INSTITUT JULES BORDET

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BSMO

12thBelgian Symposium on the
Integration of Molecular Biology
Advances into Oncology Clinical Practice

Ovarian cancer : therapeutic news

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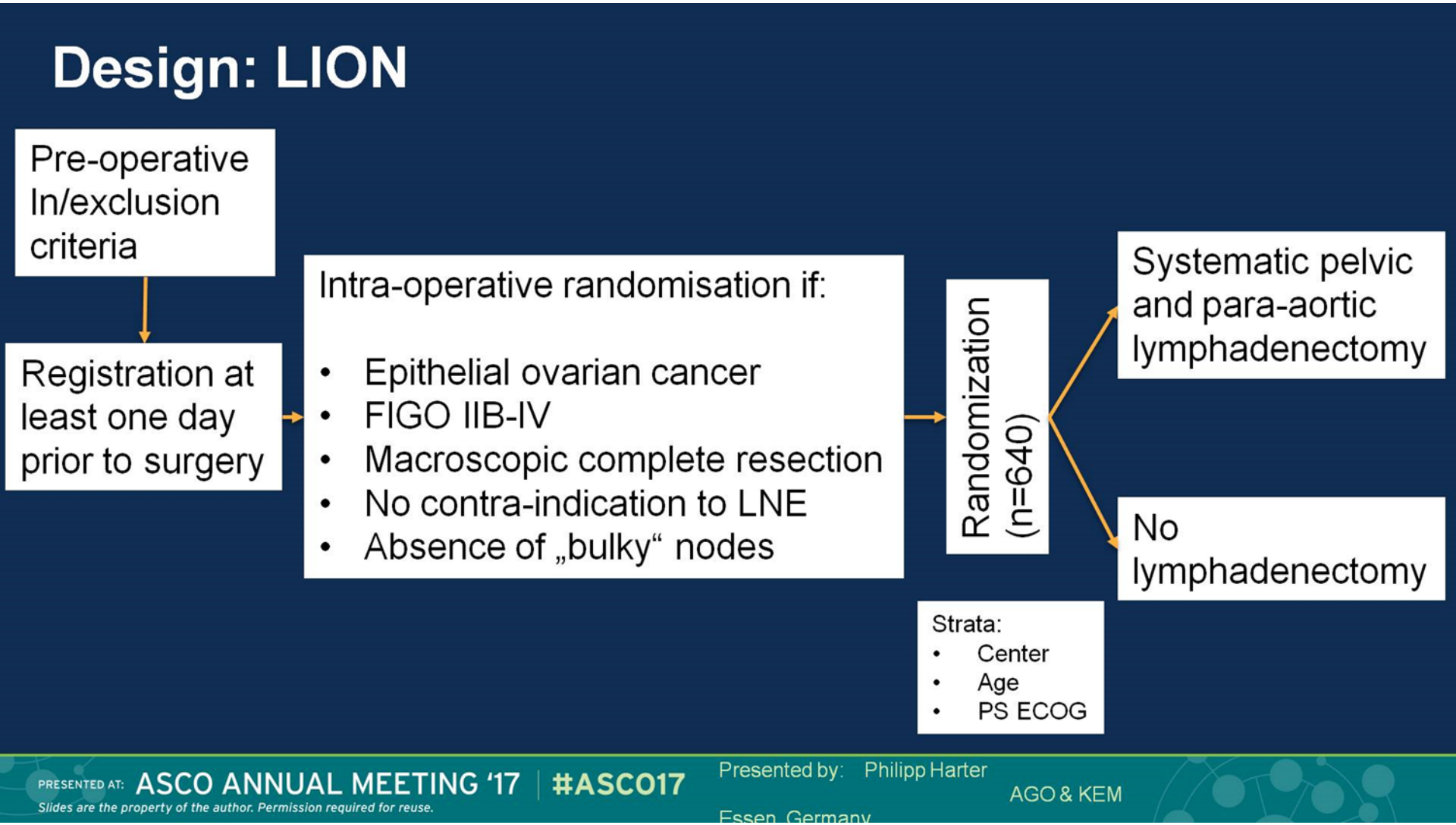
First-line therapy

- Lymphadenectomy
- Intraperitoneal chemotherapy
- HIPEC
- **PARP inhibitor as maintenance therapy in BRCAm OVCA**

Lymphadenectomy in ovarian neoplasms
LION



P. Harper et al., ASCO 2017, abstr.5500

Lymphadenectomy in ovarian neoplasms LION

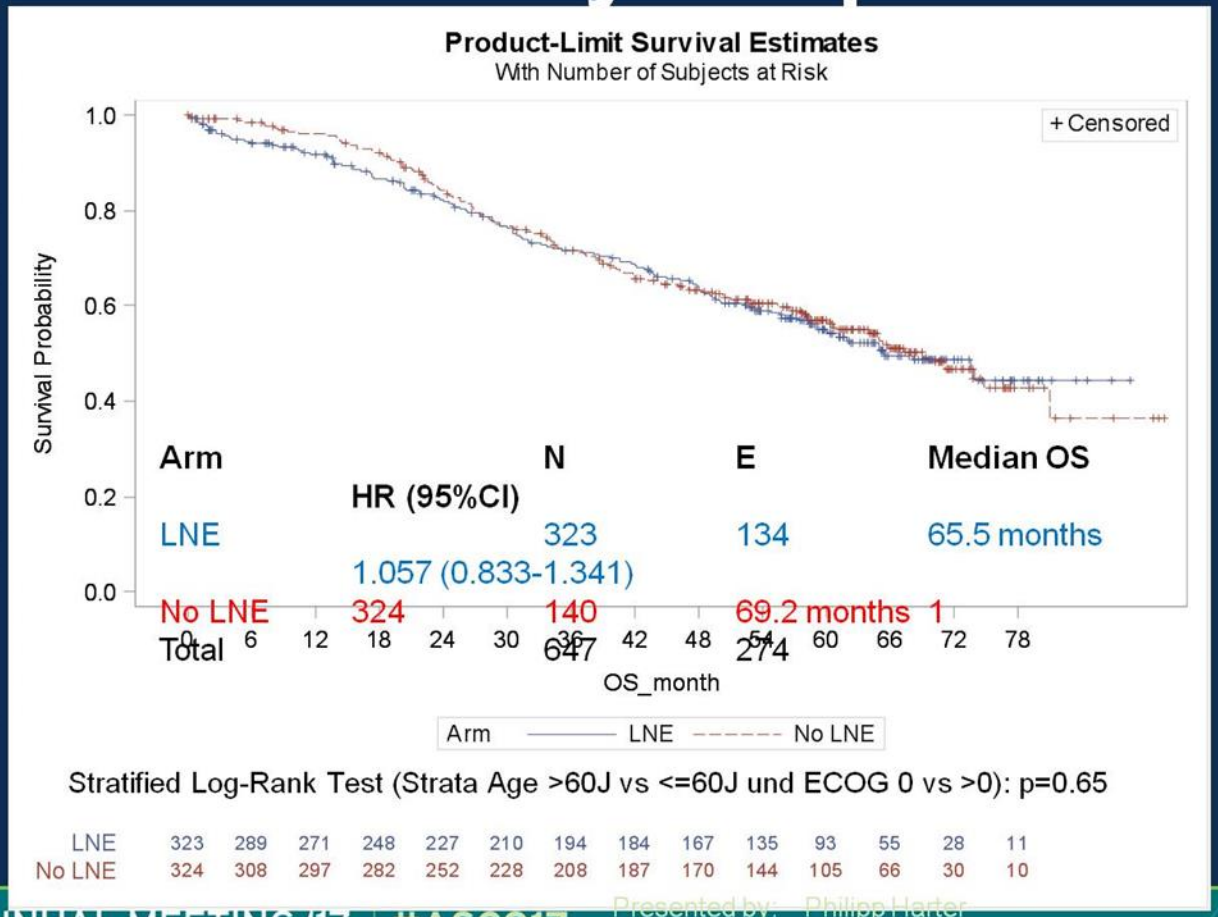
	+ LNE	- LNE	p
N pts	323	324	
complete resection	99,4%	99,4%	0,99
LN metastases	55,7%		
Infections	25,8%	18,6%	0,03
aΣ lymph cysts	4,4%	0,3%	< 0,001
Σ lymph cysts	3,1%	0%	< 0,001
60-day mortality	3,1%	0,9%	0,049

- ↑ duration of surgery
- ↑ blood loss
- ↑ transfusions
- ↑ intermediate/intensive care unit

P. Harper et al., ASCO 2017, abstr.5500

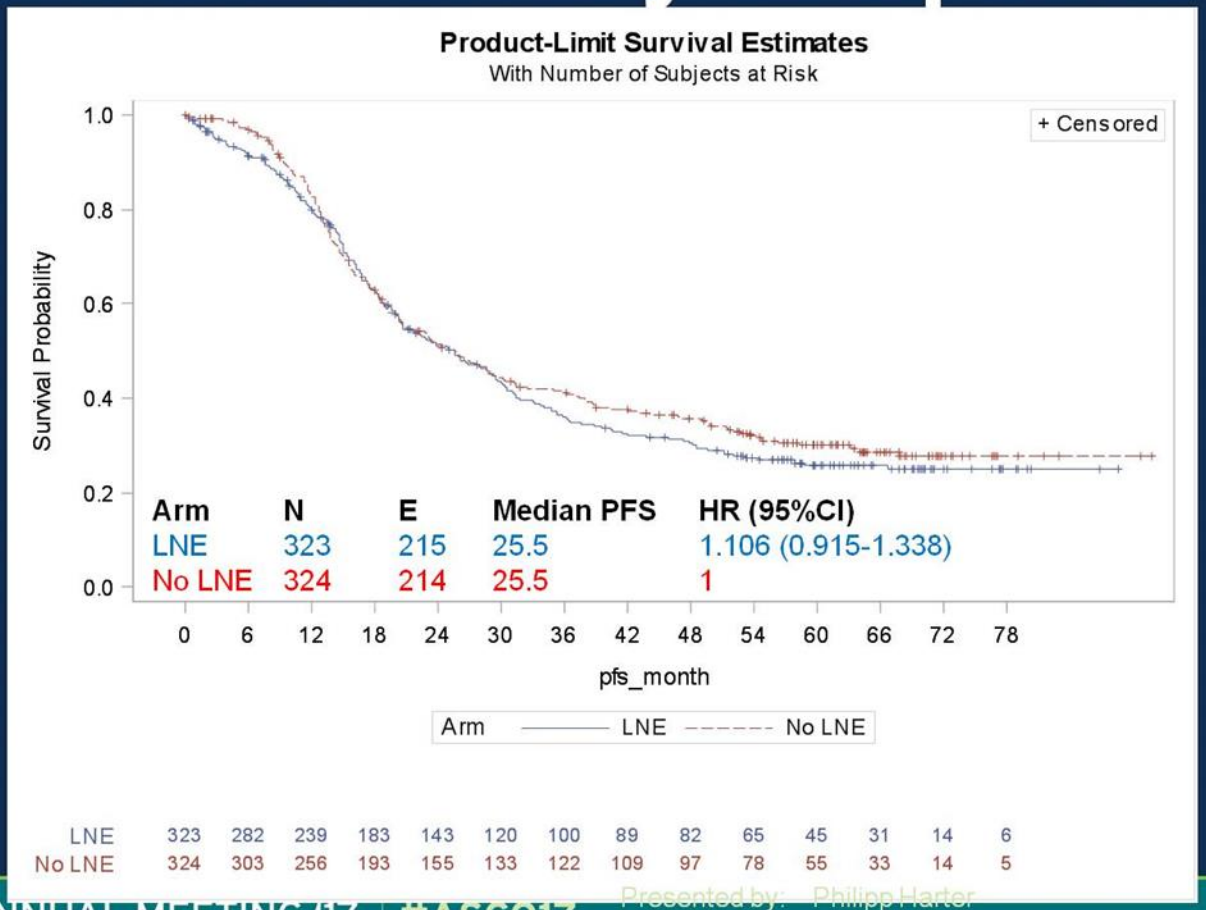
Lymphadenectomy in ovarian neoplasms
LION

LION: Primary endpoint OS



Lymphadenectomy in ovarian neoplasms
LION

LION: Secondary endpoint PFS



IV/IP chemotherapy in ovarian cancer – Study comparisons for PFS

Table 1. IV/IP chemotherapy in ovarian cancer - study comparisons for PFS.

Arm study	Median PFS (months)		Median PFS (months)	
	N	No visible disease stage III	N	≤ 1 cm visible disease
GOG114&172 IV cisplatin	117	33.4		
GOG114&172 IP cisplatin	125	43.2		
GOG172 IV cisplatin	75	43.2		18.3
GOG172 IP cisplatin	78	60.4		23.8
GOG252 IV carboplatin	297	31.3	461	26.8 (10% st. II)
GOG252 IP carboplatin	297	31.8	464	28.7 (10% st. II)
GOG252 IP cisplatin	304	33.8	456	27.8 (10% st. II)

HIPEC in first-line ovarian cancer: hope or hype?

Randomised, open-label phase III trial

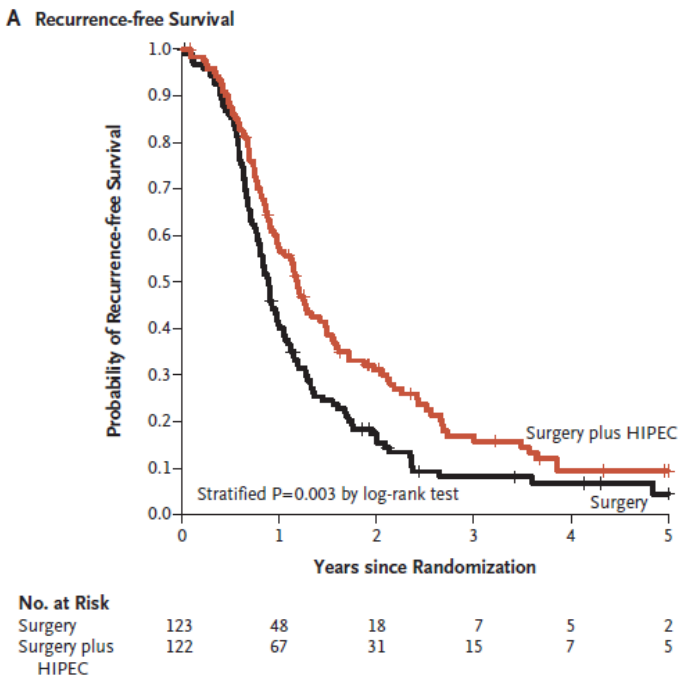
- 245 patients with stage III (FIGO) ovarian carcinoma
- Carboplatin-Paclitaxel (CP) x 3 → IDS +/- HIPEC – CP x3
- Median follow-up 4,7 years

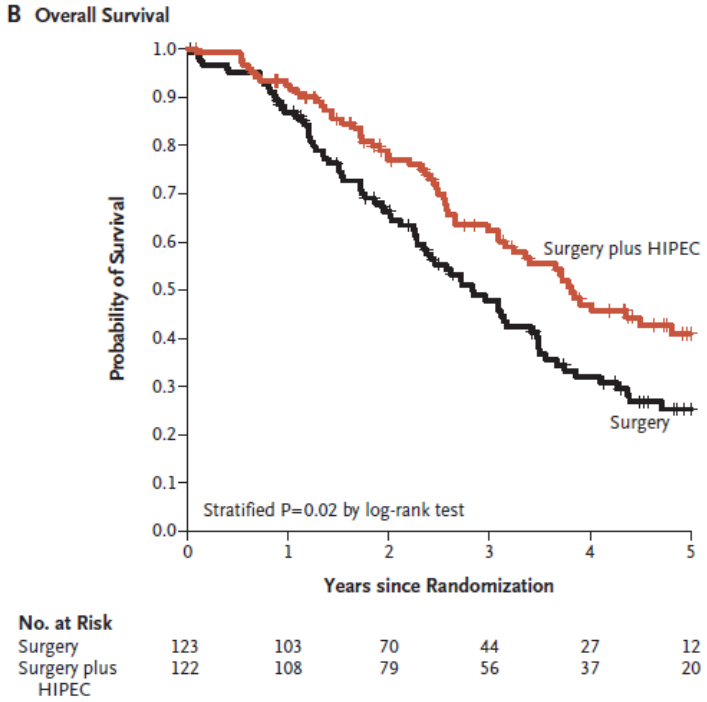
	+ HIPEC*	- HIPEC	p value
N pts	122	123	
Recurrence	81%	89%	
m RFS	14,2 mos	10,7 mos	0,003
Deaths	50%	61%	
mOS	45,7 mos	33,9 mos	0,02
63-4 toxicity	27%	25%	0,76

* Cisplatin + sodium thiosulfate

WJ Van Driel, NEJM 2018, 328, 230-240

HIPEC in first-line ovarian cancer



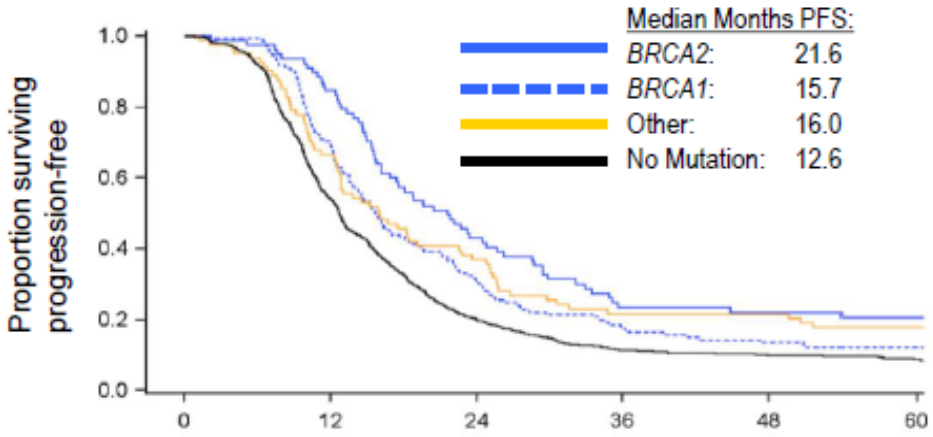


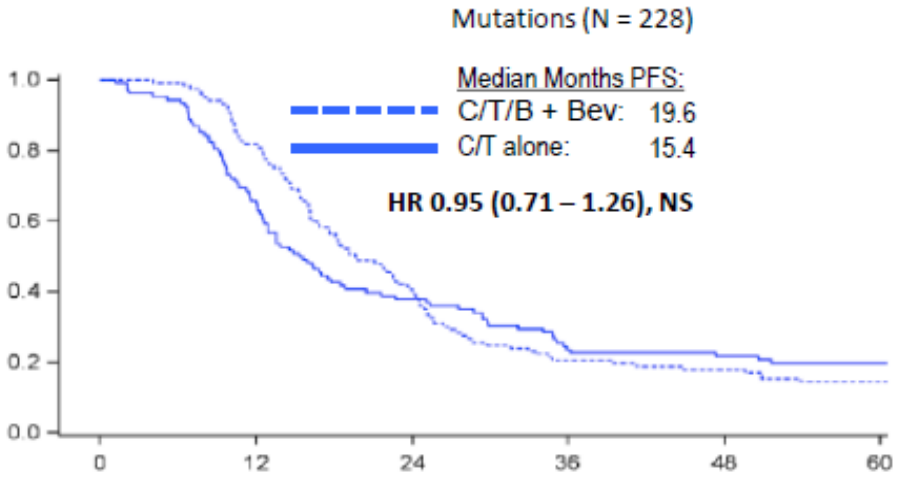
The addition of HIPEC to interval cytoreductive surgery resulted in:

- longer recurrence-free survival
- longer overall survival
- did not result in higher rate of side effects

This trial is a first step, but should not drive changes in practice yet

GOG-218: Carboplatin-Paclitaxel vs Carboplatin-Paclitaxel-Bevacizumab + Bevacizumab maintenance





BRCA1/2 mutation:

better prognosis (outcome)

no benefit for Bevacizumab

SOLO-1 phase III trial:

maintenance olaparib
in 1st line advanced ovarian cancer
responding to platinum and a BRCA mutation

Study design

- 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)

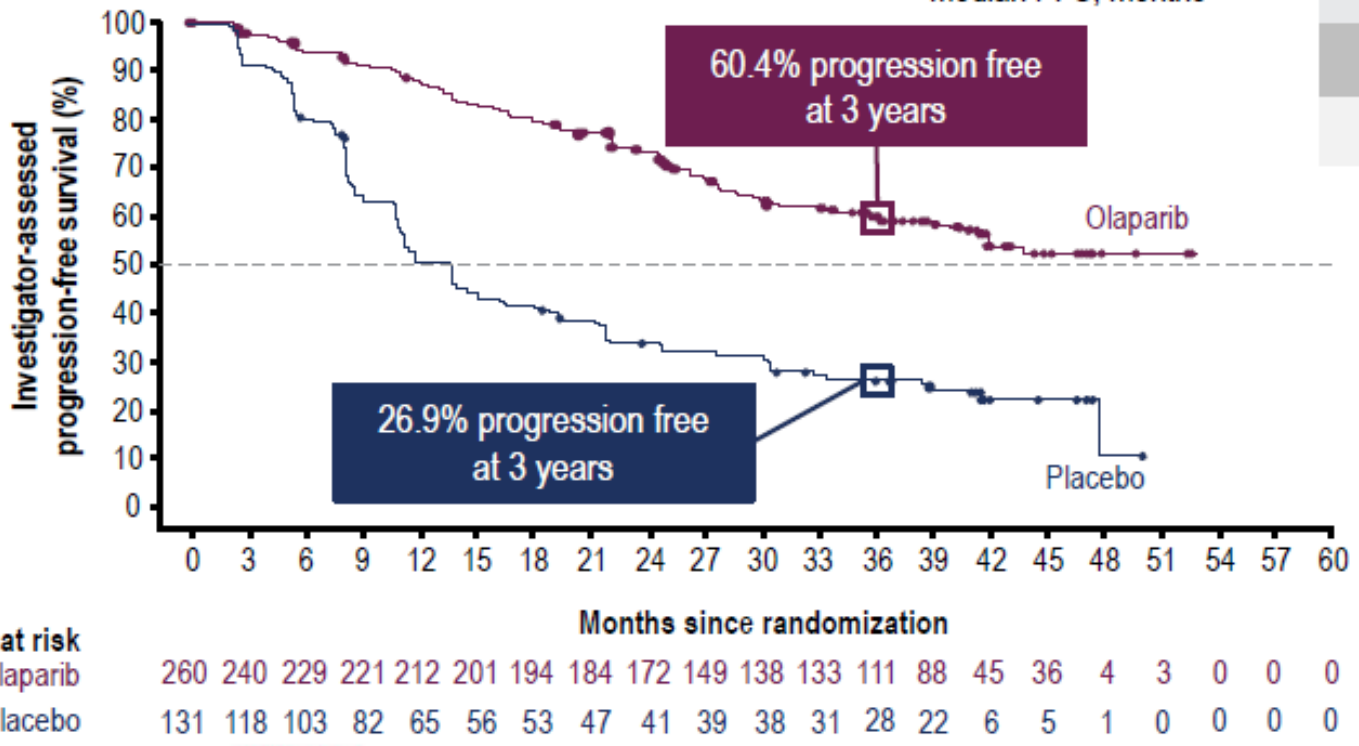
*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease.
BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; FACT-O, Functional Assessment of Cancer Therapy – 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

MUNICH 2018 ESMO congress

K. Moore et al., ESMO 2018, abstr. LBA7_PR, NEJM 21 oct 2018

SOLO-1 phase III trial : maintenance olaparib in advanced ovarian cancer and a BRCA mutation

PFS by investigator assessment



Olaparib (N=260)	Placebo (N=131)
102 (39.2)	96 (73.3)
NR	13.8
HR 0.30	
95% CI 0.23, 0.41; *P*<0.0001	

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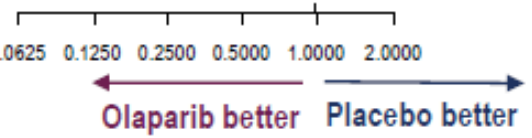
CI, confidence interval; NR, not reached

SOLO-1 phase III trial : maintenance olaparib in advanced ovarian cancer and a BRCA mutation

PFS subgroup analysis

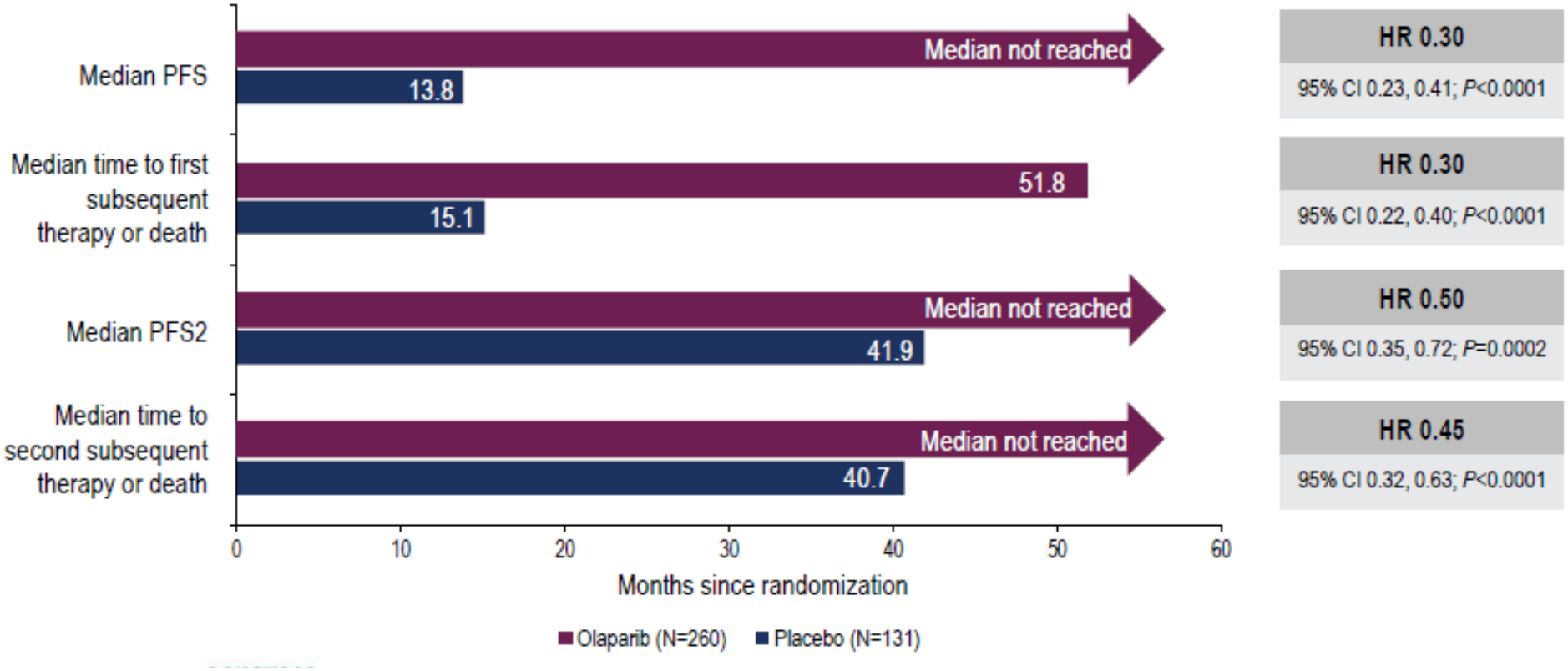
Subgroup	Olaparib 300 mg bd Number of patients with events/total number of patients (%)	Placebo bd Number of patients with events/total number of patients (%)	HR (95% CI)
All patients	102/260 (39.2)	96/131 (73.3)	0.30 (0.23, 0.41)
Response after surgery/platinum-based chemotherapy			
Clinical complete 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)



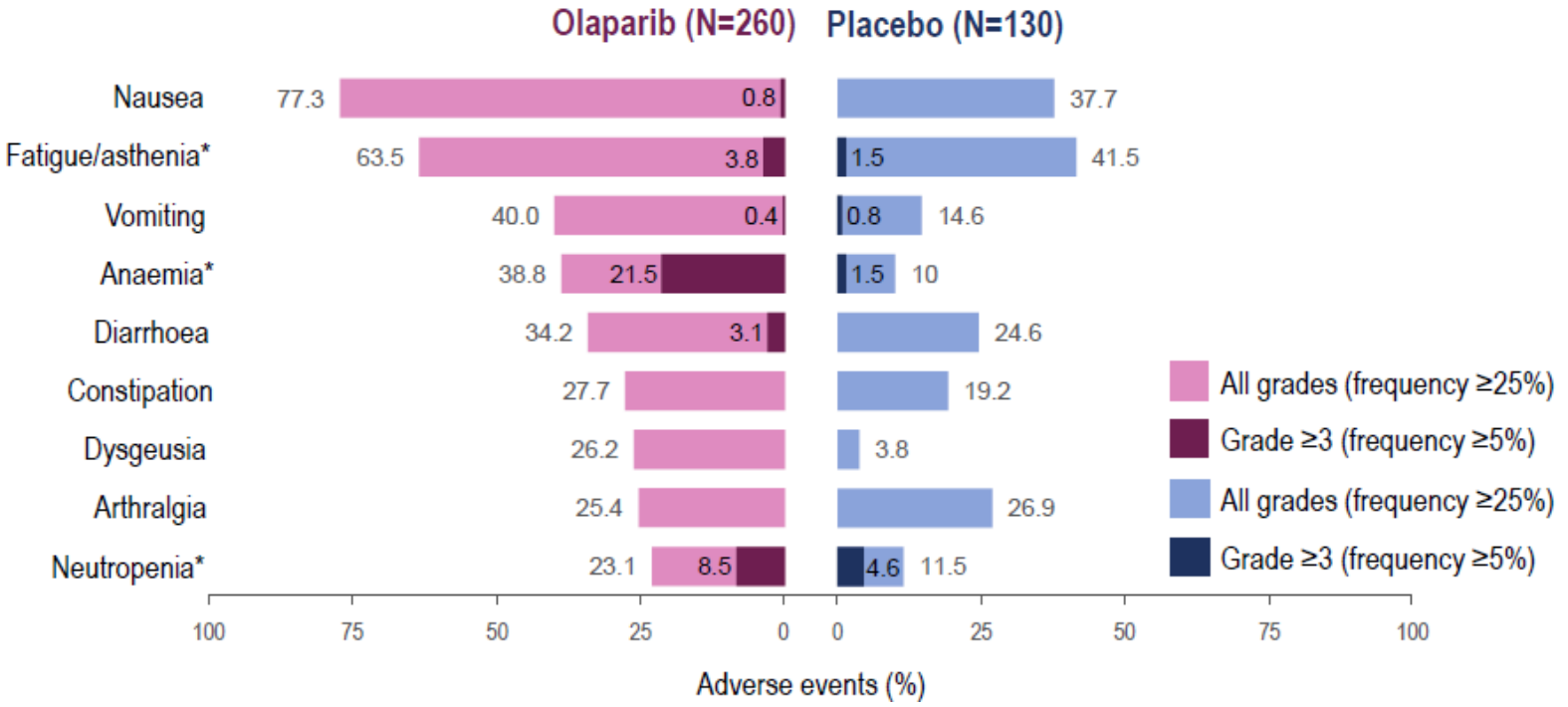
ULN, upper limit of normal

SOLO-1 phase III trial : maintenance olaparib in advanced ovarian cancer and a BRCA mutation

Summary of efficacy endpoints



Most common treatment-emergent adverse events



	Olaparib (N=260)	Placebo (N=130)
All-grade TEAEs, n (%)	256 (98.5)	120 (92.3)
Grade ≥3 TEAEs, n (%)	102 (39.2)	24 (18.5)
Serious TEAEs, n (%)	54 (20.8)	16 (12.3)
TEAEs leading to dose interruption, n (%)	135 (51.9)	22 (16.9)
TEAEs leading to dose reduction, n (%)	74 (28.5)	4 (3.1)
TEAEs leading to discontinuation, n (%)	30 (11.5)	3 (2.3)
Median (range) duration of treatment, months	24.6 (0–52.0)	13.9 (0.2–45.6)

SOLO-1 phase III trial:

maintenance olaparib
in 1st line advanced ovarian cancer
responding to platinum and a BRCA mutation

Conclusions

- Maintenance olaparib led to a substantial, unprecedented improvement in PFS in patients with newly diagnosed, advanced ovarian cancer and a *BRCA*m, with a difference in median PFS for olaparib versus placebo of approximately 3 years
  - There was no obvious change in Kaplan-Meier curves after 2 years in the olaparib group, indicating an apparent enduring treatment benefit after stopping treatment
- There was a statistically significant improvement in PFS2, suggesting that olaparib did not diminish patients' ability to benefit from subsequent therapy
- Olaparib was generally well tolerated, with a safety profile consistent with that observed in the relapsed disease setting
- Maintenance olaparib should be considered standard treatment following platinum-based chemotherapy for women with newly diagnosed, advanced ovarian cancer and a *BRCA*m

Second and further therapy lines

- Role of secondary cytoreductive surgery
- PARP inhibitors
- Immunotherapy
- Combinations

Impact of secondary cytoreductive surgery [AGO DESKTOP III, (GOG-213)]

- **in platinum-sensitive recurrence in ovarian cancer**
- **Predictive AGO score:**

  PFI > 12 months, good PS (0-1), complete resection in1st line, ascites < 500 mL

	No surgery	Surgery	HR	p
N pts.	203	204		
G 2/3 serous	77,3%	83,8%		
Prior Pt + Pacl	89,7%	93,6%		
PFI > 12 months	74,9%	76,0%		
median PFI	18,7 months	21,1 months		
Compl. resection		72,5%		
median PFS	14,0 months	19,6 months	0,66 (0,52-0,85)	< 0,001
TFST	13,9 months	21,0 months	0,61 (0,48-0,77)	< 0,001

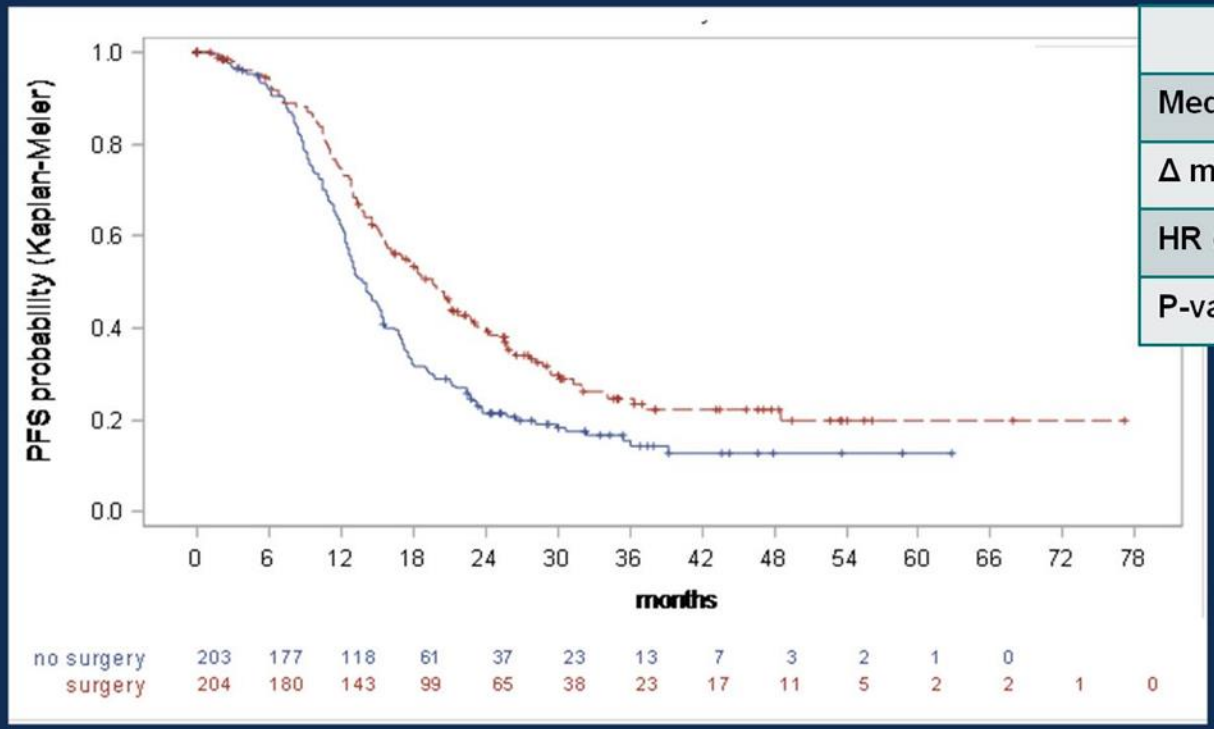
- No major postoperative complications
- Adverse events not significantly different
- Benefit only in case of complete resection
- Awaiting overall survival data

A. du Bois et –al., ASCO 2017, abstr.5501

Impact of secondary cytoreductive surgery (AGO DESKTOP III, GOG-213)

AGO DESKTOP III: Outcome 2 (PFS, ITT population)

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)



	Surgery	No surgery
Median PFS	19.6 mos	14.0 mos
Δ median PFS	5.6 mos	
HR (95% CI)	0.66 (0.52 – 0.83)	
P-value	< 0.001	

296 (73%) PFS events

Phase III experience with PARP inhibitors as maintenance after induction chemotherpy

	SOLO-2 [1]	NOVA [2]	ARIEL-3 [3]
Population	gBRCA^{mut}	I: gBRCA^{mut} II: Non-gBRCA HGSOC	HGSOC or endometrioid
Design	Phase III	Phase III	Phase III
Regimen	Olaparib vs placebo	Niraparib vs placebo	Rucaparib vs placebo
Primary endpoint	PFS	PFS	PFS
N (randomization)	295 (2:1)	469 (2:1)	540 (2:1)

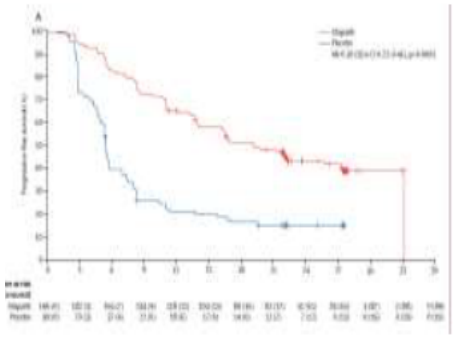
Pujade-Lauraine E et al. Lancet Oncol 2017; 18(9): 1382-1392
Mirza MR et al. N Engl J Med 2016; 375: 2154-2164
Coleman LR et al. Lancet 2017

PARPi are highly effective in BRCAmut patients

Olaparib

gBRCA mut

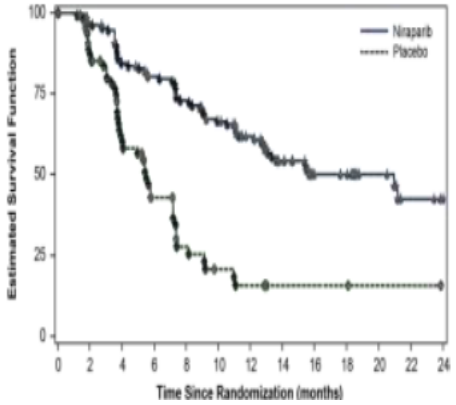
19.3 *vs* 5.5 months (HR 0.27)



Niraparib *

gBRCA mut

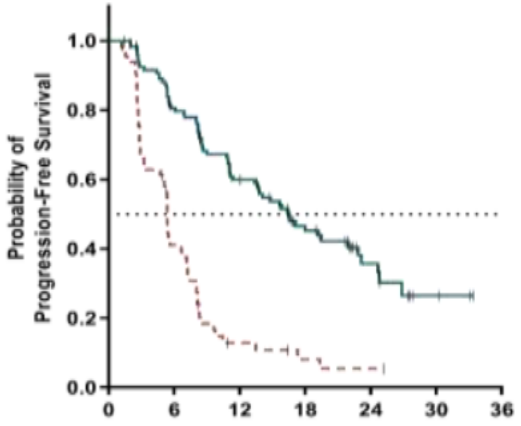
21 *vs* 5.5 months (HR 0.27)



Rucaparib

gBRCA mut

16.6*vs* 5.4 months (HR 0.27)



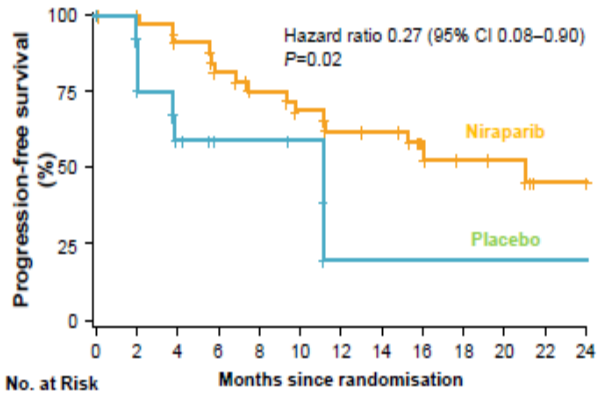
From Pignata S., Biological implications for Clinical practice in ovarian cancer. ESMO discussion

NOVA (Niraparib) exploratory analysis
PFS in BRCA*wild-type* subgroups

HRD positive

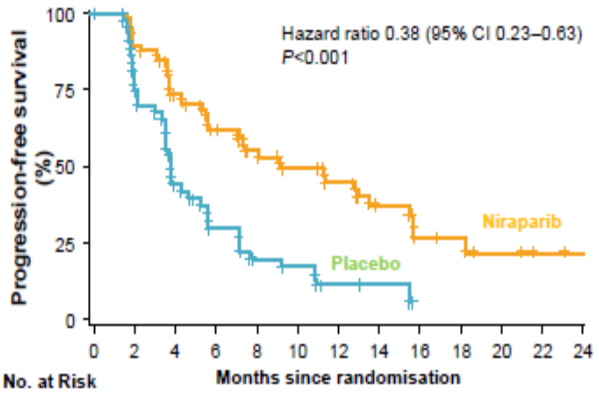
s*BRCA* mut (n=47)

	Niraparib (n=35)	Placebo (n=12)
PFS median (95% CI) (Months)	**20.9** (9.7–NR)	**11.0** (2.0–NR)
Hazard ratio (95% CI); *P* value	0.27 (0.081–0.903); *P*=0.0248	
% of patients without progression or death at 12 mo	62%	19%
% of patients without progression or death at 18 mo	**52%**	19%



BRCA wt (n=115)

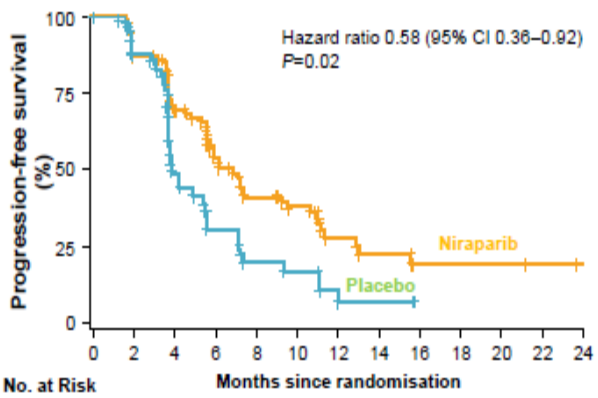
	Niraparib (n=71)	Placebo (n=44)
PFS median (95% CI) (Months)	**9.3** (5.8–15.4)	**3.7** (3.3–5.6)
Hazard ratio (95% CI); *P* value	0.38 (0.231–0.628); *P*=0.0001	
% of patients without progression or death at 12 mo	45%	11%
% of patients without progression or death at 18 mo	**27%**	6%



HRD negative

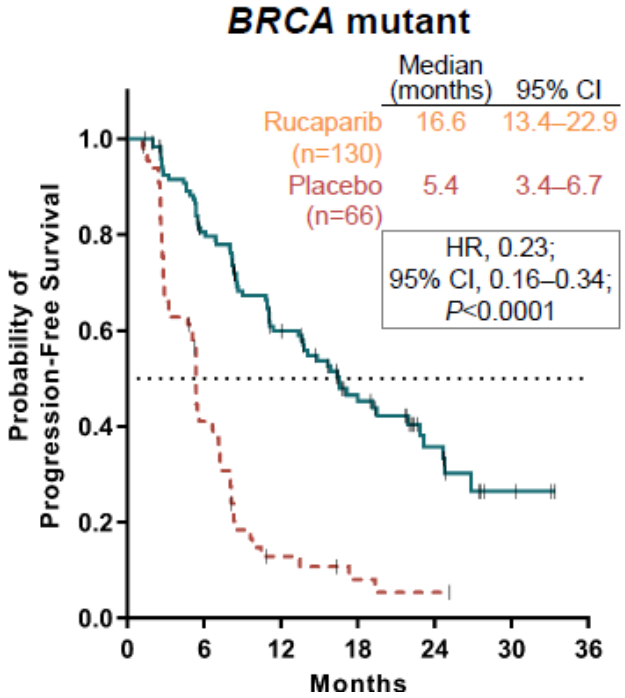
(n=134)

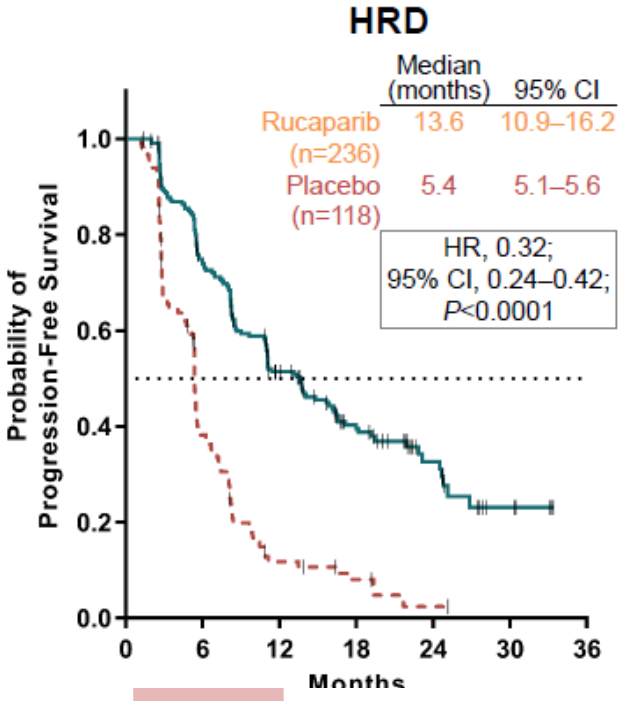
	Niraparib (n=92)	Placebo (n=42)
PFS median (95% CI) (Months)	**6.9** (5.6–9.6)	**3.8** (3.7–5.6)
Hazard ratio (95% CI); *P* value	0.58 (0.361–0.922); *P*=0.0226	
% of patients without progression or death at 12 mo	27%	7%
% of patients without progression or death at 18 mo	**19%**	7%

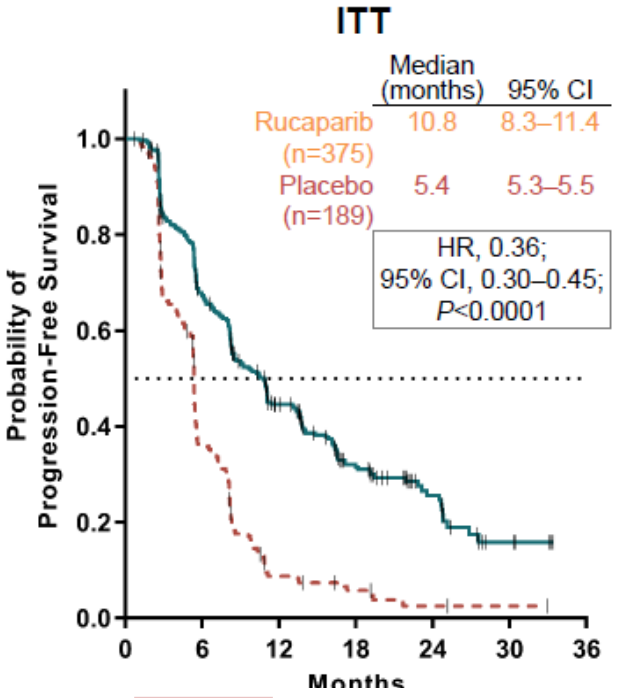


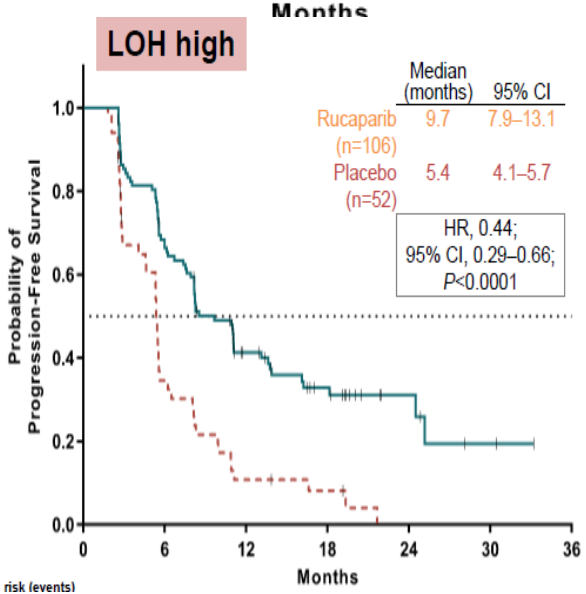
Mirza MR et al. New Engl J Med 2016; 375(22): 2154-2164
Mirza MR et al. Ann Oncol 2016; 27(suppl 6): abstr. LBA3_PR

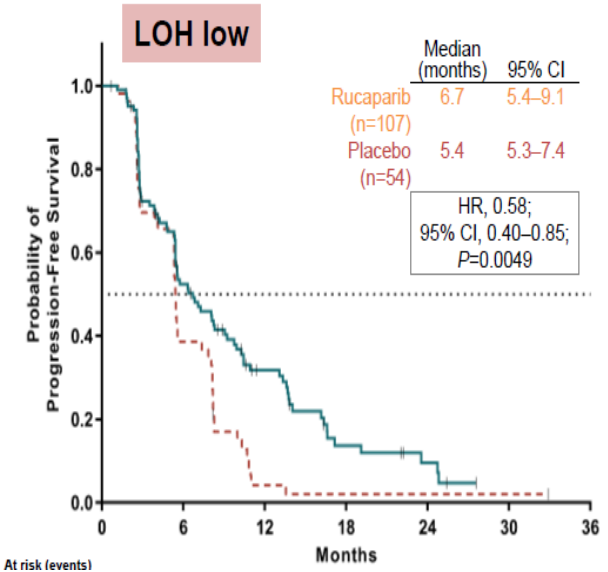
ARIEL-3 (Rucaparib): PFS











Treatment-emergent AE: grades 3/4

Adverse events	Olaparib	Niraparib	Rucaparib	Specific PARPi
overall	36 %	74 %	56 %	Olaparib (low)
nausea	3 %	3 %	4 %	
vomiting	3 %	2 %	4 %	
fatigue	4 %	8 %	7 %	
HTA	-	8 %	-	Niraparib (↑)
ALT/AST ↑	-	-	10 %	Rucaparib (↑)
anemia	19 %	25 %	19 %	
thrombocytopenia	1 %	34 %	5 %	Niraparib (↑)
neutropenia	5 %	20 %	7 %	Niraparib (↑)

Dose modifications

	Olaparib[1]	Niraparib[2]	Rucaparib[3]
Interruption rate	**45 %**	**69 %**	**64 %**
Dose reduction rate	**25 %**	**66 %**	**55 %**
Discontinuation rate	**11 %**	**15 %**	**13 %**
Anemia		1,4 %	
Thrombocytopenia		1,9 %	
Neutropenia		3,3 %	

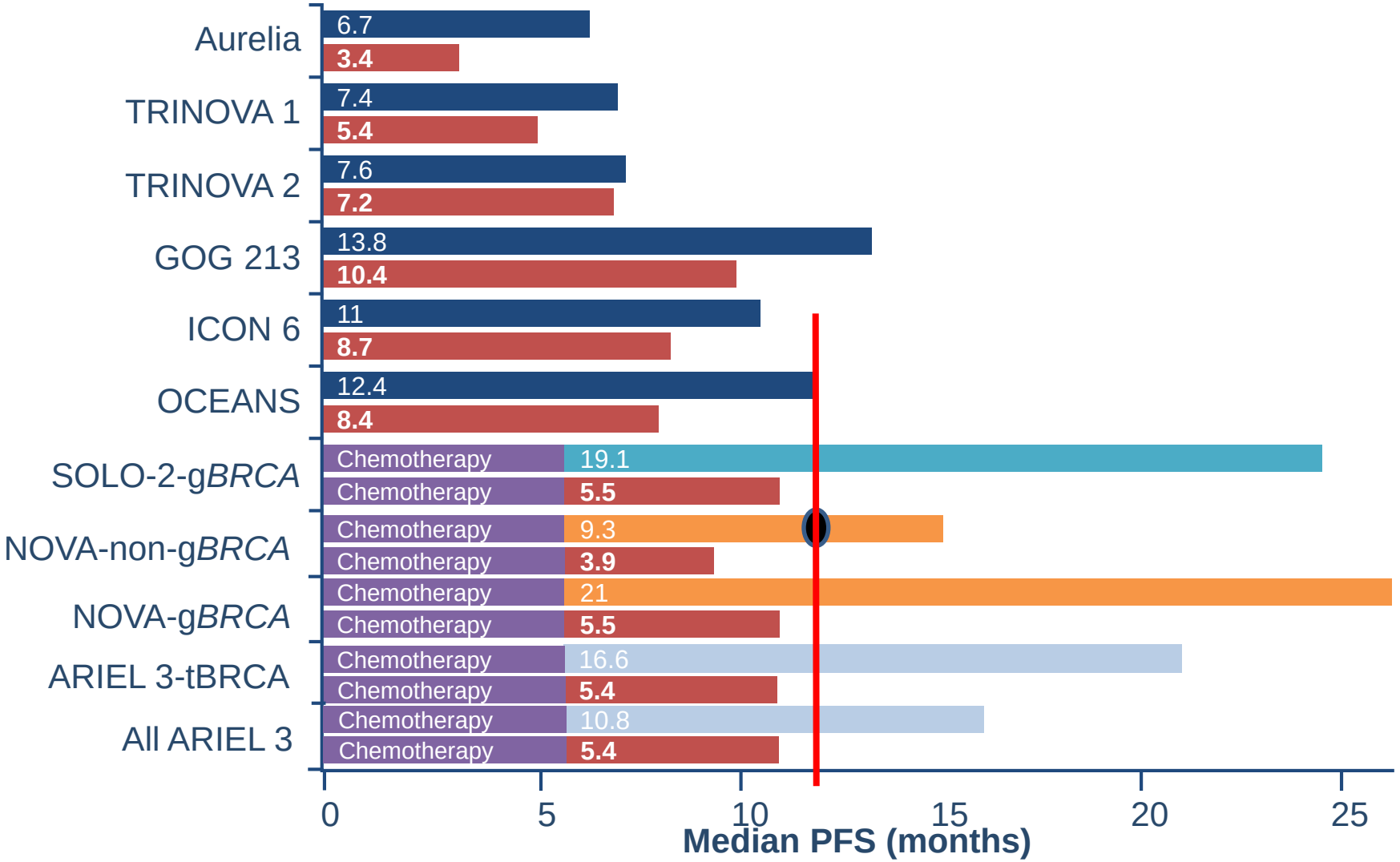
Olaparib and MDS/AML

- Overall, MDS/AML were reported in 22 of 2,618 (<1%) patients who received olaparib
- The majority of MDS/AML cases (17 of 22) were fatal

  The duration of therapy with olaparib in patients who developed secondary MDS/ cancer therapy-related AML varied from <6 months to >2 years
- All patients had received previous chemotherapy with platinum agents and/or other DNA-damaging agents

1. Pujade-Lauraine E et al. : Lancet Oncol 2017; 18(9): 1274-1284
2. Mirza MR et al.: New Engl J Med 2015; 375(12): 2154-2164
3. Coleman RL et al.: Lancet 2017 Sep 12

What is statistically significant is also clinically meaningful?



Aghajanian C et al. *J Clin Oncol*. 2012;30:2039–45; Coleman RL et al. *Gynecologic Oncol*. 2015;137:386–91; Ledermann J et al. *Lancet Oncol*. 2014;15:852–61; Ledermann JA et al. *Lancet*. 2016;387:1066–74; Marth C et al. *Eur J Cancer*. 2017;70:111–21; Monk BJ et al. *Lancet Oncol*. 2014;15:799–808; Pujade-Lauraine E et al. *J Clin Oncol*. 2014;32:1302–8; Mirza MR et al. *N Engl J Med*. 2016;375:2154–64; Coleman RL et al. *Lancet.* 2017;doi:10.1016/S0140-6736(17)32440-6..

Maintenance therapy with PARPi in ovarian cancer: where are we now …

- **Increase in progression-free survival across all groups of patients with high grade ovarian cancer responding to platinum**
  - Greatest benefit in germline or somatic BRCA^{mut}
  - Significant but lesser benefit in BRCA^{wt}
  - Benefit present irrespective of HRD status
  - Better HRD tests are needed to separate responders from non-responders.
  - Until then (beyond BRCA) platinum-sensitivity remains the best “biomarker” for response to PARPi
- **Secondary endpoints – prolongation of**
  - Time to first subsequent treatment (TFST)
  - Time to second subsequent treaatment (TSST)
- **Long-term (5yr) benefit in about 11 %**

Front-line for stage III/IV with PARPi / IO / Bev in *non-mutated BRCA wild-type* ovarian carcinoma

Trial	Setting	Patient Selection	Arms
AGO/DUO-O ENGOT Ov46	Front-line	t*BRCA*non-mut* PDS or IDS any residual LGSOC excluded	CP-bev-placebo-placebo CP-bev-durvalumab-placebo CP-bev-durvalumab-olaparib
BGOG/ENGOT Ov43	Front-line	t*BRCA*non-mut, any histotype PDS or IDS any residual Bev optional	CP-placebo-placebo CP-pembro-placebo CP-pembro-olaparib
GINECO/FIRST ENGOT Ov44	Front-line	PDS (high-risk) or IDS Bev optional Mucinous excluded	CP-placebo-placebo CP-placebo-niraparib CP-TSR042-niraparib
ATHENA GOG3020/ENGOT Ov45	Maintenance after front-line	Stage III-IV and high grade PDS or IDS Response to platinum	Rucaparib-nivolumab Rucaparib-placebo Nivolumab-placebo Placebo-placebo

Immune checkpoint inhibitors in recurrent ovarian carcinoma

	Nivolumab [1]	Pembrolizumab[2] Keynote-028	Avelumab [3] Phase Ib	Atezolizumab [4]
Population (N)	20 PROC 55% ≥ 4L	26 Phase Ib 65% ≥ 3L	124 PROC 65% ≥ 3L	12 Phase Ib 58% > 6L
Global ORR	15% (10% CR)	11,5% (4%CR)	5,7% (0%CR)	25%
Cut off PD-L1 ORR PD-L1- ORR PD-L1+	IHC2/3+ (80%) 1/4 (25%) 2/16 (12,5%)	≥ 1% (100%) - 3/26 (11,5%)	≥ 1% (77%) 1/23 (5,9%) 7/77 (12,3%)	IHC2/3+ (83%) - -

[1] Hamanaslu et al. J Clin Oncol 2015
[2] Varga et al. J Clin Oncol 2015; 33 (suppl): abstr. 5510
[3] Disis et al. J Clin Oncol 2016; 34 (suppl): abstr. 5533
[4] Insomtile et al. Ann Oncol 2016; 27 (suppl. 6): abstr. 871 p

Optimizing immune checkpoint inhibitors in AOC

- **Better selection:**

  more efficient biomarkers
  - CPS [total nb. PD-L1+ cells (T, Ly, MΦ)] / (total nb. of cells) x 100
    CPS ≥ 10 (Pembrolizumab)
  - T-cell inflamed gene expression profil (GEP)
  - HRD analyses (WES) using HRD-LOH genomic scar score
  - not HRD or BRCA status
  - TMB ?
  - OVCA mainly TMB low, GEP low

- **Combination**
  - Chemotherapy
  - VEGF inhibition
    Phase II Nivolumab + Bevacizumab
    ORR: 28,9% (PS 8/20 + PR 3/18)
    mPFS: 8,1 months
  - PARP inhibitors

Phase II trials of checkpoint inhibitor + PARP inhibitor in recurrent ovarian cancer

Author	N	Population	ORR (Y.)	DCR (Y.)
MEDIOLA Durva + Olaparib Drew, SGOZOK	32	gBRCA PSROC	63% (19y CR / 44% PR)	81%
TOPACIO Pembro + niraparib Konstantinopoulos, ASCO 2018	60	+/- BRCA mut. 77% +/- BRCA mut. 19% PRROC 50% P refractory 29%	25% (5% CR / 20 Y – PR) 23% 24%	67%
Lee et al. Durva + Olaparib ESMO 2018	35	PRROC 83%	14%	37%

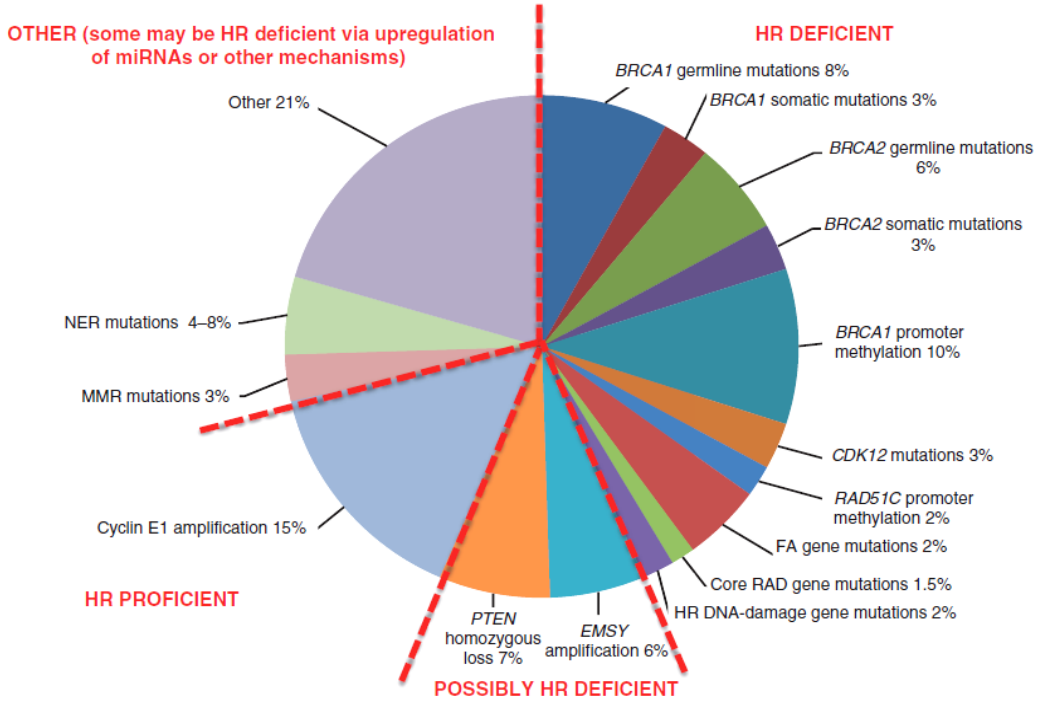
Do HGSOC BRCA / HRD + patients respond better to immune therapy?

Background:

- 50% of HGSOC have HRD
- 20% are BRCA mutated (germline + somatic)

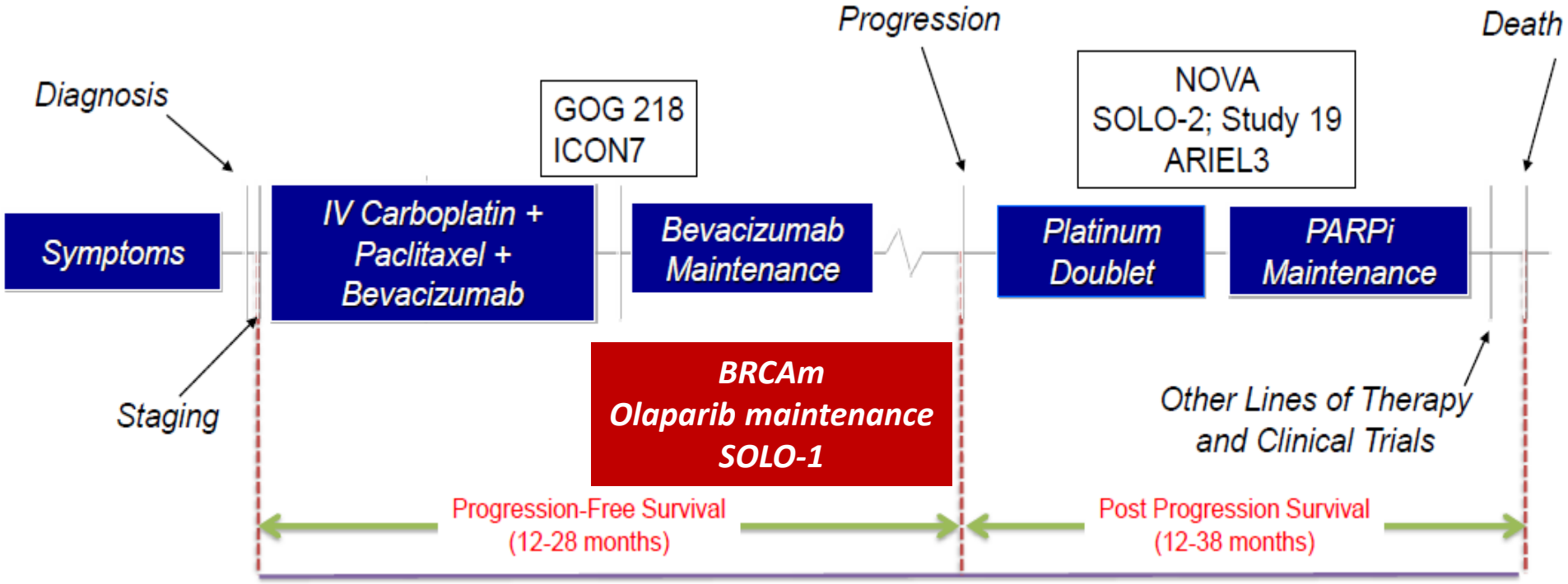
Hypothesis:

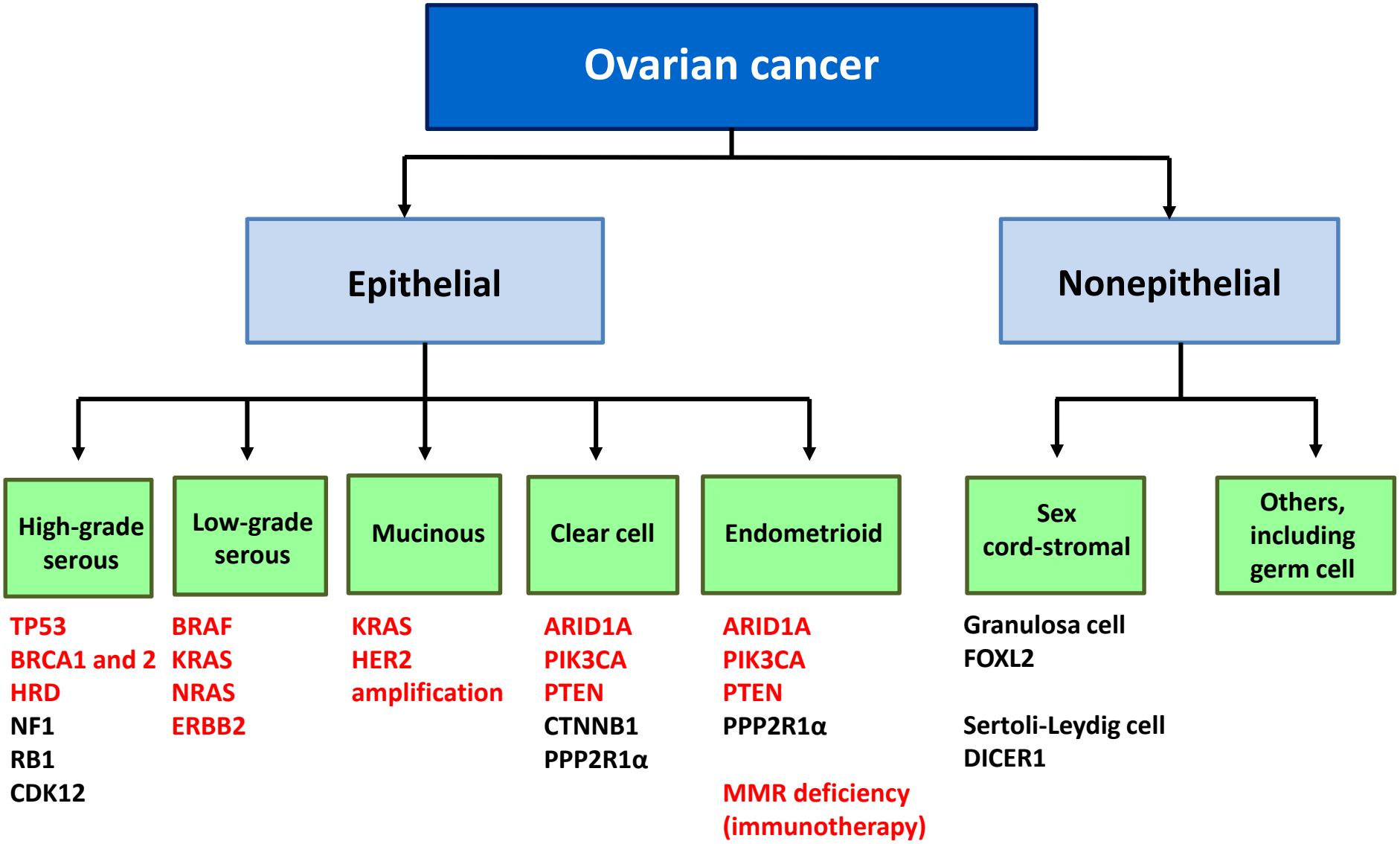
- Higher mutational burden
- More tumor specific neoantigens
- Higher TIL infiltration
- Upregulation of PD-1/PD-L1



Konstantinopulos PA et al Cancer Discovery 2015

The new treatment landscape in advance ovarian cancer





Pathway alterations:
PI3K/RAS/NOTCH/FOXM1

Banerjee S and Kaye S B Clin Cancer Res 2013; 19:961-968

Medicine asks you to make perfect decisions with imperfect information

S. Mukherjee, The laws of medicine