An Open-Label Phase 1b/2 Study of Surufatinib in Combination with Tislelizumab in Patients with Advanced Solid Tumors

Arvind Dasari MD, MS[1]; Jennifer W. Carlisle MD[2]; John Kauh MD, FACP[3]; Christopher Tucci MBS, CCRP[3]; Shivani Nanda MS[3]; Marek Kania MD, MBA[3]; Andrew Scott Paulson MD[4]

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [3]HUTCHMED International Corporation, Florham Park, NJ, USA; [4]Baylor Sammons Cancer Center, Dallas, TX, USA

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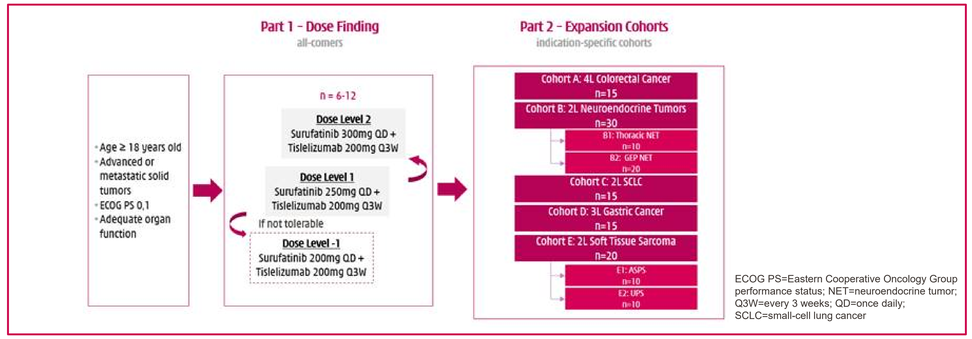
INTRODUCTION

- Surufatinib is an inhibitor of vascular endothelial growth factor receptor (VEGFR) 1, 2, & 3; fibroblast growth factor receptor 1 (FGFR1); and colony-stimulating factor 1 receptor (CSF-1R).
- In two phase 3 randomized trials (SANET-ep; NCT02588170 & SANET-p; NCT02589821)[1,2] surufatinib demonstrated a manageable safety profile and statistically significant efficacy.
- Patients (pts) with extrapancreatic neuroendocrine tumors (epNETs) achieved a median progression free survival (PFS) of 9.2 vs. 3.8 months (mo) (hazard ratio [HR] 0.334; p<0.0001). Patients with pancreatic NETs (pNETs) achieved a median PFS of 10.9 vs. 3.7 mo (HR 0.491; p=0.0011), with surufatinib vs. placebo, respectively.
- Surufatinib was recently approved for the treatment of patients with epNET in China.
- A New Drug Application for surufatinib has been submitted to the United States Food and Drug Administration for review.
- Tislelizumab is a humanized immunoglobulin G4 anti-programmed cell death protein 1 (PD-1) monoclonal antibody engineered to minimize binding to Fc-gamma-receptor on macrophages.
- Tislelizumab is approved in China in combination with chemotherapy for squamous non-small cell lung cancer (SCLC) and has conditional approval for Hodgkin's lymphoma and locally advanced or metastatic urothelial carcinoma with programmed death ligand 1 (PD-L1) high expression.
- The objective of this study (NCT04579757) is to evaluate the safety and efficacy of combination therapy with surufatinib and tislelizumab, which may have synergistic effects, where inhibition of angiogenesis along with stimulation of an immune response may enhance the overall antitumor activity.

METHODS

- This study will include pts, ≥18 years of age, with advanced metastatic solid tumors, who have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and have progressed on or are intolerant to standard therapies.
- The primary objective of Part 1 (dose escalation) will be to evaluate the safety and tolerability of surufatinib and tislelizumab to determine the recommended phase 2 dose (RP2D) and/or maximum tolerated dose (MTD) of the combination.
- The starting dose in Part 1 will be 250 mg of surufatinib, orally, daily, and 200 mg of tislelizumab, intravenously, every 3 weeks. The dose of surufatinib will be escalated during Part 1, while the dose of tislelizumab will remain fixed.
- The primary objective of Part 2 (dose expansion) will be to evaluate the objective response rate (ORR) of the combination per RECIST v1.1 at 12 weeks. Enrollment in the United States is open and ongoing, and enrollment in Europe is planned for fourth quarter of 2021.

STUDY DESIGN



ECOG PS=Eastern Cooperative Oncology Group performance status; NET=neuroendocrine tumor; Q3W=every 3 weeks; QD=once daily; SCLC=small-cell lung cancer

KEY INCLUSION CRITERIA

- **Part 1**: evaluable lesions (according to RECIST v1.1)
- **Part 2**: measurable lesions (according to RECIST v1.1)
- Performance status of 0 or 1 on the ECOG scale

- **Cohort A**: Adenocarcinoma of the colon or rectum that is microsatellite stable and previously treated with ≥ 3 prior lines of therapy.
- **Cohort B**: Progressive, low, or intermediate grade (Grade 1 or Grade 2) NETs of thoracic (B1) or gastroenteropancreatic (B2) origins that have progressed on ≥ 1 line of standard therapy
- **Cohort C**: SCLC that has progressed on standard first-line chemotherapy treatment
- **Cohort D**: Adenocarcinoma of the stomach or gastroesophageal junction and have progressed on at least 2 prior lines of therapy
- **Cohort E**: Alveolar soft part sarcoma (E1) or undifferentiated pleomorphic sarcoma (E2) that have progressed on ≥1 line of standard therapy

KEY EXCLUSION CRITERIA

- Adverse events (AEs) due to previous antitumor therapy has not recovered to Common Terminology Criteria for Adverse Events (CTCAE) ≤Grade 1, except alopecia and peripheral neurotoxicity with CTCAE ≤Grade 2
- Part 2 patients with colorectal cancer (CRC), NETs, and soft tissue sarcoma: previous treatment with anti-PD-1, anti PD-L1/L2 antibodies, anti-cytotoxic T lymphocyte associated antigen-4 antibody, or any other antibody acting on T cell costimulatory or checkpoint pathway
  - Patients in the Part 1 and patients in Part 2 with SCLC and GC may have received previous treatment with anti-PD-1, anti-PD-L1/L2 antibodies, CTLA-4 antibody, or any other antibody acting on T cell costimulatory or checkpoint pathway
- Previous treatment with surufatinib
- History or presence of a serious hemorrhage (>30 mL within 3 mo), hemoptysis (>5 mL blood within 4 weeks), or life-threatening thromboembolic event within 6 months
- Clinically significant cardiovascular disease
- Any clinically significant active infection, including, but not limited to, known human immunodeficiency virus infection

OBJECTIVES

Primary Objective	Primary Endpoint
Part 1 To evaluate the safety and tolerability of surufatinib, thereby determining the RP2D and/or MTD of surufatinib in combination with tislelizumab	Part 1 Safety, including dose-limiting toxicities, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), AEs leading to discontinuation, electrocardiogram (ECGs,) clinical laboratory abnormalities, and vital signs
Part 2 To evaluate the ORR as assessed by the investigator in patients with advanced solid tumors when treated with surufatinib in combination with tislelizumab according to RECIST v1.1	Part 2 ORR at 12 weeks
Secondary Objectives	**Secondary Endpoints**
Part 1 • To evaluate the antitumor activity in patients with advanced solid tumors when treated with surufatinib in combination with tislelizumab according to RECIST v1.1 • To characterize the pharmacokinetics (PK) and immunogenicity of tislelizumab and surufatinib in combination	Part 1 • ORR, progression free survival (PFS), disease control rate (DCR), clinical benefit rate (CBR), duration of response (DoR), time to response (TTR) • Concentrations of surufatinib in plasma and tislelizumab in serum • Incidence of anti-drug antibody (ADA) to tislelizumab
Part 2 • To evaluate further anticancer effects of surufatinib in combination with tislelizumab • To characterize the safety and tolerability of surufatinib in combination with tislelizumab • To characterize the PK and immunogenicity of tislelizumab and surufatinib in combination	Part 2 • PFS, DCR, CBR, DoR, TTR • Safety, including TEAEs, SAEs, AEs leading to discontinuation, ECGs, clinical laboratory abnormalities, and study drug discontinuation due to AEs • Concentrations of surufatinib in plasma and tislelizumab in serum • Incidence of ADA to tislelizumab
Exploratory Objectives	**Exploratory Endpoints**
Part 2 • To assess the overall survival (OS) in patients enrolled to expansion Cohort A (CRC) • Distribution of PD-L1 expression and potential association between PD-L1 expression and tislelizumab treatment effect	Part 2 • OS • PD-L1 expression

STATISTICAL ANALYSIS

- Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and PK measurements.
- Time to event variables will be summarized descriptively using Kaplan-Meier medians and quartiles.
- Analyses will be performed using SAS® (Version 9.1 or higher).
- No formal hypothesis testing is planned for this study.
- For efficacy endpoints, the study will provide the estimates and the corresponding 2-sided Clopper Pearson 95% confidence interval for precision.

SUMMARY

- Surufatinib is an inhibitor of VEGFR1, 2, & 3; FGFR1; and CSF-1R.
- The objective of this study (NCT04579757) is to evaluate the safety and efficacy of combination therapy with surufatinib and tislelizumab, which may have synergistic effects, where inhibition of angiogenesis along with stimulation of an immune response may enhance the overall antitumor activity.
- Enrollment in the United States is open and ongoing, and enrollment in Europe is planned for fourth quarter of 2021.

CONTACT EMAIL

Lan Nguyen
lann@hmplglobal.com

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REFERENCES

1. Xu et al. *The Lancet Oncology*. 2020; 21: 1489-99.
2. Xu et al. *The Lancet Oncology*. 2020; 21: 1500-12.

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