An Open-Label, Phase 1b/2 Study to Evaluate the Safety and Efficacy of Fruquintinib in Combination with Tislelizumab in Patients with Advanced Triple Negative Breast Cancer

#3495

Debu Tripathy [1], Stacey M. Ukrainskyj [2], Zhao Yang[3], Marek Kania [2], William R. Schelman [2], Erika Hamilton [4]

[1]The University of Texas MD Anderson Cancer Center, 1515 Holcombe, Houston, TX 77030, US; [2]HUTCHMED International, Florham Park, NJ, US; [3]Hutchison MediPharma, No. 4, 720 Cailun Road, Zhangjiang, Shanghai, China 20120; [4]Sarah Cannon Research Institute/Tennessee Oncology, 250 25th Ave N, Nashville, TN 37203, US

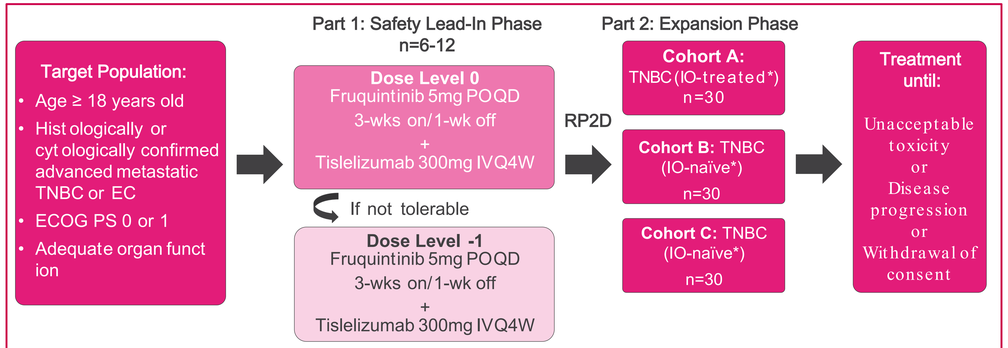
INTRODUCTION

- Immune checkpoint inhibitors (ICIs) have improved clinical outcomes in triple negative breast cancer (TNBC) and in endometrial cancer (EC), but many patients (pts) do not respond to ICIs or will develop resistance.1
- Combining VEGFR inhibitors with ICIs (with demonstrated clinical efficacy in TNBC and EC) may potentiate efficacy and suppress tumor growth and reduce metastasis[2] by:
  - Normalizing vascular immune crosstalk
  - Improving immune effector cell infiltration
- Fruquintinib: a novel, highly selective, oral, tyrosine kinase inhibitor of VEGF-1, 2, 3 administered orally 5 mg/daily on a 3-week on, 1-week off schedule.
- Tislelizumab: a humanized, IgG4-variant monoclonal antibody against PD-1, administered intravenously, 300 mg, on Day 1 of each 4-week cycle.
- Safety and preliminary efficacy of fruquintinib have been demonstrated in metastatic breast cancer, including TNBC.
  - Phase 1 study in China (2009-013-00CH1)
  - Ongoing phase 1/1b study in the US (2015-013-00US1)
- This open-label, phase 1b/2 study (NCT04579757) will assess safety, PK, and efficacy of fruquintinib in combination with tislelizumab in pts with:
  - Locally advanced or metastatic TNBC, independent of PD-L1 status, (immunotherapy (IO) pre-treated and naïve)
  - EC (IO-naïve) in the second line setting
- Hypothesis: Addition of fruquintinib can enhance the clinical activity of or potentially overcome resistance to ICI and improve clinical activity in TNBC and EC.

METHODS

- The study consists of a safety lead-in phase (Part 1) and dose expansion phase (Part 2).
- Part 1: Assess safety and tolerability of fruquintinib and tisleizumab and confirm RP2D of the combination.
- Part 2: Determine the clinical actiivtyDetermine clinical activity and safety of the combination at the RP2Din pts with TNBCand EC.
- Patients will be treated until radiologically determined progressive disease per RECIST v1.1, unacceptable toxicity, death, or withdrawal from study.

STUDY DESIGN



2L=second line; ECOG=Eastern Cooperative Oncology Group; EC=endometrial cancer; IO=immuno-oncology; n=total number of subjects; PS=performance status; QD=once daily; PO=orally; IV=intravenous; Q4W=once every 4 weeks; TNBC=triple negative breast cancer; *defined by IO agents given in the metastatic setting

KEY INCLUSION CRITERIA

- Cohorts A and B: Histologically or cytologically confirmed, locally advanced or metastatic TNBC (per American Society for Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines).
  - TNBC progressed on at least 1, but not >3, prior lines of cytotoxic therapy in the metastatic setting.
  - For pts who recur within 12 months of adjuvant therapy, adjuvant therapy will count as 1st line chemotherapy in the metastatic or recurrent setting.
- Cohort C: Histologically or cytologically confirmed, locally advanced, metastatic or recurrent EC.
  - EC must have progressed on 1 prior platinum-based chemotherapy.
  - Pts may have received up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant setting.
  - Pts must not have received an ICI or other immunotherapy.
- IO-treated and IO-naïve pts are defined by prior IO agents in the metastatic setting.
- Tumor tissue collected for:
  - Retrospective analysis of PD-L1 expression.
  - Exploratory biomarkers related to response and resistance.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
- Measurable disease according to RECIST version 1.1.
- Expected survival ⩾12 weeks.

KEY EXCLUSION CRITERIA

- Adverse events (AEs) due to previous anti-tumor therapy that have not recovered to ≤CTCAE Grade 1,
  - Except alopecia and peripheral neurotoxicity (≤CTCAE Grade 2).
- Other malignancies that have been adequately treated during the 5 years prior to screening.
  - Except non-melanoma skin cancer, *in situ* cervical cancer, or bladder cancer (Tis and T1).
- Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy.
  - Excluding pts requiring steroids within 4 weeks prior to start of study drug.
- Systemic anti-neoplastic therapies or any investigational therapy within 4 weeks prior to the first dose of study drug.
- Systemic small molecule-targeted therapies (e.g., tyrosine kinase inhibitors) within 5 half lives or 4 weeks (whichever is shorter) prior to the first dose of study drug.
- Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the initiation of study drug.

OBJECTIVES: Part 1

Primary Objectives	Primary Endpoints
Confirm recommended phase 2 dose (RP2D) of fruquintinib in combination with tislelizumab	• RP2D
Assess the safety and tolerability of fruquintinib in combination with tislelizumab	• Occurrence and severity of adverse events (AE) • Relative dose intensity and dose modification • Electrocardiogram (ECG) and clinical laboratory abnormalities
Secondary Objectives	**Secondary Endpoints**
Evaluate the anti-tumor activity of fruquintinib in combination with tislelizumab	• Objective response rate (ORR) • Disease control rate (DCR) • Duration of response (DoR) • Progression-free survival (PFS) • Overall survival (OS)
Characterize the pharmacokinetic (PK) profile of fruquintinib in combination with tislelizumab	• Plasma concentrations of fruquintinib and M11 metabolite
Evaluate the immunogenicity of fruquintinib in combination with tislelizumab	• Serum concentrations of tislelizumab and anti-drug antibody (ADA) response to tislelizumab

STATISTICAL ANALYSIS

- The primary efficacy and safety population will include pts who received at least 1 dose of fruquintinib or tislelizumab.
- Data will be summarized using descriptive statistics.
- No formal hypothesis testing is planned.
- Kaplan-Meier method will be used to summarize the time to event endpoints (DoR, PFS, OS).
- The point estimate and its associated 95% Clopper-Pearson confidence interval (CI) will be provided for binary endpoints (ORR, DCR).
- Analyses will be conducted using SAS®(version 9.1 or higher).

OBJECTIVES: Part 2

Primary Objective	Primary Endpoint
Evaluate the ORR of fruquintinib in combination with tislelizumab	• ORR
Secondary Objectives	**Secondary Endpoints**
Further evaluate the anti-tumor activity of fruquintinib in combination with tislelizumab	• DCR • DoR • PFS • OS
Assess the safety and tolerability of fruquintinib in combination with tislelizumab	• Occurrence and severity of adverse events (AE) • Relative dose intensity and dose modification • ECG and clinical laboratory abnormalities
Characterize the PK profile of fruquintinib in combination with tislelizumab	• Plasma concentrations of fruquintinib and M11 metabolite
Evaluate the immunogenicity of fruquintinib in combination with tislelizumab	• Serum concentrations of tislelizumab and ADA response to tislelizumab
Detect the expression of PD-L1 and other biomarkers in tumor tissues and evaluate their association with study drug, anti-tumor activity, and safety	• Changes from baseline in tumor markers • Associations between tumor biomarkers and drug exposure, efficacy and safety parameters

DISCLOSURES

D Tripathy discloses research funding paid directly to the institution from Novartis and Polyphor and receipt of fees for consulting, educational lectures, and participation in steering committees and advisory boards from Pfizer, Exact Sciences, GlaxoSmithKline, OncoPep and Immunomedics.

WR Schelman, SM Ukrainskyj, Z Yang, and M Kania are employed by HUTCHMED.

ACKNOWLEDGMENTS

We would like to thank all patients and their families who participated in this trial.

We would like to thank all investigators, study coordinators and the entire project team.

We would like to acknowledge the sponsor for this trial: HUTCHMED International.

References

1. Hossain et al. *Cancers* 2021 13:3739
2. Li et al. *Clin Cancer Res* 2020 Apr 1;26(7):1712-1724