I PARPi nella terapia del carcinoma ovarico

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Disclosures

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- Research funding from AstraZeneca, Roche, MSD

Ovarian cancer in Italy

- 5200 new cases in 2017
- 3130 deaths in 2014
- 80% stage III and IV

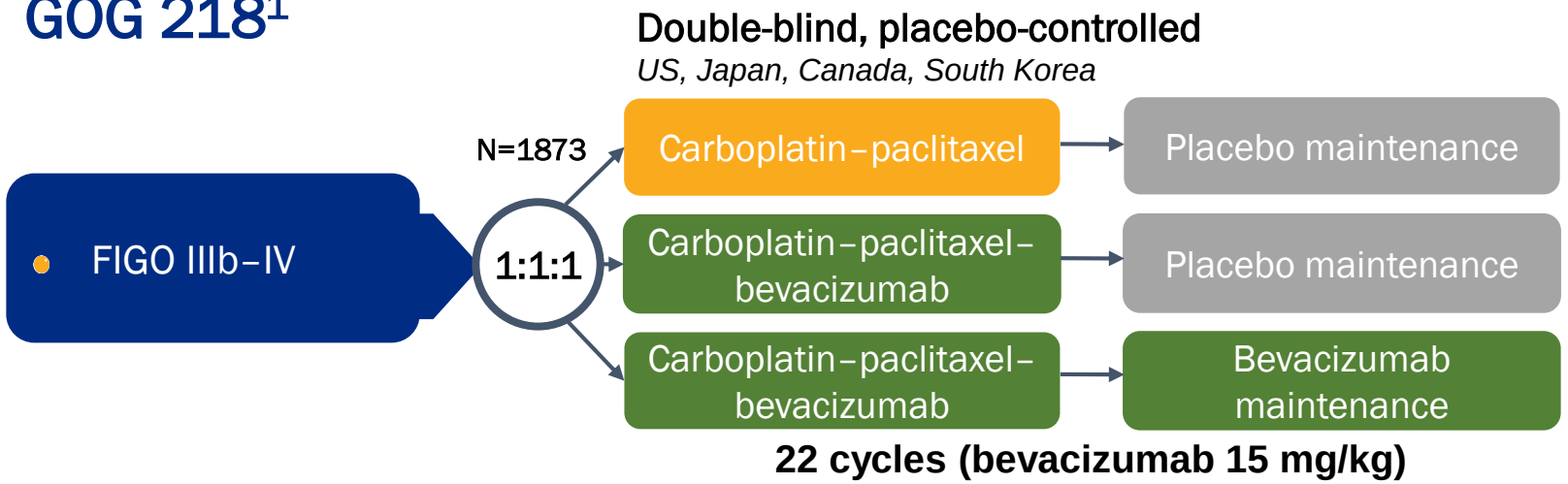
Standard of care: First-line setting

Current standard of care (Stage II-IV):

- 3-weekly carboplatin and paclitaxel[1]
  - Weekly paclitaxel not confirmed

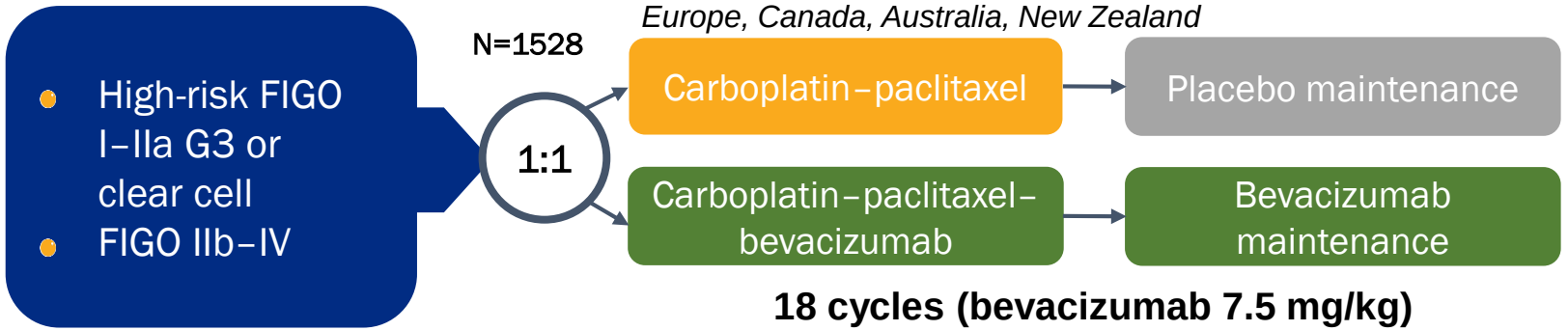
What is the current role of bevacizumab in first-line?

GOG 218[1]



mPFS (months)	mOS (months)
CP: 10.3	CP: 39.3
CPB: 11.2* P=0.16	CPB: 38.7† P=0.76
CPBB: 14.1‡ P<0.0001	CPBB: 39.7§ P=0.45

ICON7[2]

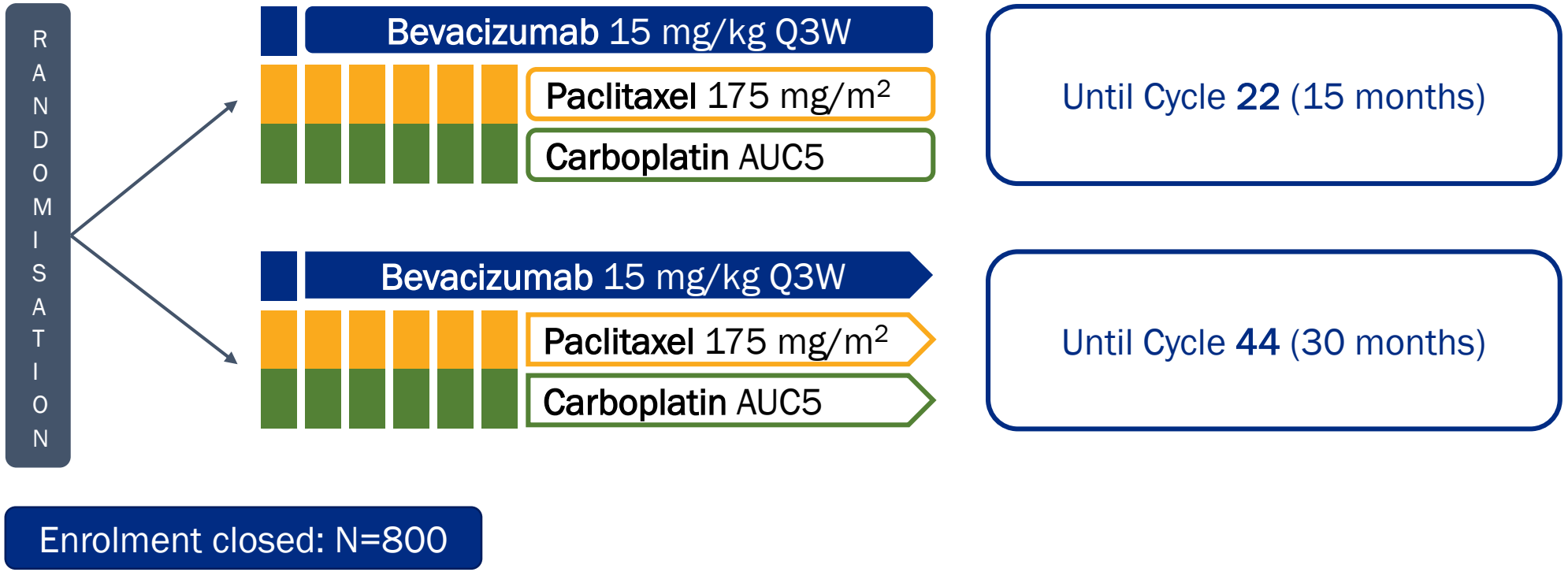


mPFS (months)	mOS (months)
CP: 17.5	CP: 58.6
CPBB: 19.9¶ P=0.25	CPBB: 58.0** P=0.85

*HR 0.908 (95% CI 0.80–1.04); †HR 1.04 (95% CI 0.83–1.3); ‡HR 0.717 (95% CI 0.63–0.82); §HR 0.915 (95% CI 0.73–1.15); ¶HR 0.93 (95% CI 0.83–1.05); **HR 0.99 (95% CI 0.85–1.14). CP, carboplatin–paclitaxel; CPB, carboplatin–paclitaxel–bevacizumab; CPBB, carboplatin–paclitaxel–bevacizumab–bevacizumab; FIGO, International Federation of Gynecology and Obstetrics; mOS, median overall survival; mPFS, median progression-free survival. 1. Burger RA *et al. N Engl J Med* 2011;365:2473–2483; 2. Oza AM *et al. Lancet Oncol* 2015;16:928–936

BOOST trial: Phase III trial evaluating 22 cycles versus 44 cycles of bevacizumab maintenance[1]

ENGOT-ov15/AGO OVAR 17[2] evaluation of optimal initial treatment duration of bevacizumab in combination with standard chemotherapy



Enrolment closed: N=800

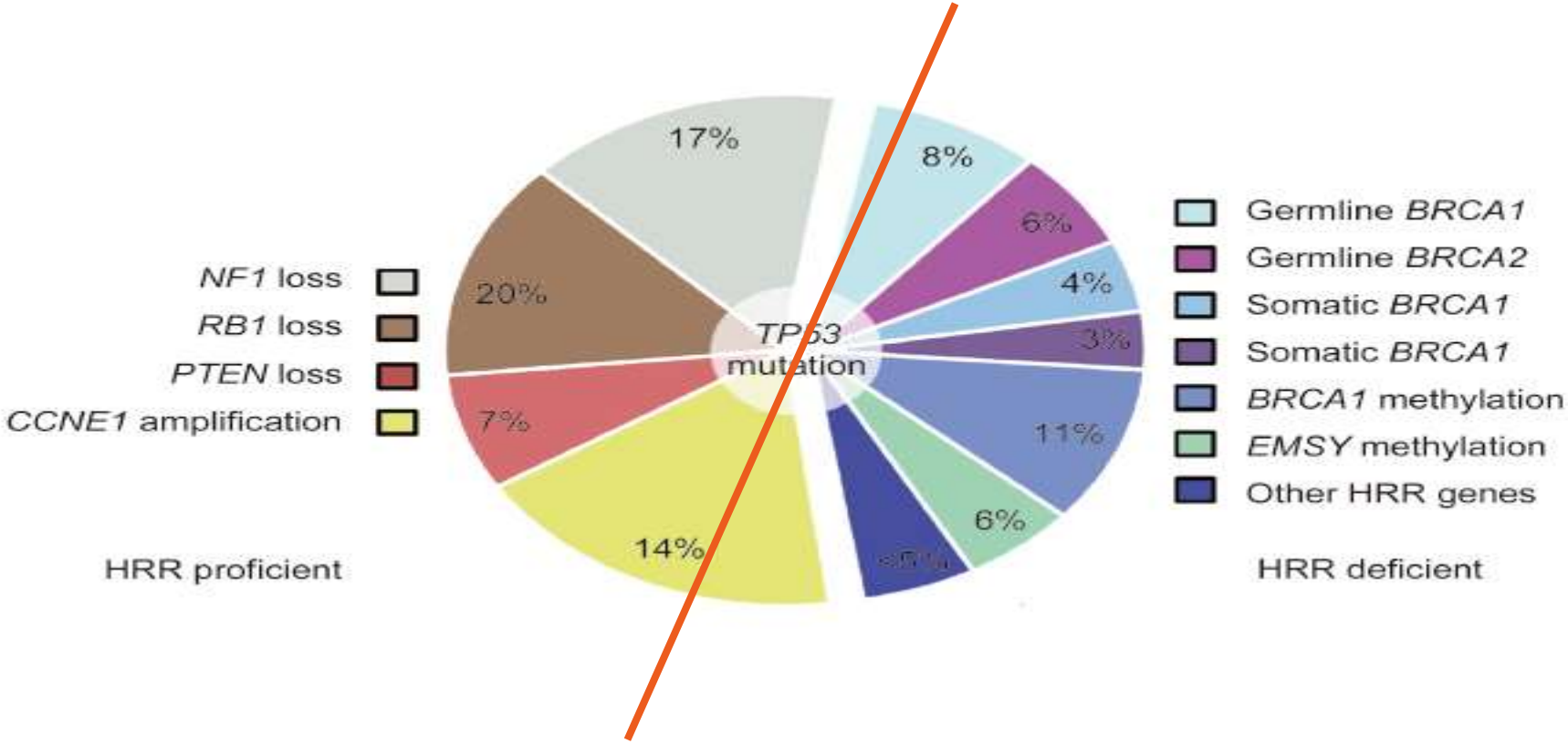
1. ClinicalTrials.gov. NCT01462890 (accessed 03 October 2018); 2. ENGOT. Available at: https://engot.esgo.org/clinical-trials/current-clinical-trials/ovarian/ (accessed 24 September 2018)

Standard of care: second line setting

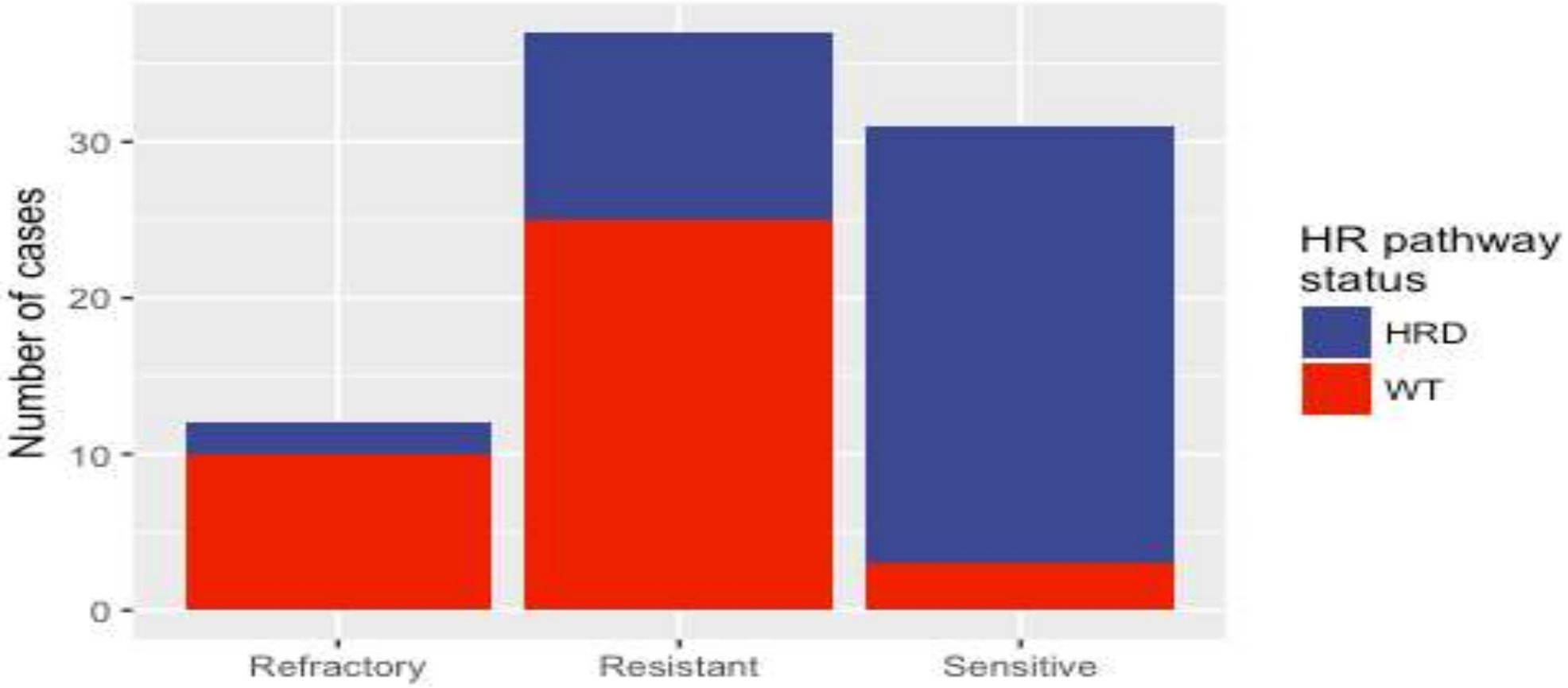
Current standard of care

- Patients candidate to a new treatment with platinum
- Patients uneligible to a new treatment with platinum

GENE MUTATIONS IN OC AT DIAGNOSIS



HRD IN DIFFERENT PHASES OF THE DISEASE



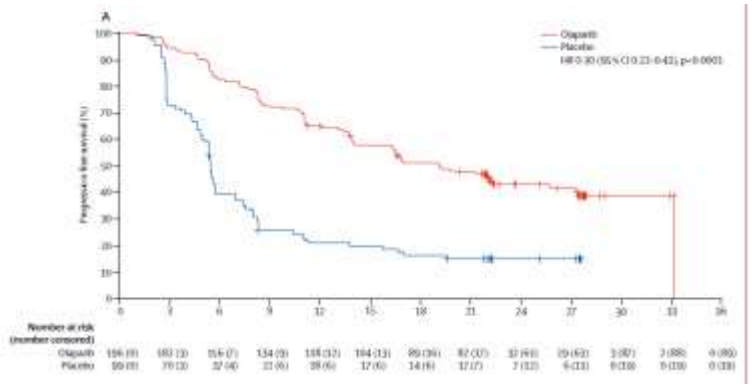
Patch et al Nature 2015

Platinum based chemotherapy

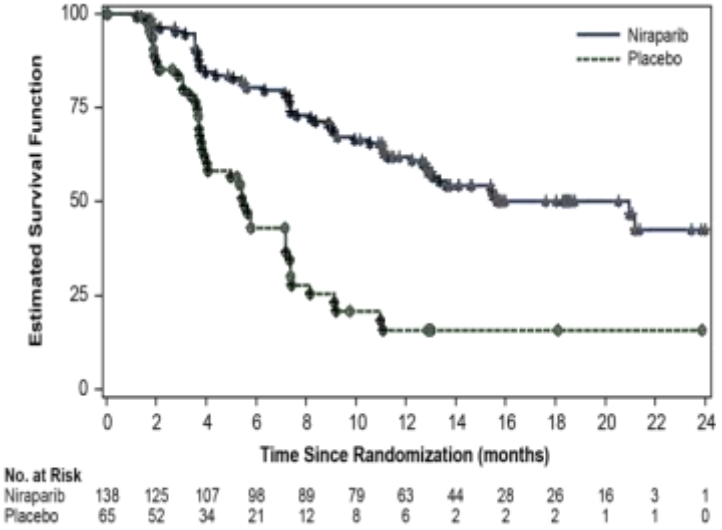
- Sei cicli di chemio
- Response rate in funzione del PFI
- Progressione dopo mediana di 5 mesi nelle pazienti che rispondono al platino

OLAPARIB, NIRAPARIB AND RUCAPARIB HIGHLY EFFECTIVE IN BRCA MUT

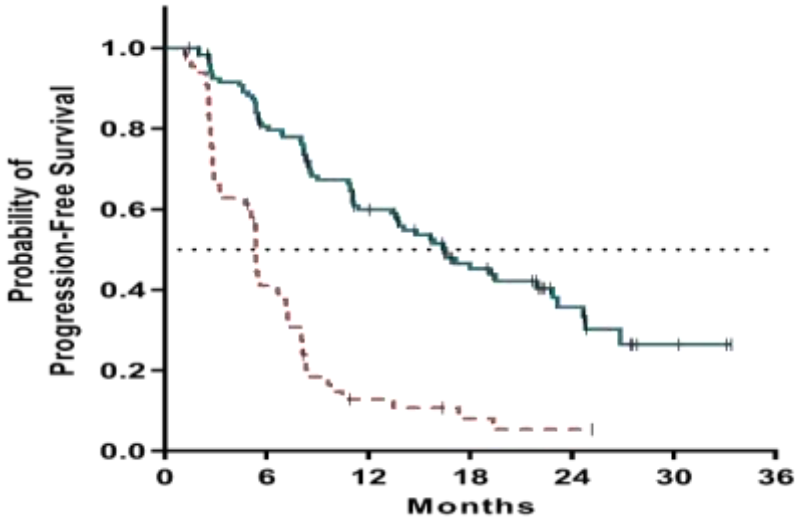
Olaparib
gBRCA mut
19.3 *vs* 5.5 months (HR 0.27)



Niraparib *
gBRCA mut
21 *vs* 5.5 months (HR 0.27)



Rucaparib
gBRCA mut
16.6*vs* 5.4 months (HR 0.27)

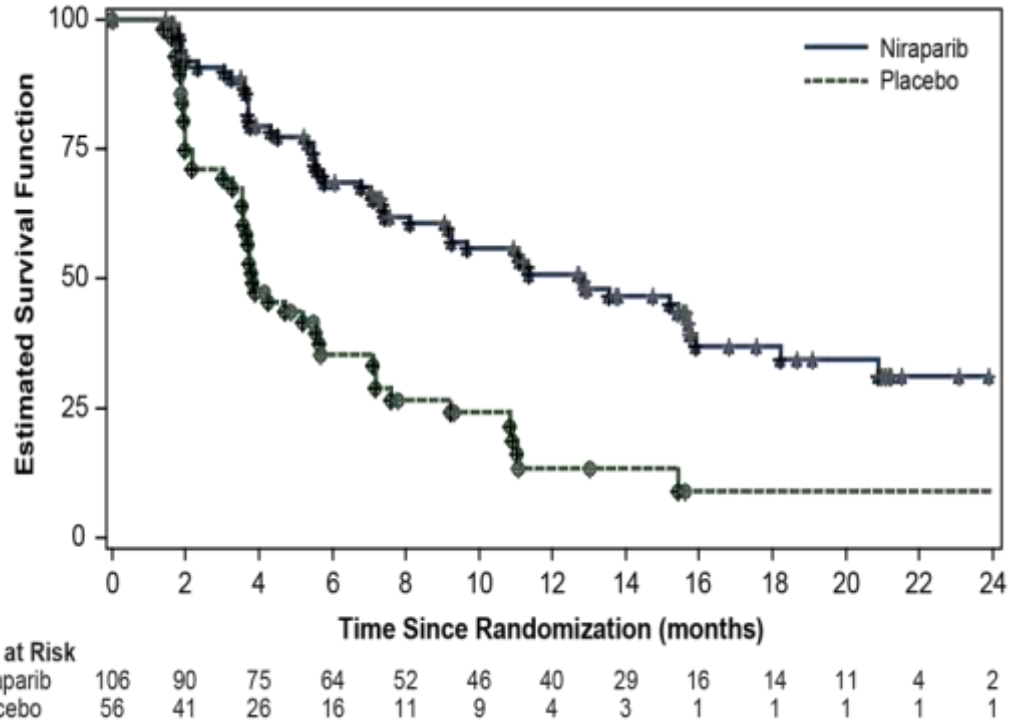


* Central radiological review

NOVA TRIAL : IN gBRCA WT PATIENTS NIRAPARIB IS PARTICULARLY ACTIVE IN HRD POSITIVE

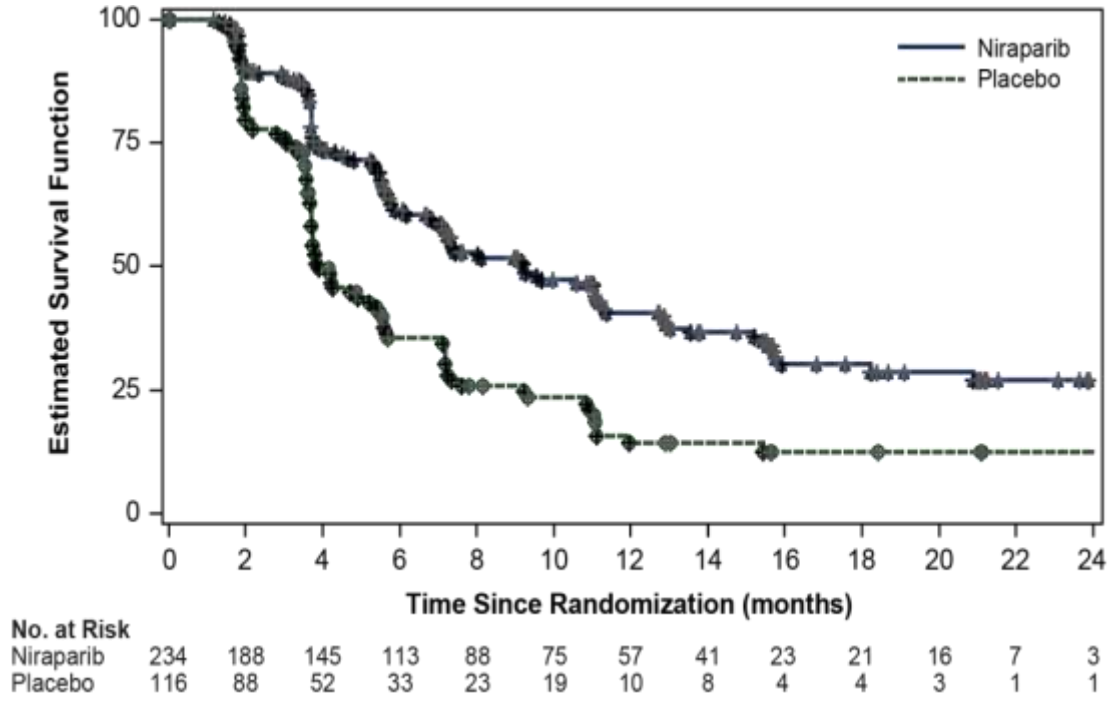
gBRCA wt - HRD positive

12.9 *vs* 3.8 months (HR 0.38)



All gBRCA wt

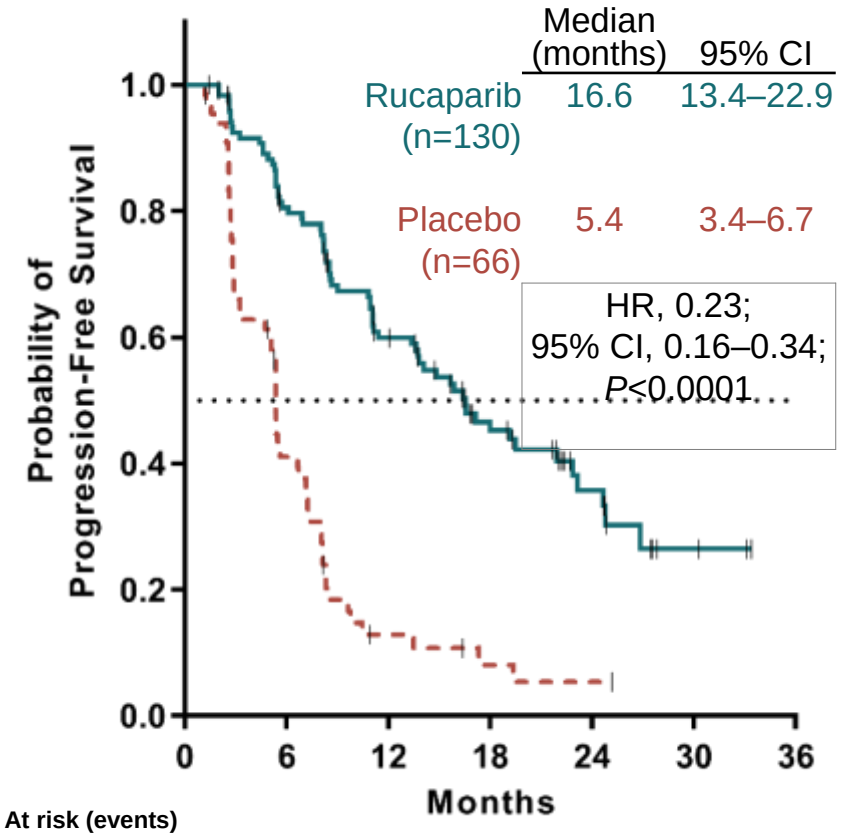
9.3 *vs* 3.9 months (HR 0.45)



Mirza et al NEJM 2016

ARIEL3: Investigator-Assessed Progression-Free Survival

BRCA mutant

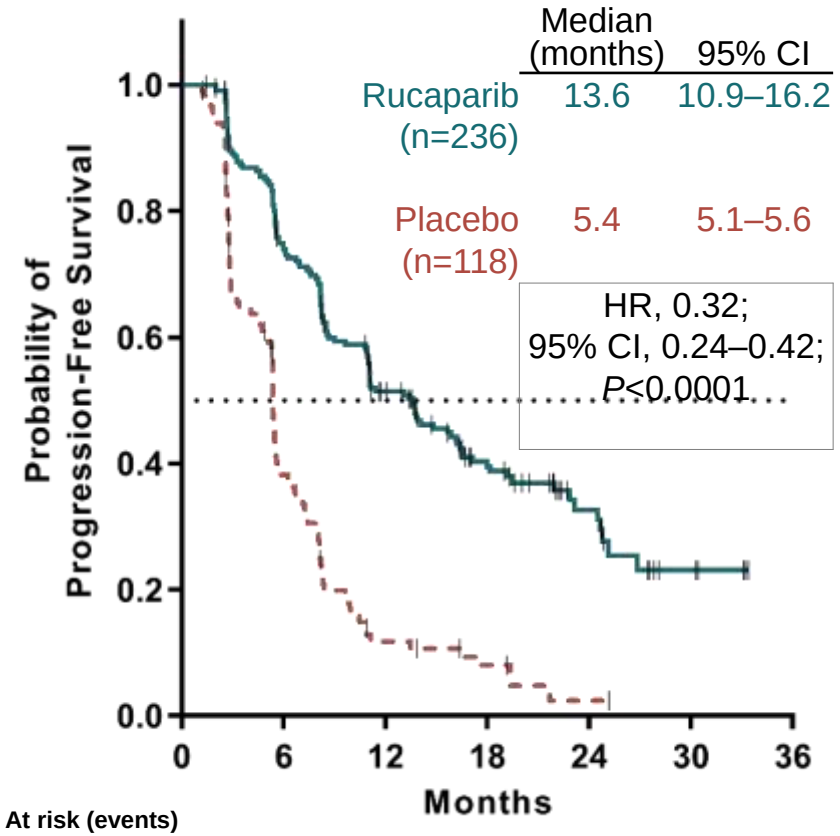


At risk (events)

Rucaparib	130 (0)	93 (23)	63 (46)	35 (58)	15 (64)	3 (67)	0 (67)
Placebo	66 (0)	24 (37)	6 (53)	3 (55)	1 (56)	0 (56)	

Rucaparib, 48% censored Placebo, 15% censored

HRD

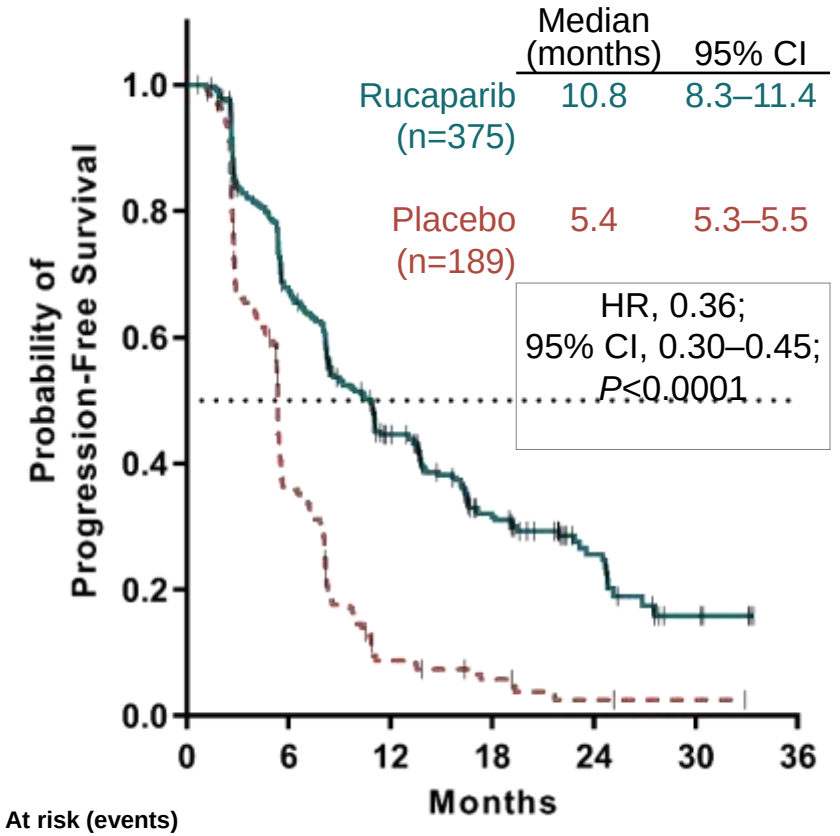


At risk (events)

Rucaparib	236 (0)	161 (55)	96 (104)	54 (122)	21 (129)	5 (134)	0 (134)
Placebo	118 (0)	40 (68)	11 (95)	6 (98)	1 (101)	0 (101)	

Rucaparib, 43% censored Placebo, 14% censored

ITT



At risk (events)

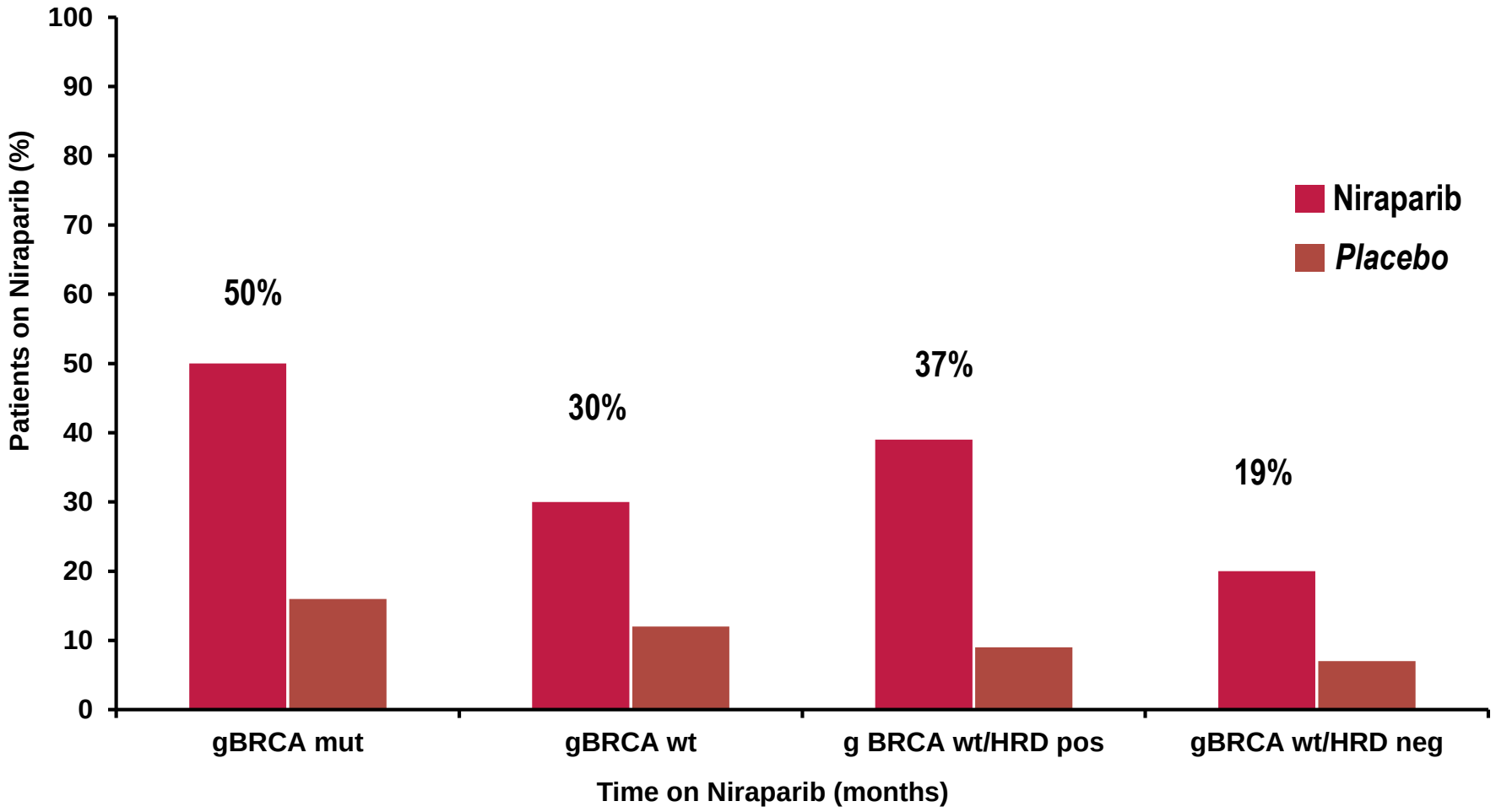
Rucaparib	375 (0)	228 (111)	128 (186)	65 (217)	26 (226)	5 (234)	0 (234)
Placebo	189 (0)	63 (114)	13 (160)	7 (164)	2 (167)	1 (167)	0 (167)

Rucaparib, 38% censored Placebo, 12% censored

Visit cutoff date: 15 April 2017.

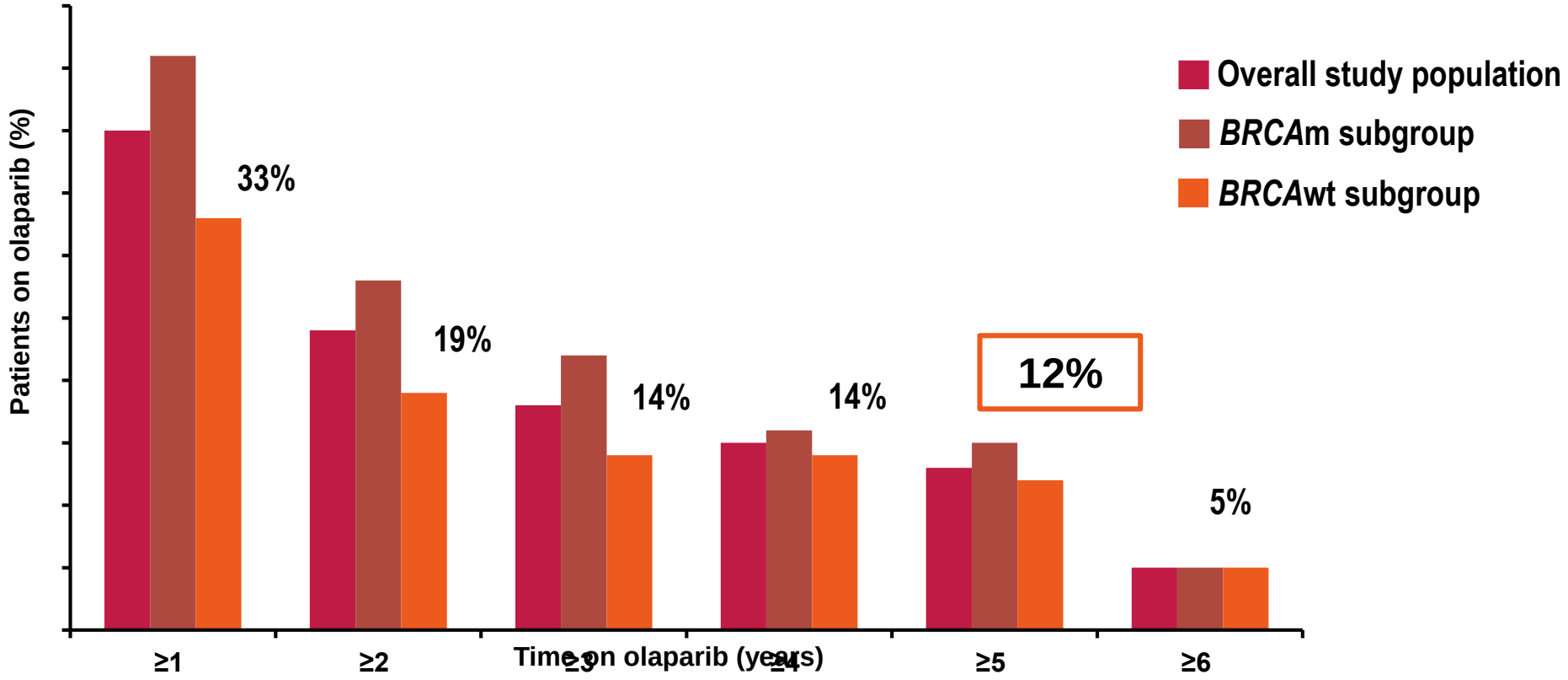
LONG-TERM EXPOSURE TO NIRAPARIB

Patients on treatment at 18 months



Long-term exposure to Olaparib in Study 19

- Median follow-up of 5.9 years: **15 patients (11%)** still receiving **olaparib** (**8 *BRCA*m**, 7 *BRCA*wt); one patient (<1%) still receiving placebo (*BRCA*m)



Courtesy of J Ledermann ASCO 2016

Standard of care: First-line setting

- Bevacizumab can be combined with chemotherapy according to GOG 218, and maintenance therapy should be considered[1]
  - The maintenance duration has not been defined[1]
  - Therapy according to risk categories is not universally accepted[2]
    - ICON7 showed no OS benefit with bevacizumab; however, in an exploratory analysis of a predefined patient group with poor prognosis disease, a significant difference in OS was noted with bevacizumab
  - No biomarker is currently available
    - However, two are under validation[3,4]
  - There is no clear evidence that bevacizumab added to neo-adjuvant chemotherapy improves outcome[5]

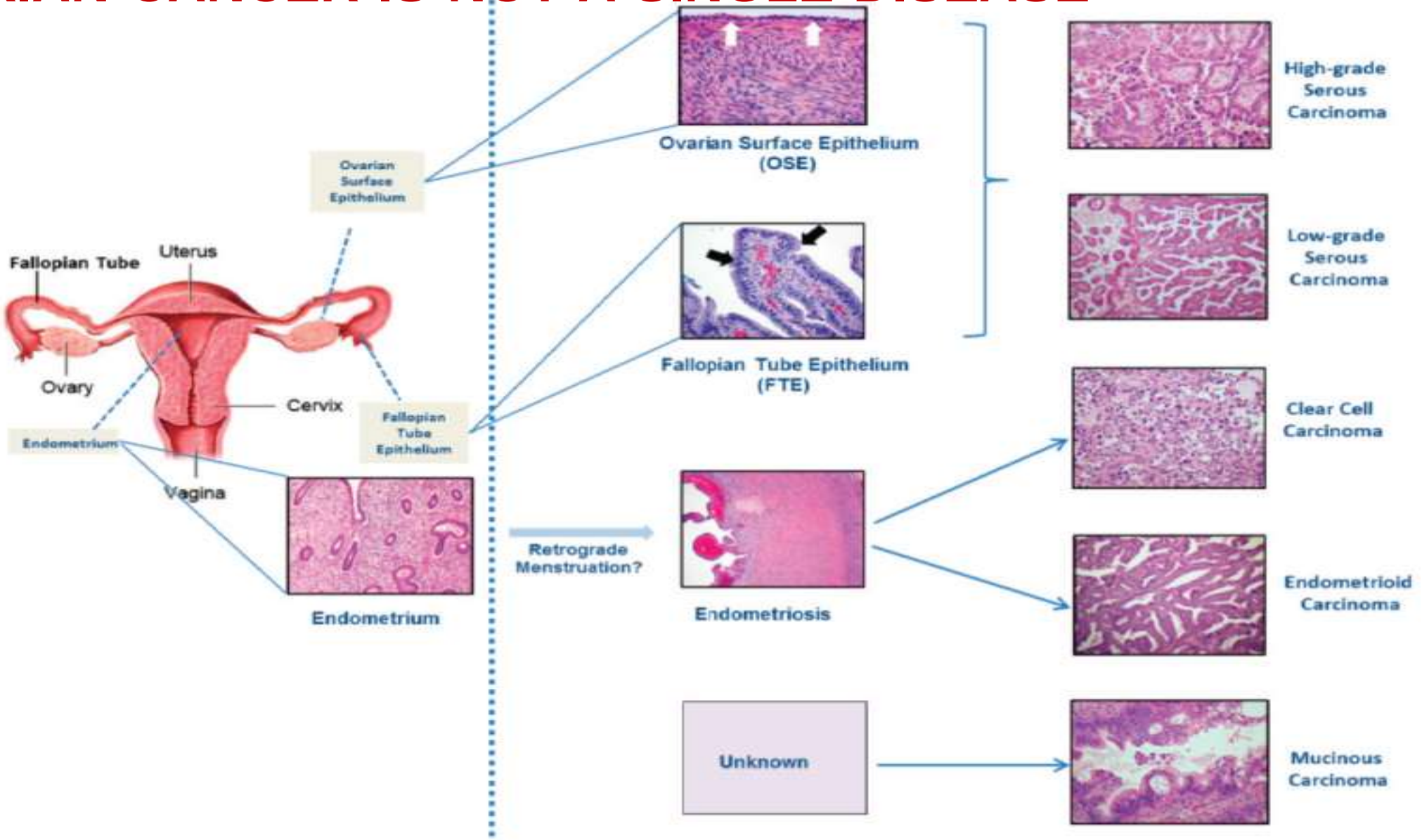
OS, overall survival

1. Burger RA *et al. N Engl J Med* 2011;365:2473–2483; 2. Ledermann JA *et al. Ann Oncol* 2013;24 Suppl 6:vi24–32; 3. Gourley C *et al. J Clin Oncol* 2014;32 (suppl): abstract 5502; 4. Bais C *et al. JNCI* 2017;109:djx066; 5. Oza AM *et al. Lancet Oncol* 2015;16:928–936

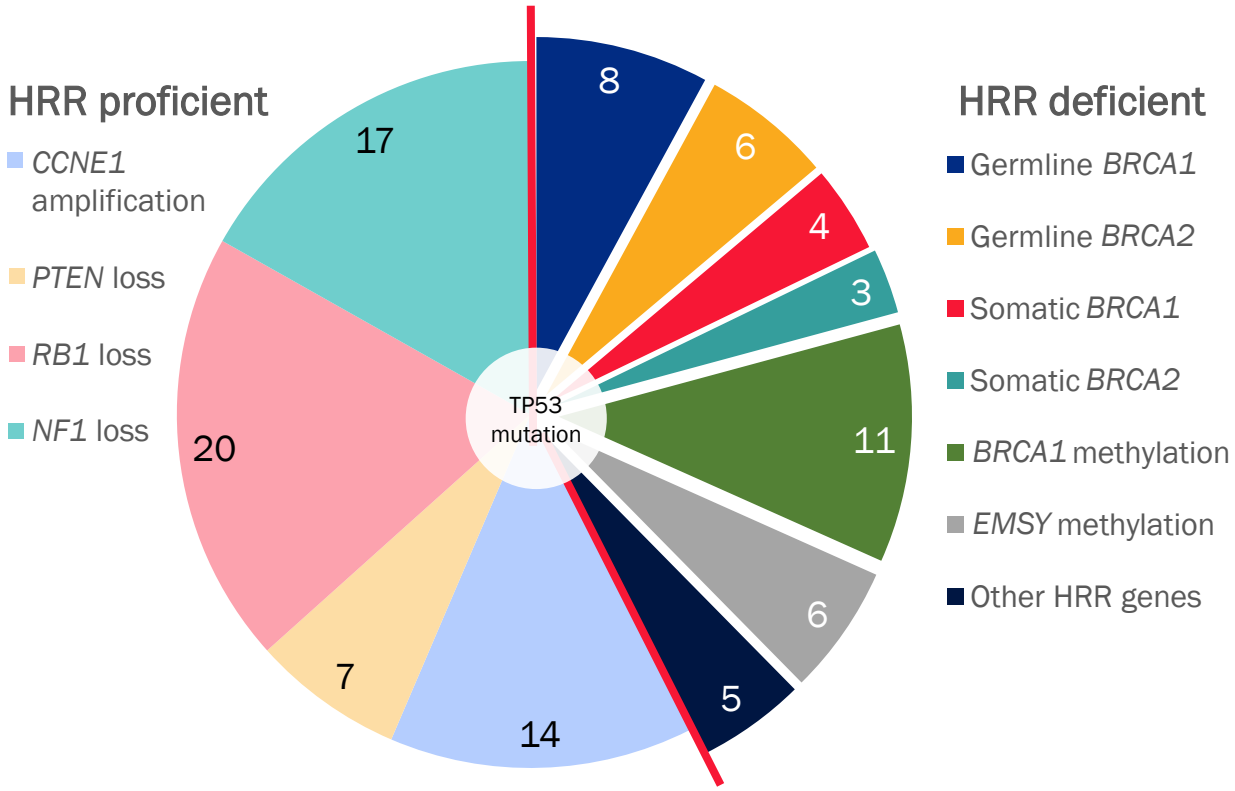
First-line setting

How can we move forward?

OVARIAN CANCER IS NOT A SINGLE DISEASE



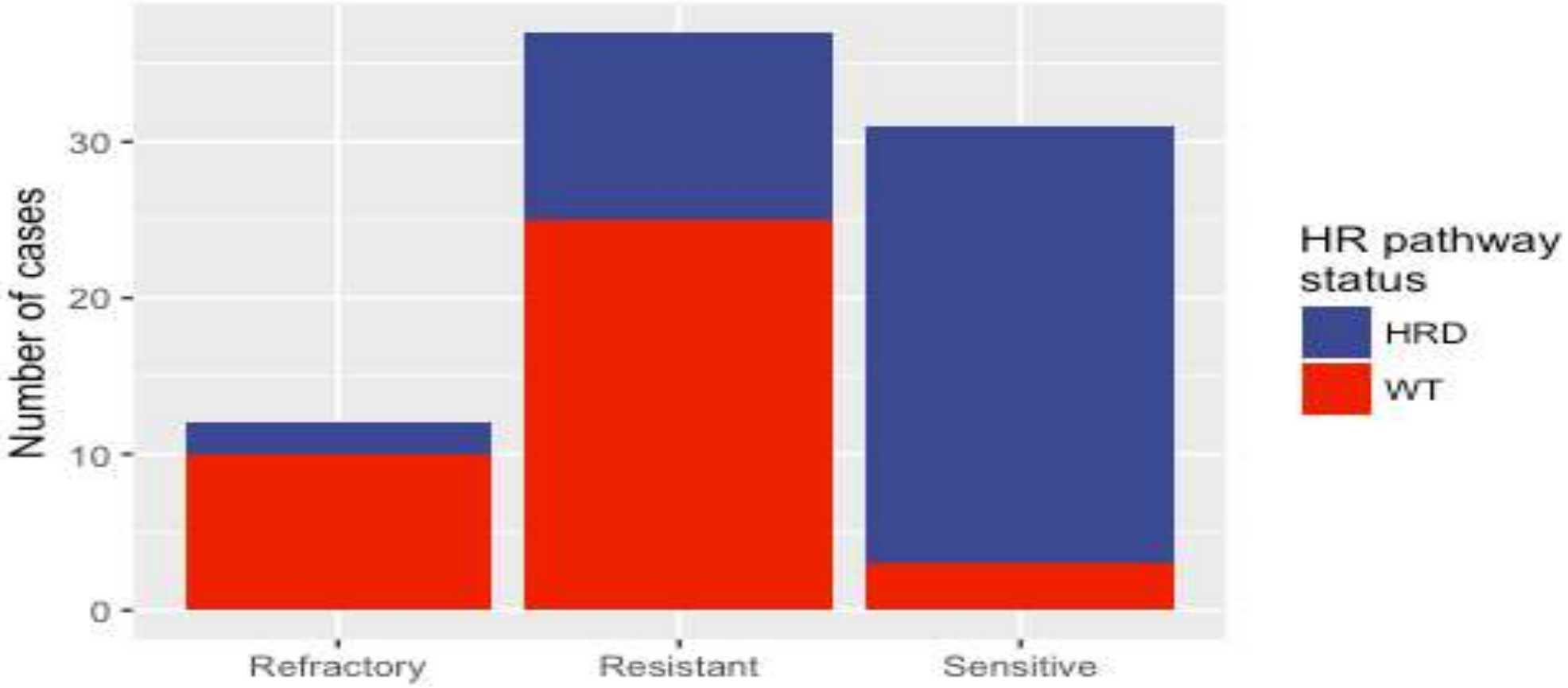
High grade ovarian cancer is a disease with HRD



HR, homologous recombination; HRD, homologous recombination deficiency; OC, ovarian cancer; PARPi, poly-ADP ribose polymerase inhibitor; TCGA, The Cancer Genome Atlas

Adapted from Liu JF, Konstantinopoulos PA. Translational Advances in Gynecologic Cancers 2017, Pages 111-128. Available at: https://doi.org/10.1016/B978-0-12-803741-6.00006-9 (accessed 03 October 2018) and Patch AM *et al. Nature* 2015;521:489–94

HRD IN DIFFERENT PHASES OF THE DISEASE



Patch et al Nature 2015

SOLO1 trial

- 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)

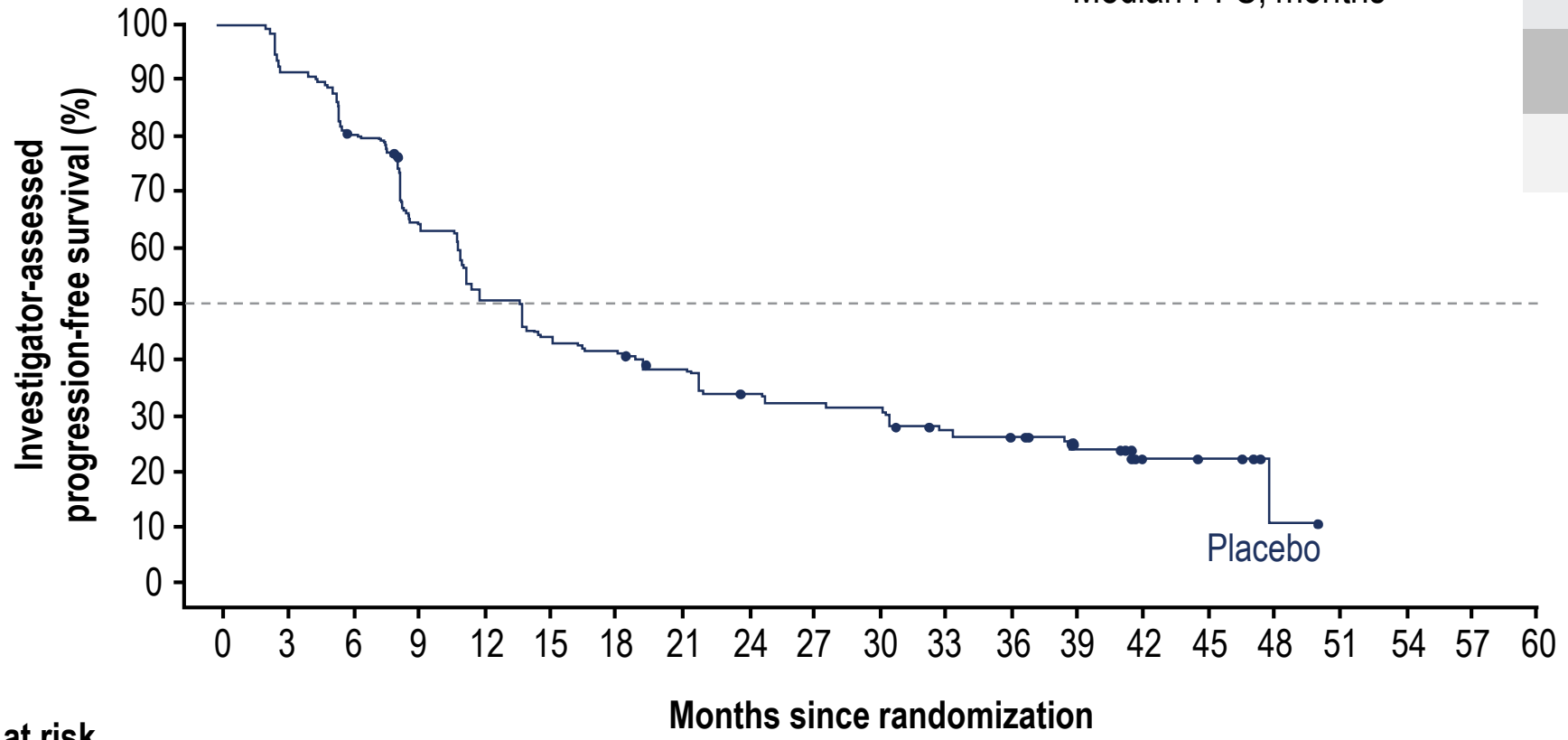
*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease.
BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; FACT-O, Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO, International Federation of Gynecology and Obstetrics; HRQoL, health-related quality of life; PFS, progression-free survival; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TOI, Trial Outcome Index

Patient characteristics

	Olaparib (N=260)	Placebo (N=131)
History of cytoreductive surgery, n (%)		
Upfront surgery	161 (61.9)	85 (64.9)
Residual macroscopic disease	37 (23.0)	22 (25.9)
No residual macroscopic disease	123 (76.4)	62 (72.9)
Unknown	1 (0.6)	1 (1.2)
Interval cytoreductive surgery	94 (36.2)	43 (32.8)
Residual macroscopic disease	18 (19.1)	7 (16.3)
No residual macroscopic disease	76 (80.9)	36 (83.7)
No surgery	4 (1.5)	3 (2.3)
Stratification factors		
Response after surgery/platinum-based chemotherapy, n (%)		
Clinical complete response	213 (81.9)	107 (81.7)
Partial response	47 (18.1)	24 (18.3)

PFS by investigator assessment

	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]		96 (73.3)
Median PFS, months		13.8



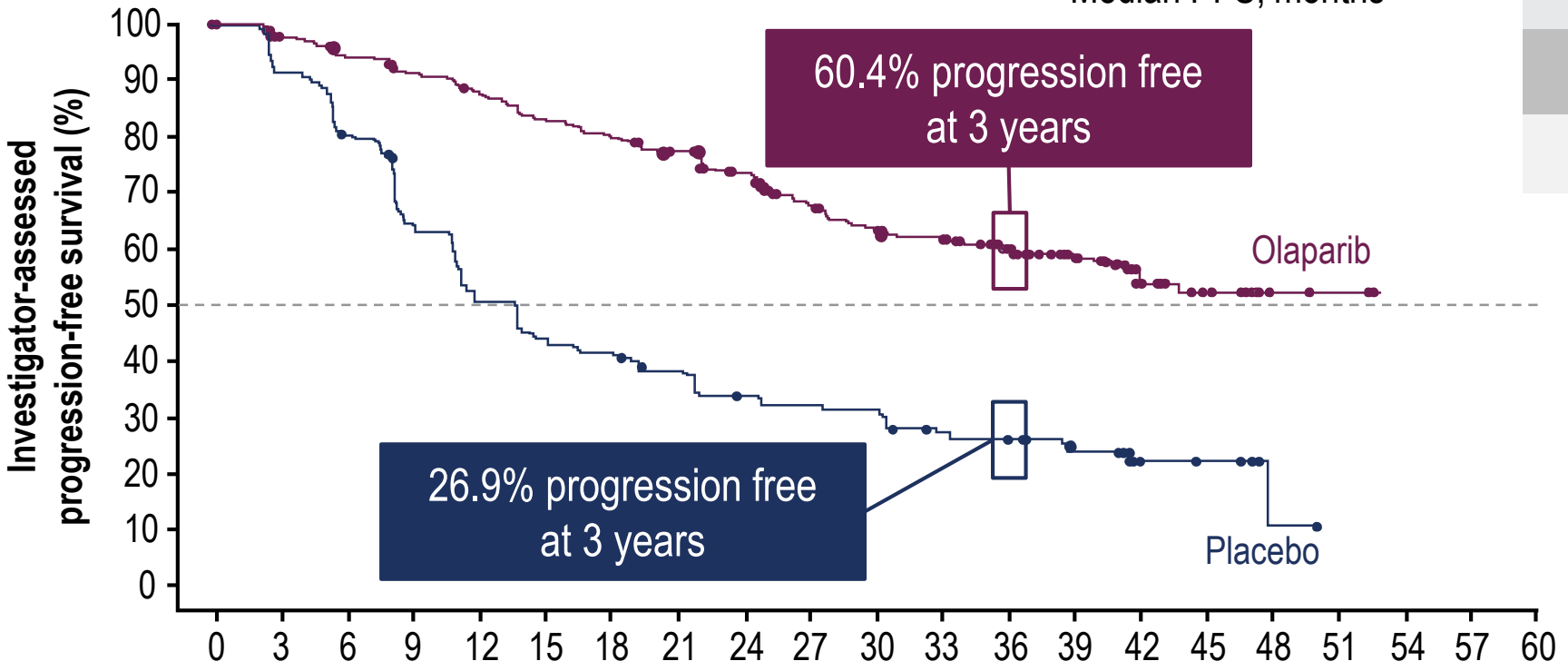
No. at risk

Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

MUNICH 2018 ESMO congress

PFS by investigator assessment

	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
HR 0.30		
95% CI 0.23, 0.41; *P*<0.0001		



No. at risk

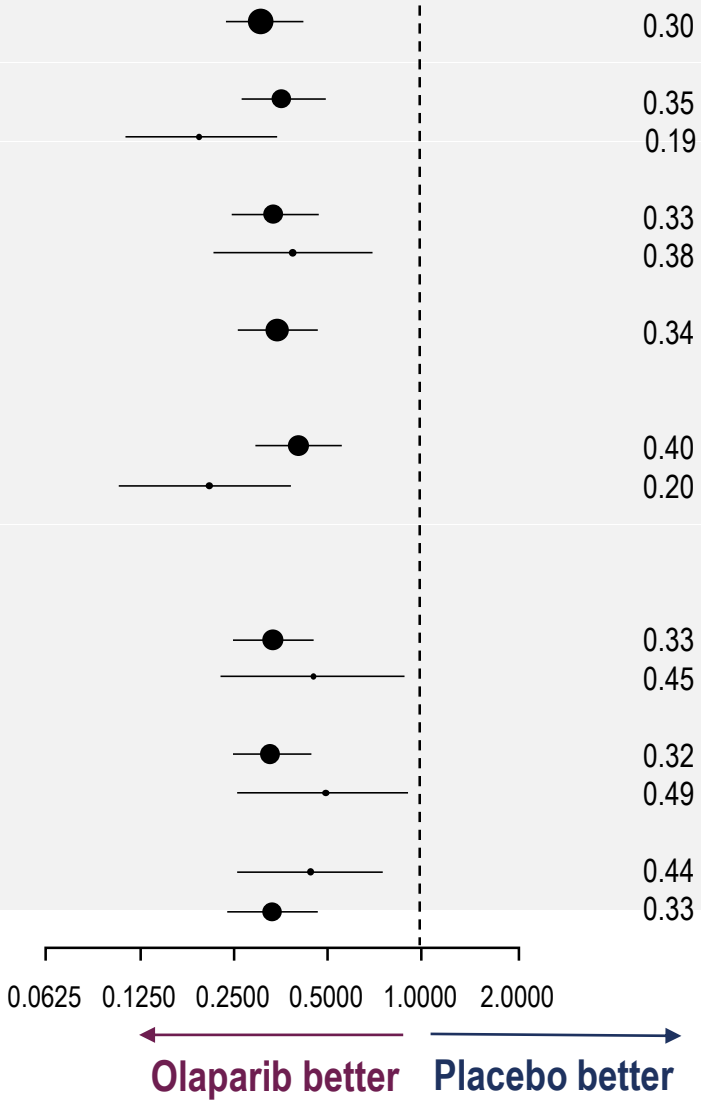
Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

MUNICH 2018 ESMO congress

CI, confidence interval; NR, not reached

PFS subgroup analysis

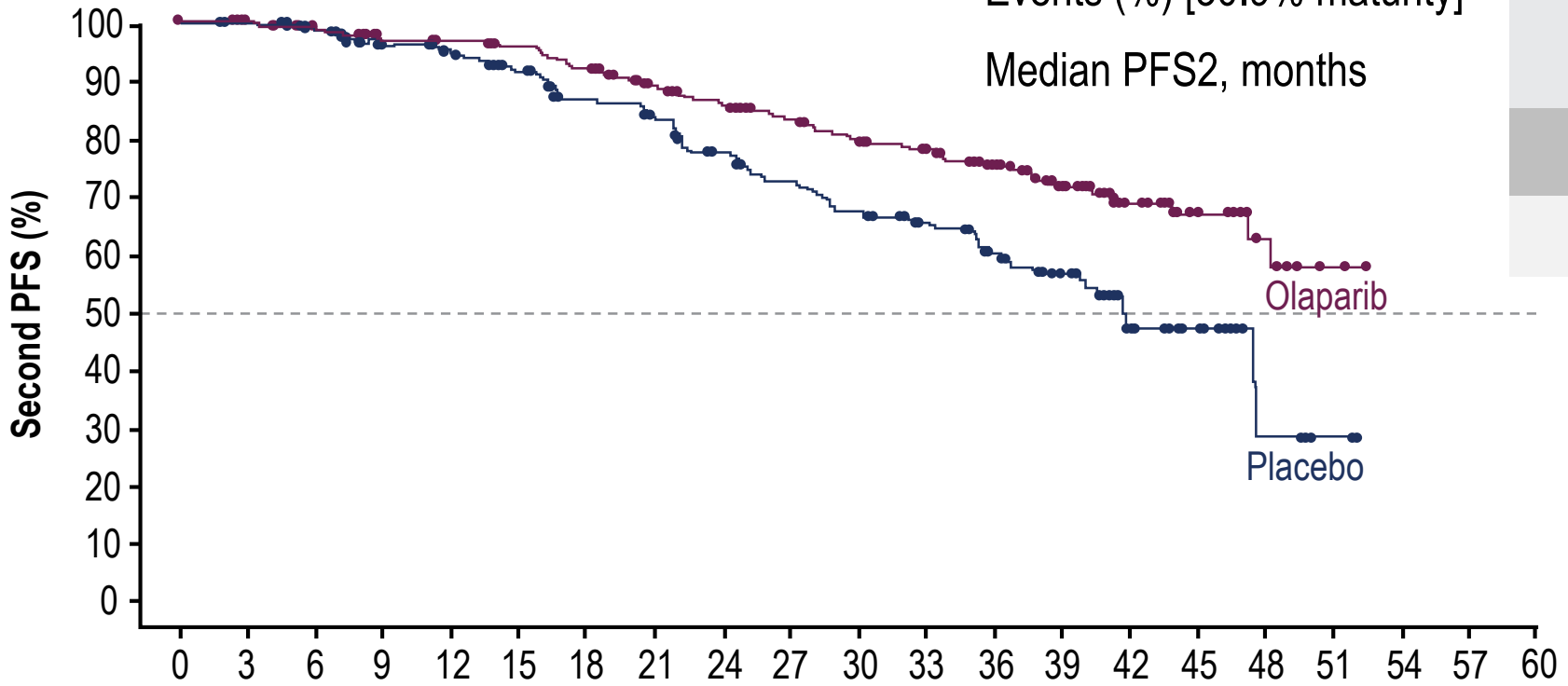
Subgroup	Olaparib 300 mg bd Number of patients with events/total number of patients (%)	Placebo bd Number of patients with events/total number of patients (%)	HR (95% CI)
All patients	102/260 (39.2)	96/131 (73.3)	0.30 (0.23, 0.41)
Response after surgery/platinum-based chemotherapy			
Clinical complete response	73/213 (34.3)	73/107 (68.2)	0.35 (0.26, 0.49)
Partial response	29/47 (61.7)	23/24 (95.8)	0.19 (0.11, 0.34)
ECOG performance status at baseline			
Normal activity	75/200 (37.5)	76/105 (72.4)	0.33 (0.24, 0.46)
Restricted activity	27/60 (45.0)	20/25 (80.0)	0.38 (0.21, 0.68)
Baseline CA-125 value			
≤ULN	92/247 (37.2)	89/123 (72.4)	0.34 (0.25, 0.46)
>ULN	10/13 (76.9)	7/7 (100.0)	NC
g*BRCA* mutation type by Myriad testing			
BRCA1	84/188 (44.7)	69/91 (75.8)	0.40 (0.29, 0.56)
BRCA2	15/62 (24.2)	26/39 (66.7)	0.20 (0.10, 0.38)
BRCA1/2 (both)	0/3	0/0	NC
Negative	3/7 (42.9)	1/1 (100.0)	NC
Age			
<65 years	85/225 (37.8)	82/112 (73.2)	0.33 (0.24, 0.45)
≥65 years	17/35 (48.6)	14/19 (73.7)	0.45 (0.22, 0.92)
Stage of disease at initial diagnosis			
Stage III	83/220 (37.7)	79/105 (75.2)	0.32 (0.24, 0.44)
Stage IV	19/40 (47.5)	17/26 (65.4)	0.49 (0.25, 0.94)
Following debulking surgery prior to study entry			
Residual macroscopic disease	29/55 (52.7)	23/29 (79.3)	0.44 (0.25, 0.77)
No residual macroscopic disease	70/200 (35.0)	69/98 (70.4)	0.33 (0.23, 0.46)



ULN, upper limit of normal

PFS2*

	Olaparib (N=260)	Placebo (N=131)
Events (%) [30.9% maturity]	69 (26.5)	52 (39.7)
Median PFS2, months	NR	41.9
HR 0.50		
95% CI 0.35, 0.72; *P*=0.0002		



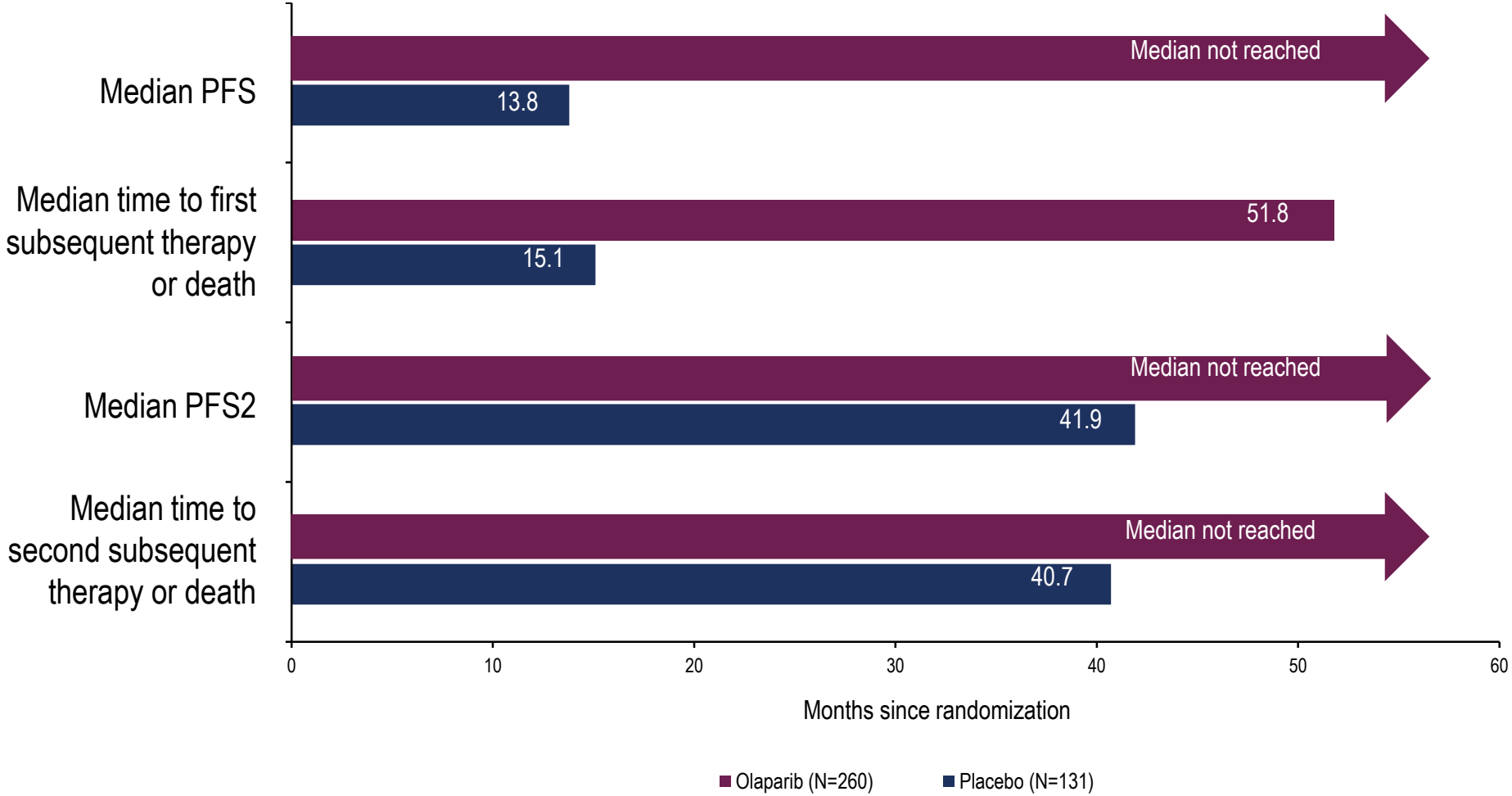
No. at risk

Olaparib	260	246	239	231	229	225	216	204	194	177	168	163	140	111	61	48	13	5	0	0	0
Placebo	131	126	122	113	108	100	92	88	79	73	68	63	55	44	18	11	3	1	0	0	0

In second line, a PARP inhibitor was used in 33/94 (35%) patients in the placebo arm and 10/91 (11%) patients in the olaparib arm

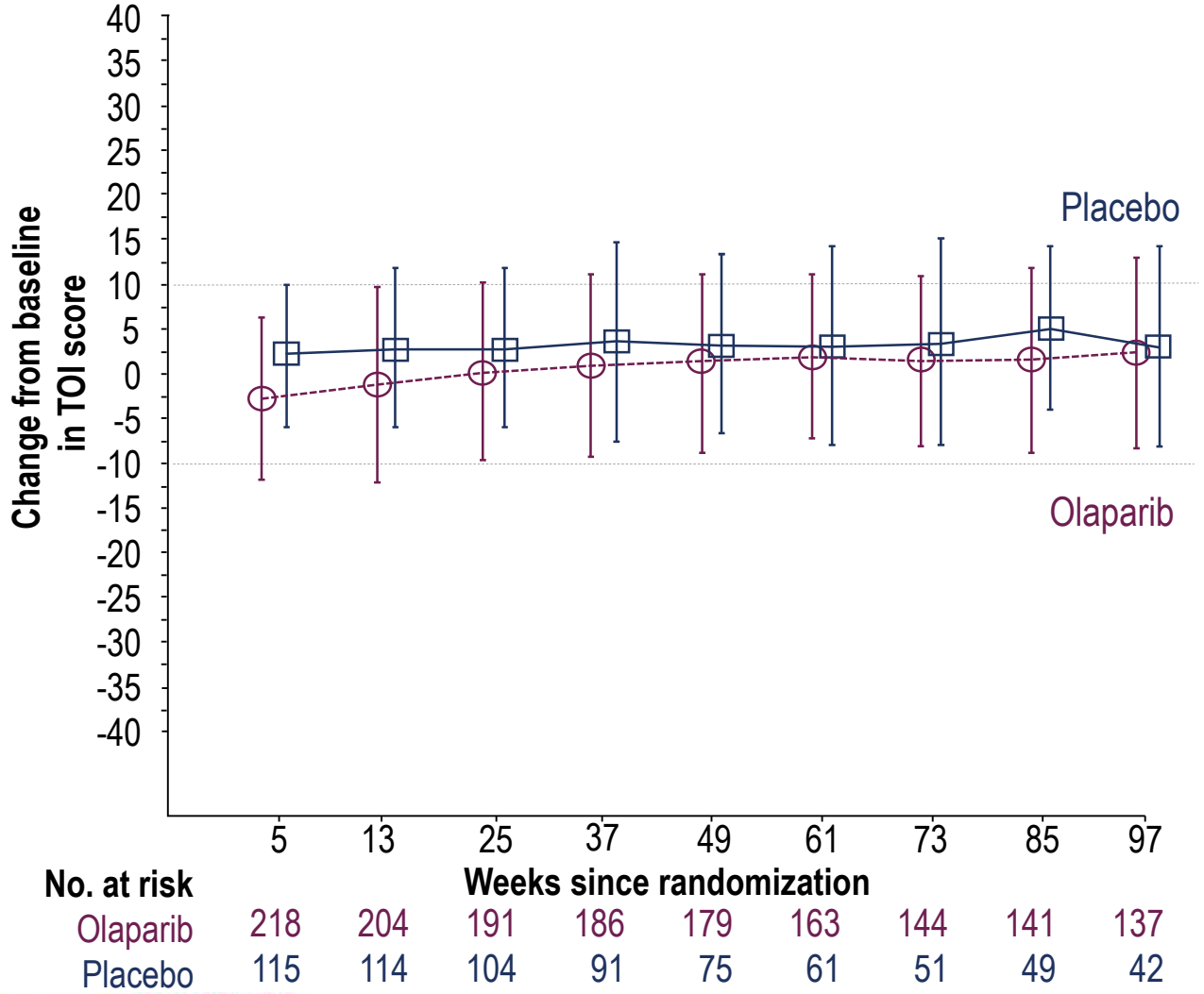
*Time from randomization to second progression or death

Summary of efficacy endpoints



HR 0.30	95% CI 0.23, 0.41; *P*<0.0001
HR 0.30	95% CI 0.22, 0.40; *P*<0.0001
HR 0.50	95% CI 0.35, 0.72; *P*=0.0002
HR 0.45	95% CI 0.32, 0.63; *P*<0.0001

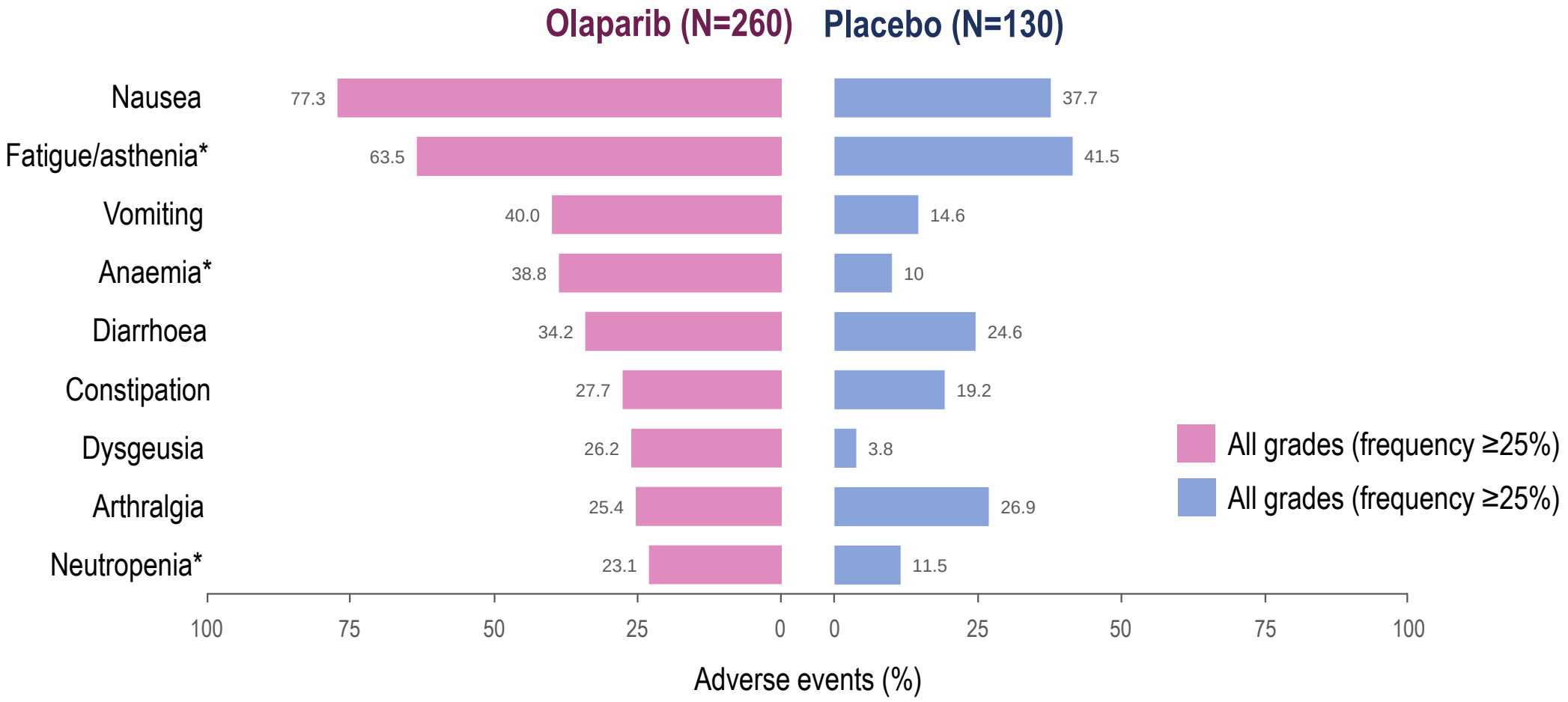
Health-related quality of life: FACT-O TOI score*



The difference between olaparib and placebo in the mean change from baseline in TOI score over 24 months (−3.00; 95% CI −4.779, −1.216) was not clinically meaningful

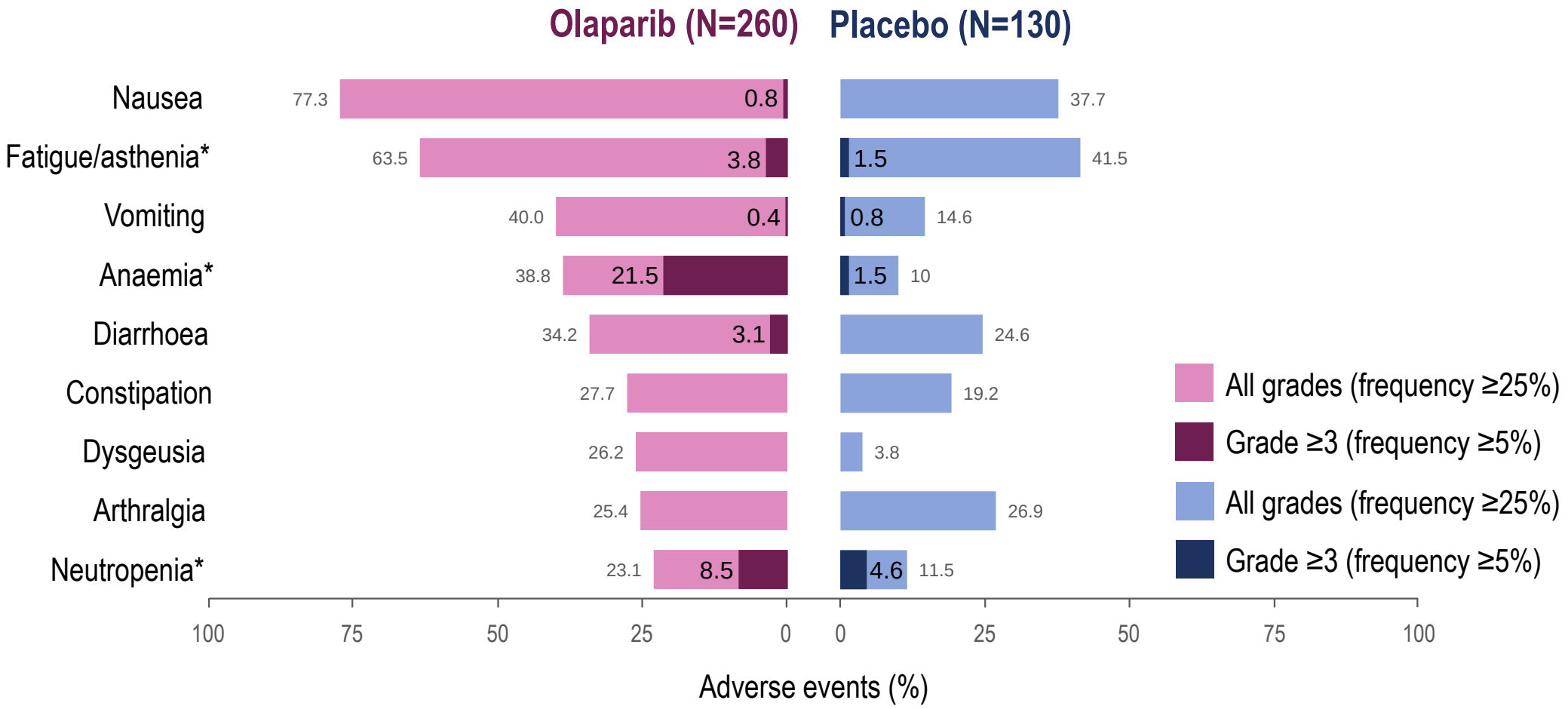
*TOI scores range from 0 to 100, with higher scores indicating better HRQoL and a clinically meaningful difference defined as ±10 points

Most common treatment-emergent adverse events



*Grouped terms. All-grade thrombocytopenia (grouped term) occurred in 11.2% of patients in the olaparib group, and 3.8% of patients in the placebo group

Most common treatment-emergent adverse events



*Grouped terms. All-grade thrombocytopenia (grouped term) occurred in 11.2% of patients in the olaparib group and 3.8% of patients in the placebo group and grade ≥3 thrombocytopenia (grouped term) occurred in 0.8% and 1.5%, respectively.

Adverse events of special interest

	Olaparib (N=260)	Placebo (N=130)
MDS/AML,* n (%)	3 (1.2)	0
New primary malignancies,† n (%)	5 (1.9)	3 (2.3)
Pneumonitis/ILD, n (%)	5 (1.9)	0

*The three cases of AML occurred 1.7–5.7 months after stopping olaparib (duration of olaparib therapy of 14.3–24.9 months). †Including breast cancer (n=3), head and neck cancer (n=1) and thyroid cancer (n=1) in the olaparib group, and breast cancer (n=3) in the placebo group. AML, acute myeloid leukaemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome

New concepts under investigation: The near horizon

First-line – PARPi/Bev-based regimens

Carboplatin–paclitaxel	PARPi maintenance	SOLO-1, PRIMA, MITO-25
Carboplatin–paclitaxel–bev	PARPi and bev maintenance	PAOLA-1
Carboplatin–paclitaxel–bev–PARPi	PARPi maintenance	MITO-25

First-line – Checkpoint inhibitor/Bev-based regimens

Carboplatin–paclitaxel +/- checkpoint inhibitor	Checkpoint inhibitor maintenance	JAVELIN OVARIAN 100
Carboplatin–paclitaxel +/- checkpoint inhibitor–bev	Checkpoint inhibitor + bev maintenance	ENGOT-ov39, IMagyn050

Resistant/refractory OC – Checkpoint inhibitor-based regimens

Checkpoint inhibitor monotherapy or in combination with liposomal doxorubicin	KEYNOTE-100, JAVELIN OVARIAN 200
Immunotherapy in combination with PARPi	TOPACIO/KEYNOTE-162

Resistant/refractory OC – (FRα)-targeting ADC

Mirvetuximab soravtansine	FORWARD I

ADC, antibody-drug conjugate; Bev, bevacizumab; OC, ovarian cancer; PARPi, poly-ADP ribose polymerase inhibitor

The near horizon: PARP-based regimens

First-line – PARPi/Bev-based regimens

Carboplatin–paclitaxel	→ PARPi maintenance	SOLO-1, PRIMA, MITO-25
Carboplatin–paclitaxel–bev	→ PARPi and bev maintenance	PAOLA-1
Carboplatin–paclitaxel–bev–PARPi	→ PARPi maintenance	MITO-25

OC, ovarian cancer; PARP, poly-ADP ribose polymerase; PARPi, poly-ADP ribose polymerase inhibitor

Is the benefit confined only to BRCA mutated patients?

PRIMA / ENGOT-OV26/GOG-3012: Phase 3 trial of niraparib maintenance treatment in patients with advanced ovarian cancer following response on front-line platinum-based chemotherapy

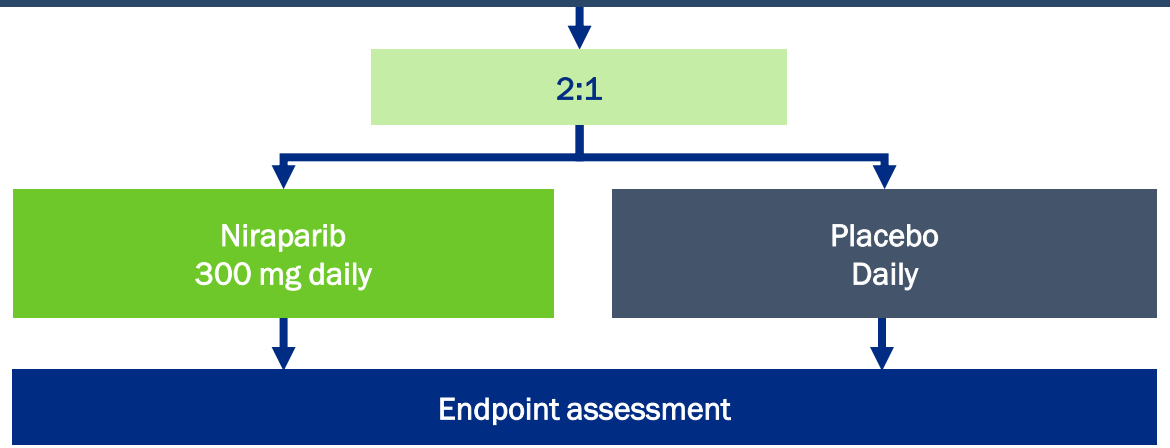
High-grade Stage III or IV ovarian cancer (all comers) and achieved a CR or PR following front-line platinum-based chemotherapy

Stratification factors

- Neoadjuvant chemotherapy administered: Yes or No
- Best response to 1st platinum therapy: CR or PR
- HRD status: positive or negative/not determined

Enrolment completed June 2018 (N=733)

Results expected end 2019



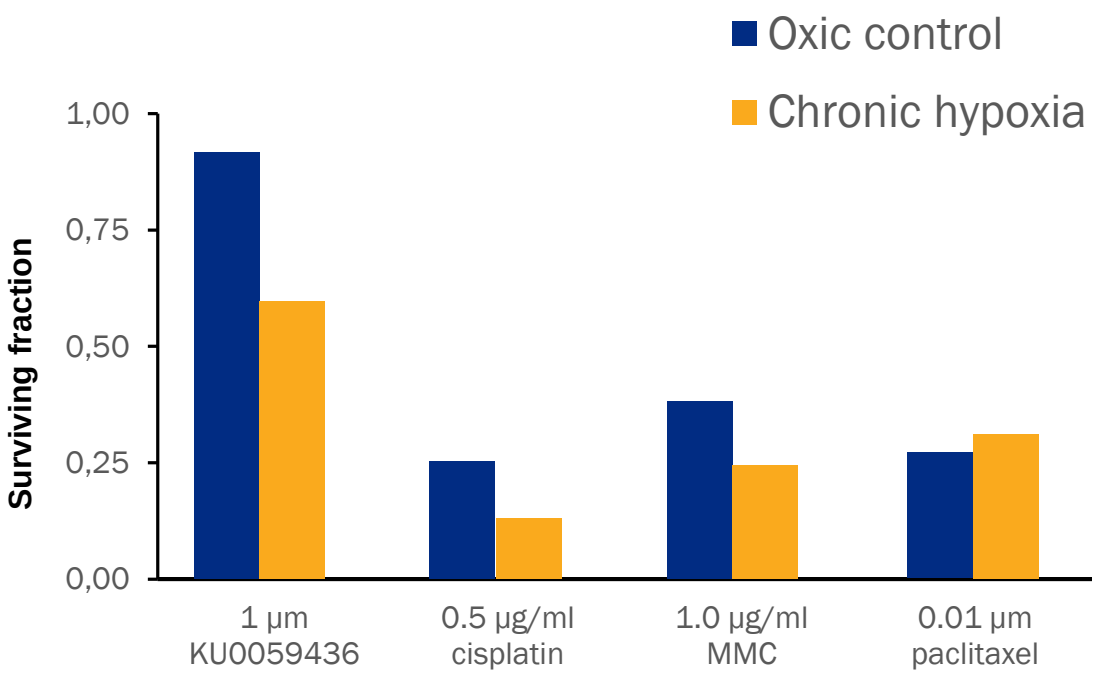
Primary Endpoint	**Hierarchical Testing for PFS (radiologic, central review)** · PFS in HRD pos population (HR 0.5) · PFS in ITT population (HR 0.65)
Key Secondary Endpoints	Overall survival | Patient-reported outcomes (FOSI, EQ-5D-5L, EORTC-QLQ-30, EORTC-QLQ-OV28) | Safety & Tolerability | PFS2 | Time to CA-125 progression

ClinicalTrials.gov. NCT02655016

CR, complete response; EORTC-QLQ-30, European Organisation for Research and Treatment of Cancer; EORTC-QLQ-OV28, EORTC–Ovarian Cancer Module; EQ-5D-5L, European QoL five-dimension five-level questionnaire; FOSI, FACIT ovarian cancer symptom index; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention to treat; PFS, progression free survival; PK, pharmacokinetic; PR, partial response; QoL, quality of life

Combination of PARPi with anti-angiogenic agents: Is there a benefit?

Hypoxia-induced HR defects sensitise tumour cells to DNA-damaging agents[1]

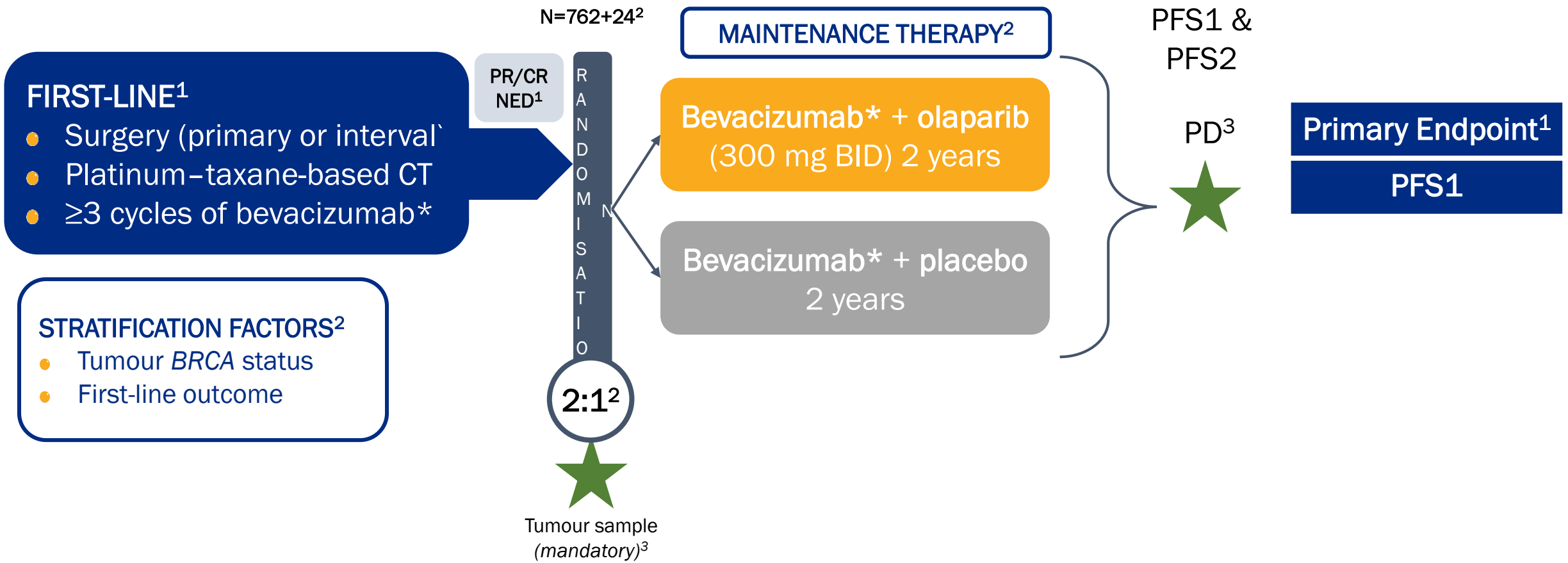


- Potential enhancement of sensitivity to PARPi by increasing HRD through changes in oxygenation caused by anti-angiogenic agents[1]
- PARPis downregulate *BRCA1* and *RAD 51*, increasing HRD[2]

HR, homologous recombination; HRD, homologous recombination deficiency; MMC, mitomycin C; PARPi, poly-ADP ribose polymerase inhibitor

1. Chan N, Bristow RG. *Clin Cancer Res* 2010:16;4553–4560; 2. Hegan DC *et al. PNAS* 2010;107:2201–2206

PAOLA-1: Olaparib + bevacizumab maintenance in all comers



*Bevacizumab: 15 mg/kg Q3W for 15 months

BID, twice daily; CR, complete response; CT, chemotherapy; NED, without evidence of disease; PD, progressive disease; PFS1, progression-free survival; PFS2, second progression-free survival; PR, partial response

1. ClinicalTrials.gov. NCT02477644 (accessed 03 October 2018); 2. Ray-Coquard IL *et al. J Clin Oncol* DOI: 10.1200/JCO.2017.35.15_suppl.TPS5605; 3. Gynecologic Cancer Intergroup. 2017. Available at: https://gciggroup.com/system/files/2017%20June%20SLIDES%20%20PAOLA-1-%20mai%202017.pdf (accessed 03 October 2018)

MITO-25: Phase II study evaluating bevacizumab and rucaparib with carboplatin-paclitaxel

FIGO Stage IIIb–IV high-grade serous, or endometrioid or clear cell ovarian cancer, primary peritoneal and/or fallopian tube cancer[1]

STRATIFICATION FACTORS[2]

- Residual tumour at primary surgery
- Stage of disease
- HRD status (*BRCA*-mutated vs HRD+)

N=216[2]

RANDOMISATION

1:1:1[1]

ARM A: Carboplatin–paclitaxel + bevacizumab 15 mg/kg Q3W for 22 cycles[2]

ARM B: Carboplatin–paclitaxel + bevacizumab 15 mg/kg for 22 cycles + **rucaparib** 600 mg BID Q4W until progression or unacceptable toxicity[2]

ARM C: Carboplatin–paclitaxel + rucaparib 600 mg BID Q4W until progression or unacceptable toxicity[2]

Primary Endpoints[1]

MTD
PFS

BID, twice daily; HRD, homologous recombination deficiency; MTD, maximum tolerated dose; PFS, progression-free survival

1. ClinicalTrials.gov. NCT03462212 (accessed 03 October 2018); 2. MITO 25. https://slideplayer.com/slide/10383586/ (accessed 03 October 2018)

The near horizon: Immunotherapy

First-line – Checkpoint inhibitor/Bev-based regimens

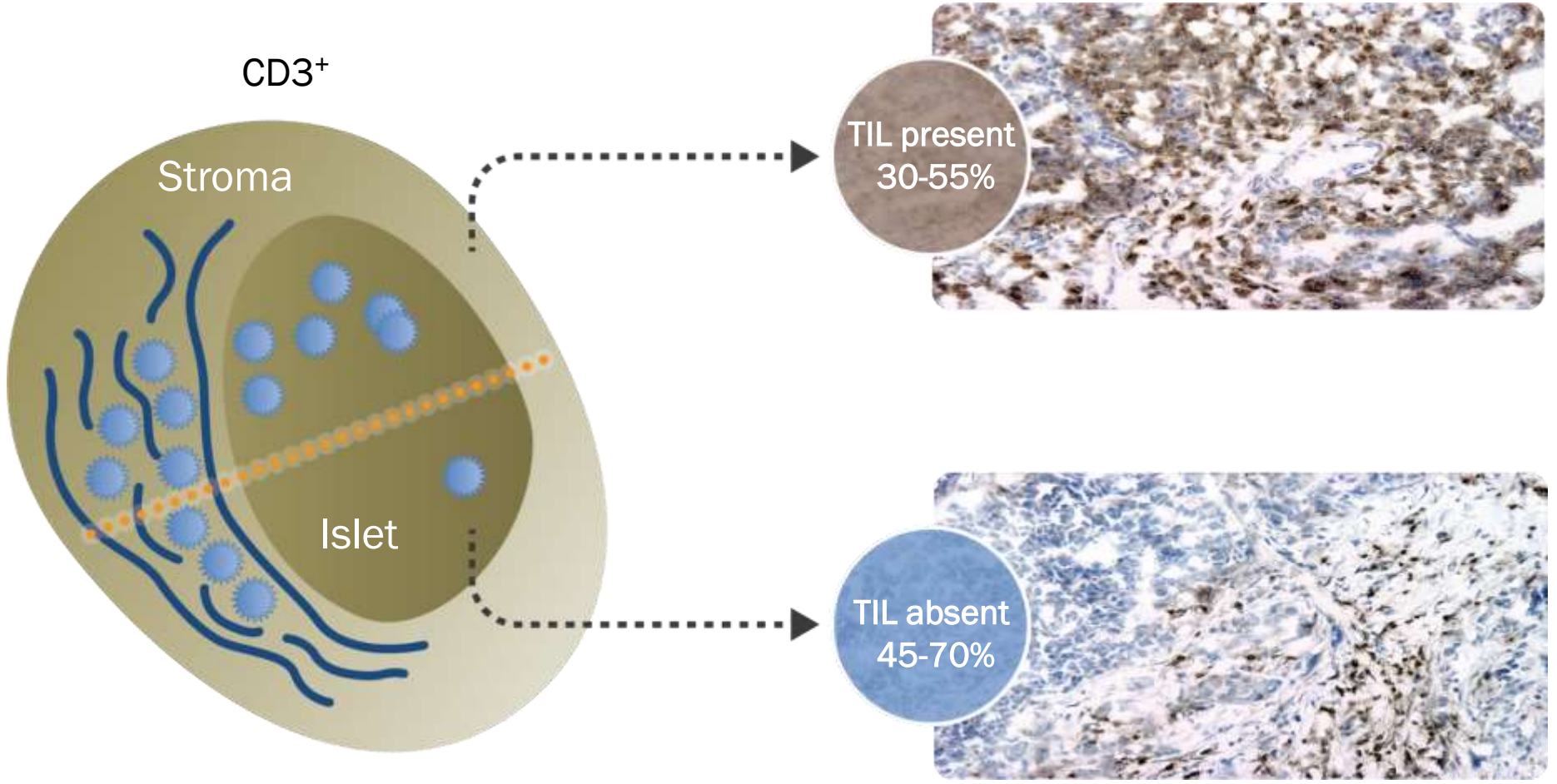
Carboplatin–paclitaxel +/- checkpoint inhibitor →	Checkpoint inhibitor maintenance	JAVELIN OVARIAN 100
Carboplatin–paclitaxel +/- checkpoint inhibitor–bev →	Checkpoint inhibitor + bev maintenance	ENGOT-ov39, IMagyn050

Resistant/refractory OC – Checkpoint inhibitor-based regimens

Checkpoint inhibitor monotherapy or in combination with liposomal doxorubicin	KEYNOTE-100, JAVELIN OVARIAN 200
Immunotherapy in combination with PARPi	TOPACIO/KEYNOTE-162

OC, ovarian cancer; PARPi, poly-ADP ribose polymerase inhibitor

Is there a role for immunotherapy in OC?



OC, ovarian cancer; TIL, tumour-infiltrating lymphocyte

Zhang L *et al. N Engl J Med* 2003;348:203–213

Anti-PD-L1/PD1 monotherapy data in recurrent OC

Therapeutic agent	Phase and trial name	N	Setting	ORR, n/N (%)
Pembrolizumab	II (KEYNOTE-100)[1]	378	ROC	(9)
Nivolumab	II (UMIN000005714)[2]	20[2]	PR ROC[3]	3/20 (15)[2]
Atezolizumab	I (PCD4989g)[4]	12[5]	PR ROC[5]	2/8 (25)[5]

PD-L1/PD-1 inhibitors demonstrate encouraging but modest activity in recurrent OC, suggesting an opportunity for combinations

OC, ovarian cancer; ORR, objective response rate; PR, platinum-resistant; ROC, recurrent ovarian cancer

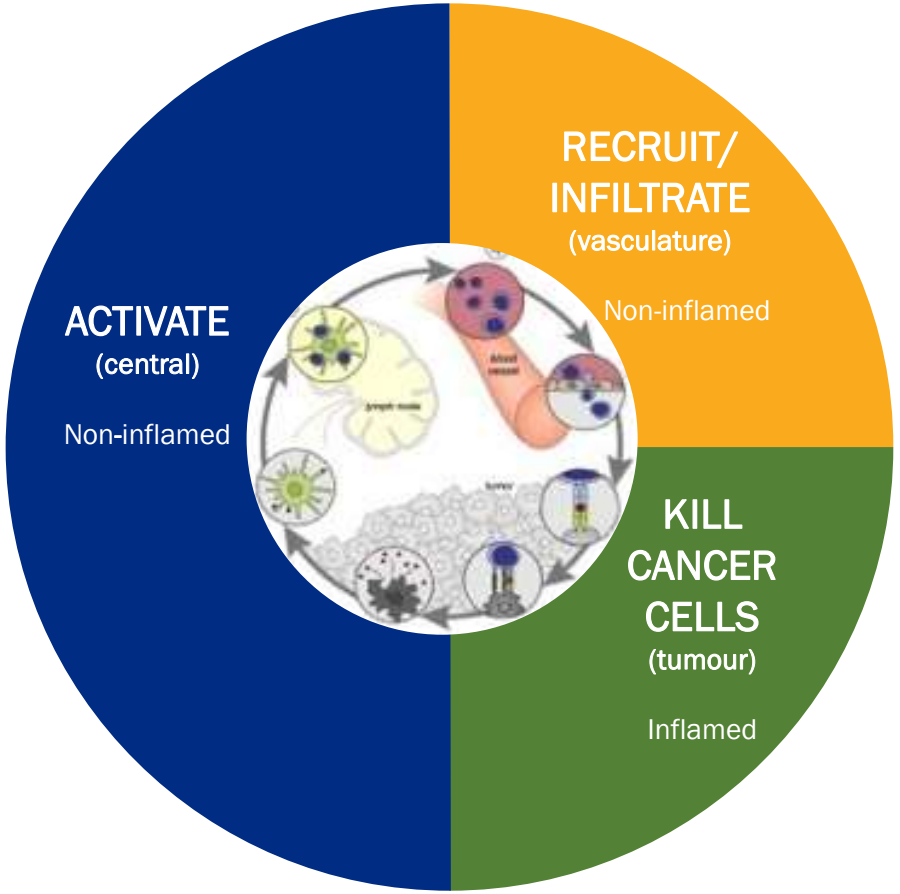
1. Matulonis U *et al. J Clin Oncol* 36, no. 15_suppl (May 20 2018) 5511–5511; 2. Hamanishi J *et al. J Clin Oncol* 33,no.15_suppl (May 20 2015) 5570–5570; 3. UMIN-CTR clinical trial. Available at: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000006754 (accessed 24 September 2018); 4. ClinicalTrials.gov. NCT01375842 (accessed 03 October 2018); 5. Infante JR *et al. Ann Oncol* 2016;27:296–312;abstract 871P

Combination opportunities in cancer immunotherapy

Enhance antigen presentation and T-cell activation

EGFR inhibitors
ALK inhibitors
BRAF inhibitors
MEK inhibitors
Chemotherapy
HDAC

Radiotherapy
Anti-CD40
IFN-g
Oncolytic viruses
Neo-epitope vaccine
Anti-CEA-IL2v
Anti-FAP-IL2v
Anti-OX40
Anti-CTLA4
Anti-CD27
Anti-41BB
PARPi



Increase T-cell trafficking and infiltration into tumours

Anti-VEGF

Block immunosuppression within the tumour microenvironment and enhance tumour cell death

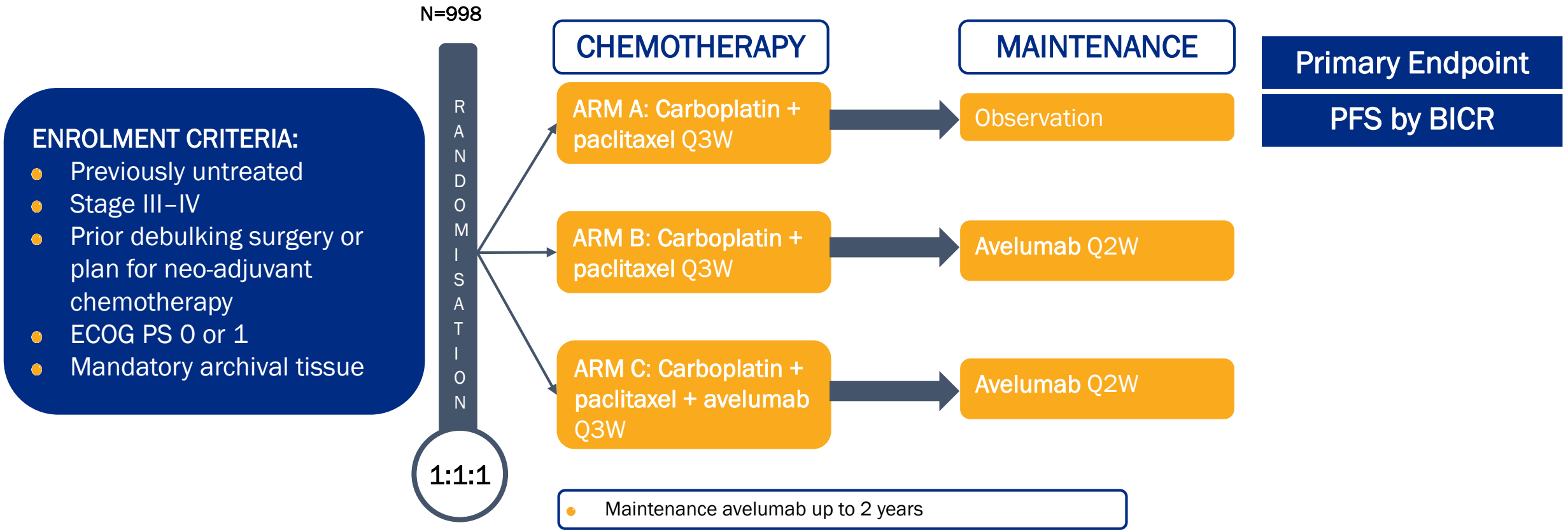
TCBs
ImmTACs
CAR-T
BiTes
Anti-PD-L1
Anti-PD1

Anti-CSF-1R
IDO inhibitors
Anti-TIGIT
Anti-TIM3
Anti-LAG3

Adapted from: Arend RC. Available at: https://www.fda.gov/downloads/Drugs/NewsEvents/UCM613064.pdf (accessed 03 October 2018)

JAVELIN OVARIAN 100: Avelumab platinum combo + maintenance in first-line

Randomised Phase III study



BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PFS, progression-free survival; PS, performance status

ClinicalTrials.gov. NCT02718417 (accessed 03 October 2018); Ledermann *et al. Int J Gynecol Cancer*. IGCS 2016; abstract 753

JAVELIN OVARIAN 200: Avelumab in platinum-resistant/ -refractory OC

Randomised Phase III study

ENROLMENT CRITERIA[1]:

- Platinum-resistant/-refractory disease (resistant: progression ≤6 months from last dose of platinum-based therapy; refractory: no response/progression to most recent platinum-based therapy)
- Up to 3 lines of systemic anti-cancer therapy for PS* disease, most recently platinum-containing, and no prior therapy for PR† disease

N=566[1]

RANDOMISATION

1:1:1[2]

Treatment until confirmed disease progression, unacceptable toxicity or withdrawal[2]

- **Avelumab** 10 mg/kg Q2W[1]
- **Pegylated liposomal doxorubicin** 40 mg/m^2 Q4W + **avelumab** 10 mg/kg Q2W[1]
- **Pegylated liposomal doxorubicin** 40 mg/m^2 Q4W[1]

Primary Endpoints[1]

OS
PFS by BICR

*Platinum-sensitive disease; †Platinum-resistant disease
BICR, blinded independent central review; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival
1. ClinicalTrials.gov. NCT02580058 (accessed 03 October 2018); 2. Pujade-Lauraine L *et al. Future Oncol* 2018;14:2103–2113

Immunotherapy and PARPi combination – A new strategy TOPACIO/KEYNOTE-162 (Phase I/II: pembrolizumab + niraparib): PROC cohort

- Response for ≥6 months to first-line platinum (but secondary platinum-refractory allowed)
- PROC or platinum-ineligible
- ≤5 prior treatment lines

Niraparib 200 mg + **pembrolizumab** 200 mg Q3W

Primary Endpoint

ORR (RECIST v1.1)

Baseline characteristics	N=62
Prior bevacizumab	39 (63%): 7 first-line, 24 ROC, 8 both
Platinum status	21% ineligible, 50% resistant, 29% refractory
t*BRCA* status	19% mutant, 77% wild-type
HRD status	39% positive, 52% negative
PD-L1 status	57% positive, 34% negative

HRD, homologous recombination deficiency; ORR, objective response rate; PARPi, poly-ADP ribose polymerase inhibitor; PROC, platinum-resistant ovarian cancer; ROC, recurrent ovarian cancer

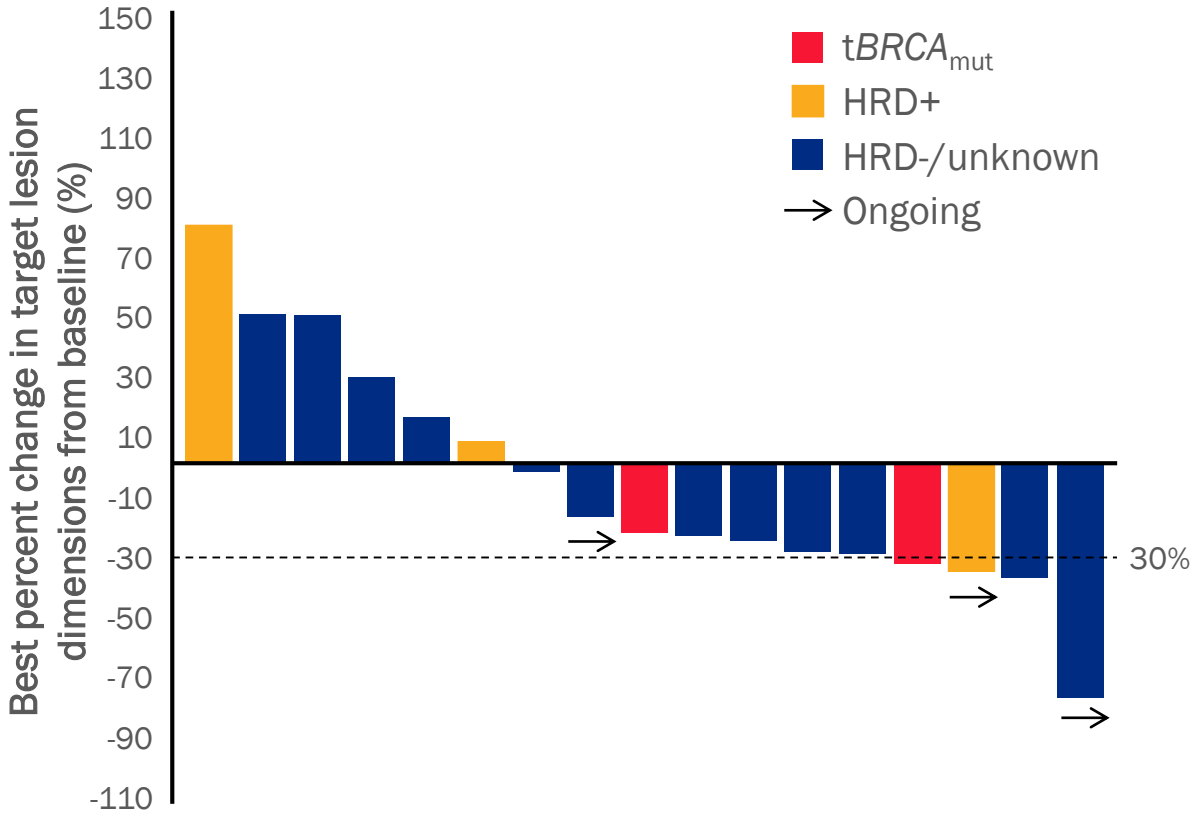
Konstantinopoulos PA *et al. J Clin Oncol* 36, no. 15_suppl (May 20 2018) 106–106

TOPACIO (platinum-resistant/-refractory subgroup, n=47)

Response, n (%)	All (n=47)	t*BRCA*$_{mut}$ (n=8)	HRD+ (n=16)	t*BRCA*$_{wt}$ (n=37)	HRD- (n=26)
ORR	11 (23)	2 (25)	4 (25)	9 (24)	7 (27)
DCR	30 (64)	5 (63)	11 (69)	24 (65)	15 (58)

- Similar ORR irrespective of HRD and t*BRCA* in platinum-resistant/-refractory subgroup

24% ORR in platinum-refractory OC (n=17)



DCR, disease control rate (defined as responses + stable disease); HRD, homologous recombination deficiency; OC, ovarian cancer; ORR, objective response rate

Konstantinopoulos PA *et al. J Clin Oncol* 36, no. 15_suppl (May 20 2018) 106–106

Combination of immunotherapy and PARPi: New Phase III trials

- JAVELIN Ovarian PARP 100[1]
  - Avelumab
  - Talazoparib
- FIRST (Gineco, ENGOT-ov44)[2]
  - TSR - 042
  - Niraparib
- DUO (AGO, ENGOT-ov46)[3]
  - Durvalumab
  - Olaparib
- Athena (MRC, ENGOT-ov45)[4]
  - Nivolumab
  - Rucaparib
- BGOG (ENGOT-ov43)[3]
  - Pembrolizumab
  - Olaparib

More than 4000 patients

PARPi, poly-ADP ribose polymerase inhibitor

1. ClinicalTrials.gov. NCT03642132 (accessed 03 October 2018); 2. Clinicaltrials.gov. NCT03602859 (accessed 03 October 2018); 3. ENGOT. Available at: https://engot.esgo.org/clinical-trials/current-clinical-trials/ovarian/ (accessed 24 September 2018); 4. Clinicaltrials.gov. NCT03522246 (accessed 03 October 2018)

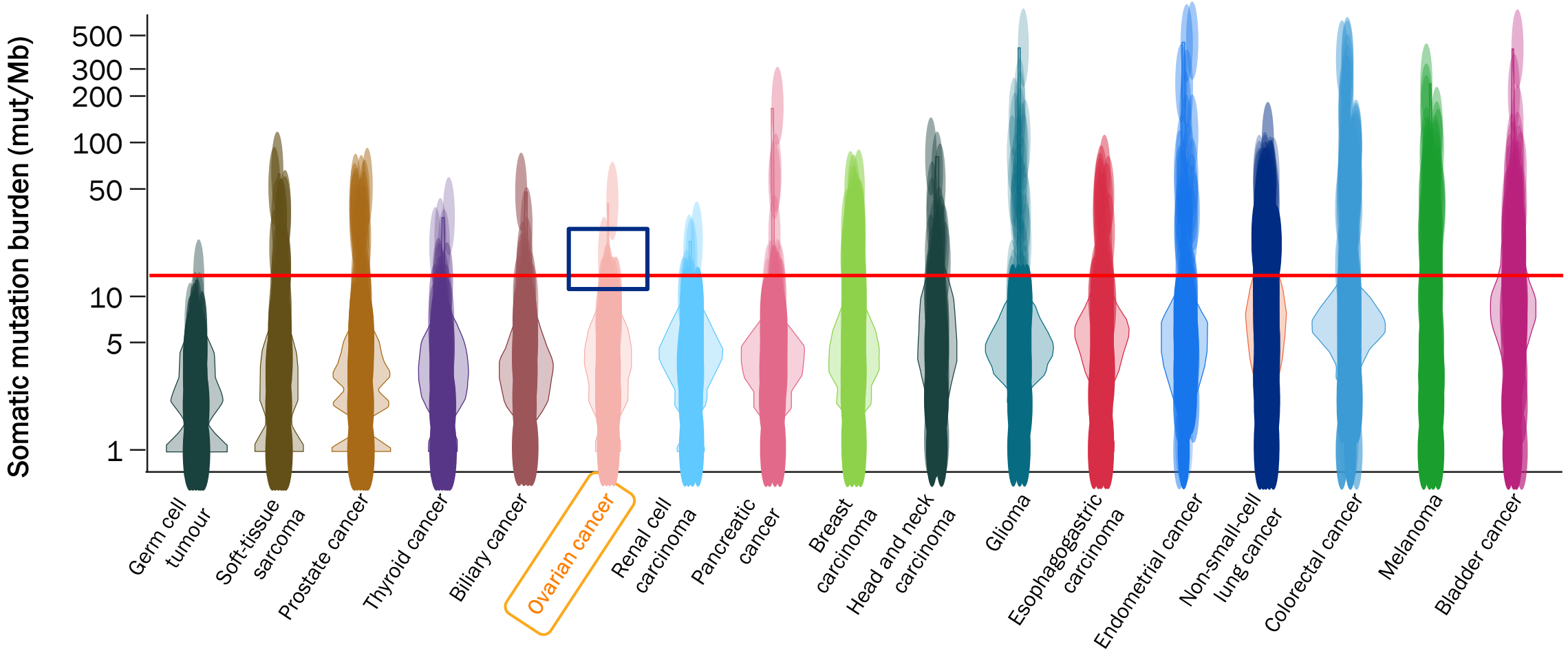
Combination of immunotherapy and PARPi

The new war!

- HRD/DDR correlated with genetic instability
- Mutations correlated with TILs
- Possible synergism

HRD, homologous recombination deficiency; PARPi, poly-ADP ribose polymerase inhibitor; TIL, tumour-infiltrating lymphocyte

OC carries significant levels of mutational load

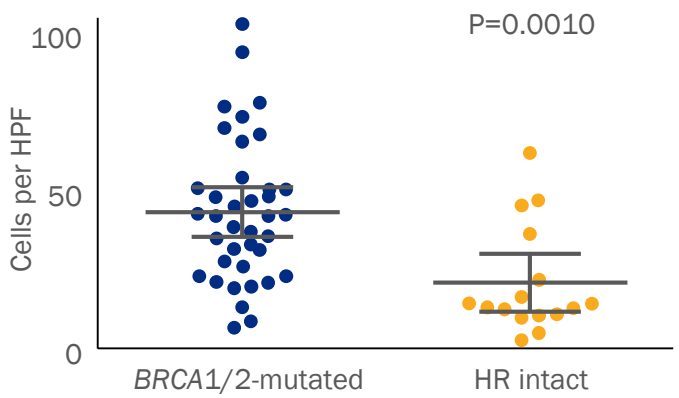


Red line indicates the threshold for samples with a high mutation burden (13.8 mutations/Mb). OC, ovarian cancer; Mb, megabase

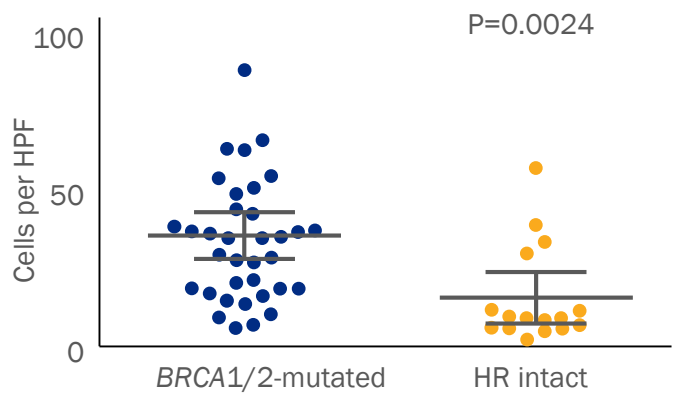
Zehir A *et al. Nat Med* 2017;23:703–713

HRD status and infiltrating lymphocytes

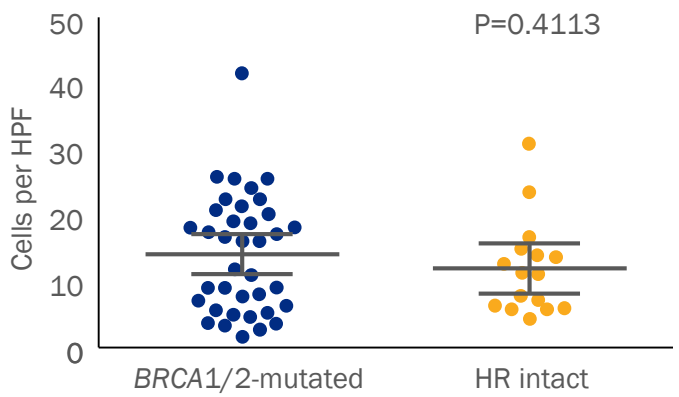
CD3+ intraepithelial lymphocytes



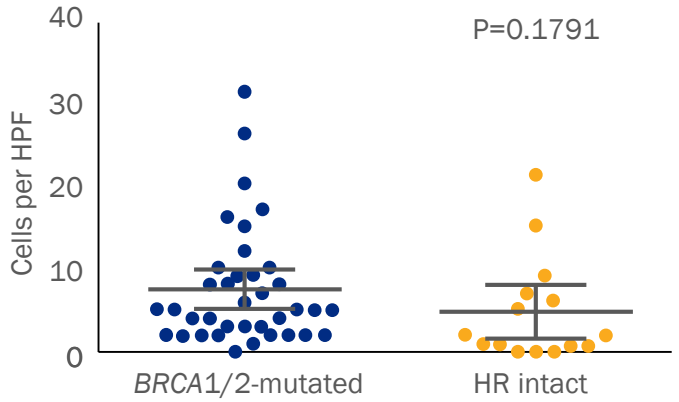
CD8+ intraepithelial lymphocytes



CD4+ intraepithelial lymphocytes



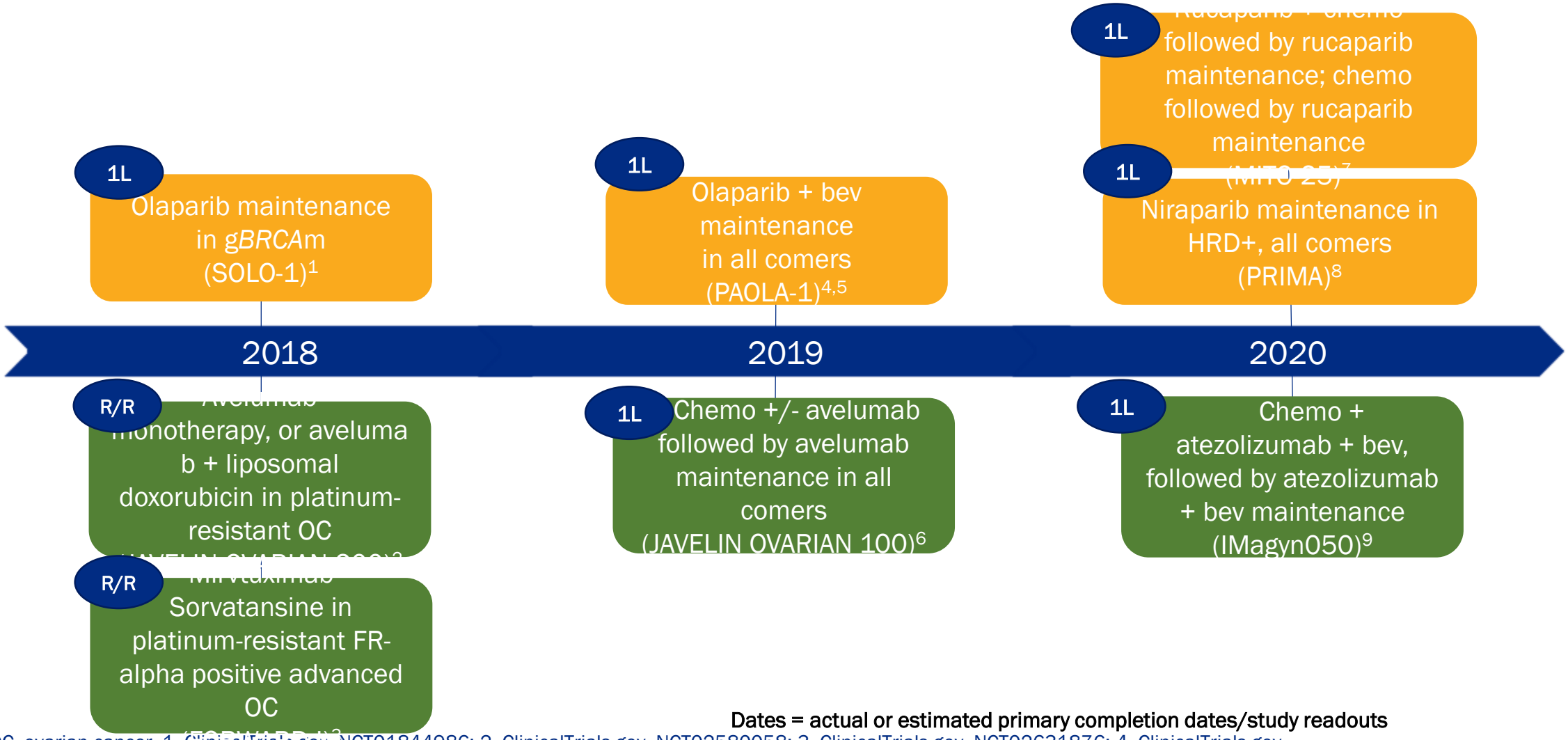
CD20+ intraepithelial lymphocytes



HPF, high power field; HR, homologous recombination; HRD, homologous recombination deficiency

Strickland KC *et al. Oncotarget* 2016;7:13587–13598

New concepts under assessment: What is on the near horizon?



Dates = actual or estimated primary completion dates/study readouts

OC, ovarian cancer. 1. ClinicalTrials.gov. NCT01844986; 2. ClinicalTrials.gov. NCT02580058; 3. ClinicalTrials.gov. NCT02631876; 4. ClinicalTrials.gov. NCT02477644; 5. AstraZeneca Press Release. 2018. Available at: https://www.astrazeneca.com/media-centre/press-releases/2018/lynparza-significantly-delays-disease-progression-in-phase-iii-1st-line-solo-1-trial-for-ovarian-cancer.html; 6. ClinicalTrials.gov. NCT02718417; 7. ClincalTrials.gov. NCT03462212; 8. ClinicalTrials.gov. NCT02655016; 9. ClinicalTrials.gov. NCT03038100

Summary

- Solo1 data represent a new standard for BRCA mutated patients
- PARPi standard of care as maintenance after CT in the recurrence
- Many new promising strategies are under evaluation in OC
- Immunotherapy alone in the recurrent setting is unsatisfactory
- Combination of immunotherapy with chemotherapy, PARPi and bevacizumab promises to change the treatment landscape in OC

OC, ovarian cancer; PARPi, poly-ADP ribose polymerase inhibitor