State of the Art Therapies in Gynecologic Oncology

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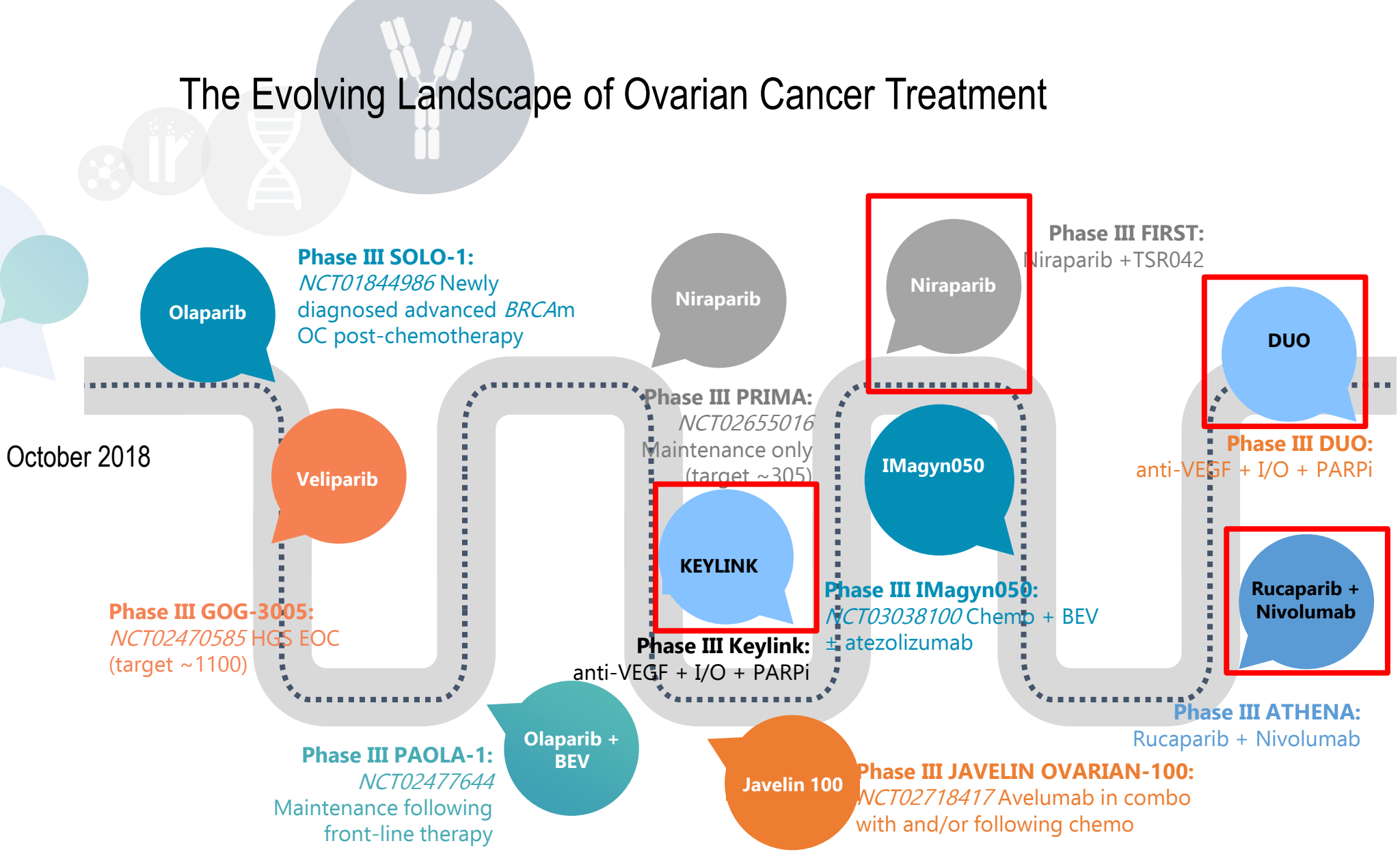
Disclosures

- I am on the speaker's bureau for AstraZeneca
- I have served on an advisory board for GlaxoSmithKline

Overview

- Ovarian cancer
  - PARP Inhibitors
    - Maintenance in upfront treatment
    - Role in recurrence
  - Secondary debulking in ovarian cancer
- Endometrial cancer
  - Lenvatinib/Pembrolizumab
- Cervical cancer
  - Ipilumimab/Nivolumab

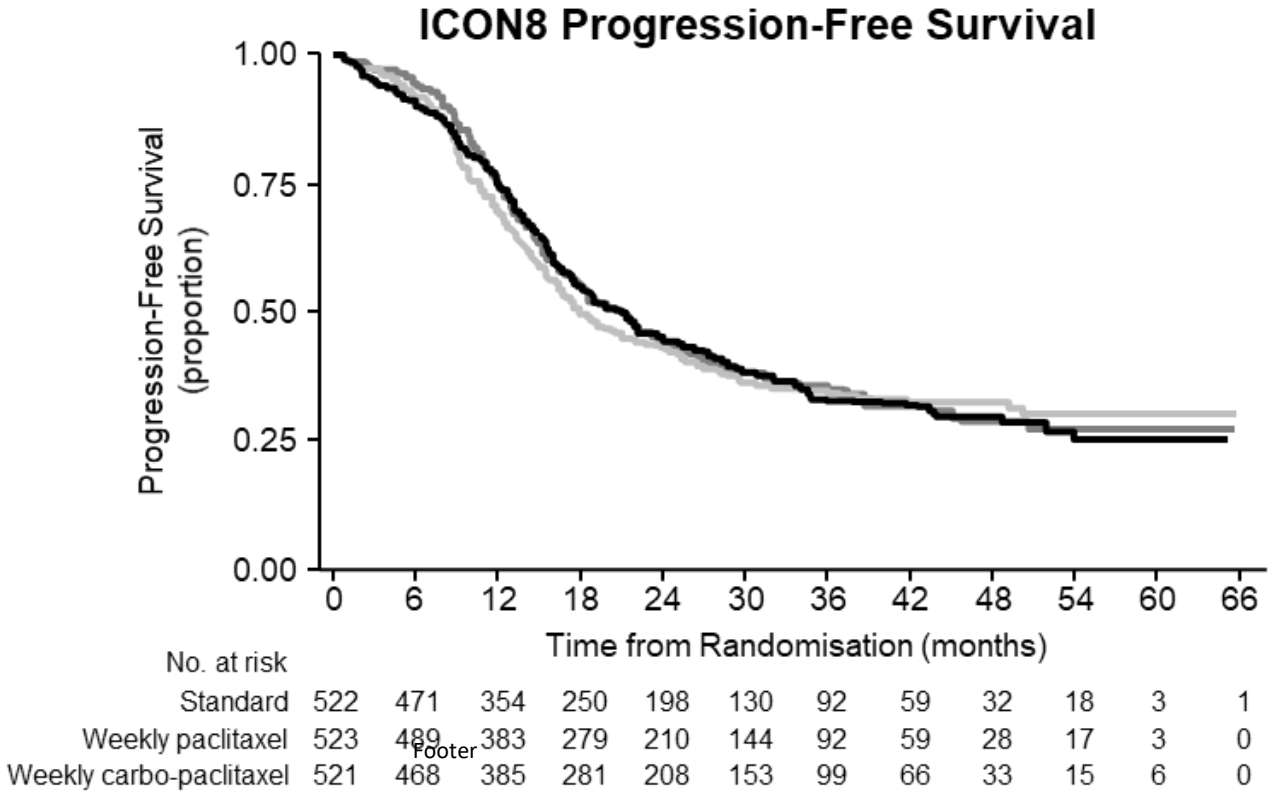
The Evolving Landscape of Ovarian Cancer Treatment



Adapted from K. Moore

The Land Before PARPi

First-Line Chemotherapy Standard of Care: Carboplatin and Paclitaxel (Dose Dense Vs Every 21 Days)



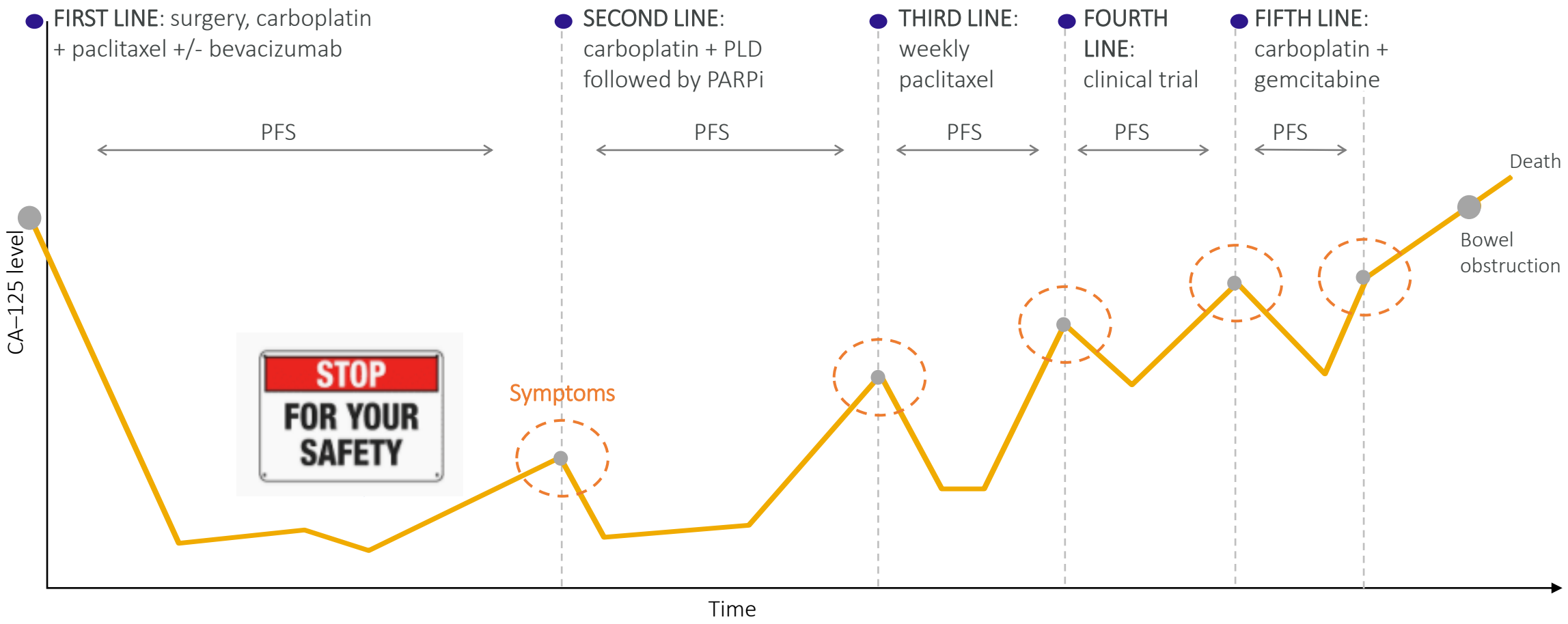
Footer

	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 mo	25.3 mo

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

Adapted from K. Moore

What happens after SOC?
The Typical Course of Advanced Ovarian Cancer Patient



PARPi=PARP inhibitor; PFS=progression-free survival; PLD=pegylated liposomal doxorubicin.

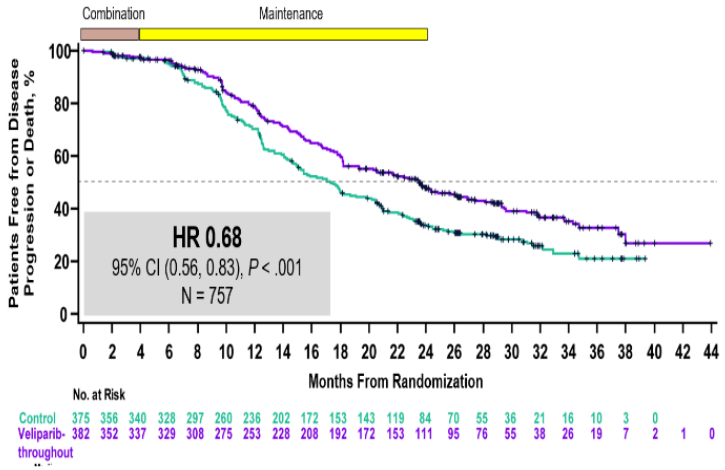
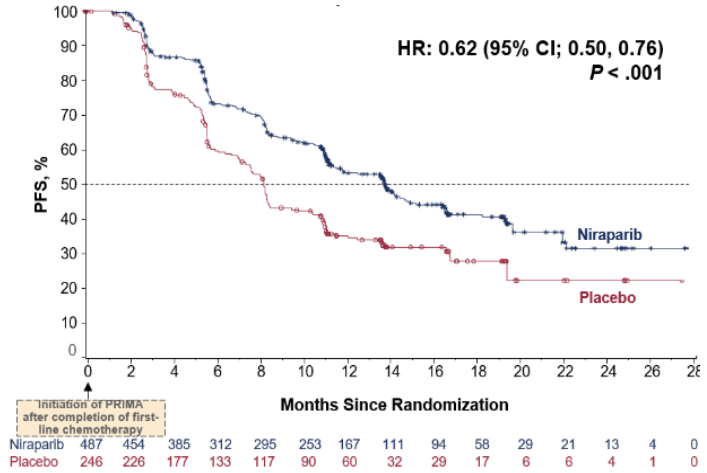
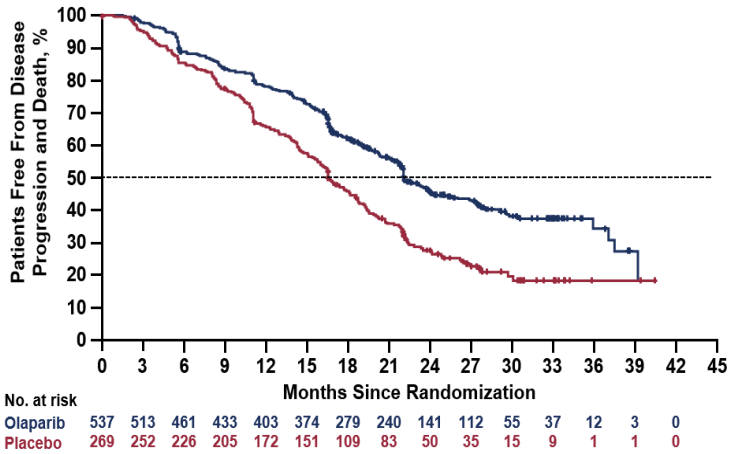
Ledermann JA et al. *Ann Oncol.* 2013;24(Suppl 6):vi24-vi32.

PARPi in Upfront Ovarian Cancer Treatment

	SOLO-1[1] (n=391)	**PRIMA[2]** (n=733)	**PAOLA-1[3]** (n=806)	**VELIA[4]** (n=1140)
Drug	Olaparib	Niraparib	Olaparib (and Bev)	Veliaparib
Arms	1. Olaparib 2. Placebo	1. Niraparib (2:1) 2. Placebo	1. Olaparib + Bev (2:1) 2. Placebo + Bev	1. Chemo/veliparib->veliparib 2. Chemo/veliparib-> placebo 3. Chemo/placebo -> placebo
Stage	III-IV, 1° or ITDB attempted for stg III	III with residual DZ after 1° TDB, inoperable or NAC, any stg IV	III-IV none vs any residual dz	III-IV
		1° TDB ~ 35%	1° TDB ~50%	1°TDB ~ 67%
		NAC + ITDB ~ 65%	NAC + ITDB ~42%	NAC + ITDB ~ 28%
			No surgery ~ 8%	No surgery ~5%
Population	HGS/endometrioid & BRCAm	HGS/endometrioid	HGS/endometrioid or BRCAm	HGS
Primary endpoint	PFS (inv)	PFS (BICR) Hierarchical: HRD -> ITT	PFS (inv) Predefined SG: tBRCA & HRD	PFS (inv) Hierarchical: BRCAm -> HRD -> ITT
Outcome	13.8 mo vs NR	8.2 vs 13.8 mo	16.6 v 22.1 mo	17.3 v 23.5 mo (arm 1 v 3)
	HR 0.3	HR 0.62	HR 0.59	HR 0.68

[1]Moore NEJM 2018; [2]Gonzalez-Martin NEJM 2019; [3]Ray-Coquard NEJM 2019; [4]Colmean NEJM 2019

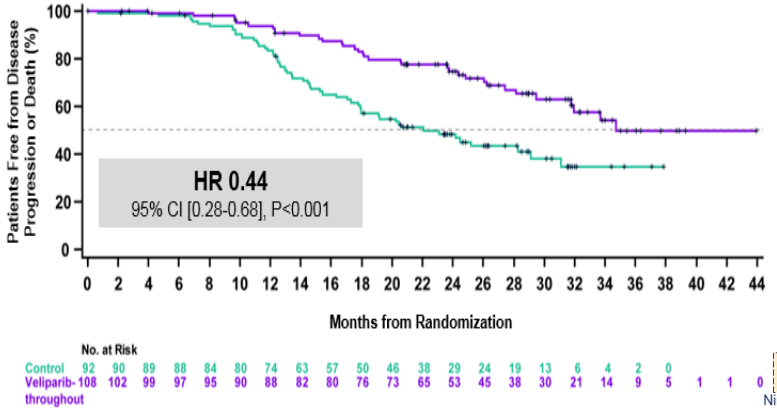
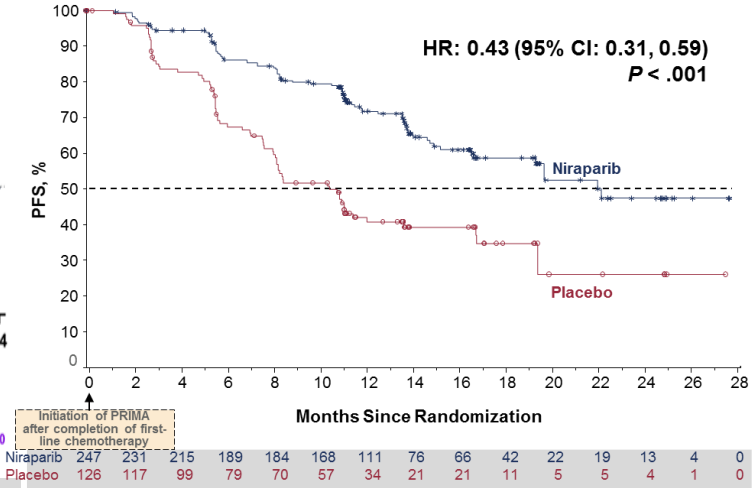
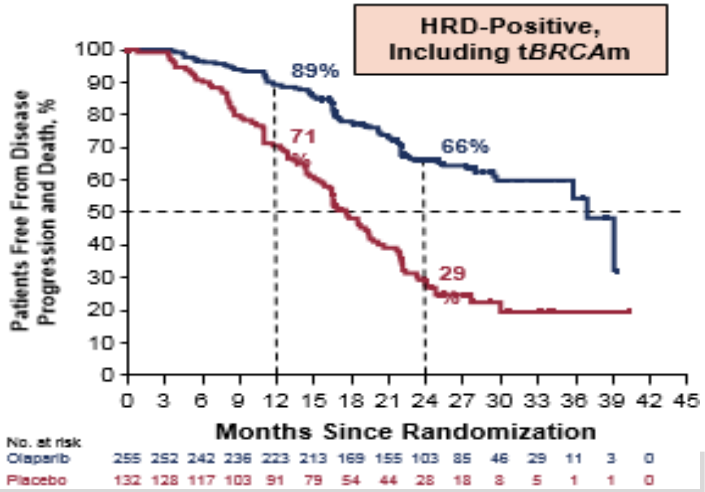
ITT Front Line Maintenance: 3 POSITIVE RANDOMIZED TRIALS

VELIA[1]	PRIMA[2]	PAOLA-1[3]	
Chemo/veliparib -> Veliparib vs chemo, stg 3-4, 67% 1TDB	Maint Niraparib vs placebo high risk stg 3-4, 35% 1TDB	Olaparib+Bev vs Bev maintenance, stg 3-4, 1TDB 50%	
			
23.5-17.3 HR 0.68 (95% CI: 0.56-0.83)		22.1 vs 16.6 mo HR 0.59 (95% CI 0.49-0.72)	INV REVIEW
	13.8 vs 8.3 months HR 0.62 (95% CI 0.50-0.76)		BICR REVIEW

1. Coleman R et al. *N Engl J Med.* 2019;381(25):2403-2415. 2. Gonzalez 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.

Adapted from K. Moore

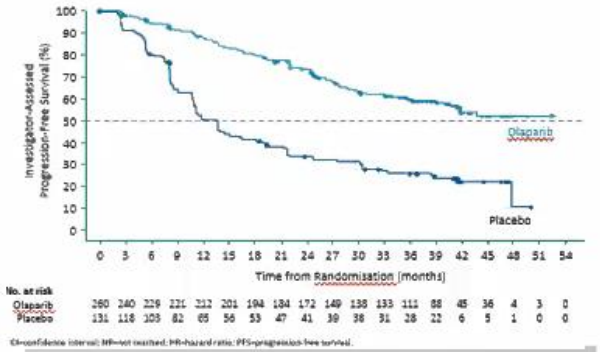
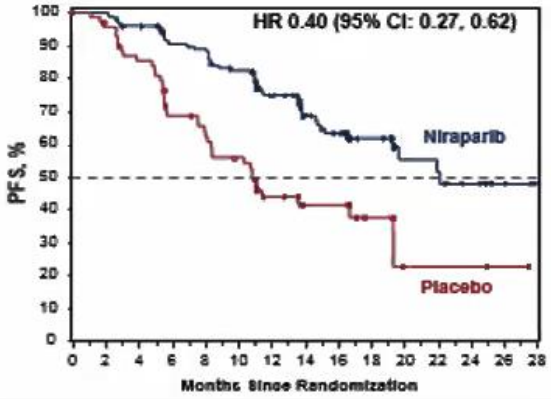
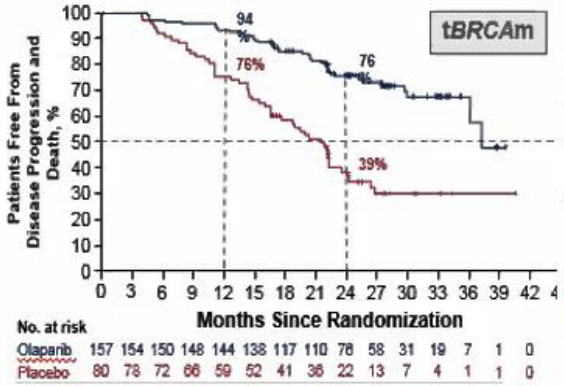
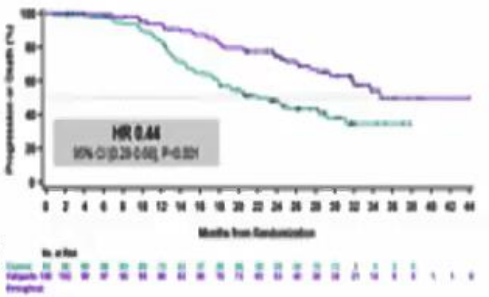
Clear Benefit in PFS in HRD+ Patients

VELIA [a]	PRIMA [b]	PAOLA-1 [c]	
Chemo/veliparib -> Veliparib vs chemo, stg 3-4, 67% 1TDB	Maint Niraparib vs placebo high risk stg 3-4, 35% 1TDB	Olaparib+Bev vs Bev maintenance, stg 3-4, 1TDB 50%	
			
34.7 vs 22 months **HR 0.44(95% CI: 0.28-0.68)**		**37.2 vs 17.7 mo** **HR 0.33 (95% CI 0.25-0.45)**	**INV REVIEW**
	21.9 vs 10.4 months **HR 0.43 (95% CI 031-0.59)**		**BICR REVIEW**

- a. Coleman R et al. NEJM. 2019: 381 (25): 2403-2415. b. Gonzalez Martin A, et al. NEJM. 2019: 381(25):2391-2402. c. Ray-Coquard I, et al. NEJM. 2019: 381(25):2416-2428.

Adapted from K. Moore

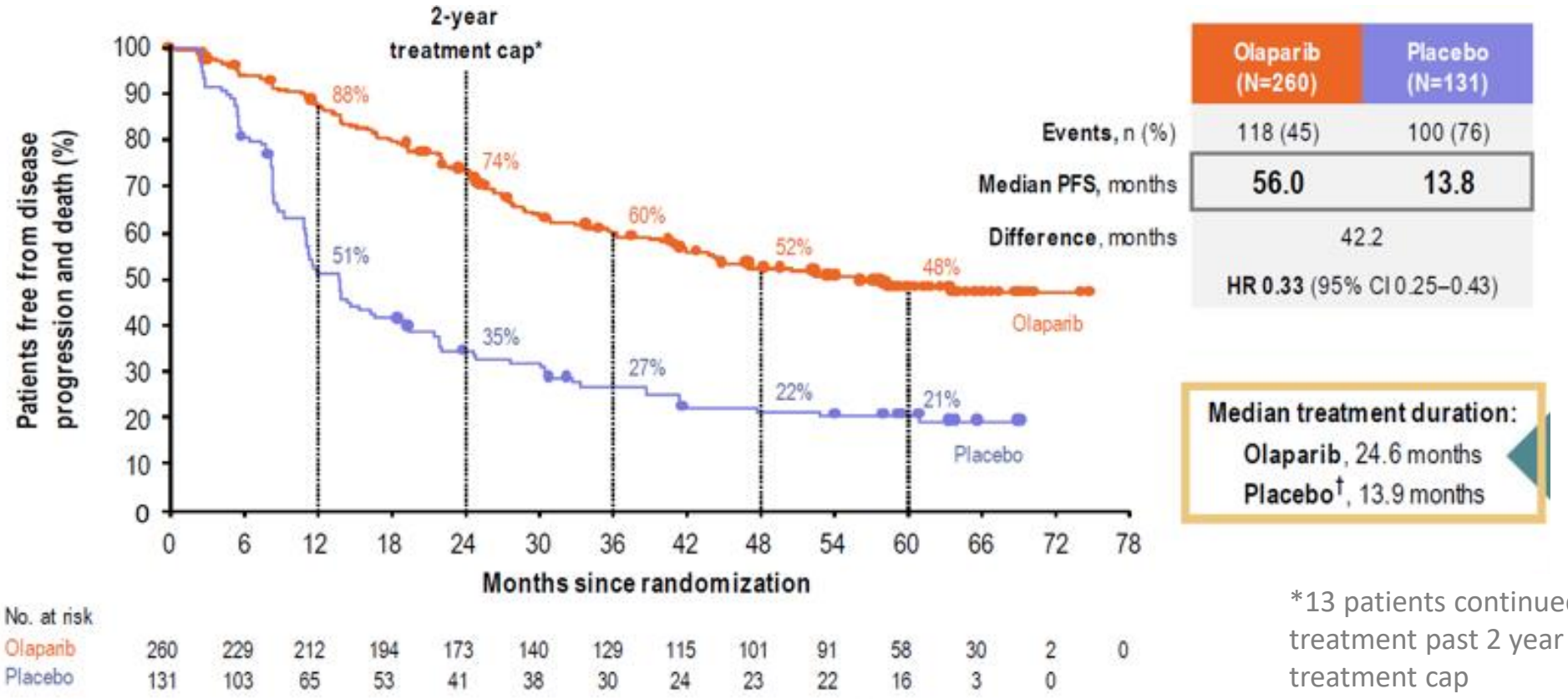
PARPi Front Line Maintenance for *BRCA* Associated Cancers: 4 POSITIVE RANDOMIZED TRIALS!

	SOLO1 - g*BRCA*m[a]	PRIMA - g*BRCA*m[b]	PAOLA-1[c]	VELIA[d]
				
INV REVIEW	**NR mo vs 13 mo HR 0.30 (95% CI: 0.23, 0.41)**		**37.2 vs 17.7 mo HR 0.33 (95% CI 0.25-0.45)**	**34.7 vs. 22 months HR 0.44(95% CI: 0.28-.68)**
BICR REVIEW	**NR vs. 14.1 mo HR 0.28 (95% CI 0.2-0.39)**	**21.9 vs. 10.4 HR 0.43 (95% CI 0.31-0.59)**		

a. Moore K, et al. *N Engl J Med.* 2018;379:2495-2505. b. Gonzalez Martin A, et al. NEJM. 2019: 381(25):2391-2402. c. Ray-Coquard I, et al. NEJM. 2019: 381(25):2416-2428. d. Coleman et al. NEJM. 2019: 381 (25)

Adapted from K. Moore

Updated SOLO1 Results – PFS Benefit of Maintenance Olaparib in BRCAm Patients After Primary Treatment Continues Past End of Treatment



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

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

*13 patients continued treatment past 2 year treatment cap

Banerjee ESMO 2020

What about PARPi in HR Proficient Patients?

PRIMA[1]

- Stage III-IV disease, with visible disease after surgery, inoperable, any stage IV, any neoadjuvant chemo (NAC)
  - ~ 65% received NAC
  - Higher risk population

Outcome	Niraparib	Placebo	HR	95% CI
Median PFS	8.1 mo	5.4 mo	0.68	0.49-0.94
In NAC patients	13.9 mo	8.2 mo	0.59	0.46-0.76
If CR to chemo	16.4 mo	9.5 mo	0.6	0.46-0.77
Interim 2 year OS	81%	59%	0.51	0.27-0.97

[1]Gonzalez-Martin NEJM 2019

PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline

William P. Tew, MD[1]; Christina Lacchetti, MHSc[2]; Annie Ellis[3,4]; Kathleen Maxian, BSW[5]; Susana Banerjee, PhD[6]; Michael Bookman, MD[7]; Monica Brown Jones, MD[8]; Jung-Min Lee, MD[9]; Stéphanie Lheureux, MD, PhD[10]; Joyce F. Liu, MD[11]; Kathleen N. Moore, MD[12]; Carolyn Muller, MD[13]; Patricia Rodriguez, MD[14]; Christine Walsh, MD[15]; Shannon N. Westin, MD[16]; and Elise C. Kohn, MD[9]

PURPOSE To provide recommendations on the use of poly(ADP-ribose) polymerase inhibitors (PARPis) for management of epithelial ovarian, tubal, or primary peritoneal cancer (EOC).

METHODS Randomized, controlled, and open-labeled trials published from 2011 through 2020 were identified in a literature search. Guideline recommendations were based on the review of the evidence, US Food and Drug Administration approvals, and consensus when evidence was lacking.

RESULTS The systematic review identified 17 eligible trials.

RECOMMENDATIONS The guideline pertains to patients who are PARPi naïve. All patients with newly diagnosed, stage III-IV EOC whose disease is in complete or partial response to first-line, platinum-based chemotherapy with high-grade serous or endometrioid EOC should be offered PARPi maintenance therapy with niraparib. For patients with germline or somatic pathogenic or likely pathogenic variants in *BRCA1* (g/s*BRCA*1) or *BRCA2* (g/s*BRCA2*) genes should be treated with olaparib. The addition of olaparib to bevacizumab may be offered to patients with stage III-IV EOC with g/s*BRCA1/2* and/or genomic instability and a partial or complete response to chemotherapy plus bevacizumab combination. Maintenance therapy (second line or more) with single-agent PARPi may be offered for patients with EOC who have not received a PARPi and have responded to platinum-based therapy regardless of *BRCA* mutation status. Treatment with a PARPi should be offered to patients with recurrent EOC that has not recurred within 6 months of platinum-based therapy, who have not received a PARPi and have a g/s*BRCA1/2*, or whose tumor demonstrates genomic instability. PARPis are not recommended for use in combination with chemotherapy, other targeted agents, or immune-oncology agents in the recurrent setting outside the context of a clinical trial. Recommendations for managing specific adverse events are presented. Data to support reuse of PARPis in any setting are needed.

Additional information is available at www.asco.org/gynecologic-cancer-guidelines.

J Clin Oncol 38:3468-3493. © 2020 by American Society of Clinical Oncology

Pivotal studies of PARP-inhibitors in patients with recurrent ovarian cancer after response to platinum

Study	Study 19[1]	SOLO-2[2] g*BRCA*m	NOVA[3] g*BRCA*m	NOVA[3] Non-g*BRCA*m	ARIEL-3[4] *BRCA*m	ARIEL-3[4] ITT
Agent	**Olaparib**	**Olaparib**	**Niraparib**	**Niraparib**	**Rucaparib**	**Rucaparib**
Difference in PFS (months)	8.4 vs 4.8	19.1 vs 5.5	21.0 vs 5.5	9.3 vs 3.9	16.6 vs 5.4	10.8 vs 5.4
PFS HR (investigator assessed)	**0.35** (95% CI 0.25 - 0.49; p<0.001)	**0.30** (95% CI 0.22-0.41; p<0.0001)	**0.27** (95% CI 0.18-0.40)	**0.53** (95% CI 0.41, 0.68)	**0.23** (95% CI 0.16-0.34, p<0.0001)	**0.36** (95% CI 0.30-0.45; p<0.0001)
PFS HR (BICR)	**0.39** (95% CI 0.27-0.55; P<0.001)	**0.25** (95% CI 0.18-0.35; p<0·0001)	**0.27** (95% CI 0.17-0.41; p<0.0001)	**0.45** (95% CI 0.34-0.61; p<0.0001)	**0.20** (95% CI 0.13-0.32; p<0.0001)	**0.35** (95% CI 0.28-0.45; p<0.0001)

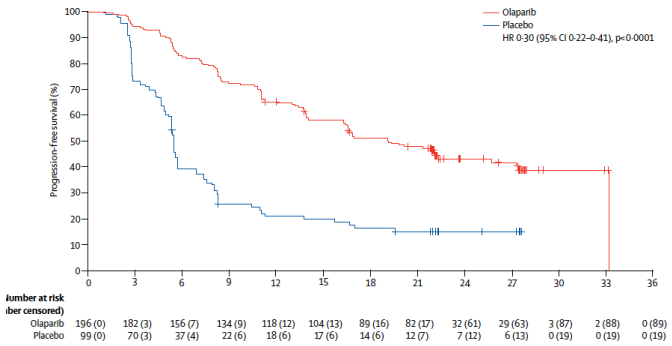
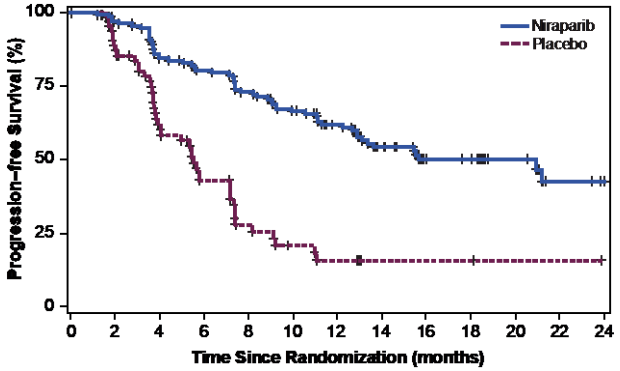
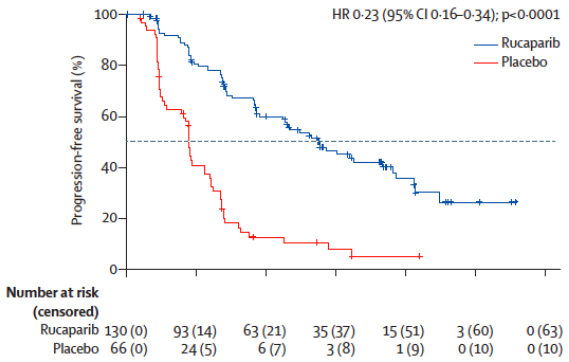
•**Note**: In the absence of head to head data between PARPi efficacy and safety comparisons between PARPi are not to be made or communicated

•1. Ledermann J, et al. NEJM. 2012;366:1382-1392. 2. Pujade-Lauraine E et al. Lancet Oncol. 2017 Sep;18(9):1274-1284. 3. FDA NDA review ref 4074987, application no 208447. 4. Coleman RL et al. Lancet. 2017 Oct 28;390(10106):1949-1961.

Adapted from K Moore

Efficacy of PARP inhibitors in *BRCA*m patients

But What About Overall Survival?

SOLO-2 - g*BRCA*m[1]	NOVA – g*BRCA*m[2]	ARIEL-3 - t*BRCA*m[3]	
			
19.1 vs 5.5 months **HR 0.30 (95% CI: 0.22-0.41)**	14.8 vs 5.5 months HR 0.27 (95% CI 0.18-0.40)	**16.6 vs 5.4 months** **HR 0.23 (0.16-0.34)**	INV REVIEW
30.2 vs 5.5 months HR 0.25 (95% CI: 0.18–0.35)	**21.0 vs. 5.5 months** **HR 0.27 (95% CI: 0.17-0.41)**	26.8 vs 5.4 months HR 0.20 (0.13-0.32)	BICR REVIEW

1. Pujade et al. Lancet Oncol 2017; 18: 1274–84 2. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208447Orig1s000MultidisciplineR.pdf, Last accessed August 2018
• 3. Coleman RL et al. Lancet. 2017 Oct 28;390(10106):1949-1961

Adapted from K Moore

PARP inhibition challenged this paradigm – regardless of *BRCA*

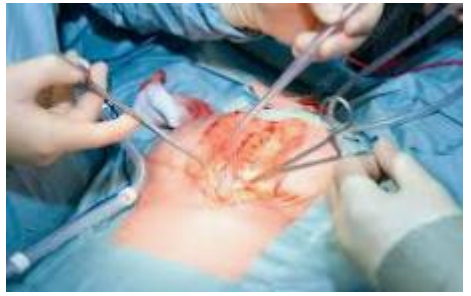
	OLAPARIB (LYNPARZA)[1-3]	TALAZOPARIB[4-6]	RUCAPARIB (RUBRACA)[7]	NIRAPARIB (ZEJULA)[8]
Company	AstraZeneca	Pfizer, Inc.	Clovis Oncology	Tesaro, Inc
MoA	PARP-1, PARP-2, PARP-3 inhibitor	Dual-mechanism PARP inhibitor	PARP-1, PARP-2, PARP-3 inhibitor	PARP-1, PARP-2 inhibitor
Treatment Indication	Second-line or greater chemotherapy with deleterious or suspected g*BRCA*m HER2– mBC Third-line or greater chemotherapy with deleterious or suspected g*BRCA*m OC	Deleterious or suspected deleterious g*BRCA*m, HER2– locally advanced or mBC	Second-line or greater chemotherapy with deleterious g/s*BRCA*m OC	Not indicated
Maintenance Indication	Second-line maintenance for recurrent EOC, FTC, PPC First-line maintenance for high-risk advanced (FIGO stage III-IV) *BRCA*m high-grade EOC, FTC, PPC	Not indicated	Second-line maintenance for recurrent EOC, FTC, PPC	Second-line maintenance for recurrent EOC, FTC, PPC
Recommended Dose	300 mg PO BID	1 mg PO QD	600 mg PO BID	300 mg PO QD
Approval Date(s)	January 2018; December 2014; August 2017; December 2018	October 2018	December 2016 and April 2018	March 2017

BID, twice daily; FIGO, International Federation of Gynecology and Obstetric; FTC, fallopian tube cancer; g/s*BRCA*m, germline and/or somatic *BRCA* mutant; HER2–, human epidermal growth factor receptor 2 negative; HGSOC, high-grade serous ovarian cancer; MoA, mechanism of action; PPC, primary peritoneal cancer; PO, by mouth; QD, once daily.

1. Robson M, et al. Presented at: AACR 2018; April 14-18, 2018; Chicago, IL. 2. LYNPARZA [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017. 3. www.clinicaltrials.gov/NCT01844986. 4. www.clinicaltrials.gov/NCT01945775. 5. Litton J, et al. Presented at: San Antonio Breast Cancer Symposium 2017. December 4-8, 2017; San Antonio, TX. Abs GS6-07. 6. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm623540.htm

7. RUBRACA [prescribing information]. Boulder, CO: Clovis Oncology, Inc., 2016. 8. ZEJULA [prescribing information]. Waltham, MA: TESARO, Inc, 2017.

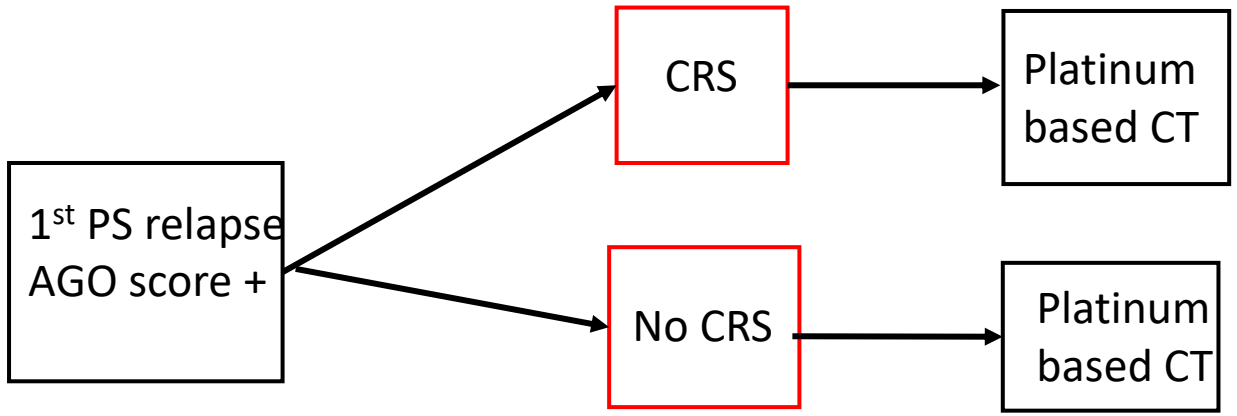
A Chance to Cut is a Chance to……



- Debate about secondary cytoreduction longstanding
- NCCN CR and relapse > 6 mo after completing chemo ->
  "Consider secondary cytoreductive surgery"
- GOG 213[1] showed worse outcomes but less stringent surgical decision making criteria used
- Two recent studies[2,3] challenge this
  - DESKTOPIII
  - SOC-1

[1]Coleman et al, Secondary Cytoreduction for Ovarian Cancer. NEJM 2019
[2] Du Bois et al. Abstract 6000 ASCO 2020 Annual Meeting
[3] Zang et al. Abstract 6001 ASCO 2020 Annual Meeting

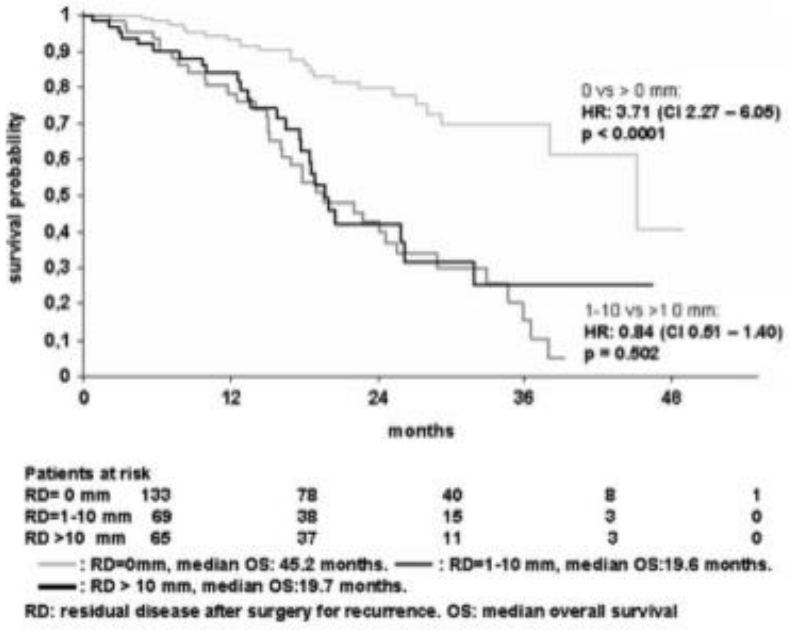
Randomized controlled Phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: the final analysis of AGO DESKTOP III/ ENGOT ov 20 du Bois et al. Abstract 6000

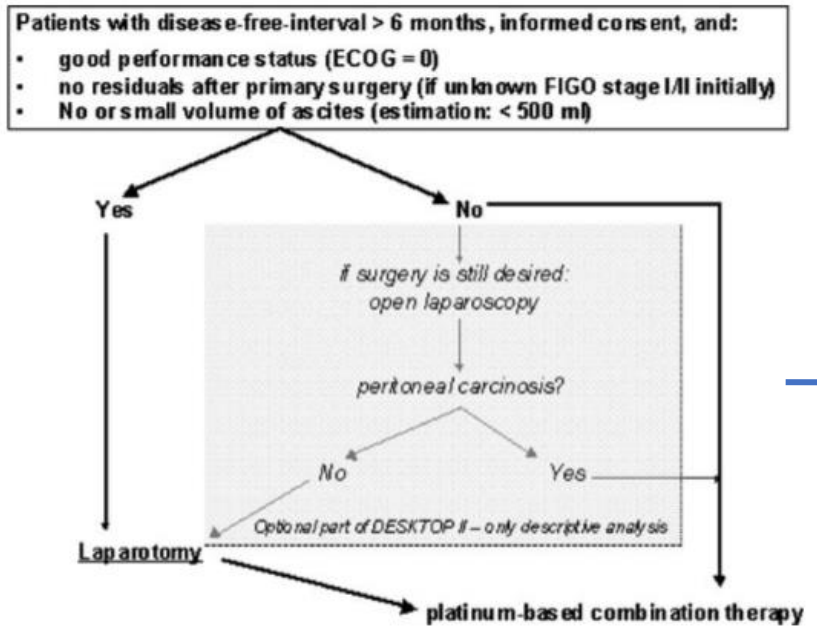


Primary outcome is OS
N= 408 patients

AGO score includes:
1) ECOG PS = 0
2) Complete resection at primary CRS
3) < 500 ml ascites

DESKTOP II confirmed the predictive value of this score.
51% of patients have + score
>2/3 of patients had complete resection





DESKTOP I established the AGO score which would appear to predict patients at higher likelihood of complete resection

Adapted from K Moore

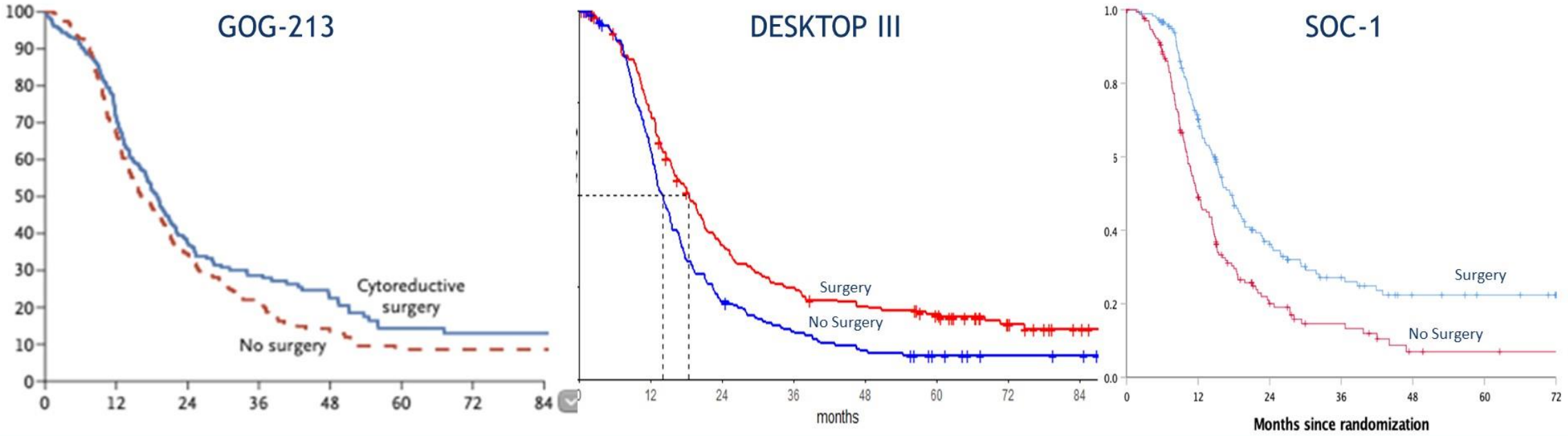
Harter P et al. Annals of Surgical Oncology, 2006; Harter P et al. Int J Gynecol Cancer 2011

Comparison of Recent Ovarian Cancer Secondary Cytoreduction Trials

	GOG-213	AGO Desktop III	SGOG SOC-1
Age	57 years	60.5 years	54 years
Initial Stage III-IV	86%	74.6%	82%
Selection criteria	**Individualized** for CGR	AGO model	iMODEL + PET-CT
Histology: Serous	86%	85%	81%
Median Platinum-Free Interval	19.7 mos	19.9 mos	16.1 mos
Cross-over to surgery (Control Violation)	2%	4%	6.3%
Complete Gross Resection	**67%**	74.2	76.7%
Mortality	30-day: 0.4%	90-day: 0.5%	60-day: 0%
Subsequent Surgery in Control Arm after Relapse	NA	11.0%	36.9%
Platinum-based Combination Therapy	100%	89%	? (100%)
The 2nd line bevacizumab	**84%**	23%	1%
The 2nd line PARPi maintenance	NA	<5%	10%

Comparison of PFS in Recent Ovarian Cancer Secondary Cytoreduction Trials: GOG 213, DESKTOPIII, SOC-1

	GOG-213	AGO Desktop III	SGOG SOC-1
PFS - Surgery (median)	18.2 mos	18.4 mos	17.4 mos
PFS - No Surgery (median)	**16.5 mos**	14.0 mos	11.9 mos
HR, 95% CI	0.88 (0.70-1.11)	0.66 (0.54-0.82)	0.58 (0.45-0.74) **P < 0.001**

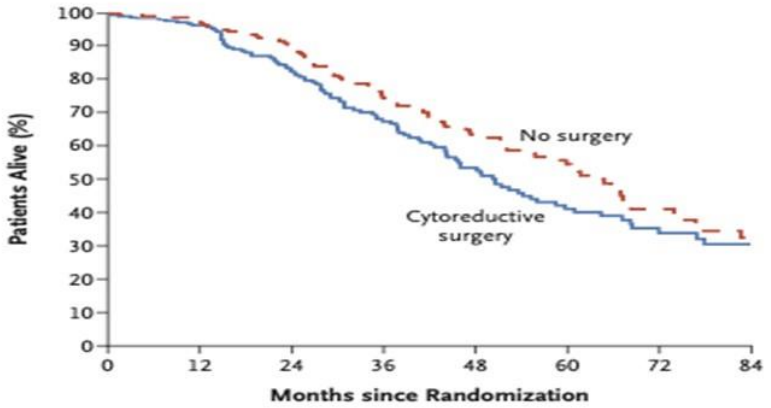


Adaptation of ASCO Presentation By Robert Coleman at TBD

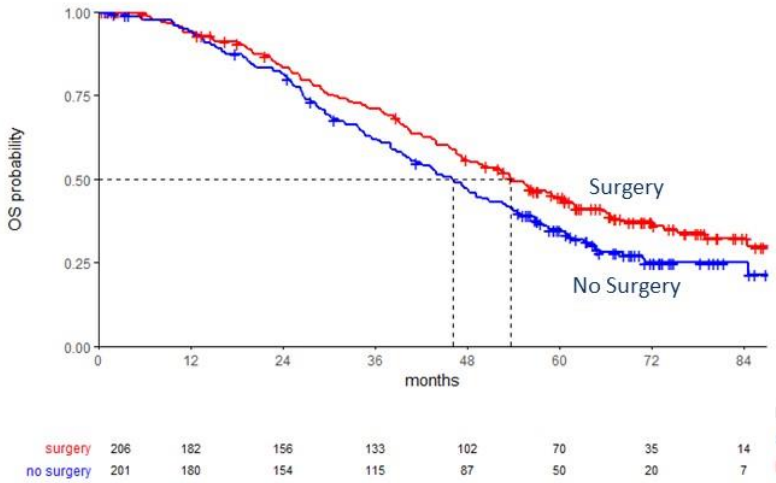
Comparison of OS in Recent Ovarian Cancer Secondary Cytoreduction Trials: GOG 213, DESKTOPIII, SOC-1

	GOG-213	AGO Desktop III	SGOG SOC-1
OS – Surgery (median)	53.6 mos	53.7 mos	58.1 mos
OS - No Surgery (median)	**65.7 mos**	46.0 mos	53.9 mos
HR, 95% CI	1.28 (0.92-1.78) **P = NS**	0.75 (0.58-0.96) **P = 0.04**	0.82 (0.57-1.19) **P = NS**

GOG-213



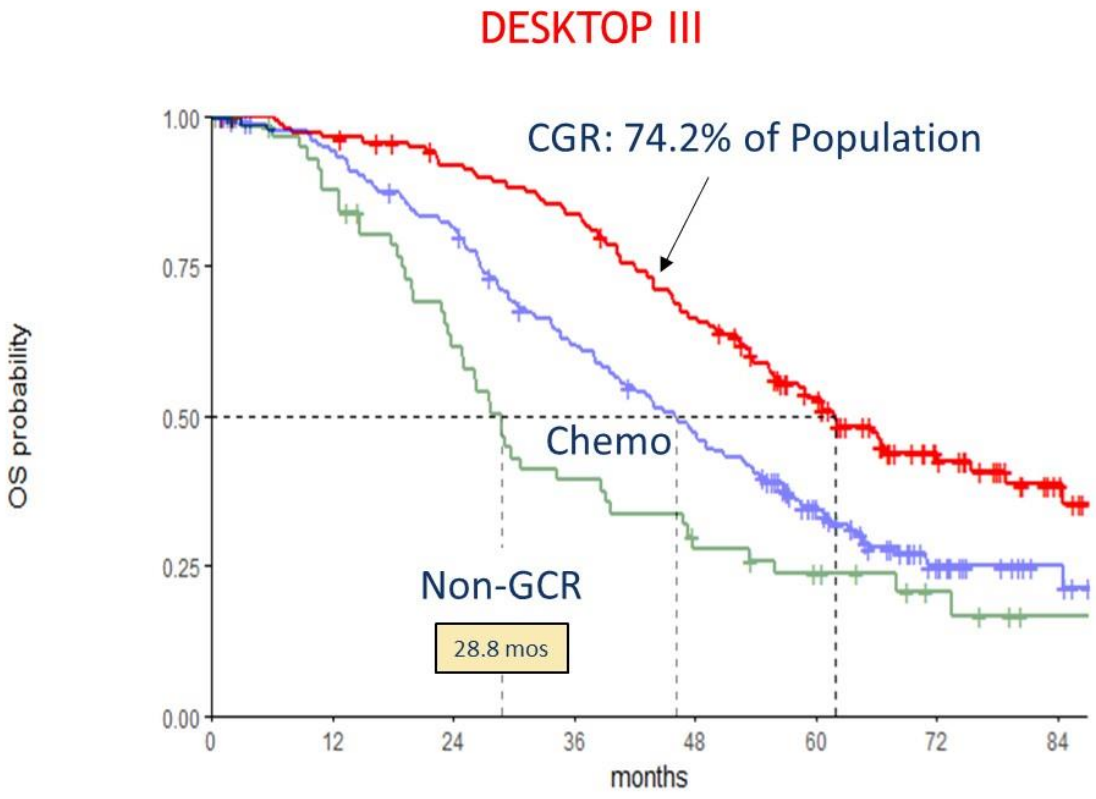
DESKTOP III

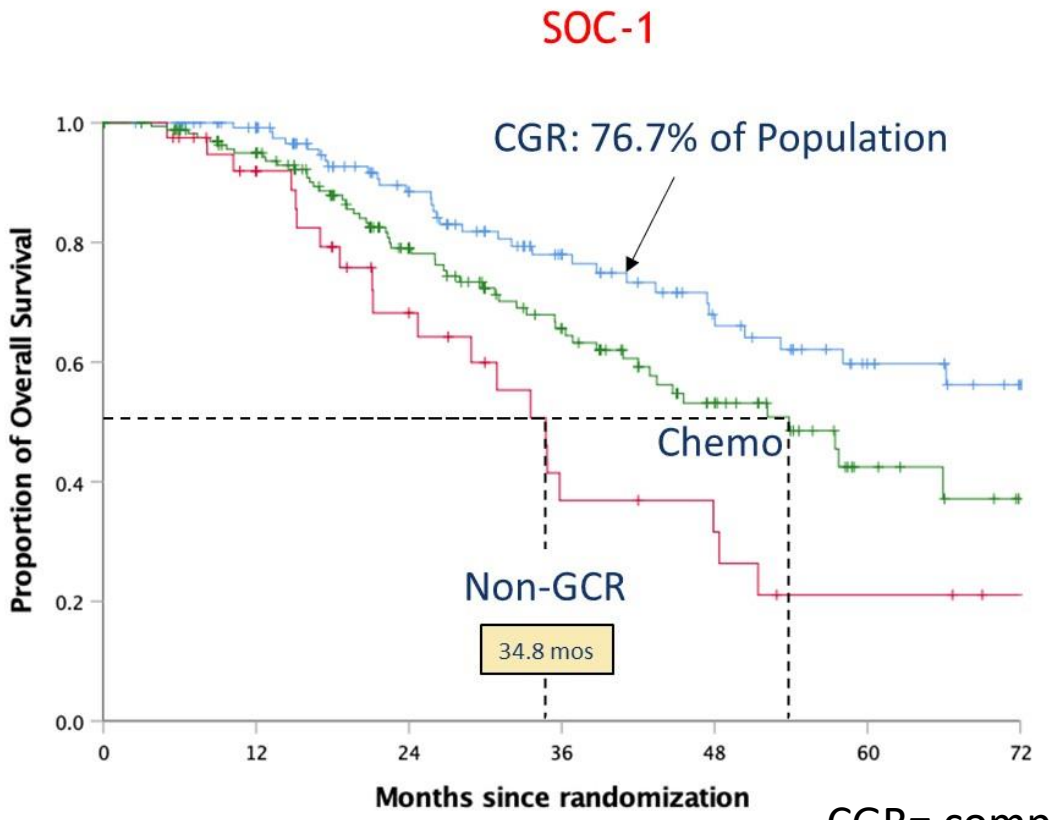


SOC-1

Adaptation of ASCO Presentation By Robert Coleman at TBD

Impact of Gross Residual Disease on OS in Recent Ovarian Cancer Secondary Cytoreduction Trials: DESKTOPIII and SOC-1





CGR= complete gross resection

Adaptation of ASCO Presentation By Robert Coleman at TBD

Conclusions – Secondary Cytoreduction

- May benefit the right patients
- Use your algorithm wisely
- Consider laparoscopy
- High stakes – residual disease may harm
- Bevacizumab may be the great equalizer *but can also be used down the road*

What is the best anti-angiogenic for endometrial cancer?

Are TKIs interchangeable with one another? With bev?

	RCC	HCC	Ovary
Cediranib	33%	0%	23%
Sunitinib	37%	12%	8%
Sorafenib	23%	10%	3%
Axitinib	22-44%	10% (2L)	NA
Tivozinib	33%	21% (1L) (small n)	NA
Pazopanib	30%	Liver tox	NA
Lenvatinib	27% (2L)	24% (1L)	NA
Regorafenib	40% (small n)	11% (2L)	0%
Cabozantinib	20%	4% (2L)	8%
bevacizumab	13%	20%	22%

Data in Endometrial Cancer Looks Pretty Similar Across Agents with a Big Signal in Combinations

Treatment	N	ORR	mPFS	OS
Bevacizumab[1]	52	13.5%	4.2 mo	10.6 mo
Cediranib[2]	48	12.5%	3.65 mo	12.5 mo
Lenvatinib[3]	133	21.8%	5.6 mo	10.6 mo
Pembro[4]	24	13%	1.8 mo	ND
Lenvatinib + Pembro[5]	**53**	**45.3%**	**7.4 mo**	**ND**

[5] Makker V et al. J Clin Oncol 36, 2018 (suppl; abstr 5596); [4] Ott et al. J Clin Oncol. 2017 Aug 1;35(22):2535-2541.; [3] Vergote I et al. J Clin. Oncol. 2013 31:15_suppl, 5520-5520; [1] Aghajanian C et al J Clin Oncol 2011: 2259-65; [2] Bender D et al. Gynecol Oncol (2015) 507-12

Adapted from K. Moore

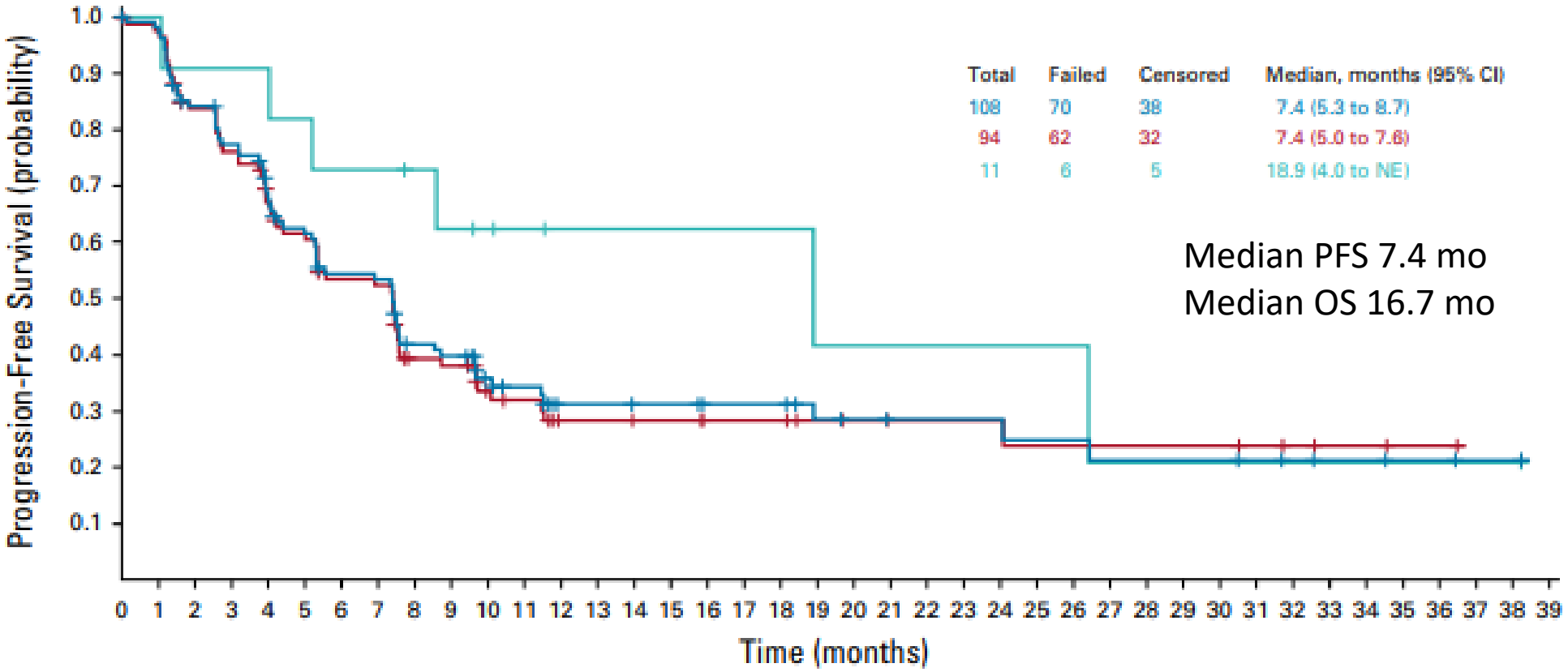
Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer

Vicky Makker, MD[1]; Matthew H. Taylor, MD[2]; Carol Aghajanian, MD[1]; Ana Oaknin, MD, PhD[3]; James Mier, MD[4]; Allen L. Cohn, MD[5]; Margarita Romeo, MD, PhD[6]; Raquel Bratos, MD[7]; Marcia S. Brose, MD, PhD[8]; Christopher DiSimone, MD[9]; Mark Messing, MD[10]; Daniel E. Stepan, MD[11]; Corina E. Dutcus, MD[12]; Jane Wu, PhD[12]; Emmett V. Schmidt, MD, PhD[13]; Robert Orlowski, MD[13]; Pallavi Sachdev, PhD[12]; Robert Shumaker, PhD[11]; and Antonio Casado Herraez, MD, PhD[14]

- Endometrial cancer
  - Up to 2 prior lines
  - Measurable disease
  - ECOG 0-1
- Lenvatinib 20 mg po q day + Pembrolizumab 200 mg IV q 3 weeks
- Primary endpoint:
  - ORR at 24 weeks
- DOR, PFS, OS

Parameter	Previously Treated EC[a] MSS/pMMR (n = 94)	MSI-H/dMMR (n = 11)	Total[b] (n = 108)	All EC (N = 124)
Histologic subtype				
Endometrioid adenocarcinoma	46 (48.9)	8 (72.7)	55 (50.9)	67 (54.0)
FIGO grade 1	10 (10.6)	2 (18.2)	12 (11.1)	15 (12.1)
FIGO grade 2	15 (16.0)	4 (36.4)	19 (17.6)	22 (17.7)
FIGO grade 3	21 (22.3)	2 (18.2)	24 (22.2)	30 (24.2)
Serous adenocarcinoma	33 (35.1)	0	35 (32.4)	39 (31.5)
Clear-cell adenocarcinoma	5 (5.3)	1 (9.1)	6 (5.6)	6 (4.8)
Dedifferentiated/ undifferentiated carcinoma	0	1 (9.1)	1 (0.9)	1 (0.8)
Adenocarcinoma, not otherwise specified	1 (1.1)	0	1 (0.9)	1 (0.8)
Other[c]	9 (9.6)	1 (9.1)	10 (9.3)	10 (8.1)
PD-L1 status[d]				
Positive	46 (48.9)	7 (63.6)	53 (49.1)	60 (48.4)
Negative	39 (41.5)	4 (36.4)	43 (39.8)	52 (41.9)
Not available	9 (9.6)	0	12 (11.1)	12 (9.7)
Prior treatment regimens for endometrial carcinoma[e]				
0	0	0	0	9 (7.3)
1	48 (51.1)	7 (63.6)	57 (52.8)	60 (48.4)
2	36 (38.3)	3 (27.3)	40 (37.0)	43 (34.7)
≥ 3	10 (10.6)	1 (9.1)	11 (10.2)	12 (9.7)

Updated Primary Efficacy Analysis: PFS



Maker et al, J clin Oncol 2020

Lenvatinib/Pemrolizumab – Good but has Toxicity

- ORR among patients previously treated: 38%
  - 30% had ≥ 50% tumor shrinkage
  - ORR in MSS 37%
- Median DOR 21.2 mo
  - Among responders, 87% had DOR > 6 mo, 63% > 12 mo
  - Median duration of treatment 8.5 mo
- Toxicity
  - 18% discontinuation rate
- 70% dose interruption
  - 63% dose reduced Lenvatinib
- 4 treatment AE related deaths, 2 treatment related deaths

Maker et al, J clin Oncol 2020

FDA Approves Pembrolizumab/Lenvatinib for Advanced Endometrial Carcinoma

September 17, 2019
Lisa Astor

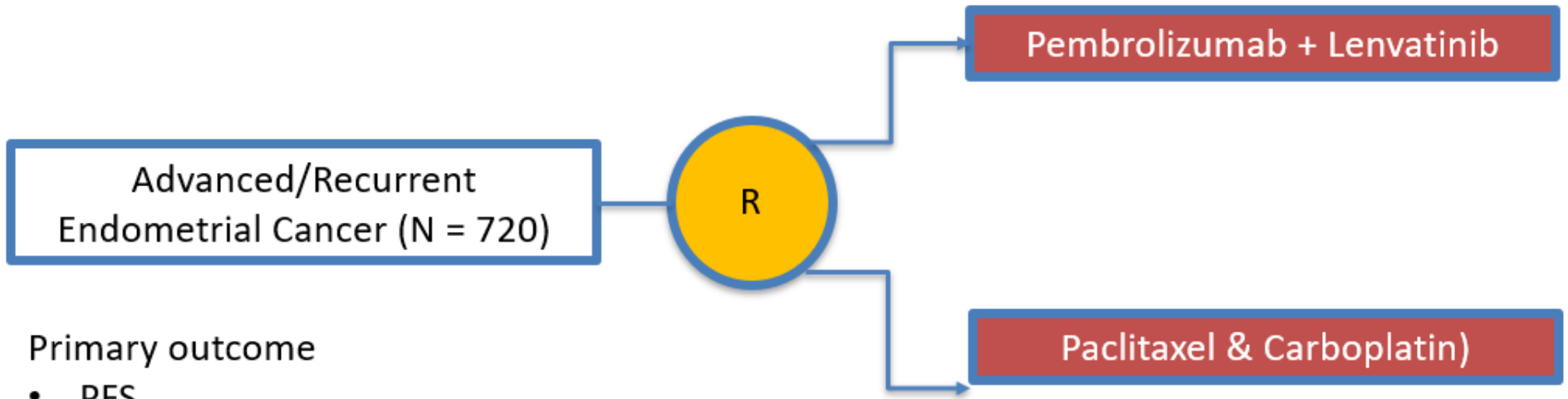
Relevant Topics

The FDA has granted an accelerated approval to the combination of pembrolizumab and lenvatinib for the treatment of patients with advanced endometrial cancer who have disease progression following prior systemic therapy. The indication applies to patients who are not candidates for curative surgery or radiation and who have disease that is not microsatellite instability–high or mismatch repair deficient.

The FDA has granted an accelerated approval to the combination of pembrolizumab (Keytruda) and lenvatinib (Lenvima) for the treatment of patients with advanced endometrial cancer who have disease progression following prior systemic therapy. The indication applies to patients who are not candidates for curative surgery or radiation and who have disease that is not microsatellite instability‐high (MSI-H) or mismatch repair deficient (dMMR).[1,2]

Combinatorial IO approach: Lenvatinib + Pembrolizumab E7080/MK-7902

- Randomized, international phase 3 trial in patients with advanced/ recurrent endometrial cancer/ 1L metastatic



Primary outcome
- PFS
- OS

Key eligibility criteria (NCT03884101):
- Advanced/Recurrent endometrial cancer
- No prior chemotherapy (chemo with RT is allowed, hormones are allowed)
- Measurable or Non measurable disease

Adapted from K. Moore

Nivolumab and Ipilumumab: CheckMate 358

- Phase Ib2/2 study in virus associated solid tumors
- Recurrent/metastatic SCCA cervix (n=91)
  - ≤ 2 priors
- Two different combinations evaluated
  - A: Nivo 3 mg/kg q2 w + Ipi 1 mg/kg q 6 w
  - B: Nivo 1 mg/kg +Ipi 3 mg/kg q 3w x 4 -> Nivo 240 mg q 2 w
- PDL1 expression evaluable in 82% (A) and 74% (B)
  - ≥1% in 62% (A) and 68% (B)
  - <1% in 38% (A) and 32% (B)
- Prior platinum in 87% (A) and 91% (B)
- Prior bev in 53%(A) and 54% (B)

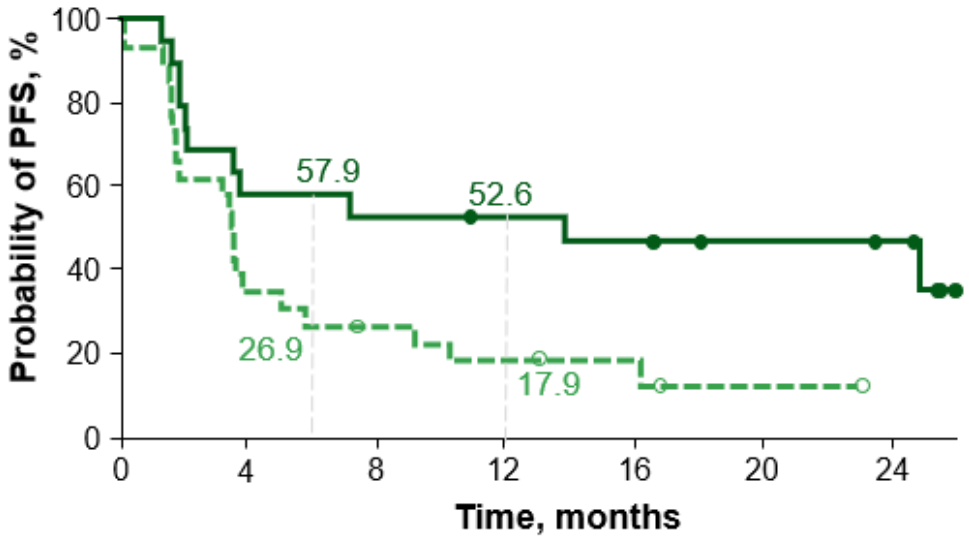
Naumann RW. CheckMate 358. ESMO Abstract 5630. 2019.

Checkmate 358: Progression Free Survival

Combo A

PFS no prior treatment: 13.8 mo

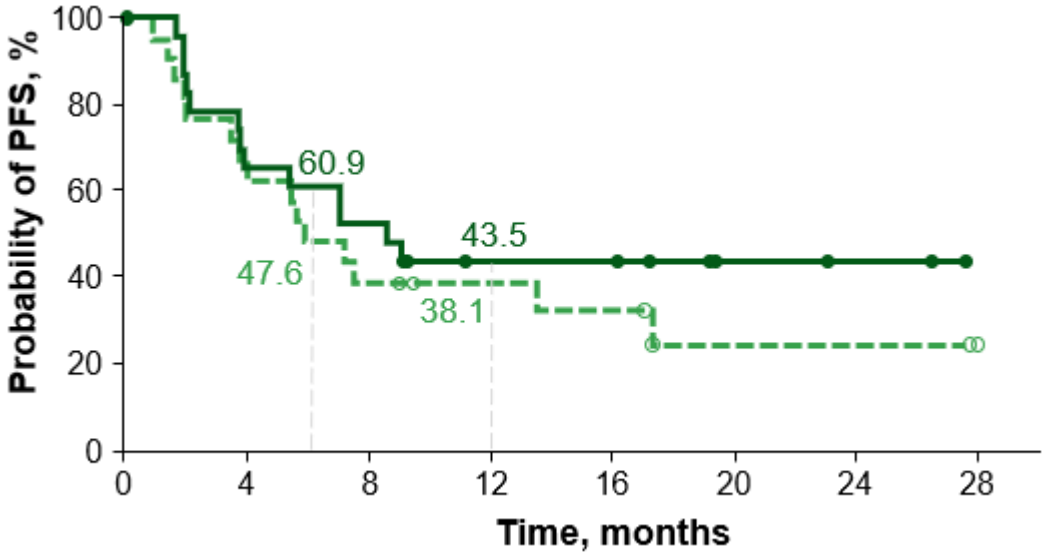
PFS prior treatment: 3.6 mo



Combo B

PFS no prior treatment: 8.5 mo

PFS prior treatment: 5.8 mo



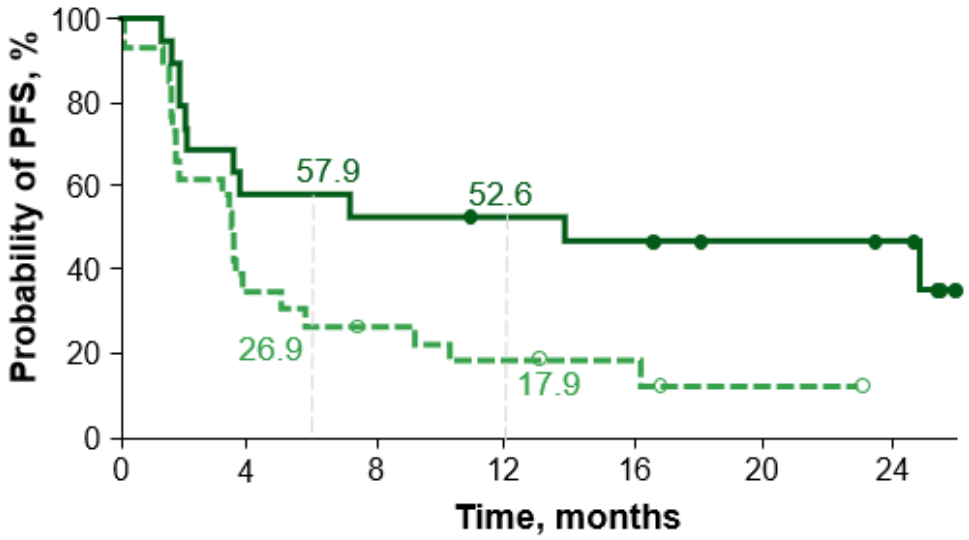
Naumann RW. CheckMate 358. ESMO Abstract 5630. 2019.

Checkmate 358: Progression Free Survival

Combo A

PFS no prior treatment: NR

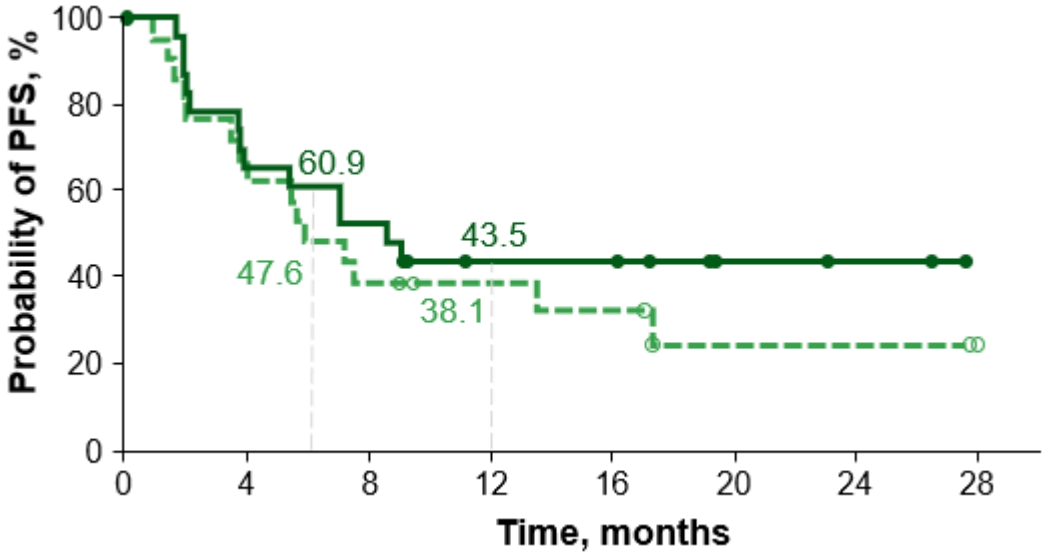
PFS prior treatment: 10.3 mo



Combo B

PFS no prior treatment: NR

PFS prior treatment: 25.4



Naumann RW. CheckMate 358. ESMO Abstract 5630. 2019.

Response and Toxicity: Checkmate 359

	A: Nivo (3 mg/kg) q2w + Ipi (1 mg/kg) q 6w		B: Nivo (1 mg/kg) + Ipi (3 mg/kg) x 4 -> Nivo 240 mg q2w	
	No prior tx for R/M disesease	Prior treatment for R/M disease	No prior tx for R/M disesease	Prior treatment for R/M disease
ORR (%)	31.6	23.1	45.8	36.4
PDL1 negative	*33.3*	*9.1*	*0*	*57.1*
PDL1 positive	30.8	40	36.4	16.7
DOR (months)	NR	NR	14.6	9.5
CBR (%)	63.2	53.8	70.8	72.7
Median PFS (months)	13.8	3.6	8.5	5.8
12 month PFS (months)	52.6	17.9	43.5	38.1
OS (%)	NR	10.3	NR	25.4
12 mo OS (%)	83.5	37.5	89.7	78
GI toxicity % all grades (3-4)	35.6 (8.9)		56.5 (13.0)	
Discontinuation (%)	18		33	
TRAE -> discontinuation all (3-4)	13.3 (4.4)		19.6 (13.0)	

Naumann RW. CheckMate 358. ESMO Abstract 5630. 2019.

Checkmate 358 Conclusions

- Clinical benefit of both combinations in patients with recurrent/metastatic cervical cancer
- *Responses seen regardless of PDL1 expression*
- Combo B – efficacy in previously treated population
- Long DOR
- Expansion cohort B ongoing
- Need further prospective data

Conclusions

- Upfront ovarian cancer
  - Strongly consider PARPi maintenance after primary treatment if BRCAm or HRD
  - Consider if HRP
- Recurrent ovarian cancer
  - Strongly consider PARPi maintenance if platinum sensitive
  - Consider secondary TDB in select candidates, though no gross residual disease is important
- Endometrial cancer
  - Lenvatinib/Pembrolizumab effective combination but with some toxicity
- Cervical cancer
  - Ipi/Nivo likely up and coming

Acknowledgements

- Kathleen Moore, MD
- Ritu Salani, MD
- Rob Coleman, MD
- Wendel Nauman, MD
- Patients and investigators