Implications of Recent Data Sets for the Current and Future Management of Gynecologic Cancers

Part 1 of a 3-Part Post-ESMO Congress 2023 CME/MOC-Accredited Live Webinar Series

Tuesday, November 7, 2023
5:00 PM – 6:00 PM ET

Faculty

Richard T Penson, MD, MRCP
Krishnansu S Tewari, MD

Moderator

Neil Love, MD

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Faculty

Richard T Penson, MD, MRCP
Associate Professor of Medicine
Harvard Medical School
Clinical Director, Medical Gynecologic Oncology
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Boston, Massachusetts

Krishnansu S Tewari, MD
Professor
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Department of Obstetrics and Gynecology
University of California, Irvine
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Neil Love, MD
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Dr Tewari — Disclosures

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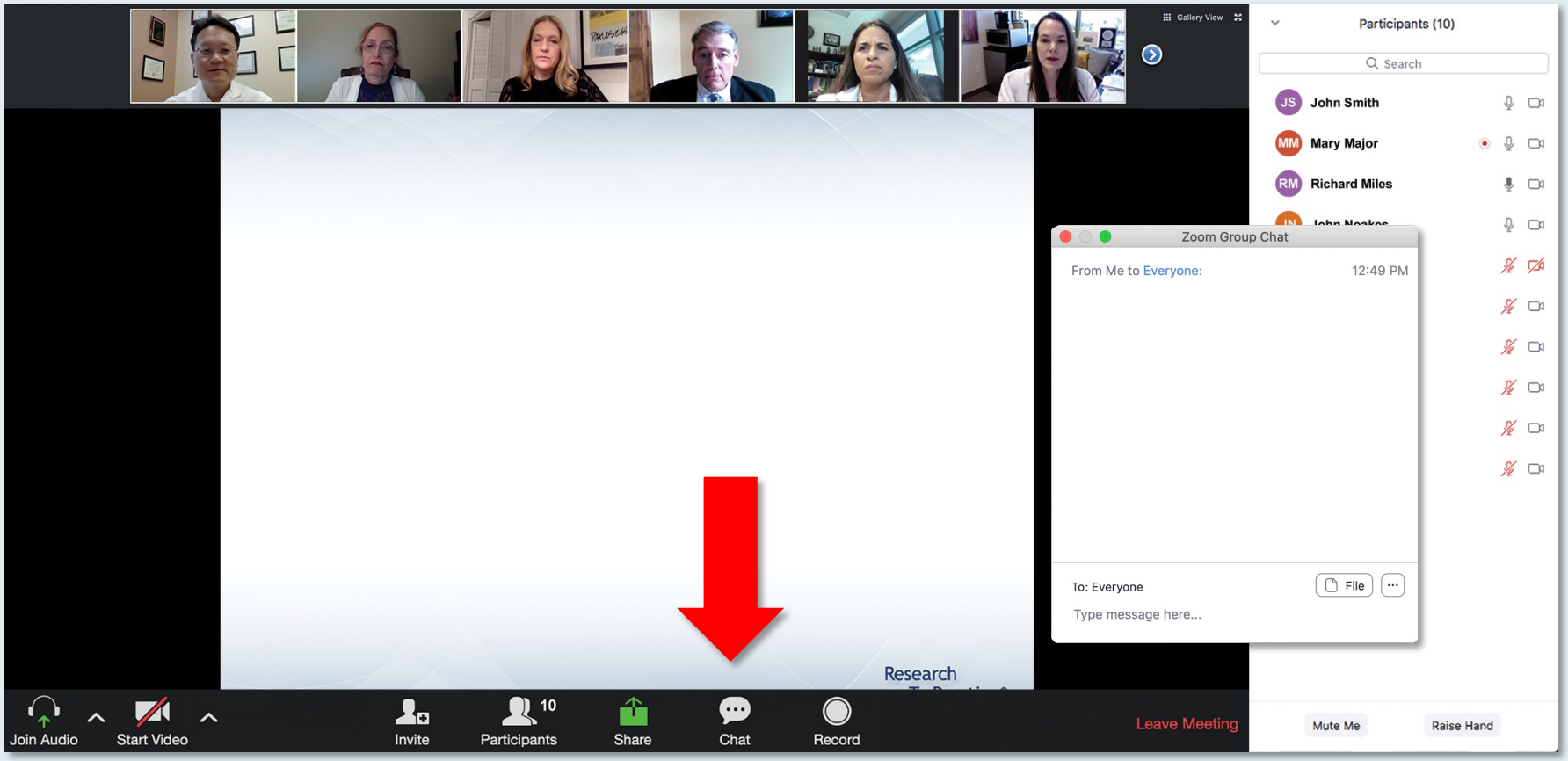

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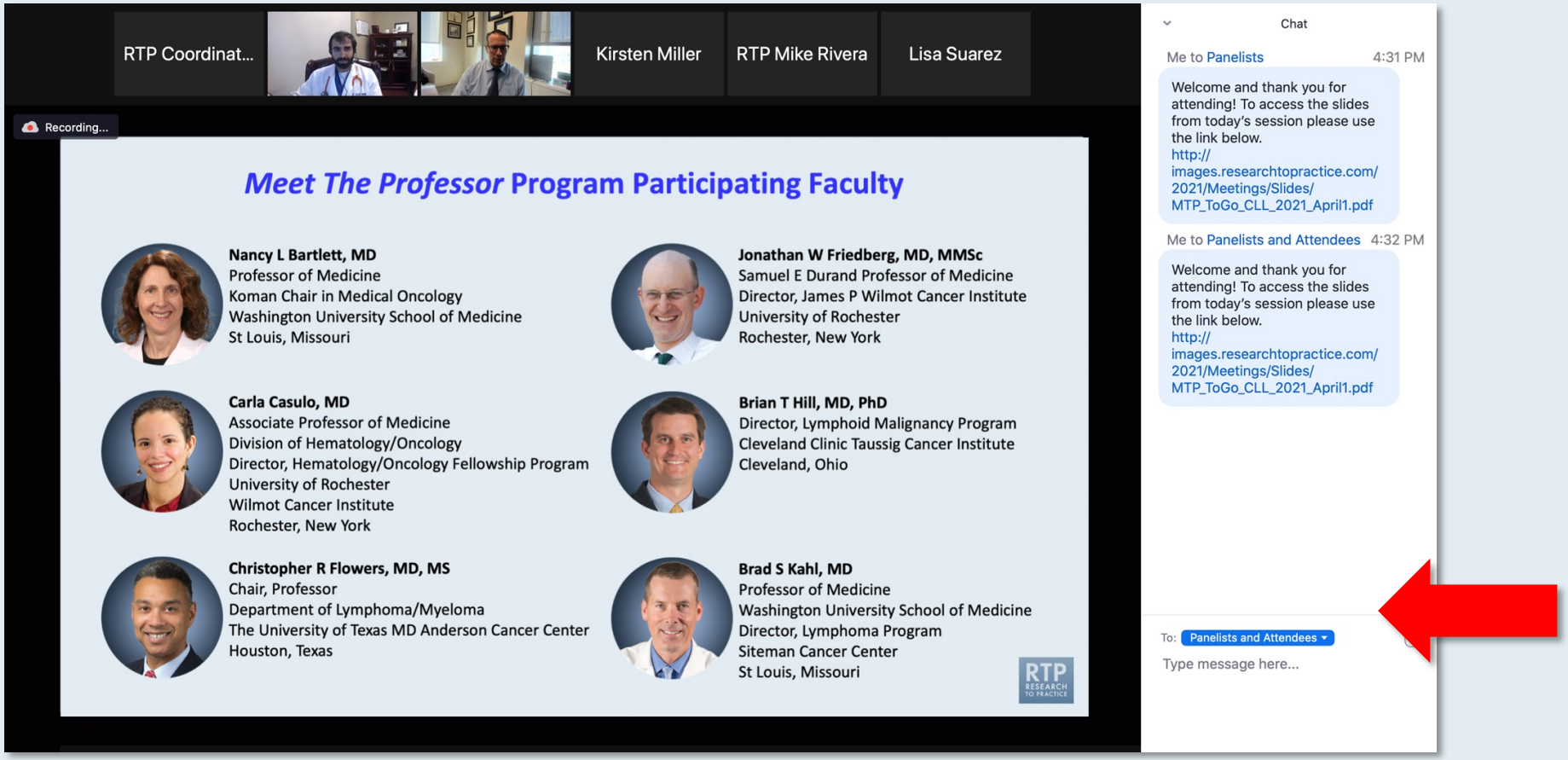

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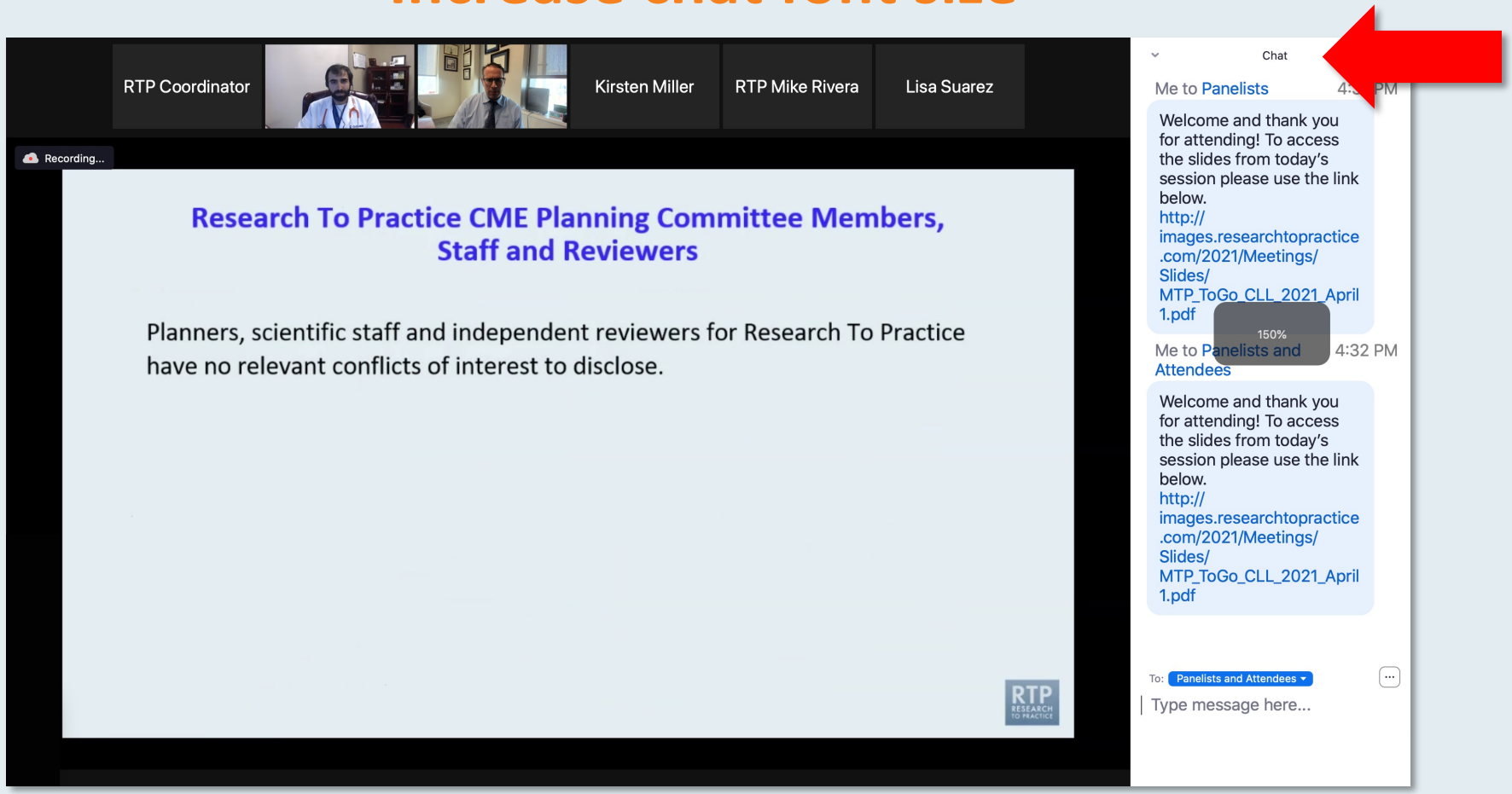

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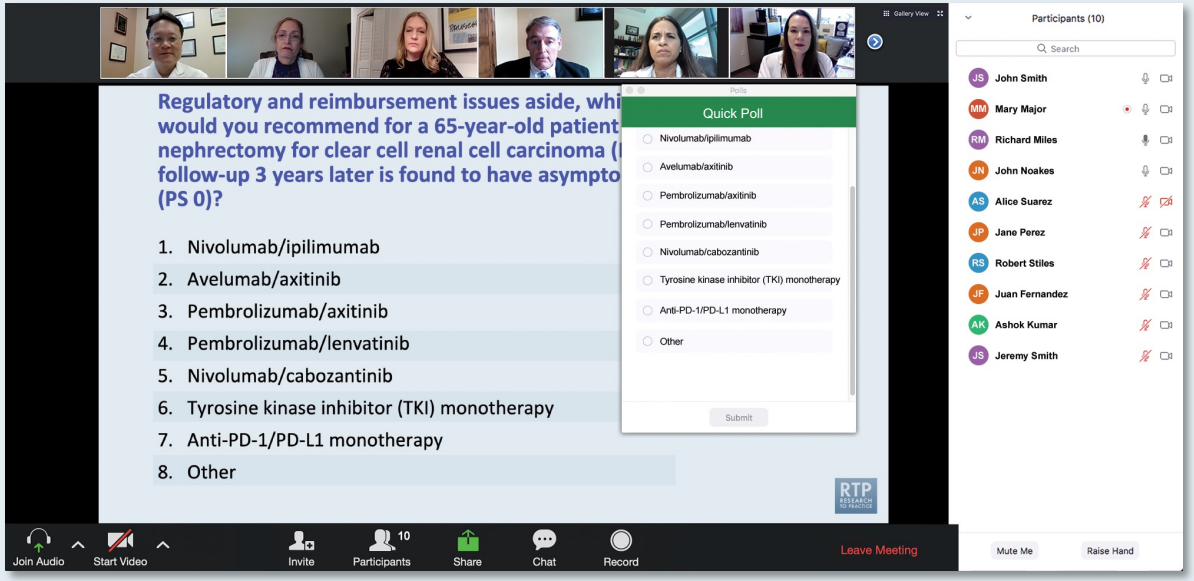

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Special Edition — Key Presentations on Gynecologic Cancers from the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting

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THE JAMES CANCER HOSPITAL - COLUMBUS

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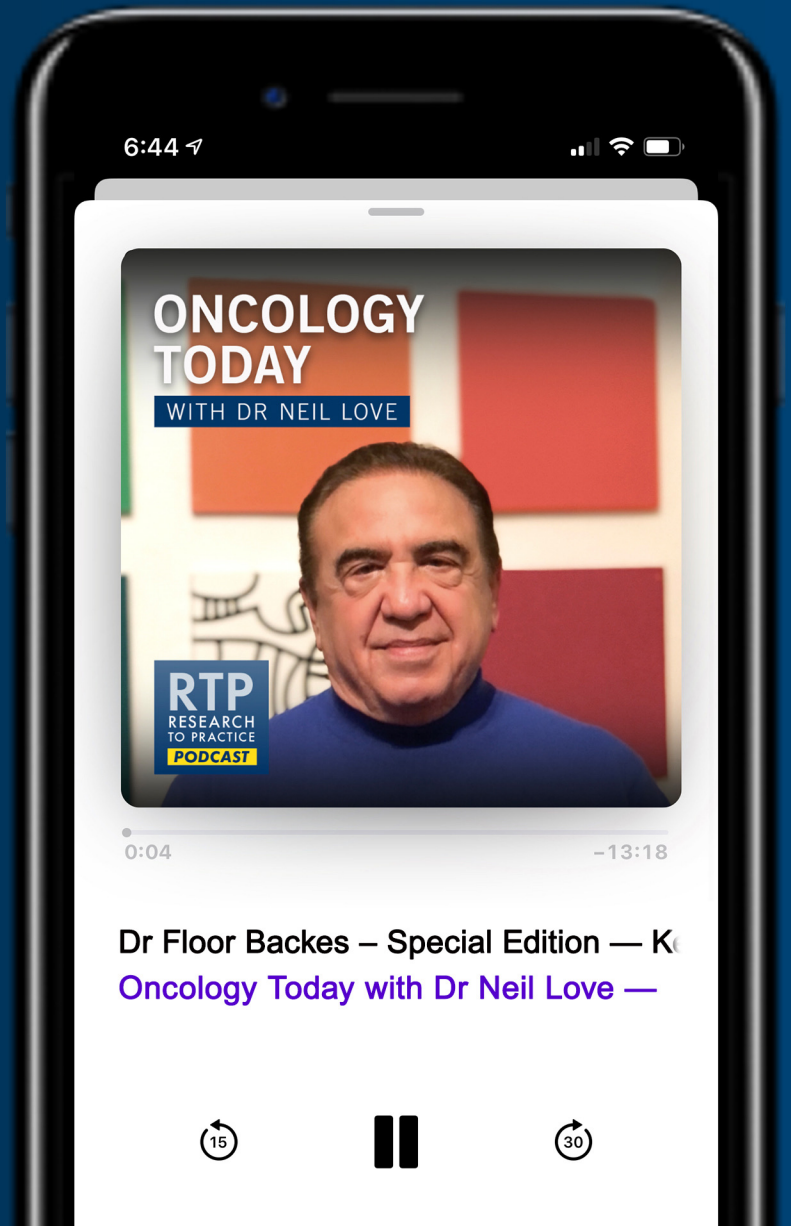

Implications of Recent Data Sets for the Current and Future Management of Breast Cancer

Part 2 of a 3-Part Post-ESMO Congress 2023 CME/MOC-Accredited Live Webinar Series

Thursday, November 9, 2023
5:00 PM – 6:00 PM ET

Faculty

Aditya Bardia, MD, MPH
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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Implications of Recent Data Sets for the Current and Future Management of Lung Cancer

Part 3 of a 3-Part Post-ESMO Congress 2023 CME/MOC-Accredited Live Webinar Series

Tuesday, November 14, 2023
5:00 PM – 6:30 PM ET

Faculty

Luis Paz-Ares, MD, PhD
Zofia Piotrowska, MD, MHS
David R Spigel, MD

Moderator

Neil Love, MD

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Meet The Professor
Optimizing the Management of Gastroesophageal Cancers

Thursday, November 16, 2023
5:00 PM – 6:00 PM ET

Faculty

Samuel J Klempner, MD

Moderator

Neil Love, MD

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Inside the Issue: Targeted and Immunotherapeutic Approaches for Biliary Tract Cancers

A CME/MOC-Accredited Live Webinar

Wednesday, November 29, 2023
5:00 PM – 6:00 PM ET

Faculty

Lipika Goyal, MD, MPhil
Milind Javle, MD

Moderator

Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Breast Cancer

A 3-Part CME Satellite Symposium Series Held in Conjunction with the 2023 San Antonio Breast Cancer Symposium®

ER-Positive Metastatic Breast Cancer

Tuesday, December 5, 2023

7:15 PM – 9:15 PM CT

Localized HER2-Negative Breast Cancer

Wednesday, December 6, 2023

7:15 PM – 9:15 PM CT

HER2-Low Breast Cancer

Thursday, December 7, 2023

7:15 PM – 8:45 PM CT

Moderator

Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Hematologic Cancers

A 4-Part CME Friday Satellite Symposium Series Preceding the 65th ASH Annual Meeting and Exposition

Friday, December 8, 2023

Follicular, Mantle Cell and Hodgkin Lymphoma
7:30 AM – 10:00 AM PT

Diffuse Large B-Cell Lymphoma
11:30 AM – 1:30 PM PT

Chronic Lymphocytic Leukemia
3:15 PM – 5:15 PM PT

Multiple Myeloma
7:00 PM – 9:00 PM PT

Moderator
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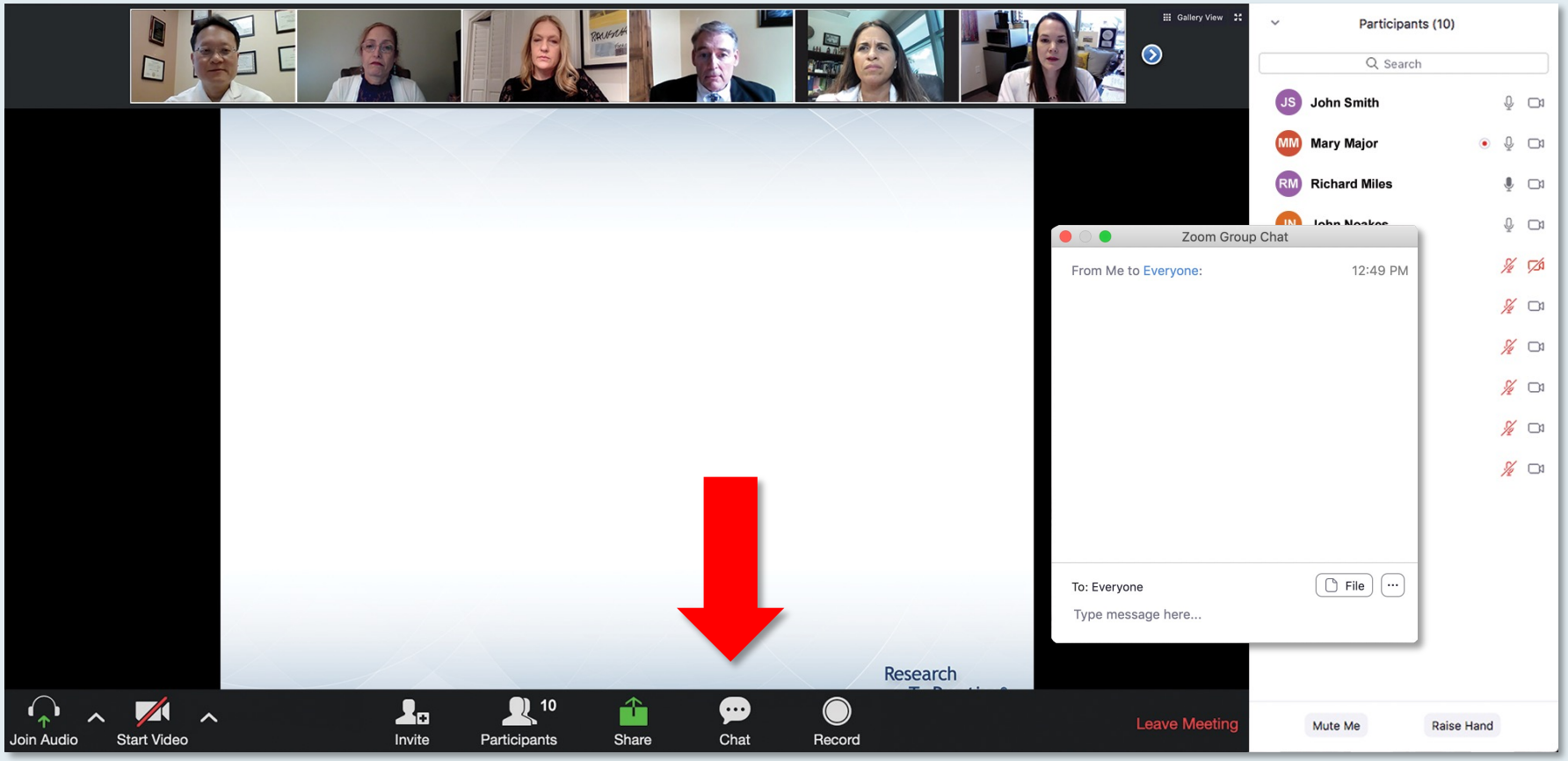

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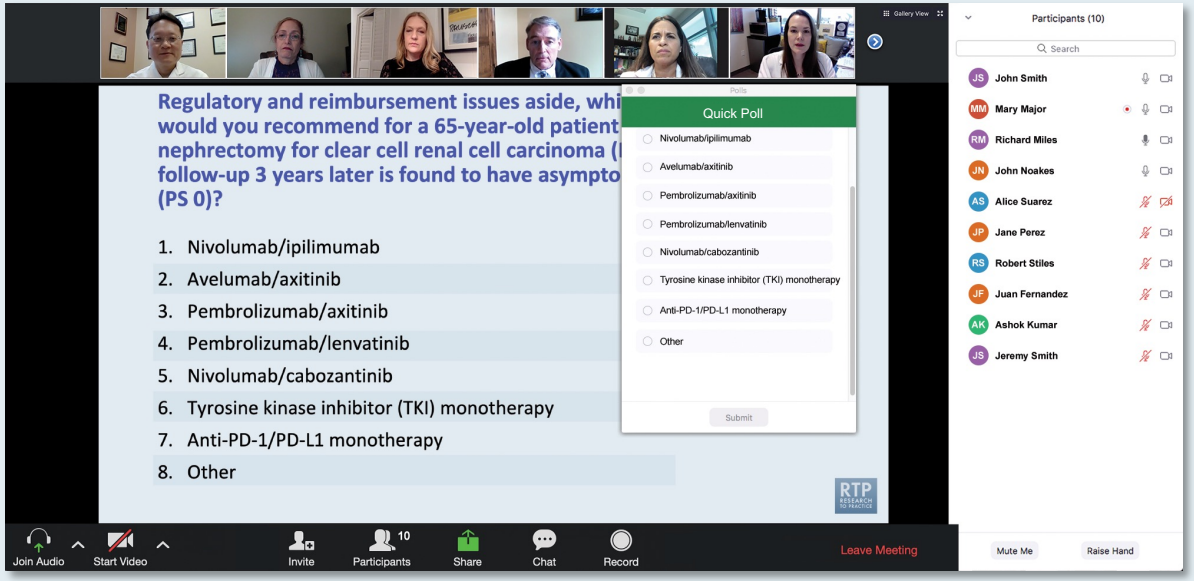

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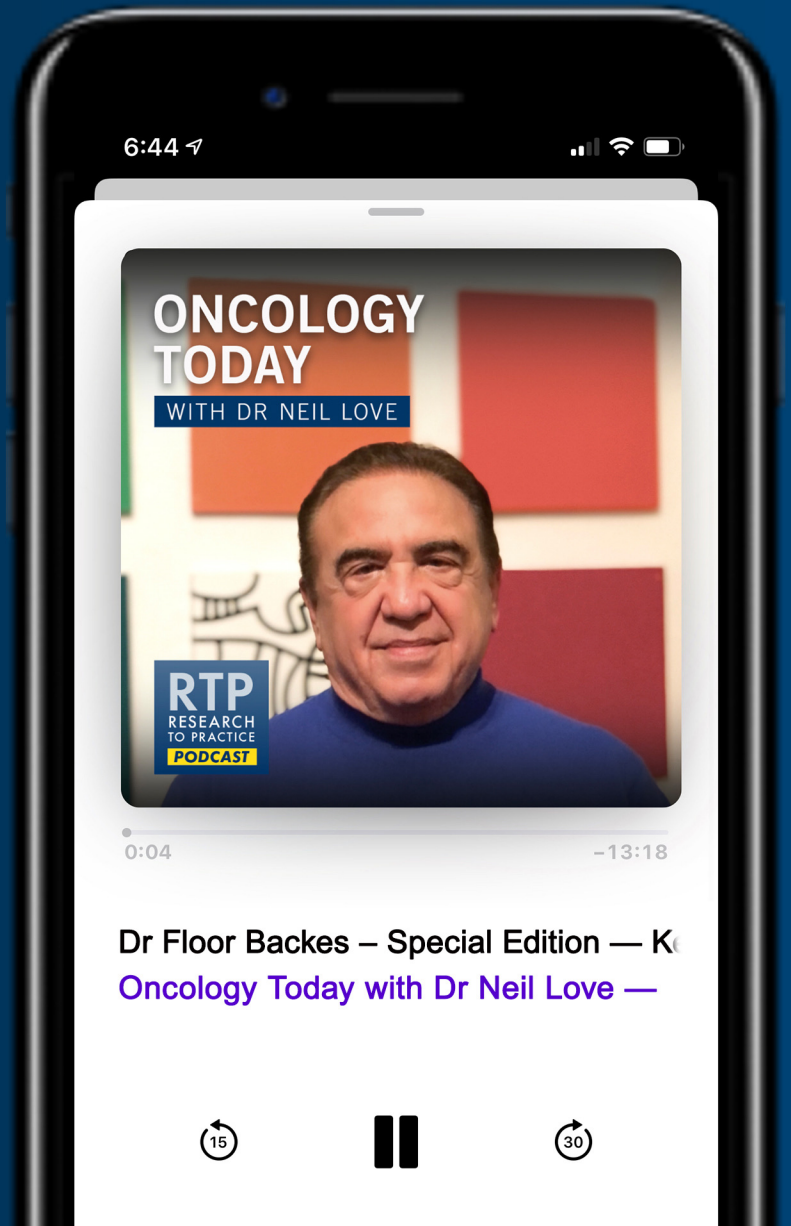

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Key Data Sets

Krishnansu S Tewari, MD

- De Bruyn M et al. Neoadjuvant immune checkpoint blockade in mismatch repair deficient endometrial cancer. ESMO 2023;Abstract 742MO.
- Mirza MR et al. Dostarlimab + chemotherapy for the treatment of primary advanced or recurrent endometrial cancer (pA/rEC): Analysis of progression free survival (PFS) and overall survival (OS) outcomes by molecular classification in the ENGOT-EN6-NSGO/GOG-3031/RUBY trial. ESMO 2023;Abstract 740MO.
- Eskander RN et al. Updated response data and analysis of progression free survival by mechanism of mismatch repair loss in endometrial cancer (EC) patients (pts) treated with pembrolizumab plus carboplatin/paclitaxel (CP) as compared to CP plus placebo (PBO) in the NRG GY018 trial. ESMO 2023;Abstract LBA43.
- Colombo N et al. Phase III double-blind randomized placebo controlled trial of atezolizumab in combination with carboplatin and paclitaxel in women with advanced/recurrent endometrial carcinoma. ESMO 2023;Abstract LBA40.

Key Data Sets

Krishnansu S Tewari, MD (continued)

- Westin SN et al. Durvalumab (durva) plus carboplatin/paclitaxel (CP) followed by maintenance (mtx) durva ± olaparib (ola) as a first-line (1L) treatment for newly diagnosed advanced or recurrent endometrial cancer (EC): Results from the phase III DUO-E/GOG-3041/ENGOT-EN10 trial. ESMO 2023;Abstract LBA41.
- Lobbedez FJ et al. Olaparib vs placebo as maintenance therapy after platinum-based chemotherapy in advanced/metastatic endometrial cancer patients: The GINECO randomized phase IIb UTOLA trial. ESMO 2023;Abstract LBA42.
- Colombo E et al. Outcomes for patients (pts) with advanced endometrial cancer (aEC) who completed pembrolizumab (pembro) and continued lenvatinib (LEN) in the phase III Study 309/KEYNOTE-775. ESMO 2023;Abstract 748P.
- McCormack M et al. A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer: The GCIG INTERLACE trial. ESMO 2023;Abstract LBA8.

Key Data Sets

Krishnansu S Tewari, MD (continued)

- Lorusso D et al. Pembrolizumab plus chemoradiotherapy for high-risk locally advanced cervical cancer: A randomized, double-blind, phase III ENGOT-cx11/GOG-3047/KEYNOTE-A18 study. ESMO 2023;Abstract LBA38.
- Monk BJ et al. KEYNOTE-826: Final overall survival results from a randomized, double-blind, phase 3 study of pembrolizumab + chemotherapy vs placebo + chemotherapy for first-line treatment of persistent, recurrent, or metastatic cervical cancer. ASCO 2023;Abstract 5500.
- Vergote IB et al. innovaTV 301/ENGOT-cx12/GOG-3057: A global, randomized, open-label, phase III study of tisotumab vedotin vs investigator's choice of chemotherapy in 2L or 3L recurrent or metastatic cervical cancer. ESMO 2023;Abstract LBA9.
- Meric-Bernstam F et al. Trastuzumab deruxtecan (T-DXd) for pretreated patients (pts) with HER2-expressing solid tumors: Primary analysis from the DESTINY-PanTumor02 (DP-02) study. ESMO 2023;Abstract LBA34.

Key Data Sets

Richard T Penson, MD, MRCP

- Richardson DL et al. Effectiveness of PARP inhibitor maintenance therapy (mPARPi) in advanced ovarian cancer (OC) by BRCA1/2 and HRD signature in real-world practice. ASCO 2023;Abstract 5583.
- Wu X et al. Efficacy and safety of senaparib as maintenance treatment in patients with newly diagnosed advanced ovarian cancer (FLAMES study): A randomized, double-blind, placebo-controlled, phase III trial. ESMO 2023;Abstract LBA36.
- Harter P et al. Durvalumab with paclitaxel/carboplatin (PC) and bevacizumab (bev), followed by maintenance durvalumab, bev, and olaparib in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) without a tumor BRCA1/2 mutation (non-tBRCAm): Results from the randomized, placebo (pbo)-controlled phase III DUO-O trial. ASCO 2023;Abstract LBA5506.
- Gonzalez Martin A et al. Atezolizumab (atezo) combined with platinum-based chemotherapy (CT) and maintenance niraparib for recurrent ovarian cancer (rOC) with a platinum-free interval (TFIp) >6 months: Primary analysis of the double-blind placebo (pbo)-controlled ENGOT-Ov41/GEICO 69-O/ANITA phase III trial. ESMO 2023;Abstract LBA37.

Key Data Sets

Richard T Penson, MD, MRCP (continued)

- Liu JF et al. Overall survival (OS) outcomes from NRG-GY004, a phase III study comparing single-agent olaparib or combination cediranib and olaparib to platinum (plat) based chemotherapy in recurrent plat sensitive ovarian cancer (OvCa). ESMO 2023;Abstract LBA45.
- Moore KN et al. Phase III MIRASOL (GOG 3045/ENGOT-ov55) study: Initial report of mirvetuximab soravtansine vs. investigator's choice of chemotherapy in platinum-resistant, advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression. ASCO 2023;Abstract LBA5507.
- Moore KN et al. Raludotatug deruxtecan (R-DXd; DS-6000) monotherapy in patients with previously treated ovarian cancer (OVC): Subgroup analysis of a first-in-human phase I study. ESMO 2023;Abstract 745MO.

Agenda

INTRODUCTION: Pan-tumor Indications for New Therapies

MODULE 1: Endometrial Cancer

- Key Issue – Immunotherapy

MODULE 2: Cervical Cancer

- Key Issue – Immunotherapy
- Key Issue – Tisotumab vedotin

MODULE 3: Ovarian Cancer

- Key Issue – PARP inhibitors in primary management (maintenance) and relapsed disease
- Key Issue – Mirvetuximab soravtansine and other antibody-drug conjugates

Agenda

INTRODUCTION: Pan-tumor Indications for New Therapies

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DESTINY-PanTumor02 Study

Trastuzumab Deruxtecan for HER2-expressing solid tumors

	n		ORR, %		mPFS, mo (95% CI)		mOS, mo (95% CI)	
	All	IHC 3+	All	IHC 3+	All	IHC 3+	All	IHC 3+
Total	267	75	37.1	61.3	6.9 (5.6, 8.0)	11.9 (8.2, 13.0)	13.4 (11.9, 15.5)	21.1 (15.3, 29.6)

	n		ORR, %		mPFS, mo (95% CI)		mOS, mo (95% CI)	
	All	IHC 3+	All	IHC 3+	All	IHC 3+	All	IHC 3+
BTC	41	16	22.0	56.3	4.6 (3.1, 6.0)	7.4 (2.8, 12.5)	7.0 (4.6, 10.2)	12.4 (2.8, NR)
URO	41	16	39.0	56.3	7.0 (4.2, 9.7)	7.4 (3.0, 11.9)	12.8 (11.2, 15.1)	13.4 (6.7, 19.8)
CC	40	8	50.0	75.0	7.0 (4.2, 11.1)	NR (3.9, NR)	13.6 (11.1, NR)	NE (3.9, NR)
EC	40	13	57.5	84.6	11.1 (7.1, NR)	NR (7.3, NR)	26.0 (12.8, NR)	26.0 (18.9, NR)
OC	40	11	45.0	63.6	5.9 (4.0, 8.3)	12.5 (3.1, NR)	13.2 (8.0, 17.7)	20.0 (3.8, NR)
PC	25	2	4.0	0	3.2 (1.8, 7.2)	5.4 (2.8, NR)	5.0 (3.8, 14.2)	12.4 (8.8, NR)
Other	40	9	30.0	44.4	8.8 (5.5, 12.5)	23.4 (5.6, NR)	21.0 (12.9, 24.3)	24.3 (11.1, NR)

NR, not reached

Presented by Meric-Bernstam F, et al. ESMO 2023

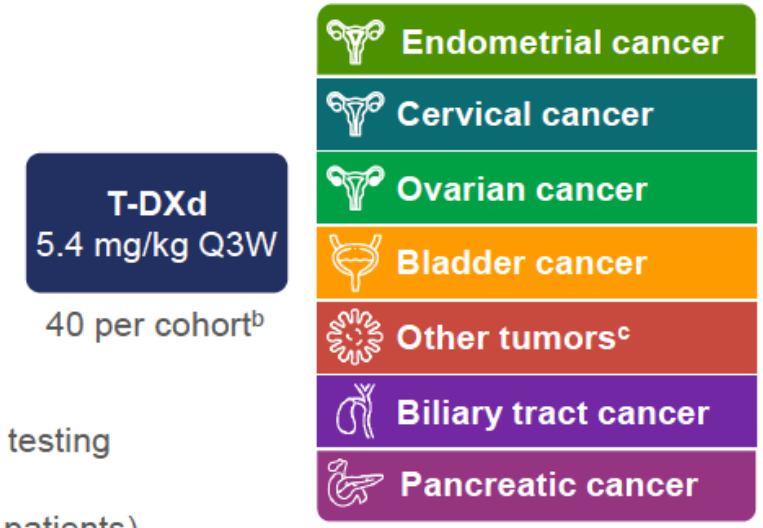
Courtesy of Krishnansu S Tewari, MD

DESTINY-PanTumor02: a Phase 2 study of T-DXd for HER2-expressing solid tumors

An open-label, multicenter study (NCT04482309)

Key eligibility criteria

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer scoring[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR, DCR, PFS, OS
- Safety

Exploratory analysis

- Subgroup analyses by HER2 status

Primary analysis
data cutoff: Jun 8, 2023
Median follow up: 12.75 mo

Baseline characteristics

- 267 patients received treatment; 202 (75.7%) based on local HER2 testing
  - 111 (41.6%) patients were IHC 3+ based on HER2 test (local or central) at enrollment, primary efficacy analysis (all patients)
  - **75 (28.1%) patients were IHC 3+ on central testing**, sensitivity analysis on efficacy endpoints (subgroup analyses)
- Median age was 62 years (23–85) and **109 (40.8%) patients had received ≥3 lines of therapy**

[a]Patients were eligible for either test. All patients were centrally confirmed; [b]planned recruitment, cohorts with no objective responses in the first 15 patients were to be closed; [c]patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer

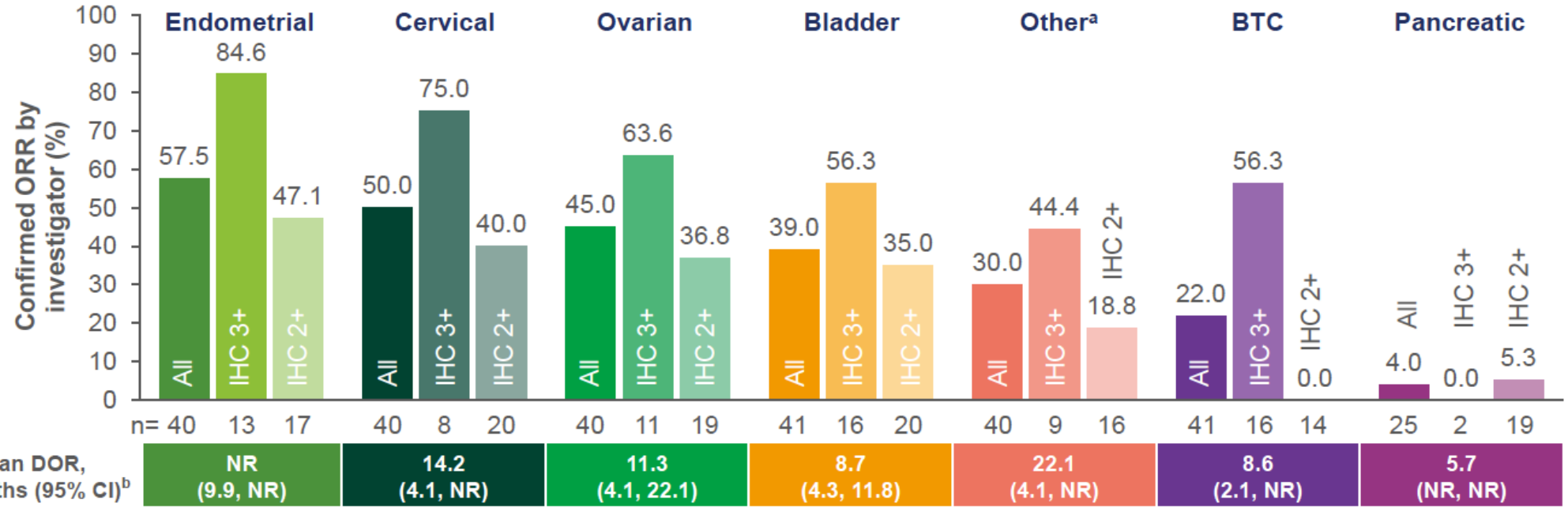
2L, second-line; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization

1. Hofmann M, et al. *Histopathology*. 2008;52:797–805

Meric-Bernstam F et al. ESMO 2023;Abstract LBA34.

DESTINY-PanTumor02: Objective Response and Duration of Response

Objective response and duration of response



	All patients (N=267)	IHC 3+ (n=75)	IHC 2+ (n=125)
ORR, % (95% CI)	37.1 (31.3, 43.2)	61.3 (49.4, 72.4)	27.2 (19.6, 35.9)
Median DOR, months (95% CI)[b]	11.3 (9.6, 17.8)	22.1 (9.6, NR)	9.8 (4.3, 12.6)

Analysis of ORR by investigator was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer; [b]includes patients with a confirmed objective response only

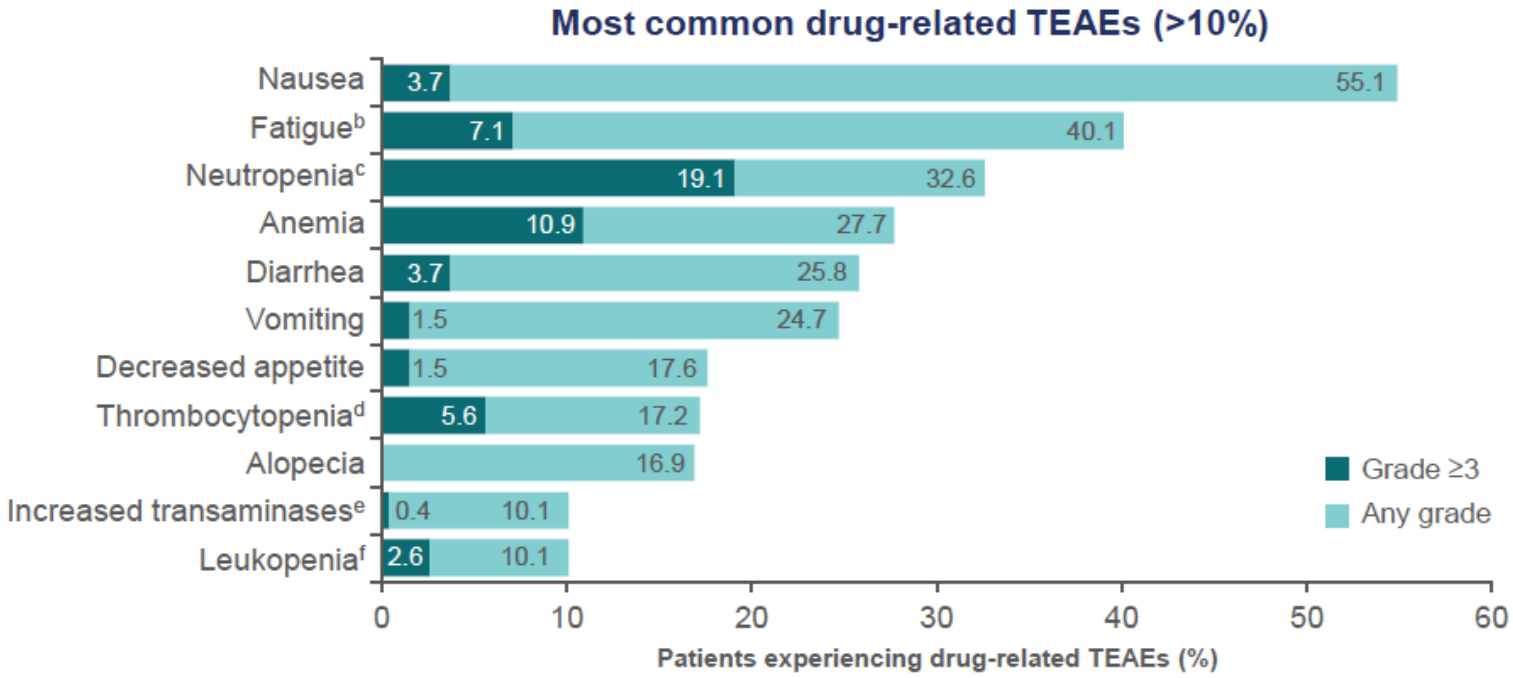
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; ORR, objective response rate; T-DXd, trastuzumab deruxtecan

Meric-Bernstam F et al. ESMO 2023;Abstract LBA34.

RTP RESEARCH TO PRACTICE

DESTINY-PanTumor02: Safety Summary

n (%)	All patients (N=267)
Any drug-related TEAEs	226 (84.6)
Drug-related TEAEs Grade ≥3	109 (40.8)
Serious drug-related TEAEs	36 (13.5)
Drug-related TEAEs associated with dose discontinuations	23 (8.6)
Drug-related TEAEs associated with dose interruptions	54 (20.2)
Drug-related TEAEs associated with dose reductions	54 (20.2)
Drug-related TEAEs associated with deaths	4 (1.5)[a]

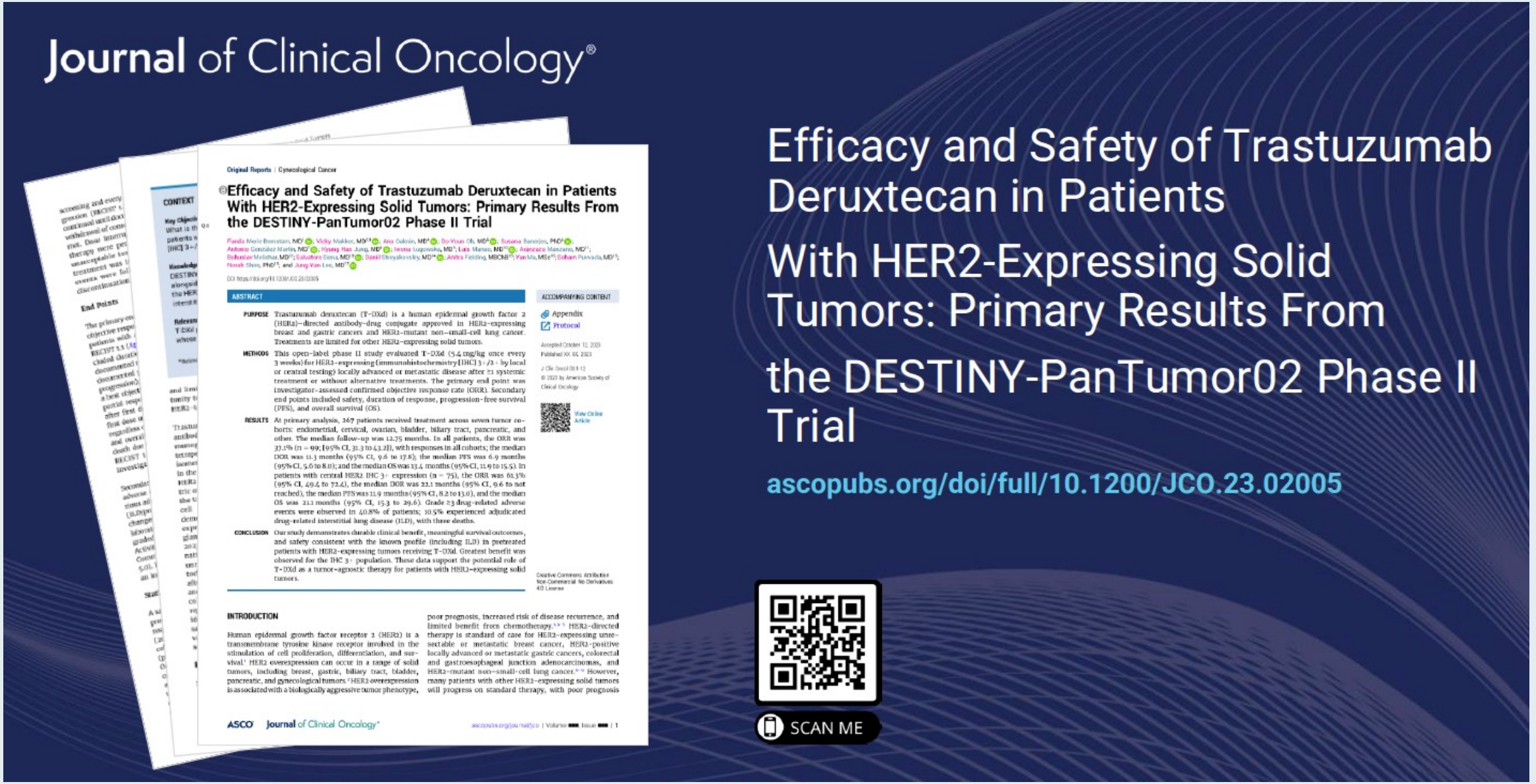


ILD/pneumonitis adjudicated as T-DXd related, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All patients (N=267)	7 (2.6)	17 (6.4)	1 (0.4)	0	3 (1.1)	28 (10.5)

Analyses were performed in patients who received ≥1 dose of T-DXd (N=267); median total treatment duration 5.6 months (range 0.4–31.1)
[a]Included pneumonia (n=1), organizing pneumonia (n=1), pneumonitis (n=1), and neutropenic sepsis (n=1); [b]category includes the preferred terms fatigue, asthenia, and malaise; [c]category includes the preferred terms neutrophil count decreased and neutropenia; [d]category includes the preferred terms platelet count decreased and thrombocytopenia; [e]category includes the preferred terms aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, hypertransaminasemia; [f]category includes the preferred terms white blood cell count decreased and leukopenia
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event

Meric-Bernstam F et al. ESMO 2023;Abstract LBA34.

RTP RESEARCH TO PRACTICE



Meric-Bernstam F et al. ESMO 2023;Abstract LBA34.

RTP RESEARCH TO PRACTICE

MADRID 2023 ESMO congress

Raludotatug deruxtecan (R-DXd; DS-6000) monotherapy in patients with previously treated ovarian cancer (OVC): subgroup analysis of a first-in-human Phase 1 study

Kathleen Moore,[1,2] Alexander Philipovskiy,[2,3] Kenichi Harano,[4] Brian Rini,[5] Kazuki Sudo,[6] Shigehisa Kitano,[7] David R. Spigel,[2,8] Jie Lin,[9] Madan G. Kundu,[9] Amine Bensmaine,[10] Yusuke Myobatake,[9] Erika Hamilton[2,8]

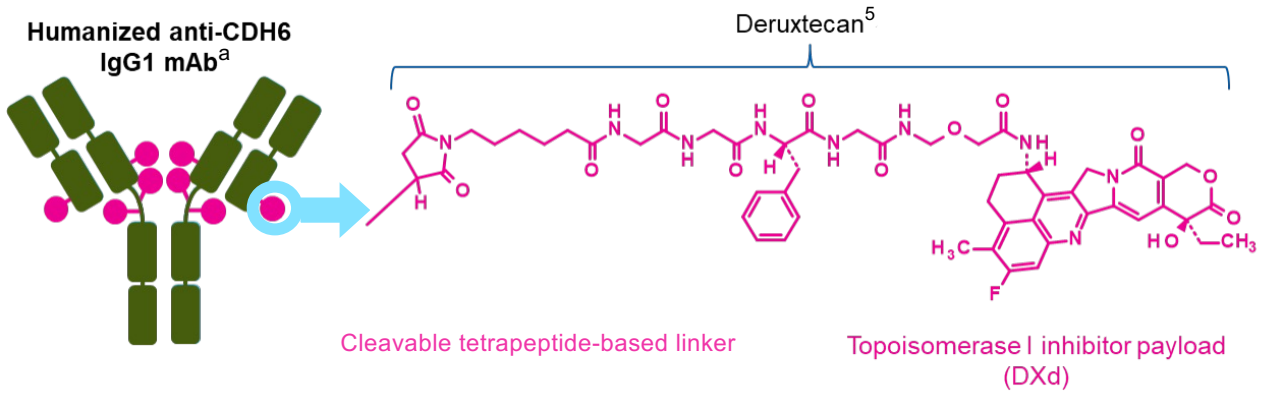
[1]University of Oklahoma, Oklahoma City, OK, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]Florida Cancer Specialists, Lake Mary, FL, USA; [4]National Cancer Center Hospital East, Kashiwa, Japan; [5]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [6]National Cancer Center Hospital, Tokyo, Japan; [7]Japanese Foundation for Cancer Research, Tokyo, Japan; [8]Tennessee Oncology, PLLC, Nashville, TN, USA; [9]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [10]Daiichi Sankyo, Inc., Rueil-Malmaison, France.

Courtesy of Richard T Penson, MD, MRCP

Background

- The emergence of platinum resistance in recurrent OVC is inevitable; these patients have a clear need for novel treatments[1]
- Mirvetuximab soravtansine-gynx received accelerated approval from the FDA for the treatment of patients with platinum-resistant, FRα-positive OVC (ORR: 31.7%, median DOR: 6.9 months)[2]
- Expression of CDH6 is observed in ~65–85% of patients with OVC[3,4]
- Raludotatug deruxtecan (R-DXd; DS-6000) is a CDH6-directed ADC composed of three parts: a humanized anti-CDH6 IgG1 mAb, covalently linked to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker[5]

R-DXd was designed with 7 key attributes



Payload mechanism of action: topoisomerase I inhibitor[5,b]
High potency of payload[5,b]
High drug-to-antibody ratio ≈8[5,b]
Payload with short systemic half-life[6,b,c]
Stable linker-payload[5,b]
Tumor-selective cleavable linker[5,b]
Bystander antitumor effect[5,b]

[a]Image is for illustrative purposes only; actual drug positions may vary. [b]The clinical relevance of these features is under investigation. [c]Based on animal data.
ADC, antibody–drug conjugate; CDH6, cadherin 6; DOR, duration of response; DXd, deruxtecan; FDA, United States Food and Drug Administration; FRα, folate receptor alpha; IgG1, immunoglobulin G1; mAb, monoclonal antibody; ORR, objective response rate; OVC, ovarian cancer.

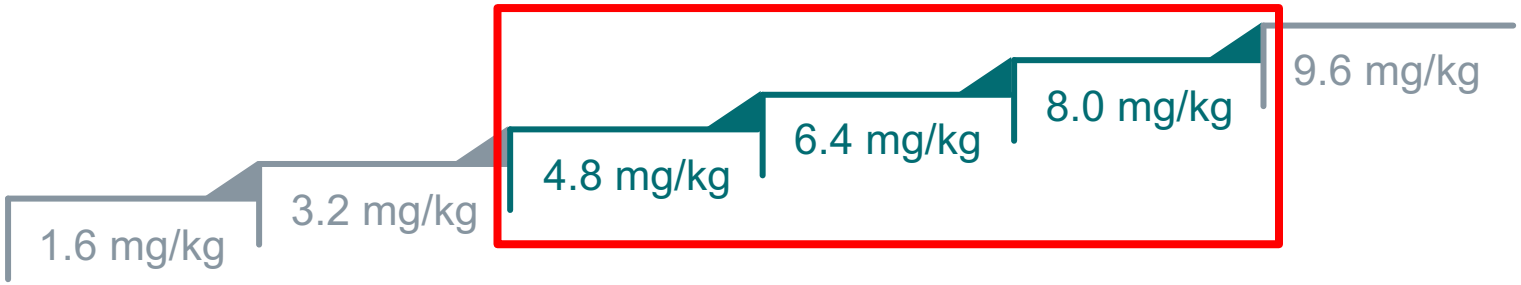
1. Richardson DL, et al. *JAMA Oncol.* 2023;9:851–859; 2. ELAHERE™ (mirvetuximab soravtansine-gynx) prescribing information. Accessed September 1, 2023; 3. Bartolomé RA, et al. *Mol Oncol.* 2021;15:1849–1865;
4. Shintani D, et al. *Gynecol Oncol.* 2022;166(Suppl. 1):S116; 5. Suzuki H, et al. *Ann Oncol.* 2021;32(Suppl. 5):S361–S375; 6. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67:173–185.

Courtesy of Richard T Penson, MD, MRCP

First-in-human phase 1 study of R-DXd (NCT04707248)[1,2]

Subgroup analysis of patients with OVC who received R-DXd at 4.8–8.0 mg/kg[a]

Part A
Dose escalation: R-DXd IV Q3W



Part B
Dose expansion: R-DXd IV Q3W

- OVC cohort: 4.8 mg/kg
- OVC cohort: 6.4 mg/kg
- OVC cohort: 5.6 mg/kg
- OVC cohort: 8.0 mg/kg

Enrollment criteria:

- Advanced/metastatic OVC not amenable to SOC therapy
- ECOG PS 0–1
- Prior taxane and platinum-based chemotherapy
- No previous CDH6-targeting agents or ADCs with a linked topoisomerase I inhibitor
- Patients were not selected based on tumor CDH6 expression

Key primary objectives:

- Safety and tolerability
- Determine MTD and RDEs for dose expansion
- Determine ORR per RECIST v1.1 for dose expansion

Key secondary objectives:

- PK: ADC, total anti-CDH6 antibody, and the DXd payload
- Antitumor activity per RECIST v1.1
- Immunogenicity

[a]4.8–8.0 mg/kg R-DXd dose cohorts were initially prioritized for dose expansion due to a favorable benefit/risk profile.

ADC, antibody–drug conjugate; CDH6, cadherin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerated dose; ORR, objective response rate; OVC, ovarian cancer; PK, pharmacokinetics; Q3W, every 3 weeks; RDE, recommended doses for expansion; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SOC, standard of care.

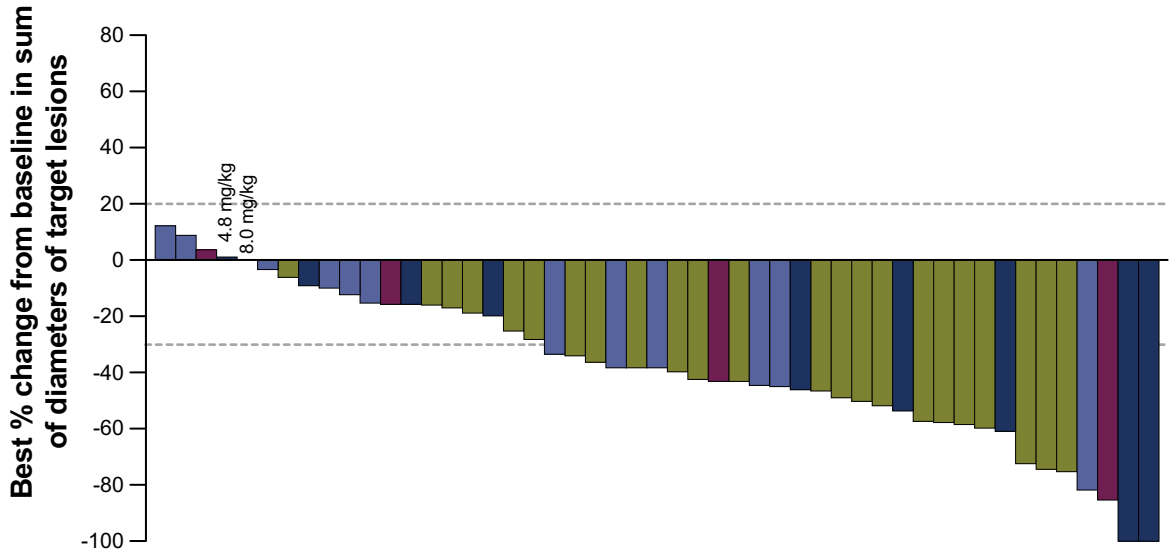
1. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT04707248. Accessed July 20, 2023; 2. Data on file. Daiichi Sankyo, Inc. DS6000-A-U101 protocol, version 3; 2020.

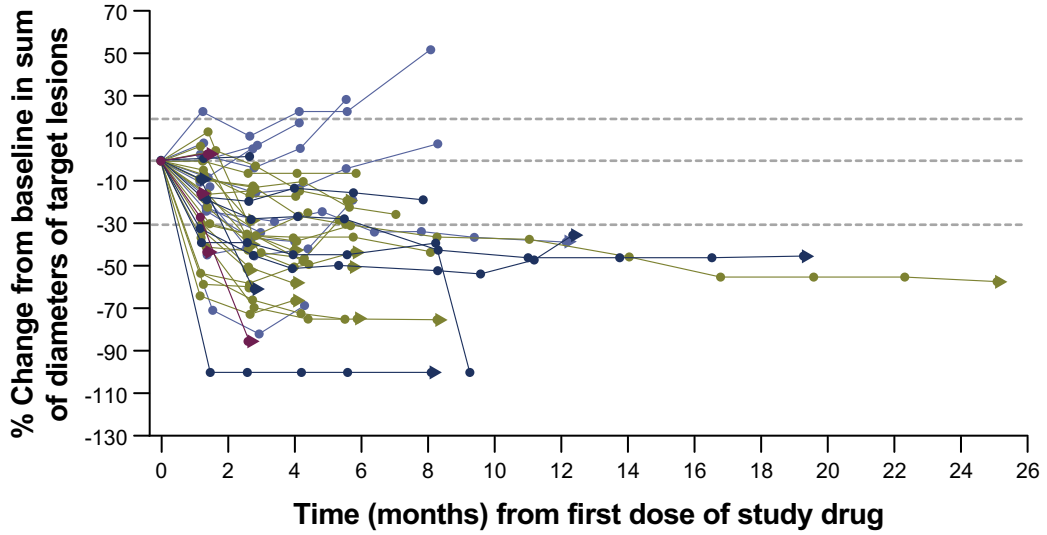
Courtesy of Richard T Penson, MD, MRCP

Preliminary efficacy data for R-DXd are promising in pretreated OVC patients

- **Confirmed ORR: 46%** in the 4.8–8.0 mg/kg OVC cohort (23/50; 95% CI: 32–61); one CR and 22 PRs
  - 4 unconfirmed responses were ongoing at data cutoff
- **Disease control rate**[a]: **98%**

- Median time to response: 6 weeks (95% CI: 5–11)
- Median **DOR**[b]: **11.2 months** (95% CI: 3.0–NE)
- Median **PFS**[c]: **7.9 months** (95% CI: 4.4–12.4)





Starting dose level

4.8 mg/kg (n=9) 5.6 mg/kg (n=4) 6.4 mg/kg (n=23) 8.0 mg/kg (n=13)

Data cutoff: July 14, 2023.
[a]CR + PR + stable disease. [b]Median follow-up for DOR: 5.8 months (95% CI: 3.0–8.1). [c]Median follow-up for PFS: 5.6 months (95% CI: 2.8–7.0).

The efficacy evaluable population included patients who received ≥1 dose of study treatment and completed ≥1 post-baseline tumor assessment or discontinued treatment for any reason. Change from baseline in target tumor size was assessed per RECIST v1.1. Two patients with no measurable lesions at baseline and one patient who discontinued and did not have a post-baseline tumor assessment were not included in the waterfall or spider plots.

CI, confidence interval; CR, complete response; DOR, duration of response; NE, not estimable; ORR, objective response rate; OVC, ovarian cancer; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Courtesy of Richard T Penson, MD, MRCP

Safety profile of R-DXd is manageable

Patients with OVC who received R-DXd at 4.8–8.0 mg/kg

Overview of TEAEs

	n (%) N=60
Any TEAEs	57 (95.0)
TEAE with CTCAE Grade ≥3	31 (51.7)
TEAE associated with drug discontinuation	9 (15.0)
TEAE associated with dose interruption	22 (36.7)
TEAE associated with dose reduction	15 (25.0)
Any treatment-related CTCAE Grade ≥3 TEAE	22 (36.7)
Treatment-related TEAE associated with death	2 (3.3)[a]

Most common (≥10%) treatment-related TEAEs

Preferred term	n (%) N=60	
	All grades	Grade ≥3
Nausea	35 (58.3)	1 (1.7)
Fatigue	27 (45.0)	2 (3.3)
Vomiting	20 (33.3)	1 (1.7)
Anemia	17 (28.3)	11 (18.3)
Decreased neutrophil count	15 (25.0)	7 (11.7)
Diarrhea	16 (26.7)	1 (1.7)
Decreased appetite	15 (25.0)	1 (1.7)
Decreased platelet count	10 (16.7)	3 (5.0)
Alopecia	7 (11.7)	0
Malaise	6 (10.0)	0

Data cutoff: July 14, 2023.

[a]Grade 5 ILD. [b]6/15 (40.0%) patients in the 8.0-mg/kg OVC cohort experienced serious and Grade ≥3 TEAEs.

CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; OVC, ovarian cancer; TEAE, treatment-emergent adverse event.

Courtesy of Richard T Penson, MD, MRCP

Conclusions

- R-DXd is the first CDH6-directed ADC to demonstrate promising efficacy in patients with heavily pretreated platinum-resistant OVC who were not selected based on tumor CDH6 expression
  - ORR: 46% in the 4.8–8.0 mg/kg OVC cohort; one CR and 22 PRs
  - Median DOR: 11.2 months[a]
  - Median PFS: 7.9 months[b]
- Safety profile is manageable, and toxicities are consistent with those observed with other DXd ADCs[1,2]
- Based on the accumulated overall safety, tolerability, PK and efficacy profile of R-DXd, the 8.0 mg/kg cohort was closed, and further assessment is ongoing at three dose levels: 4.8 mg/kg, 5.6 mg/kg and 6.4 mg/kg
- These data support further clinical evaluation of R-DXd in a late-phase study in patients with OVC

[a]Median follow-up for DOR: 5.8 months (95% CI: 3.0–8.1). [b]Median follow-up for PFS: 5.6 months (95% CI: 2.8–7.0).

ADC, antibody–drug conjugate; CDH6, cadherin 6; CI, confidence interval; CR, complete response; DOR, duration of response; DXd, deruxtecan; ORR, objective response rate; OVC, ovarian cancer; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response.

1. Guo Z, et al. *J Clin Pharm Ther*. 2022;47:1837–1844; 2. Jänne PA, et al. *Cancer Discov*. 2022;12:74–89.

Courtesy of Richard T Penson, MD, MRCP

Agenda

INTRODUCTION: Pan-tumor Indications for New Therapies

MODULE 1: Endometrial Cancer

- Key Issue – Immunotherapy

MODULE 2: Cervical Cancer

- Key Issue – Immunotherapy
- Key Issue – Tisotumab vedotin

MODULE 3: Ovarian Cancer

- Key Issue – PARP inhibitors in primary management (maintenance) and relapsed disease
- Key Issue – Mirvetuximab soravtansine and other antibody-drug conjugates

ENGOT-EN6-NSGO/GOG-3031/RUBY (NCT03981796)

Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin/paclitaxel in patients with primary advanced or recurrent EC

Eligible patients

- Histologically/cytologically proven advanced or recurrent EC
- Stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
  - Carcinosarcoma, clear cell, serous, or mixed histology permitted
- Naïve to systemic therapy or systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment
- ECOG PS 0-1
- Adequate organ function

Stratification

- MMR/MSI status
- Prior external pelvic radiotherapy
- Disease status

R1:1

Dostarlimab IV 500 mg
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m^2 Q3W for 6 cycles

Dostarlimab IV 1000 mg Q6W up to 3 years[a]

Placebo IV
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m^2 Q3W for 6 cycles

Placebo IV Q6W up to 3 years[a]

Follow-up

Primary endpoints

- PFS by INV per RECIST v1.1
- OS

Secondary endpoints

- PFS by BICR per RECIST v1.1
- PFS2
- ORR
- DOR
- DCR
- HRQOL/PRO
- Safety

Further study details can be found at Mirza MR, et al. N Engl J Med. 2023 Jun 8;388(23):2145-2158.
[a]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the Investigator. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response, EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; HRQOL, health-related quality of life; IHC, immunohistochemistry; INV, investigator assessment; MMR, mismatch repair; MSI, microsatellite instability; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcome; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

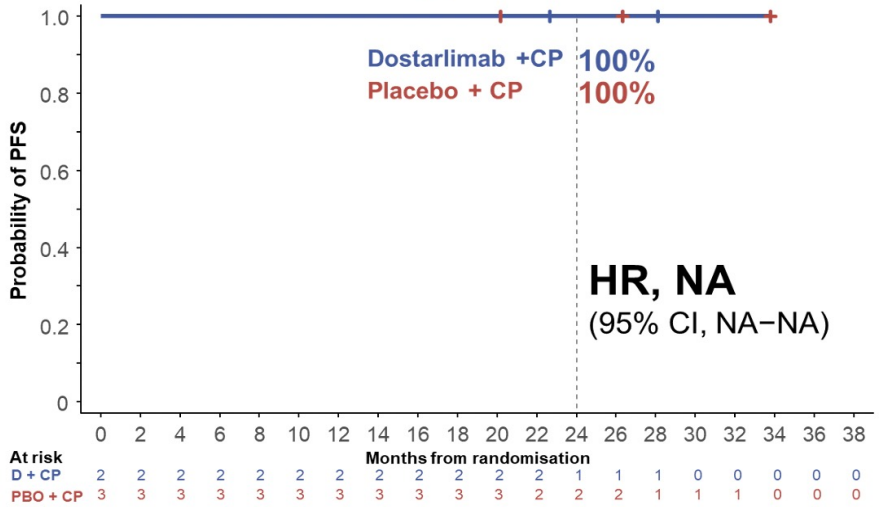
Presented by Mirza MR, et al. ESMO 2023

Courtesy of Krishnansu S Tewari, MD

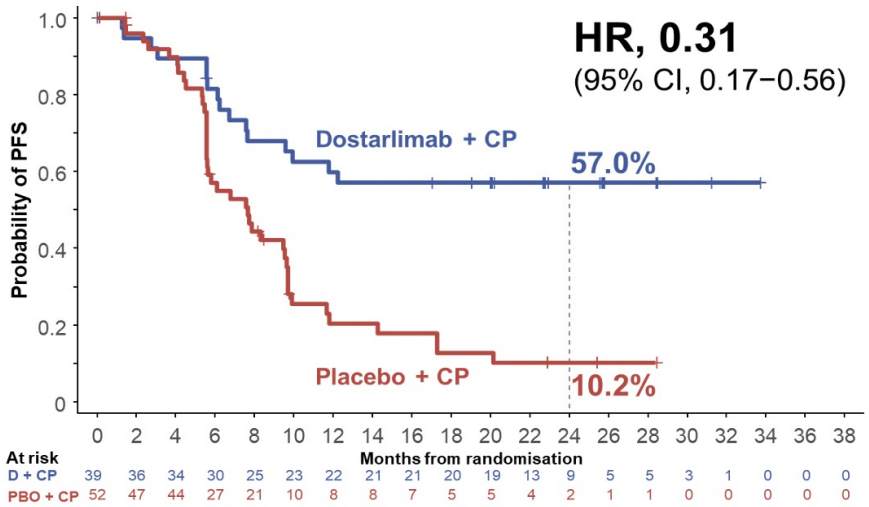
RUBY

PFS According to Molecular Subgroup

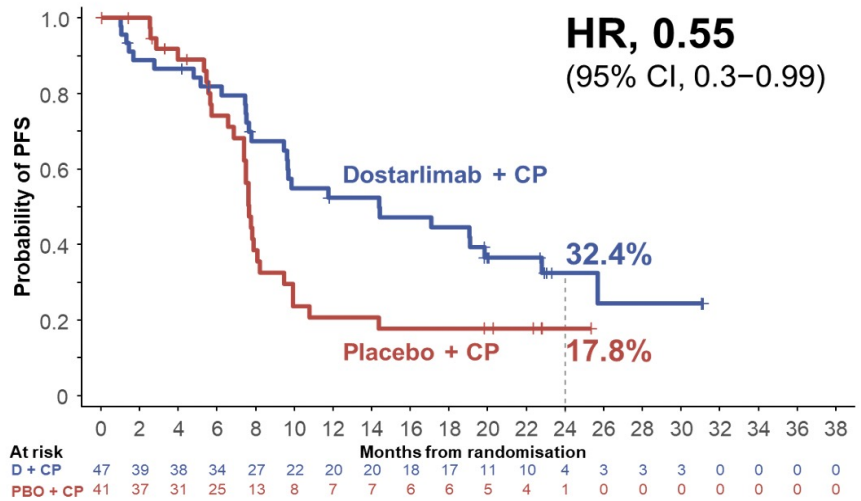
POLε mut



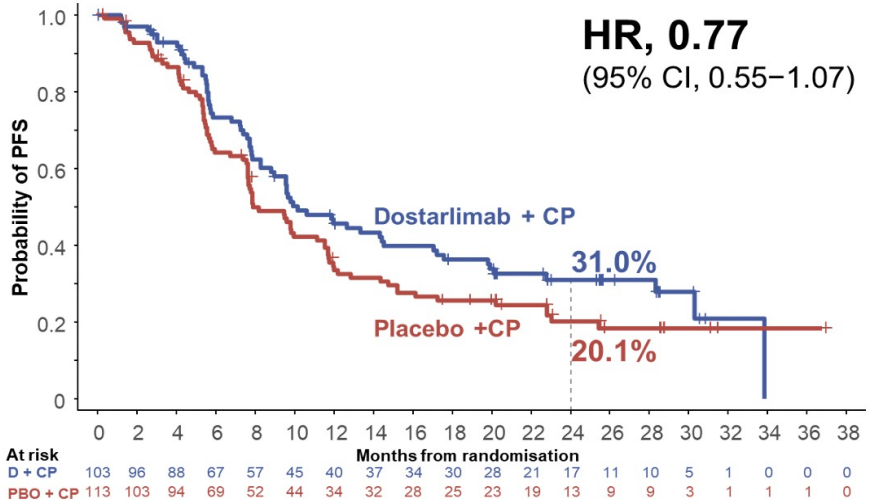
dMMR/MSI-H



TP53 mut



NSMP

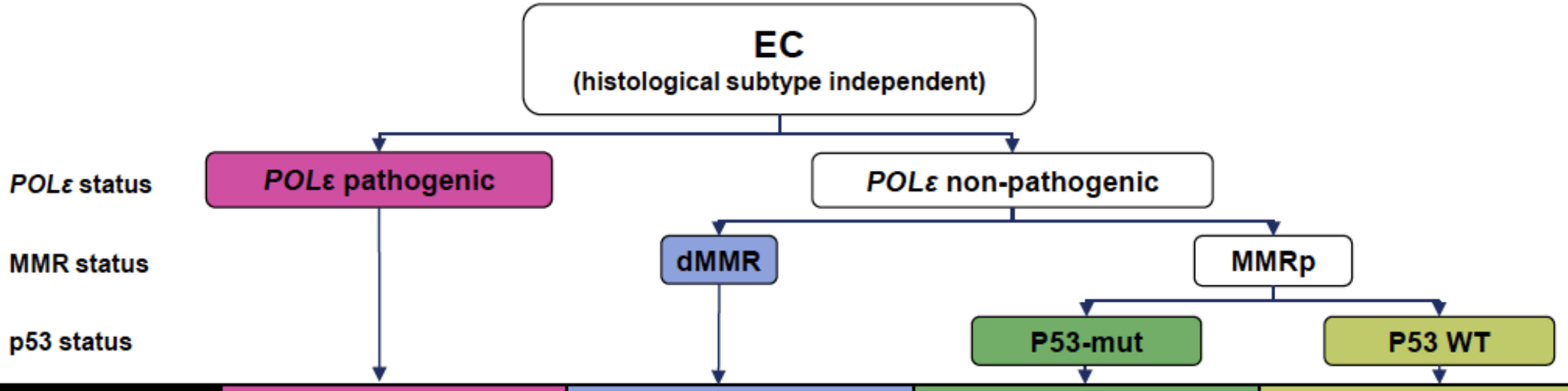


Presented by Mirza MR, et al. ESMO 2023

Courtesy of Krishnansu S Tewari, MD

RUBY Molecular Classification Algorithm

- In RUBY Part 1, molecular classification was performed for all participants with WES results – 400 of 494 patients



Integrated diagnosis	POLεmut (EDM)	dMMR (or MSI-H)	TP53 aberrant	NSMP
Prevalence in RUBY, % (n/N)	1.25% (5/400)	22.75% (91/400)	22% (88/400)	54% (216/400)
Diagnostic test	WES	Results of local (IHC, NGS, PCR) or central test (IHC) provided for RUBY at randomization	WES	

Efficacy per molecular classification was an exploratory analysis.
dMMR, mismatch repair deficient; EC, endometrial cancer; EDM, exonuclease domain; IHC, immunohistochemistry; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; mut, mutated; NGS, next generation sequencing; NSMP, no specific molecular profile; PCR, polymerase chain reaction; POLε, polymerase epsilon; TP53, tumor protein 53; WES, whole exome DNA sequencing; WT, wild type.

Mirza MR et al. ESMO 2023;Abstract 740MO.

Phase III RUBY Trial of Dostarlimab with Chemotherapy Meets Endpoint of Overall Survival for Patients with Primary Advanced or Recurrent Endometrial Cancer

Press Release: October 30, 2023

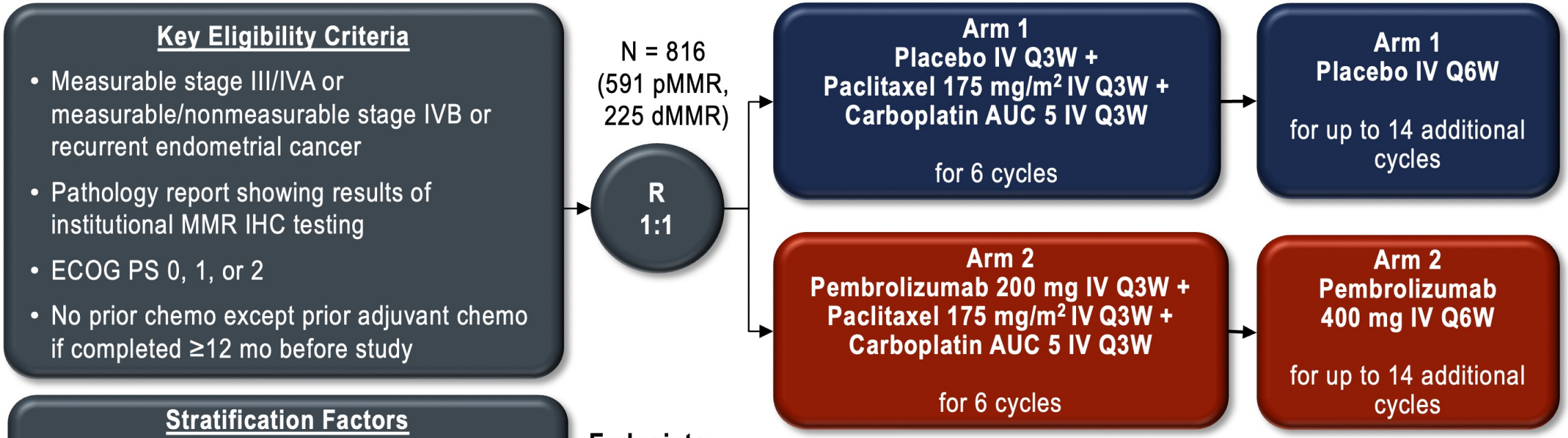
"Positive headline results [were announced] from a planned analysis of Part 1 of the RUBY/ENGOT-EN6/GOG3031/NSGO phase III trial investigating dostarlimab plus standard-of-care chemotherapy (carboplatin and paclitaxel), followed by dostarlimab as a single agent, compared to placebo plus chemotherapy followed by placebo in adult patients with primary advanced or recurrent endometrial cancer. The trial met its primary endpoint of overall survival (OS), demonstrating a statistically significant and clinically meaningful benefit in the overall patient population.

A clinically meaningful OS benefit was observed in both prespecified subpopulations in the trial: mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) and mismatch repair proficient (MMRp)/microsatellite stable (MSS) patient subgroups. OS is one of two primary endpoints in the RUBY Part 1 trial. Previously, the trial met its other primary endpoint of progression-free survival (PFS), demonstrating a 72% and 36% reduction in the risk of disease progression or death observed in the dMMR/MSI-H population (HR: 0.28 [95% CI: 0.16-0.50]) and overall patient population (HR: 0.64 [95% CI: 0.51–0.80]), respectively."

https://www.gsk.com/en-gb/media/press-releases/phase-iii-ruby-trial-of-jemperli-dostarlimab-plus-chemotherapy-meets-endpoint-of-overall-survival-in-patients-with-primary-advanced-or-recurrent-endometrial-cancer/

NRG GY018

Study Design



Endpoints

- **Primary:** PFS per RECIST v1.1 by investigator in pMMR and dMMR populations
- **Secondary:** Safety, ORR/DOR per RECIST v1.1 by BICR or investigator by treatment arm and MMR IHC status, OS in pMMR and dMMR populations, PRO/QoL in pMMR population, and concordance of MMR IHC testing at institution vs centralized

Median follow-up:

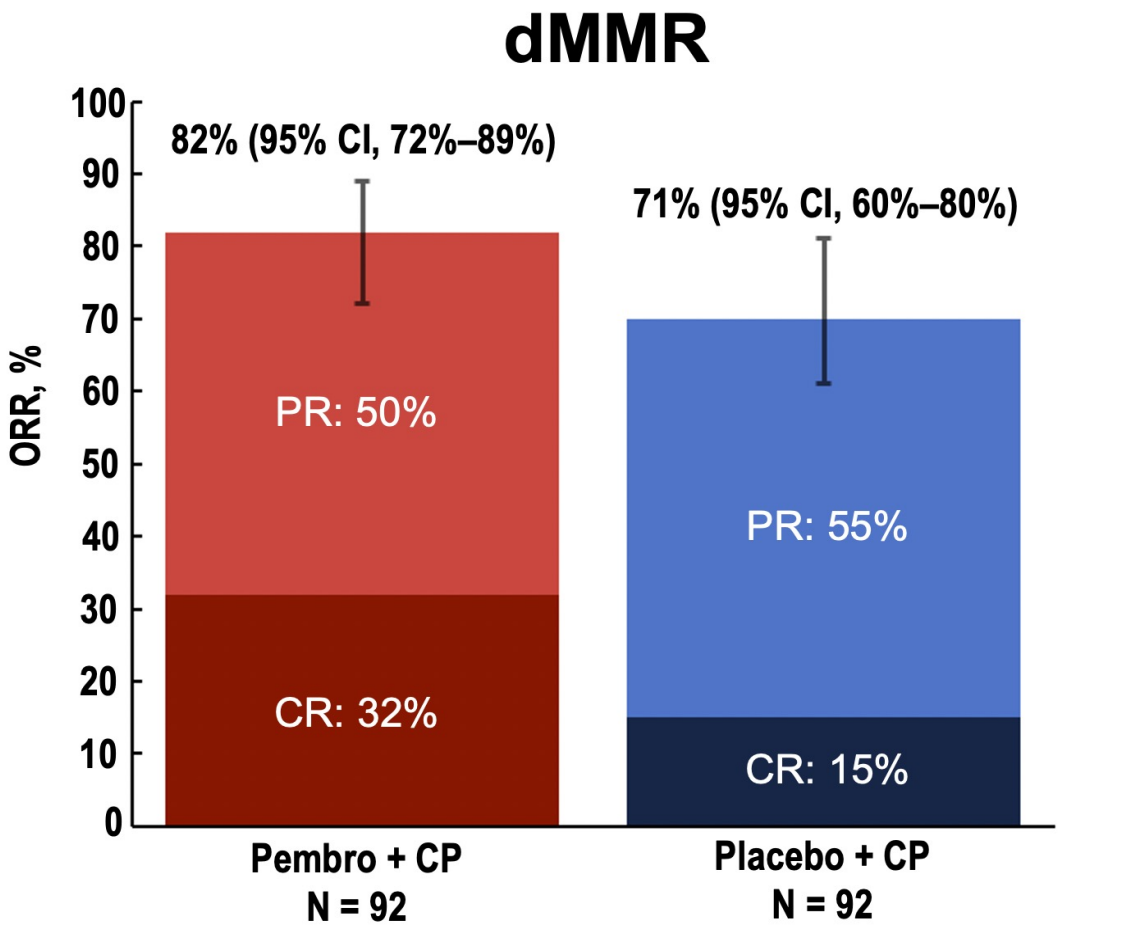
- IA1 data cutoff date of December 16, 2022: dMMR cohort, 12 months; pMMR cohort, 7.9 months
- **Current analysis data cutoff date of August 18, 2023**: dMMR cohort, 20.6 months; pMMR cohort, 15.8 months

Presented by Eskander RN, et al. ESMO 2023

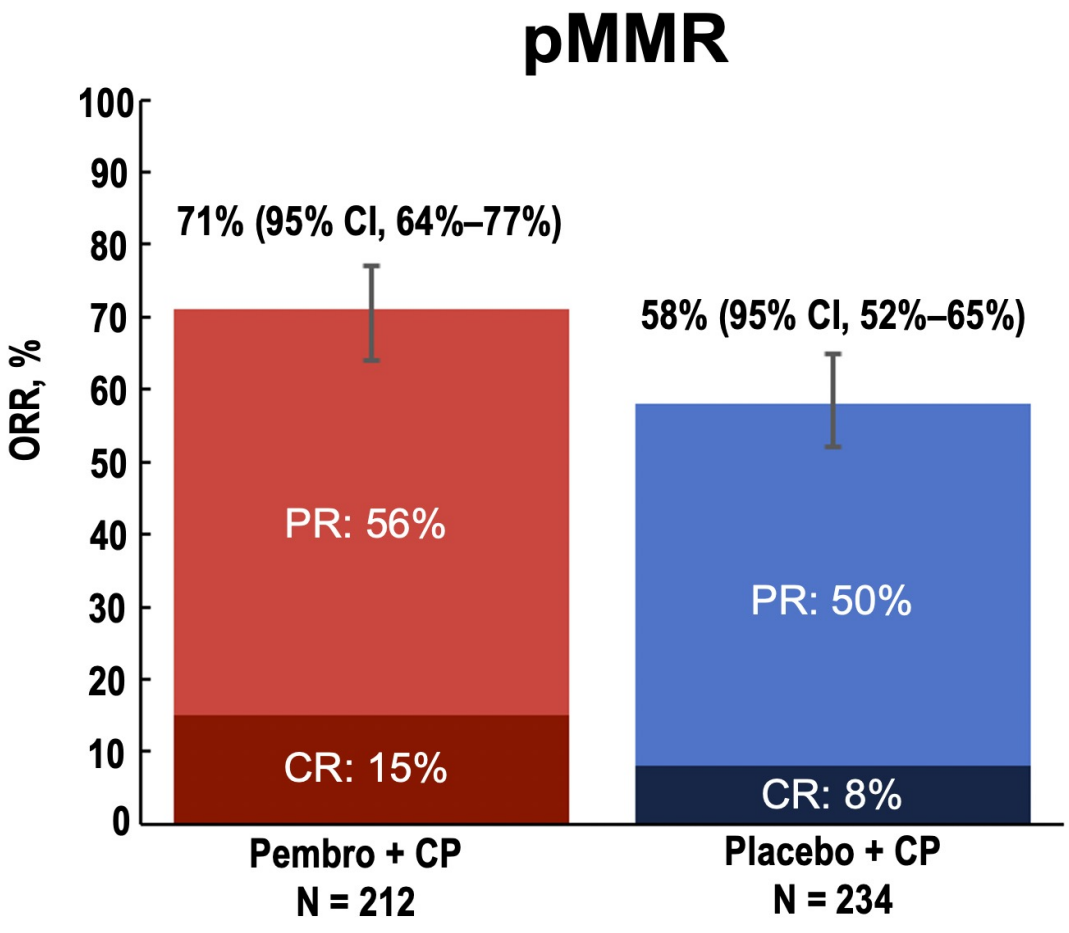
Courtesy of Krishnansu S Tewari, MD

NRG GY018

ORR in dMMR and pMMR Populations



Odds ratio for response with Pembro + CP: 1.83 (95% CI, 0.92–3.66)



Odds ratio for response with Pembro + CP: 1.74 (95% CI, 1.18–2.58)

Presented by Eskander RN, et al. ESMO 2023

Courtesy of Krishnansu S Tewari, MD

AtTEnd Study Design

- Endometrial carcinoma or carcinosarcoma
- Patients with advanced (stage III-IV) newly diagnosed or recurrent disease with no prior systemic chemotherapy for recurrence.
- In recurrent patients, one prior line of systemic platinum-based regimen is permitted with a platinum-free interval ≥ 6 months.
- ECOG 0-2
- Normal organ and bone marrow function

R 2:1

- Paclitaxel 175mg/m² carboplatin AUC 5 or 6 → Maintenance atezolizumab 1200mg
- Paclitaxel 175mg/m² carboplatin AUC 5 or 6 → Maintenance placebo

Confirmed PD

Stratified by:

- Country
- Endometrioid vs. other histotypes
- Recurrent disease vs newly diagnosed
- pMMR vs dMMR vs non evaluable *(centrally evaluated)*

Endpoints

Hierarchical order

PFS dMMR	IF POSITIVE α=4%	PFS All comers	IF POSITIVE α=4%	OS* All comers
α (two-sided) 4%		α (two-sided) 4%		α (two-sided) 5%
HR: 0.5		HR: 0.7		HR: 0.7

ECOG: Eastern Cooperative Oncology Group. pMMR: mismatch repair proficient. dMMR: mismatch repair deficient. AUC: area under the curve. PD: progressive disease. PFS: Progression free survival. OS: overall survival. HR: hazard ratio.

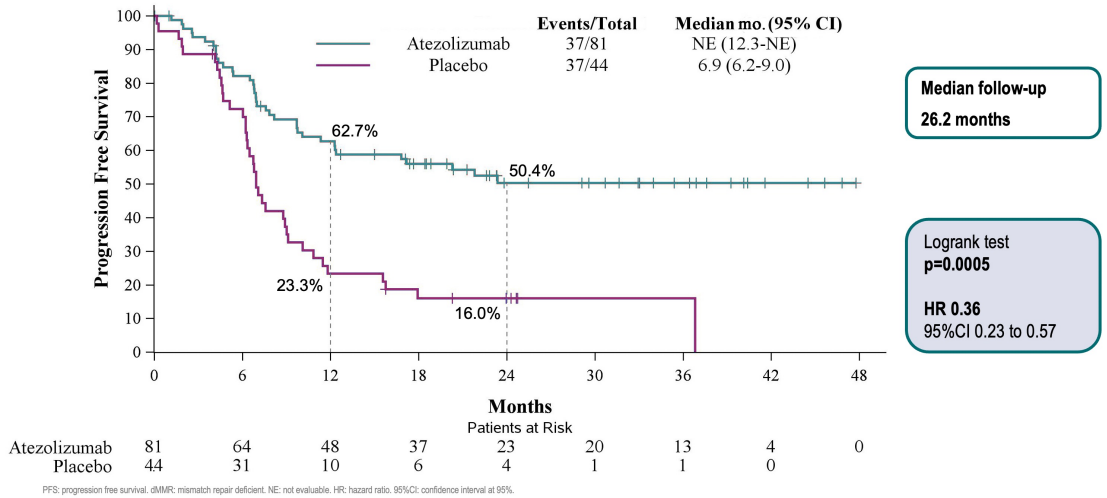
*OS interim analysis planned with a 63% power

Presented by Colombo N, et al. ESMO 2023

Courtesy of Krishnansu S Tewari, MD

AtTEnd

Primary Endpoint: PFS in dMMR

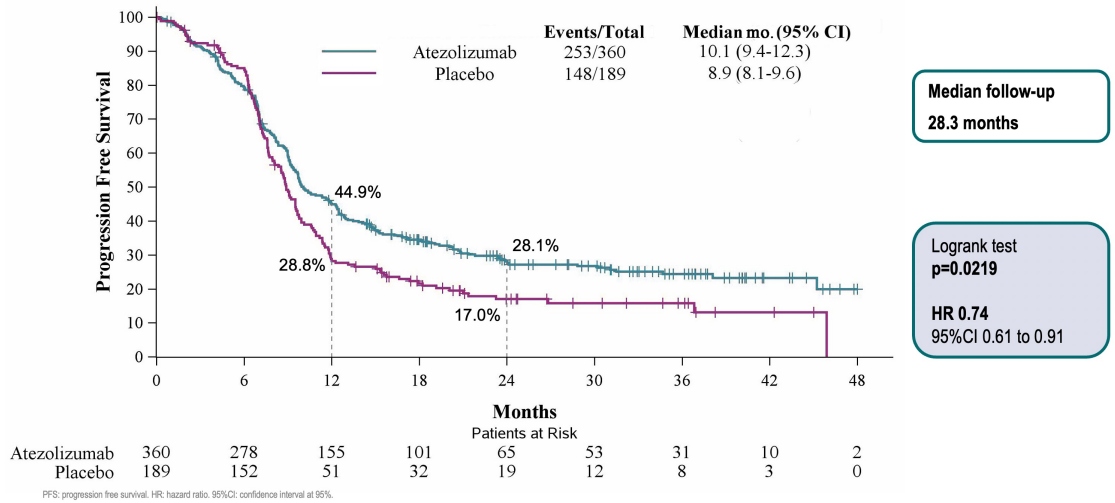


Median follow-up
26.2 months

Logrank test
p=0.0005

HR 0.36
95%CI 0.23 to 0.57

Primary Endpoint: PFS in All Comers



Median follow-up
28.3 months

Logrank test
p=0.0219

HR 0.74
95%CI 0.61 to 0.91

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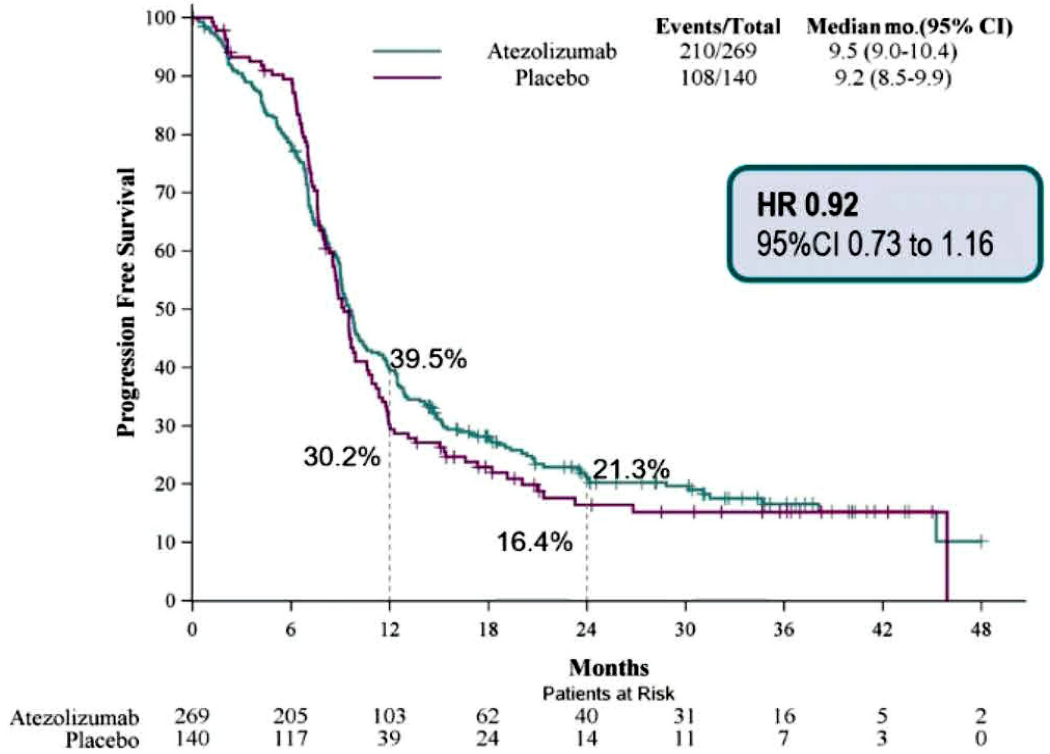
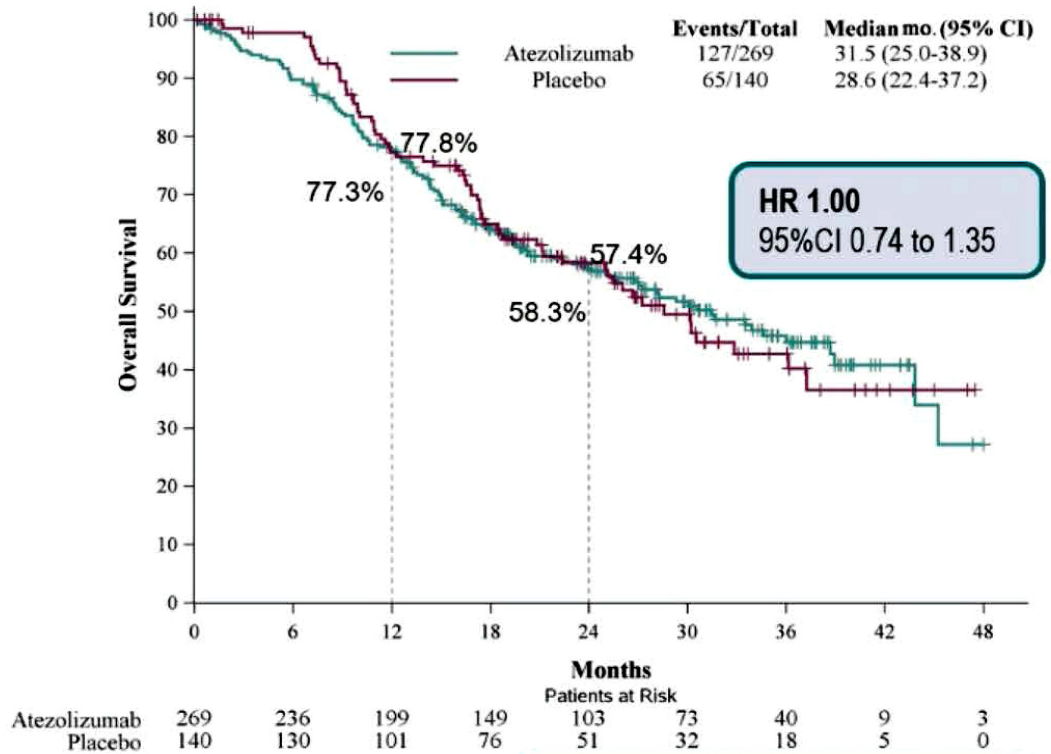
Courtesy of Krishnansu S Tewari, MD

AtTEnd

PFS and OS in pMMR





Subsequent immunotherapy

Atezolizumab arm	*9.8%*
Placebo arm	*19.1%*

PFS: progression free survival. OS: overall survival. pMMR: mismatch repair proficient. HR:hazard ratio. 95%CI: confidence interval at 95%.

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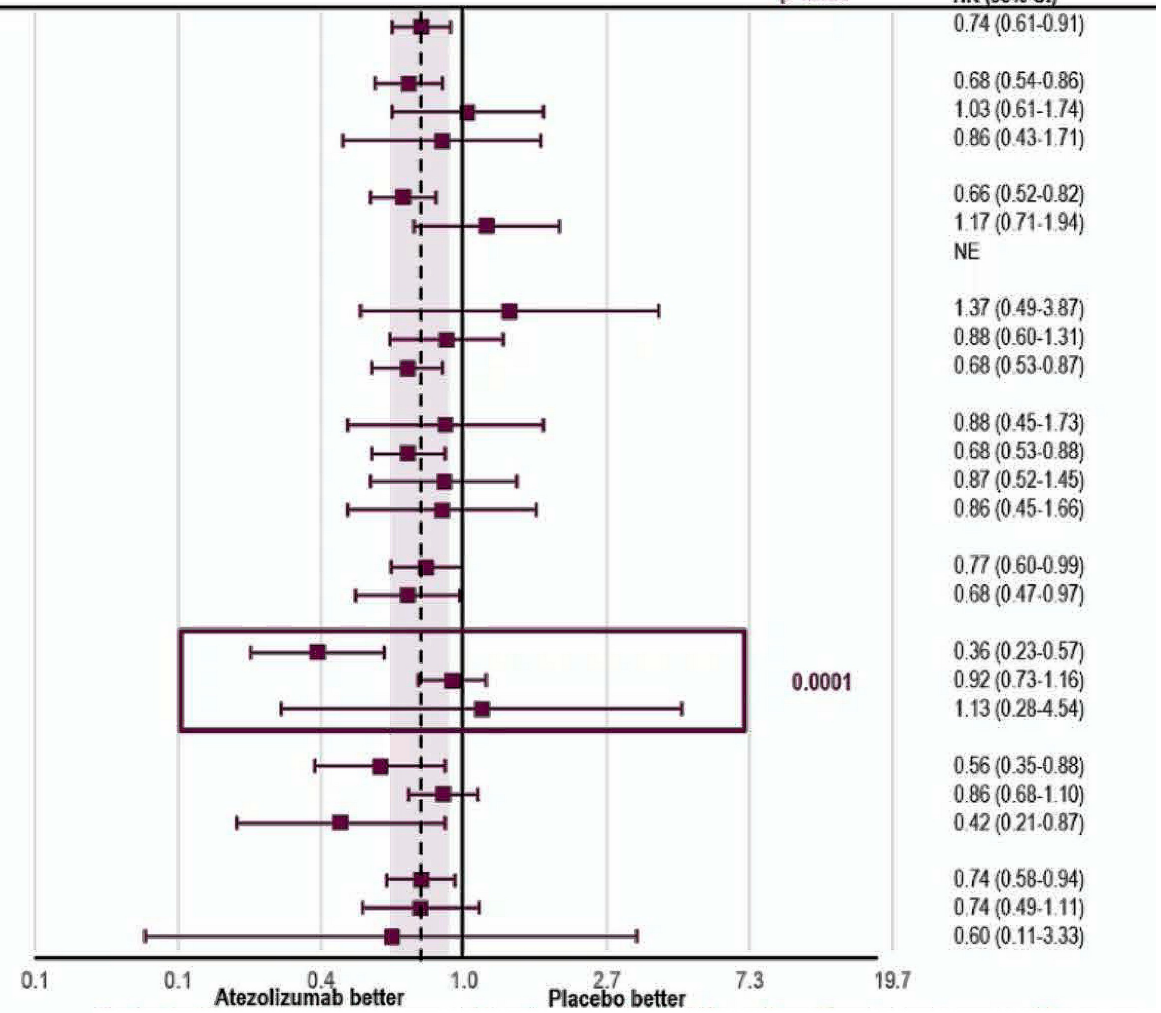
AtTEnd

Subgroup Analysis of PFS in All Comers

Subgroup	Placebo no. events/no. pts	Atezolizumab no. events/no. pts	Interaction test p-value	HR (95% CI)
Overall	148/189 (78%)	253/360 (70%)		0.74 (0.61-0.91)
Geographic region				
Europe	114/134 (85%)	189/264 (72%)		0.68 (0.54-0.86)
Asia	21/37 (57%)	41/66 (62%)		1.03 (0.61-1.74)
Australia/New Zealand	13/18 (72%)	23/30 (77%)		0.86 (0.43-1.71)
Race				
Caucasian	123/143 (86%)	207/289 (72%)		0.66 (0.52-0.82)
Asian	23/43 (53%)	44/69 (64%)		1.17 (0.71-1.94)
Other	2/3 (67%)	2/2 (100%)		NE
Status of disease*				
Newly diagnosed-Stage III	5/10 (50%)	13/21 (62%)		1.37 (0.49-3.87)
Newly diagnosed-Stage IV	39/52 (75%)	72/96 (75%)		0.88 (0.60-1.31)
Recurrent	103/126 (82%)	168/243 (69%)		0.68 (0.53-0.87)
Histological type				
Carcinosarcoma	12/15 (80%)	30/35 (86%)		0.88 (0.45-1.73)
Endometrioid	99/125 (79%)	150/227 (66%)		0.68 (0.53-0.88)
Papillary serous	23/29 (79%)	47/59 (80%)		0.87 (0.52-1.45)
Other	14/20 (70%)	26/39 (67%)		0.86 (0.45-1.66)
Pre-treated with chemotherapy				
No	100/129 (78%)	172/253 (68%)		0.77 (0.60-0.99)
Yes	48/60 (80%)	81/107 (76%)		0.68 (0.47-0.97)
Mismatch repair status				
Deficient	37/44 (84%)	37/81 (46%)		0.36 (0.23-0.57)
Proficient	108/140 (77%)	210/269 (78%)	0.0001	0.92 (0.73-1.16)
Not evaluable	3/5 (60%)	6/10 (60%)		1.13 (0.28-4.54)
PD-L1 (IC) expression				
Positive	32/44 (73%)	49/86 (57%)		0.56 (0.35-0.88)
Negative	102/129 (79%)	186/247 (75%)		0.86 (0.68-1.10)
Not evaluable	14/16 (88%)	18/27 (67%)		0.42 (0.21-0.87)
ARID1A expression				
Intact	107/131 (82%)	188/248 (76%)		0.74 (0.58-0.94)
Loss	39/55 (71%)	61/104 (59%)		0.74 (0.49-1.11)
Not evaluable	2/3 (67%)	4/8 (50%)		0.60 (0.11-3.33)



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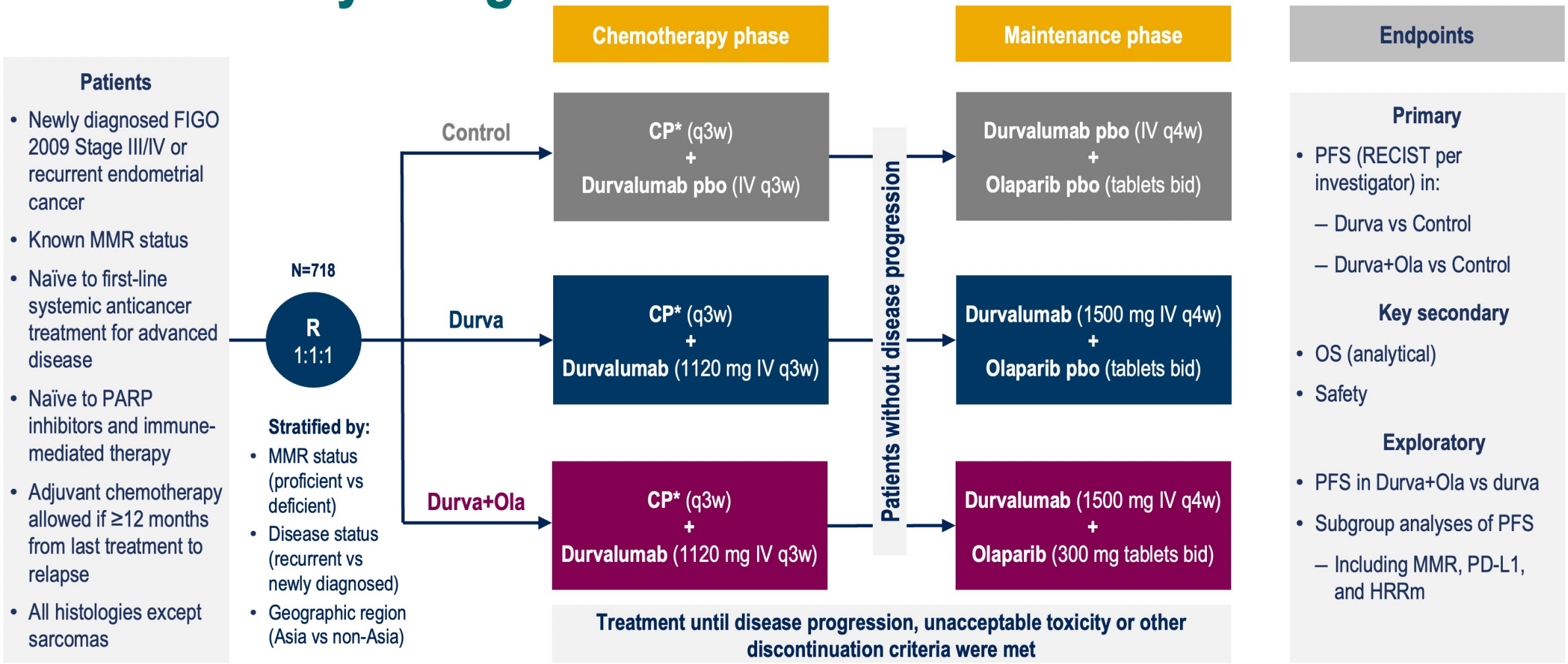
DUO-E study design



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Courtesy of Krishnansu S Tewari, MD

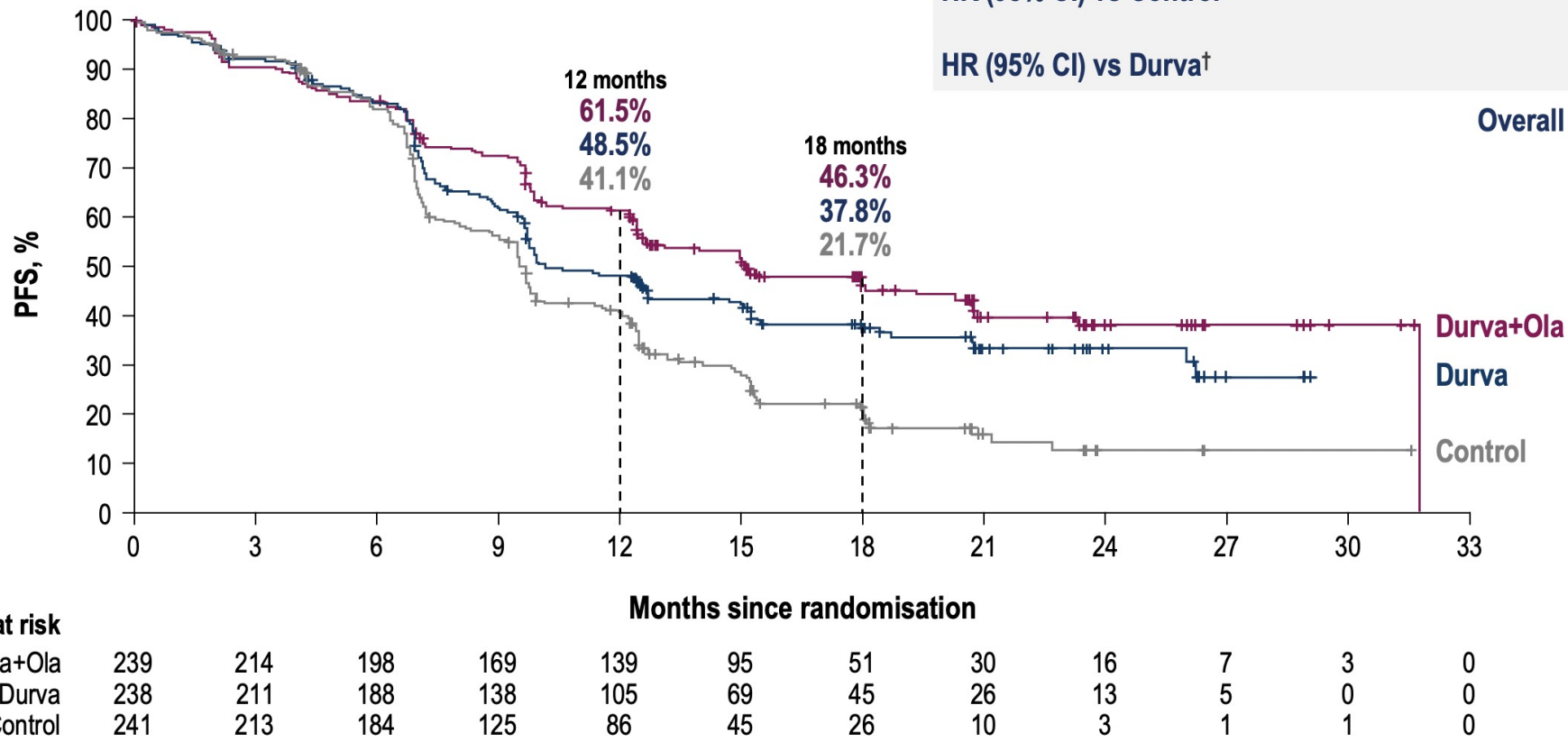
DUO-E

PFS: ITT population

Primary endpoint

	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI),* months	9.6 (9.0–9.9)	10.2 (9.7–14.7)	15.1 (12.6–20.7)
HR (95% CI) vs Control†		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs Durva†			0.78 (0.61–0.99)

Overall data maturity 61.0%



No. at risk

Durva+Ola	239	214	198	169	139	95	51	30	16	7	3	0
Durva	238	211	188	138	105	69	45	26	13	5	0	0
Control	241	213	184	125	86	45	26	10	3	1	1	0

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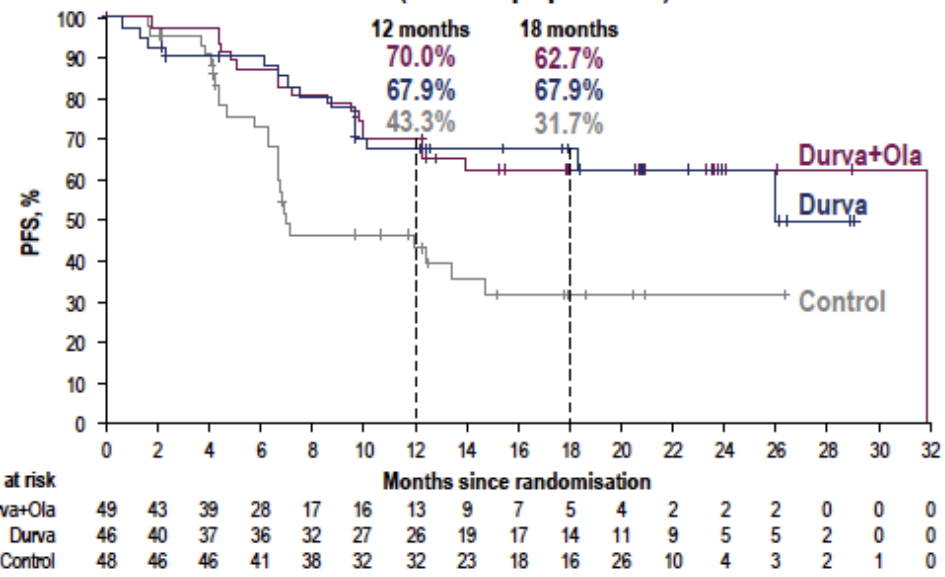
DUO-E: PFS by MMR Status

Prespecified exploratory analysis

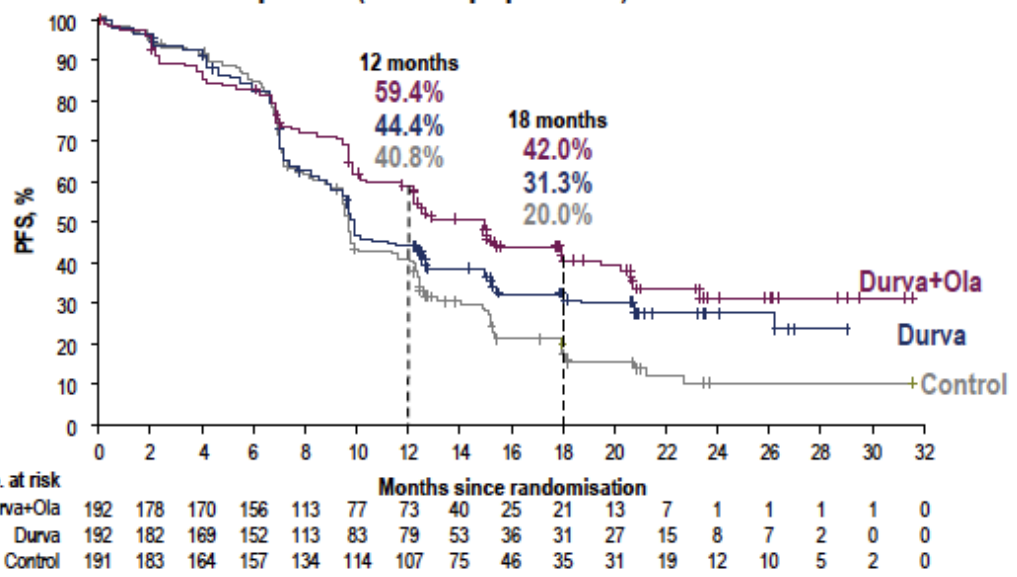
dMMR (20% of population)



No. at risk																	
Durva+Ola	49	43	39	28	17	16	13	9	7	5	4	2	2	2	0	0	0
Durva	46	40	37	36	32	27	26	19	17	14	11	9	5	5	2	0	0
Control	48	46	46	41	38	32	32	23	18	16	26	10	4	3	2	1	0

	Control (N=49)	Durva (N=46)	Durva+Ola (N=48)
Events, n (%)	25 (51.0)	15 (32.6)	18 (37.5)
Median PFS (95% CI),* months	7.0 (6.7–14.8)	NR (NR–NR)	31.8 (12.4–NR)
HR (95% CI) vs Control†		**0.42 (0.22–0.80)**	**0.41 (0.21–0.75)**
HR (95% CI) vs Durva†			**0.97 (0.49–1.98)**

pMMR (80% of population)



No. at risk																	
Durva+Ola	192	178	170	156	113	77	73	40	25	21	13	7	1	1	1	1	0
Durva	192	182	169	152	113	83	79	53	36	31	27	15	8	7	2	0	0
Control	191	183	164	157	134	114	107	75	46	35	31	19	12	10	5	2	0

	Control (N=192)	Durva (N=192)	Durva+Ola (N=191)
Events, n (%)	148 (77.1)	124 (64.6)	108 (56.5)
Median PFS (95% CI),* months	9.7 (9.2–10.1)	9.9 (9.4–12.5)	15.0 (12.4–18.0)
HR (95% CI) vs Control†		**0.77 (0.60–0.97)**	**0.57 (0.44–0.73)**
HR (95% CI) vs Durva†			**0.76 (0.59–0.99)**

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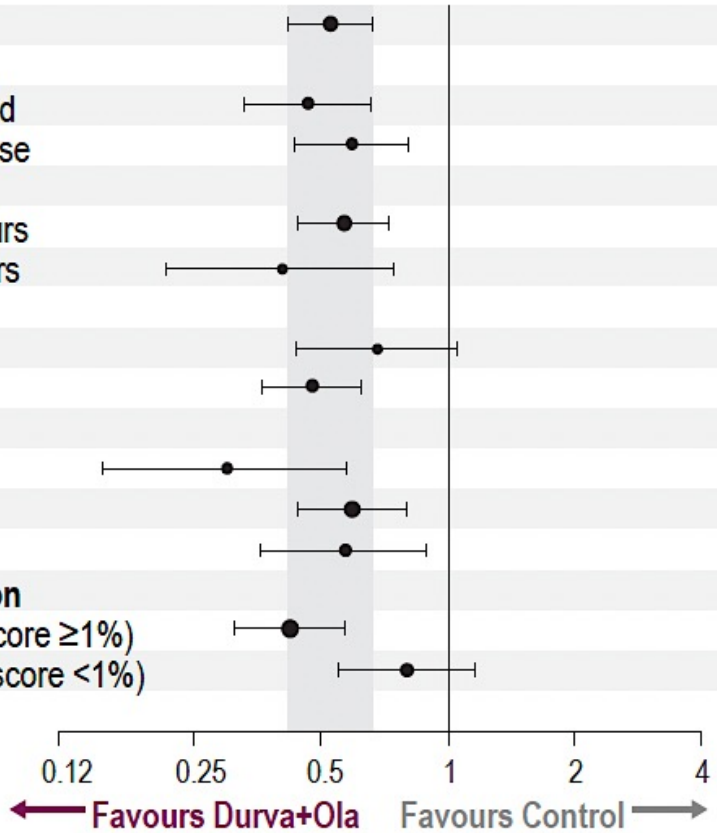
Exploratory subgroup analysis. MMR status evaluated using the Ventana immunohistochemistry MMR panel. Rates were estimated by the KM method.
*CI for median PFS was derived based on the Brookmeyer–Crowley method; †The HR and CI were estimated from an unstratified Cox proportional hazards model.

Westin SN et al. ESMO 2023;Abstract LBA41.

RTP RESEARCH TO PRACTICE

DUO-E: PFS Subgroup Analysis

By stratification factors and biomarker status

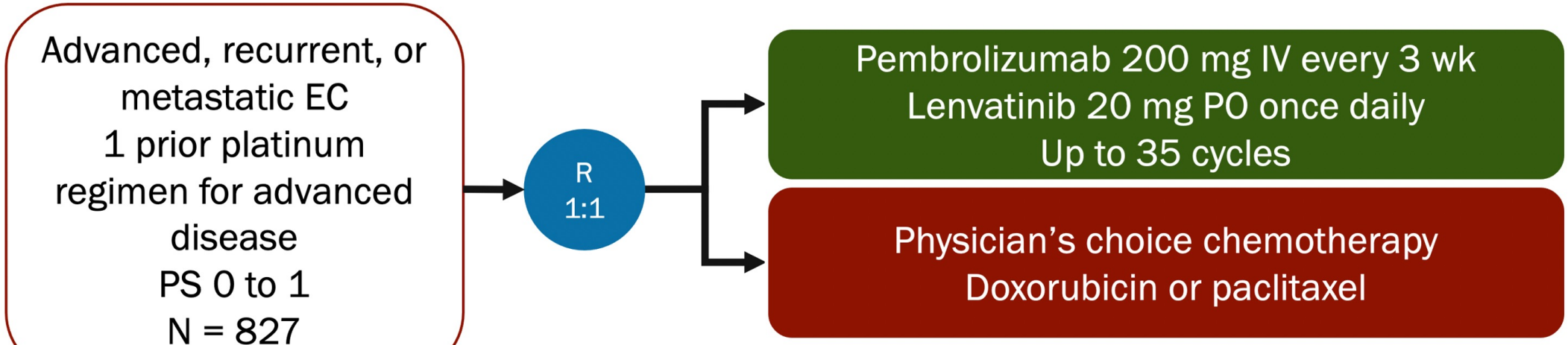


	HR (95% CI)	Durva+Ola n/N (%)	Control n/N (%)
All patients	0.53 (0.42–0.67)	126/239 (52.7)	173/241 (71.8)
Disease status			
Newly diagnosed	0.47 (0.33–0.66)	58/114 (50.9)	81/115 (70.4)
Recurrent disease	0.59 (0.43–0.81)	68/125 (54.4)	92/126 (73.0)
MMR status			
Proficient tumours	0.57 (0.44–0.73)	108/191 (56.5)	148/192 (77.1)
Deficient tumours	0.41 (0.21–0.75)	18/48 (37.5)	25/49 (51.0)
Region			
Asia	0.68 (0.44–1.06)	37/67 (55.2)	45/68 (66.2)
Non-Asia	0.48 (0.36–0.63)	89/172 (51.7)	128/173 (74.0)
HRRm status			
HRRm	0.30 (0.15–0.58)	16/39 (41.0)	23/32 (71.9)
Non-HRRm	0.59 (0.44–0.80)	81/141 (57.4)	96/132 (72.7)
Unknown	0.57 (0.36–0.89)	29/59 (49.2)	54/77 (70.1)
PD-L1 expression			
Positive (TAP score ≥1%)	0.42 (0.31–0.57)	68/150 (45.3)	114/163 (69.9)
Negative (TAP score <1%)	0.80 (0.55–1.16)	55/82 (67.1)	57/75 (76.0)
Unknown	NC (NC–NC)	3/7 (42.9)	2/3 (66.7)

Westin SN et al. ESMO 2023;Abstract LBA41.

KEYNOTE-0775

2nd Line Pembrolizumab + Lenvatinib Confirmatory Trial



NCT03517449

Treatment until PD or unacceptable toxicity

Primary endpoints: PFS, OS

Secondary endpoints: ORR, TTF, safety, QoL

Primary and key secondary data are forthcoming

Presented by Colomba E, et al. ESMO 2023

Courtesy of Krishnansu S Tewari, MD

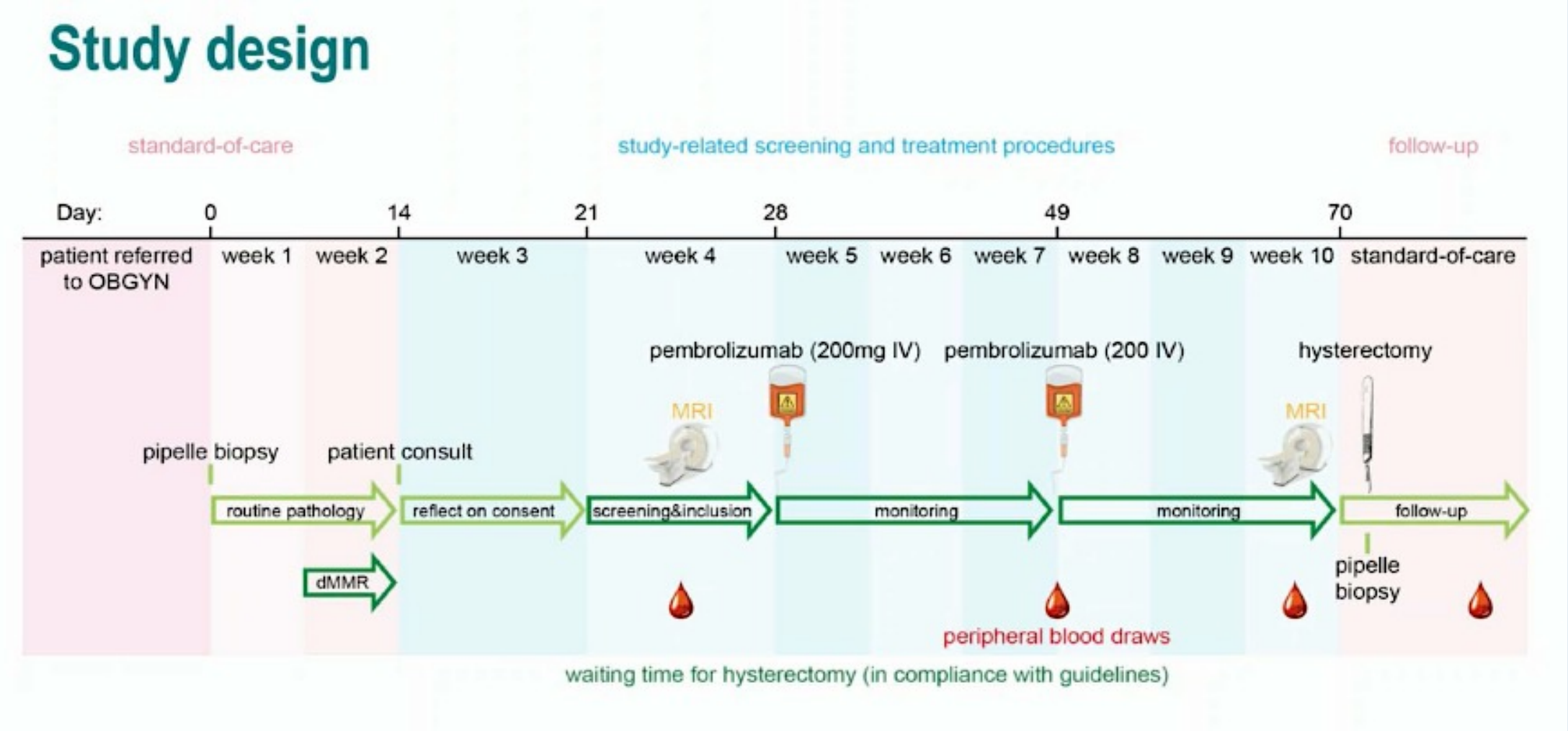
KEYNOTE-775

	pMMR pembro completers (n=30)	All-comer pembro completers (n=41)
Median PFS[a,b] (95% CI), mos	34.1 (20.1-NE)	34.1 (27.7-NE)
Median OS[b] (95% CI), mos	NR (NE-NE)	NR (NE-NE)
OS rate at 36 mos[b] (95% CI), %	84.3 (63.2-93.8)	89.0 (73.1-95.7)
ORR[a] (95% CI), %	63.3 (43.9-80.1)	63.4 (46.9-77.9)
CR[a] (95% CI), %	23.3 (9.9-42.3)	19.5 (8.8-34.9)
Median DOR[a,b] (range), mos	NR (3.5-39.5+)	NR (3.5-39.5+)
Probability of pts with extended DOR[a], %[b] ≥24 mos ≥36 mos	78.3 69.6	83.8 70.9
Drug-related AEs[c], n (%) any grade, Grade ≥3		41 (100), 33 (80.5)

Presented by Colomba E, et al. ESMO 2023

Courtesy of Krishnansu S Tewari, MD

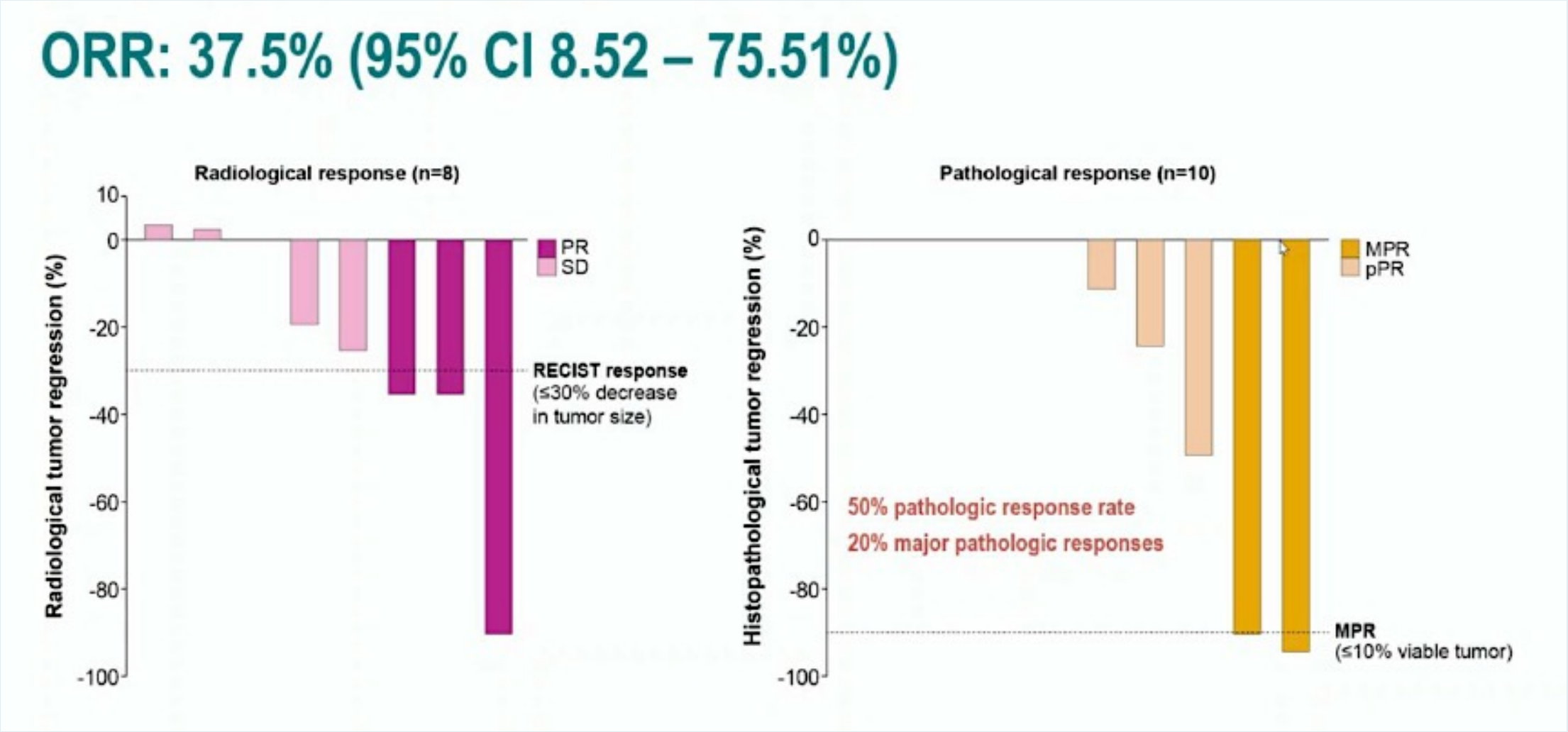
Neoadjuvant Pembrolizumab for Mismatch Repair-Deficient Endometrial Cancer



de Bruyn M et al. ESMO 2023;Abstract 742MO.

RTP RESEARCH TO PRACTICE

Tumor Responses with Neoadjuvant Pembrolizumab for Mismatch Repair-Deficient Endometrial Cancer

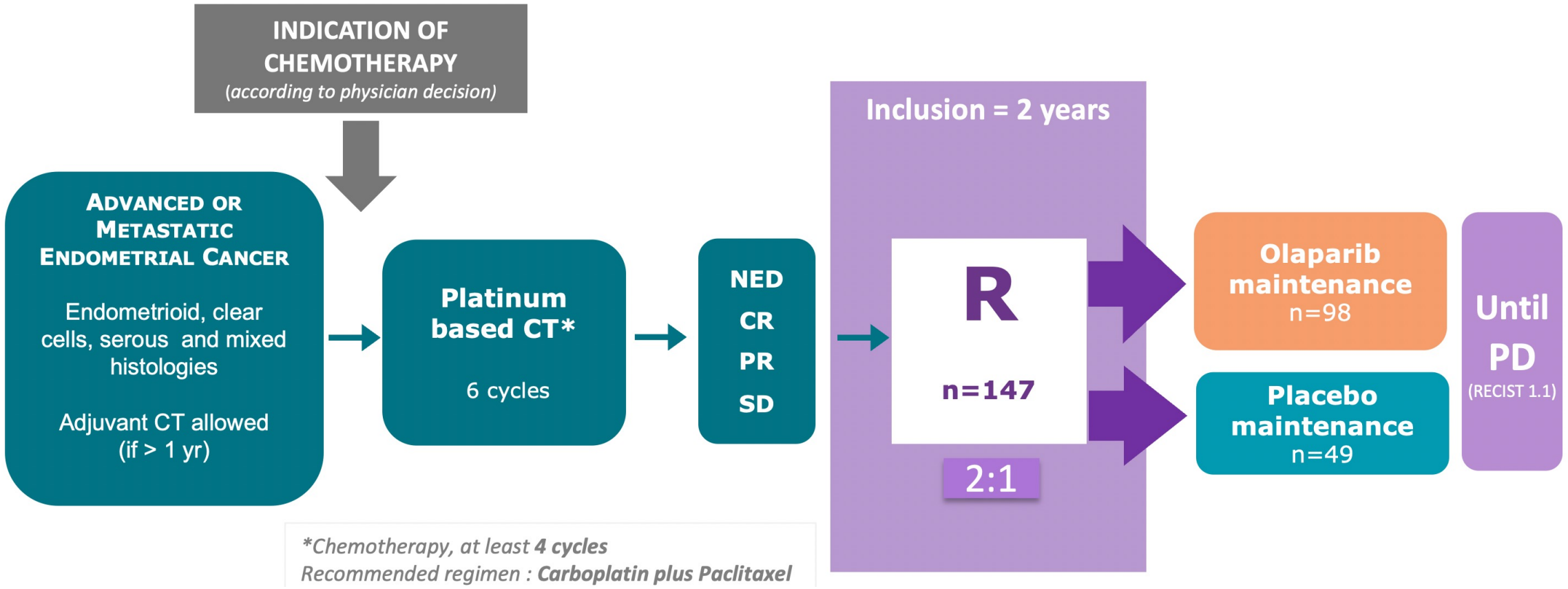


de Bruyn M et al. ESMO 2023;Abstract 742MO.

RTP RESEARCH TO PRACTICE

UTOLA study design

Randomized phase II trial



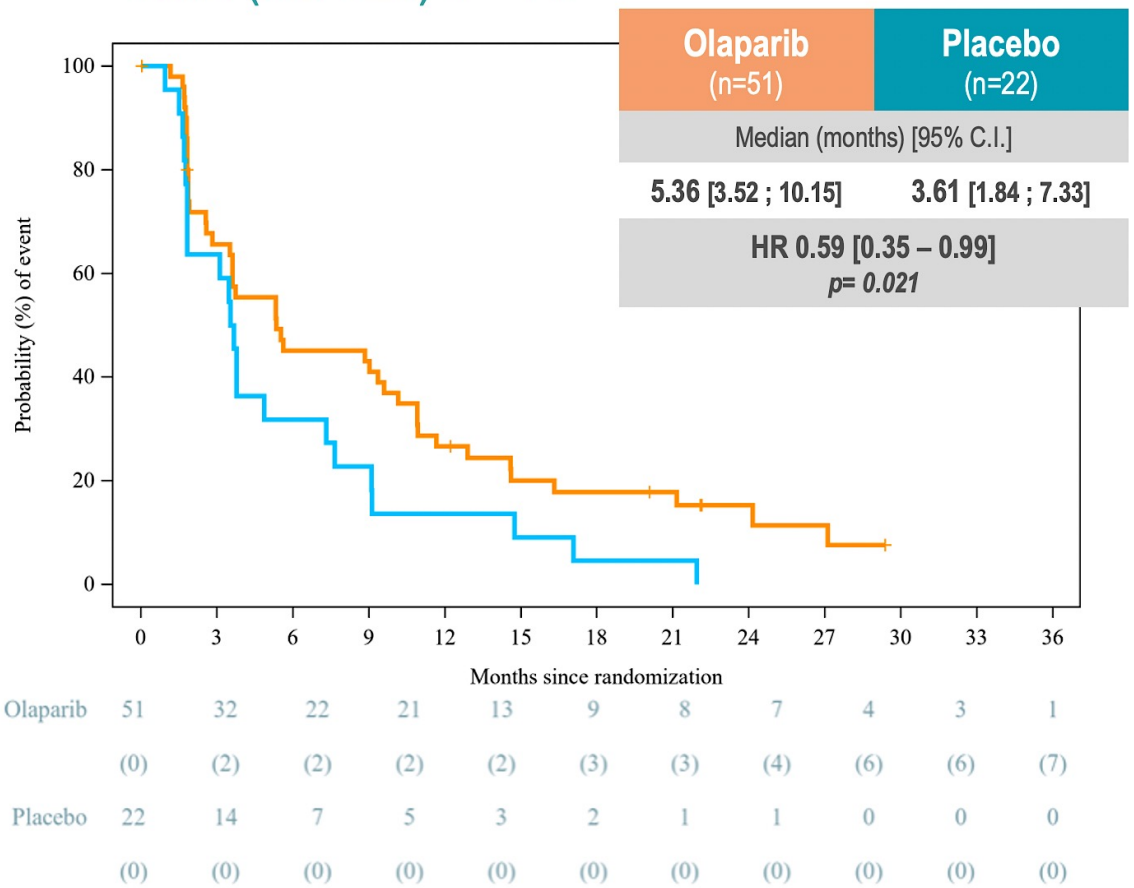
Presented by Joly F, et al. ESMO 2023

Courtesy of Krishnansu S Tewari, MD

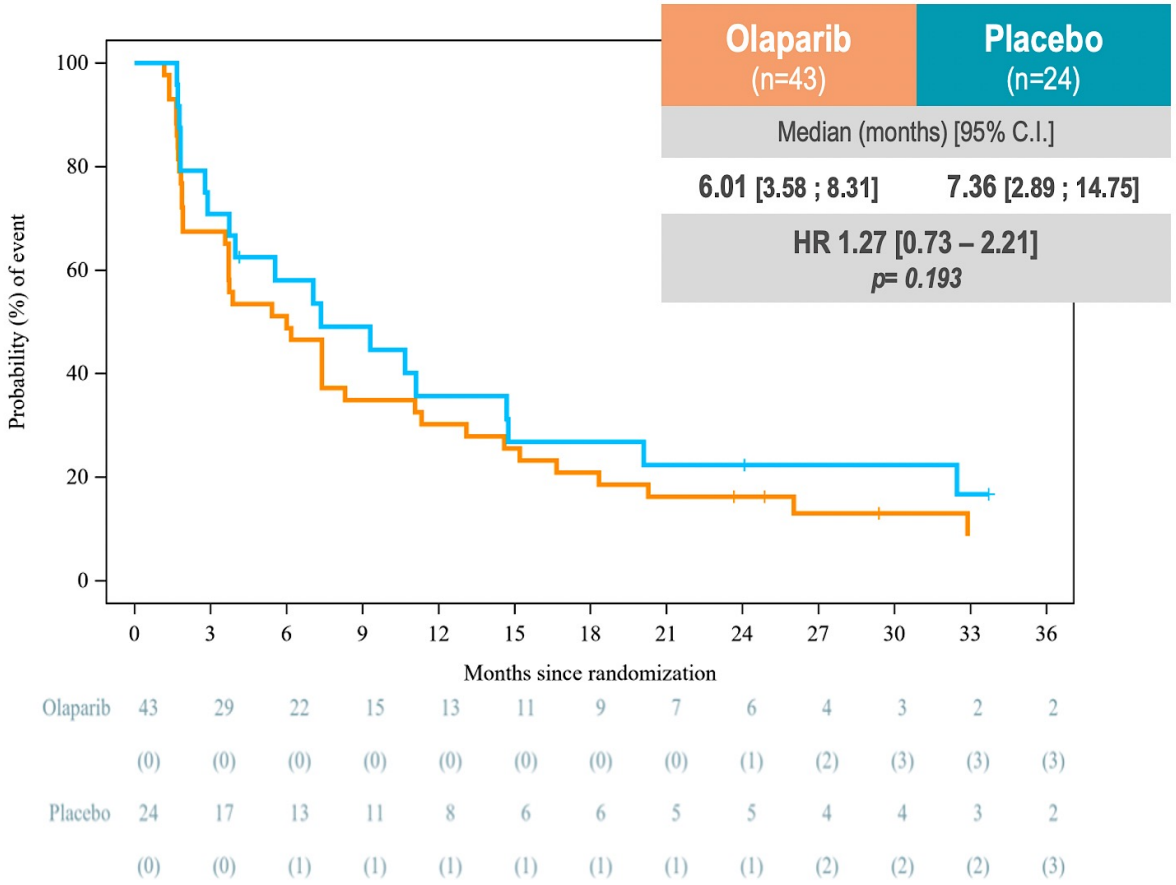
UTOLA

PFS: According to HRD status

HRD (LGE ≥6) n = 73



HRp (LGE <6) n = 67

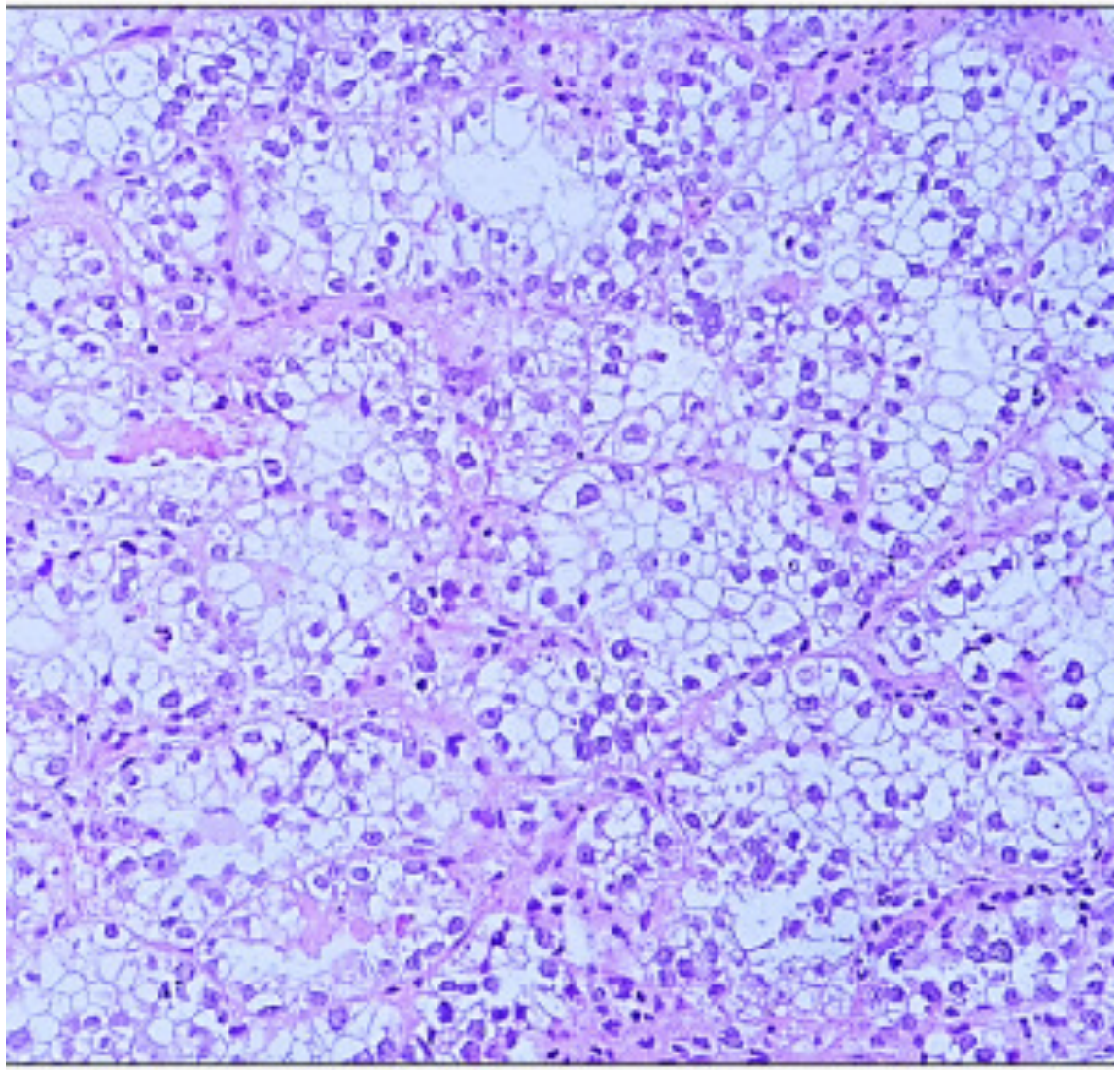


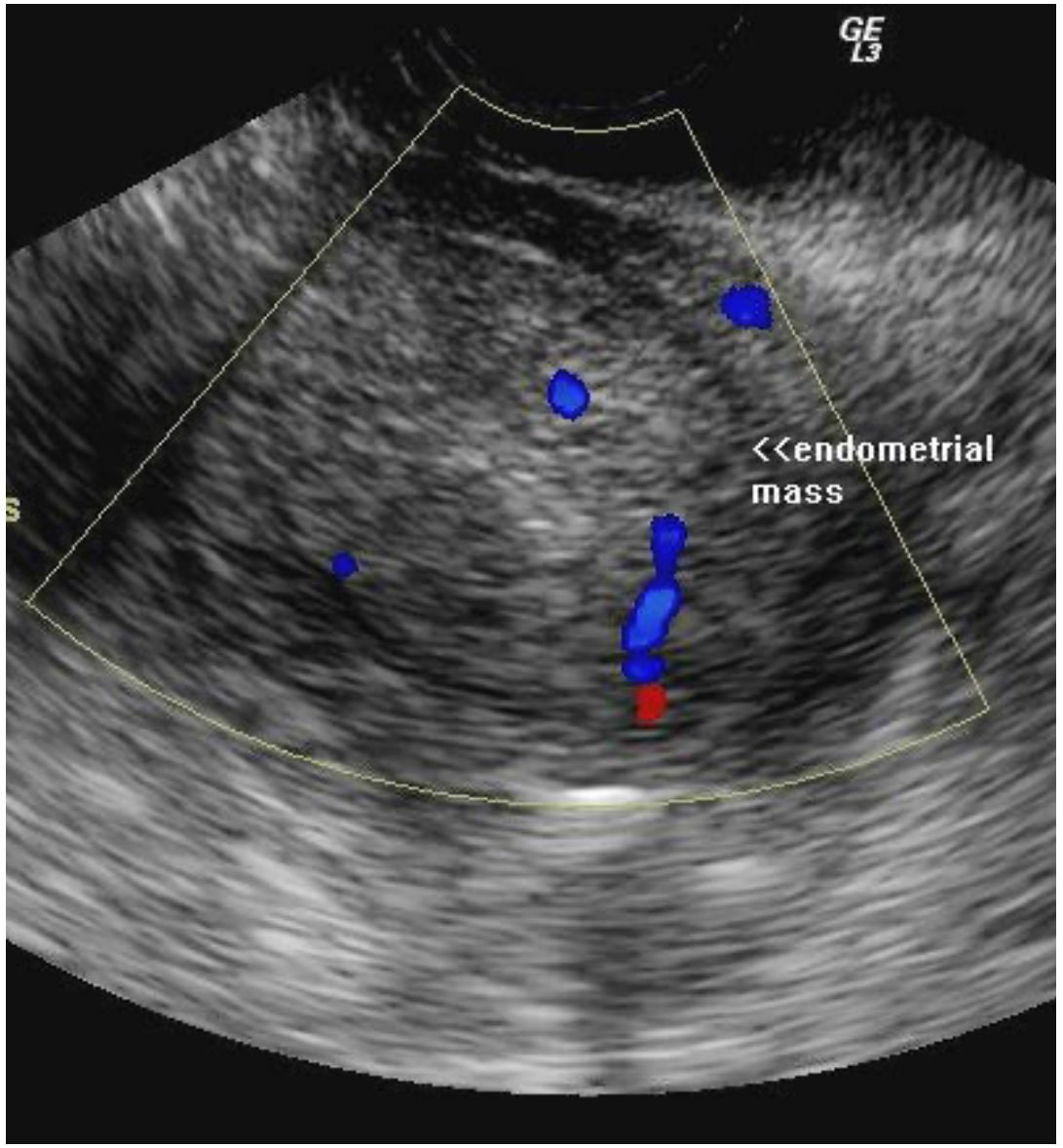
Presented by Joly F, et al. ESMO 2023

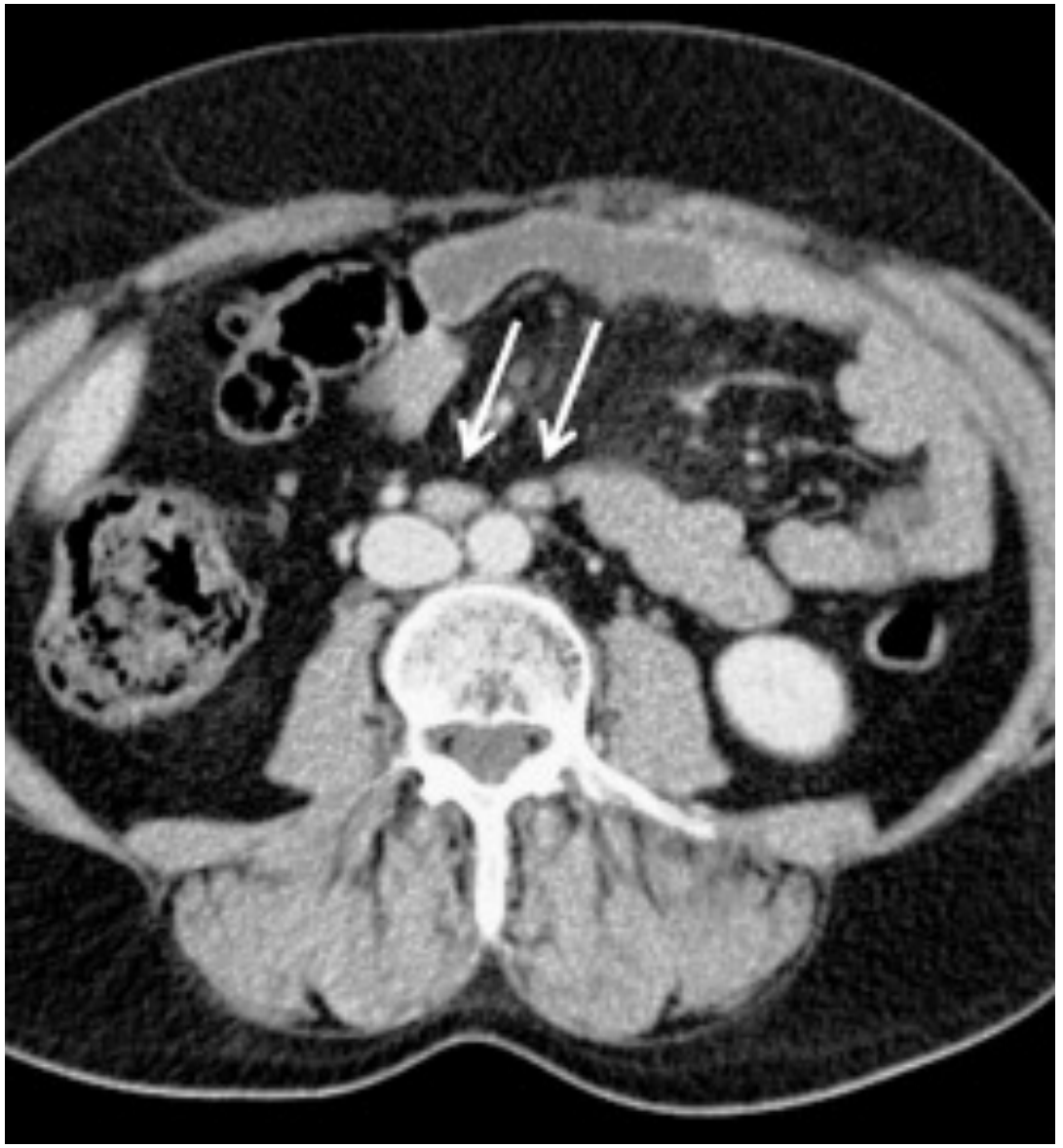
Courtesy of Krishnansu S Tewari, MD

Dr Tewari – Case 1:
Advanced Endometrial Cancer

- 69 y/o Asian nulliparous businesswoman
  - PMP VB
- TVUS: 9 cm uterus
  - Hypervascular endometrial mass
  - Non-visualization of ovaries
  - Absence of free fluid
- EMB: FIGO grade 3 clear cell adenocarcinoma
- CT chest/abdomen/pelvis:
  - 3 cm aorto-caval nodes
- PMH: non-contributory
- PSH: no prior surgeries
- BMI: 23




GE
L3
<<endometrial
mass



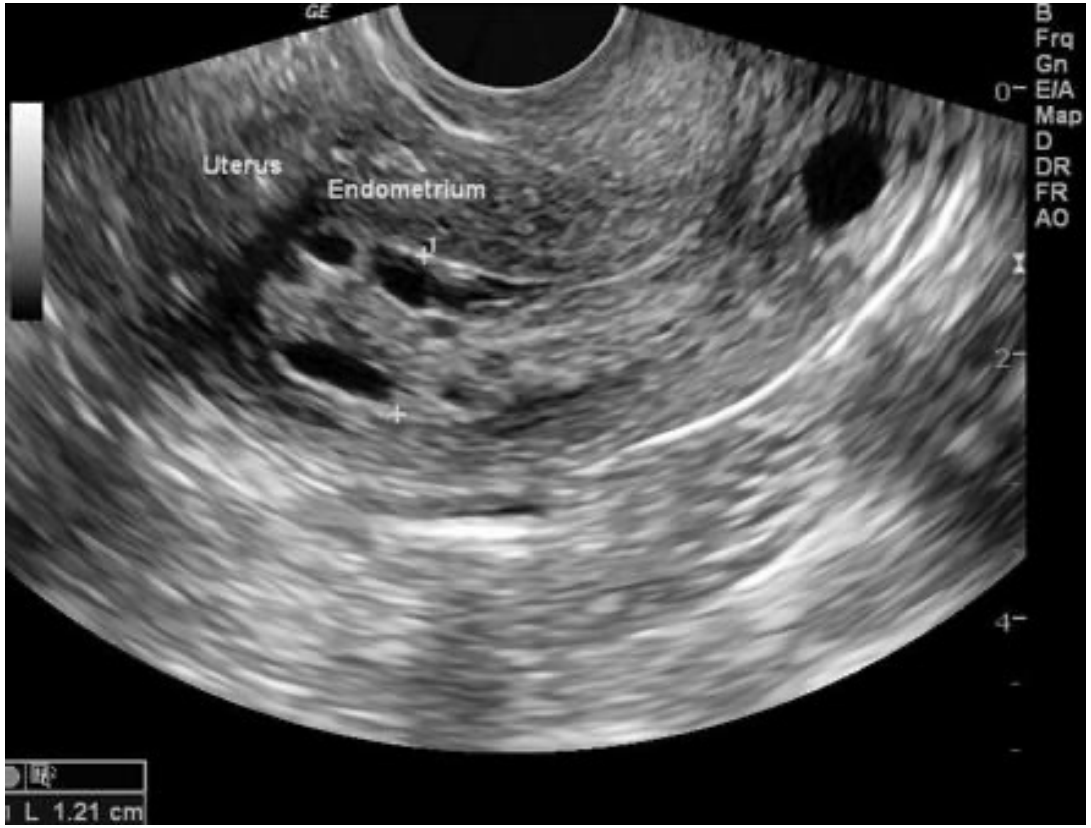
Dr Tewari – Case 1 (continued)

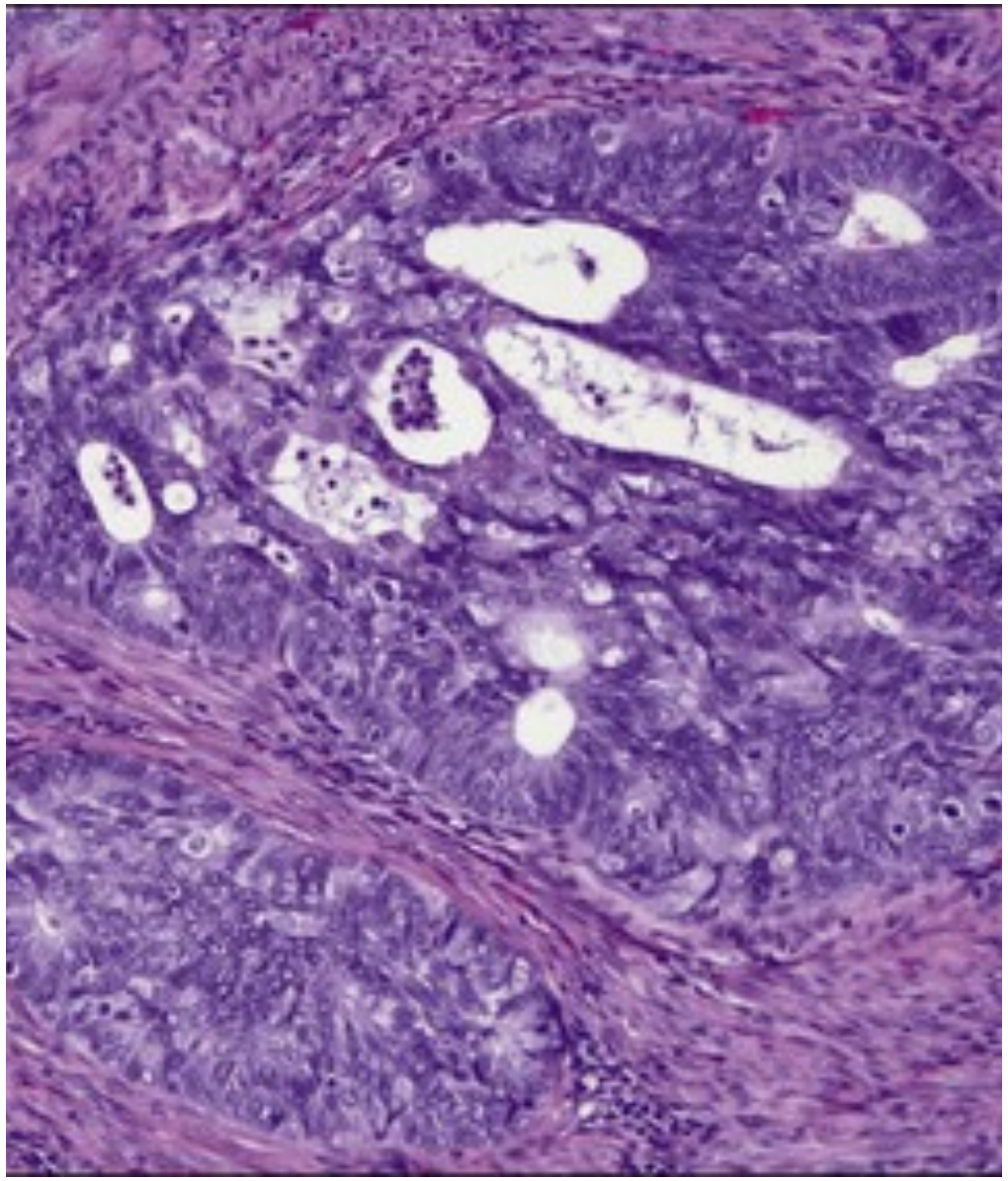
- Robotic hysterectomy with bilateral salpingoophorectomy & para-aortic/pelvic lymphadenectomy

- dMMR: carboplatin + paclitaxel & dostarlimab
  - Tolerating well, currently receiving cycle 3

Dr Tewari – Case 2:
Recurrent Endometrial Cancer

- 62 y/o Indian Para-2 PMP VB
- TVUS: 10 x 6 x 8 cm uterus w/12 mm EMS
- No adnexal masses or free fluid
- EMB: Grade 2 endometrioid adenocarcinoma
- PMH: Obesity (BMI 34), well-controlled htn, NIDDM, and hypercholesterolemia
- PSH: C/2 x 2 (Pfannensteil), LSC cholecystectomy
- ROS: denies SOB, chest pain, etc
- Robotic hyst-BSO, sentinel lymphatic mapping, MMR IHC





Dr Tewari – Case 2 (continued)

- FIGO stage IIIC1, pMMR
- Adjuvant carboplatin plus paclitaxel x 6 cycles
- NED x 1.5 yrs
- Recurrence confirmed by CT-guided bx (retroperitoneal nodes)
  - Pembrolizumab plus lenvatinib
    - Dose reduction lenvatinib 10 mg daily (Cycle 4+)

Agenda

INTRODUCTION: Pan-tumor Indications for New Therapies

MODULE 1: Endometrial Cancer

- Key Issue – Immunotherapy

MODULE 2: Cervical Cancer

- Key Issue – Immunotherapy
- Key Issue – Tisotumab vedotin

MODULE 3: Ovarian Cancer

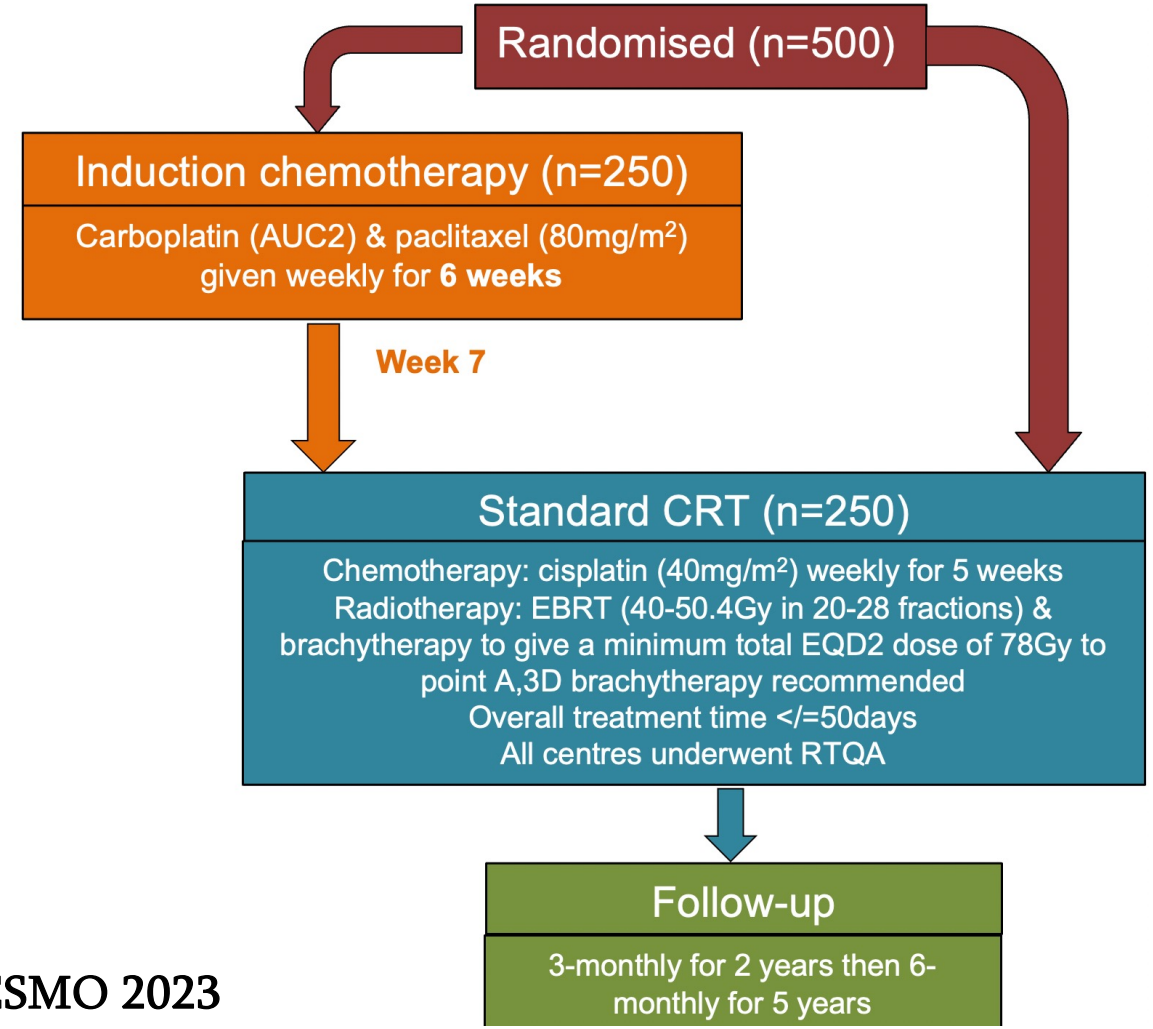
- Key Issue – PARP inhibitors in primary management (maintenance) and relapsed disease
- Key Issue – Mirvetuximab soravtansine and other antibody-drug conjugates

INTERLACE Trial Design

Key eligibility criteria

- Newly diagnosed histologically confirmed FIGO (2008) stage IB1 node+,IB2 ,II,IIIB,IVa squamous, adeno, adenosquamous cervical cancer
- No nodes above aortic bifurcation
- Adequate renal/liver and bone marrow function
- Fit for chemotherapy & radical RT
- No prior pelvic RT

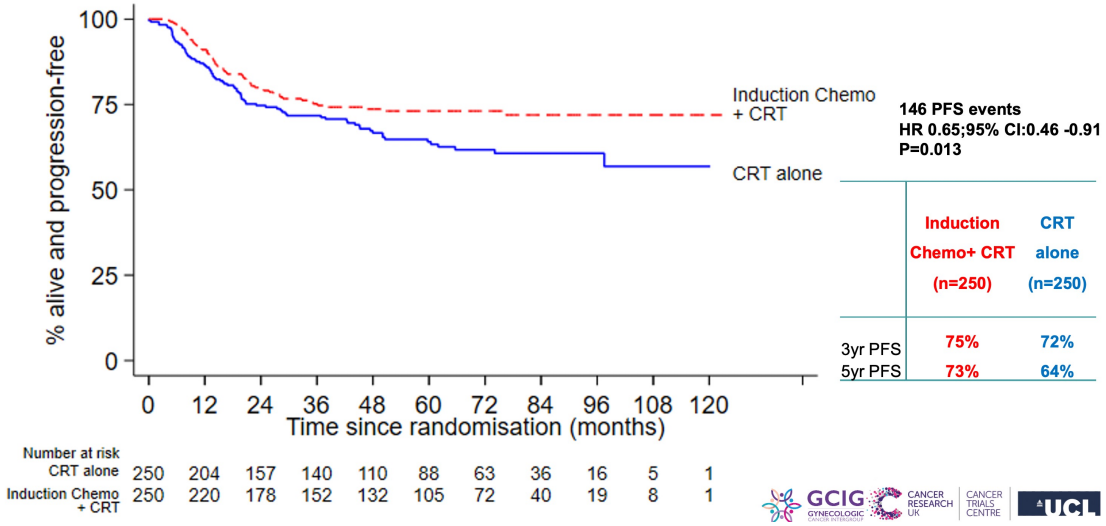
RT=Radiation
IMRT=Intensity modulated radiation
EBRT=External beam radiation
BT= Brachytherapy
RTQA=Radiation quality assurance



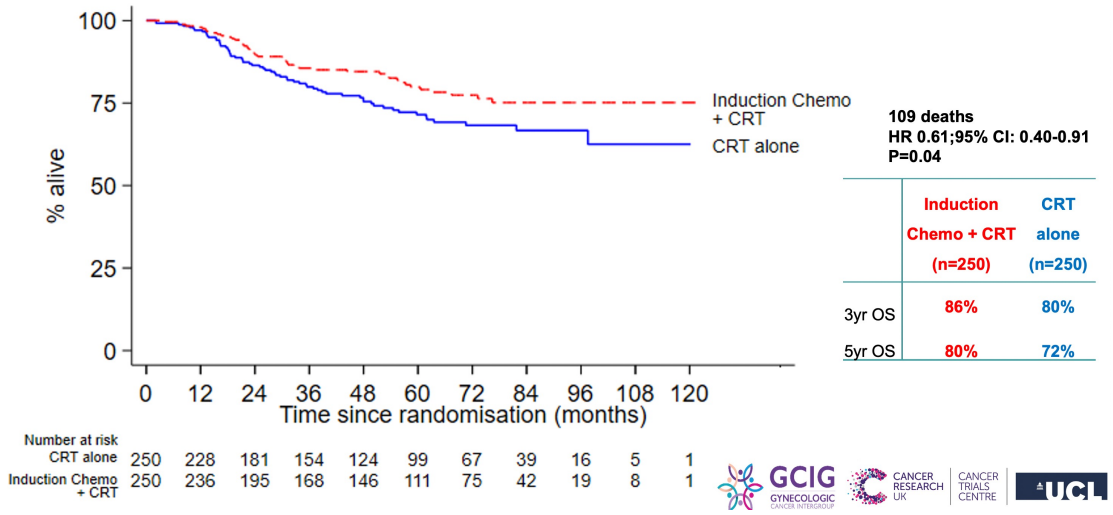
Presented by McCormack M, et al. ESMO 2023

Courtesy of Krishnansu S Tewari, MD

INTERLACE Progression-Free Survival (median FU 64m)



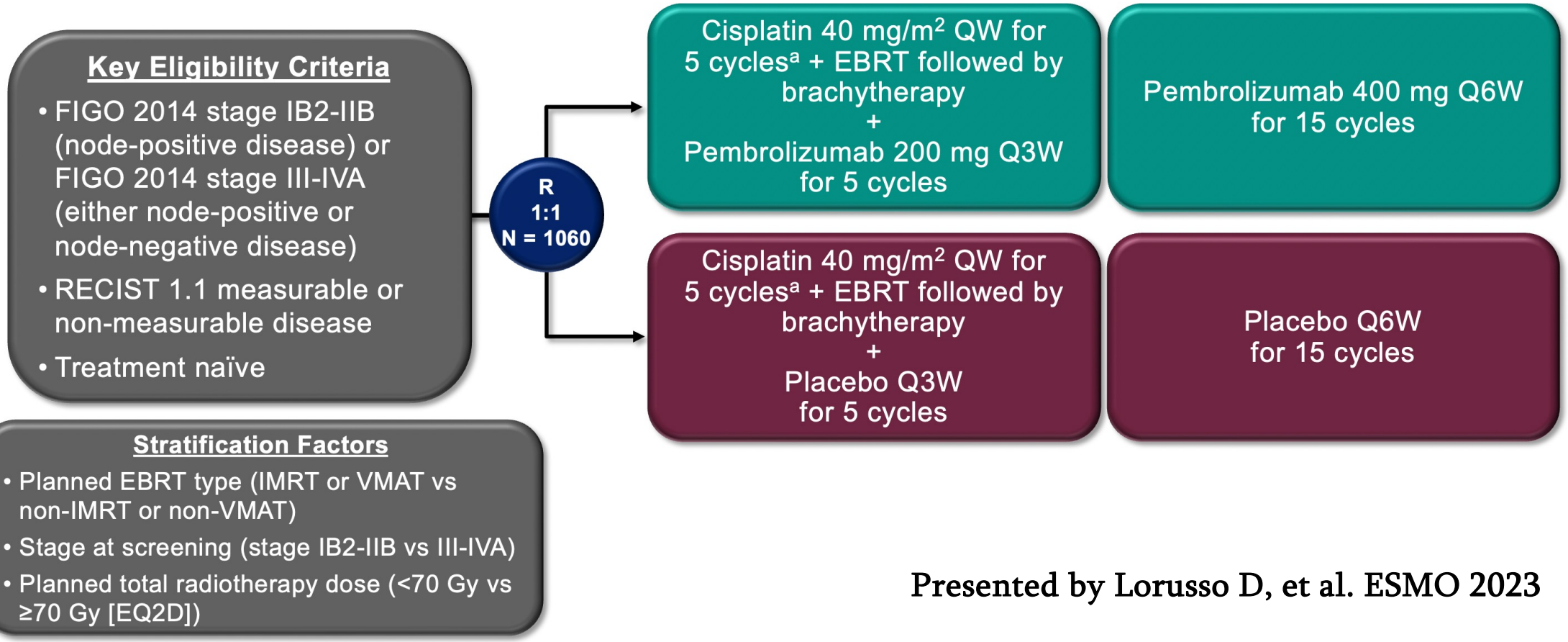
INTERLACE Overall Survival (median FU 64m)



Presented by McCormack M, et al. ESMO 2023

Courtesy of Krishnansu S Tewari, MD

ENGOT-cx11/GOG-3047/KEYNOTE-A18: Randomized, Double-Blind, Phase 3 Study



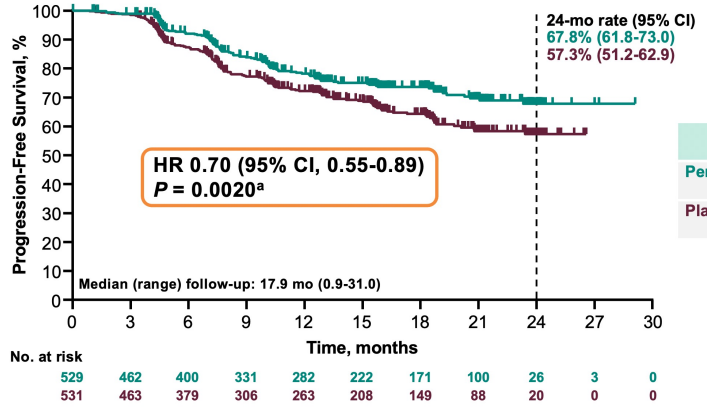
Presented by Lorusso D, et al. ESMO 2023

[a]A 6th cycle was allowed per investigator discretion. EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; Gy, grays; IMRT, intensity-modulated radiotherapy; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; VMAT, volumetric-modulated arc therapy. ENGOT-cx11/GOG-3047/KEYNOTE-A18 ClinicalTrials.gov identifier, NCT04221945.

Courtesy of Krishnansu S Tewari, MD

KEYNOTE-A18

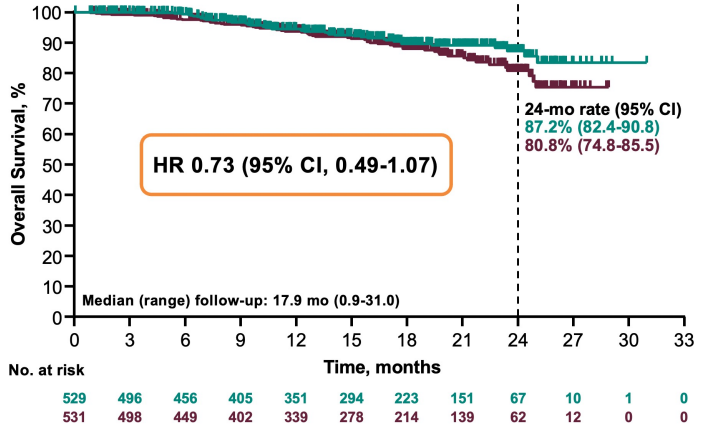
Primary Endpoint: Progression-Free Survival



	Pts w/ Event	Median, mo (95% CI)
Pembro Arm	21.7%	NR (NR-NR)
Placebo Arm	29.0%	NR (NR-NR)

Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation. [a]With 269 events (88.5% information fraction), the observed *P* = 0.0020 (1-sided) crossed the prespecified nominal boundary of 0.0172 (1-sided) at this planned first interim analysis. The success criterion of the PFS hypothesis was met, and thus no formal testing of PFS will be performed at a later analysis. Data cutoff date: January 9, 2023.

Primary Endpoint: Overall Survival



	Pts w/ Event*	Median, mo (95% CI)
Pembro Arm	8.3%	NR (NR-NR)
Placebo Arm	11.1%	NR (NR-NR)

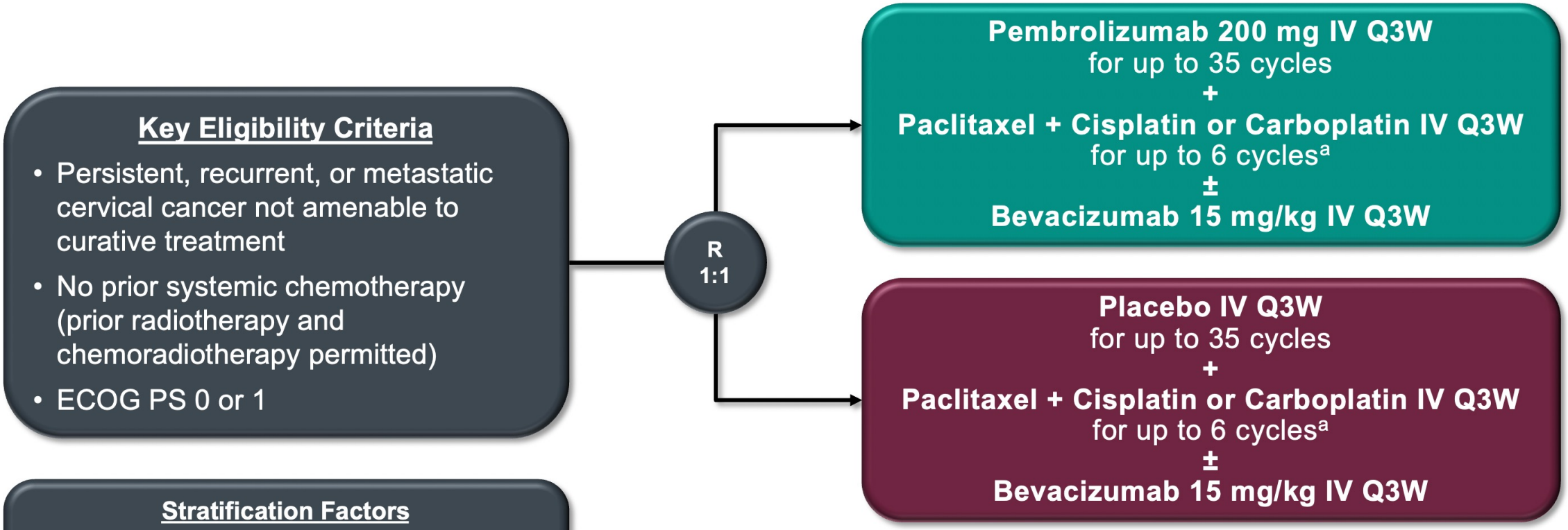
*42.9% information fraction[a]

[a]At this analysis, 103 of the 240 deaths expected at the final analysis had occurred.
Data cutoff date: January 9, 2023.

Presented by Lorusso D, et al. ESMO 2023

Courtesy of Krishnansu S Tewari, MD

KEYNOTE-826 FINAL OVERALL SURVIVAL



End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by investigator
- **Secondary:** ORR, DOR, 12-mo PFS, and safety
- **Exploratory:** PROs assessed per EuroQol EQ-5D-5L VAS

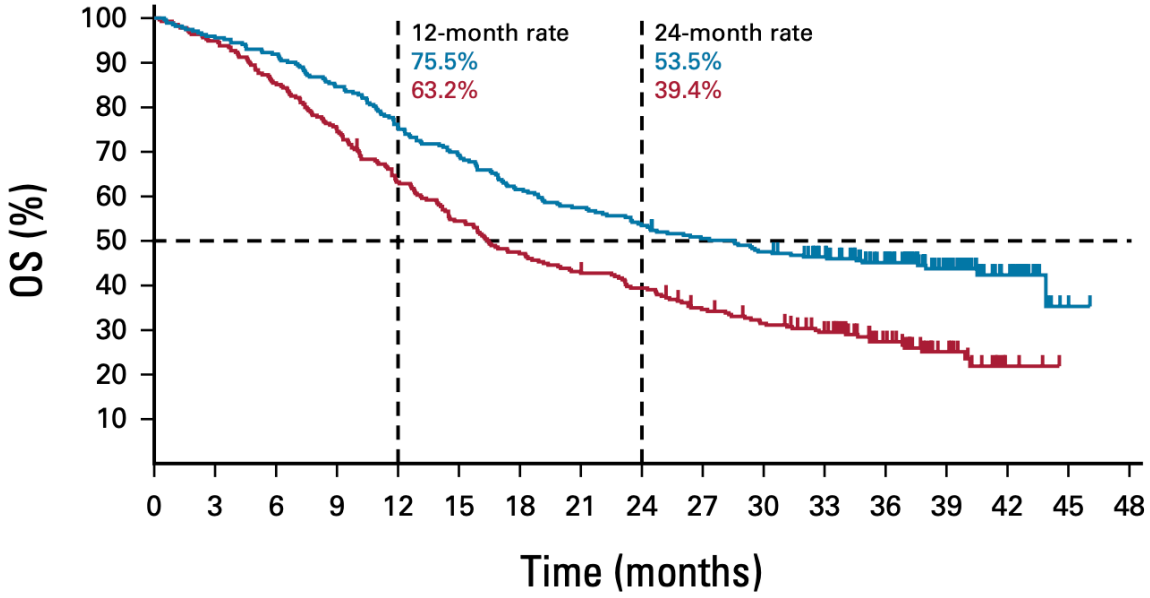
Presented by Monk BJ, et al. ASCO 2023

Courtesy of Krishnansu S Tewari, MD

KEYNOTE-826

A OS: PD-L1 CPS ≥1 Population

Treatment Group	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)	HR (95% CI)
Pembro + chemo ± bev	153/273 (56.0)	28.6 (22.1 to 38.0)	0.60 (0.49 to 0.74)
Placebo + chemo ± bev	201/275 (73.1)	16.5 (14.5 to 20.0)	

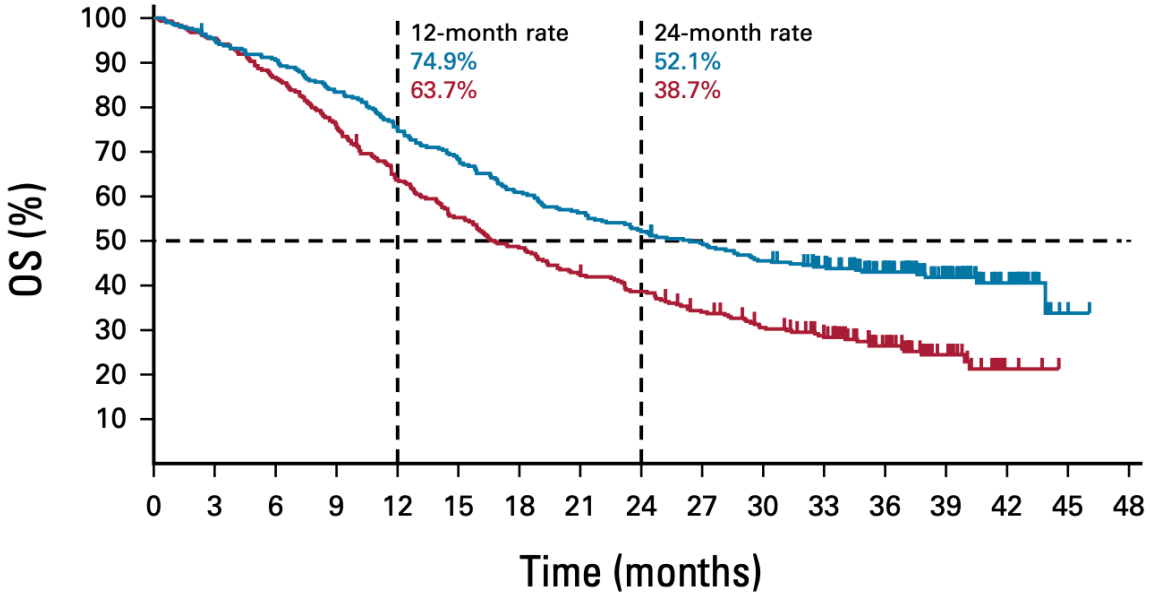


No. at risk:

273	261	251	231	206	189	168	157	146	136	128	116	90	52	22	2	0
275	261	235	207	173	149	129	117	107	91	81	68	45	24	3	0	0

B OS: All-Comer Population

Treatment Group	No. of Events/ No. of Patients (%)	Median OS, Months (95% CI)	HR (95% CI)
Pembro + chemo ± bev	178/308 (57.8)	26.4 (21.3 to 32.5)	0.63 (0.52 to 0.77)
Placebo + chemo ± bev	228/309 (73.8)	16.8 (14.6 to 19.4)	



No. at risk:

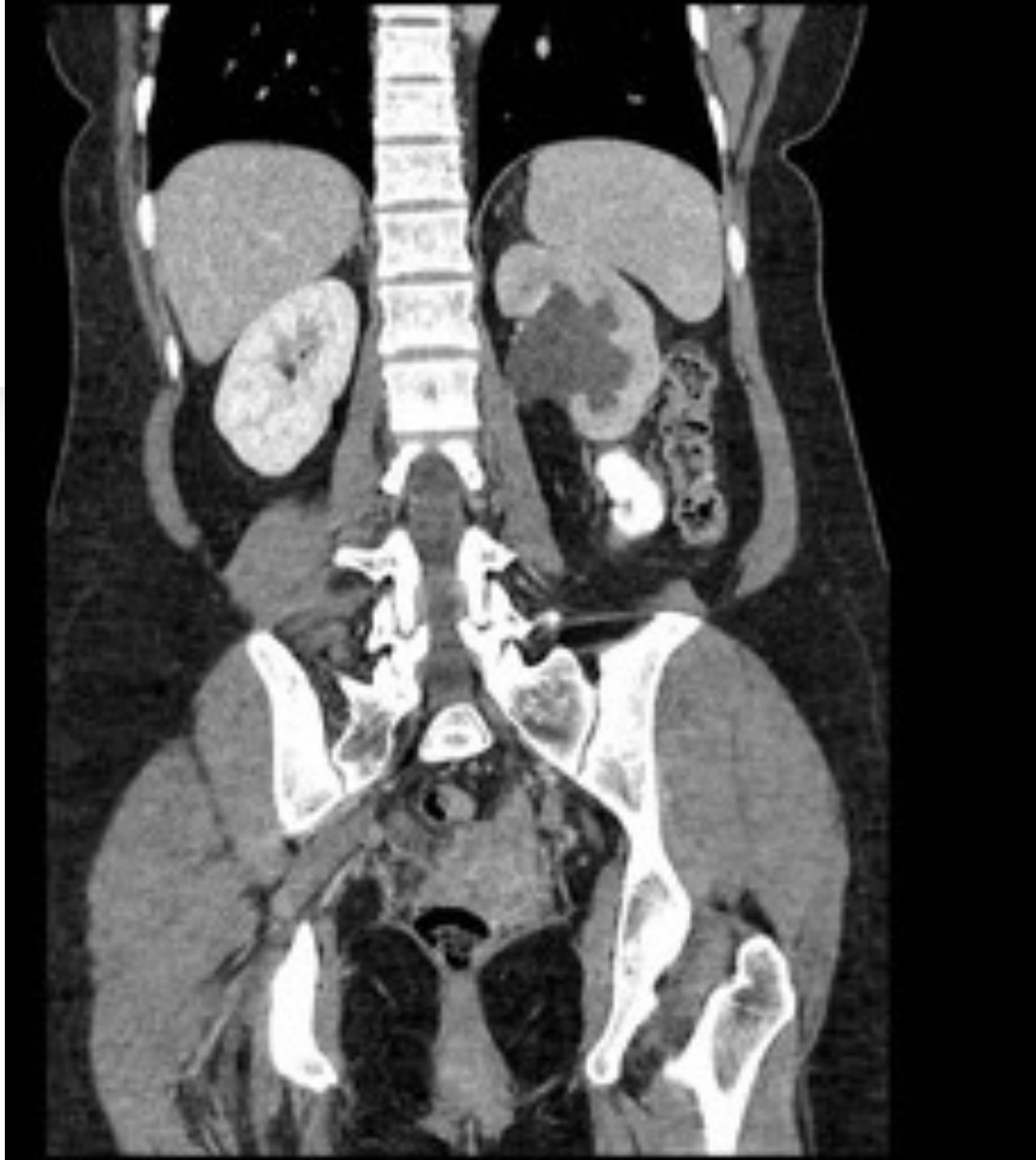
308	292	278	256	230	210	187	173	160	150	138	125	95	55	22	2	0
309	295	268	235	196	170	149	130	118	101	87	72	48	26	3	0	0

Monk BJ, et al. J Clin Oncol 2023 Nov 2 [Epub ahead of print].

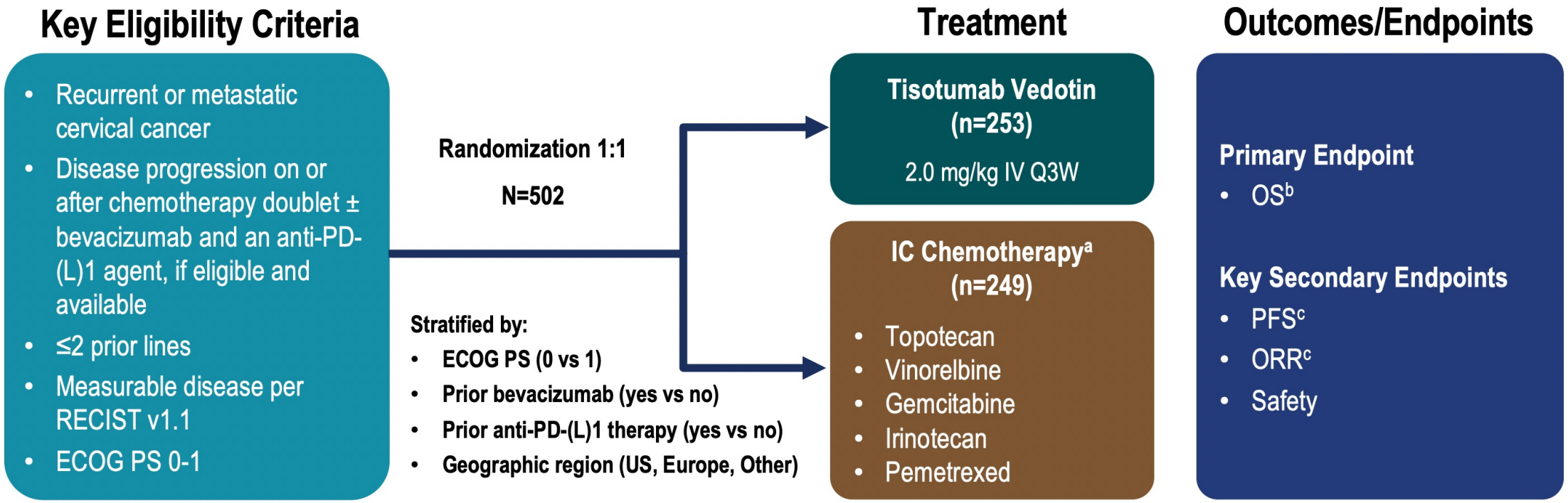
Courtesy of Krishnansu S Tewari, MD

Dr Tewari – Case 3
Locally Advanced Cervical Cancer

- 56 y/o w/VB, vaginal discharge, left flank pain
- Speculum: fungating 5 cm mass replacing cervix and upper vagina
  - Bx: G3 SCCA
- Bimanual & Rectovaginal exam
  - Bilateral parametrial involvement
  - Left pelvic sidewall extension
  - No rectal infiltration
- No peripheral adenopathy
- PET/CT
  - Left hydronephrosis (moderate)
  - Left pelvic adenopathy (SUV 9, 3 nodes short axis 1.6-2.0 cm)
- FIGO stage IIICr
- Treatment options
  - CDDP-based chemoradiation plus HDR Intracavitary Brachytherapy
  - Induction chemoRx (INTERLACE) followed by chemoRT
  - ChemoRT plus Pembrolizumab (KEYNOTE-A18)
  - INTERLACE plus KEYNOTE-A18?



innovaTV 301: A Randomized, Open-Label, Phase 3 Trial



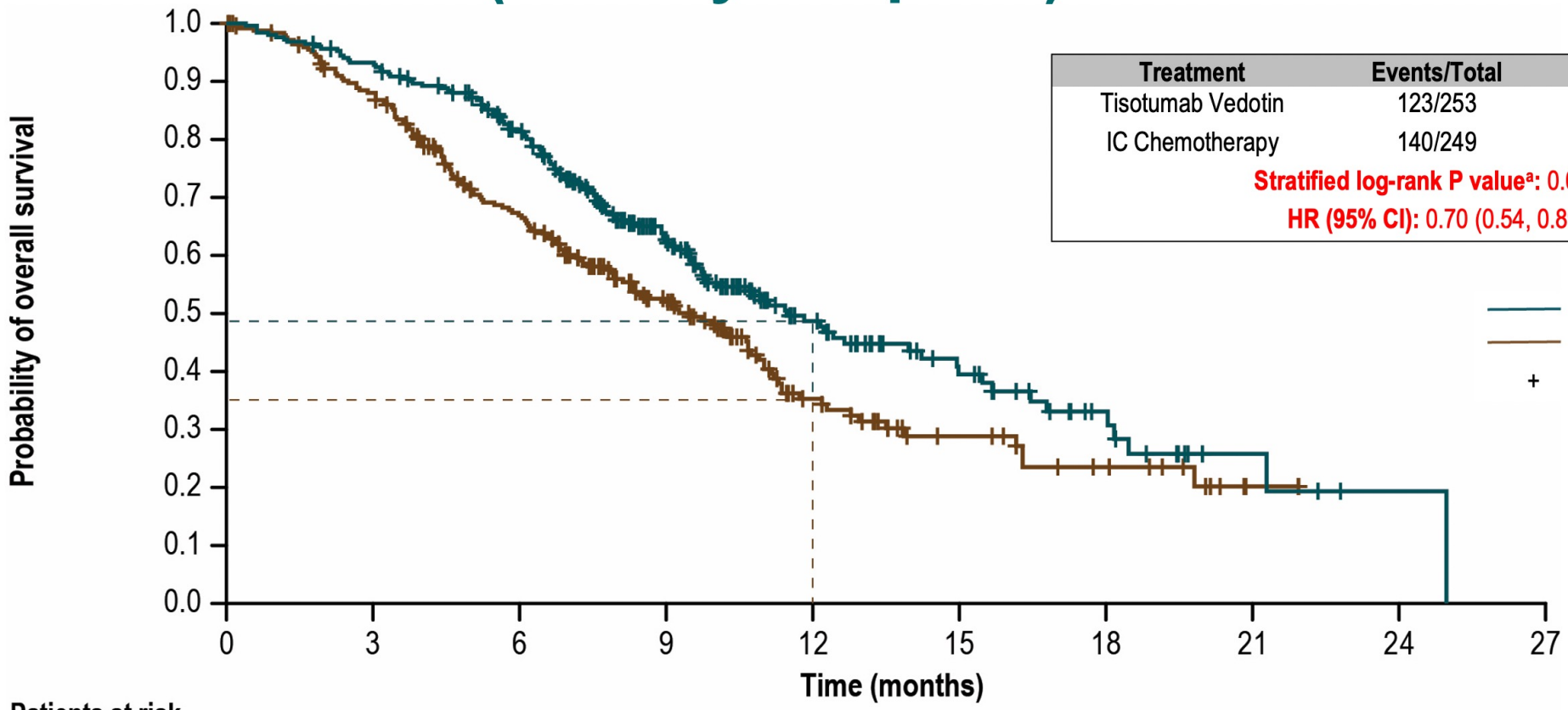
- Data presented herein are a planned interim analysis

IC, investigator's choice
End of treatment visit occurred 30 days after the last dose of treatment. Survival follow-up occurred every 60 days after the last dose of treatment.
[a]Chemotherapy regimens were given at the following doses: topotecan: 1 or 1.25 mg/m^2 IV on Days 1 to 5, every 21 days; vinorelbine: 30 mg/m^2 IV on Days 1 and 8, every 21 days; gemcitabine: 1000 mg/m^2 IV on Days 1 and 8, every 21 days; irinotecan: 100 or 125 mg/m^2 IV weekly for 28 days, every 42 days; pemetrexed: 500 mg/m^2 on Day 1, every 21 days; [b]OS was defined as the time from the date of randomization to the date of death due to any cause; [c]Assessed by investigator.

Presented by Vergote I, et al. ESMO 2023

Courtesy of Krishnansu S Tewari, MD

Overall Survival (Primary Endpoint)



Treatment	Events/Total	Median (95% CI)
Tisotumab Vedotin	123/253	11.5 (9.8, 14.9)
IC Chemotherapy	140/249	9.5 (7.9, 10.7)

Stratified log-rank P value[a]: 0.0038

HR (95% CI): 0.70 (0.54, 0.89)

Patients at risk

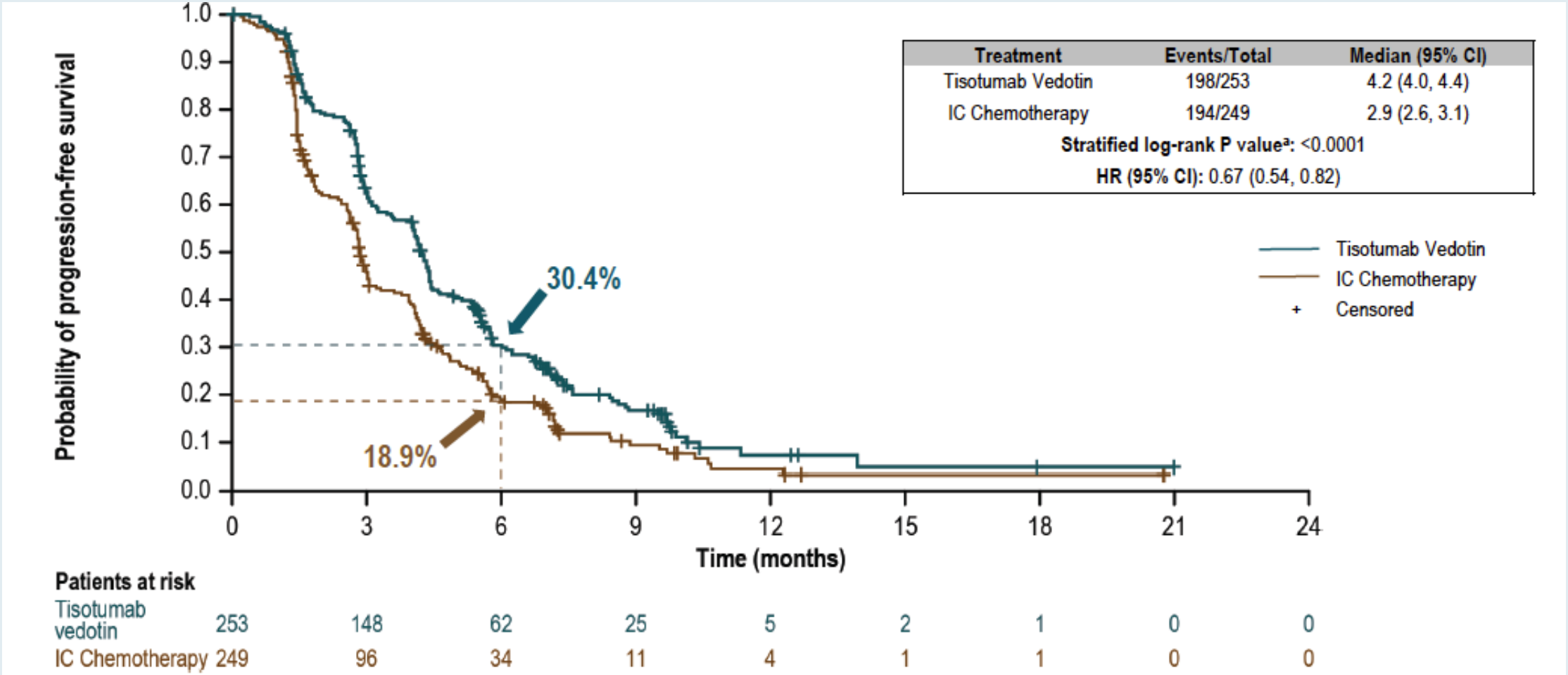
Tisotumab vedotin	253	234	191	109	52	29	14	4	1	0
IC Chemotherapy	249	212	150	87	37	19	11	1	0	0

[a]The threshold for statistical significance is 0.0226 (2-sided), based on the actual number of OS events at interim analysis.

Presented by Vergote I, et al. ESMO 2023

Courtesy of Krishnansu S Tewari, MD

innovaTV 301: PFS by Investigator



Treatment	Events/Total	Median (95% CI)
Tisotumab Vedotin	198/253	4.2 (4.0, 4.4)
IC Chemotherapy	194/249	2.9 (2.6, 3.1)

Stratified log-rank P value[a]: <0.0001

HR (95% CI): 0.67 (0.54, 0.82)

Patients at risk

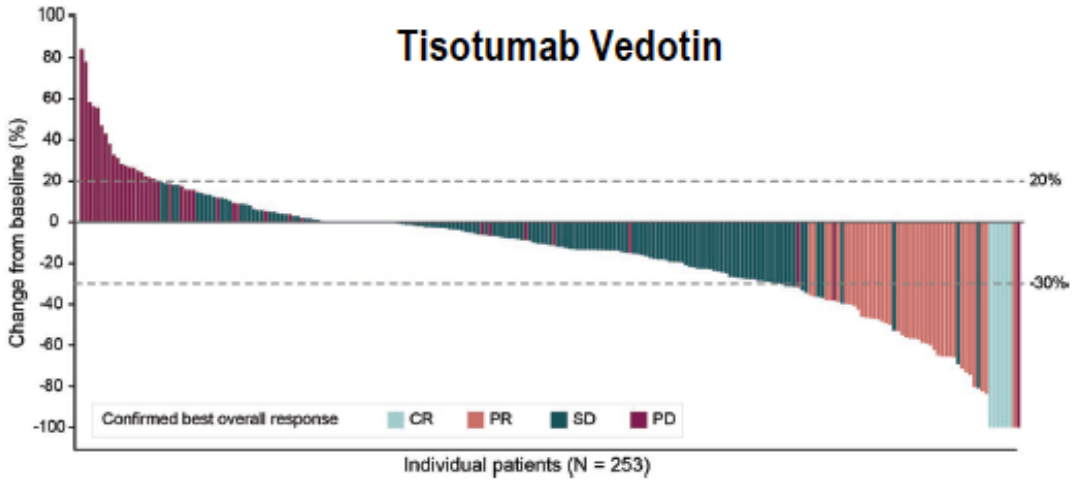
Tisotumab vedotin	253	148	62	25	5	2	1	0	0
IC Chemotherapy	249	96	34	11	4	1	1	0	0

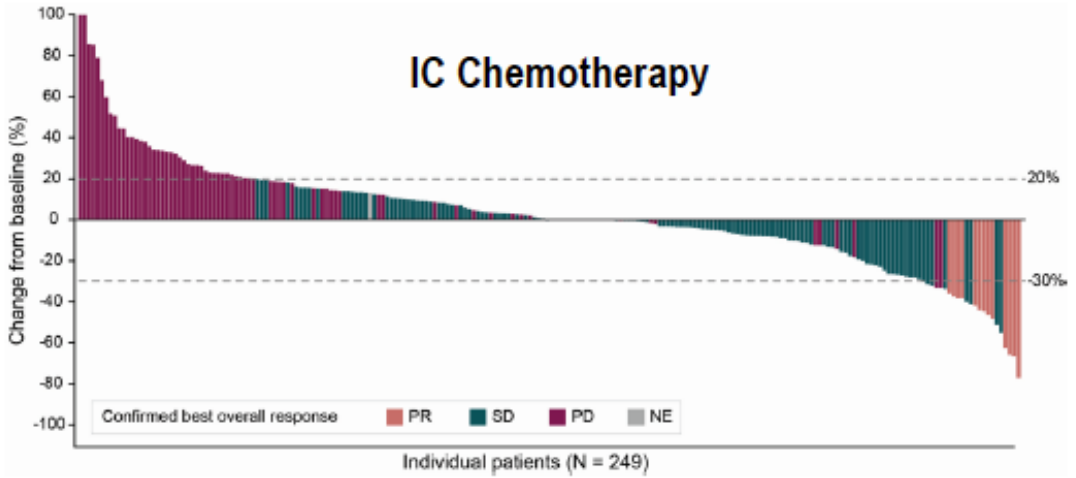
[a]The threshold for statistical significance is 0.0453 (2-sided), based on the actual number of PFS events at interim analysis.

Vergote IB et al. ESMO 2023;Abstract LBA9.

innovaTV 301: Antitumor Activity

	Tisotumab Vedotin (N=253)	IC Chemotherapy (N=249)
ORR, % (95% CI)	17.8 (13.3-23.1)	5.2 (2.8-8.8)
Odds ratio (95% CI)	4.0 (2.1-7.6)	
P value	p<0.0001	
Best Overall Response, n (%)		
CR	6 (2.4)	0
PR	39 (15.4)	13 (5.2)
SD	147 (58.1)	132 (53.0)
PD	46 (18.2)	74 (29.7)
Not evaluable/Not available	15 (5.9)	30 (12.0)
DCR[a], % (95% CI)	75.9 (70.1-81.0)	58.2 (51.8-64.4)
Median DOR (95% CI)	5.3 (4.2-8.3)	5.7 (2.8-NR)

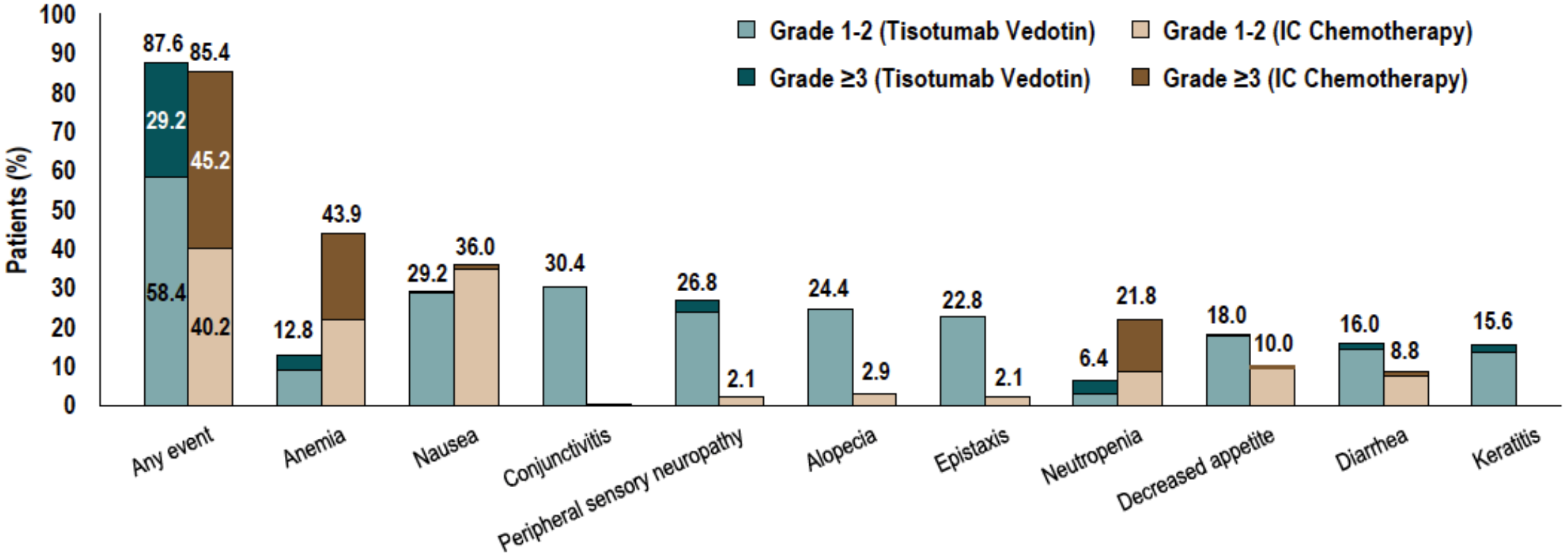




[a]DCR defined as CR+PR+SD; CR and PR were confirmed responses. The minimum criteria for SD duration was ≥5 weeks after the date of randomization.

Vergote IB et al. ESMO 2023;Abstract LBA9.

innovaTV 301: Most Common Treatment-Emergent Adverse Events (TRAEs)



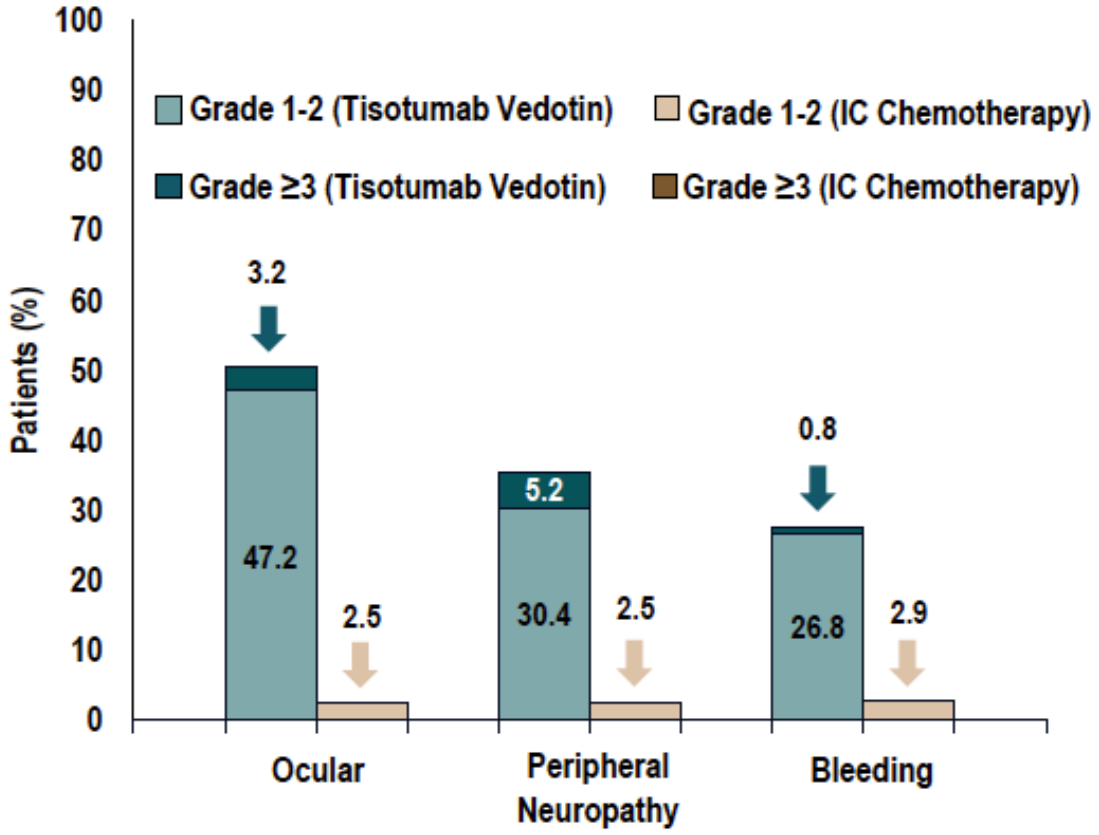
- Grade 5 TRAEs occurred in 2 (0.8%) and 1 (0.4%) patients in the tisotumab vedotin and IC chemotherapy arms, respectively[b]
- Median relative dose intensity was 96.1% and 90.0% in the tisotumab vedotin and IC chemotherapy arms, respectively

[a]TRAEs listed are those occurring in ≥15% of patients on either arm; [b]Grade 5 TRAEs included acute kidney injury (n=1) and Stevens-Johnson syndrome (n=1) in the tisotumab vedotin arm and pancytopenia (n=1) in the IC chemotherapy arm.

Vergote IB et al. ESMO 2023;Abstract LBA9.

RTP RESEARCH TO PRACTICE

innovaTV 301: Adverse Events of Special Interest with Tisotumab Vedotin



AESI, adverse event of special interest
[a]Treatment-related AESIs

- There were no grade 4 or 5 AESIs
- Dose discontinuation due to ocular and peripheral neuropathy events occurred in 5.6% of patients for each

Three most common preferred terms for each AESI	
Ocular	Conjunctivitis (30.4%), keratitis (15.6%), dry eye (13.2%)
Peripheral neuropathy	Peripheral sensory neuropathy (26.8%), paresthesia (2.8%), muscular weakness (2.4%), peripheral sensorimotor neuropathy (2.4%)
Bleeding	Epistaxis (22.8%), hematuria (3.2%), vaginal hemorrhage (3.2%)

Vergote IB et al. ESMO 2023;Abstract LBA9.

Agenda

INTRODUCTION: Pan-tumor Indications for New Therapies

MODULE 1: Endometrial Cancer

- Key Issue – Immunotherapy

MODULE 2: Cervical Cancer

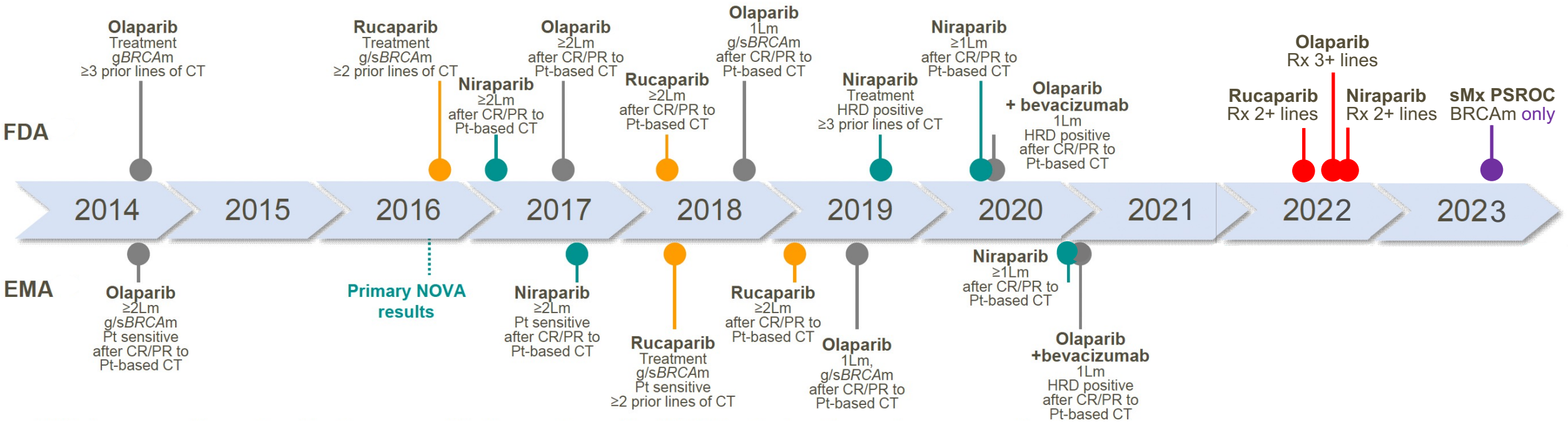
- Key Issue – Immunotherapy
- Key Issue – Tisotumab vedotin

MODULE 3: Ovarian Cancer

- Key Issue – PARP inhibitors in primary management (maintenance) and relapsed disease
- Key Issue – Mirvetuximab soravtansine and other antibody-drug conjugates

RTP RESEARCH TO PRACTICE

Ovarian Cancer: PARPi Approval History



MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Courtesy of Richard T Penson, MD, MRCP

Voluntary Withdrawal of Indications

Direct Healthcare Professional Communication (DHPC)

5/5/22 Niraparib (NOVA) OS disadvantage 2L+
Non-gBRCAmut HRDpos subgroup
mOS 37 vs. 41 months (HR = 1.32 [95% CI 0.84, 2.06])

6/28/22 Rucaparib (ARIEL4) 2L+
mOS 19 vs. 25 months (HR of 1.31 [95% CI 1.00, 1.73]) p= 0.0507

8/10/22 Olaparib (SOLO3) for 3L+ treatment of gBRCAm
mOS 30 vs. 39 months (HR of 1.33 [95% CI 0.84, 2.18])

Tew WP, et al. ASCO Guideline Update. JCO 2022:JCO2201934.
Tattersall A, et al. Cochrane Database Syst Rev. 2022;2(2):CD007929.
Kristeleit R, et al. Lancet Oncol. 2022;23(4):465-478.
Penson RT, et al. JCO 2020;38(11):1164-1174.

Courtesy of Richard T Penson, MD, MRCP

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Case Discussion

Patient with a germline BRCA mutation (or other homologous recombination deficiency)

- **Usual upfront treatment approach, including maintenance therapy for a Stage III ovarian cancer**
- **Usual approach to progressive metastatic ovarian cancer for patients who have not received a PARP inhibitor**

ASCO 2023

Effectiveness of PARP inhibitor maintenance therapy (mPARPi) in advanced ovarian cancer (OC) by *BRCA1/2* and a novel HRD signature (HRDsig) in real-world practice

Debra Richardson[1], Julia C. F. Quintanilha[2], Ryon P. Graf[2], Natalie Danziger[2], Alexa B. Schrock[2], Christina Washington[1], Lauren Dockery[1], Tamara Snow[3], Anosheh Afghahi[3], Anthony Frachioni[3], Julia Elvin[2], Kathleen Moore[1]

[1]Oklahoma University, Oklahoma City, OK [2]Foundation Medicine, Inc., Cambridge, MA; [3]Flatiron Health, New York, NY

BACKGROUND

- mPARPi following surgery and platinum chemotherapy (PCT) is a standard of care treatment for newly diagnosed advanced OC.
- Clinical trials have demonstrated benefit of mPARPi for patients with and without BRCA1/2 mutations (BRCA+/-).
- The degree of benefit of mPARPi for patients without homologous recombination deficiency (HRD) biomarkers detected remains in question.
- This study aimed to compare the effectiveness of mPARPi in real world practice by biomarker status (*BRCA1/2* mutations and a novel HRDsig).

MATERIALS AND METHODS

- This study included **platinum-sensitive** patients with advanced OC who received 1st-line PCT with real-world progression-free survival (rwPFS) of at least 10 months after treatment initiation and received either mPARPi (without bevacizumab) or no maintenance therapy.
- This study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine ovarian cancer clinico-genomic database (FH-FMI CGDB), originating from ~280 US cancer clinics (~800 sites of care) between 01/2015 and 12/2022. Retrospective longitudinal clinical data were derived from electronic health record data, comprising patient-level structured and unstructured data, curated via technology-enabled abstraction, and were linked to genomic data derived from Foundation Medicine comprehensive genomic profiling (CGP) tests in the Flatiron FH-FMI CGDB by de-identified, deterministic matching.
- rwPFS and real-world overall survival (rwOS) were compared between patients +/- biomarkers by Cox models, adjusted for propensity scores accounting for disease stage at diagnosis, ECOG, age, and BRCA status (for the HRDsig analysis).
- **Foundation Medicine's HRDsig** was assessed using a machine learning based algorithm with copy number features and select indel features used as inputs. HRDsig status was determined by pre-specified cutoff.

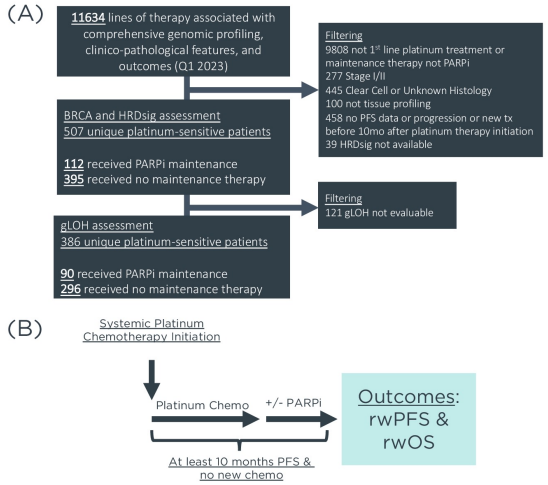


FIGURE 1: Cohort Selection and analysis overview.
Cohort selection diagram (A) and temporal visualization of the analysis cohort (B) are shown.

PATIENTS CHARACTERISTICS

TABLE 1: Patients baseline clinical and demographic characteristics.

	none (N=395)	mPARPi (N=112)	Total (N=507)	p value
Age				0.952
Median (Q1, Q3)	67.0 (58.0, 73.0)	66.0 (59.8, 73.2)	66.0 (59.0, 73.0)	
ECOG PS				0.794
0	149 (37.7%)	45 (40.2%)	194 (38.3%)	
1	135 (34.2%)	38 (33.9%)	173 (34.1%)	
2+	32 (8.1%)	6 (5.4%)	38 (7.5%)	
Unknown	79 (20.0%)	23 (20.5%)	102 (20.1%)	
Stage at Diagnosis				0.018
Stage III	262 (66.3%)	61 (54.5%)	323 (63.7%)	
Stage IV	86 (21.8%)	39 (34.8%)	125 (24.7%)	
Unknown/not documented	47 (11.9%)	12 (10.7%)	59 (11.6%)	
Histology				0.156
Epithelial NOS	35 (8.9%)	15 (13.4%)	50 (9.9%)	
Serous	360 (91.1%)	97 (86.6%)	457 (90.1%)	
Extent of Debulking				0.075
Optimal	296 (74.9%)	83 (74.1%)	379 (74.8%)	
Suboptimal	31 (7.8%)	3 (2.7%)	34 (6.7%)	
Unknown/not documented	68 (17.2%)	26 (23.2%)	94 (18.5%)	
Residual Disease Status				0.042
No residual disease	186 (47.1%)	64 (57.1%)	250 (49.3%)	
Residual disease	121 (30.6%)	21 (18.8%)	142 (28.0%)	
Unknown/not documented	88 (22.3%)	27 (24.1%)	115 (22.7%)	
***TP53* Alteration**				0.086
Negative	33 (8.4%)	4 (3.6%)	37 (7.3%)	
Positive	362 (91.6%)	108 (96.4%)	470 (92.7%)	
***BRCA* group**				< 0.001
BRCA1/2	59 (14.9%)	24 (30.4%)	93 (18.3%)	
Negative	336 (85.1%)	78 (69.6%)	414 (81.7%)	
HRDsig				< 0.001
(+)	138 (34.9%)	61 (54.5%)	199 (39.3%)	
(-)	257 (65.1%)	51 (45.5%)	308 (60.7%)	

KEY TAKEAWAY

A novel HRDsig biomarker is able to predict benefit from mPARPi regardless of *BRCA* status (HR of 0.31 for PFS) in real-world OC patients, and those who are HRDsig(-) might be spared mPARPi therapy use (HR of 0.98 for PFS).

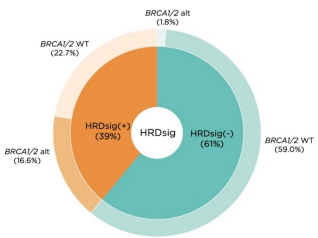


FIGURE 2: HRDsig detects 23% more patients who might benefit from mPARPi than *BRCA1/2* alterations alone.

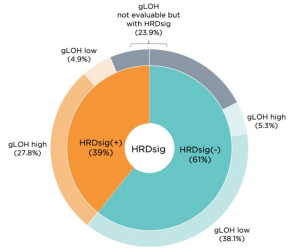


FIGURE 3: HRDsig is able to be assessed for 24% patients with gLOH not evaluable.

RESULTS

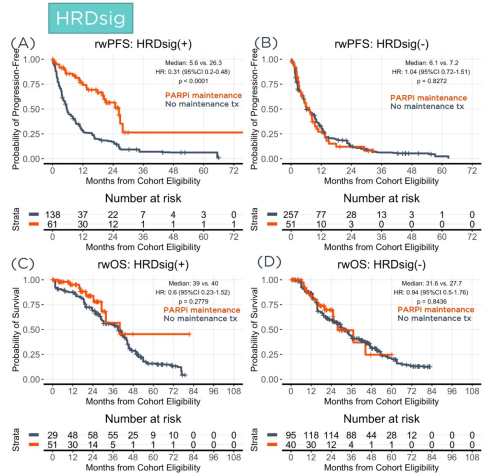


FIGURE 4: Patients receiving maintenance PARPi had more favorable outcomes when HRDsig(+) but not HRDsig(-).

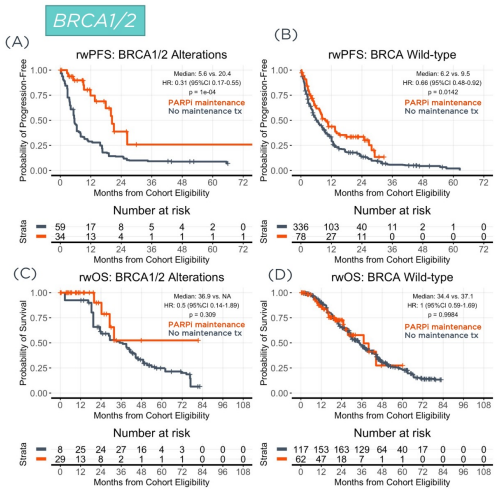


FIGURE 5: Patients receiving maintenance PARPi had more favorable outcomes when BRCAalt but not BRCAwt.

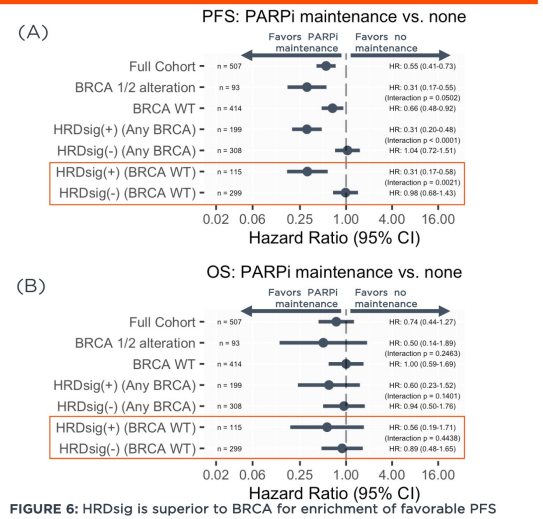


FIGURE 6: HRDsig is superior to BRCA for enrichment of favorable PFS and OS.

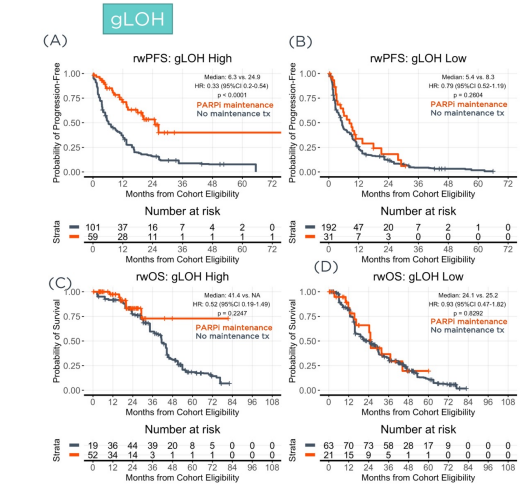


FIGURE 7: Patients receiving maintenance PARPi had more favorable outcomes when gLOH high but not gLOH low.

Courtesy of Richard T Penson, MD, MRCP

2023 ASCO® ANNUAL MEETING

Durvalumab with paclitaxel/carboplatin and bevacizumab followed by maintenance durvalumab, bevacizumab and olaparib in patients with newly diagnosed advanced ovarian cancer without a tumor *BRCA1/BRCA2* mutation: results from the randomized, placebo-controlled Phase III DUO-O/ENGOT-ov46/AGO-OVAR 23/GOG-3025 trial

Philipp Harter,[1] Fabian Trillsch,[2] Aikou Okamoto,[3] Alexander Reuss,[4] Jae-Weon Kim,[5] Maria Jesús Rubio-Pérez,[6] Mehmet Ali Vardar,[7] Giovanni Scambia,[8] Olivier Trédan,[9] Gitte-Bettina Nyvang,[10] Nicoletta Colombo,[11] Anita Chudecka-Głaz,[12] Christoph Grimm,[13] Stephanie Lheureux,[14] Els Van Nieuwenhuysen,[15] Florian Heitz,[16] Robert M. Wenham,[17] Kimio Ushijima,[18] Emily Day,[19] Carol Aghajanian[20]

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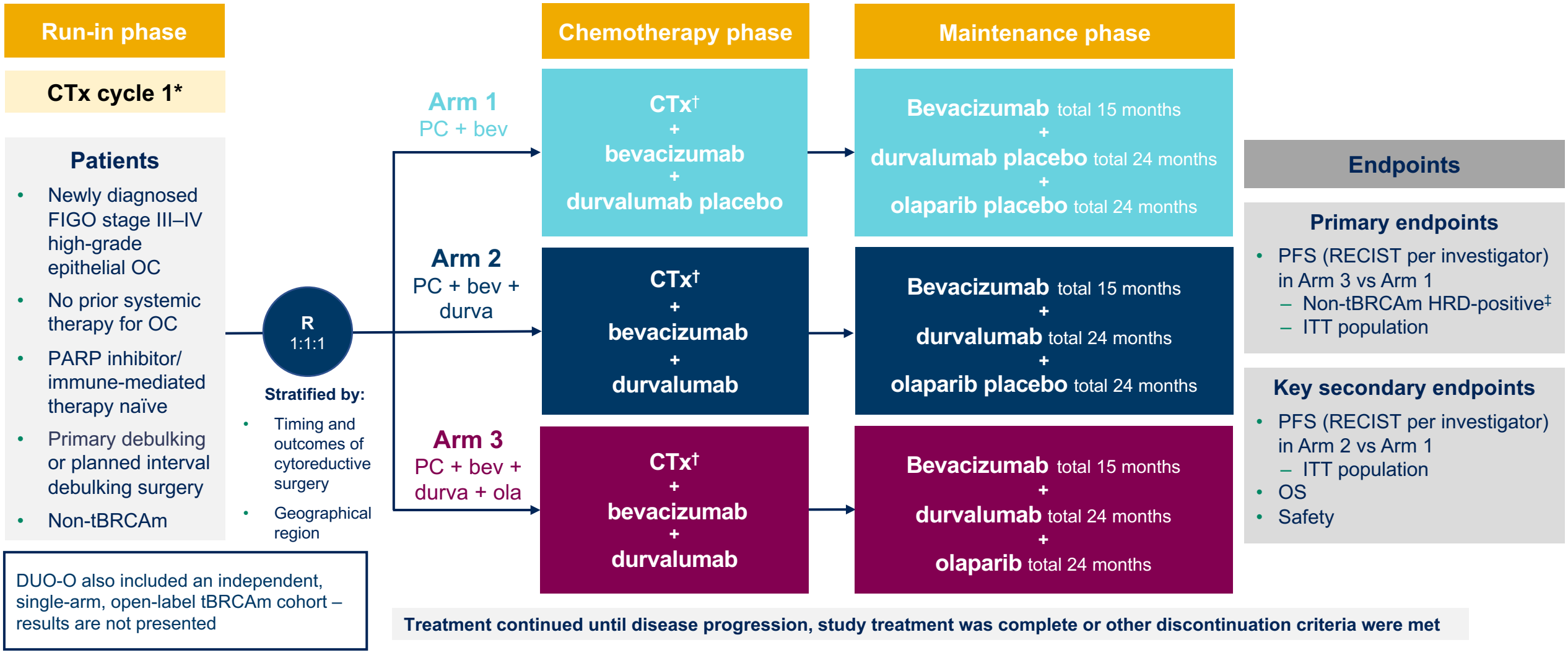
ClinicalTrials.gov identifier: NCT03737643

Courtesy of Richard T Penson, MD, MRCP

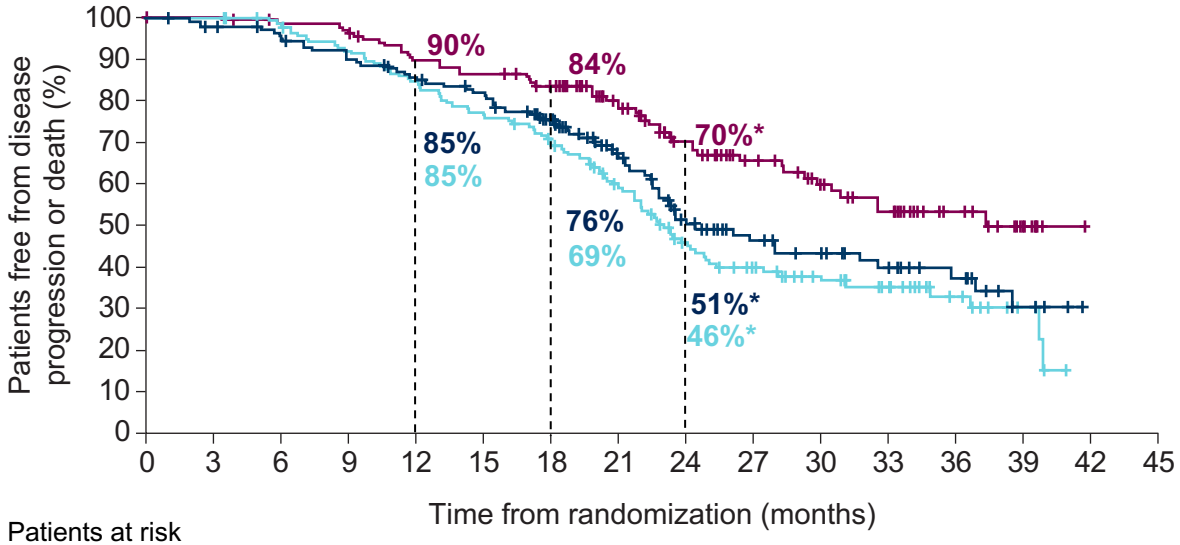
DUO-O study design



Dosing and schedule: bevacizumab (15 mg/kg IV q3w); durvalumab (1120 mg IV q3w); olaparib (300 mg po bid); chemotherapy: paclitaxel 175 mg/m^2 IV q3w and carboplatin at AUC5 or AUC6 IV q3w. PFS interim analysis DCO: December 5, 2022.
*With or without bevacizumab according to local practice; †Cycles 2–6; ‡Genomic instability score ≥42 assessed prospectively by Myriad MyChoice CDx assay.
AUC, area under the curve; bev, bevacizumab; bid, twice daily; CTx, chemotherapy; DCO, data cutoff; durva, durvalumab; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; IV, intravenous; ola, olaparib; OS, overall survival; PC, paclitaxel/carboplatin; po, by mouth; q3w, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria for Solid Tumors.

Subgroup analysis of PFS by HRD status

Non-tBRCAm HRD-positive

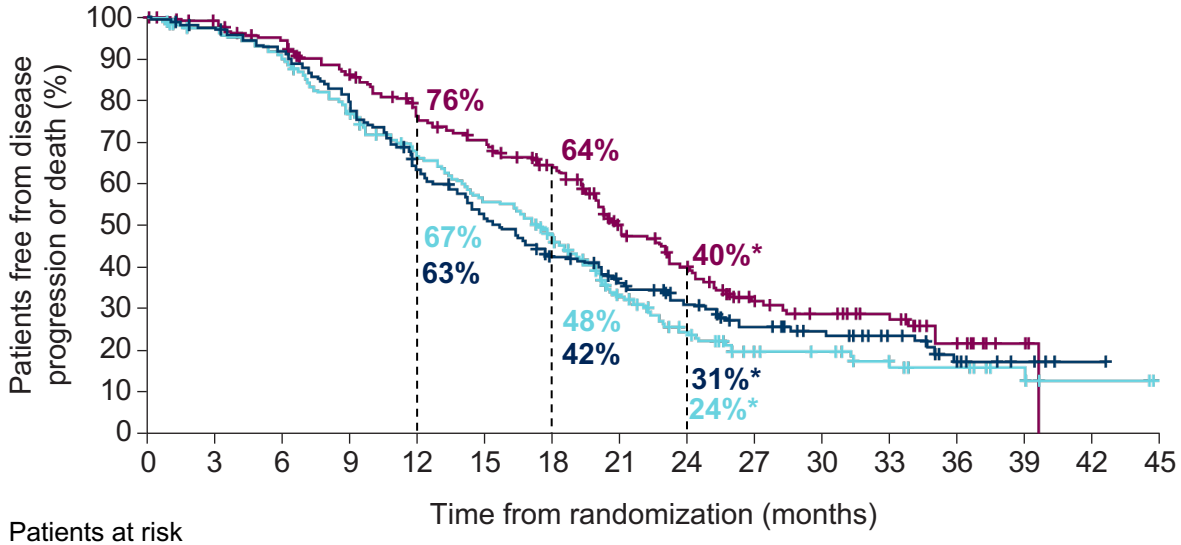


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 2	148	142	137	128	118	112	94	66	45	34	28	21	15	7	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	69 (47)	49 (35)
Median PFS, months†	23.0	24.4‡	37.3‡
HR (95% CI) vs Arm 1		**0.82** (0.60–1.12)§	**0.51** (0.36–0.72)§

HRD-negative



Patients at risk

Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 2	199	189	177	153	120	97	76	59	45	33	25	17	8	4	1	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

	Arm 1 PC + bev N=216	Arm 2 PC + bev + durva N=199	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	142 (71)	127 (60)
Median PFS, months†	17.4	15.4	20.9
HR (95% CI) vs Arm 1		**0.94** (0.75–1.18)§	**0.68** (0.54–0.86)§

*24-month PFS rates unstable; †Medians and rates were estimated by KM method; ‡Median PFS in HRD-positive subgroup Arm 3 and Arm 2 unstable; §HR and CI were estimated from an unstratified Cox proportional hazards model.

Safety summary

AEs, n (%)	Overall (chemotherapy phase + maintenance phase)			Maintenance phase		
	Arm 1 PC + bev N=376	Arm 2 PC + bev + durva N=373	Arm 3 PC + bev + durva + ola N=378	Arm 1 PC + bev N=331	Arm 2 PC + bev + durva N=323	Arm 3 PC + bev + durva + ola N=336
Any-grade AE	373 (99)	371 (99)	375 (99)	308 (93)	303 (94)	328 (98)
Grade ≥3 AE	231 (61)	245 (66)	269 (71)	88 (27)	113 (35)	164 (49)
AE with outcome of death	4 (1)	9 (2)	6 (2)	2 (1)	3 (1)	4 (1)
Serious AE (including outcome of death)	128 (34)	161 (43)	148 (39)	50 (15)	91 (28)	83 (25)
AE of special interest to olaparib						
MDS/AML*	1 (<1)	0	2 (1)	1 (<1)	0	1 (<1)
New primary malignancies*	1 (<1)	1 (<1)	4 (1)	1 (<1)	1 (<1)	3 (1)
Pneumonitis	3 (1)	5 (1)	7 (2)	1 (<1)	3 (1)	6 (2)
Any immune-mediated AEs†	132 (35)	209 (56)	200 (53)	94 (28)	139 (43)	141 (42)
AEs leading to dose modification‡,§	272 (72)	299 (80)	323 (85)	163 (49)	182 (56)	254 (76)
AEs leading to discontinuation‡	77 (20)	98 (26)	131 (35)	44 (13)	54 (17)	88 (26)
AEs leading to discontinuation of PC/bevacizumab	57 (15)	59 (16)	70 (19)	27 (8)	24 (7)	35 (10)
AEs leading to discontinuation of durvalumab/placebo	24 (6)	62 (17)	65 (17)	14 (4)	39 (12)	40 (12)
AEs leading to discontinuation of olaparib/placebo	15 (4)	19 (5)	62 (16)	14 (4)	19 (6)	61 (18)

Includes AEs with onset or worsening on or after the date of first dose of durvalumab/placebo or olaparib/placebo (overall) or first dose of olaparib/placebo (maintenance phase) until initiation of the first subsequent anticancer therapy following last dose of study treatment or until the end of the safety follow-up period.

*Includes events from first dose of durvalumab/olaparib/placebo until end of study; †Investigator-assessed; ‡Based on action taken on AE CRF for at least one treatment. For durvalumab/placebo, dose modification includes skipped or delayed doses, or interruption of the infusion; §Either dose reduction or dose interruption. AE, adverse event; AML, acute myeloid leukemia; CRF, case report form; MDS, myelodysplastic syndrome.

Conclusions

- DUO-O met its primary endpoint at the planned PFS interim analysis, demonstrating statistically significant and clinically meaningful improvement in PFS with first-line chemotherapy + bevacizumab + durvalumab followed by maintenance bevacizumab + durvalumab + olaparib compared with control in patients with non-tBRCAm advanced OC
  - Non-tBRCAm HRD-positive: HR **0.49** (0.34–0.69); *P*<0.0001
  - Non-tBRCAm ITT: HR **0.63** (0.52–0.76); *P*<0.0001
- PFS benefit was observed across subgroups, including those patients with HRD-negative disease (HR **0.68** [0.54–0.86])
- A numerical, but not statistical, improvement in PFS was shown with chemotherapy + bevacizumab + durvalumab followed by maintenance bevacizumab + durvalumab, compared with control, in the non-tBRCAm ITT population at the time of the PFS interim analysis
- Safety was generally consistent with the known profiles of each individual agent
- The trial is ongoing – final PFS, OS and other key secondary results will be reported in due course

Courtesy of Richard T Penson, MD, MRCP

MADRID 2023 ESMO congress

Efficacy and Safety of Senaparib as Maintenance Treatment in Patients with Newly Diagnosed Advanced Ovarian Cancer (FLAMES): A Randomised, Double-blind, Placebo-Controlled, Phase 3 Trial

Xiaohua Wu[1], Jihong Liu[2], Xiaobin Wang[3], Jing Wang[4], Li Wang[5], Jianqing Zhu[6], Beihua Kong[7], Junwei Fei[8], Ying Tang[9], Bairong Xia[10], Zhiqing Liang[11], Ke Wang[12], Zhongqiu Lin[13], Yi Huang[14], Hong Zheng[15], An Lin[16], Kui Jiang[17], Wei Wang[18], Xin Wang[19], Ge Lou[20]

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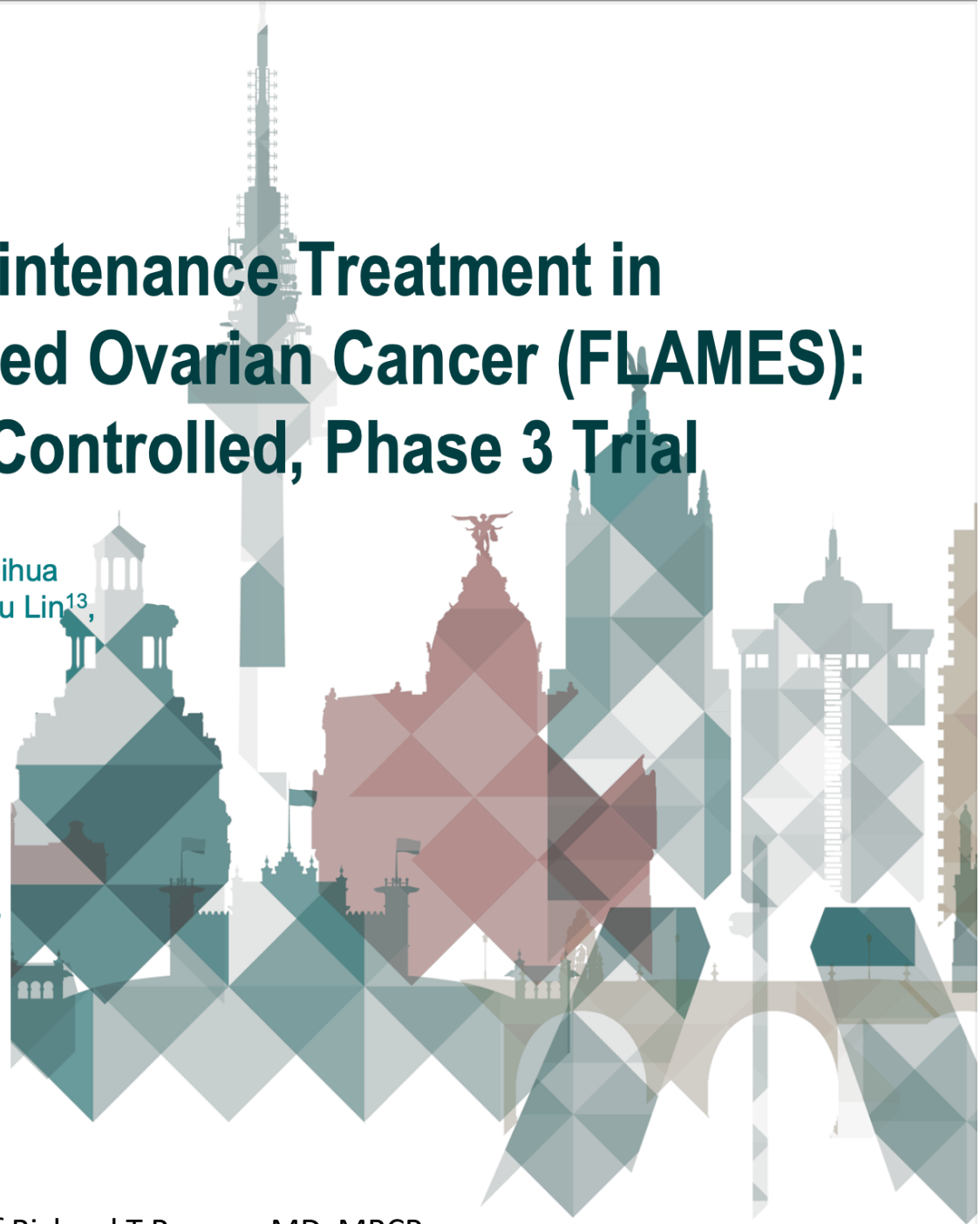


Dr. Xiaohua Wu, MD

Courtesy of Richard T Penson, MD, MRCP

FLAMES trial design

Randomised, Double-blind, Placebo-controlled

- Newly diagnosed, FIGO stage III-IV, high grade serous or endometrioid ovarian, fallopian tube or primary peritoneal cancer
- Subjects with complete response or partial response after platinum-based treatment
- Subjects must be randomised within 8 weeks after last dose of the chemotherapy

n=393

R 2:1

Senaparib 100 mg QD (n=262)

Stratification factors:
- Response to platinum-based chemotherapy
- Status of BRCA mutations (positive/negative)

Placebo 100 mg QD （n=131）

Treatment* continued for up to 2 years or until disease progression, unacceptable toxicity

Primary Endpoint
- PFS by BICR (RECIST v1.1) †

Secondary Endpoints
- PFS by investigator assessment (RECIST v1.1)
- Safety
- Time from randomisation to study treatment discontinuation or death
- Time from randomisation to first subsequent therapy or death
- OS
- Chemotherapy free interval
- HRQoL (FACT-O TOI score)

Pre-planned interim analysis (data cut-off date: March 16, 2023, median follow-up duration 22.3 months)

* Dose interruption or a sequential reduction (100mg, 80mg, 60mg, 40mg) of study drug can be implemented for adverse reaction management.

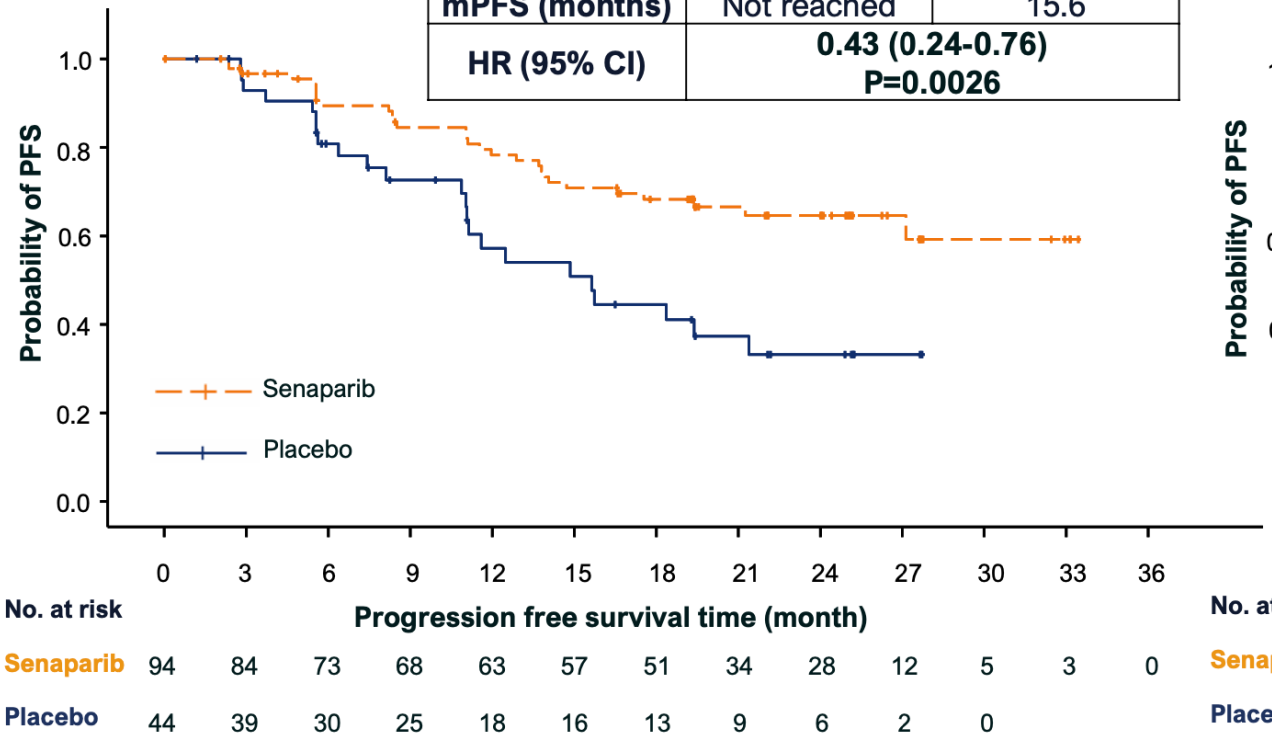
FIGO International Federation of Gynecology and Obstetrics; BRCA breast cancer susceptibility gene; BICR blinded independent central review; QD once daily; PFS progression-free survival ; OS overall survival; HRQoL health-related quality of life; FACT-O functional assessment of cancer therapy –ovarian; TOI trial outcome index

Courtesy of Richard T Penson, MD, MRCP

Substantial PFS benefit regardless of BRCA mutation status

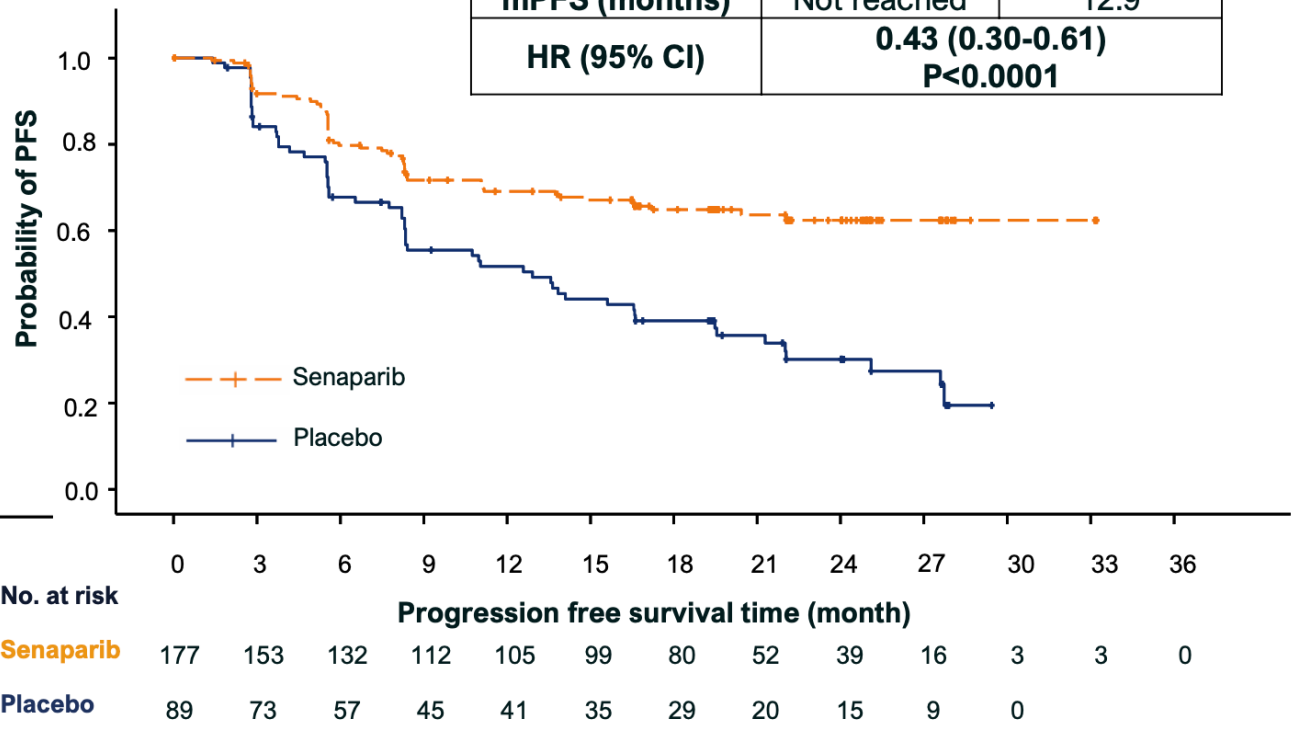
FLAMES prespecified subgroup analysis

BRCAmut-positive	Senaparib (N=94)	Placebo (N=44)
Events, n (%)	29 (30.9%)	23 (52.3%)
mPFS (months)	Not reached	15.6
HR (95% CI)	0.43 (0.24-0.76) P=0.0026	



No. at risk													
Senaparib	94	84	73	68	63	57	51	34	28	12	5	3	0
Placebo	44	39	30	25	18	16	13	9	6	2	0		

BRCAmut-negative	Senaparib (N=177)	Placebo (N=89)
Events, n (%)	59 (33.3%)	59 (66.3%)
mPFS (months)	Not reached	12.9
HR (95% CI)	0.43 (0.30-0.61) P<0.0001	



No. at risk													
Senaparib	177	153	132	112	105	99	80	52	39	16	3	3	0
Placebo	89	73	57	45	41	35	29	20	15	9	0		

Data cut-off date: March 16, 2023

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Dr. Xiaohua Wu

Courtesy of Richard T Penson, MD, MRCP

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GEICO Grupo Español de Investigación en Cáncer ginecológico

ENGOT European Network of Gynaecological Oncological Trial groups

Atezolizumab combined with platinum-based chemotherapy and maintenance niraparib for recurrent ovarian cancer with a platinum-free interval >6 months: Primary analysis of the double-blind placebo-controlled ENGOT-Ov41/GEICO 69-O/ANITA phase 3 trial

Antonio González-Martín, MD, PhD

Cancer Center Clínica Universidad de Navarra and GEICO, Madrid, Spain

On behalf of MJ Rubio Perez (GEICO, Spain), F Heitz (AGO, Germany), RD Christensen (GEICO & NSGO, Denmark), N Colombo (MaNGO, Italy), T Van Gorp (BGOG, Belgium), A Oaknin (GEICO, Spain), A Leary (GINECO, France), L Gaba (GEICO, Spain), C Lebreton (GINECO, France), LM De Sande González (GEICO, Spain), M Romeo Marin (GEICO, Spain), A Redondo (GEICO, Spain), MP Barretina Ginesta (GEICO, Spain), JA Perez-Fidalgo (GEICO, Spain), A Santaballa Bertran (GEICO, Spain), MJ Bermejo-Pérez (GEICO, Spain), I Bruchim (ISGO, Israel), I Ray-Coquard (GINECO, France), F Selle (GINECO, France)

LBA37, Madrid, Spain, 20th October 2023

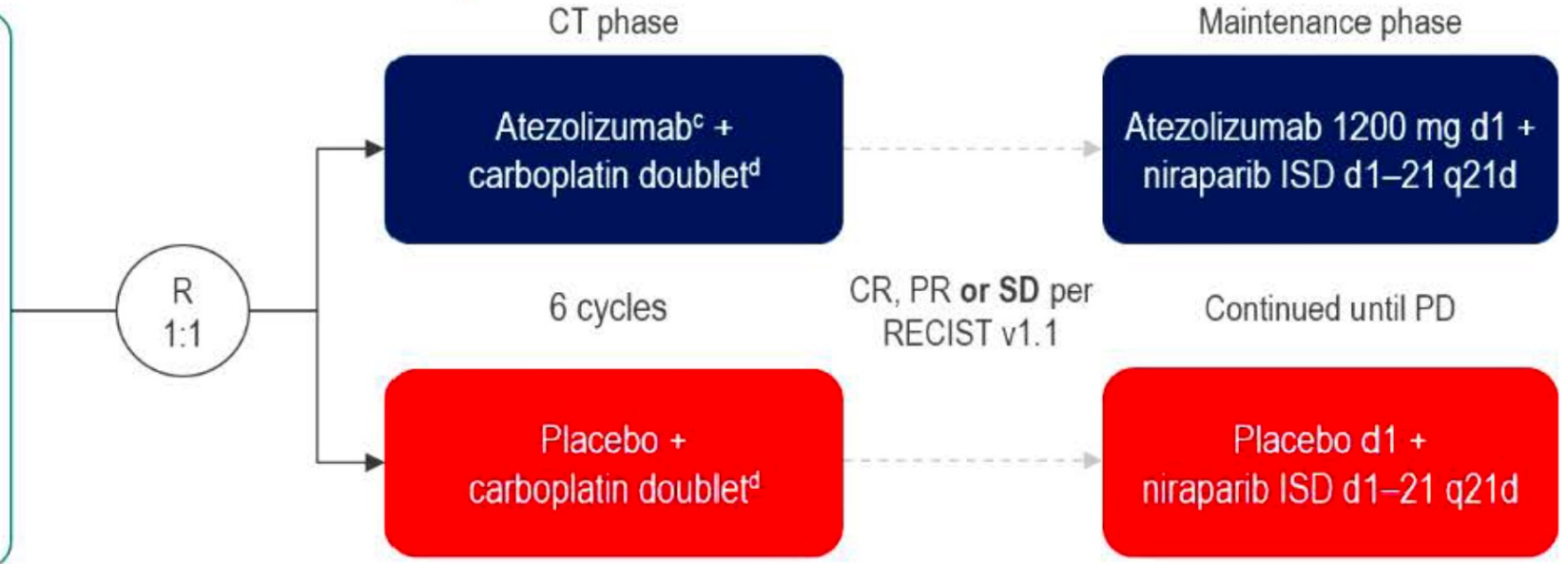
ANITA = Atezolizumab and NIraparib Treatment Association

Courtesy of Richard T Penson, MD, MRCP

ANITA/ENGOT-Ov41/GEICO 69-O (NCT03598270) trial design

Placebo-controlled multicentre randomised phase 3 trial

- Measurable high-grade serous, endometrioid or undifferentiated rOC
- TFIp >6 months
- ≤2 prior lines of CT (most recent including platinum)
- No prior PARPi for rOC[a]
- No prior immune checkpoint inhibitor (any setting)
- ECOG PS ≤1
- Mandatory de novo biopsy[b]



Stratification factors:

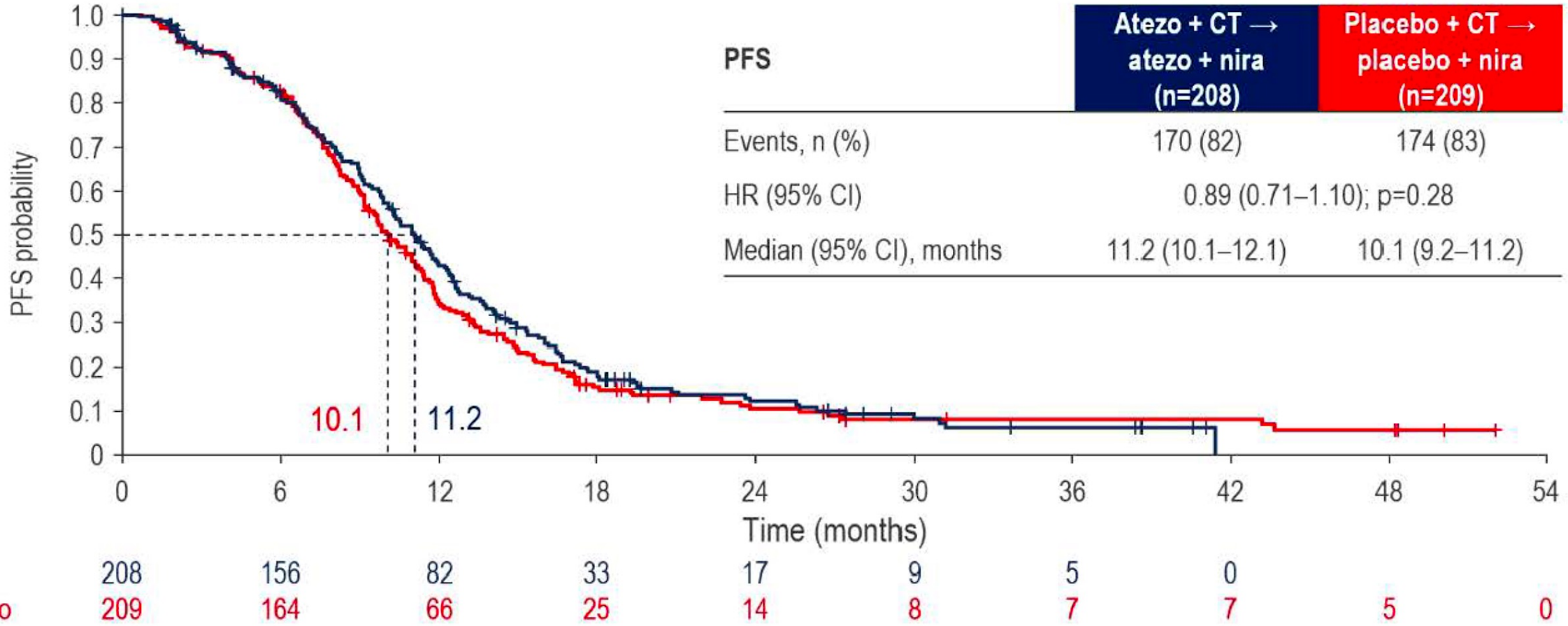
- Carboplatin doublet (PLD vs gemcitabine vs paclitaxel)
- TFIp (6–12 vs >12 months)
- *BRCA* status (mutated vs non-mutated)
- PD-L1 status (IC <1% vs ≥1% vs non-informative)[e]

AUC = area under the curve; CR = complete response; d = day; ECOG PS = Eastern Cooperative Oncology Group performance status; IC = immune cells; ISD = individualised starting dose (300 mg, or 200 mg if baseline weight is <77 kg or baseline platelet count is <150,000 µL); PD = progressive disease; PLD = pegylated liposomal doxorubicin; PR = partial response; q21d = every 21 days; R = randomisation; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease

[a]Prior PARPi after front-line therapy permitted if continued for ≥18 months (*BRCA* mutated) or ≥12 months (*BRCA* wildtype). [b]Implemented after randomisation of 82 patients (whose PD-L1 status was analysed in archival tissue). [c]Atezolizumab 1200 mg d1 q21d or 840 mg d1&8 q28d, depending on CT regimen. [d]Carboplatin AUC5 d1 + paclitaxel 175 mg/m^2 d1 q21d OR carboplatin AUC4 d1 + gemcitabine 1000 mg/m^2 d1&8 q21d OR carboplatin AUC5 d1 + PLD 30 mg/m^2 d1 q28d. [e]PD-L1-expressing IC on tumour area, determined by SP142 assay. Non-informative cases were capped at <10%

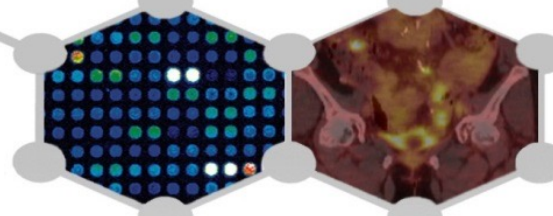
Courtesy of Richard T Penson, MD, MRCP

Primary endpoint: PFS



PFS	Atezo + CT → atezo + nira (n=208)	Placebo + CT → placebo + nira (n=209)
Events, n (%)	170 (82)	174 (83)
HR (95% CI)	0.89 (0.71–1.10); p=0.28	
Median (95% CI), months	11.2 (10.1–12.1)	10.1 (9.2–11.2)

Courtesy of Richard T Penson, MD, MRCP



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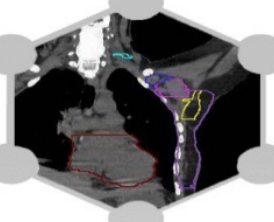


Overall Survival Outcomes from NRG-GY004, a Phase III Study Comparing Single-Agent Olaparib or Combination Cediranib and Olaparib to Platinum Based Chemotherapy in Recurrent Platinum Sensitive Ovarian Cancer

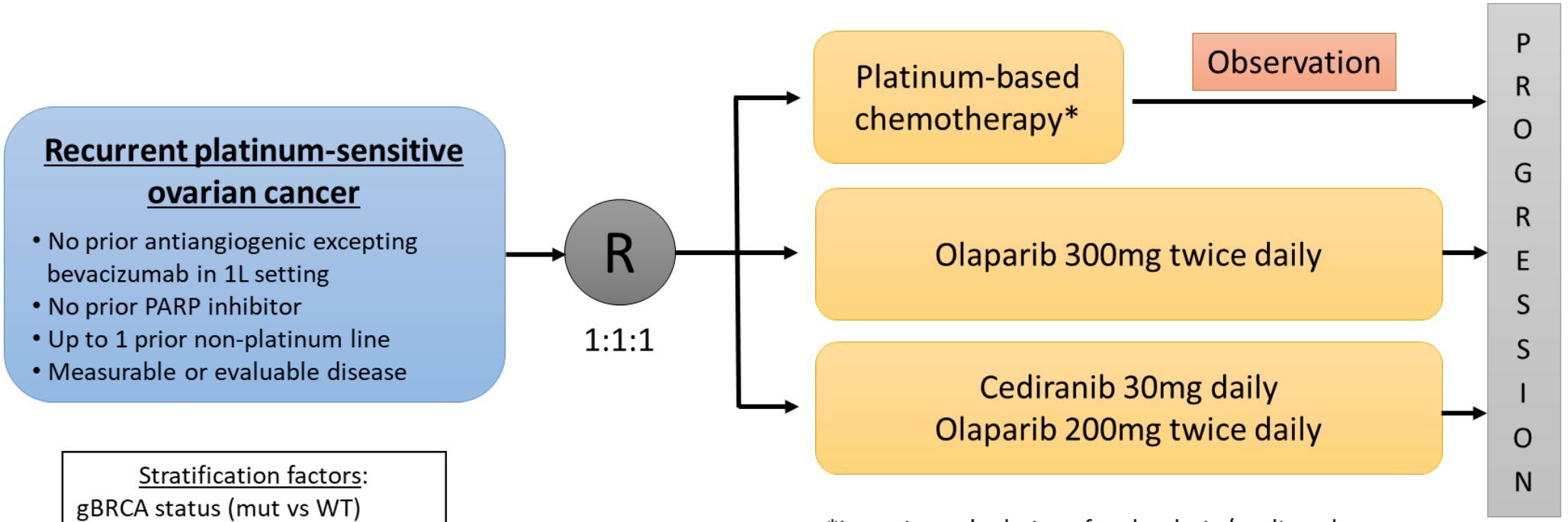
Joyce F. Liu[1], Mark F. Brady[2], Ursula A. Matulonis[1], Austin Miller[2], Elise C. Kohn[3], Elizabeth Swisher[4], William P. Tew[5], Noelle G. Cloven[6], Carolyn Muller[7], David Bender[8], Richard G. Moore[9], David Michelin[10], Steven Waggoner[11], Melissa Geller[12], Keiichi Fujiwara[13], Stacy D'Andre[14], Michael Carney[15] Angeles A. Secord[16], Joan L. Walker[17], Michael A. Bookman[18]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Roswell Park Cancer Institute, Buffalo, NY; [3]National Cancer Institute, Rockville, MD; [4]University of Washington, Seattle, WA; [5]Memorial Sloan Kettering Cancer Center, New York, NY; [6]Texas Oncology, Fort Worth, TX; [7]University of New Mexico, Albuquerque, NM; [8]University of Iowa, Iowa City, IA; [9]University of Rochester Medical Center, Rochester, NY; [10]Cancer Research Consortium of West Michigan, Grand Rapids, MI; [11]Case Western Reserve University School of Medicine, Cleveland, OH; [12]University of Minnesota, Minneapolis, MN; [13]Saitama Medical University International Medical Center, Japan; [14]Sutter Medical Group, Sacramento, CA; [15]University of Hawaii, Honolulu, HI; [16]Duke University Medical Center, Durham, NC, [17]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [18]Kaiser Permanente Northern California, San Francisco, CA

2023 ESMO Congress; 20-24 October 2023

Courtesy of Richard T Penson, MD, MRCP

NRG-GY004 Study Design (NCT02446600)



Stratification factors:
gBRCA status (mut vs WT)
Prior PFI (6-12 mos vs >12 mos)
Prior anti-angiogenic (yes vs no)

*Investigator's choice of carboplatin/paclitaxel, carboplatin/gemcitabine, or carboplatin/liposomal doxorubicin (PLD)

Primary endpoint: Progression-free survival
Secondary efficacy endpoints:
- Overall survival
- Objective response rate
- Activity in biomarker-defined populations

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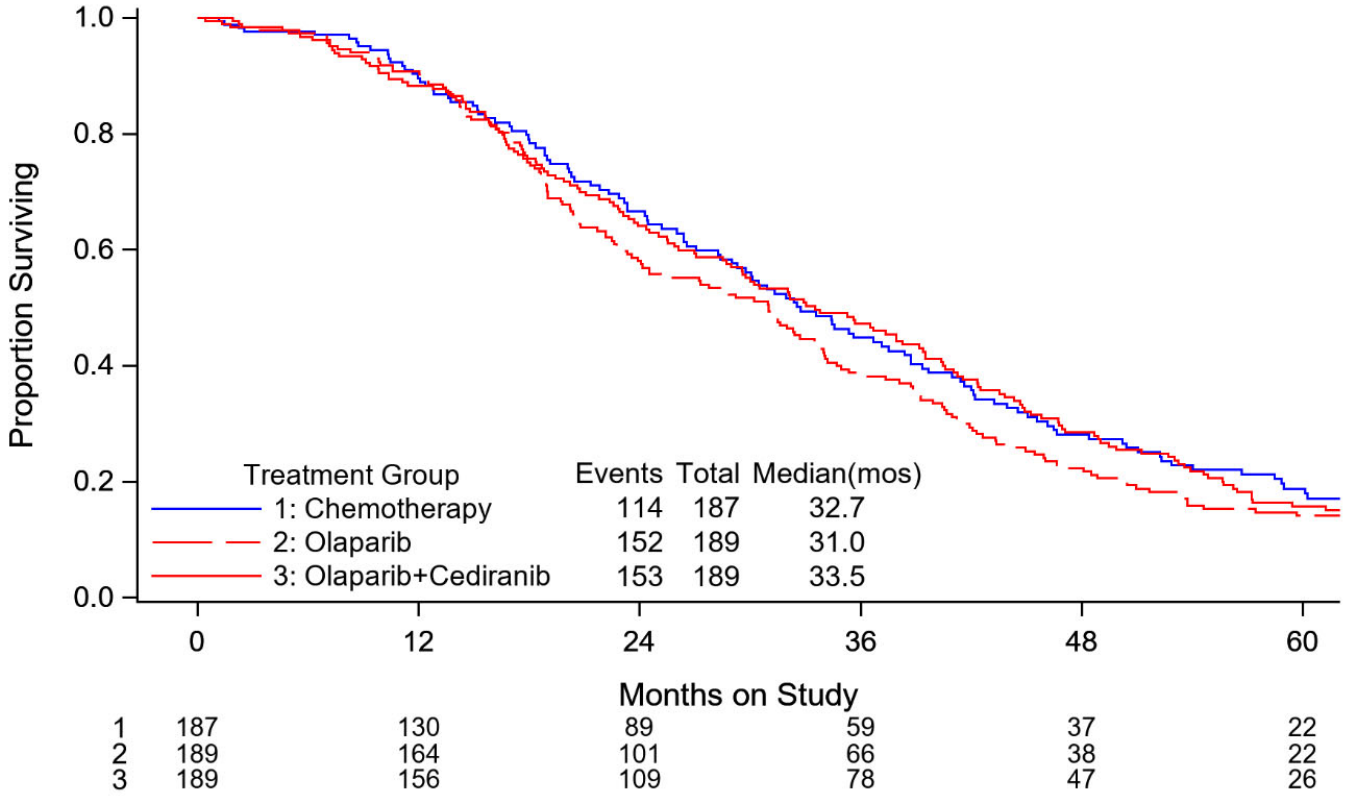
Overall Survival



Data cut-off March 7, 2023

	Chemo†	Cediranib + Olaparib	Olaparib
# of Pts	187	189	189
# of Events	114	153	152
Median OS (mos)	**32.7**	**33.5**	**31.0**
HR for OS vs chemo (95% CI)	--	1.12 (0.874-1.43)	1.27 (0.990-1.62)
Nominal p value	--	0.378	0.060

†Choice of chemotherapy, N (%)
- Carboplatin/PLD: 89 (47.6%)
- Carboplatin/gemcitabine: 51 (27.2%)
- Carboplatin/paclitaxel: 47 (25.1%)

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2023 ASCO ANNUAL MEETING

Phase III MIRASOL (GOG 3045/ENGOT-ov55) Study: Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancers with High Folate Receptor-Alpha (FRα) Expression

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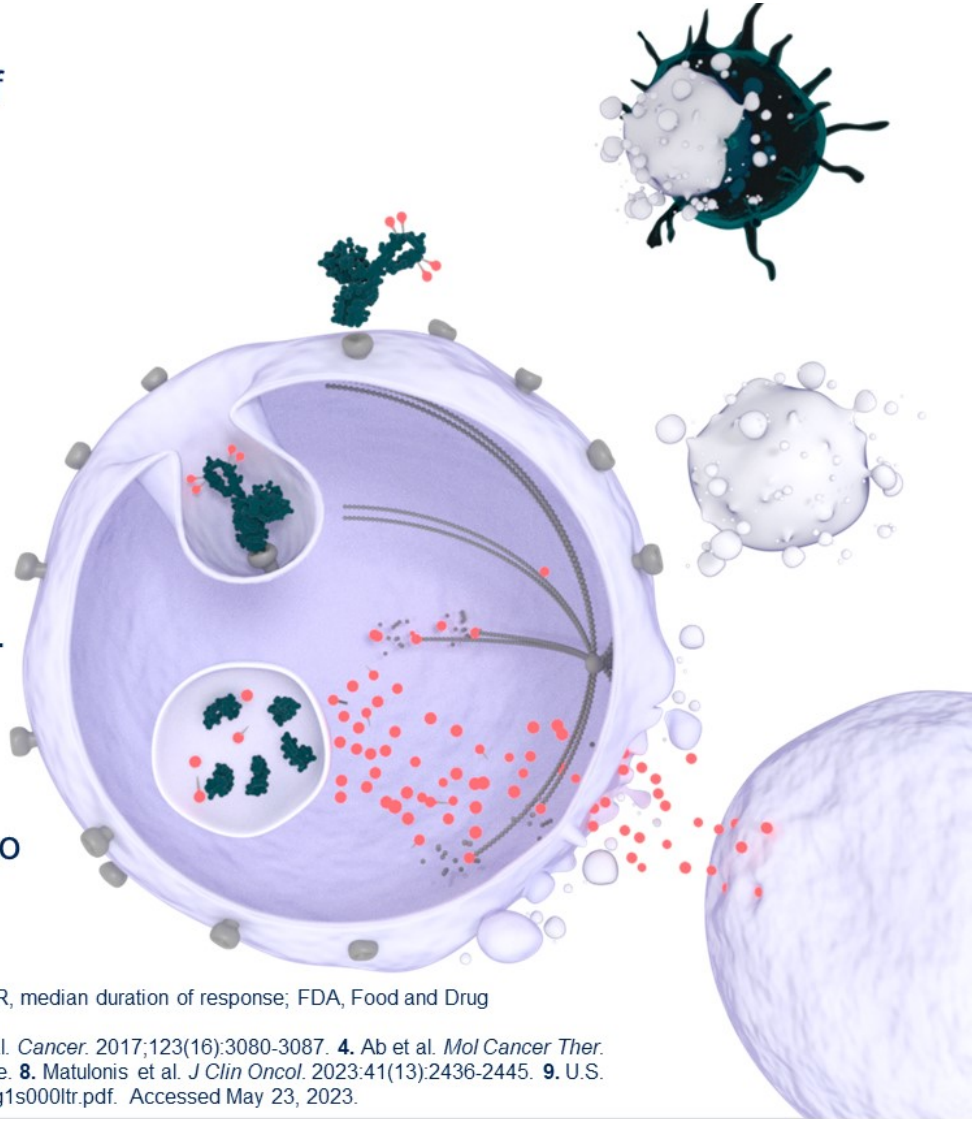
Background

- No randomized phase 3 trial has shown an overall survival (OS) benefit of a novel therapy in platinum-resistant ovarian cancer (PROC)[1, 2]
- Mirvetuximab soravtansine (MIRV) is an ADC comprising a FRα-binding antibody, cleavable linker, and maytansinoid DM4, a potent tubulin-targeting agent[3,4]
- FRα is expressed in ~90% of ovarian carcinomas,[5, 6] with 35-40%[7] of PROC tumors exhibiting high FRα expression (≥75% of tumor cells positive with ≥2+ intensity)[8]
- MIRV demonstrated an ORR of 32% and mDOR 6.9 months in the single-arm study SORAYA[8] of BEV pre-treated PROC to support accelerated approval by the FDA[9]
- MIRASOL is the confirmatory, randomized, global phase 3 trial designed to support approval worldwide



PFS, progression-free survival; OS, overall survival; FRα, folate receptor alpha; ORR, objective response rate; ADC, antibody-drug conjugate; mDOR, median duration of response; FDA, Food and Drug Administration; BEV, bevacizumab; US, United States; EU, Europe.

1. Pujade-Lauraine et al. *J Clin Oncol*. 2014;32(13):1302-1308. **2.** Richardson et al. *JAMA Oncol*. 2023;10.1001/jamaoncol.2023.0197. **3.** Moore et al. *Cancer*. 2017;123(16):3080-3087. **4.** Ab et al. *Mol Cancer Ther*. 2015;14(7):1605-1613. **5.** Markert et al. *Anticancer Res*. 2008;28(6A):3567-3572. **6.** Martin et al. *Gynecol Oncol*. 2017;147(2):402-407. 7. Data on file. **8.** Matulonis et al. *J Clin Oncol*. 2023:41(13):2436-2445. **9.** U.S. FOOD & DRUG ADMINISTRATION. BLA ACCELERATED APPROVAL. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/761310Orig1s000ltr.pdf. Accessed May 23, 2023.

Design

MIRASOL (NCT04209855)

An open-label, phase 3 randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer

Patient Population
(N=453)

Enrollment and Key Eligibility

Platinum-resistant disease
(PFI ≤6 mo)

FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells

High-grade serous histology

1º platinum-refractory disease excluded (primary PFI <3 mo)

1-3 prior lines of therapy

Prior BEV and PARPi allowed

Patients with BRCA mutations allowed

1:1 Randomization

Treatment Regimen-Experimental

MIRV
(6 mg/kg AIBW Q3W)

Treatment Regimen-Control

Investigator's Choice Chemotherapy
(Paclitaxel, PLD, or Topotecan)

Stratification Factors

IC chemo: paclitaxel, PLD, or topotecan
Prior lines of therapy: 1 vs 2 vs 3

Primary Endpoint

PFS by INV
(BICR sensitivity analysis)

Key Secondary Endpoints

1) ORR by INV
2) OS
3) PROs[a]

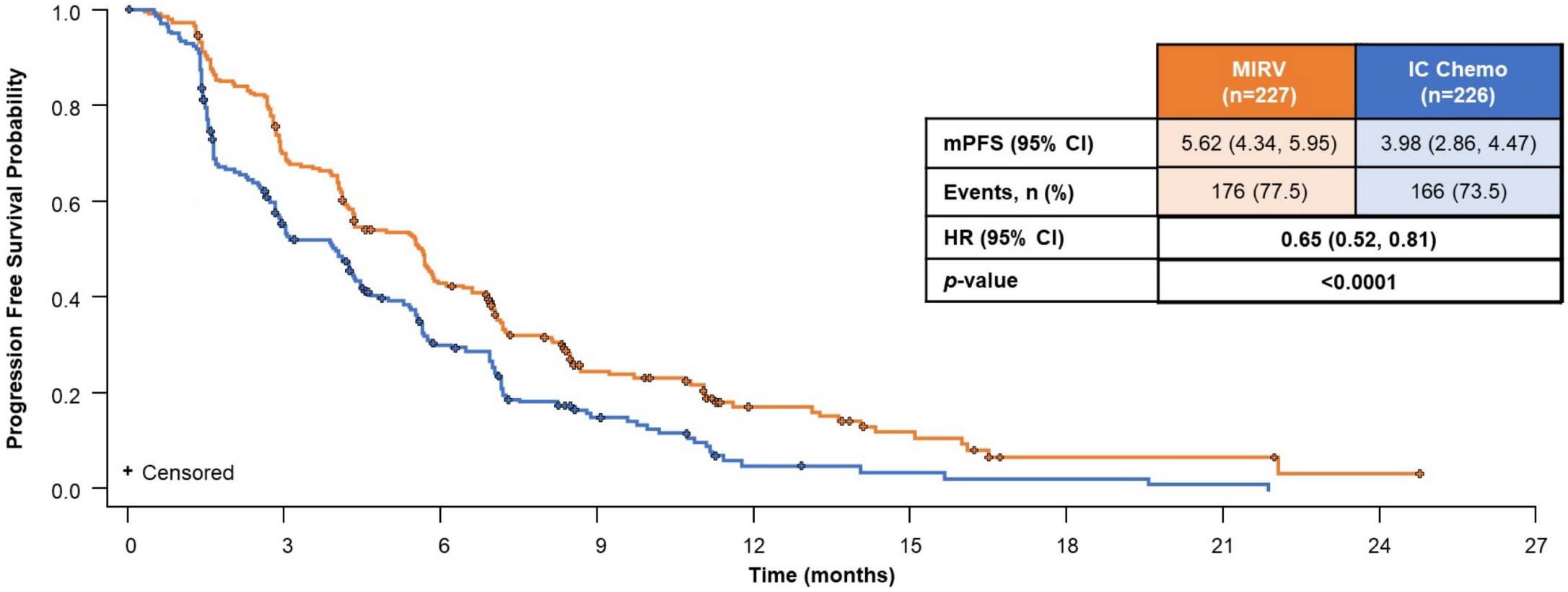
Secondary Endpoints

Safety and tolerability
DOR
CA-125 response[b]
PFS2

AIBW, adjusted ideal body weight; BEV; bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.
[a]PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument.
[b]Gynecological Cancer InterGroup (GCIG) criteria.

1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855
2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

Primary End Point: PFS by Investigator

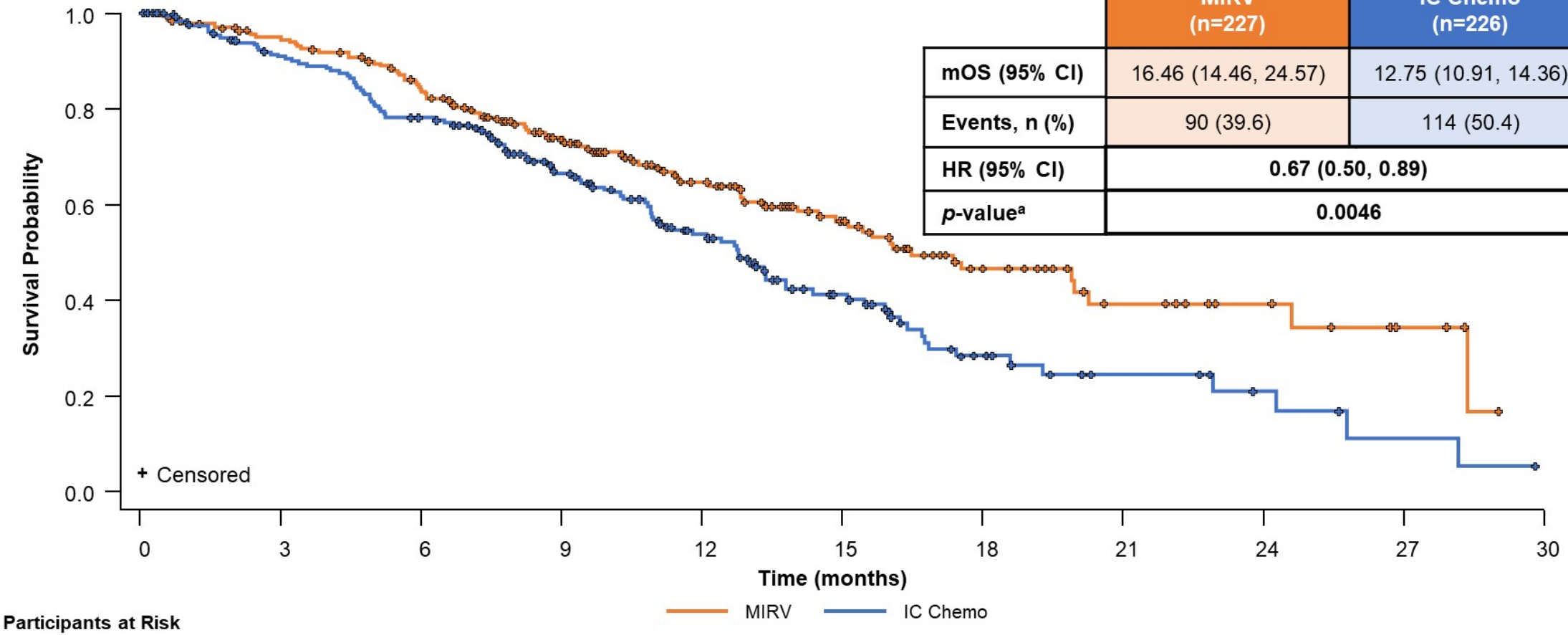


	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	0.65 (0.52, 0.81)	
p-value	<0.0001	

Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio.

Overall Survival

	MIRV (n=227)	IC Chemo (n=226)
mOS (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	0.67 (0.50, 0.89)	
p-value[a]	0.0046	

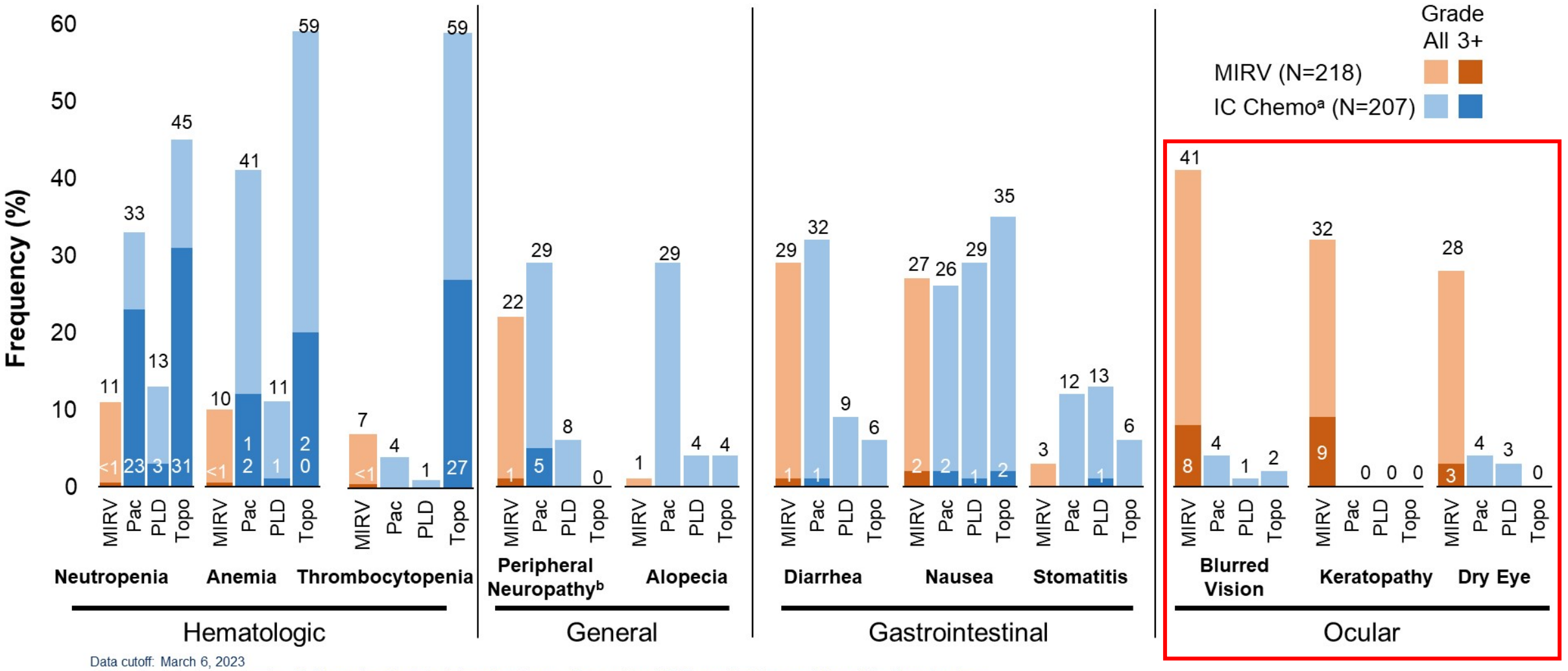


No. Participants at Risk

MIRV	227	204	175	128	82	53	28	15	9	4	0
IC Chemo	226	185	157	107	68	39	18	9	5	2	0

Data cutoff: March 6, 2023; median follow-up time: 13.11 months
MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mOS, median overall survival; CI, confidence interval; HR, hazard ratio.
[a]Overall survival is statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313

Safety Profile: TEAEs



Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo: investigator's choice chemotherapy; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan.

[a]Pac n=82 (39%), PLD n=76 (37%), Topo n=49 (24%). [b]Grade 2+ peripheral neuropathy events were observed in 12% and 16% of patients that received MIRV or paclitaxel, respectively.

MIRASOL Conclusions

- MIRV is the first novel treatment to **demonstrate a benefit in overall survival** in platinum-resistant ovarian cancer in a phase 3 trial
- MIRV demonstrated statistically significant and clinically meaningful **improvement in PFS, ORR, and OS** compared to IC chemotherapy, with a differentiated safety profile consisting predominantly of low-grade ocular and gastrointestinal events
- MIRV is the **first ADC for ovarian cancer** with proven efficacy and is the only FDA-approved biomarker-directed therapy for platinum-resistant ovarian cancer
- These data are practice-changing and position MIRV as a **new standard of care** for patients with FRα-positive PROC

Courtesy of Richard T Penson, MD, MRCP

Implications of Recent Data Sets for the Current and Future Management of Breast Cancer

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