PARIS 2022 ESMO congress

ATALANTE
Atezolizumab and Avastin
in late recurrent disease

A randomized, double-blinded, phase III study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated by platinum-based chemotherapy and bevacizumab. GINECO-OV236b/ENGOT-ov29

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Declaration of interests

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Advisory boards: AstraZeneca, Chugai, Eisai, Merck-Serono, Tesaro

Speaker/honoraria: Bristol Myers Squibb, Clovis Oncology, Mersana, Seagen

Travel expenditure: AstraZeneca, Glaxo SmithKline, PharmaMar, Roche

Research funding: none

Rationale

In patients with ovarian cancer relapsing with a platinum-free interval > 6 months:

- Carboplatin (Cb) combination with either pegylated liposomal doxorubicin (PLD)[1], gemcitabine[2] or paclitaxel[3] is a standard of care
- When added to chemotherapy, bevacizumab increases response rate and prolongs PFS[4-6]
- An objective response of 13.6% has been reported in patients with prior CR or PR to platinum-based chemotherapy when treated with single agent check-point inhibitor (CPI) blocking the PD-1/PD-L1 axis[7]
- Addition of CPI has been reported to increase chemotherapy and/or bevacizumab activity in other tumors [8-9]

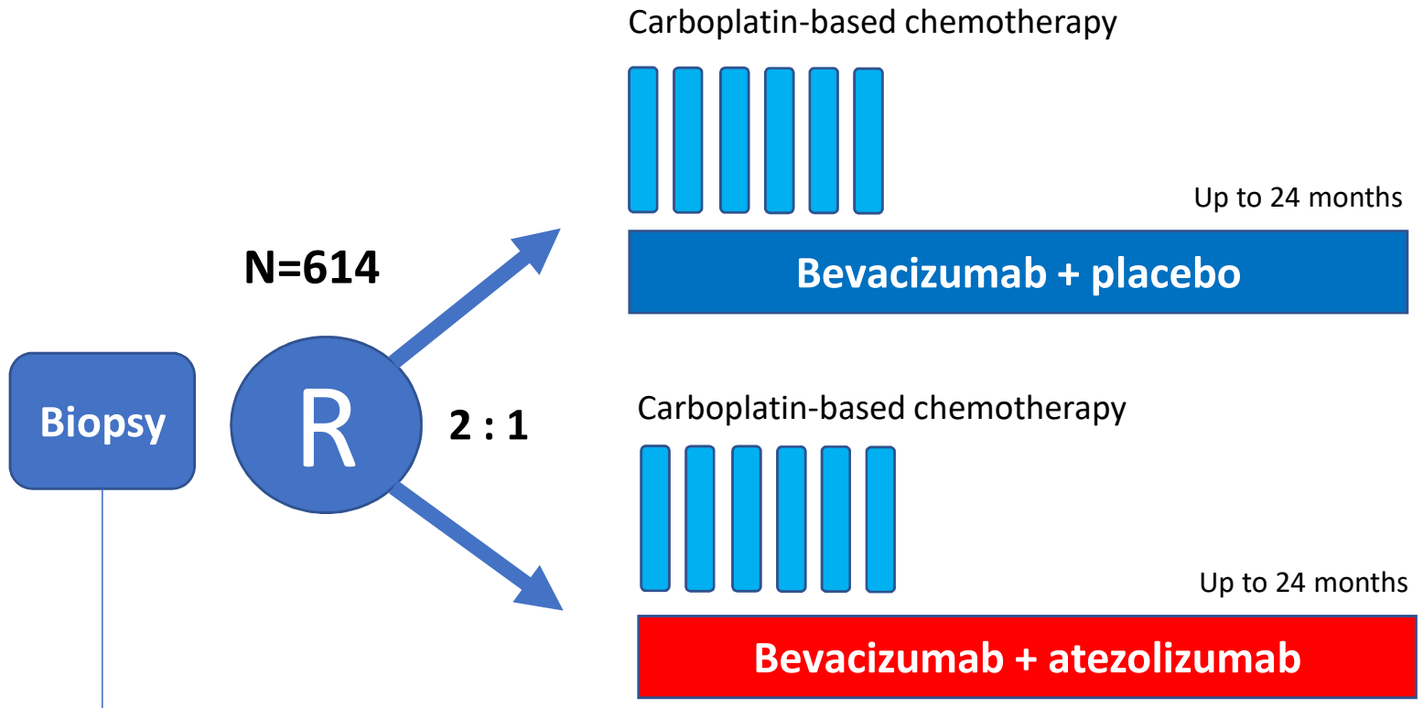
1- Pujade-Lauraine E, et al. JCO 2010; 2-Pfisterer J, et al . JCO 2006; 3-Parmar MK, et al. Lancet 2003; 4-Aghajanian C, et al. JCO 2012; 5-Coleman R, et al, Lancet Oncol 2017; 6-Pujade-Lauraine E, et al. JCO 2014; 7-Disis ML, et al. JAMA Oncol 2019; 8- Rini BI, et al. Lancet 2019; 9- Socinski MA N Engl J Med 2018

ATALANTE trial design

- Relapsed non-mucinous epithelial OC
- Platinum-free interval >6 mos
- 1 or 2 prior chemotherapy lines
- ECOG PS ≤1

Stratification factors

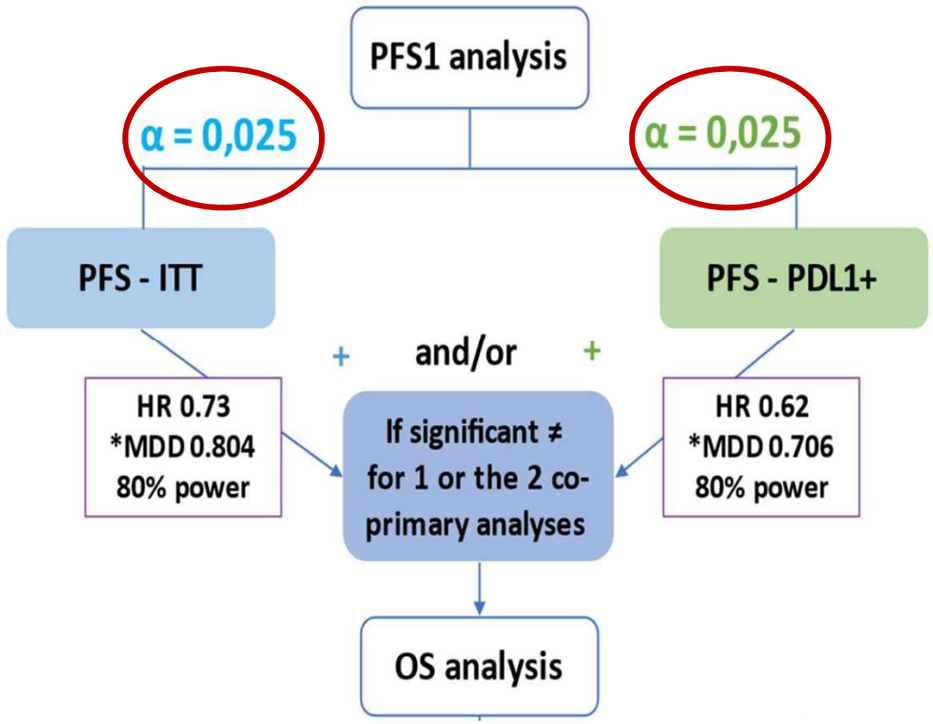
- PD-L1 ≥ 1% on immune cells vs <1% vs unknown (Ventana clone SP142)
- Chemotherapy: Cb-PLD or gemcitabine or paclitaxel
- Platinum-free interval: 6-12 vs >12 months



- **Co-primary endpoints** are progression-free survival (PFS1) according to investigator in the ITT and PD-L1-positive populations
- **Secondary endpoints:** TSST, TFST, OS, safety (NCI CTCAE V 4.03) and HrQoL (EORTC QLQ-C30, QOLQ OV-28, EQ5D-5L)

Statistical considerations

- PFS1 was analyzed using a Cox model adjusted by stratification factors with a two-sided α level at 0.025 and 80% power for each PFS co-primary in the ITT and PD-L1-positive populations
- 491 events in the ITT and 186 in the PD-L1-positive populations were expected to show a reduction in the risk of progression of 27% (difference of median PFS1 of 4.8 months) and of 38% (difference of median PFS1 of 9.0 months), respectively
- Following a hierarchical approach, if either of the co-primary PFS1 comparisons was significant, overall survival could then be analyzed in both the ITT and PD-L1-positive populations



*MDD=Minimal Detectable Difference

Baseline characteristics (1)

	Atezo (N=410)	Placebo (N=204)
Median (IQR) patient age, years	63 [55-70]	64 [55-71]
Histology, n (%)		
Serous high grade	346 (84)	169 (83)
Serous low grade	32 (8)	8 (4)
Endometrioid high grade	12 (3)	11 (5)
Clear cell	8 (2)	9 (4)
Others	12 (3)	7 (3)
ECOG, n (%)		
0	277 (68)	131 (64)
1	131 (32)	72 (35)
2	2 (<1)	0 (0)
Number of prior lines, n (%)		
1	307 (75)	147 (72)
2	103 (25)	57 (28)
Last line of therapy, n (%)		
Platinum	410 (100)	204 (100)
Bevacizumab	203 (50)	107 (52)
PARPi	74 (18)	40 (20)
Debulking surgery (within 6 months of inclusion), n (%)	62 (15)	30 (15)
Complete macroscopic resection	34 (8)	20 (10)

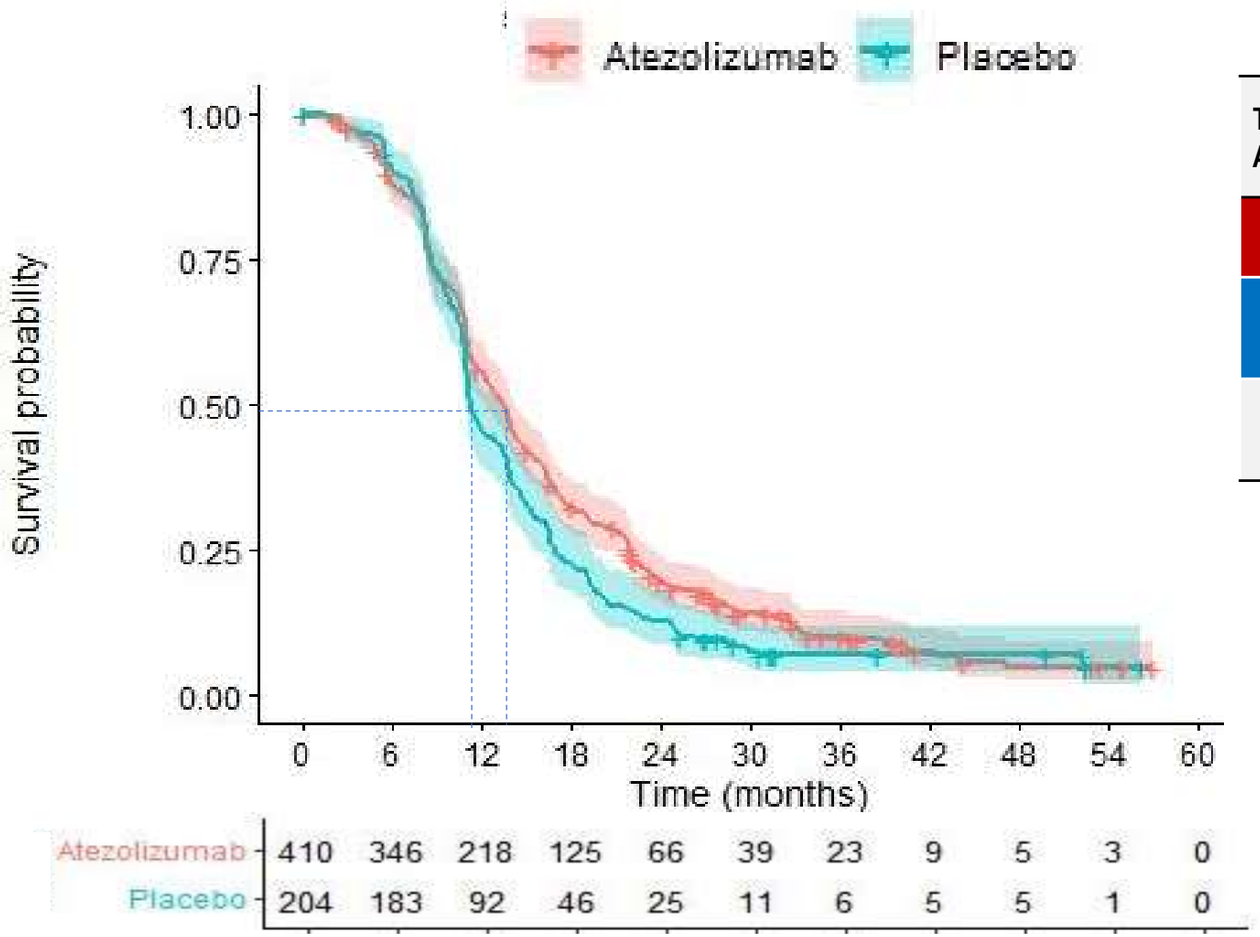
Baseline characteristics (2)

	Atezo (N=410)	Placebo (N=204)
PD-L1 status, n (%)		
≥1%	156 (38)	77 (38)
<1%	196 (48)	102 (50)
Inconclusive/missing	58 (14)	25 (12)
***BRCA* status, n (%)**		
Mutant	40 (10)	32 (16)
Non-mutant	241 (59)	118 (58)
Inconclusive/missing	129 (31)	54 (26)
Chemotherapy chosen by the investigator, n (%)		
Carboplatin-PLD	259 (63)	128 (63)
Carboplatin-gemcitabine	118 (29)	58 (28)
Carboplatin-paclitaxel	33 (8)	18 (9)

Treatment exposure

	Atezo (N=410)	Placebo (N=204)
Median (IQR) duration of treatment, months	11.1 (6.7–16.8)	11.1 (8.3-15.1)
Study drug end of treatment, reason, n (%)		
Disease progression	255 (62)	148 (73)
Adverse event	100 (24)	34 (17)
As per protocol	9 (2)	0 (0)
Consent withdrawn	9 (2)	2 (1)
Others	37 (9)	20 (10)

Progression-free survival (ITT)

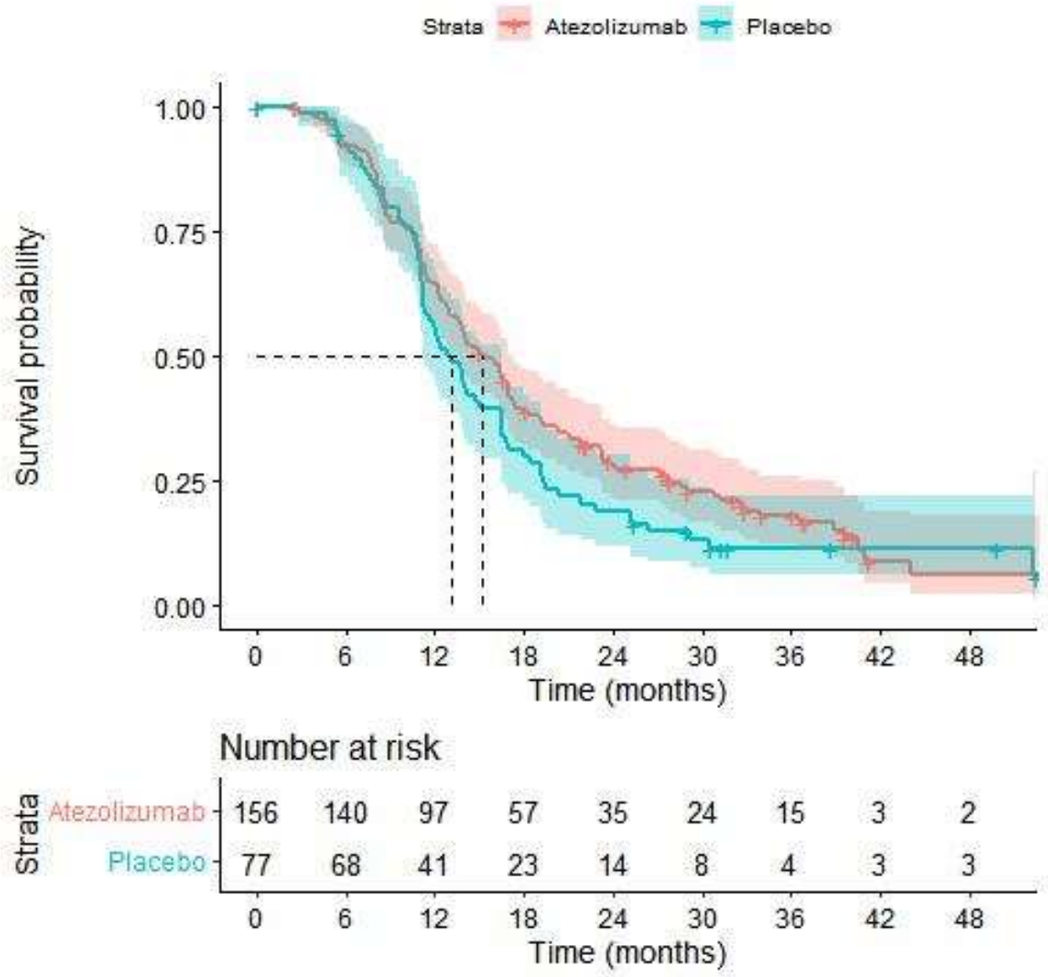


Treatment Arm	N	Event N (%)	PFS at 6m % (95% CI)	PFS at 12m % (95% CI)	PFS at 18m % (95% CI)	Median PFS (95% CI)
Atezo	410	348 (85)	88 (85-91)	56 (51- 61)	32 (28-37)	**13.5 mos** (12.2-14.2)
Placebo	204	187 (92)	91 (87- 95)	46 (39- 53)	23 (18-30)	**11.3 mos** (11.0-13.5)
		Hazard ratio= 0.83 [0.69-0.99]				**P=.041**

median follow-up : 36.6 months

The ATALANTE trial did not meet its first co-primary objective:
PFS1 in the ITT population

Progression-free survival (PD-L1 positive)



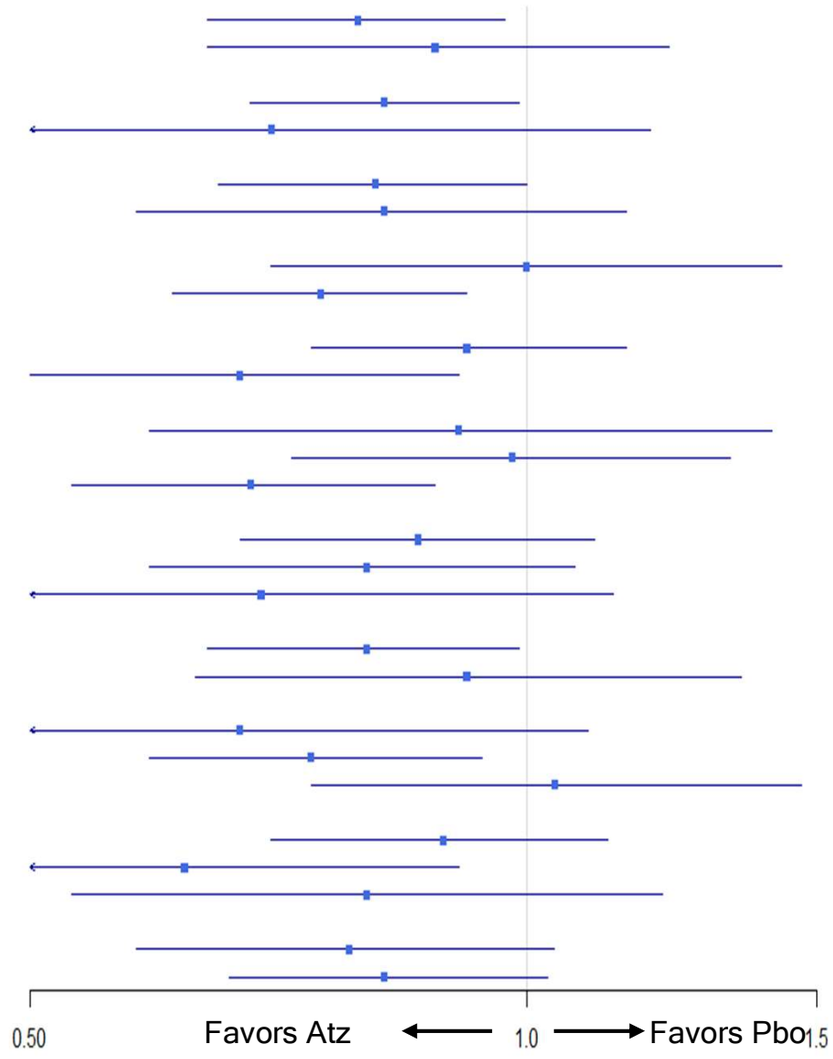
Treatment Arm	N	Events N (%)	PFS at 6m % (95% CI)	PFS at 12m % (95% CI)	PFS at 18m % (95% CI)	Median PFS (95% CI)
Atezo	156	124 (79)	93 (89-97)	64 (57- 72)	39 (32-47)	**15.2 mos** (13.6-17.3)
Placebo	77	66 (86)	92 (86- 98)	55 (45- 68)	31 (22-44)	**13.1 mos** (11.3-16.5)
		Hazard ratio= 0.86 [0.63-1.16]				***P*=.30**

The ATALANTE trial did not meet its co-primary objective:

PFS1 in the PD-L1 positive population

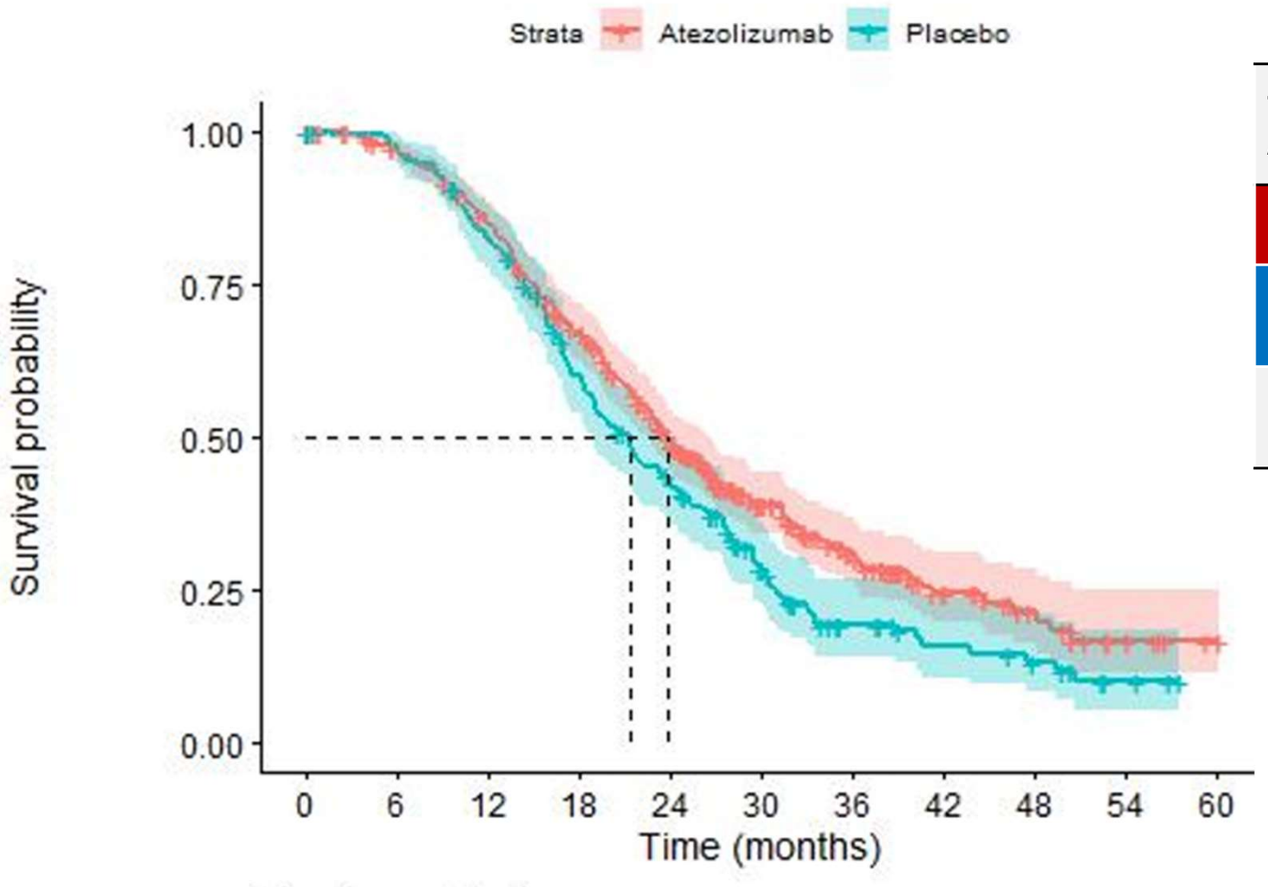
PFS analysis by subgroup (ITT)

	Atz (n)	Placebo (n)	HR (95% CI)	p
Age (years)				
< 70	305	141	0.79 (0.64 - 0.97)	0.56
≥ 70	105	63	0.88 (0.64 - 1.22)	
Adenocarcinoma type				
Serous high grade or Endometrioid Grade 2/3	358	180	0.82 (0.68 - 0.99)	0.57
Other	52	24	0.70 (0.41 - 1.19)	
Number of previous lines				
1	307	147	0.81 (0.65 - 1)	0.94
2	103	57	0.82 (0.58 - 1.15)	
Platinum-free interval				
6-12 months	103	45	1 (0.70 - 1.43)	0.16
> 12 months	307	159	0.75 (0.61 - 0.92)	
Prior Bevacizumab				
Yes	248	130	0.92 (0.74 - 1.15)	0.098
No	162	74	0.67 (0.50 - 0.91)	
Tumor size				
No measurable target	96	36	0.91 (0.59 - 1.41)	0.18
Sum of target lesions diameter ≥ 5cm	150	63	0.98 (0.72 - 1.33)	
Sum of target lesions diameter < 5cm	164	105	0.68 (0.53 - 0.88)	
PDL1 expression				
Negative	196	102	0.86 (0.67 - 1.10)	0.73
Positive	156	77	0.80 (0.59 - 1.07)	
Not informative	58	25	0.69 (0.42 - 1.13)	
CD8-PDL1				
Negative	265	131	0.80 (0.64 - 0.99)	0.53
Both positive	95	50	0.92 (0.63 - 1.35)	
BRCA mutation				
Germline or somatic mutation	40	32	0.67 (0.41 - 1.09)	0.20
No mutation	241	118	0.74 (0.59 - 0.94)	
Inconclusive	129	54	1.04 (0.74 - 1.47)	
CA-125 level at baseline				
Abnormal ≥ 100 kU/L	227	113	0.89 (0.70 - 1.12)	0.30
Abnormal <100 kU/L	88	48	0.62 (0.43 - 0.91)	
Normal	92	43	0.80 (0.53 - 1.21)	
Chemotherapy cohort				
Paclitaxel or Gemcitabine	151	76	0.78 (0.58 - 1.04)	0.76
PLD	259	128	0.82 (0.66 - 1.03)	



No significant interaction with atezolizumab treatment was found in any subgroup, including patients with CD8+/PD-L1+ tumors on biopsy at study entry

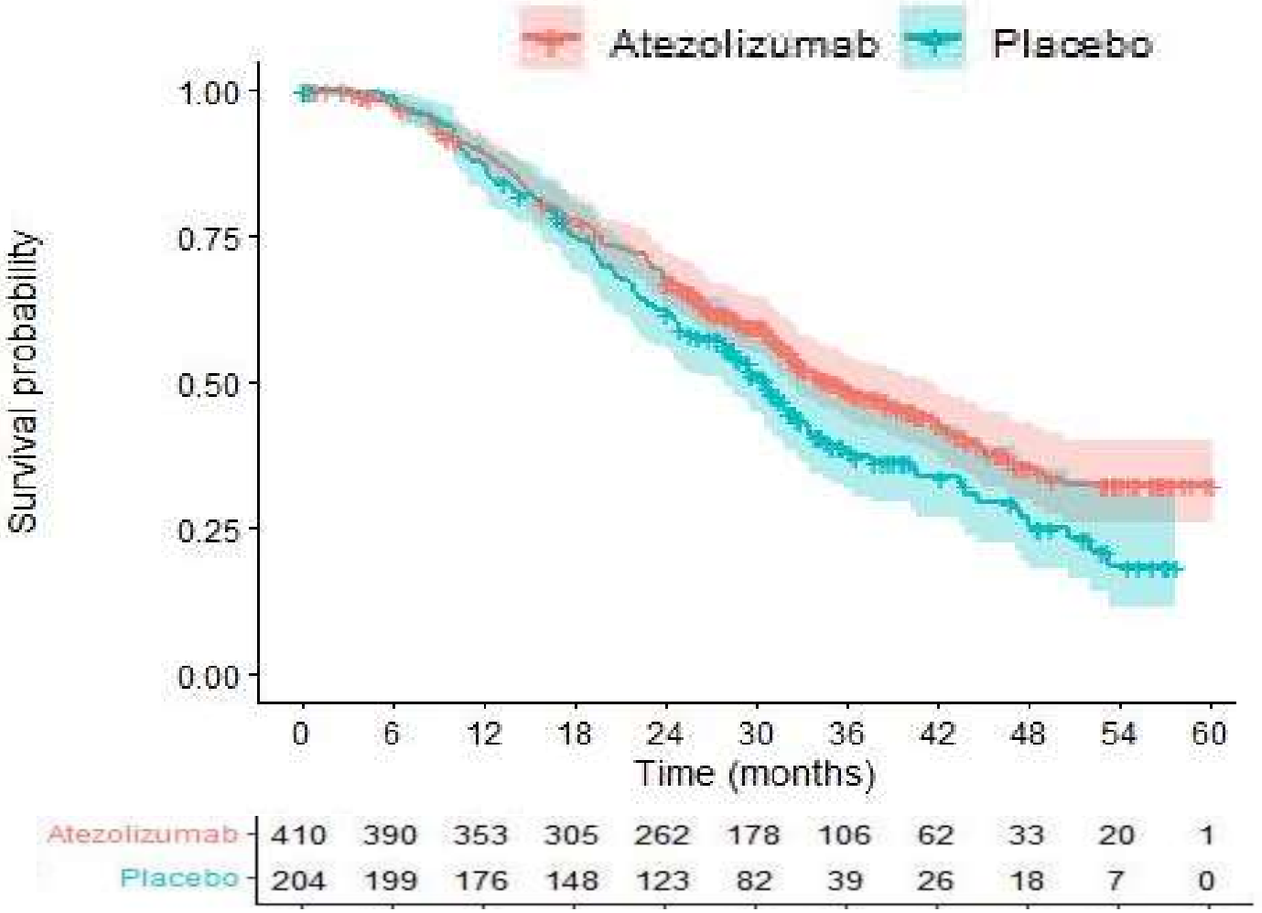
Time to second subsequent treatment (TSST)



Treatment Arm	N	TSST at 12m % (95% CI)	TSST at 24m % (95% CI)	TSST at 36m % (95% CI)	Median TSST (95% CI)
Atezo	410	85 (81-89)	49 (44-54)	31 (26-37)	**23.9 mos** (22.6-26.5)
Placebo	204	83 (78-88)	43 (36-50)	19 (14-27)	**21.4 mos** (19.0-24.0)
		Hazard ratio = 0.82 [0.67-1.01]			

- TSST was a surrogate of PFS2
- The TSST prolongation in adding Atezo to chemotherapy+Bev remains small

Overall survival (ITT)



Treatment Arm	N	Events N (%)	Median OS (95% CI)
Atezo	410	207 (51)	**35.5 mos** (32.4-41.3)
Placebo	204	126 (62)	**30.6 mos** (27.9-33.6)
	Hazard ratio= 0.81 [0.65-1.01]		

- Overall survival data are not yet mature (333 events out of 491 expected): longer follow-up is required
- Trend in favor of the atezolizumab arm in the ITT population

Overall safety

AEs, n§ (%)	Atezo (N=410)	Placebo (N=204)
All grade	409 (100)	202 (99)
Grade 3/4	360 (88)	175 (86)
treatment-related	317 (77)	143 (70)
AEs with fatal outcome	14 (3)	5 (2)
treatment-related	3 (1)	2 (1)
SAEs	293 (71)	120 (59)
treatment-related	144 (35)	50 (25)
AEs leading to any treatment discontinuation	184 (45)	84 (41)
to atezo/placebo discontinuation	101 (25)	37 (18)
to bevacizumab discontinuation	137 (33)	57 (28)
AEs leading to atezo/placebo interruption	265 (65)	128 (63)

§Number of patient with at least one event

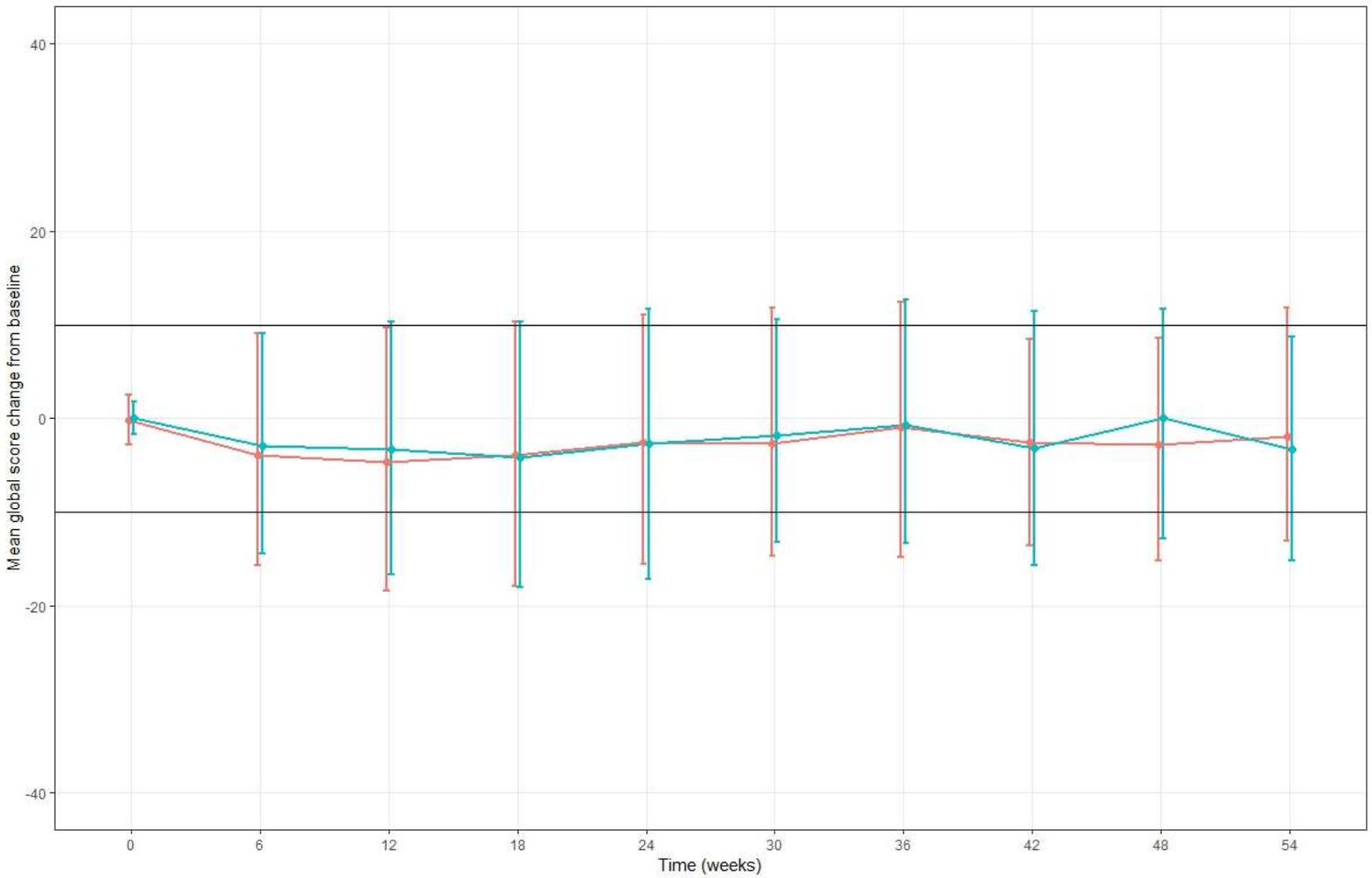
3 patients in the atezolizumab arm had fatal AEs related to treatment (cardiac arrest, peritonitis and acute myelogenous leukemia). 2 patients in the placebo arm had fatal AEs related to treatment (pulmonary embolism and bowel perforation)

Immune-related infusion reactions & auto-immune disorders (AESI)

AESI, n§ (%)	Atezo (N=410)	Placebo (N=204)
All grade AESI for atezolizumab	109 (27)	30 (15)
Grade 3/4 AESI	52 (13)	16 (8)
treatment-related	25 (6)	5 (2)
Immune related infusion reaction (all grades)	34 (8)	9 (4)
Autoimmune disorders (all grades)	91 (22)	23 (11)
Hypothyroidism	45 (11)	10 (5)
Hyperthyroidism	8 (2)	5 (2)
Hepatitis or transaminitis	9 (2)	1 (<1)
Colitis or severe diarrhea	4 (1)	4 (2)
Pancreatitis	4 (1)	0 (0)
Pneumonitis	3 (1)	0 (0)
Diabetes mellitus	2 (<1)	0 (0)
Adrenal insufficiency	2 (<1)	0 (0)
Ocular	1 (<1)	0 (0)
Nephritis	1 (<1)	0 (0)
Other	27 (7)	5 (2)

§Number of patients with at least one event

Health-related quality of life (HRQL)



No significant mean change from baseline EORTC QLQ-30 global score in either arm

Conclusions

- The ATALANTE trial evaluated the addition of atezolizumab to standard platinum-based chemotherapy in combination with bevacizumab in patients with late relapsing OC (PFI> 6 months)
- The ATALANTE trial did not meet its PFS primary objective in either ITT or PD-L1-positive populations
- Encouraging OS data warrant further analyses with more follow-up
- Safety data were consistent with the individual profile of each drug and their combination
- Further research on ATALANTE biopsy samples is required to understand better the immunological landscape of late relapsing OC

Acknowledgements

We thank all the patients, their families, the investigators, and the staff.

GINECO - France
JE KURTZ
S ABADIE-LACOURTOISIE
C ABDEDDAIM
J ALEXANDRE
P AUGEREAU
D AVENIN
M AZEMAR
N BABA-HAMED
O BALLY
J BARRIERE
F BAZAN
D BERTON
N BONICHON-LAMICHHANE
N BONNIN
E BOUGHALEM
R BOUSTANY GRENIER
PE BRACHET
F BROCARD
E BULTOT-BOISSIER
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I VERGOTE
S ALTINTAS
H DENYS
E VAN NIEUWENHUYSEN

ISGO - Israel
O ROSENGARTEN

Sponsor ARCAGY-GINECO
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Centre de Ressources Biologiques of ARCAGY-GINECO (Institut Curie)
A. Degnieau
E. Glais

Funding
Hoffmann-La Roche Ltd

Medical writing support
J. Kelly