Recent Advances and Future Directions in Oncology

A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists

Saturday, October 23, 2021
9:30 AM – 4:30 PM ET

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Saturday, October 23, 2021

9:30 AM — Breast Cancer
Ann Partridge, Mark D Pegram

10:30 AM — Lung Cancer
Lecia V Sequist, David R Spigel

11:30 AM — Gastrointestinal Cancers
Tanios Bekaii-Saab, Kristen K Ciombor

12:30 PM — Genitourinary Cancers
Neeraj Agarwal, Daniel P Petrylak

1:30 PM — Chronic Lymphocytic Leukemia and Lymphomas
Brad S Kahl, Andrew D Zelenetz

2:30 PM — Multiple Myeloma
Noopur Raje, Saad Zafar Usmani

3:30 PM — Acute Myeloid Leukemia and Myelodysplastic Syndromes
Mark Levis, David Sallman

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Commercial Support

This activity is supported by educational grants from Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Daiichi Sankyo Inc, Eisai Inc, Exact Sciences Inc, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Incyte Corporation, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Merck, Natera Inc, Novartis, Oncopeptides, Pharmacyclics LLC, an AbbVie Company and Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc and Sanofi Genzyme, Sanofi Genzyme, Seagen Inc, Taiho Oncology Inc, and Takeda Pharmaceuticals USA Inc.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, Daiichi Sankyo Inc, Eisai Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Natera Inc, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc and Verastem Inc.

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Dr Partridge — Disclosures

Travel Support	Novartis

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Dr Pegram — Disclosures

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Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP

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Dr Spigel — Disclosures

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Consultant, Mayo Clinic in Arizona
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Inventions/Patents	WO/2018/183488, WO/2019/055687

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Dr Ciombor — Disclosures

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Dr Agarwal — Disclosures

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Dr Petrylak — Disclosures

Consulting Agreements	Gilead Sciences Inc, Ipsen Biopharmaceuticals Inc
Contracted Research	Gilead Sciences Inc

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Data and Safety Monitoring Board/Committee	Celgene Corporation, MEI Pharma Inc, Takeda Pharmaceuticals USA Inc

Dr Zelenetz — Disclosures

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Contracted Research	AbbVie Inc, BeiGene Ltd, Genentech, a member of the Roche Group, Gilead Sciences Inc, MEI Pharma Inc, MethylGene Inc
Data and Safety Monitoring Board/Committee	BeiGene Ltd (DMC Chair), Bristol-Myers Squibb Company, Celgene Corporation, Juno Therapeutics, a Celgene Company
Scientific Advisory Board Chair	Lymphoma Research Foundation
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Dr Usmani — Disclosures

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No relevant conflicts of interest to disclose.

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Contracted Research	Aprea Therapeutics, Jazz Pharmaceuticals Inc
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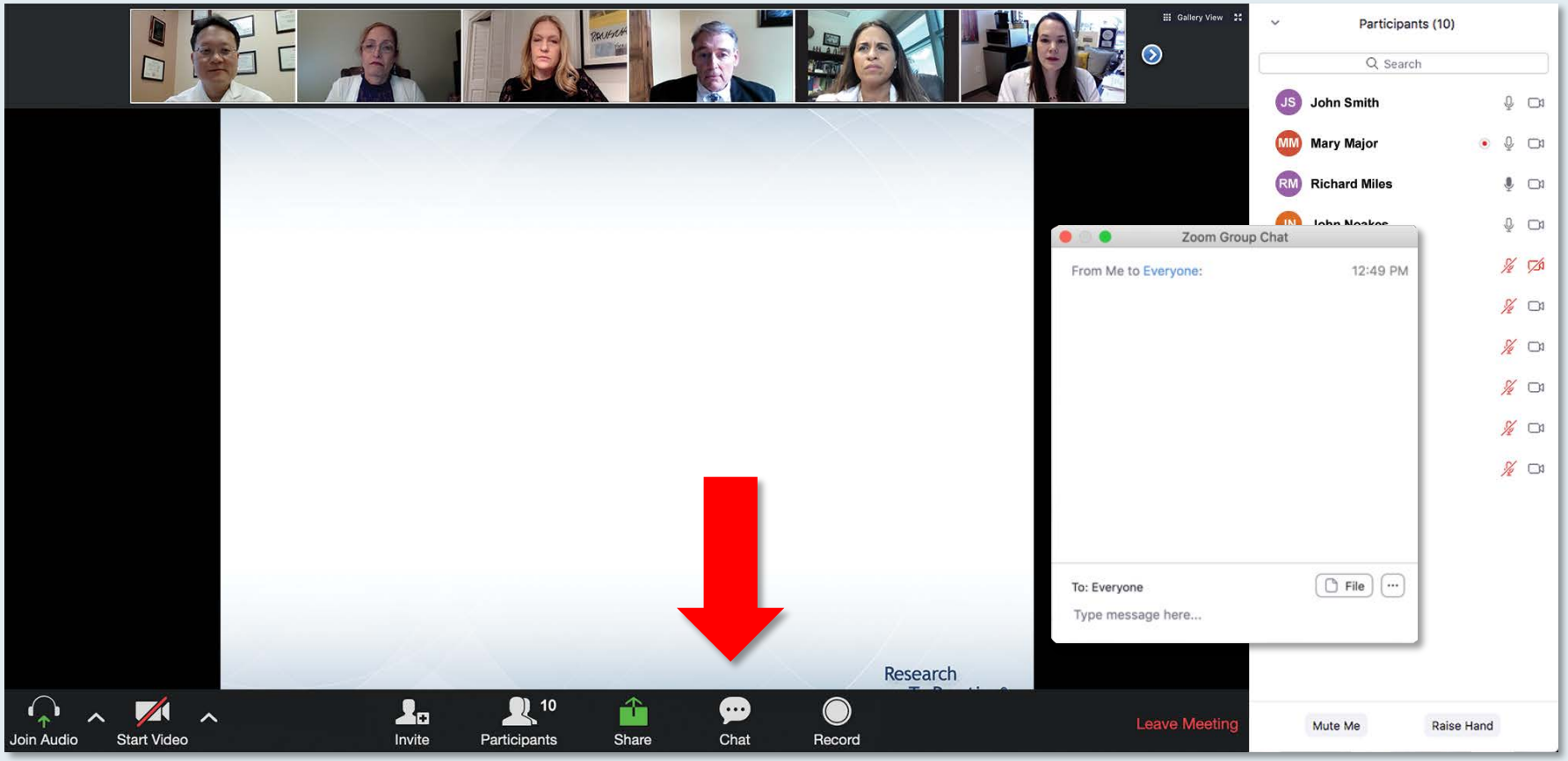
We Encourage Clinicians in Practice to Submit Questions



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

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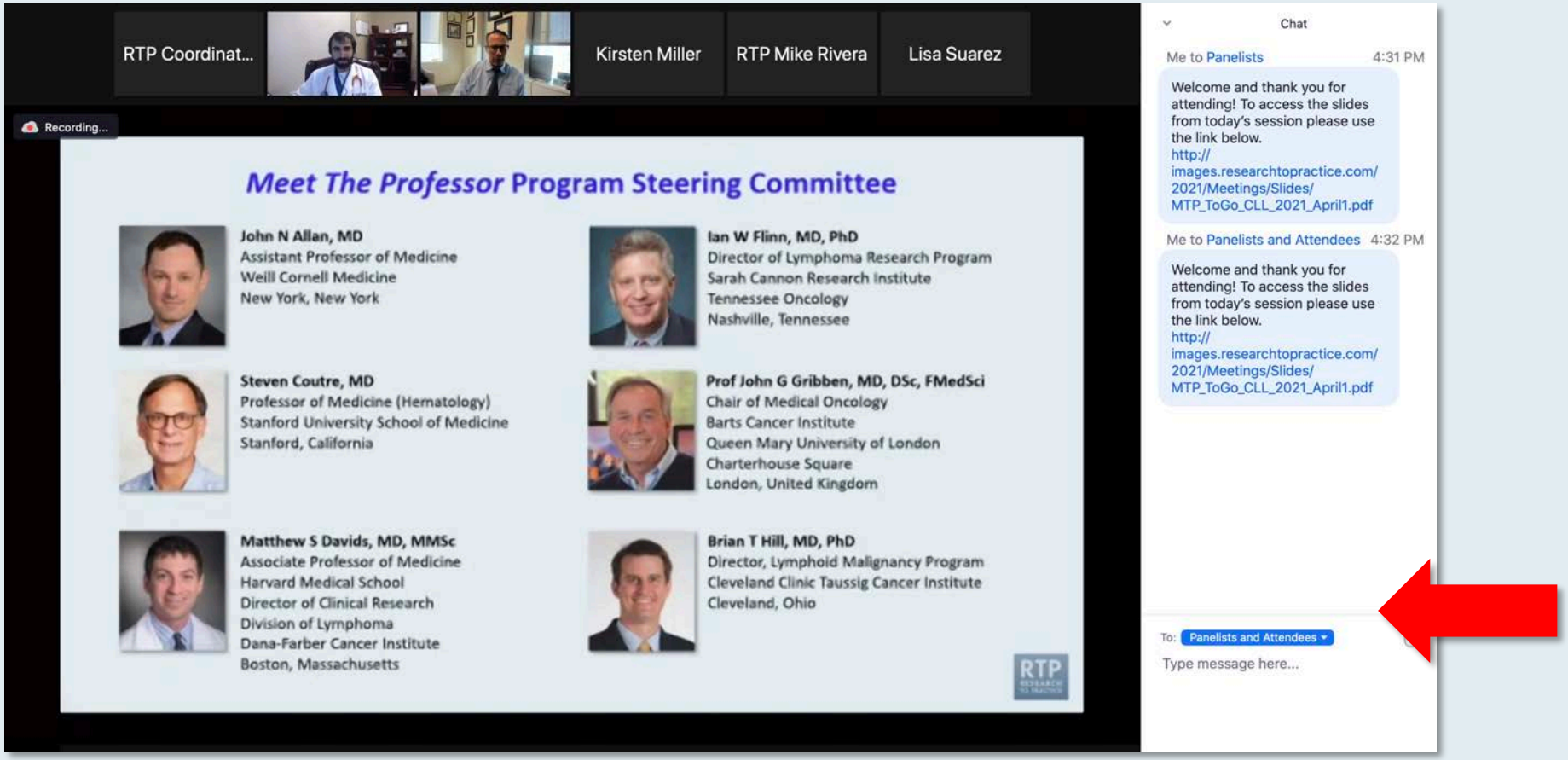
Familiarizing Yourself with the Zoom Interface

Expand chat submission box



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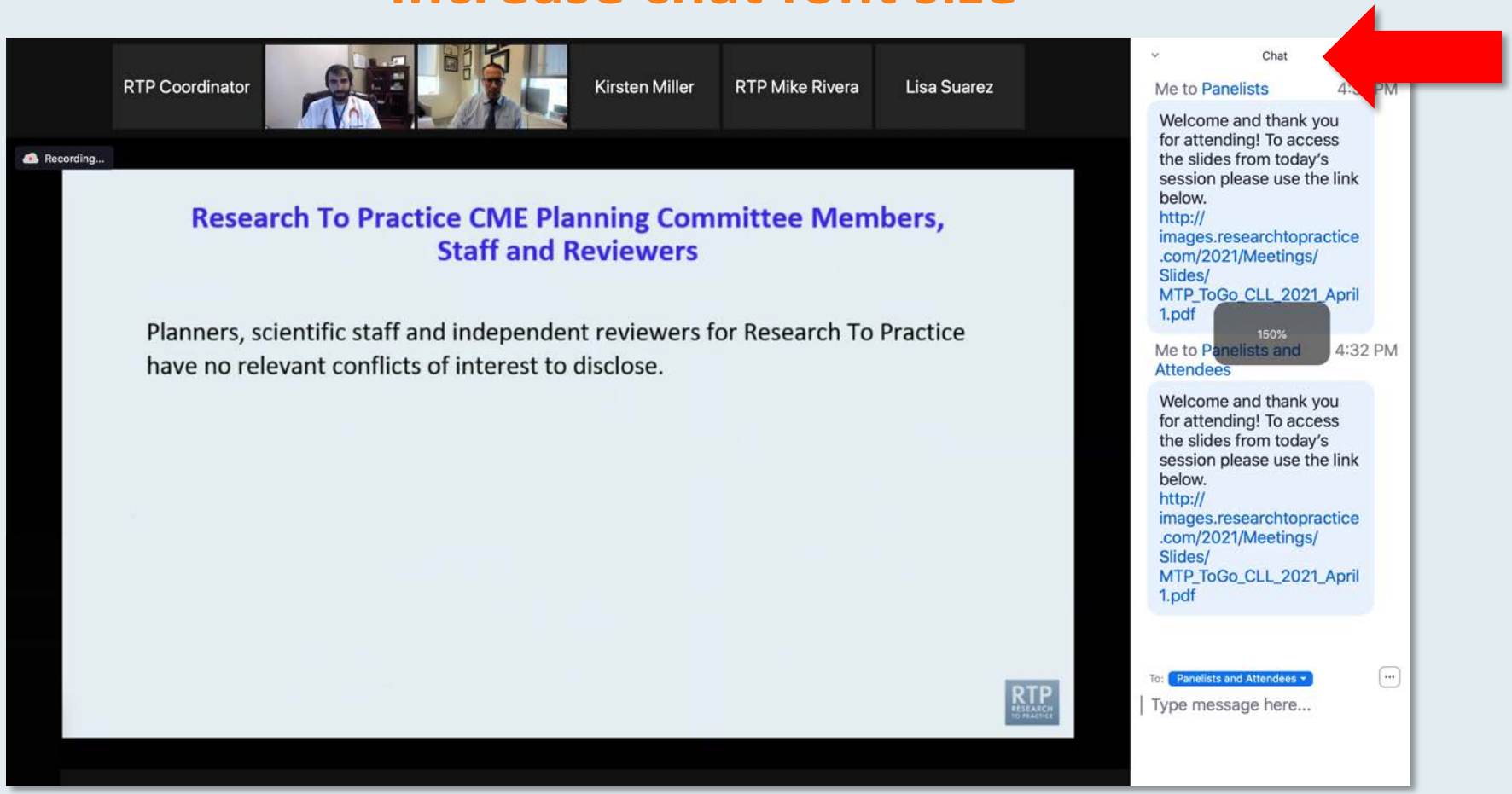

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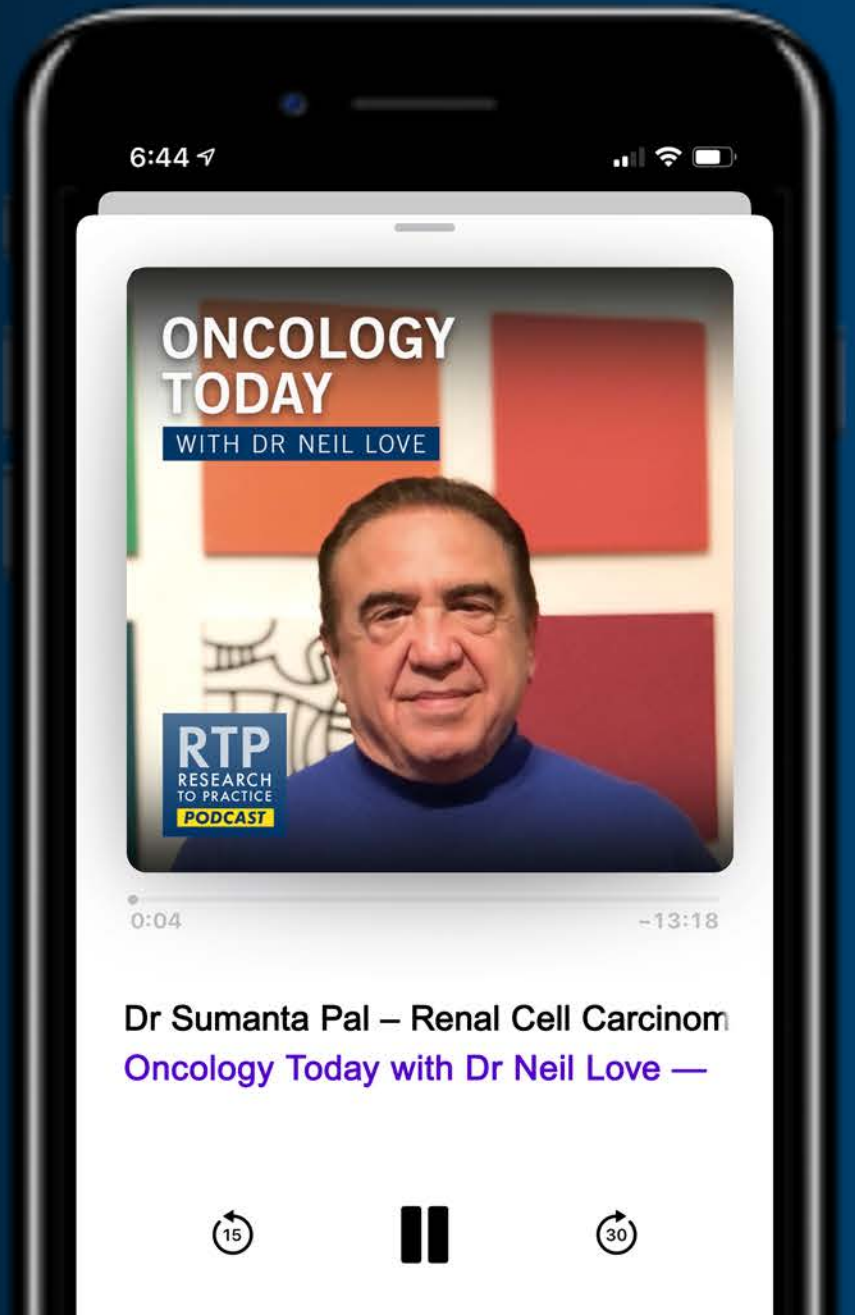

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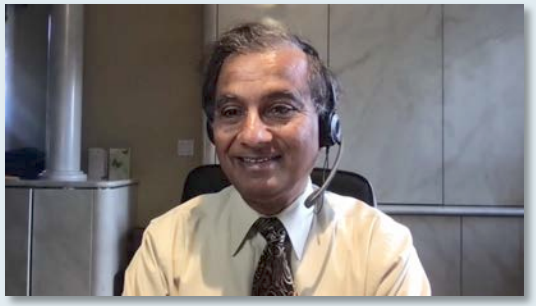

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Virtual Molecular Tumor Board: Optimizing Biomarker-Based Decision-Making for Patients with Non-Small Cell Lung Cancer with EGFR Mutations or with Other Oncogene-Addicted Lung Cancers

A 2-Part CME/MOC-Accredited Webinar Series

Role of Genomic Profiling for Patients with Non-Small Cell Lung Cancer (NSCLC) and the Optimal Application of Available Testing Platforms

Tuesday, October 26, 2021
5:00 PM – 6:00 PM ET

Guest Speaker
Joel W Neal, MD, PhD

New and Important Developments in the Management of NSCLC with EGFR Mutations or Other Novel Targets

Thursday, November 11, 2021
5:00 PM – 6:00 PM ET

Guest Speaker
Helena Yu, MD

Faculty

Marc Ladanyi, MD
Andrew J McKenzie, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Clinical Management of Hodgkin and Non-Hodgkin Lymphomas

Wednesday, October 27, 2021
5:00 PM – 6:00 PM ET

Faculty

Jonathan W Friedberg, MD, MMSc

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with ER-Positive Breast Cancer

Thursday, October 28, 2021
5:00 PM – 6:00 PM ET

Faculty

Matthew P Goetz, MD

Moderator

Neil Love, MD

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Meet The Professor

Management of BRAF-Mutant Melanoma

Monday, November 1, 2021
5:00 PM – 6:00 PM ET

Faculty

Prof Georgina Long, AO, BSc, PhD, MBBS

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Urothelial Bladder Carcinoma

Tuesday, November 2, 2021
5:00 PM – 6:00 PM ET

Faculty

Andrea Apolo, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with HER2-Positive Breast Cancer

Wednesday, November 3, 2021
5:00 PM – 6:00 PM ET

Faculty

Adam M Brufsky, MD, PhD

Moderator

Neil Love, MD

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Recent Advances and Future Directions in Oncology

A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists

Saturday, October 23, 2021
9:30 AM – 4:30 PM ET

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Agenda

Module 1 — Breast Cancer: *Drs Partridge and Pegram*

Module 2 — Lung Cancer: *Drs Sequist and Spigel*

Module 3 — Gastrointestinal Cancers: *Drs Bekaii-Saab and Ciombor*

Module 4 — Genitourinary Cancers: *Drs Agarwal and Petrylak*

Module 5 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Kahl and Zelenetz*

Module 6 — Multiple Myeloma: *Drs Raje and Usmani*

Module 7 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Levis and Sallman*

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Breast Cancer Faculty

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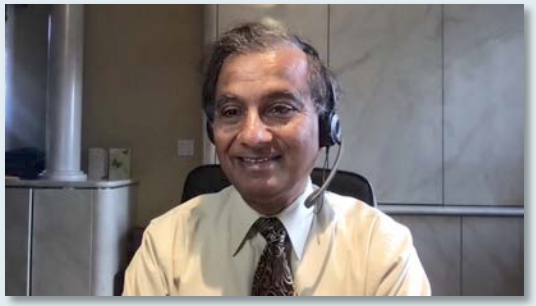

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Lowell L Hart, MD
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Agenda

Module 1: HER2-Positive

- Dr Zafar: A 48-year-old woman with ER/PR-negative, HER2-positive metastatic breast cancer (mBC)
- Dr Gandhi: A 76-year-old woman with ER-positive, PR-negative, HER2-positive mBC with bone and brain metastases
- Faculty Chalk Talks

Module 2: Hormone Receptor-Positive, HER2-Negative

- Dr Apuri: A 53-year-old woman with ER/PR-positive, HER2-negative mBC
- Dr Shameem: A premenopausal woman in her early 50s with ER/PR-positive, node-positive breast cancer
- Dr Apuri: A 62-year-old woman with ER/PR-positive breast cancer
- Faculty Chalk Talks

Module 3: Triple-Negative (TNBC)

- Dr Gandhi: A 52-year-old woman with increased creatinine after 2 years of olaparib for ovarian cancer
- Dr Choksi: A 63-year-old woman with asynchronous second primary TNBC
- Faculty Chalk Talks

Appendix: Selected Data Sets

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A 48-year-old woman with a self-palpated breast mass presents with jaundice. Biopsy is consistent with an ER-negative, HER2-positive IDC and blood work reveals alkaline phosphatase >400, ALT/AST >600 and bilirubin 2.5. Imaging shows widespread hepatic metastases. Regulatory and reimbursement issues aside, what would you recommend?

1. Capecitabine/trastuzumab +/- pertuzumab
2. AC → T/trastuzumab +/- pertuzumab
3. Taxane/trastuzumab +/- pertuzumab
4. T-DM1
5. Trastuzumab deruxtecan
6. Tucatinib + trastuzumab/capecitabine
7. Other

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Agenda

Module 1: HER2-Positive

- Dr Zafar: A 48-year-old woman with ER/PR-negative, HER2-positive metastatic breast cancer (mBC)
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- Faculty Chalk Talks

Module 2: Hormone Receptor-Positive, HER2-Negative

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Module 3: Triple-Negative (TNBC)

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- Dr Choksi: A 63-year-old woman with asynchronous second primary TNBC
- Faculty Chalk Talks

Appendix: Selected Data Sets

Case Presentation – Dr Zafar: A 48-year-old woman with ER/PR-negative, HER2-positive mBC

Dr Syed Zafar

- Left, grade III, ER/PR-negative, HER2-positive IDC
- Right breast fibrocystic changes/cystic apocrine metaplasia
- Germline testing: Negative
- Jaundiced, LFT: ALT/AST >600, Bilirubin 2.5, AI phos >400

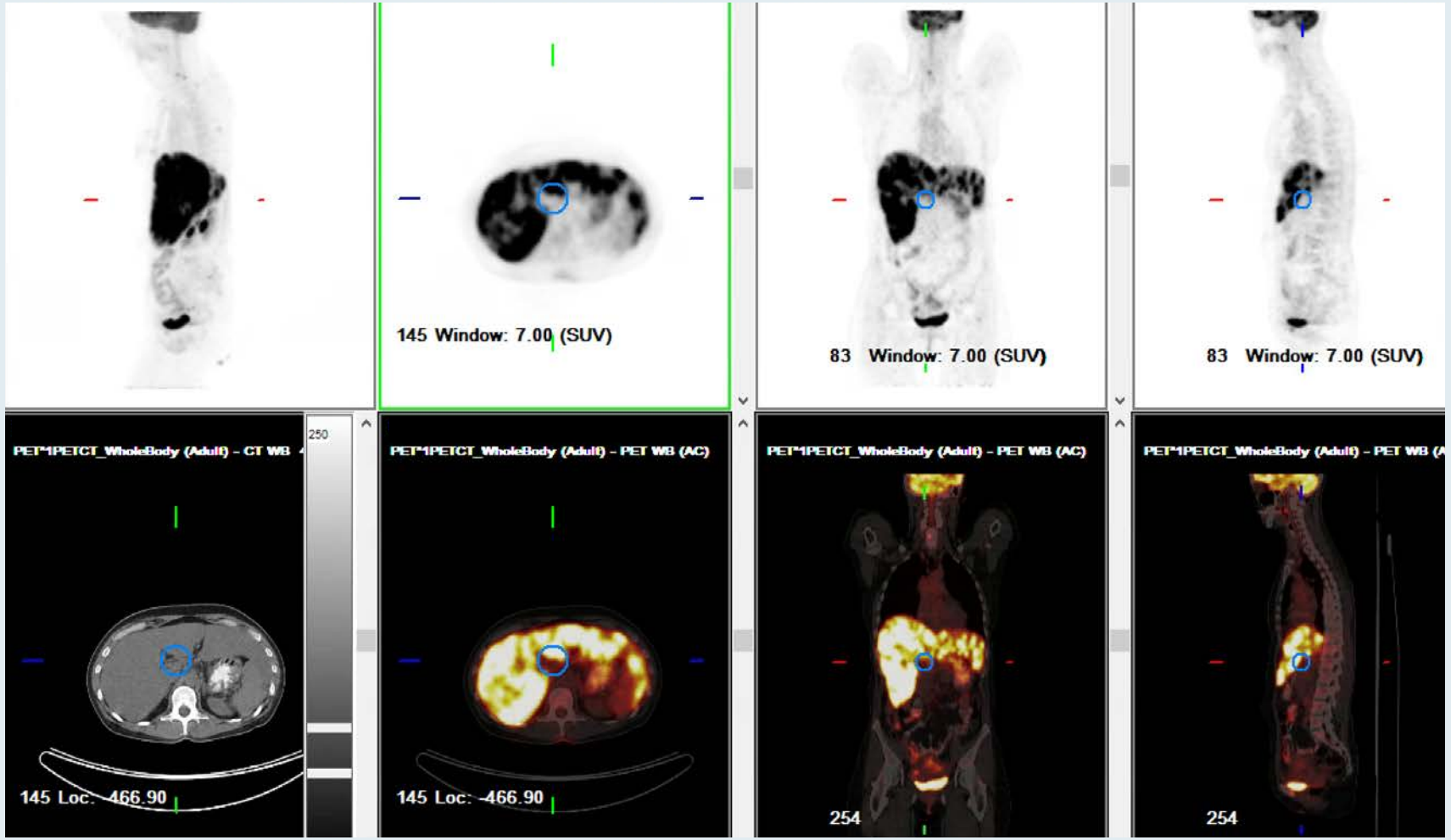
Questions

- What chemotherapy and anti-HER2 regimen should be administered?

Case Presentation – Dr Zafar: A 48-year-old woman with ER/PR-negative, HER2-positive mBC (continued)

Dr Syed Zafar

Initial Staging Scans



Case Presentation – Dr Zafar: A 48-year-old woman with ER/PR-negative, HER2-positive mBC (continued)

Dr Syed Zafar

- Left, grade III, ER/PR-negative, HER2-positive IDC
- Right breast fibrocystic changes/cystic apocrine metaplasia
- Germline testing: Negative
- Jaundiced, LFT: ALT/AST >600, Bilirubin 2.5, AI phos >400
- ***Capecitabine/trastuzumab/pertuzumab → Maintenance trastuzumab/pertuzumab***

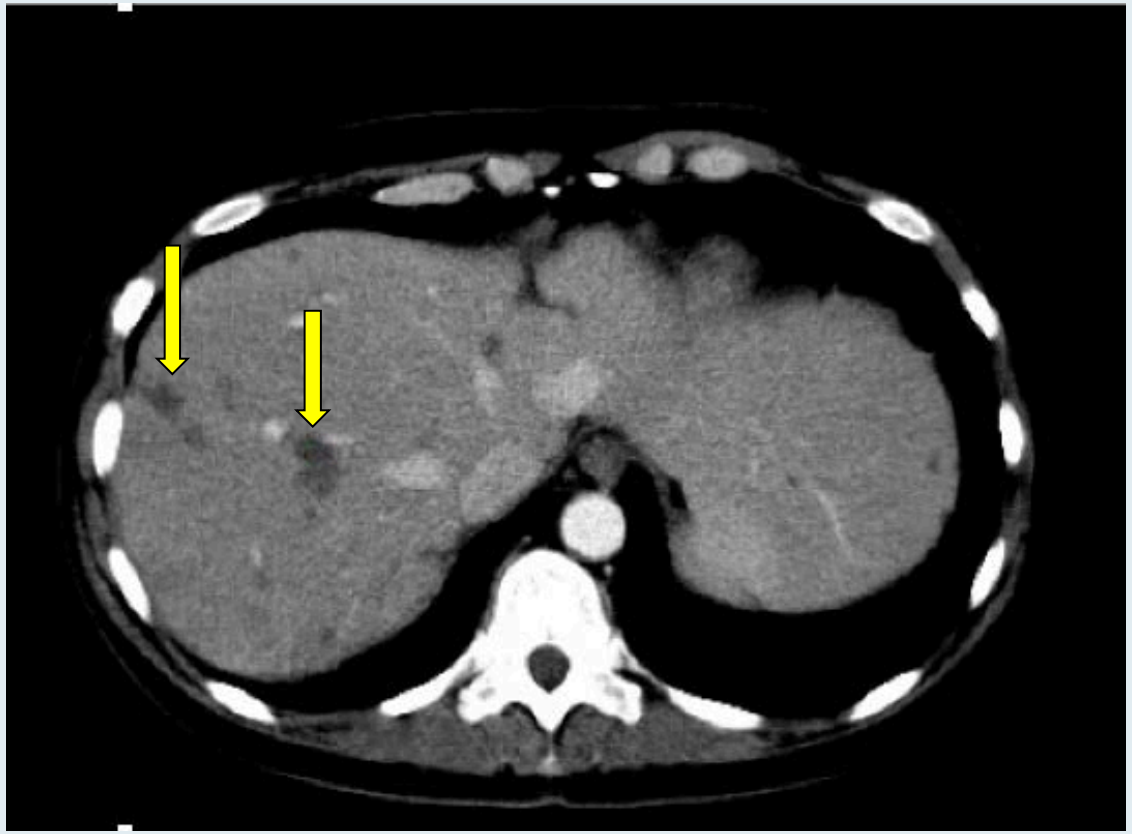
Questions

- ***Would you recommend resection of the primary breast tumor?***

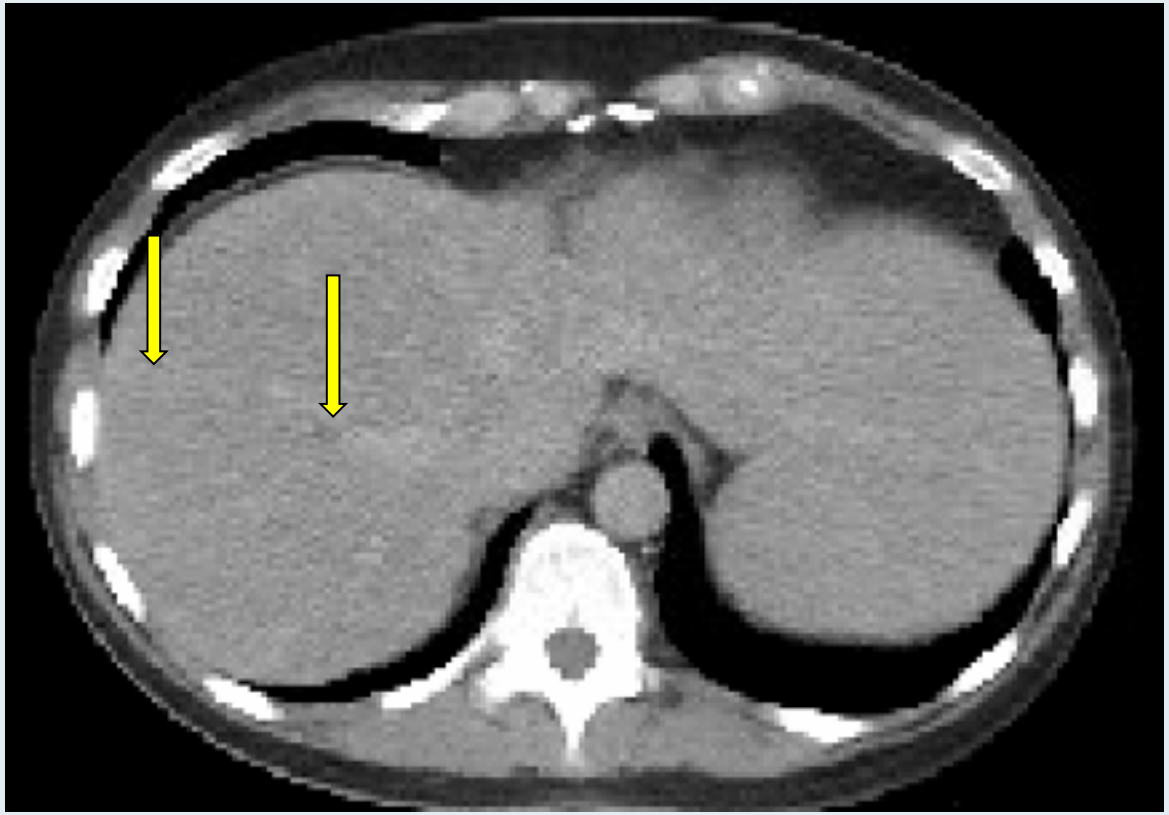
Case Presentation – Dr Zafar: A 48-year-old woman with ER/PR-negative, HER2-positive mBC (continued)

Dr Syed Zafar

Visceral crisis



CR after capecitabine/ trastuzumab/pertuzumab x 6



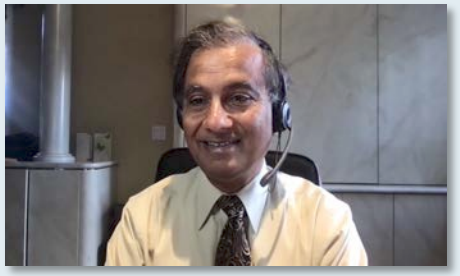
RTP RESEARCH TO PRACTICE

Mechanism of action, efficacy and safety of trastuzumab deruxtecan

Dr Elizabeth Guancial

RTP
RESEARCH
TO PRACTICE

Case Presentation – Dr Gandhi: A 76-year-old woman with ER-positive, PR-negative, HER2-positive mBC with bone and brain metastases



Dr Sunil Gandhi

- Inflammatory ER-positive, PR-negative, HER2-positive breast cancer with widespread bone metastases
- Weekly paclitaxel x 12 + pertuzumab/trastuzumab, with marked response
- Maintained on anastrozole and pertuzumab/trastuzumab
- Liver metastases → T-DM1, with marked response after 4 cycles
- Breast surgery
- Mental status changes → Multiple brain metastases → WBRT

Questions

- If I had given tucatinib, would it have made a difference combined with T-DM1 in a protocol study? Would that have prevented her brain metastases?

RTP RESEARCH TO PRACTICE

Phase III DESTINY-Breast03 trial evaluating trastuzumab deruxtecan versus T-DM1 as second-line therapy for metastatic HER2-positive breast cancer

- **FAM-trastuzumab deruxtecan (DS8201, TDxD) is a trastuzumab-based antibody drug conjugate with a fixed drug:antibody ratio (DAR) = 8, a peptide cleavable linker, and a novel (exatecan derivative) topoisomerase I inhibitor payload which boasts a bystander cell killing effect.**

- **This was the first report of DESTINY-Breast03 (NCT03529110), a multicenter, open-label, randomized phase 3 study comparing the efficacy and safety of T-DXd vs T-DM1 in pts with HER2+ mBC previously treated with trastuzumab and taxane. This is the first reported randomized study of T-DXd in BC.**

Phase III DESTINY-Breast03 trial evaluating trastuzumab deruxtecan versus T-DM1 as second-line therapy for metastatic HER2-positive breast cancer

- **As of May 21, 2021, 524 pts were randomized. Median age was 54 years (range, 20-83). The hazard ratio (HR) for PFS was 0.2840 (P = 7.8 x 10^{-22}); median PFS not reached for T-DXd vs 6.8 mo for T-DM1. The estimated 12-month OS event rates were 94.1% (95% CI, 90.3-96.4) for T-DXd and 85.9% (95% CI, 80.9-89.7) for T-DM1; HR: 0.5546 (95% CI, 0.3587-0.8576; P = 0.007172 did not cross pre-specified boundary for significance).**
- **Adjudicated drug-related interstitial lung disease (ILD) occurred in 10.5% of pts with T-DXd (most [9.7%] grade 1/2; 0 grade 4/5) vs 1.9% with T-DM1 (all grade 1/2).**
- **T-DXd demonstrated a highly statistically significant and clinically meaningful improvement in PFS vs T-DM1 in pts previously treated with trastuzumab and taxane for HER2+ mBC. These data confirm that T-DXd is tolerable with manageable toxicity and a significant improvement in ILD profile vs studies performed in more heavily pretreated pts. This study will lead to a paradigm shift in the treatment of HER2+ mBC.**

Neratinib as post-neoadjuvant/adjuvant treatment for HER2-positive breast cancer

- HER2 landscape complex, a number of agents approved in adjuvant setting: trastuzumab, pertuzumab, neratinib, TDM1

- ExteNET trial: RCT of neratinib, an irreversible pan-HER TKI, vs. placebo for 1 year after adjuvant trastuzumab
- 2-year invasive disease-free survival rate was 93·9% w/neratinib vs. 91·6% placebo (Chan et al, Lancet Onc, 2016)
  - Diarrhea (gr 3) in 40% on neratinib
  - Suggestion of greater improvement in ER+ disease
- At 5 years, absolute iDFS benefits (Chan et al, Clin Breast Ca, 2021)
  - 5.1% in HR^+/≤ 1-year (HR 0.58; 95% confidence interval [CI], 0.41-0.82)
  - 1.3% in HR^+/>1-year (HR 0.74; 95% CI, 0.29-1.84)
- At 8 years, OS absolute dif
  - 2.1% in HR^+/≤ 1-year (HR, 0.79; 95% CI, 0.55-1.13)
  - 9.1% in neoadjuvant therapy with residual disease (hazard ratio, 0.47; 95% CI, 0.23-0.92)
  - Fewer central nervous system events with neratinib

Agenda

Module 1: HER2-Positive

- Dr Zafar: A 48-year-old woman with ER/PR-negative, HER2-positive metastatic breast cancer (mBC)
- Dr Gandhi: A 76-year-old woman with ER-positive, PR-negative, HER2-positive mBC with bone and brain metastases
- Faculty Chalk Talks

Module 2: Hormone Receptor-Positive, HER2-Negative

- Dr Apuri: A 53-year-old woman with ER/PR-positive, HER2-negative mBC
- Dr Shameem: A premenopausal woman in her early 50s with ER/PR-positive, node-positive breast cancer
- Dr Apuri: A 62-year-old woman with ER/PR-positive breast cancer
- Faculty Chalk Talks

Module 3: Triple-Negative (TNBC)

- Dr Gandhi: A 52-year-old woman with increased creatinine after 2 years of olaparib for ovarian cancer
- Dr Choksi: A 63-year-old woman with asynchronous second primary TNBC
- Faculty Chalk Talks

Appendix: Selected Data Sets

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Apuri: A 53-year-old woman with ER/PR-positive, HER2-negative mBC

Dr Susmitha Apuri

- ER/PR-positive, HER2-negative left breast adenocarcinoma, with hepatic and skeletal metastases
- Letrozole/palbociclib, with response x 2.5 years
- Restaging PET/CT: Progression in liver and bone; Asymptomatic
- Liquid NGS: ESR1 D538G mutation, AR 1+, TMB 8.6 mut/Mb

Questions

- Would you use fulvestrant alone?
- Could we replace the exemestane that we use with everolimus, with fulvestrant?
- Does AR positivity provide additional treatment options?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Shameem: A premenopausal woman in her early 50s with ER/PR-positive, node-positive x 1 breast cancer

Dr Raji Shameem

- S/p surgery for ER/PR-positive, HER2-negative, node-positive x 1 breast cancer
- Onco*type* DX® RS = 16
- Adjuvant hormonal therapy with GnRH analogue

Case Presentation – Dr Apuri: A 62-year-old woman with ER/PR-positive breast cancer

Dr Susmitha Apuri

- Breast cancer at age 49, s/p lumpectomy and radiation therapy
- Presents now with second breast cancer in the contralateral breast
- ER/PR-positive, HER2-negative with a PALB2 mutation
- Bilateral mastectomy → Chemotherapy x 4 → Endocrine therapy

Question

- Would she be a candidate for olaparib?

Use of the 21 gene Recurrence Score® and other genomic assays in node-positive localized ER-positive breast cancer

- **The RxPONDER (Rx for POsitive Node, Endocrine Responsive Breast Cancer) clinical trial was a prospective trial involving 10,273 women with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, axillary node–negative breast cancer. Of the 9,719 eligible patients with follow-up information, 6,711 (69%) had a midrange recurrence score of 11 to 25 and were randomly assigned to receive either chemoendocrine therapy or endocrine therapy alone.**

- **The main objective of RxPONDER was to answer the question, “Can the 21-gene RS be used to identify patients with 1-3+ LNs who do not benefit from systemic adjuvant chemotherapy?”**

- **Endocrine therapy was noninferior to chemoendocrine therapy in the analysis of invasive disease–free survival (hazard ratio for invasive disease recurrence, second primary cancer, or death [endocrine vs. chemoendocrine therapy], 1.08; 95% confidence interval, 0.94 to 1.24; P=0.26). At 9 years, the two treatment groups had similar rates of invasive disease–free survival (83.3% in the endocrine-therapy group and 84.3% in the chemoendocrine-therapy group), freedom from disease recurrence at a distant site (94.5% and 95.0%) or at a distant or local–regional site (92.2% and 92.9%), and overall survival (93.9% and 93.8%). The chemotherapy benefit for invasive disease–free survival varied with the combination of recurrence score and age (P=0.004), with some benefit of chemotherapy found in women 50 years of age or younger with a recurrence score of 16 to 25.**
- **Postmenopausal women with 1-3+ LNs did not benefit from adjuvant chemotherapy in any subgroup (5-year adjusted iDFS HR = 0.97, 95% CI 0.78 – 1.22; p = 0.82). By contrast, in the premenopausal subset, the 5-year iDFS absolute difference was 5.2% (iDFS adjusted HR = 0.54; 95% CI 0.38-0.76; p = 0.0004).**

Selection of a first line CDK4/6 inhibitor for patients with metastatic ER-positive breast cancer

- ET backbone: Tamoxifen, AI's, SERD
- Targeted tx partner options (in order of appearance):
  - Everolimus, CDK 4/6 (palbociclib, abemaciclib, ribociclib), alpelisib

		PFS with AI first line	OS
• CDK 4/6 data for benefit-			
• **Palbo**	**PALOMA**-1, **2**, 3	28 vs 15 mos	Pending
• **Ribo**	**MONALEESA-2**, 3, 7	23 vs 16 mos	NS (sig in -7 with OS)
• **Abema**	**MONARCHE**-2, **3**	28 vs 15 mos	Pending

- Which CDK 4/6?
  - Dosing and Tolerance
    - Palbo- qD 1-21, 7 days off: neutropenia, fatigue
    - Ribo- qD 1-21, 7 days off: neutropenia, incr Cr, QTc prolongation
    - Abema- BID, continuous: GI issues, diarrhea, fatigue
  - Single agent need: abema demonstrated ~40% clinical benefit rate as single agent
  - CNS disease: abema has demonstrated CNS BBB penetration and benefit

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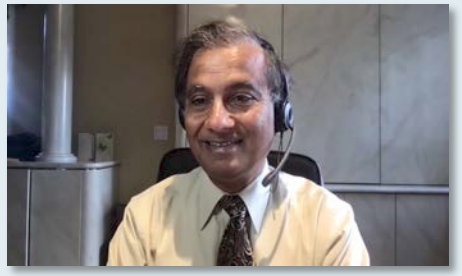
RTP RESEARCH TO PRACTICE

Case Presentation – Dr Gandhi: A 52-year-old woman with increased creatinine after 2 years of olaparib for ovarian cancer



Dr Sunil Gandhi

- Diagnosed with ovarian cancer, BRCA2 mutation-positive
- Olaparib administered
- After 2 years of olaparib therapy, her creatinine levels began to increase
- Consultation with nephrologist and all work-up studies have been negative
- Dose-reduced olaparib

Questions

- Is the increase in creatinine levels observed an actual increase that I should be concerned about?
- Is it appropriate to have dose-reduced the olaparib in response to the increased creatine levels?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Choksi: A 63-year-old woman with asynchronous second primary TNBC

Dr Mamta Choksi

- 2014: ER/PR-negative, HER2-positive, node-positive left breast cancer, s/p mastectomy and AC → paclitaxel/trastuzumab
- 2021: Contralateral right TNBC
- Carboplatin/paclitaxel/pembrolizumab

Questions

- What are your thoughts on adjuvant chemoimmunotherapy for a patient with TNBC who cannot receive more doxorubicin?

RTP RESEARCH TO PRACTICE

Phase III KEYNOTE-522 study: Anti-PD-1/PD-L1 antibody in combination with chemotherapy as neoadjuvant treatment followed by pembrolizumab adjuvant monotherapy for localized TNBC

- **The efficacy of pembrolizumab in combination with neoadjuvant chemotherapy followed by surgery and continued adjuvant treatment with pembrolizumab as a single agent was investigated in KEYNOTE-522 (NCT03036488), a randomized (2:1 randomization to pembrolizumab), multicenter, double-blind, placebo-controlled trial conducted in 1,174 patients with newly diagnosed previously untreated high-risk early-stage TNBC (tumor size >1 cm but ≤2 cm in diameter with nodal involvement or tumor size >2 cm in diameter regardless of nodal involvement). Patients were enrolled regardless of tumor PD-L1 expression.**
- **February 9, 2021 ODAC voted 10-0 to <u>wait</u> on approval of (neo)/neoadjuvant pembrolizumab in high-risk TNBC.**
- **At that time, the most recent interim analysis (N = only 602 of the planned 1,174) of KEYNOTE-522 indicated that the pCR rate difference between the two treatment arms was only 7.5% (95% CI: 1.6%, 13.4%) based on *ALL* randomized patients, <u>NOT</u> 13.6% reported in a NEJM interim analysis [Schmid P, et al. N Engl J Med 2020; 382:810-821].**
- **EFS endpoint had NOT met its pre-specified threshold for statistical significance and remained immature with only 53% of targeted EFS events having occurred.**

- **Moreover, patients who received pembrolizumab compared to placebo experienced immune-mediated adverse events (AEs) or infusion reactions, and there were four deaths in patients who received pembrolizumab which were potentially due to immune-mediated AEs.**
- **Increased immune-mediated AEs (some of which may be severe, irreversible, and/or require life-long medication) occurred in potentially curable and otherwise healthy patients.**
- **Subsequently, based upon another updated data analysis, on July 26, 2021 the Food and Drug Administration *approved* pembrolizumab for high-risk, early-stage, triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.**
- **The pCR rate was 63% (95% CI: 59.5, 66.4) for patients who received pembrolizumab in combination with chemotherapy compared with 56% (95% CI: 50.6, 60.6) for patients who received chemotherapy alone. The number of patients who experienced an EFS event was 123 (16%) and 93 (24%), respectively (HR 0.63; 95% CI: 0.48, 0.82; p=0.00031).**

Phase III OlympiA trial evaluating adjuvant olaparib in localized BRCA1- or BRCA2-mutated breast cancer; clinical implications

- Metastatic studies led to approval of olaparib and talazoparib: improvements in PFS and QOL, not OS
- NeoTala study yielded impressive ~50% pCR rates in TNBC (Litton et al ASCO 2021)

- OlympiA- RCT 1 year adjuvant olaparib vs placebo (Tutt et al, NEJM 2021)
  - High risk disease, HER2 negative disease
  - Median f/u of 2.5 years
    - 3-year iDFS 86% vs. 77% (9% absolute difference) HR for inv disease or death 0.58
    - 3-year dDFS 88% vs. 80% (8% absolute difference), HR for inv disease or death 0.57
    - Fewer deaths on Olaparib: HR 0.68 but not significant at <0.01 required
    - No excess SAEs and QOL effects limited effects

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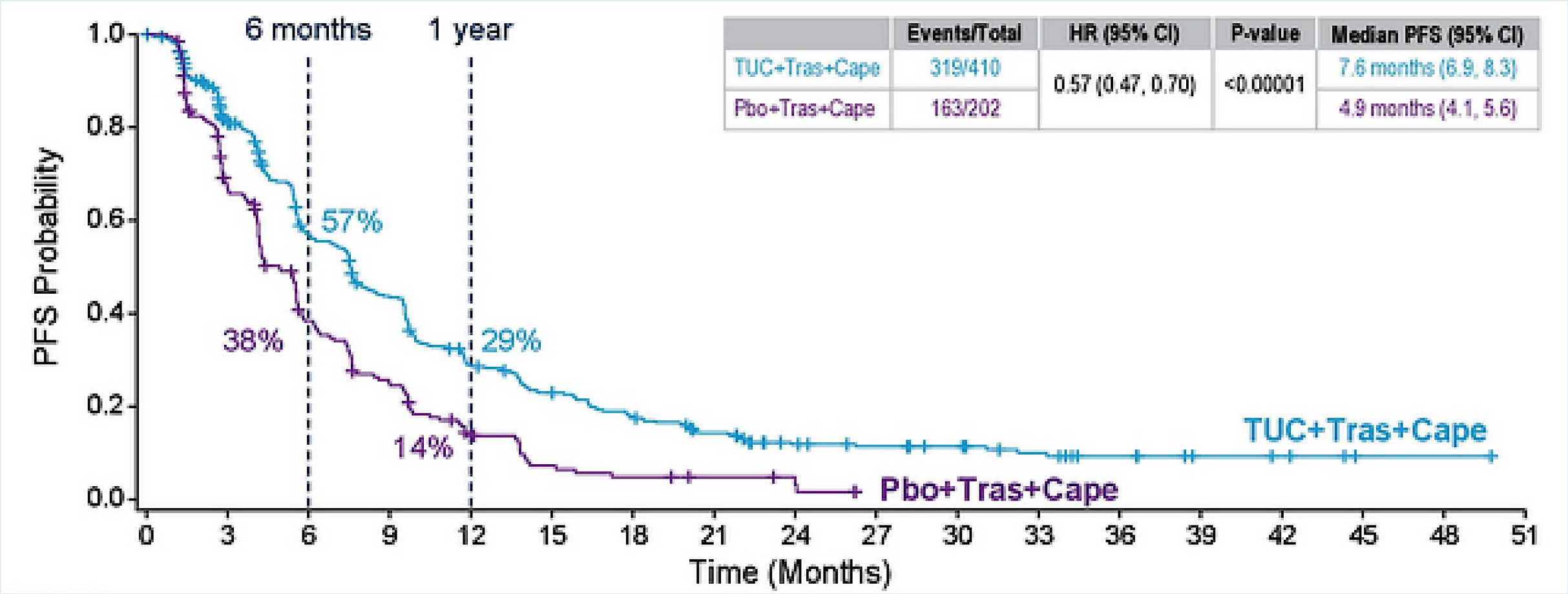
RTP RESEARCH TO PRACTICE

HER2-Positive

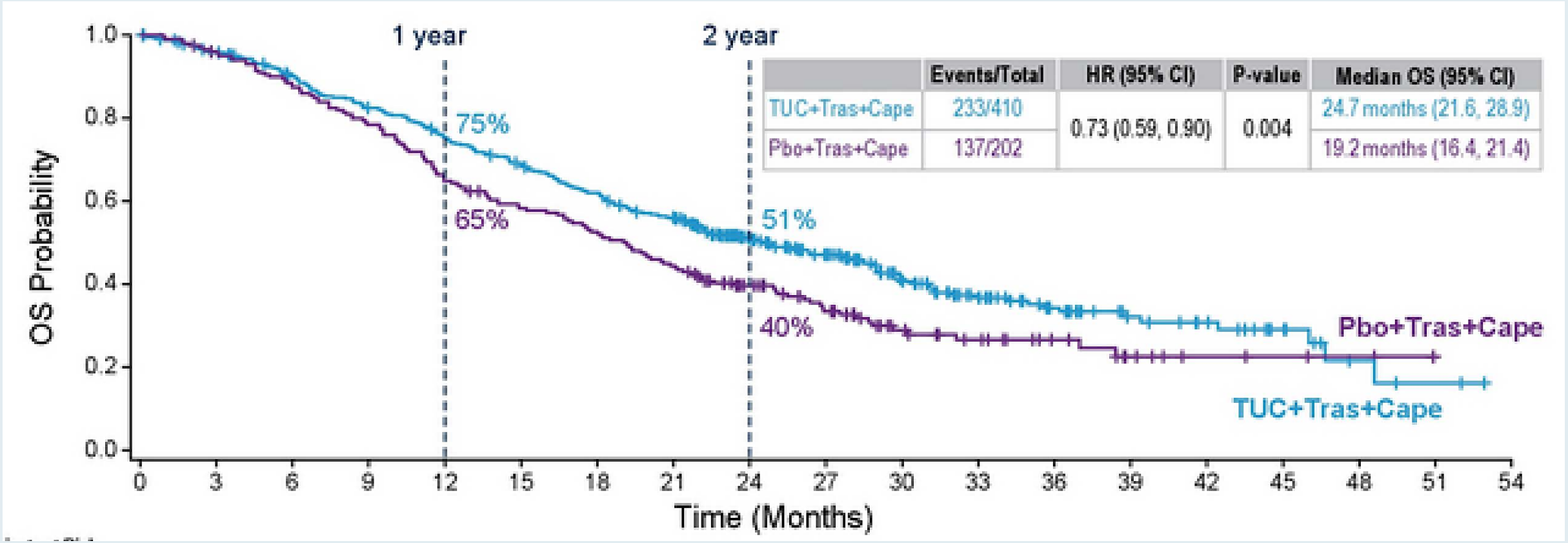
HER2CLIMB: Progression-Free Survival with Trastuzumab, Tucatinib and Capecitabine



	Events/Total	HR (95% CI)	P-value	Median PFS (95% CI)
TUC+Tras+Cape	319/410	0.57 (0.47, 0.70)	<0.00001	7.6 months (6.9, 8.3)
Pbo+Tras+Cape	163/202			4.9 months (4.1, 5.6)

Curigliano G et al. ASCO 2021;Abstract 1043.

HER2CLIMB: Overall Survival with Trastuzumab, Tucatinib and Capecitabine



	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	233/410	0.73 (0.59, 0.90)	0.004	24.7 months (21.6, 28.9)
Pbo+Tras+Cape	137/202			19.2 months (16.4, 21.4)

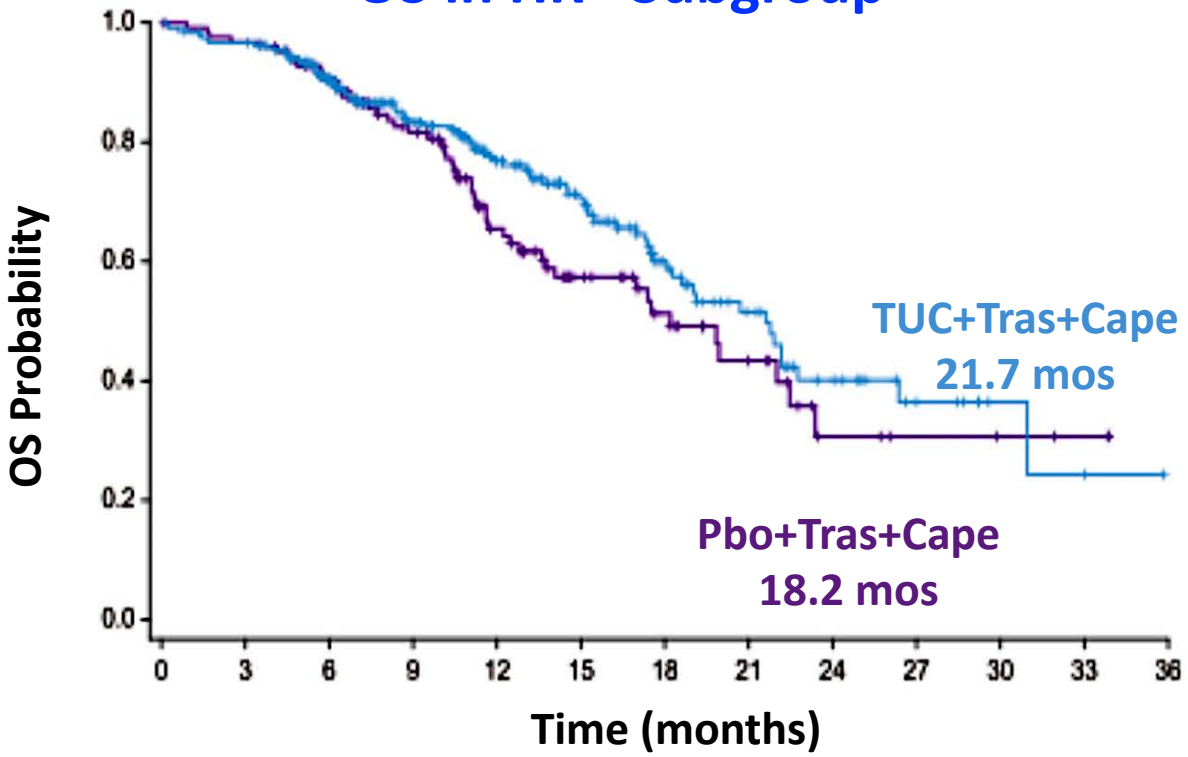
Curigliano G et al. ASCO 2021;Abstract 1043.

RTP RESEARCH TO PRACTICE

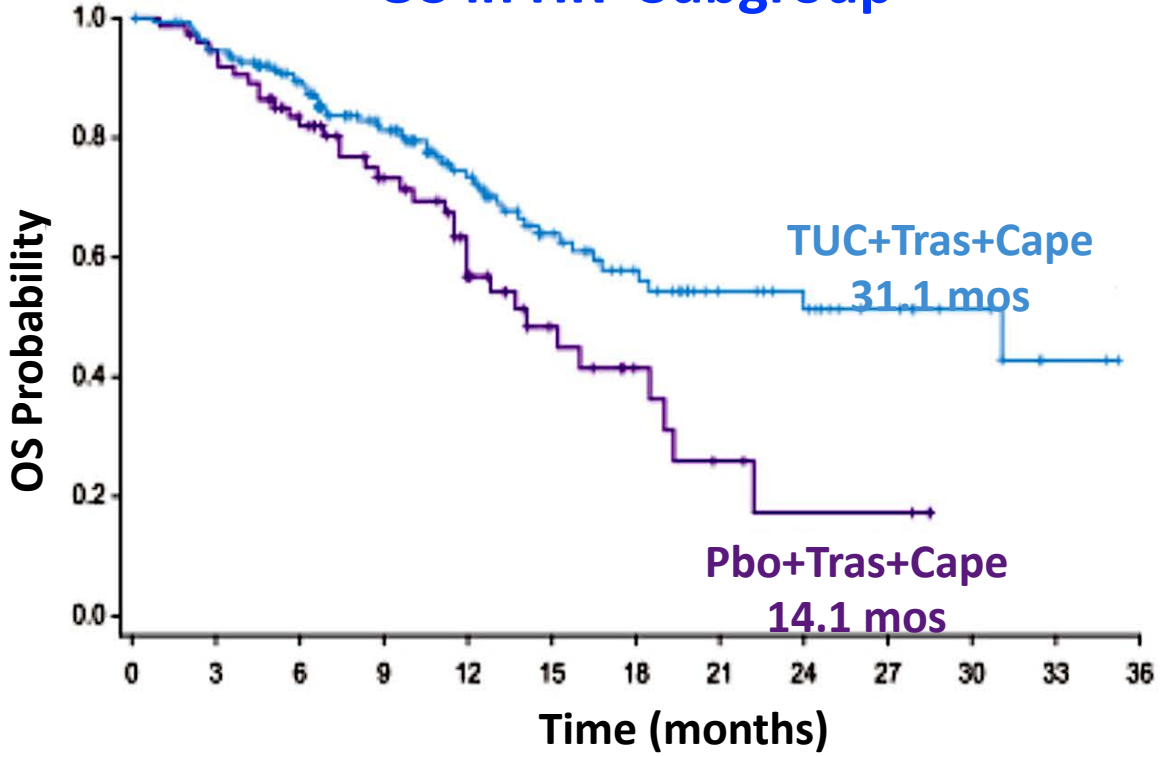
Overall Survival by HR Status in the Total Study Population

- Clinically meaningful improvement of OS was observed in patients on the tucatinib arm regardless of hormone receptor status.

OS in HR+ Subgroup



OS in HR- Subgroup



Hamilton E et al. SABCS 2020;Abstract PD3-08.

RTP RESEARCH TO PRACTICE

Hormone Receptor-Positive, HER2-Negative

FDA Approves Adjuvant Abemaciclib with Endocrine Therapy for Early Breast Cancer

Press Release: October 12, 2021

"The Food and Drug Administration approved abemaciclib with endocrine therapy (tamoxifen or an aromatase inhibitor) for adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20%, as determined by an FDA approved test. This is the first CDK 4/6 inhibitor approved for adjuvant treatment of breast cancer.

FDA also approved the Ki-67 IHC MIB-1 pharmDx assay as a companion diagnostic for selecting patients for this indication.

Efficacy was evaluated in monarchE (NCT03155997), a randomized (1:1), open-label, two-cohort multicenter trial that included adult women and men with HR-positive, HER2-negative, node-positive, resected, early breast cancer with clinical and pathological features consistent with a high risk of disease recurrence."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-abemaciclib-endocrine-therapy-early-breast-cancer

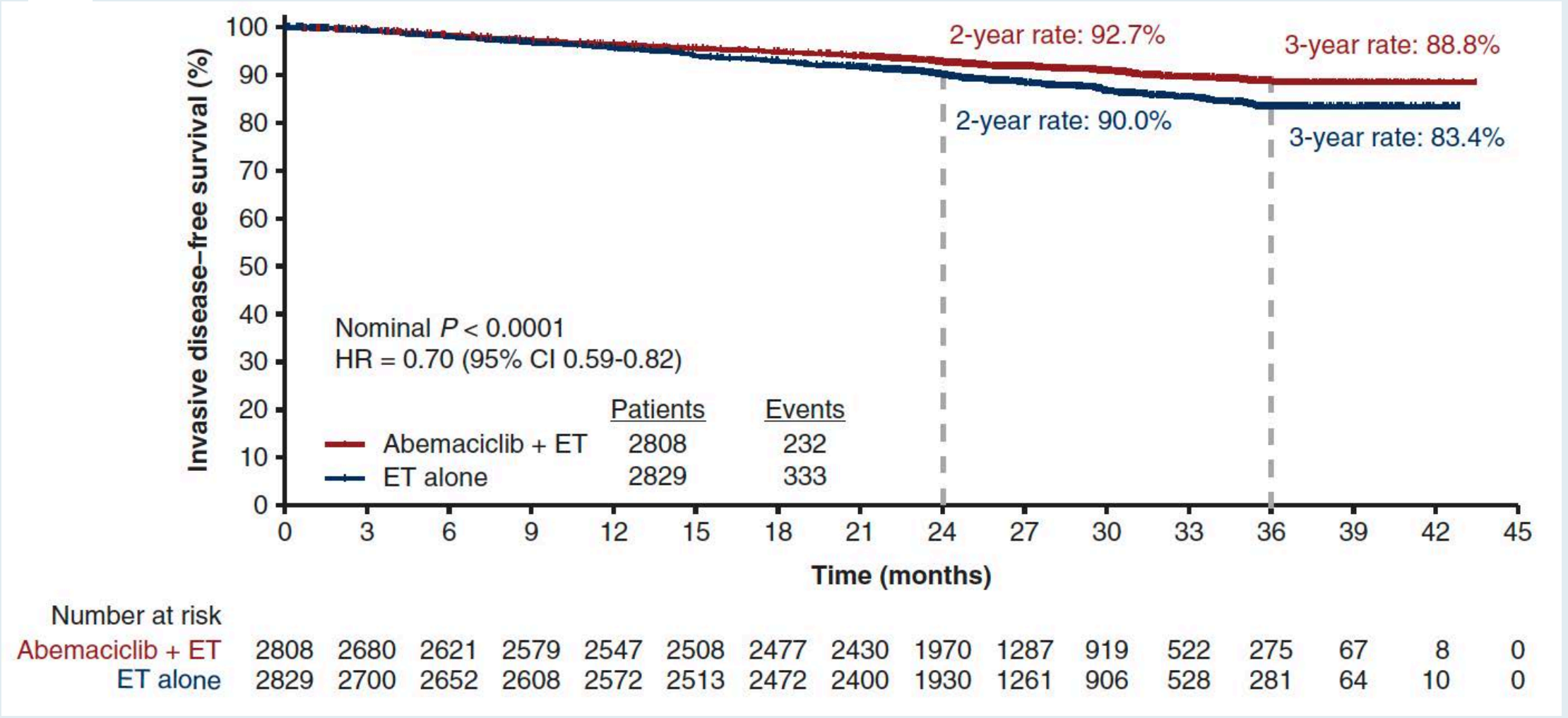
Abemaciclib Indications and Use

- in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA approved test. (1.1, 2.1, 14.1)
- in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. (1.2)
- in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. (1.2)
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. (1.2)

Revised: 10/2021

Abemaciclib package insert, accessed October 22, 2021.

monarchE: Invasive Disease-Free Survival in the Intent-to-Treat (ITT) Population with Adjuvant Abemaciclib



Harbeck N et al. *Ann Oncol* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Why are the results different from other adjuvant trials?

	PENELOPE-B	PALLAS	MONARCH-E
Sample Size	1250	5600	5637
Study population	High risk	Moderate-high risk	High risk
Study drug (duration)	Palbociclib (1 year)	Palbociclib (2 years)	Abemaciclib (3 years)
IDFS Results, Hazard Ratio (95%CI)	0.93 (0.76-1.15)	0.93 (0.74-1.17)	0.69 (0.58-0.82)
3- year IDFS (p-value)	81.2% vs. 77.7% (NS)	88.2% vs. 88.5% (NS)	88.8% vs 83.4% (<0.0001)
% Discontinued study treatment	17.5%	42.2%	17.4%
Duration of follow up	42.8 month	23.7 month	27.1 month

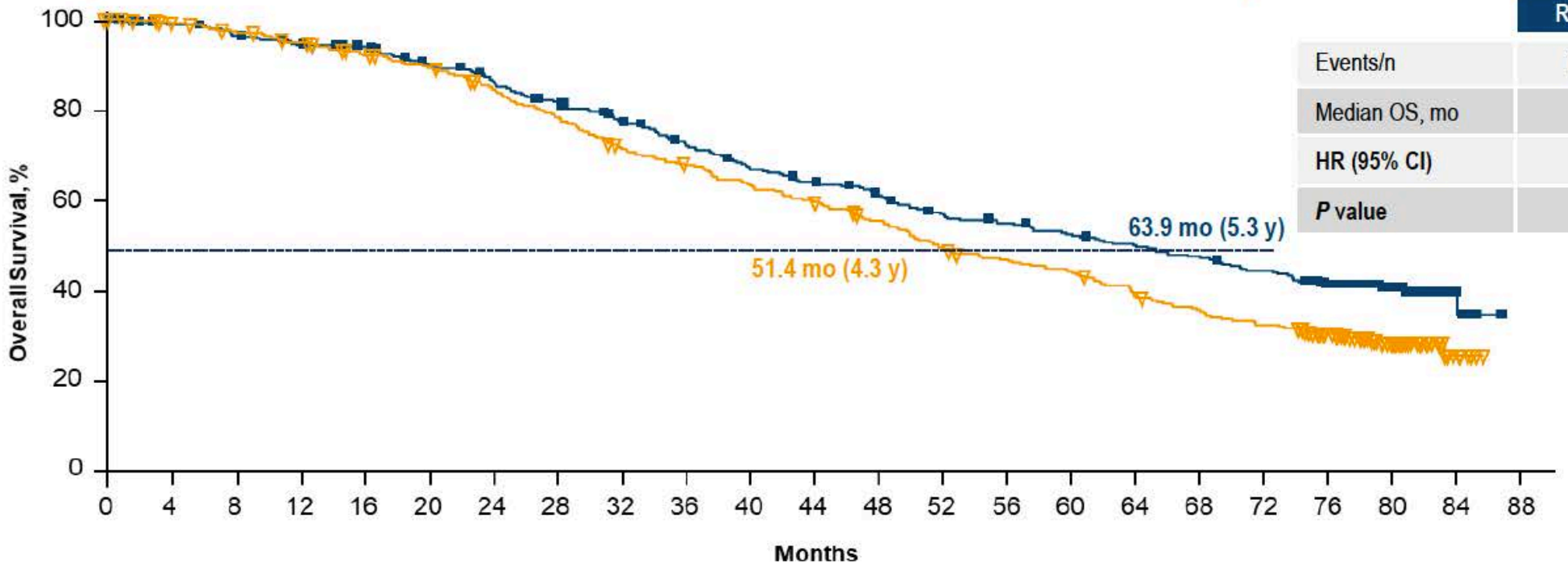
- Higher risk population
  - In PALLAS, no benefit with Palbociclib in patients with N2/N3 disease (HR:0.89, 95%CI: 0.68-1.17); however, subset analysis and need to exert appropriate caution
- % of discontinuation
  - In PALLAS, no significant differences based on dose exposure noted; however, power limited by few events

NS = Not statistically significant; IDFS = Invasive disease-free survival: CI = Confidence Interval

Loibl S et al, Breast 2021. O'Shaughnessy et al, ESMO plenary 2021.

MONALEESA-2: Overall Survival

Improvement in median OS was 12.5 months with ribociclib plus letrozole



	RIB + LET	PBO + LET
Events/n	181/334	219/334
Median OS, mo	63.9	51.4
HR (95% CI)	0.76 (0.63-0.93)	
P value	.004	

No. at risk

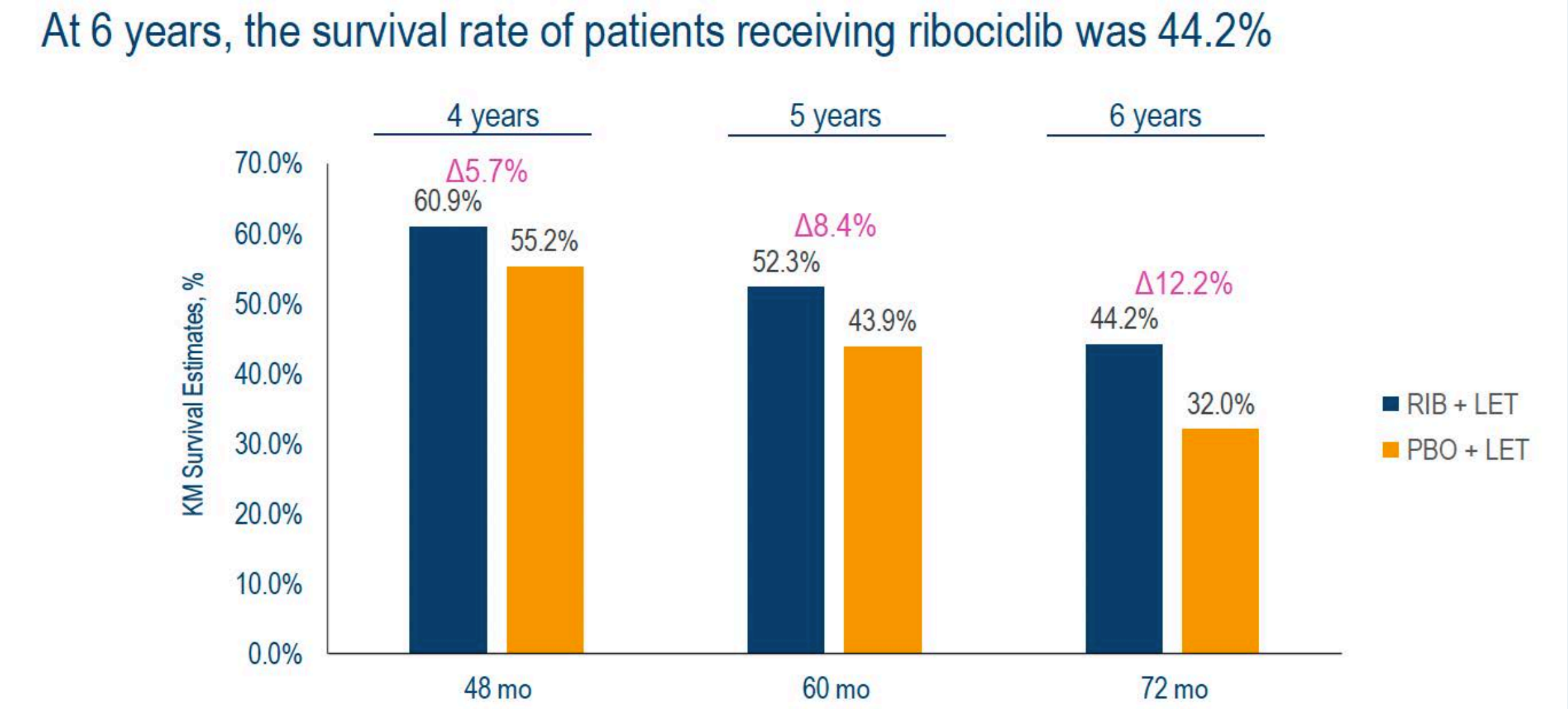
RIB + LET	334	323	315	305	300	284	270	253	237	220	202	191	180	165	158	150	142	135	125	101	48	8	0
PBO + LET	334	326	316	306	293	283	265	244	222	209	195	183	167	149	139	131	114	104	94	73	38	6	0

The P value of .004 crossed the prespecified boundary to claim superior efficacy

Hortobagyi GN et al. ESMO 2021;Abstract LBA17_PR.

RTP RESEARCH TO PRACTICE

MONALEESA-2: The Overall Survival Benefit Increased Over Time



Hortobagyi GN et al. ESMO 2021;Abstract LBA17_PR.

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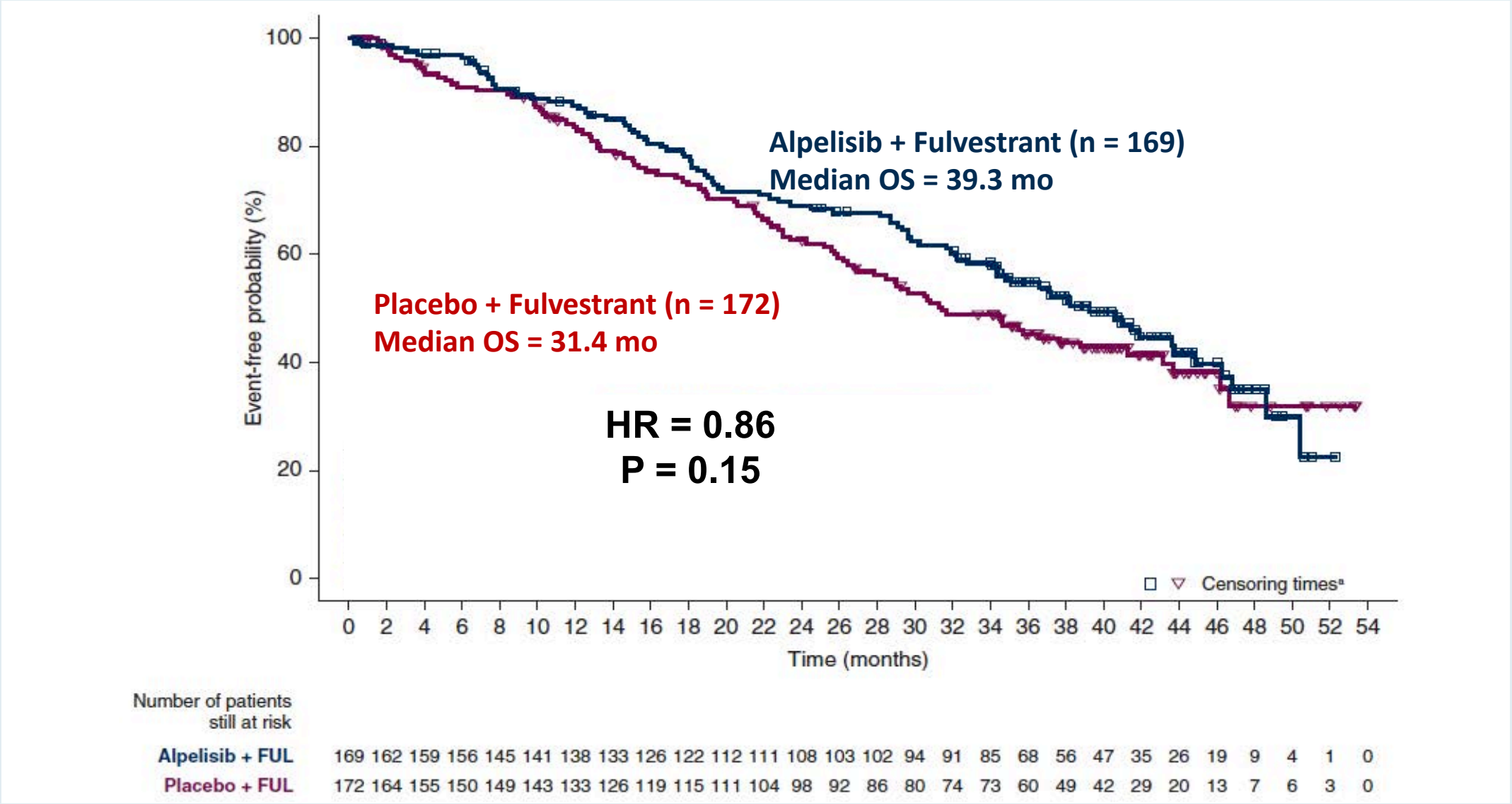
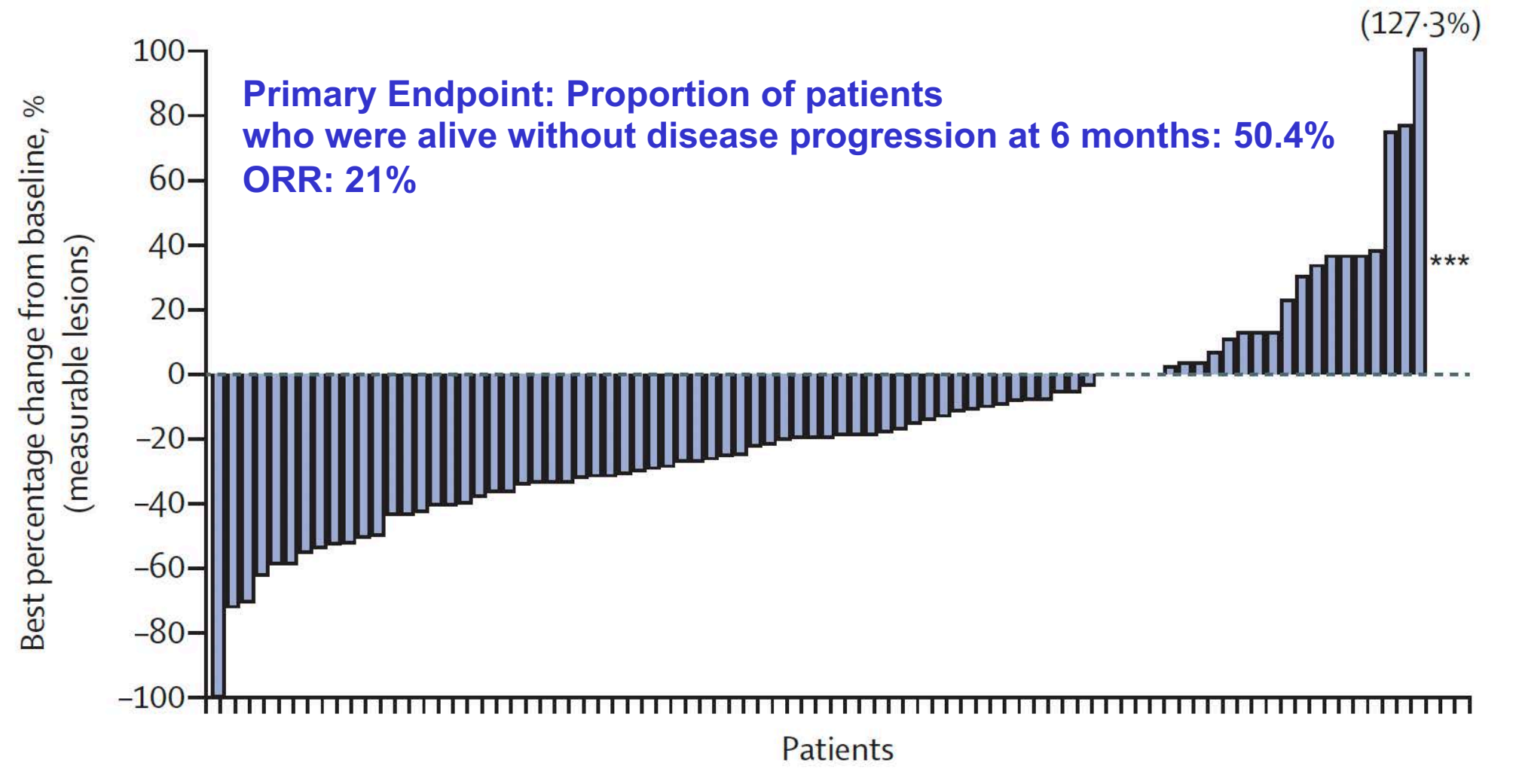
SOLAR-1: OS for Patients with Advanced Breast Cancer and a PIK3CA Mutation Receiving Alpelisib/Fulvestrant



André F et al. *Ann Oncol* 2021;32(2):208-17.

BYLieve: Efficacy Outcomes with Fulvestrant/Alpelisib for Patients with Disease Progression on a CDK4/6 Inhibitor



Rugo HS et al. *Lancet Oncol* 2021;22:489-98.

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Select Ongoing Phase II/III Trials of Oral SERDs in Development for ER-Positive, HER2-Negative Advanced Breast Cancer

Drug	Trial name (phase)	Treatment arms	Setting	Estimated study completion date
Amcenestrant (SAR439859)	AMEERA-3 (Phase II)	• Amcenestrant • Endocrine monotherapy	Prior hormonal tx	July 2025
Amcenestrant (SAR439859)	AMEERA-5 (Phase III)	• Amcenestrant + Palbociclib • Letrozole + Palbociclib	Untreated ABC	May 2027
Camizestrant (AZD9833)	SERENA-4 (Phase III)	• Camizestrant + Palbociclib • Anastrozole + Palbociclib	Untreated ABC	February 2029
Elacestrant (RAD-1901)	EMERALD (Phase III)	• Elacestrant • SoC	Prior CDK4/6 inhibitor tx + fulvestrant or AI	August 2022
Giredestrant (GDC-9545)	acelERA (Phase II)	• Giredestrant • Endocrine monotherapy	Prior systemic and/or targeted tx	January 2024
Giredestrant (GDC-9545)	persevERA (Phase III)	• Giredestrant + Palbociclib • Letrozole + Palbociclib	Untreated ABC	March 2027

SERD: Selective ER degrader

www.clinicaltrials.gov. Accessed August 2021

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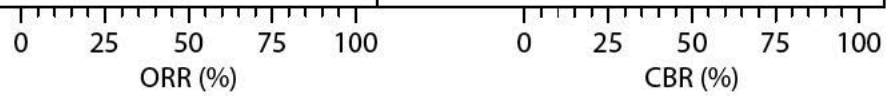
AMEERA-1: Response and Clinical Benefit Rate with Amcenestrant and Palbociclib for Endocrine-Resistant ER-Positive, HER2-Negative mBC

	N	ORR[a] n (%)	CBR[b] n (%)
Response-evaluable patients	34	11 (32.4)	25 (73.5)
Immediate prior therapy			
(Neo)adjuvant	15	4 (26.7)	8 (53.3)
Advanced	19	7 (36.8)	17 (89.5)
Baseline *ESR1* mutation status			
Wild type	26	8 (30.8)	18 (69.2)
Mutant	8	3 (37.5)	7 (87.5)
Prior AI in the adjuvant setting			
No	14	5 (35.7)	11 (78.6)
Yes	20	6 (30.0)	14 (70.0)
Prior SERM in the adjuvant setting			
No	16	4 (25.0)	11 (68.8)
Yes	18	7 (38.9)	14 (77.8)



AI, aromatase inhibitors; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.
[a]Confirmed CR or PR; [b]CR, PR, or SD ≥ 24 weeks.
Gray shading represents the 90% CI of the response-evaluable population.

RTP RESEARCH TO PRACTICE

Positive Phase III Top-Line Results from the EMERALD Trial Evaluating Elacestrant for Breast Cancer

Press Release: October 20, 2021

Positive top-line results from the EMERALD study were announced.

“The study was designed to evaluate elacestrant as a monotherapy versus the standard of care (SoC) for the treatment of ER+/HER2- advanced or metastatic breast cancer (mBC). There were two primary endpoints: progression-free survival (PFS) in the overall population and PFS in patients with tumors harboring estrogen receptor 1 (ESR1) mutations.

EMERALD met both primary endpoints, showing statistically significant PFS in the overall population and ESR1 mutation subgroup. The safety profile of elacestrant exhibited in EMERALD was similar to that of the previous clinical trial. Given these results, regulatory submissions in both the United States and European Union [are planned] in 2022. In 2018, elacestrant received fast track designation from the FDA.”

https://ir.radiuspharm.com/news-releases/news-release-details/menarini-group-and-radius-health-announce-positive-phase-3

Triple-Negative Breast Cancer (TNBC)

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FDA Approves Pembrolizumab for High-Risk Early-Stage TNBC

Press Release: July 26, 2021

"The Food and Drug Administration approved pembrolizumab for high-risk, early-stage, triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

FDA also granted regular approval to pembrolizumab in combination with chemotherapy for patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (Combined Positive Score [CPS] ≥10) as determined by an FDA approved test. FDA granted accelerated approval to pembrolizumab for this indication in November 2020.

The efficacy of pembrolizumab in combination with neoadjuvant chemotherapy followed by surgery and continued adjuvant treatment with pembrolizumab as a single agent was investigated in KEYNOTE-522 (NCT03036488), a randomized, multicenter, double-blind, placebo-controlled trial conducted in 1174 patients with newly diagnosed previously untreated high-risk early-stage TNBC (tumor size >1 cm but ≤2 cm in diameter with nodal involvement or tumor size >2 cm in diameter regardless of nodal involvement). Patients were enrolled regardless of tumor PD-L1 expression."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-high-risk-early-stage-triple-negative-breast-cancer

RTP RESEARCH TO PRACTICE

FDA Grants Regular Approval to Sacituzumab Govitecan for TNBC

Press Release: 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.

In April 2020, sacituzumab govitecan received accelerated approval for patients with mTNBC who have received at least two prior therapies for metastatic disease. The following trial was the confirmatory trial for the accelerated approval.

Efficacy and safety were evaluated in a multicenter, open-label, randomized trial (ASCENT; NCT02574455) conducted in 529 patients with unresectable locally advanced or mTNBC who had relapsed after at least two prior chemotherapies, one of which could be in the neoadjuvant or adjuvant setting, if progression occurred within 12 months. Patients were randomized (1:1) to receive sacituzumab govitecan, 10 mg/kg as an intravenous infusion, on days 1 and 8 of a 21-day (n=267) cycle or physician's choice of single agent chemotherapy (n=262)."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-sacituzumab-govitecan-triple-negative-breast-cancer

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

Recent Advances and Future Directions in Oncology

A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists

Saturday, October 23, 2021
9:30 AM – 4:30 PM ET

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Agenda

Module 1 — Breast Cancer: *Drs Partridge and Pegram*

Module 2 — Lung Cancer: *Drs Sequist and Spigel*

Module 3 — Gastrointestinal Cancers: *Drs Bekaii-Saab and Ciombor*

Module 4 — Genitourinary Cancers: *Drs Agarwal and Petrylak*

Module 5 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Kahl and Zelenetz*

Module 6 — Multiple Myeloma: *Drs Raje and Usmani*

Module 7 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Levis and Sallman*

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Lung Cancer Faculty

Lecia V Sequist, MD, MPH
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Contributing Oncologists

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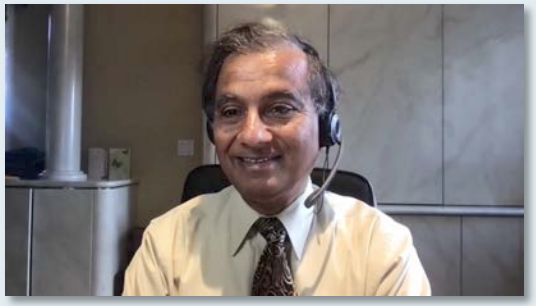

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Mamta Choksi, MD
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Elizabeth Guancial, MD
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Agenda

Module 1: Targeted Therapy

- Dr Zafar: A 72-year-old woman with MSS metastatic adenocarcinoma of the lung – HER2 mutation, PD-L1 TPS 0%
- Dr Gandhi: An 84-year-old man with localized adenocarcinoma of the lung and EGFR exon 19 deletion
- Dr Kumar: A 77-year-old woman with metastatic adenocarcinoma of the lung – Somatic BRCA2 and KRAS G12C mutations, TMB high
- Faculty Chalk Talks

Module 2: Immunotherapy

- Dr Peles: A 65-year-old man with Stage IIIA (8-cm, node-negative) adenocarcinoma of the lung
- Dr Choksi: A 56-year-old man with Stage IIIA adenocarcinoma of the lung
- Dr Gandhi: A 65-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 56%
- Faculty Chalk Talks

Module 3: Small Cell Lung Cancer

- Dr Apuri: A 53-year-old man with extensive-stage small cell lung cancer
- Dr Gandhi: A 64-year-old man with extensive-stage small cell lung cancer and concurrent prostate cancer

Appendix: Selected Data Sets

Agenda

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- Dr Apuri: A 53-year-old man with extensive-stage small cell lung cancer
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Appendix: Selected Data Sets

Case Presentation – Dr Zafar: A 72-year-old woman with microsatellite stable (MSS) metastatic adenocarcinoma of the lung – HER2 mutation, PD-L1 TPS 0%

Dr Syed Zafar

- 11/2019: 2.5-cm pT2 node-negative adenocarcinoma of the lung, EGFR wildtype s/p surgery
- No adjuvant therapy
- 4/2020: New left hilar mass, biopsy-confirmed adenocarcinoma
- NGS: MSS, PD-L1 TPS 0%, TMB 3 mut/Mb, HER2-positive
- Platinum/pemetrexed and RT
- 9/2020: Multiple left-sided lung nodules, pleural effusion
- Randomized on clinical trial to docetaxel x 6 → PD, lung collapse, endobronchial disease
- 2/2021: Nivolumab → PD with brain and liver metastases → Enrolled on a clinical trial of pertuzumab/trastuzumab

Questions

- How often have you observed pneumonitis in patients with lung cancer? Since she has only one functional lung, should I give her a chance with a better treatment or watch and wait?

Case Presentation – Dr Zafar: A 72-year-old woman with MSS HER2-positive metastatic adenocarcinoma of the lung – PD-L1 TPS 0% (continued)

Dr Syed Zafar

Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
ERBB2 (Her2/Neu)	Seq	DNA-Tumor	Pathogenic Variant Exon 20 | p.Y772_A775dup	BENEFIT	ado-trastuzumab emtansine (T-DM1)	Level 3A
ALK	IHC	Protein	Negative | 0	LACK OF BENEFIT	alectinib, brigatinib, ceritinib, crizotinib, lorlatinib	Level 1
	Seq	RNA-Tumor	Fusion Not Detected			
BRAF	Seq	DNA-Tumor	Mutation Not Detected	LACK OF BENEFIT	dabrafenib and trametinib combination therapy	Level 1
					vemurafenib	Level 2
EGFR	Seq	DNA-Tumor	Mutation Not Detected	LACK OF BENEFIT	erlotinib, gefitinib	Level 1
ROS1	Seq	RNA-Tumor	Fusion Not Detected	LACK OF BENEFIT	crizotinib	Level 1
					entrectinib	Level 1
					ceritinib, lorlatinib	Level 2
MET	CNA-Seq	DNA-Tumor	Amplification Not Detected	LACK OF BENEFIT	crizotinib	Level 3A
	Seq	RNA-Tumor	Variant Transcript Not Detected			

* Biomarker reporting classification: Level 1 - highest level of clinical evidence and/or biomarker association included on the drug label; Level 2 - strong evidence of clinical significance and is endorsed by standard clinical guidelines; Level 3 - potential clinical significance (3A - evidence exists in patient's tumor type, 3B - evidence exists in another tumor type).

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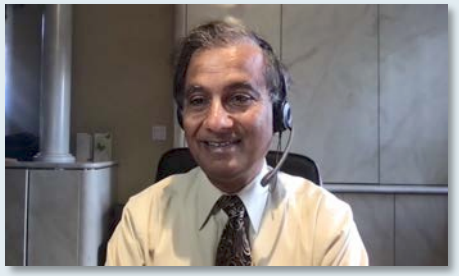
Case Presentation – Dr Gandhi: An 84-year-old man with localized adenocarcinoma of the lung and EGFR exon 19 deletion



Dr Sunil Gandhi

- PMH: Atrial fibrillation, pacemaker, CAD with dyspnea, LVEF 30%
- CT chest: LUL mass, biopsy-confirmed adenocarcinoma of the lung
- NGS: EGFR exon 19 deletion

Questions

- Is osimertinib contraindicated in patients with low LVEF? If not osimertinib, what other treatments should I use in this setting?

Case Presentation – Dr Kumar: A 77-year-old woman with metastatic adenocarcinoma of the lung – Somatic BRCA2 and KRAS G12C mutations, high tumor mutation burden (TMB)

Dr KS Kumar

- PMH: COPD, prior smoker
- 11/2014: Stage IB LLL adenocarcinoma of the lung, not a candidate for surgery, s/p carboplatin/pemetrexed x 7 and local RT
- 2/2017: New RUL primary s/p SBRT
- 9/2019: Recurrent adenocarcinoma, PD-L1 90
- Molecular testing: Somatic BRCA2 mutation, KRAS G12C mutation, TMB high
- 10/2019: Carboplatin/pemetrexed/pembrolizumab → Pembrolizumab maintenance
- 10/2020: Hyperthyroidism, immune encephalitis → Pembrolizumab discontinued
- 7/2021 CT C/A/P: No evidence of disease

Questions

- For patients who develop immune-related hyperthyroidism, do they typically end up being hypothyroid after treatment?
- What would you recommend for her next line of therapy given her BRCA2 and KRAS G12C mutations?

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Phase II DESTINY-Lung01 trial evaluating trastuzumab deruxtecan in HER2-mutant NSCLC; clinical implications

- Trastuzumab deruxtecan ADC
- Single arm trial for HER2 mutated NSCLC (2%), previously treated
- n=91
- ORR = 55% including CNS responses as well
- mPFS = 8.2 mo
- AE's = nausea, fatigue, myelosuppression, pneumonitis
- Not yet FDA-approved for NSCLC but available off-label and should be considered

Role if any for adjuvant targeted treatment of NSCLC beyond EGFR; (e.g., ALK)

- ADAURA is the Only Randomized Ph III Trial to Date (EGFR Focus)

  Randomized trials targeting other driving mutations are in progress.

- TKIs targeting ALK, ROS, MET, BRAF, RET, TRK are as Impactful in Advanced Disease as Osimertinib is in targeting EGFR in Advanced NSCLC

  Should we expect similar results? Do patients deserve access before data are available?

- *Are there Ethical Concerns about Repeating Prospective Ph III Adjuvant Trials as New Targets are Discovered (KRAS, NRG1, etc)?*

Agenda

Module 1: Targeted Therapy

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Module 3: Small Cell Lung Cancer

- Dr Apuri: A 53-year-old man with extensive-stage small cell lung cancer
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Appendix: Selected Data Sets

Case Presentation – Dr Peles: A 65-year-old man with Stage IIIA (8-cm, node-negative) adenocarcinoma of the lung

Dr Shachar Peles

- Stage III adenocarcinoma of the lung, s/p complete resection
- Adjuvant chemotherapy

Questions

- Should he also receive adjuvant immunotherapy, even though he underwent surgery with a complete resection?
- What are your thoughts about the adjuvant atezolizumab data, and would that be appropriate for this patient? Does PD-L1 level matter?
- What would you recommend if the patient had an EGFR or ALK tumor mutation?

Case Presentation – Dr Choksi: A 56-year-old man with Stage IIIA adenocarcinoma of the lung

Dr Mamta Choksi

- 10/2020: Diagnosed with Stage IIIA adenocarcinoma of the lung
- 11/2020: Neoadjuvant cisplatin/pemetrexed x 4
- Not a surgical candidate: No clear fat plane between the primary mass and the left pulmonary artery; Pulmonary nodules and evidence of lymphangitic spread
- 3/2021: Definitive RT with weekly carboplatin/paclitaxel x 6 → Consolidation durvalumab
  - Generalized skin rash requiring steroids
- 6/2021 PET/CT: Continued response

Questions

- How do you treat immune-related skin rash, pneumonitis, etc and do you consider rechallenging with immunotherapy after recovery from high-dose steroids and tapering?
- If immunotherapy had been added to neoadjuvant chemotherapy, is it more likely that surgery would have been possible?

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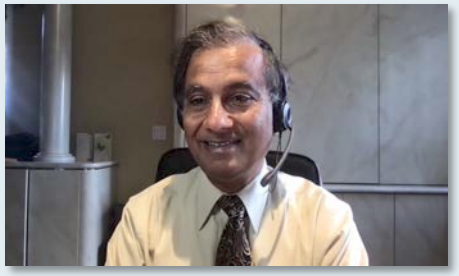
Case Presentation – Dr Gandhi: A 65-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 56%



Dr Sunil Gandhi

- Family history of lung cancer in brother, sister, mother and father
- 3/2020: Stage IIB adenocarcinoma of the lung, PD-L1 56%, EGFR wildtype s/p resection
- Cisplatin/pemetrexed x 4
- PET re-stage post-chemotherapy: Bilateral lung nodule and mediastinal LAD biopsy-confirmed metastatic NSCLC
- 8/2020: Ipilimumab/nivolumab, with CR >18 months
  - Hypothyroidism

Questions

- How long would you continue the immunotherapy? Would you stop after 2 years?
- In light of her family history of lung cancer, is there likely a genetic role for her lung cancer?

RTP RESEARCH TO PRACTICE

Selection of patients with localized NSCLC for treatment with adjuvant immunotherapy; role, if any, of PD-L1 assay and/or TMB

- Neoadjuvant v. Adjuvant Therapy

  Neoadjuvant and Adjuvant trials have shown promising efficacy for immunotherapy (+/- chemotherapy). Adjuvant FDA approval - Neoadjuvant coming

- PD-L1 Expression

  Early evidence suggests that expression predicts benefits from adjuvant atezolizumab.

- EGFR Testing

  Patients with EGFR Exon 19 deletions and 21 L858R mutations should be treated with chemotherapy followed by osimertinib – and not immunotherapy

First line treatment of PD-L1-negative metastatic NSCLC without a targetable mutation

- My top choice regimens:
  - Platinum/pemetrexed/pembrolizumab (non-squam)
  - Carboplatin/(nab)paclitaxel/pembrolizumab (squam)
- Also FDA approved, but I don't tend to use:
  - Carboplatin/paclitaxel/atezolizumab/bevacizumab (non-squam)
  - Platinum/pemetrexed/ipilimumab/nivolumab (non-squam)
  - Carboplatin/paclitaxel/ipilimumab/nivolumab (squam)
- Could consider, though would be off-label with negative PDL1 status:
  - Ipilimumab/nivolumab
  - Single agent anti-PD1 or anti-PDL1

Consolidation treatment after chemoradiation therapy for patients with locally advanced unresectable NSCLC with an EGFR activating tumor mutation

- PACIFIC regimen of 1yr durvalumab is FDA approved, but I personally favor holding off on this for 2 reasons:
  - Unlikely for immunotherapy to work in EGFR pts
  - Higher rates of toxicity with EGFR TKIs in patients previously treated with IO
- After ADAURA, one could consider off-label extrapolation of osimertinib. I personally discuss this with patients and offer
- LAURA trial will provide definitive data about this approach

Use of immune checkpoint inhibitors in patients with metastatic NSCLC and a targetable tumor mutation (e.g., EGFR)

- TKI v. Immunotherapy - Timing and Role

  TKI therapy is 1st (and in the case of ALK or ROS, 2nd+) choice. The role of immunotherapy in later lines is unclear, however, mutation may matter (e.g. EGFR v. MET exon 14) - Role of PD-L1 expression unclear.

- Consider risk of toxicity overlap in 1st line Treatment

  Risks of starting immunotherapy +/- chemotherapy 1st-line while awaiting NGS chemotherapy alone a better choice if need to start early

- Choice of Immunotherapy +/- Chemotherapy

  Immunotherapy agent and platinum doublet (+/- Bevacizumab) likely does not matter

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Appendix: Selected Data Sets

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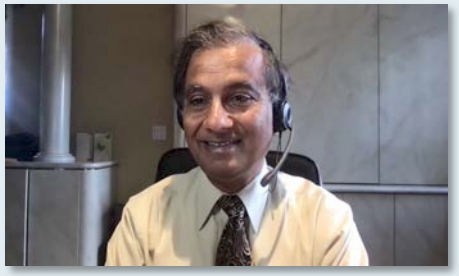
Case Presentation – Dr Apuri: A 53-year-old man with extensive-stage small cell lung cancer (SCLC)

Dr Susmitha Apuri

- Presented to the ER with neck swelling
- CT of neck: Matted LAD in right superior mediastinum and hilar regions, resulting in mass-effect of the superior vena cava
- Biopsy-positive: Synaptophysin, TTF-1, p40, CK 5 negative c/w SCLC
- Concurrent RT and cisplatin/etoposide
- Restaging 3 months later: Interval development in RLL, RUL and precarinal lymph nodes
- Lurbinectidin

Case Presentation – Dr Gandhi: A 64-year-old man with extensive-stage small cell lung cancer and concurrent prostate cancer



Dr Sunil Gandhi

- Presented to radiation oncologist for treatment of newly diagnosed prostate cancer
- Biopsy of lymph node: Small cell lung cancer → Imaging: Widespread LAD
- 10/2019: Carboplatin/etoposide/atezolizumab x 4, with CR → Atezolizumab
- 6/2021: Recurrence with multiple abdominal and pelvic lymph nodes
- Lurbinectedin

Questions

- How long can you give lurbinectedin until the patient experiences significant side effects?
- Do you have a preference for atezolizumab or durvalumab as part of first-line treatment?

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- Faculty Chalk Talks

Module 2: Immunotherapy

- Dr Peles: A 65-year-old man with Stage IIIA (8-cm, node-negative) adenocarcinoma of the lung
- Dr Choksi: A 56-year-old man with Stage IIIA adenocarcinoma of the lung
- Dr Gandhi: A 65-year-old woman with metastatic adenocarcinoma of the lung – PD-L1 56%
- Faculty Chalk Talks

Module 3: Small Cell Lung Cancer

- Dr Apuri: A 53-year-old man with extensive-stage small cell lung cancer
- Dr Gandhi: A 64-year-old man with extensive-stage small cell lung cancer and concurrent prostate cancer

Appendix: Selected Data Sets

RTP RESEARCH TO PRACTICE

Targeted Therapy

Emerging Targeted Therapies for EGFR Exon 20 Mutations

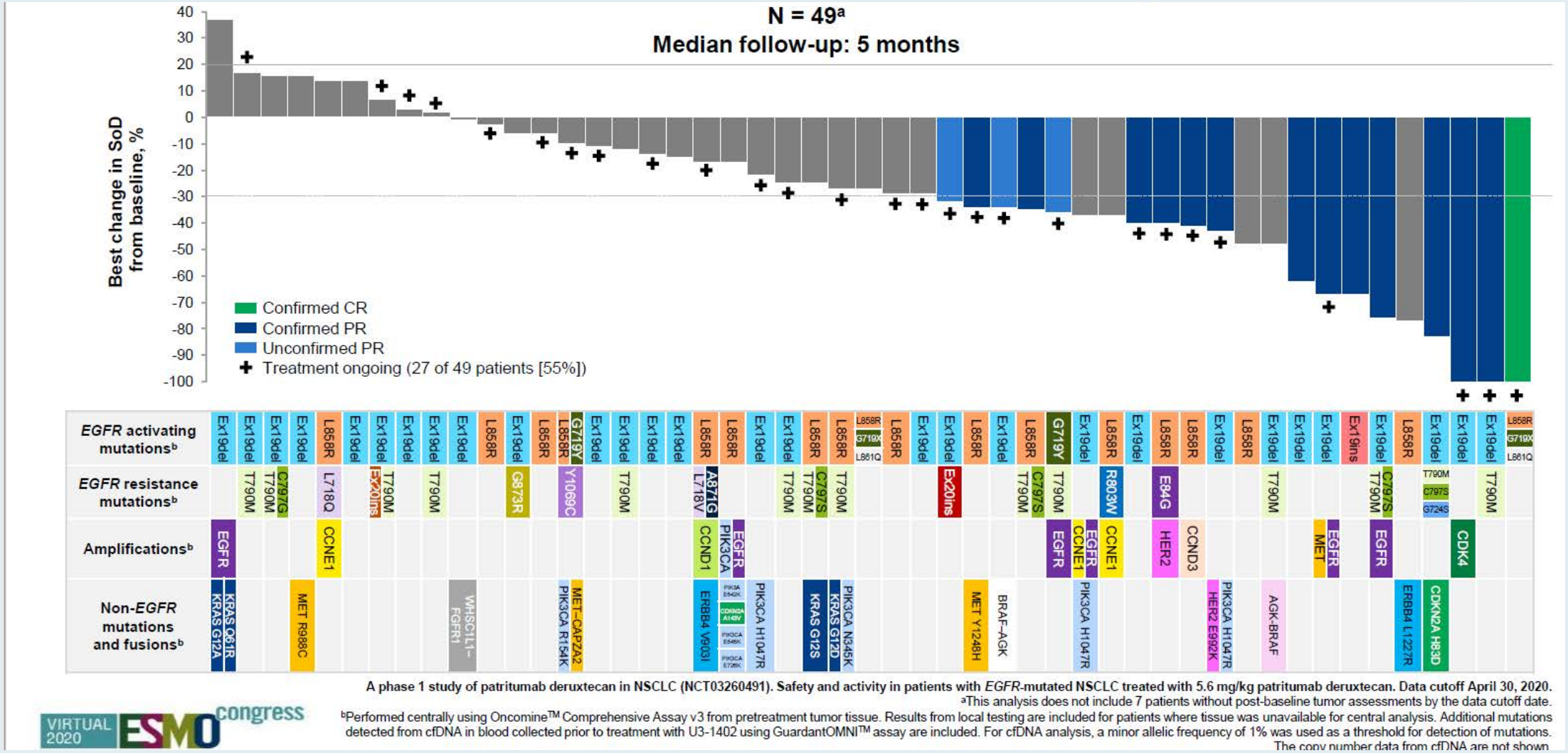
Drug	MOA	N	ORR	mPFS	Major toxicities	Discont due to toxicities	FDA Status re Exon 20
Poziotinib[1,2]	TKI	115	15%	4.2 mo	Diarrhea Rash	12%	Fast track designation March 2021
Mobocertinib[3,4]	TKI	28	43%	7.3 mo	Diarrhea Rash Nausea	14%	Breakthrough therapy designation April 2020
Amivantamab[5,6]	EGFR/MET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

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

Patritumab Deruxtecan for NSCLC with EGFR Mutation

This is a HER3 directed antibody-drug conjugate

Tested in 49 pts with EGFR+ NSCLC resistant to prior therapy



A phase 1 study of patritumab deruxtecan in NSCLC (NCT03260491). Safety and activity in patients with *EGFR*-mutated NSCLC treated with 5.6 mg/kg patritumab deruxtecan. Data cutoff April 30, 2020.

[a]This analysis does not include 7 patients without post-baseline tumor assessments by the data cutoff date.

[b]Performed centrally using Oncomine™ Comprehensive Assay v3 from pretreatment tumor tissue. Results from local testing are included for patients where tissue was unavailable for central analysis. Additional mutations detected from cfDNA in blood collected prior to treatment with U3-1402 using GuardantOMNI™ assay are included. For cfDNA analysis, a minor allelic frequency of 1% was used as a threshold for detection of mutations. The copy number data from cfDNA are not shown.

VIRTUAL 2020 ESMO congress

Yu ESMO 2020 LBA62

RTP RESEARCH TO PRACTICE

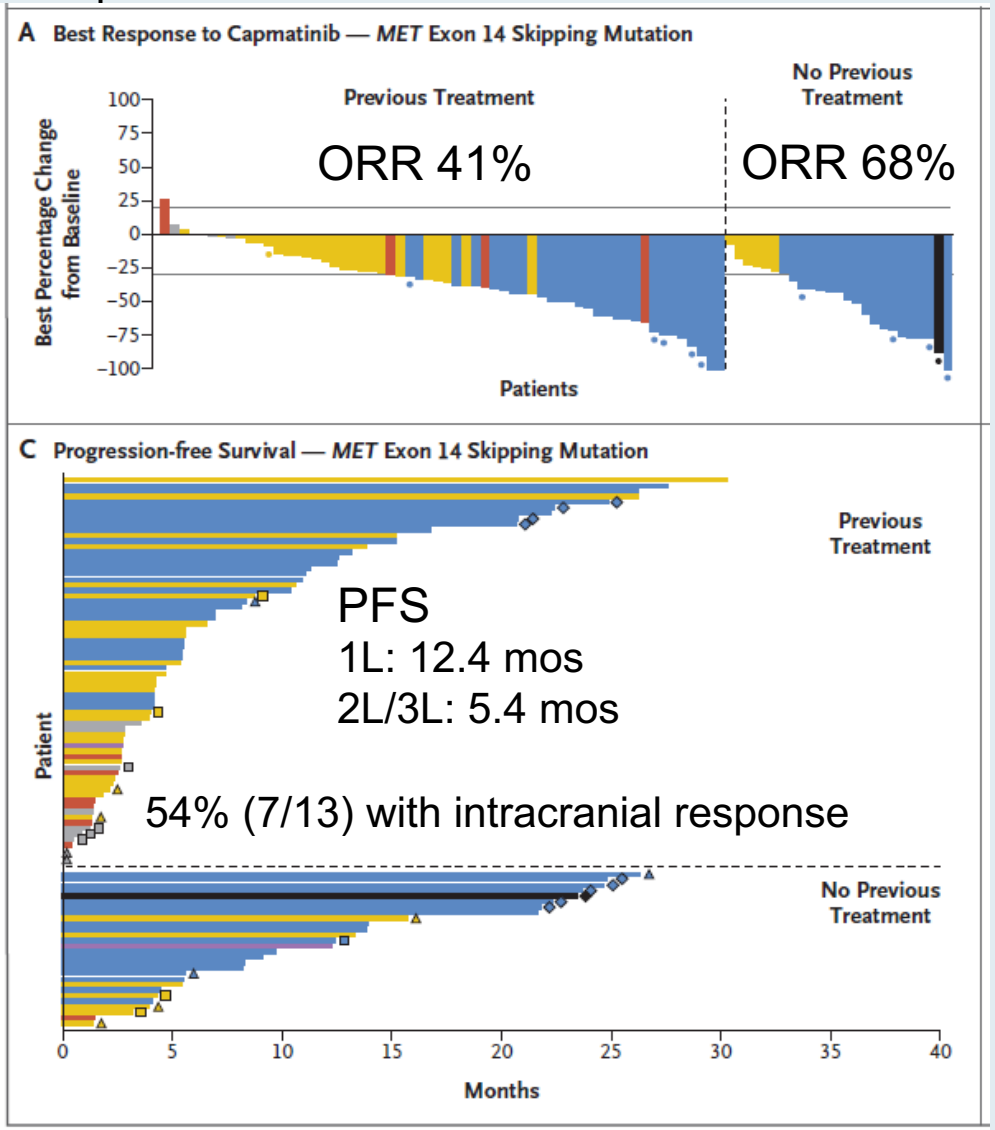
Activity of ALK TKIs in the First-Line Setting for Advanced NSCLC with ALK Rearrangement

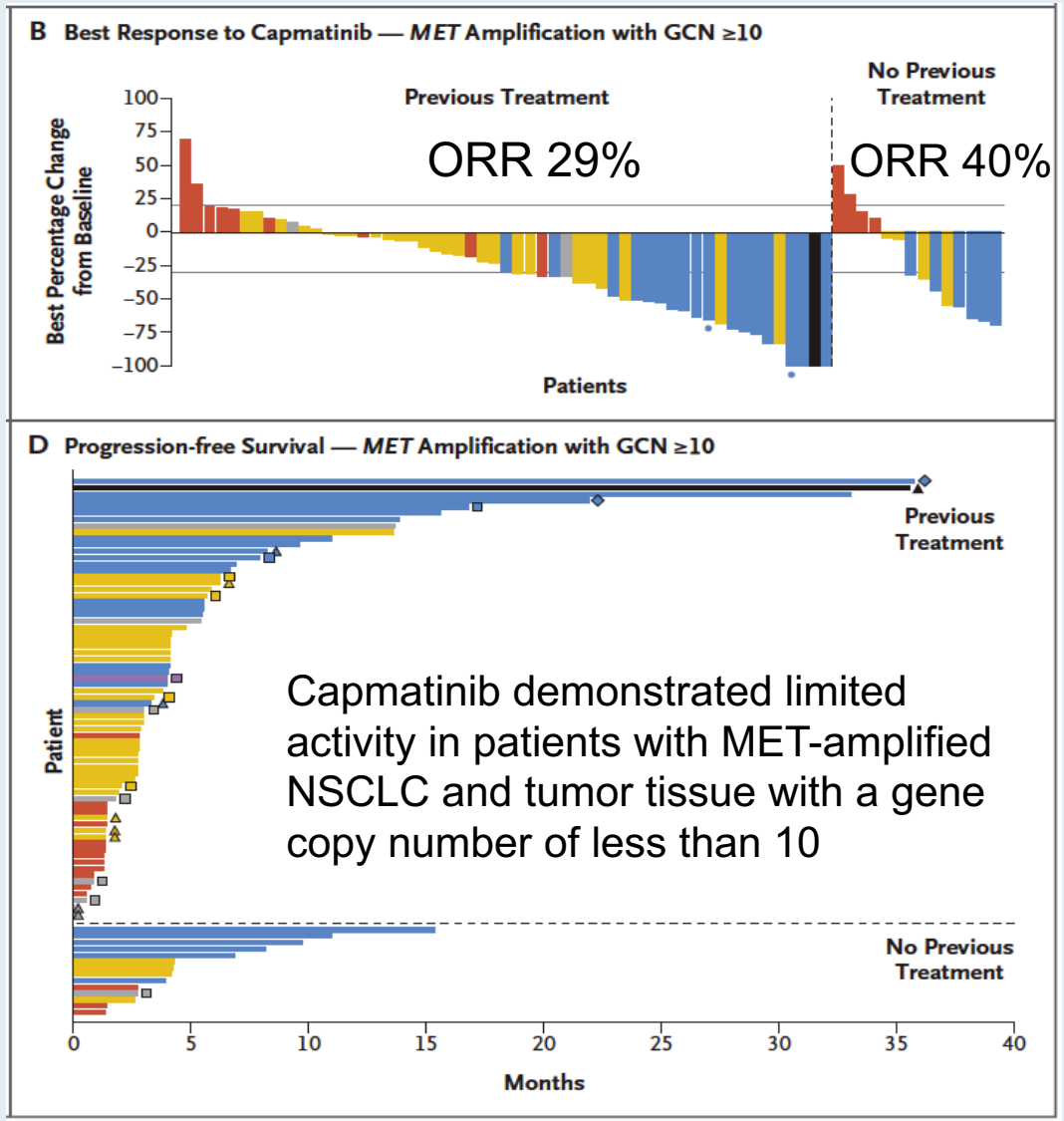
ALK TKI	Median PFS	ORR	Intracranial response
Crizotinib	10.9 mo	74%	NA
Ceritinib	16.6 mo	72.5%	72.7%
Alectinib	34.8 mo	82.9%	82.9%
Brigatinib	29.4 mo	71%	78%
Lorlatinib	Not reached	90%	66.7%
Ensartinib	26.2 mo	80%	64.3%

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

Capmatinib for Advanced NSCLC with MET Exon 14 Skipping Mutation or Amplification

364 patients across all cohorts

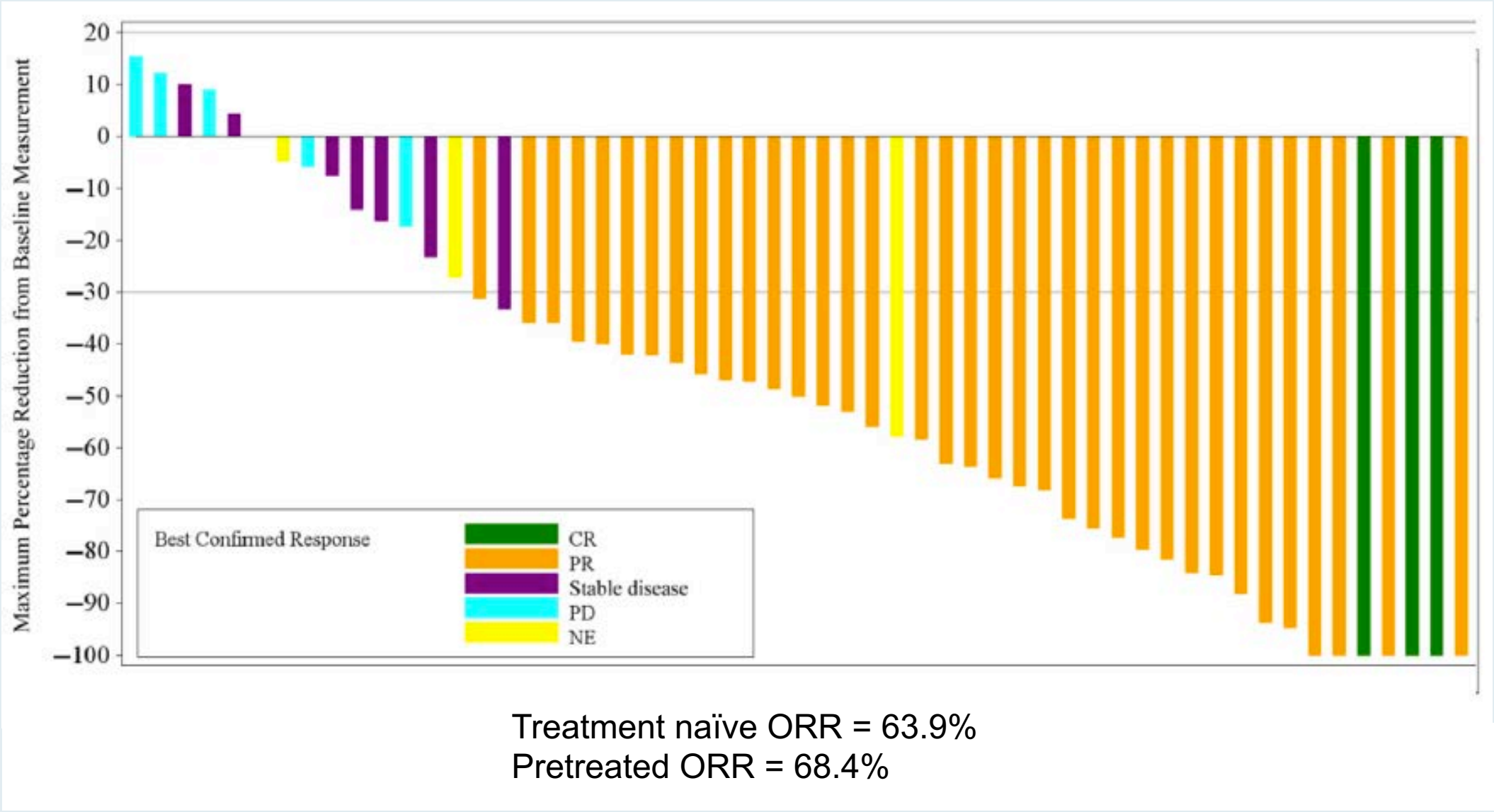




Wolf NEJM. 2020

RTP RESEARCH TO PRACTICE

Dabrafenib with Trametinib for Metastatic NSCLC with BRAF V600E Mutation



Treatment naïve ORR = 63.9%
Pretreated ORR = 68.4%

Planchard D et al. *J Thorac Oncol* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Immunotherapy

FDA Approves Atezolizumab as Adjuvant Treatment for NSCLC

Press Release: October 15, 2021

"The Food and Drug Administration approved atezolizumab for adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test.

Today, the FDA also approved the VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Inc.) as a companion diagnostic device to select patients with NSCLC for adjuvant treatment with atezolizumab.

The major efficacy outcome measure was disease-free survival (DFS) as assessed by the investigator in the primary efficacy analysis population (n=476) of patients with stage II-IIIA NSCLC with PD-L1 expression on ≥1% of tumor cells (PD-L1 ≥1% TC). Median DFS was not reached (95% CI: 36.1, NE) in patients on the atezolizumab arm compared with 35.3 months (95% CI: 29.0, NE) on the BSC arm (HR 0.66; 95% CI: 0.50, 0.88; p=0.004)."

hwww.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-adjuvant-treatment-non-small-cell-lung-cancer

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

Press Release: February 22, 2021

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

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

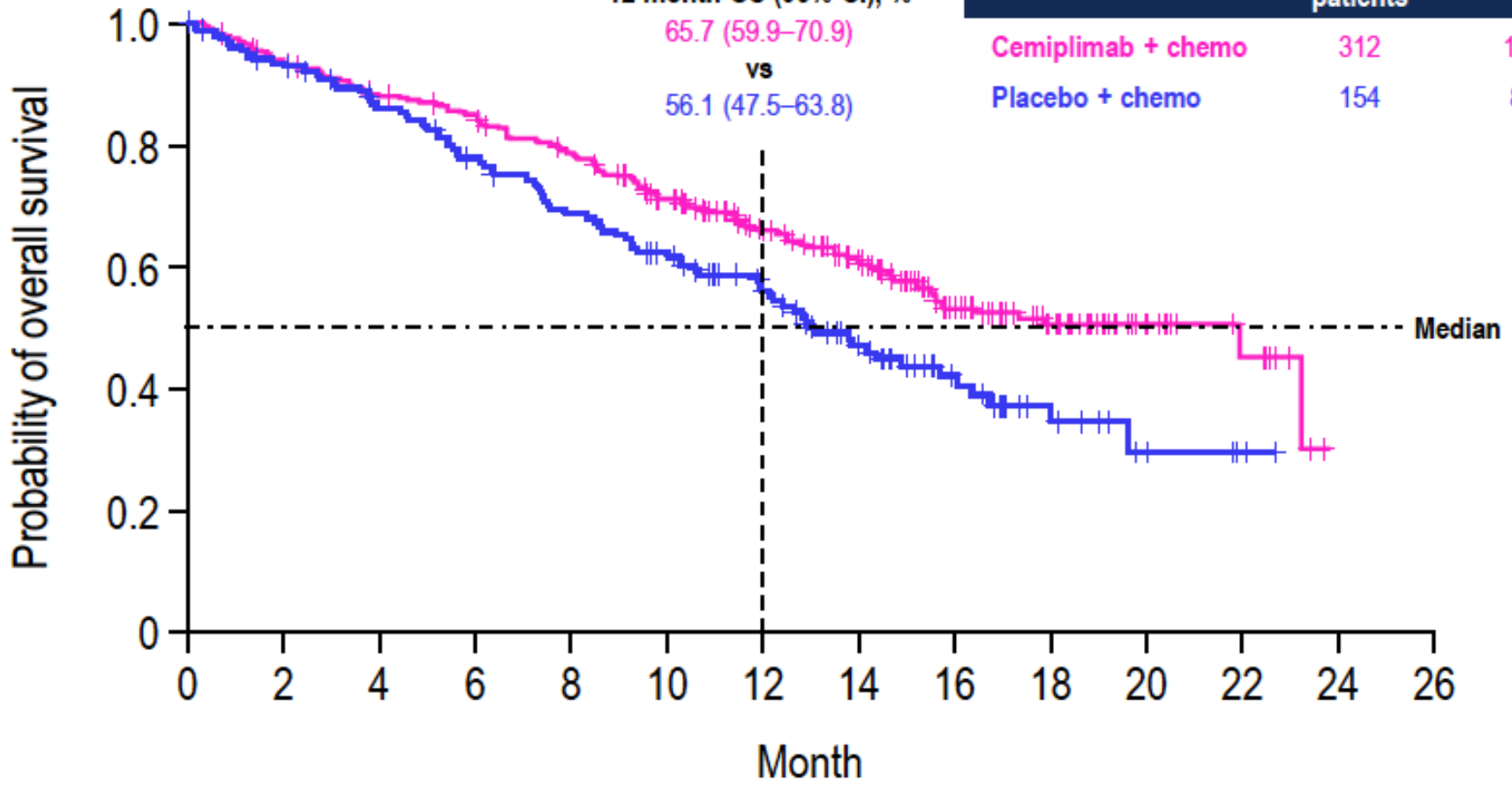
www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-cemiplimab-rwlc-non-small-cell-lung-cancer-high-pd-l1-expression

EMPOWER-Lung 3: First-Line Cemiplimab with Platinum-Doublet Chemotherapy for Advanced NSCLC

Median duration of follow-up (range): 16.4 (8.5–24.0) months

	No. of patients	No. of events, n (%)	OS, median (95% CI), months
Cemiplimab + chemo	312	132 (42.3)	21.9 (15.5–NE)
Placebo + chemo	154	82 (53.2)	13.0 (11.9–16.1)

HR (95% CI) = 0.71 (0.53–0.93); *P*=0.014



Gogishvili M et al. ESMO 2021;Abstract LBA51.

RTP RESEARCH TO PRACTICE

FDA-Approved Immunotherapy Combination Options for First-Line Therapy

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

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

FDA-Approved Immunotherapy Monotherapy Options for First-Line Therapy

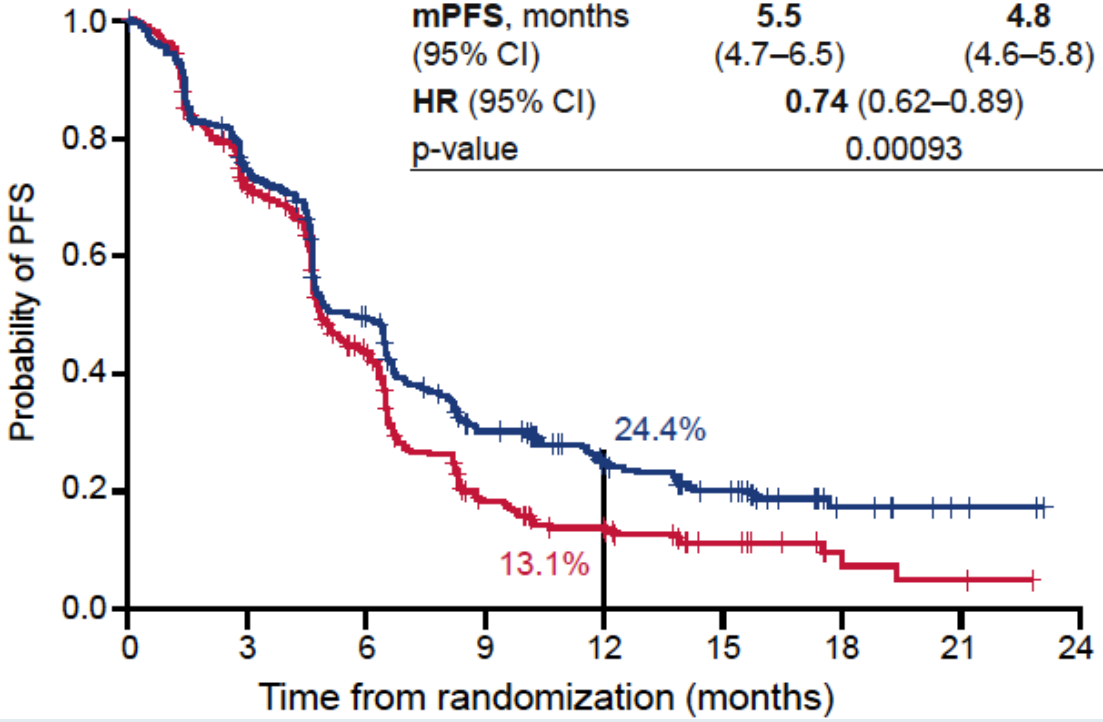
Monotherapy	FDA approval	Pivotal study	Histologic type	HR (OS)
Pembrolizumab[1,2]	4/11/19 10/24/16	KEYNOTE-042 KEYNOTE-024	PD-L1 TPS ≥1%	0.63
Atezolizumab[3]	5/18/20	IMpower110	PD-L1 TPS ≥50, EGFR and/or ALK wt	0.59
Cemiplimab[4]	2/22/2021	EMPOWER-Lung 1 (Study 1624)	PD-L1 TPS ≥50, EGFR and/or ALK and/or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

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

POSEIDON: First-Line Durvalumab with Chemotherapy for Advanced NSCLC

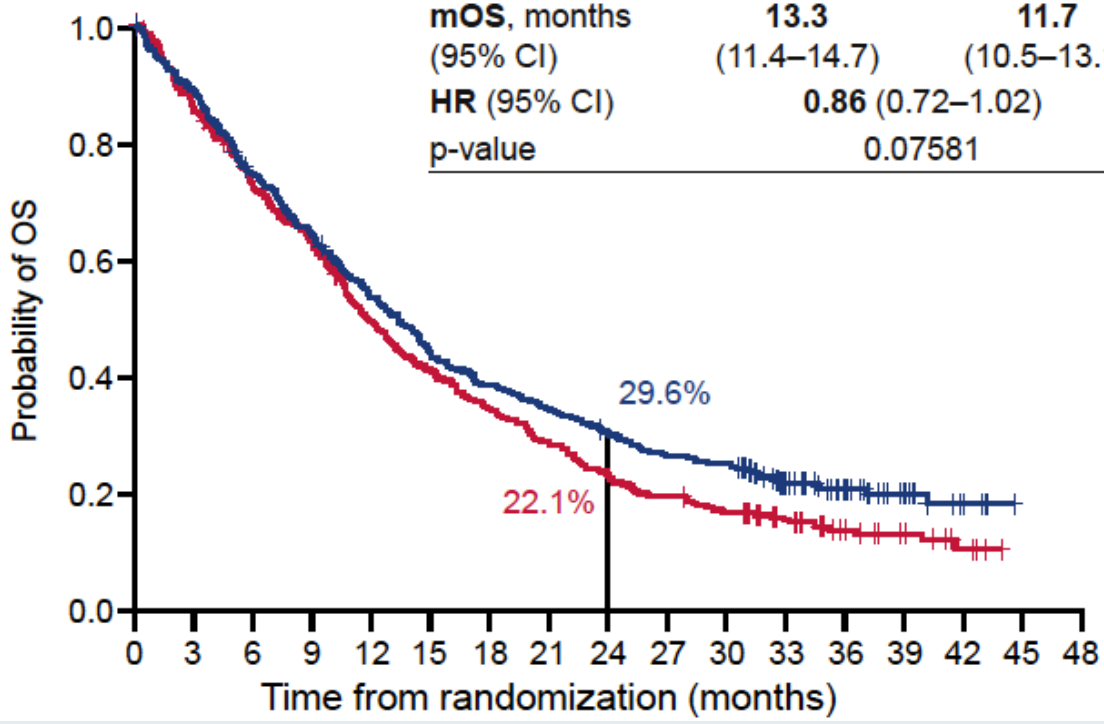
PFS

	D+CT	CT
Events, n/N (%)	253/338 (74.9)	258/337 (76.6)
mPFS, months (95% CI)	**5.5** (4.7–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.74** (0.62–0.89)	
p-value	0.00093	



OS

	D+CT	CT
Events, n/N (%)	264/338 (78.1)	285/337 (84.6)
mOS, months (95% CI)	**13.3** (11.4–14.7)	**11.7** (10.5–13.1)
HR (95% CI)	**0.86** (0.72–1.02)	
p-value	0.07581	



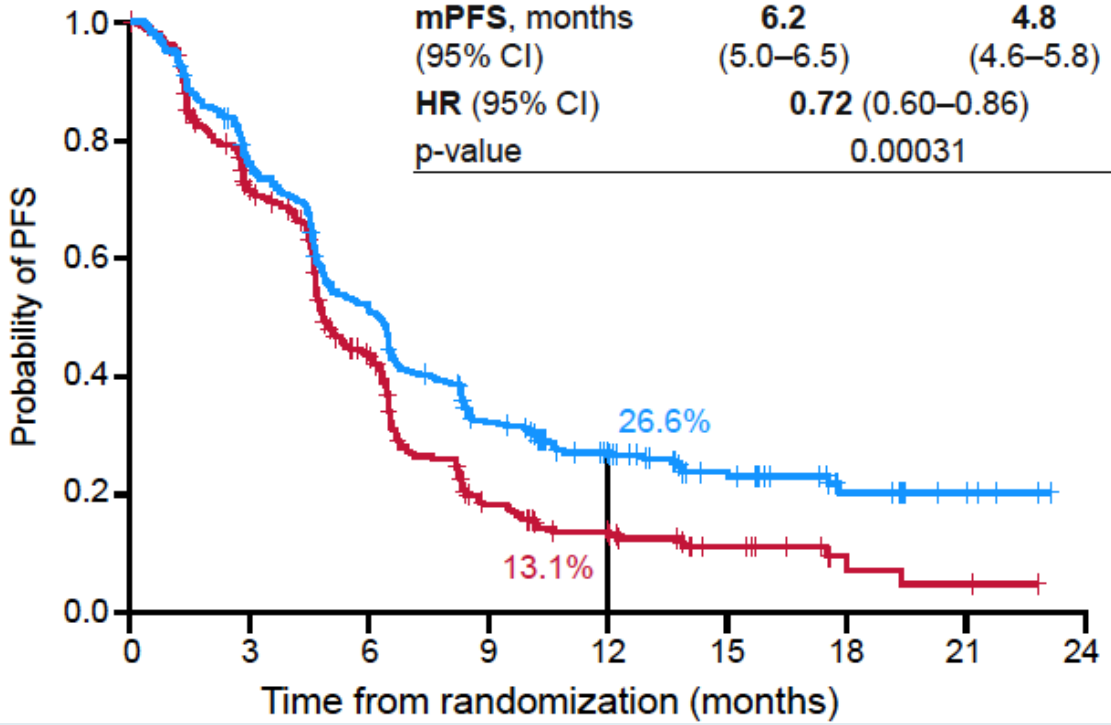
Johnson ML et al. WCLC 2021;Abstract PL02.01

RTP RESEARCH TO PRACTICE

POSEIDON: First-Line Durvalumab with Tremelimumab and Chemotherapy for Advanced NSCLC

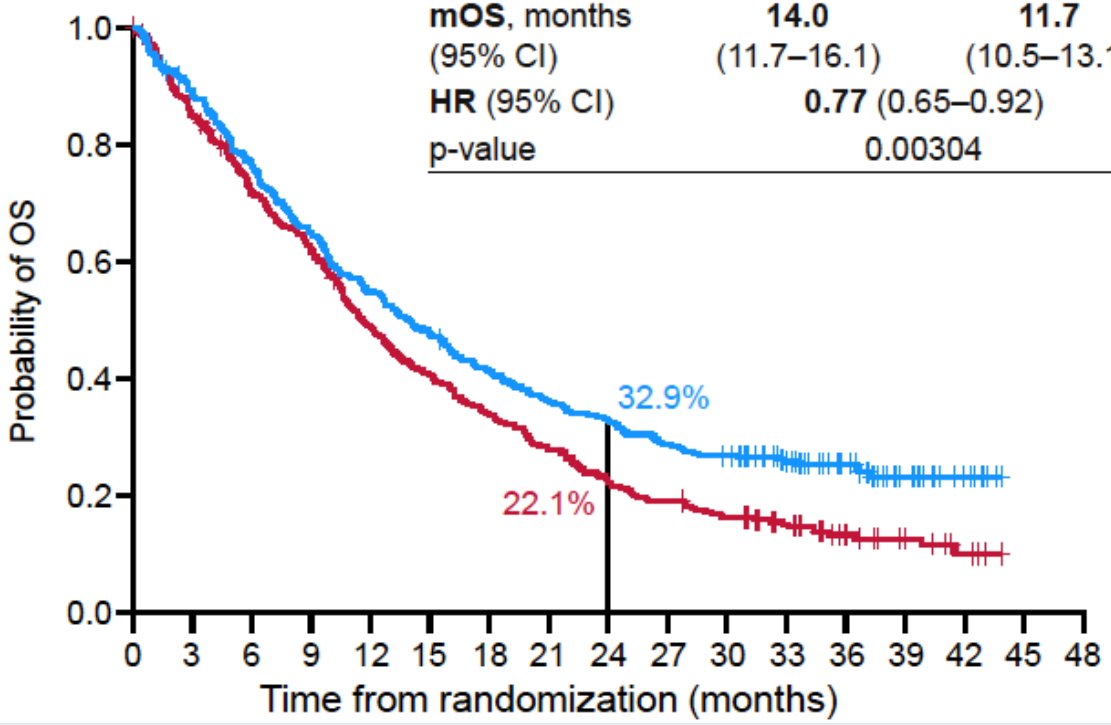
PFS

	D+T+CT	CT
Events, n/N (%)	238/338 (70.4)	258/337 (76.6)
mPFS, months (95% CI)	**6.2** (5.0–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.72** (0.60–0.86)	
p-value	0.00031	



OS

	D+T+CT	CT
Events, n/N (%)	251/338 (74.3)	285/337 (84.6)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR (95% CI)	**0.77** (0.65–0.92)	
p-value	0.00304	



Johnson ML et al. WCLC 2021;Abstract PL02.01

RTP RESEARCH TO PRACTICE

Small Cell Lung Cancer

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FDA Approves Trilaciclib to Reduce Bone Marrow Suppression Caused by Chemotherapy

Press Release: February 12, 2021

"Today the US Food and Drug Administration approved trilaciclib as the first therapy in its class to reduce the frequency of chemotherapy-induced bone marrow suppression in adults receiving certain types of chemotherapy for extensive-stage (when the cancer has spread beyond the lungs) small cell lung cancer. Trilaciclib may help protect bone marrow cells from damage caused by chemotherapy by inhibiting cyclin-dependent kinase 4/6, a type of enzyme.

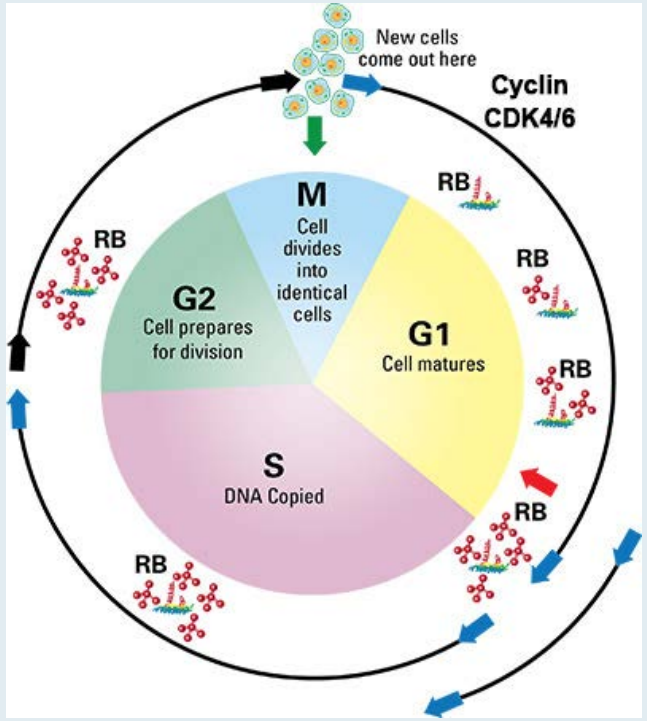
The effectiveness of trilaciclib was evaluated in three randomized, double-blind, placebo-controlled studies in patients with extensive-stage small cell lung cancer. Combined, these studies randomly assigned 245 patients to receive either an infusion of trilaciclib in their veins or a placebo before chemotherapy. The studies then compared the two groups for the proportion of patients with severe neutropenia (a very low count of white blood cells called neutrophils) and the duration of severe neutropenia in the first cycle of chemotherapy. In all three studies, patients who received trilaciclib had a lower chance of having severe neutropenia compared to patients who received a placebo. Among those who had severe neutropenia, patients who received trilaciclib, on average, had it for a shorter time than patients who received a placebo."

https://www.fda.gov/news-events/press-announcements/fda-approves-drug-reduce-bone-marrow-suppression-caused-chemotherapy

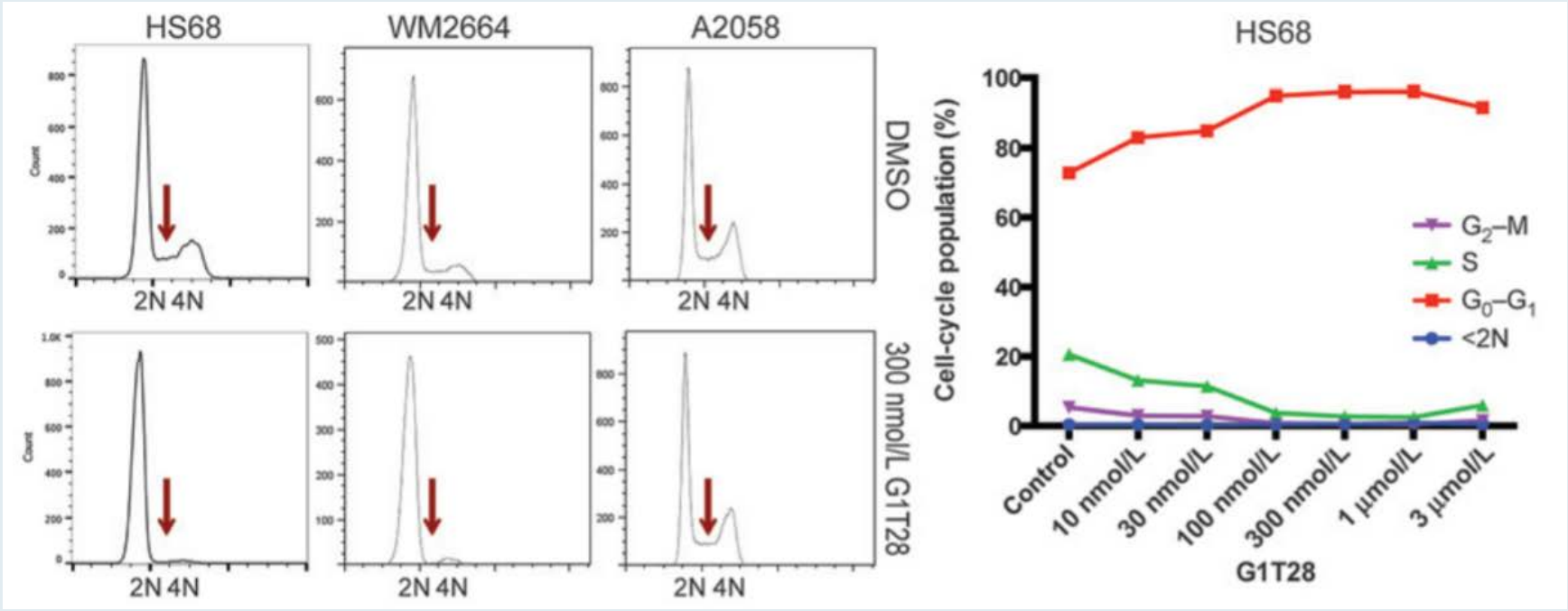
RTP RESEARCH TO PRACTICE

Trilaciclib to Prevent Myelosuppression in SCLC

CDK4/6 inhibitors (G1T28) transiently maintain G1 cell cycle arrest of hematopoietic stem and progenitor cells.



CDK4/6-dependent cell lines

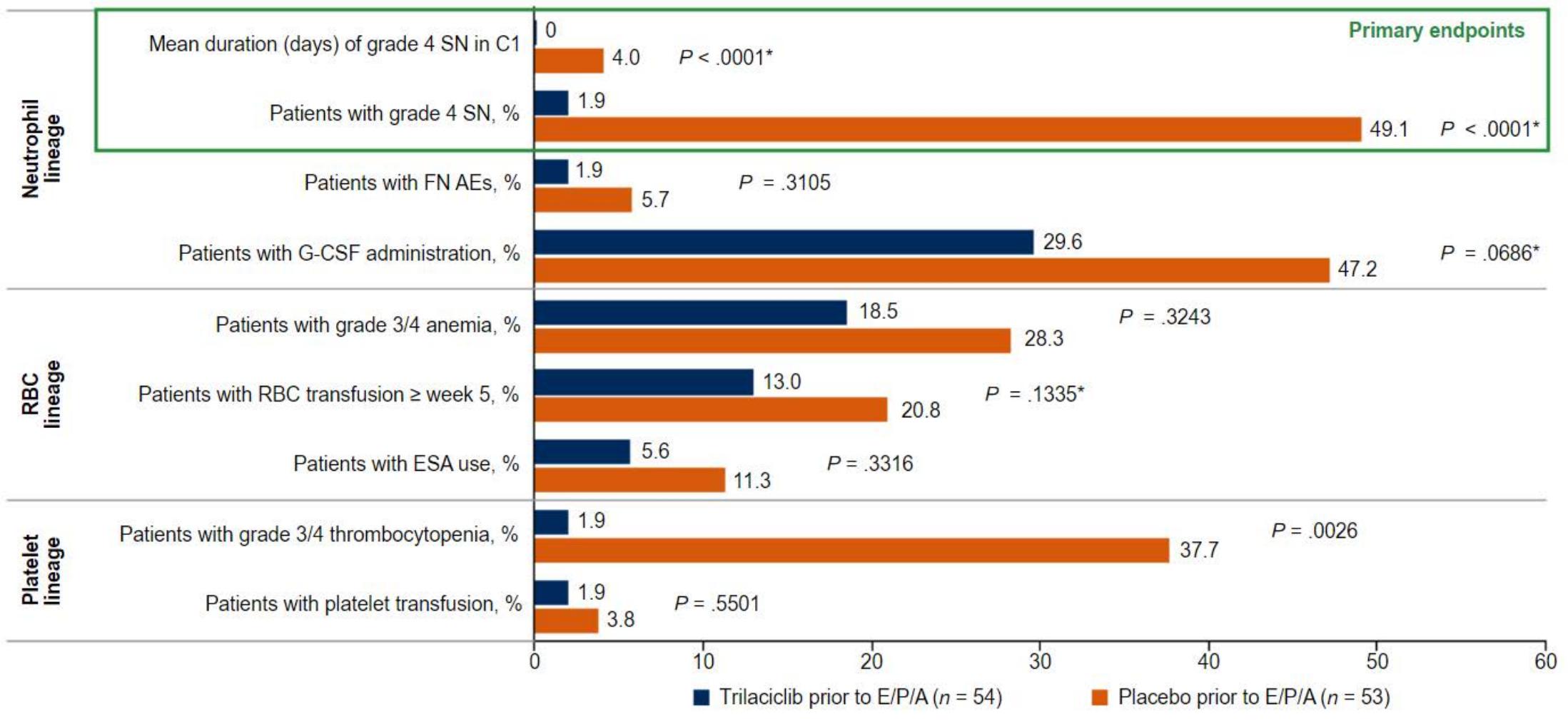


https://www.dana-farber.org/newsroom/publications/paths-of-progress-2019/wrench-in-the-works/

Bisi JE et al. *Mol Cancer Ther* 2016;15(5):783-93.

RTP RESEARCH TO PRACTICE

Trilaciclib Prior to Atezolizumab + Carboplatin/Etoposide for SCLC

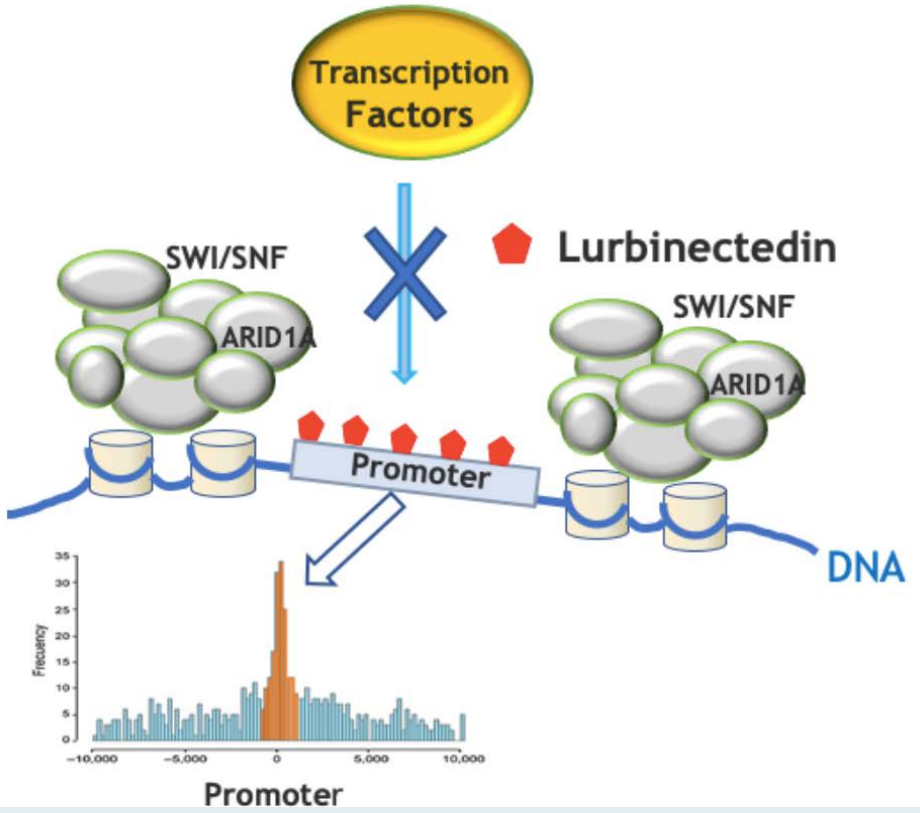


Daniel D et al. *Int J Cancer* 2020;148(10):2557-70.

RTP RESEARCH TO PRACTICE

Lurbinectedin: Mechanism of Action

- Synthetic derivative from a sea sponge
  - Inhibits gene expression
  - ? Other effects??



SCLC-ED
ECOG PS=0-2
No brain metastasis
Prior Chemotherapy

Lurbinectedin3.2 mg/m² Q 3 weeks

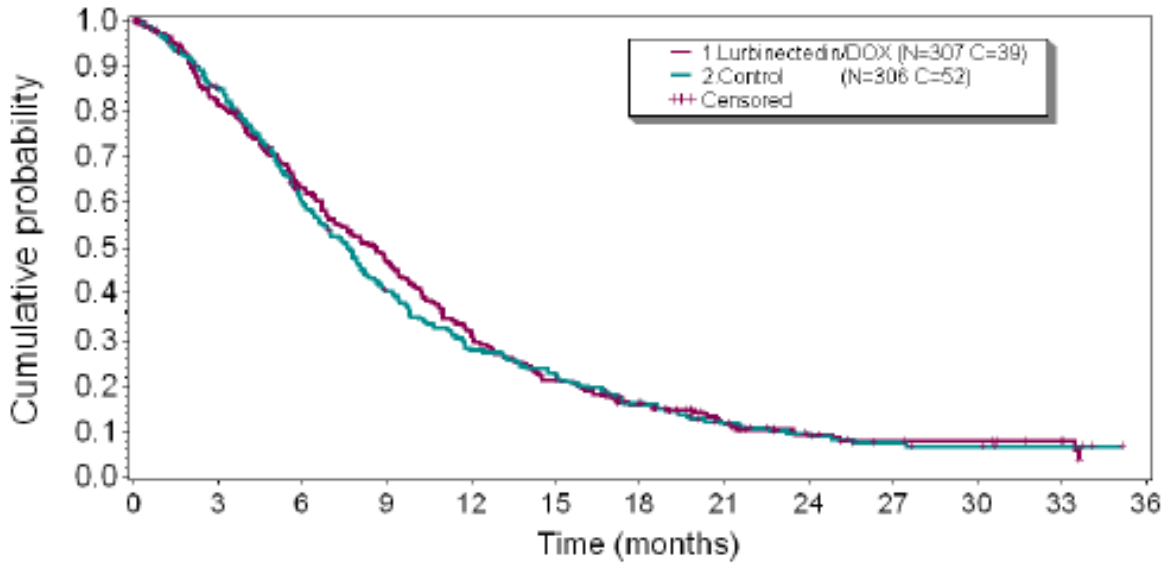
N=105 Pts

Primary endpoint:
Response Rate

RTP RESEARCH TO PRACTICE

ATLANTIS: Phase III Trial Results with Lurbinectedin/Doxorubicin versus CAV or Topotecan for Relapsed SCLC

Survival



	Lurbinectedin+DOX (N=307)	Control (N=306)	Parameter	p-value
Events, n (%)	268 (87.3)	254 (83.0)		
Censored, n (%)	39 (12.7)	52 (17.0)		
Median OS (95% CI), months	8.6 (7.1, 9.4)	7.6 (6.6, 8.2)	HR : 0.967 (0.815, 1.148)	0.7032
Mean OS, months	10.6	9.9		

Safety

	Lurbinectedin+DOX (n=303) n (%)	Control (n=289) n (%)
Any AE treatment-related	268 (88.4)	266 (92.0)
Any grade ≥3 AE	**143 (47.2)**	**218 (75.4)**
Any grade 4 AE	**49 (16.2)**	**158 (54.7)**
Any grade ≥3 SAE	38 (12.5)	83 (28.7)
Death associated with AEs	**1 (0.3)**	**10 (3.5)**
Treatment discontinuations associated with AEs	23 (7.6)	45 (15.6)
Delays associated with AEs	79 (26.1)	99 (34.3)
Reductions associated with AEs	66 (21.8)	138 (47.8)

Hematological	Lurbinectedin+DOX (n=303)	Control (n=289)	
	Grade ≥3	Grade ≥3	p-value
Anaemia	44 (14.5)	90 (31.1)	<0.0001
Neutropenia	112 (37.0)	200 (69.2)	<0.0001
Febrile neutropenia	12 (4.0)	24 (8.3)	0.0377
Thrombocytopenia	42 (13.9)	90 (31.1)	<0.0001

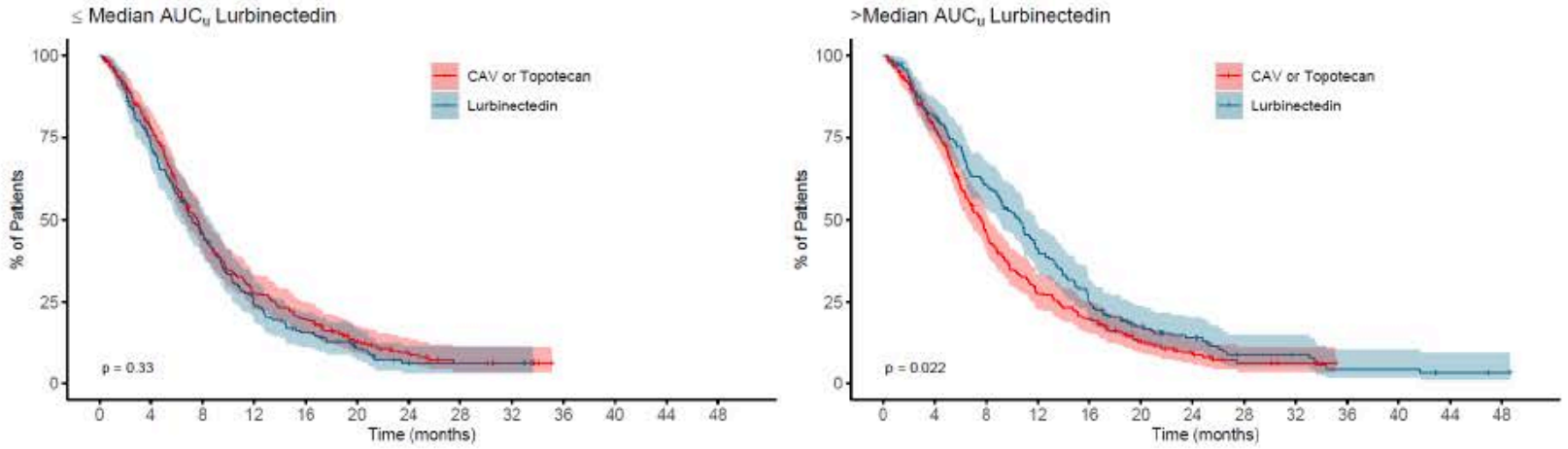
CAV = cyclophosphamide/doxorubicin/vincristine

Paz-Ares L et al. WCLC 2021;Abstract PL02.03.

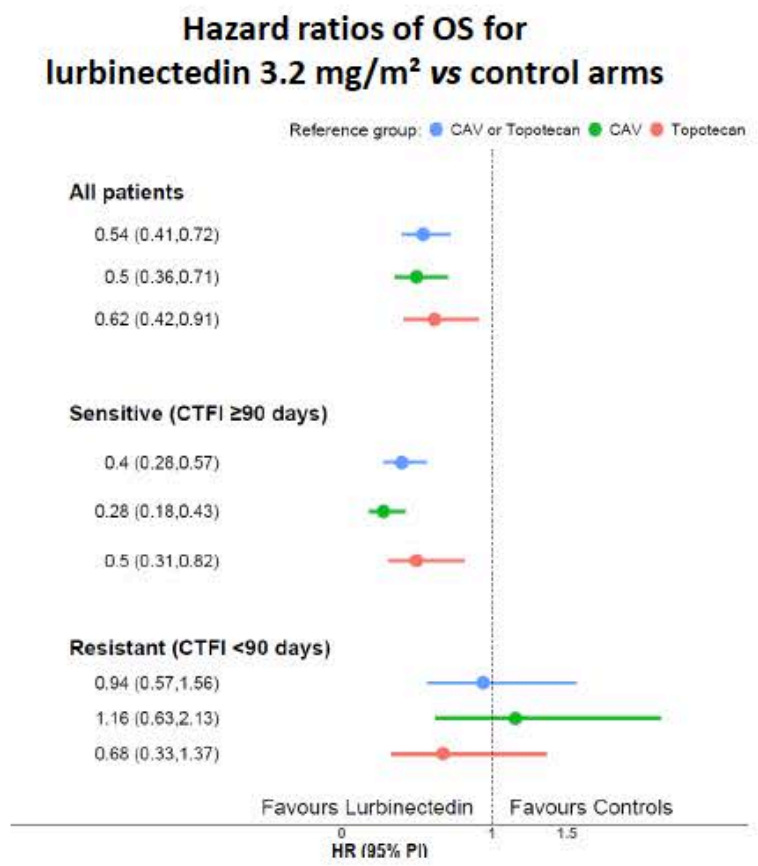
RTP RESEARCH TO PRACTICE

ATLANTIS: Exposure-Response Analysis of Lurbinectedin

- A statistically significant relationship between lurbinectedin PK exposure (AUC_u) and OS in patients with 2nd-line SCLC was observed.



Kaplan-Meier curves of OS stratified by lurbinectedin AUC_u (≤ and > median), relative to the control arm



- Therefore, an E-R model was developed to assess the contribution of lurbinectedin on OS and measure the impact of prognostic factors.
- Then, the model was used to predict OS of 3.2 mg/m² lurbinectedin as single agent in patients of ATLANTIS experimental arm, to conduct a model-based head-to head comparsion with the control arm.
- This regimen showed superiority over the standard therapy in the overall population, and in patients with sensitive disease, thus confirming the activity observed in study B-005, in a phase 3 randomized and controlled setting.

Fudio S et al. WCLC 2021;Abstract P63.02.

RTP RESEARCH TO PRACTICE

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

Recent Advances and Future Directions in Oncology

A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists

Saturday, October 23, 2021
9:30 AM – 4:30 PM ET

RTP
RESEARCH
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Agenda

Module 1 — Breast Cancer: *Drs Partridge and Pegram*

Module 2 — Lung Cancer: *Drs Sequist and Spigel*

Module 3 — Gastrointestinal Cancers: *Drs Bekaii-Saab and Ciombor*

Module 4 — Genitourinary Cancers: *Drs Agarwal and Petrylak*

Module 5 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Kahl and Zelenetz*

Module 6 — Multiple Myeloma: *Drs Raje and Usmani*

Module 7 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Levis and Sallman*

RTP
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Gastrointestinal Cancers Faculty

Tanios Bekaii-Saab, MD
Professor, Mayo Clinic College of Medicine and Science
Program Leader, Gastrointestinal Cancer
Mayo Clinic Cancer Center
Consultant, Mayo Clinic in Arizona
Chair, ACCRU Research Consortium
Phoenix, Arizona

Kristen K Ciombor, MD, MSCI
Associate Professor of Medicine
Division of Hematology/Oncology
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

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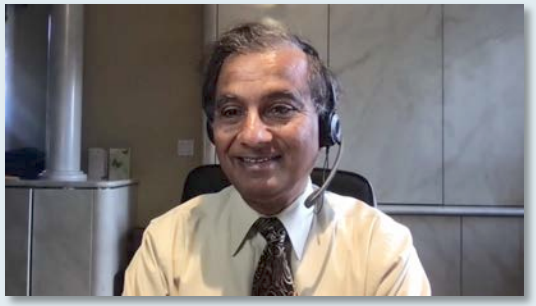
TO PRACTICE

Contributing Oncologists

Susmitha Apuri, MD
Florida Cancer Specialists
and Research Institute
Lutz, Florida



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Mamta Choksi, MD
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and Research Institute
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Elizabeth Guancial, MD
Florida Cancer Specialists and
Research Institute
Clinical Associate Professor at FSU
College of Medicine
Sarasota, Florida

Uday Dandamudi, MD
Florida Cancer Specialists
and Research Institute
New Port Richey, Florida

Lowell L Hart, MD
Scientific Director of Research
Florida Cancer Specialists and
Research Institute
Fort Myers, Florida

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Contributing Oncologists

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Physician Partner
Florida Cancer Specialists and Research Institute
New Port Richey, Florida

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

Ina J Patel, DO
Assistant Professor of Internal Medicine
Division of Hematology/Oncology
Moncrief Cancer Institute
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Shachar Peles, MD
Florida Cancer Specialists and Research Institute
Lake Worth, Florida

Ferdy Santiago, MD
Florida Cancer Specialists and Research Institute
Naples, Florida

Raji Shameem, MD
Florida Cancer Specialists and Research Institute
Deland, Florida

Syed F Zafar, MD
Hematologist and Medical Oncologist
Florida Cancer Specialists and Research Institute
Chief, Division of Hematology and Oncology
Lee Health
Fort Myers, Florida

RTP
RESEARCH TO PRACTICE

Agenda

Module 1: Hepatocellular Carcinoma

- Dr Peles: A 72-year-old woman with metastatic HCC
- Faculty Chalk Talks

Module 2: Colorectal Cancer

- Dr Patel: A 60-year-old woman with Stage IV colorectal cancer – MSI-H, BRAF V600E mutation
- Dr Apuri: A 59-year-old woman with metastatic CRC – MSS, KRAS G12C mutation
- Faculty Chalk Talks

Module 3: Pancreatic Cancer

- Dr Hart: A 67-year-old woman with metastatic pancreatic cancer

Module 4: Cholangiocarcinoma

- Dr Choksi: A 92-year-old woman with metastatic cholangiocarcinoma
- Faculty Chalk Talks

Module 5: Gastric, Gastroesophageal, Esophageal Cancers

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Case Presentation – Dr Peles: A 72-year-old woman with metastatic HCC

Dr Shachar Peles

- PMH: chronic hepatitis C infection, untreated; bilateral nephrectomies for bilateral kidney cancers
- Presented with right upper quadrant discomfort and workup revealed an infiltrative right hepatic lobe mass and a right pericardial mass
- RNA expression analysis of biopsy material reported 90% probability HCC

Case Presentation – Dr Peles: A 72-year-old woman with metastatic HCC (continued)

Dr Shachar Peles

- PMH: chronic hepatitis C infection, untreated; bilateral nephrectomies for bilateral kidney cancers
- Presented with right upper quadrant discomfort and workup revealed an infiltrative right hepatic lobe mass and a right pericardial mass
- RNA expression analysis of biopsy material reported 90% probability HCC
- ***Atezolizumab/bevacizumab initiated***

Questions

- ***Should you add in liver-directed therapy to systemic therapy, especially in patients who maybe have minimal disease outside of the liver? Is there a benefit to TACE or radioembolization on top of the systemic treatment?***
- ***How do you best sequence the available first- and second-line treatment options?***

Treatment options for Child-Pugh B HCC

Dr Mamta Choksi

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Chalk Talk – Tanios Bekaii-Saab, MD

Selection of first line systemic treatment for patients with advanced HCC and Child-Pugh B or C cirrhosis

Chalk Talk – Tanios Bekaii-Saab, MD

- Child-Pugh A HCC (BCLC C +/- some Bs)
  - ✓ Sorafenib → standard of care for advanced HCC for a decade
  - ✓ Lenvatinib → non-inferior but more tolerable than Sorafenib
  - ✓ Disappointing results with Nivolumab in 1L vs. sorafenib
  - ✓ New SOC with combining Bevacizumab to Atezolizumab
    - Significantly Better OS, PFS, ORR vs. sorafenib
    - + Clinically meaningful improvement in QOL and toxicity profile
  - ✓ More options (?) coming soon with COSMIC 312 (Cabozantinib/Atezo) and HIMALAYA (Durvalumab/Tremelimumab) reporting +ve
- Child-Pugh B7 HCC (BCLC C and PS <2) + some B8
  - ✓ Same(ish) as Child-Pugh A
- Child-Pugh B8+/C HCC (BCLC C)
  - ✓ Hospice

Optimal second line systemic treatment of advanced HCC after first line atezolizumab/bevacizumab

- If Child-Pugh A:
  - Regorafenib (RESOURCE – post sorafenib)
    - mOS 10.6 vs 7.8 mos (rego vs pbo)
  - Cabozantinib (CELESTIAL – post sorafenib)
    - mOS 10.2 vs 8.0 mos (cabo vs pbo)
  - Lenvatinib, sorafenib (or B7)
- AFP >/= 400 ng/mL:
  - Ramucirumab (REACH, REACH-2 – post sorafenib)
    - Pooled analysis: mOS 8.1 vs 5.0 mos (ram vs pbo)
- Other options:
  - Nivo/ipi (CheckMate 040 – post sorafenib)

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Case Presentation – Dr Patel: A 60-year-old woman with Stage IV colorectal cancer – microsatellite instability high (MSI-H), BRAF V600E mutation

Dr Ina Patel

- Diagnosed with Stage IV adenocarcinoma (pT3 N2b M1c) and s/p resection of primary
- Molecular analyses: MSI-H, KRAS WT, NRAS WT, BRAF V600E mutation, FLT3 amplification
- Pembrolizumab x 6 months with a mixed response and poor tolerance

Questions

- Would you switch to BRAF-targeted therapy or to chemotherapy? Would her MSI-H disease be responsive to chemotherapy?
- Would you try more immunotherapy, such as ipilimumab/nivolumab?
- In your experience, how efficacious is BRAF-targeted therapy in this setting?

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Case Presentation – Dr Apuri: A 59-year-old woman with metastatic CRC – MSS, KRAS G12C mutation

Dr Susmitha Apuri

- Presented with anemia and workup revealed a large 9-cm partially obstructing mass in the sigmoid colon and 2 nodules in the right lung
- FOLFOX/bevacizumab with stereotactic radiation to lung lesions → PD → FOLFIRI/bevacizumab
- Overall poor tolerance to chemotherapy; neuropathy
- NGS: KRAS G12C mutation

Questions

- Would regorafenib or TAS-102 be better tolerated? Would it be beneficial to add bevacizumab?
- How do you approach the dosing of regorafenib? Would your approach differ if it is combined with bevacizumab?

Chalk Talk – Tanios Bekaii-Saab, MD

Current and future use of ctDNA in the early and metastatic settings in colorectal cancer

Chalk Talk – Tanios Bekaii-Saab, MD

- Circulating tumor DNA (ctDNA) is found in the bloodstream and refers to DNA coming from cancerous CRC cells
- Multiple applications of ctDNA as Liquid Biopsies for Precision Medicine :
  - ✓ Determining the risk for relapse (MRD assessment/prognosis)
  - ✓ Identification of therapeutic targets in mCRC
- Future (potential) applications of ctDNA as Liquid Biopsies for Precision Medicine :
  - ✓ Early Detection of Cancer (diagnosis/screening)
  - ✓ Predictive role for treatment decision in adjuvant setting
  - ✓ Detection of resistance mechanisms in mCRC (serial testing)
  - ✓ Monitoring treatment response (including IO monitoring)

Choice of immunotherapy as first line treatment for MSI-high/dMMR metastatic colorectal cancer

- Pembrolizumab
  - KN-177 (phase III RCT): ORR 45.1% vs. 33.1% (pembro vs. chemo)
  - mPFS 16.5 vs 8.5 mos favoring pembro
  - No OS benefit (60% crossover)
- Nivolumab +/- ipilimumab
  - CheckMate 142 (phase II non-RCT):
  - ORR nivo/ipi: 58%/64%; mPFS, mOS not reached
  - ORR nivo: 31%

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Case Presentation – Dr Hart: A 67-year-old woman with metastatic pancreatic cancer

Dr Lowell Hart

- Neoadjuvant gemcitabine/*nab* paclitaxel; switched to 5-FU XRT due to pulmonary infiltrates concerning for gemcitabine toxicity
- Subtotal pancreatectomy and splenectomy with residual disease (ypT pN1); patient declined adjuvant chemotherapy
- Follow-up scan detected metastases
- Liposomal irinotecan/5-FU with poor tolerance with hospitalization and no real improvement
- Germline BRCA testing: negative

Questions

- What would you have recommended as neoadjuvant therapy for this patient?
- Do you test 100% of patients for germline mutations? If the patient is negative for germline mutations, would you order NGS of their tumor?
- What treatment would you recommend currently for this patient?

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Case Presentation – Dr Choksi: A 92-year-old woman with metastatic cholangiocarcinoma

Dr Mamta Choksi

- Presented with abnormal weight loss, fatigue, jaundice, and nausea
- Baseline CA 19-9 >40,000
- Workup reveals numerous liver metastases and a hypermetabolic focus in the common bile duct, clinically suggestive of primary cholangiocarcinoma with liver metastases
- NGS: no targetable mutation

Questions

- What are your treatment options for the primary metastatic cholangiocarcinoma in elderly patients?
- What are the treatment options for surgically resected cholangiocarcinoma with positive margins?

Chalk Talk – Tanios Bekaii-Saab, MD

Targeted treatment of cholangiocarcinoma (IDH1 and FGFR2 inhibitors)

Chalk Talk – Tanios Bekaii-Saab, MD

- Gemcitabine/Cisplatin is SOC for 1L in unselected BTC
- 5FU(inf) + Oxali or + Naliri SOC post Gem/Cis in unselected BTC
- BTC = Target rich disease with FGFR2 fusions (~10%) and IDH1 mutations (~20%) most common in IHCA
  - ✓ 2 agents approved for IHCA with FGFR2 fusions following Gem/Cis failure → Pemigatinib and Infigratinib
    - RR ~ 30-40% + can be durable in many
    - Watch for hypophosphatemia, skin and ocular toxicities, + other
  - ✓ 1 agent approved for IHCA with IDH1 following Gem/Cis failure → Ivosedinib
    - RR ~ 0% (SD ~ 50%) + PFS > PBO (HR=.37)
    - OS = PBO (Sec EP + crossover ?factors)
- Future directions → 1L studies with Pemig, Infig and Futibatinib vs. Gem/Cis in pts with FGFR2 fusions
- Other promising targets → BRAF V600E , Her2 amp (especially in GBCA) + others under investigation …

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Selection of patients with upper GI cancers for treatment with adjuvant immunotherapy; role, if any, of PD-L1 assay, TMB and/or MSI status

- CheckMate 577:
  - Ph III RCT – stage II/III GEJ/esophageal adeno/SCC s/p chemoRT + R0 resection with residual disease
  - mDFS: 22.4 vs 11.0 mos (nivo vs pbo)
  - PD-L1 status not an integral biomarker
  - TPS >/= or < 1% a stratification factor
  - Distant recurrence 29% vs 39% (nivo vs pbo)
  - Locoregional recurrence 12% vs 17% (nivo vs pbo)
  - Median distant metastasis-free survival: 28.3 vs 17.6 mos (nivo vs pbo)
  - mPFS2 NR vs 32.1 mos (nivo vs pbo)

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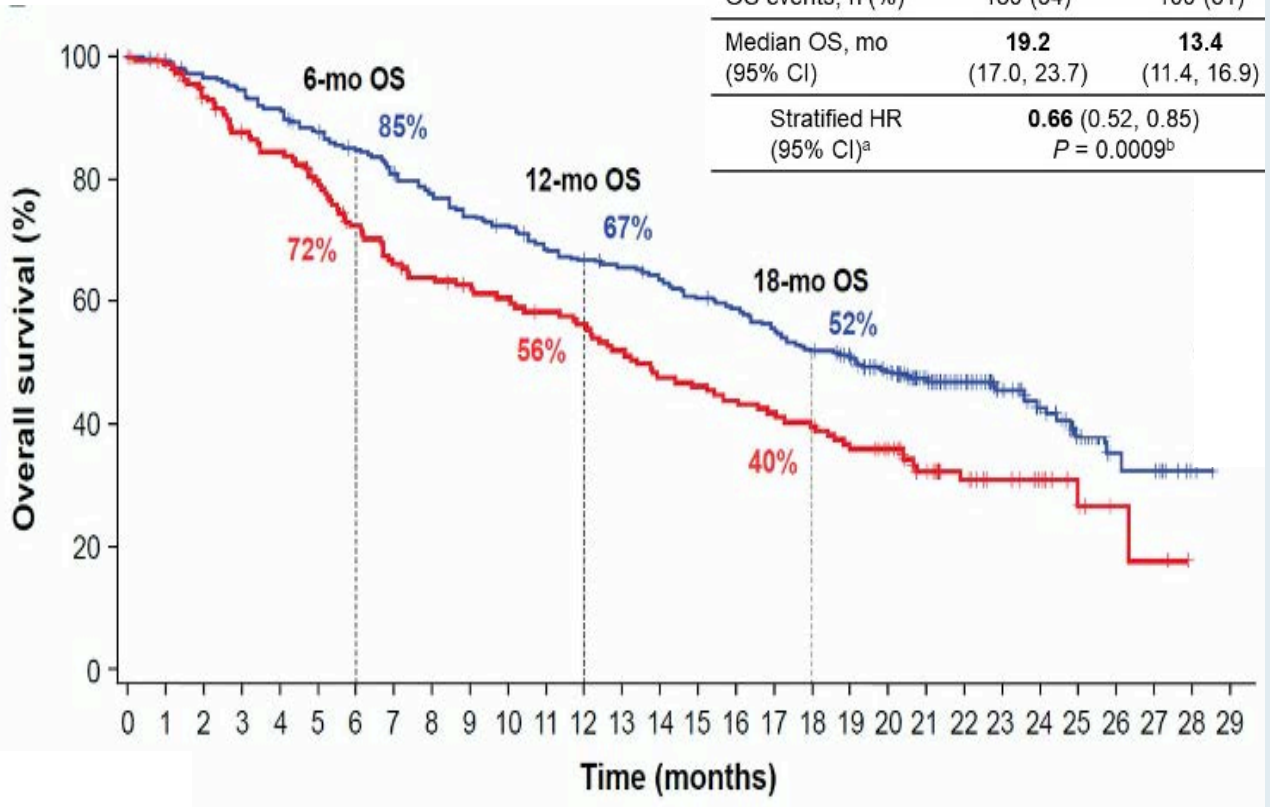
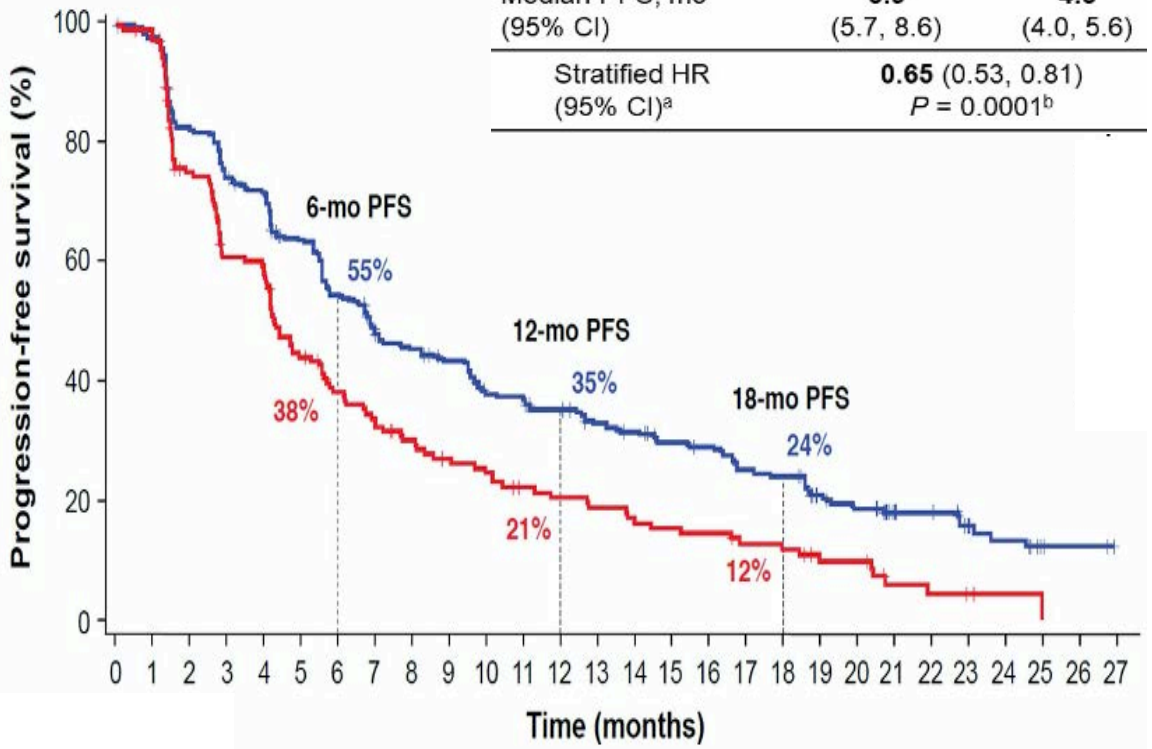
Hepatocellular Carcinoma

IMbrave150 Updated OS and PFS: Atezolizumab/Bevacizumab versus Sorafenib

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



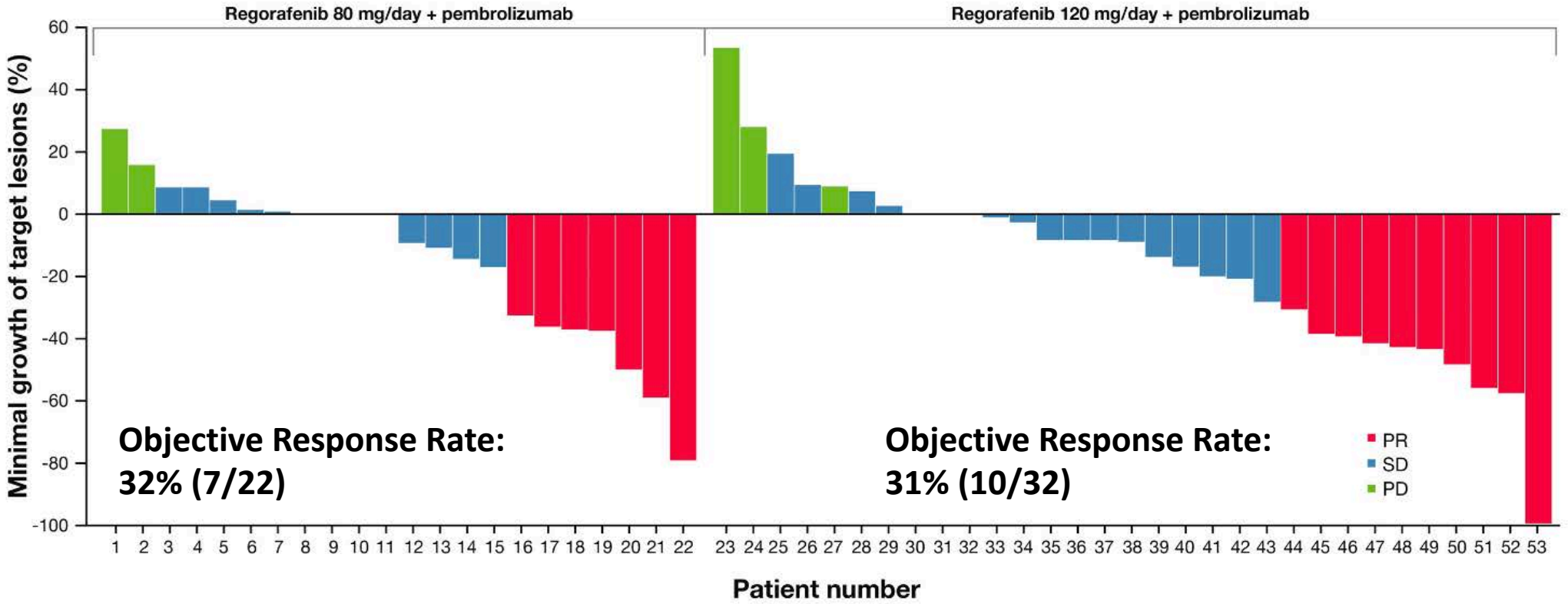
Updated PFS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
PFS events, n (%)	257 (76)	130 (79)
Median PFS, mo (95% CI)	**6.9** (5.7, 8.6)	**4.3** (4.0, 5.6)
Stratified HR (95% CI)[a]	**0.65** (0.53, 0.81) *P* = 0.0001[b]	



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

RTP RESEARCH TO PRACTICE

Efficacy of Regorafenib (80 mg or 120 mg) with Pembrolizumab as First-Line Therapy for HCC



Tumor response according to RECIST v1.1. Response data are derived from the updated efficacy analysis (April 9, 2021).
PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

El-Khoueiry AB et al. ASCO 2021;Abstract 4078.

RTP RESEARCH TO PRACTICE

Cabozantinib in Combination with an Immune Checkpoint Inhibitor Significantly Improved Progression-Free Survival in Phase 3 COSMIC-312 Pivotal Trial in Patients with Previously Untreated Advanced Liver Cancer

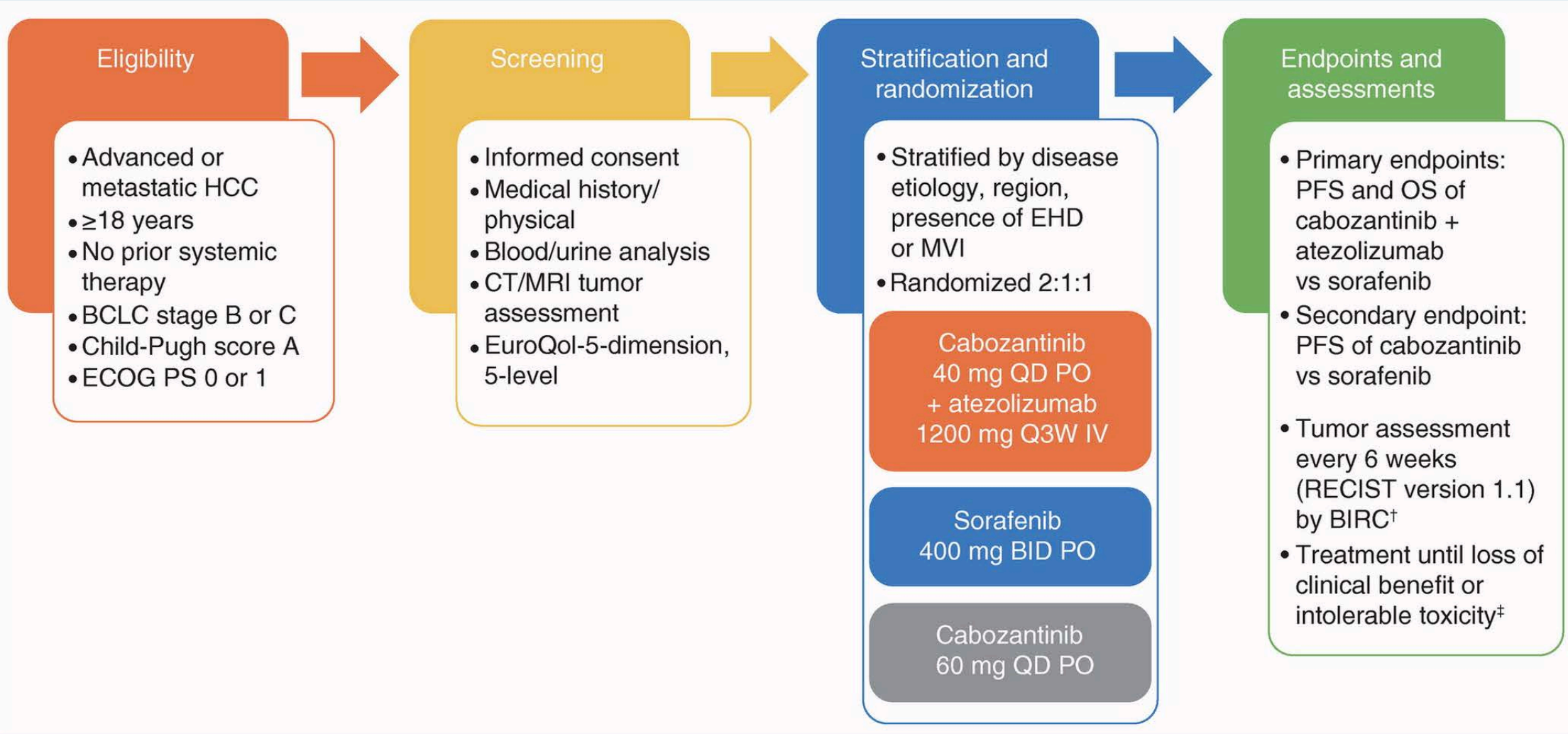
Press Release: June 28, 2021

"COSMIC-312, the ongoing phase 3 pivotal trial evaluating cabozantinib in combination with atezolizumab versus sorafenib in patients with previously untreated advanced hepatocellular carcinoma (HCC) met one of the primary endpoints, demonstrating significant improvement in progression-free survival (PFS) at the planned primary analysis. A prespecified interim analysis for the second primary endpoint of overall survival (OS), conducted at the same time as the primary analysis for PFS, showed a trend favoring the combination of cabozantinib and atezolizumab, but did not reach statistical significance.

In the analysis of the primary endpoint of PFS in the PFS intent-to-treat population, cabozantinib in combination with atezolizumab significantly reduced the risk of disease progression or death by 37% compared with sorafenib (hazard ratio [HR]: 0.63; 99% confidence interval [CI]: 0.44-0.91; P=0.0012)."

https://www.ipsen.com/press-releases/exelixis-and-ipsen-announce-cabozantinib-in-combination-with-an-immune-checkpoint-inhibitor-significantly-improved-progression-free-survival-in-phase-3-cosmic-312-pivotal-trial-in-patients-with-previo/

COSMIC-312: Ongoing Phase III Trial of Cabozantinib with Atezolizumab versus Sorafenib Alone for Treatment-Naïve Advanced HCC



Kelley RK et al. *ESMO Open* 2020;5(4):e000714.

RTP RESEARCH TO PRACTICE

Durvalumab with Tremelimumab Significantly Improved Overall Survival in HIMALAYA Phase III Trial in First-Line Unresectable Liver Cancer

Press Release: October 15, 2021

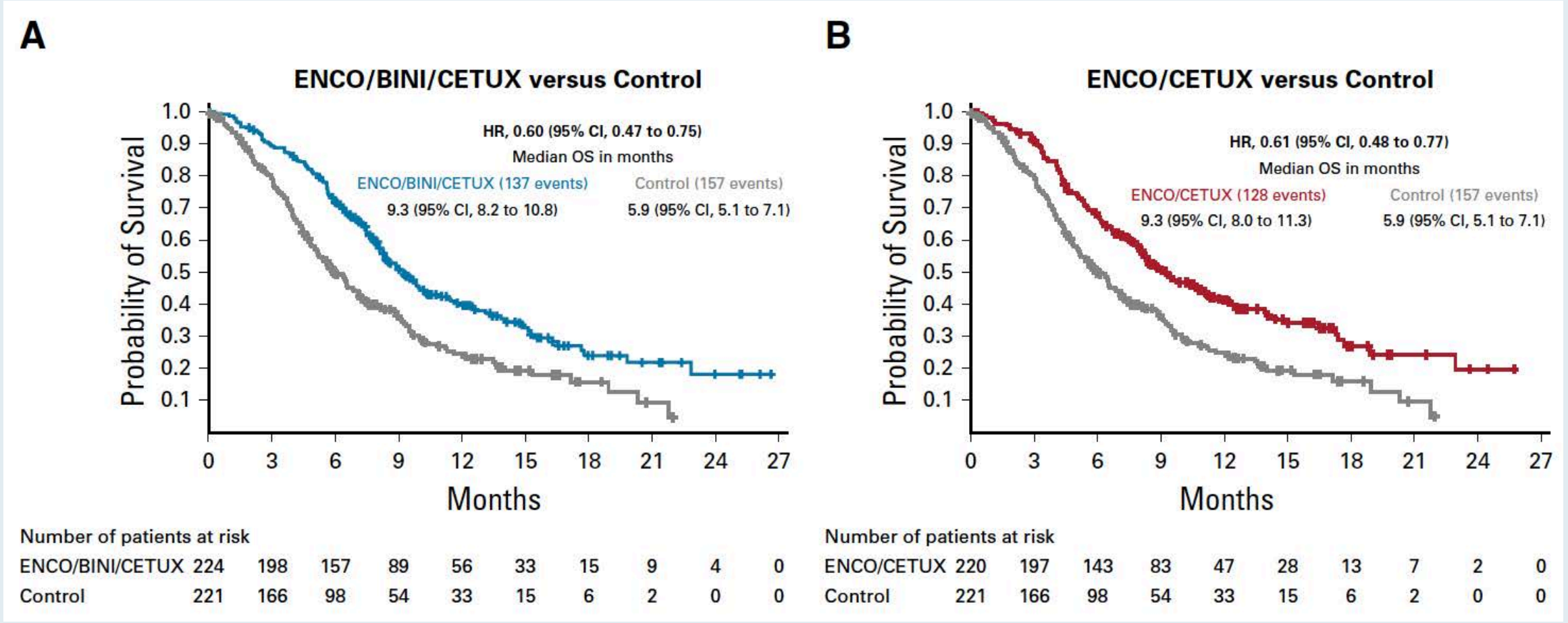
"Positive high-level results from the HIMALAYA Phase III trial showed a single, high priming dose of tremelimumab added to durvalumab demonstrated a statistically significant and clinically meaningful overall survival (OS) benefit versus sorafenib as a 1st-line treatment for patients with unresectable hepatocellular carcinoma (HCC) who had not received prior systemic therapy and were not eligible for localized treatment. This novel dose and schedule of tremelimumab, an anti-CTLA4 antibody, and durvalumab is called the STRIDE regimen (Single Tremelimumab Regular Interval Durvalumab). The combination demonstrated a favorable safety profile, and the addition of tremelimumab to durvalumab did not increase severe hepatic toxicity.

"Durvalumab alone demonstrated non-inferior OS to sorafenib with a numerical trend in favor of durvalumab and an improved tolerability profile compared to sorafenib."

https://www.astrazeneca-us.com/media/press-releases/2021/imfinzi-plus-tremelimumab-significantly-improved-overall-survival-in-himalaya-phase-iii-trial-in-1st-line-unresectable-liver-cancer-10152021.html

Colorectal Cancer

BEACON: Overall Survival Results



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

RTP RESEARCH TO PRACTICE

BREAKWATER Study Design

An open-label, multicenter, randomized phase 3 study of 1st line encorafenib plus cetuximab with or without chemotherapy versus standard of care therapy in patients with metastatic *BRAF* V600E-mutant mCRC

Safety lead-in

Patients with *BRAF*^{V600E} mutant mCRC with 0 to 1 prior regimens in the metastatic setting

Phase 3

Patients with *BRAF*^{V600E} mutant mCRC and no prior systemic therapy in the metastatic setting

Encorafenib + cetuximab + mFOLFOX6
N=30
Encorafenib + cetuximab + FOLFIRI
N=30

Dosages
- Encorafenib, 300 mg PO QD
- Cetuximab, 500 mg/m² IV Q2W
- **FOLFOX, full dose IV Q2W**
- FOLFIRI, full dose IV Q2W

Randomize 1:1:1*

Arm A**
Encorafenib + cetuximab, N=290

Arm B**
Encorafenib + cetuximab + FOLFOX or FOLFIRI$^{\beta}$, N=290

Control arm§
Physician's choice: FOLFOX, FOLFIRI, FOLFOXIRI, CAPOX, all ± anti-VEGF antibody, N=290

PRIMARY ENDPOINTS
PFS (BICR) Arm A vs Control
AND
PFS (BICR) Arm B vs Control
(BICR, blinded independent central review)

KEY SECONDARY ENDPOINTS
OS Arm A vs Control
AND
OS Arm B vs Control

OTHER ENDPOINTS
- Incidence of DLTs, adverse events, dose modifications/discontinuations due to AEs
- PK including drug-drug interactions

BREAKWATER STUDY

*Stratified by: ECOG PS 0 v. 1, Region US/Canada v. Western Europe v. ROW
**Same dosing as SLI; $^{\beta}$FOLFOX or FOLFIRI based on SLI results; § No crossover.
ClinicalTrials.gov Identifier: NCT04607421

Van Cutsem E et al. ESMO World Congress on Gastrointestinal Cancer 2021;Abstract O-10.

FDA Approves New Dosing Regimen for Cetuximab

Press Release: April 6, 2021

"The Food and Drug Administration approved a new dosage regimen of 500 mg/m^2 as a 120-minute intravenous infusion every two weeks (Q2W) for cetuximab for patients with K-Ras wild-type, EGFR-expressing colorectal cancer (mCRC) or squamous cell carcinoma of the head and neck (SCCHN).

This approval provides for a biweekly dosage regimen option in addition to the previously approved weekly dosage regimen for the approved indications when cetuximab is used as a single agent or in combination with chemotherapy.

The approval was based on population pharmacokinetic (PK) modeling analyses that compared the predicted exposures of cetuximab 500 mg Q2W to observed cetuximab exposures in patients who received cetuximab 250 mg weekly. The application was also supported by pooled analyses of overall response rates, progression-free survival, and overall survival (OS) from published literature in patients with CRC and SCCHN, and OS analyses using real-world data in patients with mCRC who received either the weekly cetuximab or Q2W regimens. In these exploratory analyses, the observed efficacy results were consistent across dosage regimens and supported the results of the population PK modeling analyses."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-new-dosing-regimen-cetuximab

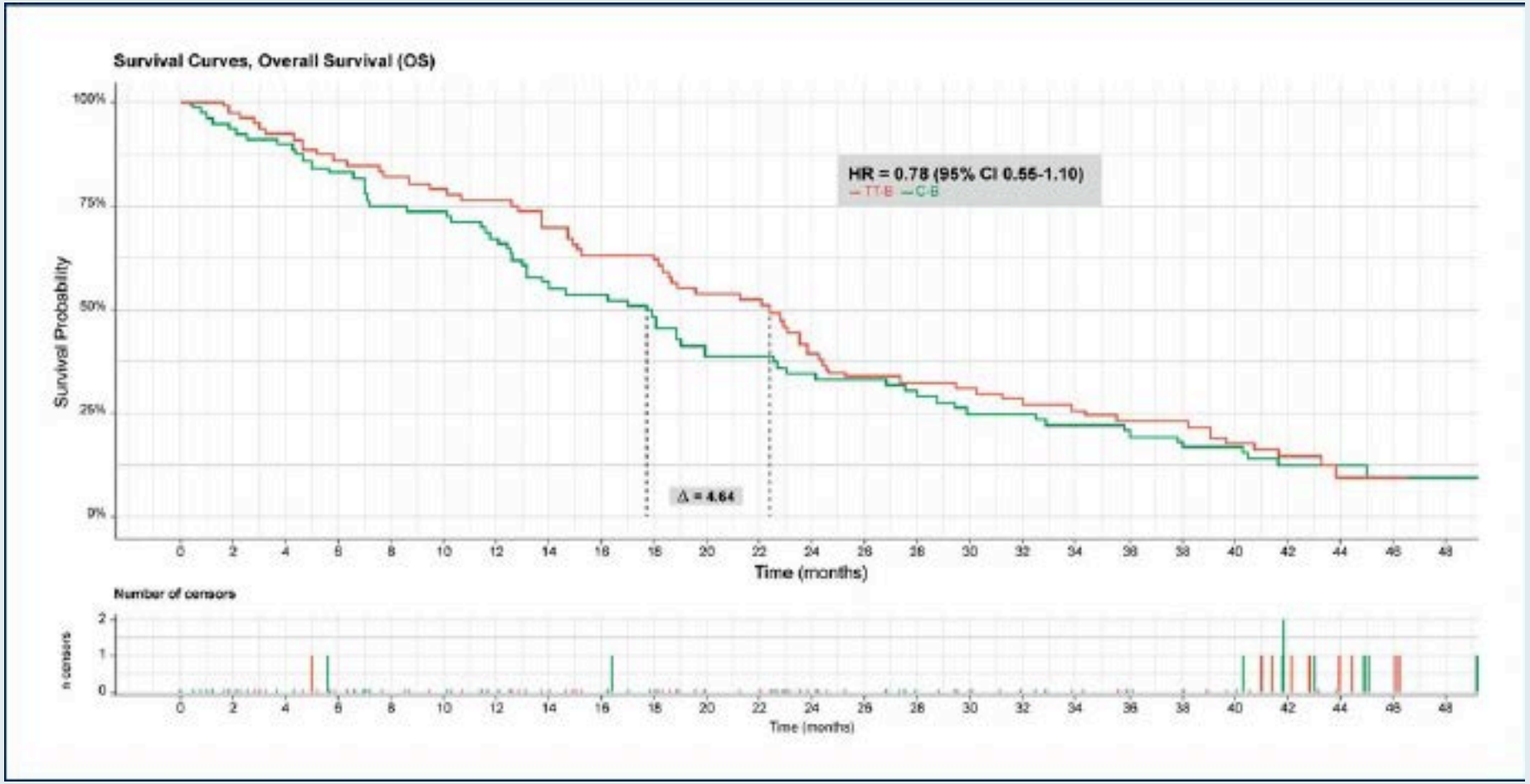
TASCO01: TAS-102/Bevacizumab (TT-B) versus Capecitabine/Bevacizumab (C-B) for First-Line mCRC — Progression-Free Survival

A difference of 14 months was demonstrated in median PFS between TT-B and C-B

Van Cutsem et al. ASCO GI 2021;Abstract 14

RTP RESEARCH TO PRACTICE

TASCO01: TAS-102/Bevacizumab (TT-B) versus Capecitabine/Bevacizumab (C-B) for First-Line mCRC — Overall Survival



A difference of 4.64 months was demonstrated for median OS between TT-B and C-B

Van Cutsem et al. ASCO GI 2021;Abstract 14

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FDA Grants Accelerated Approval to Dostarlimab-gxly for dMMR Advanced Solid Tumors

Press Release: August 17, 2021

"The Food and Drug Administration granted accelerated approval to dostarlimab-gxly for adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

The FDA also approved the VENTANA MMR RxDx Panel as a companion diagnostic device to select patients with dMMR solid tumors for treatment with dostarlimab-gxly.

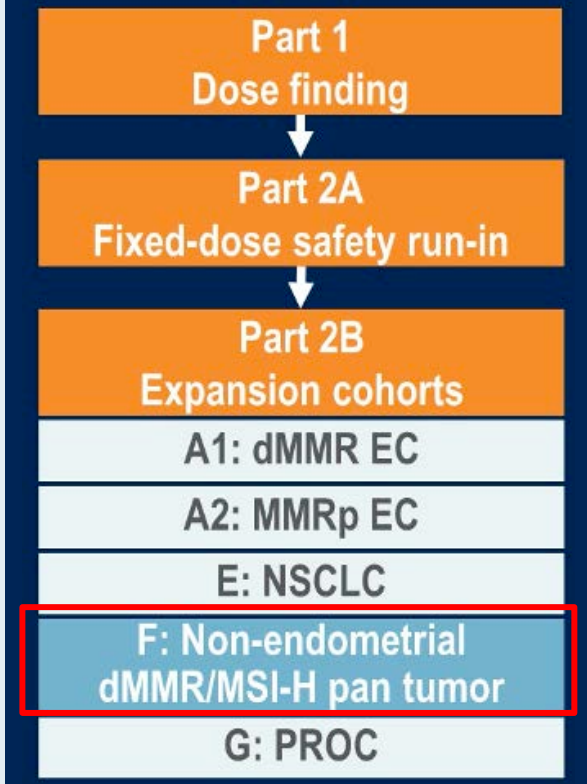
The efficacy of dostarlimab was evaluated in the GARNET Trial (NCT02715284), a non-randomized, multicenter, open-label, multi-cohort trial. The efficacy population consisted of 209 patients with dMMR recurrent or advanced solid tumors who progressed following systemic therapy and had no satisfactory alternative treatment.

The primary efficacy endpoints were overall response rate (ORR) and duration of response (DoR) as determined by blinded independent central review according to RECIST 1.1. The ORR was 41.6% (95% CI: 34.9, 48.6), with 9.1% complete response rate and 32.5% partial response rate. Median DOR was 34.7 months (range 2.6, 35.8+), with 95.4% of patients with duration ≥6 months."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dostarlimab-gxly-dmmr-advanced-solid-tumors

GARNET: Methods, Patient Characteristics and Antitumor Activity

Cohorts



Patient Characteristics

Characteristic	Cohort F N=106
Median age, years (range)	61.5 (24–85)
Sex, n (%)	
Male	58 (55)
Female	48 (45)
ECOG performance status, n (%)	
0	42 (40)
1	64 (60)
Histology, n (%)	
Colorectal	69 (65)
Small intestine	12 (11)
Gastric and gastroesophageal junction	8 (8)
Pancreatic carcinoma	4 (4)
Ovarian	2 (2)
Hepatocellular carcinoma	2 (2)
Other[a]	9 (8)

Response

Tumor type	Patients, N	Confirmed ORR (RECIST v1.1) n	95% CI[a]
Overall	**106**	**41 (38.7%)**	**(29.4%–48.6%)**
CRC	**69**	**25 (36.2%)**	**(25.0%–48.7%)**
Non-CRC	**37**	**16 (43.2%)**	**(27.1%–60.5%)**
Small intestinal cancer	12	4 (33.3%)	(9.9%–65.1%)
Gastric and gastroesophageal junction	8	3 (37.5%)	(8.5%–75.5%)
Pancreatic carcinoma	4	SD, 3 PD	
Ovarian cancer	2	PR, SD	
Hepatocellular carcinoma	2	PR, PD	
Biliary neoplasm	1	CR	
Breast cancer	1	CR	
Gallbladder	1	CR	
Adrenal cortical	1	PR	
Genital neoplasm malignant female	1	PR	
Pleural	1	PR	
Unknown origin	1	PR	
Renal cell carcinoma	1	SD	
Esophageal cancer	1	PD	

dMMR = mismatch repair-deficient; EC = endometrial cancer; MMRp = mismatch mutation repair-proficient; NSCLC = non-small cell lung cancer; PROC = platinum-resistant ovarian cancer

Andre T et al. Gastrointestinal Cancers Symposium 2021;Abstract 9.

Pancreatic Cancer

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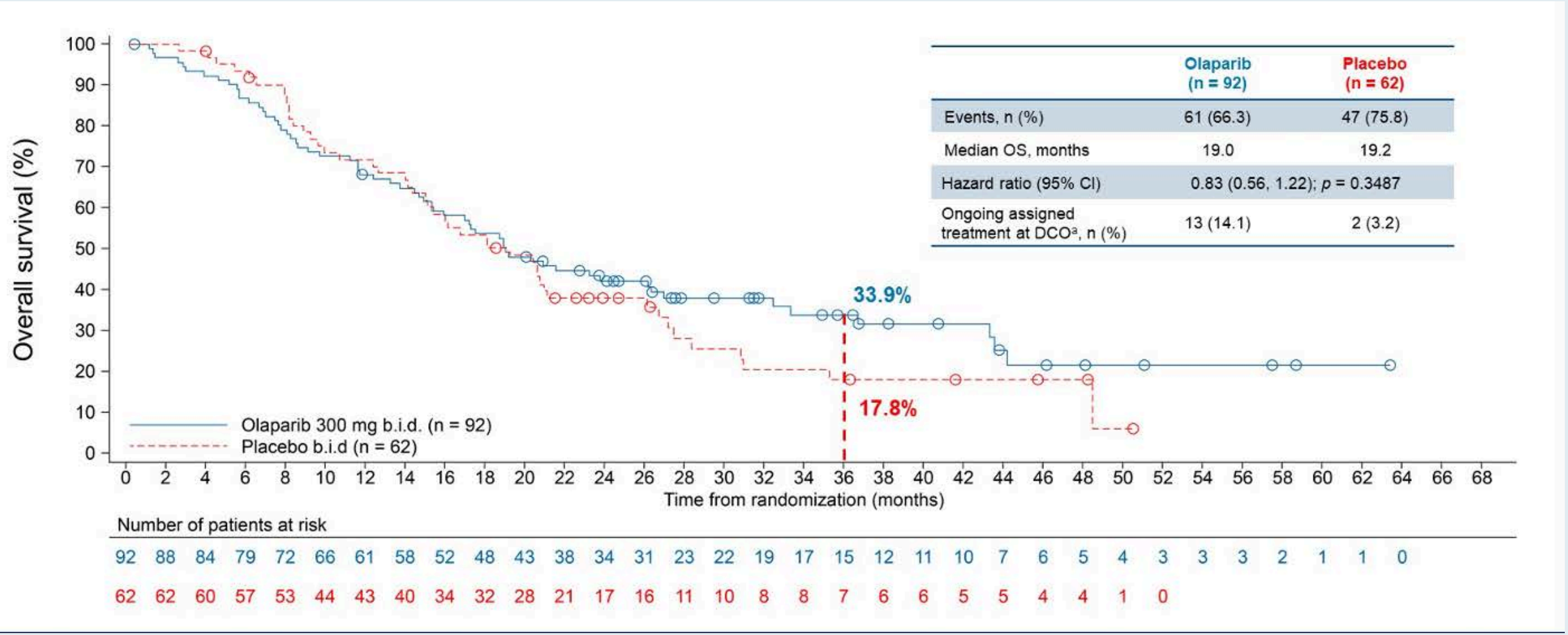
POLO: Final Overall Survival with Maintenance Olaparib for Metastatic Pancreatic Cancer with a Germline BRCA Mutation



	Olaparib (n = 92)	Placebo (n = 62)
Events, n (%)	61 (66.3)	47 (75.8)
Median OS, months	19.0	19.2
Hazard ratio (95% CI)	0.83 (0.56, 1.22); *p* = 0.3487	
Ongoing assigned treatment at DCO[a], n (%)	13 (14.1)	2 (3.2)

Golan T et al. Gastrointestinal Cancers Symposium 2021;Abstract 378.

RTP RESEARCH TO PRACTICE

Cholangiocarcinoma

FDA Approves Ivosidenib for Advanced or Metastatic Cholangiocarcinoma

Press Release: August 25, 2021

"The Food and Drug Administration approved ivosidenib for adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

Today, the FDA also approved the Oncomine Dx Target Test as a companion diagnostic device to aid in selecting patients with cholangiocarcinoma for treatment with ivosidenib.

Ivosidenib was investigated in a randomized (2:1), multicenter, double-blind, placebo-controlled clinical trial (Study AG120-C-005, NCT02989857) of 185 adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation. The patient's disease must have progressed following at least one, but not more than two prior regimens, including at least one gemcitabine- or 5-flurouracil-containing regimen. Patients were randomized to receive either ivosidenib 500 mg orally once daily or matched placebo until disease progression or unacceptable toxicity."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ivosidenib-advanced-or-metastatic-cholangiocarcinoma

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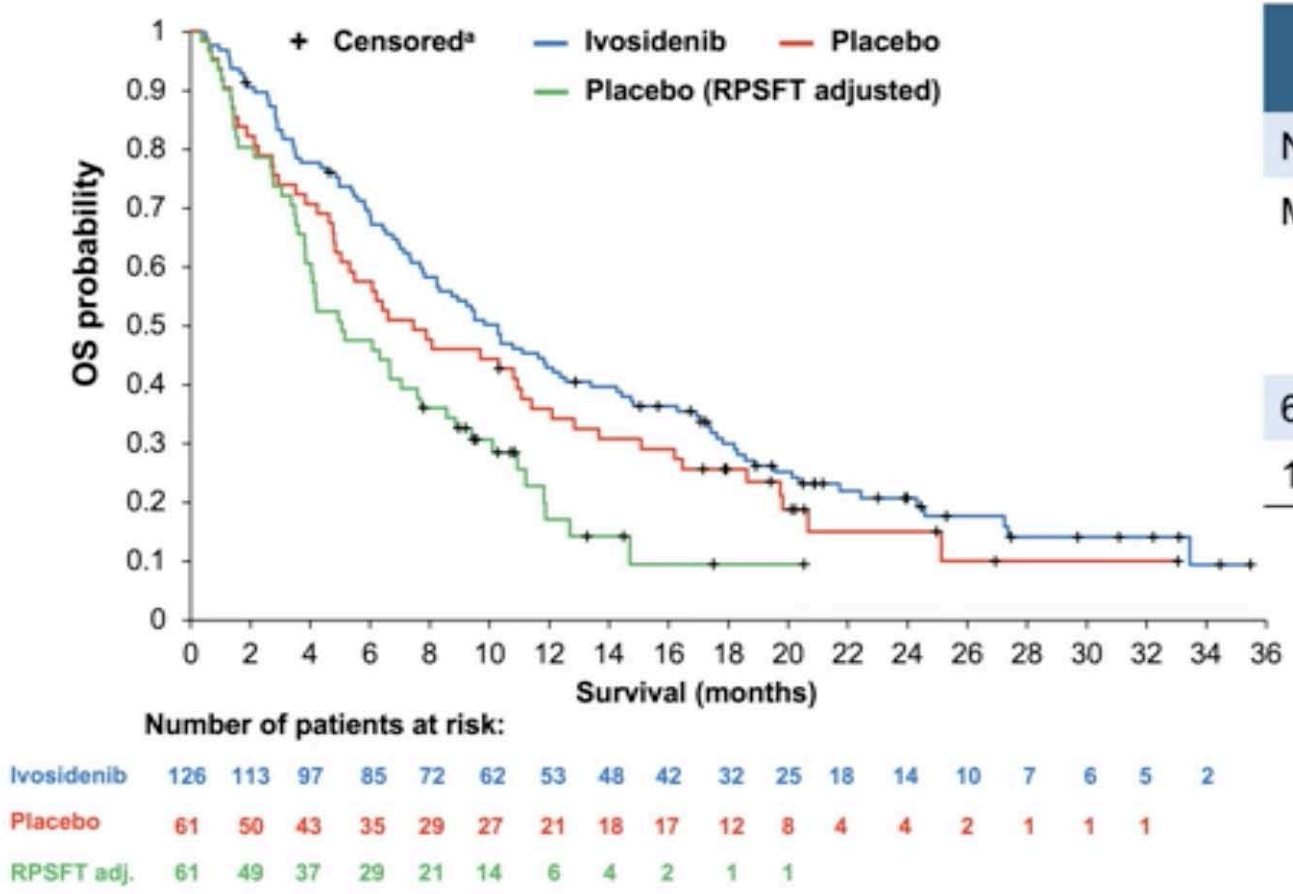
ClarIDHy: Overall Survival

The planned crossover-adjusted OS was derived using the rank-preserving structural failure time (RPSFT) model



	Ivosidenib n = 126	Placebo n = 61
Number of events (%)	100 (79.4)	50 (82.0)
Median OS, months	10.3	7.5
HR (95% CI)	0.79 (0.56, 1.12)	
1-sided p-value	0.093	
6-month OS rate, %	69	57
12-month OS rate, %	43	36

- The median OS in the placebo arm after adjustment for crossover was 5.1 months (HR = 0.49 [95% CI 0.34, 0.70]; 1-sided $p < 0.0001$)

Abou-Alfa GK et al. ASCO 2021;Abstract 4069.

FDA Grants Accelerated Approval to Infigratinib for Metastatic Cholangiocarcinoma

Press Release: May 28, 2021

"The Food and Drug Administration granted accelerated approval to infigratinib, a kinase inhibitor for adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.

The FDA also approved FoundationOne® CDx for selection of patients with FGFR2 fusion or other rearrangement as a companion diagnostic device for treatment with infigratinib.

Efficacy was demonstrated in CBGJ398X2204 (NCT02150967), a multicenter open-label single-arm trial, that enrolled 108 patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement as determined by local or central testing. Patients received infigratinib 125 mg orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles until disease progression or unacceptable toxicity."

www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-infigratinib-metastatic-cholangiocarcinoma

FDA Grants Breakthrough Therapy Status to Futibatinib for Advanced Cholangiocarcinoma

Press Release: April 01, 2021

"The FDA granted breakthrough therapy designation to futibatinib for the treatment of patients with locally advanced or metastatic cholangiocarcinoma with *FGFR2* gene rearrangements, according to a press release from the agent's manufacturer.

Futibatinib (TAS-120) — a covalently binding small-molecular inhibitor of FGFR— previously received orphan drug status for this indication. The agent is under investigation for the treatment of patients with advanced solid tumors with FGFR genetic aberrations who previously received chemotherapy or other therapies.

This decision was based on data from the phase 2 FOENIX-CCA2 study, scheduled for presentation at American Association for Cancer Research Annual Meeting this month."

https://www.healio.com/news/hematology-oncology/20210401/fda-grants-breakthrough-therapy-status-to-futibatinib-for-advanced-cholangiocarcinoma

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Gastric, Gastroesophageal, Esophageal Cancers

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FDA Approves Nivolumab for Resected Esophageal or GEJ Cancer

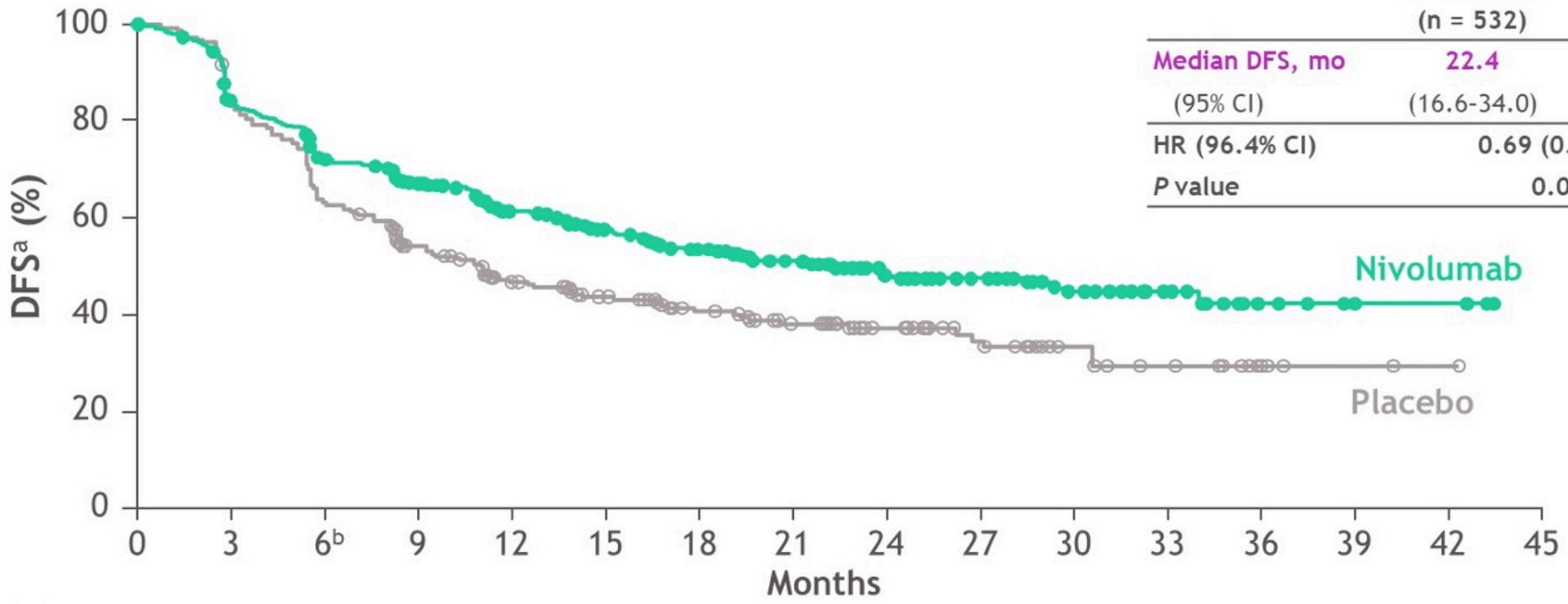
Press Release: May 20, 2021

"The Food and Drug Administration approved nivolumab for patients with completely resected esophageal or gastroesophageal junction (GEJ) cancer with residual pathologic disease who have received neoadjuvant chemoradiotherapy.

Efficacy was evaluated in CHECKMATE-577 (NCT02743494), a randomized, multicenter, double-blind trial in 794 patients with completely resected (negative margins) esophageal or GEJ cancers who had residual pathologic disease following concurrent chemoradiotherapy. Patients were randomized (2:1) to receive either nivolumab 240 mg or placebo every 2 weeks for 16 weeks followed by 480 mg of nivolumab or placebo every 4 weeks beginning at week 17 for up to one year of treatment."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-resected-esophageal-or-gej-cancer

CheckMate 577: Disease-Free Survival



	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6-34.0)	(8.3-14.3)
HR (96.4% CI)	0.69 (0.56-0.86)	
P value	0.0003[c]	

No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

Kelly RJ et al. ASCO 2021;Abstract 4003.

FDA Approves Nivolumab in Combination with Chemotherapy for Metastatic Gastric Cancer and Esophageal Adenocarcinoma

Press Release: April 16, 2021

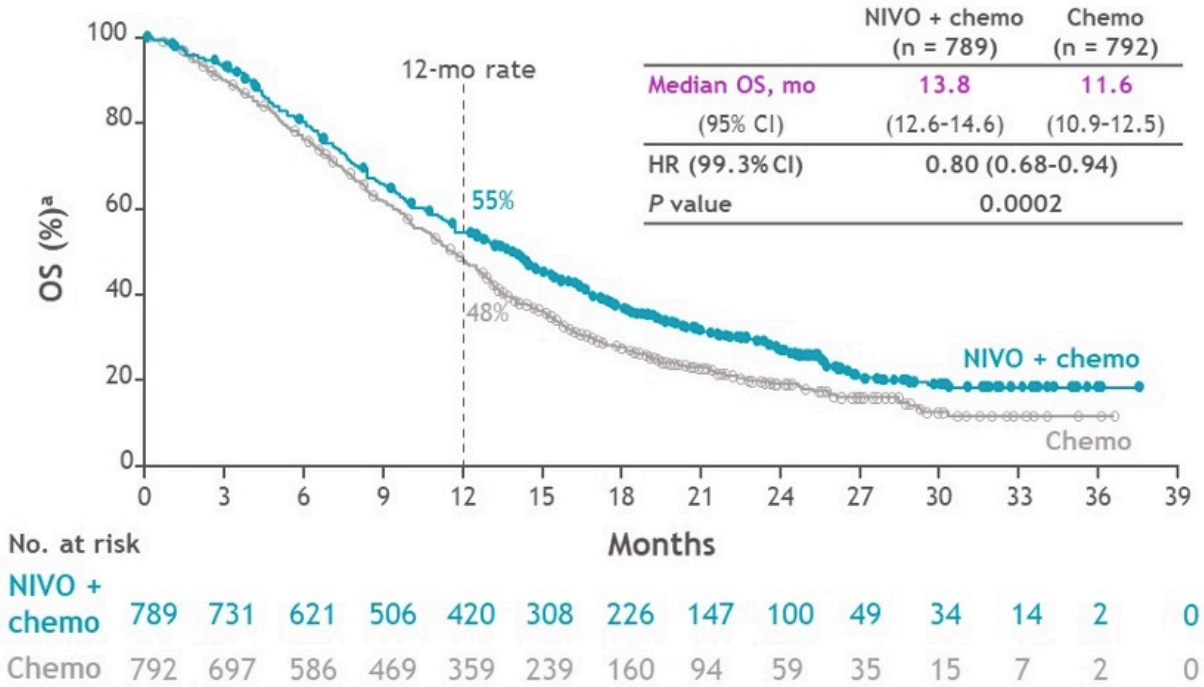
"The Food and Drug Administration approved nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

Efficacy was evaluated in CHECKMATE-649 (NCT02872116), a randomized, multicenter, open-label trial that enrolled 1,581 patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma. PD-L1 combined positive score (CPS) was determined centrally using the Agilent/Dako PD-L1 IHC 28-8 pharmDx test. Patients received nivolumab in combination with chemotherapy (n=789) or chemotherapy alone (n=792)."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-combination-chemotherapy-metastatic-gastric-cancer-and-esophageal

CheckMate 649 Dual Primary Endpoints: PFS and OS

Overall survival

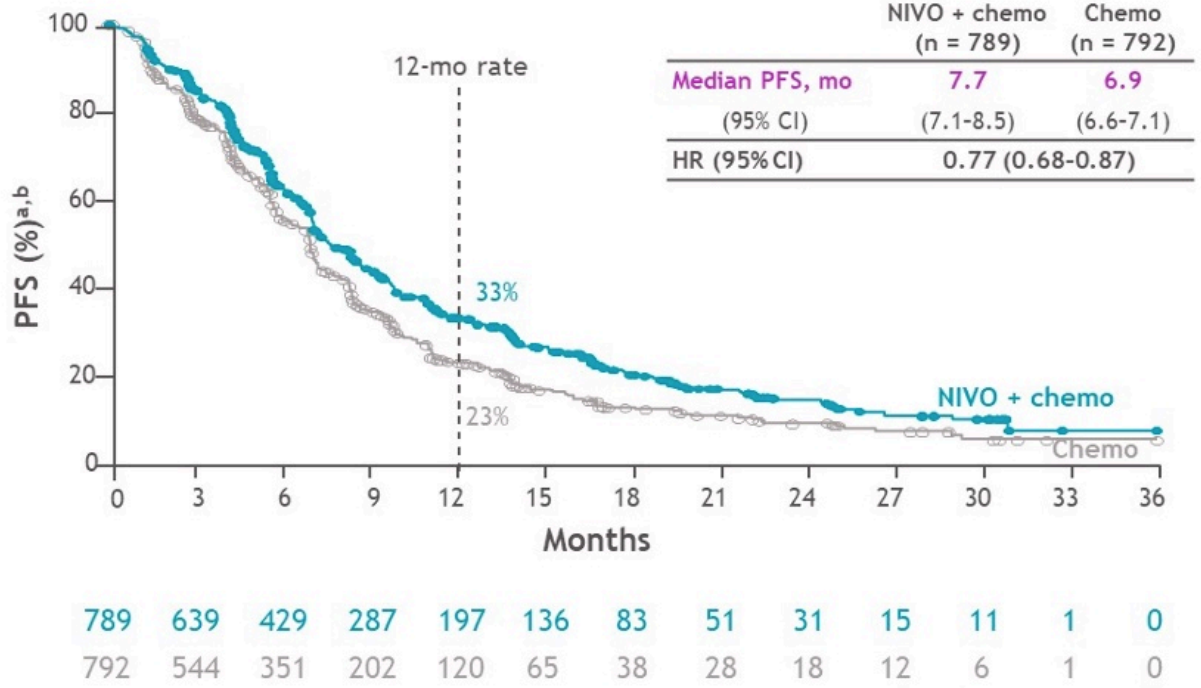


	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.8	11.6
(95% CI)	(12.6-14.6)	(10.9-12.5)
HR (99.3% CI)	0.80 (0.68-0.94)	
P value	0.0002	

No. at risk

NIVO + chemo	789	731	621	506	420	308	226	147	100	49	34	14	2	0
Chemo	792	697	586	469	359	239	160	94	59	35	15	7	2	0

Progression-free survival



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median PFS, mo	7.7	6.9
(95% CI)	(7.1-8.5)	(6.6-7.1)
HR (95% CI)	0.77 (0.68-0.87)	

NIVO + chemo	789	639	429	287	197	136	83	51	31	15	11	1	0	
Chemo	792	544	351	202	120	65	38	28	18	12	6	1	0	

- Superior OS benefit and clinically meaningful PFS improvement in all randomized patients with NIVO + chemo vs chemo
- Median OS with NIVO + chemo vs chemo in patients with PD-L1 CPS ≥ 5 was 14.4 vs 11.1 months and median PFS was 7.7 vs 6.0 months[1]

Moehler M et al. ASCO 2021;Abstract 4002.

RTP RESEARCH TO PRACTICE

FDA Approves Pembrolizumab for Esophageal or GEJ Carcinoma

Press Release: March 22, 2021

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

Efficacy was evaluated in KEYNOTE-590 (NCT03189719), a multicenter, randomized, placebo-controlled trial that enrolled 749 patients with metastatic or locally advanced esophageal or gastroesophageal junction carcinoma who were not candidates for surgical resection or definitive chemoradiation. PD-L1 status was centrally determined in tumor specimens in all patients using the PD-L1 IHC 22C3 pharmDx kit. Patients were randomized (1:1) to pembrolizumab in combination with cisplatin and fluorouracil or placebo with cisplatin and fluorouracil, until unacceptable toxicity or disease progression."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-esophageal-or-gej-carcinoma

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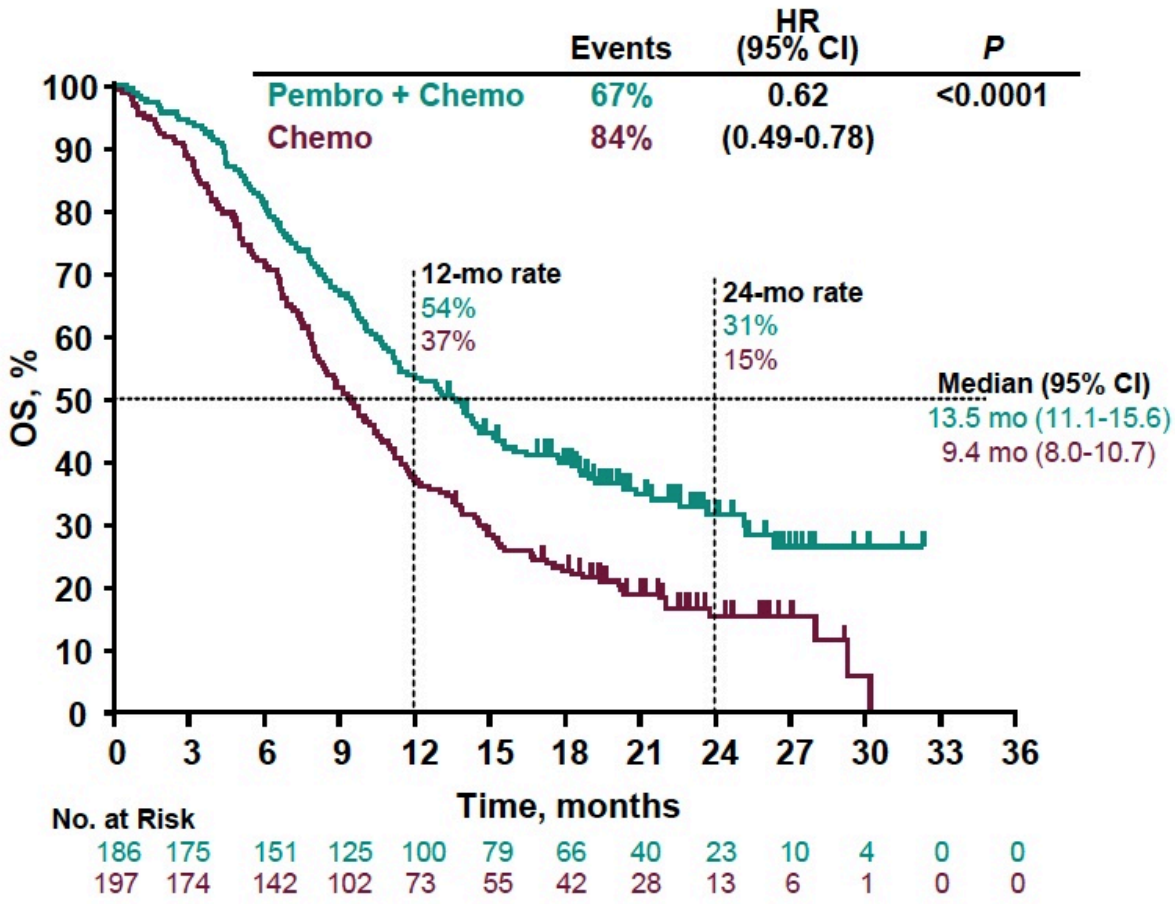
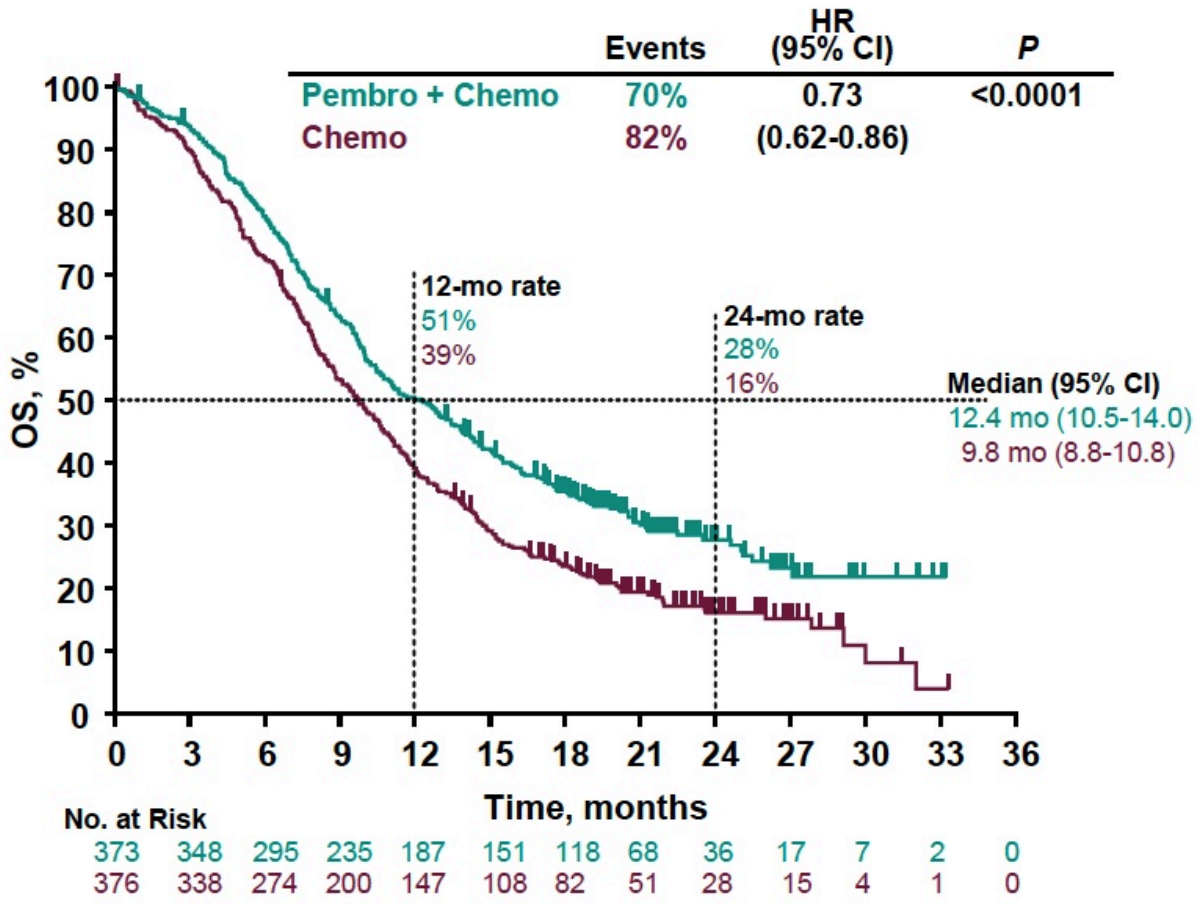
KEYNOTE-590: Overall Survival





Kato K et al. ESMO 2020;Abstract LBA8_PR.

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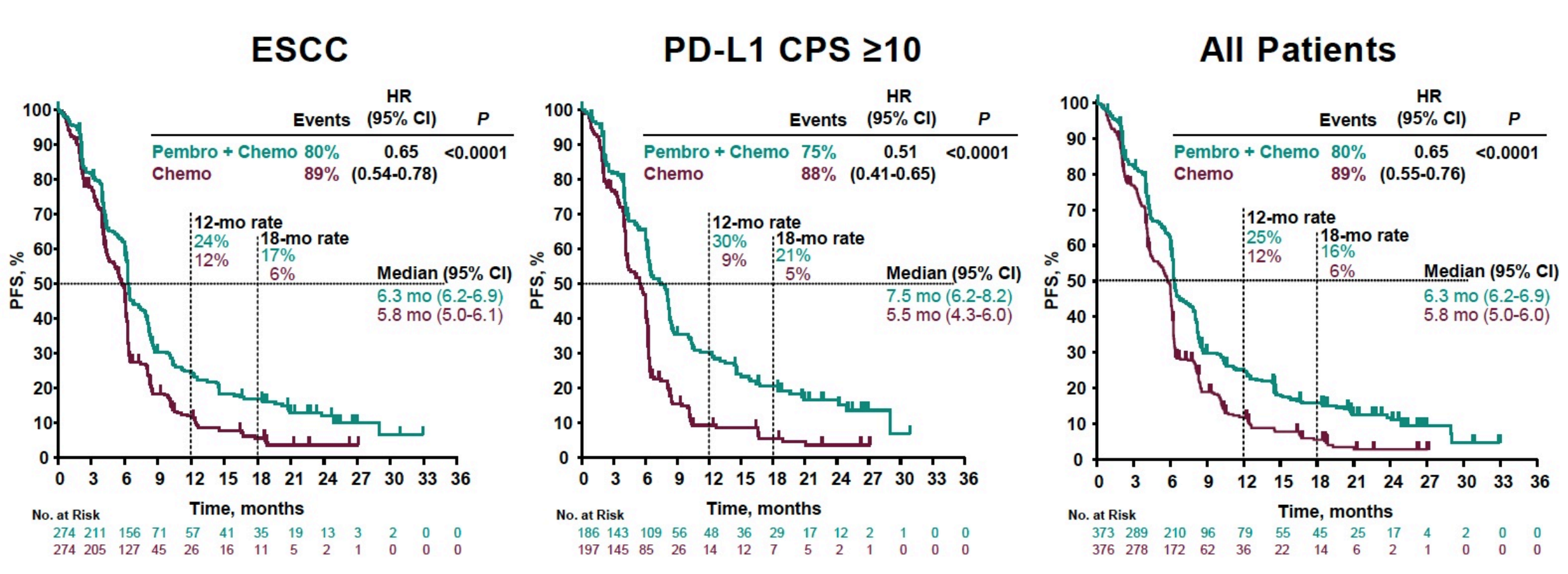
KEYNOTE-590: Progression-Free Survival



Kato K et al. ESMO 2020;Abstract LBA8_PR.

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FDA Approves Fam-Trastuzumab Deruxtecan-nxki for HER2-Positive Gastric Adenocarcinoma

Press Release: January 15, 2021

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

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

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-her2-positive-gastric-adenocarcinomas

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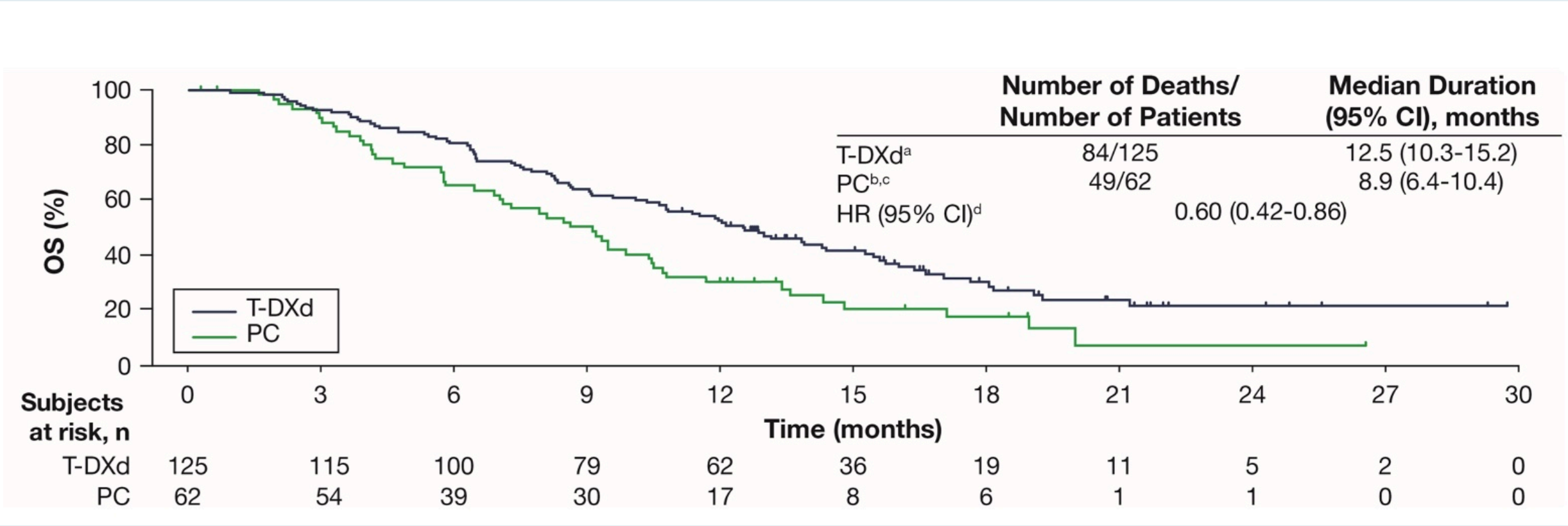
DESTINY-Gastric01: Final Overall Survival Analysis



As in the primary analysis (101 OS events; 54.0% maturity), in this updated analysis (133 OS events; 71.1% maturity), T-DXd showed superior antitumor activity compared to PC

Yamaguchi K et al. ASCO 2021;Abstract 4048.

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

Press Release: May 5, 2021

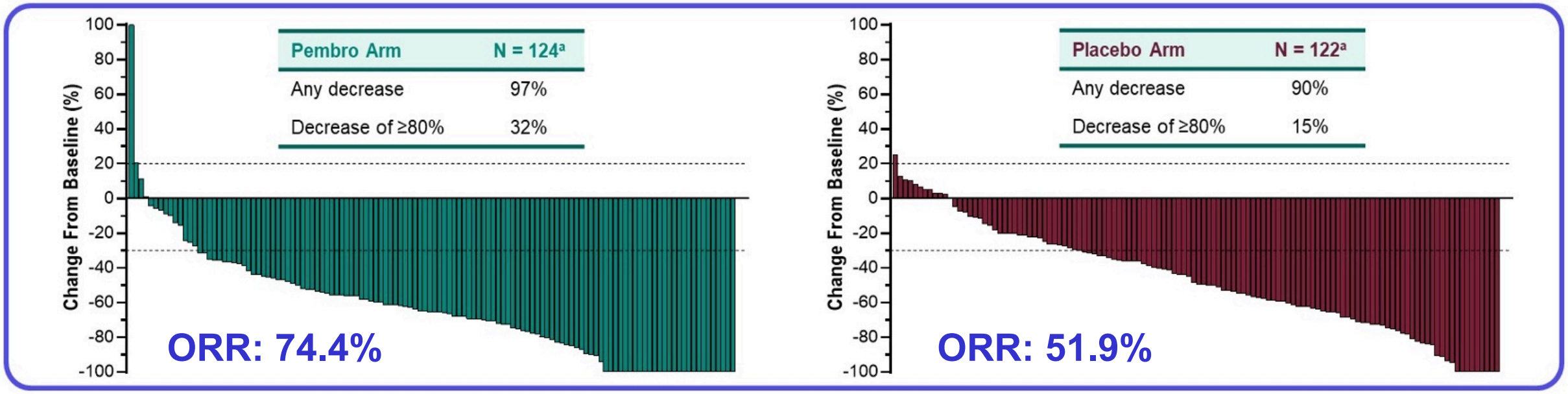
"On May 5, 2021, the Food and Drug Administration granted accelerated approval to pembrolizumab in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal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

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

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

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

KEYNOTE-811: Confirmed Response to Pembrolizumab/Trastuzumab at First Interim Analysis



Janjigian YY et al. ESMO World Congress on Gastrointestinal Cancer 2021;Abstract LBA4.

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

Recent Advances and Future Directions in Oncology

A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists

Saturday, October 23, 2021
9:30 AM – 4:30 PM ET

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Agenda

Module 1 — Breast Cancer: *Drs Partridge and Pegram*

Module 2 — Lung Cancer: *Drs Sequist and Spigel*

Module 3 — Gastrointestinal Cancers: *Drs Bekaii-Saab and Ciombor*

Module 4 — Genitourinary Cancers: *Drs Agarwal and Petrylak*

Module 5 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Kahl and Zelenetz*

Module 6 — Multiple Myeloma: *Drs Raje and Usmani*

Module 7 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Levis and Sallman*

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Genitourinary Cancers Faculty

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Huntsman Cancer Institute Presidential
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Director, Center of Investigational Therapeutics
Director, Genitourinary Oncology Program
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Contributing Oncologists

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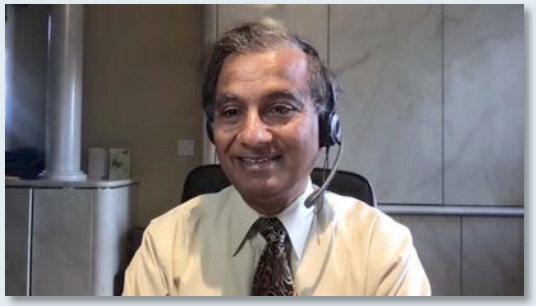

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Agenda

Module 1: Renal Cell Carcinoma

- Dr Kumar: A 53-year-old woman with metastatic RCC with rhabdoid features
- Faculty Chalk Talks

Module 2: Prostate Cancer

- Dr Guancial: A healthy 88-year-old man with locally recurrent CRPC
- Dr Zafar: An 86-year-old man with metastatic CRPC and a somatic BRCA2 mutation
- Dr Shameem: A 62-year-old man with metastatic CRPC and an ATM mutation
- Faculty Chalk Talks

Module 3: Urothelial Bladder Carcinoma (UBC)

- Dr Gandhi: A 78-year-old woman with non-muscle-invasive urothelial bladder cancer
- Dr Choksi: A 69-year-old man with localized UBC
- Dr Guancial: A 71-year-old woman with muscle-invasive UBC – High TMB, high PD-L1
- Faculty Chalk Talks

Appendix: Selected Data Sets

Agenda

Module 1: Renal Cell Carcinoma

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Appendix: Selected Data Sets

Case Presentation – Dr Kumar: A 53-year-old woman with metastatic RCC with rhabdoid features

Dr KS Kumar

- PMH: Hailey-Hailey skin disorder (benign pemphigus)
- Left clear cell RCC, with 3-4 small, bilateral pulmonary nodules
- Radical nephrectomy, clear cell RCC with 10-15% rhabdoid features
- Observation x 6 weeks
- Presents with significant nausea/vomiting and imaging reveals progression
- Lenvatinib/pembrolizumab x 3 cycles → majority of lesions regressed, 1 small new nodule appeared

Questions

- What is the best combination of TKI/IO to initiate in a patient who is rapidly progressing?
- Is the appearance of 1 new nodule an indication that I should change therapy?

Tyrosine kinase inhibitor/anti-PD-1/PD-L1 antibody versus ipilimumab/nivolumab as first line treatment of metastatic RCC

- **KEYNOTE-426 compared Pembrolizumab + Axitinib(PA) to Sunitinib(S) monotherapy in patients with metastatic RCC**
  - 36 month OS for PA was 63% vs 54% for S
- **Ipilimumab/Nivolumab (IN) was compared to Sunitinib monotherapy in patients with metastatic RCC**
  - 36 month OS for IN was 63% vs 50% for S
- **No difference in survival was seen in the favorable risk group patients in either study when compared to Sunitinib**
- **Side effects patterns are different: PA may have more cardiovascular side effects (hypertension, thrombotic events, wound healing); IN allows for TKI salvage**

Second line treatment of metastatic RCC after progression on first-line checkpoint inhibitor-based therapy

- Cabozantinib remains the agent with the strongest efficacy data as single agent in the second line. Most are very familiar with its adverse events and how to manage them.
- Patients with disease progression on Ipi/Nivo, Axitinib/Pembro, lenvatinib/pembro → cabozantinib is the preferred agent for me.
- Patients progressing on Cabozantinib+nivolumab, the only relevant option I see is the Lenvatinib+everolimus.
- There is a clinical trial ongoing testing cabozantinib+atezolizumab versus cabozantinib alone after prior progression on first line IO based combination

Agenda

Module 1: Renal Cell Carcinoma

- Dr Kumar: A 53-year-old woman with metastatic RCC with rhabdoid features
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Appendix: Selected Data Sets

Case Presentation – Dr Guancial: A healthy 88-year-old man with locally recurrent castration-resistant prostate cancer (CRPC)

Dr Elizabeth Guancial

- 7/2015: Stage IIIC Gleason 5 + 4 = 9, PSA 40 prostate cancer → radical prostatectomy → positive surgical margins at bilateral apices
- Patient offered salvage radiation and declined
- Intermittent ADT
- 2/2020: Rising PSA 25; Enzalutamide for CRPC → 7/2020 PSA: 0.56 → 6/2021 PSA: 1.07
- 9/2021 MRI prostate: Local recurrence invading bladder wall, abuts rectal wall, PSA 3.48

Questions

- What would you recommend for this patient?

Case Presentation – Dr Zafar: An 86-year-old man with metastatic CRPC and a somatic BRCA2 mutation

Dr Syed Zafar

- PMH: CKD, PN, DM
- 2013: Gleason 4 + 4 = 8 prostate cancer, PSA 26 ng/mL → Definitive RT
- 2018: Bone metastases, sacral mass → ADT/RT/abiraterone/prednisone → enzalutamide
- 2020: PD, PSA >30 ng/mL
- NGS: Somatic BRCA2 mutation
- Olaparib → painful bone metastases → Radium-223 → PD

Questions

- How can we get access to 177Lu-PSMA-167? Is there a clinical study or expanded access?
- What has been your experience with patients treated with PSMA-directed treatment? Is it well tolerated? What responses have you observed?

Case Presentation – Dr Shameem: A 62-year-old man with metastatic CRPC and an ATM mutation

Dr Raji Shameem

- PMH: Gout, HTN, DM
- 11/2020: Prostate cancer Gleason 5 + 5 = 10, PSA 14 ng/mL, with bilateral pelvic LAD, osseous metastases
- Leuprolide, with PDA decline <20 ng/mL
- 3/2021: PSA increase with rapid doubling time → PD with pelvic LAD, rib and spinal metastases
- Enzalutamide, with reduction in PSA <1 ng/mL
- NGS: ATM and TP53 mutations

Questions

- How would you incorporate a PARP inhibitor into the treatment? Would you use a PARP inhibitor? Have you seen responses? Would you use a PARP inhibitor in a patient who needs a rapid response?

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Genomic testing and use of PARP inhibitors for metastatic prostate cancer and a BRCA mutation

- Germline DNA repair mutations are found in approximately 12% of specimens in patients with mCRPC
- Germline testing can be performed in saliva, buccal smears and blood; Somatic testing can be performed in tissue biopsy, circulating tumor cells and CT DNA
- >90% concordance can be found between liquid and tissue biopsies
- Olaparib is FDA approved in mCRPC patients who have received a next generation antiandrogen; Rucaparib is approved for patients treated with both a next generation antiandrogen and taxane chemotherapy

Potential clinical role of 177Lu-PSMA-617 in metastatic castration-resistant prostate cancer

1. Patients with disease progression on abiraterone/ enzalutamide and docetaxel.
2. Can also offer to those who decline or are not eligible for docetaxel and if 177Lu-PSMA-617 is approved by insurance (would be cautious with Medicare patients given reimbursement issues/ No PA required).
3. Will make sure to check for other benign causes of anemia if this is present at baseline before starting 177Lu-PSMA-617
4. Median duration of total treatment with 177Lu-PSMA-617 is 5-6 months in case patients enquire or have travel plans. Given every 6 weeks. Concurrent NHT can be given safely.

Agenda

Module 1: Renal Cell Carcinoma

- Dr Kumar: A 53-year-old woman with metastatic RCC with rhabdoid features
- Faculty Chalk Talks

Module 2: Prostate Cancer

- Dr Guancial: A healthy 88-year-old man with locally recurrent CRPC
- Dr Zafar: An 86-year-old man with metastatic CRPC and a somatic BRCA2 mutation
- Dr Shameem: A 62-year-old man with metastatic CRPC and an ATM mutation
- Faculty Chalk Talks

Module 3: Urothelial Bladder Carcinoma (UBC)

- Dr Gandhi: A 78-year-old woman with non-muscle-invasive urothelial bladder cancer
- Dr Choksi: A 69-year-old man with localized UBC
- Dr Guancial: A 71-year-old woman with muscle-invasive UBC – High TMB, high PD-L1
- Faculty Chalk Talks

Appendix: Selected Data Sets

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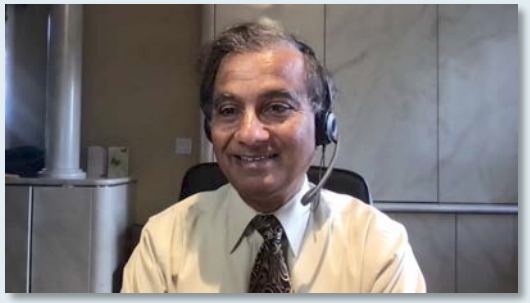
Case Presentation – Dr Gandhi: A 78-year-old woman with non-muscle-invasive urothelial bladder cancer



Dr Sunil Gandhi

- PMH: Cirrhosis of the liver, many other comorbidities
- Non-muscle-invasive bladder cancer, s/p BCG failure; not a candidate for cystectomy
- Pembrolizumab x 1 year+ and NED

Question

- If she continues to respond, how long would you continue the pembrolizumab?

Case Presentation – Dr Choksi: A 69-year-old man with localized UBC

Dr Mamta Choksi

- 2013: Diagnosed with superficial bladder cancer → TURBT: High-grade UBC
- 2015: BCG → Surveillance cystoscopy with recurrence
- 3/2021: Bilobar hypertrophy of prostate with papillary lesions consistent with urothelial carcinoma, posterior bladder with diffuse erythema
- 4/2021 TURP: High-grade UBC involving prostatic ducts
- Neoadjuvant therapy could not be given due to left-sided hearing loss
- 6/2021 Radical cysto-prostatectomy: High-grade UBC, transurethral involvement of prostatic ducts with prostatic stromal invasion, lymphovascular invasion
- 8/2021: Urethrectomy → 9/2021: Adjuvant nivolumab

Questions

- If he reoccurs or if he develops metastatic disease, as we have already used immunotherapy, what other treatment options would experts recommend in that situation?

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Case Presentation – Dr Guancial: A 71-year-old woman with muscle-invasive UBC – High tumor mutation burden (TMB), high PD-L1

Dr Elizabeth Guancial

- Diagnosed with de novo metastatic, high-grade UBC and DVT: On anticoagulation, s/p cisplatin/gemcitabine x 4
- Recurrent hospitalizations for hematuria
- 3/2021 TURBT: High-grade UBC invading lamina propria and detrusor muscle
- NGS: TMB-high, 17 mut/Mb, PD-L1-high
- 5/2021: Cisplatin/gemcitabine → Maintenance avelumab

Questions

- What are your thoughts about maintenance immunotherapy?

Second line treatment for patients with UBC and an FGFR gene alteration; side effects associated with erdafitinib

- **Approximately 10-20% of urothelial cancer specimens have FGF mutations**
- **Erdafitinib, a kinase inhibitor, targets FGFR1, FGFR2, FGFR3 and FGFR4.**
- **Erdafitinib had a 40% response rate in urothelial cancer patients who have had prior immunotherapy or chemotherapy**
- **Side effects include**
  - Hyperphosphatemia
  - Hand foot syndrome, Dry Skin, Onycholysis
  - Central Serous Retinopathy

Sequencing of enfortumab vedotin (EV) and other targeted therapies in metastatic UBC

- Better tolerated than cisplatin based therapy and no issue with renal dysfunction unlike cisplatin.
- Ideal sequencing would be upfront platinum based therapy with avelumab maintenance followed immediately by EV at the earliest evidence of disease progression. I would suggest scans every 8 weeks on patients on avelumab maintenance therapy.
- Sacituzumab Govitecan is another option which can be given immediately after disease progression on EV OR given before EV if there are contraindications or tolerability issues with EV.
- I reserve Erdafitinib for patients with FGFR alterations to after EV just because EV seems to be an efficacious option to me for all patients regardless of FGFR alterations. In these patients I suggest the following sequence: platinum+avelumab maintenance→EV→Erdafitinib.

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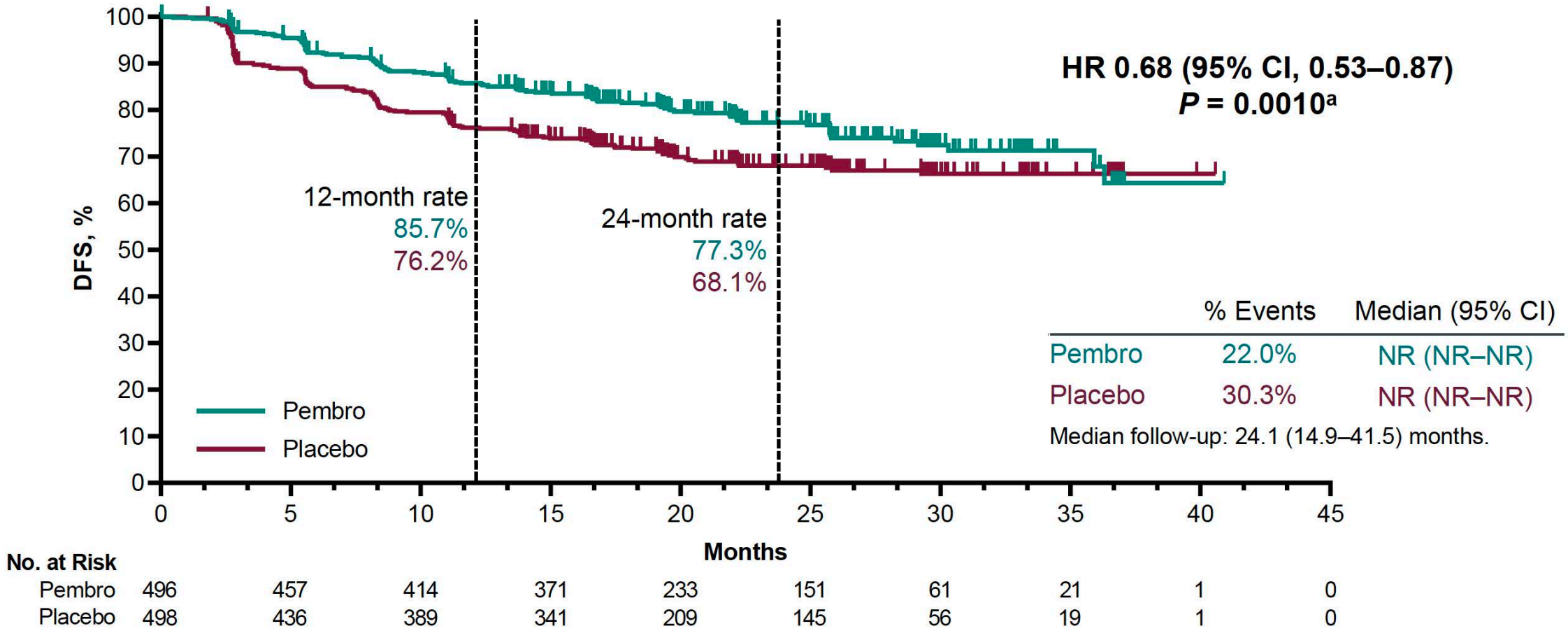
Appendix: Selected Data Sets

Renal Cell Carcinoma

KEYNOTE-564: Pembrolizumab as Adjuvant Therapy for Patients with RCC – Disease-Free Survival



Choueiri TK et al. ESMO 2021;Abstract 653O.

FDA Approves Nivolumab with Cabozantinib for Advanced Renal Cell Carcinoma

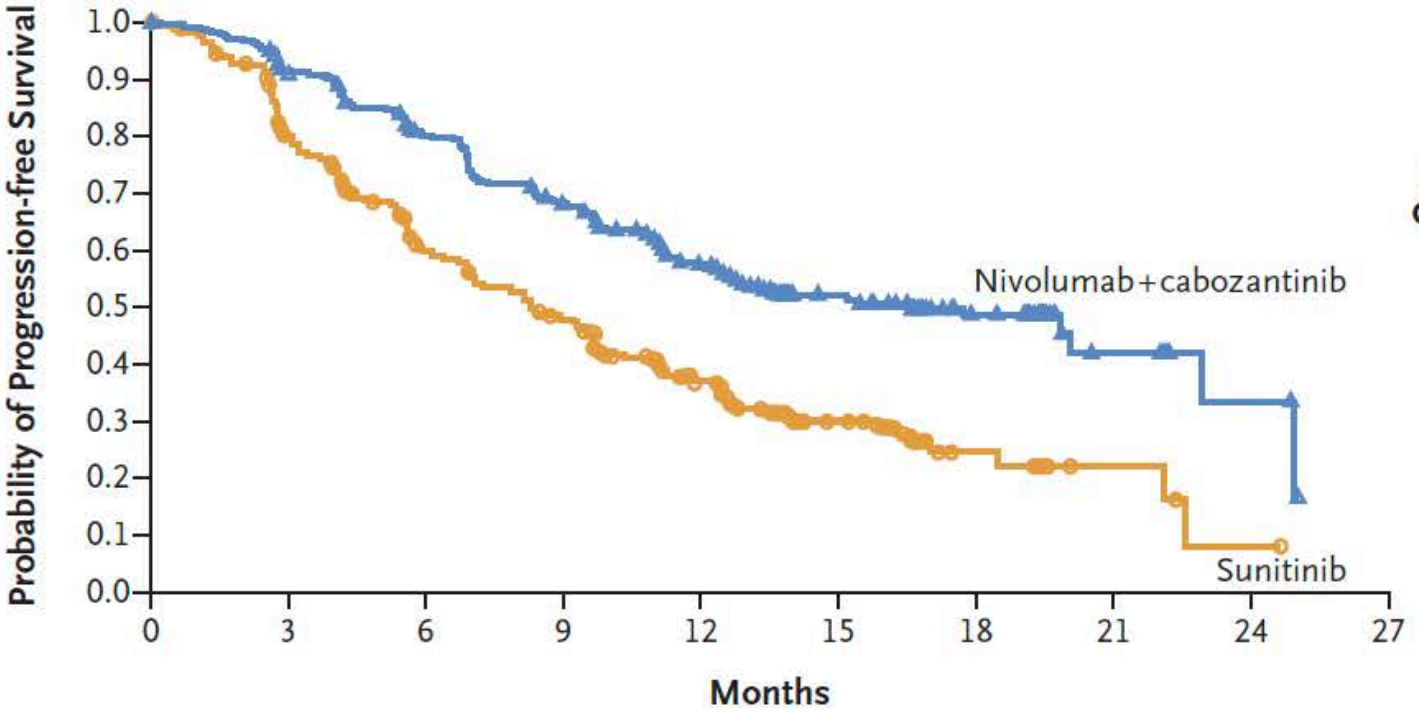
Press Release: January 22, 2021

"The Food and Drug Administration approved the combination of nivolumab and cabozantinib as first-line treatment for patients with advanced renal cell carcinoma (RCC).

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

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-plus-cabozantinib-advanced-renal-cell-carcinoma

CheckMate 9ER: Progression-Free Survival



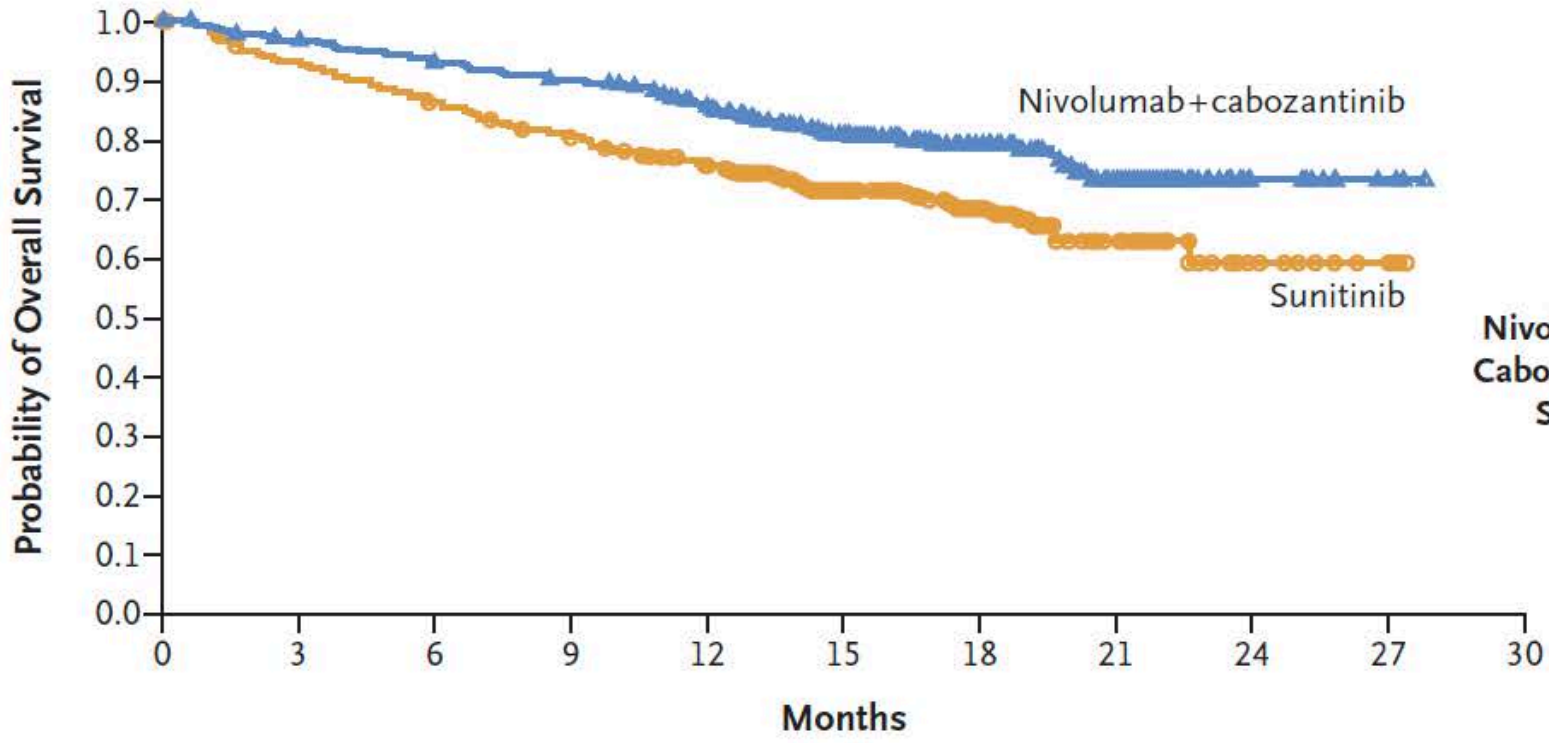
	No. of Patients	Median (95% CI) *mo*
Nivolumab+ Cabozantinib	323	16.6 (12.5–24.9)
Sunitinib	328	8.3 (7.0–9.7)

Hazard ratio for disease progression or death, 0.51 (95% CI, 0.41–0.64)
P<0.001

No. at Risk										
Nivolumab+cabozantinib	323	279	234	196	144	77	35	11	4	0
Sunitinib	328	228	159	122	79	31	10	4	1	0

Choueiri TK et al. *N Engl J Med* 2021;384(9):829-41.

CheckMate 9ER: Overall Survival



	No. of Patients	Median (95% CI) *mo*
Nivolumab+ Cabozantinib	323	NR (NE)
Sunitinib	328	NR (22.6–NE)

Hazard ratio for death, 0.60 (98.89% CI, 0.40–0.89)
P=0.001

No. at Risk

Nivolumab+cabozantinib	323	308	295	283	259	184	106	55	11	3	0
Sunitinib	328	296	273	253	223	154	83	36	10	3	0

Choueiri TK et al. *N Engl J Med* 2021;384(9):829-41.

FDA Approves Lenvatinib with Pembrolizumab for Advanced Renal Cell Carcinoma

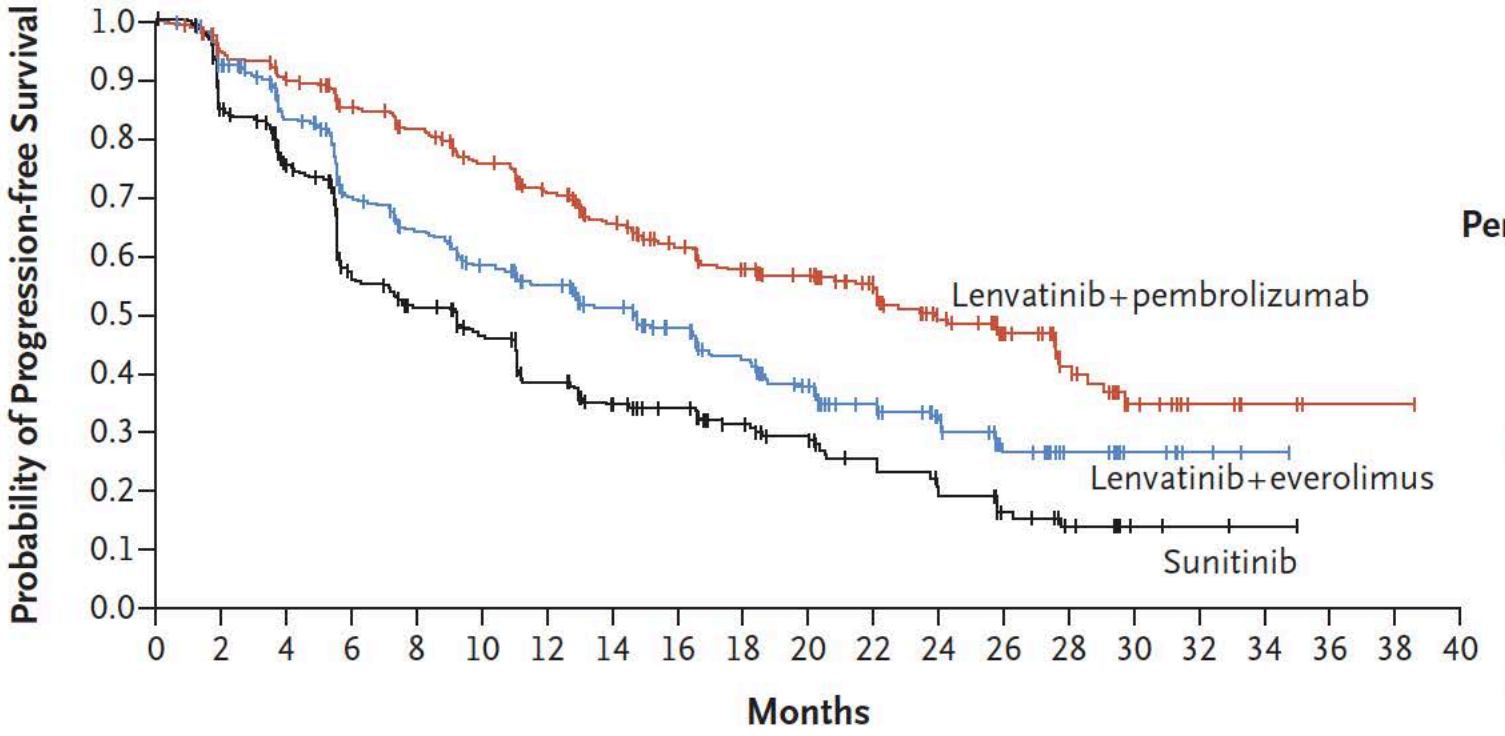
Press Release: August 10, 2021

"The Food and Drug Administration approved the combination of lenvatinib plus pembrolizumab for first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

The efficacy of this combination was investigated in CLEAR (Study 307/KEYNOTE-581; NCT02811861), a multicenter, open-label, randomized phase 3 trial in patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumor expression status. The efficacy population supporting this approval included patients randomized to lenvatinib plus pembrolizumab (n=355) compared with those randomized to single-agent sunitinib (n=357)."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenvatinib-plus-pembrolizumab-advanced-renal-cell-carcinoma

CLEAR: Progression-Free Survival



No. at Risk

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

Median Progression-free Survival (95% CI)

	mo
Lenvatinib+ Pembrolizumab	23.9 (20.8–27.7)
Lenvatinib+ Everolimus	14.7 (11.1–16.7)
Sunitinib	9.2 (6.0–11.0)

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

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

Motzer R et al. *N Engl J Med* 2021;[Online ahead of print].

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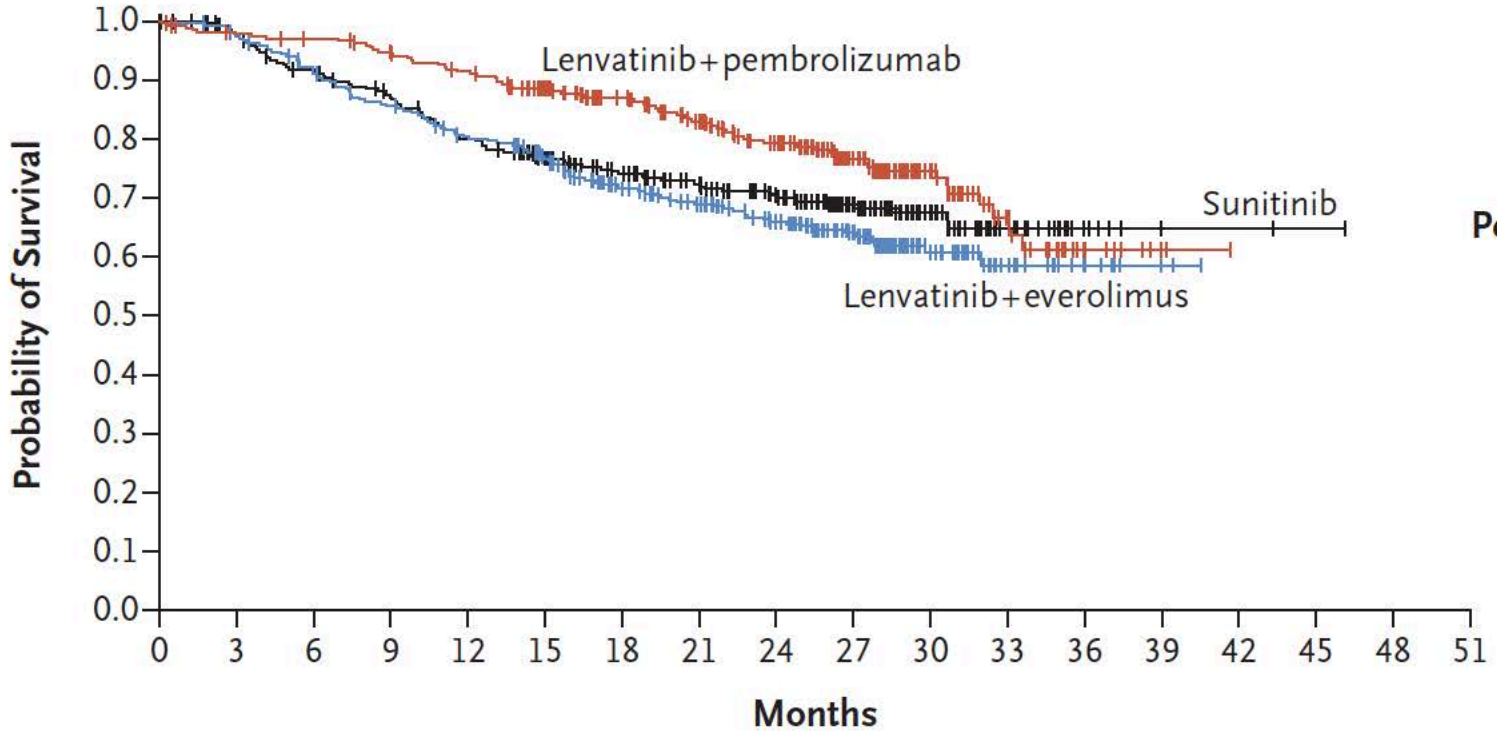
CLEAR: Overall Survival



Median Overall Survival (95% CI)	*mo*
Lenvatinib+ Pembrolizumab	NR (33.6–NE)
Lenvatinib+ Everolimus	NR (NE–NE)
Sunitinib	NR (NE–NE)

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

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

No. at Risk

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

Motzer R et al. *N Engl J Med* 2021;[Online ahead of print].

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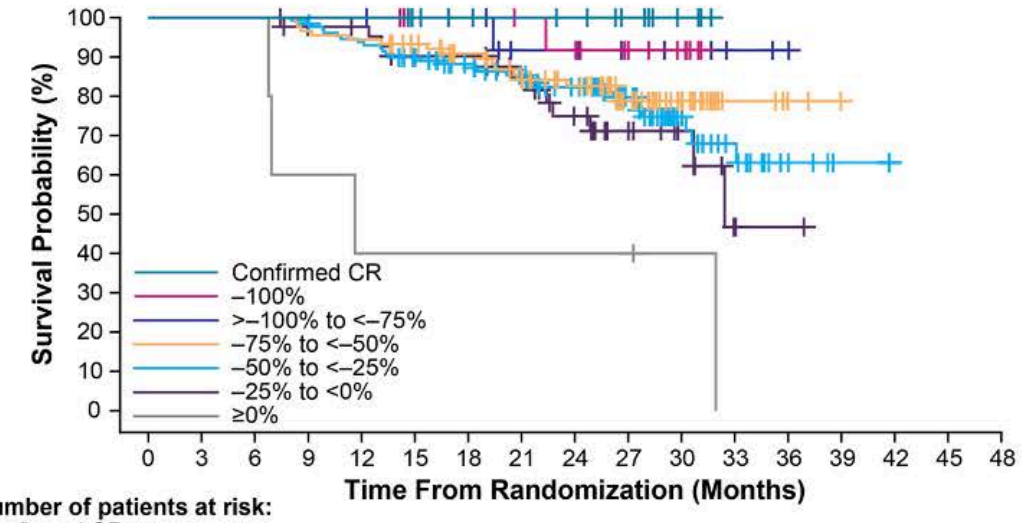
CLEAR: 6-Month OS Analysis by Depth of Response

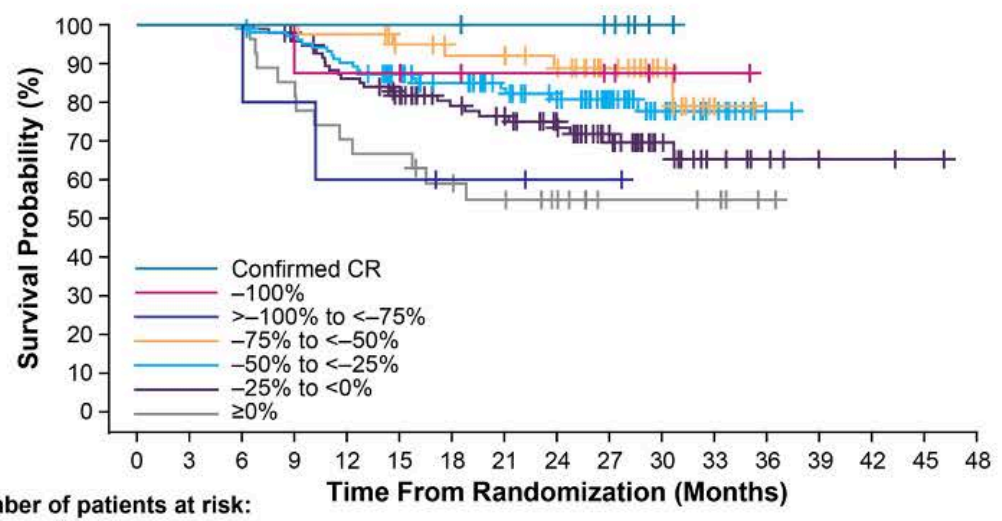
Lenvatinib plus Pembrolizumab



Number of patients at risk:

Confirmed CR	16	16	16	14	12	11	10	7	3	0	0	0	0	0	0
–100%	20	20	20	17	14	12	11	8	5	0	0	0	0	0	0
>–100% to <–75%	16	16	16	13	13	9	9	6	5	2	1	0	0	0	0
–75% to <–50%	89	86	84	78	70	61	54	37	20	5	2	0	0	0	0
–50% to <–25%	129	128	120	108	96	88	76	53	23	14	5	1	0	0	0
–25% to <0%	44	40	39	35	35	29	21	13	8	2	1	0	0	0	0
≥0%	5	3	2	2	2	2	2	2	1	0	0	0	0	0	0

Sunitinib



Number of patients at risk:

Confirmed CR	7	7	7	7	7	6	6	5	1	0	0	0	0	0	0
–100%	8	8	7	7	6	5	5	4	2	1	0	0	0	0	0
>–100% to <–75%	5	4	3	3	2	2	1	1	0	0	0	0	0	0	0
–75% to <–50%	40	40	39	35	32	32	28	19	10	2	0	0	0	0	0
–50% to <–25%	103	99	92	80	71	61	53	39	21	9	1	0	0	0	0
–25% to <0%	96	90	80	71	60	56	47	34	17	9	5	2	2	1	0
≥0%	27	23	19	18	15	13	10	5	5	4	1	0	0	0	0

Among patients treated with lenvatinib plus pembrolizumab, all those who had a complete response were alive at 2 years; survival rates were similar for patients who had more than 75% reduction in target lesions.

Tumors assessed by Independent Review Committee per RECIST v1.1

Grunwald V et al. ASCO 2021;Abstract 4560.

FDA Approves Tivozanib for Relapsed or Refractory Advanced Renal Cell Carcinoma

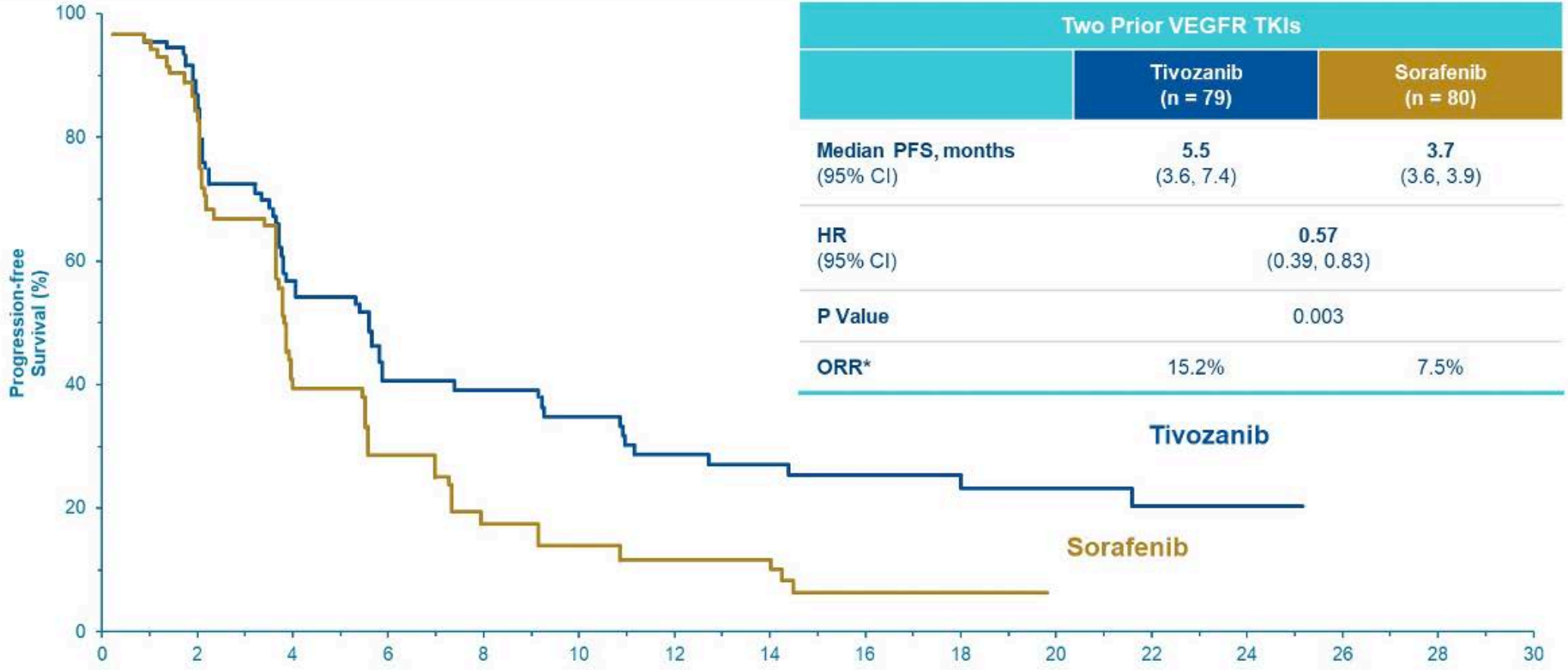
Press Release: March 10, 2021

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

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

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tivozanib-relapsed-or-refractory-advanced-renal-cell-carcinoma

TIVO-3: Progression-Free Survival and ORR in Patient Subgroup with 2 Prior TKIs



Two Prior VEGFR TKIs		
	Tivozanib (n = 79)	Sorafenib (n = 80)
Median PFS, months (95% CI)	5.5 (3.6, 7.4)	3.7 (3.6, 3.9)
HR (95% CI)	0.57 (0.39, 0.83)	
P Value	0.003	
ORR*	15.2%	7.5%

Rini BI et al. Genitourinary Cancers Symposium 2021;Abstract 278.

TIVO-3: Tivozanib After Axitinib

RCC Population	N (subjects)		mPFS (months)		HR	ORR	
	Tivo	Sor	Tivo	Sor		Tivo	Sor
ITT	175	175	5.6	3.9	0.73	18%	8%
3rd Line Any Prior Axitinib	47	46	5.5	3.9	0.71	16%	6%
4th Line Any Prior Axitinib	36	43	5.5	3.6	0.64	11%	10%
3rd and 4th Line Any Prior Axitinib	83	89	5.5	3.7	0.68	13%	8%

Rini BI et al. Genitourinary Cancers Symposium 2021;Abstract 278.

TIVO-3: Durability of Response and Updated Overall Survival of Tivozanib versus Sorafenib in Metastatic Renal Cell Carcinoma (mRCC)

Verzoni et al.
ASCO 2021;Abstract 4546.

"Tivozanib demonstrated clinically meaningful and statistically significant improvement in ORR and DoR with similar OS to sorafenib in patients with highly relapsed or refractory mRCC"

- *Median DoR was 20.3 months with tivozanib, twice that observed with sorafenib*

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Prostate Cancer

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Survival: Darolutamide, Enzalutamide, Apalutamide for Nonmetastatic CRPC

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

[1] Fizazi K et al; ARAMIS Investigators. *N Engl J Med* 2020;383:1040-9.
[2] Sternberg CN et al; PROSPER Investigators. *N Engl J Med* 2020;382(23):2197-206.
[3] Smith MR et al; SPARTAN Investigators. *Eur Urol* 2020;[Online ahead of print].

Comparison of Toxicities: Darolutamide, Enzalutamide, Apalutamide

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

Sternberg CN et al; PROSPER Investigators. *N Engl J Med* 2020;382(23):2197-206.
Fizazi K et al; ARAMIS Investigators. *N Engl J Med* 2020;383:1040-9.
Small EJ et al; SPARTAN Investigators. ASCO 2020;Abstract 5516.

FDA Approves Relugolix for Advanced Prostate Cancer

Press Release: December 18, 2020

"The 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."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-relugolix-advanced-prostate-cancer

RTP RESEARCH TO PRACTICE

Positive Results Announced for the PROpel Phase III Trial of Olaparib with Abiraterone as First-Line Treatment for mCRPC

Press Release: September 24, 2021

"Positive high-level results from the PROpel Phase III trial showed that Olaparib, in combination with abiraterone demonstrated a statistically significant and clinically meaningful improvement in radiographic progression-free survival (rPFS) versus standard-of-care abiraterone as a 1st-line treatment for men with metastatic castration-resistant prostate cancer (mCRPC) with or without homologous recombination repair (HRR) gene mutations.

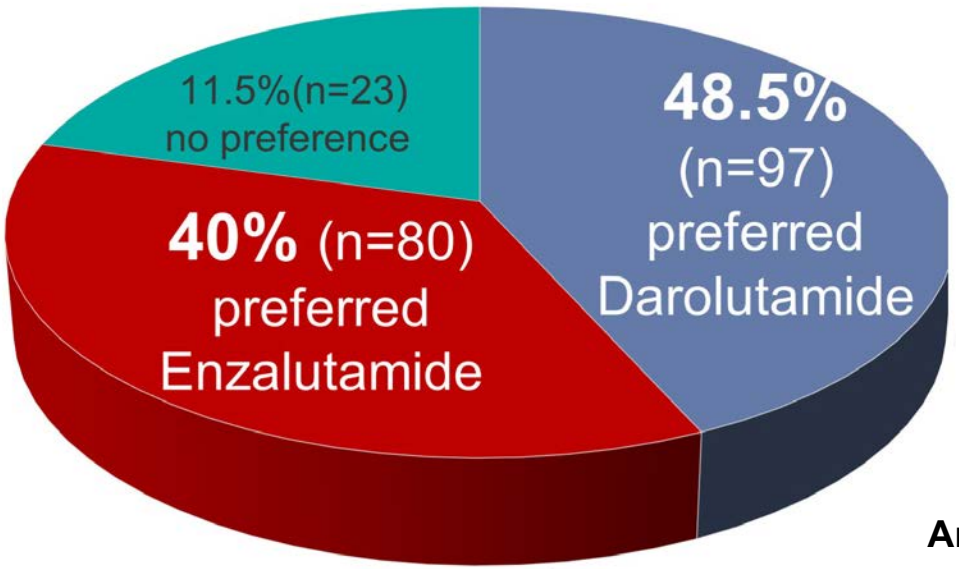
At a planned interim analysis, the Independent Data Monitoring Committee concluded that the trial met the primary endpoint of rPFS in men with mCRPC who had not received treatment in the 1st-line setting including with new hormonal agents or chemotherapy.

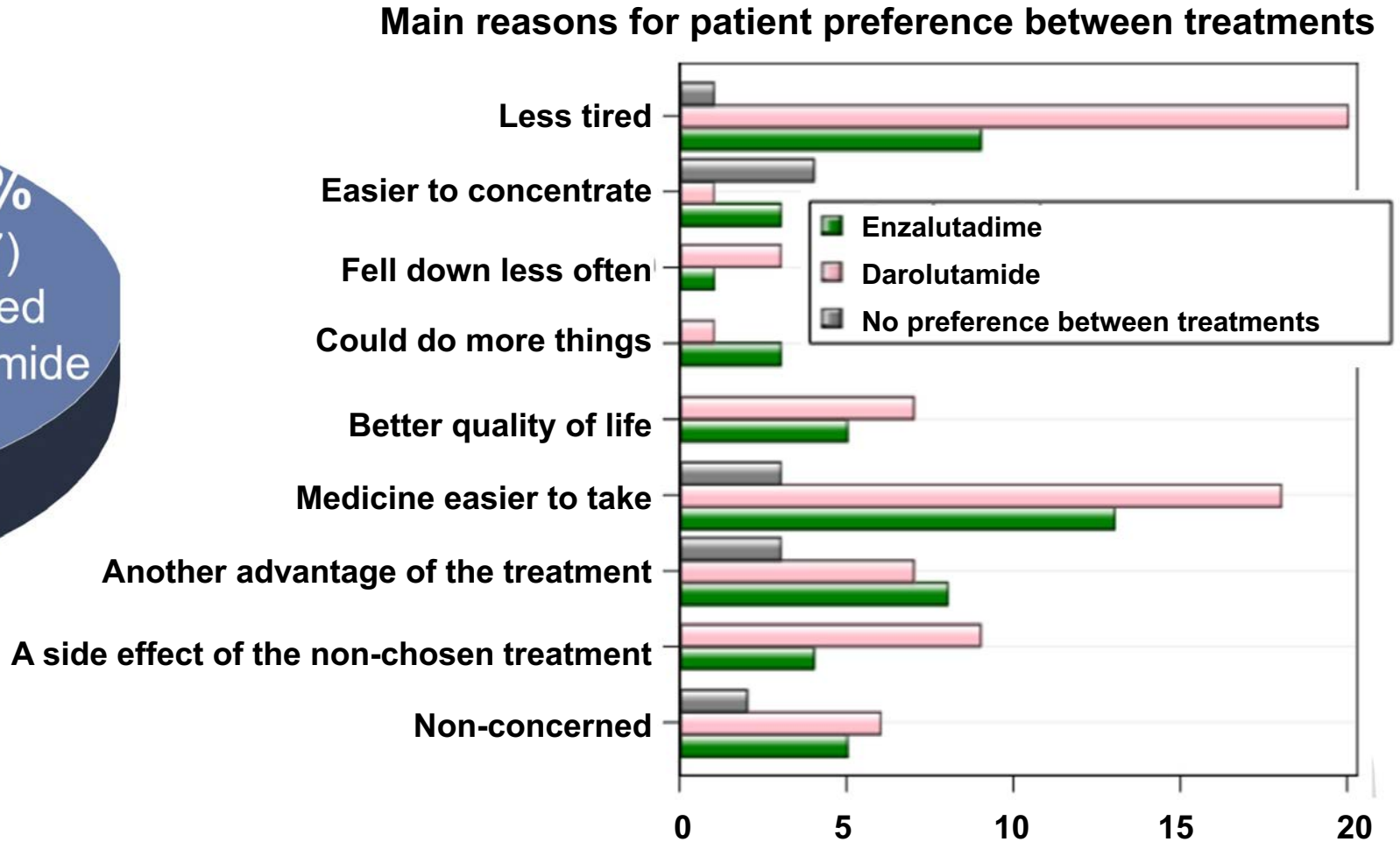
The data will be presented at an upcoming medical meeting."

https://www.astrazeneca.com/media-centre/press-releases/2021/lynparza-propel-trial-meets-primary-endpoint.html

RTP RESEARCH TO PRACTICE

ODENZA: A Phase II Crossover Trial Evaluating Preference Between Darolutamide and Enzalutamide in Men with Asymptomatic or Mildly Symptomatic mCRPC

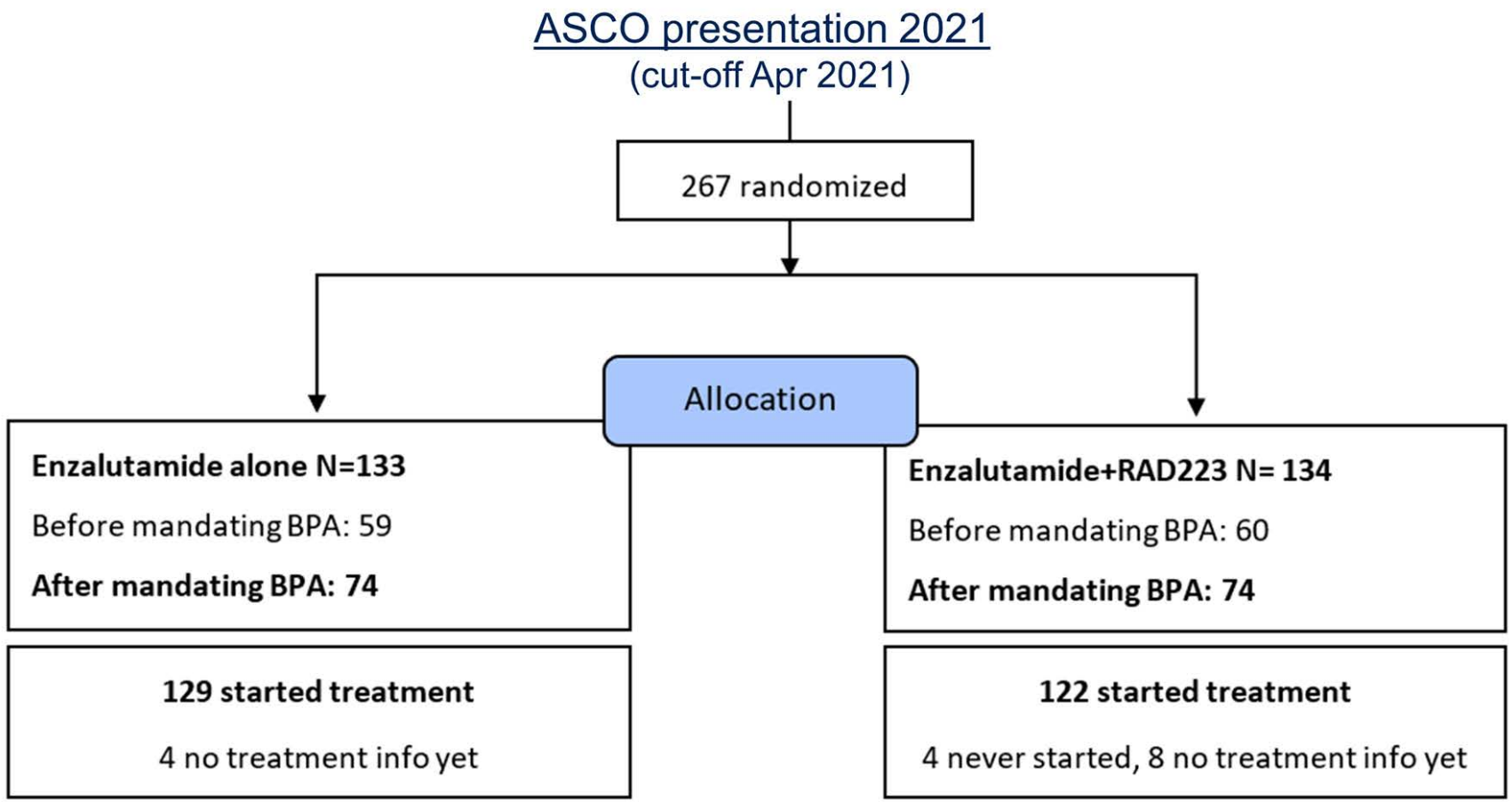




Colomba E et al. ASCO 2021;Abstract 5046.

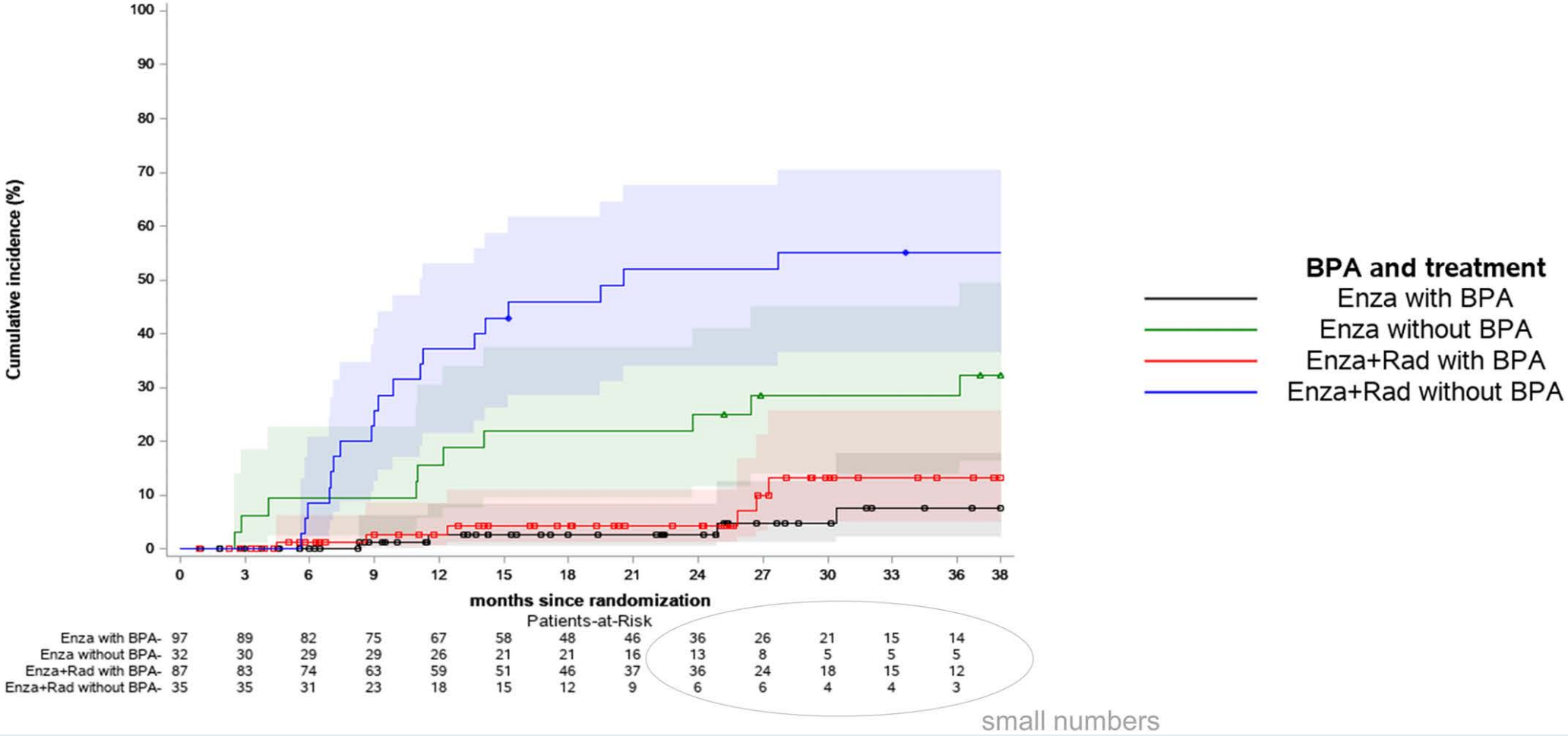
RTP RESEARCH TO PRACTICE

PEACE III: Impact of Bone-Protecting Agents (BPA) on Fracture Rates



Gillessen S et al. ASCO 2021;Abstract 5002.

PEACE III: Cumulative Incidence of Fractures by Treatment Arm and Use of Bone-Protecting Agents



Gillessen S et al. ASCO 2021;Abstract 5002.

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PEACE III: Bone Fractures and Cumulative Incidence – Safety Population

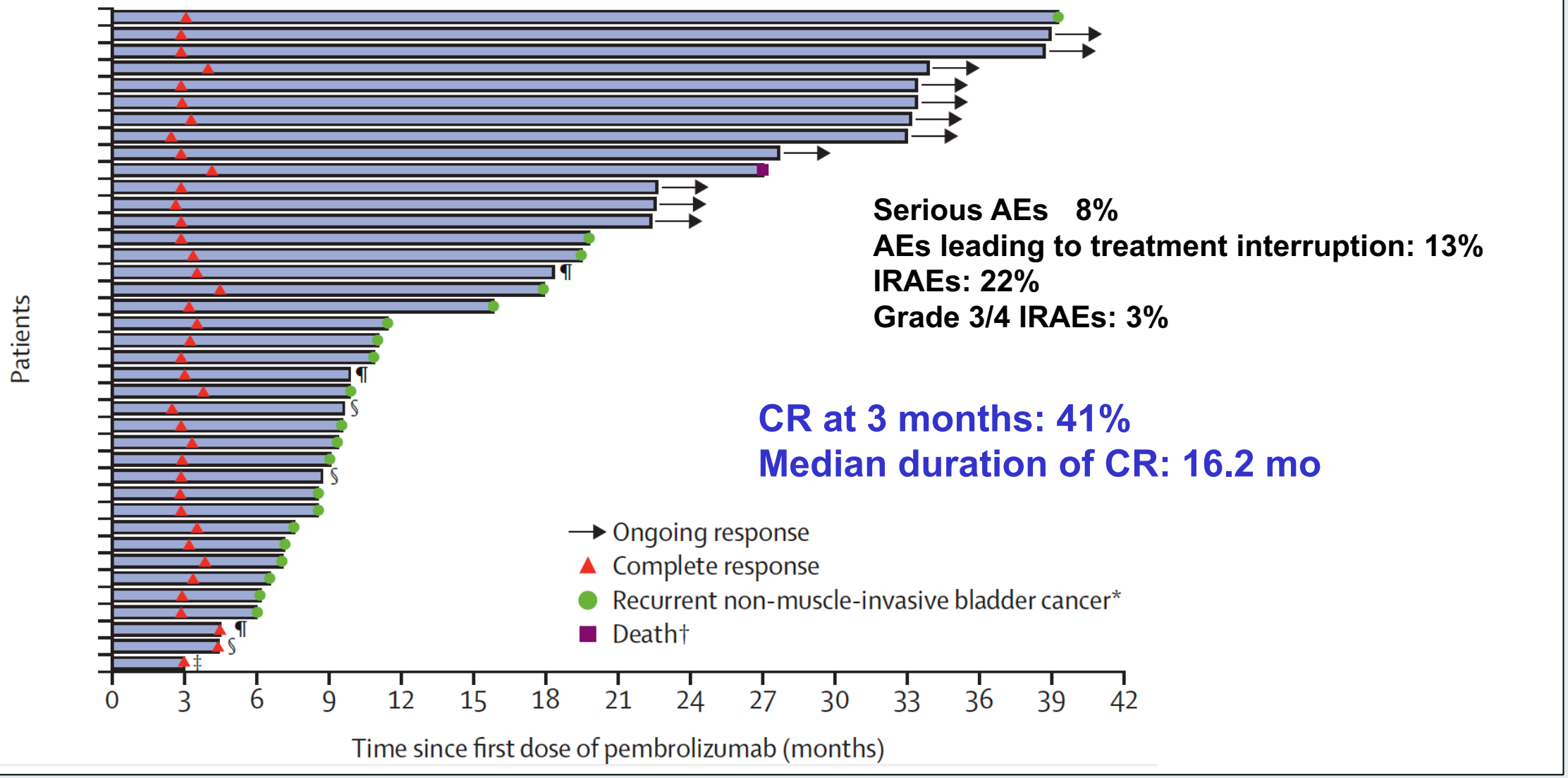
Time point	Without BPA		With BPA	
	Enza+Rad (N=35)	Enza (N=32)	Enza+Rad (N=87)	Enza (N=97)
	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)
9 months	25.7 (12.6-41.0)	9.4 (2.3-22.5)	2.7 (0.5-8.5)	1.3 (0.1-6.1)
12 months	**37.1 (21.3-53.0)**	**15.6 (5.6-30.3)**	**2.7 (0.5-8.5)**	**2.6 (0.5-8.3)**
15 months	42.9 (26.1-58.6)	21.9 (9.5-37.5)	4.3 (1.1-10.9)	2.6 (0.5-8.3)
18 months	**45.9 (28.6-61.6)**	**21.9 (9.5-37.5)**	**4.3 (1.1-10.9)**	**2.6 (0.5-8.3)**
21 months	52.0 (33.8-67.5)	21.9 (9.5-37.5)	4.3 (1.1-10.9)	2.6 (0.5-8.3)

Gillessen S et al. ASCO 2021;Abstract 5002.

RTP RESEARCH TO PRACTICE

Urothelial Bladder Carcinoma

KEYNOTE-057: Response, Duration of Response and Summary of Adverse Events



Balar AV et al. *Lancet Oncol* 2021;22:919-30.

FDA Approves Nivolumab for Adjuvant Treatment of Urothelial Carcinoma

Press Release: August 19, 2021

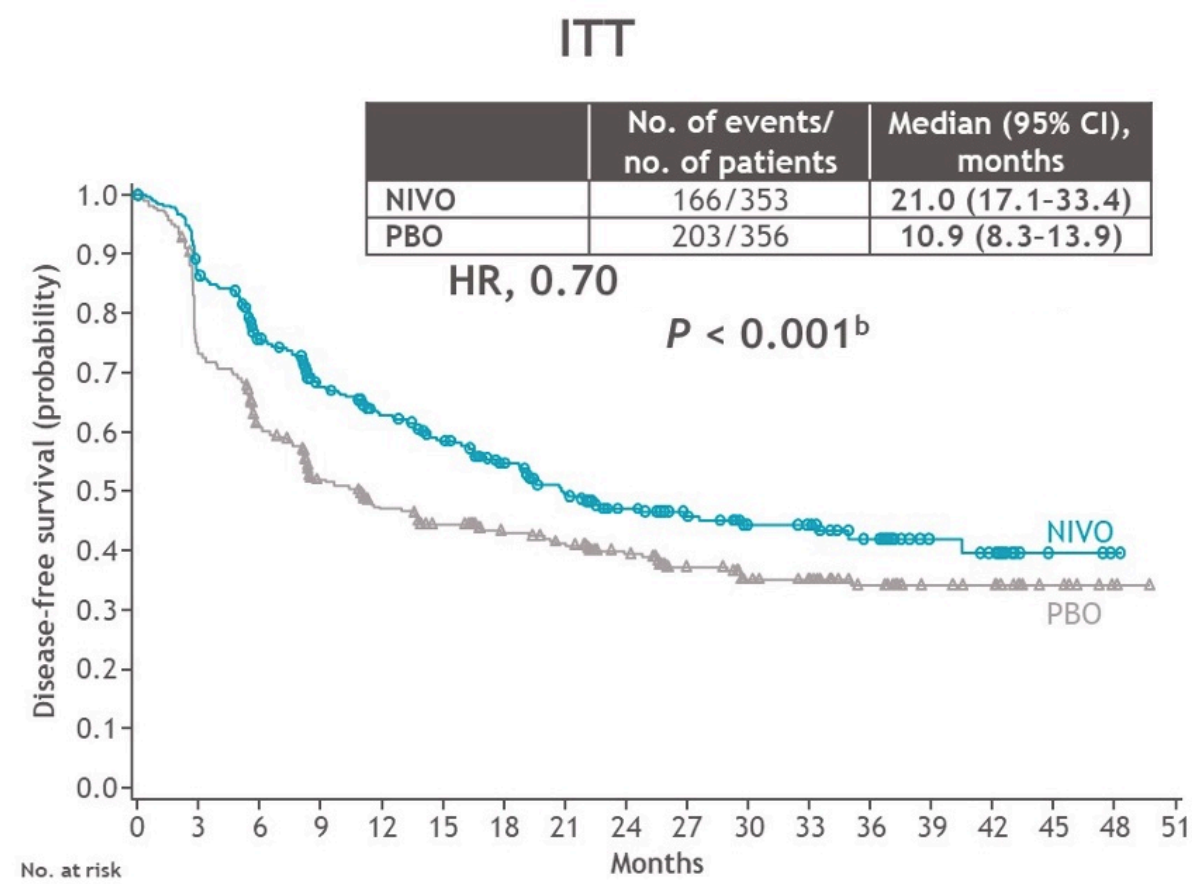
"The Food and Drug Administration approved nivolumab for the adjuvant treatment of patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection.

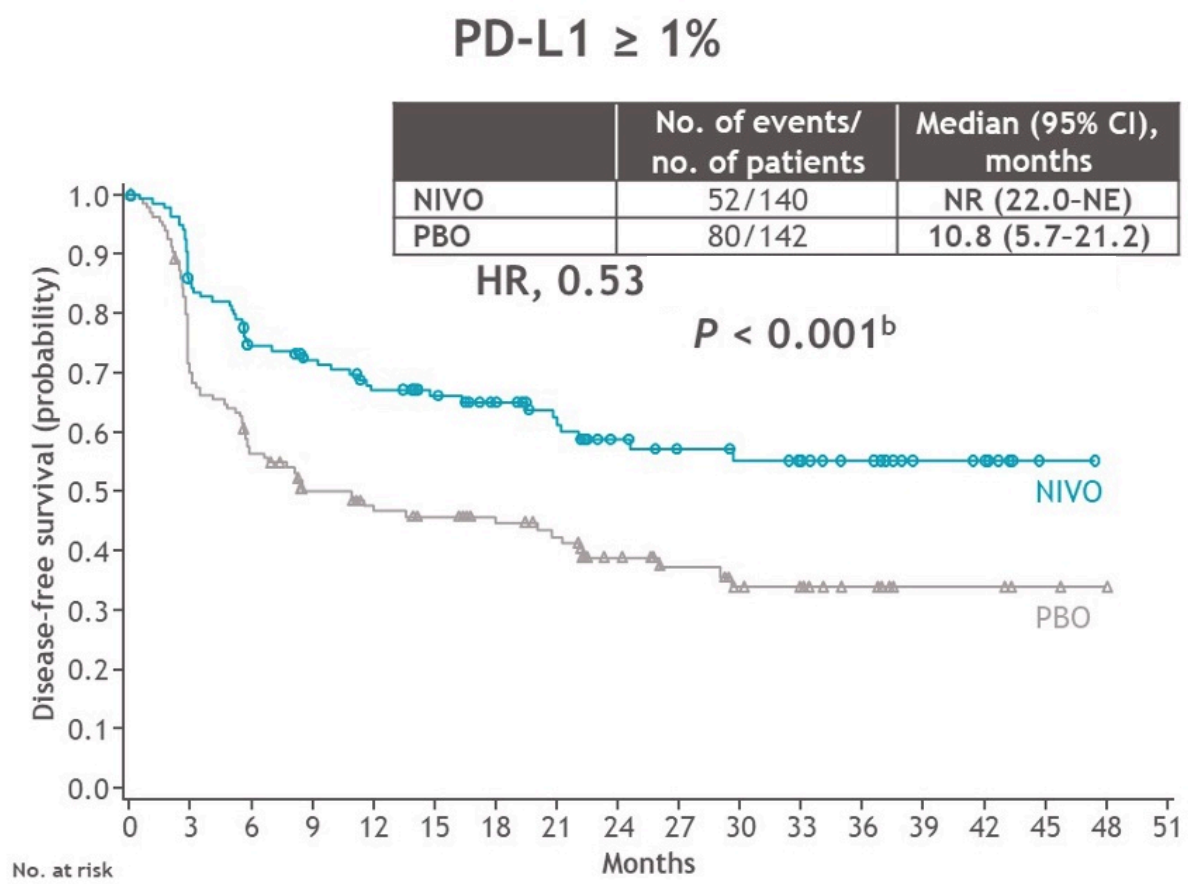
This is the first FDA approval for adjuvant treatment of patients with high-risk UC. The results supporting this approval also supported the conversion of nivolumab's accelerated approval for advanced/metastatic UC to a regular approval.

Nivolumab was investigated in CHECKMATE-274 (NCT02632409), a randomized, double-blind, placebo-controlled trial in patients who were within 120 days of radical resection of UC of the bladder or upper urinary tract (renal pelvis or ureter) at high risk of recurrence. Patients were randomized (1:1) to receive nivolumab 240 mg or placebo by intravenous infusion every 2 weeks until recurrence or until unacceptable toxicity for a maximum treatment duration of 1 year."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-adjuvant-treatment-urothelial-carcinoma

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





Bajorin DF et al. Genitourinary Cancers Symposium 2021;Abstract 391.

RTP RESEARCH TO PRACTICE

FDA Grants Regular Approval to Enfortumab Vedotin-ejfv for Locally Advanced or Metastatic Urothelial Cancer

Press Release: July 9, 2021

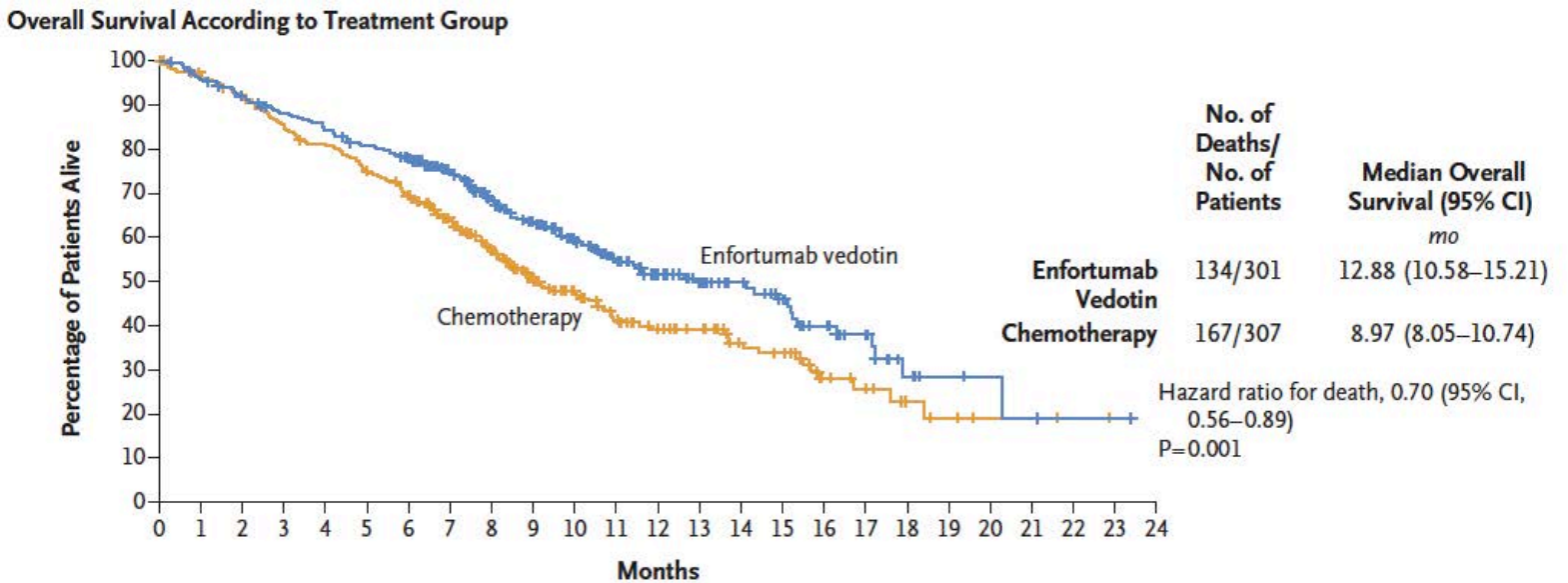
"The Food and Drug Administration approved enfortumab vedotin-ejfv, a Nectin-4-directed antibody and microtubule inhibitor conjugate, for adult patients with locally advanced or metastatic urothelial cancer who

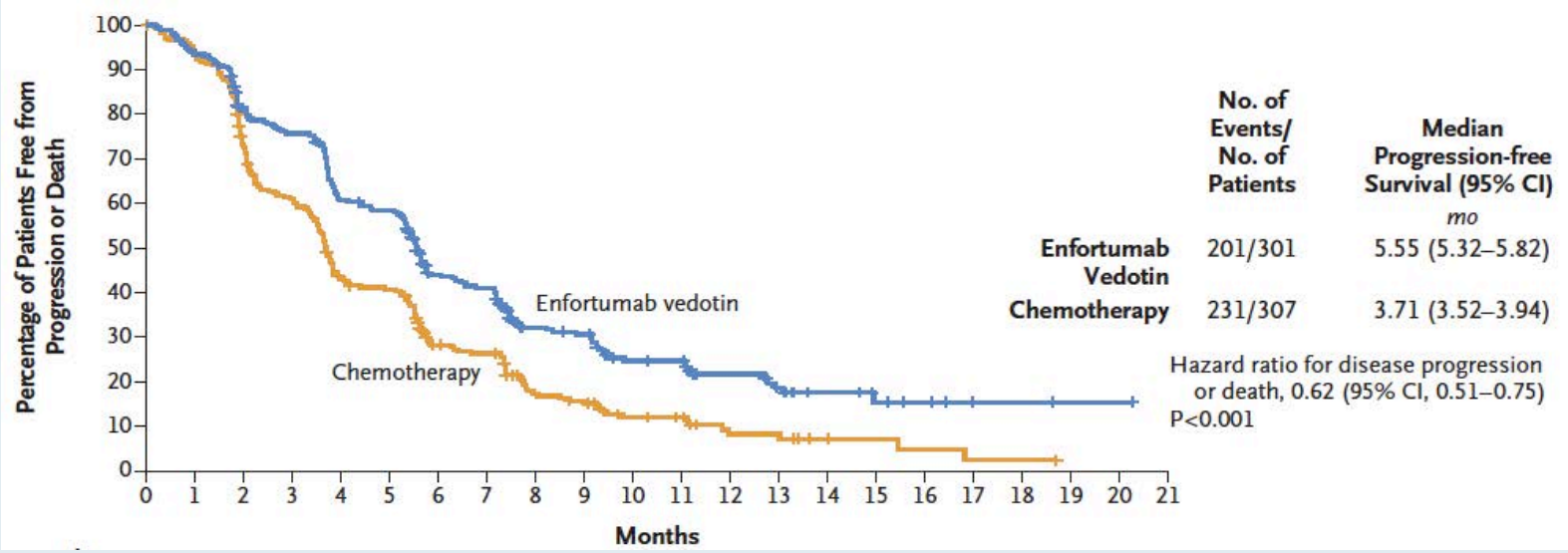
- have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand (PD-L1) inhibitor and platinum-containing chemotherapy, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

Trial EV-301 (NCT03474107) was an open-label, randomized, multicenter trial required to confirm the clinical benefit of the 2019 accelerated approval. This trial enrolled 608 patients with locally advanced or metastatic urothelial cancer who received a prior PD-1 or PD-L1 inhibitor and platinum-based chemotherapy. Patients were randomized (1:1) to receive either enfortumab vedotin-ejfv (EV) 1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle or investigator's choice of single-agent chemotherapy (docetaxel, paclitaxel, or vinflunine)."

www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-enfortumab-vedotin-ejfv-locally-advanced-or-metastatic-urothelial-cancer

EV-301: Survival and Response Analyses





	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 2 groups:

- 93.9% versus 91.8%

Incidence of events of Grade 3 or higher was also similar in the 2 groups:

- 51.4% versus 49.8%

Powles T et al. *N Engl J Med* 2021;384(12):1125-35.

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."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sacituzumab-govitecan-advanced-urothelial-cancer

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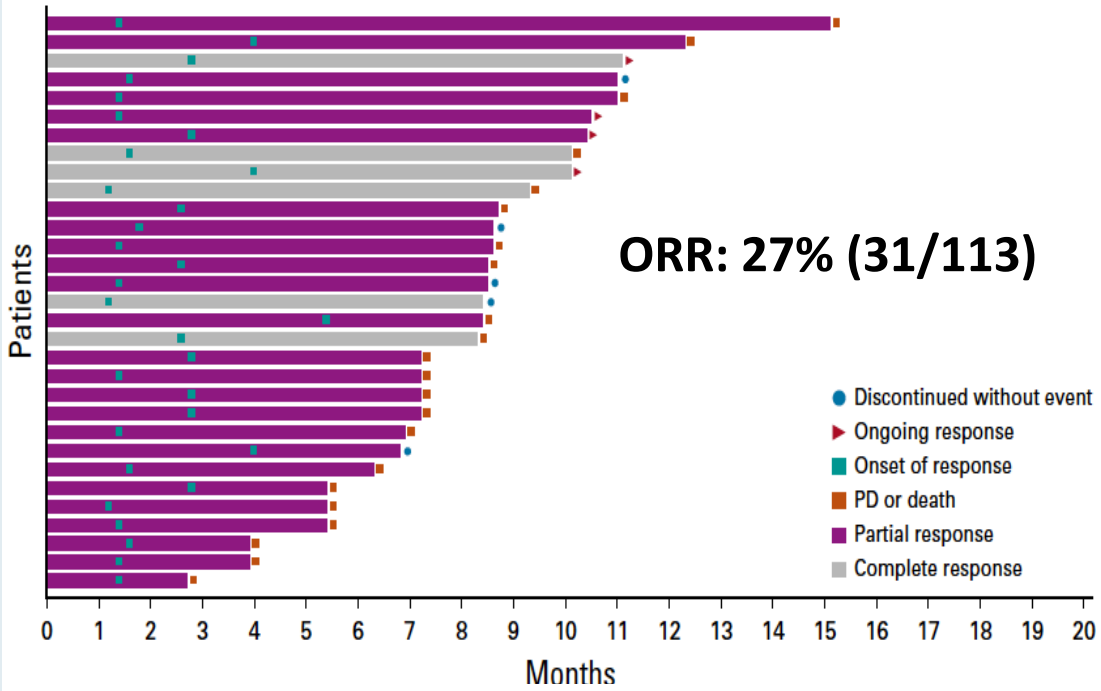
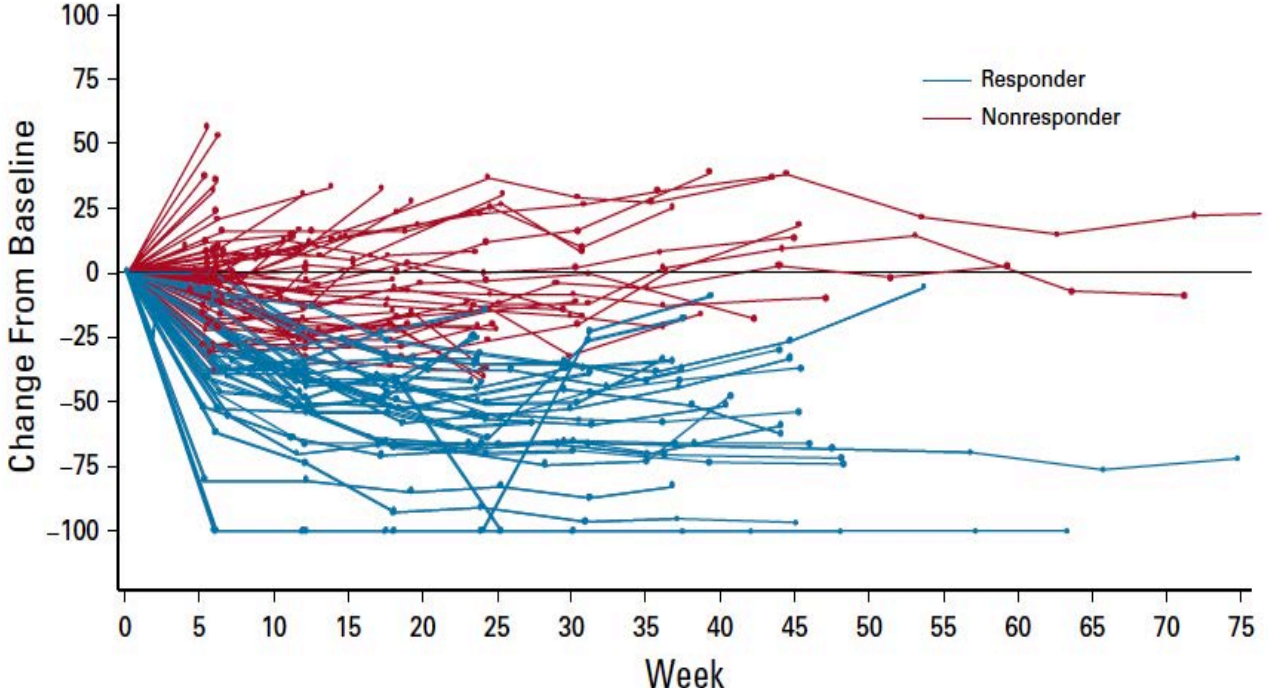
TROPHY U-01 (Cohort 1): ORR, Duration of Response and Survival

Median DOR: 7.2 mo

Median time to onset of response: 1.6 mo



ORR: 27% (31/113)



Median PFS: 5.4 mo

Median OS: 10.9 mo

Tagawa ST et al. *J Clin Oncol* 2021;[Online ahead of print]; Loriot Y et al. ESMO 2020;Abstract LBA24.

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

Recent Advances and Future Directions in Oncology

A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists

Saturday, October 23, 2021
9:30 AM – 4:30 PM ET

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Agenda

Module 1 — Breast Cancer: *Drs Partridge and Pegram*

Module 2 — Lung Cancer: *Drs Sequist and Spigel*

Module 3 — Gastrointestinal Cancers: *Drs Bekaii-Saab and Ciombor*

Module 4 — Genitourinary Cancers: *Drs Agarwal and Petrylak*

Module 5 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Kahl and Zelenetz*

Module 6 — Multiple Myeloma: *Drs Raje and Usmani*

Module 7 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Levis and Sallman*

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Chronic Lymphocytic Leukemia and Lymphomas Faculty

Brad S Kahl, MD
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Andrew D Zelenetz, MD, PhD
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Contributing Oncologists

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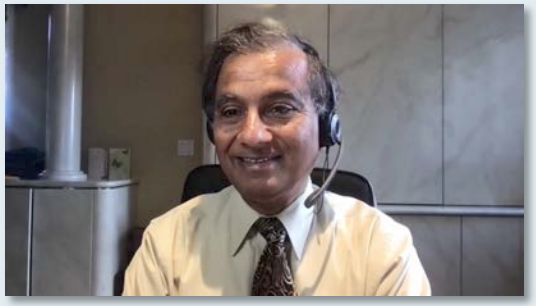

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Mamta Choksi, MD
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Elizabeth Guancial, MD
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Ina J Patel, DO
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Shachar Peles, MD
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Ferdy Santiago, MD
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Raji Shameem, MD
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Hematologist and Medical Oncologist
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Chief, Division of Hematology and Oncology
Lee Health
Fort Myers, Florida

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Agenda

Module 1: Mantle Cell Lymphoma

- Dr Lamar: A 73-year-old man with relapsed mantle cell lymphoma

Module 2: Diffuse Large B-Cell Lymphoma

- Dr Gandhi: CAR T-cell therapy and use in elderly patients
- Faculty Chalk Talks

Module 3: Hodgkin Lymphoma

- Dr Peles: A 23-year-old woman with mixed cellularity classical Hodgkin lymphoma
- Faculty Chalk Talks

Module 4: Chronic Lymphocytic Leukemia

- Dr Kumar: Treatment of p53-negative versus p53-positive disease
- Faculty Chalk Talks

Module 5: Follicular Lymphoma

- Dr Shameem: An 81-year-old man with Grade I-II follicular lymphoma
- Dr Peles: Treatment options for relapsed follicular lymphoma
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Appendix: Selected Data Sets

Case Presentation – Dr Lamar: A 73-year-old man with relapsed mantle cell lymphoma

Dr Zanetta Lamar

- Diagnosed with Stage IV mantle cell lymphoma, with GI and marrow involvement
- Bendamustine/rituximab on clinical trial then crossed over to acalabrutinib → PD
- R-DHAX

Questions

- How do you decide upon which of the 3 BTK inhibitors to use, especially with the newest agent, zanubrutinib?
- Are there any new side effects observed with zanubrutinib?
- Do you prefer transplant or CAR T-cell therapy for patients with relapsed/refractory mantle cell lymphoma?

RTP RESEARCH TO PRACTICE

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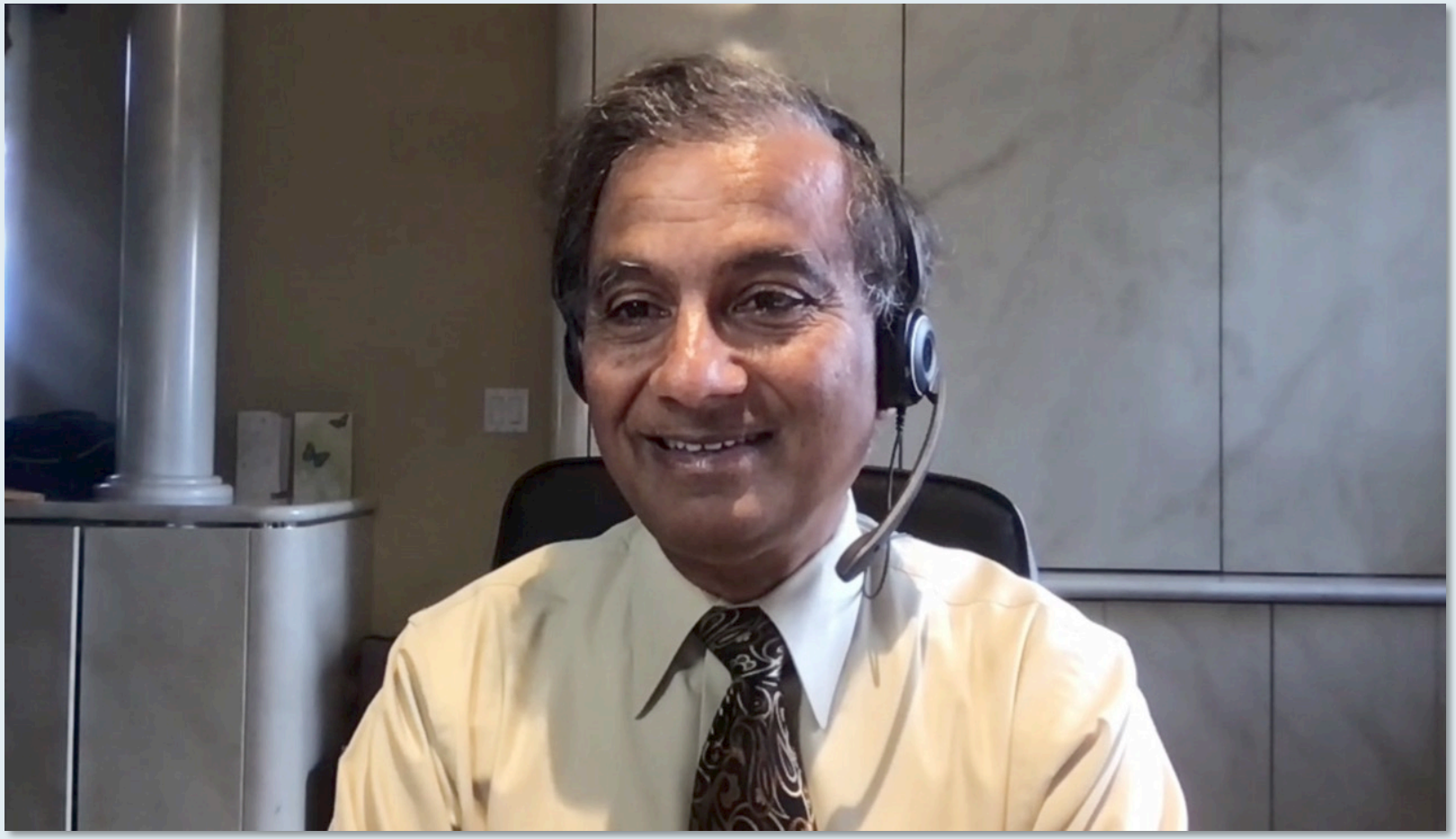
Toxicity with CAR T-cell therapy and use in elderly patients



Dr Sunil Gandhi

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Optimal second line treatment of DLBCL after R-CHOP considering the recent ZUMA-7, TRANSFORM and BELINDA press releases

Chalk Talk – Andrew D Zelenetz, MD, PhD

- Practicing medicine by press release is a hazardous undertaking
  - The announcements are for financial/regulatory means
  - The conclusion that a primary endpoint has been reached is not subject to outside review
- **ZUMA-7** Axicabtagene ciloleucel vs Platinum-based 2nd Line Therapy
  - Primary: EFS (3-year)
  - Included: DLBCL included transformed; HGL; PCDLBLC, Leg type; EBV-associated DLBCL
  - *Primary refractory or POD within 12 months (based on CORAL, 3-year EFS 20%)*
- **TRANSFORM** Lisocabtagene maraleucel v SOC
  - Inclusion: Similar to ZUMA-7 but also includes PMBL, FL, 3B
- **BELINDA** Tisagenlecleucel (may have bridging therapy) v SOC
  - Primary: EFS (5-year)
  - ZUMA-7 plus FL, 3B, intravascular DLBCL, ALK+ DLBCL, High grade, NOS, HHV8+, PCDLBCL, LT
  - *Primary refractory of POD within 365 days of last therapy*
- Who were accrued? Is response to SOC in line with expectations?
- Do not extrapolate to late relapses after 12 months, 3-year EFS in CORAL 45%

Sequencing of tafasitamab/lenalidomide among other novel agents in patient with relapsed/refractory DLBCL

- When encountering a patient with R/R DLBCL need to make fundamental initial decision
- Am I going for cure with ASCT?
  - If yes, then with select traditional salvage options to demonstrate chemo sensitivity.
- Am I going for cure with CART?
  - Some patients are not appropriate for ASCT but are appropriate for CART.
  - Will generally avoid CD19 directed treatments (Tafa, Lonca-T) and treatments notoriously hard on T cells (Bendamustine).
- Am I pursuing palliative strategies?
  - Need to balance efficacy considerations with toxicity considerations.
  - Tafa-Len is an appealing option for more frail patients. Unclear how efficacious in highly proliferative DLBCL.

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Case Presentation – Dr Peles: A 23-year-old woman with mixed cellularity classical Hodgkin lymphoma

Dr Shachar Peles

- PMH: Down syndrome
- Diagnosed with mixed cellularity classical Hodgkin lymphoma, IPS-2
- ABVD x 2 → PET: Negative, Deauville 1 → AVD

Questions

- Would you have treated her with brentuximab vedotin/AVD instead?
- Should the brentuximab vedotin regimen be reserved for patients with a high IPS?

Use of brentuximab vedotin as bridge to transplant and/or post-transplant consolidation in patients with HL who experience disease progression after first line BV-AVD

- Suppose a patient receives BV-AVD as first line therapy and later relapses, is it OK to use BV in salvage or post ASCT?
- Very little data to guide us here. I will look at length of 1st remission.
  - If patients relapses within 2 years of BV-AVD, I am unlikely to use BV-based salvage therapy.
  - If patient relapses after 2 years, more reasonable to consider.
- If a patient meets all other AETHERA criteria but has had BV-AVD frontline, I am unlikely to use BV maintenance therapy post ASCT.
- If a patient meets all other AETHERA criteria but received a BV-based salvage as the bridge to ASCT (and responded), I would offer BV maintenance post ASCT.

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RTP RESEARCH TO PRACTICE

Treatment of p53-negative versus p53-positive disease; venetoclax and cytopenias; role of MRD

Dr KS Kumar

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Selection of Bruton's tyrosine kinase inhibitor as initial therapy for patients with CLL requiring treatment

Chalk Talk – Andrew D Zelenetz, MD, PhD

- No front-line comparison of BTKi
- **ELEVATE-RR** study of ibrutinib vs acalabrutinib in R/R CLL
  - Median PFS in both arms: 38.4 months
  - AESI Afib Ibr 16% v Acala 9.4%; Cardiac Ibr 30% v Acala 24.1%; Hemorrhage Ibr 51.3 v Acala 38%; HTN Ibr 23.2% v Acala 9.4%, infections similar
- **ALPINE** study of ibrutinib v zanubrutinib in R/R CLL
  - ORR Ibr 64.4% v Zanu 76.3% (IRC); prelim PFS, 12-month Ibru 84% vs 94.9%
  - AESI Afib Ibr 10.1% v Zanu 2.5%; Cardiac Ibr 25.1% v Zanu 13.7%, Neutropenia Ibr 21.7% v Zanu 28.4%; hemorrhage, HTN, infections similar
- Currently zanubrutinib is not approved for CLL (currently under review)
  - SEQUOIA Zanubrutinib v BR met primary PFS endpoint by press release
  - ELEVATE-TN Obin Chlorambucil v Acalabrutinib v Obin-Acalabrutinib
    - Obin increases CR rate with acalabrutinib and trend for a superior PFS
- In 1L, I use a second generation BTKi, most often acalabrutinib unless there is need to continue a PPI
  - Want to see more follow up of acala+obin

Optimal schedule of venetoclax with an anti-CD20 antibody in relapsed CLL; choice of anti-CD20 antibody to pair with venetoclax for relapsed CLL

- Frontline approval from CLL 14 study
  - Obinutuzumab days 1,2,8,&15 of cycle 1. Ven ramp up starts on day 22 of cycle 1.
  - Obin on day 1 of cycles 2-6. Ven for 12 cycles.
- R/R approval from MURANO study.
  - Treatment starts with Ven ramp up, which does not count towards a cycle. Rituximab starts after completed ramp up (week 5) which is day 1 of cycle 1.
  - Rituximab on day 1 of cycles 1-6. Ven for 24 cycles.
- Ideally would like more flexibility. Many patients have had significant prior R and would be nice to offer Ven-Obin in R/R setting.
- COVID pandemic has complicated matters.
  - CLL patients do not always respond well to vaccination. They respond poorly if on active therapy and very poorly if any antiCD20 in previous 12 months.
  - I have found myself simply omitting antiCD20 on occasion.

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RTP RESEARCH TO PRACTICE

Case Presentation – Dr Shameem: An 81-year-old man with Grade I-II follicular lymphoma

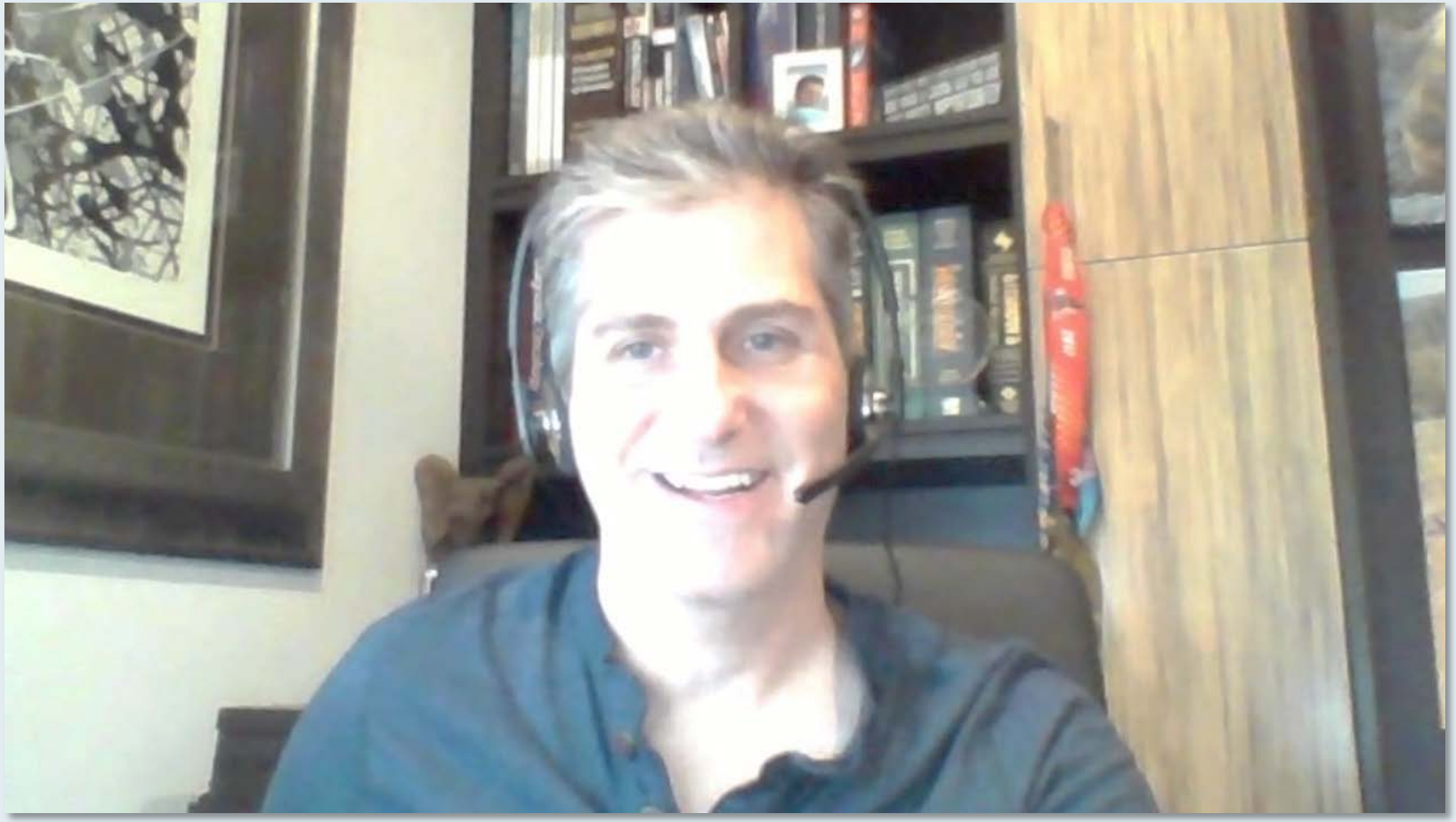
Dr Raji Shameem

- PMH: Stage IIA lung cancer, s/p resection and adjuvant chemotherapy in 2010; Prostate cancer s/p proton therapy in 2013; HTN, HLD, GERD
- COVID-19 vaccination weeks prior to diagnosis of grade 1-2 follicular lymphoma, t(14;18)
  - Adenopathy above and below the diaphragm; Biopsy: 10% lymphoma involvement
- Bendamustine/rituximab

Questions

- What is your frontline therapy of choice for follicular lymphoma? Have you chosen to initiate therapy with lenalidomide/rituximab?
- How would you sequence tazemetostat for patients with relapsed/refractory follicular lymphoma, specifically if their tumors were EZH2-mutant or wildtype?
- How do you approach treatment in patients who relapse within the first 24 months?
- Which patients do you refer for CAR T-cell therapy?

Treatment options for relapsed follicular lymphoma



Dr Shachar Peles

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Role of tazemetostat in patients with relapsed FL with and without an EZH2 mutation

Chalk Talk – Andrew D Zelenetz, MD, PhD

- EZH2 is an epigenetic regulator of gene expression and cell fate decisions, and its expression is required for germinal center formation
- Oncogenic mutations of EZH2 are gain of function (activating) mutations that suppress exit from the germinal center
- Approximately 20% of patients with FL have EZH2 mutations
- Tazemetostat is a first-in-class oral EZH2 inhibitor that suppress both mutant and wild-type EZH2 activity
- Tazemetostat is approved for treatment of both EZH2 mutant FL as third-line therapy and for FL with WT EZH2 who have "no satisfactory alternative treatment options"
- Tazemetostat is extremely well tolerated with very few grade 3-4 adverse events
  - 8% discontinuation rate for AE's (most common grade 1-2: nausea, diarrhea, fatigue, cough, URI)
- In EZH2 mutated cases the ORR was 69% (IRC) and 78% (investigator), CR 13% (IRC) and 9% (investigator), median PFS 13.8 months
- In EZH2 WT cases the ORR was 35% (IRC) and 33% (investigator), CR 4% (IRC) and 6% (investigator), median PFS 11.1 months (IRC), 5.6 months (investigator)

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Mantle Cell Lymphoma

FDA Approves Brexucabtagene Autoleucel for Relapsed or Refractory Mantle Cell Lymphoma

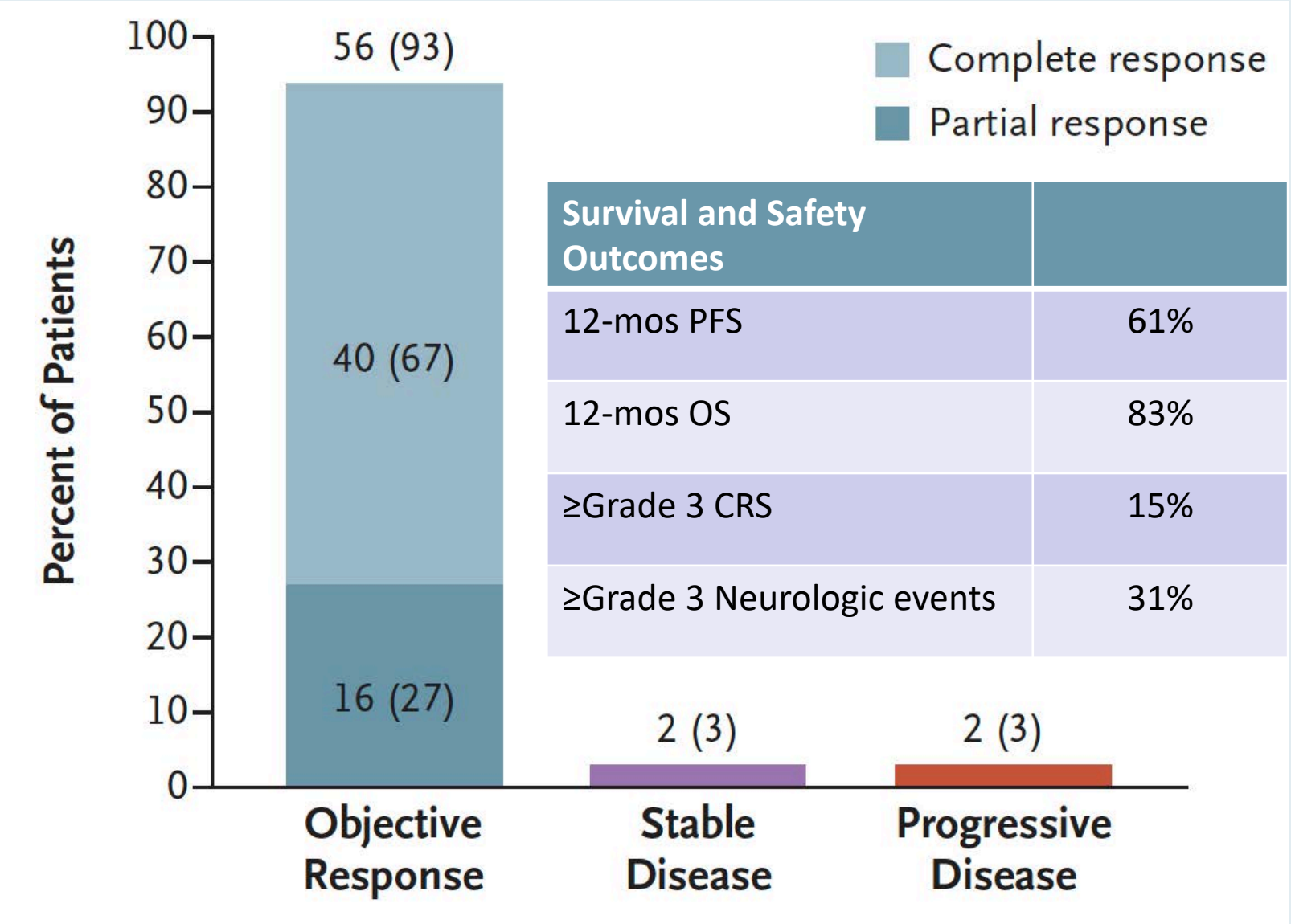
Press Release: July 24, 2020

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

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

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-brexucabtagene-autoleucel-relapsed-or-refractory-mantle-cell-lymphoma

ZUMA-2: Response Rates, Survival and Select Safety Outcomes with Brexucabtagene Autoleucel for Mantle Cell Lymphoma



Survival and Safety Outcomes	
12-mos PFS	61%
12-mos OS	83%
≥Grade 3 CRS	15%
≥Grade 3 Neurologic events	31%

Wang M et al. *N Engl J Med* 2020;382(14):1331-42.

Diffuse Large B-Cell Lymphoma

Phase III ZUMA-7 Trial of Axi-cel Meets Primary Endpoint

Press Release: June 30, 2021

"The ZUMA-7 trial (NCT03391466) demonstrated superiority of axicabtagene ciloleucel (axi-cel) compared with standard of care (SOC) autologous stem cell transplant (ASCT) after meeting the primary end point of event-free survival (EFS) improvement for patients with relapsed or refractory large B-cell lymphoma (LBCL), according to a press release from the company responsible for manufacturing the chimeric antigen receptor (CAR) T-cell therapy. A statistically significant EFS benefit (HR, 0.398; P <0.0001) was observed as well as improvement in the secondary end point of objective response rate (ORR).

The top-line results of the randomized ZUMA-7 trial paint the picture of a potential paradigm shift in the treatment of large B-cell lymphoma, Frederick L Locke, MD, ZUMA-7 lead principal investigator and co-leader of the Immuno-Oncology Program at Moffitt Cancer Center in Tampa, Florida, said in the press release. Investigators mentioned that these data are still immature and further analyses are planned for the future. The trial was conducted under a Special Protocol Agreement from the FDA where the trial design, end points, and statistical analysis were agreed in advance."

https://www.cancernetwork.com/view/zuma-7-trial-meets-event-free-survival-end-point-in-large-b-cell-lymphoma

RTP RESEARCH TO PRACTICE

Phase III TRANSFORM Trial of Liso-cel Meets Primary Endpoint

Press Release: June 10, 2021

"Data from the Phase 3 TRANSFORM trial (NCT03575351) of the chimeric antigen receptor (CAR) T-cell therapy lisocabtagene maraleucel (liso-cel) as second-line therapy for patients with relapsed/refractory large B-cell lymphoma (LBCL) resulted in a statistically significant improvement in the primary end point of event-free survival versus therapy with the standard-of-care comparator arm, according to the company responsible for developing the agent.

Additionally, the toxicity profile observed with liso-cel was consistent with the safety data reported in the TRANSCEND NHL 001 trial (NCT02631044) which led to the FDA approving the CD19-directed therapy for patients with certain types of non-Hodgkin lymphoma, including diffuse large B-cell lymphoma (DLBCL), following 2 or more prior therapies. These data represent the first time a treatment for relapsed/refractory LBCL has demonstrated benefit over high-dose chemotherapy and hematopoietic stem cell transplant (HSCT).

Results regarding the primary end point will be evaluated and shared at an upcoming medical conference as well as with regulatory authorities."

https://www.cancernetwork.com/view/liso-cel-meets-primary-end-point-of-event-free-survival-improvement-in-phase-3-trial

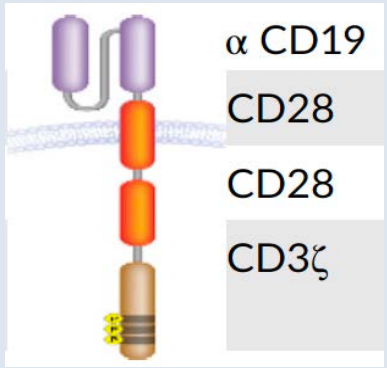
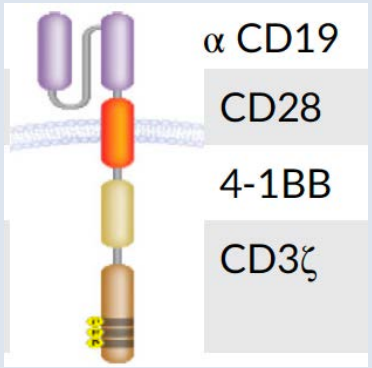
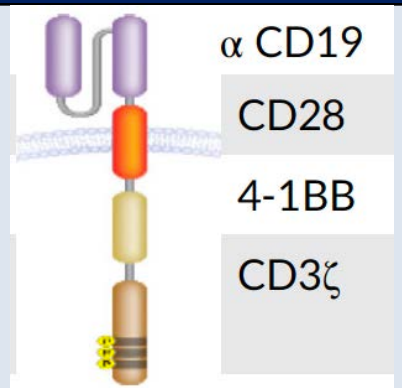
BELINDA Study Investigating Tisagenlecleucel as Second-Line Treatment for Aggressive B-Cell Non-Hodgkin Lymphoma Fails to Meet Primary Endpoint

Press Release: August 24, 2021

"The Phase III BELINDA study investigating tisagenlecleucel in aggressive B-cell non-Hodgkin lymphoma (NHL) after relapse or lack of response to first-line treatment did not meet its primary endpoint of event-free survival compared to treatment with the standard-of-care (SOC). SOC was salvage chemotherapy followed in responding patients by high-dose chemotherapy and stem cell transplant. The safety profile was consistent with the established safety profile of tisagenlecleucel."

https://www.novartis.com/news/media-releases/novartis-provides-update-belinda-study-investigating-kymriah-second-line-treatment-aggressive-b-cell-non-hodgkin-lymphoma

Summary of CAR T-Cell Pivotal Studies in DLBCL

	Axi-cel ZUMA-1 (N = 108 infused)	Tisagenlecleucel JULIET (N = 108 infused)	Liso-cel TRANSCEND (N = 294 infused)
CAR			
Transmembrane domain			
Co-stimulatory doman			
T-cell activation domain			
Leukapheresis	Fresh product	Cryopreserved product	Fresh product
Outpatient administration	Not allowed	Allowed	Allowed
Bridging therapy, %	Not allowed	92%	59%
Lymphodepletion chemotherapy	Cy/Flu 500/30 mg/m^2 × 3d	Cy/Flu 250/25 mg/m^2 x 3d Bendamustine 90 mg/m^2 x 2d	Cy/Flu 300/30 mg/m^2 x 3d

Westin JR et al. *Am J Hematol* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

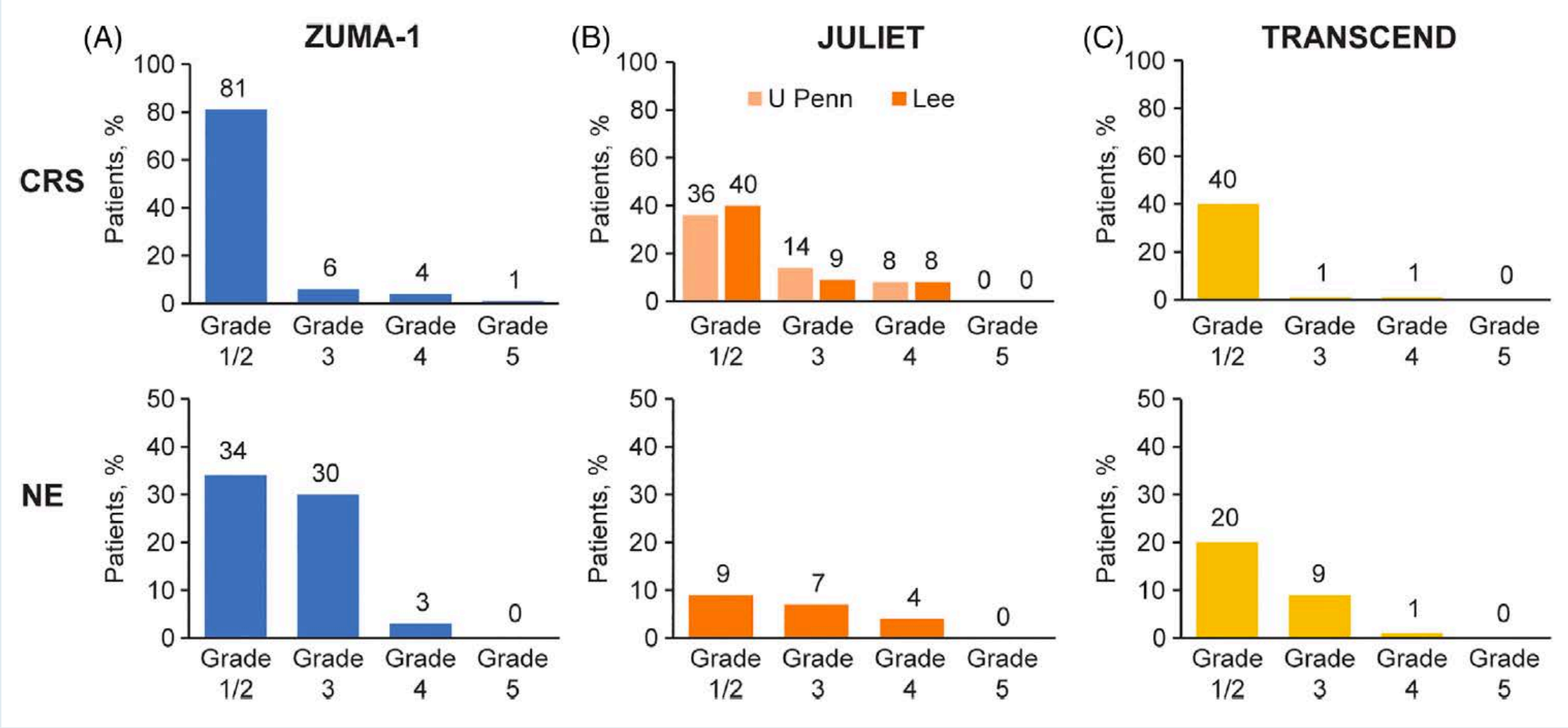
Summary of Efficacy Outcomes in Pivotal Studies of CAR T-Cell Therapy for DLBCL

	Axi-cel ZUMA-1 (N = 108 infused)	Tisagenlecleucel JULIET (N = 115 infused)	Liso-cel TRANSCEND (N = 294 infused)
Overall response rate	74%	52%	73%
Complete response rate	54%	40%	53%
24-month OS rate	50.5%	40.0%	44.9%
Indication	DLBCL, High grade, PMBCL, tFL	DLBCL, High grade, tFL	DLBCL, HGBCL, PMBCL, tFL, tIND

Westin JR et al. *Am J Hematol* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Cytokine Release Syndrome and Neurologic Events in Pivotal Studies of CAR T-Cell Therapy for DLBCL



Westin JR et al. *Am J Hematol* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Phase III Study Shows Polatuzumab Vedotin with R-CHP Is the First Regimen in 20 Years to Significantly Improve Outcomes in Previously Untreated Aggressive Form of Lymphoma

Press Release: August 9, 2021

"Pivotal Phase III POLARIX trial comparing polatuzumab vedotin in combination with chemotherapy regimen R-CHP versus the standard of care R-CHOP in treatment of first-line diffuse large B-cell lymphoma (DLBCL) met its primary endpoint of investigator assessed progression-free survival.

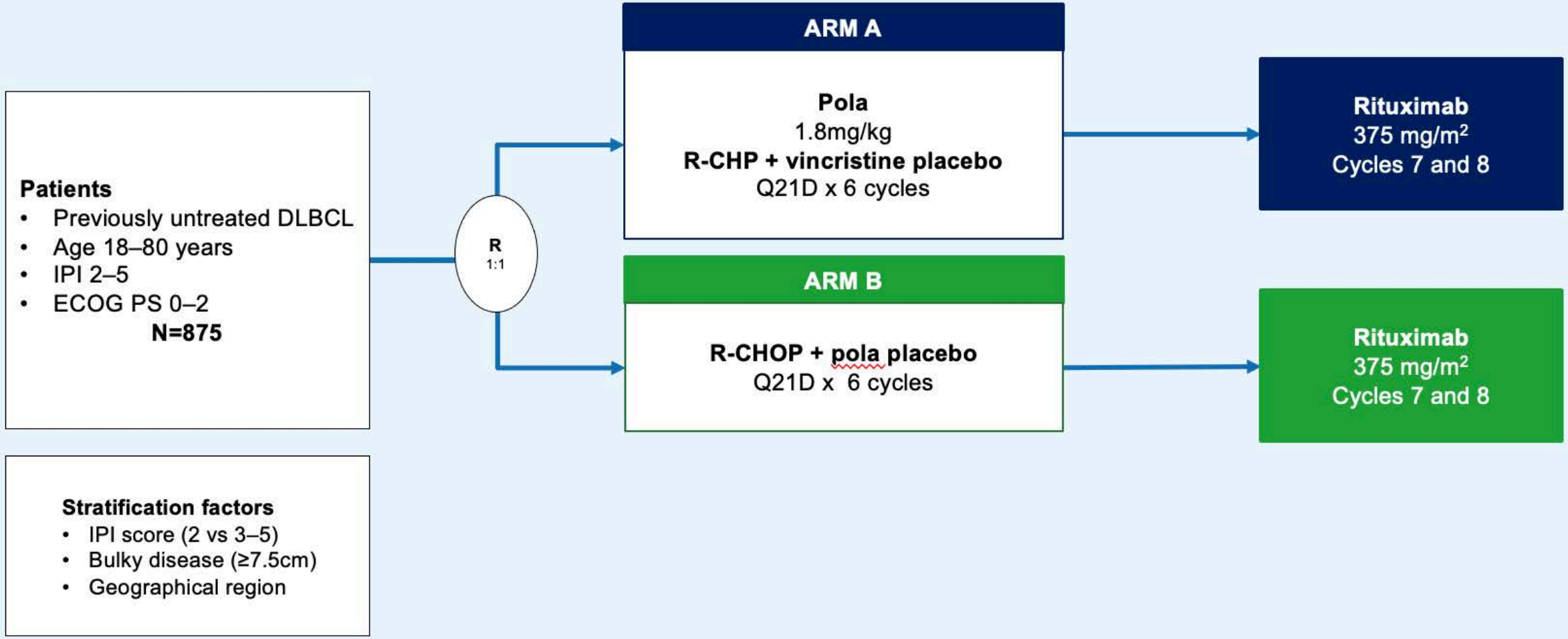
Prolonging survival without disease advancement could be transformative for newly diagnosed DLBCL patients, as currently 40% of patients relapse after disease progression.

Data will be submitted to health authorities globally as soon as possible and presented at an upcoming medical meeting."

https://finance.yahoo.com/news/phase-iii-study-shows-genentechs-050000152.html

RTP RESEARCH TO PRACTICE

POLARIX Phase III Trial Design



Courtesy of Gilles Salles MD, PhD.

FDA Grants Accelerated Approval to Loncastuximab Tesirine-lpyl for Large B-Cell Lymphoma

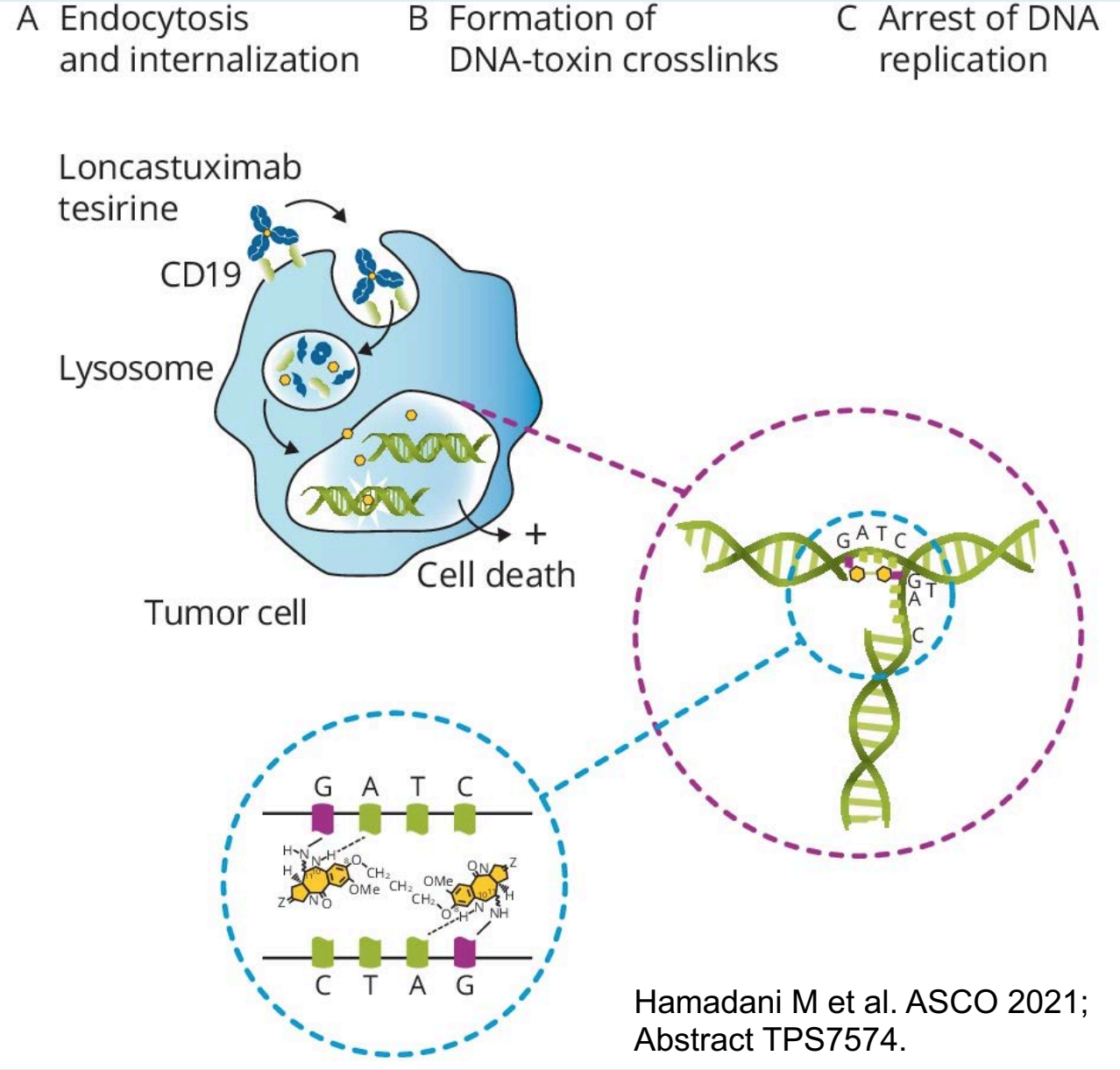
Press Release: April 23, 2021

"The Food and Drug Administration granted accelerated approval to loncastuximab tesirine-lpyl, 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. Patients received loncastuximab tesirine-lpyl 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles. Patients received treatment until progressive disease or unacceptable toxicity."

www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-loncastuximab-tesirine-lpyl-large-b-cell-lymphoma

Mechanism of Action of Loncastuximab Tesirine



Hamadani M et al. ASCO 2021; Abstract TPS7574.

Hodgkin Lymphoma

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

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

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

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

Kumar A et al. *J Clin Oncol* 2021;[Online ahead of print].

Front-Line Brentuximab Vedotin for Older Patients with HL

Best Responses per Investigator – Efficacy Evaluable Set

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

Patients who were not efficacy-evaluable included:

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

8

Yasenchak CA et al. ASH 2020;Abstract 471.

Anti-CD30 CAR T-Cell Therapy After Lymphodepletion Regimens for R/R Hodgkin Lymphoma (HL)

- Two parallel Phase I/II studies (NCT02690545 and NCT02917083) at 2 independent centers involving patients with relapsed or refractory HL
- Anti-CD30 CAR T cells were administered after lymphodepletion with either bendamustine alone, bendamustine and fludarabine or cyclophosphamide and fludarabine

Response	All Patients (N = 37)	Benda (n = 5)	Benda-Flu (n = 15)	Cy-Flu (n = 17)
ORR				
CR + PR	23 (62)	0 (0)	12 (80)	11 (65)
Response rate				
CR	19 (51)	0 (0)	11 (73)	8 (47)
PR	4 (11)	0 (0)	1 (7)	3 (18)

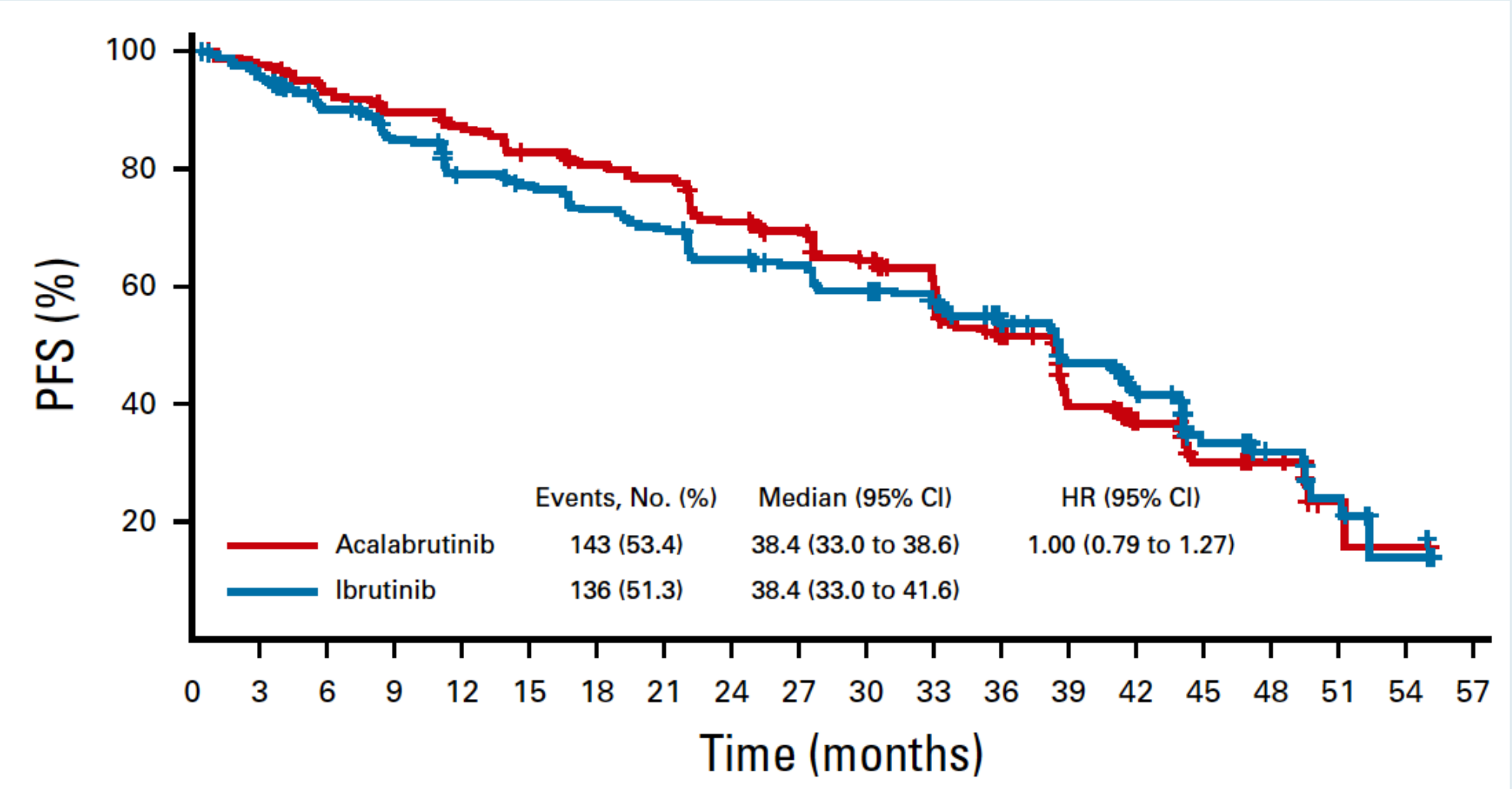
- Cytokine release syndrome was observed in 10 patients, all of which were Grade 1. No neurologic toxicity was observed

Ramos CA et al. *J Clin Oncol* 2020;38(32):3794-804.

RTP RESEARCH TO PRACTICE

Chronic Lymphocytic Leukemia

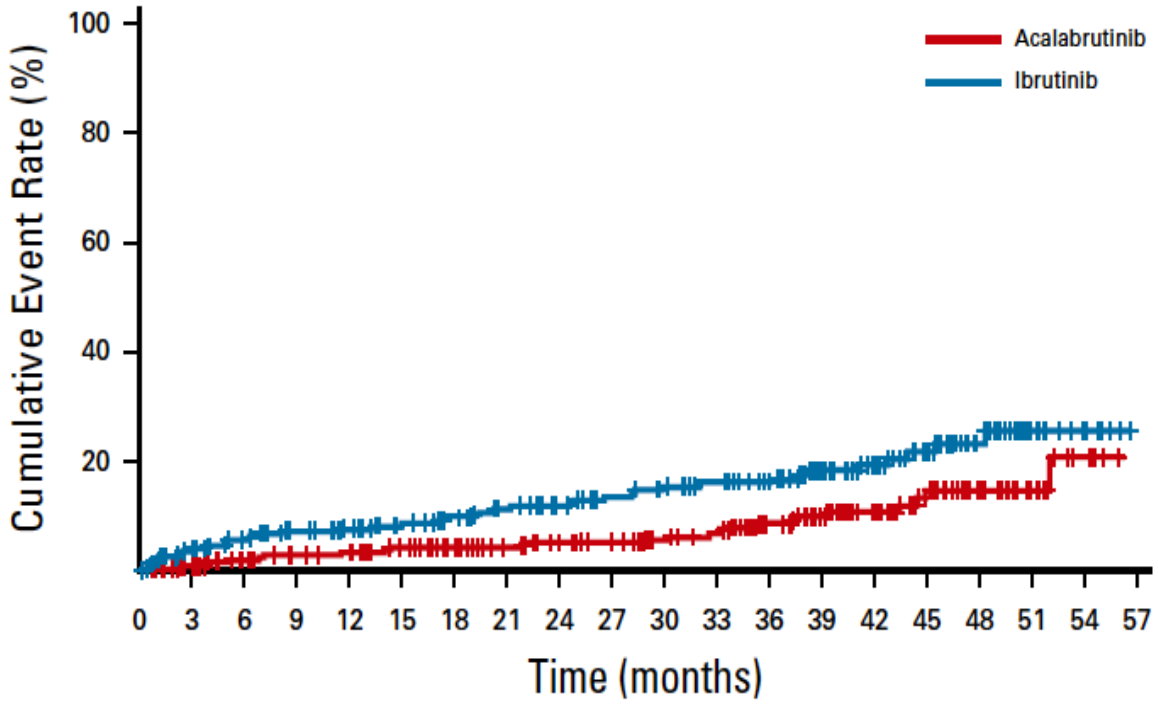
ELEVATE-RR: Primary Endpoint – Noninferiority Met on IRC-Assessed PFS



Byrd JC et al. *J Clin Oncol* 2021;[Online ahead of print]; ASCO 2021;Abstract 7500.

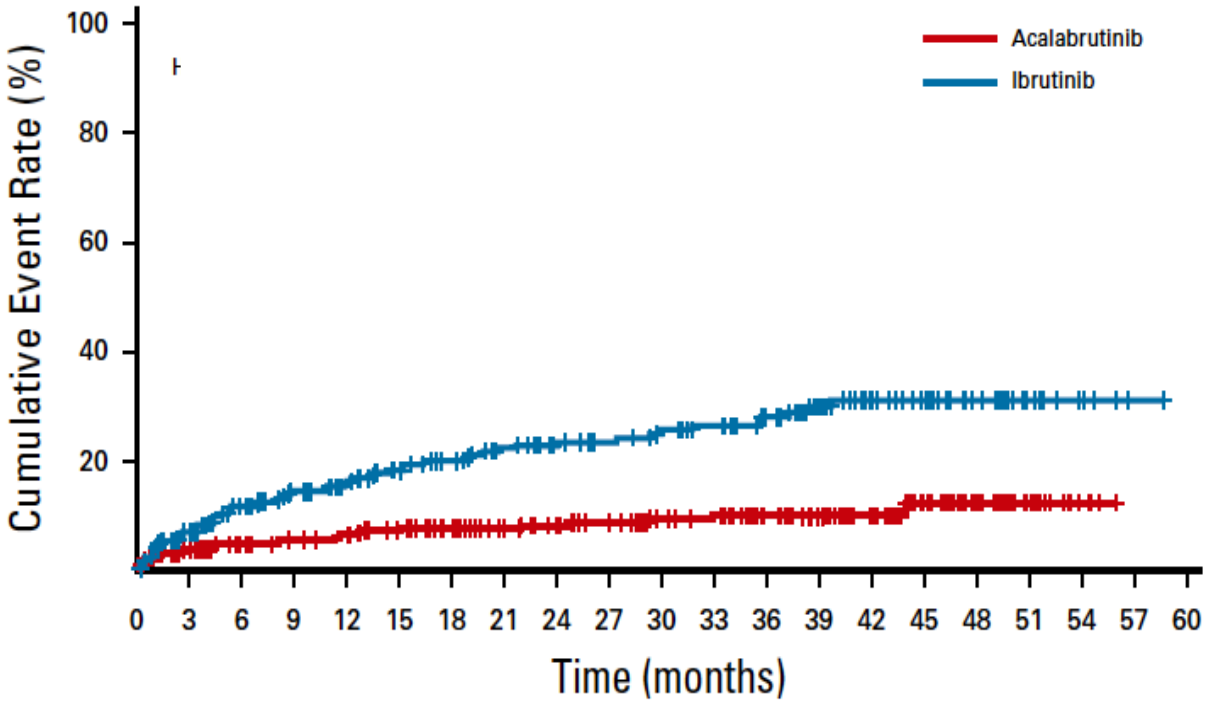
ELEVATE-RR: Cumulative Incidences of Atrial Fibrillation and Hypertension with Acalabrutinib versus Ibrutinib

Atrial Fibrillation



Acalabrutinib:Ibrutinib
HR (95% CI): 0.52 (0.32 to 0.86)

Hypertension



Acalabrutinib:Ibrutinib
HR (95% CI): 0.34 (0.21 to 0.54)

Byrd JC et al. *J Clin Oncol* 2021;[Online ahead of print]; ASCO 2021;Abstract 7500.

ELEVATE-RR: Acalabrutinib versus Ibrutinib for Previously Treated CLL

Adverse events	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%

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)

Byrd JC et al. ASCO 2021;Abstract 7500.

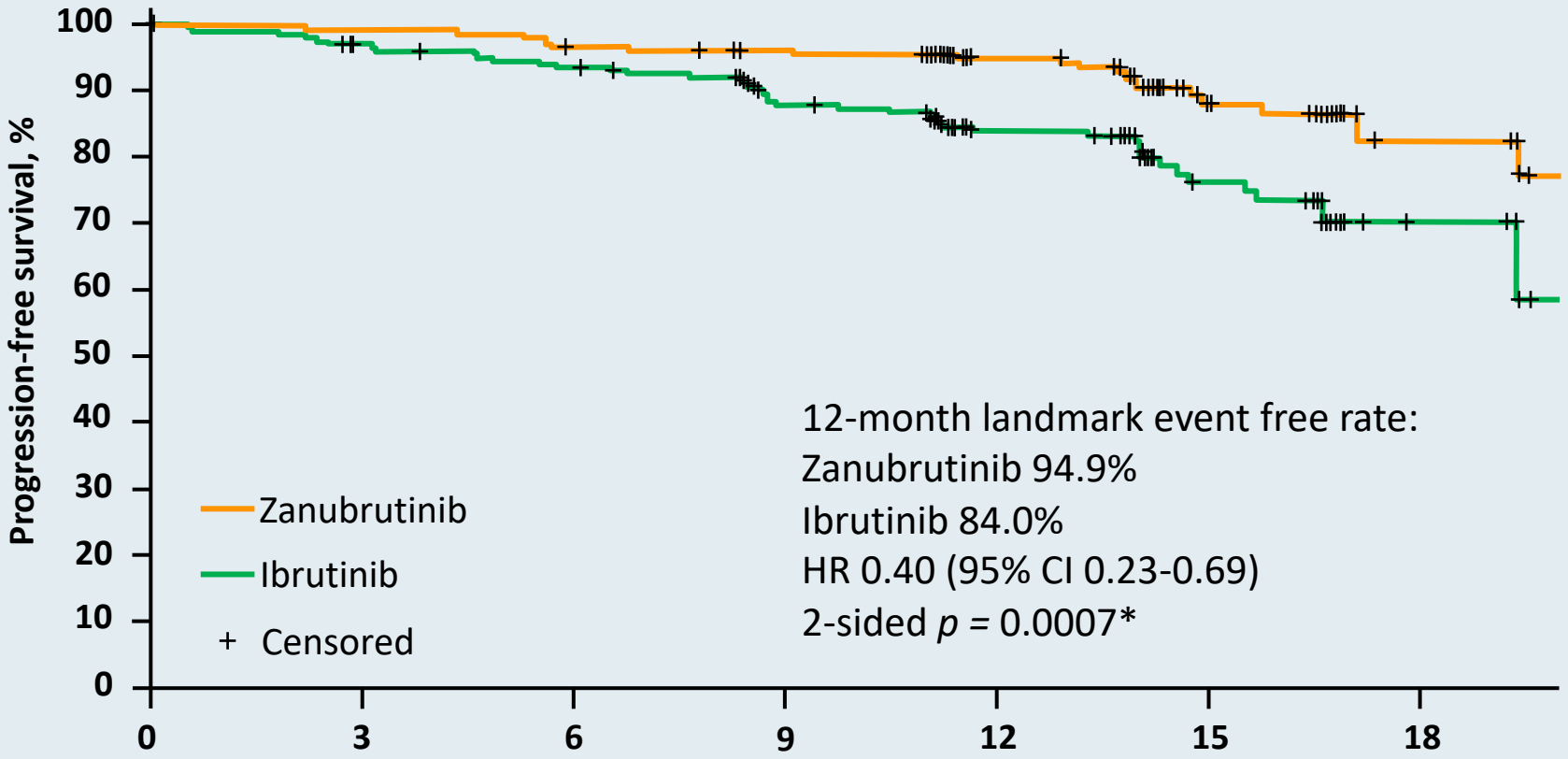
RTP RESEARCH TO PRACTICE

ALPINE: Primary Endpoint – ORR by Investigator Assessment

	Zanubrutinib (n = 207), n (%)	Ibrutinib (n = 208), n (%)
Primary endpoint: ORR (PR + CR)	162 **(78.3)** 95% CI: 72.0, 83.7	130 **(62.5)** 95% CI: 55.5, 69.1
	Superiority 2-sided *p* = 0.0006 compared with prespecified alpha of 0.0099	
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)
ORR (PR-L + PR + CR)	*183 (88.4)*	*169 (81.3)*
PR-L	21 (10.1)	39 (18.8)
SD	17 (8.2)	28 (13.5)
PD	1 (0.5)	2 (1.0)
Discontinued or new therapy prior to first assessment	6 (2.9)	9 (4.3)
	Del(17p) (n = 24), n (%)	**Del(17p) (n = 26), n (%)**
ORR (PC + CR)	20 (83.3)	14 (53.8)

Hillmen P et al. EHA 2021;Abstract LB1900.

ALPINE: PFS by Investigator Assessment



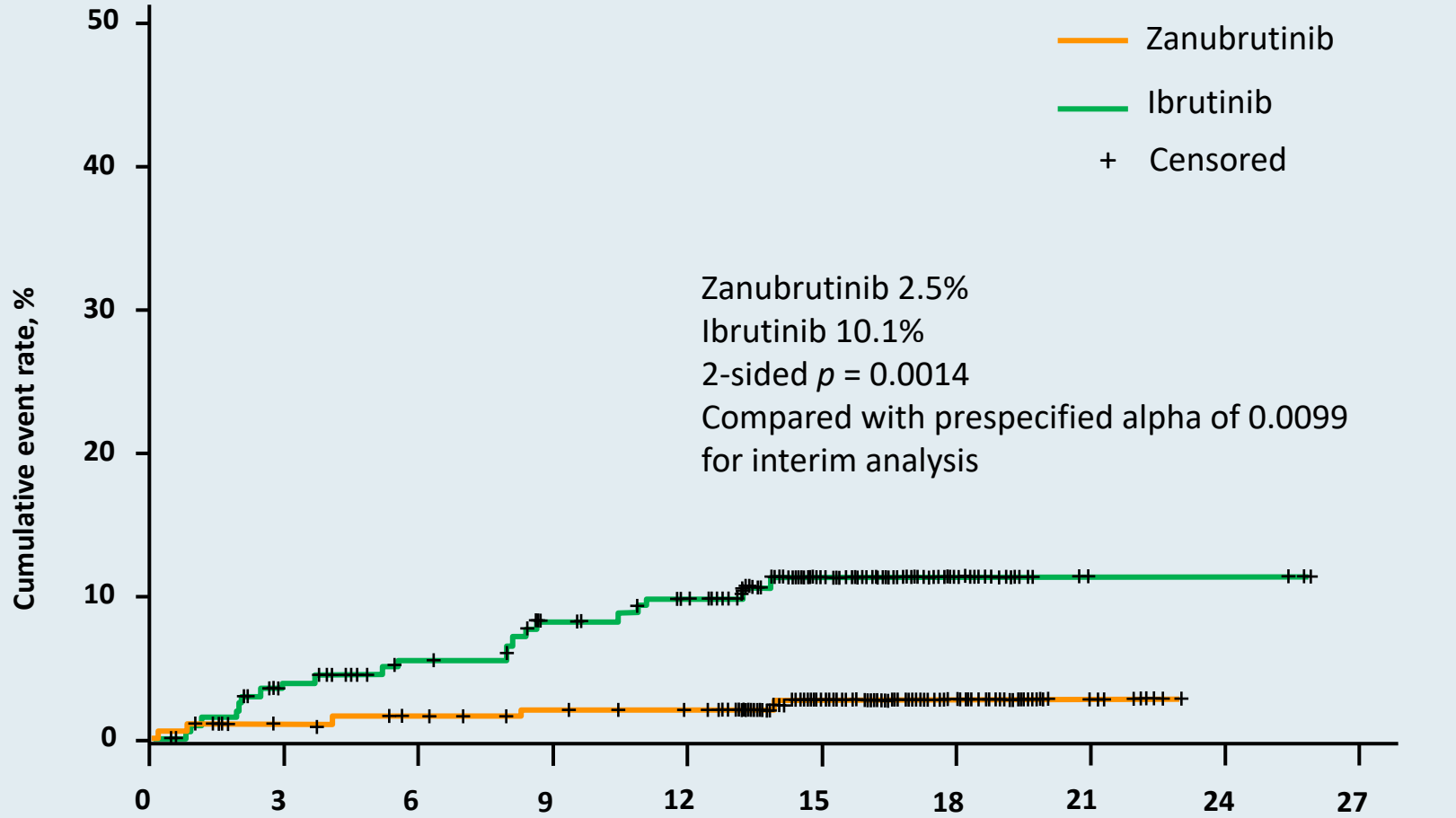
Patients at Risk							
Zanubrutinib	207	200	194	190	152	70	19
Ibrutinib	208	196	188	170	125	57	8

- Although not a pre-specified analysis, the overall 12-month PFS was higher with zanubrutinib vs ibrutinib (94.9% vs 84.0%)

*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.

Hillmen P et al. EHA 2021;Abstract LB1900.

ALPINE: Incidence of Atrial Fibrillation with Zanubrutinib versus Ibrutinib



Patients at Risk										
Zanubrutinib	204	197	194	190	187	114	40	9	0	0
Ibrutinib	207	190	179	168	160	91	26	3	3	0

Hillmen P et al. EHA 2021;Abstract LB1900.

RTP RESEARCH TO PRACTICE

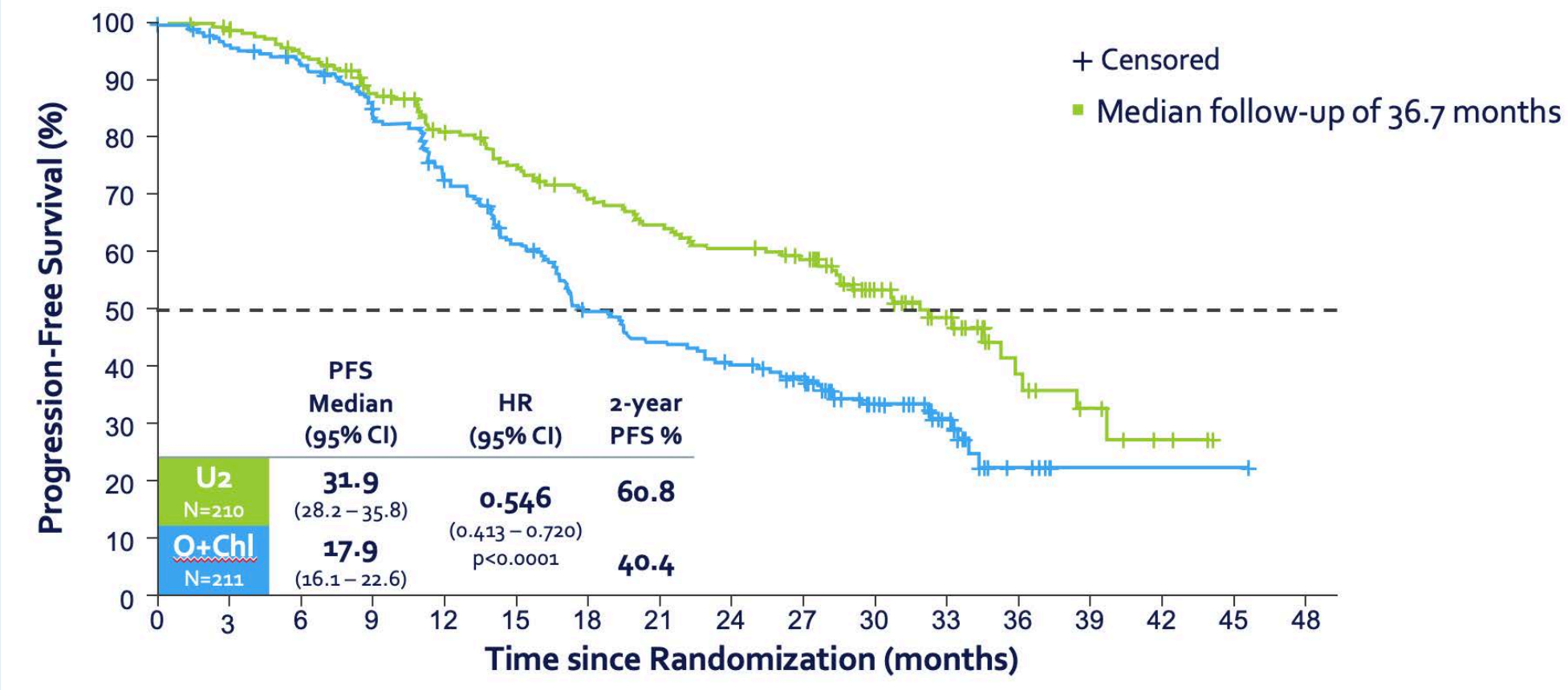
ALPINE: Adverse Events of Special Interest

Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2º endpoint)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage Major hemorrhage[b]	73 (35.8) 6 (2.9)	6 (2.9) 6 (2.9)	75 (36.2) 8 (3.9)	6 (2.9) 6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies Skin cancers	17 (8.3) 7 (3.4)	10 (4.9) 3 (1.5)	13 (6.3) 10 (4.8)	4 (1.9) 2 (1.0)

[a]Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients.
[b]Includes serious or Grade ≥3 hemorrhage or any Grade CNS hemorrhage
[c]Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.

Hillmen P et al. EHA 2021;Abstract LB1900.

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



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

Gribben JG et al. ASH 2020;Abstract 543.

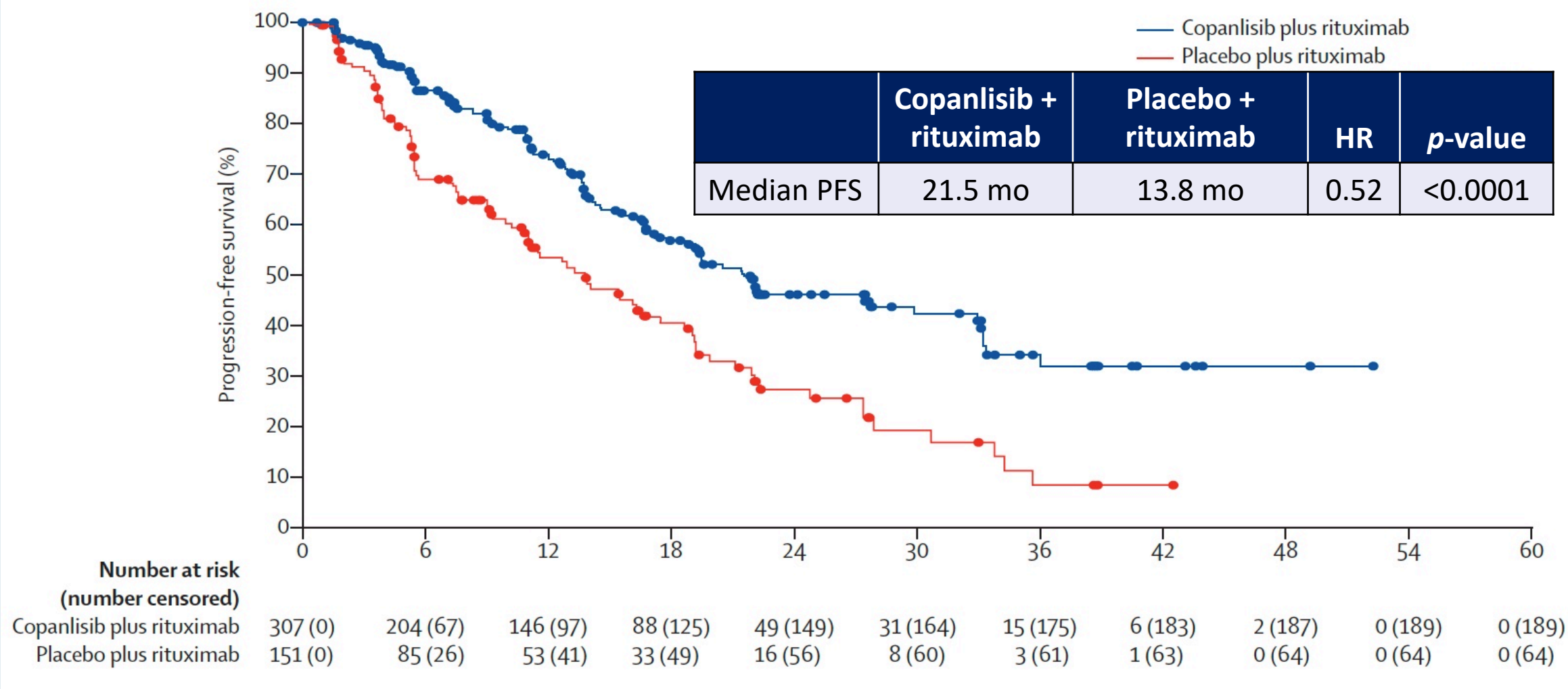
Follicular Lymphoma

Approved PI3K Inhibitors for FL: Indication and Dosing

	Idelalisib[1]	Copanlisib[2]	Duvelisib[3]	Umbralisib[4]
Mechanism of action	Selective PI3Kδ inhibitor	Dual inhibitor of PI3Kδ,α	Dual inhibitor of PI3Kδ,γ	Dual inhibitor of PI3Kδ and casein kinase CK1ε
Indication	Relapsed FL after at least 2 prior systemic therapies	Relapsed FL after at least 2 prior systemic therapies	R/R FL after at least 2 prior systemic therapies	R/R FL after at least 3 prior systemic therapies
Dosing	150 mg orally, twice daily	60 mg as a 1-hour IV infusion weekly (3 weeks on, 1 week off)	25 mg orally, twice daily	800 mg orally, once daily

[1] Gopal AK et al. *N Engl J Med* 2014;370(11):1008-18; Idelalisib package insert, January 2018.
[2] Dreyling M et al. *J Clin Oncol* 2017;35(35):3898-905; Copanlisib package insert, September 2017.
[3] Flinn IW et al. *J Clin Oncol* 2019;[Epub ahead of print]; Zinzani PL et al. EHA 2017;Abstract S777; Duvelisib package insert, September 2018. [4] Umbralisib package insert, February 2021.

CHRONOS-3: Progression-Free Survival in R/R Indolent NHL



	Copanlisib + rituximab	Placebo + rituximab	HR	*p*-value
Median PFS	21.5 mo	13.8 mo	0.52	<0.0001

Matasar MJ et al. *Lancet Oncol* 2021;22:678-89.

RTP RESEARCH TO PRACTICE

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

Press Release: February 5, 2021

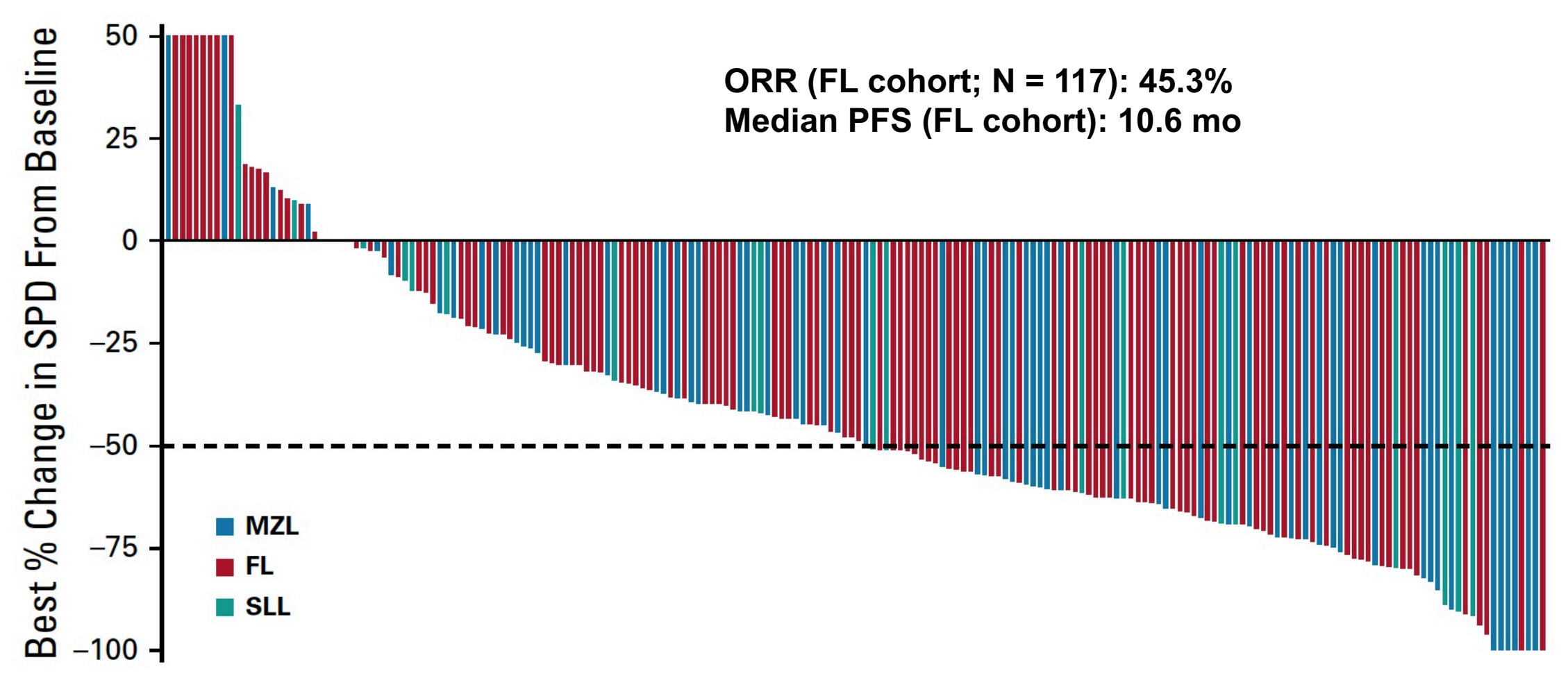
"The Food and Drug Administration granted accelerated approval to umbralisib, a kinase inhibitor including PI3K-delta and casein kinase CK1-epsilon, for the following indications:

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

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

www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-umbralisib-marginal-zone-lymphoma-and-follicular-lymphoma

Umbralisib for Heavily Pretreated R/R Indolent NHL



Fowler NH et al. *J Clin Oncol* 2021;39:1609-18.

RTP RESEARCH TO PRACTICE

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

Press Release: March 5, 2021

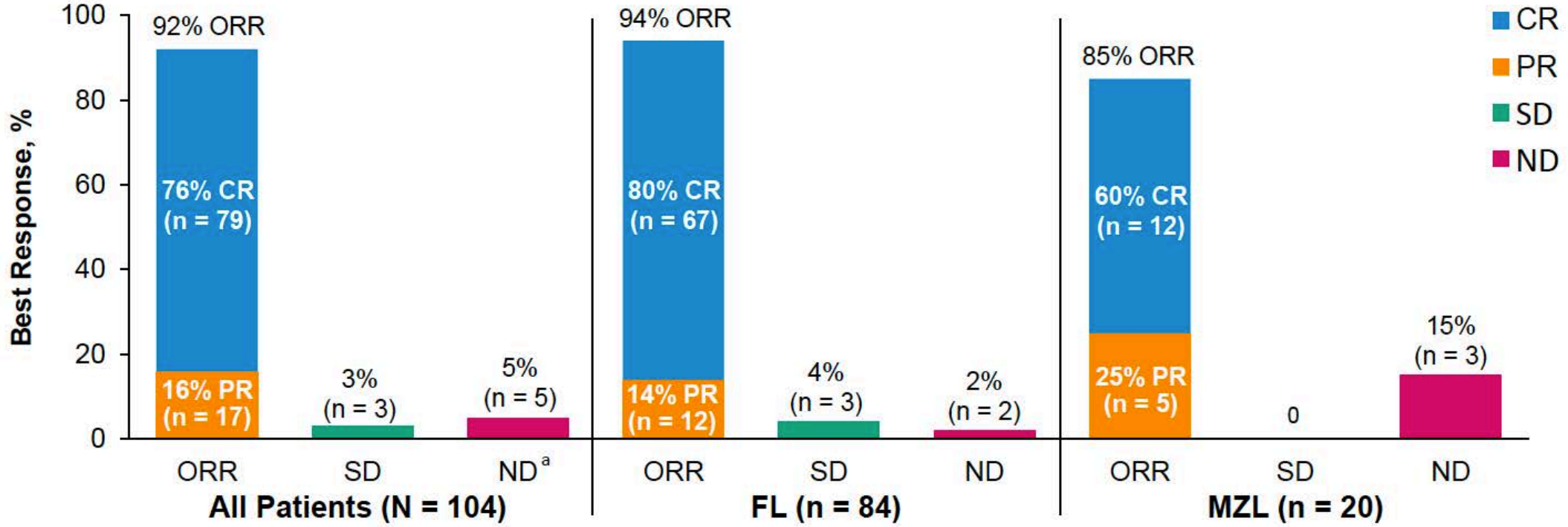
"The Food and Drug Administration granted accelerated approval to axicabtagene ciloleucel for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

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."

www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-axicabtagene-ciloleucel-relapsed-or-refractory-follicular-lymphoma

RTP RESEARCH TO PRACTICE

ZUMA-5: ORR by IRRC Assessment for Patients with Follicular Lymphoma Receiving Axicabtagene Ciloleucel



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

Jacobson C et al. ASH 2020;Abstract 700.

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

Recent Advances and Future Directions in Oncology

A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists

Saturday, October 23, 2021
9:30 AM – 4:30 PM ET

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Agenda

Module 1 — Breast Cancer: *Drs Partridge and Pegram*

Module 2 — Lung Cancer: *Drs Sequist and Spigel*

Module 3 — Gastrointestinal Cancers: *Drs Bekaii-Saab and Ciombor*

Module 4 — Genitourinary Cancers: *Drs Agarwal and Petrylak*

Module 5 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Kahl and Zelenetz*

Module 6 — Multiple Myeloma: *Drs Raje and Usmani*

Module 7 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Levis and Sallman*

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Multiple Myeloma Faculty

Noopur Raje, MD
Director, Center for Multiple Myeloma
Massachusetts General Hospital Cancer Center
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Saad Zafar Usmani, MD, MBA
Chief of Myeloma Service (starting 11/1/2021)
Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Cornell Medical College
New York, New York

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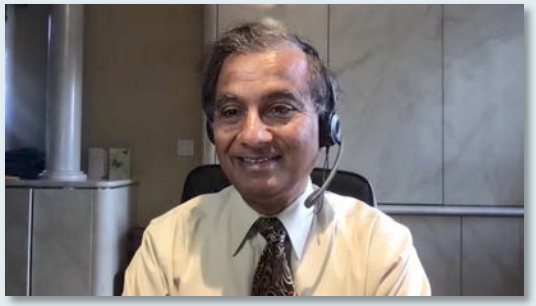
Contributing Oncologists

Susmitha Apuri, MD
Florida Cancer Specialists
and Research Institute
Lutz, Florida



Sunil Gandhi, MD
Florida Cancer Specialists
and Research Institute
Lecanto, Florida

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

Elizabeth Guancial, MD
Florida Cancer Specialists and
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Clinical Associate Professor at FSU
College of Medicine
Sarasota, Florida

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

Lowell L Hart, MD
Scientific Director of Research
Florida Cancer Specialists and
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Fort Myers, Florida

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Contributing Oncologists

Kapisthalam (KS) Kumar, MD
Physician Partner
Florida Cancer Specialists and Research Institute
New Port Richey, Florida

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

Ina J Patel, DO
Assistant Professor of Internal Medicine
Division of Hematology/Oncology
Moncrief Cancer Institute
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Shachar Peles, MD
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Lake Worth, Florida

Ferdy Santiago, MD
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Raji Shameem, MD
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Hematologist and Medical Oncologist
Florida Cancer Specialists and Research Institute
Chief, Division of Hematology and Oncology
Lee Health
Fort Myers, Florida

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RESEARCH TO PRACTICE

Agenda

Module 1: Treatment Approaches for Newly Diagnosed and Relapsed/Refractory Multiple Myeloma

- Dr Choksi: Front-line treatment for transplant-ineligible patients; incorporation of CAR T-cell therapy
- Dr Kumar: Substitution of isatuximab for daratumumab; role of transplant; role of MRD
- Faculty Chalk Talks

Module 2: CAR T-Cell Therapy; Investigational Strategies

- Dr Usmani: A 64-year-old man with relapsed/refractory multiple myeloma — t(4:14) and del(17p)
- Drs Richardson and Voorhees: Comment on Dr Usmani's 64-year-old man — high-risk cytogenetics
- Drs Richardson and Voorhees: Comment on Dr Usmani's 64-year-old man — CAR T-cell therapy
- Dr Kumar: A 71-year-old man with multiple myeloma who develops acute lymphoblastic leukemia
- Faculty Chalk Talks

Appendix: Selected Data Sets

Agenda

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Front-line treatment for transplant-ineligible patients; incorporation of CAR T-cell therapy

Dr Mamta Choksi

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Substitution of isatuximab for daratumumab; role of transplant; role of MRD in treatment decision-making

Dr KS Kumar

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Upfront management of younger patients (transplant-eligible) with multiple myeloma (MM) and adverse cytogenetics [e.g., del(17p)]

- Forte data: largest data set with transplant eligible high risk MM
- Quadruplets: Dara RVd, Dara KRd/ Transplant; dual maintenance
- Consider trials for HR disease—such as CAR T cells instead of transplant: KarMMa-4 and CARTITUDE-5
- Important to maintain deep responses—aim for MRD negativity by either next gen flow or next gen sequencing

Efficacy and tolerability of subcutaneous versus IV daratumumab in patients with MM

- Both intravenous and subcutaneous daratumumab are active and safe, showing an ORR of ~40% in the COLUMBA phase III trial. Both formulations are FDA approved for use in newly diagnosed, early relapse, and late relapse MM in combination with other therapies.

- The SC formulation is better in terms of safety and administration:
  - Administration time is 5 minutes for SC formulation
  - Infusion related reaction rate is ~13% with SC compared to 32% with IV

- The SC formulation has improved workflow in the infusion center and affords more convenience to patients.

Use of melflufen/dexamethasone in patients with multiple-regimen relapsed MM

- 29% response rate with 5.5month DOR (Horizon trial)
- The OCEAN trial of Melflufen versus Pom Dex although met primary end point of PFS all trials with Melflufen on temporary hold due to inferior OS.
- Toxicities include thrombocytopenia and neutropenia
- Needs central access although the PORT trial is looking at peripheral access for melflufen

Non-protocol role of venetoclax in the management of patients with relapsed/refractory MM and t(11;14) or Bcl-2 overexpression

- Venetoclax has shown ORR ~40% in RRMM patients with t(11;14) and Bcl2 overexpression in their MM cells.
- Venetoclax shows good efficacy and safety with bortezomib-dexamethasone, carfilzomib-dexamethasone and daratumumab in early phase clinical trials.
  - Venetoclax-bortezomib-dexamethasone showed better overall PFS but higher death rates in the BELLINI trial, the deaths were primarily infection or cardiac related in patients without t(11;14) or Bcl2 over-expression.
- Primary plasma cell leukemia (pPCL), which is an aggressive clinical phenotype of MM, is enriched for t(11;14).
- There is anecdotal use and clinical efficiacy of venetoclax in relapsed/refractory MM, including pPCL.

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Appendix: Selected Data Sets

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

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

Saturday, February 13, 2021

8:30 AM – 4:30 PM ET

RTP RESEARCH TO PRACTICE

Multiple Myeloma Faculty

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

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

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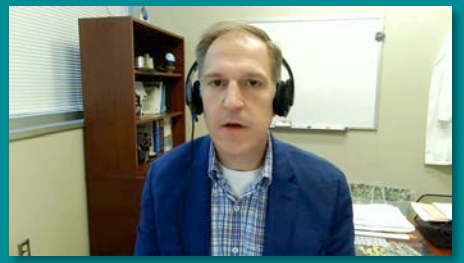
Case Presentation – Dr Usmani

- 64-year-old Caucasian man presented to his primary care physician with increasing back pain without improvement with conservative measures. X-ray of lumbar spine showed numerous lytic lesions.
  - Labs: Hb 9.7 g/dL, normal WBC/platelets, BUN 18, serum creatinine 2.3 mg/dL (0.9 mg/dL 12 months ago), normal serum total protein, serum calcium 13 mg/dL, serum albumin 3.1 g/dL, serum B2M 5.6 mg/dL.
  - Protein studies: SPEP-IFE only showed lambda light chain on IFE, serum free kappa light chains 17.5 mg/dL, serum free lambda light chains 244.3 mg/dL.
  - BM biopsy: 60% cellularity, 45% PCs with lambda light chain restriction, MM-FISH positive for t(4;14) in 35% cells.
  - PET-CT: Lytic lesions throughout axial skeleton and vertebrae, 3 FDG avid lesions in L2/L4/sacrum with SUVmax of 9.1 in sacral lesion.
- Diagnosed with revised ISS Stage III IgG kappa myeloma

How would you describe the treatment options for this patient?

Case Presentation – Dr Usmani (continued)



- 64-year-old man diagnosed with revised ISS Stage III IgG kappa myeloma.
- 1st line therapy:
  - RVd-lite induction x 4 cycles, VGPR by IMWG criteria.
  - Mel-200 ASCT, sCR by IMWG criteria.
  - Lenalidomide maintenance for 18 months (10 mg po qhs 3 weeks on/1 week off) and then stopped per patient request (superficial skin cancers).

Now presenting 2 year after stopping Len maintenance with increasing LLC and declining hemoglobin, clinically asymptomatic. Restaging BM biopsy shows 30% PCs and MM-FISH now shows deletion 17p in addition to translocation (4;14)

How would you describe the treatment options for this patient?

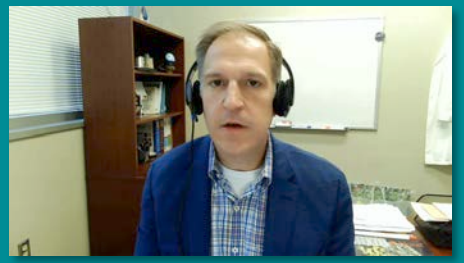
Case Presentation – Dr Usmani (continued)

- 64-year-old man diagnosed with revised ISS Stage III IgG kappa myeloma.
- 1st line therapy:
  - RVd-lite induction x 4 cycles, VGPR by IMWG criteria.
  - Mel-200 ASCT, sCR by IMWG criteria.
  - Lenalidomide maintenance for 18 months (10 mg po qhs 3 weeks on/1 week off) and then stopped per patient request (superficial skin cancers). Progression 2 years after stopping Len.
- 2nd Line therapy:
  - KRd regimen x 19 cycles, VGPR as best response after 3 cycles.
- 3rd Line therapy:
  - Dara-Pd regimen x 16 cycles, VGPR as best response.

Now presenting with clinical and biochemical relapse. Local XRT to left clavicle and scapula for pain control.

How would you describe the treatment options for this patient?

Case Presentation – Dr Usmani (continued)



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- 2nd Line therapy:
  - KRd regimen x 19 cycles, VGPR as best response after 3 cycles.
- 3rd Line therapy:
  - Dara-Pd regimen x 16 cycles, VGPR as best response.
- 4th Line Therapy:
  - Enrolled on BCMA CART trial, in sCR and currently 14 months post CART.

Case Presentation – Dr Kumar: A 71-year-old man with multiple myeloma who develops acute lymphoblastic leukemia (ALL)

Dr KS Kumar

- 3/2001: Newly diagnosed multiple myeloma s/p CyBorD and local radiation therapy
- 9/2014: VRD, with lenalidomide-associated rash → VTD → Maintenance lenalidomide
- 4/2016: Severe pneumonia
- Restarted maintenance lenalidomide → Thrombocytopenia, biopsy showed ALL
- Chemotherapy for ALL, with worsening of peripheral neuropathy
- 1/2019: All treatments stopped and in remission for both ALL and multiple myeloma

Questions

- What treatment would you recommend next if his myeloma recurs? Is there a complete restriction for using any IMiD?

RTP RESEARCH TO PRACTICE

Comparative efficacy and toxicity of idecabtagene vicleucel and ciltacabtagene autoleucel in patients with multiple-regimen relapsed MM

	Cilta-cel	Ide-cel (bb2121)
N	97	128
Dose	0.75 × 10^6 cells/kg	150-450 × 10^6 cells
Median prior lines	6 (3-18)	6 (3-16)
Triple-class refractory	88%	84%
ORR	96.9%	73%
MRD−	54.6%	39%
≥CR	67%	33%
PFS	76.6% at 12 months	8.8 months
	Madduri D et al., ASH 2020	Munshi N et al., N Engl J Med 2021

- Updated ciltacel data: PFS 66% months at 18 months
- Idecel: 20 months for patients who achieve sCR

	Cilta-cel	Ide-cel (bb2121)
N	97	54*
CRS	94.8%	96%
≥3	5.2%	6%
Tocilizumab	69.1%	67%
Corticosteroids	21.6%	22%
Anakinra	18.6%	0%

	Cilta-cel	Ide-cel (bb2121)
N	97	54*
Neurotoxicity	20.6%	20%
≥3	10.3%	6%
Other (not ICANS)†	12.4%	Not reported
≥3	9.3%	Not reported
	ASH 2020	ASCO 2020

- Early toxicity of CRS and neurotoxicity comparable
- CRS early with Idecel and at around day 7 with ciltacel
- Delayed neurotoxicity seen with Ciltacel: 10% progressive neurological movement disorder
- Mitigation strategies in CARTITUDE-2 did not show neurotoxicity

Efficacy and safety data with bispecific antibodies (e.g., teclistamab, talquetamab, cevostamab, elranatamab) under investigation for relapsed/refractory MM

- Bispecific antibodies (BsAb) represent a new wave of myeloma treatments that are highly active even in heavily pre-treated patients with ORR in the 65-80% range.
- Toxicities of BsAb mainly consist of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and low blood counts, all of which are treatable.
- There are several BsAb platforms in clinical trials. Compared to CART, they have:
  - Potential advantages: Off the shelf, better safety profile, SC administration
  - Potential disadvantages: Continuous therapy
- BCMA-directed BsAbs are showing impressive efficacy in RRMM.
  - Moving to earlier lines of therapies, combinations in the works.
  - Need to incorporate in front-line strategies in high-risk MM (Several concepts are in development)
- Novel targets for BsAbs are in early clinical development, making all IO based MM-therapy strategies realistic in the near future.
  - Treatment targeted at GPRC5D and FcRH5—which are new targets—have shown efficacy.

Agenda

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Appendix: Selected Data Sets

Newly Diagnosed Multiple Myeloma

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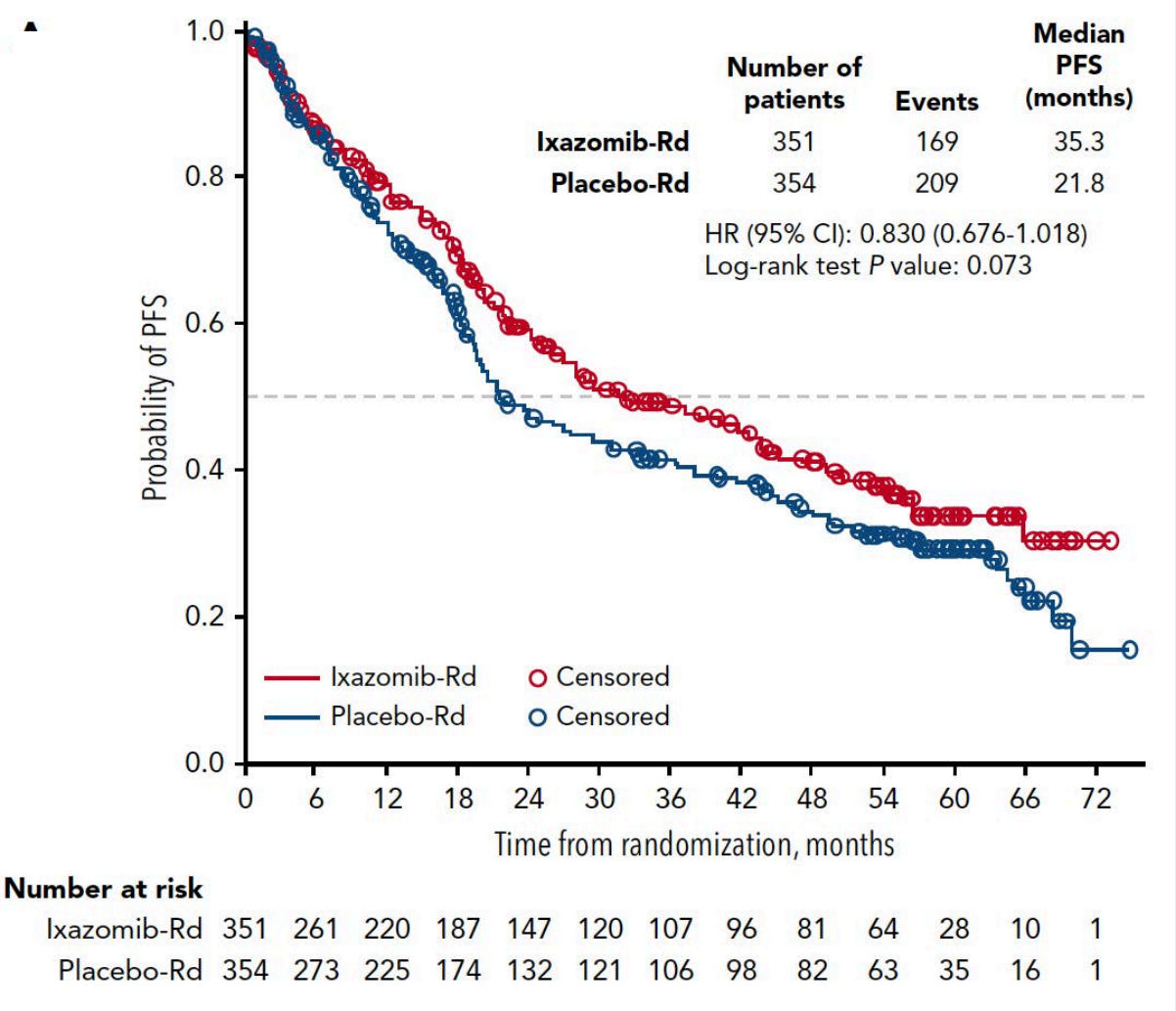
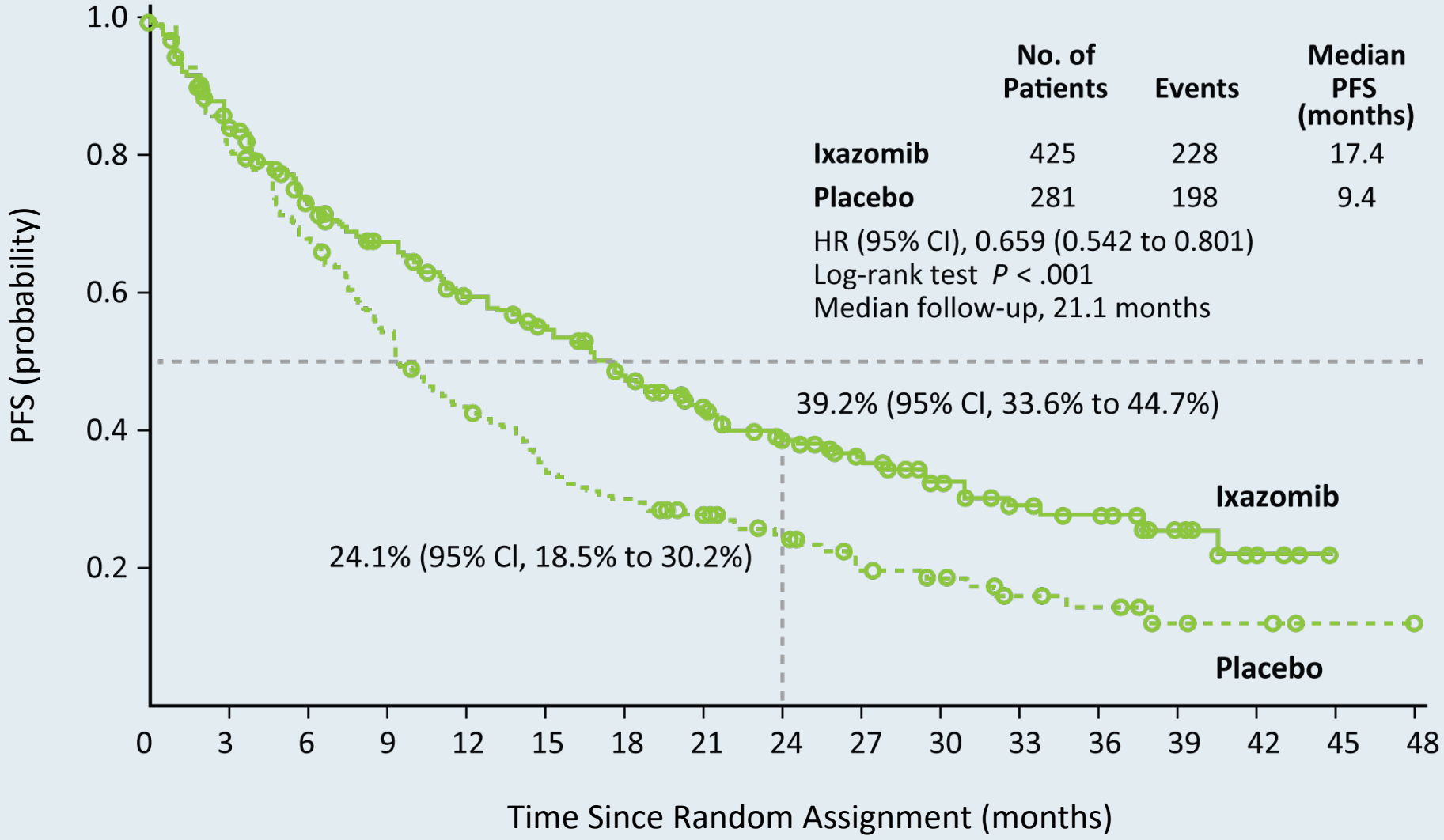
TOURMALINE-MM2: A Phase III Trial of Oral Ixazomib, Lenalidomide and Dexamethasone (IRd) for Transplant-Ineligible Patients with Newly Diagnosed MM



Facon T et al. *Blood* 2021;137(26):3616-28.

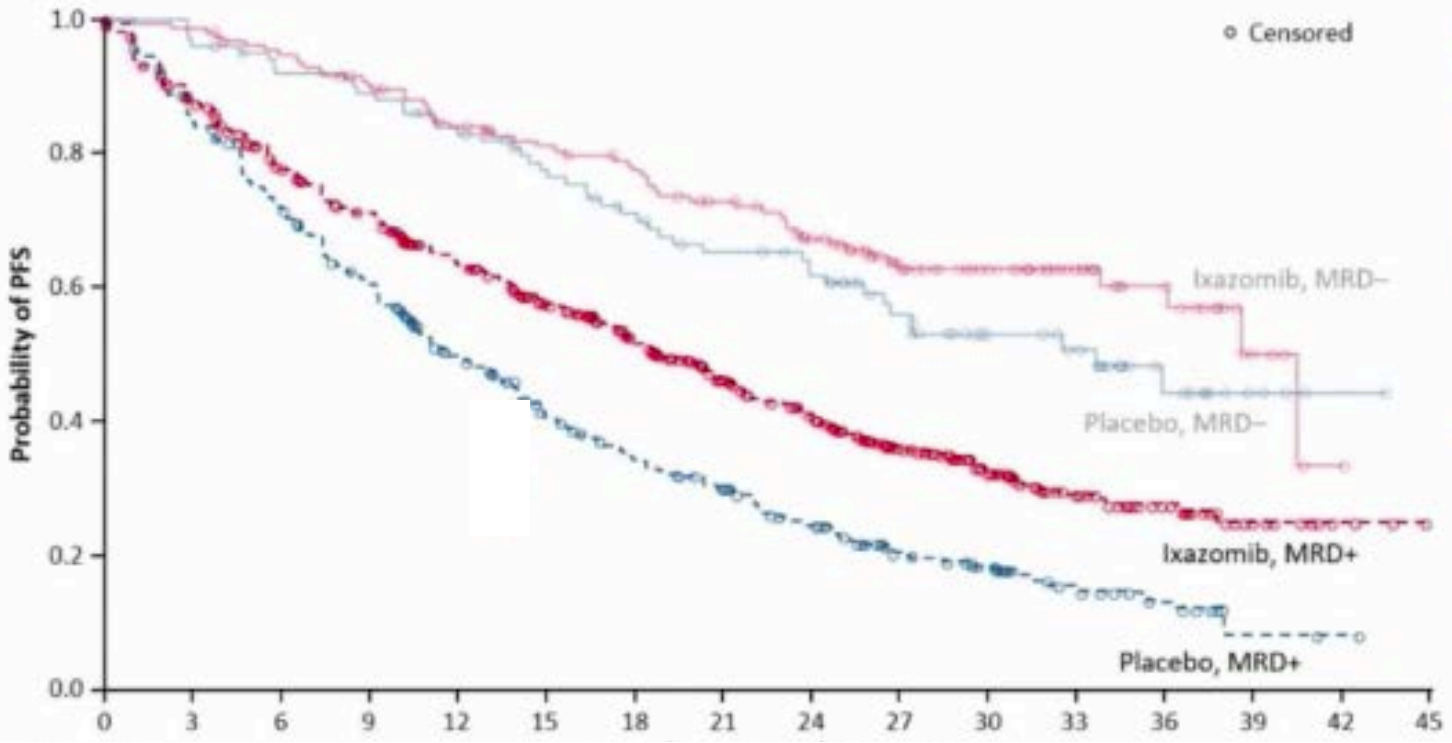
TOURMALINE-MM4: A Phase III Trial of Postinduction Maintenance Therapy with Ixazomib for Transplant-Ineligible Patients with Newly Diagnosed MM



Dimopoulos MA et al. *J Clin Oncol* 2020;38(34):4030-41.

RTP RESEARCH TO PRACTICE

Pooled Analysis of TOURMALINE-MM3 and MM4: PFS in MRD+ at Screening



MRD+ patients	n	Events	24-month PFS, %	Median PFS, months
Ixazomib	606	351	40.7	18.8
Placebo	412	298	24.3	11.6
HR 0.651, 95% CI 0.554–0.764, p<0.001				

- There was no significant difference in PFS between ixazomib and placebo among patients who were MRD– at screening

Paiva B et al. ESMO 2021;Abstract S184.

Pooled Analysis of TOURMALINE-MM3 and MM4
Conclusions

This large dataset demonstrated that the prognostic value of MRD status at the start of maintenance can be enhanced by measuring MRD kinetics during treatment

Our results support the achievement and sustainability of MRD negativity as a treatment endpoint in the maintenance setting

We demonstrated poor outcomes in patients converting from MRD– to MRD+ status and those who had persistent MRD+ status, underscoring the value of serial MRD assessments to anticipate relapse and guide treatment decisions

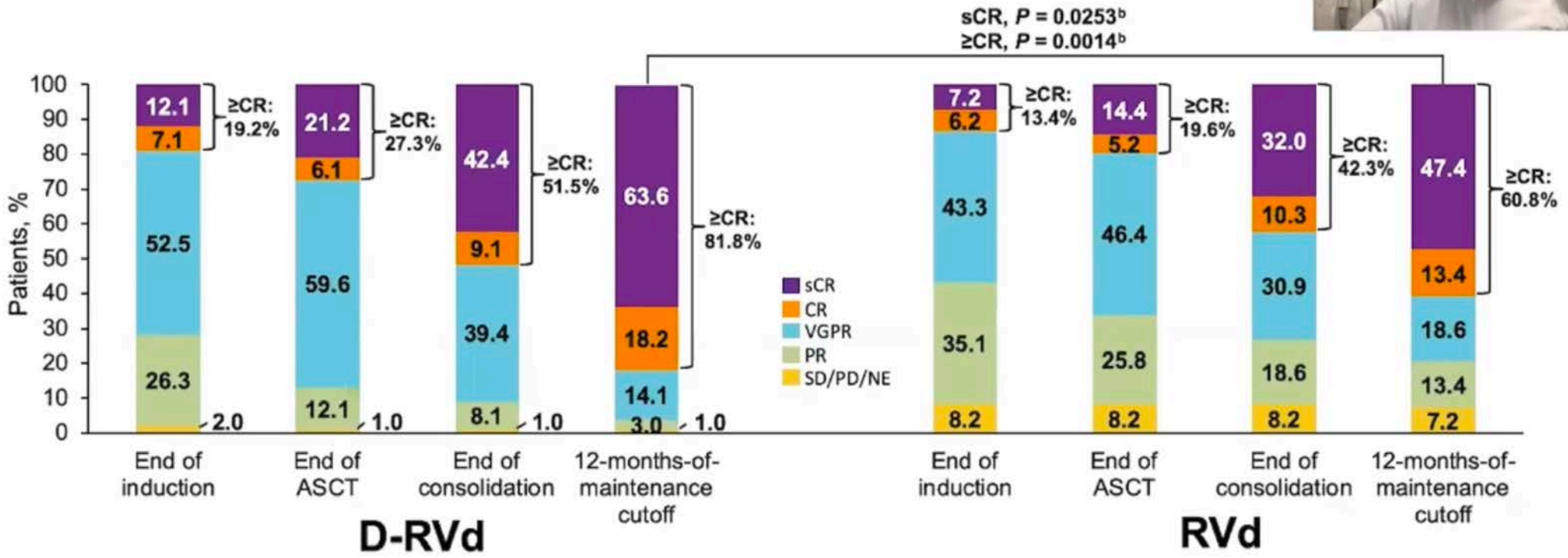
Accordingly, ixazomib showed significant PFS benefit versus placebo in patients who were MRD+ at screening and in patients with persistent MRD+ status, highlighting the value of maintenance treatment with ixazomib in NDMM patients with MRD+ status

Paiva B et al. EHA 2021;Abstract S184.

Relapsed/Refractory Disease

Update of GRIFFIN Trial

Responses Deepened over Time[a]



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

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

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

Kaufman JL et al. ASH 2020;Abstract 549.

FDA Approves Daratumumab and Hyaluronidase-fihj with Pomalidomide and Dexamethasone for Multiple Myeloma

Press Release: July 9, 2021

"The Food and Drug Administration approved daratumumab and hyaluronidase-fihj in combination with pomalidomide and dexamethasone for adult patients with multiple myeloma who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor.

Efficacy was evaluated in APOLLO (NCT03180736), an open-label, active-controlled trial with 304 patients randomized (1:1) to daratumumab and hyaluronidase-fihj with pomalidomide and dexamethasone (Pd) vs Pd alone. Patients received daratumumab and hyaluronidase-fihj 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously once weekly from Weeks 1 to 8, once every 2 weeks from Weeks 9 to 24 and once every 4 weeks starting with Week 25 until disease progression or unacceptable toxicity with pomalidomide 4 mg once daily orally on days 1-21 of each 28-day cycle; and dexamethasone 40 mg per week (or a reduced dose of 20 mg per week for patients >75 years)."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-daratumumab-and-hyaluronidase-fihj-pomalidomide-and-dexamethasone-multiple-myeloma

RTP RESEARCH TO PRACTICE

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)."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-isatuximab-irfc-multiple-myeloma

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

Press Release: February 26, 2021

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

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

www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-melphalan-flufenamide-relapsed-or-refractory-multiple-myeloma

RTP RESEARCH TO PRACTICE

OCEAN: Positive Top-Line Results Reported from Phase III Head-to-Head Trial of Melflufen versus Pomalidomide for R/R MM

Press Release: May 25, 2021

"Today positive topline results [were announced] from the head-to-head Phase III OCEAN study evaluating the efficacy and safety of melflufen (melphalan flufenamide) versus pomalidomide in patients with relapsed refractory multiple myeloma (RRMM). The randomized study was initiated in 2017 and includes 495 patients from more than 100 hospitals in 21 countries around the world. Following the accelerated approval of melflufen in combination with dexamethasone in the US earlier this year, the positive topline results from the OCEAN study mark another major milestone.

The PFS, as assessed by the independent review committee, demonstrated a Hazard Ratio favoring melflufen of 0.817 (p=0.0640) for the primary endpoint and shows that melflufen is non-inferior to pomalidomide. The Hazard Ratio for PFS as per investigator assessment was 0.790. In both assessments, the median PFS for the melflufen arm was more than 40% higher than for the pomalidomide arm. The Overall Response Rate for melflufen was 32.1% vs 26.5% for pomalidomide. Melflufen and pomalidomide had similar discontinuation rates for adverse events, and the safety profile of melflufen was in line with previous studies and consistent across age subgroups."

https://www.oncopeptides.com/en/media/press-releases/phase-3-ocean-study-demonstrates-that-melflufen-is-at-least-as-efficacious-as-pomalidomide-the-most-used-medicine-in-relapsed-refractory-multiple-myeloma

CAR T-Cell Therapy

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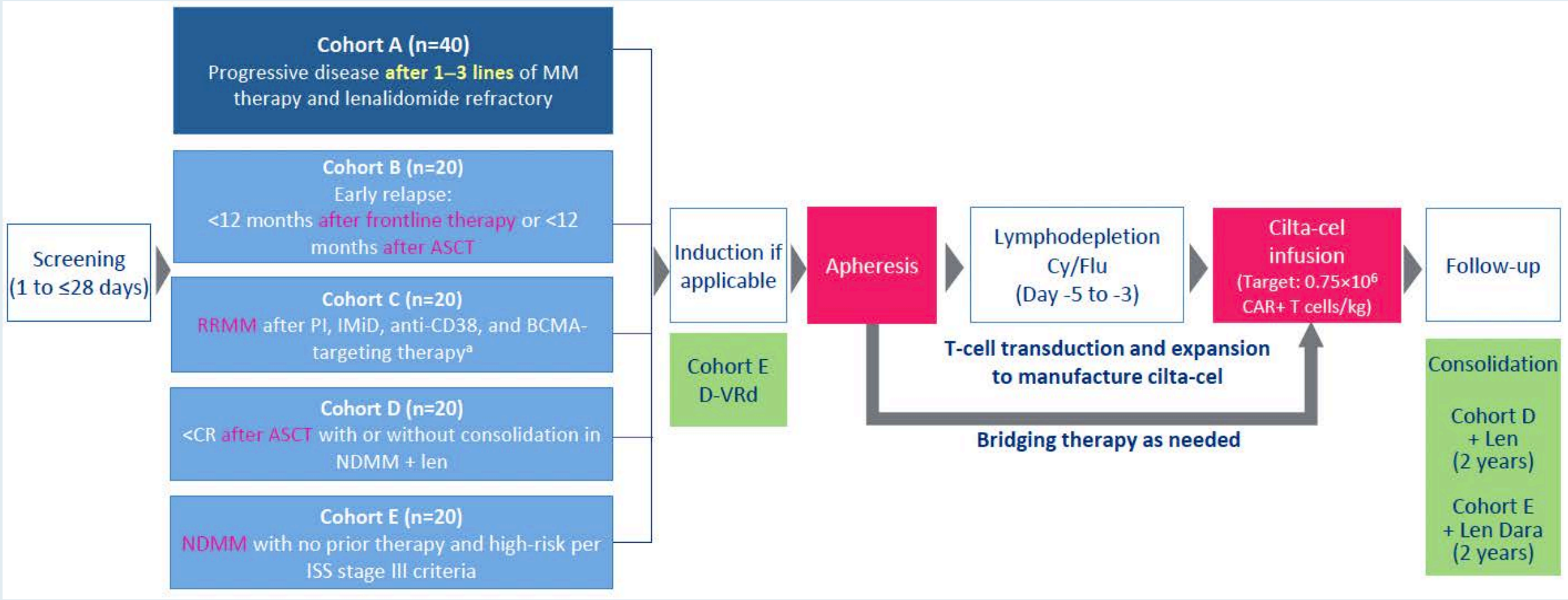
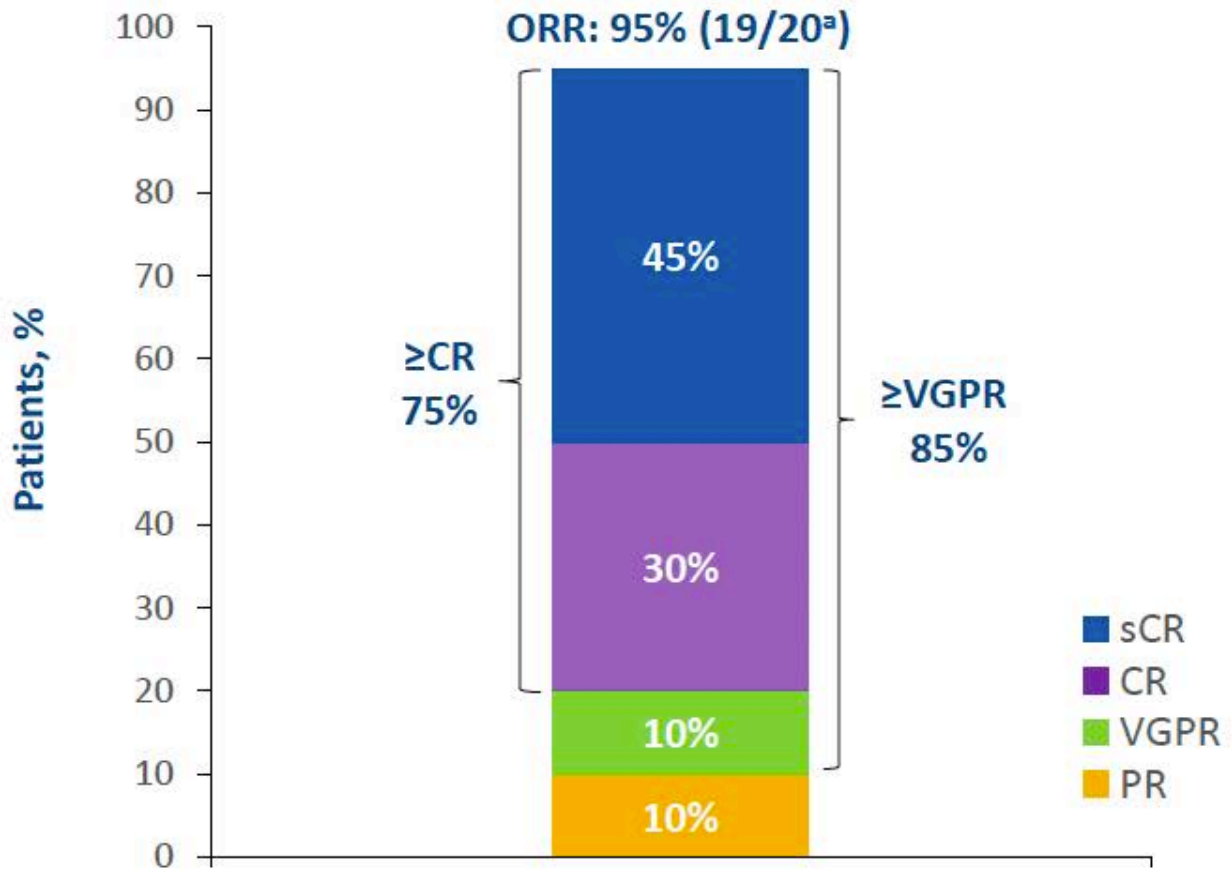
CARTITUDE-2 Study Design



Agha M et al. EHA 2021;Abstract S190.

CARTITUDE-2 Cohort A: 1-3 Lines of Therapy
Overall Response Rate



- Median time to first response: 1.0 month (range, 0.7–3.3)
- Median time to CR or better: 1.9 months (range, 0.9–5.1)
- All patients (n=4) with MRD-evaluable[b] samples at the 10^{-5} threshold were MRD negative at data cut-off

Agha M et al. EHA 2021;Abstract S190.

RTP RESEARCH TO PRACTICE

FDA Approves Idecabtagene Vicleucel for Multiple Myeloma

Press Release: March 26, 2021

"The Food and Drug Administration 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 B-cell maturation antigen (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.

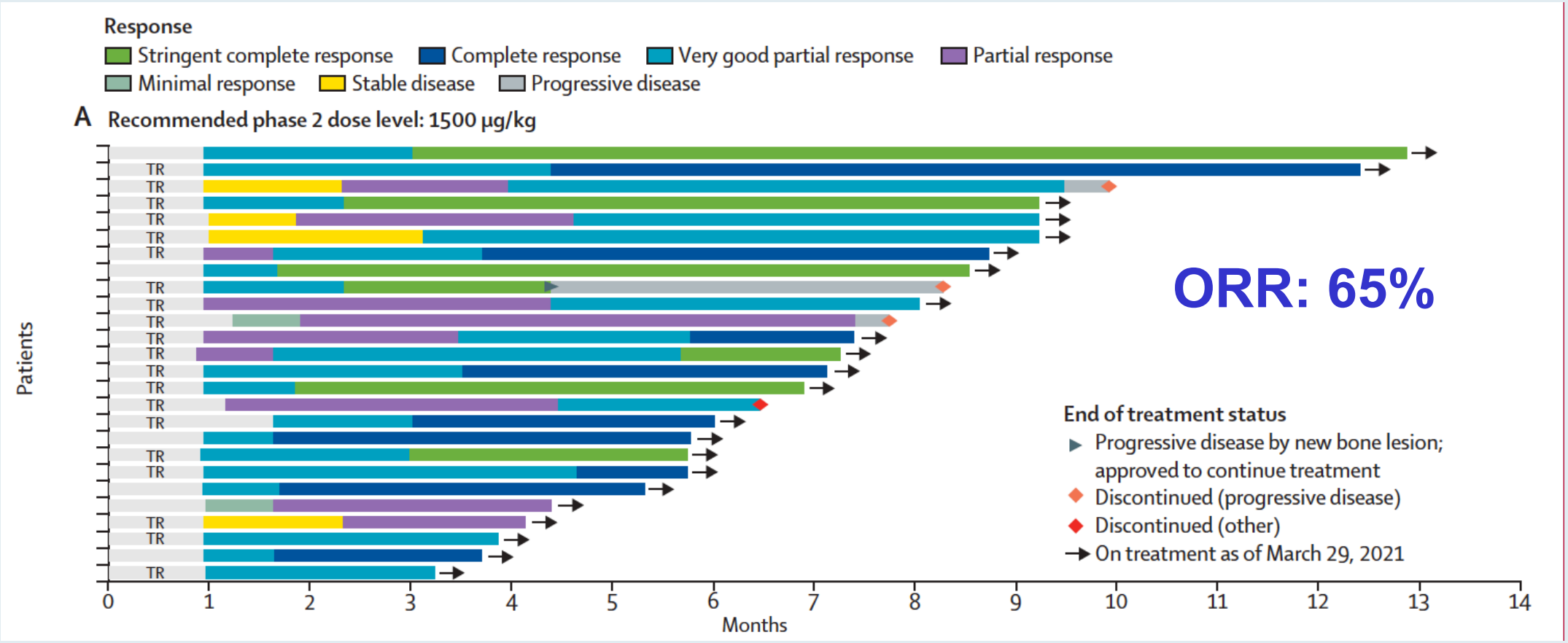
Safety and efficacy were evaluated in a multicenter study of 127 patients with relapsed and refractory multiple myeloma who received at least three prior lines of antimyeloma therapies; 88% had received four or more prior lines of therapies. Efficacy was evaluated in 100 patients who received idecabtagene vicleucel in the dose range of 300 to 460 x 106 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."

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-idecabtagene-vicleucel-multiple-myeloma

Investigational Bispecific Antibodies

MajesTEC-1: Phase I Trial of Teclistamab, a BCMA x CD33 Antibody, in Relapsed/Refractory Myeloma

Duration of response at RP2D 1500 µg/kg



Usmani SZ et al. Lancet 2021;398:665-74.

RTP RESEARCH TO PRACTICE

Clinical Results with Select Non-BCMA Bispecific Antibodies in Multiple Myeloma

Study product (Registration n.)	Study population	Schedule	CRS profile	Neurotoxicity	Response	Last cohorts (n)
G-protein coupled receptor family C group 5 member D (GPRC5D)						
Talquetatamab[1] (NCT03399799)		i.v. n=102 s.c. n=35	i.v.+ s.c.: 47% i.v. Grade 3/4: 8% s.c. Grade 3/4: 0	7/137 G1/2: 4 G3: 3 6/7 with CRS		i.v.: ORR: 14/18 s.c.: ORR: 8/12
Fc receptor-homolog 5 (FcRH5)						
Cevostamab (prev. BFCR4350A[2]) (NCT03275103)		i.v. n=51 QW	74.5% Grade 3/4: 2%	5%		

TCE: T-cell-engager; CRS: cytokine release syndrome; Dara: daratumumab; IMID: immunomodulatory drug; PI: proteasome inhibitor; EMD: extramedullary disease; i.v.: intravenous; s.c.: subcutaneous; ORR: overall response rate; CR: complete response, sCR: stringent complete response; QW: once weekly; Q2W: every 2 weeks; Q3W: every 3 weeks; NA: not applicable; NR: not reported; G: grade.

Rasche L et al. Hematologica 2021;106(10):2555-65.

RTP RESEARCH TO PRACTICE

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

Recent Advances and Future Directions in Oncology

A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists

Saturday, October 23, 2021
9:30 AM – 4:30 PM ET

RTP
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Agenda

Module 1 — Breast Cancer: *Drs Partridge and Pegram*

Module 2 — Lung Cancer: *Drs Sequist and Spigel*

Module 3 — Gastrointestinal Cancers: *Drs Bekaii-Saab and Ciombor*

Module 4 — Genitourinary Cancers: *Drs Agarwal and Petrylak*

Module 5 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs Kahl and Zelenetz*

Module 6 — Multiple Myeloma: *Drs Raje and Usmani*

Module 7 — Acute Myeloid Leukemia and Myelodysplastic Syndromes: *Drs Levis and Sallman*

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Acute Myeloid Leukemia and Myelodysplastic Syndromes Faculty

Mark Levis, MD, PhD
Professor of Oncology
Co-Division Director, Hematologic Malignancies
The Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University
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David Sallman, MD
Assistant Member
Malignant Hematology
Moffitt Cancer Center
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Contributing Oncologists

Susmitha Apuri, MD
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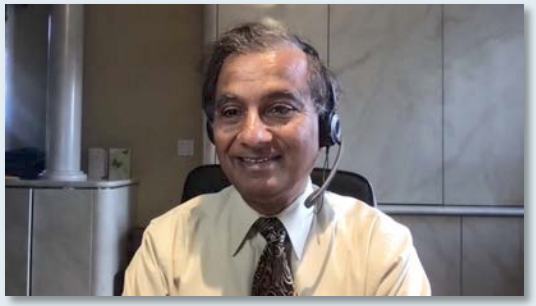

Sunil Gandhi, MD
Florida Cancer Specialists
and Research Institute
Lecanto, Florida

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

Elizabeth Guancial, MD
Florida Cancer Specialists and
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Lowell L Hart, MD
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Syed F Zafar, MD
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Chief, Division of Hematology and Oncology
Lee Health
Fort Myers, Florida

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Agenda

Module 1: Acute Myeloid Leukemia

- Dr Peles: Challenge of new treatment options for AML
- Dr Kumar: HMA/venetoclax — Appropriate candidates, tolerability and dose adjustments
- Dr Choksi: Personal experience with administering azacitidine/venetoclax
- Dr Gandhi: A 68-year-old woman with AML
- Dr Apuri: Appropriate use of antifungal agents for patients receiving venetoclax
- Dr Peles: Role of FLT3 and IDH1/2 inhibitors for patients who are ineligible for intensive induction therapy
- Dr Santiago: An 81-year-old woman initially treated for idiopathic thrombocytopenic purpura
- Faculty Chalk Talks

Module 2: Myelodysplastic Syndromes

- Dr Apuri: An 89-year-old woman with low-grade MDS with ringed sideroblasts
- Faculty Chalk Talks

Appendix: Selected Data Sets

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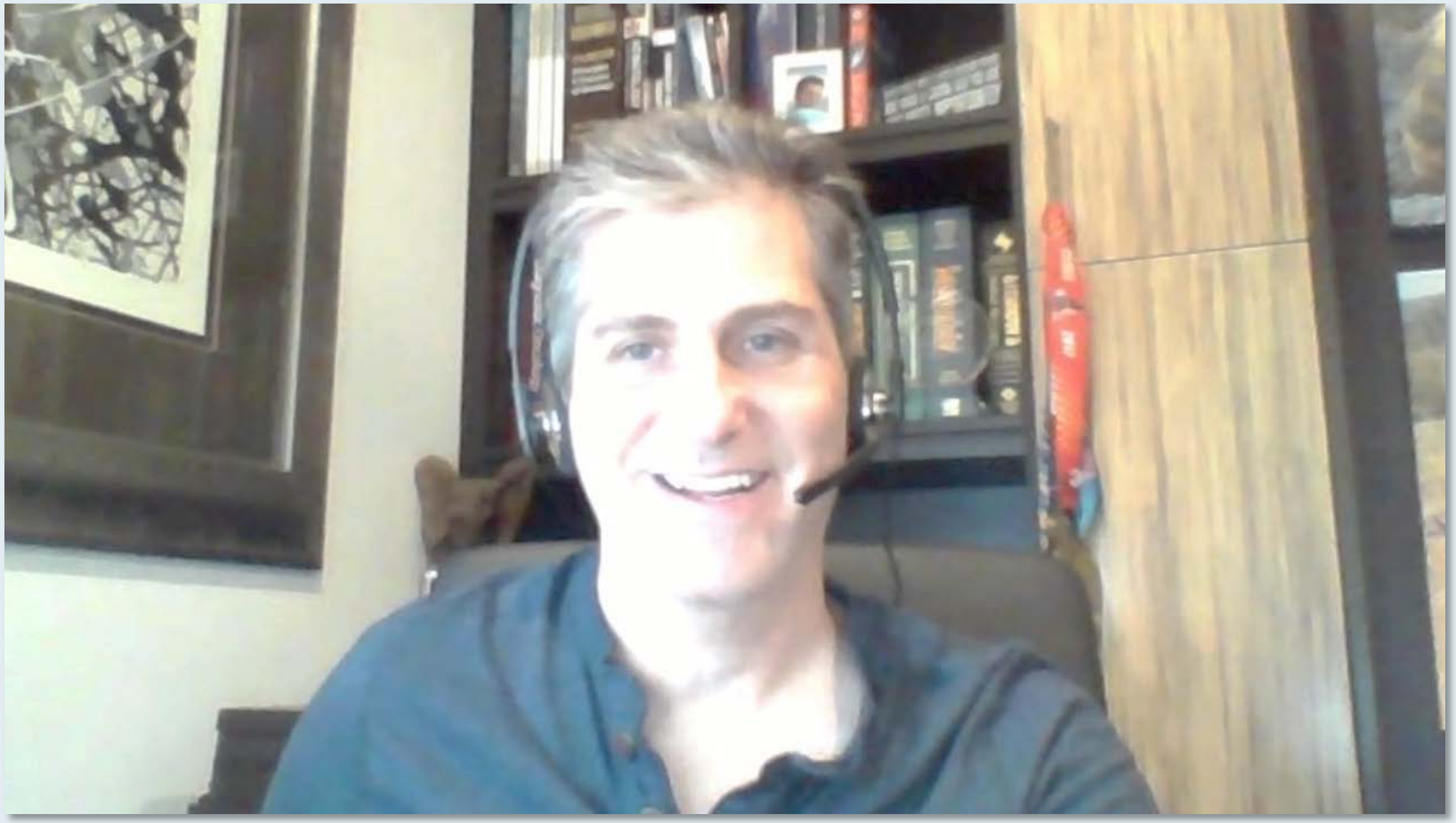
Challenge of new treatment options for AML



Dr Shachar Peles

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HMA/venetoclax: Appropriate candidates, tolerability and dose adjustments

Dr KS Kumar

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Personal experience with administering azacitidine/venetoclax

Dr Mamta Choksi

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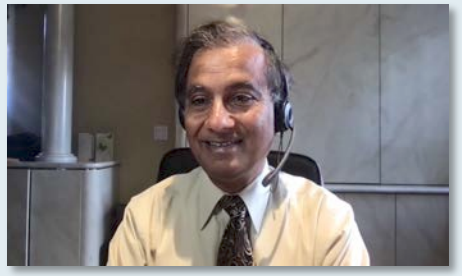
Case Presentation – Dr Gandhi: A 68-year-old woman with AML



Dr Sunil Gandhi

- Presented with serial anemia
  - Hemoglobin: 3 g | ANC: 115 | del(5q)
- MDS treated with lenalidomide. Attained transfusion independence
  - Remained on treatment approximately 4 years
- Developed cytopenia; BM biopsy confirmed classical AML
- Treated with venetoclax/decitabine → complete remission
  - Remains on venetoclax, tolerating treatment well

Appropriate use of antifungal agents for patients receiving venetoclax

Dr Susmitha Apuri

RTP
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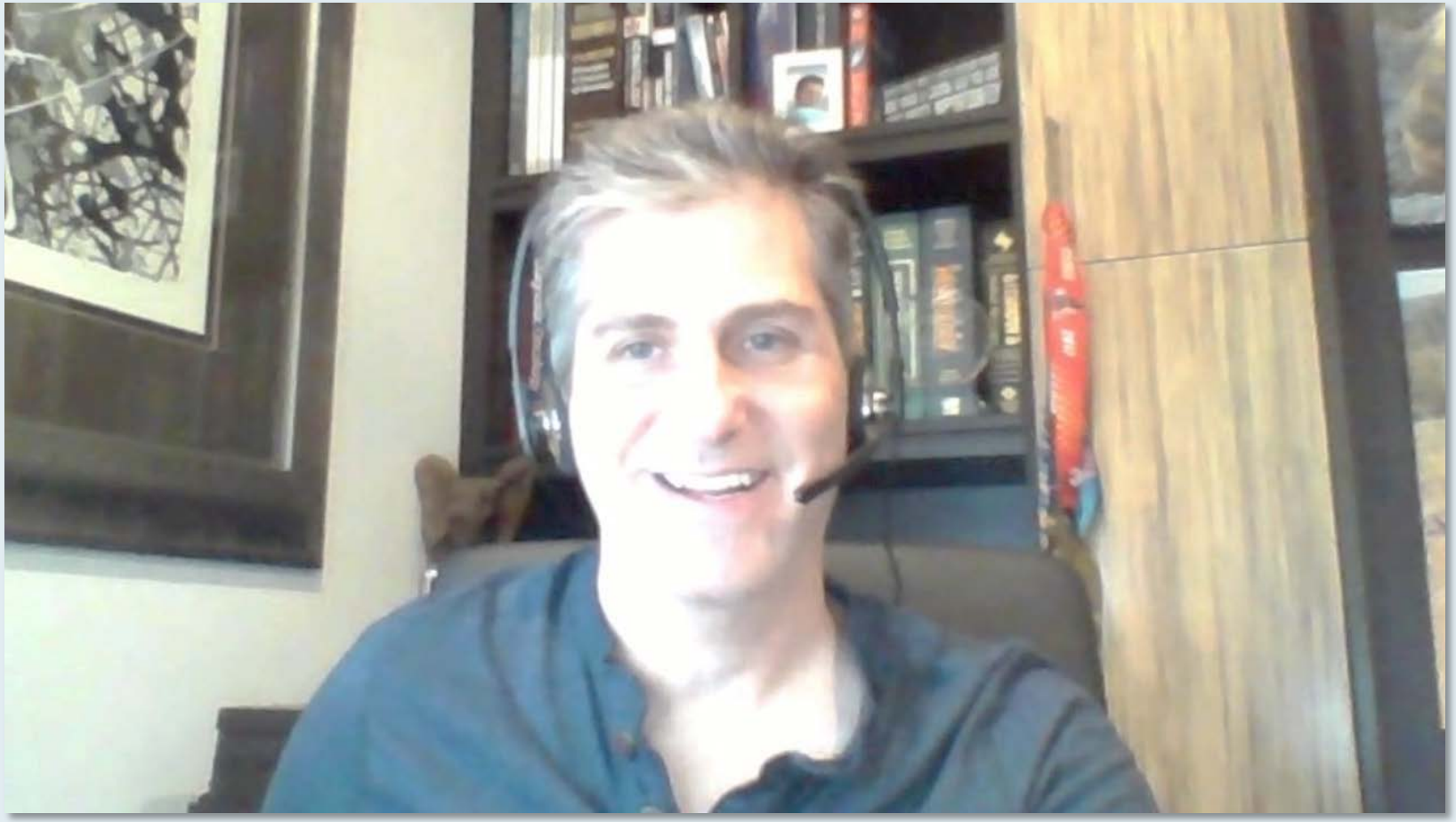
Role of FLT3 and IDH1/2 inhibitors for patients with AML who are not candidates or are borderline candidates for 7 + 3 induction



Dr Shachar Peles

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Case Presentation – Dr Santiago: An 81-year-old woman initially treated for idiopathic thrombocytopenic purpura (ITP)

Dr Ferdy Santiago

- 2019: Initially presented with ITP
- Failed treatment with prednisone/rituximab → romiplostim with good response
- Began to exhibit marked elevation in WBC to 37.2, flow with 19% blasts
  - Bone marrow biopsy consistent with AML
- Venetoclax/decitabine initiated → complete response
  - Evidence of dysplastic megakaryocytes in bone marrow

Questions

- Have the investigators seen evidence of concomitant presence of ITP and MDS before?
- If so, what is their experience in dealing with patients in this setting?

Approach to treatment-associated cytopenias and other adverse events after the first cycle of venetoclax/HMA in patients with AML

- Importance of C1 BM biopsies to evaluate for response/hypocellularity and adjustment with first cycle.
- Antimicrobial prophylaxis, TLS prophylaxis, gcsf utility?
- Timing of initiation of C2
- When to dose reduce schedule/duration of venetoclax and when to adjust the HMA agent
- Will MRD impact total treatment duration and when to hold therapy?
- Differences in MDS?

Upfront management of older patients with AML and a FLT3 mutation who are not eligible for intensive therapy

- 82 yo man with WBC 110,000:
  - AML with leukostasis
    - Gemtuzumab and hydroxyurea
  - Normal karyotype
  - DNMT3a, NPM1, FLT3-ITD mutation
- Azacitidine + venetoclax is effective for AML unfit for intensive chemo
  - VIALE-A trial
- Aza/ven less effective for FLT3-ITD AML
  - Remission achievable, but much shorter duration of response
- AML is polyclonal
  - Only a fraction of the leukemia is “addicted” to FLT3 signaling
    - Monotherapy with a FLT3 inhibitor unlikely to be effective.
  - With chemotherapy alone, the FLT3-ITD-containing progenitor cell survives
  - FLT3-ITD addicted clone emerges at relapse.
- No one is sure of what to do with this patient!
  - VIALE-A trial showed no survival benefit to venetoclax for FLT3-ITD AML
- FLT3 inhibitors:
  - Midostaurin- only effective in combination with intensive chemo
  - Gilteritinib- single agent activity for R/R AML
- Aza + ven + gilt?
  - Very myelosuppressive
- Azacitidine + gilteritinib (or midostaurin)?
  - Not very effective…
- Back to the patient:
  - After cytoreduction, starts Aza/ven
  - Achieves CR
  - After two cycles, in CR, but FLT3-ITD easily detectable
  - Two cycles Aza/gilt
  - Gilteritinib maintenance
  - In remission 15 months and ongoing

Upfront management of older patients with AML and an IDH mutation who are not eligible for intensive therapy

- Frontline and relapsed indications for ivosidenib and enasidenib
- How to incorporate IDH inhibitor options for elderly AML patients with HMA + venetoclax
- Is frontline combination (i.e. triplet) vs sequential therapy (HMA + ven followed by IDH inhibitor) better?
- How do co-mutations impact prognosis?
- Importance of MRD?
- IDH maintenance options post allo-HSCT

Management of secondary AML in younger patients

- 41 yo man with poor-risk MDS:
  - Transfusion dependent
  - Karyotype: deletion 7
  - NGS: Runx1 mutation
  - Treated with decitabine- ineffective
  - Progresses into AML
- Treatment options for (very poor-risk) secondary AML:
  - 7+3?
  - Add venetoclax to decitabine?
  - Low dose araC + ven?
  - CPX-351?
- What if this was TP53/complex karyotype?
  - No one knows what do to
  - This is almost a separate disease entity
  - Difficult to show benefit with anything
  - Magrolimab and APR-246 under investigation
- Allogeneic transplant is only known cure
  - How to get remission and leave patient in good enough shape to survive transplant?
- CPX-351
  - Liposomal AraC + daunorubicin
  - “Purple drug”
- CPX-351 versus 7+3:
  - Unselected AML:
    - No clear survival difference
  - Subgroup analysis suggested sAML benefits
- Randomized trial: CPX-351 v 7+3 for sAML
  - Clear benefit for CPX-351
- Patients achieving remission and proceeding to allo transplant after CPX-351 had remarkably good survival- Why?
  - Deeper remissions?
  - Less tissue damage, so less GVHD?
- Back to the patient:
  - Treated with CPX-351
  - LONG aplasia (this is typical)
  - CR achieved
  - Allogeneic transplant
  - Alive and well 3 years post-transplant

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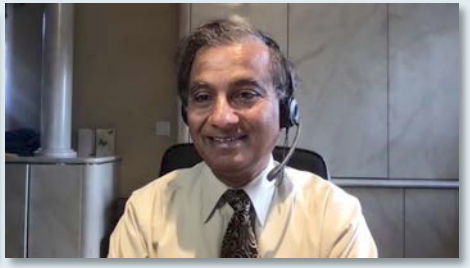
Appendix: Selected Data Sets

Case Presentation – Dr Apuri: An 89-year-old woman with low-grade MDS with ringed sideroblasts

Dr Susmitha Apuri



Dr Sunil Gandhi

- Initially treated with erythropoietin for approximately 6 years
- Transfusion requirements began to steadily increase
- Recommended treatment with luspatercept
- Fared well initially but could not continue treatment due to profuse diarrhea

Questions

- How would the investigators manage diarrhea outside the use of antidiarrheals especially in the elderly population?
- How many doses of luspatercept should I give, based on cost concerns? If the patient is responding, how long do the investigators continue administering luspatercept? Should we be switching back to erythropoietin?

RTP RESEARCH TO PRACTICE

Use of luspatercept in patients with lower-risk MDS

- Patient from clinic:
  - 80 yo woman with MDS-RS
  - Normal karyotype, SF3B1mut (spliceosome)
  - Hgb ~ 8, RBCs 2-3x/month (EPO failed)
- Spliceosome mutations associated with MDS
- Refractory anemia with ringed sideroblasts
  - Generally low risk MDS
  - Almost always harbor SF3B1
  - Classically diagnosed with iron stain of marrow…
    - …but SF3B1 is easier, more reliable
- Inflammation suppresses erythropoiesis
  - Mediated in part by the TGF-B family of cytokines that bind to Activin receptors
  - Activin signaling suppresses erythroid maturation
  - Think of anemia in patients with infection
- MDS = aberrantly inflammatory signaling
  - TGF-B signaling is activated
  - Why do SF3B1 mutations activate TGFB?
- Luspatercept
  - Monoclonal antibody-like protein
  - IgG Fc domain + Activin receptor
  - Binds up TGF-B (analogous to Avastin)
- MEDALIST trial
  - Luspatercept vs placebo
  - MDS patients with ringed sideroblasts (most had SF3B1)
    - Had to have failed EPO
  - Endpoints- transfusion independence
  - Luspatercept 38% vs placebo 13%
  - Median duration response ~ 30 weeks
- Back to our patient:
  - Luspatercept started
  - Hgb jumps to10-11 in 2 weeks…
  - Still responding at 1 year…
- Dosing
  - 1 mg/kg SQ q 3 weeks
  - Can increase dose if it doesn’t work..

Current non-protocol role, if any, of venetoclax and a hypomethylating agent (HMA) for patients with MDS

- Discuss Spectrum of disease of HR-MDS and outcomes to single agent HMA and urgent need for novel combinations
- Critical importance of enrolling prospective P3 clinical trials (as exemplified by recent failed P3 of pevonedistat and azacitidine vs aza alone).
- Discussion of *TP53* mutant MDS and impact on choice of therapy, critical importance of awaiting NGS results or predicting possible *TP53* mutation.
- What are other exciting novel therapeutic options of HR-MDS with azacitidine and potential triplet strategies?
- Should we and how should we assess MRD with frontline therapy +/- context of allo-HSCT with novel combinations?

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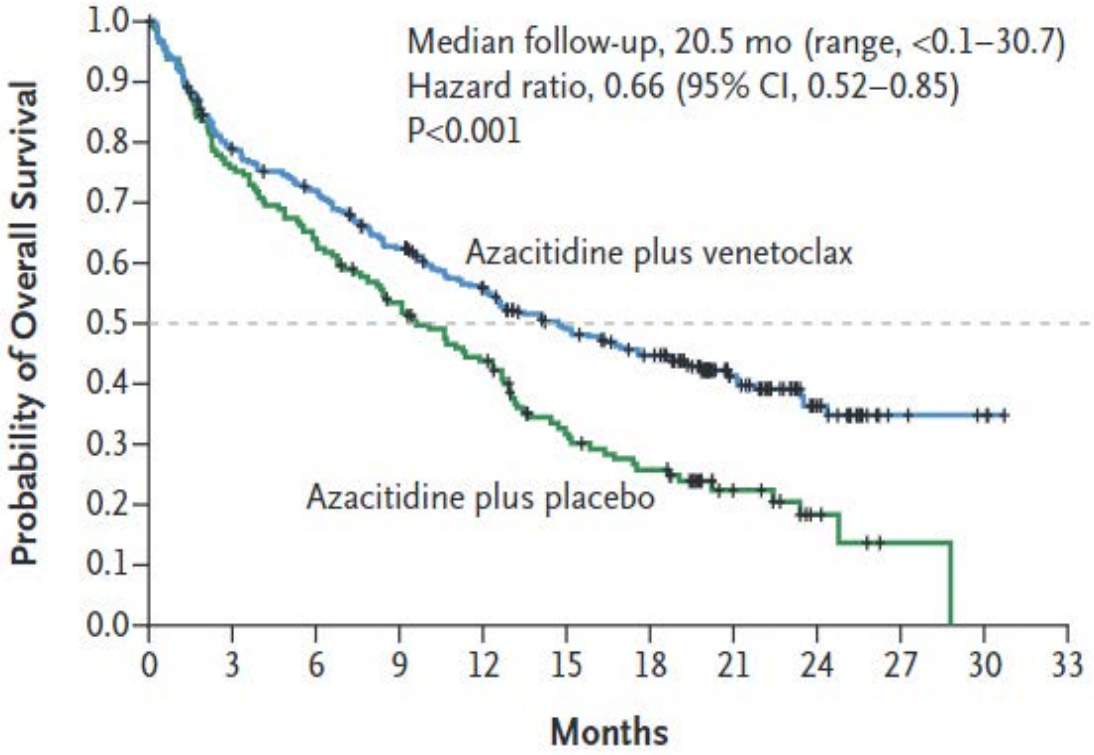
Acute Myeloid Leukemia

Results of VIALE-A: Azacitidine + venetoclax

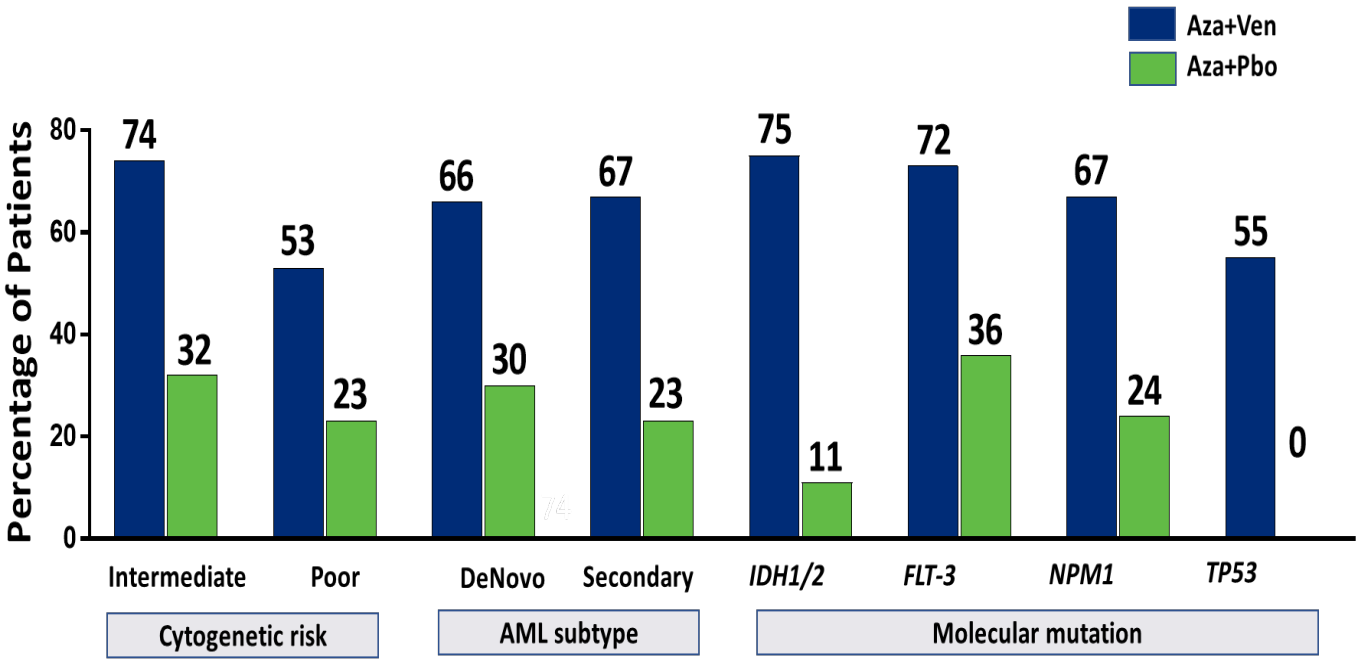
Significant OS improvement with venetoclax/azacitidine

CR rate: 36.7% vs 17.9% (*P* < .001)

CR/CRi rate: 66.4% vs 28.3% (*P* < .001)



Improved responses occurred *<u>independent</u>* of high risk genomics

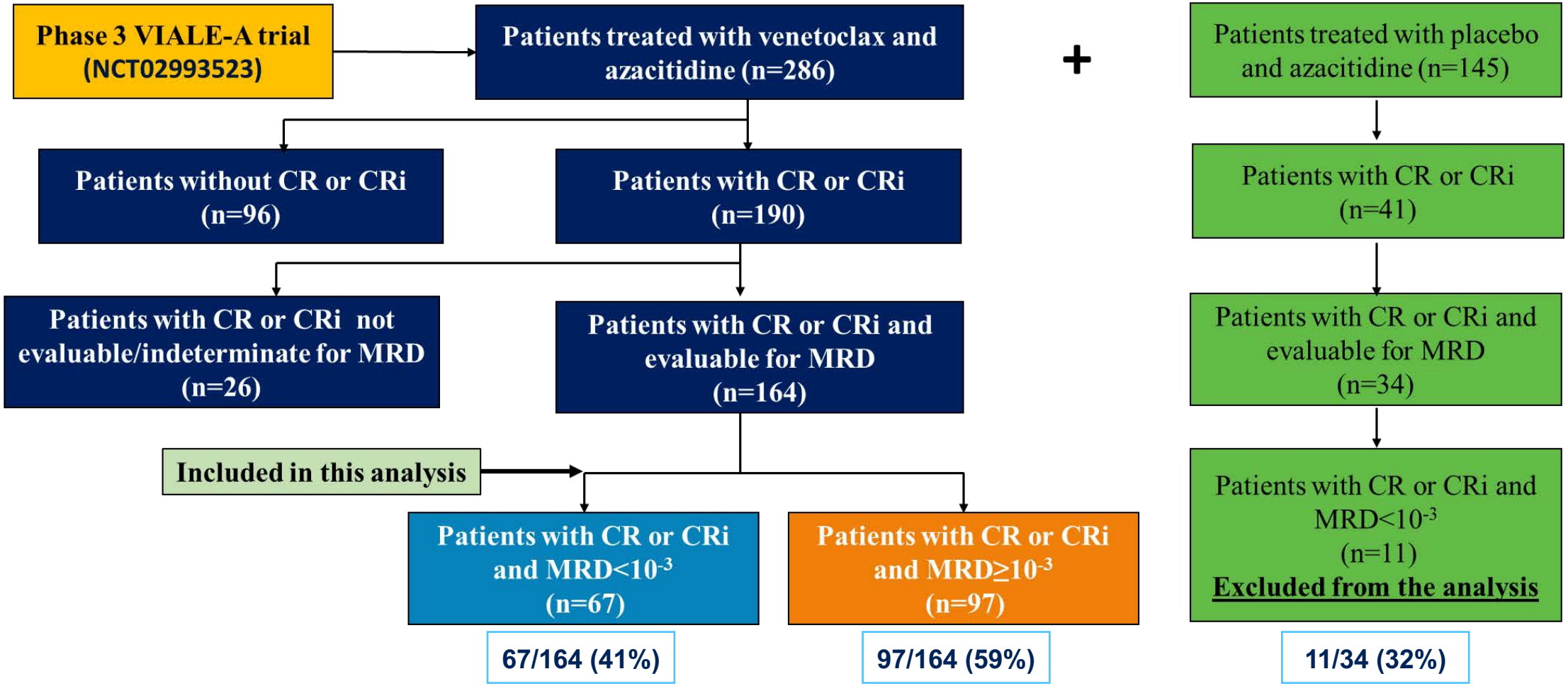


DiNardo C, et al. *N Engl J Med*. 2020;383:617-629.

VIALE-A: Flow Cytometry MRD: Response and Prognosis

ASCO 21

Analyzed patient population



Data cutoff: Jan 04, 2020
CR: Complete remissions, CRi: CR with incomplete hematological recovery; MRD: Minimal residual disease
Patients were indeterminate if the BM samples had less than a hundred thousand CD45+ leukocytes

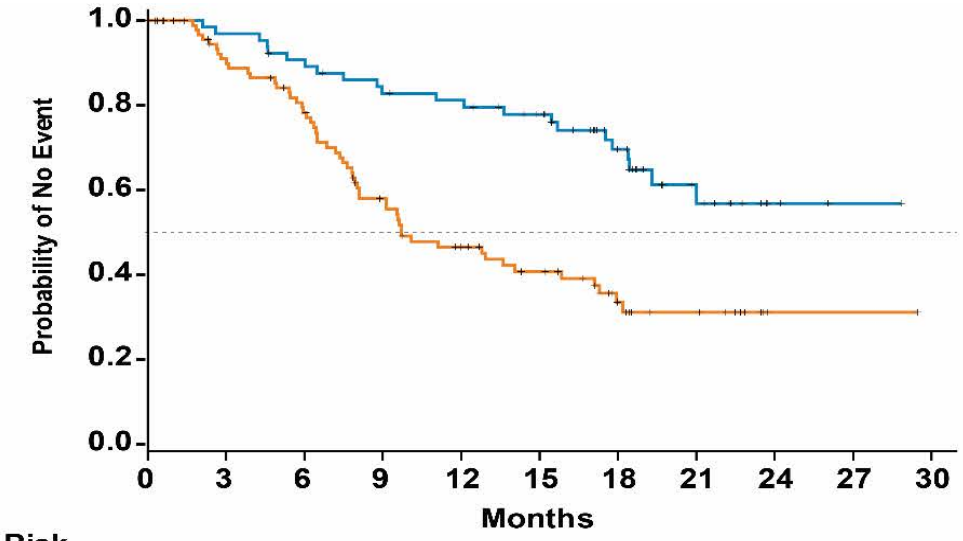
Pratz KW, et al. Abstract 7018. ASCO 2021.

Courtesy of Courtney D DiNardo, MD, MSCE

VIALE-A

ASCO 21

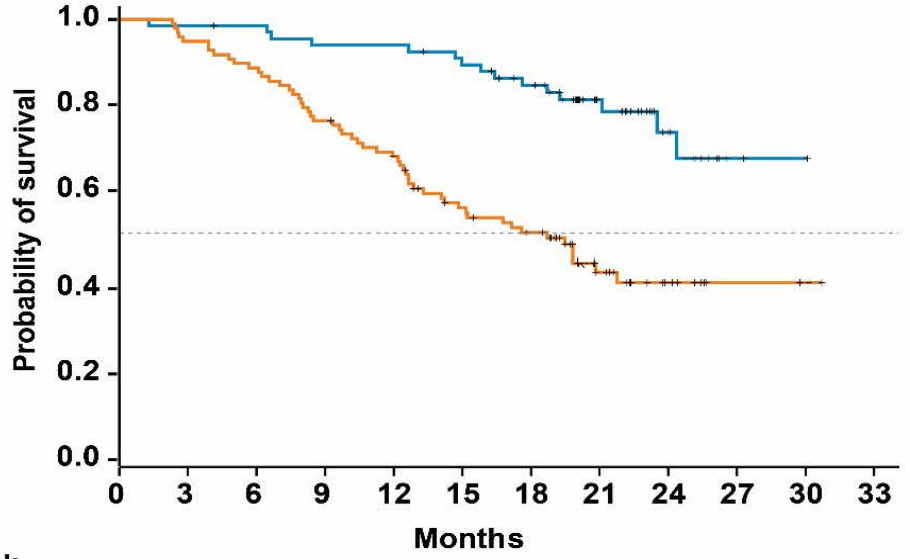
Duration of remission



Patients at Risk

CR+CRi+MRD<10^{-3}	67	63	58	52	50	44	30	14	3	1	0
CR+CRi+MRD≥10^{-3}	97	80	67	46	34	27	14	9	1	1	0

Overall survival



Patients at Risk

CR+CRi+MRD<10^{-3}	67	66	65	62	62	58	52	30	13	2	1	0
CR+CRi+MRD≥10^{-3}	97	92	86	74	64	49	42	21	10	3	2	0

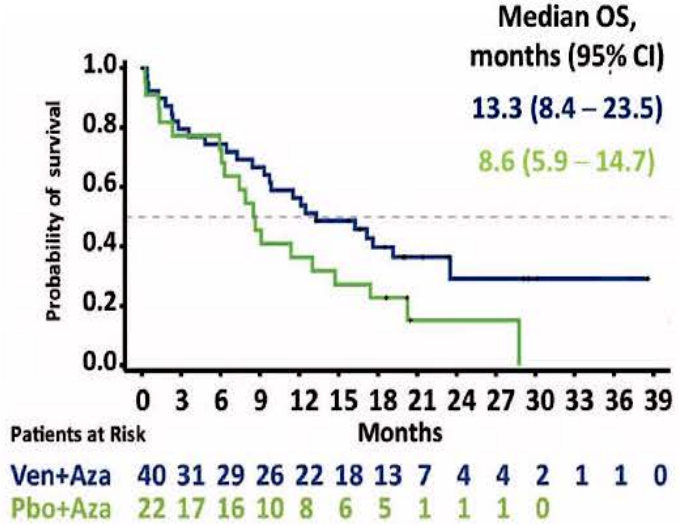
Duration of remission	# of events	12-month, %	18-month, %	Median DoR, months
CR+CRi+MRD<10^{-3}	22	81.2	69.6	NR
CR+CRi+MRD≥10^{-3}	54	46.6	33.5	9.7

Overall survival	# of events	12-month, %	18-month, %	Median OS, months
CR+CRi+MRD<10^{-3}	15	94.0	84.6	NR
CR+CRi+MRD≥10^{-3}	52	67.9	50.1	18.7

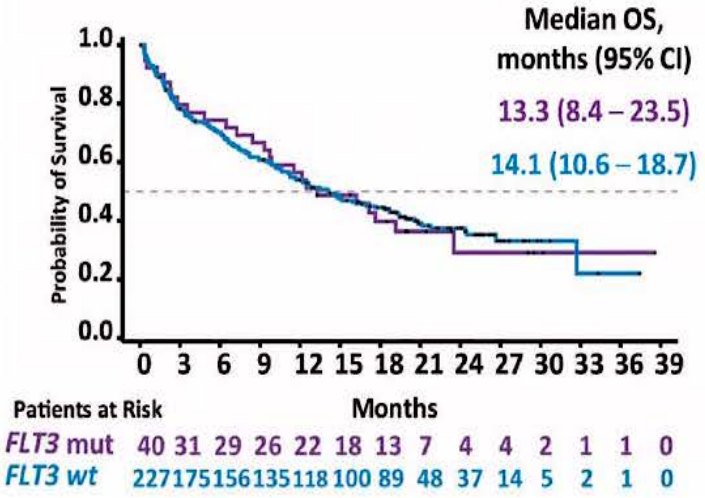
Pratz KW, et al. Abstract 7018. ASCO 2021.

AZA + VEN for FLT3-mutated ND AML: OS

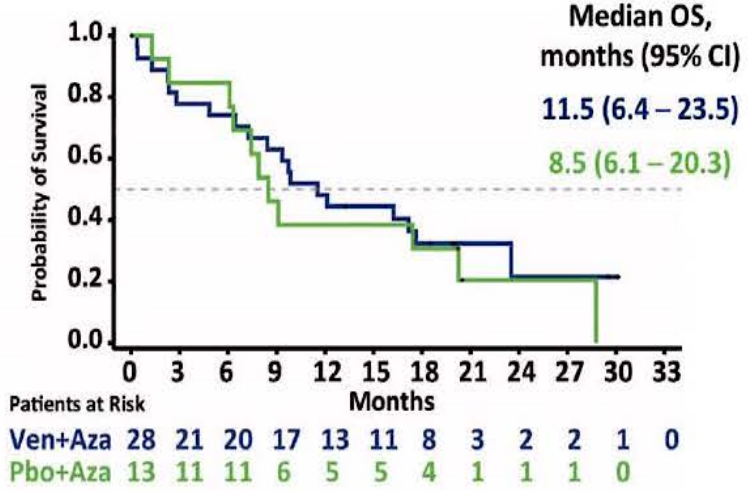
A. FLT3mut



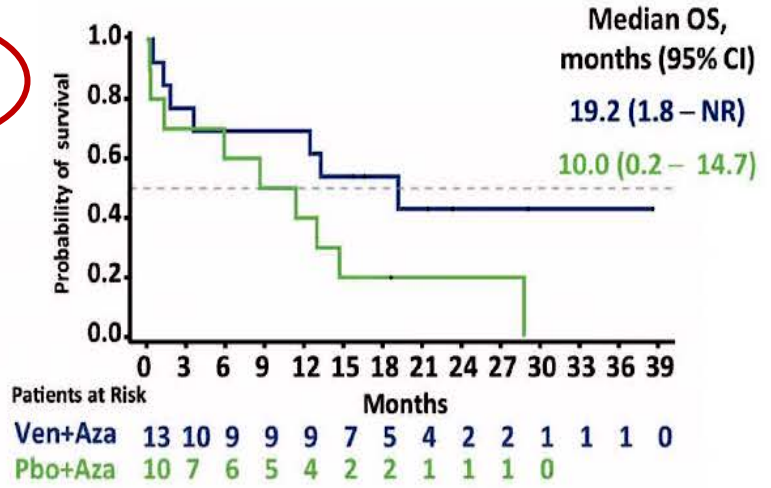
B. FLT3mut vs. wt in Ven+Aza



C. FLT3-ITD



D. FLT3-TKD



Summary

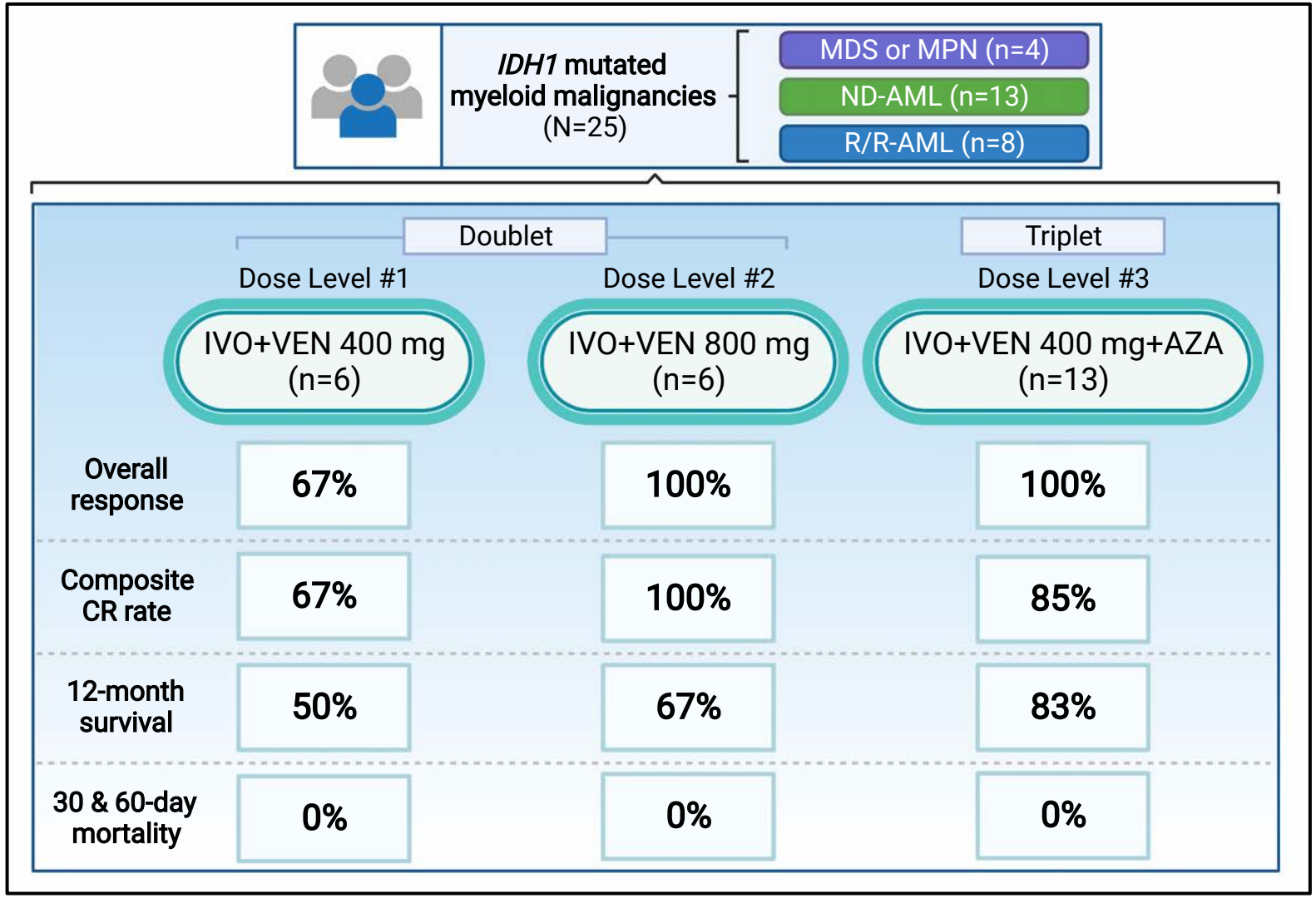
- In patients with *FLT3*$^{mut+}$ AML, response rates and OS were similar to *FLT3*^{WT} AML
- CR/CRi and OS were higher in *FLT3*$^{mut+}$ patients receiving AZA + VEN
- **FLT3-TKD patients appear to do particularly well**

Konopleva M, et al. ASH 2020. Abstract 1904.

A phase IB/II study of ivosidenib with venetoclax +/- azacitidine in *IDH1* mutated myeloid malignancies

IVO+VEN +/- AZA associated with

- Expected and acceptable safety profile
- High composite CR rates in ND and R/R-AML
  - ND-AML: **92%**
  - R/R-AML: **63%**
- MRD-negative remissions in ND and R/R-AML
  - ND-AML: **60%**
  - R/R-AML: **60%**
- Durable responses and prolonged survival across disease groups



Myelodysplastic Syndromes

FDA Fast Track Designation Granted for Sabatolimab (MBG453) in Myelodysplastic Syndromes

Press Release: May 25, 2021

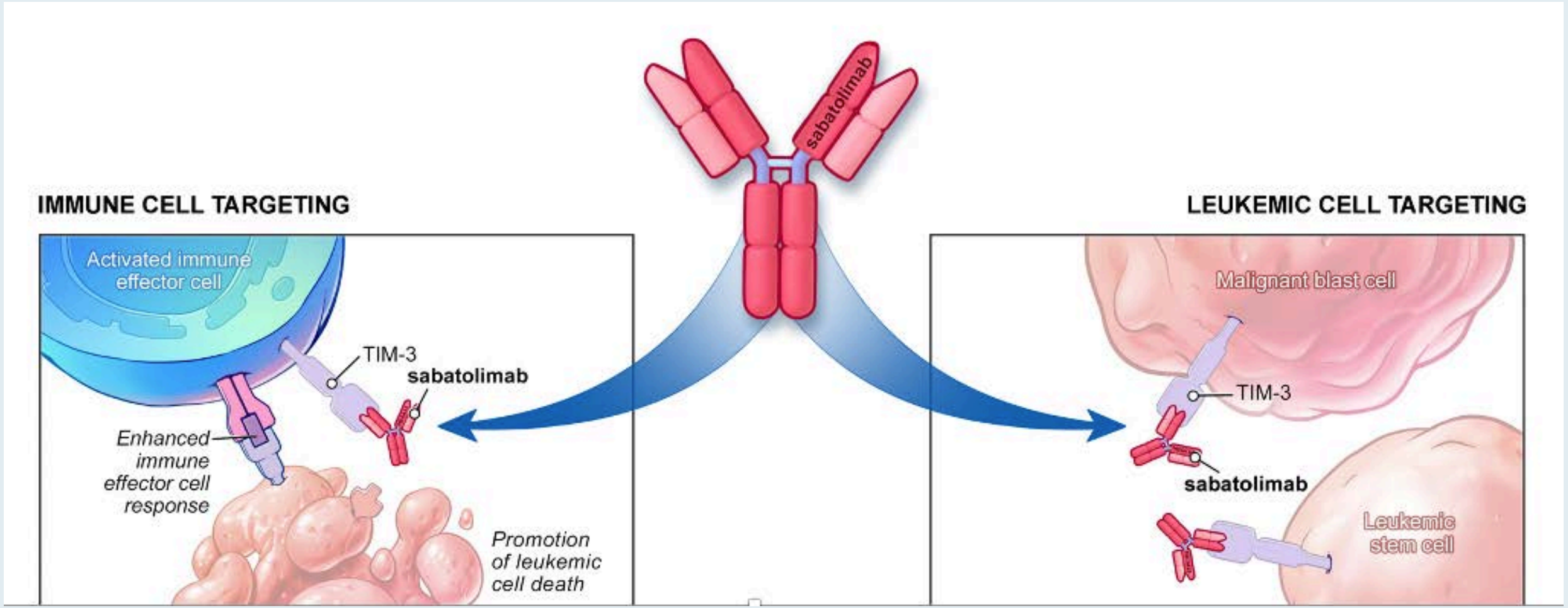
"The US Food and Drug Administration (FDA) has granted fast track designation for sabatolimab (MBG453) for the treatment of adult patients with myelodysplastic syndromes (MDS) defined with an IPSS-R risk category of high or very high risk in combination with hypomethylating agents.

Sabatolimab is a first-in-class investigational immuno-myeloid therapy that binds to TIM-3, a novel target expressed on multiple immune cell types and leukemic cells and blasts, but not on the normal stem cells that induce blood formation; it is in development for higher-risk MDS and acute myeloid leukemia (AML).

The STIMULUS clinical trial program includes multiple studies evaluating sabatolimab as part of different combination therapies in patients with MDS and AML, including the Phase II STIMULUS-MDS1, Phase III STIMULUS-MDS2, Phase II STIMULUS-MDS3 and Phase II STIMULUS-AML1 studies."

www.novartis.com/news/novartis-receives-fda-fast-track-designation-sabatolimab-mbg453-myelodysplastic-syndromes

Sabatolimab (MBG453): A TIM-3-Targeting Monoclonal Antibody



www.hcp.novartis.com/virtual-congress/disease-areas/mds-aml/

Sabatolimab in Combination with Hypomethylating Agents in AML and High-Risk MDS

	ND AML[a]		HR-MDS[a]	
Parameter	+ Dec n=22	+ Aza n=26	+ Dec n=19	+ Aza n=20
Duration of sabatolimab exposure, median (range) mo	6.8 (0.7-28.3)	3.5 (0.3-15.2)	8.0 (0.7-33.6)	2.8 (0.8-14.3)
Efficacy evaluable pts[c], n	17	17	18	17
ORR[d], n (%)	8 (47.1)	6 (35.3)	11 (61.1)	11 (64.7)
CR	6 (35.3	2 (11.8)	6 (33.3)	2 (11.8)
CRi	1 (5.9)	2 (11.8)	NA	NA
mCR	NA	NA	3 (16.7)	5 (29.4)
mCR with HI	NA	NA	3 (16.7)	2 (11.8)
PR	1 (5.9)	2 (11.8)	0	0
SD with HI	NA	NA	2 (11.1)	4 (23.5)

Brunner AM et al. ASH 2020;Abstract 657.

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