A PHASE 1B STUDY TO ASSESS SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PRELIMINARY ANTITUMOR ACTIVITY OF SITRAVATINIB IN COMBINATION WITH TISLELIZUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

¹ICON Cancer Foundation, South Brisbane, and University of Queensland, St Lucia, QLD, Australia; ²Blacktown, NSW, Australia; ⁴Austin Hospital, Heidelberg, VIC, Australia; ⁵Nucleus Network, Melbourne, VIC, Australia; ⁴Austin Hospital, Heidelberg, VIC, Australia; ⁵Nucleus Network, Melbourne, VIC, Australia; ⁶Reijing, China; ⁹BeiGene (Beijing, China; ¹⁰University of Western Australia, Crawley, and Linear Clinical Research, Perth, WA, Australia (Crawlei, China; ¹⁰University of Western Australia, Crawley, and Linear Clinical Research, Perth, WA, Australia

BACKGROUND

- Sitravatinib is an investigative, orally bioavailable, spectrum-selective receptor tyrosine kinase (RTK) inhibitor with potential antitumor activity¹ that has been shown to potently inhibit split kinase receptors (eg, VEGFR2, KIT) and TAM receptors (eg, AXL, MER), which are dysregulated in many cancers²
- Inhibition of RTKs by sitravatinib may also modulate effects on the tumor microenvironment to overcome resistance to checkpoint inhibitors, including enhanced M1/suppressed M2 macrophage cytokine response, abrogated negative regulation of antitumor natural killer cell activity, and depleted regulatory T- and myeloid-derived suppressor cells with enhanced antitumor cytotoxic T-cell activity³ (**Figure 1**)
- Tislelizumab (BGB-A317) is an investigational, humanized, immunoglobulin 4 monoclonal antibody that has been shown to have high affinity for and binding specificity to programmed cell death protein-1 $(PD-1)^4$
- Tislelizumab was specifically engineered to minimize binding to FcγR on macrophages in order to abrogate antibody-dependent phagocytosis,⁴ a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy⁵ (**Figure 2**)
- Combining an agent that has both immune modulatory and antitumor properties with an immunotherapeutic PD-1 checkpoint inhibitor could enhance the antitumor efficacy observed with either agent alone^{6,7}

METHODS

Overall Design and Study Objective

• This is an open-label, multicenter, nonrandomized, phase 1b clinical trial (NCT03666143) designed to assess the safety and tolerability of sitravatinib combined with tislelizumab in patients with advanced solid tumors

Study Population

 Adult patients with histologically or cytologically confirmed, locally advanced or metastatic, non-small cell lung cancer, renal cell carcinoma, or ovarian cancer





TREATMENT

STUDY ASSESSMENTS AND STATISTICAL ANALYSIS

Jeffrey Goh,¹ Bo Gao,² Ben Markman,³ Hui Gan,⁴ Mark Voskoboynik,⁵ Jermaine Coward,¹ Yi-Long Wu,⁶ Jun Zhao,⁷ Cheng Chen,⁸ Xiao Xiang,⁹ Jingjun Qiu,⁹ Yingying Xu,⁹ Liu Yang,⁸ Michael Millward¹⁰

• Eligibility criteria include Eastern Cooperative Oncology Group Performance Status ≤1 and adequate end-organ function

• Approximately 100 patients are expected to be enrolled in 5 cohorts (n=20 patients per cohort) (**Figure 3**)

• All patients will receive sitravatinib 120 mg given orally once daily in combination with tislelizumab 200 mg given intravenously every 3 weeks

• Treatment will be administered until progressive disease, unacceptable toxicity, death, withdrawal of consent, or study termination by the sponsor

• The primary endpoint is assessment of safety and tolerability of the combination of sitravatinib with tislelizumab by monitoring adverse events (AEs) and serious AEs



- Secondary endpoints include overall response rate, duration of response, disease control rate, progression-free survival assessed by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (v1.1), and plasma concentrations and derived pharmacokinetic parameters of single- and repeated-dose sitravatinib
- Safety and tolerability will be assessed by monitoring AEs, including immune-related AEs, and through physical examinations, electrocardiograms, and laboratory assessments
- Tumor response will be evaluated every 6 weeks during Year 1 and every 9 weeks from Year 2 onwards, in accordance with RECIST v1.1
- For ovarian cancer patients, response will be assessed using RECIST v1.1 and Gynecologic Cancer InterGroup criteria

Figure 3: Study Design

Cohort Description Eligibility A Anti-PD-(L)1 antibody-refractory/-resistant, metastatic, nonsquamous NSCLC • Radiographic progression per RECL anti-PD-1/PD-L1 as most recent treated in the second s			
 A Anti-PD-(L)1 antibody-refractory/-resistant, metastatic, nonsquamous NSCLC B Anti-PD-(L)1 antibody-naive, metastatic, nonsquamous NSCLC C Anti-PD-(L)1 antibody-naive, metastatic, nonsquamous NSCLC C Anti-PD-(L)1 antibody-refractory/-resistant, metastatic, clear cell RCC D Metastatic or advanced RCC without prior systemic therapy* Radiographic progression per RECI: anti-PD-1/PD-L1 agent ≤2 lines of therapy Radiographic progression per RECI: anti-PD-1/PD-L1 agent ≤2 lines of therapy Radiographic progression per RECI: anti-PD-1/PD-L1 agent ≤2 lines of therapy Radiographic progression per RECI: anti-PD-1/PD-L1 as most recent treated static progression per RECI: anti-PD-1/PD-L1 as most recent treated static progression per RECI: anti-PD-1/PD-L1 as most recent treated static progression per RECI: anti-PD-1/PD-L1 as most recent treated static per prior immunotherapies, in anti-CTLA-4, anti-OX40, and anti-CI anti-CTLA-4, anti-OX40, and anti-CI and per prior immunotherapies, in anti-CTLA-4, anti-OX40, and anti-CI and per prior metastatic per per per per per per per per per per	Cohort	Description	Eligibility
B Anti-PD-(L)1 antibody-naive, metastatic, nonsquamous NSCLC • Radiographic progression per RECI: for metastatic NSCLC without prior anti-PD-1/PD-L1 agent C Anti-PD-(L)1 antibody-refractory/-resistant, metastatic, clear cell RCC • Radiographic progression per RECI: anti-PD-1/PD-L1 as most recent treated structure in the structure of the structure in the structure of the structure of the structure in the structure of the structure of the structure in the structure of the structure in the structure of the	A	Anti-PD-(L)1 antibody- refractory/-resistant, metastatic, nonsquamous NSCLC	 Radiographic progression per RECIS anti-PD-1/PD-L1 as most recent treated ≤2 lines of therapy No other prior immunotherapies, ine anti-CTLA-4, anti-OX40, and anti-CE
CAnti-PD-(L)1 antibody- refractory/-resistant, metastatic, clear cell RCC• Radiographic progression per RECL anti-PD-1/PD-L1 as most recent treat • ≤2 lines of therapy • No other prior immunotherapies, in anti-CTLA-4, anti-OX40, and anti-CLDMetastatic or advanced RCC without prior systemic therapy*• Systemic therapy not available, is con has been refused by the patient • Prior neoadjuvant/adjuvant therapy 	В	Anti-PD-(L)1 antibody-naive, metastatic, nonsquamous NSCLC	 Radiographic progression per RECIS for metastatic NSCLC without prior anti-PD-1/PD-L1 agent ≤2 lines of therapy
 Metastatic or advanced RCC without prior systemic therapy* Systemic therapy not available, is considered by the patient Prior neoadjuvant/adjuvant therapy 	С	Anti-PD-(L)1 antibody- refractory/-resistant, metastatic, clear cell RCC	 Radiographic progression per RECIS anti-PD-1/PD-L1 as most recent treated ≤2 lines of therapy No other prior immunotherapies, ine anti-CTLA-4, anti-OX40, and anti-CE
completed >12 months phor to enro	D	Metastatic or advanced RCC without prior systemic therapy*	 Systemic therapy not available, is conhas been refused by the patient Prior neoadjuvant/adjuvant therapy completed >12 months prior to enrormed
 E Anti-PD(L)1 antibody-naive, recurrent, platinum-resistant, epithelial OC[†] No platinum-refractory disease (PD platinum-based chemotherapy) No prior exposure to anti-PD-1/PD- 	E	Anti-PD(L)1 antibody-naive, recurrent, platinum-resistant, epithelial OC [†]	 No platinum-refractory disease (PD platinum-based chemotherapy) No prior exposure to anti-PD-1/PD-1

*Cohort D will only enroll in China. [†]Resistance to platinum-based therapy is defined as relapse 1–6 months after last dose of platinum-based treatment. DCR=disease control rate, DOR=duration of response, IV=intravenous, NSCLC=non-small cell lung cancer, OC=ovarian cancer, OR=overall response rate, PD=progressive disease, PD-1=programmed cell death protein-1, PD-L1=programmed cell death ligand-1, PFS=progression-free survival, PK=pharmacokinetics, PO=per oral, Q3W=every 3 weeks, QD=once daily, RCC=renal cell carcinoma, RECIST=Response Evaluation Criteria In Solid Tumors, v1.1=version 1.1

TRIAL STATUS

• 21 patients have enrolled as of 28 February 2019 at the study sites in Australia and China

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