

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

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

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

# Saturday, May 22, 2021

**10:15 AM — Lung Cancer**

**John V Heymach, Stephen V Liu**

**11:30 AM — Genitourinary Cancers**

**Maha Hussain, Elizabeth R Plimack**

**12:45 PM — Chronic Lymphocytic Leukemia and Lymphomas**

**Jonathan W Friedberg, Laurie H Sehn**

**2:00 PM — Multiple Myeloma**

**Irene M Ghobrial, Sagar Lonial**

**3:15 PM — Breast Cancer**

**Virginia Kaklamani, Nancy U Lin**

## Commercial Support

This activity is supported by educational grants from Astellas and Pfizer Inc, AstraZeneca Pharmaceuticals LP, Blueprint Medicines, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Gilead Sciences Inc, GlaxoSmithKline, Incyte Corporation, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Merck, Novartis, Pharmacyclics LLC, an AbbVie Company and Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Puma Biotechnology Inc, Sanofi Genzyme, and Seagen Inc.

## Dr Love — Disclosures

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

# Lung Cancer Faculty



**John V Heymach, MD, PhD**

Professor and Chair

Thoracic/Head and Neck Medical Oncology

The University of Texas MD Anderson Cancer Center

Houston, Texas



**Stephen V Liu, MD**

Associate Professor of Medicine

Georgetown University Hospital

Washington, DC

# Dr Heymach — Disclosures

<b>Advisory Committee and Consulting Agreements</b>	AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals Inc, BrightPath Biotherapeutics Co Ltd, Bristol-Myers Squibb Company, Catalyst Pharmaceuticals, EMD Serono Inc, Foundation Medicine, Genentech, a member of the Roche Group, GlaxoSmithKline, Guardant Health, Hengrui Therapeutics Inc, Janssen Biotech Inc, Kairos Venture Investments LLC, Leads Biolabs, Lilly, Mirati Therapeutics, Nexus Health Systems, Novartis, Pneuma Respiratory, Roche Laboratories Inc, Sanofi Genzyme, Spectrum Pharmaceuticals Inc, Takeda Oncology
<b>Contracted Research</b>	AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, Spectrum Pharmaceuticals Inc
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## Dr Liu — Disclosures

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<b>Data and Safety Monitoring Board/Committee</b>	Advantagene Inc, Candel Therapeutics

# Genitourinary Cancers Faculty



**Maha Hussain, MD, FACP, FASCO**

Genevieve Teuton Professor of Medicine  
Division of Hematology/Oncology  
Deputy Director  
Robert H Lurie Comprehensive Cancer Center  
Northwestern University Feinberg School of Medicine  
Chicago, Illinois



**Elizabeth R Plimack, MD, MS**

Chief, Division of Genitourinary Medical Oncology  
Director, Genitourinary Clinical Research  
Professor, Department of Hematology/Oncology  
Fox Chase Cancer Center  
Temple Health  
Philadelphia, Pennsylvania

# Dr Hussain — Disclosures

<b>Advisory Committee</b>	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Janssen Biotech Inc, Pfizer Inc
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## Dr Plimack — Disclosures

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<b>Data and Safety Monitoring Board/Committee</b>	AstraZeneca Pharmaceuticals LP, Infinity Pharmaceuticals Inc, Pfizer Inc

# Chronic Lymphocytic Leukemia and Lymphomas Faculty



**Jonathan W Friedberg, MD, MMSc**  
Samuel E Durand Professor of Medicine  
Director, James P Wilmot Cancer Institute  
University of Rochester  
Rochester, New York



**Laurie H Sehn, MD, MPH**  
Chair, Lymphoma Tumour Group  
BC Cancer Centre for Lymphoid Cancer  
Clinical Professor of Medicine  
Division of Medical Oncology  
University of British Columbia  
Associate Editor, *Blood*  
Vancouver, British Columbia, Canada



# Dr Friedberg — Disclosures

<b>Data and Safety Monitoring Board/Committee</b>	Acerta Pharma — A member of the AstraZeneca Group, Bayer HealthCare Pharmaceuticals, Novartis
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# Dr Sehn — Disclosures

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<b>Contracted Research</b>	Teva Oncology

# Multiple Myeloma Faculty



**Irene M Ghobrial, MD**

Professor of Medicine

Lavine Family Chair of Preventative Cancer Therapies

Director, Center for Prevention of Progression of  
Blood Cancers

Director, Translational Research in Multiple Myeloma

Director, Clinical Investigator Research Program

Director, Michele and Steven Kirsch Laboratory

Harvard Medical School

Dana-Farber Cancer Institute

Boston, Massachusetts



**Sagar Lonial, MD**

Chair and Professor

Department of Hematology and  
Medical Oncology

Anne and Bernard Gray Family Chair in Cancer

Chief Medical Officer

Winship Cancer Institute

Emory University School of Medicine

Atlanta, Georgia

# Dr Ghobrial — Disclosures

<b>Advisory Committee</b>	Aptitude Health, GlaxoSmithKline, GNS Healthcare
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# Dr Lonial — Disclosures

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<b>Contracted Research</b>	Celgene Corporation, Janssen Biotech Inc, Takeda Oncology

# Breast Cancer Faculty



**Virginia Kaklamani, MD, DSc**

Professor of Medicine

Ruth McLean Bowman Bowers Chair in Breast  
Cancer Research and Treatment

AB Alexander Distinguished Chair in Oncology

Associate Director for Clinical Research

Leader of the Breast Cancer Program

UT Health San Antonio

The University of Texas MD Anderson Cancer Center  
San Antonio, Texas



**Nancy U Lin, MD**

Associate Professor of Medicine

Harvard Medical School

Associate Chief, Division of Breast Oncology

Director, Metastatic Breast Cancer Program

Dana-Farber Cancer Institute

Boston, Massachusetts

# Dr Kaklamani — Disclosures

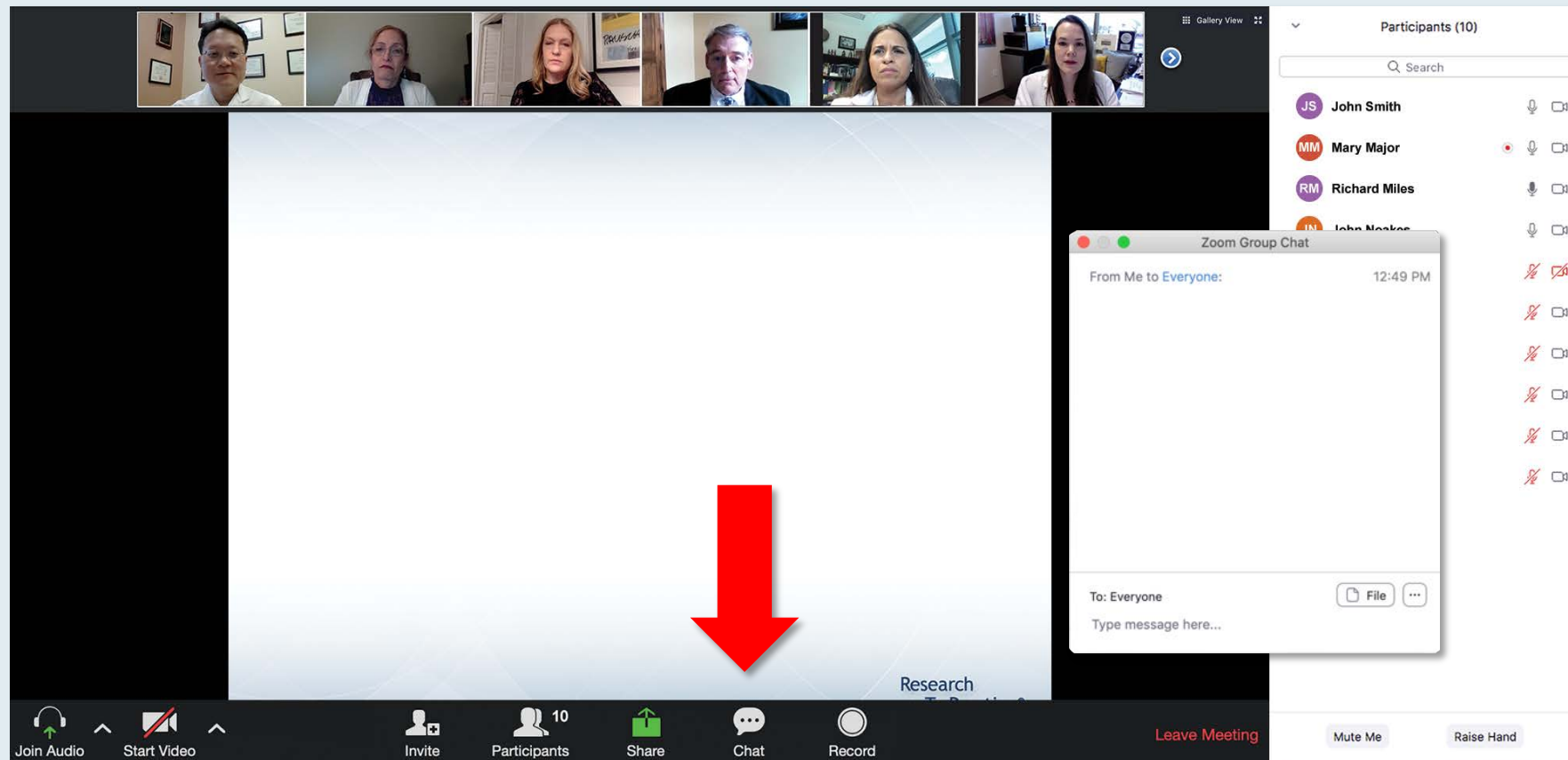
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# We Encourage Clinicians in Practice to Submit Questions



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

# Familiarizing Yourself with the Zoom Interface

## How to answer poll questions

The screenshot displays a Zoom meeting interface. At the top, a gallery view shows six participants. The main screen displays a poll question: "What is your usual treatment recommendation for a patient with MM who has been followed by ASCT for 1-5 years who then experiences an asymptomatic relapse?". Below the question is a list of ten treatment options, each preceded by a number. A "Quick Poll" dialog box is open, showing the same list of options with radio buttons for selection. The bottom of the screen features a toolbar with icons for Join Audio, Start Video, Invite, Participants (10), Share, Chat, Record, and a red "Leave Meeting" button. On the right side, a "Participants (10)" list is visible, showing names and status icons.

What is your usual treatment recommendation for a patient with MM who has been followed by ASCT for 1-5 years who then experiences an asymptomatic relapse?

Quick Poll

- ☐ Carfilzomib +/- dexamethasone
- ☐ Pomalidomide +/- dexamethasone
- ☐ Carfilzomib + pomalidomide +/- dexamethasone
- ☐ Elotuzumab + lenalidomide +/- dexamethasone
- ☐ Elotuzumab + pomalidomide +/- dexamethasone
- ☐ Daratumumab + lenalidomide +/- dexamethasone
- ☐ Daratumumab + pomalidomide +/- dexamethasone
- ☐ Daratumumab + bortezomib +/- dexamethasone
- ☐ Ixazomib + Rd
- ☐ Other

Submit

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Join Audio Start Video Invite Participants 10 Share Chat Record Leave Meeting Mute Me Raise Hand

Participants (10)

Search

- JS John Smith
- MM Mary Major
- RM Richard Miles
- JN John Noakes
- AS Alice Suarez
- JP Jane Perez
- RS Robert Stiles
- JF Juan Fernandez
- AK Ashok Kumar
- JS Jeremy Smith







When a poll question pops up, click your answer choice from the available options.

# Familiarizing Yourself with the Zoom Interface

## Expand chat submission box

The screenshot shows a Zoom meeting interface. At the top, there are video thumbnails for participants: RTP Coordinat..., Kirsten Miller, RTP Mike Rivera, and Lisa Suarez. Below the thumbnails is a slide titled "Meet The Professor Program Steering Committee" featuring six members with their photos and titles. On the right side, there is a chat window titled "Chat" with two messages from "Me to Panelists" and "Me to Panelists and Attendees". A red arrow points to the white line above the chat submission box, indicating where to drag to expand the box.

**Meet The Professor Program Steering Committee**

 <b>John N Allan, MD</b> Assistant Professor of Medicine Weill Cornell Medicine New York, New York	 <b>Ian W Flinn, MD, PhD</b> Director of Lymphoma Research Program Sarah Cannon Research Institute Tennessee Oncology Nashville, Tennessee
 <b>Steven Coutre, MD</b> Professor of Medicine (Hematology) Stanford University School of Medicine Stanford, California	 <b>Prof John G Gribben, MD, DSc, FMedSci</b> Chair of Medical Oncology Barts Cancer Institute Queen Mary University of London Charterhouse Square London, United Kingdom
 <b>Matthew S Davids, MD, MMSc</b> Associate Professor of Medicine Harvard Medical School Division of Lymphoma Dana-Farber Cancer Institute Boston, Massachusetts	 <b>Brian T Hill, MD, PhD</b> Director, Lymphoid Malignancy Program Cleveland Clinic Taussig Cancer Institute Cleveland, Ohio

**Chat**

Me to Panelists 4:31 PM

Welcome and thank you for attending! To access the slides from today's session please use the link below.  
[http://images.researchtopractice.com/2021/Meetings/Slides/MTP\\_ToGo\\_CLL\\_2021\\_April1.pdf](http://images.researchtopractice.com/2021/Meetings/Slides/MTP_ToGo_CLL_2021_April1.pdf)

Me to Panelists and Attendees 4:32 PM

Welcome and thank you for attending! To access the slides from today's session please use the link below.  
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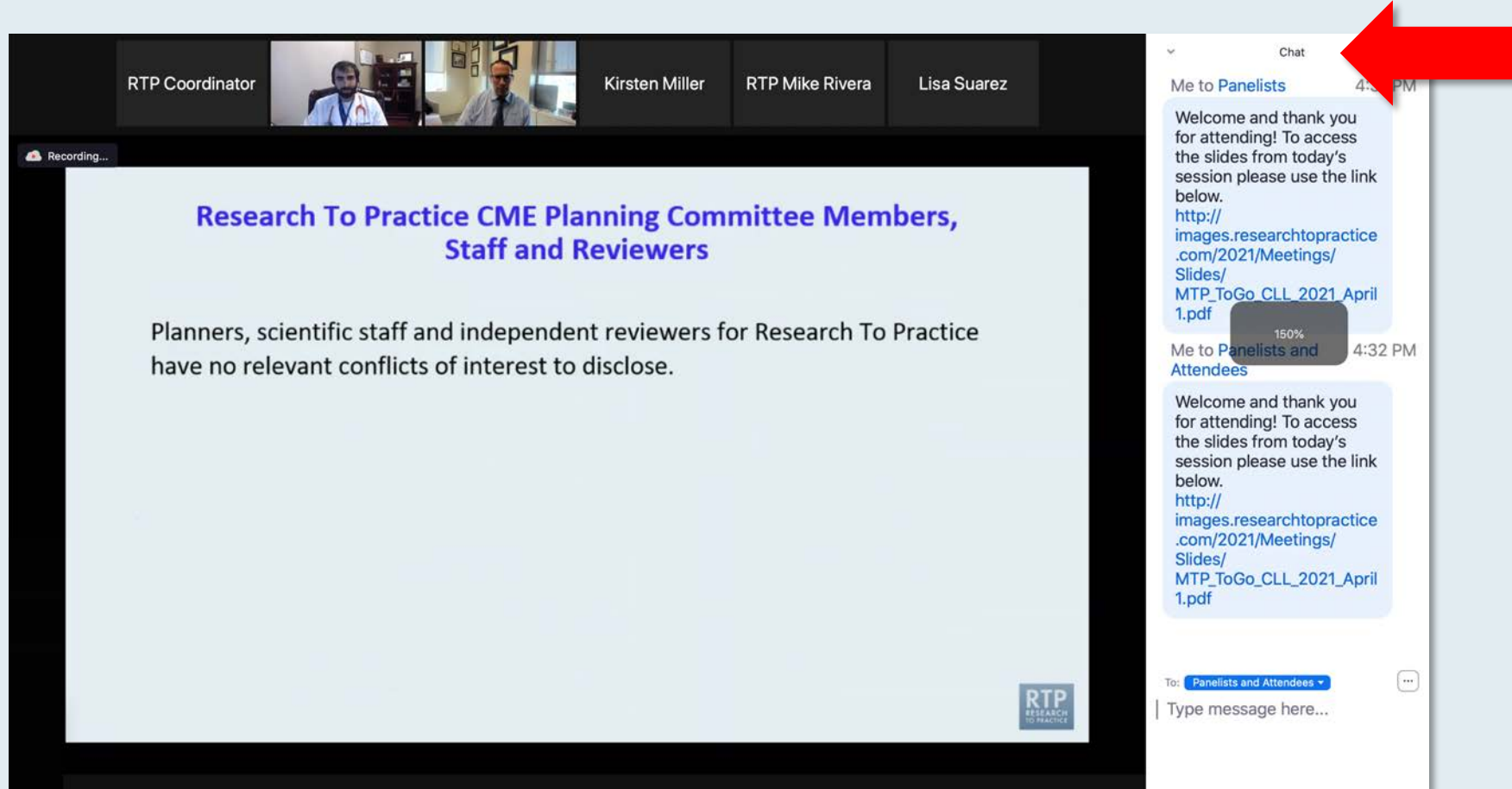
To: Panelists and Attendees

Type message here...

Drag the white line above the submission box up to create more space for your message.

# Familiarizing Yourself with the Zoom Interface

## Increase chat font size



**Press Command (for Mac) or Control (for PC) and the + symbol.  
You may do this as many times as you need for readability.**

# ONCOLOGY TODAY

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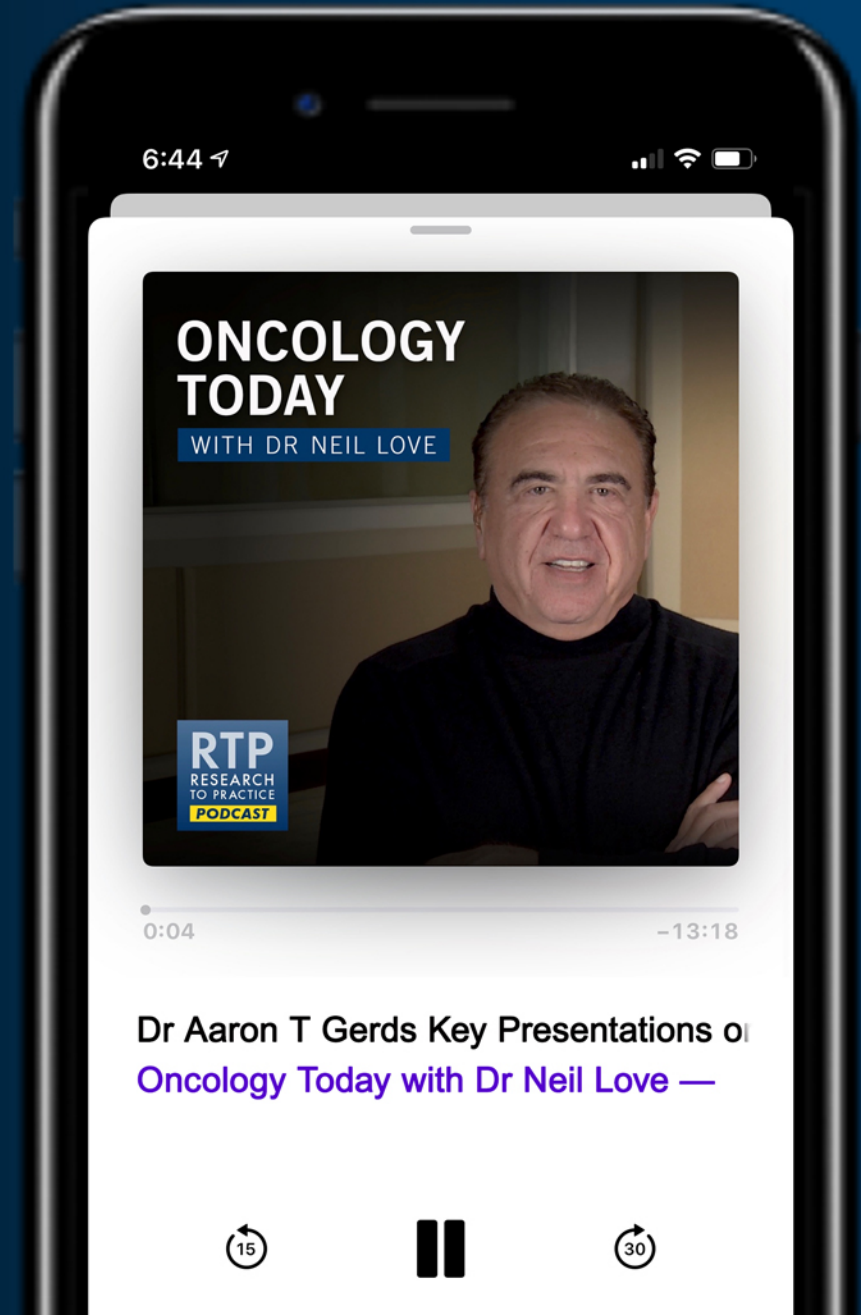
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# Contributing Oncologists



**Susmitha Apuri, MD**  
Florida Cancer Specialists  
Lutz, Florida



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



**Warren S Brenner, MD**  
Lynn Cancer Institute  
Boca Raton, Florida



**Maria Regina Flores, MD**  
Advent Health Orlando  
Orlando Regional Hospital  
Florida Cancer Specialists  
Orlando, Florida



**Gigi Chen, MD**  
Diablo Valley Oncology and  
Hematology Medical Group  
Pleasant Hill, California



**Sunil Gandhi, MD**  
Florida Cancer Specialists  
Lecanto, Florida



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



**Ranju Gupta, MD**  
Attending Physician  
Co-Director, Cardio-Oncology Program  
LVPG Hematology Oncology Associates  
Lehigh Valley Health Network  
Bethlehem, Pennsylvania

# Contributing Oncologists



**Lowell L Hart, MD**

Scientific Director of Research  
Florida Cancer Specialists  
Co-Director, Phase 1 Program  
Wake Forest Baptist Health  
Comprehensive Cancer Center  
Fort Myers, Florida



**Jeremy Lorber, MD**

Attending Hematologist-Oncologist  
Tower Hematology Oncology  
Cedars-Sinai Medical Center  
Beverly Hills, California



**KS Kumar, MD**

Physician Partner  
Florida Cancer Specialists  
New Port Richey, Florida



**Vikas Malhotra, MD**

Staff Medical Oncologist-Hematologist  
Florida Cancer Specialists  
Spring Hill, Florida



**Ferdy Santiago, MD**

Florida Cancer Specialists  
Naples, Florida



**Zanetta S Lamar, MD**

Florida Cancer Specialists  
Naples, Florida



**Raji Shameem, MD**

Florida Cancer Specialists  
Deland, Florida

# 17 Exciting CME/MOC Events You Do Not Want to Miss

*A Live Webinar Series Held in Conjunction with the 2021 ASCO Annual Meeting*

## **HER2-Positive Breast Cancer**

**Tuesday, June 22**

5:00 PM – 6:00 PM ET

## **ER-Positive and Triple-Negative Breast Cancer**

**Wednesday, June 23**

5:00 PM – 6:00 PM ET

## **Chronic Lymphocytic Leukemia and Follicular Lymphoma**

**Tuesday, June 29**

5:00 PM – 6:00 PM ET

## **Multiple Myeloma**

**Wednesday, June 30**

5:00 PM – 6:00 PM ET

## **Ovarian Cancer**

**Wednesday, July 7**

5:00 PM – 6:00 PM ET

## **Hormonal Therapy for Prostate Cancer**

**Monday, July 12**

5:00 PM – 6:00 PM ET

## **Chimeric Antigen Receptor T-Cell Therapy**

**Tuesday, July 13**

5:00 PM – 6:00 PM ET

## **Acute Myeloid Leukemia and Myelodysplastic Syndromes**

**Wednesday, July 14**

5:00 PM – 6:00 PM ET

## **Metastatic Castration-Resistant Prostate Cancer**

**Tuesday, July 20**

5:00 PM – 6:00 PM ET

## **Bladder Cancer**

**Wednesday, July 21**

5:00 PM – 6:00 PM ET

## **Endometrial and Cervical Cancers**

**Monday, July 26**

5:00 PM – 6:00 PM ET

## **Targeted Therapy for Non-Small Cell Lung Cancer**

**Tuesday, July 27**

5:00 PM – 6:00 PM ET

## **Immunotherapy and Other Nontargeted Approaches for Lung Cancer**

**Wednesday, July 28**

5:00 PM – 6:00 PM ET

## **Mantle Cell, Diffuse Large B-Cell and Hodgkin Lymphoma**

**Monday, August 2**

5:00 PM – 6:00 PM ET

## **Colorectal and Gastroesophageal Cancers**

**Tuesday, August 3**

5:00 PM – 6:30 PM ET

## **Hepatocellular Carcinoma and Pancreatic Cancer**

**Wednesday, August 4**

5:00 PM – 6:30 PM ET

## **Head and Neck Cancer**

**Wednesday, August 11**

5:00 PM – 6:00 PM ET



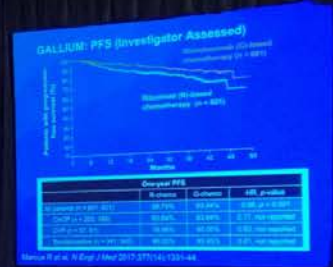
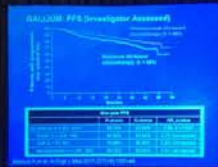
# **Up for Debate: Oncology Investigators Provide Their Take on Current Controversies in Patient Care**

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

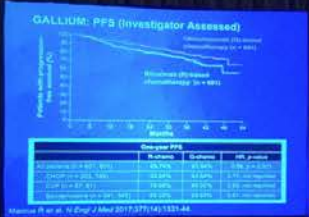
**Saturday, May 22, 2021  
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# Year in Review

A Multitumor Regional Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers  
Saturday, October 26, 2018, 8:30 AM – 4:30 PM  
Orlando, Florida

## Faculty

- |                                |                           |
|--------------------------------|---------------------------|
| Jeremy Abramson, MD            | Graig Muskowitz, MD       |
| Johnnie Sandell, MD            | Joel W. Neal, MD, PhD     |
| Michael J. Bressi, MD, PhD     | Steven M. O'Shilly, MD    |
| Julia R. Braxton, MD           | Joyce O'Shaughnessy, MD   |
| Courtney O. Dillards, MD, MACE | Mark D. Pegram, MD        |
| J. Randolph Hocht, MD          | Daniel F. Petrylak, MD    |
| Mark Lewis, MD, PhD            | David I. Quinn, MBS, PhD  |
| Ursula Metzger, MD             | Michael R. Smith, MD, PhD |

Moderator  
Neil Love, MD

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# Agenda

**Module 1 — Lung Cancer:** *Drs Heymach and Liu*

**Module 2 — Genitourinary Cancers:** *Drs Hussain and Plimack*

**Module 3 — Chronic Lymphocytic Leukemia and Lymphomas:**  
*Drs Friedberg and Sehn*

**Module 4 — Multiple Myeloma:** *Drs Ghobrial and Lonial*

**Module 5 — Breast Cancer:** *Drs Kaklamani and Lin*

# Lung Cancer Faculty



**John V Heymach, MD, PhD**

Professor and Chair

Thoracic/Head and Neck Medical Oncology

The University of Texas MD Anderson Cancer Center

Houston, Texas



**Stephen V Liu, MD**

Associate Professor of Medicine

Georgetown University Hospital

Washington, DC



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Lutz, Florida



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Florida Cancer Specialists  
New Port Richey, Florida



**Warren S Brenner, MD**  
Lynn Cancer Institute  
Boca Raton, Florida



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Advent Health Orlando  
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Orlando, Florida



**Gigi Chen, MD**  
Diablo Valley Oncology and  
Hematology Medical Group  
Pleasant Hill, California



**Sunil Gandhi, MD**  
Florida Cancer Specialists  
Lecanto, Florida



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



**Ranju Gupta, MD**  
Attending Physician  
Co-Director, Cardio-Oncology Program  
LVPG Hematology Oncology Associates  
Lehigh Valley Health Network  
Bethlehem, Pennsylvania

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Wake Forest Baptist Health  
Comprehensive Cancer Center  
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Cedars-Sinai Medical Center  
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Staff Medical Oncologist-Hematologist  
Florida Cancer Specialists  
Spring Hill, Florida



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Florida Cancer Specialists  
Naples, Florida



**Zanetta S Lamar, MD**

Florida Cancer Specialists  
Naples, Florida



**Raji Shameem, MD**

Florida Cancer Specialists  
Deland, Florida

# **Chalk Talk Topics**

## **John Heymach, MD, PhD**

- 1. Should the majority of patients with EGFR mutation-positive, Stage IB to IIIA non-small cell lung cancer (NSCLC) receive three years of osimertinib following surgery and adjuvant chemotherapy, if applicable?**
- 2. In which situations, if any, do you currently administer neoadjuvant systemic therapy for patients with resectable NSCLC, and regulatory and reimbursement issues aside, under what circumstances might you wish to include an immune checkpoint inhibitor (eg, nivolumab as in CheckMate 816)?**
- 3. What is the optimal first-line regimen for a symptomatic and asymptomatic patient with newly diagnosed metastatic NSCLC without a targetable tumor mutation with a PD-L1 TPS of 60%? Do you believe that there are discernible differences in terms of efficacy or tolerability that make one of the three FDA-approved anti-PD-1/PD-L1 monotherapies a better option?**
- 4. What is the optimal second-line treatment for a patient with extensive-stage small cell lung cancer who experiences disease progression on a front-line anti-PD-L1/chemotherapy combination?**
- 5. At the current time, should patients with HER2-mutant NSCLC receive trastuzumab deruxtecan at some point in their treatment course? When? What about patients with HER2-amplified NSCLC?**

# Chalk Talk Topics

## Stephen V Liu, MD

1. Regulatory and reimbursement issues aside, what is currently the optimal first-line therapy for a patient with metastatic ALK-positive NSCLC with brain metastases?
2. Regulatory and reimbursement issues aside, what is currently the optimal first-line therapy for a patient with metastatic ROS1-positive NSCLC with and without brain metastases?
3. What is the optimal first-line therapy for a patient with newly diagnosed RET-positive metastatic NSCLC? For patients who will receive targeted therapy, are selpercatinib and pralsetinib equally efficacious options?
4. What is the optimal first-line therapy for a patient with newly diagnosed MET exon 14-positive NSCLC? For patients who will receive targeted therapy, are capmatinib and tepotinib equally efficacious options?
5. In general, when do you believe checkpoint inhibitors should be introduced into the treatment algorithm for a patient with metastatic NSCLC with an EGFR mutation or ALK rearrangement? Does PD-L1 expression have any bearing on this decision? What regimen do you prefer for these patients?

# Agenda

## **Module 1: First-Line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) without a Targetable Mutation**

- Dr Flores: A 53-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 100%
- Dr Shameem: A 72-year-old man with metastatic adenocarcinoma of the lung – KRAS G12C mutation, PD-L1 1%

## **Module 2: Immunotherapy Consolidation After Chemoradiation Therapy for Localized or Locally Advanced NSCLC**

- Dr Lamar: A 76-year-old man with Stage IIB NSCLC

## **Module 3: Extensive-Stage Small Cell Lung Cancer (SCLC)**

- Dr Shameem: A 75-year-old man with extensive-stage SCLC

## **Module 4: Use of Targeted Treatment in NSCLC**

- Dr Apuri: An 86-year-old man with metastatic adenocarcinoma of the lung – PD-L1 90%, EGFR exon 19 deletion
- Dr Flores: An 81-year-old woman with metastatic adenocarcinoma of the lung and an EGFR exon 19 deletion
- Dr Kumar: A 70-year-old man with metastatic NSCLC – BRAF V600E mutation
- Dr Hart: A 53-year-old woman with metastatic adenocarcinoma of the lung and an ALK rearrangement
- Dr Flores: A 63-year-old man with metastatic adenocarcinoma of the lung and a ROS1 mutation



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



**Dr Shachar Peles**

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

# Agenda

## **Module 1: First-Line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) without a Targetable Mutation**

- Dr Flores: A 53-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 100%
- Dr Shameem: A 72-year-old man with metastatic adenocarcinoma of the lung – KRAS G12C mutation, PD-L1 1%

## **Module 2: Immunotherapy Consolidation After Chemoradiation Therapy for Localized or Locally Advanced NSCLC**

- Dr Lamar: A 76-year-old man with Stage IIB NSCLC

## **Module 3: Extensive-Stage Small Cell Lung Cancer (SCLC)**

- Dr Shameem: A 75-year-old man with extensive-stage SCLC

## **Module 4: Use of Targeted Treatment in NSCLC**

- Dr Apuri: An 86-year-old man with metastatic adenocarcinoma of the lung – PD-L1 90%, EGFR exon 19 deletion
- Dr Flores: An 81-year-old woman with metastatic adenocarcinoma of the lung and an EGFR exon 19 deletion
- Dr Kumar: A 70-year-old man with metastatic NSCLC – BRAF V600E mutation
- Dr Hart: A 53-year-old woman with metastatic adenocarcinoma of the lung and an ALK rearrangement
- Dr Flores: A 63-year-old man with metastatic adenocarcinoma of the lung and a ROS1 mutation

# Case Presentation – Dr Flores: A 53-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 100%



**Dr Regina Flores**

- Husband treated for lung cancer and patient has a very negative viewpoint regarding chemotherapy and radiation therapy
- Presents with severe anxiety and depression
- Diagnosed with metastatic adenocarcinoma of the lung, with possible squamous cell component
  - PD-L1 100%,
- Patient refuses chemotherapy
- Pembrolizumab x 1 year and ongoing, with objective response

## Questions

- As she has refused chemotherapy, is there a role for nivolumab/ipilimumab as next-line therapy if her disease progresses?
- Is there still a role for single-agent immunotherapy as upfront treatment?



# Case Presentation – Dr Shameem: A 72-year-old man with metastatic adenocarcinoma of the lung – KRAS G12C mutation, PD-L1 1%



**Dr Raji Shameem**

- 2/2021: Presented with left supraclavicular adenopathy, which the patient attributed to recent COVID-19 vaccine
- CT Neck: Extensive adenopathy
- PET/CT: FDG-avid mediastinal adenopathy, RLL lung mass and osseous metastases
- Supraclavicular biopsy: Lung adenocarcinoma, PD-L1 1%; NGS: KRAS G12C mutation

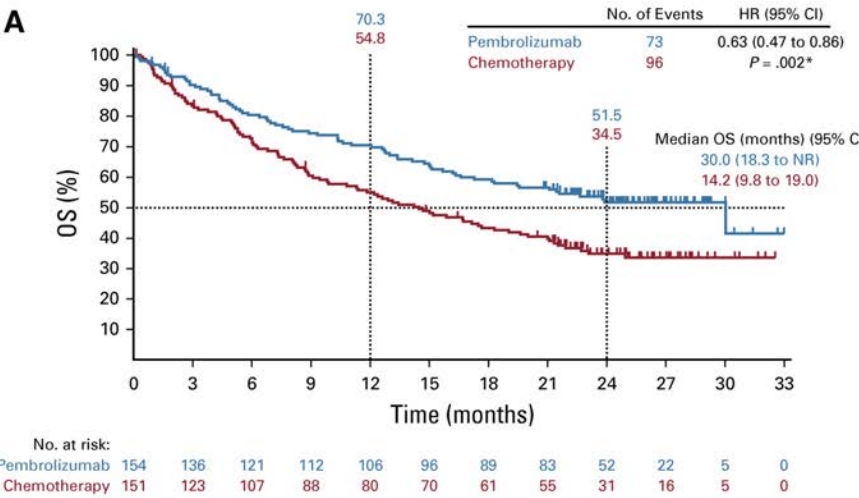
## Questions

- What is your preference for front-line therapy for lung adenocarcinomas with PD-L1 of 1% or less? What do you think of the data with nivolumab with ipilimumab? How do you select which patients should receive the different available IO-based regimens?
- What is your clinical experience with sotorasib for patients with KRAS G12C mutations?

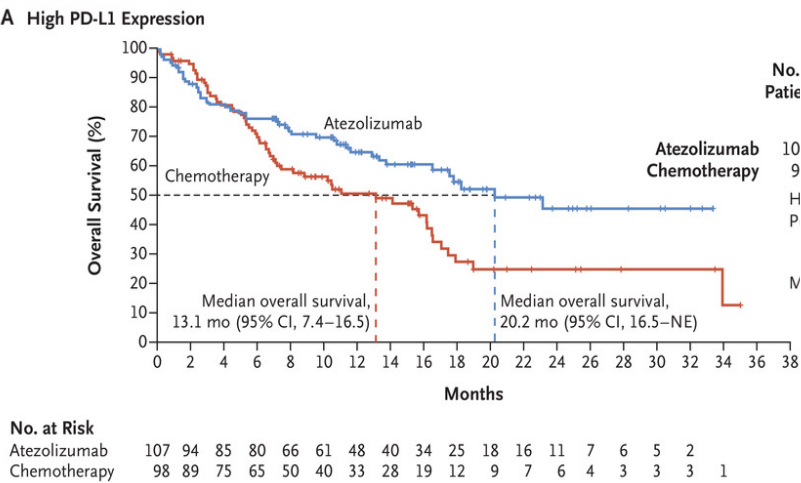
**What is the optimal first-line regimen for a symptomatic and asymptomatic patient with newly diagnosed metastatic NSCLC without a targetable tumor mutation with a PD-L1 TPS of 60%? Do you believe that there are discernible differences in terms of efficacy or tolerability that make one of the three FDA-approved anti-PD-1/PD-L1 monotherapies a better option?**

What is the optimal 1L regimen for symptomatic and asymptomatic newly diagnosed mNSCLC without a targetable tumor mutation, PD-L1 TPS 60%? Do you believe that discernible differences in efficacy or tolerability make one of the 3 FDA-approved anti-PD-1/PD-L1 monotherapies a better option?

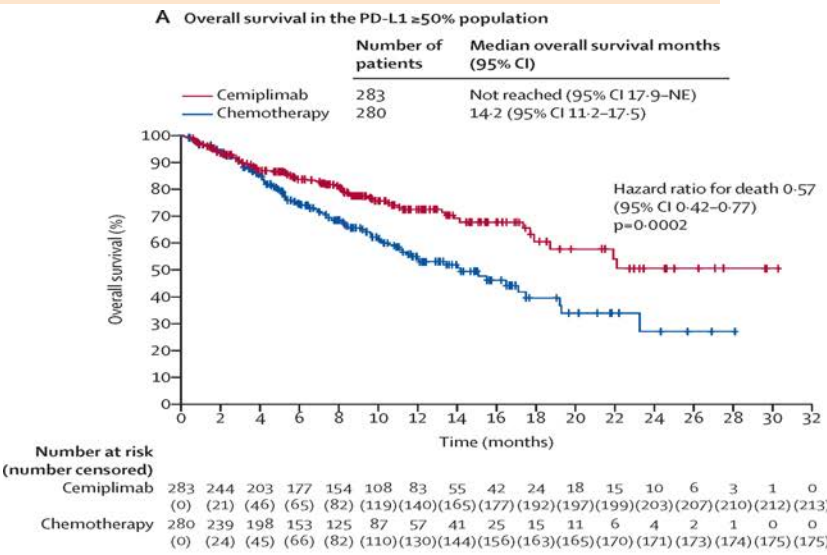
KEYNOTE-024: pembro



IMpower110: atezo



EMPOWER-Lung 1: cemiplimab



Ph III trials in 1L NSCLC (PD-L1 ≥50%)		mOS	HR	P value
KEYNOTE-024	Pembro	30.0	.63	.002
	Chemo	14.2		
IMpower110	Atezo	20.2	.59	.01
	Chemo	13.1		
EMPOWER-Lung 1	Cemiplimab	NR	.57	.0002
	Chemo	14.2		

# FDA-Approved Immunotherapy Combination Options for First-Line Therapy

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

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

# **First-Line Nivolumab (NIVO) plus Ipilimumab (IPI) plus Two Cycles of Chemotherapy (Chemo) versus Chemo Alone (4 Cycles) in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC): Two-Year Update from CheckMate 9LA**

Reck M et al.

ASCO 2021;Abstract 9000.

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

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

## **Press Release — May 7, 2021**

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

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

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

# **Circulating Tumor DNA: A Versatile Analyte to Guide the Care of Patients With Lung Cancer**

Jee J et al.

ASCO 2021;Abstract 9009.

**Friday, June 4 at 9:00 AM EDT**

# Agenda

## **Module 1: First-Line Treatment of Metastatic Non-Small Cell Lung Cancer (NSCLC) without a Targetable Mutation**

- Dr Flores: A 53-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 100%
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- Dr Lamar: A 76-year-old man with Stage IIB NSCLC

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- Dr Apuri: An 86-year-old man with metastatic adenocarcinoma of the lung – PD-L1 90%, EGFR exon 19 deletion
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# Case Presentation – Dr Lamar: A 76-year-old man with Stage IIB NSCLC



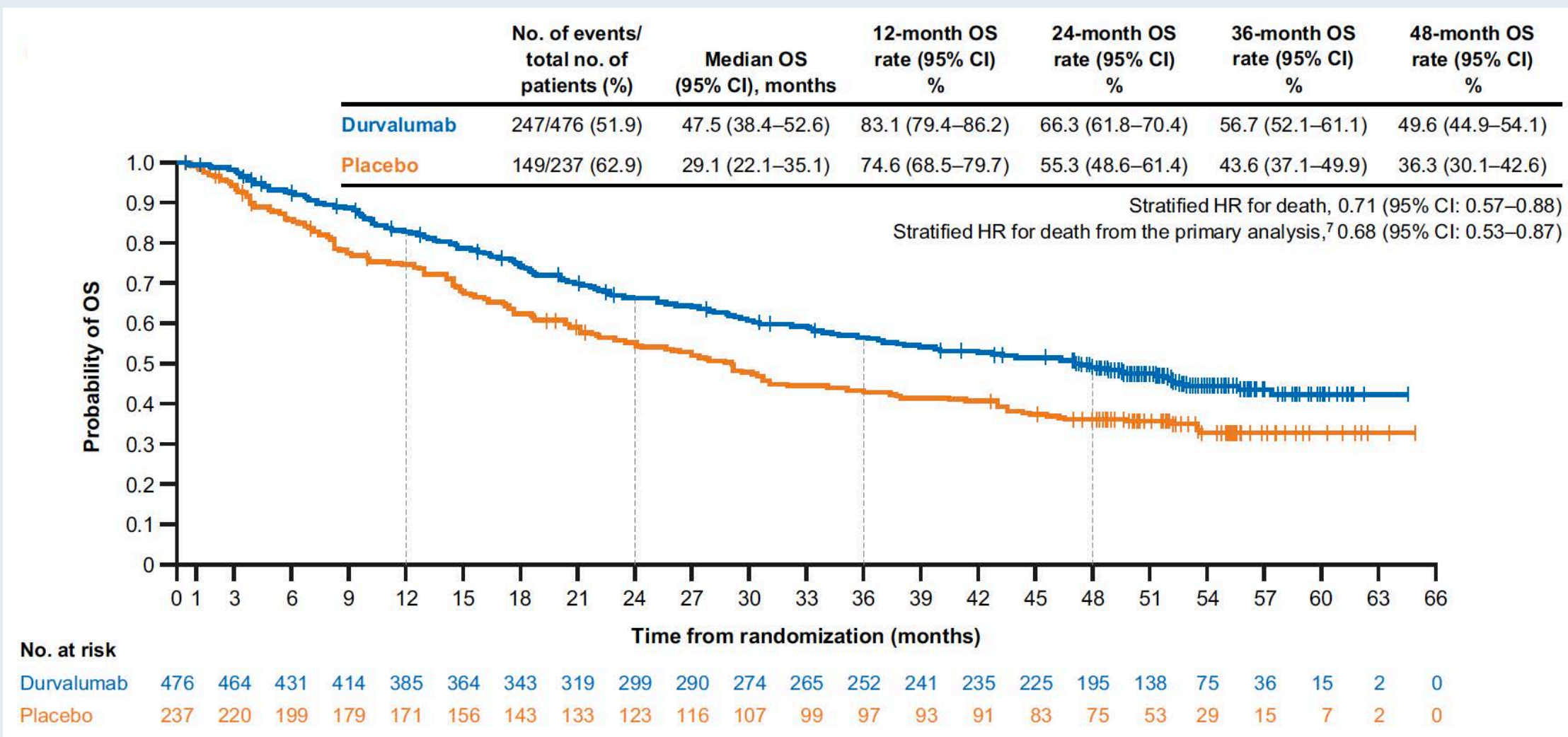
**Dr Zanetta Lamar**

- Stage IIB NSCLC, former smoker
- Carboplatin/paclitaxel and RT
- Durvalumab maintenance initiated, and patient is tolerating treatment well

## Questions

- What are your thoughts on the recent changes in the recommended schedule of durvalumab?

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



# Five-Year Survival Outcomes with Durvalumab After Chemoradiotherapy in Unresectable Stage III NSCLC: An Update from the PACIFIC Trial

Spigel DR et al.

ASCO 2021;Abstract 8511.

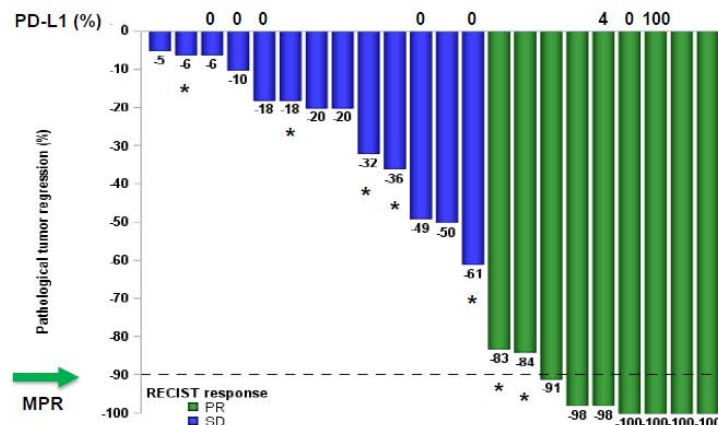
Poster Discussion Session: Friday, June 4, 2021, 9:00 AM EDT

**In which situations, if any, do you currently administer neoadjuvant systemic therapy for patients with resectable NSCLC, and regulatory and reimbursement issues aside, under what circumstances might you wish to include an immune checkpoint inhibitor (eg, nivolumab as in CheckMate 816)?**

In which situations, if any, do you currently administer neoadj systemic tx for resectable NSCLC, and regulatory and reimbursement issues aside, under what circumstances might you wish to include an immune checkpoint inhibitor (eg, nivolumab as in CheckMate 816)?

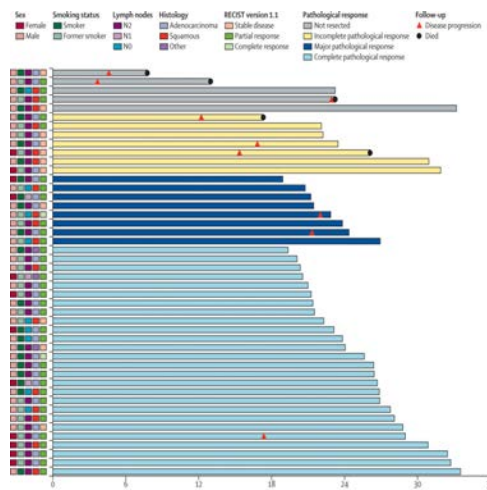
NEOSTAR in stage IB-stage IIIA

Neoadj nivo + chemo improves pathological responses in stage IB-IIIa NSCLC



pCR rate 27% (non-drivers)

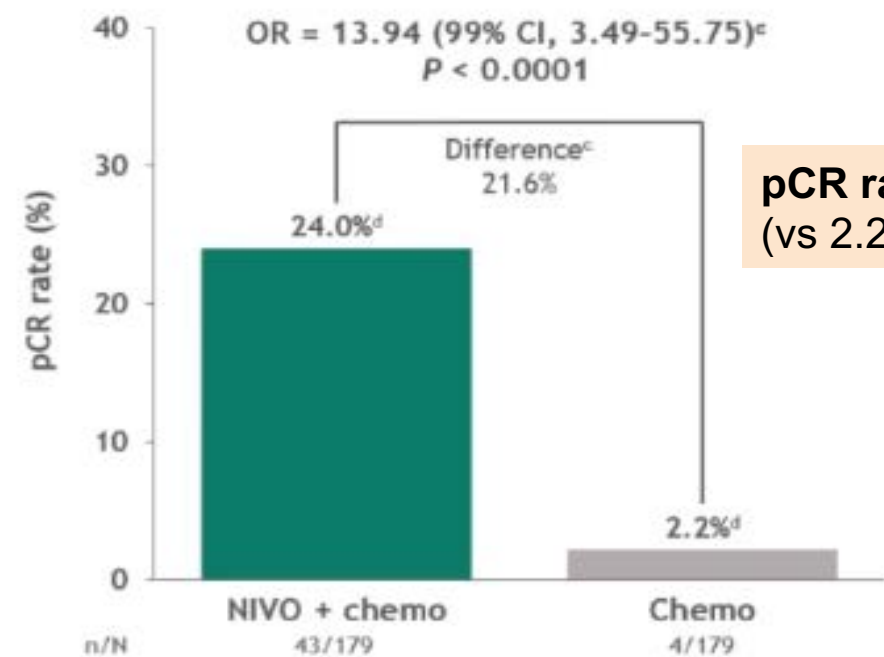
NADIM single arm phase II in stage IIIA



pCR rate 71%

RP3 CheckMate 816 study

Primary endpoint: ITT (ypT0N0)<sup>b</sup>



pCR rate 24% (vs 2.2% chemo)

Nivo plus chemo achieves co-primary endpoint of significantly improving pCR rate

# **Surgical Outcomes from the Phase 3 CheckMate 816 Trial: Nivolumab (NIVO) + Platinum-Doublet Chemotherapy (Chemo) vs Chemo Alone as Neoadjuvant Treatment for Patients with Resectable Non-Small Cell Lung Cancer (NSCLC)**

Spicer J et al.

ASCO 2021;Abstract 8503.

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

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

## **Press Release — March 22, 2021**

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

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

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

Wakelee HA et al.

ASCO 2021;Abstract 8500.

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



# IMpower010: Disease-Free Survival

	PD-L1 TC $\geq$ 1% Stage II-III A		All randomized Stage II-III A		ITT	
	Atezolizumab (n = 248)	BSC (n = 228)	Atezolizumab (n = 442)	BSC (n = 440)	Atezolizumab (n = 507)	BSC (n = 498)
Median DFS	NR	35.3 mo	42.3 mo	35.3 mo	NR	37.2 mo
Hazard ratio	0.66		0.79		0.81	
<i>p</i> -value	0.0039		0.0205		0.0395	

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



**Dr Raji Shameem**

- PMH: 50 pack years smoking, atrial fibrillation, CKD Stage 3, HTN, progressive SOB with exertion
- CT: Right hilar mass, extensive mediastinal adenopathy, lytic rib lesion, additional osseous metastases
- Bronchoscopy with pathology: SCLC
- Carboplatin/etoposide/atezolizumab, with symptomatic response
  - c/b myelosuppression, including high-grade anemia and thrombocytopenia
- Currently, maintenance atezolizumab

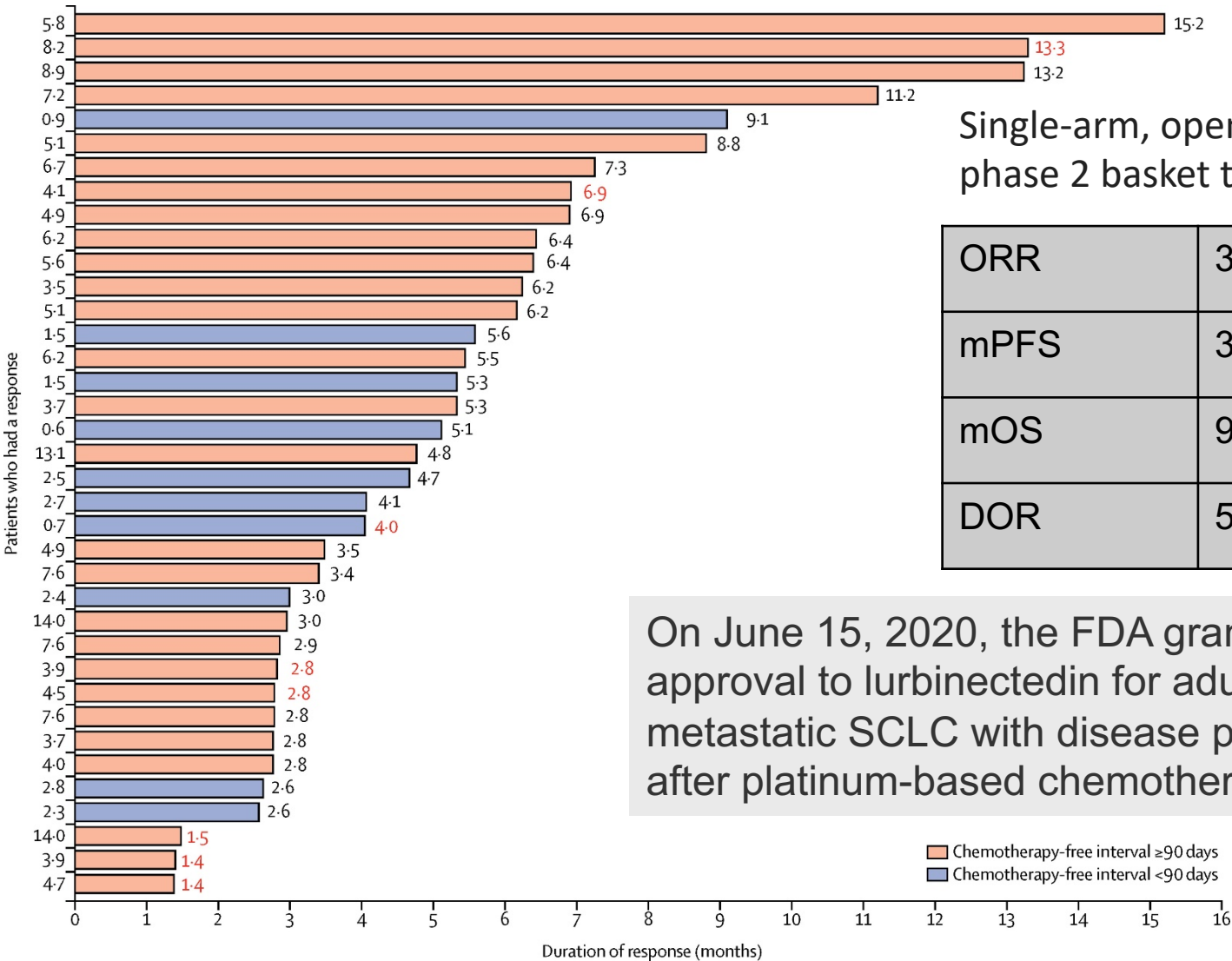
## Questions

- What has been your experience with the recently approved agent trilaciclib?
- Would you be concerned about pneumonitis if using trilaciclib in a patient with ES-SCLC who is also receiving immunotherapy?
- Do you have a preference for atezolizumab versus durvalumab?

**What is the optimal second-line treatment for a patient with extensive-stage small cell lung cancer who experiences disease progression on a front-line anti-PD-L1/chemotherapy combination?**

# What is the optimal second-line treatment for a patient with extensive-stage SCLC who experiences disease progression on a front-line anti-PD-L1/chemotherapy combination?

Lurbinectedin was active as second-line therapy for SCLC in terms of overall response



Single-arm, open-label, phase 2 basket trial

ORR	35%
mPFS	3.5 mo
mOS	9.3 mo
DOR	5.3 mo

On June 15, 2020, the FDA granted accelerated approval to lurbinectedin for adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy



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# Case Presentation – Dr Ajuri: An 86-year-old man with metastatic adenocarcinoma of the lung – PD-L1 90%, EGFR exon 19 deletion



**Dr Susmitha Apuri**

- PMH: Prostate cancer treated with RT, 12 pack year smoker (quit over 50 years ago)
- Presented to ER after a fall with weight loss and dizziness
- Imaging of head and neck demonstrated a right upper lobe lung mass of 4.3 cm
  - Biopsy consistent with adenocarcinoma
- PET scan: Multiple hypermetabolic bilateral lung lesions, osseous metastases
- Single-agent pembrolizumab x 1 cycle
- NGS: EGFR T751 exon 19 deletion | mBRCA1 | PTEN Y315 | EGFR amplification  
TMB = 14.35 | NTRK2 fusion

## Questions

- Should this patient be continued on pembrolizumab or switched to EGFR targeted therapy?
- What is the role of TKIs in elderly patients with declining performance status?

**In general, when do you believe checkpoint inhibitors should be introduced into the treatment algorithm for a patient with metastatic NSCLC with an EGFR mutation or ALK rearrangement? Does PD-L1 expression have any bearing on this decision? What regimen do you prefer for these patients?**

**In general, when do you believe ICIs should be introduced into the treatment algorithm for mNSCLC with an EGFR mutation or ALK rearrangement? Does PD-L1 have any bearing? What regimen do you prefer?**

- Important to avoid first-line immunotherapy use
  - Lack of efficacy
  - Consequence of TKI after immunotherapy
  - Important for neoadjuvant/perioperative strategies?
- EGFR mutation  $\neq$  ALK rearrangement
- EGFR-mutated disease *can* be immunotherapy responsive
  - IMpower150 with bevacizumab, TIL therapy experience
- ALK-rearranged disease is not currently immunotherapy responsive

# Case Presentation – Dr Flores: An 81-year-old woman with metastatic adenocarcinoma of the lung and an EGFR exon 19 deletion

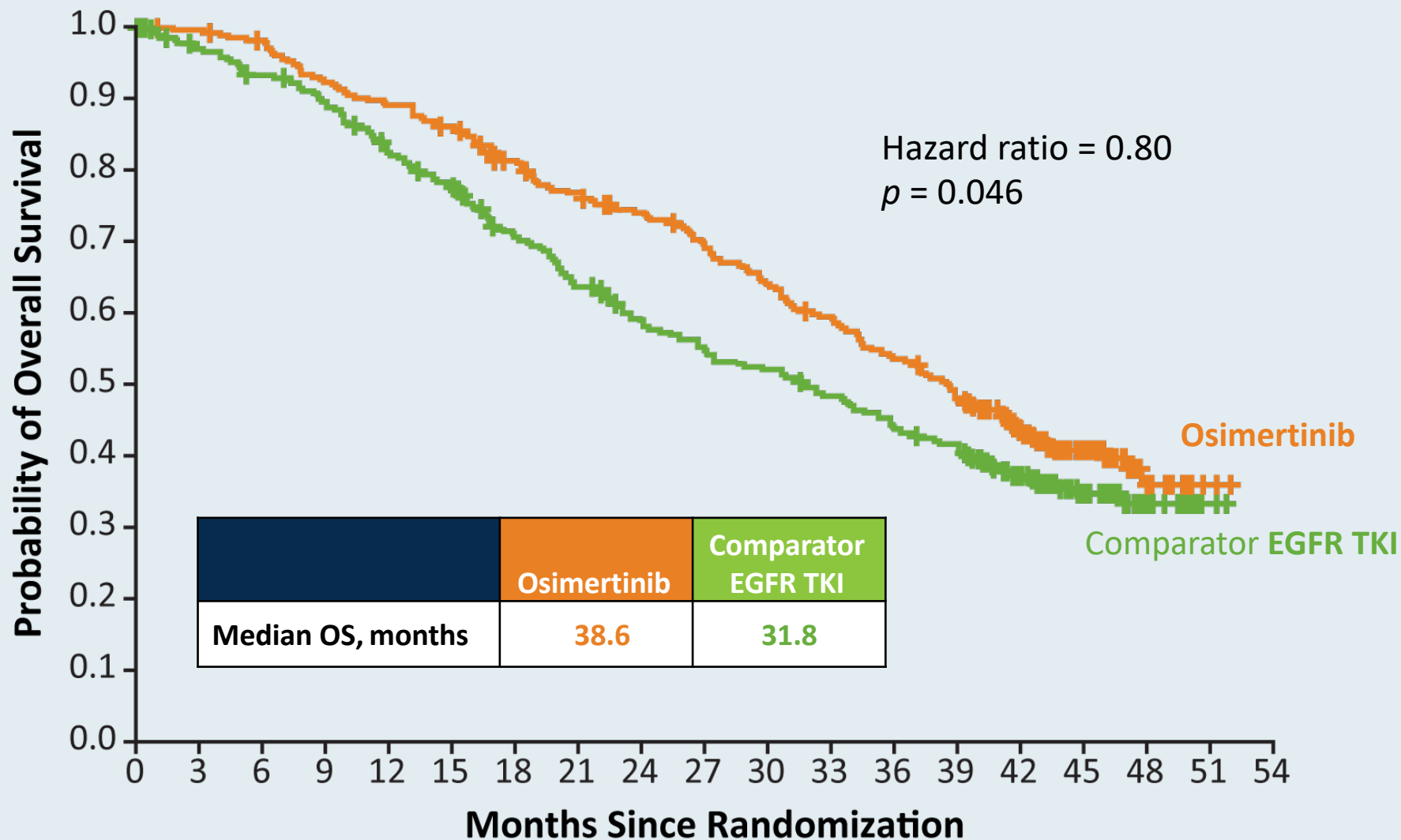


**Dr Regina Flores**

- PMH: Stage IIIA breast cancer 20 years ago, renal cell carcinoma 11 years ago
- Diagnosed with metastatic adenocarcinoma of the lung, with an EGFR exon 19 deletion and brain metastases x 3-4 lesions
- Gamma Knife
- Osimertinib x 2 years
  - Dermatitis and vaginitis



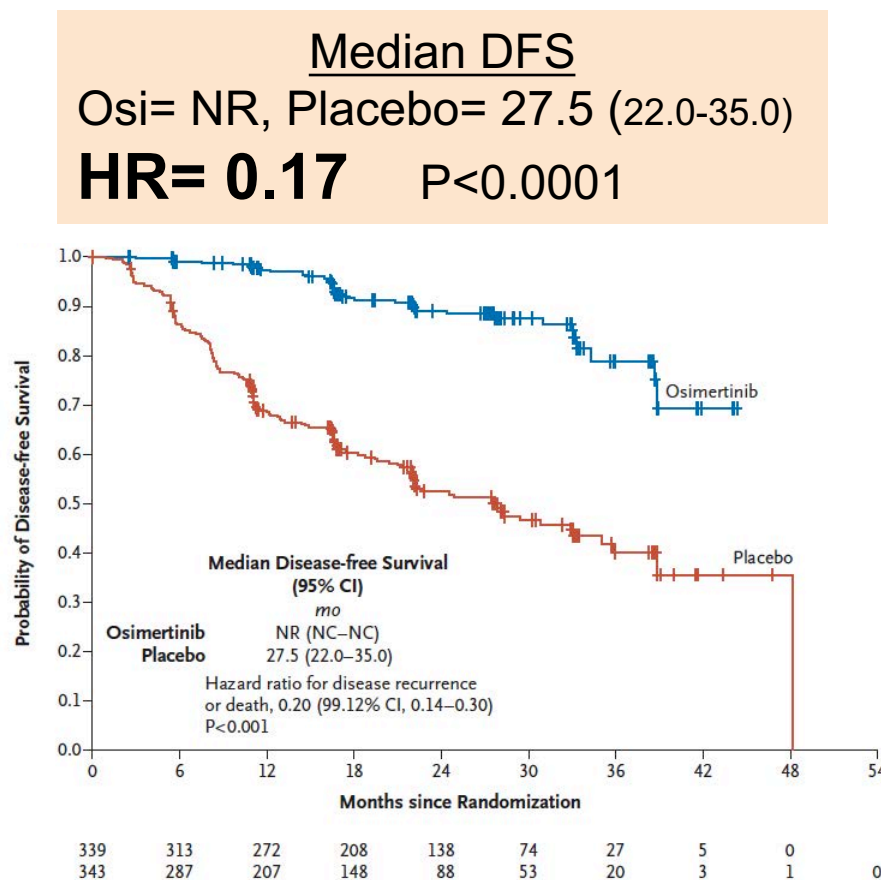
# FLAURA: Final Overall Survival Analysis



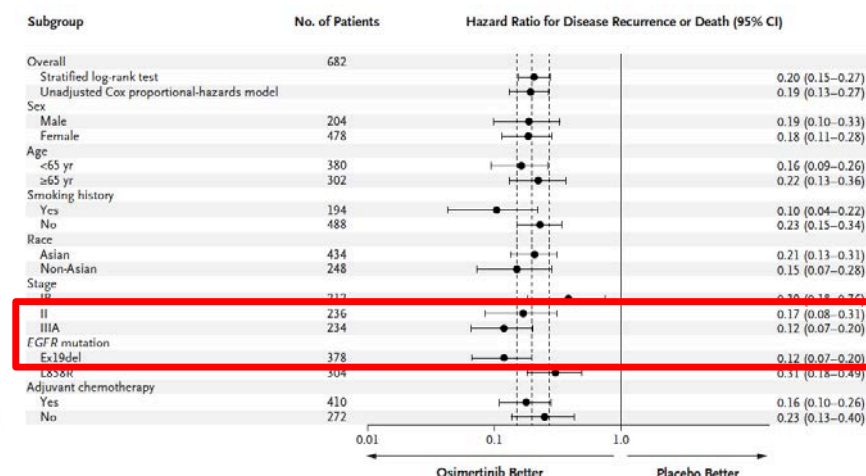
**Should the majority of patients with EGFR mutation-positive, Stage IB to IIIA non-small cell lung cancer (NSCLC) receive three years of osimertinib following surgery and adjuvant chemotherapy, if applicable?**

# Should the majority of pts with EGFR mutation-positive, Stage IB to IIIA NSCLC receive 3 years of osimertinib after surgery and adjuvant chemo, if applicable?

**Phase III ADAURA trial shows the benefits of 3y of osimertinib in resected stage IB-IIIa EGFR M+ NSCLC**



Subgroup analyses show DFS benefit across all stages



On December 18, 2020, the FDA approved osimertinib for adjuvant therapy after resection in EGFR mutant (exon 19 del/L858R) NSCLC

## 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%)

# Case Presentation – Dr Kumar: A 70-year-old man with metastatic NSCLC – BRAF V600E mutation



**Dr KS Kumar**

- 6/2020: Presented to primary care physician with abdominal pain and shortness of breath
- Workup confirms pulmonary carcinoma with post-obstructive pneumonitis and a large pleural effusion
  - Extensive peritoneal mass effects and extensive studding of the mid and lower mesentery was noted
- NGS: BRAF V600E mutation
- Smoking history: Previously smoked 2-3 ppd for 10 years, currently only smokes an occasional cigar
- Dabrafenib plus trametinib → patient faring well for the past 7 months

## Question

- What would be your approach on progression in addition to repeating NGS? An IO doublet regimen or chemotherapy with an IO?



# Case Presentation – Dr Hart: A 53-year-old woman with metastatic adenocarcinoma of the lung and an ALK rearrangement



**Dr Lowell Hart**

- Presents with back and chest pain → CT: LUL mass, bilateral nodules, numerous osseous lesions
  - Bronchoscopic biopsy: Adenocarcinoma
  - ALK rearrangement
- 12/2015: Crizotinib
  - Bilateral lower extremity edema

## Question

- In a situation like this, where the patient is stable on first-line therapy — but we know that in general the next-generation drugs are better — is it worthwhile switching somebody or should we save it in reserve?

**Regulatory and reimbursement issues aside, what is currently the optimal first-line therapy for a patient with metastatic ALK-positive NSCLC with brain metastases?**

## Regulatory and reimbursement issues aside, what is currently the optimal first-line therapy for a patient with metastatic NSCLC with ALK rearrangement and brain metastases?

- Targeted therapy is the preferred first-line treatment
  - Alectinib > crizotinib (Inv PFS HR 0.43)
  - Brigatinib > crizotinib (BIRC PFS HR 0.49)
  - Lorlatinib > crizotinib (BICR PFS HR 0.28)
- PFS with first-line therapy is quite long
- OS >>> PFS, which implies multiple lines of therapy
- Important differences in safety profile and resistance
- Biomarkers?

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

Press Release – March 3, 2021

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

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

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

# Case Presentation – Dr Flores: A 63-year-old man with metastatic adenocarcinoma of the lung and a ROS1 mutation



**Dr Regina Flores**

- Presents with a dry cough x 7 months and a stroke with minimal left sided weakness
- Diagnosed with metastatic adenocarcinoma of the lung with a ROS1 mutation
  - Bilateral lung, intrathecal thoracic and intra-abdominal, bone metastases and lymphadenopathy
  - No pain, PS 1

## Questions

- What would you recommend for first-line therapy? Would his recent stroke affect your decision?
- How would you decide between crizotinib and entrectinib?

**Regulatory and reimbursement issues aside, what is currently the optimal first-line therapy for a patient with metastatic ROS1-positive NSCLC with and without brain metastases?**



## Regulatory and reimbursement issues aside, what is currently the optimal first-line therapy for a patient with metastatic NSCLC with ROS1-rearrangement with and without brain metastases?

- Targeted therapy is the preferred first-line treatment
  - Crizotinib, RR 72%, PFS ~ 19m
  - Entrectinib, RR 67%, PFS ~ 16m
  - Based on single-arm studies, but expect outcomes > chemo
- Potential differences in CNS efficacy
- Trials separated in time
- Differences in toxicity
- Not recommended in sequence

**What is the optimal first-line therapy for a patient with newly diagnosed RET-positive metastatic NSCLC? For patients who will receive targeted therapy, are selpercatinib and pralsetinib equally efficacious options?**

## What is the optimal first-line therapy for newly diagnosed metastatic NSCLC with a RET fusion? For patients who will receive targeted therapy, are selpercatinib and pralsetinib equally efficacious?

- Targeted therapy is the preferred first-line treatment
  - Selpercatinib: RR 64%, 1L RR 85%, DOR 17.5m
  - Pralsetinib: RR 65%, 1L RR 73%, DOR NR
  - Based on single-arm studies, but expect outcomes > chemo
  - Very similar efficacy with both agents, both CNS active
- Well tolerated but different toxicity profiles
  - Only 2-4% discontinue due to adverse event
- Not recommended in sequence

**What is the optimal first-line therapy for a patient with newly diagnosed MET exon 14-positive NSCLC? For patients who will receive targeted therapy, are capmatinib and tepotinib equally efficacious options?**

**What is the optimal first-line therapy for newly diagnosed NSCLC with a MET exon 14 mutation? For patients who will receive targeted therapy, are capmatinib and tepotinib equally efficacious?**

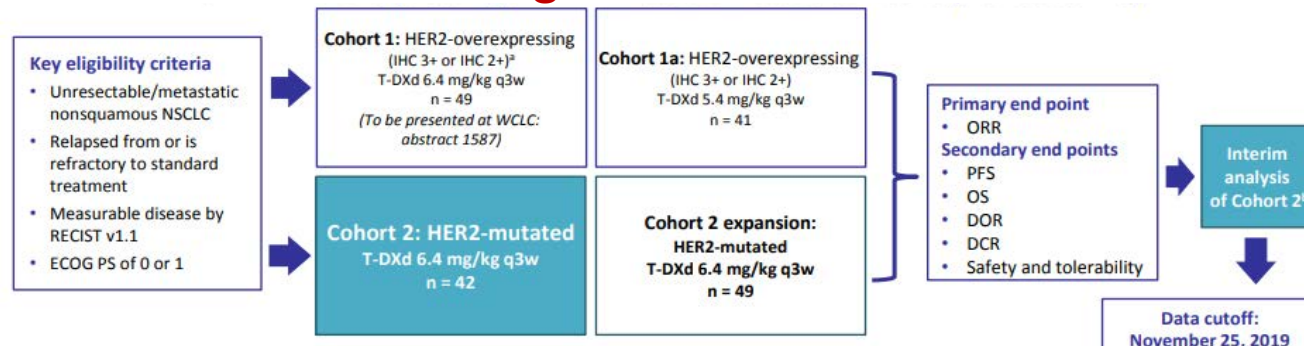
- Targeted therapy is the preferred first-line treatment
  - Capmatinib: RR 41% 2/3L, RR 68% 1L
  - Tepotinib: RR 46% overall
  - Rapid responses, durable with median DOR ~ 10-12m
- Similar toxicity profiles
- Mutation different from amplification
- Some will respond to immunotherapy

**At the current time, should patients with HER2-mutant NSCLC receive trastuzumab deruxtecan at some point in their treatment course? When? What about patients with HER2-amplified NSCLC?**



# Currently, should patients with HER2-mutant NSCLC receive trastuzumab deruxtecan at some point? When? What about patients with HER2-amplified NSCLC?

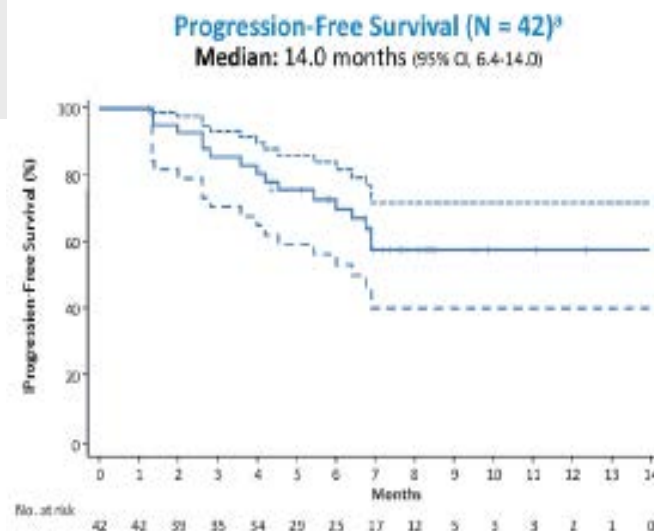
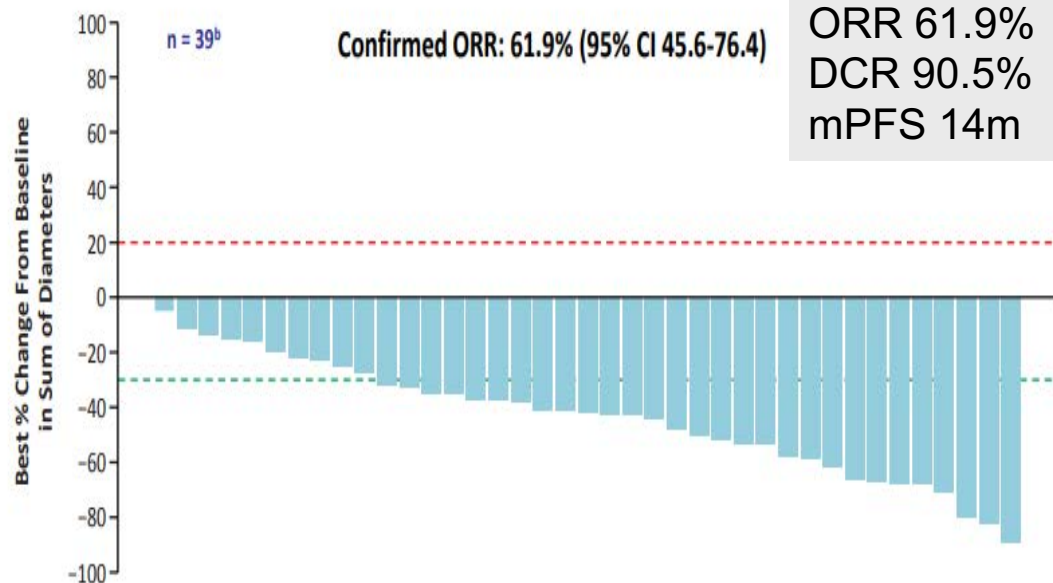
## Phase II DESTINY-Lung01 Trial of Trastuzumab Deruxtecan (T-DXd) ADC Targeting HER2



### Interstitial Lung Disease (ILD)

A concern with rates of 15.5% overall, 2.4% Gr5 in pooled analysis of trials

NCT03505710



Smit, WCLC 2020; Powell et al, AACR 2021 Ab CT167

***Thank you for joining us!***

***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 11:30 AM ET**

***Up Next...***

**Drs Maha Hussain and Elizabeth Plimack  
discuss the management of genitourinary cancers**

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

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

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

# Agenda

**Module 1 — Lung Cancer:** *Drs Heymach and Liu*

**Module 2 — Genitourinary Cancers:** *Drs Hussain and Plimack*

**Module 3 — Chronic Lymphocytic Leukemia and Lymphomas:**  
*Drs Friedberg and Sehn*

**Module 4 — Multiple Myeloma:** *Drs Ghobrial and Lonial*

**Module 5 — Breast Cancer:** *Drs Kaklamani and Lin*

# Genitourinary Cancers Faculty



**Maha Hussain, MD, FACP, FASCO**

Genevieve Teuton Professor of Medicine

Division of Hematology/Oncology

Deputy Director

Robert H Lurie Comprehensive Cancer Center

Northwestern University Feinberg School of Medicine

Chicago, Illinois



**Elizabeth R Plimack, MD, MS**

Chief, Division of Genitourinary Medical Oncology

Director, Genitourinary Clinical Research

Professor, Department of Hematology/Oncology

Fox Chase Cancer Center

Temple Health

Philadelphia, Pennsylvania



# Contributing Oncologists



**Susmitha Apuri, MD**  
Florida Cancer Specialists  
Lutz, Florida



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



**Warren S Brenner, MD**  
Lynn Cancer Institute  
Boca Raton, Florida



**Maria Regina Flores, MD**  
Advent Health Orlando  
Orlando Regional Hospital  
Florida Cancer Specialists  
Orlando, Florida



**Gigi Chen, MD**  
Diablo Valley Oncology and  
Hematology Medical Group  
Pleasant Hill, California



**Sunil Gandhi, MD**  
Florida Cancer Specialists  
Lecanto, Florida



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



**Ranju Gupta, MD**  
Attending Physician  
Co-Director, Cardio-Oncology Program  
LVPG Hematology Oncology Associates  
Lehigh Valley Health Network  
Bethlehem, Pennsylvania

# Contributing Oncologists



**Lowell L Hart, MD**

Scientific Director of Research  
Florida Cancer Specialists  
Co-Director, Phase 1 Program  
Wake Forest Baptist Health  
Comprehensive Cancer Center  
Fort Myers, Florida



**Jeremy Lorber, MD**

Attending Hematologist-Oncologist  
Tower Hematology Oncology  
Cedars-Sinai Medical Center  
Beverly Hills, California



**KS Kumar, MD**

Physician Partner  
Florida Cancer Specialists  
New Port Richey, Florida



**Vikas Malhotra, MD**

Staff Medical Oncologist-Hematologist  
Florida Cancer Specialists  
Spring Hill, Florida



**Ferdy Santiago, MD**

Florida Cancer Specialists  
Naples, Florida



**Zanetta S Lamar, MD**

Florida Cancer Specialists  
Naples, Florida



**Raji Shameem, MD**

Florida Cancer Specialists  
Deland, Florida

# **Chalk Talk Topics**

## **Elizabeth R Plimack, MD, MS**

- 1. What is the optimal therapeutic approach for a patient with BCG-unresponsive non-muscle-invasive urothelial bladder cancer (UBC), and how does this vary based on age and comorbidities?**
- 2. Regulatory and reimbursement issues aside, in what situations, if any, would you offer an adjuvant checkpoint inhibitor (eg, nivolumab) to a patient with muscle-invasive UBC following neoadjuvant chemotherapy and cystectomy?**
- 3. What is the optimal therapeutic approach for a patient with relapsed/refractory UBC with an FGFR gene alteration who has experienced disease progression on cisplatin-based chemotherapy followed by avelumab maintenance?**
- 4. What is the optimal first-line therapy for a patient with metastatic renal cell carcinoma (mRCC)? How does this vary based on risk status and patient symptomatology? Do you believe that all of the available up-front anti-PD-1/PD-L1 antibody/TKI combinations are essentially equivalent in terms of their overall efficacy and tolerability?**
- 5. Is there an optimal second-line treatment for patients with mRCC who experience disease progression on first-line checkpoint inhibitor-based therapy, based on the specific regimen the patient received up front?**

# **Chalk Talk Topics**

## **Maha Hussain, MD, FACP, FASCO**

- 1. What is the optimal therapeutic approach for a patient with M0 prostate cancer who has undergone local therapy and is experiencing PSA-only progression on ADT, and how do you factor in PSA level and PSA doubling time?**
- 2. What is the optimal therapeutic approach for a patient with hormone-sensitive metastatic prostate cancer, and how does this vary based on disease volume and symptomatology?**
- 3. What is the optimal therapeutic approach for a patient who presents with metastatic prostate cancer and a germline BRCA mutation?**
- 4. In what situations, if any, do you use radium-223 in patients with metastatic prostate cancer?**
- 5. Do you believe <sup>177</sup>Lu-PSMA-617 will gain FDA approval in the very near future, and if so, how do you envision using it relative to other evidence-based options?**

# Agenda

## **Module 1: Renal Cell Carcinoma (RCC)**

- Dr Lamar: A 64-year-old woman with metastatic clear cell RCC
- Dr Gandhi: A 73-year-old man with metastatic RCC

## **Module 2: Prostate Cancer**

- Dr Hart: A 64-year-old man with metastatic castration-resistant prostate cancer
- Dr Lamar: A 67-year-old man with metastatic castration-resistant prostate cancer and a germline BRCA2 mutation
- Dr Apuri: An 80-year-old man with metastatic hormone-sensitive prostate cancer

## **Module 3: Urothelial Bladder Cancer (UBC)**

- Dr Shameem: A 65-year-old man with nonmetastatic muscle-invasive bladder cancer
- Dr Shameem: A 48-year-old woman with metastatic bladder cancer

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# **Pembrolizumab versus Placebo as Post-Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase III KEYNOTE-564 Study**

Choueiri TK et al.

ASCO 2021;Abstract LBA5.

**Plenary Session: Sunday, June 6, 1:00 PM - 4:00 PM EDT**

# Case Presentation – Dr Lamar: A 64-year-old woman with metastatic clear cell RCC (Part 1)



**Dr Zanetta Lamar**

- PMH: Rheumatoid arthritis treated by hydroxychloroquine
- 2019: Diagnosed with clear-cell RCC, s/p radical nephrectomy
- 9/2020: Rapidly growing scalp lesion biopsy-confirmed RCC, intermediate risk
- Ipilimumab/nivolumab, with resolution of scalp lesions after 3 cycles
  - Cycle 4: Bilateral parotid swelling requiring inpatient admission and IV steroids, several months to resolution

## Questions

- What would you recommend if her disease progresses?

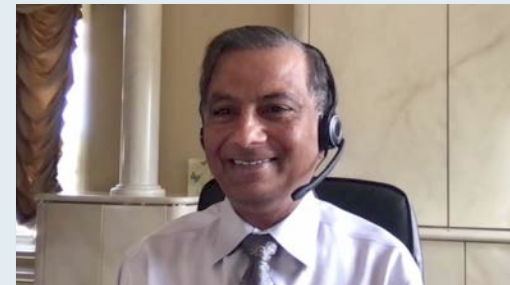
## Case Presentation – Dr Lamar: A 64-year-old woman with metastatic clear cell RCC (Part 2)



**Dr Zanetta Lamar**

- PMH: Rheumatoid arthritis treated by hydroxychloroquine
- 2019: Diagnosed with clear-cell RCC, s/p radical nephrectomy
- 9/2020: Rapidly growing scalp lesion biopsy-confirmed RCC, intermediate risk
- Ipilimumab/nivolumab, with resolution of scalp lesions after 3 cycles
  - Cycle 4: Bilateral parotid swelling requiring inpatient admission and IV steroids, several months to resolution

# Case Presentation – Dr Gandhi: A 73-year-old man with metastatic RCC



**Dr Sunil Gandhi**

- Presents to ER: Worsening night sweats, 25-lbs weight loss over 2 months, anorexia
  - CT: Left renal mass, lung nodules, widespread bone metastases
  - Bone biopsy: Clear cell RCC, extremely poorly differentiated
  - ECOG PS of 2, anemia, leukocytosis
- NIH 2<sup>nd</sup> opinion: Immunotherapy
- Ipilimumab/nivolumab, with autoimmune hepatitis after 1 dose, which responded to prednisone
- Nivolumab x 20 months → PD

## Questions

- Do you believe it was the right maneuver to continue nivolumab alone?

**What is the optimal first-line therapy for a patient with mRCC? How does this vary based on risk status and symptomatology? Do you believe that all the available up-front anti-PD-1/PD-L1 antibody/TKI combinations are essentially equivalent in overall efficacy and tolerability?**

**What is the optimal first-line therapy for a patient with mRCC? How does this vary based on risk status and symptomatology? Do you believe that all the available up-front anti-PD-1/PD-L1 antibody/TKI combinations are essentially equivalent in overall efficacy and tolerability?**

- Though it is a subset analysis, no OS benefit has been shown with combination IO therapy over sunitinib. Therefore, favorable risk patients have the option to use VEGF and PD-1 inhibitors sequentially, starting with a VEGF (I use pazopanib).
- For Int/Poor risk patient I'd recommend len/pembro: Excellent PFS, low primary progression rate, high response rate, and equivalent OS to similar combinations. Axi/pembro is also an option with the advantage that Axi tends to be better tolerated. I don't recommend ipi/nivo anymore except for patients with a contraindication to VEGF inhibitors. No advantage, high rate of irAEs needing steroids, and no OS advantage based on comparative long term follow up of the anti-VEGF/IO trials.



**Is there an optimal second-line treatment for patients with mRCC who experience disease progression on first-line checkpoint inhibitor-based therapy, based on the specific regimen the patient received up front?**

**Is there an optimal second-line treatment for patients with mRCC who experience disease progression on first-line checkpoint inhibitor-based therapy, based on the specific regimen the patient received up front?**

- Most people will use cabozantinib and this is reasonable.
- There are single-arm trial data on len/pembro post prior sequential IO and VEGF-directed tx, so this could be an option if the patient had an initial good response to IO and the team wants to keep it going.
- Belzutifan is now in trials, and at our center we would enroll the patient in the Phase II post progression on first line IO. It's well tolerated and effective.

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- Dr Apuri: An 80-year-old man with metastatic hormone-sensitive prostate cancer

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- Dr Shameem: A 65-year-old man with nonmetastatic muscle-invasive bladder cancer
- Dr Shameem: A 48-year-old woman with metastatic bladder cancer

# Case Presentation – Dr Hart: A 64-year-old man with metastatic castration-resistant prostate cancer



**Dr Lowell Hart**

- PMH: Untreated CLL diagnosed in 2015
- 2017: PSA rose to 20 and diagnosed with Gleason 3 + 4 = 7 prostate cancer
- Bicalutamide, leuprolide and RT
- Early 2019: Rising PSA, nodal metastasis
- Enzalutamide
- 9/2019: PSA rising
- 2/2020: Docetaxel, with no improvement in PSA
- 3/2020: Cabazitaxel, with no improvement in PSA, RT to bulky nodes

## Questions

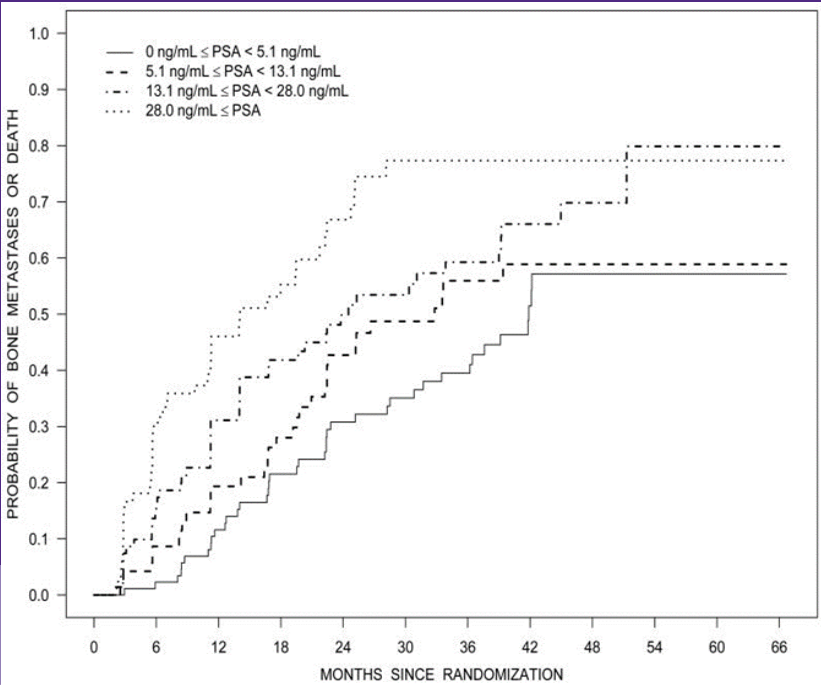
- Which is the proper drug to use for those patients that appear to be becoming castration resistant since there are now several agents available?
- Are there differences in their toxicity profiles, particularly with regard to fatigue?

**What is the optimal therapeutic approach for a patient with M0 prostate cancer who has undergone local therapy and is experiencing PSA-only progression on ADT, and how do you factor in PSA level and PSA doubling time (PSA DT)?**

What is the optimal therapeutic approach for a patient with M0 prostate cancer who has undergone local therapy and is experiencing PSA-only progression on ADT, and how do you factor in PSA level and PSA doubling time (PSA DT)?

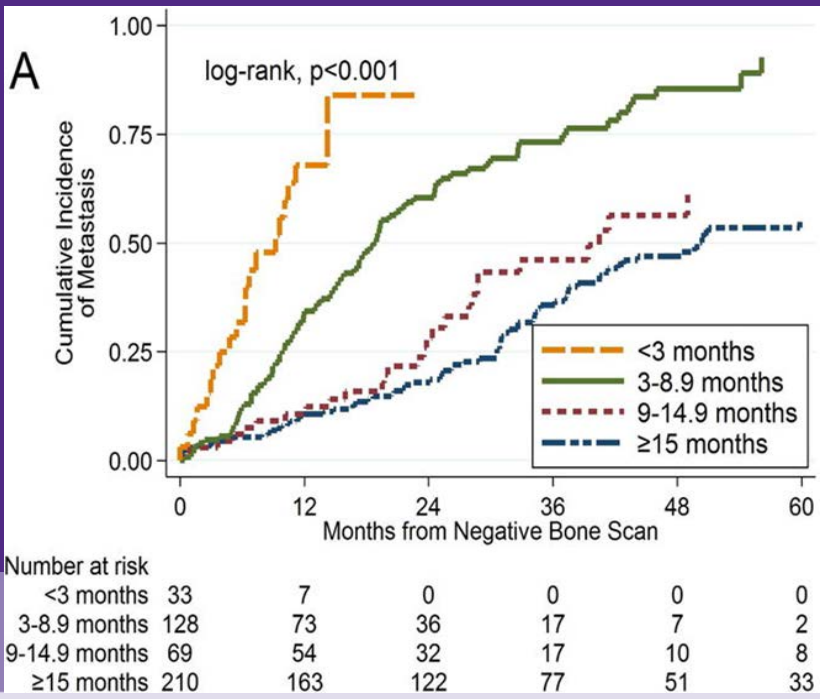
- Rising PSA while on ADT without mets on imaging is “Non Metastatic Castration-Resistant Prostate Cancer (nmCRPC)” disease state.
  - Development of metastases is predictable & is generally associated with increasing baseline PSA & PSA doubling time < 10 months.

Time to Bone Metastases or Death by Baseline PSA Quartiles

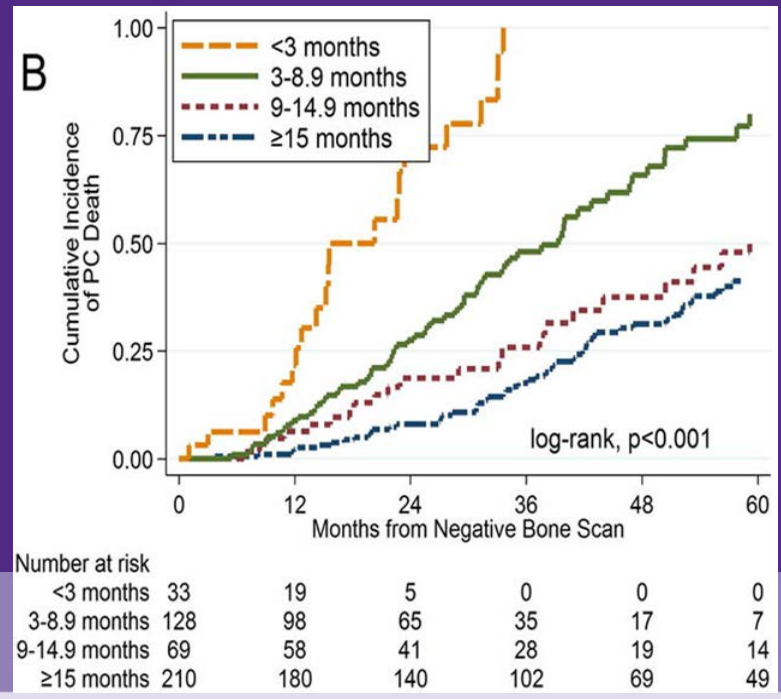


Smith MR, et al. Cancer. 2011

Metastases by PSA DT



PCa-specific mortality by PSA DT



Howard et al, BJU Int 2017

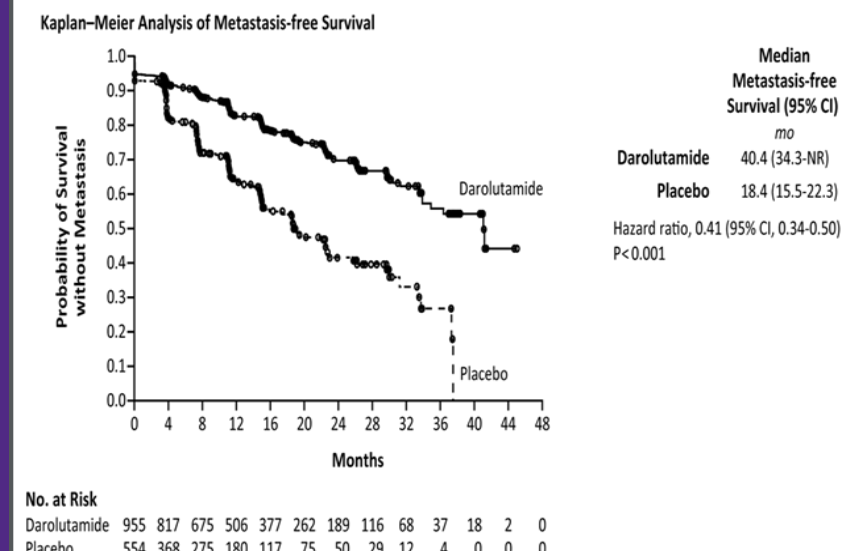
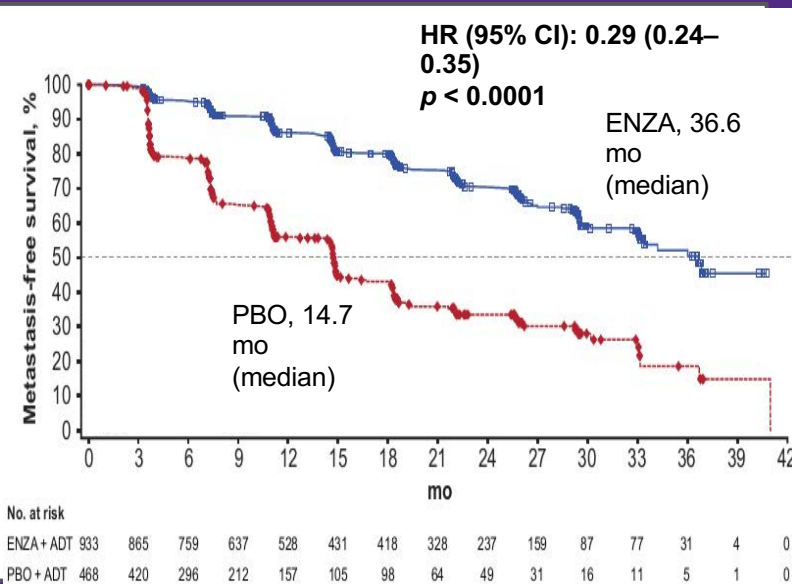
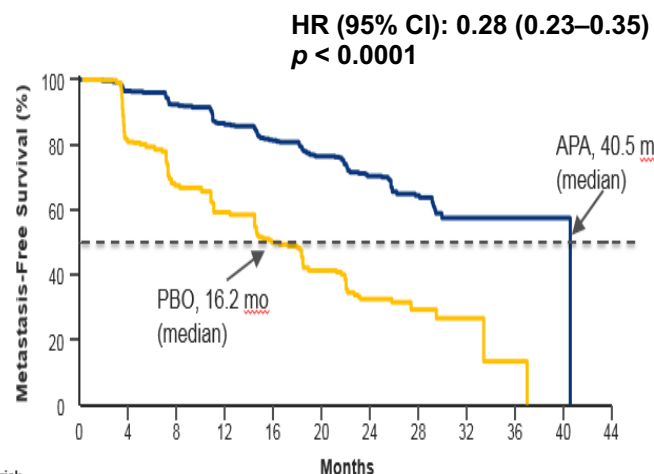
## Approach for M0 after local tx with PSA-only progression on ADT, and factoring in PSA level and PSADT — Cont

**Apalutamide, Enzalutamide & Darolutamide Are FDA Approved for nmCRPC: All are associated with improvement in metastasis-free survival & OS**

### Apalutamide: SPARTAN <sup>1</sup>

### Metastasis-Free Survival (MFS) Enzalutamide: PROSPER <sup>2</sup>

### Darolutamide: ARAMIS <sup>3</sup>



- **72%** reduction of distant progression or death
- **Median MFS: APA 40.5 months vs PBO 16.2**
- **24-month increase in MFS**

1. Smith MR, et al. NEJM 2018.

- **71%** reduction of distant progression or death
- **Median MFS: ENZA 36.6 months vs PBO 14.7**
- **22-month increase in MFS**

2. Hussain M, et al. NEJM 2018

- **59%** reduction of distant mets or death
- **Median MFS: DARO 40.4 months vs PBO 18.4 (22 m)**
- **22-month increase in MFS**

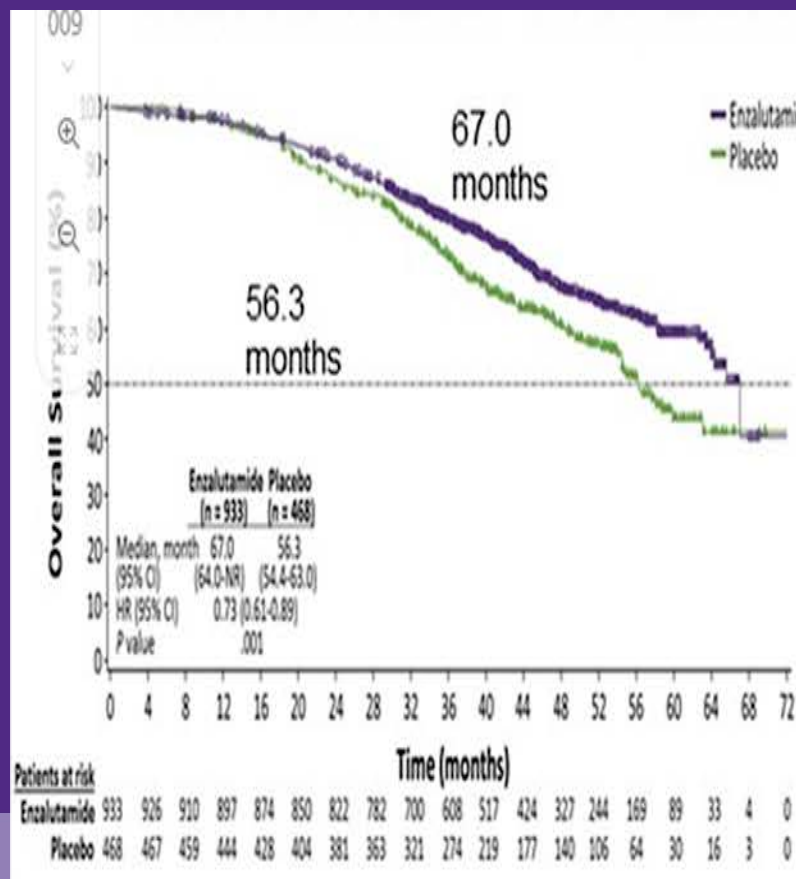
3. Fizazi K, et al. NEJM 2019



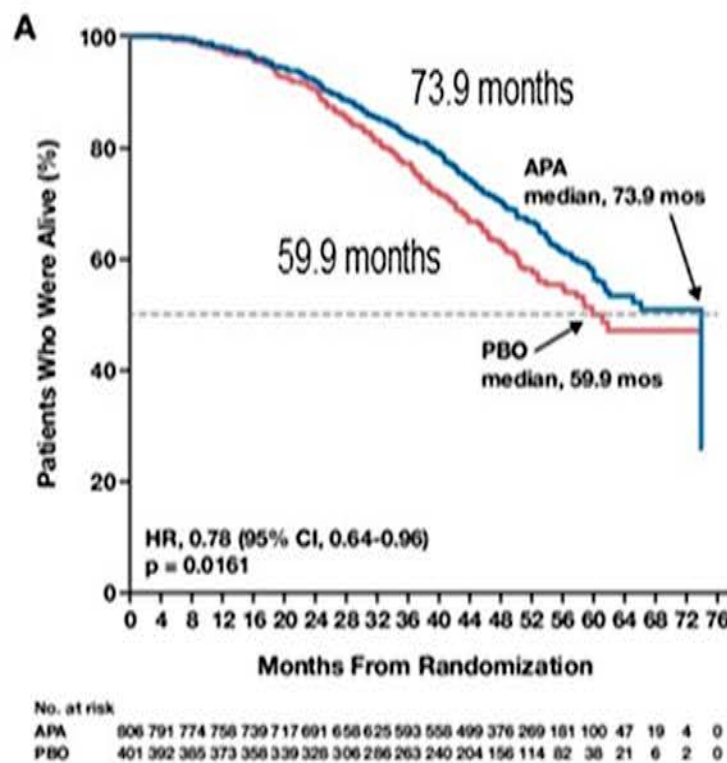
## Approach for M0 after local tx with PSA-only progression on ADT, and factoring in PSA level and PSADT – Cont

### Overall Survival

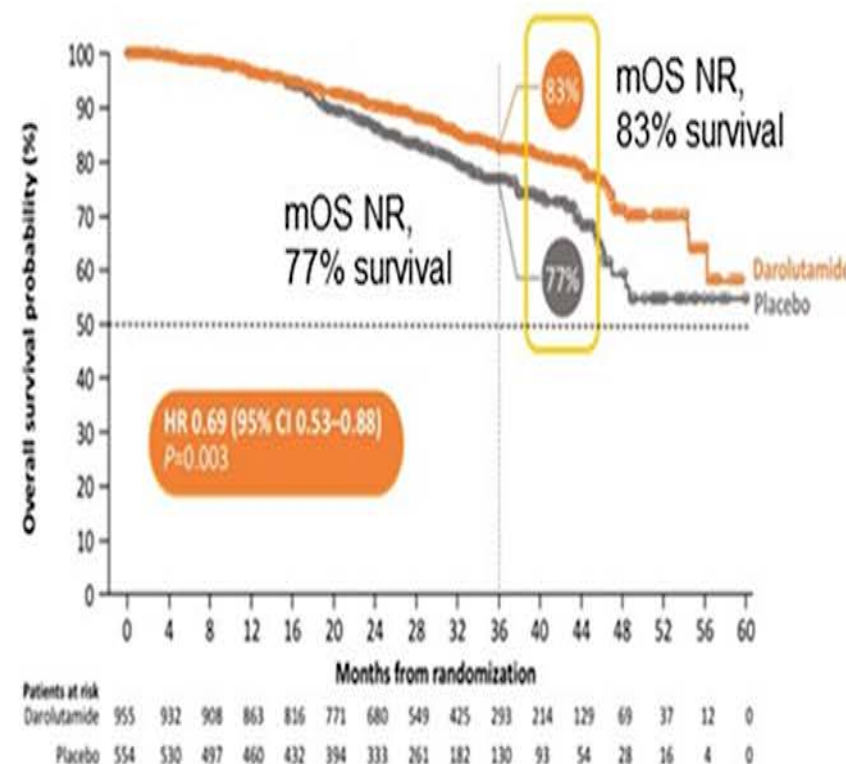
#### Enzalutamide (PROSPER)<sup>1</sup>



#### Apalutamide (SPARTAN)<sup>2</sup>



#### Darolutamide (ARAMIS)<sup>3</sup>



# Case Presentation – Dr Lamar: A 67-year-old man with metastatic castration-resistant prostate cancer and a germline BRCA2 mutation



**Dr Zanetta Lamar**

- Metastatic castration-resistant prostate cancer, with a germline BRCA2 mutation
  - All 4 offspring also have gBRCA2 mutations
- ADT + olaparib, with multiple dose adjustments required due to toxicity
  - Maintained on olaparib 150 mg BID
- Recently, PSA increasing to 9 ng/mL and scans reveal bone and lymph node involvement

## Questions

- How do you manage toxicity with PARP inhibitors? Would you consider switching to another PARP inhibitor?
- In patients with prostate cancer and BRCA mutations, what sequence do you give PARP inhibitors? Do you consider it first line? Second line? How do you go about thinking about treatment with these agents?

**What is the optimal therapeutic approach for a patient who presents with metastatic prostate cancer and a germline BRCA mutation?**

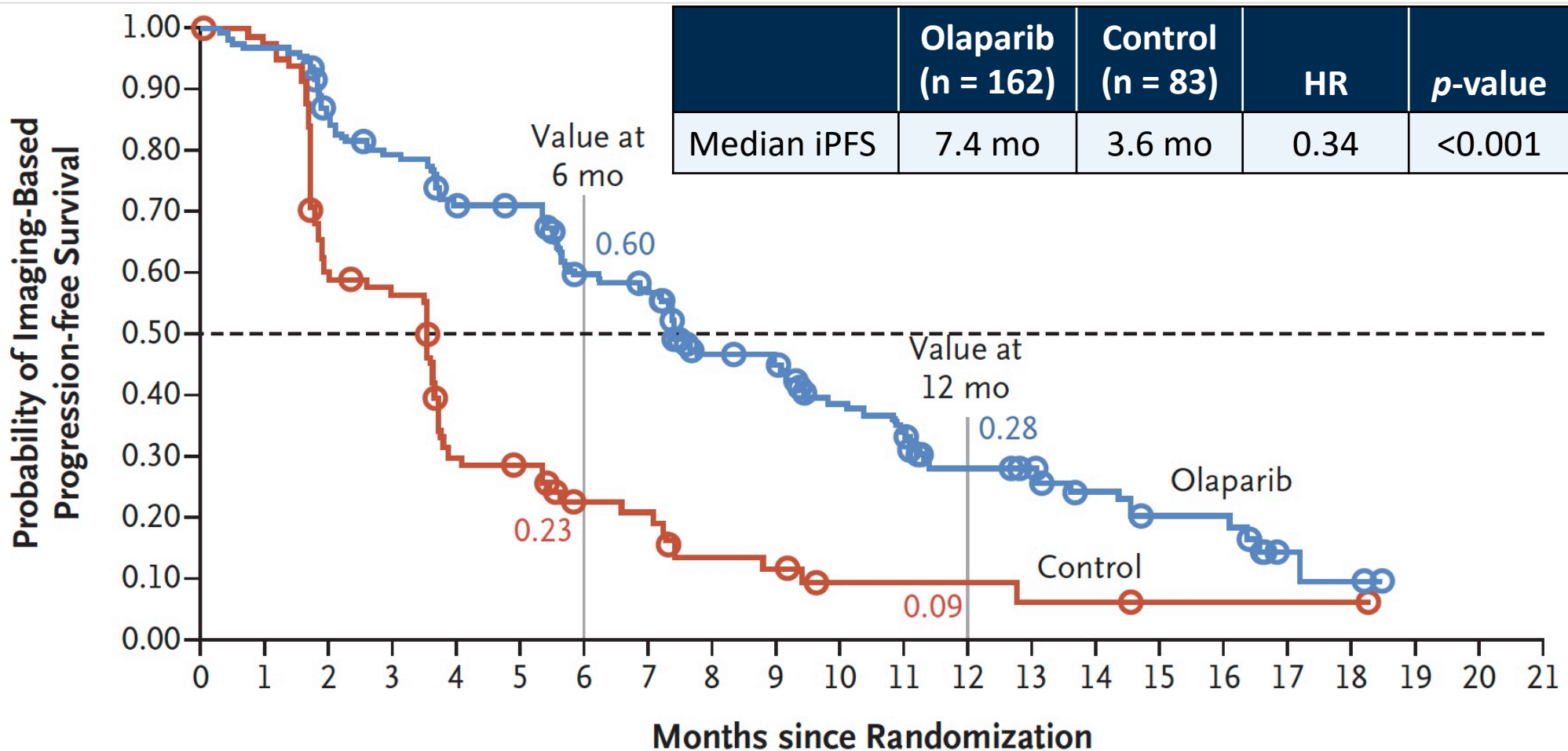
## What is the optimal therapeutic approach for a patient who presents with metastatic prostate cancer and a germline BRCA mutation?

1. For men with metastatic hormone-sensitive prostate cancer, management is per SOC or clinical trial.
2. For men with metastatic castration-resistant prostate cancer, both Olaparib and Rucaparib were FDA approved in May 2020:
  - Rucaparib: For men with deleterious BRCA mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.
  - Olaparib: deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone.

*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and/ or RAD54L.*

*FDA took out the PPP2R2A mutation from the HRRm panel given the weak biologic evidence on its role in DDR and the clinical data observed from PROfound.*

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



# Case Presentation – Dr Apuri: An 80-year-old man with metastatic hormone-sensitive prostate cancer



**Dr Susmitha Apuri**

- Previously diagnosed in 2018 with Gleason 7 (3 + 4) adenocarcinoma involving 3/12 cores, prostate tissue with spindle cell neoplasm (PSA range: 0.7-0.8 ng/mL)
- Second opinion pathology consult: Solitary fibrous tumor of the prostate
- 2020: MRI demonstrates enlarged prostate gland with stable lesion in the prostate
- Presents 3 months later to hospital due to recurrent urinary tract infections (UTIs), also exhibits baseline dementia, declining PS, multiple recent falls, worsening confusion
- CT → bladder ultrasound: 9cm mass
- Cystoscopy and biopsy demonstrate the mass originating from the left lobe of prostate
- Pathology review showed immunophenotype favoring solitary fibrous tumor of prostate cancer
- Tumor not amenable to microscopic surgery

## Question

- Is there any role for androgen deprivation therapy in this setting? What treatment would you recommend?

**What is the optimal therapeutic approach for a patient with hormone-sensitive metastatic prostate cancer, and how does this vary based on disease volume and symptomatology?**



## What is the optimal therapeutic approach for a patient with hormone-sensitive metastatic prostate cancer, and how does this vary based on disease volume and symptomatology?

Trial	Drug	Comparison
CHAARTED	docetaxel	ADT
STAMPEDE	abiraterone	ADT
LATITUDE	abiraterone	ADT
TITAN	apalutamide	ADT (+/- Docetaxel 11%)
ENZAMET	enzalutamide	ADT (+/- Docetaxel 45%)

- ADT + Docetaxel & CAD is superior to ADT alone (Phase III trials).
  - Docetaxel benefit is in high volume pts
- AR-I benefit: “all comers”.
- **Questions:**
  - **How Best to choose :** “Tradeoffs”
    - Toxicity
    - Therapy duration
    - Physical cost
    - Financial cost
- **Is ADT alone still an option?**
- **Treat the primary in addition to systemic therapy**
- **Focal mets RT in the context of “oligo metastatic disease”**

# 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.”

**In what situations, if any, do you use radium-223 in patients with metastatic prostate cancer?**

## In what situations, if any, do you use radium-223 in patients with metastatic prostate cancer?

In men with bone-only mets post frontline management for mCRPC progressing on AR-targeted therapy who are not eligible or optimal candidates for taxane chemotherapy due to age/comorbidities or have received prior docetaxel for mHSPC or mCRPC.

### Example Case:

- 76-year-old man started ADT + docetaxel x 6 cycles for G9 T3N1M1 high-volume bone-only metastatic PCa, PSA 60 ng/mL. Nadir PSA 0.1 ng/mL. Imaging improved with resolution of adenopathy.
- Developed rising PSA after 1 year post ADT + docetaxel despite castrate testosterone.
- Repeat imaging: 3 new bone lesions, no soft tissue disease.
  - He received abiraterone + prednisone, Nadir PSA 1 ng/mL, imaging improved.
- After 1.5 years he developed rising PSA and back/hip pain, PSA rising, imaging: multiple new bone lesions, no visceral lesions. ECOG PS 3.
- *No evidence of DDR mutation, TMB low, microsatellite stable*

**Do you believe  $^{177}\text{Lu}$ -PSMA-617 will gain FDA approval in the very near future, and if so, how do you envision using it relative to other evidence-based options?**

**Do you believe  $^{177}\text{Lu}$ -PSMA-617 will gain FDA approval in the very near future, and if so, how do you envision using it relative to other evidence-based options?**

- I do believe that it will gain FDA approval.
- Depending on the review of the full data and efficacy/toxicity (awaiting publication) and insurance coverage/cost to patient – I will be offering to patients with mCRPC with PSMA +ve disease (no PSMA –ve lesions) post front line or multiple prior lines of therapy for mCRPC.

# Positive Results Announced from the Phase III VISION Trial of Radioligand Therapy $^{177}\text{Lu}$ -PSMA-617 for Advanced Prostate Cancer

Press Release: Mar 23, 2021

“The Phase III VISION study [is] evaluating the efficacy and safety of  $^{177}\text{Lu}$ -PSMA-617, a targeted radioligand therapy in patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) compared to best standard of care alone.

The trial met both primary endpoints of overall survival and radiographic progression-free survival... The safety profile was consistent with data reported in previous clinical studies.

Results from the VISION trial will be presented at an upcoming medical meeting and included in US and EU regulatory submissions.”



# **Phase III Study of Lutetium-177-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer (VISION)**

Morris MJ et al.

ASCO 2021;Abstract LBA4.

**Plenary Session: Sunday, June 6, 1:00 PM - 4:00 PM EDT**

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- Dr Lamar: A 64-year-old woman with metastatic clear cell RCC
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## **Module 3: Urothelial Bladder Cancer (UBC)**

- Dr Shameem: A 65-year-old man with nonmetastatic muscle-invasive bladder cancer
- Dr Shameem: A 48-year-old woman with metastatic bladder cancer

# Case Presentation – Dr Shameem: A 65-year-old man with nonmetastatic muscle-invasive bladder cancer



**Dr Raji Shameem**

- 5/2020: Presents with hematuria → muscle-invasive urothelial carcinoma → lost to f/u due to losing job and insurance
- 12/2020 re-staged: Negative for adenopathy, metastatic disease
- Neoadjuvant cisplatin/gemcitabine → radical cystoprostatectomy with bilateral pelvic node dissection and conduit placement
  - Pathology: Residual cancer invading the peri-vesical soft tissue and prostate, 2 positive LNs (ppT4AN2)

## Questions

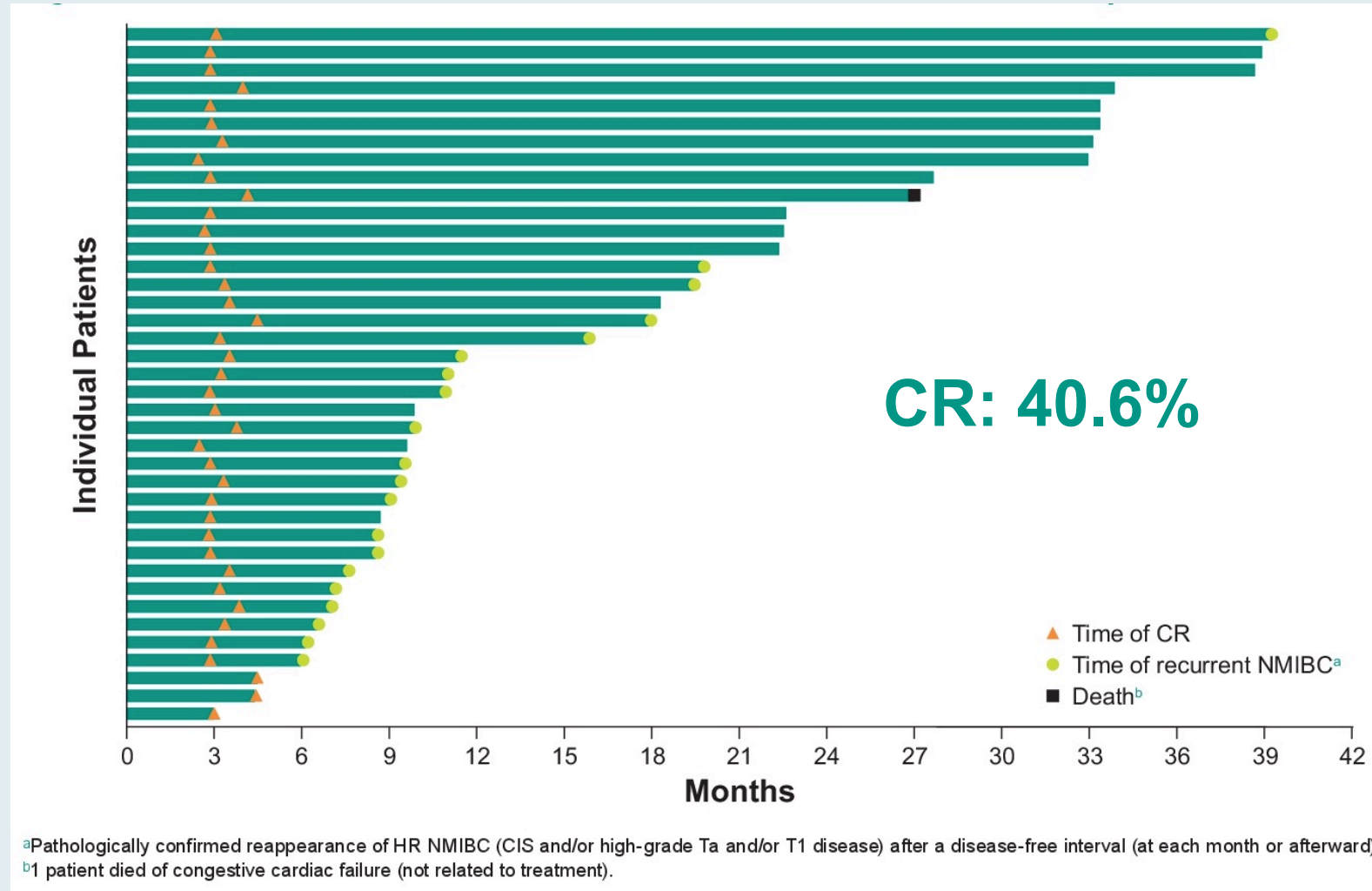
- For a patient such as this with residual disease, would you consider adjuvant nivolumab? Pending approval, have you used adjuvant nivolumab yet?

**What is the optimal therapeutic approach for a patient with BCG-unresponsive non-muscle-invasive UBC, and how does this vary based on age and comorbidities?**

## **What is the optimal therapeutic approach for a patient with BCG-unresponsive non-muscle-invasive UBC, and how does this vary based on age and comorbidities?**

- This is a curable disease, and goal of therapy should be cure
- Cystectomy gives best chance of cure
- Alternate intravesical therapies may be appropriate for those who are not cystectomy candidates, but cure rate generally declines with each line of therapy
- Systemic therapy with pembrolizumab, while FDA approved, provides a 0-16% cure rate (data still immature), with 12% rate of grade 3/4 treatment-related adverse event. Some AEs are chronic

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



**Regulatory and reimbursement issues aside,  
in what situations, if any, would you offer an adjuvant  
checkpoint inhibitor (eg, nivolumab) to a patient with  
muscle-invasive UBC following neoadjuvant chemotherapy  
and cystectomy?**

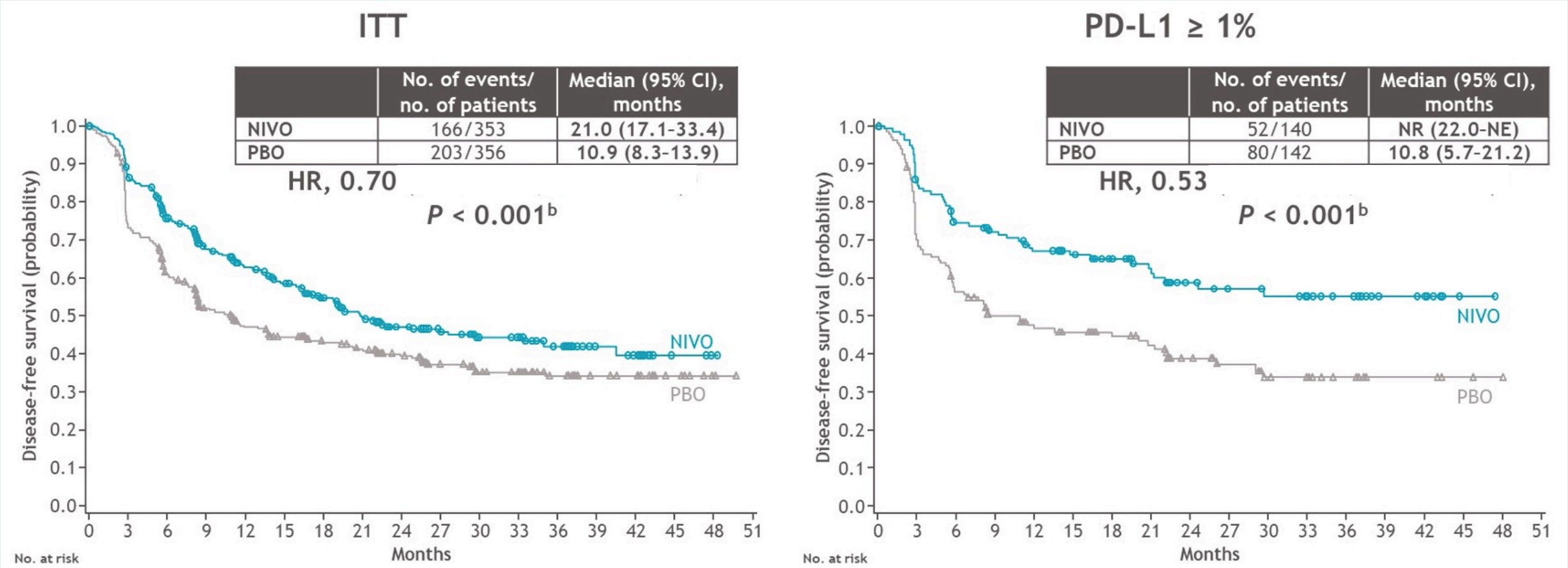


**Regulatory and reimbursement issues aside, in what situations, if any, would you offer an adjuvant checkpoint inhibitor (eg, nivolumab) to a patient with muscle-invasive UBC following neoadjuvant chemotherapy and cystectomy?**

The purpose of adjuvant therapy is to increase the % of patients we cure. To delay recurrence, at the expense of frequent infusions, risk of overtreatment (some patients are already cured by surgery alone) is not enough of a reason.

I would give adjuvant therapy to all patients meeting criteria for entry into CheckMate 274 if that trial ultimately shows an OS benefit in all comers. It may show an OS benefit in a biomarker subset (ie, dependent on PD-L1 expression level), in which case I would recommend it for the patients in that subset.

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



# Case Presentation – Dr Shameem: A 48-year-old woman with metastatic bladder cancer



**Dr Raji Shameem**

- Painless hematuria; Uninsured and presented to multiple ERs where treated for presumed UTI
- Lower abdominal pain
  - CT Abdomen: Bladder mass, retroperitoneal adenopathy
  - CT Chest: Bilateral pulmonary lesions and mediastinal adenopathy
  - Urology evaluation/pathology: High-grade urothelial carcinoma
  - CT-guided lung biopsy: Metastatic urothelial carcinoma
  - NGS: TP53 mutation
- Cisplatin/gemcitabine, with rapid response and symptom resolution
  - Cycle 4, recurrent abdominal pain; Progressive retroperitoneal adenopathy and pulmonary lesions
- Pembrolizumab
- Recent re-staging: PD, with development of hepatic metastases

## Questions

- In a patient who has progressed on platinum-based therapy and checkpoint inhibitor, what would you recommend next?

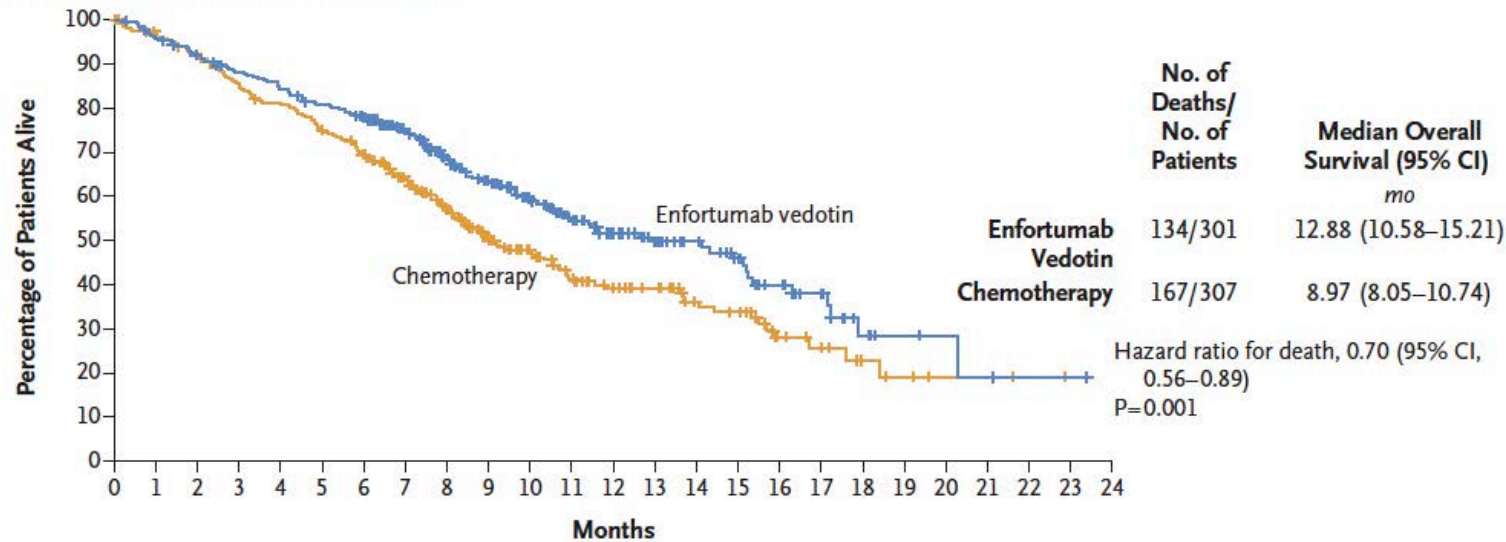
**What is the optimal therapeutic approach for a patient with relapsed/refractory UBC with an FGFR gene alteration who has experienced disease progression on cisplatin-based chemotherapy followed by avelumab maintenance?**

**What is the optimal therapeutic approach for a patient with relapsed/refractory UBC with an FGFR gene alteration who has experienced disease progression on cisplatin-based chemotherapy followed by avelumab maintenance?**

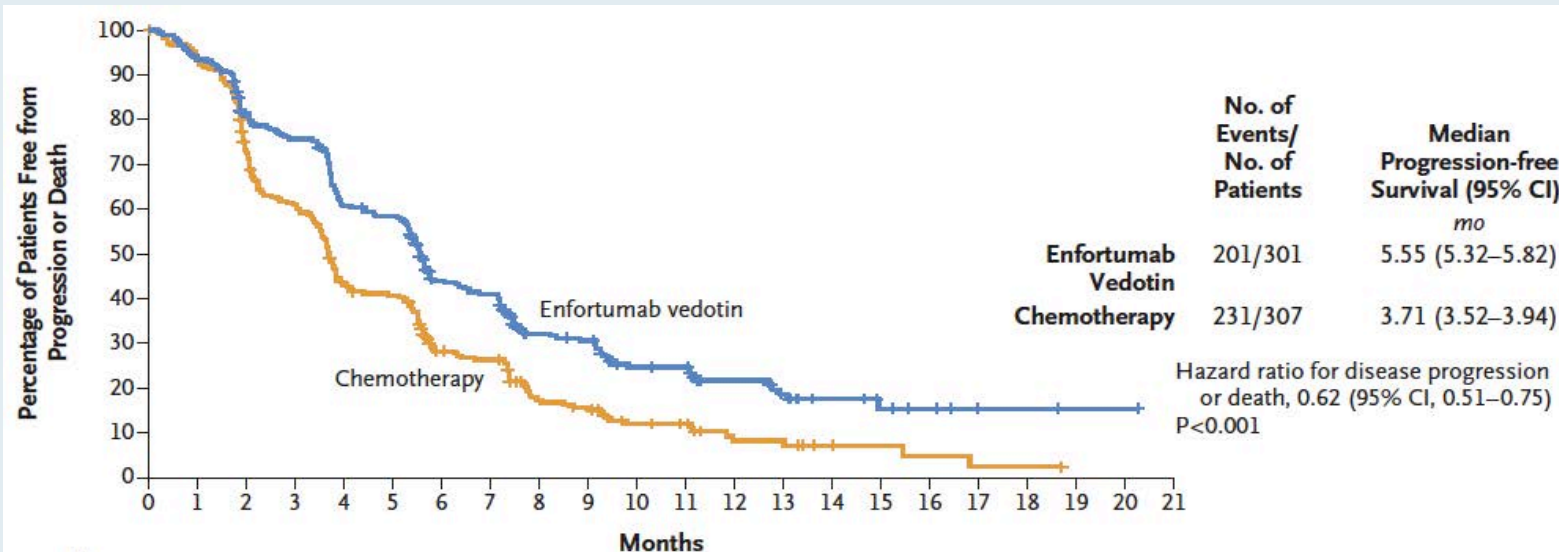
- I would have a balanced discussion.
- OS and PFS and ORR are a little better with enfortumab vedotin (EV) and there is stronger data behind it (level 1). Phase III trials for erdafitinib are pending.
- EV has the disadvantage of infusions weekly 3 of every 4 weeks. But I like it for efficacy in liver metastases (good experience in that situation).
- Erdafitinib is more convenient by virtue of its oral dosing, but eye exams are required frequently at the beginning.
- Hopefully this patient will get both agents; it's just a question of which order to use them in.

# EV-301: Survival and Response Analyses

Overall Survival According to Treatment Group



	EV (n = 301)	Chemo (n = 307)
ORR	40.6%	17.9%
DCR	71.9%	53.4%



Incidence of treatment-related adverse events was similar in the two groups:

- 93.9% versus 91.8%

Incidence of events of grade 3 or higher was also similar in the two groups:

- 51.4% versus 49.8%

# FDA Grants Accelerated Approval to Sacituzumab Govitecan for Advanced Urothelial Cancer

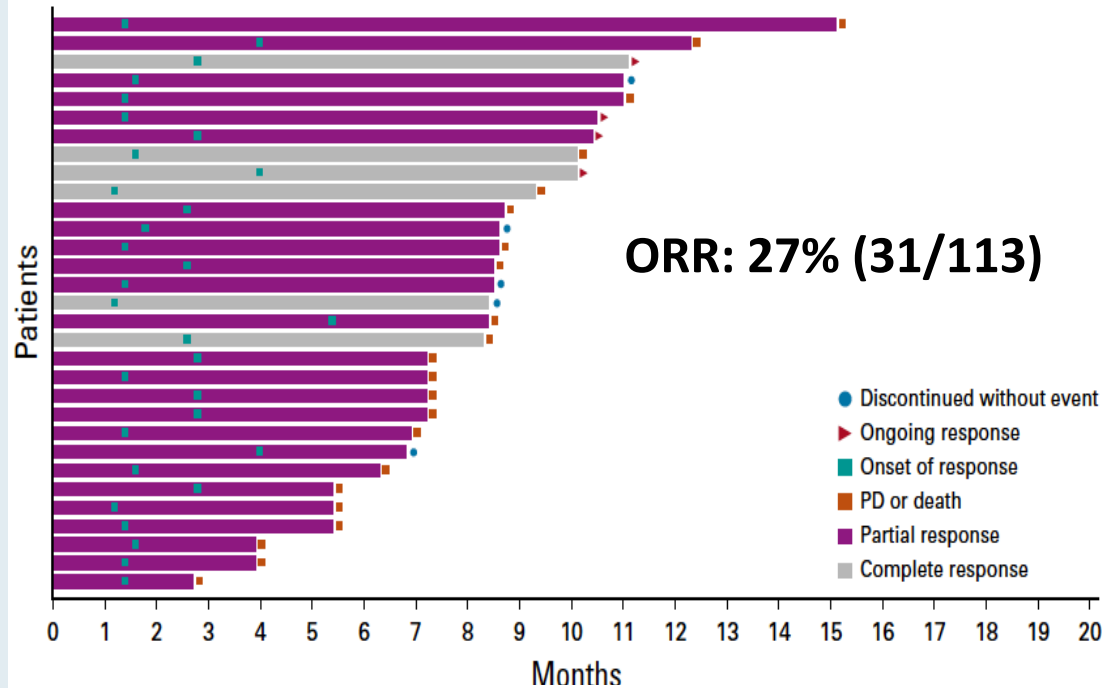
Press Release – April 13, 2021

“The Food and Drug Administration granted accelerated approval to sacituzumab govitecan for patients with locally advanced or metastatic urothelial cancer (mUC) who previously received a platinum-containing chemotherapy and either a programmed death receptor-1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor.

Efficacy and safety were evaluated in TROPHY (IMMU-132-06; NCT03547973), a single-arm, multicenter trial that enrolled 112 patients with locally advanced or mUC who received prior treatment with a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor. Patients received sacituzumab govitecan, 10 mg/kg intravenously, on days 1 and 8 of a 21-day treatment cycle.”



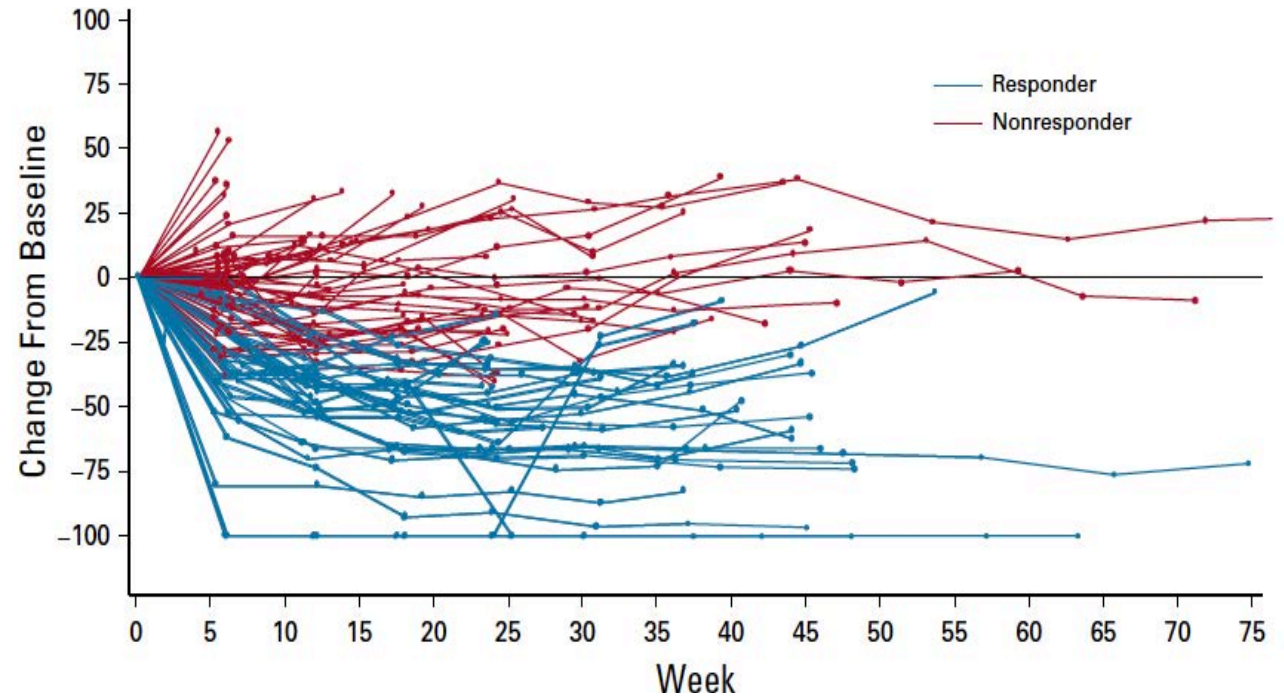
# TROPHY-U-01 (Cohort 1): ORR, Duration of Response and Survival



**Median PFS: 5.4 mo**

**Median DOR: 7.2 mo**

**Median time to onset of response: 1.6 mo**



**Median OS: 10.9 mo**

***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 12:45 PM ET**

***Up Next...***

**Drs Jonathan Friedberg and Laurie Sehn discuss the  
management of chronic lymphocytic leukemia and lymphomas**

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

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

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

# Agenda

**Module 1 — Lung Cancer:** *Drs Heymach and Liu*

**Module 2 — Genitourinary Cancers:** *Drs Hussain and Plimack*

**Module 3 — Chronic Lymphocytic Leukemia and Lymphomas:**  
*Drs Friedberg and Sehn*

**Module 4 — Multiple Myeloma:** *Drs Ghobrial and Lonial*

**Module 5 — Breast Cancer:** *Drs Kaklamani and Lin*

# Chronic Lymphocytic Leukemia and Lymphomas Faculty



**Jonathan W Friedberg, MD, MMSc**  
Samuel E Durand Professor of Medicine  
Director, James P Wilmot Cancer Institute  
University of Rochester  
Rochester, New York



**Laurie H Sehn, MD, MPH**  
Chair, Lymphoma Tumour Group  
BC Cancer Centre for Lymphoid Cancer  
Clinical Professor of Medicine  
Division of Medical Oncology  
University of British Columbia  
Associate Editor, *Blood*  
Vancouver, British Columbia, Canada

# Contributing Oncologists



**Susmitha Apuri, MD**  
Florida Cancer Specialists  
Lutz, Florida



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



**Warren S Brenner, MD**  
Lynn Cancer Institute  
Boca Raton, Florida



**Maria Regina Flores, MD**  
Advent Health Orlando  
Orlando Regional Hospital  
Florida Cancer Specialists  
Orlando, Florida



**Gigi Chen, MD**  
Diablo Valley Oncology and  
Hematology Medical Group  
Pleasant Hill, California



**Sunil Gandhi, MD**  
Florida Cancer Specialists  
Lecanto, Florida



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



**Ranju Gupta, MD**  
Attending Physician  
Co-Director, Cardio-Oncology Program  
LVPG Hematology Oncology Associates  
Lehigh Valley Health Network  
Bethlehem, Pennsylvania



# Contributing Oncologists



**Lowell L Hart, MD**

Scientific Director of Research  
Florida Cancer Specialists  
Co-Director, Phase 1 Program  
Wake Forest Baptist Health  
Comprehensive Cancer Center  
Fort Myers, Florida



**Jeremy Lorber, MD**

Attending Hematologist-Oncologist  
Tower Hematology Oncology  
Cedars-Sinai Medical Center  
Beverly Hills, California



**KS Kumar, MD**

Physician Partner  
Florida Cancer Specialists  
New Port Richey, Florida



**Vikas Malhotra, MD**

Staff Medical Oncologist-Hematologist  
Florida Cancer Specialists  
Spring Hill, Florida



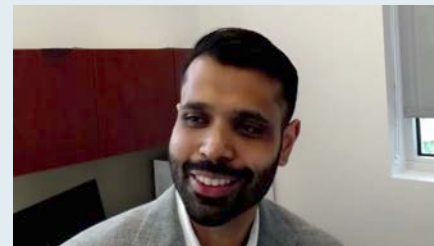
**Ferdy Santiago, MD**

Florida Cancer Specialists  
Naples, Florida



**Zanetta S Lamar, MD**

Florida Cancer Specialists  
Naples, Florida



**Raji Shameem, MD**

Florida Cancer Specialists  
Deland, Florida

# **Chalk Talk Topics**

## **Laurie H Sehn, MD, MPH**

- 1. How do you approach first-line treatment for advanced Hodgkin lymphoma, and how do patient age and risk status factor in?**
- 2. For a patient with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), how do you usually sequence polatuzumab vedotin, tafasitamab/lenalidomide, selinexor, loncastuximab tesirine and CAR T-cell therapy?**
- 3. Do you view the three available CD19-directed CAR T-cell therapies as equivalent therapeutic options for DLBCL, or are there distinct differences between these agents that would lead you to refer patients for one versus the others?**
- 4. Do you believe that there are discernible differences in terms of efficacy or tolerability that make one of the three FDA-approved BTK inhibitors for mantle cell lymphoma (MCL) a better therapeutic option?**
- 5. Where in the treatment sequence is the appropriate time to refer a patient with relapsed/refractory MCL for CAR T-cell therapy?**

# Chalk Talk Topics

## Jonathan W Friedberg, MD, MMSc

1. In what situations do you prefer a BTK inhibitor versus venetoclax/obinutuzumab as first-line treatment for patients with CLL who do not have del(17p) or a TP53 mutation? Which BTK inhibitor?
2. What is the optimal first-line therapy for a patient with CLL and del(17p) or a TP53 mutation?
3. Should community-based medical oncologists/hematologists be ordering minimal residual disease (MRD) assessment in any CLL clinical situations? If a patient with CLL receiving up-front therapy with venetoclax/obinutuzumab is found to have detectable MRD after one year, should treatment be stopped?
4. How do you generally integrate the R<sup>2</sup> regimen of lenalidomide/rituximab into the management of follicular lymphoma (FL)? In what situations, if any, do you recommend it first line? What dose, schedule and treatment duration do you use?
5. What is the optimal therapeutic approach for a patient with FL with and without an EZH2 mutation who has experienced disease progression on bendamustine/rituximab and then R<sup>2</sup>? Do you believe that there are discernible differences in terms of efficacy or tolerability that make one of the four FDA-approved PI3K inhibitors for relapsed/refractory FL a better therapeutic option?

# Agenda

## **Module 1: Hodgkin Lymphoma**

- Dr Kumar: A 59-year-old man with Stage II Hodgkin lymphoma

## **Module 2: Chronic Lymphocytic Leukemia (CLL)**

- Dr Lamar: A 65-year-old man initially diagnosed with asymptomatic CLL now experiencing symptomatic progression
- Dr Hart: A 64-year-old man with CLL – IGHV mutation, del(13q14)

## **Module 3: Mantle Cell Lymphoma (MCL)**

- Dr Shameem: An 89-year-old man with MIPI high-risk MCL

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

- Dr Gandhi: An 83-year-old man with Waldenström macroglobulinemia (WM) transformed to DLBCL

## **Module 5: Follicular Lymphoma (FL)**

- Dr Dandamudi: A 58-year-old woman with relapsed FL
- Dr Hart: A 62-year-old man with relapsed high-grade FL

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# Case Presentation – Dr Kumar: A 59-year-old man with Stage II Hodgkin lymphoma



**Dr KS Kumar**

- 8/2020: Presented with swelling in right neck in St Thomas, Virgin Islands; workup reveals nodular sclerosing Hodgkin lymphoma
  - PMH: current smoker, 40-year smoking history
- Patient moves to Florida to seek further evaluation; Stage II and asymptomatic bulky disease; treatment delays due to lack of insurance
- PET scan: multiple bilateral hypermetabolic cervical lymph nodes, subcarinal lymph nodes, no abdominal lymphadenopathy
- BV + AVD x 4 cycles → complete remission

## Questions

- We don't have any data for BV-AVD in Stage II Hodgkin lymphoma — Is 4 cycles enough treatment?

**How do you approach first-line treatment for advanced Hodgkin lymphoma, and how do patient age and risk status factor in?**



# How do you approach first-line treatment for advanced Hodgkin lymphoma, and how do patient age and risk status factor in?

---

Stages III/IV or Stages I/II with B-symptoms or bulky disease



Standard-risk (IPS 0-3) Stage III  
or Stage I/II (B-sx/bulky)

Stage IV or  
High-risk (IPS  $\geq 4$ ) Stage III

Patient unsuitable for ABVD  
>60-65 years

## ABVD x 6

- If PET-2 negative, omit Bleo
- If PET-2 positive, consider change (BEACOPP; +BV?)
- If end-of-treatment PET positive, consider XRT

## BV-AVD x 6

- If end-of-treatment PET positive, consider XRT

## Alternative Options

- Alternative chemotherapy
- BV-AVD-BV
- BV-DTIC; BV-bendamustine
- BV
- PD-1 inhibitor

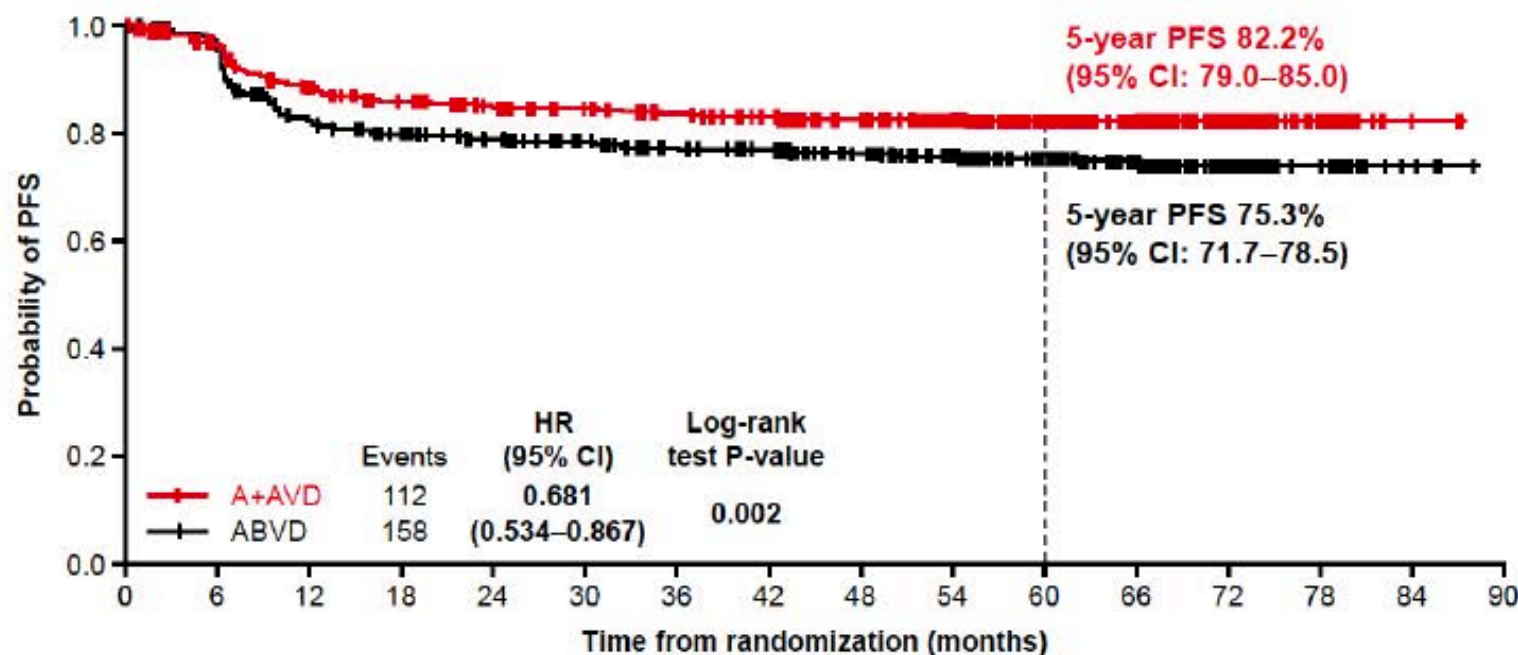
# **Brentuximab Vedotin with Chemotherapy for Patients with Previously Untreated, Stage III/IV Classical Hodgkin Lymphoma: 5-Year Update of the ECHELON-1 Study**

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

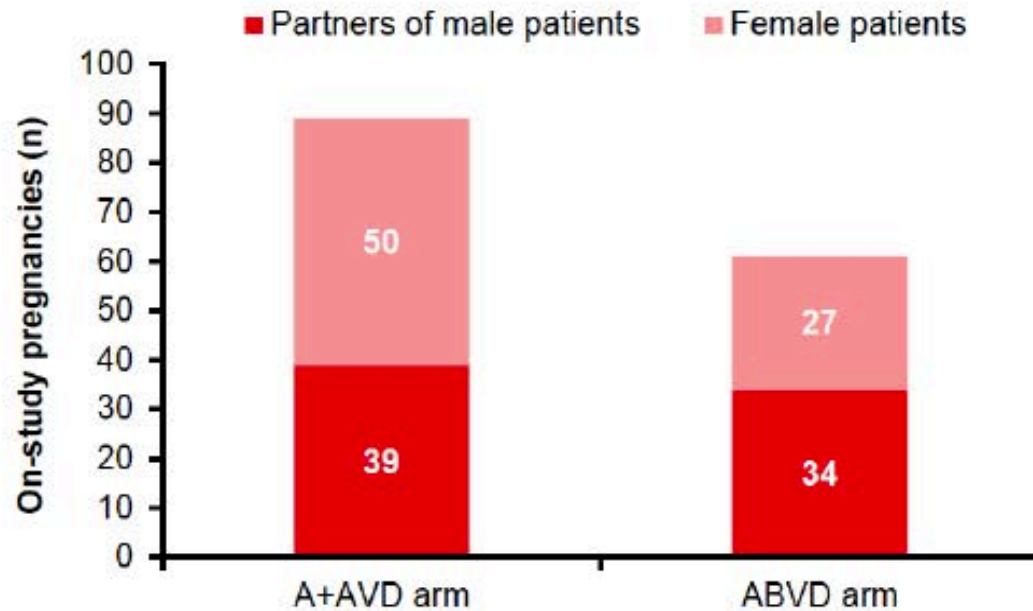
\*September 14, 2020 data cut-off.



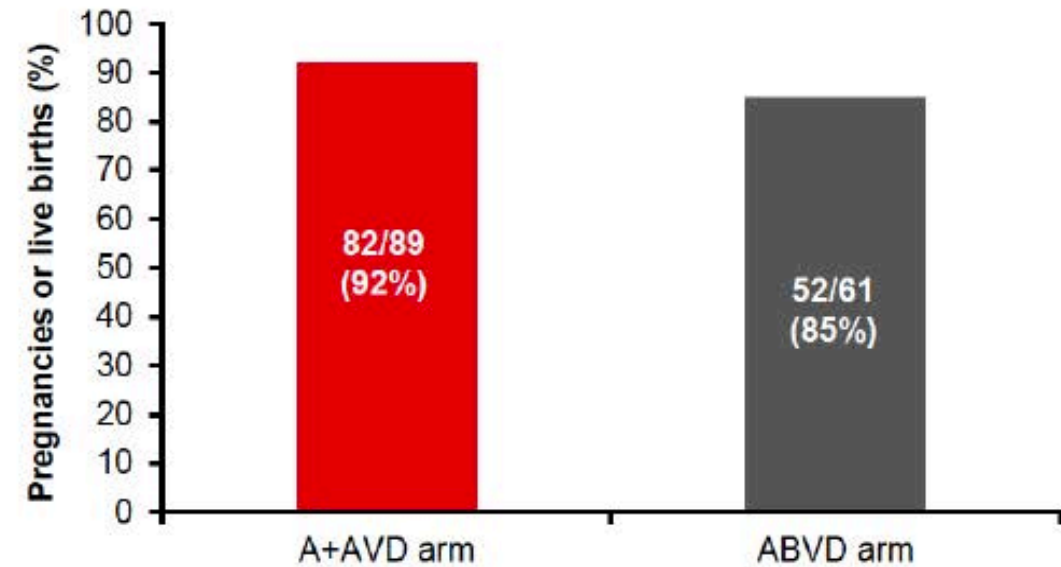
# ECHELON-1: Pregnancies

- 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



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- Dr Dandamudi: A 58-year-old woman with relapsed FL
- Dr Hart: A 62-year-old man with relapsed high-grade FL

# Case Presentation – Dr Lamar: A 65-year-old man initially diagnosed with asymptomatic CLL now experiencing symptomatic progression



**Dr Zanetta Lamar**

- Observed for many years with asymptomatic CLL
- WBC count increased to 150,000
- Patient is now symptomatic

## Questions

- Do you consider doubling time in your decision to initiate treatment in an otherwise asymptomatic patient?
- How would you approach upfront treatment of this patient with high WBC counts who is at risk for TLS?
- How would you approach initial treatment for patients who have adverse cytogenetics such as del(17p)?

# Case Presentation – Dr Hart: A 64-year-old man with CLL – IGHV mutation, del(13q14)



**Dr Lowell Hart**

- 2007: Presented with leukocytosis
- 2009: Bone marrow biopsy confirmed CLL, ZAP70-positive, splenomegaly, positive lymph nodes above and below the diaphragm
- 2010-2015: Ofatumumab on clinical trial, BR → rituximab maintenance
- 2015: Ibrutinib for 3 years → PD
- 2019: Obinutuzumab/chlorambucil
  - Recurrent infections to area of prior knee replacement surgery; eventually leg amputated above the knee
- Venetoclax initiated about a year ago and patient has done well

## Questions

- Even though he has already had anti-CD20 antibodies, would you have added obinutuzumab when he started venetoclax?
- Have there been any modifications to the guidelines on venetoclax and hospitalization?



**In what situations do you prefer a BTKi vs venetoclax/  
obinutuzumab as first-line treatment for patients with CLL  
without a del(17p) or TP53 mutation? Which BTKi?**

## In what situations do you prefer a BTKi vs venetoclax/obinutuzumab as first-line treatment for patients with CLL without a del(17p) or TP53 mutation? Which BTKi?

### BTKi: No efficacy differences

#### Ibrutinib

- Skin rash, bleeding, atrial fibrillation, HTN
- “Real world”: 41% discontinue in first 17 months
- Antibody not necessary
- Continuous treatment

#### Acalabrutinib

- Less but still some atrial fibrillation
- Headaches; often respond to caffeine
- Twice daily drug

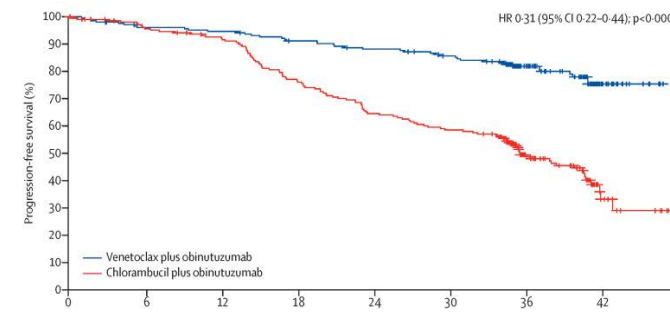
#### Zanubrutinib

- Approval in MCL; comparative trial in WM (ASPEN) shows no efficacy difference but some cardiotoxicity differences

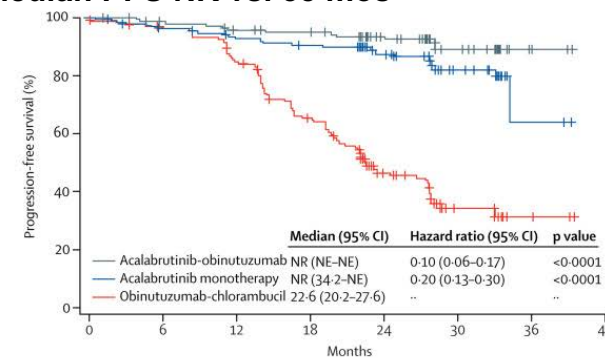
#### Venetoclax

- Limited duration therapy (1 year) when combined with obinutuzumab
- MRD higher than with ibrutinib

*Outside of clinical trials, for newly diagnosed CLL I am using single agent ibrutinib or acalabrutinib. Considerations include cardiac comorbidity, insurance coverage. I have not used venetoclax-based treatment for upfront CLL outside of a clinical trial.*

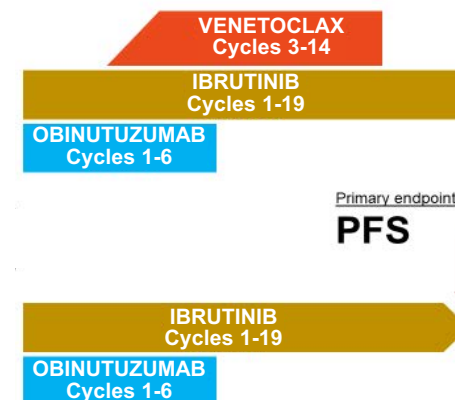


**CLL14: Venetoclax/obi vs. chlorambucil/obi**  
Median PFS NR vs. 35 mos\*



**ELEVATE-TN: Acalabrutinib +/- Obi vs. chlorambucil/obi**  
Median PFS NR vs. 22.6 mos\*\*

**EA9161 trial**



\*Al-Sawaf et al., *Lancet Oncol* 21:1188-1200 2020

\*\*Sharman et al., *Lancet* 10232:1278-91 2020

**What is the optimal first-line therapy for a patient with CLL and del(17p) or a TP53 mutation?**

# What is the optimal first-line therapy for a patient with CLL and del(17p) or a TP53 mutation?

## TP53 aberrations

- Tumor suppressor protein
- Likely ~10% have at diagnosis
- Still holds prognostic value in targeted era

## Chemoimmunotherapy is inadequate

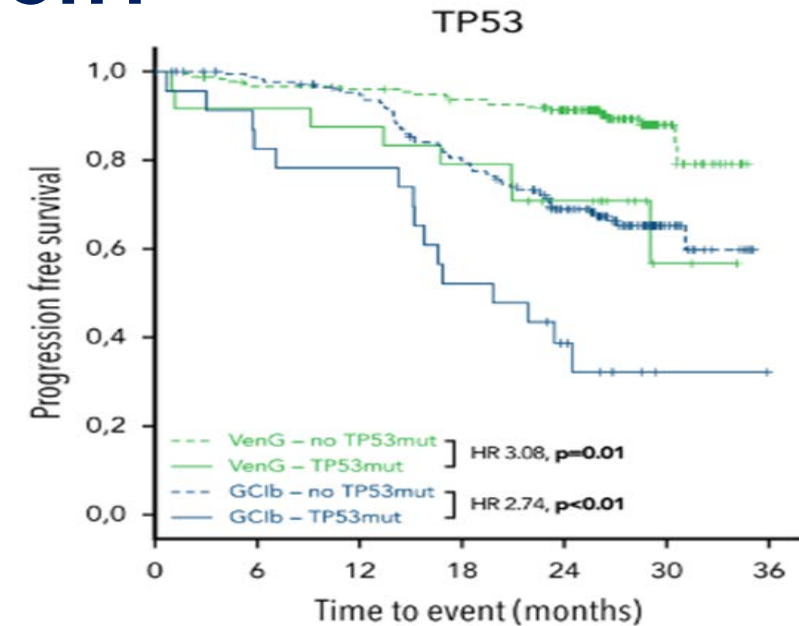
## BTK inhibition and venetoclax are both options

- Complete response may not predict response durability
- “Salvage” experience greater with venetoclax after ibrutinib
- Many patients with p53 abnormalities are older with comorbidity
- Richter’s transformation may be higher in 17p-deleted or p53-mutated CLL
- CAR-T may ultimately hold promise for 17p-deleted and p53-mutated CLL

*Outside of clinical trials, for newly diagnosed CLL with del(17p) and/or p53 mutation, I am using single agent ibrutinib or acalabrutinib. These patients should always be considered for clinical trials. I have not used venetoclax-based treatment for upfront CLL outside of a clinical trial.*

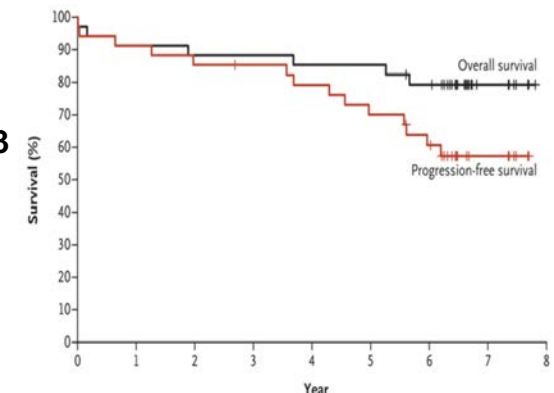
\*Tausch et al., *Blood* 135:2402-12 2020

\*\*Ahn et al., *NEJM* 10232:1278-91 38:498-500 2020



**CLL14\*: Venetoclax/Obi vs. chlorambucil/obi**  
**TP53 mutation confers inferior outcome in both arms**

**Phase 2 trial\*\*:**  
**Ibrutinib in TP53**  
**mutated CLL**  
**(N=34).**  
**Median PFS:**  
**53 mos.**



**Should community-based medical oncologists/hematologists be ordering MRD assessment in any CLL clinical situations?**  
**If a patient with CLL receiving up-front therapy with venetoclax/obinutuzumab is found to have detectable MRD after 1 year, should treatment be stopped?**

## Should community-based medical oncologists/hematologists be ordering MRD assessment in any CLL clinical situations? If a patient with CLL receiving up-front therapy with venetoclax/obinutuzumab is found to have detectable MRD after 1 year, should treatment be stopped?

### MRD in CLL

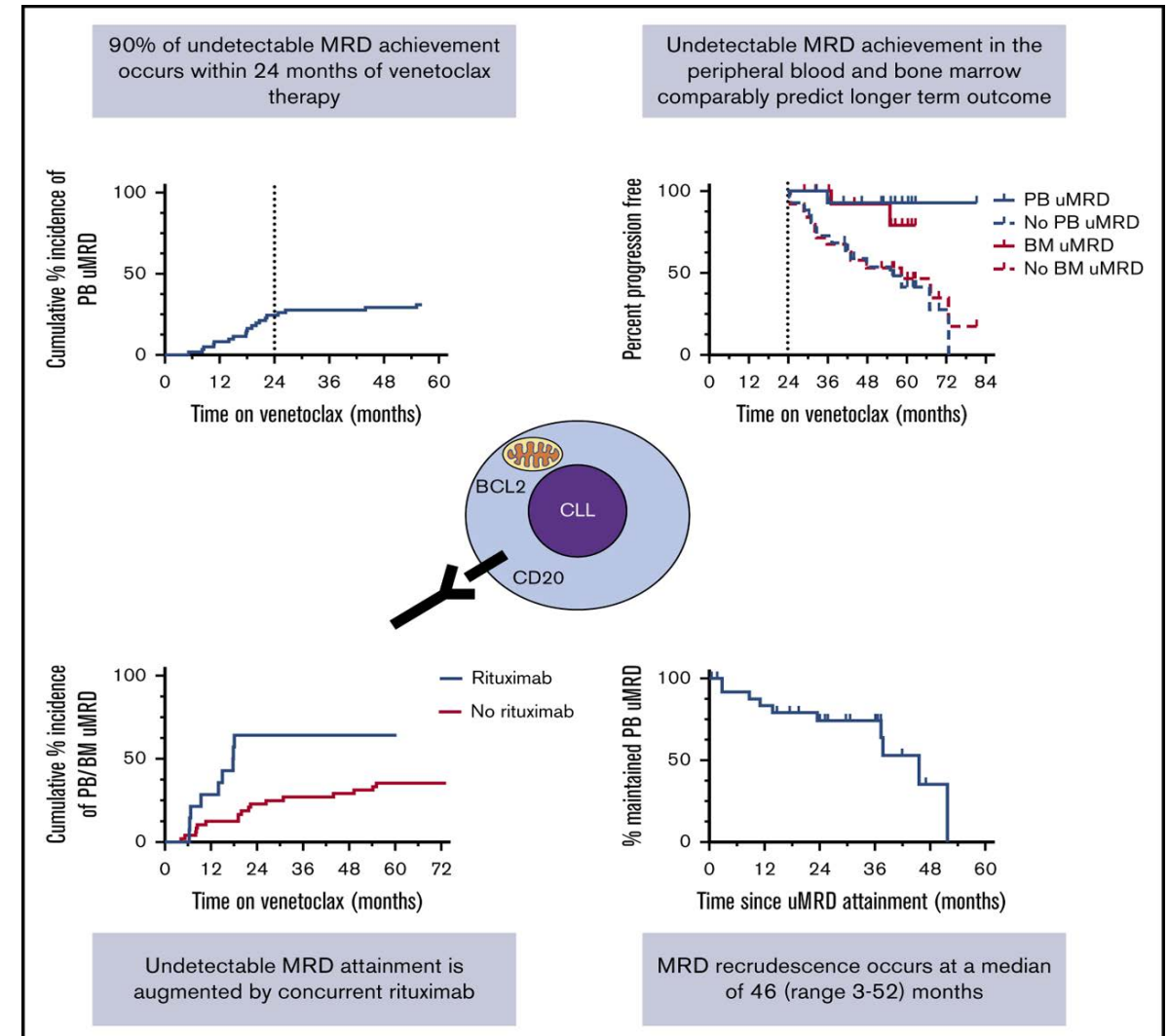
- Variations in measurement: flow vs. PCR vs. other
- Variations in compartment (marrow vs. blood)
- Variations in timing of treatment

With chemoimmunotherapy and venetoclax, achieving undetectable MRD is highly predictive of favorable outcome.

With single agent BTK inhibition, the importance of achieving undetectable MRD is less clear.

- Complete response may not predict response durability.
- Very few patients achieve undetectable MRD\*\*.
  - MRD high: 75%; 19% progress
  - MRD low: 25%, 6.3% progress (p=NS)

*Studies routinely employ MRD as a surrogate endpoint, and often as a means to incorporate response-adapted therapy. Given complexity in interpretation, I do not recommend MRD testing in practice outside of a clinical trial.*



# 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.



# **First Results of a Head-to-Head Trial of Acalabrutinib versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia**

Byrd JC et al.

ASCO 2021;Abstract 7500.

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

# ELEVATE-RR: Acalabrutinib versus Ibrutinib for Previously Treated CLL

Adverse events (AEs)	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	24.1%	8.6%	30.0%	9.5%
Atrial fibrillation	9.4%	4.9%	16.0%	3.8%
Ventricular tachyarrhythmias	0	0	0.4%	0.4%
Hypertension	9.4%	4.1%	23.2%	9.1%
Bleeding events	38.0%	3.8%	51.3%	4.6%
Major bleeding events	4.5%	3.8%	5.3%	4.6%
Infections	78.2%	30.8%	81.4%	30.0%
SPMs	9.0%	6.0%	7.6%	5.3%
Headache	34.6%		20.2%	
AEs leading to treatment discontinuation	14.7%		21.3%	

SPM = Second primary malignancies, excluding nonmelanoma skin cancers

- Median PFS: 38.4 months for both arms (HR 1.00)
- Median OS: Not reached in either arm (HR 0.82)

# Zanubrutinib Demonstrates Superior ORR and Reduced Rates of Atrial Fibrillation or Flutter in Head-to-Head Trial Against Ibrutinib for CLL

Press Release: April 28, 2021

“Positive results from a planned interim analysis of the Phase 3 ALPINE trial comparing zanubrutinib against ibrutinib in adults with relapsed or refractory CLL or SLL.

Zanubrutinib met the primary endpoint of the trial, demonstrating non-inferiority in objective response rate (ORR) by both investigator and independent review committee (IRC) assessments ( $p < 0.0001$ ). The interim analysis from this fully-enrolled, ongoing trial is based on 415 of 652 patients followed for a minimum of 12 months.

The trial also met a pre-specified secondary endpoint related to safety. Compared to ibrutinib, zanubrutinib demonstrated a statistically significant lower risk of atrial fibrillation or flutter...”

# **Fixed-Duration (FD) First-Line Treatment (tx) with Ibrutinib (I) plus Venetoclax (V) for Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): Primary Analysis of the FD Cohort of the Phase 2 Captivate Study**

Ghia P et al.

ASCO 2021;Abstract 7501.

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

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- Dr Kumar: A 59-year-old man with Stage II Hodgkin lymphoma

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- Dr Shameem: An 89-year-old man with MIPI high-risk MCL

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- Dr Gandhi: An 83-year-old man with Waldenström macroglobulinemia (WM) transformed to DLBCL

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- Dr Dandamudi: A 58-year-old woman with relapsed FL
- Dr Hart: A 62-year-old man with relapsed high-grade FL

# Case Presentation – Dr Shameem: An 89-year-old man with MIPI high-risk mantle cell lymphoma



**Dr Raji Shameem**

- PMH: Cutaneous squamous cell carcinoma, CKD, HTN and HLD
- 3/2018: Presents to hospital with GIB
- Work up: Diffuse adenopathy above and below the diaphragm; Lymphoma with high-risk MIPI score
- Bendamustine/rituximab x 6 → Partial response with residual abdominal adenopathy, including pelvic lymph nodes
  - Fatigue, myelosuppression, and infections (UTI and URTI)
- Maintenance rituximab → 1/2019: Progression of lymphadenopathy
- Acalabrutinib, with excellent response including in the pelvic lymph nodes

## Questions

- Would you ever consider stopping acalabrutinib in any patient (this patient would never want to stop)?
- Have you incorporated MRD in your practice? Has it ever influenced your treatment decision?  
Would you consider MRD in your decision to stop therapy for a patient?

**Do you believe there are discernible differences in efficacy or tolerability that make one of the 3 FDA-approved BTK inhibitors for mantle cell lymphoma (MCL) a better therapeutic option?**



## Do you believe there are discernible differences in efficacy or tolerability that make one of the 3 FDA-approved BTK inhibitors for mantle cell lymphoma (MCL) a better therapeutic option?

	Ibrutinib (median 3 prior tx)	Acalabrutinib (median 2 prior tx)	Zanabrutinib (median 2 prior tx)
<b>Efficacy</b>			
ORR	68%	81%	84%
CR	21%	43%	69%
Median PFS (m)	13.9	20	22
<b>Pooled Safety Data</b>			
Headache, any (grade ≥3)	10% (0%)	42% (2%)	4% (NR)
Diarrhea, any (grade ≥3)	40% (4%)	38% (2%)	18% (1%)
Hypertension, grade ≥3	5%	<3%	3%
Atrial Fibrillation, any (grade ≥3)	11% (6%)	2% (1%)	2% (1%)
Bleeding, serious or grade ≥3	5%	3%	3%
Discontinuation due to AEs	10%	6%	10%

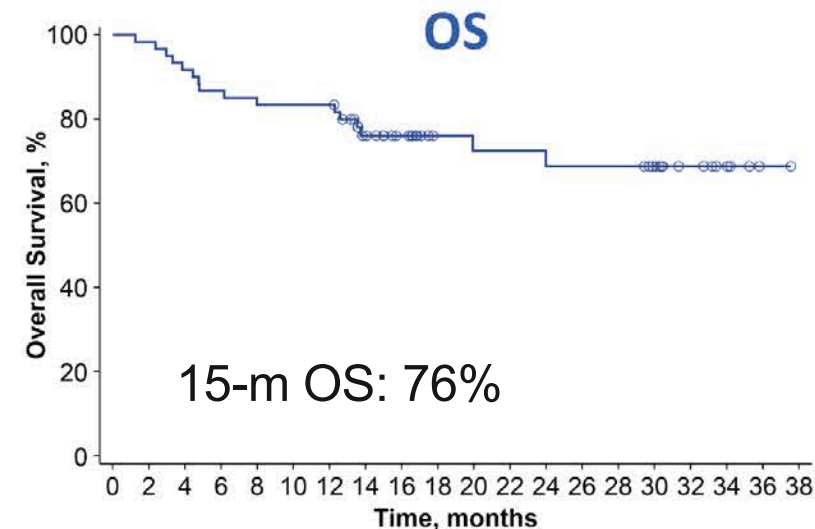
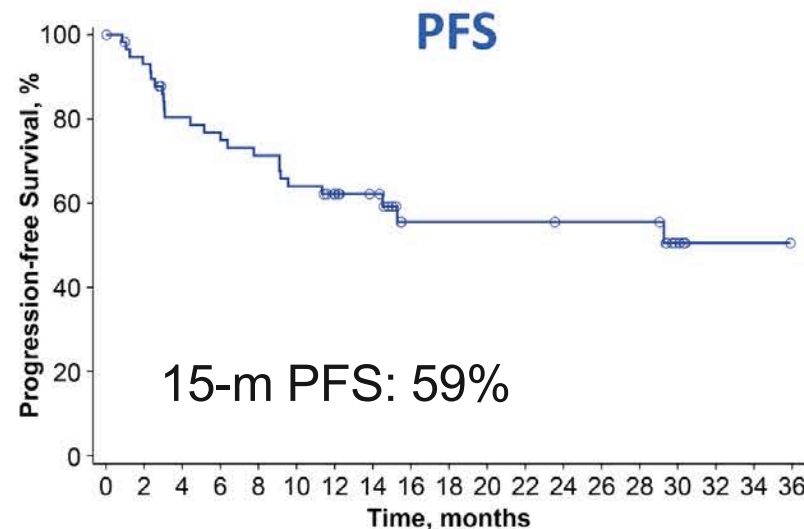
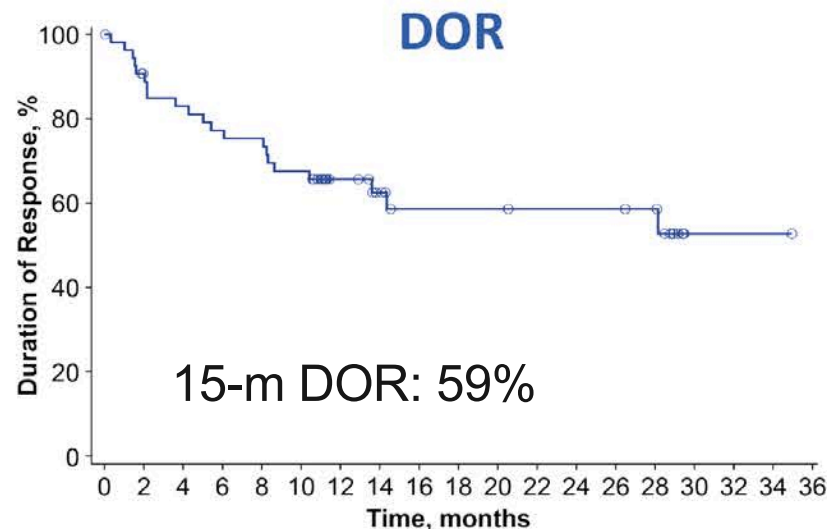
- No comparative trials, all agents effective
- Second generation drugs likely have improved safety profile

**Where in the treatment sequence is the appropriate time to refer a patient with relapsed/refractory MCL for CAR T-cell therapy?**

## Where in the treatment sequence is the appropriate time to refer a patient with relapsed/refractory MCL for CAR T-cell therapy?

- Immunotherapy (+/- ASCT) and maintenance rituximab is standard of care for untreated MCL
- BTK inhibitors are highly effective and commonly used second-line
- Outcomes following BTKi's are poor and no standard of care exists

Update of Brexucabtagene Autoleucel (KTE-X19) in MCL (median f/up: 17.5 m) Wang et al, ASH 2020



N=60, ORR 92%, CR 67%

# Agenda

## **Module 1: Hodgkin Lymphoma**

- Dr Kumar: A 59-year-old man with Stage II Hodgkin lymphoma

## **Module 2: Chronic Lymphocytic Leukemia (CLL)**

- Dr Lamar: A 65-year-old man initially diagnosed with asymptomatic CLL now experiencing symptomatic progression
- Dr Hart: A 64-year-old man with CLL – IGHV mutation, del(13q14)

## **Module 3: Mantle Cell Lymphoma (MCL)**

- Dr Shameem: An 89-year-old man with MIPI high-risk MCL

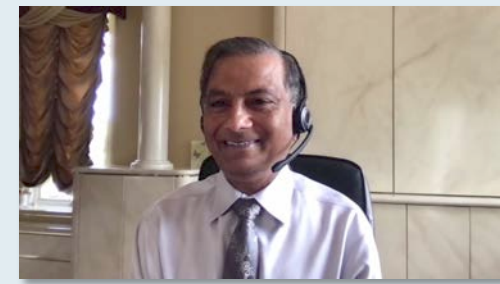
## **Module 4: Diffuse Large B-Cell Lymphoma (DLBCL)**

- Dr Gandhi: An 83-year-old man with Waldenström macroglobulinemia (WM) transformed to DLBCL

## **Module 5: Follicular Lymphoma (FL)**

- Dr Dandamudi: A 58-year-old woman with relapsed FL
- Dr Hart: A 62-year-old man with relapsed high-grade FL

# Case Presentation – Dr Gandhi: An 83-year-old man with Waldenström macroglobulinemia (WM) transformed to DLBCL



**Dr Sunil Gandhi**

- 1995: Waldenström macroglobulinemia → Observed until 2006
  - Wife also diagnosed with WM
- RFND, with CR
- 2015: Sacral bone metastases, biopsy-proven WM → Rituximab, with good response
- 2017: Nasopharyngeal mass (WM) → Bendamustine/rituximab, with CR
- 2019: Acute MI with severe cardiomyopathy (LVEF: 30%)
- New lymphadenopathy, biopsy-proven DLBCL, CD30-positive
- R-GCVP, with good PR but poorly tolerated
- Brentuximab vedotin

## Questions

- What therapeutic options would you suggest? What is your experience with regimens such as tafasitamab/lenalidomide and R<sup>2</sup>?

**For a patient with relapsed/refractory DLBCL, how do you usually sequence polatuzumab vedotin, tafasitamab/lenalidomide, selinexor, loncastuximab tesirine and CAR T-cell therapy?**

**For a patient with relapsed/refractory DLBCL, how do you usually sequence polatuzumab vedotin, tafasitamab/lenalidomide, selinexor, loncastuximab tesirine and CAR T-cell therapy?**

- **Consider goal of therapy, efficacy, side effects, patient co-morbidities, convenience/duration, sequencing**

### **CAR T**

- 40-58% CR;  
52-83% ORR
- 30-40% cured
- Need disease control
- CRS, neurotox
- Fit patients
- One-time tx
- +++ resources, costly
- ≥ 3<sup>rd</sup>-line tx

### **Pola-BR**

- 40% CR;  
42% ORR
- ~30% durable remission
- Neutropenia, neuropathy
- Fit-Unfit
- 6 cycles
- ≥ 3<sup>rd</sup>-line tx
- ?sequence with CD19 CAR T

### **Tafa-Len**

- 43% CR;  
60% ORR
- ~40% durable
- Good-risk pts
- Cytopenias, rash, fatigue
- Fit-frail
- Indefinite tx
- ≥ 2<sup>nd</sup>-line tx
- ?sequence with CD19 CAR T

### **Selinexor**

- 12% CR;  
28% ORR
- ? durability
- Good-risk pts
- Cytopenias, GI toxicity, fatigue
- Fit-frail
- Oral, indefinite tx
- ≥ 3<sup>rd</sup>-line tx

### **Lonca**

- 25% CR;  
48% ORR
- ? durability
- Cytopenias, transaminitis
- Fit-frail
- Long-term tx
- ≥ 3<sup>rd</sup>-line tx
- ?sequence with CD19 CAR T



**Do you view the 3 available CD19-directed CAR T-cell therapies as equivalent options for DLBCL, or are there distinct differences between these agents that would lead you to refer patients for one versus the others?**

**Do you view the 3 available CD19-directed CAR T-cell therapies as equivalent options for DLBCL, or are there distinct differences between these agents that would lead you to refer patients for one versus the others?**

---

- **No comparative trials, data evolving, rely on CAR T specialist**
- **Clinical trials of novel constructs desirable**

	Axicabtagene ciloleucel “Axi-cel”	Tisagenlecleucel “Tisa-cel”	Lisocabtagene maraleucel “Liso-cel”
<b>Efficacy</b>			
ORR	83%	52%	73%
CR	58%	40%	53%
PFS at 1 year	44%	33%	44%
<b>Safety</b>			
CRS	93%	58%	42%
Grade ≥3 CRS	13%	22%	2%
Rate of tocilizumab use on trial	43%	14%	19%
Neurotoxicity	64%	21%	30%
Grade ≥3 neurotoxicity	28%	12%	10%

# FDA Grants Accelerated Approval to Loncastuximab Tesirine-Ipyl for Large B-cell Lymphoma

Press Release – April 23, 2021

“On April 23, 2021, the Food and Drug Administration granted accelerated approval to loncastuximab tesirine-ipy, a CD19-directed antibody and alkylating agent conjugate, for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.

Approval was based on LOTIS-2 (NCT03589469), an open-label, single-arm trial in 145 adult patients with relapsed or refractory DLBCL or high-grade B-cell lymphoma after at least two prior systemic regimens.

The ORR was 48.3% (95% CI: 39.9, 56.7) with a complete response rate of 24.1% (95% CI: 17.4, 31.9). After a median follow-up of 7.3 months, median response duration was 10.3 months (95% CI: 6.9, NE).”

# Agenda

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## **Module 5: Follicular Lymphoma (FL)**

- Dr Dandamudi: A 58-year-old woman with relapsed FL
- Dr Hart: A 62-year-old man with relapsed high-grade FL

# Case Presentation – Dr Dandamudi: A 58-year-old woman with relapsed follicular lymphoma



**Dr Uday Dandamudi**

- 2002: Initial diagnosis of follicular lymphoma
- 2016: Presents to ER after motor vehicle accident and imaging shows suspicious findings; she complained of having on and off fevers, night sweats, and 20-lb weight loss
  - Biopsy: Grade 1-2 follicular lymphoma
- 2017 - 2019: Relapse treated with single-agent rituximab
- 2020: Presents with fevers, fatigue, unexplained weight loss, palpable axillary and cervical lymph nodes
  - Biopsy: Grade 3B follicular lymphoma
- Enrolled on clinical trial of polatuzumab vedotin combined with a bispecific monoclonal antibody

## Questions

- How would you treat this patient who clearly now has transformed disease?

# Case Presentation – Dr Hart: A 62-year-old man with relapsed high-grade follicular lymphoma



**Dr Lowell Hart**

- High-grade follicular lymphoma that relapsed quickly on prior treatments that included rituximab
- Obinutuzumab with lenalidomide → CR and tolerating treatment well

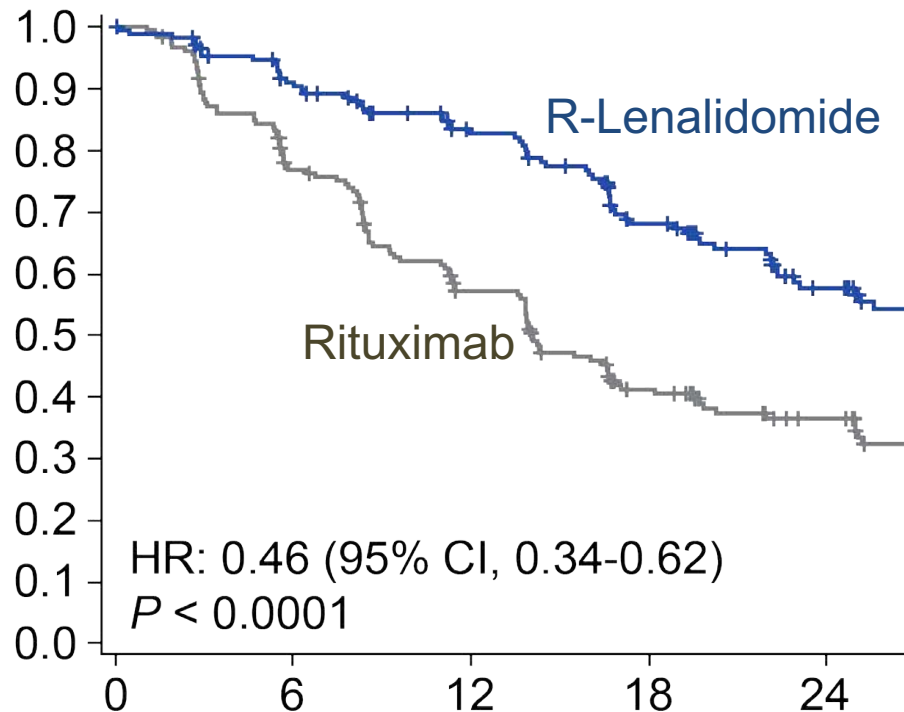
## Questions

- Do you think that obinutuzumab with lenalidomide was a reasonable treatment choice?
- If his disease relapses, would he be a candidate for allogeneic or autologous transplant?
- Would he be a candidate for CAR T-cell therapy? What is the role of CAR T-cell therapy in follicular lymphoma?

**How do you generally integrate the R2 regimen of lenalidomide/rituximab into the management of follicular lymphoma (FL)? In what situations, if any, do you recommend it first line? What dose, schedule and treatment duration do you use?**

## How do you generally integrate the R<sup>2</sup> regimen of lenalidomide/rituximab into the management of follicular lymphoma (FL)? In what situations, if any, do you recommend it first line? What dose, schedule and treatment duration do you use?

**PFS AUGMENT Trial\***  
**All patients (Primary endpoint)**  
**12 cycles of treatment**  
**Lenalidomide 20 mg 21/28**



First line management low burden:  
Observation vs. rituximab

First line management high burden:  
Chemoimmunotherapy (BR)

*R<sup>2</sup> not superior to chemo front line, with less follow-up. Chemoimmunotherapy provides very long PFS (>40% PFS at 10 years); we do not have follow-up yet on R<sup>2</sup>.*

Second line (fixed duration per AUGMENT):  
Lenalidomide with rituximab  
Lenalidomide with obinutuzumab\*\*

\*Leonard et al., *JCO* 37:1188-99 2019

\*\*Houot et al., *Leukemia* 33:776-780 2019



**What is the optimal treatment for a patient with FL  $\pm$  an EZH2 mutation who has experienced PD on BR and then R2? Do you believe that discernible differences in efficacy or tolerability make one of the 4 FDA-approved PI3K inhibitors for R/R FL a better option?**

## What is the optimal treatment for a patient with FL ± an EZH2 mutation who has experienced PD on BR and then R<sup>2</sup>? Do you believe that discernible differences in efficacy or tolerability make one of the 4 FDA-approved PI3K inhibitors for R/R FL a better option?

### PI3K Efficacy appears equivalent

#### Toxicity considerations:

- Prophylax: PJP; antivirals; monitor CMV reactivation

#### Idelalisib and Duvelisib:

- Hepatic, Severe Diarrhea, Colitis, Pneumonitis, and Intestinal Perforation

#### Umbralisib:

- Lower incidence

#### Copanlisib (IV):

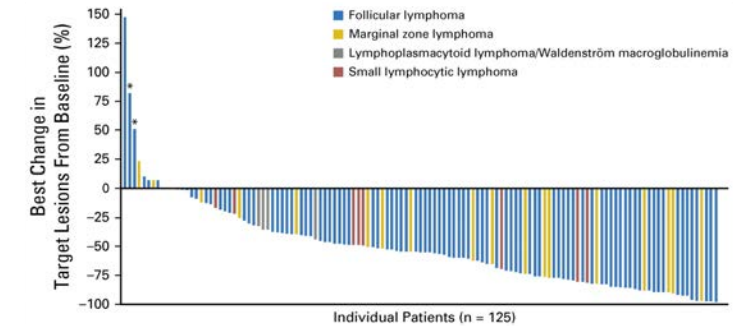
- Hepatic, HTN, Hyperglycemia

*I've not used copanlisib; have generally been using idelalisib and umbralisib (on trial); will probably increase use of umbralisib now it's FDA approved for FL and MZL.*

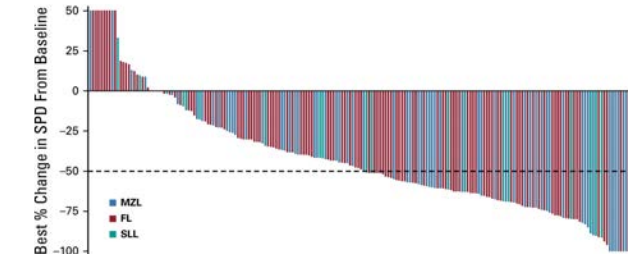
#### Tazemetostat: EZH2 inhibitor

- Approved for mutant and wild-type EZH2
- Increased ORR and PFS in mutant
- Testing not routinely done

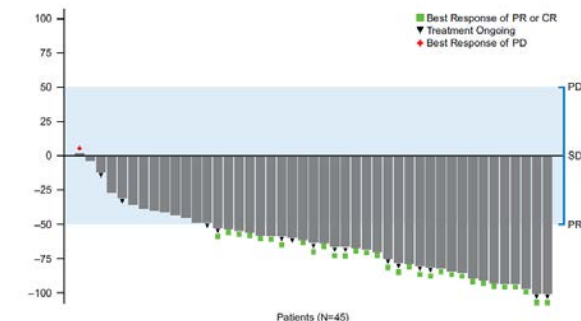
*I'm now obtaining EZH2 mutation assessment on all relapsed FL; expect 20% to be EZH2 mutant, and would favor earlier use of tazemetostat in those cases.*



**Copanlisib FL: ORR 59%; CR 14%; PFS 11 months\***



**Umbralisib FL: ORR 45%; CR 6%; PFS 10.6 months\*\***



**Tazemetostat mEZH2: ORR 69%; PFS 13 mos\*\*\***

\*Dreyling et al., JCO 35:3898 2017

\*\*Fowler et al., JCO online 2021

\*\*\*Morschhauser et al., Lancet Oncol 21:1433-42 2020

# FDA Grants Accelerated Approval to Axicabtagene Ciloleucel for Relapsed or Refractory Follicular Lymphoma

Press Release – March 5, 2021

“The Food and Drug Administration granted accelerated approval to axicabtagene ciloleucel for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Approval in FL was based on a single-arm, open-label, multicenter trial (ZUMA-5; NCT03105336) that evaluated axicabtagene ciloleucel, a CD19-directed chimeric antigen receptor (CAR) T cell therapy, in adult patients with relapsed or refractory FL after two or more lines of systemic therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. Following lymphodepleting chemotherapy, axicabtagene ciloleucel was administered as a single intravenous infusion.

The main efficacy measures were objective response rate (ORR) and duration of response (DOR) as determined by an independent review committee. Among 81 patients in the primary efficacy analysis, the ORR was 91% with a complete remission (CR) rate of 60% and a median time-to-response of 1 month. The median DOR was not reached, and the 1-year rate of continued remission was 76.2%. For all leukapheresed patients in this trial (n=123), the ORR was 89% with a CR rate of 62%.”

***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 2:00 PM ET**

***Up Next...***

**Drs Irene Ghobrial and Sagar Lonial  
discuss the management of multiple myeloma**

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

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

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

## Agenda

**Module 1 — Lung Cancer:** *Drs Heymach and Liu*

**Module 2 — Genitourinary Cancers:** *Drs Hussain and Plimack*

**Module 3 — Chronic Lymphocytic Leukemia and Lymphomas:**  
*Drs Friedberg and Sehn*

**Module 4 — Multiple Myeloma:** *Drs Ghobrial and Lonial*

**Module 5 — Breast Cancer:** *Drs Kaklamani and Lin*

# Multiple Myeloma Faculty



**Irene M Ghobrial, MD**

Professor of Medicine

Lavine Family Chair of Preventative Cancer Therapies

Director, Center for Prevention of Progression of  
Blood Cancers

Director, Translational Research in Multiple Myeloma

Director, Clinical Investigator Research Program

Director, Michele and Steven Kirsch Laboratory

Harvard Medical School

Dana-Farber Cancer Institute

Boston, Massachusetts



**Sagar Lonial, MD**

Chair and Professor

Department of Hematology and  
Medical Oncology

Anne and Bernard Gray Family Chair in Cancer

Chief Medical Officer

Winship Cancer Institute

Emory University School of Medicine

Atlanta, Georgia



# Contributing Oncologists



**Susmitha Apuri, MD**  
Florida Cancer Specialists  
Lutz, Florida



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



**Warren S Brenner, MD**  
Lynn Cancer Institute  
Boca Raton, Florida



**Maria Regina Flores, MD**  
Advent Health Orlando  
Orlando Regional Hospital  
Florida Cancer Specialists  
Orlando, Florida



**Gigi Chen, MD**  
Diablo Valley Oncology and  
Hematology Medical Group  
Pleasant Hill, California



**Sunil Gandhi, MD**  
Florida Cancer Specialists  
Lecanto, Florida



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



**Ranju Gupta, MD**  
Attending Physician  
Co-Director, Cardio-Oncology Program  
LVPG Hematology Oncology Associates  
Lehigh Valley Health Network  
Bethlehem, Pennsylvania

# Contributing Oncologists



**Lowell L Hart, MD**

Scientific Director of Research  
Florida Cancer Specialists  
Co-Director, Phase 1 Program  
Wake Forest Baptist Health  
Comprehensive Cancer Center  
Fort Myers, Florida



**Jeremy Lorber, MD**

Attending Hematologist-Oncologist  
Tower Hematology Oncology  
Cedars-Sinai Medical Center  
Beverly Hills, California



**KS Kumar, MD**

Physician Partner  
Florida Cancer Specialists  
New Port Richey, Florida



**Vikas Malhotra, MD**

Staff Medical Oncologist-Hematologist  
Florida Cancer Specialists  
Spring Hill, Florida



**Ferdy Santiago, MD**

Florida Cancer Specialists  
Naples, Florida



**Zanetta S Lamar, MD**

Florida Cancer Specialists  
Naples, Florida



**Raji Shameem, MD**

Florida Cancer Specialists  
Deland, Florida

# Chalk Talk Topics

## Irene M Ghobrial, MD

1. What is the optimal first-line and maintenance therapy for a transplant-eligible patient with newly diagnosed average-risk multiple myeloma (MM)?
2. What is the optimal first-line and maintenance therapy for a transplant-eligible patient with newly diagnosed high-risk (eg, del[17p]) MM?
3. What is the optimal first-line and maintenance therapy for an otherwise healthy 80-year-old patient with standard-risk MM?
4. In what situations, if any, do you employ ixazomib instead of a parenteral proteasome inhibitor as part of maintenance therapy? How do you prepare a patient for ixazomib and manage these patients clinically?
5. In the relapsed/refractory setting, do you consider daratumumab and isatuximab to be essentially equivalent therapeutic options (when combined with the same agents)? Is it reasonable to employ isatuximab for a patient whose disease has progressed on daratumumab?

# Chalk Talk Topics

## Sagar Lonial, MD

1. When in the treatment course is the optimal time to recommend belantamab mafodotin?
2. Given its recent FDA approval, where in the treatment sequence are you planning to integrate idecabtagene vicleucel for your patients with relapsed/refractory MM?
3. Is it reasonable to use BCMA-directed CAR T-cell therapy in a patient who has previously received belantamab mafodotin and vice versa?
4. Where in the treatment sequence are you typically incorporating selinexor, and is it best administered solely with dexamethasone or as part of a triplet regimen? What is the optimal dose and schedule of selinexor?
5. Is it reasonable to employ venetoclax for a patient with relapsed/refractory t(11;14) MM? If so, would you use it solely with dexamethasone or as part of a triplet regimen? What is the optimal dose and schedule of venetoclax in MM, and is tumor lysis syndrome prophylaxis necessary?

# Agenda

## **Module 1: Newly Diagnosed Multiple Myeloma**

- Dr Shameem: A 79-year-old woman with newly diagnosed multiple myeloma and several comorbidities
- Dr Gupta: A 44-year-old woman with high-risk multiple myeloma and acute kidney injury

## **Module 2: Relapsed Multiple Myeloma**

- Dr Gandhi: A 62-year-old woman with relapsed multiple myeloma
- Dr Brenner: A 72-year-old man with multiregimen-relapsed multiple myeloma – t(11;14)

## **Module 3: Related Cases**

- Dr Chen: A 65-year-old man with AL amyloidosis and renal failure
- Dr Santiago: A 65-year-old man with IgM = 5,000, negative MYD88 and hyperviscosity

# Agenda

## Module 1: Newly Diagnosed Multiple Myeloma

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# Case Presentation – Dr Shameem: A 79-year-old woman with newly diagnosed multiple myeloma and several comorbidities



**Dr Raji Shameem**

- PMH: Diabetes, neuropathy (grade 2), HTN, hyperlipidemia, prior tobacco use
- Presents with MGUS → Moves to Florida but resumed care delayed by COVID-19
- Multiple myeloma, t(11;14)
- Patient not interested nor a candidate for auto SCT
- Daratumumab/lenalidomide/dexamethasone (SubQ daratumumab)

## Questions

- For elderly, transplant-ineligible patients in this day and age, what's your go-to front-line therapy? Have you started using daratumumab/lenalidomide and dexamethasone, or have you stuck with RVd or RVd lite?
- For my younger patients I tend to use RVd. Have you tried daratumumab-based or even quadruplet regimens in your younger patients?

# Case Presentation – Dr Gupta: A 44-year-old woman with high-risk multiple myeloma and acute kidney injury



**Dr Ranju Gupta**

- Presents with pain and acute kidney injury (AKI) and is diagnosed with IgG lambda myeloma with extraosseous involvement including pleural effusion
- Cytogenetics: c-MYC+, TP53 deletion, 1q duplication, monosomy 13, and IGH/MAFB fusion, usually representing a t(14;20), trisomy 7 and 8
- CyBorD x 4 cycles → daratumumab added x 6 cycles → PR
- 12/2020: New painful bone metastases leading to hospitalization → VTD-PACE salvage therapy

## Questions

- How would you manage this patient?
- For patients with myeloma who present with AKI, we always start with CyBorD because of the renal insufficiency. Should we switch regimens after that, or continue with CyBorD?
- Should we be adding any fourth drug? What about the role of daratumumab?
- Are there any other treatment options that can be used preferentially in patients who have AKI?

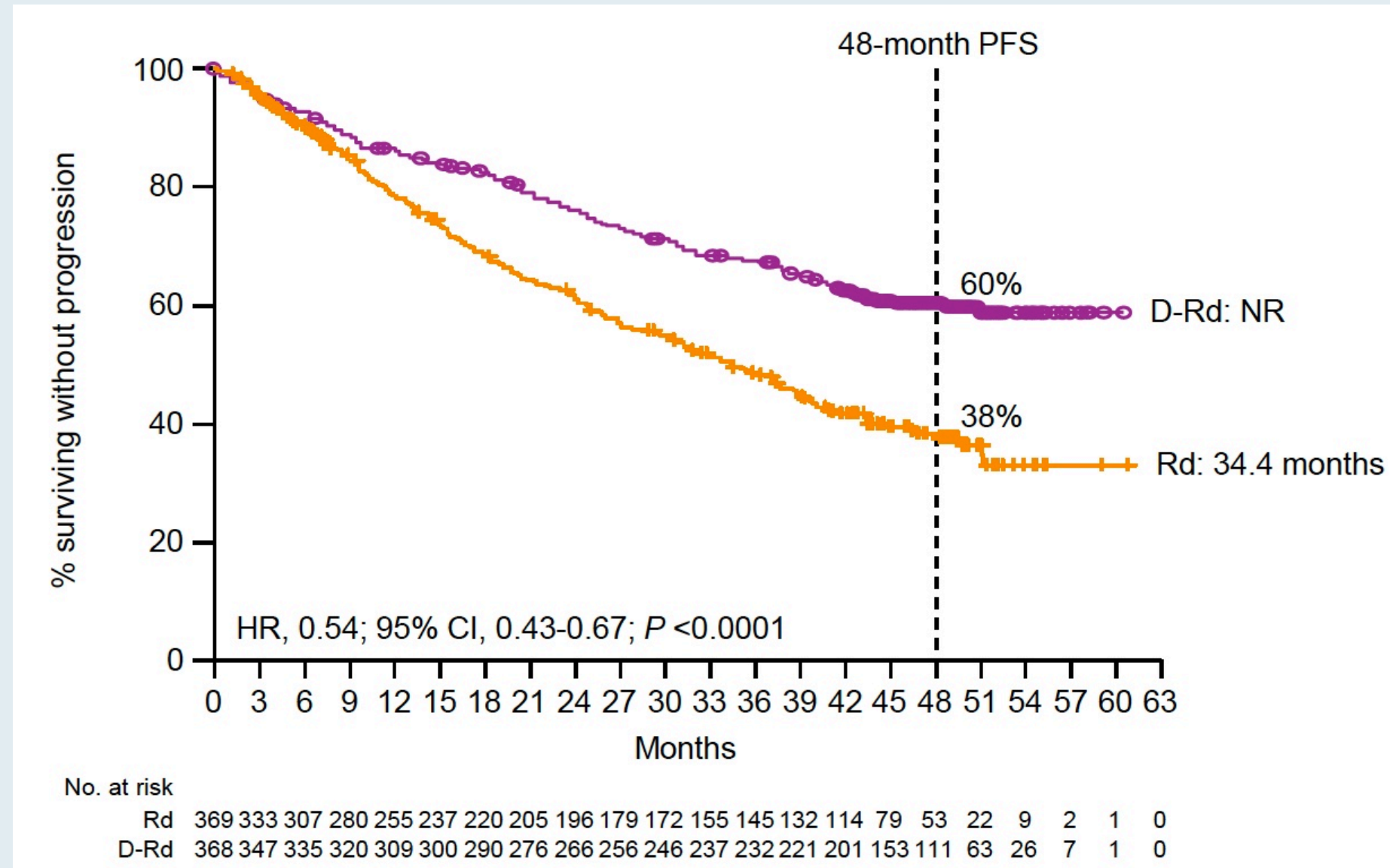


**What is the optimal first-line and maintenance therapy for an otherwise healthy 80-year-old patient with standard-risk MM?**

## **What is the optimal first-line and maintenance therapy for an otherwise healthy 80-year-old patient with standard-risk MM?**

- Fit or not fit?
- If fit, same as for a transplant-eligible patient with average-risk MM
- Consider RVD lite
- Dara-RD
- No transplant
- Don't push the dose, make sure patients can tolerate it
- Cut the dex

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

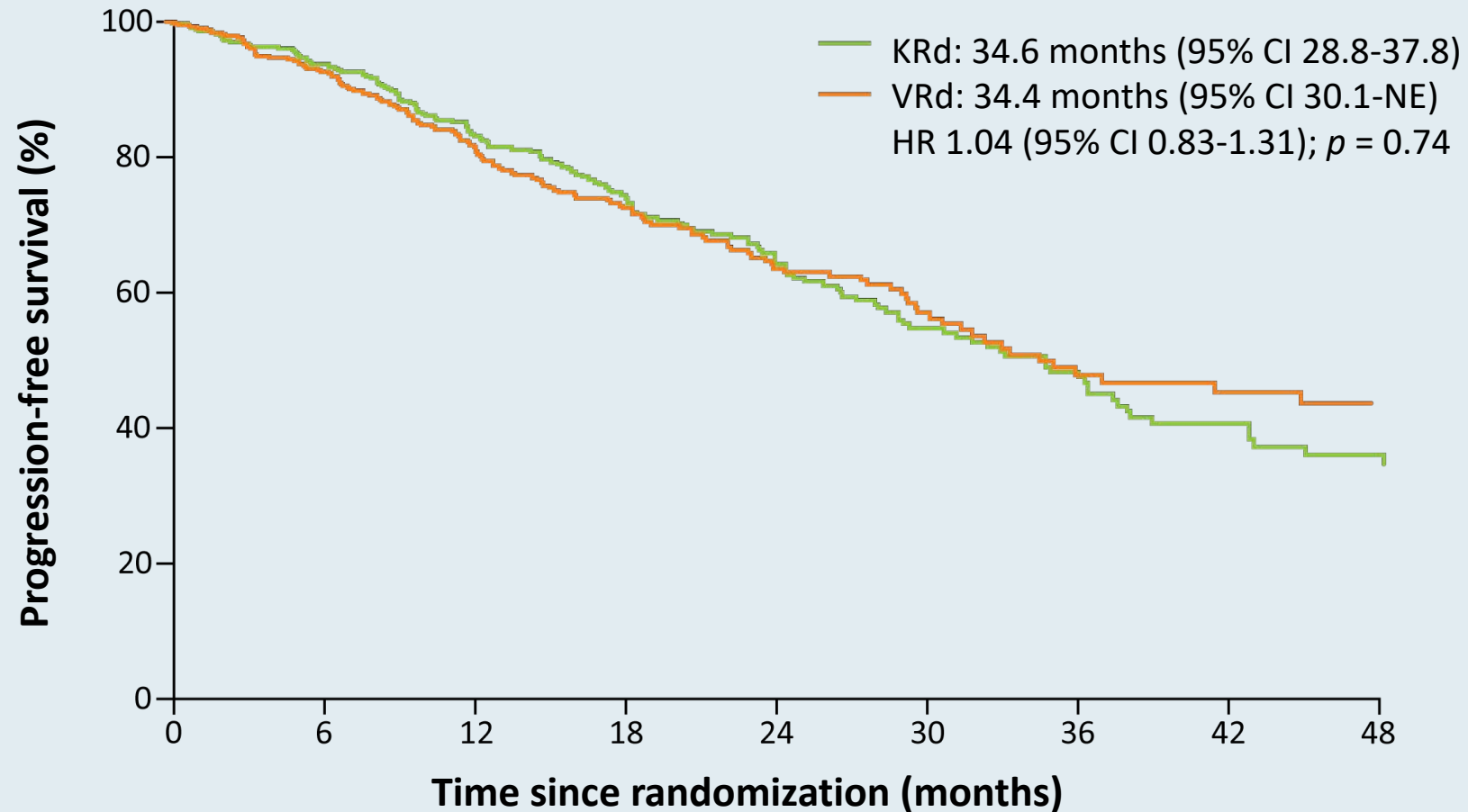


**What is the optimal first-line and maintenance therapy for a transplant-eligible patient with newly diagnosed average-risk multiple myeloma (MM)?**

## **What is the optimal first-line and maintenance therapy for a transplant-eligible patient with newly diagnosed average-risk multiple myeloma (MM)?**

- Dara-RVD
- RVD
- Maintenance lenalidomide
- How about t(11;14) MM? Venetoclax in the future
- Should we tailor maintenance based on sustained MRD-negative status?
- Treat earlier (high-risk SMM)

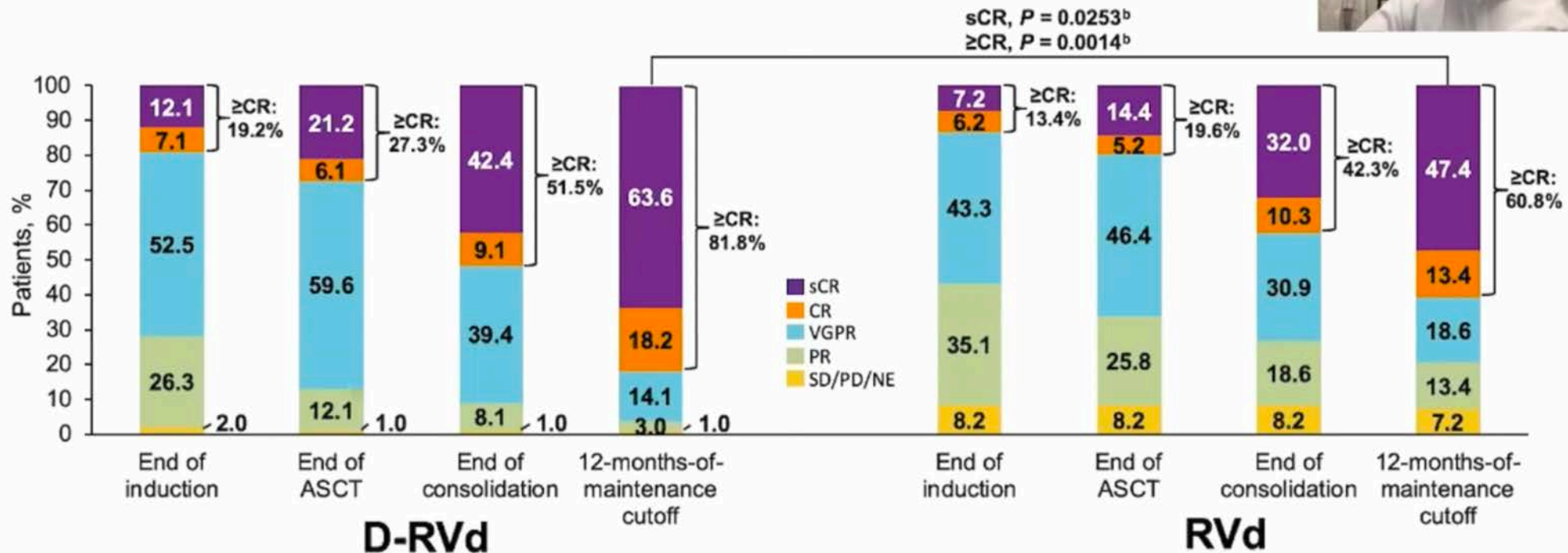
## ENDURANCE (E1A11): Primary PFS Endpoint (Second Interim Analysis)



- 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

# GRIFIN: Daratumumab/RVd (D-RVd) versus RVd

## Responses Deepened over Time<sup>a</sup>



- 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. <sup>a</sup>Data are shown for the response-evaluable population. <sup>b</sup> $P$  values (2-sided) were calculated using the Cochran-Mantel-Haenszel chi-square test.



American Society of Hematology

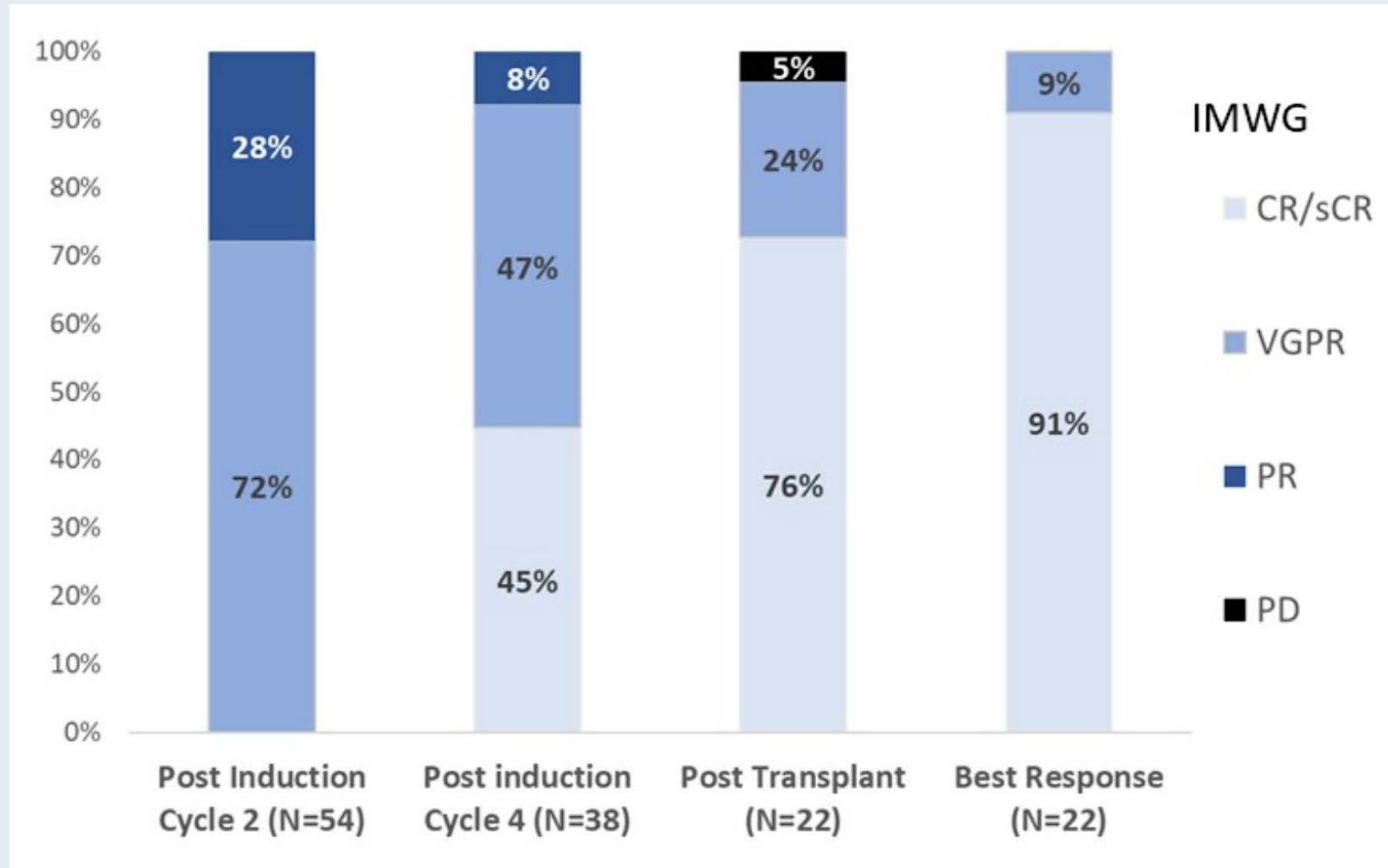
**What is the optimal first-line and maintenance therapy for a transplant-eligible patient with newly diagnosed high-risk (eg, del[17p]) MM?**



**What is the optimal first-line and maintenance therapy for a transplant-eligible patient with newly diagnosed high-risk (eg, del[17p]) MM?**

- Biallelic deletion vs only one copy
- Is there p53 mutation?
- Dara-KRD induction
- CART up front if possible and can be covered by insurance or on a trial
- Bispecific trials if available
- Need better therapies in general

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



**In what situations, if any, do you employ ixazomib instead of a parenteral proteasome inhibitor as part of maintenance therapy? How do you prepare a patient for ixazomib and manage these patients clinically?**

**In what situations, if any, do you employ ixazomib instead of a parenteral proteasome inhibitor as part of maintenance therapy? How do you prepare a patient for ixazomib and manage these patients clinically?**

- Great option to change from bortezomib to ixazomib for easier use and less visits to clinic
- COVID era was a great time to show that oral agents are important
- Older patients — it is easier to give them Ixa compared to bortezomib

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## Module 3: Related Cases

- Dr Chen: A 65-year-old man with AL amyloidosis and renal failure
- Dr Santiago: A 65-year-old man with IgM = 5,000, negative MYD88 and hyperviscosity

# Case Presentation – Dr Gandhi: A 62-year-old woman with relapsed multiple myeloma



**Dr Sunil Gandhi**

- Diagnosed with Ig kappa multiple myeloma, normal karyotype with no high-risk features
- Induction RVd → autologous SCT → lenalidomide maintenance for 1.5 years
- Developed symptomatic disease progression
- Daratumumab in combination with pomalidomide/dexamethasone → achieved a CR after 5 months

## Questions

- How long do you continue treatment in this patient who has responded well?
- What is the role of MRD and when should it be assessed?
- What is your experience with some of the later line therapies such as belantamab vedotin and selinexor?

**In the relapsed/refractory setting, do you consider daratumumab and isatuximab to be essentially equivalent therapeutic options (when combined with the same agents)? Is it reasonable to employ isatuximab for a patient whose disease has progressed on daratumumab?**

**In the relapsed/refractory setting, do you consider daratumumab and isatuximab to be essentially equivalent therapeutic options (when combined with the same agents)? Is it reasonable to employ isatuximab for a patient whose disease has progressed on daratumumab?**

- Dara and Isa are almost the same
- More potential for immune response with Isa but hard to prove in patients
- Higher HR in some of the new data shown with IsaKD (IKEMA) vs Dara-KD, but both are great choices
- SubQ vs IV
- More clinical experience with Dara
- Would not go to Isa if refractory to Dara — change to BCMA- or GPRC5D-targeted therapy, not another anti-CD38 therapy



# FDA Approves Isatuximab-irfc for Multiple Myeloma

Press Release: March 31, 2021

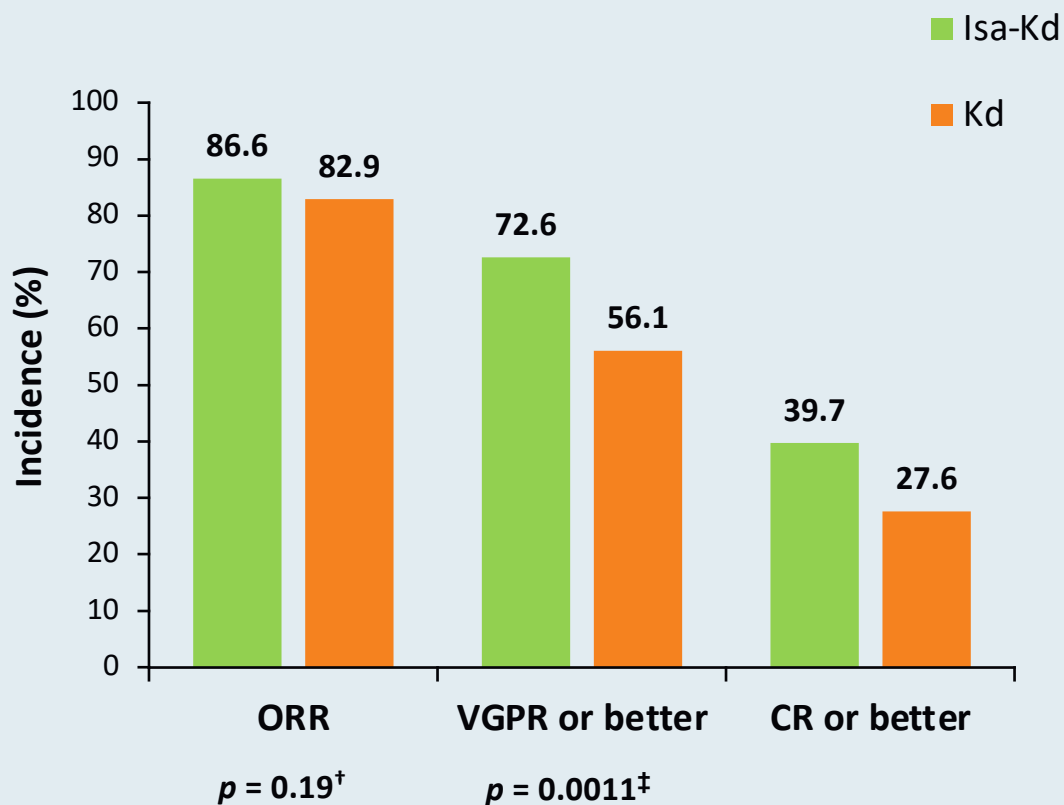
“The Food and Drug Administration approved isatuximab-irfc in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy.

The efficacy and safety of isatuximab-irfc in combination with carfilzomib and dexamethasone was evaluated in IKEMA (NCT03275285), a multicenter, multinational, randomized, open-label, two-arm, phase 3 trial in patients with relapsed and/or refractory multiple myeloma who had received one to three prior lines of therapy. The trial randomized 302 patients (3:2) to receive isatuximab-irfc with carfilzomib and dexamethasone (Isa-Kd) or carfilzomib and dexamethasone (Kd).

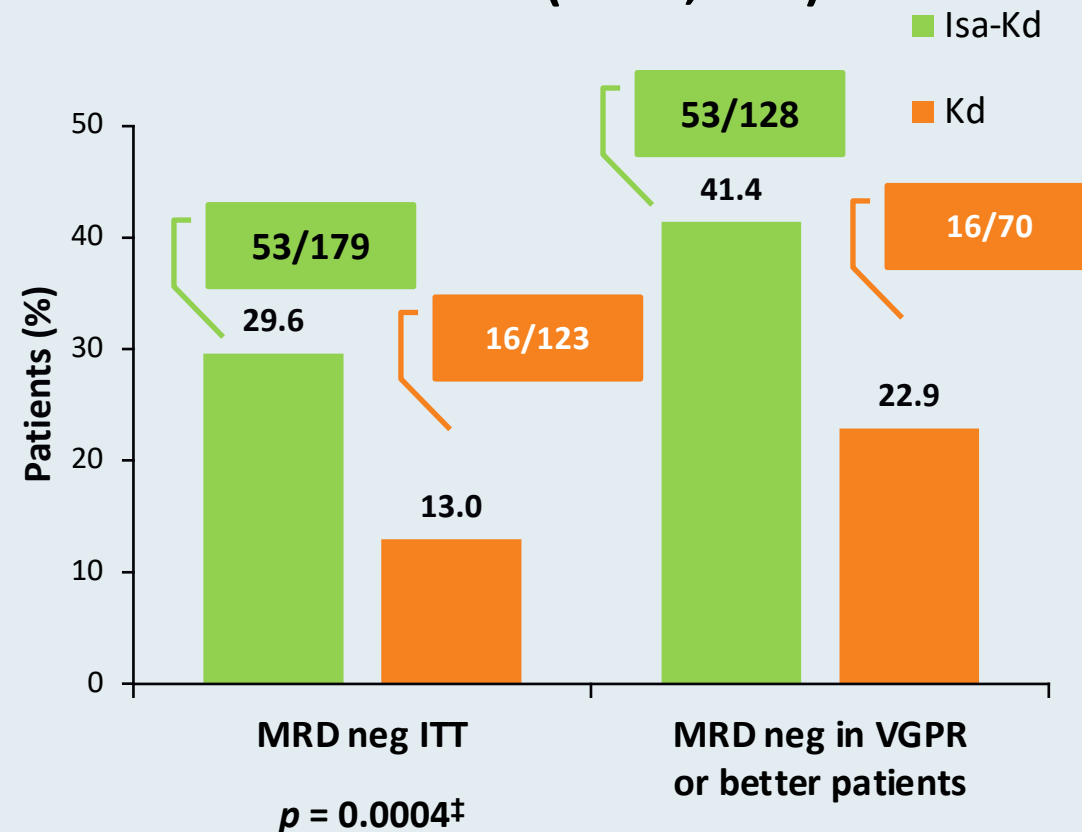
The main efficacy outcome measure was progression-free survival (PFS), assessed by an independent response committee based on central laboratory data for M-protein and central radiologic imaging review using International Myeloma Working Group criteria.”

# IKEMA – Isatuximab + Kd: Depth of Response

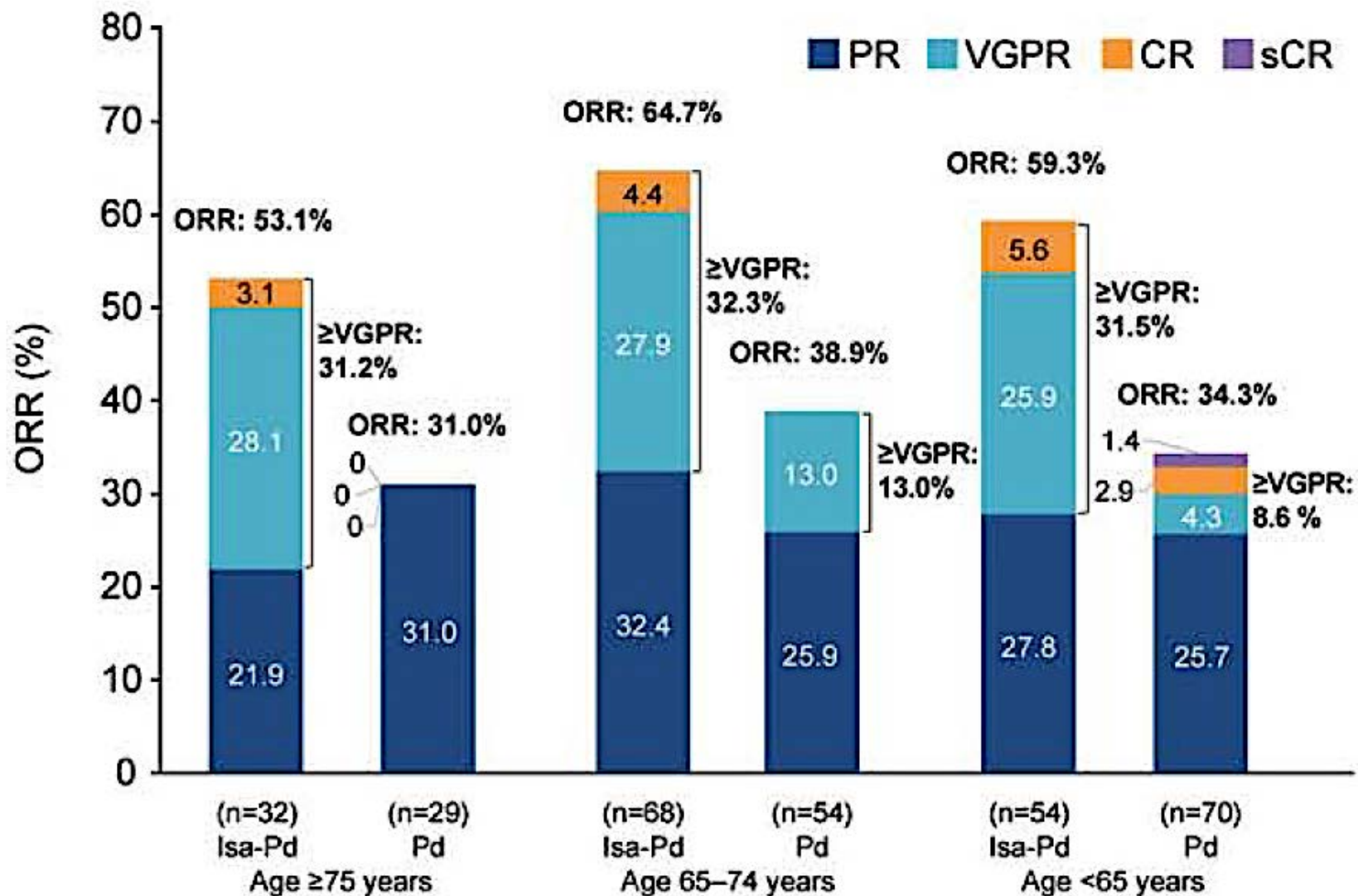
## Best overall response



## MRD rate (NGS\*, 10<sup>-5</sup>)



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



**When in the treatment course is the optimal time to recommend belantamab mafodotin?**

## **When in the treatment course is the optimal time to recommend belantamab mafodotin?**

- FDA label is after 4 lines of therapy.
- I consider using this for triple-class refractory (PI/IMiD/anti-CD38).
- Given the frequency of visits, may be preferable to more intensive chemo-based regimens.
- Partnering with Ophthalmology is helpful early on to minimize challenging scheduling.
- Risk/benefit of ocular issues needs to be put in context of other available options.

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

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

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

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

Figure 3. Investigator-assessed\* best confirmed response

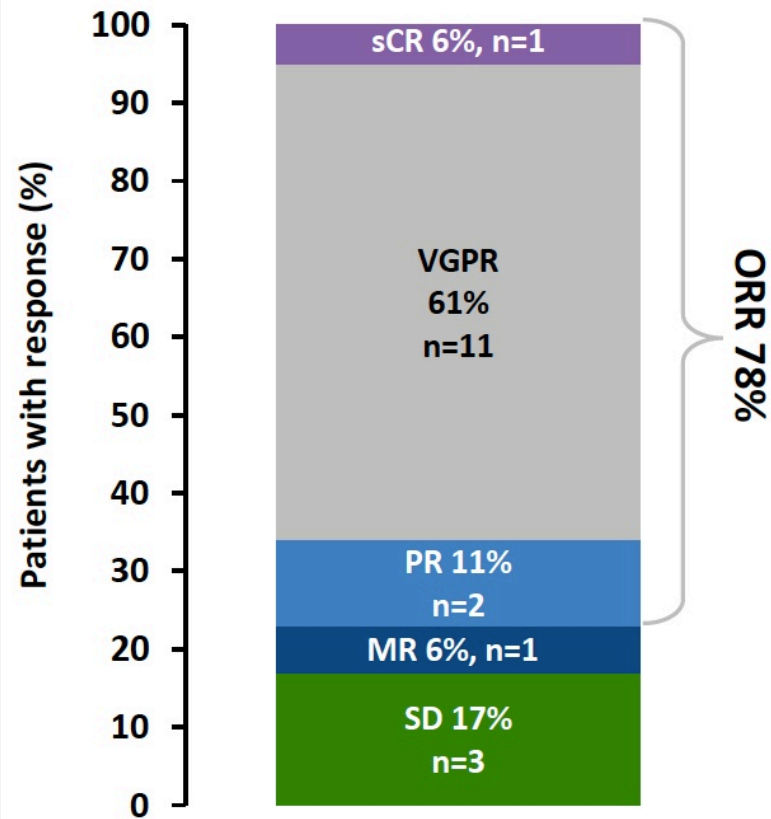
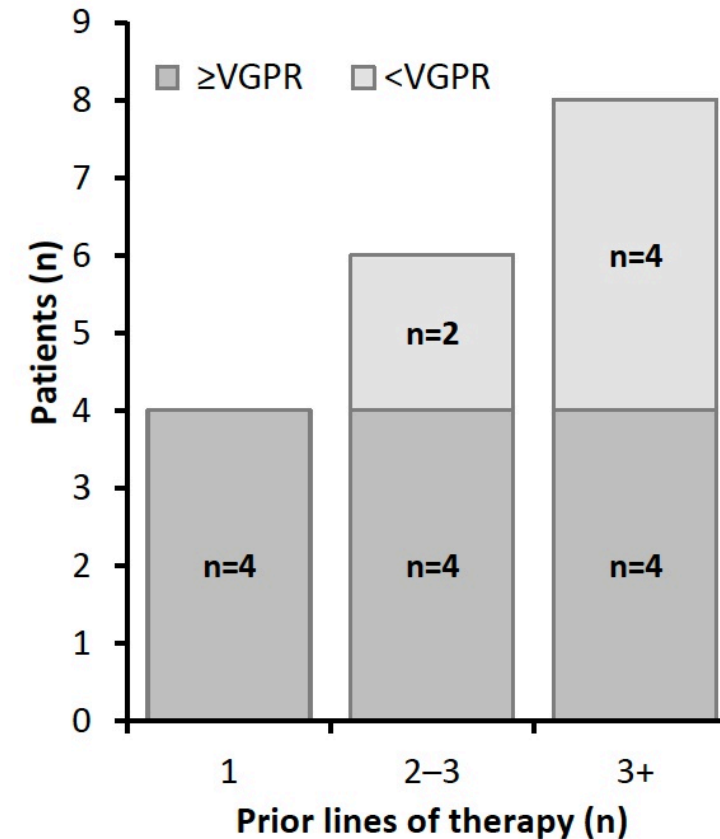


Figure 4. Investigator-assessed\* best confirmed response per prior number of LOT



# Case Presentation – Dr Brenner: A 72-year-old man with multiregimen-relapsed multiple myeloma – t(11;14)



**Dr Warren Brenner**

- 2013: Diagnosed with kappa light chain myeloma, ISS stage I, t(11;14),
  - RVD → ASCT → Lenalidomide maintenance
- 2/2017 – 11/2020: Repeated disease progressions treated with multiple treatment regimens
  - ixazomib/lenalidomide/dex, pomalidomide/clarithromycin/dex, ixazomib/venetoclax/dex, carfilzomib/cyclophosphamide/dex, daratumumab/pomalidomide/dex
  - Treatment course involved multiple dose reductions due to toxicity; transcatheter aortic valve replacement and pacemaker in 2020
- Selinexor/bortezomib/dex initiated

## Questions

- How do we choose among the agents available for patients with heavily pretreated myeloma? How do you use selinexor? Supportive care management for patients receiving selinexor?
- Will patients who receive belantamab be candidates for anti-BCMA targeted CAR-T therapy?
- Is there a role for rechallenging patients with anti-CD38 antibodies once they have progressed on daratumumab or isatuximab?



**Where in the treatment sequence are you typically incorporating selinexor, and is it best administered solely with dexamethasone or as part of a triplet regimen?  
What is the optimal dose and schedule of selinexor?**

**Where in the treatment sequence are you typically incorporating selinexor, and is it best administered solely with dexamethasone or as part of a triplet regimen? What is the optimal dose and schedule of selinexor?**

- Triple-class refractory is where we typically go.
- Optimal schedule is weekly — hard to keep patients on twice-weekly Selinexor with dex.
- Partnering with Bortezomib or Carfilzomib is optimal based on phase 2 and 3 data.
- Needs aggressive symptom management from the outset, not reactionary.

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

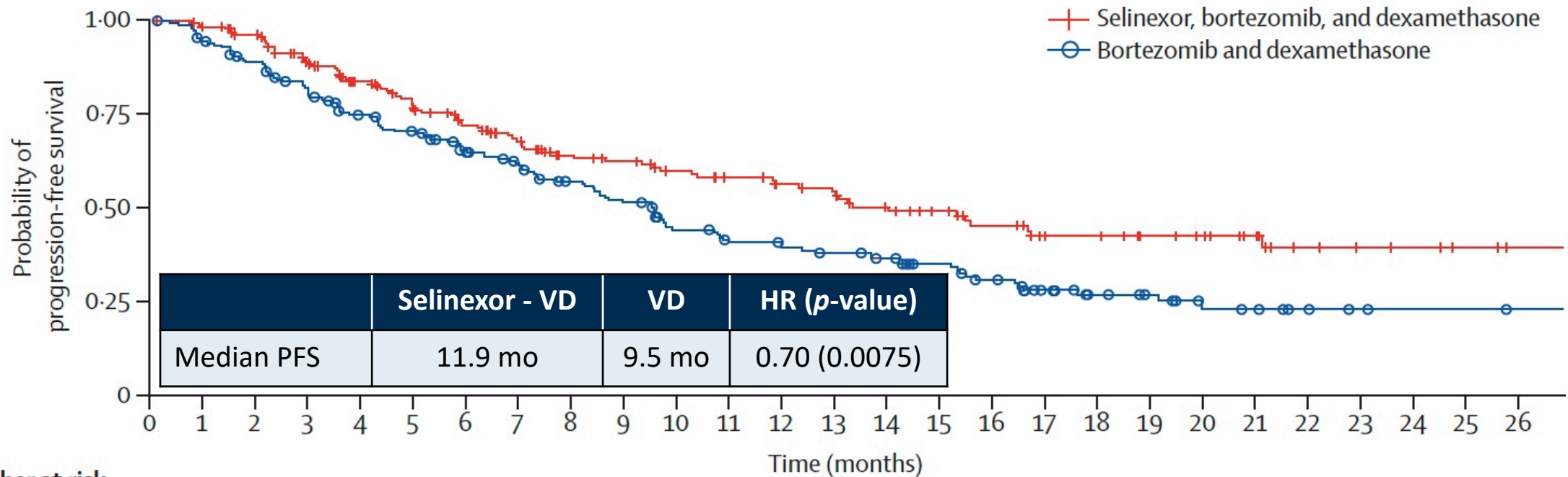
Press Release – December 18, 2020

“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.”

# 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)		

**Is it reasonable to employ venetoclax for a patient with relapsed/refractory t(11;14) MM? If so, would you use it solely with dexamethasone or as part of a triplet regimen? What is the optimal dose and schedule of venetoclax in MM, and is tumor lysis syndrome prophylaxis necessary?**

**Is it reasonable to employ venetoclax for a patient with relapsed/refractory t(11;14) MM? If so, would you use it solely with dexamethasone or as part of a triplet regimen? What is the optimal dose and schedule of venetoclax in MM, and is tumor lysis syndrome prophylaxis necessary?**

- I use ven for t(11;14) MM in relapse, and typically partner with dex alone.
- There are trials combining with Car and Dara, but those have not yet completed.
- TLS prophylaxis not needed, but would check for uric acid level, etc before dosing.
- We typically give a dose in the morning of first cycle, and recheck labs later that afternoon, and if no real change in the LDH, then we continue opt treatment.
- This is different from ven dosing in CLL and NHL.
- Recent paper using flow markers to predict response is very easy to use.

**Given its recent FDA approval, where in the treatment sequence are you planning to integrate idecabtagene vicleucel for your patients with relapsed/refractory MM?**

**Given its recent FDA approval, where in the treatment sequence are you planning to integrate idecabtagene vicleucel for your patients with relapsed/refractory MM?**

- CART usage often takes time to get approvals, and apheresis, and then manufacturing
- Consider for patients who have time to wait or you have an alternative bridging option
- Younger patients
- Toxicity for BCMA-directed CART for MM much better than for CD19-directed CART so can recommend for older patients in right circumstances



**Is it reasonable to use BCMA-directed CAR T-cell therapy in a patient who has previously received belantamab mafodotin and vice versa?**

## **Is it reasonable to use BCMA-directed CAR T-cell therapy in a patient who has previously received belantamab mafodotin and vice versa?**

- Data-free zone.
- Most patients who progress on BCMA-directed therapy are not losing BCMA expression, therefore use of another BCMA-directed drug after previous exposure is reasonable to consider.
- We all have anecdotes of this working.
- Particularly, progression at 9-12 months post CAR-T therapy nearly always can be retreated with BCMA-directed therapy.

# FDA Approves Idecabtagene Vicleucel for Multiple Myeloma

Press Release – March 26, 2021

“On March 26, 2021, the FDA approved idecabtagene vicleucel for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. This is the first FDA-approved cell-based gene therapy for multiple myeloma.

Idecabtagene vicleucel is a BCMA-directed genetically modified autologous chimeric antigen receptor (CAR) T-cell therapy. Each dose is customized using a patient’s own T-cells, which are collected and genetically modified, and infused back into the patient.

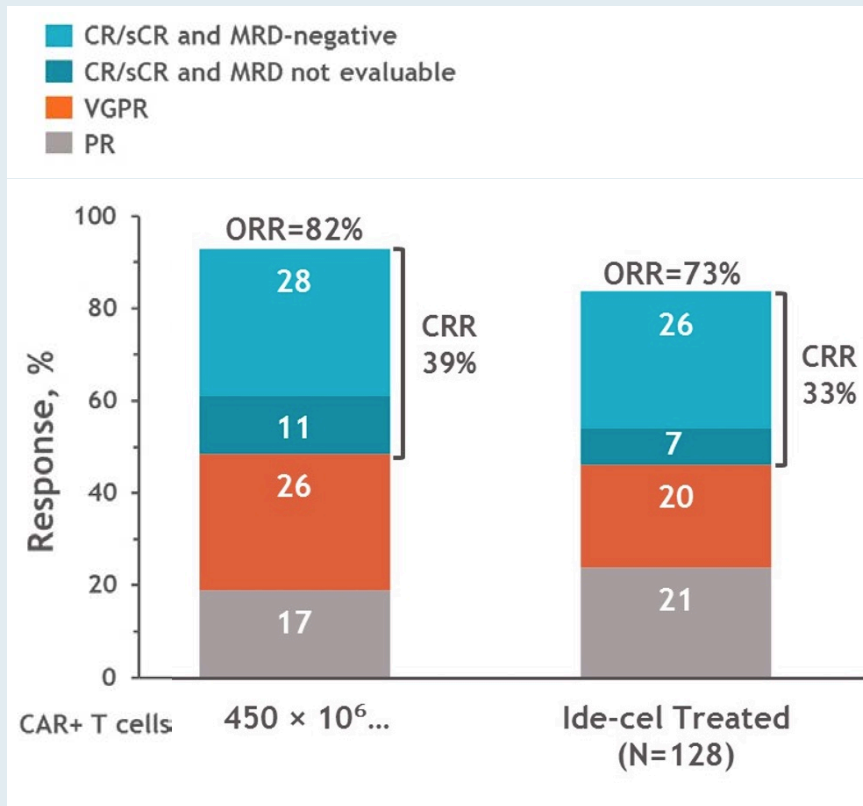
Efficacy was evaluated in 100 patients who received idecabtagene vicleucel in the dose range of 300 to 460 x 10<sup>6</sup> CAR-positive T cells. Efficacy was established based on overall response rate (ORR), complete response (CR) rate, and duration of response (DOR), as evaluated by an Independent Response committee using the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma.”

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

## KarMMA

Idecabtagene vicleucel

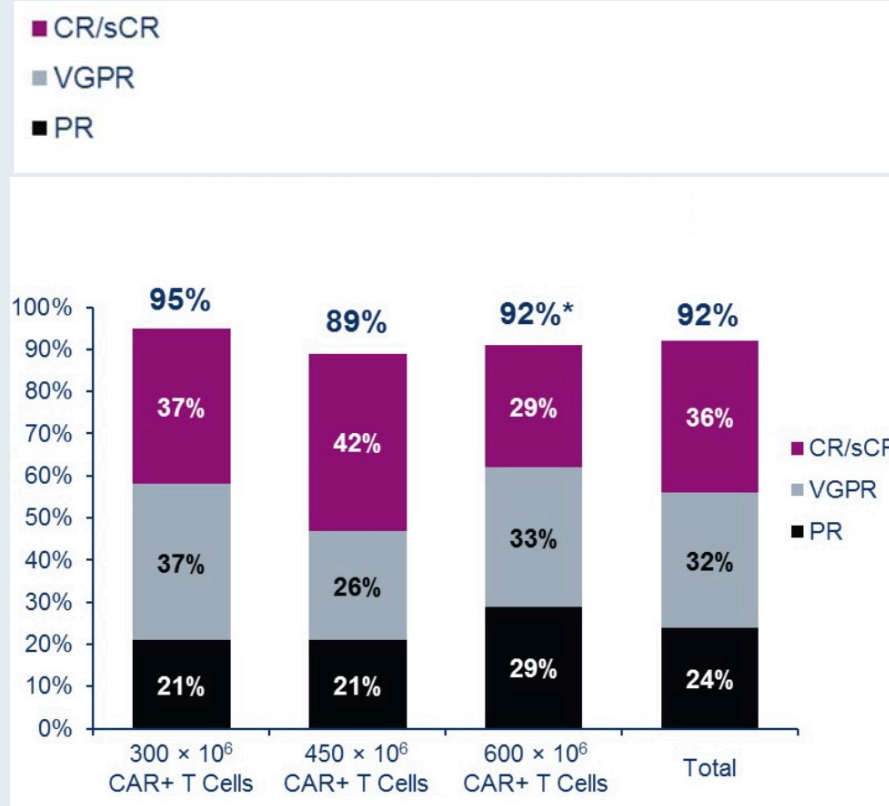
ORR: 73% | MRD-neg: 94%



## EVOLVE

Orvacabtagene autoleucel

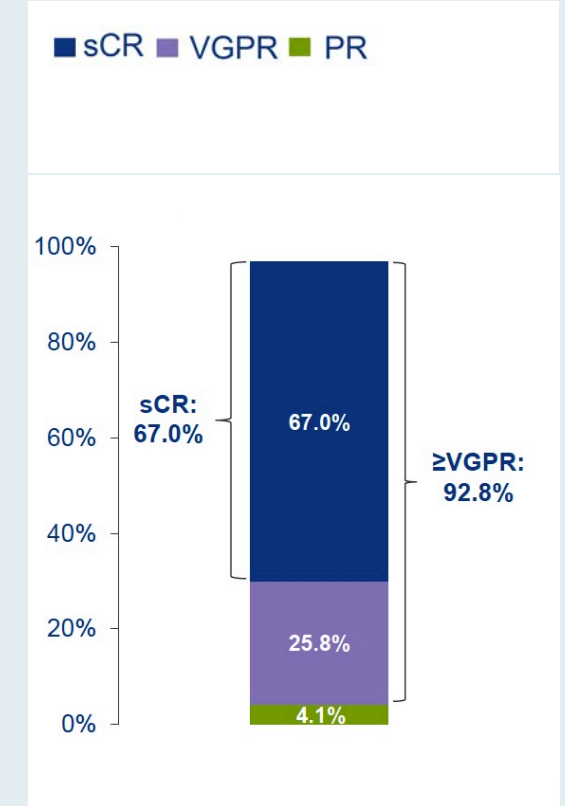
ORR: 92% | MRD-neg: 84%



## CARTITUDE-1

Ciltacabtagene autoleucel

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).

# **Ciltacabtagene Autoleucel, a B-cell Maturation Antigen (BCMA)-Directed Chimeric Antigen Receptor T-Cell (CAR-T) Therapy, in Relapsed/Refractory Multiple Myeloma (R/R MM): Updated Results from CARTITUDE-1**

Usmani SZ et al.

ASCO 2021;Abstract 8005.

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

# **Efficacy and Safety of Elranatamab (PF-06863135), a B-Cell Maturation Antigen (BCMA)-CD3 Bispecific Antibody, in Patients with Relapsed or Refractory Multiple Myeloma (MM)**

Bahlis NJ et al.

ASCO 2021;Abstract 8006.

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

# Updated Phase 1 Results of Teclistamab, a B-Cell Maturation Antigen (BCMA) x CD3 Bispecific Antibody, in Relapsed/Refractory Multiple Myeloma (MM)

Krishnan AY et al.

ASCO 2021;Abstract 8007.

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

# Agenda

## Module 1: Newly Diagnosed Multiple Myeloma

- Dr Shameem: A 79-year-old woman with newly diagnosed multiple myeloma and several comorbidities
- Dr Gupta: A 44-year-old woman with high-risk multiple myeloma and acute kidney injury

## Module 2: Relapsed Multiple Myeloma

- Dr Gandhi: A 62-year-old woman with relapsed multiple myeloma
- Dr Brenner: A 72-year-old man with multiregimen-relapsed multiple myeloma – t(11;14)

## Module 3: Related Cases

- Dr Chen: A 65-year-old man with AL amyloidosis and renal failure
- Dr Santiago: A 65-year-old man with IgM = 5,000, negative MYD88 and hyperviscosity



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



**Dr Gigi Chen**

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

## Questions

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



blood®

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

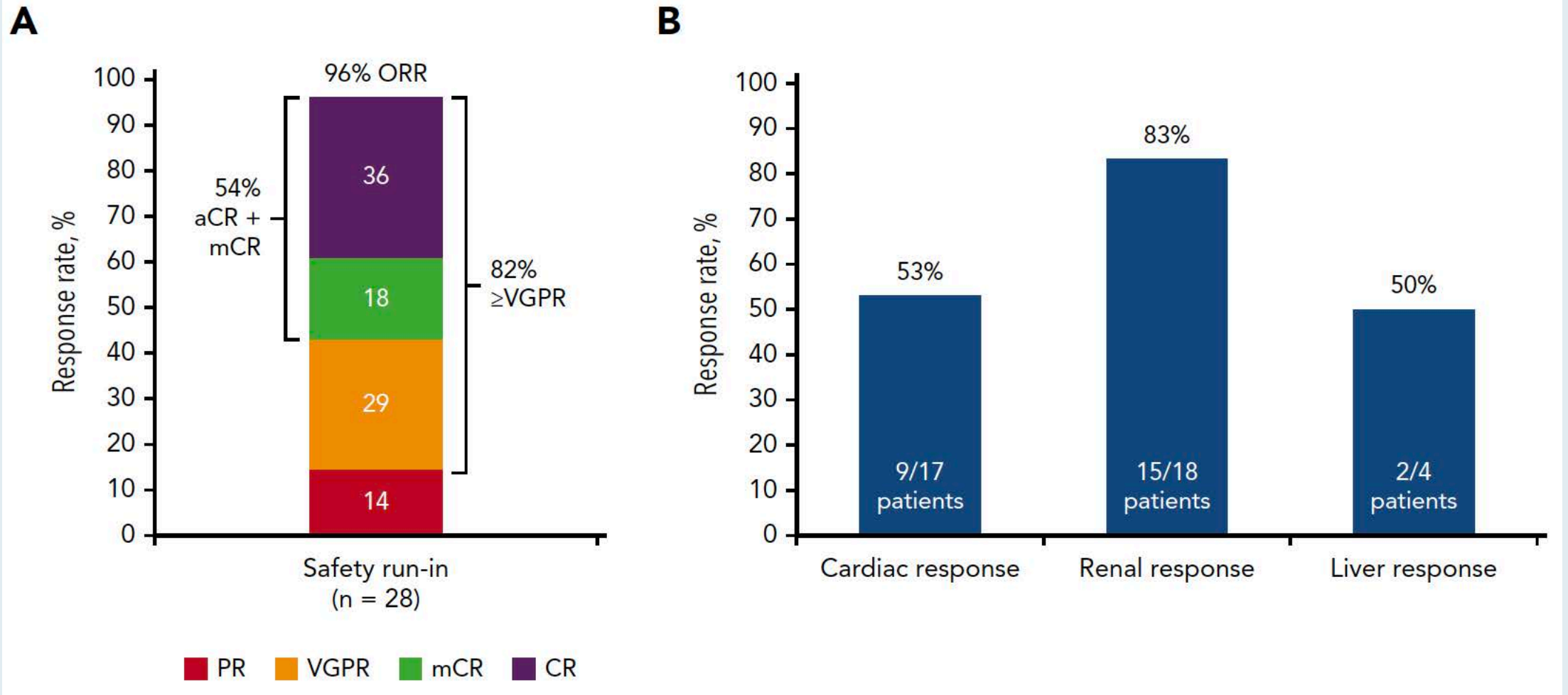
## Regular Article

### CLINICAL TRIALS AND OBSERVATIONS

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

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

# ANDROMEDA: Summary of Overall Best Hematologic and Organ Responses



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

Press Release – January 15, 2021

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

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

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

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

Kastritis E et al.

ASCO 2021;Abstract 8003.

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

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

Comenzo RL et al.

ASH 2020;Abstract 552.

# Case Presentation – Dr Santiago: A 65-year-old man with IgM = 5,000, negative MYD88 and hyperviscosity



**Dr Ferdy Santiago**

- PMH: prostate cancer, s/p prostatectomy in 2016
- 4/2021: IgM = 5,000, MYD88, PET, bone marrow biopsy ordered
- Unable to obtain specimen due to clotting → Sent to hospital with concerns for hyperviscosity
  - Plasmapheresis x 2, viscosity: 5
- Treated as WM with bendamustine/rituximab x 1 inpatient
- MYD88: Negative
- Consulted with Moffitt Cancer Center: IgM myeloma, M-spike 2.73, viscosity 2.5
- Bortezomib/lenalidomide/daratumumab/dexamethasone

## Questions

- In a patient who presents with such a high IgM, what helps you to differentiate between Waldenström's and an IgM myeloma in a patient with a solitary lytic lesion?
- How tolerable is the RVD/daratumumab regimen and how do you deal with the cytopenias – do you dose reduce at the first sign of cytopenias?



***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 3:15 PM ET**

***Up Next...***

**Drs Virginia Kaklamani and Nancy Lin  
discuss the management of breast cancer**

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

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

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

# Agenda

**Module 1 — Lung Cancer:** *Drs Heymach and Liu*

**Module 2 — Genitourinary Cancers:** *Drs Hussain and Plimack*

**Module 3 — Chronic Lymphocytic Leukemia and Lymphomas:**  
*Drs Friedberg and Sehn*

**Module 4 — Multiple Myeloma:** *Drs Ghobrial and Lonial*

**Module 5 — Breast Cancer:** *Drs Kaklamani and Lin*

# Breast Cancer Faculty



**Virginia Kaklamani, MD, DSc**

Professor of Medicine

Ruth McLean Bowman Bowers Chair in Breast  
Cancer Research and Treatment

AB Alexander Distinguished Chair in Oncology

Associate Director for Clinical Research

Leader of the Breast Cancer Program

UT Health San Antonio

The University of Texas MD Anderson Cancer Center  
San Antonio, Texas



**Nancy U Lin, MD**

Associate Professor of Medicine

Harvard Medical School

Associate Chief, Division of Breast Oncology

Director, Metastatic Breast Cancer Program

Dana-Farber Cancer Institute

Boston, Massachusetts

# Contributing Oncologists



**Susmitha Apuri, MD**  
Florida Cancer Specialists  
Lutz, Florida



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



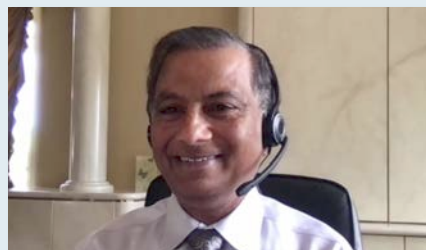
**Warren S Brenner, MD**  
Lynn Cancer Institute  
Boca Raton, Florida



**Maria Regina Flores, MD**  
Advent Health Orlando  
Orlando Regional Hospital  
Florida Cancer Specialists  
Orlando, Florida



**Gigi Chen, MD**  
Diablo Valley Oncology and  
Hematology Medical Group  
Pleasant Hill, California



**Sunil Gandhi, MD**  
Florida Cancer Specialists  
Lecanto, Florida



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



**Ranju Gupta, MD**  
Attending Physician  
Co-Director, Cardio-Oncology Program  
LVPG Hematology Oncology Associates  
Lehigh Valley Health Network  
Bethlehem, Pennsylvania

# Contributing Oncologists



**Lowell L Hart, MD**

Scientific Director of Research  
Florida Cancer Specialists  
Co-Director, Phase 1 Program  
Wake Forest Baptist Health  
Comprehensive Cancer Center  
Fort Myers, Florida



**Jeremy Lorber, MD**

Attending Hematologist-Oncologist  
Tower Hematology Oncology  
Cedars-Sinai Medical Center  
Beverly Hills, California



**KS Kumar, MD**

Physician Partner  
Florida Cancer Specialists  
New Port Richey, Florida



**Vikas Malhotra, MD**

Staff Medical Oncologist-Hematologist  
Florida Cancer Specialists  
Spring Hill, Florida



**Ferdy Santiago, MD**

Florida Cancer Specialists  
Naples, Florida



**Zanetta S Lamar, MD**

Florida Cancer Specialists  
Naples, Florida



**Raji Shameem, MD**

Florida Cancer Specialists  
Deland, Florida



# **Chalk Talk Topics**

## **Virginia Kaklamani, MD, DSc**

- 1. We know that the results of the OlympiA trial will soon be presented. If the findings mirror what was seen in ovarian cancer in the BRCA population (eg, SOLO-1 with a hazard ratio for progression-free survival of 0.33 but no overall survival data), which patients with localized breast cancer (BC) would require some sort of genomic evaluation? What type (germline, somatic, panel versus one-off testing, etc)?**
- 2. In what situations, if any, do you order a genomic assay for patients with node-positive, ER-positive, HER2-negative localized BC? Which assay? What adjuvant therapy would you generally recommend for a premenopausal woman with a 1.5-cm, Grade 2, ER-positive, HER2-negative IDC with 2 positive sentinel nodes and a 21-gene Recurrence Score® of 24?**
- 3. Which patients, if any, with high-risk ER-positive, HER2-negative localized BC should be offered treatment with adjuvant abemaciclib?**
- 4. How do you approach the treatment of patients with ER-positive, HER2-negative metastatic BC (mBC) with disease progression on a CDK4/6 inhibitor/endocrine therapy, and where does alpelisib fit in?**
- 5. What is the optimal first-line therapy for patients with metastatic PD-L1-positive TNBC with a BRCA germline mutation? In what line of therapy do you generally administer a PARP inhibitor to these patients?**

# Chalk Talk Topics

## Nancy U Lin, MD

1. Which patients, if any, with HER2-positive localized BC should be offered one year of extended adjuvant therapy with neratinib?
2. What is the optimal third-line therapy for an asymptomatic and symptomatic patient with HER2-positive mBC with and without brain metastases who experiences disease progression on docetaxel/trastuzumab/pertuzumab and then T-DM1?
3. At what grade of interstitial lung disease (ILD) do you permanently discontinue therapy in your patients receiving trastuzumab deruxtecan? In situations for which you reintroduce trastuzumab deruxtecan following the resolution of ILD symptoms, how do you approach dosing?
4. In what situations, if any, is it reasonable to administer an anti-PD-1/PD-L1 antibody in combination with chemotherapy as neoadjuvant therapy for patients with TNBC?
5. Generally, in what line of therapy should sacituzumab govitecan be used in metastatic TNBC?



# Agenda

## **Module 1: HER2-Positive Breast Cancer**

- Dr Kumar: A 36-year-old man with ER-positive/HER2-positive localized BC
- Dr Gandhi: A 66-year-old woman with ER/PR-positive, HER2-positive mBC who receives trastuzumab deruxtecan
- Dr Santiago: A 69-year-old woman with ER-positive, PR-negative, HER2-positive metastatic breast cancer (mBC)

## **Module 2: ER-Positive, HER2-Negative Breast Cancer**

- Dr Apuri: A 67-year-old woman with ER/PR-positive, HER2-negative metastatic breast cancer
- Dr Lamar: A 36-year-old woman with ER/PR-positive, HER2-negative, T3N1 IDC
- Dr Gandhi: A 66-year-old man with ER/PR-positive, HER2-negative mBC with PI3KCA and ATM copy loss

## **Module 3: Triple-Negative Breast Cancer (TNBC)**

- Dr Santiago: A 68-year-old woman with metastatic TNBC and a gBRCA1 mutation
- Dr Kumar: A 77-year-old woman with history of ER-positive/HER2-negative ILC now presents with mTNBC
- Dr Hart: A 44-year-old woman with localized TNBC

# Agenda

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- Dr Hart: A 44-year-old woman with localized TNBC

# Case Presentation – Dr Kumar: A 36-year-old man with ER-positive/HER2-positive localized breast cancer



**Dr KS Kumar**

- Diagnosed with ER-positive/HER2-positive IDC of the right breast, Grade II, stage T1cN0M0
  - CHEK2 mutation detected in germline
- PMH: familial history of breast cancer in sister, who is CHEK2 mutation-positive
- Patient weighs 560 pounds; body surface area is 3.2
- Plan is to proceed with initial surgery followed by adjuvant weekly paclitaxel and trastuzumab

## **Question**

- What are your thoughts about treating him with olaparib?

**Which patients, if any, with HER2+ localized BC should be offered one year of extended adjuvant therapy with neratinib?**

## ***Chalk Talk – Nancy U Lin, MD***

### **Which patients, if any, with HER2+ localized BC should be offered one year of extended adjuvant therapy with neratinib?**

- ExteNET: phase III, double-blind, 1 yr of neratinib (240 mg) vs placebo (n=2,820)
  - Initial report: (2y median f/u: iDFS 93.9% vs 91.6%, HR 0.67)
  - In HR+/ $<1$  yr subset: absolute iDFS benefit at 5y = 5.1% (HR 0.58); absolute OS benefit at 8 y = 2.1% (HR 0.79)
  - In n=354 pts who received neoadj tx, 295 with residual disease: absolute iDFS benefit at 5y = 7.4%; absolute OS benefit at 8 y = 9.1%
- APHINITY: phase III, placebo-controlled; 1 yr +/- pertuzumab added to trastuzumab (n=4,805)
  - At 45 mo median f/u: 6-yr iDFS 91% vs 88% (HR 0.76); no diff in OS (95% vs 94%)
  - N+: iDFS 88% vs 83% (HR 0.72); No benefit in N-
  - HR+  $\rightarrow$  HR 0.73; HR-  $\rightarrow$  HR 0.83
- Practical considerations:
  - Increased use of neoadjuvant tx (with T-DM1 post op for residual dz) for clinical stage II or higher

# Case Presentation – Dr Gandhi: A 66-year-old woman with ER/PR-positive, HER2-positive metastatic breast cancer who receives trastuzumab deruxtecan



**Dr Sunil Gandhi**

- 2010: T2N0MO ER/PR-positive, HER2-negative breast cancer s/p bilateral mastectomies
- Adjuvant anastrozole
- 2014: Biopsy-proven bone metastases, ER/PR-positive, HER2-positive
- Vinorelbine/trastuzumab and zoledronic acid → PD
- T-DM1 → PD within 7 months (changed oncologist)
- *Nab*-paclitaxel/trastuzumab → rash → Gemcitabine/trastuzumab → rash → Dermatologist
- Biopsy of rash: Cutaneous lupus → Hydroxychloroquine, with no subsequent rash
- Eribulin on clinical trial
- Trastuzumab deruxtecan x 1 year and ongoing

## Question

- Does trastuzumab deruxtecan cause pulmonary toxicity and how should I follow these patients?

# Case Presentation – Dr Santiago: A 69-year-old woman with ER-positive, PR-negative, HER2-positive metastatic breast cancer



**Dr Ferdy Santiago**

- 2000: DCIS s/p mastectomy
- 2008: Right ER-positive, PR-negative, HER2-positive IDC s/p mastectomy, ddAC→T, trastuzumab x 1 year, AI x 5 years
- 2016: Recurrent right ER-positive, PR-negative, HER2-positive IDC
  - Neoadjuvant TCHP, repeat mastectomy with positive margins x 2, chest wall RT
  - 1 year trastuzumab, anastrozole
- 2/2019: Recurrence in right supraclavicular and axillary nodes, right intramuscular metastatic deposits
- 2/2019: T-DM1, with CR, with dose reduction due to cytopenias and drug holiday
- 2/2020: Trastuzumab/pertuzumab and continues on AI

## Questions

- If her disease progresses, what would you recommend next – tucatinib or trastuzumab deruxtecan?
- How would possible brain metastases play a role with the CNS penetration we have with the newer TKIs in this space?
- Do you still use lapatinib?

**What is the optimal 3rd-line therapy for an asymptomatic or symptomatic pt with HER2+ MBC with or without brain mets who has progressed on THP then T-DM1?**



## ***Chalk Talk – Nancy U Lin, MD***

**What is the optimal 3rd-line therapy for an asymptomatic or symptomatic pt with HER2+ MBC with or without brain mets who has progressed on THP then T-DM1?**

- HER2CLIMB (n=612)
  - Median PFS 7.8 vs 5.6 mo (HR 0.54); Median OS 21.9 vs 17.4 mo (HR 0.66)
  - In n=511 pts with meas dz at BL: ORR 40.6% vs 22.8%
  - Brain mets subset: median CNS-PFS 9.9 mo vs 4.2 mo (HR 0.32); median OS 18.1 vs 12.1 mo (HR 0.58); ORR-IC 47% vs 20%
  - G3 or higher: diarrhea (12.9%), PPE (13.1%), nausea (3.7%), ALT (5.4%)
- DESTINY-Breast01 (n=184)
  - Median PFS 16.4 months; median OS not reached
  - ORR 60.9%; median DoR 14.8 mo
  - G3 or higher: neutropenia (20%), anemia (8.7%), nausea (7.6%)
  - Active brain mets excluded; n=24 with stable brain mets showed comparable extracranial ORR and PFS

**At what grade of ILD do you permanently discontinue T-DXd? In situations where you reintroduce T-DXd following ILD resolution, how do you approach dosing?**

## ***Chalk Talk – Nancy U Lin, MD***

**At what grade of ILD do you permanently discontinue T-DXd? In situations where you reintroduce T-DXd following ILD resolution, how do you approach dosing?**

- Grading system for ILD; grade 1 = asymptomatic; gr 2 = symptomatic, limiting instrumental activities of daily living, no O<sub>2</sub> needed
- Incidence of ILD: 9% any grade (13.6% in DESTINY-Breast01); fatal in ~2%; median time to onset 4.1 months
- Discontinue for grade 2 or higher; initiate steroids (1 mg/kg prednisolone or equivalent)
- Hold for grade 1; consider steroids ( $\geq 0.5$  mg/kg prednisolone or equivalent)
  - If resolved in  $\leq 28$  days, resume and maintain dose
  - If resolved  $> 28$  days, reduce by one dose level

*Chalk Talk – Nancy U Lin, MD*

At what grade of ILD do you permanently discontinue T-DXd? In situations where you reintroduce T-DXd following ILD resolution, how do you approach dosing? (Continued)

ILD identification<sup>3</sup>

Severity	Description (NCI-CTCAE <sup>b</sup> grading)
Grade 1	Asymptomatic, clinical or diagnostic observations only
Grade 2	Symptomatic, limiting instrumental activities of daily living
Grade 3	Severe symptoms, limiting self-care activities of daily living; oxygen indicated
Grade 4	Life-threatening respiratory compromise
Grade 5	Death

<sup>b</sup>Toxicity grades are in accordance with the National Cancer Institute—Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v.4.03).

# **Trastuzumab plus Endocrine Therapy or Chemotherapy as First-Line Treatment for Metastatic Breast Cancer with Hormone Receptor- Positive and HER2-Positive: The SYSUCC-002 Randomized Clinical Trial**

Yuan Z et al.

ASCO 2021;Abstract 1003.

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

# Agenda

## Module 1: HER2-Positive Breast Cancer

- Dr Kumar: A 36-year-old man with ER-positive/HER2-positive localized BC
- Dr Gandhi: A 66-year-old woman with ER/PR-positive, HER2-positive mBC who receives trastuzumab deruxtecan
- Dr Santiago: A 69-year-old woman with ER-positive, PR-negative, HER2-positive metastatic breast cancer (mBC)

## Module 2: ER-Positive, HER2-Negative Breast Cancer

- Dr Apuri: A 67-year-old woman with ER/PR-positive, HER2-negative metastatic breast cancer
- Dr Lamar: A 36-year-old woman with ER/PR-positive, HER2-negative, T3N1 IDC
- Dr Gandhi: A 66-year-old man with ER/PR-positive, HER2-negative mBC with PI3KCA and ATM copy loss

## Module 3: Triple-Negative Breast Cancer (TNBC)

- Dr Santiago: A 68-year-old woman with metastatic TNBC and a gBRCA1 mutation
- Dr Kumar: A 77-year-old woman with history of ER-positive/HER2-negative ILC now presents with mTNBC
- Dr Hart: A 44-year-old woman with localized TNBC

# Case Presentation – Dr Apuri: A 67-year-old woman with ER/PR-positive, HER2-negative metastatic breast cancer



**Dr Susmitha Apuri**

- Family history of MDS (mother), breast cancer (maternal aunt)
  - PMH: TAH with BSO for endometriosis
- Left ER/PR-positive, HER2-negative 0.7-cm, grade 3 IDC s/p lumpectomy
  - *Oncotype DX*® RS: 34
- Adjuvant docetaxel/cyclophosphamide → Endocrine therapy x 10 years
- Six months after completion of ET: Progressive SOB
  - Multiple pleural nodules, large left pleural effusion → Biopsy cw ER/PR-positive, HER2-negative breast adenocarcinoma
  - NGS liquid biopsy: Androgen receptor 2+, TMB-low, PTEN-positive 20%
  - Genetic panel: BRCA1/2 wildtype, CHEK2 mutation, APC gene deletion

## Question

- Would you have treated her with a CDK4/6 inhibitor or would you have proceeded with dual-agent chemotherapy?

**In what situations, if any, do you order a genomic assay for patients with node-positive, ER-positive, HER2-negative localized BC? Which assay? What adjuvant therapy would you generally recommend for a premenopausal woman with a 1.5-cm, Grade 2, ER-positive, HER2-negative IDC with 2 positive sentinel nodes and a 21-gene Recurrence Score of 24?**

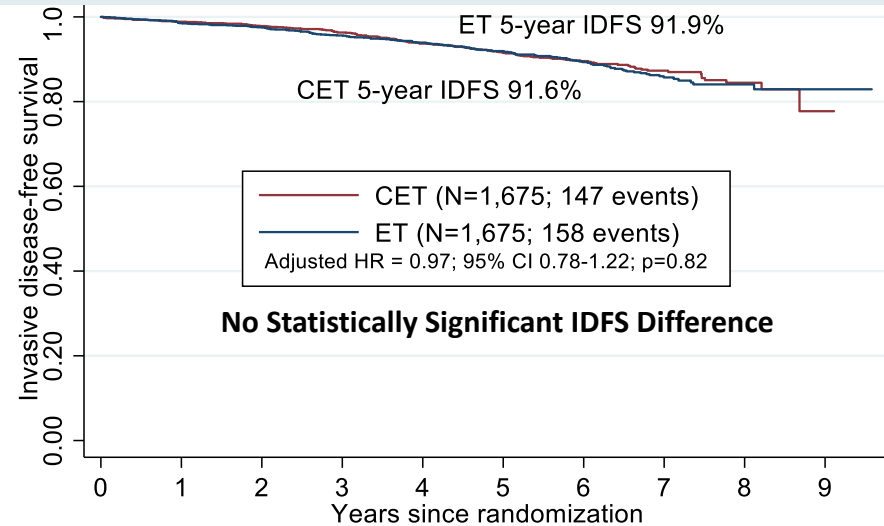


**In what situations, if any, do you order a genomic assay for patients with node-positive, ER-positive, HER2-negative localized BC? Which assay? What adjuvant therapy would you generally recommend for a premenopausal woman with a 1.5-cm, Grade 2, ER-positive, HER2-negative IDC with 2 positive sentinel nodes and a 21-gene Recurrence Score of 24?**

- 1-3 ALN pos postmenopausal 21-gene Recurrence Score assay based on results from RxPONDER clinical trial
- Chemotherapy with TC6 or ACT; Results from ABC and Plan B trials

# RxPONDER: IDFS Stratified by Menopausal Status

## Postmenopausal

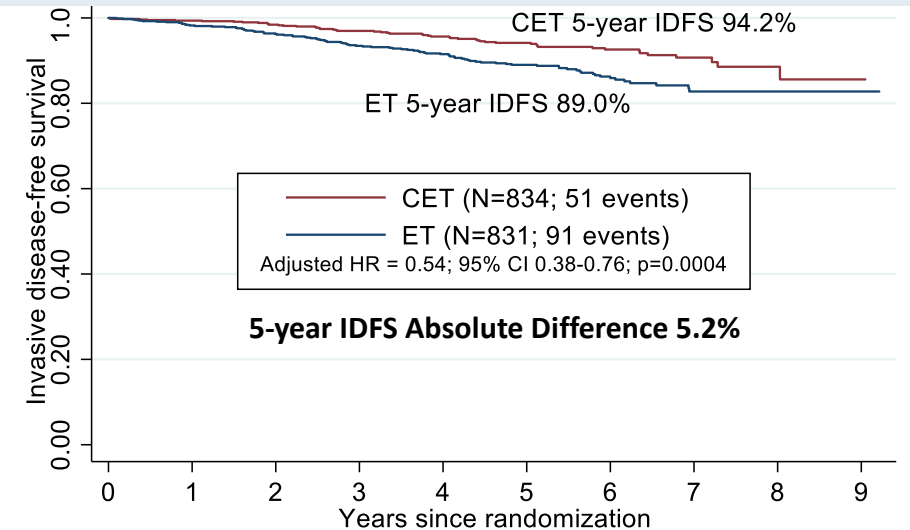


Number at risk										
CET	1675	1514	1400	1268	1113	943	585	287	88	3
ET	1675	1567	1462	1308	1167	975	601	298	104	9

IDFS Event	CET	ET	Total (%)
Distant	39	44	83 (27%)
Local-Regional	10	14	24 (8%)
Contralateral	10	9	19 (6%)
Non-Breast Primary	44	47	91 (30%)
Recurrence Not Classified	9	7	16 (5%)
Death not due to Recurrence or Second Primary	35	37	72 (24%)

**Absolute Difference in Distant Recurrence as 1<sup>st</sup> site: 0.3% (2.3% CET vs. 2.6% ET)**

## Premenopausal



Number at risk										
CET	834	763	704	625	535	454	272	116	34	1
ET	831	760	699	602	529	429	245	99	31	2

IDFS Event	CET	ET	Total (%)
Distant	26	50	76 (54%)
Local-Regional	8	17	25 (18%)
Contralateral	4	8	12 (8%)
Non-Breast Primary	10	10	20 (14%)
Recurrence Not Classified	1	1	2 (1%)
Death not due to Recurrence or Second Primary	2	5	7 (5%)

**Absolute Difference in Distant Recurrence as 1<sup>st</sup> site: 2.9% (3.1% CET vs. 6.0% ET)**

## Case Presentation – Dr Lamar: A 36-year-old woman with ER/PR-positive, HER2-negative, T3N1 IDC



Dr Zanetta Lamar

- ER/PR-positive, HER2-negative T3N1 IDC
- Dose-dense AC-T → Mastectomy, with residual disease (pT2N1a)
- Ovarian suppression and AI

### Questions

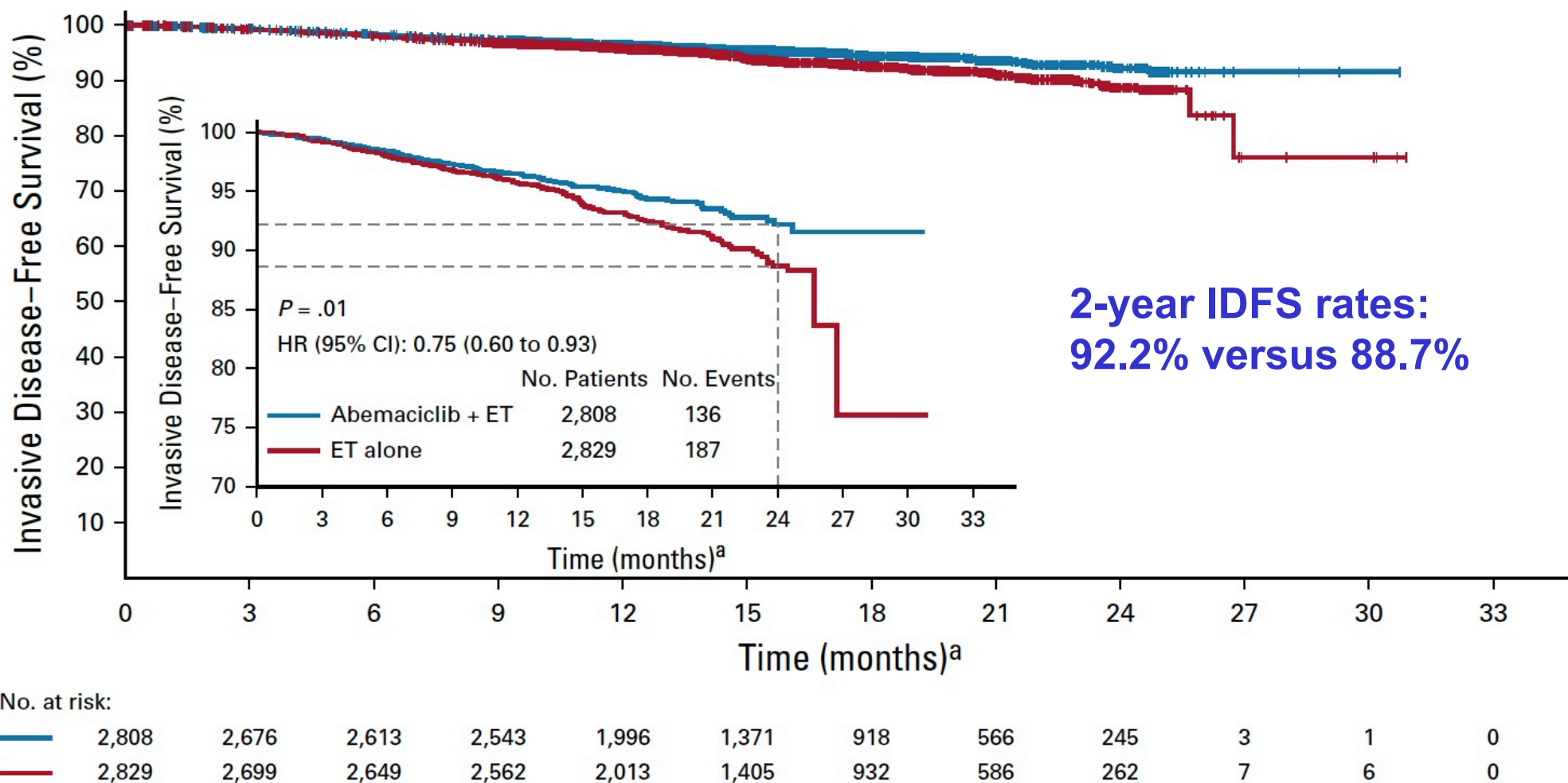
- With the new data for abemaciclib in patients that are high risk for recurrence, are you changing your practice, especially in a patient this young who has significant residual disease post-mastectomy? Would you give this patient abemaciclib?
- How do we use the *Oncotype* DX assay in premenopausal women, especially those who are node-positive? Are you using the MammaPrint assay at all?

**Which patients, if any, with high-risk ER-positive, HER2-negative localized BC should be offered treatment with adjuvant abemaciclib?**

## **Which patients, if any, with high-risk ER-positive, HER2-negative localized BC should be offered treatment with adjuvant abemaciclib?**

- Inclusion criteria for MonarchE
  - $\geq 4$  ALN OR
  - 1-3 ALN and at least 1 of the below:
    - Histologic Grade 3
    - Tumor size  $\geq 5$  cm
  - 1-3 ALN and
    - Centrally tested Ki-67  $\geq 20\%$
    - No Grade 3 and tumor size not  $\geq 5$  cm

## monarchE: Invasive Disease-Free Survival (IDFS)



# Case Presentation – Dr Gandhi: A 66-year-old man with ER/PR-positive, HER2-negative metastatic breast cancer with PI3KCA and ATM copy loss



**Dr Sunil Gandhi**

- 2016: Presents with a breast mass that was noticeable for the past year, but attributed to an injury
  - Fixed breast mass, severe anemia (Hgb: 6), weakness, widespread bone involvement
  - Breast biopsy: ER-positive, PR-positive, HER2-negative, PIK3CA mutation, gBRCA1/2 wildtype, ATM copy loss
- Letrozole/Palbociclib + zoledronic acid, with little response and remained transfusion dependent
- Paclitaxel x 6 months, and became transfusion independent
- Fulvestrant/abemaciclib until PD in 10/2020
- Fulvestrant/alpelisib

## Questions

- With regard to alpelisib, should I be giving metformin routinely, or just monitor his blood sugar?
- If a patient is HER2-positive and has a BRCA mutation, would you administer standard TCHP chemotherapy, or would you give olaparib?

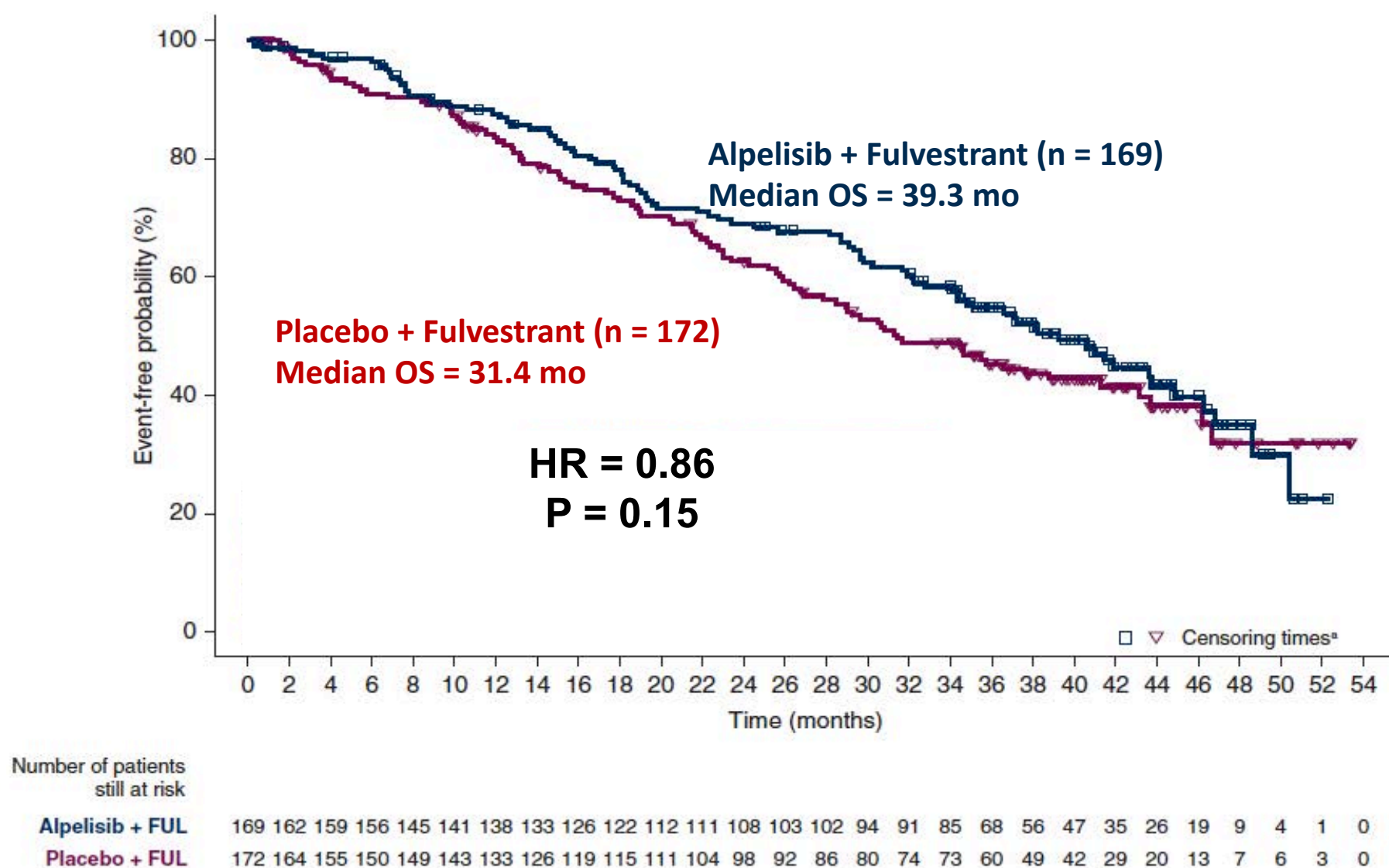
**How do you approach the treatment of patients with ER-positive, HER2-negative metastatic BC (mBC) with disease progression on a CDK4/6 inhibitor/endocrine therapy, and where does alpelisib fit in?**



**How do you approach the treatment of patients with ER-positive, HER2-negative metastatic BC (mBC) with disease progression on a CDK4/6 inhibitor/endocrine therapy, and where does alpelisib fit in?**

- PIK3CA testing on tumor or liquid biopsy. Primary tumor can be used as well
- CDK4/6 progression
  - SOLAR-1 clinical trial (alpelisib+fulvestrant)
  - BOLERO-2 (everolimus+exemestane) - no data on CDK4/6
  - PrE0102 (everolimus+fulvestrant) - no data on CDK4/6

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



# Agenda

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- Dr Santiago: A 68-year-old woman with metastatic TNBC and a gBRCA1 mutation
- Dr Kumar: A 77-year-old woman with history of ER-positive/HER2-negative ILC now presents with mTNBC
- Dr Hart: A 44-year-old woman with localized TNBC

# Case Presentation – Dr Santiago: A 68-year-old woman with metastatic, triple-negative breast cancer and a gBRCA1 mutation



**Dr Ferdy Santiago**

- Weakly ER-positive, PR-negative, HER2-negative, infiltrating carcinoma, grade 3, with ductal and lobular features
  - Germline BRCA1 mutation
  - Metastases to liver, lymph nodes, lungs and adrenals
- Letrozole/Palbociclib, with rash and continued increase in breast mass
- 10/2019: TC chemotherapy x 3, with rapid decrease in tumor size (near CR)
  - Declined additional chemotherapy due to side effects
- Left mastectomy (5-mm tumor)
- 5/2020: Olaparib, with dose reduction due to cytopenias → 4/2021: Stable disease

## Questions

- In patients receiving PARP inhibitors who develop cytopenias, at what point do you consider doing a bone marrow to rule out the development of MDS?
- If the adjuvant olaparib trial is positive, will it change our routine testing for patients in the adjuvant setting?

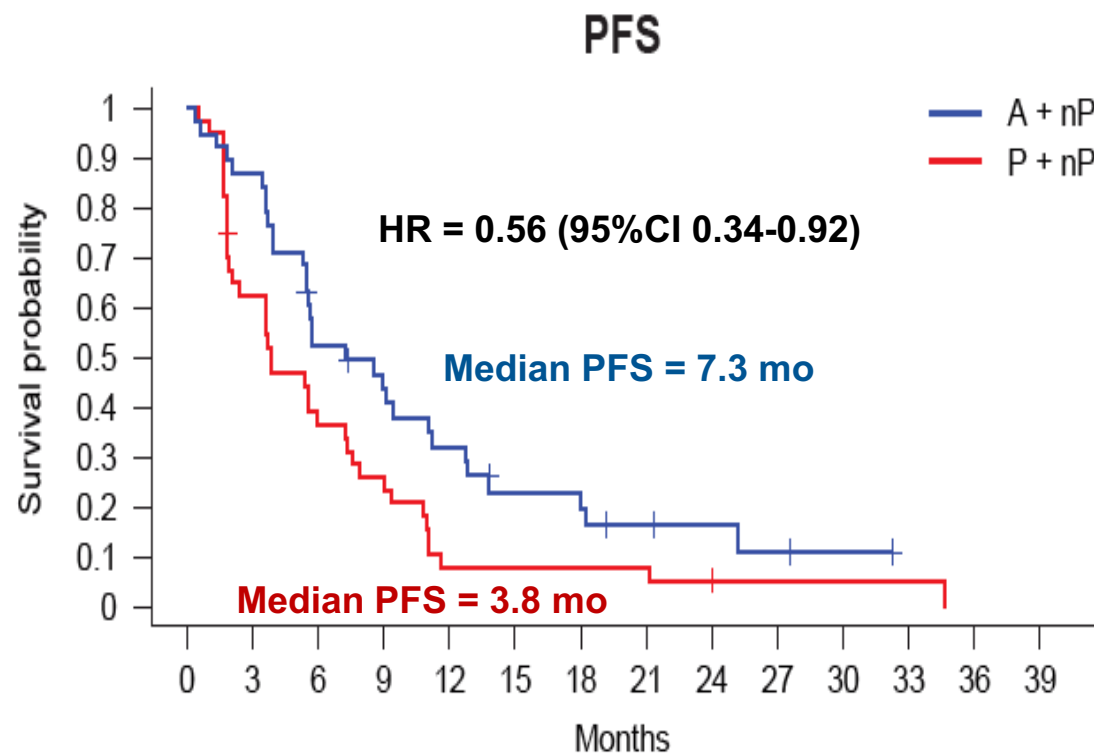
**What is the optimal first-line therapy for patients with metastatic PD-L1-positive triple-negative BC (TNBC) with a BRCA germline mutation? In what line of therapy do you generally administer a PARP inhibitor to these patients?**

**What is the optimal first-line therapy for patients with metastatic PD-L1-positive triple-negative BC (TNBC) with a BRCA germline mutation? In what line of therapy do you generally administer a PARP inhibitor to these patients?**

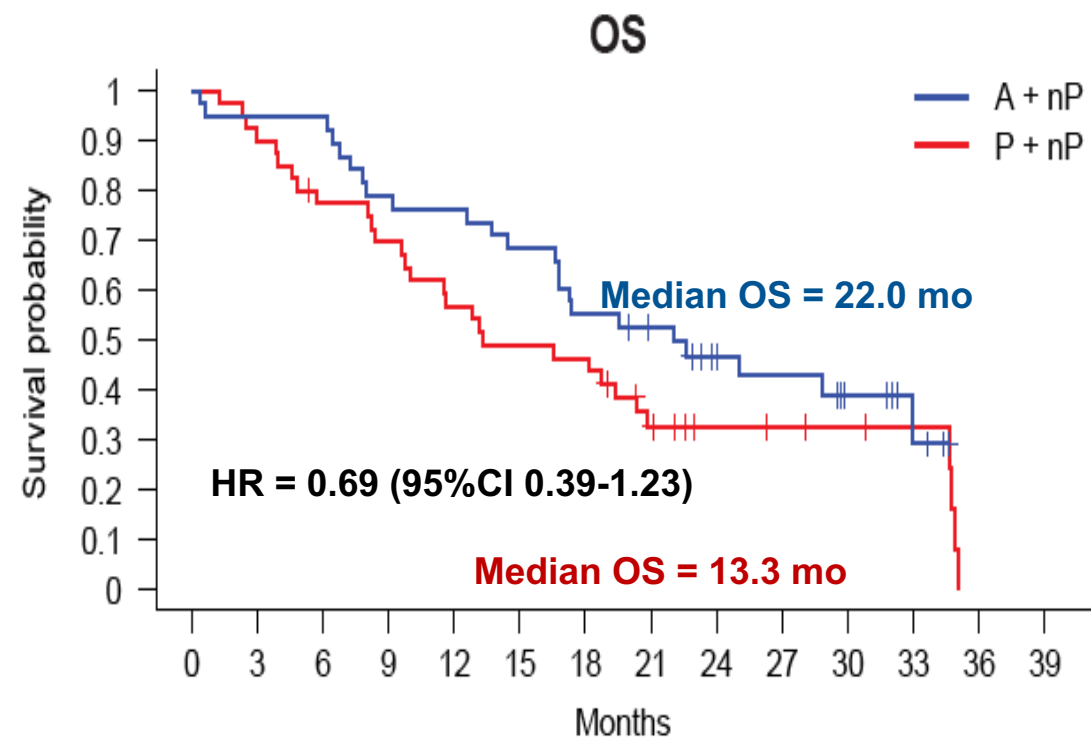
- First line trials
  - IMpassion130 – OS benefit
  - KEYNOTE-355 – OS not presented yet
- Trials including first line patients
  - OlympiAD – No OS benefit
  - EMBRACA – No OS benefit
- I start with IO and as second line I will give a PARPi

# IMpassion130: Distribution of PD-L1 TC-Positive Subgroup

PD-L1 TC+  
(TC ≥ 1%)



A + nP	38	33	19	15	11	7	7	4	3	2	1	0	0	0
P + nP	40	24	14	10	3	3	3	3	1	1	1	1	0	0



A + nP	38	36	36	30	29	26	21	18	12	11	7	3	0	0
P + nP	40	36	30	27	22	19	18	11	7	6	5	4	0	0

**We know that the results of the OlympiA trial will soon be presented. If the findings mirror what was seen in ovarian cancer in the BRCA population (eg, SOLO-1 with a hazard ratio for progression-free survival of 0.33 but no overall survival data), which patients with localized breast cancer (BC) would require some sort of genomic evaluation? What type (germline, somatic, panel versus one-off testing, etc)?**



**We know that the results of the OlympiA trial will soon be presented. If the findings mirror what was seen in ovarian cancer in the BRCA population (eg, SOLO-1 with a hazard ratio for progression-free survival of 0.33 but no overall survival data), which patients with localized breast cancer (BC) would require some sort of genomic evaluation? What type (germline, somatic, panel versus one-off testing, etc)?**

- Benefits of germline to somatic testing
  - No del/dup analysis therefore deletions aren't captured
  - Some deleterious mutations may be called VUS due to different data sets
  - It may be somatic mutation and not germline
  - Somatic reversion mutations (germline mutation gets “corrected” in cancer tissue)
  - Some companies do both at the same time
  - Types of somatic testing matter. Is there full sequencing analysis?
  - Intronic changes may also be missed (coverage level of NGS)-see above
- Patients to test
  - NCCN guidelines (may miss up to 50% of patients)
  - OlympiA inclusion:
    - TNBC  $\geq$ pT2 or  $\geq$ pN1 in the adjuvant and non-pCR in the neoadjuvant setting.
    - HR+  $\geq$ 4 positive lymph nodes in the adjuvant and non-pCR and CPS&EG score  $\geq$ 3 in the neoadjuvant setting.
- Primary endpoint IDFS (sustainable and clinically relevant)

# Phase III OlympiA Trial of Adjuvant Olaparib for High-Risk HER2-Negative Localized Breast Cancer with a BRCA Mutation Crossed the Superiority Boundary for Invasive Disease-Free Survival

Press Release – February 17, 2021

“The OlympiA Phase III trial of [olaparib] will move to early primary analysis and reporting following a recommendation from the Independent Data Monitoring Committee (IDMC).

Based on the planned interim analysis, the IDMC concluded that the trial crossed the superiority boundary for its primary endpoint of invasive disease-free survival (iDFS) and demonstrated a sustainable, clinically relevant treatment effect for olaparib versus placebo for patients with germline BRCA-mutated (gBRCAm) high-risk human epidermal growth factor receptor 2 (HER2)-negative early breast cancer, and recommend primary analysis now take place.

In its communication, the IDMC did not raise any new safety concerns. The trial will continue to assess the key secondary endpoints of overall survival and distant disease-free survival.”

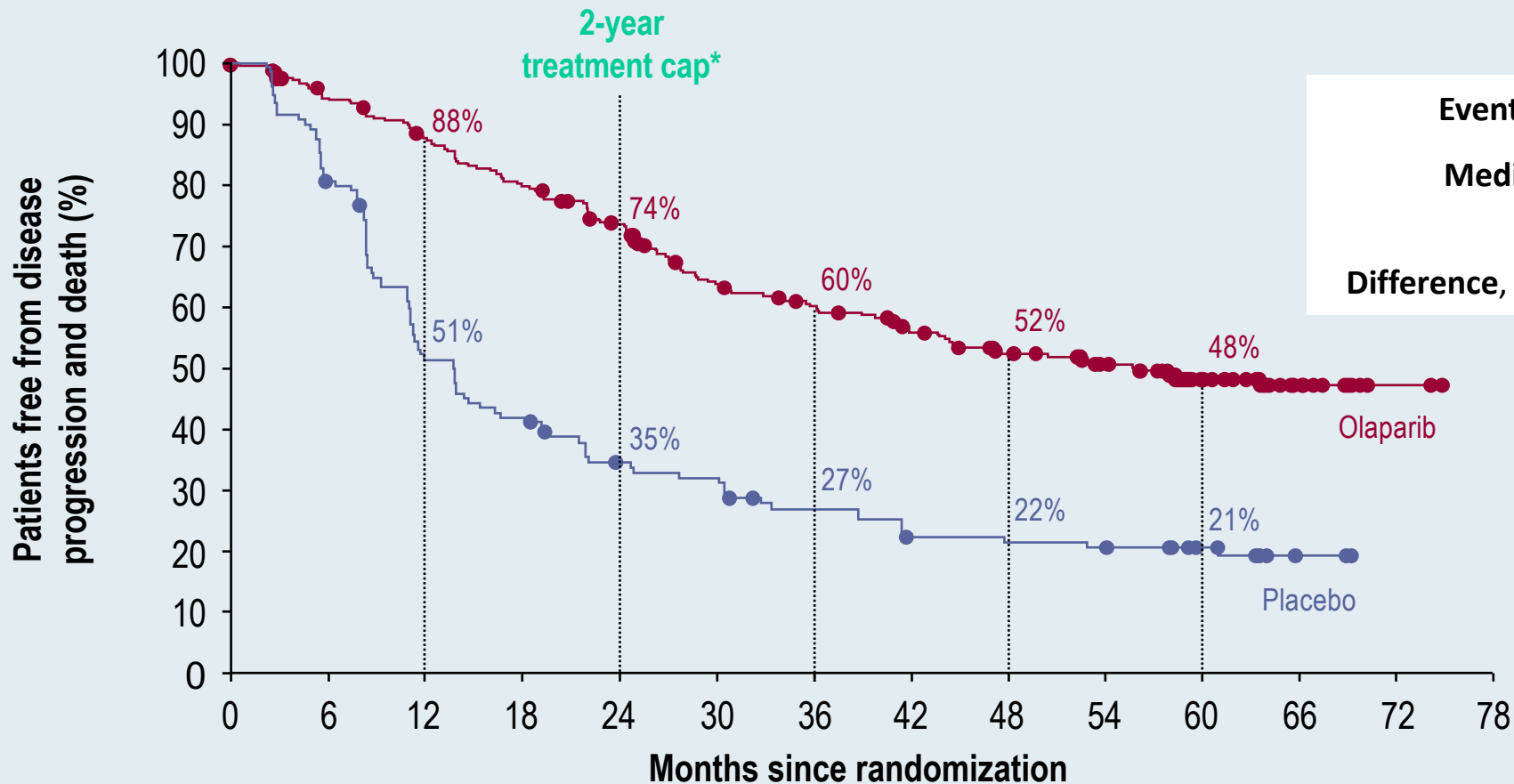
# **OlympiA: A Phase III, Multicenter, Randomized, Placebo-Controlled Trial of Adjuvant Olaparib After (Neo)Adjuvant Chemotherapy in Patients with Germline BRCA1/2 Mutations and High-Risk HER2-Negative Early Breast Cancer**

Tutt A et al.

ASCO 2021;Abstract LBA1.

**Sunday, June 6, 1:00 PM - 4:00 PM EDT**

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



No. at risk

Olaparib

Placebo

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

Events, n (%)

Median PFS, months

Difference, months

Olaparib  
(N=260)

118 (45)

**56.0**

Placebo  
(N=131)

100 (76)

**13.8**

42.2

**HR 0.33 (95% CI 0.25–0.43)**

**Median treatment duration:**

**Olaparib, 24.6 months**

**Placebo<sup>†</sup>, 13.9 months**

# SOLO-1 Trial 5-Year Update: Safety Profile

	n (%)	Olaparib (n=260)	Placebo (n=130)
<b>Any AE</b>		256 (98)	120 (92)
<b>Grade <math>\geq 3</math> AE</b>		103 (40)	25 (19)
<b>Serious AE</b>		55 (21)	17 (13)
<b>AE leading to dose interruption</b>		136 (52)	22 (17)
<b>AE leading to dose reduction</b>		75 (29)	4 (3)
<b>AE leading to treatment discontinuation</b>		30 (12)	4 (3)
<b>MDS/AML</b>		3 (1)	0 (0)
<b>New primary malignancy</b>		7 (3)	5 (4)

**No additional cases of MDS/AML reported;  
incidence remained <1.5%**

**Follow-up for MDS/AML continued until death due to any cause**

# Case Presentation – Dr Kumar: A 77-year-old woman with history of ER-positive/HER2-negative ILC now presents with mTNBC



Dr KS Kumar

- 2012: Diagnosed with ER-positive/HER2-negative ILC of the left breast, Stage III → ddAC/T with AI
- 1/2020: losing weight over a period of 2 years, tumor markers normal, negative CT scan
- Intermittent diarrhea with anorexia → *H. pylori* detected and treated with some symptom improvement
- Imaging studies show abnormalities in the liver and moderate, diffuse gastric wall thickening, omental nodularity and caking – gastric cancer suspected
- NGS results: ER/PR/HER2-negative, mammoglobin-positive, PD-L1 70%, TMB 5, AR 3+
- Triple-negative breast cancer metastasis to the stomach

## Question

- How would you manage this patient?

# Case Presentation – Dr Hart: A 44-year-old woman with localized TNBC



**Dr Lowell Hart**

- Presented with palpable right breast mass and nipple inversion
  - Biopsy: IDC, triple-negative
  - Germline genetic testing: negative
  - PET showed the right breast mass and several right axillary lymph nodes.
- 3/2020: Completed neoadjuvant dose-dense AC-paclitaxel
- 4/2020: Right lumpectomy showed residual 9 mm of grade II IDC.
  - SNL biopsy: 3/4 SNL positive
  - ypT1b ypN1a
- Radiation therapy → adjuvant capecitabine

## Questions

- Do you think that in the near future there will be a role for checkpoint inhibitors as neoadjuvant therapy for a patient such as this, with a high-risk, aggressive malignancy?
- Do you think it is worthwhile to administer capecitabine concurrently with radiation as a radiation enhancer?

**In what situations, if any, is it reasonable to administer anti-PD-1/PD-L1 with chemo as neoadjuvant tx in TNBC?**



## ***Chalk Talk – Nancy U Lin, MD***

**In what situations, if any, is it reasonable to administer anti-PD-1/PD-L1 with chemo as neoadjuvant tx in TNBC?**

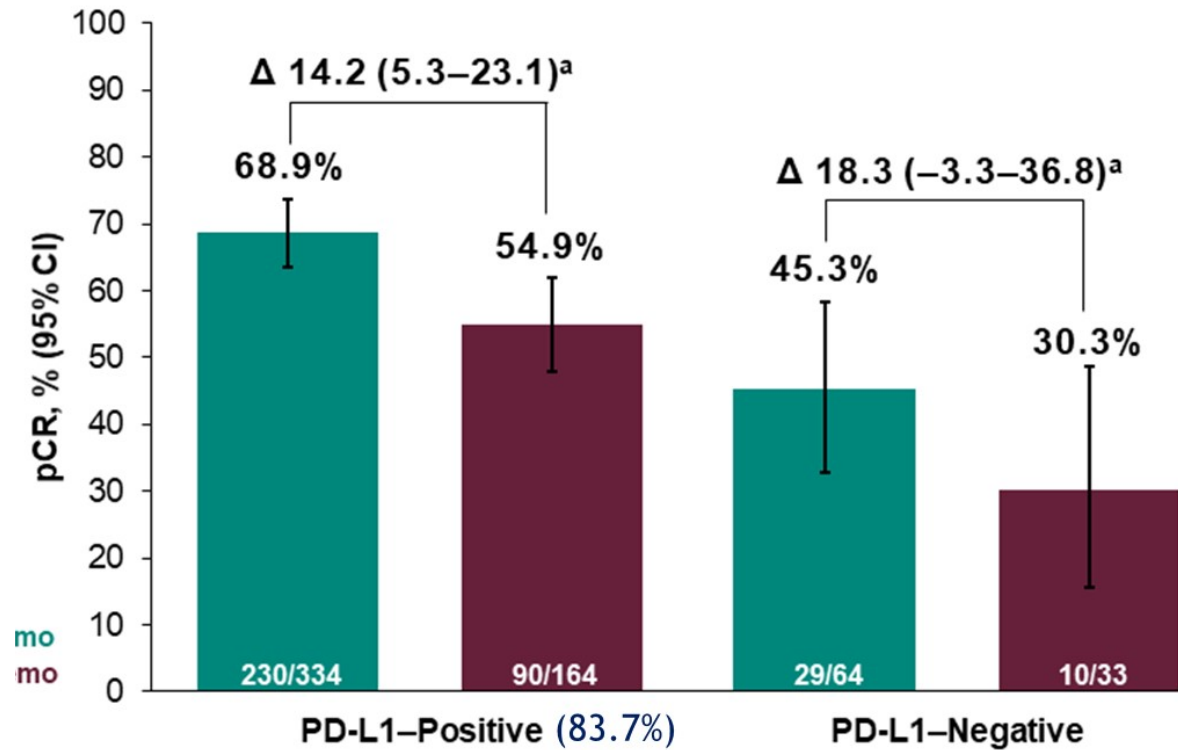
	<b>I-SPY2 Pembrolizumab</b>	<b>KEYNOTE-522 Pembrolizumab</b>	<b>NEOTRIP Atezolizumab</b>	<b>IMpassion 031 Atezolizumab</b>	<b>GEPARNUEVO Durvalumab</b>
Total patients	69/181	602/1174	280	333	174
Stage	II/III	II/III	I-III	II/III	35% stage I
Anthracycline	Yes	Yes	No	Yes	Yes
Carboplatin	No	Yes	Yes	No	No
pCR rate	60% vs 22% (graduated)	65% vs 51% (p=0.00055)	44% vs 41% (p=0.66)	57.6% vs 41.1% (p=0.0044)	53% vs 44% (p=0.287)

- KEYNOTE-522: FDA submission data: 18 mo EFS 91.3% vs 85.3%; HR 0.63; p=0.0089
- IRAEs: 10-15% can be permanent
  - Hypothyroid (14.9%), adrenal insufficiency (2.7%), hypophysitis (1.8%)

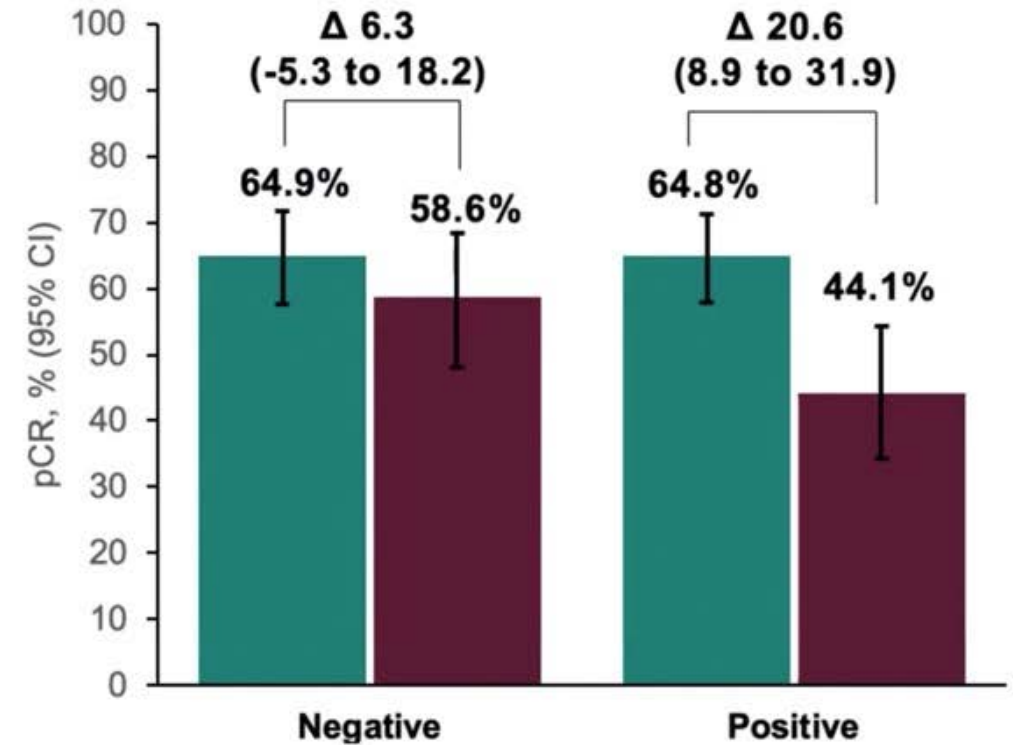
## Chalk Talk – Nancy U Lin, MD

In what situations, if any, is it reasonable to administer anti-PD-1/PD-L1 with chemo as neoadjuvant tx in TNBC? (Continued)

pCR by PD-L1 Status



pCR by Nodal Status



# Phase III KEYNOTE-522 Trial Meets Dual Primary Endpoint of Event-Free Survival (EFS) in Patients with High-Risk Early-Stage TNBC

Press Release – May 13, 2021

“Today positive results [were announced] from the pivotal neoadjuvant/adjuvant Phase 3 KEYNOTE-522 trial investigating pembrolizumab, an anti-PD-1 therapy, in combination with chemotherapy as pre-operative (neoadjuvant) treatment and then continuing as a single agent (adjuvant) treatment after surgery. KEYNOTE-522 met its dual primary endpoint of event-free survival (EFS) for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC).

Based on an interim analysis conducted by the independent Data Monitoring Committee (DMC), neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab as monotherapy showed a statistically significant and clinically meaningful improvement in EFS compared with neoadjuvant chemotherapy alone. As previously communicated, KEYNOTE-522 met its other dual primary endpoint of pathological complete response (pCR). The safety profile of pembrolizumab in this trial was consistent with that observed in previously reported studies; no new safety signals were identified.”

# **Durvalumab Improves Long-Term Outcome in TNBC: Results from the Phase II Randomized GeparNUEVO Study Investigating Neoadjuvant Durvalumab in Addition to an Anthracycline/Taxane Based Neoadjuvant Chemotherapy in Early Triple-Negative Breast Cancer (TNBC)**

Loibl S et al.

ASCO 2021;Abstract 506.

**Sunday, June 6, 8:00 AM - 11:00 AM EDT**

**Generally, in what line of tx should sacituzumab  
govitecan be used in metastatic TNBC?**

## ***Chalk Talk – Nancy U Lin, MD***

### **Generally, in what line of tx should sacituzumab govitecan be used in metastatic TNBC?**

- On April 7, 2021, the Food and Drug Administration granted regular approval to sacituzumab govitecan for patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received **two or more prior systemic therapies, at least one of them for metastatic disease.**
- ASCENT: Ph 3 RCT
  - TNBC w/o brain mets who had relapsed after  $\geq 2$  prior chemo (one could be neo/adj if DFI < 12 months)
  - Sacituzumab govitecan 10 mg/kg D1,8 Q21 days vs MD choice single-agent chemotherapy
  - Median PFS 5.6 months vs 1.7 months (HR 0.41;  $p < 0.001$ )
  - ORR 35% vs 5%
  - Median OS 12.1 months vs 6.7 months (HR 0.51;  $p < 0.0001$ )
  - G3+ AEs: neutropenia (51%), diarrhea (10%), anemia (8%), febrile neutropenia (6%).
  - All grade AEs: fatigue, alopecia, nausea/vomiting, constipation, rash, decreased appetite, and abdominal pain.



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

- SG is distinct from other ADCs<sup>1-4</sup>
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and enzymatic cleavage by tumor cell not required for SN-38 liberation from antibody
  - Hydrolysis of the linker also releases SN-38 extracellularly in the tumor microenvironment (bystander effect)
- Granted FDA accelerated approval for mTNBC<sup>5</sup>
- Landmark ASCENT study demonstrated a significant survival improvement of SG over chemotherapy, with a tolerable safety profile in pretreated mTNBC<sup>6</sup>
  - Median PFS of 5.6 vs 1.7 months (HR 0.41,  $P < 0.0001$ )
  - Median OS of 12.1 vs 6.7 months (HR 0.48,  $P < 0.0001$ )

## Linker for SN-38

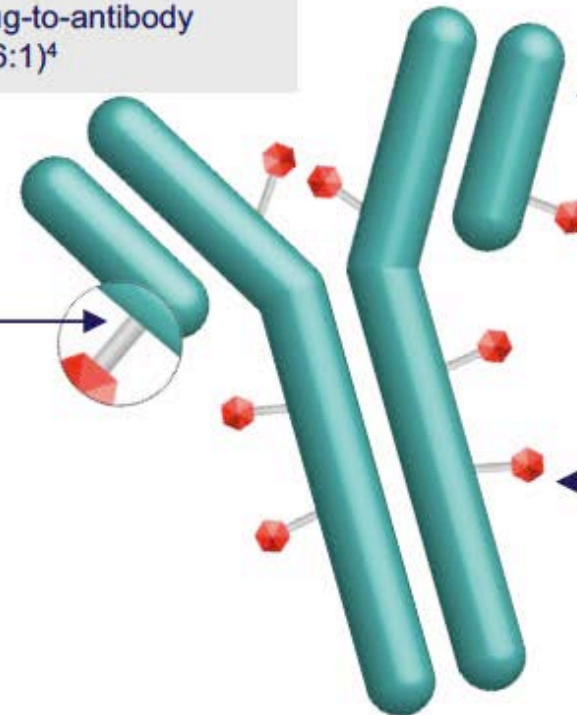
- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7.6:1)<sup>4</sup>

## Humanized anti-Trop-2 antibody

- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

## SN-38 payload

- SN-38 more potent than parent compound, irinotecan

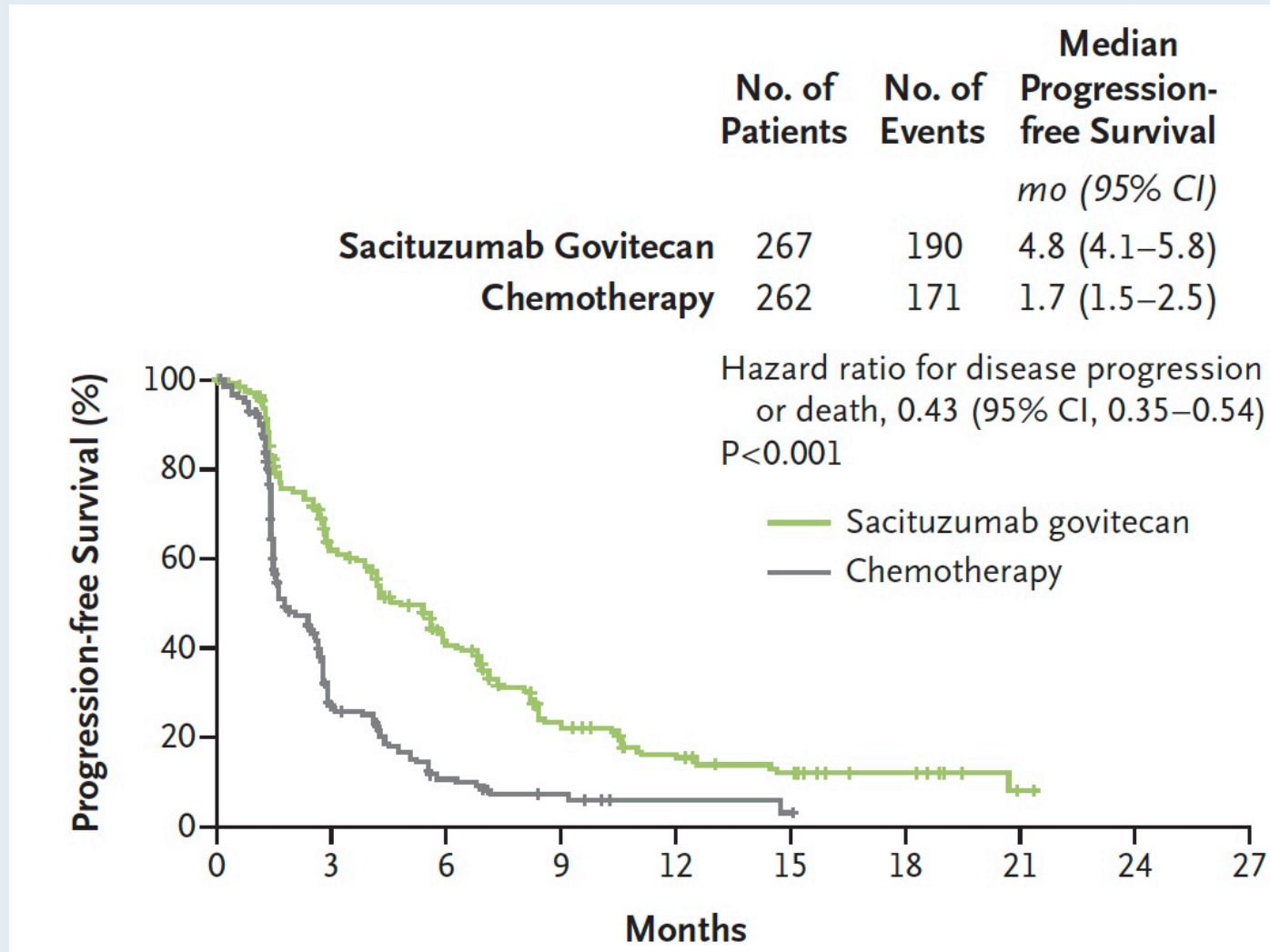


ADC, antibody-drug conjugate; FDA, US Food and Drug Administration; OS, overall survival; PFS, progression-free survival; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Goldenberg DM, et al. *Expert Opin Biol Ther*. 2020;20:871-885. 2. Nagayama A, et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 3. Cardillo TM, et al. *Bioconjugate Chem*. 2015;26:919-931. 4. Goldenberg DM, et al. *Oncotarget*. 2015;6:22496-224512. 5. Press Release. <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hzly-metastatic-triple-negative-breast-cancer>. Accessed August 26, 2020. 6. Bardia A, et al. ESMO 2020. Abstract LBA17.

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# ASCENT: Progression-Free Survival (Overall Population)





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