A phase 1b/2 study of rebastinib and paclitaxel in advanced or metastatic platinum-resistant ovarian cancer

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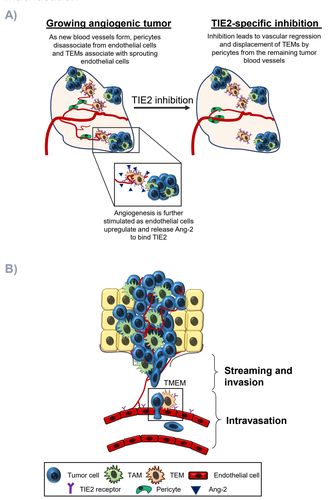
INTRODUCTION

- Rebastinib is a switch control inhibitor targeting tunica interna endothelial cell kinase (TIE2)[1]
- TIE2 is primarily expressed in endothelial cells and TIE2-expressing macrophages (TEMs), and plays a role in angiogenesis as part of the angiopoietin/TIE2 signaling axis (**Figure 1**)[2,3]
- TEMs are also located on a subset of perivascular macrophages that form portals (TMEMs) mediating tumor cell intravasation and metastasis. Recruitment of TEMs to TMEM structures has been linked to paclitaxel treatment and chemoresistance[4,5]
- This is a 2-part open-label, phase 1b/2 study with orally administered rebastinib in combination with weekly paclitaxel 80 mg/m^2
- In Part 1, we observed antitumor activity across multiple tumor types (5 partial responses [PRs] in 24 patients at 50 mg twice daily (BID) and 3 PRs in 19 patients at 100 mg BID), including 3 PRs in platinum-resistant ovarian cancer[6]
- The preliminary results from the ongoing endometrial cohort in Part 2 showed an objective response rate of 39% and a clinical benefit rate of 72% at 8 weeks in 18 heavily pretreated patients[7]
- Here we summarize preliminary results of rebastinib in combination with paclitaxel in patients with platinum-resistant ovarian cancer from Part 2

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

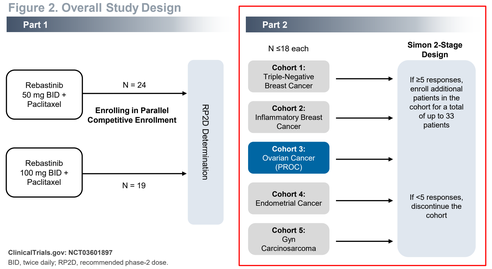


Ang-2, angiopoietin 2; TAM, tumor-associated macrophages; TEM, TIE2-expressing macrophage; TIE2, tunica interna endothelial cell kinase 2; TMEM, tumor microenvironment of metastasis.

METHODS

- Part 1 enrolled adults with locally advanced/metastatic solid tumors into 1 of 2 rebastinib dose cohorts (50 mg BID or 100 mg BID) in combination with paclitaxel using a parallel cohort design to determine the recommended dose for Part 2 (**Figure 2**)
- Part 2 of this study has 5 disease-specific cohorts (triple-negative breast cancer, inflammatory breast cancer, platinum-resistant ovarian cancer, endometrial cancer, and gynecological carcinosarcoma) (**Figure 2**)
- Part 2 used a Simon 2-stage design: In each cohort, if ≥5 responses are observed for the first 18 patients, then an additional 15 patients are enrolled
- Patients were treated with rebastinib (50 or 100 mg BID) in combination with 80 mg/m^2 intravenous weekly paclitaxel (day 1, day 8, and day 15 of repeated 28-day cycles)
- In this interim analysis of Part 2, results are reported for patients in the platinum-resistant ovarian cancer expansion cohort who initiated treatment as of June 3, 2020, with follow-up data through July 31, 2020
- 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
- Antitumor activity was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[8] and Gynecological Cancer Intergroup CA-125 response criteria[9]
  - Objective response rate (ORR) was defined as the proportion of patients achieving a complete response (CR) or partial response (PR) according to RECIST v1.1; the ORR includes both confirmed and unconfirmed responses
  - Patients were evaluable for CA-125 response assessment if the baseline value was at least 2x upper limit of normal and had ≥2 postbaseline assessments or discontinued treatment; a CA-125 response was defined as a confirmed ≥50% reduction in CA-125 levels from baseline that was maintained for at least 28 days

Figure 2. Overall Study Design



ClinicalTrials.gov: NCT03601897
BID, twice daily; RP2D, recommended phase-2 dose.

Table 1 . Key Inclusion and Exclusion Criteria

Inclusion criteria

- ≥18 years old
- Histologically confirmed diagnosis of recurrent epithelial ovarian, peritoneal, fallopian tube carcinoma (excluding low grade serous, mucinous, clear cell carcinoma)
- Progressed or relapsed within 6 months (excluding platinum refractory[a]) after completion of a platinum-based therapy
- ≥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

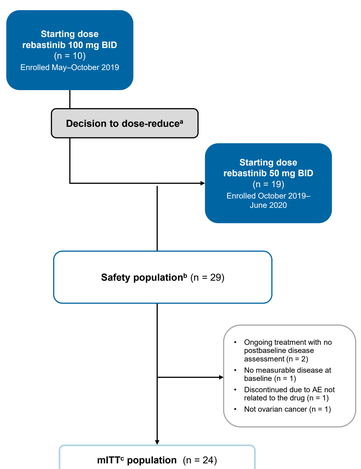
[a]Platinum refractory patients are those who progressed during treatment or within 1 month after completion of first platinum-based therapy.
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricle ejection fraction; RECIST, Response Evaluation Criteria In Solid Tumors.

RESULTS

Patient Disposition and Demographics

- In this interim analysis, the safety population was defined as patients with platinum-resistant ovarian cancer who initiated treatment with rebastinib in combination with weekly paclitaxel 80 mg/m^2 as of June 3, 2020 (n = 29)
- Median follow up was 3.7 months (range: 1.2, 10.8)
- The safety population consisted of 10 patients with starting dose of rebastinib 100 mg BID (3 patients remained at this dose and 7 patients reduced to rebastinib 50 mg BID, October 2019), and 19 patients with starting dose of rebastinib 50 mg BID (**Figure 3**)
- 24/29 patients met the modified intention-to-treat (mITT) criteria (**Figure 3**)
- 17/29 (59%) patients have discontinued treatment, while 12 (41%) are ongoing
- Reasons for discontinuation include radiological progression (n = 6), clinical progression (n = 6), AE (n = 4), and death (n = 1)

Figure 3. Patient Disposition



[a]Decision to dose-reduce to rebastinib 50 mg BID due to observed, reversible muscular weakness.
[b]Safety population: Patients who initiated study drug as of June 3, 2020.
[c]mITT population: Patients from safety population who had had measurable disease at baseline and ≥1 postbaseline disease assessment or discontinued for reason other than unrelated AE or withdrawal of consent. One patient without ovarian cancer was excluded from the mITT population.
AE, adverse event; BID, twice daily; mITT, modified intent-to-treat.

Table 2. Patient Demographics and Prior Therapy from the Platinum-resistant Ovarian Cancer Cohort

	N = 29
Age, years, median (min, max)	61 (36, 76)
Race, n (%)	
Black or African American	3 (10)
White	21 (72)
Asian	1 (3)
Other	2 (7)
Not Reported/Missing	2 (7)
Prior Anticancer Therapies, n (%)	
Chemotherapy	29 (100)
Platinum-based Therapy	29 (100)
Paclitaxel	29 (100)
Docetaxel	1 (3)
Bevacizumab	26 (90)
PARP Inhibitor	18 (62)
Immunotherapy	9 (31)
Other[a]	12 (41)
Number of Prior Anticancer Regimens, median (min, max)	5 (2, 7)
2–3, n (%)	6 (21)
4+, n (%)	23 (79)

*Other: investigational therapies, trametinib, cabozantinib, tamoxifen, plant alkaloids, natural products. ADP, adenosine diphosphate; max, maximum; min, minimum; PARP, poly (ADP-ribose) polymerase; VEGF, vascular endothelial growth factor.

Drug Exposure and Safety

- The median duration of treatment in the safety population was 2.8 months (range 0.7, 10.2+)
- 66% of patients had a dose interruption of rebastinib due to AE, while 45% of patients had a dose interruption of paclitaxel due to an AE
- 10% of patients had a dose reduction of rebastinib due to AE, while 3% of patients had a dose reduction of paclitaxel due to an AE

Table 3. Dose Modification

	N = 29
Dosage Interruptions Due to AE, n (%)	
Rebastinib or Paclitaxel	21 (72)
Rebastinib	19 (66)
Paclitaxel	13 (45)
Dose Reduction Due to AE, n (%)	
Rebastinib or Paclitaxel	4 (14)
Rebastinib	3 (10)
Paclitaxel	1 (3)

AE, adverse event.

Safety

Adverse Events

- Commonly reported treatment-emergent AEs (TEAEs) (≥10% of total) regardless of relatedness are shown in **Table 4**
- 11 patients (38%) had a TEAE of Grade ≥3

Table 4. TEAEs Occurring in ≥10% of Patients with Platinum-resistant Ovarian Cancer

Preferred Term	N = 29	
	Any Grade	Grade ≥3
Fatigue	12 (41)	2 (7)
Dry Mouth	11 (38)	0
Nausea	10 (34)	1 (3)
Diarrhea	9 (31)	2 (7)
Stomatitis	9 (31)	0
Abdominal Pain	8 (28)	2 (7)
Peripheral Sensory Neuropathy	8 (28)	0
Alopecia	7 (24)	0
Urinary Tract Infection	7 (24)	1 (3)
Constipation	6 (21)	0
Muscular Weakness	6 (21)	2 (7)
Edema Peripheral	6 (21)	0
Vomiting	6 (21)	1 (3)
Dehydration	5 (17)	1 (3)
Dizziness	5 (17)	0
Dysgeusia	5 (17)	0
Hypokalemia	5 (17)	1 (3)
Vision Blurred	5 (17)	0
Abdominal Distension	4 (14)	0
Ascites	4 (14)	1 (3)
Decreased Appetite	4 (14)	0
Dry Eye	4 (14)	0
Dysphonia	4 (14)	0
Dyspnea	4 (14)	1 (3)
Gastroesophageal Reflux Disease	4 (14)	0
Anemia	3 (10)	1 (3)
Arthralgia	3 (10)	0
Hypertension	3 (10)	1 (3)
Intraocular Pressure Increased	3 (10)	0
Nail Discoloration	3 (10)	0
Oropharyngeal Pain	3 (10)	0
Weight Decreased	3 (10)	0

The most frequent AEs are also commonly observed in single agent paclitaxel.
AE, adverse event; TEAE, treatment-emergent AE.

- Two patients experienced serious AEs possibly related to rebastinib: muscular weakness/fatigue (starting dose rebastinib 100 mg BID and resolved with drug interruption) and urinary tract infection (starting dose rebastinib 50 mg BID)

Antitumor Activity

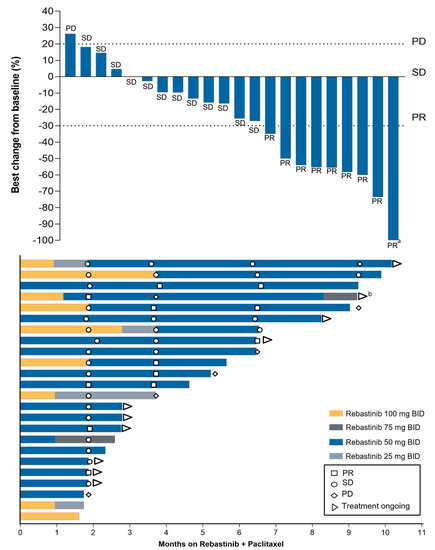
- From 24 patients in the mITT population, there were 9 PRs (3 confirmed) and 12 stable disease for an ORR of 38% and a clinical benefit rate at 8 weeks of 88% (**Table 5; Figure 4A**)
- Of 17 patients who were evaluable for a CA-125 response, 10 (59%) had a response
- Median treatment duration for the mITT population was 4.2 months (range 1.6, 10.2+) (**Figure 4B**)

Table 5. Best Overall Response and Clinical Benefit Rate for the Platinum-resistant Ovarian Cancer Cohort (mITT Population[a])

	N = 24
Best Overall Response, n (%)	
Complete Response	0
Partial Response (Confirmed + Unconfirmed)[b]	9 (38)
Stable Disease	12 (50)
Radiological Progression	1 (4)
Early Discontinuation[c]	2 (8)
Clinical Benefit Rate[d] (8 weeks), n (%)	21 (88)
Clinical Benefit Rate[d] (16 weeks), n (%)	14 (58)

[a]mITT population: Patients from safety population who had had measurable disease at baseline, ≥1 postbaseline disease assessment or discontinued for reason other than unrelated AE or withdrawal of consent.
[b]3 confirmed, 3 to be confirmed at future follow-up, and 3 unable to be confirmed.
[c]Discontinuations due to death and AEs.
[d]Complete response + partial response + stable disease.
mITT, modified intent-to-treat.

Figure 4. Best Percent Change from Baseline in the Sum of Target Lesion Diameters (A) and Time on Treatment (B)



*Target lesions were classified as a complete response; non-target lesion was non-CR/non-PD. †Patient continued treatment beyond PD for clinical benefit.
BID, twice daily; PD, progressive disease; PR, partial response; SD, stable disease.

CONCLUSIONS

- In this ongoing study, preliminary activity of rebastinib in combination with paclitaxel was encouraging in heavily pretreated patients with platinum-resistant ovarian cancer
  - The objective response rate was 38% (confirmed + unconfirmed) and the clinical benefit rate at 8 weeks was 88% in the 24 patients in the mITT population
  - A CA-125 response occurred in 10/17 patients (59%)
  - 23 (79%) patients received ≥4 prior anticancer regimens, and all patients received prior platinum and taxane-based therapy; 90% received bevacizumab, 62% received a PARP inhibitor, and 31% received immunotherapy
- Treatment with rebastinib 50 mg BID in combination with paclitaxel was generally well tolerated
- Enrollment in Stage 2 of the platinum-resistant ovarian cancer cohort at the rebastinib 50 mg BID dose is near completion and further efficacy and safety evaluation is ongoing

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Conflicts of Interest

Dr. Hamilton receives travel/accommodation/expenses from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Eisai, EMD Serono, Foundation Medicine, Genentech, Genentech/Roche, Genzyme, Guardant Health, Helsinn Therapeutics, HERON, Lexicon, Lilly, Medivation, Merck, Novartis, Pfizer, Roche, Sysmex, and Tesaro; research funding to Dr. Hamilton's institution from AbbVie, Acerta Pharma, Arcvire, ArQule, Arvinas, AstraZeneca, BerGenBio, Black Diamond, Boehringer Ingelheim, Clovis Oncology, Compugen, Curis, CytomX Therapeutics, Daiichi Sankyo, Deciphera, eFFECTOR Therapeutics, Eisai, EMD Serono, Fochon, Fujifilm, G1 Therapeutics, Genentech/Roche, H3 Biomedicine, Harpoon, Hutchison MediPharma, Immunomedics, InventisBio, Karyopharm Therapeutics, Leap Therapeutics, Lilly, Lycera, Macrogenics, MedImmune, Medivation, Mersana, Merus, Millennium, Molecular Templates, Novartis, Nucana, OncoMed, Onivoe, Pfizer, Puma Biotechnology, Radius Health, Regeneron, Rgenix, Seattle Genetics, Sermonix Pharmaceuticals, Silverback, Stem CentRx, Sutro, Syndax, Syros Pharmaceuticals, Taiho Pharmaceutical, Takeda, Tiplmmune Inc., Tesaro, Torque, Torque, Unum Therapeutics, Verastem, Zenith Epigenetics, and Zymeworks; and advisory/consultancy relationships via Dr. Hamilton's institution with AstraZeneca, Black Diamond, Boehringer Ingelheim, Daiichi Sankyo, Genentech/Roche, Lilly, Mersana, Novartis, Pfizer, Puma Biotechnology, and Silverback Therapeutics.