#COSA21

Safety/Tolerability and Preliminary Antitumour Activity of Sitravatinib Plus Tislelizumab in Patients With Advanced Platinum-Resistant Ovarian Cancer (PROC)

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Disclosure Information

Jeffrey C. Goh

I have the following financial relationships to disclose:

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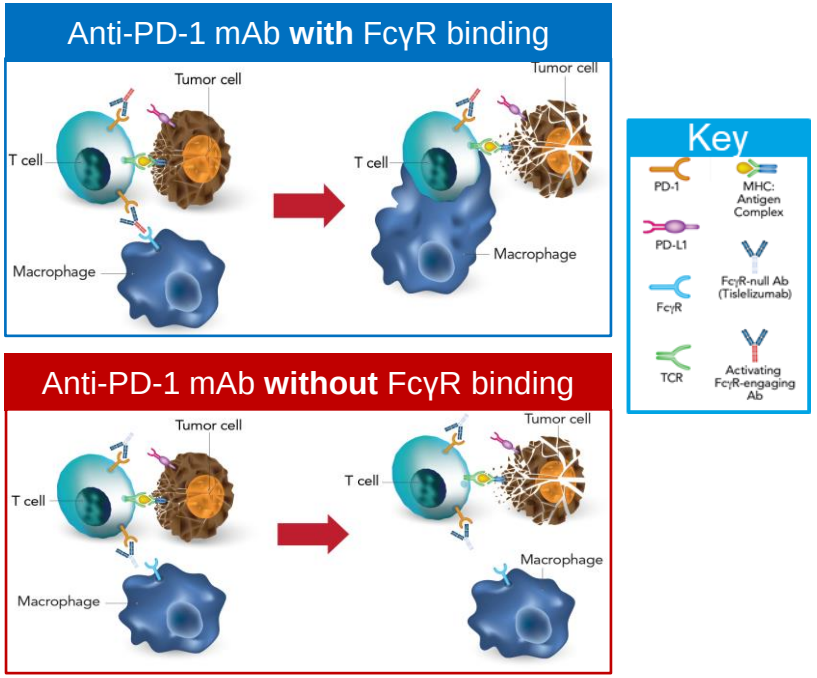
Background

- The 1L standard of care for OC is platinum-based chemotherapy ± bevacizumab[1]
- Disease recurrence is frequent and almost all patients become refractory or resistant to platinum-based therapy[2]
- Based on several Phase 1/2 studies, the efficacy of anti-PD-1/PD-L1 immune checkpoint inhibitors remains limited as a monotherapy in heavily pretreated patients with OC, generally producing ORRs of ~10–15%[3–6]
- Tislelizumab is an anti-PD-1 antibody engineered to minimize FcγR binding on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential anti-PD-1 resistance[7–9]

Tislelizumab MoA



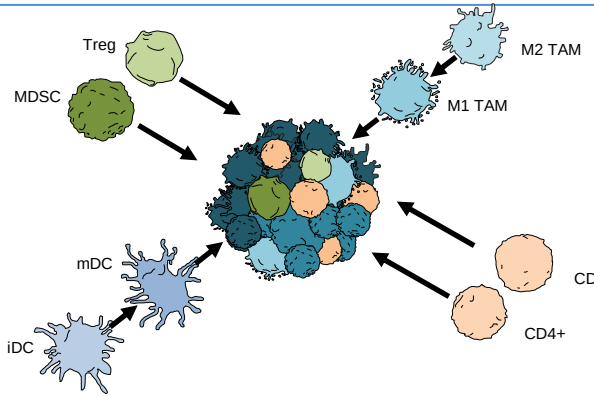
1. Hodi FS, et al. *N Engl J Med*. 2010;363:711–723. 2. Robert C, et al. *N Engl J Med*. 2015;372:2521–2532. 3. Larkin J, et al. *N Engl J Med*. 2015;373:23–34. 4. Gide TN, et al. *Clin Cancer Res*. 2018;24:1260–1270. 5. Le Saux O, et al. *Bull Cancer*. 2020;107:465–473. 6. Demircan NC, et al. *Ann Transl Med*. 2020;8:1714. 7. Zhang T, et al. *Cancer Immunol Immunother*. 2018;67:1079–1090. 8. Dahan R, et al. *Cancer Cell*. 2015;28:285–295. 9. Qin S, et al. *Future Oncol*. 2019;15:1811–1822.

Abbreviations: 1L, first-line; Ab, antibody; mAb, monoclonal antibody; MHC, major histocompatibility complex; MoA, mechanism of action; OC, ovarian cancer; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1.

Background

- Sitravatinib is an oral spectrum-selective TKI targeting TAM (TYRO3, AXL, MER) and split (VEGFR2/KIT) receptors[1]
- Inhibition of these receptors reduces the number of MDSCs and regulatory T cells, while increasing the ratio of M1/M2-polarized macrophages, which may overcome an immunosuppressive tumor microenvironment and augment antitumor immune responses[1]
- Combining a PD-1 inhibitor and an agent with immune modulatory and antitumor properties may enhance antitumor activity of either agent[2]

Targeting split RTKs (VEGFR2, KIT)
- Targeting VEGFR2 reduces Tregs & MDSCs
- Targeting KIT also depletes MDSCs
- Releases brakes for expansion of CD8+ T cells via PD-1 inhibition



Targeting TAM (TYRO3, AXL, MER)
- Targeting MERTK & AXL shifts tumor associated macrophage (TAM) type to M1
- M1 macrophages secrete cytokines that enhance immune response (IL-12, TNF)

TAM & split RTKs cooperate to:
- Increase dendritic cell maturity & antigen presentation capacity
- Increase NK cell response
- Increase T cell expansion & trafficking into tumors

- Here, we present data from the Phase 1b study (NCT03666143) of tislelizumab in combination with sitravatinib in patients with anti-PD-1/PD-L1 antibody naïve recurrent PROC

1. Du W, et al. *JCI Insight*. 2018;3:e124184. 2. Demircan NC, et al. *Ann Transl Med*. 2020;8:1714.

Abbreviations: iDC, induced dendritic cell; mDC, myeloid dendritic cell; MDSCs, myeloid-derived suppressor cells; NK, natural killer; PROC, platinum-resistant ovarian cancer; RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; Treg, regulatory T cell.

Study design

Eligibility criteria:

- Age ≥18 years old
- Histologically or cytologically confirmed advanced or metastatic, unresectable solid tumors
- ECOG PS 0,1
- Adequate organ function

Cohort E: Anti-PD-1/PD-L1 Ab naïve recurrent platinum-resistant OC
(PROC, defined as relapse 1–6 months after last dose of platinum-based treatment)
Tislelizumab 200 mg IV Q3W + sitravatinib 120 mg PO QD

N = 20 for all cohorts
Cohort A: Nsq NSCLC; Anti-PD-1/PD-L1 Ab R/R
Cohort B: Nsq NSCLC; Anti-PD-1/PD-L1 Ab naïve
Cohort C: RCC; Anti-PD-1/PD-L1 Ab R/R
Cohort D: (China): RCC; Metastatic/advanced without prior systemic therapy
Cohort F: Sq NSCLC; Anti-PD-1/PD-L1 Ab treated metastatic
Cohort G: Melanoma; Anti-PD-1/PD-L1 R/R Ab unresectable or metastatic
Cohort H: Nsq NSCLC; Treatment-naïve, metastatic, positive (≥1%) PD-L1
Cohort I: Sq NSCLC; Treatment-naïve, metastatic, positive (≥1%) PD-L1

- Progressive disease
- Unacceptable toxicity
- Death
- Withdrawal of consent
- Study termination by sponsor

Key eligibility for Cohort E PROC (N = 60):

- No platinum-refractory disease (PD <1 month of last dose of platinum-based chemotherapy)
- No prior exposure to anti-PD-1/PD-L1 agent

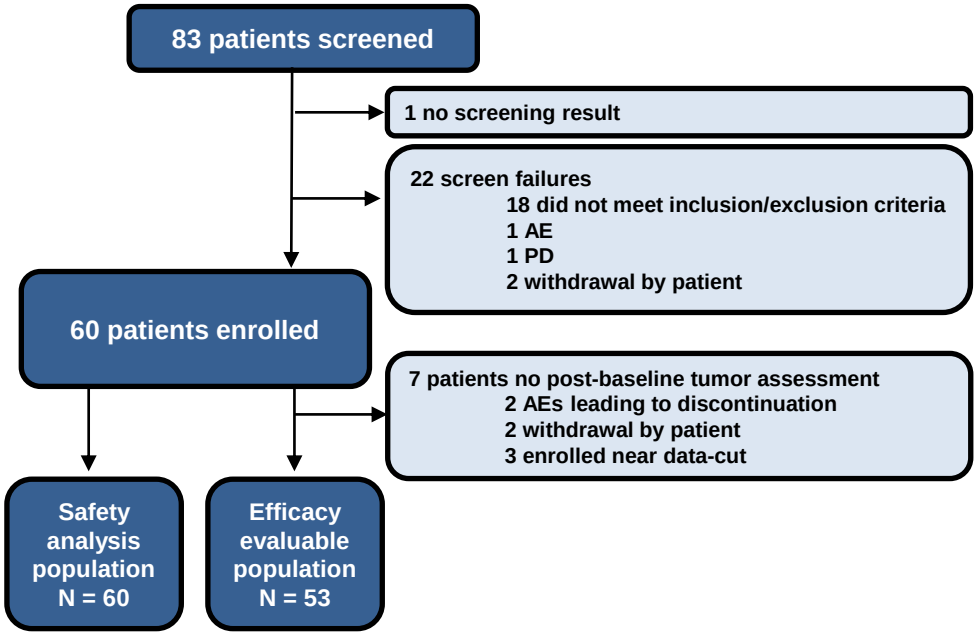
Data cut-off 13 Oct 2020

Key endpoints:

- **Primary**: Safety and tolerability
- **Secondary**: Antitumor activity
- **Exploratory**: PK and immunogenicity, potential pharmacodynamic biomarkers, retrospective analysis of PD-L1 expression

Abbreviations: Ab, antibody; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; NSCLC, non-small cell lung cancer; NSq, non-squamous; PD, progressive disease; PK, pharmacokinetic; PO, orally; PROC, platinum-resistant ovarian cancer; QD, once daily; Q3W, once every three weeks; RCC, renal cell carcinoma; R/R, resistant/refractory; Sq, squamous.

Patient disposition- Cohort E



At the data cut-off, October 13, 2020, a total of 60 patients had been enrolled into the cohort and 13 patients remained on treatment

	PROC (N = 60)
Median duration of follow-up, months (range)	6.0 (0.2–23.4)

Abbreviations: AE, adverse event; PD, progressive disease; PROC, platinum-resistant ovarian cancer.

Baseline characteristics

Baseline characteristics		PROC (N = 60)
Age, years	Median (range)	64 (26–80)
Race, n (%)	Asian	9 (15)
	White*	48 (80)
	Other	3 (5)
ECOG PS, n (%)	0	26 (43)
	1	34 (57)
Primary location, n (%)	Ovary	44 (73)
	Fallopian tube	7 (12)
	Peritoneum	5 (8)
	Other	4 (7)
Epithelial type, n (%)	Serous	57 (95)
	Mucinous	1 (2)
	Endometrioid	1 (2)
	Clear cell	1 (2)
Number of prior regimens	Median (range)	4 (1–11)

Baseline characteristics		PROC (N = 60)
Type of prior systemic therapy, n (%)	Metastatic	50 (83)
	Adjuvant	40 (67)
	Neo-adjuvant	21 (35)
	Locally advanced	11 (18)
	Metastatic and locally advanced	6 (10)
Prior bevacizumab treatment, n (%)	Yes	21 (35)
	No	39 (65)
Duration of last therapy, months	Median (range)	4 (0–57)
PD-L1 expression (tumor cell, TC), n (%)	≥1%	20 (33)
	<1%	29 (48)
	Not available	11 (19)
PD-L1 expression (immune cell, IC), n (%)	≥10%	26 (43)
	<10%	23 (38)
	Not available	11 (19)

PD-L1 membrane staining on tumor cells and immune cells was assessed by the VENTANA PD-L1 (SP263) assay.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PROC, platinum-resistant ovarian cancer.

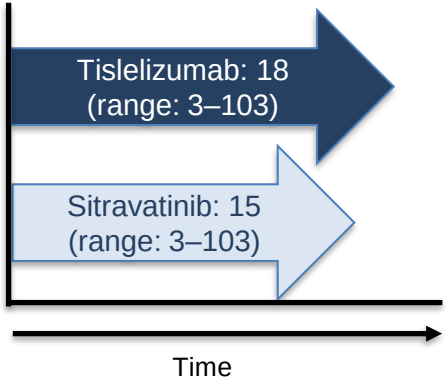
Safety summary

Event, n (%)	PROC N = 60
Patients with at least one TEAE	58 (97)
Treatment-related	55 (92)
Grade ≥3 TEAE	41 (68)
Treatment-related	24 (40)
Serious TEAE	42 (70)
Treatment-related	17 (28)
TEAE leading to death	4 (7)
Treatment-related	0 (0)
TEAE leading to tislelizumab discontinuation	9 (15)
Treatment-related	7 (12)
TEAE leading to sitravatinib discontinuation	14 (23)
Treatment-related	12 (20)

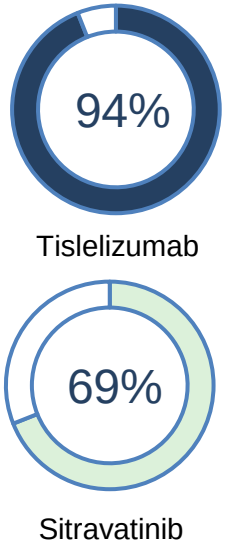
Abbreviations: PROC, platinum-resistant ovarian cancer; TEAE, treatment-emergent adverse event.

Safety summary

Median duration of treatment in weeks



Mean dose intensity



Tislelizumab

43% had their dose delayed*

2% had their dose interrupted*†

Sitravatinib

83% had their dose interrupted

50% had their dose reduced

*Dose delay was defined as drug is withheld beyond the visit window. Dose interruption was defined as an interruption of the infusion.†Due to an infusion-related reaction (muscle spasms of the lower back).

All Grade and Grade ≥3 TEAEs

All Grade with a frequency of ≥20%

Event, n (%)	All Grades N = 60
Diarrhea	40 (67)
Nausea	34 (57)
Fatigue	29 (48)
Hypertension	24 (40)
Decreased appetite	22 (37)
Vomiting	22 (37)
Abdominal pain	21 (35)
Constipation	20 (33)
Increased ALT	18 (30)
Urinary tract infection	16 (27)
Increased AST	12 (20)
Dysphonia	12 (20)
Headache	12 (20)
Palmar-plantar erythrodysesthesia syndrome	12 (20)

Grade ≥3 with a frequency of ≥5%

Event, n (%)	Grade ≥ 3 N = 60
Hypertension	11 (18)
Abdominal pain	7 (12)
Increased ALT	4 (7)
Diarrhea	4 (7)
Dyspnea	4 (7)
Fatigue	4 (7)
Anemia	3 (5)
Intestinal obstruction	3 (5)
Pain	3 (5)
Small intestinal obstruction	3 (5)
Vomiting	3 (5)

Hypertension (18%) and abdominal pain (12%) were the most commonly reported Grade ≥3 TEAEs

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase.

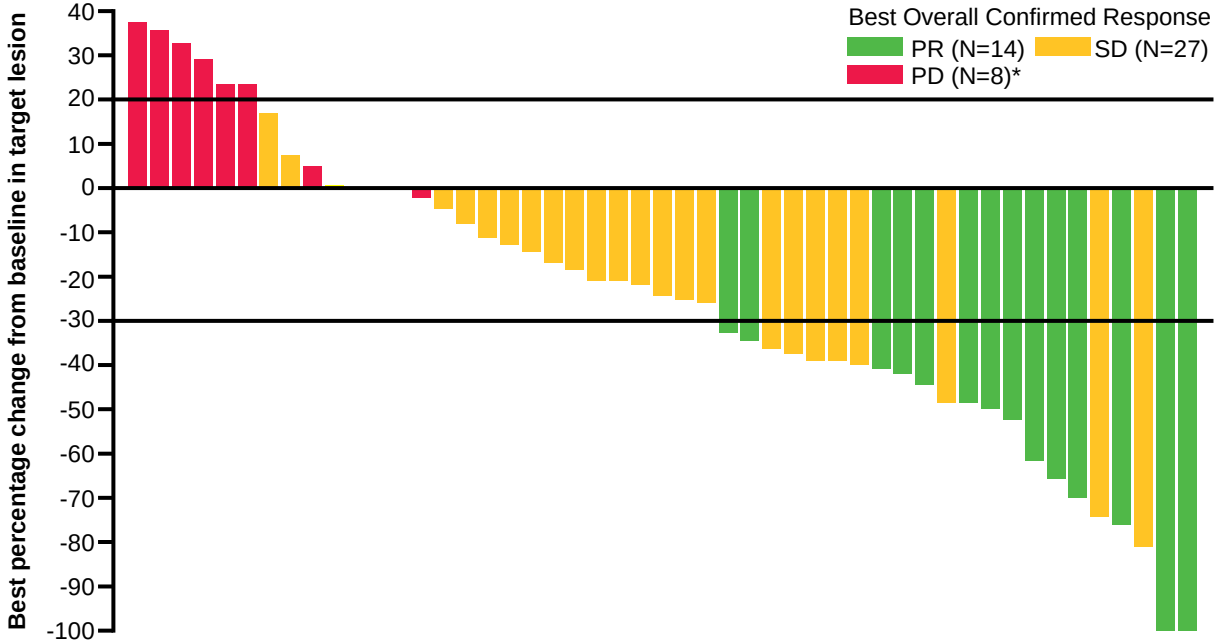
Clinical efficacy

Clinical activity	Efficacy evaluable (n = 53)
ORR, % (95% CI)	26 (15.3–40.3)
Best overall response, n (%)	
Complete response	0 (0)
Partial response	14 (26)
Stable disease	27 (51)
Progressive disease	9 (17)
NE*	3 (6)
DCR, % (95% CI)	77 (63.8–87.7)
Median DoR, months (95% CI)	4.7 (2.83–NE)

*Death or clinical progression before first tumor assessment.

Abbreviations: CI, confidence interval; DCR, disease control rate; DoR, duration of response; NE, non-evaluable, ORR, objective response rate.

Maximum change in target lesion from baseline



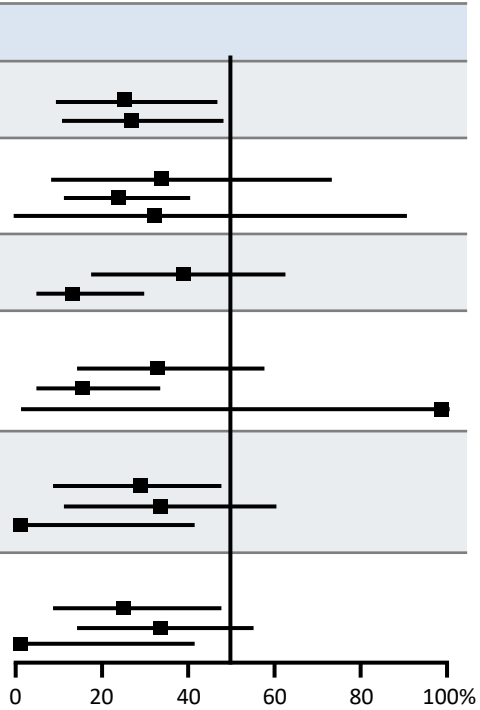
*One patient had disease progression due to new lesion and target lesion was not evaluated.

Abbreviations: PD, progressive disease; PR, partial response; SD, stable disease.

ORR subgroup analysis

BOR per RECIST V1.1, n (%)

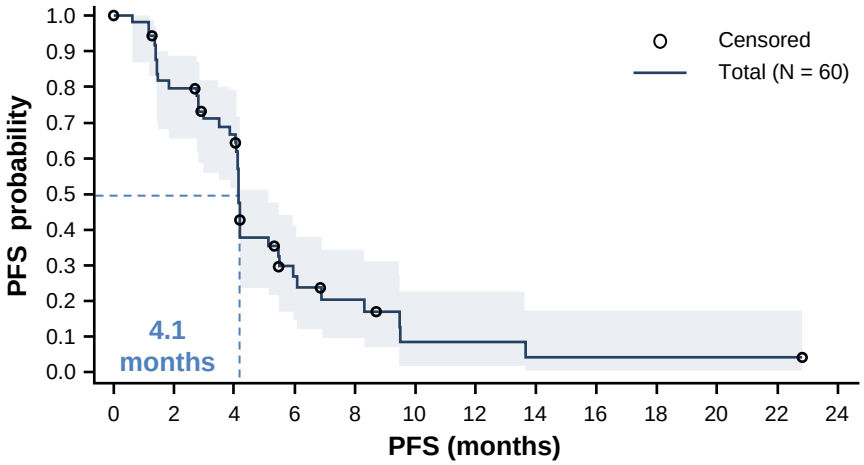
	CR	PR	SD	PD	NE	N	Response	ORR (Exact 95% CI)
Age								
<65	0 (0.0)	7 (25.9)	12 (44.4)	5 (15.5)	3 (11.1)	27	7	25.9 (11.11, 46.28)
≥65	0 (0.0)	7 (26.9)	15 (57.7)	4 (15.4)	0 (0.0)	26	7	26.9 (11.57, 47.79)
Race								
Asian	0 (0.0)	3 (37.5)	4 (50.0)	1 (12.5)	0 (0.0)	8	3	37.5 (8.52, 75.51)
White	0 (0.0)	10 (23.8)	22 (52.4)	8 (19.0)	2 (4.8)	42	10	23.8 (12.05, 39.45)
Other	0 (0.0)	1 (33.3)	1 (33.3)	0 (0.0)	1 (33.3)	3	1	33.3 (0.84, 90.57)
Baseline ECOG								
0	0 (0.0)	9 (39.1)	9 (39.1)	4 (17.4)	1 (4.3)	23	9	39.1 (19.71, 61.46)
1	0 (0.0)	5 (16.7)	18 (60.0)	5 (16.7)	2 (6.7)	30	5	16.7 (5.64, 34.72)
Last line of prior therapy category								
≤3	0 (0.0)	8 (34.8)	7 (30.4)	6 (26.1)	2 (8.7)	23	8	34.8 (16.38, 57.27)
≥4	0 (0.0)	5 (17.2)	20 (69.0)	3 (10.3)	1 (3.4)	29	5	17.2 (5.85, 35.77)
NA	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1	1	100.0 (2.50, 100.0)
PD-L1 expression level of TC 1%								
<1%	0 (0.0)	8 (27.6)	18 (62.1)	1 (3.4)	2 (6.9)	29	8	27.6 (12.73, 47.24)
≥1%	0 (0.0)	6 (35.3)	6 (35.3)	5 (29.4)	0 (0.0)	17	6	35.3 (14.21, 61.67)
NA	0 (0.0)	0 (0.0)	3 (42.9)	3 (42.9)	1 (14.3)	7	0	0.0 (0.00, 40.96)
PD-L1 expression level of IC 10%								
<10 %	0 (0.0)	6 (26.1)	13 (56.5)	3 (13.0)	1 (4.3)	23	6	26.1 (10.23, 48.41)
≥10 %	0 (0.0)	8 (34.8)	11 (47.8)	3 (13.0)	1 (4.3)	23	8	34.8 (16.38, 57.27)
NA	0 (0.0)	0 (0.0)	3 (42.9)	3 (42.9)	1 (14.3)	7	0	0.0 (0.00, 40.96)



Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; IC, immune cell; NA, not available; NE, non-evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TC, tumor cell.

Clinical efficacy

PFS

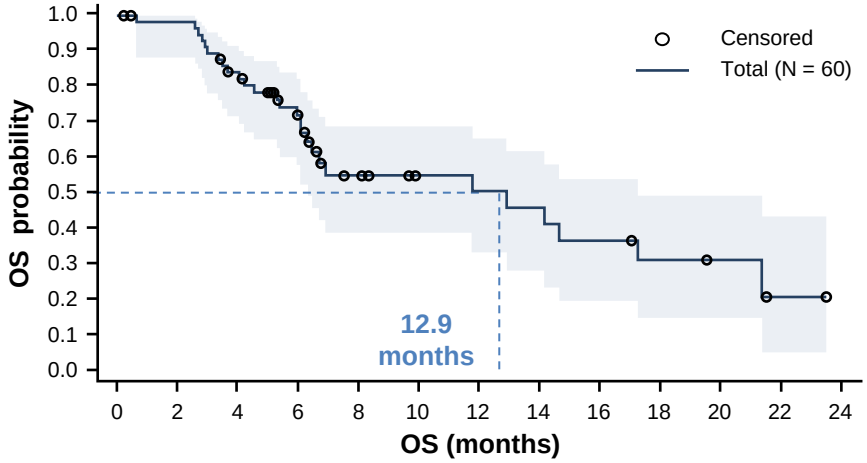


Number of Patients at Risk:

OC Total	60	39	30	9	6	2	2	1	1	1	1	1	0

Median follow-up: 6.9 months (95% CI: 4.0–22.8)

OS



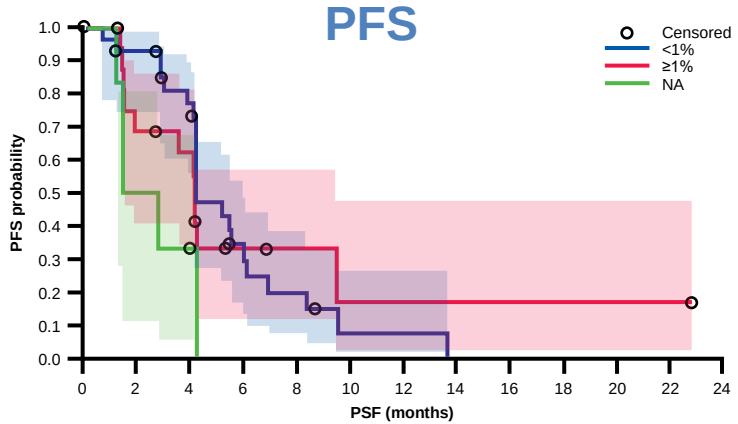
Number of Patients at Risk:

OC Total	60	56	45	31	16	12	11	10	8	6	3	1	0

Median follow-up: 7.5 months (95% CI: 6.2–17.0)

Abbreviations: CI, confidence interval; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival.

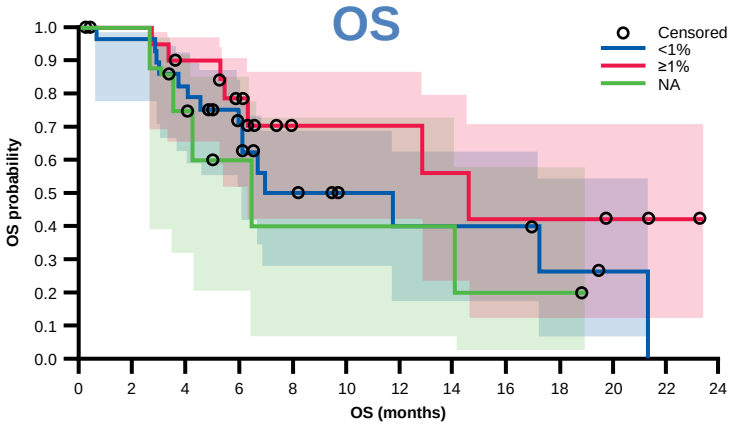
PFS and OS according to PD-L1 expression (TC 1%)



Number of patients at risk:

<1%	29	25	19	6	4	1	1	0	0	0	0	0	0	0
≥1%	20	11	9	3	2	1	1	1	1	1	1	1	0	0
NA	11	3	2	0	0	0	0	0	0	0	0	0	0	0

	Median PFS, months (95% CI)
TC ≥1% (n = 20)	4.1 (1.5–9.5)
TC <1% (n = 29)	4.2 (4.1–6.0)
Not available (n = 11)	2.1 (1.2–4.2)
Total (N = 60)	**4.1 (4.0–5.1)**



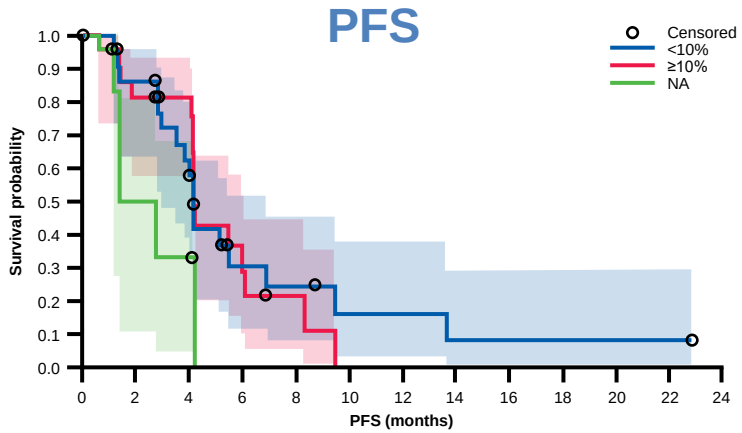
Number of patients at risk:

<1%	29	28	23	17	8	5	4	4	4	2	1	0	0	
≥1%	20	20	16	11	6	5	5	4	3	3	2	1	0	
NA	11	8	6	3	2	2	2	2	1	1	0	0	0	

	Median OS, months (95% CI)
TC ≥1% (n = 20)	14.6 (6.3–NE)
TC <1% (n = 29)	11.8 (6.1–21.3)
Not available (n = 11)	6.5 (2.6–NE)
Total (N = 60)	**12.9 (6.3–17.2)**

Abbreviations: CI, confidence interval; NA, not available; NE, non-evaluable; OS, overall survival; PFS, progression-free survival; TC, tumor cell.

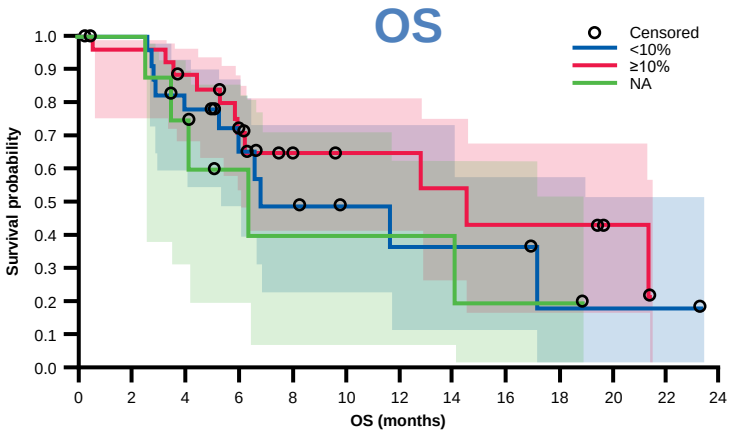
PFS and OS according to PD-L1 expression (IC 10%)



Number of patients at risk:

<10%	23	19	13	5	4	2	2	1	1	1	1	1	1	0
≥10%	26	17	15	4	2	0	0	0	0	0	0	0	0	0
NA	11	3	2	0	0	0	0	0	0	0	0	0	0	0

	Median PFS, months (95% CI)
IC ≥10% (n = 26)	4.1 (4.1–6.1)
IC <10% (n = 23)	4.2 (3.0–6.9)
Not available (n = 11)	2.1 (1.2–4.2)
Total (N = 60)	**4.1 (4.0–5.1)**



Number of patients at risk:

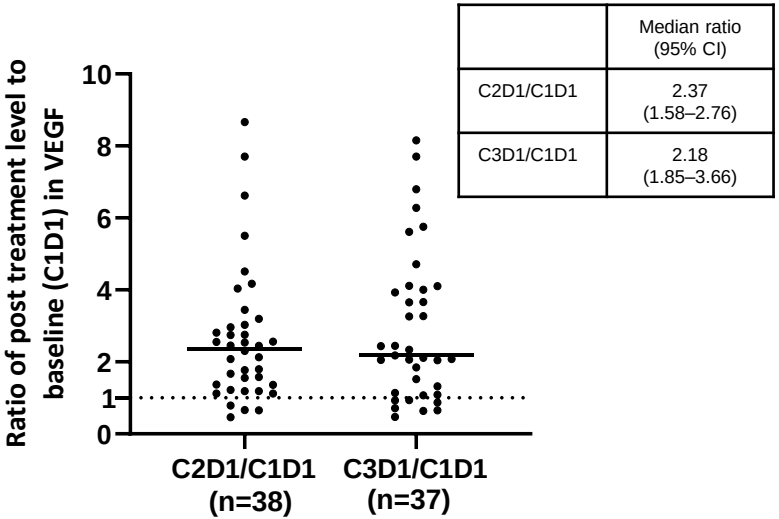
<10%	23	23	18	11	6	4	3	3	3	1	1	1	0	
≥10%	26	25	21	17	8	6	6	5	4	4	2	0	0	
NA	11	8	6	3	2	2	2	2	1	1	0	0	0	

	Median OS, months (95% CI)
IC ≥10% (n = 26)	14.6 (6.1–NE)
IC <10% (n = 23)	6.9 (5.29–NE)
Not available (n = 11)	6.5 (2.60–NE)
Total (N = 60)	**12.9 (6.3–17.2)**

Abbreviations: CI, confidence interval; IC, immune cell; NA, not available; NE, non-evaluable; OS, overall survival; PFS, progression-free survival.

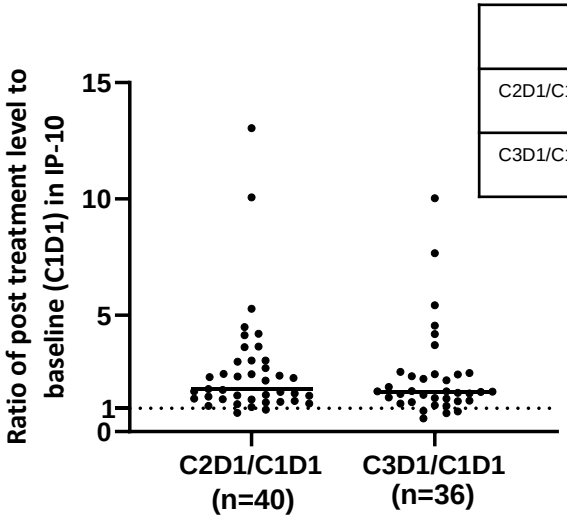
Plasma VEGF and serum IP-10 increased after treatment

Fold change of plasma VEGF and serum IP-10 after tislelizumab and sitravatinib combination treatment



	Median ratio (95% CI)
C2D1/C1D1	2.37 (1.58–2.76)
C3D1/C1D1	2.18 (1.85–3.66)

C2D1 vs C1D1 (n=38): *P*<0.0001
C3D1 vs C1D1 (n=37): *P*<0.0001



	Median ratio (95% CI)
C2D1/C1D1	1.81 (1.55–2.47)
C3D1/C1D1	1.71 (1.45–2.28)

C2D1 vs C1D1 (n=40): *P*<0.0001
C3D1 vs C1D1 (n=36): *P*<0.0001

P-value is determined by one sample Wilcoxon signed-rank test on the fold change.

Abbreviations: C1D1, Cycle 1 Day 1 predose, 21 days per cycle; C2D1, Cycle 2 Day 1 predose; C3D1, Cycle 3 Day 1 predose; CI, confidence interval; IP-10, Interferon-gamma-induced protein 10; vEGF, Vascular endothelial growth factor.

Conclusions

- Tislelizumab in combination with sitravatinib was generally well tolerated and had a manageable safety/tolerability profile in patients with anti-PD-1/PD-L1 antibody naïve recurrent platinum-resistant epithelial OC
- The combination treatment also demonstrated preliminary antitumor activity, with patients achieving an ORR of 26%, DCR of 77%, and median PFS of 4.1 months (95% CI: 4.0–5.1)
- There was a trend toward longer OS in patients with PD-L1 IC expression ≥10%; however, the sample size is small
- The results from this Phase 1b study support tislelizumab in combination with sitravatinib as a potential treatment option for patients with PROC and further investigation (randomized study) is warranted

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