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Advanced Ovarian Cancer: New Insights on Making the Most of Mutations and Biomarkers to Inform Treatment Plans

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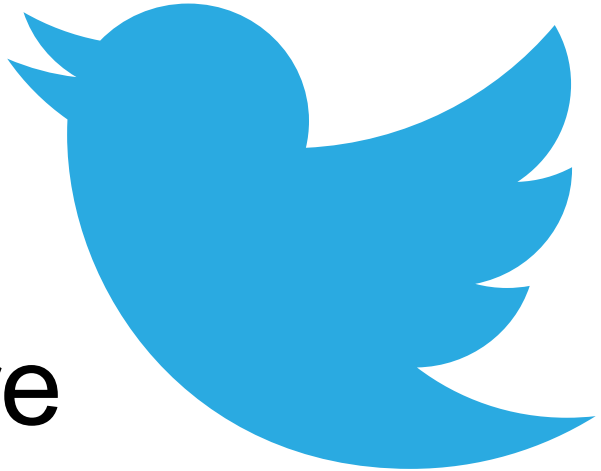

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Learning Objective 1

Incorporate germline and somatic genetic, genomic, and other biomarker testing that is necessary to inform treatment decision-making in OC.

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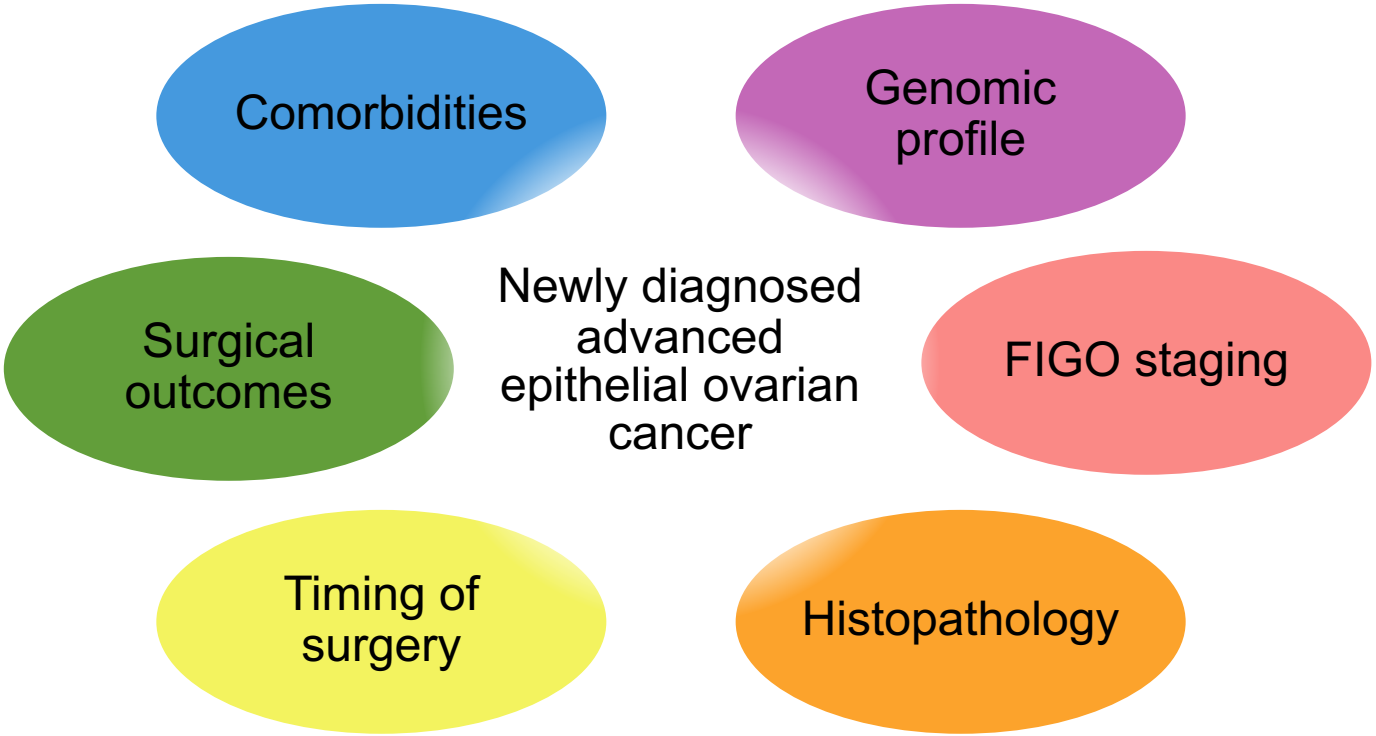
Learning Objective 2

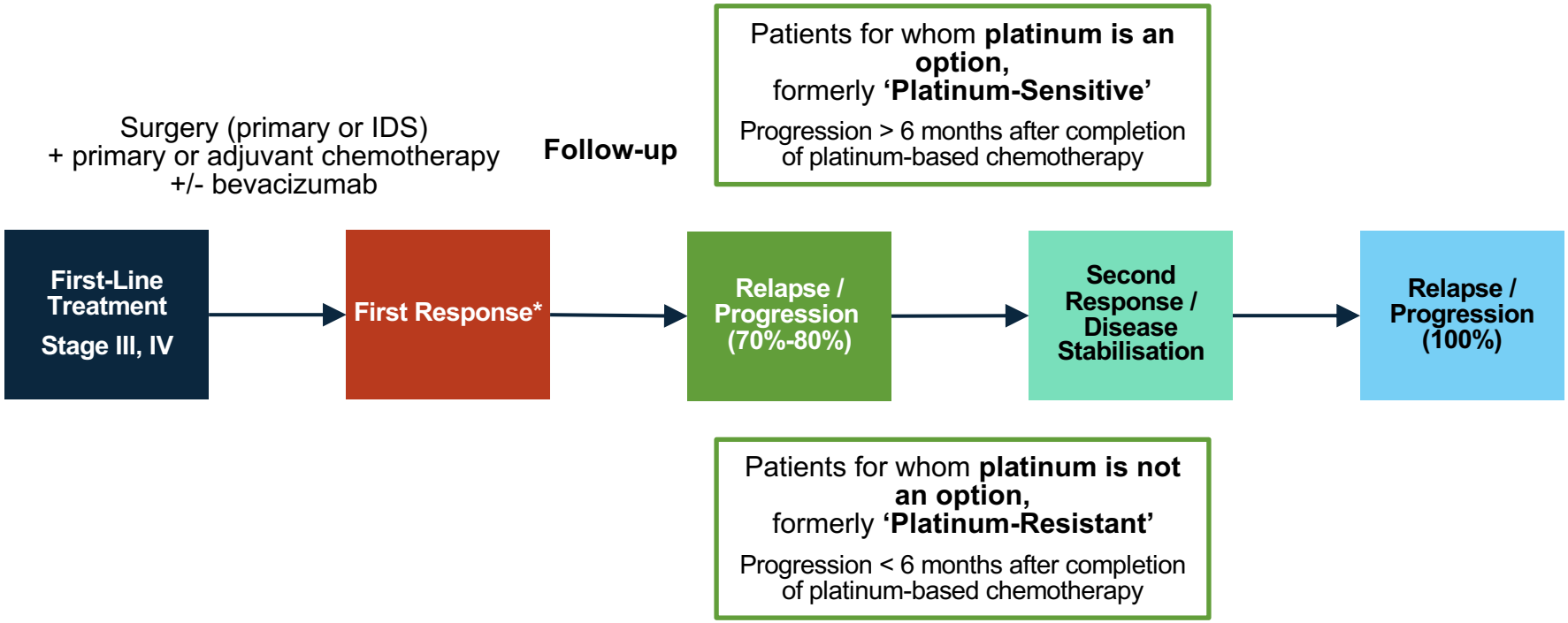
Evaluate recent evidence of mutation and biomarker connection to treatment efficacy.

Considerations for Selection of Frontline Therapy in Ovarian Cancer



FIGO = International Federation of Gynecology and Obstetrics.
Nero C, et al. *Cancers (Basel)*. 2021;13(6):1298.

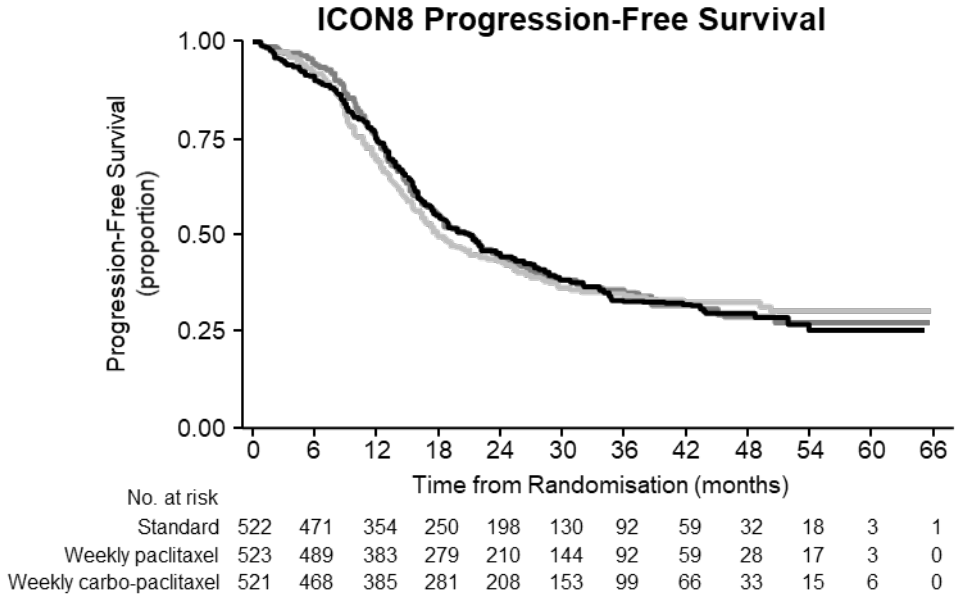
The Typical Course of Advanced Ovarian Cancer



*Around 5% of patients are primary treatment-refractory, meaning disease progressed during therapy or within 4 weeks after the last dose.
IDS = Interval debulking surgery.

1. Ledermann JA, et al. *Ann Oncol*. 2013;24(Suppl 6):vi24-vi32. 2. Giornelli GH. *Springerplus*. 2016;5(1):1197. 3. Pignata S, et al. *Ann Oncol*. 2017;28(suppl_8):viii51-viii56. 4. du Bois A, et al. *Cancer*. 2009;115(6):1234-1244. 5. Wilson MK, et al. *Ann Oncol*. 2017;28(4):727-732.

Platinum Therapy Can't Get Much Better



	Standard (n = 522)	Weekly paclitaxel (n = 523)	Weekly carbo-paclitaxel (n = 521)
Progressions	330 (63%)	335 (64%)	338 (65%)
Median PFS, mo	17.9	20.6	21.1
Log rank (vs. standard)		P=0.45	P=0.56
HR vs. Standard (97.5% CI)		0.92 (0.77–1.09)	0.94 (0.79–1.12)
Restricted means	24.4 mos	24.9 mos	25.3 mos

Weekly dose-dense chemotherapy can be delivered successfully as first-line epithelial ovarian cancer treatment without substantial toxicity increase; it does not significantly improve PFS compared to standard 3-weekly chemotherapy

CI = Confidence interval. HR = Hazard ratio. Mos = Months. N = number. PFS = Progression-free survival.

Clamp AR, et al. *Ann Oncol*. 2017;28(suppl_5):v605-v649.

Polling Question

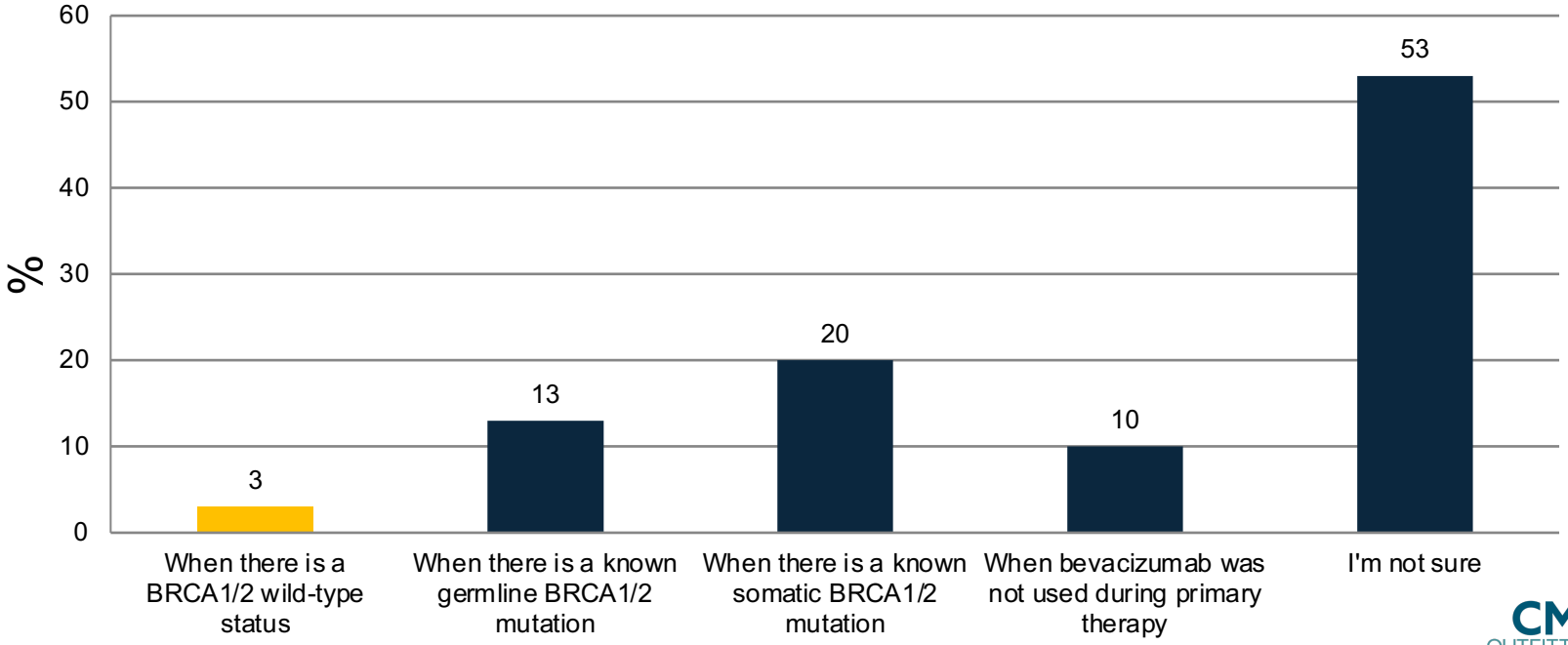
Following primary treatment with platinum-based chemotherapy resulting in a partial response, in which scenario will HRD testing inform next steps in therapy decisions?

A. When there is a BRCA1/2 wild-type status
B. When there is a known germline BRCA1/2 mutation
C. When there is a known somatic BRCA1/2 mutation
D. When bevacizumab was not used during primary therapy
E. I'm not sure

HRD = Homologous recombination deficiency.

Audience Response

Following primary treatment with platinum-based chemotherapy resulting in a partial response, in which scenario will HRD testing inform next steps in therapy decisions?



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Which Patients Should Receive Genetic Testing?

Leading oncology societies recommend testing all women with ovarian cancer

NCCN
Genetic counseling and testing should be considered in women with a history of ovarian carcinoma, fallopian tube cancer, or primary peritoneal cancer[1]

SGO
Women diagnosed with epithelial ovarian, tubal, and peritoneal cancers should receive genetic counseling and be offered genetic testing, even in the absence of family history[2]

ASCO
Genetic counseling and testing should be considered in women with epithelial ovarian, fallopian tube, or primary peritoneal cancer, even in the absence of family history[3]

ESMO
Patients with high-grade tumours should be tested for a germline BRCA mutation. Consideration should be given to testing tumours for a somatic *BRCA* mutation

Recommended testing sequence: Tumor *BRCA* first (larger population), Germline testing second (genetic counseling)

ASCO = American Society of Clinical Oncology. ESMO = European Society of Medical Oncology. NCCN = National Comprehensive Cancer Network. SGO = Society of Gynecologic Oncology.

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer, Version 1.2022. NCCN Website. 2022. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed January 30, 2022. 2. Society of Gynecologic Oncology (SGO). SGO clinical practice statement: Genetic testing for ovarian cancers (SGO, October 2014). SGO Website. 2014. https://www.sgo.org/resources/genetic-testing-for-ovarian-cancer/. Published 2014. Accessed February 21, 2022. 3. Lu JF, et al. *J Clin Oncol*. 2014;32:833-840. 4. Ledermann JA, et al. *Ann Oncol*. 2013;24(S6):vi24–vi32

PARP Inhibitors Approved for Treatment of Recurrent Ovarian Cancer

STUDY	STUDY 1[1] N = 137	ARIEL2/STUDY 10[2] BRCAmut N = 106	QUADRA[3] gBRCAmut N = 63	QUADRA[3] HRD+ (BRCAwt)/ (Platinum Sensitive) N = 35
AGENT	**Olaparib**	**Rucaparib**	**Niraparib**	**Niraparib**
ORR	**34%** [95% CI, 26-42]	**54%** [95% CI, 44-64]	**39% (platinum sensitive)** [95% CI, 17-64] **29 % (platinum resistant)** [95% CI, 11-52] **19% (platinum refractory)** [95% CI, 4-46]	**20%** [95% CI, 8-37]
DOR	**7.9 mo** [95% CI, 5.6-9.6]	**9.2 mo** [95% CI, 6.6-11.6]	**8.3 mo** [6.5-NR] (entire population)	**8.3 mo** [6.5-NR] (entire population)
LOT	≥ 3	≥ 2	≥ 3	≥ 3

DOR = Duration of response. LOT = Line of treatment. NR = Not reported. ORR = Objective response rate.

1. Domchek SM, et al. *Gynecol Oncol*. 2016;140:199-203. 2. Oza AM, et al. *Gynecol Oncol*. 2017;12:267-275. 3. Moore KN, et al. *Lancet Oncol*. 2019;20:636-648.

PARP Inhibitors Approved for Switch Maintenance

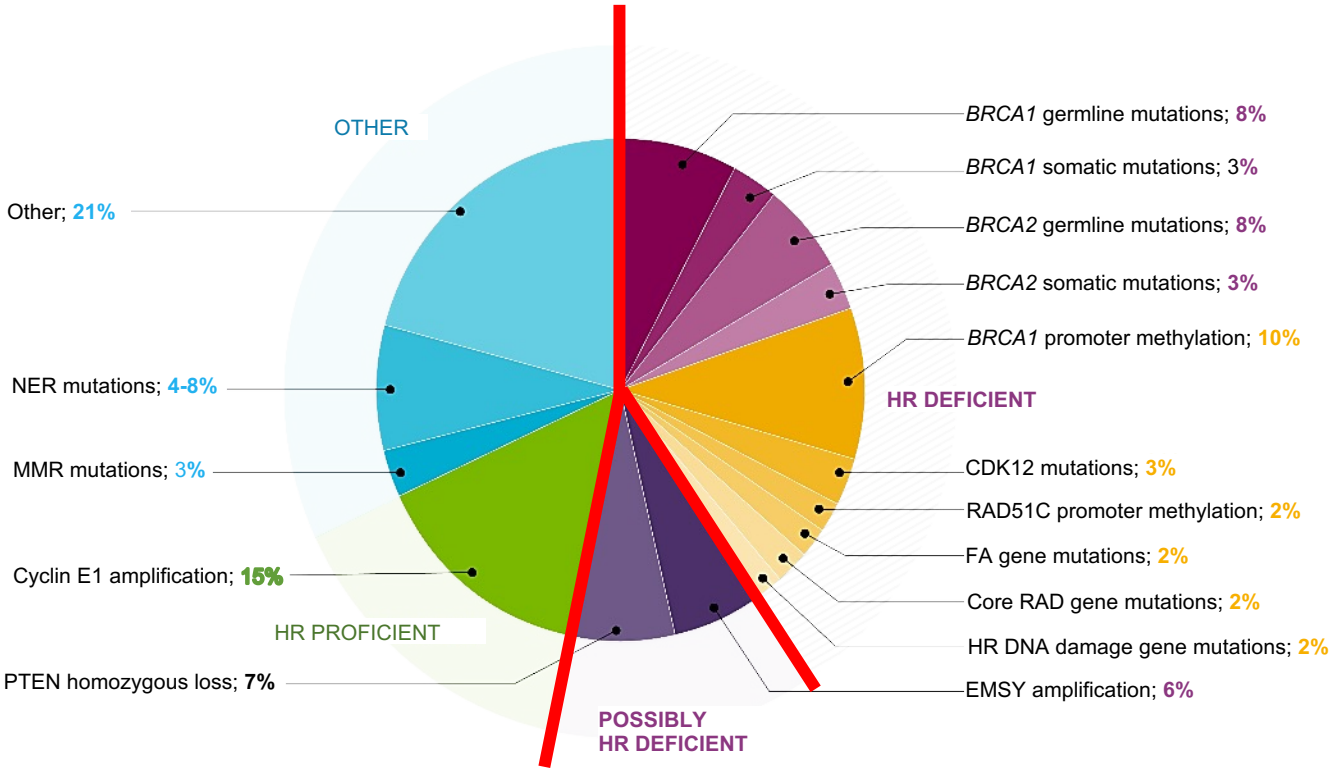
	OLAPARIB[1,2]	RUCAPARIB[3]	NIRAPARIB[4]
MOA	PARP-1/2/3 inhibitor	PARP-1/2/3 inhibitor	PARP-1/2 inhibitor
Treatment indication	≥ 3 lines of chemo with deleterious or suspected gBRCAmut OC	≥ 2 lines of chemo with deleterious g/sBRCAmut EOC, FTC, PPC	≥ 3 lines of chemo with HRD$^+$ OC, FTC, PPC • Deleterious or suspected BRCAmut, or • Genomic instability and progression > 6 mo after response to last platinum-based chemo
Maintenance indication	First-line maintenance for high-risk advanced (FIGO stage III-IV) BRCAmut high-grade EOC, FTC, PPC Second-line maintenance for recurrent EOC, FTC, PPC	Second-line maintenance for recurrent EOC, FTC, PPC	Second-line maintenance for recurrent EOC, FTC, PPC
Dose	300 mg PO twice daily	600 mg PO twice daily	300 mg PO once daily

EOC = Epithelial ovarian cancer. FTC = Fallopian tube cancer. Mg = Milligrams. OC = Ovarian cancer. PO = Oral administration. PPC = Primary peritoneal cancer.

1. LYNPARZA® (olaparib). Wilmington, DE: AstraZeneca Pharmaceuticals LP. 2022. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=741ff3e3-dc1a-45a6-84e5-2481b27131aa. Accessed February 21, 2022. 2. RUBACA® (rucaparib). Boulder, CO: Clovis Oncology, Inc. 2020. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a6d46c03-bb1d-417b-b8e5-3bffe352fe29. Accessed February 21, 2022. 3. ZEJULA® (niraparib). Research Triangle Park, NC: GlaxoSmithKline LLC. 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c15c7b7e-4b7f-4489-bbbc-884caeee0669. Accessed February 21, 2022.

Rationale for PARPi Treatment of Ovarian Cancer

- PARP repairs SSBs
- Normal and HR-proficient cancer cells can repair DSBs
- HR-deficient cancer cells rely on PARP to repair DSBs
- Inhibition of PARP results in "synthetic lethality"



DSB = Double-stranded DNA break. HR = Homologous recombination. MMR = Mismatch repair. NER = Nucleotide excision repair. PARPi = Poly(ADP-ribose) polymerase inhibitor. SSB = Single-stranded DNA break.

Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5:1137-1154. McCabe N, et al. *Cancer Res*. 2006;66:8109-8115.

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STAGE II, III, IV[v]
POST PRIMARY TREATMENT

Stage II–IV[v] (post primary treatment)
- **Imaging[a] as clinically indicated:**
- **Chest/ abdominal/ pelvic CT, MRI, PET/CT, or PET (skull base to mid-thigh)**

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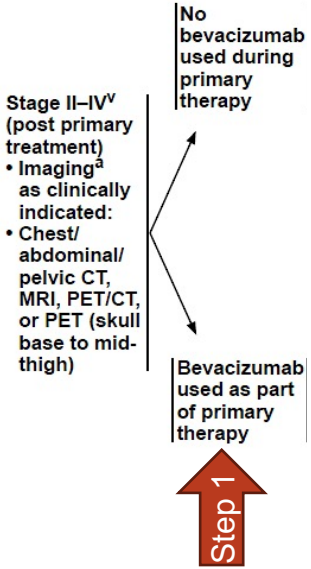
MAINTENANCE THERAPY[m,x]



Trial	Study Arm	Median PFS (months)	Median OS (months)
GOG-0218[1]	Arm 1: carbo/pac/placebo → placebo	10.3	39.3
	Arm 2: carbo/pac/bev → placebo	11.2	38.7
	Arm 3: carbo/pac/bev → bev	14.1	39.7
ICON7[2]	Arm 1: carbo/pac → none	17.5	58.6
	Arm 2: carbo/pac/bev → bev	19.9	58.0

CT = Computed tomography. MRI = Magnetic resonance imaging. OS = Overall survival. PET = Positron emission tomography.

1. Burger RA, et al. *N Engl J Med*. 2011;365(26):2473-2483. 2. Perren TJ, et al. *N Engl J Med*. 2011;365(26):2484-2496.

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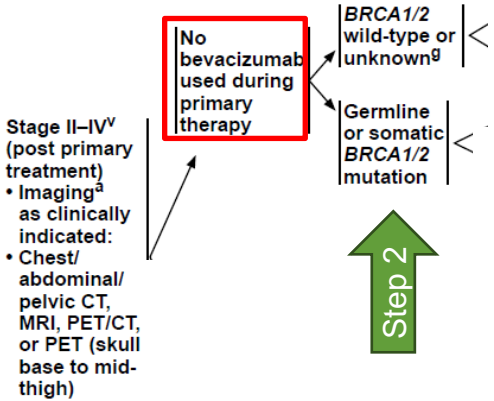
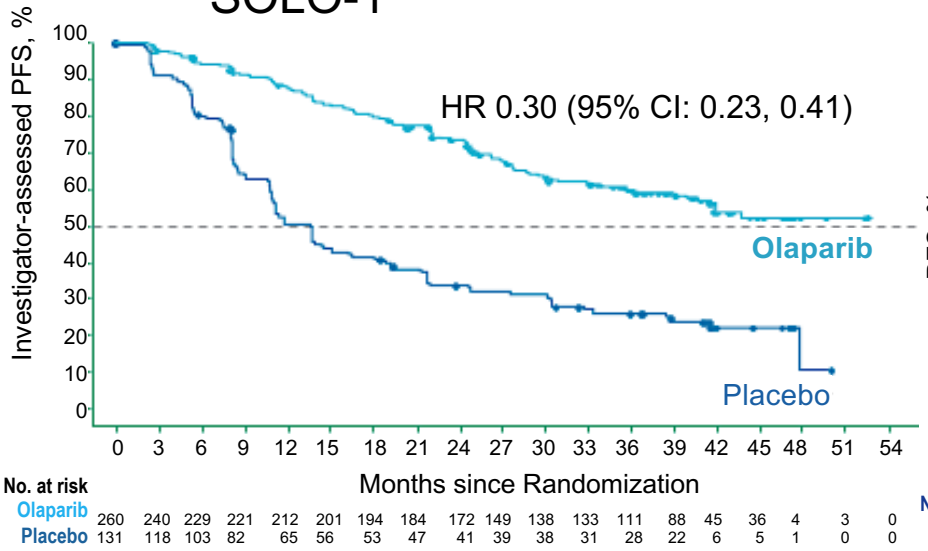


Trial	Study Arm	Median PFS (months)
SOLO-1[1]	Olaparib	56.0
	Placebo	13.8
PRIMA[2,3]	Niraparib	13.8
	Placebo	8.2

1. Moore K, et al. *N Engl J Med*. 2018;379:2495-2505. 2. González-Martin A, et al. *N Engl J Med*. 2019; 381; 2391-2402. 3. González-Martín A, et al. *Ann Oncol*. 2019;30(suppl_5):v851-v934.

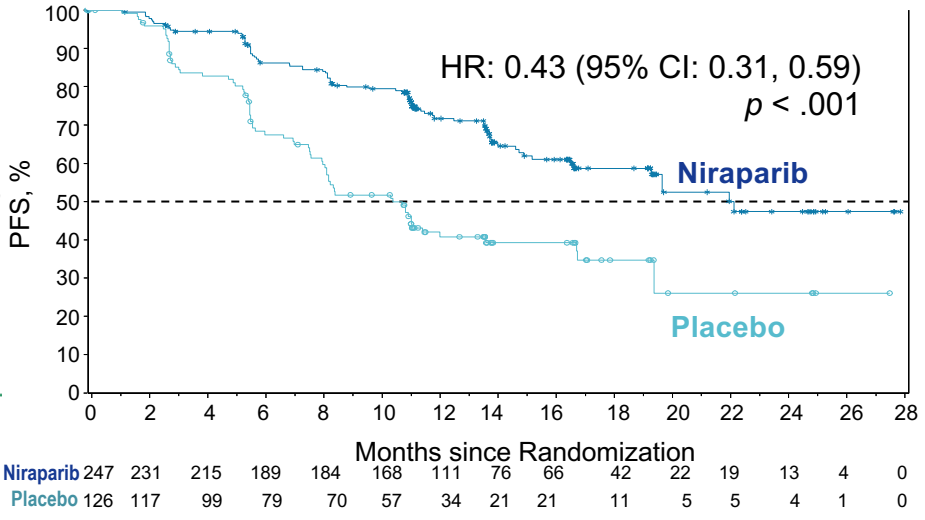
PARPi Treatment of BRCA-Mutated Tumors

SOLO-1[1]



No. at risk																		
Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0

PRIMA[2,3]

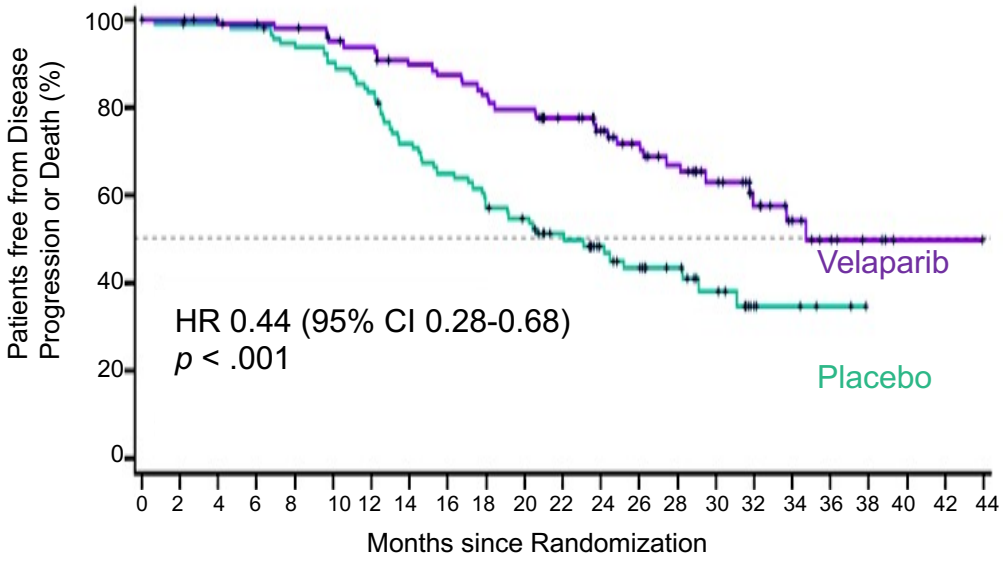


Niraparib	247	231	215	189	184	168	111	76	66	42	22	19	13	4	0
Placebo	126	117	99	79	70	57	34	21	21	11	5	5	4	1	0

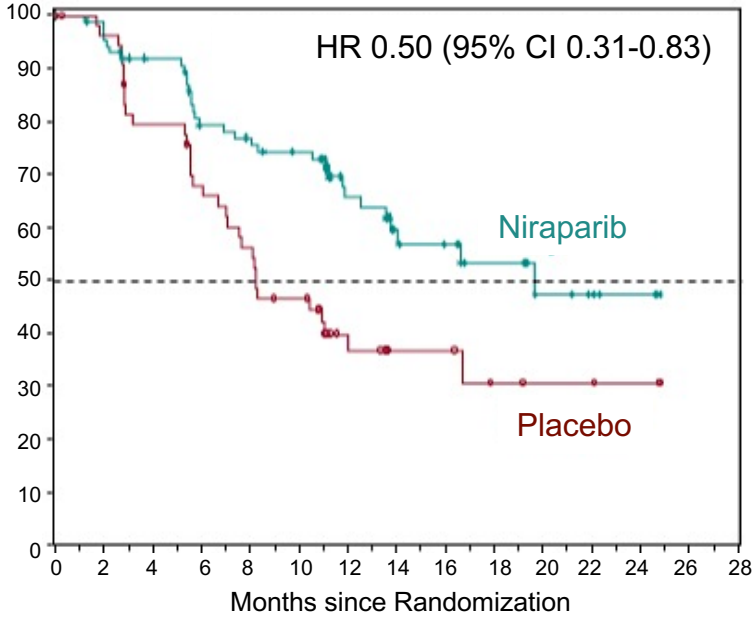
1. Moore K, et al. *N Engl J Med*. 2018;379:2495-2505. 2. González-Martin A, et al. *N Engl J Med*. 2019;381;2391-2402. 3. González-Martín A, et al. *Ann Oncol*. 2019;30(suppl_5):v851-v934.

PARPi Treatment of HRD + BRCAwt Tumors

VELIA[1]



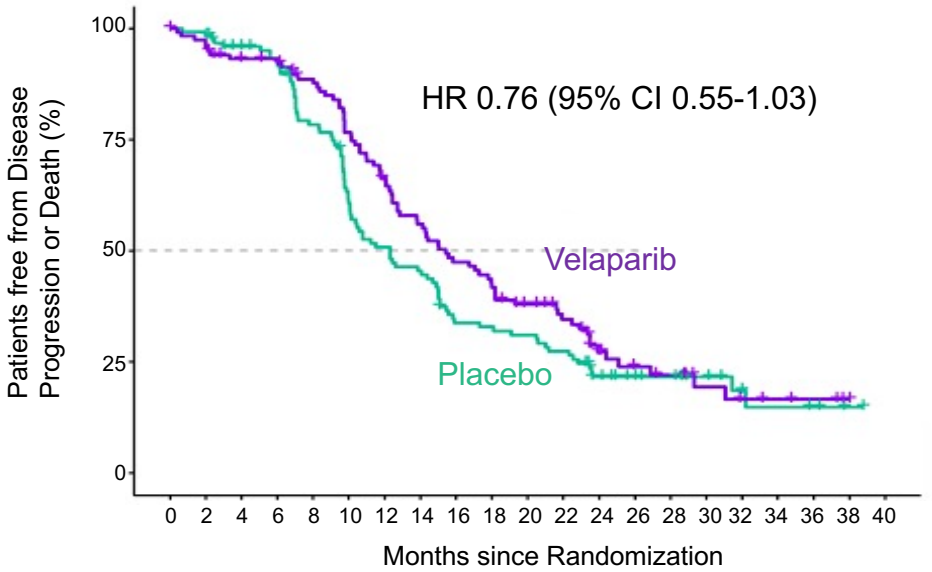
PRIMA[2,]



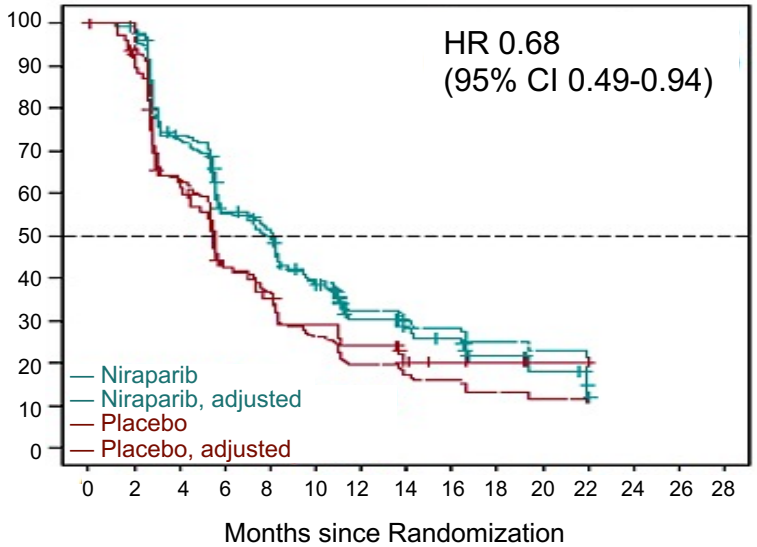
1. Coleman R, et al. *N Engl J Med*. 2019:381(25):2403-2415. 2. González-Martin A, et al. *N Engl J Med*. 2019;381;2391-2402.

PARPi Treatment of HR-Proficient Tumors

VELIA[1]



PRIMA[2]



1. Coleman R, et al. *N Engl J Med*. 2019:381(25):2403-2415. 2. González-Martin A, et al. *N Engl J Med*. 2019;381;2391-2402.

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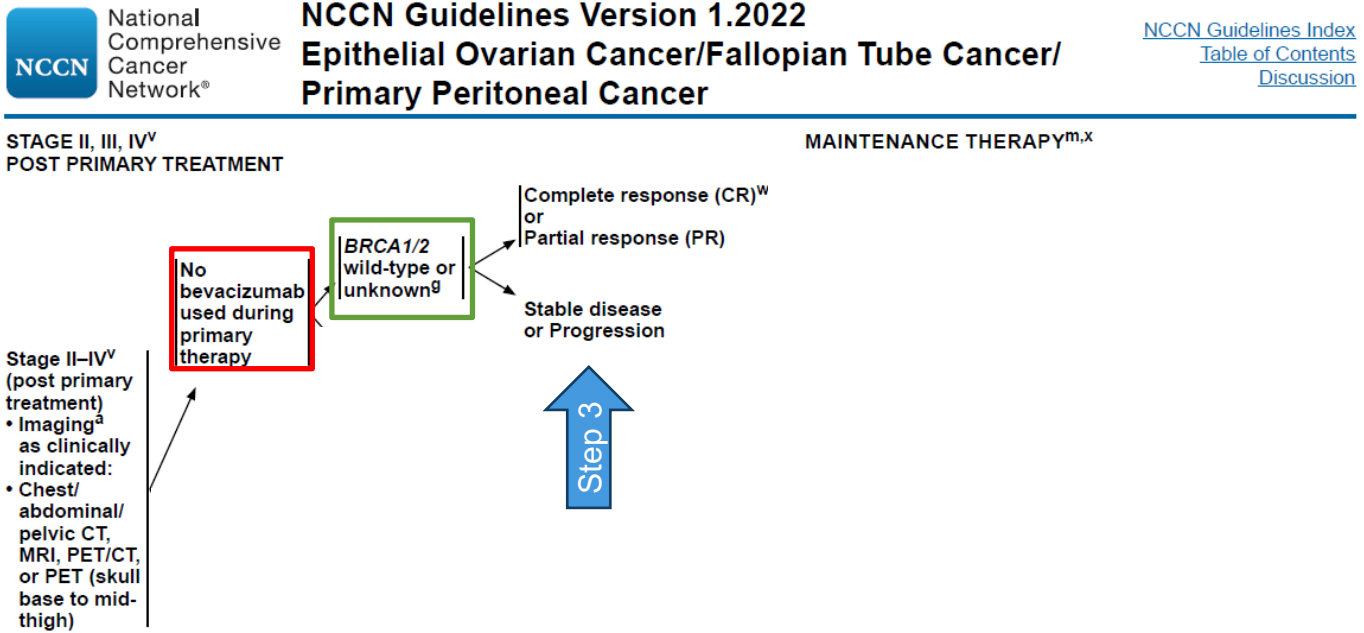

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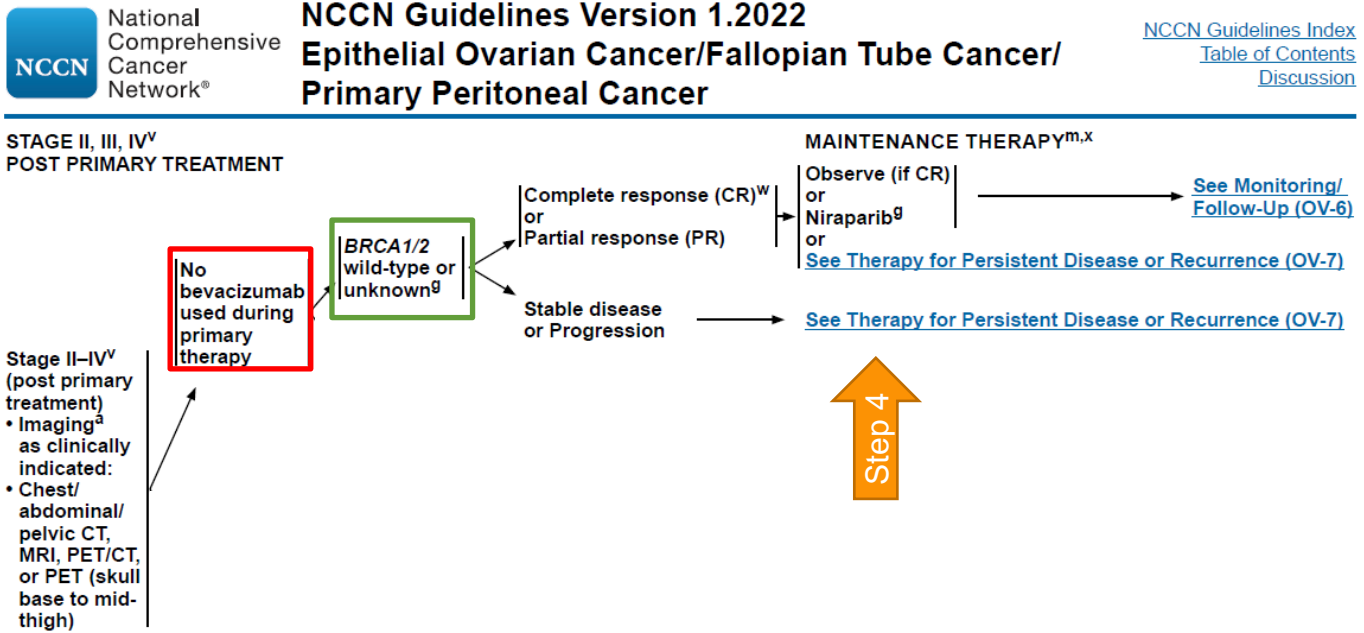

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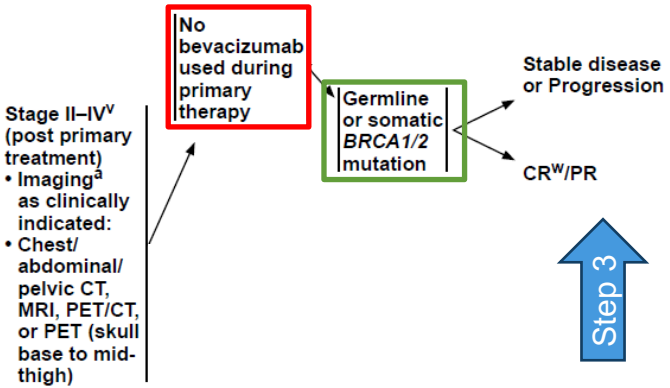

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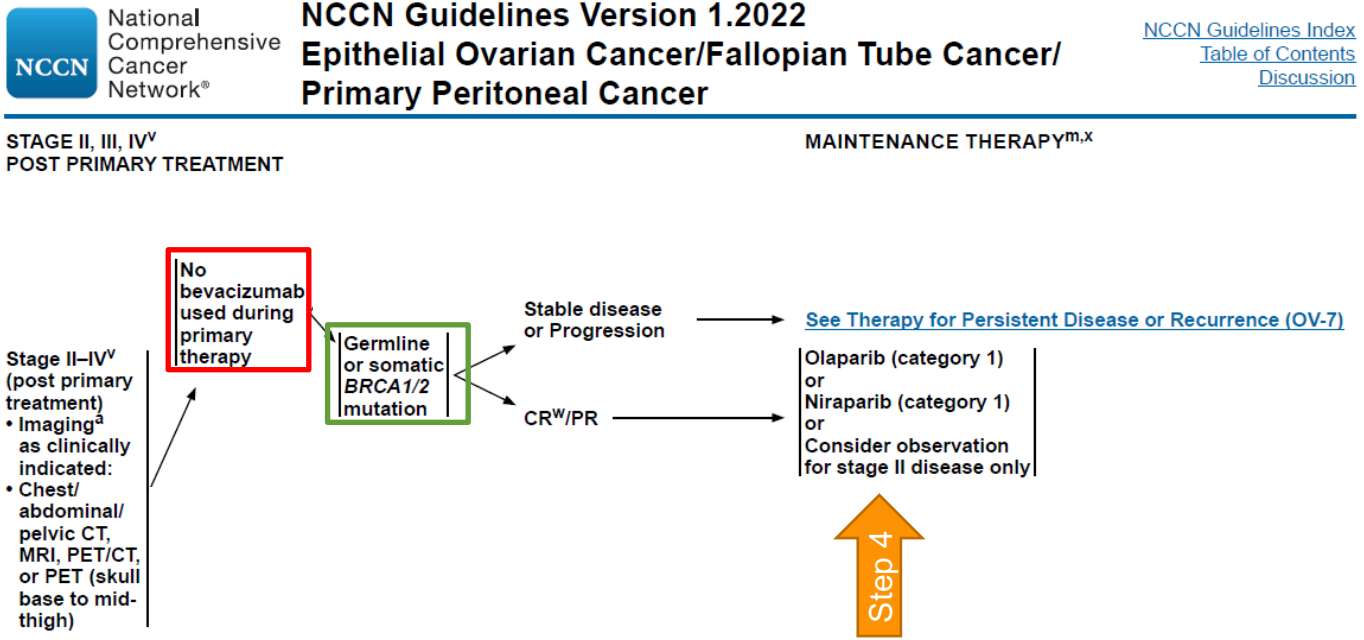

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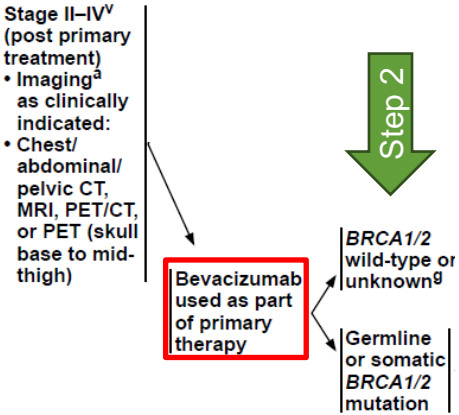

Trial	Study Arm	Median PFS (months)
SOLO-1[1]	Olaparib	56.0
	Placebo	13.8
PRIMA[2,3]	Niraparib	13.8
	Placebo	8.2

1. Moore K, et al. *N Engl J Med*. 2018;379:2495-2505. 2. González-Martin A, et al. *N Engl J Med*. 2019;381;2391-2402. 3. González-Martin A, et al. *Ann Oncol*. 2019;30(suppl_5):v851-v934.

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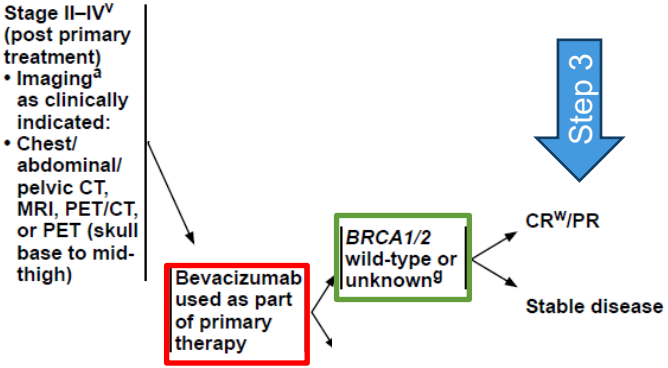

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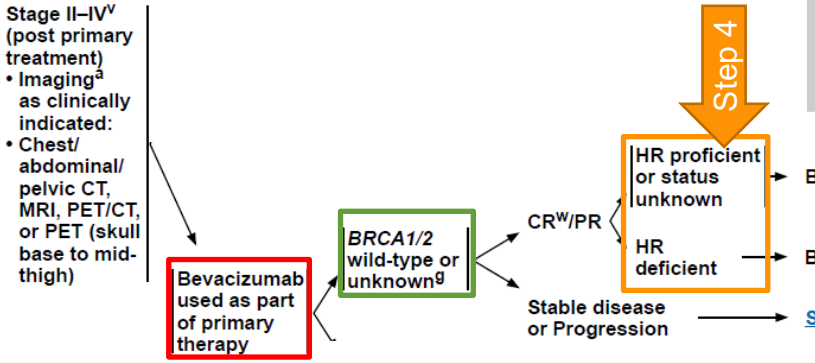
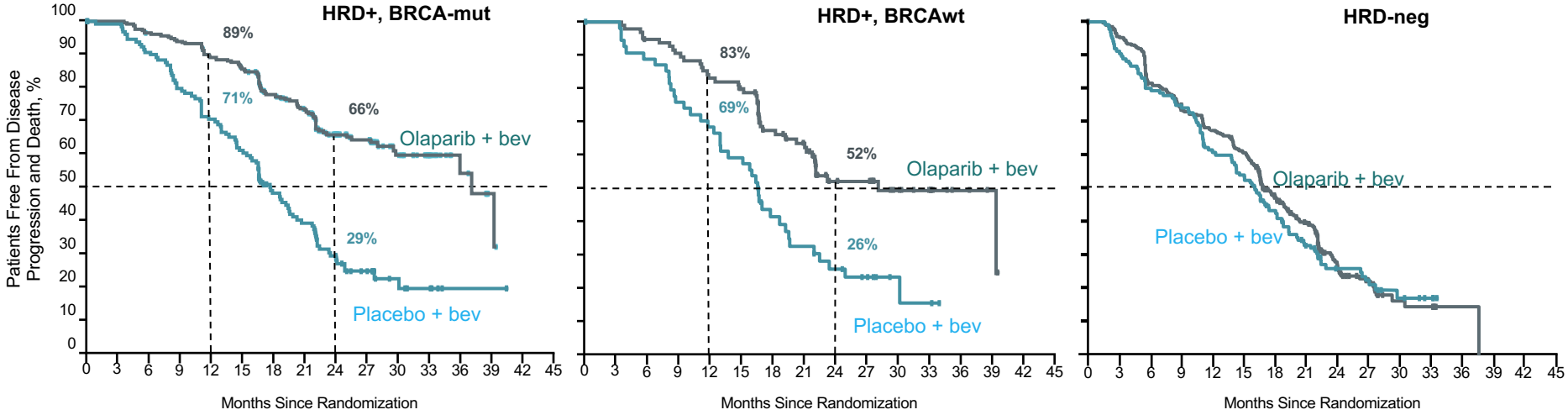


MAINTENANCE THERAPY[m,x]

Trial	Study Arm	Median PFS (months)
PAOLA1	Olaparib + bev	22.1
	Placebo + bev	16.6

Ray-Coquard I, et al. *N Engl J Med*. 2019:381(25):2416-2428.

PAOLA-1: Bevacizumab ± Olaparib



HRD+, BRCA-mut	Median PFS (months)
Olaparib + bev	37.2
Placebo + bev	17.7

HRD+, BRCA-mut	Median PFS (months)
Olaparib + bev	28.1
Placebo + bev	16.6

HRD+, BRCA-mut	Median PFS (months)
Olaparib + bev	16.9
Placebo + bev	16.0

Ray-Coquard I, et al. *N Engl J Med*. 2019:381(25):2416-2428.

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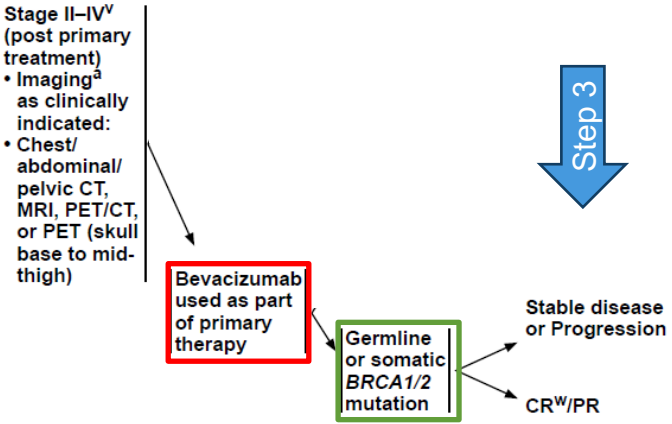

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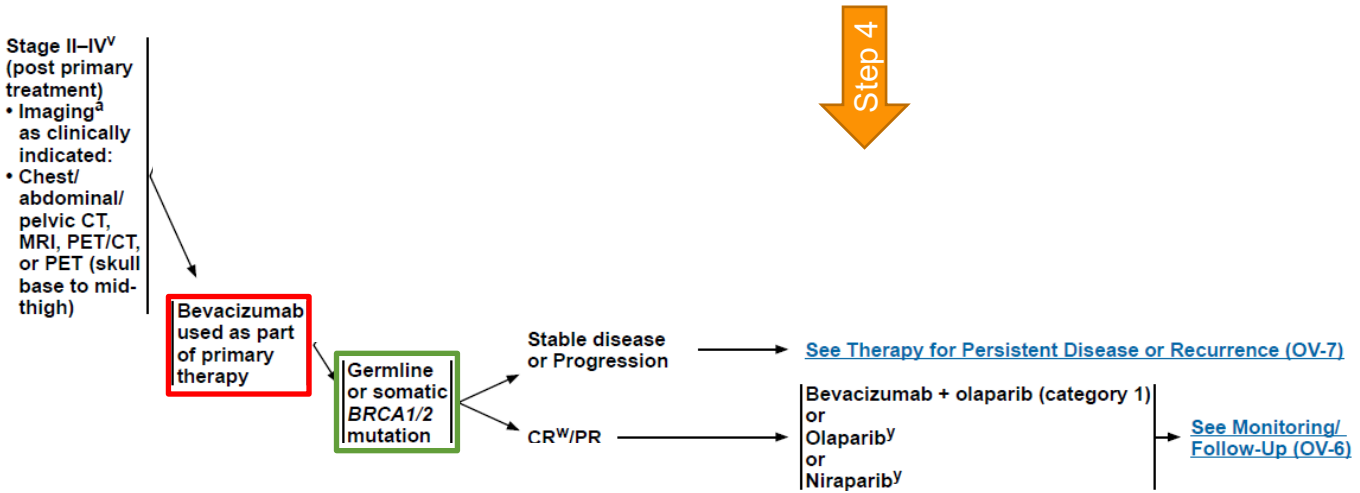
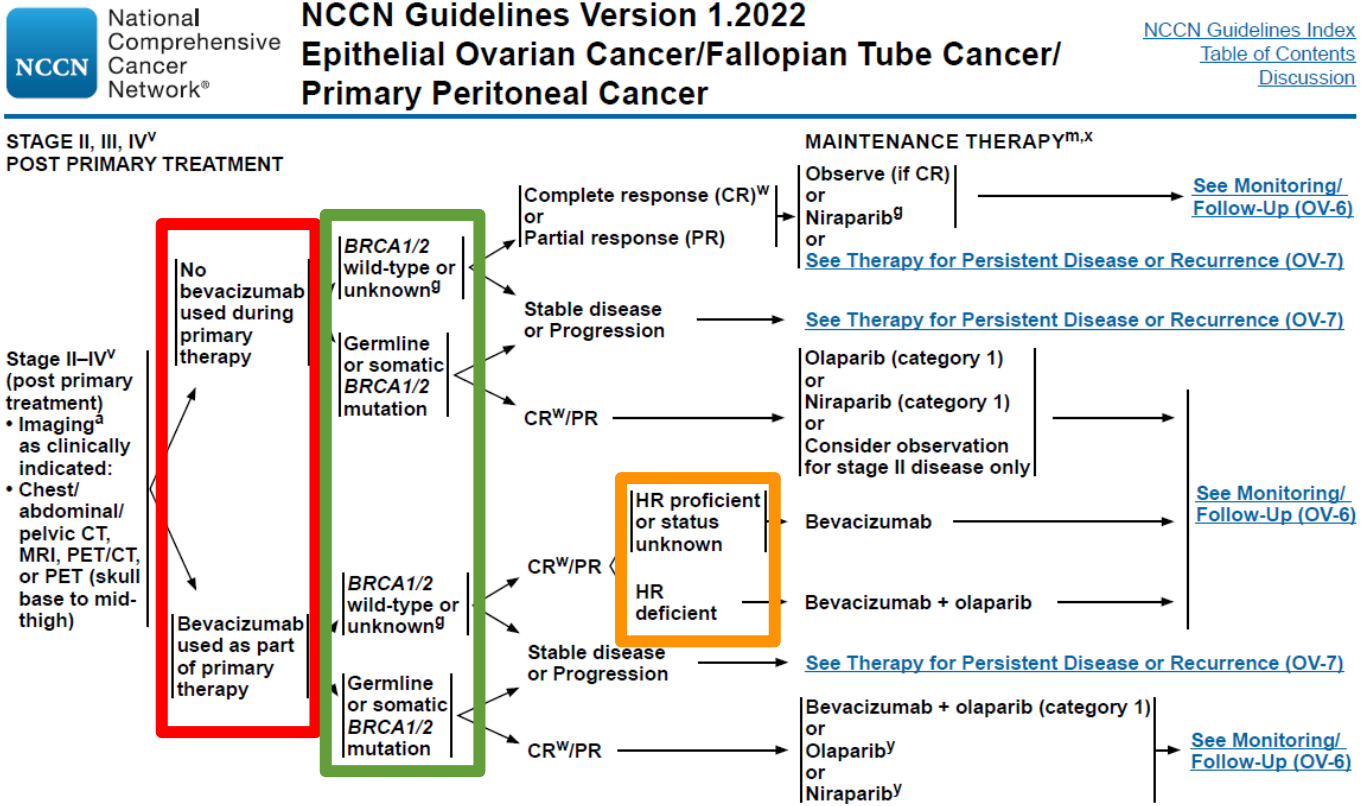
STAGE II, III, IV[v]
POST PRIMARY TREATMENT

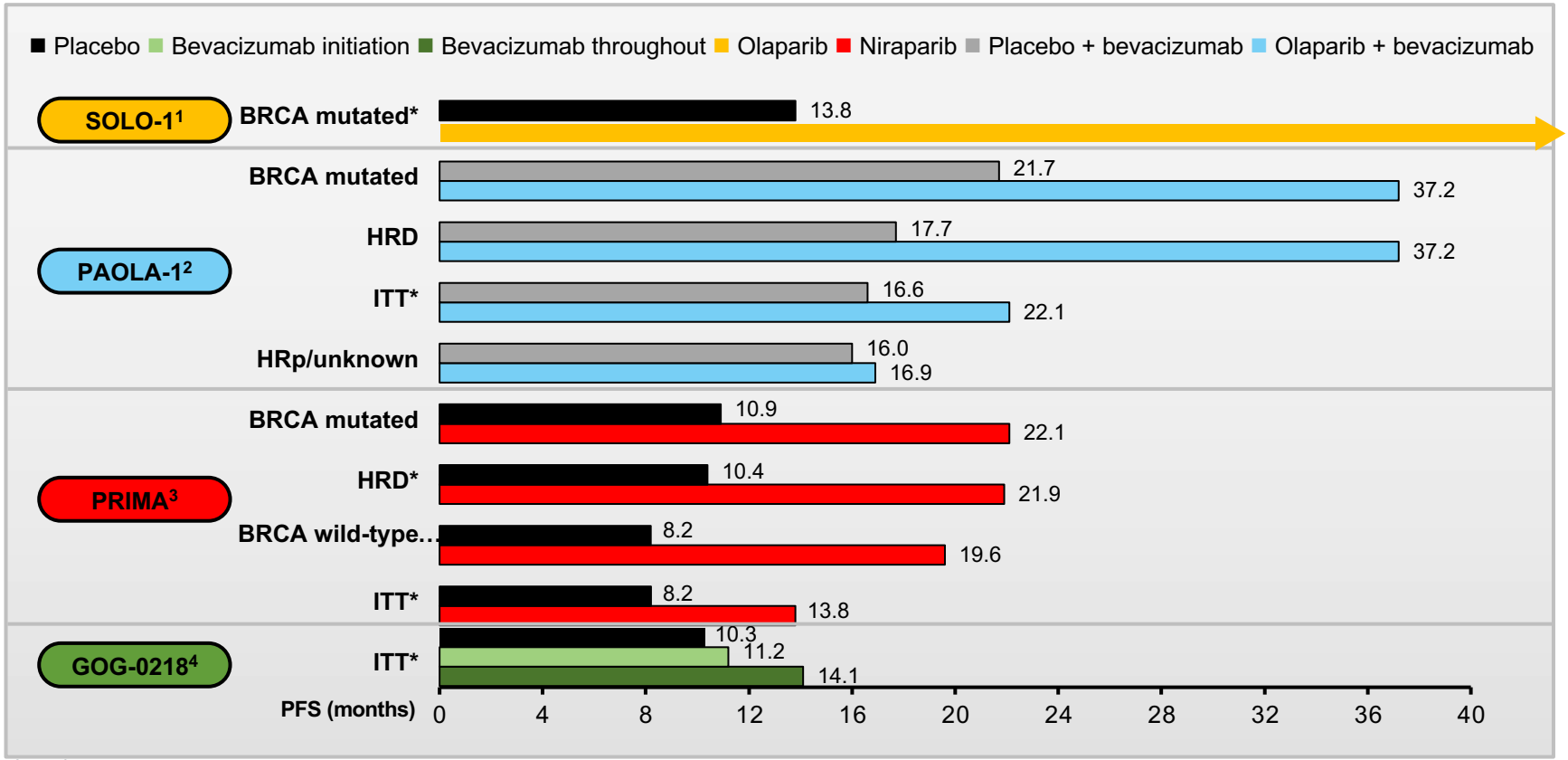
MAINTENANCE THERAPY[m,x]



How to Put Together IF All Options Are Available



Summary Of First-line Maintenance Studies



ITT = Intention to treat.

1. Moore K, et al. *N Engl J Med*. 2018;379:2495-2505. 2. González-Martin A, et al. *N Engl J Med*. 2019: 381(25):2391-2402. 3. Ray-Coquard I, et al. *N Engl J Med*. 2019:381(25):2416-2428.

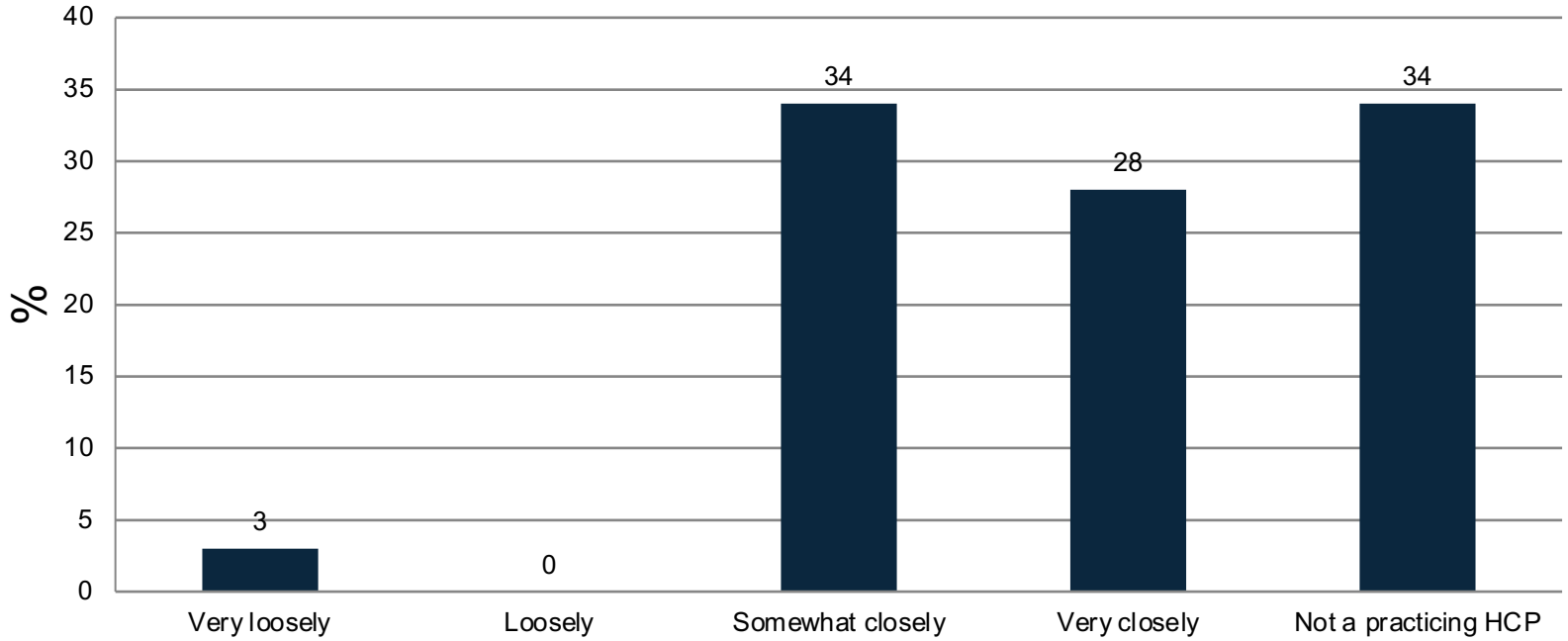
Polling Question

Now, how closely will you try to adhere to the NCCN frontline treatment guideline algorithm for ovarian cancer?

A. Very loosely
B. Loosely
C. Somewhat closely
D. Very closely
E. Not a practicing HCP

Audience Response

Now, how closely will you try to adhere to the NCCN frontline treatment guideline algorithm for ovarian cancer?



CME OUTFITTERS

Genetic Testing

- EOC has the highest percentage of hereditary cases observed, irrespective of selection criteria.
  - 20%-25% of unselected epithelial EOCs carry pathogenic variants (PVs) in several proteins involved in DNA repair pathways (BRCA1/2, CDK12, RAD51C, FA)
  - 10%-15% of hereditary EOC involve mismatch repair (MMR) pathway genes.
- Identification of HR deficient ovarian cancers has significant prognostic and predictive value for treatment planning.
- Tumor genetic testing should be obtained early in the treatment planning process.

Visit the CMEO Oncology Hub for a toolkit for talking to patients about genetic testing and counseling.

Monotherapy Anti-PD-L1/PD-1 in OC

Therapeutic agent	Phase and trial name	N	Setting	ORR, n/N (%)
Atezolizumab	Ia (PCD4989g)[1]	12	PR−ROC	2/8 (25)[a,b]
Avelumab	Ib (JAVELIN solid tumor)[2]	75	ROC	8/75 (11)
Nivolumab	II (UMIN000005714)[3]	20	PR−ROC	3/20 (15)
Pembrolizumab	Ib (KEYNOTE-100)[4]	376	ROC	8.0

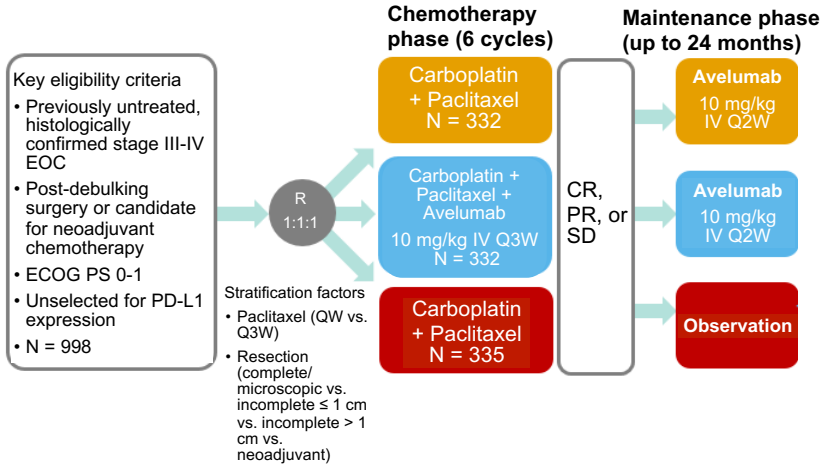
PD-L1/PD-1 inhibitors demonstrate modest activity in ROC, suggesting an opportunity for combinations and better patient selection

[a]Efficacy-evaluable population included only patients who received ≥ 1 mg/kg (2 patients excluded; n = 10). [b]An additional patient without measurable disease at baseline was excluded (n = 9). Kg = Kilogram. PR = Platinum resistant. ROC = Recurrent ovarian cancer.

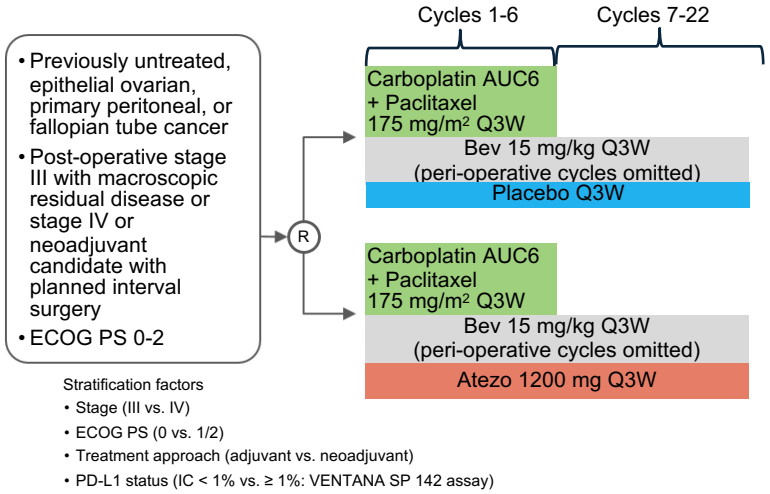
1. Infante JR, et al. *Ann Oncol.* 2016;27(Suppl 6):vi300. 2. Disis ML, et al. *JAMA Oncology.* 2019;5(3):393-401. 3. Hamanishi J, et al. *J Clin Oncol.* 2015;33(15_suppl):5570. 4. Matulonis UA, et al. *J Clin Oncol* 2018;36(15_suppl):5511.

ICI as Front-Line Therapy in Ovarian Cancer

Javelin 100 (avelumab)[1]



IMagyn050 (atezolizumab + bev)[2]



Both trials:

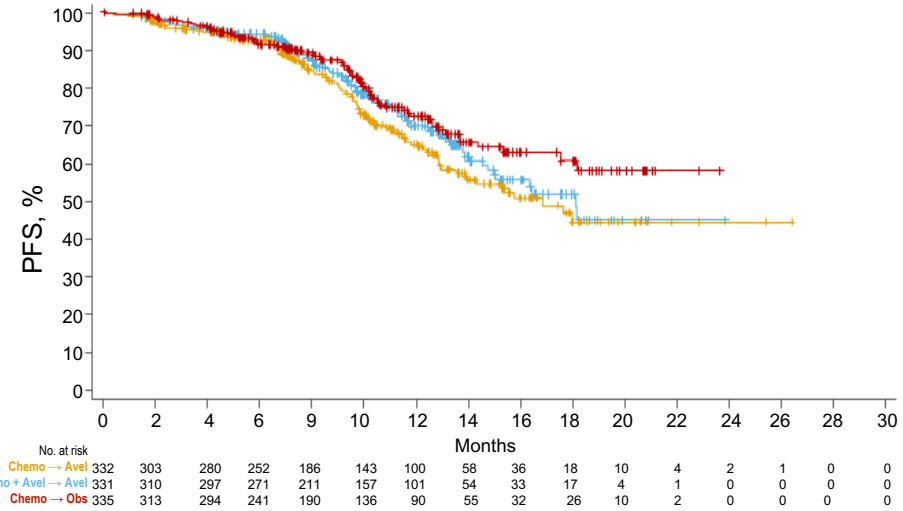
- 60% PD-L1 positive
- Primary endpoint: PFS

Cm = Centimeters. ECOG = Eastern Cooperative Oncology Group. IC = Immune cells. PD-L1 = Programmed death-ligand 1. PS = Performance status. Q2W = Once every 2 weeks. Q3W = Once every 3 weeks.

1. Ledermann JA, et al. *Gynecologic Oncology*. 2020;159(Suppl 1):S13-S14. 2. Moore KN, et al. *J Clin Oncol*. 2021;39(17):1842-1855.

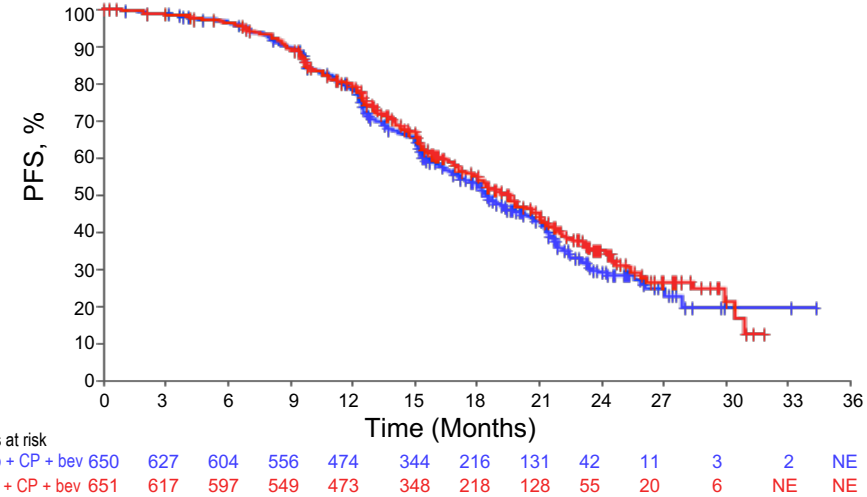
ICI Trials: Primary Endpoint

Javelin 100 (avelumab)



	Chemo → Avel (N = 332)	Chemo + Avel → Avel (N = 331)	Chemo → Obs (N = 335)
Events, n (%)	99 (29.8)	88 (26.6)	70 (20.9)
Median (95% CI), months	16.8 (13.5-NE)	18.1 (14.8-NE)	NE (18.2-NE)
Stratified HR vs. control (95% CI)	1.43 (1.01-1.946)	1.14 (0.832-1.565)	--
p value vs. control	.9890	.7935	--

IMagyn050 (atezolizumab + bev)



	Placebo + CP + bev (n = 650)	Atezo + CP + bev (n = 651)
Patients with events, n (%)	341 (52.5)	323 (49.6)
Median PFS, months (95% CI)	18.4 (17.2-19.8)	19.5 (18.1-20.8)
Stratified HR (95% CI)	0.92 (0.79-1.07)	
Stratified log-rank *p*-value	0.2785	
2-year event-free rate (95% CI)	29.1(23.9-34.3)	35.1 (30.0-40.3)

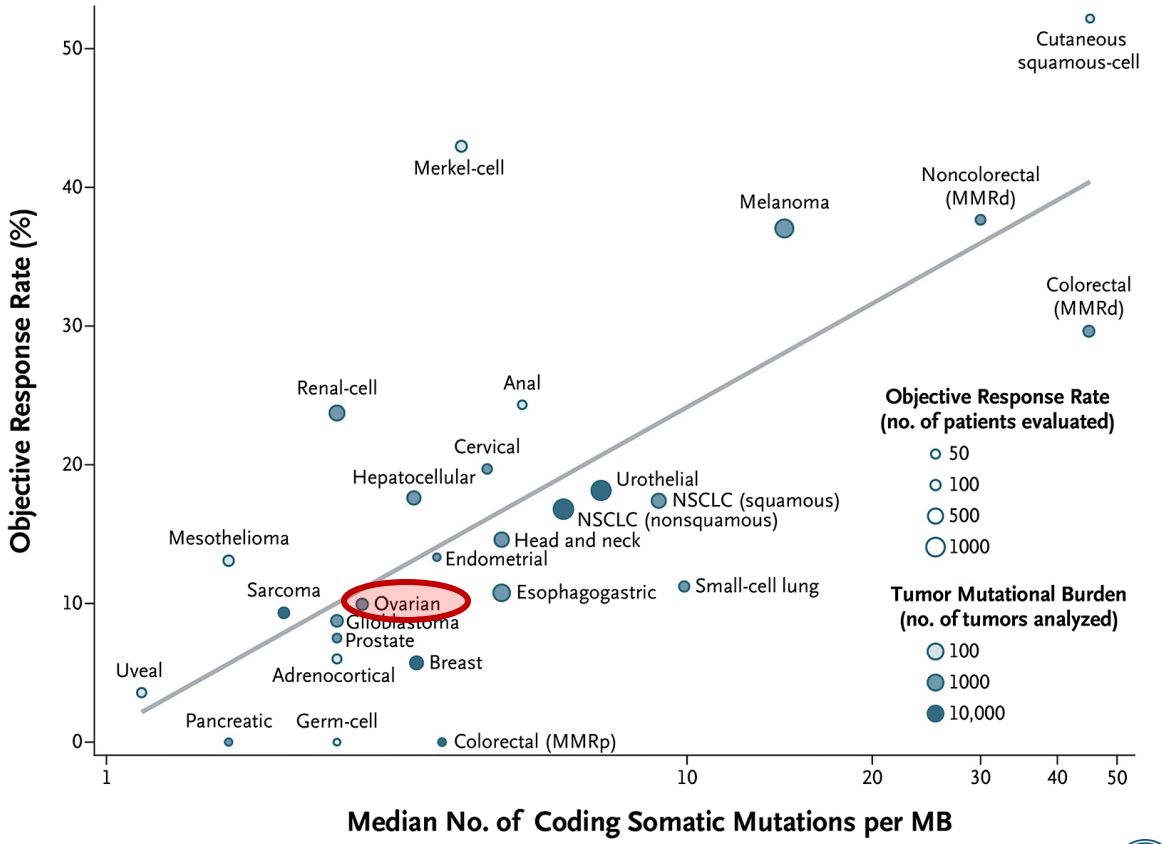
No differences seen between study arms in either trial

NE = Not evaluable.

1. Ledermann JA, et al. *Gynecologic Oncology*. 2020;159(Suppl 1):S13-S14. 2. Moore KN, et al. *J Clin Oncol*. 2021;39(17):1842-1855.

Why Were ICI Therapies Ineffective?

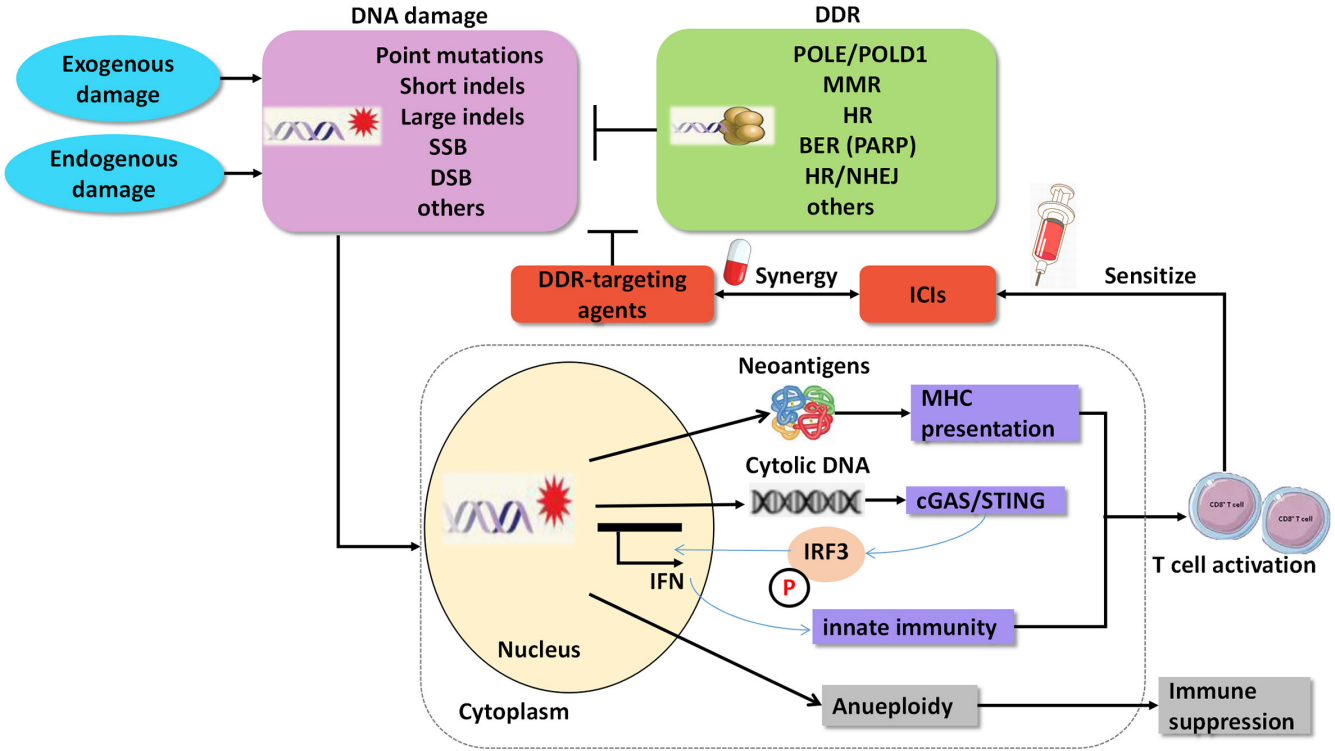
- At baseline, most of epithelial ovarian cancer has a lower probability of responding to immunotherapy[1,2]
- Over-expression of FasL, VEGF and may impair T-cell trafficking, although if this were major obstacle, IMagyn050 should have worked
- No biomarkers for patient selection
- How about combinations?



MB = Megabase. VEGF = Vascular endothelial growth factor.

1. Borella F, et al. *Diagnostics (Basel)*. 2020;10(3):146. 2. Arora S, et al. *Adv Ther*. 2019;36(10):2638-2678.

Rationale for ICI + PARPi Combination Therapy

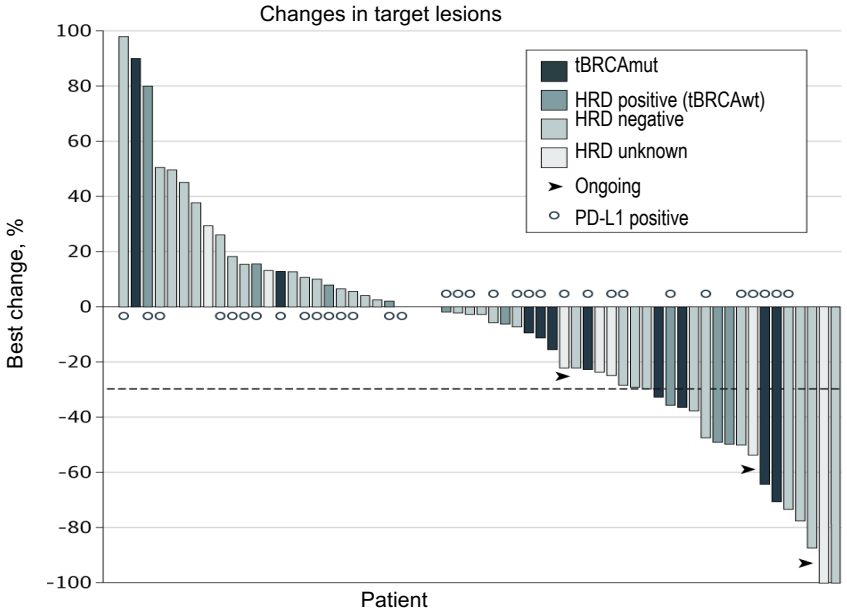


- DDR deficiency leads to somatic mutations and neoantigens, which can lead to an immune response
- Damaged DNA which transfers from the nucleus to the cytoplasm = cytosolic DNA. This can activate stimulator of interferon genes (STING), which can trigger an immune response

BER = Base excision repair. cGAS = cGAMP synthase. DDR = DNA damage repair. ICI = Immune checkpoint inhibitor. IFN = Interferon. MHC = Major. Histocompatibility complex. NHEJ = Non-homologous end joining. POLE/POLD1 = Polymerase epsilon and delta 1.
Sun W, et al. *Front Oncol*. 2021;11:648687

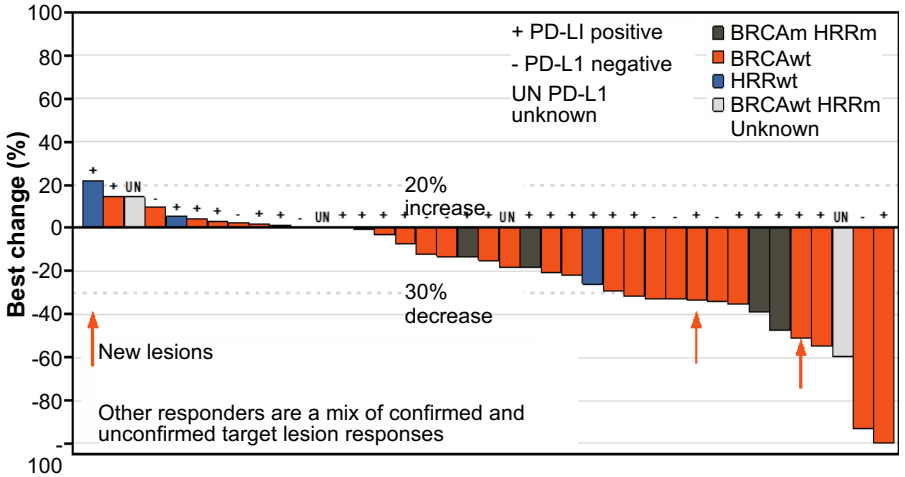
ICI + Niraparib

TOPACIO[1]
Niraparib + Pembrolizumab



ORR, 18% (11%-29%), DOR, not reached

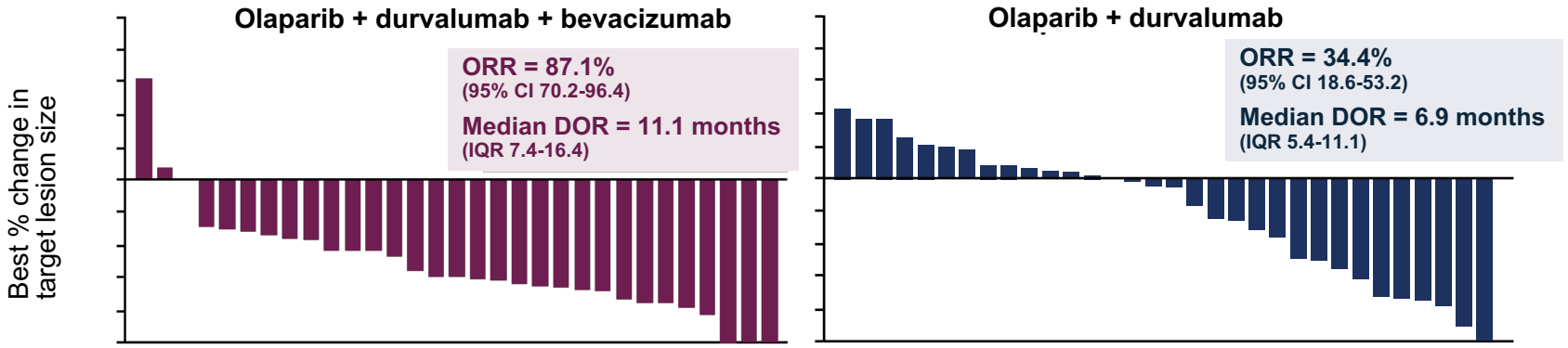
OPAL[2]
Niraparib + Dostarlimab + Bevacizumab



ORR, 17.9% (8.7%-31.3%)

1. Konstantinopoulos PA, et al. *JAMA Oncol*. 2019;5(8):1141-1149. 2. Liu JF, et al. *Gynecologic Oncology*. 2021;162(Suppl 1):S17-S18.

MEDIOLA: Durvalumab + Olaparib ± Bevacizumab

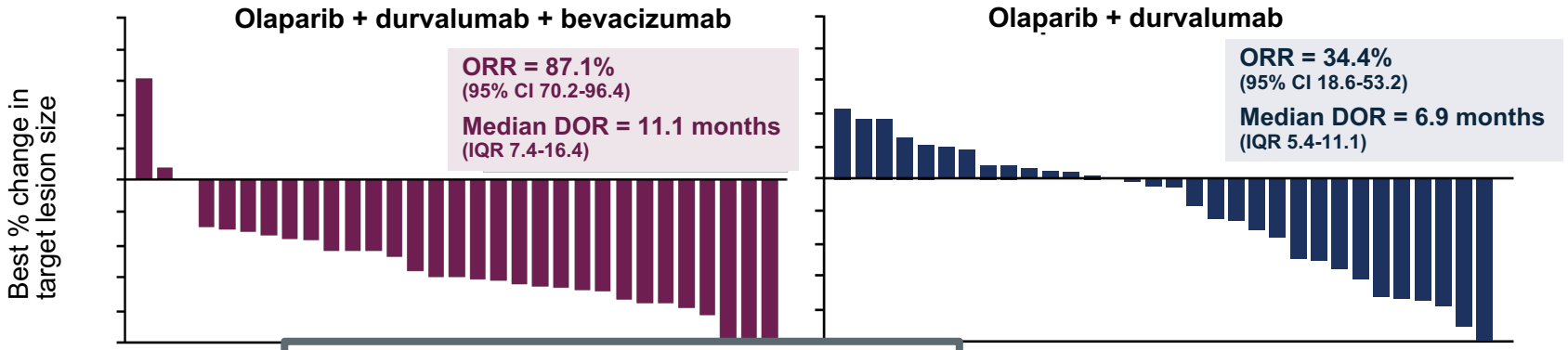


Genomic instability status* subgroup	Olaparib + durvalumab + bevacizumab		Olaparib + durvalumab	
	ORR (95% CI), %	n/N patients	ORR (95% CI), %	n/N patients
GIS-positive	100.0 (69.2-100.0)	10/10	50.0 (18.7-81.3)	5/10
GIS-negative	75.0 (34.9-96.8)	6/8	16.7 (0.4-64.1)	1/6
GIS-unknown	84.6 (54.6-98.1)	11/13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

GIS = Genomic instability score. IQR = Interquartile range.

Drew Y, et al. *Ann Oncol*. 2020;31(suppl 4):S615-S616.

MEDIOLA: Durvalumab + Olaparib ± Bevacizumab



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Drew Y, et al. *Ann Oncol*. 2020;31(suppl 4):S615-S616.

Ongoing Front-Line Studies

Trial	Size	Anti-angiogenic	PARPi	ICI	Start	Estimated Primary Completion
KEYLYNK-001 / ENGOT OV-43 (NCT03740165)[1]	~ 1086	± Bevacizumab	Olaparib	Pembrolizumab	Dec 2018	Aug 2025
FIRST / ENGOT OV-44 (NCT03602859)[2]	1405	± Bevacizumab	Niraparib	Dostarlimab	Oct 2018	Jan 2023
ATHENA / GOG-3020 / ENGOT OV-45 (NCT03522246)[3]	~ 1000	--	Rucaparib	Nivolumab	May 2018	Dec 2024
DUO-O / ENGOT OV-46 (NCT03737643)[4]	~ 1254	Bevacizumab	Olaparib	Durvalumab	Jan 2019	June 2023

ClinicalTrials.gov Identifiers: NCT03740165, NCT0362859, NCT03522246, and NCT03737643.

Summary

- Standard platinum therapy has reached its maximum potential.
- Our current guidelines are based on knowledge of tumor biomarker status.
  - Prognostic and predictive biomarkers have value in treatment planning
  - A third to half of ovarian cancers have HRD, making them susceptible to PARP inhibitors.
  - Early determination of BRCA1/2 status informs maintenance therapy
  - HRD status in the absence of BRCA1/2 mutations may inform maintenance therapy
- Ongoing trials are examining new combinations of chemotherapy, PARP inhibitors, bevacizumab, and immune checkpoint inhibitors.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Order early tumor genetic testing to determine BRCA and HRD status in all ovarian cancers
- Adhere to treatment guidelines that incorporate MSI, MMR, and TMB biomarker data to inform treatment
- Recommend participation in clinical trials that explore PARPi and ICI combination therapies

TMB = Tumor mutational burden.

CME OUTFITTERS

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