Meet The Professor
Immunotherapy and Novel Agents in Gynecologic Cancers

Brian M Slomovitz, MD
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Commercial Support

These activities are supported by educational grants from Eisai Inc, Merck, Seattle Genetics and Tesaro, A GSK Company.

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Dr Love — Disclosures

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Dr Slomovitz — Disclosures

No financial interests or affiliations to disclose

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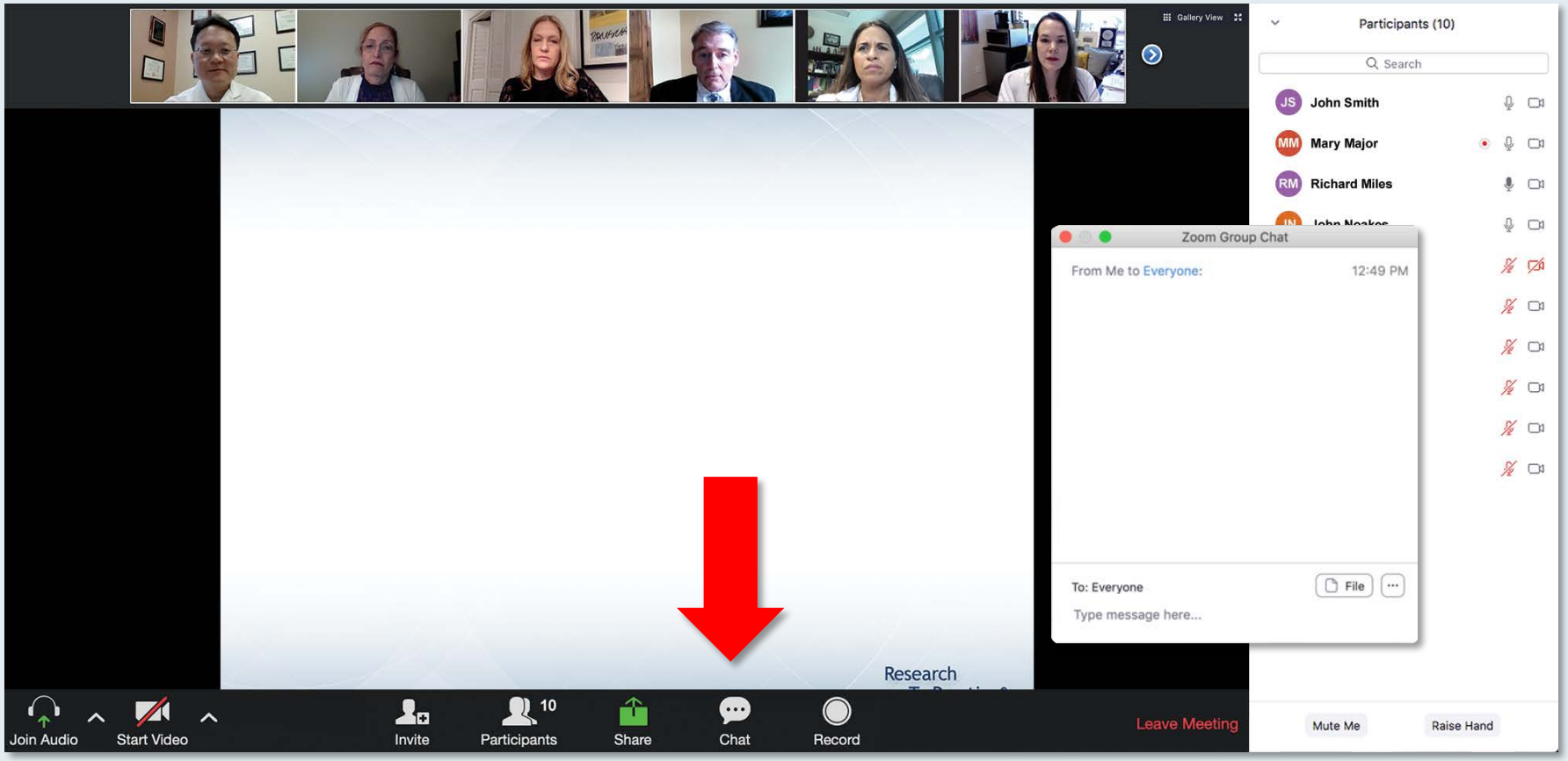
We Encourage Clinicians in Practice to Submit Questions



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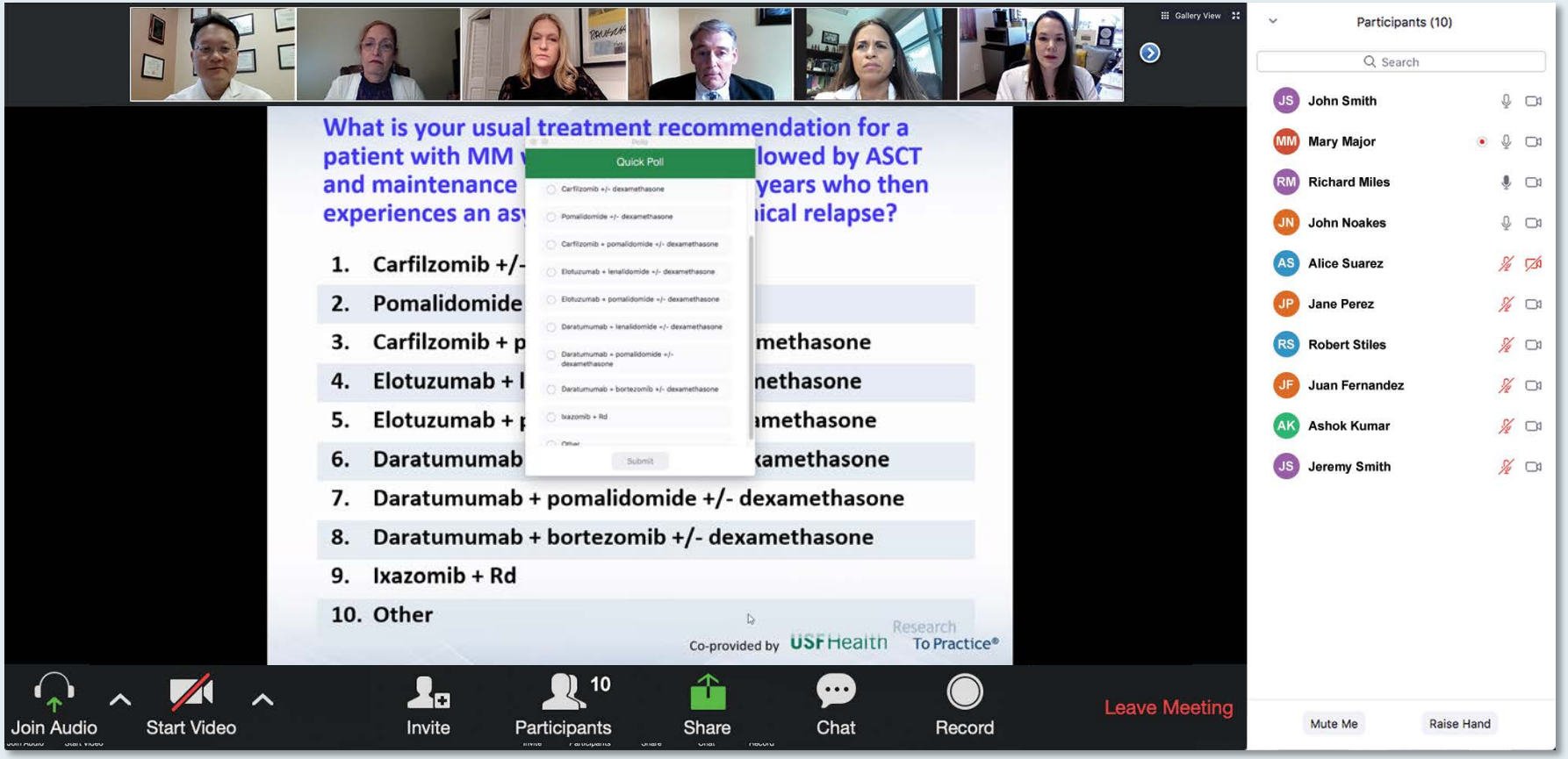

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Upcoming Webinars

Tuesday, October 13, 2020
12:00 PM – 1:00 PM ET

Meet The Professor: Management of Lung Cancer

Faculty
Paul K Paik, MD

Moderator
Neil Love, MD

Wednesday, October 14, 2020
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Meet The Professor: Management of Chronic Lymphocytic Leukemia

Faculty
John M Pagel, MD, PhD

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Meet The Professor: Management of Ovarian Cancer

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Kathleen Moore, MD

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Friday, October 16, 2020
11:00 AM – 12:00 PM ET

Addressing Current Questions and Controversies in the Management of Non-Small Cell Lung Cancer with an EGFR Mutation

Faculty
Roy S Herbst, MD, PhD
Suresh S Ramalingam, MD
Helena Yu, MD

Moderator
Neil Love, MD

Thank you for joining us!

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

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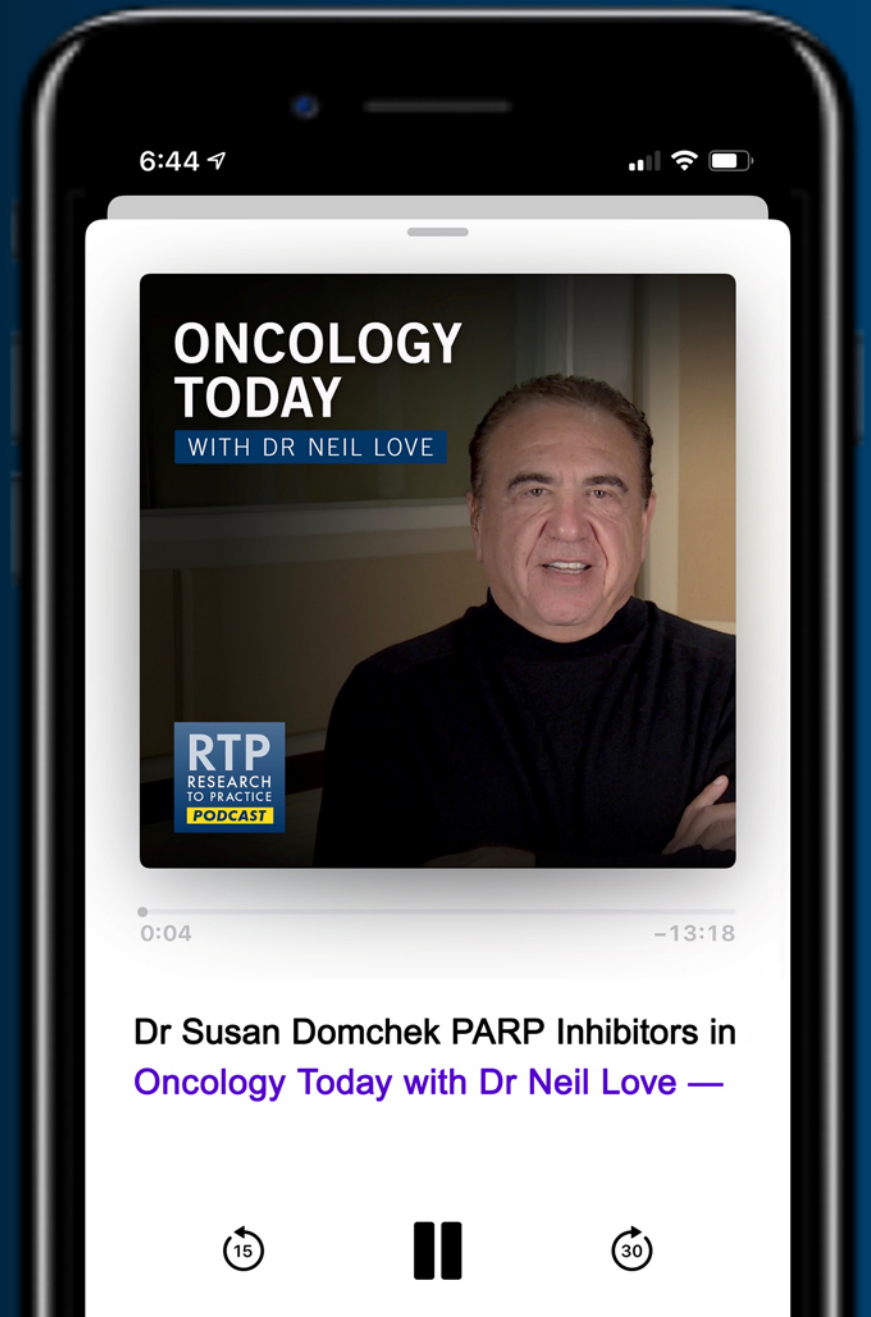

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Director, Winthrop P Rockefeller Cancer Institute
Director, Cancer Service Line
University of Arkansas for Medical Sciences
Little Rock, Arkansas

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Vall d'Hebron Barcelona Hospital Campus
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The Woodlands, Texas

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Professor
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The Ohio State University and The James Cancer Center
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Meet The Professor Program Participating Faculty

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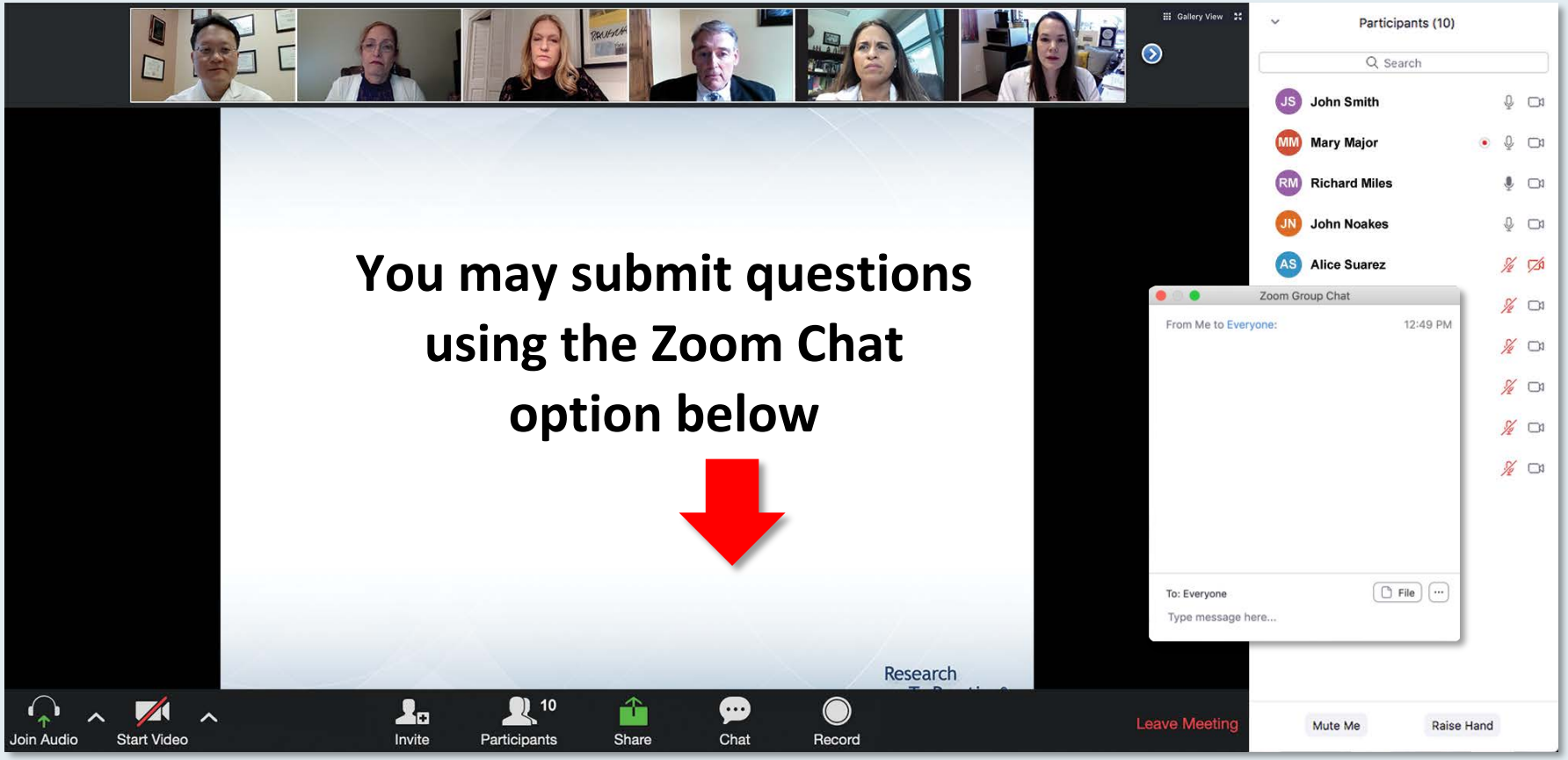

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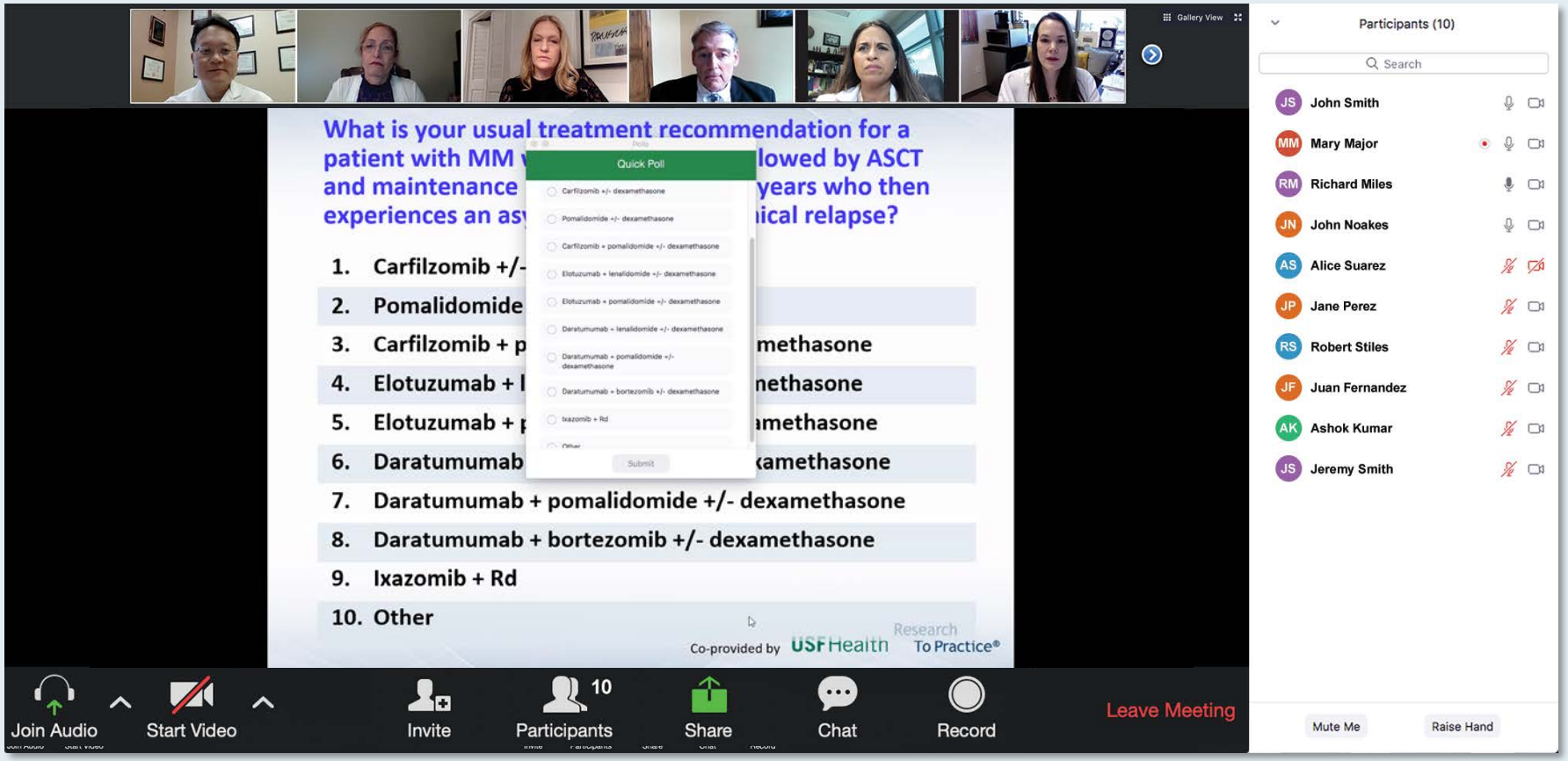

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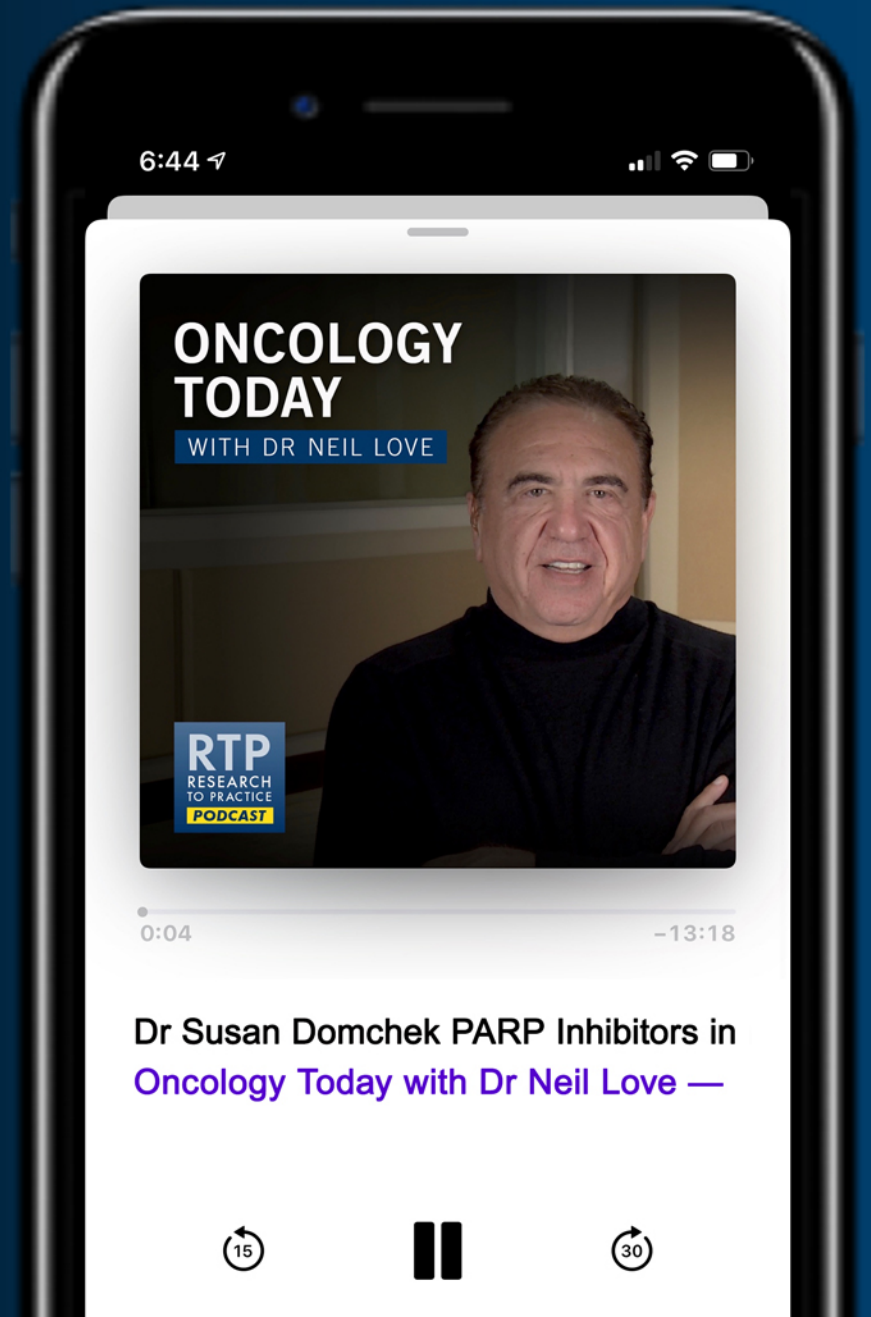

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Gigi Chen, MD
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Erik J Rupard, MD
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Tower Health – McGlinn Cancer Institute
West Reading, Pennsylvania

Laurie Matt-Amaral, MD, MPH
Attending Physician
Cleveland Clinic Akron General Medical Center
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Meet The Professor with Dr Slomovitz

MODULE 1: Cases from Drs Chen, Matt-Amaral and Rupard

- Dr Rupard: A 72-year-old woman with vulvar squamous cell carcinoma
- Dr Chen: A 63-year-old woman who presents with metastatic endometrial cancer
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Gynecologic Oncology 156 (2020) 715–725

Contents lists available at ScienceDirect

Gynecologic Oncology

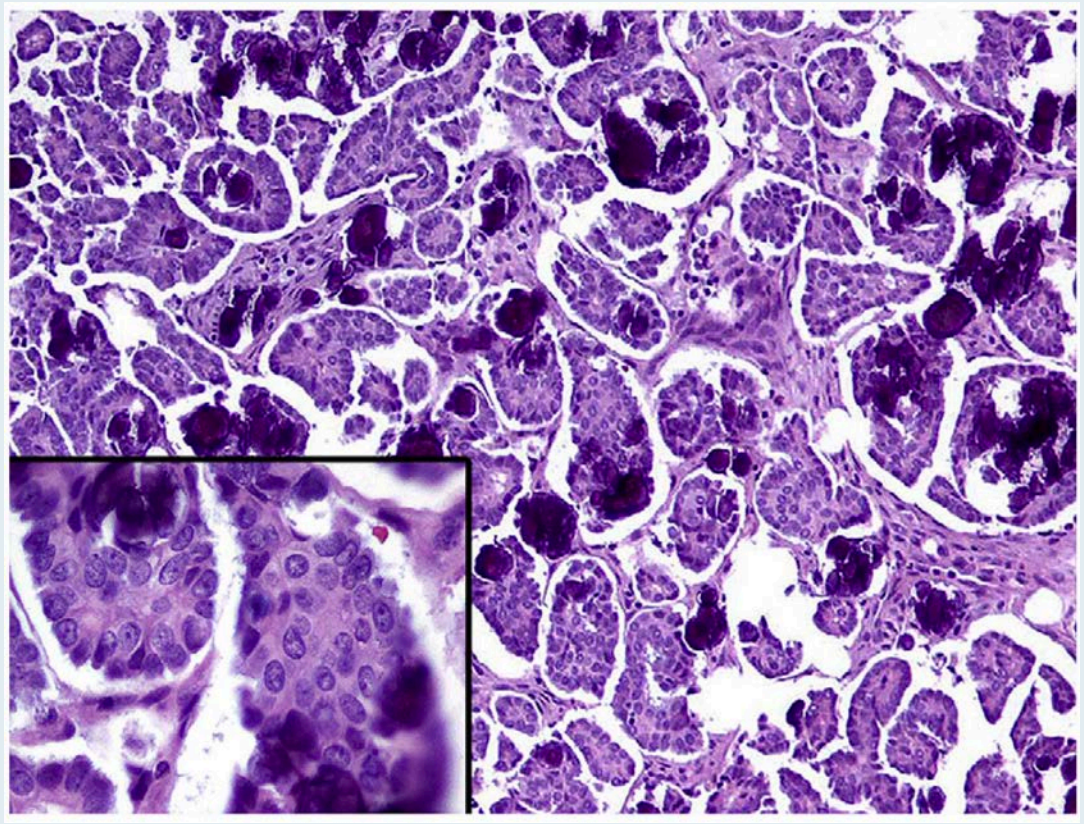
journal homepage: www.elsevier.com/locate/ygyno

Invited Review

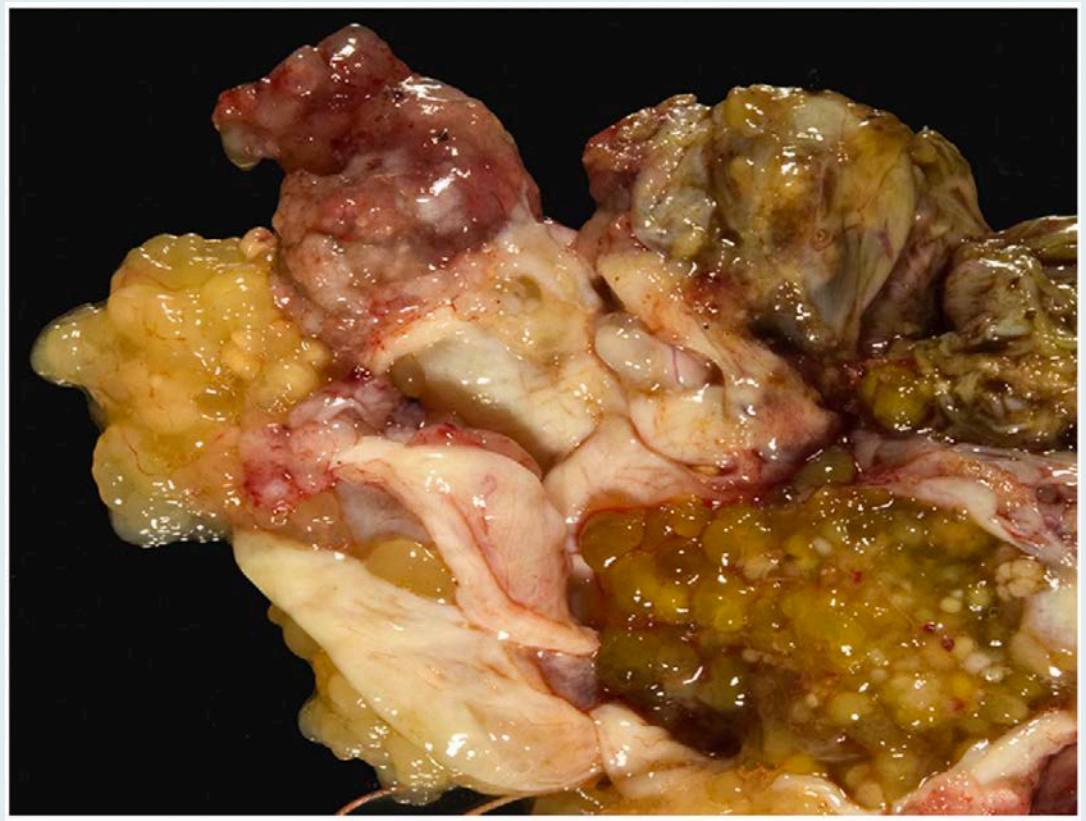
Low-grade serous ovarian cancer: State of the science

Brian Slomovitz [a,*], Charlie Gourley [b], Mark S. Carey [c], Anais Malpica [d], Ie-Ming Shih [e], David Huntsman [f], Amanda N. Fader [e], Rachel N. Grisham [g,h], Matthew Schlumbrecht [a], Charlotte C. Sun [i], Jane Ludemann [j], Gail Austin Cooney [k], Robert Coleman [l], Anil K. Sood [l], Haider Mahdi [m,n], Kwong K. Wong [l], Allan Covens [o], David M. O'Malley [p], Fabrice Lecuru [q,r], Lauren P. Cobb [l], Thomas A. Caputo [s], Taymaa May [t], Marilyn Huang [a], John Siemon [a], Marta Llauradó Fernández [c], Isabelle Ray-Coquard [u], David M. Gershenson [l]

Pathologic and Gross Features of Low-Grade Serous Carcinoma



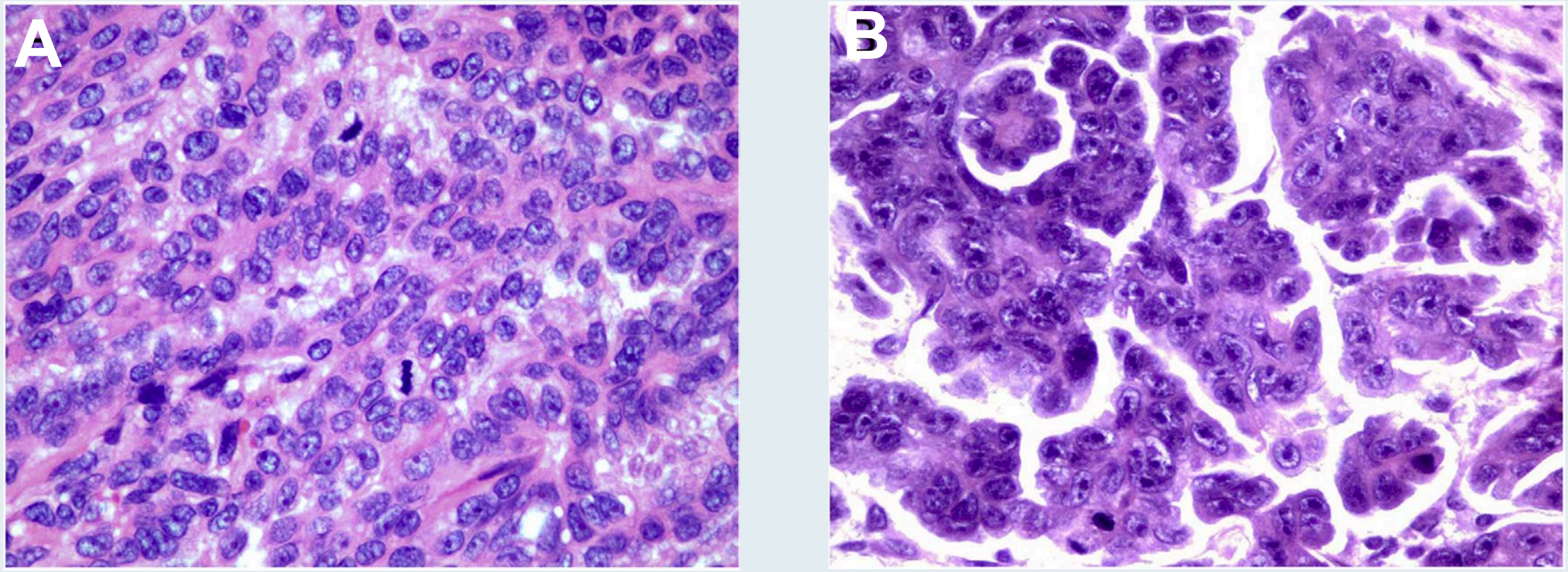
Low-grade serous carcinoma: Monotonous cells with mild atypia



Low-grade serous carcinoma: Gross image; the tumor has cystic spaces, papillary excrescences, and nodular areas

Slomovitz B et al. Gynecol Oncol 2020;156(3):715-25.

Low-Grade Serous Carcinoma: Mitotic Index



Low-grade serous carcinoma with a high mitotic index (A) and associated high-grade serous carcinoma component (B).

The mitotic index is generally low. The presence of numerous mitotic figures should prompt a very careful histological evaluation to rule out the rare association with a HGSC component (A, B)

Slomovitz B et al. Gynecol Oncol 2020;156(3):715-25.

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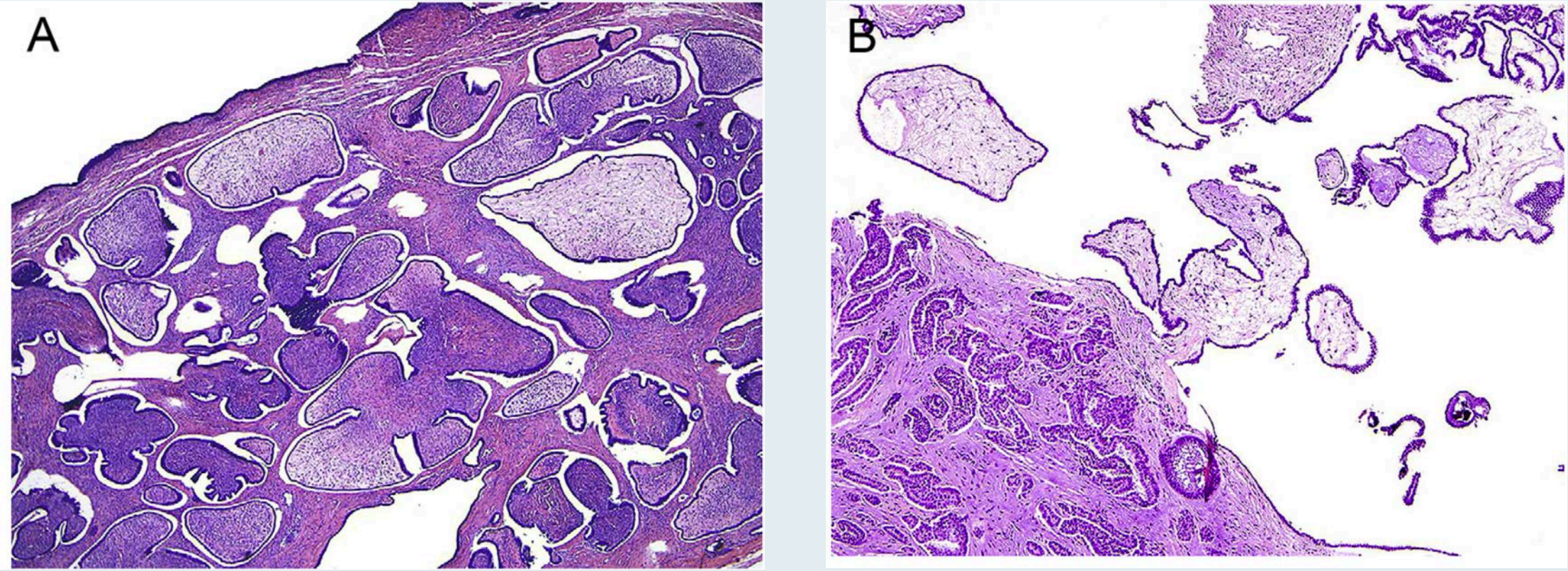
Low-Grade Serous Carcinoma: Microscopic Features



Low-grade serous carcinoma, macropapillae invading the stroma in an area >3mm (A), micropapillary pattern in area of invasion associated with stromal changes (B)

LGSC shows destructive invasion, which is recognized by the presence of neoplastic cells in the tumor/ovarian stroma in an area that either measures ≥3.0 mm in linear dimension or has desmoplasia

Slomovitz B et al. Gynecol Oncol 2020;156(3):715-25.

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Original Article

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

Low grade serous ovarian carcinoma: identifying variations in practice patterns

John Siemon,[1] David M Gershenson,[2] Brian Slomovitz,[1] Matthew Schlumbrecht[1]

Int J Gynecol Cancer 2019;29(1):174-80

Case Presentation – Dr Rupard: A 72-year-old woman with vulvar squamous cell carcinoma

Dr Erik J Rupard

- Vulvar squamous cell carcinoma → resection and RT
- Repeatedly declined chemotherapy, but began inquiring about immunotherapy in 2016
- 1/2020: Pembrolizumab, with good response

Questions

- What are your thoughts about the NCCN vulvar carcinoma guidelines?
- What are your thoughts about the use of PD-1/PD-L1 inhibitors in squamous cell or other vulvar cancers? Have you had success with the checkpoint inhibitors in vulvar cancers?

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JDDG

Journal of the German Society of Dermatology

CME Article

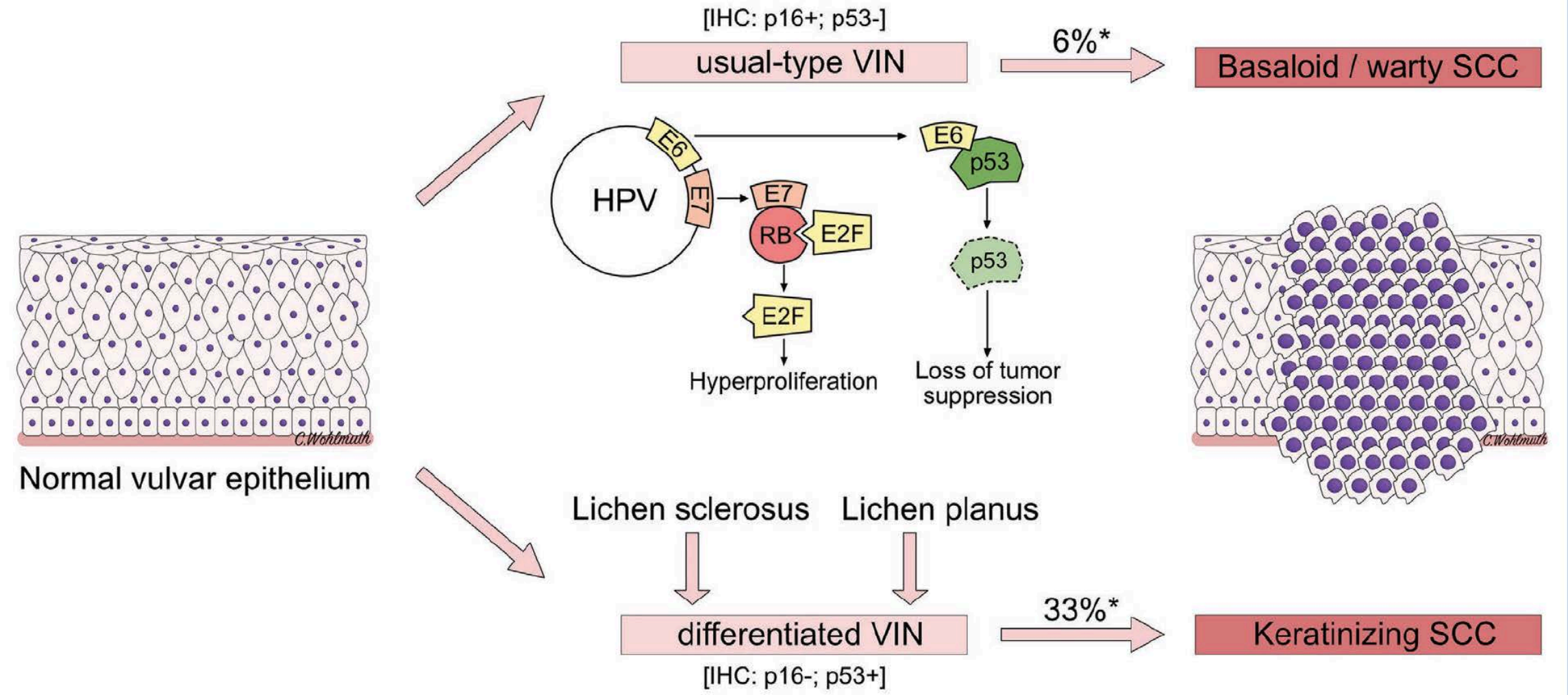
Submitted: 19.8.2019
Accepted: 30.10.2019
Conflict of interest
None.

DOI: 10.1111/ddg.13995

Vulvar malignancies: an interdisciplinary perspective

Wohlmuth C, Wohlmuth-Wieser I. *J Dtsch Dermatol Ges* 2019;17(12):1257-76

Pathophysiology of Vulvar Intraepithelial Neoplasia (VIN) and Its Progression to SCC



Wohlmuth C, Wohlmuth-Weiser I. JJDG 2019;17(12):1257-76.

Validation of Sentinel Lymph Biopsy in Patients with Early Stage Vulvar Cancer: A Prospective Trial of 1552 Women (GROINSS-V II/GOG270)

Slomovitz B et al.

SGO 2020;Abstract 2.

Radiotherapy as an Alternative Treatment for Inguinofemoral Lymphadenectomy in Vulvar Cancer Patients with a Metastatic Sentinel Node: Results of GROINSS-V II

van Der Zee AG et al.

SGO 2020;Abstract LBA 3.

Case Presentation – Dr Chen: A 63-year-old woman who presents with metastatic endometrial cancer

Dr Gigi Chen

- 7/2017: S/p robotic total hysterectomy, BSO, lysis of pelvic lesions
- Pathology: pT3aNx, with involvement of the mesorectal compartment (Stage IV)
  - Biopsy of mesorectal mass: Adenocarcinoma consistent with endometrial primary
  - Strongly positive for CK 7, ER; Negative for CK 20; MLH1 promotor hypermethylation
- Carboplatin/paclitaxel x 4 → PD
- 12/2017: Pembrolizumab, with CR
  - Hypothyroidism, on levothyroxine

Questions

- Can we stop the immunotherapy, since she has been on pembrolizumab for the past 2 years?
- If this patient presented today with MSI-H disease, what would be the best upfront treatment – chemotherapy or immunotherapy?

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Case Presentation – Dr Chen: A 68-year-old woman with longstanding metastatic endometrial cancer

Dr Gigi Chen

- 2008: TAH/BOS → GOG-209 protocol: Carboplatin/paclitaxel
- Progressive lung disease → Carboplatin/liposomal doxorubicin x 2 → PD
- 9/2009 – 10/2013: Tamoxifen, with PD → Anastrozole x 2 months → PD
- Carboplatin/paclitaxel (carbo infusion reaction) → Paclitaxel monotherapy x 12
- 8/2014: Progression in retroperitoneal mass – RT to lymph nodes
- Cisplatin/gemcitabine x 6 (completed 5/2015) → Megestrol acetate → 4/2018: PD
- FoundationOne®: MSS, TMB 5 mut/Mb, AKT1, BCOR, CTNNB1, FGFR2 and PIK3R1
- Letrozole/everolimus x 2 years
- Currently, progression of disease in lung and abdomen

Questions

- Would pembrolizumab/lenvatinib be a good option, and if so, at what dose should I start the lenvatinib?

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Case Presentation – Dr Matt-Amaral: A 66-year-old woman with high-grade papillary serous carcinoma

Dr Laurie Matt-Amaral

- High-grade papillary serous carcinoma, ER: 90%, MSS
  - CA125: >1200
- Neoadjuvant carboplatin/paclitaxel/bevacizumab, with PD after 5 cycles
- Pembrolizumab/lenvatinib (10 mg)
  - Preexisting hypertension exacerbated (now on 3-drug combination regimen with Cardiology)
  - CA125: 45

Questions

- Since she has had such a great response, would reducing the dose of lenvatinib to 5 mg still provide benefit?
- If dose reduce lenvatinib and her CA125 began rising, would they recommend going back up to 10 mg and then just dealing with the hypertension issues?

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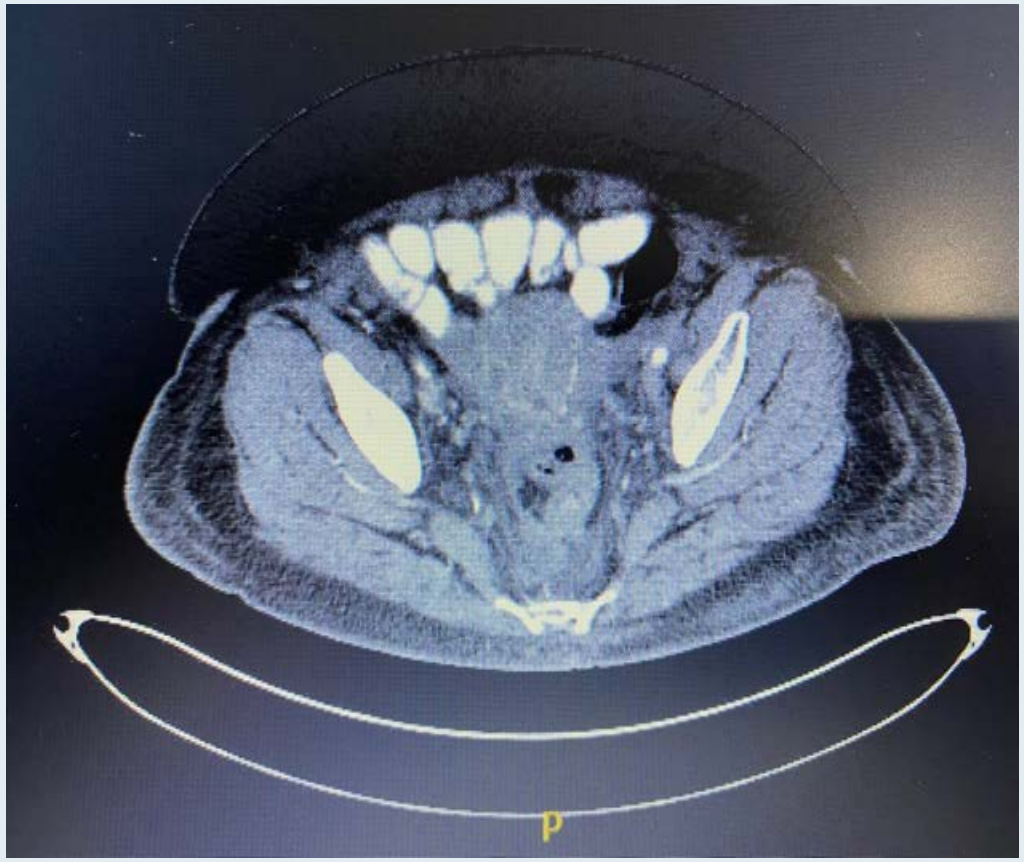
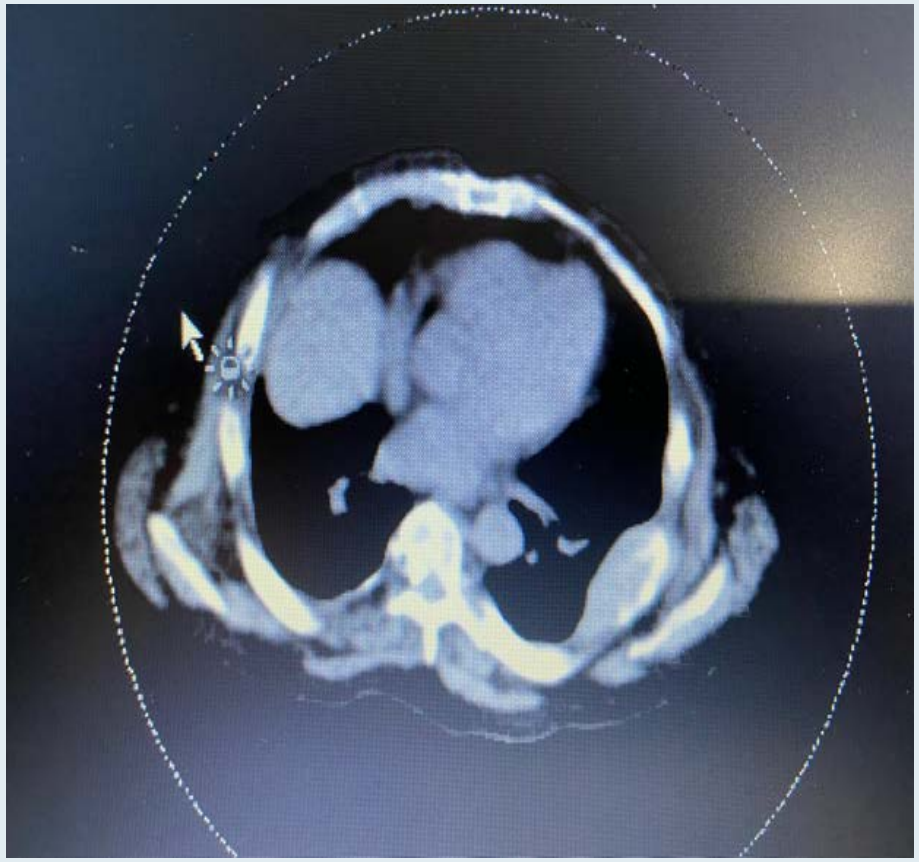
Case Presentation – Dr Matt-Amaral: A 66-year-old woman with high-grade papillary serous carcinoma





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Lancet Oncol 2019;20(3):383-93

Tisotumab vedotin in patients with advanced or metastatic solid tumours (InnovaTV 201): a first-in-human, multicentre, phase 1–2 trial

Johann S de Bono, Nicole Concin, David S Hong, Fiona C Thistlethwaite, Jean-Pascal Machiels, Hendrik-Tobias Arkenau, Ruth Plummer, Robert Hugh Jones, Dorte Nielsen, Kristian Windfeld, Srinivas Ghatta, Brian M Slomovitz, James F Spicer, Jeffrey Yachnin, Joo Ern Ang, Paul Morten Mau-Sørensen, Martin David Forster, Dearbhaile Collins, Emma Dean, Reshma A Rangwala, Ulrik Lassen

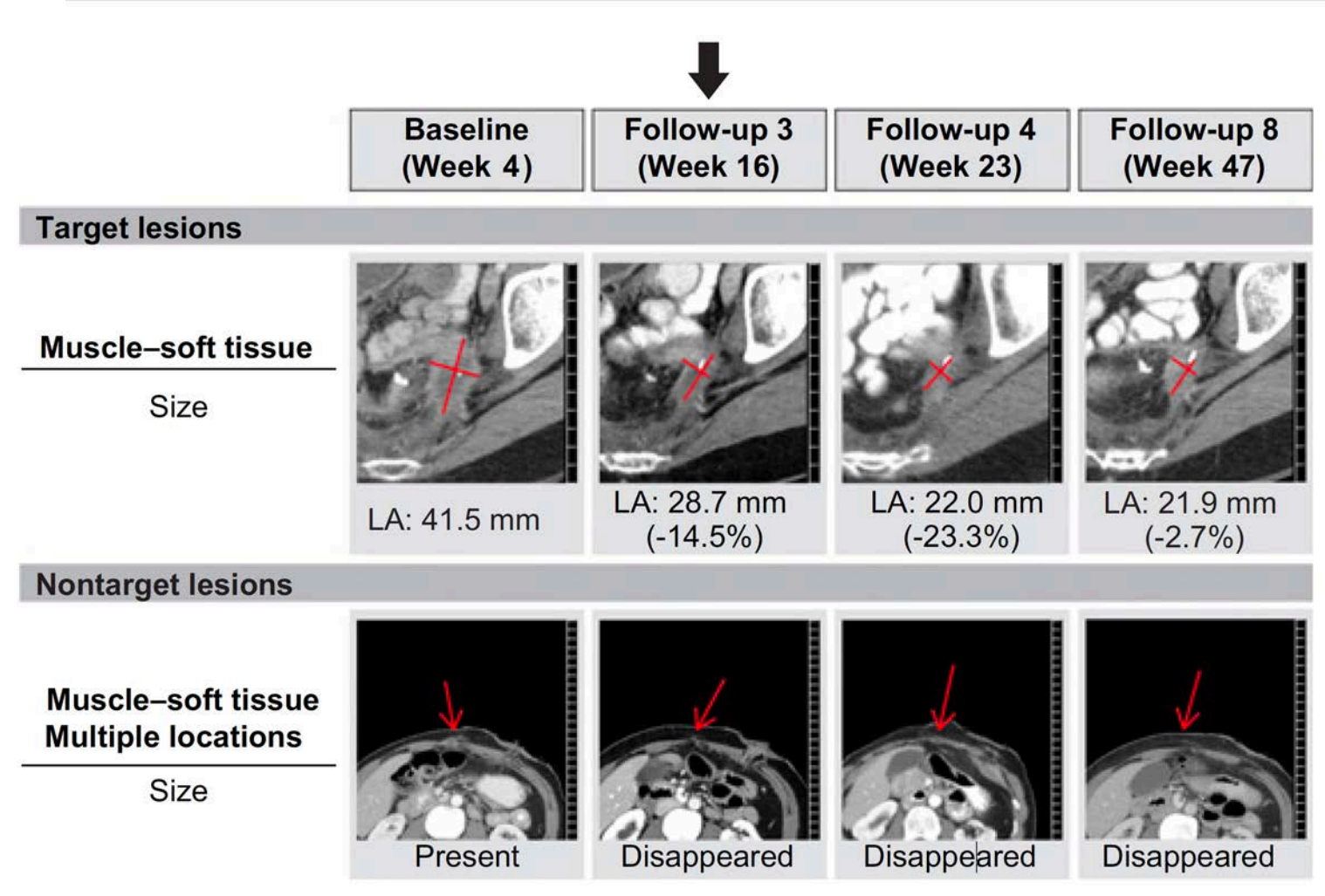
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Tisotumab Vedotin in Previously Treated Recurrent or Metastatic Cervical Cancer

David S. Hong[1], Nicole Concin[2], Ignace Vergote[2], Johann S. de Bono[3], Brian M. Slomovitz[4], Yvette Drew[5], Hendrik-Tobias Arkenau[6], Jean-Pascal Machiels[7], James F. Spicer[8], Robert Jones[9], Martin D. Forster[10], Nathalie Cornez[11], Christine Gennigens[12], Melissa L. Johnson[13], Fiona C. Thistlethwaite[14], Reshma A. Rangwala[15], Srinivas Ghatta[16], Kristian Windfeld[17], Jeffrey R. Harris[18], Ulrik Niels Lassen[19], and Robert L. Coleman[20]

Clin Cancer Res 2020;26(6):1220-8

Target and Nontarget Lesion Scans at Baseline and Follow-up Visits for a 43-Year-Old Female with Squamous Cell Carcinoma Previously Treated with Paclitaxel and Carboplatin



Weeks are measured from cycle 1 day 1 of tisotumab vedotin. The patient achieved a PR and discontinued tisotumab vedotin due to an adverse event at week 16 (black arrow).

Hong DS et al. Clin Cancer Res 2020;26(6):1220-8.

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Tisotumab Vedotin in Previously Treated Recurrent or Metastatic Cervical Cancer: Results from the Phase II innovaTV 204/GOG-3023/ENGOT-cx6 Study

Coleman RL et al.

ESMO 2020;Abstract LBA32.

A Randomised Double-Blind Placebo-Controlled Phase II Trial of Palbociclib Combined with Letrozole (L) in Patients (pts) with Oestrogen Receptor-Positive (ER+) Advanced/Recurrent Endometrial Cancer (EC): NSGO-PALEO/ENGOT-EN3 Trial

Mirza MR et al.

ESMO 2020;Abstract LBA28.

ENGOT-EN6/NSGO-RUBY: A Phase III, Randomized, Double-Blind, Multicenter Study of Dostarlimab + Carboplatin-Paclitaxel versus Placebo + Carboplatin-Paclitaxel in Recurrent or Primary Advanced Endometrial Cancer (EC)

Mirza MR et al.

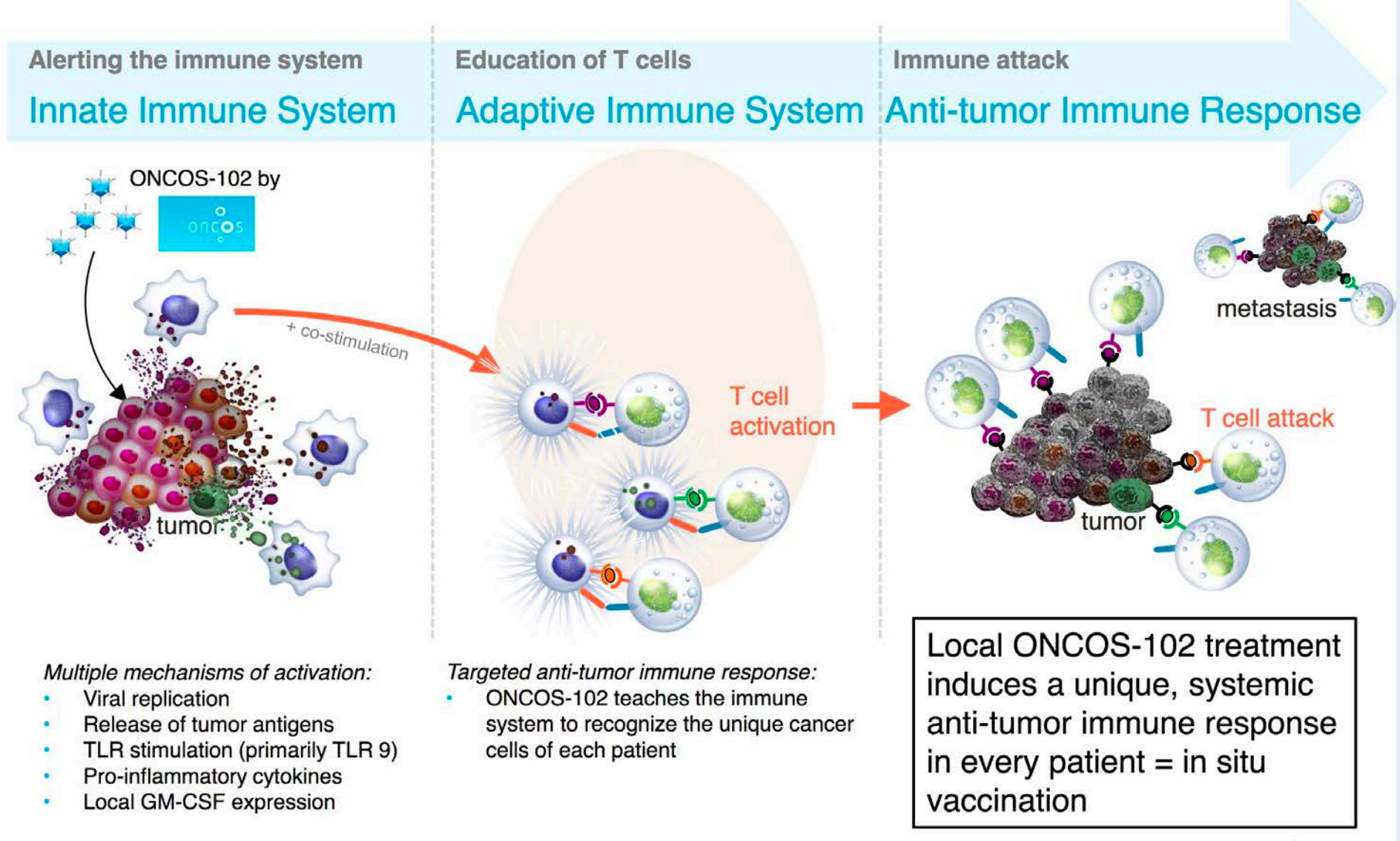
ASCO 2020;Abstract TPS6107.

Phase I/II Study to Evaluate Systemic Durvalumab + Intraperitoneal (IP) ONCOS-102 in Patients with Peritoneal Disease Who Have Epithelial Ovarian (OC) or Metastatic Colorectal Cancer (CRC): Interim Phase I Clinical and Translational Results

Zamarin D et al.

ASCO 2020;Abstract 3017.

ONCOS-102 Effectively Activates the Immune System



Zamarin D et al. ASCO 2020;Abstract 3017.

Safety and Efficacy of Adoptive Cell Transfer Using Autologous Tumor Infiltrating Lymphocytes (LN-145) for Treatment of Recurrent, Metastatic, or Persistent Cervical Carcinoma

Jazaeri AA et al.

ASCO 2019;Abstract 2538.

Cryopreserved Autologous TIL (LN-145)

EXCISE: Patient's tumor is removed via surgical resection of a lesion

EXTRACT: Tumor is fragmented and placed in media for TIL to leave the tumor and enter media

EXPAND: TIL expanded via IL-2 + OKT3 exponentially *ex vivo* to yield $10^9 – 10^{11}$ TIL

PREPARE & INFUSE: Patient receives non-myeloablative lymphodepletion and is infused with their expanded TIL and IL-2

Process time: 22 days

- Courier from clinical site
- Co-culture TIL and feeder cells for expansion *ex vivo*
- Harvest and cryopreserved TIL infusion product
- Courier to clinical site for infusion

Jazaeri AA et al. ASCO 2019;Abstract 2538.

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- Tisotumab vedotin in metastatic solid tumors and cervical cancer
- NSGO-PALEO trial: Palbociclib/letrozole in ER-positive advanced/recurrent endometrial cancer
- Ongoing Phase III RUBY study of dostarlimab plus chemotherapy for recurrent endometrial cancer
- Vulvar malignancies: An interdisciplinary perspective
- GOG-270: Validation of sentinel lymph node biopsy for patients with early-stage vulvar cancer
- Radiation therapy as an alternative treatment for inguinofemoral lymphadenectomy in vulva cancer
- Durvalumab plus intraperitoneal ONCOS-102 in patients with OC or CRC with peritoneal disease
- Adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for cervical cancer

MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

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In general, what treatment would you recommend for a patient with microsatellite-stable metastatic endometrial cancer who experienced disease progression on carboplatin/paclitaxel?

1. Cisplatin/doxorubicin
2. Carboplatin/docetaxel
3. Lenvatinib/pembrolizumab
4. Test for PD-L1 combined positive score (CPS) and administer pembrolizumab if 1% or higher
5. Pembrolizumab
6. Other chemotherapy
7. Other

In general, what treatment would you recommend for a patient with MSI-high metastatic endometrial cancer who experienced disease progression on carboplatin/paclitaxel?

1. Cisplatin/doxorubicin
2. Carboplatin/docetaxel
3. Lenvatinib/pembrolizumab
4. Pembrolizumab
5. Other chemotherapy
6. Other

In general, what treatment would you recommend for a patient with metastatic endometrial cancer who experienced disease progression on carboplatin/paclitaxel if their disease was…

	Microsatellite stable (MSS)	MSI high (MSI-H)
 MICHAEL J BIRRER, MD, PHD	Lenvatinib/pembrolizumab	Pembrolizumab
 ROBERT L COLEMAN, MD	Lenvatinib/pembrolizumab	Pembrolizumab
 ANA OAKNIN, MD, PHD	Lenvatinib/pembrolizumab	Dostarlimab
 DAVID M O'MALLEY, MD	Lenvatinib/pembrolizumab	Pembrolizumab
 RICHARD T PENSON, MD, MRCP	Lenvatinib/pembrolizumab	Pembrolizumab
 MATTHEW A POWELL, MD	Lenvatinib/pembrolizumab	Pembrolizumab
 BRIAN M SLOMOVITZ, MD	Lenvatinib/pembrolizumab	Pembrolizumab
 KRISHNANSU S TEWARI, MD	Lenvatinib/pembrolizumab	Pembrolizumab
 PROFESSOR IGNACE VERGOTE	Lenvatinib/pembrolizumab	Pembrolizumab

For a patient with MSI-high metastatic endometrial cancer, outside of a clinical trial setting and regulatory and reimbursement issues aside, what is the earliest point at which you would introduce an anti-PD-1/PD-L1 antibody? Which regimen would you generally use?

	Earliest timing	Regimen
 MICHAEL J BIRRER, MD, PHD	Second line	Pembrolizumab
 ROBERT L COLEMAN, MD	Second line	Pembrolizumab
 ANA OAKNIN, MD, PHD	Second line	Dostarlimab
 DAVID M O'MALLEY, MD	First line	Pembrolizumab
 RICHARD T PENSON, MD, MRCP	First line	Pembrolizumab
 MATTHEW A POWELL, MD	Second line	Pembrolizumab
 BRIAN M SLOMOVITZ, MD	Second line	Pembrolizumab
 KRISHNANSU S TEWARI, MD	Second line	Pembrolizumab
 PROFESSOR IGNACE VERGOTE	First line	Pembrolizumab

In general, what would be your preferred first-line therapy for a patient with MSS metastatic cervical cancer who has received no prior systemic treatment?

 MICHAEL J BIRRER, MD, PHD	Cisplatin/paclitaxel/bevacizumab
 ROBERT L COLEMAN, MD	Cisplatin/paclitaxel/bevacizumab
 ANA OAKNIN, MD, PHD	Carboplatin/paclitaxel
 DAVID M O'MALLEY, MD	Cisplatin/paclitaxel/bevacizumab
 RICHARD T PENSON, MD, MRCP	Cisplatin/paclitaxel/bevacizumab
 MATTHEW A POWELL, MD	Cisplatin/paclitaxel/bevacizumab
 BRIAN M SLOMOVITZ, MD	Cisplatin/paclitaxel/bevacizumab
 KRISHNANSU S TEWARI, MD	Cisplatin/paclitaxel/bevacizumab
 PROFESSOR IGNACE VERGOTE	Carboplatin/paclitaxel/bevacizumab

In general, what would be your preferred first-line therapy for a patient with MSS metastatic cervical cancer who experienced relapse 12 months after receiving cisplatin-based chemoradiation therapy for Stage IIIB disease?

 MICHAEL J BIRRER, MD, PHD	Carboplatin/paclitaxel/bevacizumab
 ROBERT L COLEMAN, MD	Carboplatin/paclitaxel/bevacizumab
 ANA OAKNIN, MD, PHD	Cisplatin/paclitaxel/bevacizumab
 DAVID M O'MALLEY, MD	Carboplatin/paclitaxel/bevacizumab
 RICHARD T PENSON, MD, MRCP	Cisplatin/paclitaxel/bevacizumab
 MATTHEW A POWELL, MD	Carboplatin/paclitaxel/bevacizumab
 BRIAN M SLOMOVITZ, MD	Test for PD-L1 CPS and administer pembrolizumab if 1% or higher
 KRISHNANSU S TEWARI, MD	Carboplatin/paclitaxel/bevacizumab
 PROFESSOR IGNACE VERGOTE	Carboplatin/paclitaxel/bevacizumab

CPS = combined positive score

In general, what would be your preferred second-line therapy for a patient with MSS metastatic cervical cancer who experiences disease progression on carboplatin/paclitaxel/bevacizumab?

1. Other chemotherapy
2. Test for PD-L1 CPS and administer pembrolizumab if 1% or higher
3. Pembrolizumab
4. Other

In general, what would be your preferred second-line therapy for a patient with MSS metastatic cervical cancer who experienced disease progression on carboplatin/paclitaxel/bevacizumab?

 MICHAEL J BIRRER, MD, PHD	Pembrolizumab
 ROBERT L COLEMAN, MD	Test for PD-L1 CPS and administer pembrolizumab if 1% or higher
 ANA OAKNIN, MD, PHD	Anti-PD-1/PD-L1 antibody in general
 DAVID M O'MALLEY, MD	Test for PD-L1 CPS and administer pembrolizumab if 1% or higher
 RICHARD T PENSON, MD, MRCP	Test for PD-L1 CPS and administer pembrolizumab if 1% or higher
 MATTHEW A POWELL, MD	Test for PD-L1 CPS and administer pembrolizumab if 1% or higher
 BRIAN M SLOMOVITZ, MD	Test for PD-L1 CPS and administer pembrolizumab if 1% or higher
 KRISHNANSU S TEWARI, MD	Test for PD-L1 CPS and administer pembrolizumab if 1% or higher
 PROFESSOR IGNACE VERGOTE	Tisotumab vedotin

Based on your clinical experience and/or the published literature, how would you characterize the tolerability of tisotumab vedotin in the treatment of metastatic cervical cancer?

 MICHAEL J BIRRER, MD, PHD	Well tolerated except for epistasis
 ROBERT L COLEMAN, MD	Similar to other single-agent chemotherapy
 ANA OAKNIN, MD, PHD	Moderate toxicity
 DAVID M O'MALLEY, MD	Reasonable toxicity
 RICHARD T PENSON, MD, MRCP	Excited by it
 MATTHEW A POWELL, MD	Reasonable toxicity
 BRIAN M SLOMOVITZ, MD	Well tolerated; ocular side effects
 KRISHNANSU S TEWARI, MD	Relatively well tolerated so far
 PROFESSOR IGNACE VERGOTE	Good tolerability

A patient with PD-L1-positive metastatic cervical cancer experiences disease progression on platinum-based therapy and has significant symptoms from her disease. If tisotumab vedotin were approved, what would likely be your next line of treatment?

1. Pembrolizumab
2. Tisotumab vedotin
3. Other

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Do you generally evaluate microsatellite instability status in your patients with advanced ovarian cancer?

1. Yes
2. No

Do you generally evaluate microsatellite instability status in your patients with advanced ovarian cancer?

 MICHAEL J BIRRER, MD, PHD	Yes
 ROBERT L COLEMAN, MD	Yes
 ANA OAKNIN, MD, PHD	No
 DAVID M O'MALLEY, MD	Yes
 RICHARD T PENSON, MD, MRCP	Yes
 MATTHEW A POWELL, MD	Yes
 BRIAN M SLOMOVITZ, MD	No
 KRISHNANSU S TEWARI, MD	No
 PROFESSOR IGNACE VERGOTE	No

Meet The Professor with Dr Slomovitz

MODULE 1: Cases from Drs Chen, Matt-Amaral and Rupard

- Dr Rupard: A 72-year-old woman with vulvar squamous cell carcinoma
- Dr Chen: A 63-year-old woman who presents with metastatic endometrial cancer
- Dr Chen: A 68-year-old woman with longstanding metastatic endometrial cancer
- Dr Matt-Amaral: A 66-year-old woman with high-grade papillary serous carcinoma

MODULE 2: Gynecologic Oncology Journal Club with Dr Slomovitz

- State of the Science in low-grade serous ovarian cancer (OC)
- Variations in practice patterns in low-grade serous OC
- Tisotumab vedotin in metastatic solid tumors and cervical cancer
- NSGO-PALEO trial: Palbociclib/letrozole in ER-positive advanced/recurrent endometrial cancer
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MODULE 3: Beyond the Guidelines – Clinical Investigator Approaches to Common Clinical Scenarios

MODULE 4: Key Recent Data Sets

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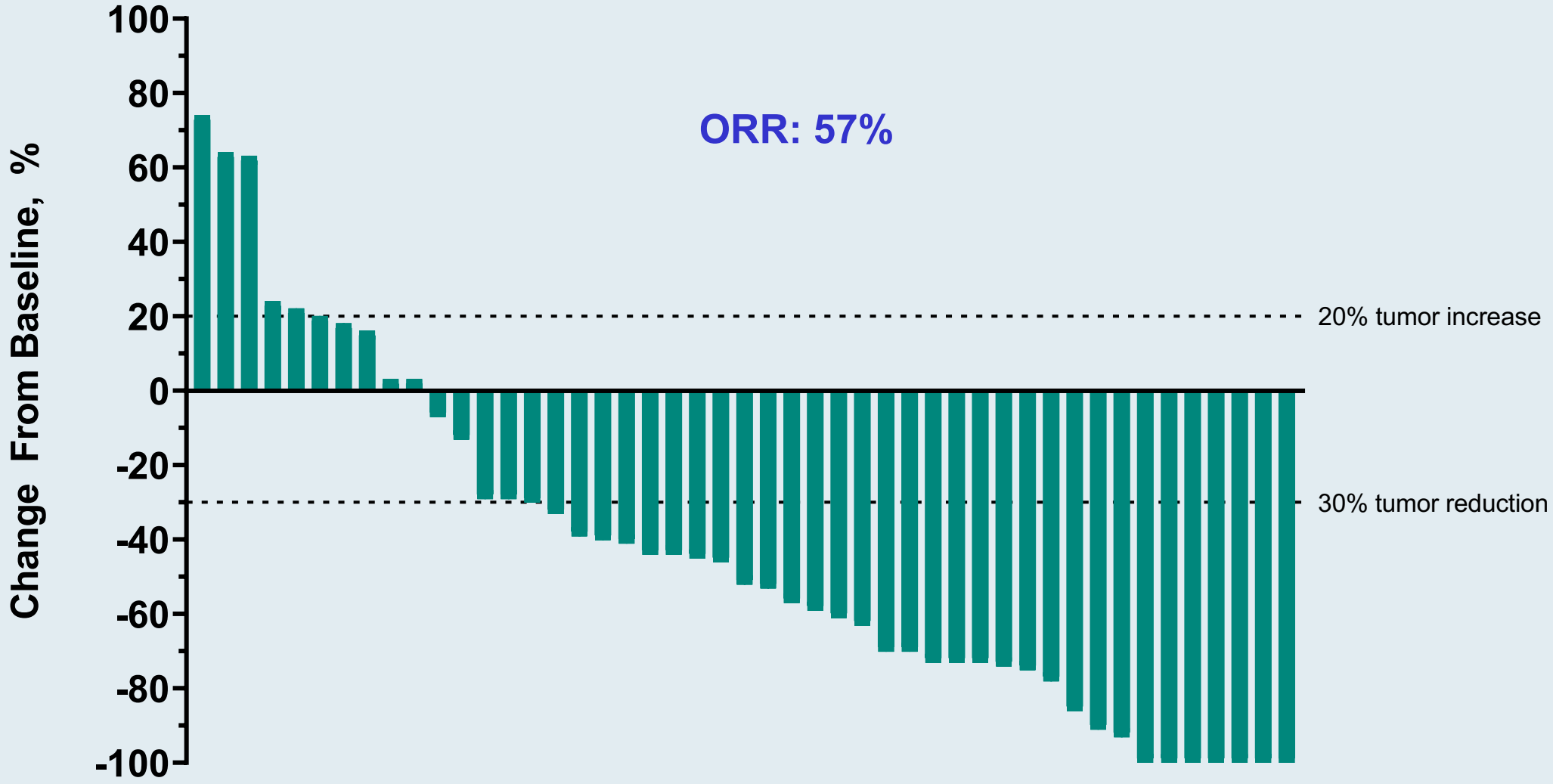
KEYNOTE-158: Best Percentage Change from Baseline in Target Lesion Size with Pembrolizumab Monotherapy in MSI-H Endometrial Cancer



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

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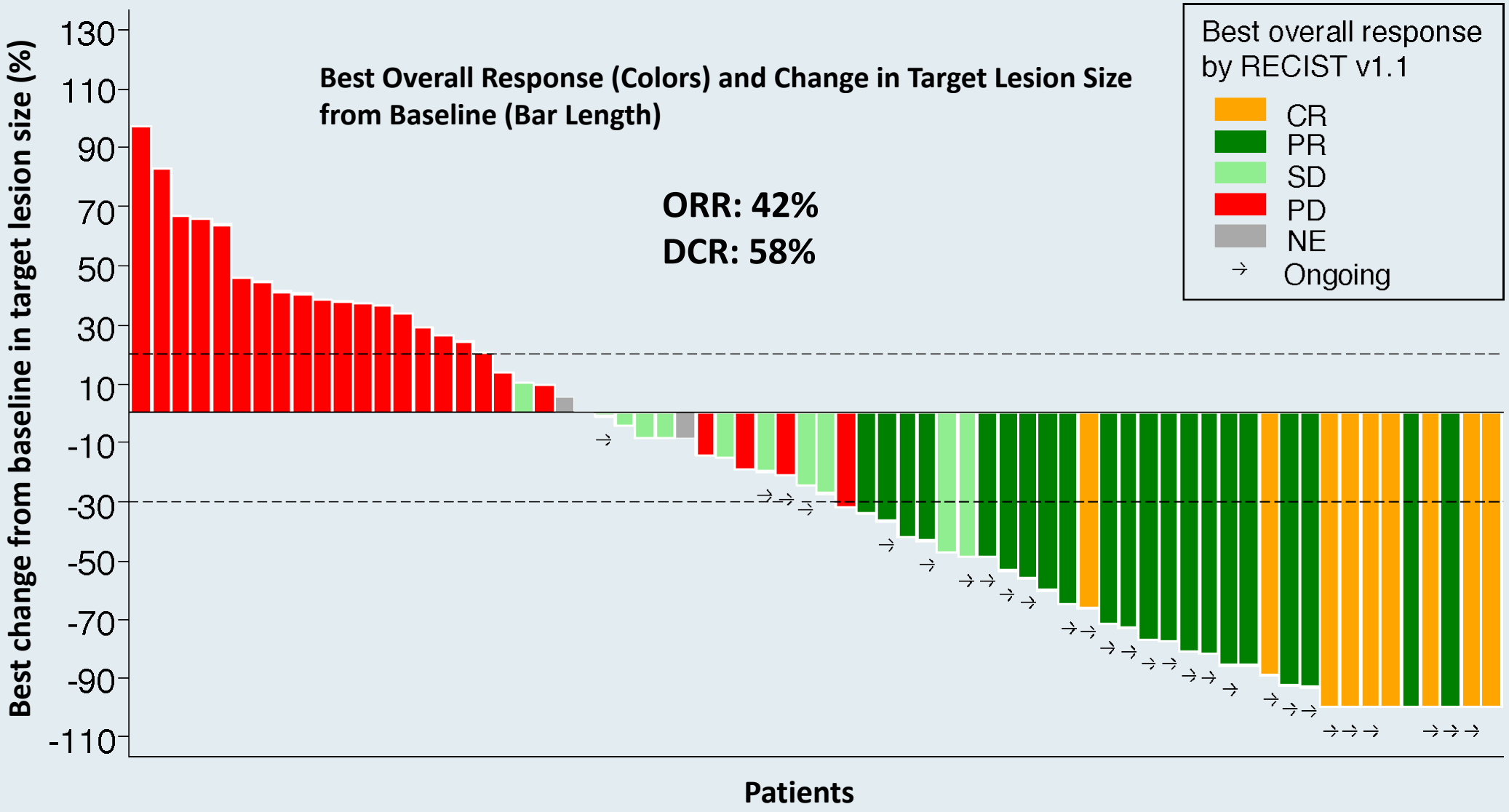
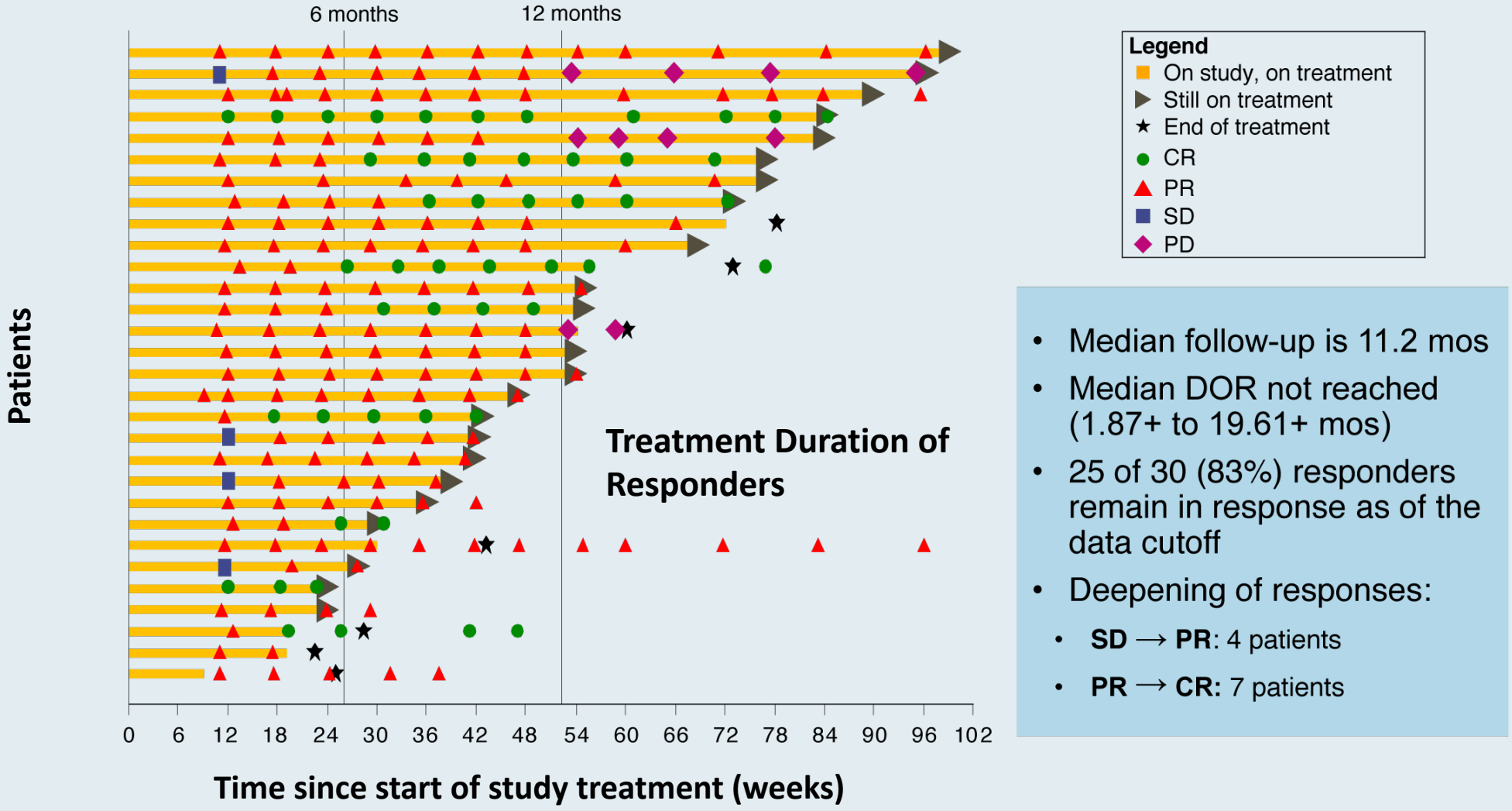
GARNET: Dostarlimab in Recurrent or Advanced dMMR Endometrial Cancer



Oaknin A et al. SGO 2020;Abstract LBA9.

GARNET: Dostarlimab in Recurrent or Advanced dMMR Endometrial Cancer

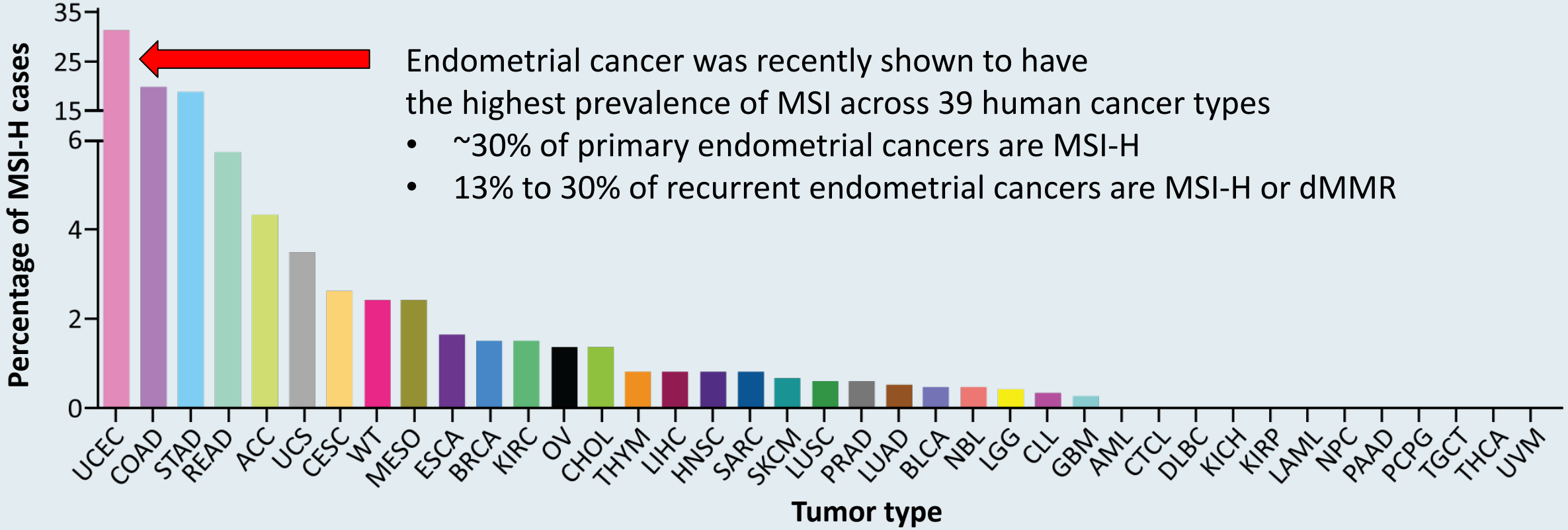


- Median follow-up is 11.2 mos
- Median DOR not reached (1.87+ to 19.61+ mos)
- 25 of 30 (83%) responders remain in response as of the data cutoff
- Deepening of responses:
  - **SD → PR**: 4 patients
  - **PR → CR:** 7 patients

Oaknin A et al. SGO 2020;Abstract LBA9.

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

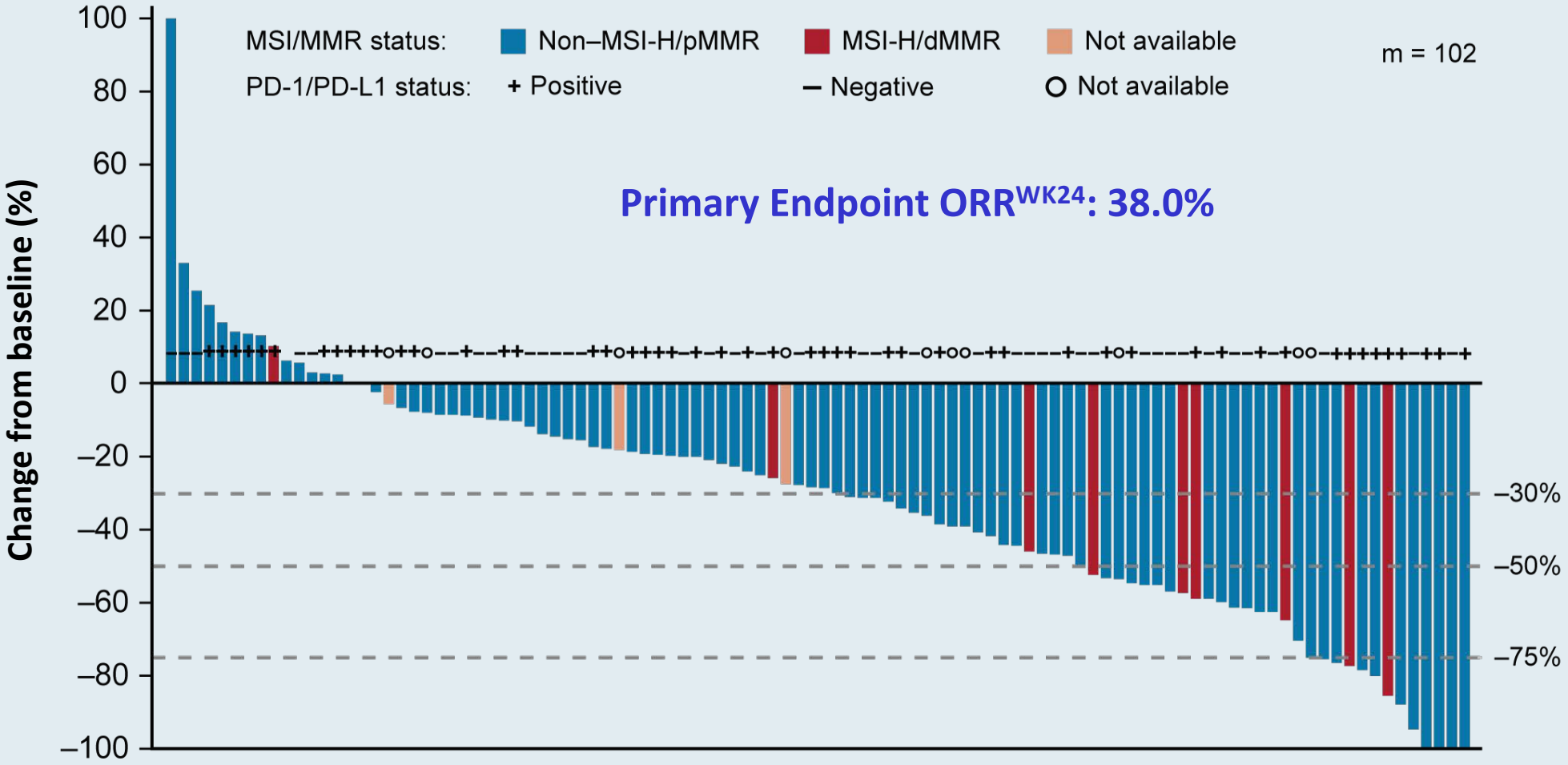
- ~30% of primary endometrial cancers are MSI-H
- 13% to 30% of recurrent endometrial cancers are MSI-H or dMMR

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.

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].

RTP RESEARCH TO PRACTICE

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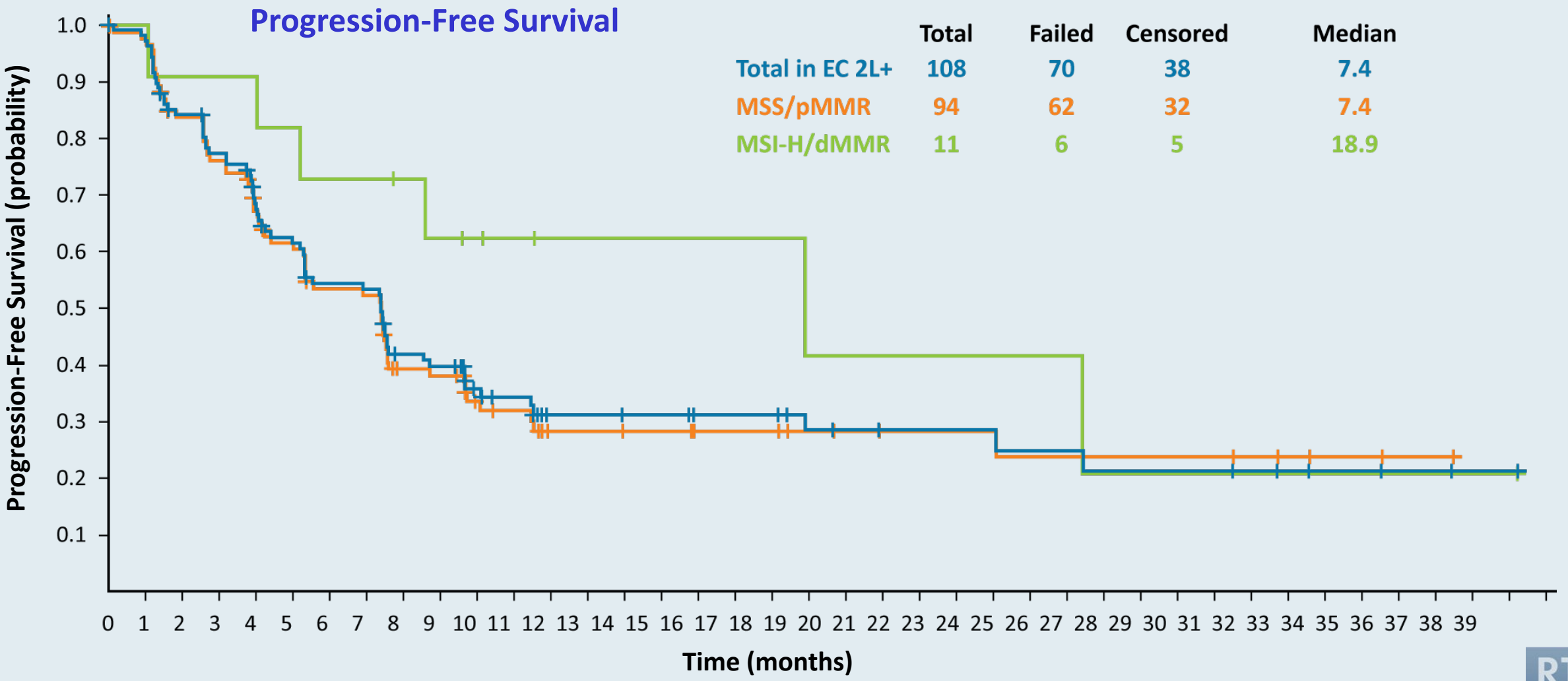

Makker V et al. *J Clin Oncol* 2020;[Online ahead of print].

RTP RESEARCH TO PRACTICE

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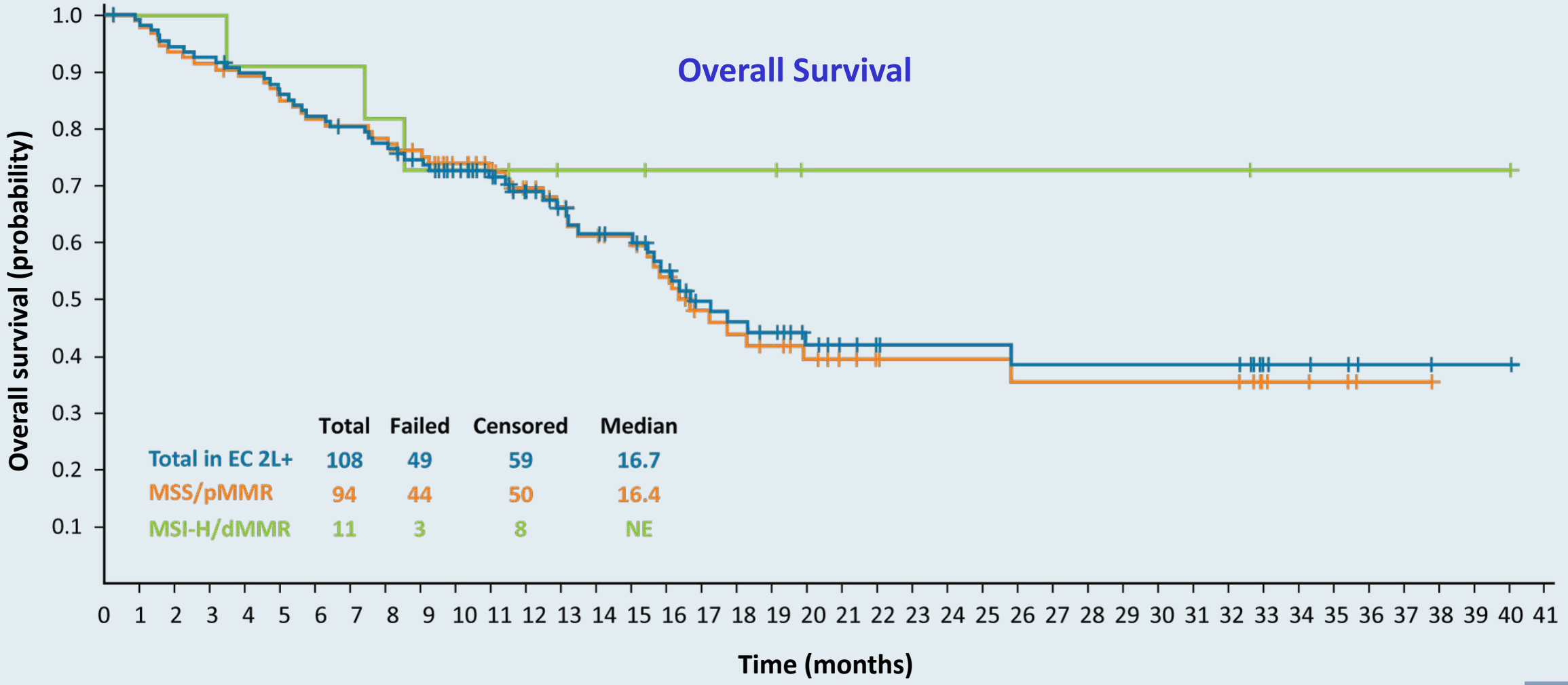


Makker V et al. *J Clin Oncol* 2020;[Online ahead of print].

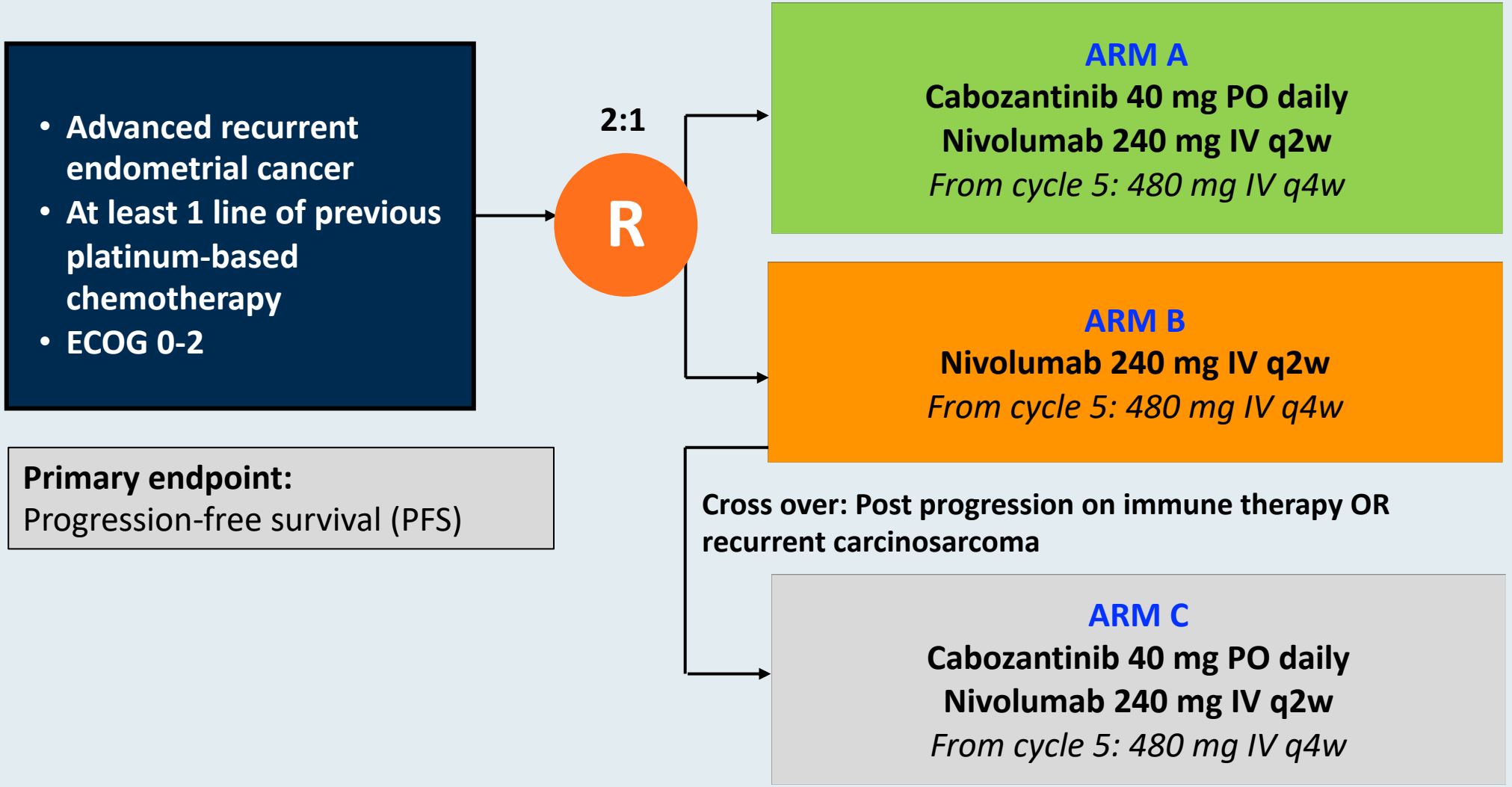
RTP RESEARCH TO PRACTICE

NCI 10104: A Randomized Phase 2 Study of Cabozantinib in Combination with Nivolumab in Advanced, Recurrent Metastatic Endometrial Cancer

Lheureux S et al.

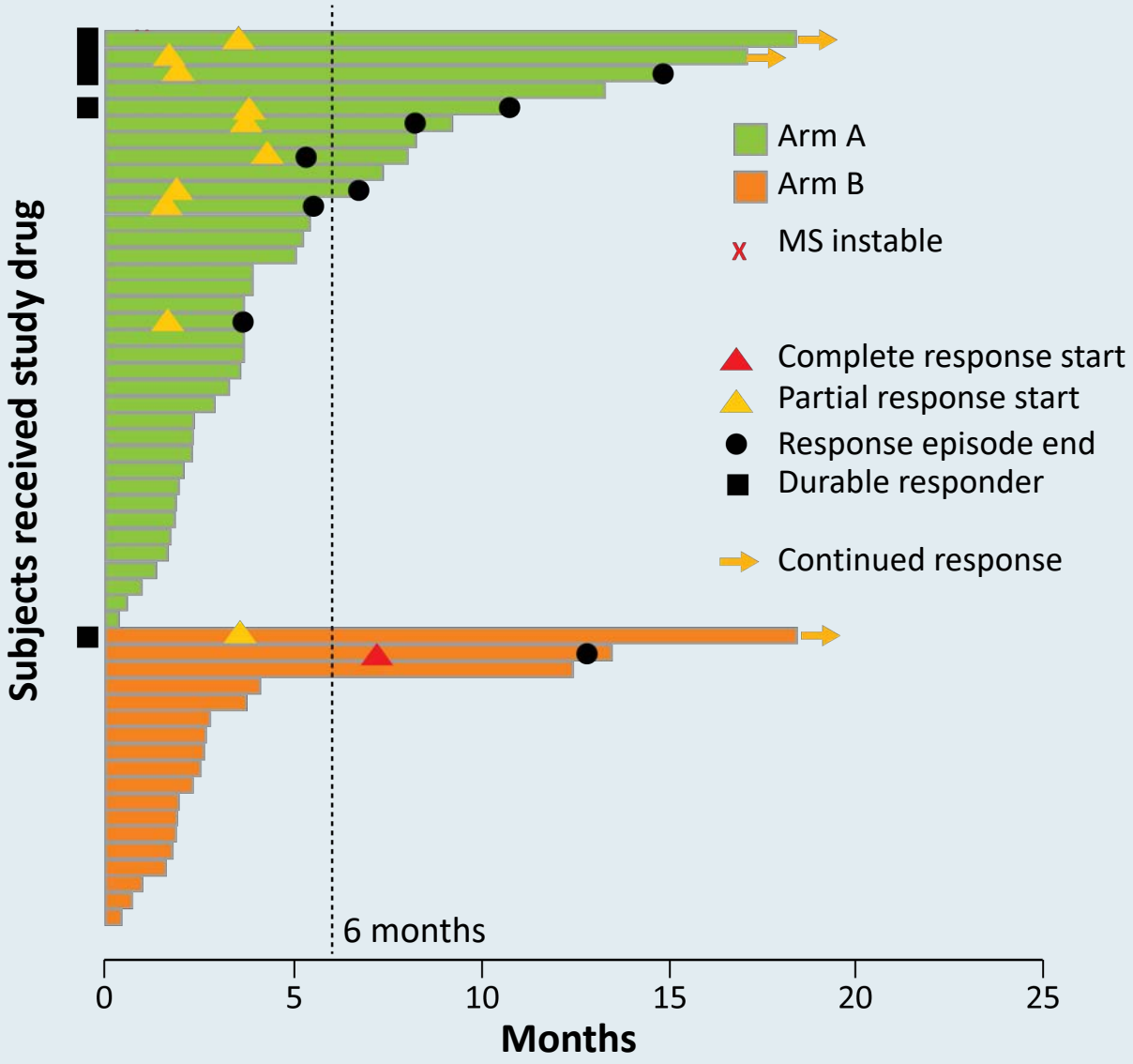
ASCO 2020;Abstract 6010.

NCI 10104 Phase II Study Schema



Lheureux S et al. ASCO 2020;Abstract 6010.

NCI 10104: Response Rate and Duration and Survival Analyses



	Arm A Cabo/nivolumab (n = 36)	Arm B Nivolumab (n = 18)
ORR	25%	11%
SD as best response	44%	11%
CBR	69%	22%
Median PFS*	5.3 mo	1.9 mo
Median OS†	13.0 mo	7.9 mo

* HR: 0.59, significant

† Immature, 55% events

Lheureux S et al. ASCO 2020;Abstract 6010.

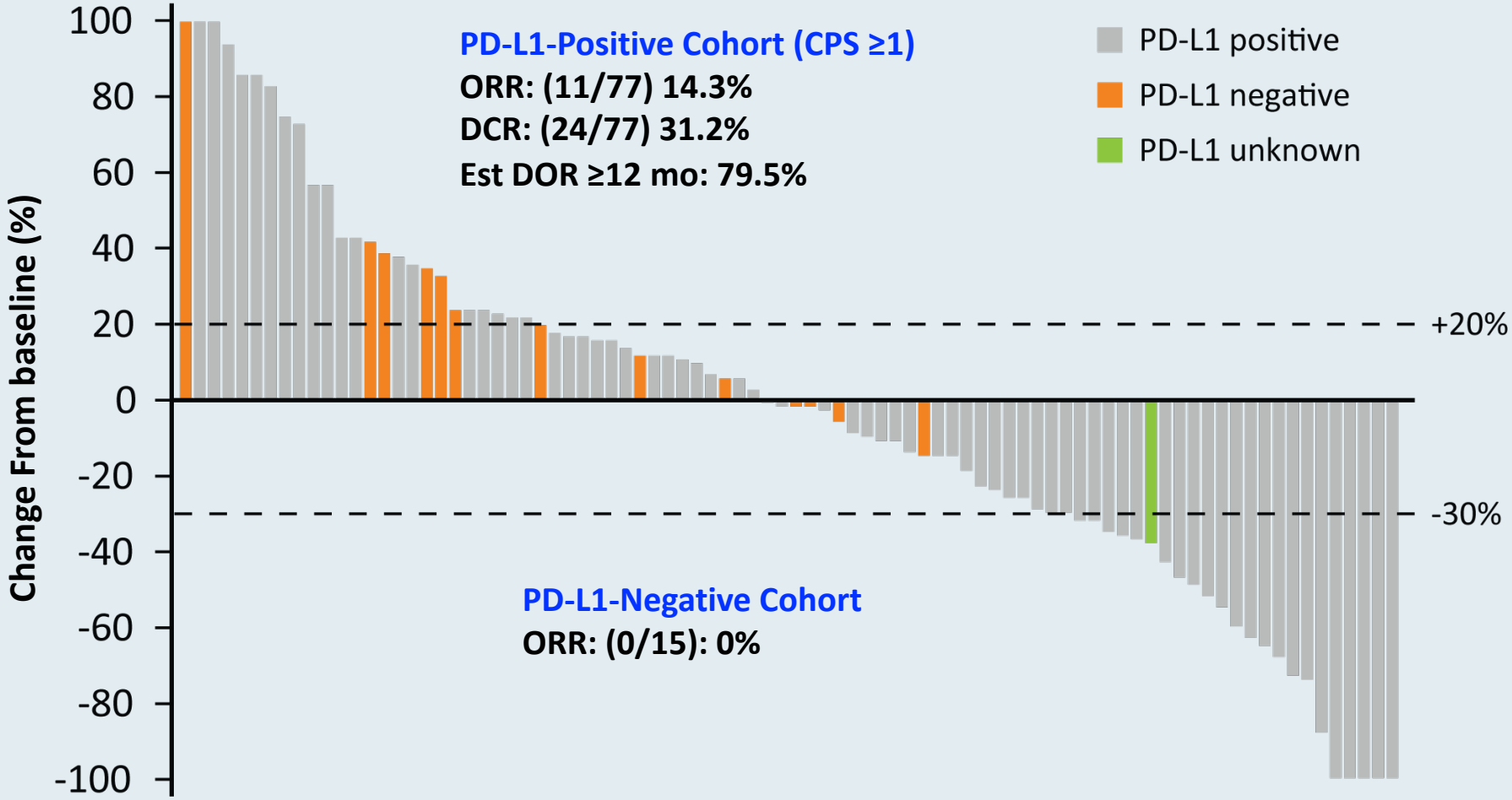
Select Ongoing Phase III Immune Checkpoint Inhibitor Combination Studies

Trial	N	Eligibility	Randomization
KEYNOTE-775	780	• Advanced, recurrent or metastatic EC • PD after 1 prior platinum-based chemo regimen	• 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
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 August 18, 2020; Green AK et al. *ASCO Ed Book* 2020.

Anti-PD-1/PD-L1 Antibodies in Cervical Cancer

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.

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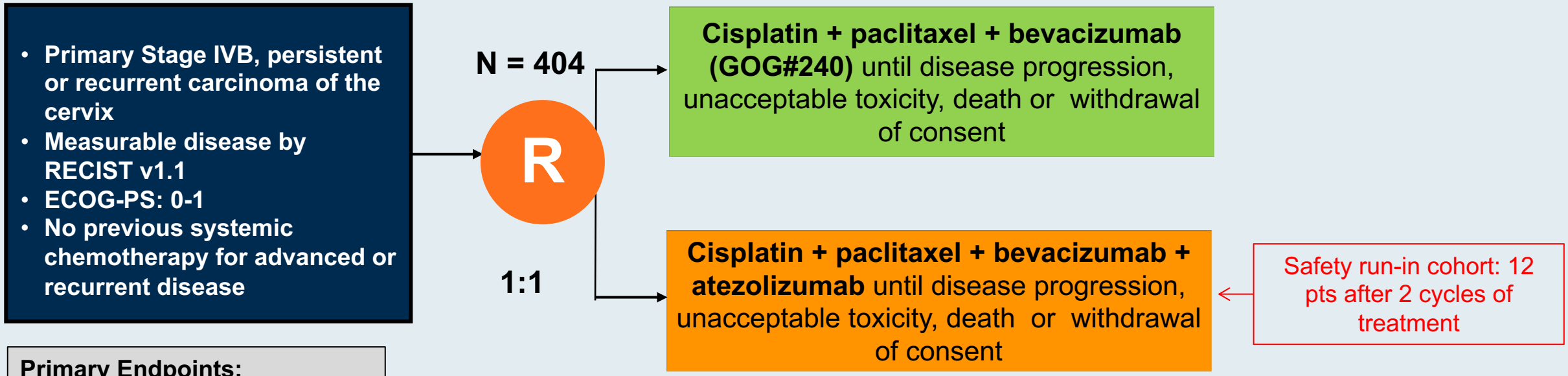
BEATcc Phase III Randomized Front-Line Trial of Atezolizumab



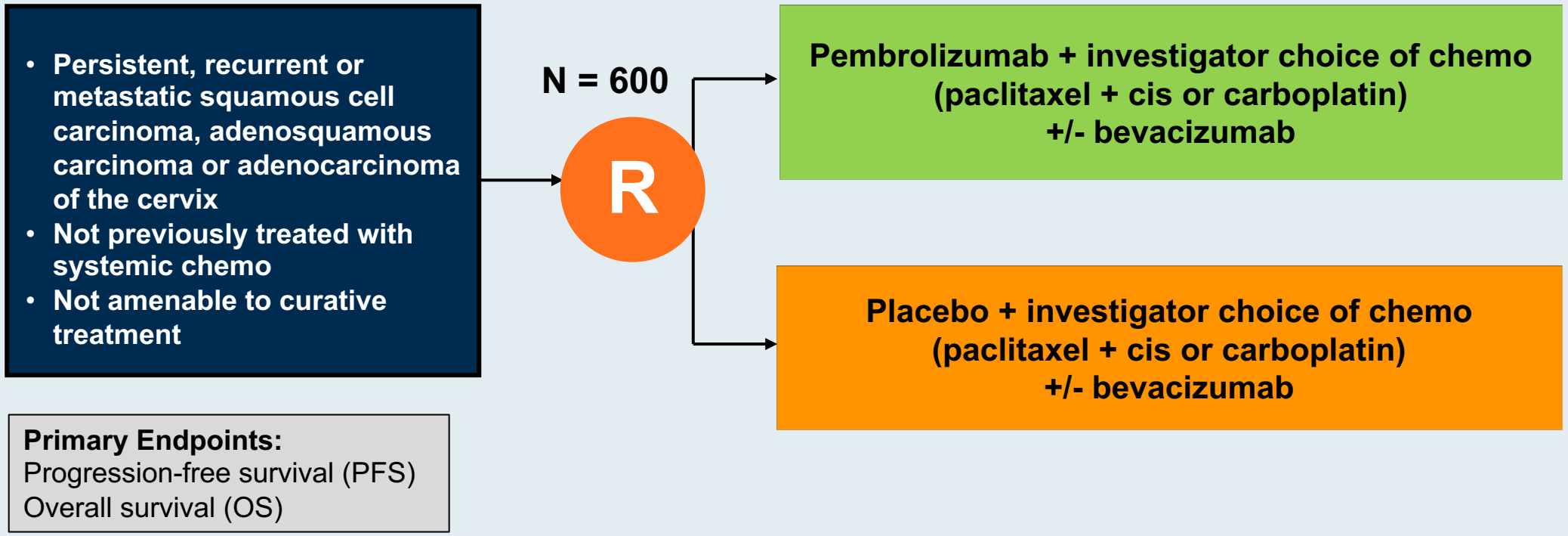
Primary Endpoints:
Overall survival (OS)
Secondary Endpoints:
- PFS
- ORR
- DOR
- Safety
- HR-QOL

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

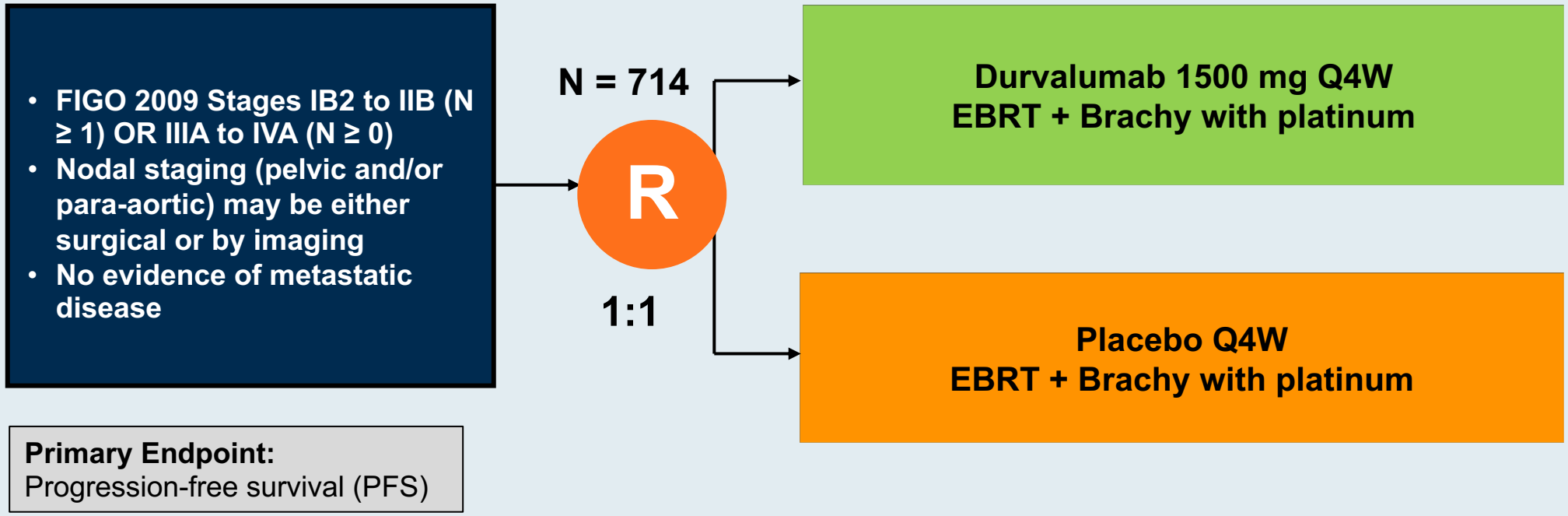
KEYNOTE-826 Phase III Schema



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

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

CALLA Phase III Schema



Primary Endpoint:
Progression-free survival (PFS)

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

Anti-PD-1/PD-L1 Antibodies in Ovarian Cancer

FDA-Approved Indications for Immunotherapy in Ovarian Cancer

Pembrolizumab: 2017 FDA approval for MSI-high/MMR deficient cancers

- The incidence of germline MMR gene mutations in high grade serous cancers is 1-8%
- MMR deficiency is more common in non-serous ovarian cancer

2020 ASCO ovarian cancer genetics guidelines re MMR testing:

- Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for mismatch repair deficiency
- Testing for MMR deficiency may be offered to women diagnosed with other histologic types of epithelial ovarian cancer

Xiao X, et al. *Gynecol Oncol.* 2014.; Morice P, et al. *N Engl J Med.* 2019.; Konstantinopoulos PA, et al. *J Clin Oncol.* 2020; Murphy MA Cancer 2011

Courtesy of Ursula Matulonis, MD

Final Results from the KEYNOTE-100 Trial of Pembrolizumab in Patients with Advanced Recurrent Ovarian Cancer

Matulonis UA et al.

ASCO 2020;Abstract 6005.

KEYNOTE-100 Phase II, 2-Cohort Study Schema

Patients (N = 376)

- Recurrent, advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer
- ECOG PS 0 or 1
- Provision of a tumor sample for biomarker analysis

Key exclusion criteria

- Mucinous histology
- No bowel obstruction within 3 months
- No active autoimmune disease
- No active CNS metastases and/or carcinomatous meningitis

Cohort A
1-3 prior lines
PFI or TFI of 3-12 months

Total enrollment: n = 285

Pembrolizumab 200 mg IV q3wk until PD, prohibitive toxicity, death, or completion of 2 years

Cohort B
4-6 prior lines
PFI or TFI of ≥3 months

Total enrollment: n = 91

PFI = platinum-free interval; TFI = treatment-free interval

Matulonis UA et al. ASCO 2020;Abstract 6005.

KEYNOTE-100: Summary of Efficacy, Including by PD-L1 Status

Endpoint	Cohort A 1-3 prior lines PFI/TFI 3-12 months			Cohort B 4-6 prior lines PFI/TFI ≥3 months			Cohorts A + B All comers		
	All n = 285	CPS ≥1 n = 101	CPS ≥10 n =43	All n = 91	CPS ≥1 n = 49	CPS ≥10 n = 22	All n = 376	CPS ≥1 n = 150	CPS ≥10 n = 65
ORR	8.1%	6.9%	11.6%	9.9%	10.2%	18.2%	8.5%	8.0%	13.8%
DoR	8.3 mo	Not reported	Not reported	23.6 mo	Not reported	Not reported	10.2 mo	Not reported	Not reported
OS	18.7 mo	20.6 mo	21.9 mo	17.6 mo	20.7 mo	24.0 mo	Not reported	Not reported	Not reported

Matulonis UA et al. ASCO 2020;Abstract 6005.

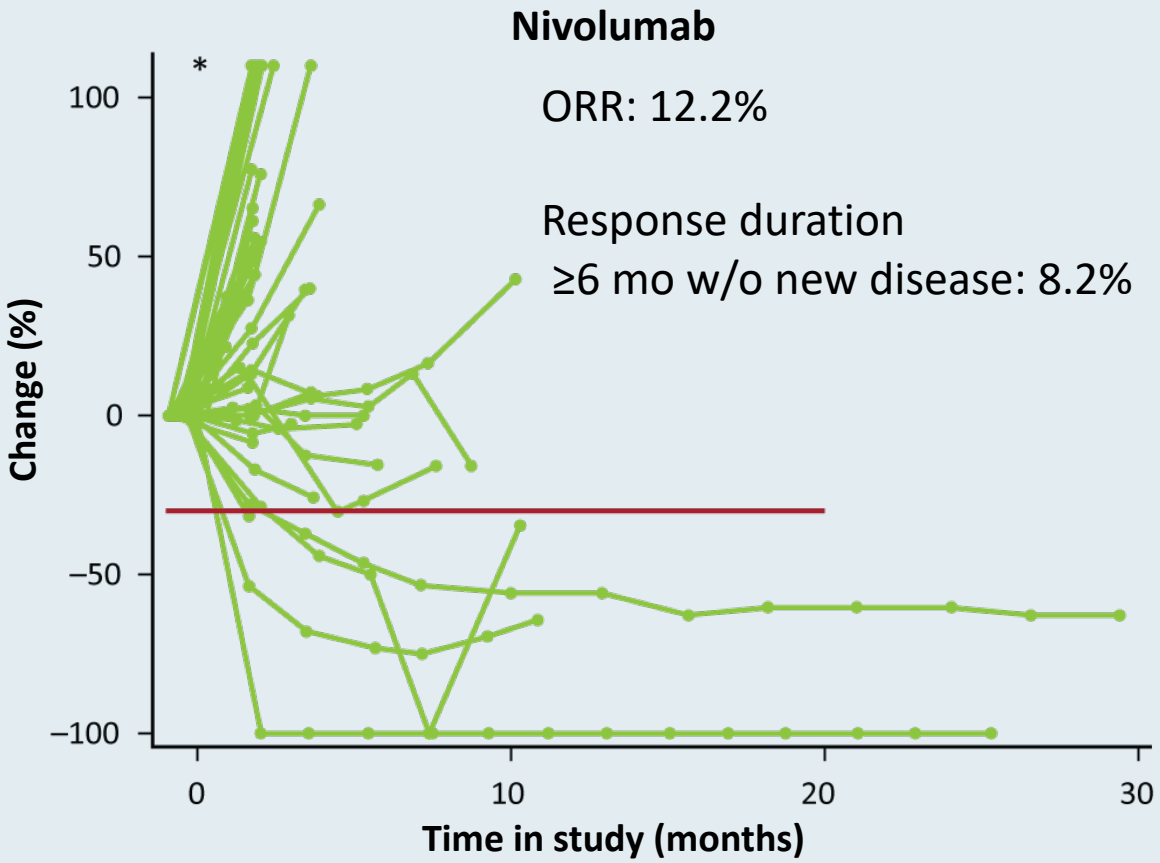
JAVELIN Ovarian 200: Avelumab Alone or in Combination with Pegylated Liposomal Doxorubicin (PLD) versus PLD Alone in Platinum-Resistant or Refractory OC

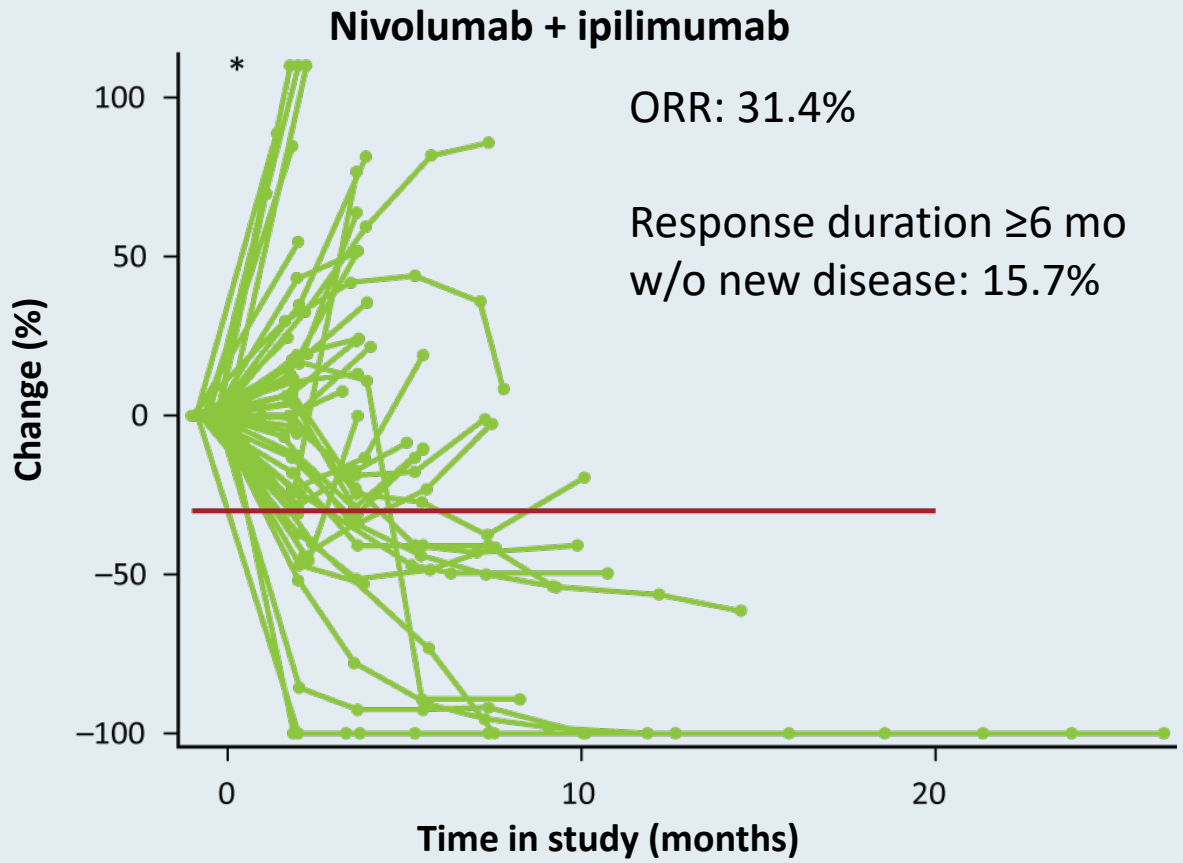
	Avelumab (n = 188)		Avelumab + PLD (n = 188)		PLD (n = 190)	
All patients						
Median OS	11.8 mo		15.7 mo		13.1 mo	
	HR: 1.14, *p* = 0.83		HR: 0.80, *p* = 0.21		Reference	
Median PFS	1.9 mo		3.7 mo		3.5 mo	
	HR: 1.68, *p* > 0.99		HR: 0.78, *p* = 0.03		Reference	
PD-L1 evaluable	**PD-L1+ (n = 91)**	**PD-L1- (n = 62)**	**PD-L1+ (n = 92)**	**PD-L1- (n = 58)**	**PD-L1+ (n = 73)**	**PD-L1- (n = 66)**
Median OS	13.7 mo	10.5 mo	18.4 mo	12.7 mo	13.8 mo	13.1 mo
	HR: 0.80	HR: 1.4	HR: 0.72	HR: 1.1	Ref	Ref
Median PFS	1.9 mo	1.8 mo	3.7 mo	3.9 mo	1.9 mo	3.7 mo
	HR: 1.3	HR: 1.8	HR: 0.59	HR: 0.92	Ref	Ref

Pujade-Lauraine E et al. SGO 2019; Abstract LBA1.

NRG GY003 Phase II Study of Nivolumab with or without Ipilimumab in Recurrent or Persistent OC

(PFI <6 months: 62%, ≥2 prior cytotoxic regimens: 70%+ of patients)

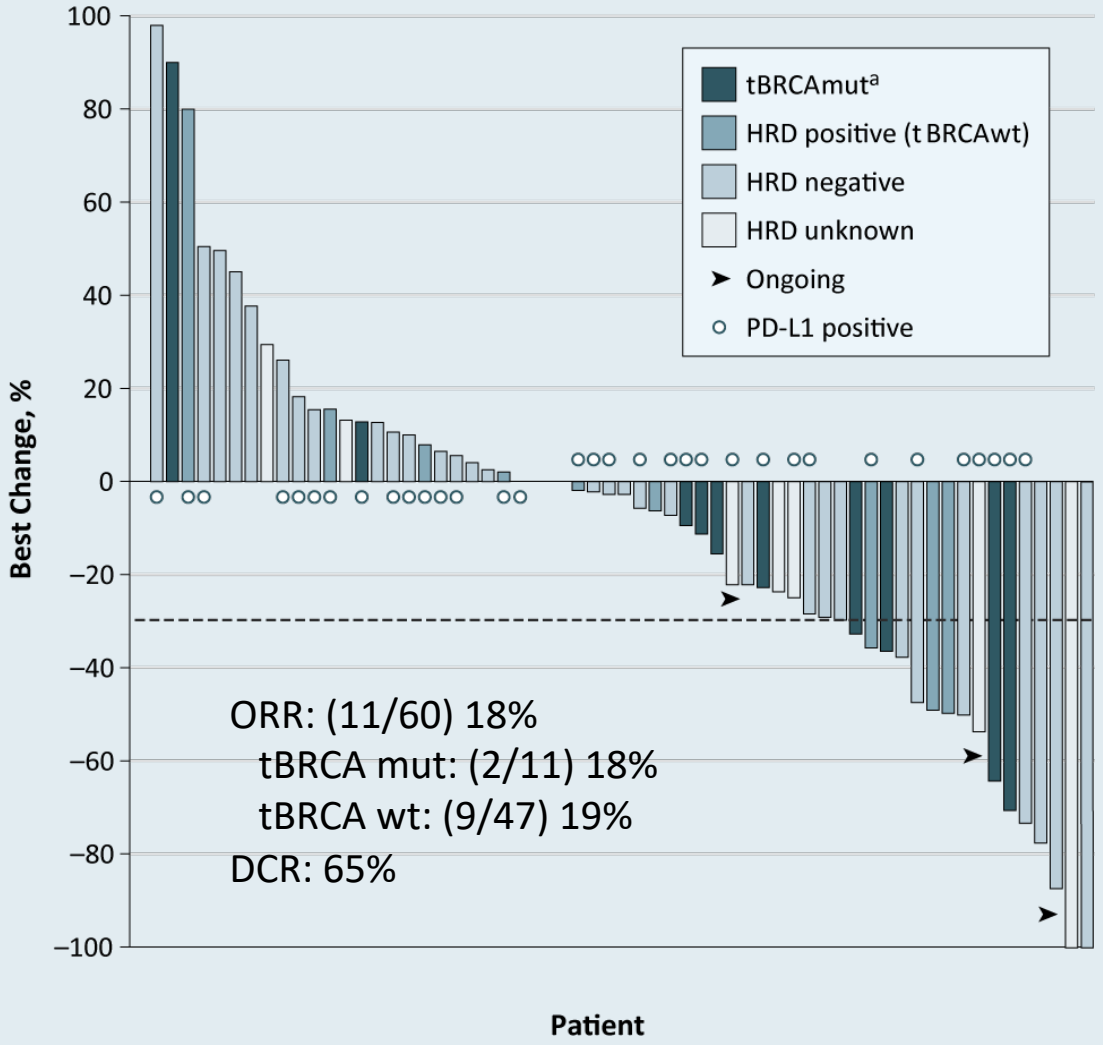


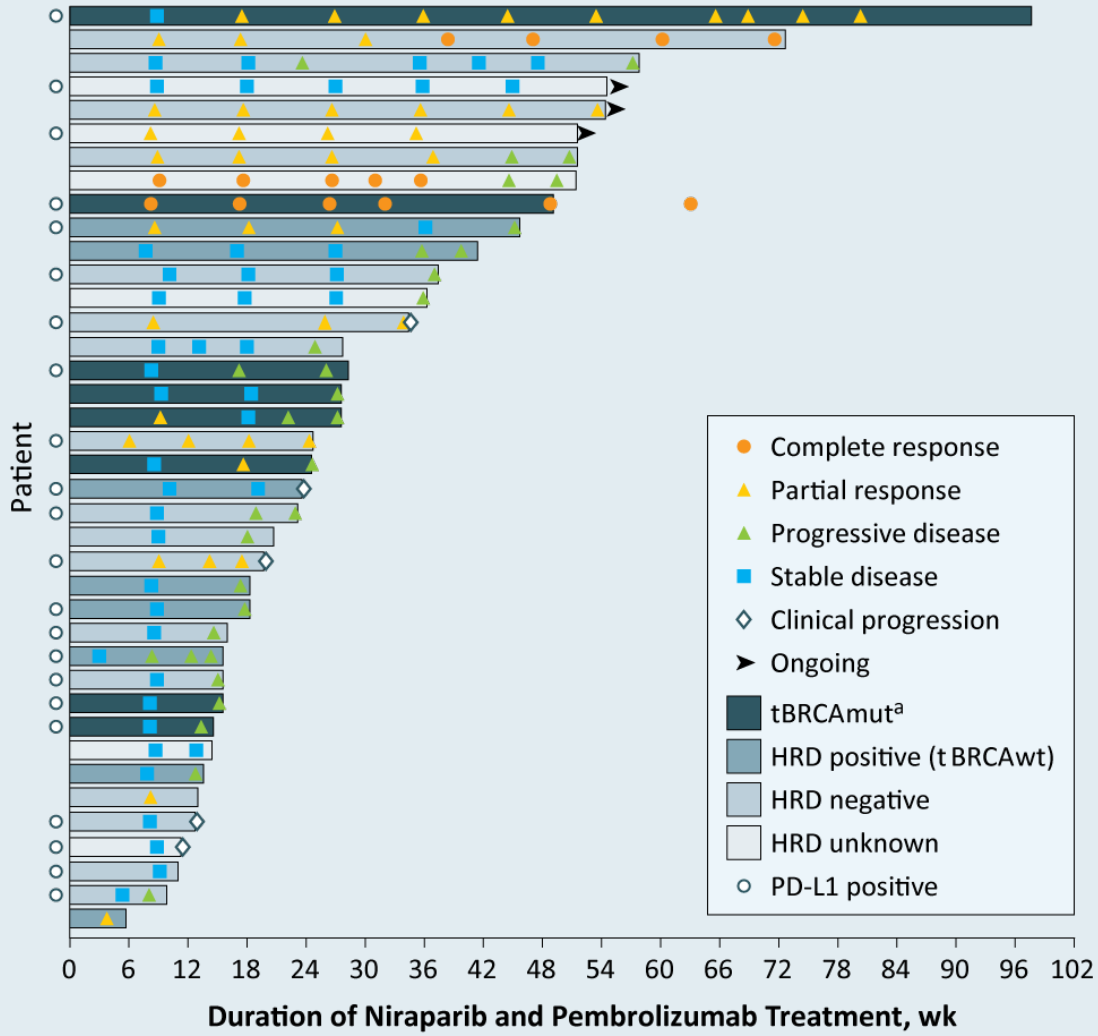


PD-L1 expression was not significantly associated with response in either treatment group

Zamarin D et al. *J Clin Oncol* 2020;38:1814-23.

TOPACIO/KEYNOTE-162: Niraparib and Pembrolizumab in Recurrent Platinum-Resistant Ovarian Cancer

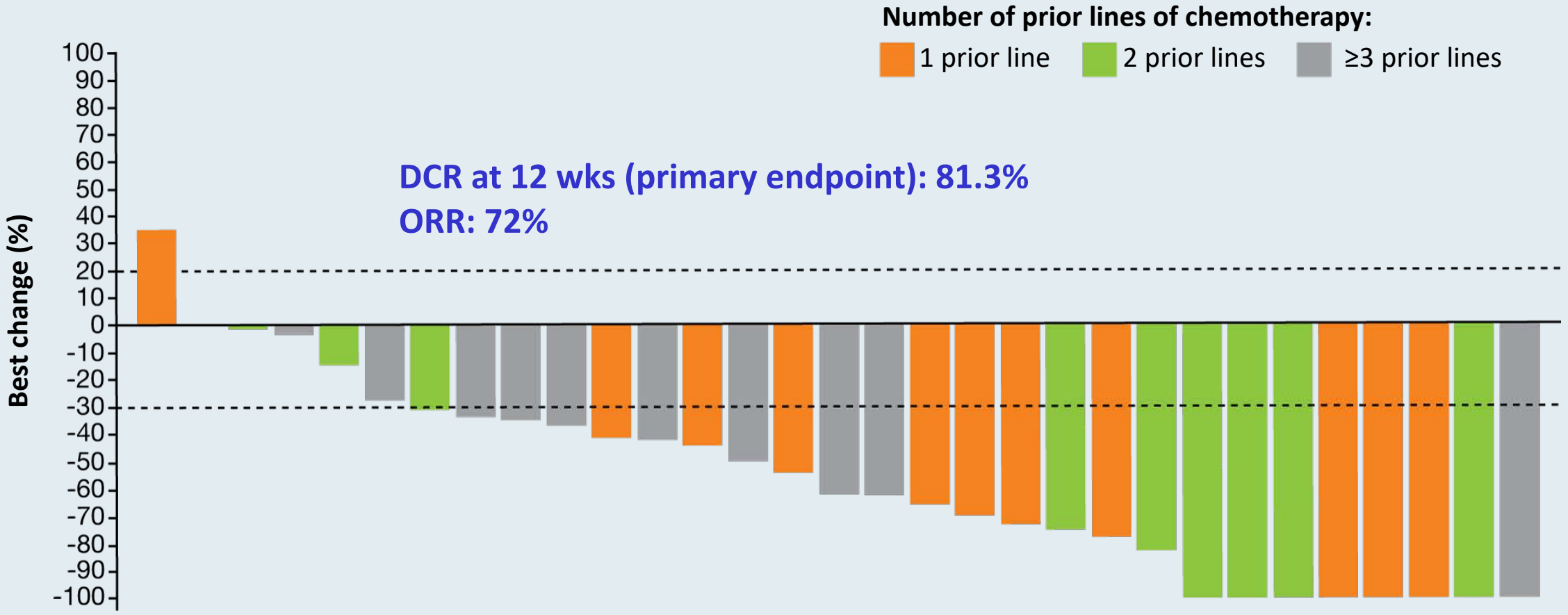




Konstantinopoulos PA, et al. *JAMA Oncol* 2019;5(8):1141-9.

RTP RESEARCH TO PRACTICE

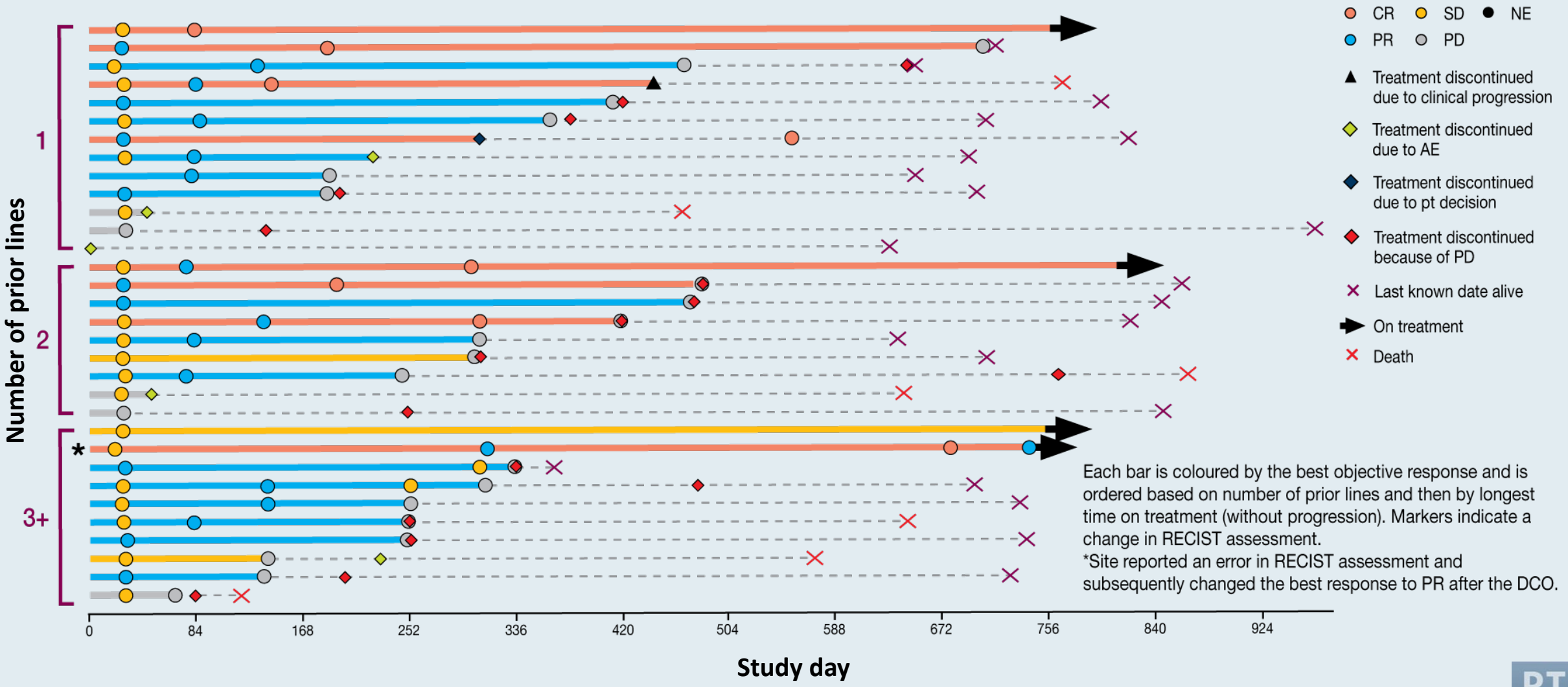
MEDIOLA: A Phase II Study of Olaparib and Durvalumab in gBRCA-Mutated Platinum-Sensitive Relapsed OC



Drew Y et al. ESMO 2019;Abstract 1190PD.

RTP RESEARCH TO PRACTICE

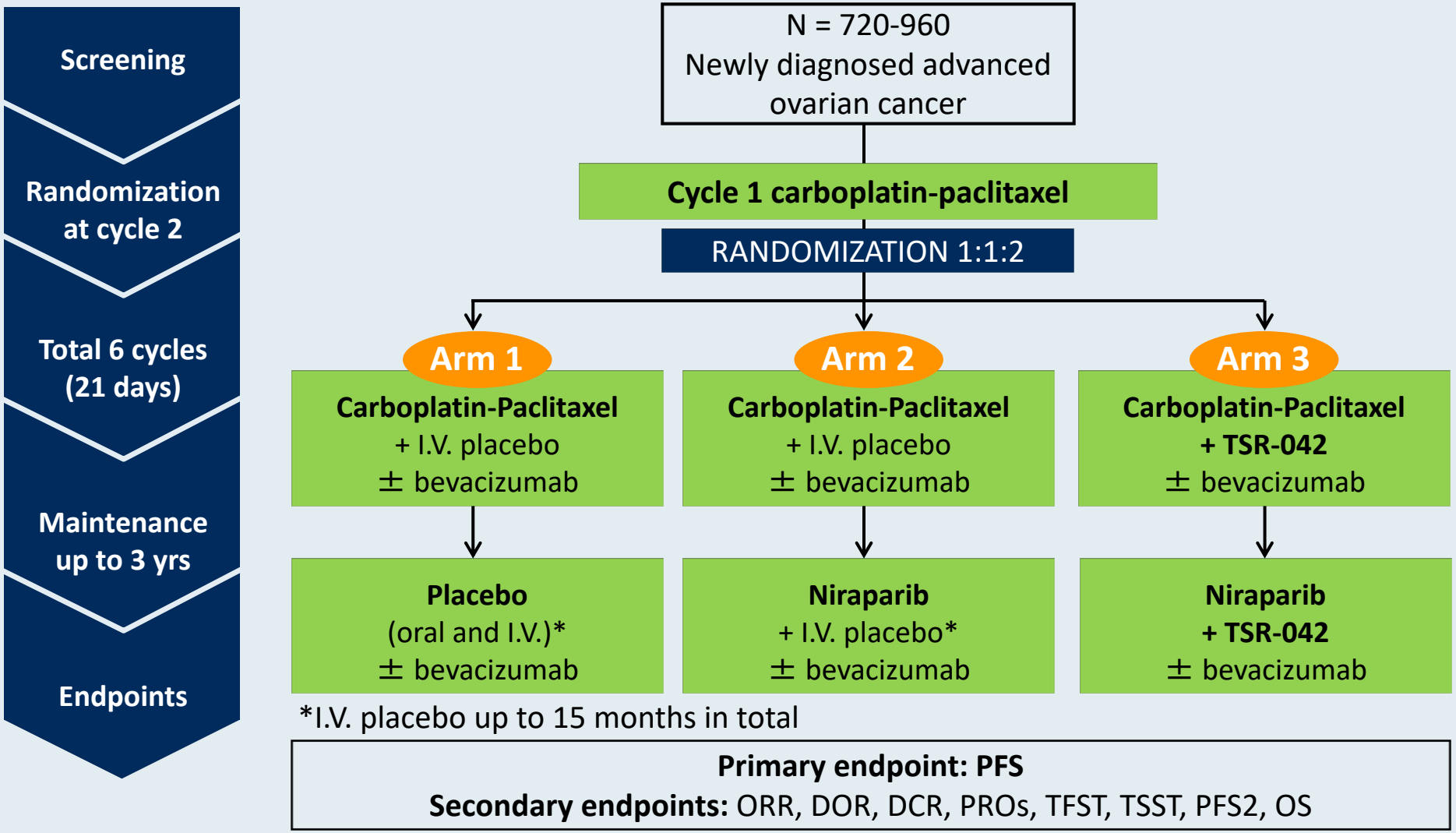
MEDIOLA: Time to Disease Progression or Treatment Discontinuation, Based on Number of Prior Lines of Therapy



Drew Y et al. ESMO 2019;Abstract 1190PD.

RTP RESEARCH TO PRACTICE

FIRST Phase III Trial of Dostarlimab (TSR-042) in Newly Diagnosed Ovarian Cancer



www.clinicaltrials.gov/ct2/show/NCT03602859

Courtesy of Ursula Matulonis, MD

Phase II MOONSTONE Study Design

Eligibility

- Completed 1-3 prior lines of therapy for advanced or metastatic ovarian cancer
- Previously treated with platinum-based chemo, taxane and bevacizumab
- Resistant to last administered platinum agent
- No known BRCA 1 or 2 mutation

N=150

Niraparib + Dostarlimab

Primary endpoint: ORR
Secondary endpoints: DOR, PFS, OS, DCR

https://clinicaltrials.gov/ct2/show/NCT03955471?term=MOONSTONE&draw=2&rank=1

Select Ongoing Phase III Trials of Immunotherapy in Combination with PARP Inhibitors

Trial name (Trial identifier)	N	Setting	Treatment arms
ATHENA (NCT03522246)	1,012	Maintenance therapy after 1L platinum-based chemo	• Rucaparib + nivolumab • Rucaparib + placebo • Nivolumab + placebo • Placebo
DUO-O (NCT03737643)	1,056	Maintenance therapy after 1L platinum-based chemo/bev ± durvalumab	• Bevacizumab • Bevacizumab + durvalumab • Bevacizumab + durvalumab + olaparib

www.clinicaltrials.gov. Accessed August 2020.

HER2-Positive Endometrial Cancer

HER2 Testing in Endometrial Serous Carcinoma

Current Criteria (Approved or Proposed) for HER2 Positivity by Immunohistochemistry (IHC) and Fluorescence In Situ Hybridization (FISH) in Different Tumor Types

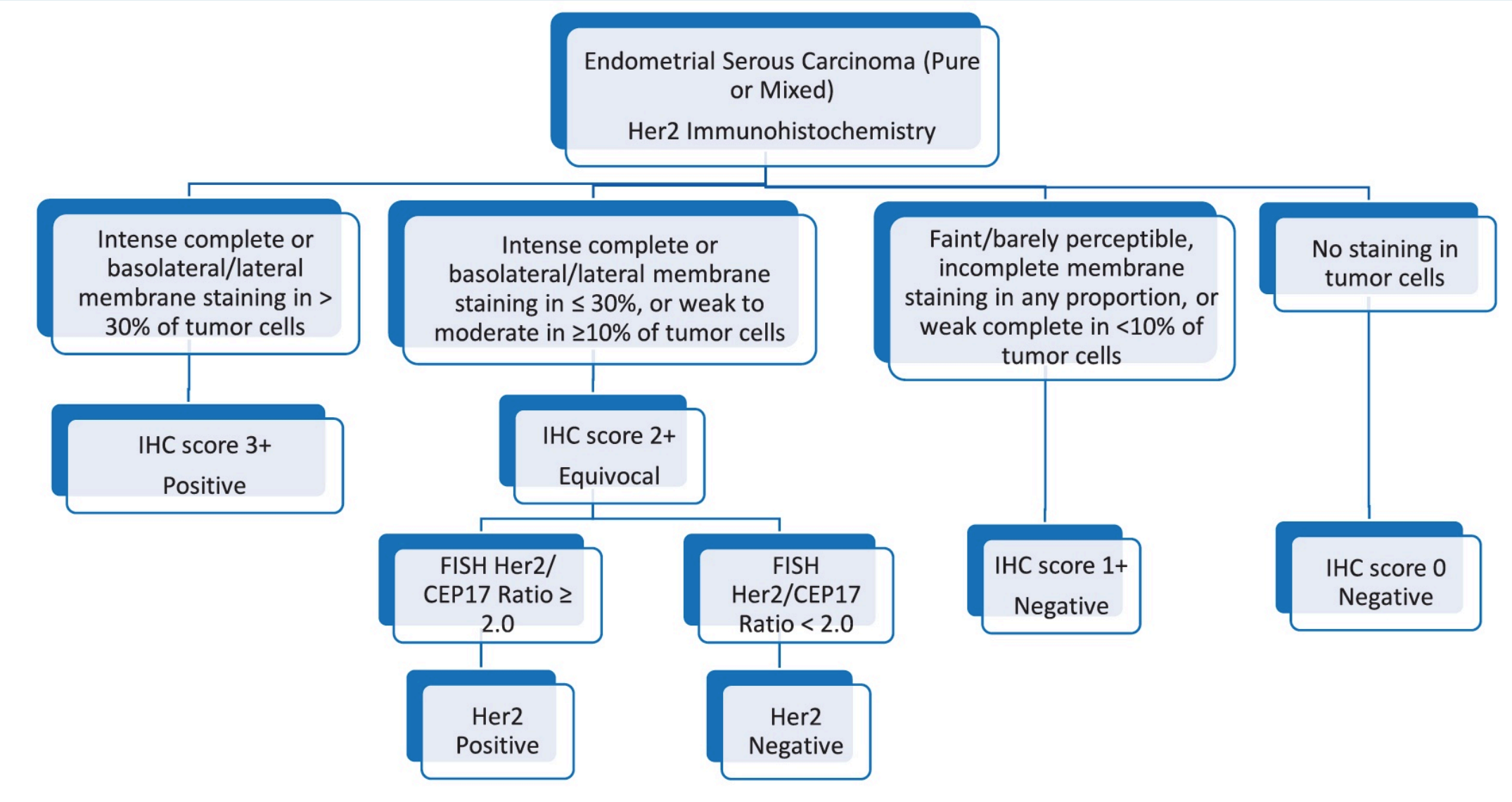
	Breast (ASCO/CAP 2018)[23]	Gastric (ASCO/CAP 2016)[36]	Colorectal (HERACLES Trial)[39]	Endometrial Serous (Fader et al Clinical Trial)[21]
HER2 IHC 3+	>10% circumferential, strong, complete	≥10%, strong complete, or basolateral/lateral	≥50% strong complete, or basolateral/lateral	>30% strong complete or basolateral/lateral
HER2 FISH amplification	*HER2*/CEP17 ratio ≥2.0 and *HER2* signal ≥4.0 per nucleus OR ratio <2.0 and *HER2* signal ≥6.0 per nucleus (if IHC score 2+ or 3+)	*HER2*/CEP17 ratio ≥2.0 OR ratio <2.0 and *HER2* signal >6.0 per nucleus	*HER2*/CEP17 ratio ≥2.0 in ≥50% of cells	*HER2*/CEP17 ratio ≥2.0

Abbreviations: ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists.

Buza N. *Arch Pathol Lab Med* 2020;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Proposed HER2 Testing Algorithm for Endometrial Serous Carcinoma



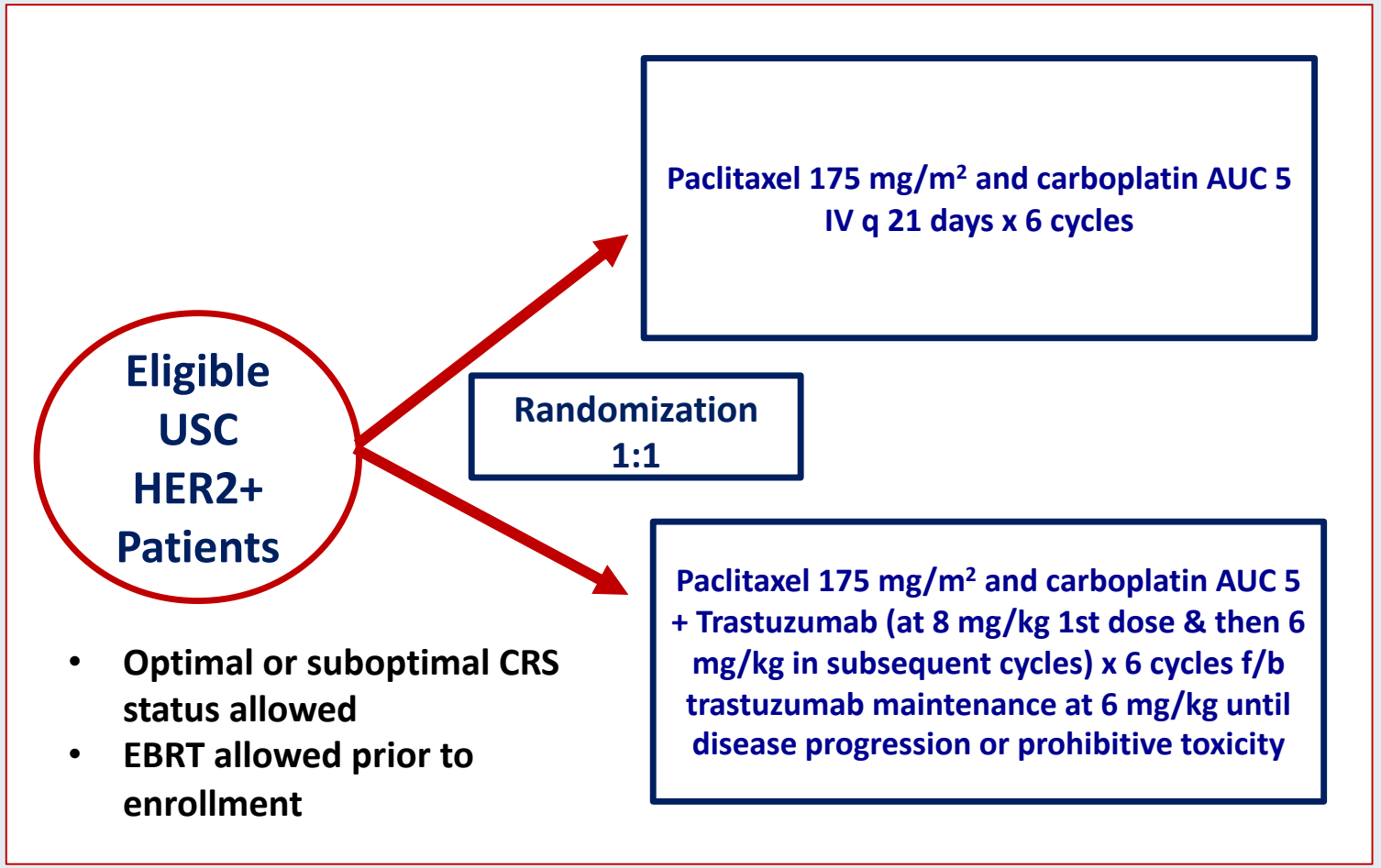
Buza N. *Arch Pathol Lab Med* 2020;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Randomized Phase II Trial of Carboplatin/Paclitaxel versus Carboplatin/Paclitaxel/Trastuzumab for Uterine Serous Carcinoma That Overexpresses HER2/Neu: Updated Survival Analysis

Eligibility

- FIGO Stage III-IV USC or recurrent USC
- HER2/neu+ USC as defined by IHC score of 3+ (ASCO/CAP 2007 criteria) or 2+ with gene amplification confirmed by FISH
- Patients diagnosed with recurrence were required to have measurable disease, defined as at least one target lesion per RECIST 1.1
- Patients with recurrent disease may not have received >3 prior chemotherapies for treatment of their EC, and a treatment-free interval of >6 months from last C/T was required for patients with recurrent disease

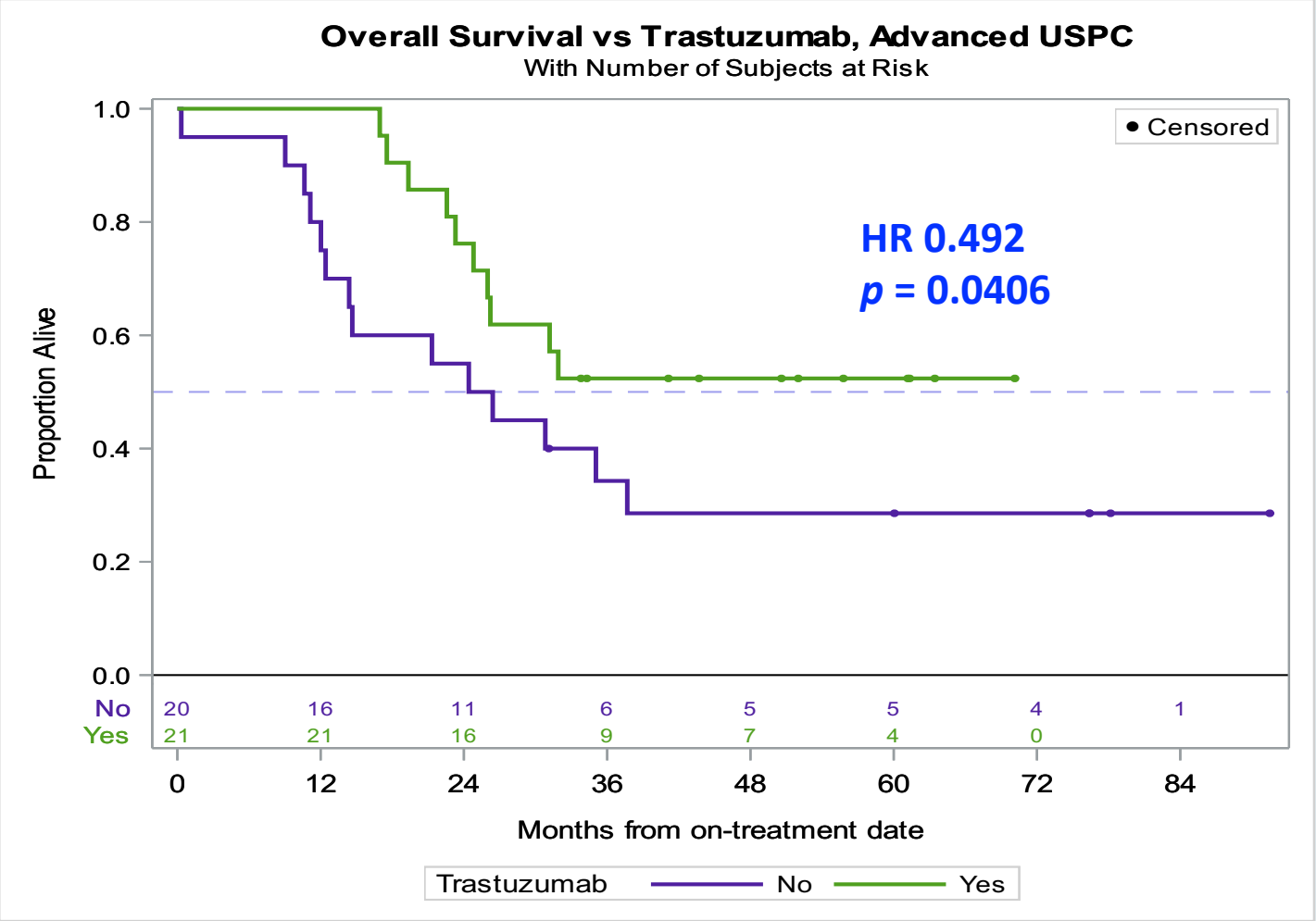


Fader AN et al. *Clin Cancer Res* 2020;26:3928-35.

Courtesy of David M O'Malley, MD

Overall Survival with the Addition of Trastuzumab to Carboplatin/ Paclitaxel for Advanced Uterine Serous Papillary Carcinoma (USPC)

- Benefit was particularly striking in the Stage III-IV pts, with a median OS of 25.4 mo (control) compared with an unreached median OS (experimental; *p* = 0.0406, HR 0.492)



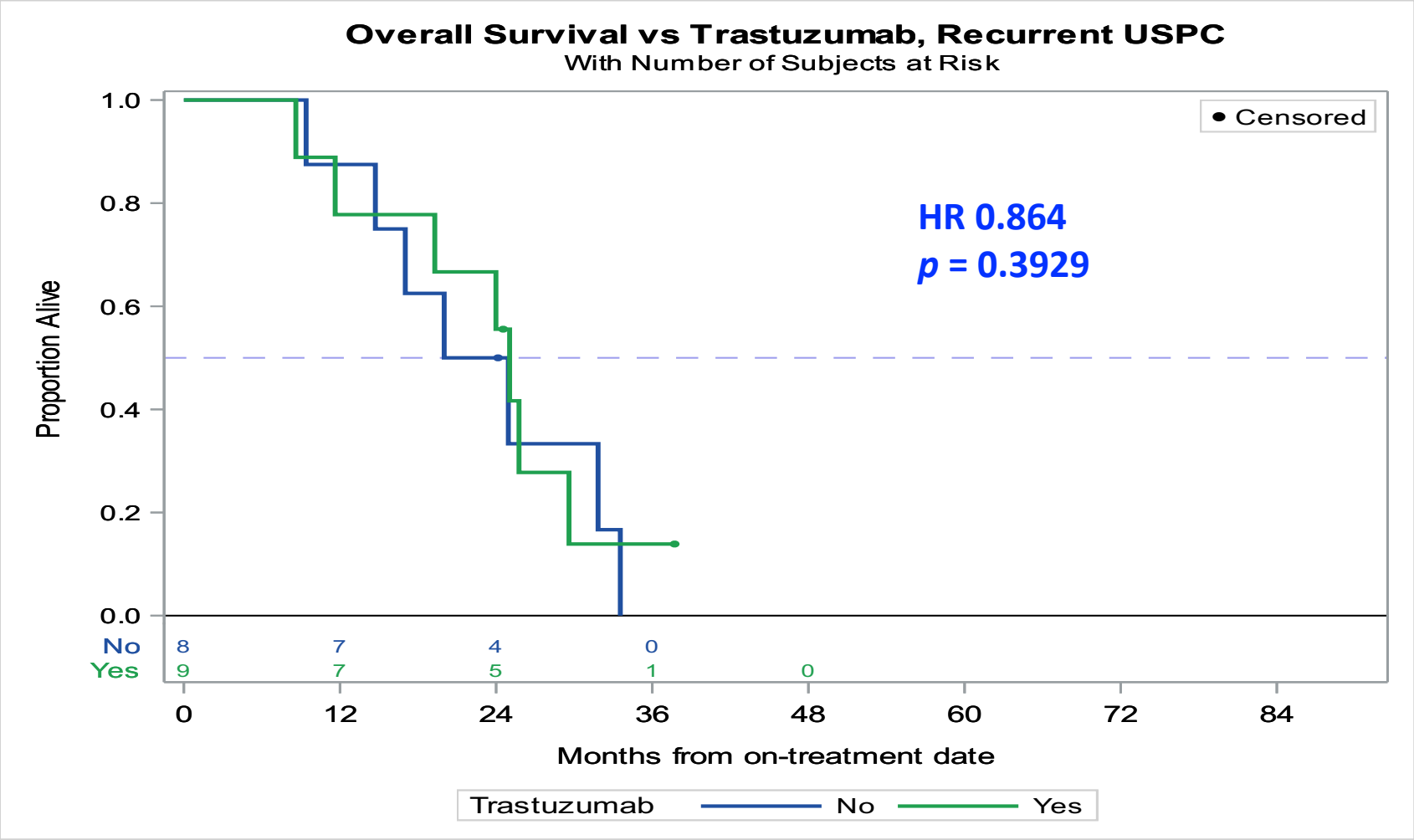
Fader AN et al. *Clin Cancer Res* 2020;26:3928-35.

Courtesy of David M O'Malley, MD

RTP RESEARCH TO PRACTICE

Overall Survival with the Addition of Trastuzumab to Carboplatin/Paclitaxel for Recurrent USPC

- No significant OS benefit was observed in the recurrence cohort



Fader AN et al. *Clin Cancer Res* 2020;26:3928-35.

Courtesy of David M O'Malley, MD

Carboplatin/Paclitaxel/Trastuzumab: Summary

- First trial of targeted therapy in USC ONLY patients
- Demonstration that HER2 is an important prognostic and actionable target in USC
- NCCN designation of C/T/Trastuzumab as a preferred regimen in HER2+ USC (Level IIA)

Fader AN et al. SGO 2020

Courtesy of David M O'Malley, MD

Phase II DESTINY-PanTumor02 Study Design

Trial Identifier: NCT04482309 (Not yet recruiting)
Estimated Enrollment: 280

Eligibility

- Locally advanced, unresectable or metastatic disease
- Disease progression after prior treatment or no satisfactory alternative treatment option
- Prior HER2-targeted therapy allowed
- HER2 expression may be based on local or central assessment

Trastuzumab deruxtecan

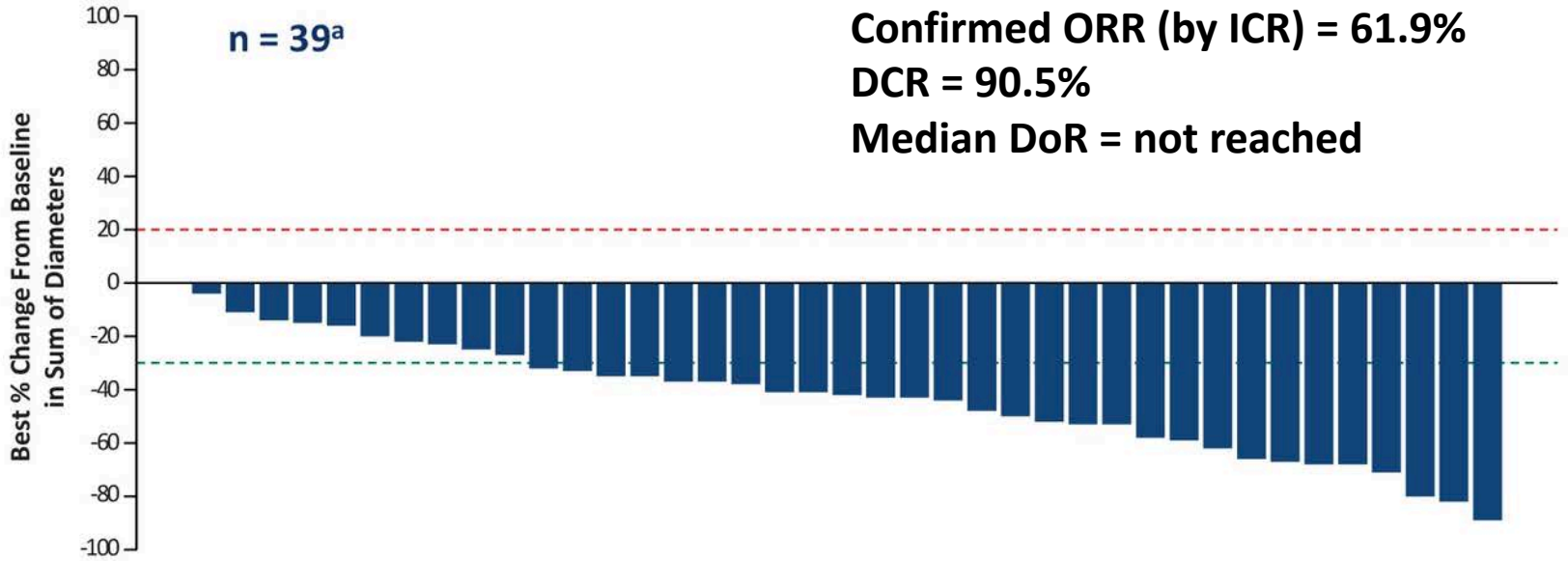
7 cohorts will be evaluated:
Endometrial cancer, cervical cancer, ovarian cancer, bladder cancer, biliary tract cancer, pancreatic cancer and rare tumors

Primary endpoint: ORR
Secondary endpoints include DOR, PFS, OS, DCR

https://www.clinicaltrials.gov/ct2/show/NCT04482309.

DESTINY-Lung01: Best Change in Tumor Size

Trastuzumab Deruxtecan in Lung Cancer



Based on independent central review. Baseline is last measurement taken before enrollment. Shown is best (minimum) percent change from baseline in the sum of diameters for all target lesions.

[a] One patient was missing a baseline assessment and 2 additional patients were missing post-baseline assessments.

Median PFS = 14.0 months

Smit EF et al. ASCO 2020;Abstract 9504.

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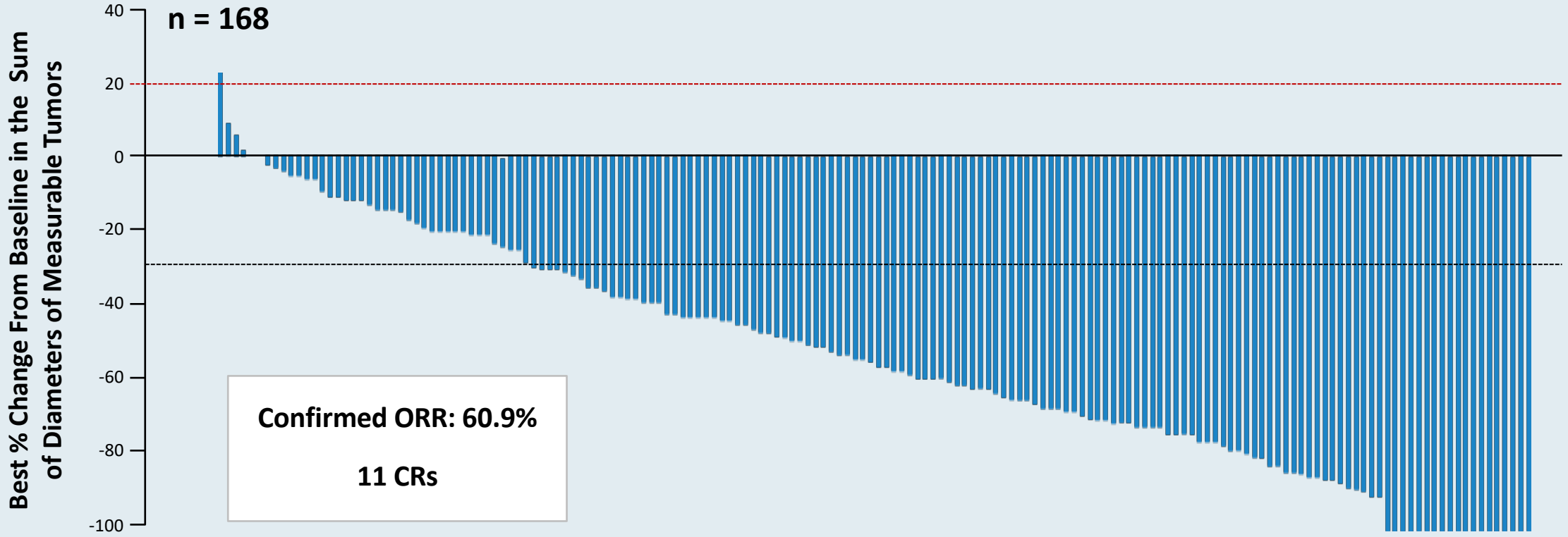
DESTINY-Breast01: Best Change in Tumor Size

Trastuzumab Deruxtecan in Breast Cancer

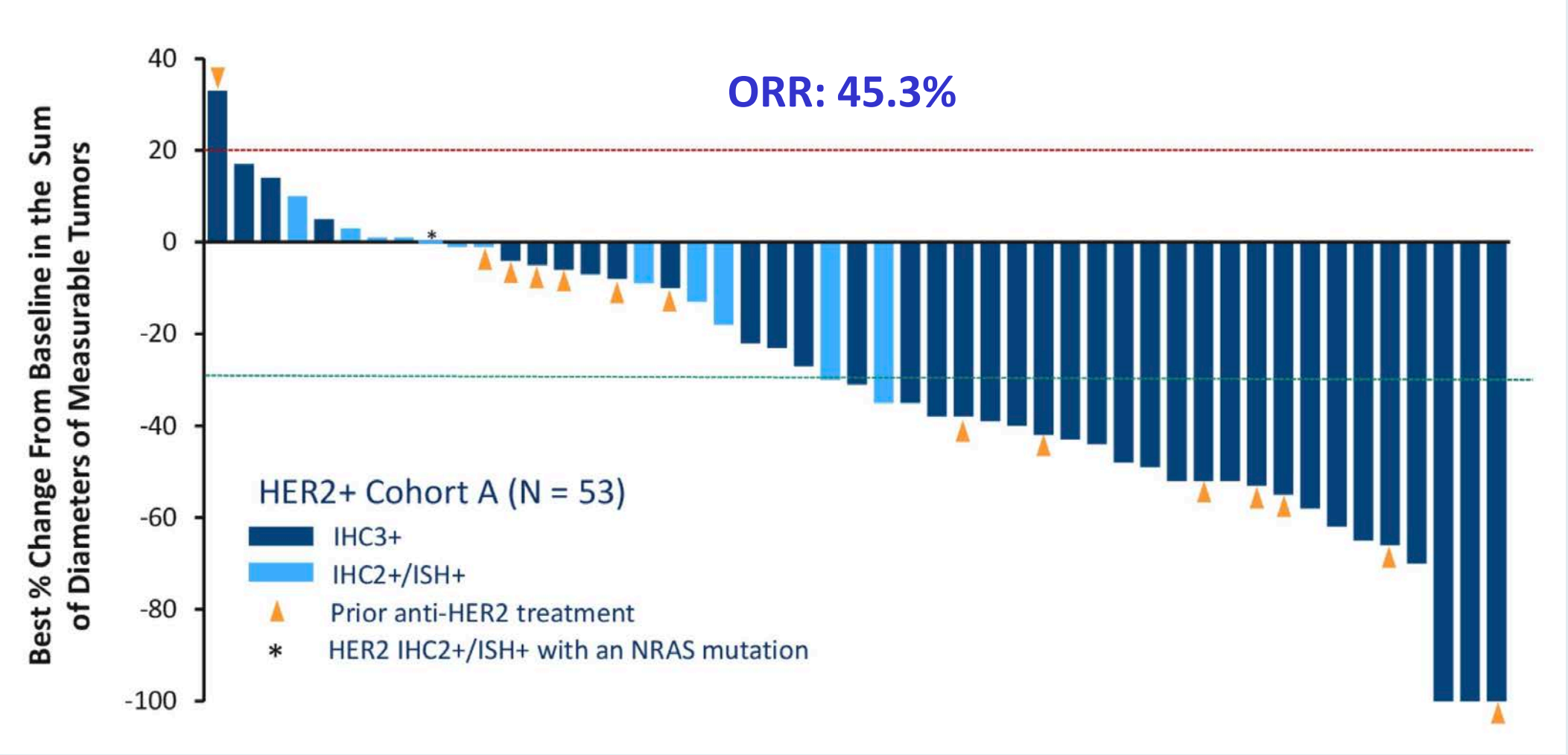


By independent central review.
The line at 20% indicates progressive disease; the line at −30% indicates partial response.
Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184).

Krop IE et al. San Antonio Breast Cancer Symposium 2019;Abstract GS1-03.

DESTINY-CRC01: Best Change in Tumor Size

Trastuzumab Deruxtecan in Colorectal Cancer

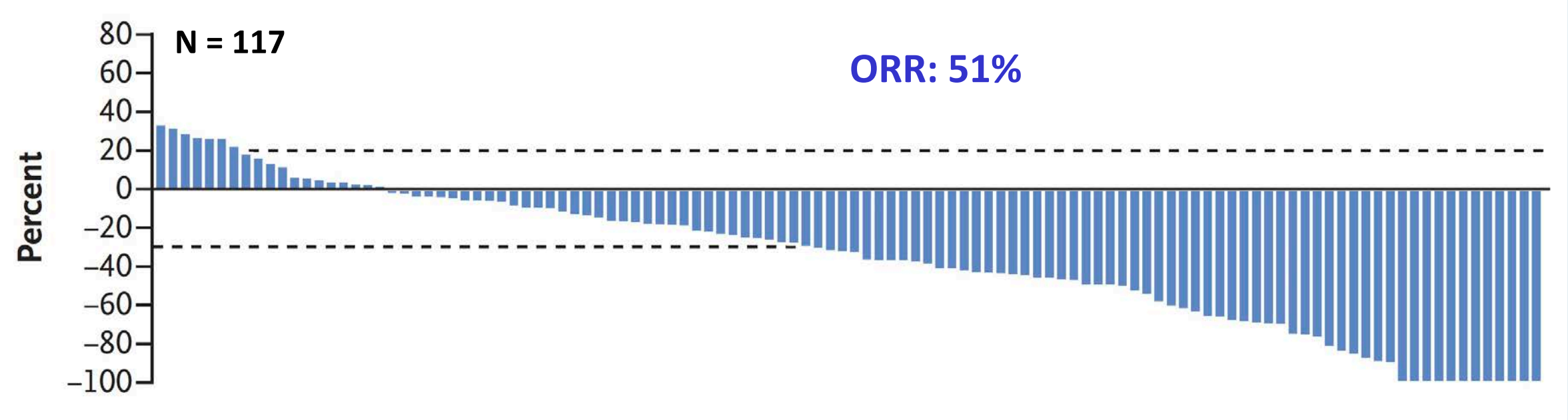


Siena S et al. ASCO 2020;Abstract 4000.

RTP RESEARCH TO PRACTICE

DESTINY-Gastric01: Best Change in Tumor Size

Trastuzumab Deruxtecan in Gastric Cancer



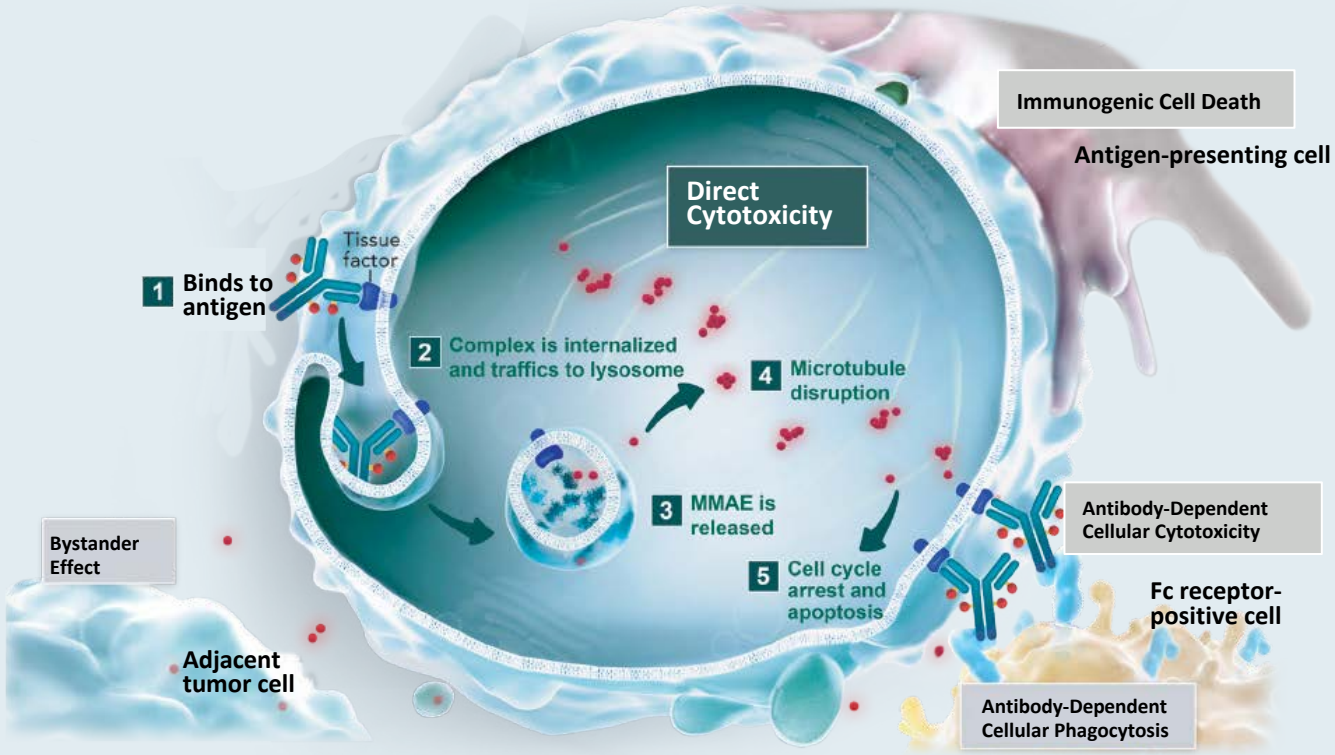
Shitara K et al. N Engl J Med 2020;382:2419-30.

RTP RESEARCH TO PRACTICE

Tisotumab Vedotin and Other Novel Agents in Gynecologic Cancers

Mechanism of Action of Tisotumab Vedotin

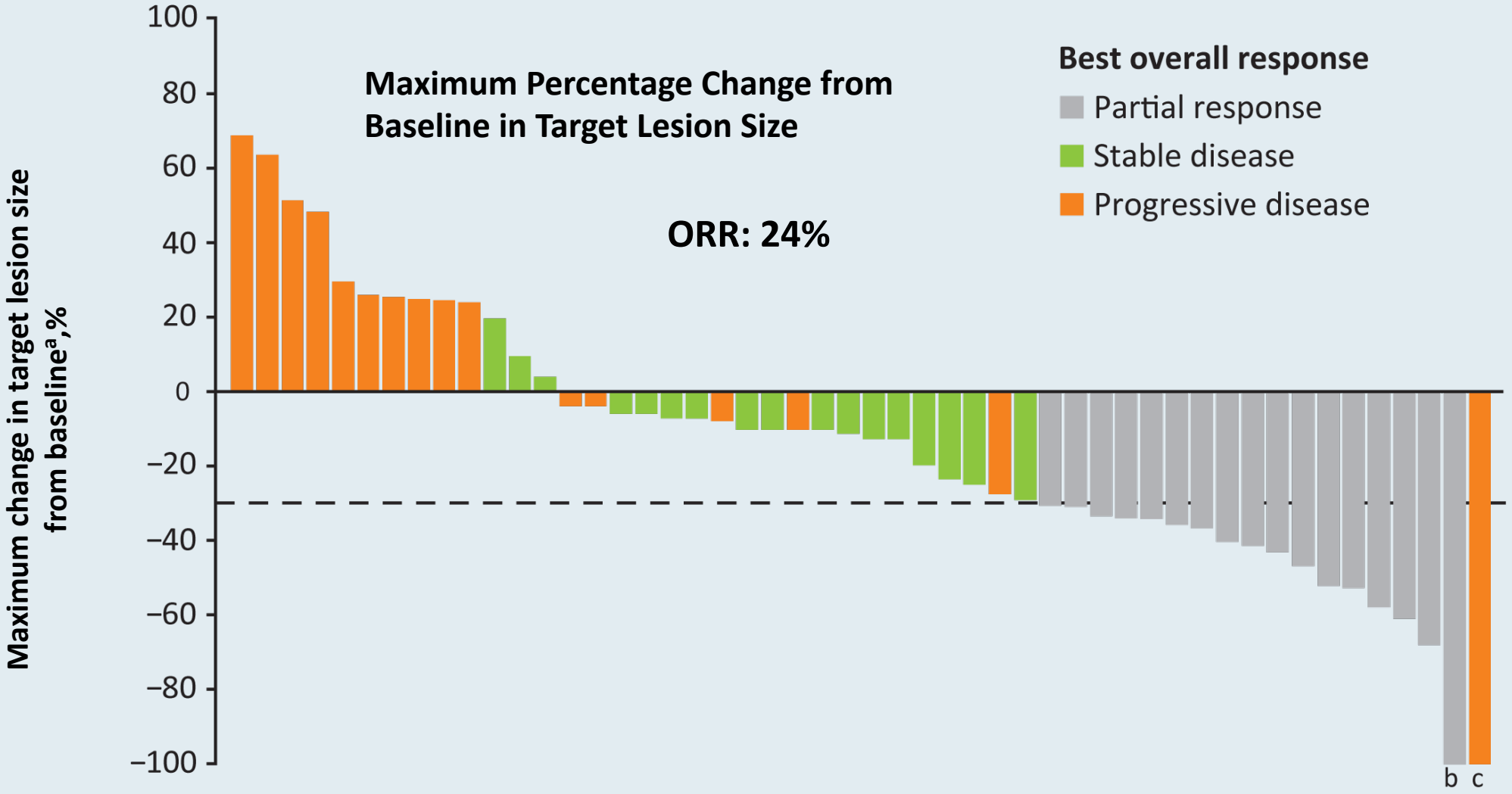
- Tissue factor (TF) is aberrantly expressed in a broad range of solid tumours, including cervical cancer,[1,2] and TF expression has been associated with higher tumour stage and grade, higher metastatic burden and poor prognosis[2]
- TF expression in cervical cancer makes TF a novel target for patients 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.

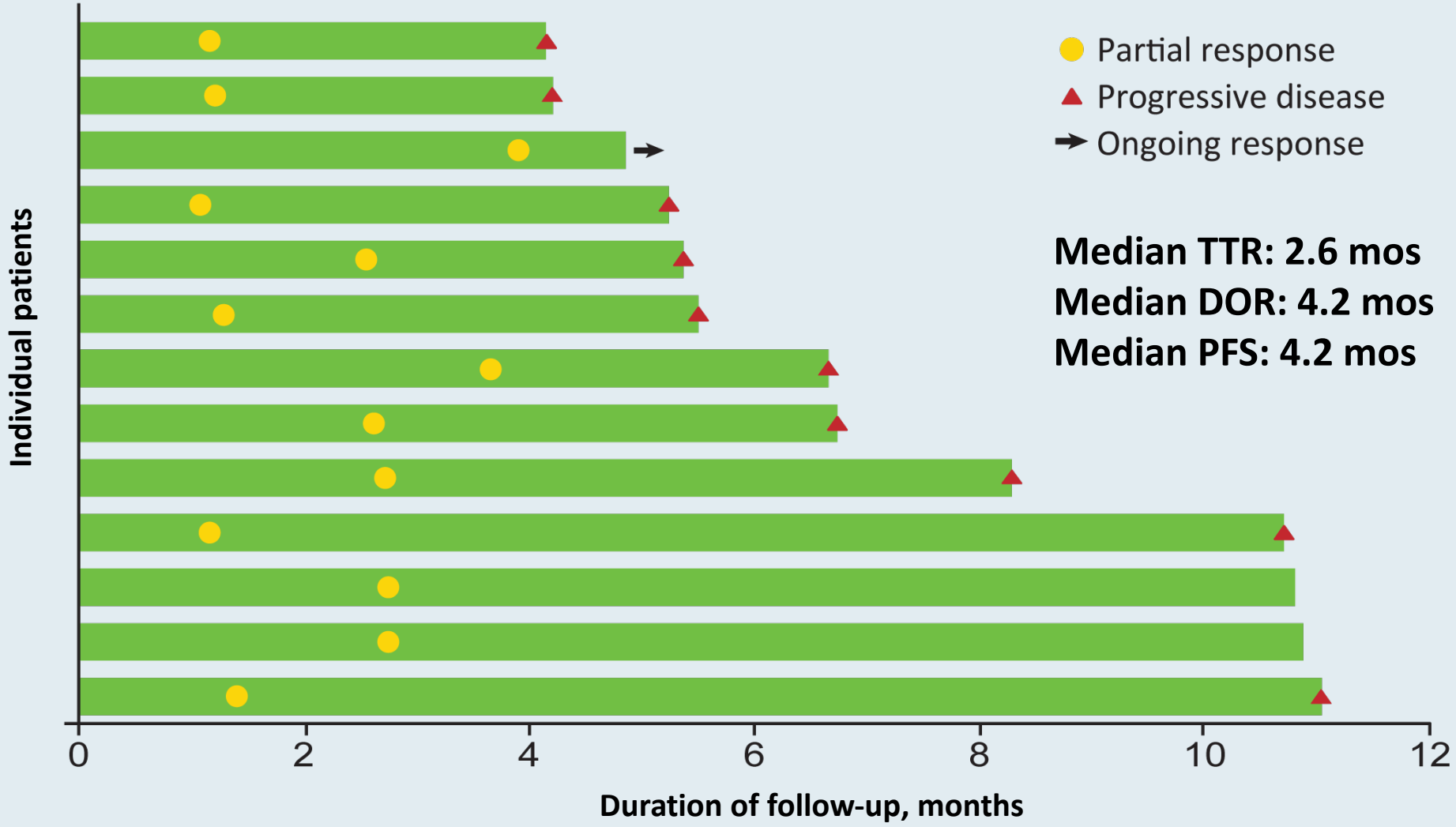
Courtesy of David M O'Malley, MD

innovaTV 201: Best Overall Response to TV



Hong DS et al. *Clin Cancer Res* 2020;26:1220-8.

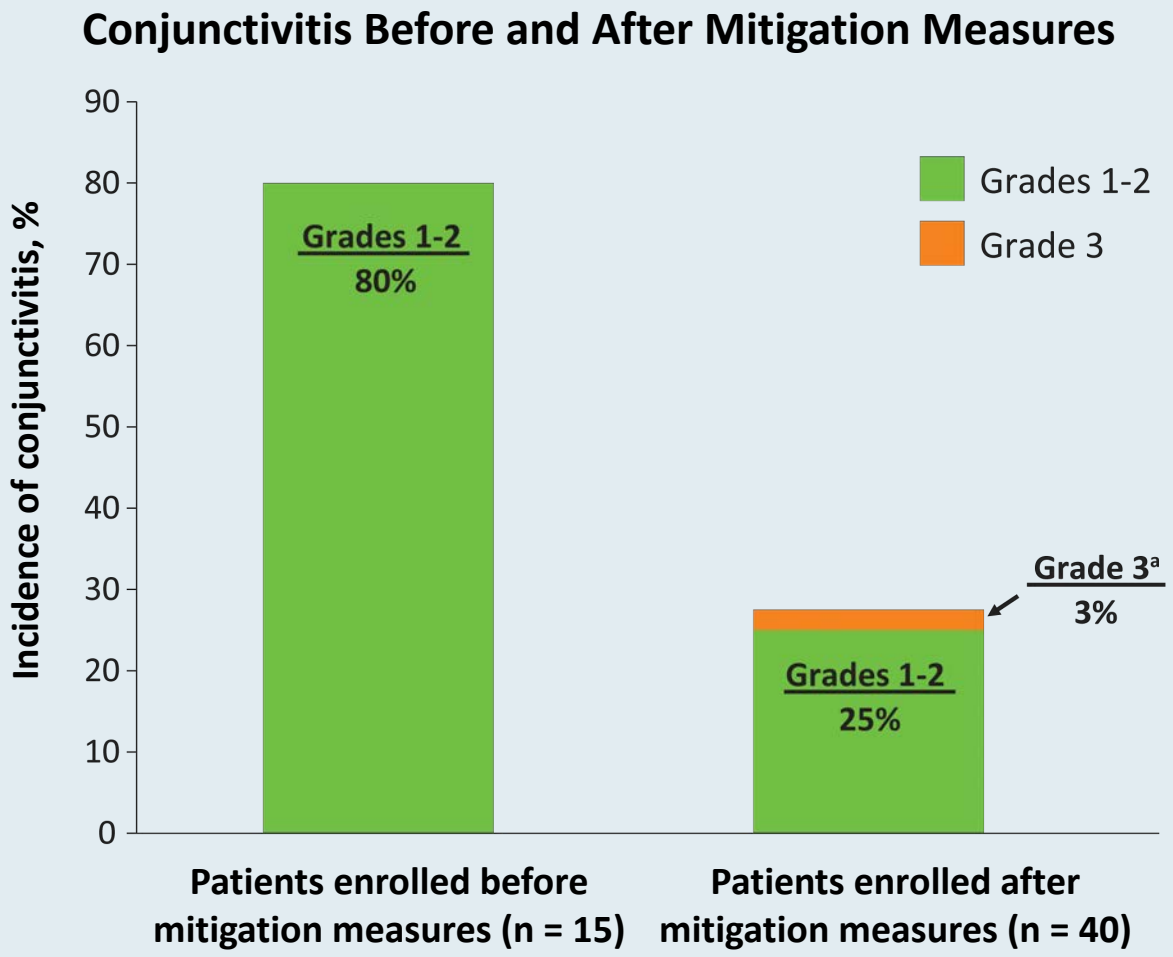
innovaTV 201: Time to Response and Duration of Response in Patients with a Confirmed PR to TV



Hong DS et al. *Clin Cancer Res* 2020;26:1220-8.

innovaTV 201: Treatment-Emergent Adverse Events

Adverse events	N = 55	
	All grade	Grade ≥3
Fatigue	51%	9%
Nausea	49%	5%
Neuropathy	55%	11%
Bleeding-related AEs	73%	5%
Ocular AEs	65%	2%
Conjunctivitis	42%	2%
Dry eye	24%	0
Ulcerative keratitis	7%	0
Blepharitis	5%	0
Keratitis	5%	0



Hong DS et al. *Clin Cancer Res* 2020;26:1220-8.

[a] One patient with grade 3 conjunctivitis after mitigation measures were implemented. No grade 3 events were observed before mitigation measures were implemented.

RTP RESEARCH TO PRACTICE

Positive Topline Results with Tisotumab Vedotin in the Phase II InnovaTV 204 Trial

Press Release – June 30, 2020

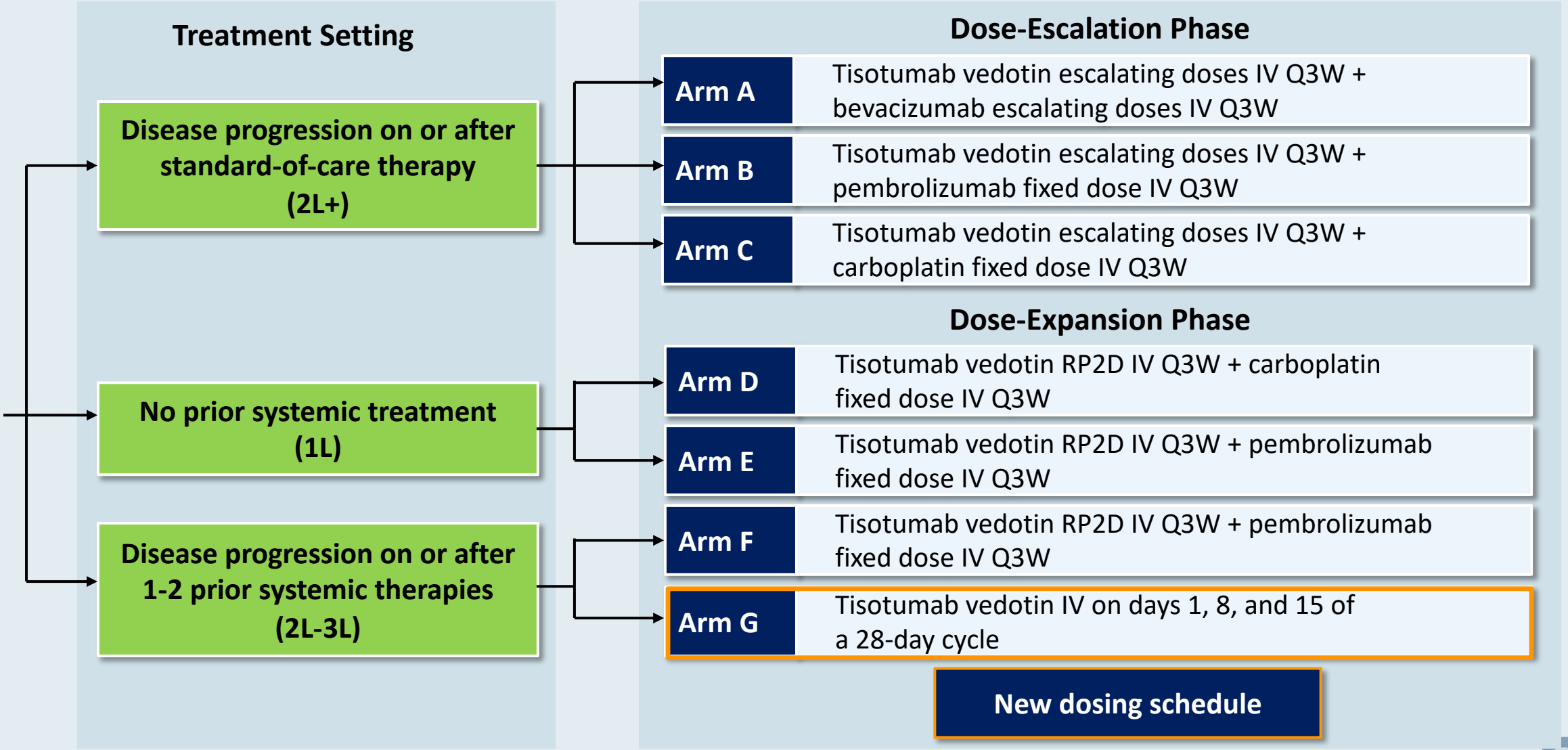
"Positive topline results [were announced] from the single-arm, phase 2 innovaTV 204 trial evaluating tisotumab vedotin administered every 3 weeks for the treatment of patients who have relapsed or progressed on or after prior treatment for recurrent or metastatic cervical cancer.

Overall, 101 patients were treated with tisotumab vedotin at multiple centers across the US and Europe. Results from the trial demonstrated a 24% confirmed ORR by independent central review with a median DOR of 8.3 months. The most common treatment-related adverse events included alopecia, epistaxis, nausea, conjunctivitis, fatigue, and dry eye."

https://www.cancernetwork.com/view/tisotumab-vedotin-sees-positive-topline-results-in-the-phase-2-innovatv-204-trial

RTP RESEARCH TO PRACTICE

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



Courtesy of David M O'Malley, MD

Meet The Professor
Management of Lung Cancer

Tuesday, October 13, 2020
12:00 PM – 1:00 PM ET

Faculty

Paul K Paik, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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