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

FACULTY

Courtney D DiNardo, MD, MSCE
Robert Dreicer, MD, MS
Justin F Gainor, MD
Sara Hurvitz, MD
Ian E Krop, MD, PhD
John M Pagel, MD, PhD
Alexander Perl, MD
Daniel P Petrylak, MD
Philip A Philip, MD, PhD, FRCP
Paul G Richardson, MD
Mitchell R Smith, MD, PhD
Eric Van Cutsem, MD, PhD
Peter Voorhees, MD
Heather Wakelee, MD

MODERATOR

Neil Love, MD

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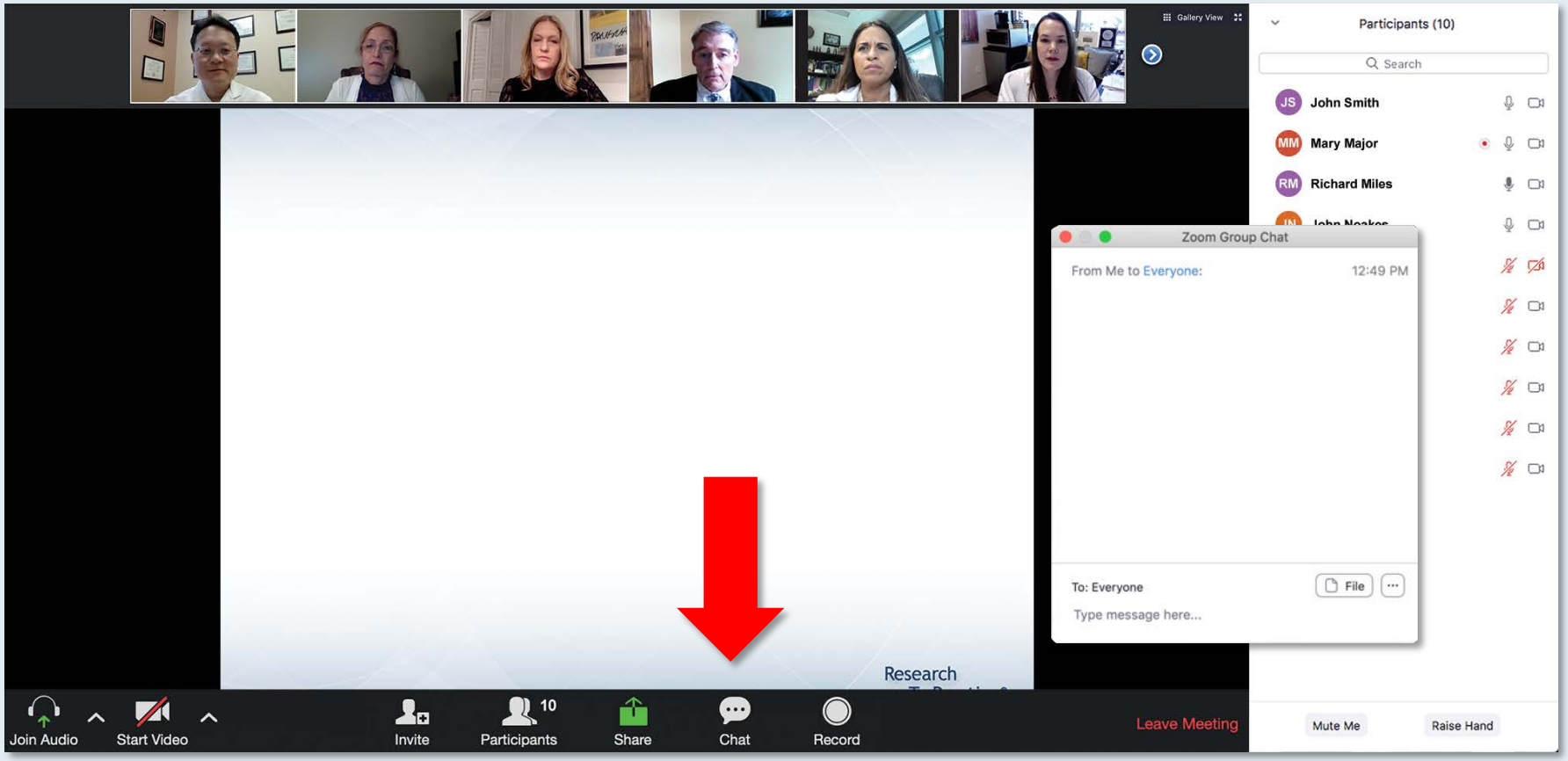
We Encourage Clinicians in Practice to Submit Questions



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

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Agenda

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

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

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

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

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

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

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

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Gastrointestinal Cancers Faculty

Philip A Philip, MD, PhD, FRCP
Kathryn Cramer Endowed Chair in Cancer Research
Professor of Oncology and Pharmacology
Leader, GI and Neuroendocrine Oncology
Karmanos Cancer Institute
Wayne State University
Detroit, Michigan

Eric Van Cutsem, MD, PhD
Professor of Medicine
Digestive Oncology
University Hospitals Leuven
Leuven, Belgium

The patients I saw today…

69	M	Extranodal MZL - Single agent rituximab SQ
46	F	Colorectal Cancer - 1st line FOLFOXIRI, at least 80% burden reduction a year out
69	F	Gastric/Gastroesophogeal cancer - Started FLOT but was interrupted due to GI (tumor) bleeding recovering from gastrectomy Stage III neg margins
68	F	Breast Cancer - FU 13y post mastectomy, AC→T, XRT, TNBC Stage IIIA
58	M	Pancreatic cancer - 1st line FOLFIRINOX, now FOLFIRI due to neuropathy, imaging still improving since May of 2017
39	F	Gastric cancer - 3rd line paclitaxel/ramucirumab, MSI normal. NGS neg. Dx 08/17
75	F	Colorectal Cancer - 3rd line RAS WT CPT-11/panitumumab, 2 y out
54	F	Duodenal Cancer - 2nd line FOLFIRI MSI normal
69	M	Colorectal Cancer - IIIB adjuvant FOLFOX
73	F	Breast Cancer - IIIB ER/PR Neg, HER2 3+ (on mastectomy with small amount of residual ds, neg on original bx); Adjuvant paclitaxel/trastuzumab, now on trastuzumab mono

70	F	Colorectal Cancer - Stage III post FOLFOX, 18 mos after had recurrence, now on FOLFIRI/bevacizumab
50	F	Breast Cancer - Original IIA ER/PR neg, HER2 pos. Stroke 4 days prior to adjuvant, slow recovery unable to engage on therapy. Four mos later: Local recurrence. Now clinical CR on paclitaxel/carbo/trastuzumab. Too weak for pertuzumab
86	F	Myeloproliferative neoplasm - ET on observation
51	F	Breast Cancer - IIA TNBC FU 4th year
63	M	Head and neck cancer - 2nd line Nivolumab, NED until last scan, single pulmonary nod, SQ CA, pending RFA
72	M	Benign Hematology - Recurrent DVT after interruption of rivaroxaban for dental surgery
55	M	Multiple myeloma - NED post ASCT 2013
42	F	Breast Cancer - 1st line Palbociclib/letrozole
26	F	Benign Hematology - SC disease routine FU recent initiation of L-Glutamine, on iron chelation
22	F	Benign Hematology - ITP close monitoring last trimester 1st pregnancy

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Contributing Oncologists

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

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

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

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

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

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

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

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Contributing Oncologists

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

Nasfat Shehadeh, MD
Medical Oncologist
Oncology Specialists of Charlotte
Charlotte, North Carolina

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

Saad Zafar Usmani, MD, MBA
Division Chief, Plasma Cell Disorders
Levine Cancer Institute, Carolinas Medical Center
Charlotte, North Carolina

Maria E Picton, MD
Hematology Oncology, Physicians East
Greenville, North Carolina

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

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Agenda

Module 1: Colorectal Cancer

- Dr Deutsch: A 55-year-old man with mCRC – MSS, BRAF V600E mutation

Module 2: Gastric/Gastroesophageal and Esophageal Cancers

- Dr Favaro: An 82-year-old man with gastric/esophageal cancer with HER2 amplification

Module 3: Hepatocellular Carcinoma (HCC)

- Dr Shehadeh: A 70-year-old man with newly diagnosed Child-Pugh A HCC
- Dr Mitchell: A woman in her 80s with unresectable HCC and cirrhosis

Module 4: Pancreatic Adenocarcinoma (PAD)

- Dr Deutsch: A 56-year-old man with localized PAD
- Dr Mohamed: A 57-year-old man with metastatic PAD and a BRCA2 mutation

Module 5: Cholangiocarcinoma

- Dr Shehadeh: A 59-year-old man with unresectable cholangiocarcinoma with a HER2 mutation

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Case Presentation – Dr Deutsch: A 55-year-old man with metastatic colorectal cancer (mCRC) – Microsatellite stable (MSS), BRAF V600E mutation

Dr Margaret Deutsch

- Diagnosed with 2.4 cm cecal mass with a solitary liver metastasis
- Neoadjuvant FOLFIRI x 3 cycles (deferred oxaliplatin due to diabetes); progression in liver and peritoneal implants noted
- Genetic testing: BRAF V600E (FoundationOne®)
- FOLFOX/bevacizumab initiated x 4 cycles
  - Slight decrease in liver metastases and peritoneal nodules resolved

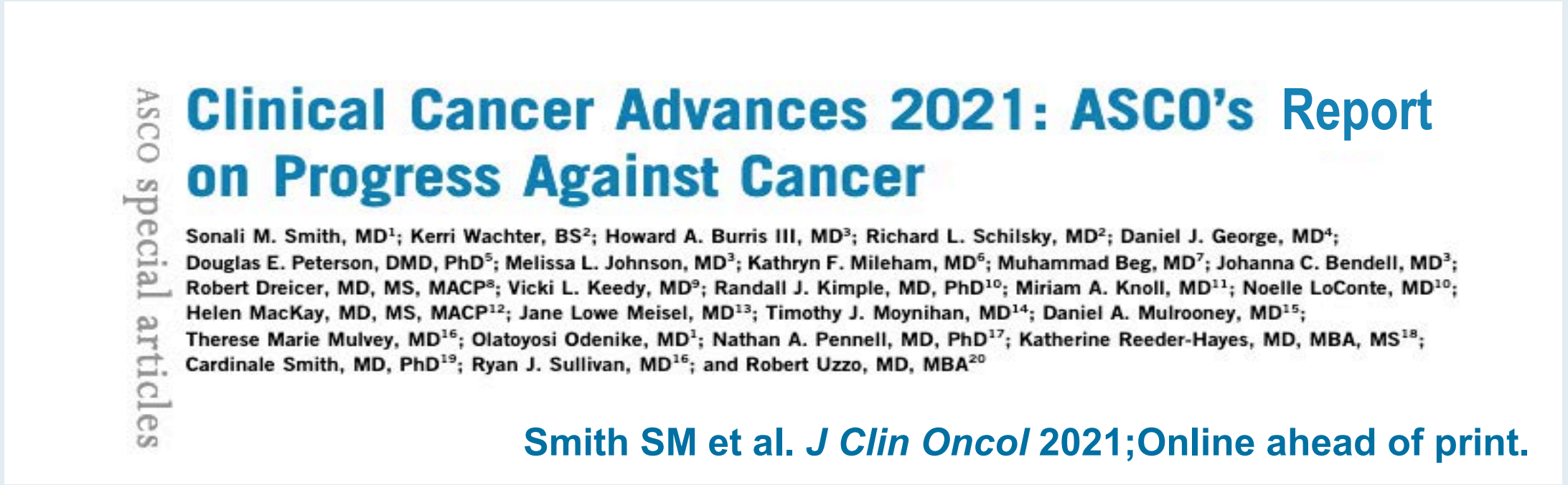
Questions

- Are FOLFOX and FOLFIRI considered equivalent as initial therapies?
- When would it be appropriate to administer BRAF-targeted therapy for this patient?

RTP RESEARCH TO PRACTICE

ASCO Names Advance of the Year: Molecular Profiling Drives Progress in Gastrointestinal Cancers

The ASCO Post Staff (February 02, 2021)



"Gastrointestinal cancers account for 26% of the global cancer incidence and 35% of all cancer-related deaths... The ability to molecularly profile a gastrointestinal tumor has expanded the treatment options for patients with gastrointestinal cancers—extending survival, while minimizing adverse effects."

https://ascopost.com/news/february-2021/asco-names-advance-of-the-year-molecular-profiling-drives-progress-in-gastrointestinal-cancers/

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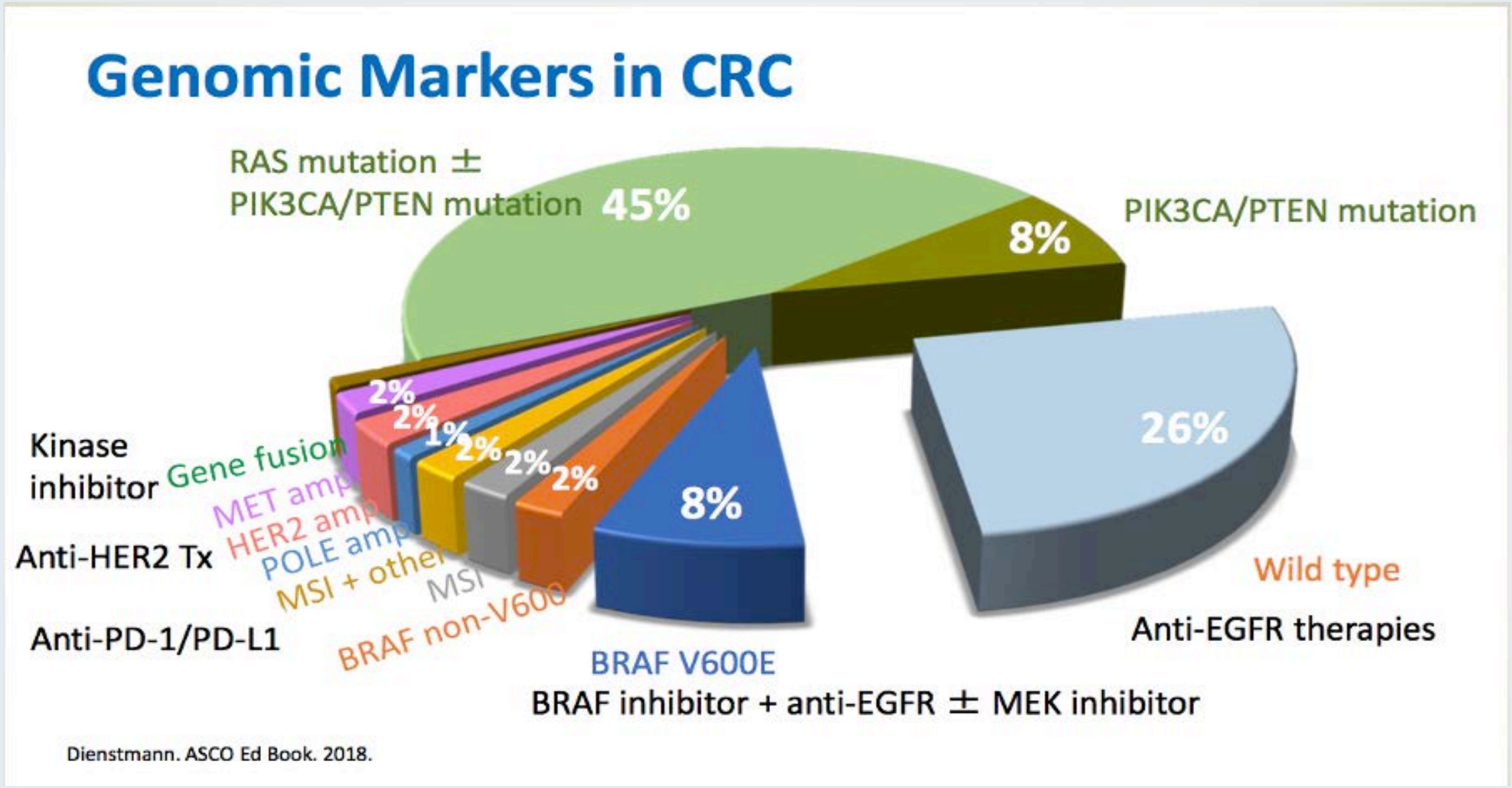
Genomic Markers in CRC



Dienstmann. ASCO Ed Book. 2018.

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

Press Release – April 8, 2020

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

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

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

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

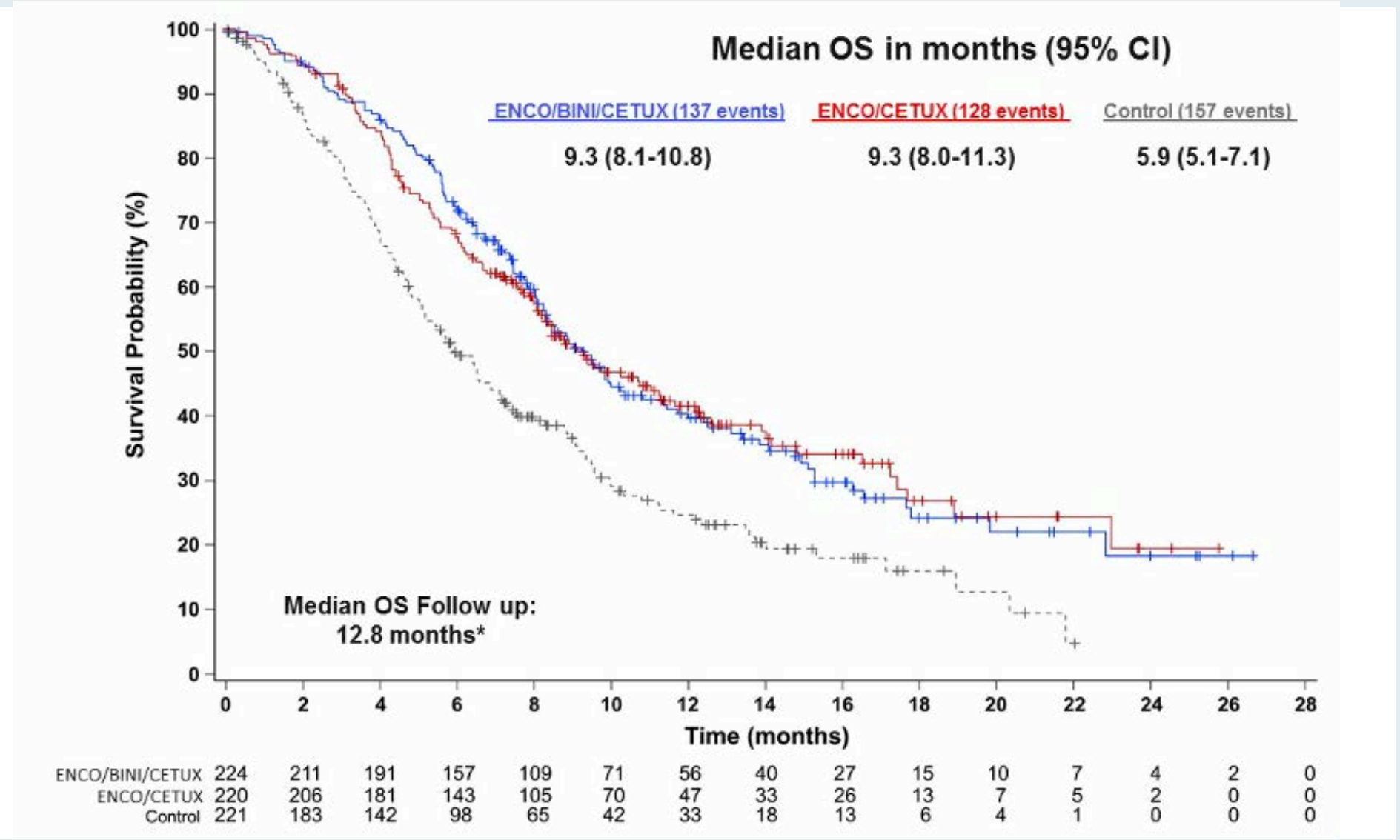
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-encorafenib-combination-cetuximab-metastatic-colorectal-cancer-braf-v600e-mutation

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

Kopetz S et al.

ASCO 2020;Abstract 4001.

BEACON CRC: Updated Overall Survival Analysis



Kopetz S et al. ASCO 2020;Abstract 4001.

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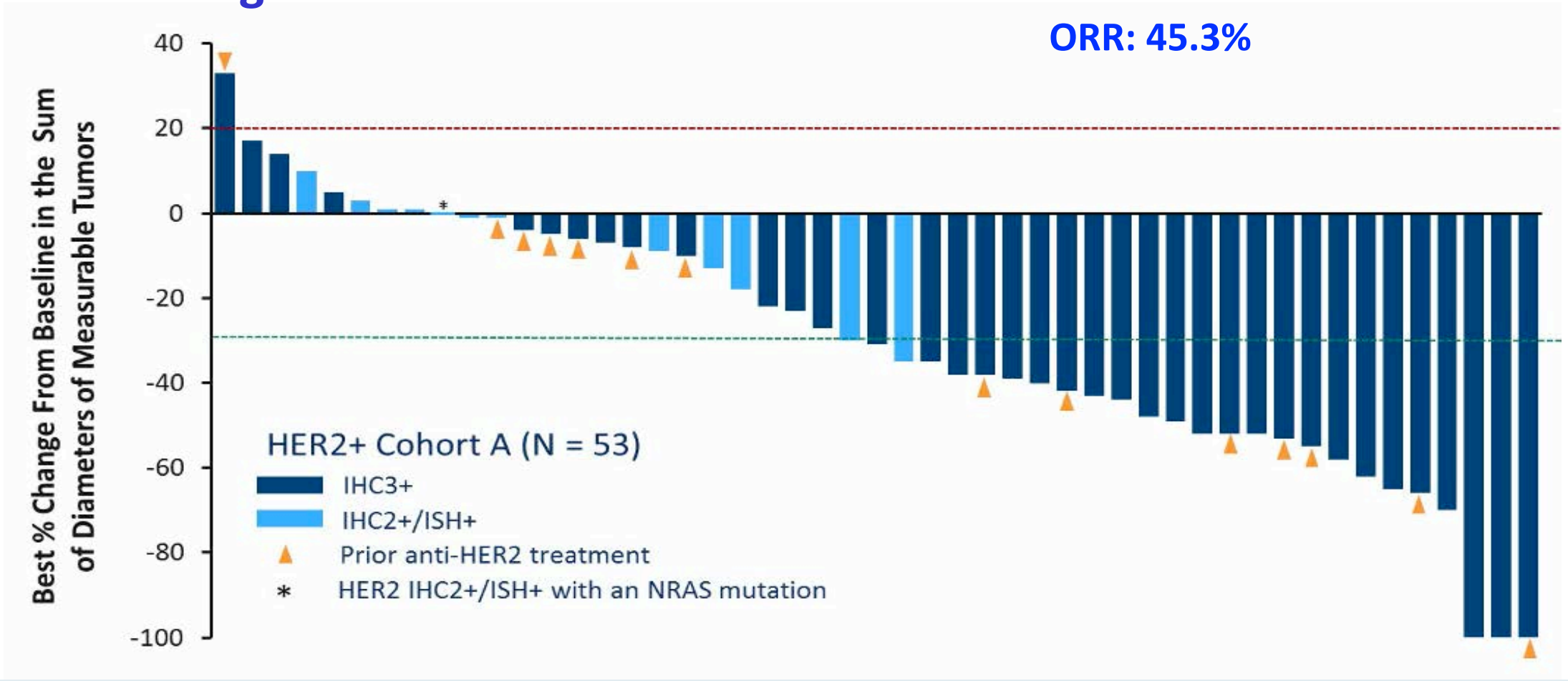
A Phase II, Multicenter, Open-Label Study of Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients (pts) with HER2-Expressing Metastatic Colorectal Cancer (mCRC): DESTINY-CRC01

Siena S et al.

ASCO 2020;Abstract 4000.

DESTINY-CRC01: Response

Best Change in Tumor Size



Siena S et al. ASCO 2020;Abstract 4000.

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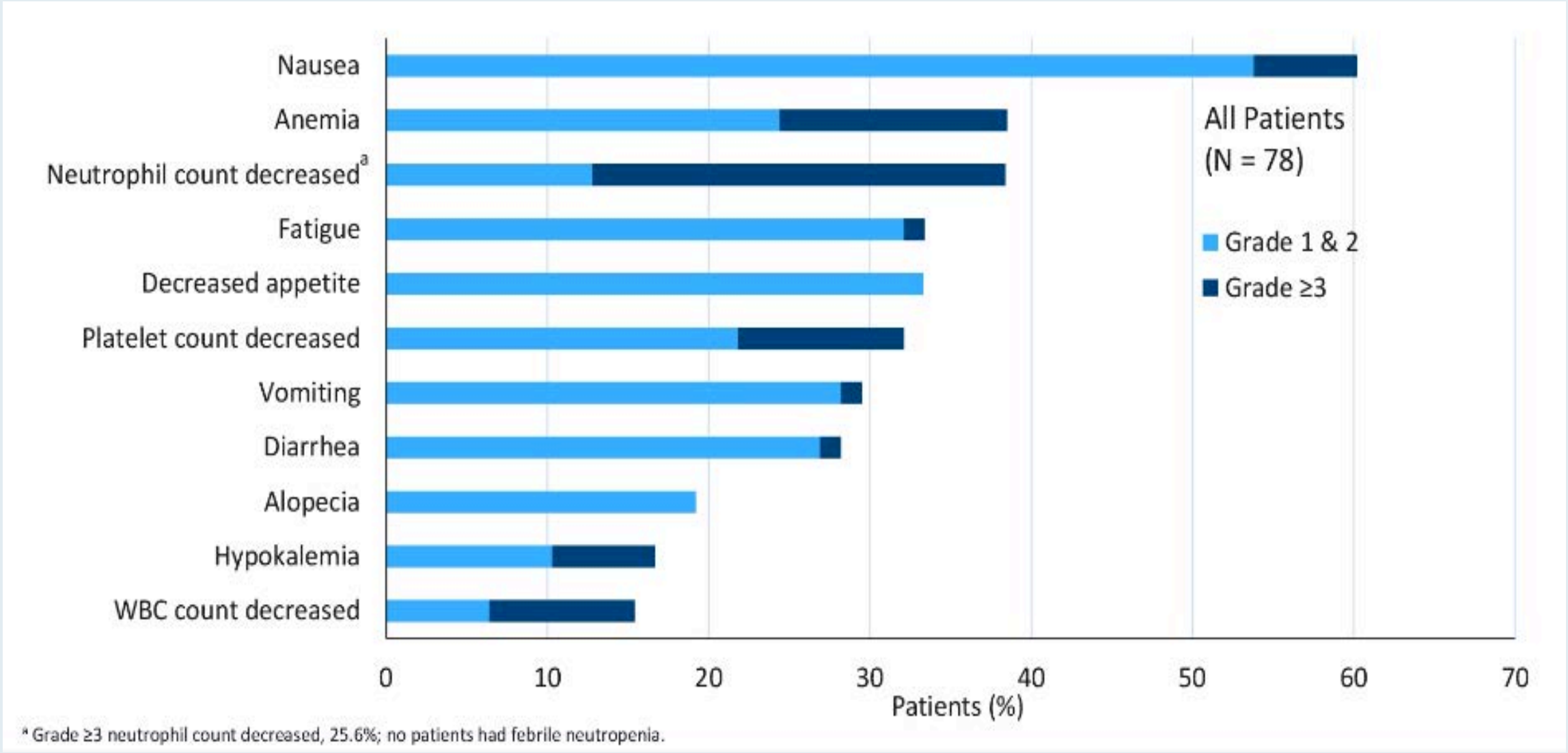
DESTINY-CRC01: Treatment-Emergent Adverse Events in >15% of Patients



[a] Grade ≥3 neutrophil count decreased, 25.6%; no patients had febrile neutropenia.

Siena S et al. ASCO 2020;Abstract 4000.

Ann Oncol 2020;31(9):1160-8.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Trifluridine/tipiracil plus bevacizumab in patients with untreated metastatic colorectal cancer ineligible for intensive therapy: the randomized TASCO1 study☆

E. Van Cutsem[1*], I. Danielewicz[2], M. P. Saunders[3], P. Pfeiffer[4], G. Argilés[5], C. Borg[6], R. Glynne-Jones[7], C. J. A. Punt[8], A. J. Van de Wouw[9], M. Fedyanin[10], D. Stroyakovskiy[11], H. Kroening[12], P. Garcia-Alfonso[13], H. Wasan[14], A. Falcone[15], A. Kanehisa[16], A. Egorov[16], P. Aubel[16], N. Amellal[16] & V. Moiseenko[17]

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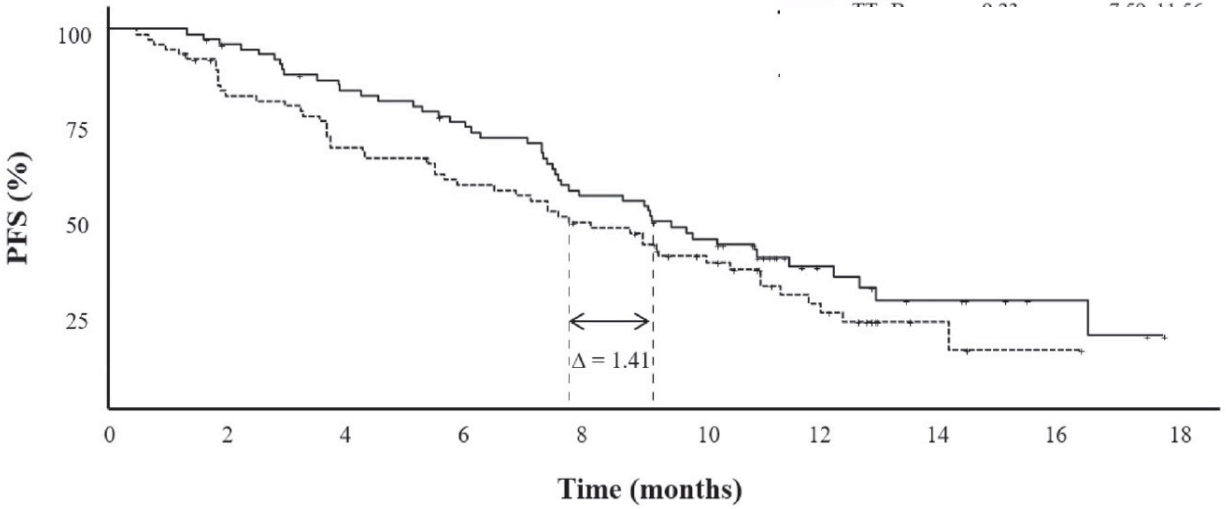
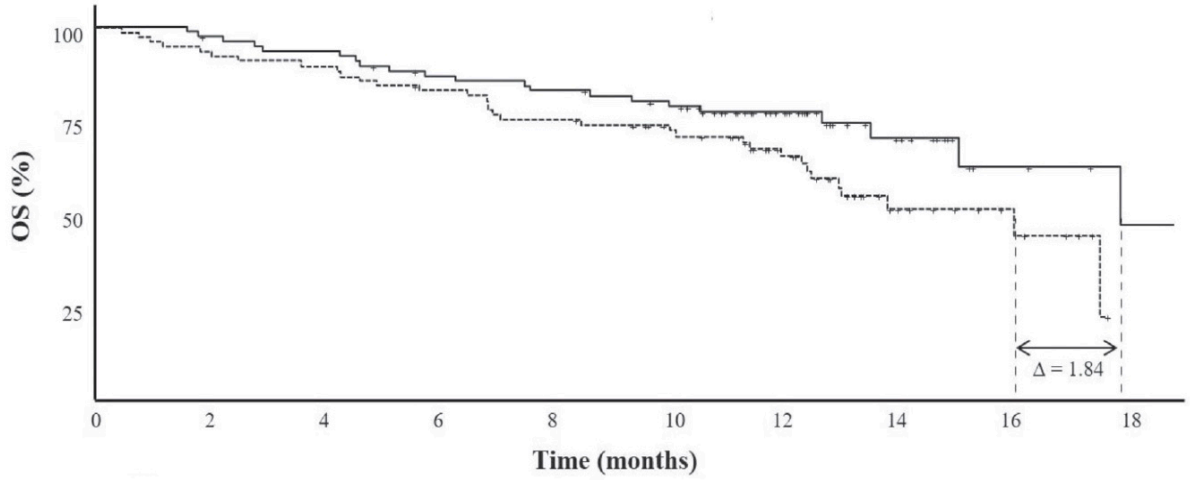
TASCO1: TAS-102 plus Bevacizumab for Untreated mCRC Ineligible for Intensive Therapy

	Cape/Bev (n = 76)	TAS-102/Bev (n = 77)
mPFS	7.8 mo	9.2 mo
	HR: 0.71	



	Cape/Bev (n = 76)	TAS-102/Bev (n = 77)
mOS	16.2 mo	18.0 mo
	HR: 0.56	



Van Cutsem E et al. *Ann Oncol* 2020;31(9):1160-8.

RTP RESEARCH TO PRACTICE

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

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

Lancet Oncol 2020; 21: 412–20

TAS-102 with Bevacizumab for Chemorefractory mCRC

- Randomized study with N = 93 patients with chemorefractory mCRC

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

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

Pfeiffer P et al. *Lancet Oncol* 2020;21(3):412-20; Pfeiffer P et al. ESMO World Congress GI 2019;Abstract O-014.

RTP RESEARCH TO PRACTICE

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

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

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

Courtesy of Axel Grothey, MD

Factors Associated with Effectiveness of Trifluridine/Tipiracil versus Regorafenib in Patients with Pretreated mCRC

Grell P et al.

Gastrointestinal Cancers Symposium 2020;Abstract 137.

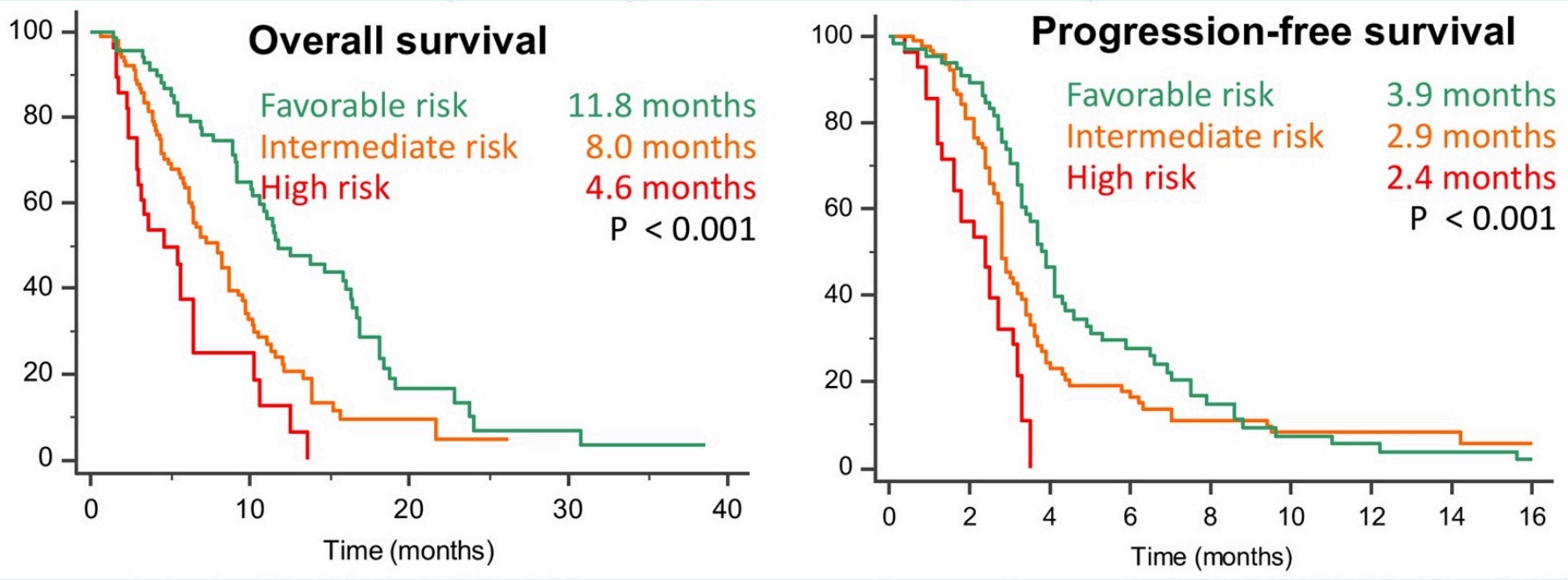
Factors Significantly Associated with Longer OS in Patients with Previously Treated mCRC Who Received TAS-102 or Regorafenib

Factors significantly associated with longer OS:

- Time ≥24 months from diagnosis of mCRC
- Time ≥3 months from 5FU or capecitabine in TAS-102, anti-VEGF in regorafenib
- ECOG PS 0 versus 1
- Normal baseline CRP level
- Baseline WBC <8 x 10^9/L

TASREG prognostic scoring system (1 point each)

- High risk (0 to 1)
- Intermediate risk (2 to 3)
- Favorable risk (≥4)



Grell P et al. Gastrointestinal Cancers Symposium 2020;Abstract 137.

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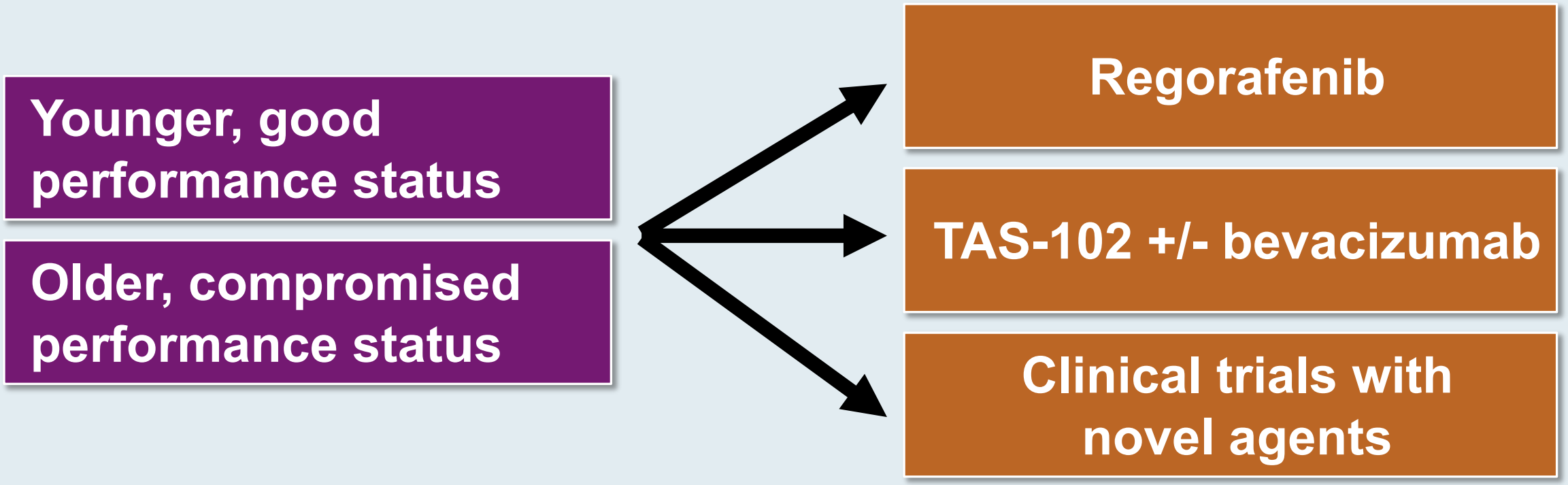
What is the preferred approach by clinical investigators to metastatic colorectal cancer after chemotherapy and immunotherapy?



Data sets with the potential to change clinical (and research) algorithms

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

Press Release – June 29, 2020

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

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

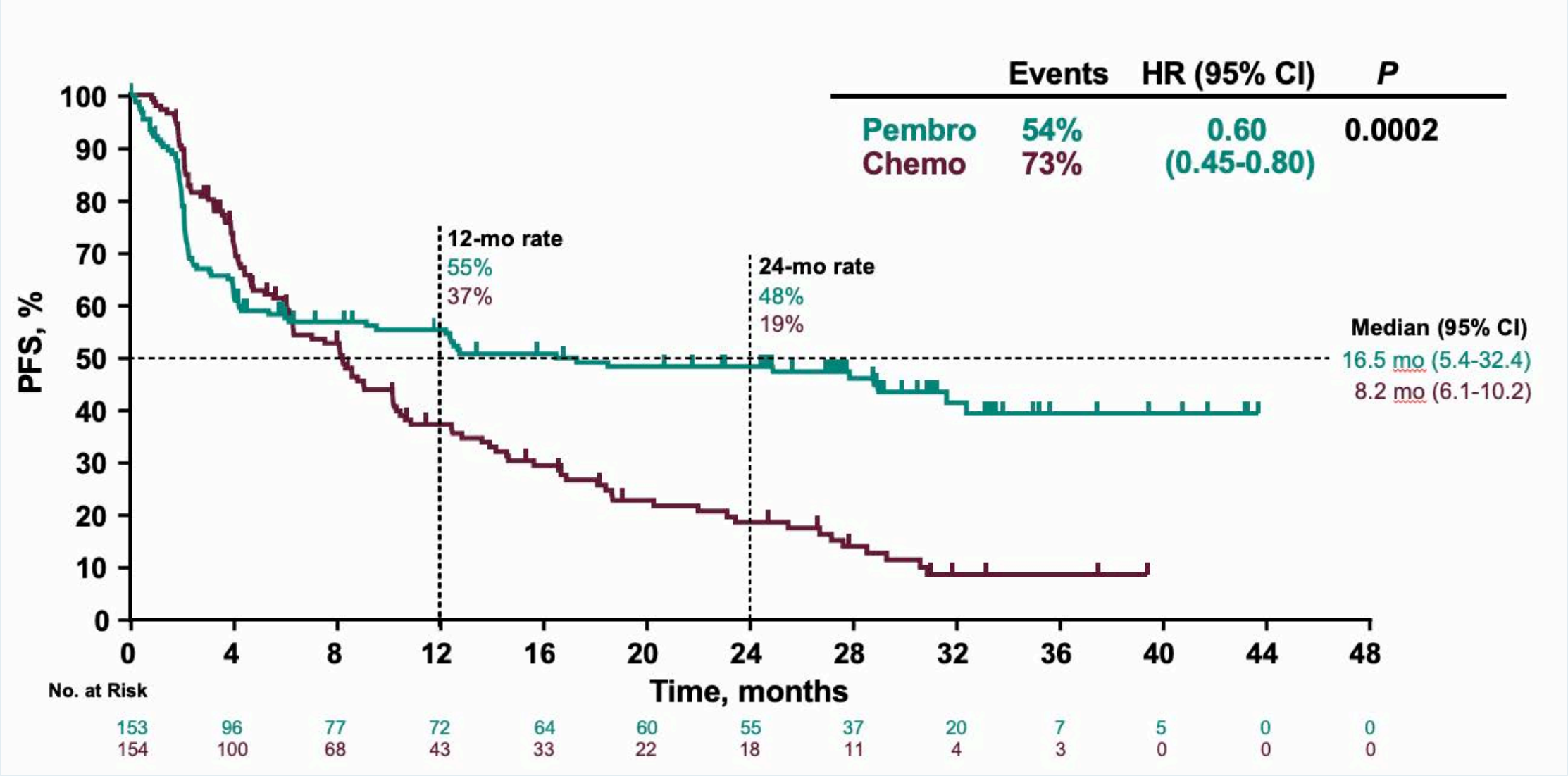
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-first-line-treatment-msi-hdmmr-colorectal-cancer

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

Andre T et al.

ASCO 2020;Abstract LBA4.

KEYNOTE-177: Progression-Free Survival Analysis



Andre T et al. ASCO 2020;Abstract LBA4.

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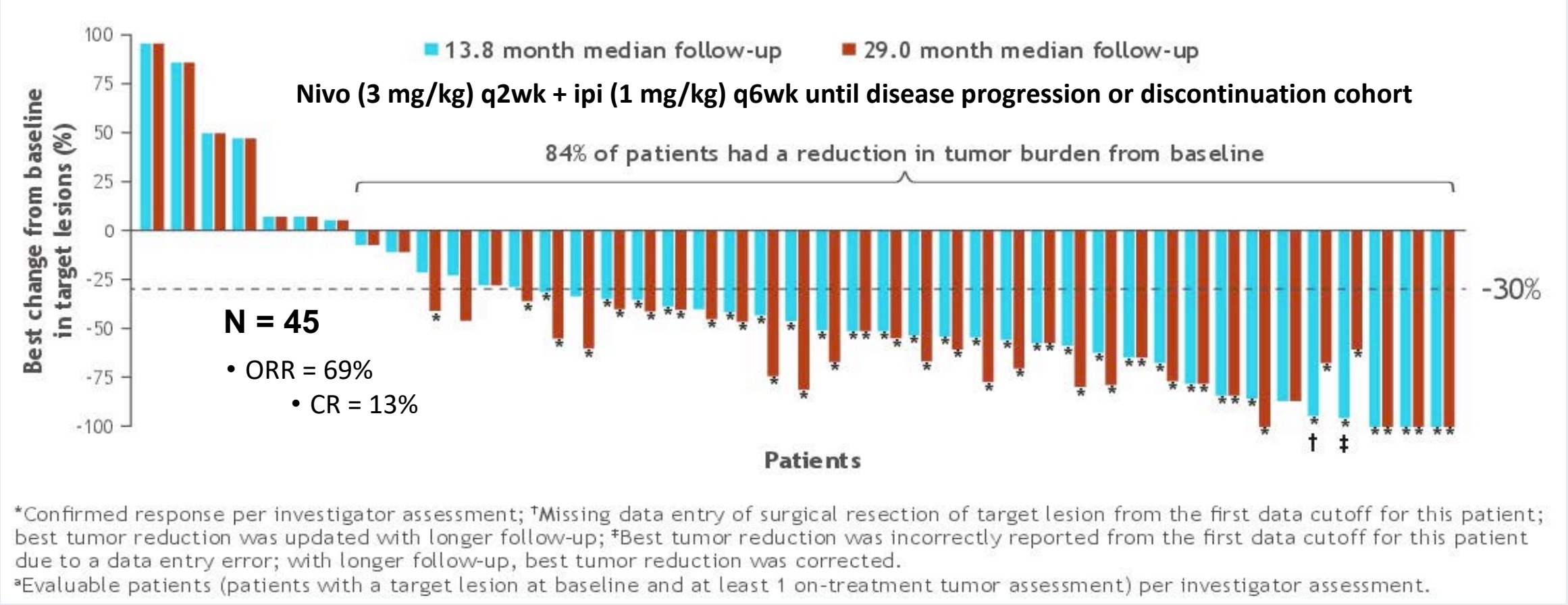
Nivolumab (NIVO) + Low-Dose Ipilimumab (IPI) as First-Line (1L) Therapy in Microsatellite Instability-High/Mismatch Repair-Deficient (MSI-H/dMMR) Metastatic Colorectal Cancer (mCRC): Two-Year Clinical Update

Lenz HJ al.

ASCO 2020;Abstract 4040.

CheckMate 142: 2-Year Update of Nivolumab + Low-Dose Ipilimumab in Untreated dMMR/MSI-H mCRC



*Confirmed response per investigator assessment; †Missing data entry of surgical resection of target lesion from the first data cutoff for this patient; best tumor reduction was updated with longer follow-up; ‡Best tumor reduction was incorrectly reported from the first data cutoff for this patient due to a data entry error; with longer follow-up, best tumor reduction was corrected.
[a]Evaluable patients (patients with a target lesion at baseline and at least 1 on-treatment tumor assessment) per investigator assessment.

- 2-year PFS = 74%
- 2- year OS = 79%

- No Grade 5 TRAEs reported
- 10 (22%) had Grade 3/4 TRAEs
- 3 (7%) had Grade 3-4 TRAEs leading to discontinuation

Lenz HJ et al. ASCO 2020;Abstract 4040.

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Module 1: Colorectal Cancer

- Dr Deutsch: A 55-year-old man with mCRC – MSS, BRAF V600E mutation

Module 2: Gastric/Gastroesophageal and Esophageal Cancers

- Dr Favaro: An 82-year-old man with gastric/esophageal cancer with HER2 amplification

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Case Presentation – Dr Favaro: An 82-year-old man with gastric/esophageal cancer with HER2 amplification

Dr Justin Peter Favaro

- Presents with neck stiffening and right neck lymphadenopathy
  - Biopsy d/w esophageal or gastric primary; PET scan showed no other sites of disease
- CPS score 1, TMB high (14 Mut/Mb), HER2 amplified, MYC amplified
- FOLFOX trastuzumab x 5 months → trastuzumab x 2 months
- Recurrence of the neck lesions
- Trastuzumab-deruxtecan (T-Dxd) initiated with good clinical response after first cycle

Questions

- This patient has a CPS score of 1, but a high tumor mutation burden. In these patients, do you feel immunotherapy, which is approved for patients with high tumor mutation burden, is a great option? When do you incorporate checkpoint inhibitors in patients such as this?
- Which mutation do you target first, the HER2 amplification or the high TMB?

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A 65-year-old patient with locally advanced MSS gastric cancer responds to carboplatin/paclitaxel and radiation therapy but then develops recurrent disease 3 months later. CPS = 5. Regulatory and reimbursement issues aside, what treatment would you recommend?

1. FOLFOX
2. Other chemotherapy
3. Pembrolizumab
4. Nivolumab
5. Nivolumab + chemotherapy
6. Other

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

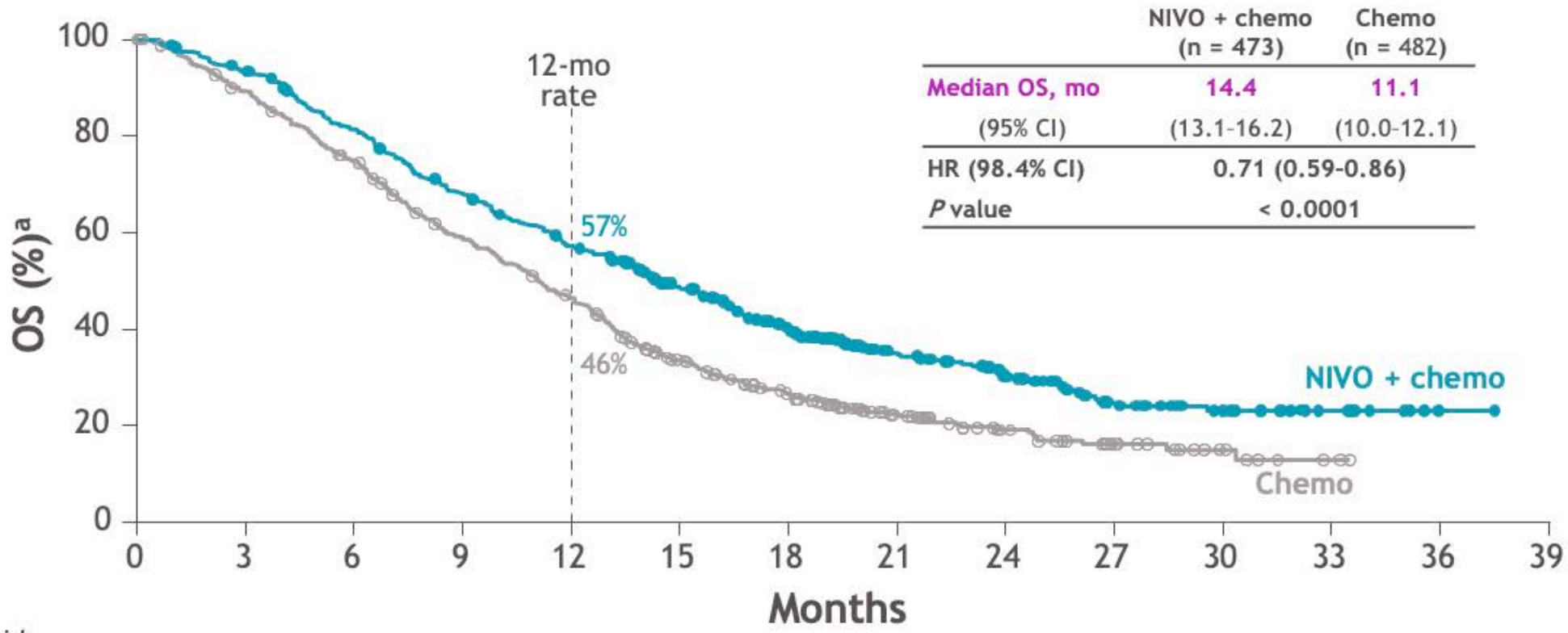
1. TAS-102
2. Other chemotherapy
3. Pembrolizumab
4. Nivolumab
5. Trastuzumab deruxtecan
6. Palliative care
7. Other

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

Moehler M et al.

ESMO 2020;Abstract LBA6.

CheckMate 649: Dual Primary Endpoint – OS (PD-L1 CPS ≥5)



	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P value	< 0.0001	

No. at risk														
NIVO + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

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

[a]Minimum follow-up 12.1 months.

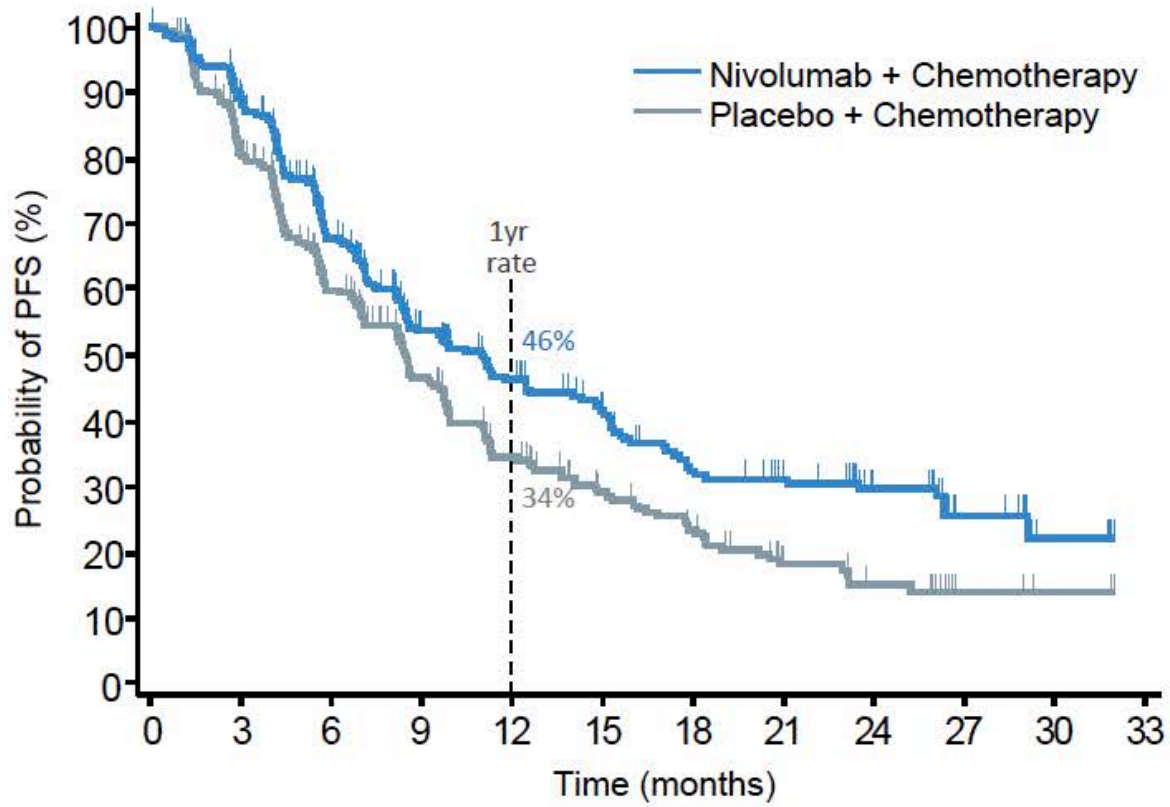
Moehler M et al. ESMO 2020;Abstract LBA6.

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

Boku N et al.

ESMO 2020;Abstract LBA7.

ATTRACTION-4: Survival (Final Analysis)



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

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

Boku N et al. ESMO 2020;Abstract LBA7.

RTP RESEARCH TO PRACTICE

Original Investigation

September 3, 2020

Efficacy and Safety of Pembrolizumab or Pembrolizumab Plus Chemotherapy vs Chemotherapy Alone for Patients With First-line, Advanced Gastric Cancer

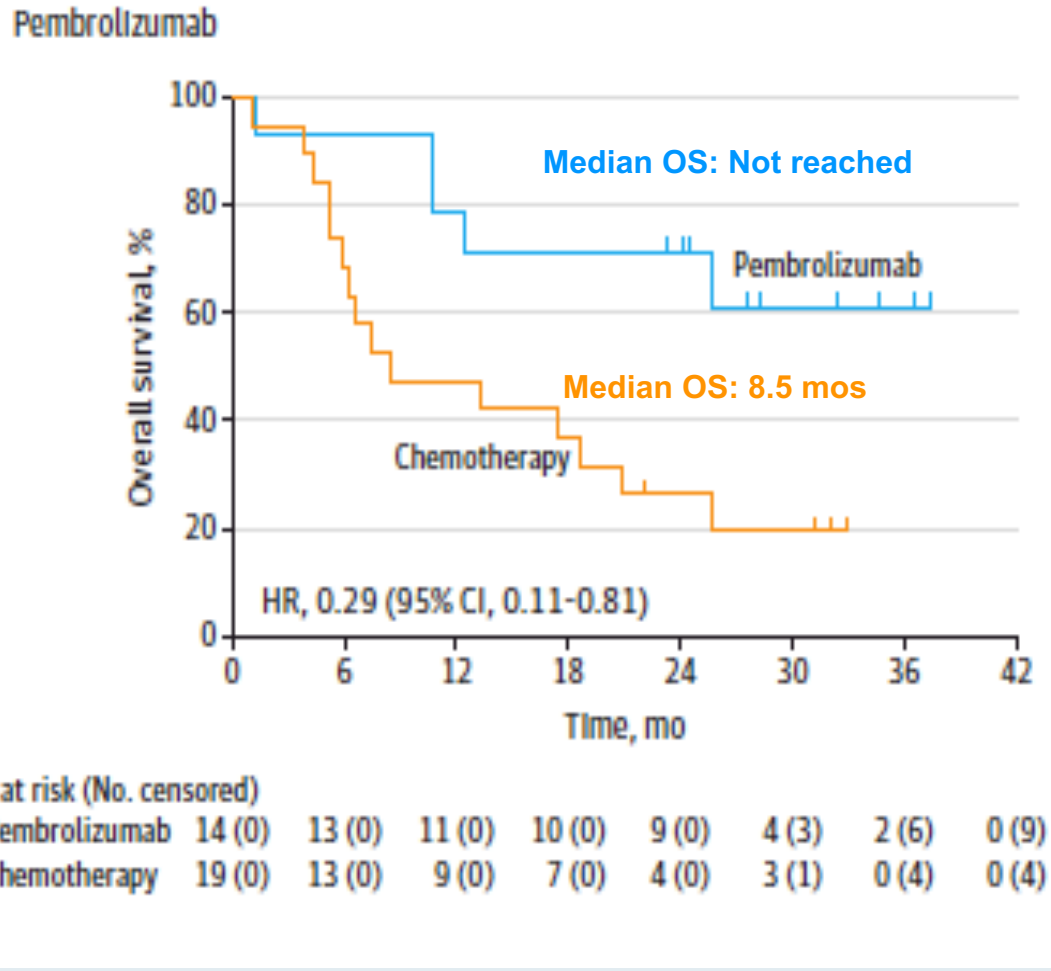
The KEYNOTE-062 Phase 3 Randomized Clinical Trial

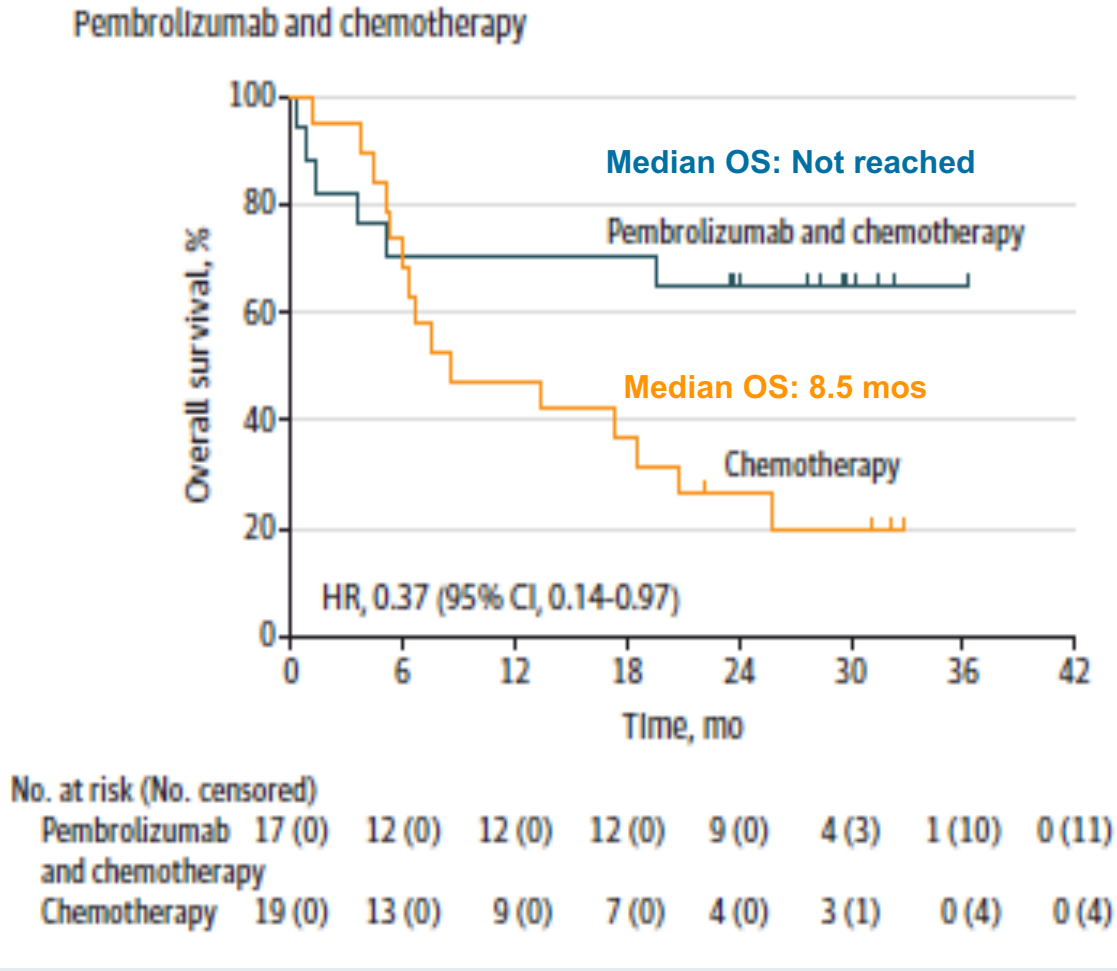
Kohei Shitara, MD[1]; Eric Van Cutsem, MD[2]; Yung-Jue Bang, MD[3]; et al

» Author Affiliations

JAMA Oncol. 2020;6(10):1571-1580. doi:10.1001/jamaoncol.2020.3370

KEYNOTE-062: Exploratory Analysis of OS in MSI-H Tumors with PD-L1 CPS ≥1





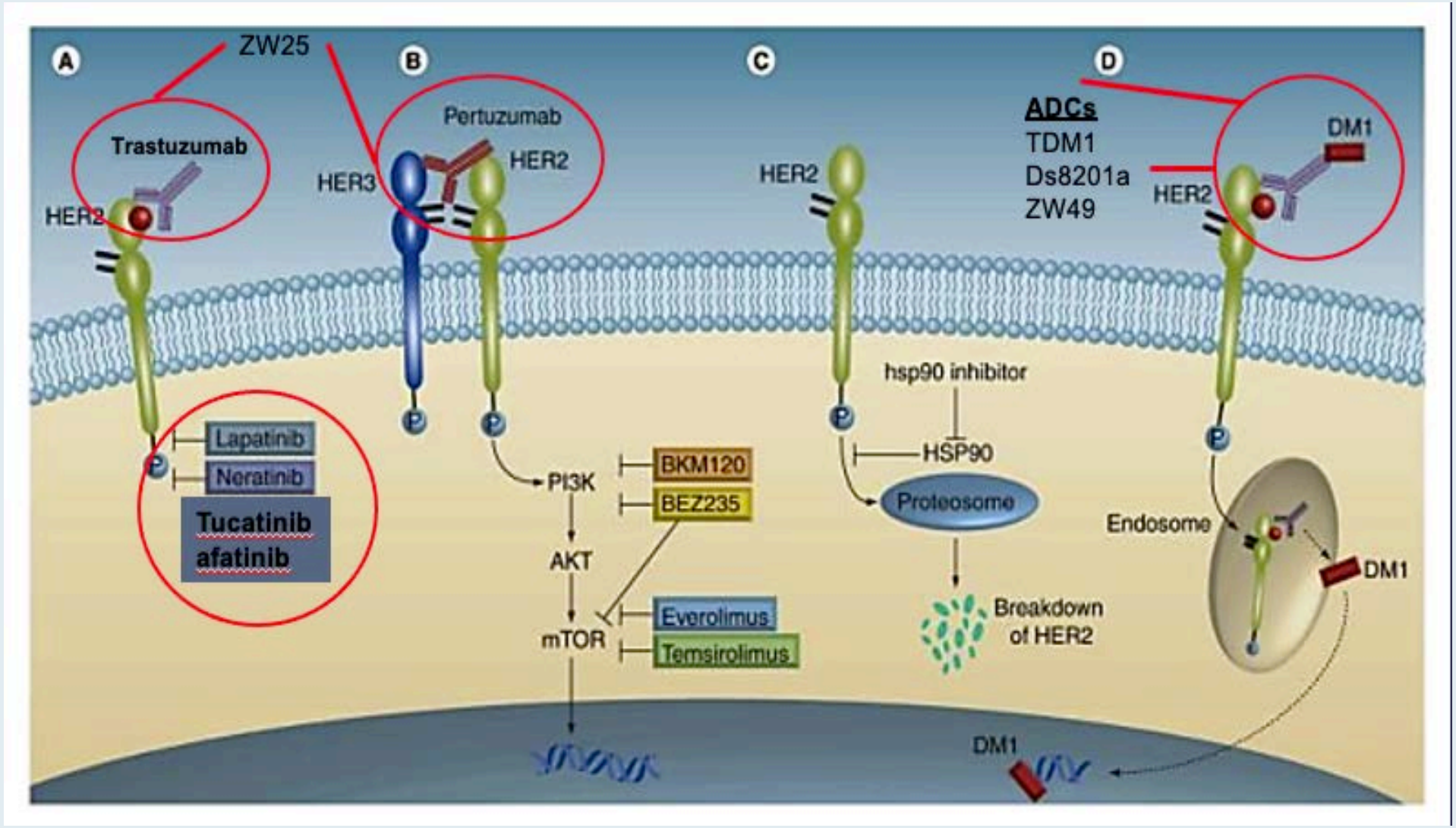
Shitara K et al. *JAMA Oncol* 2020;6(10):1571-80.

RTP RESEARCH TO PRACTICE

Anti-HER2 Therapies

HER2 amp
~10-15% GEA

~10% Gastric
~15-20% EGJ



Gajria, Chandarlapaty. HER2-amplified breast cancer: mechanisms of trastuzumab resistance and novel targeted therapies. *Expert Rev Anticancer Ther* 2011

RTP RESEARCH TO PRACTICE

FDA Approves Trastuzumab Deruxtecan for HER2-Positive Gastric Adenocarcinomas

Press Release – January 15, 2021

"On 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."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-fam-trastuzumab-deruxtecan-nxki-her2-positive-gastric-adenocarcinomas

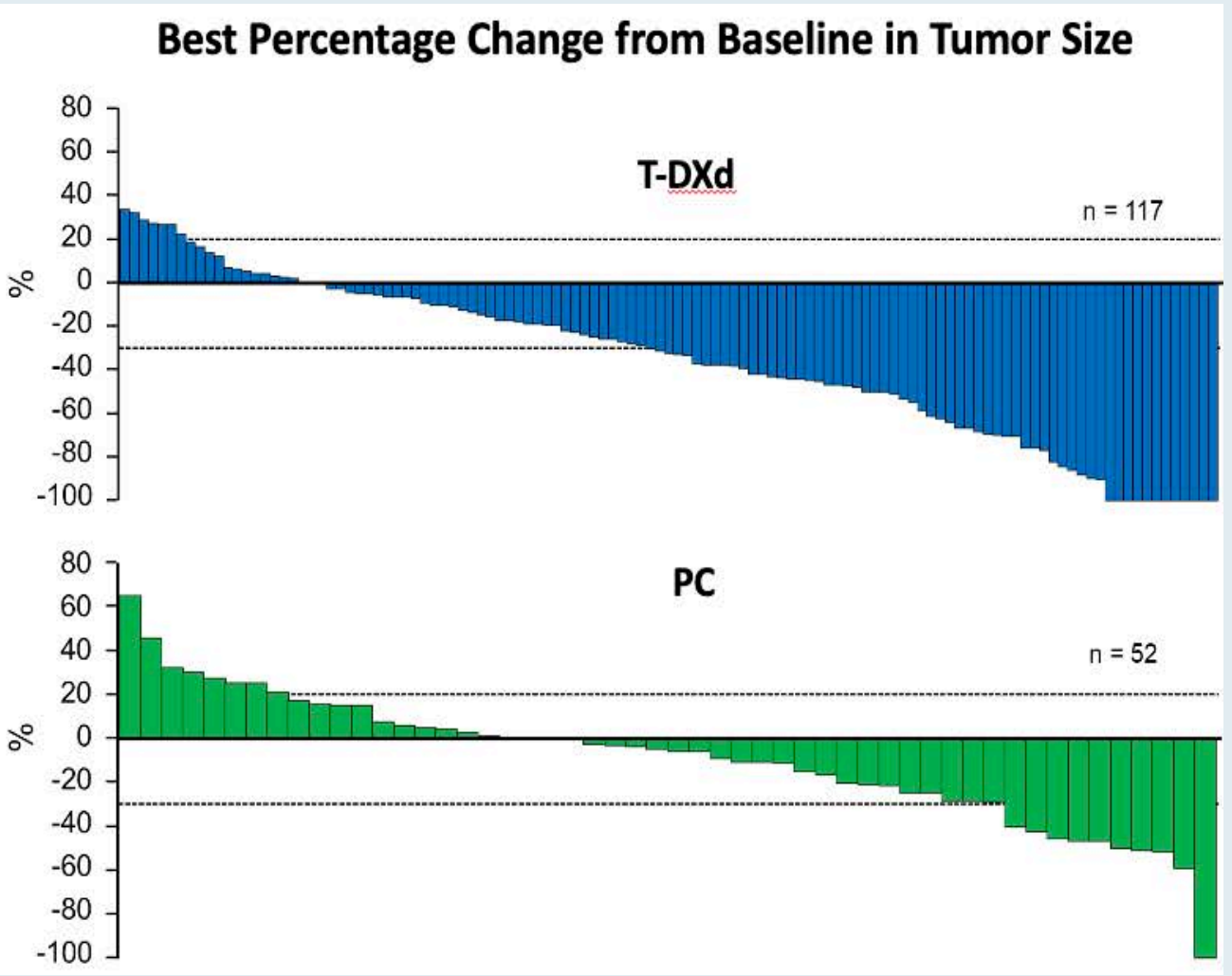
Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients (pts) with HER2-Positive Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma: A Randomized, Phase 2, Multicenter, Open-Label Study (DESTINY-Gastric01)

Yamaguchi K et al.

ESMO World GI Congress 2020;Abstract O-11.

DESTINY-Gastric01: Objective Response Rate (Primary Endpoint)

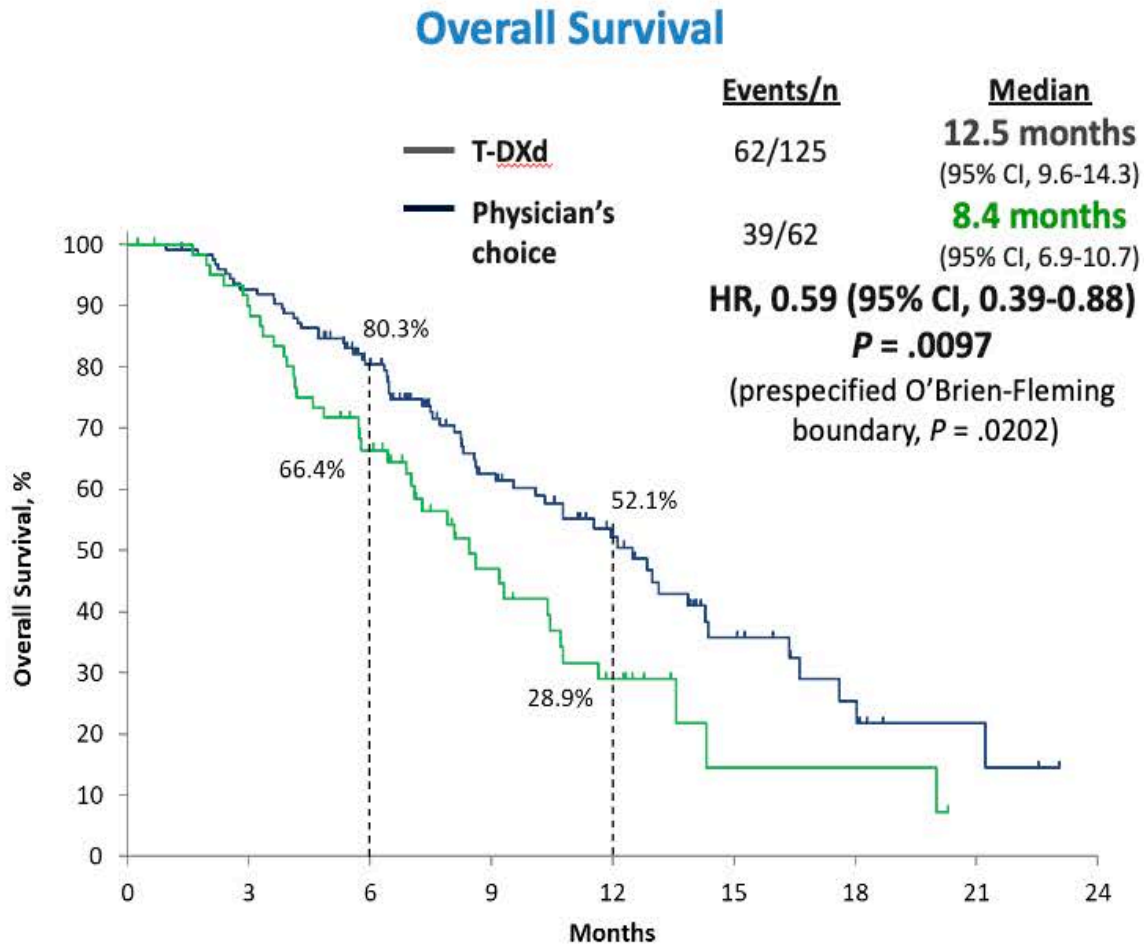
	T-DXd (n = 119)	PC (n = 56)
ORR by ICR (CR + PR)	**51.3% (n = 61)** 95% CI, 41.9-60.5; *P* < .0001	**14.3% (n = 8)** 95% CI, 6.4-26.2
Confirmed ORR by ICR (CR + PR)	**42.9% (n = 51)** 95% CI, 33.8-52.3	**12.5% (n = 7)** 95% CI, 5.2-24.1
CR	8.4% (n = 10)	0
PR	34.5% (n = 41)	12.5% (n = 7)
SD	42.9% (n =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

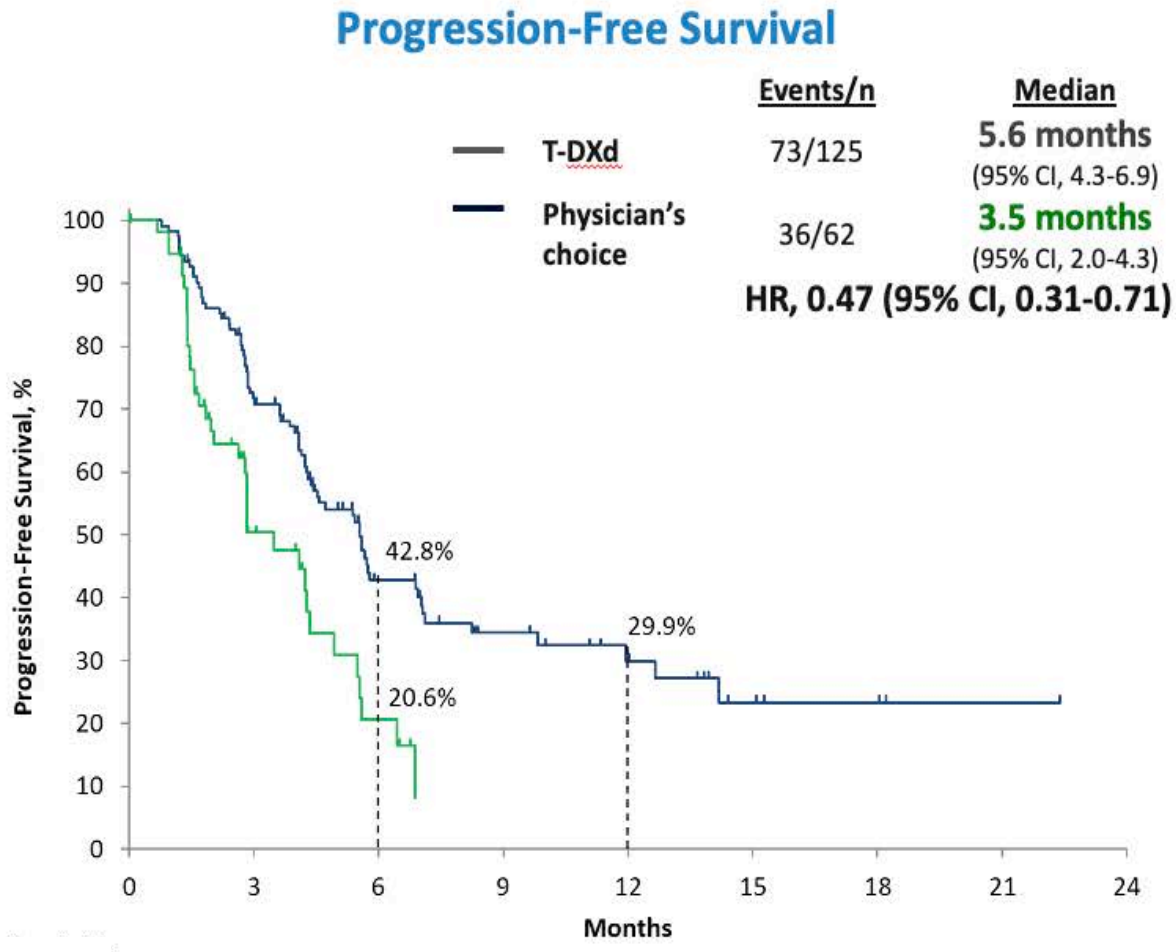


Yamaguchi K et al. ESMO World GI Congress 2020;Abstract O-11.

RTP RESEARCH TO PRACTICE

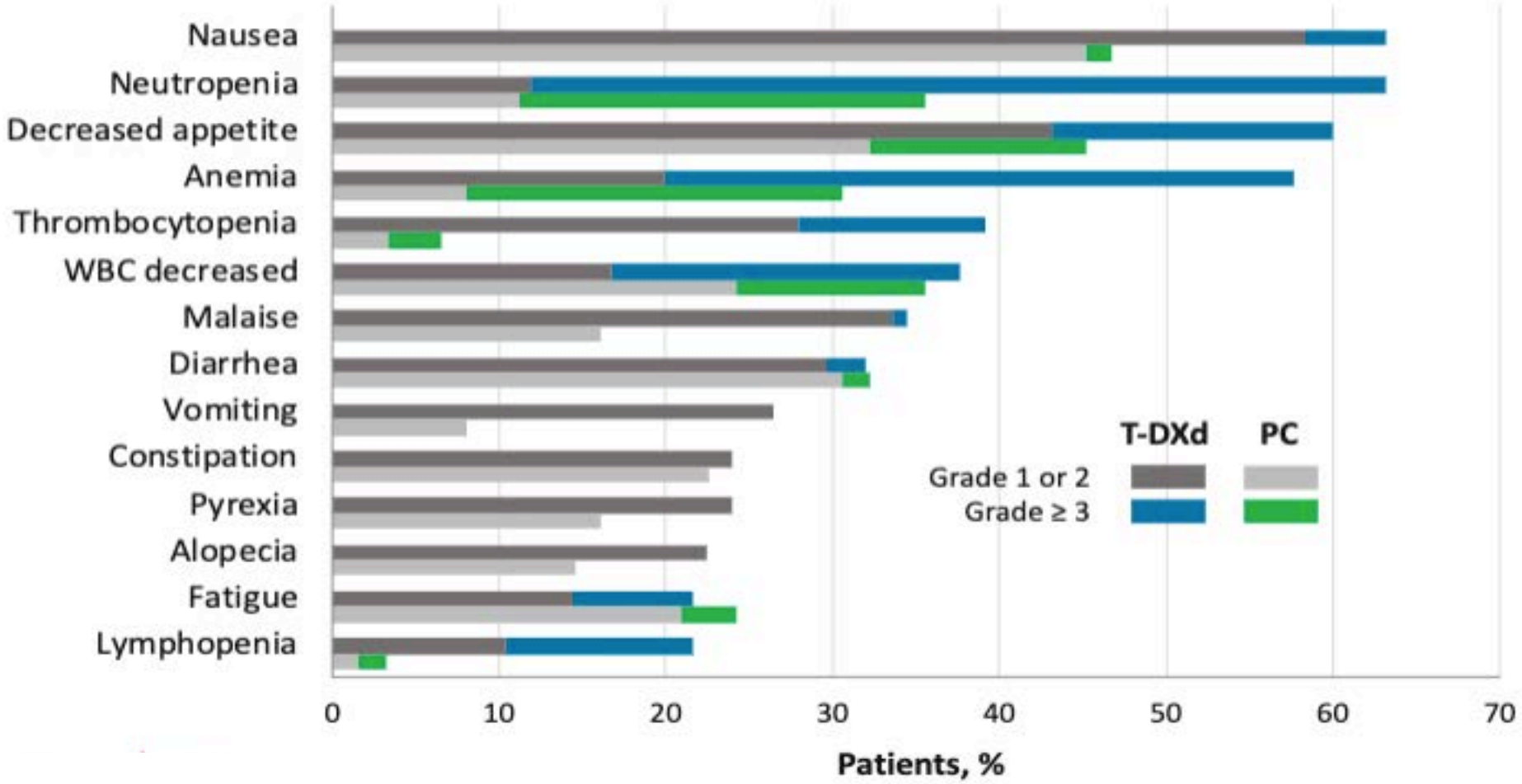
DESTINY-Gastric01: Survival





Yamaguchi K et al. ESMO World GI Congress 2020;Abstract O-11.

DESTINY-Gastric01: Treatment-Emergent Adverse Events in ≥20% of Patients



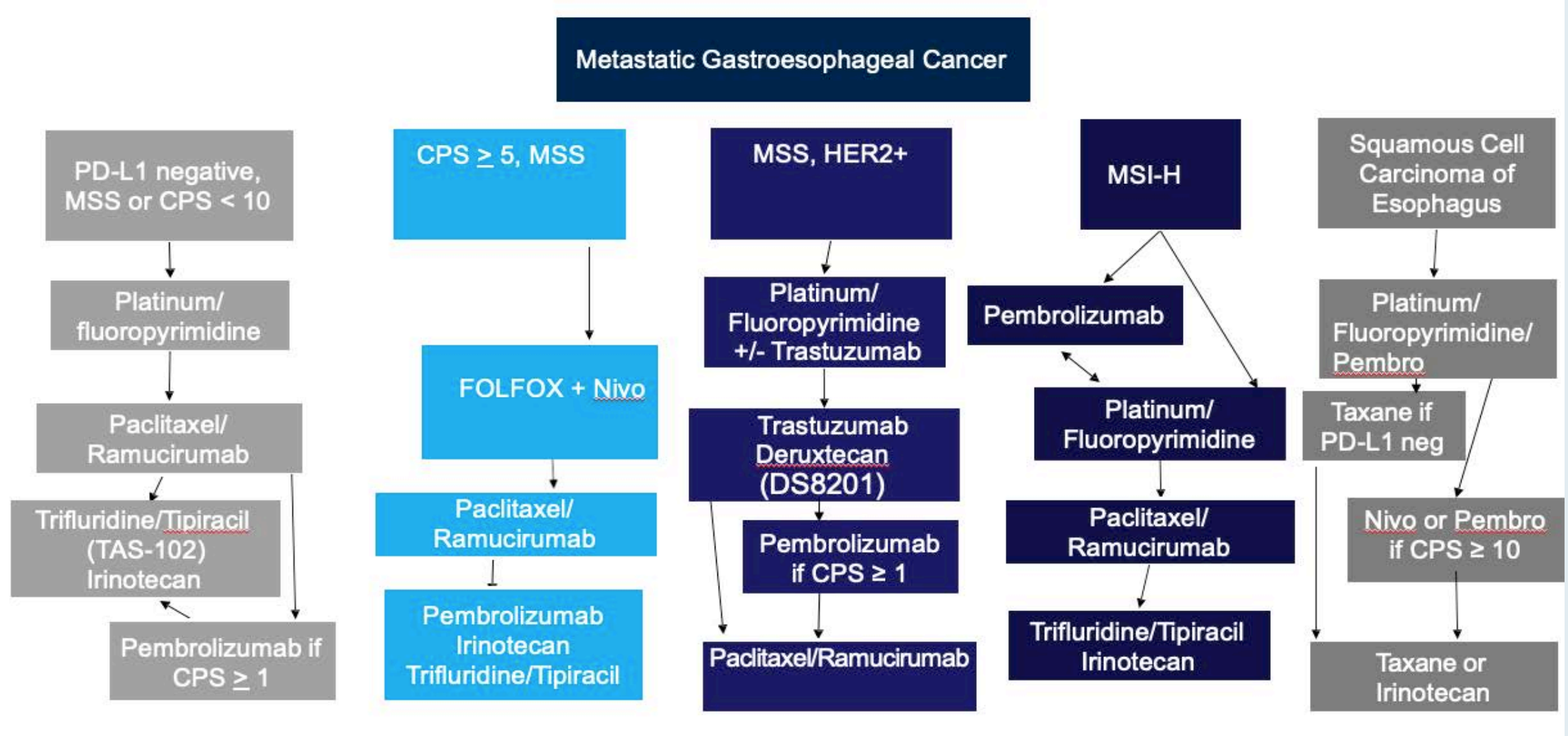
Yamaguchi K et al. ESMO World GI Congress 2020;Abstract O-11.

Ongoing Phase III Trial of Trastuzumab Deruxtecan in HER2-Positive Gastric Cancer

Trial (NCT#)	Phase	Target (N)	Setting	Treatment arms
DESTINY-Gastric04 (NCT04704934)	III	490	Metastatic and/or unresectable gastric or GEJ adenocarcinoma; Progression on/after trastuzumab-based regimen	• Trastuzumab deruxtecan • Ramucirumab + paclitaxel

Clinicaltrials.gov; Accessed February 2021.

How to Treat Gastroesophageal Cancer in 2020?



Courtesy of Zev Wainberg, MD, MSc.

FDA Approves Nivolumab for Esophageal Squamous Cell Carcinoma

Press Release – June 10, 2020

"On June 10, 2020, the Food and Drug Administration approved nivolumab for patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.

Efficacy was investigated in ATTRACTION-3 (NCT02569242), a multicenter, randomized (1:1), active-controlled, open-label trial in 419 patients with unresectable advanced, recurrent, or metastatic ESCC. Patients who were refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen received nivolumab 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=210), or investigator's choice of taxane chemotherapy consisting of docetaxel (75 mg/m^2 intravenously every 3 weeks) or paclitaxel (100 mg/m^2 intravenously once a week for 6 weeks followed by 1 week off) (n=209)."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-nivolumab-esophageal-squamous-cell-carcinoma

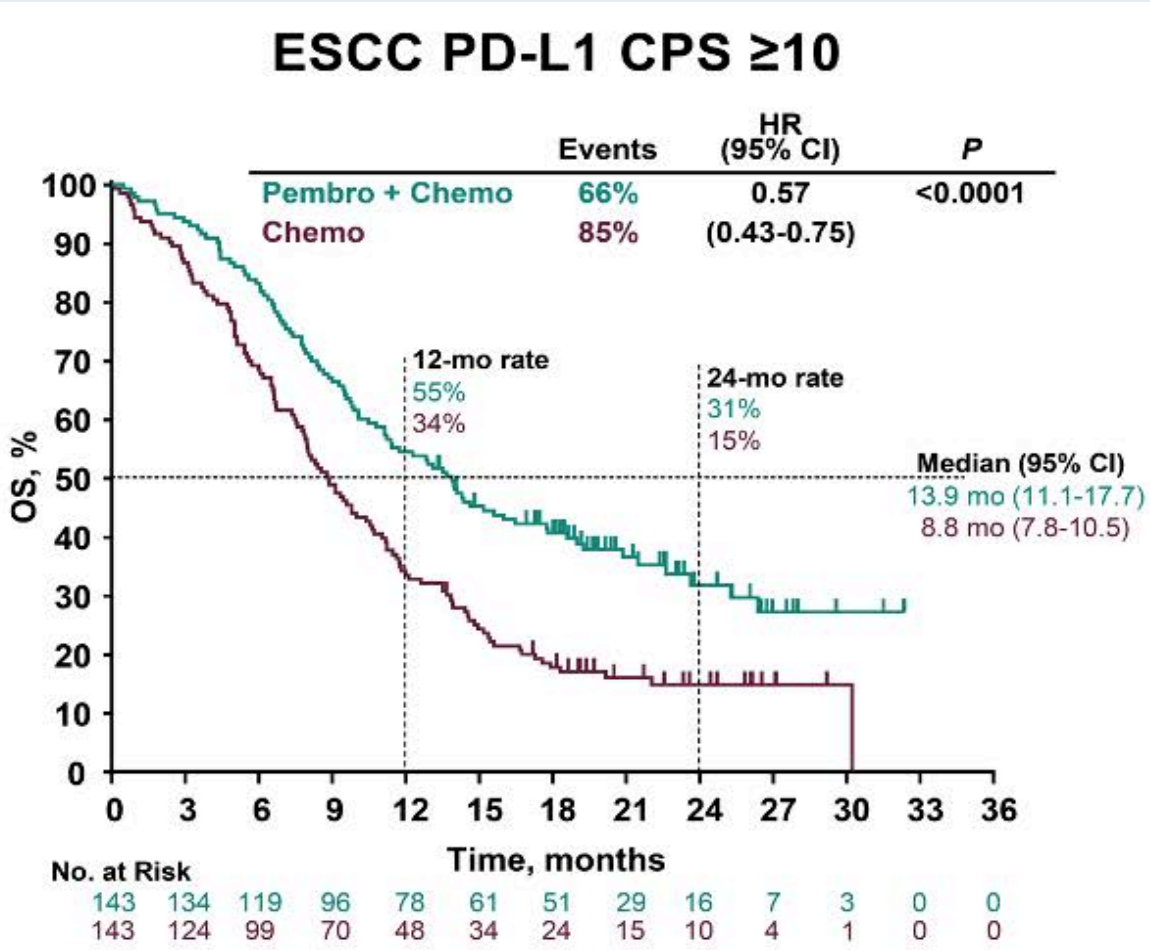
RTP RESEARCH TO PRACTICE

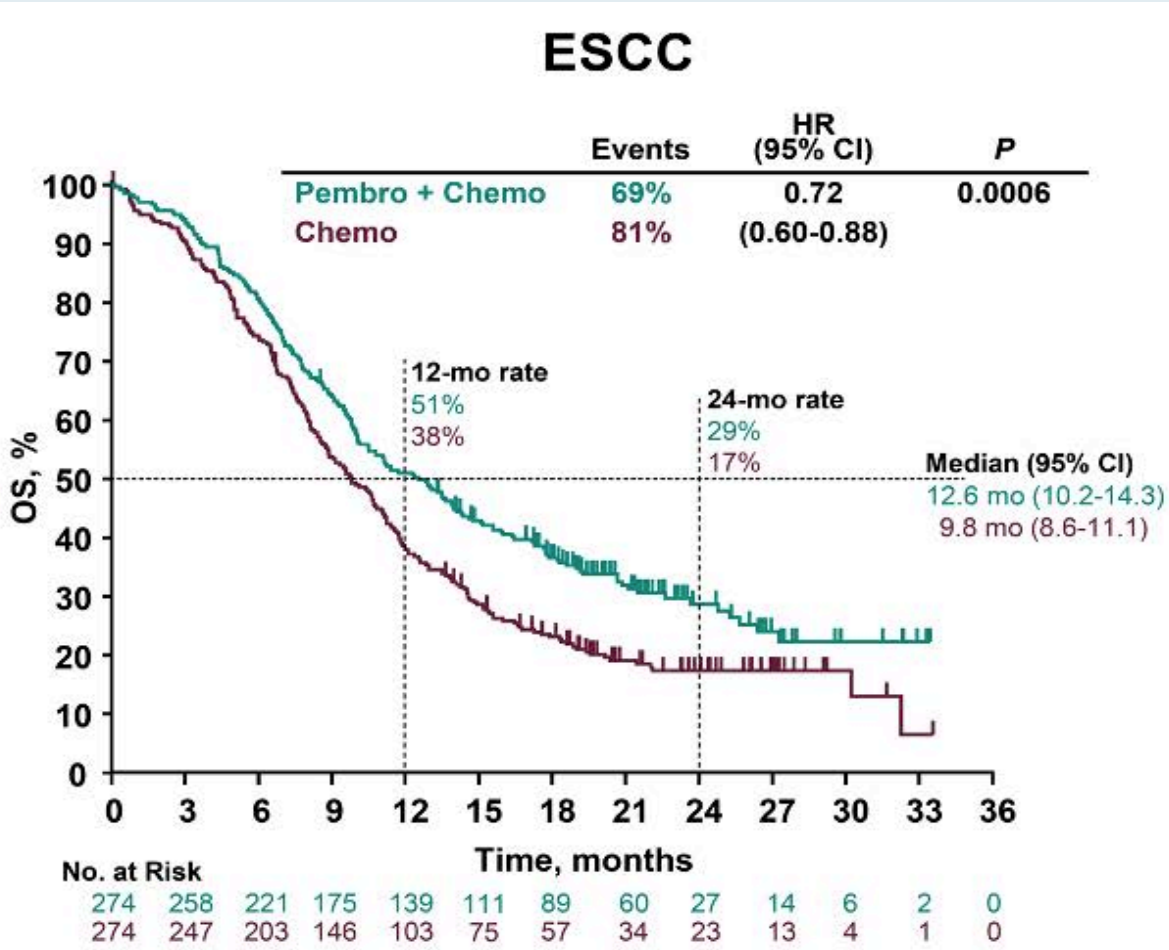
Pembrolizumab plus Chemotherapy versus Chemotherapy as First-Line Therapy in Patients with Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study

Kato K et al.

ESMO 2020;Abstract LBA8_PR.

KEYNOTE-590: OS in Patients with ESCC

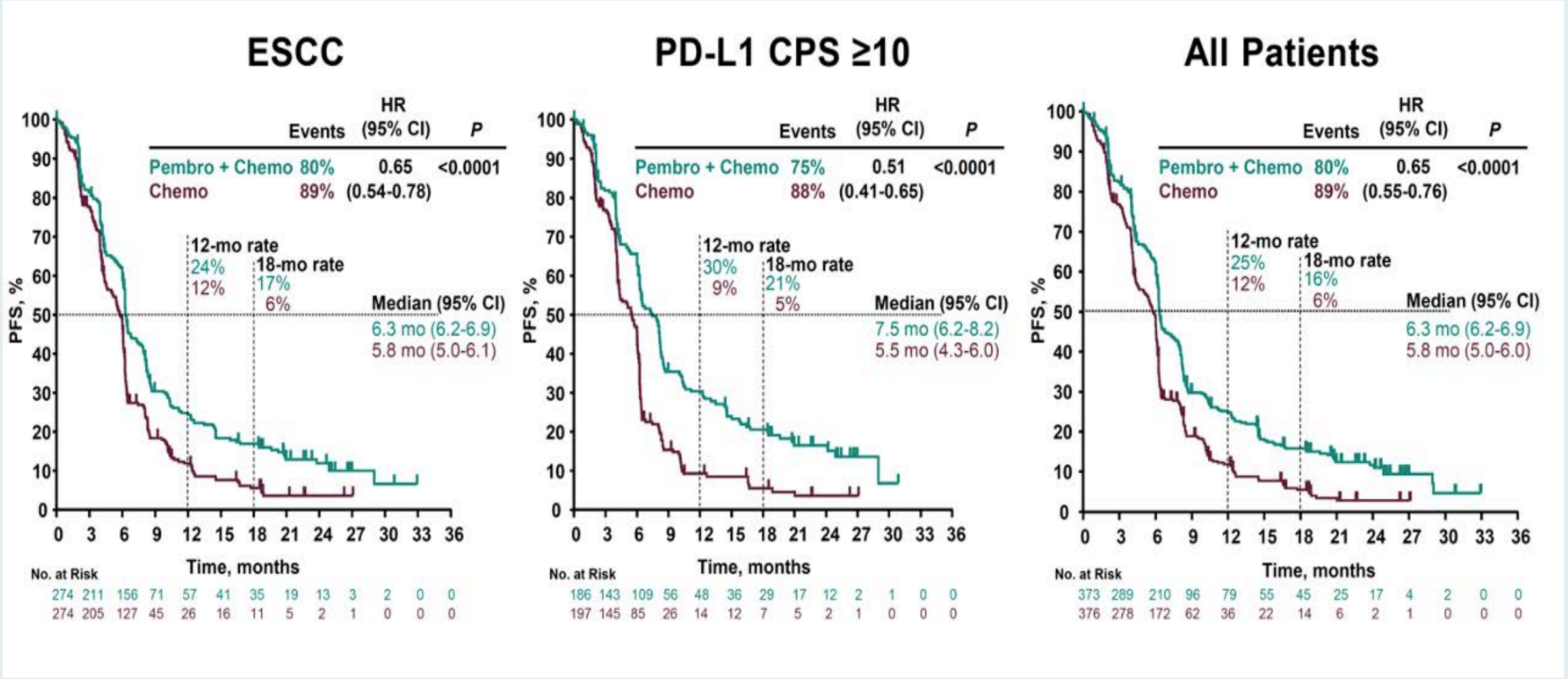




Kato K et al. ESMO 2020;Abstract LBA8.

RTP RESEARCH TO PRACTICE

KEYNOTE-590: PFS Results

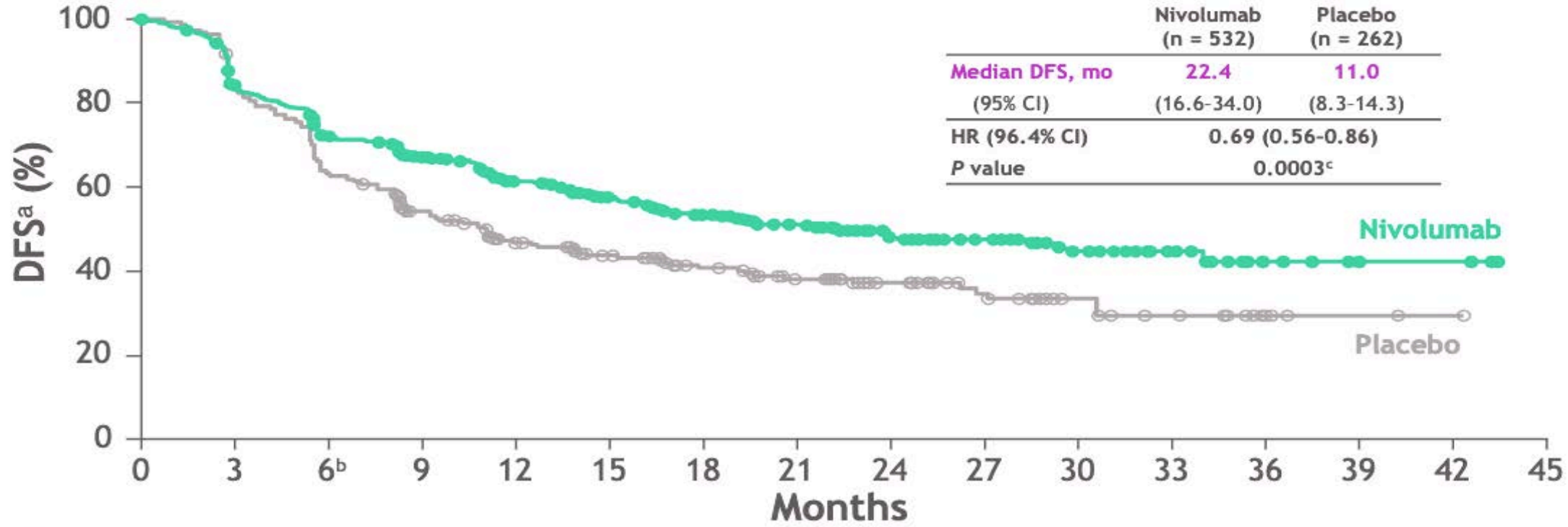


Kato K et al. ESMO 2020;Abstract LBA8.

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer (EC/GEJC) Following Neoadjuvant Chemoradiation Therapy (CRT): First Results of the CheckMate 577 Study

Kelly RJ et al.
ESMO 2020;Abstract LBA9_PR.

CheckMate 577: Adjuvant Nivolumab After Neoadjuvant CRT/Resection in Esophageal/GEJ Cancer



	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

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

Kelly RJ et al. ESMO 2020;Abstract LBA9_PR.

Agenda

Module 1: Colorectal Cancer

- Dr Deutsch: A 55-year-old man with mCRC – MSS, BRAF V600E mutation

Module 2: Gastric/Gastroesophageal and Esophageal Cancers

- Dr Favaro: An 82-year-old man with gastric/esophageal cancer with HER2 amplification

Module 3: Hepatocellular Carcinoma (HCC)

- Dr Shehadeh: A 70-year-old man with newly diagnosed Child-Pugh A HCC
- Dr Mitchell: A woman in her 80s with unresectable HCC and cirrhosis

Module 4: Pancreatic Adenocarcinoma (PAD)

- Dr Deutsch: A 56-year-old man with localized PAD
- Dr Mohamed: A 57-year-old man with metastatic PAD and a BRCA2 mutation

Module 5: Cholangiocarcinoma

- Dr Shehadeh: A 59-year-old man with unresectable cholangiocarcinoma with a HER2 mutation

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Shehadeh: A 70-year-old man with newly diagnosed Child-Pugh A HCC

Dr Nasfat Shehadeh

- PMH: Treated hepatitis C, alcohol abuse
- 11/2020: Child-Pugh A HCC (MELD: 7) heavily involving the right lobe (see images), with no extrahepatic disease
  - AFP: 63,000 ng/mL
- Referred for liver-directed therapy (delayed due to social issues)
- 1/2021: Admitted with SOB, wide complex tachycardia, probably alcohol-induced cardiomyopathy
  - Currently stable on medications, EF: 35%, PS 1
- Interventional radiology/radiation oncology plan: yttrium-90 radioembolization

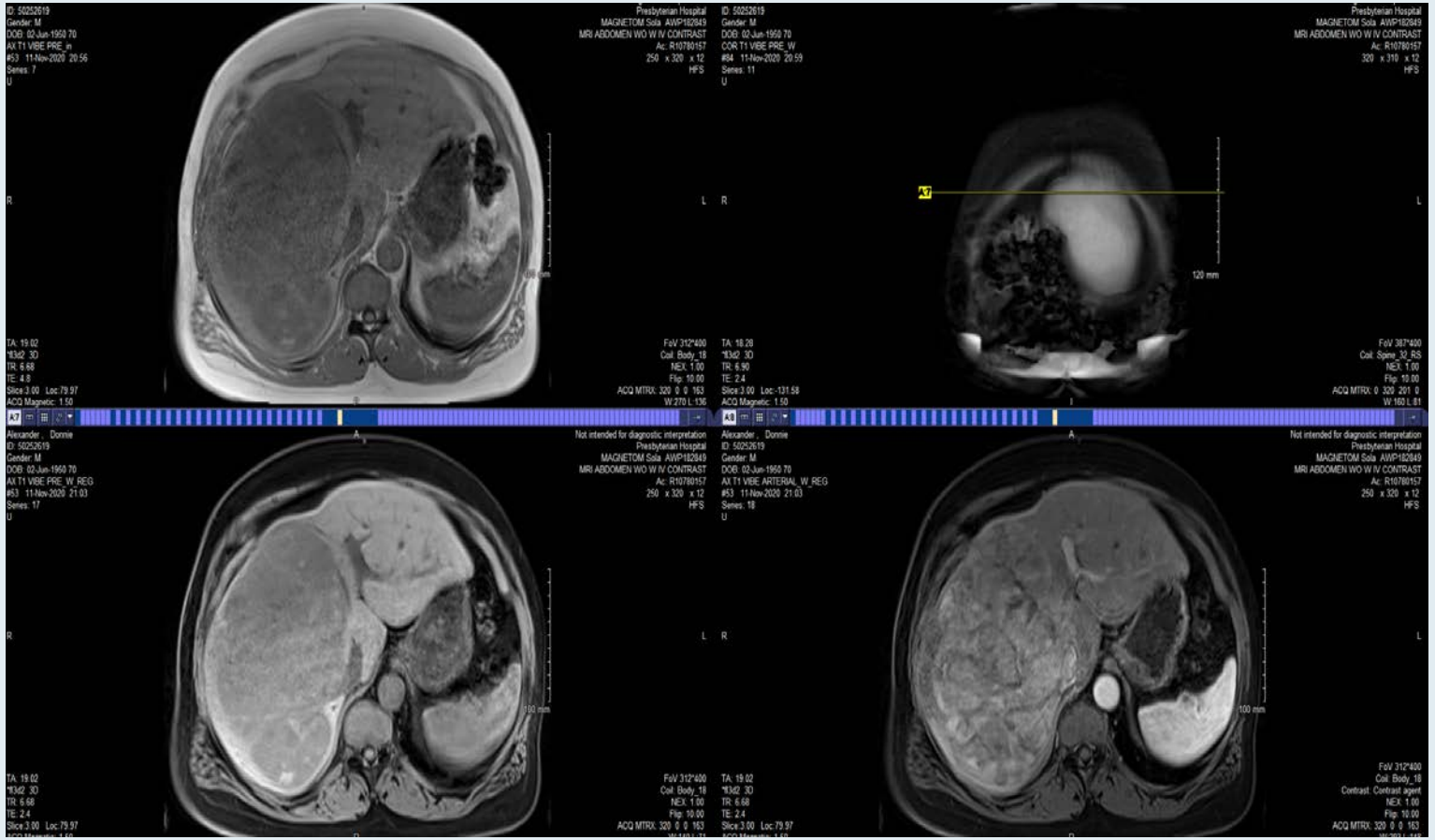
Questions

- How to decide between radioembolization vs chemoembolization for patients like him? Since his right lobe is almost totally occupied by HCC, do you consider multi-stage embolization, and how often?
- What about future TKI and IO in the context of his significant cardiomyopathy?

Case Presentation – Dr Shehadeh: A 70-year-old man with newly diagnosed Child-Pugh A HCC (continued)

Dr Nasfat Shehadeh

MRI Abdomen (11/11/2020)



Case Presentation – Dr Mitchell: A woman in her 80s with unresectable HCC and cirrhosis

Dr William Robert Mitchell

- Diagnosed with unresectable HCC with cirrhosis
- Patient has end-stage renal disease (dialysis 3 times a week)
- Preference would be to administer immunotherapy plus bevacizumab, however concerns exist regarding the use of bevacizumab in patients with renal disease
- Patient is currently treated with single-agent immunotherapy

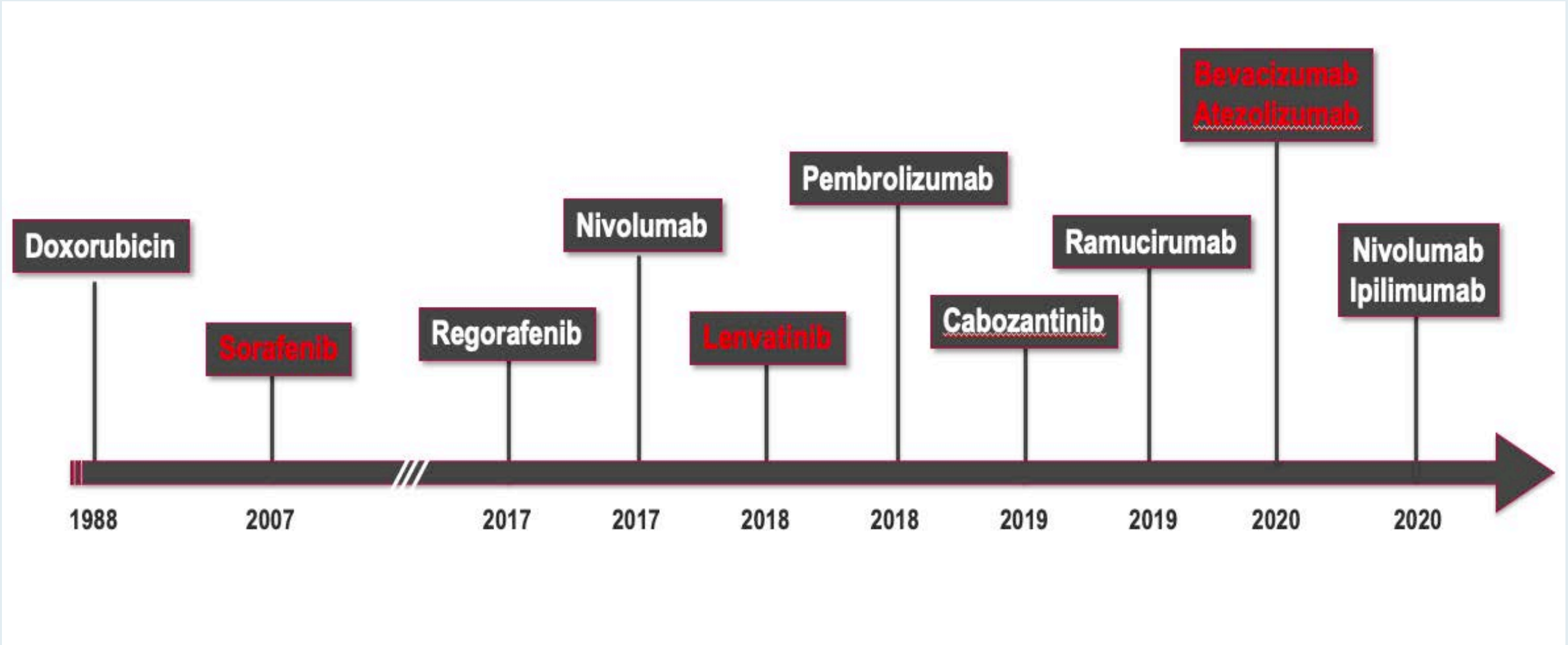
Questions

- There are so many treatment options when dealing with advanced disease, how do you select among them? Where is the sweet spot in terms of considering efficacy, compliance, cost and quality of life?

What would be your second-line therapy for a 65-year-old patient with HCC, a Child-Pugh A score and PS 0 who received first-line atezolizumab/bevacizumab and experienced disease progression after 18 months (AFP 2,500 ng/mL)?

1. Cabozantinib
2. Lenvatinib
3. Anti-PD-1 antibody
4. Nivolumab/ipilimumab
5. Ramucirumab
6. Regorafenib
7. Sorafenib
8. Other

Timeline of the FDA approval for HCC treatments



Courtesy of Tim Greten, MD

RTP RESEARCH TO PRACTICE

FDA Approves Atezolizumab in Combination with Bevacizumab for Unresectable HCC

Press Release – May 29, 2020

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

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

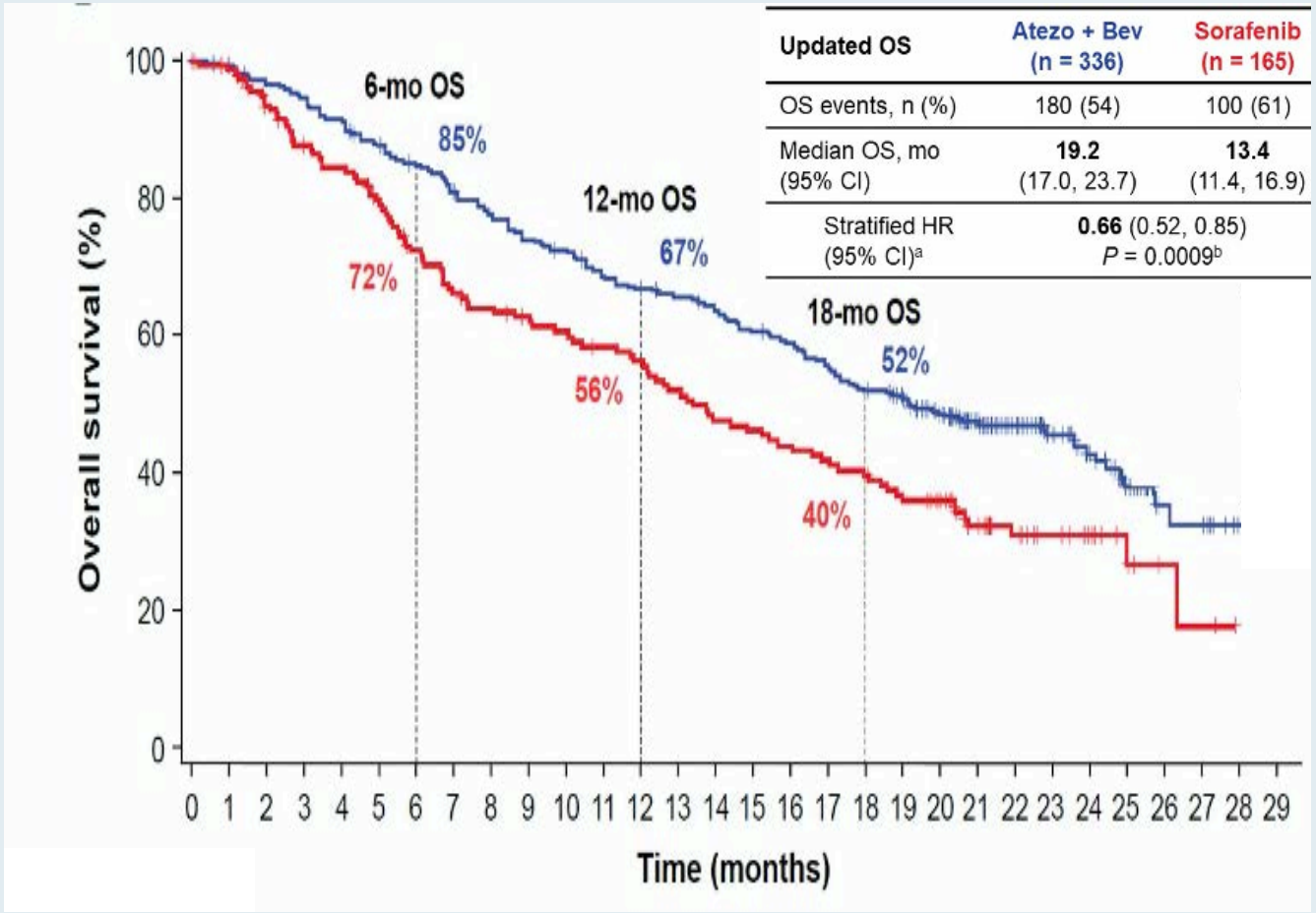
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-nivolumab-esophageal-squamous-cell-carcinoma

IMbrave150: Updated Overall Survival (OS) Data from a Global, Randomized, Open-Label Phase III Study of Atezolizumab (atezo) + Bevacizumab (bev) versus Sorafenib (sor) in Patients (pts) with Unresectable Hepatocellular Carcinoma (HCC)

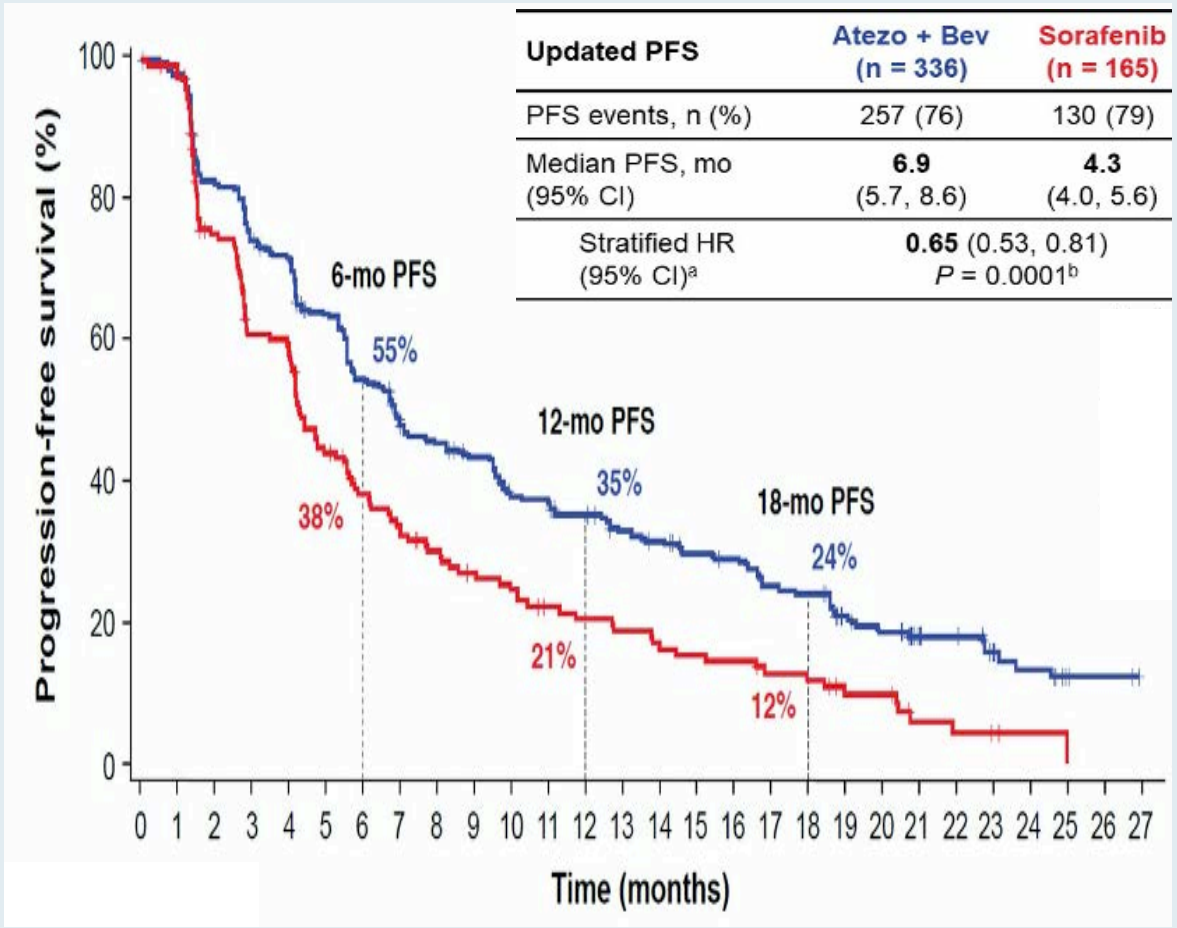
Finn RS et al.

Gastrointestinal Cancers Symposium 2021;Abstract 267.

IMbrave150: Updated OS and PFS (Median Follow-Up = 15.6 Months)



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

IMbrave150: Safety Data

Overall Safety Summary

AEs, n (%)	Atezo + bev (n=329)	Sorafenib (n=156)
Any grade AEs	323 (98)	154 (99)
Treatment-related	276 (84)	147 (94)
Grade 3/4 AEs	186 (57)	86 (55)
Treatment-related Grade 3/4	117 (**36**)	71 (**46**)
Grade 5 AEs	15 (5)	9 (6)
Treatment-related Grade 5	6 (**2**)	1 (**0.6**)
Serious AEs	125 (38)	48 (31)
Treatment-related	56 (17)	24 (15)
AE leading to withdrawal from any drug	51 (16)	16 (10)
AE leading to dose interruption of any treatment	163 (50)	64 (41)
AE leading to dose modification of sorafenib	0	58 (37)

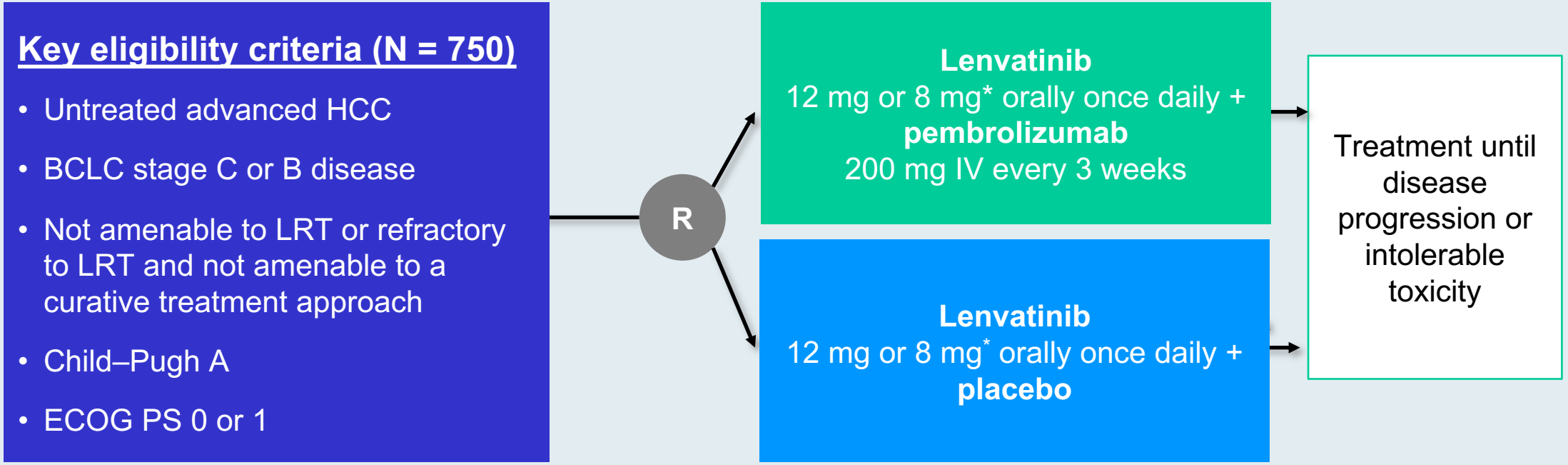
Common AEs (Any Grade ≥15%)

	Atezo + bev (n=329)		Sorafenib (n=156)	
n (%)	All	G3/4	All	G3/4
Hypertension	98 (30)	50 (15)	38 (24)	19 (12)
Fatigue	67 (20)	8 (2)	29 (19)	5 (3)
Proteinuria	66 (20)	10 (3)	11 (7)	1 (0.6)
AST increased	64 (20)	23 (7)	26 (17)	8 (5)
Pruritus	64 (20)	0	15 (10)	0
Diarrhoea	62 (19)	6 (2)	77 (49)	8 (5)
Pyrexia	59 (18)	4 (1)	15 (10)	2 (1)
Decreased appetite	58 (18)	4 (1)	38 (24)	6 (4)
PPES	3 (1)	0	75 (48)	13 (8)
Rash	41 (13)	0	27 (17)	4 (3)
Abdominal pain	40 (12)	4 (1)	27 (17)	4 (3)
Nausea	40 (12)	1 (0.3)	25 (16)	1 (0.6)

Cheng AL et al. ESMO Asia 2019;Abstract LBA3.

Courtesy of Ahmed Kaseb, MD

Ongoing Phase III LEAP-002 Trial Design



- **Primary endpoints:** OS and PFS
- **Secondary endpoints:** ORR, DOR, DCR, and safety

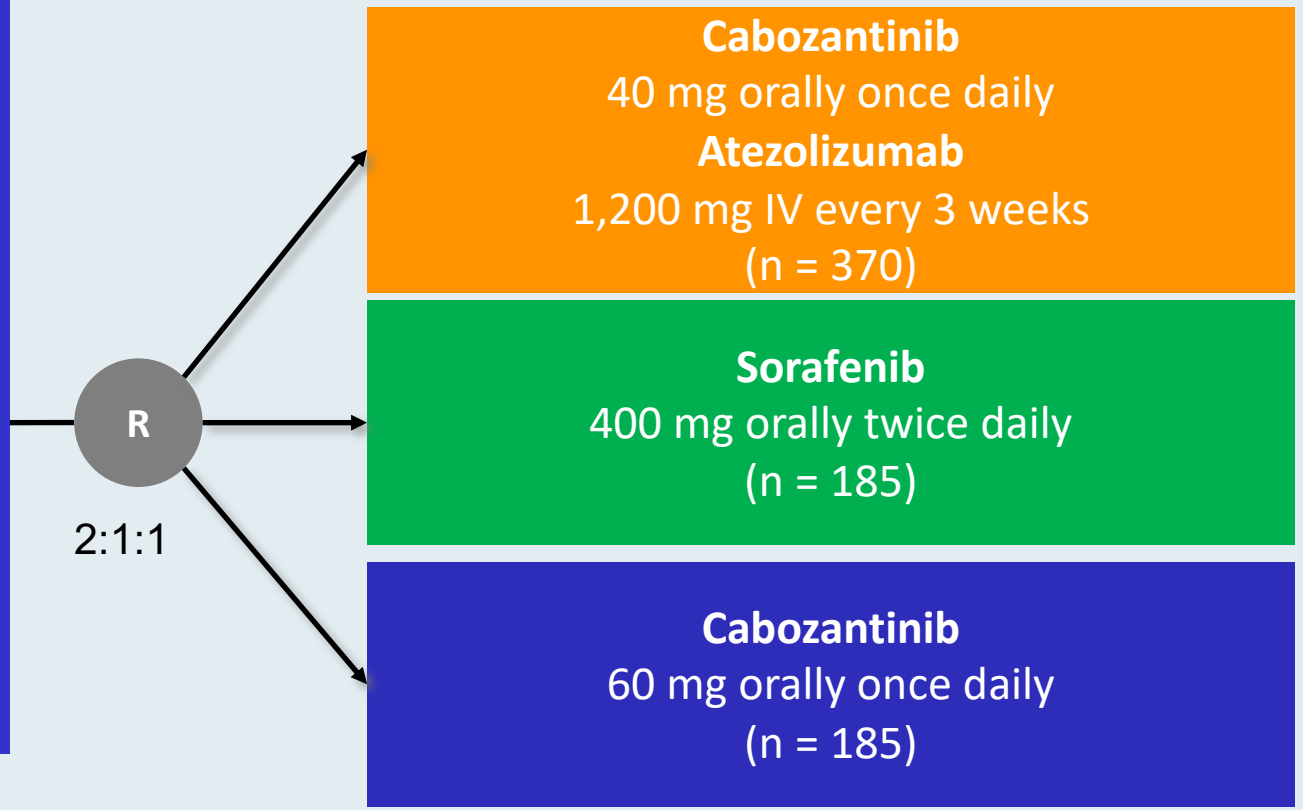
*12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg).

Llovet JM et al. ASCO 2019;Abstract TPS4152.

Ongoing Phase III COSMIC-312 Trial Design

Key eligibility criteria (N = 740)

- Patients with advanced HCC who have not received prior systemic anticancer therapy in the advanced setting
- Histologic or cytologic diagnosis of HCC not amenable to curative treatment
- Measurable disease per RECIST 1.1
- BCLC stage B or C; Child–Pugh A
- ECOG PS of 0 or 1



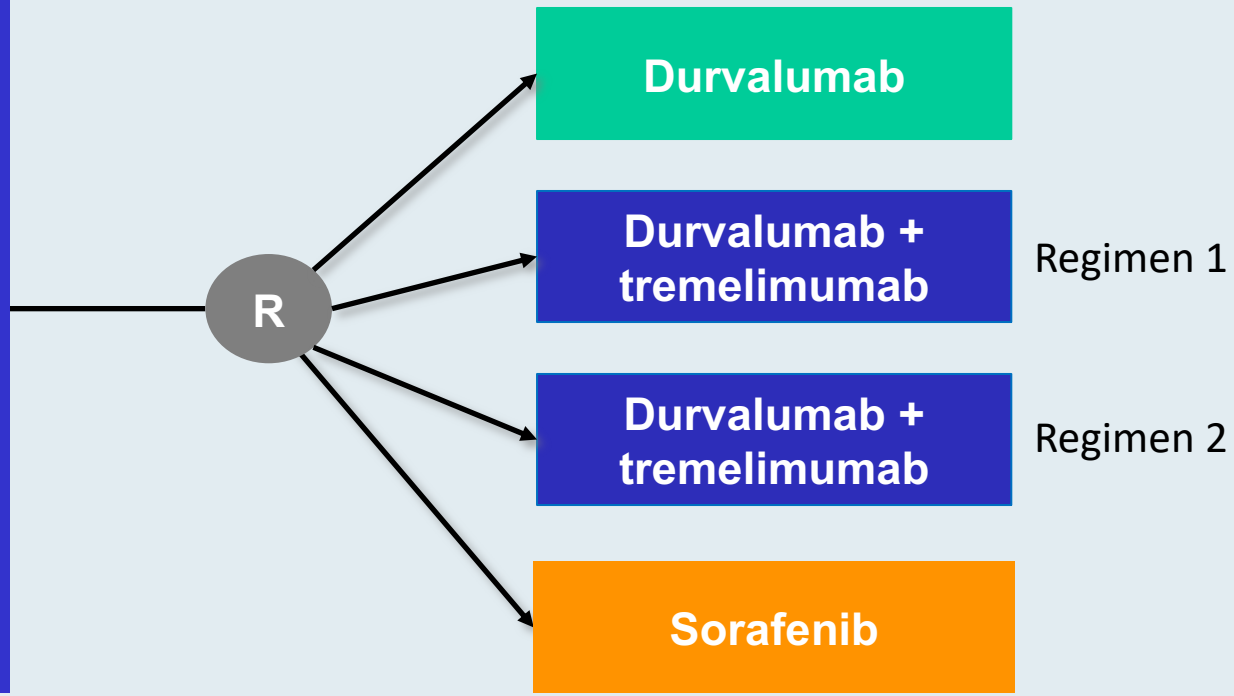
- **Primary endpoints:** PFS and OS

Clinicaltrials.gov/NCT03755791 (Accessed February 2021).

Ongoing Phase III HIMALAYA Trial Design

Key eligibility criteria (N = 1,504)

- Unresectable advanced HCC not eligible for LRTs
- BCLC stage B or C
- Child–Pugh A
- No prior systemic therapy



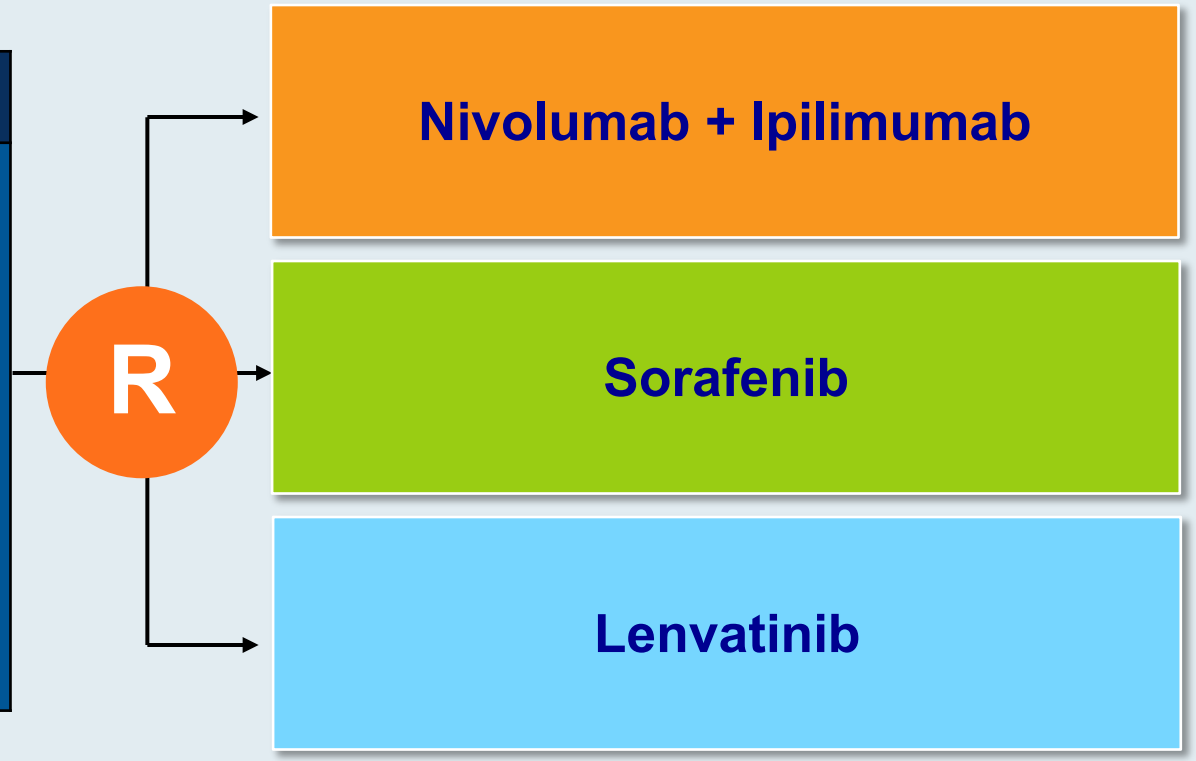
- **Primary endpoint:** OS
- **Other endpoints:** TTP, PFS, ORR, DCR, DoR, and QoL

Clinicaltrials.gov/NCT03298451 (Accessed February 2021).

Ongoing Phase III CheckMate 9DW Trial Design

Key eligibility criteria (N = 650)

- Previously untreated advanced HCC
- Child-Pugh 5 or 6
- ECOG PS 0-1
- No active brain metastases or leptomeningeal metastases



Primary endpoint: Overall survival

Secondary endpoints: ORR, DoR and time to symptom deterioration

Clinicaltrials.gov/NCT04039607 (Accessed February 2021).

FDA Grants Accelerated Approval to Nivolumab and Ipilimumab Combination for HCC

Press Release – March 10, 2020

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

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

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

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-and-ipilimumab-combination-hepatocellular-carcinoma

JAMA Oncology | Original Investigation

Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib

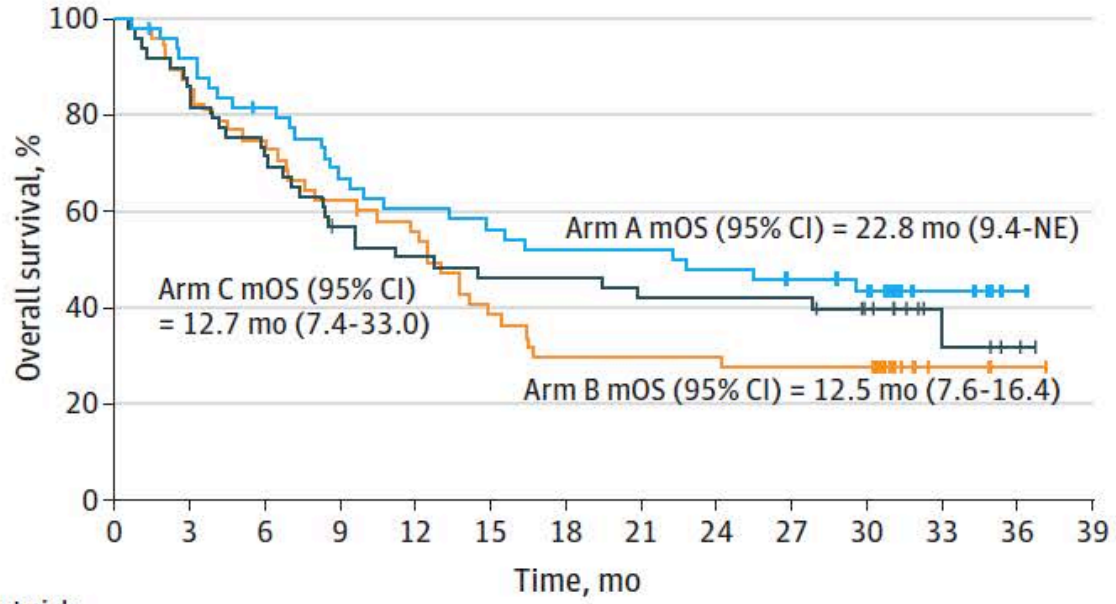
The CheckMate 040 Randomized Clinical Trial

Thomas Yau, MD; Yoon-Koo Kang, MD; Tae-You Kim, MD; Anthony B. El-Khoueiry, MD; Armando Santoro, MD; Bruno Sangro, MD; Ignacio Melero, MD; Masatoshi Kudo, MD; Ming-Mo Hou, MD; Ana Matilla, MD; Francesco Tovoli, MD; Jennifer J. Knox, MD; Aiwu Ruth He, MD; Bassel F. El-Rayes, MD; Mirelis Acosta-Rivera, MD; Ho-Yeong Lim, MD; Jaclyn Neely, PhD; Yun Shen, PhD; Tami Wisniewski, MPH; Jeffrey Anderson, MD; Chiun Hsu, MD, PhD

JAMA Onc 2020;6(11):e204564.

Phase I/II CheckMate-040 Trial: OS Results

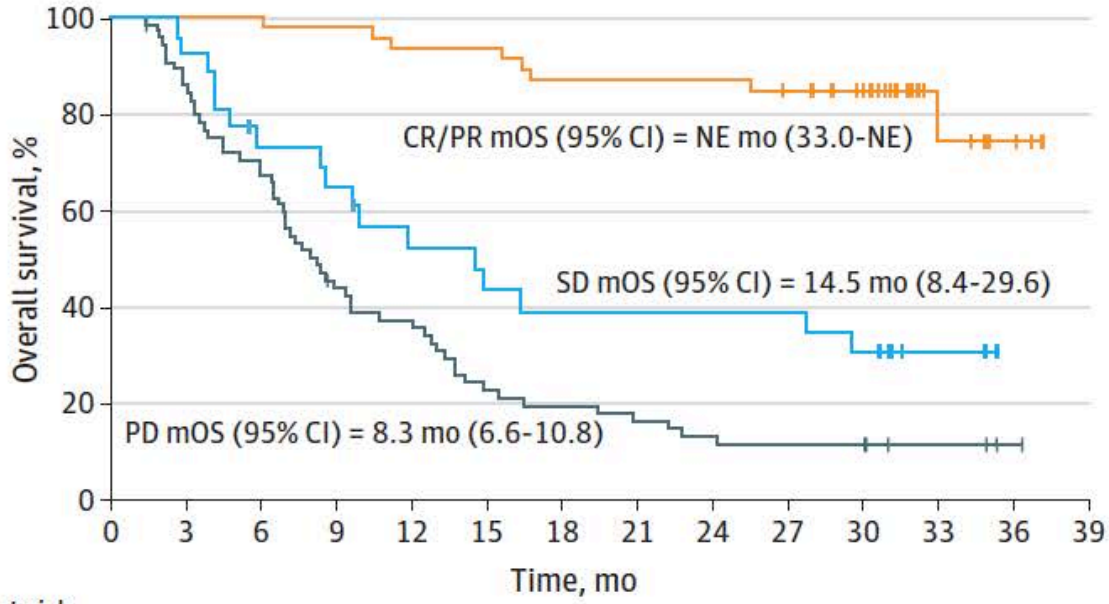
OS by treatment arm



No. at risk (censored)

Arm A	50	45	39	32	29	27	25	25	23	21	19	7	2	0
	(0)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(3)	(4)	(16)	(21)	(23)
Arm B	49	41	36	30	26	18	14	14	14	13	13	2	1	0
	(0)	(1)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(13)	(14)	(15)
Arm C	49	42	36	27	24	22	22	20	20	20	15	4	2	0
	(0)	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(5)	(15)	(17)	(19)

OS by best overall response



No. at risk (censored)[a]

CR/PR	46	46	46	45	43	43	40	40	40	38	33	7	3	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(6)	(31)	(35)	(38)
SD[b]	26	24	18	16	12	10	9	9	9	9	7	2	0	0
	(0)	(0)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(7)	(9)	(9)
PD	65	55	45	27	23	14	12	10	8	7	7	4	2	0
	(0)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(5)	(7)	(9)

Arm A = Nivolumab 1 mg/kg + ipilimumab 3 mg/kg, administered q3wks (4 doses), followed by nivolumab 240 mg q2wks
Arm B = Nivolumab 3 mg/kg + ipilimumab 1 mg/kg, administered q3wks (4 doses), followed by nivolumab 240 mg q2wks
Arm C = Nivolumab 3 mg/kg q2wks + ipilimumab 1 mg/kg q6wks

Yau T et al JAMA Onc 2020;6(11):e204564.

Agenda

Module 1: Colorectal Cancer

- Dr Deutsch: A 55-year-old man with mCRC – MSS, BRAF V600E mutation

Module 2: Gastric/Gastroesophageal and Esophageal Cancers

- Dr Favaro: An 82-year-old man with gastric/esophageal cancer with HER2 amplification

Module 3: Hepatocellular Carcinoma (HCC)

- Dr Shehadeh: A 70-year-old man with newly diagnosed Child-Pugh A HCC
- Dr Mitchell: A woman in her 80s with unresectable HCC and cirrhosis

Module 4: Pancreatic Adenocarcinoma (PAD)

- Dr Deutsch: A 56-year-old man with localized PAD
- Dr Mohamed: A 57-year-old man with metastatic PAD and a BRCA2 mutation

Module 5: Cholangiocarcinoma

- Dr Shehadeh: A 59-year-old man with unresectable cholangiocarcinoma with a HER2 mutation

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Deutsch: A 56-year-old man with localized PAD

Dr Margaret Deutsch

- 8/2020: Presents with left abdominal pain
  - CT scan: 3.9 cm mass in distal body/tail of pancreas
  - EUS with no peripancreatic adenopathy
- Surgical resection : 5.6 cm mass, 0/14 LN positive
  - Stage pT3, pN0, stage IIA
- Adjuvant FOLFIRINOX initiated

Questions

- For young or otherwise healthy patients is FOLFIRINOX now the adjuvant treatment of choice? If he had been stage IA would adjuvant therapy still be recommended?
- Does prognosis vary given location of the malignancy in the pancreas, head versus tail?

Case Presentation – Dr Mohamed: A 57-year-old man with metastatic PAD with a BRCA2 mutation, MSS

Dr Mohamed K Mohamed

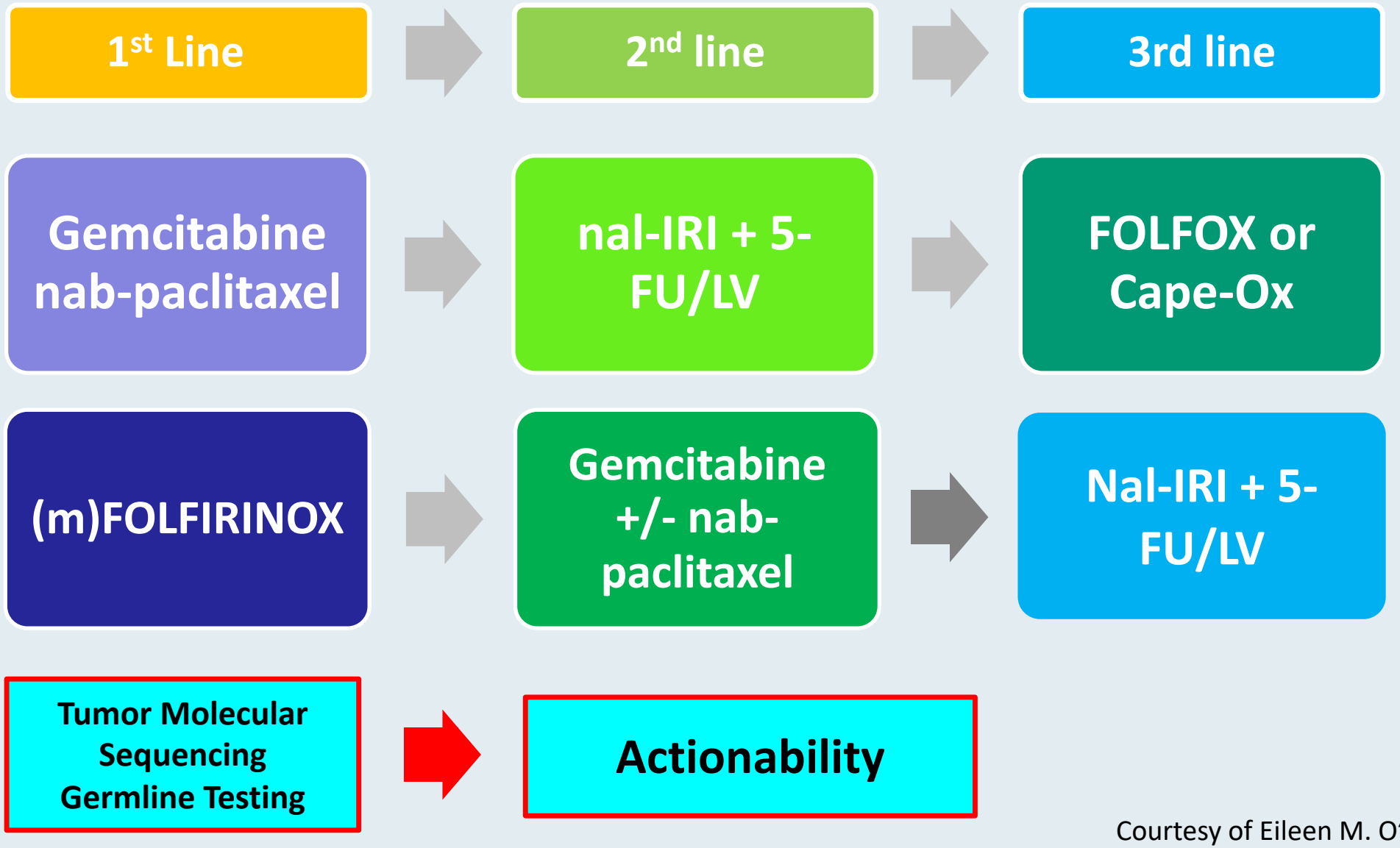
- 2/2018: Presents with abdominal pain, anorexia, weight loss and nausea
  - CT scan: pancreas head mass, peritoneal nodules, liver metastases.
- Genetic testing: MSS, TMB 6 Mut/Mb, BRCA2 exon 11 rearrangement
- 1/2019 - 7/2019: FOLFIRINOX with marked clinical improvement
- 8/2019: Treatment changed to FOLFIRI with continued response in CT scans
- 5/2020: New left chest wall mass detected and FOLFIRINOX resumed
- 1/2021: CT scan shows enlarging destructive chest wall mass, no other evidence of progression, ca19-9 higher, now with mild chest wall pain

Questions

- What treatment would you recommend next? Should we just radiate the chest wall?
- Should I switch to gemcitabine/nab-paclitaxel or should I use a PARP inhibitor due to the BRCA2 mutation?

RTP RESEARCH TO PRACTICE

Therapeutic Approach: Advanced PDAC 2020



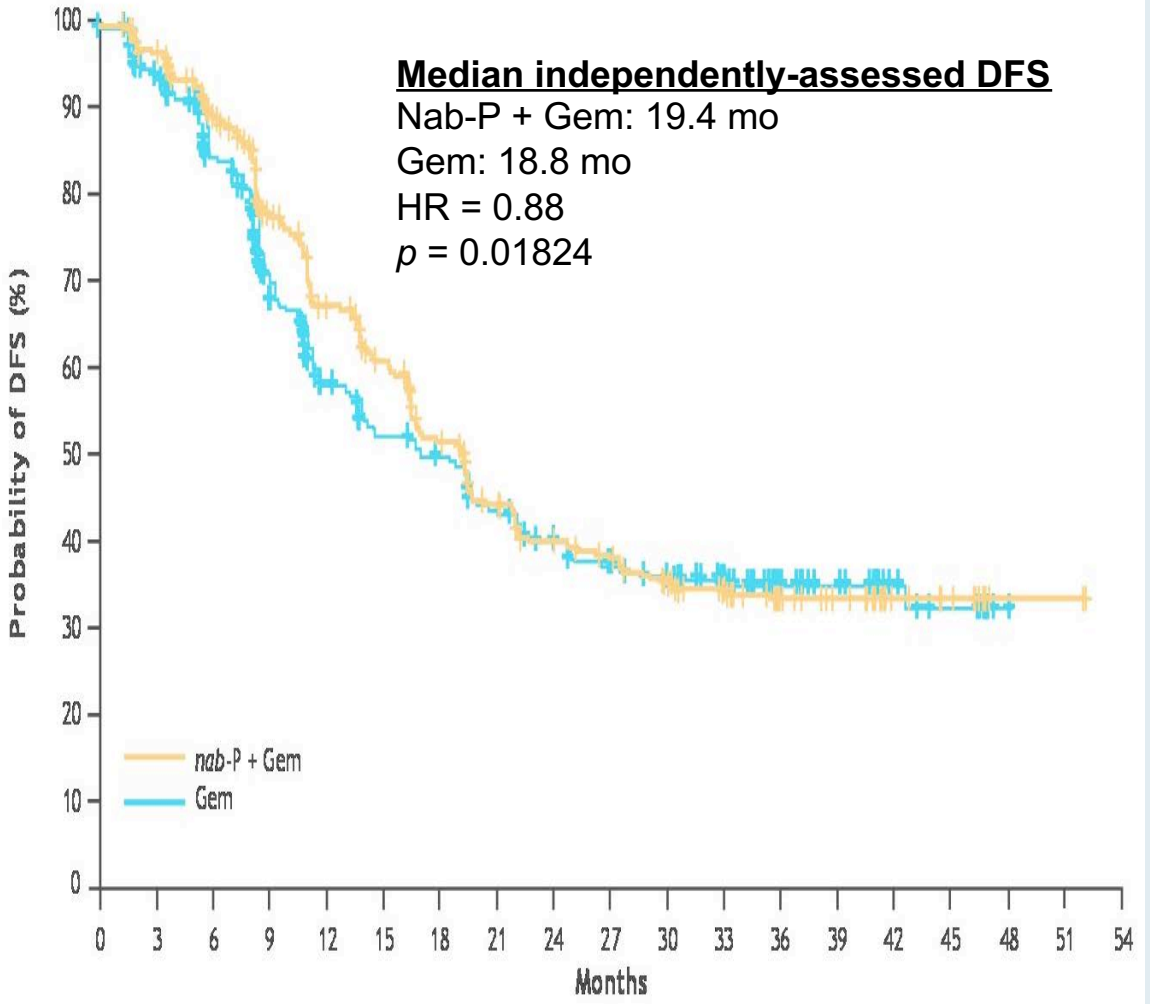
Courtesy of Eileen M. O'Reilly, MD

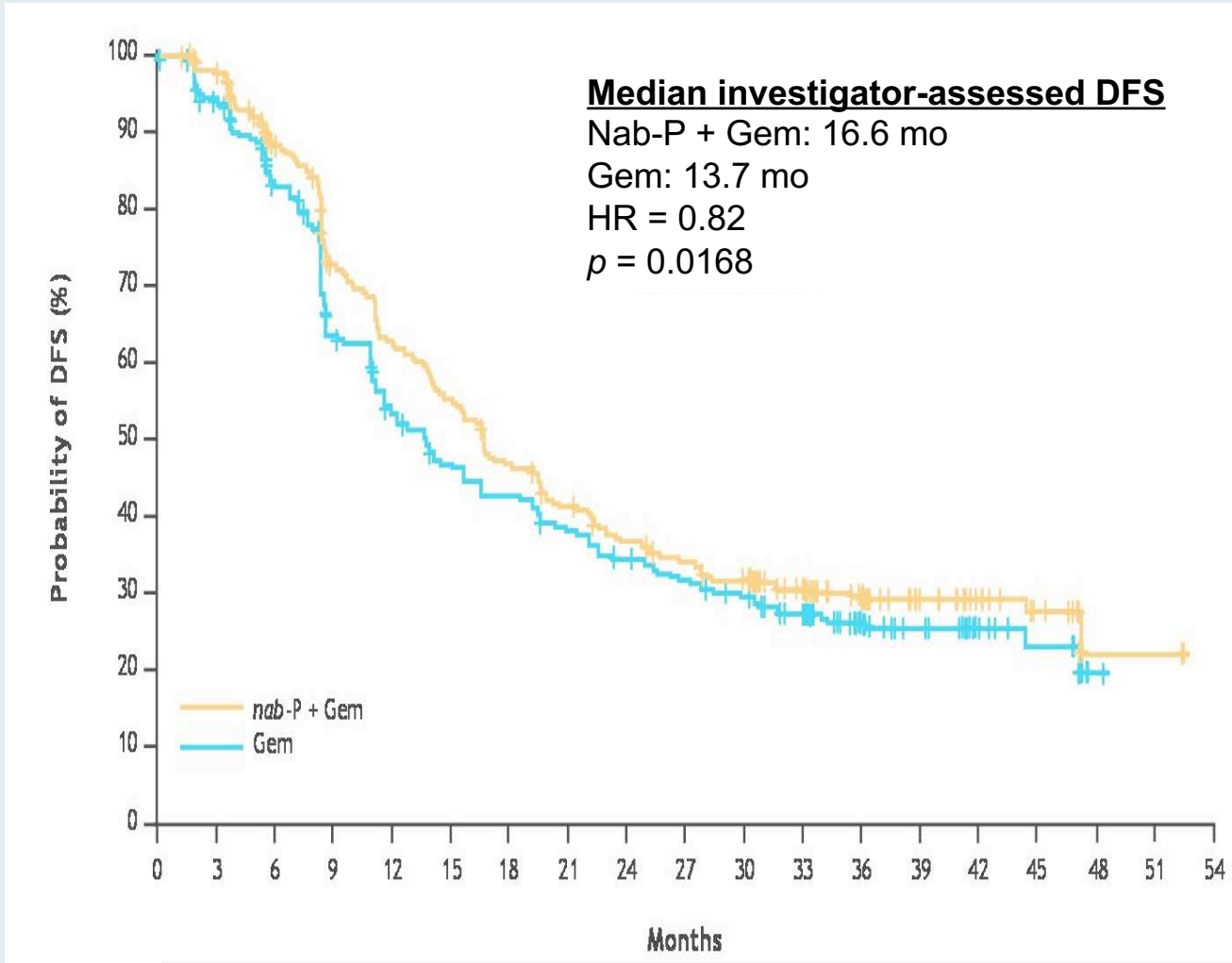
Concordance Between Independent and Investigator Assessment of Disease-Free Survival (DFS) in the APACT Trial

Reni M et al.

ASCO 2020;Abstract 4618.

APACT: Primary Endpoint (DFS Results)





Conclusion: The overall concordance rate and K coefficient suggest a moderate concordance between independent and investigator-assessed DFS.

Reni M et al. ASCO 2020;Abstract 4618.

RTP RESEARCH TO PRACTICE

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

Press Release – December 27, 2019

"On December 27, 2019, the Food and Drug Administration approved olaparib for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated metastatic pancreatic adenocarcinoma, as detected by an FDA-approved test, whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

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

Efficacy was investigated in POLO (NCT02184195), a double-blind, placebo-controlled, multi-center trial that randomized (3:2) 154 patients with gBRCAm metastatic pancreatic adenocarcinoma to olaparib 300 mg orally twice daily or placebo until disease progression or unacceptable toxicity."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-gbrcam-metastatic-pancreatic-adenocarcinoma

RTP RESEARCH TO PRACTICE

Maintenance Olaparib in Patients Aged ≥65 Years with a Germline BRCA Mutation and Metastatic Pancreatic Cancer: Phase III POLO Trial[1]

Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer[2]

Olaparib as Maintenance Treatment Following First-Line Platinum-Based Chemotherapy (PBC) in Patients with a Germline BRCA Mutation and Metastatic Pancreatic Cancer: Phase III POLO Trial[3]

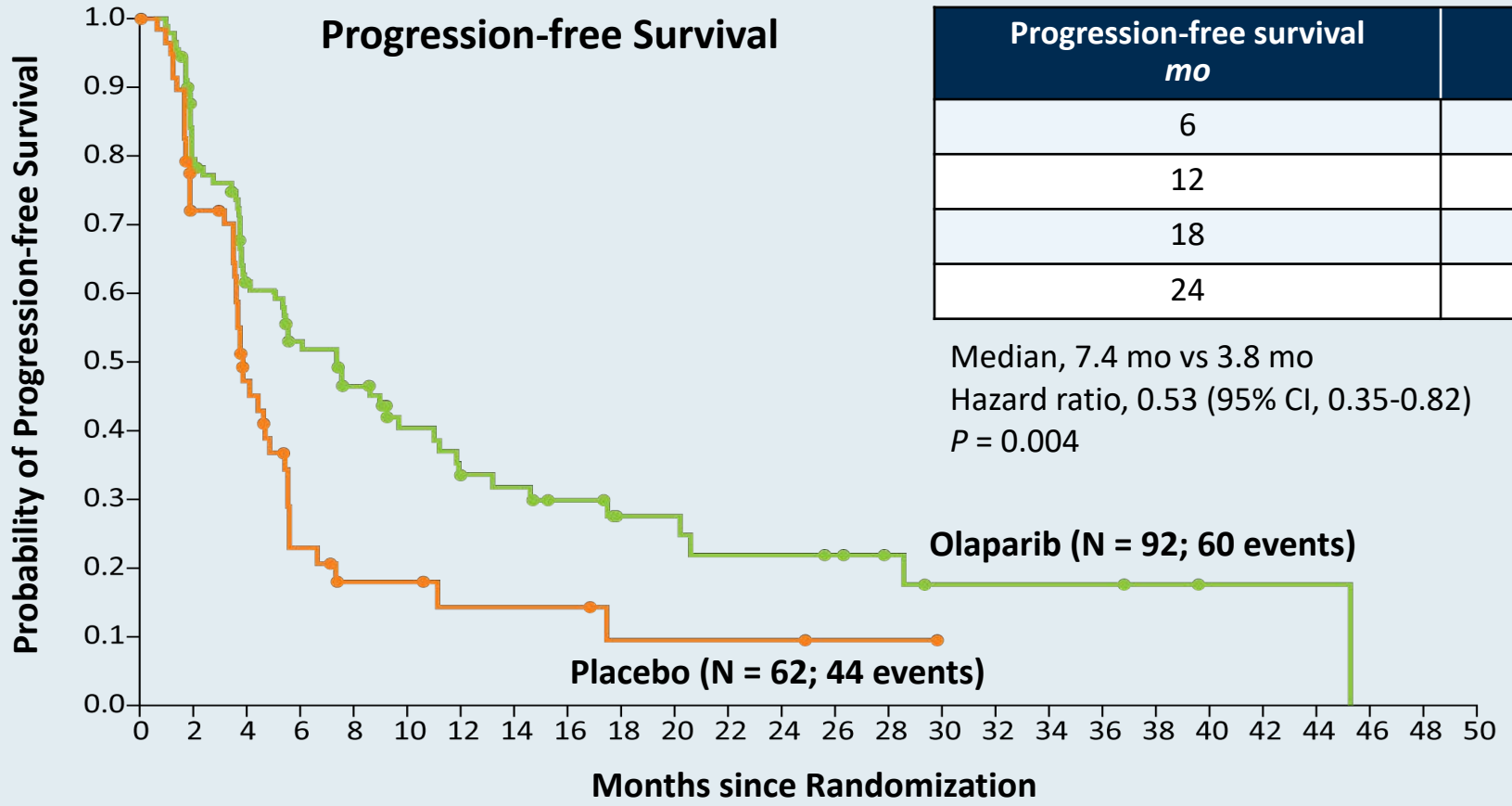
[1] Kindler HL et al.
ESMO 2020;Abstract SO-3.

[2] Golan T et al.
N Engl J Med 2019;381(4):317-27.

[3] Kindler HL et al.
ASCO 2019;Abstract LBA4.

RTP RESEARCH TO PRACTICE

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



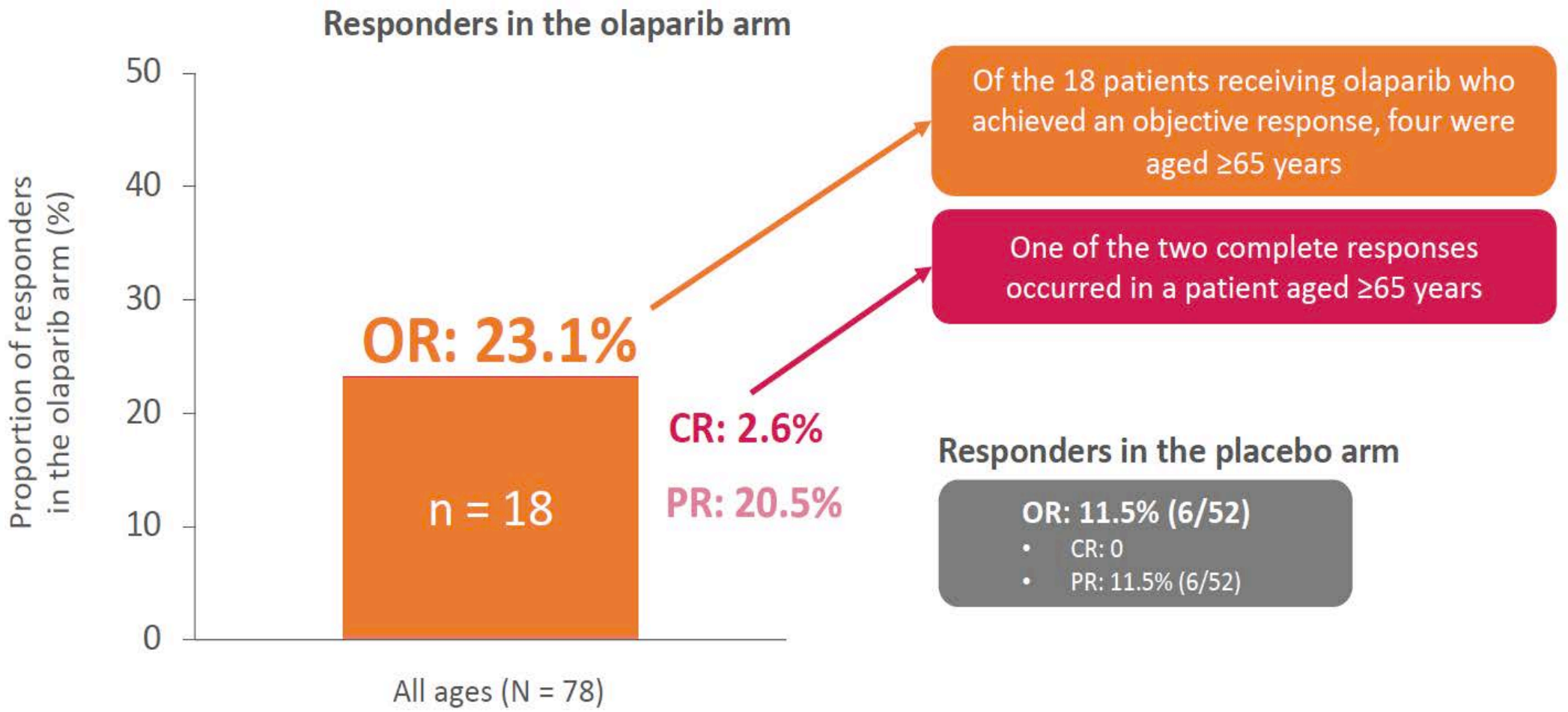
Progression-free survival *mo*	Olaparib group	Placebo group
6	53.0%	23%
12	33.7%	14.5%
18	27.6%	9.6%
24	22.1%	9.6%

Median, 7.4 mo vs 3.8 mo
Hazard ratio, 0.53 (95% CI, 0.35-0.82)
P = 0.004

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

Kindler HL et al. ESMO 2020;Abstract SO-3; Golan T et al. *N Engl J Med* 2019;381(4):317-27; Kindler HL et al. ASCO 2019;Abstract LBA4.

POLO: Patients Receiving Olaparib with an Objective Response (CR or PR)



Kindler HL et al. ESMO 2020;Abstract SO-3.

Select Ongoing Trials of Olaparib in PAD

Trial (NCT#)	Phase	Target (N)	Setting	Treatment arms
SWOG-S2001 (NCT04548752)	II	88	Metastatic PAD; Germline BRCA1/2 mutation-positive; Received 1L platinum-based chemotherapy	• Olaparib + pembrolizumab • Olaparib
STUDY00019211 (NCT04005690)	I	14	Resectable, borderline resectable, locally advanced or metastatic PAD; Untreated or previously treated	• Cobimetinib • Olaparib

Clinicaltrials.gov; Accessed February 2021.

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RTP RESEARCH TO PRACTICE

Case Presentation – Dr Shehadeh: A 59-year-old man with localized, unresectable cholangiocarcinoma with a HER2 mutation

Dr Nasfat Shehadeh

- 6/2020: presents with painless jaundice
  - MRI/MRCP reveals high-grade stricture of the proximal common bile duct; s/p ERCP and stent, bilirubin normalized
  - CT scan: no metastases
- 8/2020: Diagnostic laparoscopy: positive nodes, no peritoneal disease, unresectable
- 9/2020: Capecitabine/gemcitabine x 4 cycles
- Capecitabine with XRT
- 12/2020: CT scan shows no progression
- Genetic testing: HER2+, IHC3+, no IDH or FGFR mutation

Question

- Where does trastuzumab or trastuzumab deruxtecan fit into the treatment algorithm for such a patient?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Shehadeh: A 59-year-old man with localized, unresectable cholangiocarcinoma with a HER2 mutation (continued)

Dr Nasfat Shehadeh

Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL
ERBB2 (Her2/Neu)	CISH	DNA-Tumor	Amplified	[redacted]	pertuzumab, trastuzumab	Level 3A
	IHC	Protein	Positive | 3+, 70%			

* 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).

RTP RESEARCH TO PRACTICE

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

Press Release – April 17, 2020

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

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

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

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pemigatinib-cholangiocarcinoma-fgfr2-rearrangement-or-fusion

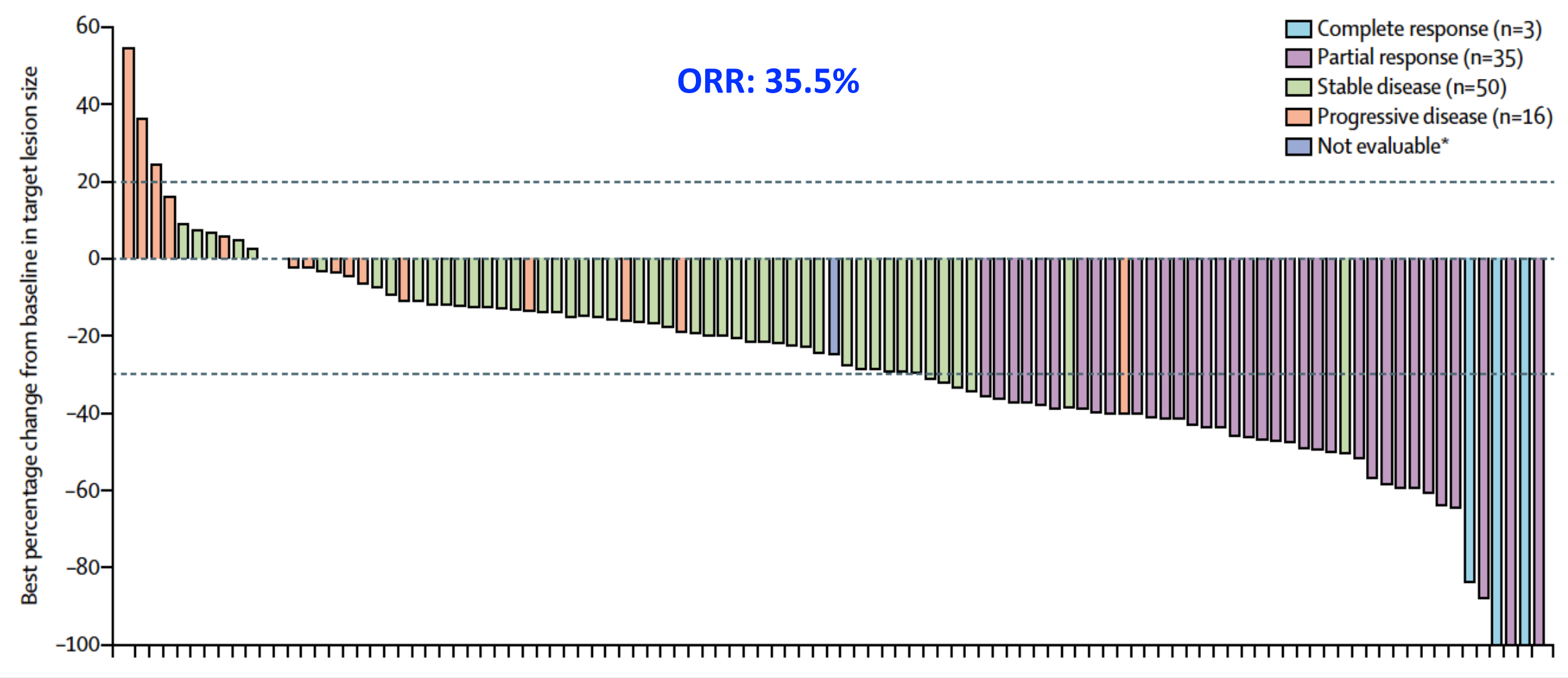
RTP RESEARCH TO PRACTICE

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

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

Lancet Oncol 2020; 21: 671–84

FIGHT-202: Response with Pemigatinib



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

FIGHT-202: Select Treatment-Related Adverse Events

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

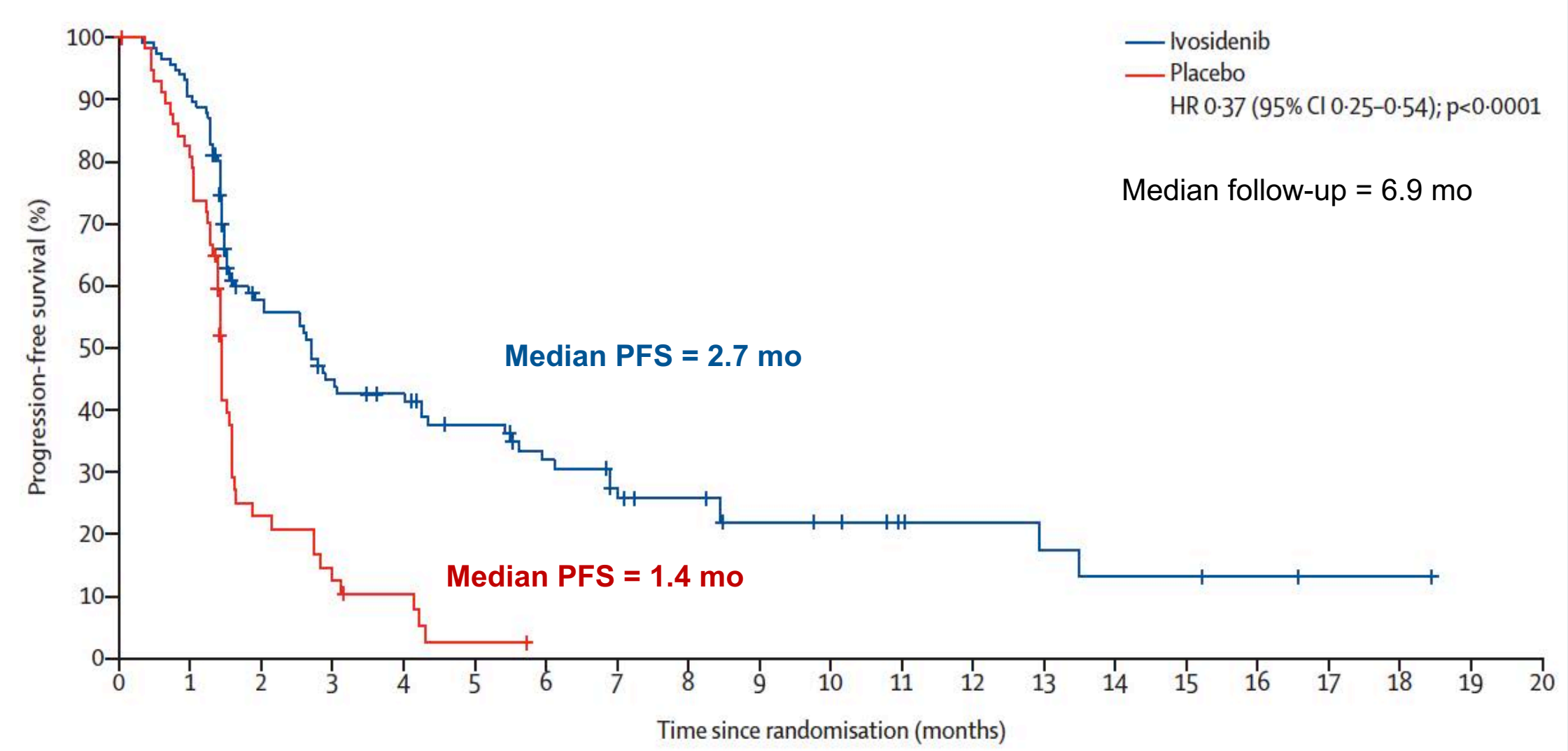
Abou-Alfa GK et al. *Lancet Oncol* 2020;21:671-84.

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

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

Lancet Oncol **2020; 21: 796–807**

ClarIDHy: Progression-Free Survival



Abou-Alfa GK et al. *Lancet Oncol* 2020;21:796-807.

RTP RESEARCH TO PRACTICE

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

Current Concepts and Recent Advances in Oncology

Real World Oncology Rounds

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

Saturday, February 13, 2021

8:30 AM – 4:30 PM ET

RTP RESEARCH TO PRACTICE

Agenda

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

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

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

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

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

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

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

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Breast Cancer Faculty

Sara Hurvitz, MD
Professor of Medicine
David Geffen School of Medicine at UCLA
Director, Breast Cancer Clinical Research Program
Co-Director, Santa Monica-UCLA Outpatient Oncology Practice
Santa Monica, California

Ian E Krop, MD, PhD
Associate Chief, Division of Breast Oncology
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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The patients I saw today…

66	M	Breast Cancer – Observation after adjuvant chemo
59	M	Benign Hematology - New consult leukocytosis
57	M	Renal Cell Carcinoma - 2nd line Nivolumab
53	F	Benign Hematology - Hereditary hemochromatosis
78	M	Colorectal Cancer - FOLFIRI and bevacizumab
73	M	Diffuse Large B Cell Lymphoma - Routine f/u in CR since 2018 after 6 cycles RCHOP
83	M	Myelofibrosis – Anemia, chronic kidney disease, receiving ruxolitinib and darbepoetin Alfa
62	M	Bladder cancer - Metastatic since 2015. Receiving pemetrexed and has PD. Hospice discussion after failing all std therapies. Not a trial candidate due to cirrhosis and prior sarcoma
74	F	Breast Cancer – Metastatic triple positive On pertuzumab, trastuzumab and letrozole
69	F	Head and neck cancer - Concurrent chemoRT with cisplatin high dose as sensitizing agent

50	F	Breast Cancer - Metastatic, ER-pos, Her2-neg to lung and liver. On weekly paclitaxel
77	M	Lung Cancer - Recurrent disease on maintenance atezolizumab
70	F	Cervical cancer - Metastatic, weekly carbo/paclitaxel. Patient had CKD, Crohns and GI fistula
64	M	Lung Cancer - Maintenance atezolizumab
57	M	Lung Cancer - 2nd-line atezolizumab Diagnosed 2016 with Stage IV adeno: Carbo/pemetrexed/bev and then maintenance pemetrexed/bev until PD 2019
56	F	Pancreatic cancer - Whipple for IIB disease at academic center. Released with wound vac. FOLFIRINOX now
80	M	Gastric Cancer – S/p gastrectomy for Stage I disease. Post op f/u to discuss surveillance
79	F	Breast Cancer – Palbociclib/anastrozole/denosumab
77	M	Pancreatic cancer - Liposomal irinotecan, 5FU and LV
57	F	Multiple myeloma - Diagnosed 2004, transplanted 2007 and in CR for last 12 years!

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RESEARCH
TO PRACTICE

Contributing Oncologists

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

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

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

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

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

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

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

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RESEARCH
TO PRACTICE

Contributing Oncologists

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

Nasfat Shehadeh, MD
Medical Oncologist
Oncology Specialists of Charlotte
Charlotte, North Carolina

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

Saad Zafar Usmani, MD, MBA
Division Chief, Plasma Cell Disorders
Levine Cancer Institute, Carolinas Medical Center
Charlotte, North Carolina

Maria E Picton, MD
Hematology Oncology, Physicians East
Greenville, North Carolina

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

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TO PRACTICE

Agenda

Module 1: Triple-Negative Breast Cancer (TNBC)

Dr Zelkowitz: A 50-year-old Korean woman with Stage IA TNBC

Dr Zelkowitz – Questions and Comments: Incorporation and tolerability of sacituzumab govitecan

Dr Zelkowitz – Questions and Comments: Impact of mask wearing on patients during COVID-19

Module 2: HER2-Positive BC

Dr Choksi: A 67-year-old woman with past history of TNBC develops ER/PR-positive, HER2-positive BC

Dr Zelkowitz: A 53-year-old woman with Stage IIA triple-positive BC

Dr Shehadeh: A 35-year-old premenopausal woman with ER/PR-negative, HER2-positive mBC

Dr Zelkowitz – Questions and Comments: Later-line treatment options for HER2-positive mBC

Module 3: ER-Positive, HER2-Negative BC

Dr Favaro: A 58-year-old postmenopausal woman with ER-positive, node-positive localized BC

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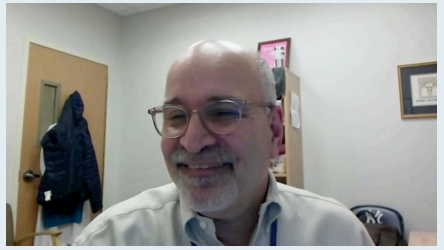

Dr Richard Zelkowitz

- Diagnosed with a right 16-mm ER-negative, PR-negative, HER2-negative, node-negative breast cancer, with a metaplastic component – PD-L1: 80%
- AC x 3 with plan to proceed to full dose-dense AC-T, with pegfilgrastim
- Present to ER after 3rd cycle of AC: Fever 103.5, pulse 120 bpm, blood pressure: 90
  - WBC 200, Hgb: 9, platelet count: 27,000
  - SARS CoV2-positive → Treated with monoclonal antibody bamlanivimab → Full recovery

Questions

- When would you comfortably resume her chemotherapy?
- Is that degree of pancytopenia characteristic of the COVID infection in patients receiving chemotherapy?

Questions and Comments: Incorporation of sacituzumab govitecan in the treatment of metastatic TNBC; tolerability and toxicity

Richard Zelkowitz, MD

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Questions and Comments: Impact of mask wearing on patient encounters during the era of COVID-19

Richard Zelkowitz, MD

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In general, what first-line treatment would you recommend for a patient with PD-L1-positive metastatic TNBC with a BRCA germline mutation?

1. Atezolizumab/paclitaxel
2. Atezolizumab/*nab* paclitaxel
3. Atezolizumab/paclitaxel or atezolizumab/*nab* paclitaxel — coin flip
4. Pembrolizumab/chemotherapy
5. PARP inhibitor monotherapy
6. Chemotherapy → PARP inhibitor maintenance
7. Chemotherapy + anti-PD-1/PD-L1 antibody → PARP inhibitor maintenance
8. Other

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

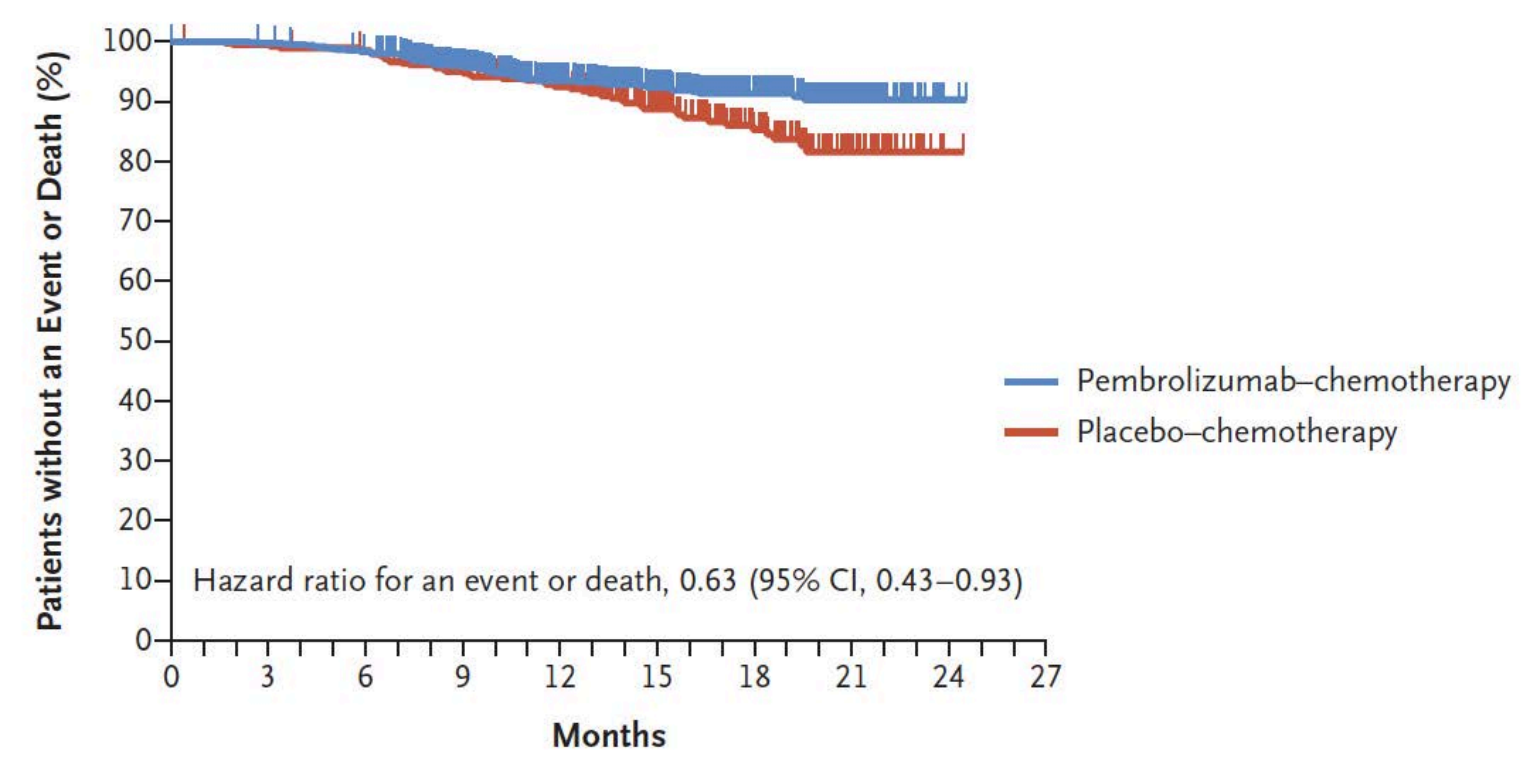
Pembrolizumab for Early Triple-Negative Breast Cancer

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

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

KEYNOTE-522 Primary Endpoints: pCR and EFS

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



Schmid P et al. *N Engl J Med* 2020;382(9):810-21.

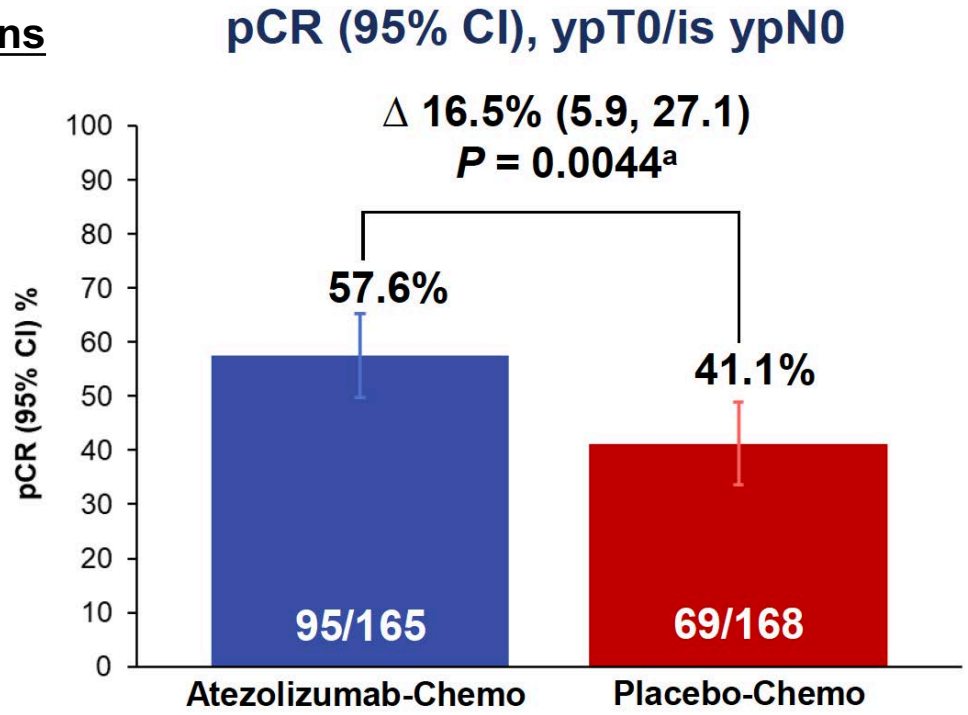
Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial

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

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

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

ITT and PD-L1+ Populations



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

*Did not cross significance boundary of 0.0184.

Mittendorf EA et al. *Lancet* 2020;396(10257):1090-1100; Harbeck N et al. ESMO 2020;Abstract LBA11.

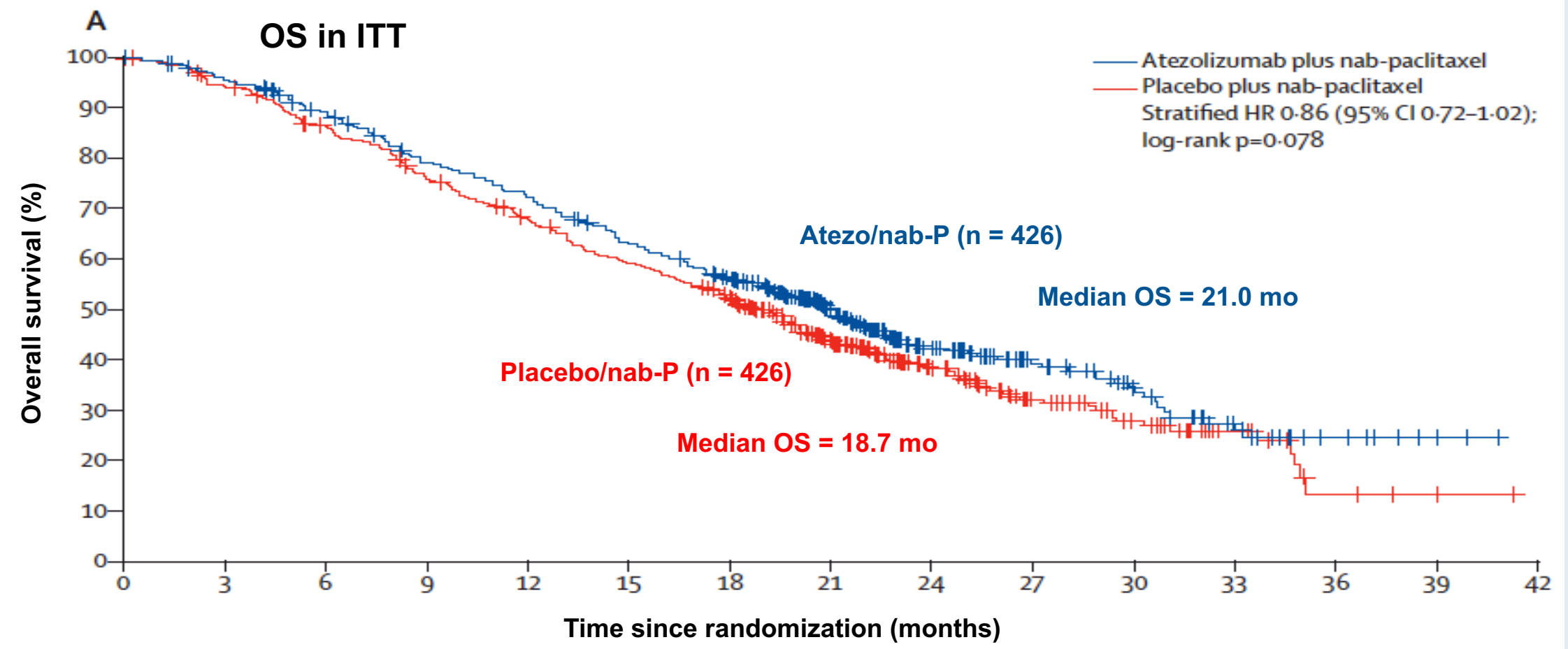
Articles

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

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

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

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



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

Schmid P et al. *Lancet* 2020;21(1):44-59.

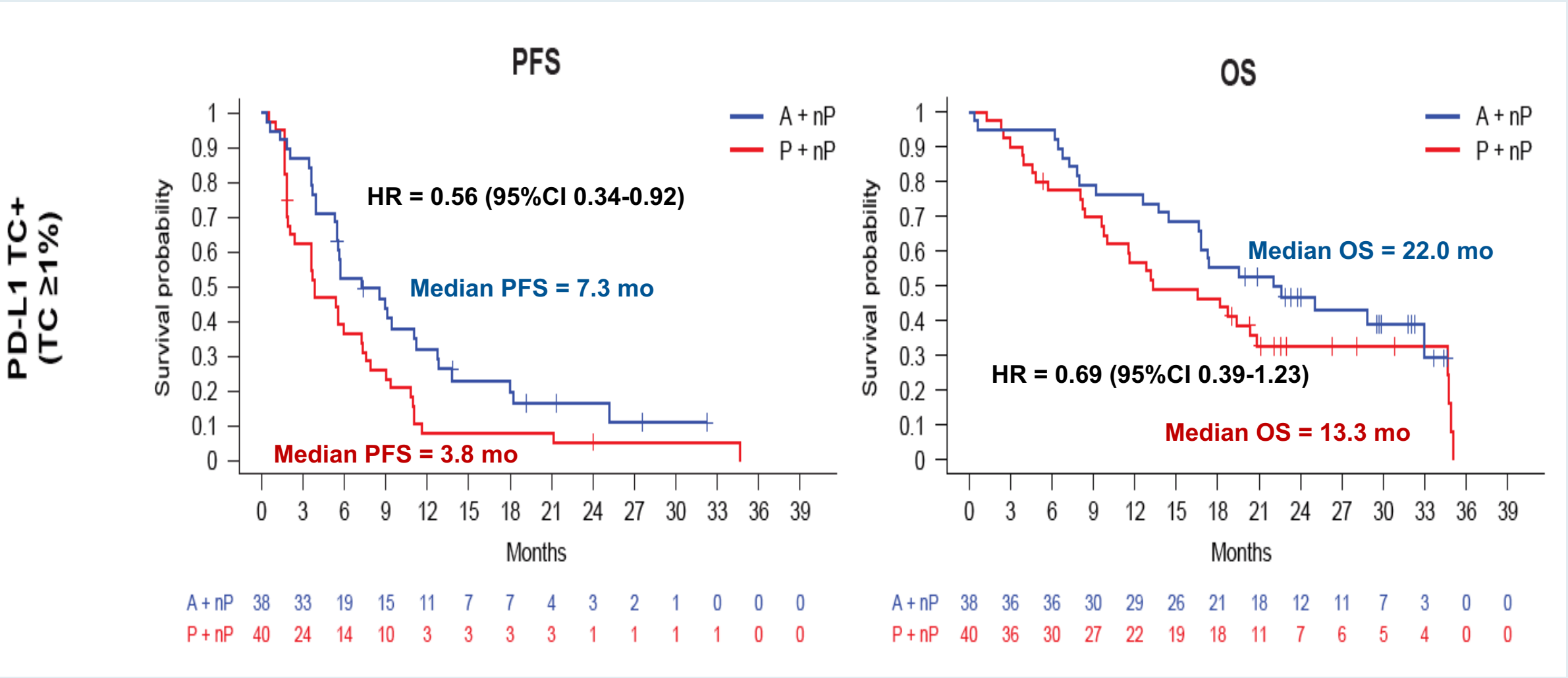
RTP RESEARCH TO PRACTICE

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

Emens LA et al.

J Natl Cancer Inst 2021;Online ahead of print.

IMpassion130: Distribution of PD-L1 TC-Positive Subgroup



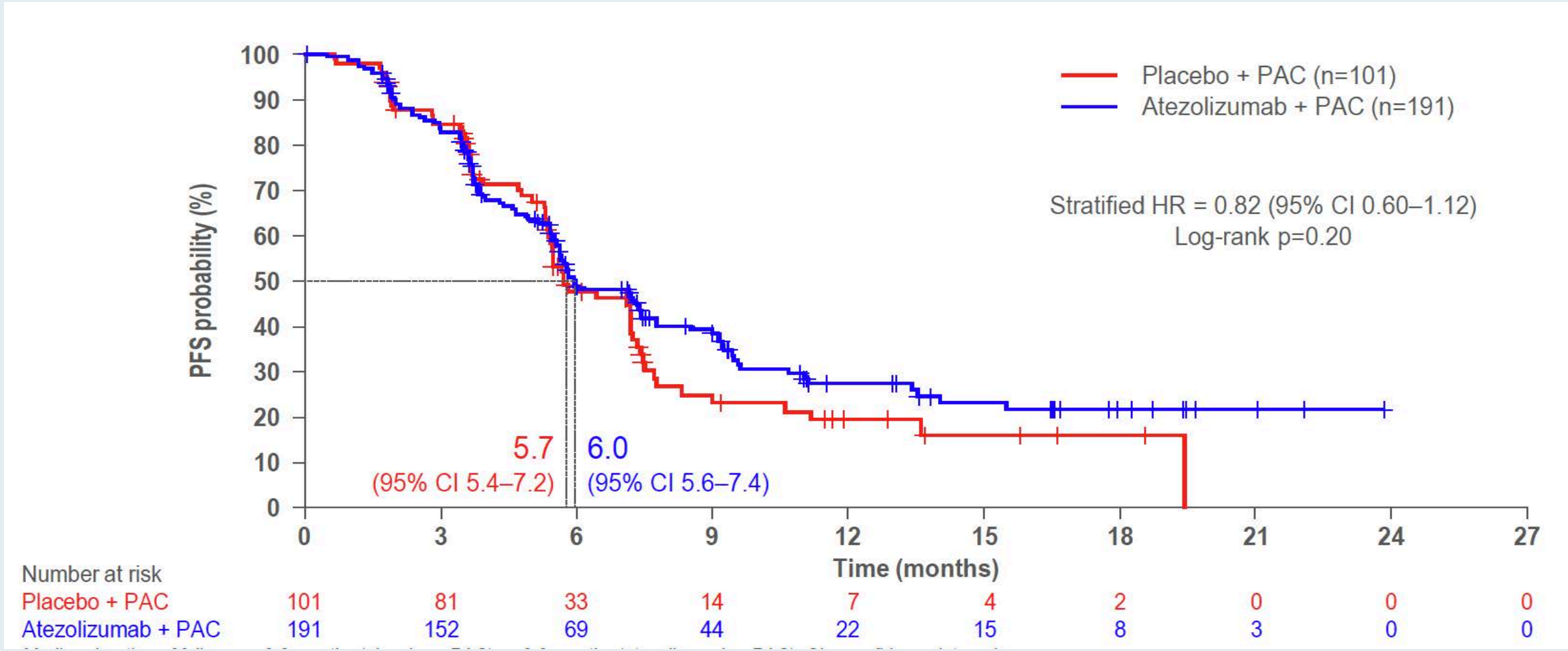
Emens LA et al. J Natl Cancer Inst 2021;Online ahead of print.

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

Miles D et al.

ESMO 2020;Abstract LBA15.

IMpassion131: PFS in the PD-L1-Positive Population



Miles D et al. ESMO 2020;Abstract LBA15.

RTP RESEARCH TO PRACTICE

FDA Alert Regarding Efficacy and Potential Safety Concerns with Atezolizumab in Combination with Paclitaxel for Treatment of Breast Cancer

Press Release – September 8, 2020

"The Food and Drug Administration alerted health care professionals, oncology clinical investigators, and patients that a clinical trial studying the use of atezolizumab and paclitaxel in patients with previously untreated inoperable locally advanced or metastatic triple negative breast cancer (mTNBC) showed the drug combination did not work to treat the disease.

Health care professionals should not replace paclitaxel protein-bound with paclitaxel in clinical practice.

The trial, IMpassion131, was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of atezolizumab in combination with paclitaxel compared with placebo and paclitaxel for patients with mTNBC."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-issues-alert-about-efficacy-and-potential-safety-concerns-atezolizumab-combination-paclitaxel

RTP RESEARCH TO PRACTICE

FDA Grants Accelerated Approval to Pembrolizumab for Locally Recurrent Unresectable or mTNBC

Press Release – November 13, 2020

"On November 13, 2020, the Food and Drug Administration granted accelerated approval to pembrolizumab in combination with chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (CPS ≥10) as determined by an FDA approved test.

FDA also approved the PD-L1 IHC 22C3 pharmDx as a companion diagnostic for selecting patients with TNBC for pembrolizumab.

Approval was based on KEYNOTE-355 (NCT02819518), a multicenter, double-blind, randomized, placebo-controlled trial in patients with locally recurrent unresectable or metastatic TNBC, who had not been previously treated with chemotherapy in the metastatic setting."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-pembrolizumab-locally-recurrent-unresectable-or-metastatic-triple

RTP RESEARCH TO PRACTICE

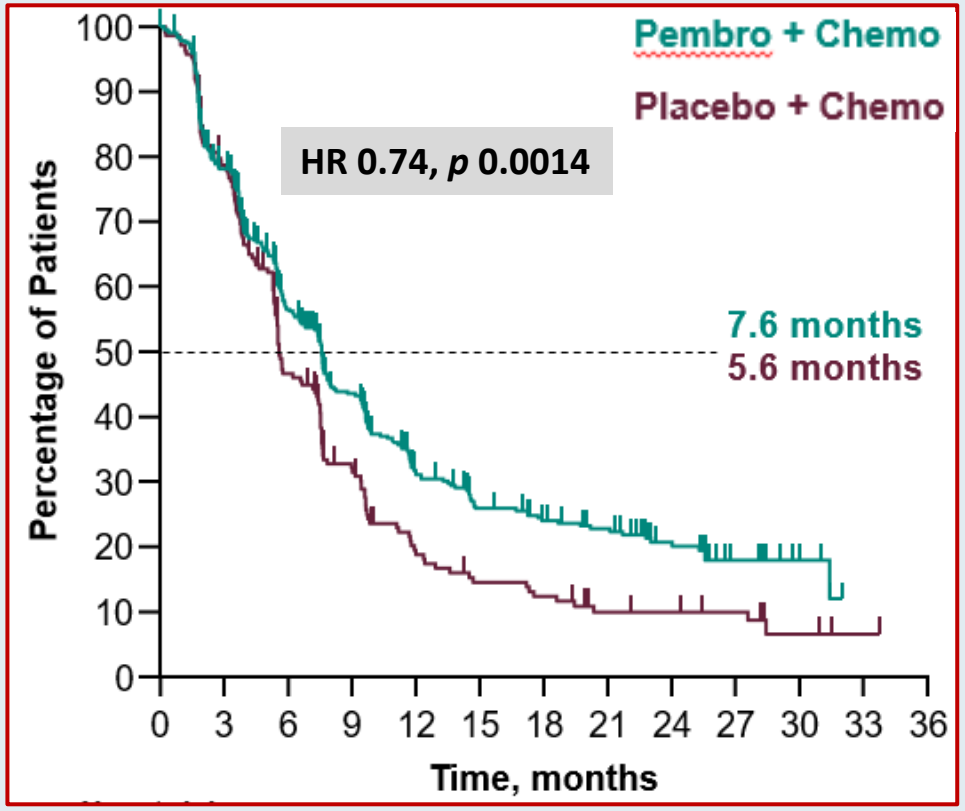
Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial

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

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

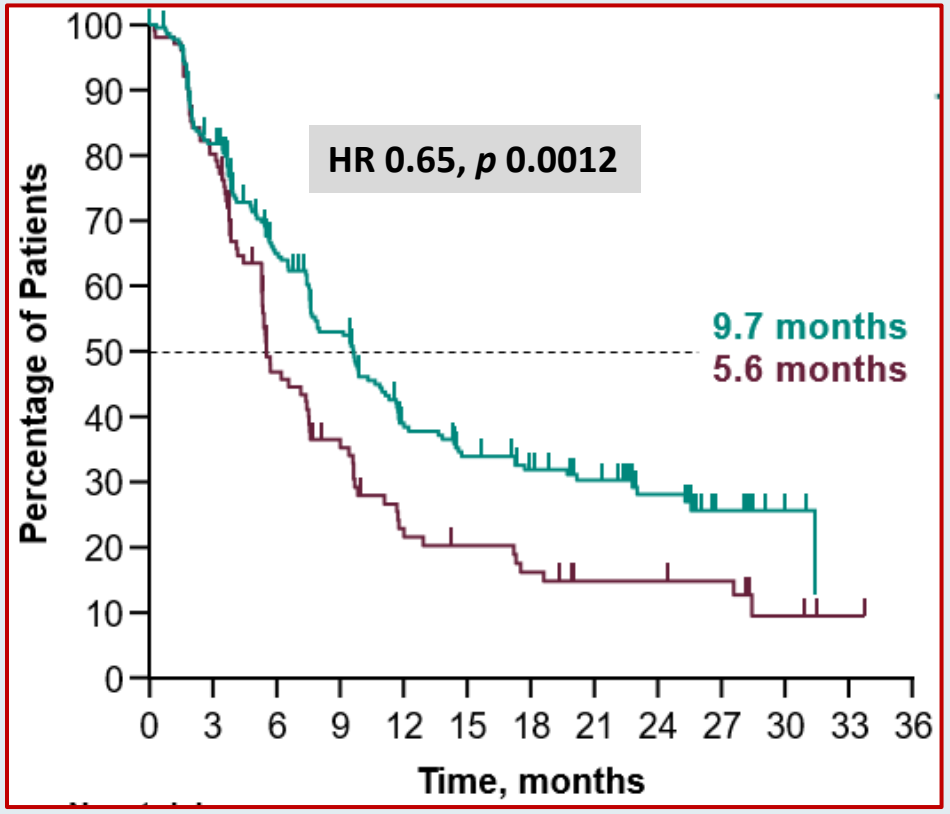
KEYNOTE-355: PFS for Patients with PD-L1-Positive Tumors

PD-L1 CPS ≥1



Prespecified *p* value boundary of 0.00111 not met

PD-L1 CPS ≥10



Prespecified *p* value boundary of 0.00411 met

Cortes J et al. *Lancet* 2020;396(10265):1817-28; Cortes J et al. ASCO 2020;Abstract 1000.

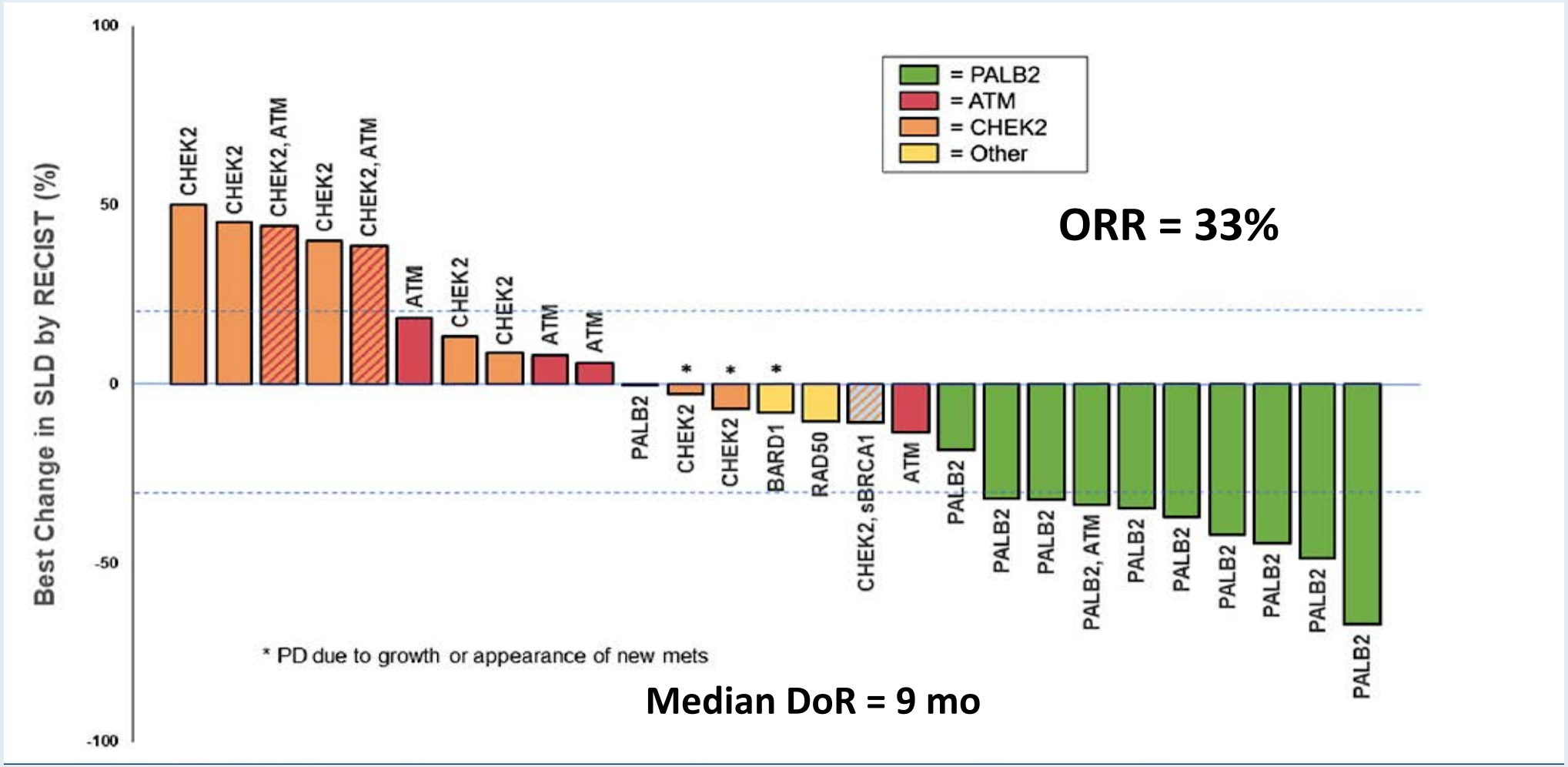
original reports

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

Nadine M. Tung, MD[1,2]; Mark E. Robson, MD[3]; Steffen Ventz, PhD[4]; Cesar A. Santa-Maria, MD, MSCI[5]; Rita Nanda, MD[6]; Paul K. Marcom, MD[7]; Payal D. Shah, MD[8]; Tarah J. Ballinger, MD[9]; Eddy S. Yang, MD, PhD[10]; Shaveta Vinayak, MD, MS[11]; Michelle Melisko, MD[12]; Adam Brufsky, MD, PhD[13]; Michelle DeMeo, BS[4]; Colby Jenkins, MS[1]; Susan Domchek, MD[8]; Alan D'Andrea, MD[2,4]; Nancy U. Lin, MD[2,4]; Melissa E. Hughes, MS[4]; Lisa A. Carey, MD[14]; Nick Wagle, MD[2,4]; Gerburg M. Wulf, MD, PhD[1,2]; Ian E. Krop, MD, PhD[2,4]; Antonio C. Wolff, MD[5]; Eric P. Winer, MD[2,4]; and Judy E. Garber, MD, MPH[2,4]

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

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



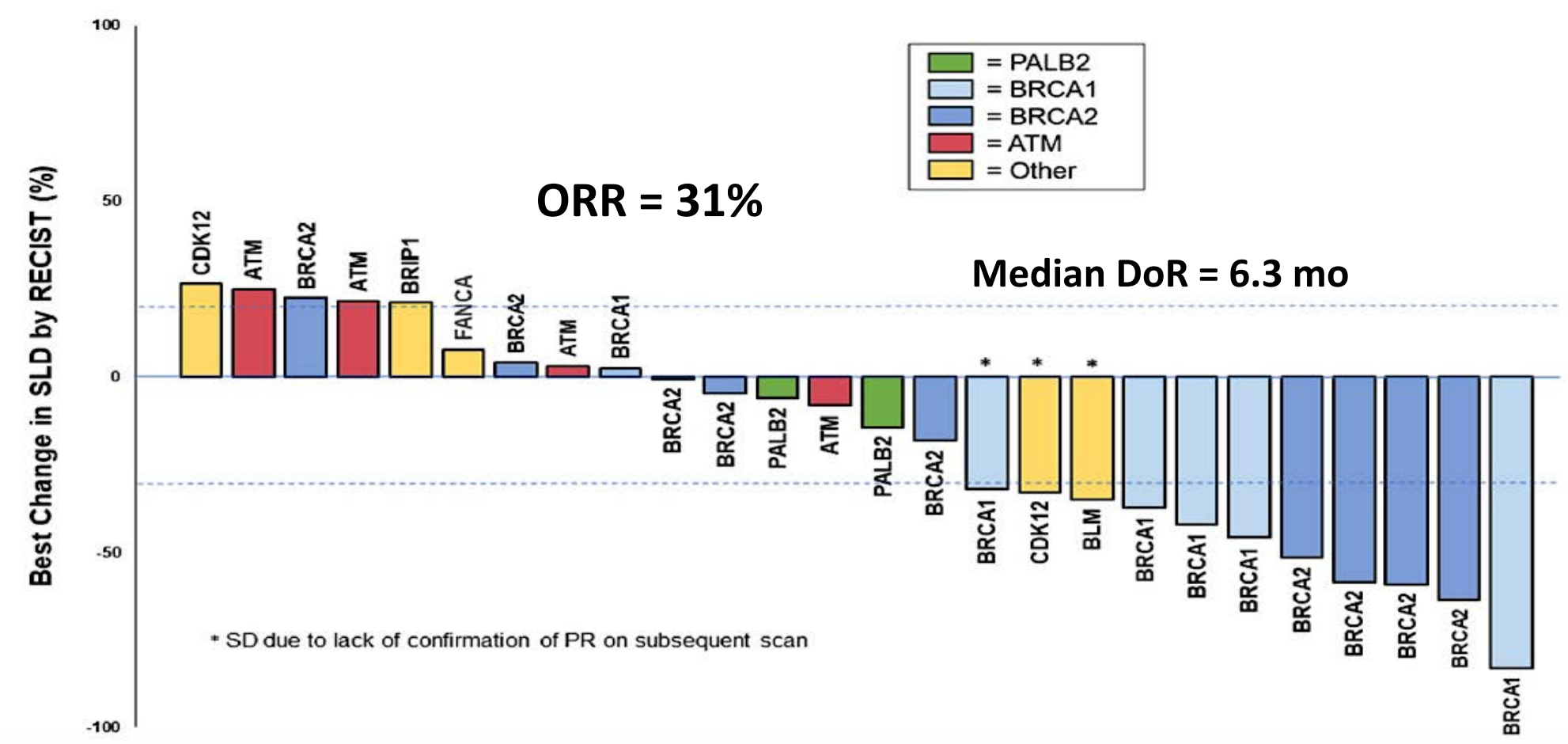
Median PFS = 4.5 mo

Median time to onset of response = 12.1 weeks

Tung NM et al. *J Clin Oncol* 2020;38(36):4274-82; Tung N et al. ASCO 2020;Abstract 1002.

RTP RESEARCH TO PRACTICE

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



Median PFS = 4.1 mo

Median time to onset of response = 10.3 weeks

Tung NM et al. *J Clin Oncol* 2020;38(36):4274-82; Tung N et al. ASCO 2020;Abstract 1002.

RTP RESEARCH TO PRACTICE

TBCRC 048: Responses for 5 Most Common Genes

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

15 patients remain on study

* 1 sPALB2- lost to follow-up after 1st tumor assessment with skin and tumor marker response
^ includes patient from Cohort 1 with sBRCA1 and gCHEK2
** Not included: patient with both gCHEK2 & sBRCA1; patient with gATM and gPALB2

Tung NM et al. *J Clin Oncol* 2020;38(36):4274-82; Tung N et al. ASCO 2020;Abstract 1002.

FDA Grants Accelerated Approval to Sacituzumab Govitecan-hziy for mTNBC

Press Release – April 22, 2020

"The Food and Drug Administration granted accelerated approval to sacituzumab govitecan-hziy for adult patients with metastatic triple-negative breast cancer who received at least two prior therapies for metastatic disease.

Efficacy was demonstrated in IMMU-132-01 (NCT01631552), a multicenter, single-arm, trial enrolling 108 patients with metastatic triple negative breast cancer (mTNBC) who received at least two prior treatments for metastatic disease.

The recommended sacituzumab govitecan-hziy dose is 10 mg/kg administered by intravenous infusion administered on days 1 and 8 every 21 days until disease progression or unacceptable toxicity."

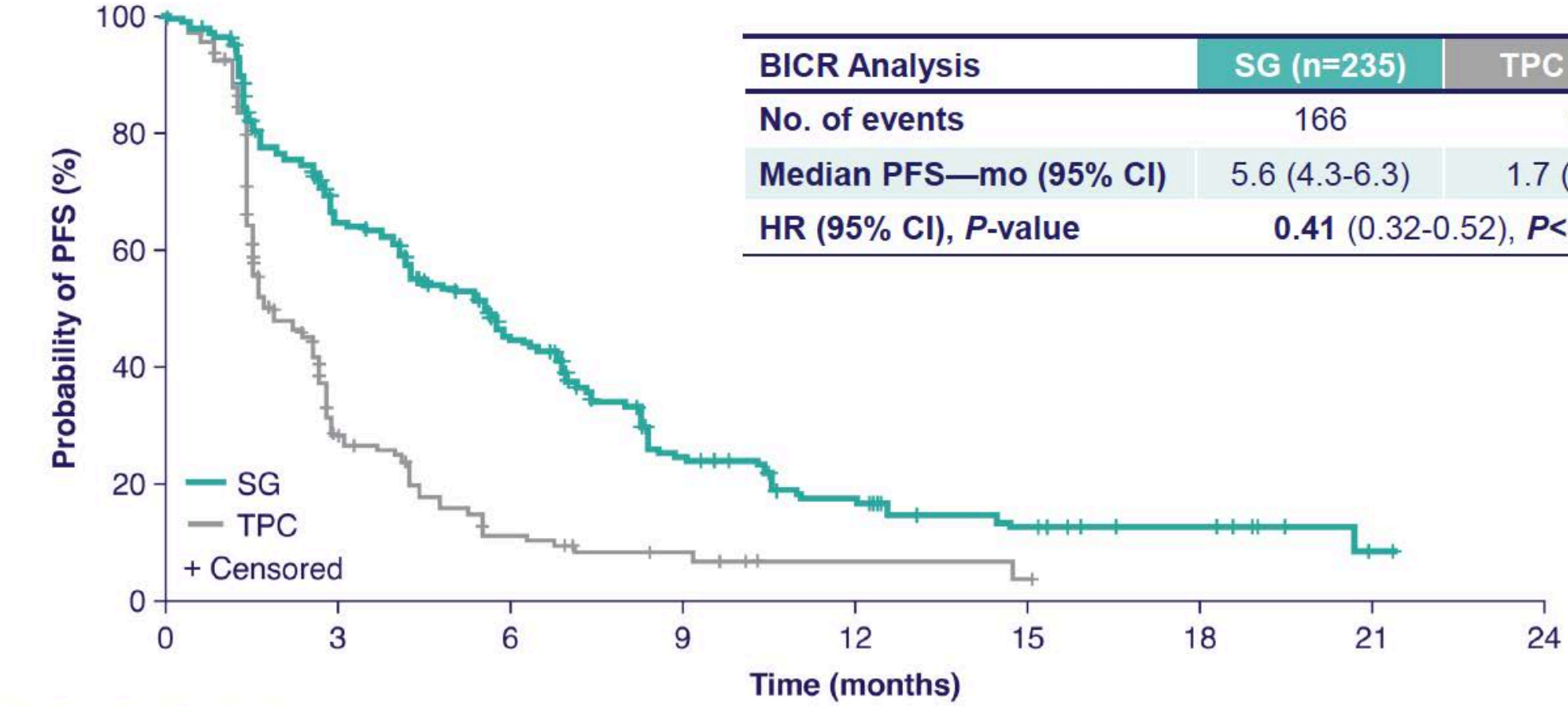
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer

ASCENT: A Randomized Phase III Study of Sacituzumab Govitecan (SG) vs Treatment of Physician's Choice (TPC) in Patients (pts) with Previously Treated Metastatic Triple-Negative Breast Cancer (mTNBC)

Bardia A et al.

ESMO 2020;Abstract LBA17.

ASCENT Trial of Sacituzumab Govitecan (SG): PFS (BICR Analysis)



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

Bardia A et al. ESMO 2020;Abstract LBA17.

Agenda

Module 1: Triple-Negative Breast Cancer (TNBC)

Dr Zelkowitz: A 50-year-old Korean woman with Stage IA TNBC

Dr Zelkowitz – Questions and Comments: Incorporation and tolerability of sacituzumab govitecan

Dr Zelkowitz – Questions and Comments: Impact of mask wearing on patients during COVID-19

Module 2: HER2-Positive BC

Dr Choksi: A 67-year-old woman with past history of TNBC develops ER/PR-positive, HER2-positive BC

Dr Zelkowitz: A 53-year-old woman with Stage IIA triple-positive BC

Dr Shehadeh: A 35-year-old premenopausal woman with ER/PR-negative, HER2-positive mBC

Dr Zelkowitz – Questions and Comments: Later-line treatment options for HER2-positive mBC

Module 3: ER-Positive, HER2-Negative BC

Dr Favaro: A 58-year-old postmenopausal woman with ER-positive, node-positive localized BC

Case Presentation – Dr Choksi: A 67-year-old woman with past history of TNBC develops ER/PR-positive, HER2-positive BC

Dr Mamta Choksi

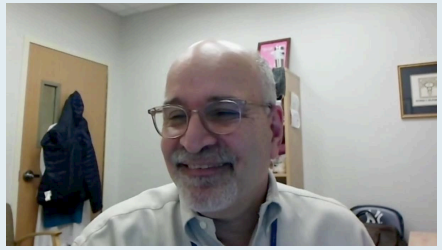
- 2/2017 – 7/2018: Diagnosis of grade 3, ER/PR-negative, HER2-negative, infiltrating poorly differentiated carcinoma in the right breast
  - Carboplatin/paclitaxel → dd AC → lumpectomy and XRT → capecitabine → no evidence of malignancy on CT scan
- 1/2020: Tumor markers mildly elevated; no evidence of malignancy on clinical exam and CT scan
- 5/2020: Annual screening mammogram shows abnormality in left breast
  - Lumpectomy/biopsy: Grade 2, pT2pN1a(sn); ER/PR-positive, HER2-positive
- Chemotherapy with radiation recommended → docetaxel with trastuzumab/pertuzumab

Questions

- Would you have considered anything different for this patient? What about offering neratinib to this patient?
- Would you administer adjuvant T-DM1 concurrently with radiation or afterwards?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Zelkowitz: A 53-year-old woman with Stage IIA triple-positive breast cancer



Dr Richard Zelkowitz

- Diagnosed with a left ER-positive, PR-positive, HER2-positive, node-negative breast cancer (T2N0M)
  - IHC 2+, HER2 FISH ratio: 2.4, copy number: 4.4
- Neoadjuvant TCHP x 5 (pt declined cycle 6 for no overt toxicity)
- Bilateral mastectomy: Pathologic T2NO, ER-positive, PR-positive, HER2 IHC 1+
- Tamoxifen, T-DM1 x 14

Question

- Would you give her neratinib per the ExteNET trial, even though she had pertuzumab?

RTP RESEARCH TO PRACTICE

A 65-year-old woman presents with a 3.4-cm, ER-positive, HER2-positive IDC with biopsy-proven axillary nodes, receives neoadjuvant TCHP and at surgery is found to have a pathologic complete response. Regulatory and reimbursement issues aside, what adjuvant anti-HER2 therapy would you recommend?

1. Trastuzumab
2. Trastuzumab/pertuzumab
3. T-DM1
4. Trastuzumab → neratinib
5. Trastuzumab/pertuzumab → neratinib
6. T-DM1 → neratinib
7. Other

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Case Presentation – Dr Shehadeh: A 35-year-old premenopausal woman with ER/PR-negative, HER2-positive metastatic breast cancer

Dr Nasfat Shehadeh

- 10/2015: DCIS with ER/PR-negative, HER2-positive microinvasion s/p right-sided mastectomy; no adjuvant chemotherapy
- 8/2019: Diffuse bone, liver and nodal metastases (ER/PR-negative, HER2-positive)
- 9/2019: Paclitaxel/trastuzumab/pertuzumab → Maintenance trastuzumab/pertuzumab
- 9/2020: Right facial numbness → MRI brain: Multiple supratentorial and infratentorial lesions
- CT chest/abdomen/pelvis: No extracranial progression
- Tucatinib/capecitabine/trastuzumab and WBRT
- 11/2020: COVID infection, with very mild symptoms (capecitabine held for 3 weeks)
- 1/2021 MRI brain: Excellent response, clinically doing well

Questions

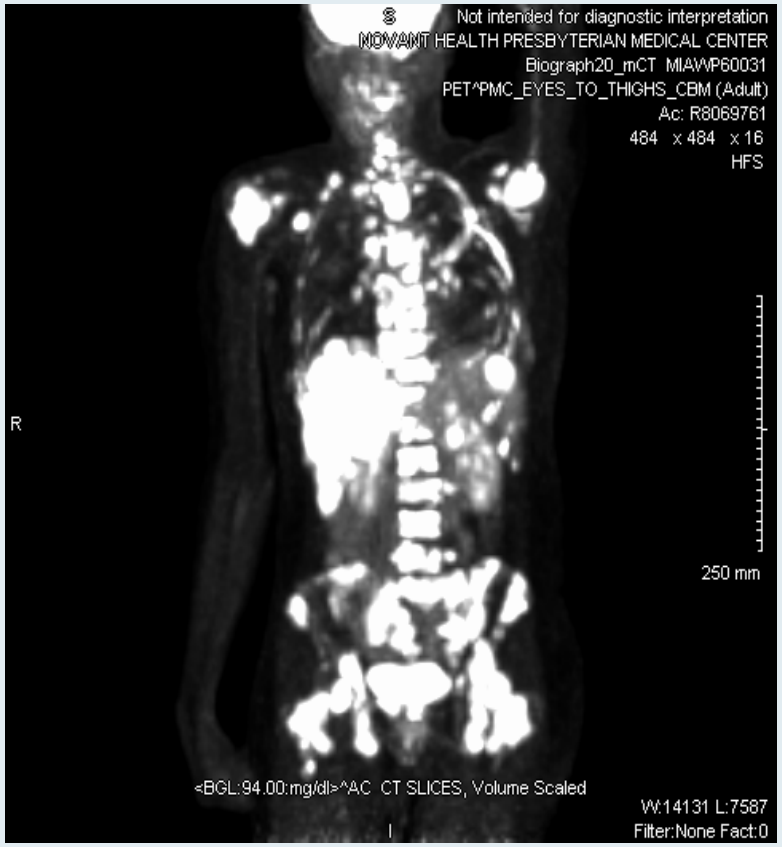
- When using the CLEOPATRA regimen with pertuzumab are you using paclitaxel more often than docetaxel due to better tolerability?
- How much time should you allow for tucatinib/capecitabine/trastuzumab in a patient with symptomatic neurologic deficits – such as numbness – due to CNS metastases?

RTP RESEARCH TO PRACTICE

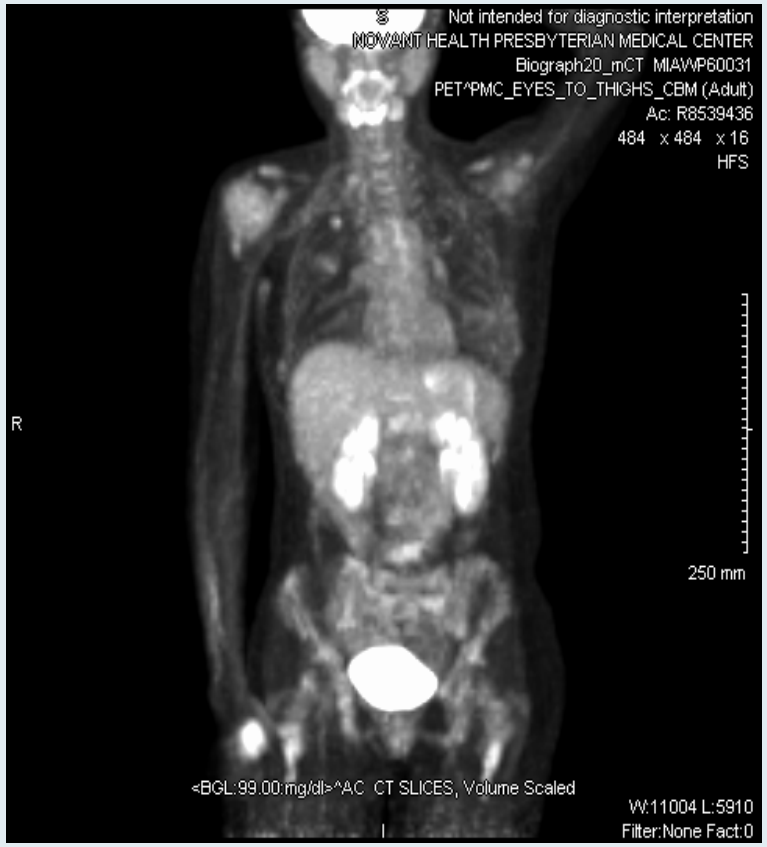
Case Presentation – Dr Shehadeh: A 35-year-old woman with ER/PR-negative, HER2-positive metastatic breast cancer

Dr Nasfat Shehadeh

9/2019 PET Scan



11/2019 PET Scan after 4 cycles of TPH



RTP RESEARCH TO PRACTICE

Questions and Comments: Later-line treatment options for HER2-positive metastatic breast cancer

Richard Zelkowitz, MD

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TO PRACTICE

A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line THP and second-line T-DM1 but then experiences disease progression, including multiple brain metastases. What systemic treatment would you most likely recommend next?

1. Trastuzumab/lapatinib
2. Neratinib/capecitabine (cape)
3. Tucatinib/trastuzumab/cape
4. Trastuzumab deruxtecan
5. Margetuximab/chemotherapy
6. Other

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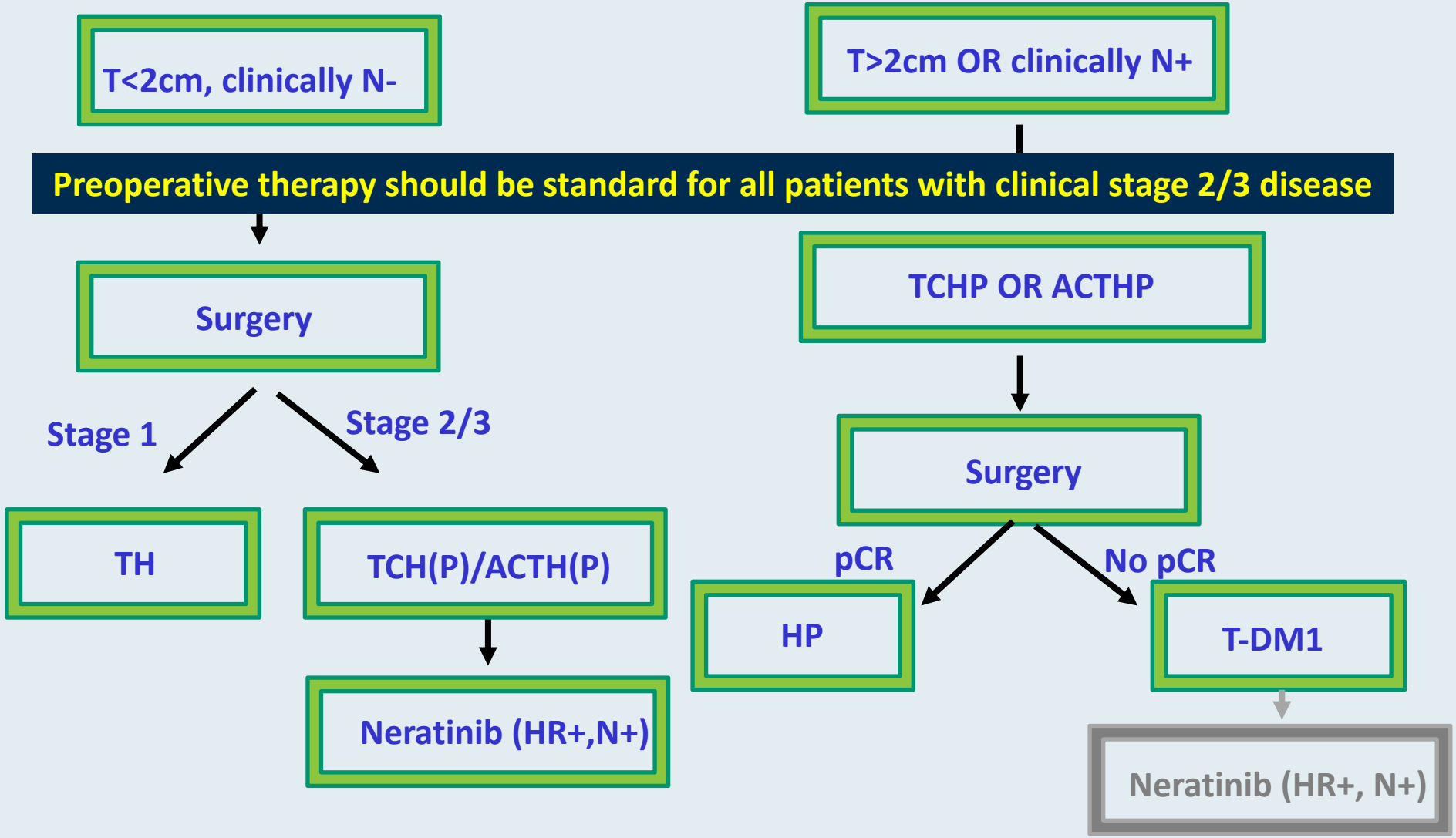
FDA-Approved Agents for Early-Stage HER2-Positive BC

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

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

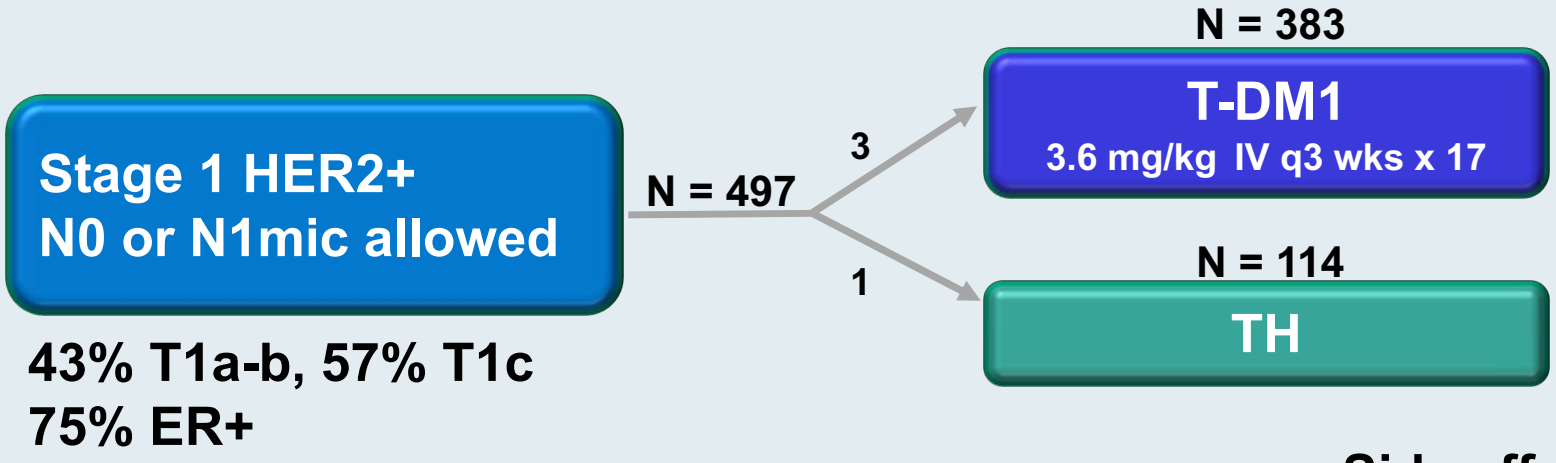
Choong GM et al. *CA Cancer J Clin* 2020;70:355-374.

Current Approach for Treatment of HER2-Positive Breast Cancer: 2020



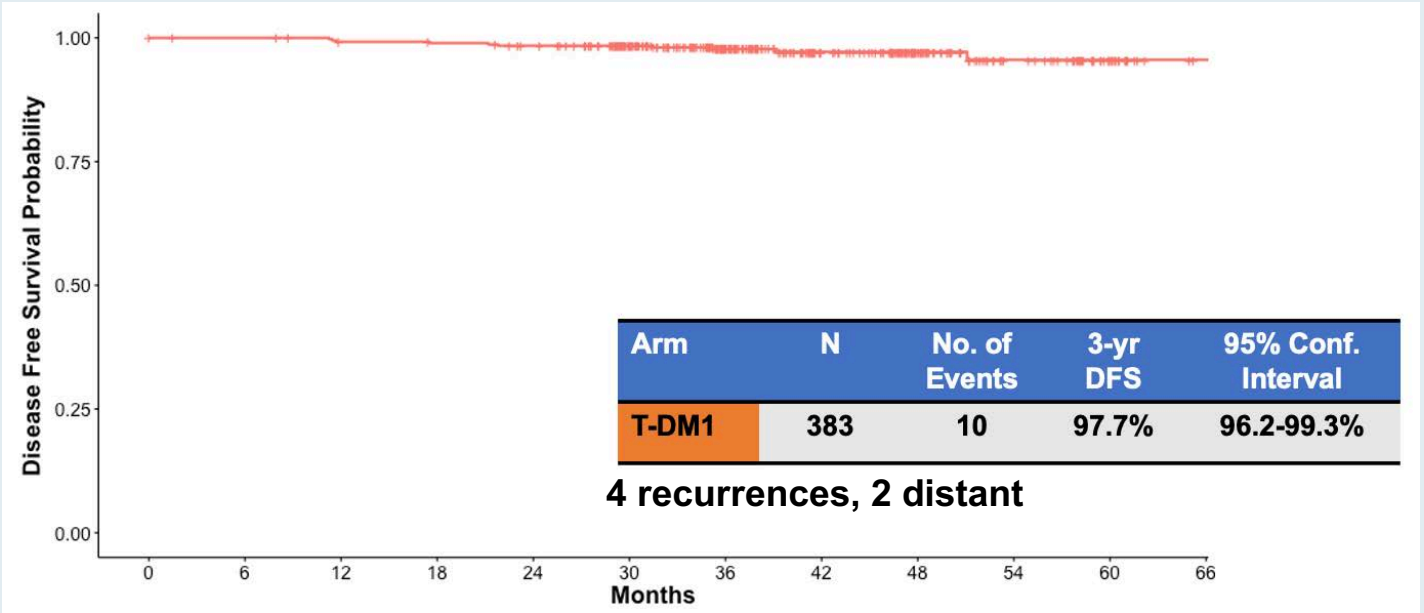
Courtesy of Sara M Tolaney, MD, MPH

ATEMPT (TBCRC 033) Phase II Trial: T-DM1 for Stage I Disease



1º endpoint
iDFS T-DM1 arm

43% T1a-b, 57% T1c
75% ER+



4 recurrences, 2 distant

Side effects T-DM1 vs TH:

Grade ≥2 TRAE	T-DM1 (n = 383)	TH (n = 114)
Neuropathy	11%	24%
Thrombocytopenia	11%	1%
Increased ALT	9%	4%
Increased bilirubin	5%	1%
Infusion-related reaction	5%	11%

Tolaney SM et al. SABCS 2019;Abstract GS1-05.

RTP RESEARCH TO PRACTICE

Original Study

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

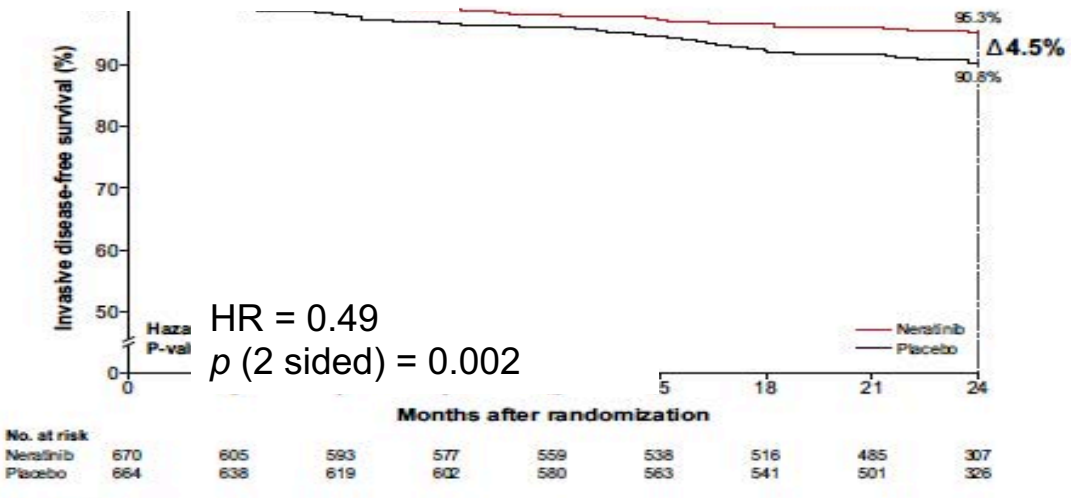
Arlene Chan,[1] Beverly Moy,[2] Janine Mansi,[3] Bent Ejlertsen,[4] Frankie Ann Holmes,[5] Stephen Chia,[6] Hiroji Iwata,[7] Michael Gnant,[8] Sibylle Loibl,[9] Carlos H. Barrios,[10] Isil Somali,[11] Snezhana Smichkoska,[12] Noelia Martinez,[13] Mirta Garcia Alonso,[14] John S. Link,[15] Ingrid A. Mayer,[16]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

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

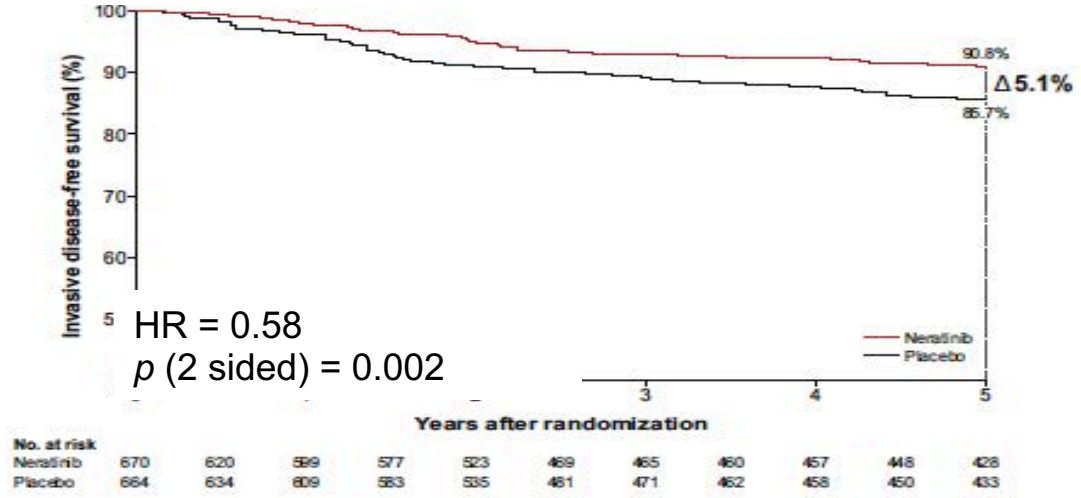
RTP RESEARCH TO PRACTICE

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

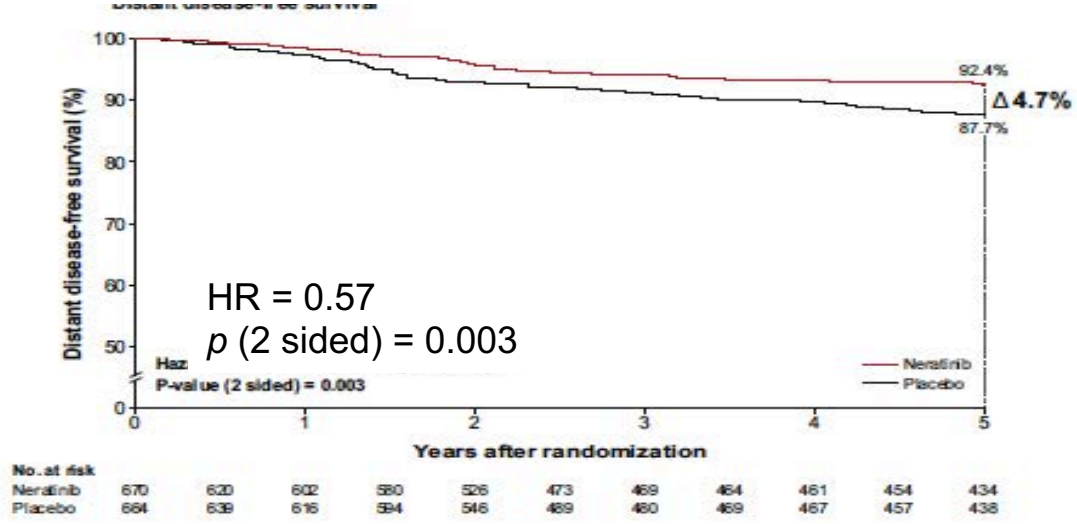
IDFS at 2 Years



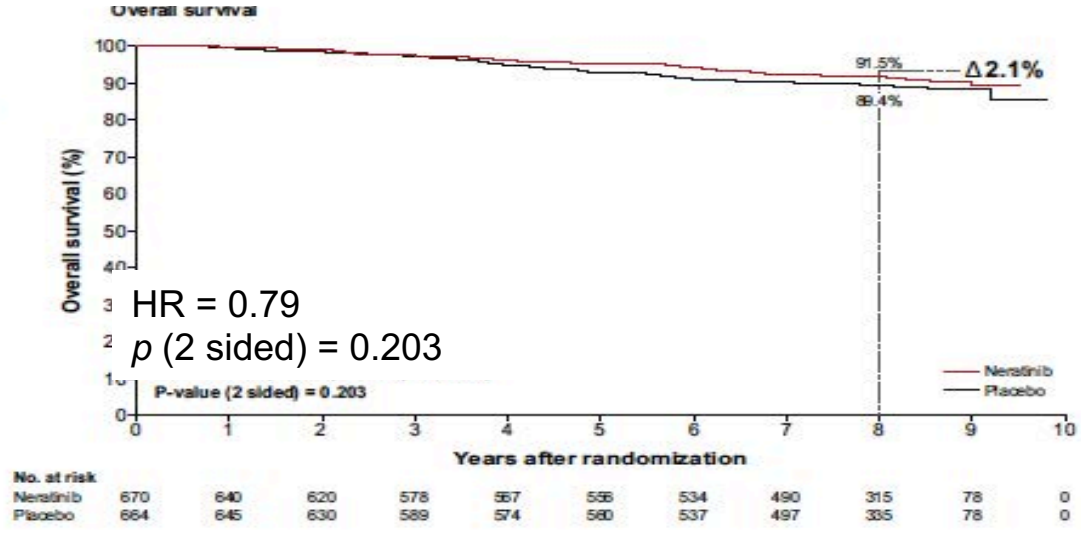
IDFS at 5 Years



Distant DFS at 5 Years



OS



Chan A et al. *Clin Breast Cancer* 2021;21(1):80-91.e.7.

RTP RESEARCH TO PRACTICE

CONTROL Trial: Strategies to Improve Neratinib Tolerability

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

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

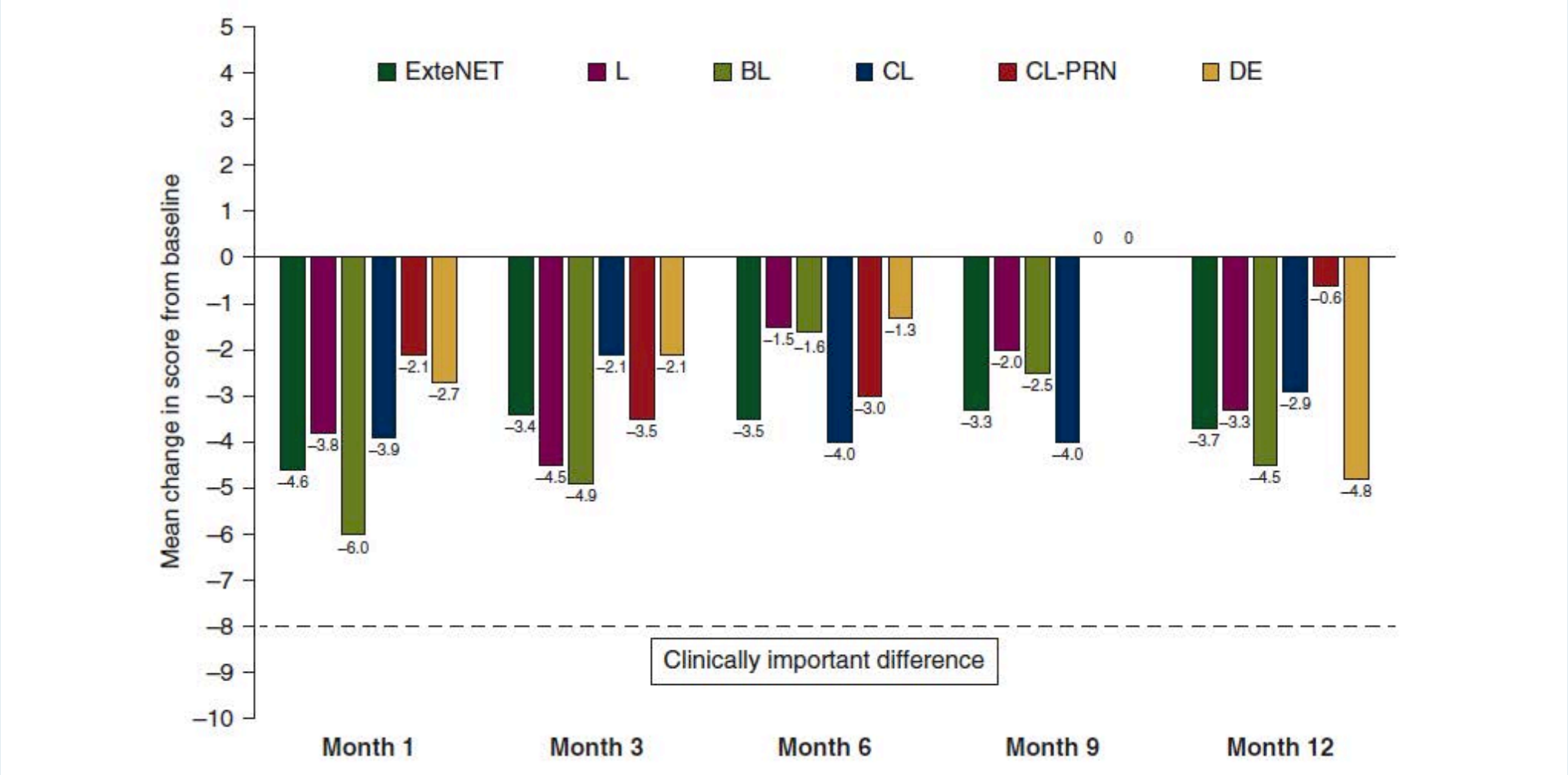
Objective: Improve GI tolerability of neratinib

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

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

Barcenas CH et al. *Ann Oncol* 2020;31(9):1223-30.

CONTROL: Mean Change in Functional Assessment of Cancer Therapy*



*A higher score indicates better quality of life.

Barcenas CH et al. *Ann Oncol* 2020;31(9):1223-30.

FDA Approval of the Combination of Pertuzumab, Trastuzumab and Hyaluronidase-zzxf for HER2-Positive Breast Cancer

Press Release – June 29, 2020

"The Food and Drug Administration approved a new fixed-dose combination of pertuzumab, trastuzumab, and hyaluronidase–zzxf for subcutaneous injection for the following indications:

Use in combination with chemotherapy as:

- Neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer;
- Adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.

Use in combination with docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Efficacy was investigated in FeDeriCa (NCT03493854), an open-label, multicenter, randomized trial enrolling 500 patients with operable or locally advanced HER2-positive breast cancer."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-combination-pertuzumab-trastuzumab-and-hyaluronidase-zzxf-her2-positive-breast-cancer

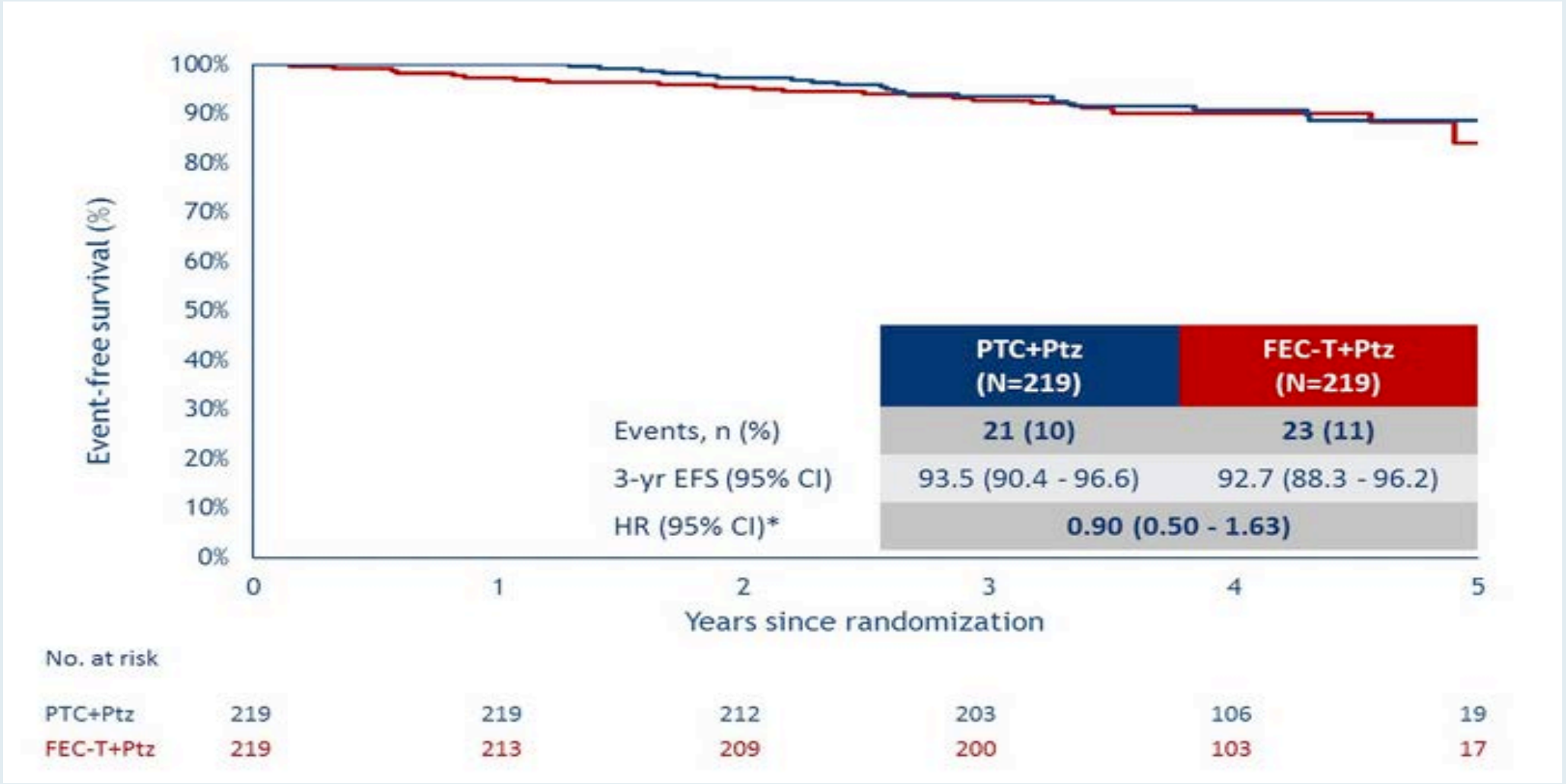
RTP RESEARCH TO PRACTICE

Three-Year Follow-Up of Neoadjuvant Chemotherapy With or Without Anthracyclines in the Presence of Dual HER2-Blockade for HER2-Positive Breast Cancer (TRAIN-2): A Randomized Phase III Trial

van der Voort A et al.

ASCO 2020;Abstract 501.

TRAIN-2: Event-Free Survival (EFS) in All Patients



Conclusion: No evidence that higher-risk HER2-positive BC requires anthracyclines

van der Voort A et al. ASCO 2020;Abstract 501.

RTP RESEARCH TO PRACTICE

Select Ongoing Phase III Trials in HER2-Positive Localized BC

Trial Name (NCT#)	N	Setting	Treatment arms	Estimated primary completion date
DESTINY-Breast05 (NCT04622319)	1,600	High-risk with residual invasive BC following neoadjuvant therapy	• Trastuzumab deruxtecan • T-DM1	December 2025
CompassHER2RD (NCT04457596)	1,031	HR-negative disease in breast and/or lymph nodes; T1-4, N0-3 dx at presentation and residual invasive disease postoperatively	• T-DM1 • Tucatinib + T-DM1	January 2028

Clinicaltrials.gov; Accessed February 2021.

RTP RESEARCH TO PRACTICE

FDA Approves Tucatinib for Patients with HER2-Positive Metastatic Breast Cancer

Press Release – April 17, 2020

"The Food and Drug Administration approved tucatinib in combination with trastuzumab and capecitabine, for adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

Efficacy was demonstrated in the HER2CLIMB trial (NCT02614794) enrolling 612 patients with HER2-positive metastatic breast cancer who had prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine. Patients received either tucatinib 300 mg twice daily plus trastuzumab and capecitabine (tucatinib arm, n = 410) or placebo plus trastuzumab and capecitabine (control arm, n = 202).

The primary endpoint was progression-free survival (PFS), assessed by a blinded independent central review, evaluated in the initial 480 randomized patients. The median PFS in patients receiving tucatinib was 7.8 months compared to 5.6 months for patients enrolled on the control arm (HR 0.54; $p < 0.00001$)."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tucatinib-patients-her2-positive-metastatic-breast-cancer

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 13, 2020 VOL. 382 NO. 7

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

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

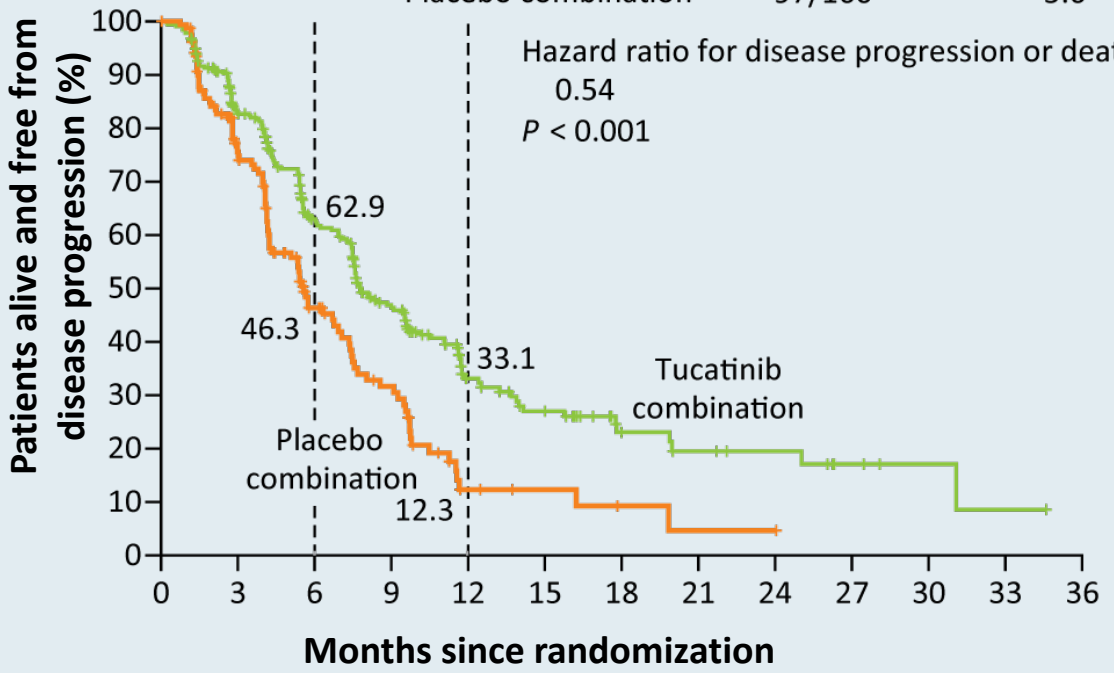
HER2CLIMB: Survival Outcomes

Among the patients with brain metastases:

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

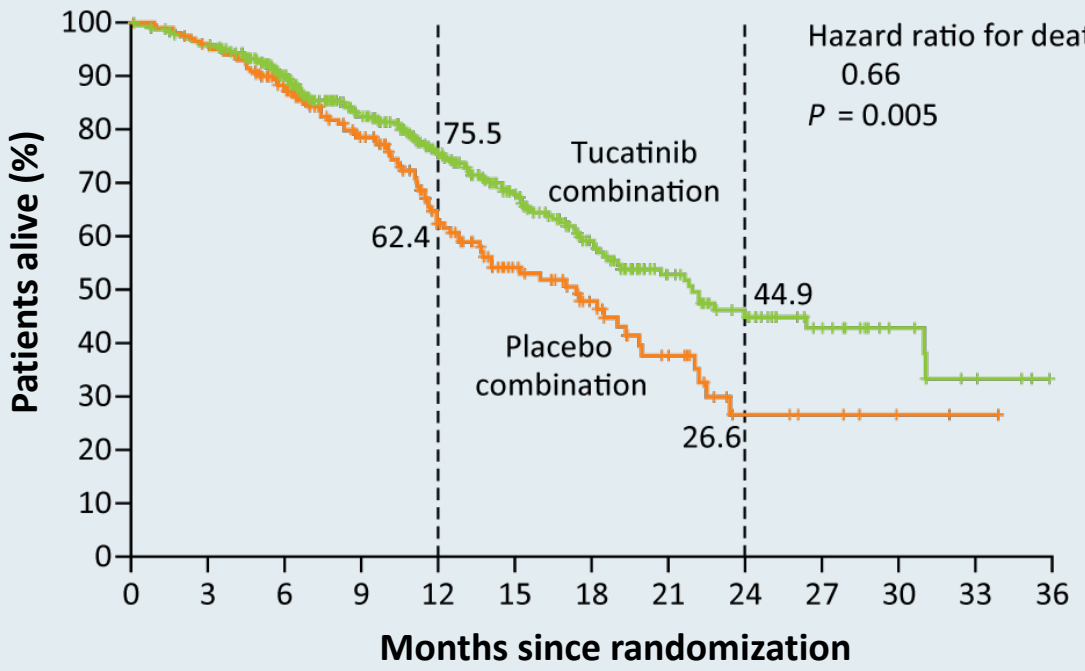
PFS

	No. of events/ No. of patients	Median duration *mo*
Tucatinib combination	178/320	7.8
Placebo combination	97/160	5.6



OS

	No. of deaths/ No. of patients	Median duration *mo*
Tucatinib combination	130/410	21.9
Placebo combination	85/202	17.4



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

RTP RESEARCH TO PRACTICE

HER2CLIMB: Safety Outcomes

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

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

rapid communications

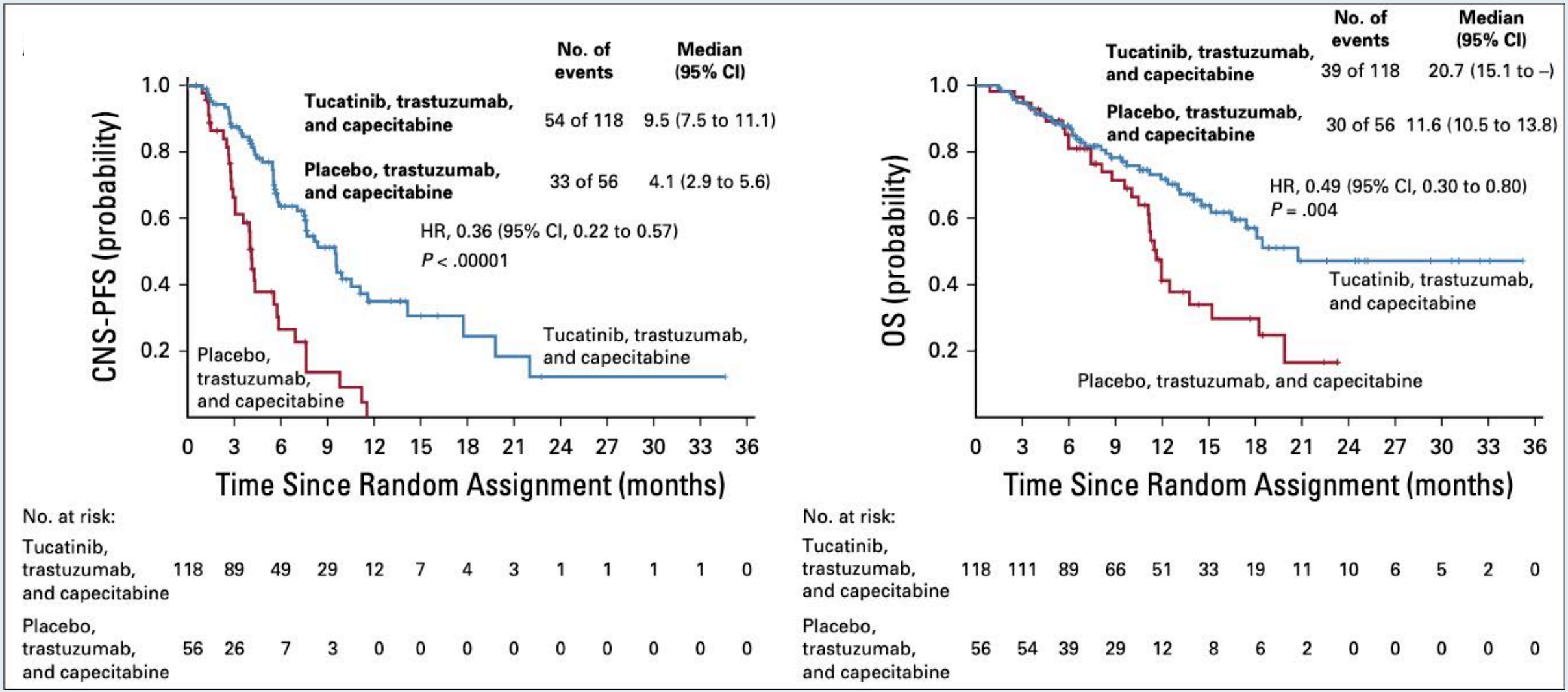
Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial

Nancy U. Lin, MD[1]; Virginia Borges, MMSc, MD[2]; Carey Anders, MD[3]; Rashmi K. Murthy, MD, MBE[4]; Elisavet Paplomata, MD[5]; Erika Hamilton, MD[6]; Sara Hurvitz, MD[7]; Sherene Loi, MD, PhD[8]; Alicia Okines, MBChB, MD[9]; Vandana Abramson, MD[10]; Philippe L. Bedard, MD[11]; Mafalda Oliveira, MD, PhD[12]; Volkmar Mueller, MD[13]; Amelia Zelnak, MD[14]; Michael P. DiGiovanna, MD, PhD[15]; Thomas Bachelot, MD[16]; A. Jo Chien, MD[17]; Ruth O'Regan, MD[5]; Andrew Wardley, MBChB, MSc, MD[18]; Alison Conlin, MD, MPH[19]; David Cameron, MD, MA[20]; Lisa Carey, MD[21]; Giuseppe Curigliano, MD, PhD[22]; Karen Gelmon, MD[23]; Sibylle Loibl, MD, PhD[24]; JoAl Mayor, PharmD[25]; Suzanne McGoldrick, MD, MPH[25]; Xuebei An, PhD[25]; and Eric P. Winer, MD[1]

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

RTP RESEARCH TO PRACTICE

HER2CLIMB: CNS PFS and OS in Pts with Active Brain Metastases



Lin NU et al. *J Clin Oncol* 2020;38(23):2610-9.

RTP RESEARCH TO PRACTICE

FDA Approval of Trastuzumab Deruxtecan for Unresectable or Metastatic HER2-Positive Breast Cancer

Press Release – December 20, 2019

"The Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki for patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

Efficacy was investigated in DESTINY-Breast01 (NCT03248492), a multicenter, single-arm trial enrolling 184 female patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2 therapies. Patients received fam-trastuzumab deruxtecan-nxki 5.4 mg/kg by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2-positive-breast-cancer

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

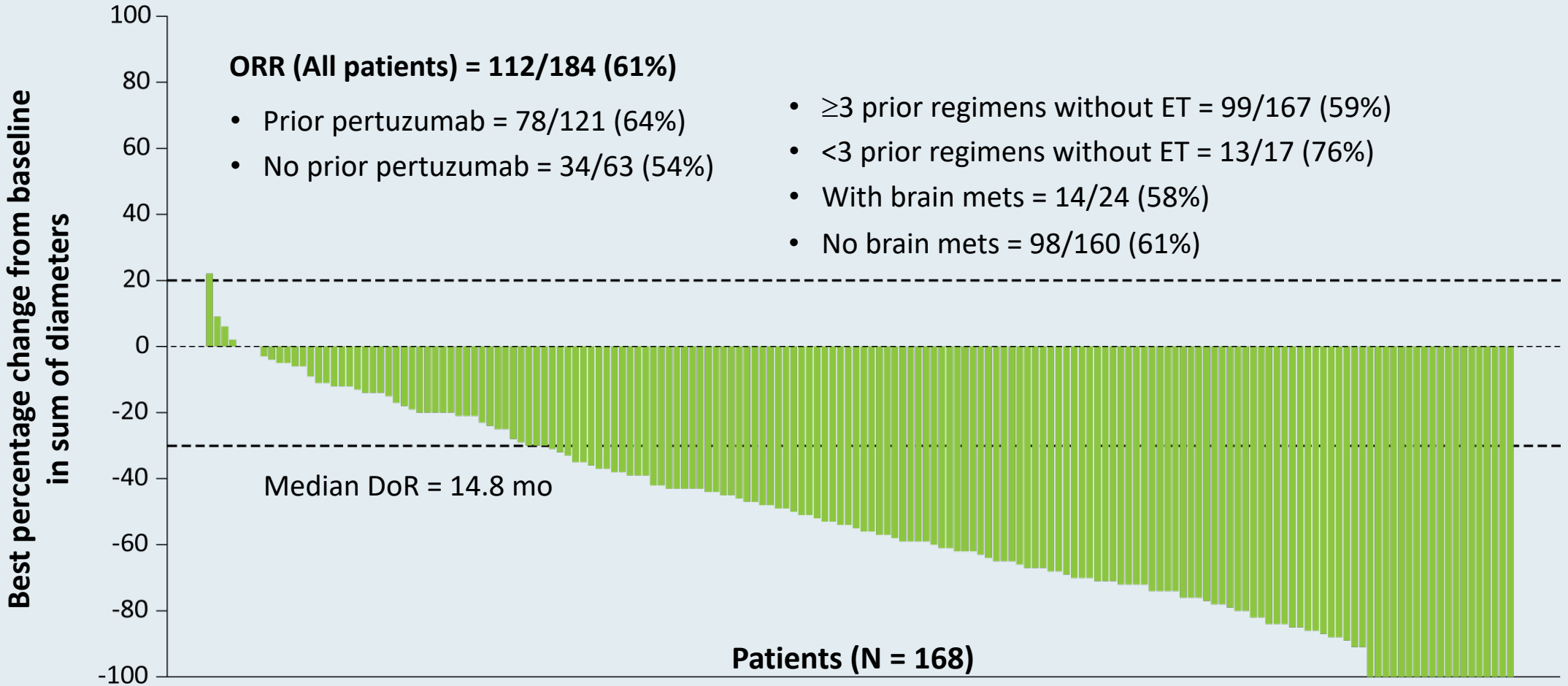
ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

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

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

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



Modi S et al. *N Engl J Med* 2020;382(7):610-21.

RTP RESEARCH TO PRACTICE

DESTINY-Breast01: Survival and Safety

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

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

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

Modi S et al. *N Engl J Med* 2020;382(7):610-21.

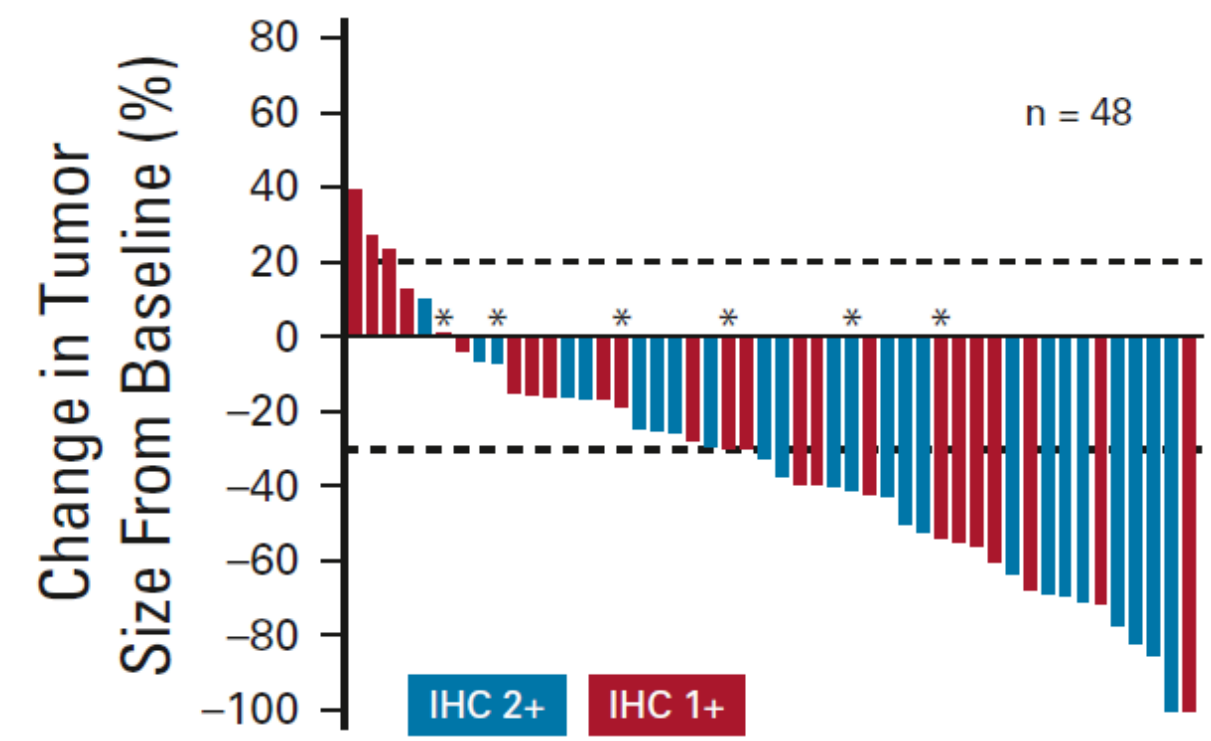
original reports

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

Shanu Modi, MD[1]; Haeseong Park, MD, MPH[2]; Rashmi K. Murthy, MD, MBE[3]; Hiroji Iwata, PhD, MD[4]; Kenji Tamura, MD, PhD[5]; Junji Tsurutani, MD, PhD[6]; Alvaro Moreno-Aspitia, PhD[7]; Toshihiko Doi, MD, PhD[8]; Yasuaki Sagara, MD[9]; Charles Redfern, MD[10]; Ian E. Krop, MD, PhD[11]; Caleb Lee, MD, PhD[12]; Yoshihiko Fujisaki, MS[13]; Masahiro Sugihara, PhD[13]; Lin Zhang, MD, PhD[12]; Javad Shahidi, MD[12]; and Shunji Takahashi, MD[14]

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

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



Clinical activity (by independent review)

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

* Median of 7.5 prior regimens

Modi et al. *J Clin Oncol* 2020;38(17):1887-96.

Courtesy of Ian E Krop, MD, PhD

RTP RESEARCH TO PRACTICE

FDA Approves Neratinib for HER2-Positive mBC

Press Release – February 25, 2020

"On February 25, 2020, the Food and Drug Administration approved neratinib in combination with capecitabine for adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.

Efficacy of neratinib with capecitabine was investigated in NALA (NCT01808573), a randomized, multicenter, open-label clinical trial in 621 patients with metastatic HER2-positive breast cancer who received two or more prior anti-HER2 based regimens in the metastatic setting."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neratinib-metastatic-her2-positive-breast-cancer

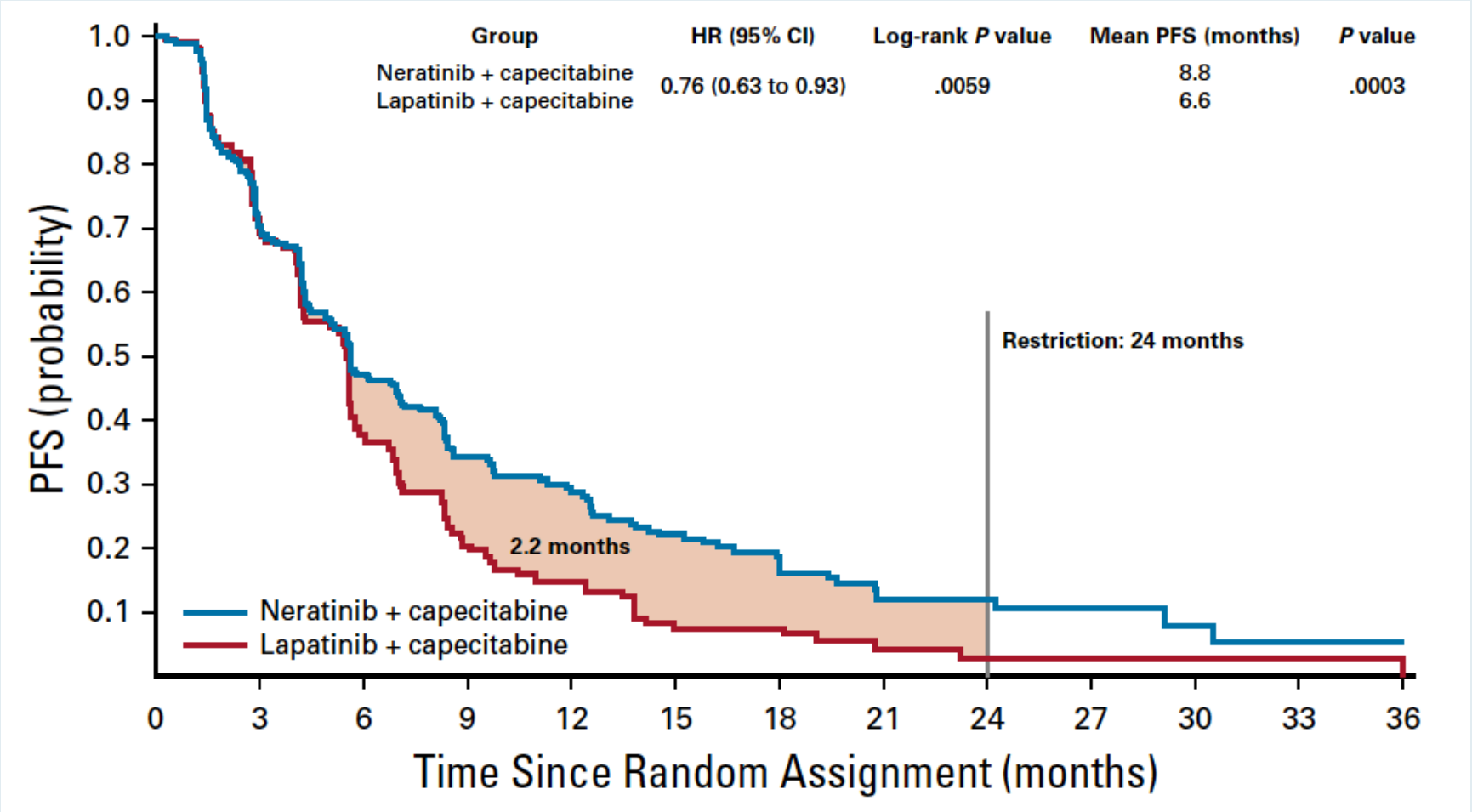
original reports

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

Cristina Saura, MD[1]; Mafalda Oliveira, MD, PhD[1]; Yin-Hsun Feng, MD, PhD[2]; Ming-Shen Dai, MD, PhD[2]; Shang-Wen Chen, MD[2]; Sara A. Hurvitz, MD[3]; Sung-Bae Kim, MD, PhD[4]; Beverly Moy, MD, PhD[5]; Suzette Delaloge, MD, MSc[6]; William Gradishar, MD[7]; Norikazu Masuda, MD, PhD[8]; Marketa Palacova, MD[9]; Maureen E. Trudeau, MD[10]; Johanna Mattson, MD, PhD[11]; Yoon Sim Yap, MBBS[12]; Ming-Feng Hou, MD[13]; Michelino De Laurentiis, MD, PhD[14]; Yu-Min Yeh, MD[15]; Hong-Tai Chang, MD[16]; Thomas Yau, MBBS, MD[17]; Hans Wildiers, MD, PhD[18,19]; Barbara Haley, MD[20]; Daniele Fagnani, MD[21]; Yen-Shen Lu, MD, PhD[22]; John Crown, MBBCh, MD[23]; Johnson Lin, MD[24]; Masato Takahashi, MD, PhD[25]; Toshimi Takano, MD[26]; Miki Yamaguchi, MD, PhD[27]; Takaaki Fujii, MD, PhD[28]; Bin Yao, MS[29]; Judith Bebchuk, ScD[29]; Kiana Keyvanjah, PharmD[29]; Richard Bryce, MBChB[29]; and Adam Brufsky, MD, PhD[30]; for the NALA Investigators

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

NALA Trial – Centrally Confirmed Coprimary Endpoints: PFS and OS



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

Saura C et al. *J Clin Oncol* 2020;38(27):3138-49.

FDA Approves Margetuximab for HER2-Positive mBC

Press Release – December 16, 2020

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

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

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-margetuximab-metastatic-her2-positive-breast-cancer

Research

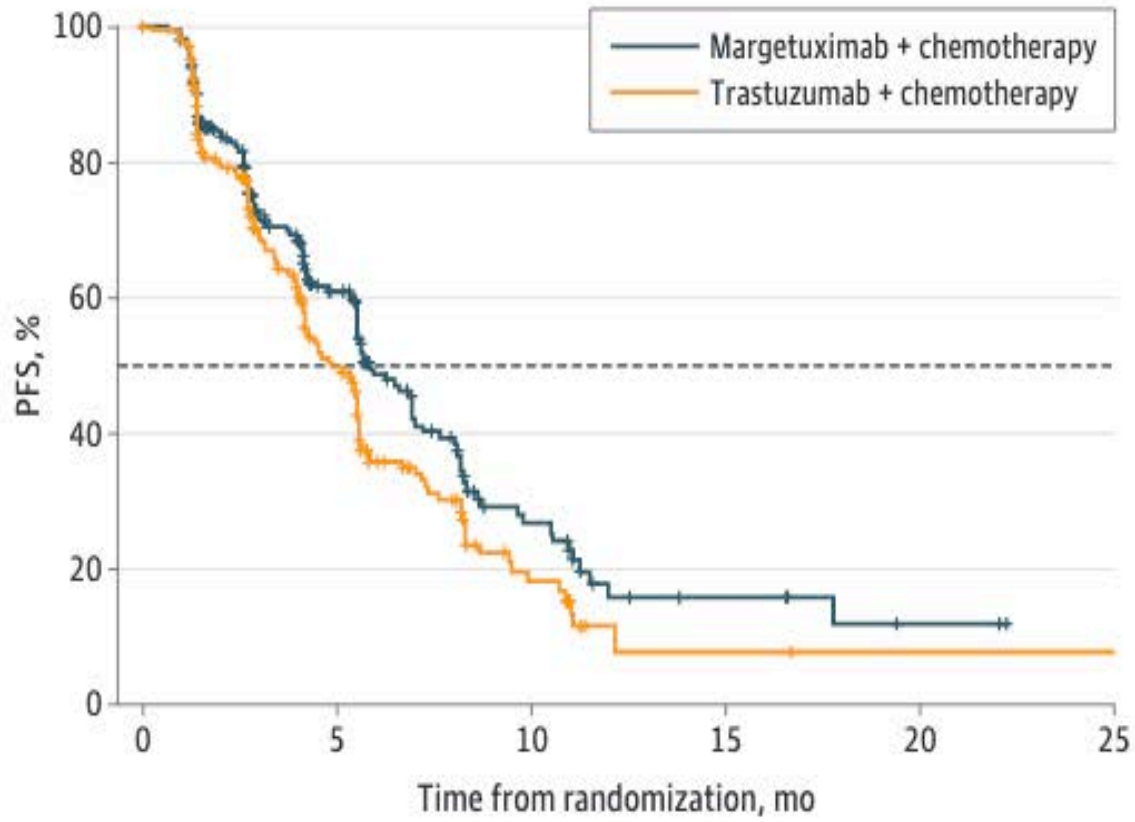
JAMA Oncology | Original Investigation

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

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

***JAMA Oncol* 2021;Online ahead of print.**

SOPHIA: PFS by Central Blinded Analysis (ITT Population)

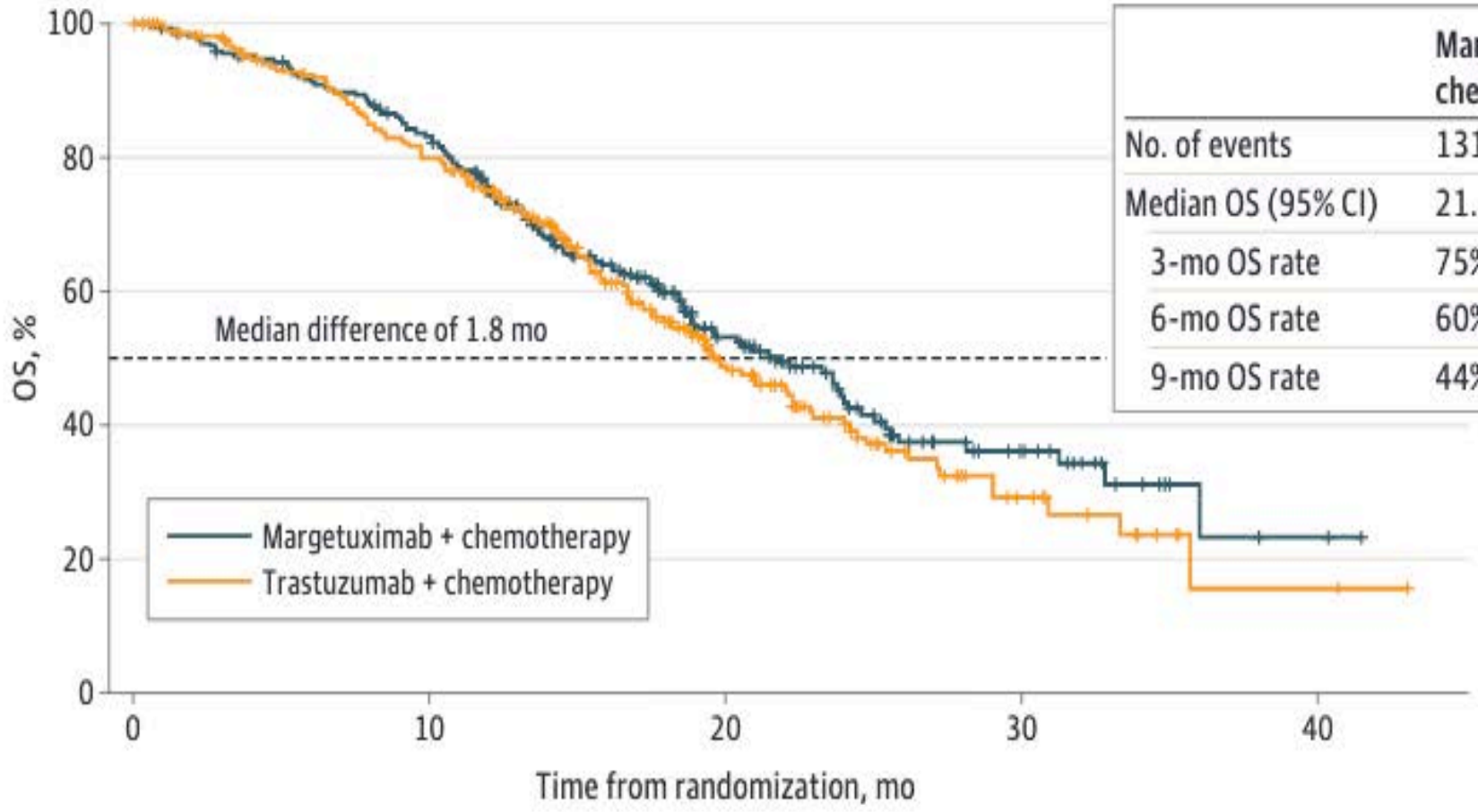


	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	130	135
Median PFS (95% CI)	5.8 mo (5.52-6.97)	4.9 mo (4.17-5.59)
3-mo PFS rate	72% (65%-77%)	70% (63%-76%)
6-mo PFS rate	48% (41%-56%)	36% (28%-44%)
9-mo PFS rate	30% (22%-38%)	22% (15%-30%)

HR by stratified Cox model, 0.76 (95% CI, 0.59-0.98)
Stratified log-rank $P = .03$
24% Risk reduction of disease progression[a]
Median follow-up, 2.8 mo

Rugo HS et al. *JAMA Oncol* 2021;Online ahead of print.

SOPHIA: OS Analysis (ITT Population)



	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	131	139
Median OS (95% CI)	21.6 mo (18.86-24.05)	19.8 mo (17.54-22.28)
3-mo OS rate	75% (70%-80%)	75% (70%-80%)
6-mo OS rate	60% (53%-66%)	56% (49%-62%)
9-mo OS rate	44% (36%-51%)	40% (33%-48%)

HR by stratified Cox model, 0.89 (95% CI, 0.69-1.13)
Stratified log-rank $P = .33$
Median follow-up, 15.6 mo

Rugo HS et al. *JAMA Oncol* 2021;Online ahead of print.

Agenda

Module 1: Triple-Negative Breast Cancer (TNBC)

Dr Zelkowitz: A 50-year-old Korean woman with Stage IA TNBC

Dr Zelkowitz – Questions and Comments: Incorporation and tolerability of sacituzumab govitecan

Dr Zelkowitz – Questions and Comments: Impact of mask wearing on patients during COVID-19

Module 2: HER2-Positive BC

Dr Choksi: A 67-year-old woman with past history of TNBC develops ER/PR-positive, HER2-positive BC

Dr Zelkowitz: A 53-year-old woman with Stage IIA triple-positive BC

Dr Shehadeh: A 35-year-old premenopausal woman with ER/PR-negative, HER2-positive mBC

Dr Zelkowitz – Questions and Comments: Later-line treatment options for HER2-positive mBC

Module 3: ER-Positive, HER2-Negative BC

Dr Favaro: A 58-year-old postmenopausal woman with ER-positive, node-positive localized BC

Case Presentation – Dr Favaro: A 58-year-old postmenopausal woman with ER-positive, node-positive localized breast cancer

Dr Justin Peter Favaro

- Referred for Stage IB cutaneous T-cell lymphoma
- Scan revealed left axillary lymphadenopathy
- Work up: Right ER-positive, HER2-negative, high-grade IDC, with 3 positive lymph nodes and 1 node with extranodal extension

Questions

- Is it appropriate to use Onco*type* DX to help determine the role of adjuvant chemotherapy for this patient, based on the RxPONDER trial?
- Does the focal extranodal extension and the high grade of her tumor make her too high risk to warrant sending for an Onco*type* DX assay?

RTP RESEARCH TO PRACTICE

A premenopausal woman presents with a Grade 2, ER/PR-positive, HER2-negative 2.1-cm IDC with 2 positive sentinel lymph nodes. Would you order a genomic assay for this patient?

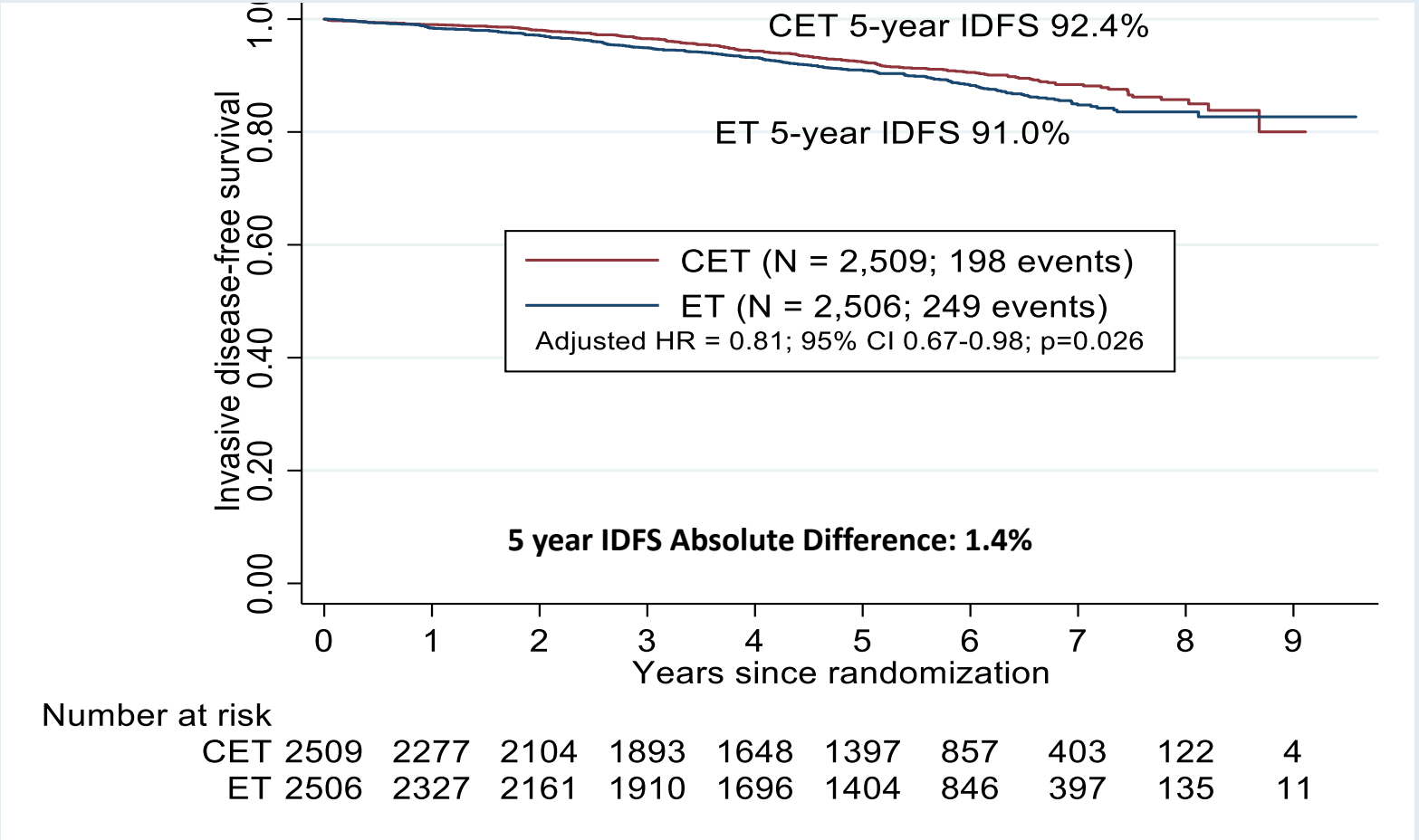
1. No
2. Yes, the 21-gene assay
3. Yes, the 70-gene signature
4. Yes, Prosigna® PAM50
5. Yes, Breast Cancer Index
6. Yes, other

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

Kalinsky K et al.

SABCS 2020;Abstract GS3-00.

RxPONDER: IDFS in Overall Population by Treatment Arm



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

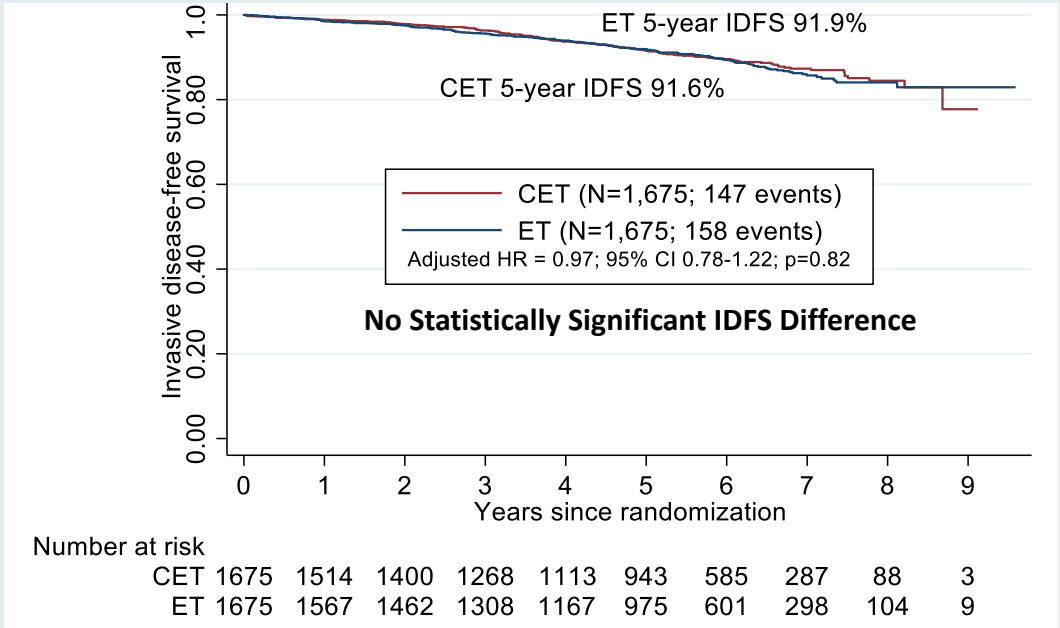
447 observed IDFS events (54% of expected at final analysis) at a median follow-up of 5.1 years

Kalinsky K et al. SABCS 2020;Abstract GS3-00.

RTP RESEARCH TO PRACTICE

RxPONDER: IDFS Stratified by Menopausal Status

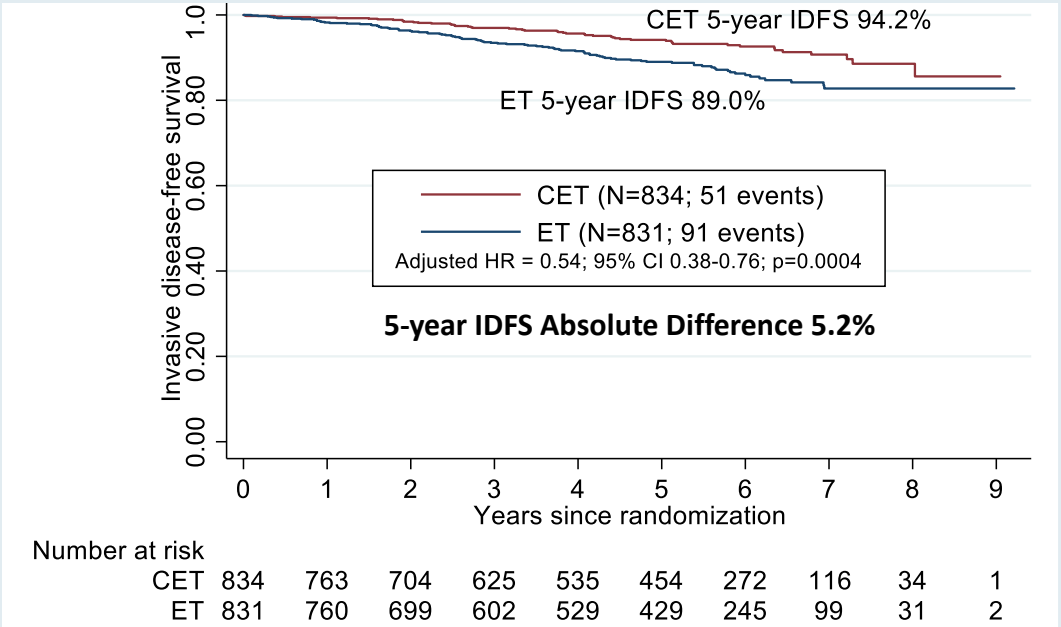
Postmenopausal



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

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

Premenopausal



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

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

Kalinsky K et al. SABCS 2020;Abstract GS3-00.

RTP RESEARCH TO PRACTICE

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

Harbeck N et al.

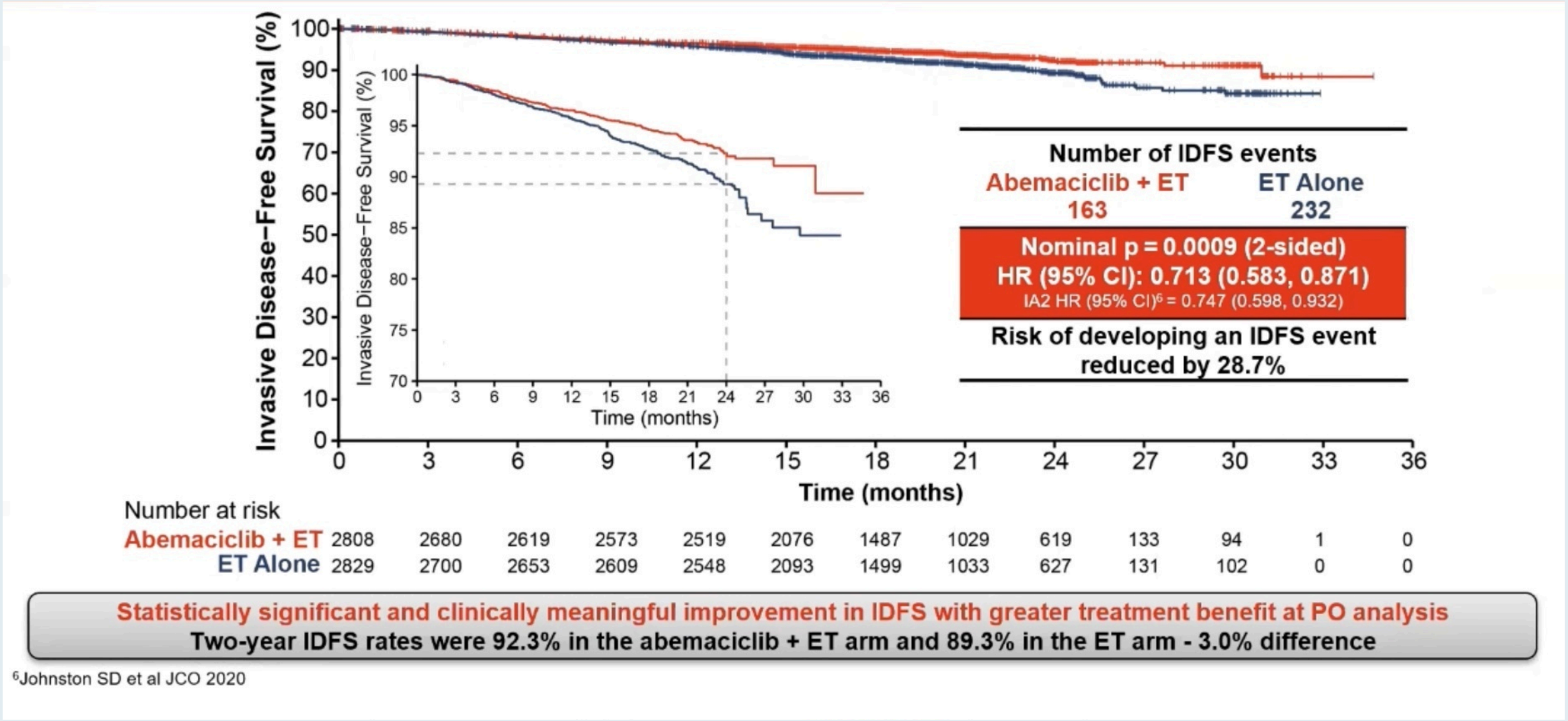
SABCS 2020;Abstract GS4-04.

Primary Outcome Analysis of Invasive Disease-Free Survival for monarchE: Abemaciclib Combined with Adjuvant Endocrine Therapy for High-Risk Early Breast Cancer

O’Shaughnessy JA et al.

SABCS 2020;Abstract GS1-01.

monarchE: Invasive Disease-Free Survival at Primary Outcome Analysis



Statistically significant and clinically meaningful improvement in IDFS with greater treatment benefit at PO analysis

Two-year IDFS rates were 92.3% in the abemaciclib + ET arm and 89.3% in the ET arm - 3.0% difference

[6]Johnston SD et al JCO 2020

O'Shaughnessy JA et al. SABCS 2020;Abstract GS1-01.

Key AEs with CDK4/6 Inhibitors: Monitoring and Prevention

Diarrhea	Hepatobiliary Toxicity	QT Prolongation	Neutropenia	VTE	ILD/ Pneumonitis
Abemaciclib (more) **Palbociclib** **Ribociclib**	**Abemaciclib** **Ribociclib**	**Ribociclib**	Abemaciclib (less) Palbociclib Ribociclib	Abemaciclib	Abemaciclib Palbociclib Ribociclib
Antidiarrheal therapy Increase oral hydration Notify HCP	LFTs before starting tx, Q2W x 2 mos, then: ▪ *abemaciclib,* as indicated ▪ *ribociclib,* at start of cycle x 4 cycles	EKG before cycle 1, Day 14 of cycle 1, start of cycle 2, then as indicated Electrolytes at start of cycle x 6 cycles, then as indicated	CBC before starting tx, then: ▪ *abemaciclib,* Q2W x 2 mos, QM x 2 mos, then as indicated ▪ *palbociclib,* Days 1 and 15 of cycles 1-2, then as indicated ▪ *ribociclib,* Q2W x 2 cycles, start of next 4 cycles, then as indicated	Monitor for signs and symptoms of thrombosis or pulmonary embolism	Monitor for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea)

Courtesy of Sara M Tolaney MD, MPH

RTP RESEARCH TO PRACTICE

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

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

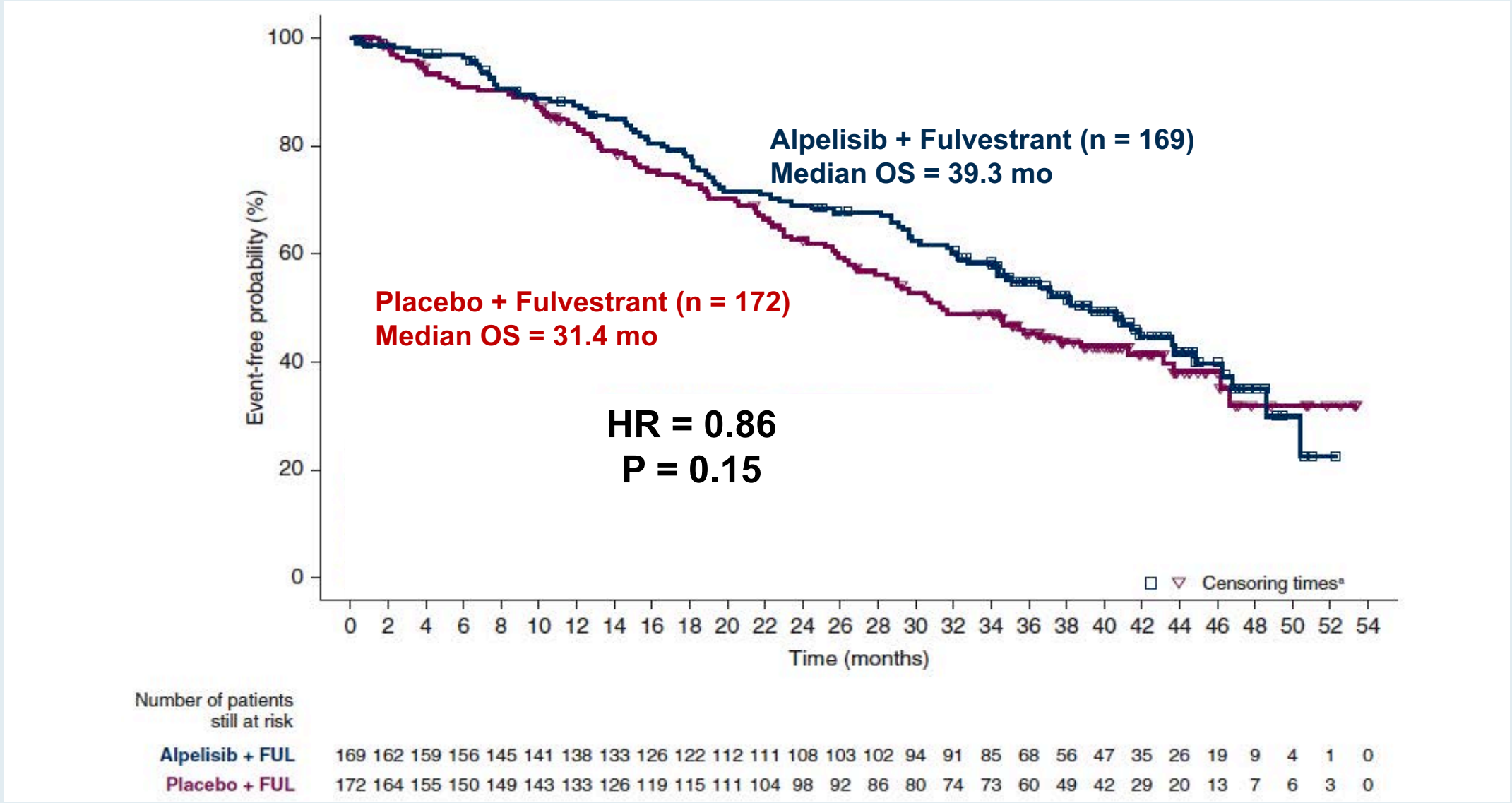
F. André[1*], E. M. Ciruelos[2], D. Juric[3], S. Loibl[4], M. Campone[5], I. A. Mayer[6], G. Rubovszky[7], T. Yamashita[8], B. Kaufman[9], Y.-S. Lu[10], K. Inoue[11], Z. Pápai[12], M. Takahashi[13], F. Ghaznawi[14], D. Mills[15], M. Kaper[14], M. Miller[14], P. F. Conte[16], H. Iwata[17] & H. S. Rugo[18]

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

Available online 25 November 2020

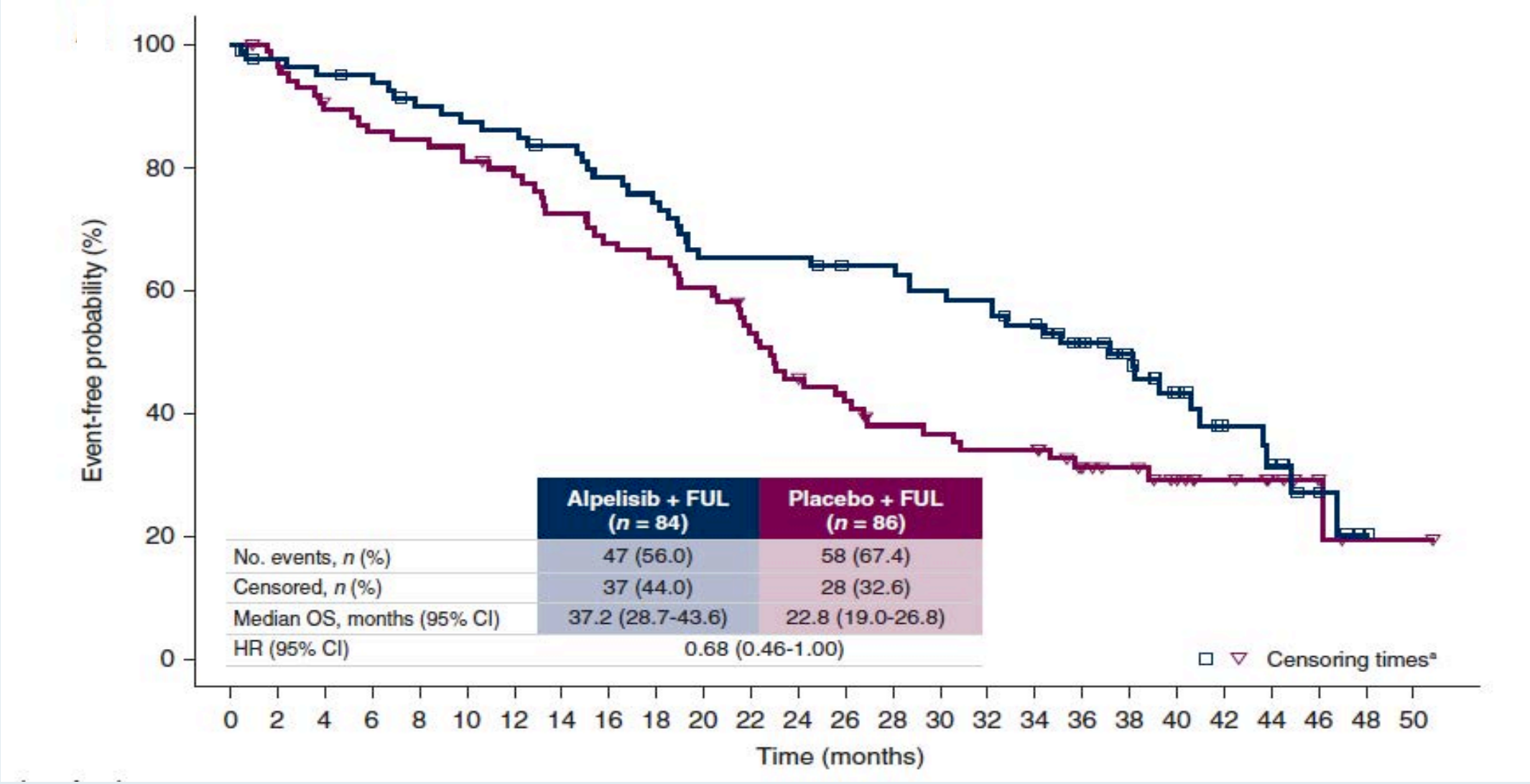
***Ann Oncol* 2021;32(2):208-17.**

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



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

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



	Alpelisib + FUL (*n* = 84)	Placebo + FUL (*n* = 86)
No. events, *n* (%)	47 (56.0)	58 (67.4)
Censored, *n* (%)	37 (44.0)	28 (32.6)
Median OS, months (95% CI)	37.2 (28.7-43.6)	22.8 (19.0-26.8)
HR (95% CI)	0.68 (0.46-1.00)	

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

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

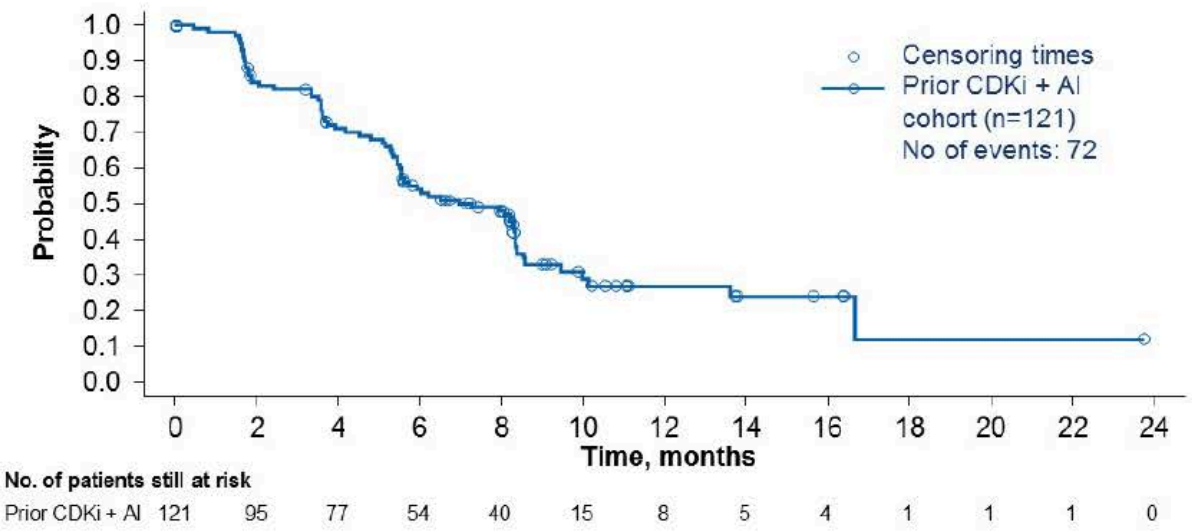
Rugo HS et al.

ASCO 2020;Abstract 1006.

BYLieve COHORT A: Primary Endpoint and PFS

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

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

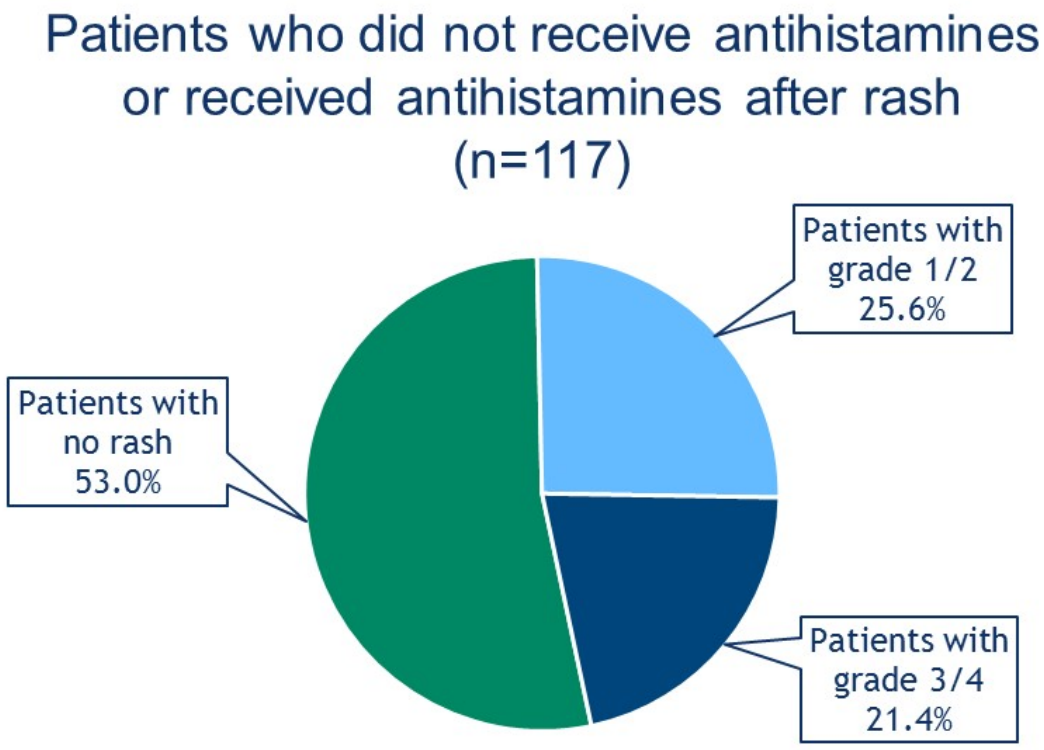


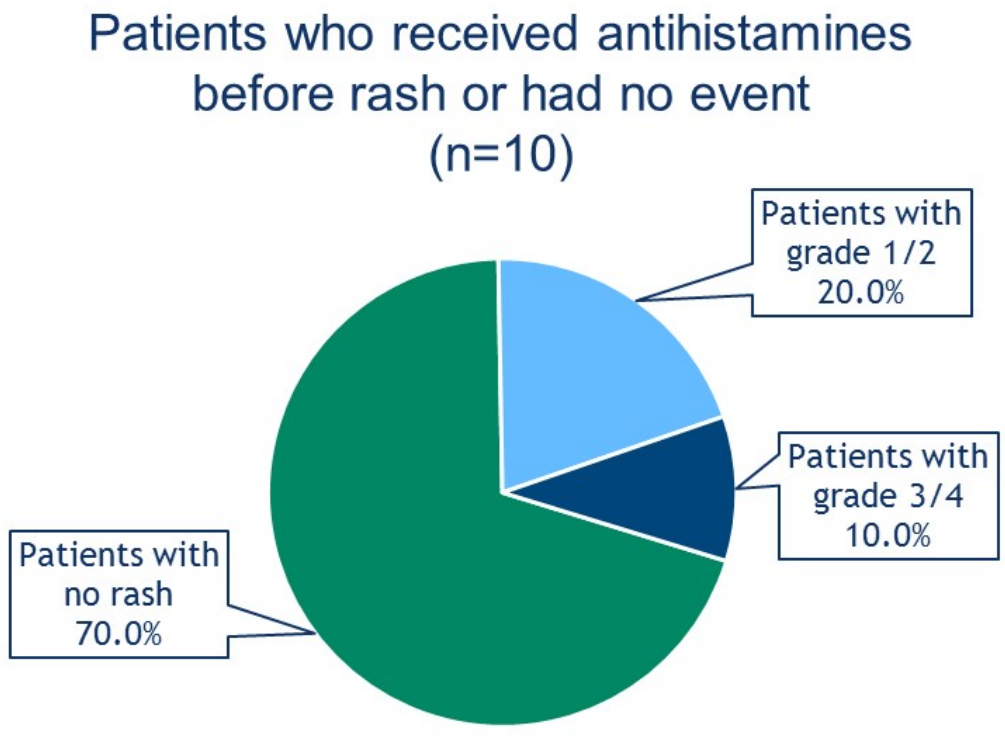
The primary endpoint for the prior CDKi + AI cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months

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

Rugo HS et al. ASCO 2020;Abstract 1006.

BYLieve: Incidence of Rash with and without Prophylactic Antihistamines





Rugo HS et al. ASCO 2020;Abstract 1006.

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

We are taking a short break!

The program will resume at 3:30 PM ET

Up Next…

Drs Courtney D DiNardo and Alexander Perl discuss the management of acute myeloid leukemia and myelodysplastic syndromes

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TO PRACTICE

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

Agenda

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

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

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

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

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

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

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

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RESEARCH
TO PRACTICE

Acute Myeloid Leukemia and Myelodysplastic Syndromes Faculty

Courtney D DiNardo, MD, MSCE
Associate Professor, Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Alexander Perl, MD
Associate Professor of Medicine
Perelman School of Medicine
Member, Leukemia Program
Abramson Cancer Center
University of Pennsylvania
Philadelphia, Pennsylvania

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The patients I saw today…

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

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

RTP RESEARCH TO PRACTICE

Contributing Oncologists

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

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

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

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

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

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

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

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TO PRACTICE

Contributing Oncologists

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

Nasfat Shehadeh, MD
Medical Oncologist
Oncology Specialists of Charlotte
Charlotte, North Carolina

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

Saad Zafar Usmani, MD, MBA
Division Chief, Plasma Cell Disorders
Levine Cancer Institute, Carolinas Medical Center
Charlotte, North Carolina

Maria E Picton, MD
Hematology Oncology, Physicians East
Greenville, North Carolina

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

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Agenda

Module 1: Newly Diagnosed AML

- Dr Chojecki: A 73-year-old man with AML

Module 2: Relapsed/Refractory AML with a FLT3 Mutation

- Dr Chojecki: A 69-year-old woman with AML and a FLT3 ITD mutation

Module 3: Newly Diagnosed AML with an IDH1 Mutation

- Dr Chojecki: An 86-year-old man with AML and an IDH1 mutation

Module 4: Secondary AML

- Dr Chojecki: A 60-year-old woman with AML and a TP53 mutation

Module 5: Myelodysplastic Syndromes

- Dr Chojecki: A 78-year-old man with “low risk” MDS
- Dr Favaro: A 77-year-old man with MDS

Agenda

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- Dr Chojecki: A 78-year-old man with “low risk” MDS
- Dr Favaro: A 77-year-old man with MDS

Case Presentation – Dr Chojecki: A 73-year-old man with AML

Dr Aleksander Chojecki

- PMH: HTN, HLD
- New onset pancytopenia → extensive work up: AML
- NGS: U2AF1, DDX41 mutations
- Azacitidine and venetoclax

Questions

- What starting dose of venetoclax do you use?
  - When do you do your first bone marrow biopsy – after cycle 1 or cycle 2?
- Would you combine oral decitabine or oral azacitidine with venetoclax?
- Would it be unreasonable to continue venetoclax as a single agent once the patient is in remission? Or, what about just continuing the hypomethylating agent alone due to complications with neutropenia?
- Do you use low-dose cytarabine with venetoclax over an HMA? What would be the typical patient to whom you would offer venetoclax/LDAC versus venetoclax/HMA?

RTP RESEARCH TO PRACTICE

What initial treatment would you recommend for a 65-year-old man with AML with a PS of 1 and pancytopenia, 35% marrow myeloblasts, a complex karyotype and a TP53 mutation?

1. 7 + 3 induction
2. Azacitidine
3. Decitabine
4. Azacitidine + venetoclax
5. Decitabine + venetoclax
6. Low-dose cytarabine + venetoclax
7. Other

FDA Grants Regular Approval to Venetoclax in Combination for Untreated Acute Myeloid Leukemia

Press Release – October 16, 2020

"The Food and Drug Administration granted regular approval to venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine (LDAC) for newly-diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities precluding intensive induction chemotherapy.

Venetoclax was initially granted accelerated approval for this indication in November 2018.

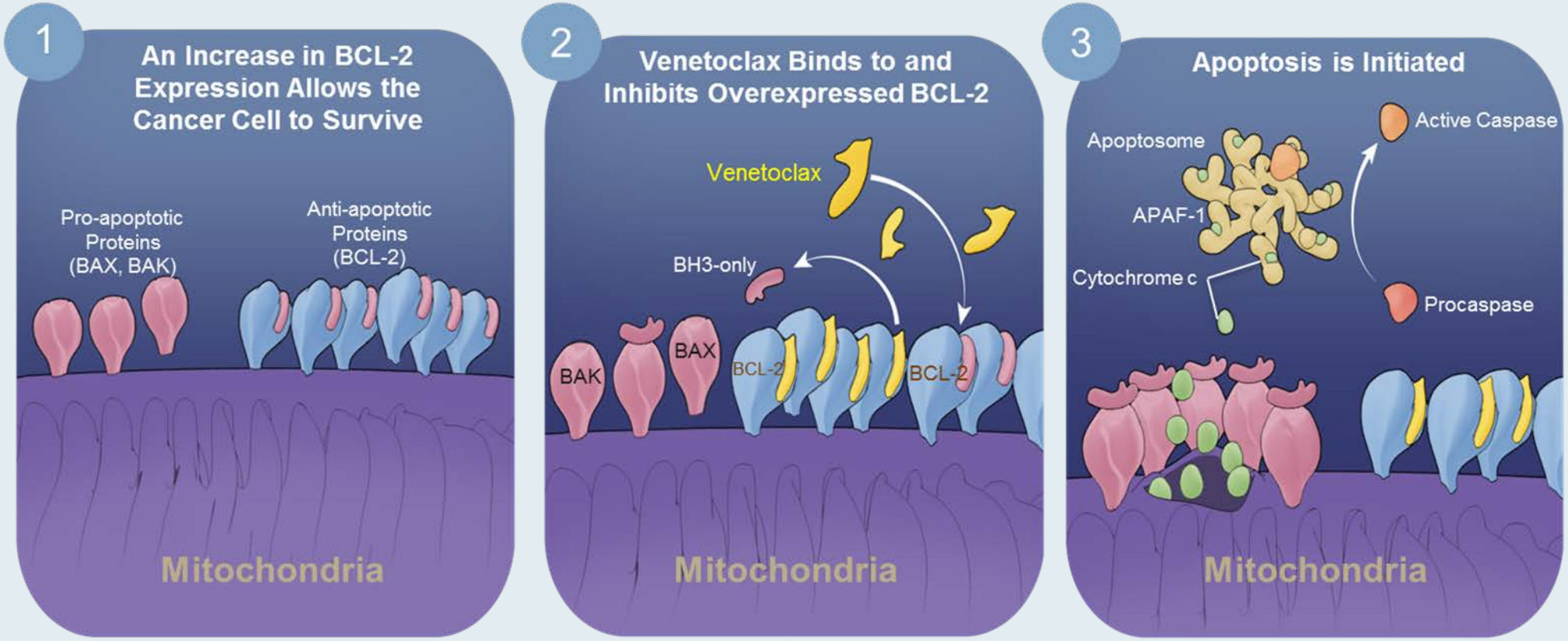
Efficacy was confirmed in two randomized, double-blind, placebo-controlled trials in patients with AML described above.

In VIALE-A (NCT02993523), patients were randomized to receive venetoclax plus azacitidine (n=286) or placebo plus azacitidine (n=145). Efficacy was established based on an improvement in overall survival (OS).

In VIALE-C (NCT03069352), patients were randomized to receive venetoclax plus LDAC (n=143) or placebo plus LDAC (n=68). Efficacy was based on CR rate and duration of CR."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-regular-approval-venetoclax-combination-untreated-acute-myeloid-leukemia

Venetoclax Mechanism of Action



- Cancer cells increase the expression of anti-apoptotic proteins to offset the increase in pro-apoptotic proteins, tipping the balance toward cell survival
- The large # of pro-apoptotic proteins bound and sequestered by Bcl-2 in AML make them “primed” for death

Kumar et al. *Proc ASCO* 2015;Abstract 8576.

N Engl J Med 2020;383:617-29.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 13, 2020 VOL. 383 NO. 7

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

C.D. DiNardo, B.A. Jonas, V. Pullarkat, M.J. Thirman, J.S. Garcia, A.H. Wei, M. Konopleva, H. Döhner, A. Letai, P. Fenaux, E. Koller, V. Havelange, B. Leber, J. Esteve, J. Wang, V. Pejsa, R. Hájek, K. Porkka, Á. Illés, D. Lavie, R.M. Lemoli, K. Yamamoto, S.-S. Yoon, J.-H. Jang, S.-P. Yeh, M. Turgut, W.-J. Hong, Y. Zhou, J. Potluri, and K.W. Pratz

VIALE-A Study Design

(NCT02993523)

Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ❖ ≥75 years of age
  - ❖ 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤65% or FEV_1 ≤65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Randomization 2:1
N = 433*

Treatment

Venetoclax + Azacitidine
(n = 286)
Venetoclax 400 mg PO, daily, days 1–28 +
Azacitidine 75 mg/m² SC /IV days 1–7

Placebo + Azacitidine
(n = 145)
Placebo daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

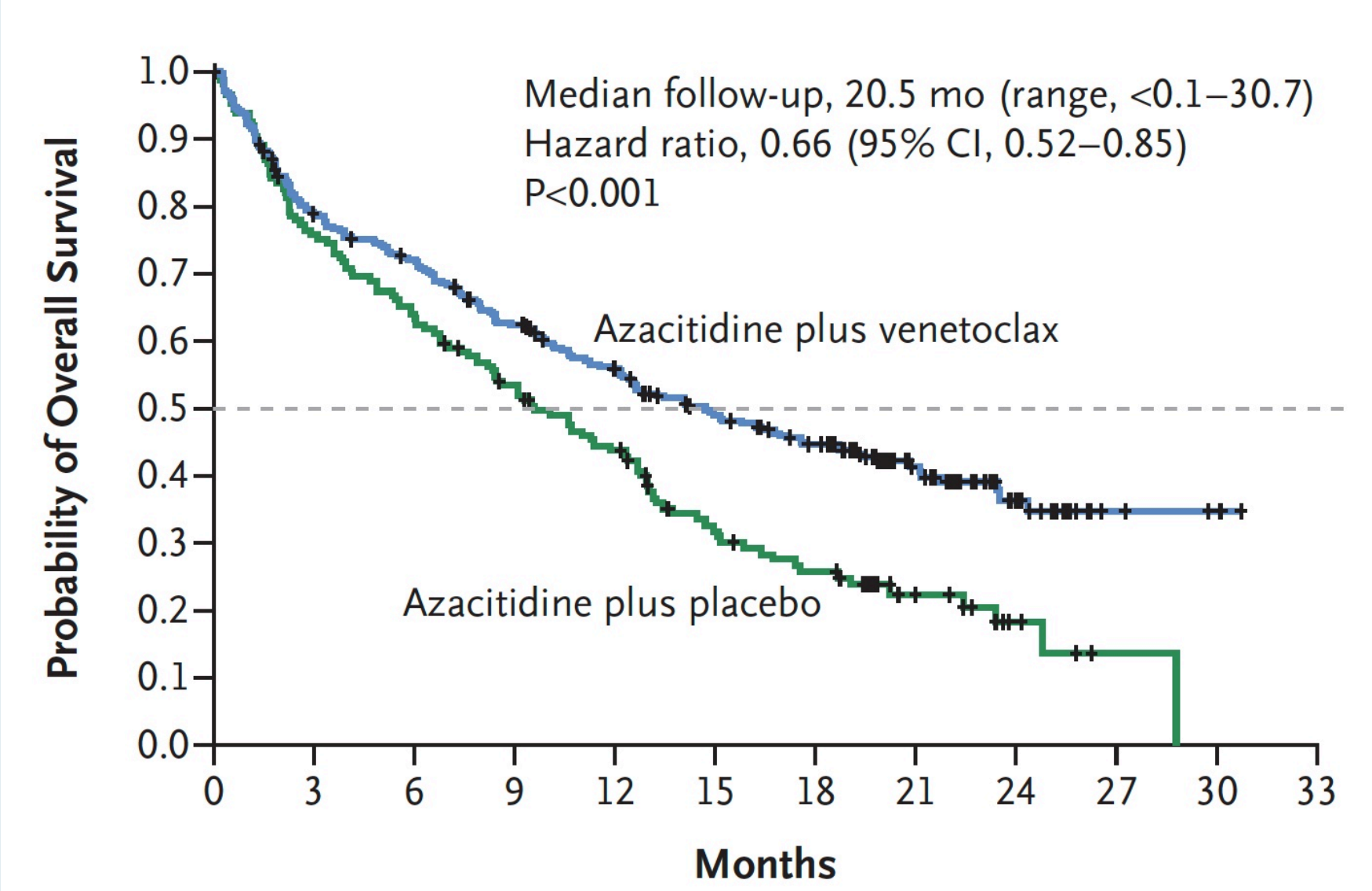
Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors	Age (<75 vs. ≥75 years); Cytogenetic risk (intermediate, poor); region
Venetoclax dosing ramp-up	**Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg **Cycle 2** Day 1-28: 400 mg

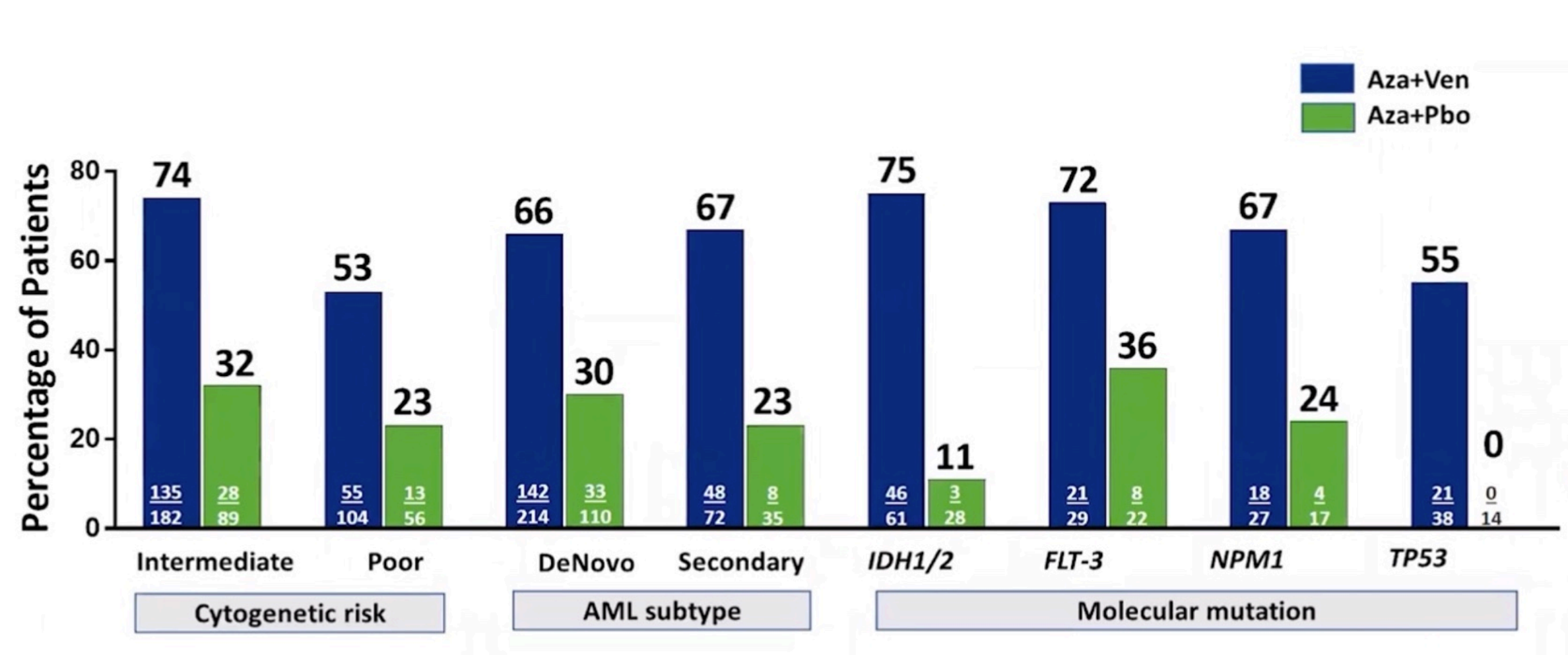
DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

VIALE-A: Overall Survival (N = 431)



DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

VIALE-A: Response Rates (CR + CRi) Subgroups



DiNardo C et al. EHA 2020;Abstract LB2601.

VIALE-A: Selected Key AML Serious Adverse Events

Event	Azacitidine–Venetoclax Group (N = 283)		Azacitidine–Placebo Group (N = 144)	
	All Grades†	≥Grade 3‡	All Grades†	≥Grade 3‡
	number of patients (percent)			
Serious adverse events§	235 (83)	232 (82)	105 (73)	102 (71)
Febrile neutropenia	84 (30)	84 (30)	15 (10)	15 (10)
Anemia	14 (5)	14 (5)	6 (4)	6 (4)
Neutropenia	13 (5)	13 (5)	3 (2)	3 (2)
Atrial fibrillation	13 (5)	10 (4)	2 (1)	2 (1)
Pneumonia	47 (17)	46 (16)	32 (22)	31 (22)
Sepsis	16 (6)	16 (6)	12 (8)	12 (8)

DiNardo CD et al. *N Engl J Med* 2020;383:617-29.

blood®
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial

Andrew H. Wei,[1,2] Pau Montesinos,[3,4] Vladimir Ivanov,[5] Courtney D. DiNardo,[6] Jan Novak,[7,8] Kamel Laribi,[9] Inho Kim,[10] Don A. Stevens,[11] Walter Fiedler,[12] Maria Pagoni,[13] Olga Samoilova,[14] Yu Hu,[15] Achilles Anagnostopoulos,[16] Julie Bergeron,[17] Jing-Zhou Hou,[18] Vidhya Murthy,[19] Takahiro Yamauchi,[20] Andrew McDonald,[21] Brenda Chyla,[22] Sathej Gopalakrishnan,[22] Qi Jiang,[22] Wellington Mendes,[22] John Hayslip,[22] and Panayiotis Panayiotidis[23]

Blood 2020;135(24):2137-45.

VIALE-C Phase 3 Study Design

- Randomized 2:1, double-blind, placebo-controlled trial

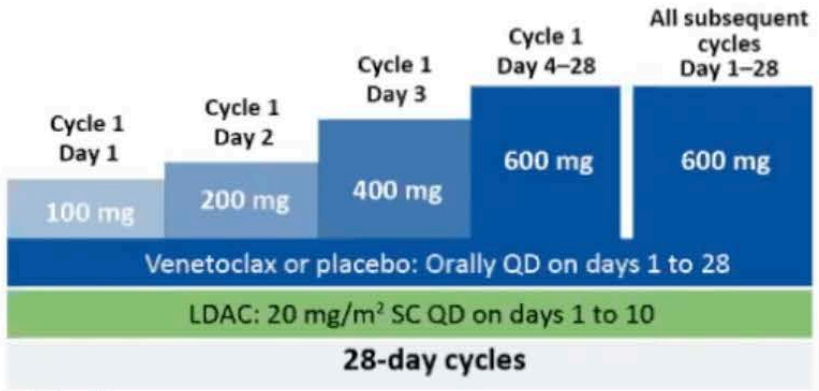
2:1 Randomization via IRT
N=211

- **Venetoclax + LDAC (n=143)**
- **Placebo + LDAC (n=68)**

Patients could continue receiving treatment until progression or until study treatment discontinuation criteria were met

Patients remained on study for OS assessment and follow-up, even if they initiated additional lines of treatment

Stratification factors
- AML status (secondary vs de novo)
- Age (18 to <75 vs ≥75)
- Region (US, EU, China, Japan, ROW)



Primary endpoint: overall survival

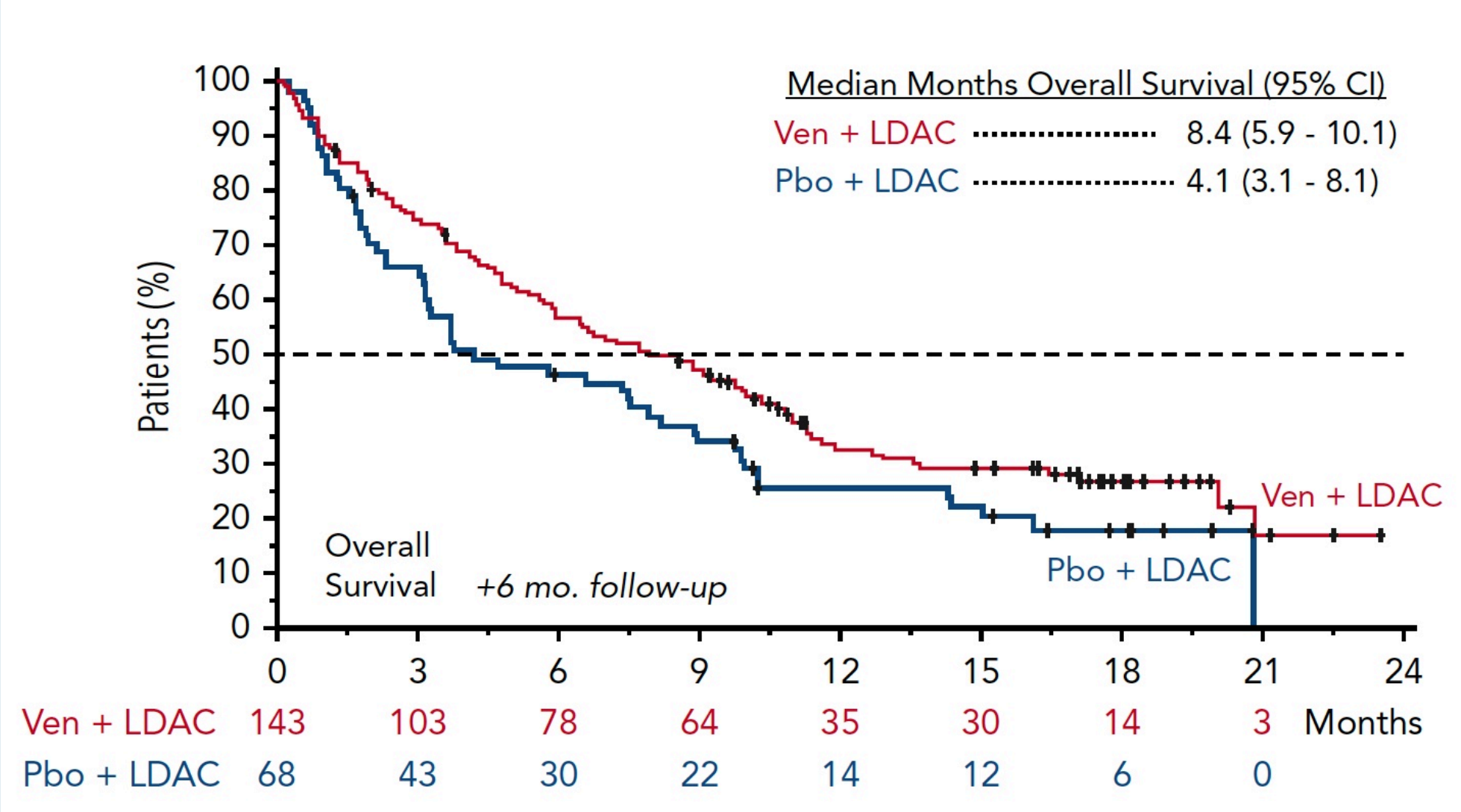
Secondary endpoints
- CR, CRh, and CRi (modified IWG criteria[1])
- Rate of transfusion independence
- EFS
- MRD

Progressive disease was defined per ELN recommendations.[2]

AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery; CRi, CR with incomplete blood count recovery; EFS, event-free survival; ELN, European LeukemiaNet; IRT, Interactive Response Technology; IWG, International Working Group; LDAC, low-dose cytarabine; MRD, minimal residual disease; OS, overall survival; QD, once a day; ROW, rest of world; SC, subcutaneous.

1. Cheson BD, et al. *J Clin Oncol.* 2003;21:4642-4649; 2. Döhner H, et al. *Blood.* 2017;129:424-447.

VIALE-C: Overall Survival



Wei AH et al. *Blood* 2020;135(24):2137-45.

VIALE-C: Response Rates and Other Efficacy Endpoints

End point	% (95% CI)		P
	Placebo + LDAC (n = 68)	Venetoclax + LDAC (n = 143)	
Remission rate			
CR*	7 (2-16)	27 (20-35)	<.001
CR/CRi†	13 (6-24)	48 (39-56)	<.001
By initiation of cycle 2	3 (0-10)	34 (27-43)	<.001
CR/CRh‡	15 (7-25)	47 (39-55)	<.001
By initiation of cycle 2	4 (1-12)	31 (23-39)	<.001
Other			
EFS, mo			.002
Median	2.0	4.7§	
95% CI	1.6-3.1	3.7-6.4	
Transfusion independence			
Red blood cells	18 (10-29)	41 (32-49)	.001
Platelets	32 (22-45)	48 (39-56)	.040
Both	16 (8-27)	37 (29-46)	.002

Wei AH et al. *Blood* 2020;135(24):2137-45.

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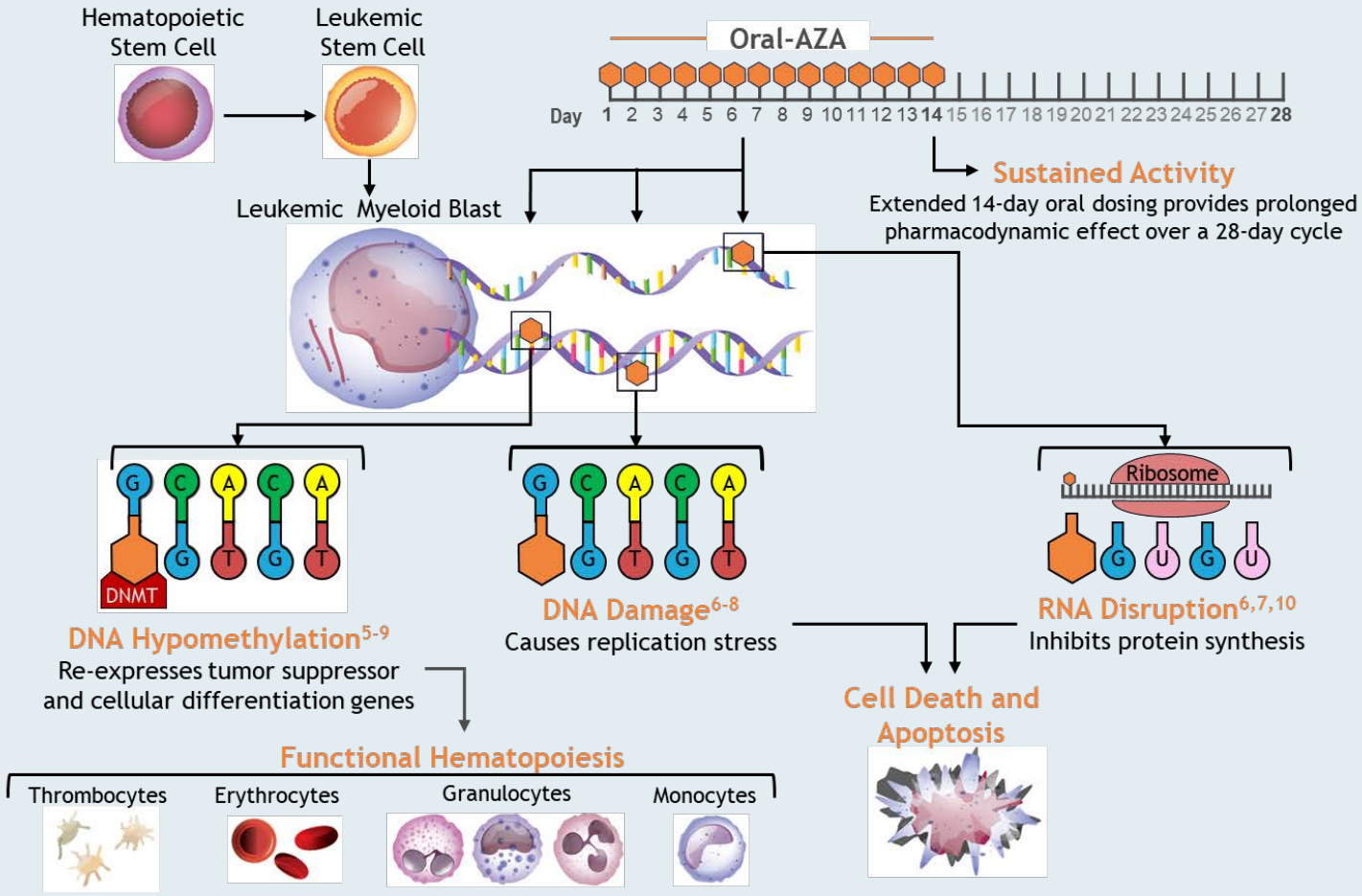
VIALE-C: Selected Key AML Serious Adverse Events

AE	n (%)	
	Placebo + LDAC (n = 68)	Venetoclax + LDAC (n = 142)
Selected key AML serious AEs		
Febrile neutropenia	12 (18)	23 (16)
Pneumonia	7 (10)	18 (13)
Sepsis	4 (6)	8 (6)
Thrombocytopenia	2 (3)	7 (5)
Anemia	0	4 (3)
Neutropenia	0	4 (3)

Wei AH et al. *Blood* 2020;135(24):2137-45.

Oral Azacitidine (CC-486)

- Oral azacitidine (Oral-AZA [CC-486]):
- **Oral HMA with a distinct PK/PD profile from injectable AZA; the two are not bioequivalent[1,2]**
- **Approved in the United States for continued Tx of adult pts with AML in first CR/CRi post-IC and not able to complete intensive curative therapy (eg, HSCT)[3]**
  - **Oral dosing allows for extended drug exposure during each Tx cycle to prolong AZA activity[1,2]**



1. Garcia-Manero et al. *J Clin Oncol*. 2011;29(18):2521–7. 2. Laille et al. *PLoS One*. 2015;10(8):e0135520. 3. ONUREG® (azacitidine) tablets [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Rev. 9/2020. 4. Savona et al. *Am J Hematol*. 2018;93(10):1199–206. 5. Stresemann et al. *Mol Cancer Ther*. 2008;7:2998–3005. 6. Hollenbach et al. *PLoS One*. 2010;5(2):e9001. 7. Scott LJ. *Drugs*. 2016;76(8):889–900. 8. Stresemann C, Lyko F. *Int J Cancer*. 2008;123(1):8–13. 9. Aimiuwu et al. *Blood*. 2012;119(22):5229–38.

AML, acute myeloid leukemia; AZA, azacitidine; CR, complete remission; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IC, intensive chemotherapy; PD, pharmacodynamic; PK, pharmacokinetic; pts, patients; Tx, treatment.

Courtesy of Richard M Stone, MD

FDA Approves Azacitidine Tablets for Acute Myeloid leukemia

Press Release – September 1, 2020

"The Food and Drug Administration approved azacitidine tablets for continued treatment of patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

Efficacy was investigated in QUAZAR (NCT01757535), a multicenter, randomized, double-blind, placebo-controlled trial. Patients (n=472) who achieved CR or CRi with intensive induction chemotherapy with or without receiving subsequent consolidation therapy were randomized 1:1 to receive azacytidine tablets 300 mg (n=238) or placebo (n=234) orally on days 1 to 14 of each 28-day cycle."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-onureg-azacitidine-tablets-acute-myeloid-leukemia

RTP RESEARCH TO PRACTICE

ORIGINAL ARTICLE

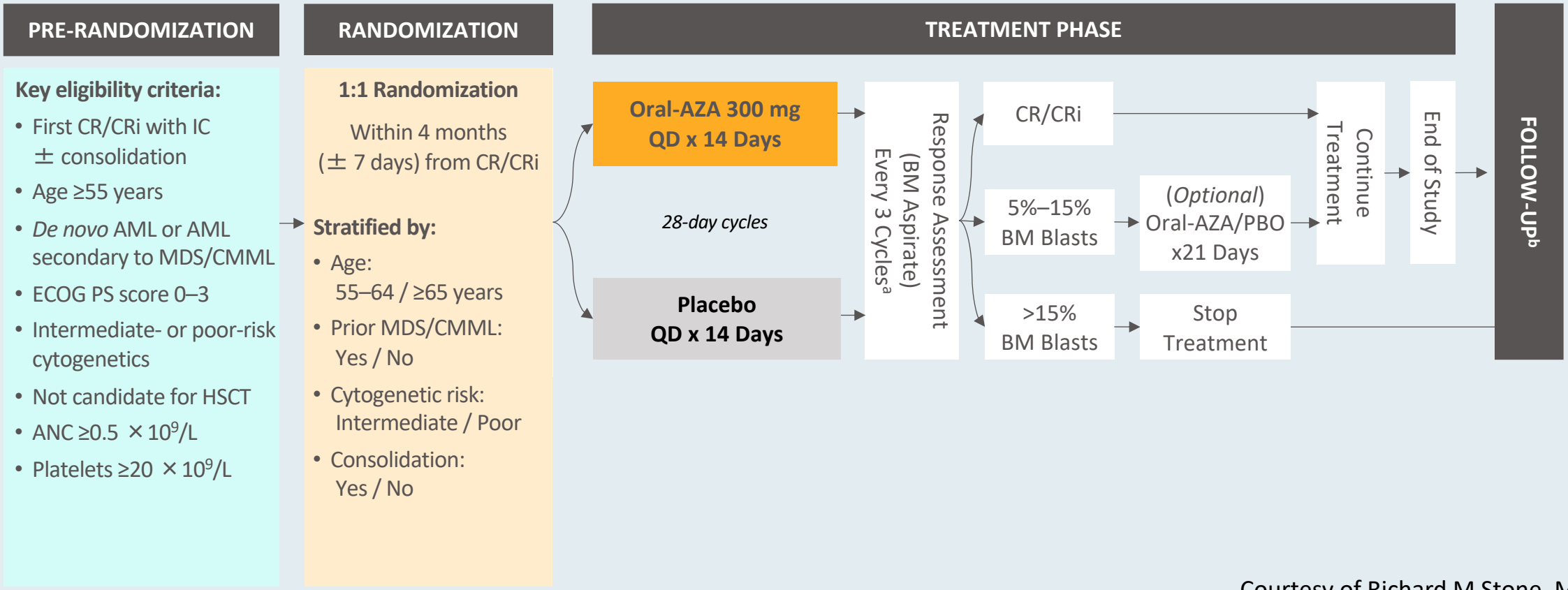
Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission

A.H. Wei, H. Döhner, C. Pocock, P. Montesinos, B. Afanasyev,* H. Dombret, F. Ravandi, H. Sayar, J.-H. Jang, K. Porkka, D. Selleslag, I. Sandhu, M. Turgut, V. Giai, Y. Ofran, M. Kizil Çakar, A. Botelho de Sousa, J. Rybka, C. Frairia, L. Borin, G. Beltrami, J. Čermák, G.J. Ossenkoppele, I. La Torre, B. Skikne, K. Kumar, Q. Dong, C.L. Beach, and G.J. Roboz, for the QUAZAR AML-001 Trial Investigators†

N Engl J Med 2020;383:2526-37.

QUAZAR AML-001: Study design and eligibility criteria

International, multicenter, placebo (PBO)-controlled, double-blind, randomized, phase III study of Oral-AZA as maintenance Tx in pts with AML in first remission post-IC

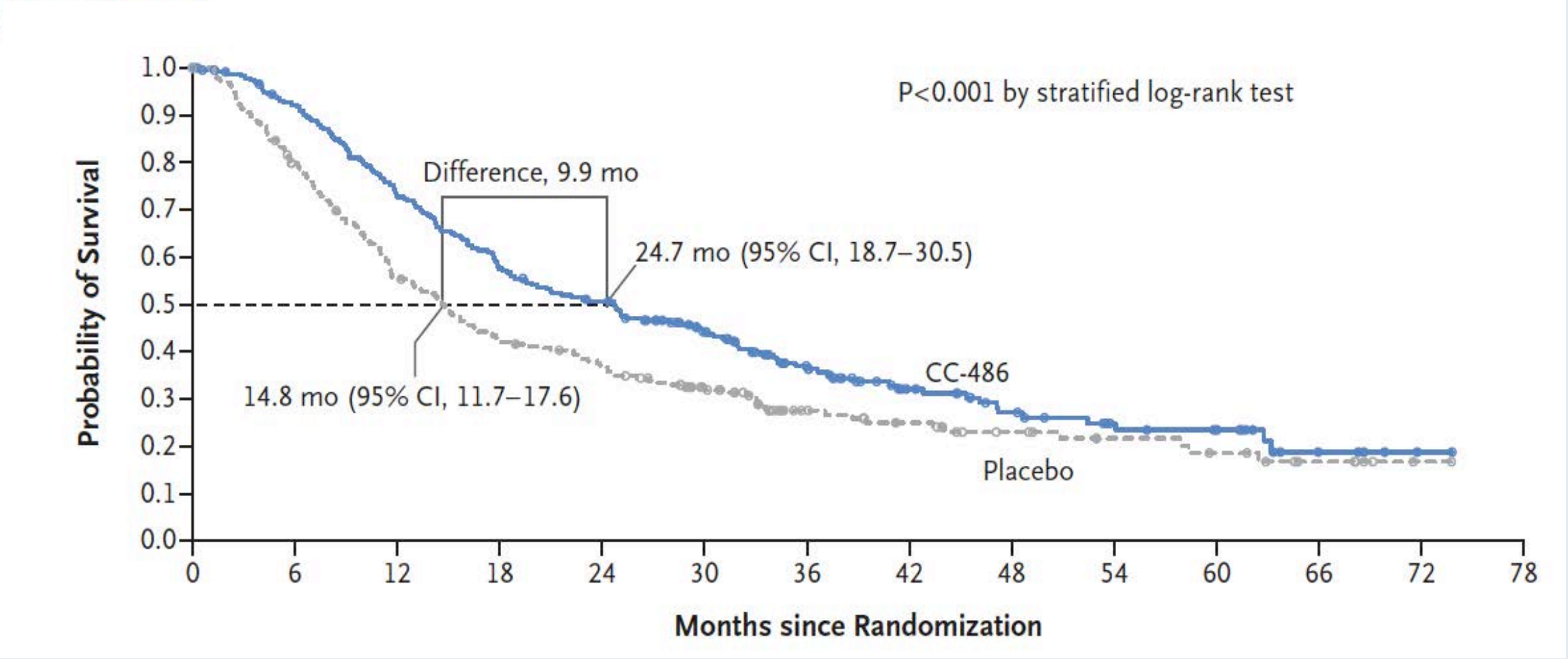


Courtesy of Richard M Stone, MD

[a]BM aspirates were collected every 3 cycles through cycle 24, at cycle 30 and cycle 36, and as clinically indicated thereafter. BM assessments were also performed as clinically indicated. [b]Patients were followed until death, withdrawal of consent, study termination, or loss to follow-up.

AML, acute myeloid leukemia; ANC, absolute neutrophil count; AZA, azacitidine; BM, bone marrow; CMML, chronic myelomonocytic leukemia; CR, complete remission; CRi, CR with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant; IC, induction chemotherapy; IWG, International Working Group; MDS, myelodysplastic syndromes; PBO, placebo.

QUAZAR AML-001: Overall Survival



Wei AH et al. *N Engl J Med* 2020;383:2526-37.

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Newly Diagnosed AML

- Dr Chojecki: A 73-year-old man with AML

Module 2: Relapsed/Refractory AML with a FLT3 Mutation

- Dr Chojecki: A 69-year-old woman with AML and a FLT3 ITD mutation

Module 3: Newly Diagnosed AML with an IDH1 Mutation

- Dr Chojecki: An 86-year-old man with AML and an IDH1 mutation

Module 4: Secondary AML

- Dr Chojecki: A 60-year-old woman with AML and a TP53 mutation

Module 5: Myelodysplastic Syndromes

- Dr Chojecki: A 78-year-old man with “low risk” MDS
- Dr Favaro: A 77-year-old man with MDS

Case Presentation – Dr Chojecki: A 69-year-old woman with AML and a FLT3 ITD mutation

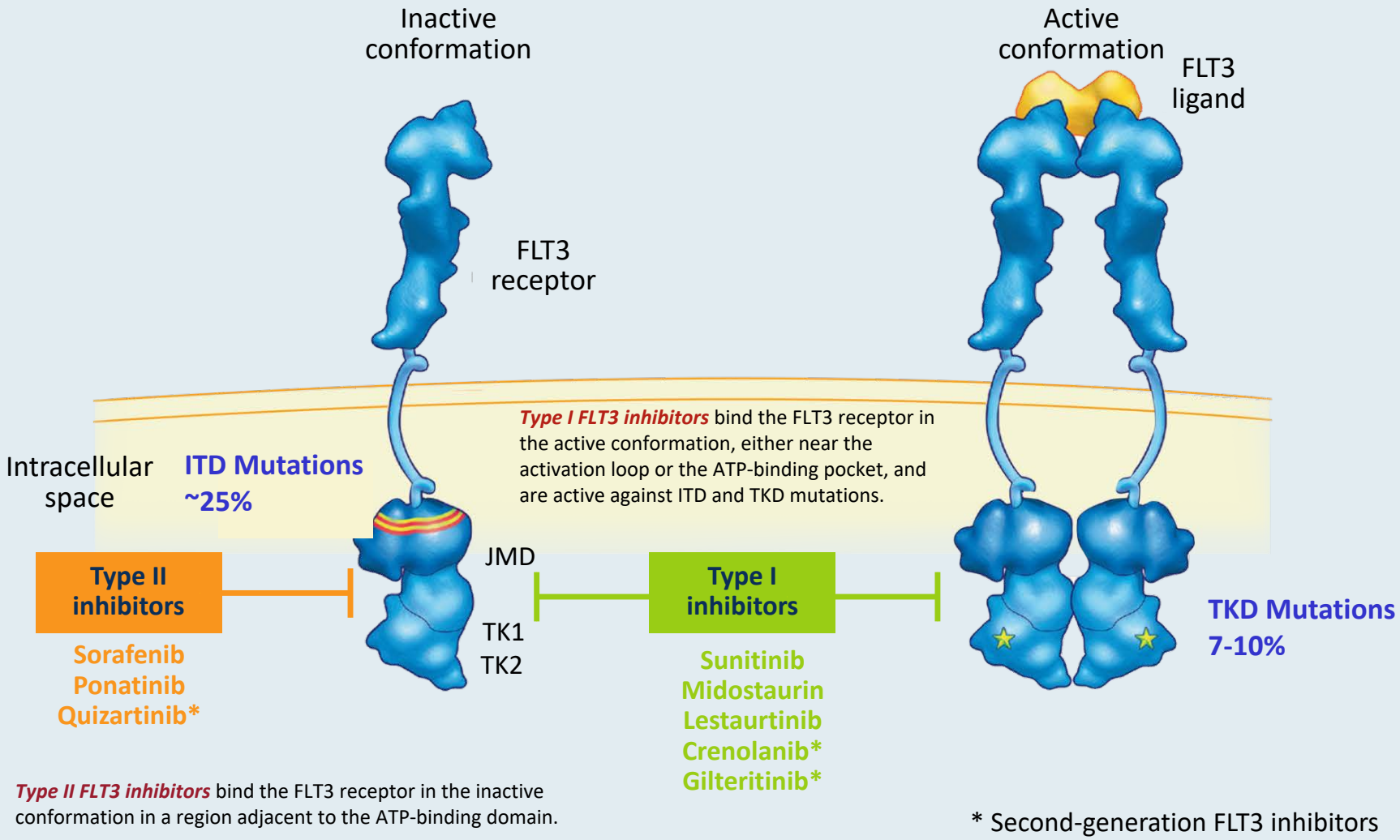
Dr Aleksander Chojecki

- Presents as very ill, with progressive deterioration over a few days
- Diagnosed with AML
- NGS: FLT3 ITD, NPM1, TET2, and DNMT3A mutations
- Leukapharesis and hydroxyurea
  - Pancytopenia
- Azacitidine and gilteritinib

Questions

- Is it unreasonable to offer gilteritinib as an upfront setting, especially in a patient that could not undergo aggressive induction chemotherapy with 7+3 with midostaurin?
- Where does gilteritinib stand in the queue as upfront treatment? The recent Phase III LACEWING data showed that upfront gilteritinib with an HMA did not meet its primary endpoint. Can you comment a little bit more about that? Have you offered patients gilteritinib upfront?

FLT3 Mutations (ITD and TKD) Occur in Approximately 30% to 35% of Patients with AML



Daver N et al. *Leukemia* 2019;33:299-312.

Characteristics of Select FLT3 Inhibitors

FLT3 inhibitor	Inhibitory type	FLT3 kinase inhibition IC50 (nmol/L)	Non-FLT3 targets	FLT3-TKD mutation activity	Major toxicities
Sorafenib 400 mg BID	II	58	c-KIT PDGFR RAF VEGFR	No	Rash Hemorrhage Myelosuppression
Midostaurin 50 mg BID	I	6.3	c-KIT PDGFR PKC VEGFR	Yes	GI toxicity Myelosuppression
Quizartinib 30 – 60 mg QD	II	1.6	c-KIT	No	QTc prolongation Myelosuppression
Gilteritinib 120 mg QD	I	0.29	AXL LTK ALK	Yes	Elevated transaminases Diarrhea

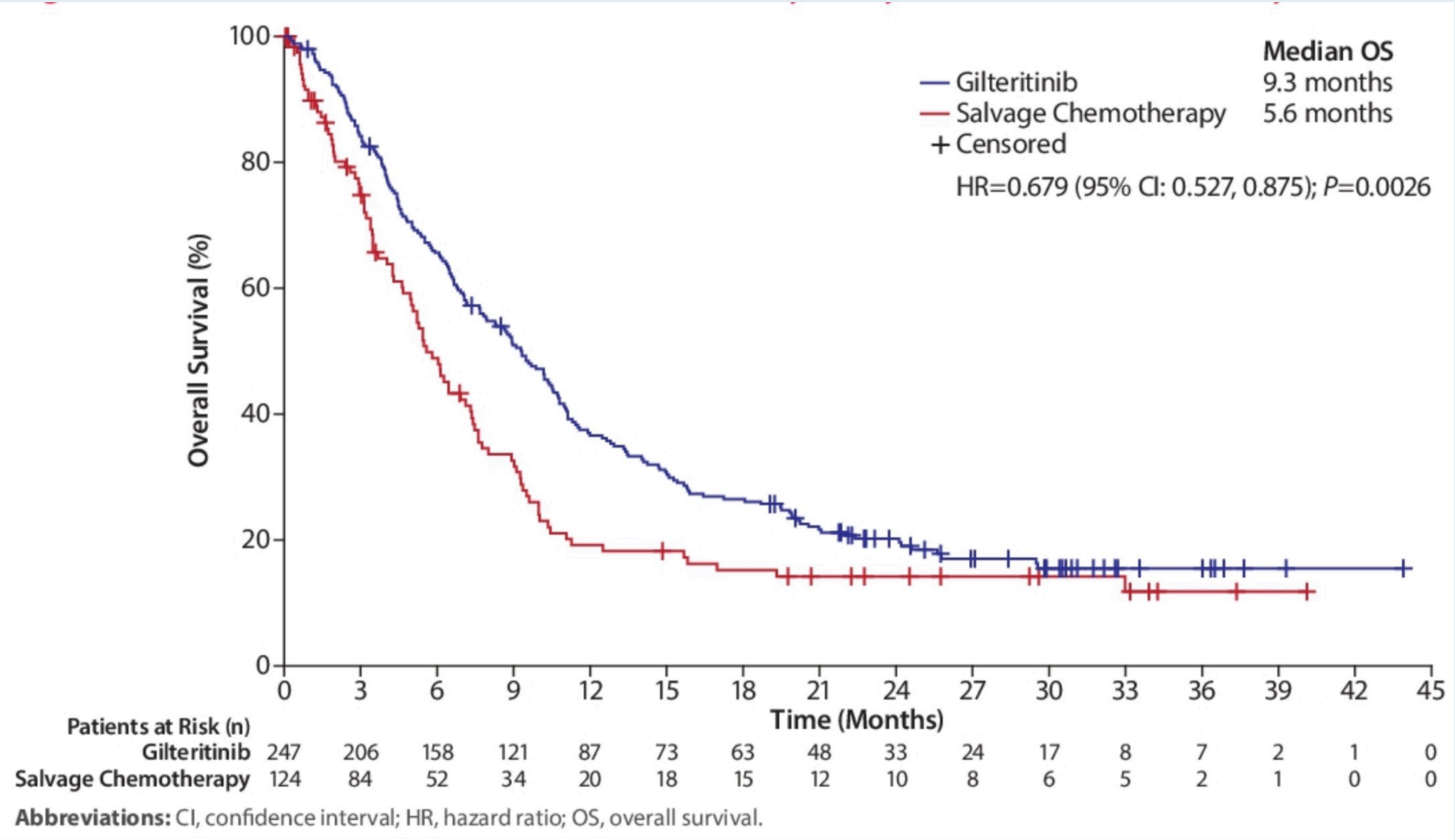
Kiyoi H et al. *Cancer Science* 2019;[Epub ahead of print];
Short NJ et al. *Ther Adv Hematol* 2019;10:2040620719827310.

Long-Term Survivors and Gilteritinib Safety Beyond One Year in *FLT3*-mutated R/R AML: ADMIRAL Trial Follow-Up

Perl AE et al.

ASCO 2020;Abstract 7514

ADMIRAL: Overall Survival at 1 Year After the Primary Analysis



Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Perl AE et al. ASCO 2020;Abstract 7514.

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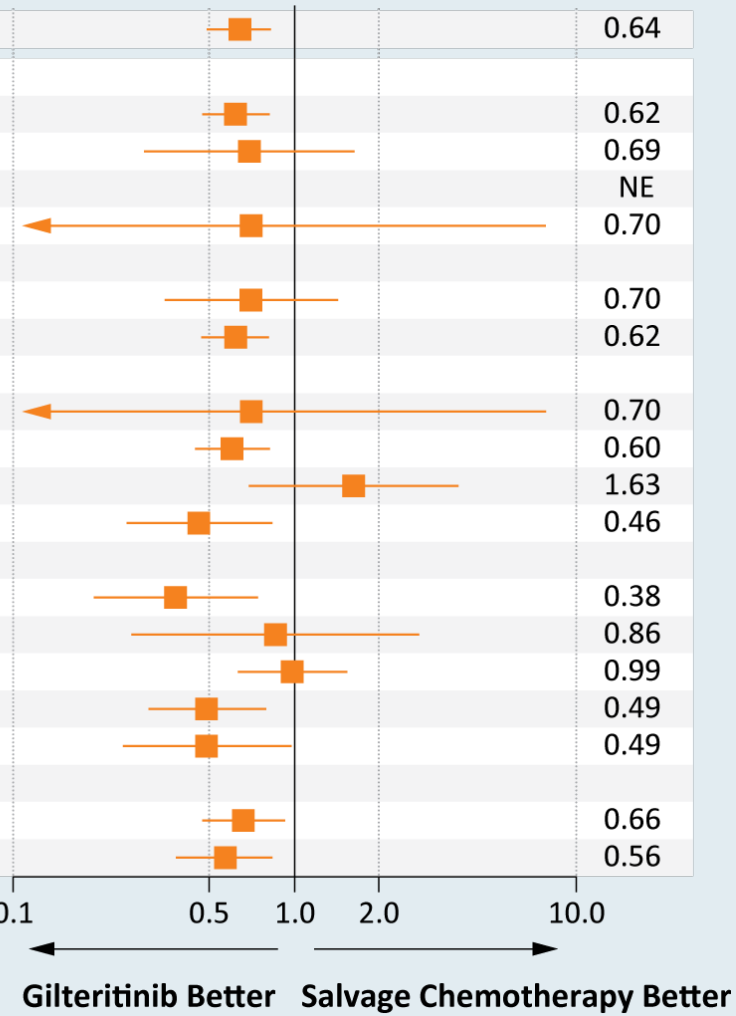
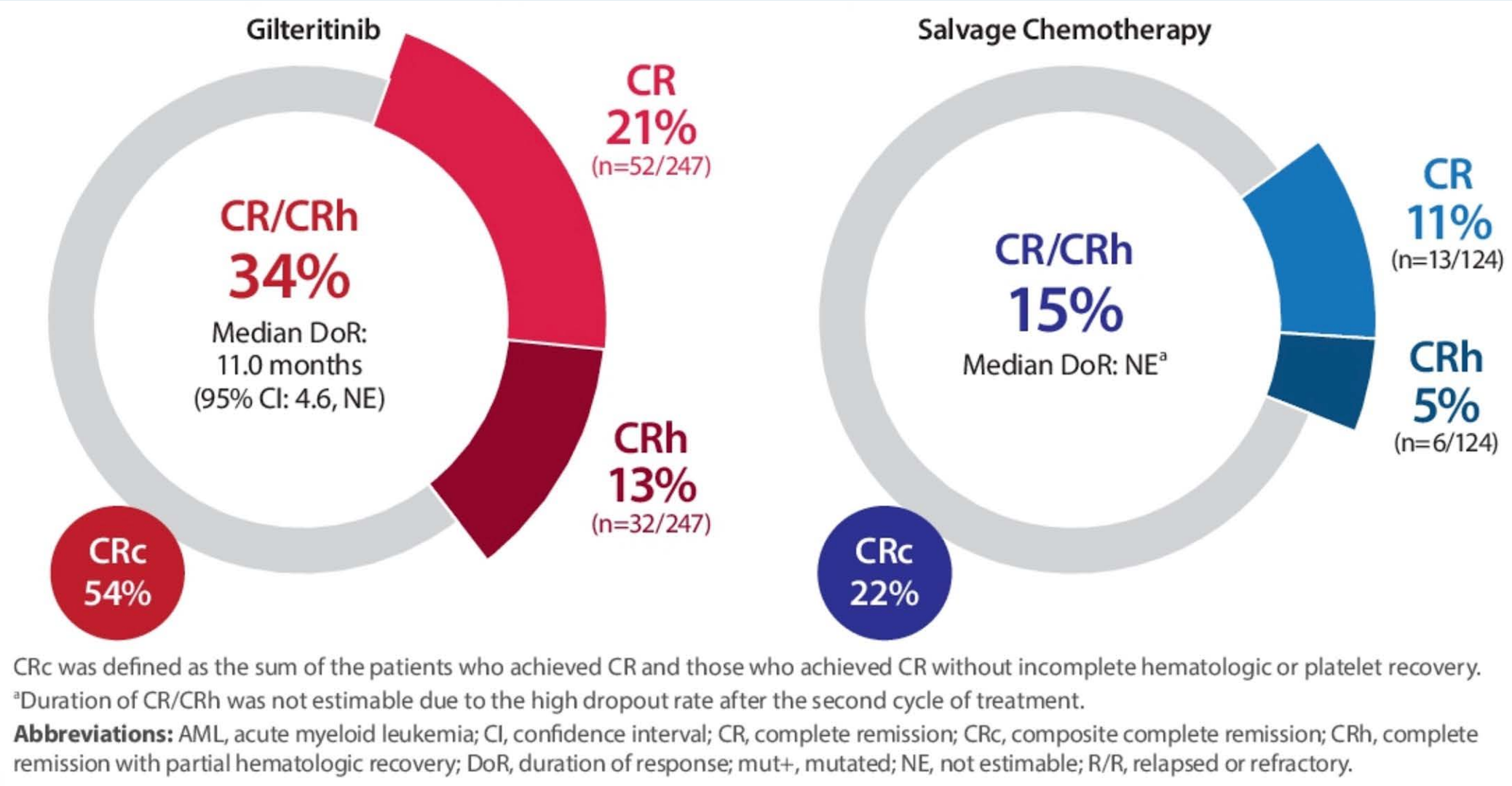
ADMIRAL: Subgroup Analysis of Overall Survival

Subgroup	Gilteritinib	Salvage Chemotherapy	Hazard Ratio for Death
	no. of events/total no. of patients		
All patients	171/247	90/124	0.64
FLT3 mutation type			
FLT3 ITD alone	145/215	81/113	0.62
FLT3 TKD alone	16/21	8/10	0.69
FLT3 ITD and FLT3 TKD	6/7	0	NE
Other	4/4	1/1	0.70
Previous use of FLT3 inhibitor			
Yes	26/32	11/14	0.70
No	145/215	79/110	0.62
Cytogenetic risk status			
Favorable	3/4	1/1	0.70
Intermediate	119/182	63/89	0.60
Unfavorable	22/26	7/11	1.63
Unknown	27/35	19/23	0.46
Response to first-line therapy per IRT			
Relapse ≤6 mo after allogeneic HSCT	24/31	16/17	0.38
Relapse >6 mo after allogeneic HSCT	10/17	4/8	0.86
Primary refractory disease without HSCT	70/98	28/48	0.99
Relapse ≤6 mo after composite complete remission and no HSCT	47/67	28/34	0.49
Relapse >6 mo after composite complete remission and no HSCT	20/34	14/17	0.49
Preselected chemotherapy per IRT			
High intensity	96/149	52/75	0.66
Low intensity	75/98	38/49	0.56



Perl AE et al. *N Engl J Med* 2019;381:1728-40.

ADMIRAL: Response Rates



CRc was defined as the sum of the patients who achieved CR and those who achieved CR without incomplete hematologic or platelet recovery.

[a]Duration of CR/CRh was not estimable due to the high dropout rate after the second cycle of treatment.

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CRc, composite complete remission; CRh, complete remission with partial hematologic recovery; DoR, duration of response; mut+, mutated; NE, not estimable; R/R, relapsed or refractory.

Perl AE et al. ASCO 2020;Abstract 7514.

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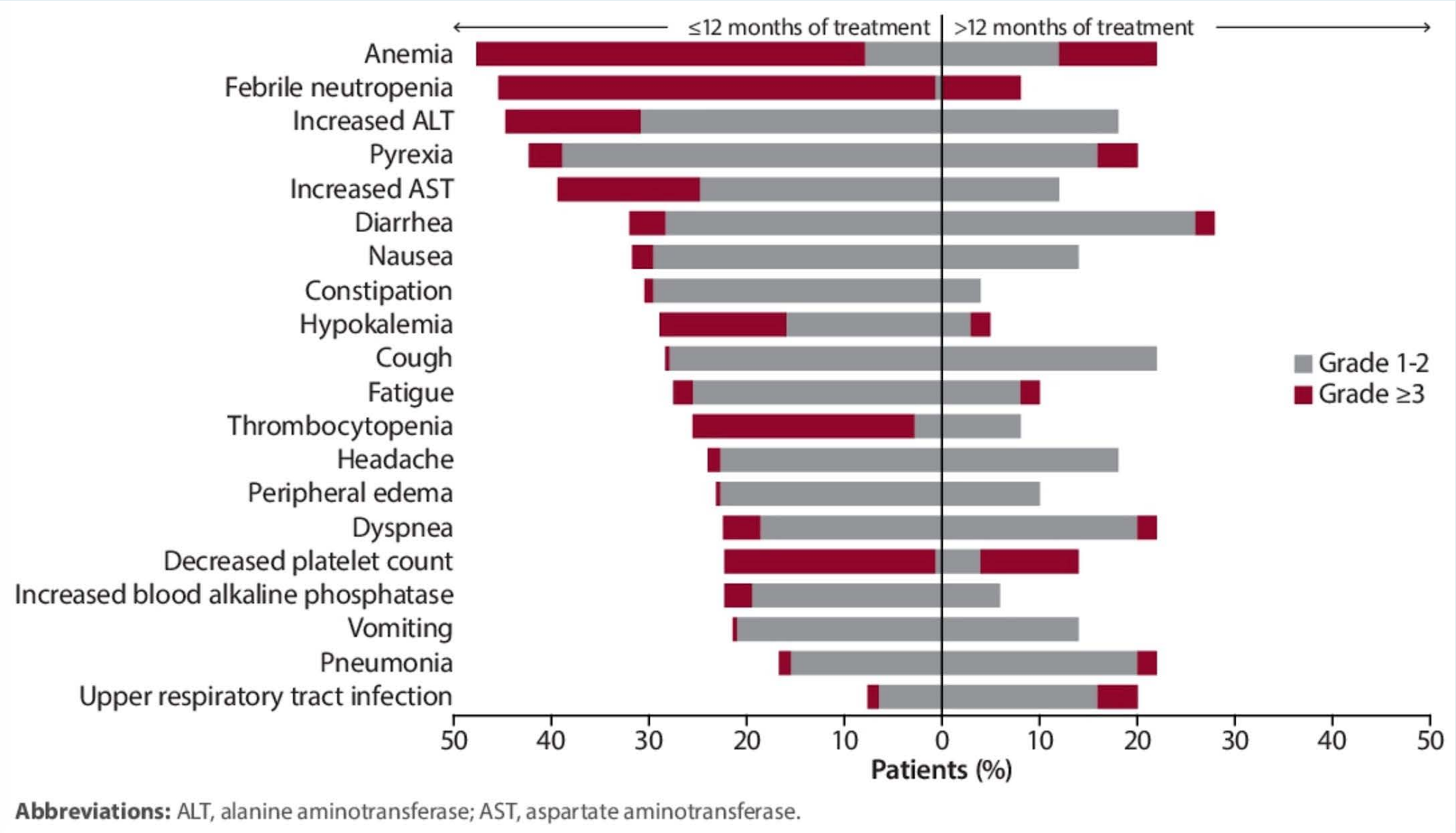
ADMIRAL: Adverse Events Occurring in ≥20% of Patients Treated with Gilteritinib



Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Perl AE et al. ASCO 2020;Abstract 7514.

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ADMIRAL: Adverse Events Leading to Death

AEs Leading to Death[a,b], n (%)		≤12 Months of Treatment (n=246)	>12 Months of Treatment (n=50)
Cardiac disorders	Cardiac arrest	4 (1.6)	0
	Pericardial effusion	2 (0.8)	0
Infections and infestations	Septic shock	7 (2.8)	0
	Sepsis	5 (2.0)	0
	Lung infection	4 (1.6)	0
	Pneumonia	3 (1.2)	0
Gastrointestinal disorders	Large intestinal perforation	2 (0.8)	0
Nervous system disorders	Cerebral hemorrhage	2 (0.8)	0
Respiratory, thoracic, and mediastinal disorders	Respiratory failure	2 (0.8)	0

[a]Patients may have had more than one fatal AE; [b]Excludes deaths stemming from AML progression or relapse.
Abbreviation: AE, adverse event.

Perl AE et al. ASCO 2020;Abstract 7514.

RTP RESEARCH TO PRACTICE

Phase 3 LACEWING Trial Fails to Meet Primary End Point of OS in Newly Diagnosed FLT3+ AML

Press Release – December 21, 2020

"The phase 3 LACEWING trial of the FMS-like tyrosine kinase 3 (FLT3) inhibitor gilteritinib plus azacitidine versus azacitidine alone in patients with newly diagnosed *FLT3* mutation-positive acute myeloid leukemia (AML) who were ineligible for intensive induction chemotherapy did not meet its primary end point of overall survival (OS) at a planned interim analysis, according to Astellas Pharma, the developer of the agent.[1]

Based on these results, an independent data monitoring committee recommended the study be terminated for futility, citing that the results are unlikely to demonstrate a statistically significant increase in OS. Astellas indicated it has since halted enrollment in the trial and is reviewing the results for other action as needed."

https://www.cancernetwork.com/view/phase-3-lacewing-trial-fails-to-meet-primary-end-point-of-os-in-newly-diagnosed-flt3-aml

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Newly Diagnosed AML

- Dr Chojecki: A 73-year-old man with AML

Module 2: Relapsed/Refractory AML with a FLT3 Mutation

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- Dr Chojecki: A 78-year-old man with “low risk” MDS
- Dr Favaro: A 77-year-old man with MDS

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Chojecki: An 86-year-old man with AML and an IDH1 mutation

Dr Aleksander Chojecki

- Diagnosed with AML and an IDH1 mutation
- Azacitidine x 6 cycles, with excellent tolerability → BMB: Persistent AML
- Decitabine (5 days) and ivosidenib (250 mg/d) → BMB: Persistent AML
  - Pancytopenia
- Gemtuzumab ozogamicin
  - Neutropenic sepsis

Questions

- Would you consider upfront IDH inhibitors in patients with IDH mutations who are not candidates for aggressive chemotherapy?
- In younger patients, would you give standard induction with an IDH inhibitor? What are the typical patients that you see who respond?
- With ivosidenib, how closely to you watch the patient, given concerns about differentiation syndrome? What do you tell the patients about that risk? Have you seen differentiation syndrome and how do you treat it?

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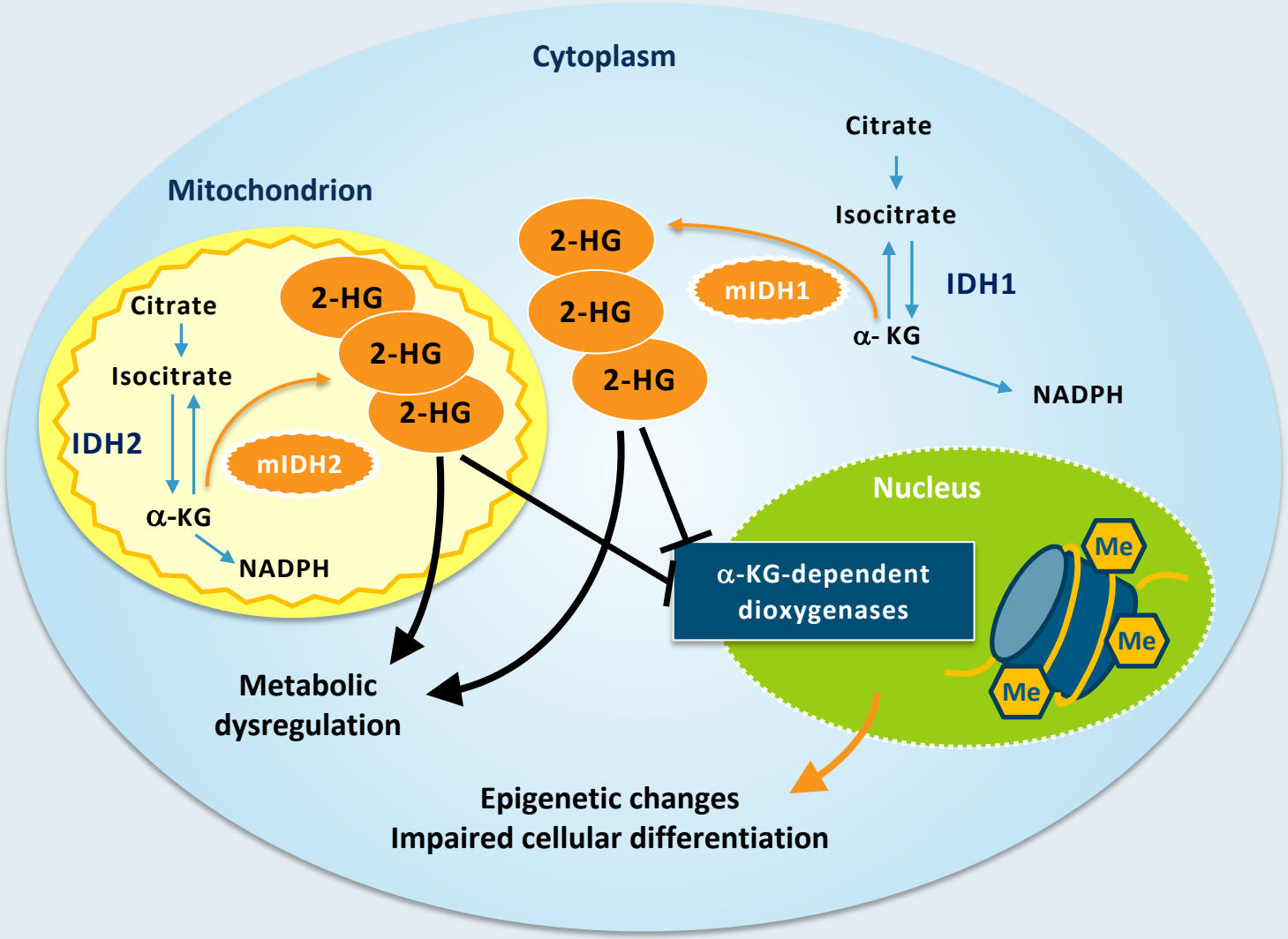
IDH1 and IDH2 Mutations in AML

IDH mutations are found in ~16-20% of AML cases

- IDH1 mutations in ~7.5%
- IDH2 mutations in ~8-19%



Buege MJ et al. *Cancers* 2018;10:187; Döhner H et al. *N Engl J Med* 2015;373(12):1136-52; Bullinger L et al. *J Clin Oncol* 2017;35(9):934-46.

Blood 2020;135(7):463-71

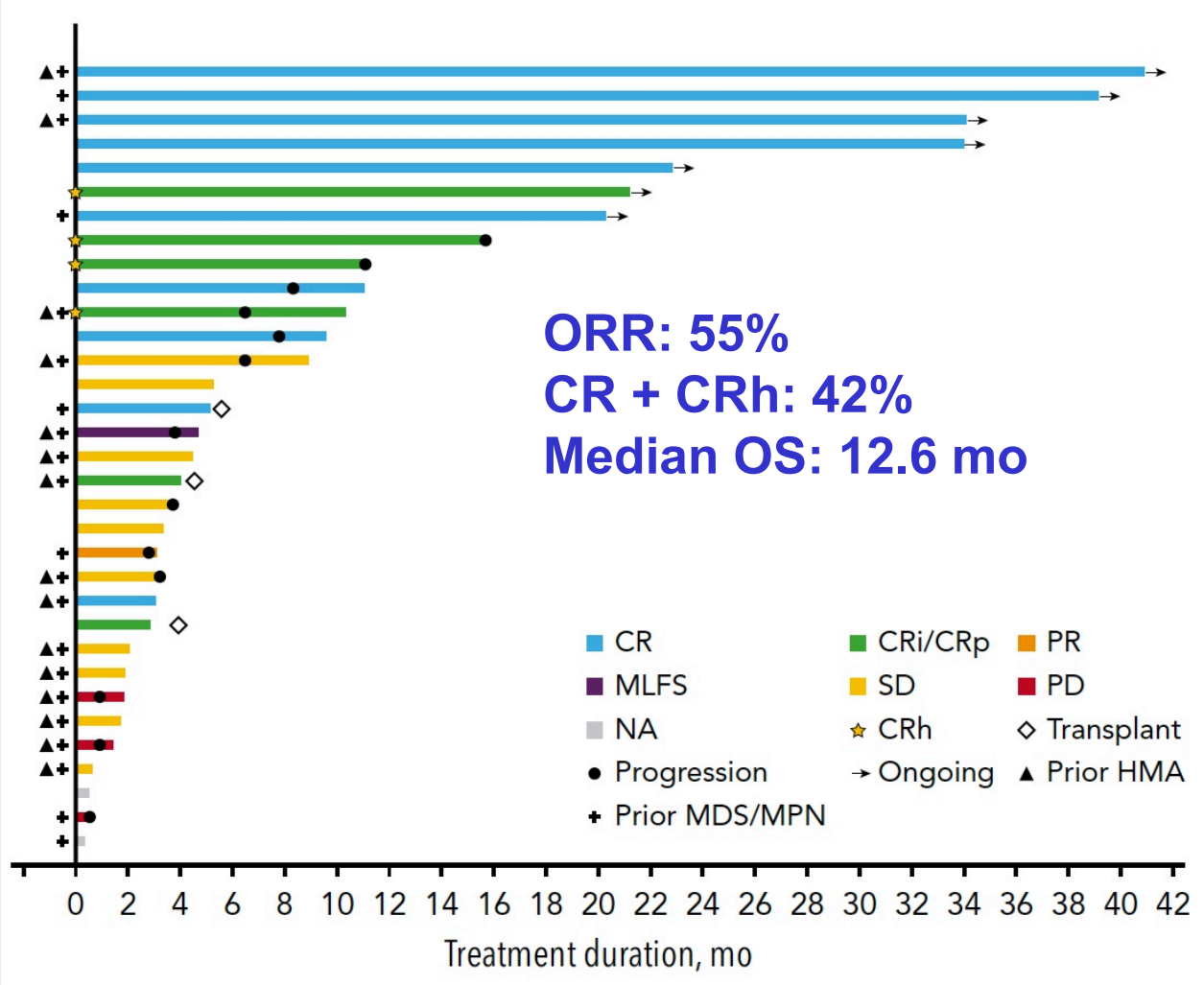
Plenary Paper

MYELOID NEOPLASIA

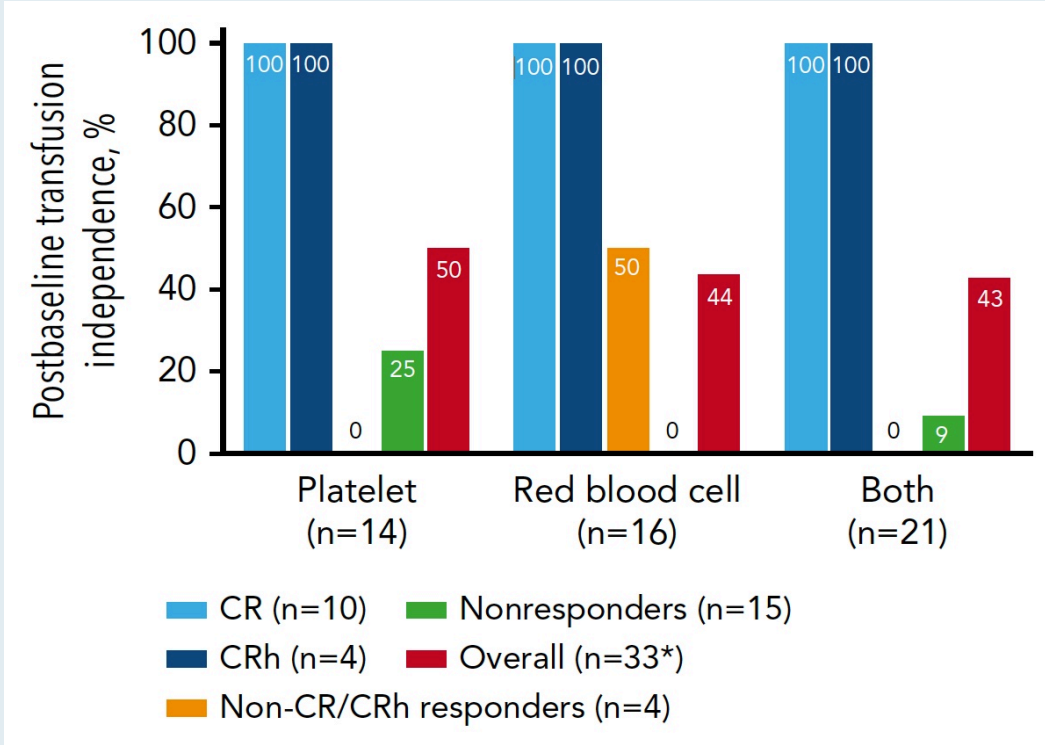
Ivosidenib induces deep durable remissions in patients with newly diagnosed *IDH1*-mutant acute myeloid leukemia

Gail J. Roboz,[1,*] Courtney D. DiNardo,[2,*] Eytan M. Stein,[3] Stéphane de Botton,[4] Alice S. Mims,[5] Gabrielle T. Prince,[6] Jessica K. Altman,[7] Martha L. Arellano,[8] Will Donnellan,[9] Harry P. Erba,[10] Gabriel N. Mannis,[11] Daniel A. Pollyea,[12] Anthony S. Stein,[13] Geoffrey L. Uy,[14] Justin M. Watts,[15] Amir T. Fathi,[16] Hagop M. Kantarjian,[2] Martin S. Tallman,[3] Sung Choe,[17] David Dai,[17] Bin Fan,[17] Hongfang Wang,[17] Vickie Zhang,[17] Katharine E. Yen,[17] Stephanie M. Kapsalis,[17] Denice Hickman,[17] Hua Liu,[17] Samuel V. Agresta,[17] Bin Wu,[17] Eyal C. Attar,[17] and Richard M. Stone[18]

Response, Survival and Transfusion Independence with Ivosidenib in Newly Diagnosed AML



Transfusion independence in patients who were transfusion dependent at baseline



Roboz GJ et al. *Blood* 2020;135(7):463-71.

RTP RESEARCH TO PRACTICE

Enasidenib Monotherapy is Effective in Older Patients with Newly Diagnosed IDH2 Mutated Acute Myeloid Leukemia and Addition of Azacitidine Rescues Enasidenib Monotherapy Failures: A Phase 2/1B Study of the BEAT AML Master Trial

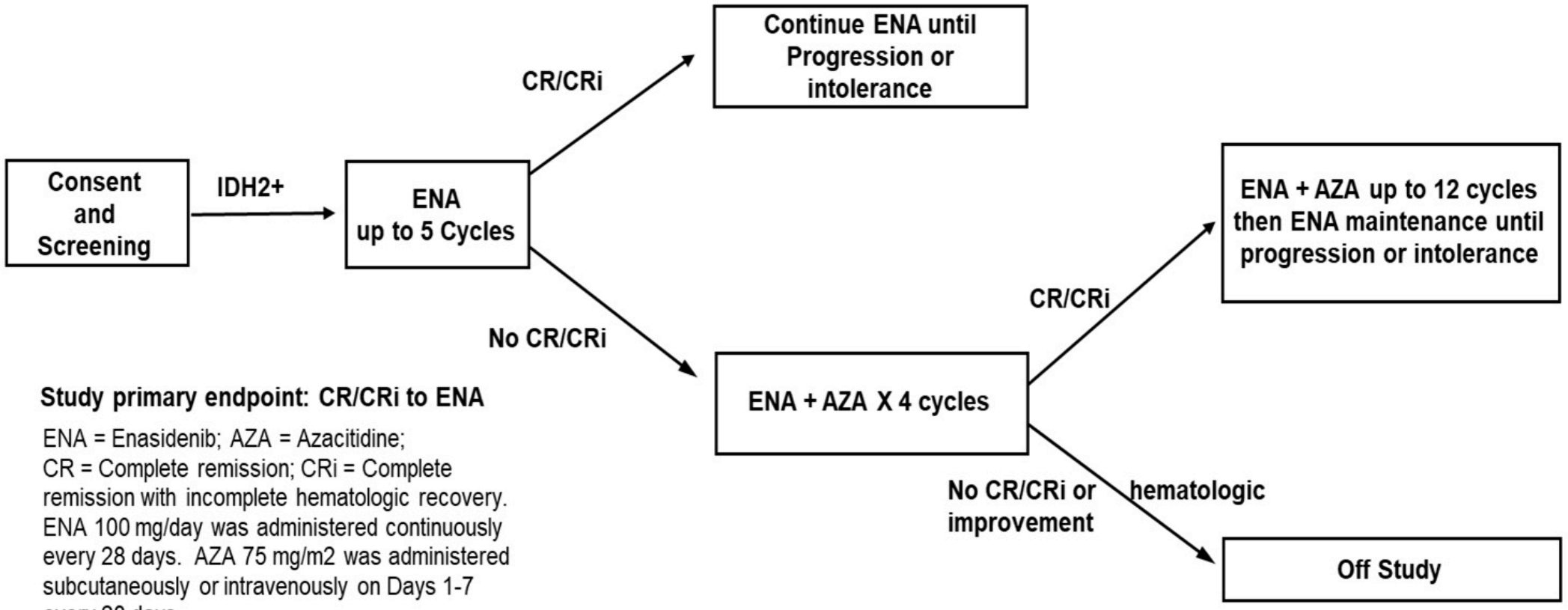
Stein EM et al.

ASH 2020;Abstract 636

LEUKEMIA & LYMPHOMA SOCIETY®

RTP RESEARCH TO PRACTICE

BEAT AML S3 Study Design and Objectives



Study primary endpoint: CR/CRi to ENA

ENA = Enasidenib; AZA = Azacitidine;
CR = Complete remission; CRi = Complete remission with incomplete hematologic recovery.
ENA 100 mg/day was administered continuously every 28 days. AZA 75 mg/m2 was administered subcutaneously or intravenously on Days 1-7 every 28 days.

Response to Enasidenib Monotherapy in Newly Diagnosed AML and Efficacy of Azacitidine in Rescuing Enasidenib Failures

	Enasidenib (n = 60)	Failed to Respond to Enasidenib, Azacitidine Added (n = 17)
Overall Response Rate	50%	47%
CR/CRi Rate	47%	41%
Median Overall Survival	24.4 mo	8.9 mo

Stein EM et al. ASH 2020;Abstract 636.

original reports

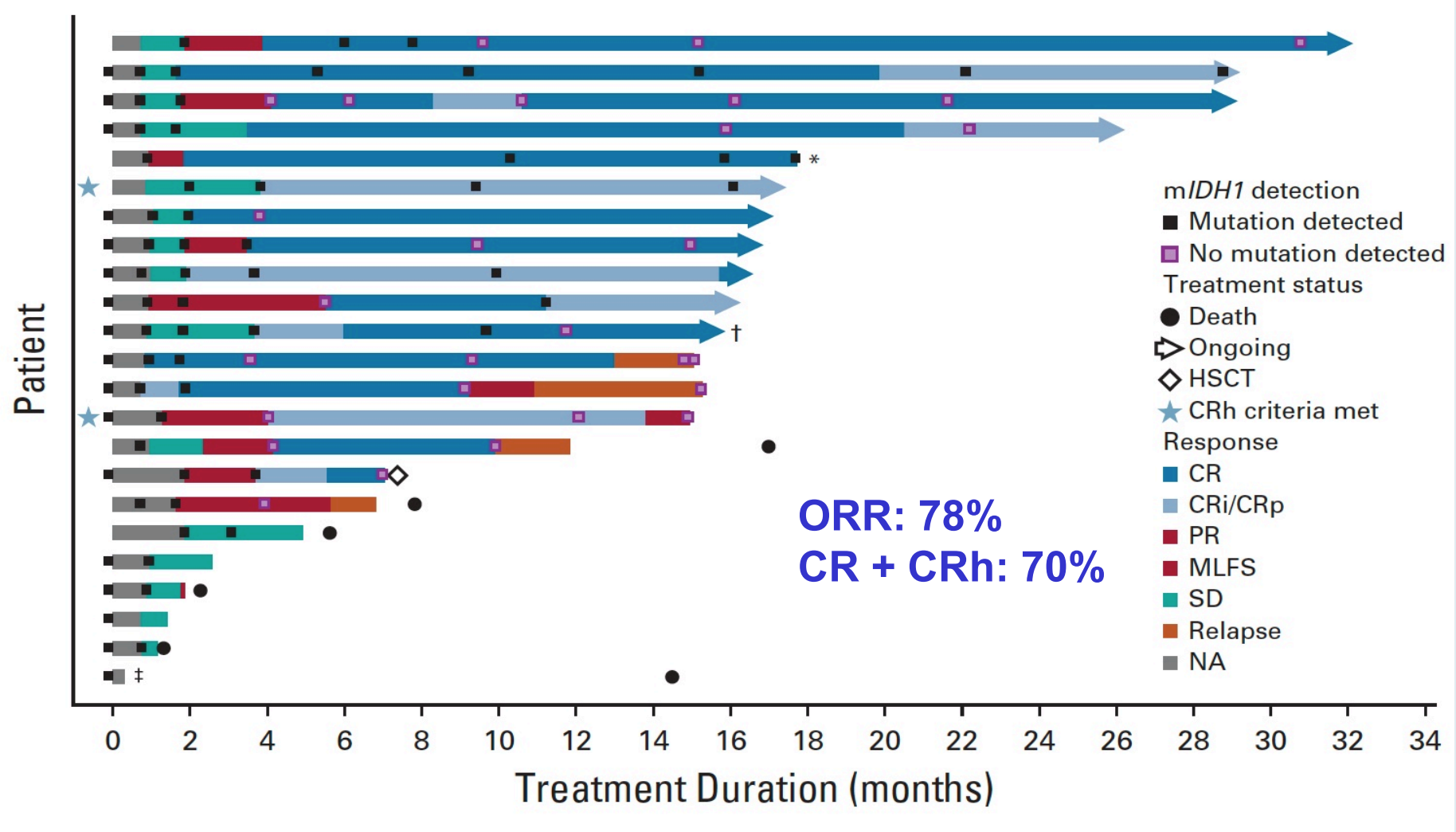
Mutant Isocitrate Dehydrogenase 1 Inhibitor Ivosidenib in Combination With Azacitidine for Newly Diagnosed Acute Myeloid Leukemia

Courtney D. DiNardo, MD[1]; Anthony S. Stein, MD[2]; Eytan M. Stein, MD[3]; Amir T. Fathi, MD[4]; Olga Frankfurt, MD[5]; Andre C. Schuh, MD[6]; Hartmut Döhner, MD[7]; Giovanni Martinelli, MD[8]; Prapti A. Patel, MD[9]; Emmanuel Raffoux, MD[10]; Peter Tan, MBBS[11]; Amer M. Zeidan, MBBS[12]; Stéphane de Botton, MD, PhD[13]; Hagop M. Kantarjian, MD[1]; Richard M. Stone, MD[14]; Mark G. Frattini, MD, PhD[15]; Frederik Lersch, RN[16]; Jing Gong, PhD[15]; Diego A. Gianolio, PhD[17]; Vickie Zhang, PhD[17]; Aleksandra Franovic, PhD[18]; Bin Fan, PhD[17]; Meredith Goldwasser, ScD[17]; Scott Daigle, MS[17]; Sung Choe, PhD[17]; Bin Wu, PhD[17]; Thomas Winkler, MD[17]; and Paresh Vyas, MD, PhD[19]

J Clin Oncol 2021;39(1):57-65.

RTP RESEARCH TO PRACTICE

Treatment Duration, Response Over Time, and IDH1 Mutation Status



DiNardo CD et al. *J Clin Oncol* 2021;39(1):57-65.

2020 ASCO ANNUAL MEETING
UNITE AND CONQUER: ACCELERATING PROGRESS TOGETHER

Enasidenib (ENA) Plus Azacitidine (AZA) Significantly Improves Complete Remission and Overall Response versus AZA Monotherapy in Mutant-*IDH2* (m*IDH2*) Newly Diagnosed Acute Myeloid Leukemia (ND-AML)

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Presentation Number 7501

RTP RESEARCH TO PRACTICE

AG221-AML-005: Response and Survival

	Enasidenib + Azacitidine (n = 68)	Azacitidine Alone (n = 33)	*p*-value
ORR CR	71% 53%	42% 12%	0.0064 0.0001
Duration of response	24.1 mo	12.1 mo	
Event-free survival	17.2 mo	10.8 mo	HR: 0.59, 0.1278
Overall survival	Not powered for significance		

DiNardo CD et al. ASCO 2020;Abstract 7501.

Commonly Observed and Noteworthy IDH Inhibitor-Related Adverse Events (AEs)

Commonly Observed Treatment-Emergent AEs (Any Grade, >20%)

- **Enasidenib:** Hyperbilirubinemia, nausea
- **Ivosidenib:** Diarrhea, leukocytosis, nausea, fatigue, febrile neutropenia, dyspnea, anemia, QT prolongation, peripheral edema

Noteworthy Grade 3/4 AEs

- **IDH-differentiation syndrome: 5-6%**
- **Prolongation of the QT interval**
  - Enasidenib: Not reported
  - Ivosidenib: ~8%
- **Leukocytosis: 2-3%**
- **Hyperbilirubinemia**
  - Enasidenib: 12%
  - Ivosidenib: Not reported

Stein EM et al. *Blood* 2017;130(6):722-31; DiNardo CD et al. *N Engl J Med* 2018;378:2386-98; Fathi AT et al. *JAMA Oncol* 2018;4(8):1106-10.

IDH Differentiation Syndrome (IDH-DS)

- **Potentially fatal complication of effective leukemia treatment**
  - First described in patients with APL treated with ATRA
- **Signs and symptoms of DS are not specific**
  - Fever, edema, weight gain, leukocytosis, rash, hypotension, renal dysfunction, and pleural and pericardial effusions
  - A rising leukocyte count, comprising increasing neutrophils with a parallel decrease in leukemic blasts
- **Median time to onset:** ~30 days (range: 5-340 days)
- **Frequency:** 5-6% Grade 3 or higher
  - Frequent dose interruptions but not associated with treatment discontinuation
- **Treatment**
  - Corticosteroids for IDH-DS
  - Hydroxyurea for leukocytosis, which frequently accompanies IDH-DS
  - Hyperuricemia agents for tumor lysis syndrome, which may co-occur

Stein EM et al. *Blood* 2017;130(6):722-31; Stein EM et al. *Blood* 2019;133(7):676-87;
DiNardo CD et al. *N Engl J Med* 2018;378:2386-98; Birendra KC, DiNardo CD. *Clin Lymphoma Myeloma Leuk* 2016;16(8):460-5.

Agenda

Module 1: Newly Diagnosed AML Ineligible for Intensive Induction Therapy

- Dr Chojecki: A 73-year-old man with AML

Module 2: Relapsed/Refractory AML with a FLT3 Mutation

- Dr Chojecki: A 69-year-old woman with AML and a FLT3 ITD mutation

Module 3: Newly Diagnosed AML with an IDH1 Mutation

- Dr Chojecki: An 86-year-old man with AML and an IDH1 mutation

Module 4: Secondary AML

- Dr Chojecki: A 60-year-old woman with AML and a TP53 mutation

Module 5: Myelodysplastic Syndromes

- Dr Chojecki: A 78-year-old man with “low risk” MDS
- Dr Favaro: A 77-year-old man with MDS

Case Presentation – Dr Chojecki: A 60-year-old woman with AML and a TP53 mutation

Dr Aleksander Chojecki

- PMH: Burkitt lymphoma in 2004 treated with CODOX-M and CNS prophylaxis
  - Cumulative dose of anthracycline: 240 mg/m^2, LVEF: 55%
- Presents with fevers, nightsweats and chills; pancytopenia
- Diagnosed with AML
  - NGS: TP53 mutation
- CPX-351, with CR → referred for allogeneic HCT
  - Neutropenic fevers, maculopapular rash and mild mucositis

Questions

- What is the typical patient to whom you would offer CPX-351?
- Are there any particular molecular findings that would indicate a higher likelihood of response? Do you tend to give CPX-351 as an inpatient or outpatient? Is it clearly more tolerable than standard induction therapy?
- Have you ever given CPX with additional targeted chemotherapy? Do you tend to offer CPX-351 to a less fit, older patient compared to those that would not be candidates to 7+3? If this patient was 70 years old, would you still have offered CPX?

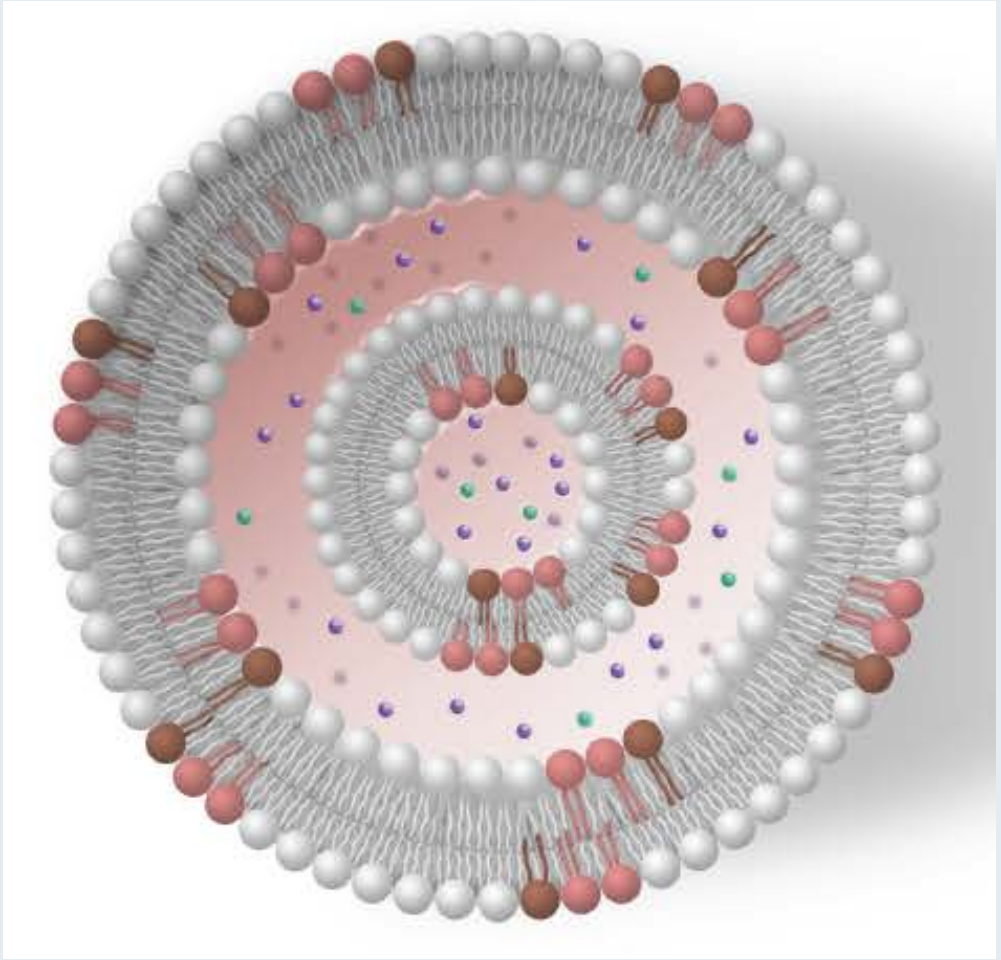
RTP RESEARCH TO PRACTICE

What initial treatment would you recommend for a 64-year-old woman with a history of breast cancer, for which she received adjuvant chemotherapy, who now presents with bone marrow findings consistent with therapy-related AML?

1. 7 + 3 induction
2. CPX-351
3. Decitabine
4. Decitabine + venetoclax
5. Azacitidine + venetoclax
6. Low-dose cytarabine + venetoclax
7. Other

CPX-351

- CPX-351 is a liposomal co-formulation of cytarabine and daunorubicin designed to achieve synergistic antileukemia activity
  - 5:1 molar ratio of cytarabine:daunorubicin provides synergistic leukemia cell killing *in vitro*[1]
  - In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days[2]
  - Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]



1. Tardi P et al. *Leuk Res.* 2009;33(1):129-139. 2. Feldman EJ et al. *J Clin Oncol.* 2011;29(8):979-985;
3. Lim WS et al. *Leuk Res.* 2010;34(9):1245-1223.

ASH 2020; Abstract 635.

Five-year Final Results of a Phase 3 Study of CPX-351 Versus 7+3 in Older Adults with Newly Diagnosed High-risk/Secondary Acute Myeloid Leukemia (AML): Outcomes by Age Subgroup and Among Responders

Presenter: Jeffrey E. Lancet

H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL

Jeffrey E. Lancet,[1] Geoffrey L. Uy,[2] Laura F. Newell,[3] Tara L. Lin,[4] Donna Hogge,[5] Scott R. Solomon,[6] Gary J. Schiller,[7] Matthew J. Wieduwilt,[8] Daniel H. Ryan,[9] Stefan Faderl,[10] Yu-Lin Chang,[10] Jorge E. Cortes[11,12]

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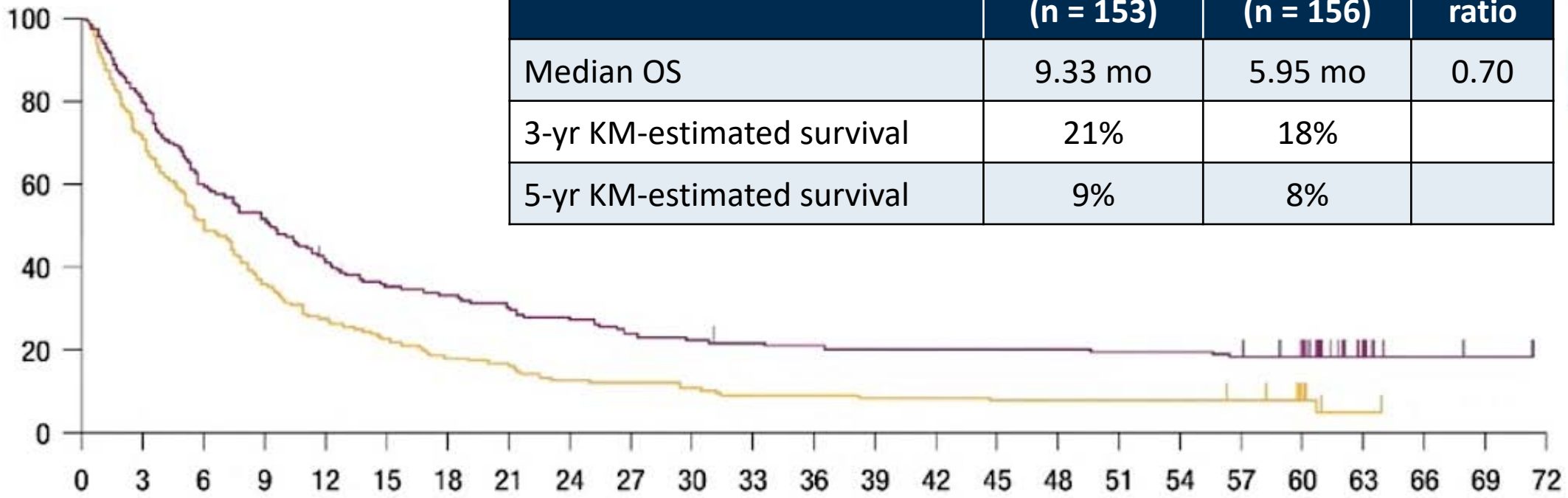
62nd ASH Annual Meeting & Exposition; December 5-8, 2020

Five-Year Final Overall Survival Results of CPX-351 versus 7+3 in Older Patients with Newly Diagnosed High-Risk or Secondary AML

	CPX-351 (n = 153)	7+3 (n = 156)	Hazard ratio
Median OS	9.33 mo	5.95 mo	0.70
3-yr KM-estimated survival	21%	18%	
5-yr KM-estimated survival	9%	8%	

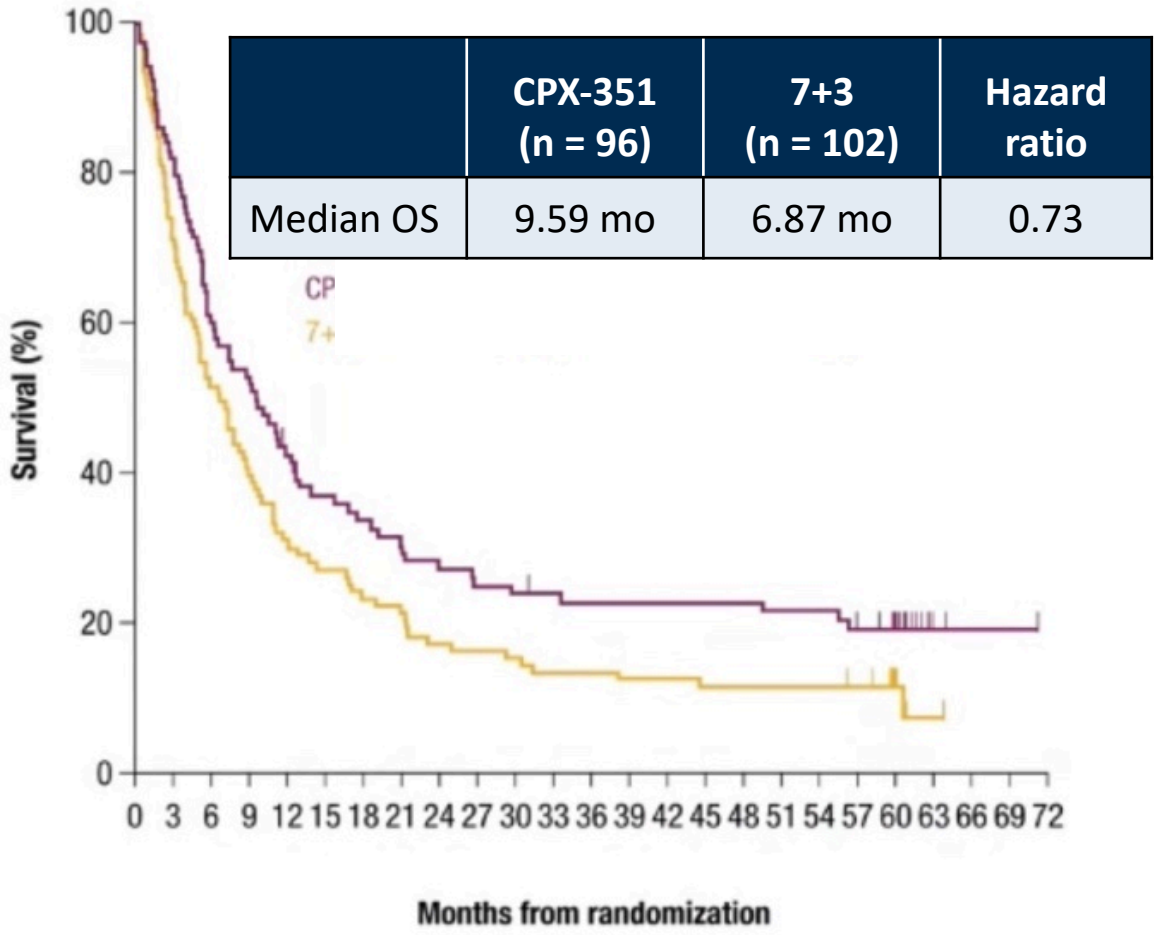


Lancet JE et al. ASH 2020;Abstract 635.

Overall Survival Results by Age

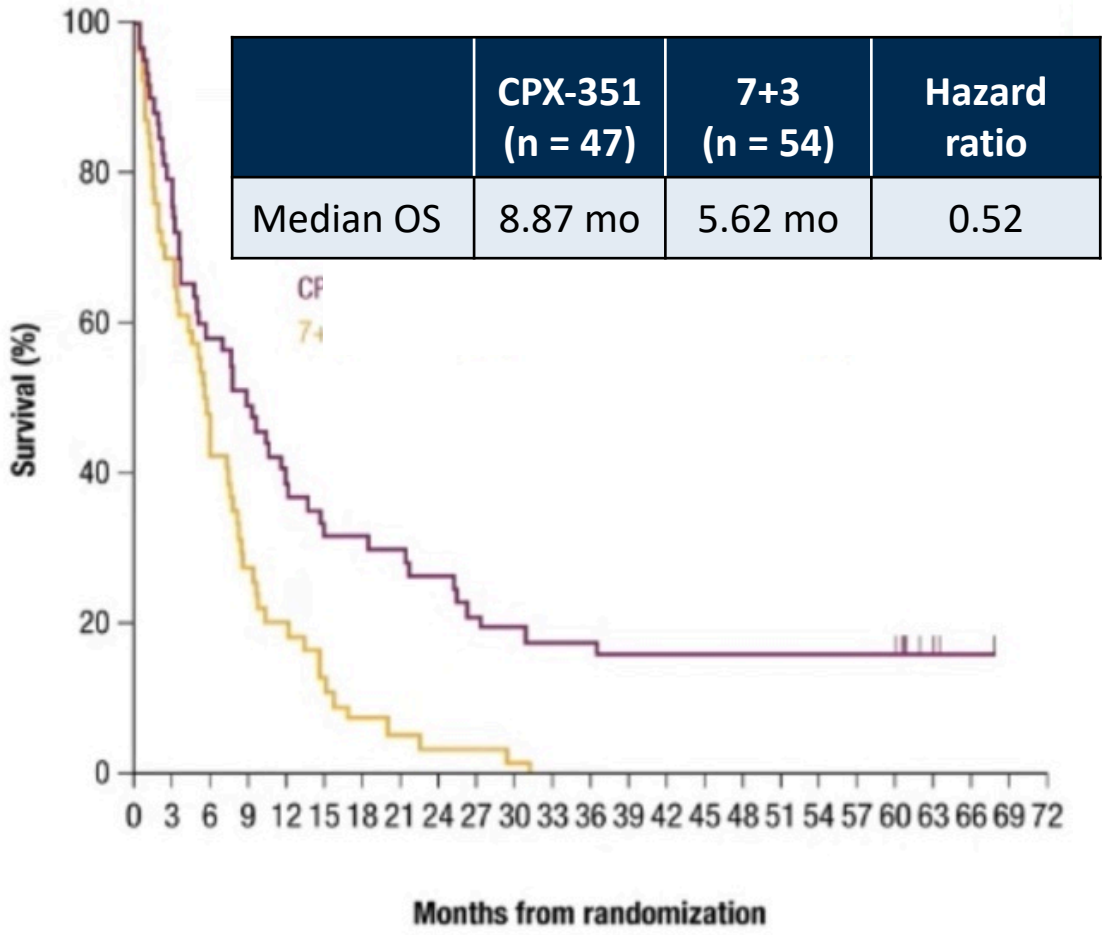
Ages 60 to 69 Years

	CPX-351 (n = 96)	7+3 (n = 102)	Hazard ratio
Median OS	9.59 mo	6.87 mo	0.73



Ages 70 to 75 Years

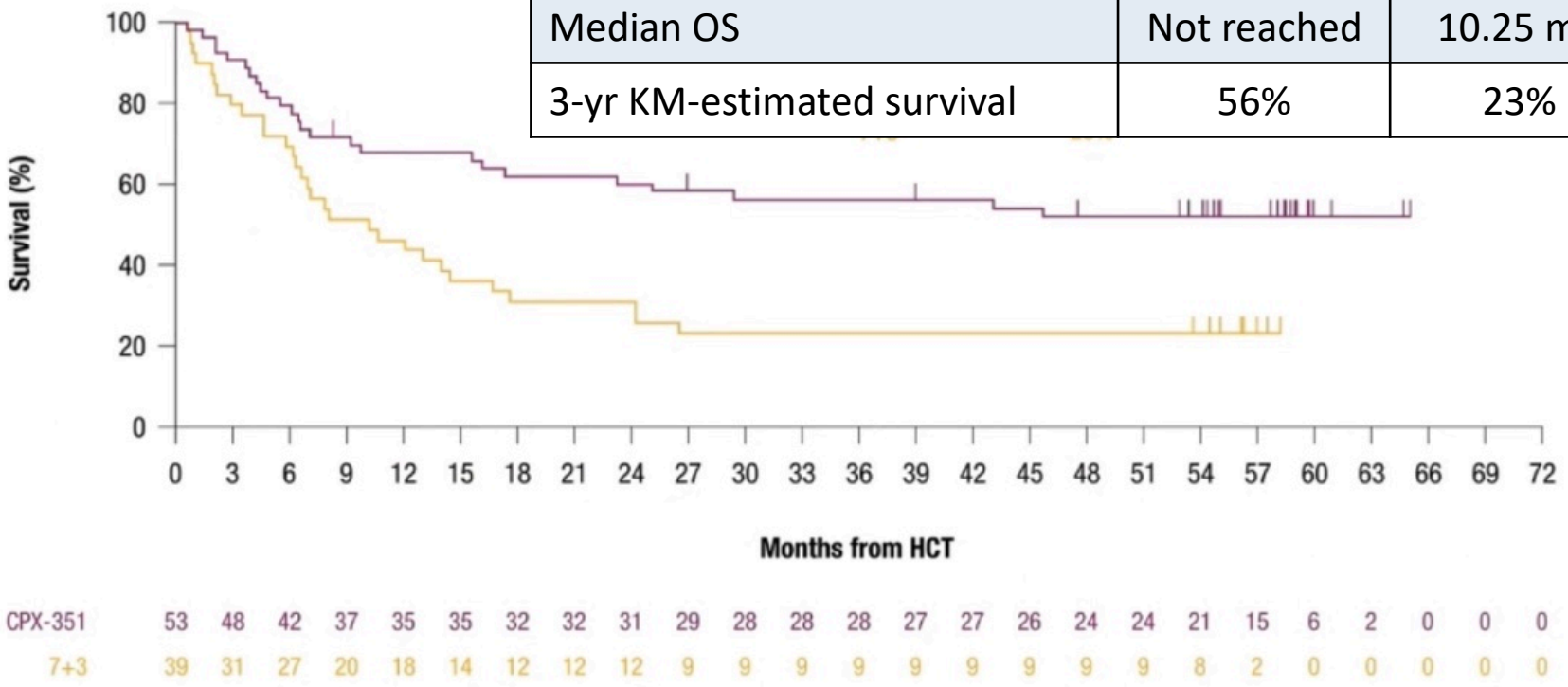
	CPX-351 (n = 47)	7+3 (n = 54)	Hazard ratio
Median OS	8.87 mo	5.62 mo	0.52

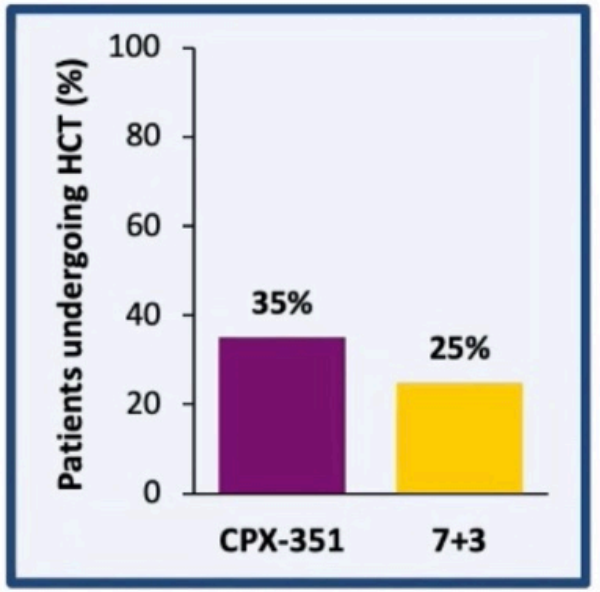


Lancet JE et al. ASH 2020;Abstract 635.

Overall Survival Landmarked from the HCT Date

	CPX-351 (n = 153)	7+3 (n = 156)	Hazard ratio
Median OS	Not reached	10.25 mo	0.51
3-yr KM-estimated survival	56%	23%	





- **Kaplan-Meier–estimated survival rate landmarked from the date of HCT was >50% at 3 and 5 years for patients treated with CPX-351**

Lancet JE et al. ASH 2020;Abstract 635.

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Newly Diagnosed AML

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Module 5: Myelodysplastic Syndromes

- Dr Chojecki: A 78-year-old man with “low risk” MDS
- Dr Favaro: A 77-year-old man with MDS

Case Presentation – Dr Chojecki: A 78-year-old man with “low risk” MDS

Dr Aleksander Chojecki

- PMH: HTN, HLD, early-stage prostate cancer 20 years ago
- Presents with normocytic anemia → transfusion dependence
- Diagnosed with MDS with ringed sideroblasts (R-IPSS: 3.5, IPSS: 0.5)
- FISH MDS panel: Unremarkable
- NGS: ASXL1, IDH2, SRSF2 and SF3B1 mutations
- Luspatercept 1 mg/kg → 1.33 mg/kg q3wks, with hemoglobin improved to 8-10

Questions

- There are very good data that patients who have an erythropoietin level less than 500 may respond to ESAs. What if a patient has neutropenia or thrombocytopenia? Does luspatercept help those counts as well, or do you give additional stimulating agents?
- How quickly, in your experience, have you seen patients achieve a response to luspatercept? And how robust are those responses?
- Do you see hemoglobin concentrations normalize with luspatercept, or do you just see it go to a range of about 8 to 10 in these patients?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Favaro: A 77-year-old man with MDS

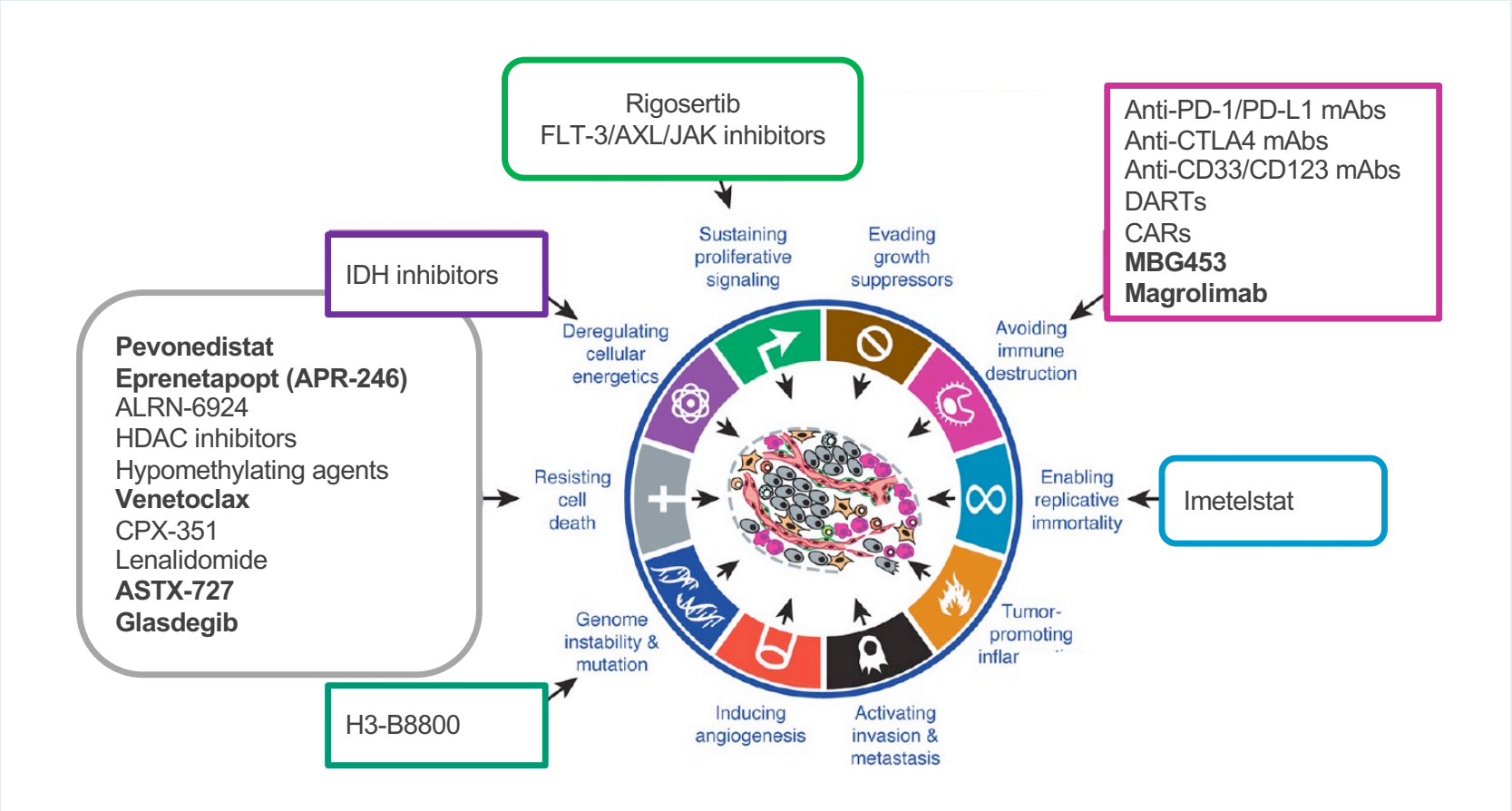
Dr Justin Peter Favaro

- Presents with a hemoglobin of 7, multilineage dysplasia, 4% blasts
- Diagnosed with MDS, normal cytogenetics
- Azacitidine
  - Still anemic after 4 cycles, no improvement in blood counts, bone marrow unchanged
  - Requires monthly transfusions

Questions

- How would you proceed with treatment? Would you switch to decitabine? Would you consider using the new oral drug – decitabine combined with cedazuridine? What is the role of this new oral drug for myelodysplasia? How are you incorporating decitabine/cedazuridine into the treatment of CMML and MDS?
- What is the best treatment option for 5q- disease – lenalidomide, antisense oligonucleotide inhibitor, or telomerase inhibitor?

Treating MDS| Disease Biology

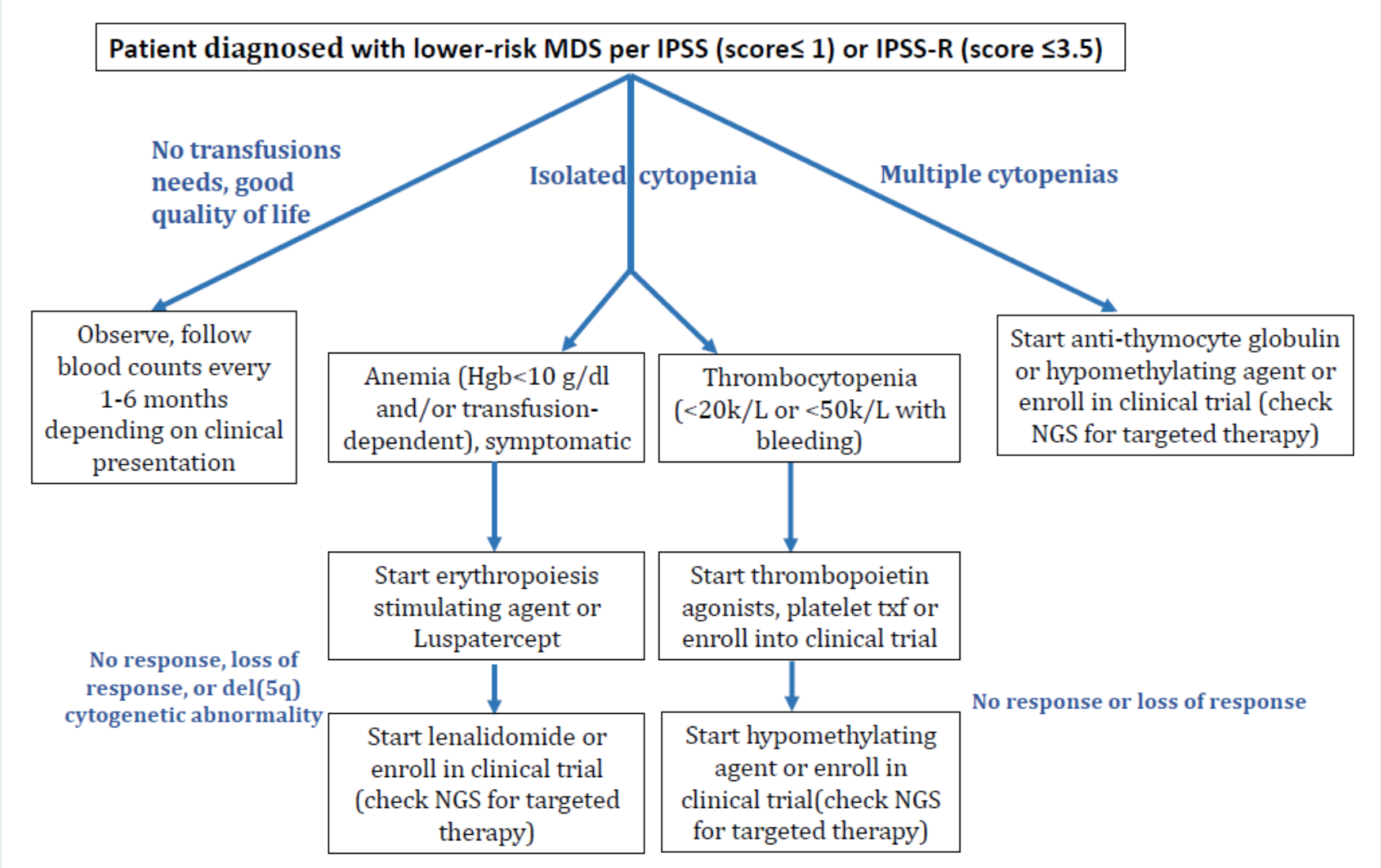


Courtesy of Mikkael A Sekeres, MD, MS

Figure adapted from Hanahan D, Weinberg RA. *Cell* 2011;144:646–74

BH3, bcl homology domain 3; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DARTs, dual affinity retargeting agents; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; mAb, monoclonal antibody; PARP, poly adenosine diphosphate ribose polymerase; VEGF, vascular endothelial growth factor

MDS | Treatment – Lower-risk



Sekeres and Patel Hematology (ASH Educ Book) 2019.

Courtesy of Mikkael A Sekeres, MD, MS

RTP RESEARCH TO PRACTICE

FDA Approves Oral Combination of Decitabine and Cedazuridine for Myelodysplastic Syndromes

Press Release – July 7, 2020

"The Food and Drug Administration approved an oral combination of decitabine and cedazuridine for adult patients with myelodysplastic syndromes (MDS) including the following:

- previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and
- intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

The combination was investigated in two open-label, randomized, crossover trials. Trial ASTX727-01-B (NCT02103478) included 80 adult patients with MDS (International Prognostic Scoring System [IPSS] Intermediate-1, Intermediate-2, or high-risk) or CMML and trial ASTX727-02 (NCT03306264) included 133 adult patients with MDS or CMML, including all French-American-British classification criteria and IPSS Intermediate-1, Intermediate-2, or high-risk prognostic scores."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-oral-combination-decitabine-and-cedazuridine-myelodysplastic-syndromes

blood®
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study

Guillermo Garcia-Manero,[1] Elizabeth A. Griffiths,[2] David P. Steensma,[3] Gail J. Roboz,[4] Richard Wells,[5] James McCloskey II,[6] Olatoyosi Odenike,[7] Amy E. DeZern,[8] Karen Yee,[9] Lambert Busque,[10] Casey O'Connell,[11] Laura C. Michaelis,[12] Joseph Brandwein,[13] Hagop Kantarjian,[1] Aram Oganesian,[14] Mohammad Azab,[14] and Michael R. Savona[15]

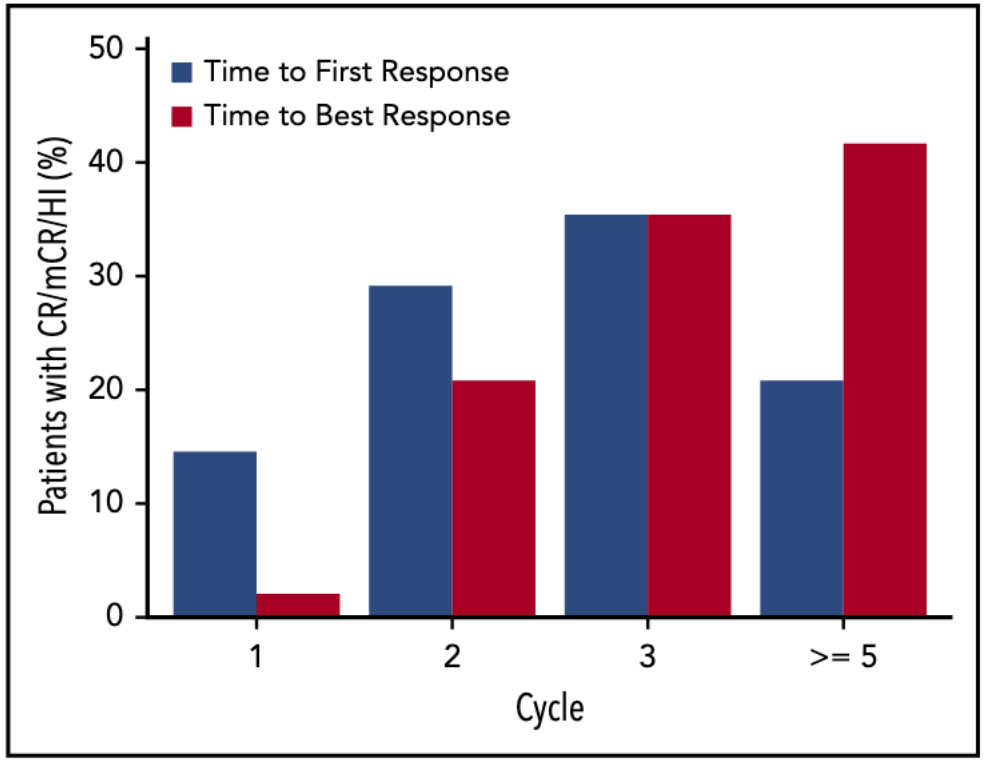
Blood 2020;136(6):674-83.

ASTX727-01-B: Response Summary

Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13-32
PR	0	
mCR	18 (22)	14-33
mCR with HI	6 (7)	3-16
HI	13 (16)	9-26
HI-E	8 (10)	4-19
HI-N	2 (2)	0-9
HI-P	11 (14)	7-23
Overall response* (CR + PR + mCR + HI)	48 (60)	48-71
No response	32 (40)	29-52

CR, complete response; HI, hematologic improvement; HI-E, erythroid response; HI-N, neutrophil response; HI-P, platelet response; mCR, marrow complete response; PR, partial response.

*Patients are counted only once with their best response as per the table hierarchy.



Garcia-Manero G et al. *Blood* 2020;136(6):674-83.

ASTX727-01-B: Adverse Events

Preferred term, n (%)	IV decitabine cycle 1 or 2 (n = 75)	Oral cedazuridine/ decitabine cycle 1 or 2 (n =78)	All oral cedazuridine/ decitabine cycles (n = 78)
Patients with grade ≥3 TEAEs	44 (59)	45 (58)	65 (83)
Most common grade ≥3 TEAEs (≥10% of patients)			
Neutropenia	20 (27)	16 (21)	36 (46)
Thrombocytopenia	21 (28)	18 (23)	30 (38)
Febrile neutropenia	12 (16)	9 (12)	23 (29)
Leukopenia	8 (11)	7 (9)	19 (24)
Anemia	9 (12)	9 (12)	17 (22)
Pneumonia	5 (7)	7 (9)	10 (13)
Sepsis	1 (1)	4 (5)	8 (10)

Garcia-Manero G et al. *Blood* 2020;136(6):674-83.

Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross-Over Phase 3 Study (ASCERTAIN) of an Oral Hypomethylating Agent ASTX727 (Cedazuridine/Decitabine) Compared to IV Decitabine

Garcia-Manero G et al.

ASH 2019;Abstract 846.

ASCERTAIN: Primary Endpoint of Total 5-Day Decitabine AUC Equivalence

Decitabine 5-day AUC_{0-24} (h·ng/mL)		IV DEC		Oral ASTX727		Ratio of Geo. LSM Oral/IV, % (90% CI)	Intrasubject (%CV)
		N	Geo. LSM	N	Geo. LSM		
Primary Analysis	Paired[1]	123	864.9	123	855.7	98.9 (92.7, 105.6)	31.7

[1] Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All Sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

Garcia-Manero G et al. *ASH* 2019;Abstract .

ASCERTAIN: Preliminary Response in MDS/CMML

	Evaluable Patients[1] N=101 n (%)
Complete response (CR)	12 (11.9%)
Partial response (PR)	0
Marrow CR (mCR)	46 (45.5%)
mCR with hematologic improvement	14 (13.9%)
Hematologic improvement (HI)	7 (5.3%)
HI-erythroid	2 (2.0%)
HI-neutrophils	1 (1.0%)
HI-platelet	6 (5.9%)
Overall response (CR + PR + mCR + HI)	65 (64.4%)
Stable disease	28 (27.7%)
Progressive disease	8 (7.9%)

[1] Due to short median follow up (~ 5 months) at data cutoff, 32 patients could not be evaluated for response by the Central IRC. Response was assessed by IWG 2006 criteria

Garcia-Manero G et al. *ASH* 2019;Abstract .

FDA Approves Luspatercept-aamt for Anemia in Adults with MDS

Press Release – April 3, 2020

"The Food and Drug Administration approved luspatercept-aamt for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell (RBC) units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

Efficacy was demonstrated in the MEDALIST trial (NCT02631070), a randomized, multi-center, double-blind, placebo-controlled trial in 229 patients with IPSS-R very low, low, or intermediate-risk myelodysplastic syndromes who had ring sideroblasts and required RBC transfusions (2 or more RBC units over 8 weeks).

The recommended starting dose of luspatercept-aamt is 1 mg/kg once every 3 weeks by subcutaneous injection. Review hemoglobin results prior to each administration."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-luspatercept-aamt-anemia-adults-mds

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

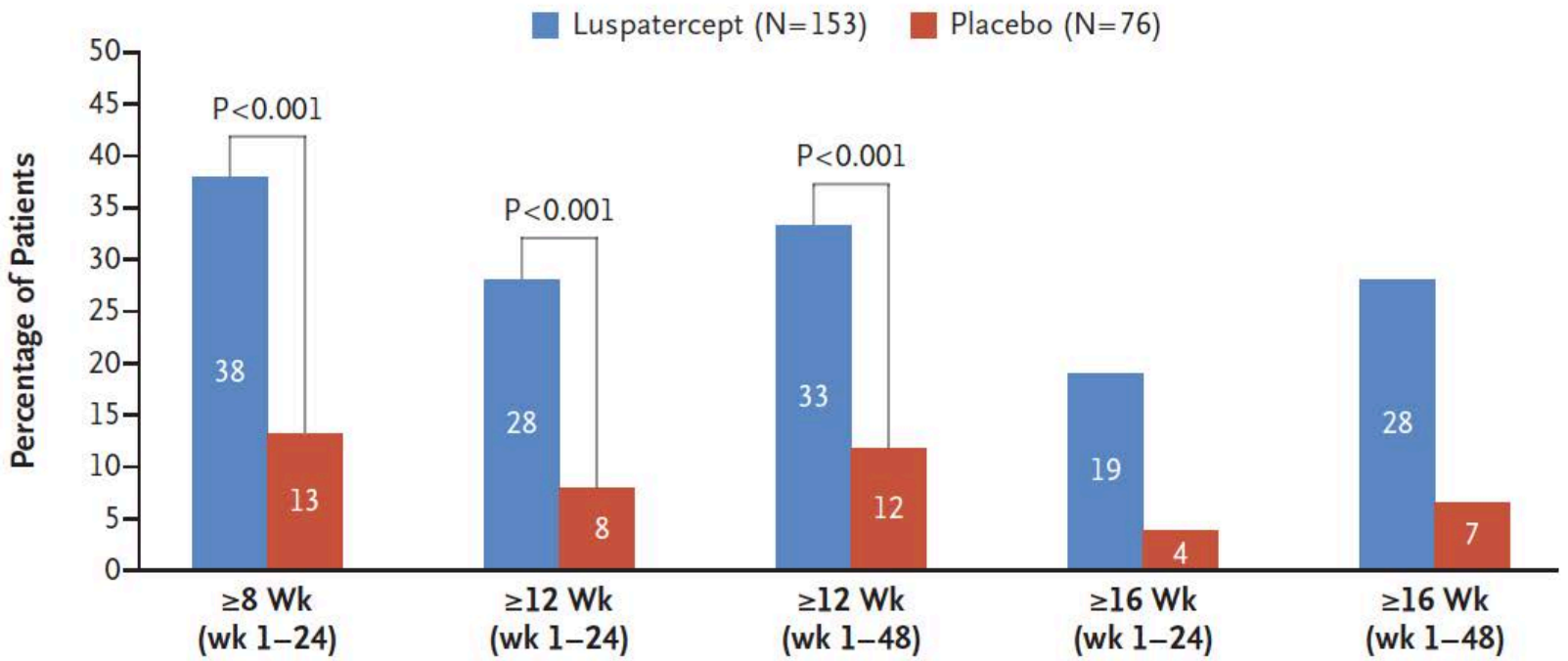
ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

P. Fenaux, U. Platzbecker, G.J. Mufti, G. Garcia-Manero, R. Buckstein, V. Santini, M. Díez-Campelo, C. Finelli, M. Cazzola, O. Ilhan, M.A. Sekeres, J.F. Falantes, B. Arrizabalaga, F. Salvi, V. Giai, P. Vyas, D. Bowen, D. Selleslag, A.E. DeZern, J.G. Jurcic, U. Germing, K.S. Götze, B. Quesnel, O. Beyne-Rauzy, T. Cluzeau, M.-T. Voso, D. Mazure, E. Vellenga, P.L. Greenberg, E. Hellström-Lindberg, A.M. Zeidan, L. Adès, A. Verma, M.R. Savona, A. Laadem, A. Benzohra, J. Zhang, A. Rampersad, D.R. Dunshee, P.G. Linde, M.L. Sherman, R.S. Komrokji, and A.F. List

***N Engl J Med* 2020;382(2):140-51.**

MEDALIST: Independence from Red-Cell Transfusion in Phase II Trial of Luspatercept



No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

Fenaux P et al. *N Engl J Med* 2020;382:140-51.

FDA Grants Breakthrough Therapy Designation to the Novel Anti-CD47 Antibody Magrilomab for the Treatment of MDS

Press Release – September 15, 2020

"The U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation for magrolimab, a first-in-class, investigational anti-CD47 monoclonal antibody for the treatment of newly diagnosed myelodysplastic syndrome (MDS).

The FDA granted Breakthrough Therapy designation for magrolimab based on positive results of an ongoing Phase 1b study, which evaluated magrolimab in combination with azacitidine in previously untreated intermediate, high and very high-risk MDS."

https://www.gilead.com/news-and-press/press-room/press-releases/2020/9/gileads-magrolimab-an-investigational-anticd47-monoclonal-antibody-receives-fda-breakthrough-therapy-designation-for-treatment-of-myelodysplastic

RTP RESEARCH TO PRACTICE

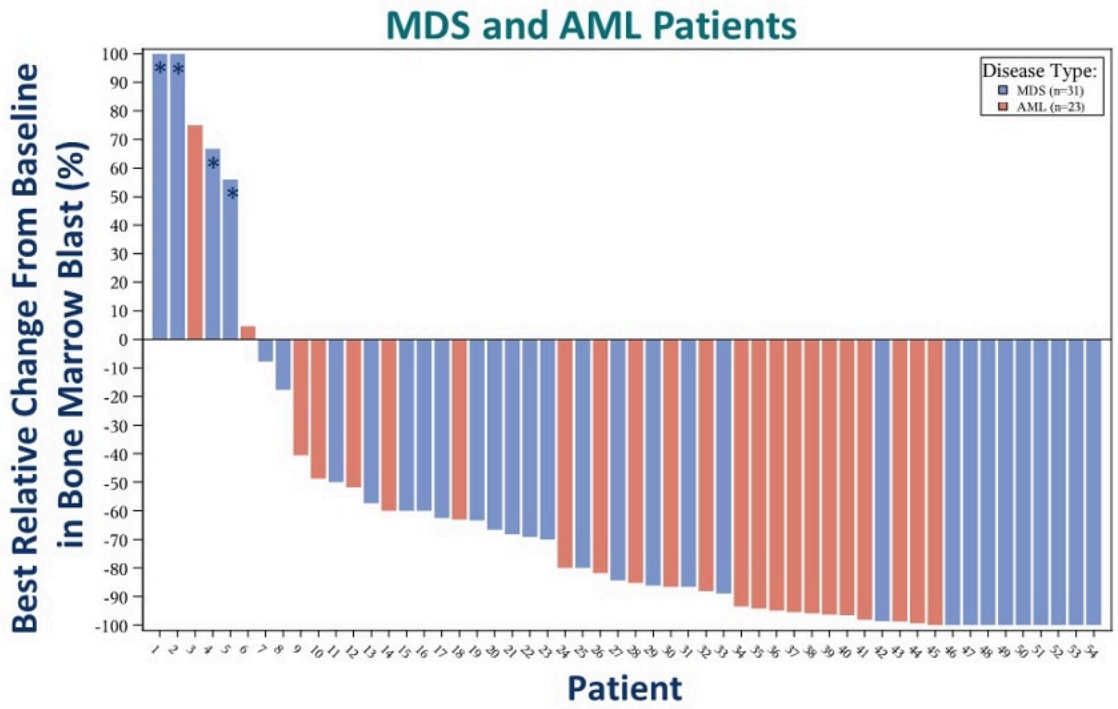
Tolerability and Efficacy of the First-in-Class Anti-CD47 Antibody Magrolimab Combined with Azacitidine in MDS and AML Patients: Phase Ib Results

Sallman D et al.
ASCO 2020;Abstract 7507.

Magrolimab with Azacitidine Induces High Response Rates in MDS and AML

Best Overall Response	1L MDS N=33	1L AML N=25
ORR	30 (91%)	16 (64%)
CR	14 (42%)	10 (40%)
CRi	NA	4 (16%)
PR	1 (3%)	1 (4%)
MLFS/marrow CR	8 (24%) 4 with marrow CR + HI	1 (4%)
Hematologic improvement (HI)	7 (21%)	NA
SD	3 (9%)	8 (32%)
PD	0	1 (4%)

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML patients (1 AE, 2 early withdrawal).



Four patients not shown due to missing values; <5% blasts imputed as 2.5%. *Baseline bone marrow blasts ≤5%.

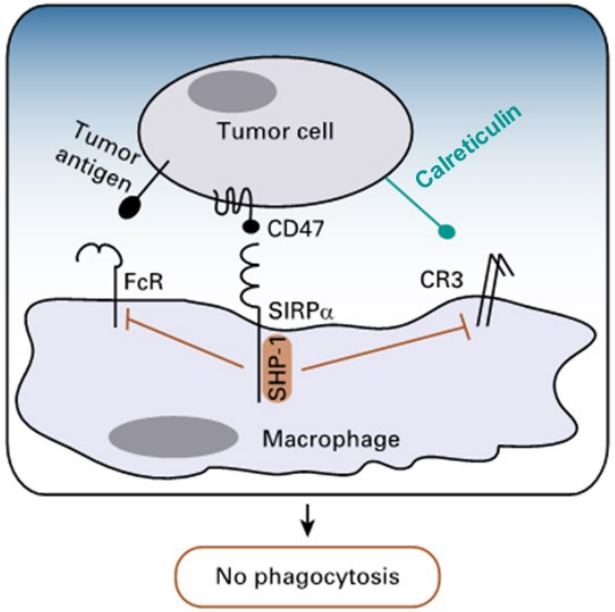
- Magrolimab + AZA induces a 91% ORR (42% CR) in MDS and 64% ORR (56% CR/CRi) in AML
- Responses deepened over time with a 56% 6-month CR rate in MDS patients (assessed in all patients 6 months after initial treatment)
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 6-17%[1,2])

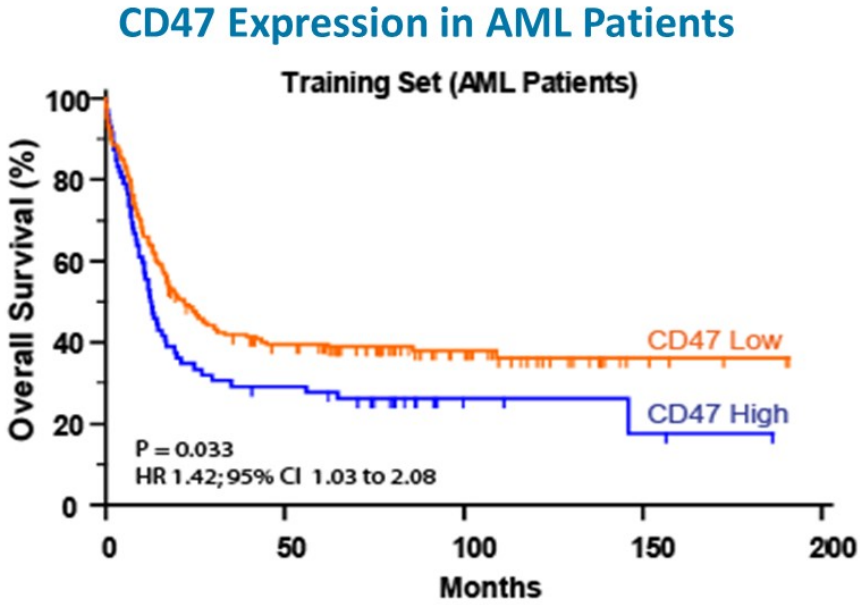
1. Azacitidine USPI. 2. Fenaux P, et al. *Lancet Oncol.* 2009 ;10(3):223-232.

Sallman D et al. ASCO 2020;Abstract 7507.

RTP RESEARCH TO PRACTICE

CD47 Is a Major Macrophage Immune Checkpoint and 'Do Not Eat Me' Signal in Myeloid Malignancies Including MDS and AML





- CD47 is a "do not eat me" signal on cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in AML patients

Figure at left adapted from Veillette A, Tang Z. *J Clin Onc*. 2019;37(12)1012-1014, and Chao MP, et al. *Current Opin Immunol*. 2012; 24(2):225-232.
Figure at right adapted from Majeti R, et al. *Cell*. 2009;138(2):286-299.

Sallman D et al. ASCO 2020;Abstract 7507.

FDA Grants Breakthrough Therapy Designation for Pevonedistat to Treat Higher-Risk MDS

Press Release – July 30, 2020

"The FDA granted breakthrough therapy designation to pevonedistat for the treatment of patients with higher-risk myelodysplastic syndromes (HR-MDS). The investigational drug, pevonedistat, is a NEDD8-activating enzyme (NAE) inhibitor that could be the first novel treatment for patients with HR-MDS in more than a decade.

The breakthrough therapy designation comes in response to the final analysis of the Pevonedistat-2001 phase 2 study evaluating pevonedistat plus azacitidine (Vidaza) versus azacitidine alone to treat patients with HR-MDS among other rare leukemias.

Primary end points included overall survival, event-free survival, complete remission, and transfusion independence. The FDA also considered the adverse event profile of the results."

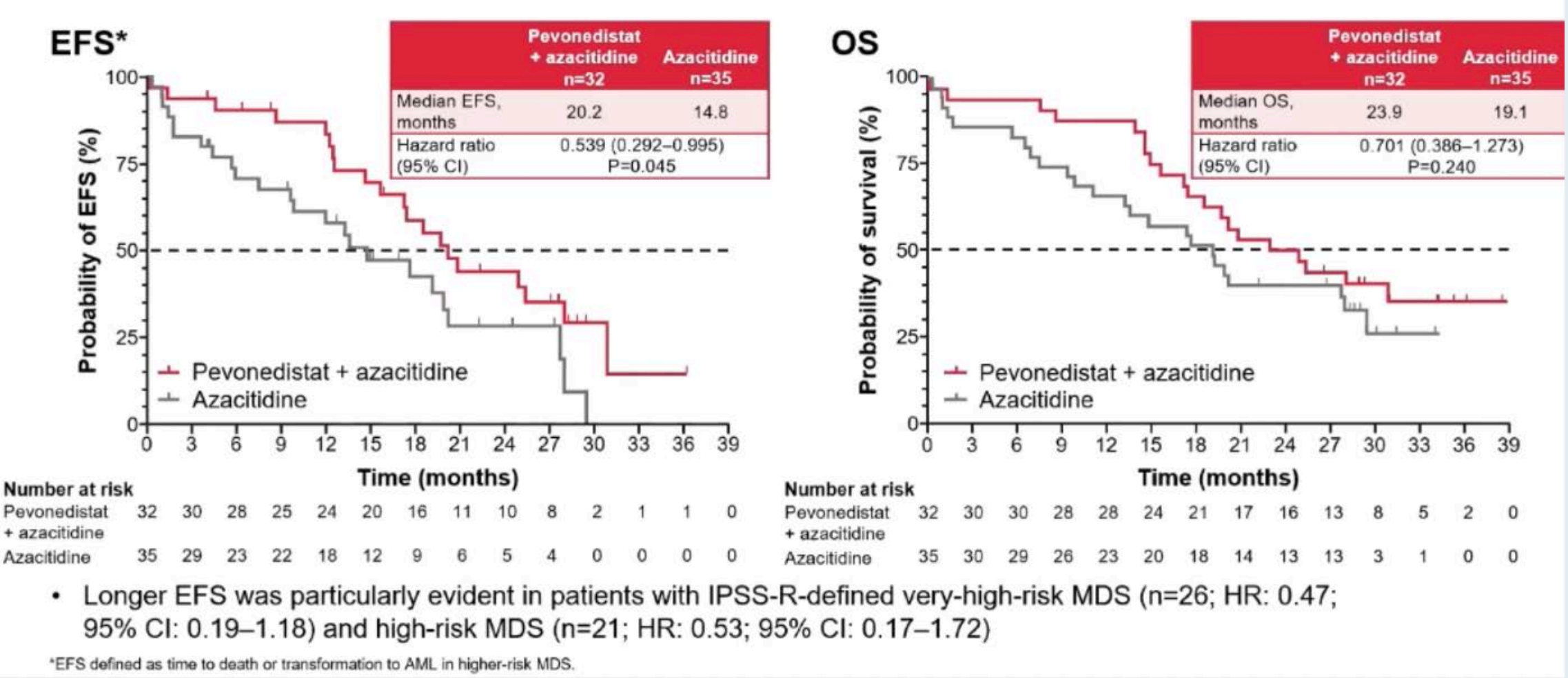
https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-designation-for-pevonedistat-to-treat-higher-risk-mds

Efficacy and Safety of Pevonedistat plus Azacitidine vs Azacitidine Alone in Higher-Risk Myelodysplastic Syndromes (MDS) from Study P-2001 (NCT02610777)

Sekeres MA et al.

ASH 2020;Abstract 653.

Event-Free Survival and Overall Survival with Pevonedistat with Azacitidine



- Longer EFS was particularly evident in patients with IPSS-R-defined very-high-risk MDS (n=26; HR: 0.47; 95% CI: 0.19–1.18) and high-risk MDS (n=21; HR: 0.53; 95% CI: 0.17–1.72)

*EFS defined as time to death or transformation to AML in higher-risk MDS.

Sekeres MA et al. ASH 2020;Abstract 653

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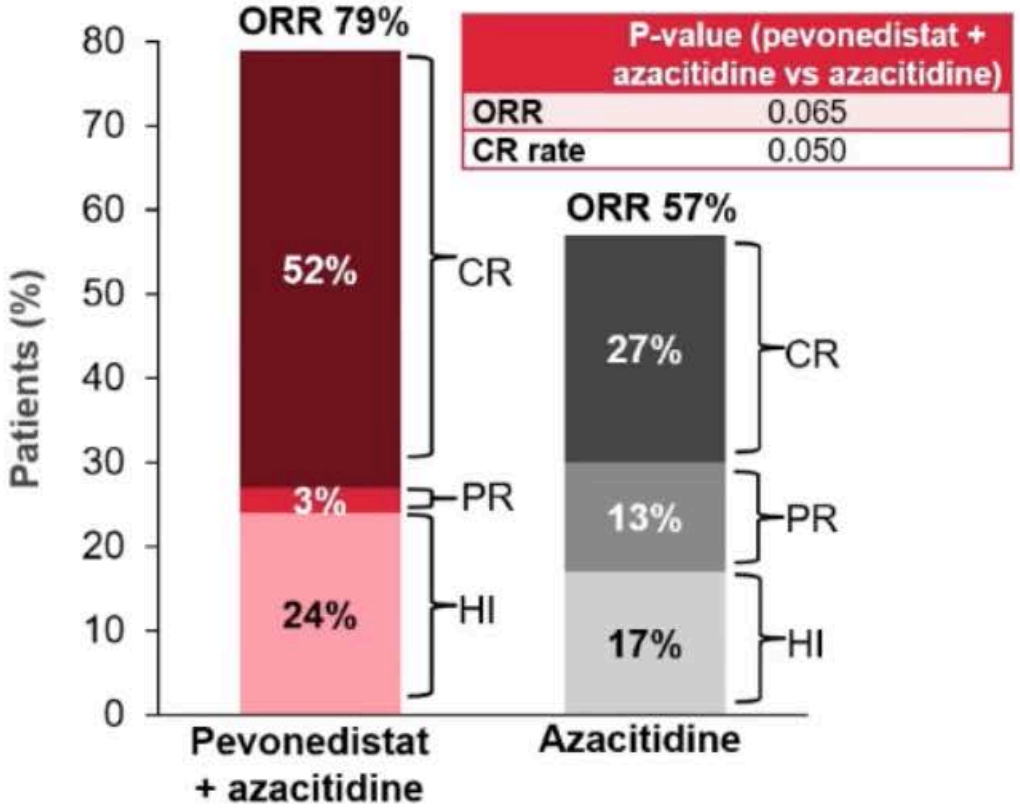
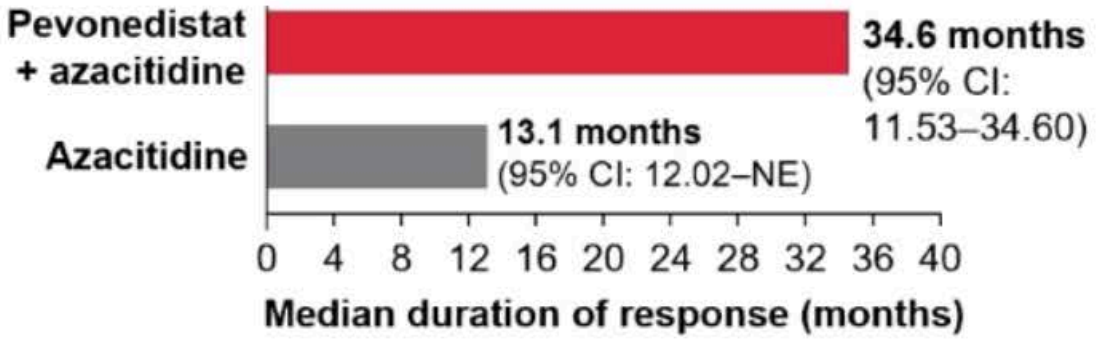
Response Rates with Pevonedistat with Azacitidine

Response-evaluable patients with higher-risk MDS (n=59):



	P-value (pevonedistat + azacitidine vs azacitidine)
ORR	0.065
CR rate	0.050



	Pevonedistat + azacitidine n=16	Azacitidine n=12
Median time to first CR or PR among responders, months (range)	3.83 (1.8–25.8)	4.29 (2.0–13.2)

CR, complete response; HI, hematologic improvement; NE, not evaluable; PR, partial response.

Sekeres MA et al. ASH 2020;Abstract 653

Exposure Adjusted AE Rates with Pevonedistat with Azacitidine

- Median number of azacitidine treatment cycles: 13.5 (pevonedistat + azacitidine) versus 10.0 (azacitidine).
- Median azacitidine dose intensity: 98% in both treatment arms.

Rates of AEs, SAEs, and grade ≥3 AEs normalized by the mean number of azacitidine cycles dosed:

	Pevonedistat + azacitidine n=32	Azacitidine n=35
Any AE, normalized n* (n)	1.96 (32)	3.27 (35)
Treatment-related AE, normalized n* (n)	1.35 (22)	2.52 (27)
SAE, normalized n* (n)	1.47 (24)	1.87 (20)
Treatment-related SAE, normalized n* (n)	0.25 (4)	0.28 (3)
Grade ≥3 AE, normalized n* (n)	1.84 (30)	2.71 (29)

*Normalized n=AE (n)/azacytidine cycles dosed (mean)
AE, adverse event; SAE, serious adverse event.

Sekeres MA et al. ASH 2020;Abstract 653

STIMULUS REPORT

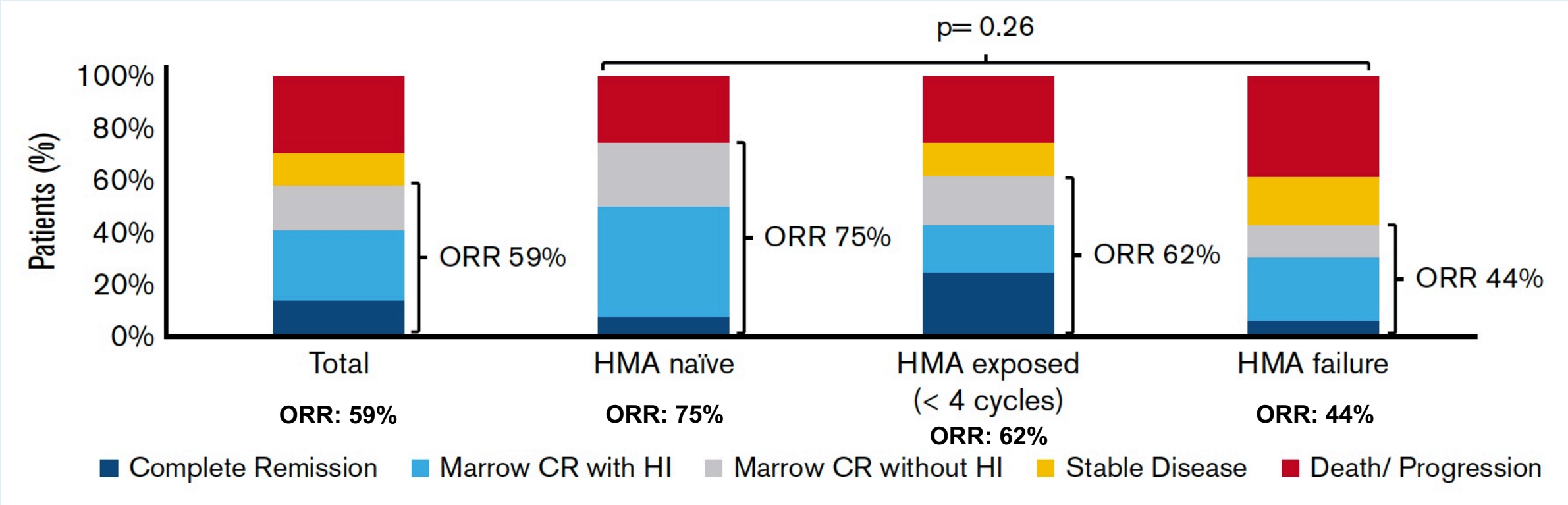
blood advances

Venetoclax and hypomethylating agents (HMAs) induce high response rates in MDS, including patients after HMA therapy failure

Brian J. Ball,[1] Christopher A. Famulare,[2] Eytan M. Stein,[1] Martin S. Tallman,[1] Andriy Derkach,[3] Mikhail Roshal,[1] Saar I. Gill,[4] Benjamin M. Manning,[4] Jamie Koprivnikar,[5] James McCloskey,[5] Rebecca Testi,[5] Thomas Prebet,[6] Najla H. Al Ali,[7] Eric Padron,[7] David A. Sallman,[7] Rami S. Komrokji,[7,*] and Aaron D. Goldberg[1,*]

Blood Adv 2020;4(13):2866-70

Response of Patients with MDS Receiving Venetoclax Plus Hypomethylating Agent Therapy



Median OS: 19.5 months

Median OS with HMA failure: 11.4 months

Ball BJ et al. *Blood Adv* 2020;4(13):2866-70.

Thank you for joining us!

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

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