SAFETY/TOLERABILITY AND PRELIMINARY ANTITUMOR ACTIVITY OF SITRAVATINIB PLUS TISLELIZUMAB IN PATIENTS WITH PD-(L)1 REFRACTORY/RESISTANT UNRESECTABLE OR METASTATIC MELANOMA FROM A PHASE 1B STUDY

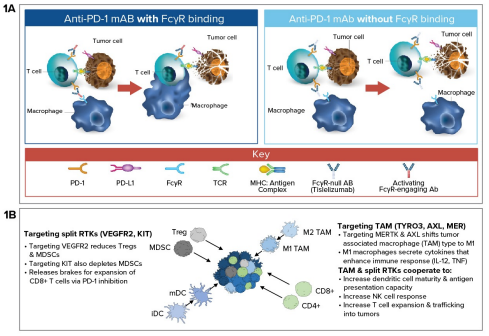
Chuanliang Cui,[1] Hongming Pan,[2] **Matteo Carlino**,[3] Jiuwei Cui,[4] Xuan Wang,[1] Xin Li,[5] Jingchao Sun,[5] Liu Yang,[5] Jun Guo[1]

[1]Beijing Cancer Hospital, Beijing, China; [2]Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China; [3]Blacktown Hospital, Blacktown NSW, Australia; [4]The First Hospital of Jilin University, Changchun, China; [5]BeiGene (Beijing) Co., Ltd., Beijing, China

INTRODUCTION

- Immune checkpoint inhibitors (CPIs) are established as the standard of care in the first-line setting for patients with unresectable or metastatic melanoma;[1-3] however, not all patients respond and a subset of patients who initially respond to CPI later relapse and develop drug resistance[4]
- 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[5-7] (**Figure 1a**)
- Sitravatinib is an oral spectrum-selective tyrosine kinase inhibitor (TKI) targeting TAM (TYRO3, AXL, MER) and split (VEGFR2/KIT) receptors[8]
  - Inhibition of these receptors reduces the number of myeloid-derived suppressor cells 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[8] (**Figure 1b**)
- Combining an anti-PD-1 CPI with an agent that has both pleiotropic and antitumor properties could enhance the antitumor efficacy observed with either agent alone[9,10]
- Tislelizumab plus sitravatinib is currently being investigated in several solid tumor types, including metastatic melanoma (NCT03666143)

Figure 1. Mechanism of Action of Tislelizumab (A) and Sitravatinib (B)



Abbreviations: Ab, antibody; iDC, induced dendritic cell; mAb, monoclonal antibody; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; Treg, regulatory T cell.

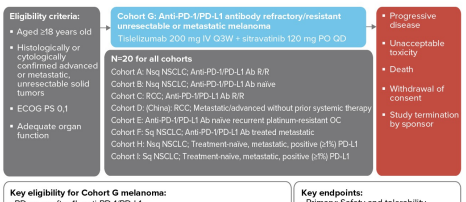
OBJECTIVE

- To assess the safety/tolerability and preliminary antitumor activity of sitravatinib plus tislelizumab in solid tumors

METHODS

- Eligible patients had unresectable or metastatic melanoma refractory/resistant to PD-(L)1 inhibitors and had not received other prior immunotherapy (eg, anti-CTLA-4, -OX40, or -CD137) or anti-BRAF/MEK therapy (**Figure 2**)
  - Cohort G consisted of patients with melanoma
- Patients received oral sitravatinib 120 mg once daily and intravenous tislelizumab 200 mg once every 3 weeks until discontinuation
- The primary endpoint was safety/tolerability; key secondary endpoints included investigator-assessed objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS)

Figure 2. Study Design (BGB-900-103; NCT03666143)

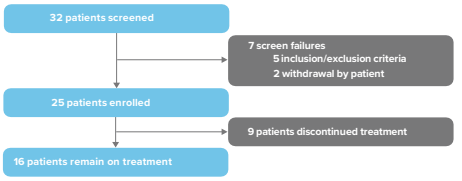


Abbreviations: 1L, first-line; Ab, antibody; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; NSq, nonsquamous; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PK, pharmacokinetic; PO, orally; QD, once-daily; Q3W, once every 3 weeks; RCC, renal cell carcinoma; R/R, resistant/refractory; Sq, squamous; VEGF, vascular endothelial growth factor; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

RESULTS

- As of October 13, 2020, 25 patients were enrolled; 16 patients (64%) remained on treatment (**Figure 3**)
- Median study follow-up was 5.5 months (range: 1.5-13.3)

Figure 3. Patient Disposition – Cohort G



Baseline Characteristics

- All patients received one prior line of PD-(L)1 therapy; median age was 51 years (range: 23-79)
- Baseline histology included cutaneous (n=12; 48%), acral (n=7; 28%), and mucosal (n=4; 16%) subtypes (**Table 1**)

Table 1. Baseline Characteristics

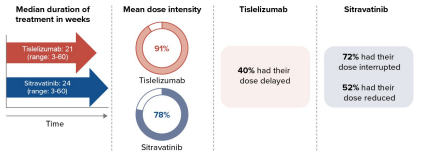
Baseline Characteristics		Melanoma (N=25)
Age, years	Median (range)	51 (23-79)
Sex, n (%)	Male	13 (52)
	Female	12 (48)
Race, n (%)	Asian	23 (92)
	White	2 (8)
ECOG PS, n (%)	0	3 (12)
	1	22 (88)
Histology at initial diagnosis, n (%)	Cutaneous, chronic sun-induced damage	4 (16)
	Cutaneous, without chronic sun-induced damage	8 (32)
	Acral	7 (28)
	Mucosal	4 (16)
	Unknown	2 (8)
***BRAF* mutation, n (%)**	Positive	7 (28)
	Negative	18 (72)
Prior systemic therapy, n (%)	Anti-PD-1/PD-L1	25 (100)
Prior lines of anticancer therapy, n (%)	1	25 (100)
Duration of last therapy, months	Median (range)	7 (2-28)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

Safety

- Tislelizumab treatment resulted in a dose delay in 40% of patients, while sitravatinib resulted in dose interruption in 72% of patients and dose reduction in 52% of patients (**Figure 4**)

Figure 4. Treatment Summary



- One patient (4%) reported a serious adverse event (AE) (**Table 2**)
  - No AE led to death
- Increased ALT and AST were the most common TEAEs; hypertension (n=3; 12%) was the most common grade ≥3 AE

Table 2. Summary of Tolerability

Event, n (%)		Melanoma (N=25)
Patients with at least one TEAE		25 (100)
Treatment-related		25 (100)
Grade ≥3 TEAE		12 (48)
Treatment-related		9 (36)
Serious TEAE[a]		1 (4)
Treatment-related		1 (4)
TEAE leading to treatment discontinuation	Tislelizumab	1 (4)[b]
	Sitravatinib	1 (4)[c]
TRAE leading to treatment discontinuation	Tislelizumab	0 (0)
	Sitravatinib	1 (4)

TEAEs With a Frequency of ≥20%

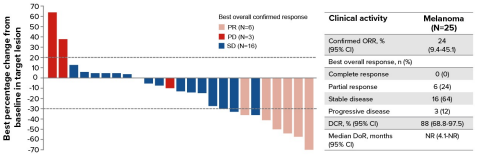
Event, n (%)	All Grades (N=25)	Event, n (%)	All Grades (N=25)
Increased ALT	19 (76)	Increased BB	9 (36)
Increased AST	17 (68)	Abnormal electrocardiogram T wave	9 (36)
Increased blood cholesterol	14 (56)	Hypertension	9 (36)
Hypertriglyceridemia	13 (52)	Palmar-Plantar erythrodysesthesia syndrome	8 (32)
Hypothyroidism	12 (48)	CK-MB increased	7 (28)
Weight decreased	12 (48)	Hyperuricemia	7 (28)
Increased BCK	10 (40)	Upper abdominal pain	6 (24)
Diarrhea	10 (40)	Vomiting	6 (24)
Increased GGT	10 (40)	Hypokalemia	5 (20)
Proteinuria	10 (40)		

[a]Serious TEAE was an anal abscess associated with sitravatinib.
[b]Tislelizumab discontinuation was due to vaginal hemorrhage.
[c]Sitravatinib discontinuation was due to increased blood creatine phosphate.
Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Antitumor Activity

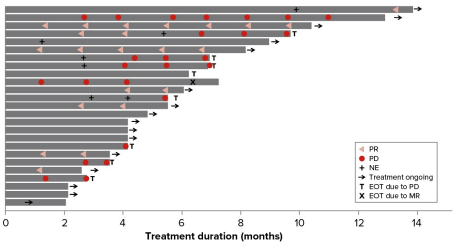
- Treatment with sitravatinib plus tislelizumab resulted in a reduction in tumor burden (**Figure 5**)
  - Confirmed ORR was 24.0% (95% CI: 9.36-45.13; all partial responses, n=6); DCR was 88.0% (95% CI: 68.78-97.45)
- Responses to sitravatinib plus tislelizumab have lasted over 12 months; treatment is ongoing in 16 patients (**Figure 6**)
- Median PFS was 6.7 months (95% CI: 4.07, not evaluable; **Figure 7**)

Figure 5. Antitumor Activity



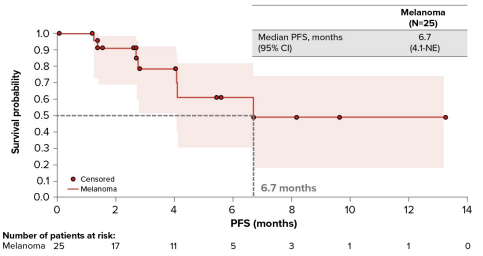
Abbreviations: CI, confidence interval; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 6. Duration of Treatment and Response in Melanoma



Abbreviations: EOT, end of treatment; MR, multiple reason; NE, non-evaluable; PD, disease progression; PR, partial response.

Figure 7. Investigator-Assessed PFS



Abbreviations: CI, confidence interval; NE, non-evaluable; PFS, progression-free survival.

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 refractory/resistant unresectable or metastatic melanoma
  - Most TEAEs were mild or moderate in severity and manageable
  - No TEAEs lead to death
- The combination treatment also demonstrated preliminary antitumor activity, with patients achieving an ORR of 24%, DCR of 88%, and median PFS of 6.7 months (95% CI: 4.1-not evaluable)
- The results from this phase 1b study support tislelizumab in combination with sitravatinib as a potential treatment option for patients with refractory/resistant unresectable or metastatic melanoma and further investigation is warranted

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DISCLOSURES

Chuanliang Cui: No conflicts of interest. **Hongming Pan**: No conflicts of interest. **Matteo Carlino:** Consulting/Advisory Role for BMS, MSD, Novartis, Amgen, Sanofi, Merck serono, Pierre Fabre, Roche, Ideaya, Regeneron, Nektar, Eisai, Qbiotics, Oncosec. Honoraria from BMS, MSD, Novartis. **Jiuwei Cui**: No conflicts of interest. **Xuan Wang:** Consulting/Advisory Role for Oriengene. **Xin Li**: Employment, Stock or Other Ownership at BeiGene. **Jingchao Sun:** Employment, Stock or Other Ownership at BeiGene. **Liu Yang:** Employment, Stock or Other Ownership at BeiGene. **Jun Guo:** Consulting/Advisory Role for MSD, Roche, Pfizer, Bayer, Novartis, Simcere Pharmaceutical Group, Shanghai Junshi Biosciences, Oriengene.

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Correspondence: Email: matteo.carlino@health.nsw.gov.au

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