Updates on Gynecologic Malignancies

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Disclosures

- Advisory board: Iovance
- Research funding: Merck

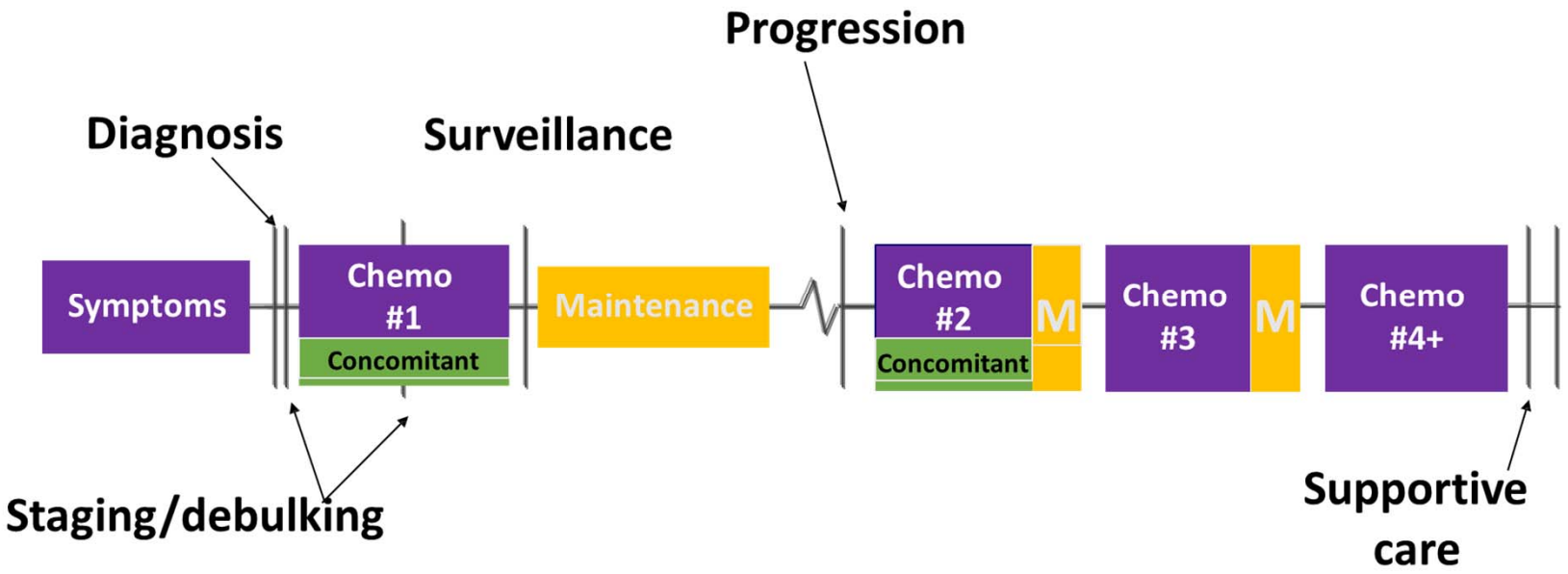
Overview

- **Ovarian cancer**
  - Updates on frontline treatment
- **Endometrial cancer**
  - New approved treatment option
- **Cervical cancer**
  - New results from emerging clinical trials

First-Line Treatment in Advanced Ovarian Cancer (AOC):

Facts and Figures

- Platinum and Paclitaxel are the two main drugs that have been in standard use for over 20 years.
- Over recent decades, the 5-year OS of women with AOC has improved but largely due to more treatment lines rather than better first-line therapy.



What is happening in the front line maintenance setting?

- In 2011,two key front-line trials incorporating BVZ **(GOG#218 and ICON-7)** showed a global benefit in both
  PFS and OS in selected populations: **These trials led to a new SOC in first-line therapy.**

  - GOG#218**: PFS HR:0.72** (95% CI, 0.63 to 0.82; P<0.001). **OS (Stage IV) HR 0.75** (95% CI, 0.59 to 0.95)

  - ICON-7: **PFS HR:0.81 (**95% CI, 0.70 to 0.94; P=0.004). **OS (High -Risk) HR 0.78** (95% CI, 0.63 to 0.97)

- **Additionally, the GOG#218 has broadened knowledge:**
  - Clearly confirmed the prognostic impact of BRCA mut in OS.
  - There is no evidence that BRCAmut predicts BVZ activity alongside paclitaxel/carboplatin.

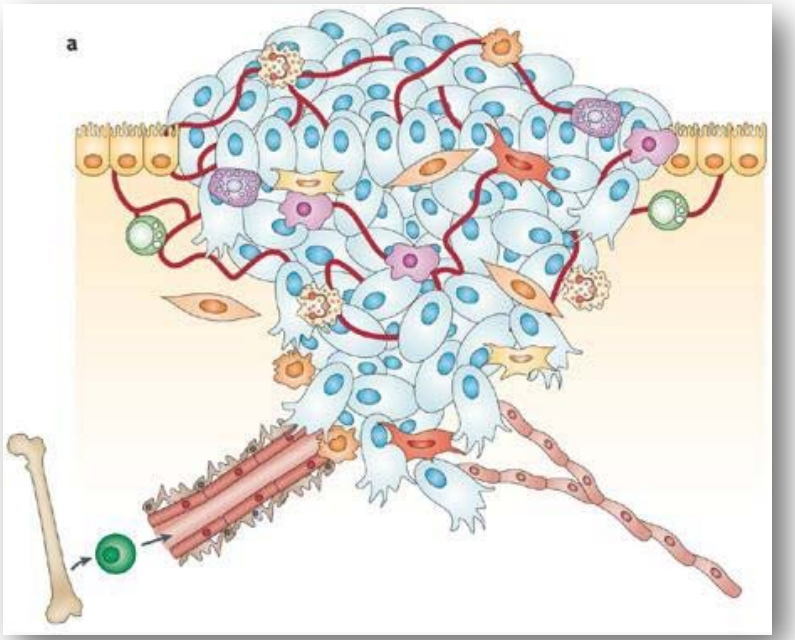
PDS, primary debulking surgery; NACT, neoadjuvant chemotherapy; IDS, Interval Debulking Surgery ;BVZ, Bevacizumab; PFS, Progression Free Survival; OS. Overall Survival; SOC, Standard of care; CI, confidence interval; HR, hazard ratio

Colombo N. et al ; Ann Oncol 2019;30:672-705; Burger et al. *N Engl J Med* 2011;365:2473-83; Perren TJ et al: *N Engl J Med* 2011;365:2484-96;
Oza A. et al. *Lancet Oncol* 2015;16:928; Tewari K et al.J Clin Oncol. 2019 Sep 10;37(26):2317-2328.

In the last 12 months……

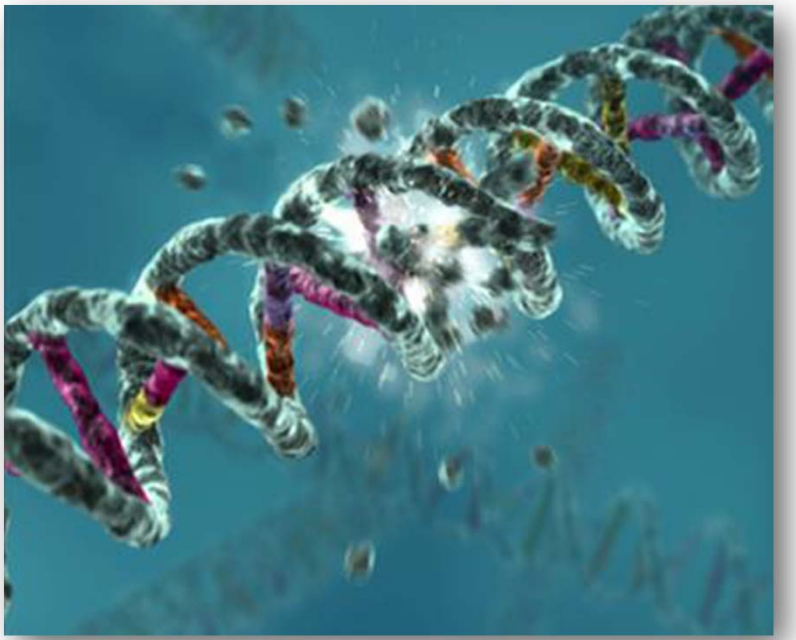
Clinical Debate

Anti-angiogenesis



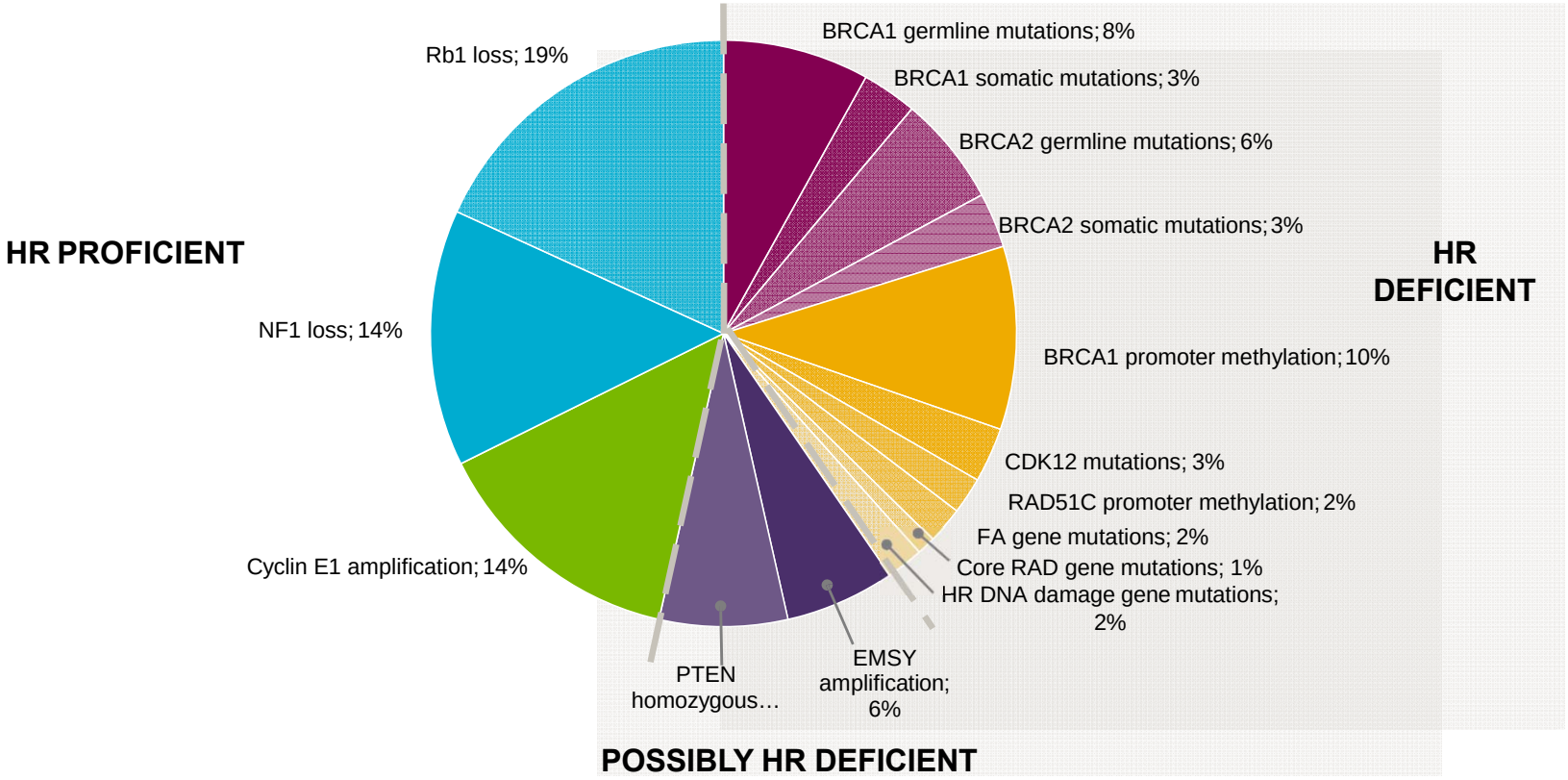
vs.

PARPi



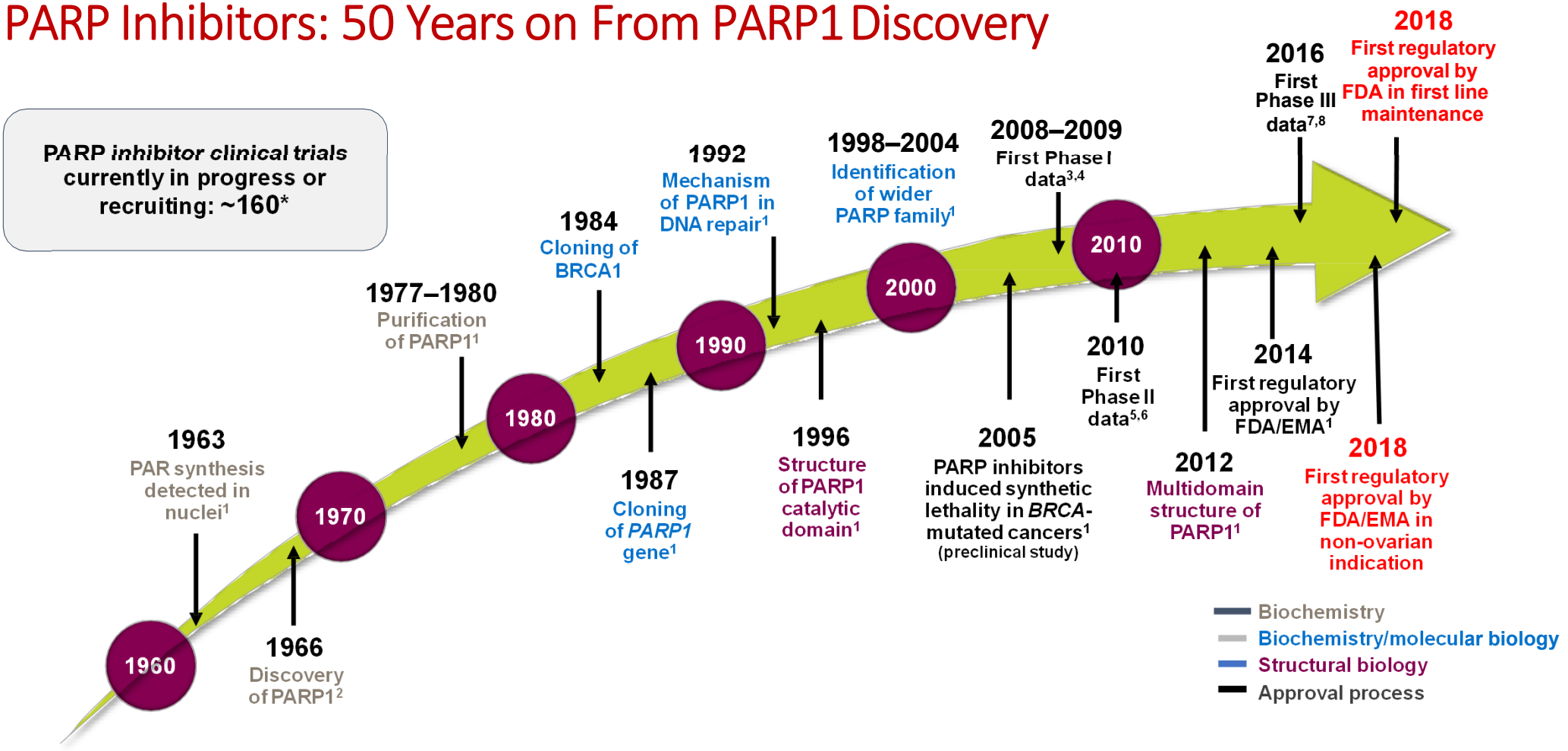
DEFINE THE CHALLENGE

General assumption 1: HR deficiency = PARP inhibitor sensitivity



Adapted from Konstantinopoulos et al, Canc Disc 2015 and Patch et al, Nature 2015

PARP Inhibitors: 50 Years on From PARP1 Discovery



*Source: ClinicalTrials.gov. EMA, European Medicines Agency; FDA, Food and Drug Administration; PARP, poly ADP-ribose polymerase.

1. Kraus WL. *Mol Cell.* 2015;58:902-910; 2. Chambon P, et al. *Biochem Biophys Res Commun.* 1966;25:638-643; 3. Plummer R, et al. *Clin Cancer Res.* 2008;14:7917-7923; 4. Fong PC, et al. *N Engl J Med.* 2009:361:123-134; 5. Audeh MW, et al. *Lancet.* 2010;376:245-251; 6. Tutt A, et al. *Lancet.* 2010;376:235-244; 7. Bang Y-J, et al. *Ann Oncol.* 2016;27:abst 2742; 8. Mirza MR, et al. *N Engl J Med.* 2016;375(22):2154-2164.

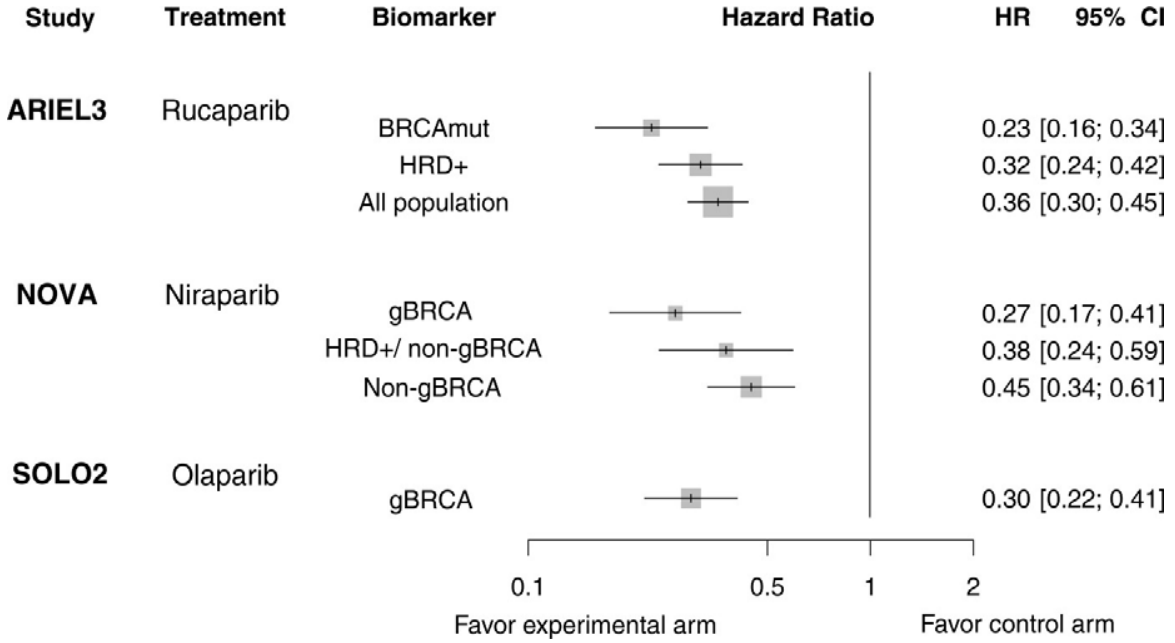
PARP inhibitors - The last decade

- Initial licence for olaparib as maintenance therapy in recurrent high grade serous *BRCA*^{mut} ovarian cancer following response to platinum-based therapy
- FDA monotherapy licence in *BRCA*^{mut} ovarian cancer after ≥ 3 lines of treatment
- Licence for maintenance extended to all recurrent high-grade ovarian cancers irrespective of *BRCA* status responding to platinum-based therapy - **niraparib (NOVA), olaparib (SOLO2/Study 19) and rucaparib (ARIEL3)**

Ledermann et al Lancet Oncol 2014; Mirza et al NEJM 2016; Pujade-Lauraine et al Lancet Oncol 2017; Coleman et al Lancet 2017; Oza et al Gynecol Oncol 2017

What have we learnt from PARPi studies in OC platinum sensitive recurrent setting?

- Three randomized phase 3 trials have shown that, in those patients who had achieved a PR or CR following platinum therapy, PARPi agents (O,N,R) as a maintenance therapy significantly improve PFS compared to placebo.
- In this setting, O,N,R are approved by the Regulatory Agencies (EMA & FDA) regardless of BRCA 1/2 and HRD status.



OC, Ovarian Cancer; PSR, Platinum Sensitive Recurrence;O, Olaparib; N, Niraparib, R, Rucaparib; gBRCA, germline BRCA; BRCA mut, *BRCA1* and/or *BRCA2* mutation;HRD, Homologous Recombination Deficiency

*Forest plot adapted from:Coleman RL. et al.*The Lancet*, Vol.390, Nº10106, p1949-1961; Mirza MR. et al. *N Engl J Med.* 2016;375(22):2154-2164;Pujade-Lauraine E. et al Lancet Oncol. 2017 Sep;18(9):1274-1284;

LAST YEAR…..

SOLO1: Olaparib maintenance therapy after front-line treatment in women with *BRCA*^{mut} OC

- **Newly diagnosed**, FIGO **stage III–IV**, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic *BRCA*m
- ECOG performance status 0–1
- **Cytoreductive surgery***
- In **clinical complete response or partial response** after platinum-based chemotherapy

Olaparib 300 mg bd (N=260)

2:1 randomization

Stratified by response to platinum- based chemotherapy

Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2 years' treatment if no evidence of disease

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

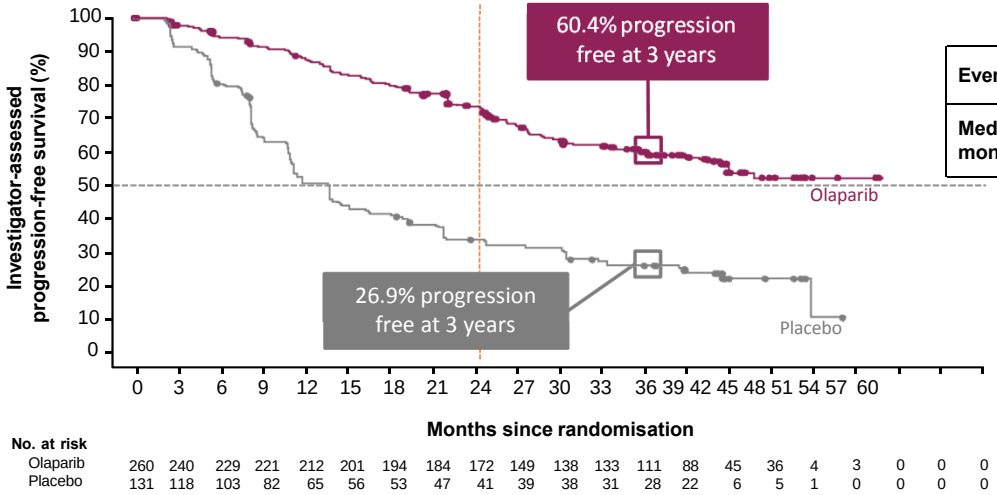
Secondary endpoints

- PFS using BICR
- PFS2
- Overall survival
- Time from randomization to first subsequent therapy or death
- Time from randomization to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

Moore et al ESMO 2018; NEJM 2018

SOLO-1: Progression-free survival by investigator assessment

After a median follow-up of 41 months, the median PFS had not been reached in the olaparib arm (vs. 13.8 months in the placebo arm)[1,2]



	Olaparib	Placebo
Events, n (%)	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
	HR=0.30 95% CI: 0.23–0.41 p<0.001	

- In 2018,in the Phase-3 trial **SOLO-1, the PARPi O,** provided an unprecedented benefit in PFS for newly-diagnosed AOC pts whose tumors harbor a **BRCAmut**: **PFS HR 0.30** (95% CI, 0.23 to 0.41; P<0.001). **These results led to a new SOC for this group of AOC pts.**
- Significant benefit in PFS. PFS2 shows that 60% women on olaparib are free of progression at 48 months - a 36 month difference in time to subsequent treatment
- **Early testing for BRCA mutations** needed if decisions between bevacizumab and olaparib are needed

1. Moore K. et al. *N Engl J Med*. 2018;379:2495–2505;

WHERE DO **WE** STAND **WITH** PARP INHIBITORS **FOR** OVARIAN **CANCER** TREATMENT IN OCTOBER 2019?

Niraparib therapy in Patients with Newly-Diagnosed Advanced Ovarian Cancer: **PRIMA/ENGOT-Ov26/GOG-3012 Study**

Olaparib plus Bevacizumab as maintenance therapy in Patients with Newly-Diagnosed Advanced Ovarian Cancer: **PAOLA-1/ENGOT-Ov25 Trial**

VELIA/GOG-3005: Integration of veliparib with front-line chemotherapy and maintenance in women with high-grade serous carcinoma of ovarian, fallopian tube, or primary peritoneal origin

A Paradigm Shift in the First-Line Treatment for Advanced Ovarian Cancer Patients?

Niraparib Therapy in Patients With Newly-Diagnosed Advanced Ovarian Cancer

(PRIMA/ENGOT-OV26/GOG-3012)

A. González-Martín,[1] B. Pothuri,[2] I. Vergote,[3] R.D. Christensen,[4] W. Graybill,[5] M.R. Mirza,[6] C. McCormick,[7] D. Lorusso,[8] P. Hoskins,[9] G. Freyer,[10] F. Backes,[11] K. Baumann,[12] A. Redondo,[13] R. Moore,[14] C. Vulsteke,[15] R.E. O'Cearbhaill,[16] B. Lund,[17] Y. Li,[18] D. Gupta,[18] B.J. Monk[19]

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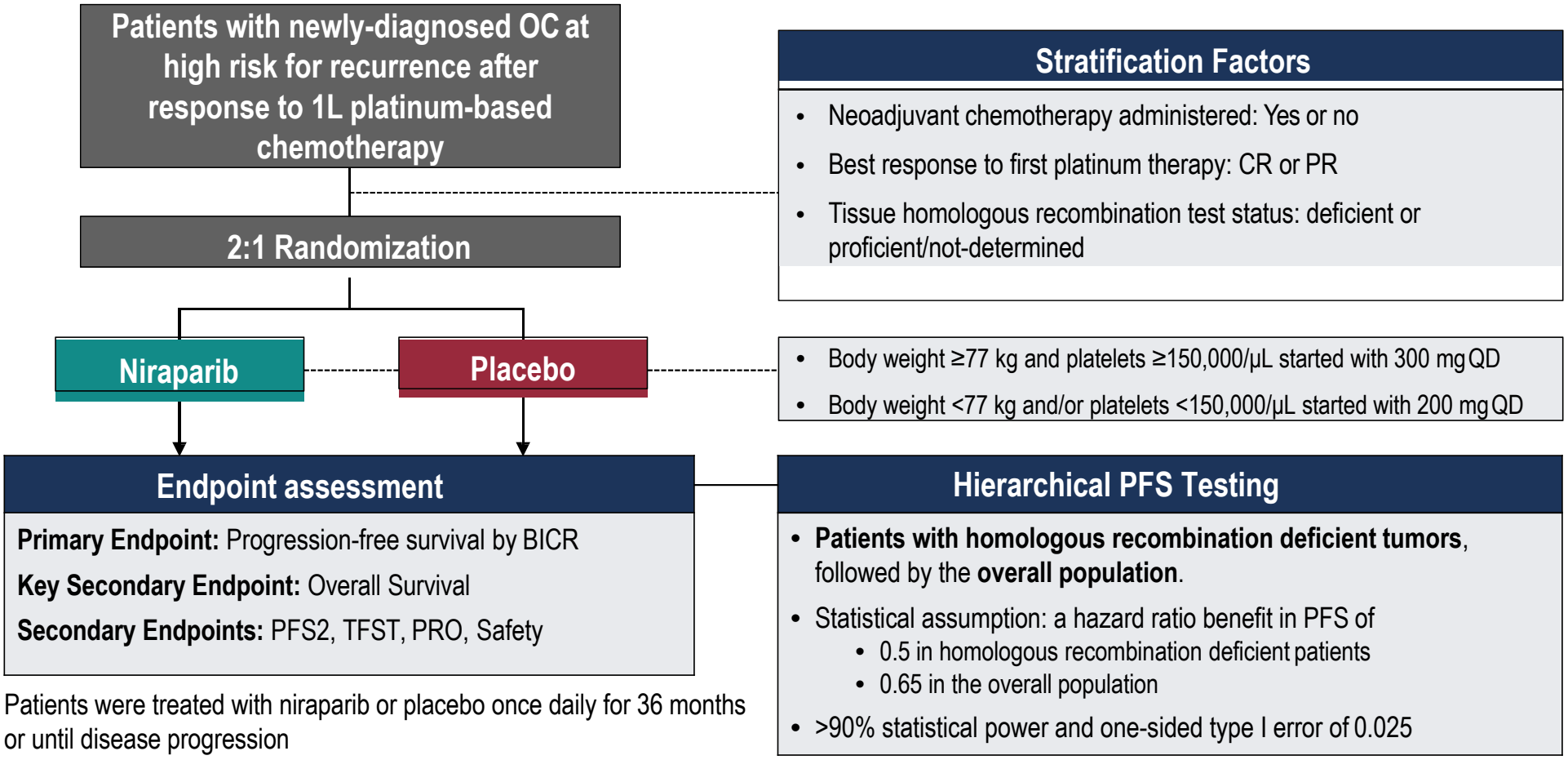
PRIMA Trial Design



Patients were treated with niraparib or placebo once daily for 36 months or until disease progression

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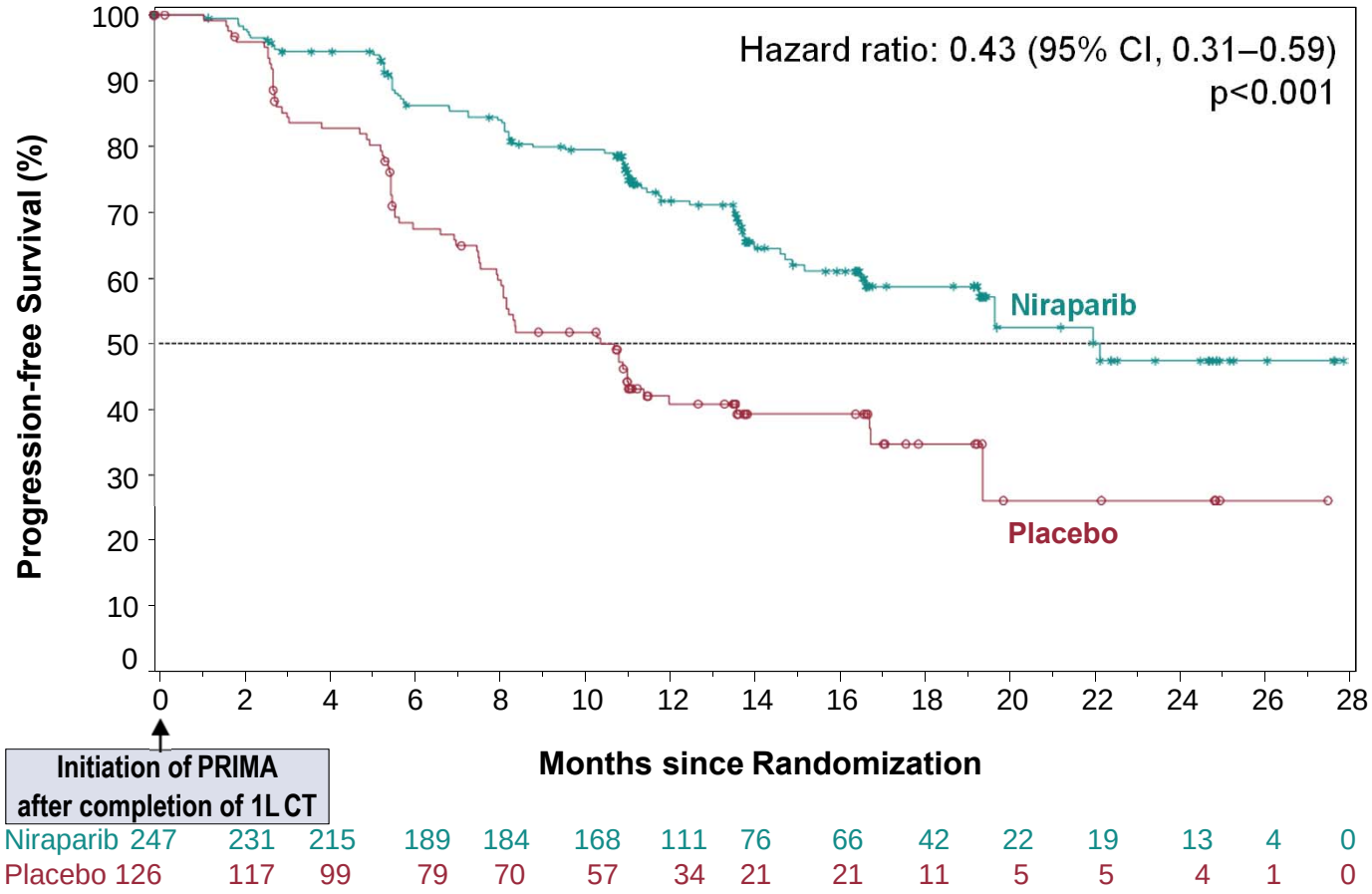
1L, first-line; BICR, blinded independent central review; CR, complete response; OC, ovarian cancer; PFS2, progression-free survival 2; PR partial response; PRO, patient-reported outcomes; TFST, time to first subsequent therapy.

PRIMA Primary Endpoint, PFS Benefit in the HR-deficient Population



57% reduction in hazard of relapse or death with niraparib

	Niraparib (n=247)	Placebo (n=126)
Median PFS		
months (95% CI)	21.9 (19.3–NE)	10.4 (8.1–12.1)
Patients without PD or death (%)		
6 months	86%	68%
12 months	72%	42%
18 months	59%	35%

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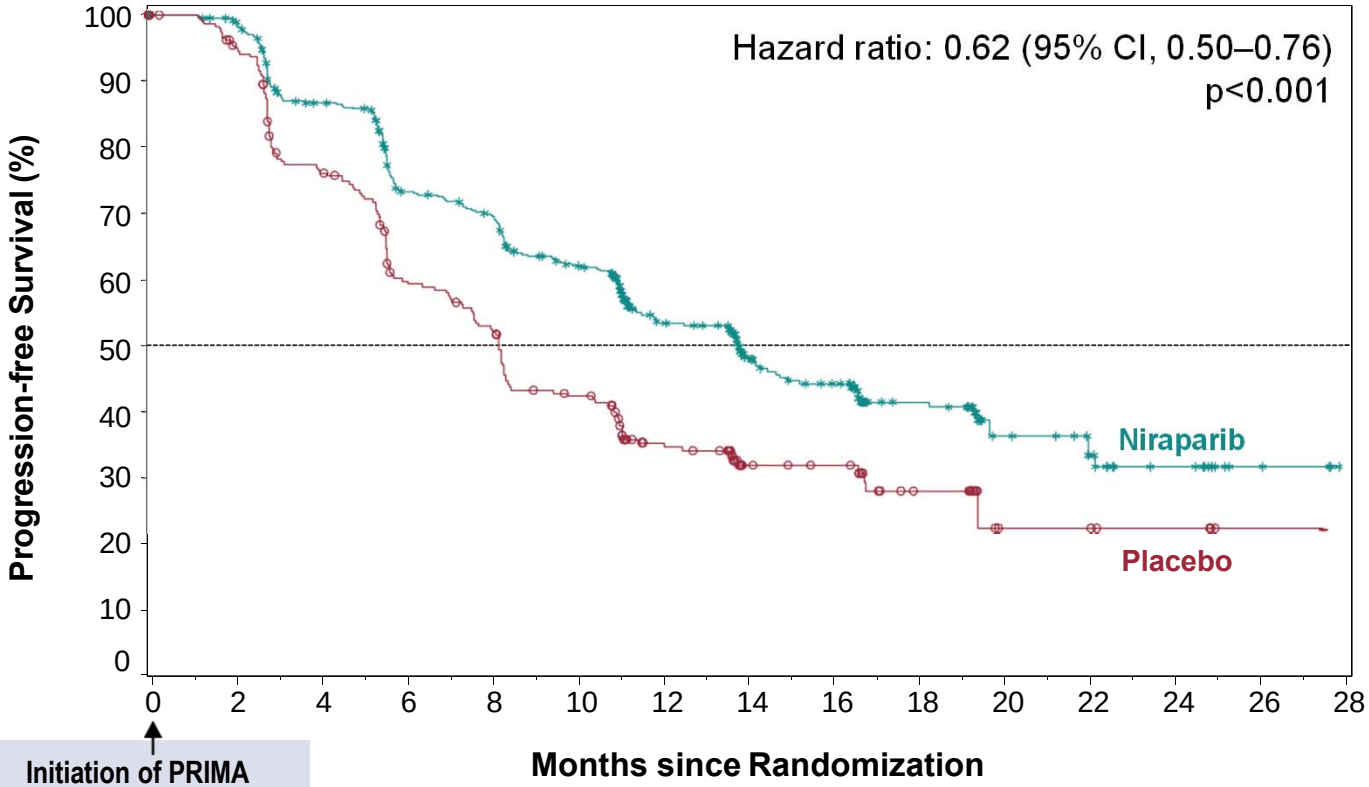
1L, first-line; CI, confidence interval; CT, chemotherapy; HR, homologous recombination; NE, not estimable; PD, progressive disease; PFS, progression-free survival.
Sensitivity analysis of PFS by the investigator was similar to and supported the BICR analysis.

PRIMA Primary Endpoint, PFS Benefit in the Overall Population



38% reduction in hazard of relapse or death with niraparib

	Niraparib (n=487)	Placebo (n=246)
Median PFS		
months (95% CI)	13.8 (11.5–14.9)	8.2 (7.3–8.5)
Patients without PD or death (%)		
6 months	73%	60%
12 months	53%	35%
18 months	42%	28%

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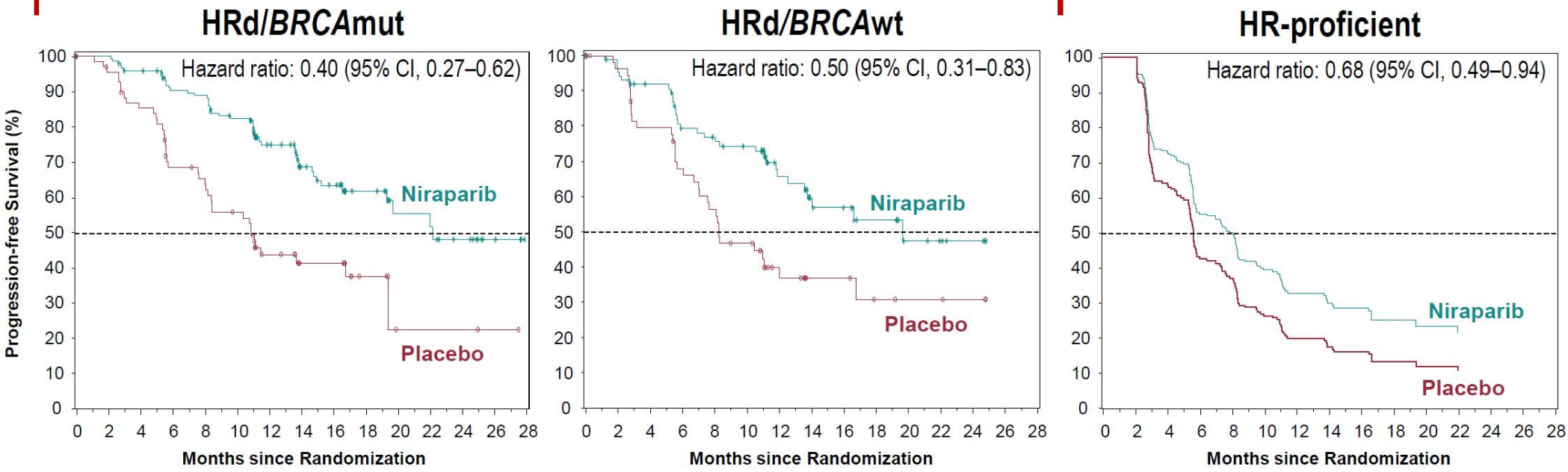
1L, first-line; CI, confidence interval; CT, chemotherapy; PD, progressive disease; PFS, progression-free survival.
Discordance in PFS event between investigator assessment vs BICR ≈12%.

PRIMA PFS Benefit in Biomarker Subgroups

Homologous Recombination Deficient (HRd)



- Niraparib provided similar clinical benefit in the HRd subgroups (*BRCA*mut and *BRCA*wt)
- Niraparib provide clinically significant benefit in the HR-proficient subgroup with a 32% risk reduction in progression or death

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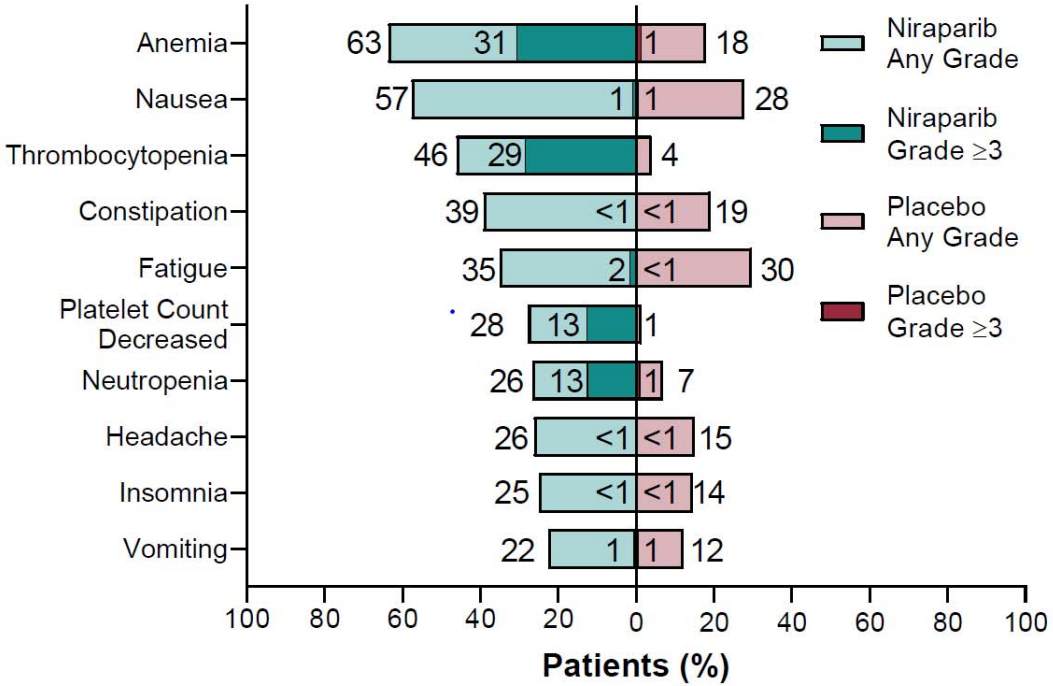
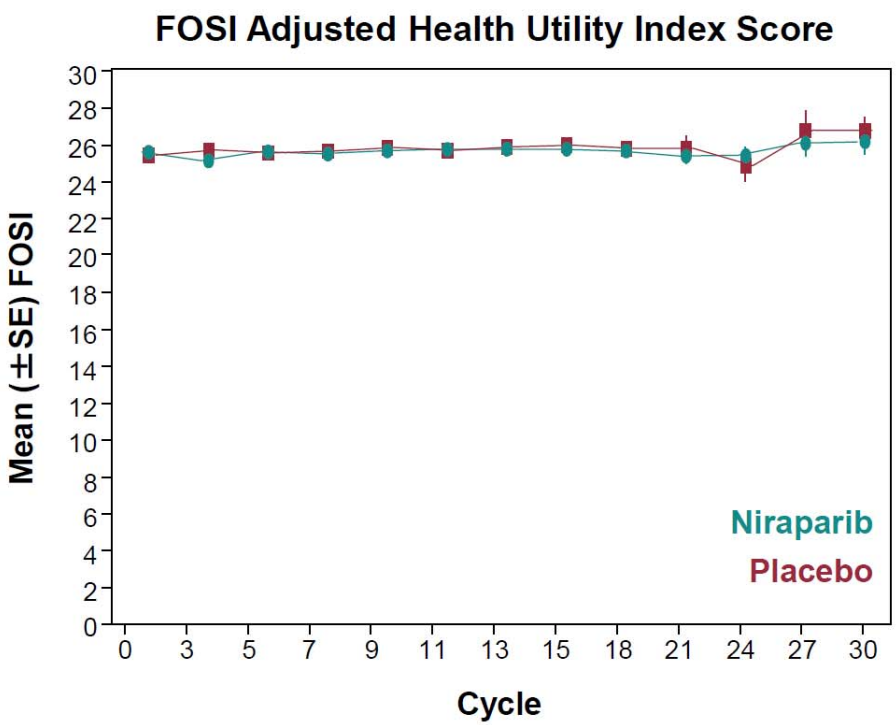
PRIMA Safety and Patient-Reported Outcomes (PRO)





- No new safety signals were identified for niraparib
- Most common TEAE was reversible myelosuppression
- One patient was diagnosed with MDS after 9 months of niraparib treatment

- No impact in PRO with niraparib treatment

TEAEs ≥20% incidence in niraparib arm. Note: Hematologic TEAEs are not combined with laboratory results
FOSI, FACIT ovarian cancer symptom index; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.

Phase III PAOLA-1/ENGOT-ov25: maintenance olaparib with bevacizumab in patients with newly-diagnosed, advanced ovarian cancer treated with platinum-based chemotherapy and bevacizumab as standard of care

Isabelle Ray-Coquard, Patricia Pautier, Sandro Pignata, David Pérol, Antonio González-Martin, Paul Sevelda, Keiichi Fujiwara, Ignace Vergote, Nicoletta Colombo, Johanna Mäenpää, Frédéric Selle, Jalid Sehouli, Domenica Lorusso, Eva Maria Guerra Alia, Claudia Lefeuvre-Plesse, Ulrich Canzler, Alain Lortholary, Frederik Marmé, Eric Pujade-Lauraine, Philipp Harter

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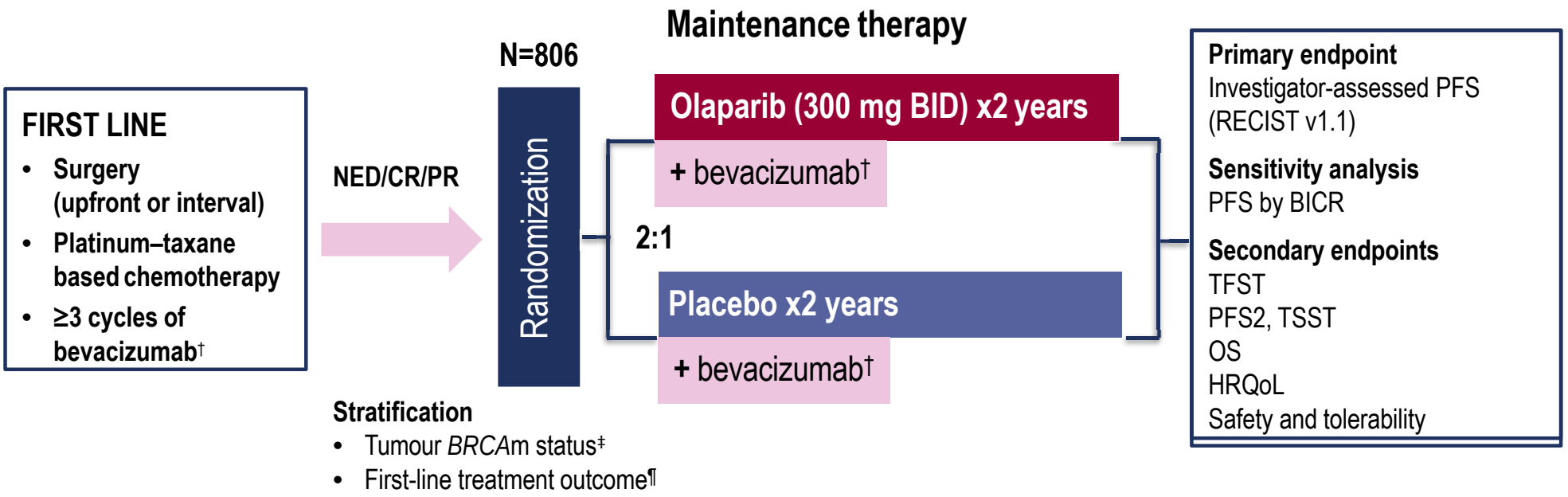
ClinicalTrials.gov identifier: NCT02477644
This study was sponsored by ARCAGY Research

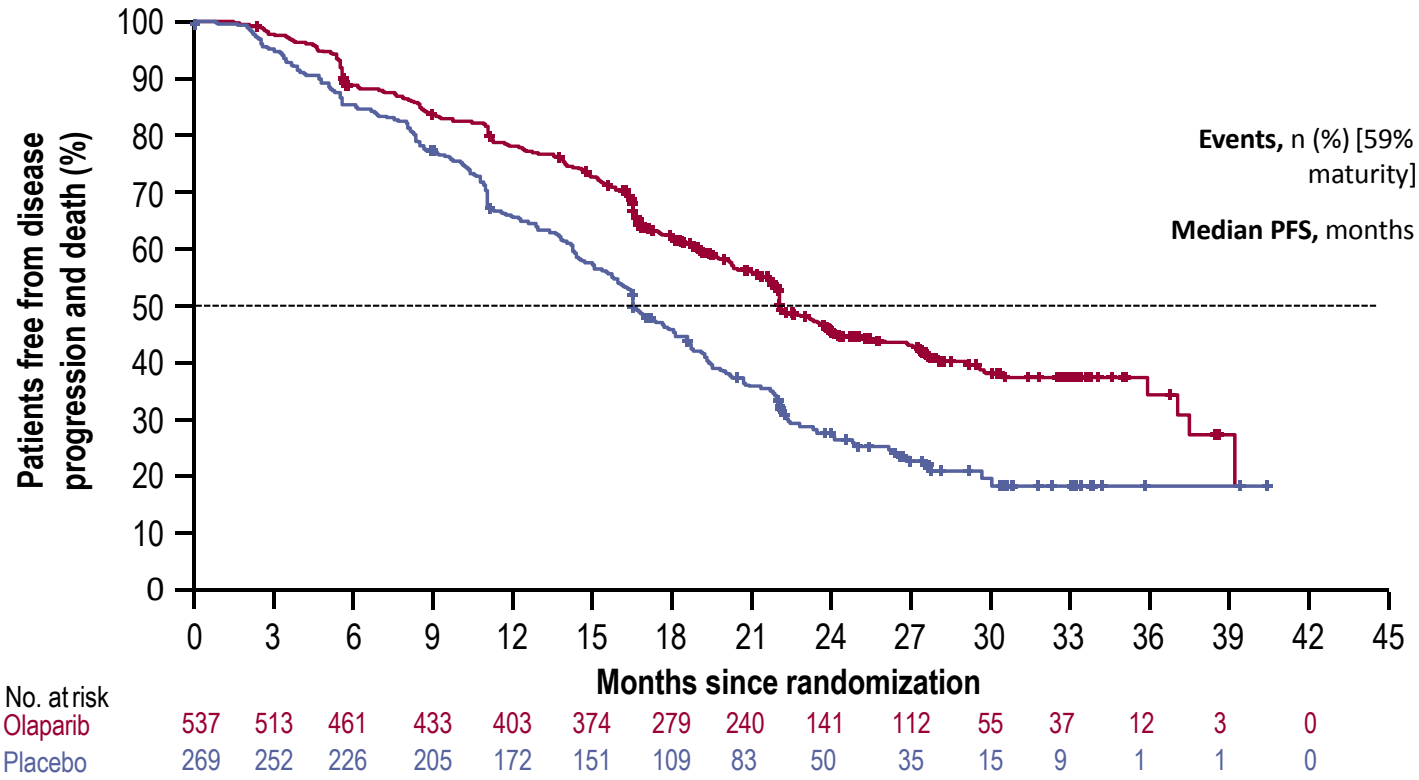
PAOLO-1 Study design

Newly-diagnosed FIGO stage III–IV high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer*



*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation
†Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; ‡By central labs; ¶According to timing of surgery and NED/CR/PR
BICR, blinded independent central review; HRQoL, health-related quality of life; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

PAOLA-1:PFS by investigator assessment: ITT population



	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [59% maturity]	280 (52)	194 (72)
Median PFS, months	**22.1**	**16.6**

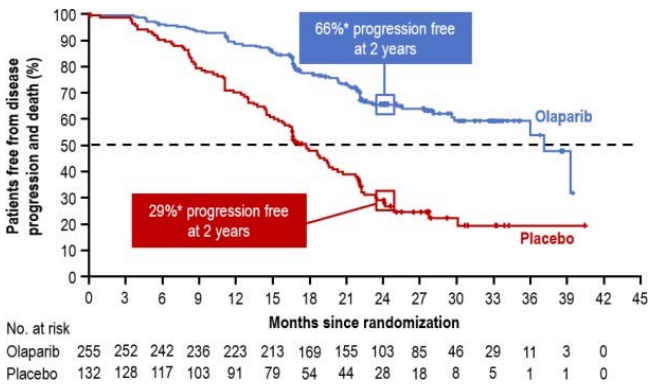
HR 0.59 (95% CI 0.49–0.72; *P*<0.0001)

Median time from first cycle of chemotherapy to randomization = 7 months

ITT, intent-to-treat population

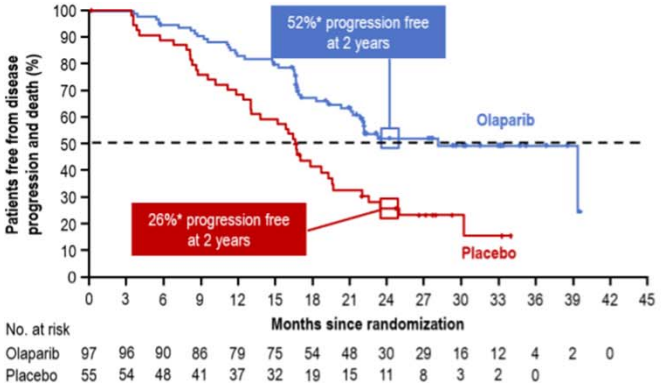
PAOLA1: PFS by HRD status

HRD-positive, including tBRCA (48%)



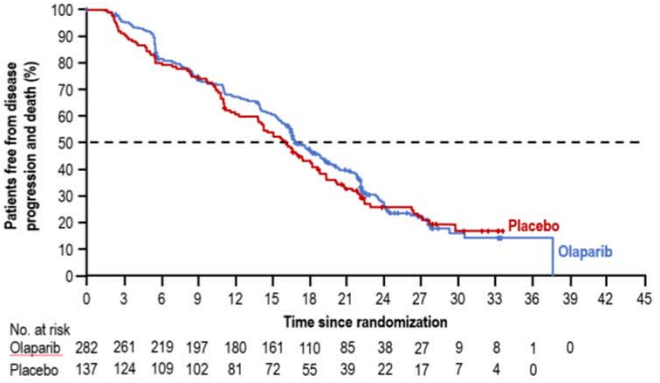
	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	87 (34)	92 (70)
Median PFS, months	37.2	17.7
	HR 0.33	
	95% CI 0.25–0.45	

HRD-positive, excluding tBRCA (19%)



	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
Events, n (%)	43 (44)	40 (73)
Median PFS, months	28.1	16.6
	HR 0.43	
	95% CI 0.28–0.66	

HRD-negative/unknown (34%)



	Olaparib + bevacizumab (n=282)	Placebo + bevacizumab (n=137)
Events, n (%)	193 (68)	102 (74)
Median PFS, months	16.9	16.0
	HR 0.92	
	95% CI 0.72–1.17	

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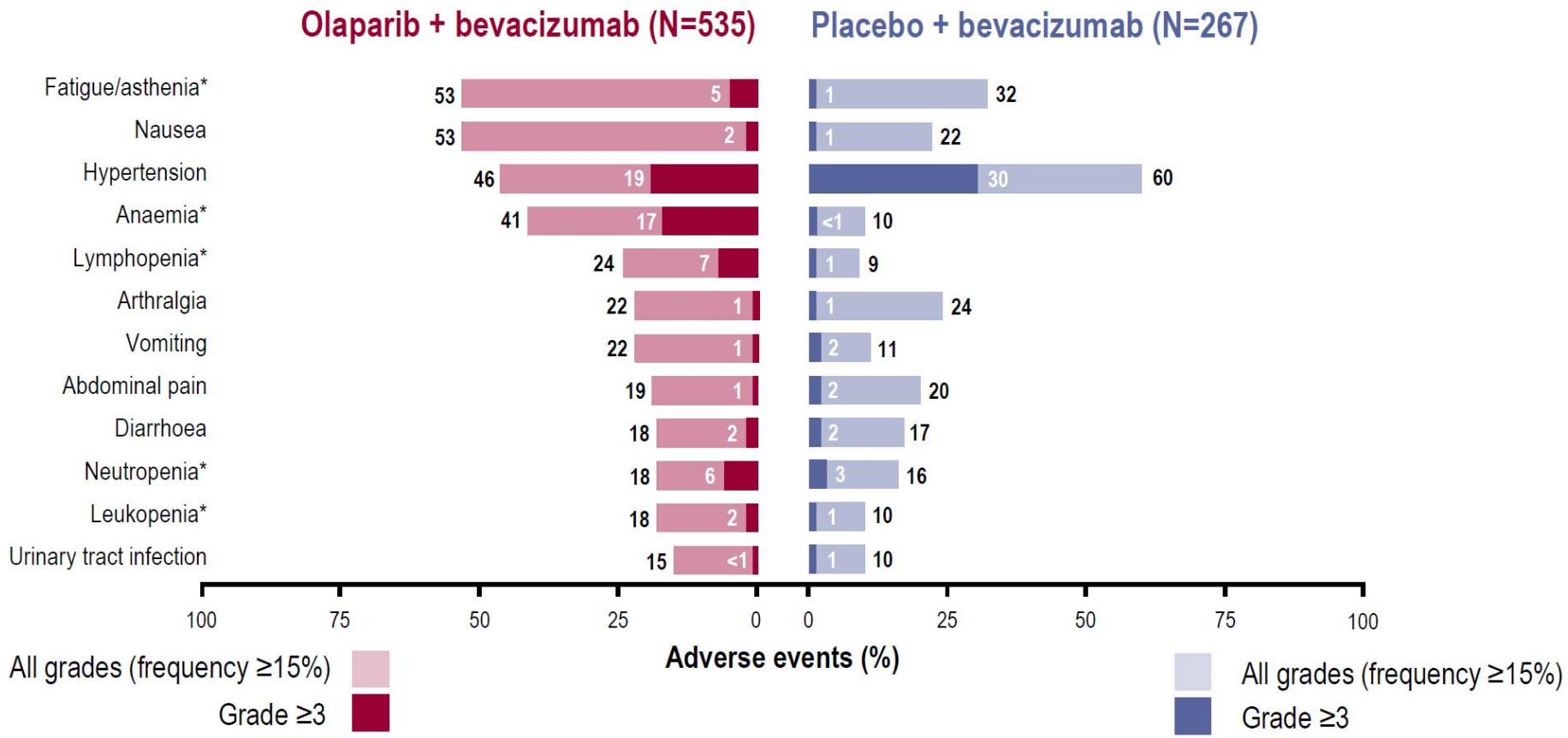
HRD-positive is an HRD score ≥42

*based on Kaplan-Meier estimates

Most common AEs



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*Grouped terms. All-grade thrombocytopenia (grouped term) occurred in 8% of patients in the olaparib group and 3% of patients in the placebo group, grade ≥3 thrombocytopenia occurred in 2% of patients in the olaparib group and <1% of patients in the placebo group

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VELIA/GOG-3005: Integration of veliparib with front-line chemotherapy and maintenance in women with high-grade serous carcinoma of ovarian, fallopian tube, or primary peritoneal origin

Robert L. Coleman[1], Gini F. Fleming[2], Mark F. Brady[3], Elizabeth M. Swisher[4], Karina D. Steffensen[5], Michael Friedlander[6], Aikou Okamoto[7], Kathleen N. Moore[8], Noa Ben-Baruch[9], Theresa L. Werner[10], Ana Oaknin[11], Joo-Hyun Nam[12], Charles A. Leath III[13], Shibani Nicum[14], David Cella[15], Danielle M. Sullivan[16], Peter J. Ansell[16], Minh H. Dinh[16], Carol Aghajanian[17], Michael A. Bookman[18]

[1]The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [2]The University of Chicago Medicine, Chicago, IL, USA;[3]NRG Oncology Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY, USA; [4]University of Washington, Seattle, Washington, USA; [5]Vejle University Hospital of Southern Denmark, Vejle, Denmark; [6]Prince of Wales Clinical School UNSW and Prince of Wales Hospital, Sydney, Australia; [7]The Jikei University School of Medicine, Tokyo, Japan; [8]Stephenson Cancer Center at the University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [9]Kaplan Medical Center, Rehovot, Israel;[10]Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA;[11]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [12]University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; [13]University of Alabama at Birmingham, Birmingham, AL, USA; [14]Oxford University Hospitals, Oxford, United Kingdom;[15]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA;[16]AbbVie Inc., North Chicago, IL, USA; [17]Memorial Sloan Kettering Cancer Center, New York, NY, USA;[18]Kaiser Permanente Northern California, San Francisco, CA, USA

VELIA STUDY

GOG Foundation/Partners

ANZ GOG

Study Design: VELIA/GOG-3005 (NCT02470585)

Patient Population

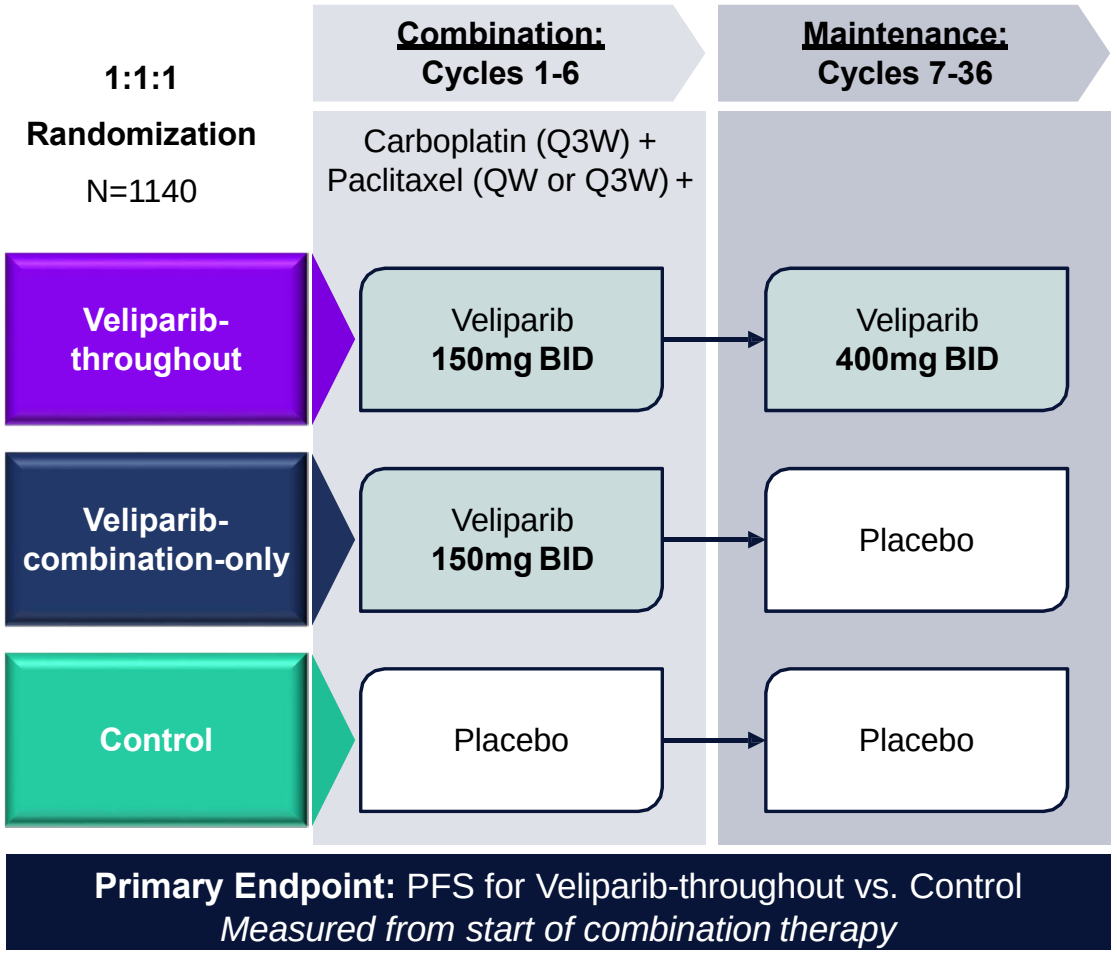
- High-Grade Serous Cancer
- FIGO Stage III or IV
- No prior systemic therapy
- ECOG 0 to 2
- No CNS metastases

Stratification Factors

- Stage of Disease
- Region
- Primary vs Interval Cytoreduction
- Residual Disease
- Chemotherapy Regimen*
- g*BRCA* Status **

* Carboplatin AUC 6 Q3W + Paclitaxel 80 mg/m^2 QW or 175 mg/m^2 Q3W

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



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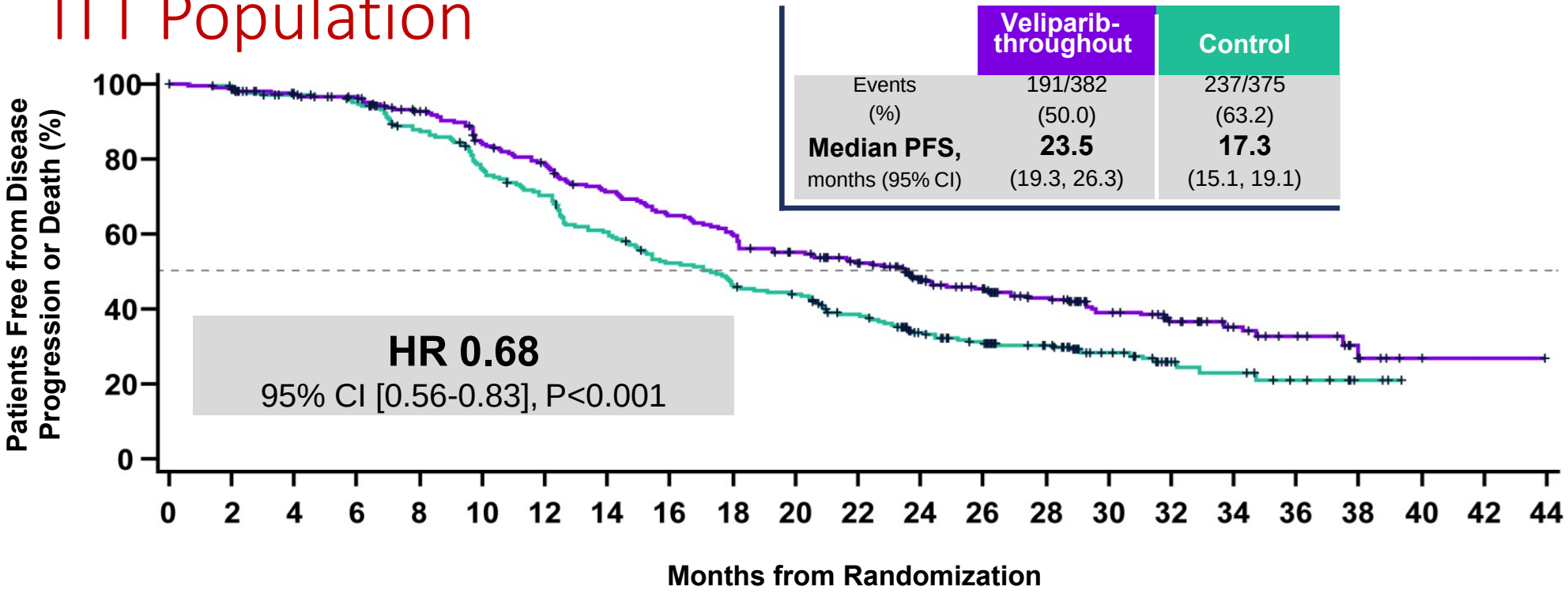
VELIA PFS by Investigator Assessment ITT Population



No. at Risk

Control	375	356	340	328	297	260	236	202	172	153	143	119	84	70	55	36	21	16	10	3	0	
Veliparib-throughout	382	352	337	329	308	275	253	228	208	192	172	153	111	95	76	55	38	26	19	7	2	1	0

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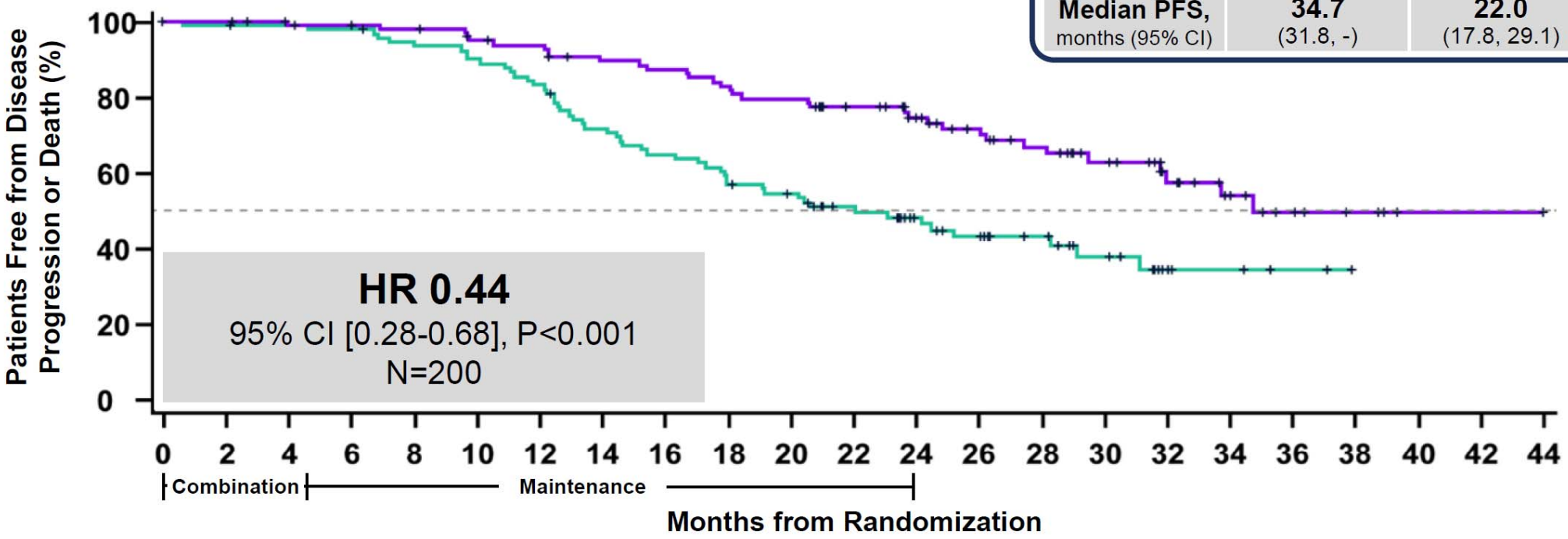
Median duration of follow-up was 28 months at the time of database lock.

PFS by Investigator Assessment
*BRCA*m Population

*BRCA*m | HRD | Non-HRD

*BRCA*m	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)



No. at Risk

Control	92	90	89	88	84	80	74	63	57	50	46	38	29	24	19	13	6	4	2	0		
Veliparib-throughout	108	102	99	97	95	90	88	82	80	76	73	65	53	45	38	30	21	14	9	5	1	1	0

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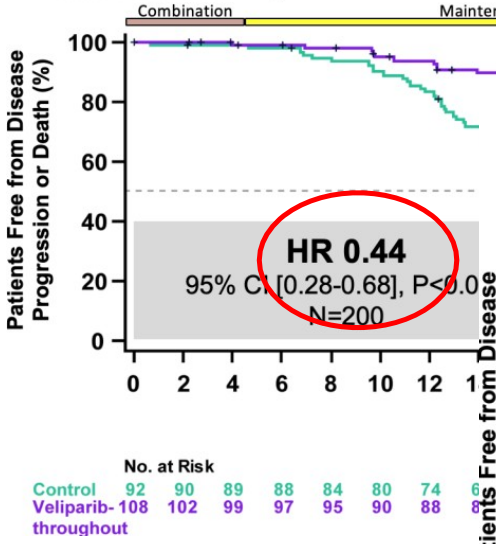
Median duration of follow-up was 28 months at the time of database lock.

VELIA subsets by *BRCA*^{mut} and HRD

PFS by Investigator Assessment
***BRCA*m Population**

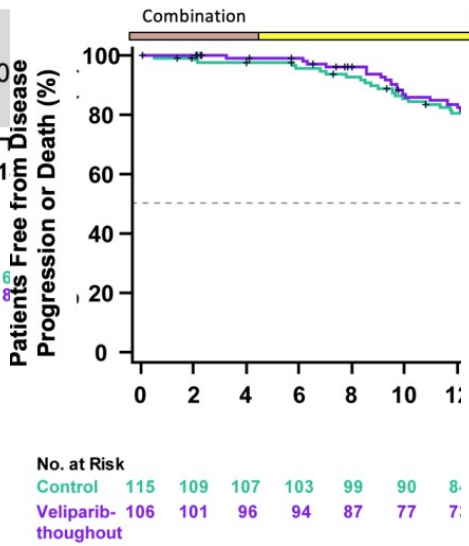
*BRCA*m	Veliparib-throughout	Control
Events (%)	34/108 (31.5)	51/92 (55.4)
Median PFS, months (95% CI)	**34.7** (31.8, -)	**22.0** (17.8, 29.1)



PFS: *BRCA*wt/HRD Population

BRCA	*BRCA*wt/HRD	WT

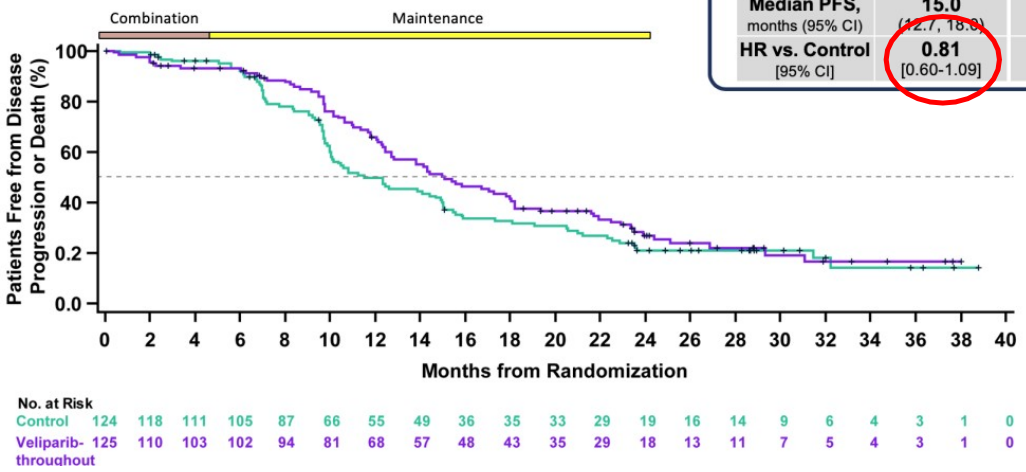
*BRCA*wt/HRD	Veliparib-throughout	Control
Median PFS, months (95% CI)	**22.9** (18.2, 37.5)	**19.8** (16.7, 22.2)
HR vs. Control [95% CI]	**0.74** [0.52-1.06]	–



PFS: Non-HRD Population

BRCA	*BRCA*wt/HRD	WT

Non-HRD	Veliparib-throughout	Control
Median PFS, months (95% CI)	**15.0** (12.7, 18.6)	**11.5** (10.1, 14.9)
HR vs. Control [95% CI]	**0.81** [0.60-1.09]	–



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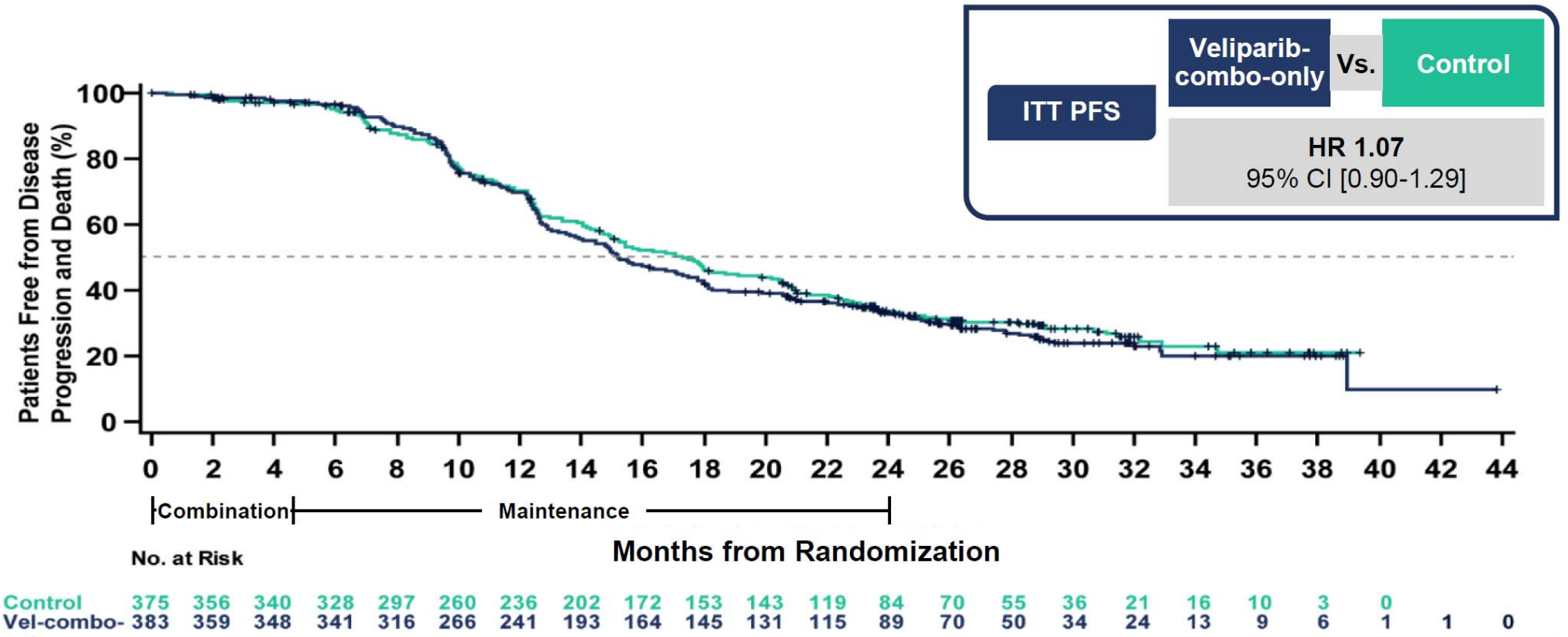
PFS for Veliparib-combo-only vs. Control



Across *BRCA*m, HRD, and ITT, the veliparib-combo-only arm and the control arm demonstrated similar PFS

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Summary of Adverse Events

	Veliparib-throughout N = 377	Veliparib-combo-only N = 376	Control N = 371
Any Treatment-Emergent AE	377 (100)	376 (100)	371 (100)
Grade 3 or 4 AEs	332 (88)	329 (88)	285 (77)
Serious AEs	141 (37)	129 (34)	141 (38)
AEs Leading to Discontinuation of Veliparib/Placebo	97 (26)	49 (13)	43 (12)
Related to Disease Progression	6 (2)	11 (3)	18 (5)
Not Related to Disease Progression (Combination: Cycles 1-6)	40 (11)	29 (8)	22 (6)
Not Related to Disease Progression (Maintenance: Cycles 7-36) *	53 (14)	9 (3)	3 (1)
AEs Leading to Death	8 (2)	7 (2)	6 (2)

* Most discontinuations of veliparib occurred during Cycles 7-8

What is the position of PARPi in first-line treatment of ovarian cancer from October 2019?

- Clear evidence of benefit of PARP inhibitor maintenance in first line therapy in intention to treat populations
  - Olaparib
  - Niraparib
  - Veliparib

- Greatest effect seen in women with *BRCA*^{mut}

Olaparib (SOLO1)	HR 0.30
Olaparib (PAOLA-1)	HR 0.31
Niraparib(PRIMA)	HR 0.40
Veliparib (VELIA)	HR 0.44

- **Diminishing effect from *BRCA*^{mut} > *BRCA*^{wt}/HRD^{+} > HRD^{-}**

1. Is the benefit of adding a PARPi as maintenance therapy to first-line treatment clinically meaningful enough to justify its use as a new standard of care?

Yes, but while the benefit is clinically meaningful in the overall population, we should consider PFS outcomes according to the Biomarker status in the selection of optimal therapy:

Companion Diagnostic Test will be needed.

1. **Is the benefit of adding a PARPi as maintenance therapy to first-line treatment clinically meaningful enough to justify its use as a new standard of care?**

- **HRD BRCA mut:** The greatest magnitude of benefit(from O plus BVZ and N)confirming PARPi as first-line.
  - **The key question: What is the contribution of BVZ to the benefit observed in PAOLA since it was consistent with the benefit observed in the SOLO-1 with O monotherapy?**
    - PAOLA's weakness: Lack of an O monotherapy arm.
    - PFS's benefit: Addition of O or a synergistic effect of the combination? The latter seems not be supported by previous Phase-2 studies[1].
- **HRD BRCA wt:**
  - The results in HRD without a BRCA mutation **identify a new population which significantly benefits from treatment with O plus BEV and N.**

1.Liu J.F et al. Lancet Oncol 2014;15:1207-14; Liu J F et al. *Annals of Oncology*. 2019;30:551–557; Mirza MR et al; Lancet Oncol. 2019 Aug 29.

3. Can we hypothesize which sequence of therapies is the best for our patients?

- **In the HRD population (BRCA mut and BRCA wt).** There is a robust reduction of risk of progression with O plus BVZ and N that **strongly justify moving PARPi to first line**.
  - The only opportunity to "cure" our AOC pts is with the first-line therapy.
  - Previous data suggest that prior PARPi treatment does not compromise subsequent therapy benefits[1,2].
  - **COST:** How much would be the cost of the combination compared to N or O alone? **Should this matter in the clinical decision-making process?**
    - BVZ use at relapse is only approved for those pts who have not previously received BVZ. The benefit at first-line and at relapse should be taken into account.

1.Coleman RL et al; Journal of Clin Oncol 37, 15_suppl (May 20, 2019) 5522-5522; 2.Oaknin A et al. #995PD Presented at ESMO 2019.

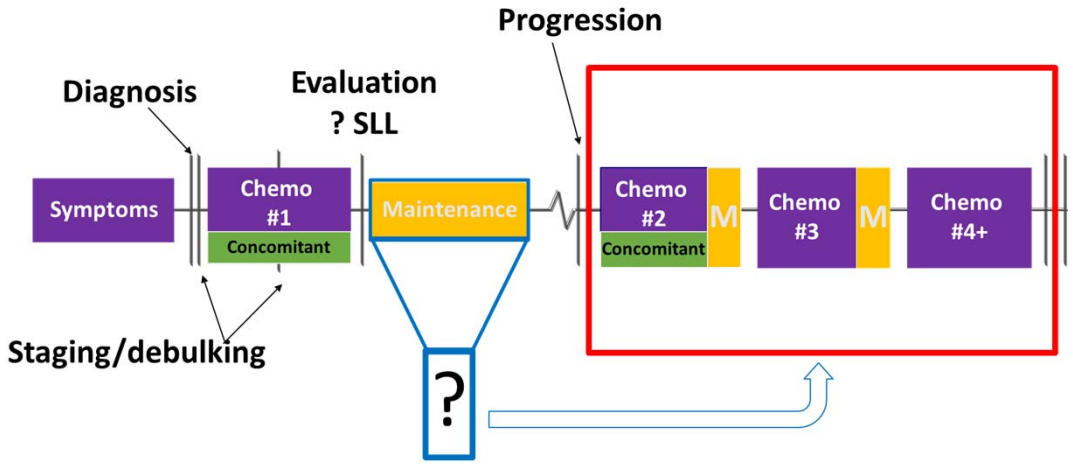
4. Are there any toxicity concerns about the use of O plus BVZ or N in first-line therapy?

- Globally, the reported toxicity profile was as expected: Class specific AEs.
- **In PAOLA-1, the AEs leading to treatment discontinuation was 20%: this is the highest figure reported across PARPi trials[1].**
- The incidence of MDS/AML/AA reported was aligned with previous trials: 6 cases (1.1 %) in PAOLA-1 and 1 case in PRIMA.
- **There was no impact in quality of life with Niraparib or Olaparib plus BVZ.**

[1]Pujade-Lauraine E. et al Lancet Oncol. 2017 Sep;18(9):1274-1284; Mirza MR. et al. *N Engl J Med.* 2016;375(22):2154-2164; Coleman RL. et al, *The Lancet*, Vol.390, Nº10106, p1949-1961; MooreK. et al. *N Engl J Med* 2018;379:2495-505

What next?

- Moving PARP inhibitors to first-line for all or subset BRCA/ HRD +ve?
- How will first-line PARP inhibitors impact on use in recurrent disease?
- Can patients benefit from a rechallenge with same or different PARP inhibitor?

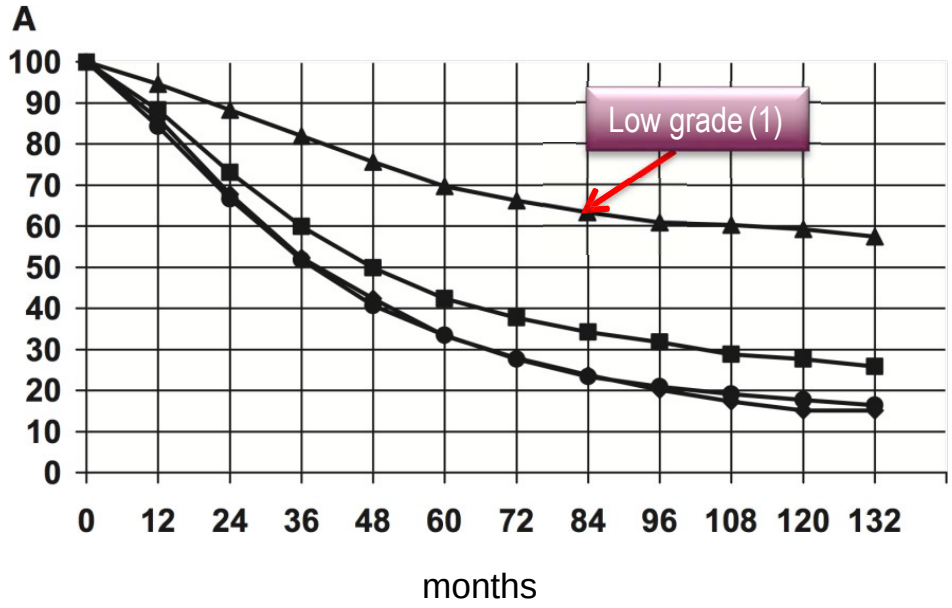


Last year front-line use of a PARP inhibitor in BRCA mutated ovarian cancer heralded a change. In 2019 new front-line data introduces a paradigm shift in PARP inhibitor use with a major improvement in progression-free survival of ovarian cancer

Low Grade Serous Ovarian Cancer

LOW GRADE SEROUS OVARIAN CANCER

- 10% serous ovarian cancers
- May arise *de novo* or following diagnosis of serous borderline tumour
- Characteristics in comparison to High grade OC
  - Younger age at diagnosis
  - Chemoresistance
  - Longer survival
  - Aberrations within the MAP kinase signalling pathway



Median survival: SEER data

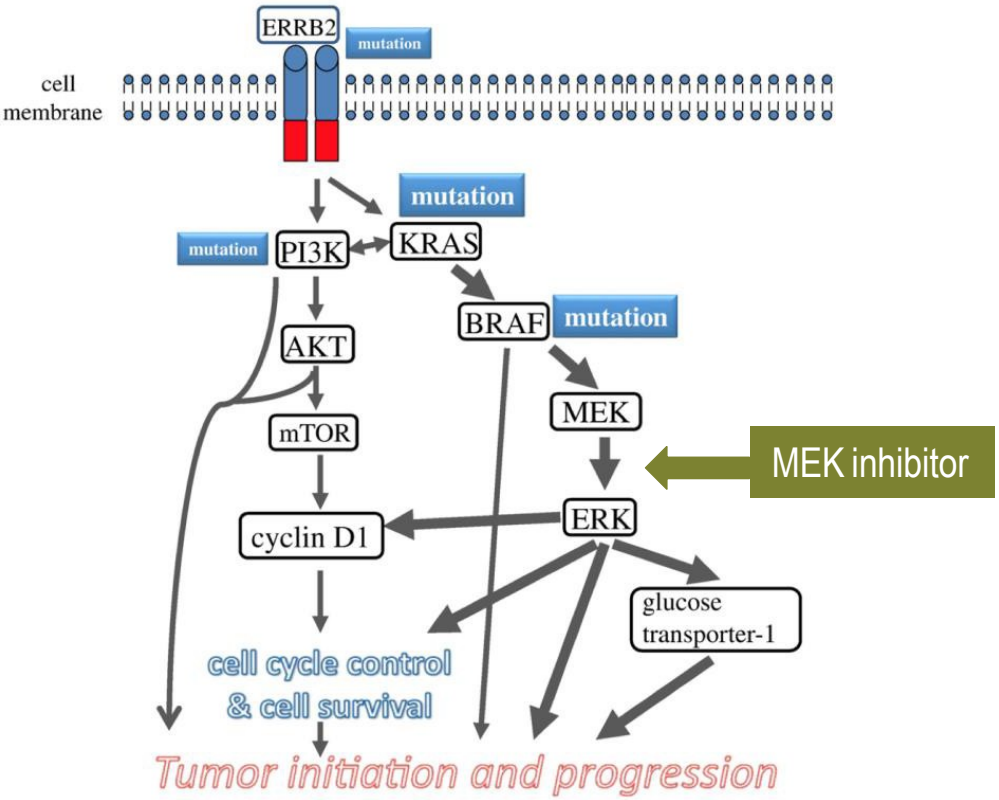
From Plaxe et al Am J Obstet & Gynecol 2008

RECURRENT LOW GRADE SEROUS OVARIAN CANCER

Responds poorly to chemotherapy

	ORR	SD	Number
Carboplatin	3	15	25
PLD	0	11	21
Paclitaxel	1	11	18
Carbo/Paclitaxel	0	7	10
Topotecan	0	5	10
Carbo/ Gemcitabine	0	1	1
Percentage	5%	59%	N=85

Gershenson et al Gyne Oncol 2009



Kurman & Shih 2011

STANDARD THERAPY FOR LOW GRADE SEROUS CANCER

Gershenson et. al…

Control arm

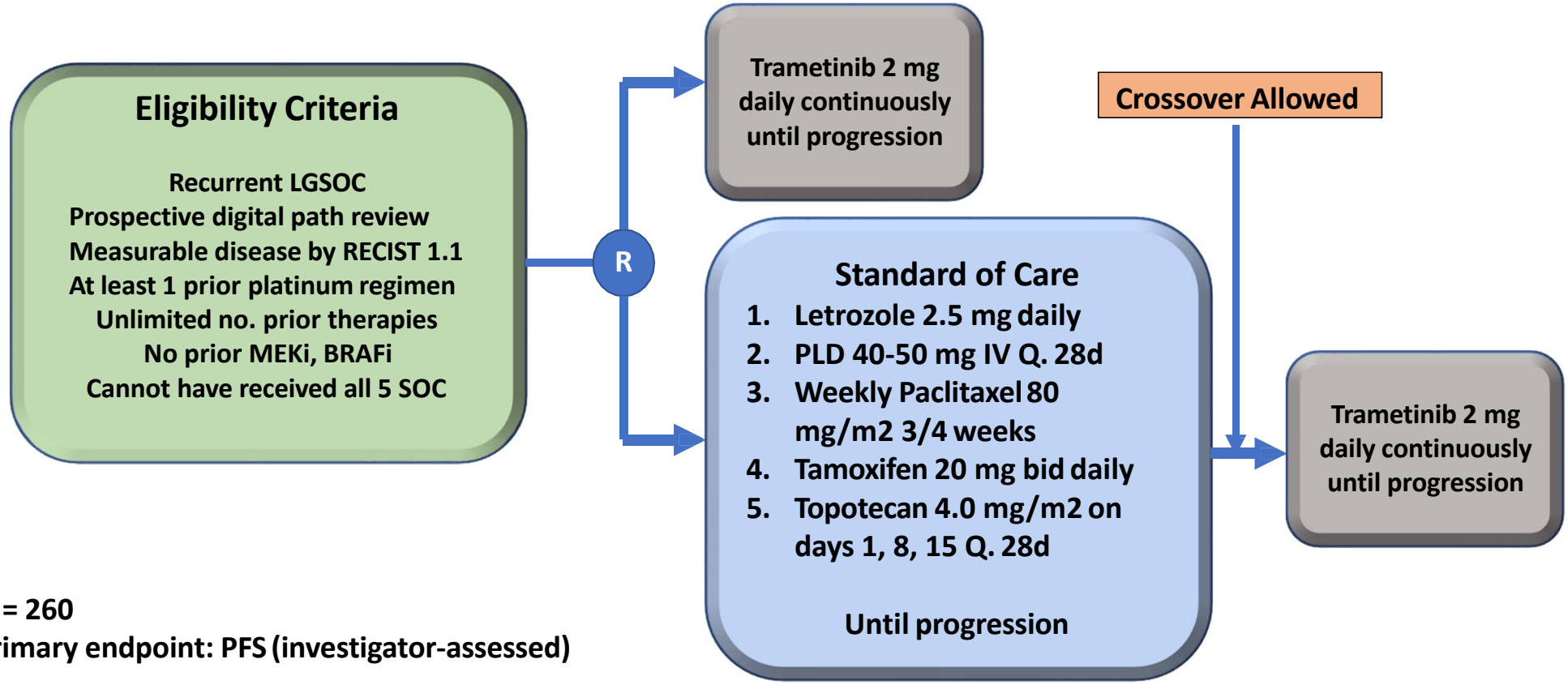
Drug	Response Rate %
Letrozole	13.6
Tamoxifen	0
Paclitaxel	9.1
PLD	2.5
Topotecan	0

- Low response rate to chemotherapy
- Highest response rate in patients on letrozole
- Stable disease rate (8 weeks) 70.8 %
- Med duration of Response 5.9 (2.8-12.2) months
- Median PFS 7.2 (5.6-9.9) months
- 48% ≥ 3 prior lines of treatment

Despite the poor response rate, progression relatively slow

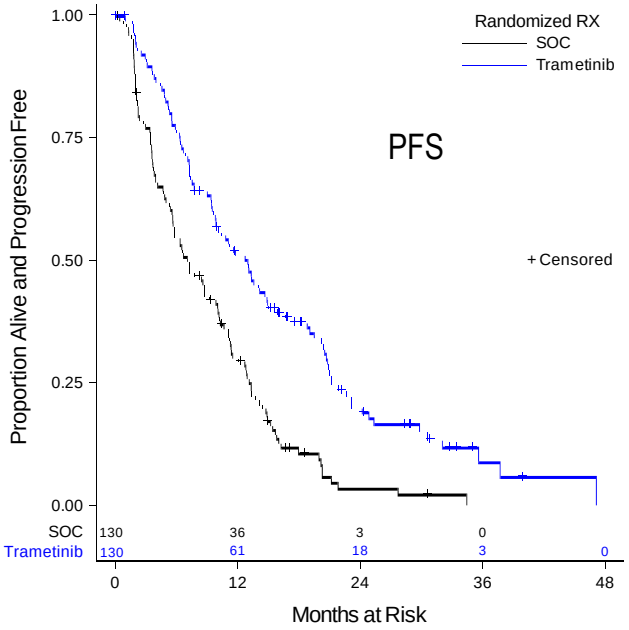
This disease has a long natural history - Where in the pathway of disease were these patients treated?

Study Design

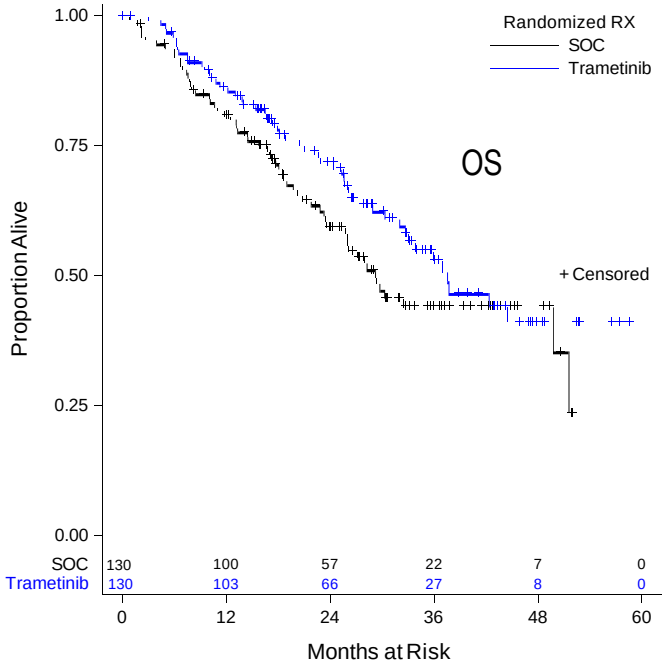


N = 260
Primary endpoint: PFS (investigator-assessed)

TREMETANIB IN LGSOC



	Trametinib	Control (SOC)
Median (Months) 95% CI	13.0 (9.9 – 15.0)	7.2 (5.6 - 9.9)
Hazard Ratio 95% CI	0.48 (0.36 – 0.64)	
One-sided p-value	<0.0001	



	Trametinib	Control (SOC)
Median (Months) 95% CI	37.0 (30.3 to NE)	29.2 (23.5 to 51.6)
Hazard Ratio 95% CI	0.75 (0.51 – 0.1.11)	
One-sided p-value	0.054	

- Significant benefit in PFS
- Borderline OS benefit but cross over in 68%
- In cross-over patients Trametinib is active median PFS10.8 months
- Skin rash; Fatigue; diarrhoea
- 35% stopped due to AE
- Cardiac function; pneumonitis ?

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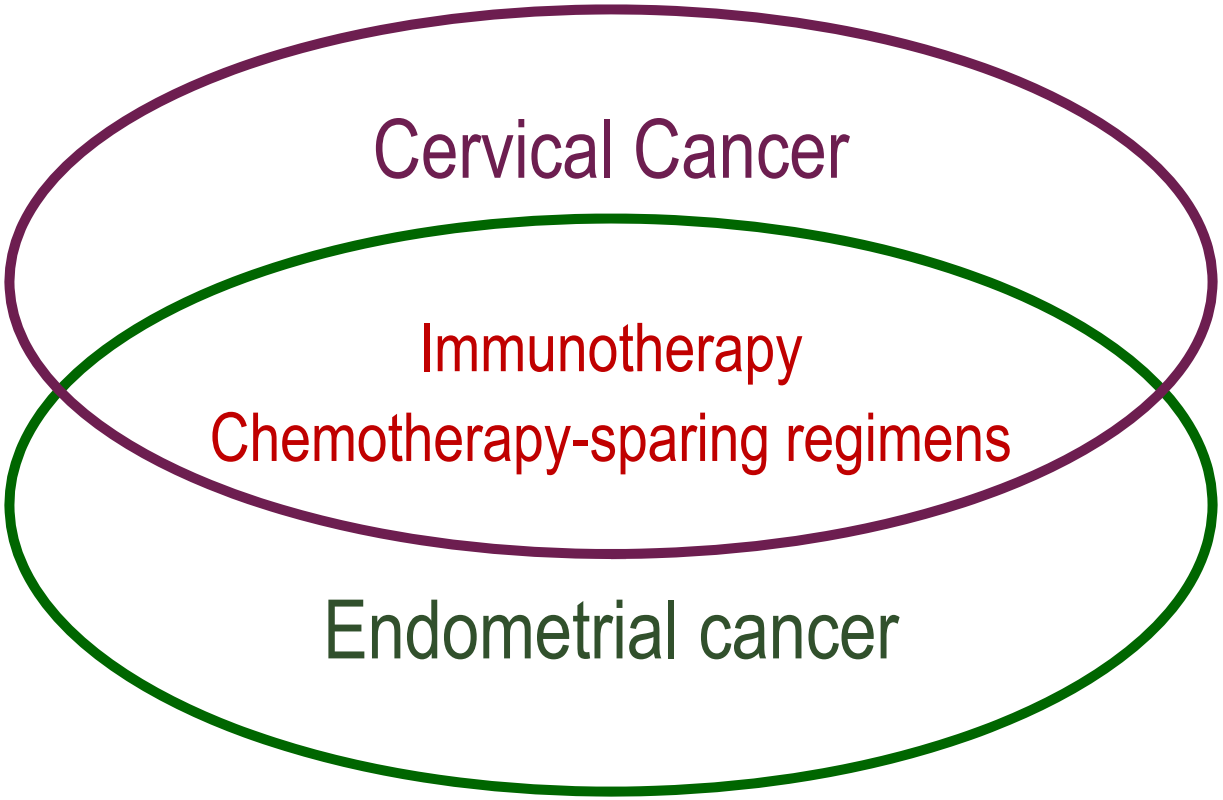
A NEW TREATMENT FOR LGSOC?

- Recurrent low grade serous ovarian cancer responds very poorly to chemotherapy
- It has a long natural history, so evaluation of disease stabilisation with interventions can be difficult
- Trametinib led to a significant improvement in PFS
- Side effects were mostly low grade but 35 % discontinued due to AE/complication
- How would trametinib have compared to a letrozole control arm- the drug with the highest RR?

- This is the first positive randomised trial in LGCS and demonstrates that trametinib is a new treatment for LGSOC
  - Need to identify which patients benefit from MEK inhibitors
  - When trametinib should be used
  - How to manage common toxicities – rash, fatigue, diarrhea, and nausea

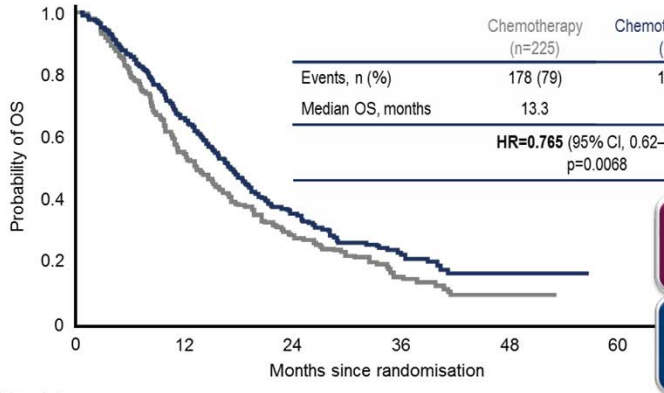
Updates on uterine and cervical cancer



Recurrent/Persistent and Metastatic cervical cancer: A HIGH UNMET CLINICAL NEED!

- Metastatic and recurrent CC has a median survival of 17 months with standard-of-care frontline platinum/taxane-based chemotherapy and bevacizumab
- No standard second line available: very limited effective options including topotecan, gemcitabine, vinorelbine, pemetrexed

GOG-0240: final OS analysis
Addition of Bevacizumab to chemotherapy



	Chemotherapy (n=225)	Chemotherapy + Bev (n=227)
Events, n (%)	178 (79)	170 (75)
Median OS, months	13.3	16.8

HR=0.765 (95% CI, 0.62–0.95)
p=0.0068

Regulatory approvals
FDA (August 2014)
EMA (April 2015)

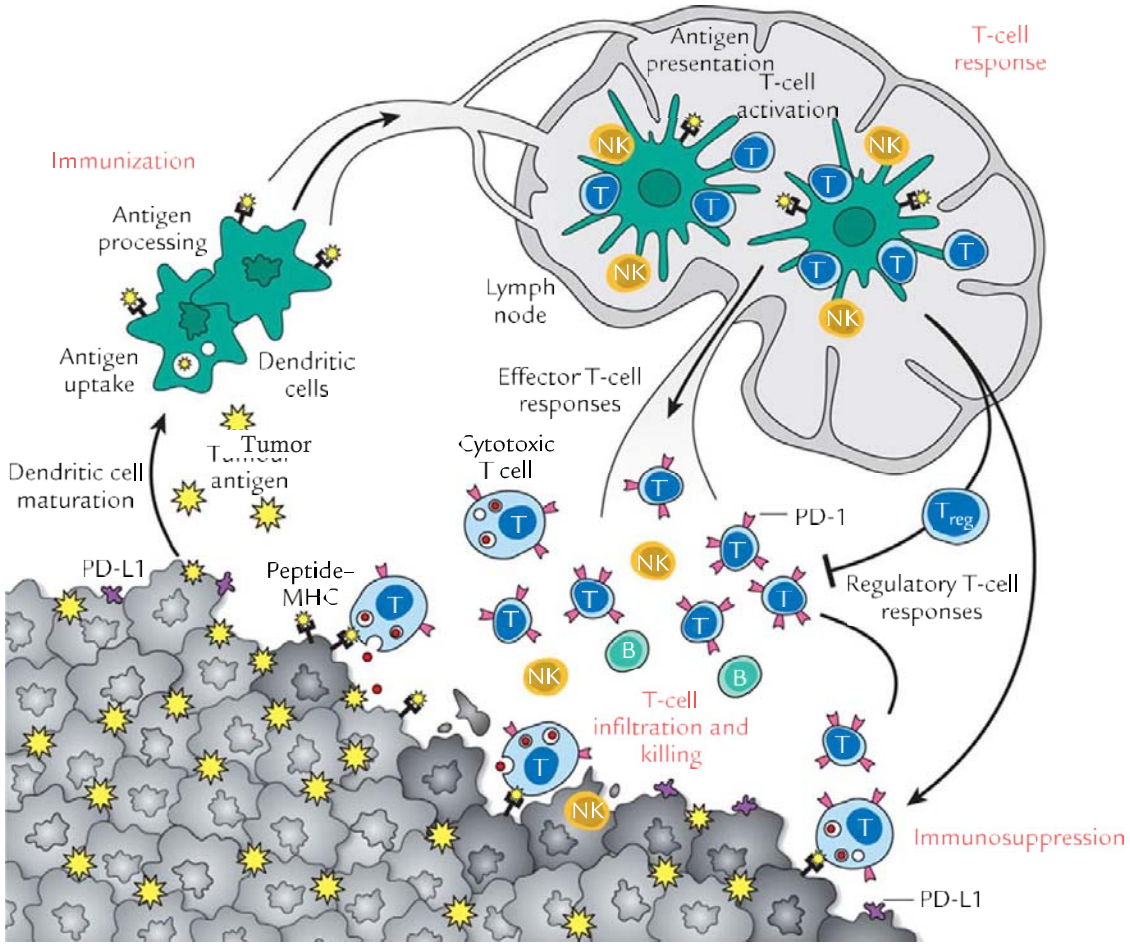
Treatment guidelines
Category 1 recommendation in NCCN 2015 guidelines[2]

CI, confidence interval; HR, hazard ratio; OS, overall survival

Lancet. 2017 Oct 7;390(10103):1654-1663.

LBA62

Is Immunotherapy a rational option in cervical cancer ?

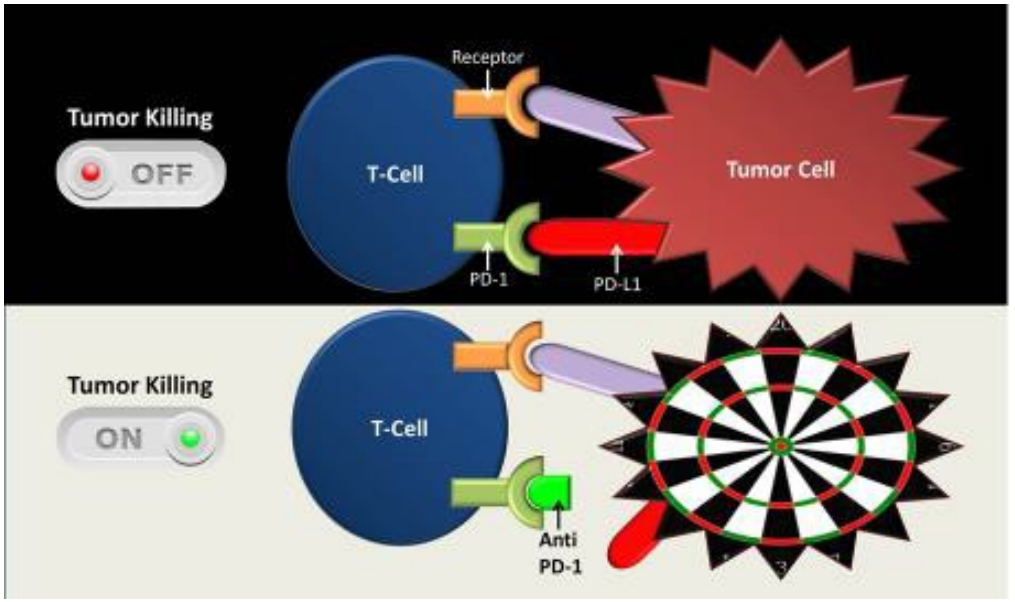


Eskander RN, et al. *Clin Ther*. 2015;37(1):20-38.

LBA62

Rationale: Anti-programmed death (PD)-1 therapy for cervical cancer

- Human papillomavirus (HPV) infection is the cause of more than 90% of cervical cancers
- HPV+ Tumor Microenvironment is enriched for PD-1+ CD8+ T Cells
- PD-L1 is significantly up-regulated in cervical cancer and detectable by immunohistochemistry in tumor cells:
  - **Squamous Cervical cancer between 54%-80**% according to different series
  - **Adenocarcinoma: 14%**



Liu C, et al. *Mol Med Rep* 2017;15:1063–1070; Mezache L, et al. *Mod Pathol* 2015;28:1594–1602; Heeren AM et al. *Mod Pathol.* 2016;29:753–763.

LBA62

Checkpoint Inhibitors in Cervical Cancer

	Lheureux et al.[1]	KEYNOTE-028[2]	KEYNOTE-158[3] (Cohort E)[b]	Checkmate 358[4]
Phase(s)	2	1b	2	1/2
Population	Metastatic or recurrent cervical cancer with progression after prior platinum chemotherapy	PD-L1+ advanced cervical squamous cell cancers after failure of prior systemic therapy	Advanced cervical cancer with progression on or intolerance to ≥1 line of prior therapy, PD-L1+ (CPS ≥1)	HPV-associated tumors, including recurrent or metastatic cervical, vaginal, vulvar cancers
Patients, n	42[a]	24	77[d]	24
Treatment	Ipilimumab	Pembrolizumab	Pembrolizumab	Nivolumab
ORR, %	8.8[c]	12.5[c]	14.3	ITT: 20.8[c] Cervical cancer pts: 26.3%
DCR, %	32.3	25.0	—	70.8
mDOR	—	19.3 wk	NR (range: 4.1–18.6+ mo)	NR
PFS	mPFS: 2.5 mo	6-mo PFS: 13.0%	—	mPFS: 5.5 mo
OS	—	6-mo OS: 66.7%	—	NR
Safety	Manageable toxicities	≥Gr 3 TRAEs: 20.8%	Serious AEs: 39%	Gr 3/4 TRAEs: 12.5%
Follow-up	—	48.9 wk	11.7 mo	31 wk

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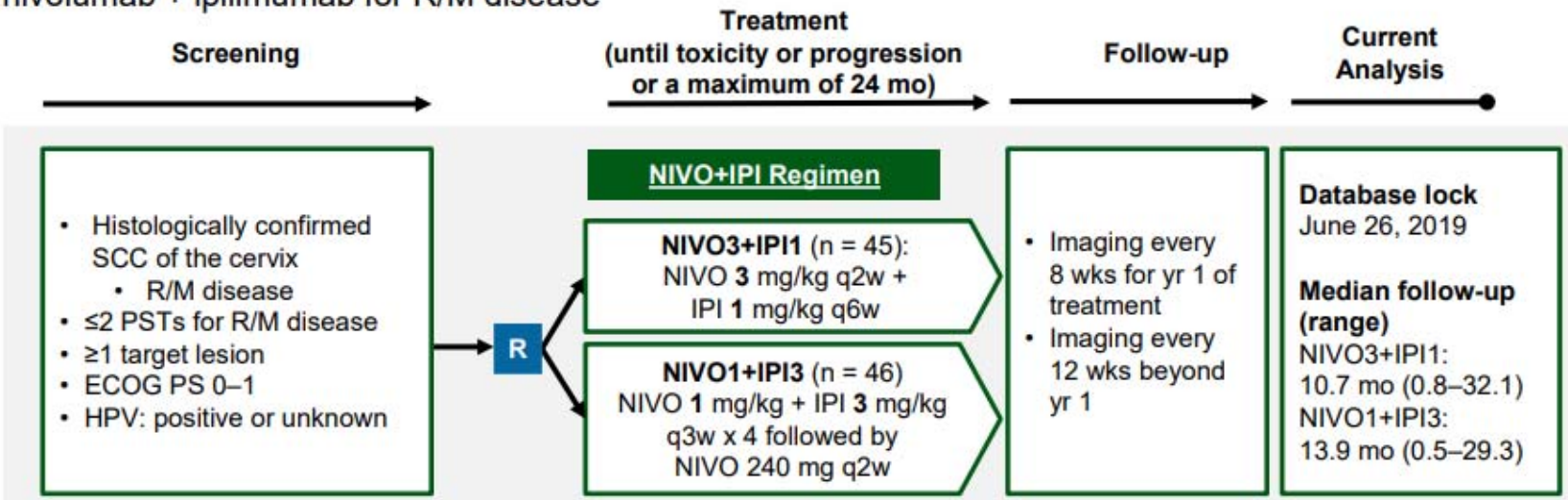
1. Lheureux S, et al. Presented at ASCO Annual Meeting, 2015. Abstract 3061. **2.** Frenel JS, et al. Presented at ASCO Annual Meeting, 2016. Abstract 5515.
3.. J Clin Oncol. 2019 Jun 10;37(17):1470-1478 ; 4. Hollebecque A, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5504.

Study Design and Current Analysis

Randomized cervical cancer cohorts of CheckMate 358 (NCT02488759) testing 2 combination regimens of nivolumab + ipilimumab for R/M disease



- **Study start date:** October 2015
- **Estimated completion date:** December 2019
- **Primary endpoint:** Investigator-assessed ORR by RECIST 1.1
- **Secondary endpoints:** OS, PFS, duration of response

ECOG, Eastern Cooperative Oncology Group; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; PFS, progression-free survival; PS, performance status; PST, prior systemic therapy; q2w, every 2 weeks; q3w, every 3 weeks; RECIST, response evaluation criteria in solid tumors; SCC, squamous cell carcinoma.

LBA62

Randomized cervical cancer cohorts of CheckMate 358 (NCT02488759) testing 2 combination regimens of nivolumab + ipilimumab for R/M disease

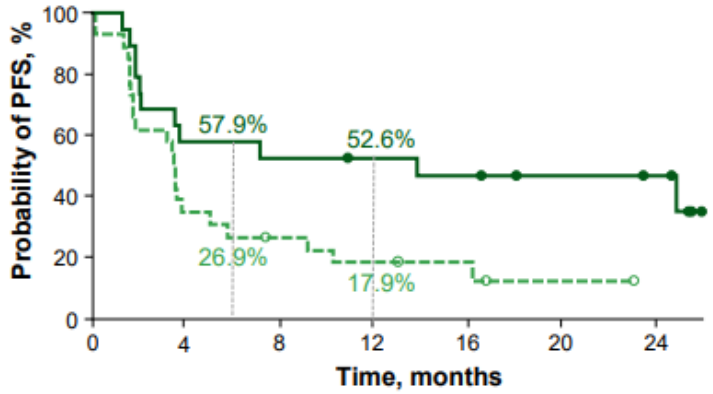
Primary endpoint: Tumor Response

	NIVO3+IPI1		NIVO1+IPI3	
Response in all treated patients	**No PST for R/M disease, n = 19**	**PST for R/M disease, n = 26**	**No PST for R/M disease, n = 24**	**PST for R/M disease, n = 22**
ORR, % (95% CI)	31.6 (12.6–56.6)	23.1 (9.0–43.6)	45.8 (25.6–67.2)	36.4 (17.2–59.3)
Clinical benefit rate,* % (95% CI)	63.2 (38.4–83.7)	53.8 (33.4–73.4)	70.8 (48.9–87.4)	72.7 (49.8–89.3)
Best overall response†				
Complete response	3 (15.8)	1 (3.8)	1 (4.2)	3 (13.6)
Partial response	3 (15.8)	5 (19.2)	10 (41.7)	5 (22.7)
Stable disease	6 (31.6)	8 (30.8)	6 (25.0)	8 (36.4)
Progressive disease	7 (36.8)	11 (42.3)	6 (25.0)	5 (22.7)
Duration of response, median, mo (95% CI)	NR (6.6–NR)	14.6 (7.5–NR)	NR (4.6–NR)	9.5 (1.9–NR)
ORR by tumor cell PD-L1 expression,‡				
PD-L1 ≥1%, # responders/# treated (%) [95% CI]	4/13 (30.8) [9.1–61.4]	4/10 (40.0) [12.2–73.8]	4/11 (36.4) [10.9–69.2]	2/12 (16.7) [2.1–48.4]
PD-L1 <1%, # responders/# treated (%) [95% CI]	1/3 (33.3) [0.8–90.6]	1/11 (9.1) [0.2–41.3]	0/4 (0) [0.0–60.2]	4/7 (57.1) [18.4–90.1]

* Proportion of patients with a complete response, a partial response, or stable disease; † Responses could not be determined in 1 patient with PST in NIVO3+IPI1 and in 1 patient each with and without PST in NIVO1+IPI3. ‡ Tumor cell PD-L1 expression was defined as the percentage of tumor cells exhibiting plasma membrane staining at any intensity.
CI, confidence interval; NR, not reached; PST, prior systemic therapy.

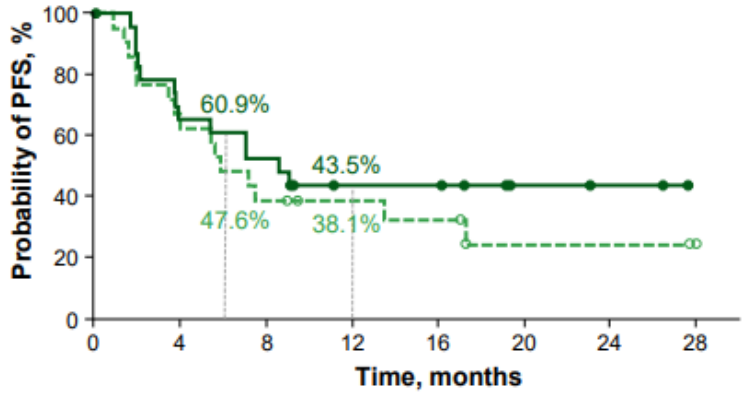
Progression-free Survival

NIVO3+IPI1	
Median PFS, mo (95% CI)	
No PST for R/M disease	13.8 (2.1–NR)
PST for R/M disease	3.6 (1.9–5.1)



No. at risk							
No PST	19	11	10	9	8	6	5
PST	26	9	6	4	3	1	0

NIVO1+IPI3	
Median PFS, mo (95% CI)	
No PST for R/M disease	8.5 (3.7–NR)
PST for R/M disease	5.8 (3.5–17.2)

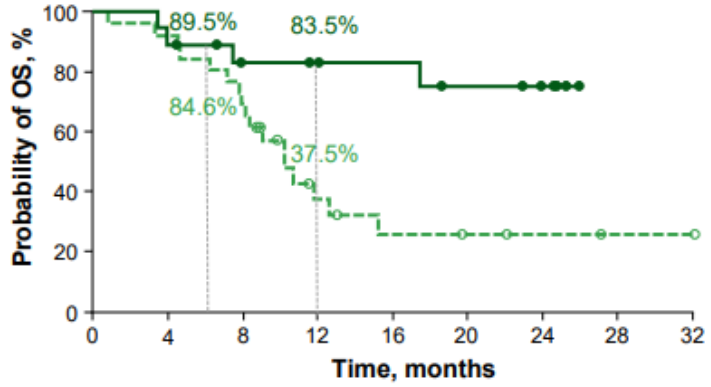


No. at risk								
No PST	24	15	12	7	7	3	2	0
PST	22	14	8	6	5	2	2	0

Owing to the high percentage of censored responses, median and rate estimators may be misleading. PST, prior systemic therapy.

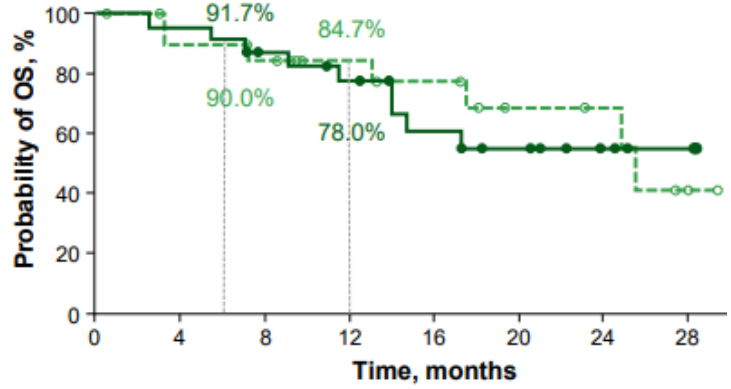
Overall Survival

NIVO3+IPI1	
Median OS, mo (95% CI)	
No PST for R/M disease	NR (17.4–NR)
PST for R/M disease	10.3 (7.9–15.2)



No. at risk									
No PST	19	17	13	12	11	9	6	0	0
PST	26	24	18	7	4	3	2	1	1

NIVO1+IPI3	
Median OS, mo (95% CI)	
No PST for R/M disease	NR (13.9–NR)
PST for R/M disease	25.4 (17.5–NR)



No. at risk								
No PST	24	23	19	16	11	8	4	2
PST	22	18	16	12	10	6	5	1

Owing to the high percentage of censored responses, median and rate estimators may be misleading. NR, not reached; PST, prior systemic therapy.

LBA62

Randomized cervical cancer cohorts of CheckMate 358 (NCT02488759) testing 2 combination regimens of nivolumab + ipilimumab for R/M disease

Primary endpoint: Tumor Response

Response in all treated patients	31/91	34%
No PST	17/43	39%
PST	14/48	29%

Regardless of tumor cell PD-L1 expression

LBA62

Summary of TRAEs

Event, n (%)	NIVO3+IPI1 (n = 45)		NIVO1+IPI3 (n = 46)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
TRAEs	36 (80.0)	13 (28.9)	38 (82.6)	17 (37.0)
Treatment-related SAEs	12 (26.7)	8 (17.8)	16 (34.8)	10 (21.7)
TRAEs leading to treatment discontinuation	6 (13.3)	2 (4.4)	9 (19.6)	6 (13.0)
Treatment-related SAEs leading to treatment discontinuation	2 (4.4)	1 (2.2)	5 (10.9)	5 (10.9)

- No new safety signals
- **Higher incidence of TRAEs and treatment-related SAEs leading to treatment discontinuation in NIVO1+IPI3 compared with NIVO3+IPI1**
- No treatment-related deaths

SAE, serious adverse event; TRAE, treatment-related adverse event.

LBA62

Take home message

The good:

- The combination of ipilimumab and nivolumab confirmed a strong activity in cervical cancer as seen in other tumor types
- High response rate and prolonged survival particularly in no PST population
- Activity seen regardless of tumor cell PD-L1 expression
- Chemotherapy-sparing regimen !!!

The bad:

- Toxicity is not trivial : probably NIVO3+IPI1 preferred

The Ugly:

No control arm !!!!!.

LBA62

Take home message

Where are we going from here?

- Do you think these data deserve further investigation in a phase 3?
- Are we ready to move to a chemotherapy sparing regimen in front line?
  - Randomized trial in front line against standard chemotherapy + bevacizumab ?
  - Randomized trial in second line vs investigator choice?

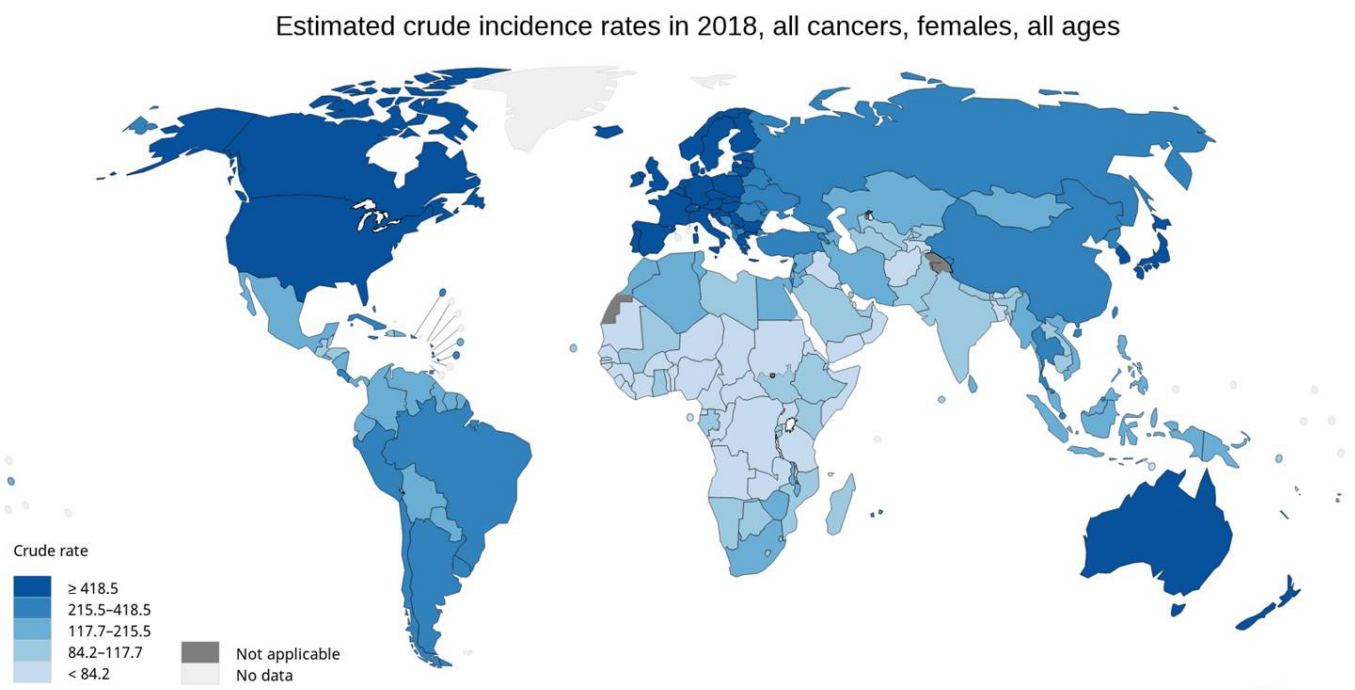
Will Immunotherapy change the Outlook for Patients with Cervical Cancer ?

Abs 9940: The context

Endometrial cancer

The most common gynecological cancer in the developed world

- In 2018: 382.000 new cases of endometrial cancer diagnosed and 90,000 endometrial cancer-related deaths globally.
- Limited effective treatment options in women with advanced or recurrent disease



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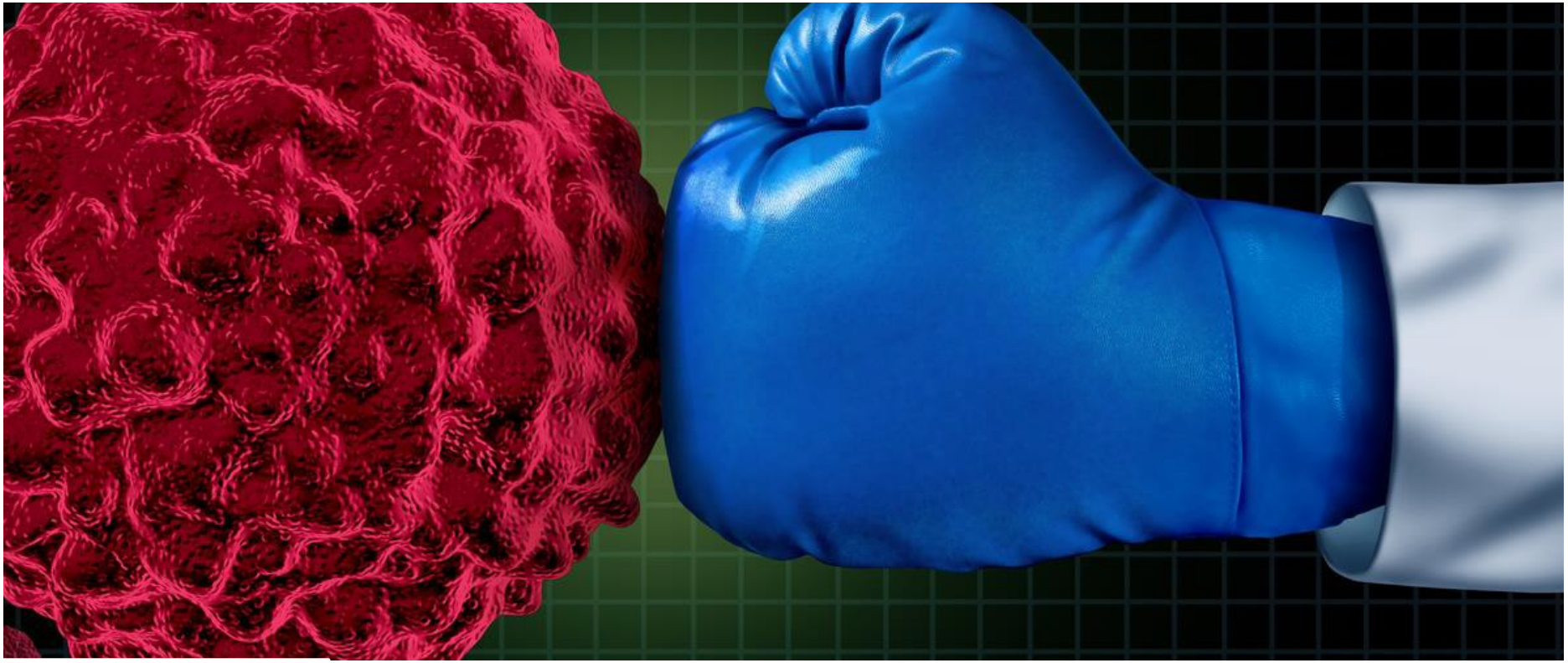
Can Immunotherapy improve the systemic treatment of advanced/recurrent endometrial cancer ?



Clinical Evidence for Immune Checkpoint Inhibition in Endometrial Cancer

Study	Drug	N	Patient Selection	ORR(%)
Le et al. (2017)	Pembro	15	MMRd EC	53%
Ott et al. (2017)	Pembro	24	PDL1+	13%
Fleming et al. (2017)	Atezo	15	All	13%
Hasegawa et al. (2018)	Nivo	23	All	23%
Oaknin (2019)	Dostarlimab	125	All	29.6% d-MMR 48.8% p-MMR 20,3%
Antill (2019)	Durvalumab	70	All	d-MMR 43% p-MMR 3%
Konstantinopoulos (2019)	Avelumab	31	All	d-MMR 27% p-MMR 6%

BA 2019

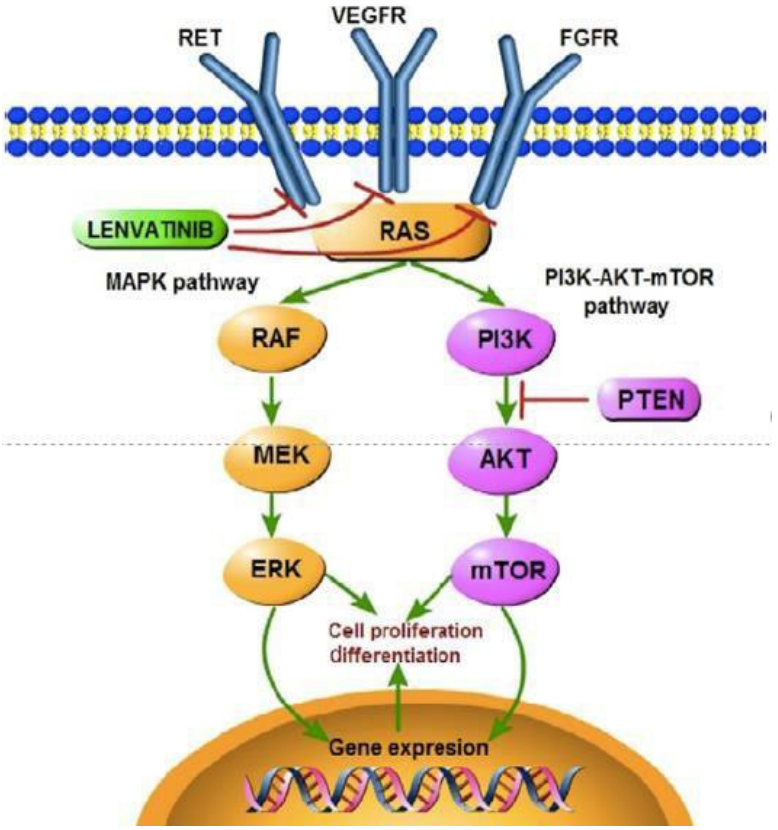
Le et al. NEJM. 2015; 372;2509-20; Ott et al. J Clin Oncol. 2017; 35(22):2535-41; Fleming et al. J Clin Oncol 35, 2017 (suppl; abstr 5585): Hasegawa et al. J Clin Oncol 36, 2018 (suppl: abstr 5594) , Le Science 2017; Oaknin, SGO 2019; Antill ASCO 2019 ; Konstantinopoulos ASCO 2019

Pembrolizumab was approved by the FDA for MSI-H or d-MMR endometrial cancer

- Only 25-30% of endometrial cancer have MSI-H or d-MMR
- What about the 70-75% with MSS or p-MMR ?

LENVATINIB

- Levatinib is an oral multikinase inhibitor that targets VEGFR1-3, FGFR1-4, PDGFRa and the oncogenes RET and KIT
- In a phase 2 study of lenvatinib monotherapy in pts with advanced, previously treated endometrial cancer, 19 (14%) of 133 pts had a objective response and median PFS= 5.4 months



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Study Design

Phase 2, Open-label, Single-arm Study (NCT02501096)

Key Eligibility Criteria

- Aged ≥18 years
- Pathologically confirmed and metastatic endometrial carcinoma
- ≤2 Prior systemic therapies
- Measurable disease by irRECIST
- ECOG performance status ≤1
- Life expectancy ≥12 weeks

Lenvatinib
20 mg/day (oral)
+
Pembrolizumab
200 mg Q3W (IV)

Primary End Point*

- ORR at Week 24

Key Secondary End Points*

- Overall ORR
- DOR
- PFS
- OS
- DCR
- CBR
- Safety and tolerability

Prespecified Exploratory End Points

- Independent imaging review per irRECIST and RECIST v1.1
- Antitumor activity by PD-L1 status

Post Hoc Exploratory Analysis

- Antitumor activity by tumor histology
- Antitumor activity by MSI status

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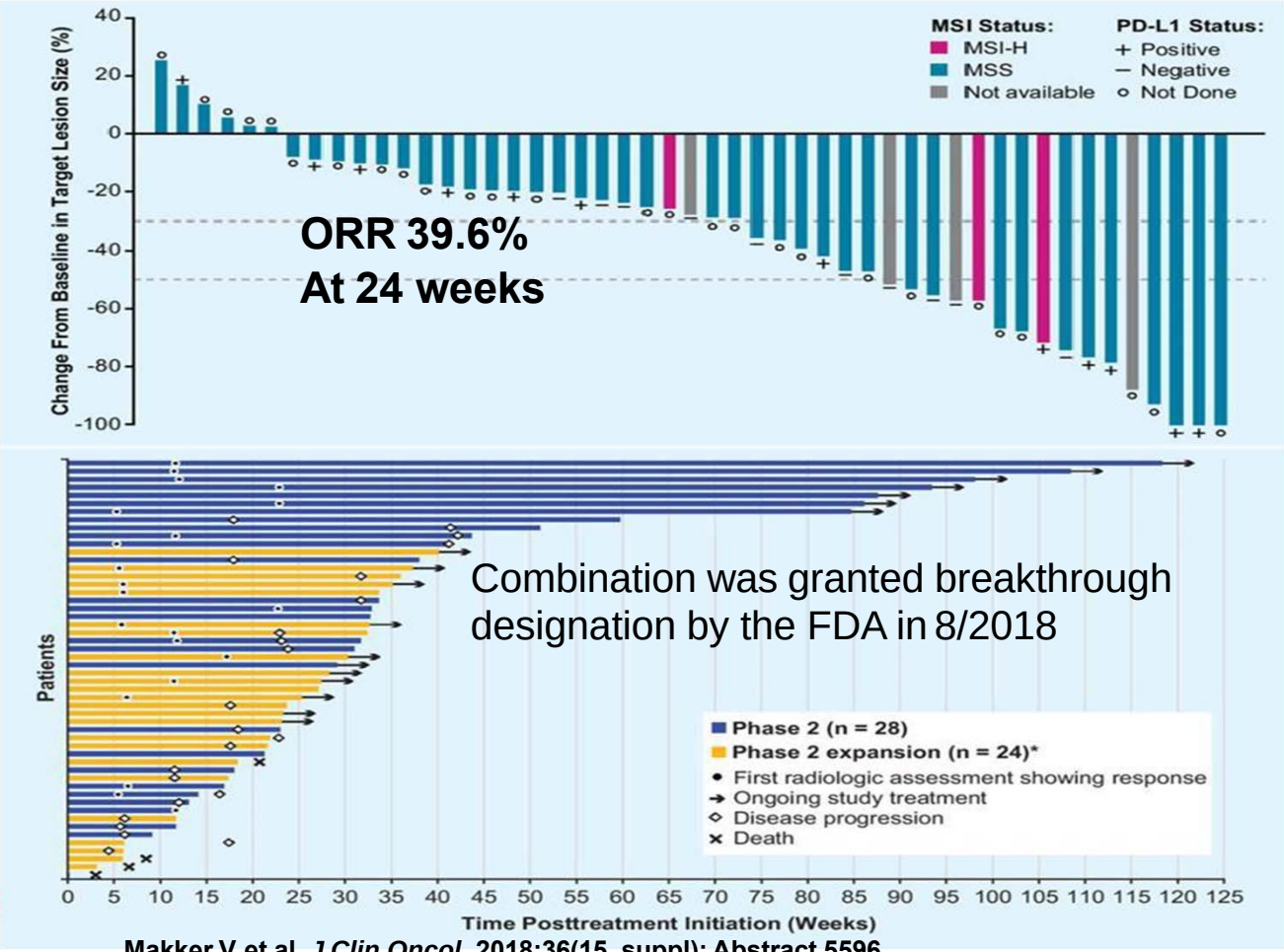
*Tumor responses for primary and secondary end points were assessed by the investigator per irRECIST.

Pembrolizumab and Lenvatinib in Patients with Endometrial Cancer: phase 2 trial

Too good to wait!!! Interim analysis published



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Makker V, et al. *J Clin Oncol.* 2018;36(15_suppl): Abstract 5596.

Lancet Oncol. 2019 Mar 25. pii: S1470-2045(19)30020-8. doi: 10.1016/S1470-2045(19)30020-8. [Epub ahead of print]


TOO GOOD
TO BE TRUE?

Abs 9940

Primary endpoint:

Tumor Response at 24 weeks (Investigator Assessment; irRECIST)

Response Category	Total (n = 108)	Not MSI-H or dMMR (n = 94)[a]	MSI-H / dMMR (n = 11)[a]
		Week 24	
Objective response rate (complete response + partial response), n (%)[b]	41 (38.0)	**34 (36.2)**	7 (63.6)
95% CI	28.8–47.8	26.5–46.7	30.8–89.1

[a]3 patients could not be assessed for MSI or MMR status; [b]ORR_{wk24} and the exact 95% CIs were calculated with the Clopper-Pearson method, as was 95% CIs for ORR; [c]Duration of response was estimated with the Kaplan-Meier method, and 95% CIs were calculated with a generalized Brookmeyer and Crowley method [d]Probabilities of patients achieving a duration of response ≥ 6 months or ≥ 12 months were calculated using the Kaplan-Meier product-limit method and Greenwood formula.

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Tumor Response at Data Cut-off (Independent Imaging Review; RECIST version 1.1)

Endpoint	Not MSI-H or dMMR (n = 94)
Objective response rate (complete response + partial response)	
ORR (95% CI)	38.3 % (29,49)
Complete response	10.6 %
Partial response	27.7 %
Duration of response	
Median in months (range)	NR (1.2+,33.1+)
% with duration ≥ 6 months	69%

Data reported In the label

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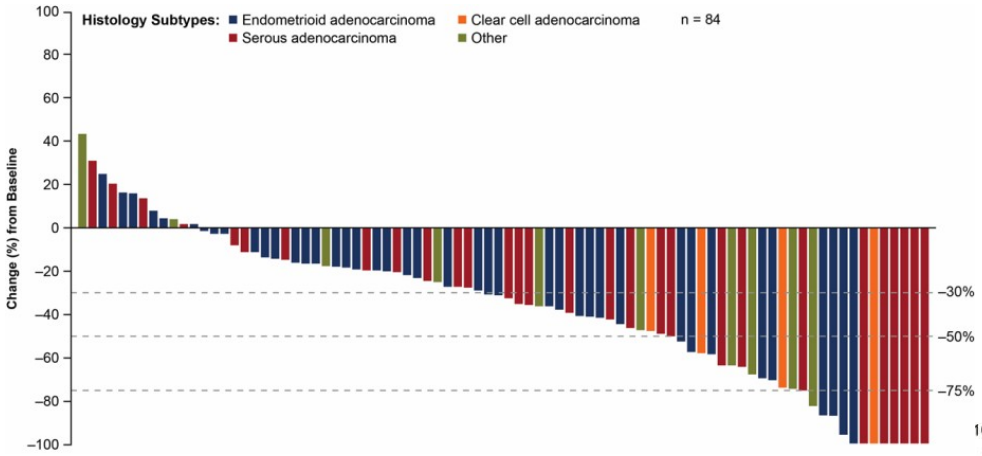
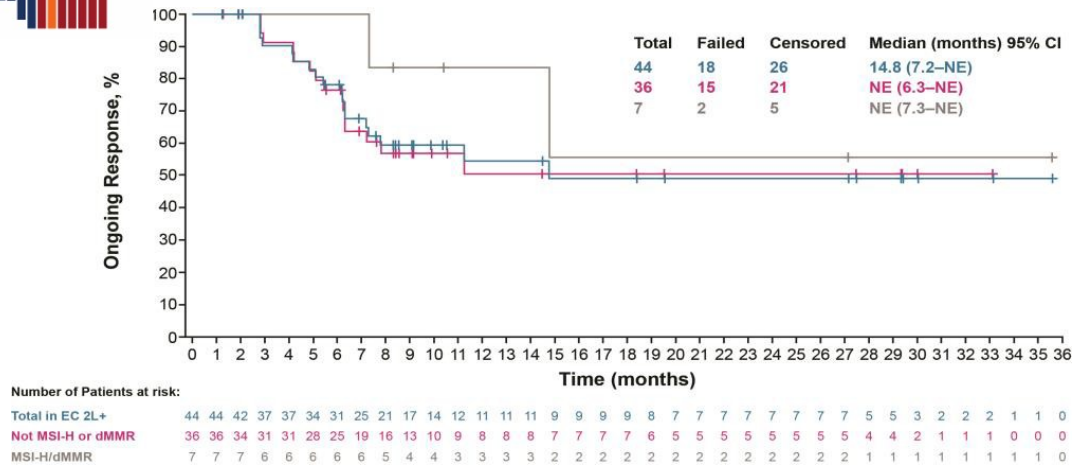
Percentage Change in Sum of Diameters of Target Lesions at Postbaseline Nadir by Histologic Subtype (Independent Imaging Review; RECIST version 1.1)



Kaplan-Meier Plot (Independent Imaging Review; RECIST version 1.1): Duration of Response



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n = the number of previously treated not-MSI-H or dMMR patients with both baseline and at least 1 postbaseline target lesion assessment.

TUESDAY, SEPTEMBER 17, 2019

FDA Approves KEYTRUDA® (pembrolizumab) plus LENVIMA® (lenvatinib) Combination Treatment for Patients with Certain Types of Endometrial Carcinoma

- *Disease Progression Following Prior Systemic Therapy*
- *Not candidate for curative surgery or radiation*
- *Not Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR)*
- *Under New FDA-Initiated Program, Project Orbis, Combination Treatment Is the First to Receive Simultaneous Review Decisions in the U.S., Australia and Health Canada*

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NOTHING COMES WITHOUT A PRICE

- Grade 3-4 AEs in 69,4% of pts (Hypertension 32.4%)
- Most frequent AEs of any grade : hypertension, diarrhea, decrease appetite, fatigue, hypothyroidism, nausea)
- Study drug discontinuation in 20% of pts, interruption in 72.2 %, reduction in 65%
- Drug-related deaths?

Abs 9940

Take home message

The good:

- The combination of pembrolizumab and lenvatinib led to unprecedented results in patients with advanced /recurrent previously treated endometrial cancer, MSS.
- For the first time, a chemotherapy-free regimen demonstrated a high rate of deep and durable responses in this clinical setting with a high unmet need.

The bad:

- Toxicity was as remarkable as activity.

The Ugly: No control arm!!!!!

Abs 9940

EXCITING RESULTS TODAY !!!

Different diseases but similar high unmet need

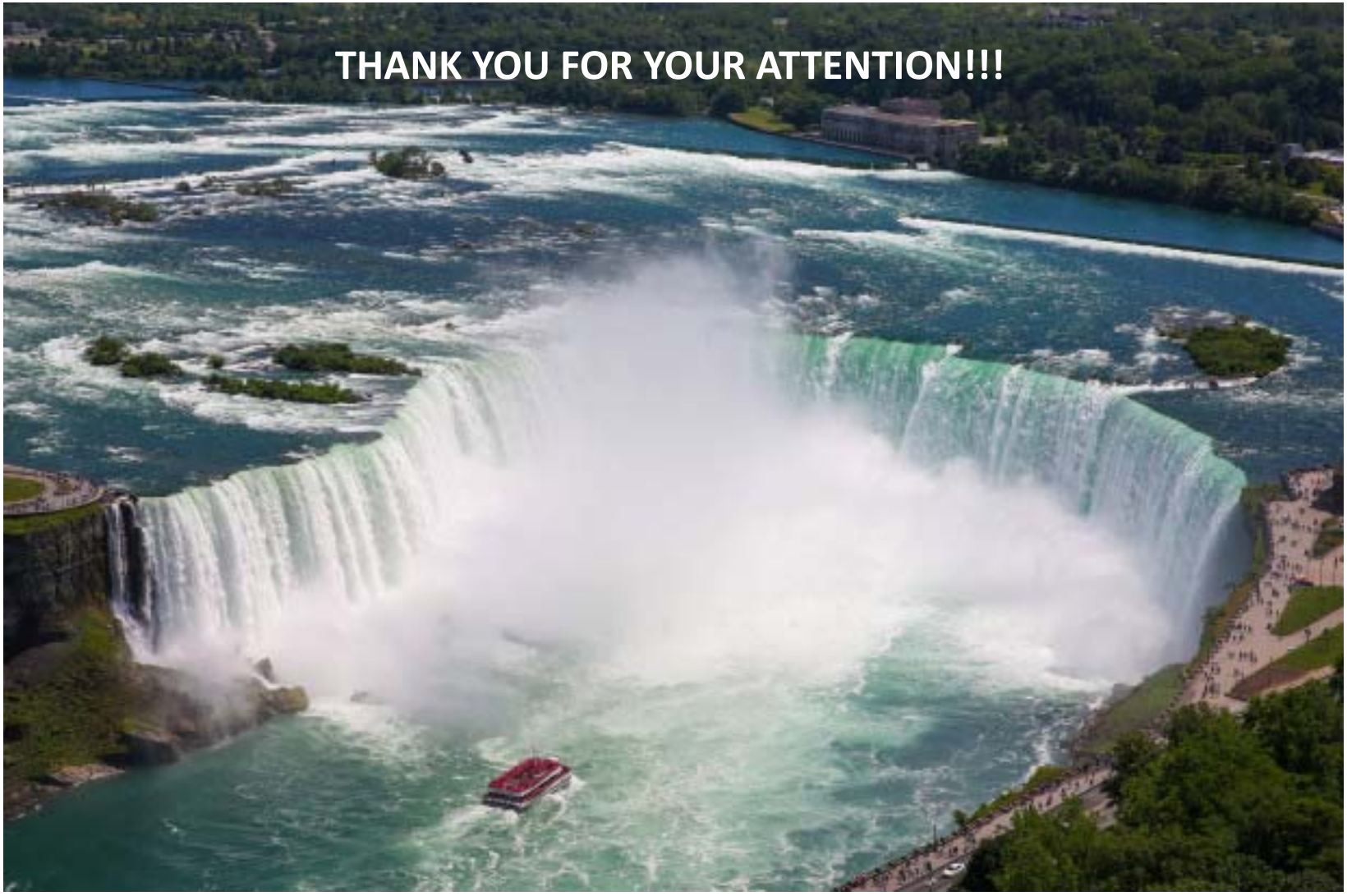
Different combinations, but both IO based

In both trials: High response rate, **deep and durable responses in unselected populations**

In both trials: significant toxicity

Both regimens need confirmation in a prospective clinical trial

Immunotherapy has changed the face of many cancers in the past decade, and finally, this is happening also for gynecological cancers


THANK YOU FOR YOUR ATTENTION!!!