Safety/tolerability and antitumor activity of sitravatinib plus tislelizumab in patients with advanced platinum-resistant ovarian cancer

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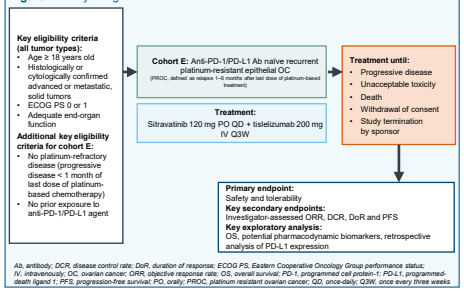
Introduction

- The first-line standard of care for ovarian cancer (OC) is platinum-based chemotherapy, with the option to add the anti-angiogenic agent bevacizumab[1]
- There are currently no immune checkpoint inhibitors (CPI) approved for treatment of OC, however, several Phase 1/2 studies have shown promising results of programmed cell protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibition in patients with platinum-resistant ovarian cancer (PROC), generally producing objective response rates (ORRs) of ~10%[2,3]
- Tislelizumab is an anti-PD-1 antibody with high affinity and binding specificity for PD-1 that has been engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapy[4,5]
- Sitravatinib is an oral spectrum-selective tyrosine kinase inhibitor targeting TAM (TYRO3, AXL, MER) and split tyrosine-kinase domain-containing receptors (VEGFR2, KIT)[6]
- Tislelizumab plus sitravatinib is currently being investigated in several solid tumor types (NCT03666143). In this cohort of patients, data from the primary cut-off (October 13, 2020), showed that the combination of tislelizumab plus sitravatinib had preliminary antitumor activity and was generally well tolerated[7]
- Here we report updated results, in the PROC cohort, from the Phase 1b study

Methods

- An open-label, multicentre, non-randomized, multi-cohort, Phase 1b study was conducted (NCT03666143)
- Study design and endpoints are summarized in **Figure 1**
- PD-L1 expression was assessed retrospectively using the Ventana SP263 immunohistochemistry assay. Samples were deemed PD-L1 positive at a cut-off of ≥ 1% on tumor cells (TC) or ≥ 10% on immune cells (IC)

Figure 1. Study design



Ab, antibody; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; OC, ovarian cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell protein-1; PD-L1, programmed-death ligand 1; PFS, progression-free survival; PO, orally; PROC, platinum resistant ovarian cancer; QD, once-daily; Q3W, once every three weeks

Results

Patients

- As of March 29, 2021, 63 patients were enrolled into cohort E (n=59, efficacy evaluable population), and 27 patients (42.9%) remained on treatment
- Median follow-up was 8.9 months (range: 0.6–28.9), an additional 2.9 months compared with the primary data cut off (October 13, 2020, 6.0 months)
- Patients received a median of four prior regimens (range: 1–11)
- Baseline characteristics are summarized in **Table 1**

Conclusions

- **Tislelizumab plus sitravatinib combination had a manageable safety and tolerability profile with a longer follow-up period, similar to data previously reported[7]**
- **The combination demonstrated antitumor activity, in patients with anti-PD-1/PD-L1 antibody naïve recurrent PROC, with an ORR of 28.8%, DCR of 79.7%, PFS of 4.1 months and OS of 11.8 months**
- **These results support further investigation of tislelizumab plus sitravatinib in this patient population**

Table 1. Demographics and baseline characteristics

		Total (N=63)
Age, years	Median (range)	66.0 (26.0–80.0)
Race, n (%)	Asian	10 (15.9)
	White	50 (79.4)
	Other	3 (4.8)
ECOG PS, n (%)	0	26 (41.3)
	1	37 (58.7)
Epithelial type, n (%)	Serous	60 (95.2)
	Mucinous	1 (1.6)
	Endometrioid	1 (1.6)
	Clear cell	1 (1.6)
Prior bevacizumab treatment	Yes	22 (34.9)
	No	41 (65.1)
PD-L1 expression TC, n (%)	≥ 1%	21 (33.3)
	< 1%	33 (52.4)
	NA	9 (14.3)
PD-L1 expression IC, n (%)	≥ 10%	27 (42.9)
	< 10%	27 (42.9)
	NA	9 (14.3)

ECOG PS, Eastern Cooperative Oncology Group performance status; IC, immune cell; NA, not available; PD-L1, programmed-death ligand 1; TC tumor cell

Safety

- Median duration of exposure was 16.0 weeks (range: 0.3–106.0) for sitravatinib and 18.0 weeks (range: 3.0–109.0) for tislelizumab
- All patients had at least one treatment-emergent adverse event (TEAE) and 95.2% (n=60) had at least one treatment-related adverse event (TRAE) (**Table 2**)
- There were five fatal TEAEs, which were unrelated to treatment (**Table 2**)
- Most patients (n=56, 88.9%) had sitravatinib dose modification
- The most common TEAE leading to tislelizumab discontinuation was increased transaminases (4.8%). The most common TEAEs leading to sitravatinib discontinuation was abdominal pain, hypertension, increased transaminases, fatigue and nausea (each 3.2%)
- The most frequently observed TEAEs were diarrhea (68.3%), nausea (55.6%) and fatigue (50.8%)
- Hypertension and fatigue were the most common ≥ Grade 3 TEAEs 17.5% and 9.5%, respectively

Table 2. Summary of TEAE and TRAE incidence (safety analysis set)

Patients, n (%)	Total (N=63)	
	TEAEs	TRAEs
Any AE	63 (100.0)	60 (95.2)
≥ Grade 3 AE	47 (74.6)	27 (42.9)
Serious AE	47 (74.6)	20 (31.7)
≥ Grade 3 serious AE	41 (65.1)	17 (27.0)
AE leading to death	5 (7.9)	0 (0.0)
AE leading to sitravatinib discontinuation	16 (25.4)	13 (20.6)
AE leading to tislelizumab discontinuation	12 (19.0)	9 (14.3)
AE leading to sitravatinib dose modification[a]	56 (88.9)	49 (77.8)
AE leading to tislelizumab dose modification[a]	28 (44.4)	22 (34.9)
≥ Grade 3 TEAEs reported in ≥ 5% of patients[b]		
Hypertension	11 (17.5)	
Fatigue	6 (9.5)	
Abdominal pain	5 (7.9)	
Diarrhea	5 (7.9)	
Alanine aminotransferase increased	4 (6.3)	
Dyspnoea	4 (6.3)	
Small intestine obstruction	4 (6.3)	

[a]AE leading to sitravatinib dose modification includes dose reduction and/or interruption; [b]AE leading to tislelizumab dose modification includes dose delay and/or interruption; [b] Incidences reported by preferred term for any TEAE reported in ≥ 5% of patients
AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

Efficacy

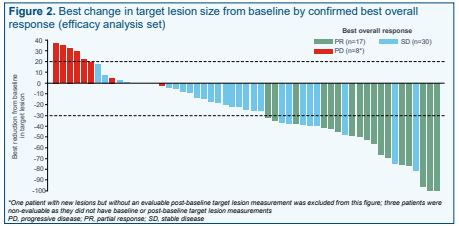
- In the efficacy evaluable population, confirmed ORR was 28.8%, partial response, and stable disease were reported in 17 (28.8%) and 30 (50.8%) patients, respectively. Few patients (n=9 [15.3%]) had progressive disease and 3 (5.1%) patients were non-evaluable
- Disease control was achieved in 79.7% of patients and median duration of response was 5.6 months (95% CI: 2.8, 22.3)
- Best change in target lesion for patients in the efficacy evaluable population is shown in **Figure 2**
- In the overall population, median progression-free survival (PFS) was 4.1 months (95% CI: 3.5, 5.1) (**Figure 3A**) and median overall survival (OS) was 11.8 months (95% CI: 6.7, 17.2) (**Figure 3B**). OS data are immature median follow-up was 11.7 months (95% CI: 10.6, 15.4)
- Using PD-L1 TC 1% or IC 10% as a cut off, no clear association was observed between PD-L1 expression and ORR, PFS or OS in the analysis population (**Table 3, Figure 3C–3F**)

Table 3 Analysis of confirmed response per RECIST v1.1 by PD-L1 expression (efficacy analysis set)

PD-L1 expression level	ORR, % (95% CI)
TC ≥ 1% (n=18)	33.3 (13.3, 59.0)
TC < 1% (n=33)	30.3 (15.6, 48.7)
IC ≥ 10% (n=24)	37.5 (18.8, 59.4)
IC < 10% (n=27)	25.9 (11.1, 46.3)
PD-L1 NA (n=8)	12.5 (0.3, 52.7)

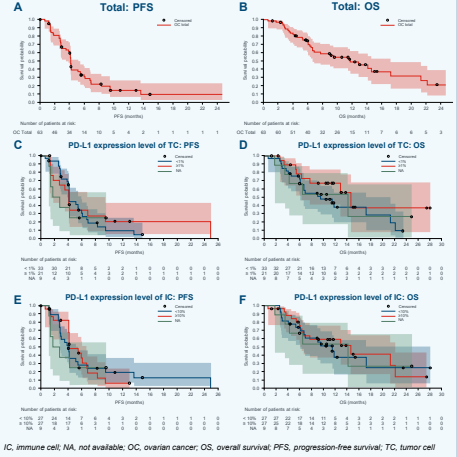
CI, confidence interval; IC, immune cell; NA, not available; ORR, objective response rate; PD-L1; programmed death-ligand 1; RECIST, response evaluation criteria in solid tumors; TC, tumor cell

Figure 2. Best change in target lesion size from baseline by confirmed best overall response (efficacy analysis set)



One patient with new lesions but without an evaluable post-baseline target lesion measurement was excluded from this figure; three patients were non-evaluable as they did not have baseline or post-baseline target lesion measurements
PD, progressive disease; PR, partial response; SD, stable disease

Figure 3. PFS and OS (safety analysis set)

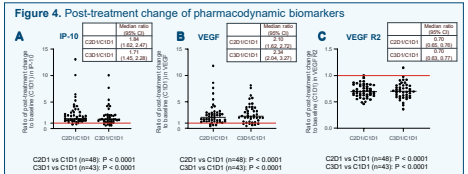


IC, immune cell; NA, not available; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; TC, tumor cell

Pharmacodynamic (PD) analysis

- Increase of interferon gamma-induced protein 10 (IP-10) and vascular endothelial growth factor (VEGF), and decrease of VEGF R2 at C2D1 or C3D1 from baseline (C1D1) were observed after treatment (**Figure 4**)

Figure 4. Post-treatment change of pharmacodynamic biomarkers



C2D1 vs C1D1 (n=48): P < 0.0001
C3D1 vs C1D1 (n=43): P < 0.0001

P values were determined by pairwise Wilcoxon signed rank test
C1D1, cycle 1 day 1 pre-dose; C2D1: cycle 2 day 1 pre-dose; C3D1: cycle 3 day 1 pre-dose; IP-10, interferon gamma-induced protein 10; VEGF, vascular epithelial growth factor; VEGF R2, vascular epithelial growth factor receptor 2

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