ESMO IMMUNO-ONCOLOGY

Safety and Antitumor Activity of Sitravatinib in Combination With Tislelizumab in Patients With Advanced Solid Tumors: Ovarian Cancer Cohort Data

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Disclosures

- Bo Gao has served on an advisory board for Merck Sharp & Dohme (outside the submitted work)
- Jeffrey Goh has served on advisory boards for Bristol-Myers Squibb, AstraZeneca, and Ipsen and received payment from Merck Sharp & Dohme for speaking engagements (outside the submitted work)
- Ben Markman has served on an advisory board for Novartis
- Mark Voskoboynik has received honoraria from AstraZeneca and MSD Oncology and received travel, accommodations, or expenses support from Bristol-Myers Squibb
- Hui Gan has served in a consulting or advisory role for AbbVie, Bristol-Myers Squibb, and Merck Sharp & Dohme, served on speakers bureaus for Eisai and Merck Serono, and received research funding from AbbVie
- Jermaine Coward has served on advisory boards for Takeda and Merck Sharp & Dohme and received research funding from AstraZeneca
- David Palmieri, Jane So, and Tarek Meniawy have no conflicts to disclose
- Cheng Chen, Xiao Xiang, Jingjun Qiu, Yingying Xu, and Liu Yang are employees of BeiGene and may have stock, stock options, or restricted stock units in that company
- Michael Millward has served on advisory boards for Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, and AstraZeneca (outside the submitted work)

Phase 1B BGB-900-103 Study Design (NCT03666143)

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)
Sitravatinib 120 mg PO QD + Tislelizumab 200 mg IV Q3W

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:

- 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 cutoff 17 July 2019

Key Endpoints:

- **Primary**: Safety and tolerability
- **Secondary**: Antitumor activity, PK profile
- **Exploratory**: PK and immunogenicity, potential pharmacogenomics biomarkers (PGx)

Retrospective analysis of PD-1 expression

Ab=antibody, ECOG PS=Eastern Cooperative Oncology Group performance status, IV=intravenous, Nsq NSCLC=non-squamous non-small cell lung cancer, PD=progressive disease, PD-1=programmed cell death protein-1, PD-L1=programmed cell death ligand-1, PGx=pharmacogenomics, PK=pharmacokinetics, PO=per oral, PROC=platinum-resistant ovarian cancer, QD=once daily, RCC=renal cell carcinoma, RP2D=recommended phase 2 dose, R/R=refractory/resistant, Sq NSCLC=squamous non-small cell lung cancer, Q3W=every 3 weeks

Background

- **Sitravatinib** is an investigational, orally bioavailable, spectrum-selective RTK inhibitor[1]
  - Modulates tumor microenvironment to overcome checkpoint inhibitor resistance[2]
- **Tislelizumab (BGB-A317)** is an investigational, humanized IgG4 monoclonal antibody with high affinity/binding specificity for PD-1[3]
  - Engineered to minimize binding to FcγR on macrophages to abrogate ADCP[3]
- Combining agents could enhance antitumor efficacy observed with either agent alone[4,5]

Baseline Characteristics - PROC Cohort

Baseline characteristics	Total (N=20)
Age, median, years (range)	66.0 (26–80)
<65 years, n (%)	10 (50.0)
≥65 years, n (%)	10 (50.0)
Race, n (%)	
White	11 (55.0)
Asian	7 (35.0)
Other	2 (10.0)
ECOG PS, n (%)	
0	9 (45.0)
1	11 (55.0)
Primary location, n (%)	
Ovary	15 (75.0)
Fallopian tube	3 (15.0)
Peritoneum	2 (10.0)
Prior bevacizumab, n (%)	6 (30.0)
Number of prior regimens, median (range)	5.0 (2–12)
≥5 lines, n (%)	13 (65.0)

1. Patwardhan PP et al. Oncotarget. 2016;7:4093-4109. 2. Du W et al. JCI Insight. 2018;3:e124184. 3. Zhang T et al. Cancer Immunol Immuother. 2018;67:1079-1090. 4. Leal TA et al. Ann Oncol. 2018;29(suppl 8):viii400-vii441. 5. Leal T et al. IASCL 18th World Conference on Lung Cancer; 15-18 October 2017; Yokohama, Japan; abstract MA 02.01.

ADCP=antibody-dependent cellular phagocytosis, ECOG PS=Eastern Cooperative Oncology Group performance status, FcγR=Fc gamma receptor, IgG4=immunoglobulin G4, PD-1=programmed cell death protein-1, RTK=receptor tyrosine kinase

Safety Data (PROC Cohort) – TEAEs

TEAEs, n (%)	Total (N=20)
Patients reporting ≥1 TEAEs	20 (100)
Grade ≥3 TEAEs	15 (75)
Serious TEAEs	17(85)
TEAEs leading to death (non-TRAE) Abdominal pain Respiratory failure	2 (10) 1 (5) 1 (5)
TEAEs leading to any treatment discontinuation Sitravatinib Tislelizumab	6 (30) 6 (30) 3 (15)
TEAEs leading to sitravatinib dose modification Reduction Interruption	15 (75) 5 (25) 15 (75)
TEAEs leading to tislelizumab dose modification Delay Interruption	9 (45) 8 (40) 1 (5)
Grade ≥3 treatment-related TEAEs Sitravatinib Tislelizumab Both sitravatinib and tislelizumab	 8 (40) 2 (10) 0

- Most common Grade ≥3 TRAEs were hypertension (25%) and fatigue (10%), both sitravatinib-related; of these, none were Grade 4 or 5

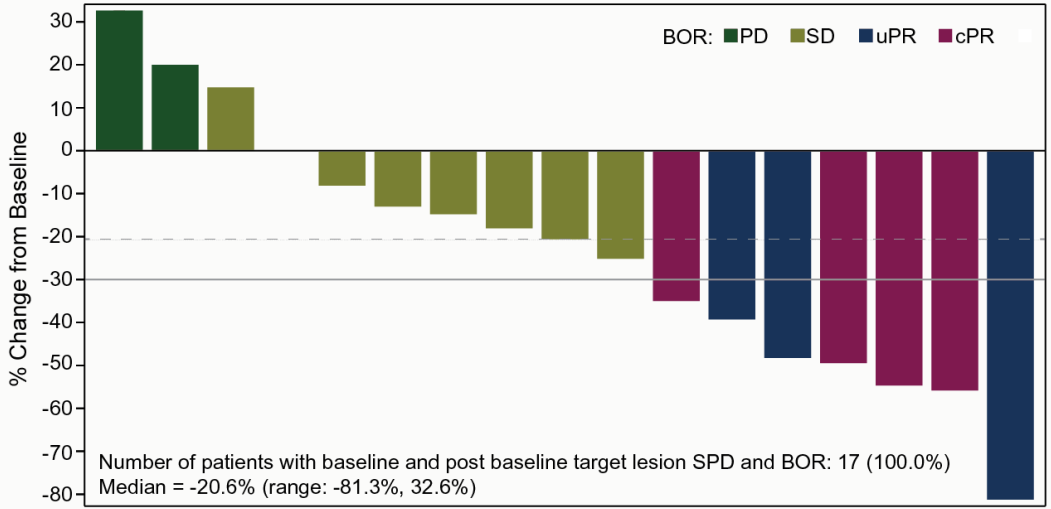
TEAEs in ≥15%, n (%)	Grade 1/2	Grade ≥3		Total
		Any	TRAE	
Diarrhea	9 (45)	2 (10)	1 (5)	11 (55)
Hypertension	5 (25)	5 (25)	5 (25)	10 (50)
Abdominal pain	6 (30)	3 (15)	-	9 (45)
Nausea	9 (45)	0		9 (45)
Fatigue	6 (30)	2 (10)	2 (10)	8 (40)
Decreased appetite	6 (30)	0	-	6 (30)
Hypomagnesia	5 (25)	1 (5)	-	6 (30)
Constipation	5 (25)	0	-	5 (25)
Cough	5 (25)	0	-	5 (25)
Palmar-plantar erythrodysesthesia	5 (25)	0	-	5 (25)
Rash	4 (20)	1 (5)	1 (5)	5 (25)
Urinary tract infection	5 (25)	0	-	5 (25)
Vomiting	5 (25)	0	-	5 (25)
Hypothyroidism	4 (20)	0	-	4 (20)
Weight decreased	4 (20)	0	-	4 (20)
Abdominal pain upper	1 (5)	2 (10)	1 (5)	3 (15)
Dyspnea	2 (10)	1 (5)	-	3 (15)
Gastroesophageal reflux disease	3 (15)	0	-	3 (15)
Hypokalemia	2 (10)	1 (5)	-	3 (15)
Increased transaminases	1 (5)	2 (10)	2 (10)	3 (15)
Immune-related TEAEs, n (%)				
Hypothyroidism	4 (20)	0	-	4 (20)
Diarrhea	3 (15)	0	-	3 (15)
Rash	2 (10)	1 (5)	-	3 (15)

PROC=platinum-resistant ovarian cancer, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event

Preliminary Antitumor Activity (PROC Cohort)

	Total (N=17)
Best Response Confirmed PR, n Unconfirmed PR, n SD, n PD, n	 4 3 8 2
Confirmed ORR, % (95% CI)	23.5 (6.8–49.9)
Median DOR, weeks (95% CI)	NR (12.29, NR)
DCR, % (95% CI)	88.2 (63.6–98.5)
Median PFS, weeks (95% CI)	18 (12.29, NR)
3-month PFS rate, % (95% CI)	88.2 (60.6–96.9)
6-month PFS rate, % (95% CI)	35.3 (9.0–63.8)

Best Response in Target Lesions



- Of 17 efficacy-evaluable patients, 7 had PR (4 confirmed PR), 8 had SD, and 2 had PD

BOR=best overall response, CI=confidence interval, cPR=confirmed partial response, DCR= disease control rate, DOR=duration of response, NR=not reached, ORR=objective response rate, PD=progressive disease, PFS=progression-free survival, PR=partial response, PROC= platinum-resistant ovarian cancer, SD=stable disease, SPD=sum of the products of perpendicular dimensions, uPR=unconfirmed partial response

Conclusions

- Combination treatment with sitravatinib and tislelizumab had a generally manageable safety profile and showed promising antitumor activity in patients with platinum-resistant ovarian cancer
- A generally manageable safety profile was supported by the following:
  - Common (frequency ≥10%) Grade ≥3 TRAEs as assessed by investigators
    - As related to sitravatinib, were hypertension (25%) and fatigue (10%)
    - As related to tislelizumab, were increased transaminases (10%)
  - 6 patients had TEAEs that led to discontinuation of sitravatinib; 3 had TEAEs that led to discontinuation of tislelizumab
- Promising antitumor activity was supported by the following:
  - Of 17 efficacy-evaluable patients, 7 had PR (4 confirmed PR), 8 had SD, and 2 had PD
  - Median PFS was 18 weeks; median DOR was not reached
- Further investigation of this combination treatment in patients with ovarian cancer is warranted

DOR=duration of response, PD=progressive disease, PFS=progression-free survival, PR=partial response, SD=stable disease, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event