A phase 1 study of rebastinib and carboplatin in patients with metastatic solid tumors

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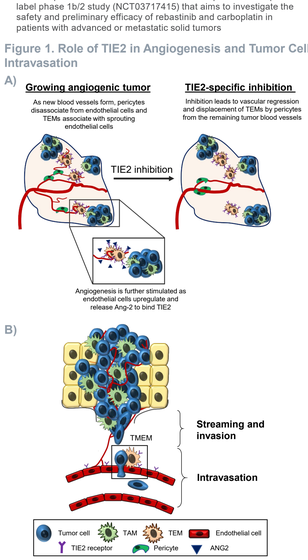
INTRODUCTION

- Tunica interna endothelial cell kinase 2 (TIE2) is a cell-surface receptor tyrosine kinase that is primarily expressed in endothelial cells and a subset of macrophages, called TIE2-expressing macrophages (TEMs)[1,2]
- In endothelial cells, the angiopoietin (Ang)/TIE2 signaling axis is a key regulator of angiogenesis and vascular remodeling.[1,3] Results from two Deciphera-sponsored clinical studies (NCT00827138 and NCT03601897) demonstrated that rebastinib treatment led to an increase in Ang-2 levels and was indicative of systemic TIE2 inhibition[4,5]
- TEMs are also located on a subset of perivascular macrophages that form portals (TMEMs) mediating tumor cell intravasation and metastasis (**Figure 1**).[1,3] Recruitment of TEMs to TMEM structures has been linked to anticancer treatment and chemoresistance[2,6]
- Rebastinib is a novel switch control inhibitor targeting TIE2.[1] In preclinical studies, rebastinib blocked the recruitment and function of TEMs and reversed chemotherapy-induced TMEM activity[4,7]
- In a Deciphera-sponsored phase 1b/2 study (NCT03601897) assessing the safety, tolerability, antitumor activity, and pharmacokinetics of rebastinib in combination with paclitaxel in patients with advanced or metastatic solid tumors, encouraging preliminary activity in a heavily pretreated patient population has been presented (dose-ranging part 1 and dose-expansion endometrial cohort),[5,8] and preliminary activity in ovarian cancer patients will be presented in a separate poster (839P)
- Here we present data from the dose escalation phase of an open-label phase 1b/2 study (NCT03717415) that aims to investigate the safety and preliminary efficacy of rebastinib and carboplatin in patients with advanced or metastatic solid tumors

Figure 1. Role of TIE2 in Angiogenesis and Tumor Cell Intravasation

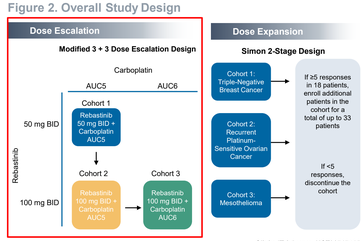


Ang-2, angiopoietin 2; TAM, tumor-associated macrophages; TIE2, tunica interna endothelial cell kinase 2; TEM, TIE2-expressing macrophage; TMEM, tumor microenvironment of metastasis.

METHODS

- Patients enrolled into the dose escalation phase were adults with locally advanced or metastatic solid tumors for which carboplatin was considered appropriate treatment
- Patients were treated with orally administered rebastinib 50 mg twice daily (BID) + carboplatin AUC5, rebastinib 100 mg BID + carboplatin AUC5, or rebastinib 100 mg BID + carboplatin AUC6 infused every 3 weeks (Q3W) using 3 + 3 dose escalation rules to determine the recommended phase 2 dose (RP2D) (**Figure 2**)
- Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities v21.0 and graded according to Common Terminology Criteria for Adverse Events v5.0
- Preliminary antitumor activity was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- All data are reported as of July 6, 2020

Figure 2. Overall Study Design



BID, twice daily. ClinicalTrials.gov: NCT03717415

Table 1. Key Inclusion and Exclusion Criteria

Inclusion criteria

- ≥18 years old
- Histologically confirmed diagnosis of a locally advanced or metastatic solid tumor for which carboplatin is considered appropriate treatment
- Progressed despite standard therapies, or for whom conventional therapy is not considered effective or tolerable, as judged appropriate by the investigator
- ≥1 measurable lesion per RECIST v1.1
- ECOG Performance Status score of ≤2
- Adequate organ function and bone marrow reserve

Exclusion criteria

- Prior anticancer therapy or other investigational therapy ≤28 days or 5x half-life
- Not recovered from toxicities from prior therapy to Grade 1 (or baseline)
- Grade >1 peripheral neuropathy (any etiology)
- Known active CNS metastases
- Use of systemic corticosteroids within 7 days prior to first dose
- History or presence of clinically relevant cardiovascular abnormalities
- LVEF <50% at screening
- Known retinal neovascularization, macular edema, or macular degeneration

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricle ejection fraction; RECIST, Response Evaluation Criteria In Solid Tumors.

Table 2. Dose Escalation Study Objectives

Primary objectives

1. Safety and tolerability of rebastinib 50 and 100 mg BID in combination with carboplatin
2. RP2D of rebastinib + carboplatin

Secondary objectives

1. Preliminary efficacy
2. Pharmacokinetics of rebastinib

Relevant exploratory objectives

1. Biomarker changes in the plasma

BID, twice daily; RP2D, recommended phase 2 dose.

RESULTS

Patient demographics and disposition

- 22 patients with advanced or metastatic solid tumors were enrolled in the Dose Escalation portion of the study between January 02, 2019, and January 17, 2020 (**Table 3**)
- Patients were enrolled into 1 of 3 dose escalation cohorts:
  - Rebastinib 50 mg BID + carboplatin AUC5 Q3W
  - Rebastinib 100 mg BID + carboplatin AUC5 Q3W
  - Rebastinib 100 mg BID + carboplatin AUC6 Q3W

Table 3. Patient Demographics and Clinical Characteristics

	Reb 50 mg BID + Carb AUC5 (N = 3)	Reb 100 mg BID + Carb AUC5 (N = 14)	Reb 100 mg BID + Carb AUC6 (N = 5)	Total (N = 22)
Age, years, median (min, max)	54 (33, 59)	63 (27, 73)	54 (48, 68)	61 (27, 73)
Female, n (%)	3 (100)	8 (57)	4 (80)	15 (68)
Male, n (%)	0	6 (43)	1 (20)	7 (32)
Cancer Type, n (%)				
Breast Cancer	1 (33)	3 (21)	1 (20)	5 (23)
Neuroendocrine Carcinoma	1 (33)	1 (7.1)	1 (20)	3 (14)
Pancreatic Adenocarcinoma	0	2 (14)	0	2 (9.1)
Non-Small Cell Lung Cancer	0	1 (7.1)	1 (20)	2 (9.1)
Ovarian Cancer	0	1 (7.1)	1 (20)	2 (9.1)
Cholangiocarcinoma	1 (33)	1 (7.1)	0	2 (9.1)
Other*	0	5 (36)	1 (20)	6 (27)

*(n = 1): colorectal cancer, endometrial cancer, mesothelioma, testicular cancer, prostate cancer, ocular melanoma. Carb, carboplatin; Reb, rebastinib.

Table 4. Prior Regimens

	Reb 50 BID mg + Carb AUC5 (N = 3)	Reb 100 mg BID + Carb AUC5 (N = 14)	Reb 100 mg BID + Carb AUC6 (N = 5)	Total (N = 22)
Prior regimens, median (min, max)	2.0 (2, 6)	4.0 (2, 9)	2.0 (2, 11)	3.5 (2, 11)
2–3, n (%)	2 (67)	6 (43)	3 (60)	11 (50)
4+, n (%)	1 (33)	8 (57)	2 (40)	11 (50)
Prior treatment, n (%)				
Chemotherapy	2 (67)	14 (100)	3 (60)	19 (86)
Platinum-Based Chemotherapy	2 (67)	12 (86)	2 (40)	16 (73)
Immunotherapy	2 (67)	6 (43)	3 (60)	11 (50)
Monoclonal Antibodies (Not Immunotherapy)	0 (0)	5 (36)	3 (60)	8 (36)
Targeted Therapy	1 (33)	4 (29)	3 (60)	8 (36)
Hormonal Therapy	1 (33)	1 (7.1)	2 (40)	4 (18)
Other	1 (33)	3 (21)	1 (20)	5 (23)

Carb, carboplatin; Reb, rebastinib.

- All patients received ≥2 prior anticancer regimens (**Table 4**)
- 50% received ≥4 prior regimens
- The median number of prior regimens was 3.5
- 73% of patients received prior platinum-based chemotherapy

Table 5. Patient Disposition

n (%)	Reb 50 mg BID + Carb AUC5 (N = 3)	Reb 100 mg BID + Carb AUC5 (N = 14)	Reb 100 mg BID + Carb AUC6 (N = 5)
Radiological Progression	2 (67)	4 (29)	3 (60)
Clinical Progression	0	5 (36)	1 (20)
Adverse Event	1 (33)	3 (21)	0
Withdrawal by Patient	0	2 (14)	1 (20)

Carb, carboplatin; Reb, rebastinib.

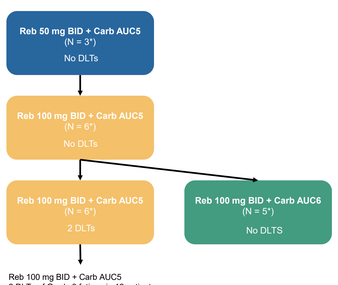
- Patients discontinued study treatment due to disease progression, withdrawal of consent, and AEs (**Table 5**)
- AEs leading to discontinuation of treatment:
  - Rebastinib 50 mg BID + carboplatin AUC5: Grade 2 retinal vascular disorder (n = 1; possibly related to rebastinib)
  - Rebastinib 100 mg BID + carboplatin AUC5: Grade 3 syncope (n = 1; not related), Grade 1 tumor pain (n = 1; not related), Grade 3 fatigue (n = 1; possibly related)
  - Rebastinib 100 mg BID + carboplatin AUC6: None
- All patients have discontinued treatment

Safety

Dose-Limiting Toxicities

- No dose-limiting toxicities (DLTs) were observed in the rebastinib 50 mg BID + AUC5 and rebastinib 100 mg BID + AUC6 cohorts (**Figure 3**)
- 2 DLTs were observed within a total of 12 patients in the rebastinib 100 mg BID + AUC5 cohort

Figure 3. Dose Escalation Flow and DLTs



*Evaluable patients, patients that received ≥80% of planned doses of rebastinib and 1 dose of carboplatin in Cycle 1 or experienced a dose limiting toxicity.
Carb, carboplatin; DLT, dose-limiting toxicity; Reb, rebastinib.

Adverse Events

- Commonly reported treatment-emergent AEs (TEAEs) (≥5% of total) regardless of relatedness are shown in **Table 6**
  - The majority of TEAEs were Grade 1 and Grade 2

Table 6. Common (≥5%, ≥2 Patients) TEAEs All Causality

Preferred Term, n (%)	Reb 50 mg BID + Carb AUC5 (N = 3)		Reb 100 mg BID + Carb AUC5 (N = 14)		Reb 100 mg BID + Carb AUC6 (N = 5)		Total (N = 22)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Thrombocytopenia	1 (33)	0	5 (36)	3 (21)	2 (40)	0	8 (36)	3 (14)
Constipation	0	0	5 (36)	1 (7.1)	2 (40)	0	7 (32)	1 (4.5)
Fatigue	1 (33)	0	3 (21)	2 (14)	2 (40)	0	6 (27)	2 (9.1)
Nausea	0	0	4 (29)	0	2 (40)	0	6 (27)	
Anemia	1 (33)	1 (33)	3 (21)	0	0	0	4 (18)	1 (4.5)
Alanine Aminotransferase Increased	0	0	2 (14)	0	1 (20)	0	3 (14)	0
Arthralgia	1 (33)	0	0	0	2 (40)	0	3 (14)	0
Aspartate Aminotransferase Increased	0	0	2 (14)	0	1 (20)	0	3 (14)	0
Dry Mouth	0	0	2 (14)	0	1 (20)	0	3 (14)	0
Dyspepsia	1 (33)	0	2 (14)	0	0	0	3 (14)	0
Headache	0	0	3 (21)	0	0	0	3 (14)	0
Neutrophil Count Decreased	0	0	3 (21)	1 (7.1)	0	0	3 (14)	1 (4.5)
Peripheral Sensory Neuropathy	0	0	3 (21)	0	0	0	3 (14)	0
Pyrexia	2 (67)	0	1 (7.1)	0	0	0	3 (14)	0
Vision Blurred	0	0	2 (14)	0	1 (20)	0	3 (14)	0
Abdominal Pain	0	0	2 (14)	0	0	0	2 (9.1)	0
Asthenia	0	0	1 (7.1)	0	1 (20)	0	2 (9.1)	0
Blood Alkaline Phosphatase Increased	0	0	1 (7.1)	0	1 (20)	0	2 (9.1)	0
Chills	0	0	1 (7.1)	0	1 (20)	0	2 (9.1)	0
Cough	1 (33)	0	0	0	1 (20)	0	2 (9.1)	0
Dehydration	1 (33)	0	1 (7.1)	1 (7.1)	0	0	2 (9.1)	1 (4.5)
Diarrhea	0	0	1 (7.1)	0	1 (20)	0	2 (9.1)	0
Dizziness	0	0	1 (7.1)	0	1 (20)	0	2 (9.1)	0
Dyspnea	1 (33)	0	1 (7.1)	0	0	0	2 (9.1)	0
Hypertension	0	0	2 (14)	1 (7.1)	0	0	2 (9.1)	1 (4.5)
Insomnia	1 (33)	0	1 (7.1)	0	0	0	2 (9.1)	0
Intraocular Pressure Increased	0	0	2 (14)	0	0	0	2 (9.1)	0
Leukopenia	0	0	2 (14)	0	0	0	2 (9.1)	0
Malignant Pleural Effusion	1 (33)	0	1 (7.1)	1 (7.1)	0	0	2 (9.1)	1 (4.5)
Platelet Count Decreased	0	0	2 (14)	1 (7.1)	1 (20)	0	2 (9.1)	1 (4.5)
Vomiting	0	0	1 (7.1)	1 (7.1)	1 (20)	0	2 (9.1)	1 (4.5)

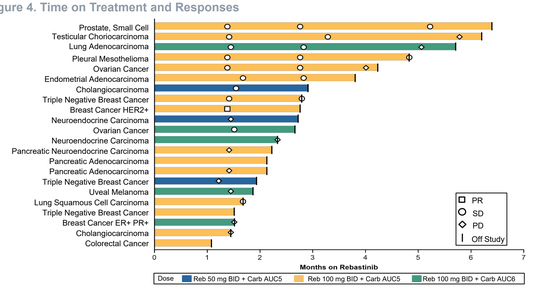
Carb, carboplatin; Reb, rebastinib; TEAE, treatment-emergent adverse event.

- One patient experienced a rebastinib-related serious AE (Grade 2 retinal vascular disorder)
- Rebastinib 50 mg BID + carboplatin AUC5 is the current RP2D
  - Carboplatin AUC5 is standard of care for later lines of treatment in advanced tumors and was chosen for the RP2D
  - Rebastinib 100 mg BID was chosen as the initial RP2D
    - One patient in the Dose Escalation phase experienced Grade 2 reversible muscular weakness (rebastinib 100 mg BID). There was a higher observed frequency of reversible muscular weakness (Grade 1–2) in preliminary data from the initial Dose Expansion phase at 100 mg BID; therefore, the RP2D was adjusted to rebastinib 50 mg BID + carboplatin AUC5

Duration of Treatment and Preliminary Antitumor Activity

- The median duration of treatment was 7.8 weeks (range 0.9–22.6)
- 1 partial response (PR; unconfirmed) in a patient with human epidermal growth factor receptor 2 (HER2)+ breast cancer (rebastinib 100 mg BID + carboplatin AUC5) (4.5%)
- 10 of 22 patients had stable disease (SD) in this heterogeneous heavily treated population (46%)
- The clinical benefit rate, defined as the proportion of patients with best overall response of complete response (CR), PR, or SD per RECIST v1.1, was 50% at 6 weeks and 36% at 12 weeks

Figure 4. Time on Treatment and Responses

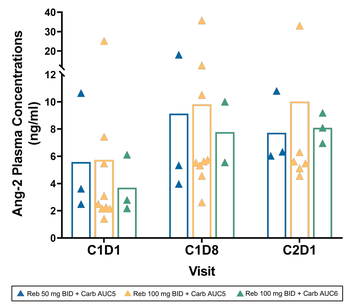


BID, twice daily; Carb, carboplatin; ER+, estrogen receptor-positive; HER2, human epidermal growth factor receptor 2; PD, progressive disease; PR, partial response; PR+, progesterone receptor-positive; Reb, rebastinib; SD, stable disease.

Pharmacokinetics and Pharmacodynamics

- The exposure of rebastinib 100 mg BID dose is consistent with previous data.[3] At the rebastinib 50 mg BID dose level, the exposure of rebastinib was generally comparable to previous data[3] when considering the range of observed values and the limited sample size (n = 3)
- Ang-2 plasma levels were examined to evaluate TIE2 receptor inhibition by rebastinib. Plasma samples were collected from patients prior to the first dose of rebastinib on Cycle 1 Day 1 (baseline), Cycle 1 Day 8, and Cycle 2 Day 1; Ang-2 concentration was assessed by standard Luminex methods
- An increase in Ang-2 concentration was observed after 8 days of treatment, with a similar trend noted between the rebastinib 50 mg BID and 100 mg BID cohorts (**Figure 5**)

Figure 5. Angiopoietin-2 induction during rebastinib treatment



The top of the column represents the mean, and the triangles are individual measurements.
Ang-2, angiopoietin-2; BID, twice daily; C, cycle; Carb, carboplatin; D, day; Reb, rebastinib

CONCLUSIONS

- Rebastinib in combination with carboplatin was generally well tolerated in patients with advanced tumors
- 1 PR (4.5%) and 10 SD (46%) were observed in this heterogeneous heavily treated population with a clinical benefit rate of 50% at 6 weeks
- Mean circulating Ang-2 levels increased by 8 days of treatment for all doses, indicating TIE2 inhibition
- The RP2D for rebastinib is 50 mg BID in combination with carboplatin AUC5 Q3W
- The Dose Expansion portion of the study is currently enrolling, and will evaluate the safety and efficacy of rebastinib in combination with carboplatin in patients with triple-negative breast cancer, recurrent platinum-sensitive ovarian cancer, and mesothelioma

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References

1) Parikh SM. *Curr Opin Hematol*. 2017; 24:432–8. 2) Sanchez LR, et al. *J Leukoc Biol*. 2019; 106:259–74. 3) Augustin HG, et al. *Nat Rev Mol Cell Biol*. 2009; 10:165–77. 4) Harney AS, et al. *Mol Cancer Ther*. 2017; 16:2486–501. 5) Janku F, et al. *Mol Cancer Ther*. 2019; 18(12 suppl):Abstract nr B055. 6) Harney AS, et al. *Cancer Discov*. 2015; 5:932–43. 7) Karagiannis GS, et al. *Sci Transl Med*. 2017; 9: eaan0026 8) Janku, F et al. *J Clin Oncol*. 2020; 38(15 suppl): 6085.

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Conflicts of Interest

Dr. Janku serves on scientific advisory boards/consults for Deciphera; Foundation Medicine; Guardant Health; IDEAYA Biosciences; IFM Therapeutics; Immunomet; Jazz Pharmaceuticals; Novartis; PureTech; Sequenom; Sotio; Syntogic; Cardiff Oncology; Valeant/Dendreon; and holds ownership interests in Cardiff Oncology. Research funding was provided to Dr. Janku's institution by Agios; Asana Biosciences; Astellas Pharma; Astex Pharmaceuticals; BioMed Valley Discoveries; Bristol-Myers Squibb; Deciphera; Fujifilm; Genentech; Novartis; Piqur; Plexxikon; Proximagen; Roche; and Symphogen.