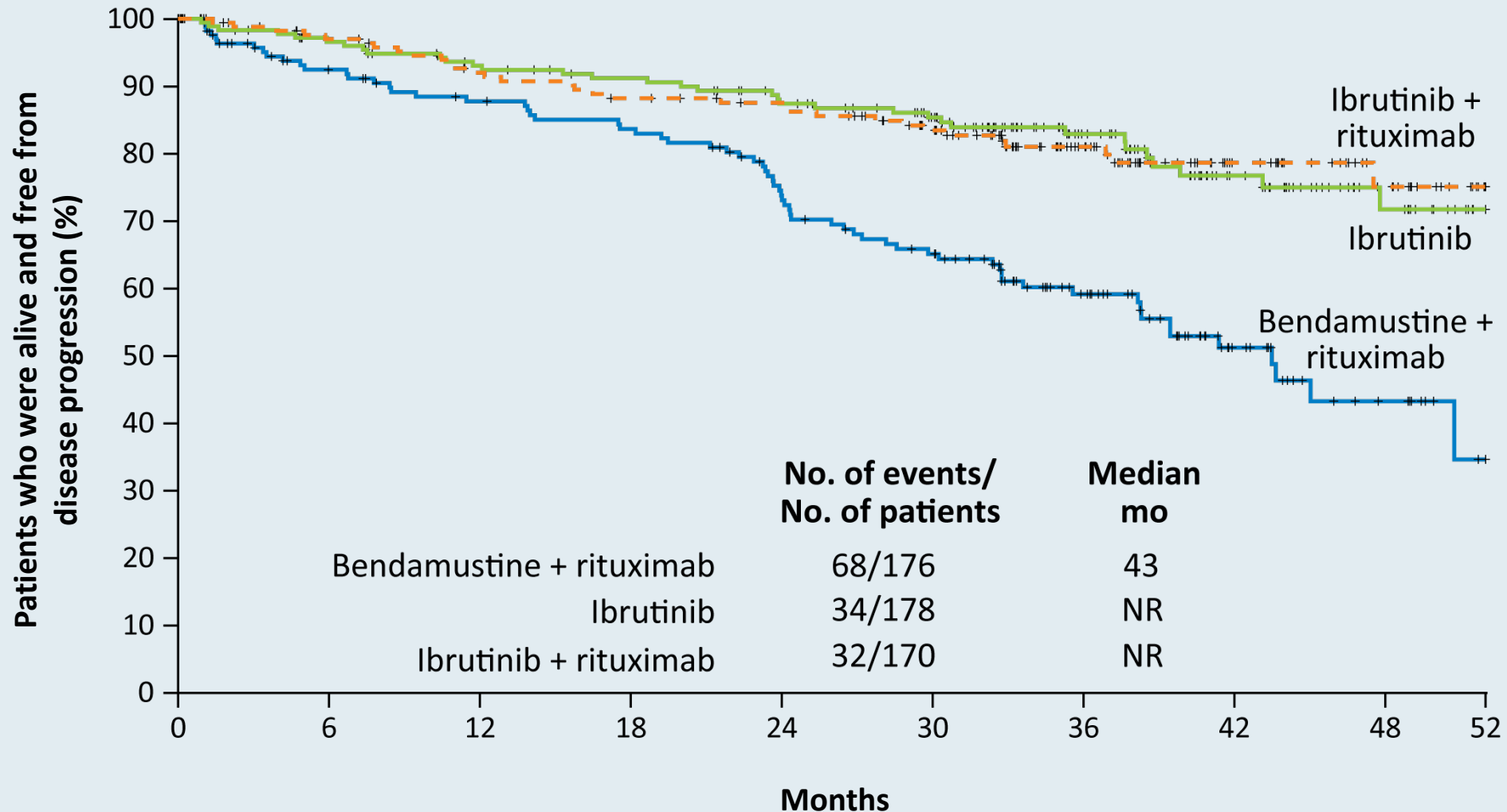
ORIGINAL ARTICLE

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.

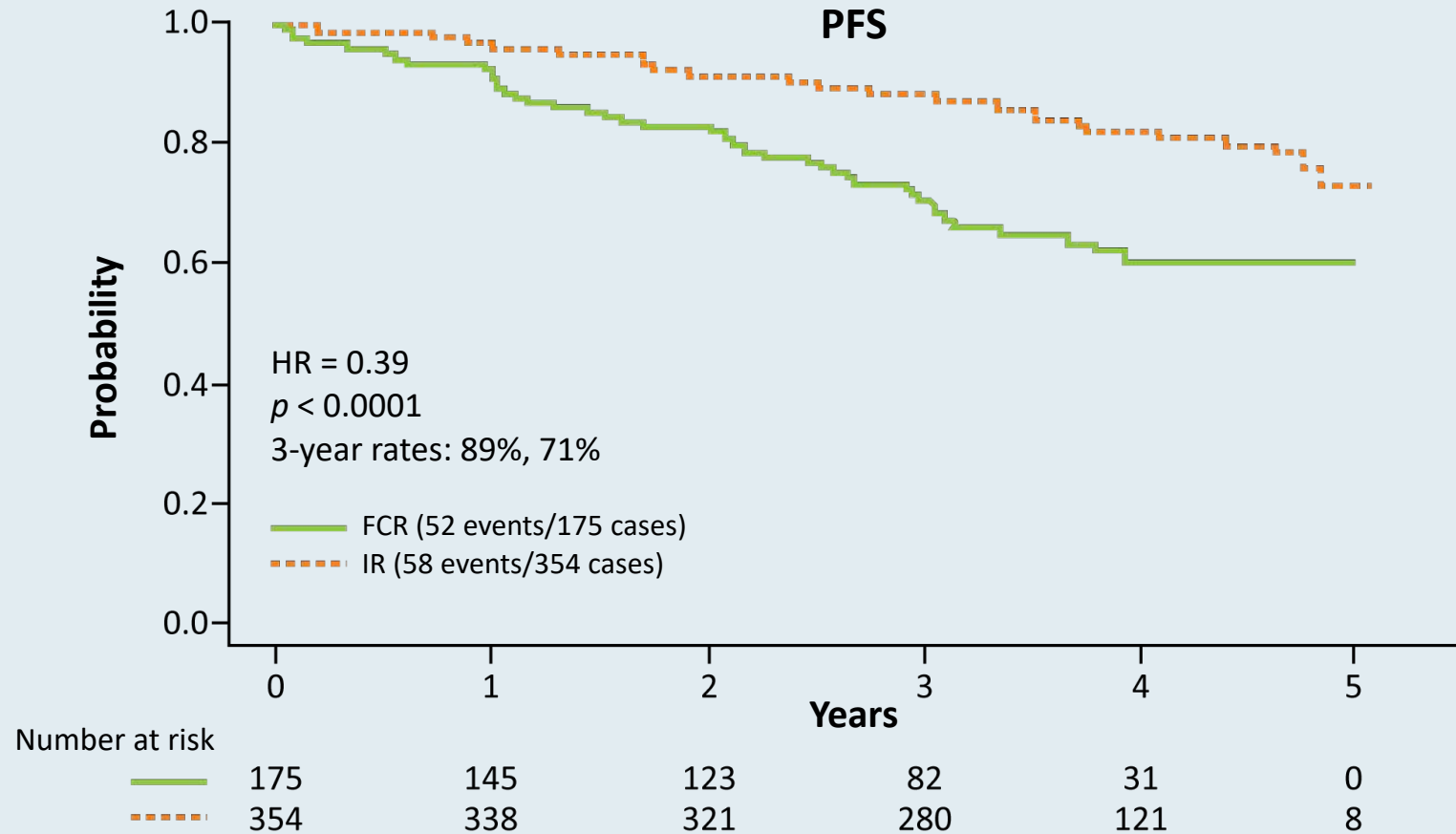
Alliance A041202: Efficacy with Ibrutinib Alone or in Combination with Rituximab Compared to Bendamustine/Rituximab



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

Shanafelt TD et al.
ASH 2019;Abstract 33.

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



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

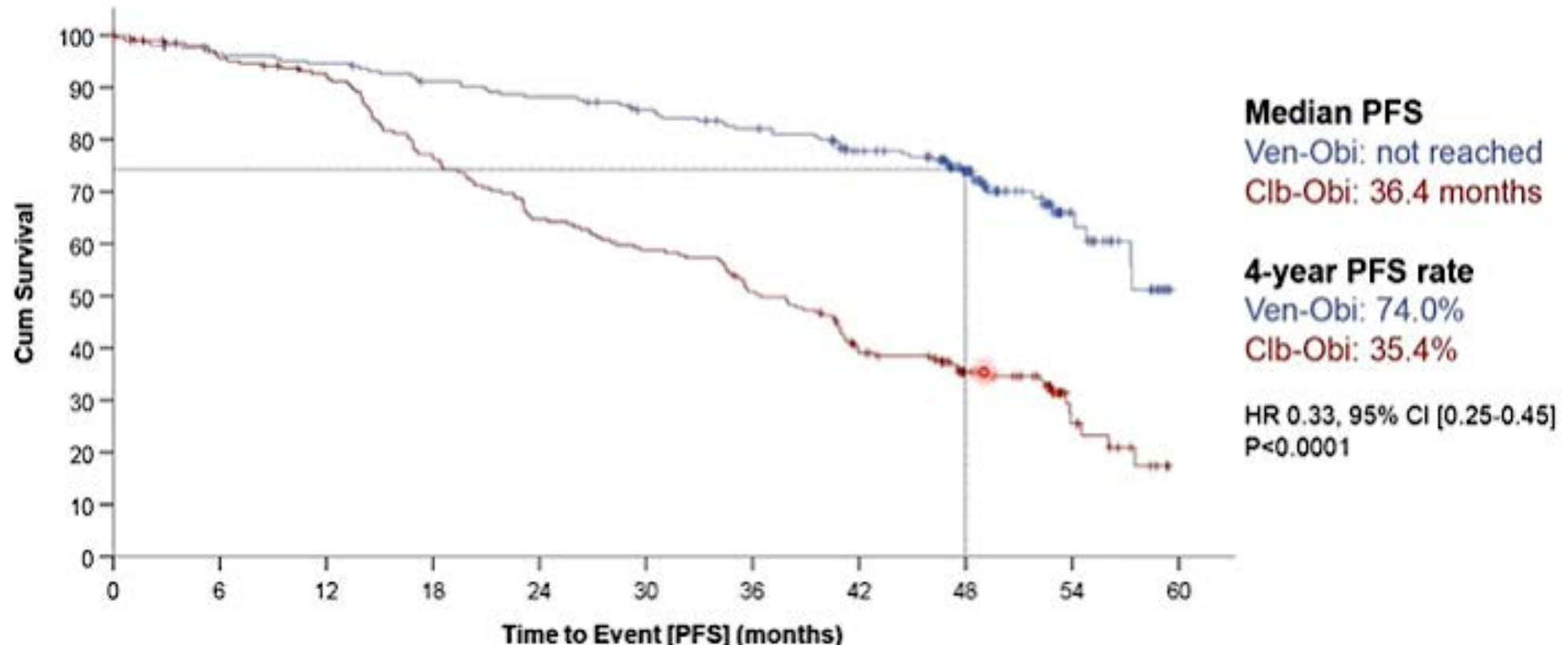
Clonal Dynamics After Venetoclax-Obinutuzumab Therapy: Novel Insights from the Randomized, Phase 3 CLL14 Trial

Al-Sawaf O et al.
ASH 2020;Abstract 127.

CLL14: Updated 4-Year PFS

4-YEAR FOLLOW-UP: PROGRESSION-FREE SURVIVAL

Median observation time 52.4 months



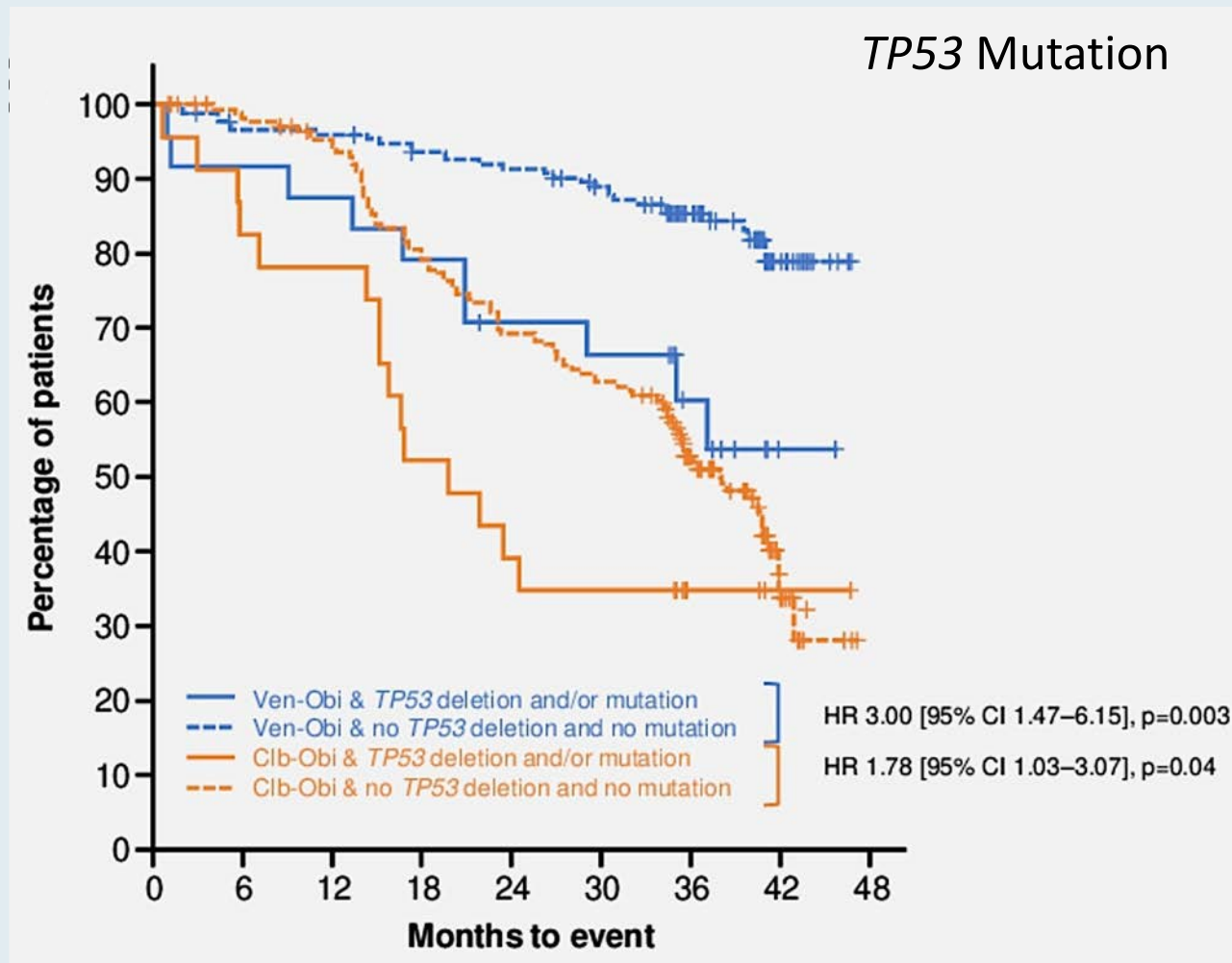
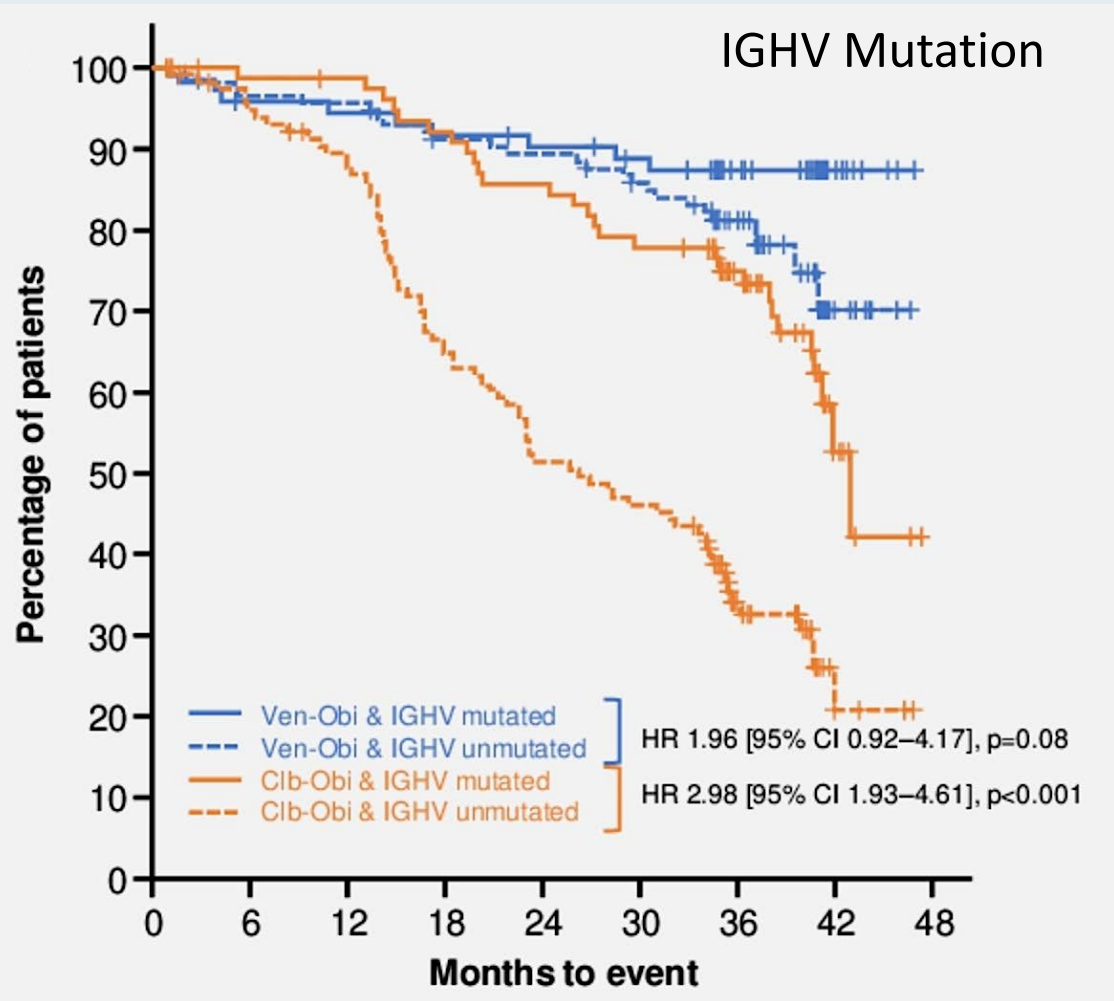


Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial

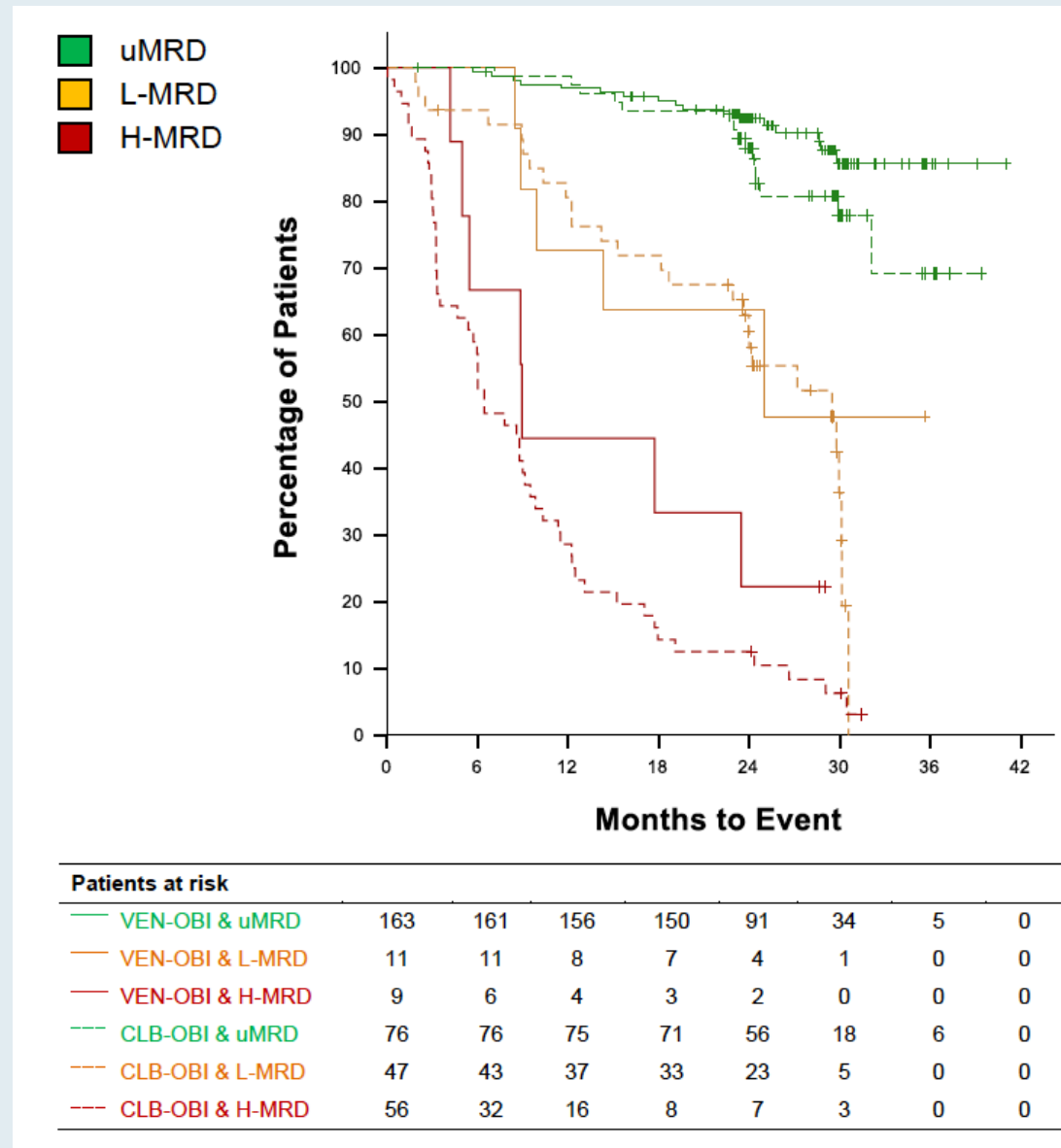
Othman Al-Sawaf, Can Zhang, Maneesh Tandon, Arijit Sinha, Anna-Maria Fink, Sandra Robrecht, Olga Samoylova, Anna M Liberati, Javier Pinilla-Ibarz, Stephen Opat, Liliya Sivcheva, Katell Le Dû, Laura M Fogliatto, Carsten U Niemann, Robert Weinkove, Sue Robinson, Thomas J Kipps, Eugen Tausch, William Schary,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

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

CLL14: PFS by IGHV and TP53 Mutation Status



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



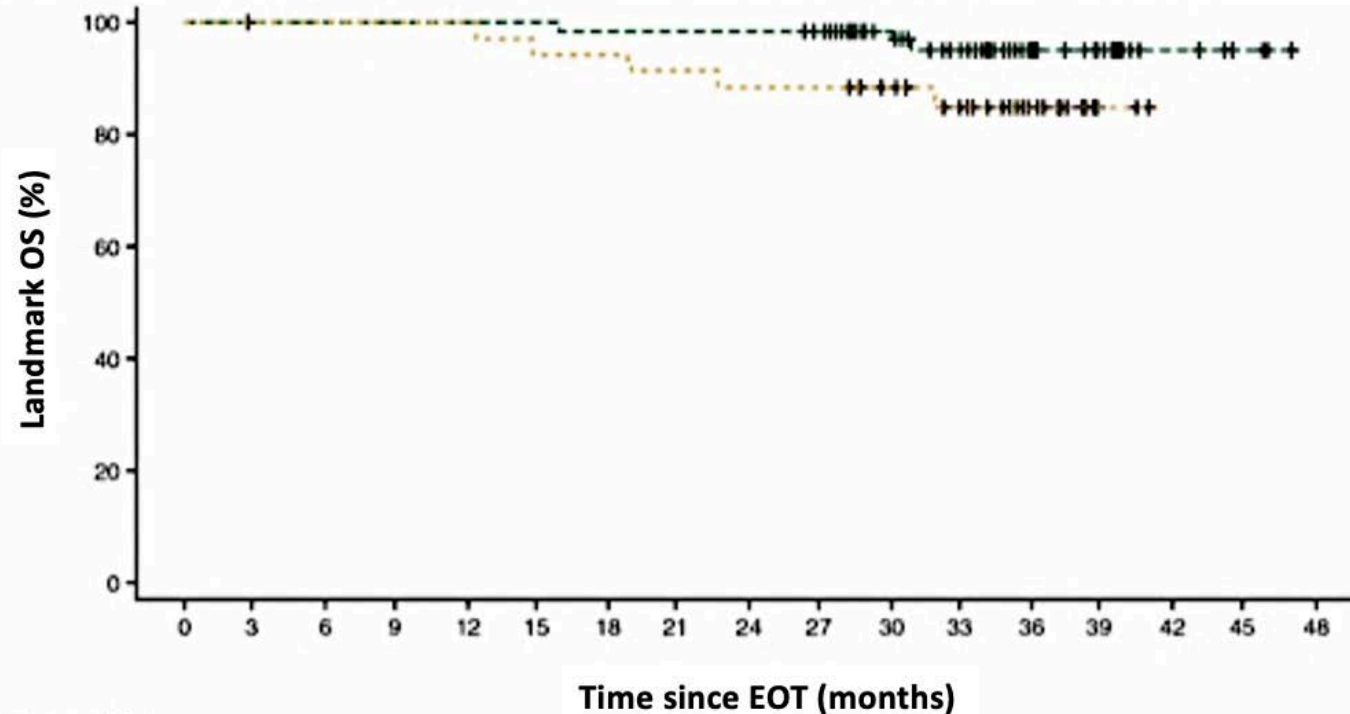
Five-Year Analysis of Murano Study Demonstrates Enduring Undetectable Minimal Residual Disease (uMRD) in a Subset of Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Patients (Pts) Following Fixed-Duration Venetoclax-Rituximab (VenR) Therapy (Tx)

Kater AP et al.

ASH 2020;Abstract 125.

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

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



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

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

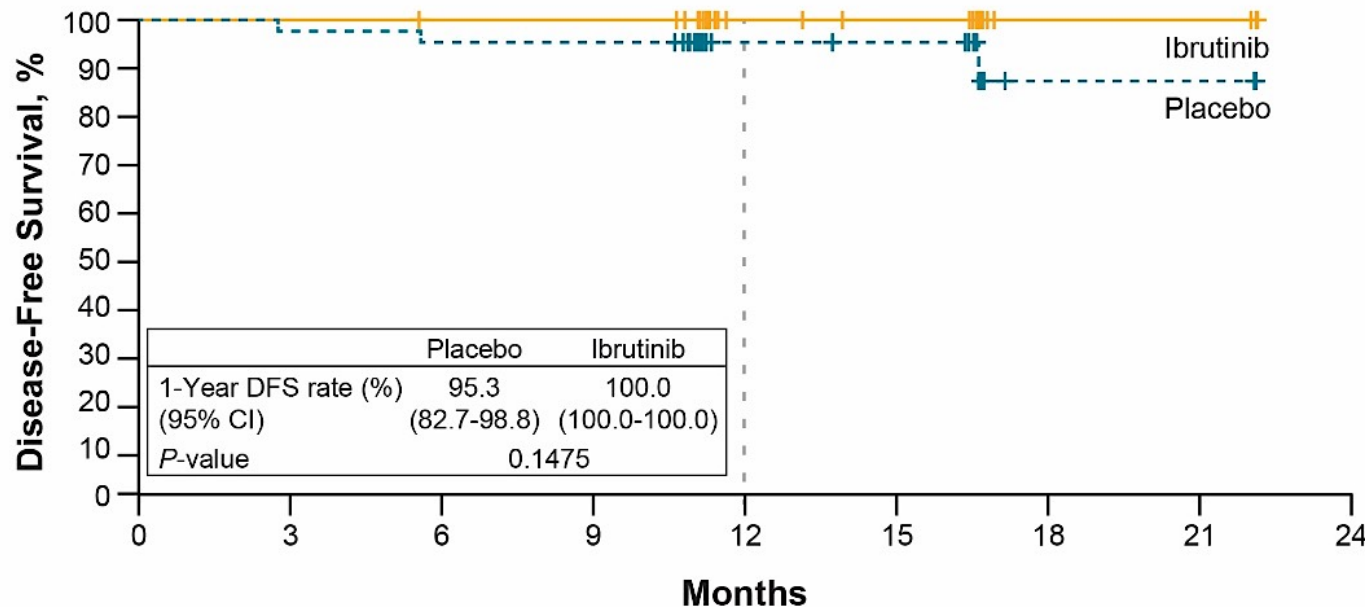
Ibrutinib (Ibr) plus Venetoclax (Ven) for First-Line Treatment of Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): 1-Year Disease-Free Survival (DFS) Results from the MRD Cohort of the Phase 2 CAPTIVATE Study Trial

Wierda WG et al.

ASH 2020;Abstract 123.

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

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



Patients at Risk

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

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

30 month PFS Rate:

Confirmed uMRD:

- 95.3% placebo
- 100% ibrutinib

Without confirmed uMRD:

- 95.2% ibrutinib
- 96.7% ibr/ven

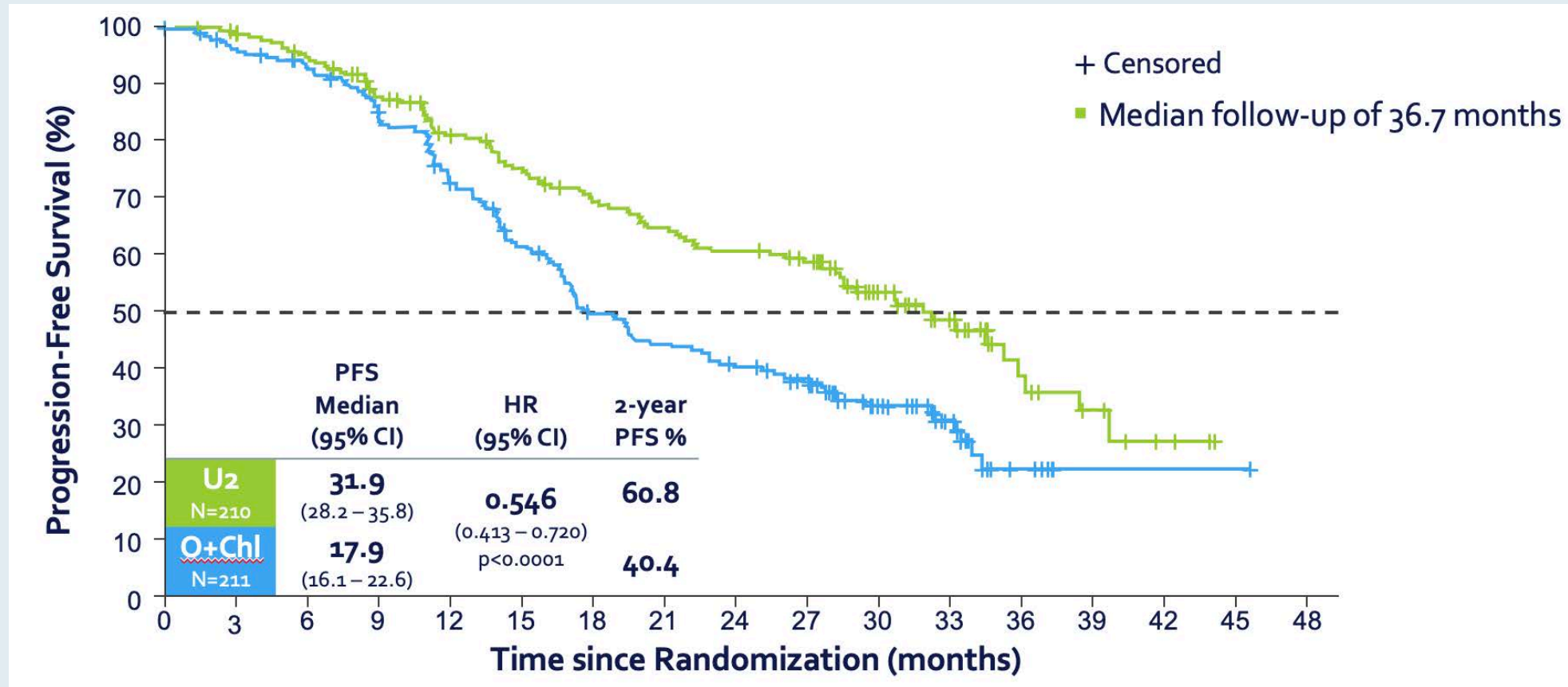
AEs were primarily grade 1/2 and mostly occurred in early cycles of Ibr + Ven, with modest differences by randomized treatment arm.

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

Gribben JG et al.

ASH 2020;Abstract 542.

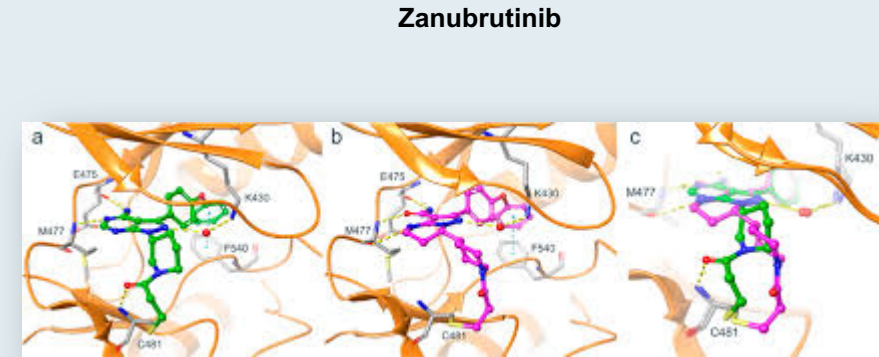
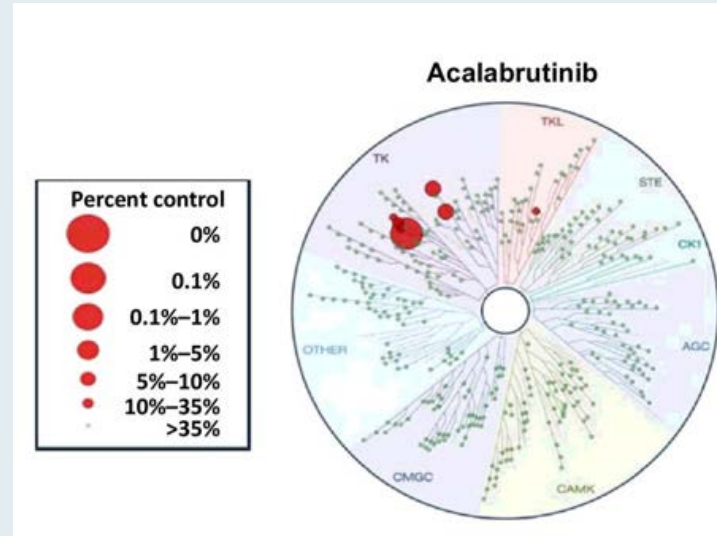
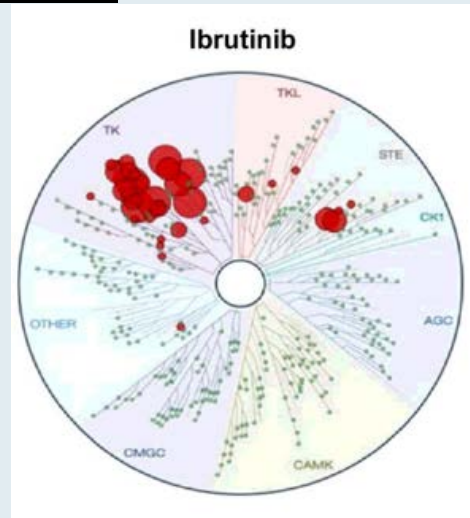
UNITY-CLL Phase III Trial of Umbralisib with Ublituximab (U2) versus Obinutuzumab with Chlorambucil in CLL



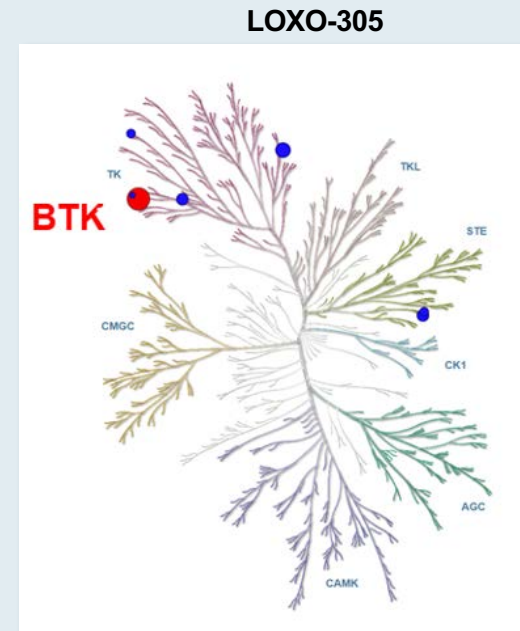
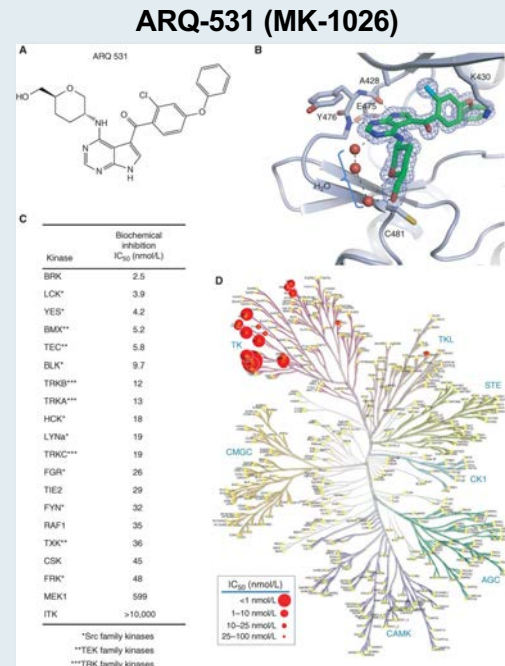
- PFS in treatment-naïve patients (U2 vs O+Chl): 38.5 vs 26.1 mo
- PFS in R/R patients (U2 vs O+Chl): 19.5 vs 12.9 mo
- Grade 3+ colitis in 3.4%, transaminitis Grade 3+ in 8.3%, Grade 3+ pneumonitis in 2.9%

Overview of BTK Inhibitors in CLL

Irreversible



Reversible



Courtesy of Matthew S Davids, MD, MMSc

ELEVATE-RR Trial Meets Primary and Secondary Endpoints

Press Release: January 25, 2021

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

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

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

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

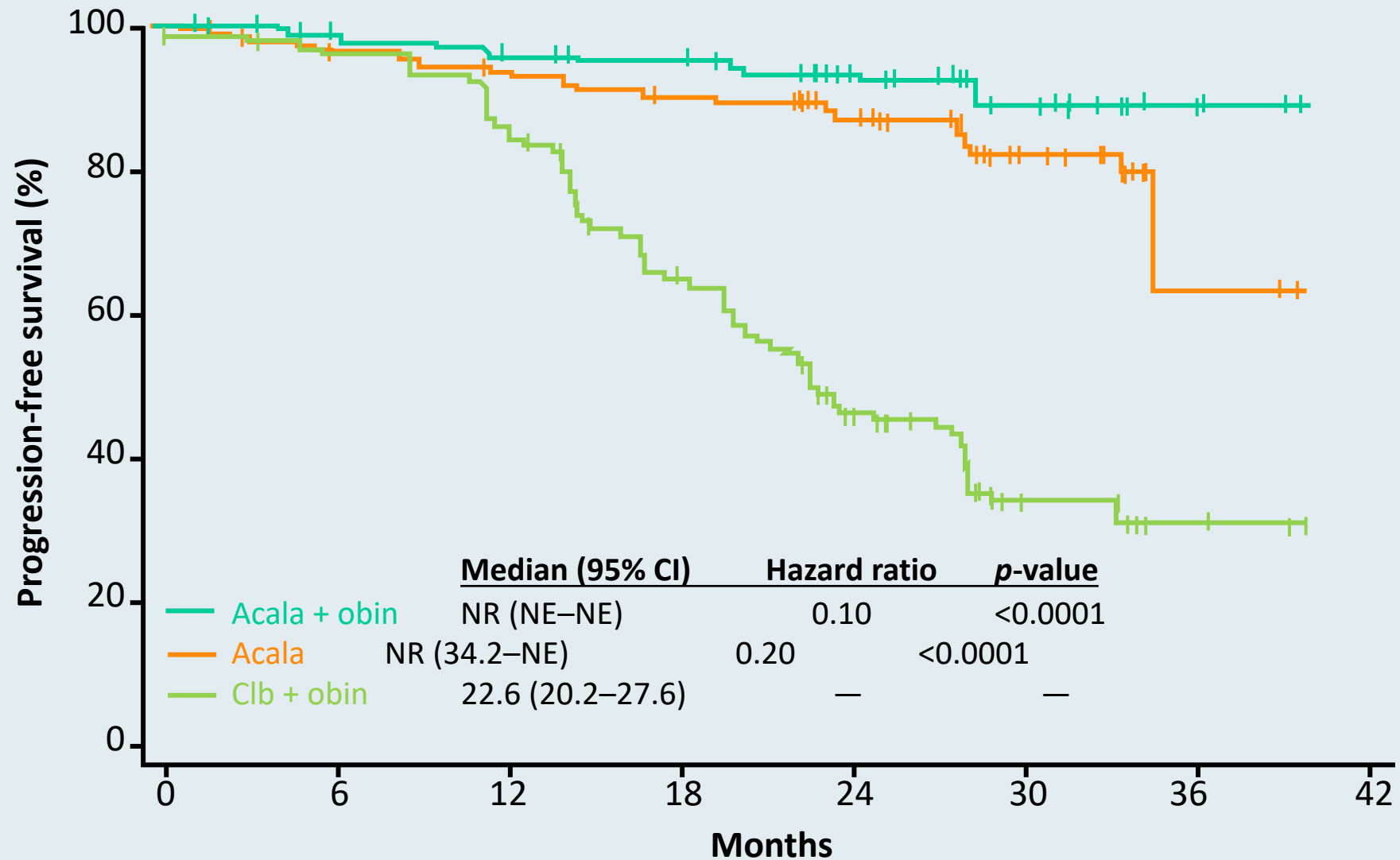


Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE-TN): a randomised, controlled, phase 3 trial

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

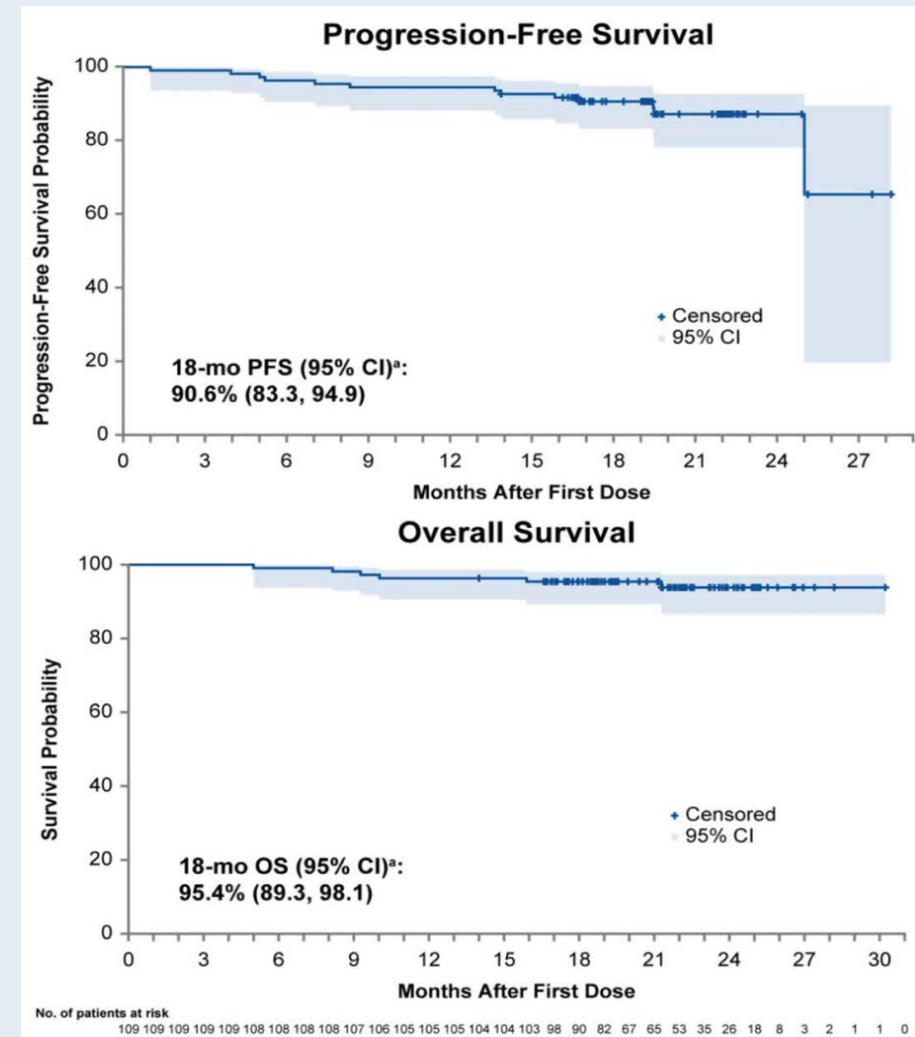
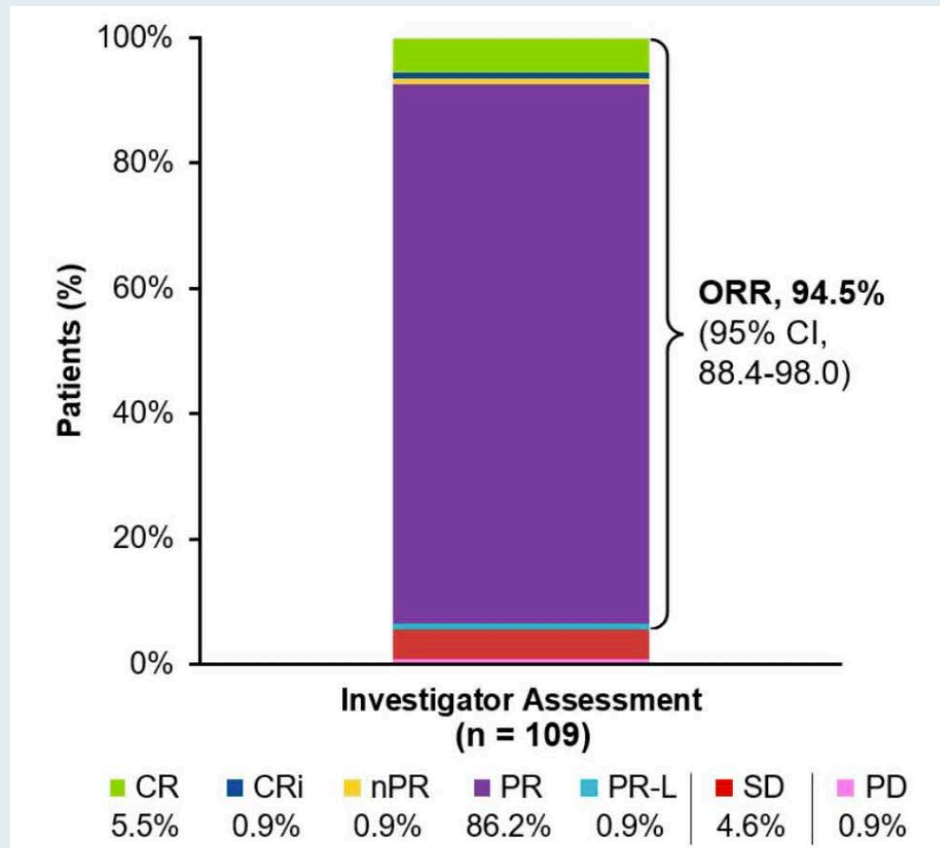
Lancet 2020;395(10232):1278-91.

ELEVATE-TN: PFS (IRC)



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

Best Overall Response



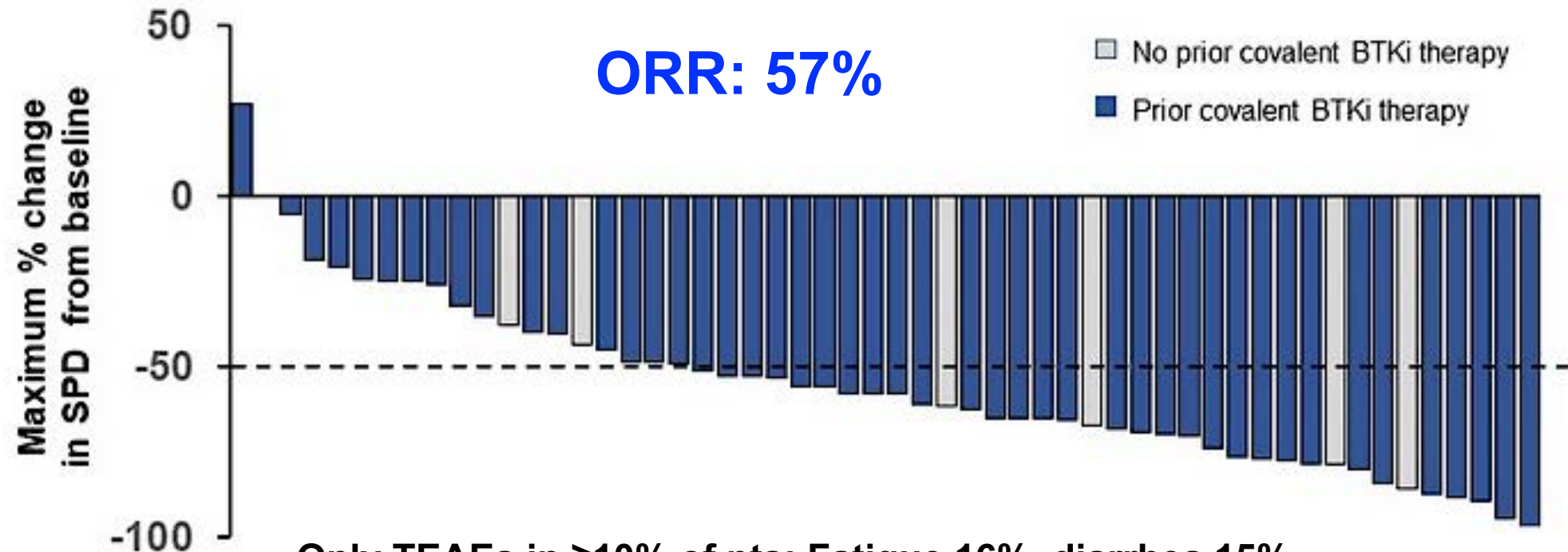
Median follow-up: 21.9 months (range, 5.0-30.2)

LOXO-305, a Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Results from the Phase 1/2 BRUIN Study

Mato AR et al.

ASH 2020;Abstract 542.

BRUIN: LOXO-305 for Previously Treated CLL/SLL (Median prior therapies: 4)



Only TEAEs in $\geq 10\%$ of pts: Fatigue 16%, diarrhea 15%

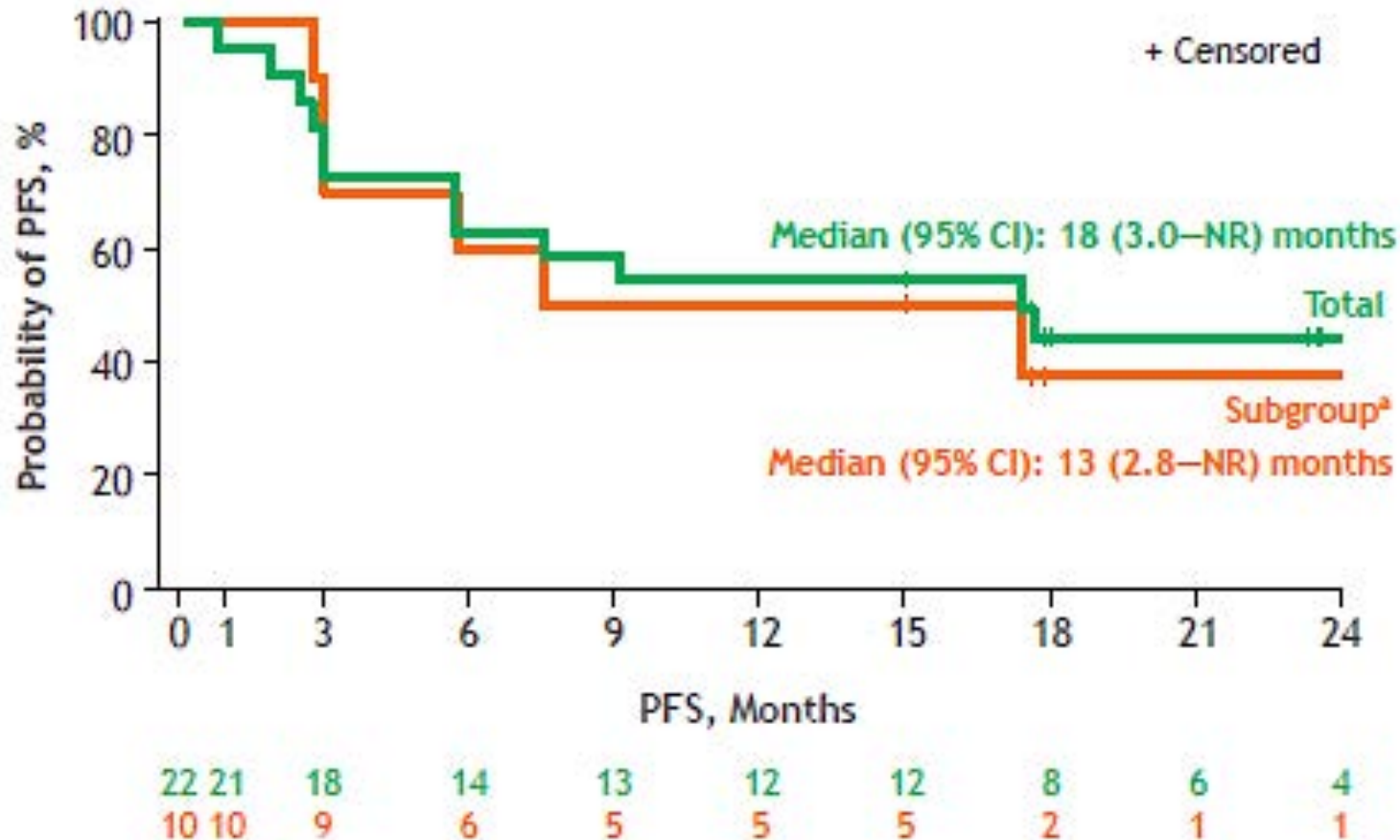
* 11 efficacy-evaluable pts are not included in the waterfall plot, including 1 pt who discontinued prior to first response assessment, and 10 pts (4 pts with PR/PR-L and 6 pts with SD) with incomplete tumor lesion measurement data at the time of data cut

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

Siddiqi T et al.

ASH 2020;Abstract 546.

TRANSCEND CLL 04: Liso-cel Monotherapy Cohort



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

Agenda

Module 1: Chronic Lymphocytic Leukemia (CLL)

- Case Presentation – Dr Deutsch: A 65-year-old man with relapsed CLL – del(11q)
- Case Presentation – Dr Lamar: An asymptomatic 81-year-old man with newly diagnosed CLL

Module 2: Follicular Lymphoma

- Dr Favaro: A 61-year-old man with low volume of relapsed FL

Module 3: Mantle Cell Lymphoma (MCL)

- Dr Deutsch: A 62-year-old man with relapsed MCL

Module 4: Diffuse Large B-Cell Lymphoma (DLBCL)

- Dr Favaro: A moderately frail 74-year-old woman with Stage III DLBCL

Module 5: Hodgkin Lymphoma

- Dr Mohamed: A 26-year-old woman with classical Hodgkin lymphoma
- Dr Mohamed: A 55-year-old man with late-stage Hodgkin lymphoma

Case Presentation – Dr Favaro: A 61-year-old man with low volume of relapsed FL



Dr Justin Peter Favaro

- Presented with follicular lymphoma with an enlarged spleen and WBC: 279
- Bendamustine/rituximab → consolidation/maintenance, with CR
- Now, with relapse in the inguinal lymph nodes → Plan for RT

Questions

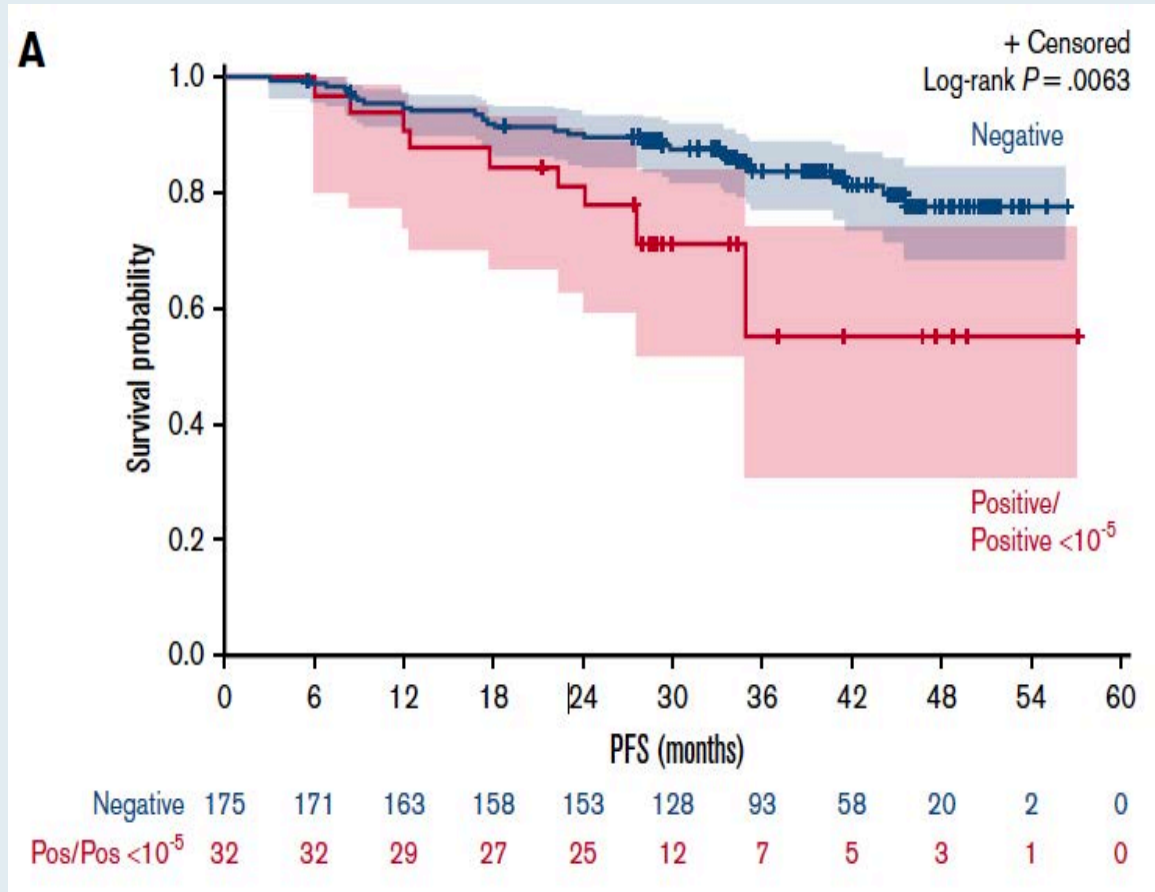
- In a patient that has a local relapse of follicular lymphoma, how would you treat them?
- After using radiation therapy for localized recurrence of follicular lymphoma, would you consider using maintenance rituximab?
- For future relapse, how do you choose among all the targeted PI3K inhibitors and telomerase inhibitors?
- Do you still use radioactive immunotherapy for consolidation in follicular lymphoma? And at the end of the line, where do CAR T and transplant come into play?
- How are you interdigitating COVID vaccines and rituximab therapy? Are you considering holding rituximab therapy, and for how long would you hold it to allow for the patients to have a good immune response to the COVID vaccine?

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

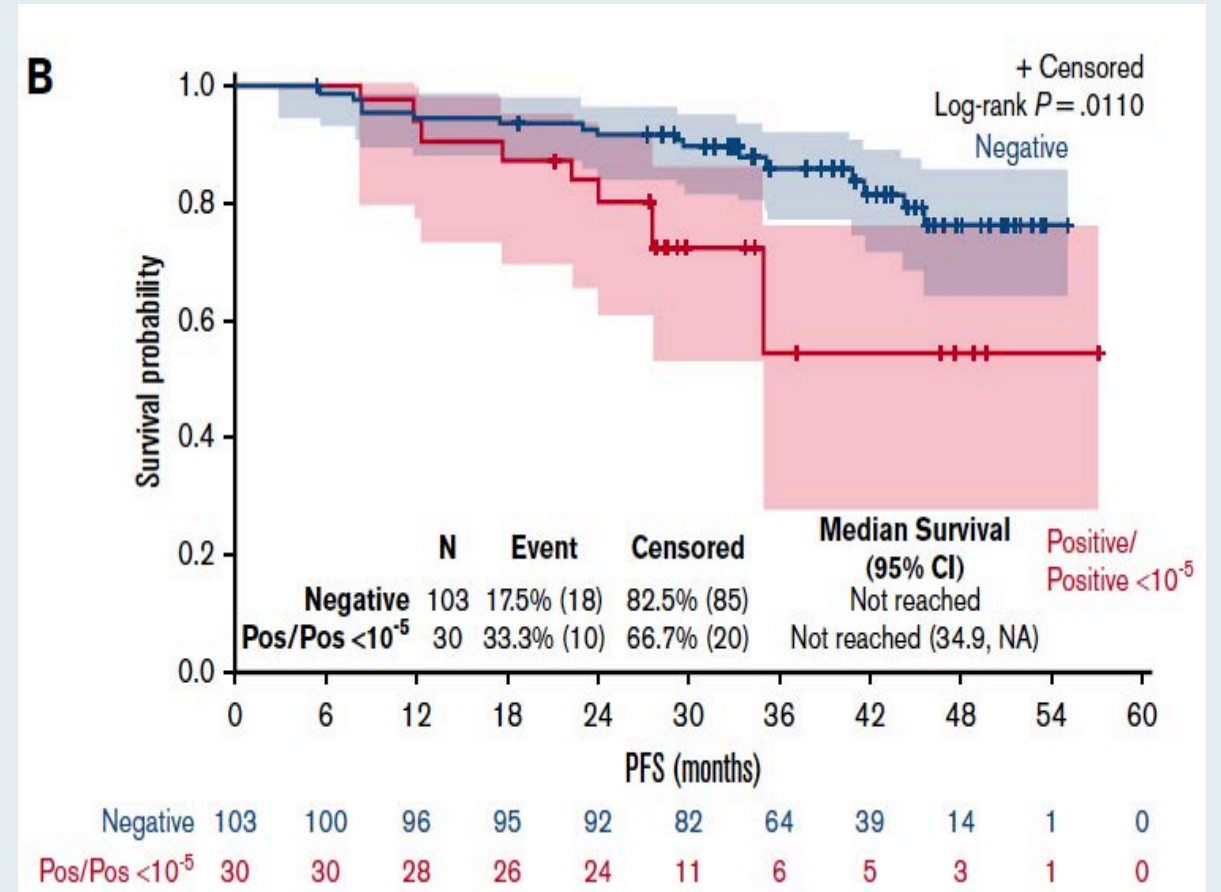
1. Idelalisib
2. Copanlisib
3. Duvelisib
4. Umbralisib
5. Tazemetostat
6. R-CHOP
7. Obinutuzumab +/- chemotherapy
8. Other

RELEVANCE Trial: R² Induces High Molecular Response in Untreated FL

Impact of positive MRD at week 24 on PFS in PB and/or BM



Impact of positive MRD at week 24 on PFS in BM



CHRONOS-3 Trial: Copanlisib + Rituximab Meets Primary Endpoint in Relapsed iNHL

Press Release: October 14, 2020

The Phase III study CHRONOS-3 evaluating copanlisib in combination with rituximab in indolent Non-Hodgkin's Lymphoma (iNHL) patients (n=458) who have relapsed after one or more prior lines of rituximab-containing therapy has met its primary endpoint of prolonged progression-free survival (PFS). The study predominantly included patients with follicular lymphoma (FL) and marginal zone lymphoma, as well as patients with small lymphocytic lymphoma and lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia.

Safety observed in the trial was generally consistent with previously published data on the individual components of the combination and no new safety signals were identified.

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

Press Release: February 5, 2021

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

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

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

FDA Grants Accelerated Approval to Tazemetostat for Follicular Lymphoma

Press Release – June 18, 2020

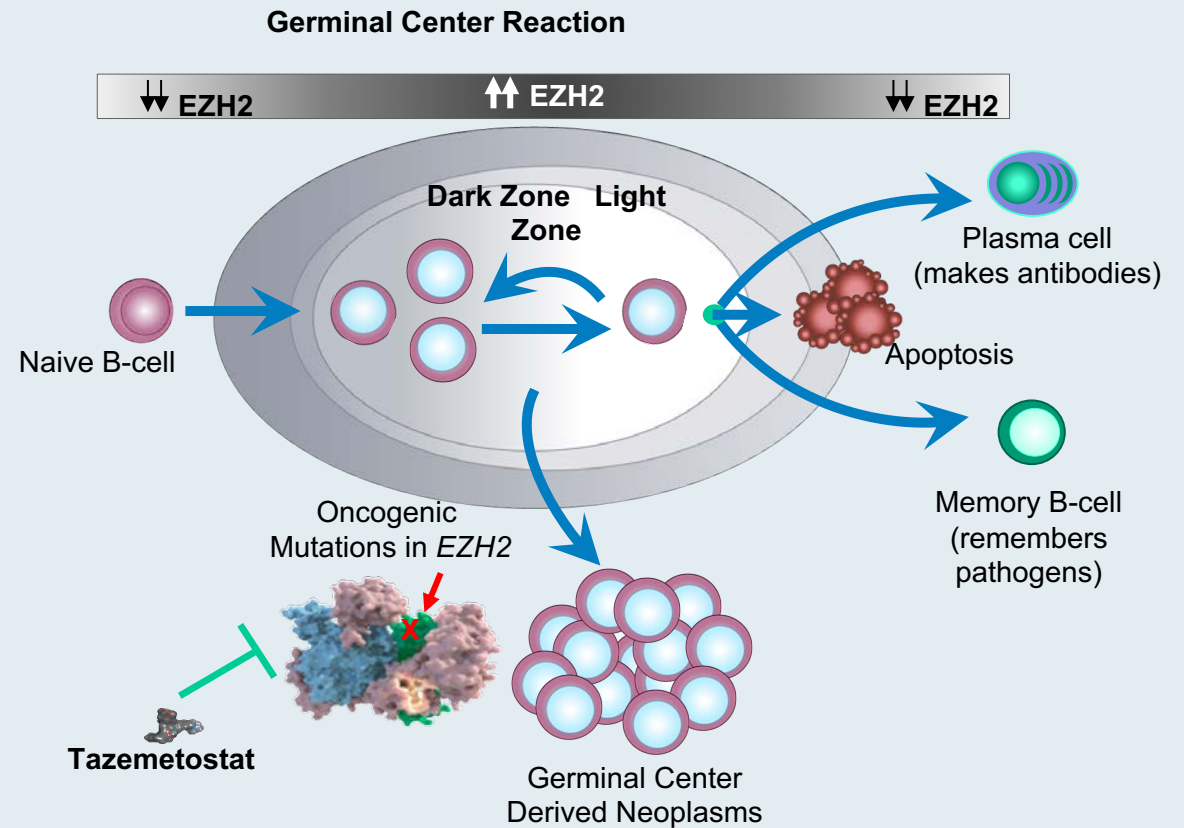
“The Food and Drug Administration granted accelerated approval to tazemetostat, an EZH2 inhibitor, for adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic 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® EZH2 Mutation Test. Patients received tazemetostat 800 mg orally twice daily until confirmed disease progression or unacceptable toxicity.

Follicular Lymphoma and EZH2

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



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

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

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

Salles G et al.

ASH 2020;Abstract 2047.

Phase 2 Efficacy Outcomes

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

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

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

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

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




American Society of Hematology

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

Target accrual (N = 518)

- Must have Grade I to IIIA FL
- Received at least 1 prior line of therapy
- No prior EZH2 inhibitor
- No prior lenalidomide for FL

R



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

**Placebo
+
R²**

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

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

Fowler NH et al.

ASH 2020;Abstract 1149.

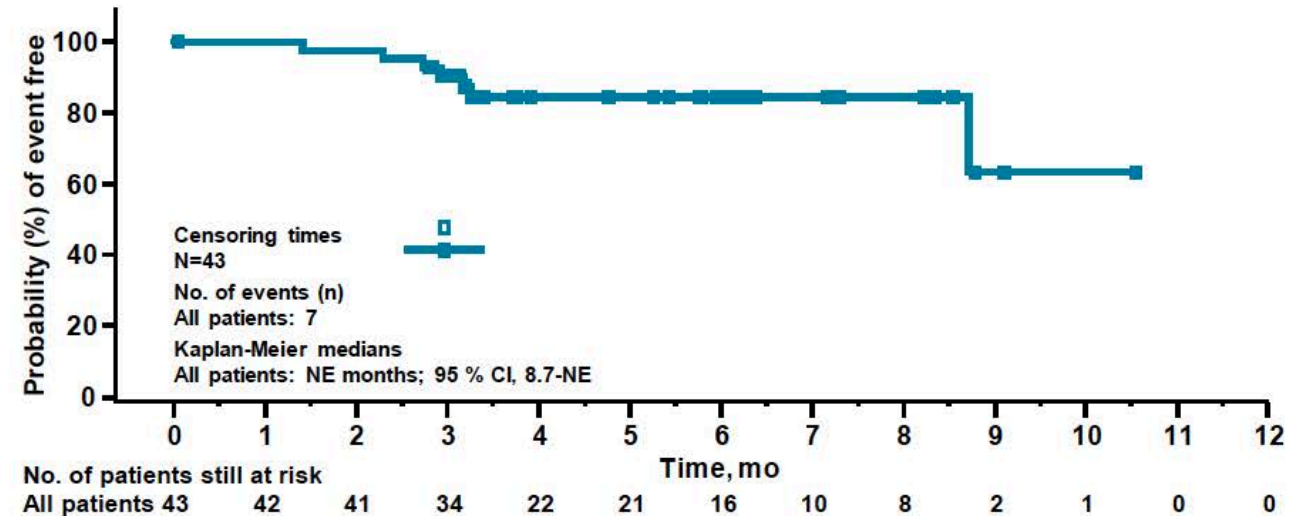
ELARA Interim Analysis: Primary CR Endpoint

Best Overall Response Rate

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

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

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



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

ELARA: Overall Safety Profile

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

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

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

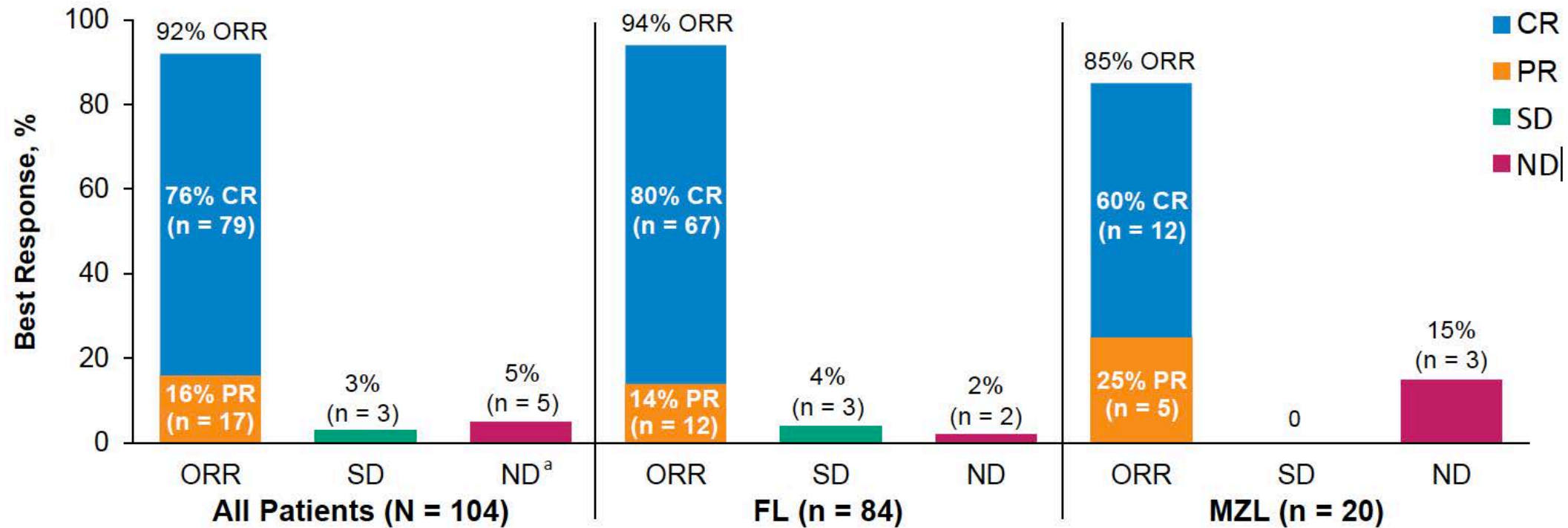
- **All neurological and CRS events resolved with appropriate management**

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

Jacobson CA et al.

ASH 2020;Abstract 700.

ZUMA-5 Primary Endpoint: ORR by IRRC Assessment



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

ASH 2020: Advent of Bispecifics in Lymphoma

- **CD20 x CD3**
 - REGN1979 — Bannerji ASH 2020 #400
 - Mosunetuzumab — Olszewski ASH 2020 #401
 - Epcoritamab — Hutchings ASH 2020 #402
 - Glofitamab — Hutchings ASH 2020 #403
- **CD19 x CD3**
 - MB-CART2019.1 — Borchman ASH 2020 #404

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- Dr Mohamed: A 26-year-old woman with classical Hodgkin lymphoma
- Dr Mohamed: A 55-year-old man with late-stage Hodgkin lymphoma

Case Presentation – Dr Deutsch: A 62-year-old man with relapsed MCL



Dr Margaret Deutsch

- 4/2017: Diagnosed with Stage IV MCL, with significant bowel involvement and diffuse neck, chest and abdominal lymphadenopathy
- Bendamustine/rituximab (BR) x 7, with resolution of FDG uptake on PET imaging
- 11/2020 PET: FDG positive cecal mass and mesenteric lymphadenopathy biopsy-positive for MCL
- Plan to re-treat with BR

Question

- What are your thoughts about alternative treatments, such as ibrutinib, for this patient? What about stem cell transplantation?

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

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

Overview of FDA-Approved BTK Inhibitors for MCL: Ibrutinib, Acalabrutinib and Zanubrutinib

- **Similar overall response rates, ~70-80%**
 - Better when used earlier (2nd or 3rd line)
- **Improved toxicity profile for acalabrutinib and zanubrutinib**
 - More specific BTKi inhibition (zanubrutinib similar to acalabrutinib)
 - Less afibrillation, bruising/bleeding, arthralgia
 - Prefer over ibrutinib if concurrent anticoagulation and/or anti-platelet therapy

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

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

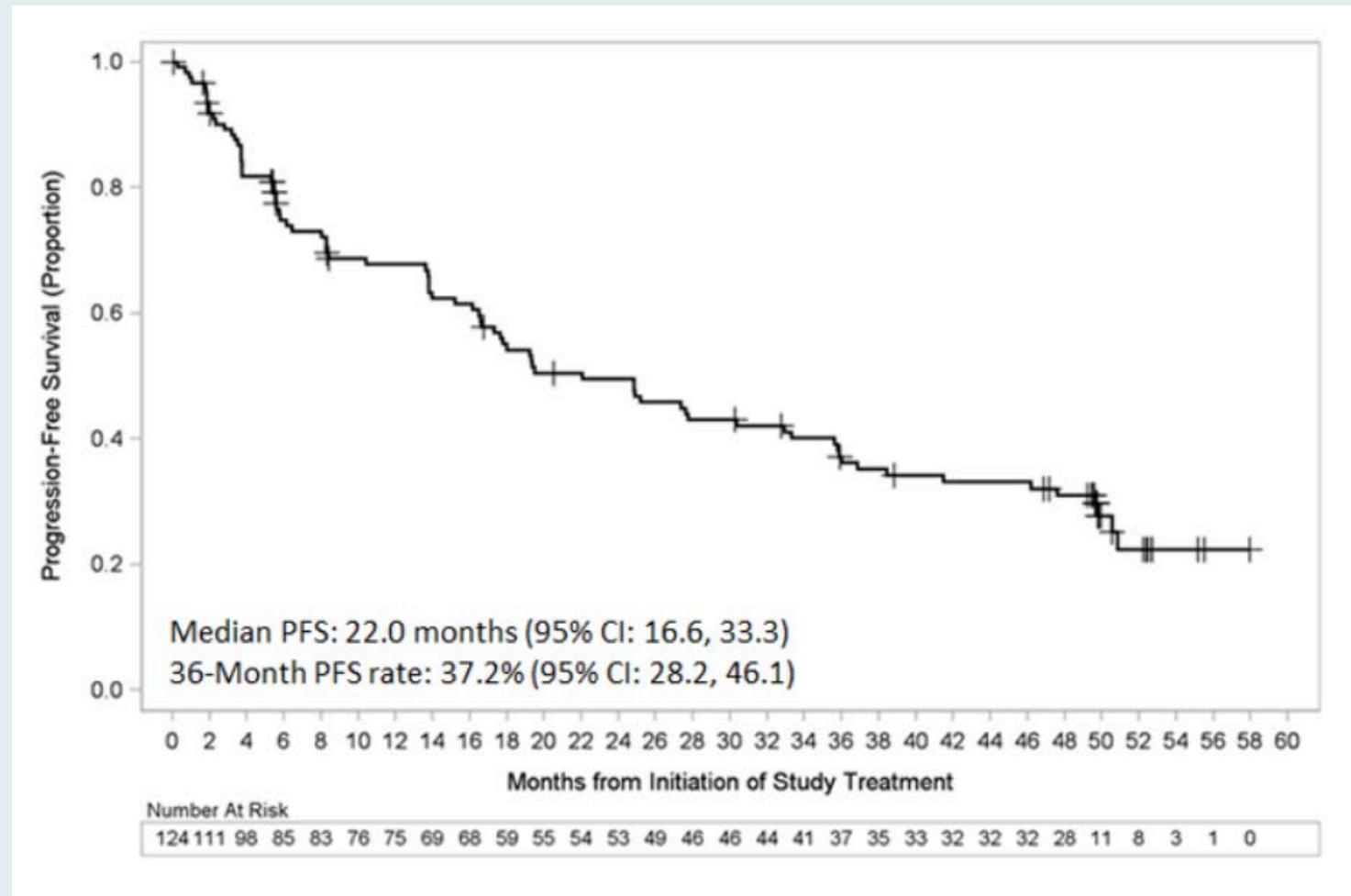
Endpoint	Overall (N = 370)	Prior lines of therapy	
		1 (n = 99)	>1 (n = 271)
Median PFS	12.5 mo	25.4 mo	10.3 mo
Median PFS by best response CR (n = 102) PR (n = 156)	67.7 mo 12.6 mo	68.5 mo 24.2 mo	67.7 mo 10.5 mo
Median OS	26.7 mo	61.6 mo	22.5 mo
Median OS by best response CR (n = 102) PR (n = 156)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

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

Wang M et al.

ASH 2020;Abstract 2040.

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



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

Efficacy of Zanubrutinib for MCL

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

Venetoclax Monotherapy for BTK Inhibitor-Resistant MCL: Results Summary

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

No cases of clinical TLS were observed.

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.

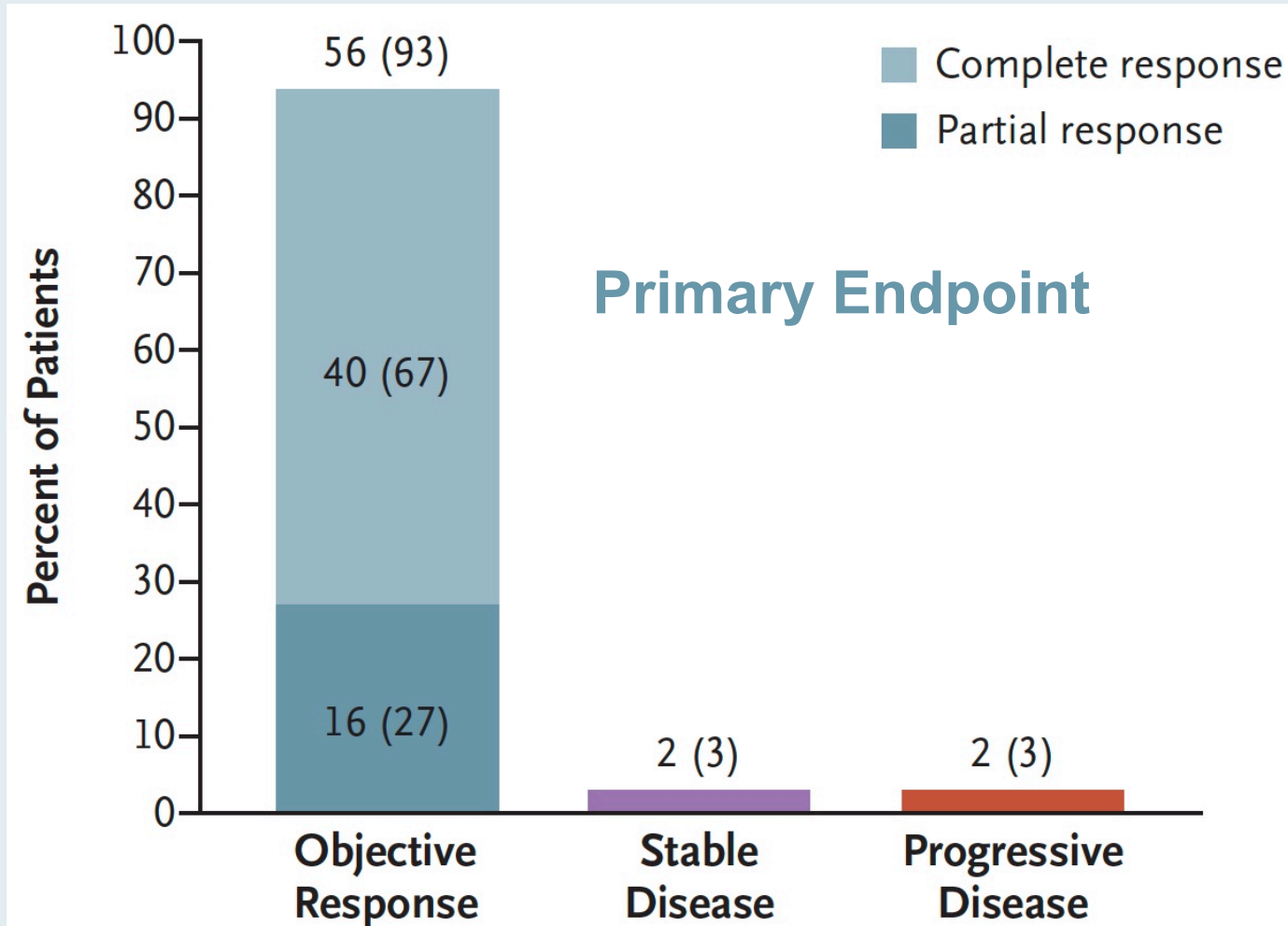
ORIGINAL ARTICLE

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%

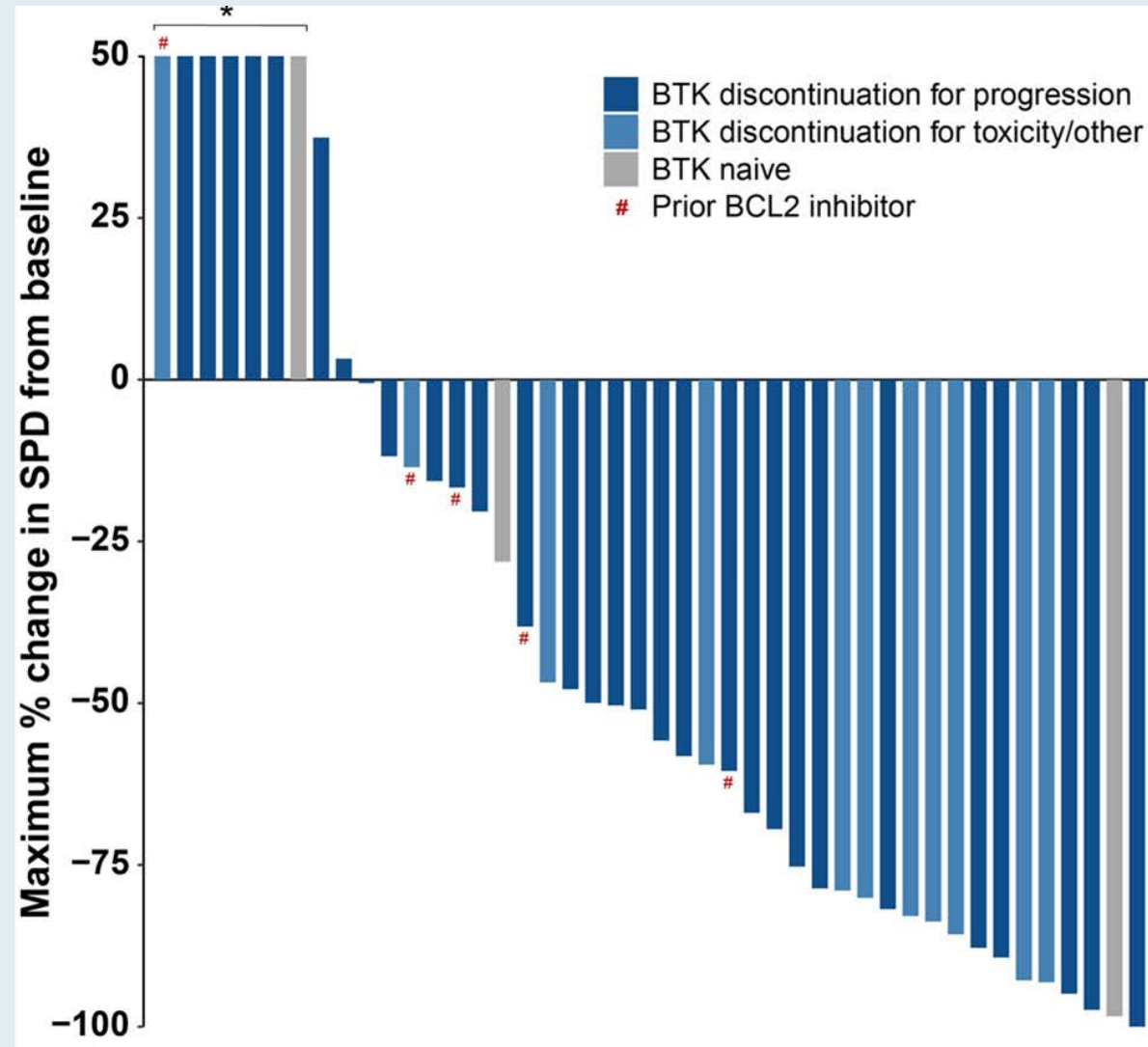
Key toxicities		
	Grade 1-2	Grade 3-4
Cytokine release syndrome	76%	15%
Neurologic events	32%	31%
Cytopenias	—	94%
Infections	23%	32%

LOXO-305, a Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated Mantle Cell Lymphoma, Waldenström's Macroglobulinemia, and Other Non-Hodgkin Lymphomas: Results from the Phase 1/2 BRUIN Study

Wang M et al.

ASH 2020;Abstract 117.

BRUIN: Efficacy of LOXO-305 in Mantle Cell Lymphoma



BRUIN: Response Rates in Mantle Cell Lymphoma

All MCL Patients ^a	n=56
Overall Response Rate ^b , % (95% CI)	52% (38-65)
Best Response	
CR, n (%)	14 (25)
PR, n (%)	15 (27)
SD, n (%)	10 (18)
BTK Pre-Treated MCL Patients ^a	n=52
Overall Response Rate ^b , % (95% CI)	52% (38-66)
Best Response	
CR, n (%)	13 (25)
PR, n (%)	14 (27)
SD, n (%)	9 (17)

Efficacy also seen in patients with prior:

- Stem cell transplant: ORR 64% (9/14)
- CAR-T therapy: ORR 100% (2/2)

Agenda

Module 1: Chronic Lymphocytic Leukemia (CLL)

- Case Presentation – Dr Deutsch: A 65-year-old man with relapsed CLL – del(11q)
- Case Presentation – Dr Lamar: An asymptomatic 81-year-old man with newly diagnosed CLL

Module 2: Follicular Lymphoma

- Dr Favaro: A 61-year-old man with low volume of relapsed FL

Module 3: Mantle Cell Lymphoma (MCL)

- Dr Deutsch: A 62-year-old man with relapsed MCL

Module 4: Diffuse Large B-Cell Lymphoma (DLBCL)

- Dr Favaro: A moderately frail 74-year-old woman with Stage III DLBCL

Module 5: Hodgkin Lymphoma

- Dr Mohamed: A 26-year-old woman with classical Hodgkin lymphoma
- Dr Mohamed: A 55-year-old man with late-stage Hodgkin lymphoma

Case Presentation – Dr Favaro: A moderately frail 74-year-old woman with Stage III DLBCL



Dr Justin Peter Favaro

- Diagnosed with bulky Stage III DLBCL, germinal-center type
 - c-Myc translocation-negative
- R-CHOP x 6 → Deauville score: 4, residual lymphadenopathy

Questions

- What would you recommend next, given that she is not a great transplant candidate? Do you recommend going with CAR T therapy? Should we move on and just give her radiation therapy to the residual sites of disease and observe her? Or, are there any systemic therapies that would be recommended?
- What is the role of CAR T therapy in patients with more aggressive DLBCL, like the activated B-cell type? Is there any role for using that in consolidation upfront as opposed to waiting for relapse?
- In what other types of lymphoma or leukemia will we see new approvals for CAR T therapy?

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

1. Polatuzumab vedotin/BR
2. Tafasitamab/lenalidomide
3. Selinexor
4. CAR T-cell therapy
5. I don't know

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

Press Release – February 5, 2021

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

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

Pivotal CAR-T Studies in DLBCL: Summary of Efficacy

	ZUMA-1 Axicabtagene ciloleucel	JULIET Tisagenlecleucel	TRANSCEND NHL 001 Lisocabtagene maraleucel
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.

Pivotal CAR-T Studies in DLBCL: Select Toxicities

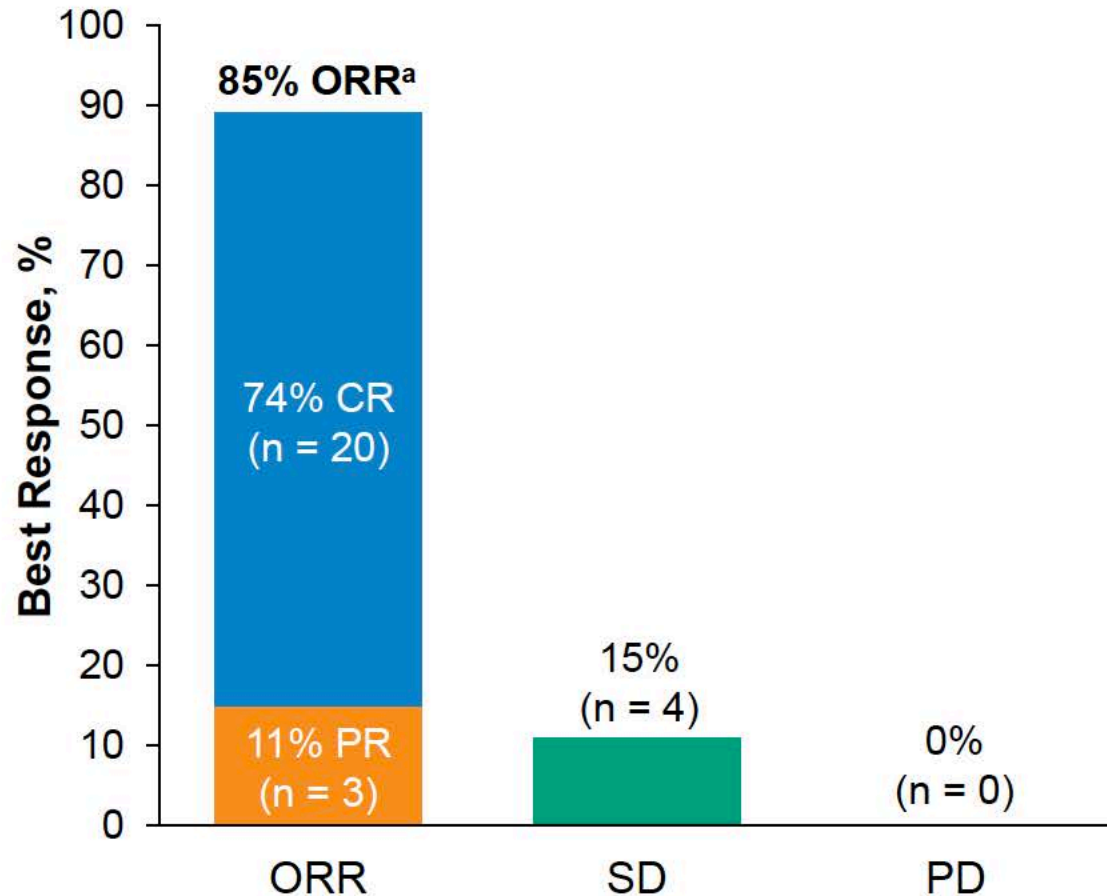
	ZUMA-1 Axicabtagene ciloleucel	JULIET Tisagenlecleucel	TRANSCEND NHL 001 Lisocabtagene maraleucel
All grades CRS	93%	58%	37%
Grade ≥3 CRS	13%	23%	1%
All grades neurotoxicity	64%	21%	23%
Grade ≥3 neurotoxicity	28%	12%	13%
Tocilizumab use	43%	15%	17%
Steroid treatment	27%	11%	21%

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.

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

Neelapu SS et al.
ASH 2020;Abstract 405.

ZUMA-12: Response Rates



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

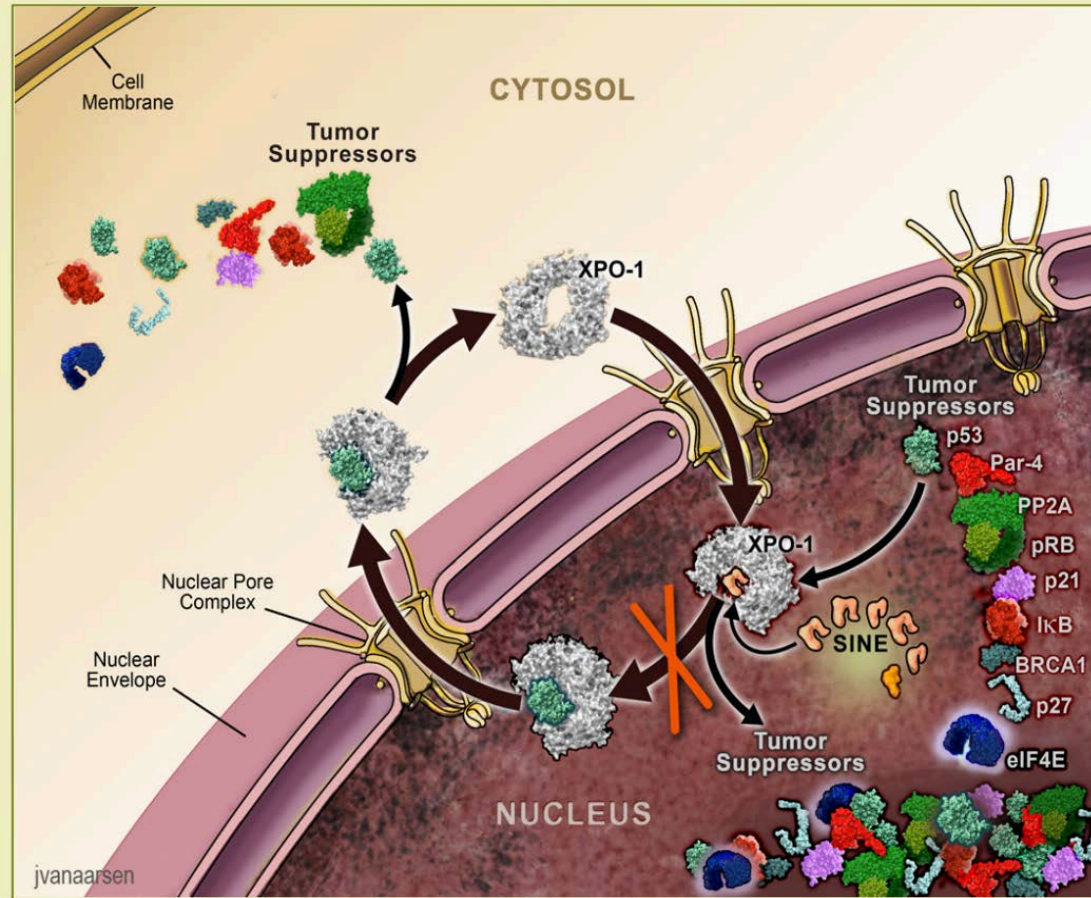
FDA Approves Selinexor for Relapsed/Refractory Diffuse Large B-Cell Lymphoma

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.”

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



XPO1 over-expressed in DLBCL and correlates with poor prognosis

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

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

Kalakonda. Lancet Heme 2020

Courtesy of Ann S LaCasce, MD, MMSc

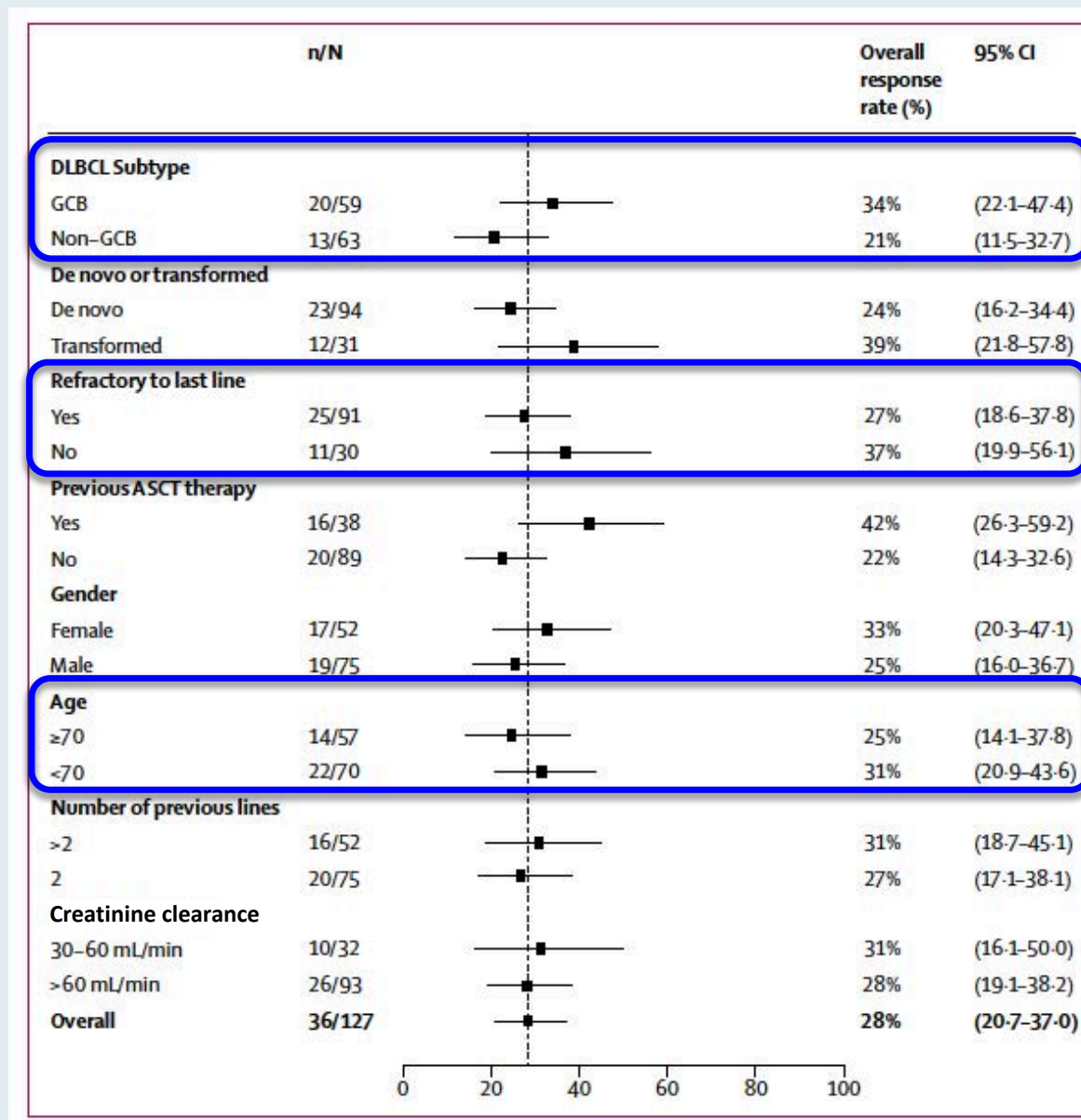
SADAL: Phase II Trial of Selinexor Monotherapy in R/R DLBCL

Patient characteristics:

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

Results:

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



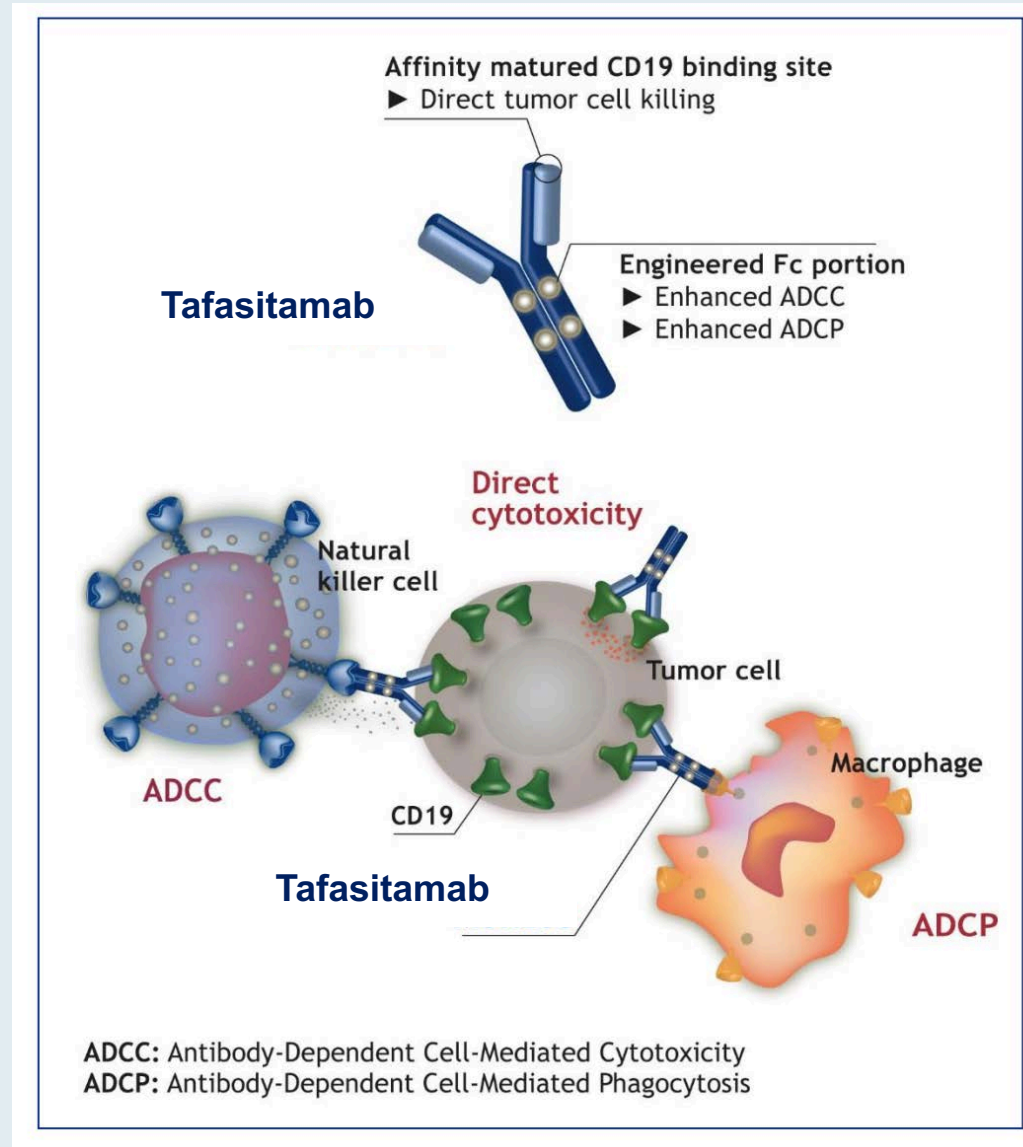
FDA Grants Accelerated Approval to Tafasitamab-cxix for Diffuse Large B-cell Lymphoma

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 (MOR208)



Lenalidomide enhances
NK function with
enhanced ADCC in vitro

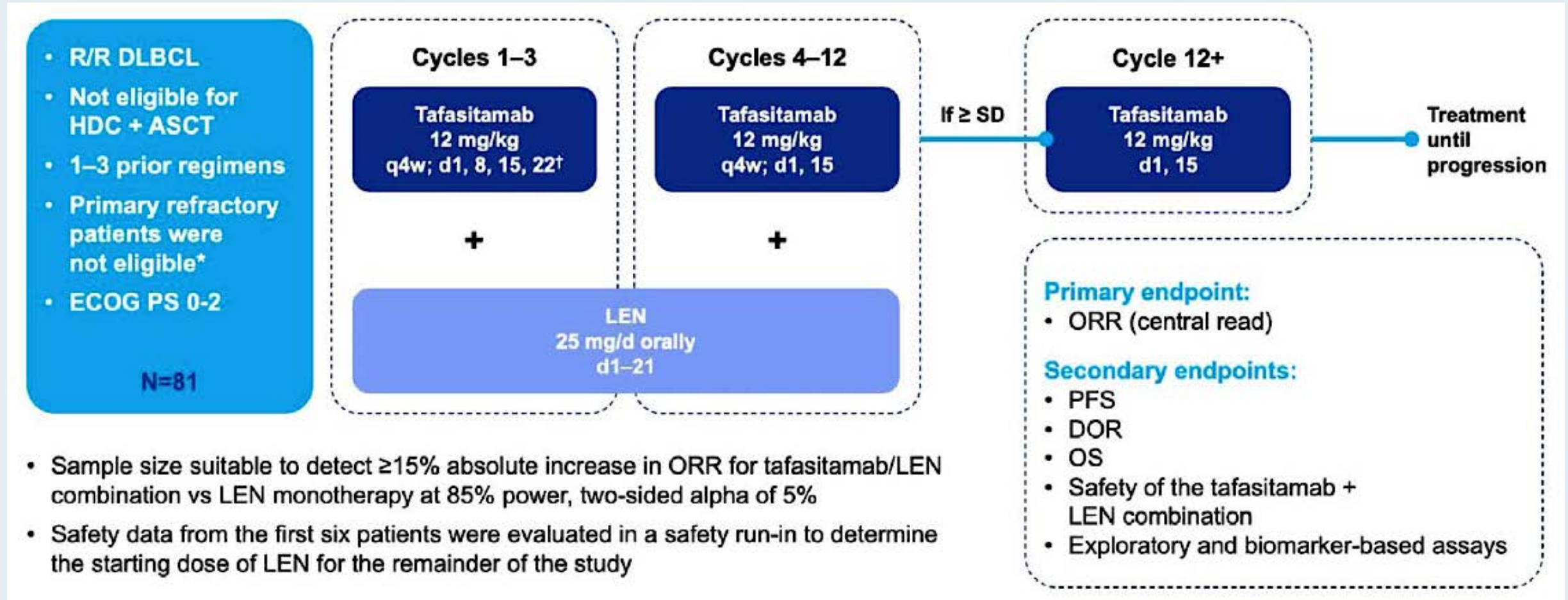
Salles et al. Lancet Onc 2020

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

Maddocks KJ et al.

ASH 2020;Abstract 3021.

L-MIND: Study Design



L-MIND: Summary

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

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

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

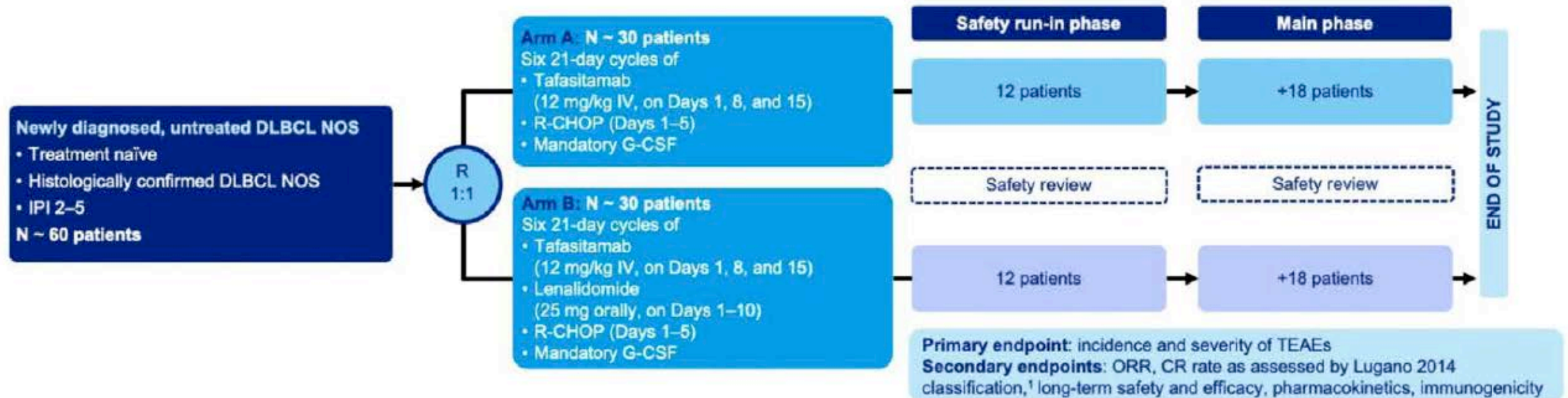
A Phase Ib, Open-Label, Randomized Study to Assess Safety and Preliminary Efficacy of Tafasitamab (MOR208) or Tafasitamab + Lenalidomide in Addition to R-CHOP in Patients with Newly Diagnosed Diffuse Large B-Cell Lymphoma: Analysis of the Safety Run-in Phase

Belada D et al.

ASH 2020;Abstract 3028.

First-MIND: Study Design

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



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

First-MIND: Treatment Emergent Adverse Events

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

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

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

Agenda

Module 1: Chronic Lymphocytic Leukemia (CLL)

- Case Presentation – Dr Deutsch: A 65-year-old man with relapsed CLL – del(11q)
- Case Presentation – Dr Lamar: An asymptomatic 81-year-old man with newly diagnosed CLL

Module 2: Follicular Lymphoma

- Dr Favaro: A 61-year-old man with low volume of relapsed FL

Module 3: Mantle Cell Lymphoma (MCL)

- Dr Deutsch: A 62-year-old man with relapsed MCL

Module 4: Diffuse Large B-Cell Lymphoma (DLBCL)

- Dr Favaro: A moderately frail 74-year-old woman with Stage III DLBCL

Module 5: Hodgkin Lymphoma

- Dr Mohamed: A 26-year-old woman with classical Hodgkin lymphoma
- Dr Mohamed: A 55-year-old man with late-stage Hodgkin lymphoma

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



Dr Mohamed K Mohamed

- 5/2020: Presents to ER with sore throat and lump on her neck
 - Biopsy: Classical Hodgkin lymphoma, nodular sclerosis subtype, bone marrow: Negative
- ABVD x 2
 - Repeat PET: Near complete resolution of hypermetabolic activity and size of tumor in the neck and mediastinum (Deauville 2)

Question

- What would you do – give an additional 2 cycles of ABVD, radiation therapy, or observe?

Case Presentation – Dr Mohamed: A 55-year-old man with late-stage Hodgkin lymphoma



Dr Mohamed K Mohamed

- 9/2020: Presents to ER with 2-month history of bulky adenopathy in left neck and axilla
- Imaging: Hypermetabolic activity in neck, porta hepatis, spleen and narrow space of pelvis, spine and ribs
 - Biopsy: Classical Hodgkin lymphoma, nodular sclerosing subtype, Stage IV (IPS: 4)
- Brentuximab vedotin + AVD x 3
- Repeat PET: Marked improvement in neck, abdomen and nodes but not the spleen
- Plan for BV + AVD x 3 more cycles

Question

- What additional treatment, if any, would you recommend after he completed BV + AVD x 6?

Regulatory and reimbursement issues aside, what would generally be your preferred bridge to transplant for a patient with HL who is experiencing relapse after up-front ABVD?

1. ICE (ifosfamide/carboplatin/etoposide)
2. Brentuximab vedotin
3. Brentuximab vedotin + nivolumab
4. Brentuximab vedotin + pembrolizumab
5. Other

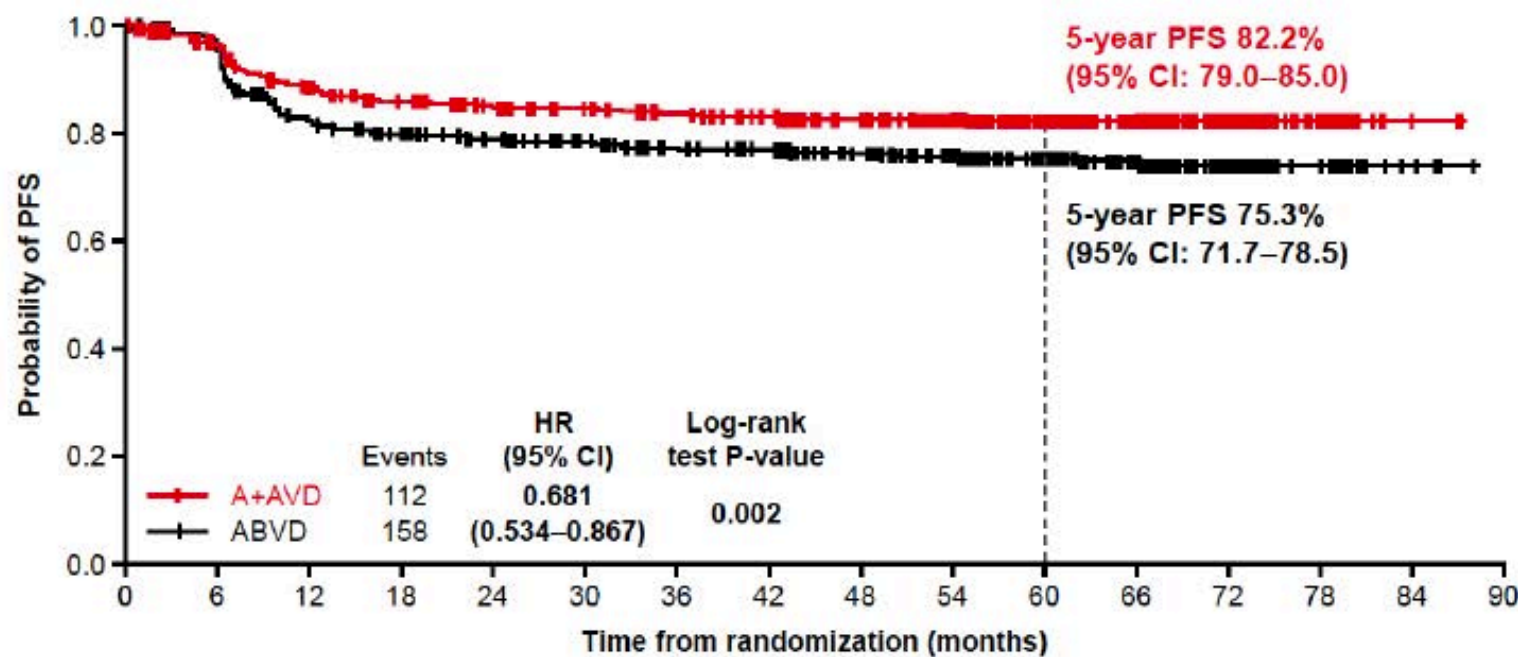
Brentuximab Vedotin with Chemotherapy for Patients with Previously Untreated, Stage III/IV Classical Hodgkin Lymphoma: 5-Year Update of the ECHELON-1 Study

Straus DJ et al.

ASH 2020;Abstract 2973.



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



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

Number of patients at risk

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

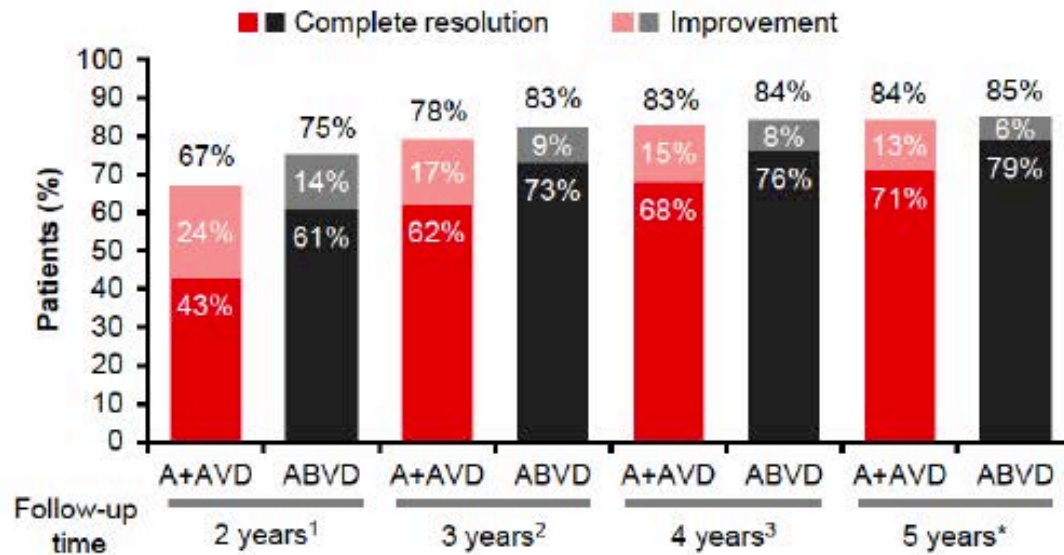
*September 14, 2020 data cut-off.



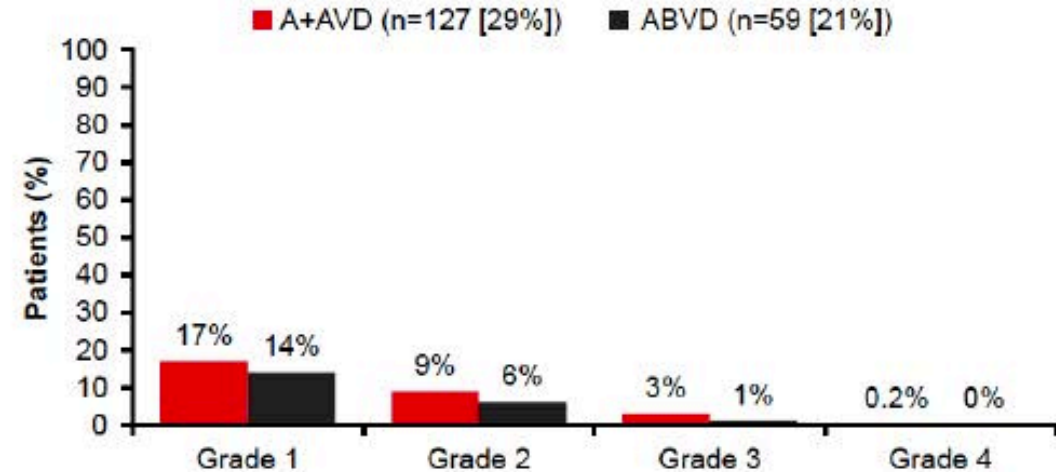
ECHELON-1: PN resolution and improvement

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

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

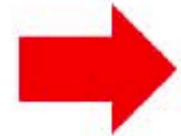


Patients with ongoing PN by grade at last follow-up[†]



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

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

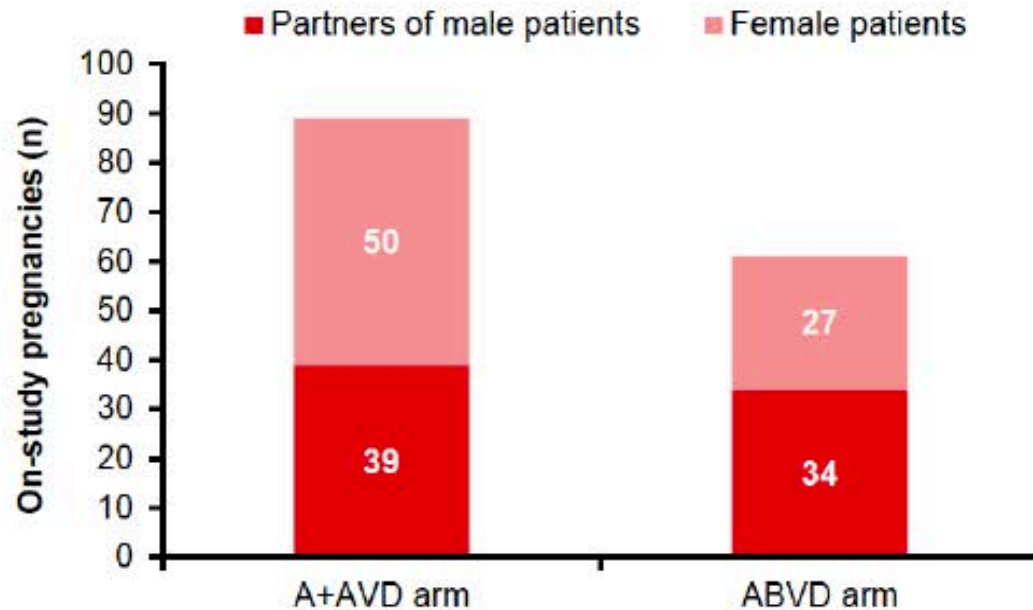




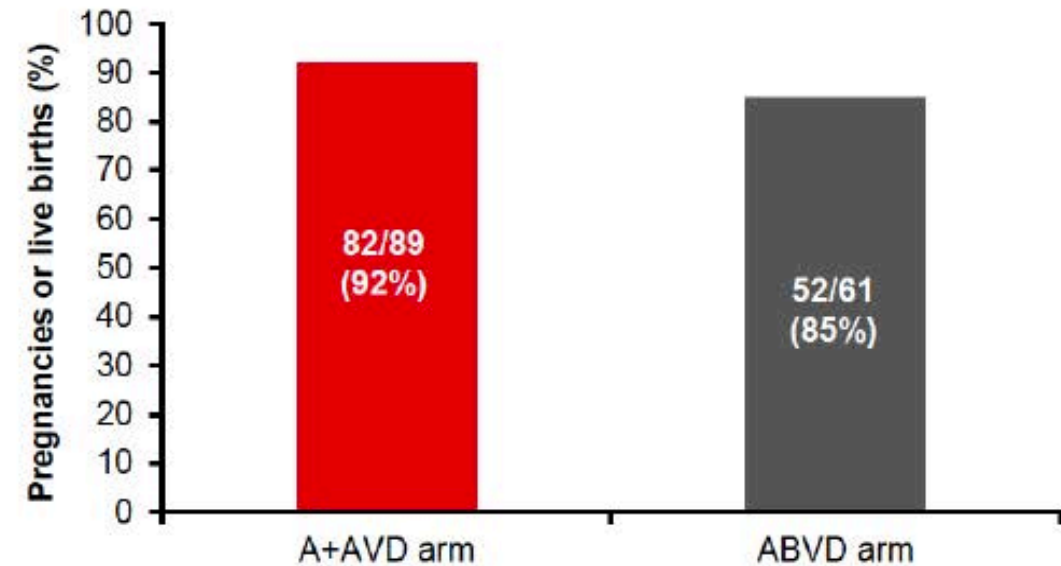
ECHELON-1: Pregnancies

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

On-study pregnancies in patients or their partners



Ongoing pregnancies or live births



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

Yasenchak CA et al.
ASH 2020;Abstract 471.

Best Responses per Investigator – Efficacy Evaluable Set

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

Patients who were not efficacy-evaluable included:

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

Summary

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

- **BV monotherapy**

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

- **BV combination treatments**

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

FDA Extends Approval of Pembrolizumab for Classical Hodgkin Lymphoma

Press Release – October 14, 2020

“The Food and Drug Administration extended the approval of pembrolizumab for the following indications:

- Adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) and
- Pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy

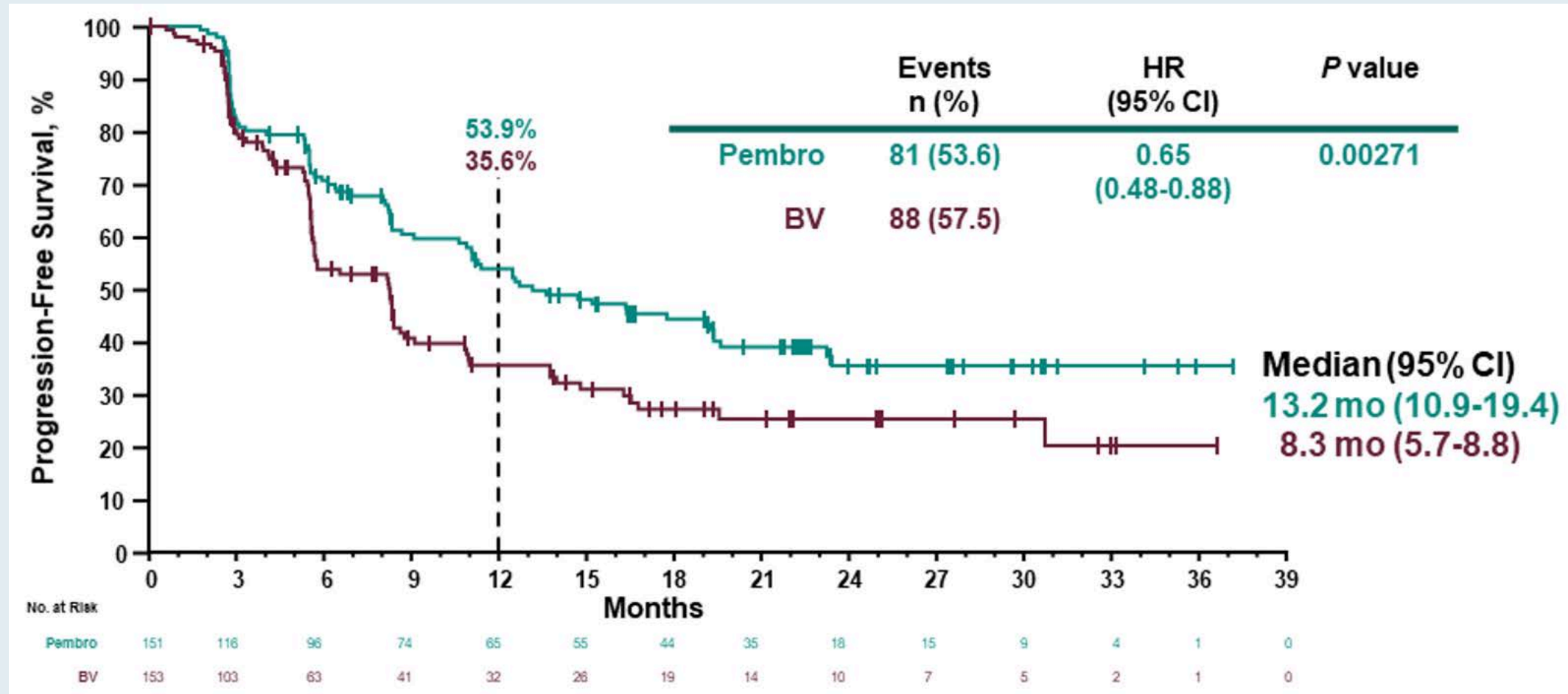
Approval was based on KEYNOTE-204 (NCT02684292), a phase 3, randomized, open-label trial in 304 adult patients with relapsed or refractory cHL after at least one multiagent regimen. Patients were randomized (1:1) to receive either pembrolizumab 200 mg every 3 weeks or brentuximab vedotin (BV) 1.8 mg/kg every 3 weeks for up to 2 years.

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

Kuruville J et al.

ASCO 2020;Abstract 8005.

KEYNOTE-204: PFS Primary Endpoint



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

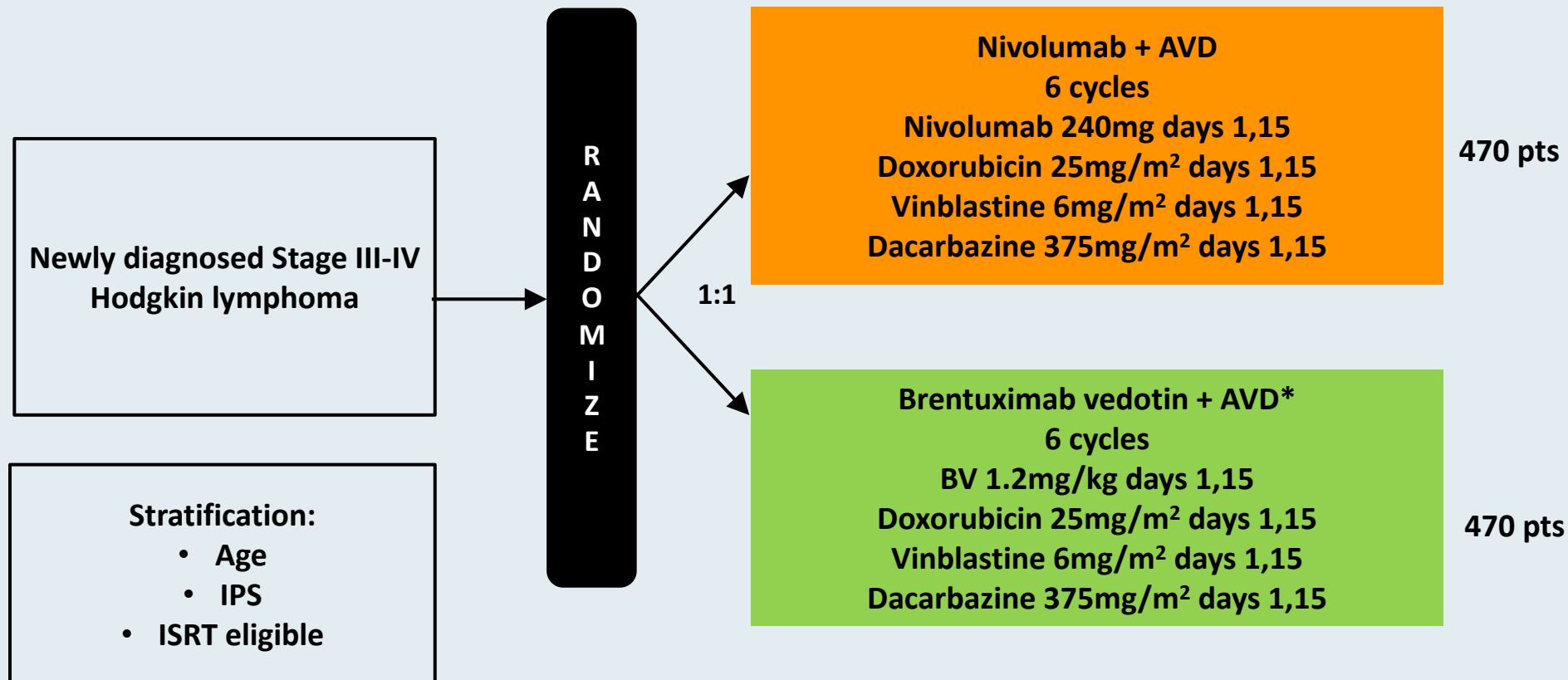
Herrera AF et al.

ASH 2020;Abstract 472.

Summary Conclusions

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

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



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

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

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

**A Daylong Clinical Summit Hosted in Partnership with
North Carolina Oncology Association (NCOA) and
South Carolina Oncology Society (SCOS)**

Saturday, February 13, 2021

8:30 AM – 4:30 PM ET

Agenda

Module 1 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Pagel and Smith*

Module 2 — Multiple Myeloma: *Drs Richardson and Voorhees*

Module 3 — Genitourinary Cancers: *Drs Dreicer and Petrylak*

Module 4 — Lung Cancer: *Drs Gainor and Wakelee*

Module 5 — Gastrointestinal Cancers: *Dr Philip and Prof Van Cutsem*

Module 6 — Breast Cancer: *Drs Hurvitz and Krop*

Module 7 — Acute Myeloid Leukemia and Myelodysplastic Syndromes:
Drs DiNardo and Perl

Multiple Myeloma Faculty



Paul G Richardson, MD

Clinical Program Leader and Director of Clinical Research
Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
RJ Corman Professor of Medicine
Harvard Medical School
Boston, Massachusetts



Peter Voorhees, MD

Professor of Medicine
Member, Plasma Cell Disorders Division
Levine Cancer Institute, Atrium Health
Charlotte, North Carolina

The patients I saw today...

57	F	Low grade gastric NET - octreotide
64	M	MM - Post ASCT on lenalidomide maintenance
66	M	Castrate-resistant metastatic prostate cancer - PD on enzalutamide, to start docetaxel
42	F	Breast cancer, refused adjuvant chemotherapy, now with metastatic disease in the right axilla and bone.
66	F	CML – CR to imatinib
98	F	MDS – receiving ESAs
58	F	Glioblastoma multiforme - Maintenance temozolomide and optune device
85	F	Recurrent atypical meningioma on observation
60	F	Metastatic ER + HER2 - breast cancer - almost complete response in the breast after 4 months
82	M	Breast cancer 8 years ago - followup
48	M	CML – considering third line bosutinib
61	M	Primary appendyceal low grade cancer - surgery

62	F	IgM MGUS for years, now with pancytopenia, bone marrow biopsy showing low grade NHL (possibly WM)
38	F	mCRC – 2L FOLFIRI/Bevacizumab
59	M	Lupus anticoagulant/Pulmonary embolism - rivaroxaban
70	M	Metastatic melanoma - in remission on nivolumab for almost 3 years
67	M	Melanoma – PD on ipi/nivo, pt not doing well
67	F	Metastatic RCC – cape/bev maintenance
68	M	Metastatic lung adenocarcinoma, PD-L1 70% - 1L pembro, SD for 3 months
59	M	Stage IIIB Lung adenocarcinoma - Consolidation durvalumab post XRT/Chemo
59	F	Breast cancer 11 years ago – follow up
86	M	Anemia secondary to chronic kidney disease - ESA
48	F	Recurrent cervical SCC – CR to cis/pac/bev, on bev maint 18 months later

Contributing Oncologists



Daniel R Carrizosa, MD, MS
Atrium Health Levine Cancer Institute
Associate Program Director –
Hematology/Oncology Fellowship
Medical Director: Diversity/Disparities and
Outreach Committee
Section Head: Head and Neck Division
Member: Head and Neck and Thoracic Sections
Charlotte, North Carolina



Aleksander Chojecki, MD
Department of Hematology and Cellular Therapy
Atrium Health Levine Cancer Institute
Charlotte, North Carolina



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



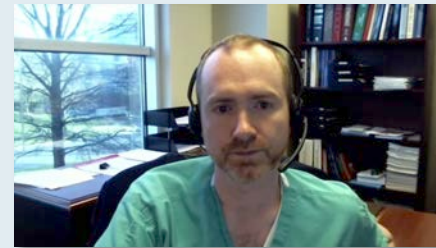
Margaret Deutsch, MD
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Raleigh, North Carolina



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Charlotte, North Carolina



Zanetta S Lamar, MD
Florida Cancer Specialists
and Research Institute
Naples, Florida



Claud Grigg, MD
Genitourinary Oncology
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Hematologist/ Medical Oncologist
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Richard Zelkowitz, MD
Regional Director of the Breast Program
Hematology and Oncology
Hartford HealthCare Cancer Institute
Bridgeport, Connecticut

Agenda

Module 1: Newly Diagnosed Multiple Myeloma

- Dr Usmani: A 64-year-old man with multiple regimen-refractory multiple myeloma – del(17p) and t(11;14)
 - Parts 1-4

Module 2: Relapsed Multiple Myeloma

- Dr Deutsch: A 73-year-old man with multiply relapsed multiple myeloma

Module 3: Novel Agents and Approaches

- Dr Usmani: A 76-year-old woman with relapsed multiple myeloma – t(11;14)
 - Parts 1, 2 and 3

Agenda

Module 1: Newly Diagnosed Multiple Myeloma

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Regulatory and reimbursement issues aside, what is your preferred pretransplant induction regimen for a younger, otherwise healthy patient with MM and del(17p)?

1. RVd (lenalidomide/bortezomib/dexamethasone)
2. KRd (carfilzomib/lenalidomide/dexamethasone)
3. CyBorD
4. Rd/daratumumab
5. RVd/daratumumab
6. KRd/daratumumab
7. MPV (melphalan/prednisone/bortezomib)/daratumumab
8. Other

Case Presentation – Dr Usmani (Part 1): A 64-year-old man with multiple regimen-refractory multiple myeloma – del(17p) and t(11;14)



Dr Saad Zafar Usmani

- Initial diagnosis of revised ISS Stage III IgG kappa myeloma, t(11;14)
- RVd induction x 4 cycles → VGPR
- Mel-200 ASCT → sCR
- Lenalidomide maintenance x 18 months (stopped per patient request due to superficial skin cancers)
- 2 years after stopping lenalidomide, biochemical relapse (patient is clinically asymptomatic)
- Restaging bone marrow shows 30% plasma cells
- FISH: del(17p) in addition to t(4;14)

Question

- What treatment would you recommend next for this patient with high-risk disease based on the available clinical data?

Case Presentation – Dr Usmani (Part 2): A 64-year-old man with multiple regimen-refractory multiple myeloma – del(17p) and t(11;14)



Dr Saad Zafar Usmani

- Initial diagnosis of revised ISS Stage III IgG kappa myeloma, t(11;14)
- RVd induction x 4 cycles → ASCT → lenalidomide maintenance x 1 year
- Biochemical relapse 2 years after stopping lenalidomide
- FISH demonstrates acquisition of del(17p) in addition to t(4;14)
- ***KRd regimen x 19 cycles → VGPR as best response after 3 cycles***
- ***Patient presents with clinical relapse with increasing midback pain***

Question

- What treatment would you recommend next for this patient?

Case Presentation – Dr Usmani (Part 3): A 64-year-old man with multiple regimen-refractory multiple myeloma – del(17p) and t(11;14)



Dr Saad Zafar Usmani

- Initial diagnosis of revised ISS Stage III IgG kappa myeloma, t(11;14)
- RVd induction x 4 cycles → ASCT → lenalidomide maintenance x 1 year
- Biochemical relapse 2 years after stopping lenalidomide; FISH demonstrates acquisition of del(17p) in addition to t(4;14)
- KRd regimen x 19 cycles → VGPR as best response after 3 cycles
- Patient presents with clinical relapse with increasing midback pain
- ***Local RT therapy → daratumumab with pomalidomide/dexamethasone x 16 cycles → VGPR***
- ***Patient presents with biochemical and clinical relapse***

Question

- What treatment would you recommend next for this patient who is now proteasome inhibitor-IMiD- and daratumumab-refractory?

Case Presentation – Dr Usmani (Part 4): A 64-year-old man with multiple regimen-refractory multiple myeloma – del(17p) and t(11;14)



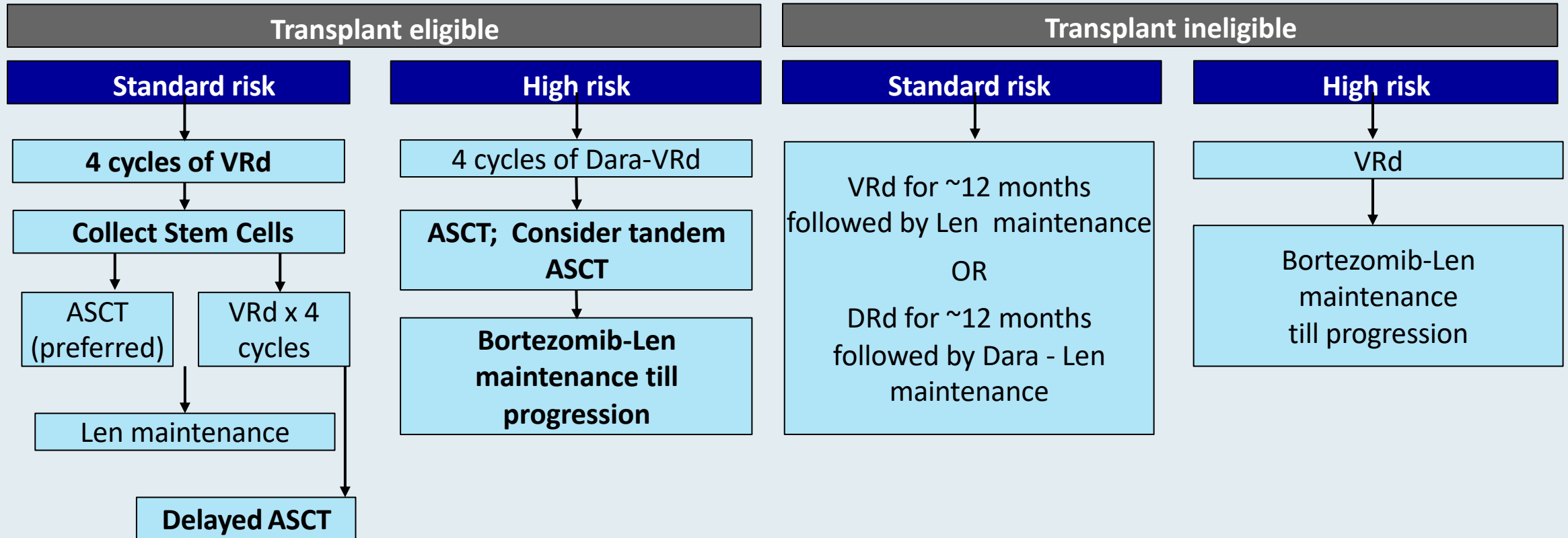
Dr Saad Zafar Usmani

- Initial diagnosis of revised ISS Stage III IgG kappa myeloma, del (17p) and t(11;14)
- RVd induction x 4 cycles → VGPR
 - Mel-200 ASCT → sCR
 - Lenalidomide maintenance x 18 months (stopped per patient request due to superficial skin cancers) → progression 2 years after stopping lenalidomide
- KRd regimen x 19 cycles → VGPR as best response after 3 cycles
- Dara-Pd regimen x 16 cycles → VGPR as best response
- Patient presents with clinical and biochemical relapse
- ***Enrollment on BCMA-directed CAR T-cell clinical trial → sCR that is maintained after 14 months***

Question

- What is your experience with CRS or neurotoxicity, as well as count recovery in patients that you have taken care of who have received CAR T-cell therapy?

Approach to Newly Diagnosed MM



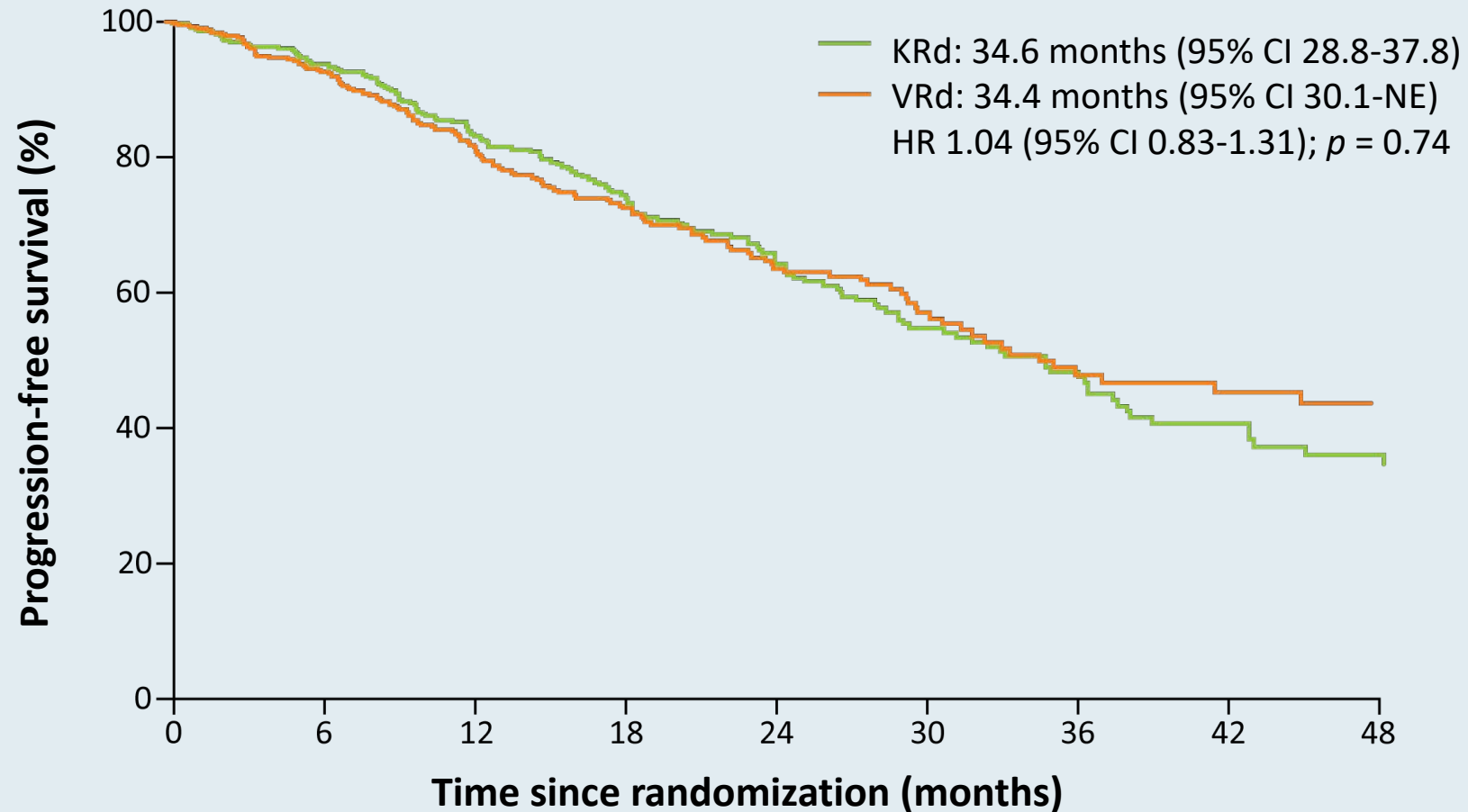


Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial

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

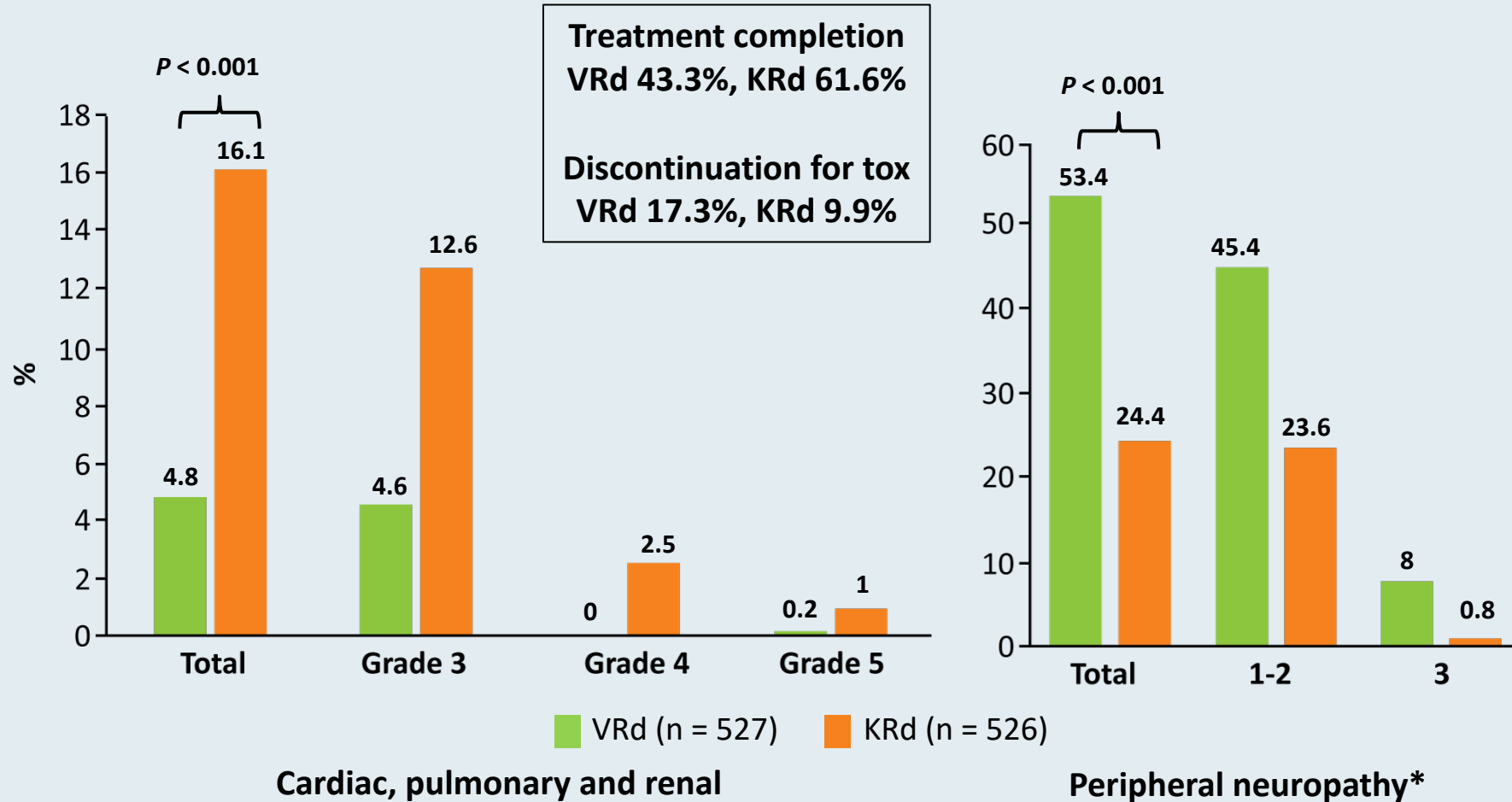
Lancet Oncol 2020;21(10):1317-30

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



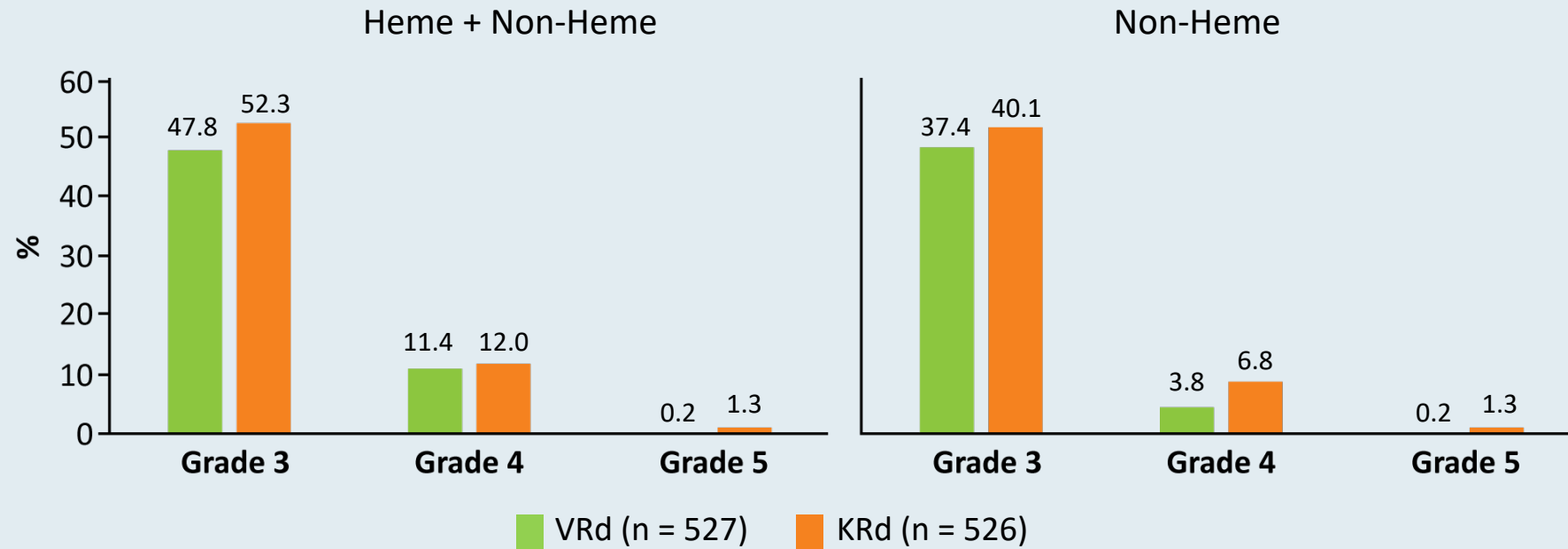
- Median OS has not been reached in either group at median follow-up of 24 months; patients will continue on long-term follow-up for overall survival

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



* Grades 1-2 not required reporting

ENDURANCE (E1A11): Treatment-Related AEs

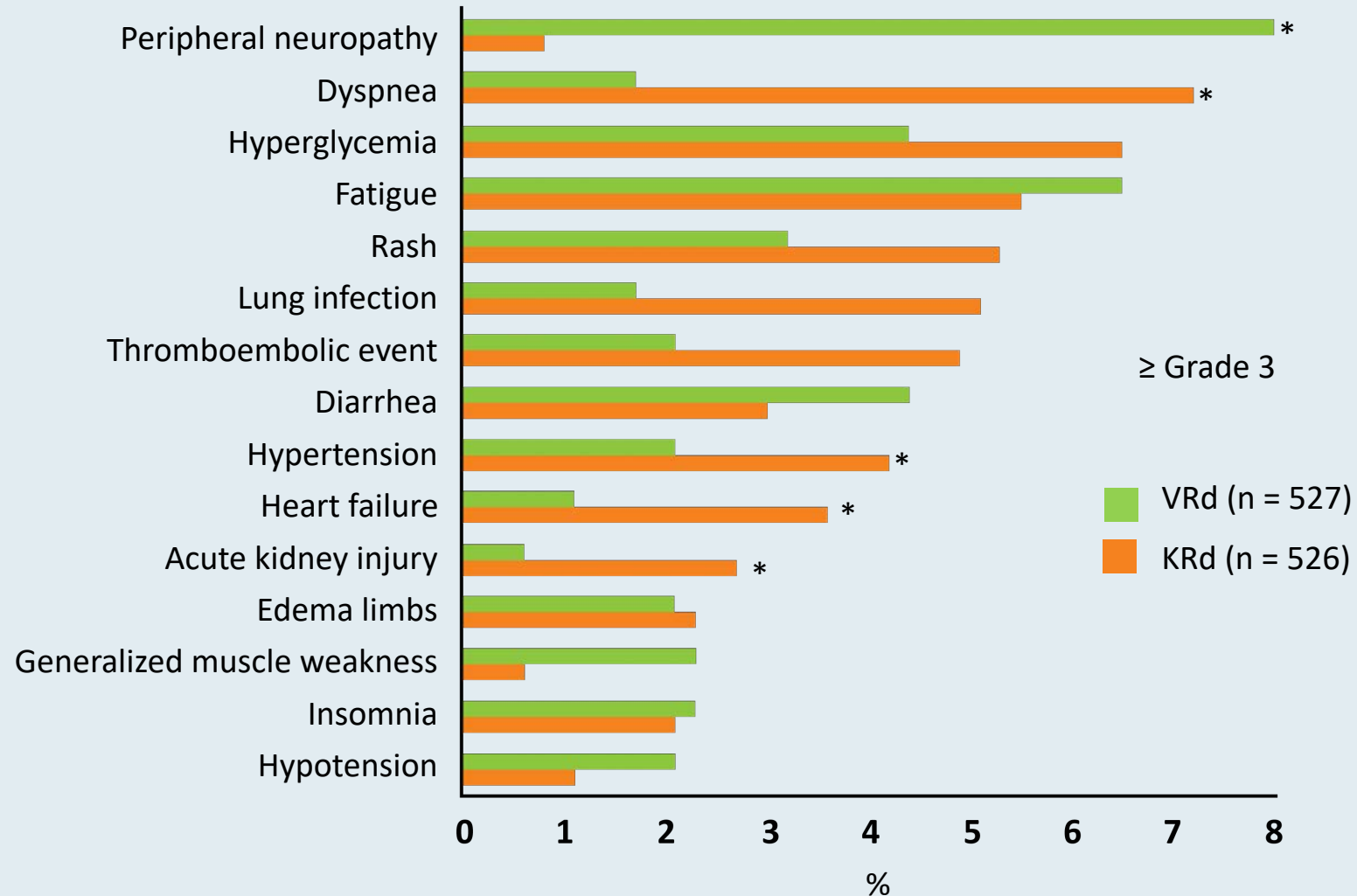


Step 1 treated patients	VRd (n = 527)	KRd (n = 526)		
Rates	N (%)	N (%)	Diff KRd-VRd	Chisq p-value
Grade 3-5	313 (59.4)	345 (65.6)	6.2	0.038
(95% CI)	(55.1-63.6)	(61.3-69.6)		
Grades 4-5	61 (11.6)	70 (13.3)	1.7	0.394
(95% CI)	(9.0-14.6)	(10.5-16.5)		

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

* Grade 3 heme not required reporting

ENDURANCE (E1A11): Treatment-Related AEs ($\geq 2\%$)

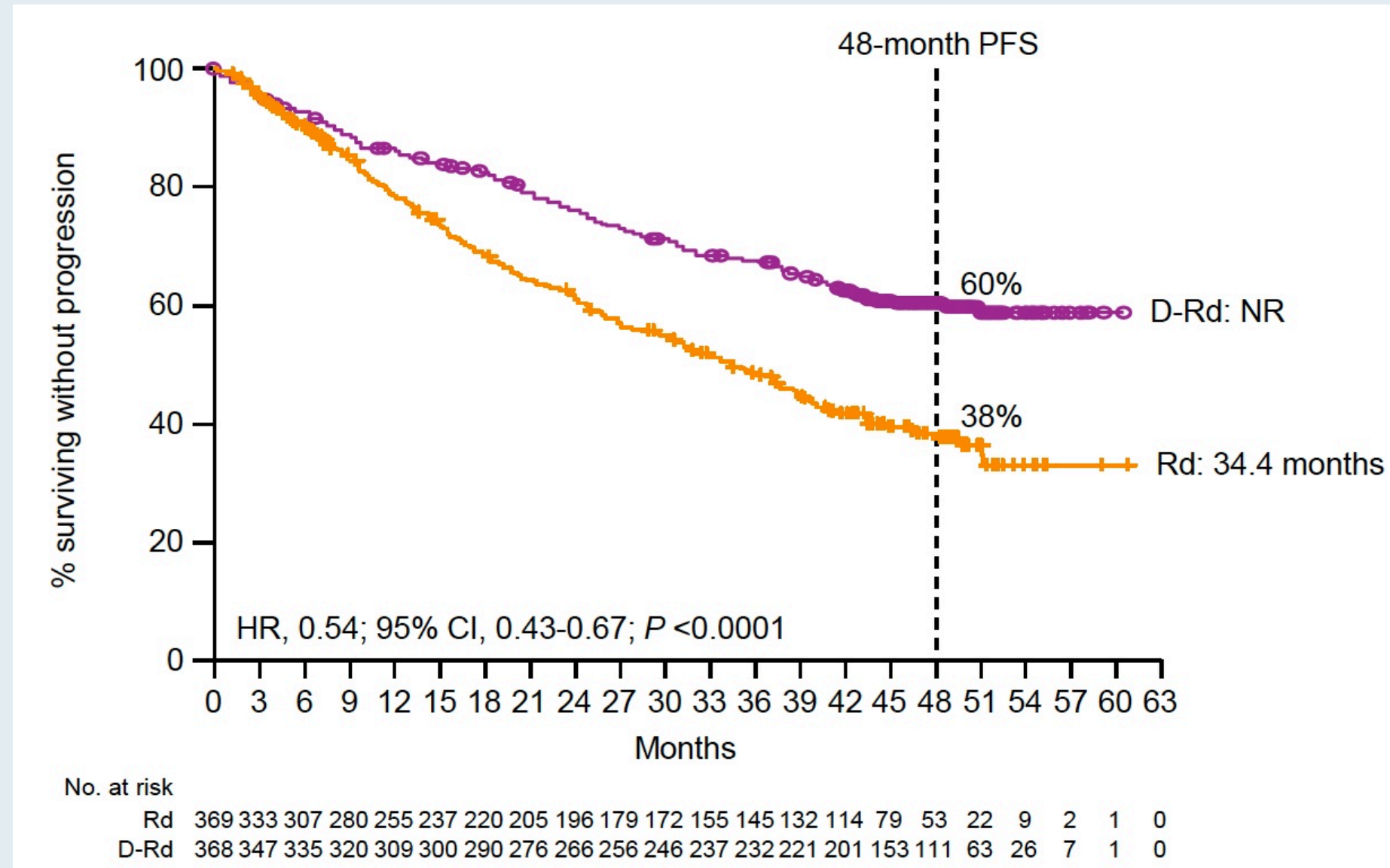


Updated Analysis of Daratumumab plus Lenalidomide and Dexamethasone (D-Rd) versus Lenalidomide and Dexamethasone (Rd) in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma (NDMM): The Phase 3 Maia Study

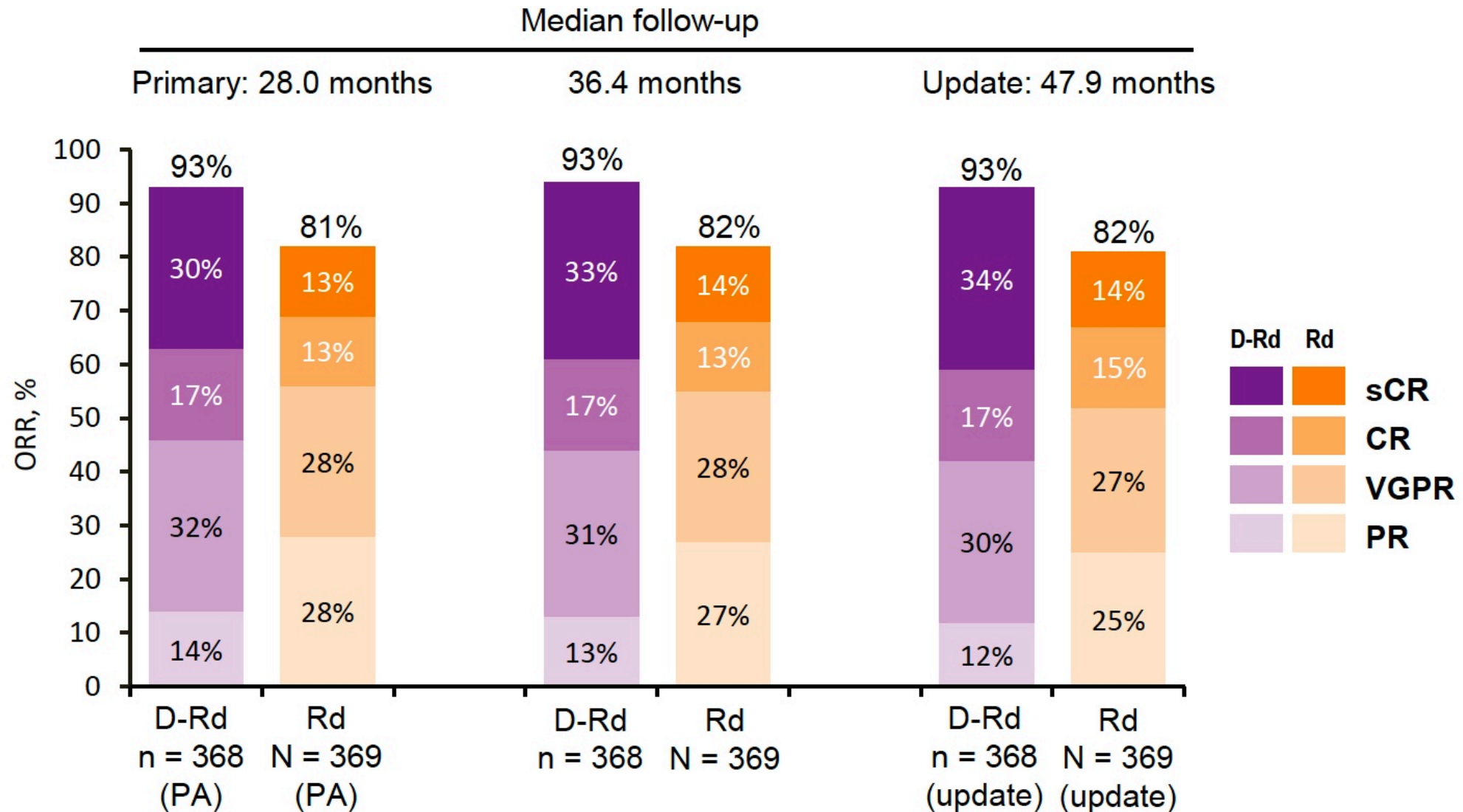
Kumar SK et al.

ASH 2020;Abstract 2276.

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



MAIA: Updated Response



MAIA: Updated Overall Response

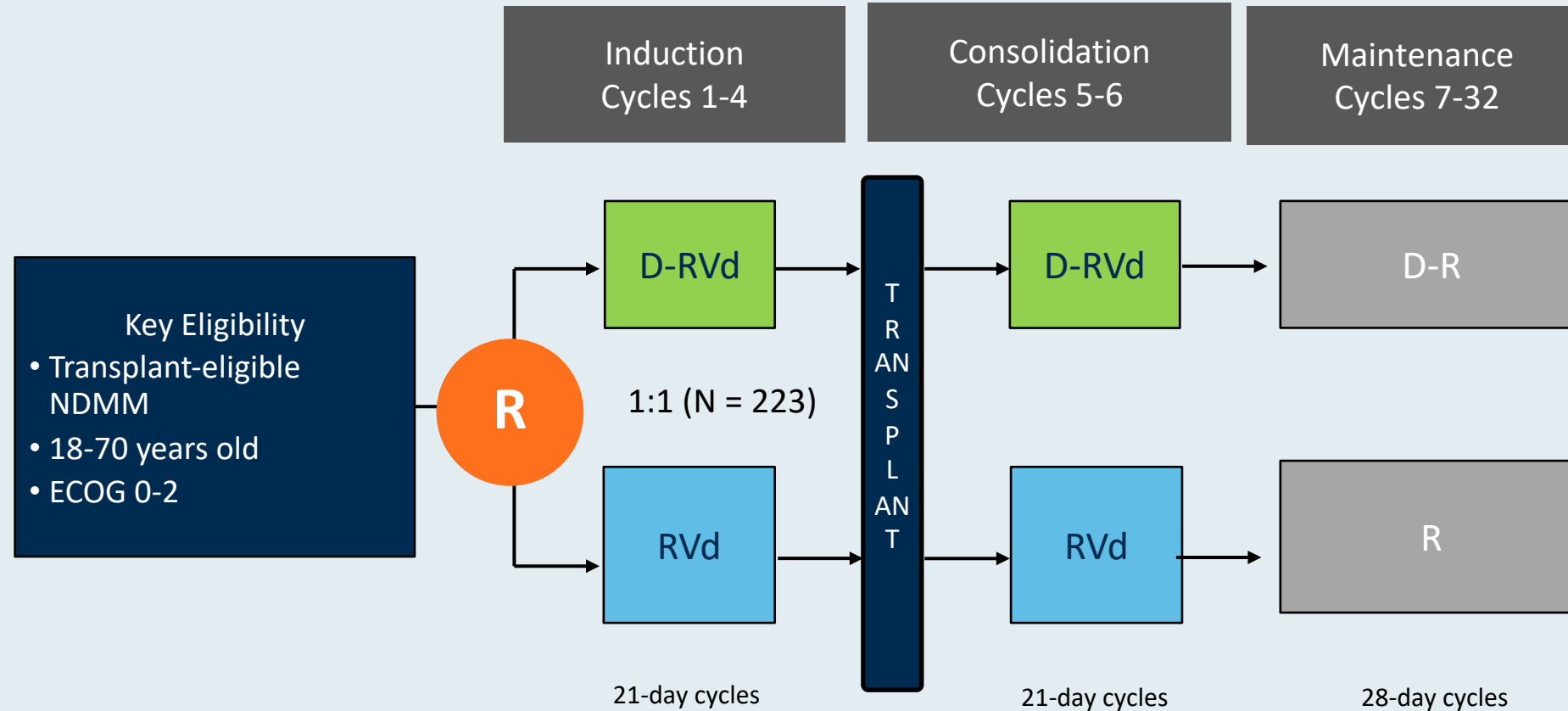
	D-Rd (n = 368)	Rd (n = 369)	<i>p</i> -value
ORR	93%	82%	<0.0001
sCR	34%	14%	<0.0001
CR	17%	15%	—
VGPR	30%	27%	—
PR	12%	25%	—
≥VGPR	81%	57%	<0.0001
≥CR	51%	30%	<0.0001

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

Kaufman JL et al.

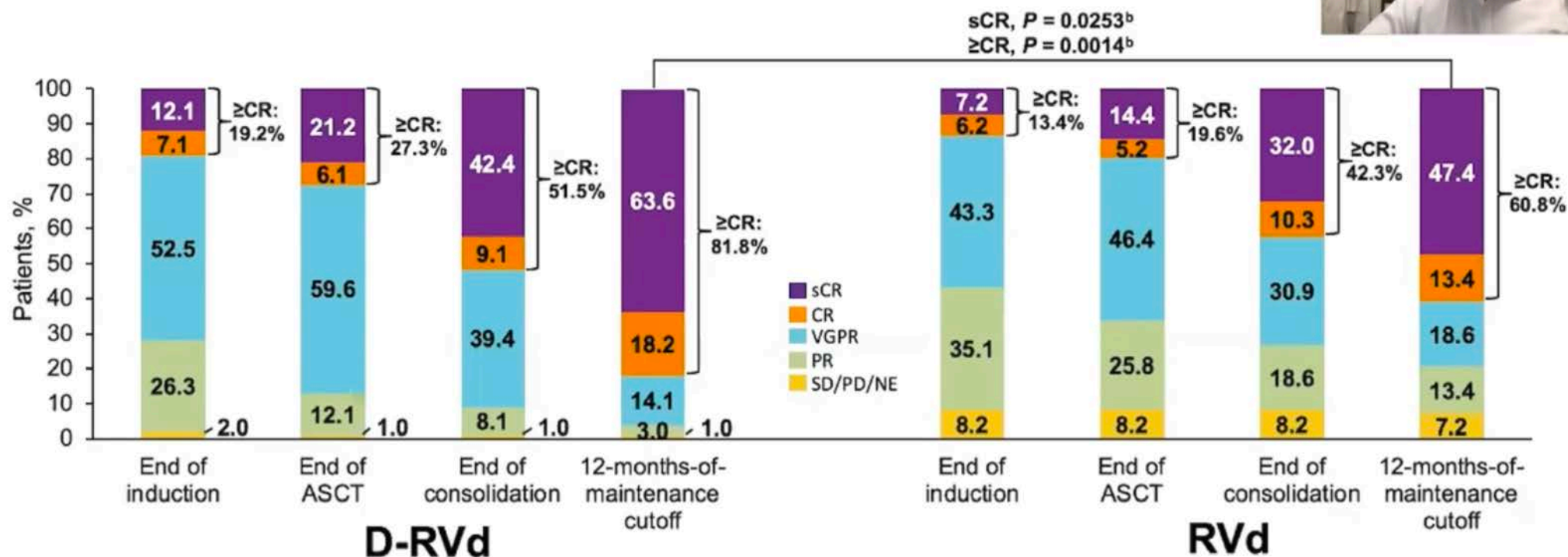
ASH 2020;Abstract 549.

GRIFFIN Randomized Phase II Study Design



Primary endpoint: Stringent CR by end of consolidation

Responses Deepened over Time^a



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

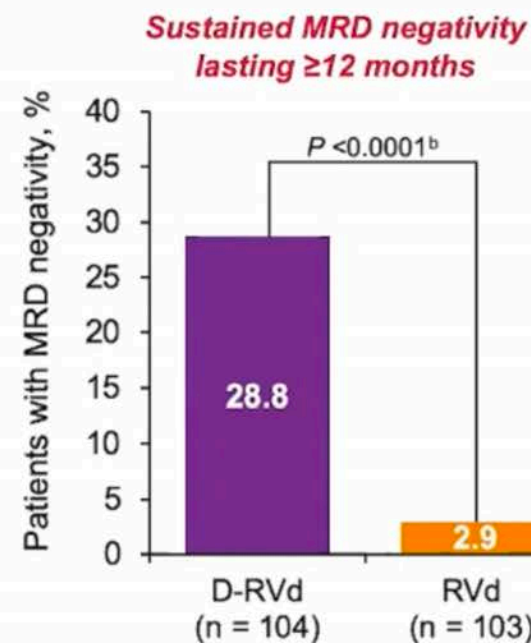
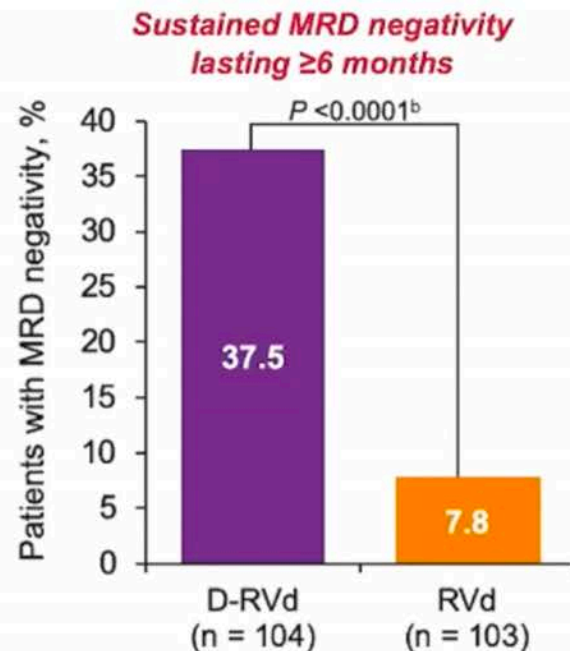
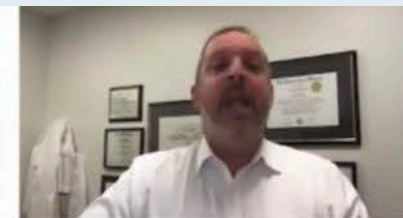
Response rates and depths were greater for D-RVd at all time points

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



American Society of Hematology

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



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

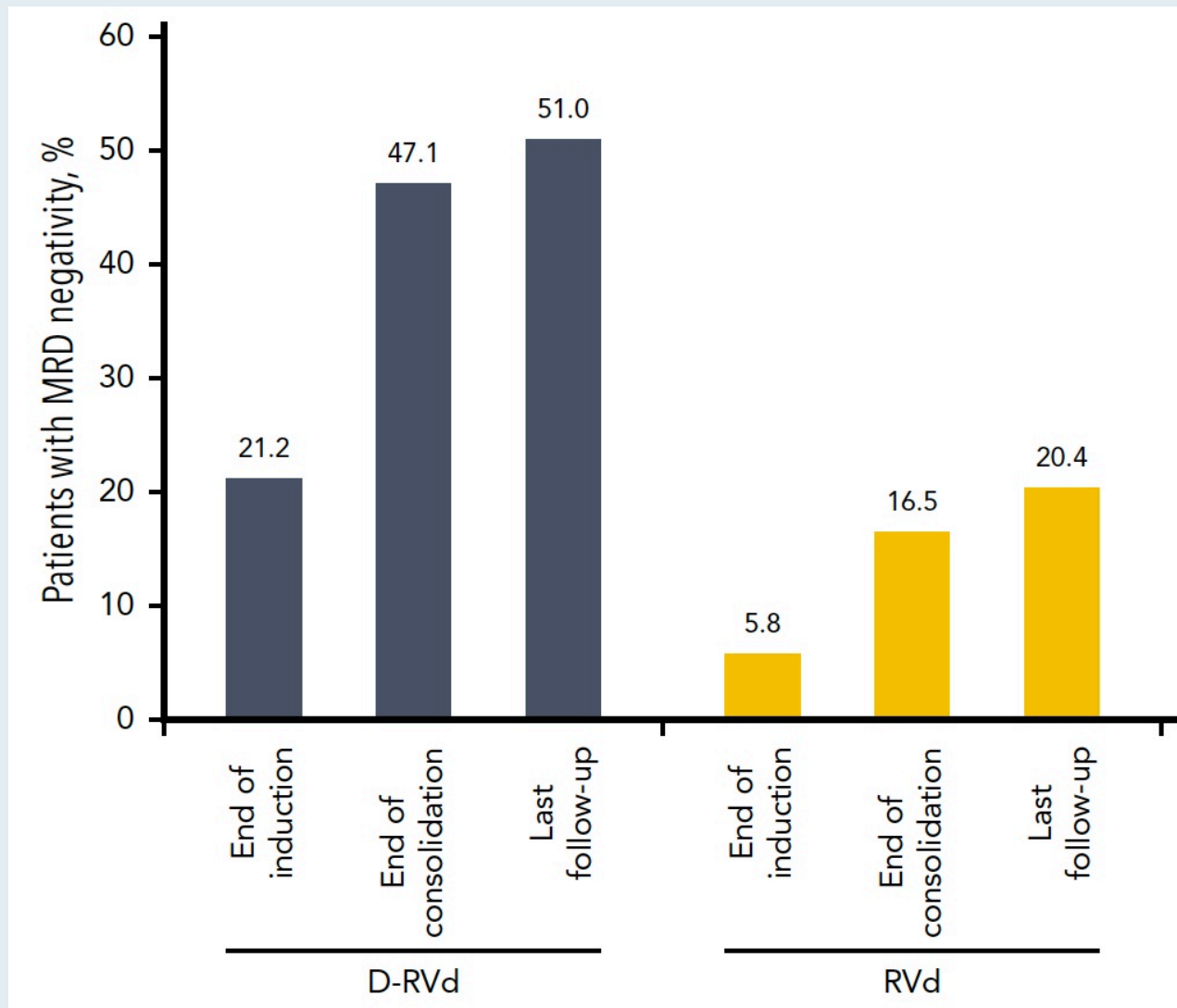
D-RVd improved rates of sustained MRD negativity versus RVd

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



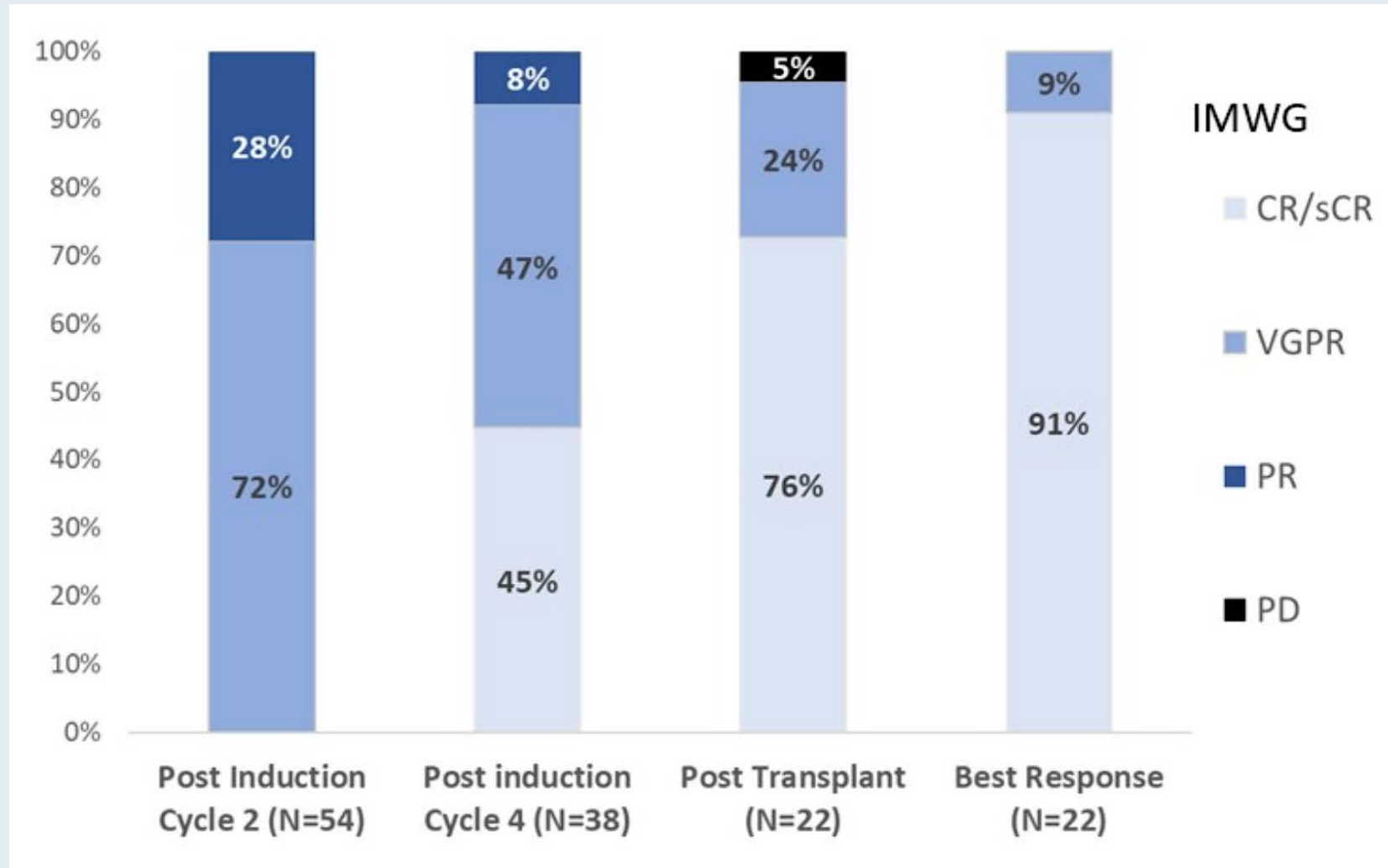
American Society of Hematology

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

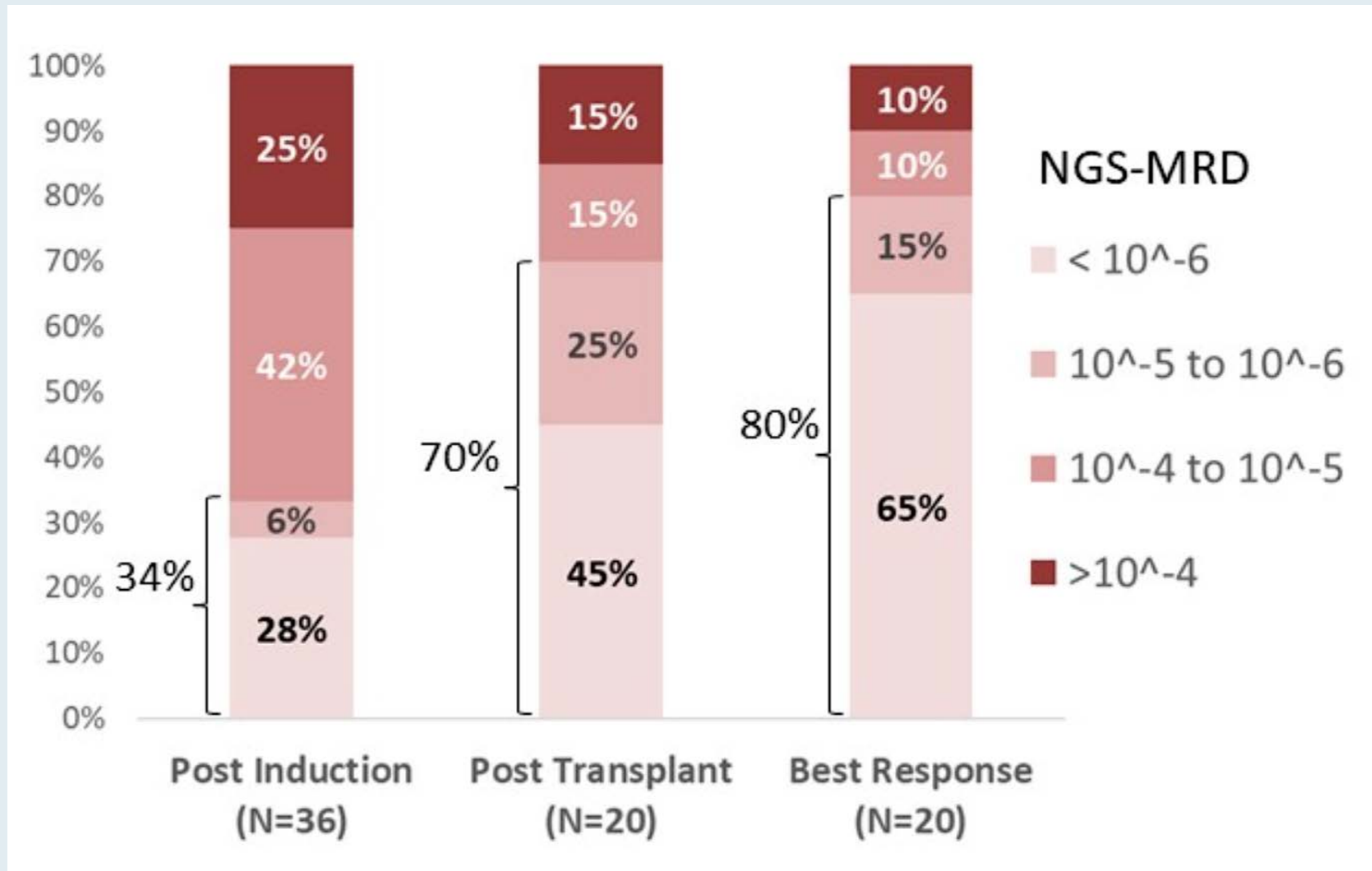


- MRD negativity (10^{-5}) rates in the intent-to-treat population by the end of induction therapy, end of consolidation and last follow-up
- All MRD data are from the analysis with a median follow-up of 22.1 months
- MRD was evaluated at baseline, first evidence of suspected CR or sCR, at the end of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

MASTER — Daratumumab + KRd Induction → MRD-Based Consolidation: Responses Over Time



MASTER: MRD-Negative Remissions



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

Giri S et al.

ASCO 2020;Abstract 8540.

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

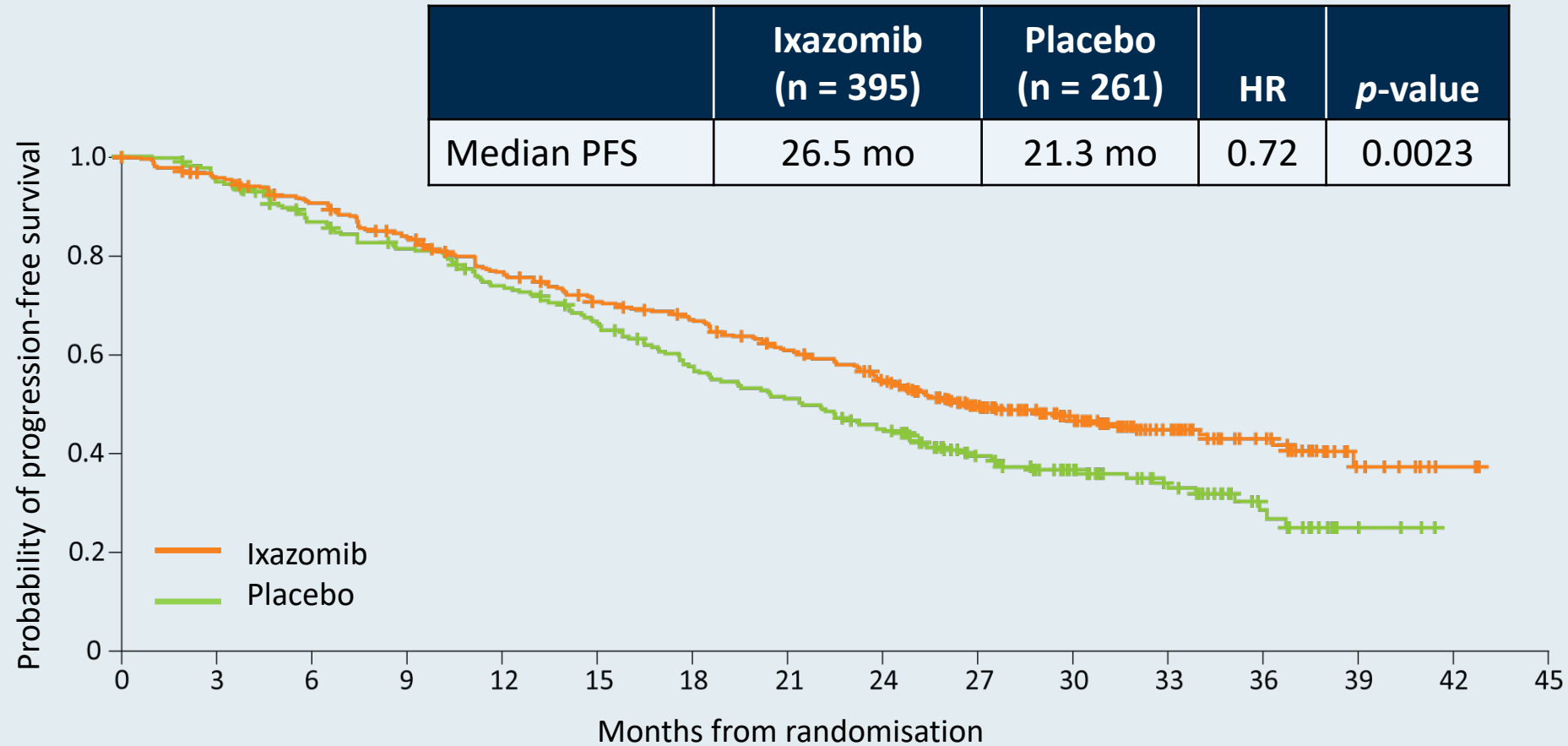
Study	Intervention	Control	Hazard ratio	<i>p</i> -value
ALCYONE	DaraVMP	VMP	0.78	0.42
MAIA	DaraRD	RD	0.57	0.06
CASSIOPEIA	DaraVTD	VTD	0.67	0.23
<i>Pooled Effect Size</i>			0.67	0.025
CASTOR	DaraVD	VD	0.41	0.01
POLLUX	DaraRD	RD	0.37	0.01
CANDOR	DaraKD	KD	0.58	0.11
<i>Pooled Effect Size</i>			0.45	<0.001

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)

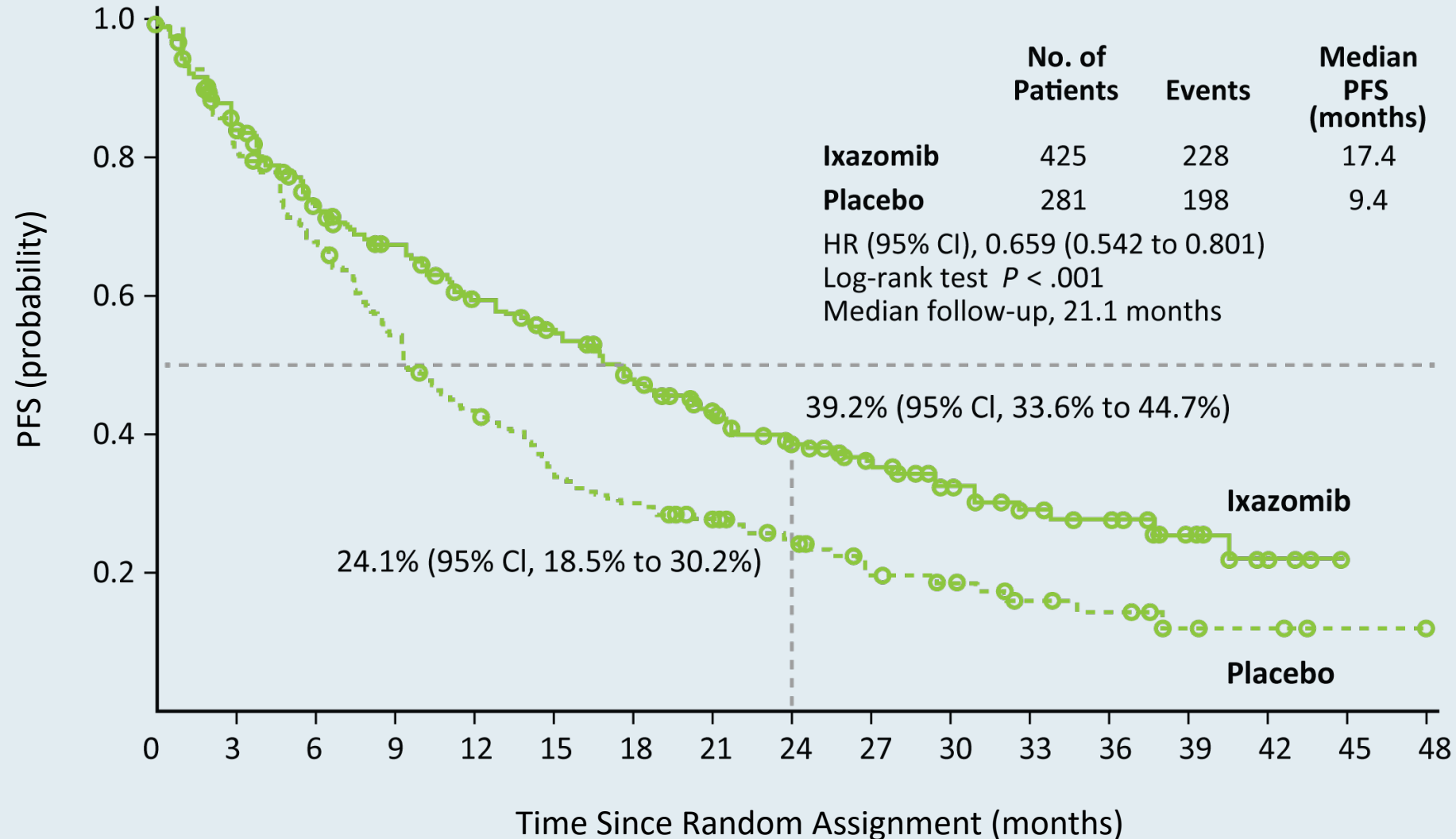


Ixazomib as Postinduction Maintenance for Patients With Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 Trial

Meletios A. Dimopoulos, MD¹; Ivan Špička, MD²; Hang Quach, MD³; Albert Oriol, MD⁴; Roman Hájek, MD⁵; Mamta Garg, MD⁶; Meral Beksac, MD⁷; Sara Bringhen, MD⁸; Eirini Katodritou, MD⁹; Wee-Joo Chng, MD¹⁰; Xavier Leleu, MD¹¹; Shinsuke Iida, MD¹²; María-Victoria Mateos, MD¹³; Gareth Morgan, MD¹⁴; Alexander Vorog, MD¹⁵; Richard Labotka, MD¹⁵; Bingxia Wang, PhD¹⁵; Antonio Palumbo, MD¹⁵; and Sagar Lonial, MD¹⁶; on behalf of the TOURMALINE-MM4 study group

J Clin Oncol 2020;38(34):4030-41.

TOURMALINE-MM4 Primary Endpoint: Progression-Free Survival

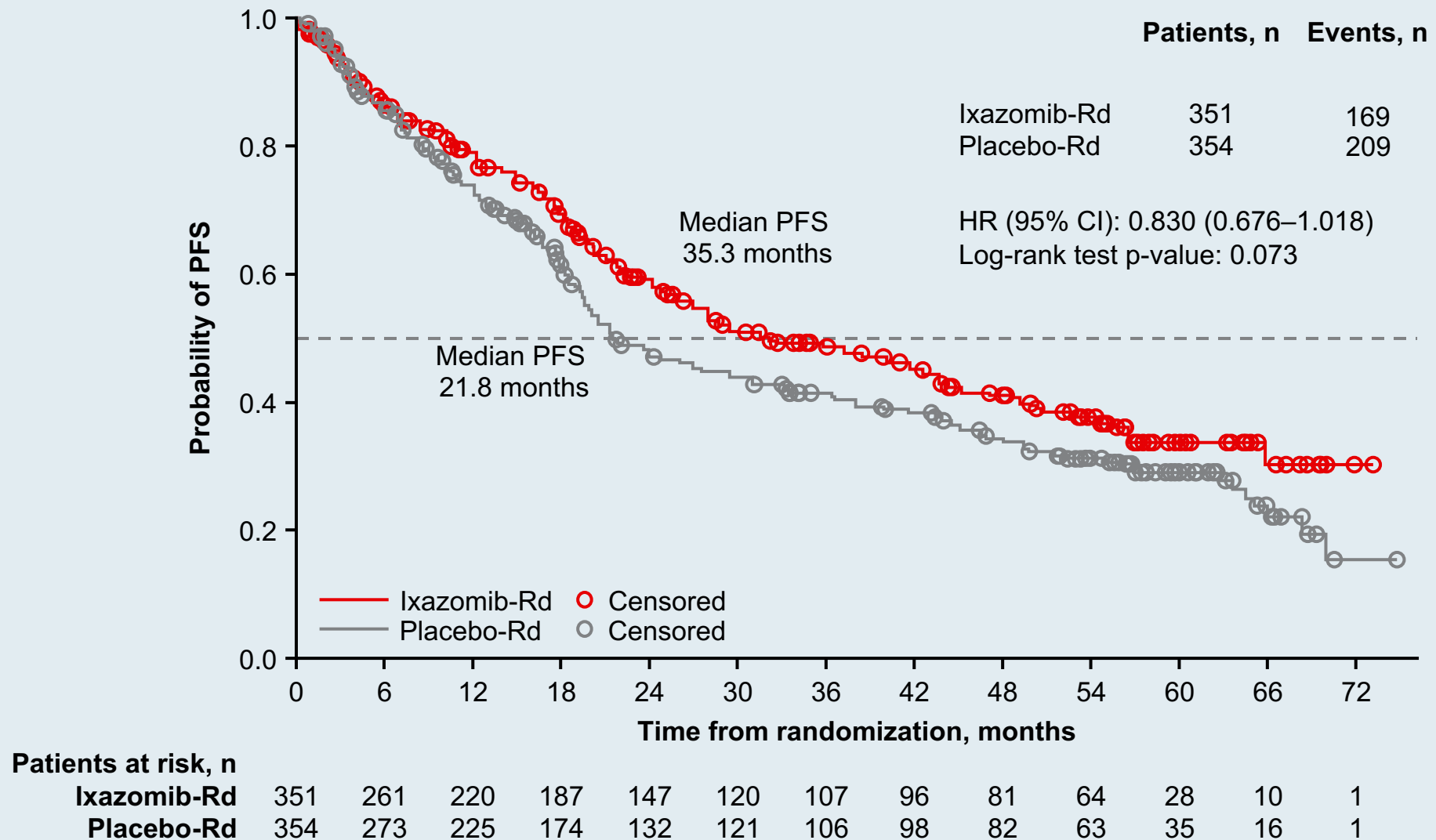


The Phase 3 TOURMALINE-MM2 Trial: Oral Ixazomib, Lenalidomide, and Dexamethasone (IRd) vs Placebo-Rd for Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma (NDMM)

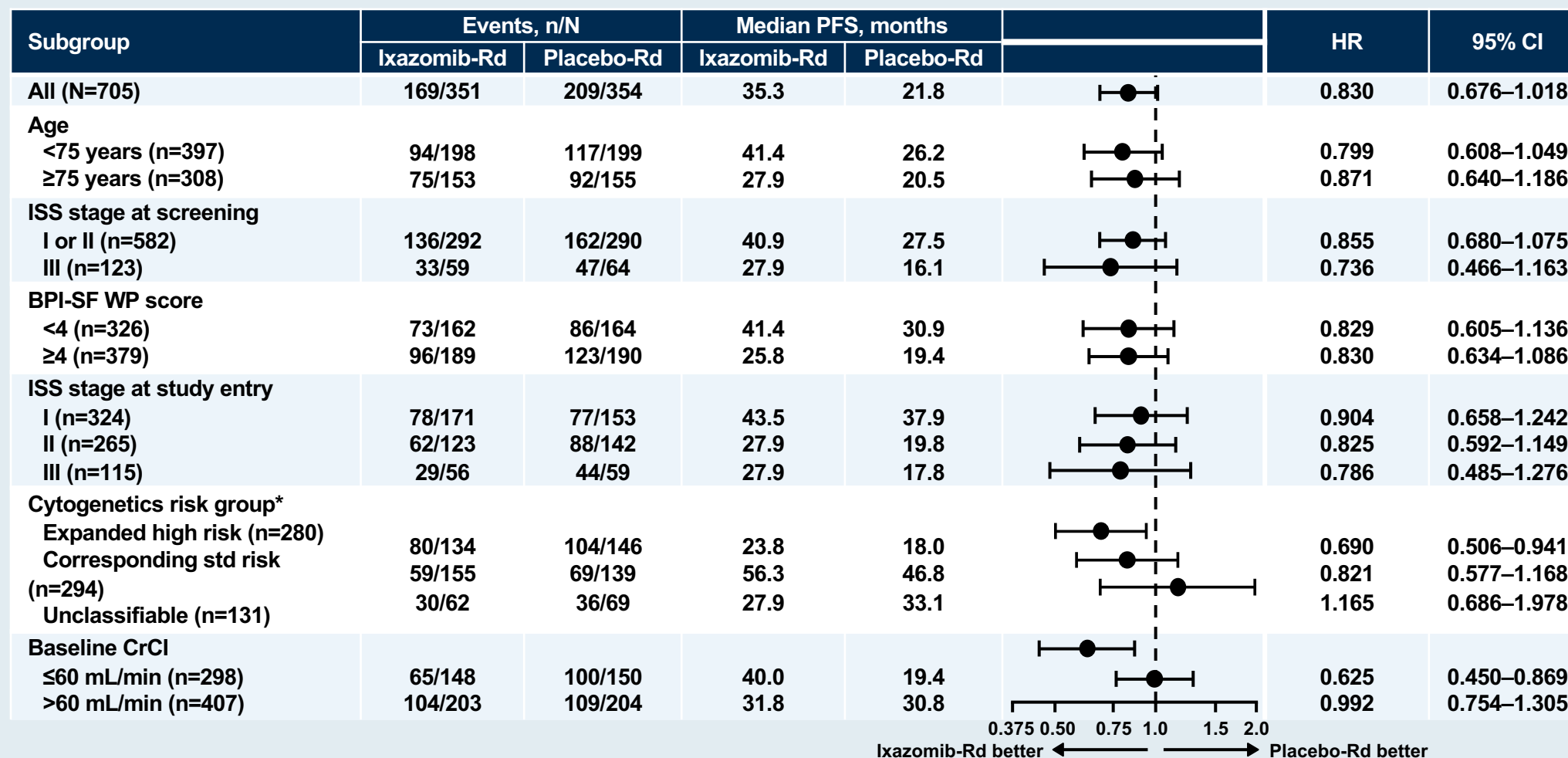
Facon T et al.

ASH 2020;Abstract 551

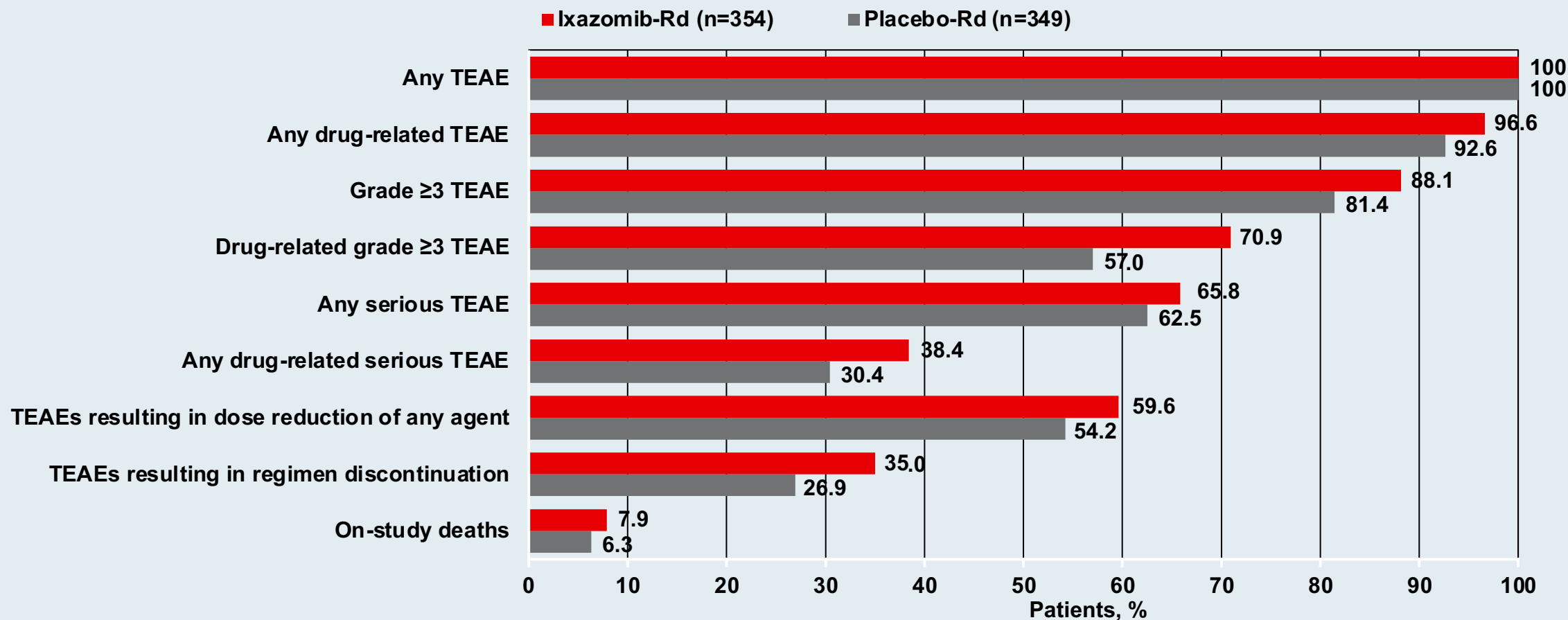
TOURMALINE-MM2: Progression-Free Survival



TOURMALINE-MM2: Progression-Free Survival



TOURMALINE-MM2: Safety Profile



Agenda

Module 1: Newly Diagnosed Multiple Myeloma

- Dr Usmani: A 64-year-old man with multiple regimen-refractory multiple myeloma – del(17p) and t(11;14)
 - Parts 1-4

Module 2: Relapsed Multiple Myeloma

- Dr Deutsch: A 73-year-old man with multiply relapsed multiple myeloma

Module 3: Novel Agents and Approaches

- Dr Usmani: A 76-year-old woman with relapsed multiple myeloma – t(11;14)
 - Parts 1, 2 and 3

Case Presentation – Dr Deutsch: A 73-year-old man with multiply relapsed multiple myeloma



Dr Margaret Deutsch

- 6/2012: Initial diagnosis of IgA kappa myeloma complicated by transient acute renal failure at diagnosis (no dialysis)
 - RVD x 4 with normalization of renal function
- 9/2012: Stem cell transplant, no maintenance initially; lenalidomide maintenance initiated 7/2014
- 11/2019: Rapidly rising M-spike noted; bone marrow biopsy reveals 20% plasma cells in 30% cellular marrow
- 12/2019: PET shows no osseous lesions; carfilzomib 70 mg/m²/week with initial good response
- M-protein is slowly rising at 0.7 gm/dl, no evidence of cytopenias, renal insufficiency or hypercalcemia; patient has past history of recurrent pulmonary embolisms and is currently on apixaban

Questions

- What Initial therapy would you have recommended at relapse?
- When should I change therapy, particularly in this type of circumstance where the M-spike is rising slowly and the patient has no other signs or symptoms of progressive myeloma?

Which of the following agents would you generally use first for a patient with relapsed MM who has experienced disease progression on multiple prior therapies, including daratumumab, proteasome inhibitors and IMiDs?

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

Daratumumab-Based Regimens for Relapsed and/or Refractory MM

	POLLUX¹ Dara-Rd vs Rd	CASTOR² Dara-Vd vs Vd
Prior therapies	Bortezomib: 84% Len/Thal: 18%/43% IMiD + PI: 44%	Bortezomib: 65% Len/Thal: 42%/49% IMiD + PI: 48%
Median lines prior Tx	1 (range: 1-11)	2 (range: 1-10)
Median PFS (mo) – ITT (n = 569; 498)	NR vs 17.5 HR 0.41, $p < 0.0001$	16.7 vs 7.1 HR 0.31, $p < 0.0001$
Median PFS (mo) – prior Bort (n = 479; 326)	NR vs 17.5 HR 0.40, $p < 0.0001$	12.1 vs 6.7 HR 0.35
Median PFS (mo) – prior Len (n = 100; 209)	NR vs 18.6 HR 0.32, $p = 0.0008$	9.5 vs 6.1 HR 0.38

NR = not reached

¹ Dimopoulos MA et al. *Haematologica* 2018;103(12):2088-96; ² Spencer A et al. *Haematologica* 2018;103(12):2079-87.

FDA Approves Carfilzomib and Daratumumab with Dexamethasone for Multiple Myeloma

Press Release – August 20, 2020

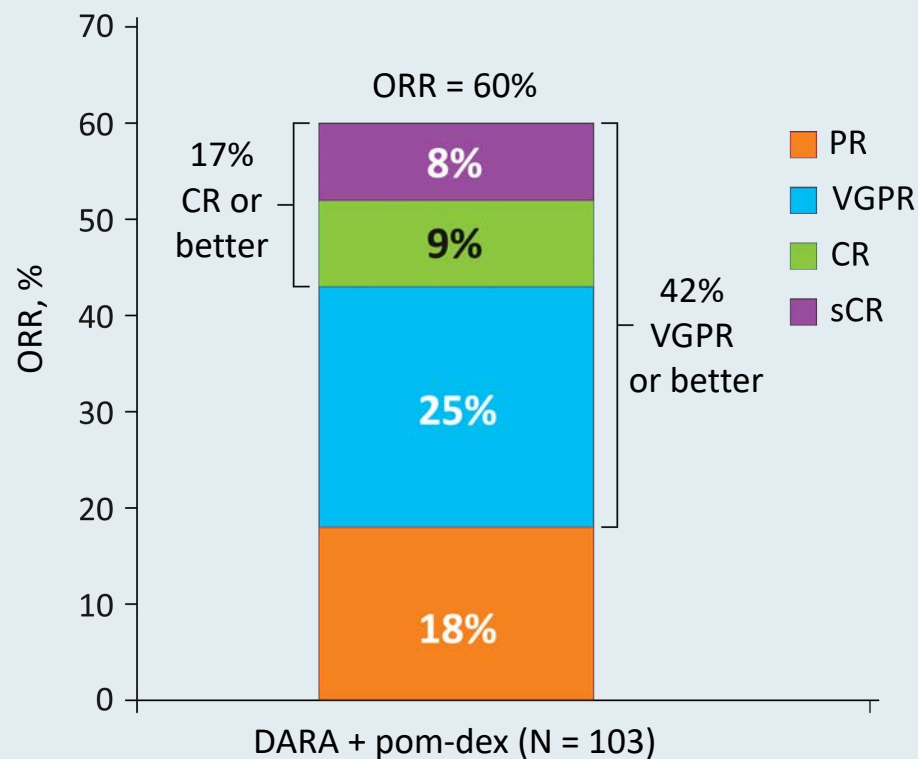
“The Food and Drug Administration approved carfilzomib and daratumumab in combination with dexamethasone for adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

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

CANDOR (NCT03158688) was a randomized, open label, multicenter trial evaluating the combination of carfilzomib (20/56 mg/m² twice weekly regimen) with intravenous daratumumab and dexamethasone (DKd) versus carfilzomib (20/56 mg/m² twice weekly regimen) and dexamethasone (Kd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. A total of 466 patients were randomized; 312 to the DKd arm and 154 to the Kd arm.

EQUULEUS (NCT01998971) was an open label, multicohort trial evaluating the combination of carfilzomib (20/70 mg/m² once weekly regimen) with intravenous daratumumab and dexamethasone (DKd). Efficacy was based on overall response rate (ORR) as assessed by IRC using IMWG response criteria.”

EQUULEUS (MMY1001): Phase Ib Study of Daratumumab with Pomalidomide and Dexamethasone in Relapsed/Refractory MM



ORR	Dara-Pom/Dex
2 prior lines of therapy (n = 22)	63.6%
3 prior lines of therapy (n = 26)	65.4%
>3 prior lines of therapy (n = 53)	54.7%
Refractory to PI and IMiD (n = 73)	57.5%

	Dara-Pom/Dex (n = 103)
IRR rate	50%
Grade 3/4 neutropenia	77%

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.

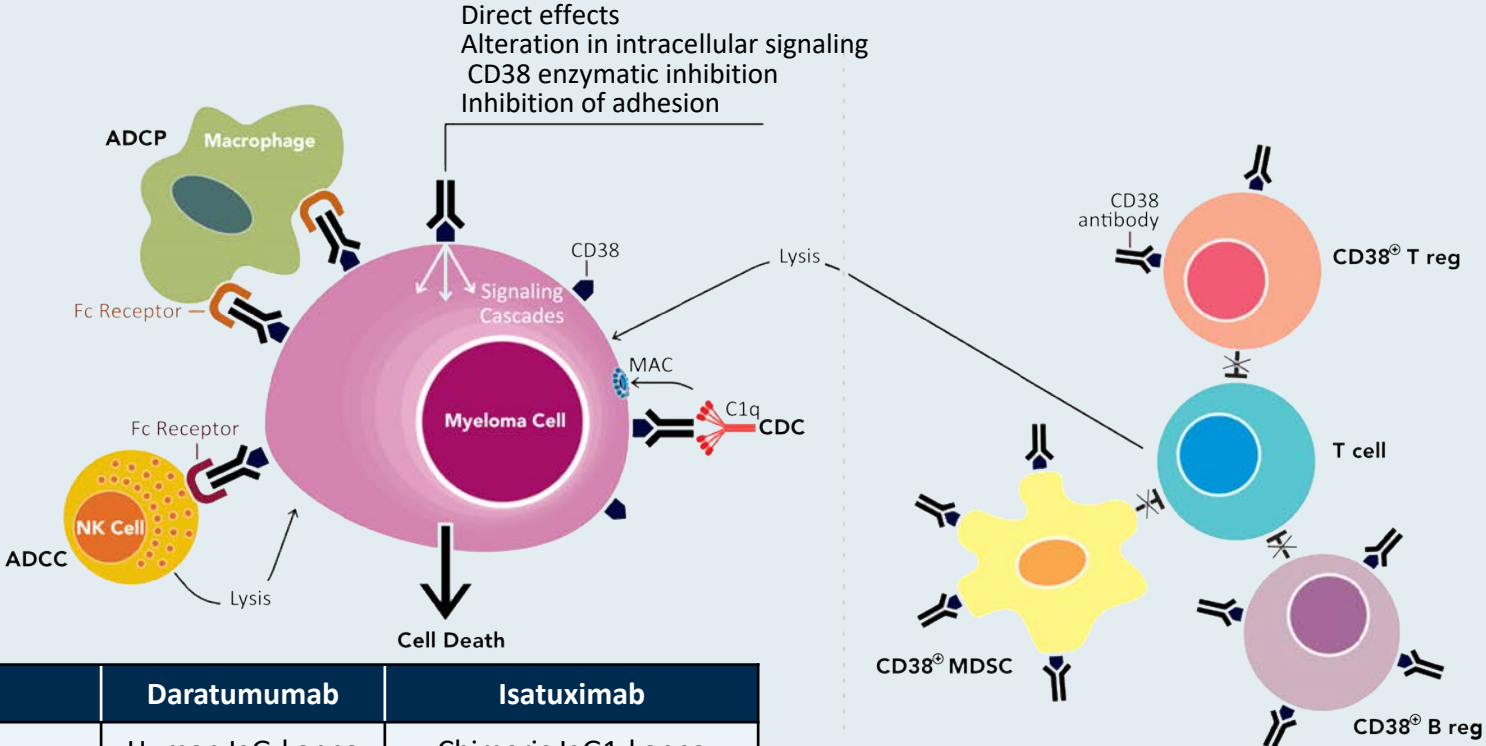
The FDA approved isatuximab-irfc based on the results of a clinical trial involving 307 patients with relapsed and refractory multiple myeloma who had received at least two prior therapies, including lenalidomide and a proteasome inhibitor.

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%.”

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

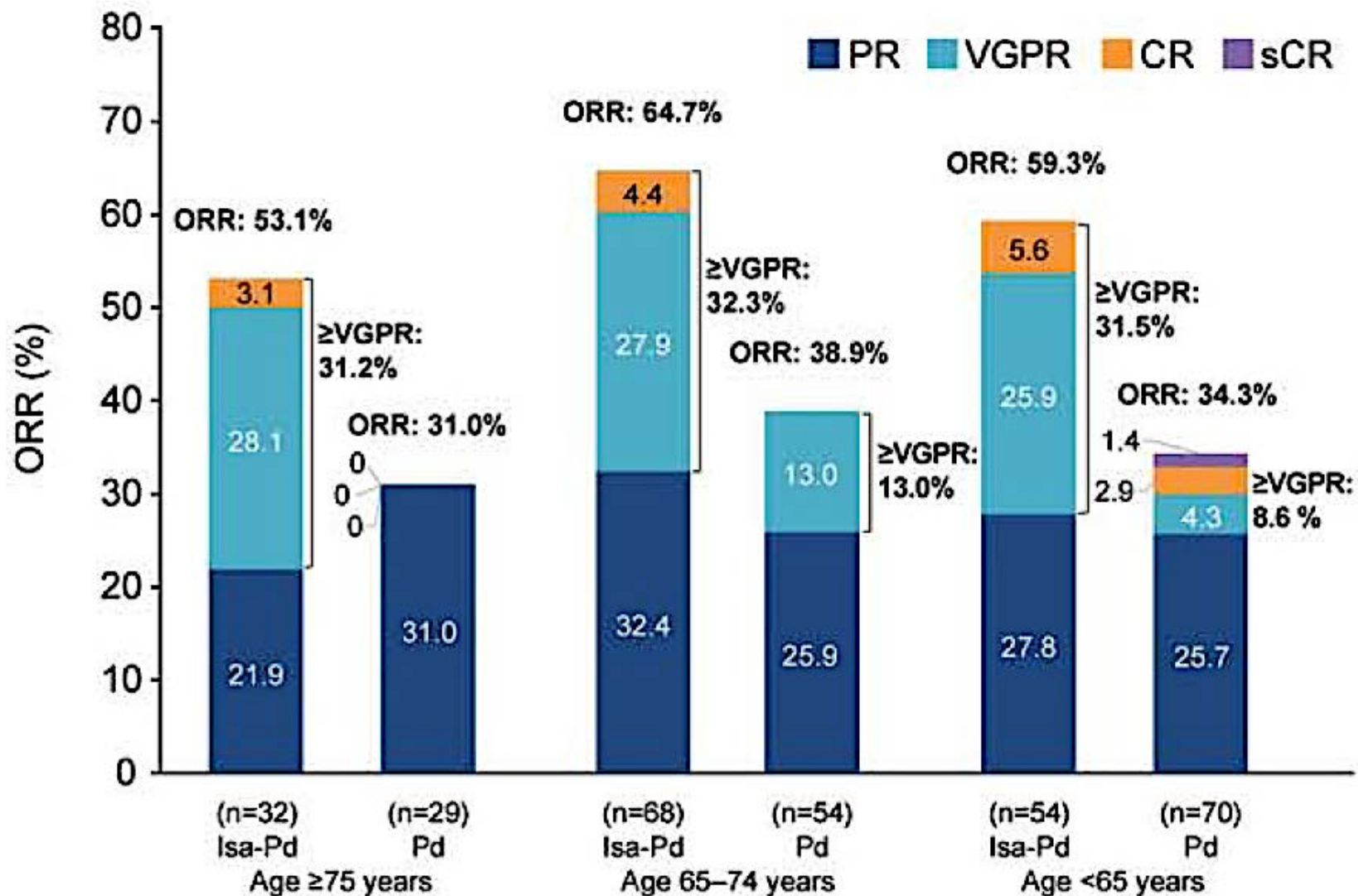
Fc-dependent immune effector mechanisms and direct effects

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	+	+++

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



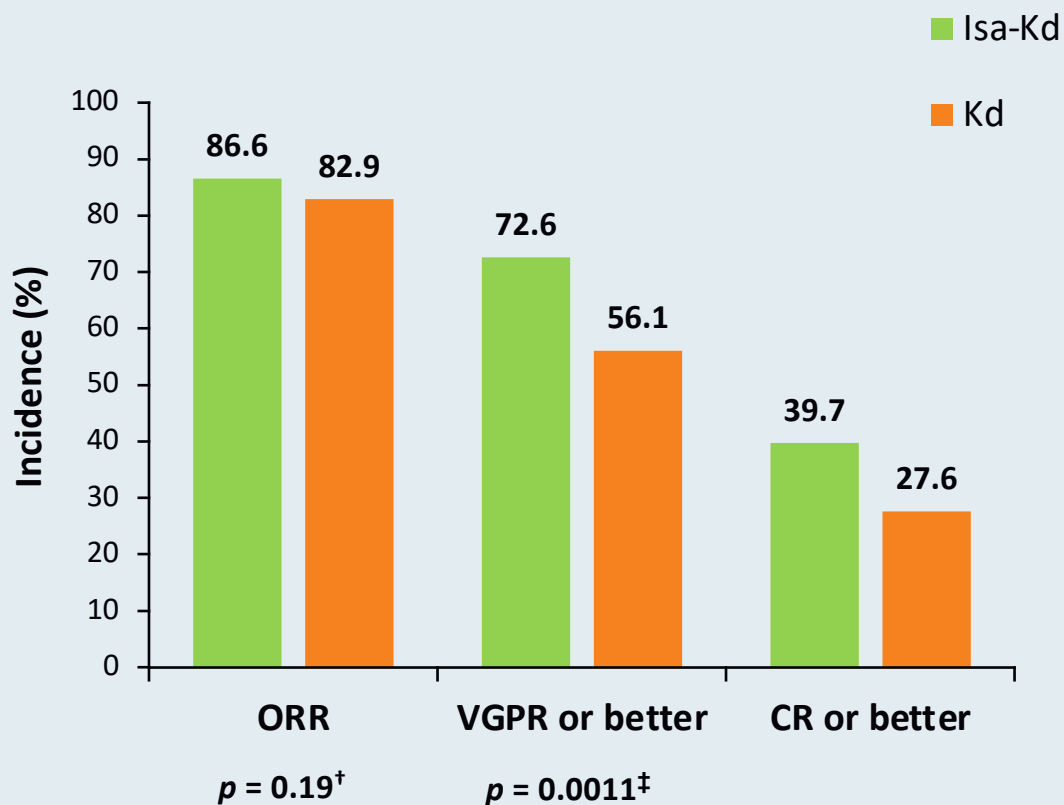
Descriptive Analysis of Isatuximab Use Following Prior Daratumumab in Patients with R/R Multiple Myeloma

Patient	High-Risk Features	Tx line Dara Last Used/Best Response to Dara Combos	Tx line Isa Used	Best Response to Isa + Pom + Dex
1	Yes	17/ PR	19	PR
2	No	5/ SD	11	PR
3	Yes	8/ PR	10	PD
4	Yes	10/ PR	12	SD
5	Yes	5/ PR	7	PR
6	Yes	5/ PR	6	PR
7	Yes	6/ PR	7	MR
8	Yes	2/ PR	6	PR
9	Yes	5/ PR	10	MR

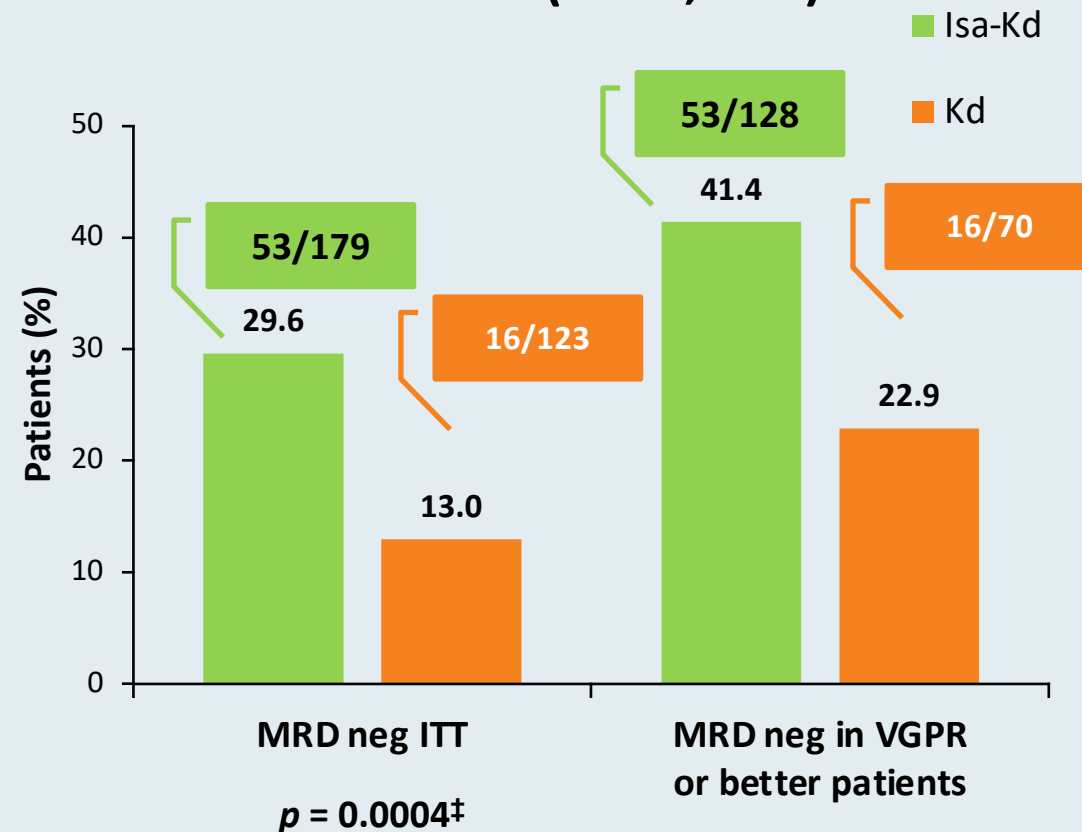
Most patients (77%) experienced a response of minimal response (MR) or better with treatment with isatuximab

IKEMA – Isatuximab + Kd: Depth of Response

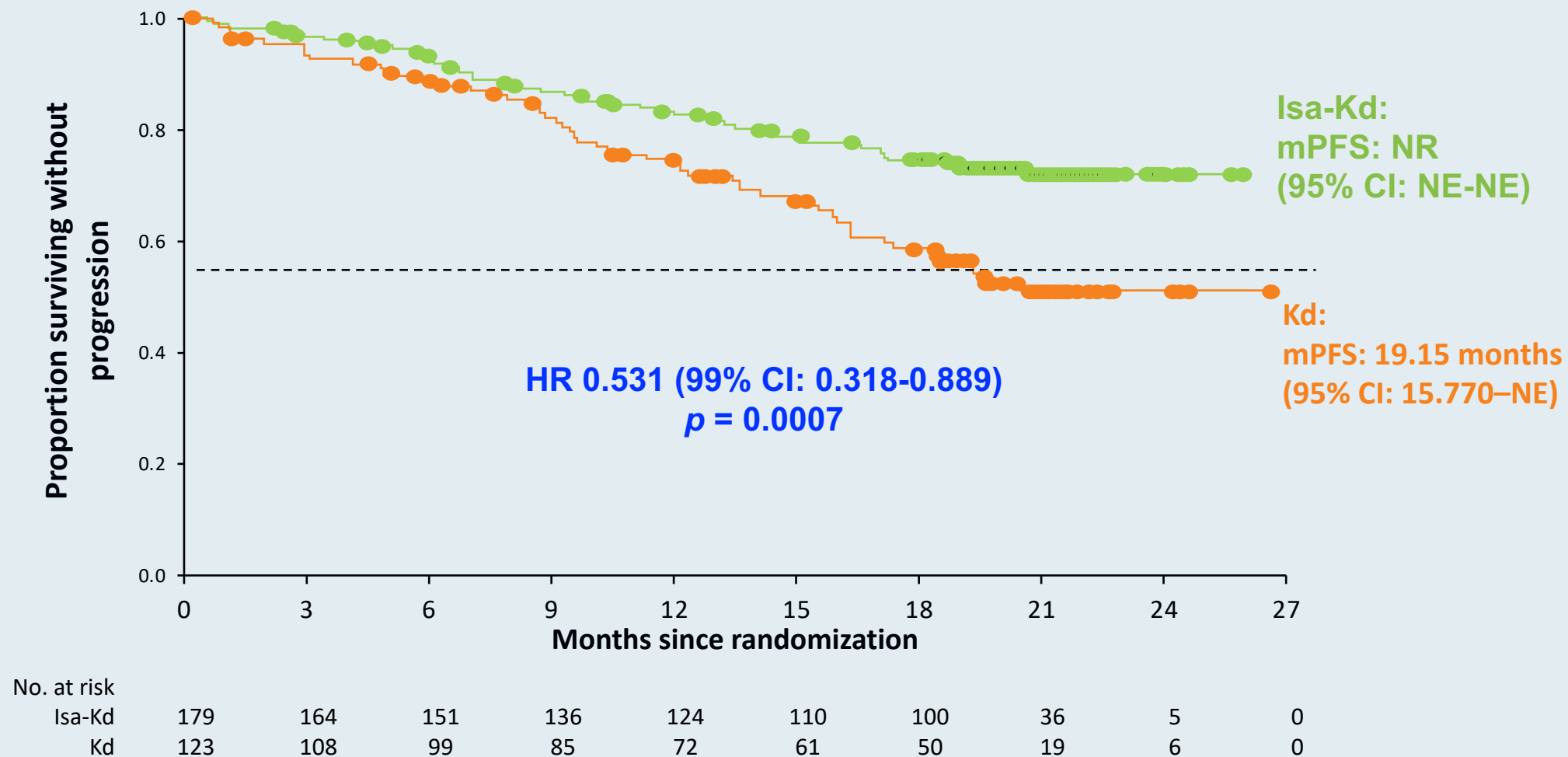
Best overall response



MRD rate (NGS*, 10⁻⁵)



IKEMA: PFS

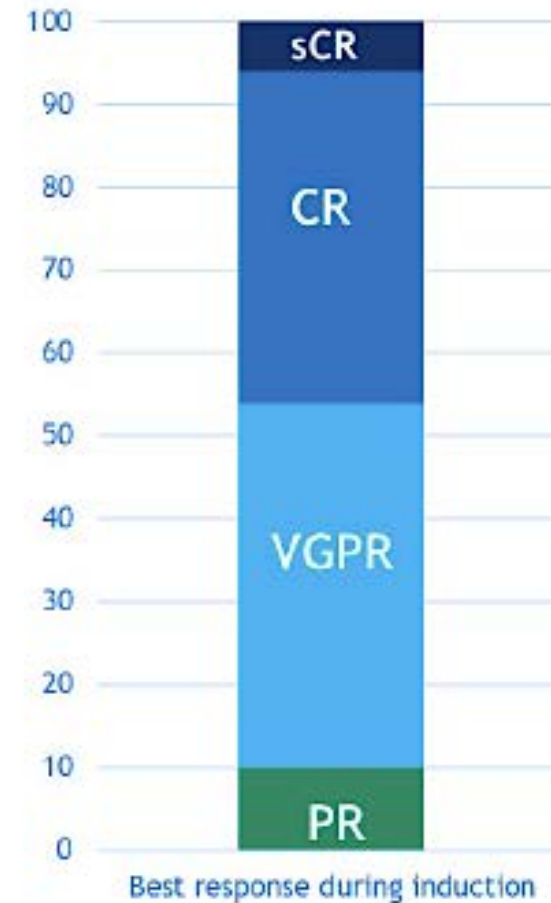


One-sided p -value, level of significance <0.005

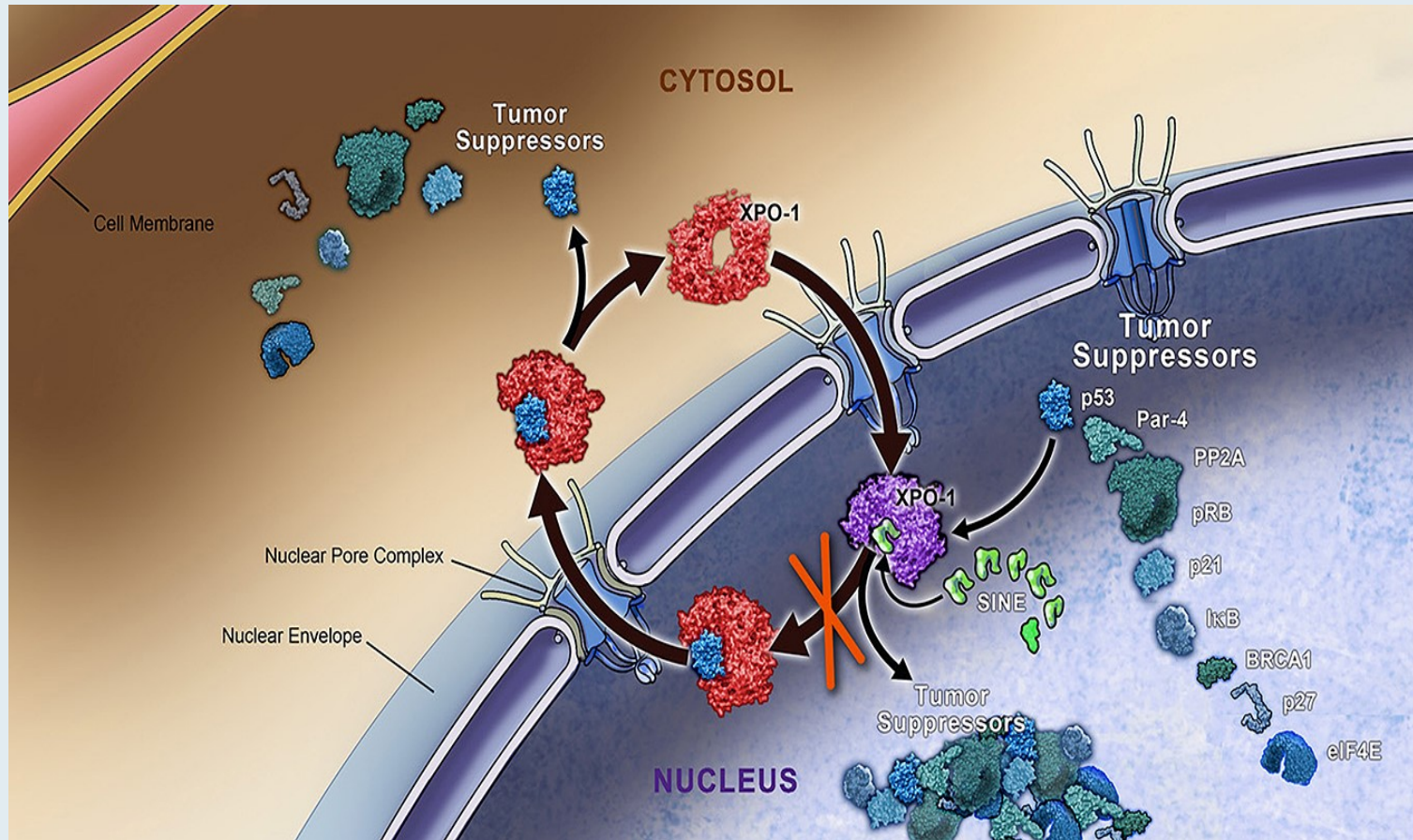
GMMG-CONCEPT – Front-Line Isa-KRd for High-Risk MM: Best Response to Therapy, 6 Induction Cycles

All evaluable patients: n = 50

- Overall response rate (ORR, \geq PR): 100%
- \geq VGPR : 90%; CR/sCR: 46%
 - Arm A: 41/46 \geq VGPR
 - Arm B: all (n = 4) VGPR
- Arm A: MRD-assessment in 33 patients during induction
 - 20 patients MRD negative
 - 11 patients MRD positive
 - 2 not assessable



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.

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

Press Release – December 18, 2020

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

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

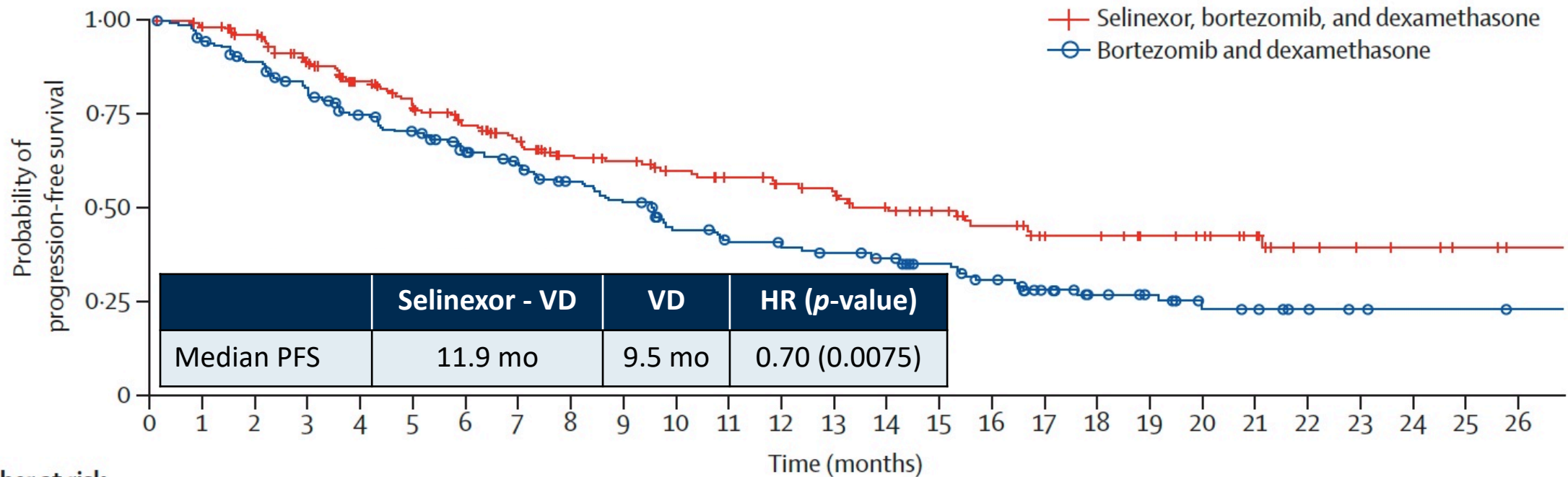
Efficacy of selinexor in combination with bortezomib and dexamethasone was evaluated in the BOSTON Trial (KCP-330-023, NCT03110562), a randomized (1:1) open-label, multicenter, active comparator-controlled trial in patients with RRMM who had previously received at least one and at most three prior therapies.”

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



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

BOSTON: Progression-Free Survival (ITT)



Number at risk (number censored)		Time (months)																											
		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81
Selinexor, bortezomib, and dexamethasone		195 (0)	187 (5)	175 (12)	152 (21)	135 (31)	117 (37)	106 (42)	89 (50)	79 (57)	76 (59)	69 (63)	64 (66)	57 (71)	51 (73)	45 (76)	41 (80)	35 (83)	27 (89)	26 (90)	22 (94)	19 (97)	14 (102)	9 (106)	7 (108)	6 (109)	4 (111)	2 (113)	
Bortezomib and dexamethasone		207 (0)	187 (8)	175 (10)	152 (15)	138 (20)	127 (22)	111 (29)	100 (32)	90 (37)	81 (37)	66 (41)	59 (43)	56 (44)	53 (45)	49 (47)	42 (52)	35 (55)	26 (60)	20 (65)	16 (69)	10 (73)	8 (75)	5 (78)	4 (79)	3 (80)	3 (80)	2 (81)	

BOSTON: Select Adverse Events

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

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.

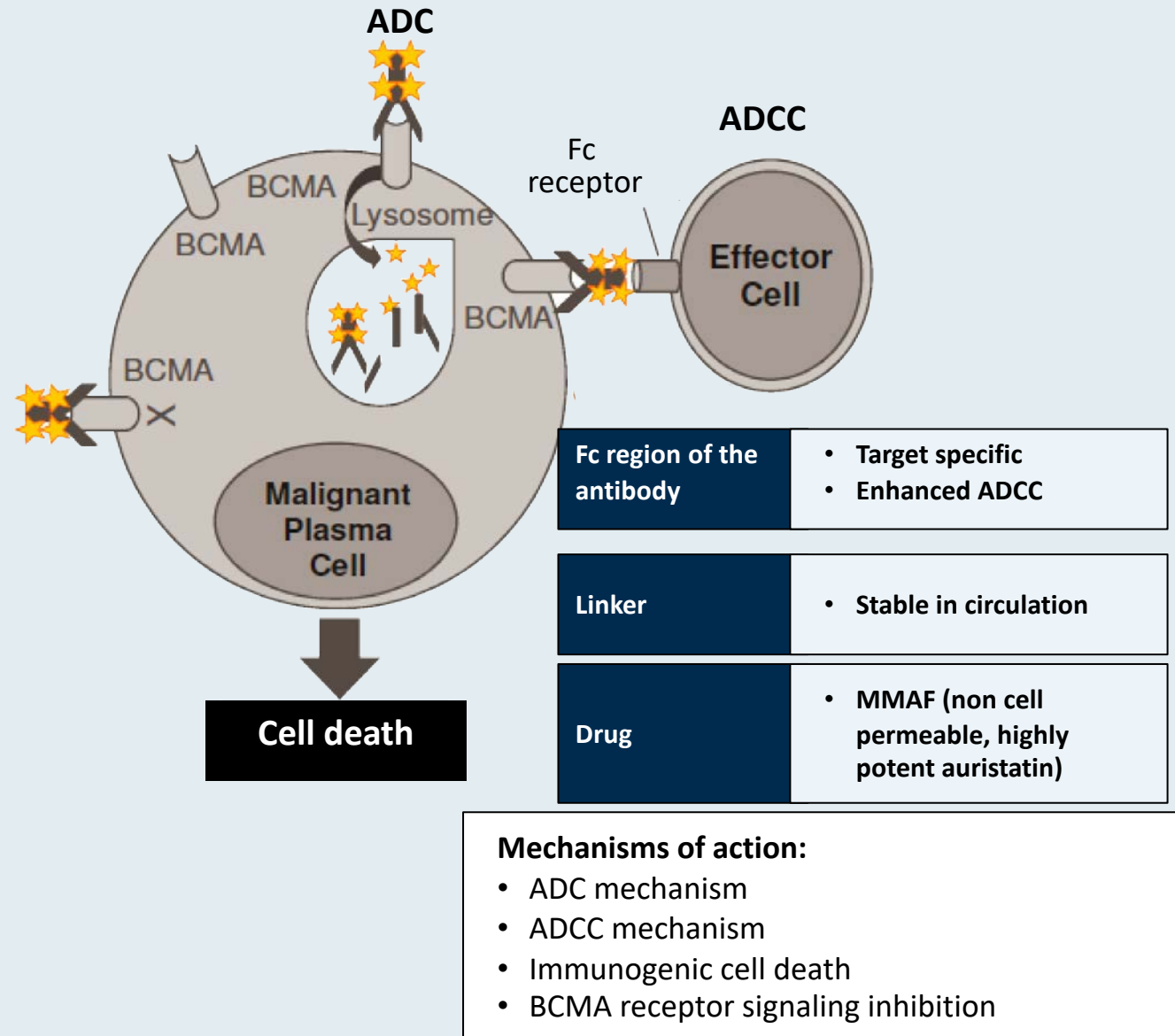
Belantamab mafodotin-blmf was evaluated in DREAMM-2 (NCT 03525678), an open-label, multicenter trial. Patients received either belantamab mafodotin-blmf, 2.5 mg/kg or 3.4 mg/kg intravenously, once every 3 weeks until disease progression or unacceptable toxicity.

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 ≥ 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.”

Belamaf: Anti-BCMA Antibody-Drug Conjugate

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



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

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

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

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

Popat R et al.

ASH 2020;Abstract 1419.

DREAMM-6: Investigator-Assessed Best Confirmed Response for Belantamab Mafodotin + Vd

Figure 3. Investigator-assessed* best confirmed response

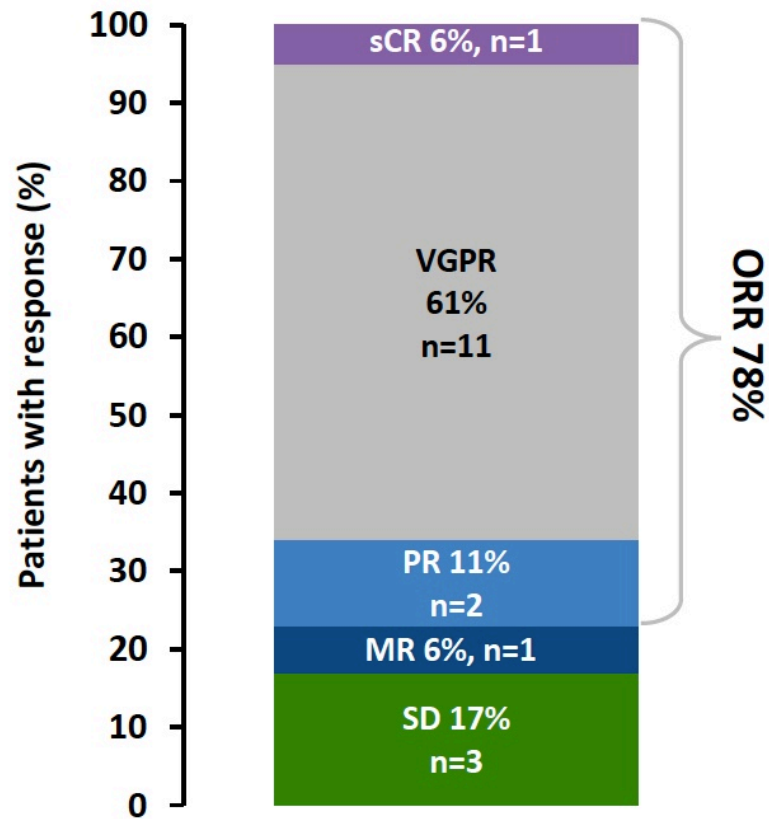
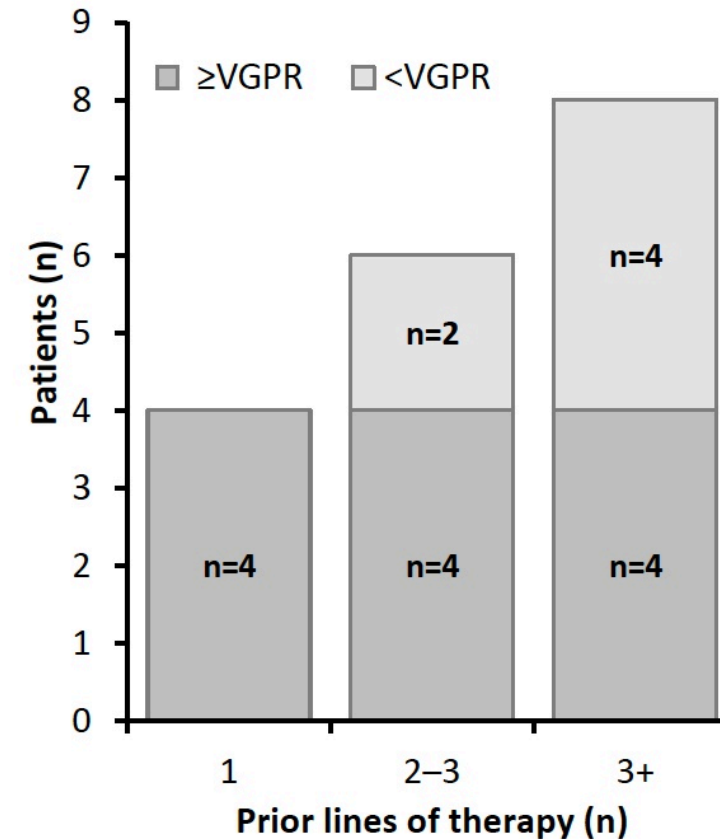


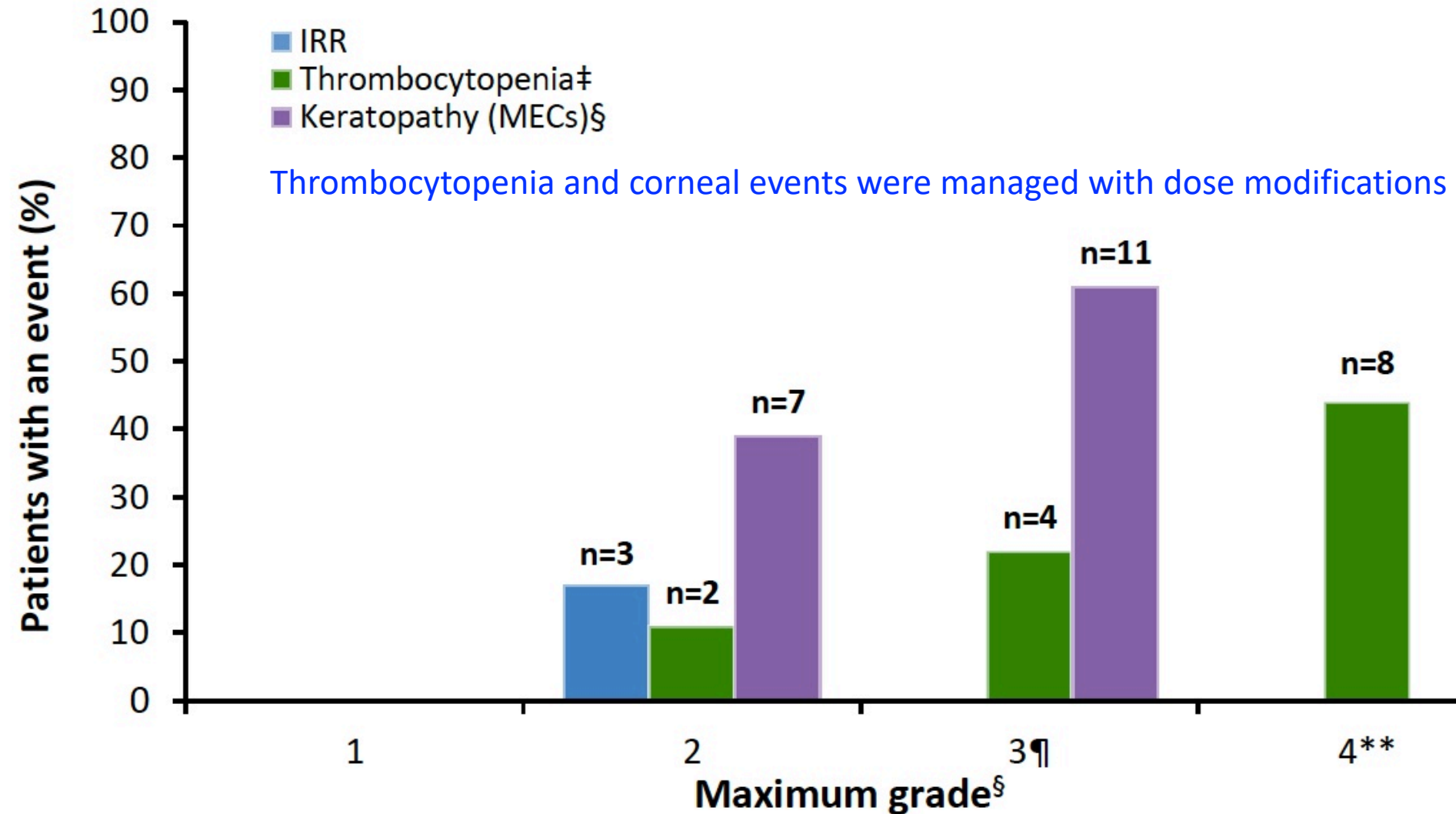
Figure 4. Investigator-assessed* best confirmed response per prior number of LOT



DREAMM-6: Overview of Adverse Events

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

DREAMM-6: Adverse Events of Special Interest



Agenda

Module 1: Newly Diagnosed Multiple Myeloma

- Dr Usmani: A 64-year-old man with multiple regimen-refractory multiple myeloma – del(17p) and t(11;14)
 - Parts 1-4

Module 2: Relapsed Multiple Myeloma

- Dr Deutsch: A 73-year-old man with multiply relapsed multiple myeloma

Module 3: Novel Agents and Approaches

- Dr Usmani: A 76-year-old woman with relapsed multiple myeloma – t(11;14)
 - Parts 1, 2 and 3

Case Presentation – Dr Usmani (Part 1): A 76-year-old woman with relapsed multiple myeloma – t(11;14)



Dr Saad Zafar Usmani

- Initial diagnosis of revised ISS Stage II IgG kappa myeloma, t(11;14)
- RVD-lite x 4 cycles → VGPR
- Lenalidomide maintenance x 1 year → patient remained in VGPR but requested to stop maintenance therapy due to fatigue
- After a year has passed, increase in M-spike is noted that is accompanied with a decline in Hb which had been normalized with induction therapy

Question

- What treatment would you recommend next for this patient?

Case Presentation – Dr Usmani (Part 2): A 76-year-old woman with relapsed multiple myeloma – t(11;14)



Dr Saad Zafar Usmani

- Initial diagnosis of revised ISS Stage II IgG kappa myeloma, t(11;14)
- RVD-lite x 4 cycles → VGPR; lenalidomide maintenance x 1 year
- Increase in M-spike with accompanying decline in Hb
- ***DRd x 16 cycles → VGPR***
- ***Patient again experienced fatigue with lenalidomide and it along with the dexamethasone was stopped***
- ***Daratumumab infusions continued***

Question

- Have you had any experience using the subcutaneous formulation of daratumumab and would you consider using subcutaneous daratumumab in this combination if you were to choose it for this patient scenario?

Case Presentation – Dr Usmani (Part 3): A 76-year-old woman with relapsed multiple myeloma – t(11;14)



Dr Saad Zafar Usmani

- Initial diagnosis of revised ISS Stage II IgG kappa myeloma, t(11;14)
- RVD-lite x 4 cycles → VGPR; lenalidomide maintenance x 1 year
- DRd x 16 cycles → VGPR
- ***Clinical relapse 25 months later***

Questions

- What treatment would you recommend next for this patient? Do you have experience with using venetoclax-based regimens for patients with multiple myeloma with a t(11;14) mutation?

Characteristics of Select BCMA CAR-T Studies in Multiple Myeloma

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

* Included +1q21

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

Safety of Select BCMA CAR-T Studies in Multiple Myeloma

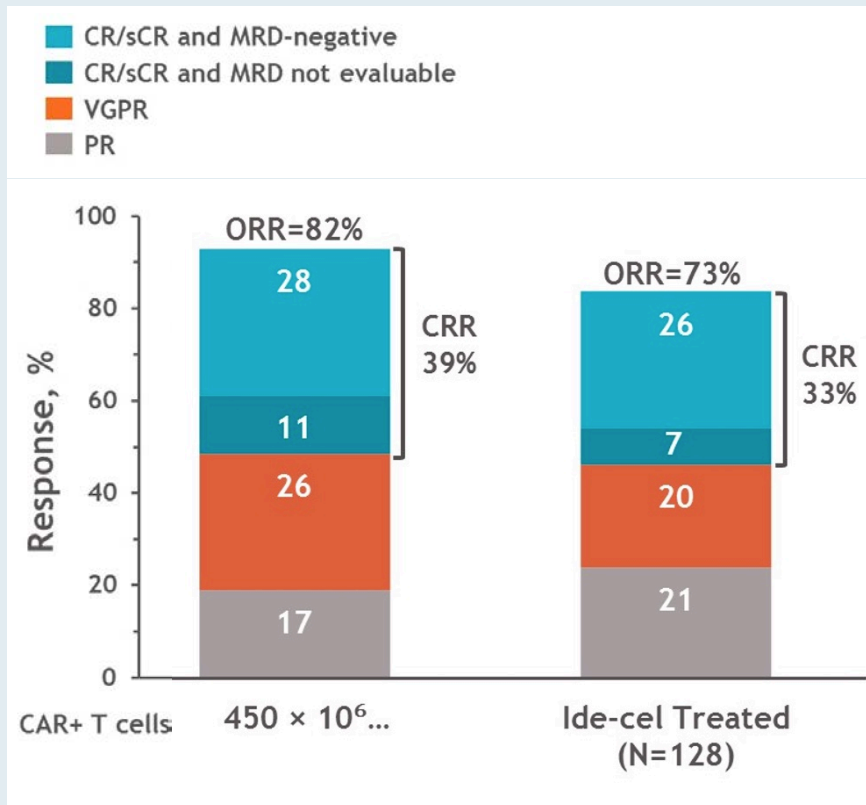
	KarMMa	EVOLVE	CARTITUDE-1
ANC \geq G3 ↓	89%	90%	100%
plts \geq G3 ↓	52%	47%	69%
CRS: all, \geq G3	84%, 6%	89%, 3%	93%, 7%
Median time to CRS Median duration of CRS	1 (1-12) days 5 (1-63) days	2 (1-4) days 4 (1-10) days	7 (2-12) days 4 (2-64) days
ICANS: all, \geq G3	17%, 3%	13%, 3%	10%, 3%
Infections: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

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

Efficacy of Select BCMA CAR-T Studies in Multiple Myeloma

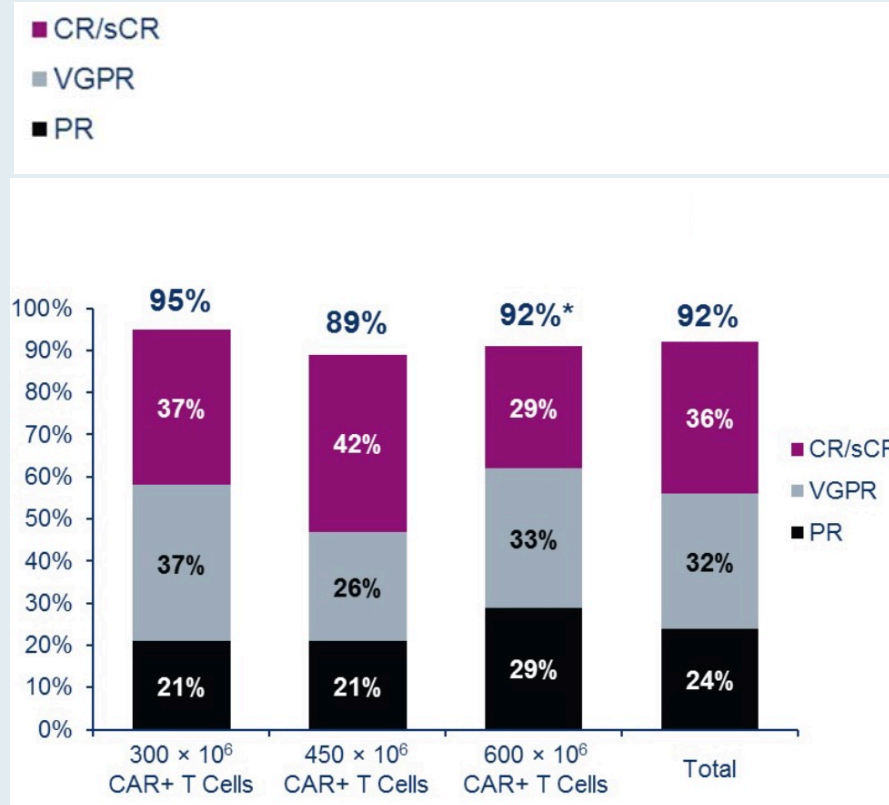
KarMMa

ORR: 73% | MRD-neg: 94%



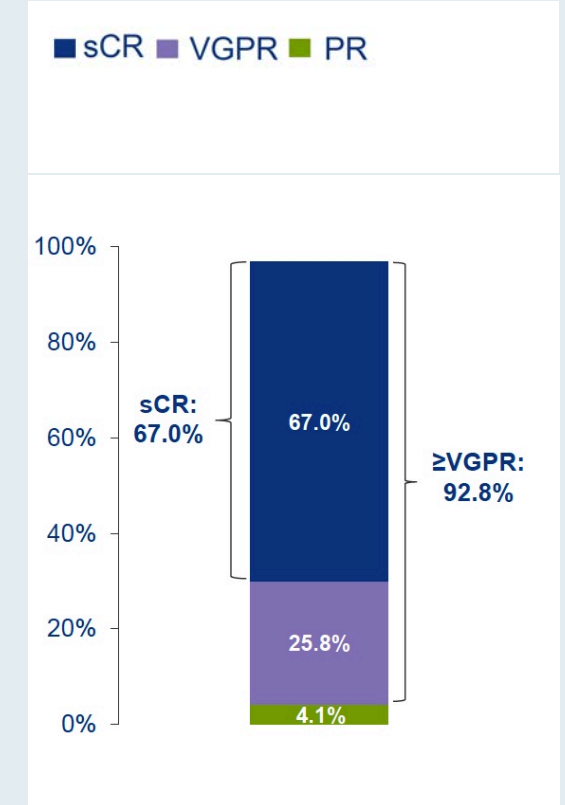
EVOLVE

ORR: 92% | MRD-neg: 84%



CARTITUDE-1

ORR: 97% | MRD-neg: 93%



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

KarMMa-3: A Phase 3 Study of Idecabtagene Vicleucel (ide-cel, bb2121), a BCMA-Directed CAR T Cell Therapy vs Standard Regimens in Relapsed and Refractory Multiple Myeloma

Delforge M et al.

ASH 2020;Abstract 2323

KarMMa-4: Idecabtagene Vicleucel (ide-cel, bb2121), a BCMA-Directed CAR T-Cell Therapy, in High-Risk Newly Diagnosed Multiple Myeloma

Usmani S et al.

ASH 2020;Abstract 1418

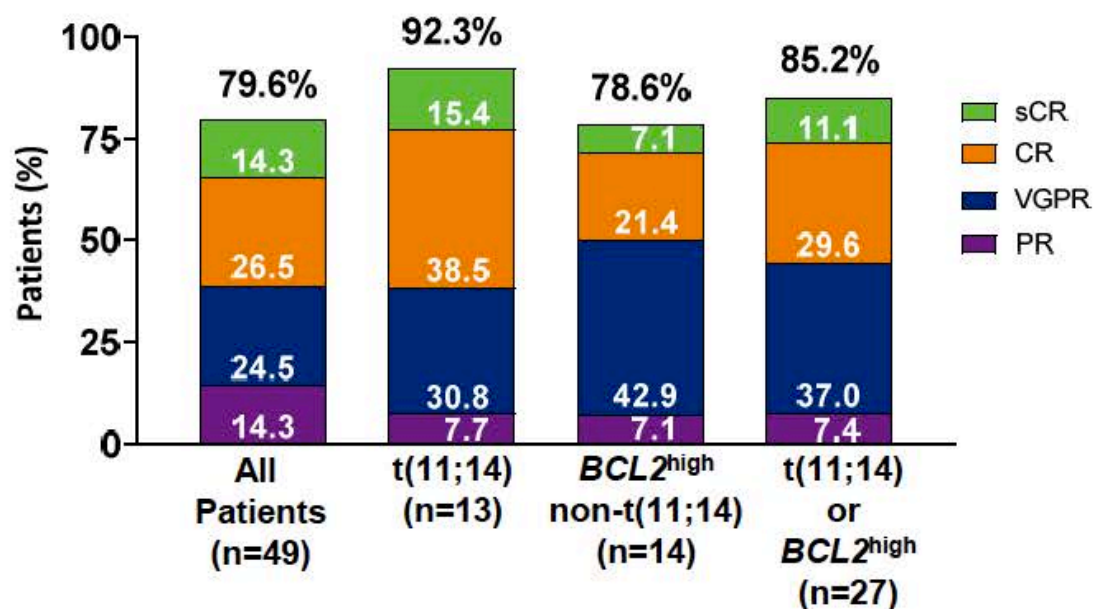
Assessment of Minimal Residual Disease By Next-Generation Sequencing and Fluorodeoxyglucose-Positron Emission Tomography in Patients with Relapsed/Refractory Multiple Myeloma Treated with Venetoclax in Combination with Carfilzomib and Dexamethasone

Costa LJ et al.

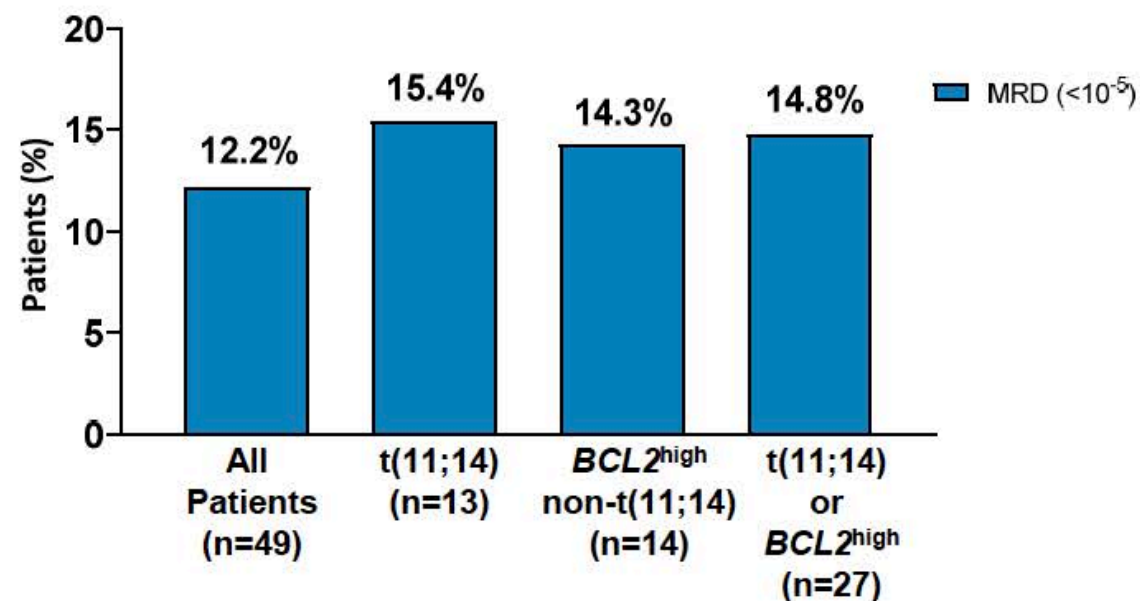
ASH 2020;Abstract 2251

Response Rates in Overall Population and Biomarker Sub-groups

Response rates

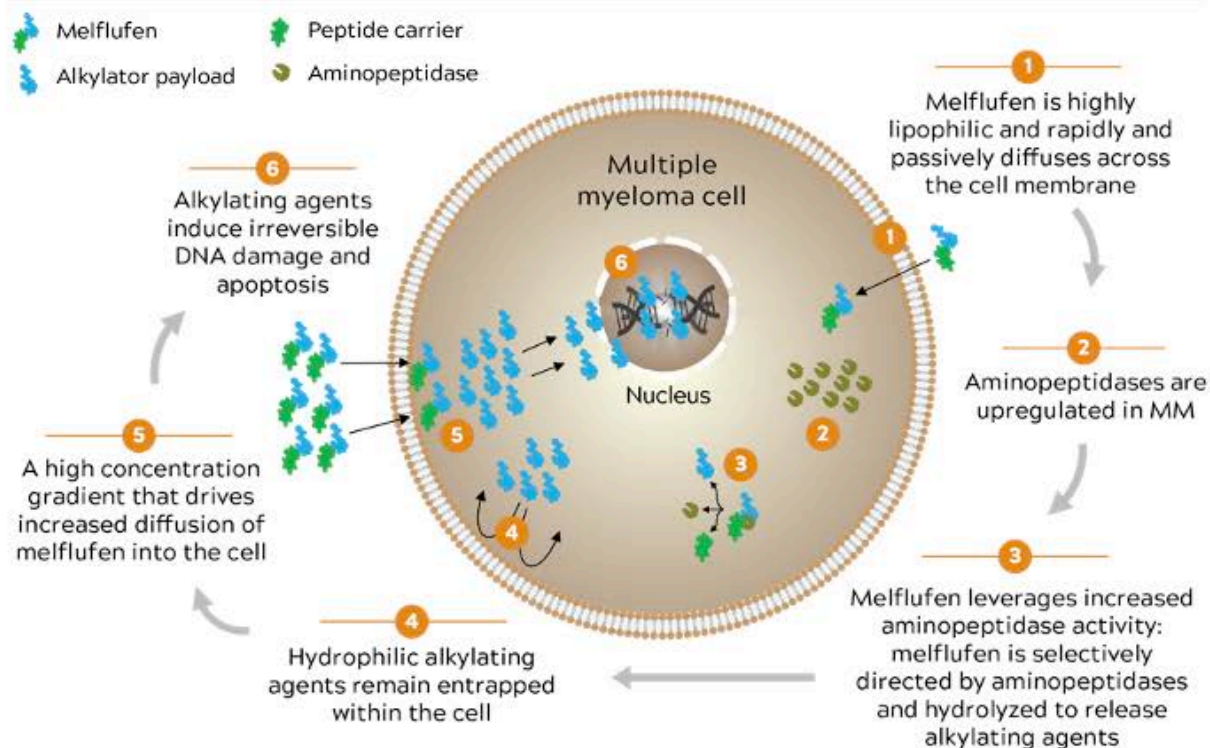


MRD negative (<10⁻⁵) rates



Melphalan Flufenamide (Melflufen): Mechanism of Action

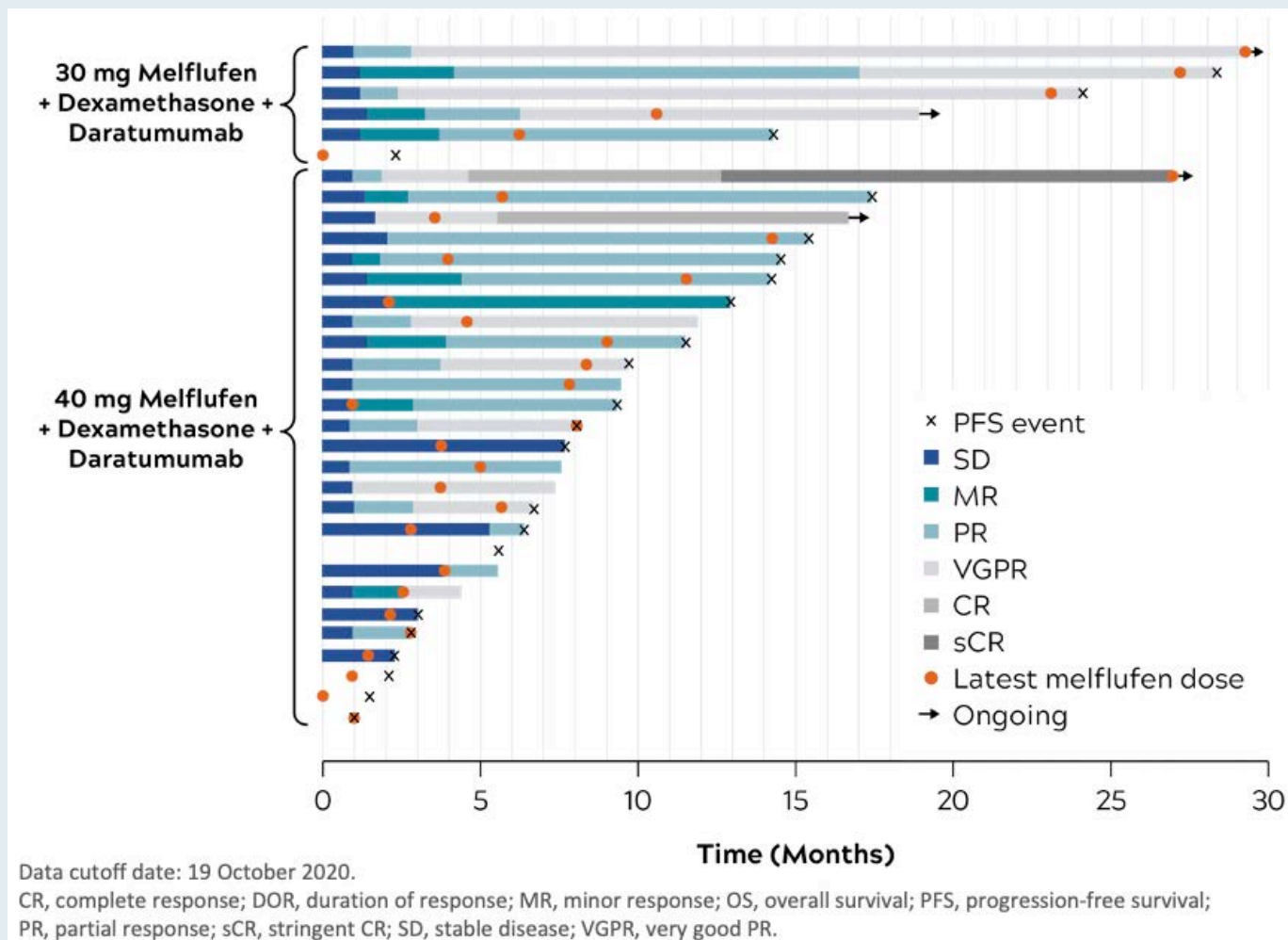
Melflufen is an investigational first-in-class peptide-drug conjugate (PDC) that **targets aminopeptidases and rapidly releases alkylating agents into tumor cells.**¹⁻⁵



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

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

ANCHOR: Melflufen with Dexamethasone and Daratumumab



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

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 Robert Dreicer and Daniel P Petrylak
discuss the management of
genitourinary cancers**

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

**A Daylong Clinical Summit Hosted in Partnership with
North Carolina Oncology Association (NCOA) and
South Carolina Oncology Society (SCOS)**

Saturday, February 13, 2021

8:30 AM – 4:30 PM ET

Agenda

Module 1 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Pagel and Smith*

Module 2 — Multiple Myeloma: *Drs Richardson and Voorhees*

Module 3 — Genitourinary Cancers: *Drs Dreicer and Petrylak*

Module 4 — Lung Cancer: *Drs Gainor and Wakelee*

Module 5 — Gastrointestinal Cancers: *Dr Philip and Prof Van Cutsem*

Module 6 — Breast Cancer: *Drs Hurvitz and Krop*

Module 7 — Acute Myeloid Leukemia and Myelodysplastic Syndromes:
Drs DiNardo and Perl

Genitourinary Cancers Faculty



Robert Dreicer, MD, MS

Section Head, Medical Oncology
Deputy Director, University of Virginia Cancer Center
Associate Director for Clinical Research
Professor of Medicine and Urology
University of Virginia School of Medicine
Charlottesville, Virginia



Daniel P Petrylak, MD

Professor of Internal Medicine
(Medical Oncology) and Urology
Yale School of Medicine
New Haven, Connecticut

The patients I saw today...

82	M	Chronic myeloid leukemia - Newly diagnosed, Sokal intermediate risk, I recommended dasatinib
42	F	Breast Cancer - Stage III TNBC s/p adjuvant DD AC-T
89	M	Acute Myeloid Leukemia - Venetoclax/azacytidine
38	F	Colorectal Cancer - Metastatic colon cancer on FOLFOX/bevacizumab
76	M	Hepatocellular carcinoma – Nivolumab
71	F	Diffuse Large B Cell Lymphoma - Completed R-CHOP
84	M	Multiple myeloma - Bortezomib/Dex
59	M	Multiple myeloma or other plasma cell dyscrasias – Maintenance Carfilzomib/Dex
62	M	Multiple myeloma - Relapsed/ Refractory- Carfilzomib/Cyclophosphamide/Dex

72	F	Breast Cancer – Anastrozole
54	F	Breast Cancer – Tamoxifen
35	M	Benign Hematology - Enoxaparin for DVT
32	F	Benign Hematology - DSVT on warfarin
40	F	Benign Hematology - Iron def anemia on oral iron
42	F	T-Cell Lymphoma - T-Cell LGL on weekly Methotrexate
68	M	Diffuse Large B Cell Lymphoma - Primary CNS lymphoma s/p HD- Methotrexate/Rituximab
57	F	Melanoma - IPI/ Nivo
62	M	Renal Cell Carcinoma - Ipi/ Nivo
62	M	Lung Cancer - Consolidative Durvalumab after chemoRT
92	M	Prostate cancer - Enzalutamide/ Leuprolide/Denosumab

Contributing Oncologists



Daniel R Carrizosa, MD, MS
Atrium Health Levine Cancer Institute
Associate Program Director –
Hematology/Oncology Fellowship
Medical Director: Diversity/Disparities and
Outreach Committee
Section Head: Head and Neck Division
Member: Head and Neck and Thoracic Sections
Charlotte, North Carolina



Margaret Deutsch, MD
Duke Cancer Center Raleigh
Raleigh, North Carolina



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



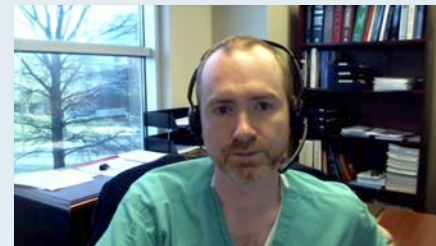
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Agenda

Module 1: Urothelial Bladder Cancer (UBC)

- Dr Grigg: A 79-year-old man with metastatic UBC – FGFR alteration
- Dr Grigg: A healthy 71-year-old man with high-risk non-muscle-invasive UBC

Module 2: Renal Cell Carcinoma (RCC)

- Dr Grigg: A 75-year-old woman and a 54-year-old woman – both with newly diagnosed metastatic clear cell RCC
- Dr Shehadeh: A 56-year-old man with metastatic clear cell RCC
- Dr Deutsch: A 64-year-old woman with metastatic RCC

Module 3: Prostate Cancer

- Dr Grigg: A 72-year-old man with nonmetastatic castration-resistant prostate cancer
- Dr Grigg: A 58-year-old man with metastatic castration-resistant prostate cancer

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Case Presentation – Dr Grigg: A 79-year-old man with metastatic UBC – FGFR alteration



Dr Claud Grigg

- PMH: HTN, remote history of prostate cancer
- Metastatic UBC, involving pelvic and retroperitoneal nodes
- Cisplatin-based chemotherapy → Asymptomatic PD
- NGS: FGFR3-TACC3 fusion
- Treatment delayed due to COVID-19 infection

Questions

- Would you treat him with immunotherapy as second-line treatment, or would you treat with an FGFR inhibitor?
- Does the situation in UBC parallel that of lung cancer, where patients with an EGFR mutation do not respond as well to immunotherapy?

Case Presentation – Dr Grigg: A healthy 71-year-old man with high-risk non-muscle-invasive UBC



Dr Claud Grigg

- 2016: Diagnosed with high-grade non-muscle invasive UBC (pTa)
- Induction intravesical BCG → maintenance BCG
- 2019 TURBT: pTis carcinoma in situ rechallenged with BCG but no response
- Patient declines cystectomy
- Pembrolizumab, with Grade 3 dermatitis

Questions

- For patients who are BCG-refractory, are you steering them toward intravesical therapies, such as chemotherapy, or are you steering them to pembrolizumab?
- Are you advising patients to go straight to cystectomy before pembrolizumab?

What would be your preferred first-line treatment regimen for a 65-year-old patient with metastatic UBC?

1. Cisplatin/gemcitabine
2. Carboplatin/gemcitabine
3. PD-1/PD-L1 monotherapy
4. Test PD-L1 level and administer anti-PD-1/PD-L1 monotherapy if PD-L1-positive
5. Cisplatin/gemcitabine → maintenance avelumab
6. Carboplatin/gemcitabine → maintenance avelumab
7. Platinum-based chemotherapy → other anti-PD-1 maintenance
8. Other

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

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

FDA Approves Pembrolizumab for BCG-Unresponsive, High-Risk Non-Muscle Invasive Bladder Cancer

Press Release – January 8, 2020

The Food and Drug Administration approved pembrolizumab for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Efficacy was investigated in KEYNOTE-057 (NCT 02625961), a multicenter, single-arm trial that enrolled 148 patients with high-risk NMIBC, 96 of whom had BCG-unresponsive CIS with or without papillary tumors. Patients received pembrolizumab 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC or progressive disease, or up to 24 months of therapy without disease progression.

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

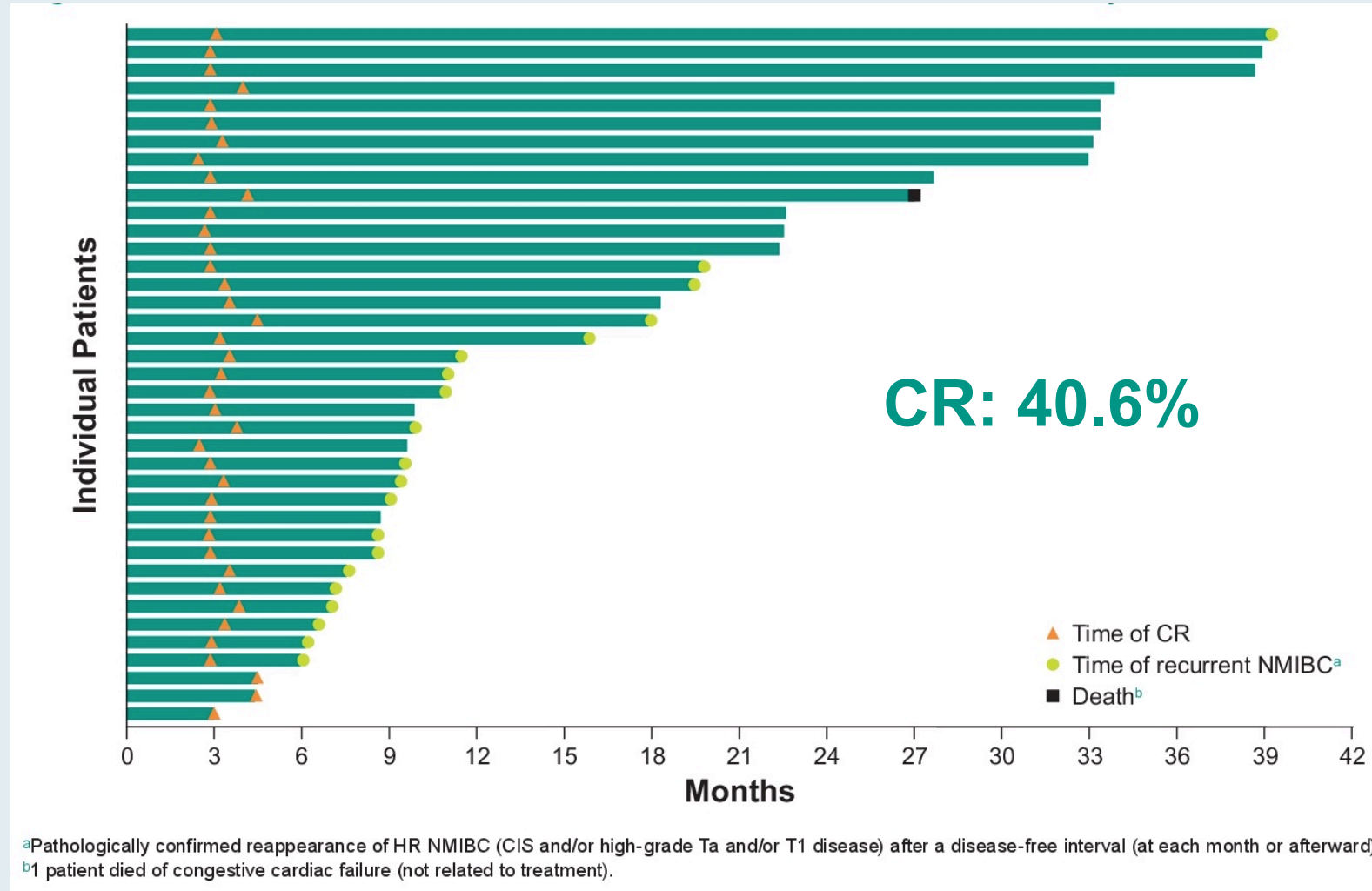
Balar AV et al.

Genitourinary Cancers Symposium 2021;Abstract 451.

February 11, 2021

8:00 AM – 6:30 PM EST

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



ORIGINAL ARTICLE

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

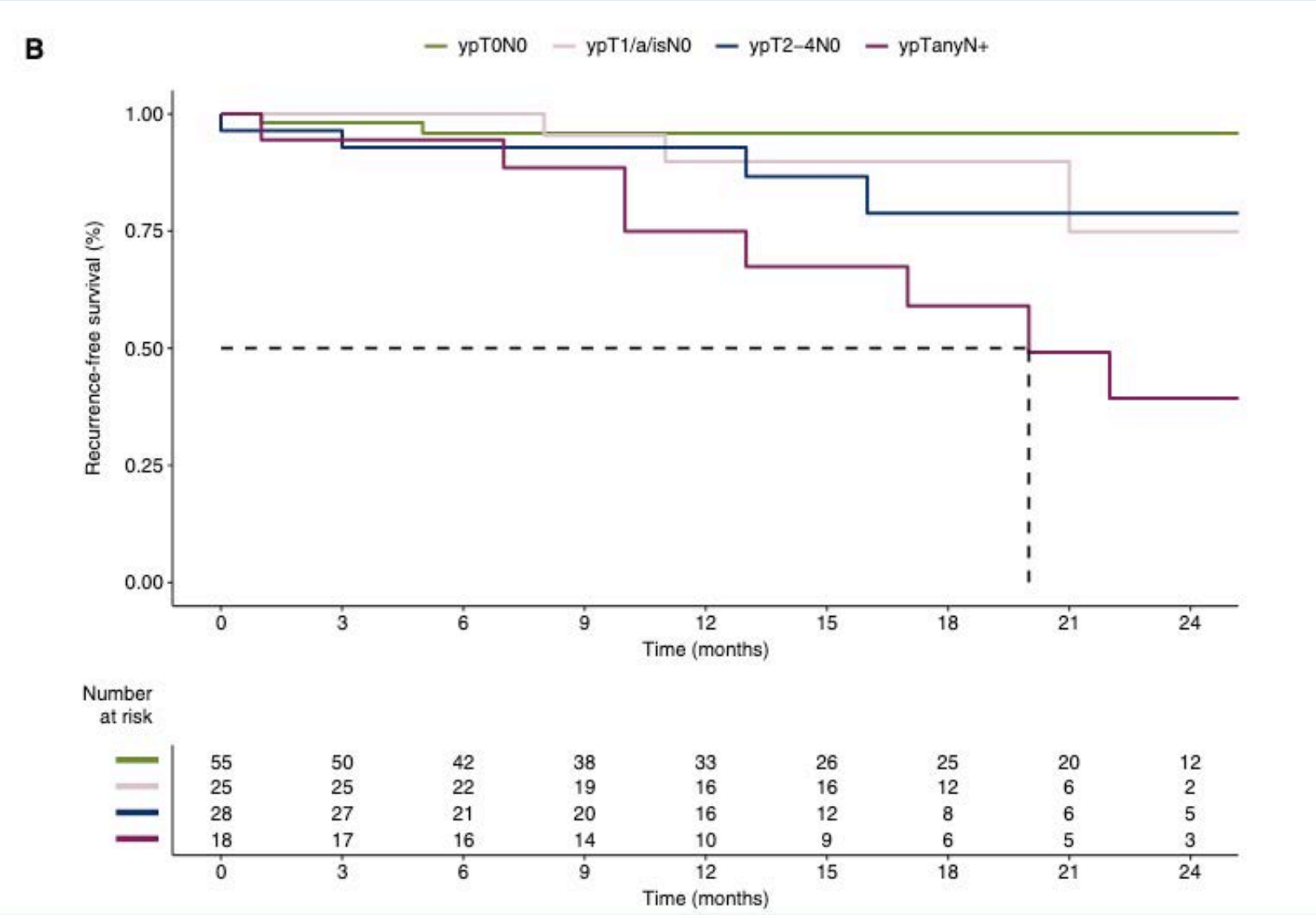
M. Bandini¹, E. A. Gibb², A. Gallina¹, D. Raggi³, L. Marandino³, M. Bianchi¹, J. S. Ross^{4,5}, M. Colecchia³, G. Gandaglia¹, N. Fossati¹, F. Pederzoli¹, R. Lucianò⁶, R. Colombo¹, A. Salonia¹, A. Briganti¹, F. Montorsi¹ & A. Necchi^{3*}

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



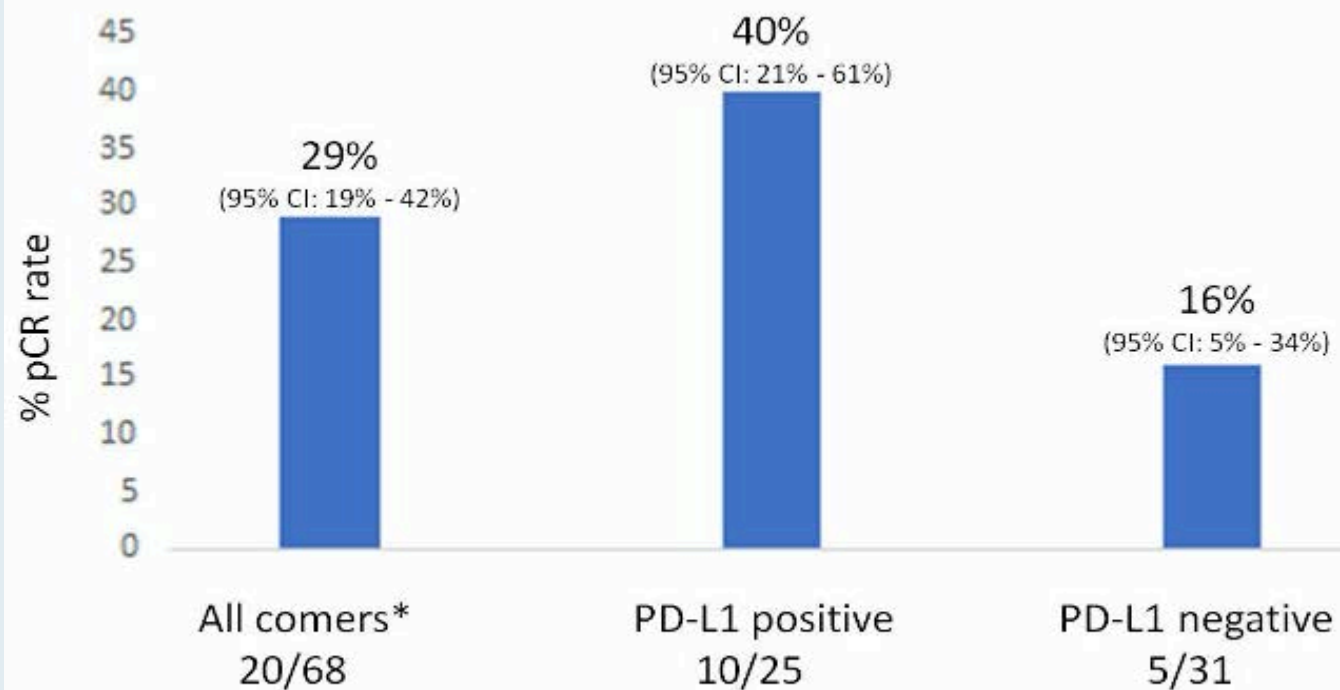
Available online 23 September 2020

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

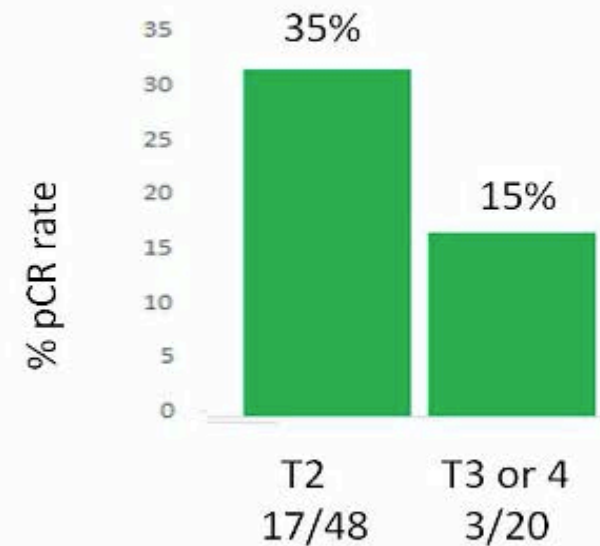


RFS	12-mo	24-mo
Overall (n = 126)	90.5%	78.3%
ypT0ypN0 (n = 55)	95.9%	95.9%
ypT _{1/a/is} ypN0 (n = 25)	89.8%	74.9%
ypT2-4 ypN0 (n = 28)	92.9%	78.8%
ypTanyN+ (n = 18)	74.9%	39.3%

ABACUS: pCR Rate in Evaluable Patients (n = 68)



pCR rate according to T stage at baseline



Nivolumab Significantly Improves DFS as Adjuvant Therapy for High-Risk, Muscle-Invasive UC in Phase III CheckMate 274 Trial

Press Release – September 24, 2020

In an interim analysis, CheckMate 274, a pivotal Phase III trial evaluating nivolumab after surgery in patients with high-risk, muscle-invasive urothelial carcinoma, has met its primary endpoints of improving disease-free survival (DFS) versus placebo in both all randomized patients and in patients whose tumor cells express PD-L1 $\geq 1\%$.

CheckMate 274 is the first and only Phase III trial in which immunotherapy has reduced the risk of relapse in the adjuvant setting for these patients. The safety profile of nivolumab was consistent with previously reported studies in solid tumors.

The company plans to complete a full evaluation of the CheckMate 274 data, work with investigators to present the results at an upcoming medical conference and submit the data to health authorities. The CheckMate 274 trial will continue as planned to allow for future analyses of secondary endpoints, including overall survival and disease-specific survival.

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

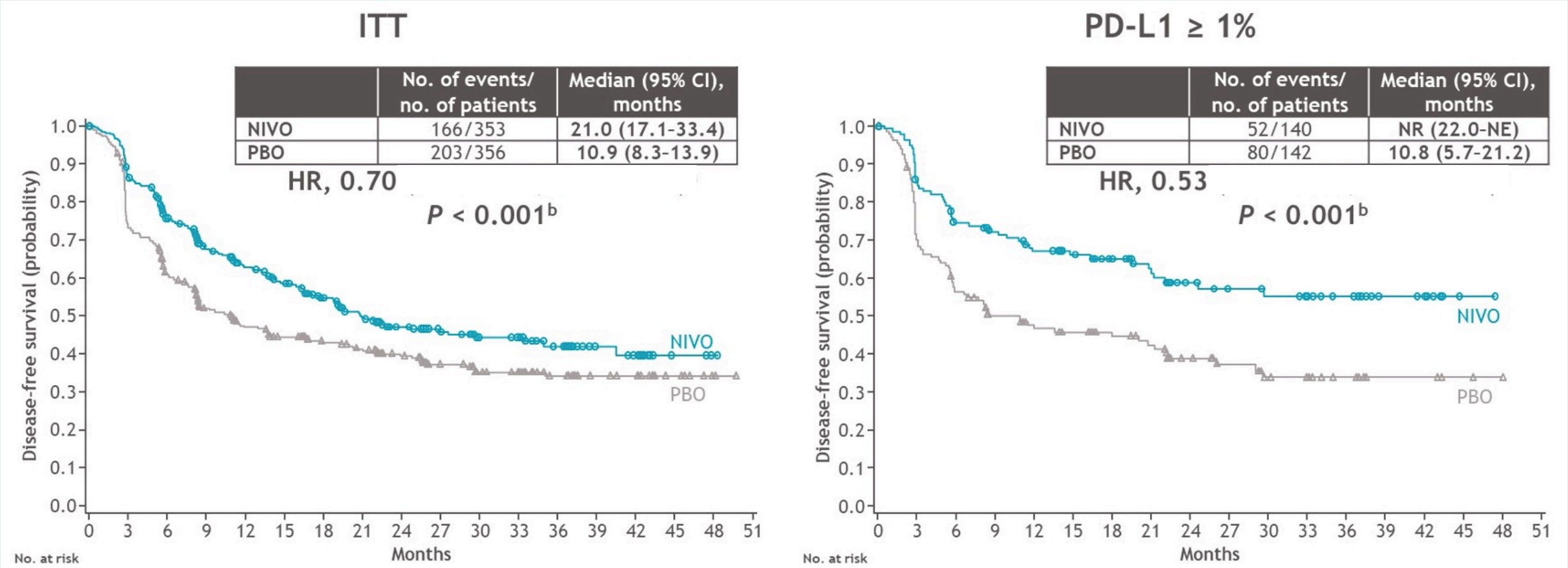
Bajorin DF et al.

Genitourinary Cancers Symposium 2021;Abstract 391.

Friday, February 12, 2021.

3:45 PM – 5:00 PM EST

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



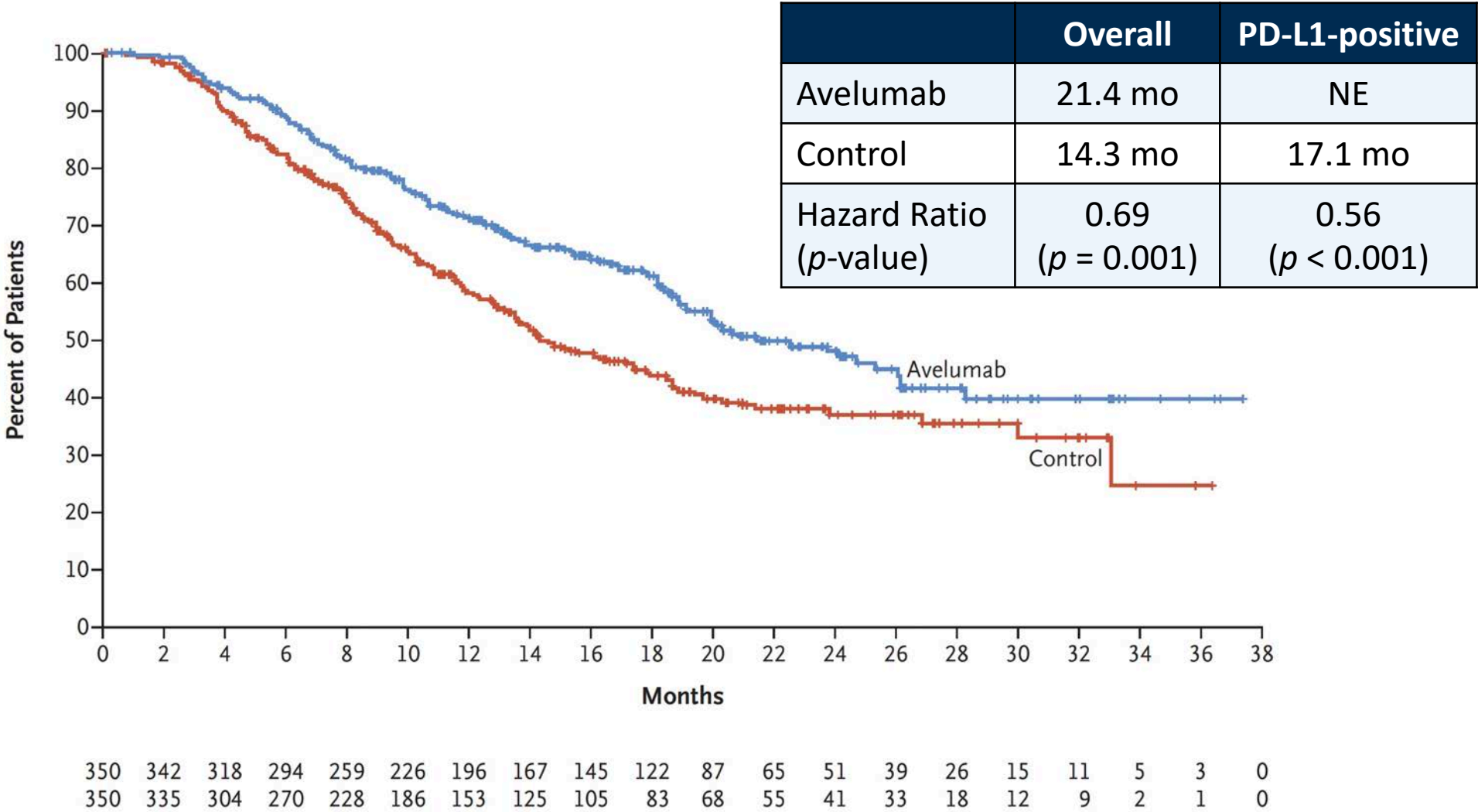
FDA Approves Avelumab for Urothelial Carcinoma Maintenance Treatment

Press Release – June 30, 2020

The Food and Drug Administration approved avelumab for maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

Efficacy of avelumab for maintenance treatment of UC was investigated in the JAVELIN Bladder 100 trial (NCT02603432), a randomized, multi-center, open-label trial that enrolled 700 patients with unresectable, locally advanced or metastatic urothelial carcinoma that had not progressed with four to six cycles of first-line platinum-containing chemotherapy. Patients were randomized (1:1) to receive either avelumab intravenously every 2 weeks plus best supportive care (BSC) or BSC alone. Treatment was initiated within 4-10 weeks after last chemotherapy dose.

JAVELIN Bladder 100 Primary Endpoint: Overall Survival

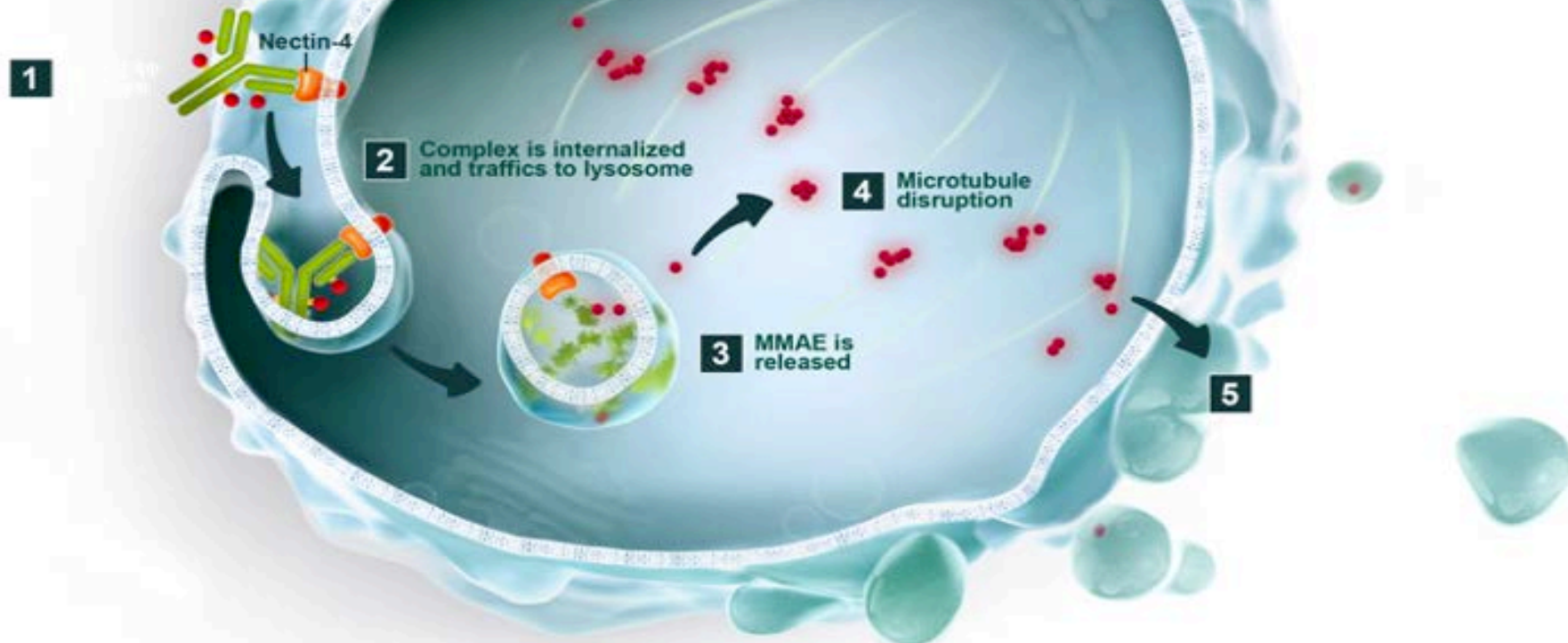
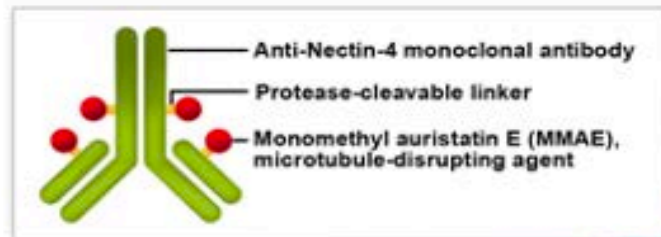


FDA Grants Breakthrough Therapy Designation to Enfortumab Vedotin in Combination with Pembrolizumab

Press Release – February 19, 2020

- The FDA has granted breakthrough therapy designation to enfortumab vedotin-ejfv in combination with pembrolizumab for the treatment of patients with unresectable locally advanced or metastatic urothelial cancer who are unable to receive cisplatin-based chemotherapy for the first-line setting.
- The designation was granted based on results from the dose-escalation cohort and expansion cohort A of the phase Ib/II EV-103 trial. Initial results from the trial were presented at the European Society of Medical Oncology (ESMO) 2019, and updated findings were presented at the 2020 Genitourinary Cancers Symposium.
- EV-103 is an ongoing, multi-cohort, open-label, multicenter phase Ib/II trial of enfortumab vedotin alone or in combination, assessing the safety, tolerability, and efficacy of the antibody-drug conjugate (ADC) in muscle invasive, locally advanced and first- and second-line metastatic urothelial cancer.

Enfortumab Vedotin: Nectin-4 Targeted Therapy



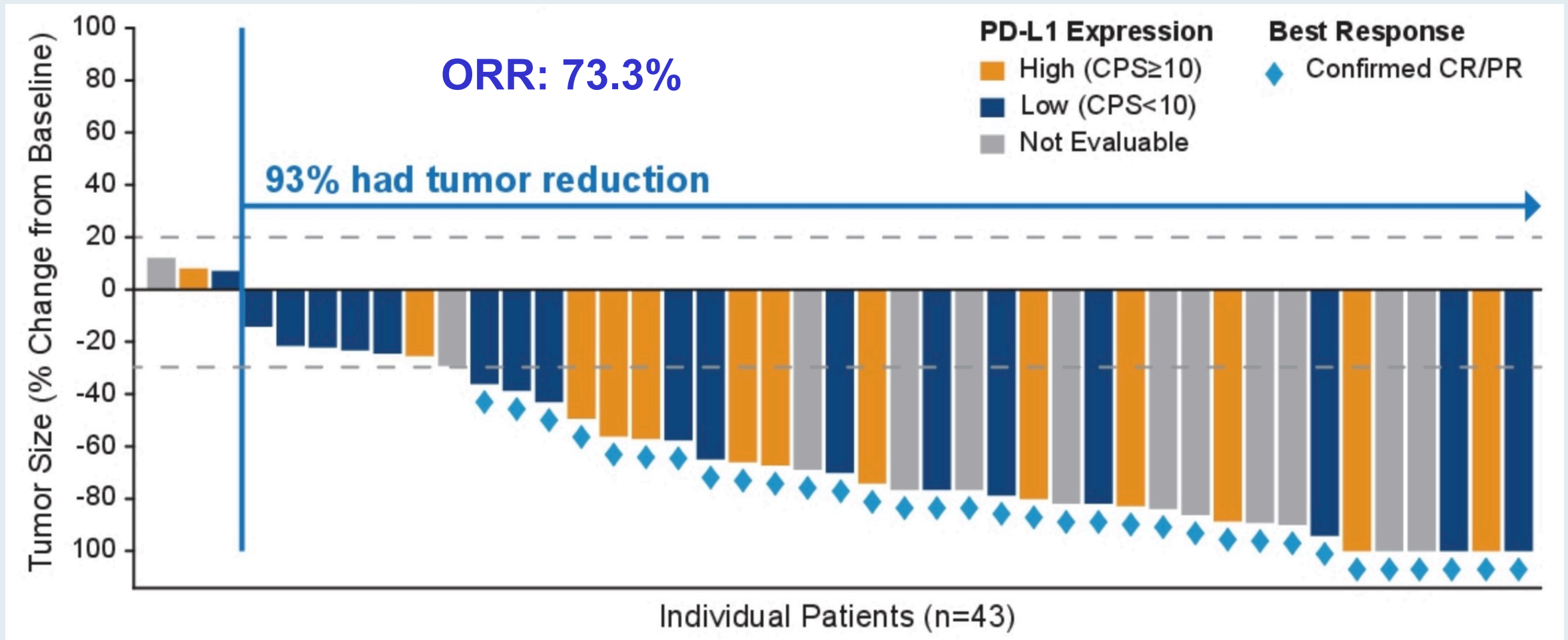
Courtesy of Jonathan Rosenberg, MD

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

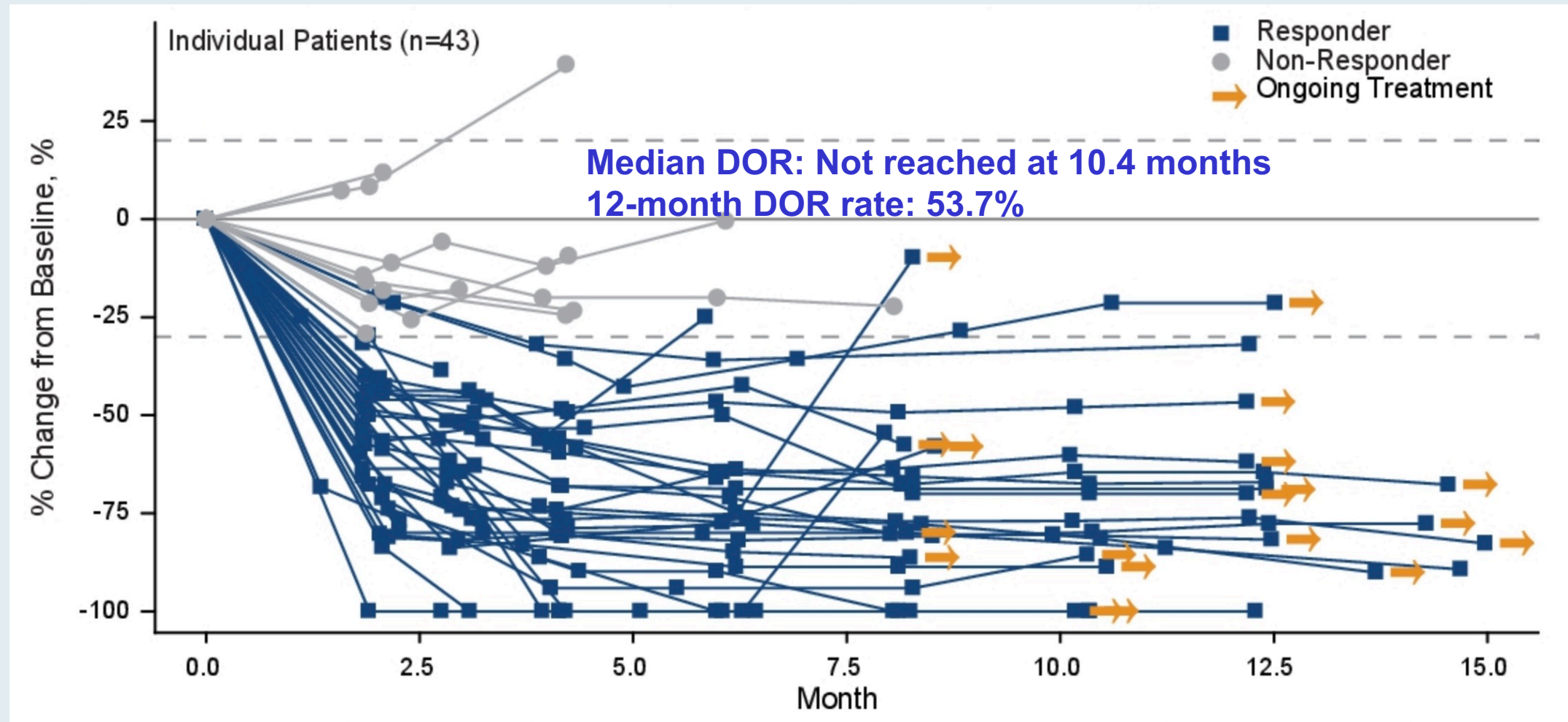
Rosenberg JE et al.

ASCO 2020;Abstract 5044.

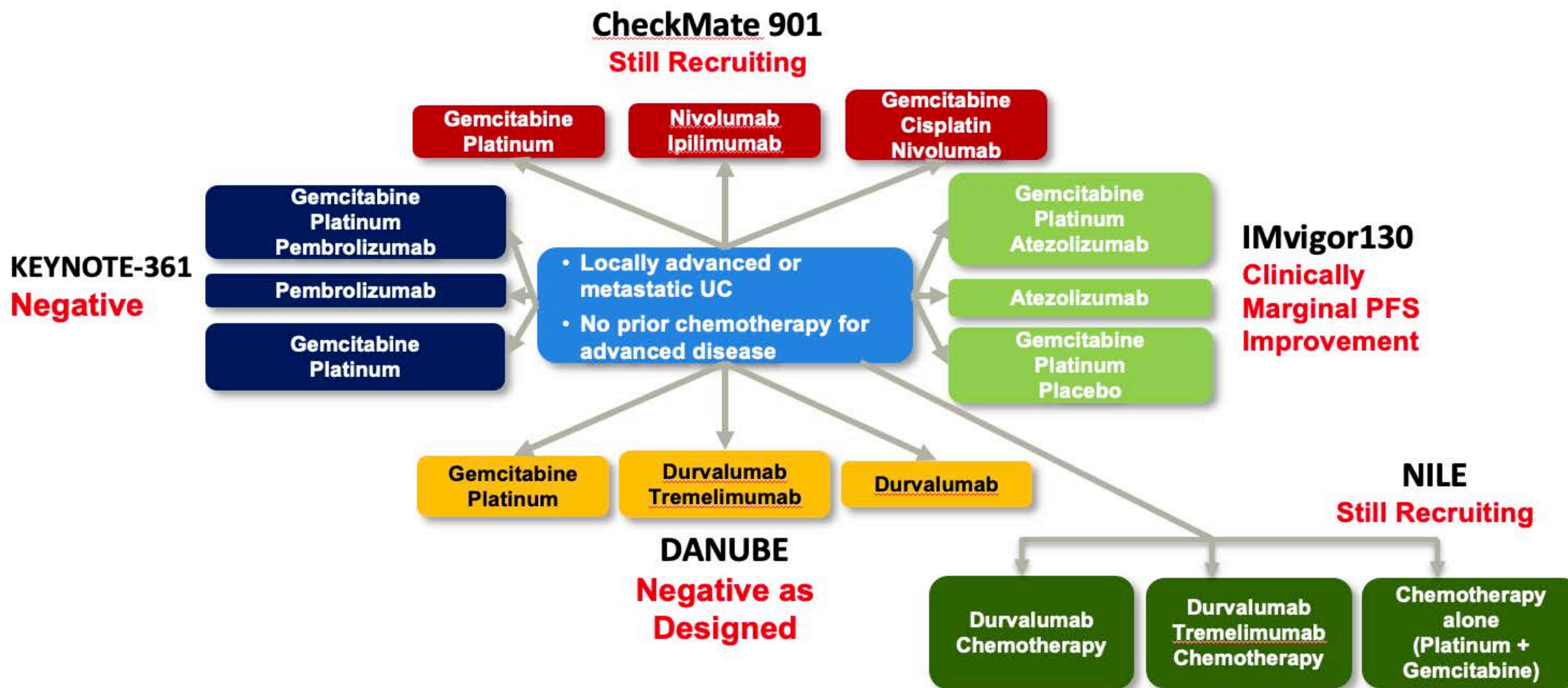
EV-103: Response to Enfortumab Vedotin with Pembrolizumab in the First-Line Setting



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



Ongoing Trials in mUBC in the First-Line Setting

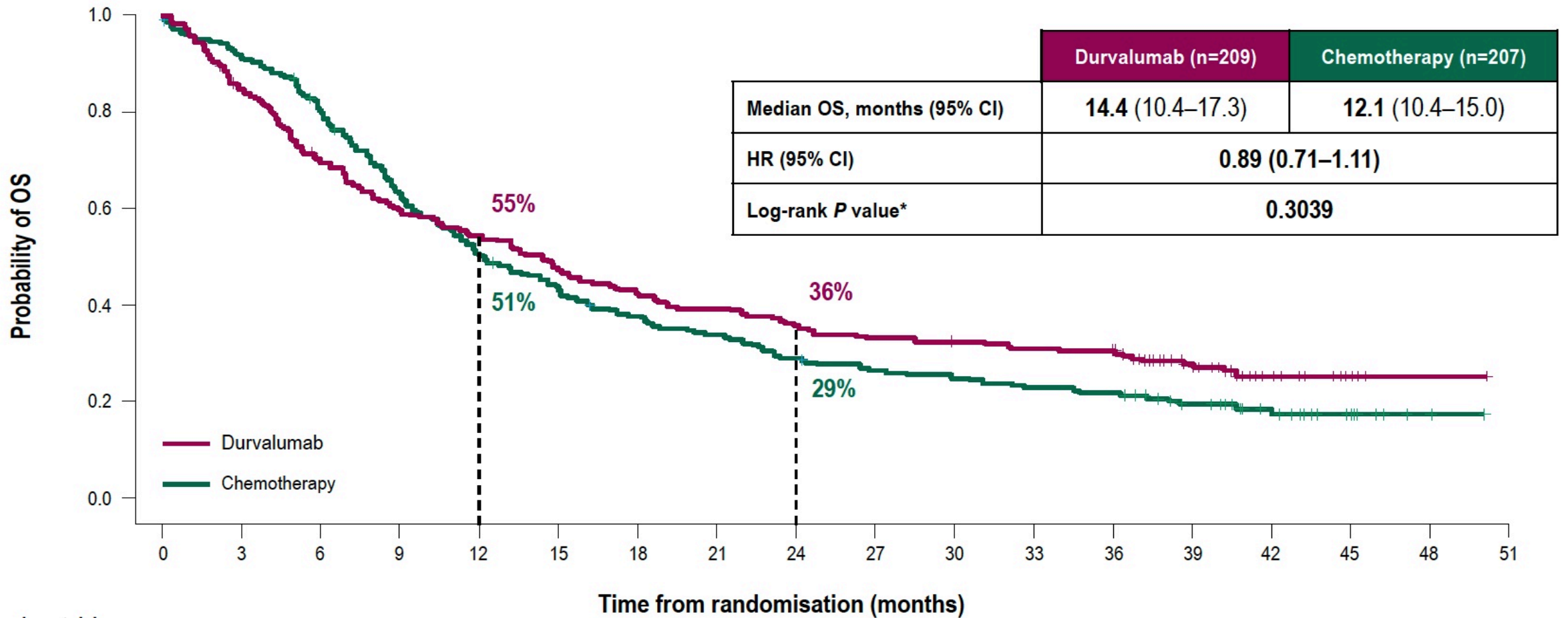




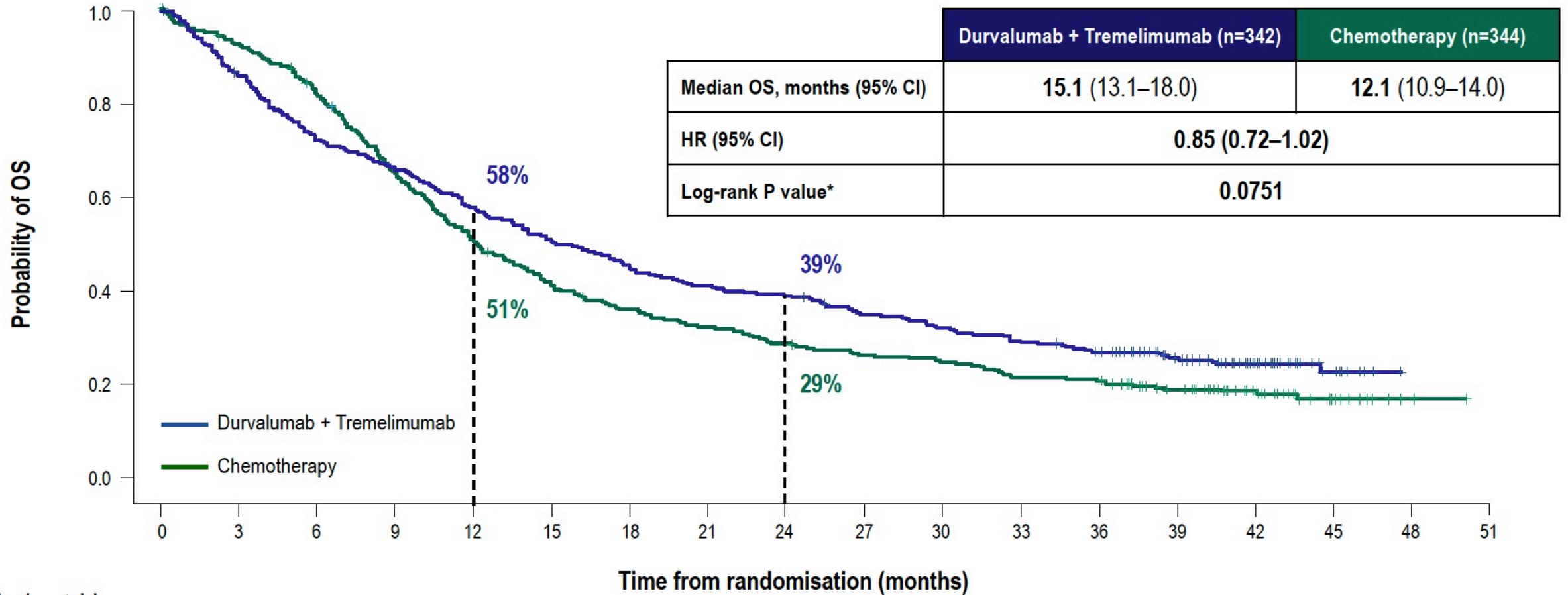
Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial

*Thomas Powles, Michiel S van der Heijden, Daniel Castellano, Matthew D Galsky, Yohann Loriot, Daniel P Petrylak, Osamu Ogawa, Se Hoon Park, Jae-Lyun Lee, Ugo De Giorgi, Martin Bögemann, Aristotelis Bamias, Bernhard J Eigl, Howard Gurney, Som D Mukherjee, Yves Fradet, Iwona Skoneczna, Marinos Tsiatas, Andrey Novikov, Cristina Suárez, André P Fay, Ignacio Duran, Andrea Necchi, Sophie Wildsmith, Philip He, Natasha Angra, Ashok K Gupta, Wendy Levin, Joaquim Bellmunt, for the DANUBE study investigators**

DANUBE Coprimary Endpoint: OS with Durvalumab vs Chemotherapy in the PD-L1-High Population



DANUBE Coprimary Endpoint: OS with Durvalumab + Tremelimumab vs Chemotherapy in the ITT Population

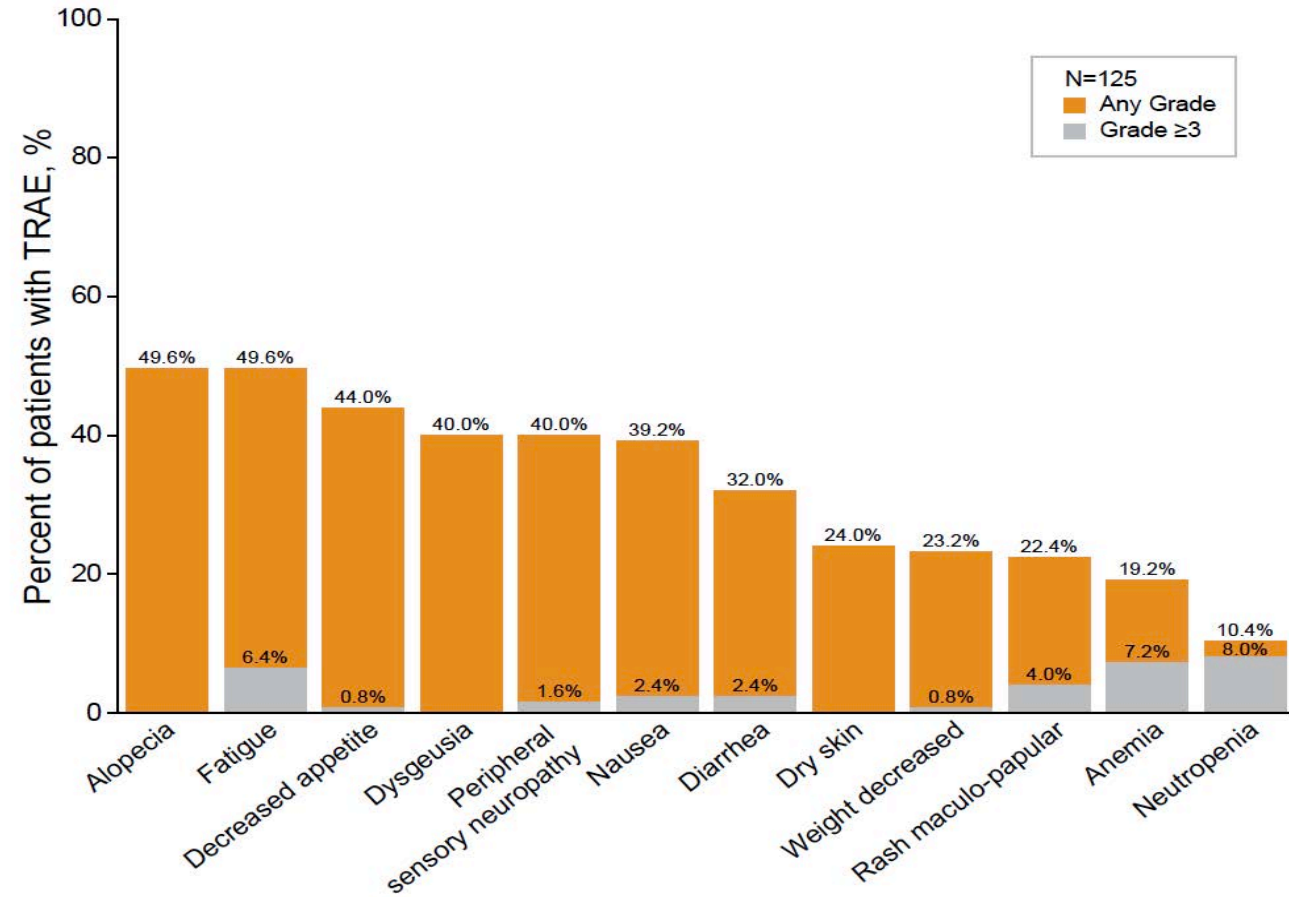
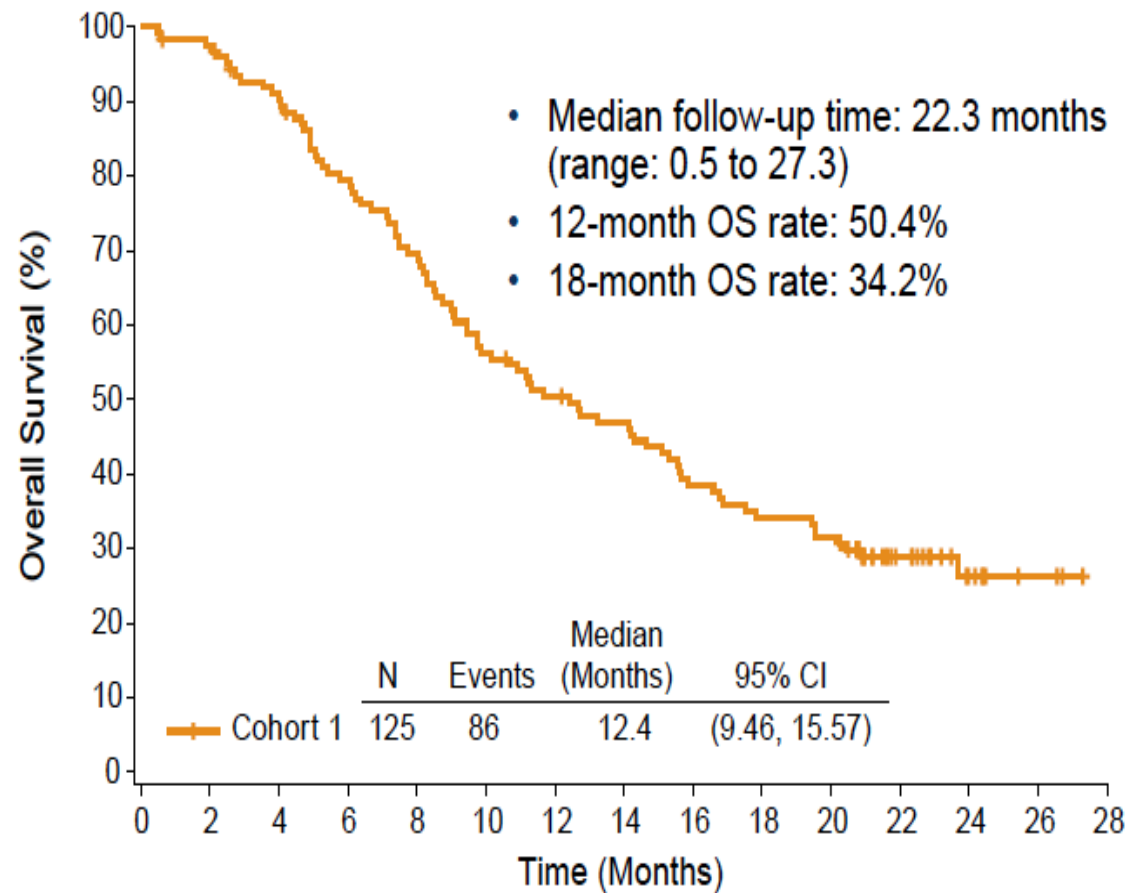


Long-Term Results of Enfortumab Vedotin Monotherapy for Locally Advanced or Metastatic Urothelial Cancer Previously Treated with Platinum and PD-1/PD-L1 Inhibitors

O'Donnell P et al.

ESMO 2020;Abstract 746P.

EV-201: OS and Safety Results in Patients Who Received Prior PD-1/PD-L1 Inhibitor/Platinum-Based Therapy



Primary Results of EV-301: A Phase III Trial of Enfortumab Vedotin versus Chemotherapy in Patients with Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

Powles T et al.

Genitourinary Cancers Symposium 2021;Abstract 393.

EV-301: Response and Survival Analyses

	Enfortumab vedotin (n = 301)	Chemotherapy (n = 307)	Hazard ratio	<i>p</i> -value
Median OS	12.9 mo	9.0 mo	0.70	0.001
Median PFS	5.6 mo	3.7 mo	0.61	<0.00001
ORR	40.6%	17.9%	—	—
DCR	71.9%	53.4%	—	—

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

Balar AV et al.

Genitourinary Cancers Symposium 2021;Abstract 394.

EV-201 Cohort 2: Response and Survival Analyses

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

Can biomarkers inform 2nd line therapy/sequence?

PD-L1



No

TMB



Possibly

Nectin-4



No, ubiquitous

Trop-2



?

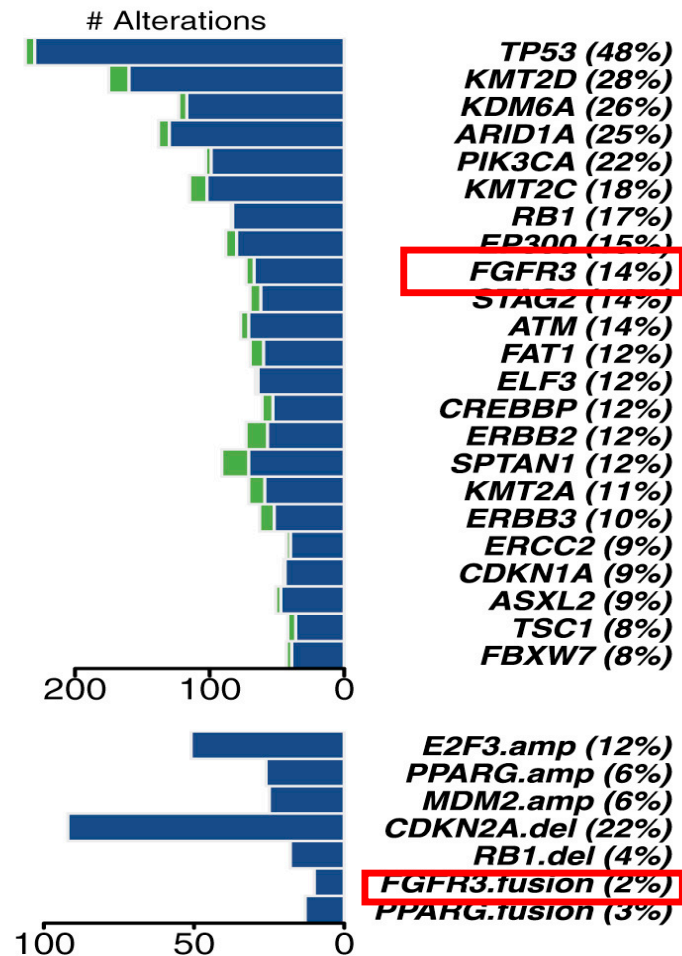
mFGFR3



Maybe?

FGFR3 Genomic Alterations in Muscle-Invasive Bladder Cancer

Genomics of MIBC: TCGA



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

Courtesy of Guru Sonpavde, MD

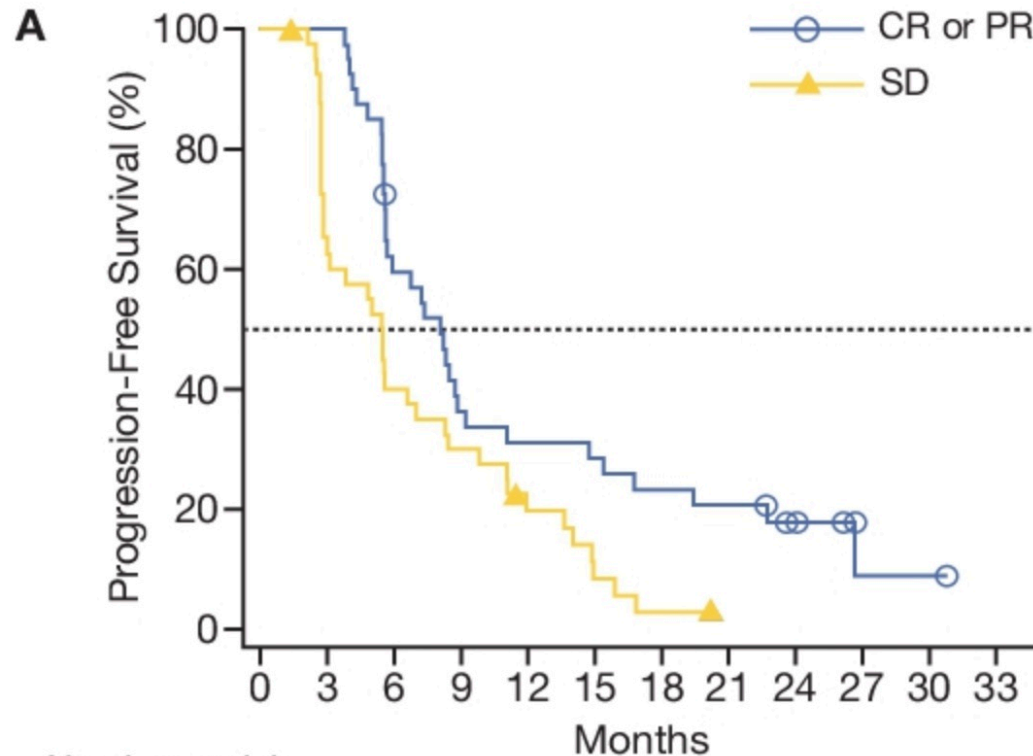
Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma (mUC): Long-Term Outcomes in BLC2001

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

BLC2001: Survival

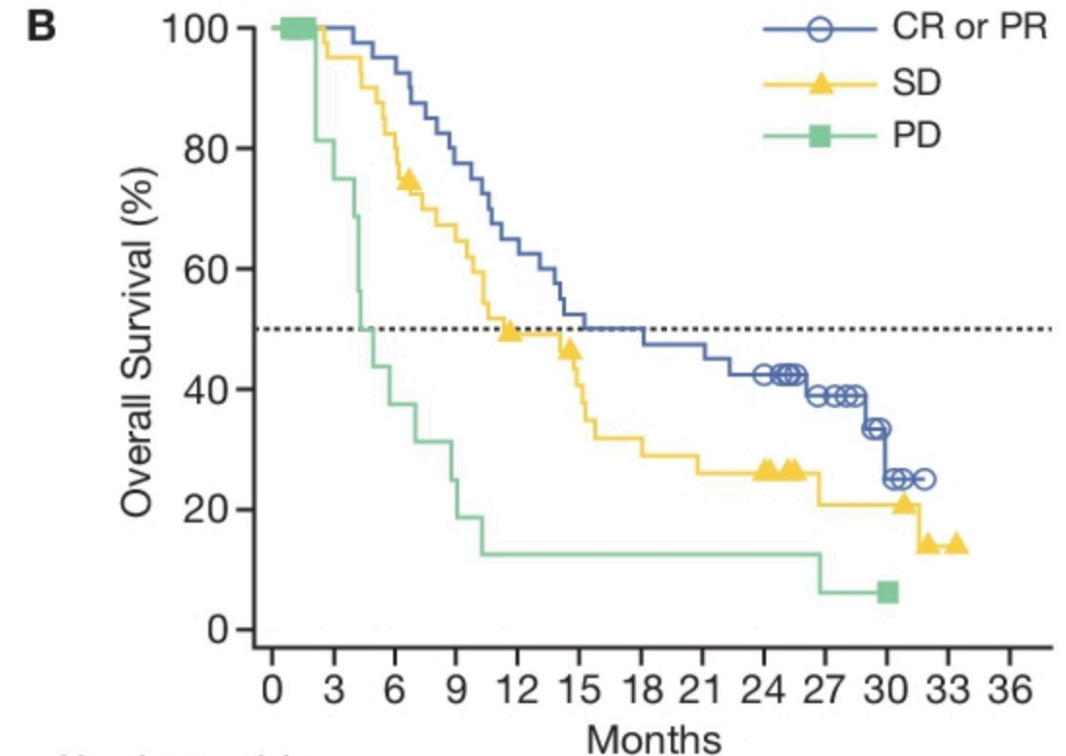
Median PFS: 5.5 months

Median OS: 11.3 months



Number at risk

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



Number at risk

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

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

Phase 2
(IMvigor 210)



N = 274

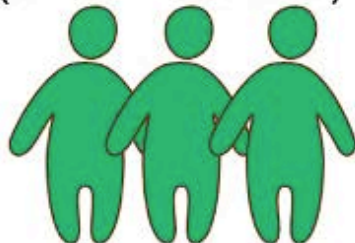
18% mFGFR

—— Objective Response Rate ——

Wild type 21% (95% CI: 16%, 27%)

Mutant 24% (95% CI: 14%, 39%)

Phase 2
(Checkmate 275)



N = 139

11% mFGFR

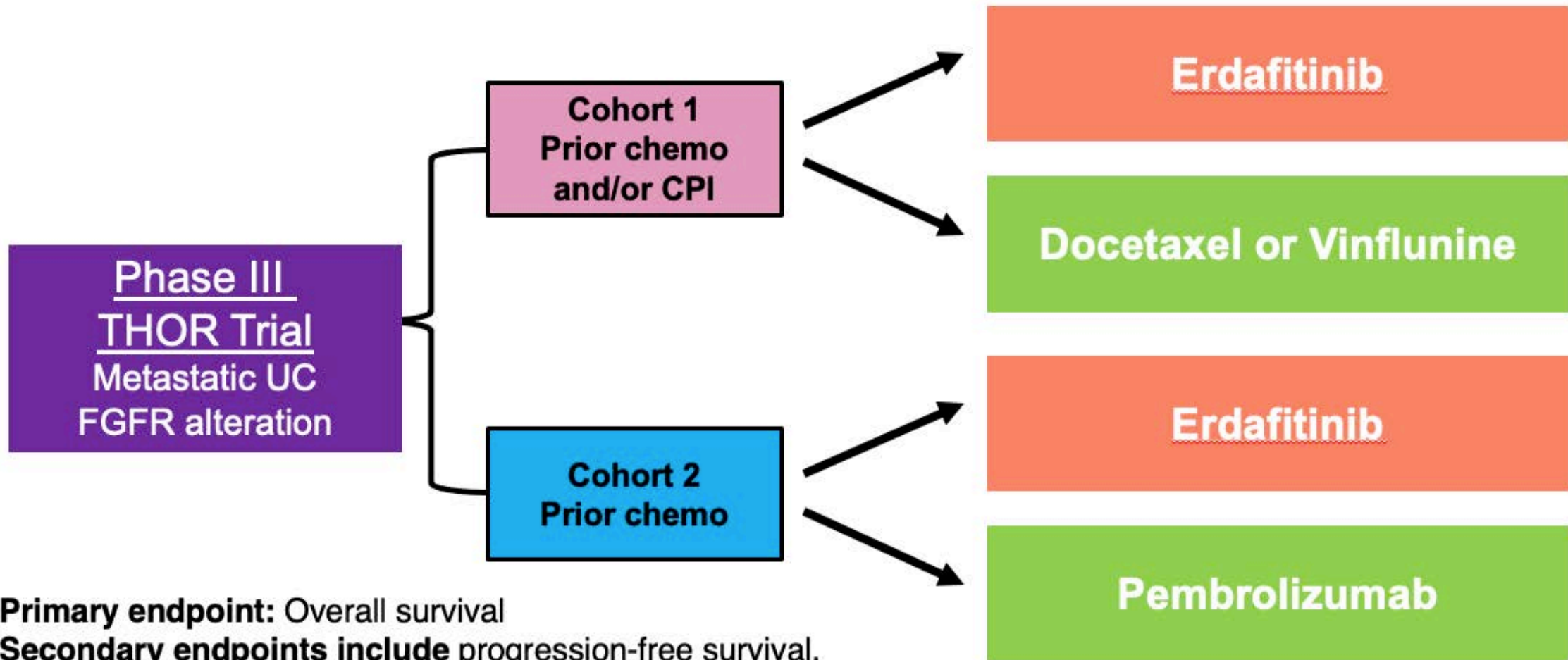
Wild type 21% (95% CI: 15%, 29%)

Mutant 21% (95% CI: 15%, 29%)

Wang, *European Urology*, 2019

Courtesy of Matthew Galsky, MD.

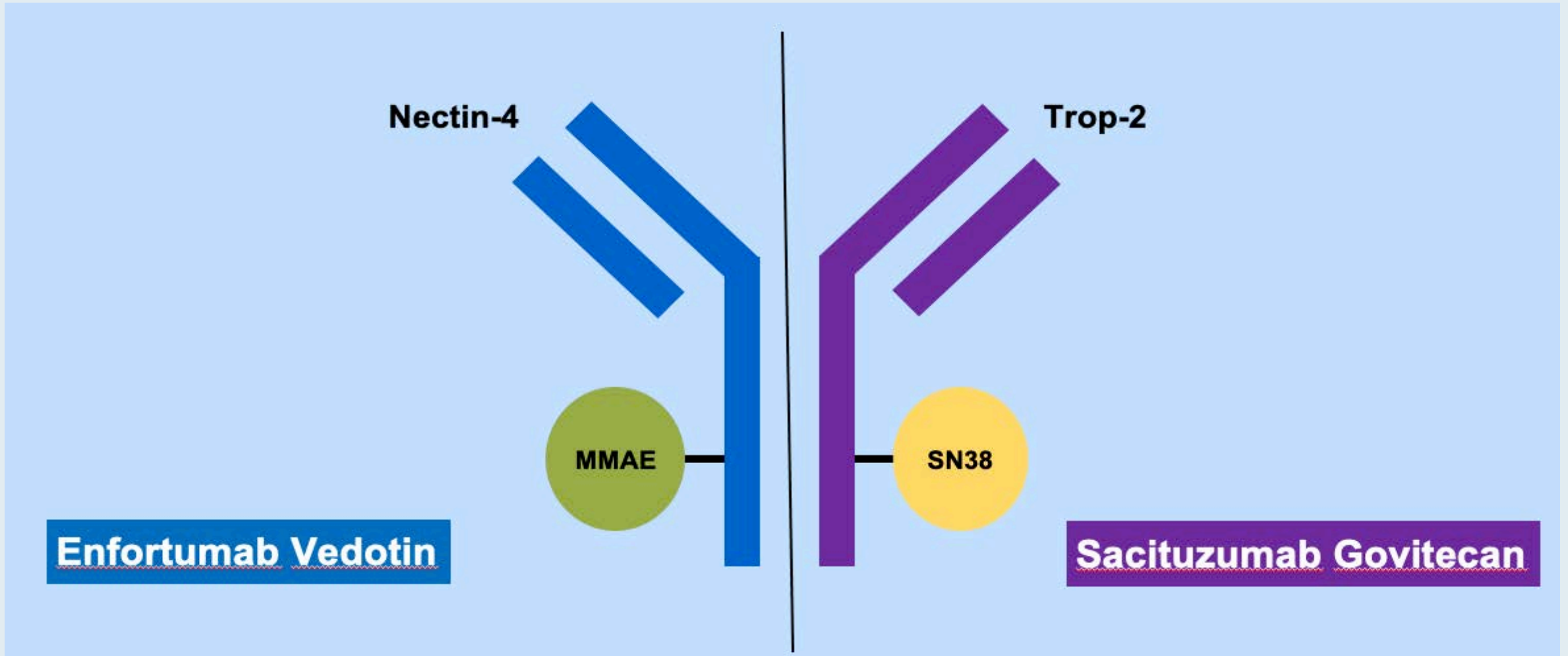
Ongoing Phase III THOR Trial Design



Primary endpoint: Overall survival

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

Antibody-Drug Conjugates in UBC



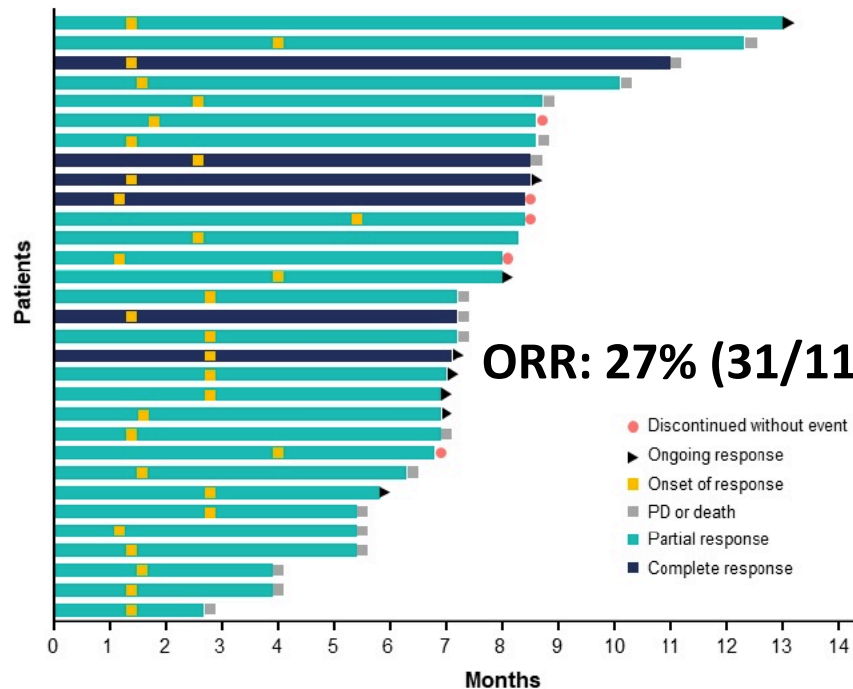
Courtesy of Matthew Galsky, MD.

Final Results from TROPHY-U-01 Cohort 1: A Phase 2 Open-Label Study of Sacituzumab Govitecan (SG) in Patients with Metastatic Urothelial Cancer (mUC) and Disease Progression After Platinum (PLT)-Based Regimens and Checkpoint Inhibitors (CPI)

Loriot Y et al.

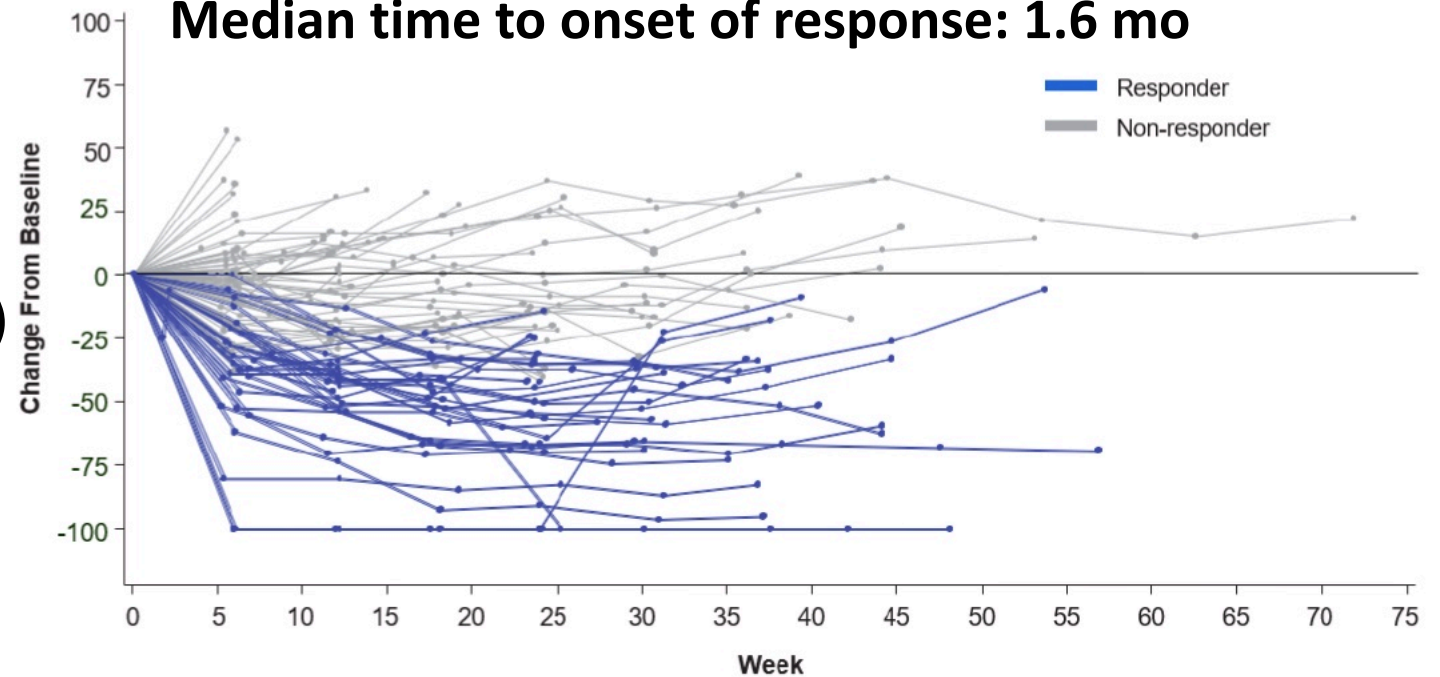
ESMO 2020;Abstract LBA24.

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



Median DOR: 5.9 mo

Median time to onset of response: 1.6 mo



- 27 of 31 responders are alive
- 8 of 31 responders have an ongoing response and are still on treatment at data cutoff

Median PFS: 5.4 mo

Median OS: 10.5 mo

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- Dr Deutsch: A 64-year-old woman with metastatic RCC

Module 3: Prostate Cancer

- Dr Grigg: A 72-year-old man with nonmetastatic castration-resistant prostate cancer
- Dr Grigg: A 58-year-old man with metastatic castration-resistant prostate cancer

Case Presentation – Dr Grigg: A 75-year-old woman and a 54-year-old woman – both with newly diagnosed metastatic clear cell RCC



Dr Claud Grigg

- 75-year-old woman (PS 1) with a left, 10-cm renal mass, with metastases to the liver and bones who has back pain and a 30-lb weight loss
- 54-year-old woman (PS 0) with a 5-cm renal mass and 3 lung nodules up to 1-cm, who had one episode of hematuria and is otherwise asymptomatic

Questions

- Absent comparative data, how to think about the differences between ipilimumab/nivolumab versus the TKI plus checkpoint inhibitor combinations?
- Now with the recent cabozantinib/nivolumab approval, how to approach the axitinib versus cabozantinib combinations?

Case Presentation – Dr Shehadeh: A 56-year-old man with metastatic clear cell RCC



Dr Nasfat Shehadeh

- 7/2020: Diagnosed with clear cell RCC, which was unresectable due to adhesion to diaphragm and colon
- 8/2020 CT: Disease progression with extension to adrenal gland and new liver lesion (IMDC: 1)
- Ipilimumab/nivolumab
- 10/2020 CT: Significant decrease in the primary and liver metastases
- Continues single-agent nivolumab

Questions

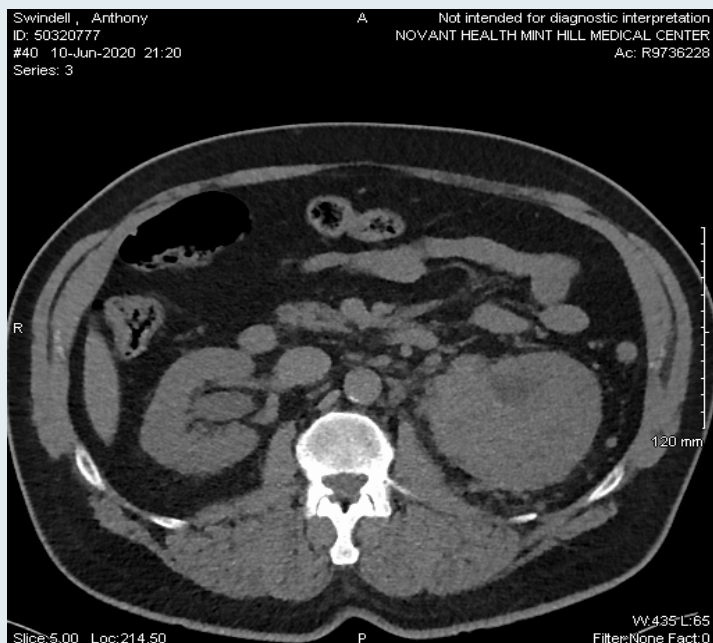
- How do you choose between a TKI and a TKI/Immunotherapy?
- What about nephrectomy – he has had a great response now?
- Should we consider nephrectomy in the era of immunotherapy? Is the CARMENA trial applicable anymore?

Case Presentation – Dr Shehadeh: A 56-year-old man with metastatic clear cell RCC — Imaging



Dr Nasfat Shehadeh

**6/2020 CT Scan
Prior to Ipi/Nivo**



**8/2020 CT Scan
PD, new liver lesion Prior to Ipi/Nivo**



**10/2020 CT Scan
After Ipi/Nivo x 4**



Case Presentation – Dr Deutsch: A 64-year-old woman with metastatic RCC



Dr Margaret Deutsch

- 10/2003: pT1N0 RCC s/p right nephrectomy
- 10/2014 CT: Biopsy-proven lung, liver and pancreatic metastases
- 11/2014: Pazopanib, with improvement in metastases
 - Severe nausea, vomiting and weight loss that persisted after dose reduction
 - 4/2019: Pazopanib discontinued
- 4/2019: Nivolumab, with PD over 2 consecutive image studies
 - Palmar rash and pruritis
- Lenvatinib/everolimus, cb by hypertension, mucositis, nausea/vomiting, palpitations
 - Patient refused to continue
- Cabozantinib initially 40 mg PO qd but hand-foot syndrome, nausea/vomiting
 - Now receiving 40 mg PO qd 2 weeks on, 2 weeks off
 - Liver lesions significantly reduced in size

Question

- What would you have used as first-line therapy now after such a long disease-free interval?

Regulatory and reimbursement issues aside, which first-line therapy would you recommend for a 65-year-old patient presenting with symptomatic metastatic clear cell RCC with extensive bone involvement?

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

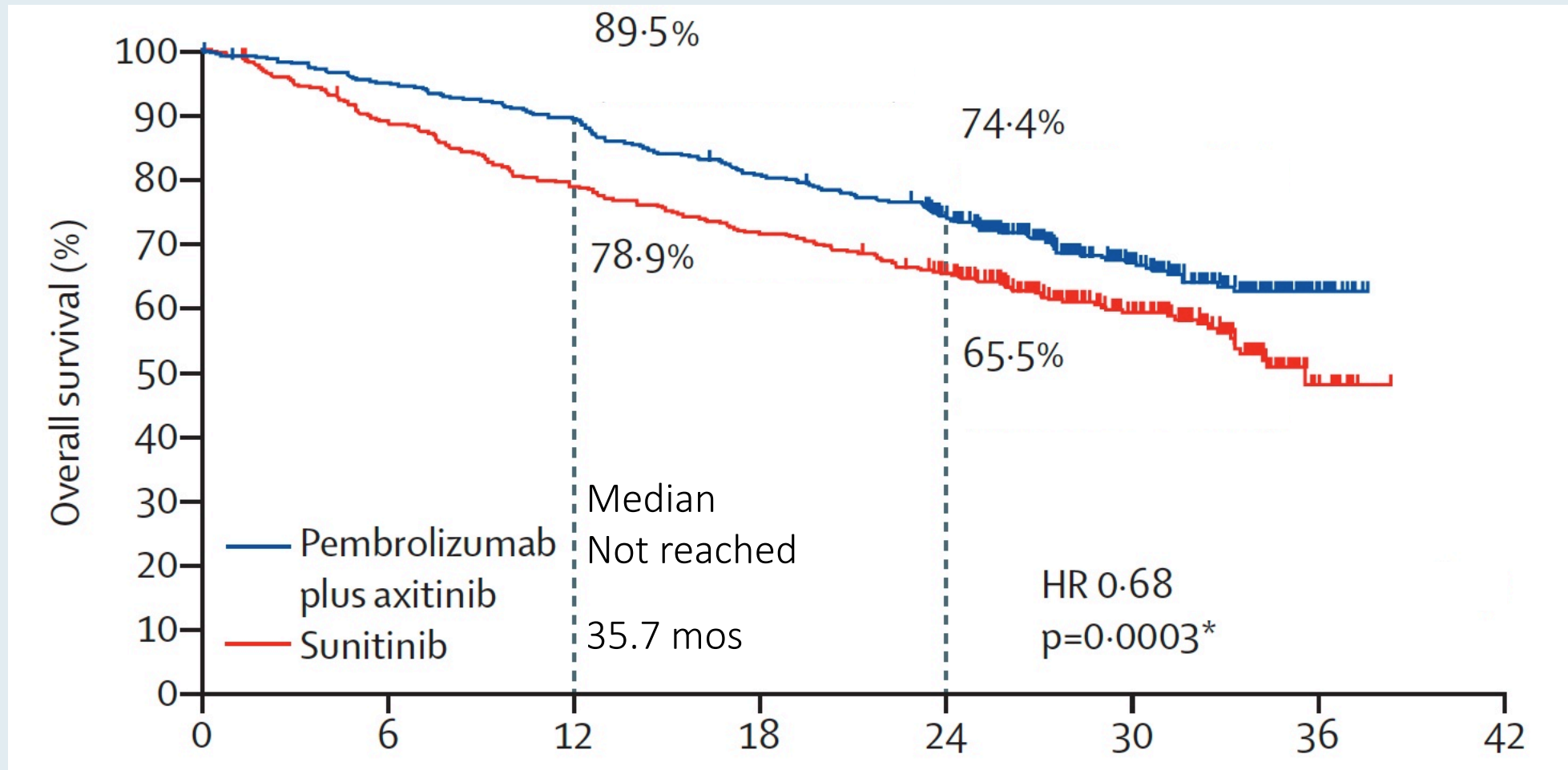
Lancet Oncol 2020;21:1563-73.

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



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

KEYNOTE-426: Overall Survival with Extended Follow-Up



ORIGINAL ARTICLE

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

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

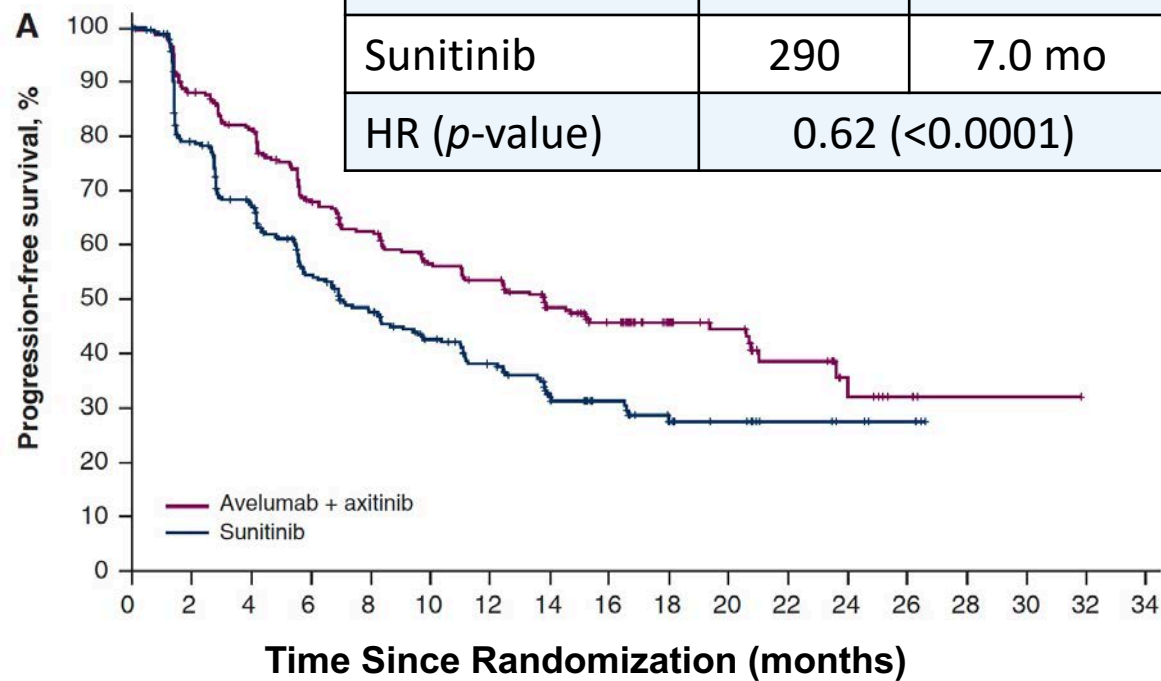
JAVELIN Renal 101: Overall Response and Best Response Rate in the PD-L1-Positive and Overall Populations

	PD-L1-Positive		Overall	
	Avelumab + Axitinib (n = 270)	Sunitinib (n = 290)	Avelumab + Axitinib (n = 442)	Sunitinib (n = 444)
Confirmed ORR	55.9%	27.2%	52.5%	27.3%
CR	5.6%	2.4%	3.8%	2.0%
PR	50.4%	24.8%	48.6%	25.2%
Stable disease	27.0%	41.4%	28.3%	43.7%
Progressive disease	11.5%	22.4%	12.4%	19.4%
Ongoing response	55.6%	53.2%	54.3%	50.4%

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

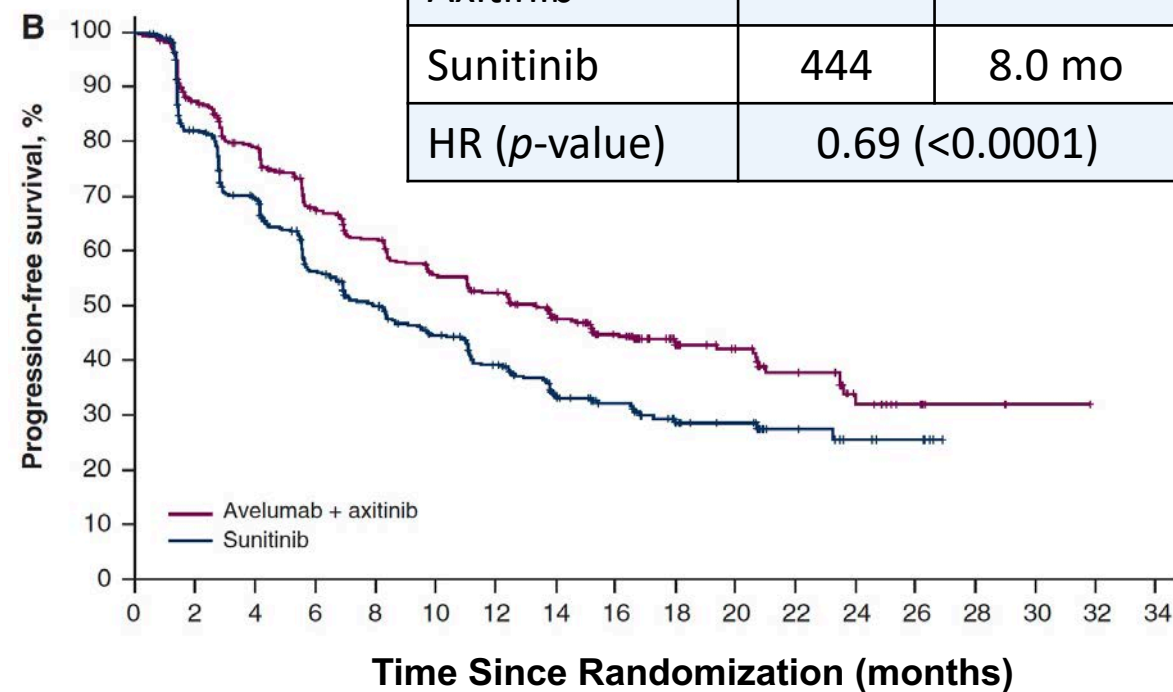
PD-L1 $\geq 1\%$ Population

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



Overall Population

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



FDA Approves Nivolumab with Cabozantinib for Advanced RCC

Press Release: January 22, 2021

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

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

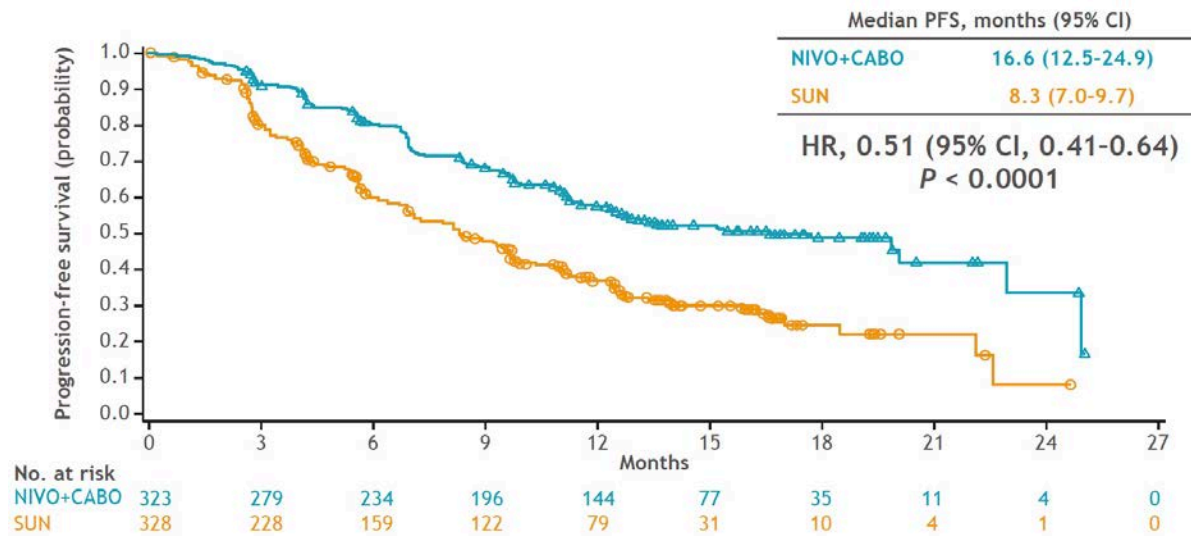
Nivolumab plus Cabozantinib versus Sunitinib in First-Line Treatment for Advanced Renal Cell Carcinoma: First Results from the Randomized Phase 3 CheckMate 9ER Trial

Choueiri TK et al.

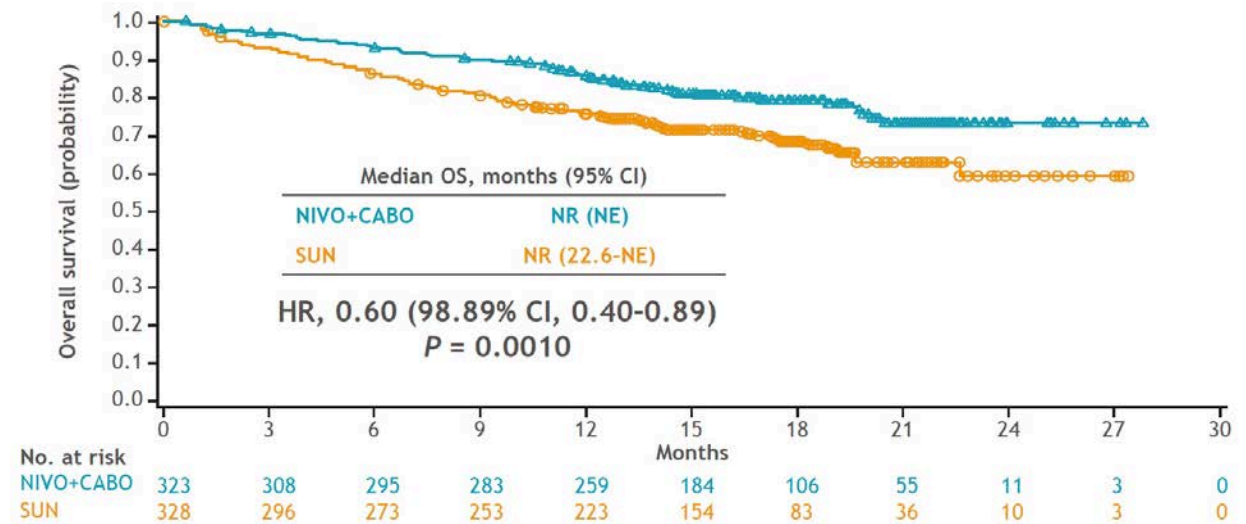
ESMO 2020;Abstract 696O.

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

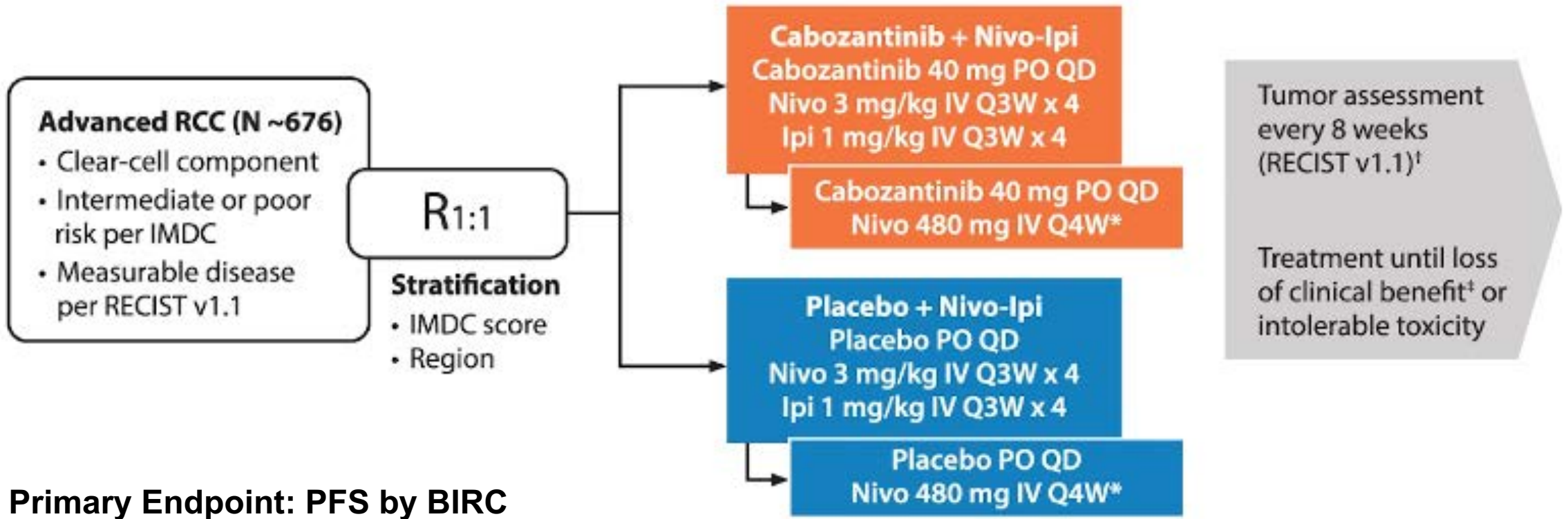
Progression-free survival per BICR



Overall survival

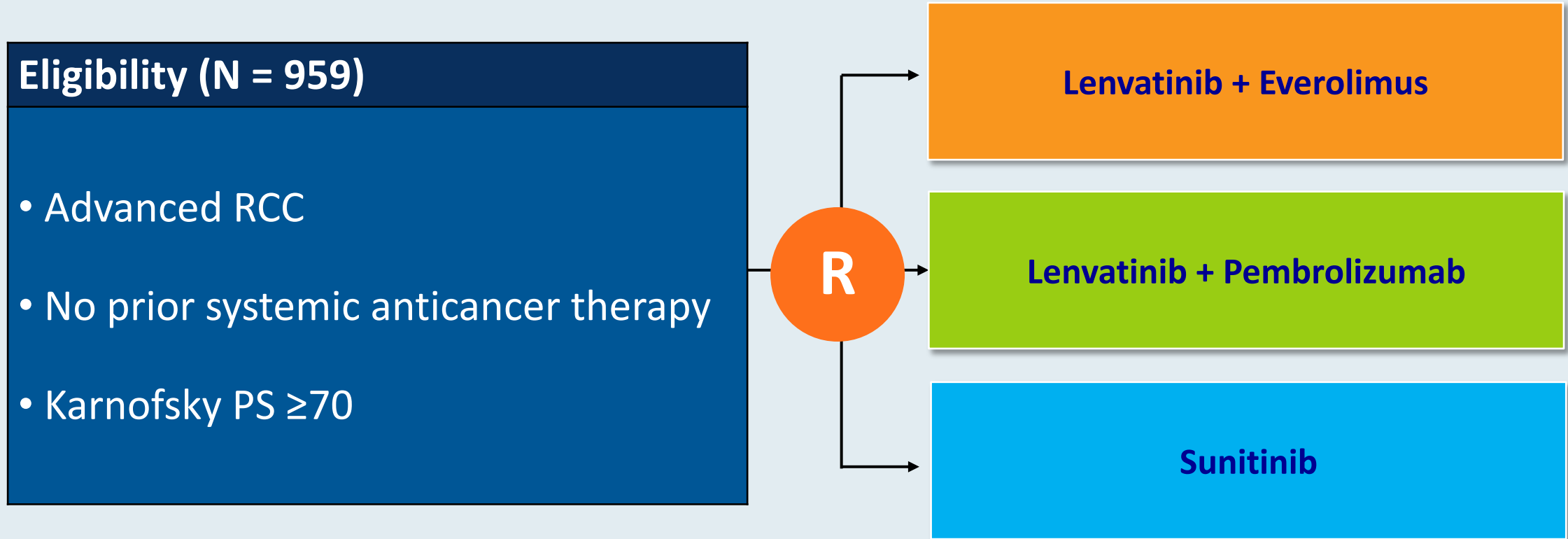


COSMIC-313 Phase III Schema



<https://www.urotoday.com/conference-highlights/asco-2020/asco-2020-kidney-cancer/121877-asco-2020-cosmic-313-phase-iii-study-of-cabozantinib-in-combination-with-nivolumab-and-ipilimumab-in-patients-with-previously-untreated-advanced-renal-cell-carcinoma-of-intermediate-or-poor-risk.html>

Ongoing Phase III KEYNOTE-581/CLEAR (Study 307) Trial Design



Primary endpoint: PFS

Secondary endpoints include: OS, Objective Response, Safety

Top-Line Results from the Pivotal Phase III KEYNOTE-581 (CLEAR) Trial

Press Release: November 10, 2020

“New investigational data were announced demonstrating positive top-line results from the pivotal Phase 3 KEYNOTE-581/CLEAR trial (Study 307). In the trial, the combinations of pembrolizumab plus lenvatinib, the orally available multiple receptor tyrosine kinase inhibitor, and LENVIMA plus everolimus were evaluated versus sunitinib for the first-line treatment of patients with advanced RCC. Pembrolizumab plus lenvatinib met the trial’s primary endpoint of PFS and its key secondary endpoints of OS and objective response rate (ORR), demonstrating a statistically significant and clinically meaningful improvement in PFS, OS and ORR versus sunitinib in the intention-to-treat (ITT) study population.

Lenvatinib plus everolimus also met the trial’s primary endpoint of PFS and a key secondary endpoint of ORR, demonstrating a statistically significant and clinically meaningful improvement in PFS and ORR versus sunitinib in the ITT study population. The ITT population included patients across all Memorial Sloan Kettering Cancer Center (MSKCC) risk groups (favorable, intermediate and poor).

The safety profiles of both pembrolizumab plus lenvatinib and lenvatinib plus everolimus were consistent with previously reported studies.”

Phase 3 Trial of Lenvatinib (LEN) plus Pembrolizumab (PEMBRO) or Everolimus (EVE) versus Sunitinib (SUN) Monotherapy as a First-line Treatment for Patients (pts) with Advanced Renal Cell Carcinoma (RCC) (CLEAR study)

Motzer RJ et al.

Genitourinary Cancers Symposium 2021;Abstract 269.

CLEAR: Response and Survival Analyses

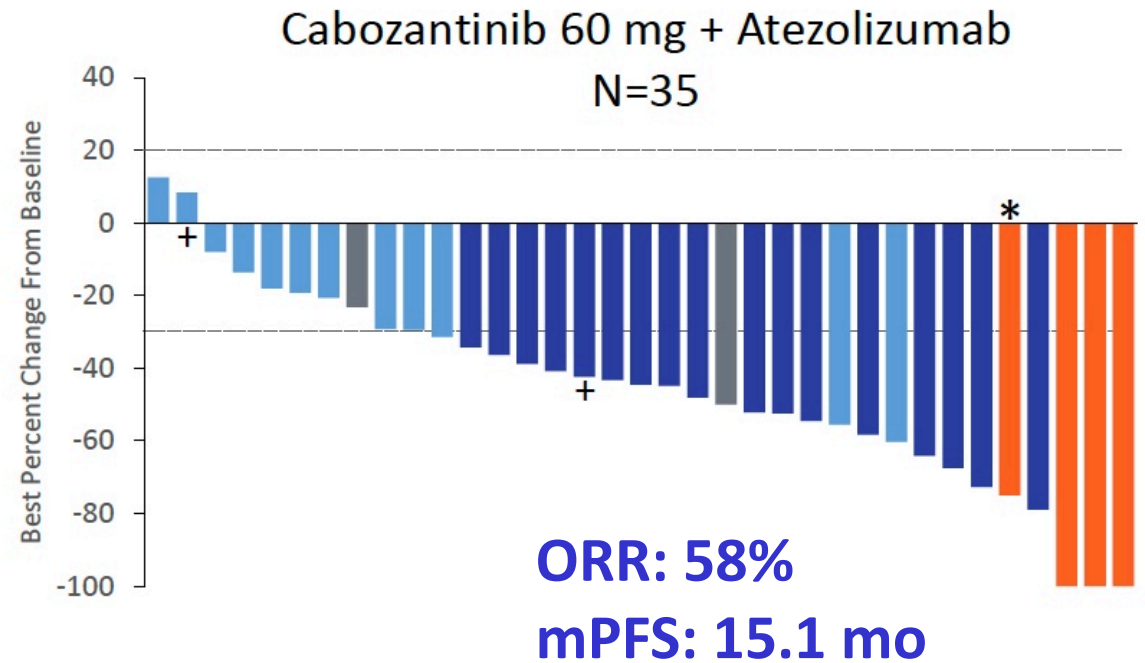
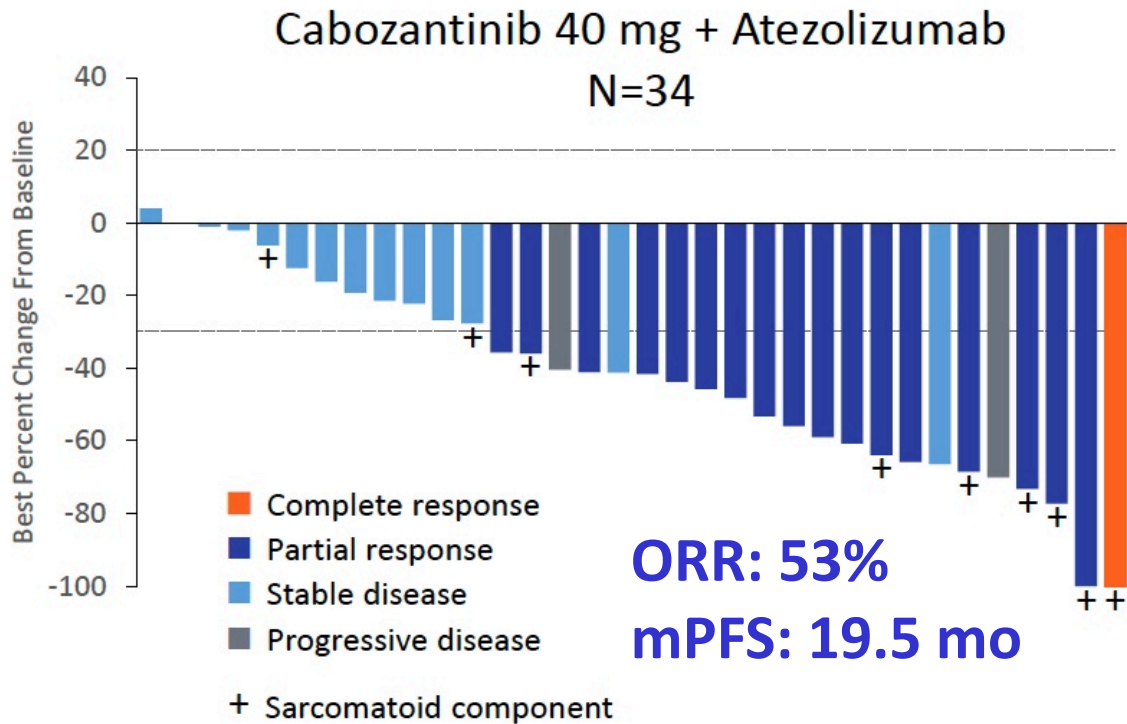
	LEN + PEMBRO (n = 355)	LEN + EVE (n = 357)	SUNITINIB (n = 357)
Median PFS	24 mo	15 mo	9 mo
PFS HR vs SUN; <i>P</i> -value	0.39 <i>p</i> < 0.0001	0.65 <i>p</i> < 0.0001	—
Median OS	NR	NR	NR
OS HR vs SUN; <i>P</i> -value	0.66 <i>p</i> = 0.0049	1.15 <i>p</i> = 0.2975	—
24-Month OS rate	79%	66%	70%
ORR	71%	54%	36%
ORR odds ratio vs SUN; Descriptive <i>P</i> -value	4.35 <i>p</i> < 0.0001	2.15 <i>p</i> < 0.0001	—
Complete response	16%	10%	4%
Median DOR	26 mo	17 mo	15 mo

Cabozantinib (C) in Combination with Atezolizumab (A) as First-Line Therapy for Advanced Clear Cell Renal Cell Carcinoma (ccRCC): Results from the COSMIC-021 Study

Pal S et al.

ESMO 2020;Abstract 7020.

COSMIC-021: Cabozantinib/Atezolizumab in Previously Untreated Advanced ccRCC



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

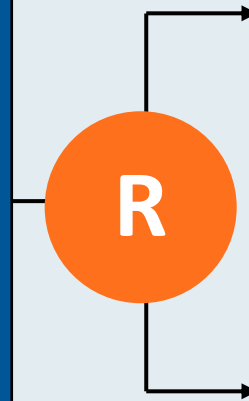
Anita Gul, MD¹; Tyler F. Stewart, MD^{2,3}; Charlene M. Mantia, MD⁴; Neil J. Shah, MD⁵; Emily Stern Gatof, MD⁴; Ying Long, PharmD²; Kimberly D. Allman, MSN, CNP¹; Moshe C. Ornstein, MD, MA¹; Hans J. Hammers, MD, PhD⁶; David F. McDermott, MD⁴; Michael B. Atkins, MD⁵; Michael Hurwitz, MD, PhD²; and Brian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

J Clin Oncol 2020;38:3088-94.

Ongoing Phase III CONTACT-03 Trial Design

Eligibility (N = 500)

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



**Atezolizumab
+
Cabozantinib**

Cabozantinib

Primary endpoints: PFS and OS

Secondary endpoints include: Objective Response, Duration of Response

Agenda

Module 1: Urothelial Bladder Cancer (UBC)

- Dr Grigg: A 79-year-old man with metastatic UBC – FGFR alteration
- Dr Grigg: A healthy 71-year-old man with high-risk non-muscle-invasive UBC

Module 2: Renal Cell Carcinoma (RCC)

- Dr Grigg: A 75-year-old woman and a 54-year-old woman – both with newly diagnosed metastatic clear cell RCC
- Dr Shehadeh: A 56-year-old man with metastatic clear cell RCC
- Dr Deutsch: A 64-year-old woman with metastatic RCC

Module 3: Prostate Cancer

- Dr Grigg: A 72-year-old man with nonmetastatic castration-resistant prostate cancer
- Dr Grigg: A 58-year-old man with metastatic castration-resistant prostate cancer

Case Presentation – Dr Grigg: A 72-year-old man with nonmetastatic castration-resistant prostate cancer



Dr Claud Grigg

- 2012: Diagnosed with pT2b, Gleason 8 adenocarcinoma of the prostate s/p radical prostatectomy
- PSA undetectable until 2016, when ADT was initiated
- Past 6 months, PSA rising despite castrate testosterone levels
- Currently, PSA: 1.1 ng/mL and the patient is anxious to “do something”
- Plan: Initiate oral anti-androgens when PSA > 2 ng/mL

Questions

- Is it true that darolutamide does not cross the blood-brain-barrier and has less cognitive symptoms and fatigue than the other oral anti-androgens? How does darolutamide compare to enzalutamide and apalutamide in terms of other side effects?

Case Presentation – Dr Grigg: A 58-year-old man with metastatic castration-resistant prostate cancer



Dr Claud Grigg

- Metastatic CRPC, with numerous bone metastases as well as liver and pelvic nodal metastases
- Germline testing: gBRCA2 mutation
- PSA rising with PSADT: 2 months after 8 months of front-line ADT + abiraterone/prednisone
 - Increasing back pain at sites of disease

Questions

- Would you treat this patient first with a PARP inhibitor, or docetaxel?
- Is there a role for carboplatin in patients with prostate cancer and homologous recombination deficiencies? If so, would you use it as a single-agent, or combine it with a taxane?
- Do you treat patients with germline versus somatic BRCA2 mutations differently? Are their responses to PARP inhibitors durable?
- When would you offer a PARP inhibitor for non-BRCA1 or BRCA2 mutations that are known to impact homologous recombination repair? Are there any specific mutations in which PARP inhibitors are more or less likely to be effective against?

Regulatory and reimbursement issues aside, what systemic therapy, if any, would you typically add to androgen deprivation therapy (ADT) for a 65-year-old patient who underwent radical prostatectomy for Gleason 8 prostate cancer but presents 3 years later with 3 asymptomatic bone metastases that are not amenable to ablative therapy?

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

FDA Approves Relugolix for Advanced Prostate Cancer

Press Release: December 18, 2020

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

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

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

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

Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer²

¹ Shore N et al.

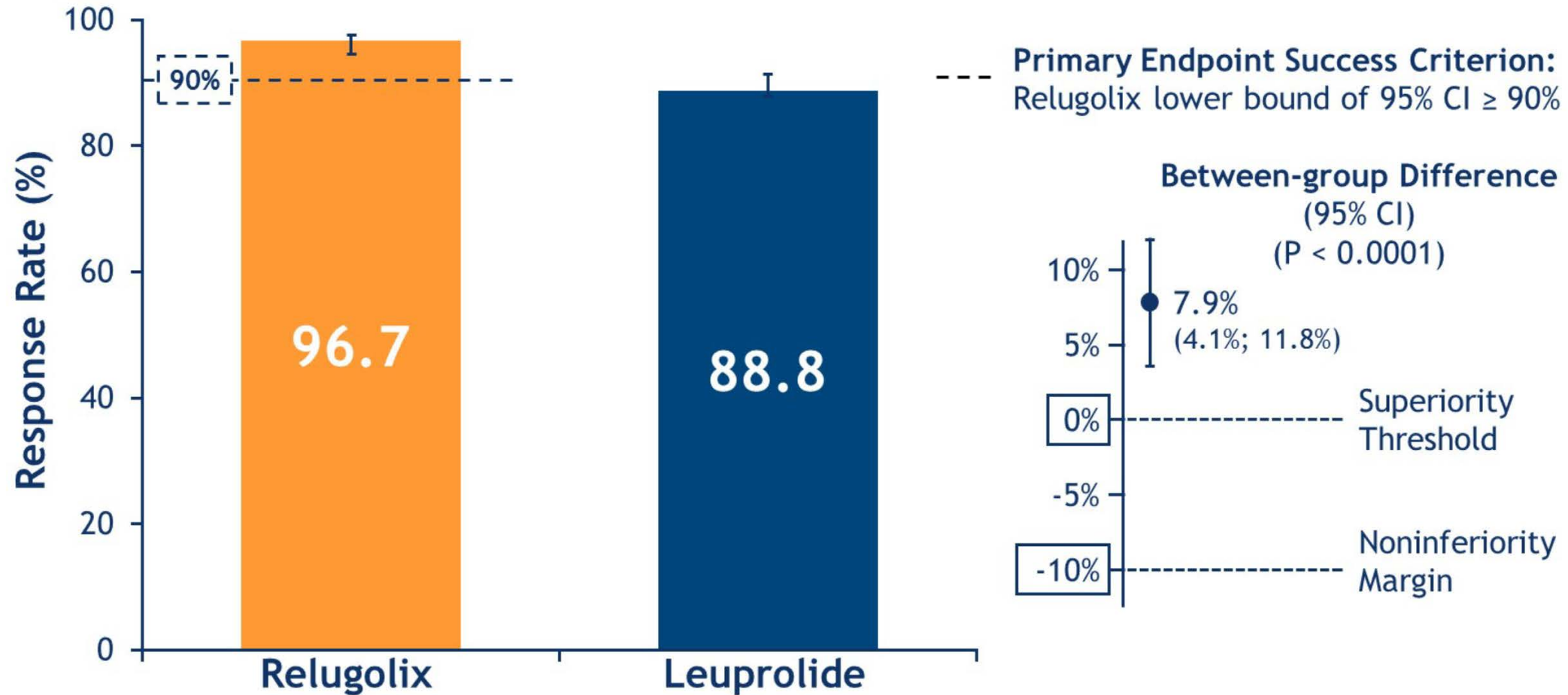
ASCO 2020;Abstract 5602.

² Shore ND et al.

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

HERO: Primary Endpoint – Sustained Castration

Key Secondary Endpoint – Noninferiority to Leuprolide



Recent FDA Approvals of Next-Generation Antiandrogens in Nonmetastatic Castration-Resistant Prostate Cancer

Agent	Approval date	Pivotal study
Darolutamide	July 30, 2020	ARAMIS
Enzalutamide	July 12, 2018	PROSPER
Apalutamide	February 14, 2018	SPARTAN

The NEW ENGLAND JOURNAL of MEDICINE

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

ORIGINAL ARTICLE

Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide

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

The NEW ENGLAND JOURNAL of MEDICINE

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

ORIGINAL ARTICLE

Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer

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



European Association of Urology

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

Prostate Cancer

Apalutamide and Overall Survival in Prostate Cancer

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

Survival: Darolutamide, Enzalutamide, Apalutamide

	ARAMIS ¹	PROSPER ²	SPARTAN ³
Antiandrogen	Darolutamide	Enzalutamide	Apalutamide
Median follow-up	49 mo	47 mo	52 mo
Median OS	Not estimated	57 vs 56 mo	74 vs 60 mo
OS hazard ratio (<i>p</i> -value)	0.69	0.73	0.78

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

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

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

Comparison of Toxicities: Darolutamide, Enzalutamide, Apalutamide

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

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

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

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

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

Press Release: December 1, 2020

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

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

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

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

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

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

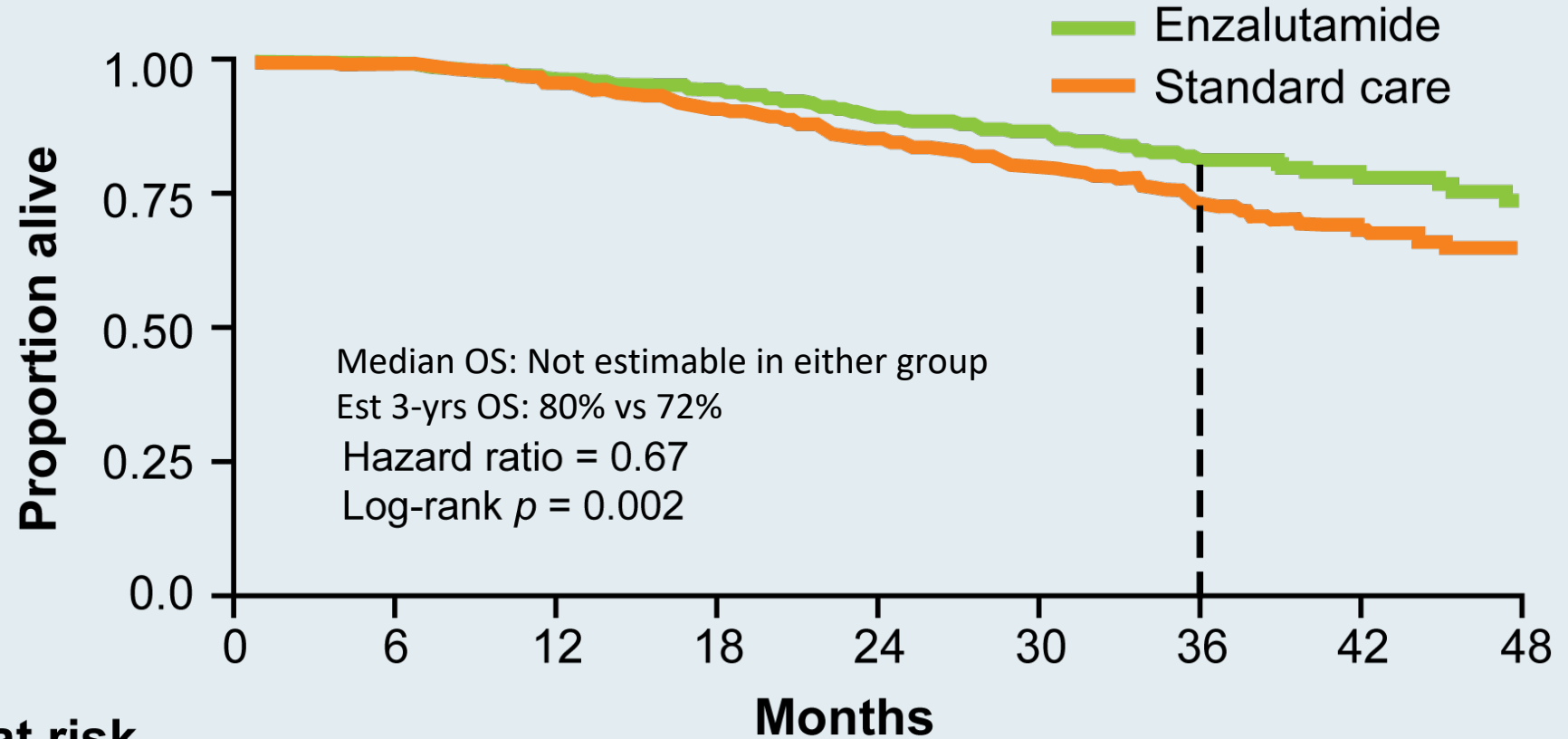
	ARCHES (N = 1,150)		TITAN (N = 1,052)	
Characteristics	<ul style="list-style-type: none"> 2/3rd high volume 17% prior docetaxel 25% prior RP/XRT 		<ul style="list-style-type: none"> 2/3rd high volume 10% prior docetaxel 17% prior RP/XRT 	
	ADT + enzalutamide (n = 574)	ADT (n = 576)	ADT + apalutamide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

NR = not reached

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

A Mixed Bag

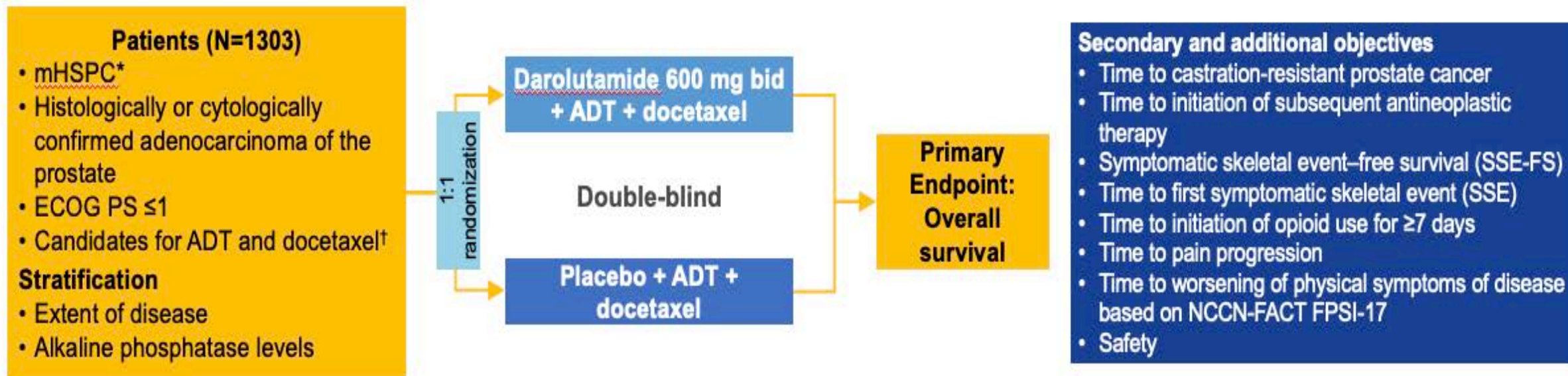
- High and Low Volume
- *De novo* vs Metach
- Concurrent Docetaxel
- Many Permutations



Number at risk

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

Phase III ARASENS Trial Design



Background treatments:

- ADT at investigators' choice (including orchiectomy)
- Docetaxel: 6 cycles (in combination with prednisone/prednisolone at the discretion of the investigator) to be administered after randomization

Enrolment completed in June 2018

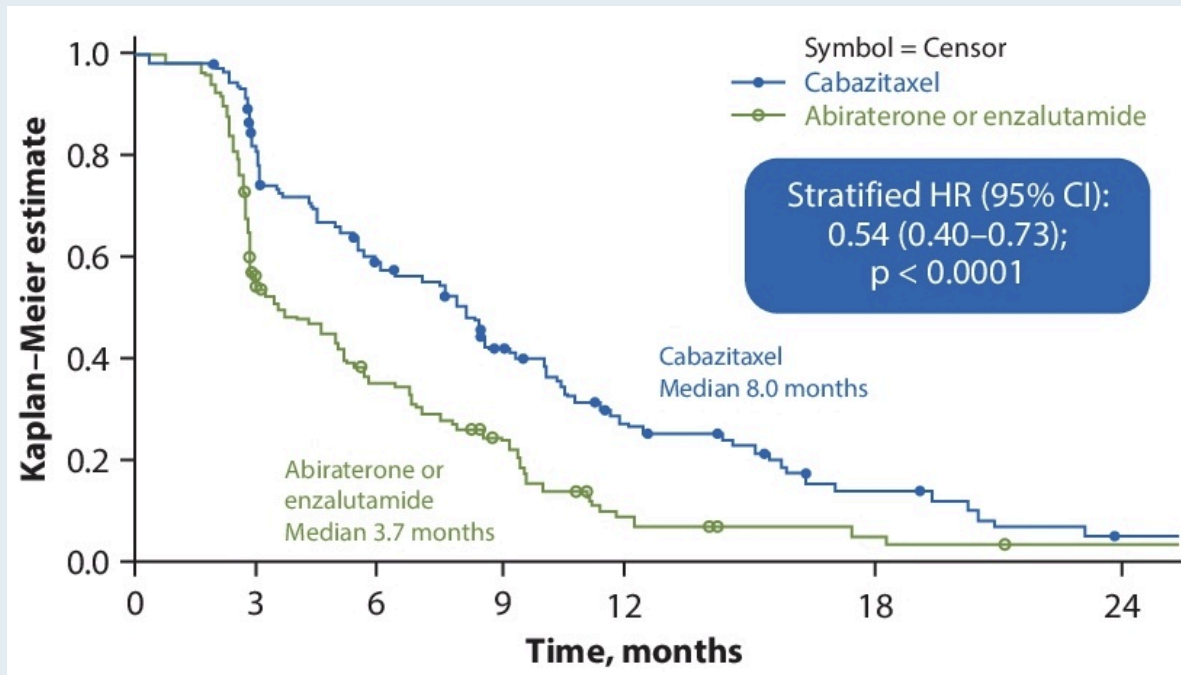
CARD: Overall Survival Analysis of Patients with Metastatic Castration-Resistant Prostate Cancer Receiving Cabazitaxel vs Abiraterone or Enzalutamide

Tombal B et al.

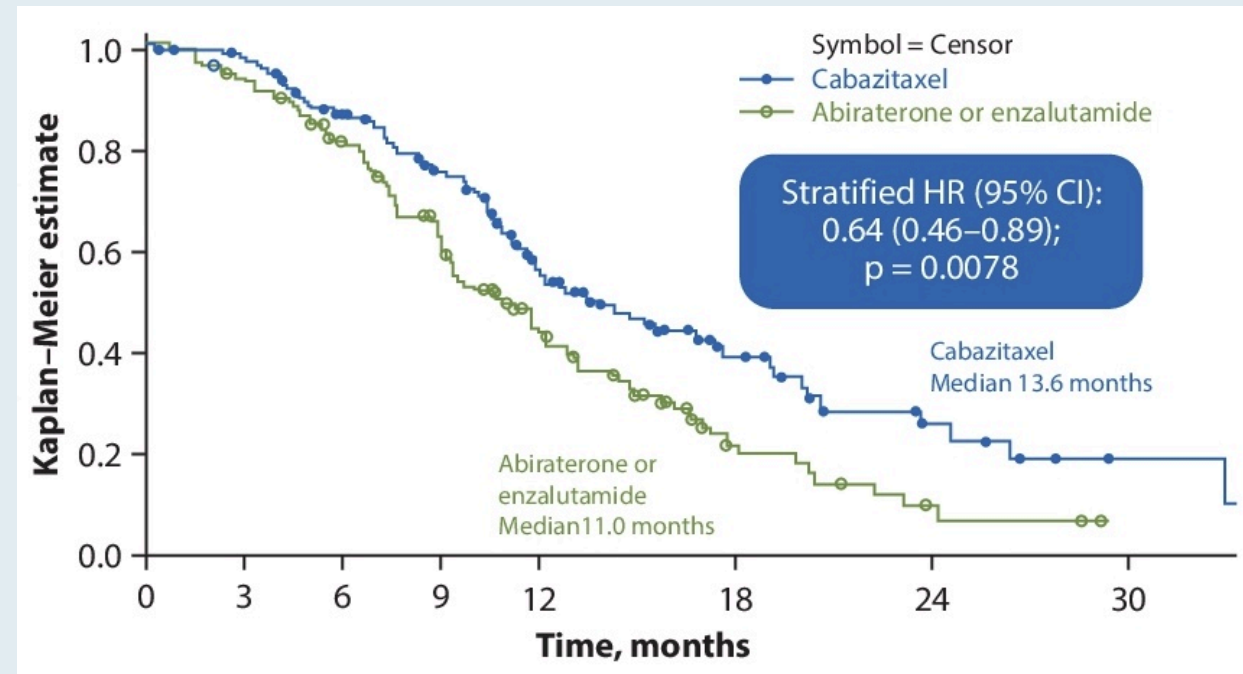
ASCO 2020;Abstract 5569.

CARD Study of Cabazitaxel: Survival Analyses

rPFS (primary endpoint)



OS (key secondary endpoint)



Results Presented from Phase III ACIS Study for Metastatic Castration-Resistant Prostate Cancer Treated with Combination Apalutamide and Abiraterone Acetate

Press Release – February 8, 2021

“The randomized, double-blind, placebo-controlled Phase 3 ACIS study met the primary endpoint of radiographic progression-free survival (rPFS) with a 31 percent reduction in the risk of radiographic progression or death in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) receiving androgen deprivation therapy (ADT). Patients in the trial received either a combination of apalutamide and abiraterone plus prednisone (combination arm) or placebo and abiraterone plus prednisone (control arm).

The primary efficacy analysis showed median rPFS was extended by six months in patients treated in the combination arm compared with patients in the control arm (22.6 vs. 16.6 months; hazard ratio [HR] 0.69; $p < 0.0001$). The HR for radiographic progression or death as assessed by blinded independent central review (BICR) was 0.864. According to an updated analysis performed at a median follow-up of 54.8 months, a 30 percent reduction in the risk of radiographic progression or death was shown in the combination arm compared with the control arm (median time to rPFS 24 vs. 16.6 months: HR 0.70).”

<https://www.prnewswire.com/news-releases/janssen-presents-results-from-phase-3-acis-study-in-patients-with-metastatic-castration-resistant-prostate-cancer-treated-with-erleada-apalutamide-and-zytiga-abiraterone-acetate-combination-301224287.html>

Final Results from ACIS, a Randomized, Placebo (PBO)-Controlled Double-Blind Phase 3 Study of Apalutamide (APA) and Abiraterone Acetate plus Prednisone (AAP) versus AAP in Patients (pts) with Chemo-naïve Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Rathkopf DE et al.

Genitourinary Cancers Symposium 2021;Abstract 9.

ACIS: Survival and Response Analyses

Endpoint	APA + AAP (n = 492)	AAP (n = 490)	HR	<i>p</i> -value
Median rPFS	22.6 mo	16.6 mo	0.69	<0.0001
PSA response (≥ 50% decline)	79.5%	72.9%	1.09	0.015
Median OS	36.2 mo	33.7 mo	0.95	0.498

FDA Approves Olaparib for HRR Gene-Mutated mCRPC

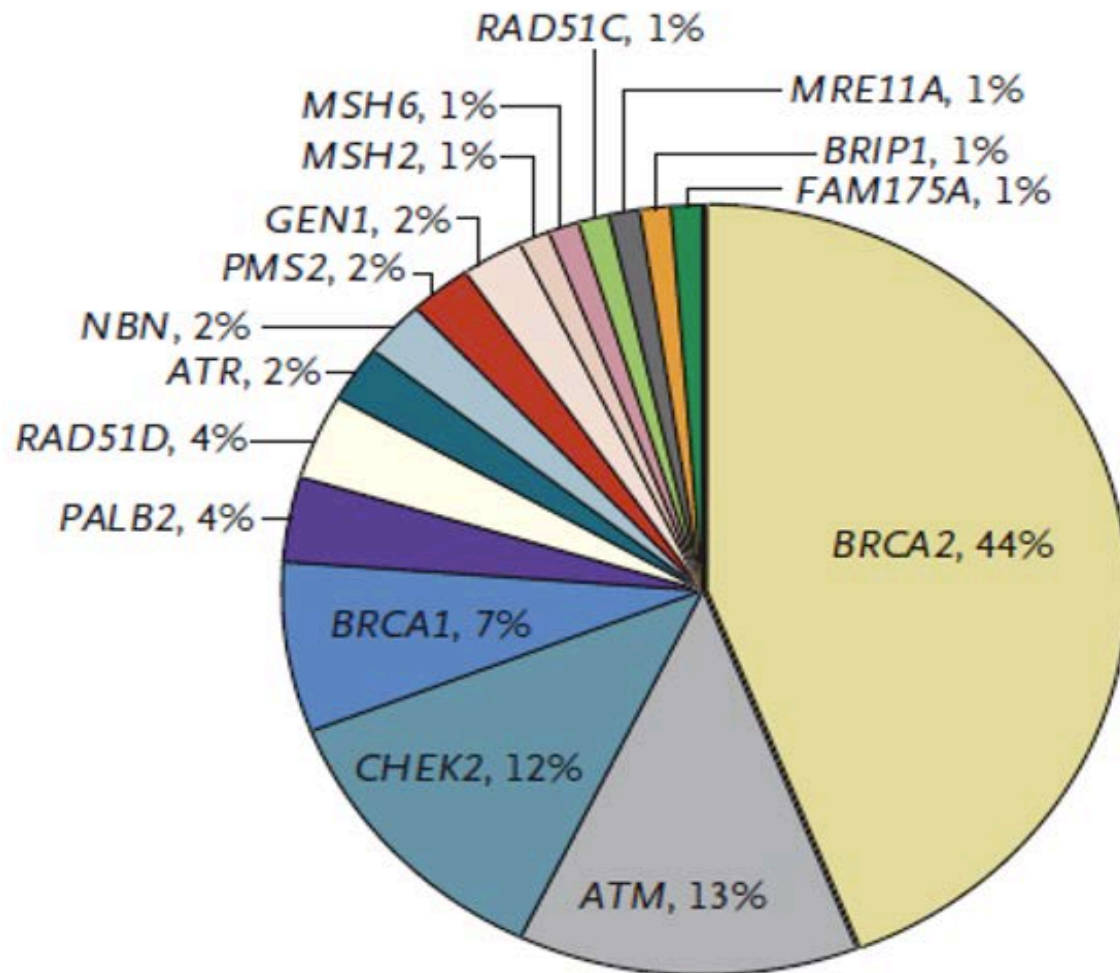
Press Release: May 19, 2020

“On May 19, 2020, the U.S. Food and Drug Administration approved approved olaparib for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), who have progressed following prior treatment with enzalutamide or abiraterone.

The FDA also approved FoundationOne CDx for selection of patients with mCRPC carrying HRR gene alterations and BRACAnalysis CDx test for selection of patients with mCRPC carrying germline *BRCA1/2* alterations as companion diagnostic devices for treatment with olaparib.

Efficacy was investigated in PROfound (NCT02987543), an open-label, multicenter trial randomizing (2:1) 256 patients to olaparib 300 mg twice daily and 131 patients to investigator’s choice of enzalutamide or abiraterone acetate. All patients received a GnRH analog or had prior bilateral orchiectomy.”

Inherited DNA Repair Gene Mutations in Men with mPC



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

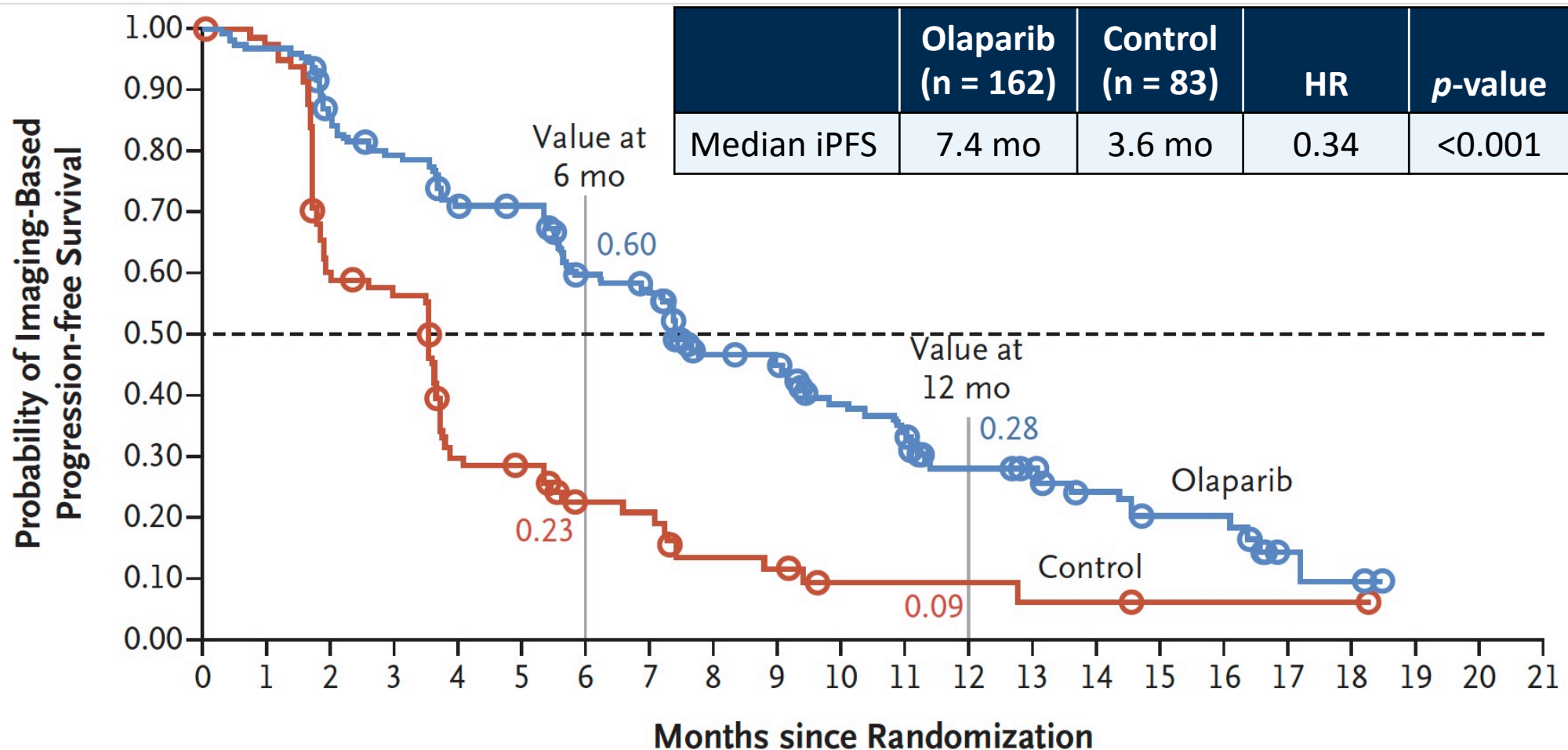
ORIGINAL ARTICLE

Olaparib for Metastatic Castration-Resistant Prostate Cancer

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

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

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



ORIGINAL ARTICLE

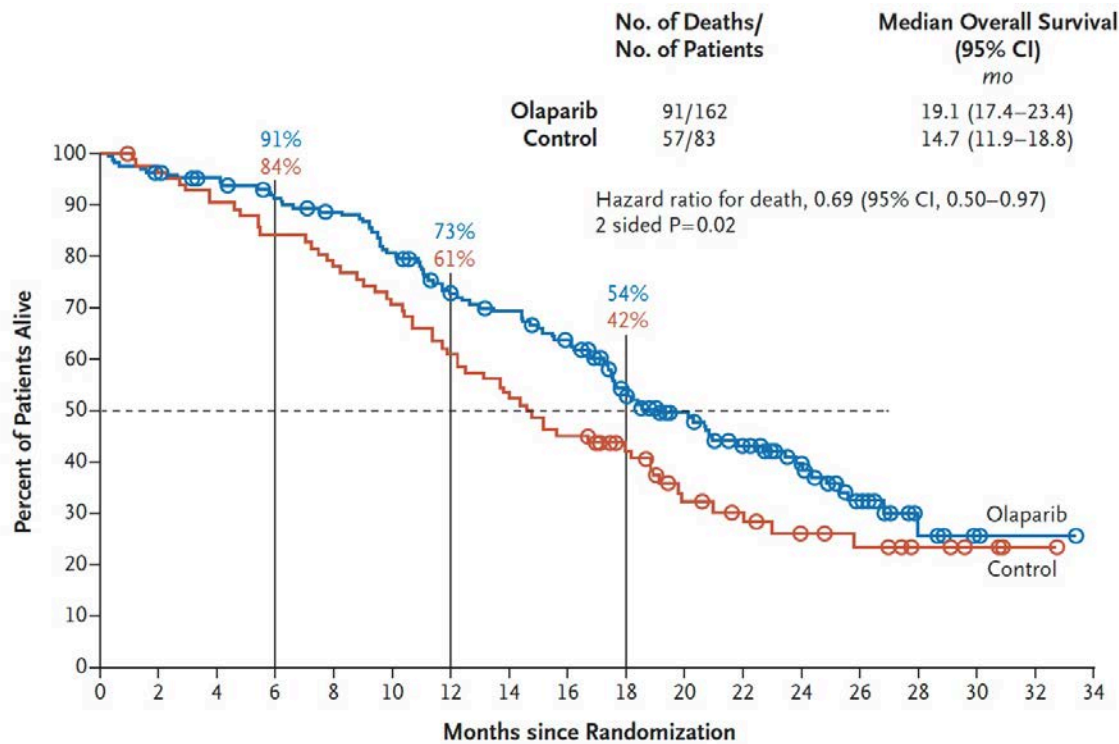
Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

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

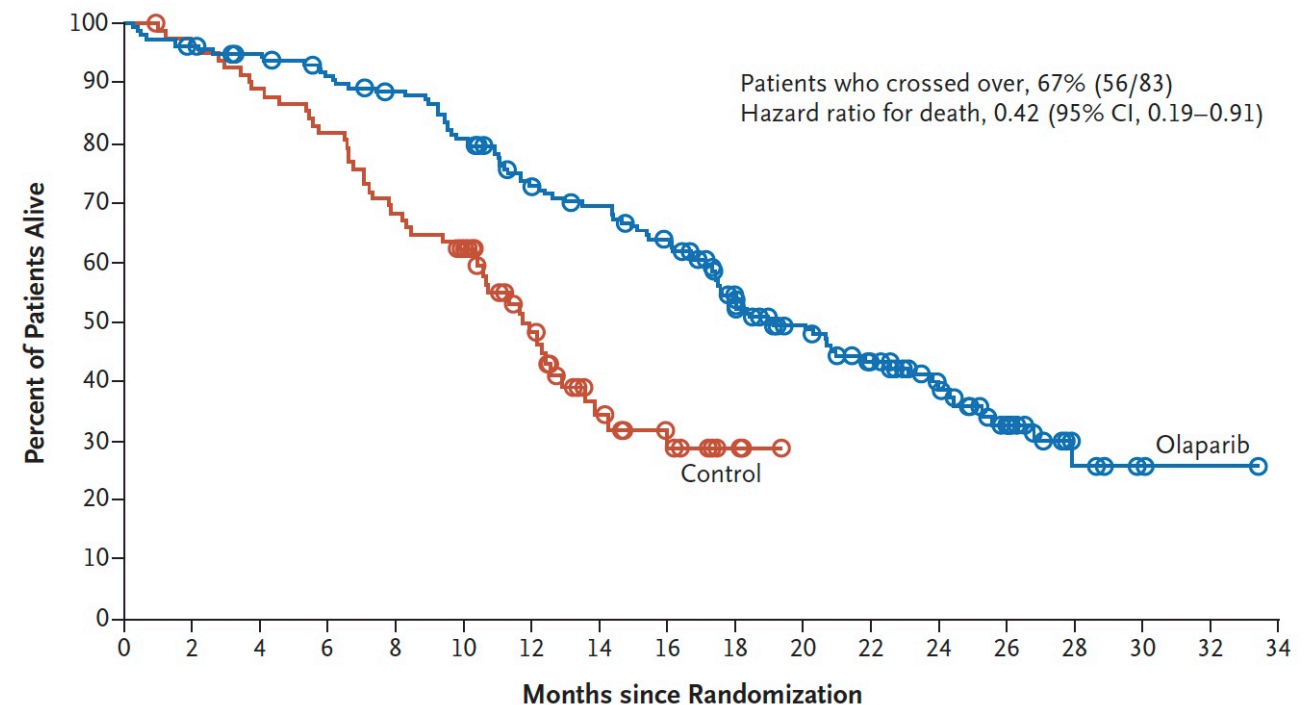
***N Engl J Med* 2020;383(24):2345-57.**

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

Overall survival



Cross-over adjusted overall survival



FDA Approves Rucaparib for mCRPC with BRCA Mutation

Press Release: August 26, 2020

Press Release: May 15, 2020

“On August 26, 2020, the Food and Drug Administration approved the liquid biopsy next-generation sequencing-based Liquid CDx test as a companion diagnostic to identify mutations in *BRCA1* and *BRCA2* genes in cell free-DNA isolated from plasma specimens from patients with mCRPC eligible for treatment with rucaparib.”

“On May 15, 2020, the Food and Drug Administration granted accelerated approval to rucaparib for patients with deleterious *BRCA* mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.

Efficacy was investigated in TRITON2 (NCT02952534), an ongoing, multi-center, single arm clinical trial in 115 patients with *BRCA*-mutated (germline and/or somatic) mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. Patients received rucaparib 600 mg orally twice daily and concomitant GnRH analog or had prior bilateral orchiectomy.”

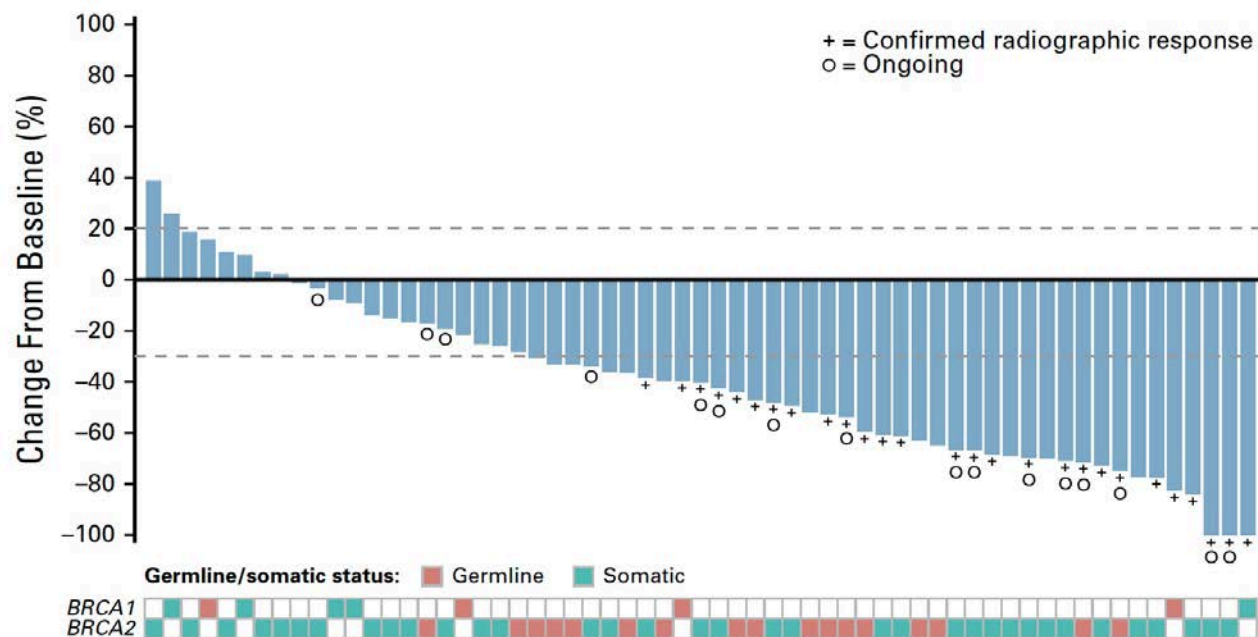
Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration

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

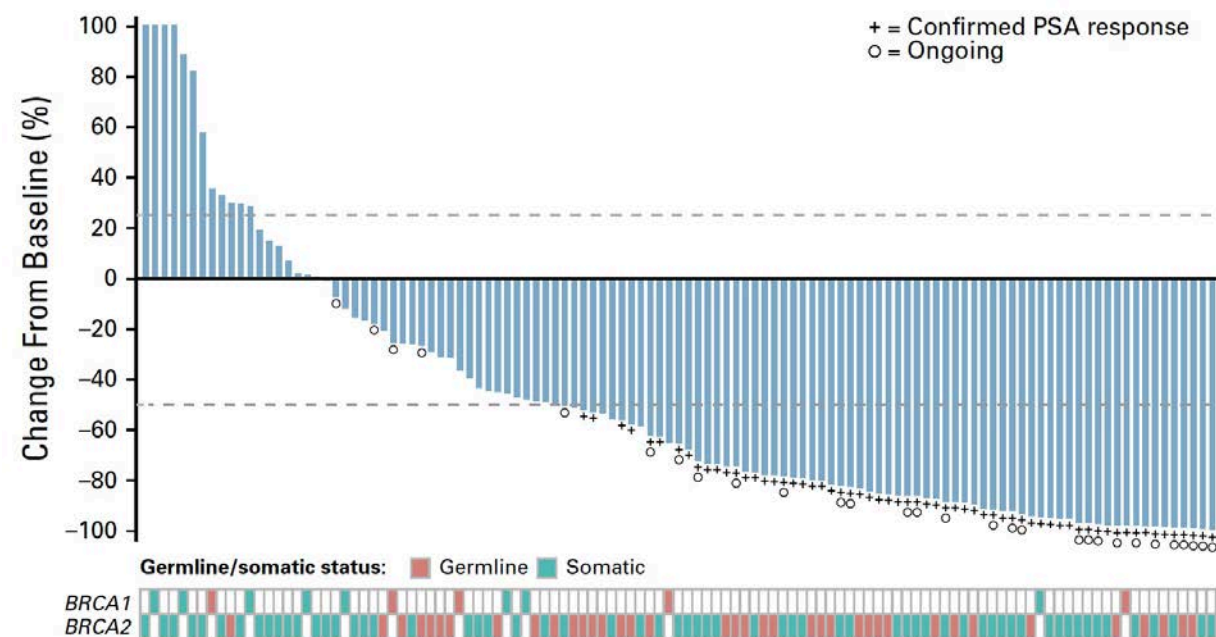
J Clin Oncol 2020;38(22):3763-72.

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

ORR per independent radiology review: 43.5%



Confirmed PSA response rate: 54.8%

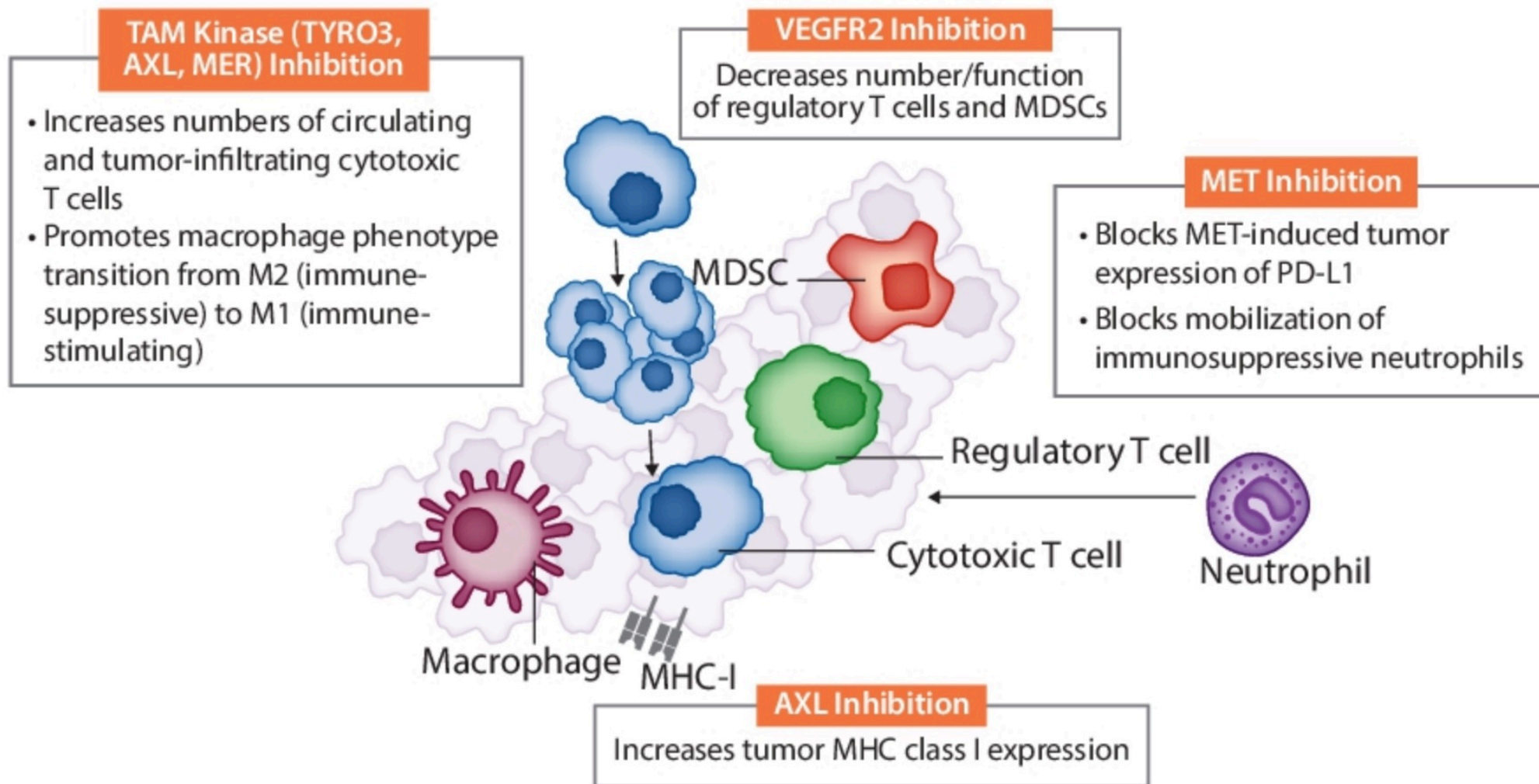


Cabozantinib in Combination with Atezolizumab in Patients with mCRPC: Results of Cohort 6 of the COSMIC-021 Study

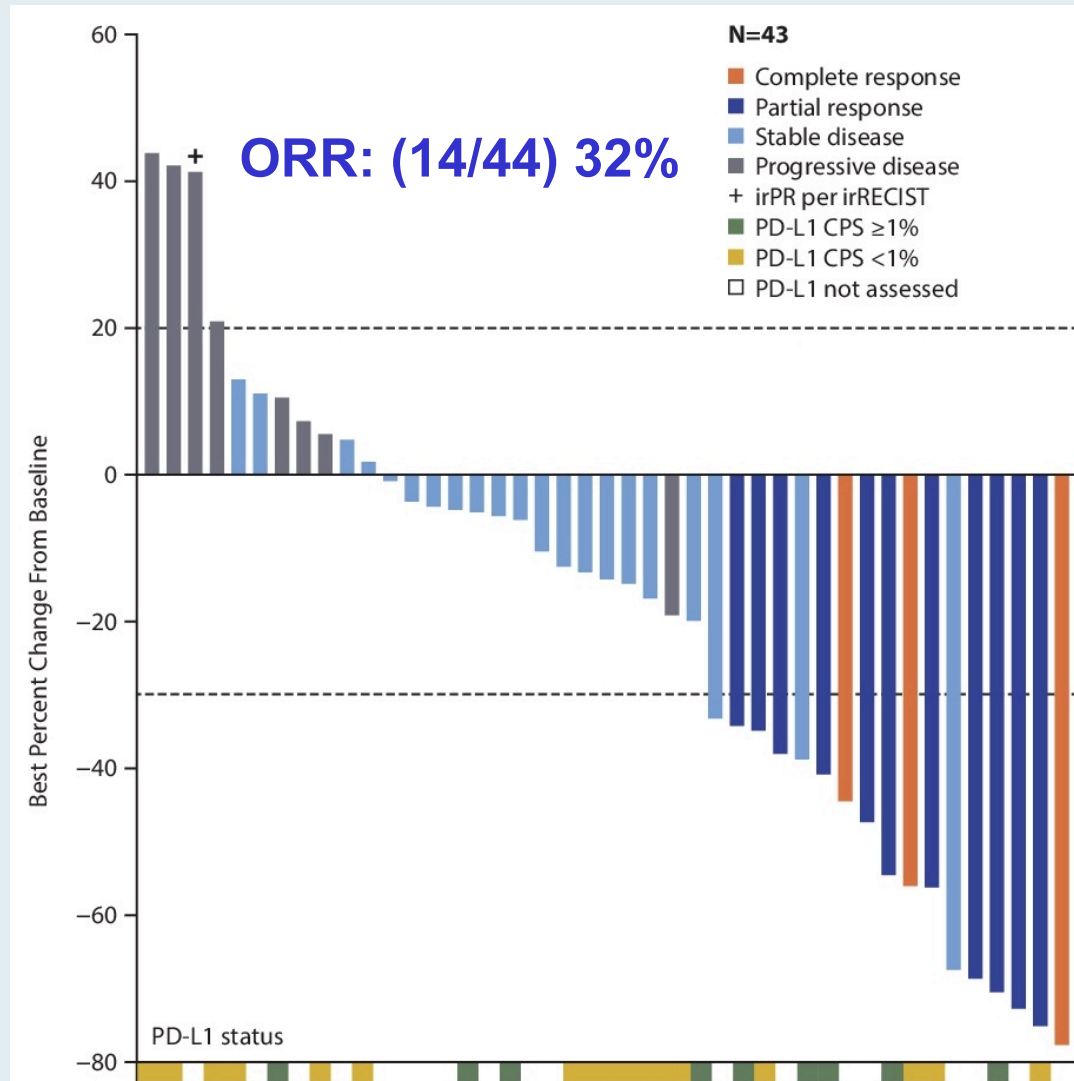
Agarwal N et al.

ASCO 2020;Abstract 5564.

Cabozantinib Targets Pathways Associated with Tumor Immune Suppression

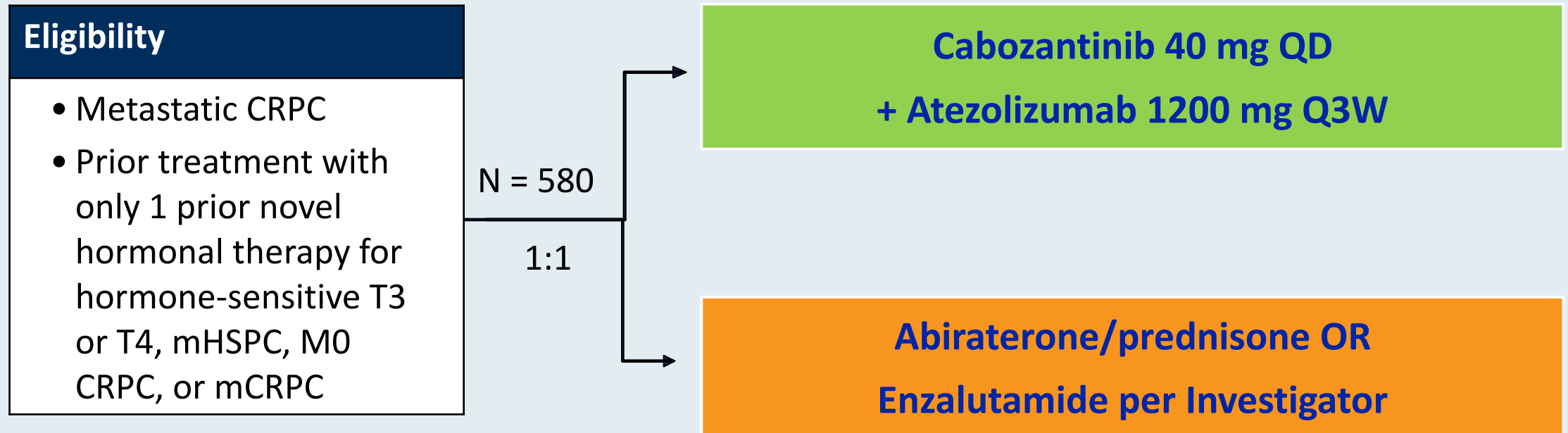


COSMIC-021 Primary Endpoint: Investigator-Assessed ORR with Cabozantinib/Atezolizumab in mCRPC



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

CONTACT-02 Phase III Study Schema



Coprimary endpoints: Duration of PFS and OS

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

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

**A Daylong Clinical Summit Hosted in Partnership with
North Carolina Oncology Association (NCOA) and
South Carolina Oncology Society (SCOS)**

Saturday, February 13, 2021

8:30 AM – 4:30 PM ET

Agenda

Module 1 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Pagel and Smith*

Module 2 — Multiple Myeloma: *Drs Richardson and Voorhees*

Module 3 — Genitourinary Cancers: *Drs Dreicer and Petrylak*

Module 4 — Lung Cancer: *Drs Gainor and Wakelee*

Module 5 — Gastrointestinal Cancers: *Dr Philip and Prof Van Cutsem*

Module 6 — Breast Cancer: *Drs Hurvitz and Krop*

Module 7 — Acute Myeloid Leukemia and Myelodysplastic Syndromes:
Drs DiNardo and Perl

Lung Cancer Faculty



Justin F Gainor, MD

Director, Center for Thoracic Cancers at
Massachusetts General Hospital
Director of Targeted Immunotherapy in the
Henri and Belinda Termeer
Center for Targeted Therapies
Assistant Professor of Medicine at Harvard
Medical School
Massachusetts General Hospital
Boston, Massachusetts



Heather Wakelee, MD

Professor of Medicine, Division of Oncology
Faculty Director, Stanford Cancer Clinical
Trials Office
Stanford University School of Medicine
Stanford Cancer Institute
Stanford, California

The patients I saw today...

79	M	CLL (serial monitoring of counts) and carcinoid tumor of the lung (active surveillance imaging)
55	F	Stage 1 node-negative TNBC - Adjuvant chemo
64	M	AML - Admitted for new onset severe pancytopenia; >50% blasts in marrow. Initiation of Induction chemo
79	F	Metastatic NSCLC, completed carbo, nab-P, pembrolizumab, now on maintenance pembro
82	M	Metastatic bladder cancer receiving 1 st -line atezolizumab; Tolerating well, with stable disease
50	M	Metastatic GIST on sunitinib since 2015
45	M	Newly diagnosed Stage IIIC rectal cancer, currently on neoadjuvant FOLFOX. Plan for subsequent chemoRT and possible resection. Non-compliance
75	F	Myelodysplastic Syndrome 5q-, receiving lenalidomide but tolerating very poorly
74	M	Locally advanced, distal esophageal cancer on concurrent chemoRT
55	M	Pancytopenia secondary to liver cirrhosis

77	M	Metastatic NSCLC post carbo, nab-P, pembrolizumab due to start pembro maintenance
81	F	Locally advanced NSCLCa-N2, refused chemo. Definitive XRT, refused durvalumab consolidation
88	F	DLBCL dx May 2018, refused chemo. Rituximab + prednisone ~8wks, complete remission. Now, relapsed disease in CNS but refuses WBRT; hospice
55	M	Gastric cancer receiving FOLFOX
82	M	Rectal cancer treatment ~10yrs ago - follow-up
57	M	CLL previously monitored, now with constitutional symptoms, weight loss and increasing WBC
73	F	Extensive stage SCLC diagnosed 2014, Relapsed in 2017, XRT with CDDP/VP-16. Remains in remission
45	M	Sokal high risk CML on dasatinib 75mg due to severe thrombocytopenia, tolerating much better, in CcyR
81	F	S/p lobectomy for incidentally diagnosed Stage 1A NSCLCa. No adjuvant treatment required
55	F	Newly diagnosed ER/PR-pos, HER2-neg locally advanced, node+ lobular carcinoma s/p bilat mastectomy. Plan: Adjuvant chemo, XRT, hormonal rx

Contributing Oncologists



Daniel R Carrizosa, MD, MS
Atrium Health Levine Cancer Institute
Associate Program Director –
Hematology/Oncology Fellowship
Medical Director: Diversity/Disparities and
Outreach Committee
Section Head: Head and Neck Division
Member: Head and Neck and Thoracic Sections
Charlotte, North Carolina



Margaret Deutsch, MD
Duke Cancer Center Raleigh
Raleigh, North Carolina



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



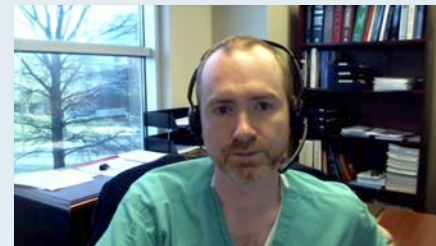
Aleksander Chojecki, MD
Department of Hematology and Cellular Therapy
Atrium Health Levine Cancer Institute
Charlotte, North Carolina



Zanetta S Lamar, MD
Florida Cancer Specialists
and Research Institute
Naples, Florida



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



Claud Grigg, MD
Genitourinary Oncology
Levine Cancer Institute of Atrium Health
Charlotte, North Carolina

Contributing Oncologists



William Robert Mitchell, MD
Southern Oncology Specialists
Charlotte, North Carolina



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Medical Oncologist
Oncology Specialists of Charlotte
Charlotte, North Carolina



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



Saad Zafar Usmani, MD, MBA
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Levine Cancer Institute, Carolinas Medical Center
Charlotte, North Carolina



Maria E Picton, MD
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Greenville, North Carolina



Richard Zelkowitz, MD
Regional Director of the Breast Program
Hematology and Oncology
Hartford HealthCare Cancer Institute
Bridgeport, Connecticut

Agenda

Module 1: NSCLC with an EGFR Tumor Mutation

- Dr Carrizosa: A 78-year-old woman with Stage IB adenocarcinoma – EGFR exon 19 deletion
 - Parts 1 and 2

Module 2: Metastatic NSCLC Harboring Other Mutations

- Dr Mitchell: A 58-year-old woman with mNSCLC – BRAF V600E mutation
- Dr Carrizosa: A man in his mid-20s and smoker with mNSCLC – NTRK mutation

Module 3: Localized or Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

- Dr Picton: A 66-year-old woman and smoker with locally advanced NSCLC

Module 4: Newly Diagnosed NSCLC with No Actionable Mutation

- Dr Lamar: A 94-year-old woman with metastatic NSCLC – PD-L1 75%, no EGFR mutation

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

- Dr Deutsch: A 66-year-old woman with extensive-stage SCLC

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Case Presentation – Dr Carrizosa: A 78-year-old woman and retired radiation oncology RN with Stage IB adenocarcinoma of the lung – EGFR exon 19 deletion – Part 1



Dr Daniel R Carrizosa

- Chest CT after car accident: 2.5-cm RUL nodule
- Work up: No mediastinal or extra-thoracic disease → RUL robotic lobectomy
- Adenocarcinoma (pT2aN0MO), with some visceral pleural invasion
- Molecular testing: EGFR exon 19 deletion
- Patient declined osimertinib

Case Presentation – Dr Carrizosa: A 78-year-old woman and retired radiation oncology RN with Stage IB adenocarcinoma of the lung – EGFR exon 19 deletion – Part 2



Dr Daniel R Carrizosa

- Chest CT after car accident: 2.5-cm RUL nodule
- Work up: No mediastinal or extra-thoracic disease → RUL robotic lobectomy
- Adenocarcinoma (pT2aN0MO), with some visceral pleural invasion
- Molecular testing: EGFR exon 19 deletion
- Patient declined osimertinib

Question

- ***If this patient had a larger tumor or a positive node, would that have affected your recommendation? Would you be thinking about using chemotherapy also, or just osimertinib?***

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

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

FDA Approves Osimertinib as Adjuvant Therapy for NSCLC with EGFR Mutations

Press Release — December 18, 2020

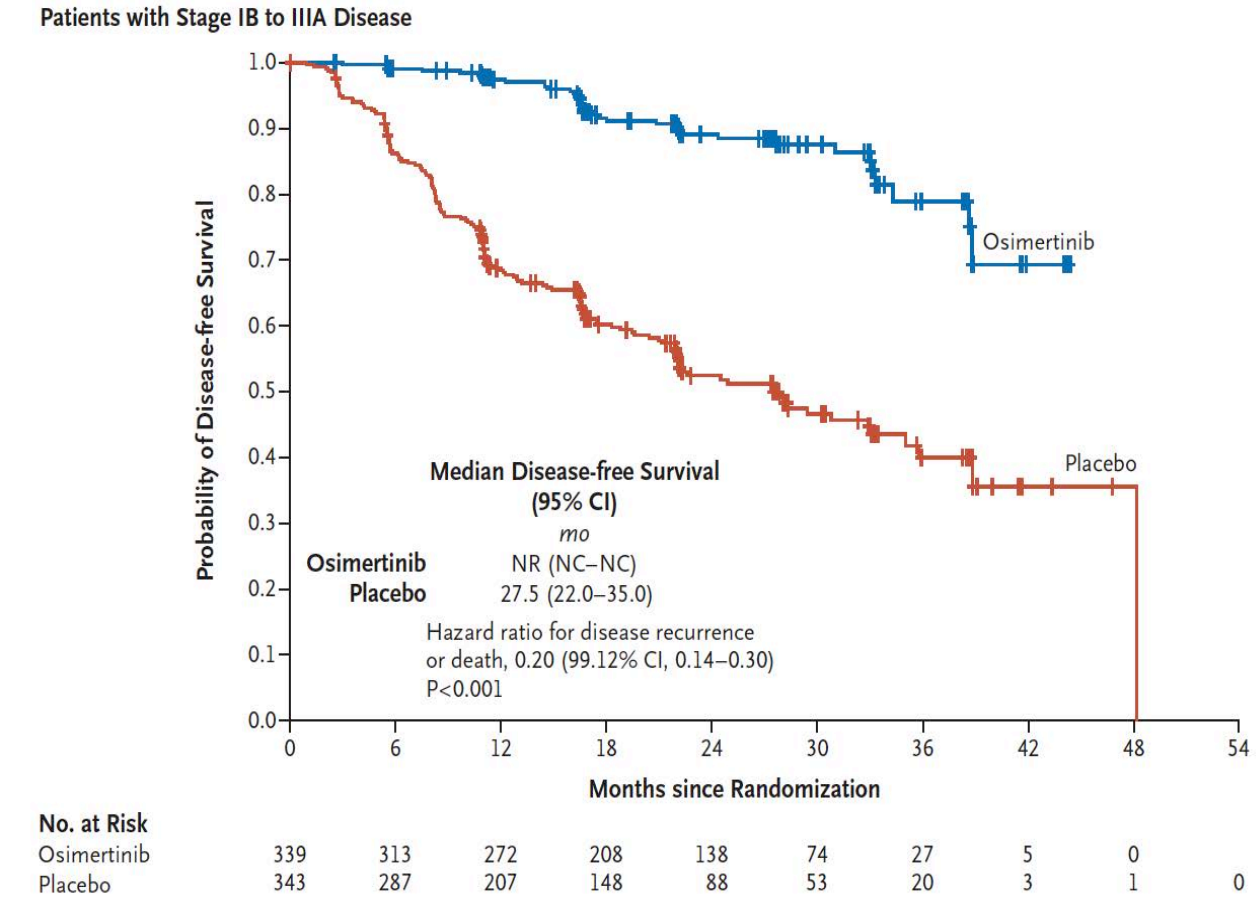
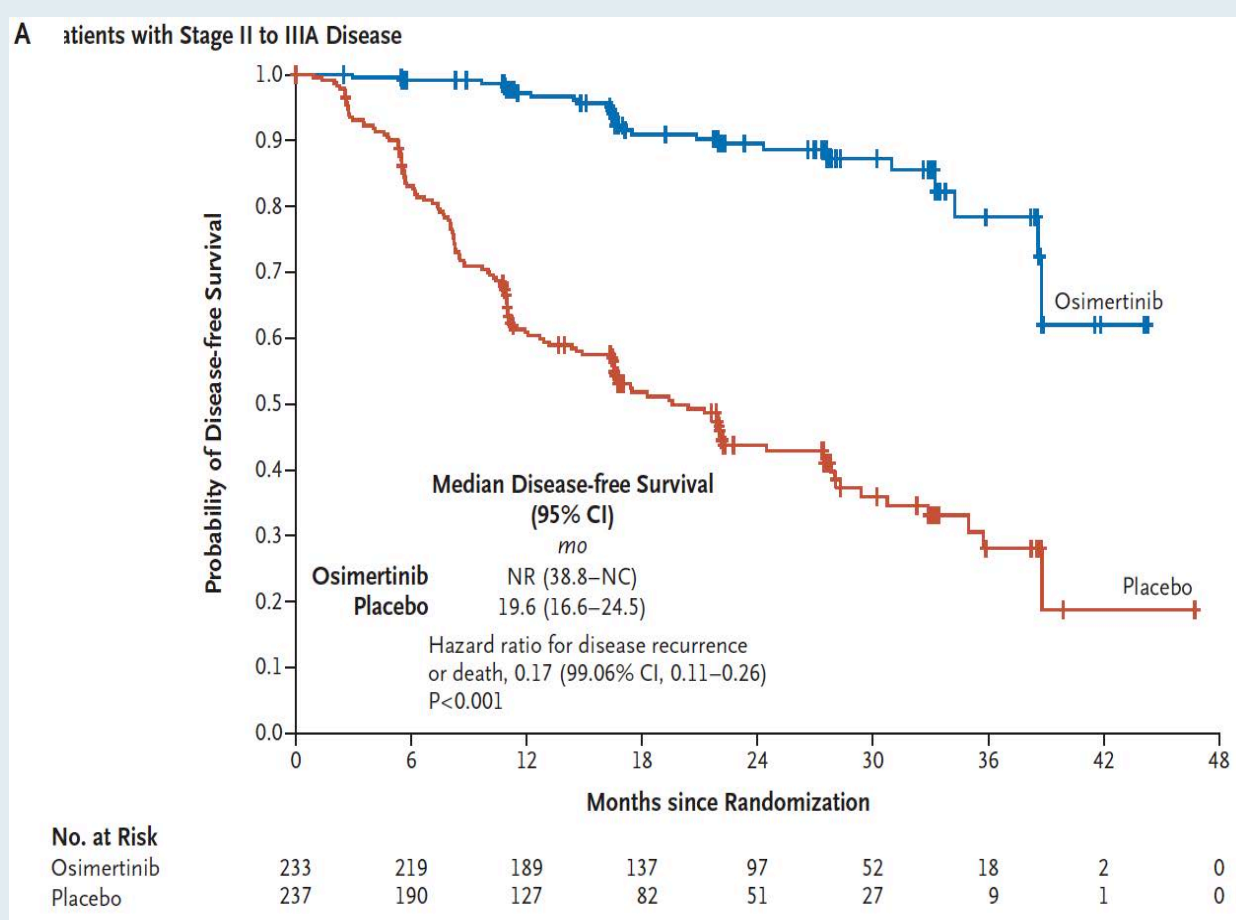
- The FDA approved osimertinib as adjuvant therapy after tumor resection in patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- Efficacy was demonstrated in the randomized, double-blind, placebo-controlled ADAURA trial for patients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

ORIGINAL ARTICLE

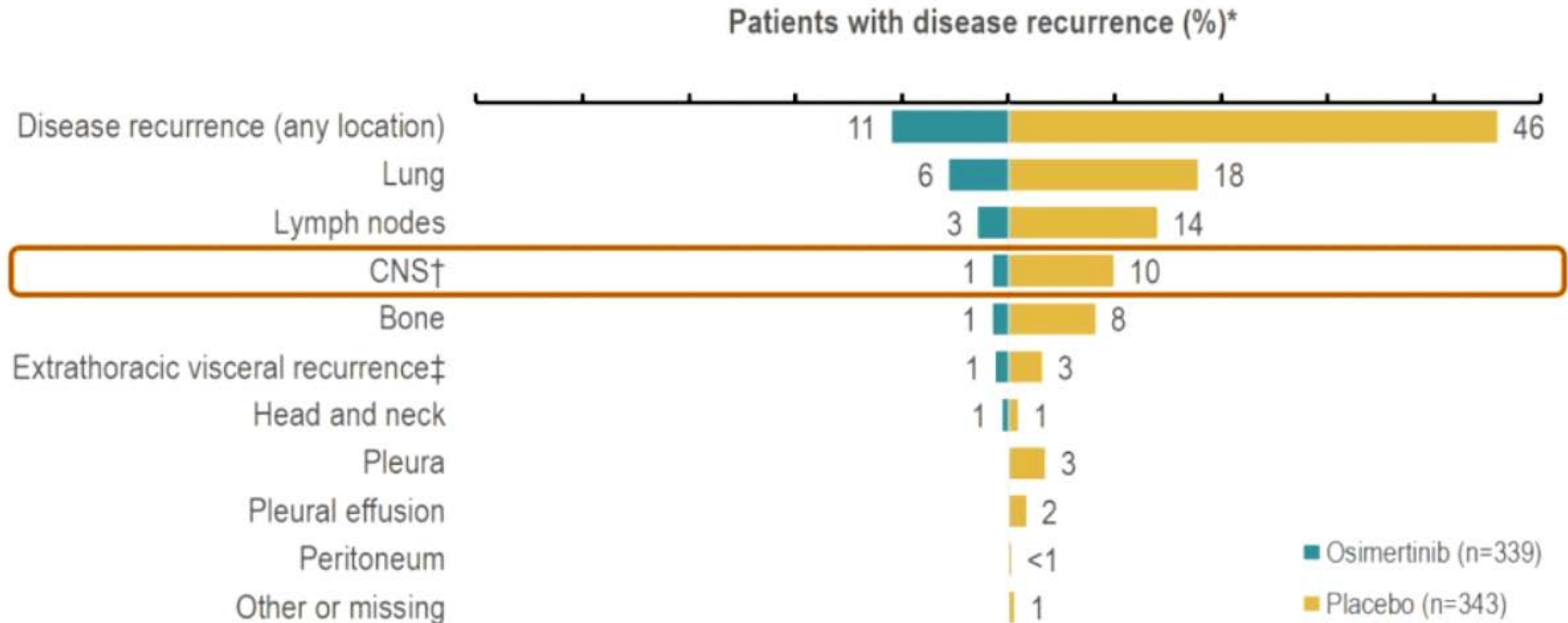
Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

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

ADAURA: Disease-Free Survival by Stage



ADAURA: Sites of Disease Recurrence

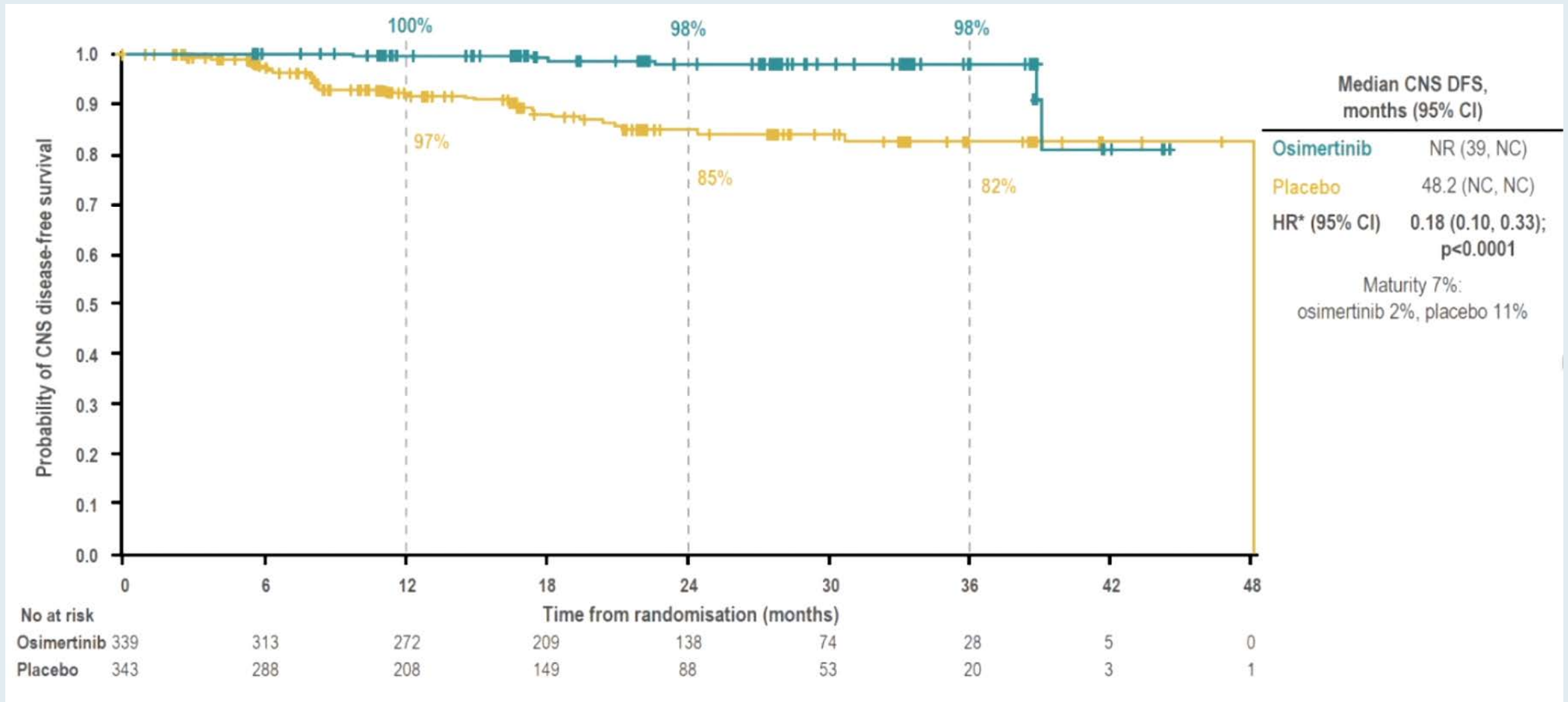


ADAURA: CNS DFS Events

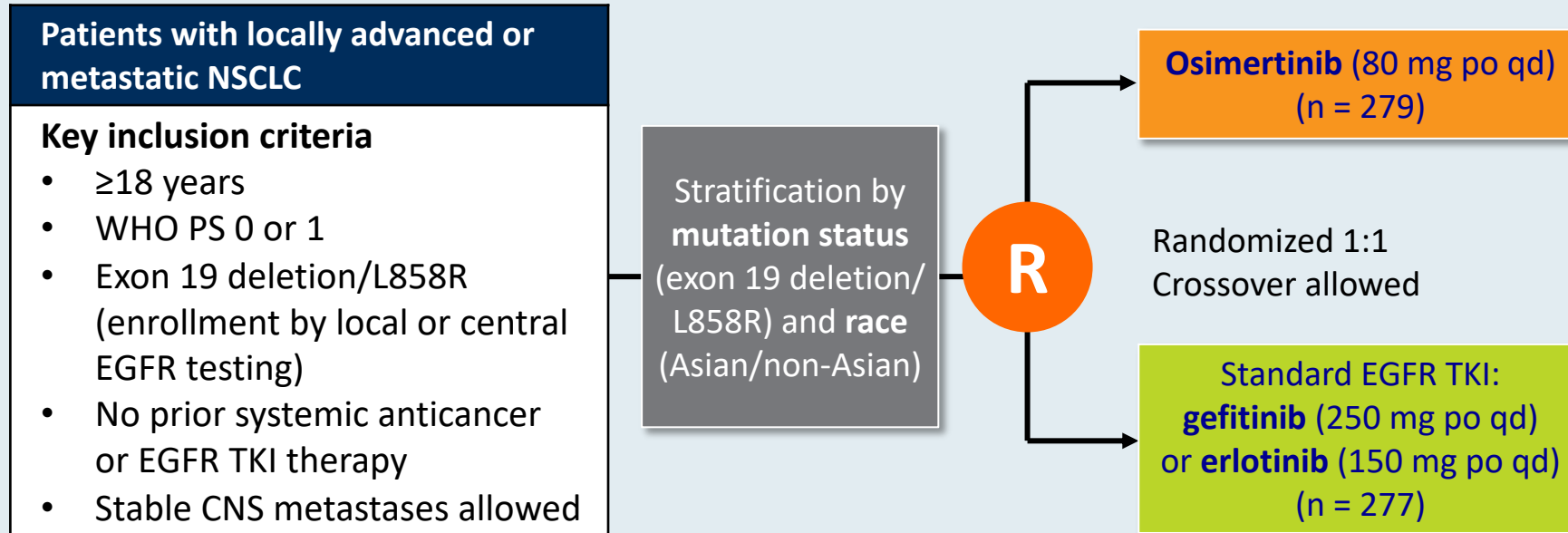
- Overall, 45 patients (osimertinib n=6, placebo n=39) had CNS DFS events

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

ADAURA: CNS DFS in Overall Population



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



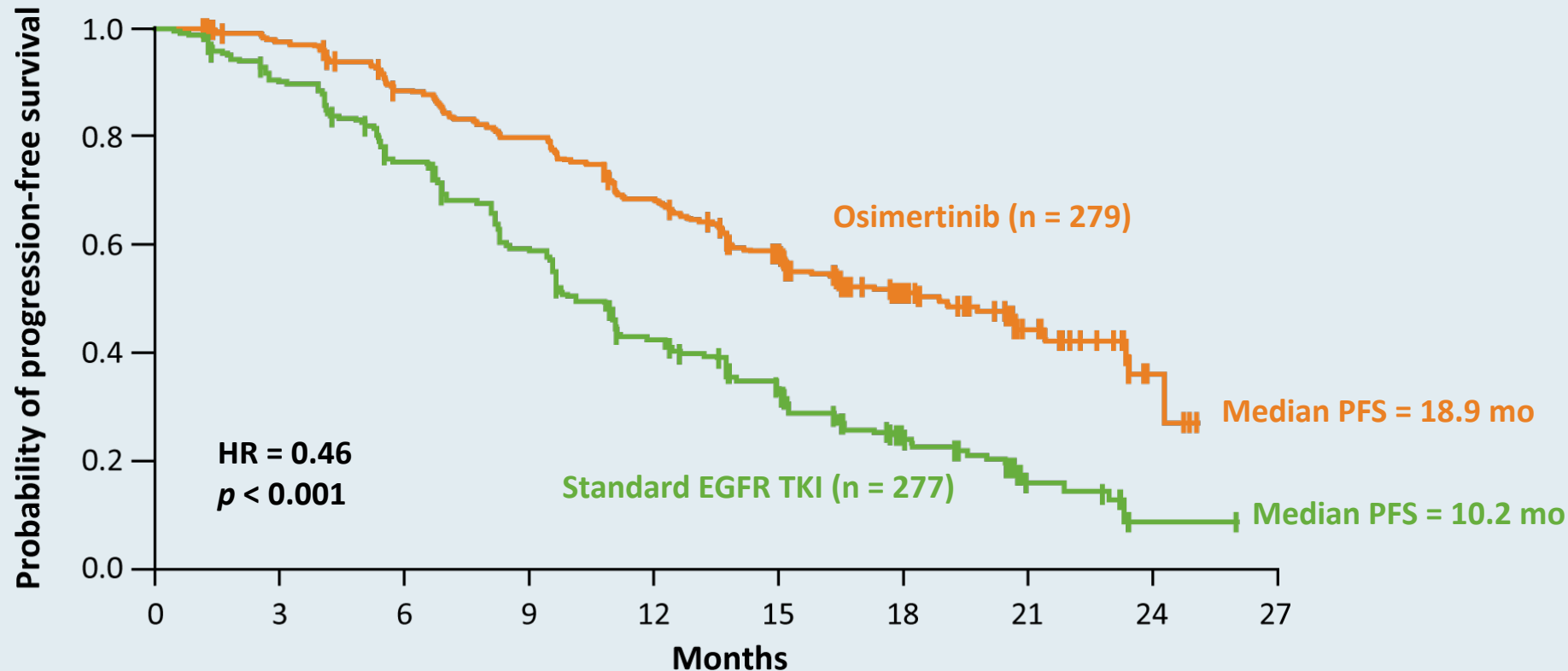
Primary endpoint: Progression-free survival (PFS) based on investigator assessment (per RECIST 1.1)

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

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

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

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

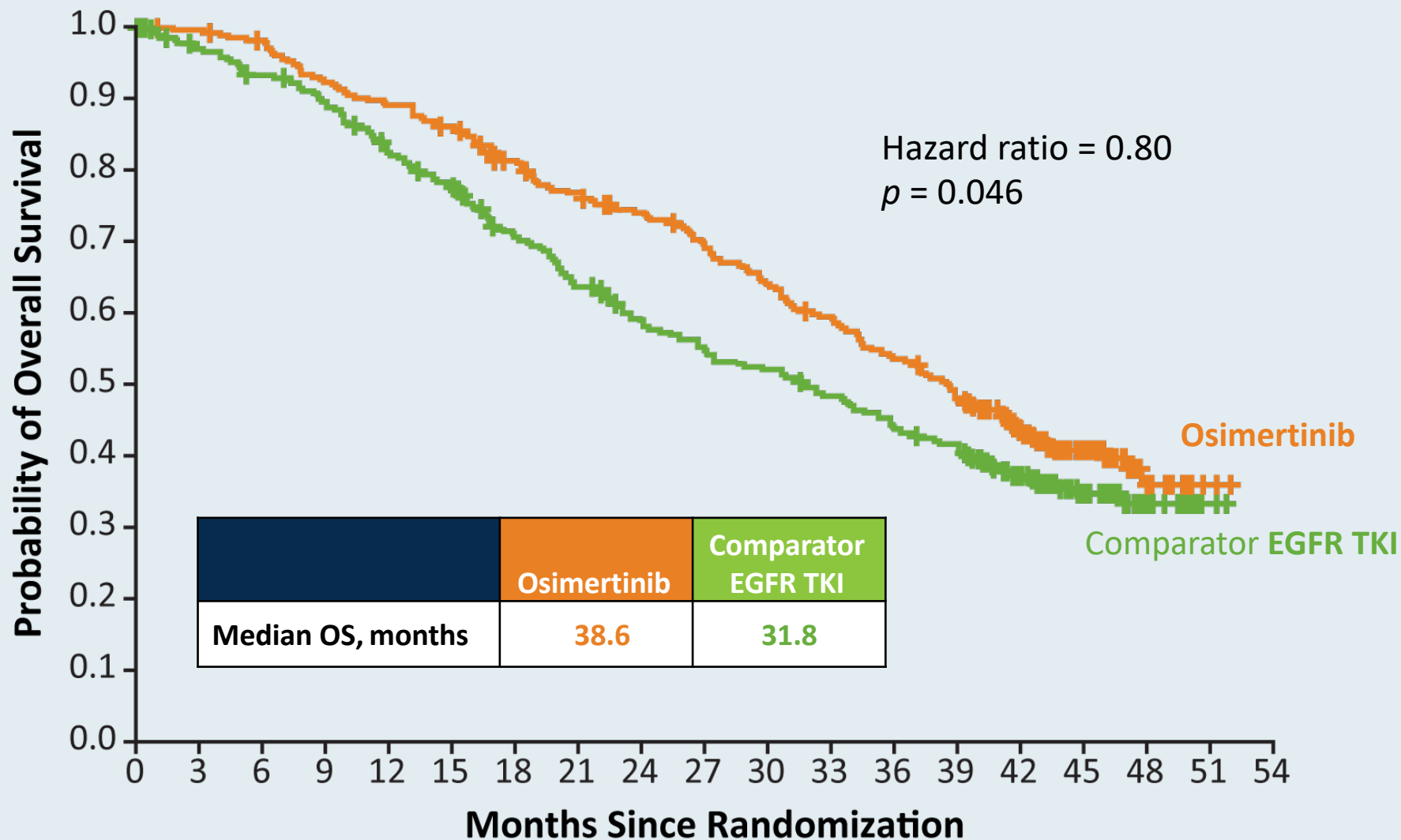


Interim overall survival (data immature), HR = 0.63, $p = 0.007^{1,2}$

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

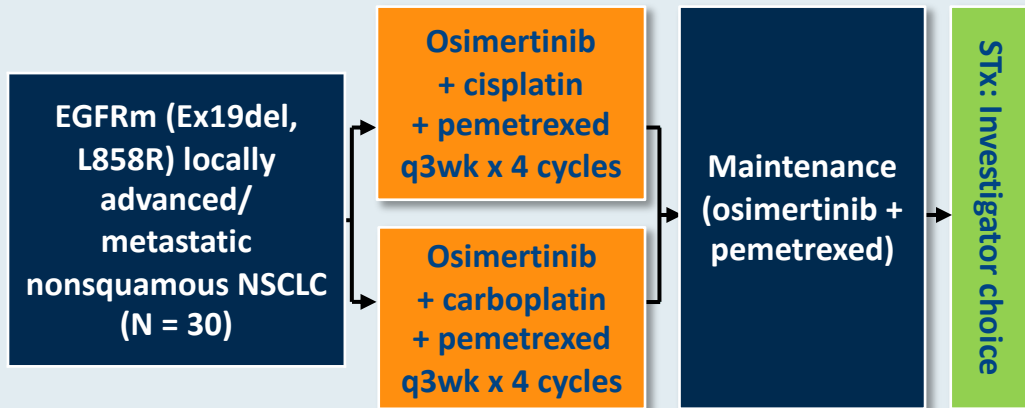
² Planchard D et al. *ELCC* 2018;Abstract 128O.

FLAURA: Final Overall Survival Analysis



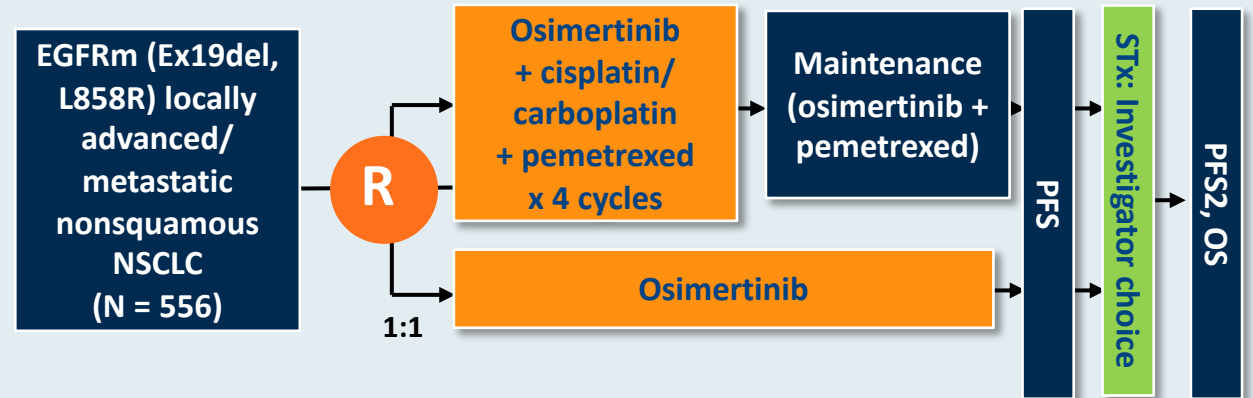
FLAURA2 Study Design: Safety Run-In and Randomization Phases

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

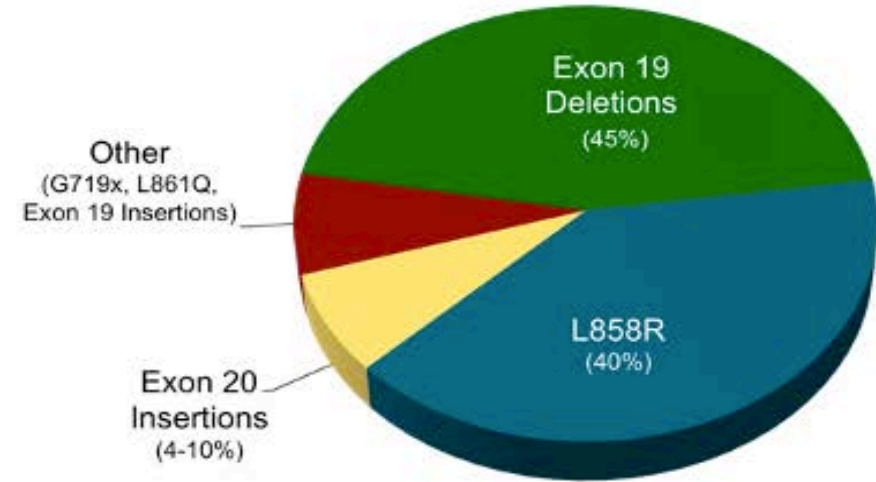
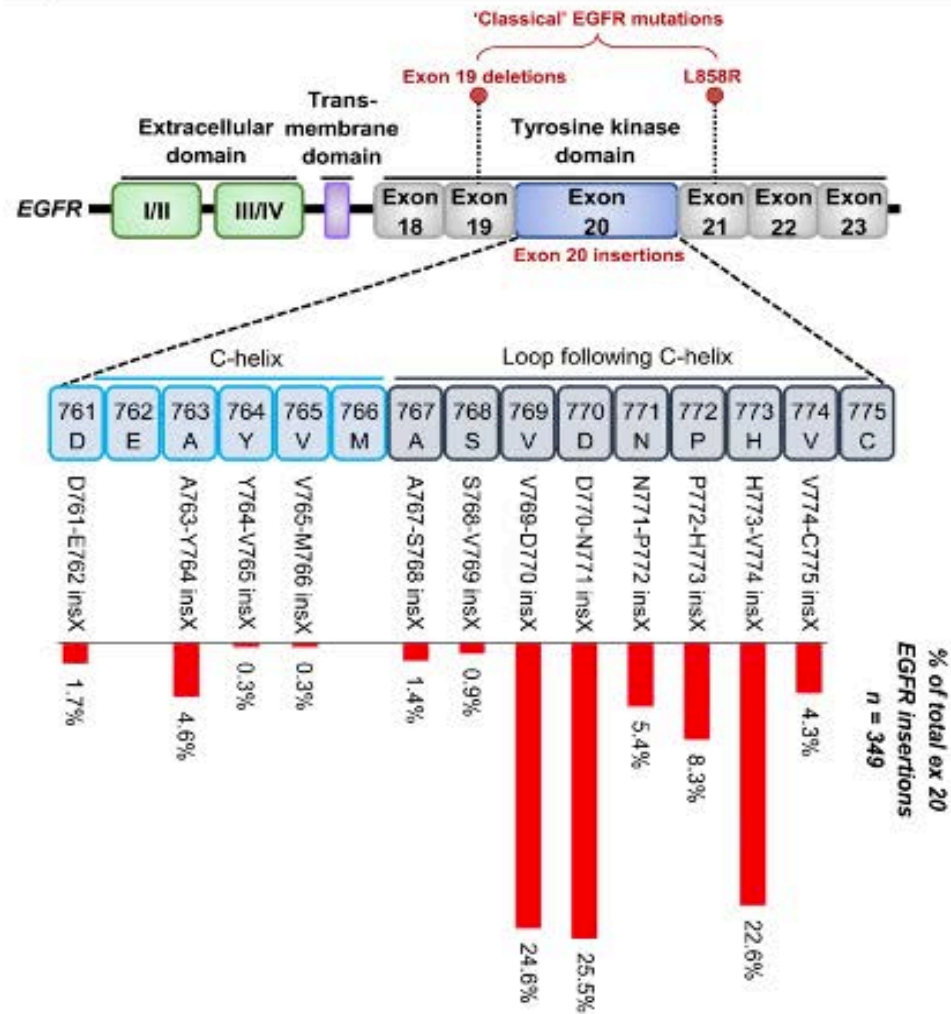
FDA Approves Ramucirumab plus Erlotinib for First-Line NSCLC

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.”

Frequency of EGFR Exon 20 Mutations



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

Courtesy of Zosia Piotrowska, MD.

Emerging Targeted Therapies for EGFR Exon 20 Mutations

Drug	MOA	n	ORR	mPFS	Major Toxicities	% Dose Reduction	% DC due to Toxicity	FDA BT Therapy
Pozotinib ^{1,2}	TKI	115	15%	4.2 mo	82% Diarrhea; 26% Gr 3+ 68% Rash; 30% Gr 3+	78%	12%	
Mobocertinib (TAK-788) ^{3,4}	TKI	28	43%	7.3 mo	85% Diarrhea; 28% Gr 3+ 36% Rash; 1% Gr 3+ 43% Nausea; 6% Gr 3+	25%	14%	X
Amivantamab (JNJ-372) ⁵	EGFR/MET Ab	39	36%	8.3 mo [95% CI, 3.0-14.8]	72% Rash; 0% Gr3 60% Infusion Reaction 34% Paronychia	10%	6%	X
Osimertinib ⁶	TKI	17	24%	9.6 mo	76% Diarrhea; 0% Gr 3+ 38% Rash; 0% Gr 3+ *10% Gr 3+ <u>plts</u> , 10% Gr 3+ QTc	NR	1/17	
CLN-081 ⁷	TKI	22	35% (unconf)	NR	60% Rash; 0% Gr 3+ 13% Stomatitis, 0% Gr 3	9%	0%	

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

Courtesy of Zosia Piotrowska, MD.

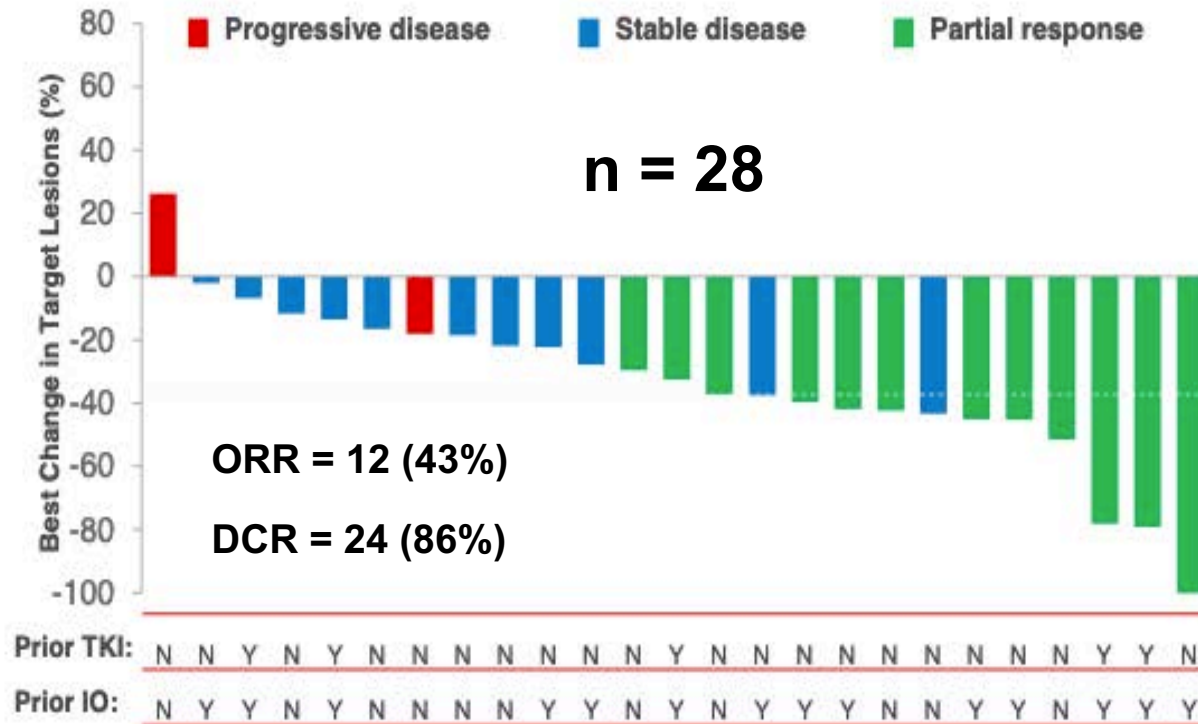
FDA Grants Breakthrough Therapy Designation for Mobocertinib (TAK-788)

Press Release – April 27, 2020

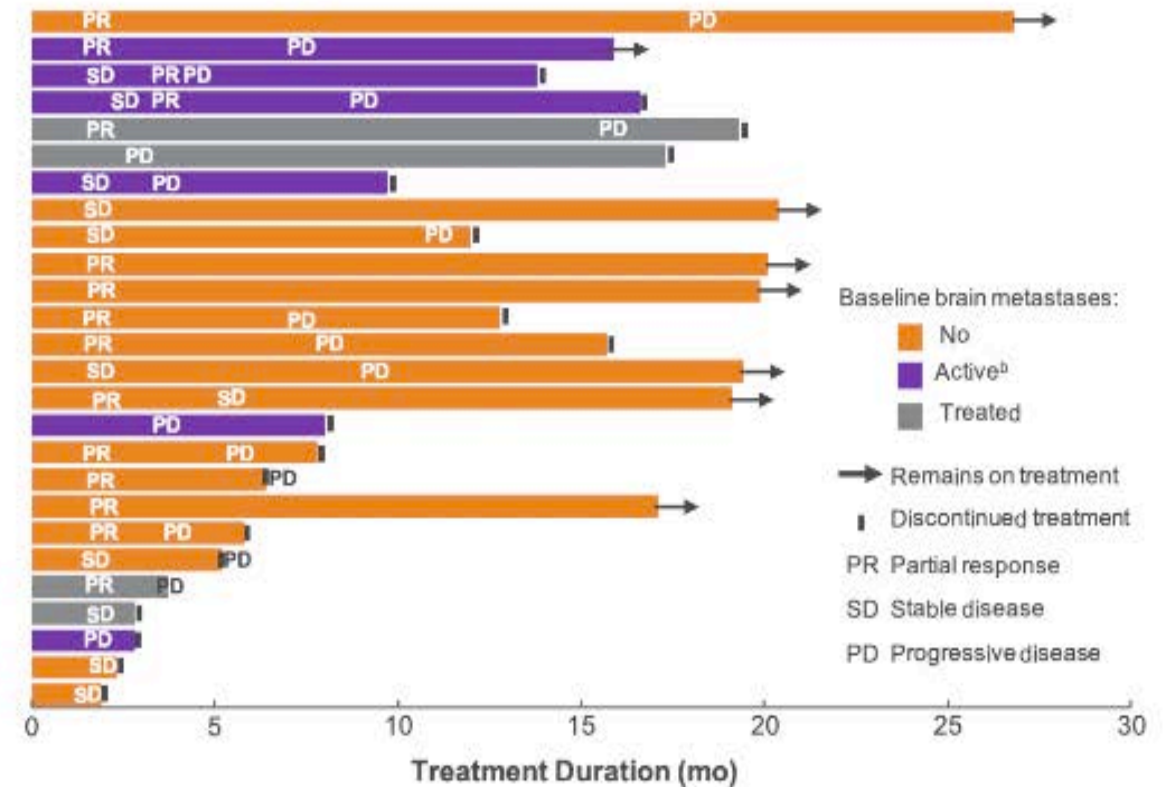
- The FDA has granted Breakthrough Therapy Designation for the investigational drug mobocertinib (TAK-788) for the treatment of patients with metastatic NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.
- There are currently no approved therapies designed to treat this specific form of NSCLC.
- Mobocertinib is a small-molecule tyrosine kinase inhibitor (TKI) designed to selectively target EGFR and human EGFR 2 (HER2) exon 20 insertion mutations.
- The Breakthrough Therapy Designation is based on the overall response rate (ORR) and the long-term benefit seen in patients who responded in a Phase 1/2 study evaluating the safety and efficacy of mobocertinib in patients with locally advanced or metastatic NSCLC whose tumors harbor EGFR exon 20 insertion mutations and have been previously treated with systemic chemotherapy.

Results from the Phase I/II Trial of Mobocertinib in NSCLC with EGFR Exon 20 Insertions

Antitumor Activity



Overall Response and Time on Treatment



IO, immuno-oncology therapy; TKI, tyrosine kinase inhibitor

^a Two patients had no postbaseline assessment and are not included in figures

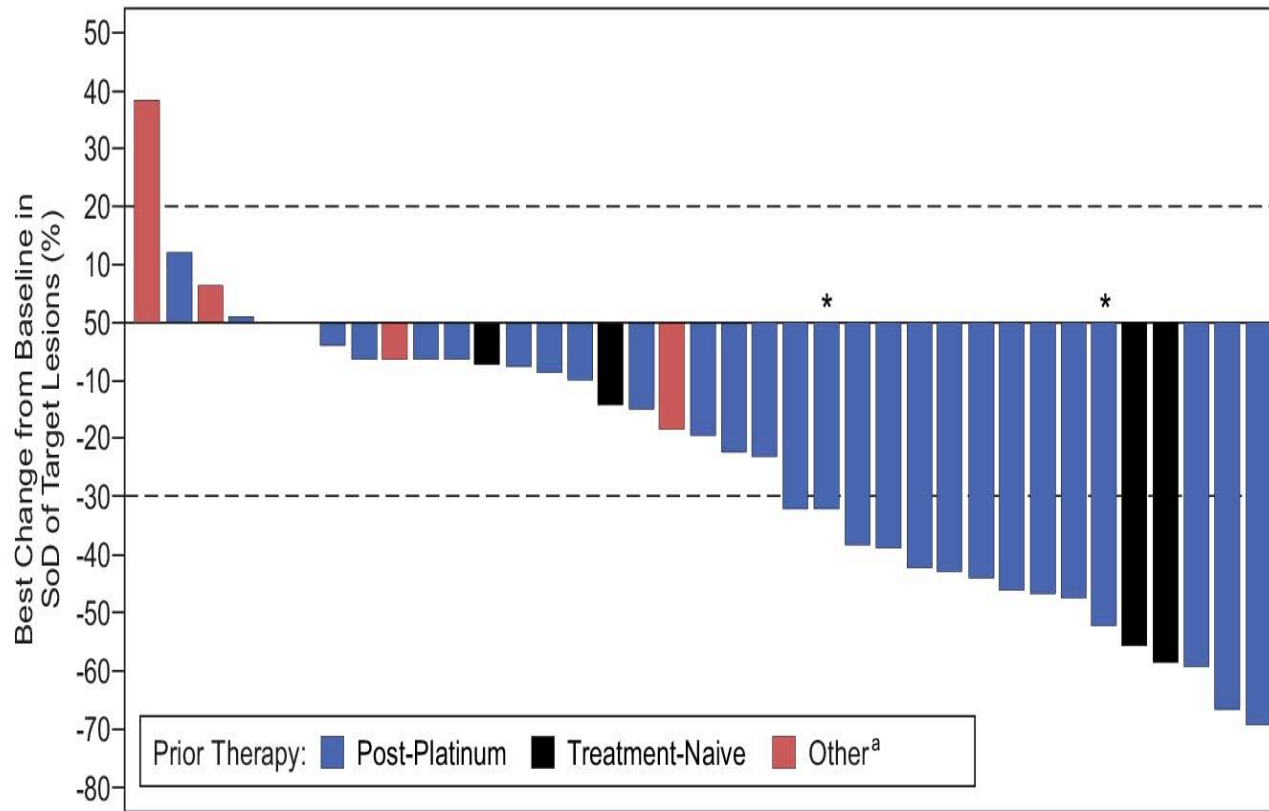
^b Active brain metastases were either never treated or progressed after radiation

FDA Grants Breakthrough Therapy Designation for Amivantamab (JNJ-61186372)

Press Release – March 10, 2020

- The FDA has granted Breakthrough Therapy Designation for amivantamab (JNJ-6372) for the treatment of patients with metastatic NSCLC with EGFR Exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy.
- Amivantamab is an EGFR-mesenchymal epithelial transition factor (MET) bispecific antibody that targets activating and resistant EGFR and MET mutations and amplifications
- Amivantamab is a novel bispecific antibody that has the potential to benefit patients with Exon 20 insertion mutations who often do not respond to currently available oral EGFR-targeted or immune checkpoint inhibitor therapies
- Currently, there are no FDA-approved targeted therapies for patients with lung cancer who have EGFR Exon 20 insertion mutations

Results from the Phase I Trial of Amivantamab in NSCLC with EGFR Exon 20 Insertions



*Unconfirmed partial response. ^a2 patients treated with EGFR TKIs, 1 with bevacizumab plus radiation therapy, 1 with adjuvant immuno-oncology chemotherapy. 2 patients did not have post-baseline disease assessments and are not included in the plot. SoD=sum of diameters



^aPartial response or better. NE=not evaluable; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable disease

Amivantamab (JNJ-61186372), an EGFR-MET Bispecific Antibody, in Combination with Lazertinib, a 3rd-Generation EGFR Tyrosine Kinase Inhibitor, in Advanced EGFR-Mutant NSCLC

Cho BC et al.

ESMO 2020;Abstract 1258O.

CHRYSLIS Phase I Study Design

Key Objectives

- Establish RP2CD
- Safety and efficacy at RP2CD

Key Eligibility Criteria

- Metastatic/unresectable NSCLC
- Measurable disease (expansion cohort)
- EGFR Exon19del or L858R mutation

Dose Escalation (n=26)

1050/1400 mg
amivantamab +
240 mg lazertinib

700/1050 mg
amivantamab +
240 mg lazertinib

RP2CD

Amivantamab
1050 mg (<80 kg)
1400 mg (≥80 kg)
Intravenous dosing
C1 QW, C2+ Q2W
+
240 mg lazertinib
Oral daily dosing



Expansion Cohorts

Osimertinib-
resistant,
Chemo-naïve

EGFR Exon19del
or L858R
(n=45)

Treatment-naïve^a

EGFR Exon19del
or L858R
(n=20)

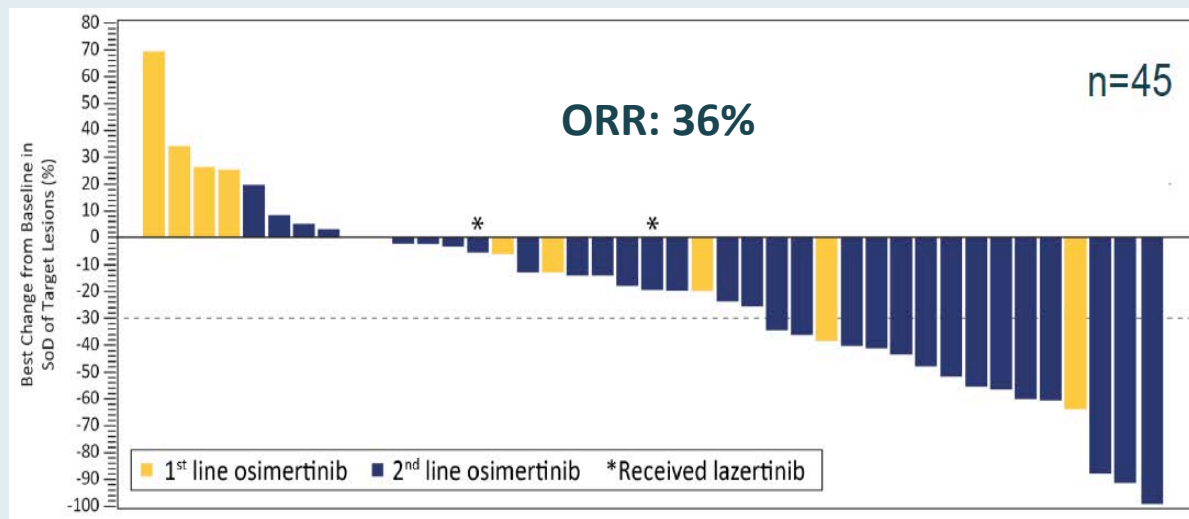
- Combination dose is at the recommended monotherapy doses of each molecule
- Proactive rash management included topical antibiotics to sun-exposed skin

CHRYSLIS: Efficacy and Tolerability of Amivantamab with Lazertinib

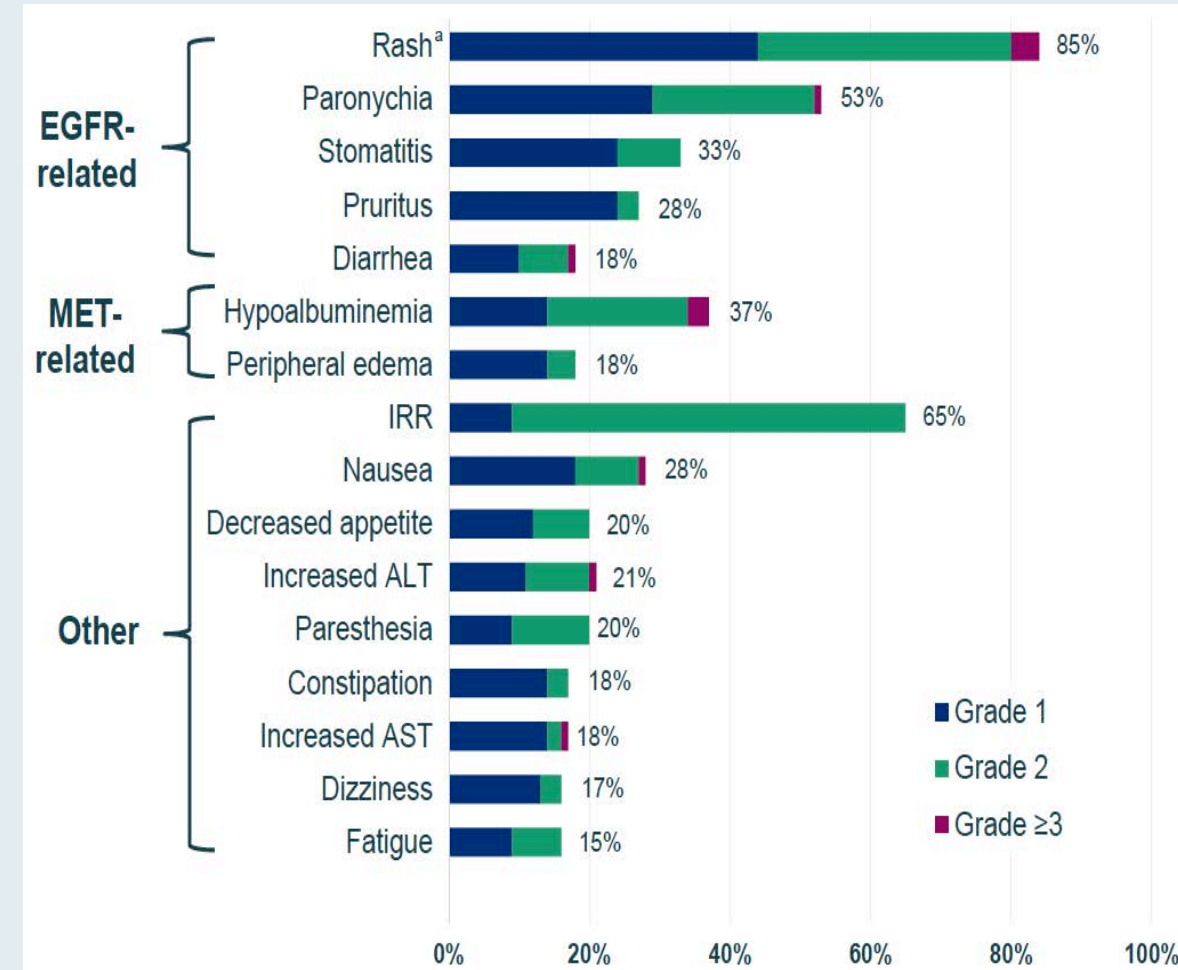
Treatment-Naïve



Osimertinib-Resistant, Chemo-Naïve



Adverse Events (≥15%)



CHRYSLIS: Conclusions

Amivantamab can be safely combined with lazertinib

- No dose-limiting toxicities identified during dose escalation
- Combination dose tolerated, with low rates of treatment discontinuation (6%) and grade ≥ 3 TRAE (11%)
- 65% of patients experienced IRR, all grade 1 – 2, occurring with the first infusion

Amivantamab with lazertinib is efficacious in advanced EGFRm NSCLC

- 100% ORR in treatment-naïve cohort
- 36% ORR in osimertinib-resistant, chemo-naïve cohort
 - Analysis of efficacy by mechanism of resistance is ongoing

New studies with amivantamab + lazertinib combination started:

- Phase 3 MARIPOSA study in frontline EGFRm NSCLC vs osimertinib
- Phase 2 CHRYSLIS-2 study in osimertinib-resistant and chemotherapy-relapsed setting

IMpower150: Updated Efficacy Analysis in Patients with EGFR Mutations

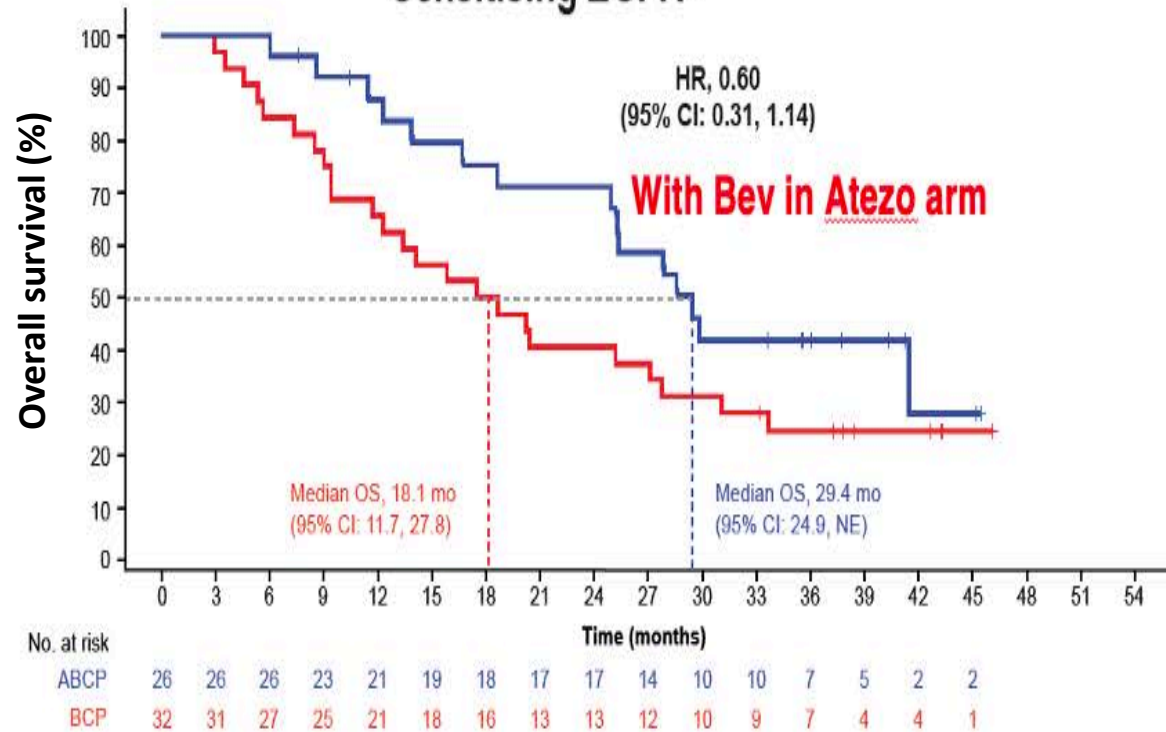
Reck M et al.

ESMO 2020;Abstract 1293P.

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

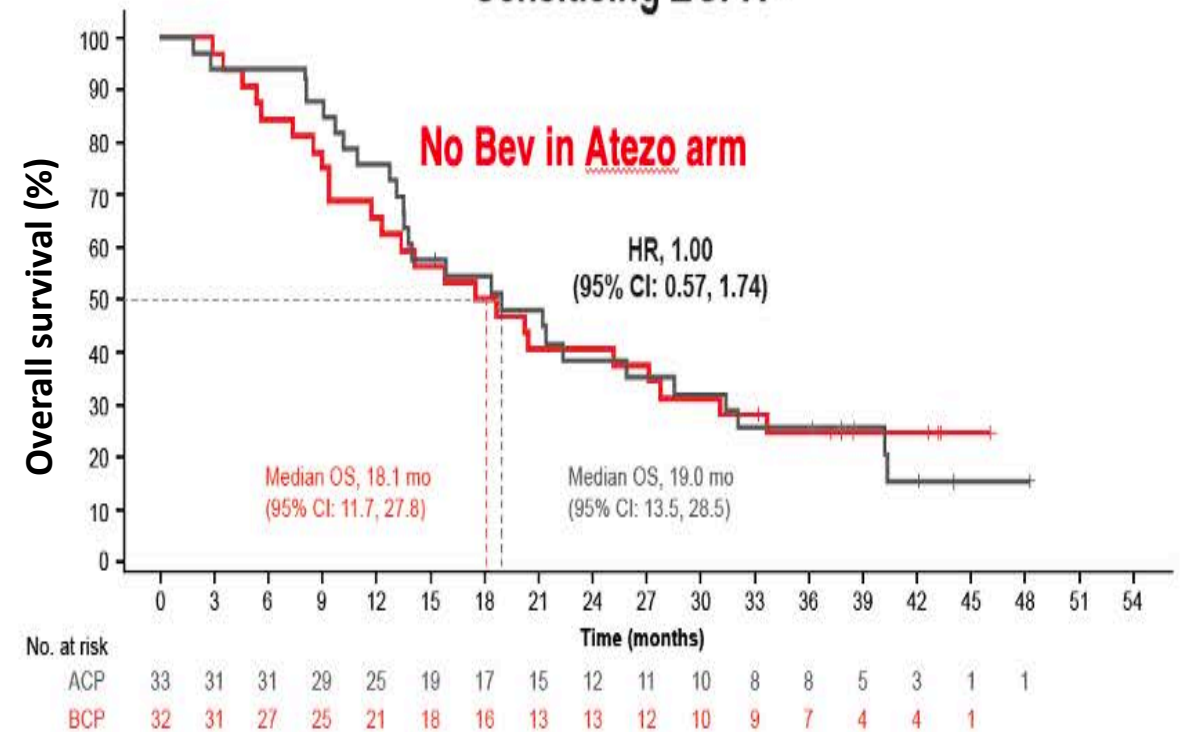
ABCP vs BCP (13% of ITT)

Sensitising EGFR+



ACP vs BCP

Sensitising EGFR+



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

Agenda

Module 1: NSCLC with an EGFR Tumor Mutation

- Dr Carrizosa: A 78-year-old woman with Stage IB adenocarcinoma – EGFR exon 19 deletion
 - Parts 1 and 2

Module 2: Metastatic NSCLC Harboring Other Mutations

- Dr Mitchell: A 58-year-old woman with mNSCLC – BRAF V600E mutation
- Dr Carrizosa: A man in his mid-20s and smoker with mNSCLC – NTRK mutation

Module 3: Localized or Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

- Dr Picton: A 66-year-old woman and smoker with locally advanced NSCLC

Module 4: Newly Diagnosed NSCLC with No Actionable Mutation

- Dr Lamar: A 94-year-old woman with metastatic NSCLC – PD-L1 75%, no EGFR mutation

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

- Dr Deutsch: A 66-year-old woman with extensive-stage SCLC

Case Presentation – Dr Mitchell: A 58-year-old woman, nonsmoker with metastatic adenocarcinoma of the lung – BRAF V600E mutation, PD-L1 TPS: 80



Dr William Robert Mitchell

- 11/2020: Diagnosed with metastatic adenocarcinoma of the lung, with hepatic and skeletal involvement
 - MRI brain: Negative
 - Guardant 360: BRAF V600E mutation
 - NGS: BRAF V600E, PD-L1 TPS: 80
- Dabrafenib/trametinib and enoxaparin
 - Systemic pruritic erythematous popular rash over entire body, affecting vision and eating
 - Placed on steroids, treatment discontinued
- 12/2020 CT (off therapy 2-3 weeks): No significant change in presumed hepatic and skeletal metastases, but considerable regression of the porta hepatis lymphadenopathy

Questions

- What are your thoughts about the use of BRAF inhibitors as first-line therapy in patients with the mutation?
- What are the data for the use of immunotherapy in patients with BRAF mutations – does it work?

Case Presentation – Dr Carrizosa: A man in his mid-20s and smoker with metastatic adenocarcinoma of the lung – PD-L1: 10%, TMB: 6 mut/Mb, NTRK mutation



Dr Daniel R Carrizosa

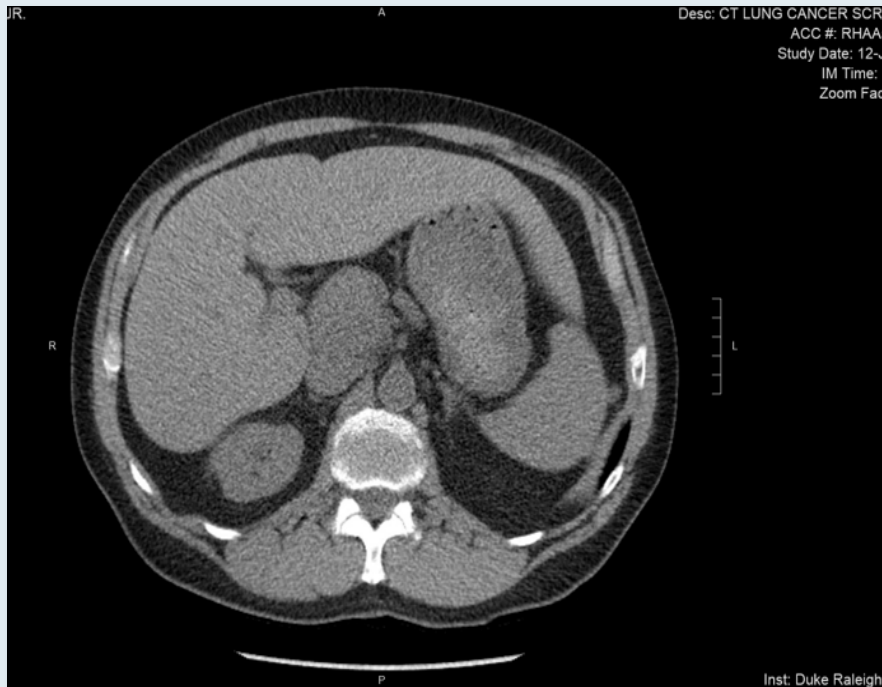
- Progressive SOB and weight loss past year unattended due to lack of insurance
- Diagnosed at a free clinic with metastatic adenocarcinoma of the lung, involving the liver and stomach
- Molecular testing: EGFR, BRAF, ALK, ROS wildtype
- NGS sent, but the patient is very hypoxic and symptomatic
- Carboplatin/paclitaxel/bevacizumab/atezolizumab, with significant response and clinical improvement after 1 cycle
- NGS: NTRK mutation, PD-L1: 10%, TMB: 6 mut/Mb
- Continued 4-drug regimen to complete 4 cycles → Entrectinib
- Currently, in near CR x 2 years

Case Presentation – Dr Carrizosa: A man in his mid-20s and smoker with metastatic adenocarcinoma of the lung – PD-L1: 10%, TMB: 6 mut/Mb, NTRK mutation

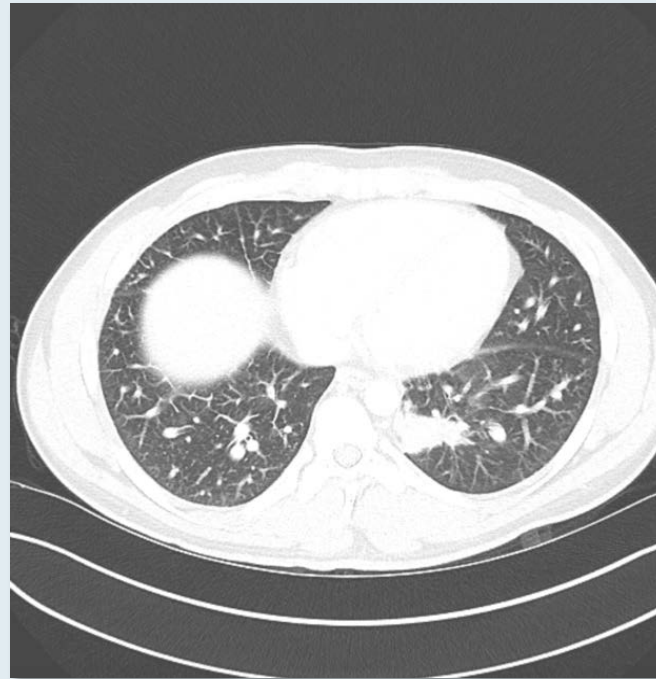


Dr Daniel R Carrizosa

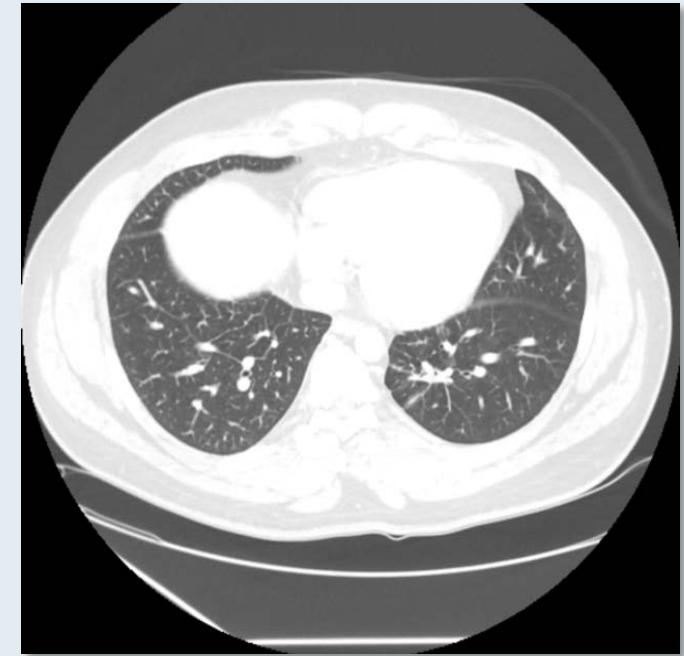
Baseline CT



CT After Carboplatin/Paclitaxel
+ Bevacizumab + Atezolizumab



CT After Entrectinib



For a patient with metastatic nonsquamous NSCLC with a RET rearrangement and a PD-L1 TPS of 10%, in what line of therapy should targeted treatment (eg, selpercatinib, pralsetinib) be used?

1. First line
2. Second line
3. Third line
4. Fourth line and beyond

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 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).

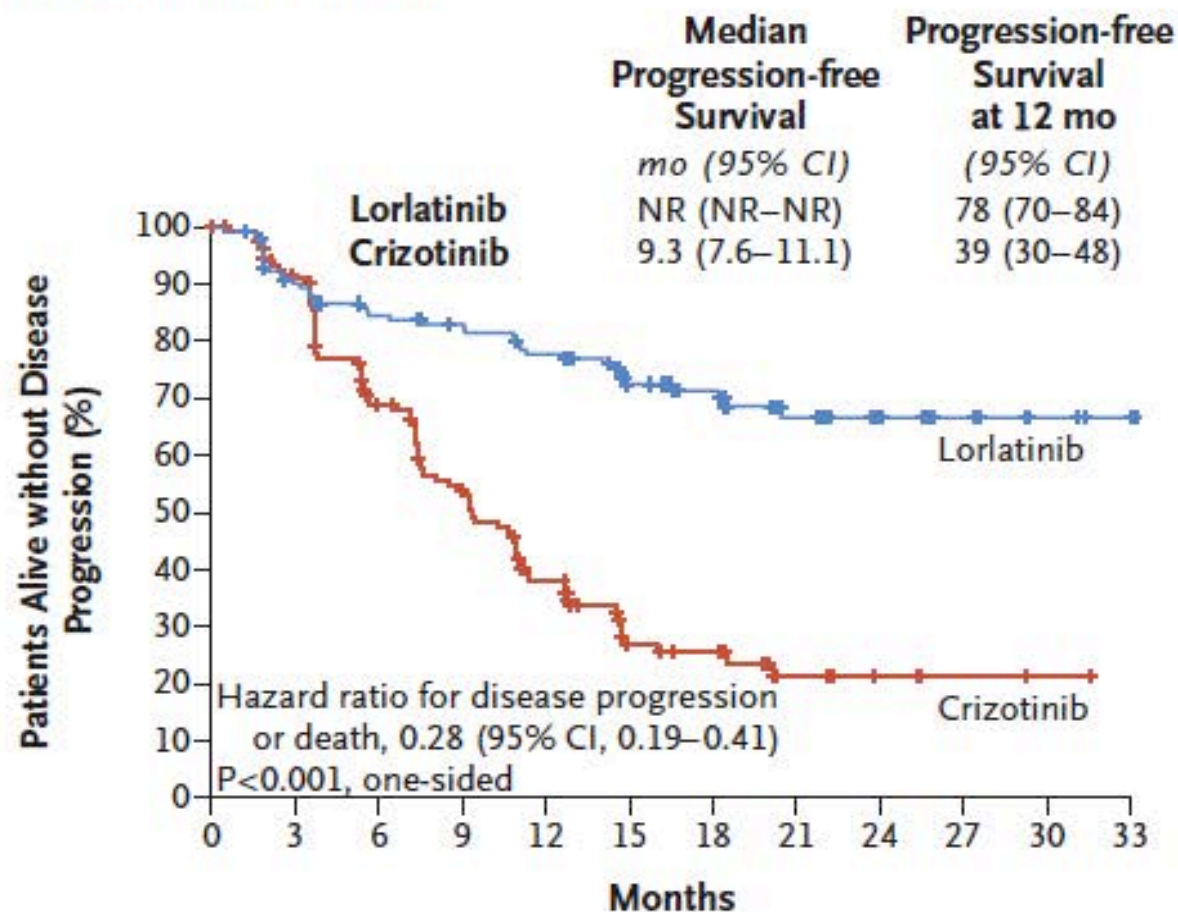
ORIGINAL ARTICLE

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

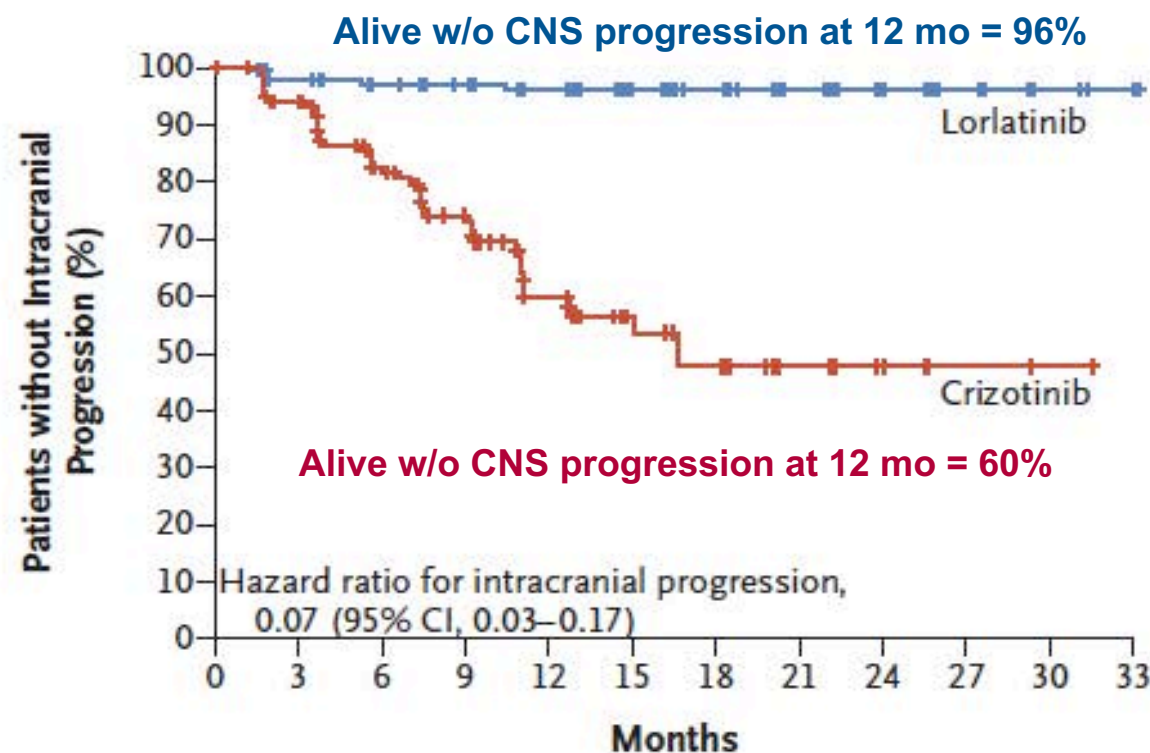
Alice T. Shaw, M.D., Ph.D., Todd M. Bauer, M.D., Filippo de Marinis, M.D., Ph.D.,
Enriqueta Felip, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Geoffrey Liu, M.D.,
Julien Mazieres, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Tony Mok, M.D.,
Anna Polli, B.Sc., Holger Thurm, M.D., Anna M. Calella, Ph.D.,
Gerson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

CROWN: PFS and Survival Without Intracranial Progression

Progression-free Survival

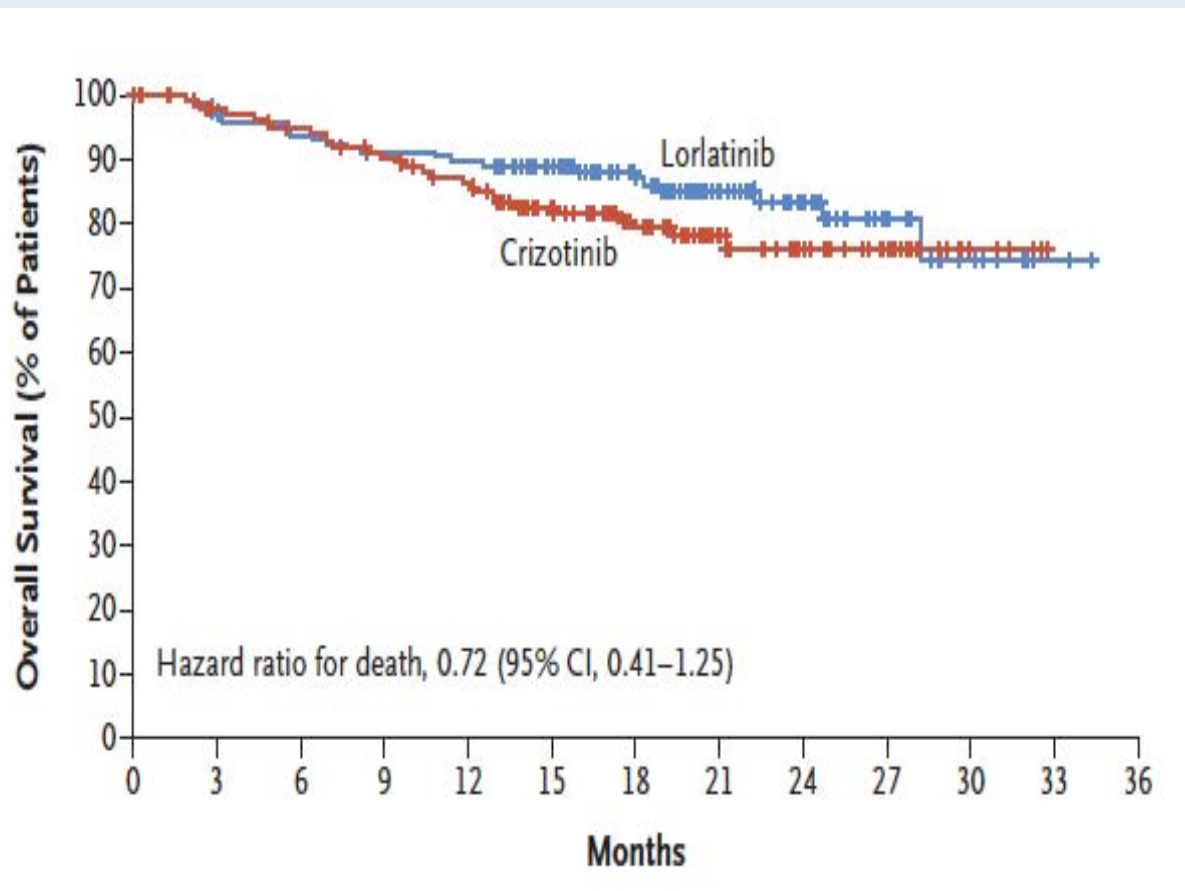


Survival without CNS Progression

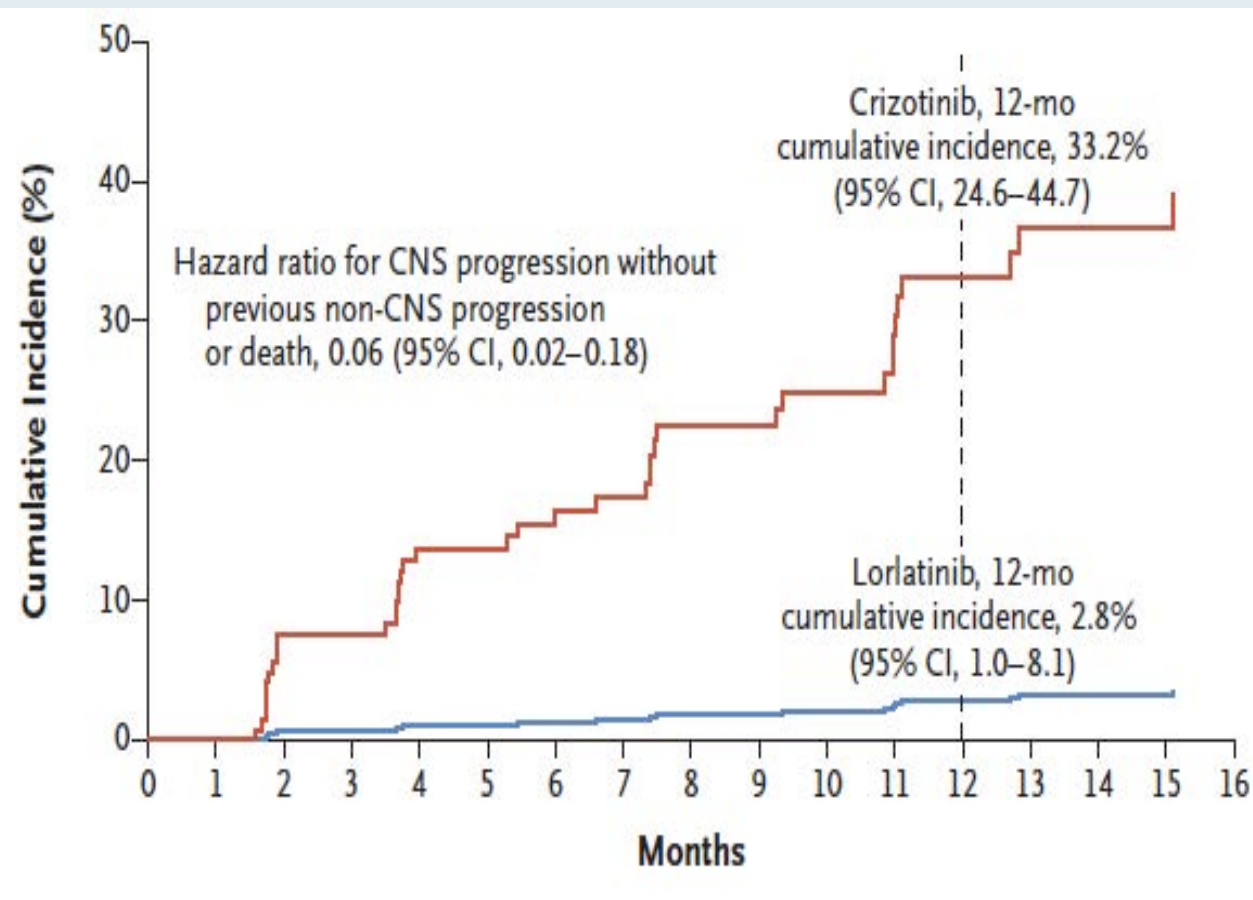


CROWN: OS and Cumulative Incidence of CNS Progression

Overall Survival



Cumulative Incidence of CNS Progression as First Event



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 ≥ 12 years of age with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy;
- Adult and pediatric patients ≥ 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.”

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

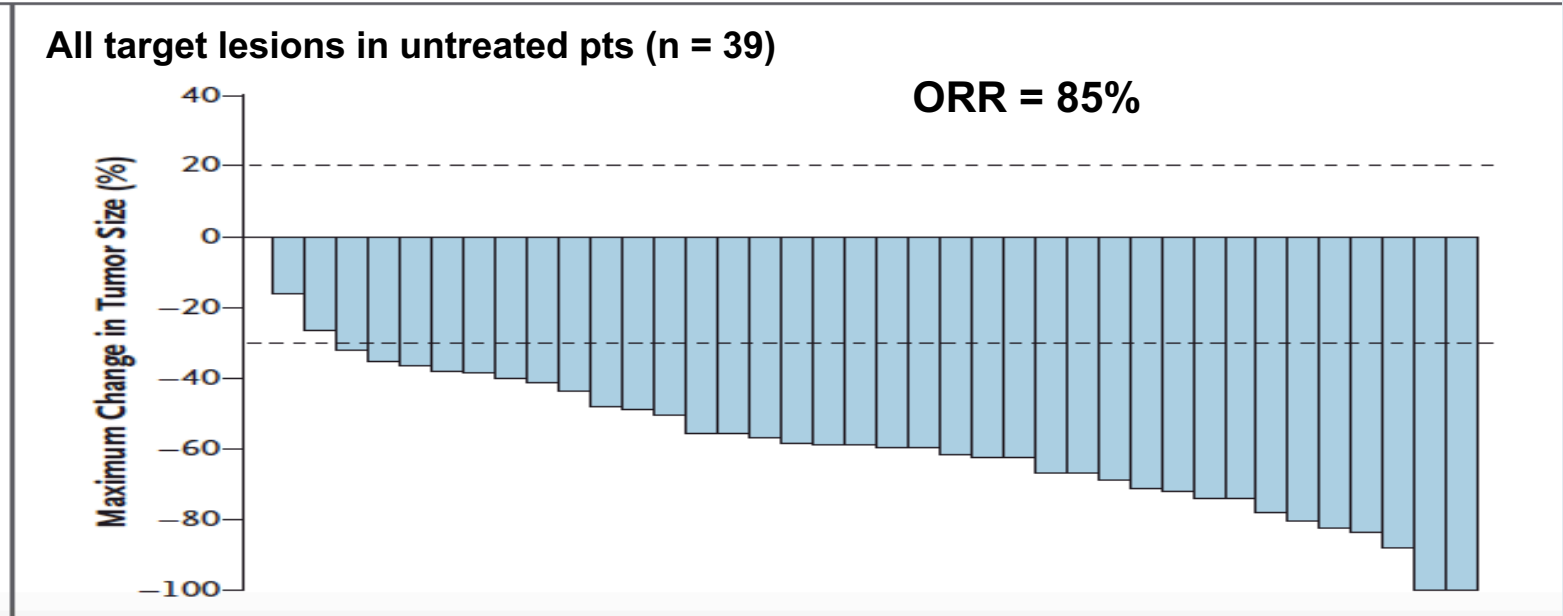
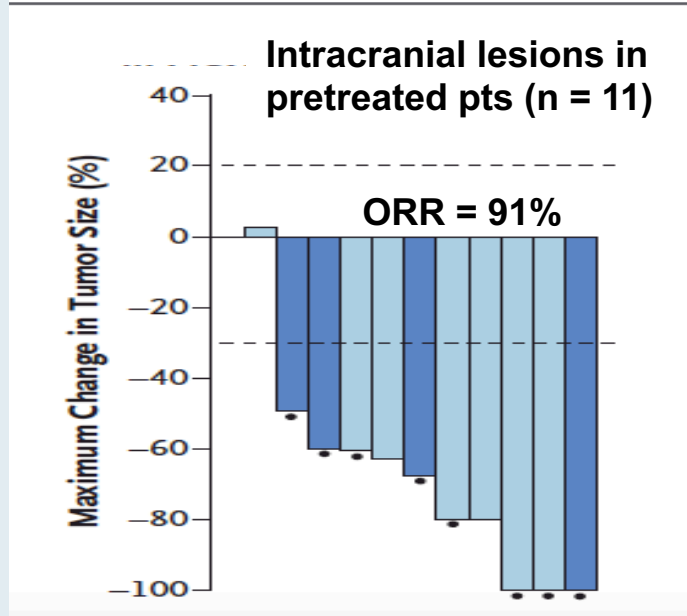
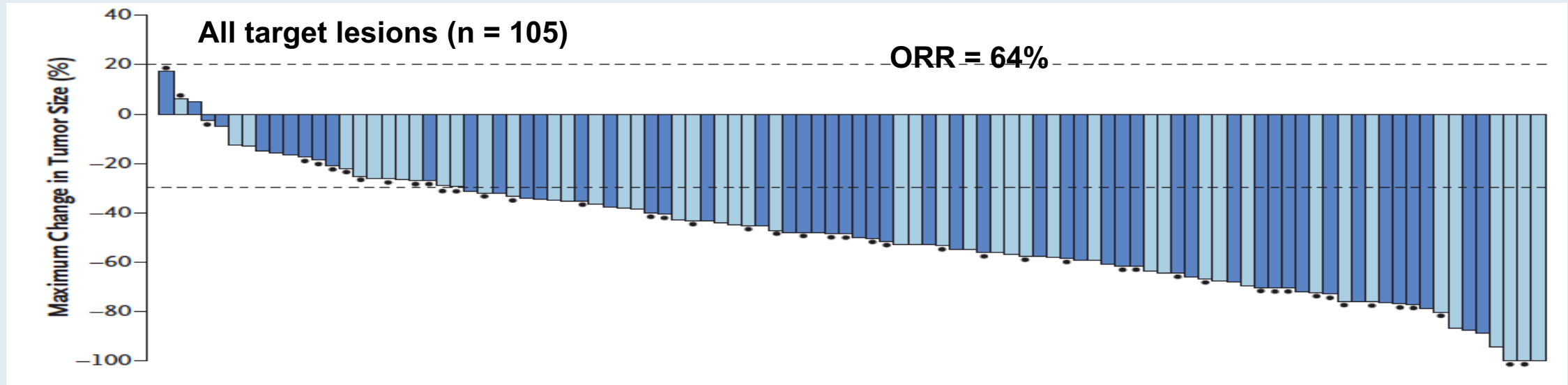
AUGUST 27, 2020

VOL. 383 NO. 9

Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

A. Drilon, G.R. Oxnard, D.S.W. Tan, H.H.F. Loong, M. Johnson, J. Gainor, C.E. McCoach, O. Gautschi, B. Besse, B.C. Cho, N. Peled, J. Weiss, Y.-J. Kim, Y. Ohe, M. Nishio, K. Park, J. Patel, T. Seto, T. Sakamoto, E. Rosen, M.H. Shah, F. Barlesi, P.A. Cassier, L. Bazhenova, F. De Braud, E. Garraalda, V. Velcheti, M. Satouchi, K. Ohashi, N.A. Pennell, K.L. Reckamp, G.K. Dy, J. Wolf, B. Solomon, G. Falchook, K. Ebata, M. Nguyen, B. Nair, E.Y. Zhu, L. Yang, X. Huang, E. Olek, S.M. Rothenberg, K. Goto, and V. Subbiah

LIBRETTO-001: Response by Independent Review



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

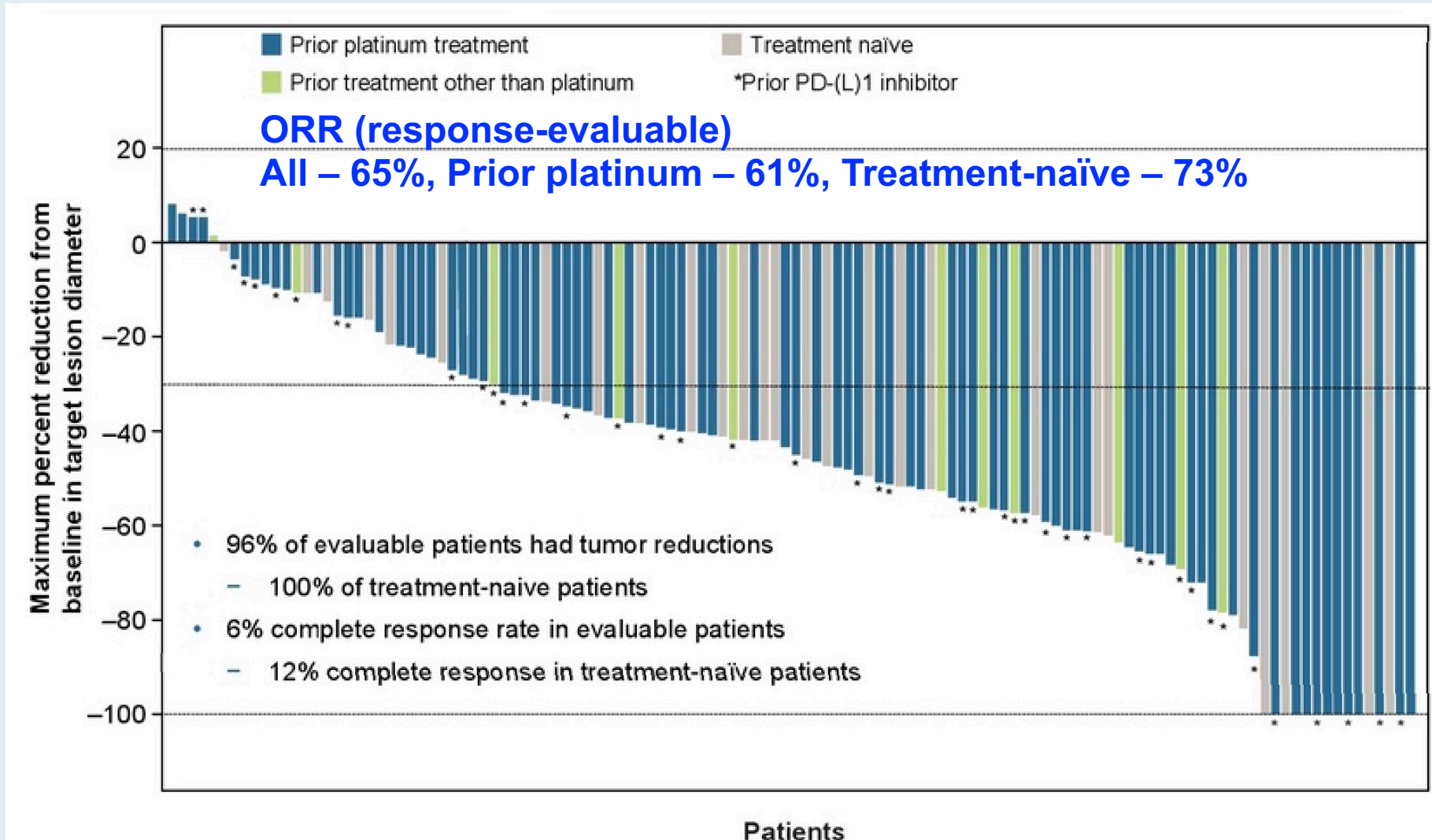
Press Release – September 4, 2020

“On September 4, 2020, the Food and Drug Administration granted accelerated approval to pralsetinib for adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

Today, FDA also approved the Oncomine Dx Target (ODxT) Test as a companion diagnostic for pralsetinib.

Efficacy was investigated in a multicenter, open-label, multi-cohort clinical trial (ARROW, NCT03037385) in patients whose tumors had RET alterations. Identification of RET gene alterations was prospectively determined in local laboratories using either next generation sequencing, fluorescence in situ hybridization, or other tests. The main efficacy outcome measures were overall response rate (ORR) and response duration determined by a blinded independent review committee using RECIST 1.1.”

ARROW Primary Endpoint: Response to Pralsetinib



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

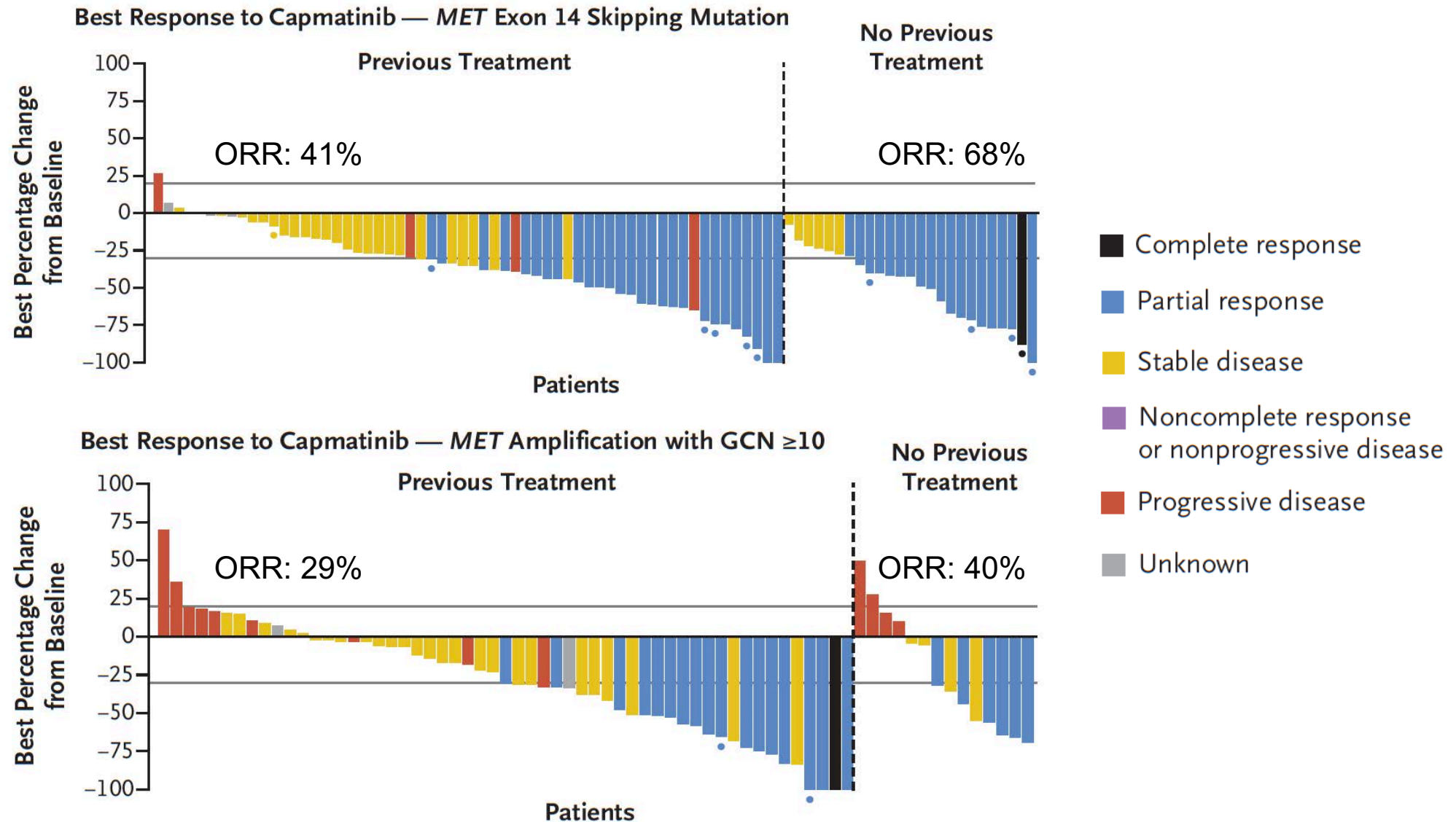
Capmatinib in *MET* Exon 14–Mutated or *MET*-Amplified Non–Small-Cell Lung Cancer

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



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

Press Release — February 03, 2021

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

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

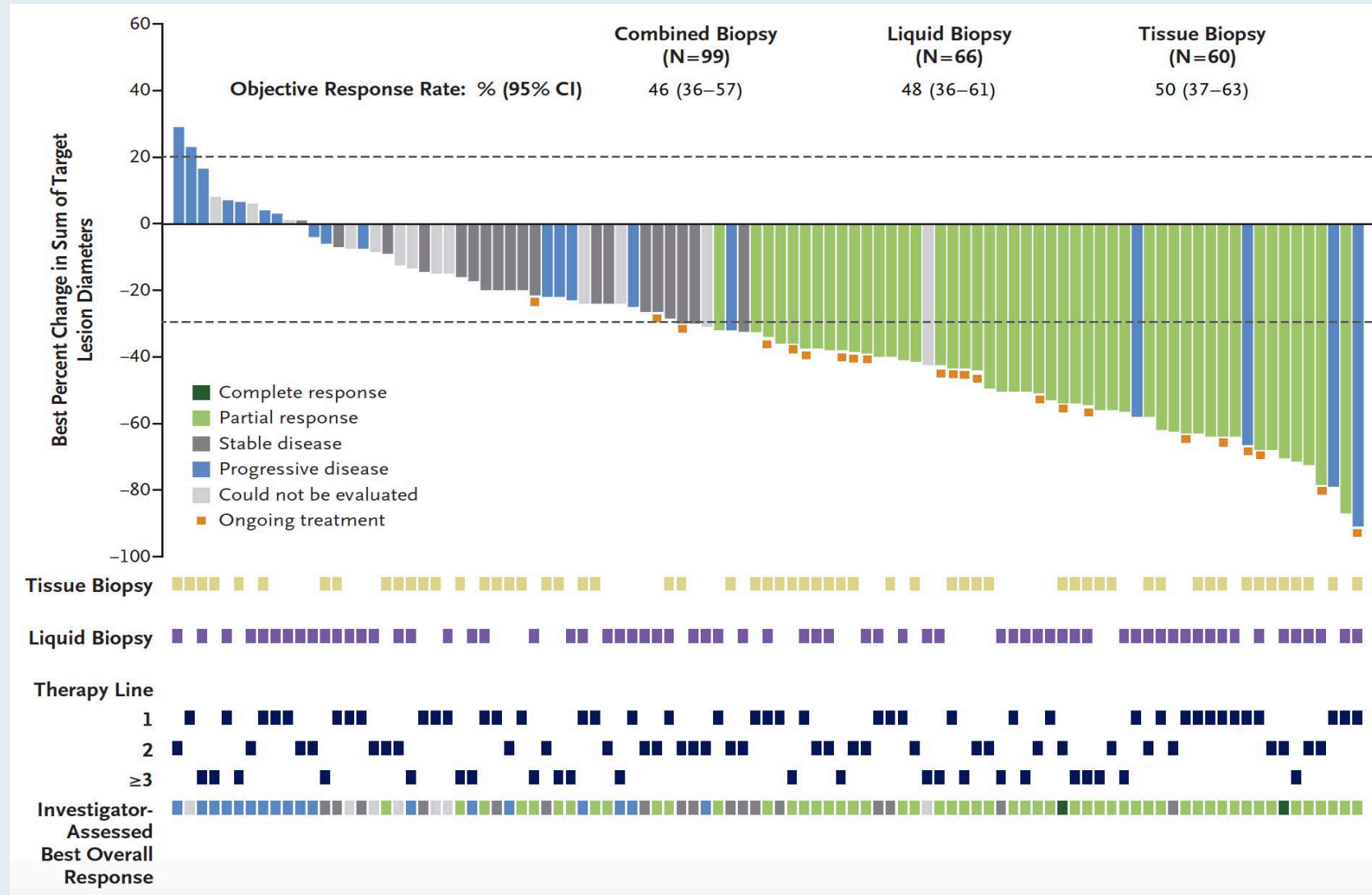
ORIGINAL ARTICLE

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

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

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

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



FDA Grants Breakthrough Therapy Designation to Trastuzumab Deruxtecan for Metastatic NSCLC with a HER2 Mutation

Press Release – May 18, 2020

- The FDA has granted breakthrough therapy designation to trastuzumab deruxtecan for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have a HER2 mutation and with disease progression on or after platinum-based therapy.
- The designation was granted based on data from the ongoing Phase II DESTINY-Lung01 trial currently testing trastuzumab deruxtecan, a HER2-directed antibody drug conjugate (ADC), in patients with HER2-mutant metastatic NSCLC.

Trastuzumab Deruxtecan in HER2-Mutated Metastatic Non-Small Cell Lung Cancer (NSCLC): Interim Results of DESTINY-Lung01¹

Trastuzumab Deruxtecan in HER2-Overexpressing Metastatic Non-Small Cell Lung Cancer (NSCLC): Interim Results of DESTINY-Lung01²

¹ Smit EF et al.

WCLC 2021;Abstract MA11.03.

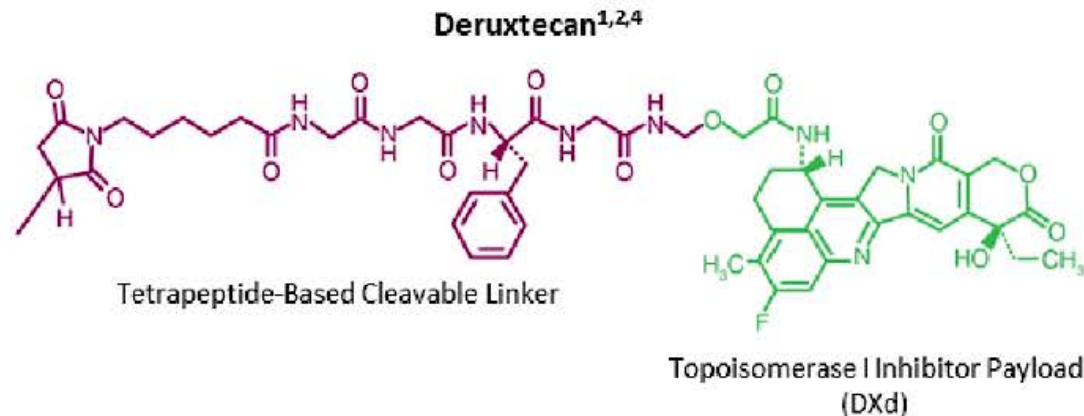
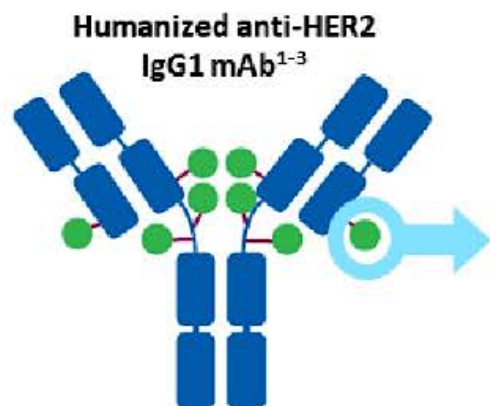
² Nakagawa K et al.

WCLC 2021;Abstract OA04.05.

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 ≈ 8

Payload with short systemic half-life

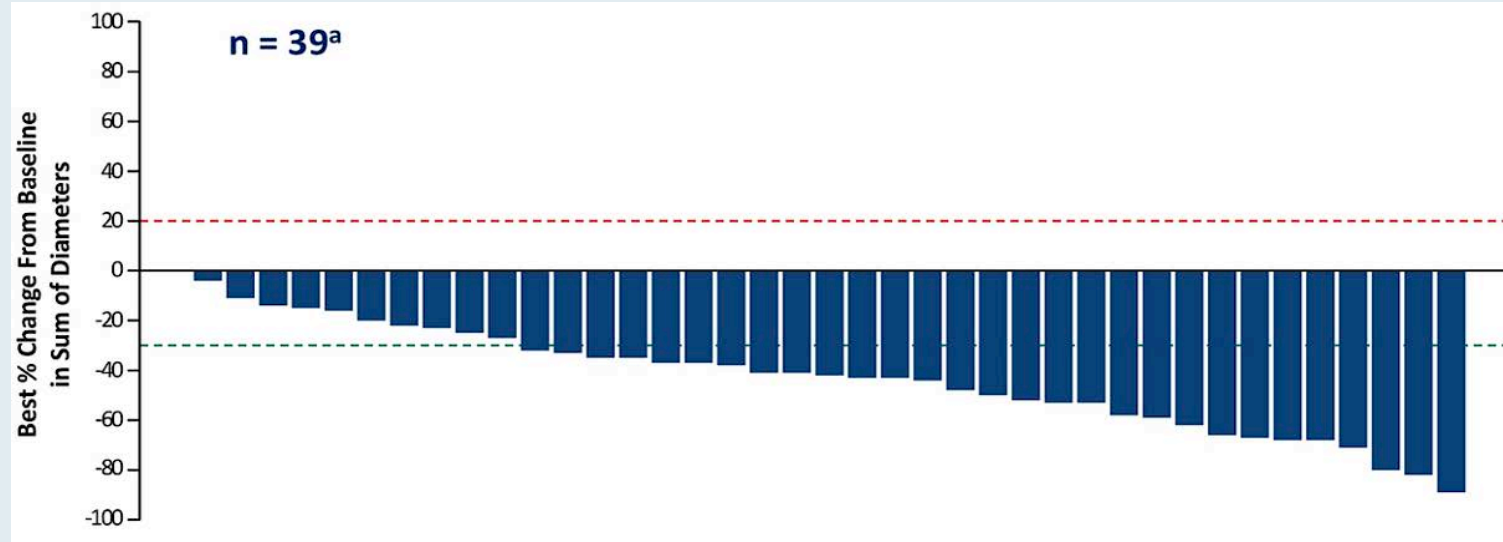
Stable linker-payload

Tumor-selective cleavable linker

Membrane-permeable payload

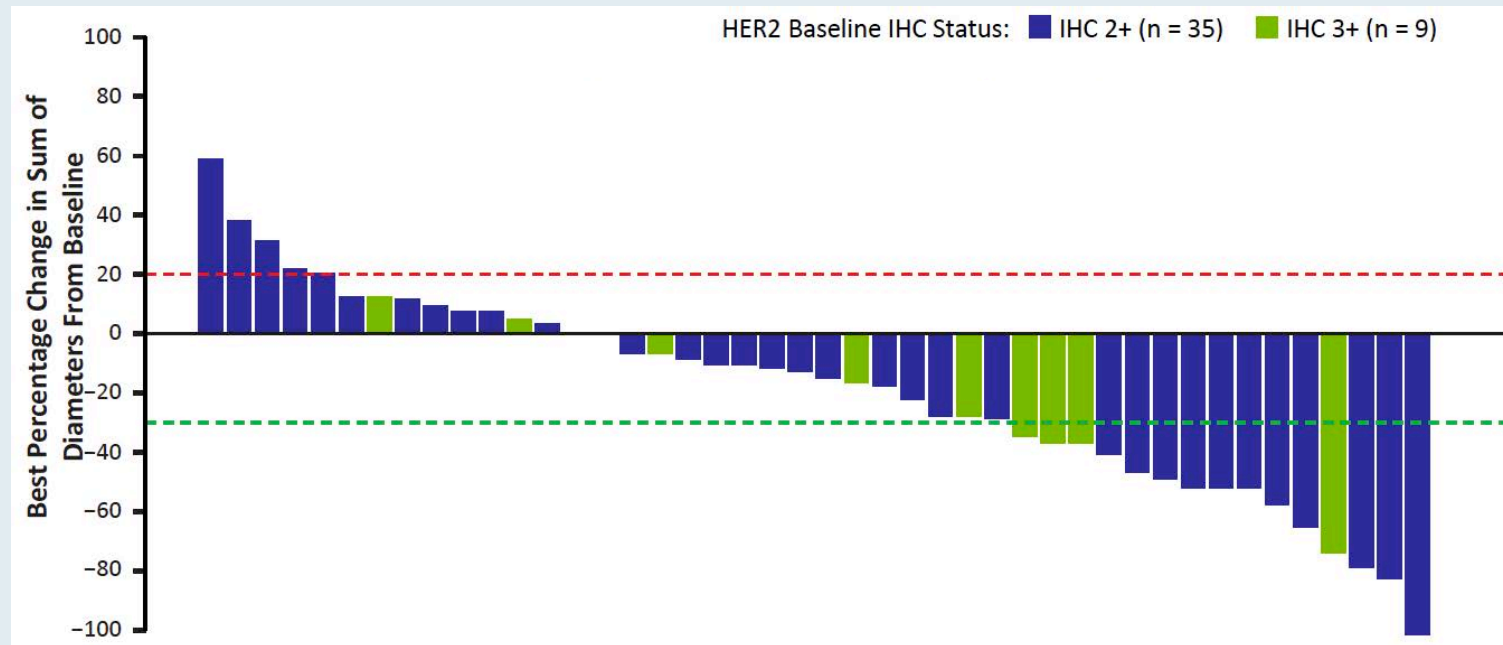
DESTINY-Lung01: Best Percentage Change in Tumor Size with T-DXd in HER2-Mutant versus Overexpressing NSCLC

Mutant



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

Overexpressing



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

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

Mutant

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

Overexpressing

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

FDA Grants Breakthrough Therapy Designation to Sotorasib for NSCLC With a KRAS G12C Mutation

Press Release – December 08, 2020

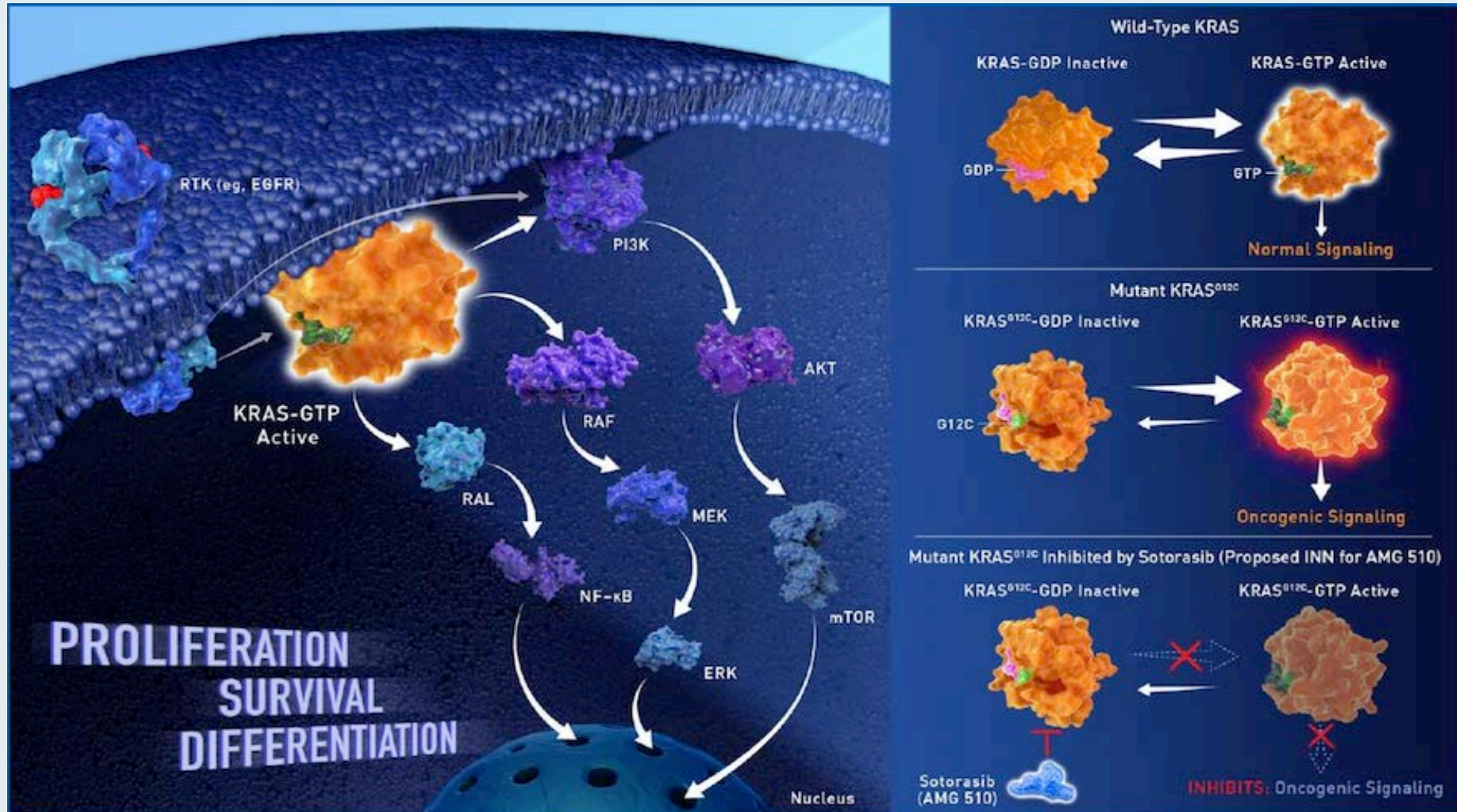
- The FDA has granted breakthrough therapy designation to the investigational KRASG12C inhibitor, sotorasib, for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *KRAS G12C* mutation, as determined by an FDA-approved test, following at least 1 prior systemic therapy.
- The designation is supported by positive phase 2 results from the CodeBreak 100 clinical study in patients with advanced NSCLC whose cancer had progressed despite prior treatment with chemotherapy and/or immunotherapy.
 - In the study, treatment with sotorasib provided patients with durable anticancer activity and a positive benefit-risk profile.
- Notably, *KRAS G12C* is the most common *KRAS* mutation in NSCLC

CodeBreakK100: Registrational Phase 2 Trial of Sotorasib in KRASp.G12C Mutated Non-small Cell Lung Cancer

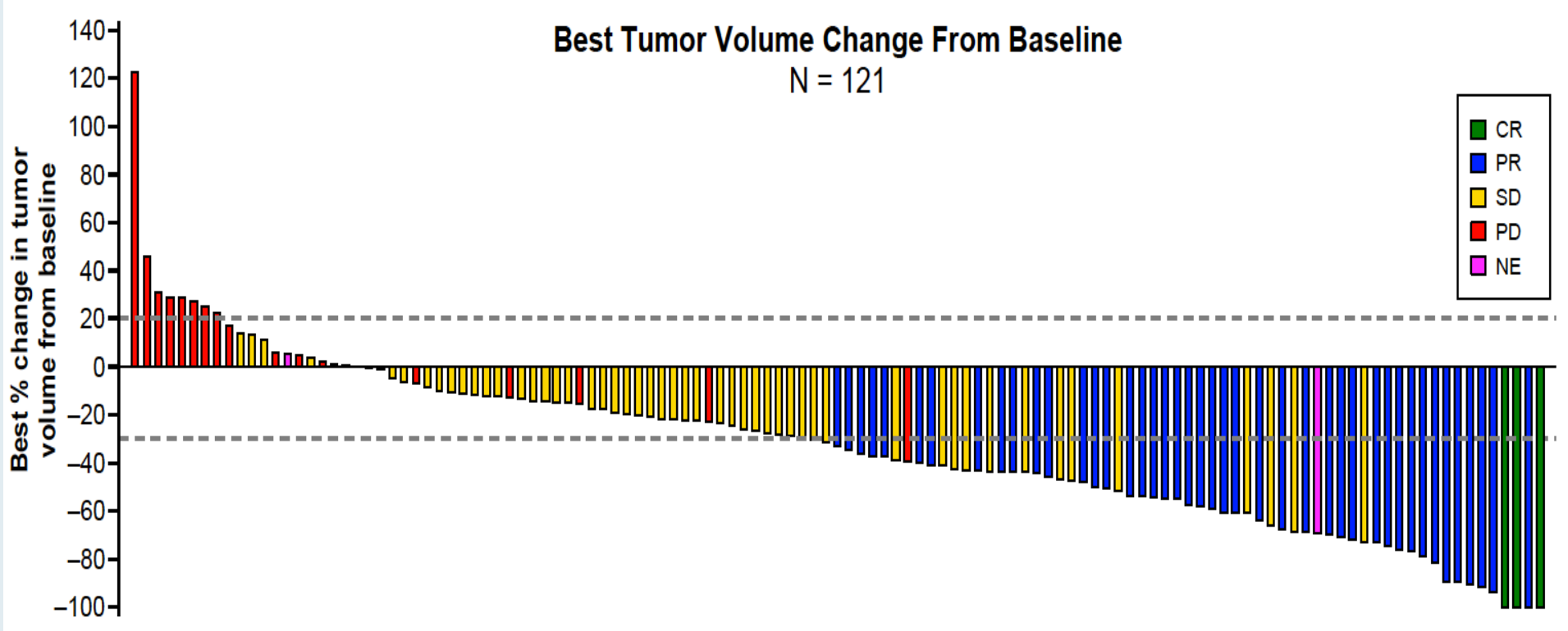
Li BT et al.

WCLC 2021;Abstract PS01.07.

Mechanism of Action of Sotorasib (AMG 510) – KRASG12C inhibitor



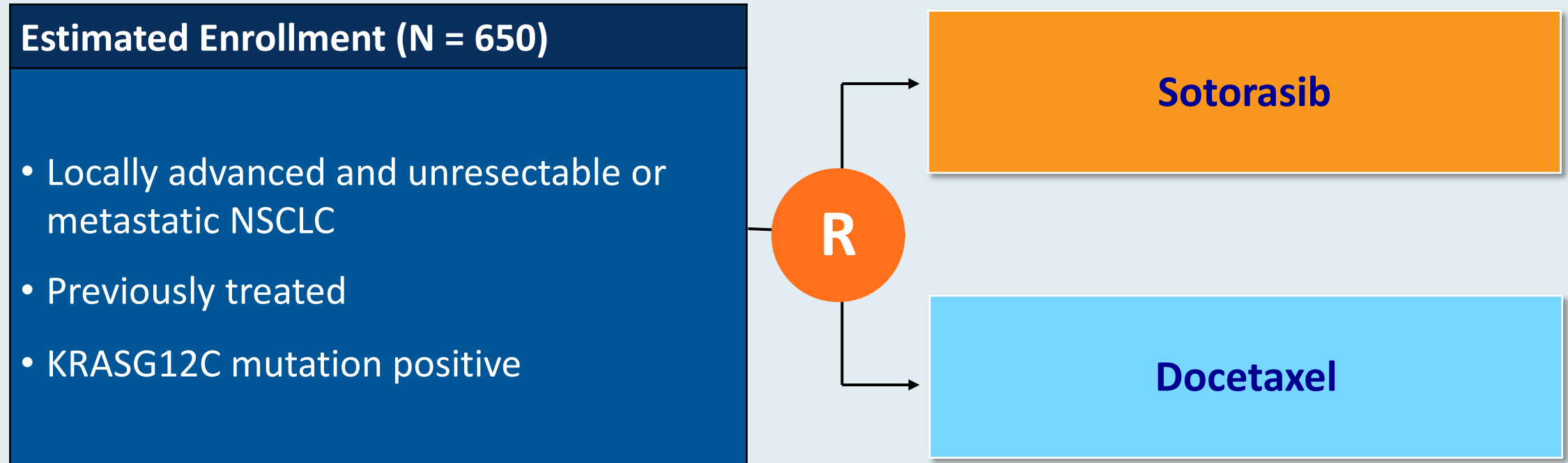
CodeBreak 100 Trial: Response and Survival Outcomes



Data cutoff: December 1, 2020; median follow-up time: 12.2 months

Outcome	960 mg (n = 124)
ORR	37.1%
DCR	80.6%
PR	43.0%
mPFS	6.8 mo
mOS	Not evaluable

Ongoing Phase III CodeBreak 200 Trial Design



Primary endpoint: PFS

Secondary endpoints include: OS, ORR, DoR and QoL

Agenda

Module 1: NSCLC with an EGFR Tumor Mutation

- Dr Carrizosa: A 78-year-old woman with Stage IB adenocarcinoma – EGFR exon 19 deletion
 - Parts 1 and 2

Module 2: Metastatic NSCLC Harboring Other Mutations

- Dr Mitchell: A 58-year-old woman with mNSCLC – BRAF V600E mutation
- Dr Carrizosa: A man in his mid-20s and smoker with mNSCLC – NTRK mutation

Module 3: Localized or Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

- Dr Picton: A 66-year-old woman and smoker with locally advanced NSCLC

Module 4: Newly Diagnosed NSCLC with No Actionable Mutation

- Dr Lamar: A 94-year-old woman with metastatic NSCLC – PD-L1 75%, no EGFR mutation

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

- Dr Deutsch: A 66-year-old woman with extensive-stage SCLC

Case Presentation – Dr Picton: A 66-year-old woman and smoker with locally advanced NSCLC



Dr Maria E Picton

- Incidentally diagnosed with locally advanced NSCLC during a work up after a fall
- Patient is not a surgical candidate due to positive stress test
- 10/2020: Chemoradiation therapy, with carboplatin/pemetrexed
- Plan to complete 4 cycles followed by maintenance durvalumab

Questions

- If this patient did not have a positive stress test and had undergone surgery, would you still offer the durvalumab maintenance?
- In patients with lung cancer and rheumatoid arthritis, should we discontinue their disease-modifying agents when treating them with chemoimmunotherapy?

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?

1. Durvalumab
2. Osimertinib
3. Durvalumab + osimertinib
4. Durvalumab followed by osimertinib
5. Other

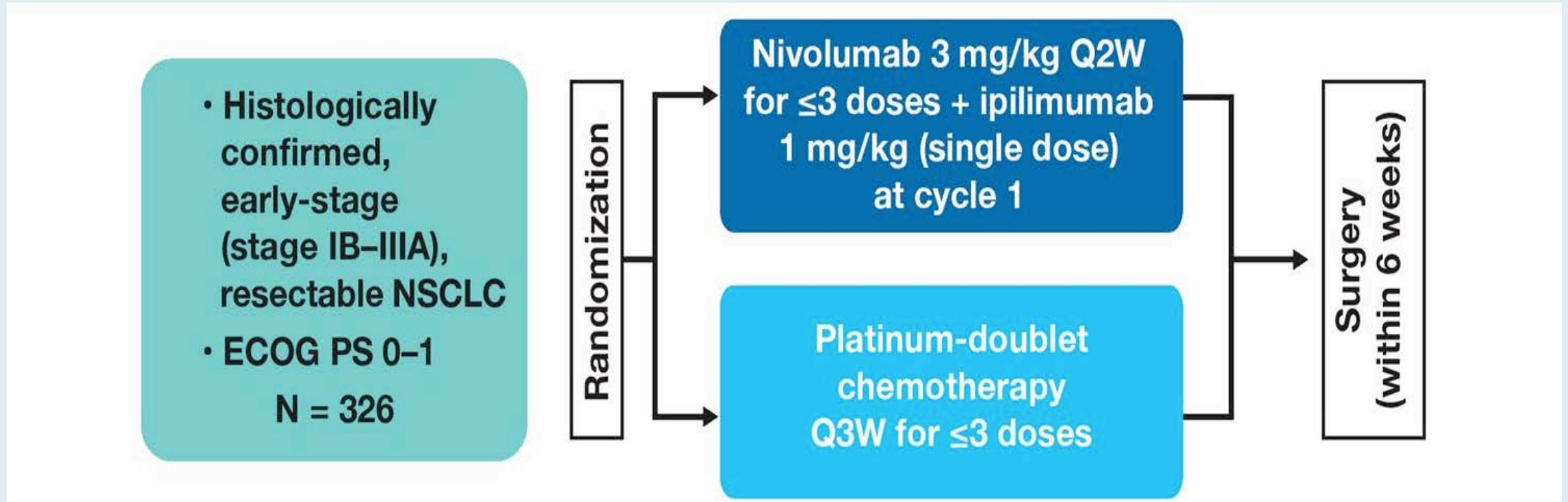
CheckMate 816 Met a Primary Endpoint of Improved pCR with Neoadjuvant Nivolumab in Combination with Chemotherapy

Press Release — October 07, 2020

“The Phase 3 CheckMate 816 trial met a primary endpoint of pathologic complete response (pCR) in resectable non-small cell lung cancer (NSCLC). In the trial, significantly more patients treated with nivolumab plus chemotherapy before surgery showed no evidence of cancer cells in their resected tissue compared to those treated with chemotherapy alone. CheckMate 816 is the first and only Phase 3 trial to demonstrate a benefit with an immune checkpoint inhibitor in combination with chemotherapy as a neoadjuvant treatment in non-metastatic NSCLC.

Patients in the experimental arm of the trial received up to three doses of nivolumab plus chemotherapy prior to surgery, a standard number of cycles of therapy in the neoadjuvant setting. The safety profile of nivolumab plus chemotherapy was consistent with previously reported studies in NSCLC.”

Phase III CheckMate 816 Trial Design



Primary endpoints: EFS and pCR

Secondary endpoints include: OS, major pathological response, time to death or distant metastases

ORIGINAL ARTICLE

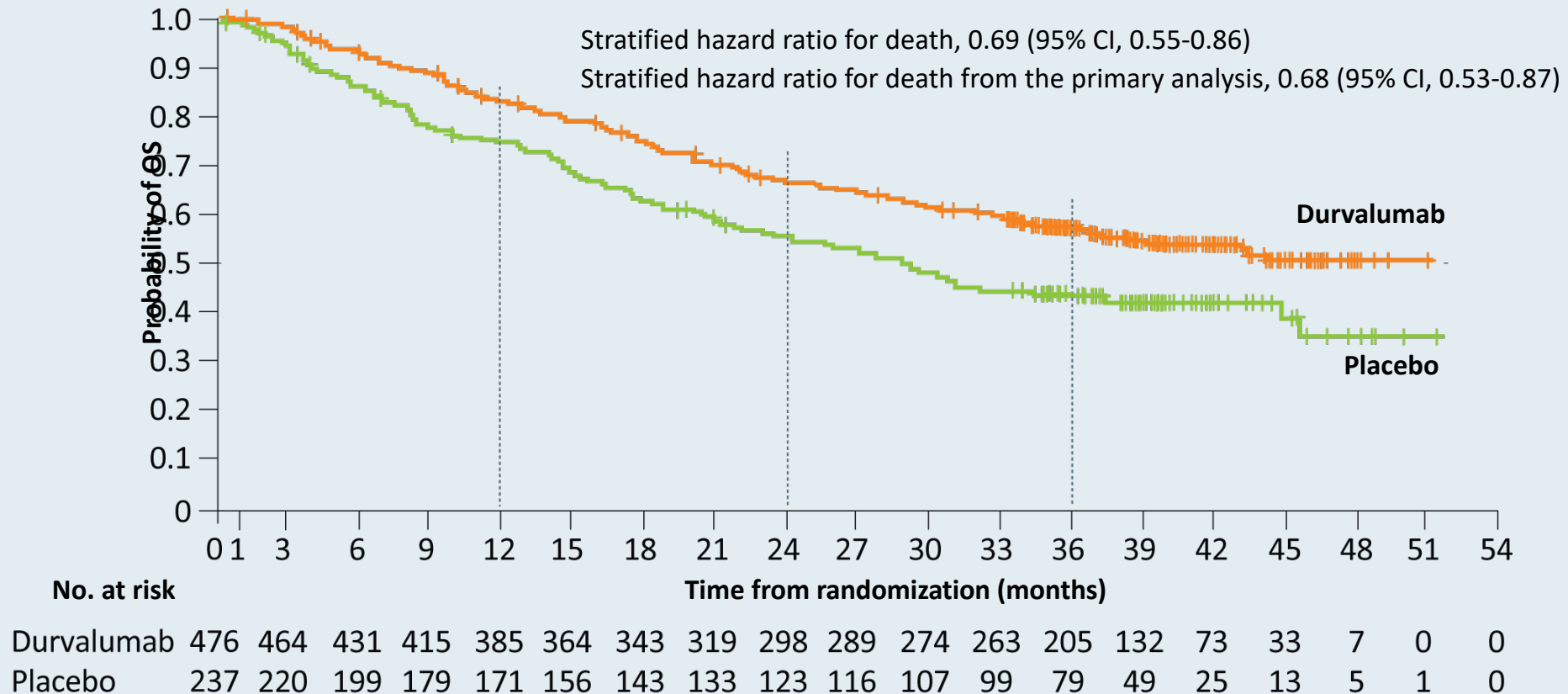
Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

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. Hiret, 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: 3-Year Overall Survival Analysis in the Intention-to-Treat Population

	No. of events/ total no. of patients (%)	Median OS (95% CI) months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %
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 ≥ 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

Agenda

Module 1: NSCLC with an EGFR Tumor Mutation

- Dr Carrizosa: A 78-year-old woman with Stage IB adenocarcinoma – EGFR exon 19 deletion
 - Parts 1 and 2

Module 2: Metastatic NSCLC Harboring Other Mutations

- Dr Mitchell: A 58-year-old woman with mNSCLC – BRAF V600E mutation
- Dr Carrizosa: A man in his mid-20s and smoker with mNSCLC – NTRK mutation

Module 3: Localized or Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

- Dr Picton: A 66-year-old woman and smoker with locally advanced NSCLC

Module 4: Newly Diagnosed NSCLC with No Actionable Mutation

- Dr Lamar: A 94-year-old woman with metastatic NSCLC – PD-L1 75%, no EGFR mutation

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

- Dr Deutsch: A 66-year-old woman with extensive-stage SCLC

Case Presentation – Dr Lamar: A 94-year-old woman with metastatic NSCLC – PD-L1 75%, no EGFR mutation



Dr Zanetta S Lamar

- ECOG performance status of 3 at diagnosis
- Pembrolizumab, with significant partial response after 4 cycles
- ECOG performance status of 0; “best she has ever felt”

Questions

- How long do you continue single-agent PD-L1 inhibitors in responding patients? Do you stop after 2 years?

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

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

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

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

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

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

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

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

⁹ Spigel DR et al. ESMO 2019;Abstract LBA78

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

Press Release — May 15, 2020

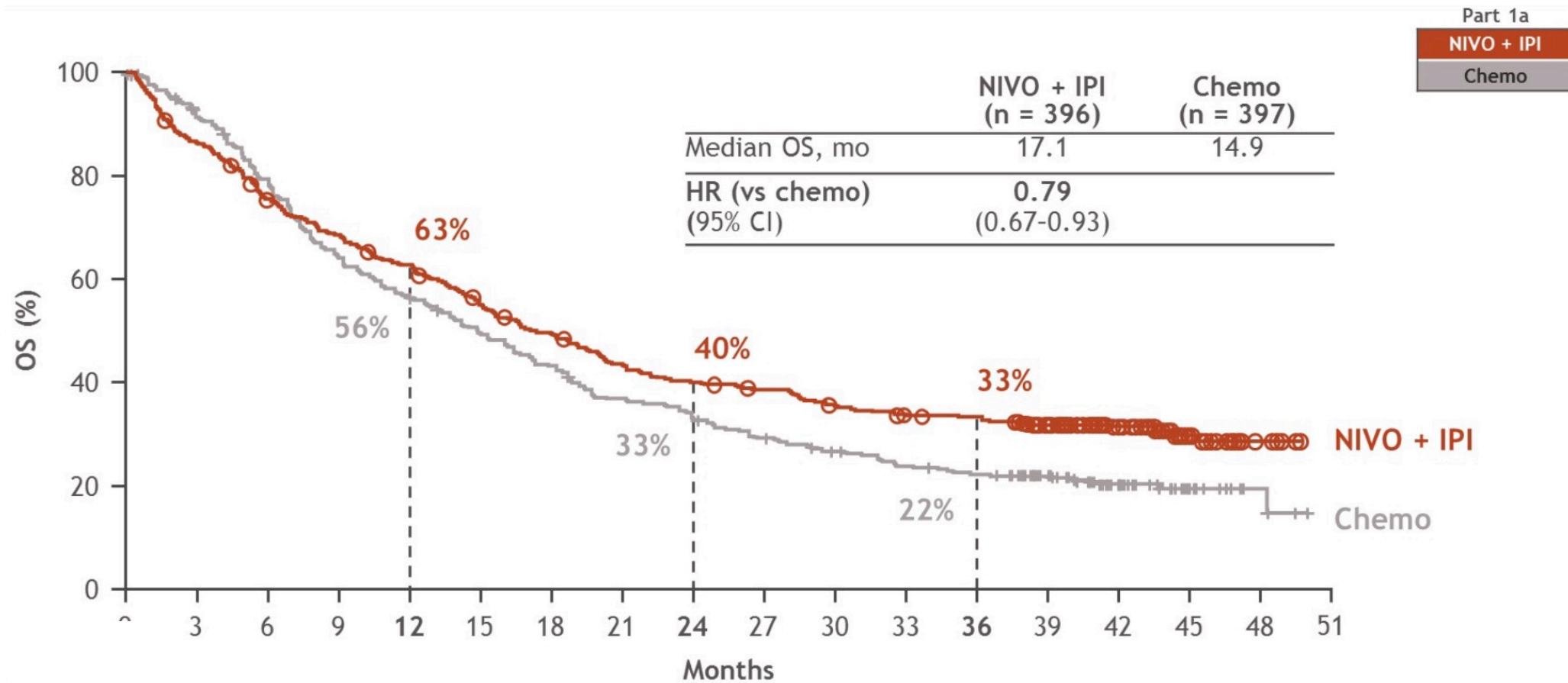
“The Food and Drug Administration approved the combination of nivolumab plus ipilimumab as first-line treatment for patients with metastatic non-small cell lung cancer whose tumors express PD-L1($\geq 1\%$), as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic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

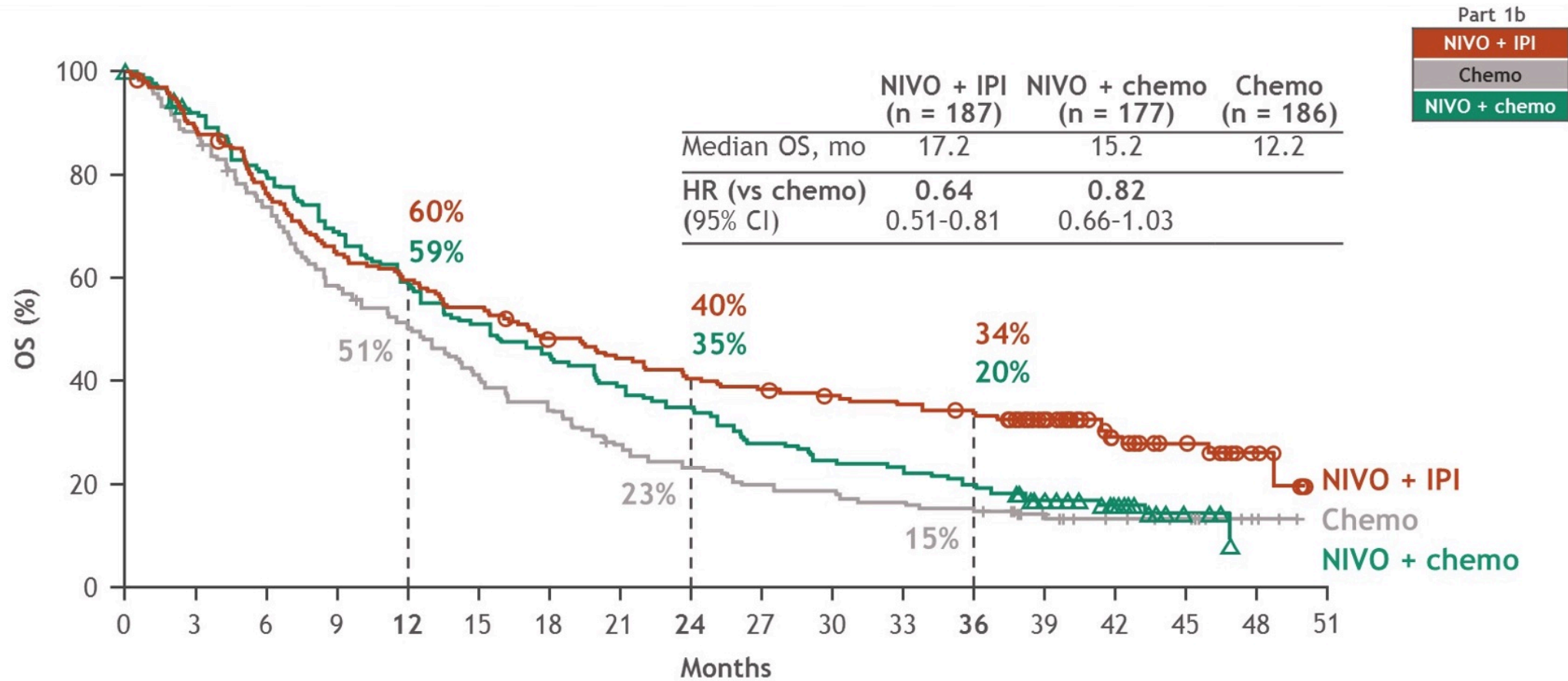
Nivolumab + Ipilimumab versus Platinum-Doublet Chemotherapy as First-Line Treatment for Advanced Non-Small Cell Lung Cancer: Three-Year Update from CheckMate 227 Part 1

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%)



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

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

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

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).”

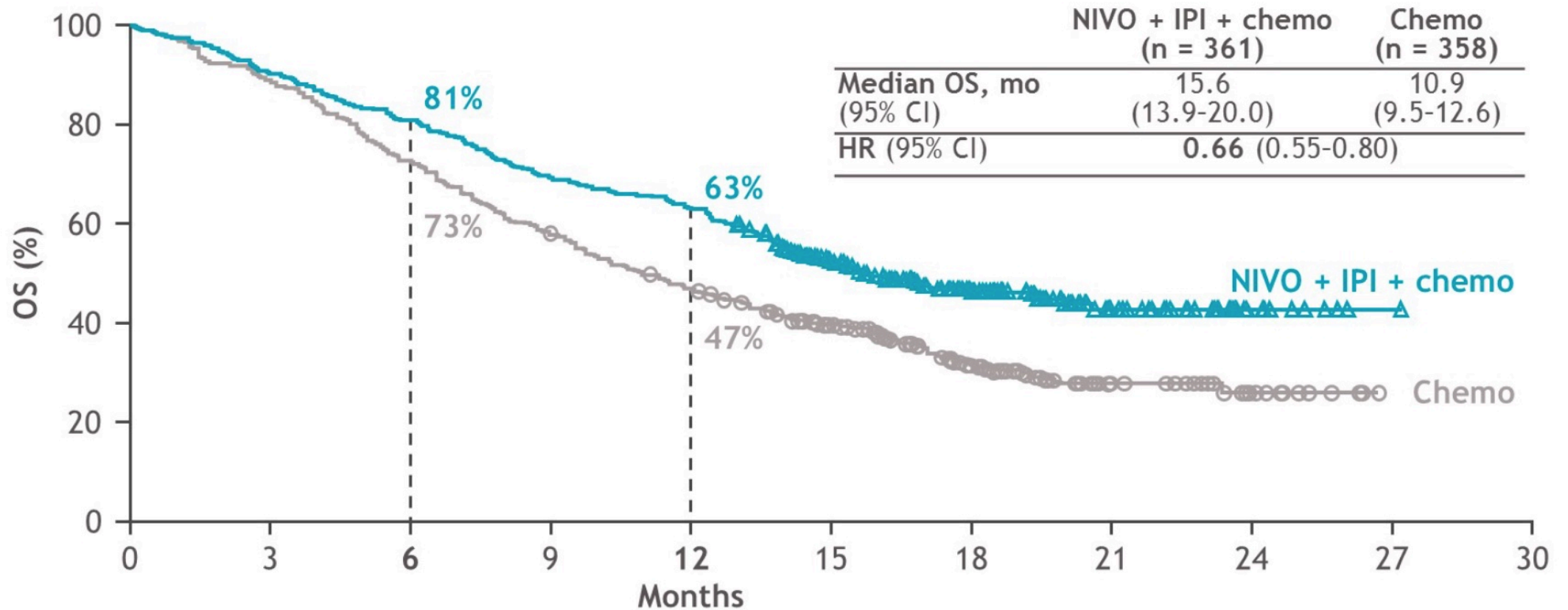
Lancet Oncol 2021;22(2):198-211.



First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial

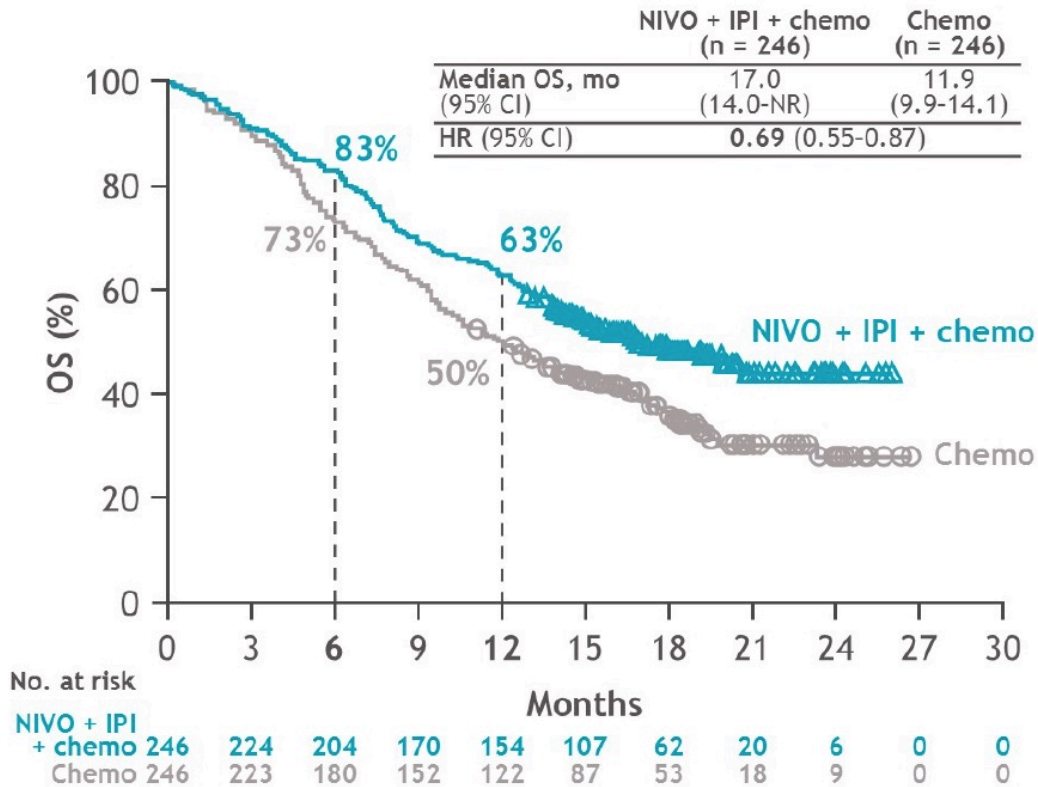
Luis Paz-Ares, Tudor-Eliade Ciuleanu, Manuel Cobo, Michael Schenker, Bogdan Zurawski, Juliana Menezes, Eduardo Richardet, Jaafar Bennouna, Enriqueta Felip, Oscar Juan-Vidal, Aurelia Alexandru, Hiroshi Sakai, Alejo Lingua, Pamela Salman, Pierre-Jean Souquet, Pedro De Marchi, Claudio Martin, Maurice Pérol,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

CheckMate 9LA: Updated OS

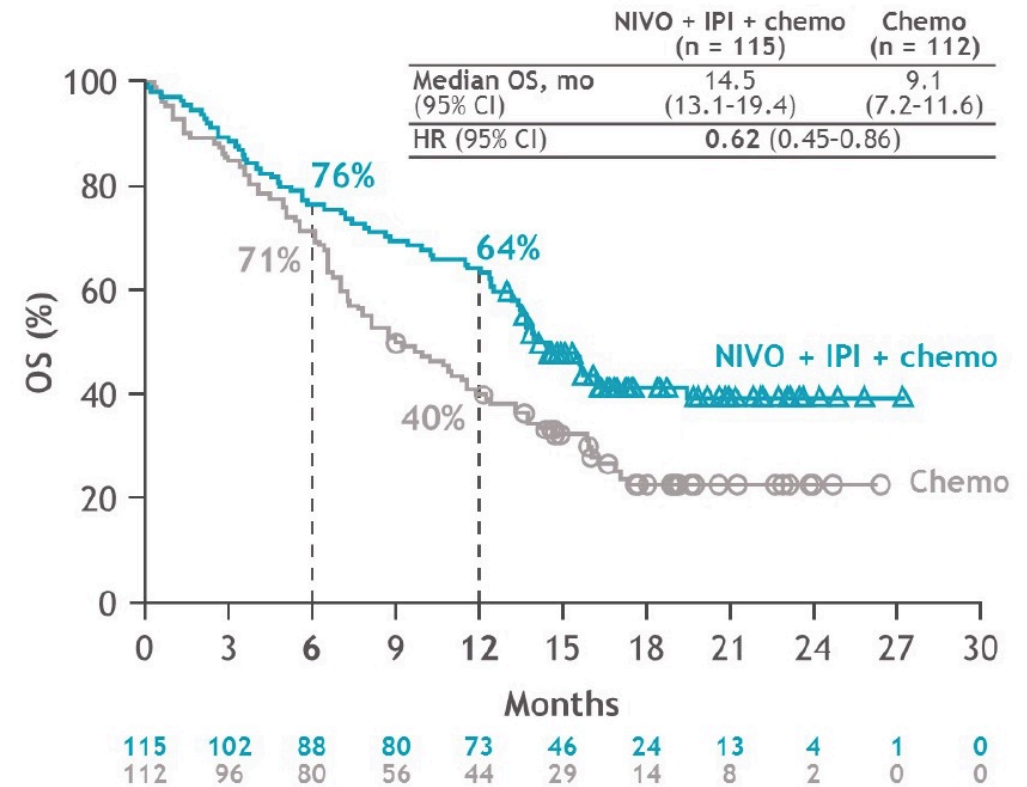


CheckMate 9LA: Updated OS by Histology

NSQ NSCLC^a



SQ NSCLC^b



FDA Grants Priority Review to Frontline Cemiplimab for PD-L1-High Advanced or Metastatic NSCLC

Press Release — October 29, 2020

“The FDA has accepted the supplemental Biologics License Application (sBLA) for cemiplimab-rwlc and granted it Priority Review for the frontline treatment of patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) with $\geq 50\%$ PD-L1 expression. The Prescription Drug User Fee Act target action date for this potential approval is set to February 28, 2021.

The sBLA for cemiplimab as treatment of this patient population was supported by findings from the phase 3 EMPOWER-Lung 1 clinical trial of cemiplimab versus chemotherapy in patients with advanced or metastatic PD-L1–positive NSCLC, for which topline results were recently presented during the European Society of Medical Oncology (ESMO) Virtual Annual Congress 2020.”

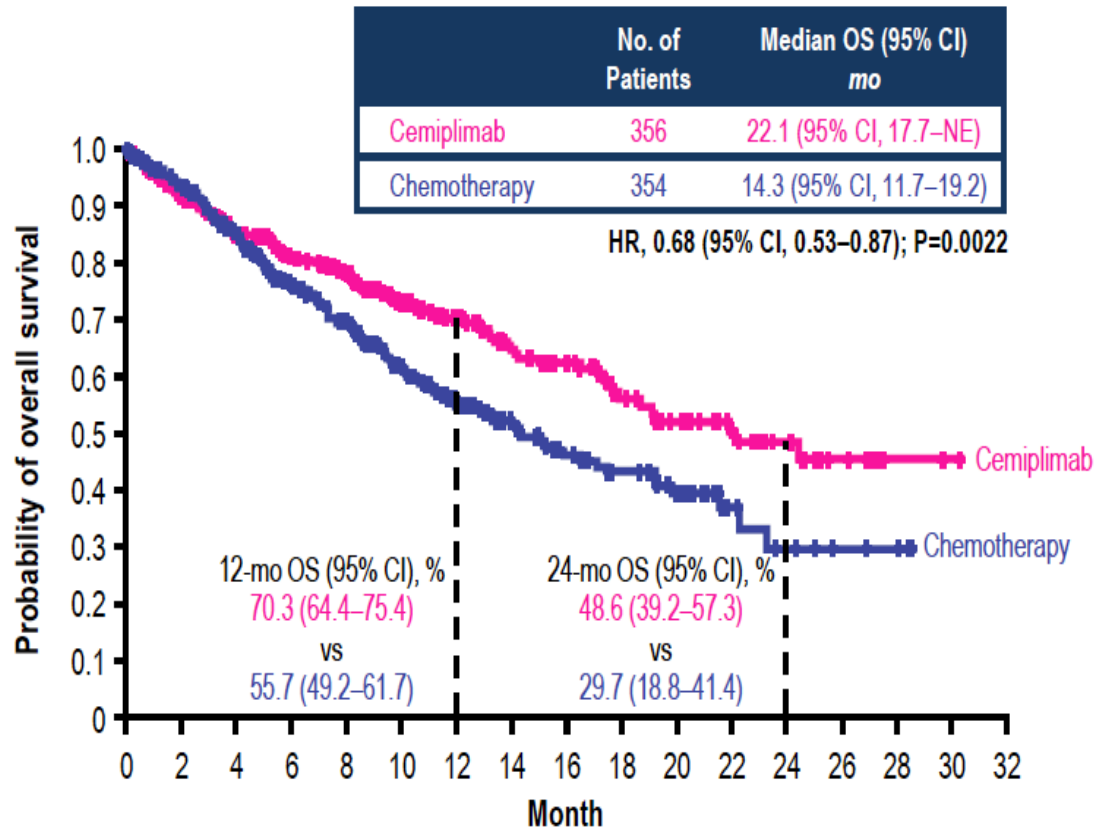
EMPOWER-Lung 1: Phase 3 First-Line (1L) Cemiplimab Monotherapy vs Platinum-Doublet Chemotherapy (Chemo) in Advanced Non-Small Cell Lung Cancer (NSCLC) with Programmed Cell Death-Ligand 1 (PD-L1) $\geq 50\%$

Sever A et al.

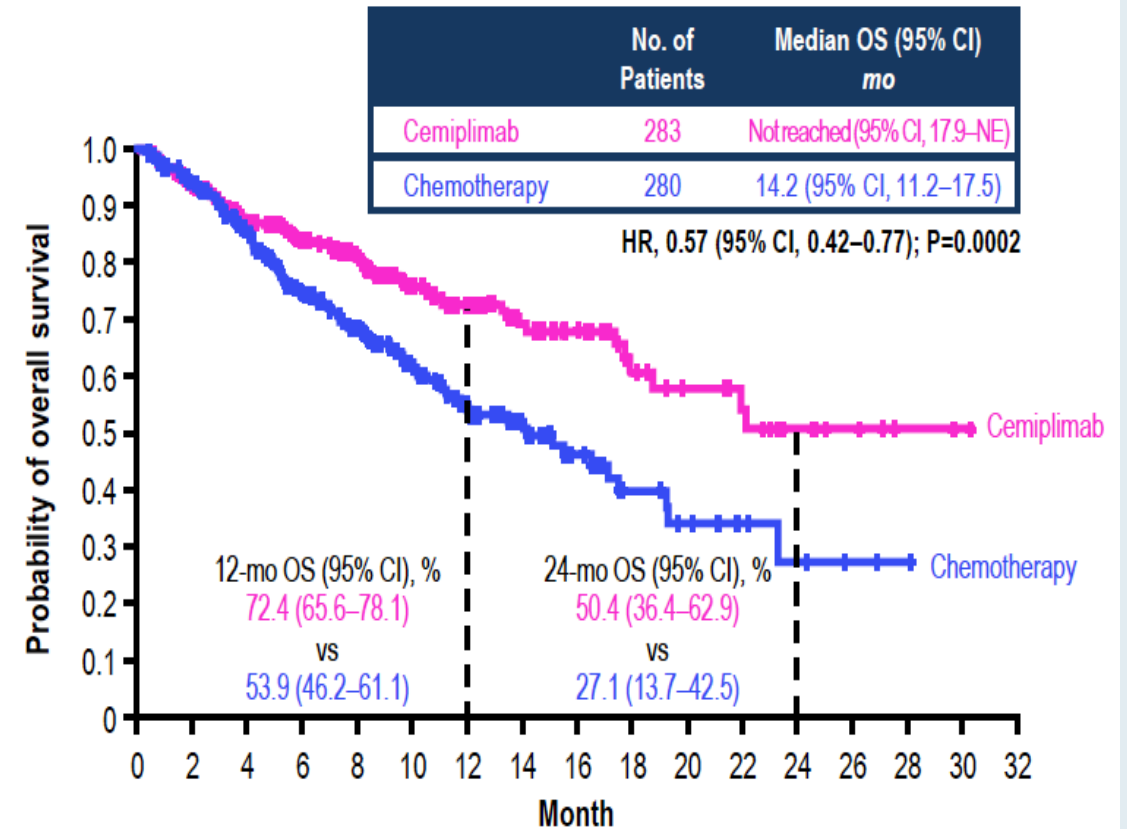
ESMO 2020;Abstract LBA52.

EMPOWER-Lung 1 Trial of 1L Cemiplimab: OS

ITT

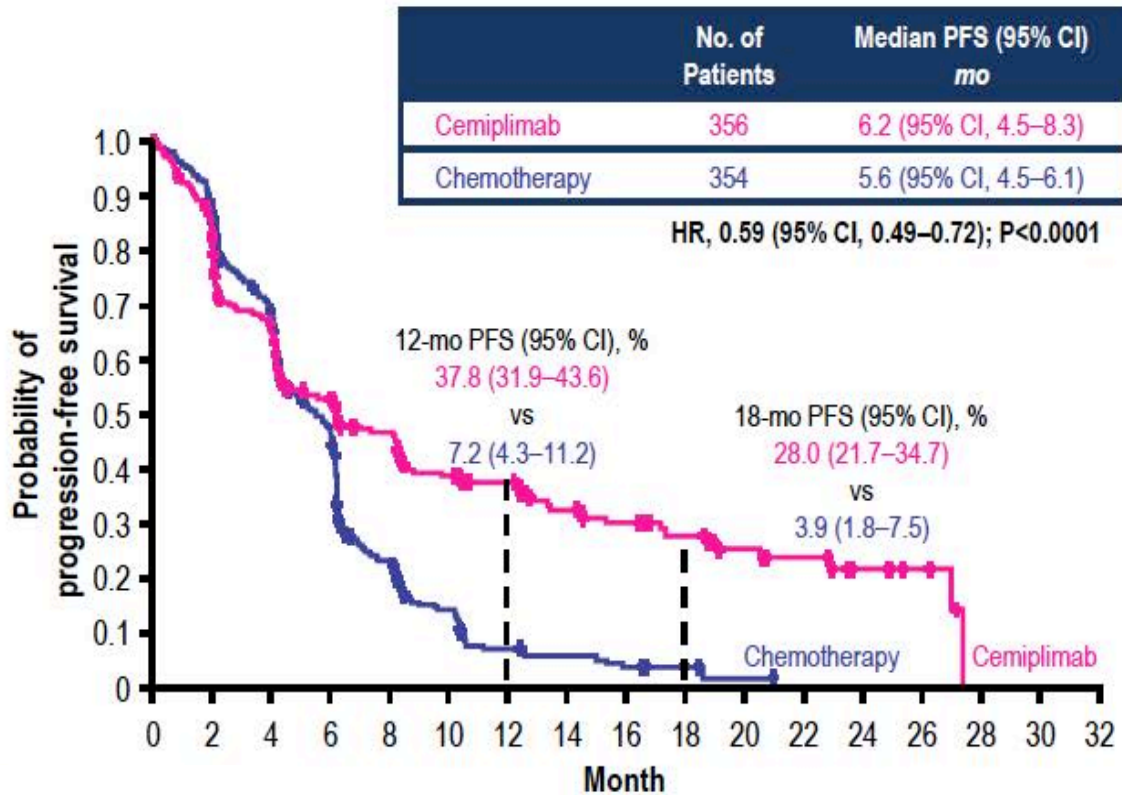


PD-L1 $\geq 50\%$ ITT

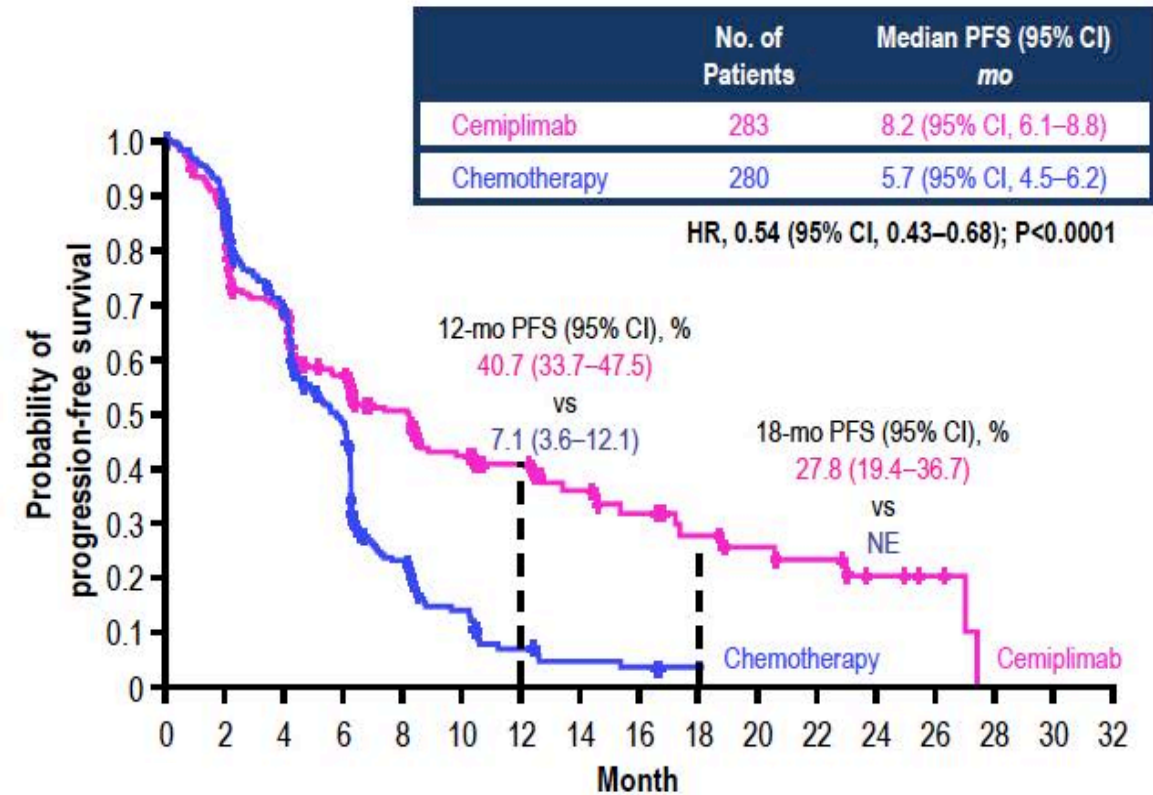


EMPOWER-Lung 1 Trial of 1L Cemiplimab: PFS

ITT



PD-L1 $\geq 50\%$ ITT



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- Dr Deutsch: A 66-year-old woman with extensive-stage SCLC

Case Presentation – Dr Deutsch: A 66-year-old woman with extensive-stage SCLC



Dr Margaret Deutsch

- 7/2018: Initially diagnosed with limited-stage SCLC and treated with cisplatin/etoposide, with BID radiation therapy and PCI
- 7/2019: New hepatic and adrenal metastatic disease → Ipilimumab/nivolumab
- 2/2020: SRS to residual adrenal disease
- 12/2020: Rapid onset (24 hours) of profound confusion
 - MRI brain: Solitary right frontal lobe metastasis, white matter changes consistent with inflammation
 - ANNA-1 antibody-positive
 - Rapid response to high-dose steroids, with improvement in mental status
 - Ipilimumab/nivolumab discontinued

Questions

- Am more inclined to believe her mental status changes are due to immune-mediated toxicity rather than a paraneoplastic syndrome – despite the positive antibody. Would you be willing to administer more immunotherapy?
- At disease progression, what treatment would you recommend – Lurbinectedin?

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

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

ORIGINAL ARTICLE

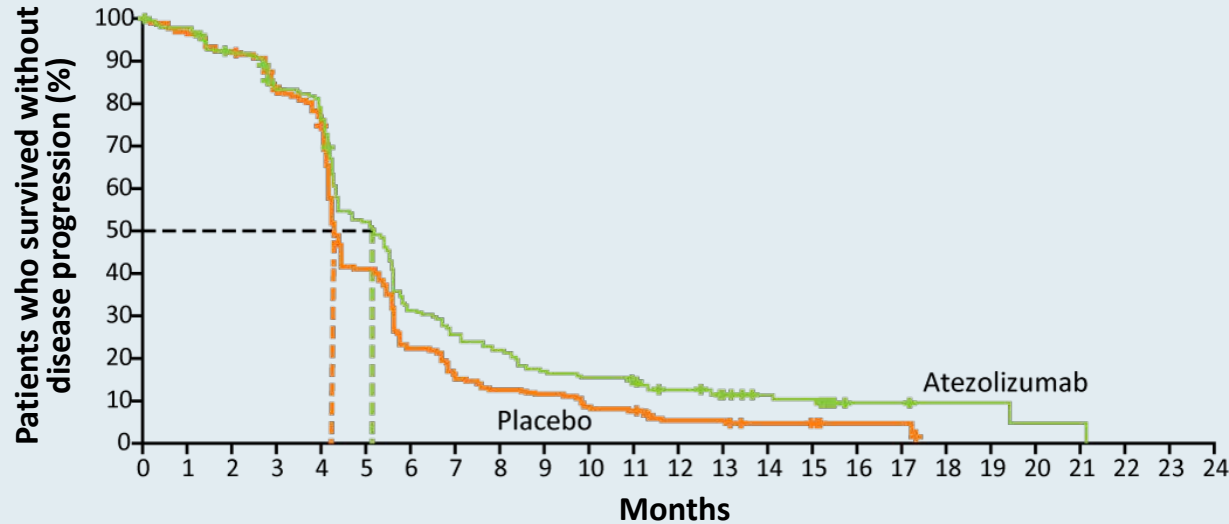
First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

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.

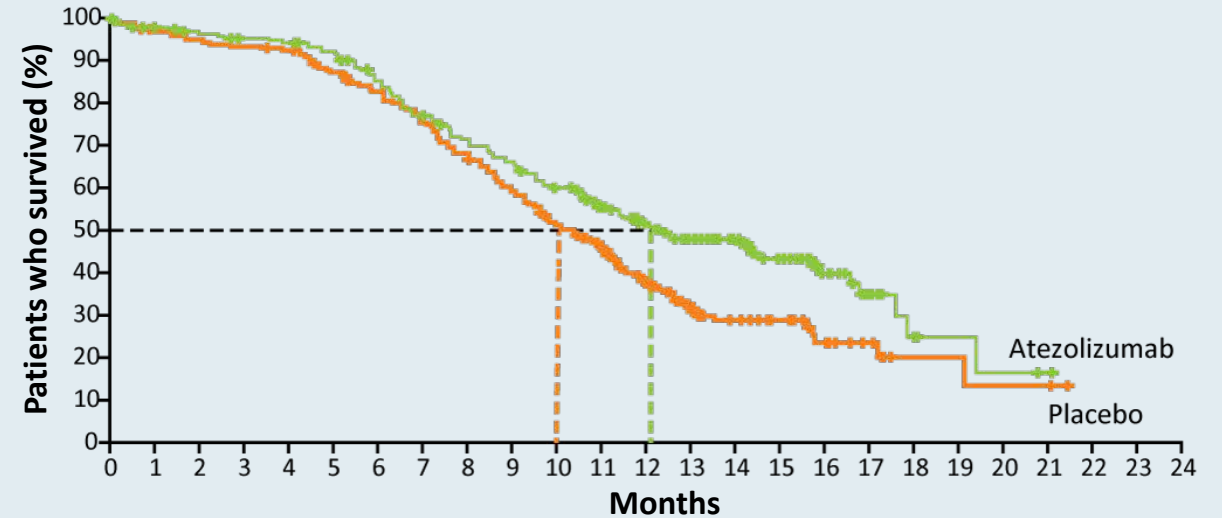
IMpower133: Survival Outcomes

Progression-free survival (PFS)



	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%		

Overall survival (OS)



	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.

FDA Approves Durvalumab for Extensive-stage Small Cell Lung Cancer

Press Release — March 27, 2020

“On March 27, 2020, the Food and Drug Administration approved durvalumab in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).

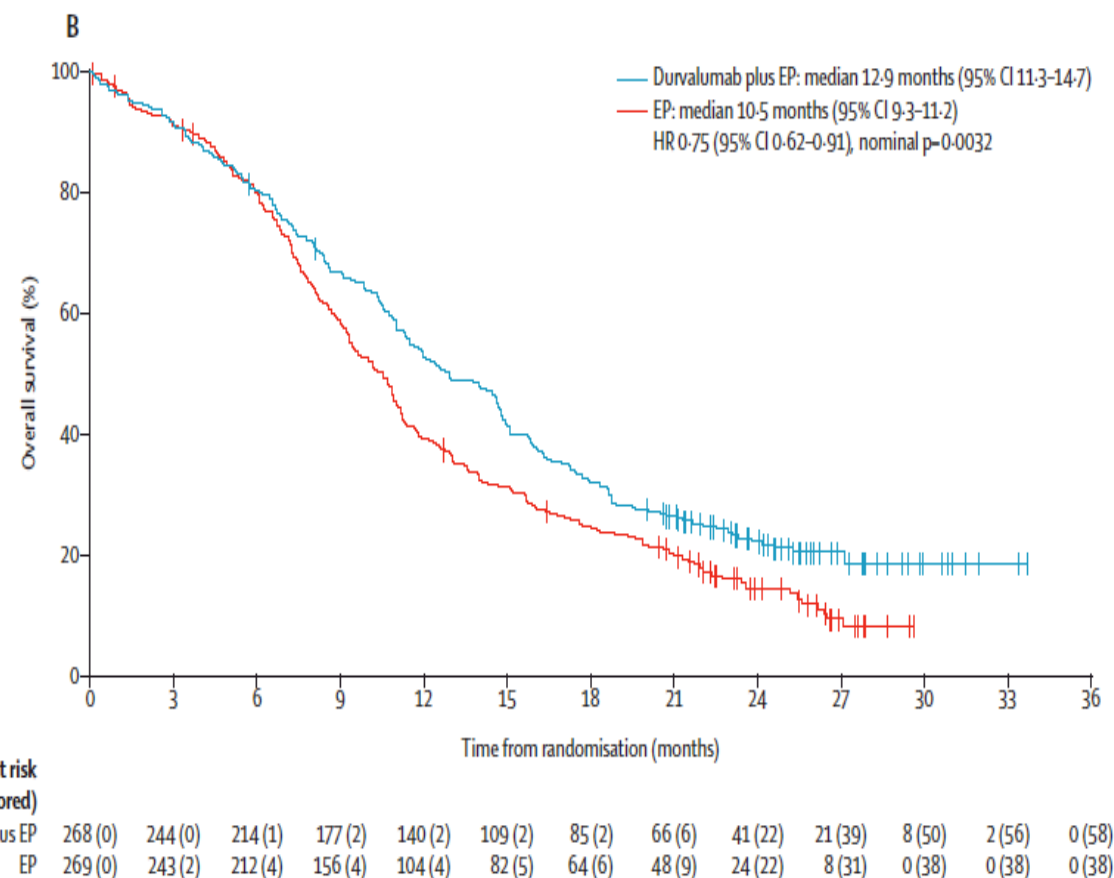
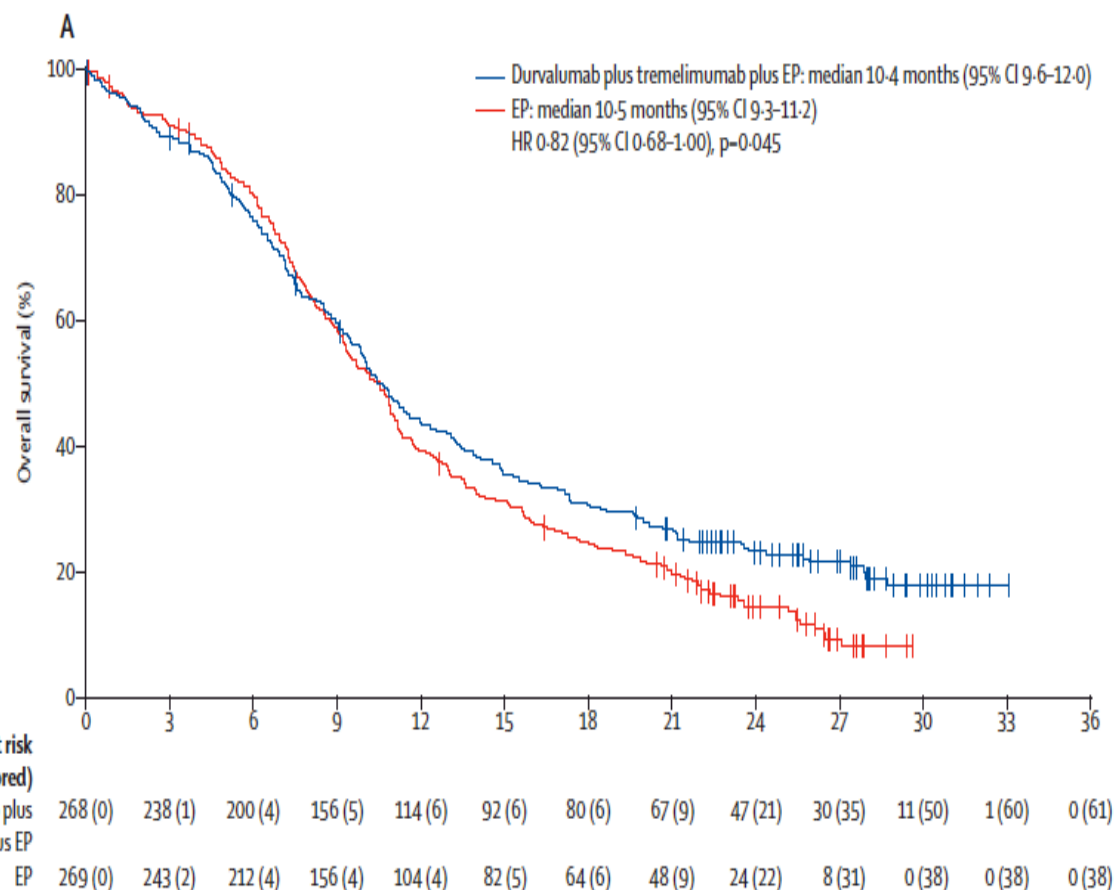
Efficacy of this combination in patients with previously untreated ES-SCLC was investigated in CASPIAN, a randomized, multicenter, active-controlled, open-label, trial (NCT03043872). The evaluation was based on the comparison of patients randomized to durvalumab plus chemotherapy vs. chemotherapy alone. The major efficacy outcome measure was overall survival (OS). Additional efficacy outcome measures were investigator-assessed progression-free survival (PFS) and objective response rate (ORR), per RECIST v1.1.”



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

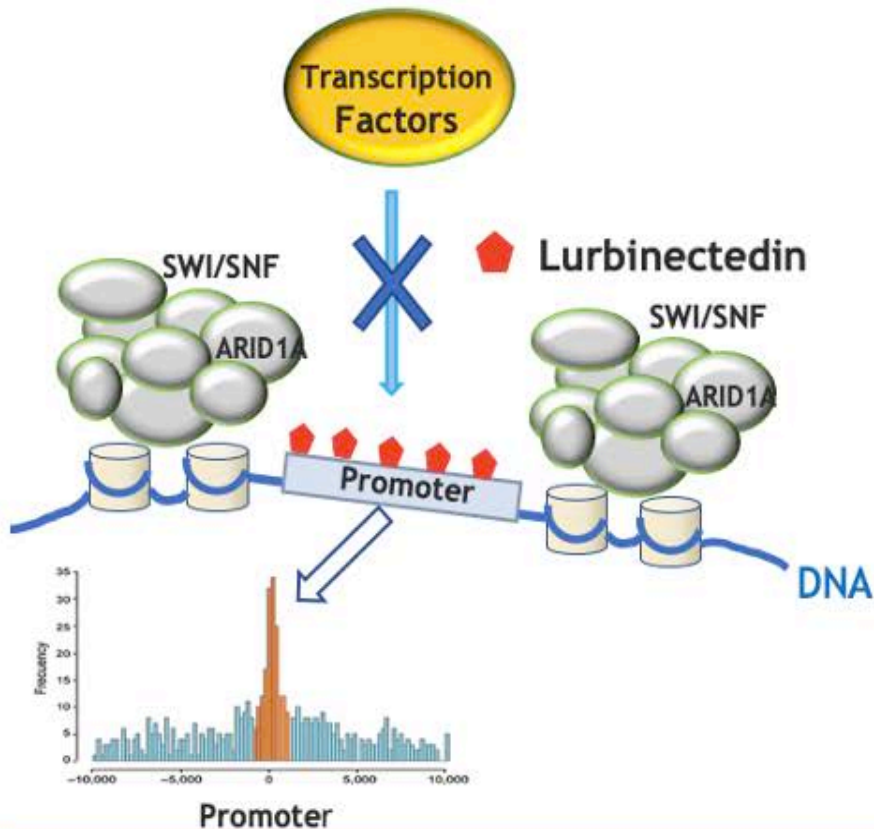
*Jonathan W Goldman, Mikhail Dvorkin, Yuanbin Chen, Niels Reinmuth, Katsuyuki Hotta, Dmytro Trukhin, Galina Statsenko, Maximilian J Hochmair, Mustafa Özgüroğlu, Jun Ho Ji, Marina Chiara Garassino, Oleksandr Voitko, Artem Poltoratskiy, Santiago Ponce, Francesco Verderame, Libor Havel, Igor Bondarenko,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

CASPIAN: Updated OS Analyses in ITT Population

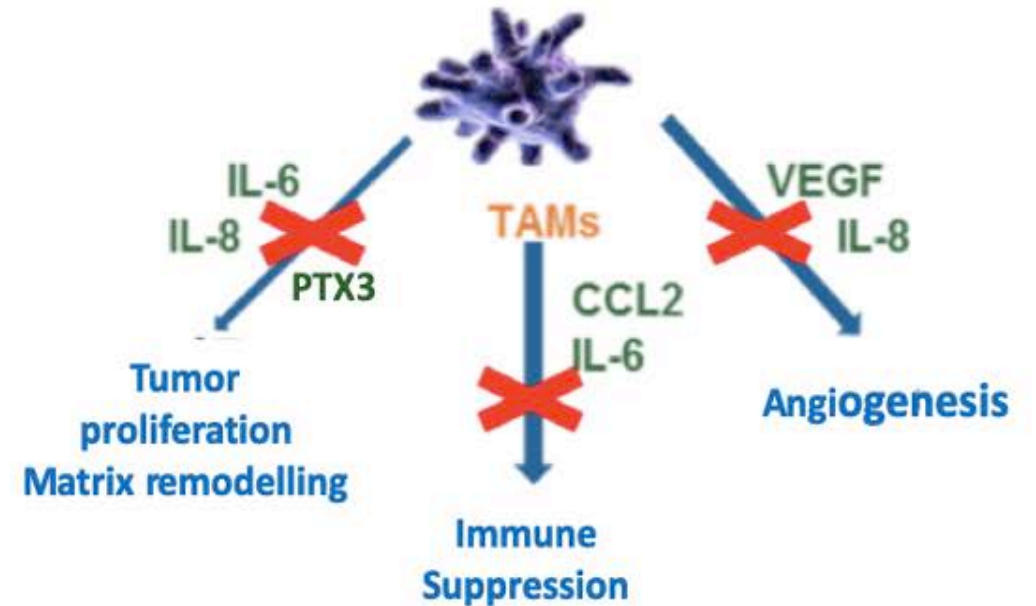


Lurbinectedin: A Selective Inhibitor of Oncogenic Transcription

Tumor-intrinsic effects



Tumor-associated macrophage effects?



How does it work?

- Alkylator
- Minor groove DNA binder

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/m² by intravenous infusion every 21 days until disease progression or unacceptable toxicity.

The recommended lurbinectedin dose is 3.2 mg/m² every 21 days.”

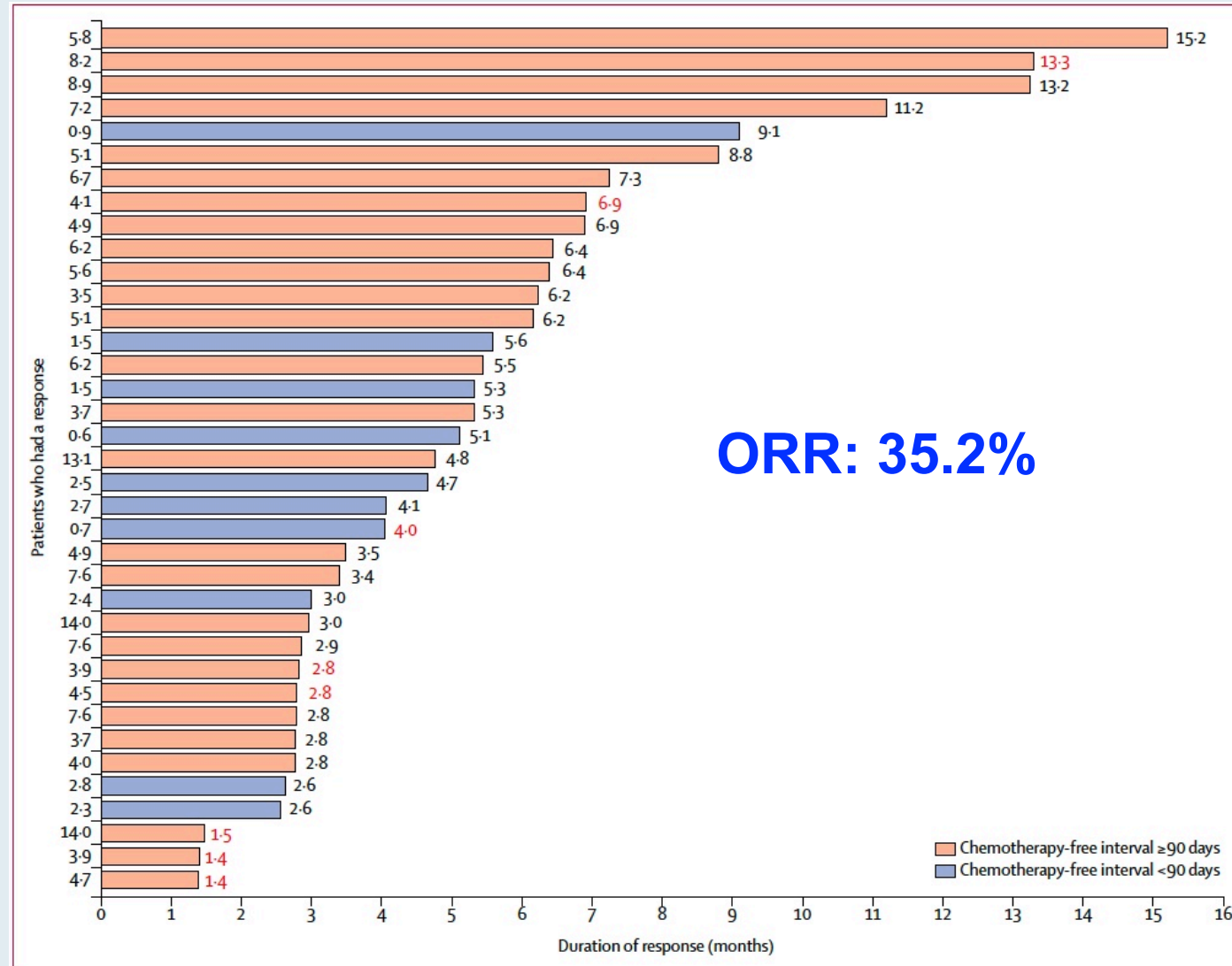
Lancet Oncol 2020;21:645-54.

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



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

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



ATLANTIS Trial Did Not Meet the Pre-Specified Criteria of Significance for the Primary Endpoint of Overall Survival

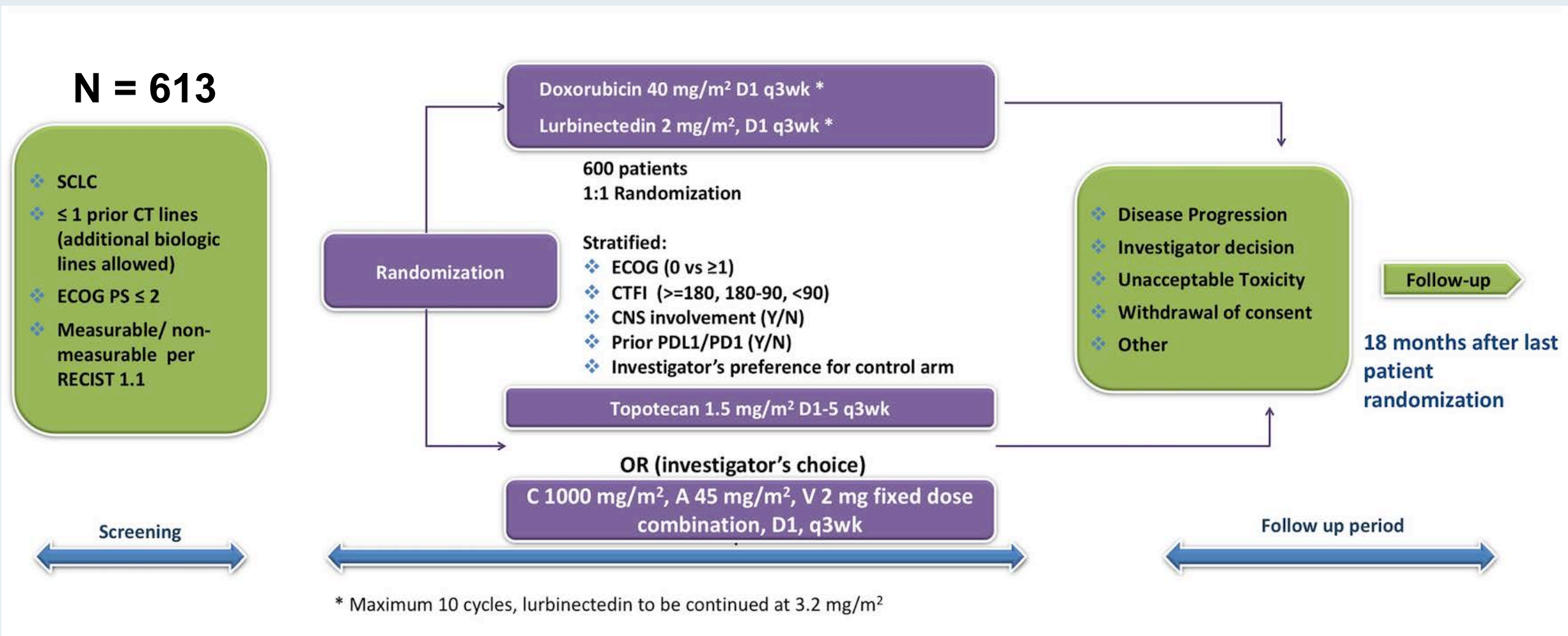
Press Release — December 03, 2020

“Results from the ATLANTIS Phase 3 multicenter, randomized, controlled study evaluating lurbinectedin in combination with doxorubicin versus physician's choice of topotecan or cyclophosphamide/doxorubicin/vincristine (CAV) for adult patients with SCLC whose disease progressed following one prior platinum-containing line. Patients received lurbinectedin at 2.0 mg/m² in the combination arm, which is lower than the FDA approved dose of lurbinectedin at 3.2 mg/m².

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

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

Ongoing Phase III ATLANTIS Trial



We are taking a 30-minute lunch break!

The program will resume at 1:15 PM ET

Up Next...

**Dr Philip A Philip and Prof Eric Van Cutsem discuss the
management of gastrointestinal cancers**