An open-label, multicenter, phase 1b/2 study of rebastinib in combination with paclitaxel in a dose expansion cohort to assess safety and preliminary efficacy in patients with advanced or metastatic endometrial cancer

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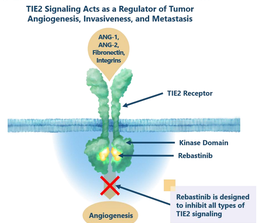
Abstract: 5576

INTRODUCTION

- Rebastinib is a first-in-class investigational, orally administered, potent, and selective switch-control tyrosine kinase inhibitor against tunica interna endothelial cell kinase 2 (TIE2)[1]
- TIE2 is the receptor for angiopoietins ANG-1 and ANG-2, an important family of vascular growth factors
- TIE2 receptors are expressed on endothelial cells and angiogenic macrophages promoting the survival, maturation, and functional integrity of the vasculature; they play an important role in regulating tumor angiogenesis, invasiveness, and metastasis (**Figure 1**)[2,3]
- This study is a 2-part open-label, phase 1b/2, multicenter study of rebastinib orally administered in combination with paclitaxel
- The expected activity of paclitaxel/chemotherapy in later-line therapy endometrial cancer patients is a response rate of 10%–20% and a progression-free survival (PFS) of 3–4 months[4–6]
  - Data presented at the Society of Gynecologic Oncology from KEYNOTE-775, a phase 3 study in advanced endometrial cancer comparing lenvatinib/pembrolizumab to physicians' choice of chemotherapy of either paclitaxel or doxorubicin. The chemotherapy arm showed a confirmed objective response rate of 15% and a median PFS of 3.8 months[4]
- In Part 1, we observed encouraging antitumor activity of rebastinib in combination with paclitaxel with 5 partial responses (PR) in 24 patients at rebastinib 50 mg twice daily (BID) and 3 PRs in 19 patients at rebastinib 100 mg BID from a heavily pretreated heterogeneous patient population[7]
- Here we summarize preliminary results of rebastinib in combination with paclitaxel from patients with endometrial cancer from Part 2

Figure 1. Rebastinib mechanism of action

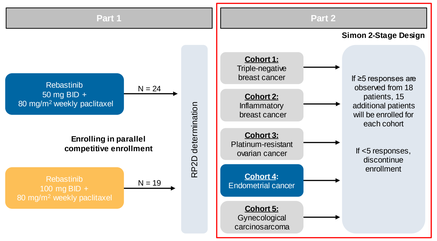


ANG-1, angiopoietin 1; ANG-2, angiopoietin 2; TIE2, tunica interna endothelial cell kinase 2.

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 recommended dose for part 2 (**Figure 2**)[7]
- 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**)
- According to the Simon 2-stage design, if ≥5 responses are observed from 18 patients, the cohort will be expanded with 15 additional patients
- 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)
- Data presented includes data through March 19, 2021
- Patients were evaluated for safety and efficacy according to CTCAE v5.0 and RECIST v1.1, respectively

Figure 2. Overall study design



ClinicalTrials.gov: NCT03601897

BID, twice daily; R2D, recommended phase 2 dose.

Table 1. Key inclusion and exclusion criteria for endometrial cohort

Inclusion criteria

- ≥18 years of age
- Histologically confirmed diagnosis of adenocarcinoma of the endometrium
- At least one prior line of platinum-based therapy in the recurrent, metastatic/high-risk disease setting
- If MSI-H or MMR-deficient, must have progressed after an anti-PD1 regimen
- ≥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

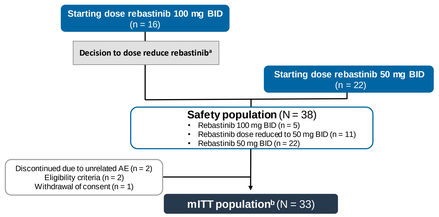
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricle ejection fraction; MMR, mismatch repair; MSI-H, microsatellite instability-high; RECIST, Response Evaluation Criteria in Solid Tumors.

RESULTS

Patient demographics and disposition

- In this analysis, 38 patients with endometrial cancer have initiated treatment with rebastinib in combination with paclitaxel and are in the safety population; 1 patient withdrew consent early, 2 patients did not meet eligibility criteria, and 2 patients discontinued due to unrelated adverse events (AEs), resulting in 33 patients in the modified intent-to-treat (mITT) population (**Figure 3**)
  - Of 38 patients, 16 patients were treated with rebastinib at a starting dose of 100 mg BID (11 reduced to 50 mg BID) and 22 pts with rebastinib at a starting dose of 50 mg BID; all received weekly paclitaxel 80 mg/m^2
  - The median follow-up time for the safety population was 4.4 months

Figure 3. Patient disposition in endometrial cohort



[a]Decision to dose reduce to 50 mg BID due to observed reversible muscular weakness.
[b]Patients were excluded from the mITT population if they did not have a post-baseline disease assessment and discontinued treatment due to unrelated AE, withdraw al of consent, or eligibility criteria.
AE, adverse event; BID, twice daily; mITT, modified intent-to-treat.

Table 2. Baseline demographics and characteristics for patients in the endometrial cohort

	Endometrial cohort (N = 38)
Age, years, median (min, max)	66 (39, 77)
Histology	
Endometrioid	21 (55.3)
Grade 1	1 (2.6)
Grade 2	7 (18.4)
Grade 3	9 (23.7)
Unknown	4 (10.5)
Serous	11 (28.9)
Other	6 (15.8)
Microsatellite instability	
High	4 (10.5)
Low	1 (2.6)
Stable	15 (39.5)
Unknown	18 (47.4)
Median number of prior regimens (min, max)	3 (1, 6)
1 regimen	2 (5.3)
2–3 regimens	19 (50.0)
≥4 regimens	17 (44.7)
Therapy type	
Chemotherapy	38 (100)
Paclitaxel	38 (100)
Docetaxel	3 (7.9)
Immunotherapy	17 (44.7)
Bevacizumab	15 (39.5)
Anti-PARP	7 (18.4)

Data shown as n (%) unless indicated otherwise.
max, maximum; min, minimum.

Drug exposure and safety

- Of the 38 patients with endometrial cancer who initiated treatment with rebastinib, the median duration of treatment was 3.7 months (**Table 3**)

Table 3. Drug exposure for patients in the endometrial cohort

	Endometrial cohort (N = 38)
Treatment duration (months), median (min, max)	3.7 (0.2, 18.4)
Interruption due to AE	
Rebastinib	23 (60.5)
Paclitaxel	15 (39.5)
Dose reduction due to AE	
Rebastinib	3 (7.9)
Paclitaxel	5 (13.2)
Discontinuation of rebastinib due to AE	12 (31.6)
Discontinuation of rebastinib due to AE (related)[1]	8 (21.1)

[1]Rebastinib-related AEs leading to discontinuation (all possibly related): Grade 2 nausea, Grade 2 muscular weakness, Grade 3 acute myocardial infarction, Grade 3 stress cardiomyopathy, Grade 3 muscular weakness, Grade 2 dermatitis bullous, Grade 2 retinal vein occlusion, and Grade 2 facial paralysis and diarrhea.
Data shown as n (%) unless indicated otherwise.
AE, adverse event; max, maximum; min, minimum.

Table 4. Common (≥15%) TEAEs regardless of relatedness from patients in the endometrial cohort (N = 38)

Preferred term	Any grade	Grade 3–4
Patients with at least one TEAE	38 (100.0)	21 (55.3)
Fatigue	19 (50.0)	1 (2.6)
Constipation	16 (42.1)	0
Edema peripheral	16 (42.1)	0
Nausea	15 (39.5)	3 (7.9)
Peripheral sensory neuropathy	15 (39.5)	0
Dyspnea	12 (31.6)	0
Alopecia	11 (28.9)	0
Hypokalemia	11 (28.9)	2 (5.3)
Diarrhea	10 (26.3)	1 (2.6)
Hypomagnesemia	10 (26.3)	0
Dry mouth	9 (23.7)	0
Dysgeusia	9 (23.7)	0
Muscular weakness	9 (23.7)	4 (10.5)
Arthralgia	8 (21.1)	1 (2.6)
Dehydration	8 (21.1)	2 (5.3)
Gastroesophageal reflux disease	8 (21.1)	0
Decreased appetite	7 (18.4)	0
Hypertension	7 (18.4)	4 (10.5)
Vomiting	7 (18.4)	0
Anemia	6 (15.8)	1 (2.6)
Dry eye	6 (15.8)	0
Insomnia	6 (15.8)	0
Stomatitis	6 (15.8)	0

Data shown as n (%).
BID, twice daily; TEAE, treatment-emergent adverse events.

- The majority of the common (≥15%) treatment-emergent adverse events (TEAEs) regardless of causality (**Table 4**) were Grade ≤2
- Nine patients experienced serious AEs at least possibly related to rebastinib, including muscular weakness (n = 3), nausea (n = 2), acute myocardial infarction (n = 1), atrial flutter (n = 1), dehydration (n = 1), noninfective encephalitis (n = 1), peritonsillitis (n = 1), and stress cardiomyopathy (n = 1)

Antitumor activity

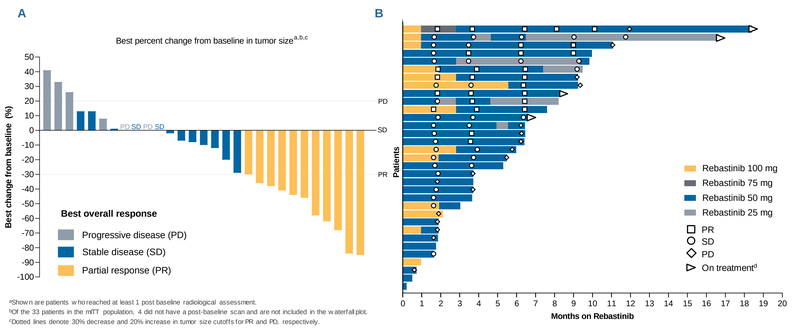
- From 33 patients in the mITT population, there were 11 PRs (8 confirmed) and 12 stable disease for an objective response rate (ORR) of 33% and a clinical benefit rate of 55% at 16 weeks (**Table 5; Figure 4A**); median duration of response was 7.4 months
- Out of 33 patients, 15 (45%) have been treated for at least 6 months (**Figure 4B**)
- Median PFS was 6.2 months (**Figure 5**)
- As of March 19, 2021, out of 4 active patients on study treatment, 1 patient has progressed per RECIST v1.1 but is continuing due to clinical benefit

Table 5. Best overall response from endometrial cohort (mITT population[a])

	Endometrial cohort (N = 33)
Best overall response	
Partial response	11 (33.3)
Confirmed partial response	8 (24.2)
Stable disease	12 (36.4)
Progressive disease	6 (18.2)
* Not evaluable	4 (12.1)
Clinical benefit rate[b] (8 weeks)	23 (69.7)
Clinical benefit rate[b] (16 weeks)	18 (54.5)

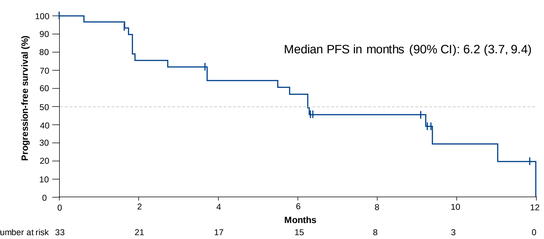
[a]Patients were excluded from the mITT population if they did not have a post-baseline disease assessment and discontinued treatment due to unrelated AE, withdraw al of consent, or eligibility criteria.
[b]Clinical benefit rate at 8 and 16 weeks was defined as overall response of CR, PR, or SD according to RECIST v1.1 at the 8- and 16-week response assessments, respectively.
[c]Patients who discontinued prior to radiological assessment.
Data shown as n (%) unless indicated otherwise.
CR, complete response, mITT, modified intent-to-treat; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Figure 4. (A) Best percent change from baseline in tumor size and (B) time on treatment for mITT patients in the endometrial cohort



[a]Shown are patients who reached at least 1 post baseline radiological assessment.
[b]Of the 33 patients in the mITT population, 4 did not have a post-baseline scan and are not included in the waterfall plot.
[c]Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for PR and PD, respectively.
[d]Patients without an arrowhead are off treatment.
mITT, modified intent-to-treat; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 5. Progression-free survival Kaplan-Meier curve for mITT patients in the endometrial cohort



Vertical slashes represent censored patients.
CI, confidence interval; mITT, modified intent-to-treat; PFS, progression-free survival.

CONCLUSIONS

- Treatment of patients with endometrial cancer with rebastinib 50 mg BID in combination with paclitaxel was manageable
  - Among 38 patients treated, median duration of treatment was 3.7 months
- Preliminary activity of rebastinib in combination with paclitaxel was encouraging in heavily pretreated patients
  - All 38 patients received prior taxane; 44% of patients received ≥4 prior anti-cancer regimens, with a median of 3
  - In the 33 patients in the mITT population, the ORR was 33% (unconfirmed and confirmed) and 24% (confirmed only)
  - The clinical benefit rate at 16 weeks was 55%
  - With 58% events, the median PFS was 6.2 months
- Safety and preliminary efficacy of rebastinib in combination with paclitaxel continues to be favorable with longer term data, supporting further development

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