MaNGO
Mario Negri Gynecologic Oncology

XVIII ASSEMBLEA MANGO

Ricerca Clinica e Traslazionale in Ginecologia Oncologica

MILANO, 2-3 LUGLIO 2021

Con il Patrocinio di:

AIOM Associazione Italiana di Oncologia Medica

FICOG | Federation of Italian Cooperative Oncology Groups

SOCIETA' ITALIANA DI CANCEROLOGIA

SIGO SOCIETA' ITALIANA DI GINECOLOGIA E OSTETRICIA

ACTO ALLEANZA CONTRO il TUMORE OVARICO

A Phase 3, Randomized, Double-Blind Study of Pembrolizumab versus Placebo in Combination With Paclitaxel With or Without Bevacizumab for the Treatment of Platinum-resistant Recurrent Ovarian Cancer

KEYNOTE-B96 / ENGOT-ov65

Sponsor MSD - Model c ENGOT – ENGOT lead group MaNGO

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Platinum resistant as High Unmet Medical Need

- While most OC patients achieve a complete remission, the majority (>85%) will recur. Almost all patients will ultimately develop a platinum-resistant disease, with about 30% demonstrating platinum resistance at the time of first recurrence. Median overall survival is poor, typically <12 months.

Scientific Rationale for pembrolizumab and paclitaxel

- Chemotherapy (paclitaxel, PLD, topotecan) +/- bevacizumab is SoC.
- Weekly paclitaxel +/- bev is a preferred regimen if possible but only approximately 30% of resistant patients are clinically eligible for bev.
- Paclitaxel induces proinflammatory cytokine secretion and immune cell activation.
- Pembrolizumab combined with chemotherapy with or without anti-angiogenic therapy (bevacizumab, lenvatinib) has shown promising activity in recurrent ovarian cancer improving both ORR and PFS (MISP data, LEAP-005).

AURELIA Results by Chemotherapy Subgroup

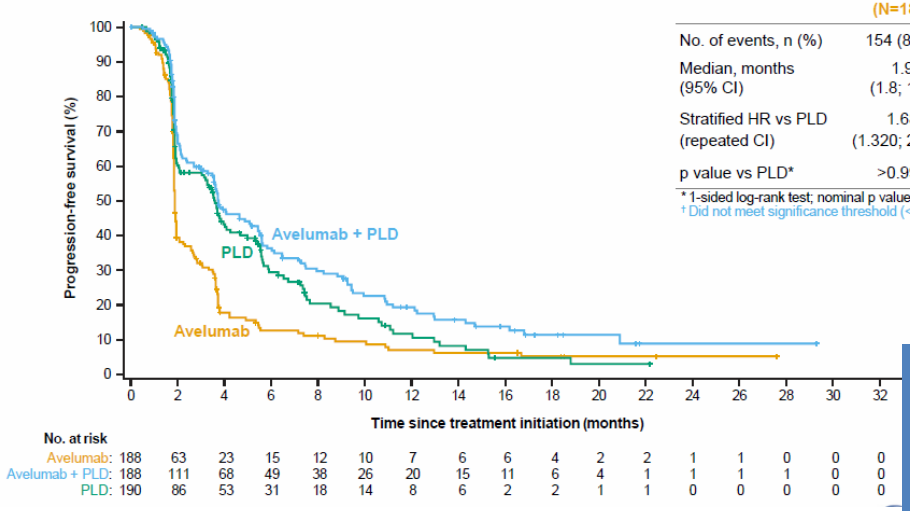
Combination	N/Lines of treatment	mPFS (CT +bev vs CT)	ORR (CT+bev vs CT)	mOS* (CT+bev vs CT)	mDoT CT+bev vs CT
Chemotherapy +/- bevacizumab10 mg/kg Q2W	361 PRROC (no refractory) up to 2L of prior treatment	6.7 vs 3.4 months HR: 0.48 (0.38, 0.60; *P* .001).	27.3% vs 11.8% (*P* .001)	16.6 vs 13.3 HR: 0.85 (0.66, 1.08); *P =0.*174; **NS**	6 cycles (1-24) vs 3 cycles (1-17) 1 cycle=4 w (except topotecan)
Paclitaxel 80mg/m^2 IV on days 1, 8, 15, and 22 every 4 weeks **+/-bevacizumab** 10 mg/kg Q2W	115 PRROC (no refractory) up to 2L of prior treatment	10.4 v 3.9 months HR: 0.46 (0.30, 0.71)	53.3% vs 30.2%	22.4 v 13.2 months Unadjusted HR: 0.65 (0.42,1.02) **NS**	
PLD 40 mg/m^2 IV on day 1 Q4W **+/- bevacizumab**10 mg/kg Q2W	126 PRROC (no refractory) up to 2L of prior treatment	5.4 v 3.5 months HR: 0.57 (0.39, 0.83)	13.7% vs 7.8%	13.7 m vs 14.1 m Unadjusted HR: 0.91 (0.62,1.36) **NS**	
Topotecan 4 mg/m^2 IV on days 1, 8, and 15 every 4 weeks or 1.25 mg/m^2 on days 1 to 5 Q3W **+/- bevacizumab** 10 mg/kg Q2W or 15 mg/kg Q3W in patients receiving topotecan in a schedule Q3W	120 PRROC (no refractory) up to 2L of prior treatment	5.8 v 2.1 months HR:0.32 (0.21, 0.49)	17.0% vs 0.0%	13.8 v 13.3 m Unadjusted HR: 1.09 (0.72,1.67) **NS**	

Pujade-Lauraine E et al, JCO 2014

IO in platinum resistant: JAVELIN Ovarian 200 – randomized trial

Avelumab appeared to nominally improve on PLD monotherapy efficacy but not enough to result in a positive trial. Avelumab monotherapy activity in PRROC was minimal; ORR was 3.7%.

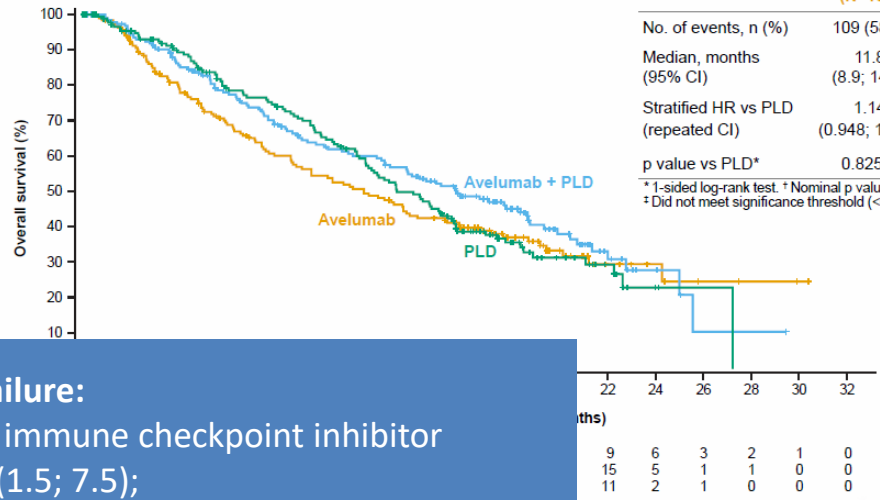
Progression-free survival by BICR



	Avelumab (N=188)	Avel. + PLD (N=188)	PLD (N=190)
No. of events, n (%)	154 (81.9)	134 (71.3)	125 (65.8)
Median, months (95% CI)	1.9 (1.8; 1.9)	3.7 (3.3; 5.1)	3.5 (2.1; 4.0)
Stratified HR vs PLD (repeated CI)	1.68 (1.320; 2.601)	0.78 (0.587; 1.244)	–
p value vs PLD*	>0.999	0.0301†	–

* 1-sided log-rank test; nominal p values (futility boundary was crossed at interim analysis)
† Did not meet significance threshold (<0.0002)

Overall survival



	Avelumab (N=188)	Avel. + PLD (N=188)	PLD (N=190)
No. of events, n (%)	109 (58.0)	102 (54.3)	104 (54.7)
Median, months (95% CI)	11.8 (8.9; 14.1)	15.7 (12.7; 18.7)	13.1 (11.8; 15.5)
Stratified HR vs PLD (repeated CI)	1.14 (0.948; 1.580)	0.89 (0.744; 1.241)	–
p value vs PLD*	0.8253†	0.2082‡	–

* 1-sided log-rank test. † Nominal p value (futility boundary was crossed at interim analysis)
‡ Did not meet significance threshold (<0.0103)

Possible reasons for failure:

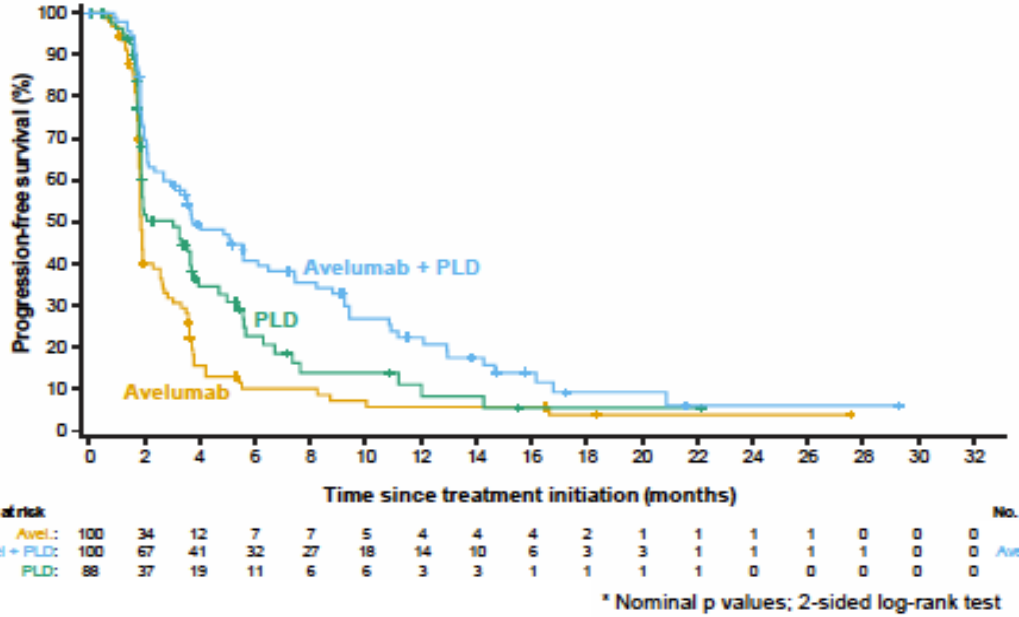
1) Avelumab is a weak immune checkpoint inhibitor
   - ORR: 3.7% (1.5; 7.5);
   - mPFS: 1.9m (1.8; 1.9) HR (vs PLD):1.68 p>0.999;
   - mOS:11.8m (8.9; 14.1) HR (vs PLD): 1.14 p=0.8253
2) PLD is not an optimal chemotherapy combination partner
   - ORR: 4.2% (1.8; 8.1);
   - mPFS: 3.5m (2.1; 4.0);
   - mOS: 13.1m
   - Combined Avelumab/PDL ORR: 13.3%
3) Study design: (#) Underpowered?

Pujade-Lauraine E et al, SGO 2018

JAVELIN Ovarian 200 Results: PFS in PD-L1+ subgroup exploratory analysis

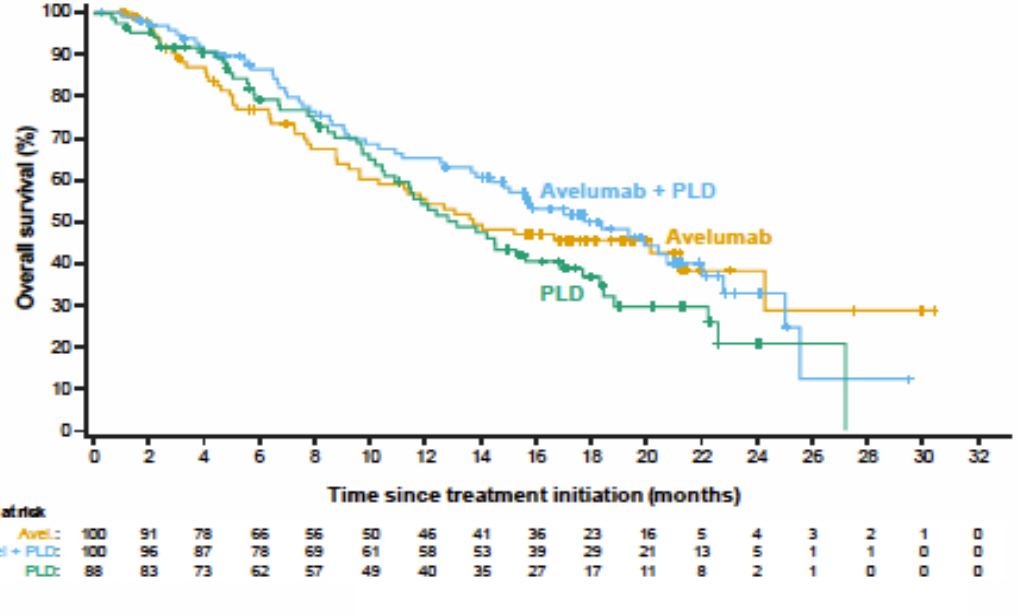
Progression-free survival

	Avelumab (N=100)	Avelumab + PLD (N=100)	PLD (N=88)
Median, mo	1.9	3.7	3.0
(95% CI)	(1.8; 2.3)	(2.7; 6.1)	(1.9; 3.7)
HR vs PLD	1.45	0.65	–
(95% CI)	(1.034; 2.043)	(0.457; 0.919)	
p value vs PLD*	0.0303	0.0143	–



Overall survival

	Avelumab (N=100)	Avelumab + PLD (N=100)	PLD (N=88)
Median, mo	13.7	17.7	13.1
(95% CI)	(9.6; 24.3)	(13.8; 22.0)	(10.5; 16.9)
HR vs PLD	0.83	0.72	–
(95% CI)	(0.567; 1.228)	(0.489; 1.048)	
p value vs PLD*	0.3580	0.0842	–



* Nominal p values; 2-sided log-rank test

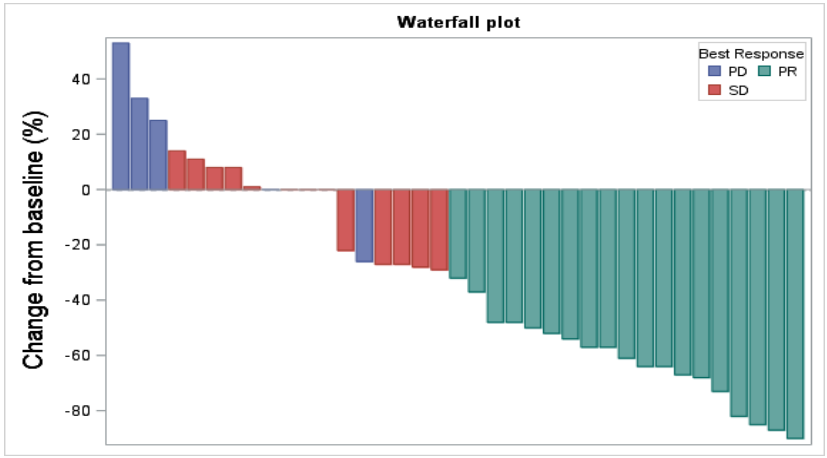
PD-L1 status was evaluable in 508 patients (SP263 Ventana platform)

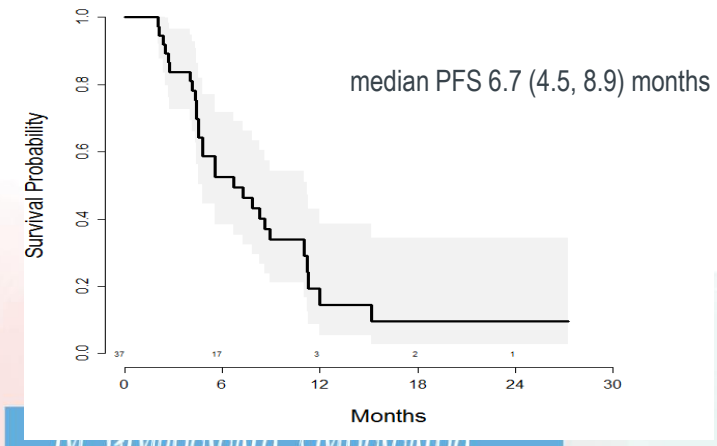
The cutoff: at least 1% of tumor cells expressing PD-L1 or more than 5% of immune cells expressing PD-L1

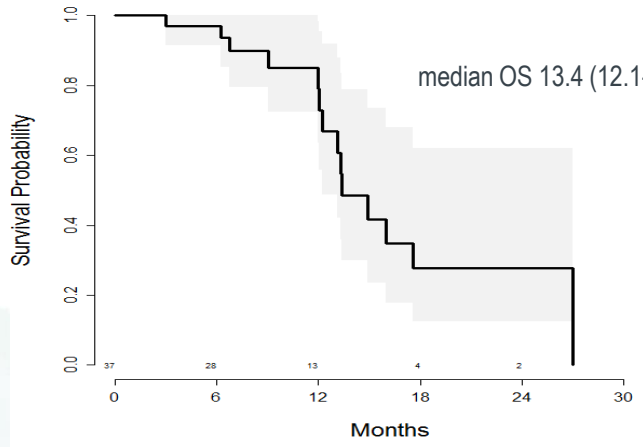
IO in PRROC: Wenham MISP – Pembrolizumab plus Paclitaxel

Paclitaxel and pembrolizumab in the platinum-resistant: 51% ORR compares to the 30% expected with paclitaxel alone.

Best Response	N of Patients	% Evaluable (n=37)	% Treated (n=41)
CR	0	0	0
PR	19	**51.4%**	46.3%
SD	13	35.1%	31.7%
PD	5	13.5%	12.2%
Unassessed	4	NA	9.8%
DCR	32	86.5%	78%







Wenham R et al, GCIG 2018

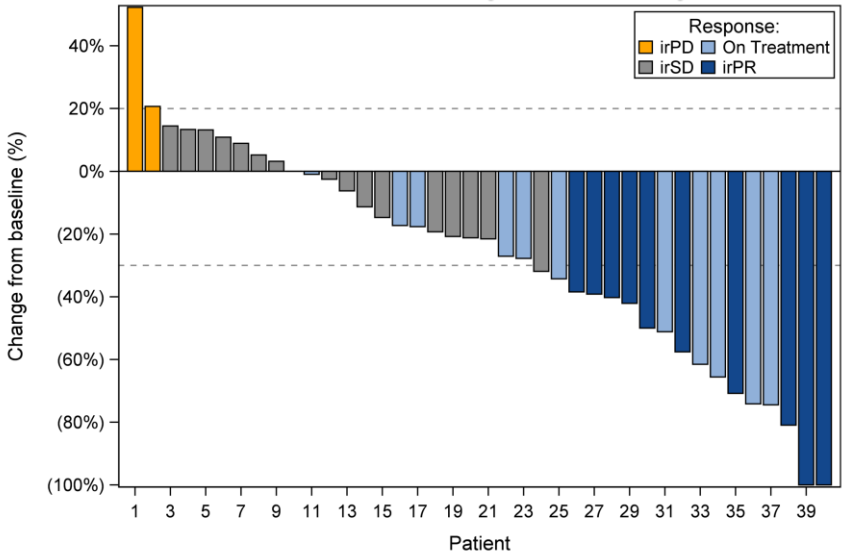
Pembrolizumab plus Cyclophosphamide and Bev

Pembrolizumab also appears to improve the chemotherapy plus bevacizumab efficacy in platinum resistant. Cyclophosphamide plus bev without pembrolizumab is associated with an ORR of approximately 25%.

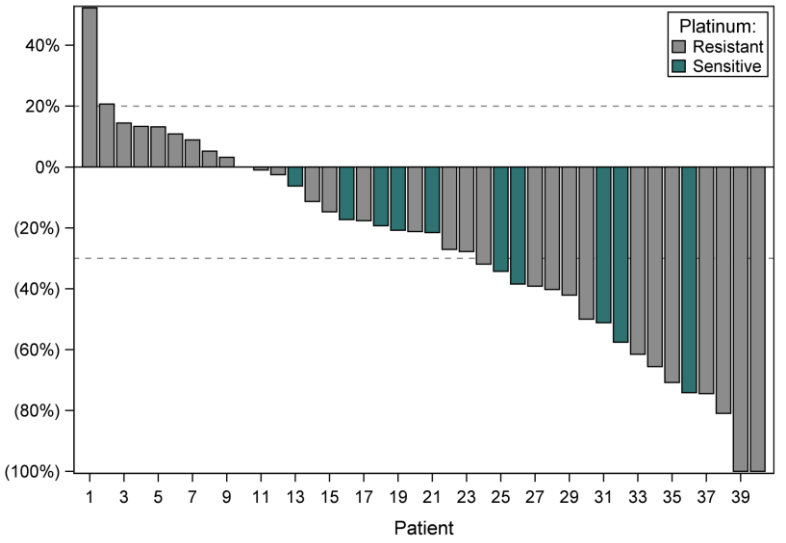
Best Clinical Response

Best Response	N (%)	Total N (%)
irPR	10 (25%)	**16 (40%)**
irSD	17 (42.5%)	**22 (55%)**
irPD	2 (5%)	**2 (5%)**
On Treatment	11 (27.5%)	
irPR	6 (15%)	
irSD	5 (12.5%)	
irPD	0 (0%)	

Best Change from Baseline in Tumor Size (irRECIST)



Efficacy Across Platinum Sensitive and Resistant Patients

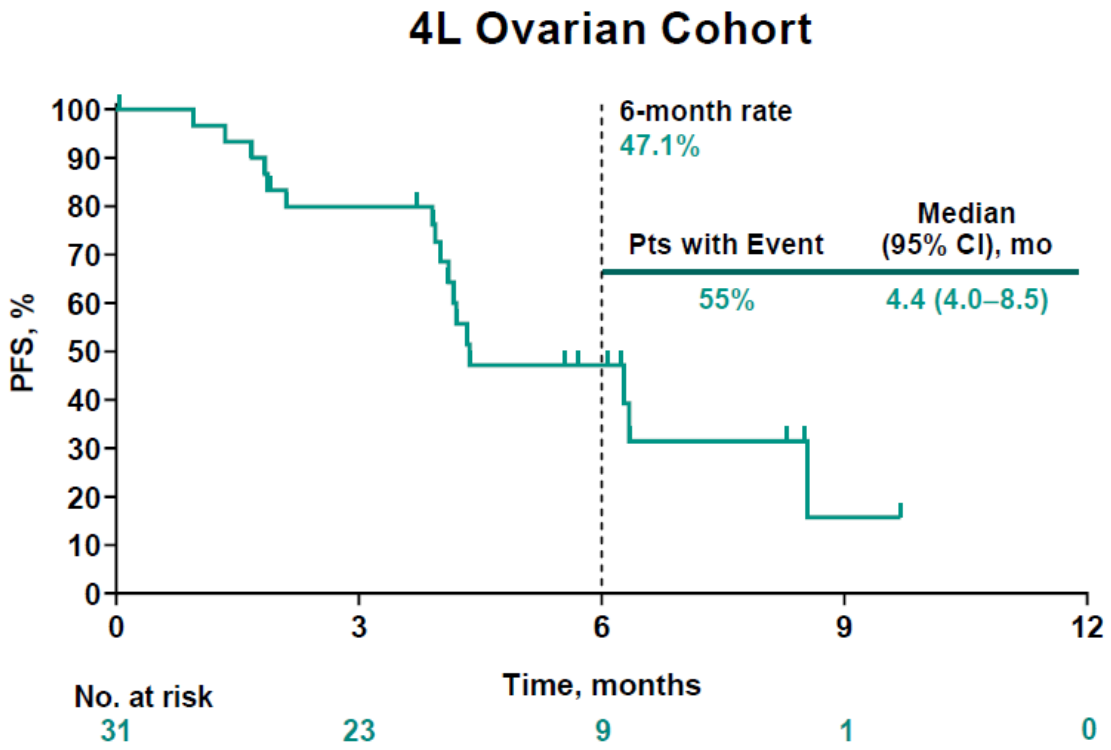


Zsiros E et al, SGO 2019

IO in PRROC: LEAP-005 in 4L Recurrent Ovarian Cancer is Informative

LEAP-005 enrolled 30 patients in 4L recurrent ovarian cancer.

Best overall confirmed response rate by BICR	Ovarian n (%)
Minimum Responders Needed for Expansion	6 (19.4%)
Objective Response (CR+PR)	**10 (32.3%)**
Complete Response (CR)	1 (3.2%)
Partial Response (PR)	9 (29.0%)
Stable Disease (SD)	13 (41.9%)
Disease Control (CR+PR+SD)	23 (74.2%)
Progressive Disease (PD)	5 (16.1%)
Non-evaluable (NE)	0 (0%)
No Assessment (NA)	2 (6.5%)



Summary:

- Pembrolizumab improves the efficacy of chemotherapy with or without bevacizumab in platinum resistant
  - Pembro is a more potent immune checkpoint inhibitor (ICI) than avelumab
  - Potent combination activity with paclitaxel (ORR improved from approximately 30% as monotherapy to 50% in combination with pembro)
  - Possible increase in activity with antiangiogenic therapy (improvement with bevacizumab and lenvatinib)
- The JAVELIN 200 Ovarian experience is informative and may be explained by the fact that
  - Avelumab is a weak ICI (monotherapy activity in PRROC of only 3.7%)
  - PLD may not be the best combination partner
  - The study was underpowered for effect

ENGOT-ov65/KEYNOTE-B96
Study design

Key Eligibility Criteria

- Platinum Resistant OC patients (refractory excluded)
- Up to 2L of prior therapy
- ECOG PS 0, 1
- Prior IO allowed
- Prior PARPi allowed
- Prior bevacizumab allowed

Randomization
1:1
N=600

Pembrolizumab
+
Paclitaxel
+/- bevacizumab

Pembrolizumab
placebo
+
Paclitaxel
+/- bevacizumab

Stratification factors for randomization

- Bevacizumab use
- PD-L1 status
- Prior IO

Statistical Considerations

- **Primary endpoints:**
  - PFS in CPS>=1 (α=0.02 1-sided)
  - PFS in all population (α=0.005 1-sided) with roll-over of alpha from PFS in CPS1 if positive
- **Key secondary endpoints**:
  - OS in CPS>=1
  - OS in all population

Hierarchical approach:

- ❖ OS in CPS1 can be tested only if both PFS analyses are positive
- ❖ OS in all pts can be tested only if OS in CPS1 will be positive

Planning Considerations

- Enrollment ~ 18 mo
- Enrollment rate: 34 patients / mo
- Enrollment start planned for Q4 2021

INVOLVED COUNTRIES

North America	Latin America	EMEA	EMEA	APAC
Country	Country	Country	Country	Country
Canada	Brazil	Russia	Poland	Australia/NZ
US	Chile	Belgium	Sweden	China
	Colombia	Denmark	Turkey	Japan
	Mexico	France	UK	South Korea
		Germany	Netherlands	Taiwan
		Ireland	Finland	
		Israel		
		Italy		
		Norway		