Safety/tolerability and antitumor activity of sitravatinib plus tislelizumab in patients with PD-(L)1 refractory/resistant unresectable or metastatic melanoma from a Phase 1b study

Chuanliang Cui*,[1] Hongming Pan,[2] Matteo Carlino,[3] Jiuwei Cui,[4] Xuan Wang,[1] Xin Li,[5] Jingchao Sun,[6] Liu Yang,[5] Jun Guo[1]

[1]Department of Renal Cancer and Melanoma, Peking University Cancer Hospital and Institute, Beijing, China; [2]Oncology Department, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China; [3]Department of Medical Oncology, Blacktown Hospital, Blacktown, NSW, Australia; [4]Cancer Center, The First Hospital of Jilin University, Changchun, China; [5]Clinical Development, BeiGene (Beijing) Co., Ltd., Beijing, China; [6]Global Statistics and Data Science, BeiGene (Beijing) Co., Ltd., Beijing, China.
*Corresponding author

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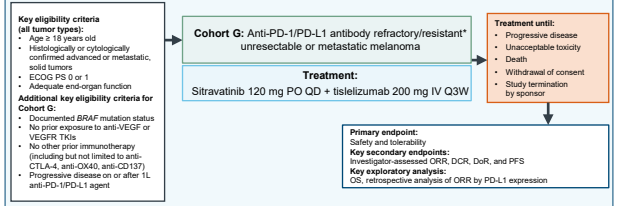
Introduction

- Immune checkpoint inhibitors (CPI) are established as the standard of care in the first-line setting for patients with unresectable and metastatic melanoma, demonstrating improved clinical outcomes for patients[1,2]
- However, a subset of patients who initially respond to CPI, later relapse and develop drug resistance[3]
- Combining an immunotherapeutic programmed cell death protein 1 (PD-1) CPI with an agent that has both pleiotropic and antitumor properties could enhance the antitumor efficacy observed with either agent alone[4]
- 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[5,6]
- Sitravatinib is an oral spectrum-selective tyrosine kinase inhibitor targeting TAM (TYRO3, AXL, MER) and split tyrosine-kinase domain-containing receptors (VEGF R2, KIT)[7]
- Tislelizumab plus sitravatinib is currently being investigated in several solid tumor types (NCT03666143). In this cohort of patients with anti-PD-1/programmed death-ligand 1 (PD-L1) antibody refractory/resistant (R/R) unresectable or metastatic melanoma, data from the primary cut-off (October 13, 2020), demonstrated that the combination of tislelizumab plus sitravatinib had preliminary antitumor activity and was generally well tolerated[8]
- Here we report updated results, in the melanoma cohort, from the Phase 1b study

Methods

- An open-label, multicenter, non-randomized, multi-cohort, Phase 1b study was conducted (NCT03666143)
- Study design and endpoints are summarized in **Figure 1**

Figure 1. Study design



*Refractory was defined as radiographic progressive disease < 12 weeks after initiation of treatment and resistant was defined as RECIST v1.1 partial, complete response or stable disease for at least 12 weeks after treatment initiation followed by radiographic progressive disease
1L, first-line; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PO, orally; Q3W, once every three weeks; QD, once-daily; RECIST, response evaluation criteria in solid tumors; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor

Results

Patients

- As of March 29, 2021, 25 patients were enrolled to Cohort G, and 10 patients (40.0%) remained on treatment
- Median follow-up was 9.6 months (range: 5.6–18.8), an additional 4.1 months compared with the primary data cut-off (October 13, 2020, 5.5 months)
- All patients received at least one prior line of anti-PD-1/PD-L1 therapy
- Baseline characteristics are summarized in **Table 1**

Table 1. Demographics and baseline characteristics

		Total (N=25)
Age, years	Median (range)	51.0 (23–79)
Sex, n (%)	Male	13 (52.0)
	Female	12 (48.0)
Race, n (%)	Asian	23 (92.0)
	White	2 (8.0)
ECOG PS, n (%)	0	3 (12.0)
	1	22 (88.0)
Histology, n (%)	Cutaneous	12 (48.0)
	Acral	7 (28.0)
	Mucosal	4 (16.0)
Number of prior regimens, n (%)	1	24 (96.0)
	≥ 2	1 (4.0)
BRAF mutation status	Positive	6 (24.0)
	Negative	19 (76.0)
Duration of last therapy, months	Median (range)	6.0 (2.1–28.3)

BRAF, v-raf murine sarcoma viral oncogene homolog B1; ECOG PS, Eastern Cooperative Oncology Group performance status

Conclusions

- **Tislelizumab plus sitravatinib combination had a manageable safety and tolerability profile with a longer follow-up period, similar to data previously reported[8]**
- **The combination demonstrated encouraging antitumor activity in patients with R/R unresectable or metastatic melanoma previously treated with a PD-(L)1 inhibitor, with an ORR of 36.0%, disease control rate of 88.0% and PFS of 6.7 months**
- **These results support further investigation of tislelizumab plus sitravatinib in this patient population**

Safety

- Median duration of exposure was 30.0 weeks (range: 3.0–83.9) for both sitravatinib and tislelizumab
- Mean relative dose intensity was 77.0% (standard deviation [SD]: 25.2) for sitravatinib and 90.9% (SD: 12.6) for tislelizumab
- All patients had at least one treatment-emergent adverse event (TEAE) and treatment-related adverse event (TRAE) (**Table 2**)
- One patient discontinued tislelizumab treatment because of a vaginal hemorrhage
- One patient discontinued sitravatinib treatment as a result of increased blood creatinine phosphokinase
- No patients discontinued treatment due to hypertension
- No TEAEs or TRAEs led to death

Table 2. Summary of TEAE and TRAE incidence

Patients, n (%)	All patients (N=25)	
	TEAEs	TRAEs
Any AE	25 (100.0)	25 (100.0)
≥ Grade 3 AE	13 (52.0)	10 (40.0)
Serious AE	3 (12.0)	3 (12.0)
≥ Grade 3 serious AE	2 (8.0)	2 (8.0)
AE leading to death	0 (0.0)	0 (0.0)
AE leading to sitravatinib discontinuation	1 (4.0)	1 (4.0)
AE leading to tislelizumab discontinuation	1 (4.0)	0 (0.0)
AE leading to sitravatinib dose modification*	18 (72.0)	16 (64.0)
AE leading to tislelizumab dose modification†	9 (36.0)	8 (32.0)

*AE leading to sitravatinib dose modification includes dose reduction and/or interruption
†AE leading to tislelizumab dose modification includes dose delay and/or interruption
AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

- The most frequently observed TEAEs were increased alanine transaminase (76.0%), increased aspartate aminotransferase (76.0%), and increased blood cholesterol (64.0%) (**Table 3**)
- Hypertension was the most common ≥ Grade 3 TEAE (16.0%), followed by increased alanine transaminase (12.0%) and increased gamma-glutamyltransferase (12.0%)

Table 3. All Grade TEAEs with ≥ 30% frequency

Event, n (%)	All Grades (N=25)	Event, n (%)	All Grades (N=25)
Increased alanine transaminase	19 (76.0)	Abnormal electrocardiogram T wave	11 (44.0)
Increased aspartate aminotransferase	19 (76.0)	Proteinuria	11 (44.0)
Increased blood cholesterol	16 (64.0)	Increased blood bilirubin	10 (40.0)
Weight decreased	16 (64.0)	Increased gamma-glutamyltransferase	10 (40.0)
Hypothyroidism	15 (60.0)	Hypertension	10 (40.0)
Hypertriglyceridemia	14 (56.0)	Increased creatine phosphokinase myocardial band isozyme	9 (36.0)
Increased blood creatinine phosphokinase	12 (48.0)	Palmar-plantar erythrodysaesthesia syndrome	9 (36.0)
Diarrhea	12 (48.0)	Vomiting	8 (32.0)

TEAE, treatment-emergent adverse event

Efficacy: Tumor response

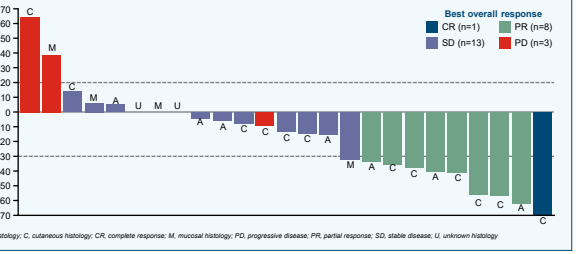
- In the overall population, confirmed objective response rate (ORR) was 36.0%, with one patient achieving a confirmed complete response. Partial response, and stable disease were reported in eight (32.0%) and 13 (52.0%) patients, respectively
- Three patients (12.0%) had progressive disease (**Table 4** and **Figure 2**)
- Disease control was achieved in 88.0% of patients (**Table 4**)
- Best change in target lesion for all patients is shown in **Figure 2**

Table 4. Analysis of confirmed objective response per RECIST v1.1

	Total (N=25)
ORR, % (95% CI)	36.0 (18.0, 57.5)
Best overall response, n (%)	
CR	1 (4.0)
PR	8 (32.0)
SD	13 (52.0)
PD	3 (12.0)
DCR, % (95% CI)	88.0 (68.8, 97.5)
Median DoR, months (95% CI)	NE (2.8, NE)

CR, complete response; DCR, disease control rate; DoR, duration of response; NE, non-evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease

Figure 2. Best change in target lesion size from baseline by confirmed best overall response

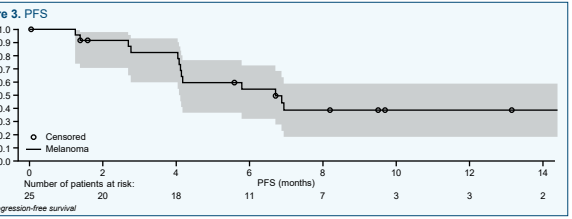


A, acral histology; C, cutaneous histology; CR, complete response; M, mucosal histology; PD, progressive disease; PR, partial response; SD, stable disease; U, unknown histology

Efficacy: Survival

- Median progression-free survival (PFS) was 6.7 months (95% CI: 4.1, non-evaluable) (**Figure 3**)
- Overall survival data are not yet mature (median follow-up duration: 10.1 months)

Figure 3. PFS



PFS, progression-free survival

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***Author contact details:** 1008ccl@163.com (Chuanliang Cui)