Current Concepts and Recent Advances in Oncology

A Daylong Clinical Summit Hosted in Partnership with Florida Cancer Specialists

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

Faculty

Arjun Balar, MD
Johanna Bendell, MD
Axel Grothey, MD
Brad S Kahl, MD
Shaji K Kumar, MD
Kathleen Moore, MD
Loretta Nastoupil, MD
William K Oh, MD
David M O'Malley, MD
Robert Z Orlowski, MD, PhD
Gregory J Riely, MD, PhD
Hope S Rugo, MD
David R Spigel, MD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Agenda

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

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

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

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

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

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

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

Genitourinary Cancers Faculty

Arjun Balar, MD
Associate Professor, Department of Medicine
Director, Genitourinary Medical Oncology Program
NYU Perlmutter Cancer Center
New York, New York

William K Oh, MD
Chief, Division of Hematology and Medical Oncology
Professor of Medicine and Urology
Ezra M Greenspan, MD Professor in Clinical Cancer Therapeutics
Icahn School of Medicine at Mount Sinai
Associate Director of Clinical Research
The Tisch Cancer Institute
Mount Sinai Health System
New York, New York

Dr Balar — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Janssen Biotech Inc, Merck, Nektar, Pfizer Inc, Seagen Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Immunomedics Inc, Janssen Biotech Inc, Merck, Nektar, Pfizer Inc, Seagen Inc

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Dr Oh — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, CPS Companion Diagnostics, Janssen Biotech Inc, Sanofi Genzyme, Sema4, TeneoBio

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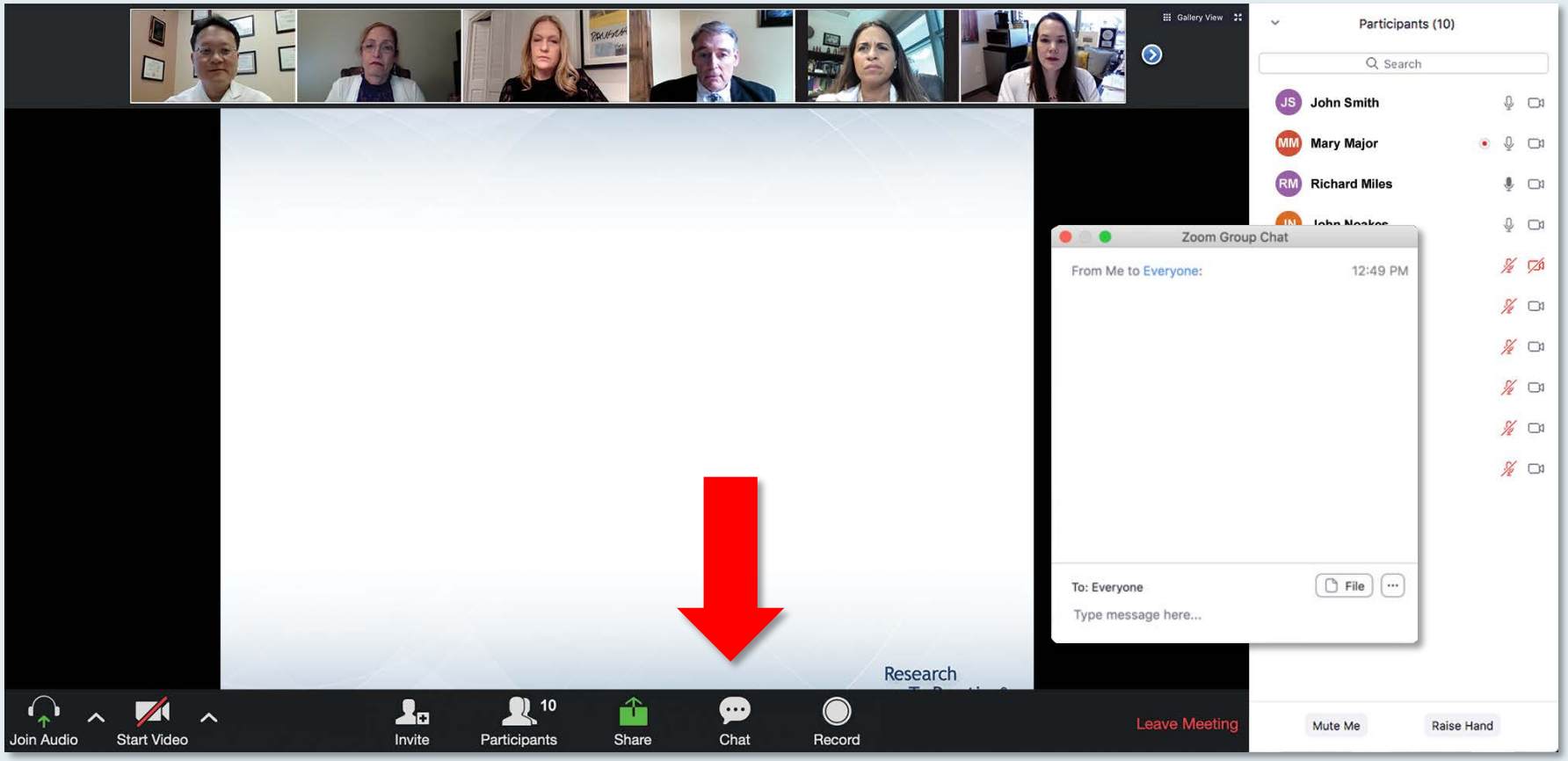
We Encourage Clinicians in Practice to Submit Questions



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

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FCS Contributing Oncologists

Mamta Choksi, MD
New Port Richey, Florida

Uday Dandamudi, MD
New Port Richey, Florida

Lowell L Hart, MD
Fort Myers, Florida

Maen Hussein, MD
Tavares, Florida

Zanetta S Lamar, MD
Naples, Florida

Vikas Malhotra, MD
Spring Hill, Florida

Shachar Peles, MD
Lake Worth, Florida

Syed F Zafar, MD
Fort Myers, Florida

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Agenda

Module 1: Prostate Cancer

- Dr Zafar: A functional, independent 90-year-old man with prostate cancer
- Dr Malhotra: An 87-year-old man with metastatic castration-resistant prostate cancer – ATM mutation

Module 2: Renal Cell Carcinoma

- Dr Choksi: A 63-year-old man with metastatic renal cell carcinoma
- Dr Dandamudi: A 68-year-old man with renal cell carcinoma

Module 3: Urothelial Bladder Cancer

- Dr Hart: A 75-year-old man with urothelial bladder cancer
- Dr Lamar: A 68-year-old man with metastatic urothelial carcinoma

What systemic treatment, if any, would you recommend for a 90-year-old man with prostate cancer who experiences PSA-only progression with negative imaging while receiving androgen deprivation therapy (ADT) for M0 disease with a PSA doubling time of 8 months?

a. Continue ADT alone
b. Continue ADT and add apalutamide
c. Continue ADT and add darolutamide
d. Continue ADT and add enzalutamide
e. Continue ADT and add abiraterone
f. Other

Case Presentation – Dr Zafar: A functional, independent 90-year-old man with prostate cancer

Dr Syed Zafar

- 2000: Diagnosed with Gleason 4 + 3 prostate cancer, PSA: 20s
  - PMH unavailable
- 2018: Biochemical relapse (PSA: 09 → 2.63 → 10), with no evidence of metastatic disease
  - No treatment offered but at patient insistence, ADT initiated
- 2020: PSA progression 2.3 → 4 → 6, with no evidence of metastatic disease
  - No treatment recommended but at patient insistence, darolutamide initiated, PSA undetectable, tolerating well
- Germline and somatic mutation testing planned

Question

- If the patient experiences PSA progression on darolutamide, he will likely insist on therapy. What would you suggest – abiraterone/prednisone, other?

Case Presentation – Dr Malhotra: An 87-year-old man with mCRPC – ATM mutation

Dr Vikas Malhotra

- Diagnosed with prostate cancer when 75 years old
- Complete androgen blockade (CAB) with bicalutamide/leuprolide
- 2013: Progressive disease while on CAB
- Subsequent treatments: Abiraterone, enzalutamide, docetaxel, cabazitaxel and mitoxantrone
- Genetic testing: ATM mutation
- Olaparib x 7 months, with good response → PD
  - Dose reduction to 200 mg BID due to anemia

Questions

- Is there data for switching from one PARP inhibitor to another? Should I rechallenge this patient at the full dose of olaparib?
- What is your experience in dosing PARP inhibitors for elderly patients and how well do they tolerate this treatment?
- Would you consider immunotherapy outside of a clinical trial, even though I have no markers (ie, MSI, TMB) to suggest it would be beneficial?

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At what point, if any, do you generally recommend a PARP inhibitor to a patient with metastatic prostate cancer and a germline BRCA mutation?

a. As part of first-line treatment, alone or as maintenance
b. After 1 line of hormonal therapy
c. After 1 line of chemotherapy
d. After at least 1 line of both hormonal therapy and chemotherapy
e. Other
f. I generally would not administer a PARP inhibitor

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

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

https://www.fda.gov/drugs/resources-information-approved-drugs/

Survival: Darolutamide, Enzalutamide, Apalutamide

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

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

Comparison of Toxicities: Darolutamide, Enzalutamide, Apalutamide

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

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

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

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

https://www.fda.gov/drugs/resources-information-approved-drugs/

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

	ARCHES (N = 1,150)		TITAN (N = 1,052)	
Characteristics	• 2/3rd high volume • 17% prior docetaxel • 25% prior RP/XRT		• 2/3rd high volume • 10% prior docetaxel • 17% prior RP/XRT	
	ADT + enzalutamide (n = 574)	**ADT (n = 576)**	**ADT + apalutamide (n = 955)**	**ADT (n = 554)**
Radiographic PFS	NR	19.0 mo	NR	22.1 mo
	HR (overall): 0.39 • HR (prior docetaxel): 0.52 • HR (high volume): 0.43 • HR (low volume): 0.25		**HR (overall): 0.48** • HR (prior docetaxel): 0.47 • HR (high volume): 0.53 • HR (low volume): 0.36	
Overall survival	NR	NR	NR	NR
	HR: 0.81 (immature)		**HR (overall): 0.67** • HR (prior docetaxel): 1.27 • HR (high volume): 0.68 • HR (low volume): 0.67	

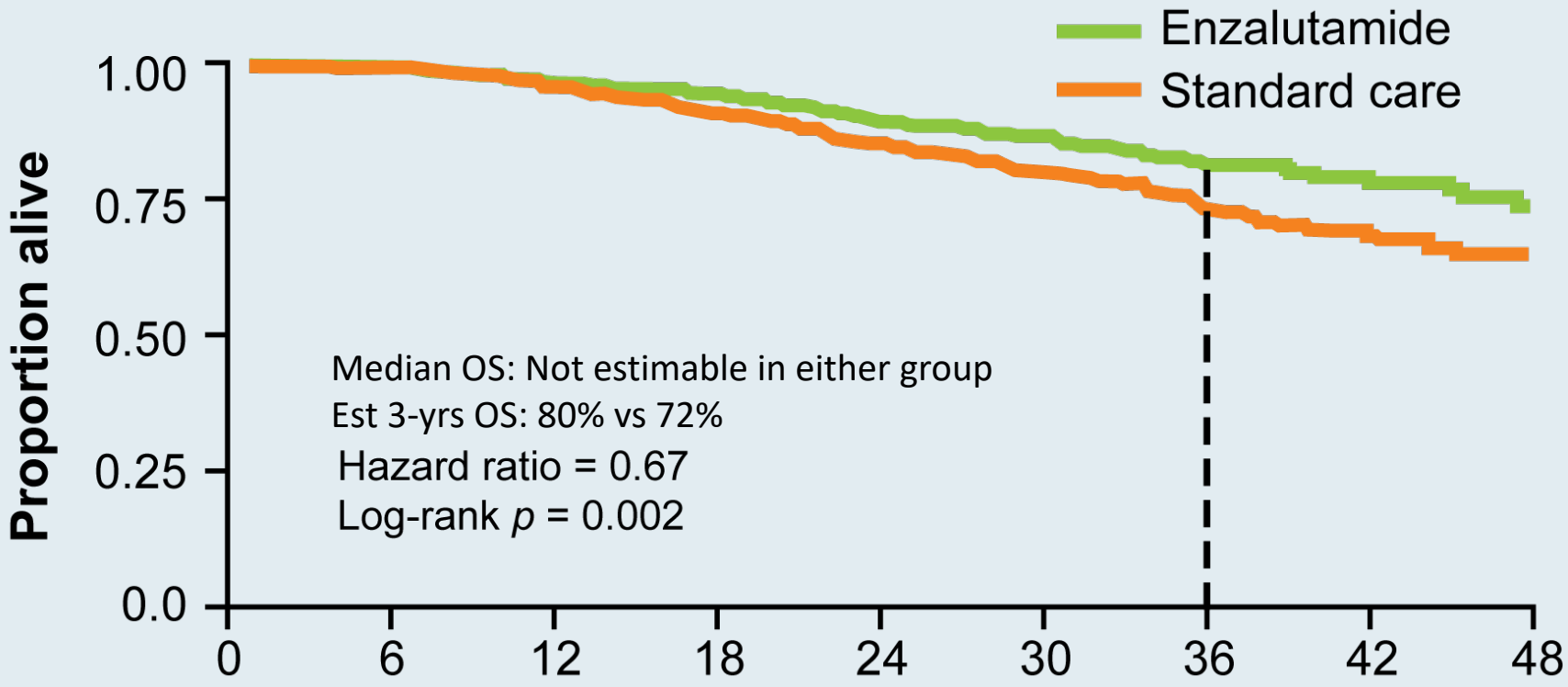
NR = not reached

Armstrong AJ et al. *J Clin Oncol* 2019;37(32):2974-86. Chi KN et al. *N Engl J Med* 2019;381(1):13-24.

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

A Mixed Bag

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



Number at risk

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

Davis ID et al. *N Engl J Med* 2019;381(2):121-31.

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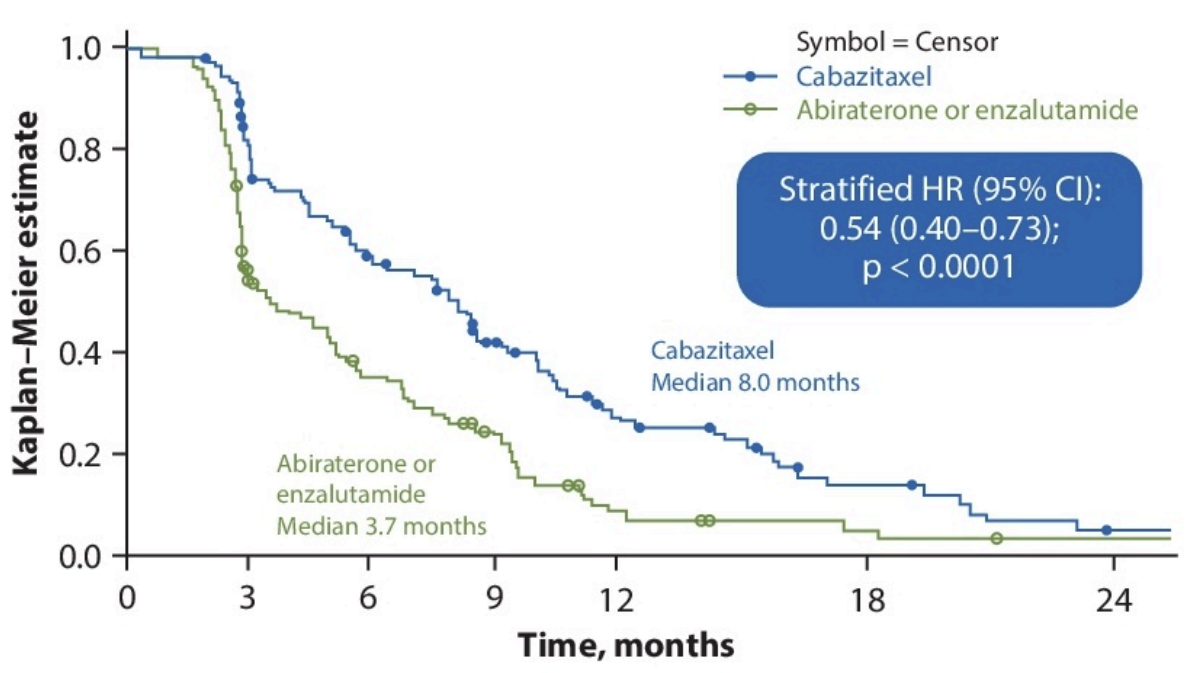
CARD: Overall Survival Analysis of Patients with Metastatic Castration-Resistant Prostate Cancer Receiving Cabazitaxel vs Abiraterone or Enzalutamide

Tombal B et al.

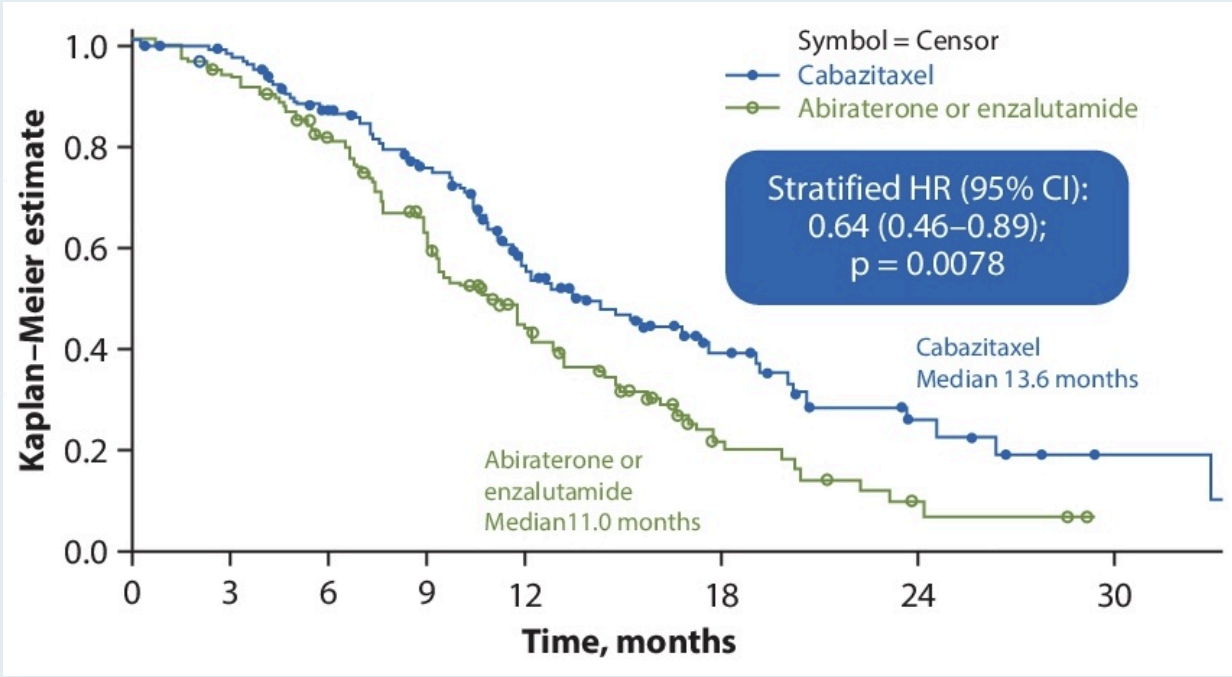
ASCO 2020;Abstract 5569.

CARD Study of Cabazitaxel: Survival Analyses

rPFS (primary endpoint)



OS (key secondary endpoint)



Tombal B et al. ASCO 2020;Abstract 5569.

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Recent FDA Approvals of PARP Inhibitors in Metastatic Castration-Resistant Prostate Cancer

PARPi	Approval date	Pivotal study
Olaparib	May 19, 2020	PROfound
Rucaparib	May 15, 2020	TRITON2

https://www.fda.gov/drugs/resources-information-approved-drugs/

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

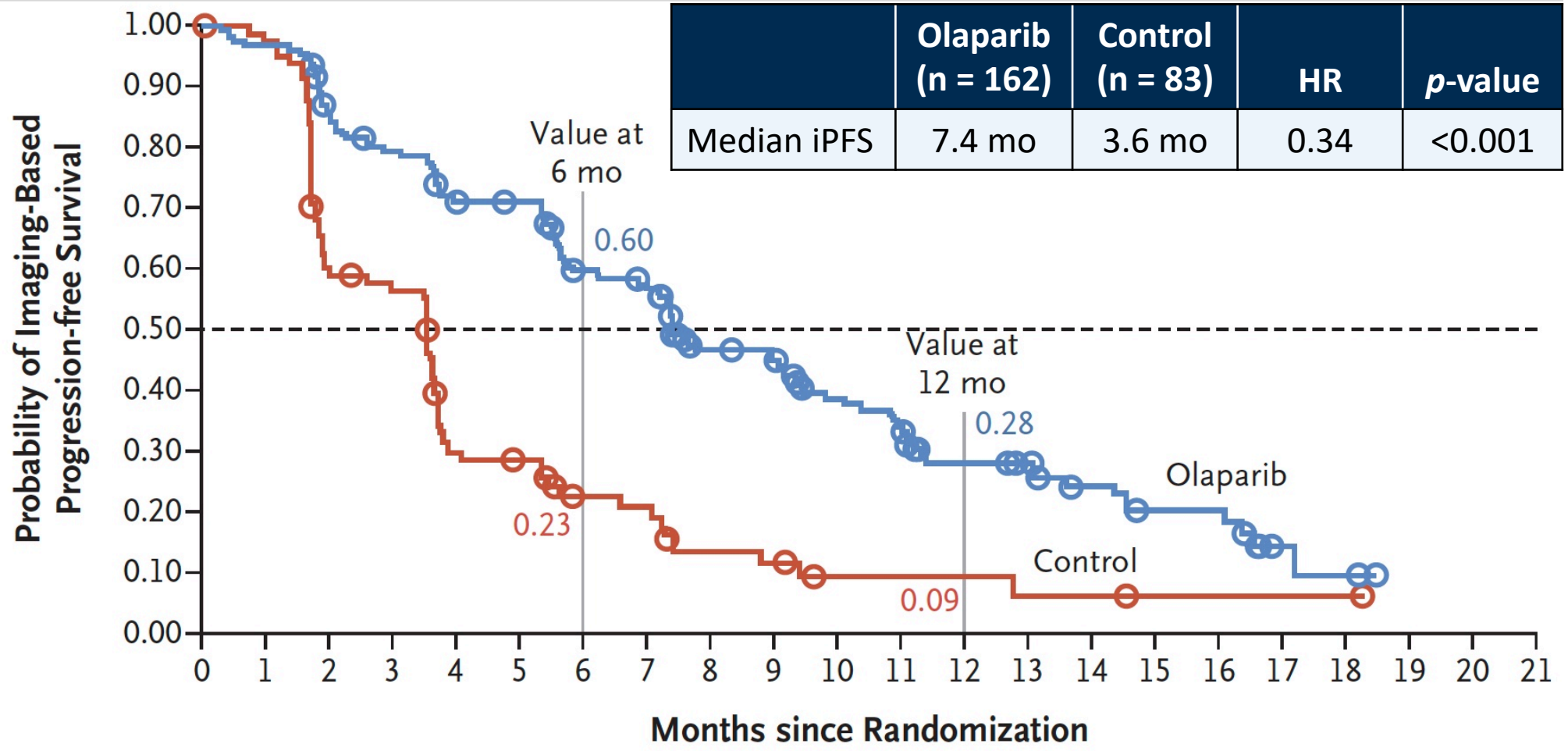
Olaparib for Metastatic Castration-Resistant Prostate Cancer

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

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

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

	Olaparib (n = 162)	Control (n = 83)	HR	*p*-value
Median iPFS	7.4 mo	3.6 mo	0.34	<0.001



de Bono J et al; PROfound investigators. *N Engl J Med* 2020;382(22):2091-102.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

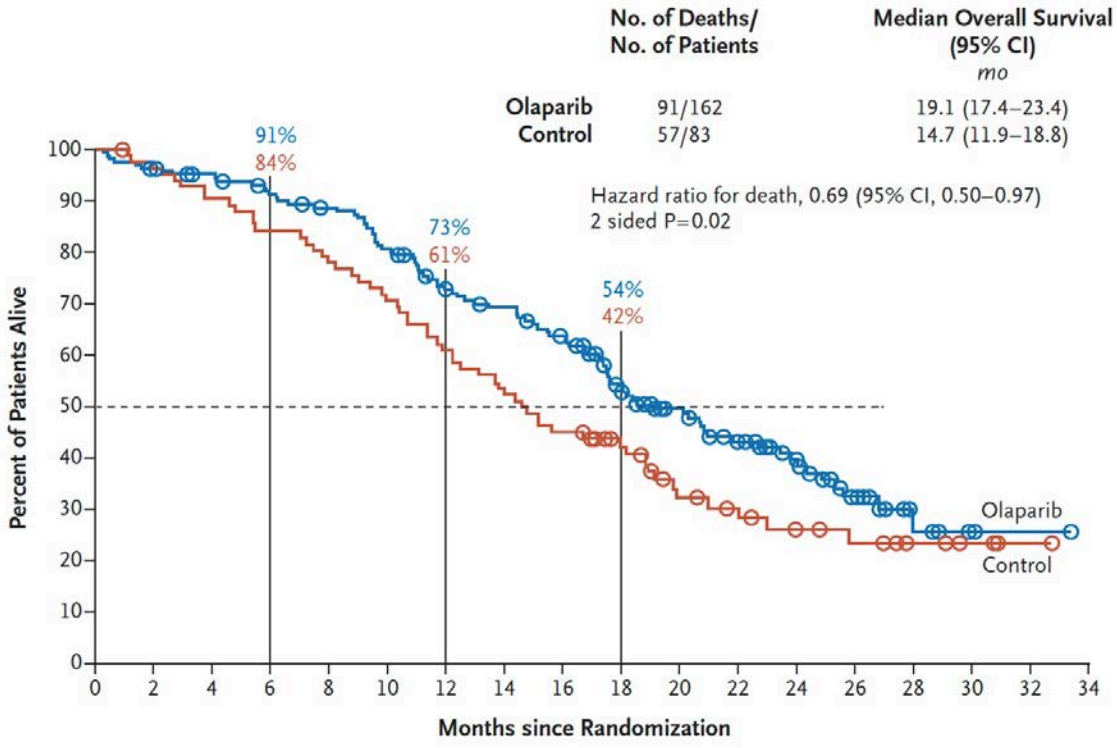
Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

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

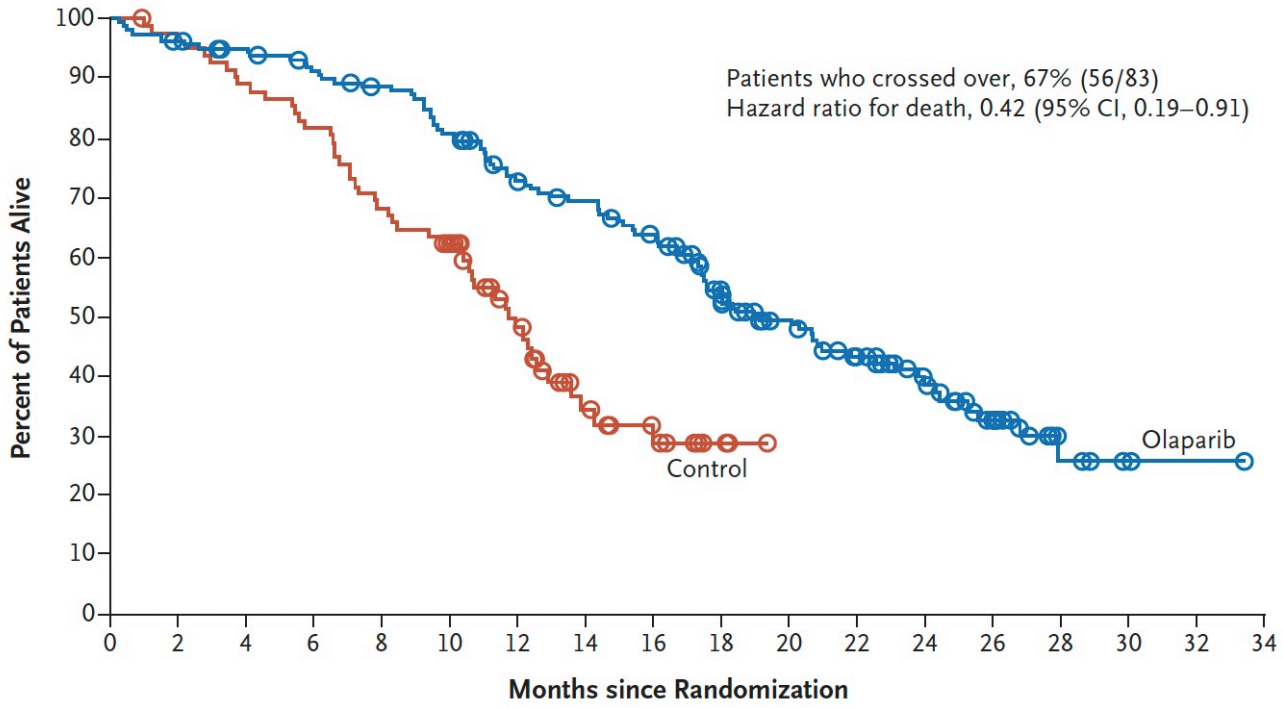
***N Engl J Med* 2020;[Online ahead of print].**

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

Overall survival



Cross-over adjusted overall survival



Hussain M et al; PROfound investigators. *N Engl J Med* 2020;[Online ahead of print].

rapid communications

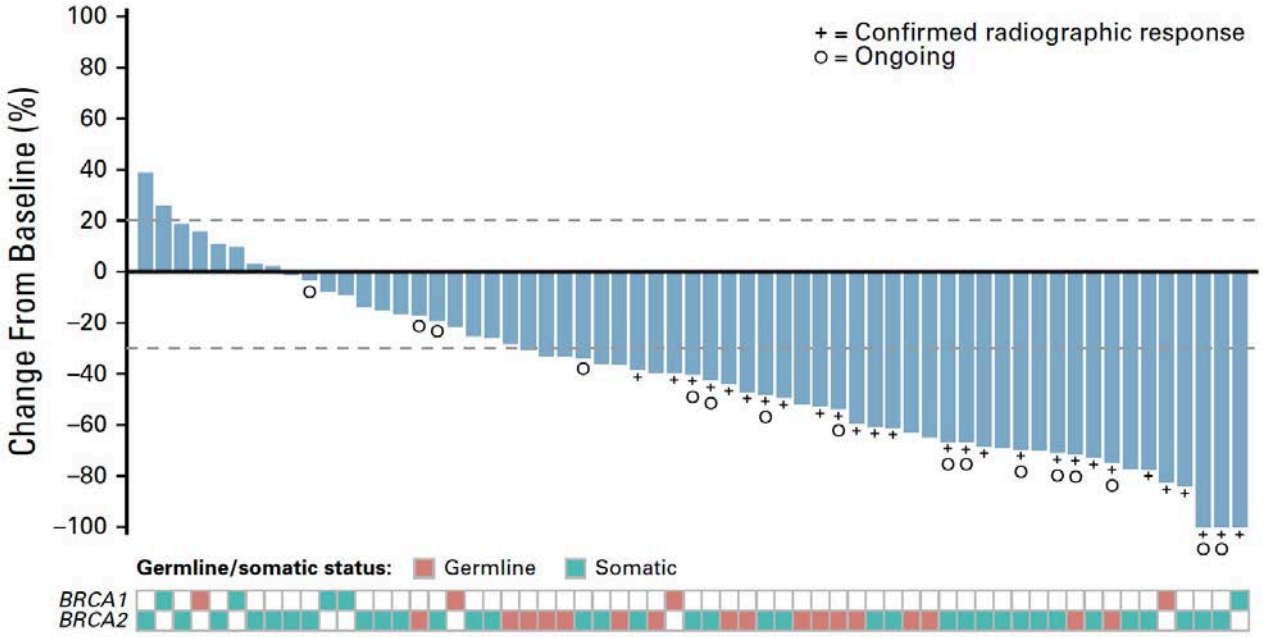
Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration

Wassim Abida, MD, PhD[1]; Akash Patnaik, MD, PhD, MMSc[2]; David Campbell, MBBS[3]; Jeremy Shapiro, MBBS[4]; Alan H. Bryce, MD[5]; Ray McDermott, MD, PhD, MBA[6]; Brieuc Sautois, MD, PhD[7]; Nicholas J. Vogelzang, MD[8]; Richard M. Bambury, MD[9]; Eric Voog, MD[10]; Jingsong Zhang, MD, PhD[11]; Josep M. Piulats, MD[12]; Charles J. Ryan, MD[13]; Axel S. Merseburger, PhD[14]; Gedske Daugaard, DMSc[15]; Axel Heidenreich, MD[16]; Karim Fizazi, MD, PhD[17]; Celestia S. Higano, MD[18]; Laurence E. Krieger, MBChB[19]; Cora N. Sternberg, MD[20]; Simon P. Watkins, PhD[21]; Darrin Despain, MStat[22]; Andrew D. Simmons, PhD[23]; Andrea Loehr, PhD[23]; Melanie Dowson, BA[24]; Tony Golsorkhi, MD[25]; and Simon Chowdhury, MD, PhD[26,27]; on behalf of the TRITON2 investigators

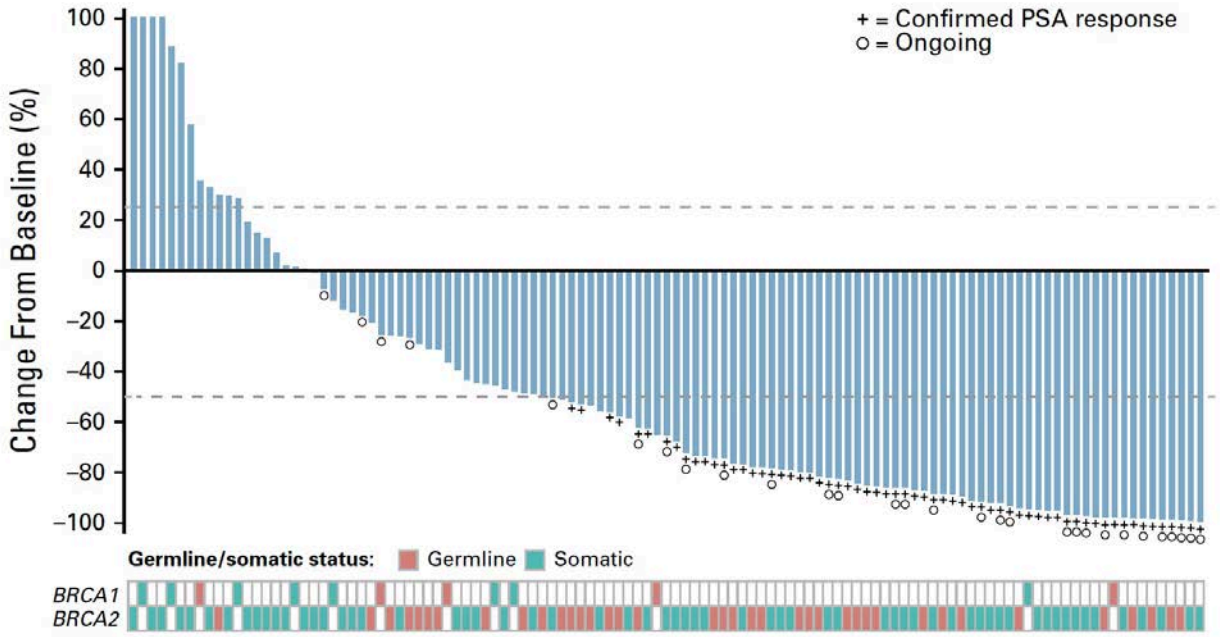
J Clin Oncol 2020;[Online ahead of print].

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

ORR per independent radiology review: 43.5%



Confirmed PSA response rate: 54.8%



Abida W et al. TRITON2 investigators. *J Clin Oncol* 2020;[Online ahead of print].

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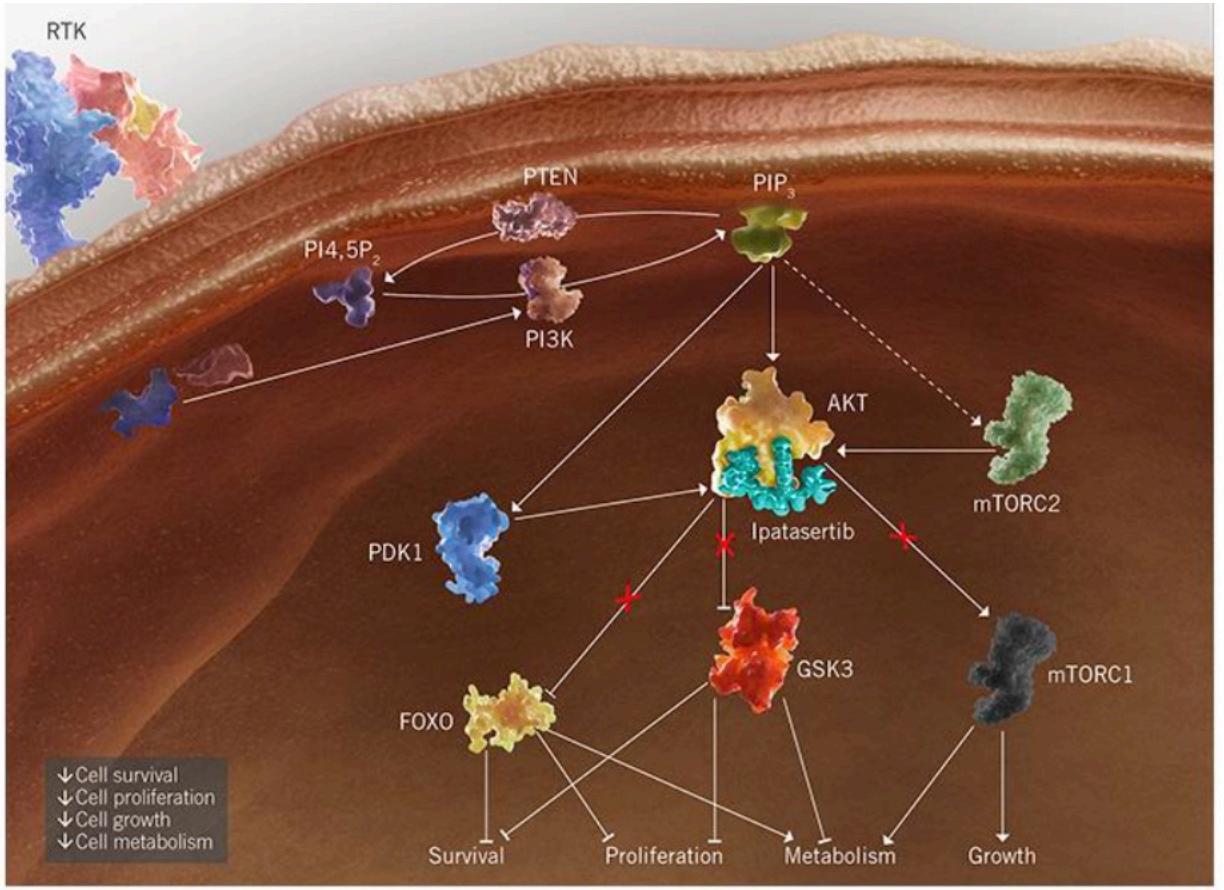
IPATential150: Phase III Study of Ipatasertib (Ipat) plus Abiraterone (Abi) vs Placebo (Pbo) plus Abi in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

De Bono JS et al.

ESMO 2020;Abstract LBA4.

Ipatasertib Mechanism of Action

- Ipatasertib is an oral investigational small molecule that binds to the ATP-binding pocket of all 3 isoforms of AKT[1,2]
- Ipatasertib inhibits AKT serine-threonine kinase activity and can improve the anti-tumour activity of AR blockade in prostate cancer models[1-3]



https://www.genentechoncology.com/pipeline-molecules/ipatasertib.html

1. Lin J, et al. *Clin Cancer Res.* 2013; 2. Nitulescu GM, et al. *Int J Oncol.* 2016; 3. Slomovitz BM, Coleman RL. *Clin Cancer Res.* 2012.

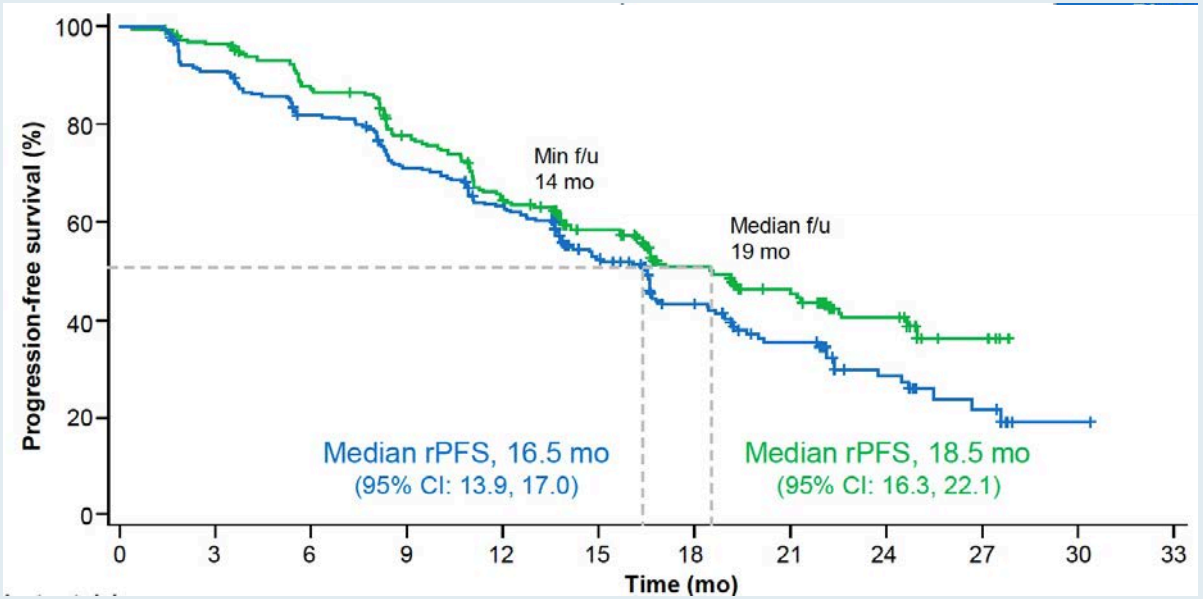
de Bono J. IPATential150. ESMO 2020. https://bit.ly/31s8gje

de Bono JS et al. ESMO 2020;Abstract LBA4.

IPATential150 Coprimary Endpoints

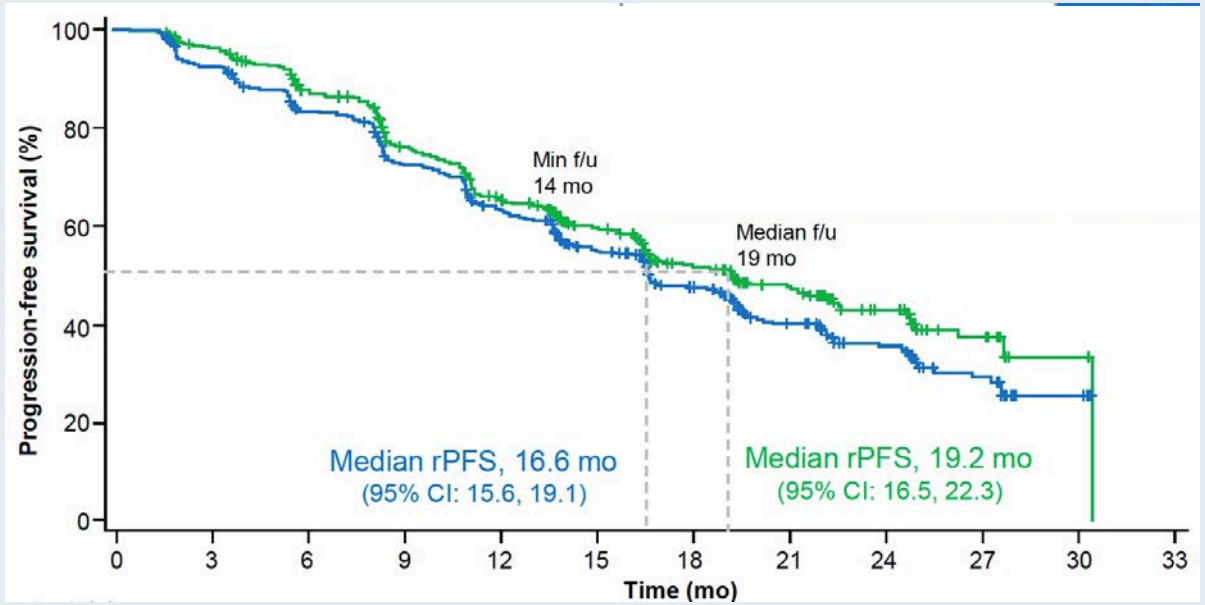
Inv-Assessed rPFS in Patients with PTEN Loss in ≥ 50% of Tumour Cells

	Pbo + abi (n = 261)	Ipat + abi (n = 260)
1-year event-free rate	63.3%	64.4%
Median PFS	16.5 mo	18.5
Hazard ratio (*p*-value)	0.77 (*P* = 0.0335)	



rPFS ITT Population

	Pbo + abi (n = 261)	Ipat + abi (n = 260)
1-year event-free rate	63.0%	65.3%
Median PFS	16.6 mo	19.2 mo
Hazard ratio (*p*-value)	0.84 (*P* = 0.0431)	



de Bono JS et al. ESMO 2020;Abstract LBA4.

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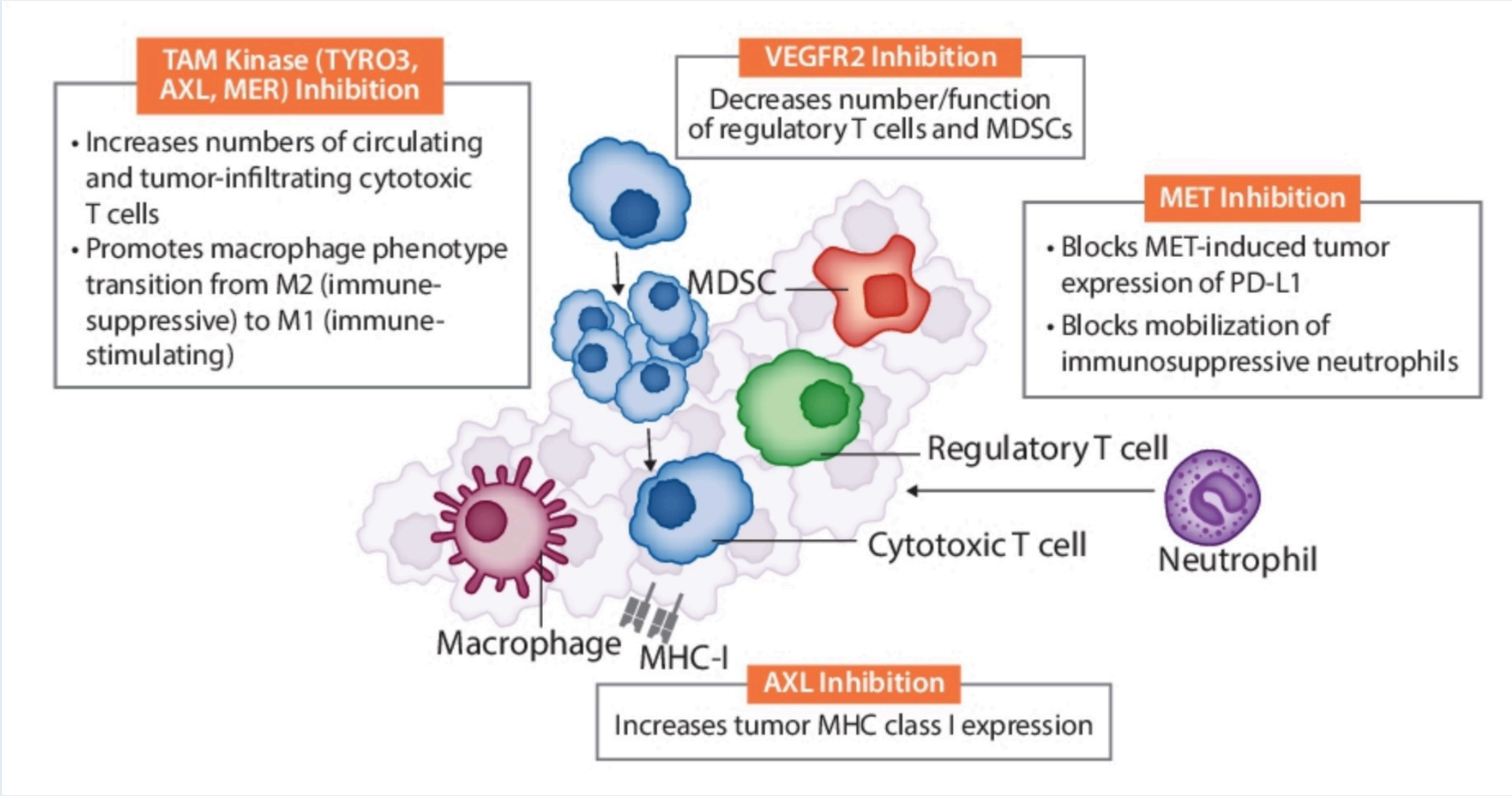
Cabozantinib in Combination with Atezolizumab in Patients with mCRPC: Results of Cohort 6 of the COSMIC-021 Study

Agarwal N et al.

ASCO 2020;Abstract 5564.

Cabozantinib Targets Pathways Associated with Tumor Immune Suppression



Agarwal N et al. ASCO 2020;Abstract 5564.

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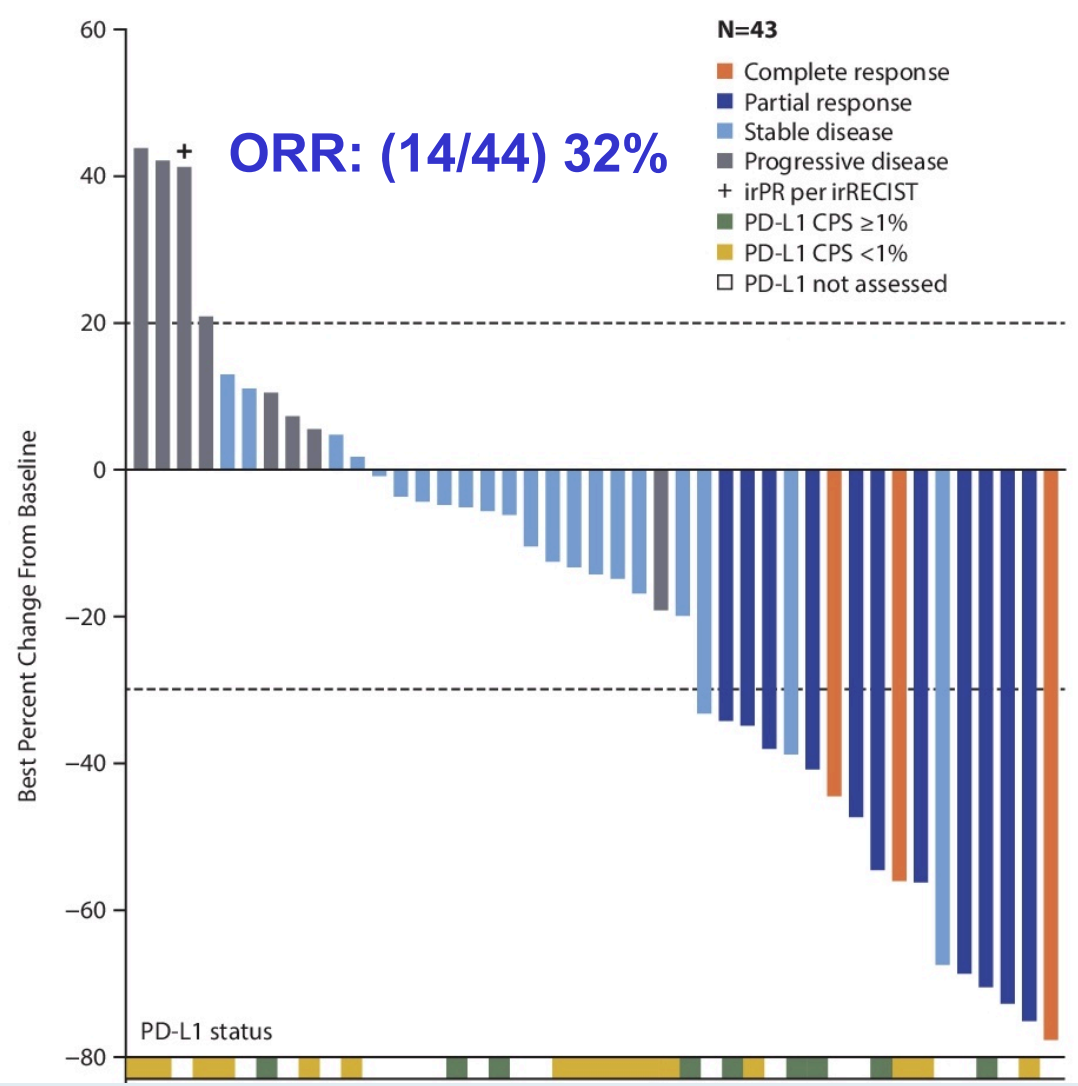
COSMIC-021 Primary Endpoint: Investigator-Assessed ORR with Cabozantinib/Atezolizumab in mCRPC



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

Agarwal N et al. ASCO 2020;Abstract 5564.

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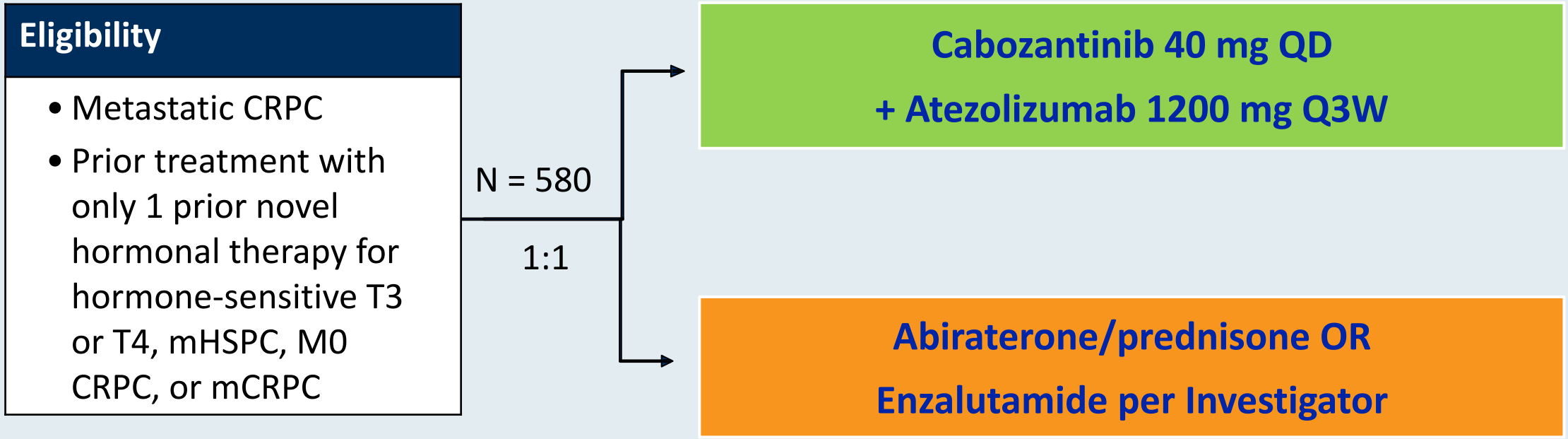
CONTACT-02 Phase III Study Schema



Coprimary endpoints: Duration of PFS and OS

Clinicaltrials.gov, Accessed October 2020 (NCT04446117)

Agenda

Module 1: Prostate Cancer

- Dr Zafar: A functional, independent 90-year-old man with prostate cancer
- Dr Malhotra: An 87-year-old man with metastatic castration-resistant prostate cancer – ATM mutation

Module 2: Renal Cell Carcinoma

- Dr Choksi: A 63-year-old man with metastatic renal cell carcinoma
- Dr Dandamudi: A 68-year-old man with renal cell carcinoma

Module 3: Urothelial Bladder Cancer

- Dr Hart: A 75-year-old man with urothelial bladder cancer
- Dr Lamar: A 68-year-old man with metastatic urothelial carcinoma

Case Presentation – Dr Choksi: A 63-year-old man with metastatic renal cell carcinoma

Dr Mamta Choksi

- PMH: Chronic liver disease and thrombocytopenia from ETOH abuse, smoker
  - Resides in an assisted living facility (ALF)
- 3/2020: Pathologic fracture after fall from bed
  - PET: Subcentimeter pulmonary nodules, hypermetabolic mass in left kidney, multiple lytic lesions
  - Hepatosplenomegaly with cirrhotic liver morphology
- 5/2020: CT-guided renal and bone biopsies: Metastatic renal cell carcinoma
  - Surgery not considered due to comorbidities, COVID-19
- Nivolumab/ipilimumab x 4 → Maintenance nivolumab (ongoing)
  - Decrease in kidney mass, improvement in bony metastases and pulmonary nodules
- Referred for palliative RT to humerus

Questions

- Should we consider nephrectomy or continue single-agent nivolumab?
- What is your preferred first-line treatment for mRCC – combination immunotherapy or immunotherapy with a targeted agent? What would influence your decision?

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Case Presentation – Dr Dandamudi: A 68-year-old man with renal cell carcinoma

Dr Uday Dandamudi

- Stage IA renal cell carcinoma → left nephrectomy, with vascular invasion (outside institution)
  - No adjuvant therapy
- 2/2018: Presented to ER unable to walk
  - Imaging: Large iliac sclerotic lesion 4 x 5 cm and soft tissue nodules over nephrectomy fossa
- 2/2019 - 12/2019: Pembrolizumab/Lenvatinib on clinical trial x 18 months → PD
  - Objective response, improvement in bone pain, well tolerated
- Cabozantinib 60 mg
  - Fatigue, weakness, calluses on upper/lower extremities → dose reduced to 40 mg
  - After 8 months, increased size of soft tissue nodules, new lymph nodes

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

a. Nivolumab/ipilimumab
b. Avelumab/axitinib
c. Pembrolizumab/axitinib
d. Nivolumab/cabozantinib
e. TKI monotherapy
f. Anti-PD-1/PD-L1 monotherapy
g. Other

Lancet Oncol 2019;20:1370-85.

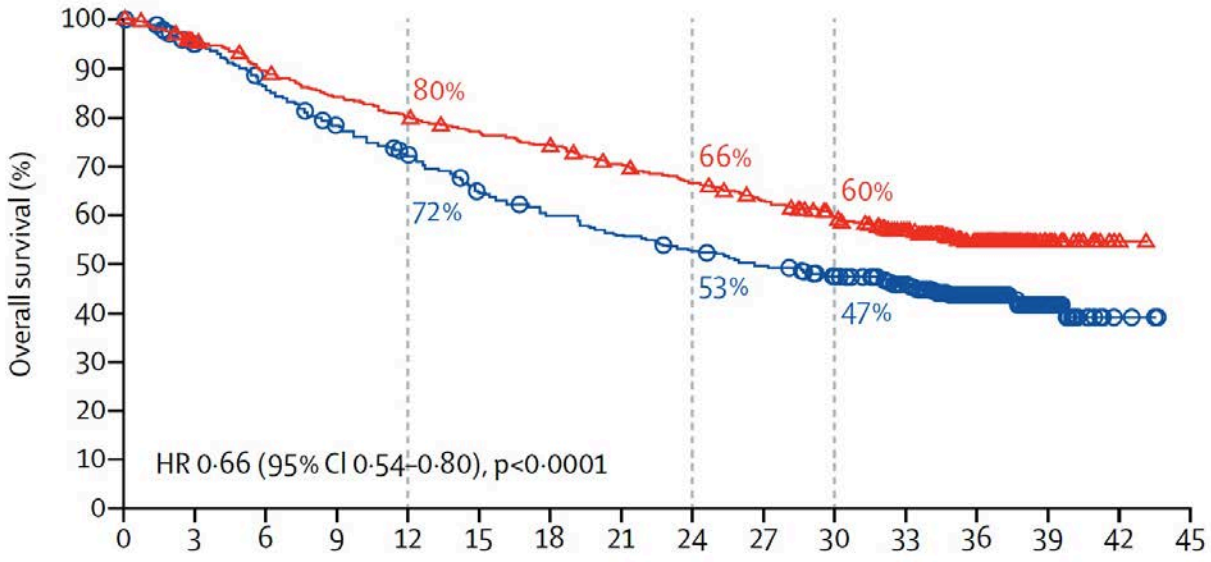
Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial

*Robert J Motzer, Brian I Rini, David F McDermott, Osvaldo Arén Frontera, Hans J Hammers, Michael A Carducci, Pamela Salman, Bernard Escudier, Benoit Beuselinck, Asim Amin, Camillo Porta, Saby George, Victoria Neiman, Sergio Bracarda, Scott S Tykodi, Philippe Barthélémy, Raya Leibowitz-Amit, Elizabeth R Plimack, Sjoukje F Oosting, Bruce Redman, Bohuslav Melichar, Thomas Powles, Paul Nathan, Stéphane Oudard, David Pook, Toni K Choueiri, Frede Donskov, Marc-Oliver Grimm, Howard Gurney, Daniel Y C Heng, Christian K Kollmannsberger, Michael R Harrison, Yoshihiko Tomita, Ignacio Duran, Viktor Grünwald, M Brent McHenry, Sabeen Mekan, Nizar M Tannir, on behalf of the CheckMate 214 investigators**

CheckMate 214: Nivolumab/Ipilimumab in Previously Untreated Advanced RCC

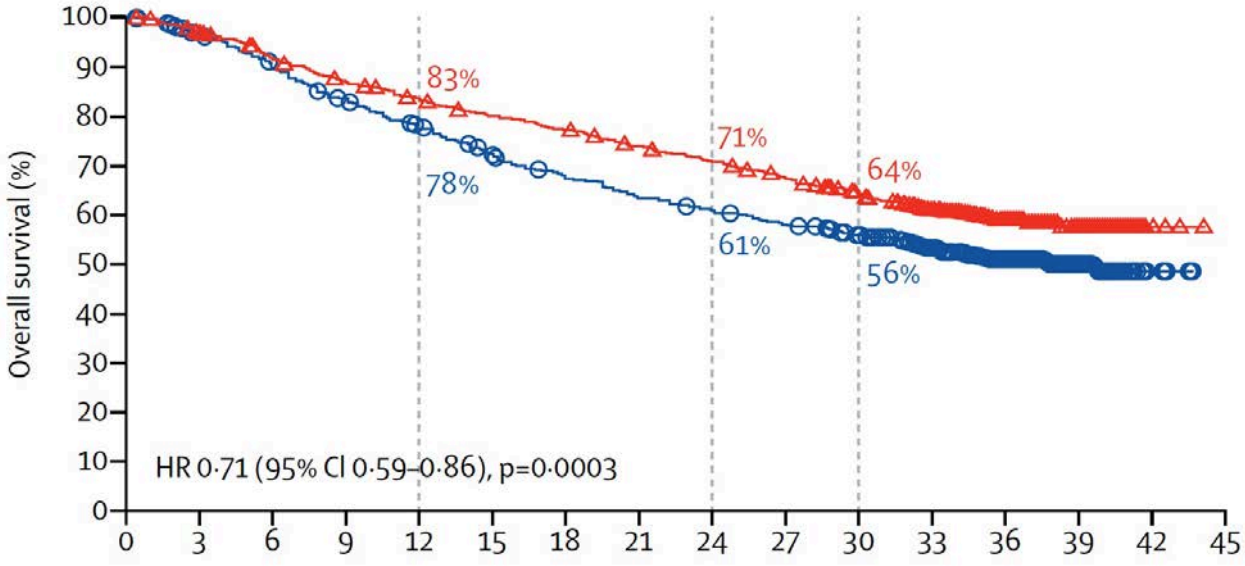
OS: Intermediate- or Poor-Risk

	Nivo/ipi (n = 425)	Sunitinib (n = 422)
Median OS	NR	26.6 mo
Hazard ratio (*p*-value)	0.66 (*P* < 0.0001)	



OS: Intenton-to-Treat (ITT)

	Nivo/ipi (n = 550)	Sunitinib (n = 546)
Median OS	NR	37.9 mo
Hazard ratio (*p*-value)	0.71 (*P* = 0.027)	



Motzer RJ et al. *Lancet Oncol* 2019;20:1370-85.

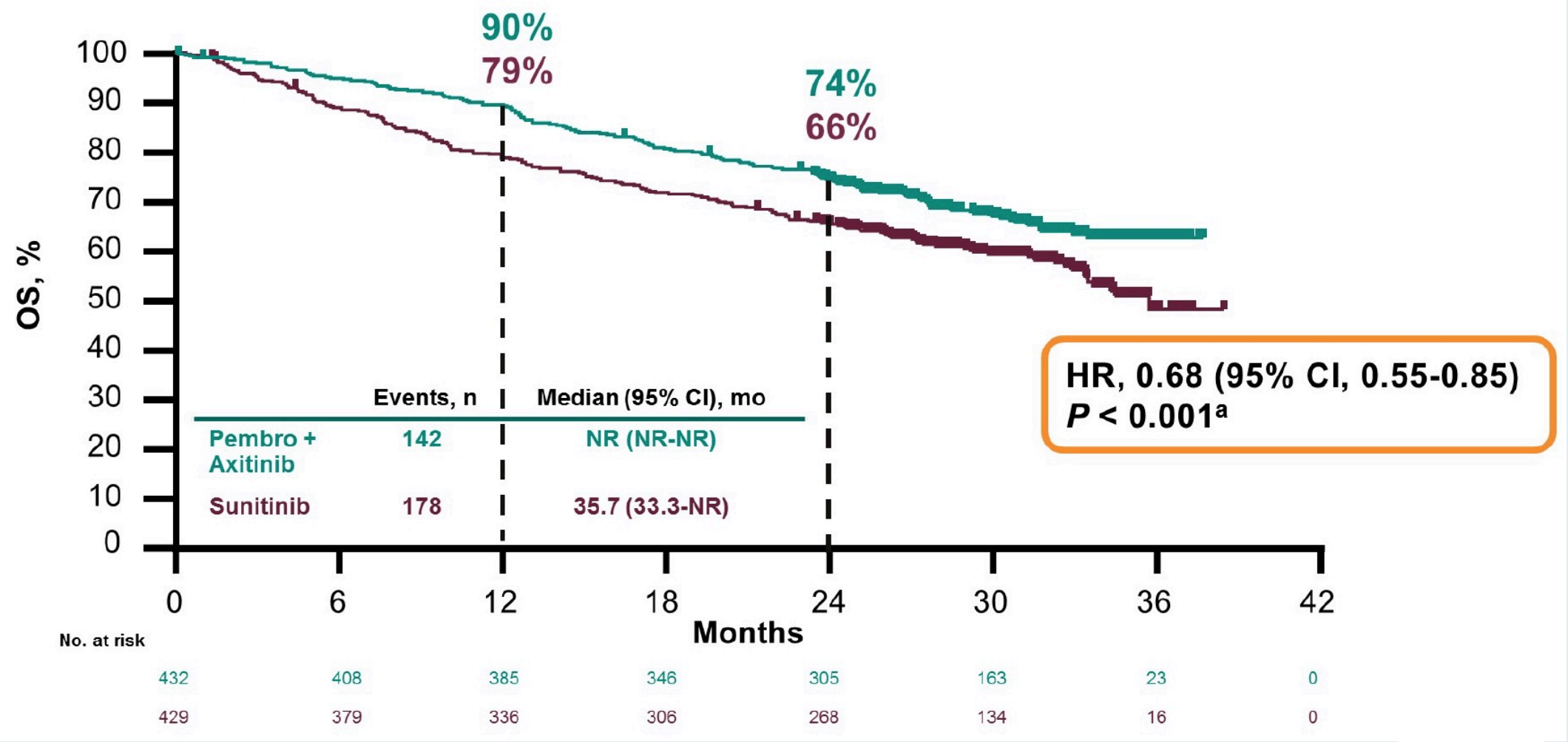
RTP RESEARCH TO PRACTICE

Pembrolizumab plus Axitinib versus Sunitinib as First-Line Therapy for Advanced Renal Cell Carcinoma (RCC): Updated Analysis of KEYNOTE-426

Plimack ER et al.

ASCO 2020;Abstract 5001.

KEYNOTE-426: Pembrolizumab/Axitinib in Previously Untreated Advanced RCC



Plimack ER et al. ASCO 2020;Abstract 5001.

RTP RESEARCH TO PRACTICE

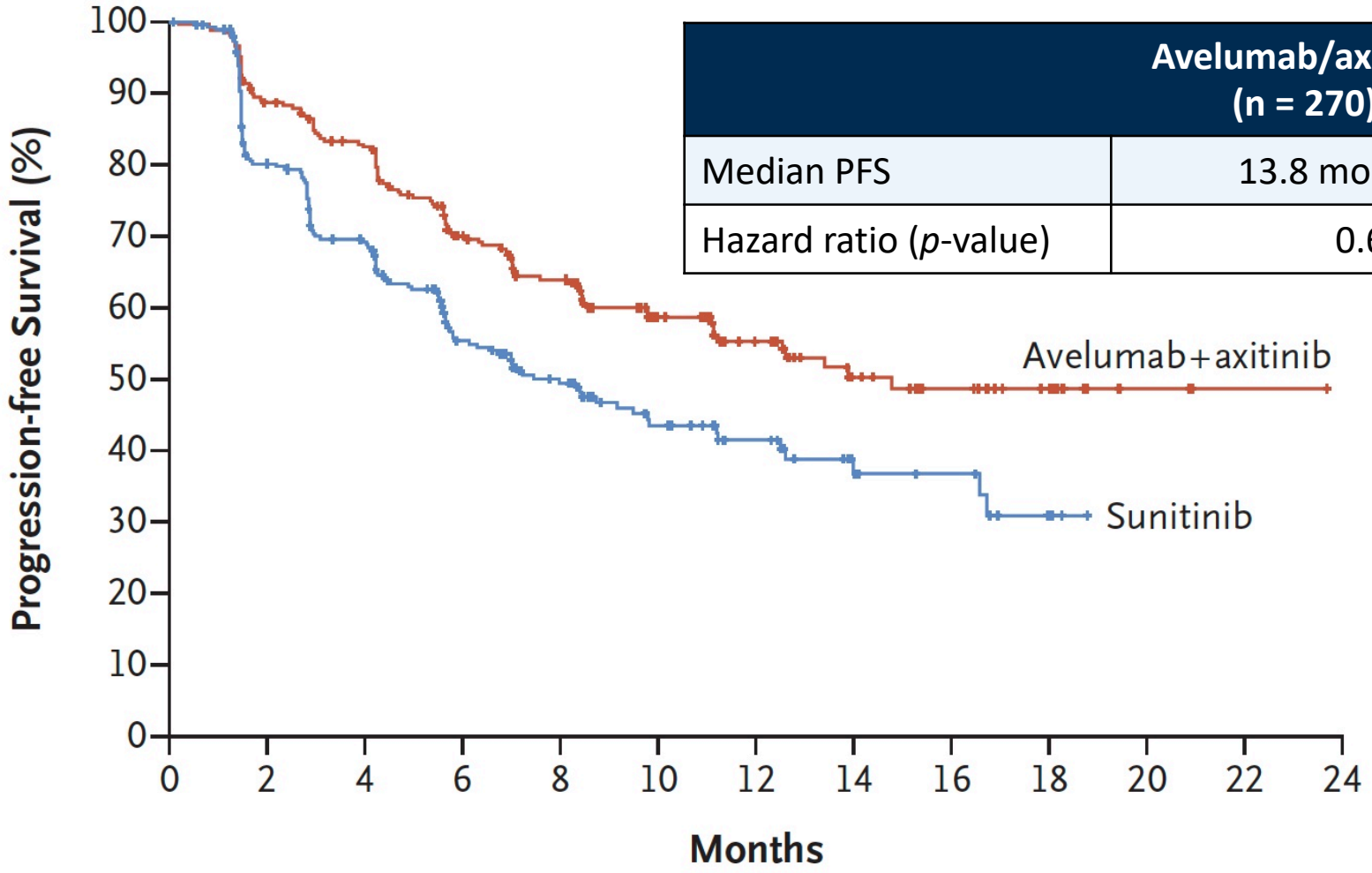
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 21, 2019 VOL. 380 NO. 12

Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

Robert J. Motzer, M.D., Konstantin Penkov, M.D., Ph.D., John Haanen, Ph.D., Brian Rini, M.D., Laurence Albiges, M.D., Ph.D., Matthew T. Campbell, M.D., Balaji Venugopal, M.D., Christian Kollmannsberger, M.D., Sylvie Negrier, M.D., Ph.D., Motohide Uemura, M.D., Ph.D., Jae L. Lee, M.D., Ph.D., Aleksandr Vasiliev, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Howard Gurney, M.D., Manuela Schmidinger, M.D., James Larkin, M.D., Ph.D., Michael B. Atkins, M.D., Jens Bedke, M.D., Boris Alekseev, M.D., Jing Wang, Ph.D., Mariangela Mariani, Ph.D., Paul B. Robbins, Ph.D., Aleksander Chudnovsky, M.D., Camilla Fowst, M.D., Subramanian Hariharan, M.D., Bo Huang, Ph.D., Alessandra di Pietro, M.D., Ph.D., and Toni K. Choueiri, M.D.

JAVELIN Renal 101: PFS with Avelumab/Axitinib in Previously Untreated, Advanced RCC with PD-L1-Positive Tumors



	Avelumab/axitinib (n = 270)	Sunitinib (n = 290)
Median PFS	13.8 mo	7.2 mo
Hazard ratio (*p*-value)	0.61 (*P* < 0.01)	

Motzer RJ et al. *N Engl J Med* 2019;380(12):1103-15.

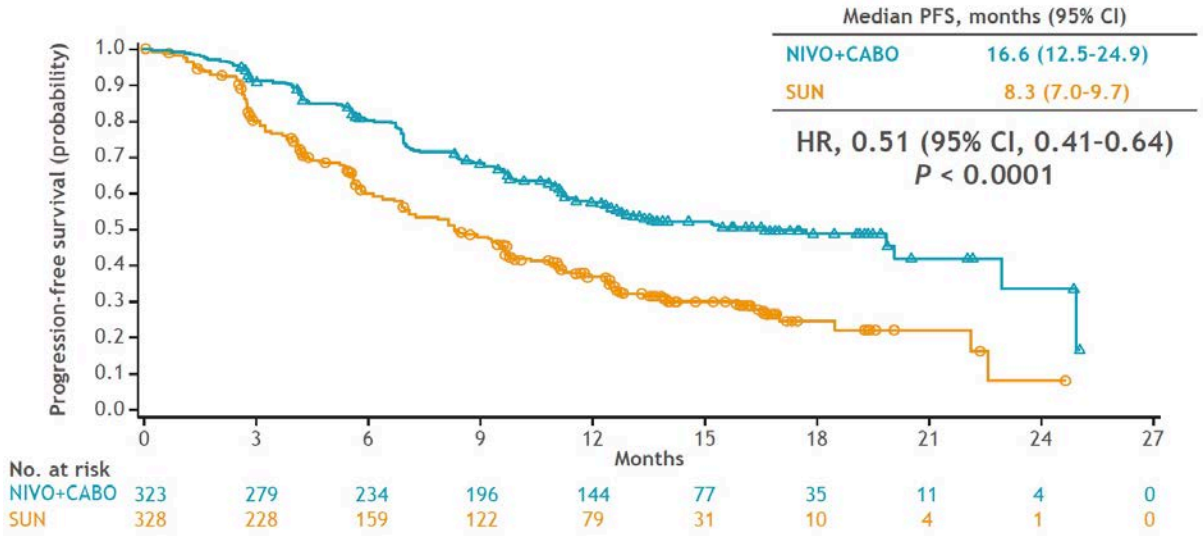
Nivolumab plus Cabozantinib versus Sunitinib in First-Line Treatment for Advanced Renal Cell Carcinoma: First Results from the Randomized Phase 3 CheckMate 9ER Trial

Choueiri TK et al.

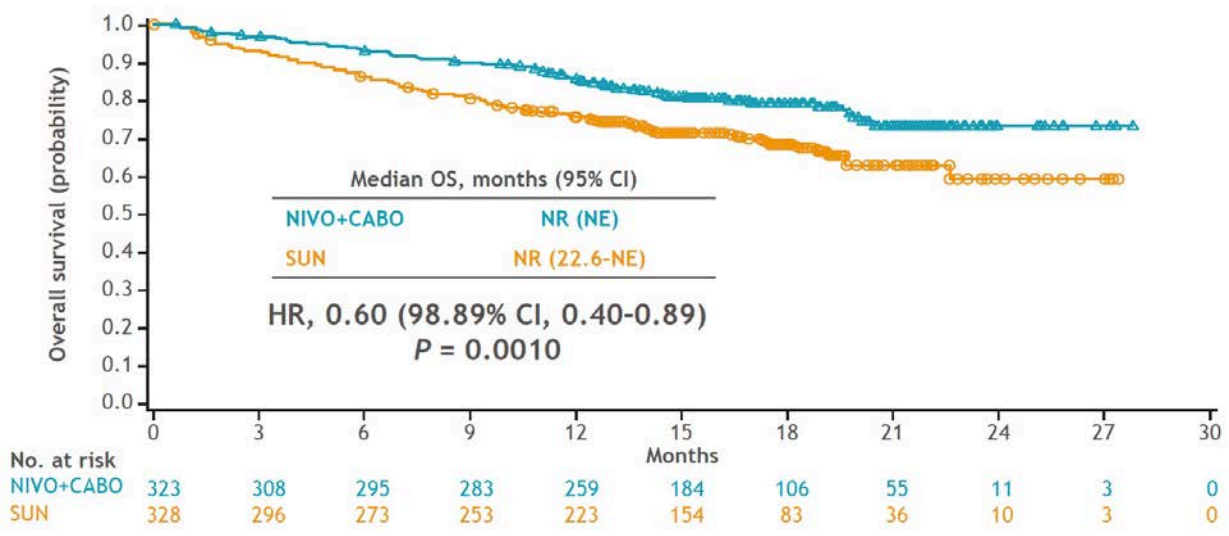
ESMO 2020;Abstract 696O.

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

Progression-free survival per BICR



Overall survival



Choueiri TK et al. ESMO 2020;Abstract 696O.

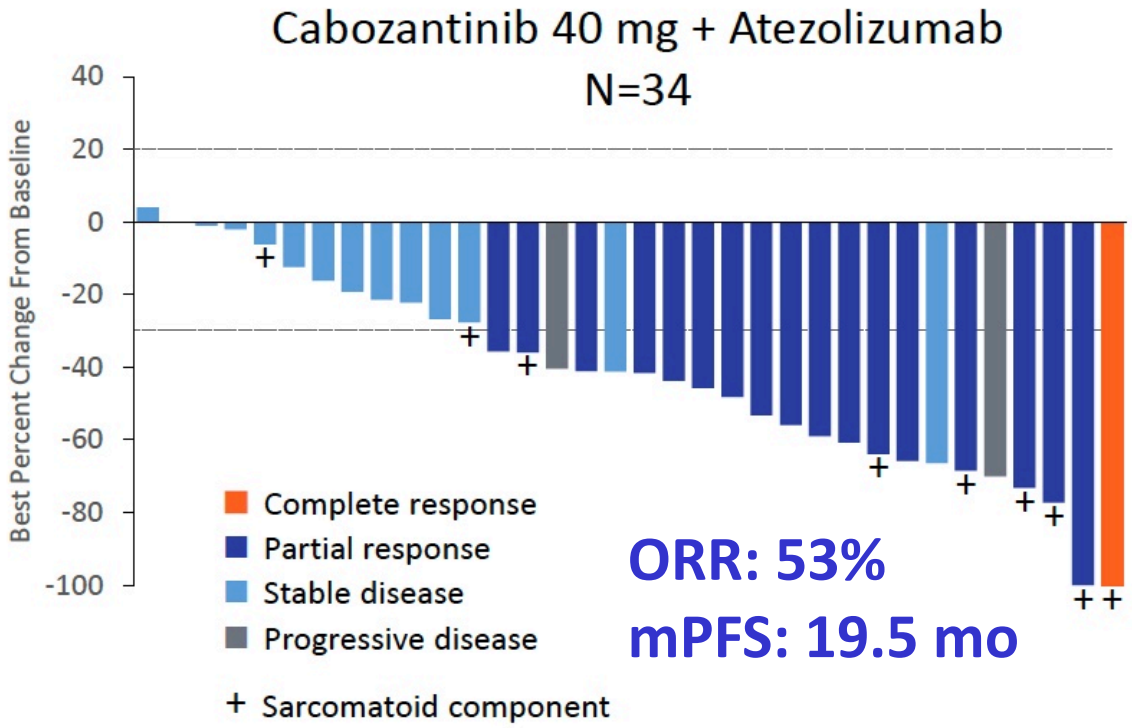
RTP RESEARCH TO PRACTICE

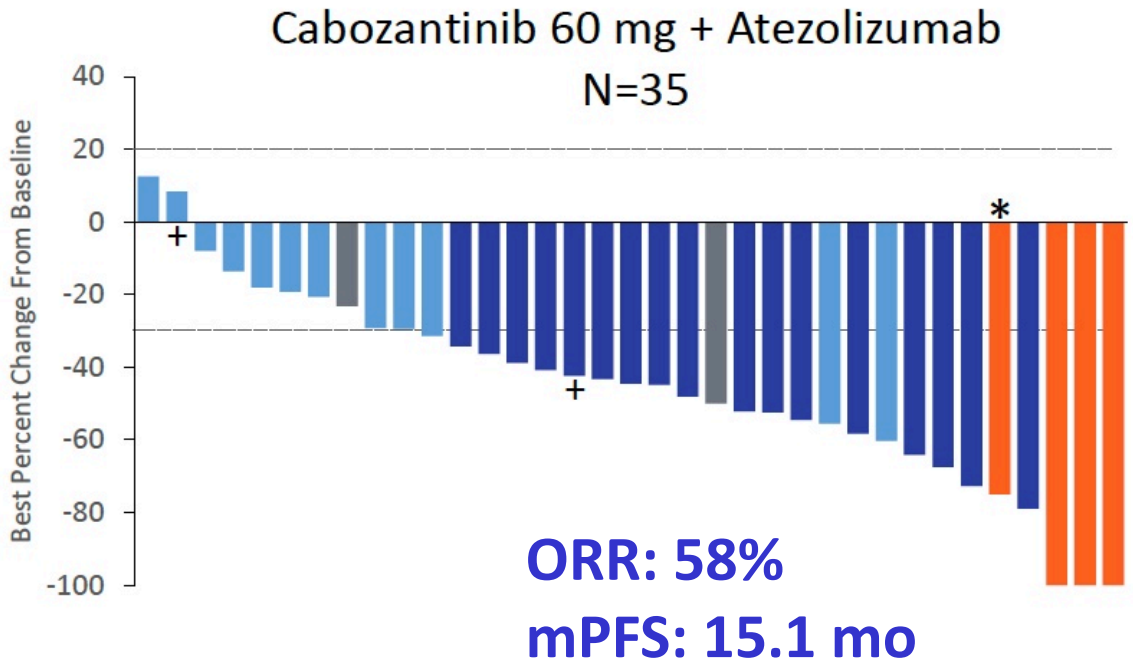
Cabozantinib (C) in Combination with Atezolizumab (A) as First-Line Therapy for Advanced Clear Cell Renal Cell Carcinoma (ccRCC): Results from the COSMIC-021 Study

Pal S et al.

ESMO 2020;Abstract 702O.

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





Pal S et al. ESMO 2020;Abstract 702O.

RTP RESEARCH TO PRACTICE

rapid communications

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

Anita Gul, MD[1]; Tyler F. Stewart, MD[2,3]; Charlene M. Mantia, MD[4]; Neil J. Shah, MD[5]; Emily Stern Gatof, MD[4]; Ying Long, PharmD[2]; Kimberly D. Allman, MSN, CNP[1]; Moshe C. Ornstein, MD, MA[1]; Hans J. Hammers, MD, PhD[6]; David F. McDermott, MD[4]; Michael B. Atkins, MD[5]; Michael Hurwitz, MD, PhD[2]; and Brian I. Rini, MD[1]

J Clin Oncol 2020;38:3088-94.

Salvage Ipilimumab/Nivolumab in mRCC After Prior ICI Therapy

Variable	No. (%)
No. of prior lines of systemic therapy	
1	9 (20)
2	12 (27)
3	8 (18)
4	6 (13)
> 4	10 (22)
Prior VEGF receptor inhibitor[a]	27 (60)
Prior immunotherapy	
Anti–PD-1[b]	34 (76)
Anti–PD-L1[b]	11 (24)
IL-2[c]	14 (31)
Best response to prior ICI	
PR	24 (53)
SD	12 (27)
PD	9 (20)

BOR to Prior ICI	No. (%)	BOR to Salvage Ipilimumab and Nivolumab	No. (%)
PR	24 (53)	PR	4 (17)
		SD	2 (8)
		PD	17 (71)
		NE	1 (4)
SD	12 (27)	PR	3 (25)
		SD	5 (42)
		PD	4 (33)
PD	9 (20)	PR	2 (22)
		PD	7 (78)

Abbreviations: BOR, best objective response; ICI, immune checkpoint inhibitor; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Gul A et al. *J Clin Oncol* 2020;38:3088-94.

Agenda

Module 1: Prostate Cancer

- Dr Zafar: A functional, independent 90-year-old man with prostate cancer
- Dr Malhotra: An 87-year-old man with metastatic castration-resistant prostate cancer – ATM mutation

Module 2: Renal Cell Carcinoma

- Dr Choksi: A 63-year-old man with metastatic renal cell carcinoma
- Dr Dandamudi: A 68-year-old man with renal cell carcinoma

Module 3: Urothelial Bladder Cancer

- Dr Hart: A 75-year-old man with urothelial bladder cancer
- Dr Lamar: A 68-year-old man with metastatic urothelial carcinoma

Case Presentation – Dr Hart: A 75-year-old man with urothelial bladder cancer

Dr Lowell Hart

- 2018: Presented with gross hematuria
- Diagnosed with high-grade papillary urothelial carcinoma invading the detrusor muscle
  - PD-L1: 10%
  - Patient declined cystectomy contrary to local and academic urology opinions
- Carboplatin/gemcitabine x 4, with residual tumor
- 6/2019: Completed carboplatin + XRT, with suspicious areas on cystoscopy
  - Patient again declined cystectomy and immunotherapy
- 6/2020 F/U cystoscopy: Low-grade papillary cancer
- 7/2020: Hydronephrosis and a large recurrence
- Nivolumab
  - Discontinued after 1 cycle due to development of insulin-dependent diabetes
  - Severe diarrhea requiring steroids
- PCN stent placed for hydronephrosis/acute renal failure
- Patient desires active treatment but few options available

Case Presentation – Dr Lamar: A 68-year-old man with metastatic urothelial carcinoma

Dr Zanetta Lamar

- 2014: Muscle-invasive high-grade urothelial carcinoma treated with TURBT → gemcitabine/cisplatin → PD
- Clinical trial with nivolumab/ipilimumab, with CR x 4 years → PD
- Enfortumab vedotin x 7 months (ongoing)
  - Mild neuropathy, dose reduction
- Pelvic adenopathy → referred for radiation therapy to site; disease stable elsewhere
- NGS: No actionable mutations

Question

- If he had an FGFR mutation and had disease progression on immunotherapy, would you prefer an FGFR inhibitor over a drug like enfortumab vedotin?

What is your usual first-line treatment strategy for metastatic urothelial bladder cancer (UBC)?

a. If PD-L1-positive, anti-PD-1/PD-L1 monotherapy; all others, chemotherapy
b. Chemotherapy
c. Chemotherapy + anti-PD-1/PD-L1 antibody
d. Chemotherapy followed by maintenance avelumab
e. Other

What would you generally recommend as second-line therapy for a patient with FGFR-mutated UBC metastatic to the liver whose disease progresses on first-line cisplatin/gemcitabine?

a. Pembrolizumab
b. Atezolizumab
c. Avelumab
d. Durvalumab
e. Nivolumab
f. Enfortumab vedotin
g. Erdafitinib
h. Other

RTP RESEARCH TO PRACTICE

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

Press Release – January 8, 2020

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

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

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-bcg-unresponsive-high-risk-non-muscle-invasive-bladder-cancer

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

Press Release – September 24, 2020

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

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

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

https://news.bms.com/news/corporate-financial/2020/Opdivo-nivolumab-Significantly-Improves-Disease-Free-Survival-vs.-Placebo-as-Adjuvant-Therapy-for-Patients-with-High-Risk-Muscle-Invasive-Urothelial-Carcinoma-in-Phase-3-CheckMate--274-Trial/default.aspx

FDA Approves Avelumab for Urothelial Carcinoma Maintenance Treatment

Press Release – June 30, 2020

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

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

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-avelumab-urothelial-carcinoma-maintenance-treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

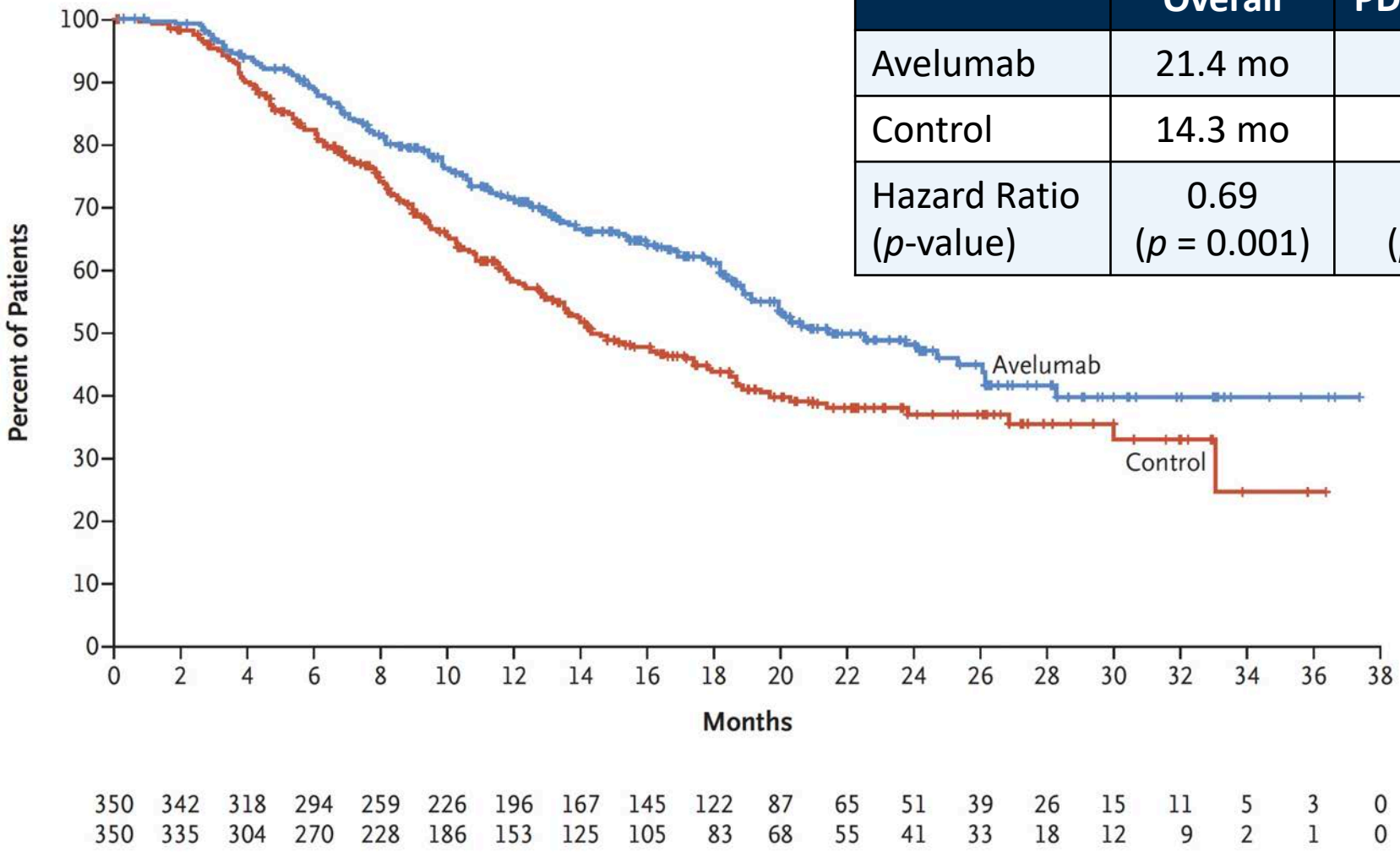
Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma

T. Powles, S.H. Park, E. Voog, C. Caserta, B.P. Valderrama, H. Gurney, H. Kalofonos, S. Radulović, W. Demey, A. Ullén, Y. Loriot, S.S. Sridhar, N. Tsuchiya, E. Kopyltsov, C.N. Sternberg, J. Bellmunt, J.B. Aragon-Ching, D.P. Petrylak, R. Laliberte, J. Wang, B. Huang, C. Davis, C. Fowst, N. Costa, J.A. Blake-Haskins, A. di Pietro, and P. Grivas

***N Engl J Med* 2020;383:1218-30.**

JAVELIN Bladder 100 Primary Endpoint: Overall Survival

	Overall	PD-L1-positive
Avelumab	21.4 mo	NE
Control	14.3 mo	17.1 mo
Hazard Ratio (*p*-value)	0.69 (*p* = 0.001)	0.56 (*p* < 0.001)



Powles T et al. *N Engl J Med* 2020;383:1218-30.

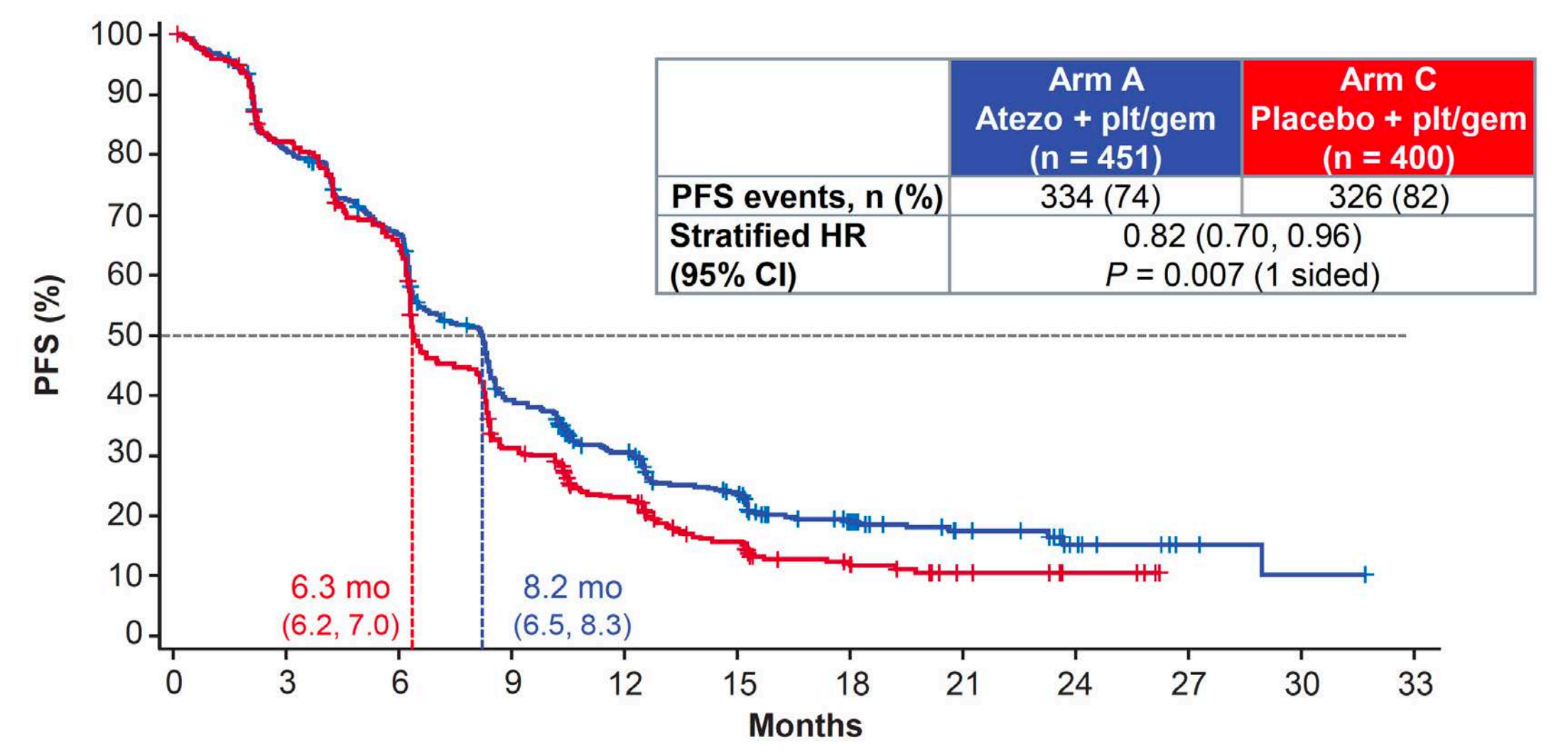
RTP RESEARCH TO PRACTICE

Patient-Reported Outcomes (PROs) from IMvigor130: A Global, Randomised, Partially Blinded Phase III Study of Atezolizumab (Atezo) + Platinum-Based Chemotherapy (PBC) vs Placebo (PBO) + PBC in Previously Untreated Locally Advanced or Metastatic Urothelial Carcinoma (mUC)

Bamias A et al.

ESMO 2020;Abstract 698O.

IMvigor130 Coprimary Endpoint: PFS (ITT)



	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (1 sided)	

Bamias A et al. ESMO 2020;Abstract 698O. Galsky MD et al. *Lancet* 2020;395:1547-57.

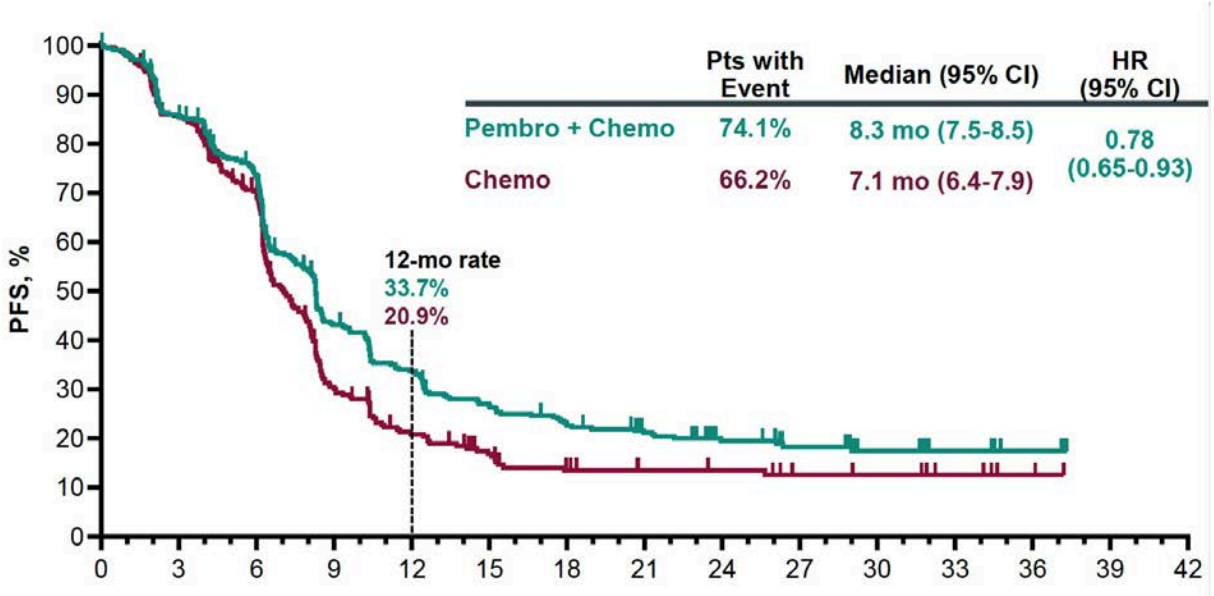
Pembrolizumab Alone or Combined with Chemotherapy vs Chemotherapy Alone as First-Line Therapy for Advanced Urothelial Carcinoma: KEYNOTE-361

Alva A et al.

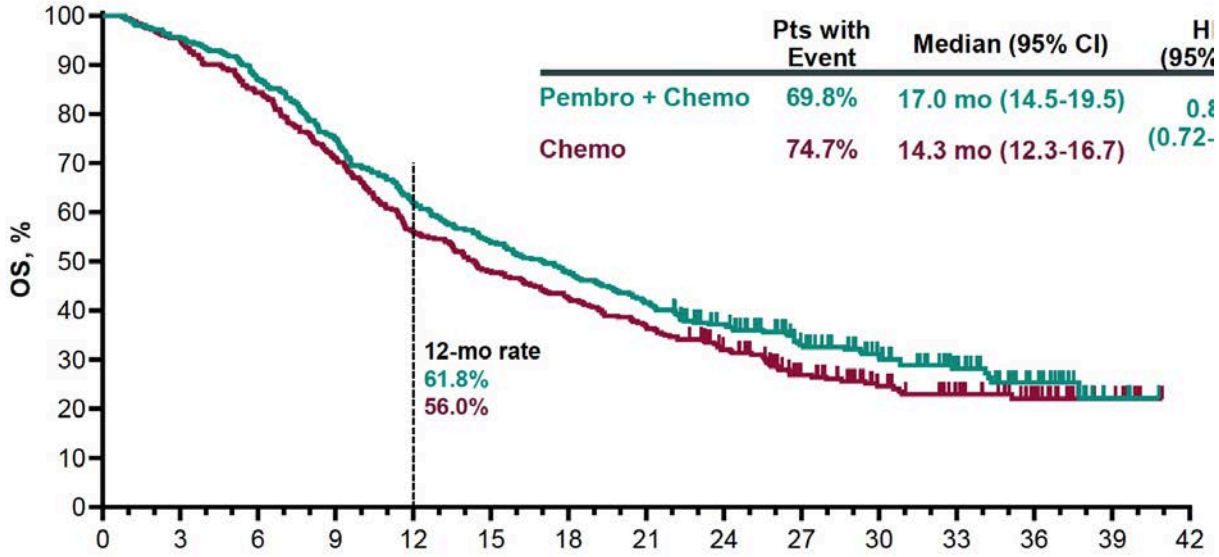
ESMO 2020;Abstract LBA23.

KEYNOTE-361 Dual Primary Endpoints: PFS by BICR and OS (ITT)

	Pembro + chemo (n = 351)	Chemo (n = 352)
Median PFS	8.3 mo	7.1 mo
Hazard ratio (*p*-value)	0.78 (0.0033)	



	Pembro + chemo (n = 351)	Chemo (n = 352)
Median OS	17.0 mo	14.3 mo
Hazard ratio (*p*-value)	0.86 (0.0407)	



Alva A et al. ESMO 2020;Abstract LBA23.

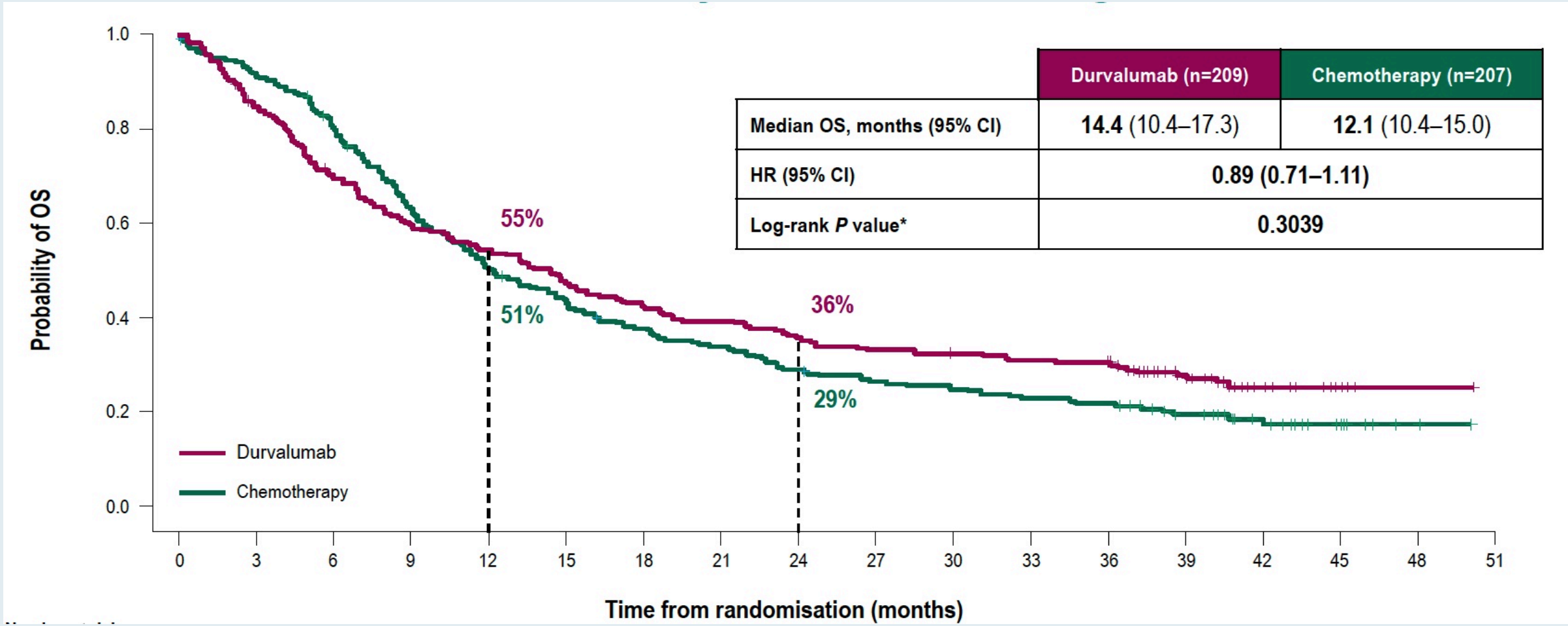
RTP RESEARCH TO PRACTICE

A Phase 3, Randomised, Open-Label Study of First-Line Durvalumab with or without Tremelimumab versus Standard of Care Chemotherapy in Patients with Unresectable, Locally Advanced or Metastatic Urothelial Carcinoma (DANUBE)

Powles T et al.

ESMO 2020;Abstract 697O.

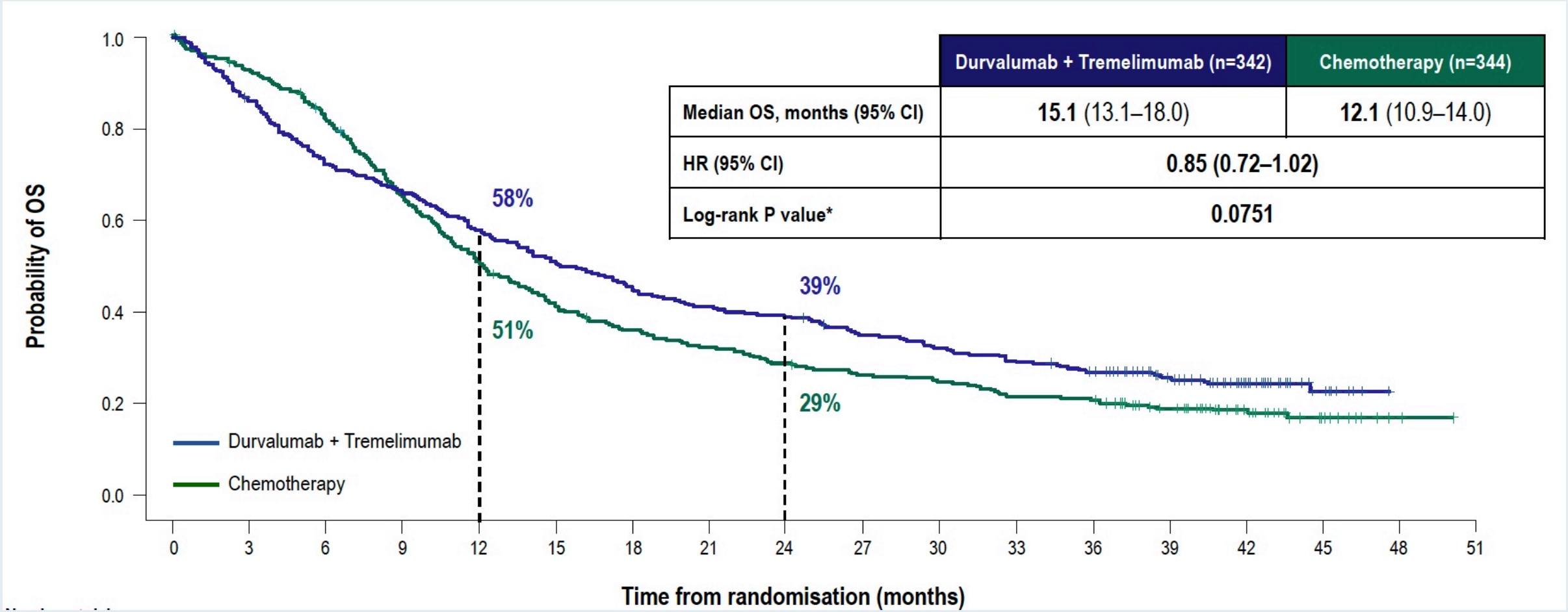
DANUBE Coprimary Endpoint: OS with Durvalumab vs Chemotherapy in the PD-L1-High Population



	Durvalumab (n=209)	Chemotherapy (n=207)
Median OS, months (95% CI)	**14.4** (10.4–17.3)	**12.1** (10.4–15.0)
HR (95% CI)	**0.89 (0.71–1.11)**	
Log-rank *P* value*	**0.3039**	

Powles T et al. ESMO 2020;Abstract 697O.

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



	Durvalumab + Tremelimumab (n=342)	Chemotherapy (n=344)
Median OS, months (95% CI)	**15.1** (13.1–18.0)	**12.1** (10.9–14.0)
HR (95% CI)	**0.85 (0.72–1.02)**	
Log-rank P value*	**0.0751**	

Powles T et al. ESMO 2020;Abstract 697O.

RTP RESEARCH TO PRACTICE

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

Press Release – February 19, 2020

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

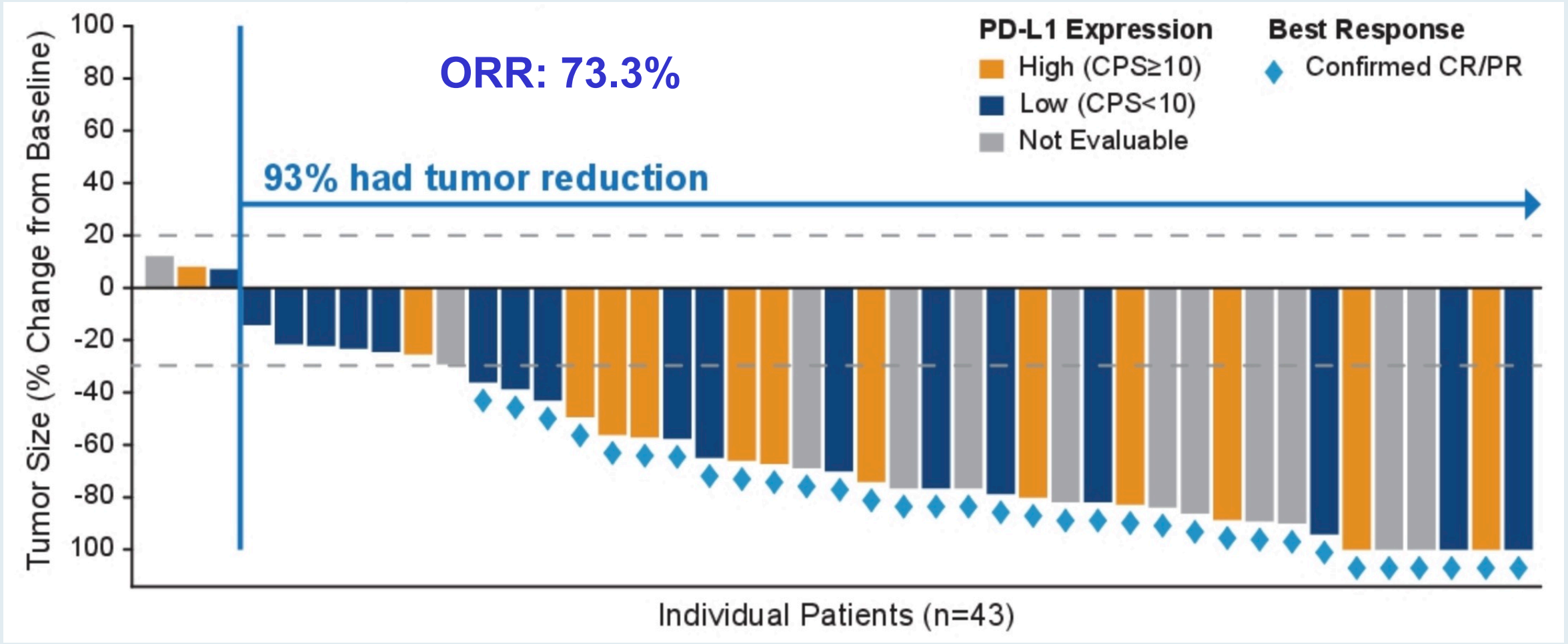
https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-designation-enfortumab-vedotin

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

Rosenberg JE et al.

ASCO 2020;Abstract 5044.

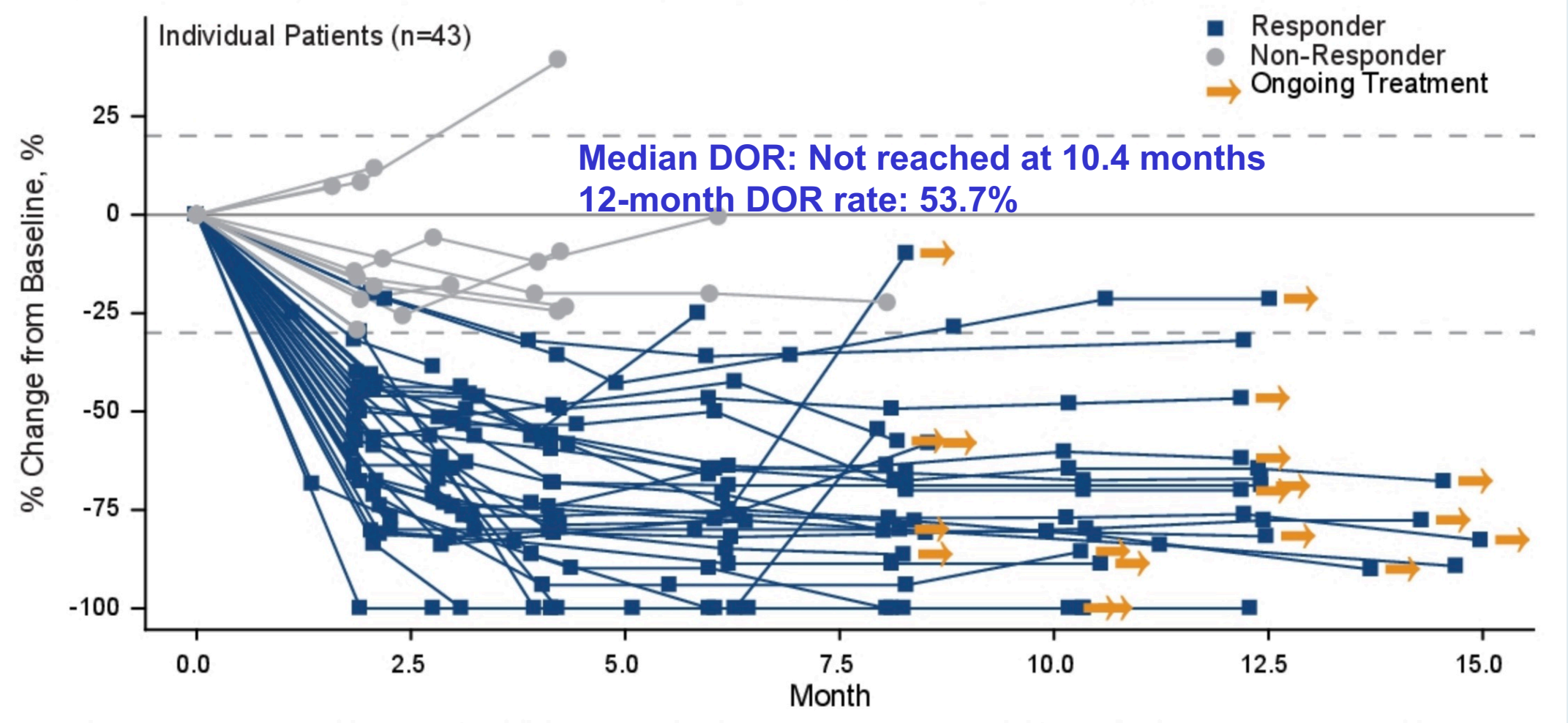
EV-103: Response to Enfortumab Vedotin with Pembrolizumab in the First-Line Setting



Rosenberg JE et al. ASCO 2020;Abstract 5044.

RTP RESEARCH TO PRACTICE

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



Rosenberg JE et al. ASCO 2020;Abstract 5044.

FDA Grants Accelerated Approval to Enfortumab Vedotin for Metastatic Urothelial Carcinoma

Press Release – December 18, 2019

"On December 18, 2019, the Food and Drug Administration granted accelerated approval to enfortumab vedotin-ejfv for adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. Enfortumab vedotin-ejfv is the first Nectin-4-directed antibody-drug conjugate to receive FDA approval.

Efficacy was investigated in EV-201 (NCT03219333), a single-arm, multicenter trial enrolling 125 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor and platinum-based chemotherapy. ORR was 44% with complete and partial response rates of 12% and 32%, respectively. The estimated median response duration was 7.6 months.

The most common adverse reactions (≥20%) included fatigue, peripheral neuropathy, decreased appetite, rash, alopecia, nausea, dysgeusia, diarrhea, dry eye, pruritus and dry skin. Diabetic ketoacidosis and death have occurred in patients treated with enfortumab vedotin-ejfv, regardless of pre-existing diabetes mellitus. Blood glucose levels should be monitored closely in patients with, or at risk, for diabetes mellitus or hyperglycemia."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-enfortumab-vedotin-ejfv-metastatic-urothelial-cancer

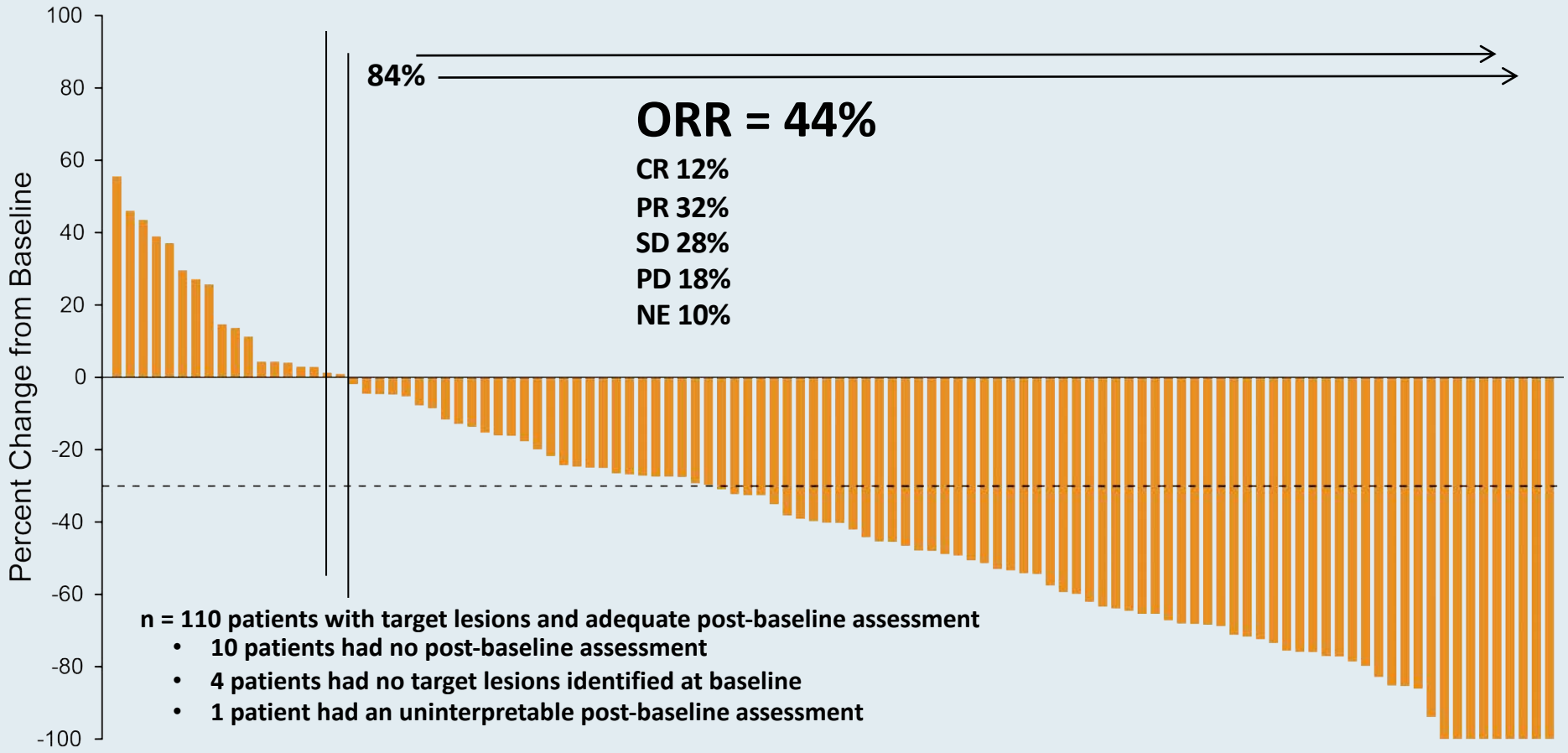
RTP RESEARCH TO PRACTICE

Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy

Jonathan E. Rosenberg, MD[1,2]; Peter H. O'Donnell, MD[3]; Arjun V. Balar, MD[4]; Bradley A. McGregor, MD[5]; Elisabeth I. Heath, MD[6]; Evan Y. Yu, MD[7,8]; Matthew D. Galsky, MD[9]; Noah M. Hahn, MD[10]; Elaina M. Gartner, MD[11]; Juan M. Pinelli, PA-C, MMSc[11]; Shang-Ying Liang, PhD[11]; Amal Melhem-Bertrandt, MD[12]; and Daniel P. Petrylak, MD[13]

J Clin Oncol 2019;37(29):2592-600.

EV-201: Change in Tumor Measurements per BICR



Rosenberg JE et al. *J Clin Oncol* 2019;37(29):2592-600; Petrylak D et al. ASCO 2019.

RTP RESEARCH TO PRACTICE

FDA Grants Accelerated Approval to Erdafitinib for Metastatic Urothelial Carcinoma

Press Release – April 12, 2019

"On April 12, 2019, the Food and Drug Administration granted accelerated approval to erdafitinib for patients with locally advanced or metastatic urothelial carcinoma, with susceptible FGFR3 or FGFR2 genetic alterations, that has progressed during or following platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Patients should be selected for therapy based on an FDA-approved companion diagnostic for erdafitinib. The FDA also approved the therascreen® FGFR RGQ RT-PCR Kit, for use as a companion diagnostic for this therapeutic indication.

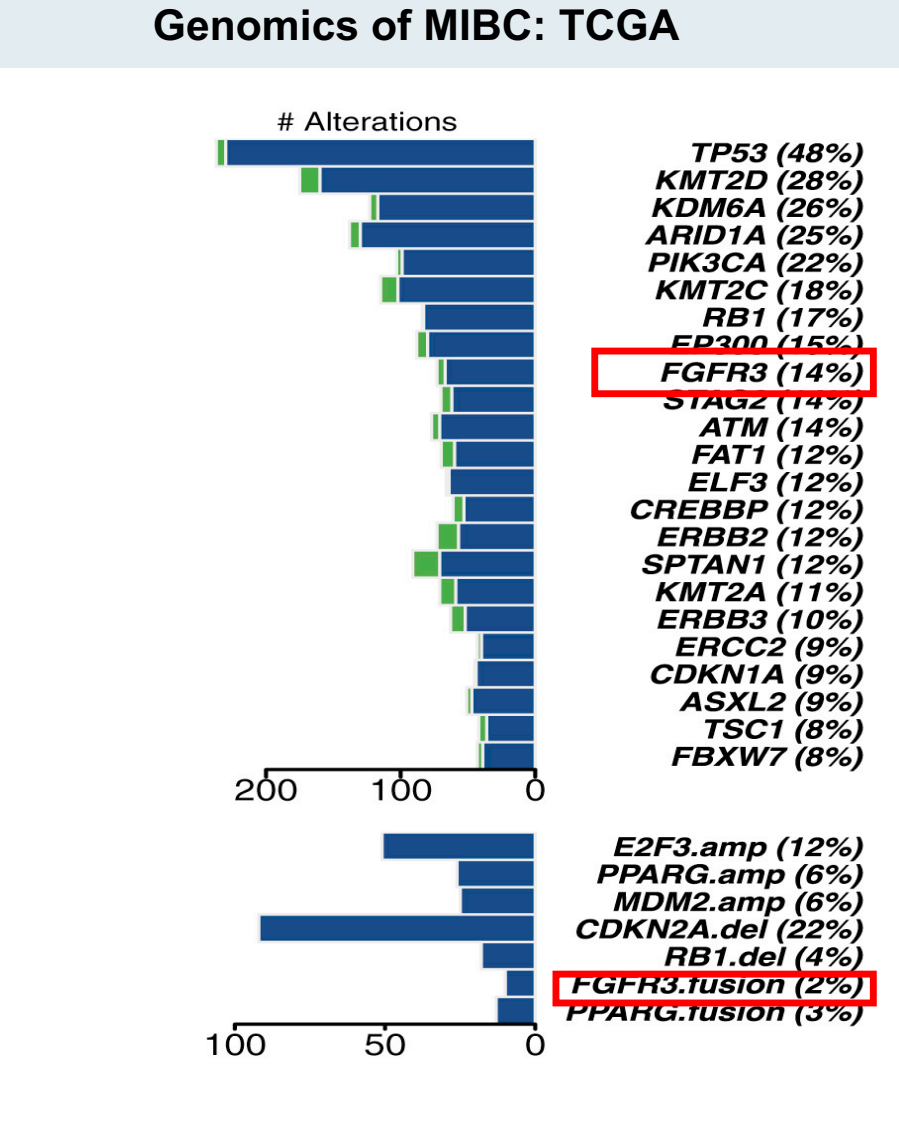
Erdafitinib approval was based on data from a cohort of 87 patients enrolled on Study BLC2001 (NCT02365597), a multicenter, open-label, single-arm trial. These patients had locally advanced or metastatic urothelial carcinoma that had progressed on or after at least one prior chemotherapy and had certain FGFR3 gene mutations or FGFR2 or FGFR3 gene fusions. ORR was 32.2%, with complete responses in 2.3% and partial responses in 29.9%. Median response duration was 5.4 months.

Erdafitinib can cause ocular disorders. Central serous retinopathy or retinal pigment epithelial detachment resulting in visual field defect was reported in 25% of patients. The most common adverse reactions reported in at least 40% of patients were increased serum phosphate, stomatitis, fatigue, increased serum creatinine, diarrhea, dry mouth, onycholysis, increased alanine aminotransferase, increased alkaline phosphatase, and decreased sodium."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-erdafitinib-metastatic-urothelial-carcinoma

RTP RESEARCH TO PRACTICE

FGFR3 Genomic Alterations in Muscle-Invasive Bladder Cancer



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

Courtesy of Guru Sonpavde, MD

Robertson AG et al. *Cell* 2017;171(3):540-56; Cappellen D et al. *Nat Genet* 1999;23:18-20; Nassar A et al. *JCO Precis Oncol* 2018; Gust KM et al. *Mol Cancer Ther* 2013;12:1245-54; Grünewald S et al. *Int J Cancer* 2019; Sfakianos JP Eur Urol 2015;68(6):970-7.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma

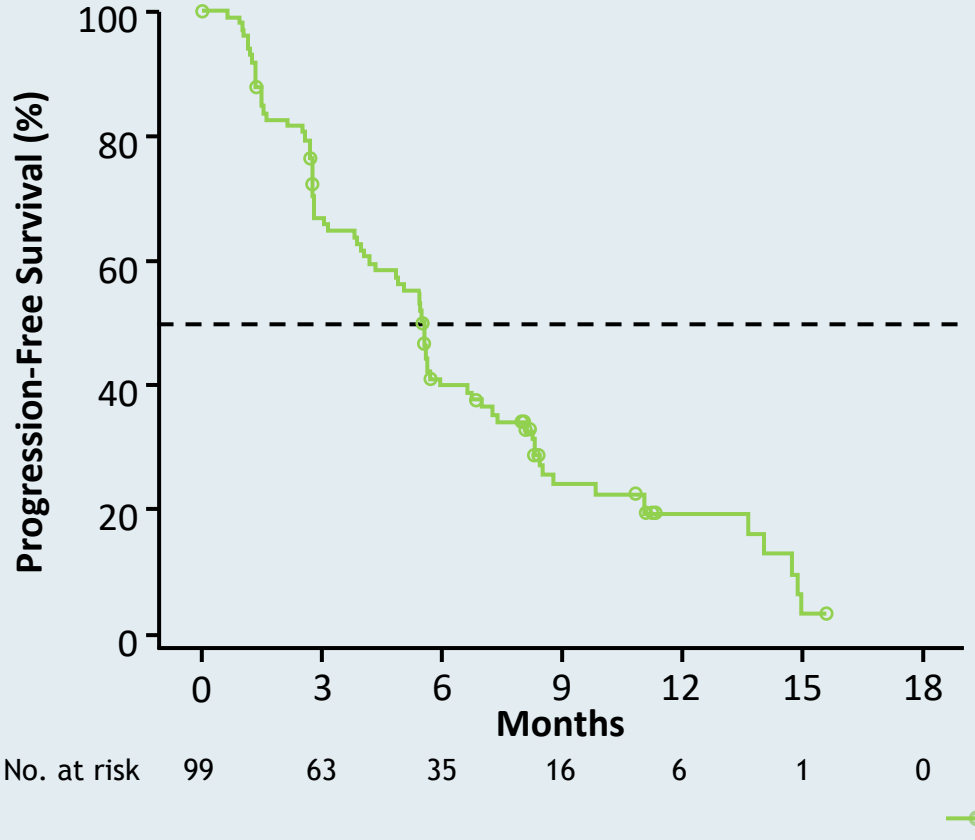
Y. Loriot, A. Necchi, S.H. Park, J. Garcia-Donas, R. Huddart, E. Burgess, M. Fleming, A. Rezazadeh, B. Mellado, S. Varlamov, M. Joshi, I. Duran, S.T. Tagawa, Y. Zakharia, B. Zhong, K. Stuyckens, A. Santiago-Walker, P. De Porre, A. O'Hagan, A. Avadhani, and A.O. Siefker-Radtke, for the BLC2001 Study Group*

***N Engl Med* 2019;381:338-48.**

BLC2001: Survival

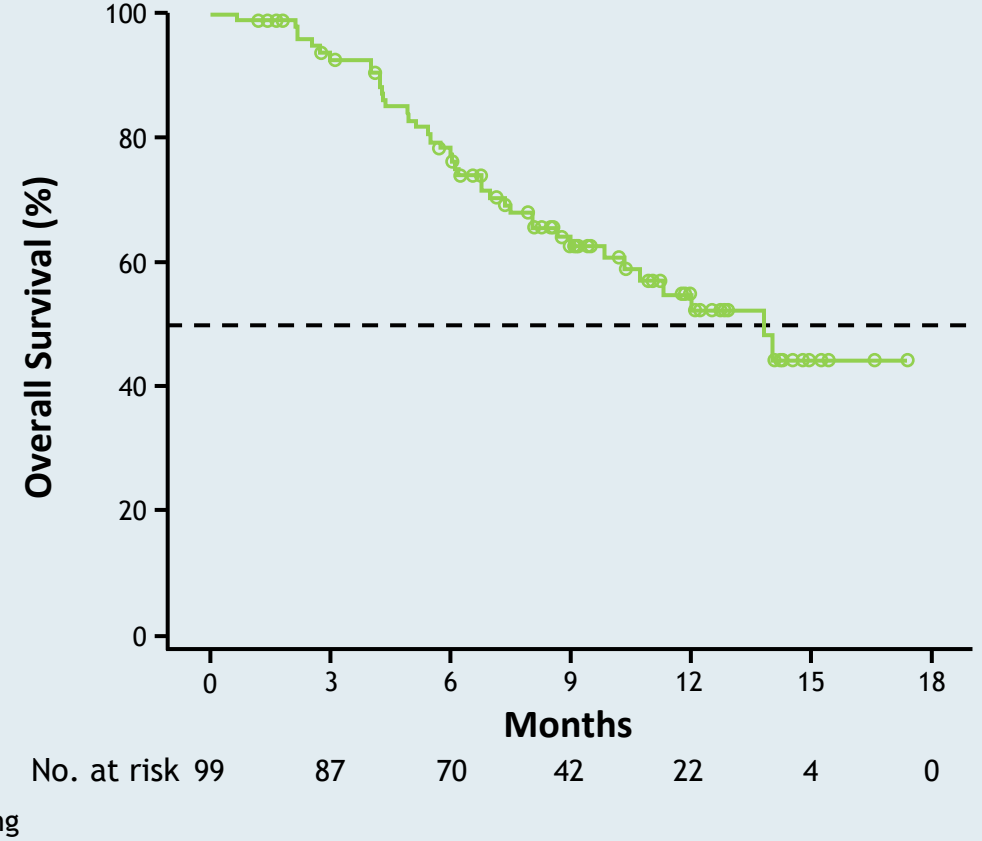
Median PFS = 5.5 months (95% CI, 4.2-6.0)

Progression/death events = 77



Median OS = 13.8 months (95% CI, 9.8–NE)

Survival events = 40



8 mg

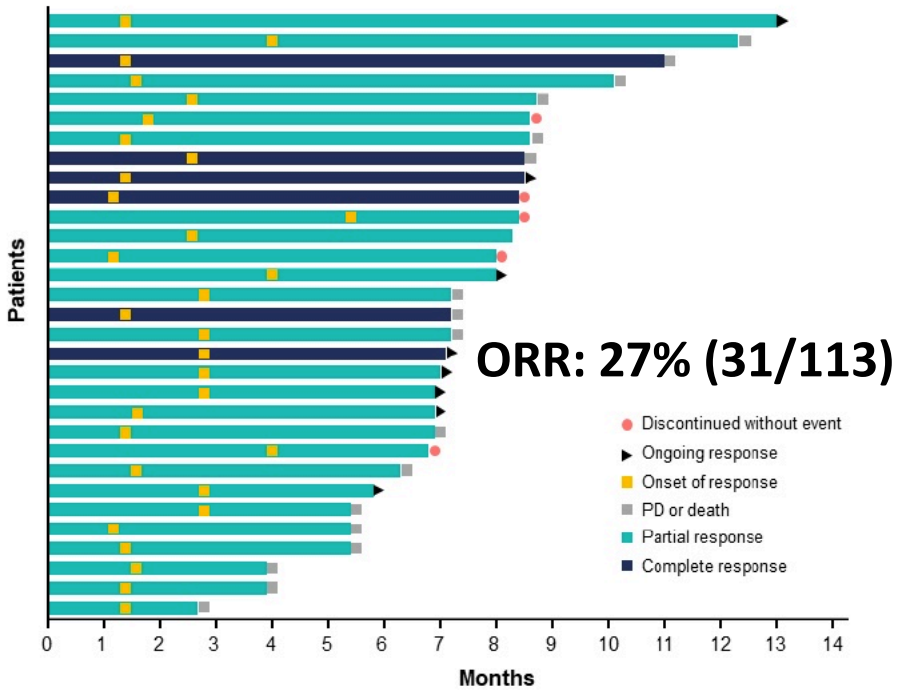
Loriot Y et al. *N Engl J Med* 2019;381(4):338-48; Siefker-Radtke AO et al. ASCO 2018.

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

Loriot Y et al.

ESMO 2020;Abstract LBA24.

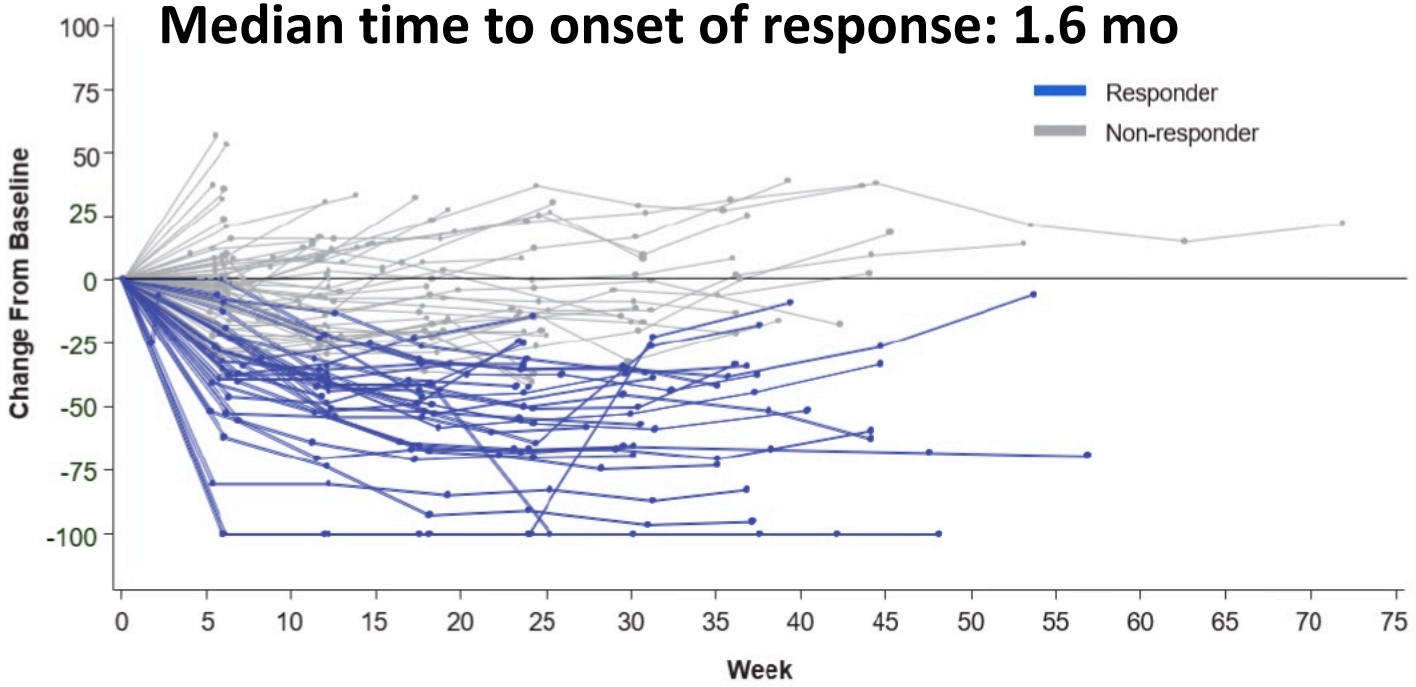
TROPHY-U-01 (Cohort 1): ORR, Duration of Response and Survival



ORR: 27% (31/113)

Median DOR: 5.9 mo

Median time to onset of response: 1.6 mo



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

Median PFS: 5.4 mo **Median OS: 10.5 mo**

Loriot Y et al. ESMO 2020;Abstract LBA24.

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

Current Concepts and Recent Advances in Oncology

A Daylong Clinical Summit Hosted in Partnership with Florida Cancer Specialists

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

Faculty

Arjun Balar, MD
Johanna Bendell, MD
Axel Grothey, MD
Brad S Kahl, MD
Shaji K Kumar, MD
Kathleen Moore, MD
Loretta Nastoupil, MD
William K Oh, MD
David M O'Malley, MD
Robert Z Orlowski, MD, PhD
Gregory J Riely, MD, PhD
Hope S Rugo, MD
David R Spigel, MD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Agenda

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

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

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

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

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

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

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

Gynecologic Cancers Faculty

Kathleen Moore, MD
The Virginia Kerley Cade Endowed Chair
in Cancer Development
Associate Director, Clinical Research
Director, Oklahoma TSET Phase I Program
Stephenson Cancer Center
Associate Professor, Section of Gynecologic Oncology
Director, Gynecologic Oncology Fellowship
Department of Obstetrics and Gynecology
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

David M O'Malley, MD
Professor
Division Director, Gynecologic Oncology
Co-Director, Gynecologic Oncology
Phase I Program
The Ohio State University and The James
Cancer Center
Columbus, Ohio

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Dr Moore — Disclosures

Advisory Committee	AbbVie Inc, Aravive Inc, AstraZeneca Pharmaceuticals LP, Eisai Inc, Genentech, a member of the Roche Group, ImmunoGen Inc, Merck, Mersana Therapeutics, Myriad Genetic Laboratories Inc, Tarveda Therapeutics, Tesaro, A GSK Company, Vavotar Life Sciences
Consulting Agreement	Akesobio
Contracted Research	Lilly, Merck, PTC Therapeutics, Tesaro, A GSK Company
Data and Safety Monitoring Board/Committee	Incyte Corporation
Employment	GOG Foundation/Partners, NRG Oncology

Dr O'Malley — Disclosures

Advisory Committee	AbbVie Inc, Agenus Inc, Ambry Genetics, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, Genelux, Genentech, a member of the Roche Group, GOG Foundation Inc, ImmunoGen Inc, Janssen Biotech Inc, Leap Therapeutics Inc, Merck, Myriad Genetic Laboratories Inc, Novocure, Regeneron Pharmaceuticals Inc, Tarveda Therapeutics, Tesaro, A GSK Company
Consulting Agreements	AbbVie Inc, Agenus Inc, Ambry Genetics, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, Genentech, a member of the Roche Group, Genmab, GOG Foundation Inc, ImmunoGen Inc, Novocure, Regeneron Pharmaceuticals Inc, Seagen Inc, Tesaro, A GSK Company
Contracted Research	AbbVie Inc, Agenus Inc, Ajinomoto Co Inc, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Clovis Oncology, Daré Bioscience, Eisai Inc, EMD Serono Inc, Ergomed Plc, Genentech, a member of the Roche Group, Genmab, GlaxoSmithKline, GOG Foundation Inc, ImmunoGen Inc, Iovance Biotherapeutics Inc, Janssen Biotech Inc, Johnson & Johnson Pharmaceuticals, Ludwig Institute for Cancer Research Ltd, Merck, New Mexico Cancer Care Alliance, Novocure, PRA Health Sciences, Regeneron Pharmaceuticals Inc, Seagen Inc, Stemcentrx, Syneos Health, Tesaro, A GSK Company, TRACON Pharmaceuticals Inc, VentiRx Pharmaceuticals Inc
Data and Safety Monitoring Board/Committee	Marker Therapeutics Inc

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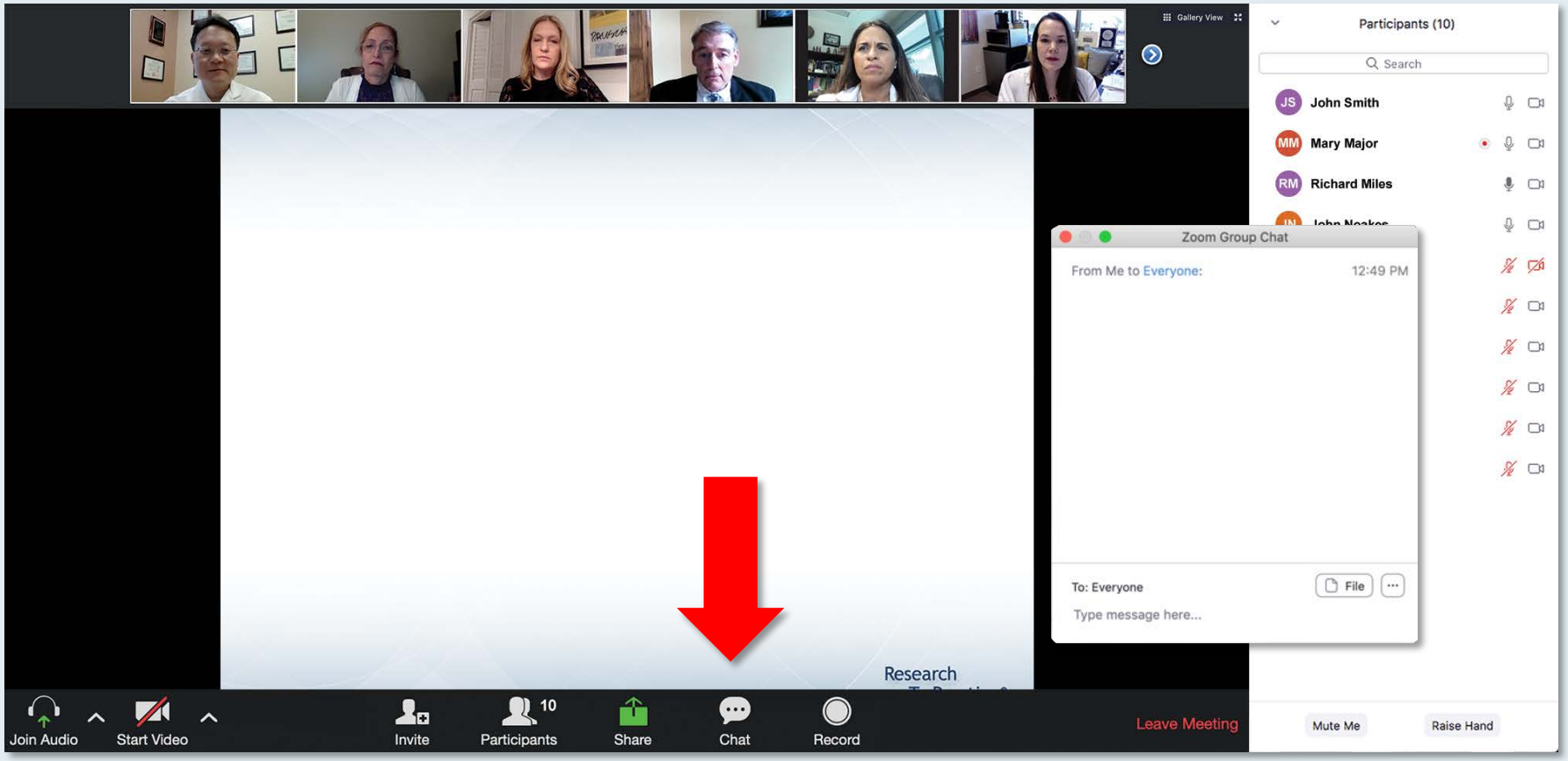
We Encourage Clinicians in Practice to Submit Questions



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

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FCS Contributing Oncologists

Mamta Choksi, MD
New Port Richey, Florida

Uday Dandamudi, MD
New Port Richey, Florida

Lowell L Hart, MD
Fort Myers, Florida

Maen Hussein, MD
Tavares, Florida

Zanetta S Lamar, MD
Naples, Florida

Vikas Malhotra, MD
Spring Hill, Florida

Shachar Peles, MD
Lake Worth, Florida

Syed F Zafar, MD
Fort Myers, Florida

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TO PRACTICE

Agenda

Module 1: MSI-High/dMMR or MSS Endometrial Cancer – Immunotherapy

- Dr Dandamudi: A 55-year-old woman with endometrial cancer
- Dr Malhotra: A 73-year-old woman with endometrial cancer

Module 2: Ovarian Cancer – PARP Inhibitors

- Dr Choksi: An 81-year-old woman with Stage IV ovarian cancer – BRCA2 mutation
- Dr Peles: A 59-year-old woman with ovarian cancer – BRCA1/2 wild type
- Dr Hart: A 46-year-old woman with ovarian cancer – BRCA1/2 wild type

Module 3: Relapsed/Refractory Cervical Cancer

- Dr Hart: A 41-year-old woman with recurrent cervical cancer – PD-L1-positive

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Case Presentation – Dr Dandamudi: A 55-year-old woman with endometrial cancer

Dr Uday Dandamudi

- 1/2018: Stage IIB endometrial cancer s/p surgery
- Patient declines adjuvant chemotherapy
- 6/2018: Presents with fatigue, weakness, 35-lb weight loss, abdominal distention/bloating
  - CT: Large mesenteric and omental masses throughout the abdomen
  - GYN pathologist: Malignant mixed Mullerian tumor
- 8/2018: Carboplatin/paclitaxel x 2, with rapid disease progression
  - NGS: Multiple genomic alterations, MSI-high, TMB 48 mut/MB
- 9/2019: Ipilimumab/nivolumab (melanoma regimen) x 1
  - Presents to ER with significant abdominal pain despite high-dose opioids
  - Comfort care and discharge to hospice, and subsequently discharged to her home
- 1/2020: Unexpectedly, patient arrives at clinic doing well
  - PET/CT: Multiple cystic masses, none FDG avid
- Ipilimumab/nivolumab x 1
  - Hypophysitis, adrenal insufficiency → treatment discontinued

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Case Presentation – Dr Malhotra: A 73-year-old woman with endometrial cancer

Dr Vikas Malhotra

- 2017: Postmenopausal bleeding resulting in biopsy (Grade 3 endometrial adenocarcinoma)
- 3/2017: TAH/BSO, Stage IIIC1 endometrial cancer
- Cisplatin and radiation therapy → carboplatin/paclitaxel x 4
  - 10/2017 CT: NED
- 4/2018: Peritoneal nodule
- Weekly carboplatin/paclitaxel/bevacizumab, with good response → 2/2020: PD
- Tumor profiling/genetic testing: Noncontributory, PD-L1 positive
- Pembrolizumab/lenvatinib (Lenvatinib dose reduced due to fatigue, other side effects)
- 9/2020: Patient remains stable

Questions

- How do you approach lenvatinib dosing – are you comfortable with dose reductions?
- How would you have managed this patient differently? What would you do when her disease progresses?

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In general, what is your usual starting dose of lenvatinib for a 70-year-old woman (PS = 0) also receiving pembrolizumab for microsatellite-stable (MSS) metastatic endometrial cancer who experienced disease progression on carboplatin/paclitaxel?

a. 20 mg
b. 18 mg
c. 12 mg
d. 10 mg
e. 5 mg
f. Other

A patient with MSI-high metastatic endometrial cancer has an excellent response to pembrolizumab. When would you recommend stopping treatment if she were tolerating it well?

a. I wouldn't stop
b. 1 year
c. 2 years
d. 3 years
e. Other

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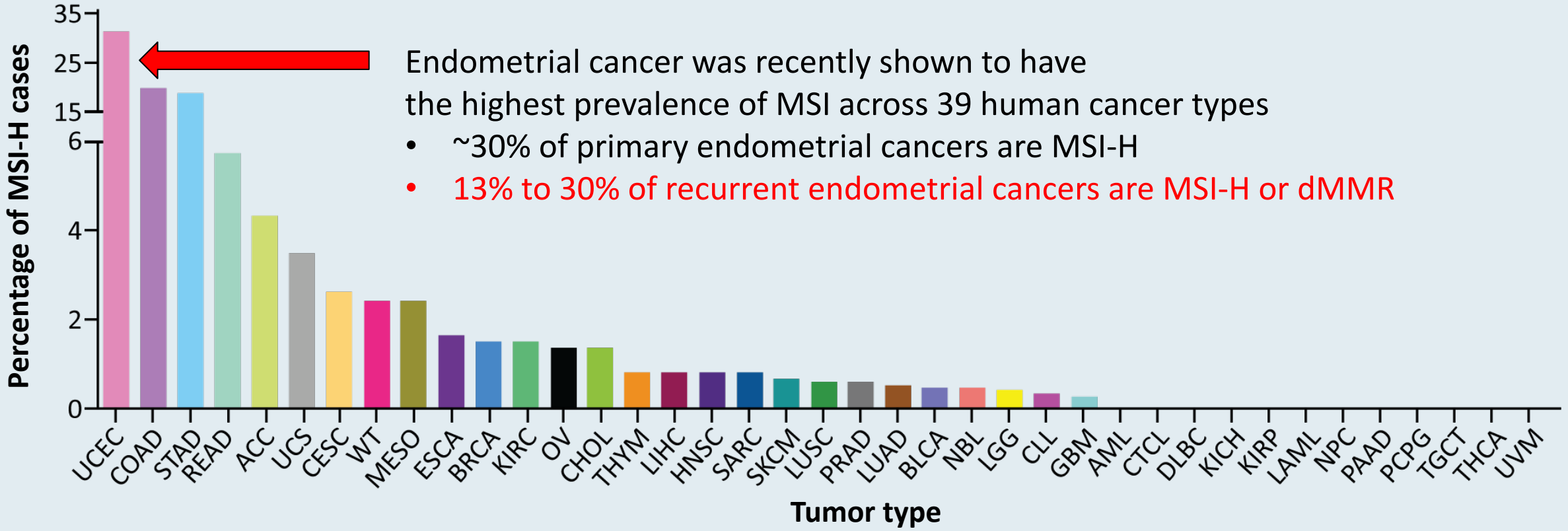
MSI-High Across 39 Cancer Types

Whole-exome data from 11,139 tumor-normal pairs from The Cancer Genome Atlas and Therapeutically Applicable Research to Generate Effective Treatments projects



Endometrial cancer was recently shown to have the highest prevalence of MSI across 39 human cancer types

- ~30% of primary endometrial cancers are MSI-H
- 13% to 30% of recurrent endometrial cancers are MSI-H or dMMR

UCEC = uterine corpus endometrial carcinoma

Bonneville R et al. *JCO Precis Oncol* 2017;2017:10.1200/PO.17.00073; Green AK et al. *ASCO Educational Book* 2020.

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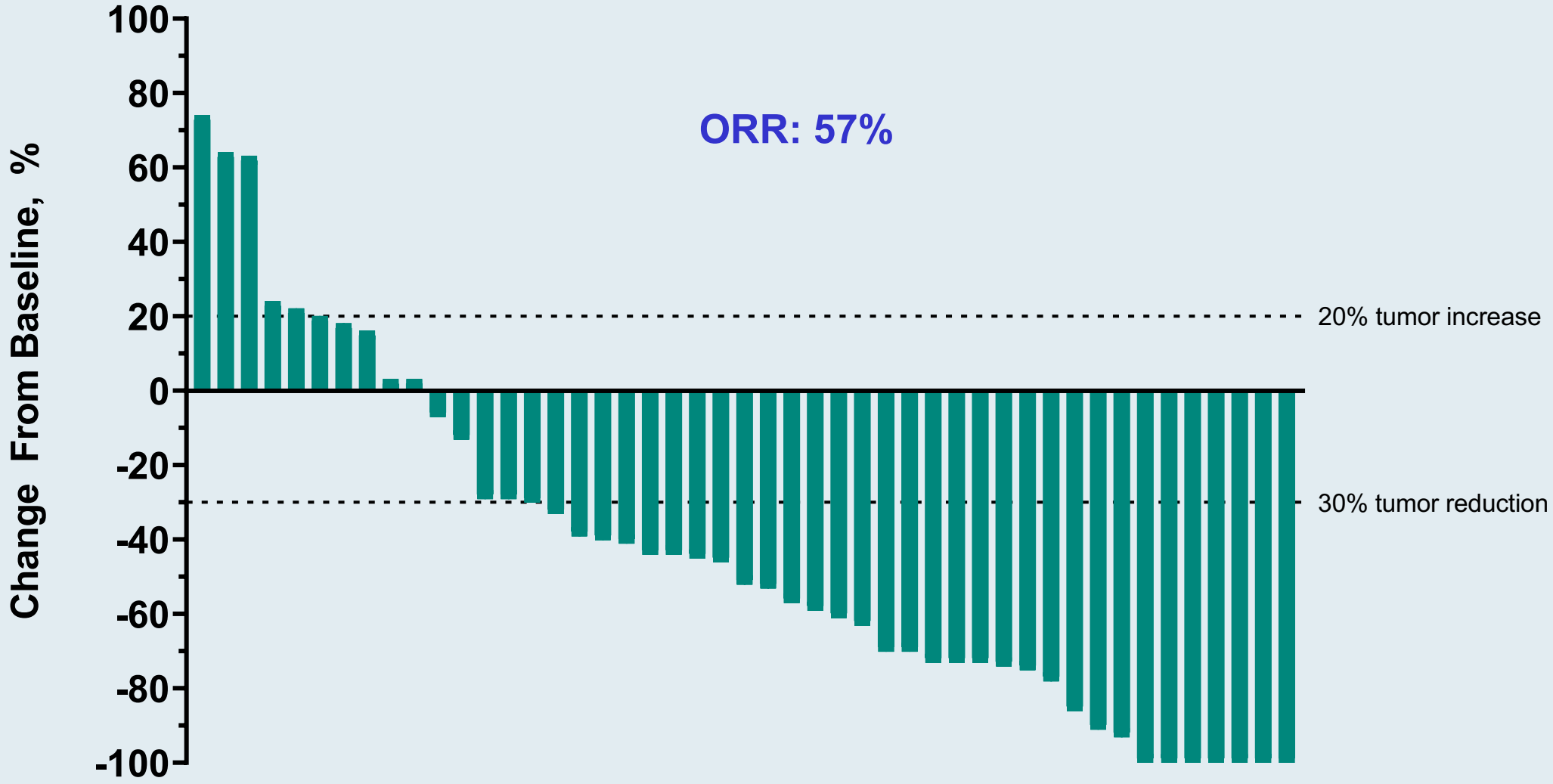
KEYNOTE-158: Best Percentage Change from Baseline in Target Lesion Size with Pembrolizumab Monotherapy in MSI-H Endometrial Cancer



O'Malley DM et al. ESMO 2019;Abstract 1044P.

Phase I/II GARNET Trial of the Anti-PD-1 Antibody Dostarlimab

Key inclusion/exclusion criteria for cohorts A1 and A2:

- Patients must have progressed on or after platinum doublet therapy
- Patients must have received ≤2 prior lines of treatment for recurrent or advanced disease
- Patients must have measurable disease at baseline
- Patients must be anti–PD-(L)1 naïve
- Patients could be screened based on local MMR/MSI testing results using IHC, PCR, or NGS performed in a certified local laboratory, but patient eligibility needs to be confirmed by MMR IHC results

- GARNET is a single-arm study of dostarlimab monotherapy in multiple tumor types
  - In part 2B, dostarlimab was dosed at the RTD determined from Part 1 and 2A
    - 500 mg IV Q3W for 4 cycles, then
      1000 mg IV Q6W until disease progression
- MMR status was determined by local immunohistochemistry
- Primary endpoint: ORR and DOR

***Cohort enrollment includes 3 patients with MMRunk/MSI-H disease; †Cohort enrollment includes 16 patients with MMRunk/MSS disease**

Oaknin A et al. ESMO 2020;Abstract 3750.

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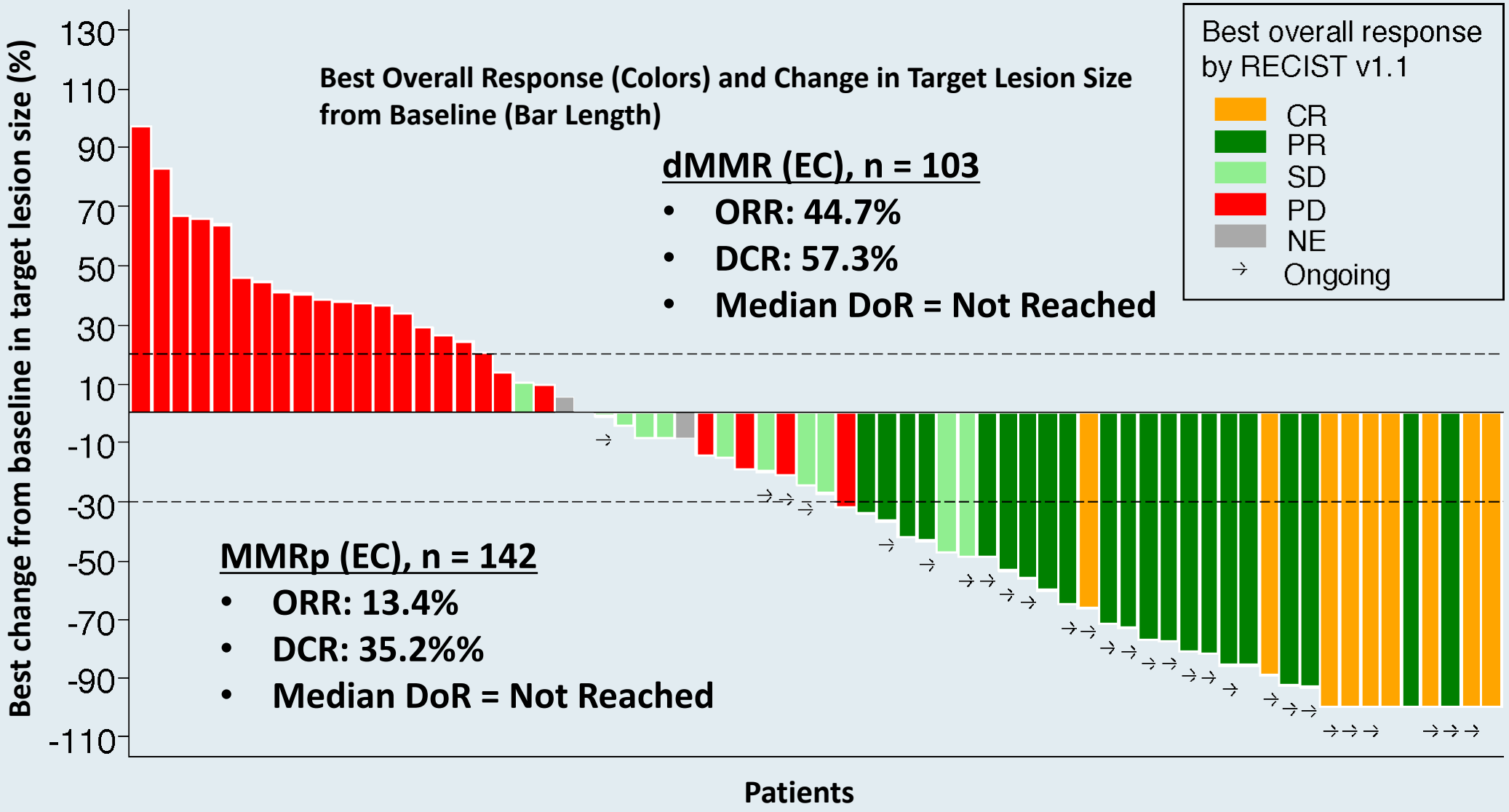
Phase I/II GARNET Trial: Dostarlimab in Recurrent or Advanced dMMR Endometrial Cancer



Oaknin A et al. ESMO 2020;Abstract 3750; Oaknin A et al. SGO 2020;Abstract LBA9.

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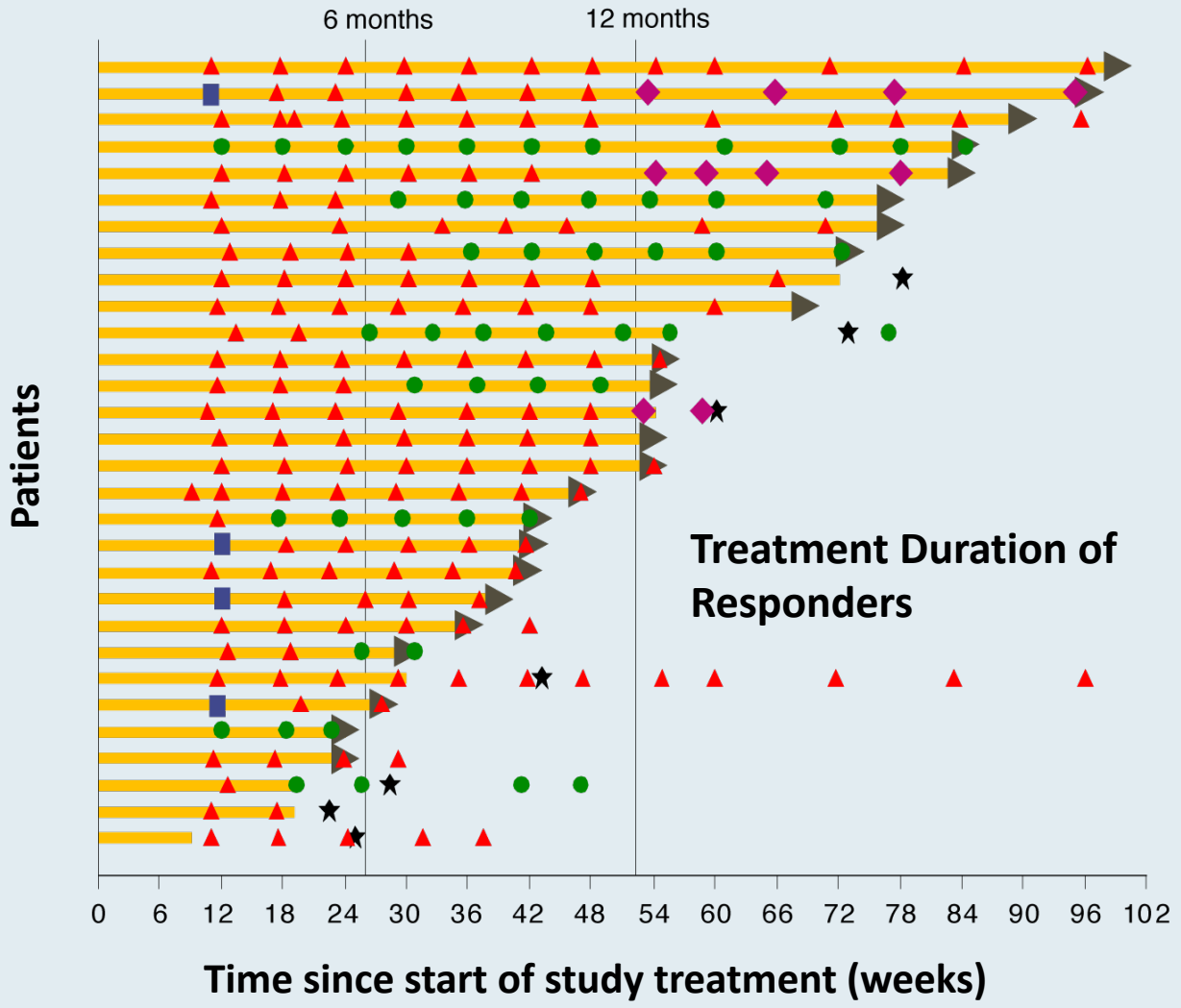
GARNET: Dostarlimab in Recurrent or Advanced dMMR Endometrial Cancer



- Median follow-up is 11.2 mos
- Median DOR not reached (1.87+ to 19.61+ mos)
- 25 of 30 (83%) responders remain in response as of the data cutoff
- Deepening of responses:
  - **SD → PR**: 4 patients
  - **PR → CR:** 7 patients

Oaknin A et al. SGO 2020;Abstract LBA9.

FDA Approves the Combination of Pembrolizumab and Lenvatinib for Advanced Endometrial Cancer

September 17, 2019

"The Food and Drug Administration granted accelerated approval to the combination of pembrolizumab plus lenvatinib for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation.

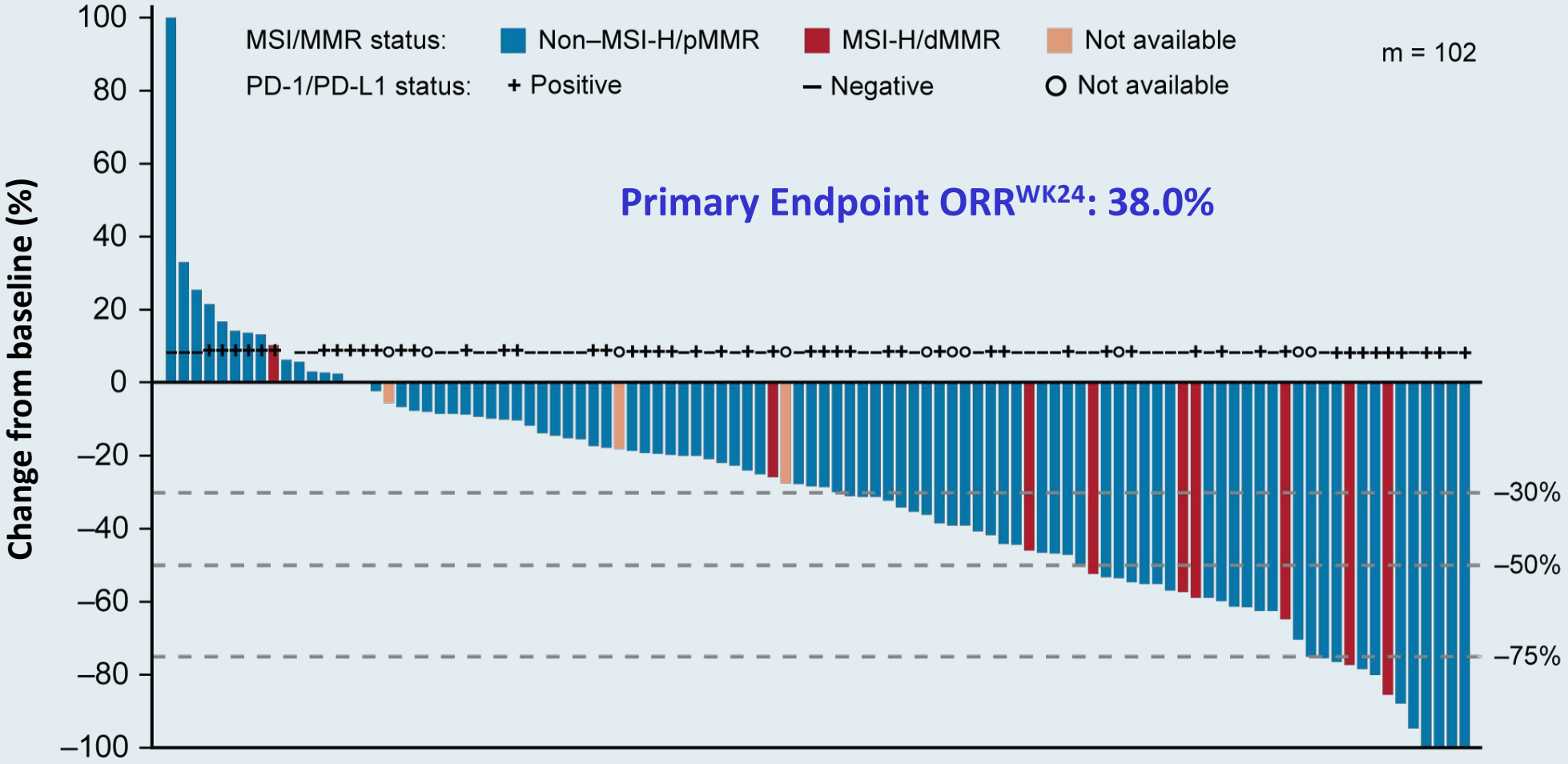
Efficacy was investigated in Study 111/KEYNOTE-146 (NCT02501096), a single-arm, multicenter, open-label, multi-cohort trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting.

The most common adverse reactions (incidence ≥20%) for the combination were fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash."

https://www.fda.gov/drugs/resources-information-approved-drugs/simultaneous-review-decisions-pembrolizumab-plus-lenvatinib-australia-canada-and-us

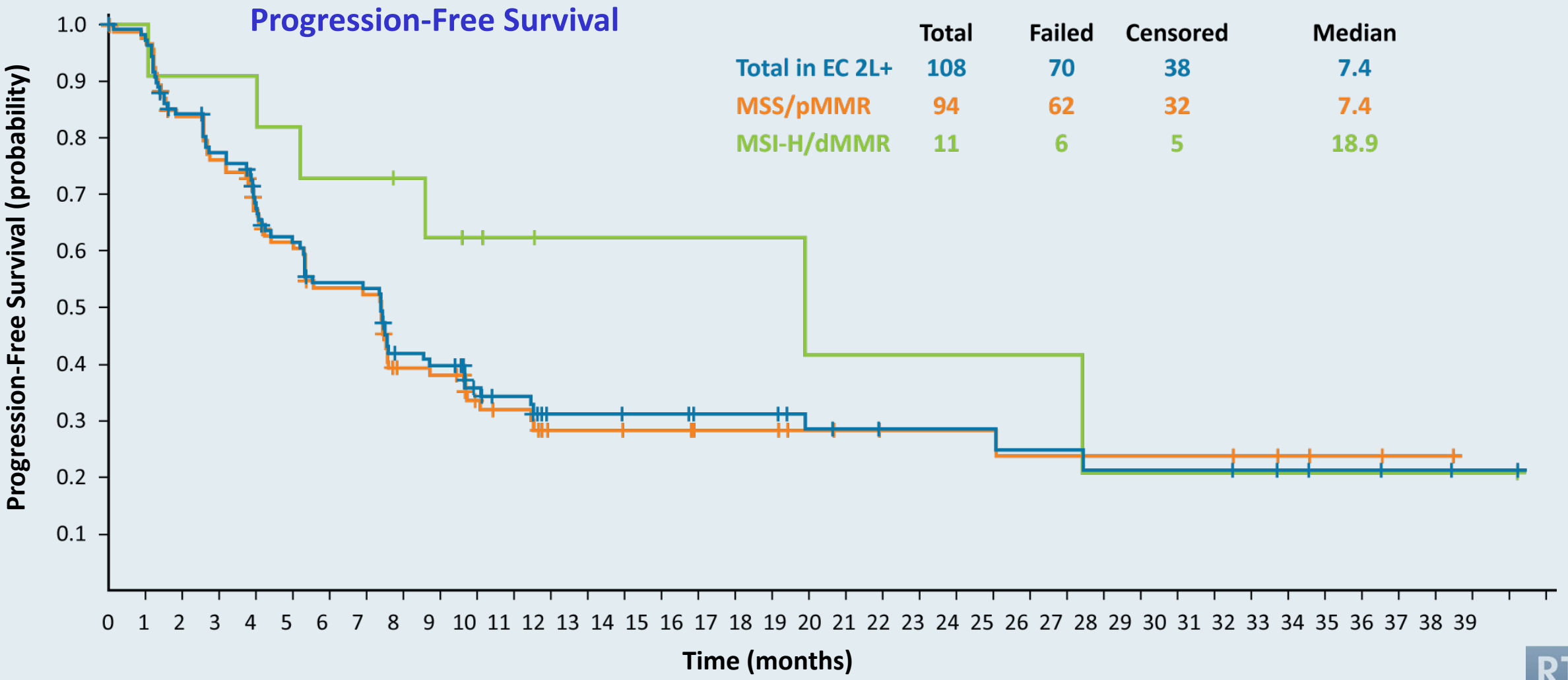
RTP RESEARCH TO PRACTICE

KEYNOTE-146: Pembrolizumab/Lenvatinib in Advanced Endometrial Cancer That Is *Not* MSI-H or dMMR After Disease Progression on Prior Systemic Therapy



Makker V et al. *J Clin Oncol* 2020;[Online ahead of print].

KEYNOTE-146: Pembrolizumab/Lenvatinib in Advanced Endometrial Cancer That Is *Not* MSI-H or dMMR After Progression on Prior Systemic Therapy



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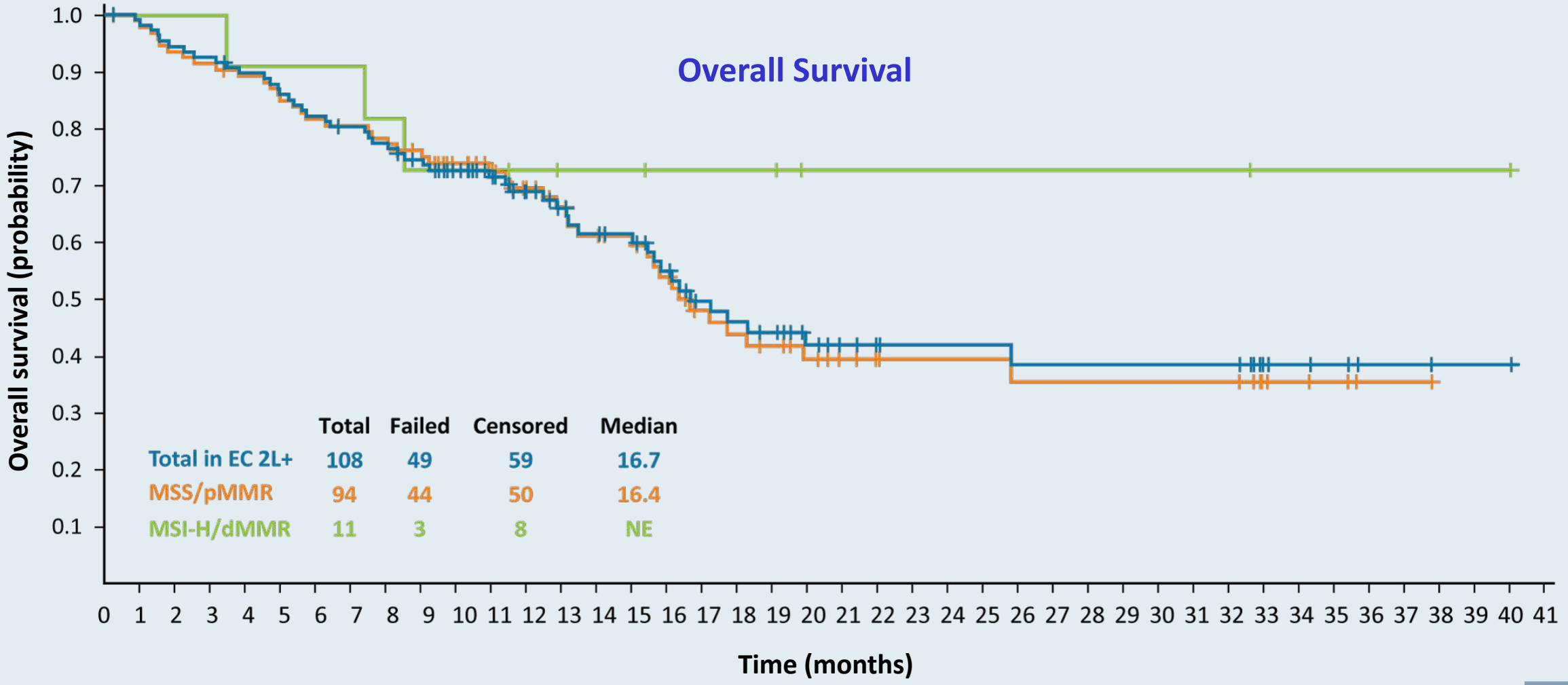

Makker V et al. *J Clin Oncol* 2020;[Online ahead of print].

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KEYNOTE-146: Overview of Treatment-Related Adverse Events

	Previously Treated EC (n = 108) n (%)
Patients with any treatment-related TEAEs	105 (97.2)
Patients with treatment-related TEAEs leading to study drug discontinuation[a]	20 (18.5)
Both lenvatinib and pembrolizumab	10 (9.3)
Lenvatinib[b]	17 (15.7)
Pembrolizumab[c]	14 (13.0)
Patients with treatment-related TEAEs leading to study-drug dose reduction of lenvatinib	70 (64.8)
Patients with treatment-related TEAEs leading to study-drug interruption[a]	78 (72.2)
Both lenvatinib and pembrolizumab	30 (27.8)
Lenvatinib[b]	73 (67.6)
Pembrolizumab[c]	43 (39.8)

[a]Drug action taken is for lenvatinib and/or pembrolizumab; [b]Drug action taken for lenvatinib, regardless of action taken for pembrolizumab; [c]Drug action taken for pembrolizumab, regardless of action taken for lenvatinib.

Makker V et al. ESMO 2019;Abstract 4101.

Select Ongoing Phase III Immune Checkpoint Inhibitor Combination Studies in Endometrial Cancer

Trial	N	Eligibility	Randomization
KEYNOTE-775	780	• Advanced, recurrent or metastatic EC • PD after 1 prior platinum-based chemo	• Pembro + lenvatinib • Paclitaxel + carboplatin
LEAP-001	720	• Stage III, IV or recurrent EC • May have received 1 prior line of platinum-based adjuvant or neoadjuvant chemo	• Pembro + lenvatinib • Paclitaxel + carboplatin
NRG-GY018	810	• Stage III, IVA or IVB or recurrent EC • No prior chemo for EC, except adjuvant	• Pembro + paclitaxel + carboplatin → Pembro • Placebo + paclitaxel + carboplatin → Placebo
DUO-E	699	• Newly dx advanced or recurrent EC	• Plat-based chemo →placebo • Plat-based chemo + durva → Durva • Plat-based chemo + durva → Durva + olaparib
RUBY	470	• Stage III, IV or first recurrent EC	• Dostarlimab + paclitaxel + carboplatin • Placebo + paclitaxel + carboplatin
AtTEnd	550	• Newly dx with residual disease after surgery, OR inoperable Stage III-IV naïve to first-line systemic treatment	• Atezolizumab + paclitaxel + carboplatin • Placebo + paclitaxel + carboplatin

Clinicaltrials.gov. Accessed October 2020; Green AK et al. *ASCO Ed Book* 2020.

Agenda

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- Dr Dandamudi: A 55-year-old woman with endometrial cancer
- Dr Malhotra: A 73-year-old woman with endometrial cancer

Module 2: Ovarian Cancer – PARP Inhibitors

- Dr Choksi: An 81-year-old woman with Stage IV ovarian cancer – BRCA2 mutation
- Dr Peles: A 59-year-old woman with ovarian cancer – BRCA1/2 wild type
- Dr Hart: A 46-year-old woman with ovarian cancer – BRCA1/2 wild type

Module 3: Relapsed/Refractory Cervical Cancer

- Dr Hart: A 41-year-old woman with recurrent cervical cancer – PD-L1-positive

Case Presentation – Dr Choksi: An 81-year-old woman with Stage IV ovarian cancer – BRCA2 mutation

Dr Mamta Choksi

- 2017: Diagnosed with Stage IV ovarian serous adenocarcinoma
  - Genetic testing: BRCA2 mutation (Family history of breast cancer)
- Reluctant to receive chemotherapy but agrees to weekly carboplatin/paclitaxel x 6
  - CA-125: Normalized from 31,700 to 31 in 3 months
  - Restaging PET/CT: Marked improvement in carcinomatosis, resolution of liver and spleen metastases
- 8/2017: Maintenance niraparib x 3 (ongoing)
  - Tolerating well, NED

Question

- Would you have approached her treatment differently?

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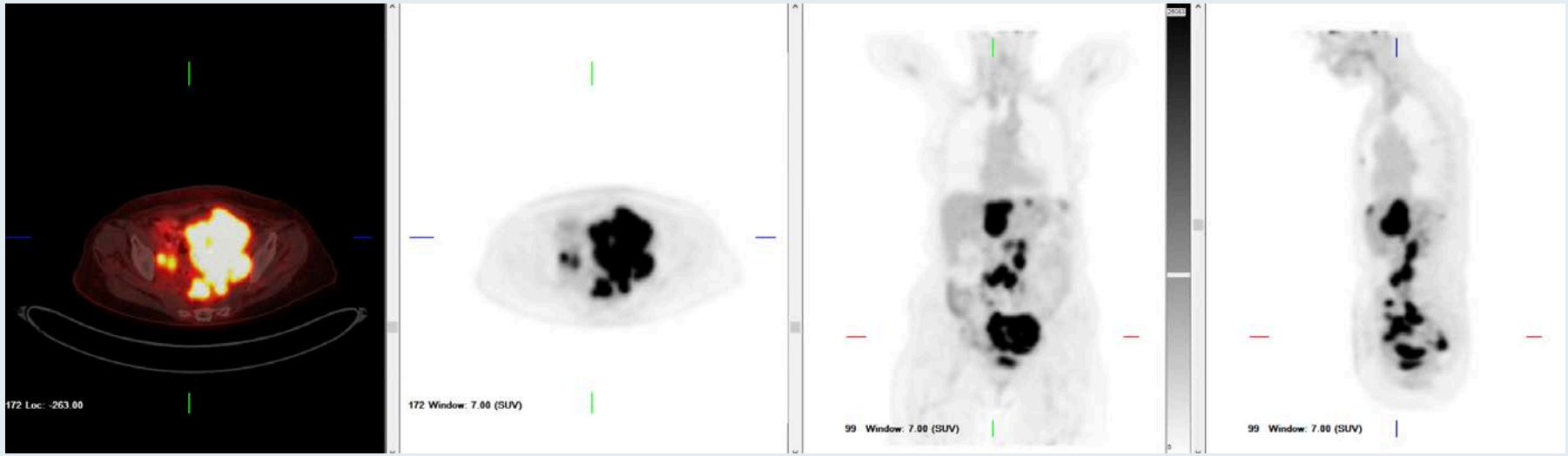
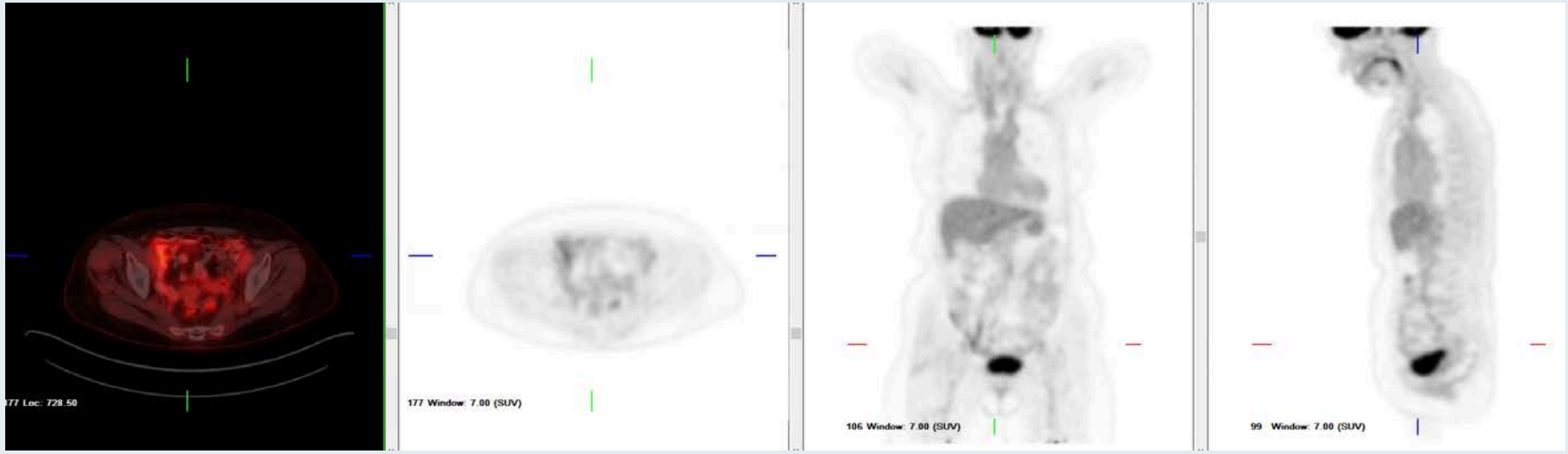
Case Presentation – Dr Choksi: An 81-year-old woman with Stage IV ovarian cancer – BRCA2 mutation (continued)

Dr Mamta Choksi



Before Niraparib



On Niraparib

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Case Presentation – Dr Peles: A 59-year-old woman with ovarian cancer – BRCA1/2 wild type

Dr Shachar Peles

- Stage IIIC ovarian cancer
- NGS: No actionable mutations
- Neoadjuvant dose-dense carboplatin/paclitaxel x 3
- TAH-BSO, omentectomy, right pelvic lymph node sampling, debulking, small bowel resection
- Adjuvant dose-dense carboplatin/paclitaxel x 3, with CR
- GYN 72 vaccine trial with folate receptor alpha peptide vaccine mixed with GM-CSF vs GM-CSF alone completed 5/2019 → PD
- 5/2019: Surgical debulking
- 6/2019 – 10/2019: Carboplatin/liposomal doxorubicin/bevacizumab
- Requested maintenance bevacizumab/olaparib per PAOLA-1 trial

Questions

- In addition to BRCA mutations, should we be testing for HRD as well?
- What are your thoughts about maintenance therapy in the recurrent setting, particularly with bevacizumab and olaparib?

RTP RESEARCH TO PRACTICE

A 60-year-old woman with a germline BRCA mutation presents with ovarian cancer, ascites and omental caking. She undergoes neoadjuvant chemotherapy and an R0 resection and receives 3 cycles of postoperative chemotherapy. What is your likely maintenance treatment?

a. Olaparib
b. Niraparib
c. Olaparib + bevacizumab
d. Niraparib + bevacizumab
e. Bevacizumab
f. Other
g. None

Case Presentation – Dr Hart: A 46-year-old woman with ovarian cancer – BRCA1/2 wild type

Dr Lowell Hart

- Stage IIB clear cell ovarian cancer
- 6/2016: TAH-BSO and adjuvant carboplatin/paclitaxel → PD
- Liposomal doxorubicin/bevacizumab, with mixed response
- Switched to gemcitabine/bevacizumab, with improvement
- 2017: MSI-high; Foundation Medicine testing: BRCA1/2 negative
- Late 2017: Pembrolizumab, with mixed response → added ipilimumab x 4 → PD
- 8/2018: Bevacizumab added to pembrolizumab, with improvement on scans
- 7/2019: Olaparib added, but discontinued after hematochezia and colitis
- 9/2019: Switched to niraparib and continues pembrolizumab, bevacizumab and niraparib
  - Stable disease, good QoL

Question

- For a patient such as this with stable disease, how long would you continue the checkpoint inhibitor?

A 60-year-old woman with Stage IIIC ovarian cancer (BRCA wild type/HR proficient) is s/p R0 debulking surgery. Regulatory and reimbursement issues aside, what would you recommend as postoperative systemic therapy?

a. Carboplatin/paclitaxel
b. Carboplatin/paclitaxel → olaparib
c. Carboplatin/paclitaxel + bevacizumab → olaparib
d. Carboplatin/paclitaxel → niraparib
e. Carboplatin/paclitaxel + bevacizumab → niraparib
f. Carboplatin/paclitaxel + bevacizumab → bevacizumab
g. Carboplatin/paclitaxel + bevacizumab → bevacizumab + olaparib
h. Carboplatin/paclitaxel + bevacizumab → bevacizumab + niraparib
i. Other

Phase III First-Line Maintenance Trials

Study	SOLO-1 (N = 451)	PAOLA-1 (N = 612)	PRIMA (N = 620)	VELIA (N = 1,140)
Treatment arms vs placebo	**Olaparib (n = 260)**	**Bevacizumab ± olaparib**	**Niraparib**	**Veliparib**
Patient population	*BRCA* mutation	All comers	All comers	*All comers*
Treatment duration	24 months	15 months for bev 24 months for Olaparib	36 months or until PD	24 months
Hazard ratio for PFS	0.33	0.59	0.62	0.68
FDA approval status (date)	12/18/2018	5/28/2020	4/29/2020	Investigational

Burger RA et al. *N Engl J Med* 2011; Norquist B et al. *Clin Cancer Res* 2018; Bevacizumab prescribing information; Moore K et al. *N Engl J Med* 2018; Gonzalez-Martin A et al. *N Engl J Med* 2019; Ray-Coquard I et al. *N Engl J Med* 2019; Coleman RL et al. *N Engl J Med* 2019

Courtesy of Shannon N Westin, MD, MPH

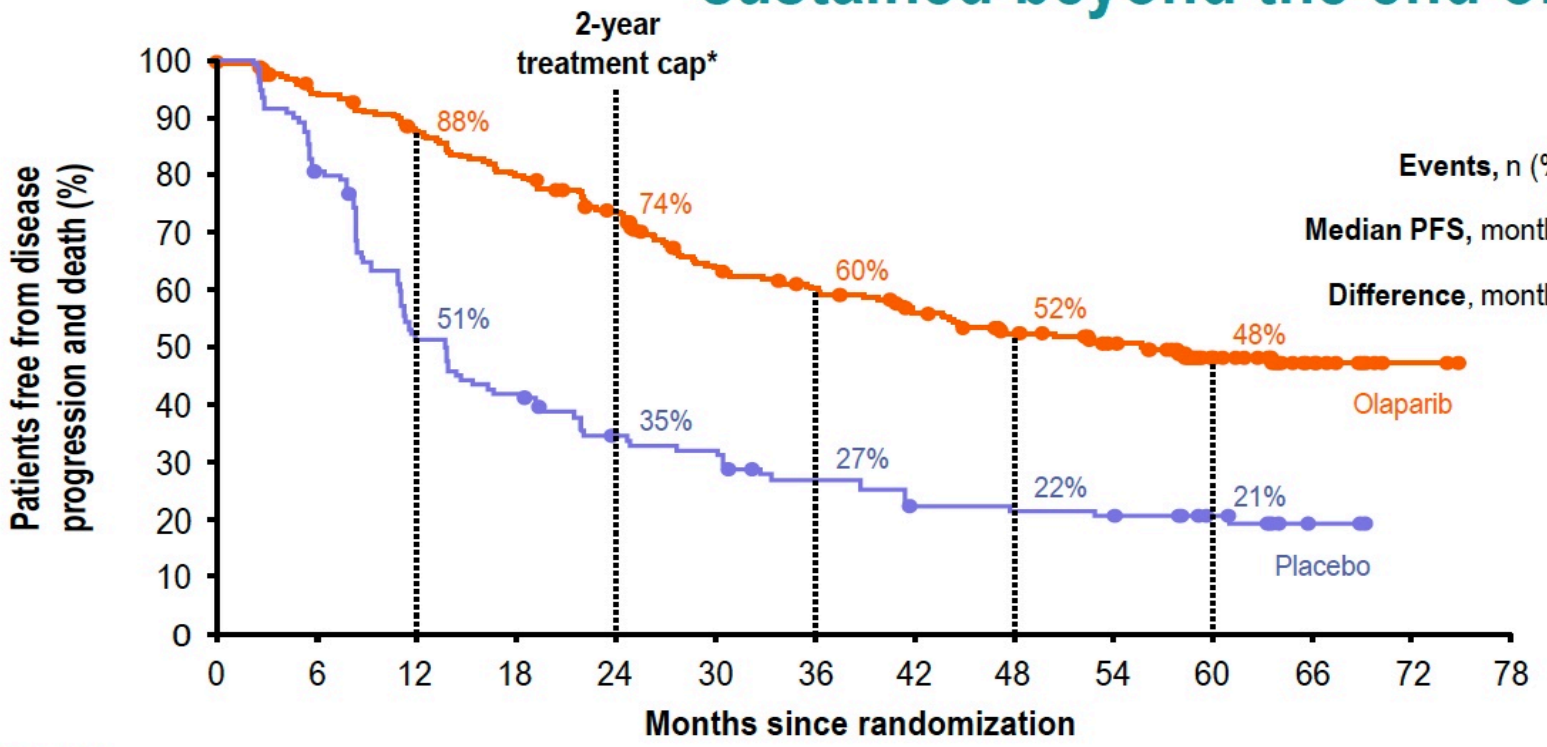
Maintenance Olaparib for Patients (pts) with Newly Diagnosed, Advanced Ovarian Cancer (OC) and a BRCA Mutation (BRCAm): 5-Year (y) Follow-Up (f/u) from SOLO1

Banerjee S et al.
ESMO 2020;Abstract 811MO.

SOLO-1 Trial 5-Year Follow-Up

VIRTUAL 2020 ESMO congress

PFS benefit of maintenance olaparib was sustained beyond the end of treatment



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	118 (45)	100 (76)
Median PFS, months	**56.0**	**13.8**
Difference, months	42.2	
	HR 0.33 (95% CI 0.25–0.43)	

Median treatment duration:
Olaparib, 24.6 months
Placebo†, 13.9 months

No. at risk														
Olaparib	260	229	212	194	173	140	129	115	101	91	58	30	2	0
Placebo	131	103	65	53	41	38	30	24	23	22	16	3	0	

*13 patients, all in the olaparib arm, continued study treatment past 2 years; †n=130 (safety analysis set)
Investigator-assessed by modified RECIST v1.1. DCO: 5 March 2020

Banerjee S et al. ESMO 2020;Abstract 811MO.

RTP RESEARCH TO PRACTICE

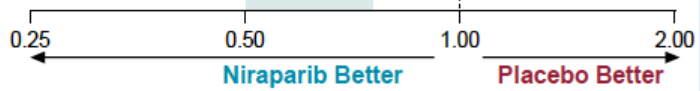
Efficacy of Niraparib Therapy in Patients with Newly Diagnosed Advanced Ovarian Cancer by BRCA and Homologous Recombination Status: PRIMA/ENGOT-OV26/GOG-3012 Study

Monk BJ et al.

SGO 2020;Abstract 31.

PRIMA: PFS Benefit in Prespecified Subgroups

	Total no. of patients		Hazard ratio for PFS (95% CI)
	Niraparib	Placebo	
Overall	487	246	0.62 (0.50–0.76)
Age group			
<65 years	297	147	0.61 (0.47–0.81)
≥65 years	190	99	0.53 (0.38–0.74)
Stage of disease at initial diagnosis			
III	318	158	0.54 (0.42–0.70)
IV	169	88	0.79 (0.55–1.12)
NACT			
Yes	322	167	0.59 (0.46–0.76)
No	165	79	0.66 (0.46–0.94)
Best response to platinum therapy			
CR	337	172	0.60 (0.46–0.77)
PR	150	74	0.60 (0.43–0.85)
Homologous recombination test status			
HRd–*BRCA*mut	152	71	0.40 (0.27–0.62)
*BRCA1*mut	105	43	0.39 (0.23–0.66)
*BRCA2*mut	47	28	0.35 (0.15–0.84)
HRd–*BRCA*wt	95	55	0.50 (0.31–0.83)
HRp	169	80	0.68 (0.49–0.94)
HRnd	71	40	0.85 (0.51–1.43)



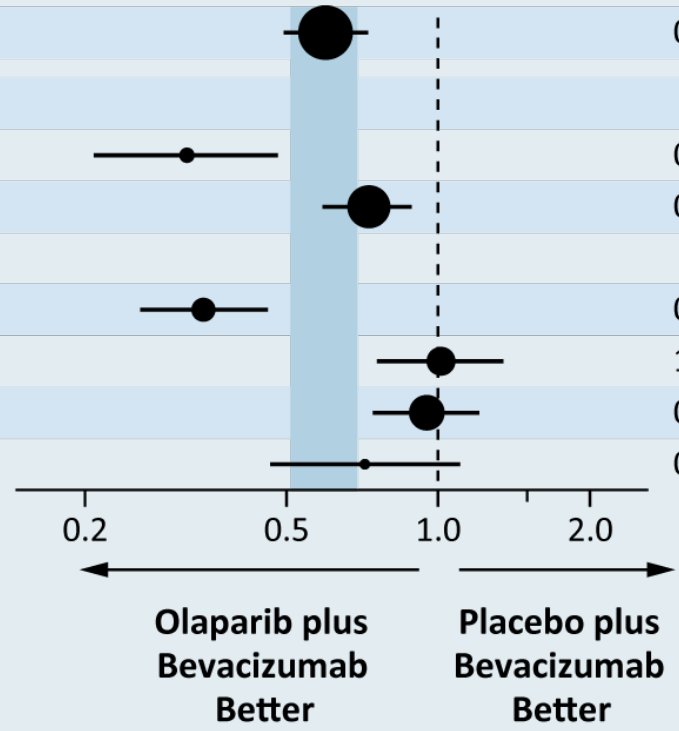
- Hazard ratios are clinically meaningful in all subgroups

CI = confidence interval; CR = complete response; HRd = homologous recombination deficient; HRnd = homologous recombination not determined; HRp = homologous recombination proficient; mut = mutant; NACT = neoadjuvant chemotherapy; PFS = progression-free survival; PR = partial response; wt = wild-type

Monk BJ et al. SGO 2020;Abstract 31.

PAOLA-1: Select Subgroup Analysis of PFS

Subgroup	Olaparib plus Bevacizumab	Placebo plus Bevacizumab	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients with disease progression or death/total no. (%)		
All patients	280/537 (52)	194/269 (72)	0.59 (0.49–0.72)
Tumor BRCA mutation status			
BRCA mutation	41/157 (26)	49/80 (61)	0.31 (0.20–0.47)
No BRCA mutation or unknown	239/380 (63)	145/189 (77)	0.71 (0.58–0.88)
Tumor HRD status			
Positive	87/255 (34)	92/132 (70)	0.33 (0.25–0.45)
Negative	145/192 (76)	66/85 (78)	1.00 (0.75–1.35)
Negative or unknown	193/282 (68)	102/137 (74)	0.92 (0.72–1.17)
Unknown	48/90 (53)	36/52 (69)	0.71 (0.46–1.10)



Ray-Coquard I et al. *N Engl J Med* 2019;381:2416-28.

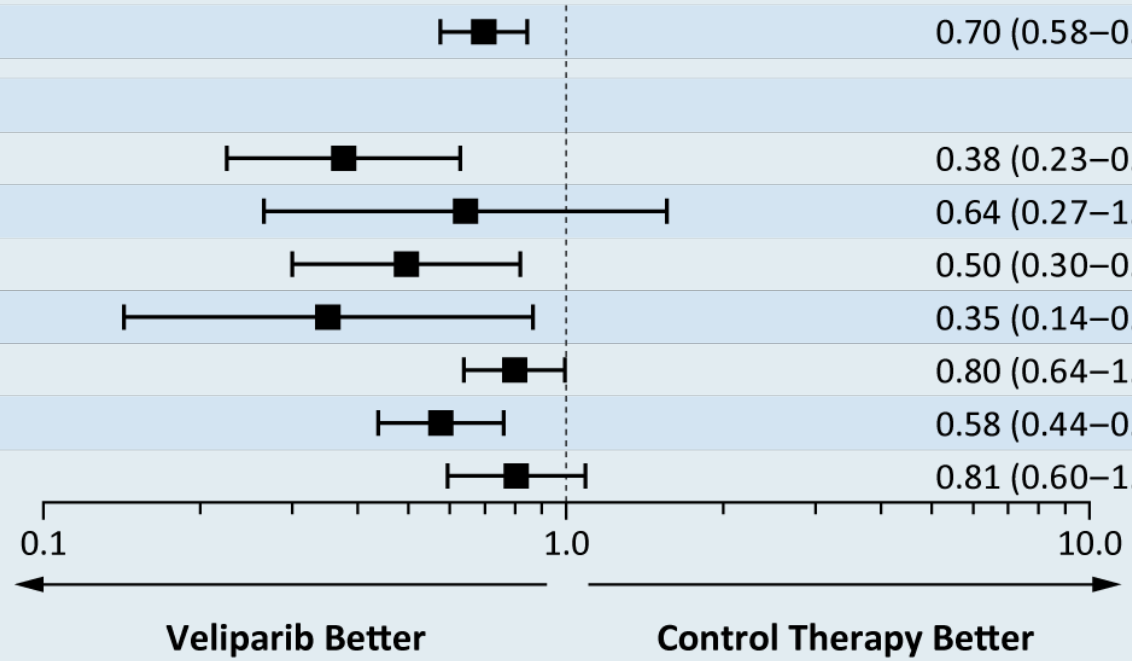
SOLO-1 and PAOLA-1: Population-Adjusted Indirect Comparison of Olaparib with or without Bevacizumab, Bev Alone and Placebo in Maintenance Therapy for Newly Diagnosed Advanced OC with BRCA Mutation

- The combination of olaparib and bevacizumab leads to a potentially meaningful improvement in PFS versus olaparib alone in women with BRCA-mutated newly diagnosed ovarian cancer.
- The relative clinical benefit of bevacizumab appears to be additive and consistent across regimens, such that its use leads to a similar level of benefit when combined with olaparib and compared with olaparib alone or used as monotherapy and compared with placebo.
- The results of this analysis should be viewed with the limitation that it is a nonrandomized comparison.

Vergote IB et al. SGO 2020;Abstract 35.

VELIA/GOG-3005: Select Subgroup Analyses of PFS

Subgroup	Veliparib	Control	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients with events/total no.		
All patients	191/382	237/375	0.70 (0.58–0.84)
Mutation status			
BRCA1	26/78	36/59	0.38 (0.23–0.63)
BRCA2	8/30	13/31	0.64 (0.27–1.56)
Germline BRCA	27/80	36/63	0.50 (0.30–0.82)
Tissue-based BRCA	7/28	15/29	0.35 (0.14–0.87)
Nonmutated BRCA	142/245	171/254	0.80 (0.64–1.00)
HRD-positive	87/214	124/207	0.58 (0.44–0.76)
HRD-negative	80/125	89/124	0.81 (0.60–1.09)



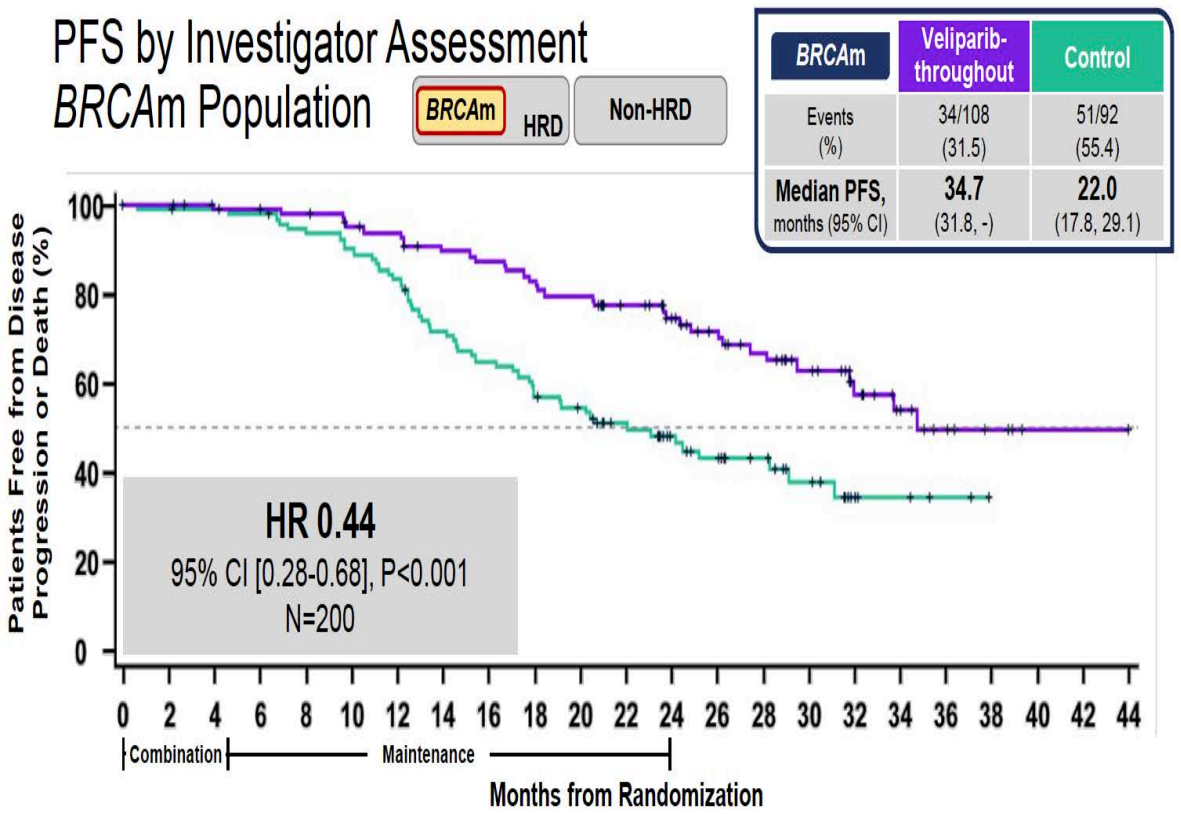
Coleman RL et al. *N Engl J Med* 2019;381:2403-15.

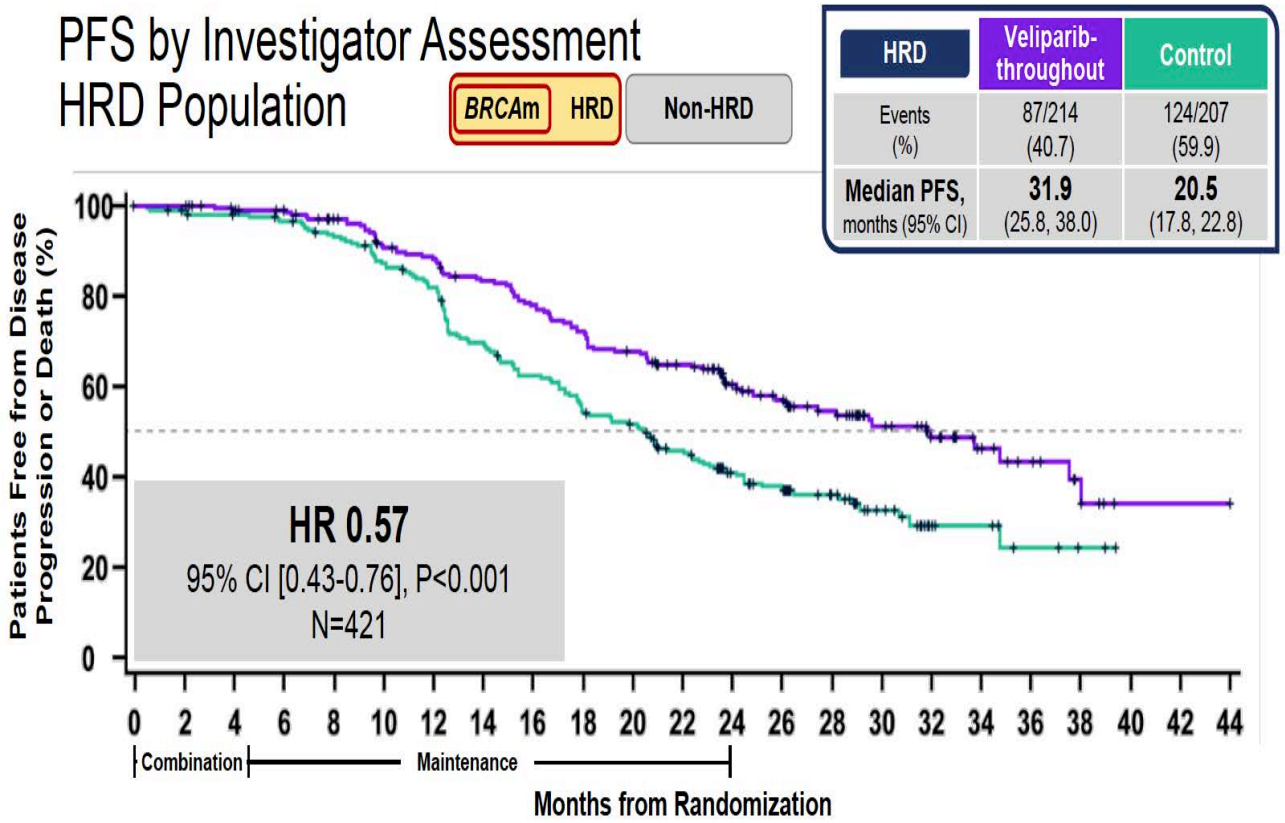
VELIA/GOG-3005: Integration of Veliparib with Front-Line Chemotherapy and Maintenance in Women with High-Grade Serous Carcinoma of Ovarian, Fallopian Tube, or Primary Peritoneal Origin

Coleman RL et al.

SGO 2020;Abstract 36.

VELIA/GOG-3005: PFS by BRCA and HRD Status



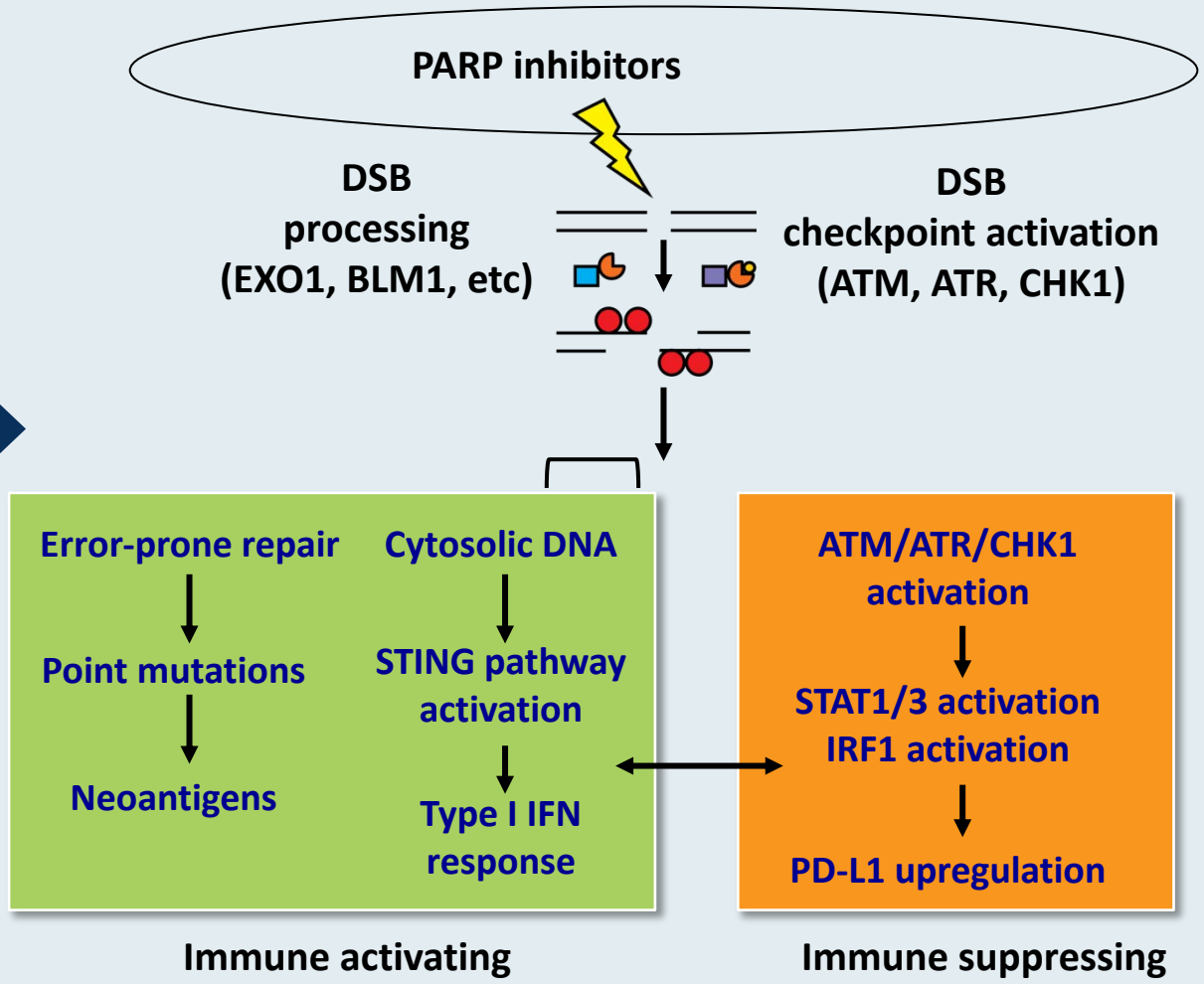


Coleman RL et al. SGO 2020;Abstract 36.

RTP RESEARCH TO PRACTICE

Biologic Rationale for the Combination of a PARP Inhibitor with an Immune Checkpoint Inhibitor

Preclinical models indicate synergy between PARPi + anti-PD-1 agents regardless of *BRCA* mutation status or PD-L1 status



Preclinical data demonstrate synergy with PARPi and anti-PD-1 combinations.

Konstantinopoulos P et al. ASCO 2018;Abstract 106.

Phase II Study of Olaparib (O) plus Durvalumab (D) and Bevacizumab (B) (MEDIOLA): Initial Results in Patients (pts) with Non-Germline BRCA-Mutated (Non-gBRCAm) Platinum Sensitive Relapsed (PSR) Ovarian Cancer (OC)

Drew Y et al.

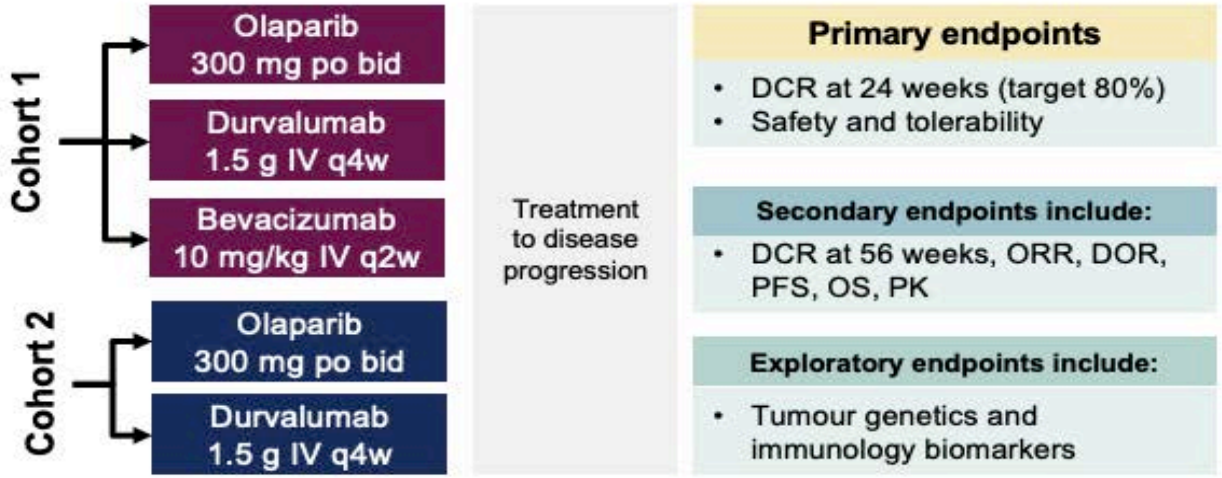
ESMO 2020;Abstract 814MO.

MEDIOLA: gBRCAwt Cohorts

Study Design

Patient population

- gBRCAwt
- PSR ovarian cancer
- ≤2 prior lines of chemotherapy
- PARP inhibitor and IO agent naïve

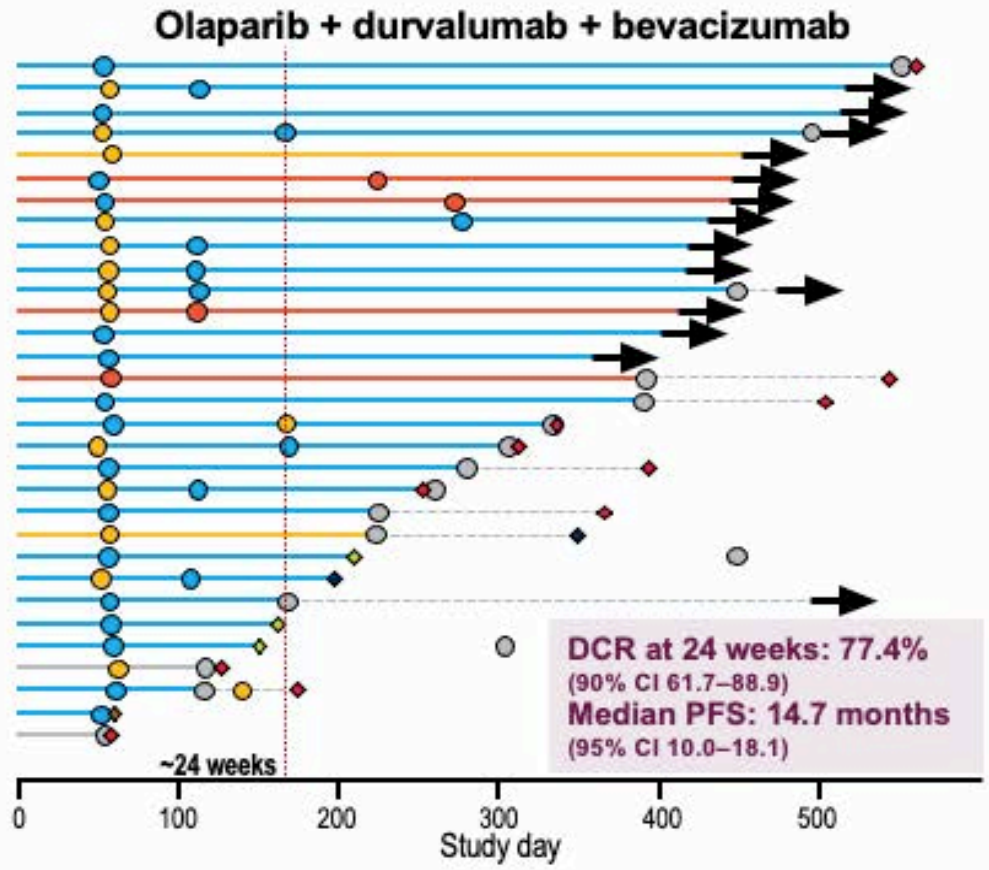


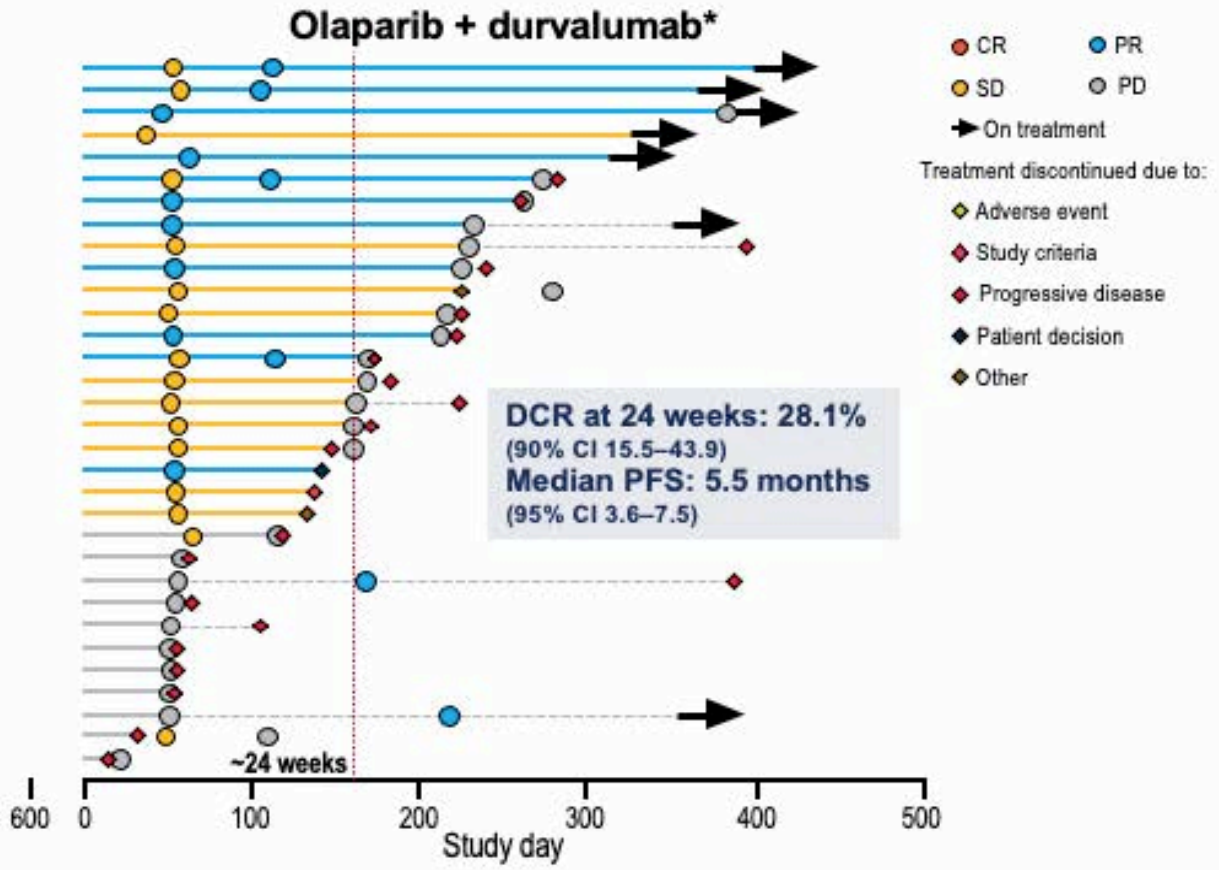
Patient Characteristics

	Olap + durva + bev (N=31)	Olap + durva (N=32)
Median age, years	64.0	68.5
Age group (years), n (%)		
<50	3 (9.7)	4 (12.5)
≥50–<65	14 (45.2)	8 (25.0)
≥65	14 (45.2)	20 (62.5)
Race, n (%)		
White	20 (64.5)	24 (75.0)
Asian	10 (32.3)	3 (9.4)
Other	1 (3.2)	5 (15.6)
Platinum sensitivity, n (%)		
>6–12 months	18 (58.1)	14 (43.8)
>12 months	13 (41.9)	18 (56.3)
Number of prior lines of chemotherapy, n (%)		
1 prior line	20 (64.5)	23 (71.9)
2 prior lines	11 (35.5)	9 (28.1)
Enrolment completed	January 2019	February 2019
Patients on study treatment at DCO, n (%) (13 February 2020)		
Olap; durva; bev	13 (41.9); 13 (41.9); 12 (38.7)	7 (21.9); 6 (18.8); NA

Drew Y et al. ESMO 2020;Abstract 814MO.

MEDIOLA: TTP or Treatment Discontinuation





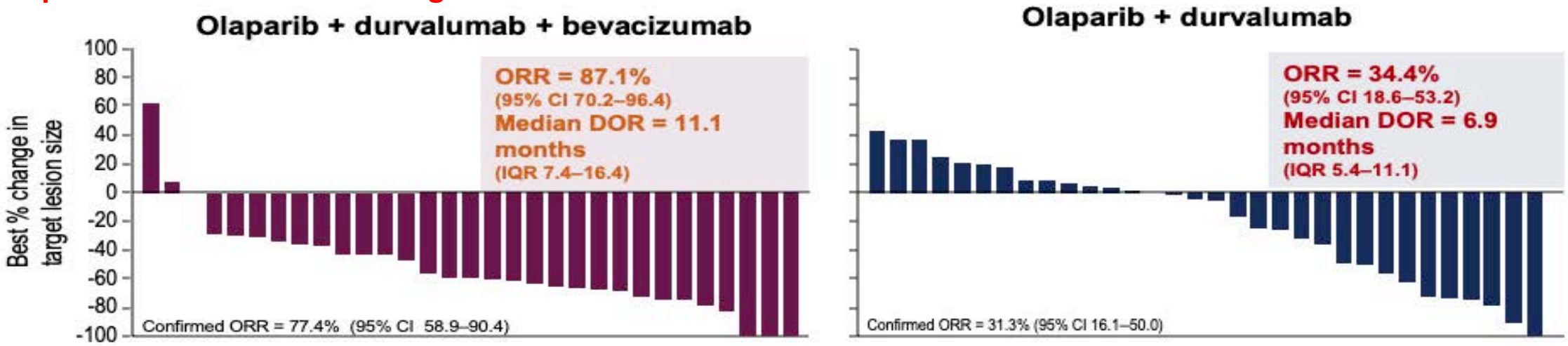
- **Triplet cohort showed high DCT at 24 weeks and a long median PFS**

Drew Y et al. ESMO 2020;Abstract 814MO.

RTP RESEARCH TO PRACTICE

MEDIOLA: Objective Response

Triplet cohort demonstrates high ORR



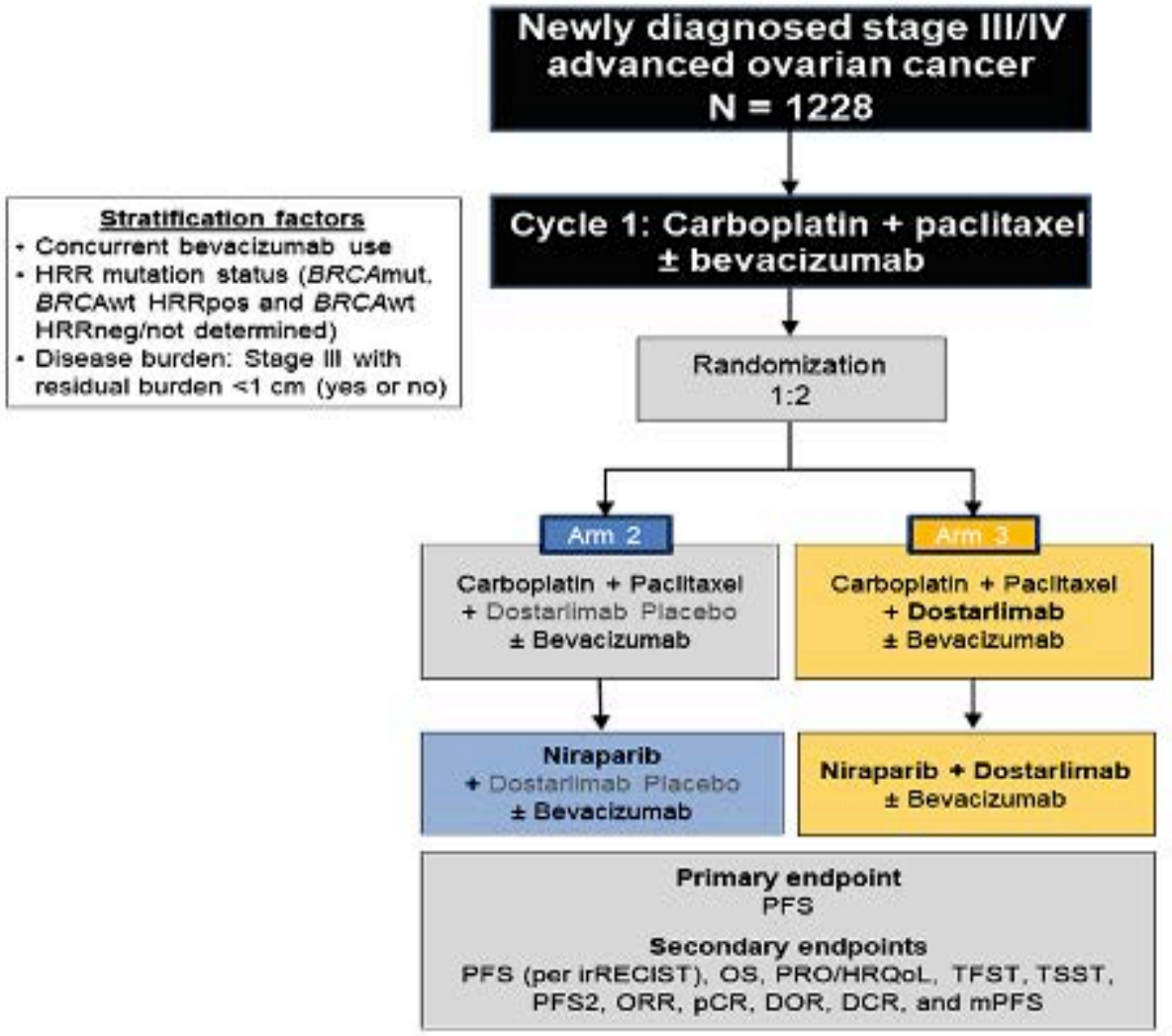
Genomic instability status* subgroup	Olaparib + durvalumab + bevacizumab		Olaparib + durvalumab	
	ORR (95% CI), %	n/N patients	ORR (95% CI), %	n/N patients
GIS-positive	100.0 (69.2–100.0)	10/10	50.0 (18.7–81.3)	5/10
GIS-negative	75.0 (34.9–96.8)	6/8	16.7 (0.4–64.1)	1/6
GIS-unknown	84.6 (54.6–98.1)	11/13	31.3 (11.0–58.7)	5/16

Exploratory analysis suggests that triplet cohort ORR is not GIS-dependent

Drew Y et al. ESMO 2020;Abstract 814MO.

RTP RESEARCH TO PRACTICE

Ongoing Phase III FIRST Trial of Dostarlimab (± Bevacizumab) in First-Line Ovarian Cancer



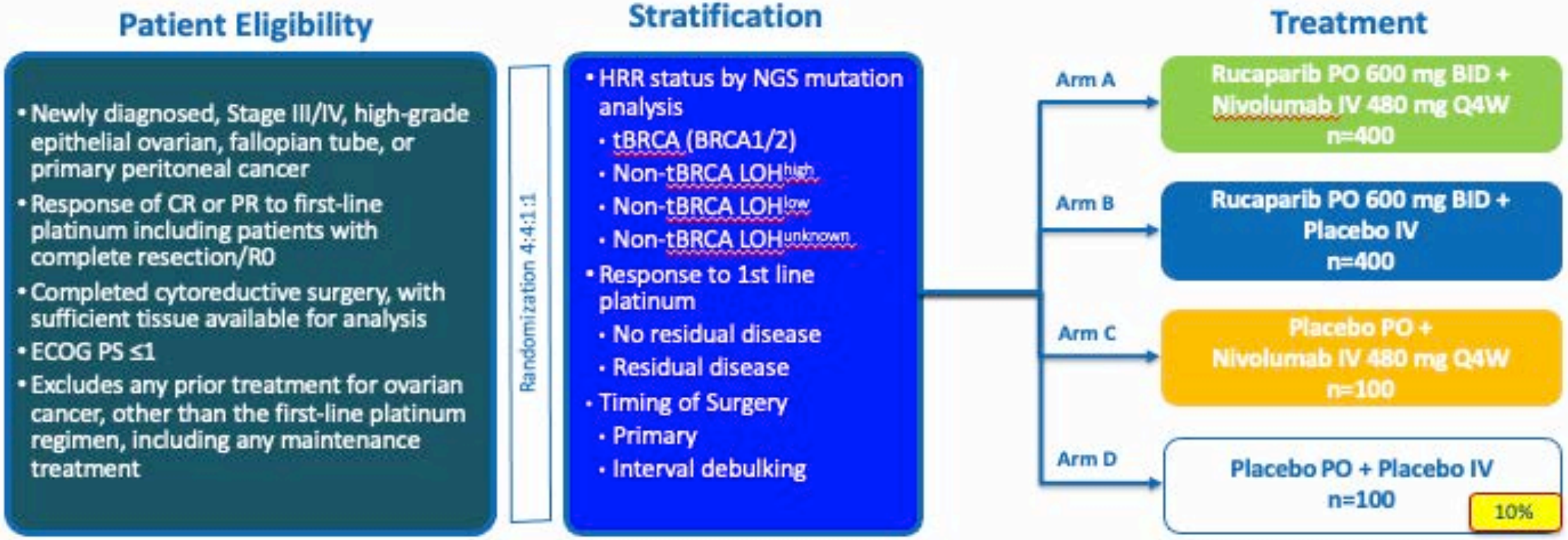
* As of 13th Dec 2019

Current Status

- Adaptive study design was selected to enable modifications
  - 2018: Arm 1 closed for *BRCA*mut patients post SOLO-1
  - 2019: Based on PRIMA data, amendment approved to drop Arm 1 (placebo) for *BRCA*wt patients

RTP RESEARCH TO PRACTICE

Ongoing Phase III ATHENA Trial of Rucaparib or Nivolumab Alone or in Combination in Newly Diagnosed Ovarian Cancer



Primary Endpoint

- PFS by Investigator in molecularly-defined HRD subgroups

Secondary Endpoints

- PFS by BICR in molecularly-defined HRD subgroups
- ORR and DOR in patients with measurable disease
- OS and Safety

Agenda

Module 1: MSI-High/dMMR or MSS Endometrial Cancer – Immunotherapy

- Dr Dandamudi: A 55-year-old woman with endometrial cancer
- Dr Malhotra: A 73-year-old woman with endometrial cancer

Module 2: Ovarian Cancer – PARP Inhibitors

- Dr Choksi: An 81-year-old woman with Stage IV ovarian cancer – BRCA2 mutation
- Dr Peles: A 59-year-old woman with ovarian cancer – BRCA1/2 wild type
- Dr Hart: A 46-year-old woman with ovarian cancer – BRCA1/2 wild type

Module 3: Relapsed/Refractory Cervical Cancer

- Dr Hart: A 41-year-old woman with recurrent cervical cancer – PD-L1-positive

Case Presentation – Dr Hart: A 41-year-old woman with recurrent cervical cancer – PD-L1-positive

Dr Lowell Hart

- Stage IIIC1 cervical cancer s/p radical hysterectomy, bilateral pelvic lymphadenopathy
- Adjuvant radiation therapy + cisplatin → NED x 20 months
- Recurrent disease, PD-L1-positive

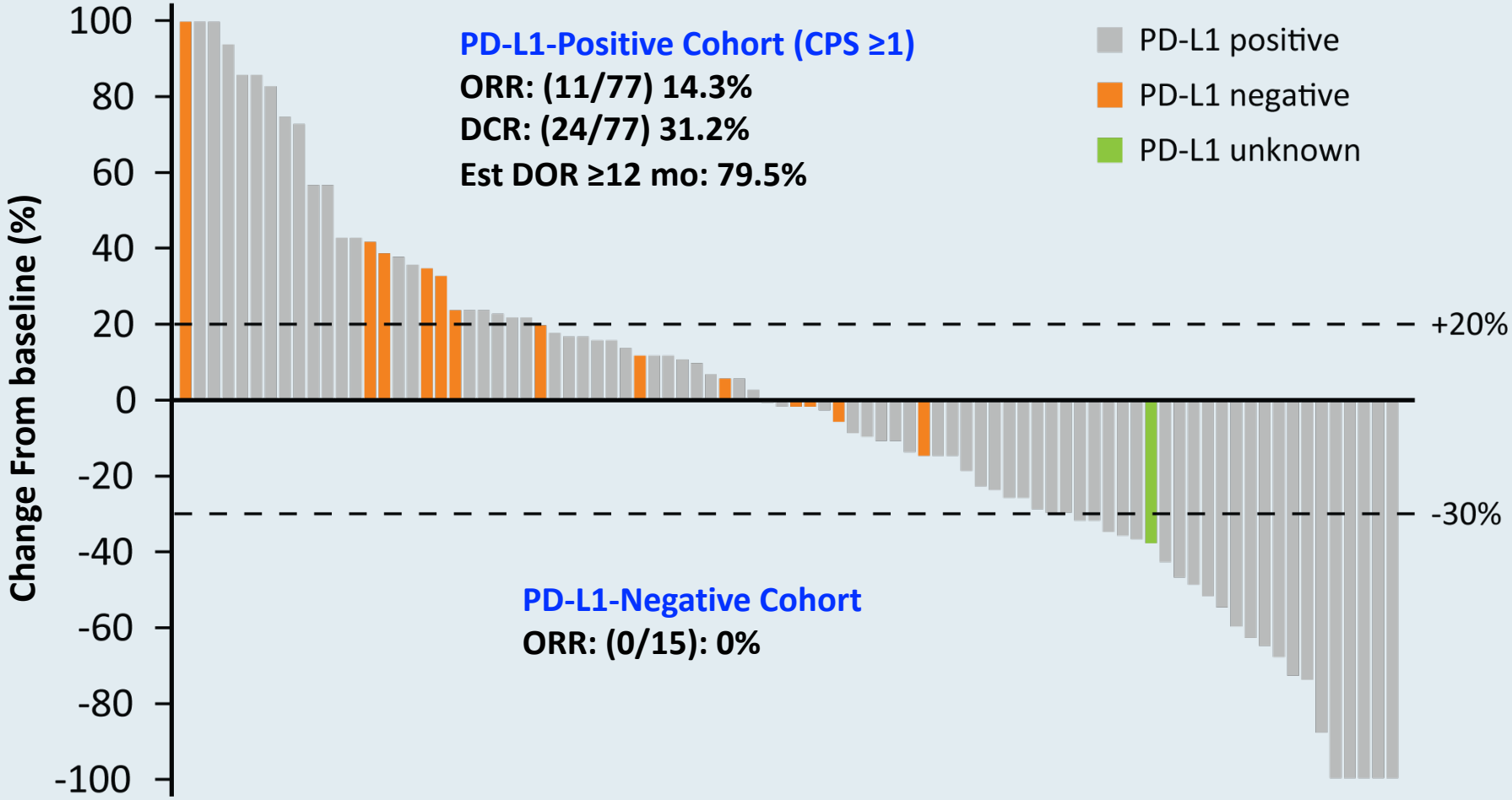
Questions

- Assuming that tisotumab vedotin receives FDA approval, where will it fit into the armamentarium for advanced and recurrent cervical cancer? Will it be used ahead of checkpoint inhibitors?
- In light of its unusual toxicities – notably the ocular toxicity – will that be an obstacle for its use in the second-line setting?

In general, assuming tisotumab vedotin were accessible, what would be your preferred second-line therapy for a patient with MSS metastatic cervical cancer who experiences symptomatic disease progression on carboplatin/paclitaxel/bevacizumab and has a PD-L1 CPS of 1%?

a. Other chemotherapy
b. Pembrolizumab
c. Tisotumab vedotin
d. Other

Phase II KEYNOTE-158: Pembrolizumab in Previously Treated Advanced Cervical Cancer

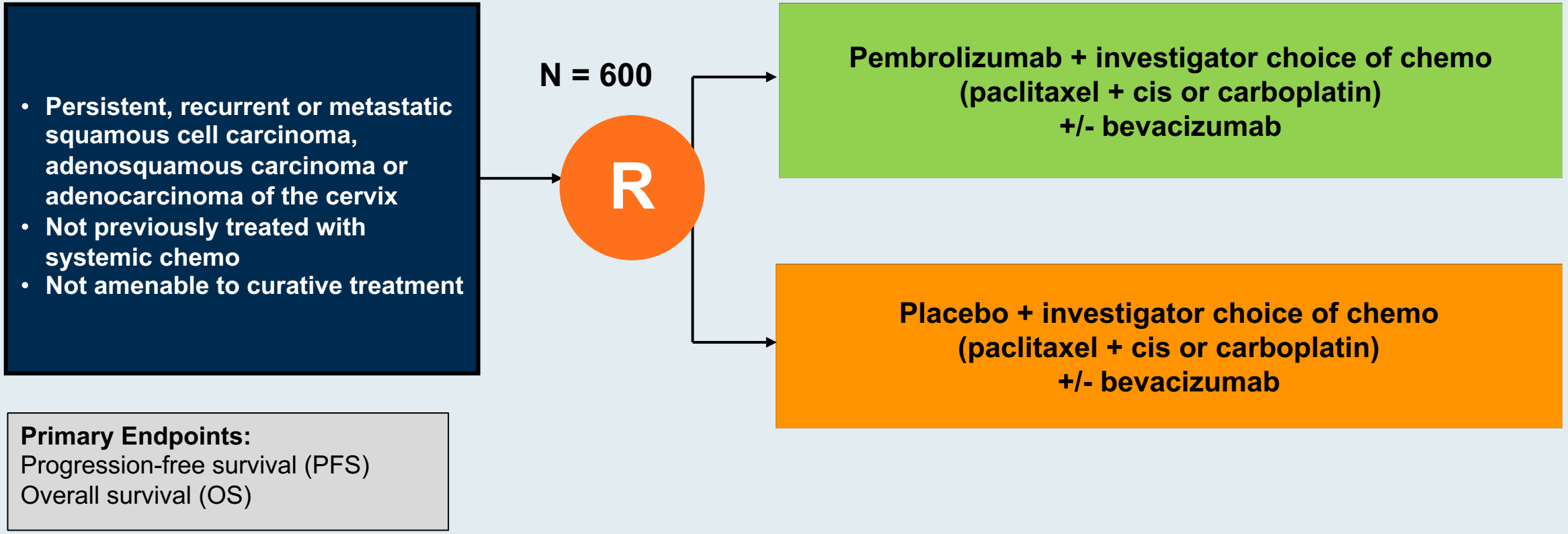


Combined Positive Score (CPS) = PD-L1+ cells (tumor cells, lymphocytes, macrophages) / Total number of tumor cells x 100

Chung HC et al. *J Clin Oncol* 2019;37:1470-8.

RTP RESEARCH TO PRACTICE

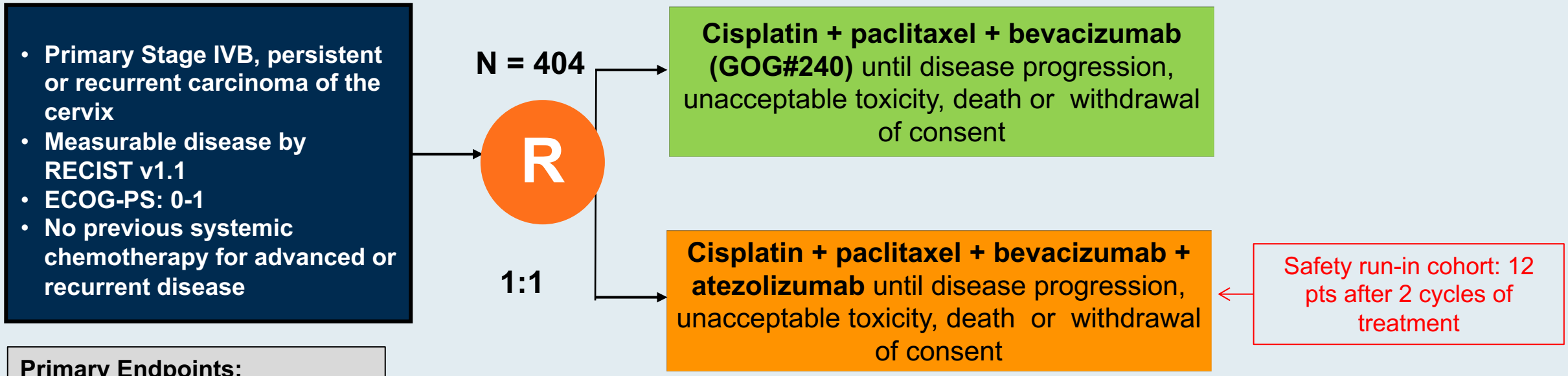
KEYNOTE-826 Phase III Schema



Primary Endpoints:
Progression-free survival (PFS)
Overall survival (OS)

ClinicalTrials.gov Identifier: NCT03635567, Accessed August 18, 2020

BEATcc Phase III Randomized Front-Line Trial of Atezolizumab



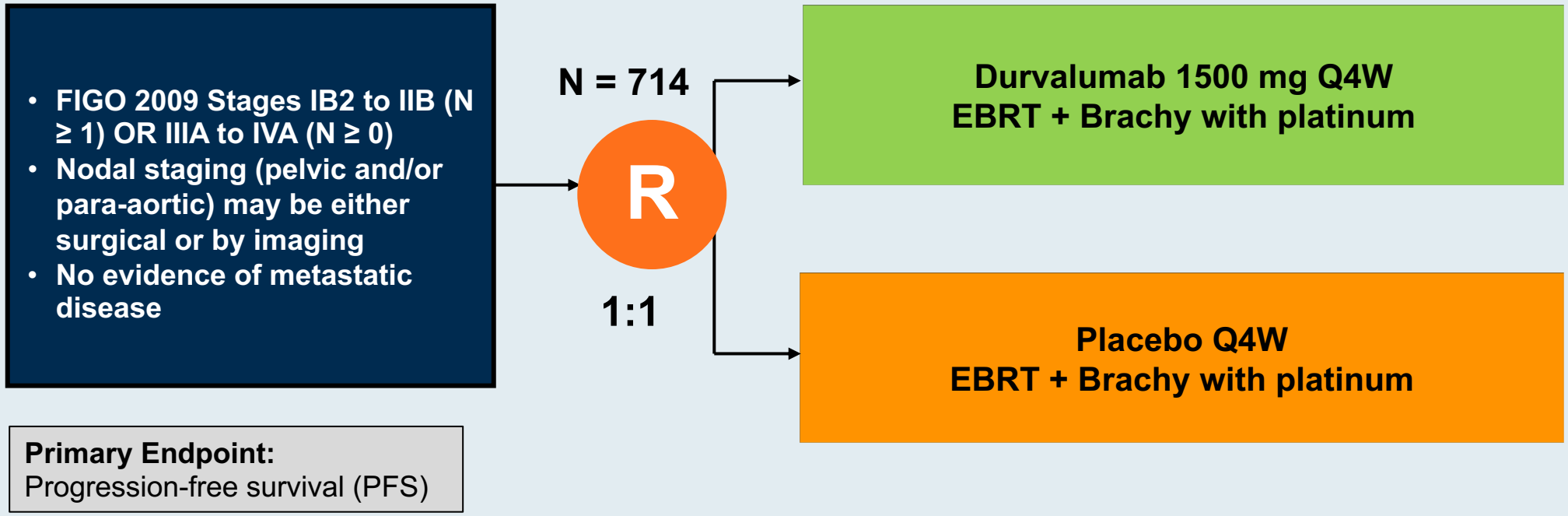
Primary Endpoints:
Overall survival (OS)
Secondary Endpoints:
- PFS
- ORR
- DOR
- Safety
- HR-QOL

Stratification Factors:
- Prior concurrent Cisplatin-RDT
- Histology: SCC vs ADK (including AdenoSquamous)
- Chemotherapy Backbone: Cisplatin vs Carboplatin

ClinicalTrials.gov Identifier: NCT03556839

Courtesy of Krishnansu S Tewari, MD

CALLA Phase III Schema

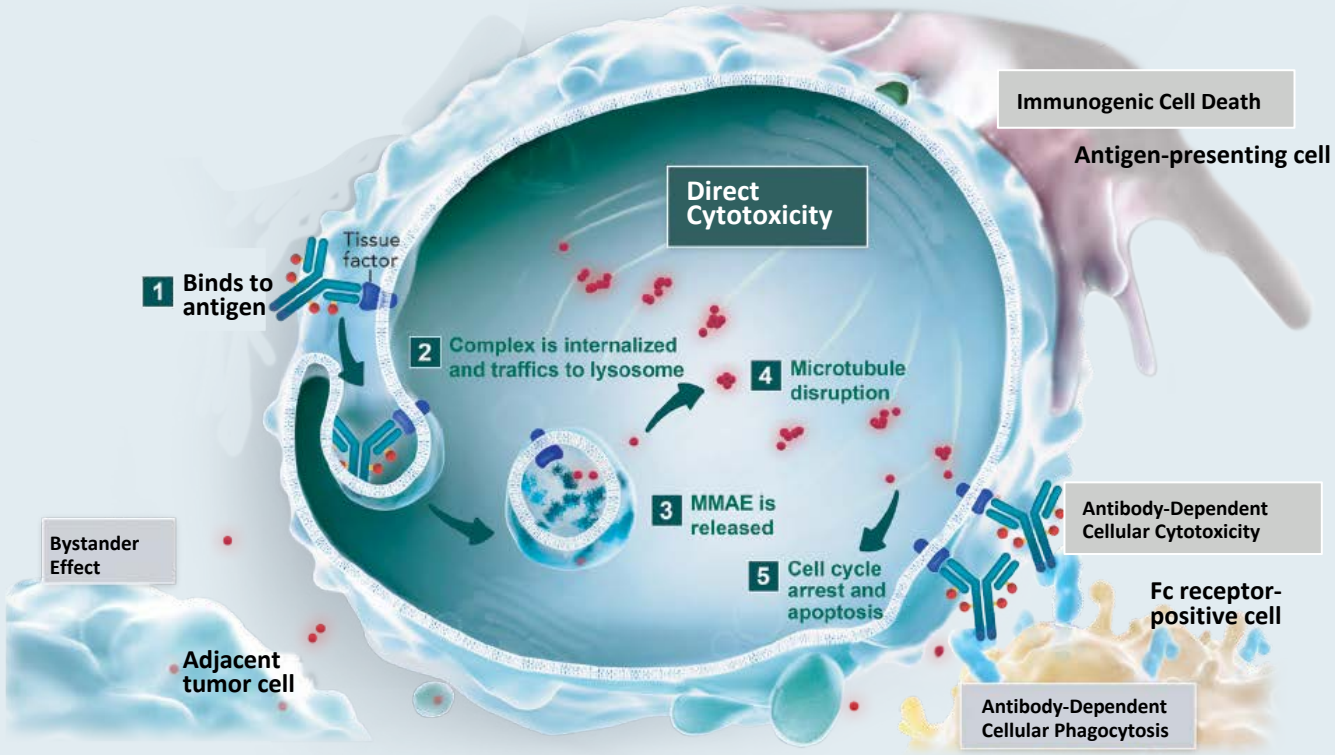


Primary Endpoint:
Progression-free survival (PFS)

Mayadev J et al. *Int J Gynecol Cancer* 2020;30:1065-1070.

Mechanism of Action of Tisotumab Vedotin

- Tissue factor (TF) is aberrantly expressed in a broad range of solid tumours, including cervical cancer,[1,2] and TF expression has been associated with higher tumour stage and grade, higher metastatic burden and poor prognosis[2]
- TF expression in cervical cancer makes TF a novel target for patients with cervical cancer
- ADC targets TF
  - Monoclonal Antibody targets TF
  - Payload: Microtubule disrupting MMAE
- Allowing for direct cytotoxicity and bystander killing, as well as antibody-dependent cellular cytotoxicity[3,4]

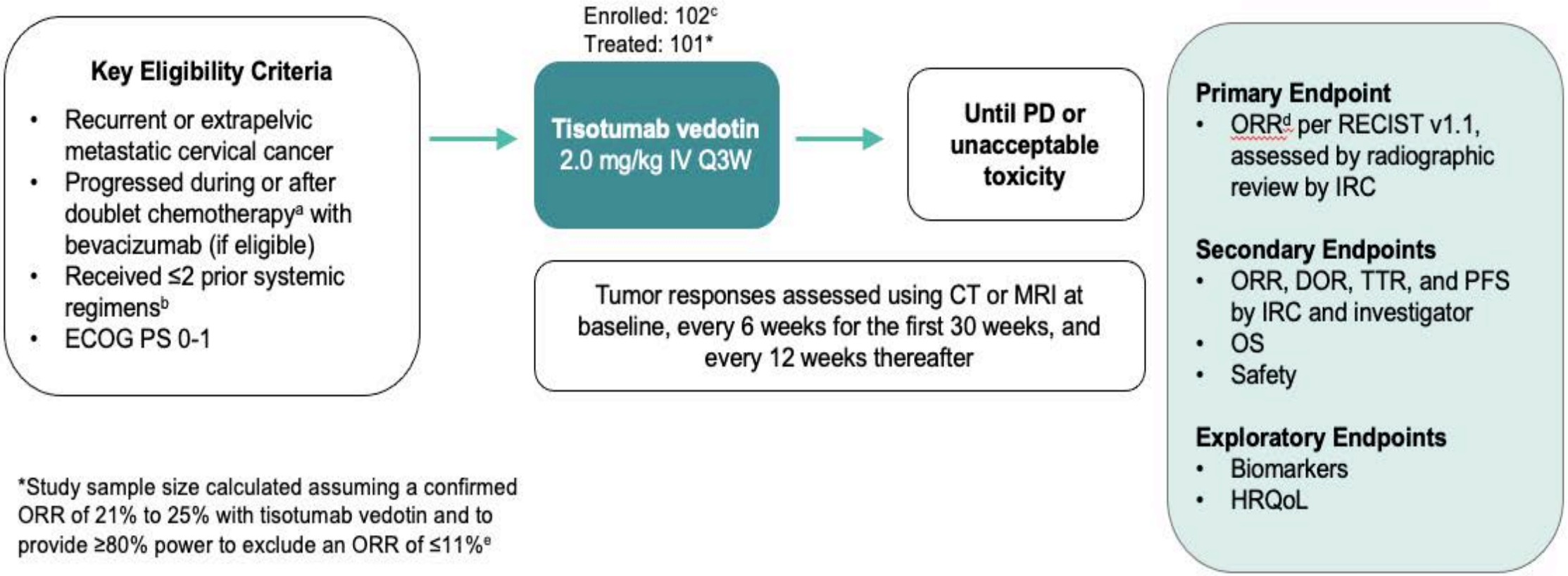


1. Förster Y et al. *Clin Chim Acta* 2006. 2. Cocco E et al. *BMC Cancer* 2011.
3. Breij EC et al. *Cancer Res* 2014. 4. De Goeij BE et al. *Mol Cancer Ther* 2015.

Courtesy of David M O'Malley, MD

RTP RESEARCH TO PRACTICE

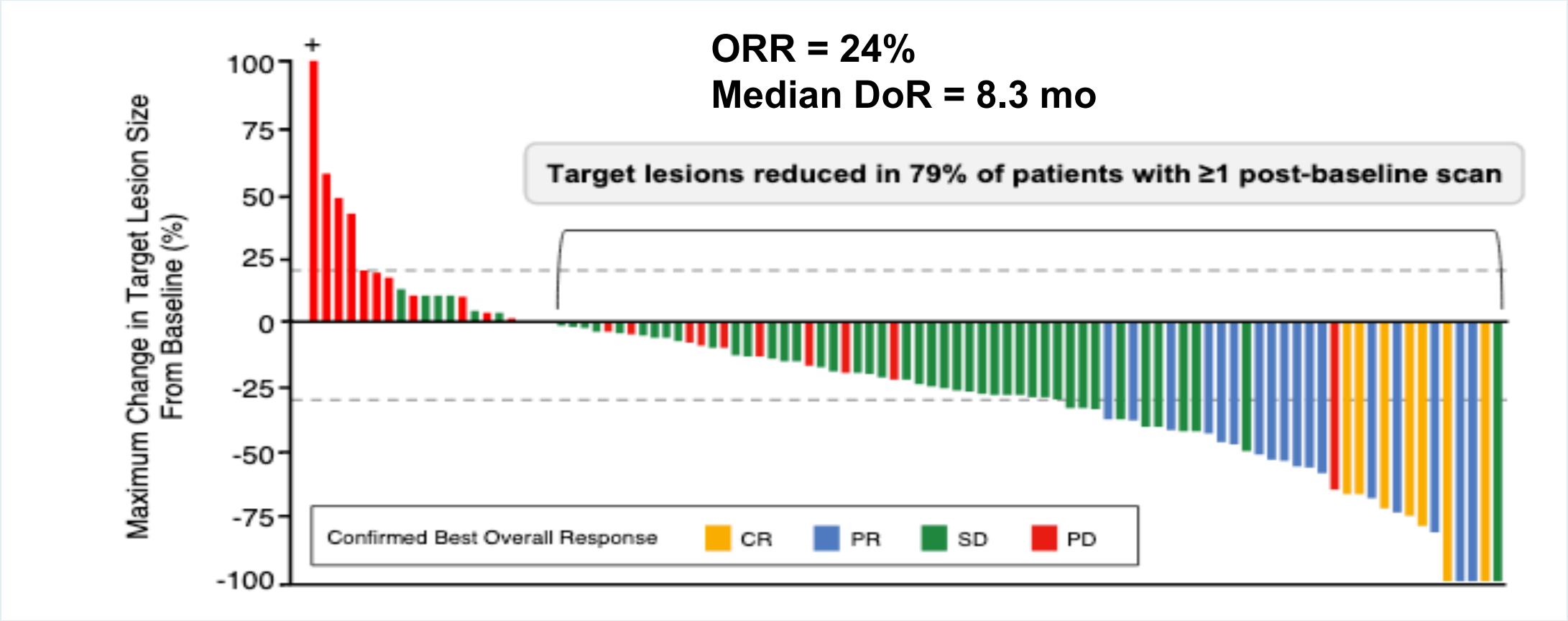
Phase II InnovaTV 204 Trial



[a]Paclitaxel plus platinum (cisplatin or carboplatin) or paclitaxel plus topotecan. [b]Adjuvant or neoadjuvant chemotherapy or if administered with radiation therapy, was not counted as a prior systemic regimen. [c]June 2018 to April 2019. [d]Responses were confirmed by subsequent repeat imaging performed ≥4 weeks after initial response assessment. [e]Using one-sided exact binomial test at 0.025 significance level.
CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IRC, independent review committee; IV, intravenous; MRI, magnetic resonance imaging; OS, overall survival; PD, progressive disease; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; TTR, time to response.

Coleman RL et al. ESMO 2020;Abstract LBA32.

InnovaTV 204: Antitumor Activity and Survival by IRC Assessment

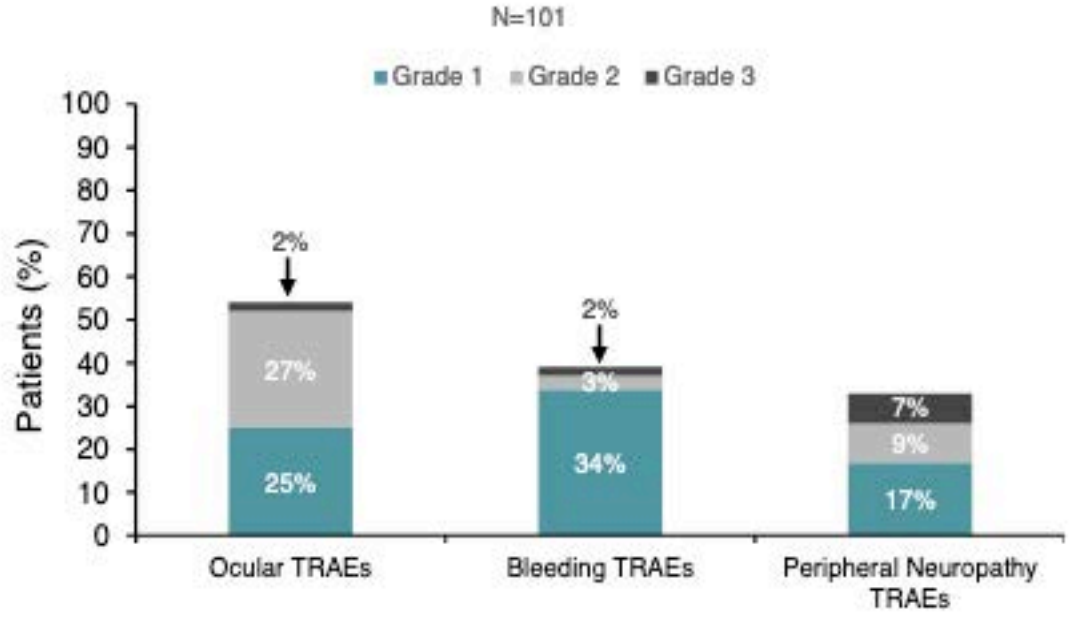


- Median Time to Response = 1.4 mo
- Median PFS = 4.2 mo
- Median OS = 12.1 mo
- Response to tisotumab vedotin was observed regardless of membrane TF expression level

Coleman RL et al. ESMO 2020;Abstract LBA32.

InnovaTV 204: Prespecified AEs of Interest

Ocular, bleeding, and peripheral neuropathy TRAEs



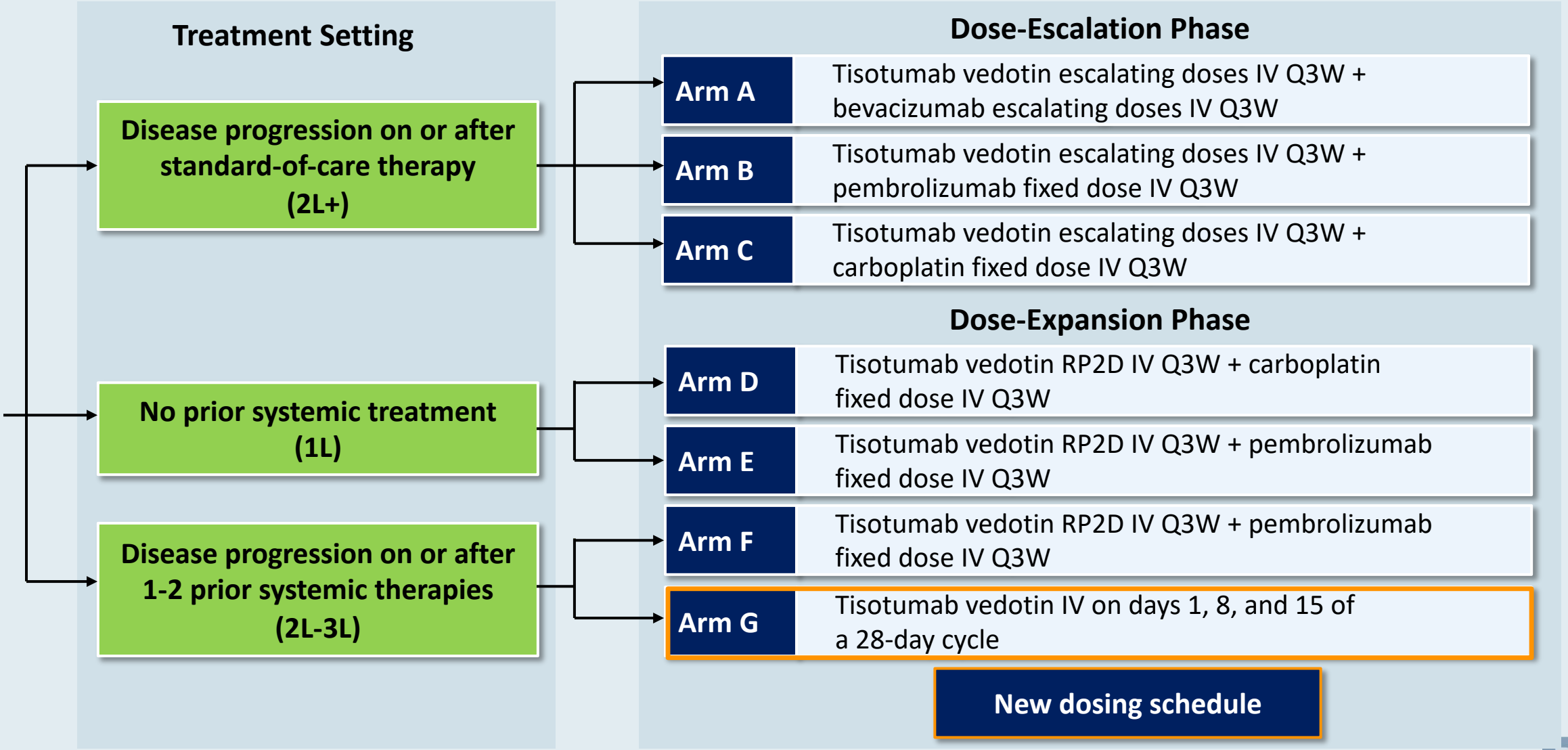
	Ocular	Bleeding	Peripheral Neuropathy
Time to onset (median, months)	1.4	0.3	3.1
Events resolved, %	86	90	21
Time to resolution (median, months)	0.7	0.5	0.6

- **Ocular AEs were mostly mild to moderate, resolved, and were manageable with an eye care plan**
- **Most bleeding events were grade 1 epistaxis (28%) of which majority resolved**
- **Most peripheral neuropathy events (known MMAE-related toxicity) were grade 1 and manageable with dose modifications; resolution was limited by follow-up period**

Coleman RL et al. ESMO 2020;Abstract LBA32.

RTP RESEARCH TO PRACTICE

InnovaTV 205 (GOG 3024): Recurrent or Metastatic Cervical Cancer



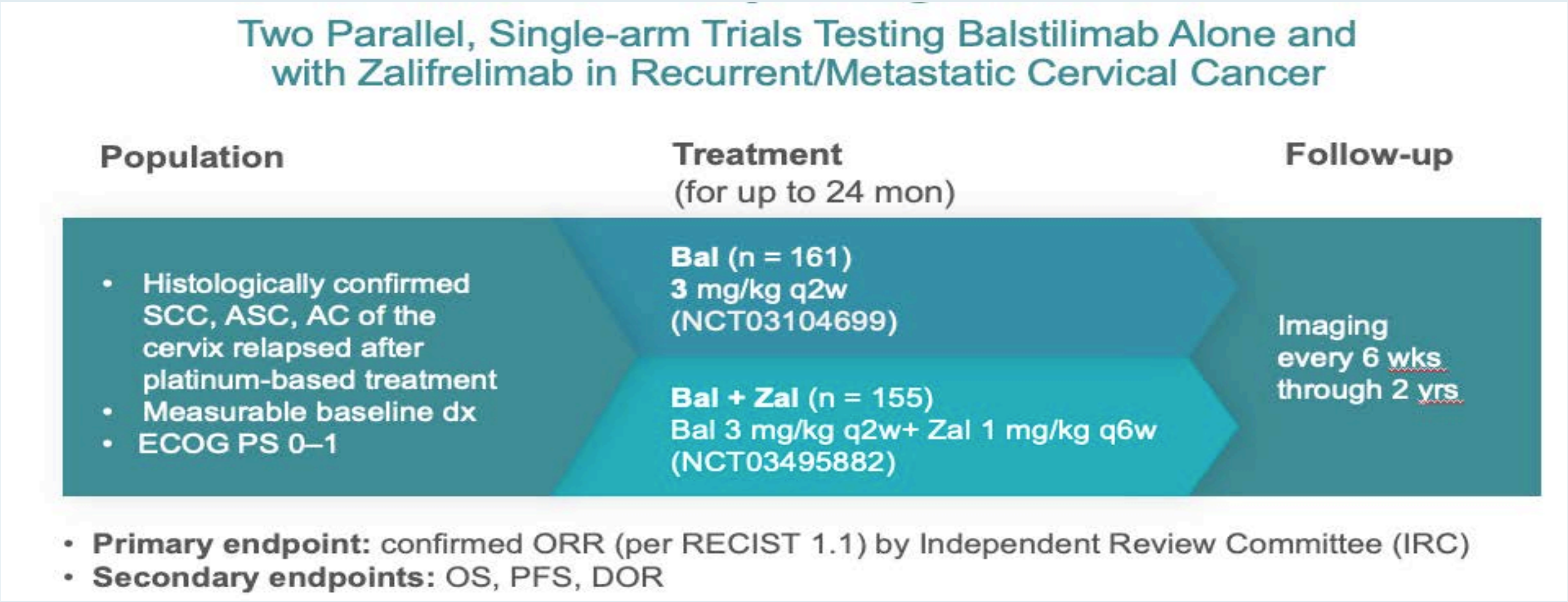
Courtesy of David M O'Malley, MD

Balstilimab (Anti-PD-1) Alone and in Combination with Zalifrelimab (Anti-CTLA-4) for Recurrent/Metastatic (R/M) Cervical Cancer (CC) Preliminary Results of Two Independent Ph2 Trials (NCT03104699 and NCT03495882)

O'Malley DM al.

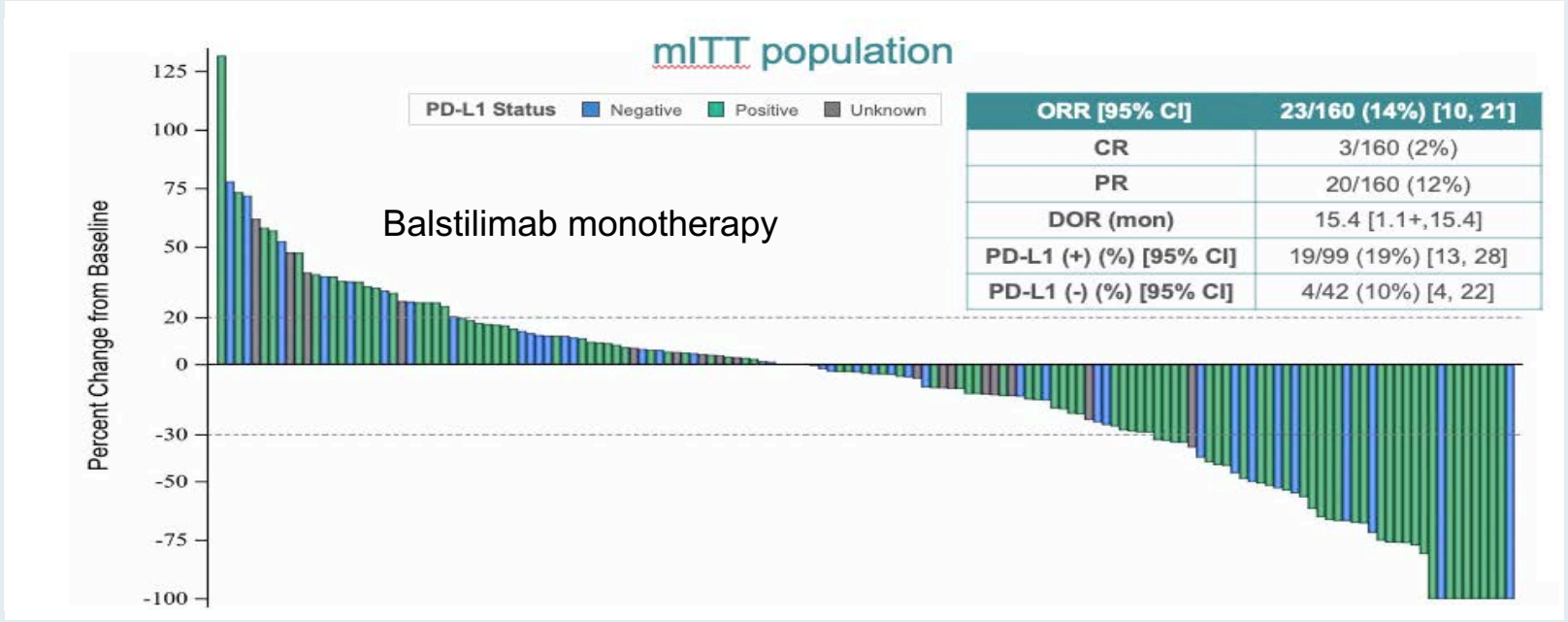
ESMO 2020;Abstract 5401.

Phase II Trial of Balstilimab with or without Zalifrelimab: Study Design



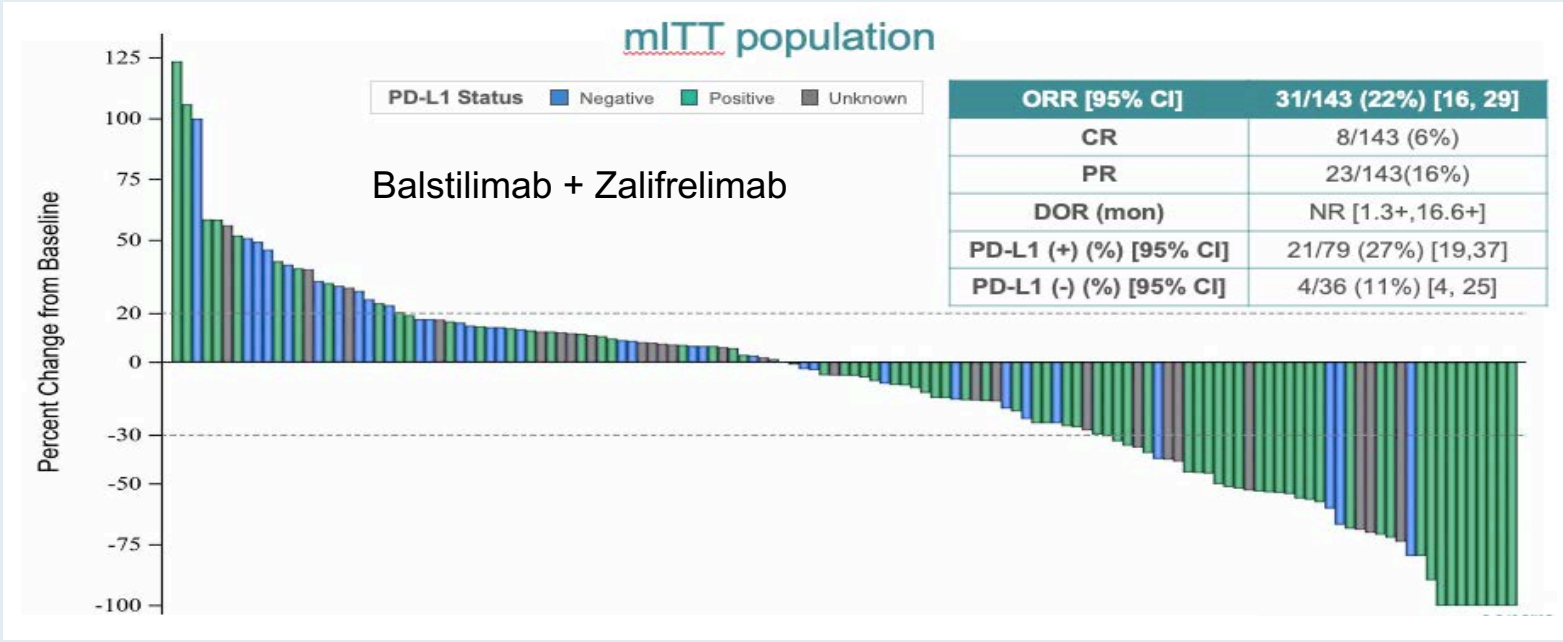
O'Malley DM et al. ESMO 2020;Abstract 5401.

Balstilimab with or without Zalifrelimab: Tumor Response



Balstilimab monotherapy

ORR [95% CI]	23/160 (14%) [10, 21]
CR	3/160 (2%)
PR	20/160 (12%)
DOR (mon)	15.4 [1.1+,15.4]
PD-L1 (+) (%) [95% CI]	19/99 (19%) [13, 28]
PD-L1 (-) (%) [95% CI]	4/42 (10%) [4, 22]



Balstilimab + Zalifrelimab

ORR [95% CI]	31/143 (22%) [16, 29]
CR	8/143 (6%)
PR	23/143(16%)
DOR (mon)	NR [1.3+,16.6+]
PD-L1 (+) (%) [95% CI]	21/79 (27%) [19,37]
PD-L1 (-) (%) [95% CI]	4/36 (11%) [4, 25]

O'Malley DM et al. ESMO 2020;Abstract 5401.

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Balstilimab with or without Zalifrelimab: Adverse Events

	Bal (n=161)		Bal/Zal (n=155)	
	Any Grade	3 and above	Any Grade	3 and above
Gastrointestinal	41 (25.5)	6 (3.7)	37 (23.9)	7 (4.5)
General disorder and administration site condition	54 (33.5)	1 (0.6)	36 (23.2)	2 (1.3)
Blood and lymphatic system disorder	23 (14.3)	3 (1.9)	15 (9.7)	5 (3.2)
Musculoskeletal and connective tissue disorder	21 (13.0)	0 (0.0)	10 (6.5)	0 (0.0)
Metabolism and nutrition	18 (11.2)	2 (1.2)	10 (6.5)	1 (0.6)
Laboratory Abnormalities	20(12.4)	4(2.5)	30 (19.4)	12 (7.7)
Respiratory, Thoracic and mediastinal disorder	13 (8.1)	1 (0.6)	9 (5.8)	1 (0.6)
Skin and subcutaneous tissue disorder	22 (13.7)	1 (0.6)	22 (14.2)	3 (1.9)
Endocrine disorders	15 (9.3)	0 (0.0)	32 (20.6)	1 (0.6)
Nervous system disorders	7 (4.3)	1 (0.6)	8 (5.2)	0 (0.0)

O'Malley DM et al. ESMO 2020;Abstract 5401.

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 Hope Rugo and Sara Tolaney
discuss the management of breast cancer

RTP
RESEARCH
TO PRACTICE

Current Concepts and Recent Advances in Oncology

A Daylong Clinical Summit Hosted in Partnership with Florida Cancer Specialists

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

Faculty

Arjun Balar, MD
Johanna Bendell, MD
Axel Grothey, MD
Brad S Kahl, MD
Shaji K Kumar, MD
Kathleen Moore, MD
Loretta Nastoupil, MD
William K Oh, MD
David M O'Malley, MD
Robert Z Orlowski, MD, PhD
Gregory J Riely, MD, PhD
Hope S Rugo, MD
David R Spigel, MD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

RTP
RESEARCH TO PRACTICE

Agenda

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

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

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

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

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

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

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

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Breast Cancer Faculty

Hope S Rugo, MD
Professor of Medicine
Director
Breast Oncology and Clinical Trials Education
University of California, San Francisco
Helen Diller Family Comprehensive
Cancer Center
San Francisco, California

Sara M Tolaney, MD, MPH
Associate Director
Susan F Smith Center for Women's Cancers
Director of Clinical Trials, Breast Oncology
Director of Breast Immunotherapy Clinical Research
Senior Physician
Breast Oncology Program
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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Dr Rugo — Disclosures

Consulting Agreements	Puma Biotechnology Inc, Samsung Bioepis
Contracted Research	Daiichi Sankyo Inc, Eisai Inc, Genentech, a member of the Roche Group, Immunomedics Inc, Lilly, MacroGenics Inc, Merck, Novartis, OBI Pharma Inc, Odonate Therapeutics, Pfizer Inc, Seagen Inc
Paid Travel	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, MacroGenics Inc, Merck, Mylan NV, Novartis, Pfizer Inc

Dr Tolaney — Disclosures

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Athenex, Bristol-Myers Squibb Company, Celldex Therapeutics, Eisai Inc, G1 Therapeutics, Genentech, a member of the Roche Group, Immunomedics Inc, Lilly, Merck, NanoString Technologies, Nektar, Novartis, Odonate Therapeutics, OncoPep, Paxman, Pfizer Inc, Puma Biotechnology Inc, Sanofi Genzyme, Seagen Inc, Silverback Therapeutics
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Cyclacel Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group, Immunomedics Inc, Lilly, Merck, NanoString Technologies, Nektar, Novartis, Odonate Therapeutics, Pfizer Inc, Sanofi Genzyme, Seagen Inc

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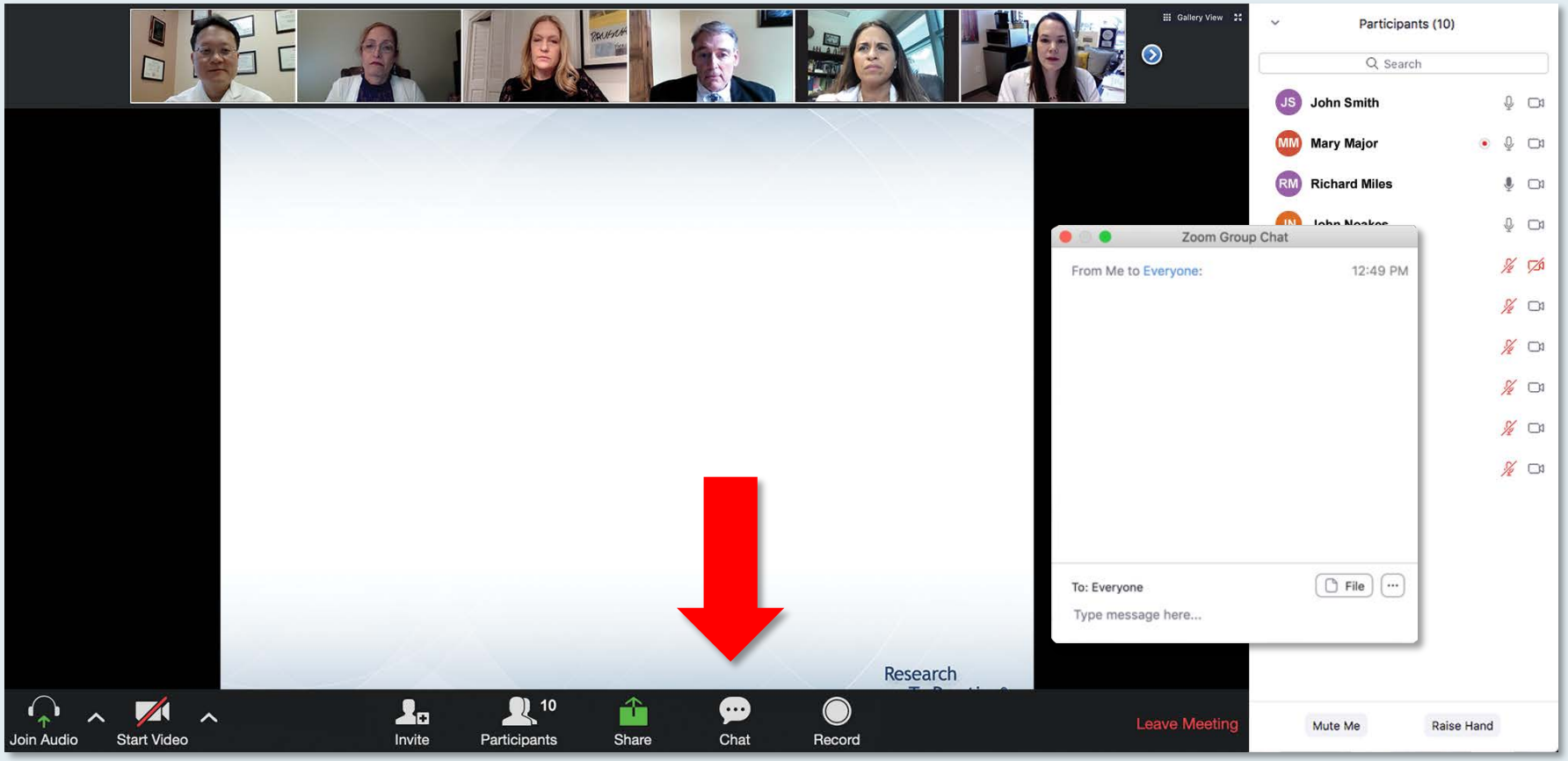
TO PRACTICE

We Encourage Clinicians in Practice to Submit Questions



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

RTP RESEARCH TO PRACTICE

FCS Contributing Oncologists

Mamta Choksi, MD
New Port Richey, Florida

Uday Dandamudi, MD
New Port Richey, Florida

Lowell L Hart, MD
Fort Myers, Florida

Maen Hussein, MD
Tavares, Florida

Zanetta S Lamar, MD
Naples, Florida

Vikas Malhotra, MD
Spring Hill, Florida

Shachar Peles, MD
Lake Worth, Florida

Syed F Zafar, MD
Fort Myers, Florida

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TO PRACTICE

Agenda

Module 1: HER2-Positive Breast Cancer

- Dr Hussein: A 29-year-old woman in need of third-line therapy for ER-positive, HER2-positive mBC
- Dr Malhotra: A 67-year-old woman with Stage IA ER-positive, HER2-positive IDC

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

- Dr Hussein: A 60-year-old woman with recurrent ER/PR-positive, HER2-negative mBC – PIK3CA mutation
- Dr Dandamudi: A 55-year-old woman with ER-positive, HER2-negative mBC

Module 3: Triple-Negative Breast Cancer (TNBC)

- Dr Hussein: A 44-year-old woman with mTNBC and a BRCA mutation
- Dr Choksi: A 67-year-old woman with past history of TNBC develops ER/PR-positive, HER2-positive BC

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Case Presentation – Dr Hussein: A 29-year-old woman in need of third-line therapy for ER-positive, HER2-positive mBC

Dr Maen Hussein

- Stage IV IDC, ER/PR-positive, HER2-positive
- Heterozygous BRCA2 mutation
- 5/2018 – 9/2019: Pertuzumab/trastuzumab/docetaxel → PD in liver, bone and brain
- Brain radiation
- 11/2019 – 8/2020 T-DM1 → PD
- Plan to administer trastuzumab deruxtecan

Questions

- What third-line therapy would you recommend for this patient that will prolong her survival and allow her to have quality of life?
- With trastuzumab deruxtecan therapy, should I be concerned about potential development of pneumonitis in this patient? How do you manage pneumonitis associated with this agent?

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Case Presentation – Dr Malhotra: A 67-year-old woman with Stage IA ER-positive, HER2-positive IDC

Dr Vikas Malhotra

- Presented with 1-cm left breast abnormality on mammogram; biopsy confirmed IDC
  - ER/PR-positive, HER2-positive; CT scan negative for metastases
- Patient refuses to undergo chemotherapy; favors natural therapy approaches
- Lumpectomy and LN sampling → Stage IA (T1c N0 M0)
- Refused recommended adjuvant chemotherapy with pertuzumab/trastuzumab
  - Agreed to trastuzumab and anastrozole, and completed post-operative radiation
- Currently completing 1 year of trastuzumab and is NED

Questions

- In this setting of a patient with a 1-cm tumor, would you consider neoadjuvant chemotherapy combined with trastuzumab/pertuzumab or would you recommend surgery first followed by adjuvant therapy? What are the data in support of each of these approaches?

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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 significant residual disease in the breast and axilla. Regulatory and reimbursement issues aside, what adjuvant anti-HER2 therapy would you recommend?

a. Trastuzumab
b. Trastuzumab/pertuzumab
c. T-DM1
d. Trastuzumab → neratinib
e. Trastuzumab/pertuzumab → neratinib
f. T-DM1 → neratinib
g. Other

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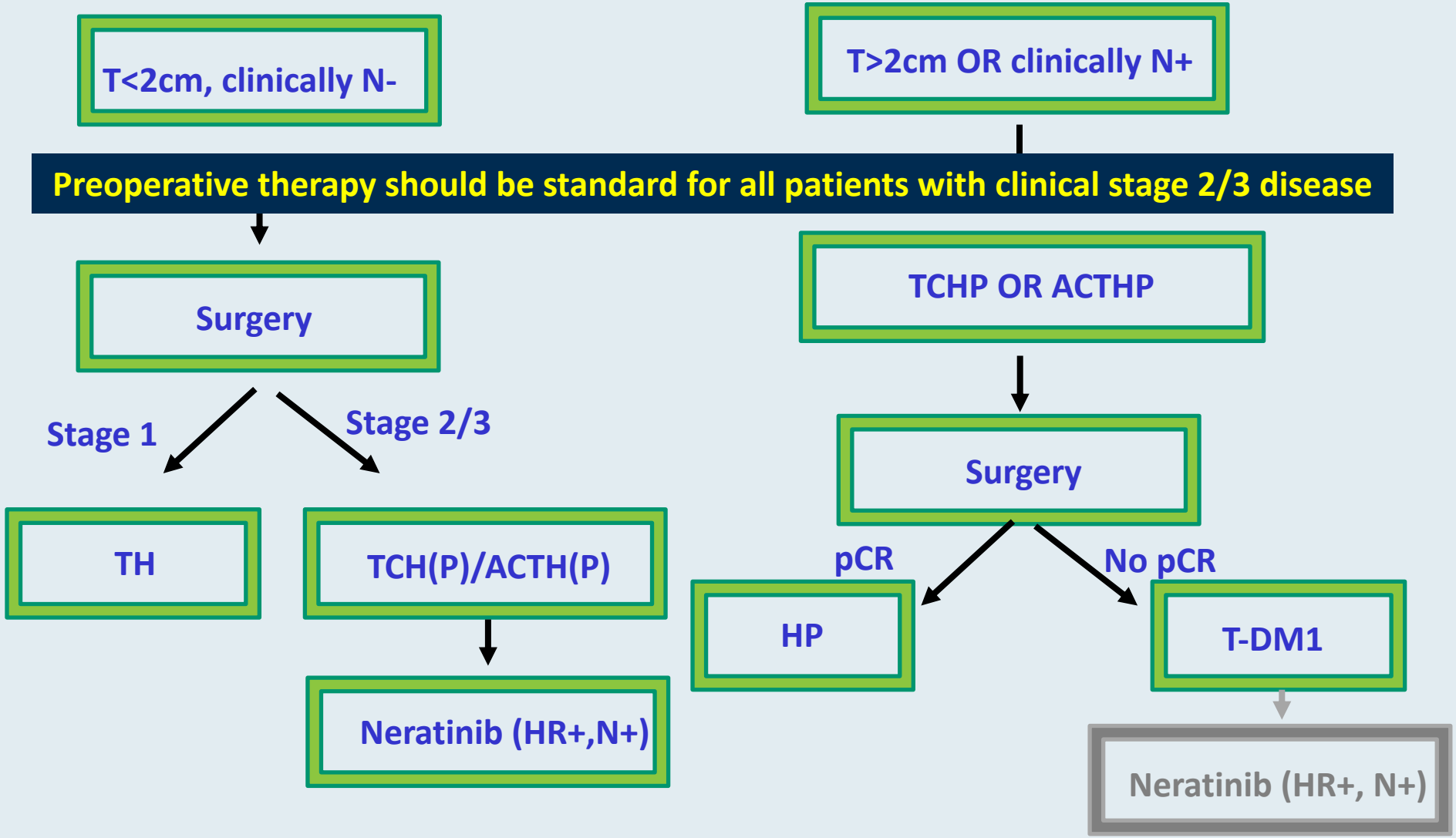
A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line THP and second-line T-DM1 but then experiences disease progression, including multiple brain metastases. What systemic treatment would you most likely recommend next?

a. Trastuzumab/lapatinib
b. Neratinib/capecitabine (cape)
c. Tucatinib/trastuzumab/cape
d. Trastuzumab deruxtecan
e. Other

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



Courtesy of Sara M Tolaney, MD, MPH

Final Efficacy Results of the ExteNET trial

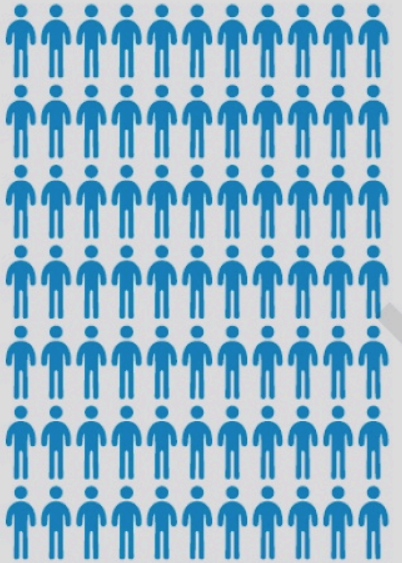
Neratinib for Early-Stage HER2-Positive Breast Cancer

International, Randomized, Phase 3 ExteNET Trial

Intention-to-treat population

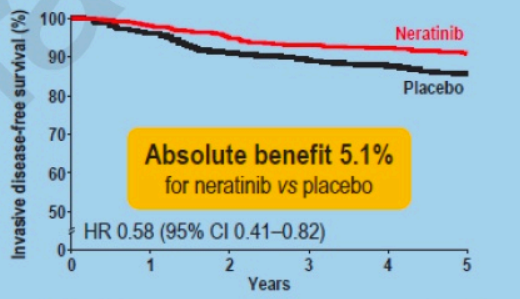
2840 patients

HER2+ early-stage breast cancer after prior trastuzumab

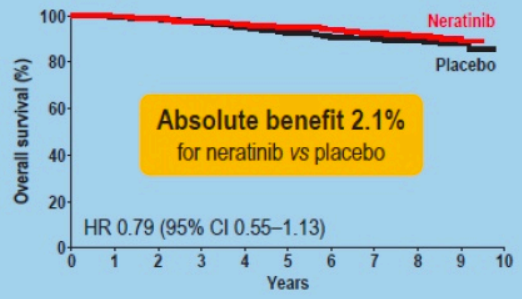


*According to labelling in the European Union and other countries

Invasive disease-free survival
5 years' follow-up



Overall survival
8 years' follow-up



HER2+/HR+ early-stage breast cancer within 1 year of prior trastuzumab*

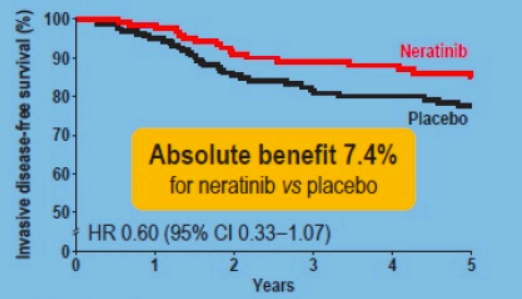
1334 patients

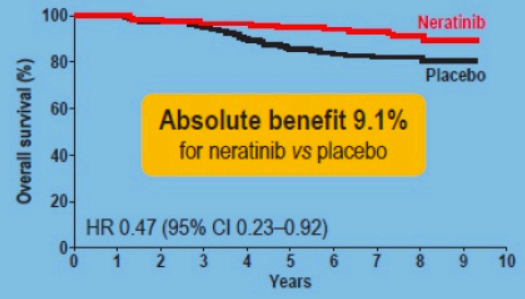
HER2+/HR+ early-stage breast cancer within 1 year of prior trastuzumab

Patients with residual disease after neoadjuvant therapy

295 patients

HER2+/HR+ early-stage breast cancer within 1 year of prior trastuzumab with residual disease after neoadjuvant therapy





Chan A et al. *Clin Breast Cancer* 2020;[Online ahead of print].

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

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

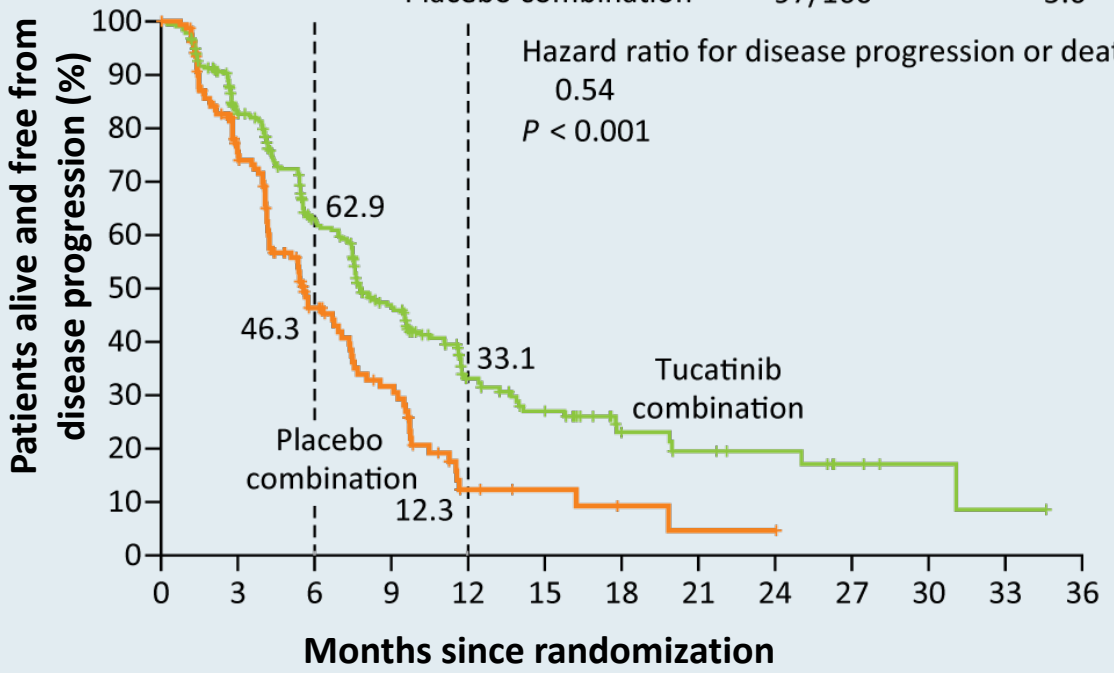
HER2CLIMB: Survival Outcomes

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)

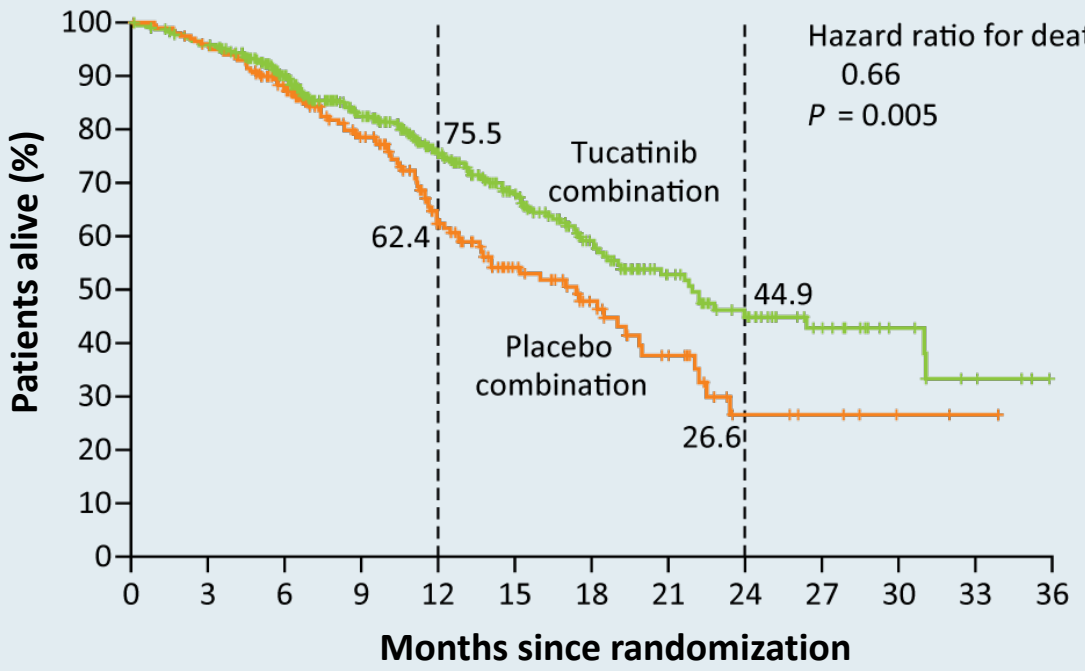
PFS

	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.

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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

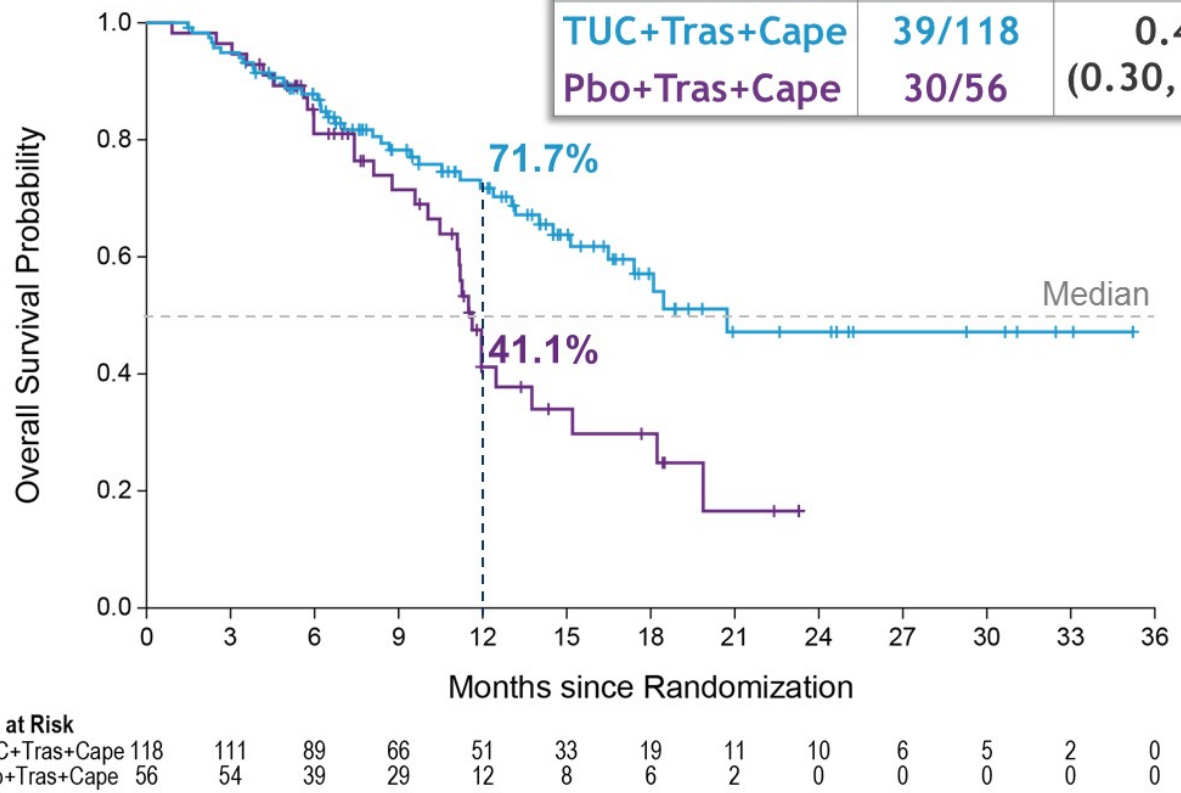
Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial

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):2610-19.

OS Benefit in Patients with Active Brain Metastases

	Events N=174	HR (95% CI)	P Value
TUC+Tras+Cape	39/118	0.49 (0.30, 0.80)	0.004
Pbo+Tras+Cape	30/56		



No. at Risk

TUC+Tras+Cape	118	111	89	66	51	33	19	11	10	6	5	2	0
Pbo+Tras+Cape	56	54	39	29	12	8	6	2	0	0	0	0	0

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

Risk of death was reduced by 51% in patients with active brain metastases

One-year OS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
71.7% (61.4, 79.7)	41.1% (25.5, 56.1)
Median OS (95% CI):	
20.7 months (15.1, NE)	11.6 months (10.5, 13.8)

NE: not estimable

Lin NU et al. *J Clin Oncol* 2020;38(23):2610-19.

Courtesy of Ian E Krop, MD, PhD

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

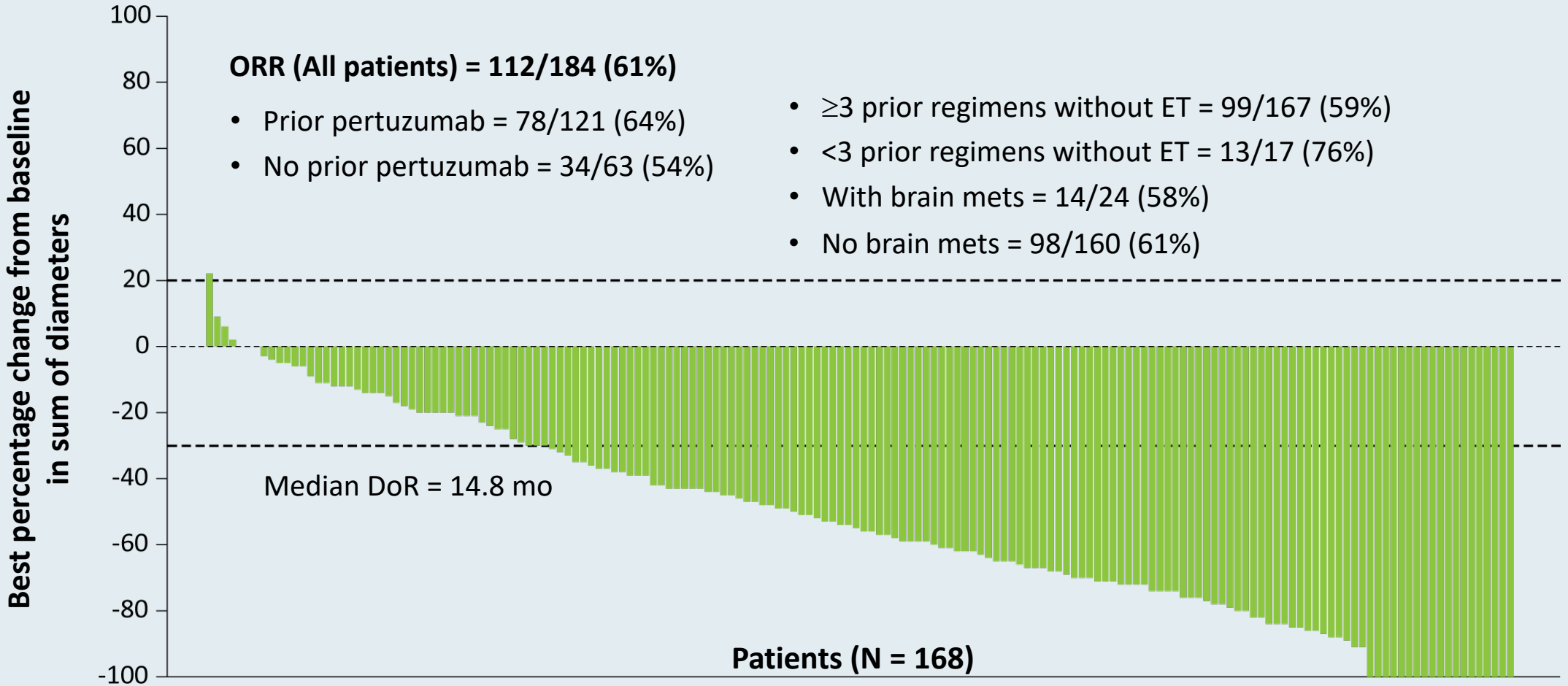
ORIGINAL ARTICLE

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.

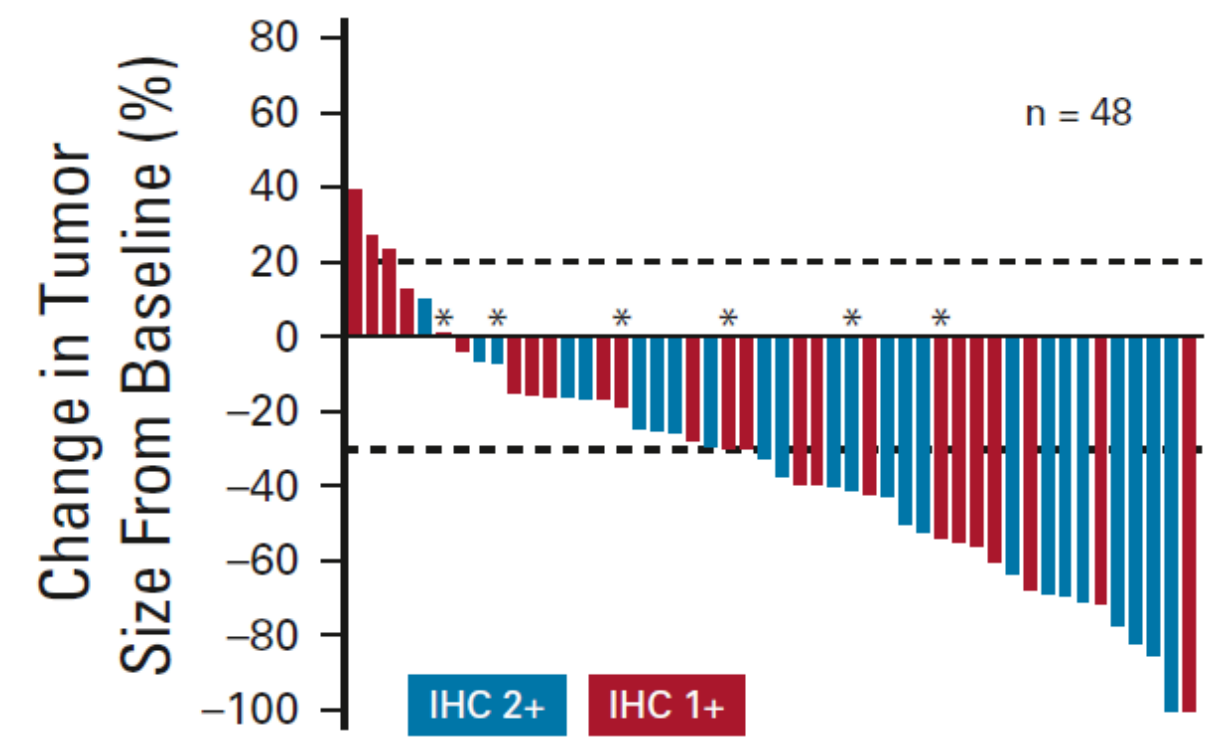
original reports

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

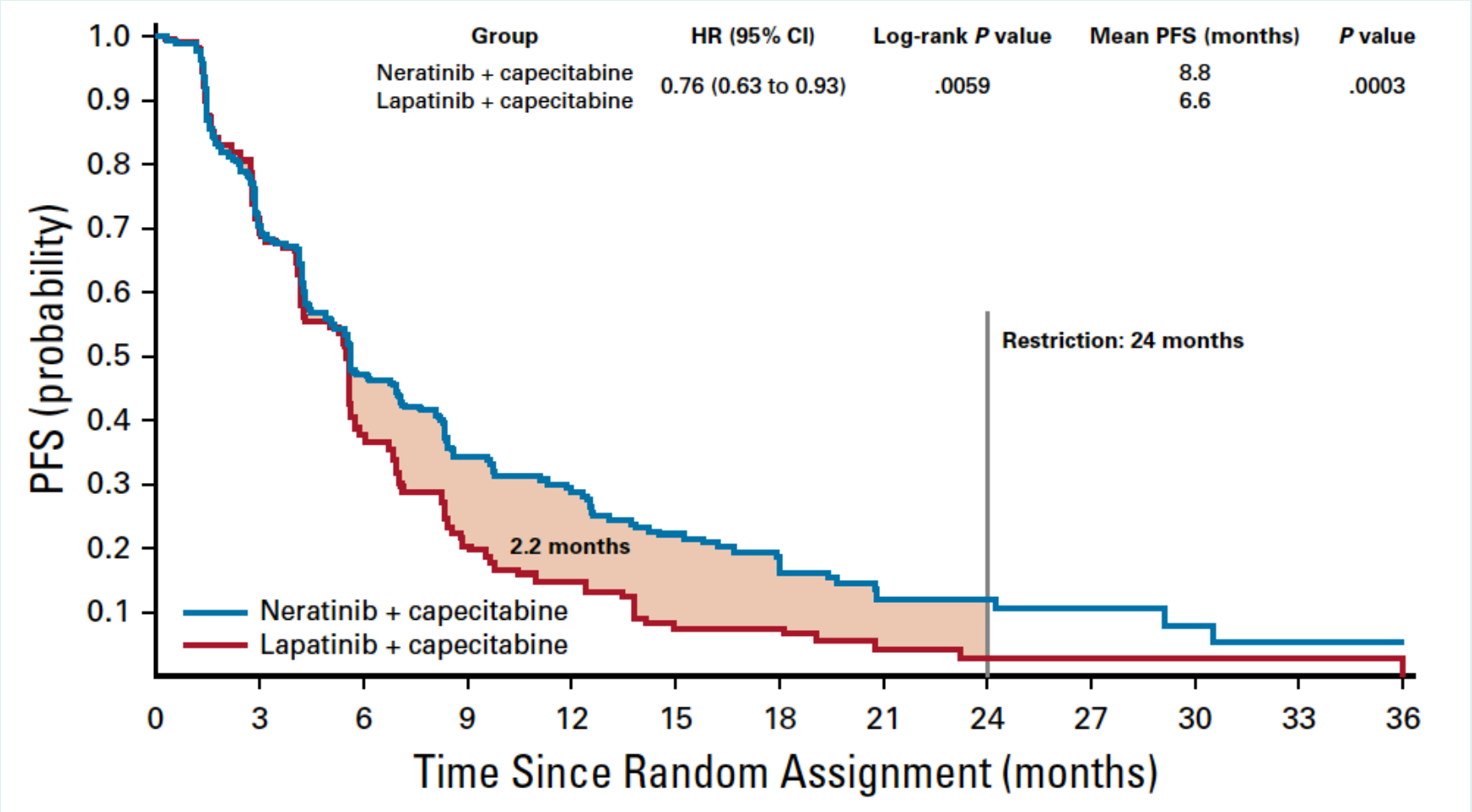
original reports

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.

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.

Neratinib and Capecitabine for CNS Disease (TBCRC 022)

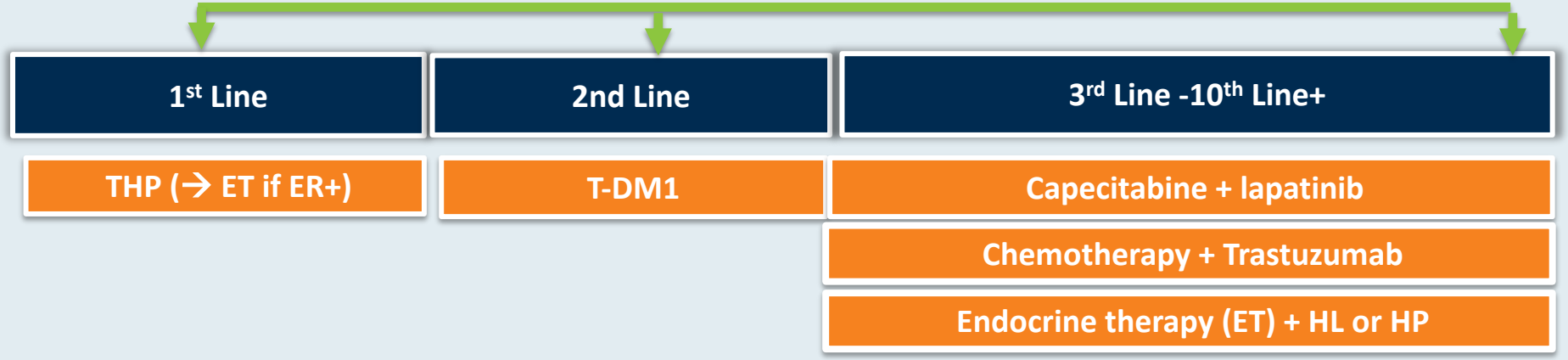
- Phase 2 trial of patients with progressive HER2+ brain metastases (N=49)
- Patients received neratinib (240 mg po QD) and capecitabine (750 mg/m^2 BID 14d on/7d off)
- Efficacy in cohort without previous lapatinib (N=37):
  - 49% CNS objective response rate*
  - 5.5 mo median PFS

* ≥50% reduction in sum of target CNS lesion volumes without progression of nontarget lesions, new lesions, escalating steroids, progressive neurologic signs or symptoms, or non-CNS progression

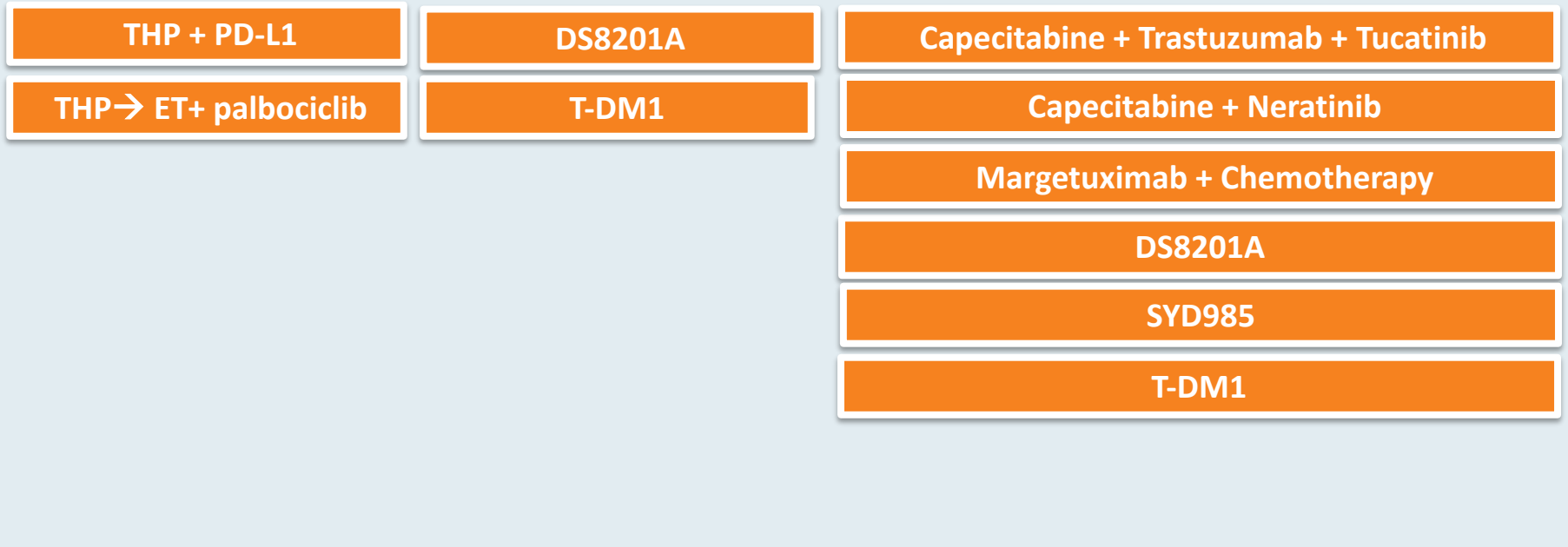
Freedman R et al. *J Clin Oncol* 2019;37:1081.

Courtesy of Ian E Krop, MD, PhD

Previous Approach for Metastatic HER2+ Breast Cancer



Where are we headed?



Courtesy of Sara M Tolaney, MD, MPH

Agenda

Module 1: HER2-Positive Breast Cancer

- Dr Hussein: A 29-year-old woman in need of third-line therapy for ER-positive, HER2-positive mBC
- Dr Malhotra: A 67-year-old woman with Stage IA ER-positive, HER2-positive IDC

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

- Dr Hussein: A 60-year-old woman with recurrent ER/PR-positive, HER2-negative mBC – PIK3CA mutation
- Dr Dandamudi: A 55-year-old woman with ER-positive, HER2-negative mBC

Module 3: Triple-Negative Breast Cancer (TNBC)

- Dr Hussein: A 44-year-old woman with mTNBC and a BRCA mutation
- Dr Choksi: A 67-year-old woman with past history of TNBC develops ER/PR-positive, HER2-positive BC

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Hussein: A 60-year-old woman with recurrent ER/PR-positive, HER2-negative mBC, PIK3CA mutation

Dr Maen Hussein

- 2015: Presented with recurrent ER/PR-positive, HER2-negative BC with metastases to the bone
- 7/2015: Fulvestrant/anastrozole x 6 months → switched to palbociclib/letrozole
- Tumor markers began rising and patient developed pleural effusions containing malignant cells
- PIK3CA mutation testing: positive
- 1/2020 – 6/2020: Alpelisib/fulvestrant with response
- Recurrent pleural effusions and increasing shortness of breath; no other sites of disease
- 7/2020: Capecitabine initiated → no recurrent pleural effusions, stable disease

Questions

- How do you manage the side effects associated with alpelisib?
- Would you administer abemaciclib in the adjuvant setting based on recently presented data?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Dandamudi: A 55-year-old woman with ER-positive, HER2-negative metastatic breast cancer

Dr Uday Dandamudi

- 2019: Diagnosed with de novo ER-positive, PR-negative, HER2-negative breast cancer with bone and liver metastases, bilateral pleural effusion
- *Nab* paclitaxel x 6, initiated due to visceral crisis, with minimal response
- 7/2020: Abemaciclib/anastrozole
  - LDH, tumor marker rising
  - CT: Increased size of liver lesions
- Genetic testing: ESR1 E380Q, CCDN1 amplification, TP53 R342P and GATA3 N320fs
- Switched to abemaciclib/fulvestrant
  - LDH, tumor markers improving
  - CT: Improvement in liver lesions

Questions

- How often do you do next-generation sequencing before making the decision to go with an AI versus fulvestrant? How often do you see ESR1 mutations, and what is their clinical significance?

RTP RESEARCH TO PRACTICE

A 65-year-old woman presents with de novo ER-positive, HER2-negative mBC with asymptomatic liver and bone metastases. What would be your most likely treatment?

a. Palbociclib + fulvestrant
b. Palbociclib + letrozole
c. Ribociclib + fulvestrant
d. Ribociclib + letrozole
e. Abemaciclib + fulvestrant
f. Abemaciclib + letrozole
g. Other

RTP
RESEARCH TO PRACTICE

A patient with ER-positive, HER2-negative mBC experiences asymptomatic disease progression on palbociclib/letrozole. Genomic testing reveals a PIK3CA mutation. What would you likely recommend?

a. Alpelisib/fulvestrant
b. Fulvestrant/everolimus
c. Exemestane/everolimus
d. Capecitabine
e. Other chemotherapy
f. Other

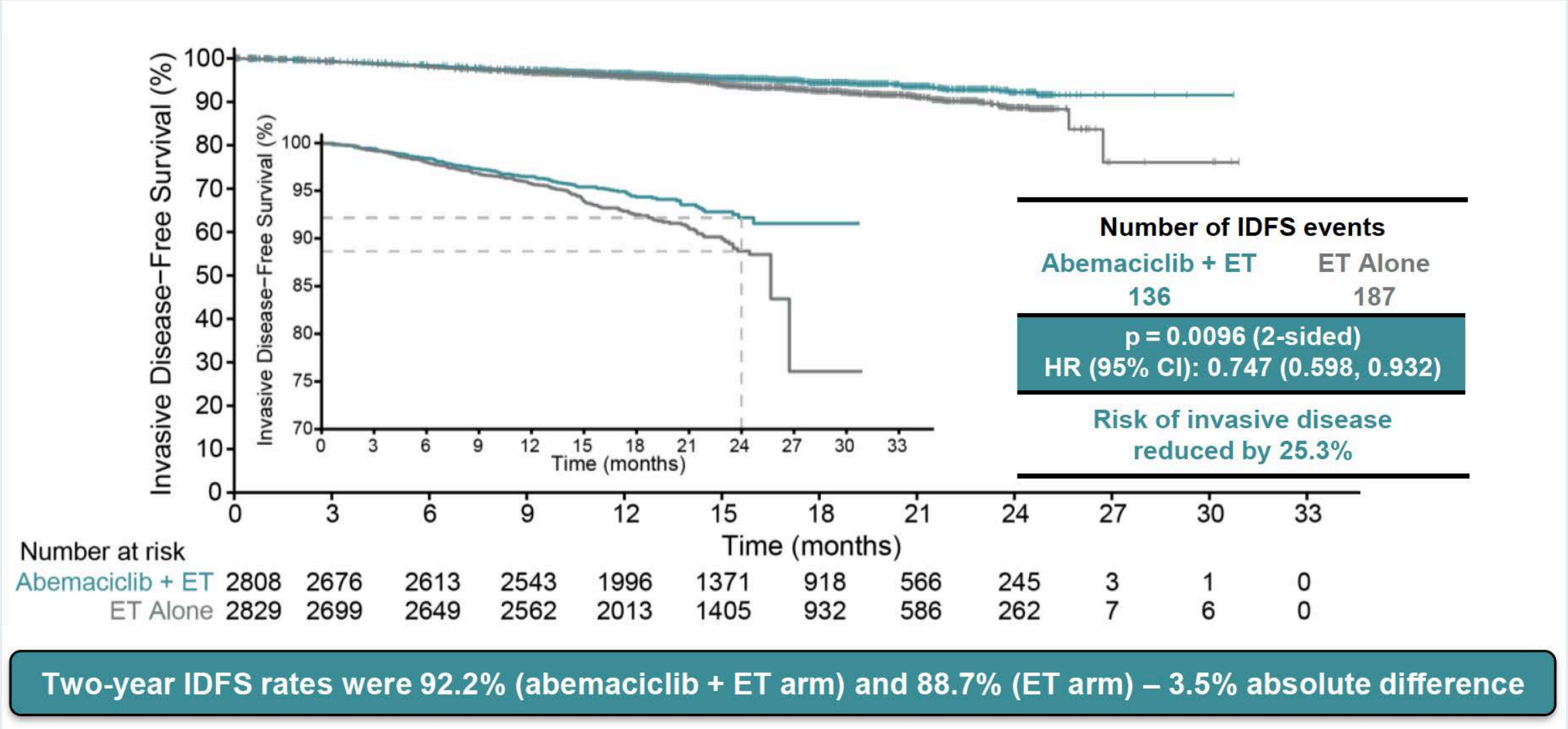
RTP
RESEARCH
TO PRACTICE

Abemaciclib Combined with Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High Risk, Early Breast Cancer (monarchE)

Johnston SRD et al.

ESMO 2020;Abstract LBA5_PR.

monarchE: Invasive Disease-Free Survival



Two-year IDFS rates were 92.2% (abemaciclib + ET arm) and 88.7% (ET arm) – 3.5% absolute difference

Johnston SRD et al. ESMO 2020;Abstract LBA5_PR.

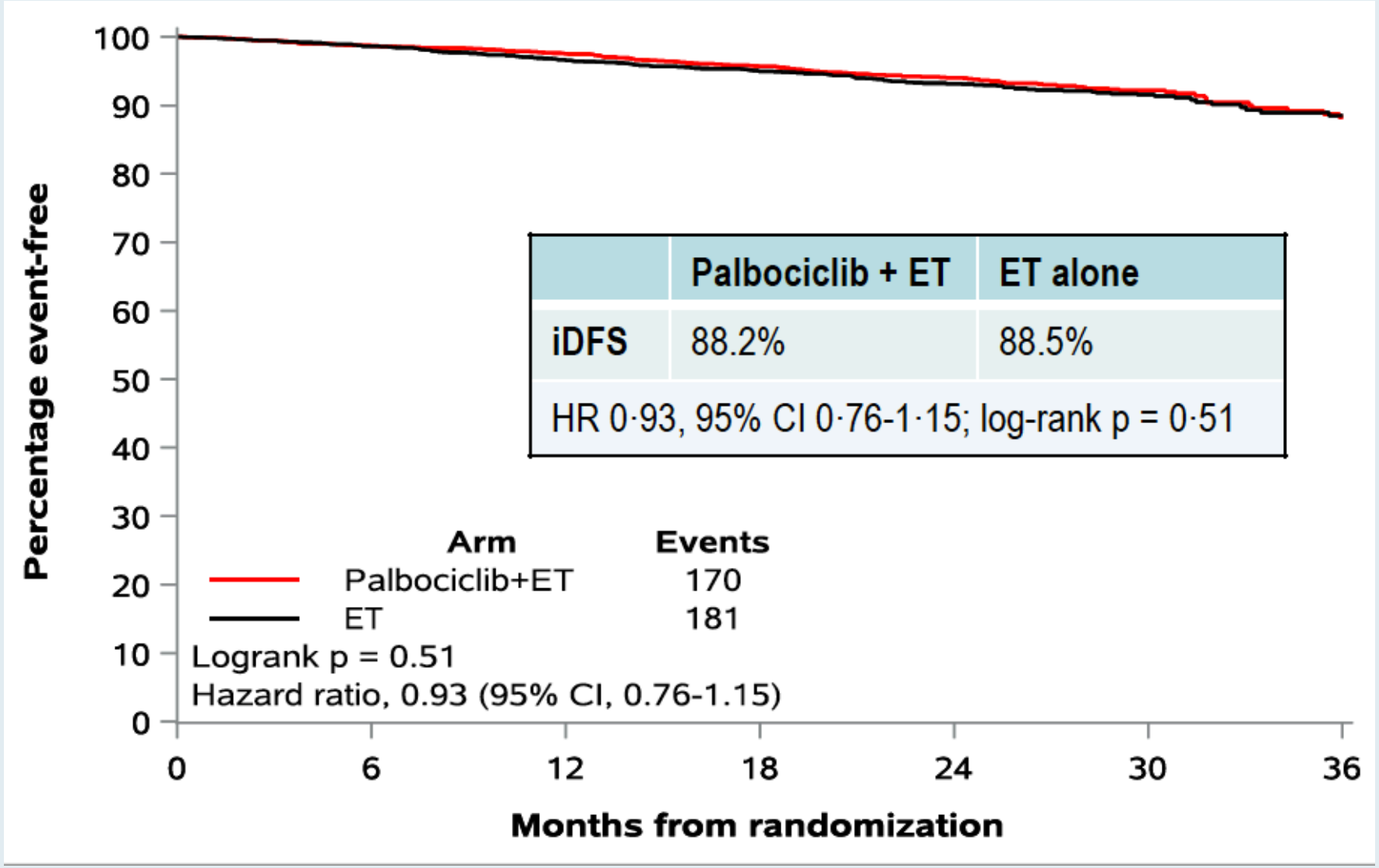
RTP RESEARCH TO PRACTICE

PALLAS: A Randomized Phase III Trial of Adjuvant Palbociclib with Endocrine Therapy versus Endocrine Therapy Alone for HR+/HER2- Early Breast Cancer

Mayer E et al.

ESMO 2020;Abstract LBA12.

PALLAS: Invasive Disease-Free Survival

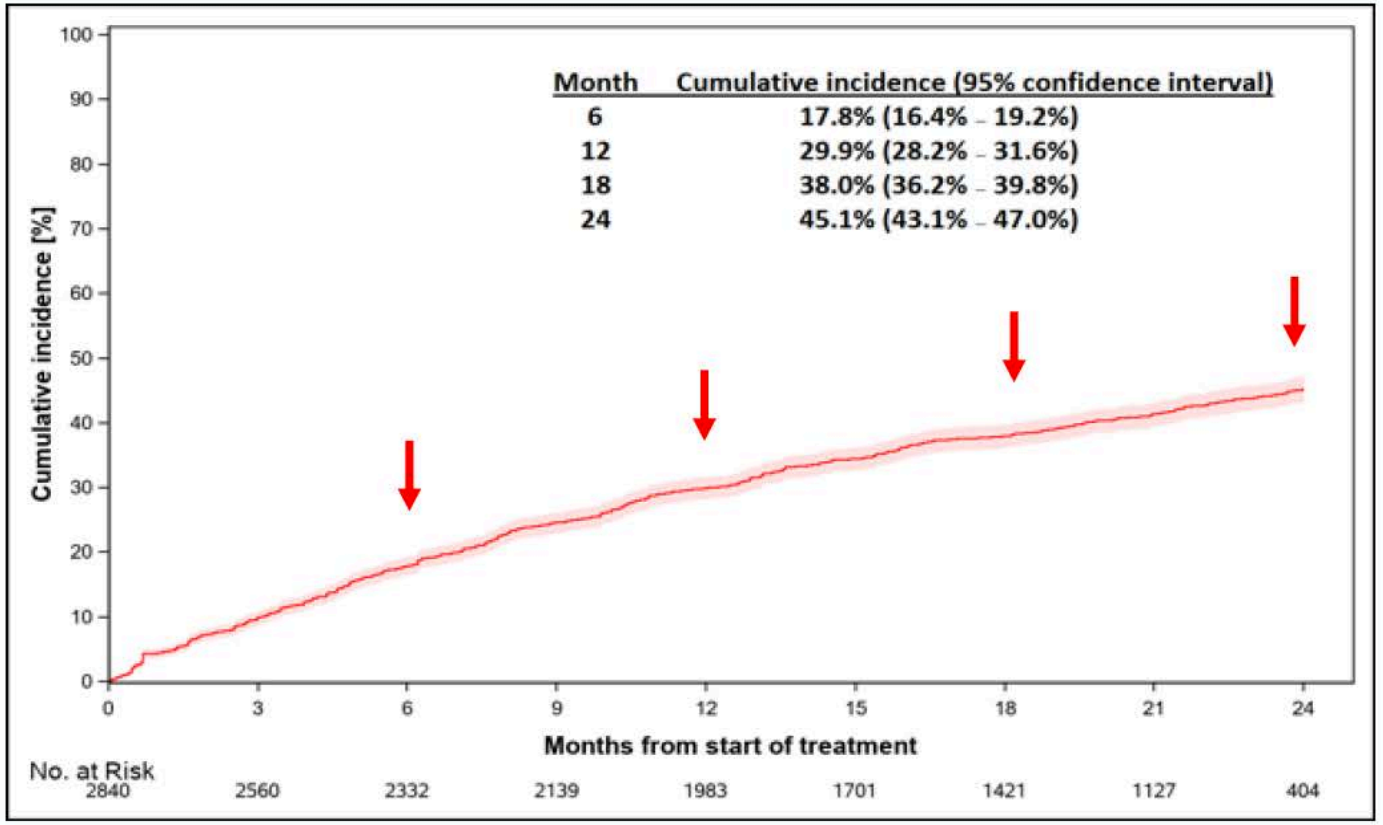


Mayer E et al. ESMO 2020;Abstract LBA12.

RTP RESEARCH TO PRACTICE

PALLAS: Palbociclib Exposure and Discontinuation

- Rates of palbociclib discontinuation were closely monitored throughout the trial.
- Active efforts including outreach and education were ongoing to reduce non-protocol related discontinuation.
- At time of data cut-off:
  - 725 (25·5%) were still receiving palbociclib
  - 916 (32·3%) had completed planned protocol therapy
  - 1199 (42·2%) had discontinued prematurely



Mayer E et al. ESMO 2020;Abstract LBA12.

RTP RESEARCH TO PRACTICE

Ongoing CDK4/6 Inhibitor Adjuvant Phase III Trial Designs

	NATALEE (Ribociclib)	PENELOPE-B (Palbociclib)
Study population	• High (stage III) and intermediate risks (stage IIB and IIA N1 or N0 G3 or N0G2 with Ki-67 ≥20% or high risk by: Onco*type* DX®, MammaPrint®, EndoPredict®, or PAM50) • ≈4000 pts	• High risk (residual invasive disease after neoadjuvant therapy for ≥16 weeks [including 6 weeks of taxane] and CPS-EG ≥3 or score 2 if ypN+) • Pre- and postmenopausal women • Men excluded • 1,250 pts
Node status	Node positive/negative	Node positive/negative
Time from ET start	≤12 months	NS
Time from BC surgery	NS	<16 weeks
CDK4/6 trt duration	3 years	13 cycles (≈ 1 year)
ET partner	AI (± ovarian suppression)	Tamoxifen or AI (± ovarian suppression)
Primary endpoint	iDFS	iDFS
Timelines	• Start of study: December 7, 2018	• Start of study: November 2013

Courtesy of Virginia Kaklamani, MD, DSc

PENELOPE-B Trial of Palbociclib in Early Breast Cancer Did Not Meet Primary Endpoint

Press Release – October 9, 2020

"The collaborative Phase 3 PENELOPE-B trial did not meet the primary endpoint of improved invasive disease-free survival (iDFS) in women with hormone receptor-positive (HR+), human epidermal growth factor-negative (HER2-) early breast cancer (eBC) who have residual invasive disease after completing neoadjuvant chemotherapy. No unexpected safety signals were observed."

https://www.pfizer.com/news/press-release/press-release-detail/penelope-b-trial-ibrancer-palbociclib-early-breast-cancer

RTP RESEARCH TO PRACTICE

First-Line CDK4/6 Inhibition Demonstrates Benefit

Phase 3 trial	PALOMA-2 (N = 666)	MONALEESA-2 (N = 668)	MONARCH-3 (N = 493)	MONALEESA-7 (N = 672)
CDK4/6i	Palbociclib	Ribociclib	Abemaciclib	Ribociclib
ET	AI	AI	AI	AI/Tam + OS
PFS (months) (CDK4/6i + ET vs ET + placebo)	27.6 vs 14.5	25.3 vs 16	28.2 vs 14.7	23.8 vs 13
HR (95% CI; *p*-value)	0.56 (0.46-0.69; *p < 0.0001*)	0.57 (0.45-0.70; *p < 0.01*)	0.54 (0.44-0.69; *p < 0.01*)	0.55 (0.44-0.69; *p < 0.01*)
OS (months) (CDK4/6i + ET vs ET + placebo)	NA	NA	NA	NE vs 40.9
HR (95% CI; *p*-value)	NA	NA	NA	0.71 (0.53-0.94; *p* = 0.0097)

*OS has been reported in MONALEESA-7

Rugo H et al. *Breast Cancer Res Treat* 2019; Hortobagyi GN et al. ASCO; Goetz MP et al. *J Clin Oncol* 2017;35(32):3638-46; Tripathy D et al. *Lancet Oncol* 2018; Im S-A et al. *N Engl J Med* 2019.

Courtesy of Sara M Tolaney MD, MPH

Second-Line CDK4/6 Inhibition Demonstrates Benefit

Phase 3 Trial	PALOMA-3 (N=521)	MONALEESA-3* (N=726)	MONARCH-2 (N=669)
CDK4/6i	Palbociclib	Ribociclib	Abemaciclib
ET	Fulvestrant	Fulvestrant	Fulvestrant
PFS (months) (CDK4/6i + ET vs ET + Placebo)	11.2 vs 4.6	20.5 vs 12.8	16.4 vs 9.3
HR (95% CI; *p*-value)	0.50 (0.40-0.62; *p < 0.01*)	0.59 (0.48-0.73; *p < 0.01*)	0.55 (0.44-0.68; *p < 0.01*)
OS (months) (CDK4/6i + ET vs ET + Placebo)	34.9 vs 28.0	NR vs 40.3	46.7 vs 37.3
HR (95% CI; *p*-value)	0.81 (0.64-1.03; *p* = 0.09)	0.72 (0.56-0.92; *p* = 0.004)	0.75 (0.60-0.94; *p* = 0.01)
HR Time to Chemotherapy	0.58 (*p* < 0.01)	NR	0.63 (*p* < 0.01)

OS BENEFIT

* Enrolled a cohort of Treatment naive patients (De Novo + DFI > 12 months from adj treatment)

Turner NC et al. *N Engl J Med* 2018;379(20):1926-36; Sledge GW Jr et al. *JAMA Oncol* 2019;
Slamon DJ et al. *N Engl J Med* 2020;382(6):51

Courtesy of Sara M Tolaney MD, MPH

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

The NEW ENGLAND JOURNAL of MEDICINE

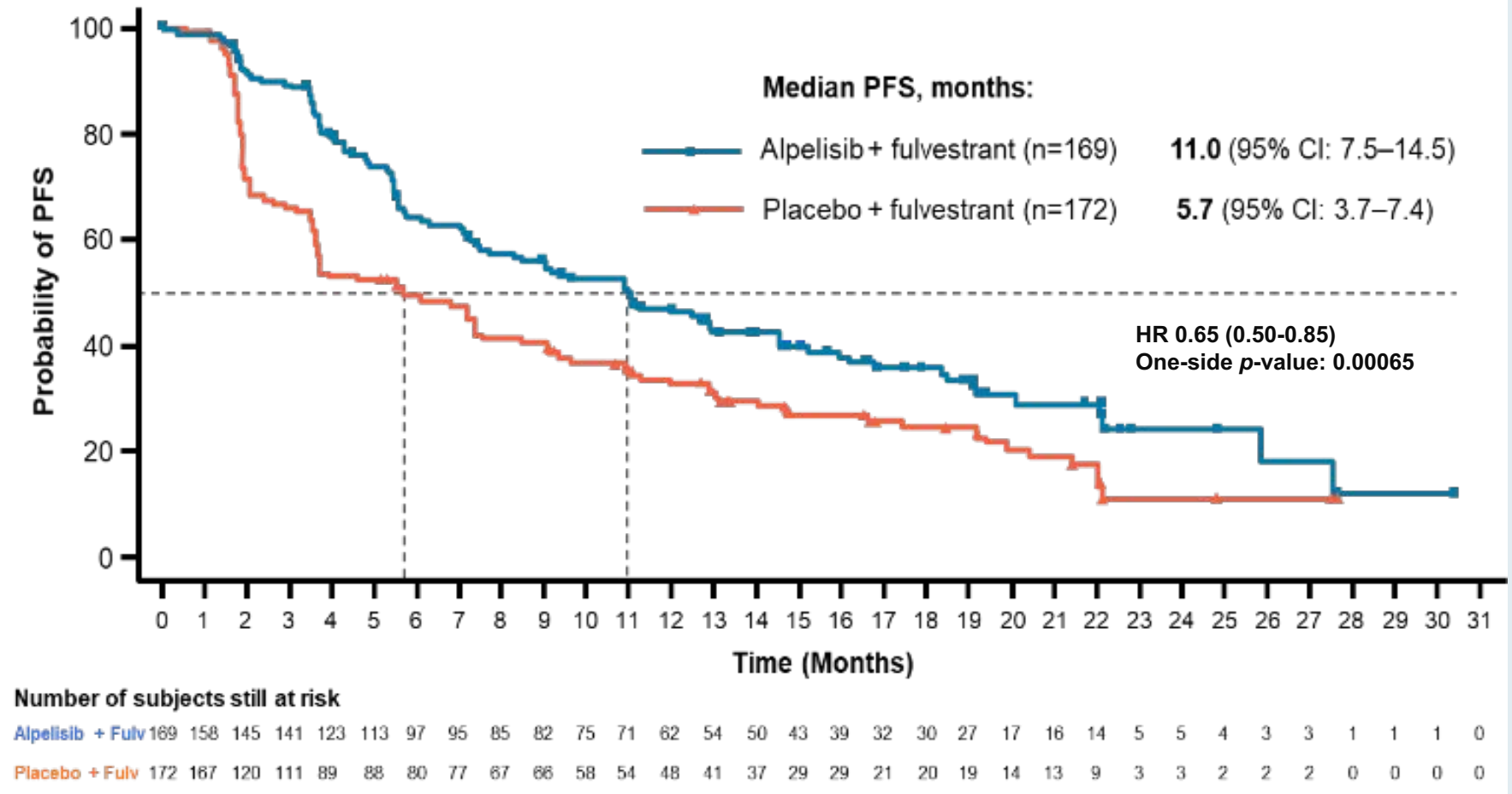
ORIGINAL ARTICLE

Alpelisib for *PIK3CA*-Mutated, Hormone Receptor–Positive Advanced Breast Cancer

F. André, E. Ciruelos, G. Rubovszky, M. Campone, S. Loibl, H.S. Rugo, H. Iwata, P. Conte, I.A. Mayer, B. Kaufman, T. Yamashita, Y.-S. Lu, K. Inoue, M. Takahashi, Z. Pápai, A.-S. Longin, D. Mills, C. Wilke, S. Hirawat, and D. Juric, for the SOLAR-1 Study Group*

***N Engl J Med* 2019;380(20):1929-40.**

SOLAR-1: Alpelisib Improved PFS in the PIK3CA-Mutation Cohort



- Treatment benefit with alpelisib was observed regardless of prior CDK4/6 inhibitor therapy
  - Median PFS in patients with prior CDK4/6 inhibitor therapy (N =20): 5.5 mo vs 1.8 mo

Andre F et al. *N Engl J Med* 2019;380(20):1929-40.

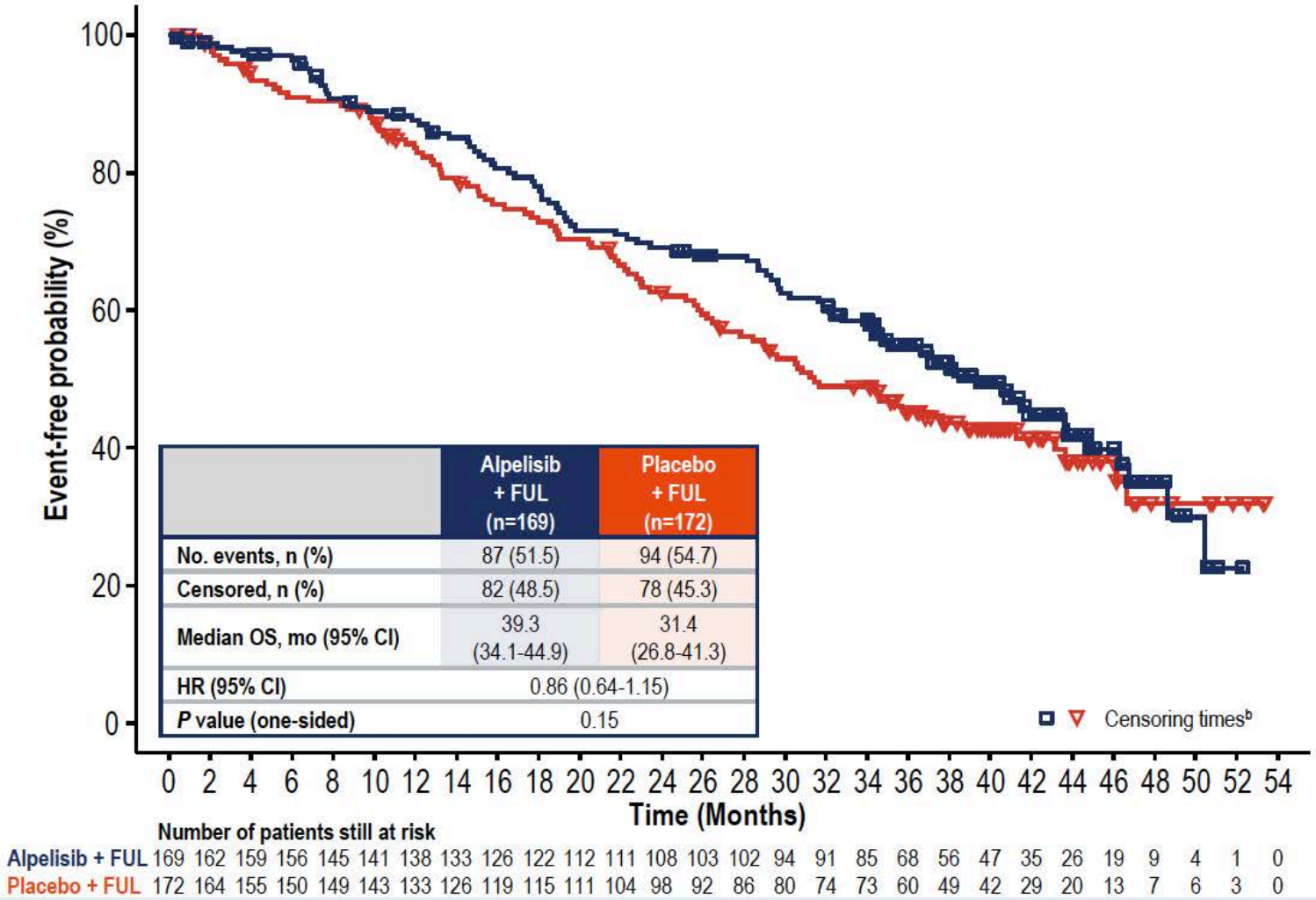
RTP RESEARCH TO PRACTICE

Overall Survival (OS) Results From SOLAR-1, a Phase 3 Study of Alpelisib (ALP) + Fulvestrant (FUL) for Hormone Receptor-Positive (HR+), Human Epidermal Growth Factor Receptor 2-Negative (HER2-) Advanced Breast Cancer (ABC)

Andre F et al.
ESMO 2020;Abstract LBA18.

SOLAR-1: OS in the PIK3CA-Mutation Cohort

- mOS was prolonged by 7.9 mo for patients in the alpelisib + fulvestrant arm
- Final OS analysis in the *PIK3CA*-mutant cohort did not cross the prespecified O'Brien-Fleming efficacy boundary (1-sided $P \leq 0.0161$)



Andre F et al. ESMO 2020;Abstract LBA18.

RTP RESEARCH TO PRACTICE

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer

H. S. Rugo[1*], F. André[2], T. Yamashita[3], H. Cerda[4], I. Toledano[5], S. M. Stemmer[6], J. C. Jurado[7], D. Juric[8], I. Mayer[9], E. M. Ciruelos[10], H. Iwata[11], P. Conte[12], M. Campone[13], C. Wilke[14], D. Mills[14], A. Lteif[15], M. Miller[15], F. Gaudenzi[14] & S. Loibl[16]

Ann Oncol 2020;31(8):1001-10.

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

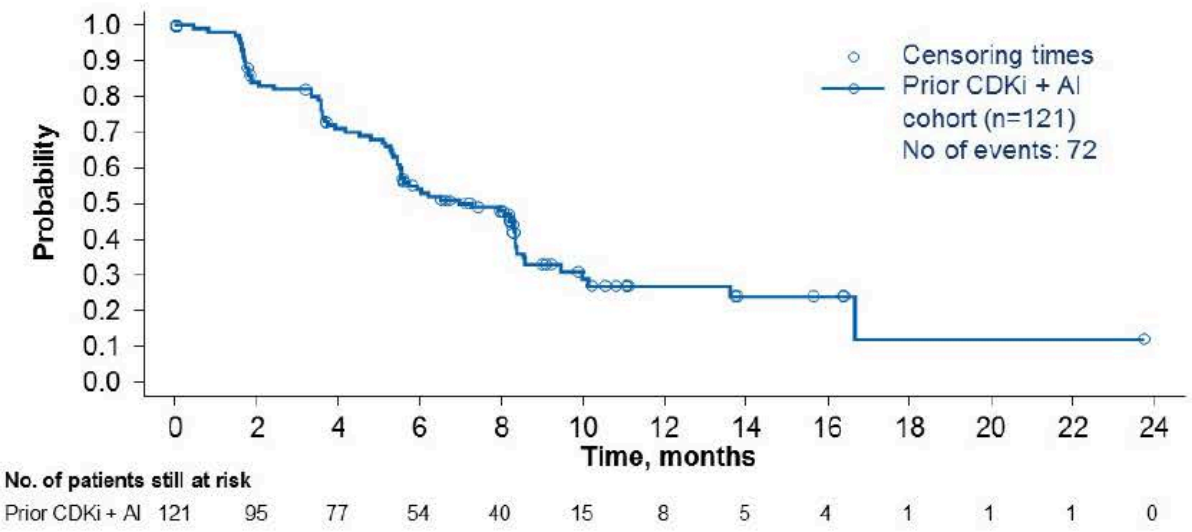
Rugo HS et al.

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)

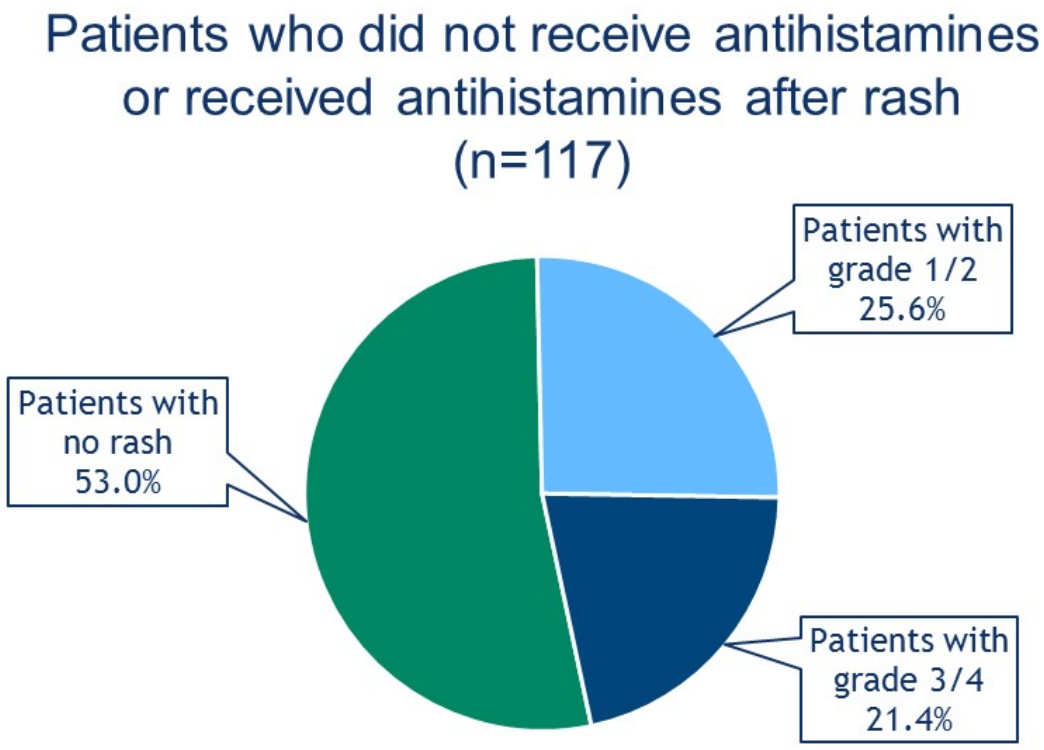


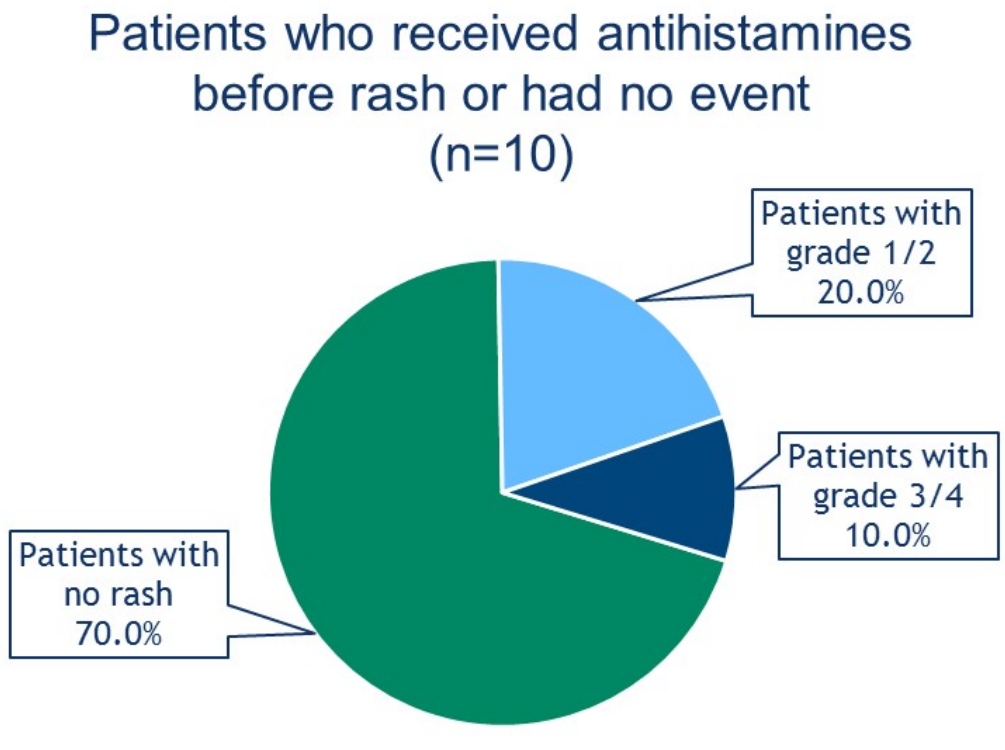
The primary endpoint for the prior CDKi + AI cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months

- 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.

Agenda

Module 1: HER2-Positive Breast Cancer

- Dr Hussein: A 29-year-old woman in need of third-line therapy for ER-positive, HER2-positive mBC
- Dr Malhotra: A 67-year-old woman with Stage IA ER-positive, HER2-positive IDC

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Module 3: Triple-Negative Breast Cancer (TNBC)

- Dr Hussein: A 44-year-old woman with mTNBC and a BRCA mutation
- Dr Choksi: A 67-year-old woman with past history of TNBC develops ER/PR-positive, HER2-positive BC

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Hussein: A 44-year-old woman with mTNBC and a BRCA mutation

Dr Maen Hussein

- Diagnosis of Stage IV ER/PR-negative, HER2-negative IDC with a BRCA mutation
- 3/2019 – 7/2019: Niraparib on protocol
- 7/2019 – 1/2020: AC + T
- Plan for capecitabine, patient refused
- Prophylactic bilateral oophorectomy, found to have breast metastases on ovary
- 8/2020 – present: Olaparib

Questions

- Would you have recommended a PARP inhibitor to this patient who is Stage IV NED? Is the toxicity profile of PARP inhibitors different in breast cancer than in ovarian cancer?
- Do you see a potential role for sacituzumab govitecan in TNBC? Do you think it can be used in the adjuvant setting?

RTP RESEARCH TO PRACTICE

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

Have you or would you add an anti-PD-1/PD-L1 antibody to chemotherapy as neoadjuvant treatment for triple-negative breast cancer (TNBC) outside of a clinical trial setting?

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

RTP RESEARCH TO PRACTICE

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

a. Atezolizumab/paclitaxel
b. Atezolizumab/*nab* paclitaxel
c. Atezolizumab/paclitaxel or atezolizumab/*nab* paclitaxel — coin flip
d. Pembrolizumab/chemotherapy
e. PARP inhibitor monotherapy
f. Chemotherapy → PARP inhibitor maintenance
g. Chemotherapy + anti-PD-1/PD-L1 antibody → PARP inhibitor maintenance
h. Other

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

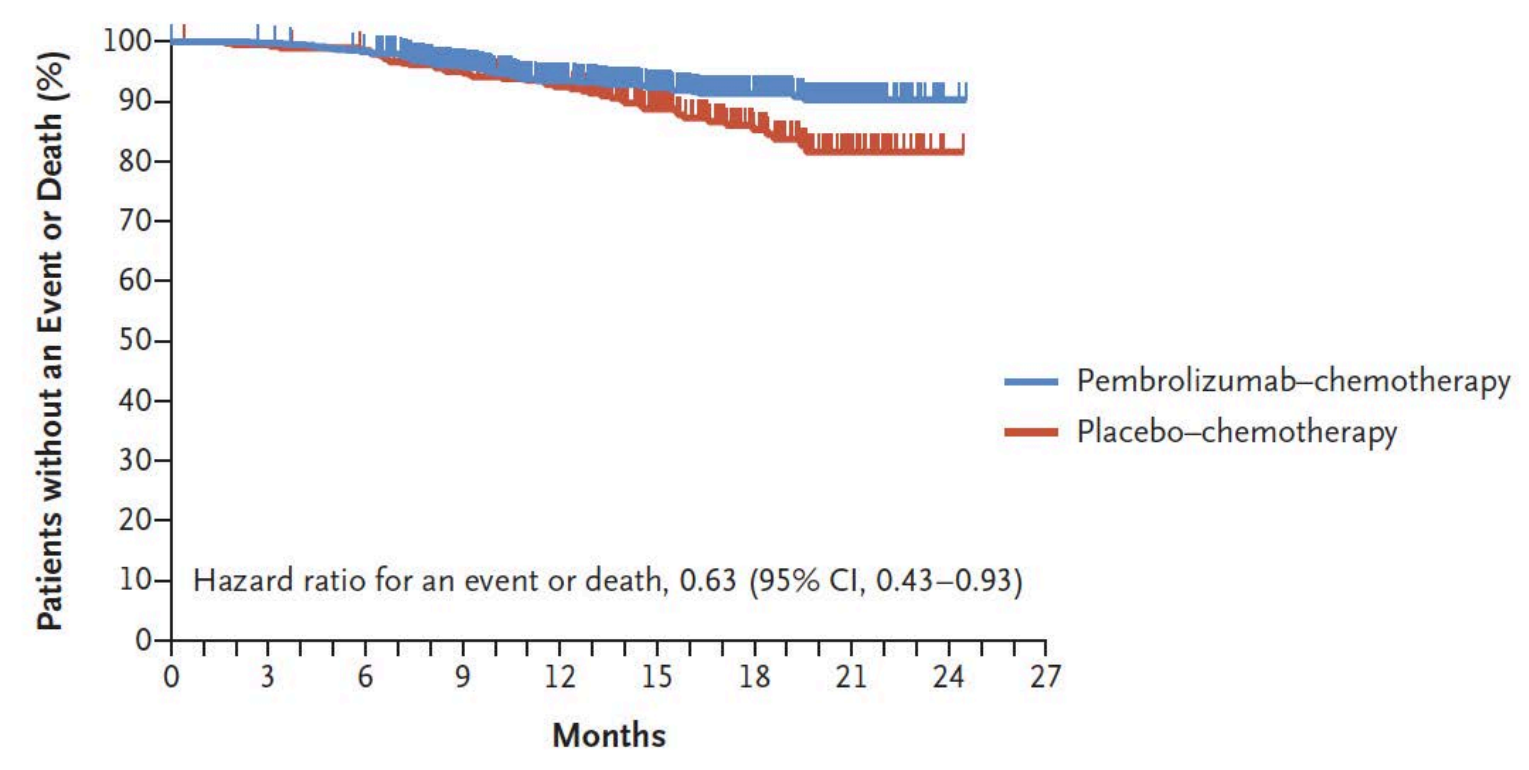
Pembrolizumab for Early Triple-Negative Breast Cancer

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.

KEYNOTE-522: Select AEs

	Pembrolizumab + chemotherapy (n = 781)		Placebo + chemotherapy (n = 389)	
Treatment-related AE	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Nausea	62.7%	3.3%	63.2%	1.3%
Anemia	55.1%	18.2%	55.3%	14.9%
Neutropenia	47.7%	34.6%	47.0%	33.2%
AE of interest	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Infusion reaction	16.9%	2.6%	11.1%	1.0%
Hypothyroidism	13.7%	0.4%	3.3%	0
Hyperthyroidism	4.6%	0.3%	1.0%	0
Severe skin reaction	4.4%	3.8%	1.0%	0.3%
Adrenal insufficiency	2.3%	1.3%	0	0

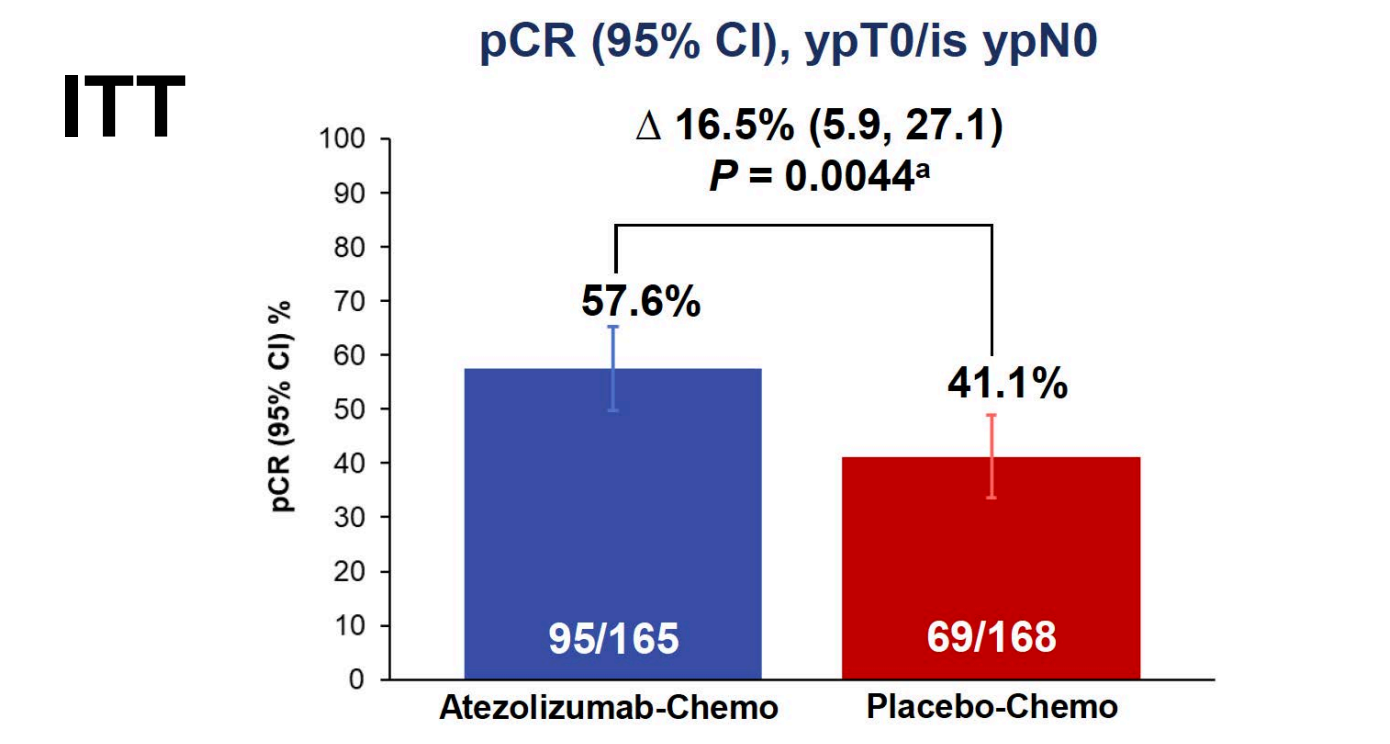
Schmid P et al. *N Engl J Med* 2020;382(9):810-21.

IMpassion031: Results from a Phase III Study of Neoadjuvant Atezolizumab + Chemotherapy in Early Triple-Negative Breast Cancer

Harbeck N et al.

ESMO 2020;Abstract LBA11.

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



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.

Harbeck N et al. ESMO 2020;Abstract LBA11.

Select Ongoing Phase III Trials of Immune Checkpoint Inhibitor-Based Therapies in Earlier Lines of Therapy

Trial	N	Entry criteria	Randomization
KEYNOTE-756 (NCT03725059)	1,140	(Neo)adjuvant, high-risk, early-stage ER-positive, HER2-negative BC	• Pembrolizumab + chemotherapy → pembrolizumab + ET • Placebo + chemotherapy → placebo + ET
IMpassion050 (NCT03726879)	453	(Neo)adjuvant, early-stage HER2-positive BC	• Atezolizumab + ddAC → paclitaxel/trastuzumab/pertuzumab • Placebo + ddAC → paclitaxel/trastuzumab/pertuzumab
A-Brave (NCT02926196)	474	(Neo)adjuvant, high-risk TNBC	• Avelumab • Observation
IMpassion030 (NCT03498716)	2,300	Adjuvant, operable TNBC	• Atezolizumab + chemotherapy • Chemotherapy
SWOG-S1418 (NCT02954874)	1,000	Adjuvant, ≥1-cm residual tumor after neoadjuvant therapy	• Pembrolizumab • Observation

ET = endocrine therapy; dd = dose-dense

www.clinicaltrials.gov. Accessed October 2020.

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†*

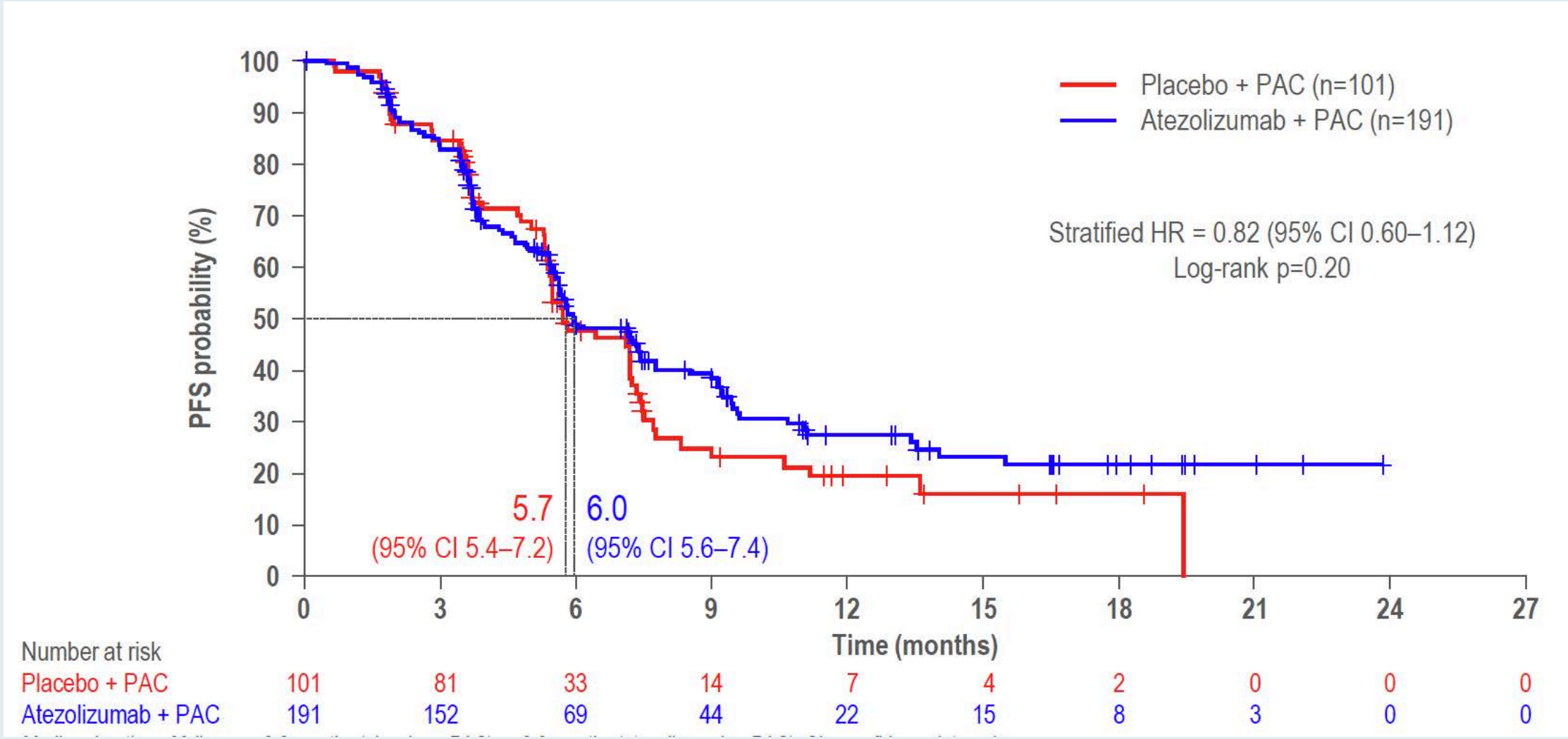
***Lancet Oncol* 2020:21(1):44-59.**

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.

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

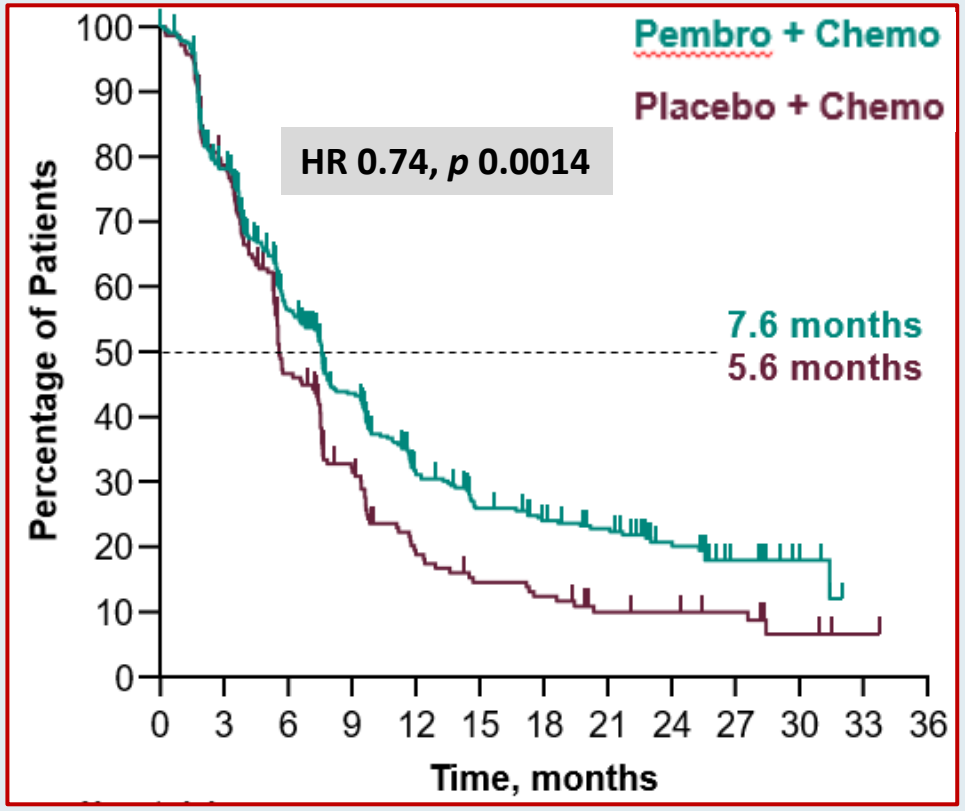
KEYNOTE-355: Randomized, Double-Blind, Phase III Study of Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer

Cortes J et al.

ASCO 2020;Abstract 1000.

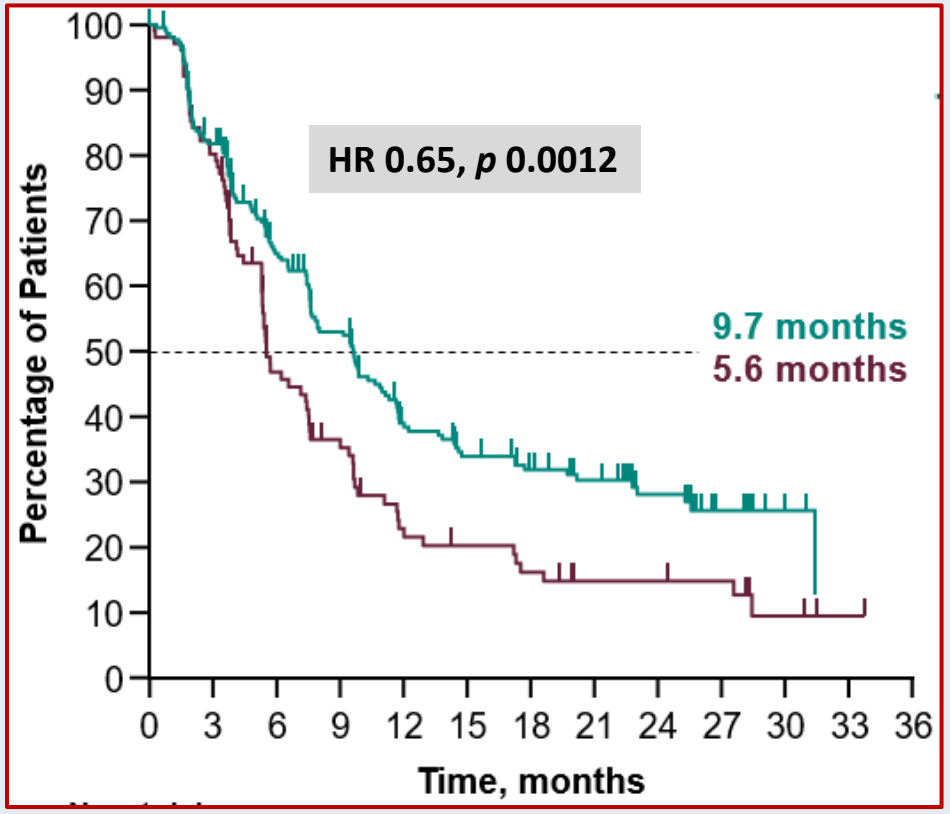
KEYNOTE-355: PFS for Patients with PD-L1-Positive Tumors

PD-L1 CPS ≥1



Prespecified *p* value boundary of 0.00111 not met

PD-L1 CPS ≥10



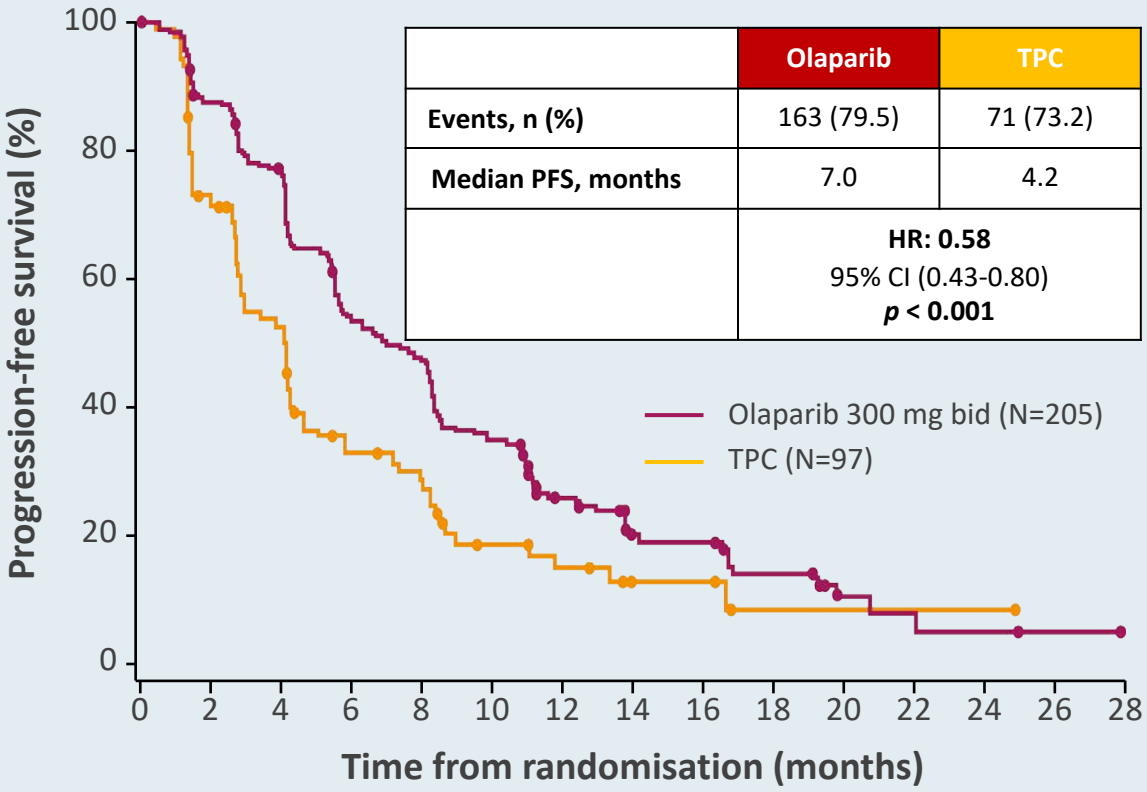
Prespecified *p* value boundary of 0.00411 met

Cortes J et al. ASCO 2020;Abstract 1000.

RTP RESEARCH TO PRACTICE

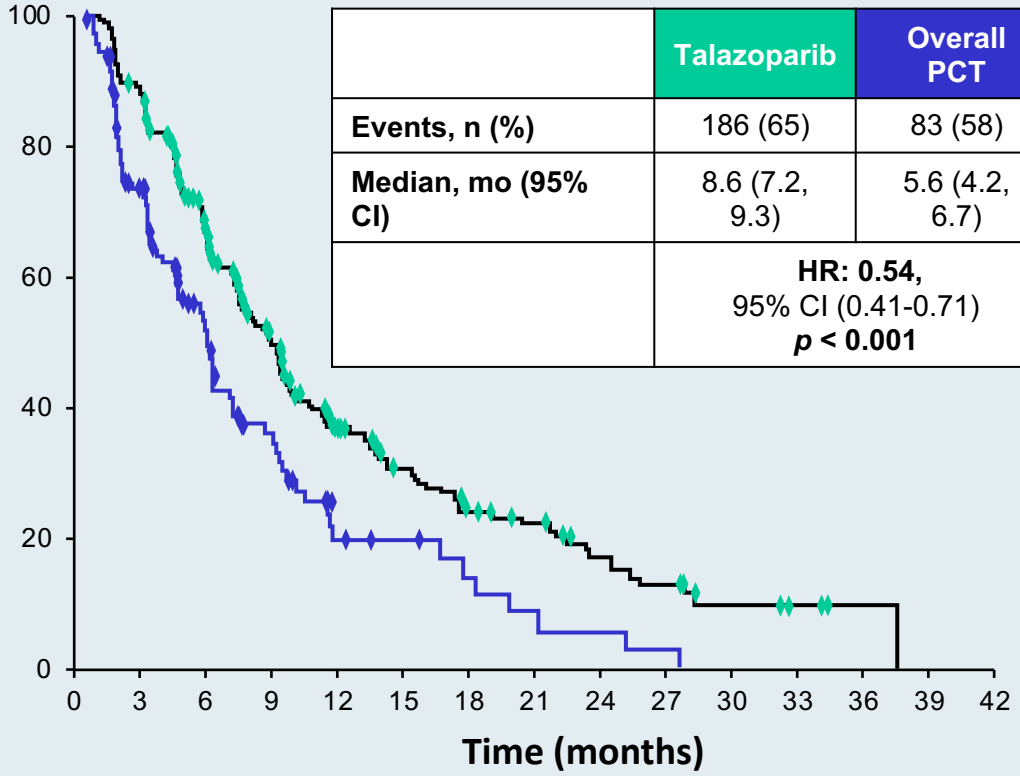
Phase III Trials of PARP Inhibitors in HER2-Negative mBC with a Germline BRCA Mutation

OLYMPIAD: Olaparib PFS[1,2]



	Olaparib	TPC
Events, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
	HR: 0.58 95% CI (0.43-0.80) ***p* < 0.001**	

EMBRACA: Talazoparib PFS[3]



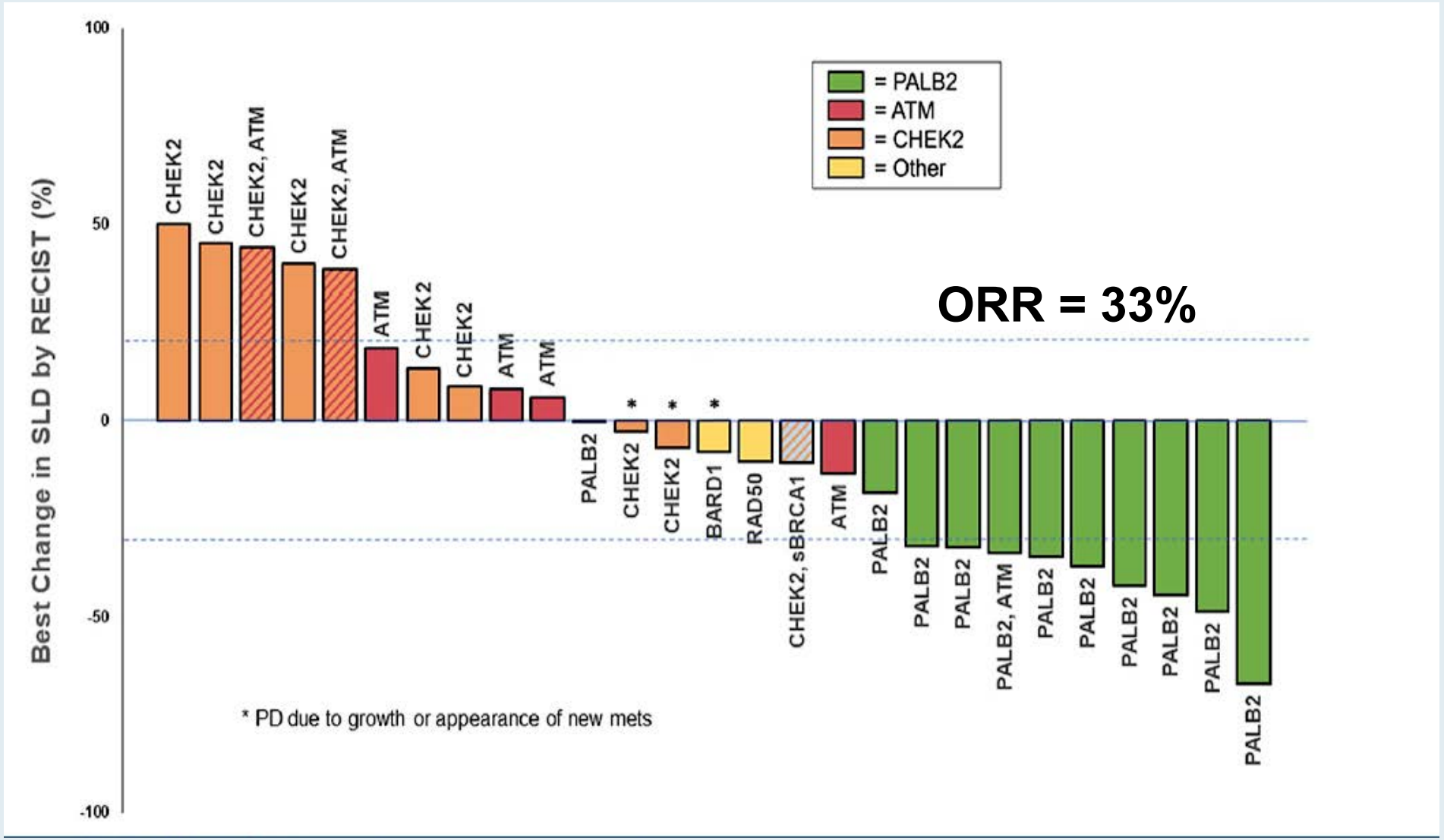
	Talazoparib	Overall PCT
Events, n (%)	186 (65)	83 (58)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	HR: 0.54, 95% CI (0.41-0.71) ***p* < 0.001**	

1. Robson M et al. *N Engl J Med* 2017;377:523-33; 2. Olaparib 150mg Film-Coated Tablets, SmPC. 2019; 3. Litton JK et al. *N Engl J Med* 2018;379:753-63 (supplementary appendix)

TBCRC 048: A Phase II Study of Olaparib Monotherapy in Metastatic Breast Cancer Patients with Germline or Somatic Mutations in DNA Damage Response (DDR) Pathway Genes (Olaparib Expanded)

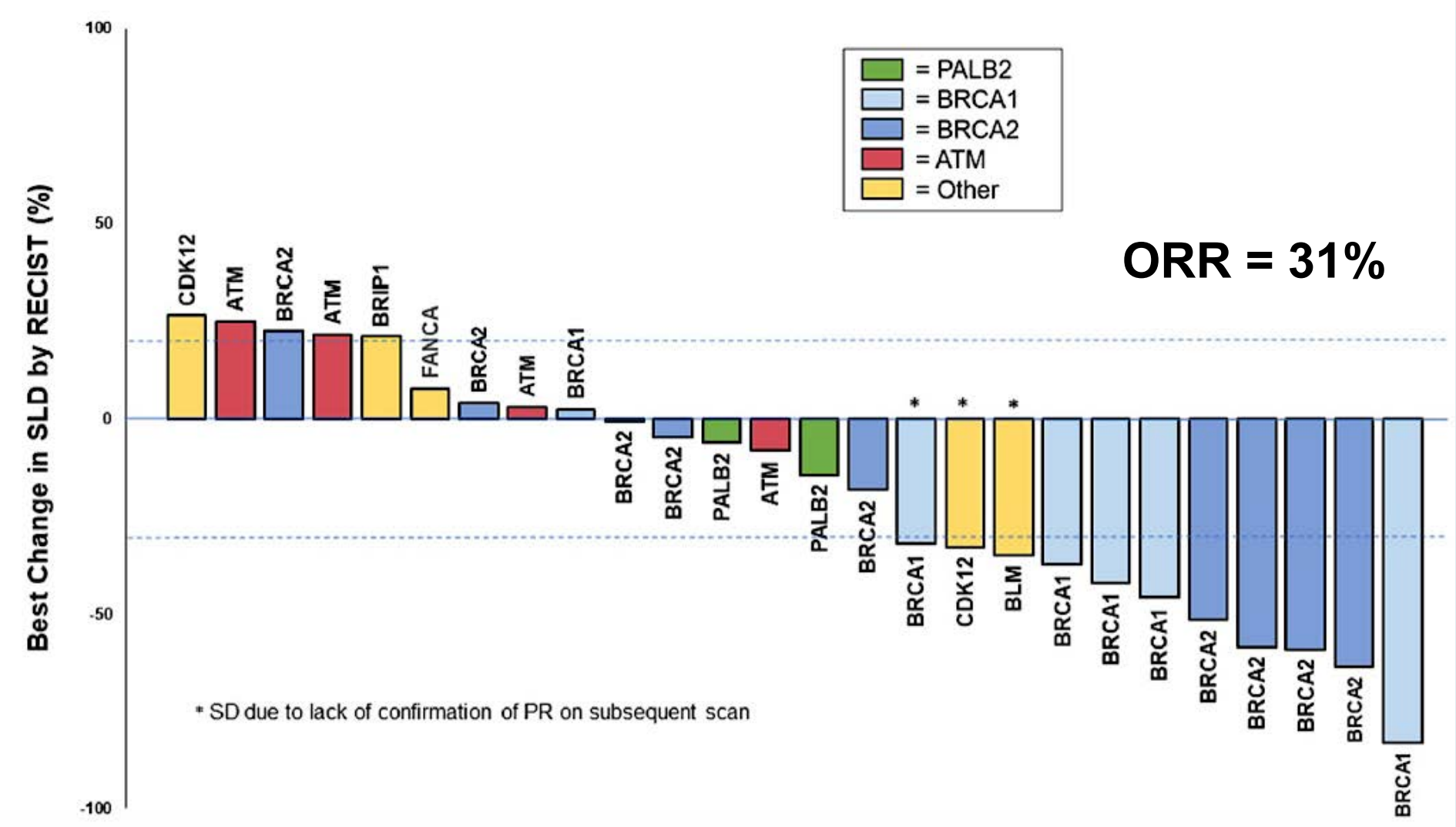
Tung N et al.
ASCO 2020;Abstract 1002.

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



Tung N et al. ASCO 2020;Abstract 1002.

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



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 N et al. ASCO 2020;Abstract 1002.

FDA Grants Acclerated 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

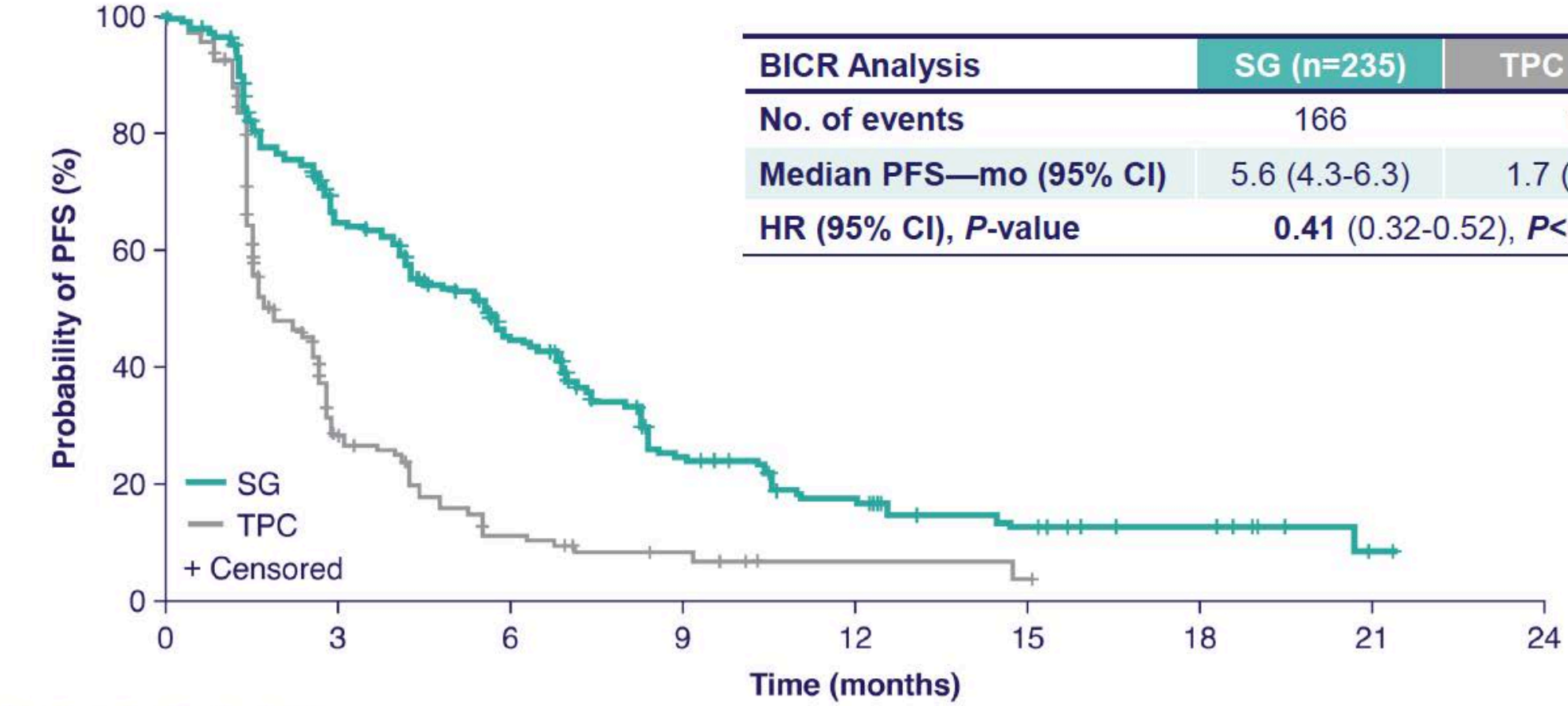
RTP RESEARCH TO PRACTICE

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: 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.

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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