Thank you for joining us.
The program will commence momentarily.

The Evolving Role of PARP Inhibition in the Management of Ovarian Cancer

Wednesday, July 29, 2020

5:00 PM – 6:00 PM ET

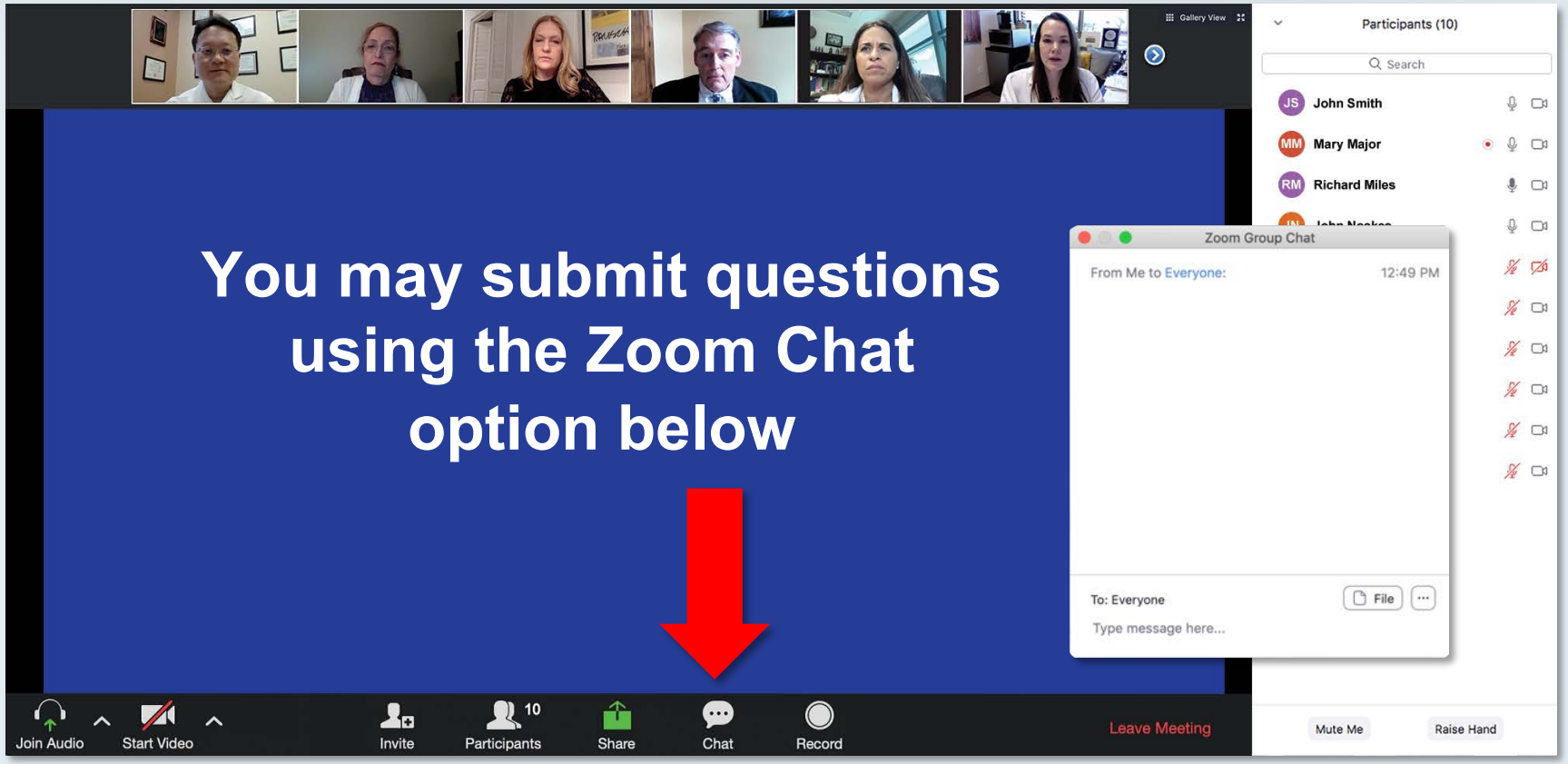
Faculty

Mansoor Raza Mirza, MD
Kathleen Moore, MD
Shannon N Westin, MD, MPH

Moderator

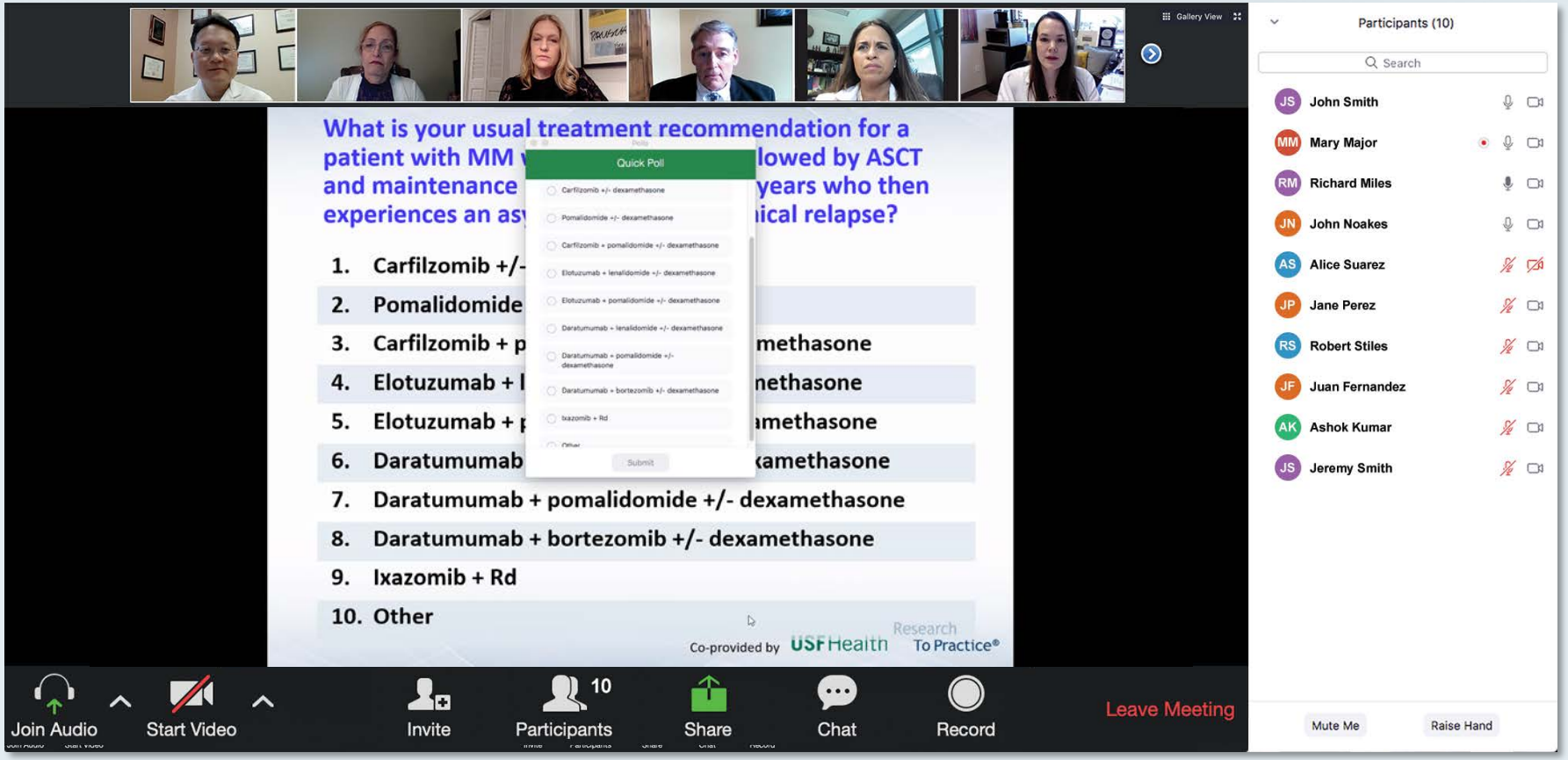
Neil Love, MD

Dr Love and Faculty Encourage You to Ask Questions



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

Familiarizing yourself with the Zoom interface
How to answer poll questions



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Dr Love — Disclosures

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Upcoming Live Webinars

Thursday, July 30, 2020
12:00 PM – 1:00 PM ET

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

Faculty
Rafael Fonseca, MD

Moderator
Neil Love, MD

Friday, July 31, 2020
9:00 AM – 10:00 AM ET

Virtual Molecular Tumor Board: Role of Genomic Profiling for Patients with Solid Tumors and the Optimal Application of Available Testing Platforms

Faculty
Andrew McKenzie, PhD
Bryan P Schneider, MD
Milan Radovich, PhD

Moderator
Neil Love, MD

Upcoming Live Webinars

Monday, August 3, 2020
5:00 PM – 6:00 PM ET

Recent Advances in Medical Oncology: Urothelial Bladder Carcinoma

Faculty
Arjun Balar, MD
Thomas Powles, MBBS, MRCP, MD
Arlene Siefker-Radtke, MD

Moderator
Neil Love, MD

Tuesday, August 4, 2020
12:00 PM – 1:00 PM CT

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

Faculty
Shaji K Kumar, MD

Moderator
Neil Love, MD

Upcoming Live Webinars

Wednesday, August 5, 2020
5:00 PM – 6:30 PM ET

Recent Advances in Medical Oncology: Immunotherapy and Other Nontargeted Approaches for Lung Cancer

Faculty

Edward B Garon, MD, MS
Stephen V Liu, MD
David R Spigel, MD

Moderator

Neil Love, MD

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Medical Director
Nordic Society of Gynaecological Oncology
Vice-Chairman
Danish Society of Gynaecologic Oncology
Executive Director, Gynecologic Cancer InterGroup
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Director, Gynecologic Oncology Fellowship
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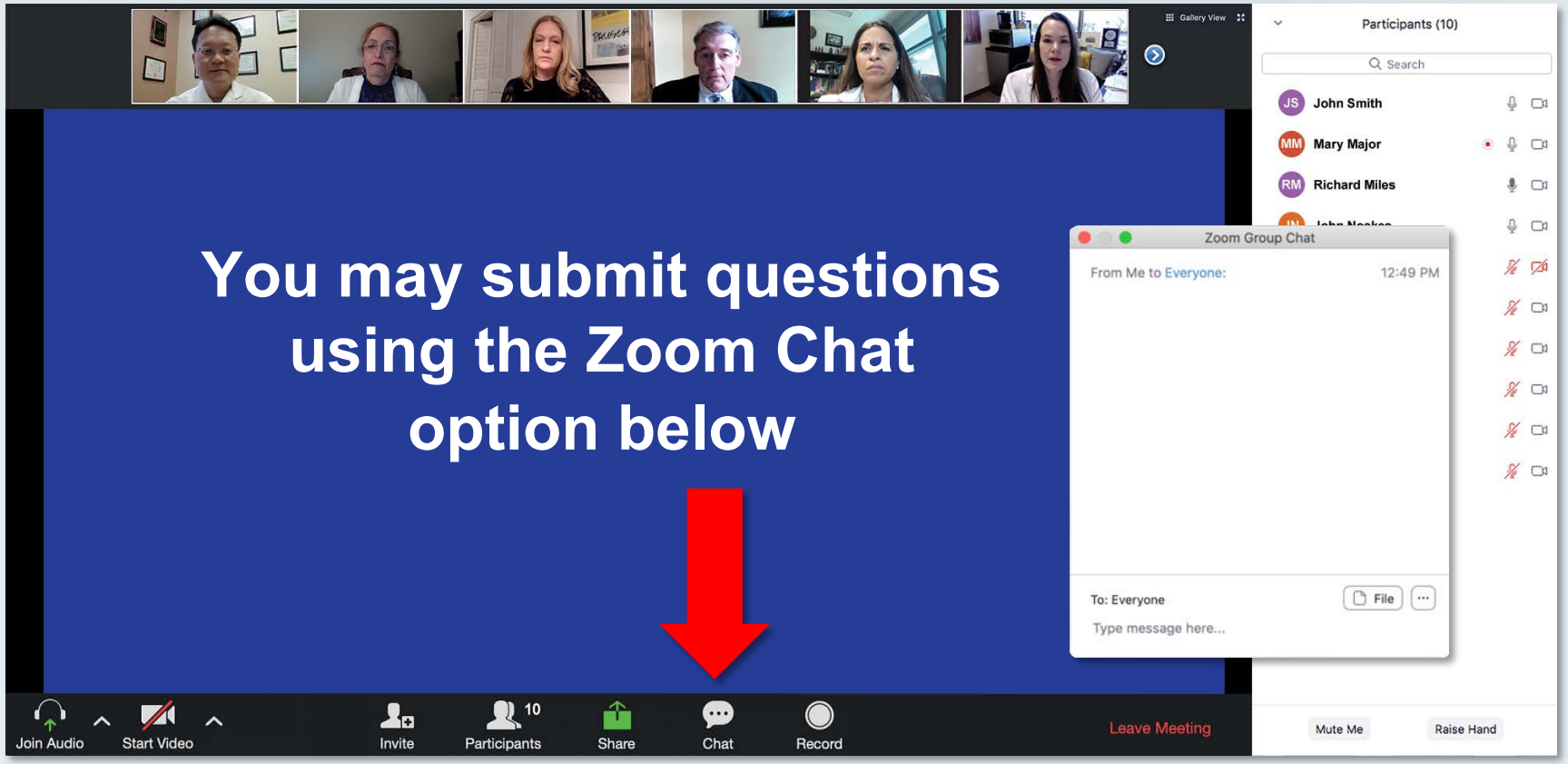

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Co-provided by USF Health RTP RESEARCH TO PRACTICE

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Identification of New and Emerging Genomic Alterations in Metastatic Non-Small Cell Lung Cancer

Friday, August 7, 2020
9:00 AM – 10:00 AM ET

Alexander E Drilon, MD

Recognition and Management of Targetable Tumor Mutations in Less Common Cancer Types

Friday, August 14, 2020
9:00 AM – 10:00 AM ET

Marcia S Brose, MD, PhD

All sessions moderated by Neil Love, MD and featuring Bryan Schneider, MD and Milan Radovich, PhD of the Indiana University Health Precision Genomics Program

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Agenda

Module 1: PARP Inhibitor Maintenance in the Up-Front Setting

- Genomic Evaluation
- Key Clinical Trial Results
  - SOLO-1, PRIMA, PAOLA-1, VELIA
- “Top 15” Clinical Questions

Module 2: Future Directions of PARP Inhibitors

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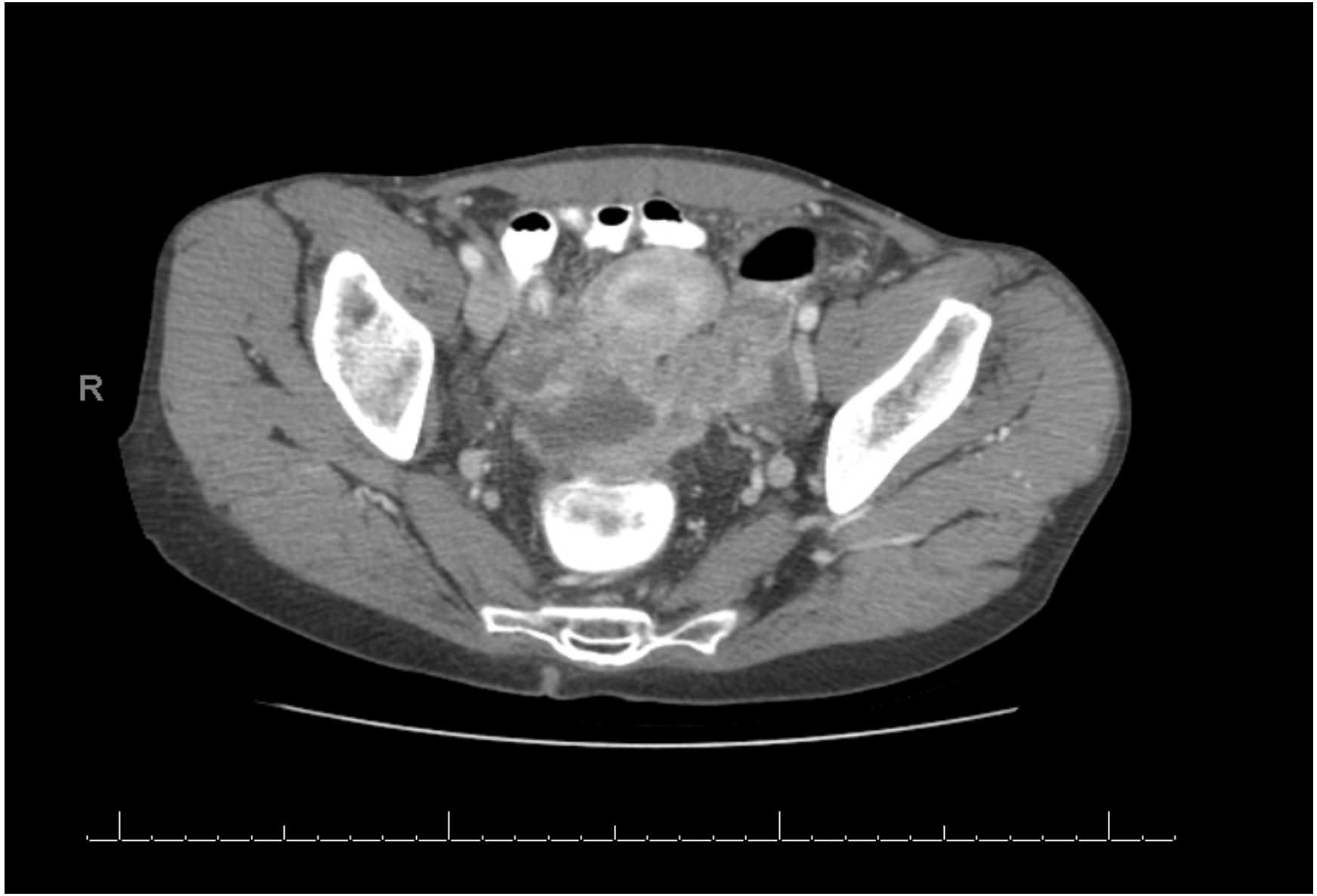
- Genomic Evaluation
- Key Clinical Trial Results
  - SOLO-1, PRIMA, PAOLA-1, VELIA
- “Top 15” Clinical Questions

Module 2: Future Directions of PARP Inhibitors

A 44-year-old woman with Stage III ovarian cancer (OC) and a somatic BRCA mutation undergoes optimal debulking surgery, then 6 cycles of carboplatin/paclitaxel. Would you offer PARP inhibitor maintenance?

a. No
b. Yes, olaparib for 2 years
c. Yes, olaparib for 3 years
d. Yes, niraparib for 2 years
e. Yes, niraparib for 3 years

Case Presentation – Dr Westin: A 44-Year-Old Woman with High-Grade Serous Ovarian Cancer



Case Presentation – Dr Westin: A 44-Year-Old Woman with High-Grade Serous Ovarian Cancer (cont'd)

- She undergoes optimal tumor reductive surgery to no gross residual disease.
- Final pathology: high grade serous ovarian cancer involving bilateral ovaries, uterine serosa, omentum and diaphragm.
- Germline *BRCA* wildtype
- Somatic *BRCA* positive

Case Presentation – Dr Westin: A 44-Year-Old Woman with High-Grade Serous Ovarian Cancer (cont'd)

- She receives 6 cycles of IV carboplatin and paclitaxel. She is NED at the completion of treatment.
- Post-treatment toxicity includes minimal neuropathy
- She is started on olaparib 300 mg PO BID

BRCA mutations in ovarian cancers

- *BRCA*-deficient tumour cells are defective in HRR and are dependent on alternative DNA repair pathways[1,2]

- *BRCA*-deficient cells are particularly sensitive to PARP inhibitors[1] targeting other DNA repair pathways

- Hallmarks of BRCA1/2-associated ovarian cancers include
  - sensitivity to platinum chemotherapy
  - improved overall survival
  - sensitivity to PARP inhibitors.

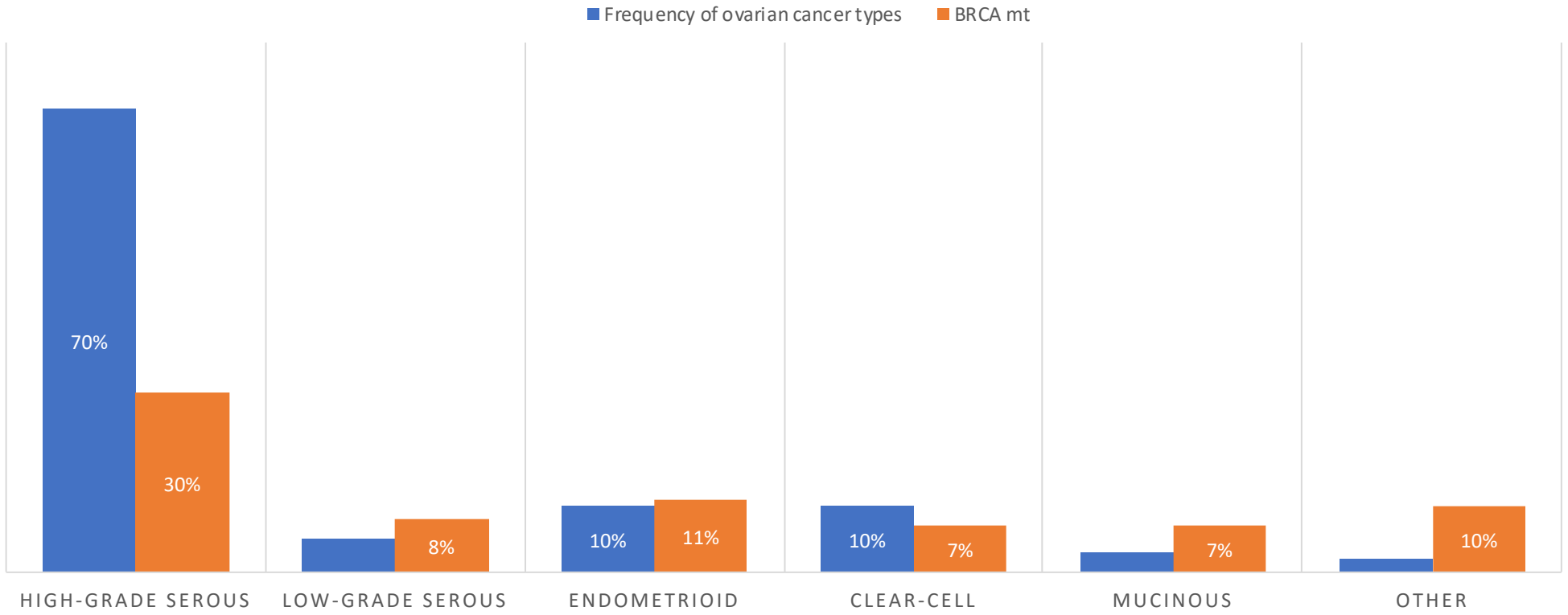
- In addition to BRCA1/2, mutations in other genes may affect the HRR pathway and increase sensitivity to DNA-damaging agents[4]

1. Walsh CS, et al. *Gynecol Oncol*. 2015;137(2):343–50; 2. Pennington KP, et al. *Clin Cancer Res*. 2014;20:764–775;
3. Ledermann JA, et al. *Ann Oncol*. 2013;24(Suppl 6):vi24–32; 4. Girolimetti G, et al. *Biomed Res Int*. 2014;787143; 5. Burgess M and Puhalla S. *Front Oncol*. 2014;4:19. 3. Pennington KP, et al. Clin Cancer Res. 2014;20:764–775; 4. Bolton KL, et al. JAMA. 2012;307:382–390.

Courtesy of Mansoor Raza Mirza, MD

Percentage of ovarian cancer patients, by histology, with germline BRCA1 or BRCA2 mutations

In unselected population studies, BRCA mutations are most frequently associated with high-grade serous OC and to a lesser extent with low-grade serous carcinoma; other homologies also harbour BRCA mutations.



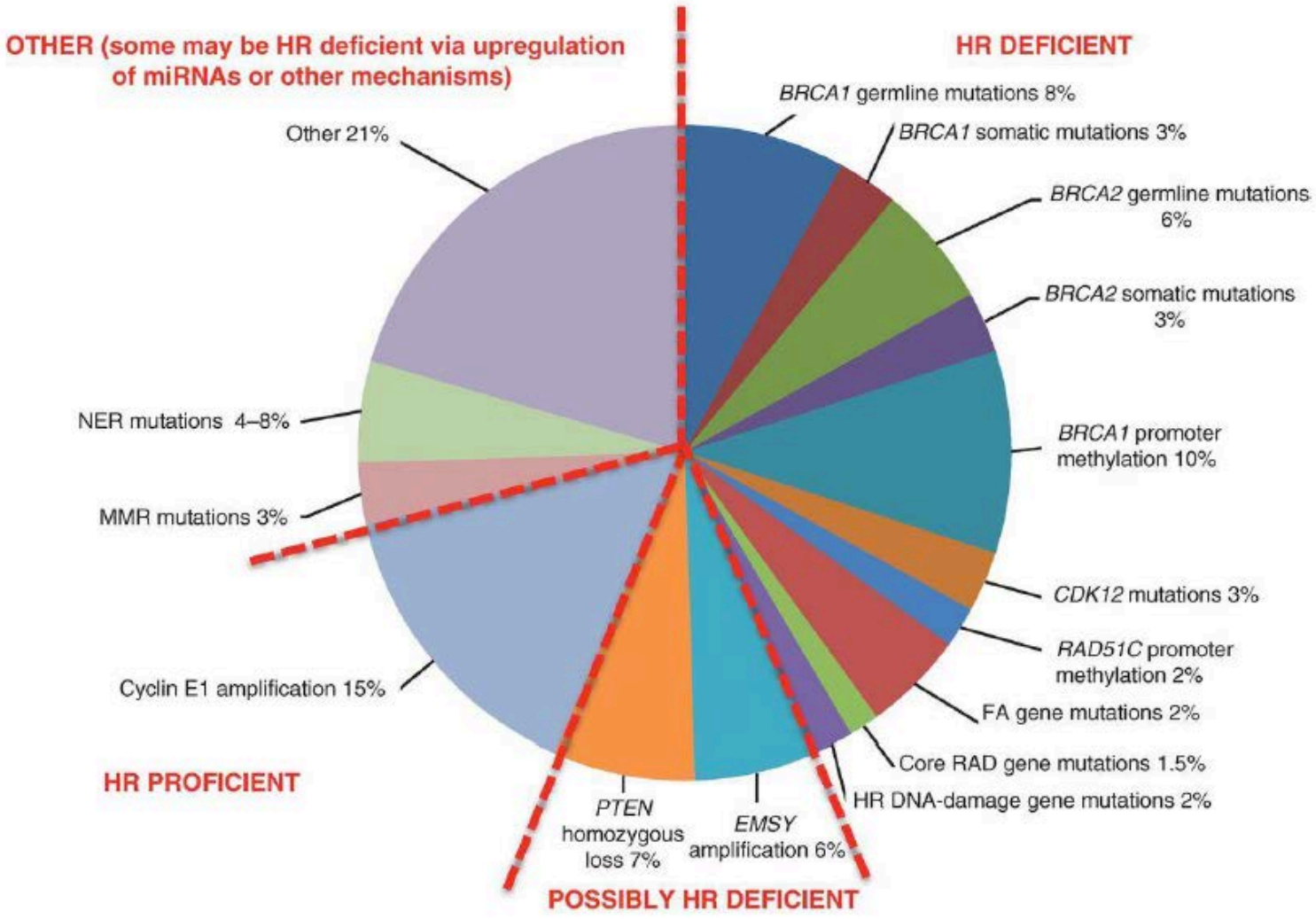
1. Prat J.. Ann Oncol 2012; 23(10): 111-117; 2. Alsop K, et al. J Clin Oncol 2012;30:2654□63; 3. Schrader KA, et al. Obstet Gynecol 2012;120:235–40; 4. Moschetta M, et al. BRCA somatic mutations and epigenetic BRCA modifications in serous ovarian cancer. Ann Oncol 2016;27:1449e55 ; Li, A., et al. Gynecol Oncol 2018;151:145

Courtesy of Mansoor Raza Mirza, MD

Homologous Recombination Defects in High-Grade Serous Ovarian Cancer

- Ovarian Cancer is a genetically heterogeneous disease

- *BRCA*1/2 deleterious mutations or chromosomal damage result in similar biology



Levine D. *The Cancer Genome Atlas, 2011*
Konstantinopoulos et al. *Cancer Discov 2015*

Courtesy of Mansoor Raza Mirza, MD

Guidelines

ESMO-ESGO

Testing for BRCA1/2 mutations is recommended for all patients with non-mucinous ovarian cancer. [1]

ASCO

All women diagnosed with epithelial OC should have germline genetic testing for BRCA1/2 and other ovarian cancer susceptibility genes. In women who do not carry a germline BRCA1/2 variant, somatic tumor testing should be performed. Women with epithelial OC should have testing at the time of diagnosis. [2]

SGO

BRCA testing for all patients with epithelial ovarian, tubal & peritoneal cancers even in the absence of family history. [3]

1- Colombo N et al. Annals of Oncology 2019;30:672-705

2- DOI: 10.1200/JCO.19.02960 Journal of Clinical Oncology

3- SGO Clinical Practice Statement: Genetic Testing for Ovarian Cancer Oct 2014: accessed April 2018: available at https://www.sgo.org/clinical-practice/guidelines/genetic-testing-for-ovarian-cancer/

Courtesy of Mansoor Raza Mirza, MD

Key takeaways…

- **Gynecologists are important stake holders** for early detection of BRCA1/2 mutations in ovarian cancer for an informed treatment decision later
- **All ovarian cancer patients** should be tested for BRCA1/2 mutations at diagnosis
- **Early detection of mutations** in ovarian cancer will help in taking the right treatment decision
- **Extended panel testing/next-generation sequencing** is the recommended method of testing

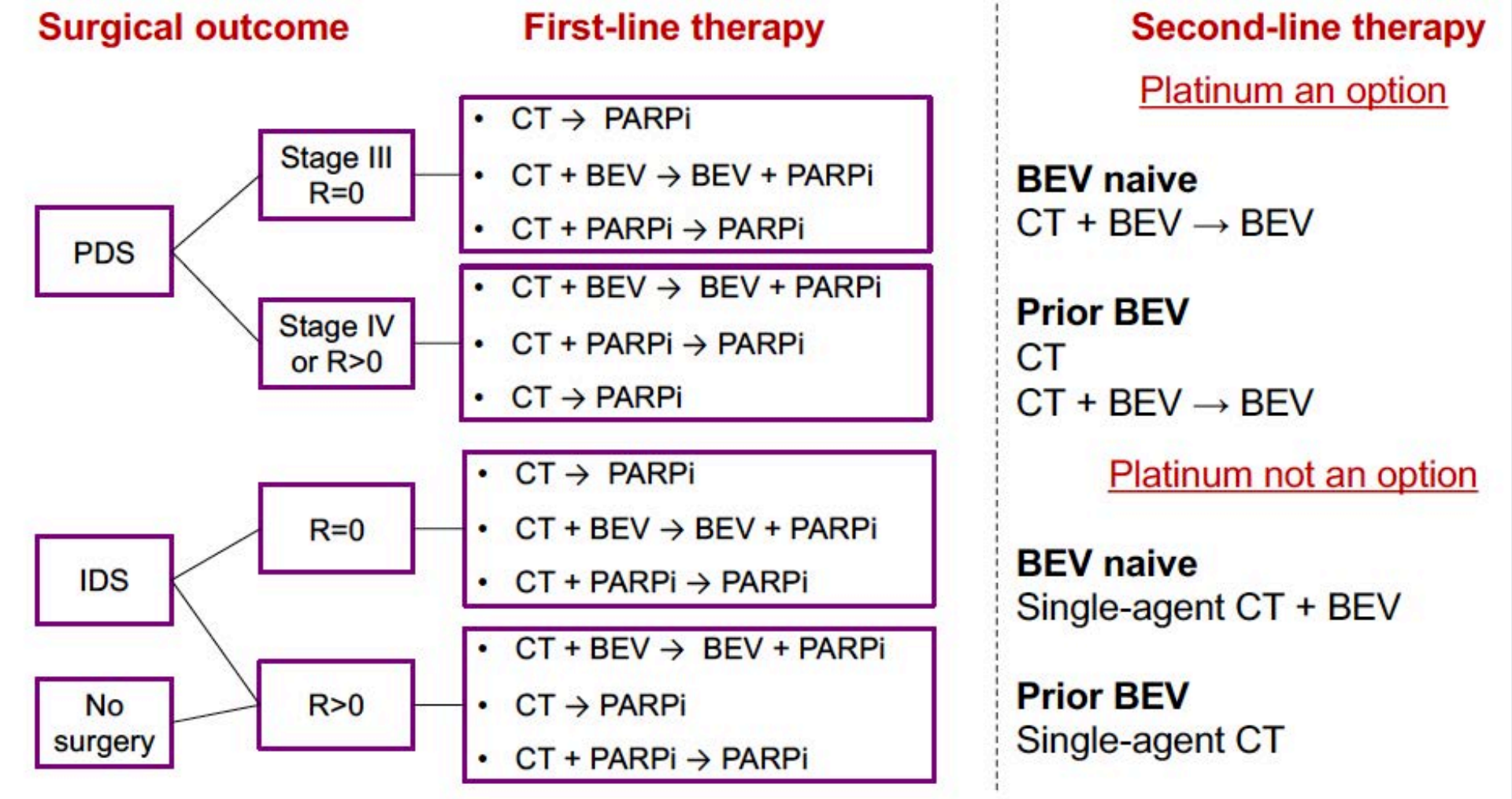
Courtesy of Mansoor Raza Mirza, MD

The Forefront of Ovarian Cancer Therapy: Update on PARP inhibitors

M.R. Mirza, R.L. Coleman, A. González-Martín, K.N. Moore, N. Colombo, I. Ray-Coquard, S. Pignata

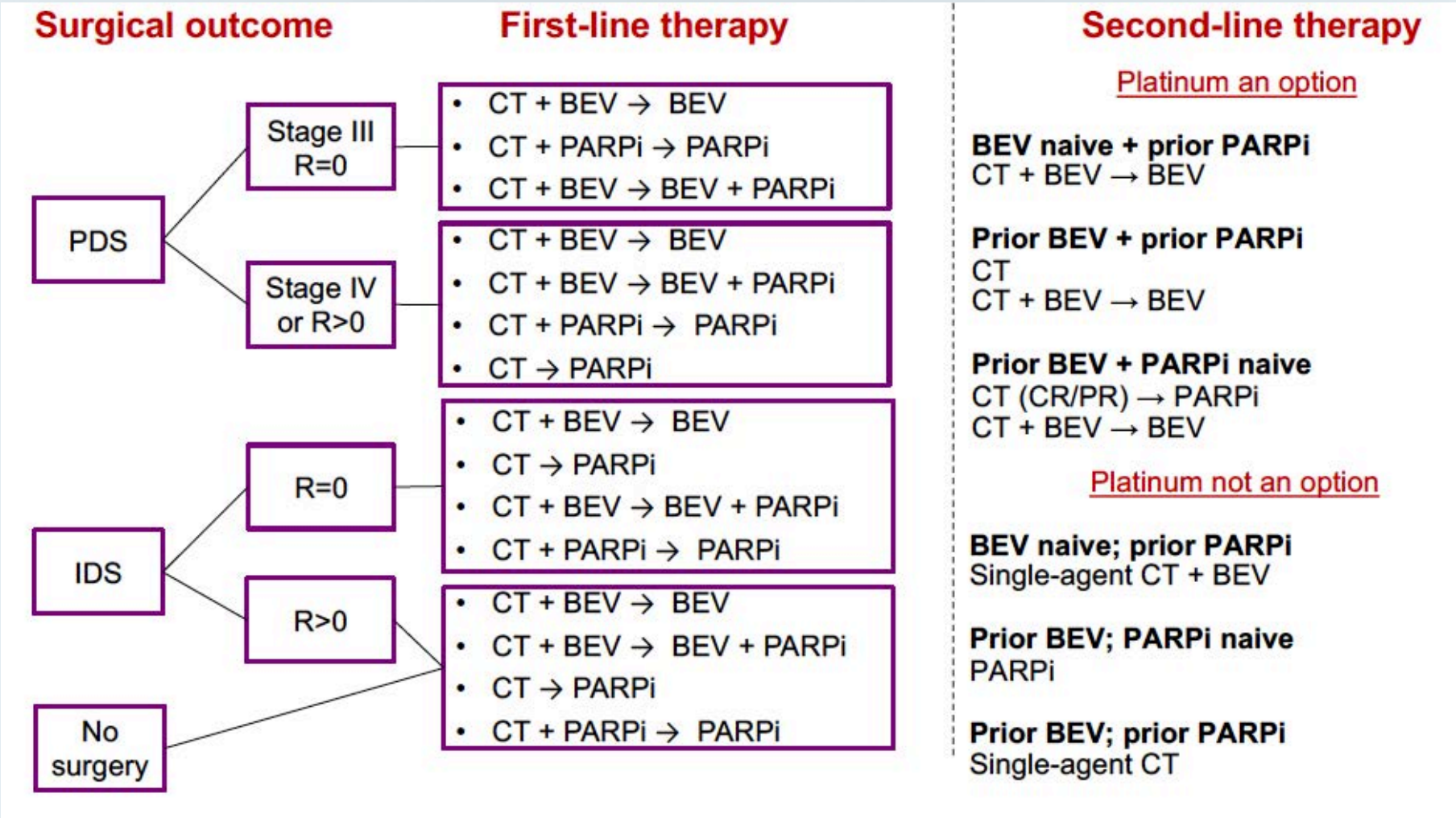
Ann Oncol **2020 Jun 19;[Epub ahead of print].**

Stage III-IV; BRCA Mutated



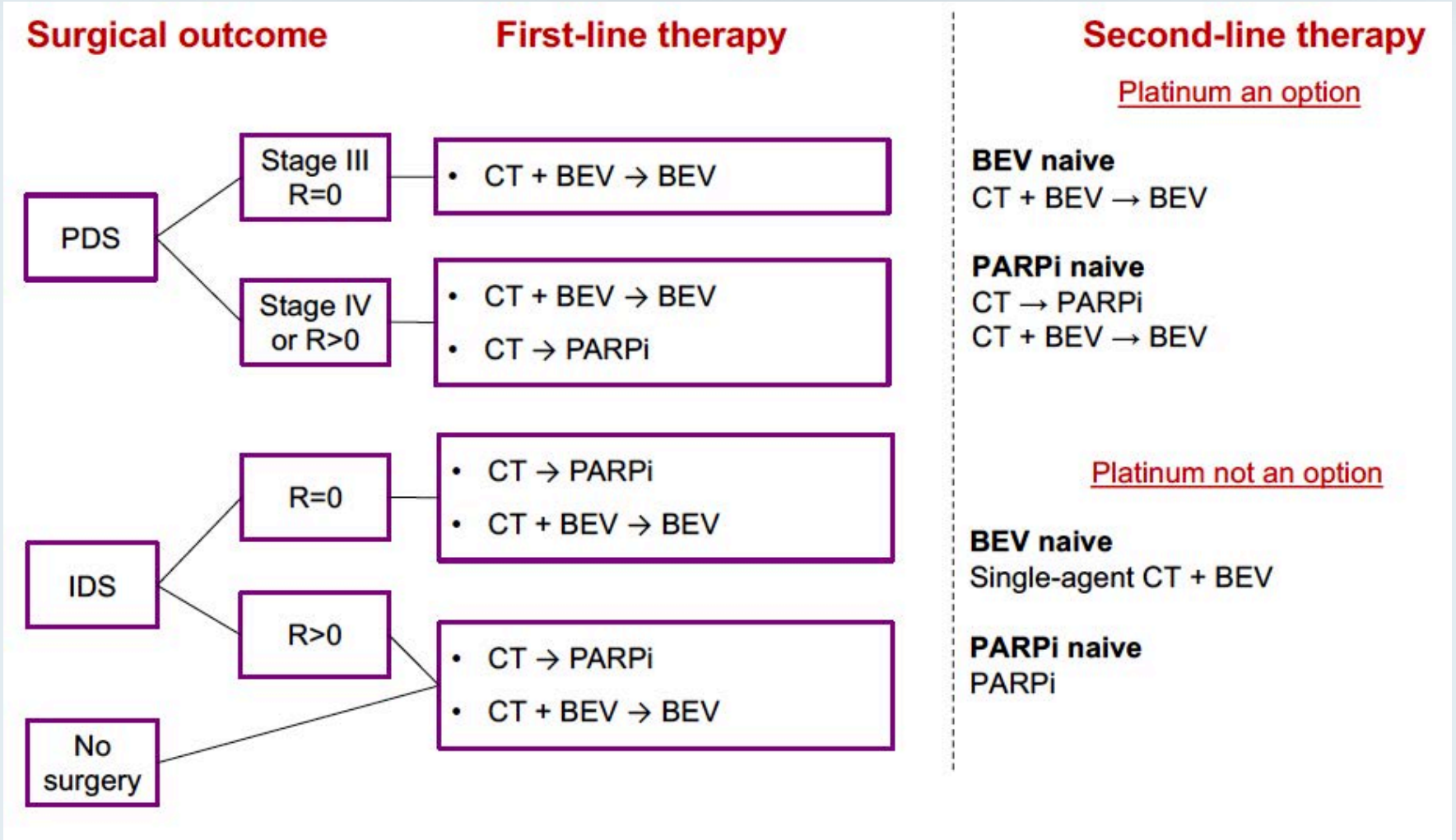
Mirza MR et al. *Ann Oncol* 2020;[Epub of ahead print].

Stage III-IV; non-BRCA Mutated; HRD-Positive



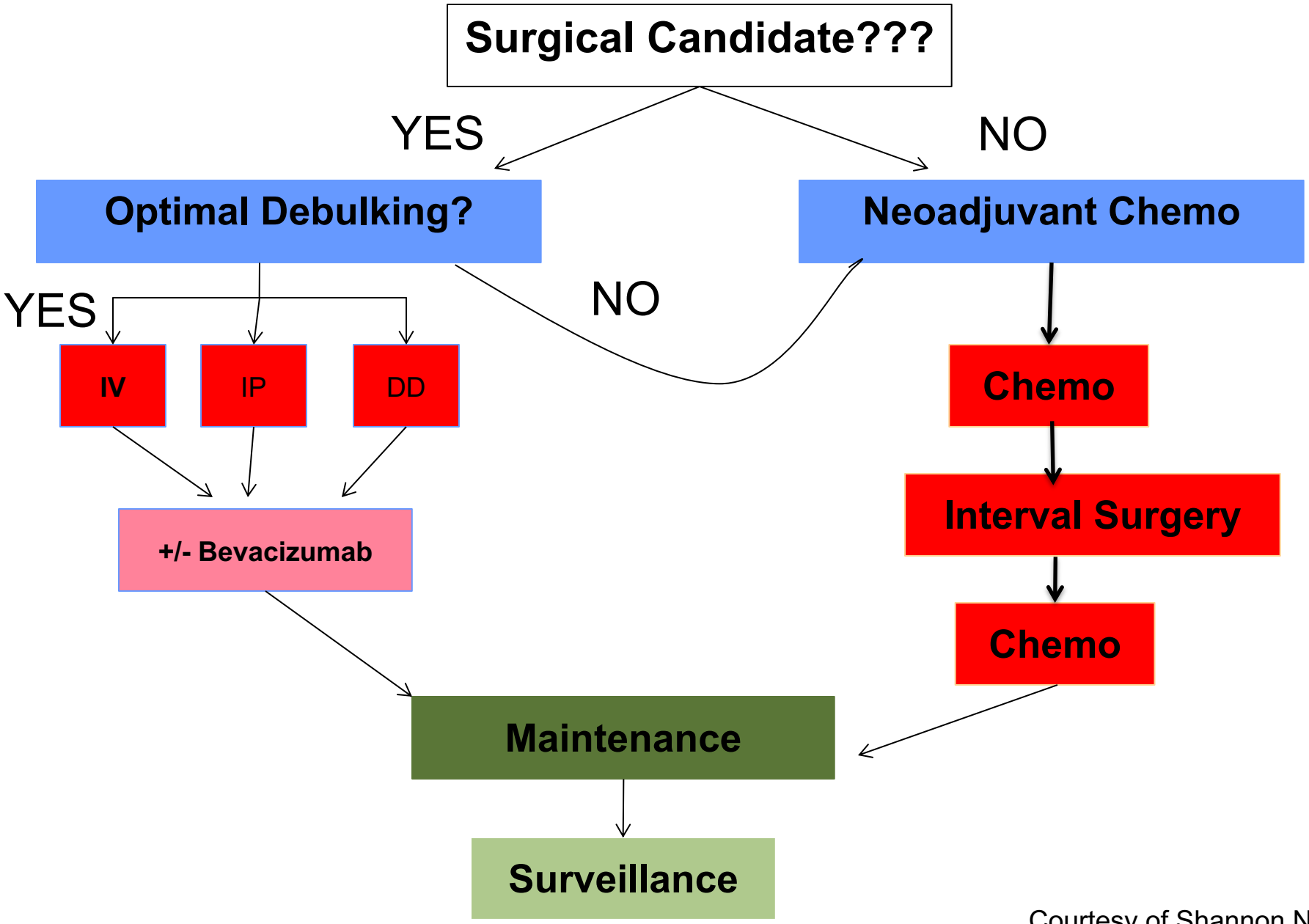
Mirza MR et al. *Ann Oncol* 2020;[Epub of ahead print].

Stage III-IV; non-BRCA Mutated; HRD-Negative



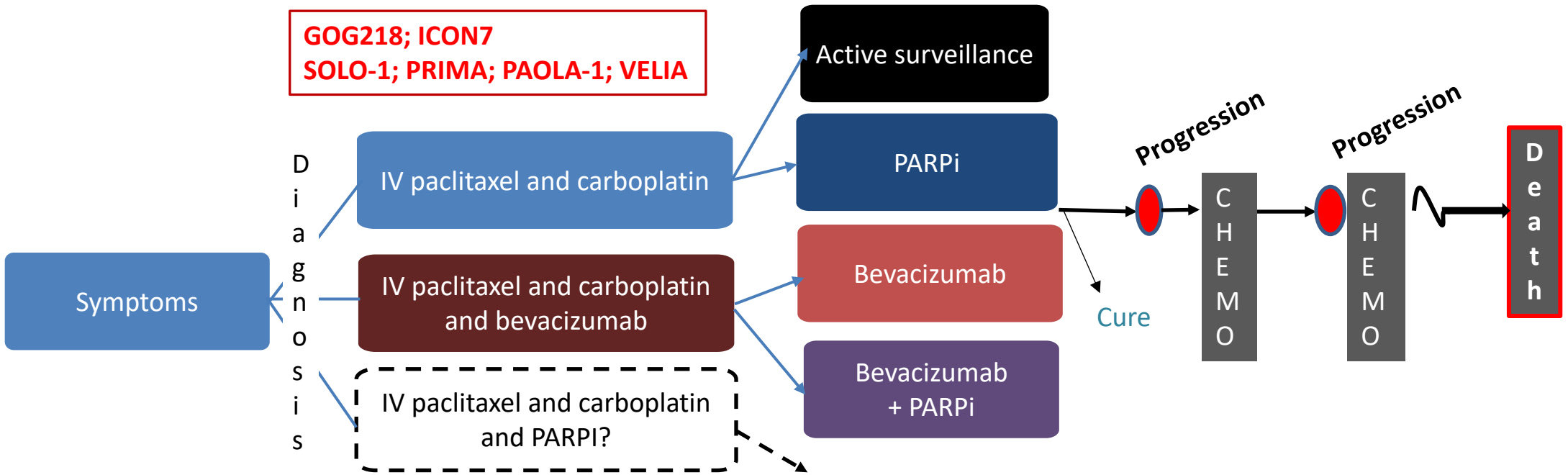
Mirza MR et al. *Ann Oncol* 2020;[Epub of ahead print].

New Advanced Ovarian Cancer



Courtesy of Shannon N. Westin, MD, MPH

2020 Treatment Paradigm: Frontline Therapy for Ovarian Cancer



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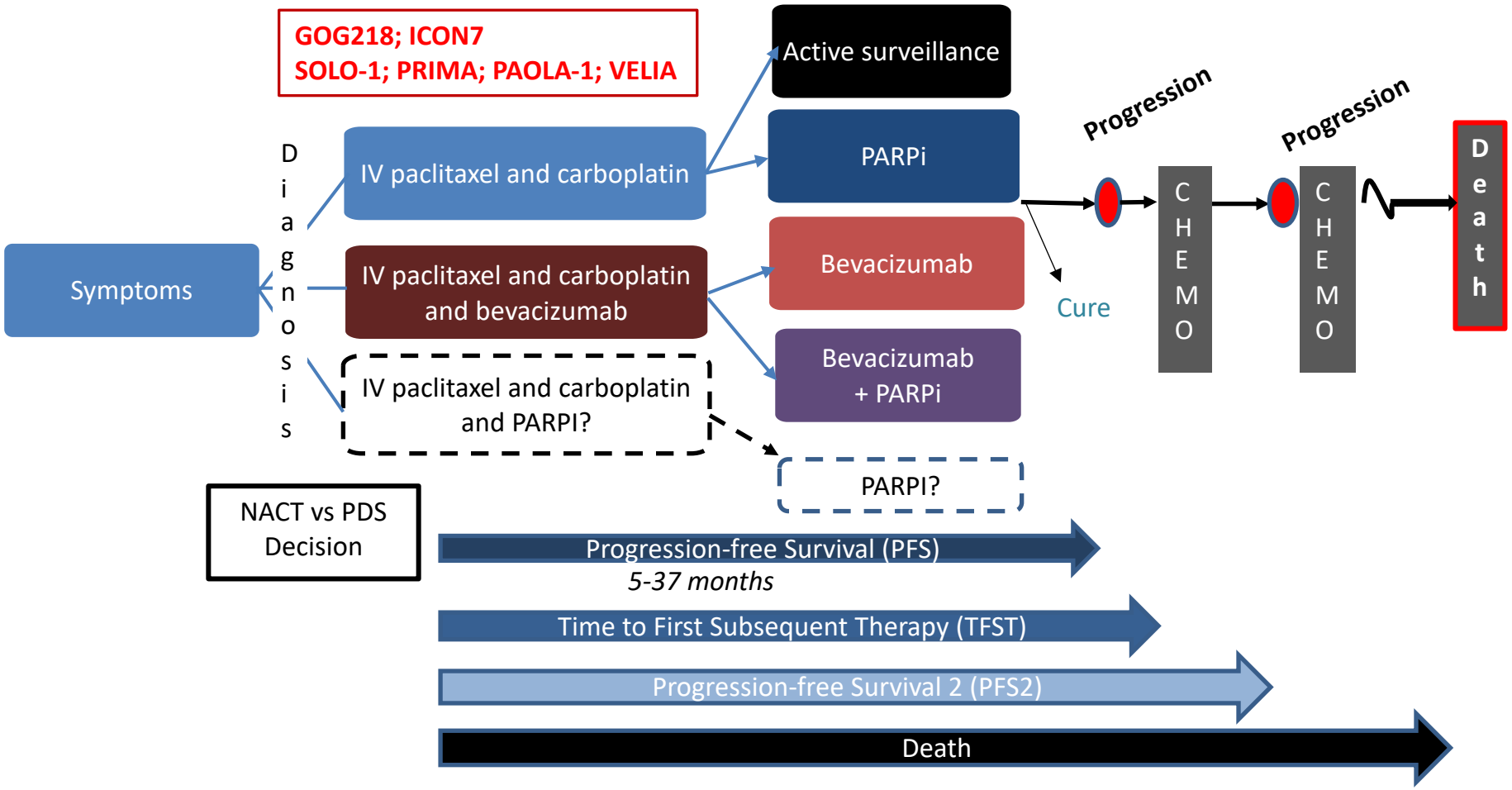
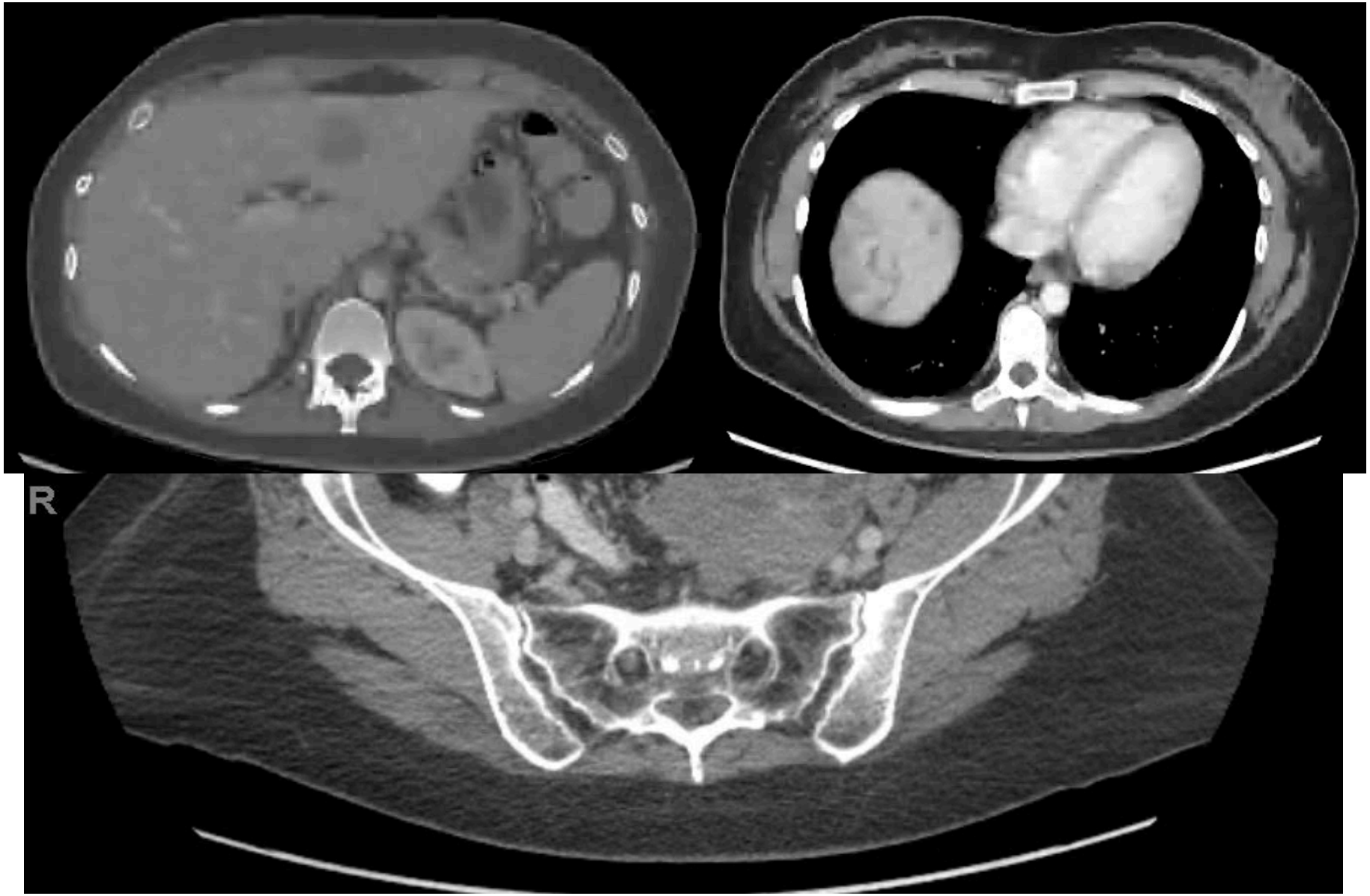


Courtesy of Shannon N. Westin, MD, MPH

Case Presentation – Dr Westin: A 66-Year-Old Woman with High-Grade Serous Ovarian Cancer



Case Presentation – Dr Westin: A 66-Year-Old Woman with High-Grade Serous Ovarian Cancer (cont'd)

- Core biopsy is obtained revealing high grade serous ovarian cancer
- She is started on neoadjuvant chemotherapy with paclitaxel, carboplatin, and bevacizumab x 3 cycles
  - Bev held cycle 3
- Germline/somatic *BRCA* wildtype
- HRD testing: genomic instability present

Case Presentation – Dr Westin: A 66-Year-Old Woman with High-Grade Serous Ovarian Cancer (cont'd)

- She undergoes interval tumor reductive surgery to R0
- Final pathology: residual high grade serous ovarian cancer in ovary, omentum, liver
- She completes additional 3 cycles of paclitaxel, carboplatin, and bevacizumab
  - bev held cycle 4
- Clinical complete response at the end of therapy
- No residual toxicity

Case Presentation – Dr Westin: A 66-Year-Old Woman with High-Grade Serous Ovarian Cancer (cont'd)

- Clinical complete response at the end of therapy
- No residual toxicity
- Continued on bevacizumab maintenance x 15 cycles with addition of olaparib maintenance x 2 years

Incorporating Maintenance Therapy

- Factors to consider
  - Indication
  - *BRCA*/HRD Status
  - Toxicity
  - Schedule
  - Type of prior therapy
  - Existing adverse events
  - Cost

Courtesy of Shannon N. Westin, MD, MPH

Phase 3 1L Maintenance Trials

Study Design		GOG-0218 (N=1873)	SOLO-1 (N=451)	PAOLA-1 (N=612)	PRIMA (N=620)	VELIA (N=1140)
Treatment arms vs placebo		Bevacizumab (n=625)	Olaparib (n=260)	Bevacizumab ± Olaparib	Niraparib	Veliparib
Patient Population		All comers	*BRCA* mutation	All comers	All comers	*All comers*
Undergo tumor testing		HRR (post-hoc)	*BRCA*	*BRCA*	HRD	*BRCA*
Stage	III	73.8%	84.6%	Eligible	Eligible: Attempt upfront debulking	Eligible
	IV	26.2%	15.4%	Eligible	Eligible: Any debulking attempts	Eligible
Surgery	Residual disease after surgery	Stage III incomplete • Macroscopic: 32.8% • >1 cm: 41.0%	Macroscopic[a] • Primary: 23.0% • Interval: 19.1%	NR[b]	Required for Stage III	Primary or Interval
	Inoperable disease	0	1.5%	NR[b]	Eligible	
Treatment Duration		15 months	24 months	15 months for Bev 24 months for Olaparib	36 months or until PD	24 months

[a]Residual disease based on stage was not reported. [b]Stage III and IV eligible, but requirements for prior surgery not reported (NR) on clinicaltrials.gov

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

Courtesy of Shannon N. Westin, MD, MPH

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Treatment Duration	24 months	15 months for Bev 24 months for Olaparib	36 months or until PD	24 months

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Courtesy of Shannon N. Westin, MD, MPH

Preclinical features of PARP inhibitors

PARP inhibitor	Olaparib tablets	Niraparib capsules	Rucaparib tablets	Talazoparib capsules	Veliparib tablets
PARylation IC_{50} (nM)[1] A549 UWB1.289 (*BRCA1*m)	 29 8	 317 89	 19 29	 2 2.5	 26 79
Clonogenic IC_{50} (nM)[1] UWB1.289 (*BRCA1*m)	63±19	98±30	123±54	1.2±0.3	~1000 (extrapolated)
Clinical doses (mg)	300 BID[2]	300 QD[3]	600 BID[4]	1 QD[5]	*In combination only*[6]
PARP-DNA trapping[7]	+	+	+	++	-

PARylation and clonogenic assays carried out in ovarian cancer, and adenocarcinoma cell lines

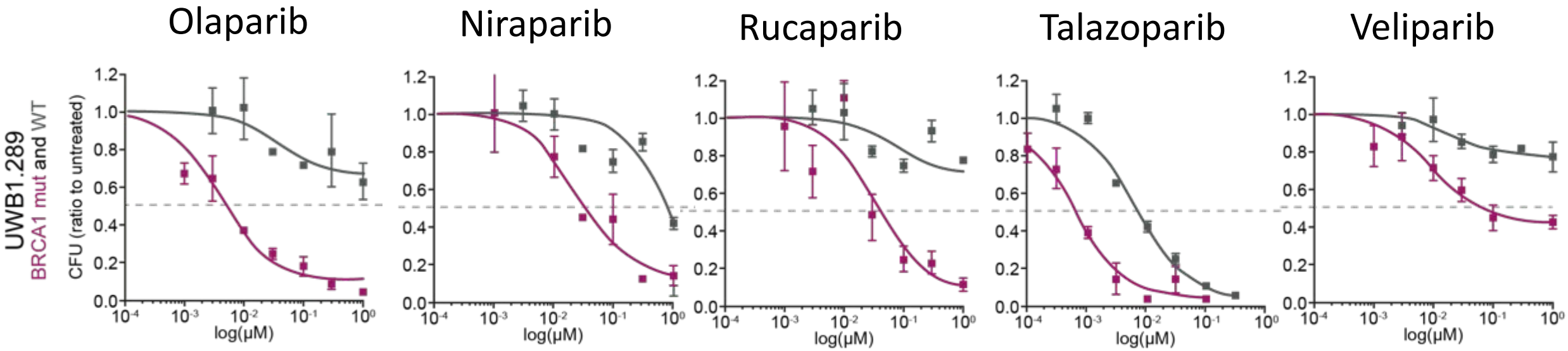
1. Leo E et al. Poster LB-273, presented at AACR 2018; 2. Pujade-Lauraine E et al., *Lancet Oncol*. 2017 Sep;18(9):1274-1284; 3. Mirza MR et al. *N Engl J Med*. 2016;375, 2154–2164. 4. Coleman RL et al. *The Lancet*. 2017; 390: 1949-61; 5. Litton J et al. *N Engl J Med* 2018; 379:753-763; 6.Wagner LM, *Onco Targets Ther.* 2015; 8: 1931–1939; 114(7): 713–715.; 7: Pilie P et al., Clin Cancer Res. 2019 Feb 13. pii: clincanres.0968.2018

Courtesy of Kathleen Moore, MD

PARP inhibitors demonstrate greater activity in HRR deficient cancer cells compared to matched non-HRR deficient cells

Colony formation assay in two isogenic pairs (HRR deficient and HRR proficient)

Assay carried out in an ovarian cancer cell line



Leo E et al. Poster LB-273, presented at AACR 2018

Courtesy of Kathleen Moore, MD

VELIA: This is where VELIA differs from the others…..

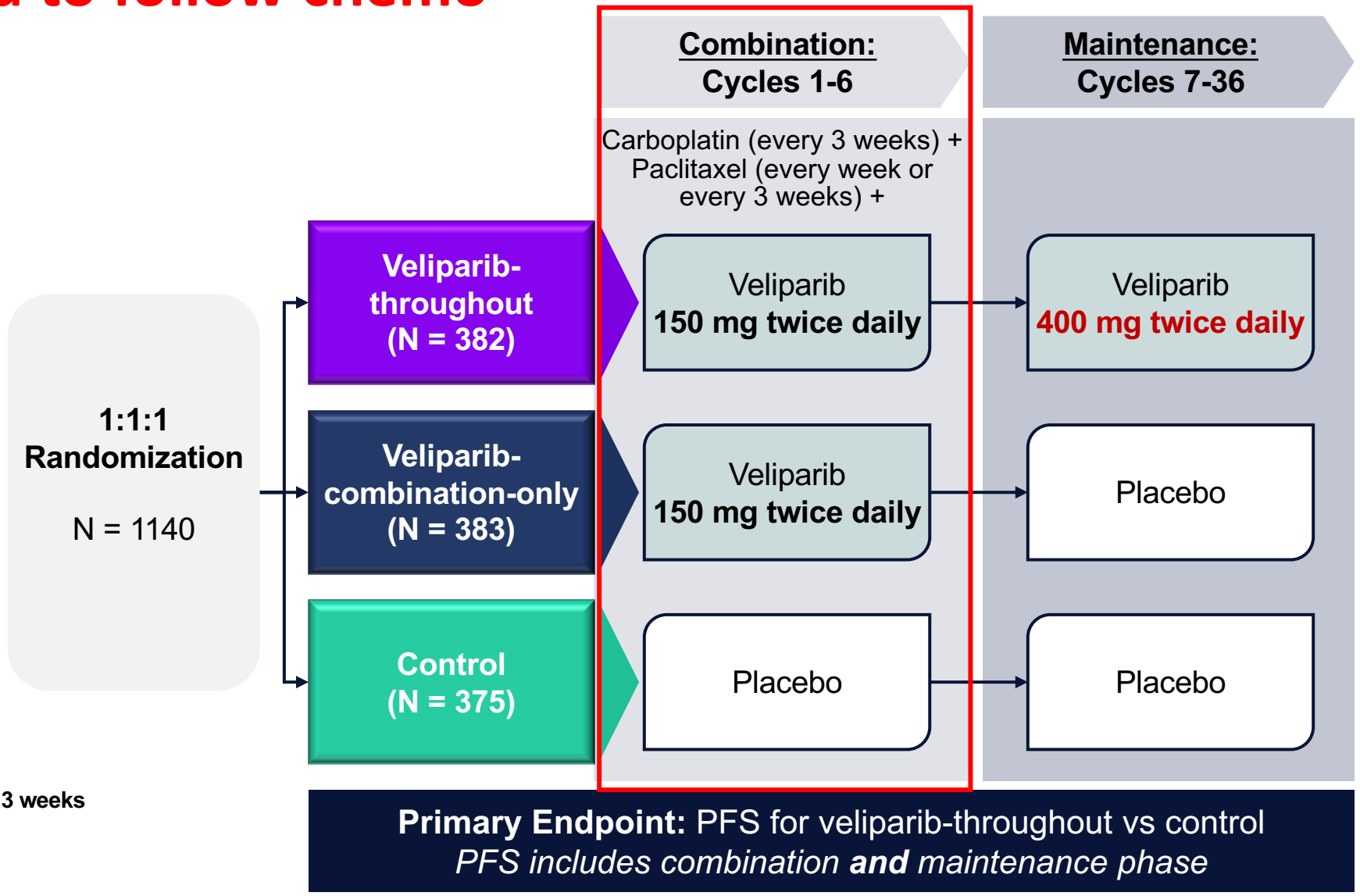
Veliparib with and to follow chemo

Patient Population

- High-grade serous cancer
- FIGO stage III or IV
- No prior systemic therapy
- ECOG 0 to 2
- No CNS metastases

Stratification Factors

- Stage of disease
- Region
- Primary vs interval Cytoreduction
- Residual disease
- Chemotherapy regimen*
- g*BRCA* status **



* Carboplatin AUC 6 every 3 weeks + Paclitaxel 80 mg/m2 QW or 175 mg/m2 every 3 weeks

** Added as stratification factor ~14 months after trial initiation due to noted imbalance

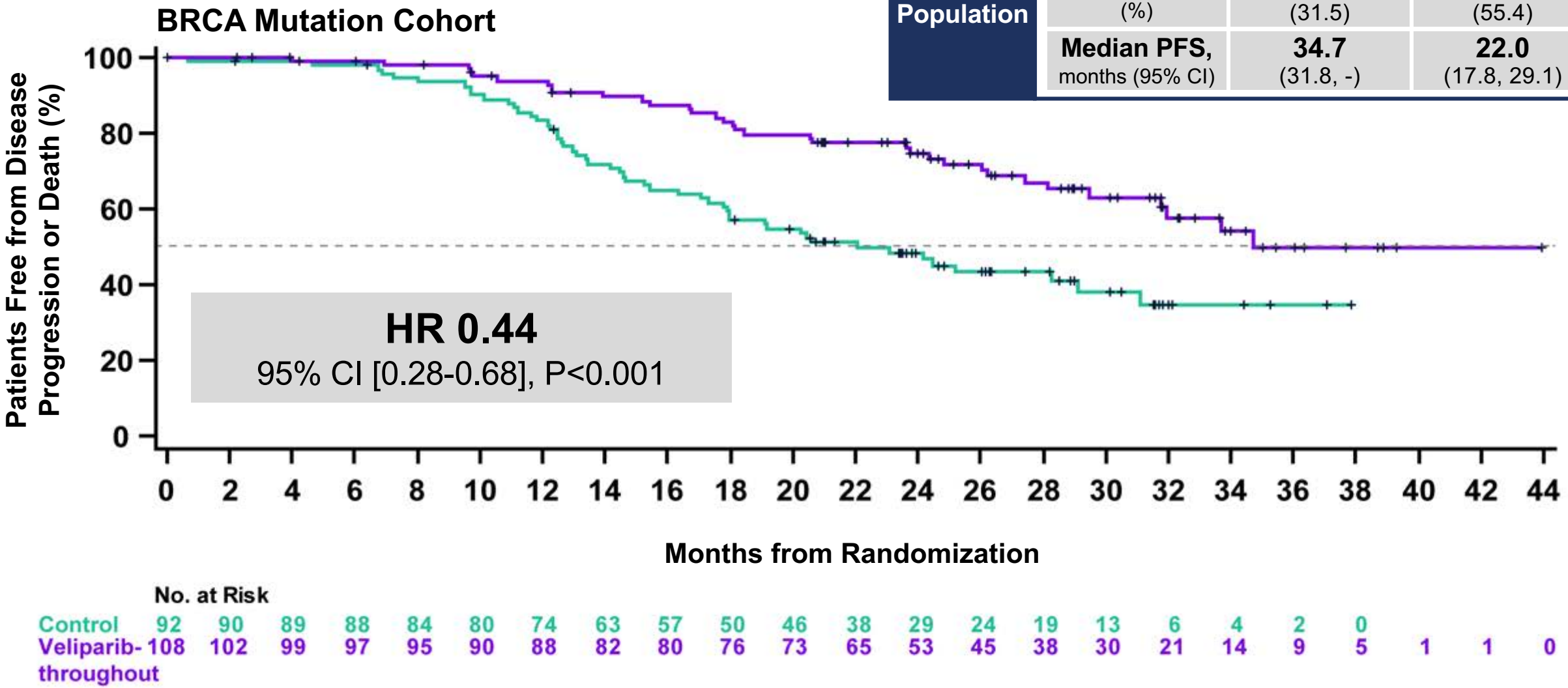
CNS = central nervous system

Coleman RL, et al. ESMO 2019. Abstract LBA3. Coleman RL, et al. *N Engl J Med.* 2019. [Epub ahead of print].

Courtesy of Kathleen Moore, MD

VELIA: PFS by Investigator Assessment

*BRCA*m Population		Veliparib-throughout	Control
	Events (%)	34/108 (31.5)	51/92 (55.4)
	Median PFS, months (95% CI)	**34.7** (31.8, -)	**22.0** (17.8, 29.1)

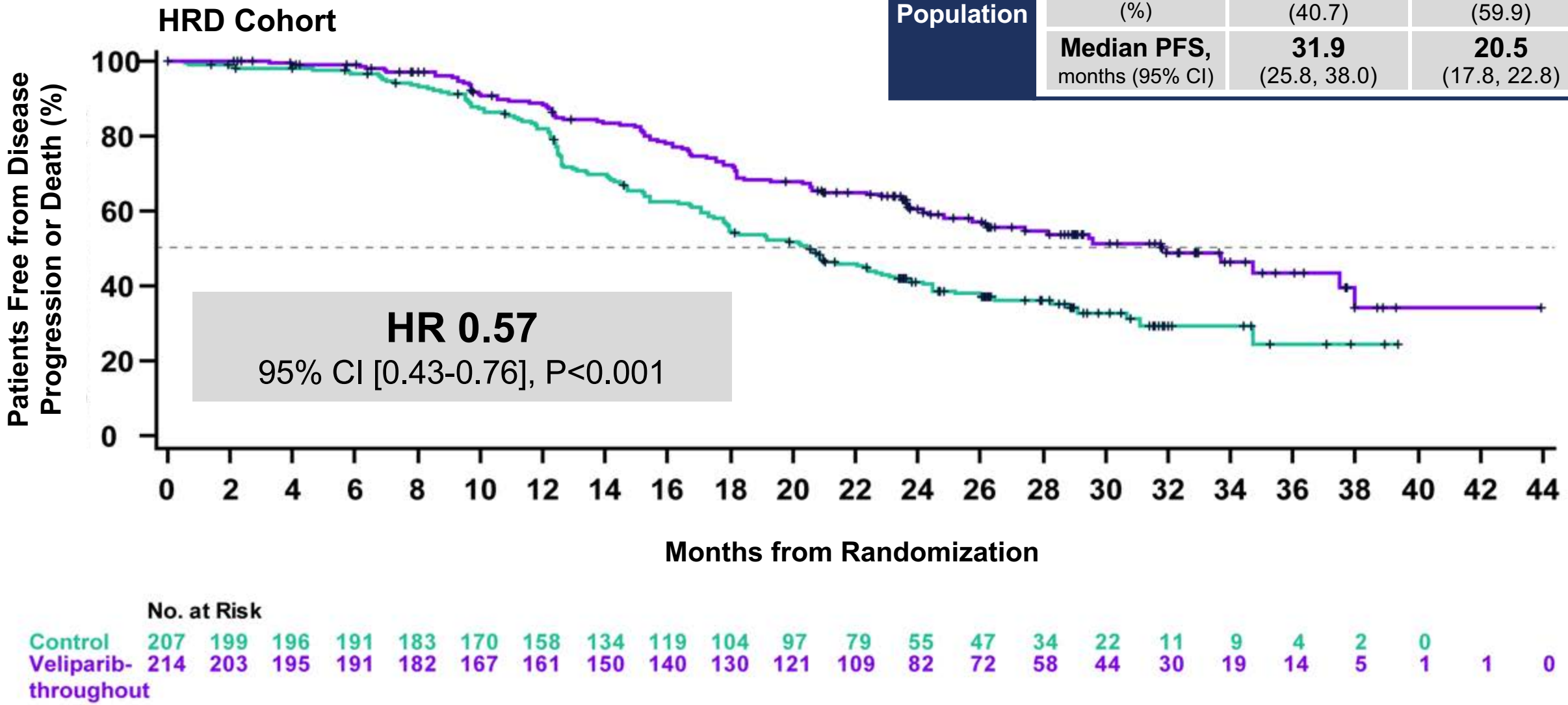


Median duration of follow-up was 28 months at the time of database lock.

Courtesy of Kathleen Moore, MD

VELIA: PFS by Investigator Assessment

HRD Population		Veliparib-throughout	Control
	Events (%)	87/214 (40.7)	124/207 (59.9)
	Median PFS, months (95% CI)	**31.9** (25.8, 38.0)	**20.5** (17.8, 22.8)



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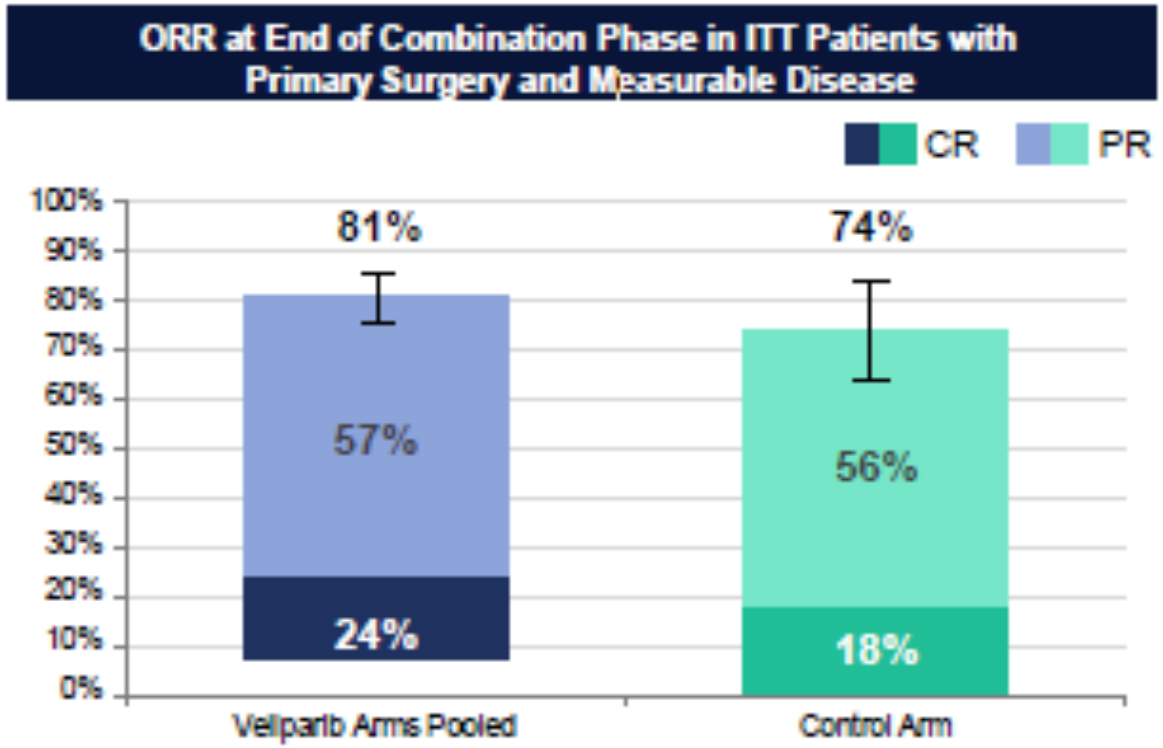
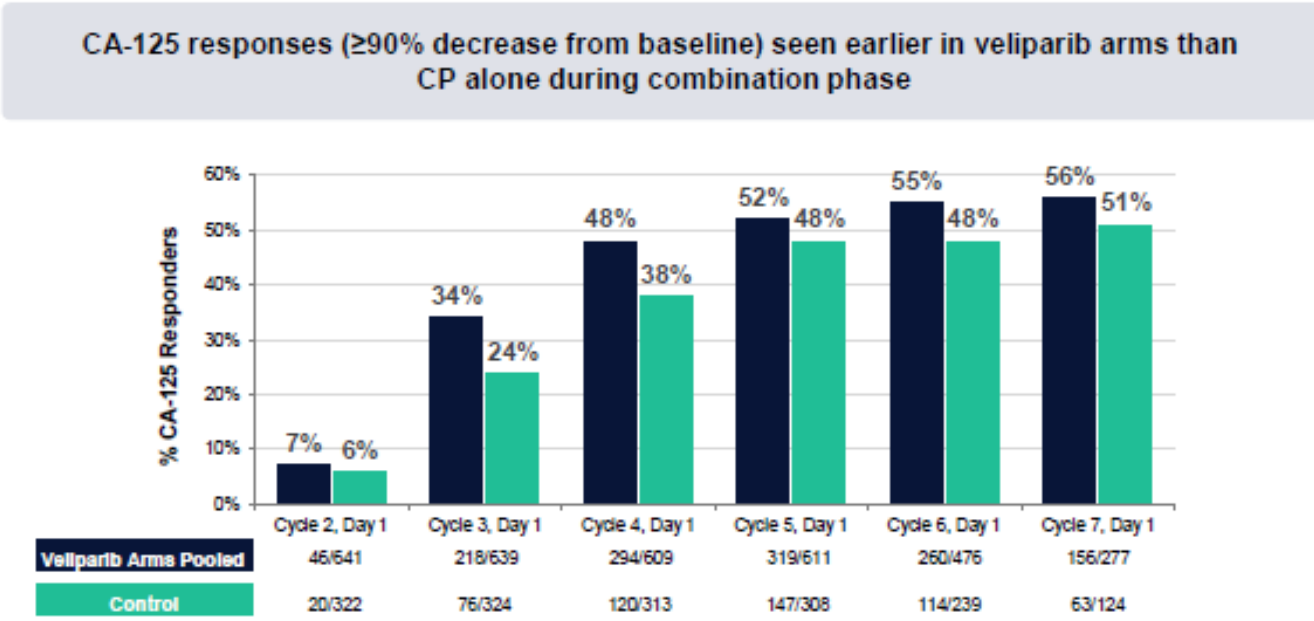
Courtesy of Kathleen Moore, MD

VELIA would suggest that responses via RECIST and Ca-125 were more robust with the addition of veliparib to chemo…

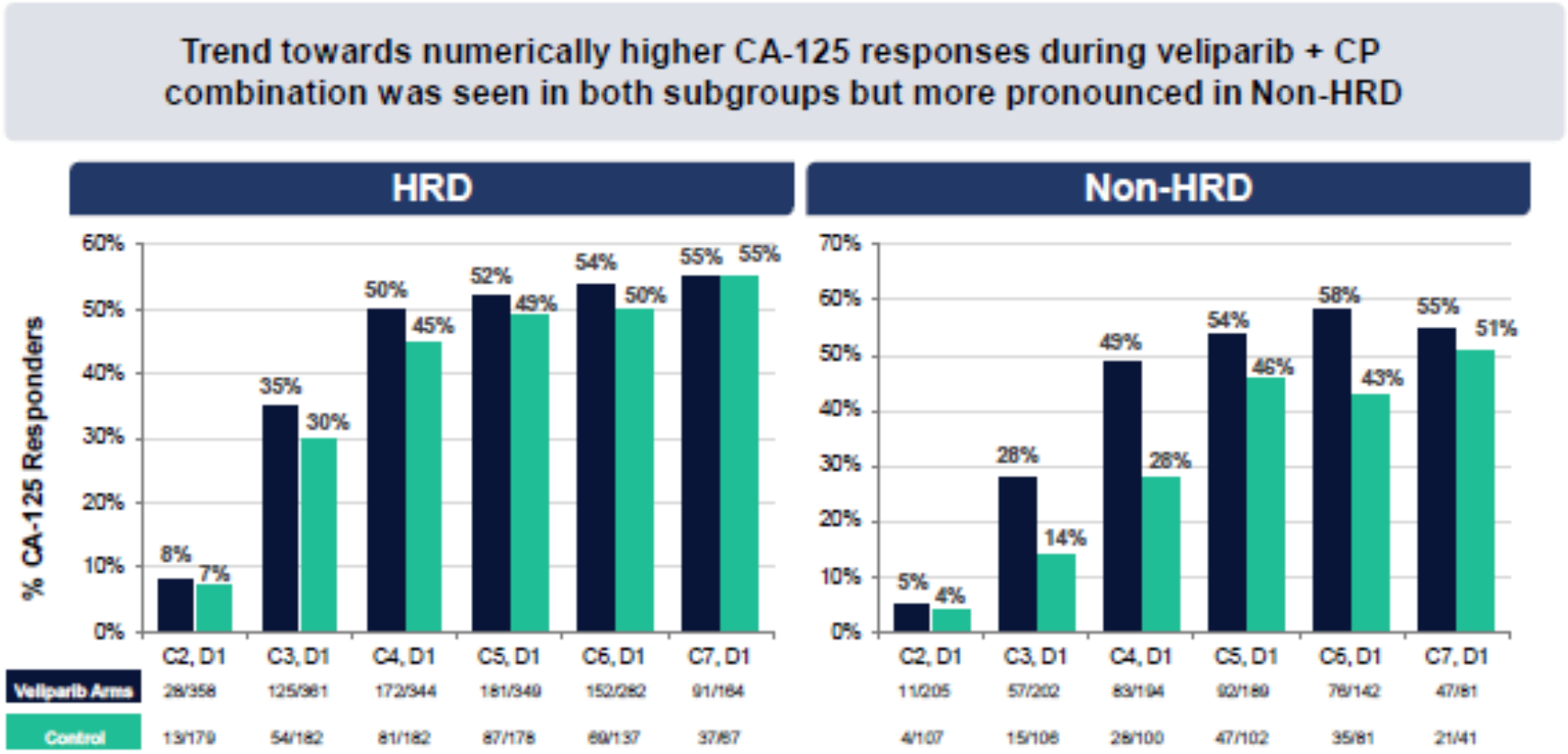




O'Malley et al. SGO 2020

Courtesy of Kathleen Moore, MD

Perhaps most striking is the improvement in Ca-125 response among those patients categorized as non-HRD



Improving outcomes among HRp tumors is the next high, unmet need.

Does addition of veliparib with chemo, increase vulnerability of tumors to DNA damage and subsequent death?

Does this = better outcomes?

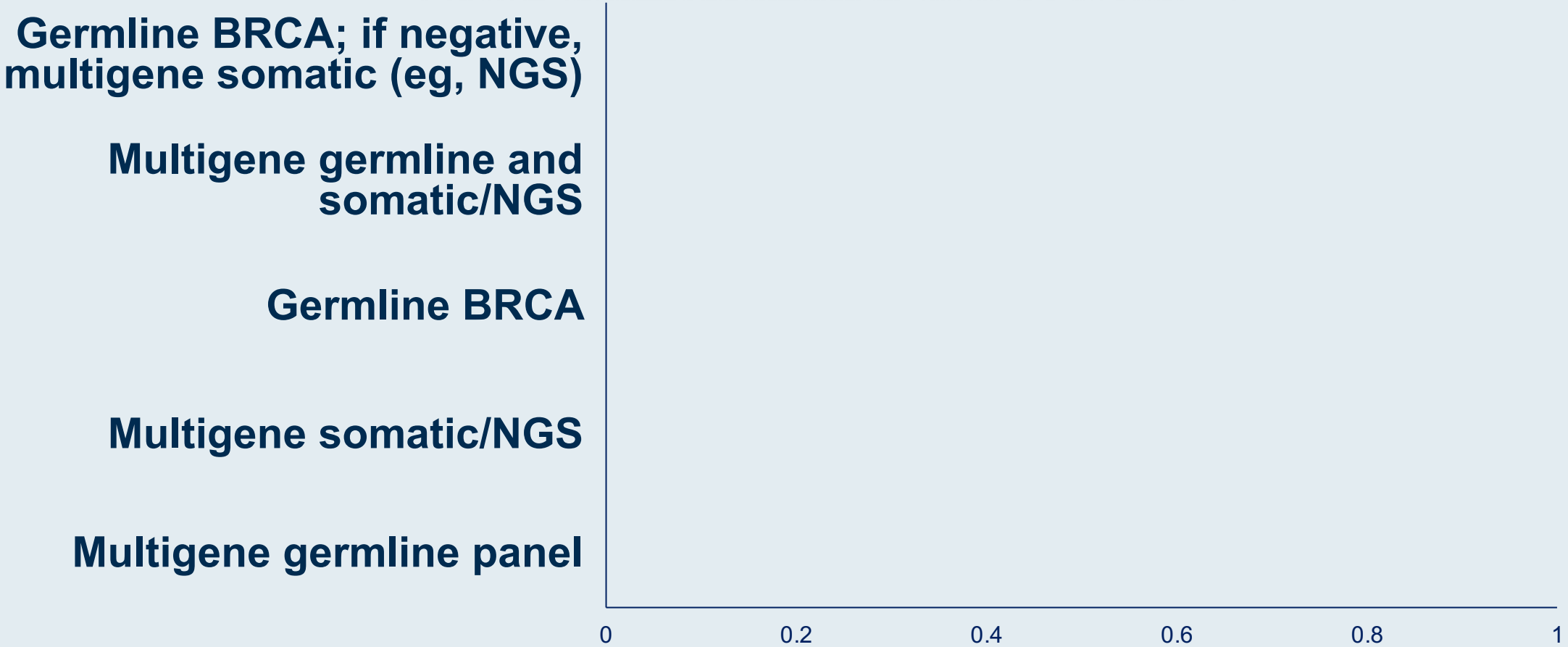
O'Malley et al. SGO 2020

Courtesy of Kathleen Moore, MD

Case Presentation – Dr Moore: A 48-Year-Old Woman with Stage IIIA, High-Grade Serous Ovarian Cancer and a BRCA1 Mutation

- A 48 year old, very healthy woman with a diagnosis of IIIA high grade serous ovarian cancer, BRCA 1 associated. She was diagnosed in 2013 and underwent primary cytoreduction followed by treatment on a clinical trial with paclitaxel, carboplatin, veliparib and bevacizumab followed by 15 cycles of bevacizumab maintenance.
- She was disease free for 5 years when diagnosed with a rising ca-125 and an oligo-met on PET/CT. She underwent resection of her only site of disease and was treated with 6 cycles of carboplatin and PLD with NED at completion. She is now on olaparib maintenance, 300 mg BID with minimal side effects and normal imaging/Ca-125

In general, what is the optimal approach to mutation testing for possible use of a PARP inhibitor for a patient with newly diagnosed ovarian cancer?



NGS = next-generation sequencing

Survey of 50 US-based medical oncologists

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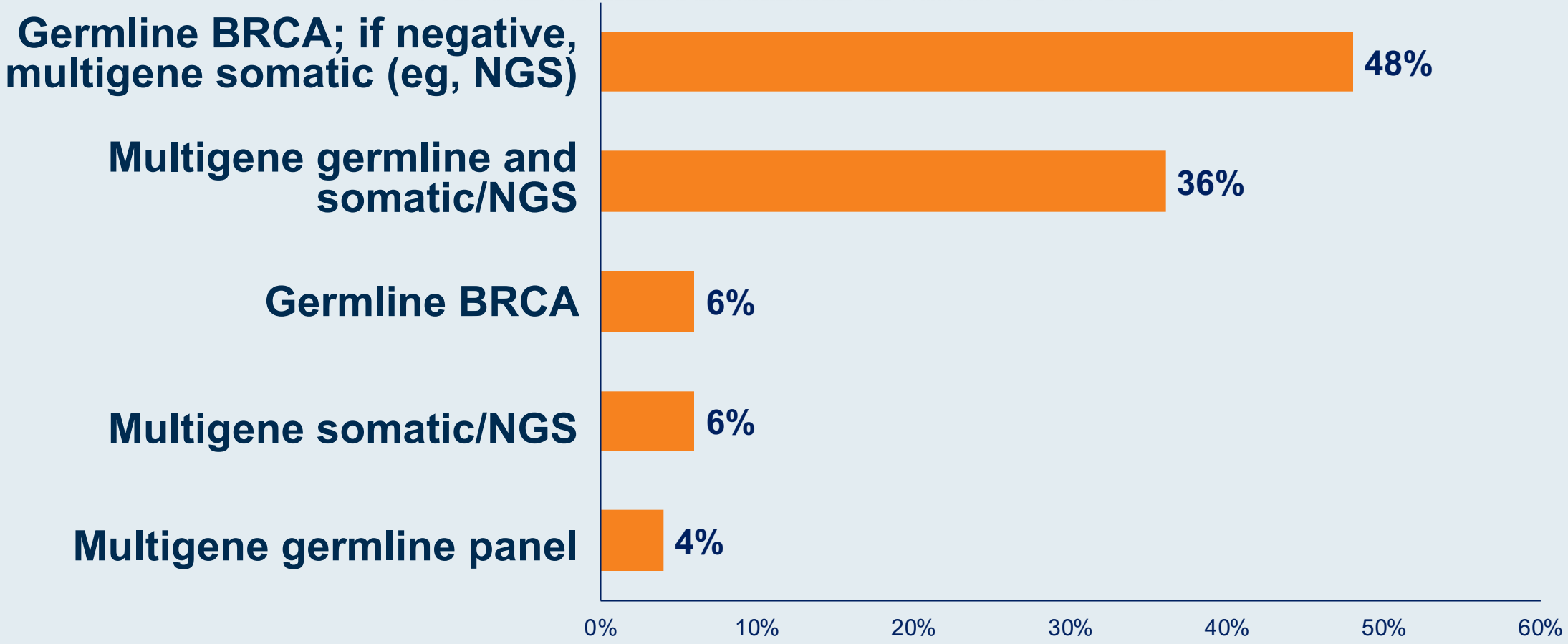

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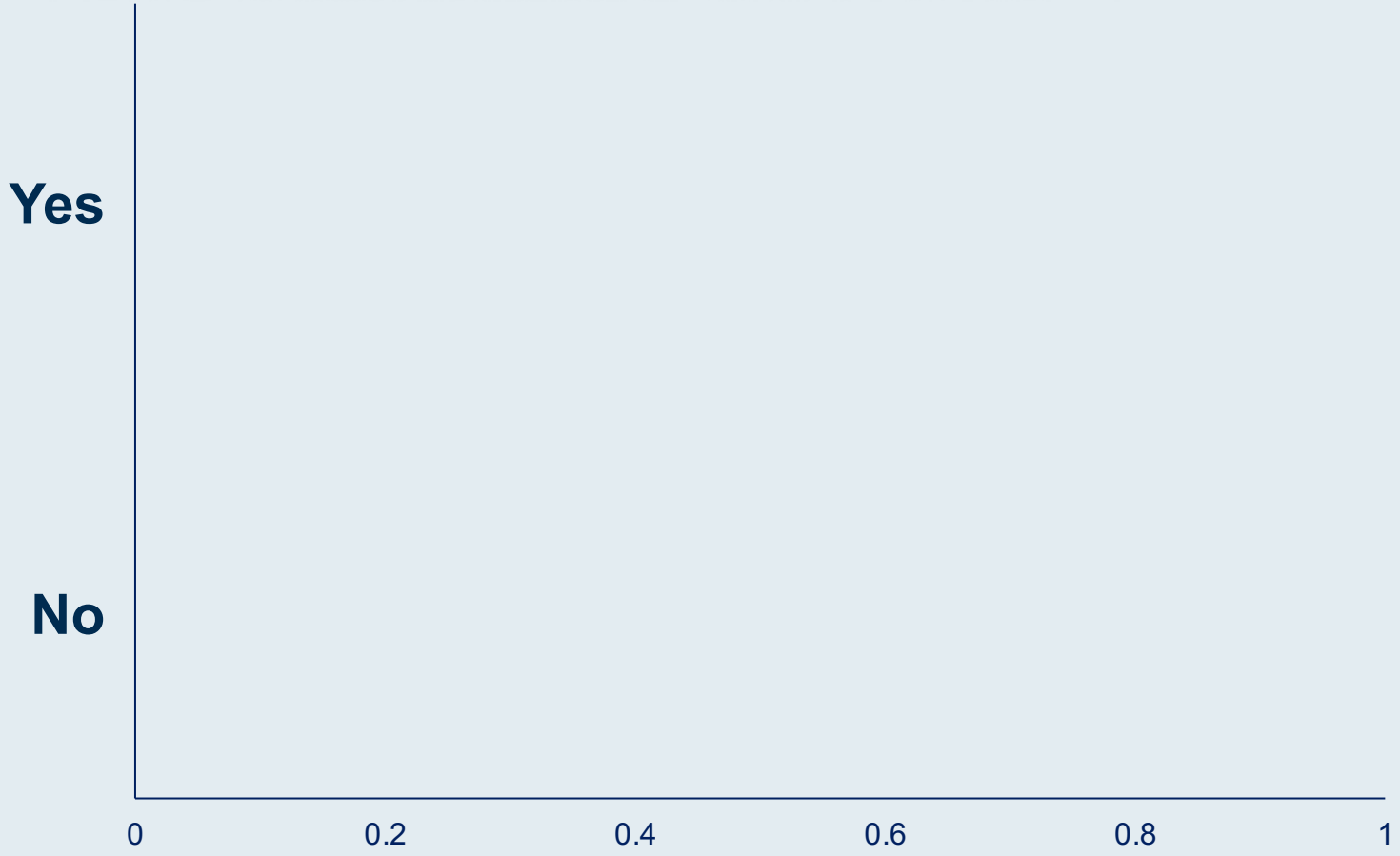
Do you routinely assess HRD status in your patients with advanced ovarian cancer?



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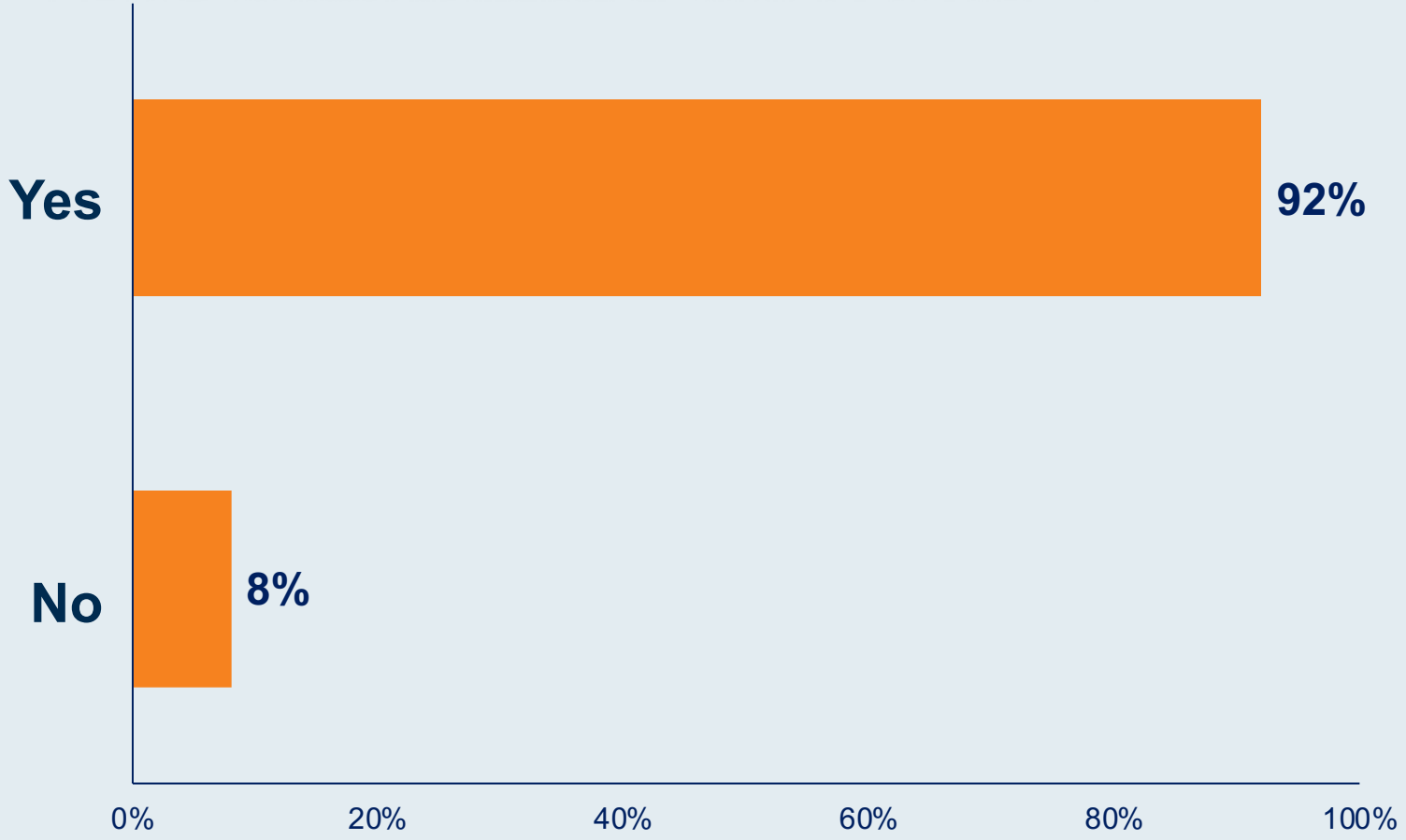

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A 60-year-old woman with Stage IIIC ovarian cancer and a germline BRCA mutation is s/p suboptimal debulking surgery with elevated CA-125. Regulatory and reimbursement issues aside, what would you recommend as postoperative systemic therapy?

Bev = bevacizumab

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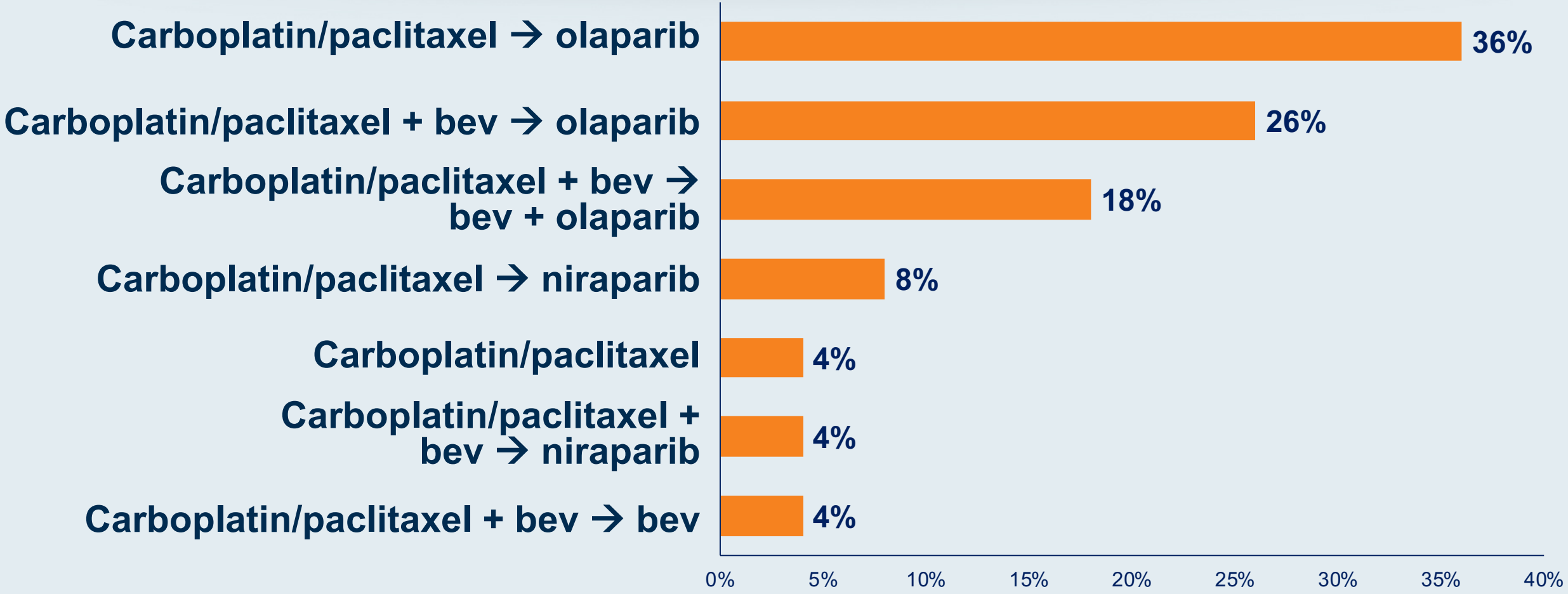

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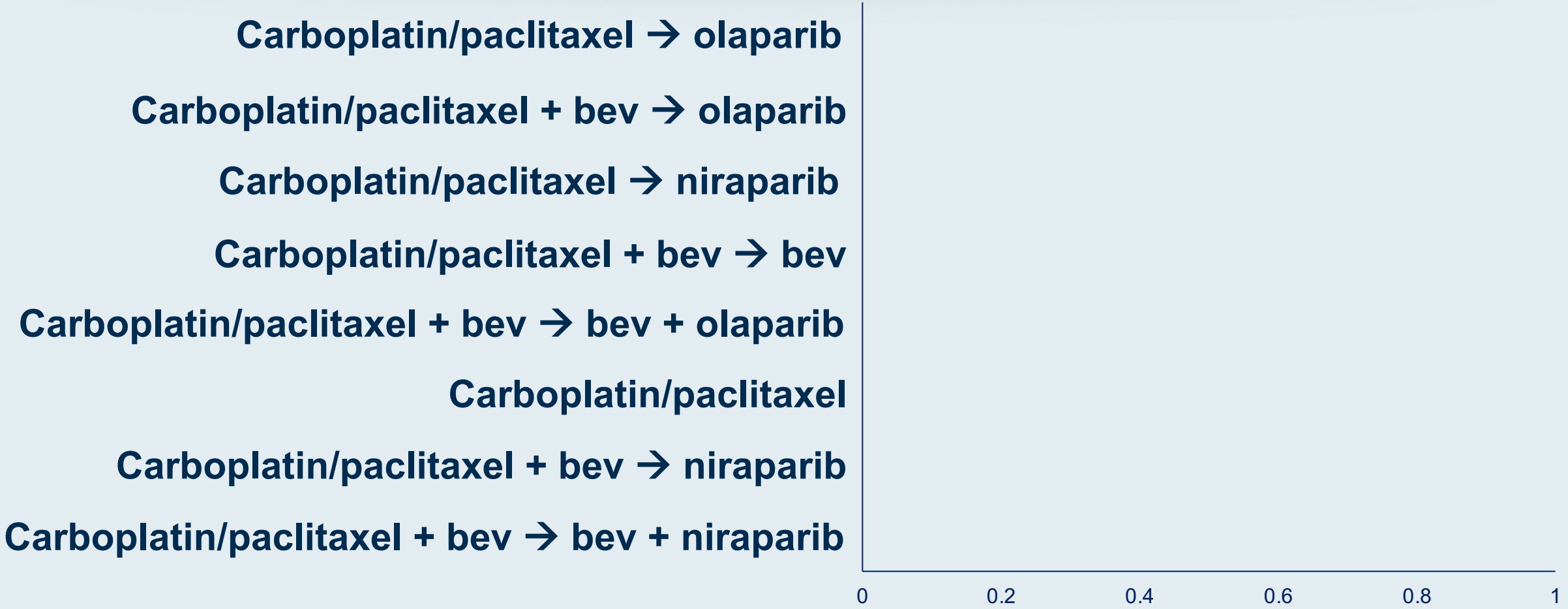

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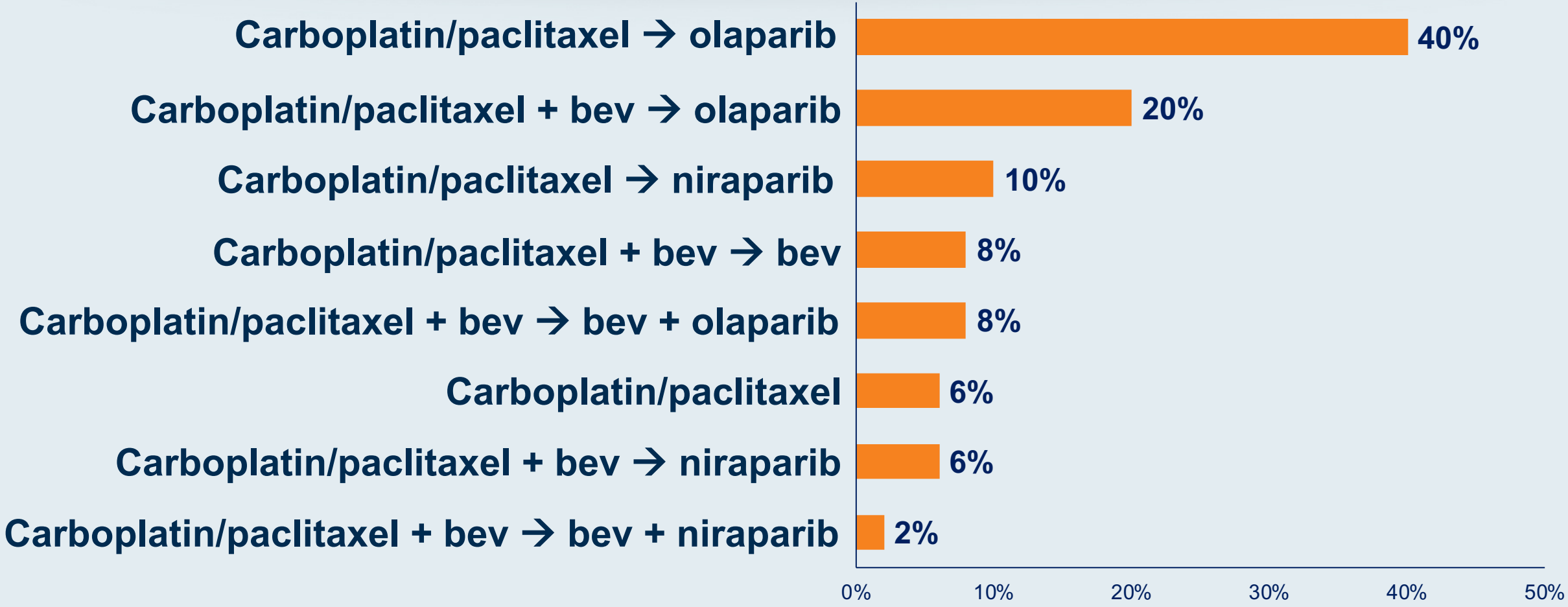

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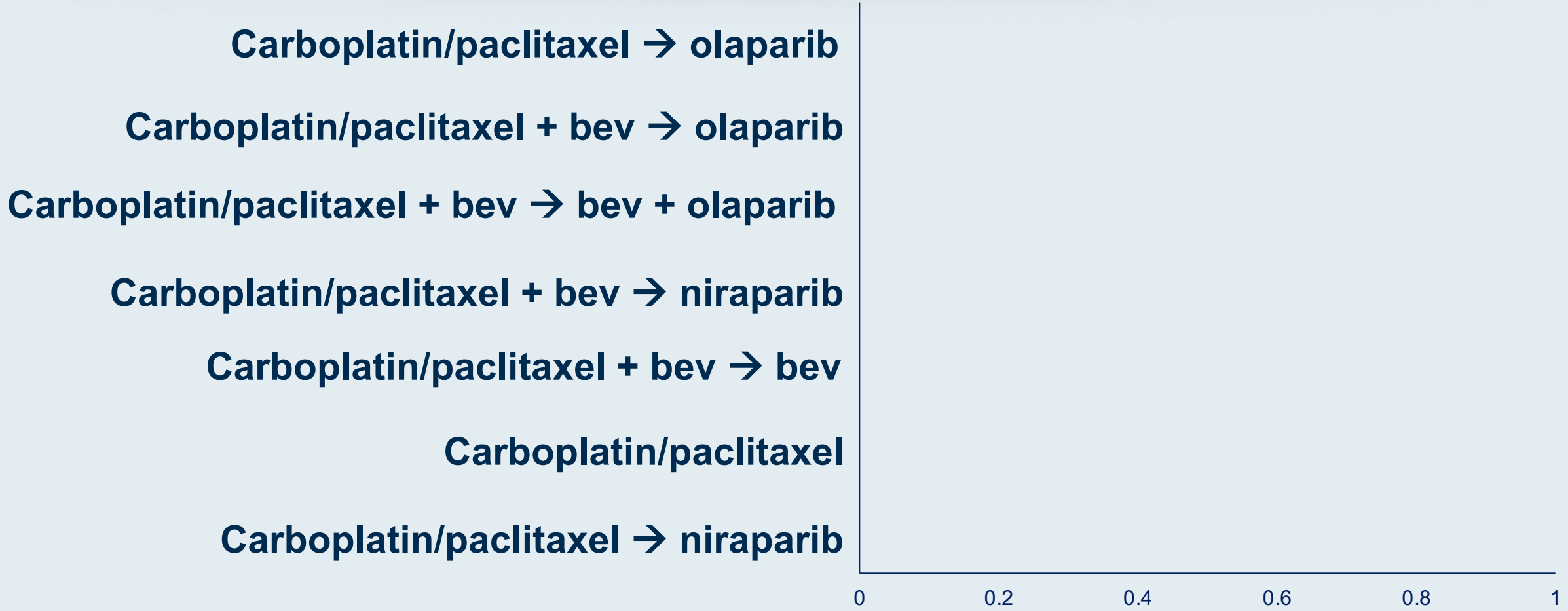

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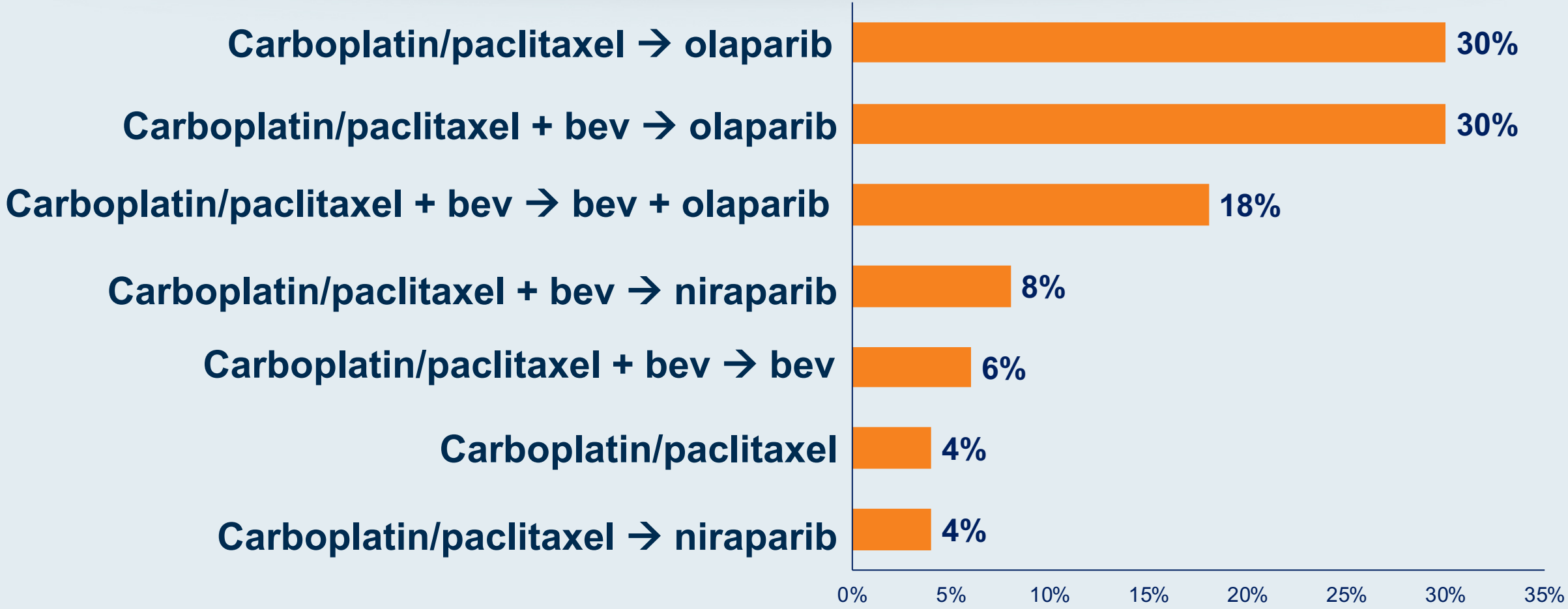

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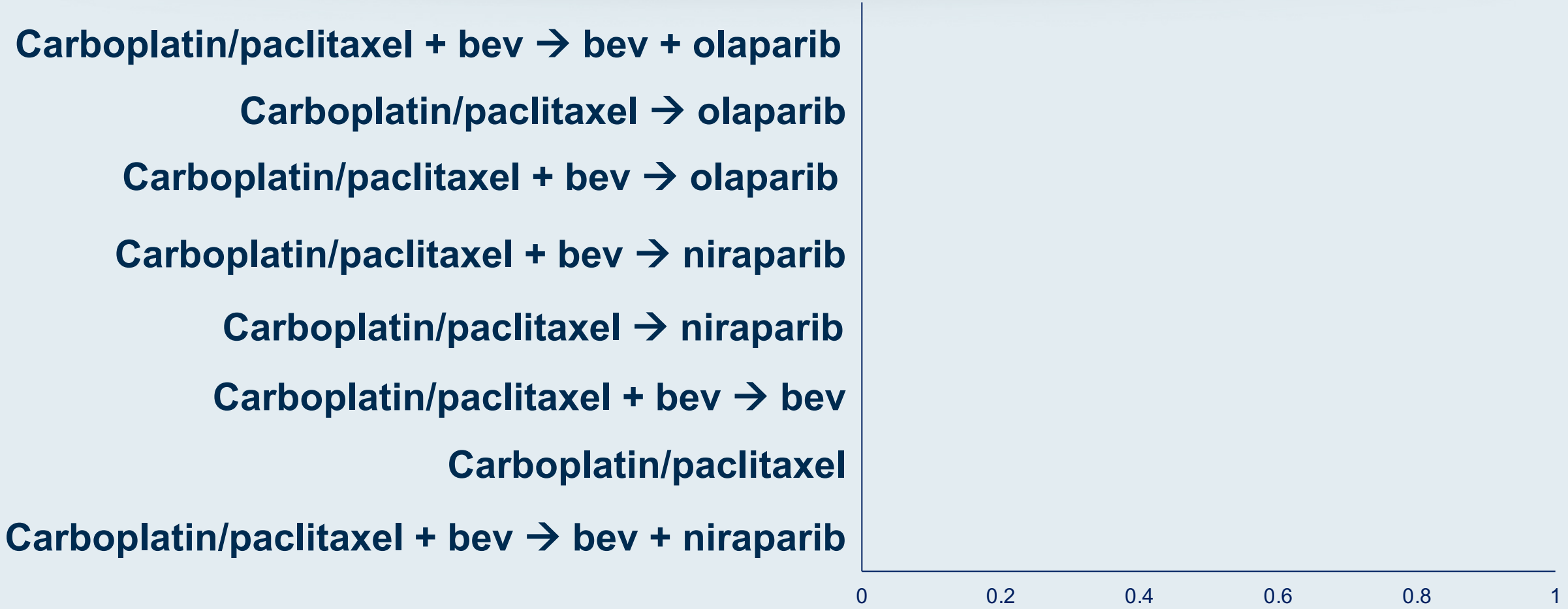

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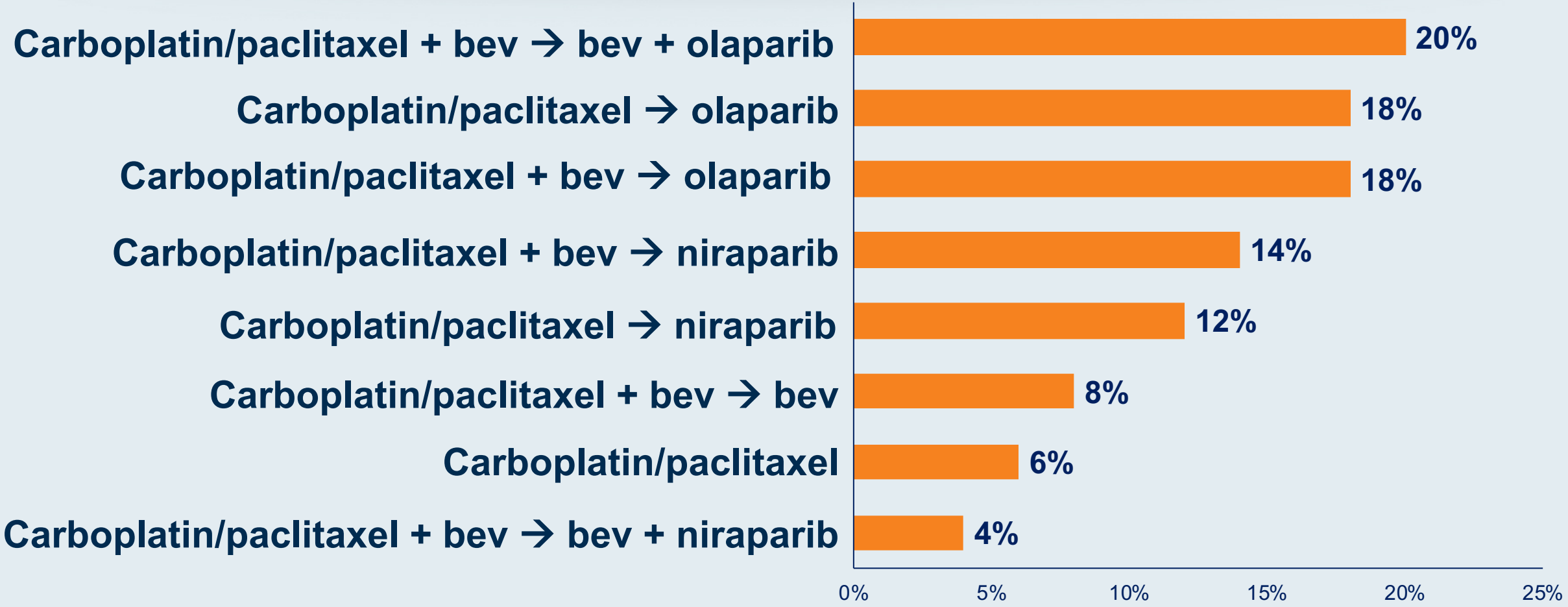

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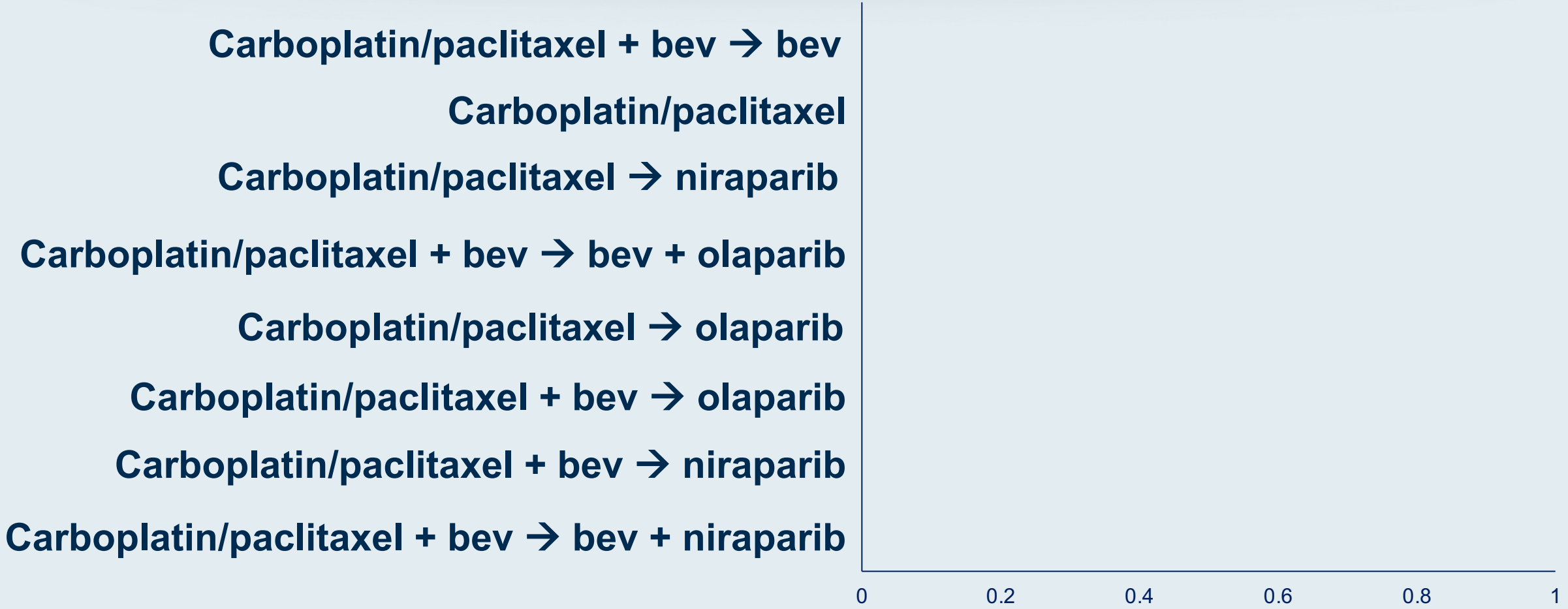

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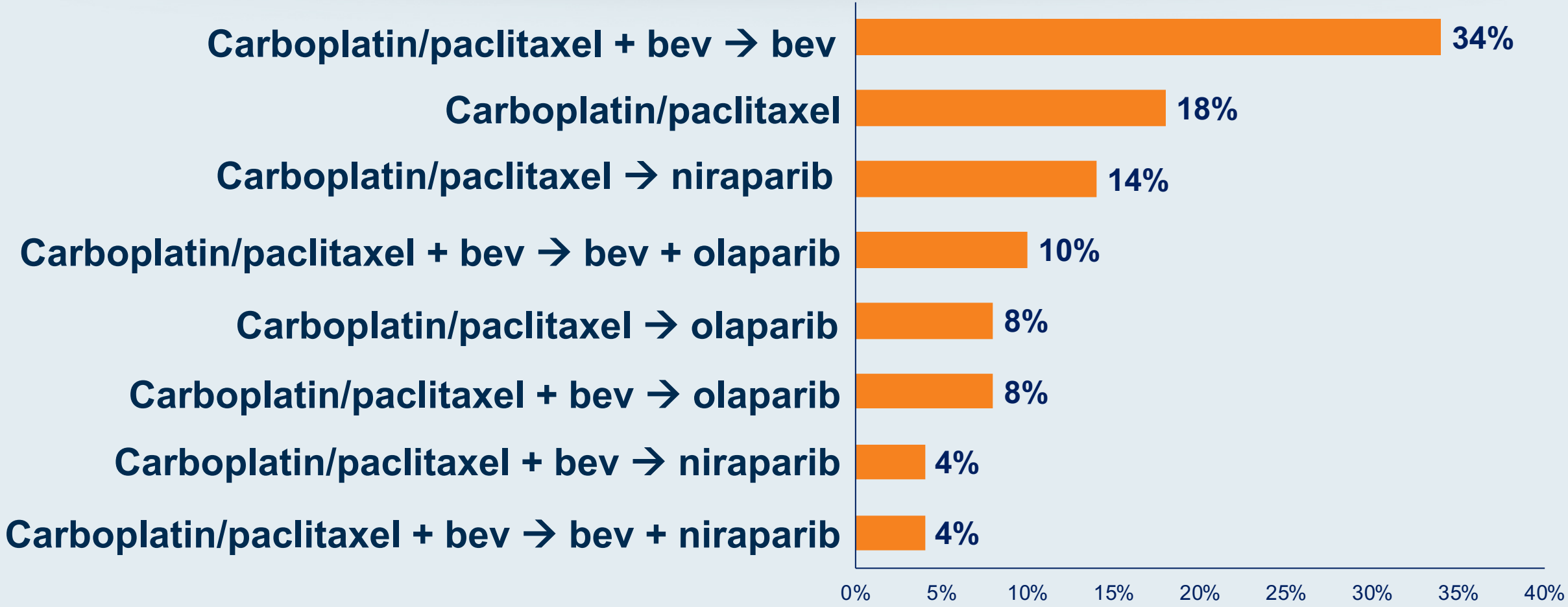

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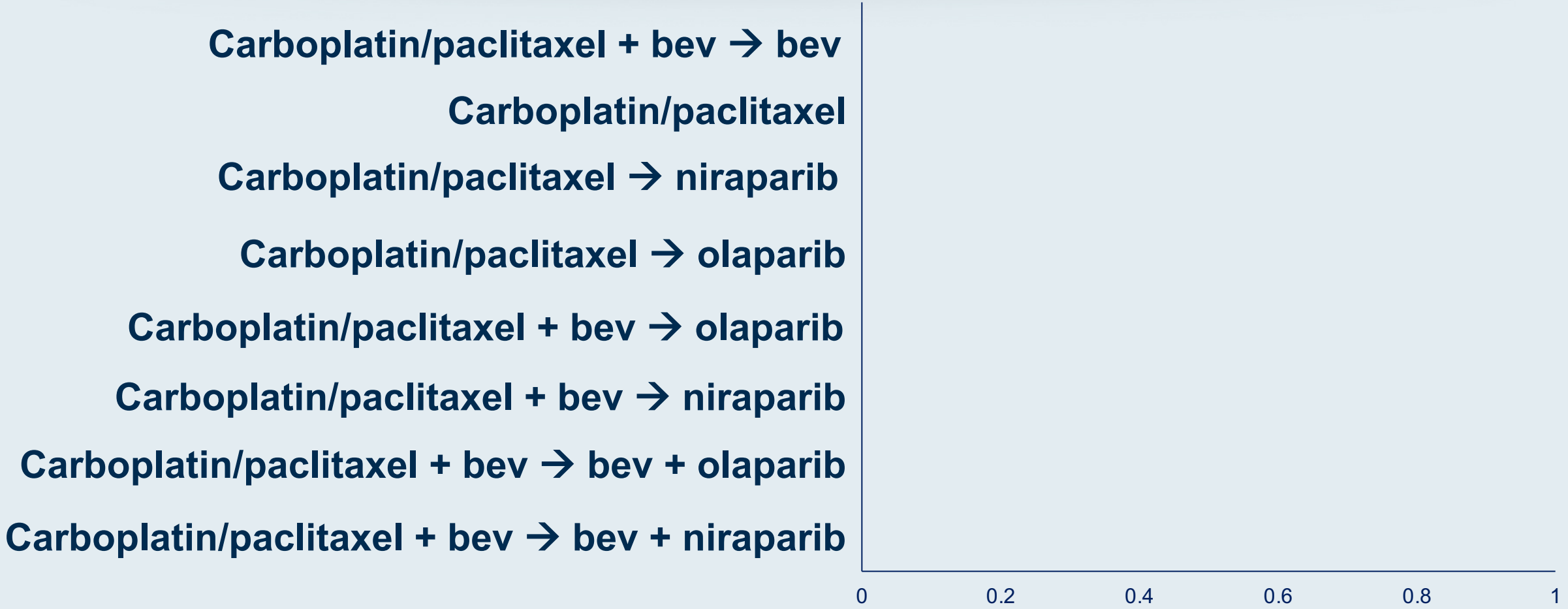

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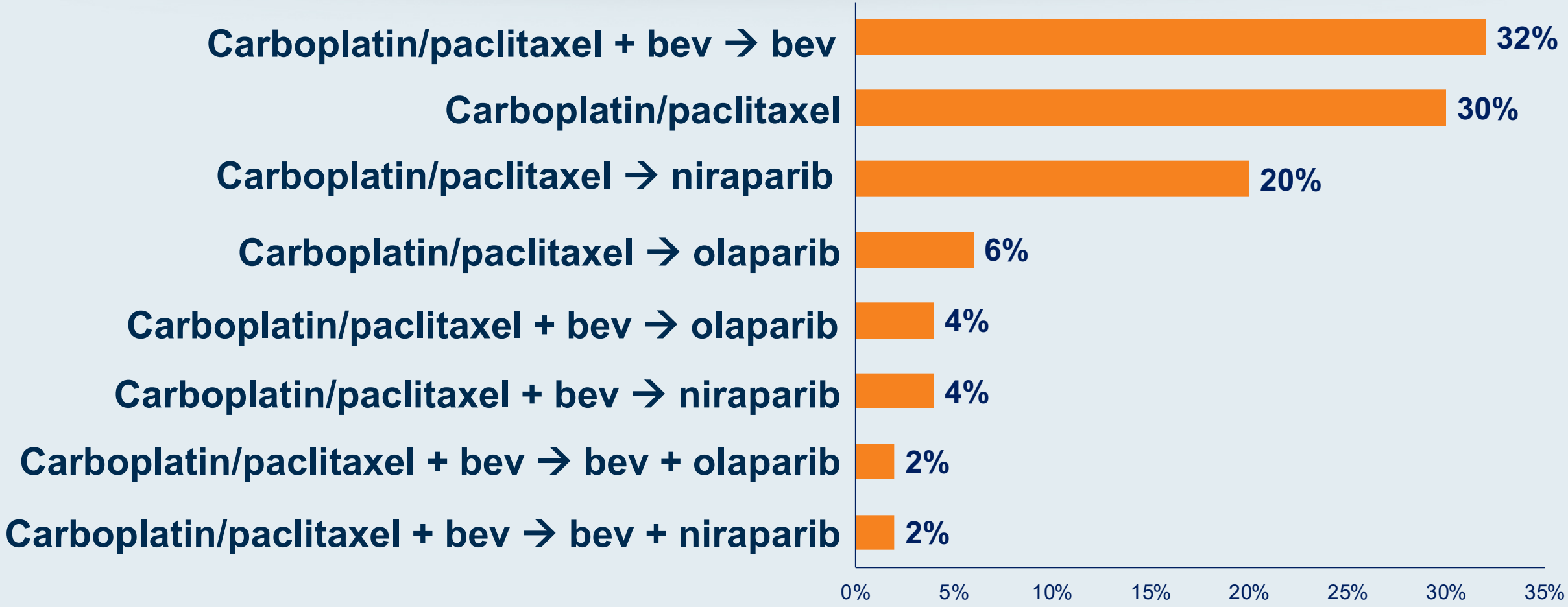

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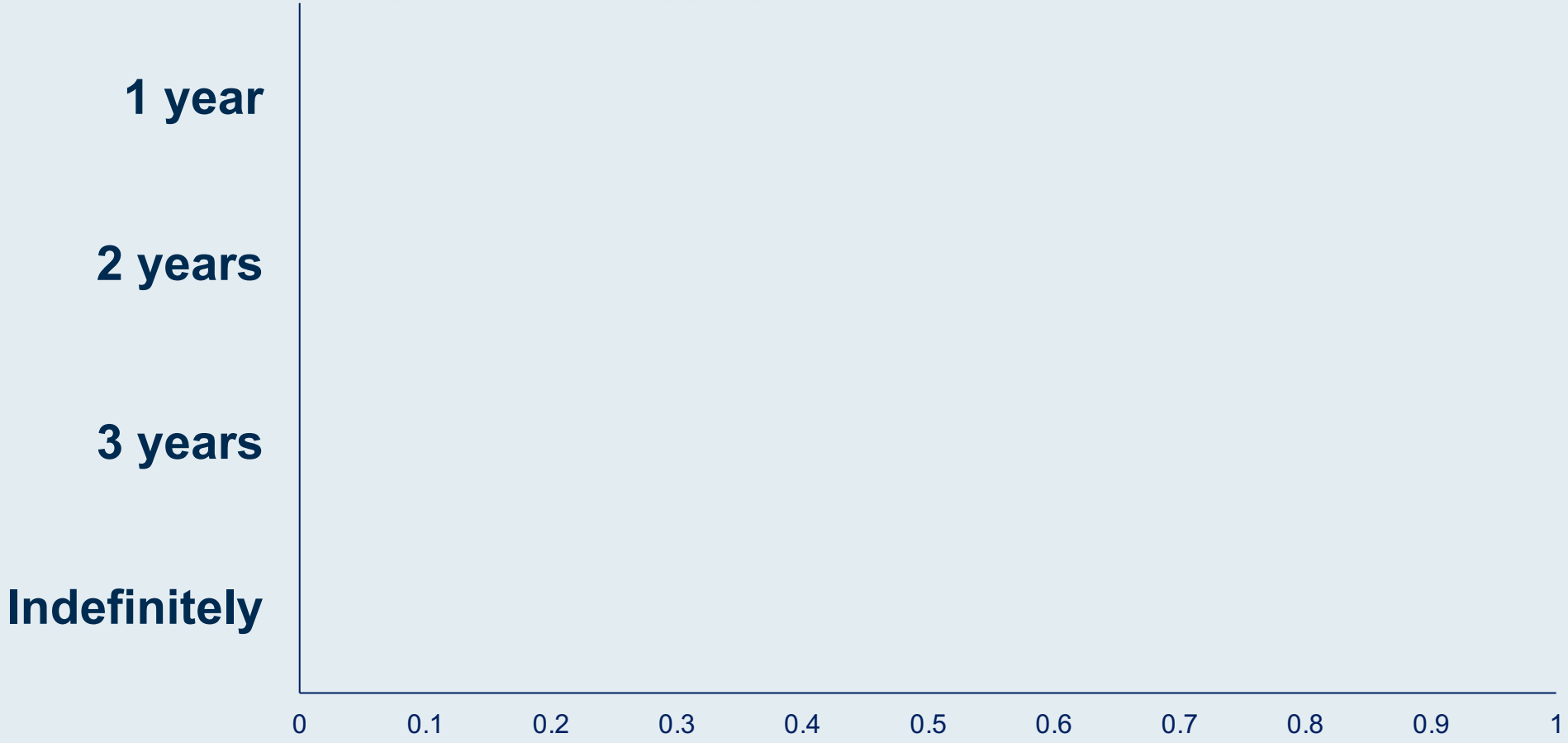

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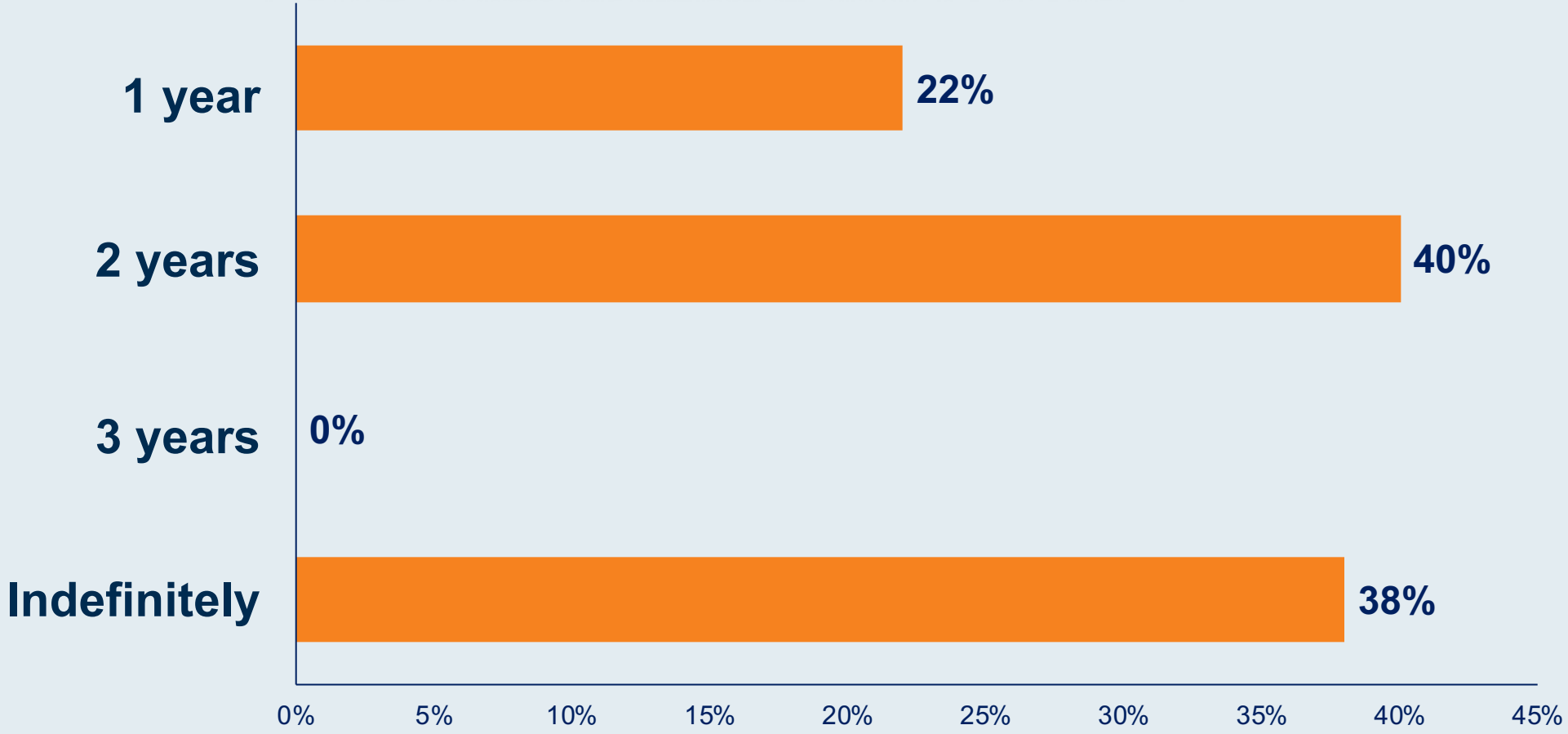

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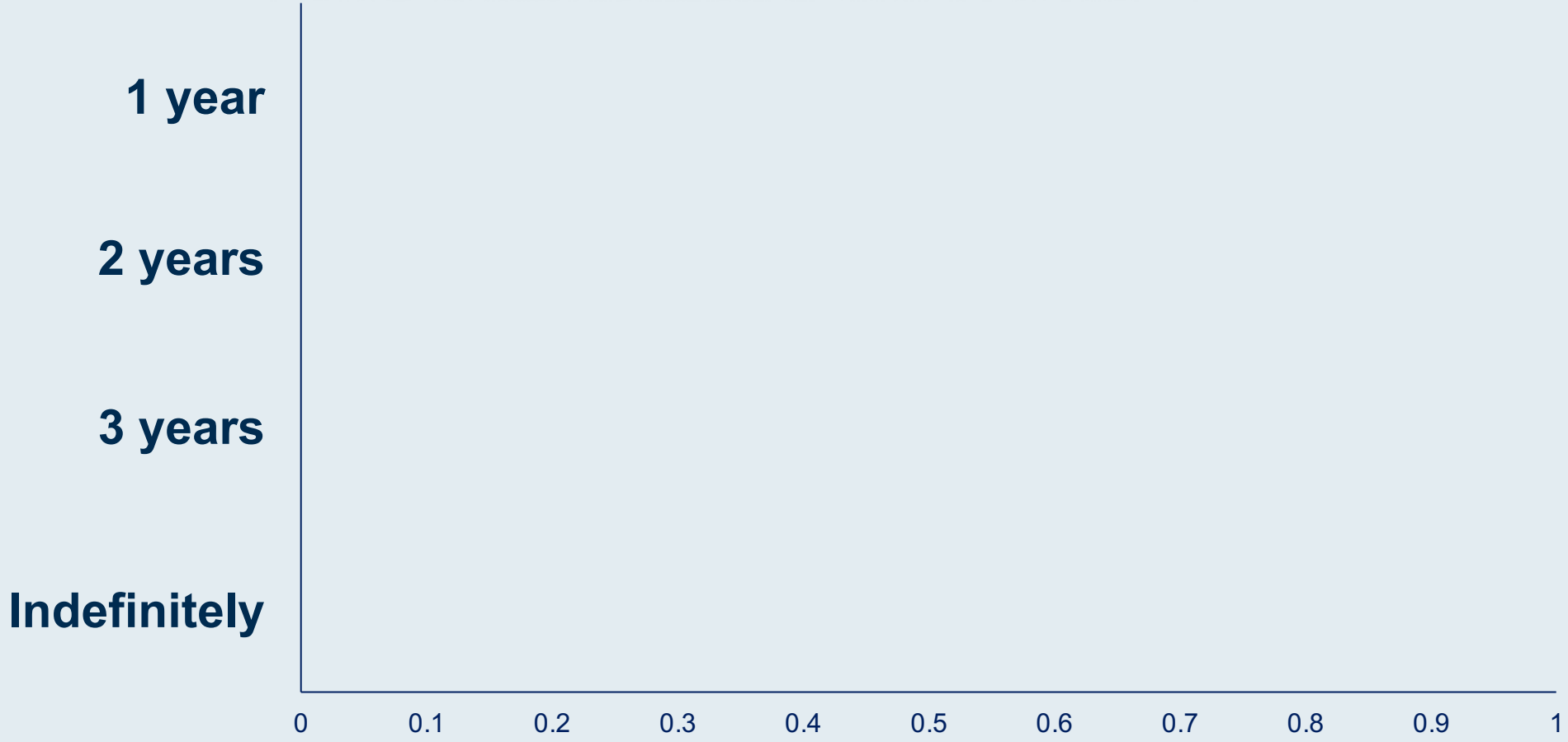
A 60-year-old woman with Stage IIIC ovarian cancer (BRCA wild type, HRD-positive) undergoes suboptimal debulking surgery and receives carboplatin/paclitaxel followed by niraparib. For how long would you typically continue the niraparib if the patient is tolerating it well?



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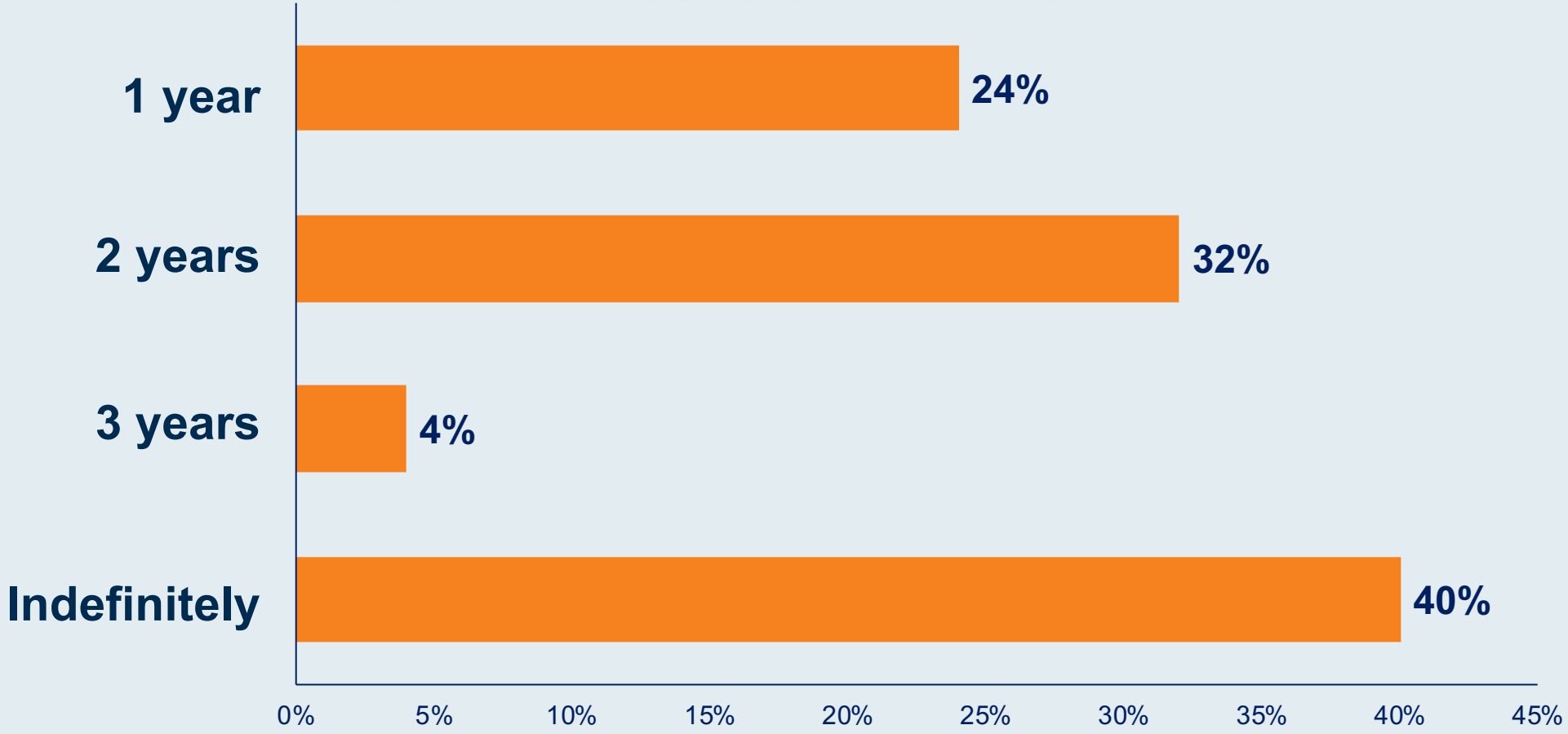
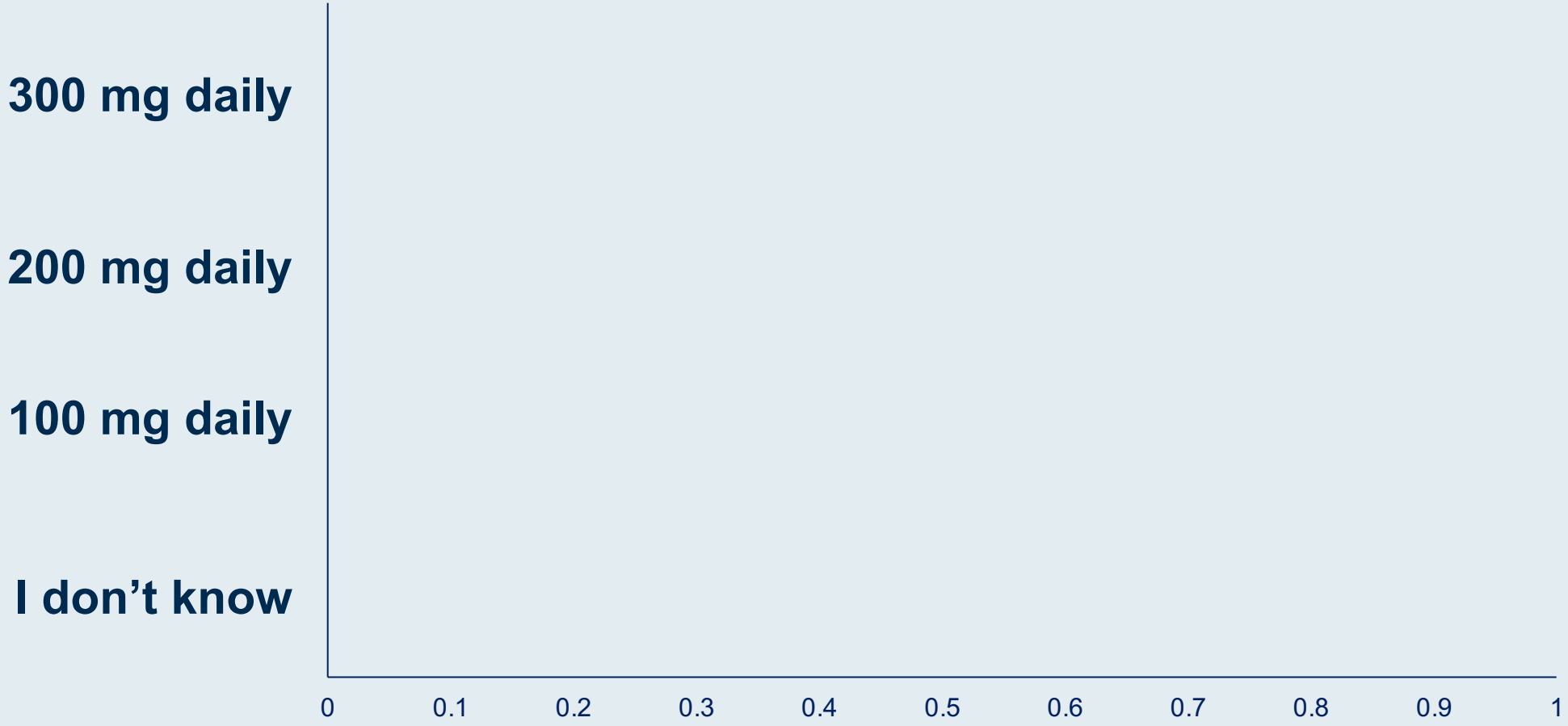


Survey of 50 US-based medical oncologists

What starting dose of niraparib would you use for a 125-lb patient with advanced ovarian cancer after response to front-line platinum-based chemotherapy with a platelet count of 200,000 for whom you are about to initiate maintenance niraparib?



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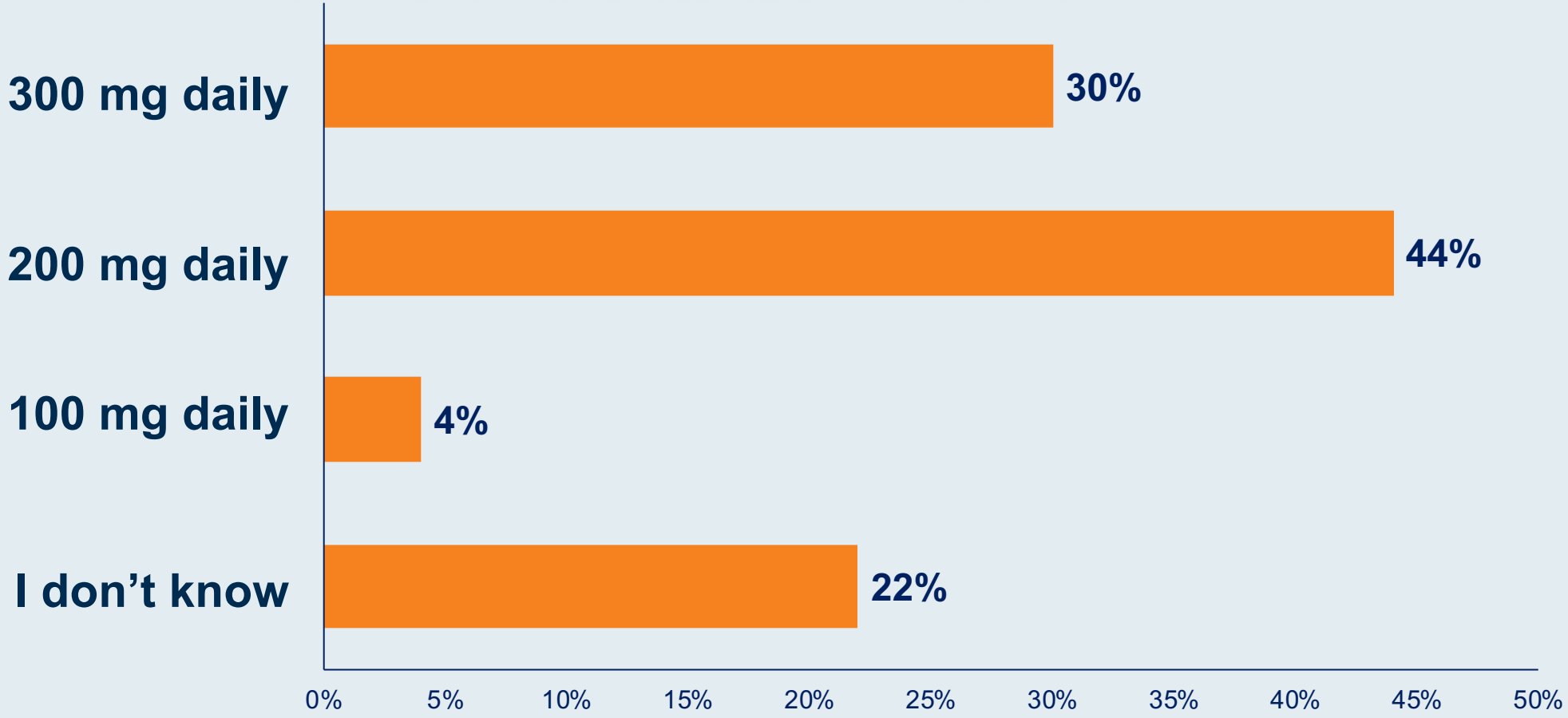

Survey of 50 US-based medical oncologists

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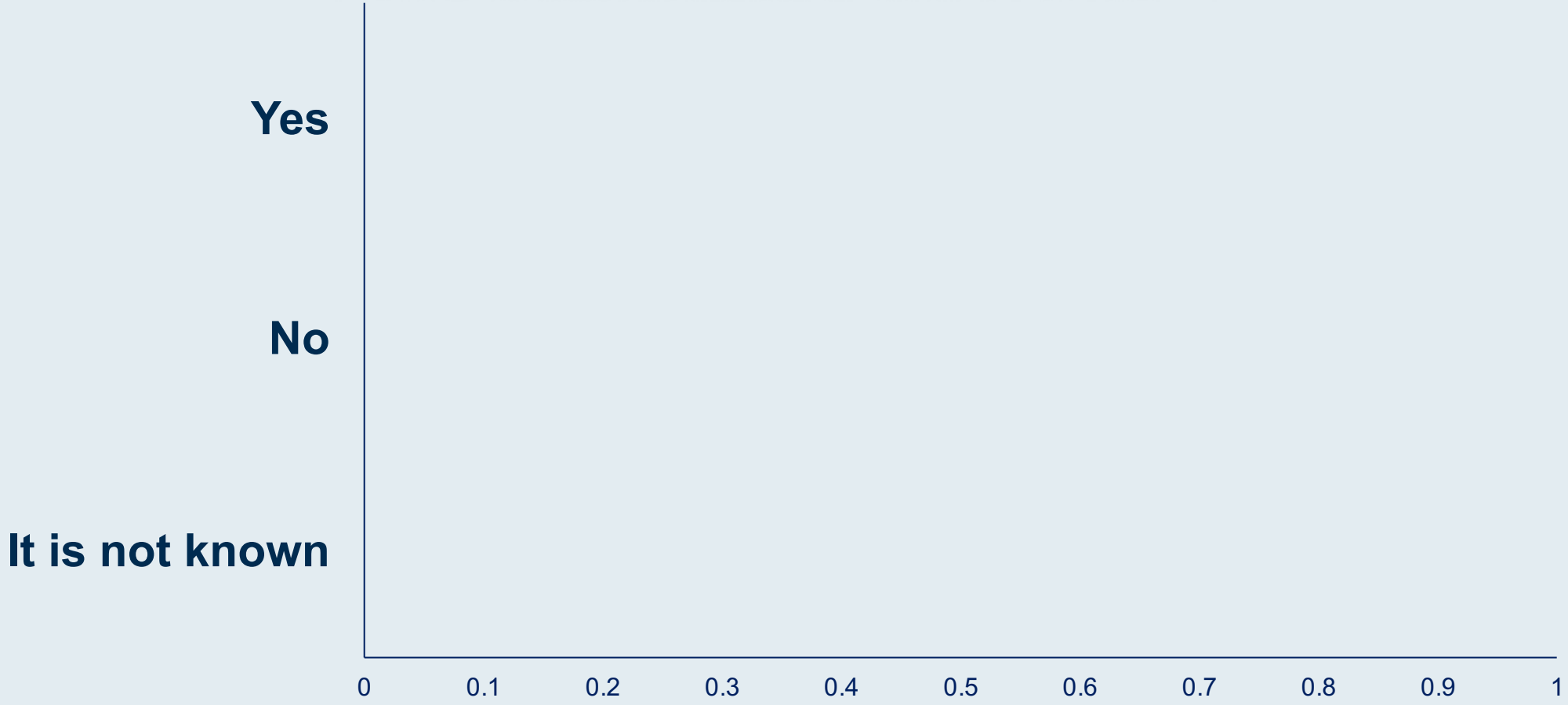

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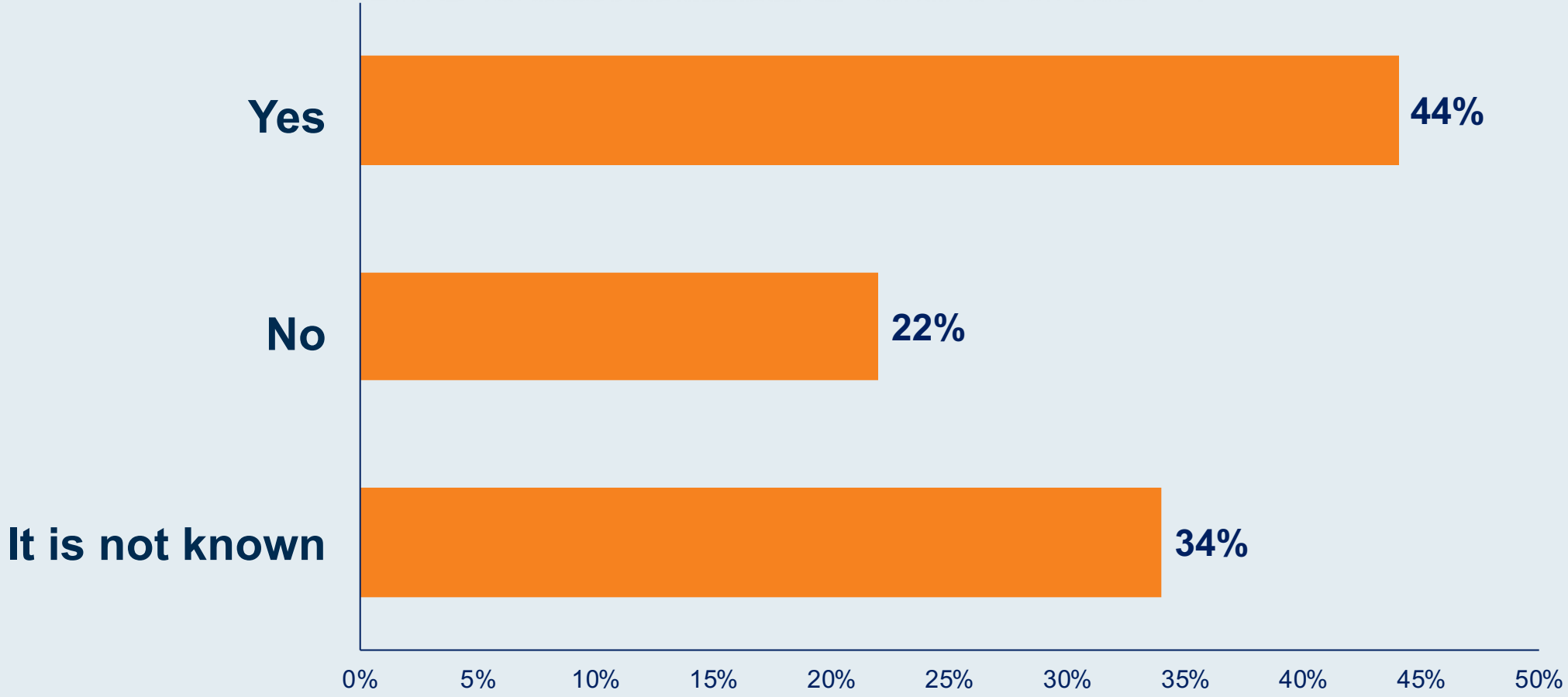
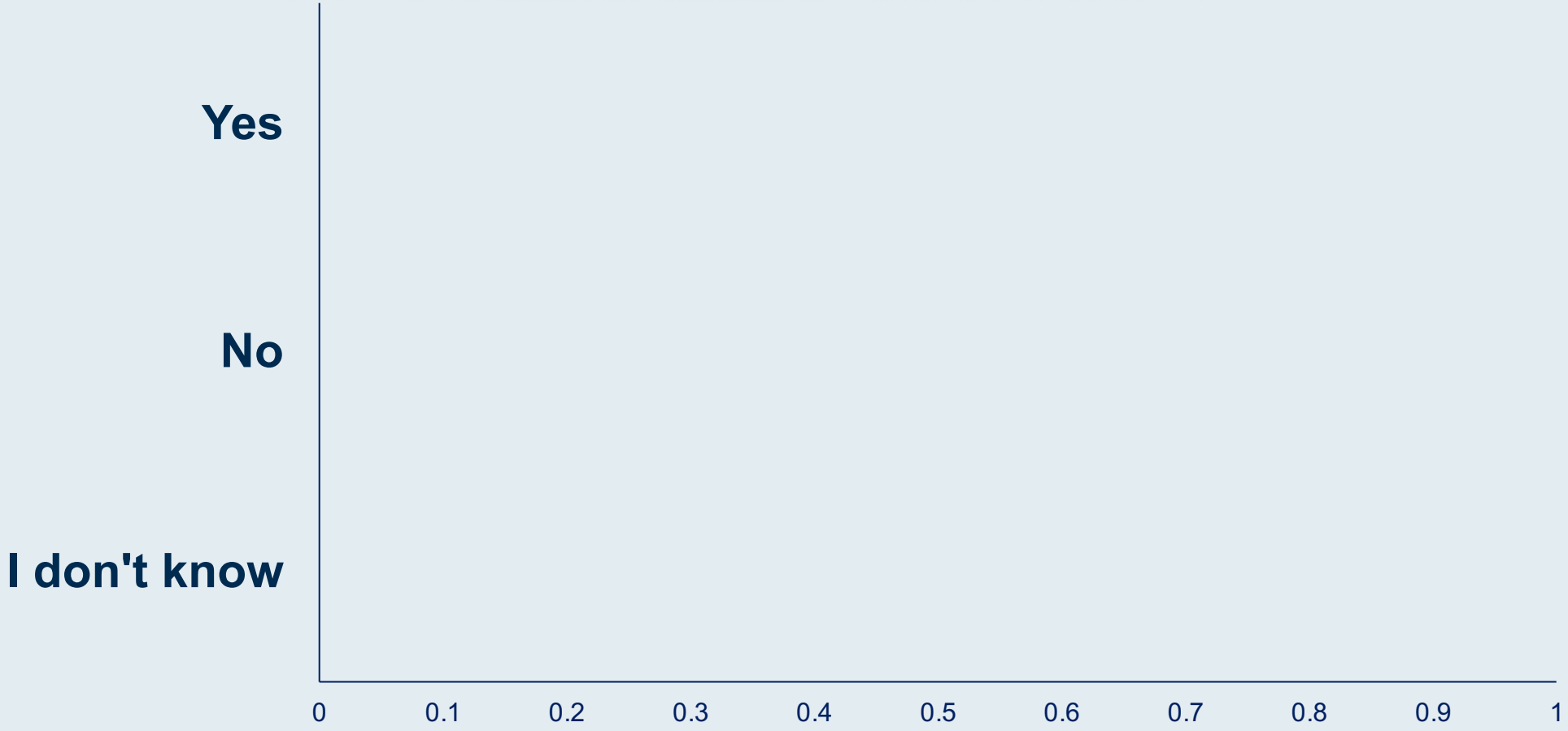


Survey of 50 US-based medical oncologists

According to your clinical experience, do PARP inhibitors cause insomnia?



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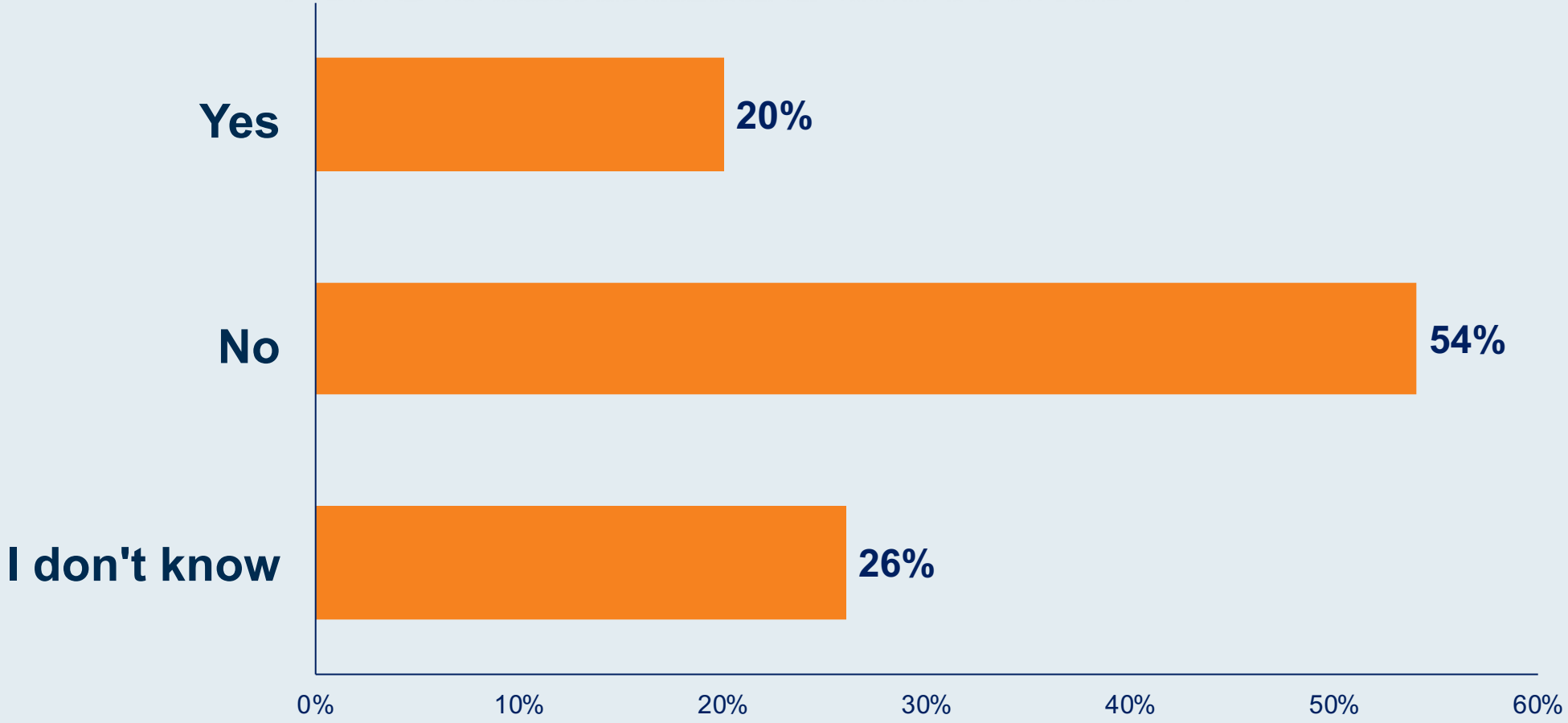

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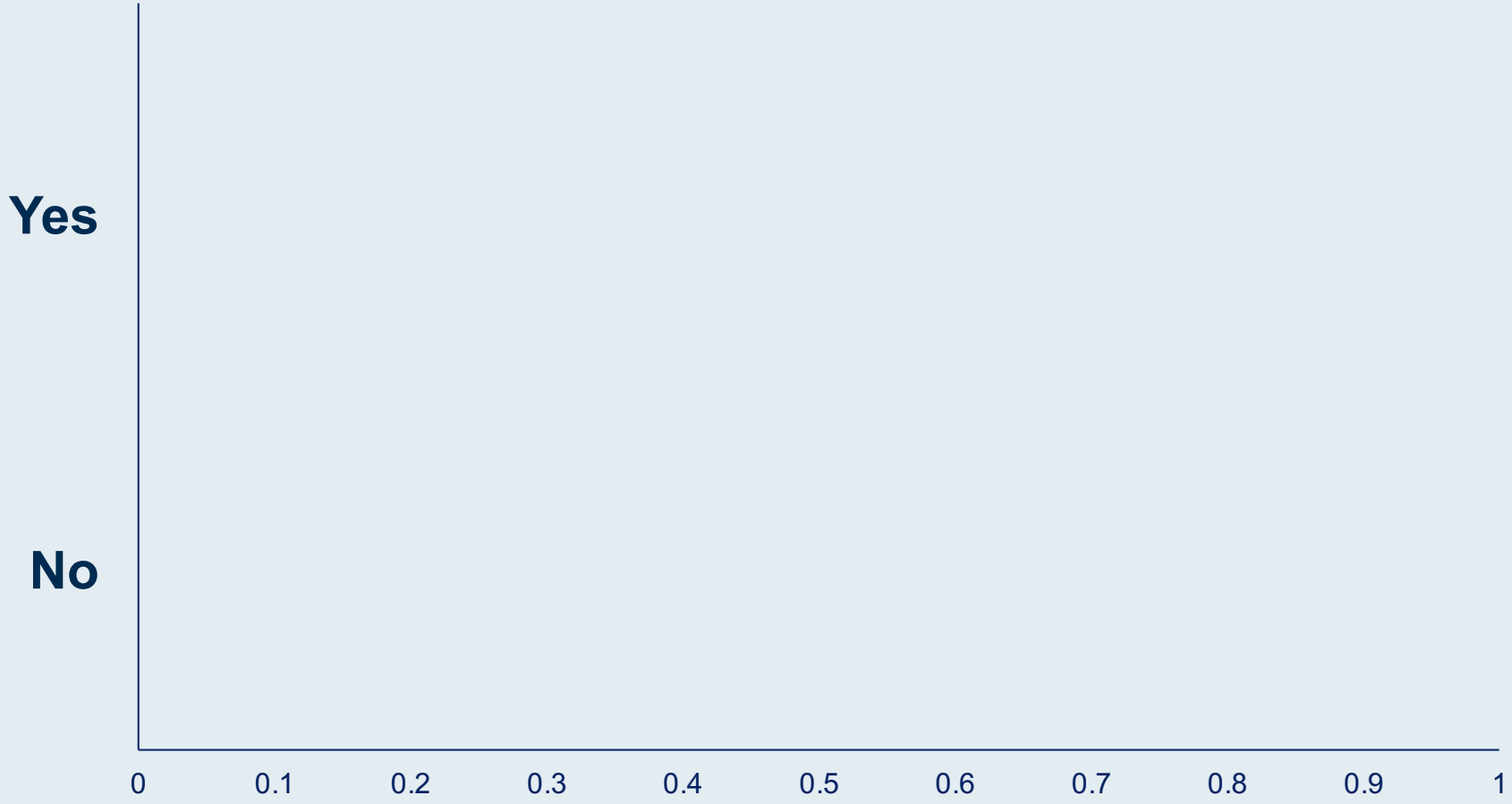

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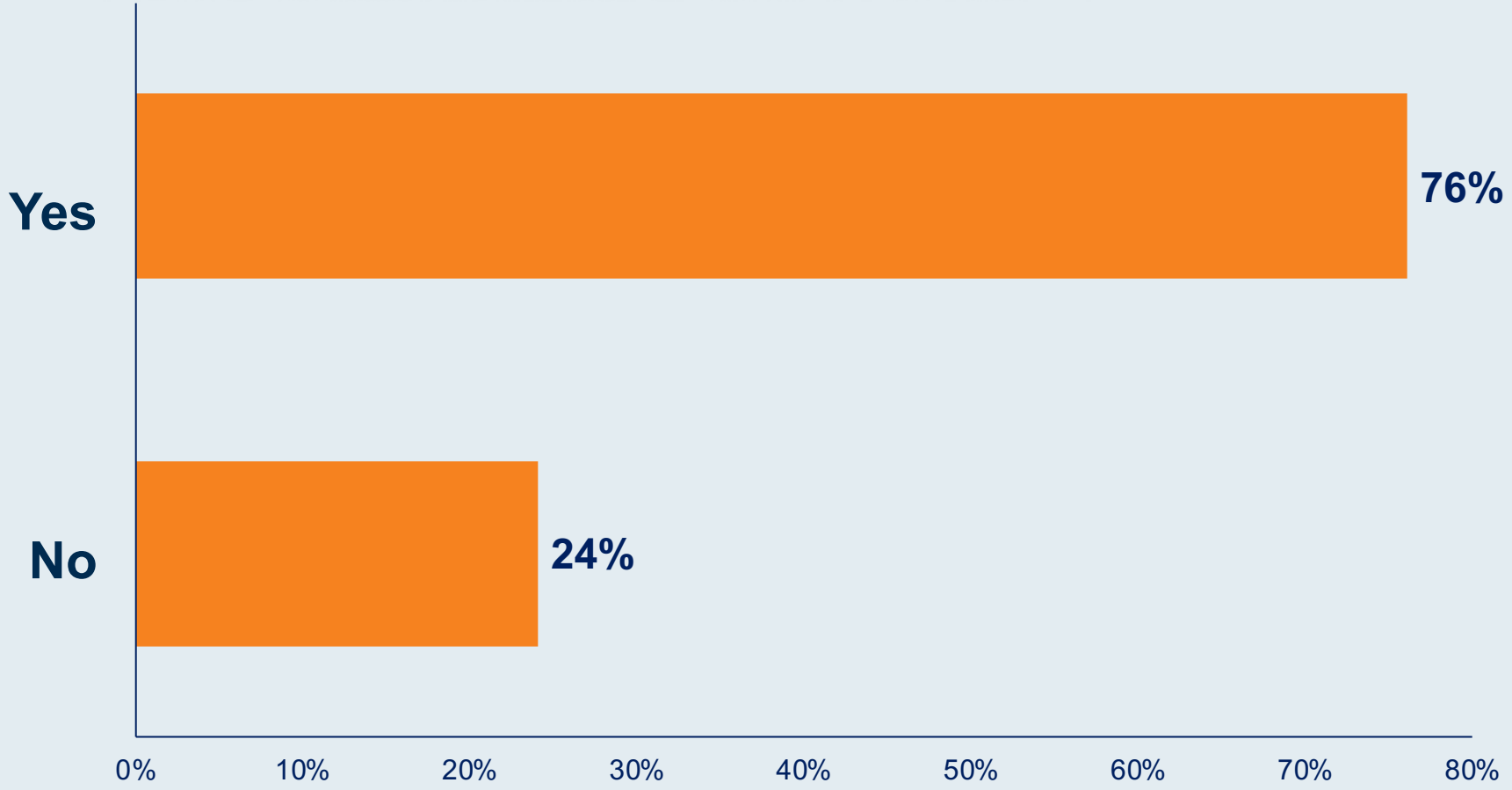

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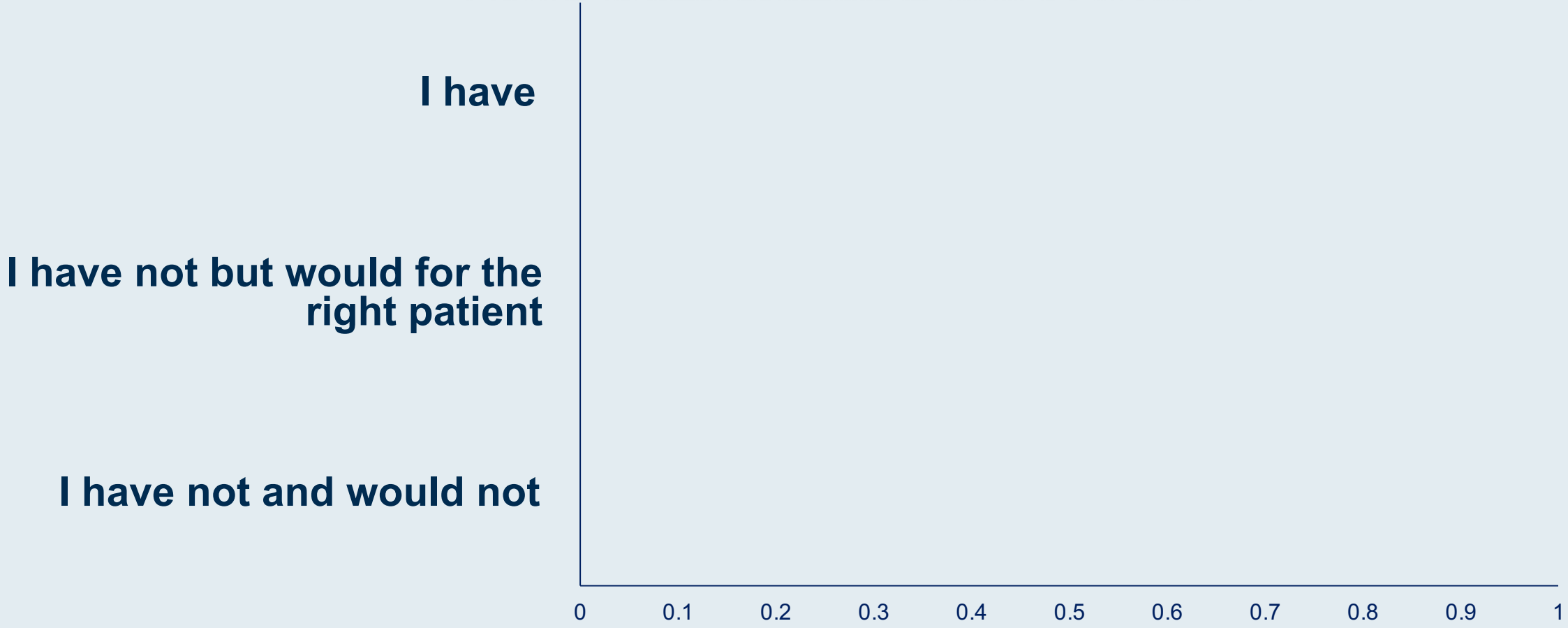
Outside of a clinical trial, have you used or would you use a second PARP inhibitor or continue the same PARP inhibitor for a patient with ovarian cancer who experienced disease progression on a PARP inhibitor?



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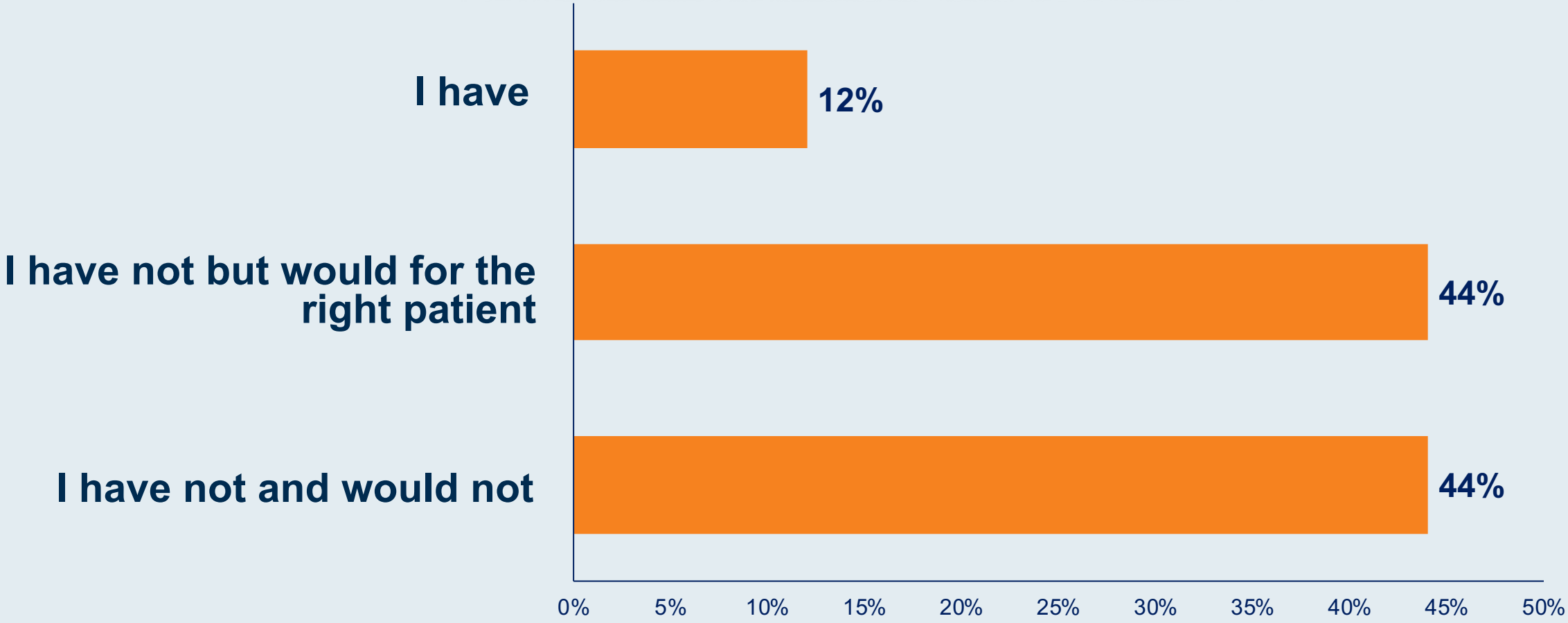

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Agenda

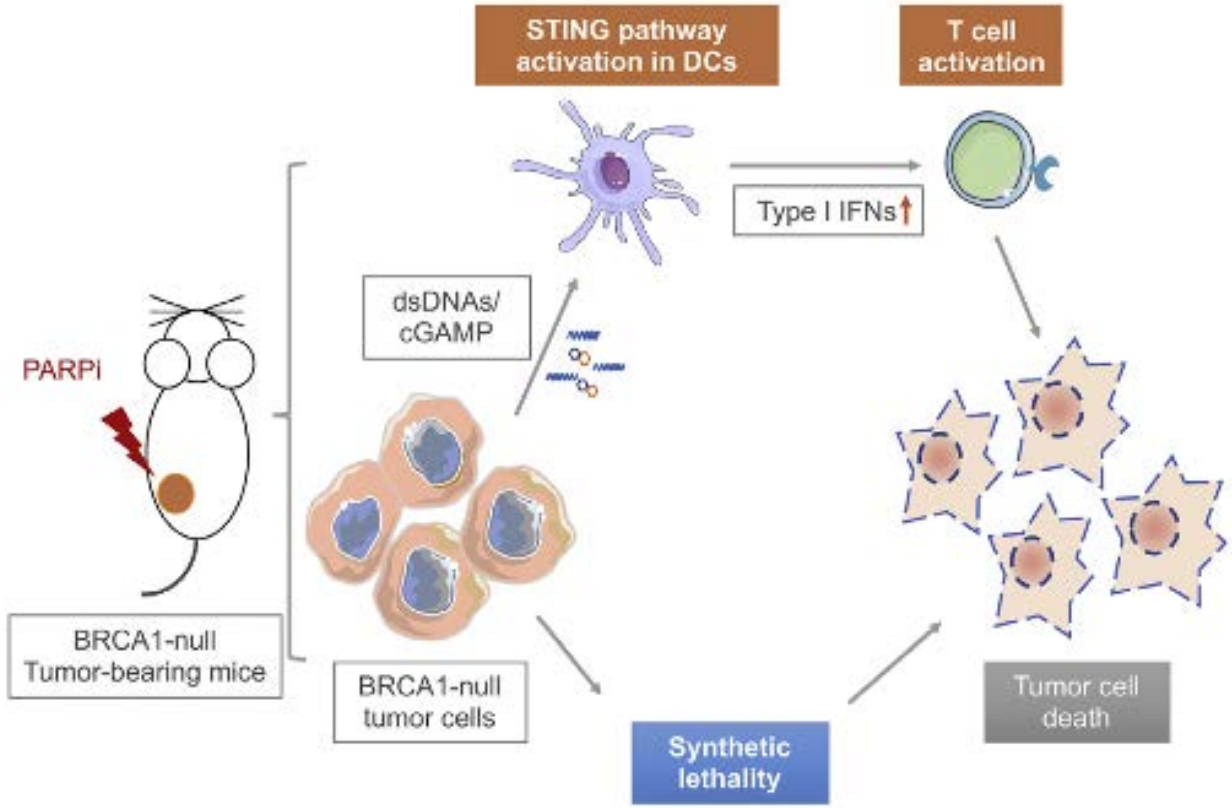
Module 1: PARP Inhibitor Maintenance in the Up-Front Setting

- Genomic Evaluation
- Key Clinical Trial Results
  - SOLO-1, PRIMA, PAOLA-1, VELIA
- “Top 15” Clinical Questions

Module 2: Future Directions of PARP Inhibitors

Immune Synergy: PARPi Elicit STING Dependent Antitumor Immunity in EOC

- **T cell-mediated cytotoxicity is important for therapeutic activity of PARP inhibition**
- **Olaparib-treated Brca1-deficient tumor cells activate the STING pathway in APCs**
- **STING pathway activation is required for the antitumor efficacy of PARP inhibition**
- **PD-1 blockade enhances the antitumor efficacy of olaparib in Brca1-deficient tumors**



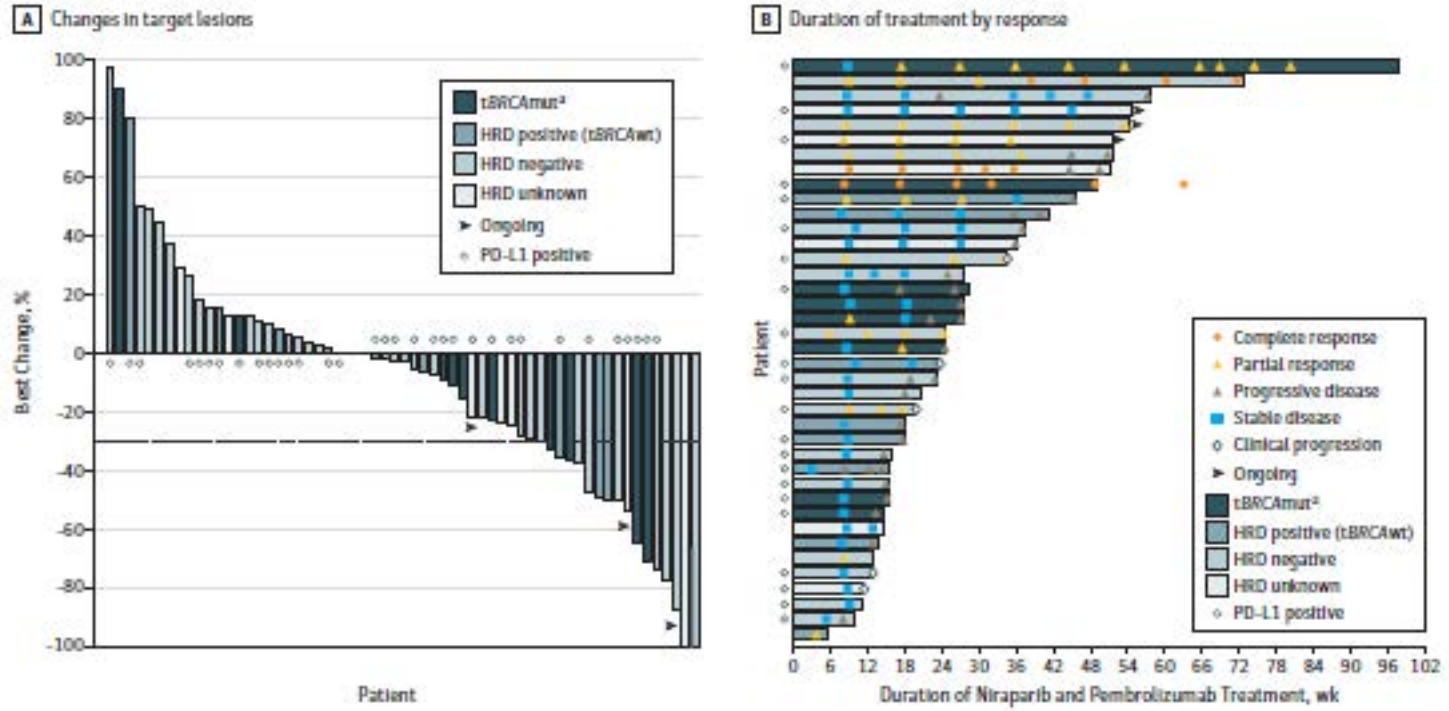
Ling et al. Cell Reports (2018); 25: 2972

Courtesy of Kathleen Moore, MD

Immune Combinations: TOPACIO: Niraparib + Pembrolizumab

Table 1. Patient Characteristics at Baseline

Characteristic	Combined Phases 1 and 2 Patients With Ovarian Carcinoma (n = 62)
Age, median (range), y	60 (46-83)
ECOG performance status, No. (%)[a]	
0	44 (71)
1	18 (29)
Prior lines of therapy, median (range)	3 (1-5)
Prior bevacizumab, No. (%)	39 (63)
Prior chemotherapy, No. (%)[b]	
Anthracycline	40 (65)
Cyclophosphamide	5 (8)
Gemcitabine hydrochloride	29 (47)
Paclitaxel	61 (98)
Platinum	62 (100)
Topotecan hydrochloride	3 (5)
Platinum status, No. (%)	
Resistant	30 (48)
Refractory	17 (27)
Not applicable[c]	15 (24)
tBRCA status, No. (%)	
BRCA1 mutation	9 (15)
BRCA2 mutation	2 (3)
BRCA wild type	49 (79)
Unknown	2 (3)
HRD status, No. (%)	
HRD positive	22 (35)
HRD negative	33 (53)
HRD unknown	7 (11)
PD-L1 status, No. (%)[d]	
Positive	35 (56)
Negative	21 (34)
Unknown	6 (10)

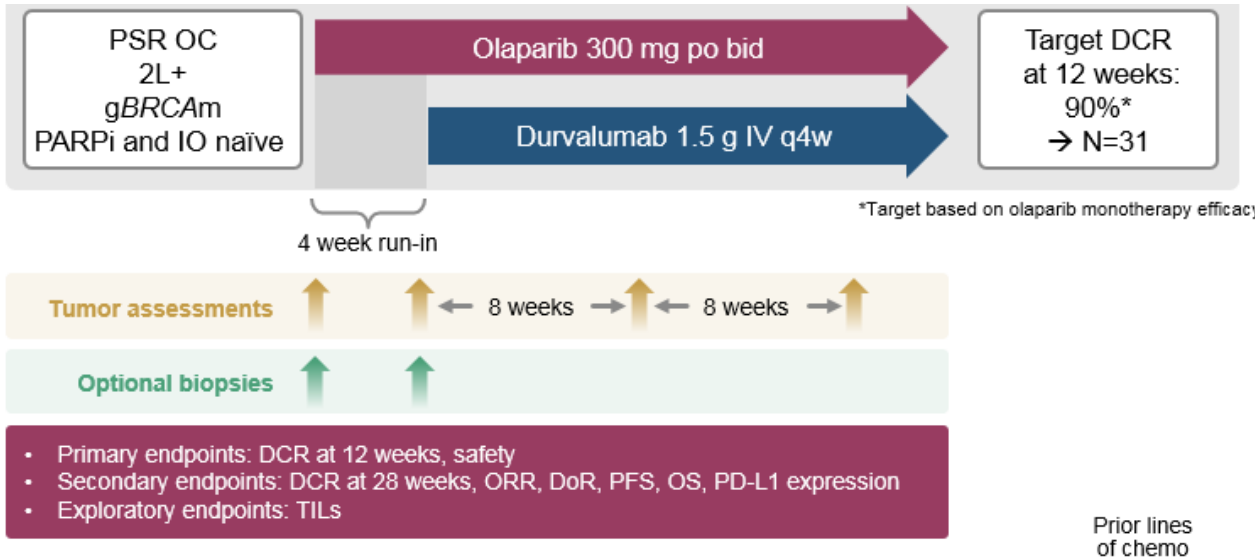


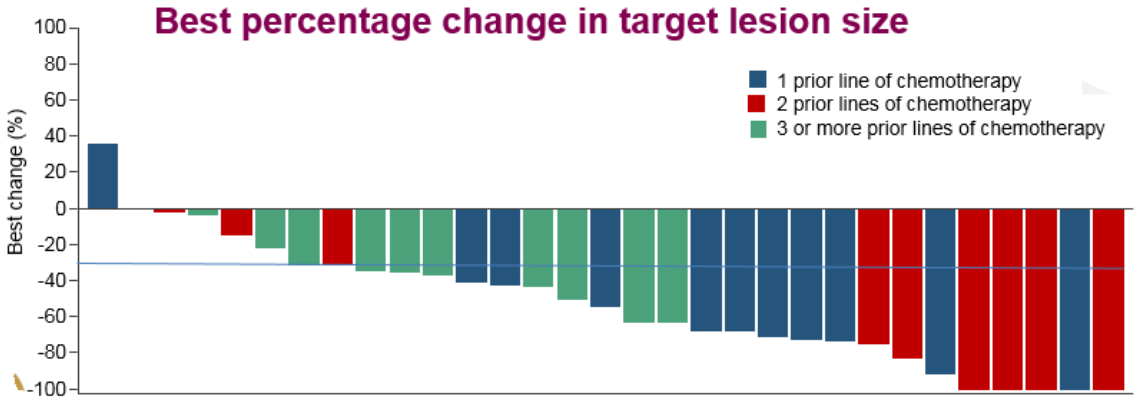
Best Overall Response	Response Data (n = 60)
Complete response, No. (%)	3 (5)
Partial response, No. (%)	8 (13)
Stable disease, No. (%)[a]	28 (47)
Progressive disease, No. (%)	20 (33)
Inconclusive, No. (%)[b]	1 (2)
ORR, % (90% CI)[c]	18 (11-29)
DCR, % (90% CI)[d]	65 (54-75)

Konstantinopoulos et al. JAMA Oncol. 2019; 5(8):1141

Courtesy of Kathleen Moore, MD

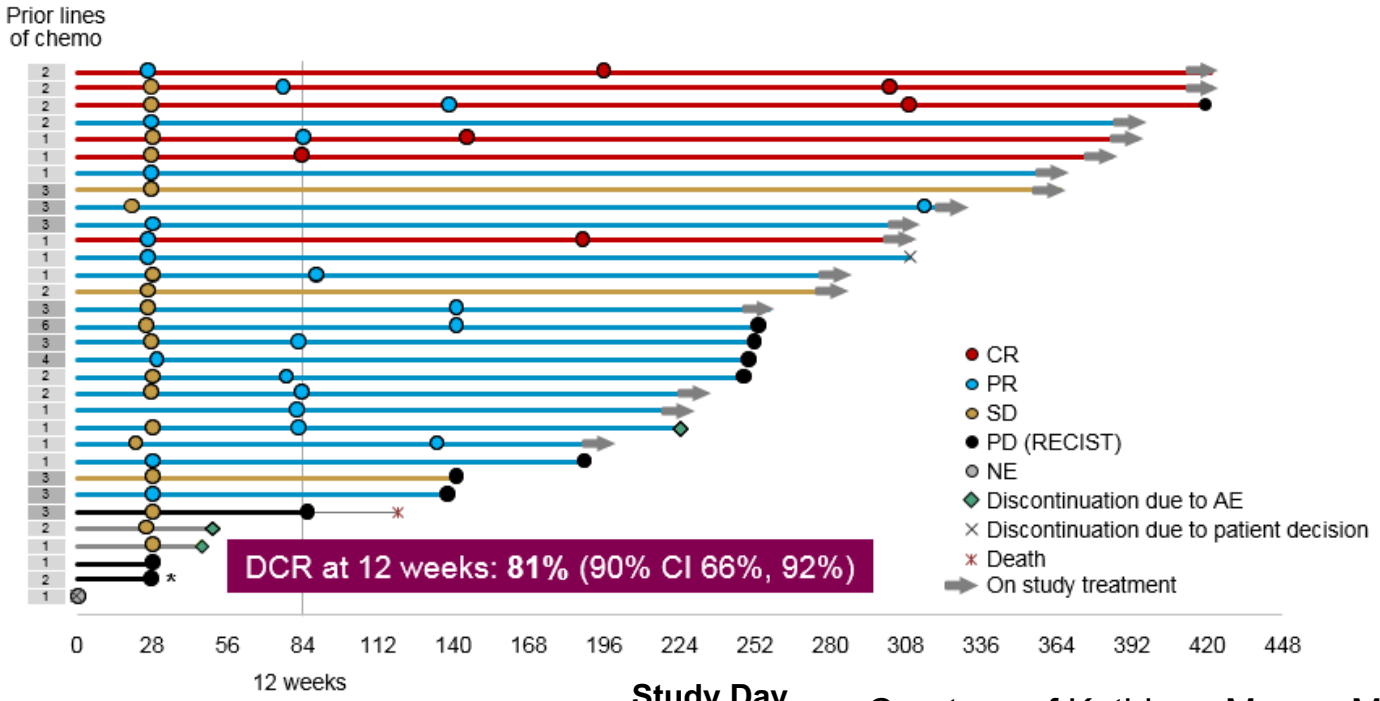
MEDIOLA: Olaparib and Durvalumab (BRCA+)/Platinum sensitive





N=32
44% with 1 prior regimen
25% with 2

ORR 72% (23/32)
CR 19%
PR 53%



Drew et al. SGO Annual Meeting,2019 Oahu, HI

Courtesy of Kathleen Moore, MD

Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

Thursday, July 30, 2020
12:00 PM – 1:00 PM ET

Faculty

Rafael Fonseca, MD

Moderator

Neil Love, MD

Co-provided by USF Health RTP RESEARCH TO PRACTICE

Thank you for joining us!

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