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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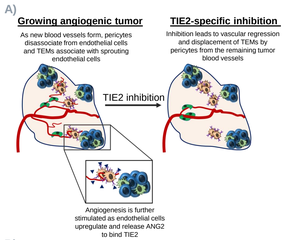
INTRODUCTION

- 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 study is a 2-part open-label, phase 1b/2, multicenter study of rebastinib orally administered in combination with paclitaxel
- In Part 1, we observed encouraging antitumor activity of rebastinib in combination with paclitaxel with 5 partial responses (PR) in 24 patients (pts) at rebastinib 50 mg twice daily (BID) and 3 PRs in 19 pts at rebastinib 100 mg BID from a heavily pretreated heterogeneous patient population[6]
- Here we summarize preliminary results of rebastinib in combination with paclitaxel from pts with endometrial cancer from Part 2

Figure 1. Role of TIE2 in angiogenesis and tumor cell intravasation

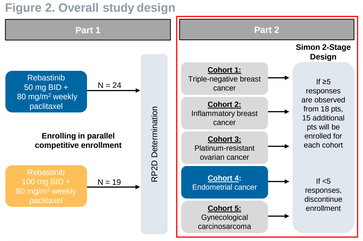


ANG2, angiopoietin 2; TAM, tumor-associated macrophages; TIE2, tunica interna endothelial cell kinase 2; TEM, TIE2-expressing macrophage; TMEM, tumor microenvironment of metastasis.

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 recommended dose for part 2 (**Figure 2**)[6]
- 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 of this study, 15 additional pts will be enrolled for each cohort if ≥5 responses are observed from 18 pts
- Pts 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, results are reported for pts with endometrial cancer who initiated treatment as of February 22, 2020 with follow-up data cut as of April 20, 2020
- Pts 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; pts, patients; RP2D, recommended phase 2 dose.

Table 1. Key inclusion and exclusion criteria from endometrial cohort

Inclusion criteria

- ≥18 years old
- 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

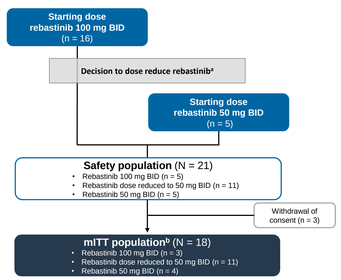
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricle ejection fraction; MMR, mismatch repair; MSI-H, microsatellite instability-high; RECIST, response evaluation criteria in solid tumors.

RESULTS

Patient demographics and disposition

- In this interim analysis, 21 pts with endometrial cancer have initiated treatment with rebastinib and are in the safety population; 3 patients withdrew consent early resulting in 18 patients in the modified intent-to-treat (mITT) population (**Figure 3**)
  - 16 pts treated with rebastinib starting dose of 100 mg BID (11 reduced to 50 mg BID) and 5 pts rebastinib starting dose of 50 mg BID + weekly paclitaxel 80 mg/m^2

Figure 3. Patient disposition (endometrial cohort)



[a]Decision to dose reduce to 50 mg BID due to observed reversible muscular weakness.
[b]mITT population excluded patients who withdrew consent before the first post-baseline assessment
AE, adverse event; C, cycle; BID, twice daily; D, day; mITT, modified intent-to-treat.

Table 2. Baseline demographics and prior therapy from patients in endometrial cohort

	Endometrial cohort (N = 21)
Age, years, median (min, max)	66 (39, 77)
Race, n (%)	
Black or African American	2 (9.5)
Asian	3 (14.3)
White	15 (71.4)
Other	1 (4.8)
Prior anti-cancer therapies, n (%)	
Chemotherapy	21 (100)
Paclitaxel	21 (100)
Docetaxel[a]	1 (4.8)
Hormonal therapy	6 (28.6)
Immunotherapy	8 (38.1)
Anti-angiogenic therapy	10 (47.6)
Anti-PARP therapy	4 (19.0)
Other	9 (42.8)
Number of prior anti-cancer regimens, median (min, max)	4 (1, 6)
1 prior regimens, n (%)	1 (4.8)
2–3 prior regimens, n (%)	8 (38.1)
>3 prior regimens, n (%)	12 (57.1)

[a]Patient also received paclitaxel

Drug exposure and safety

- Of the 21 pts 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 from endometrial cohort

	Endometrial cohort (N = 21)
Total treatment duration (months), median (min, max)	3.7 (0.3, 9.2)
Interruption due to AE, n (%)	
Rebastinib or paclitaxel	15 (71.4)
Rebastinib	15 (71.4)
Paclitaxel	13 (61.9)
Dose reduction due to AE, n (%)	
Rebastinib or paclitaxel	5 (23.8)
Rebastinib	4 (19.0)
Paclitaxel	2 (9.5)

AE, adverse event.

- The majority of the common (≥15%) treatment-emergent adverse events (TEAEs) regardless of causality (**Table 4**) were grade ≤2

Table 4. Common (≥15%) TEAEs regardless of relatedness in patients from endometrial cohort (N = 21)

Preferred Term	Any Grade	Grade ≥3
Constipation	10 (47.6)	0
Fatigue	9 (42.9)	0
Alopecia	8 (38.1)	0
Edema peripheral	8 (38.1)	1 (4.8)
Diarrhea	7 (33.3)	1 (4.8)
Dysgeusia	7 (33.3)	0
Dry mouth	6 (28.6)	0
Hypokalemia	6 (28.6)	1 (4.8)
Hypomagnesaemia	6 (28.6)	0
Muscular weakness[a]	6 (28.6)	3 (14.3)
Nausea	6 (28.6)	2 (9.5)
Peripheral sensory neuropathy	6 (28.6)	0
Vomiting	6 (28.6)	0
Anemia	5 (23.8)	1 (4.8)
Arthralgia	5 (23.8)	1 (4.8)
Decreased appetite	4 (19.0)	0
Dehydration	4 (19.0)	2 (9.5)
Dry eye	4 (19.0)	0
Dyspnea	4 (19.0)	1 (4.8)
Hypertension	4 (19.0)	2 (9.5)
Myalgia	4 (19.0)	0
Vision blurred	4 (19.0)	0

All values are n (%)
[a]Observed reversible muscular weakness that occurred at 100 mg BID.
BID, twice daily, treatment-emergent adverse events.

- Serious AEs (SAEs) at least possibly related to rebastinib occurred only at 100 mg BID and resolved after dose reductions
- Nine pts experienced SAEs at least possibly related to rebastinib including muscular weakness (n = 2), acute myocardial infarction (n = 1), atrial flutter (n = 1), dehydration (n = 1), head discomfort (n = 1), nausea (n = 1), peripheral edema (n = 1), and pneumonia (n = 1)

Antitumor activity

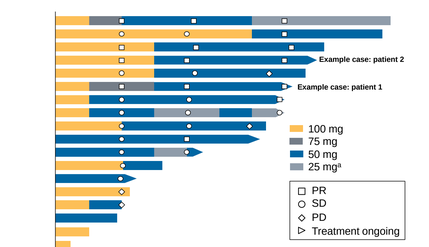
- From 18 pts in the mITT population, there were 7 PRs (4 confirmed) and 6 stable disease (SD) for an objective response rate (ORR) of 39% and a clinical benefit rate of 72% at 8 weeks (**Table 5; Figure 4**)
- 10/18 (55%) have been treated for at least 5 months (**Figure 4**)

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

	Endometrial cohort (N = 18)
Best overall response, n (%)	
Complete response	0
Partial response[b]	7 (39)
Stable disease	6 (33)
Radiological progression	2 (11)
Early discontinuation[c]	3 (17)
Clinical benefit rate[d] (8 weeks), n (%)	13 (72)
Clinical benefit rate[d] (16 weeks), n (%)	11 (61)

[a]mITT population excluded patients who withdrew consent before the first post-baseline assessment; [b]Confirmed: 4 partial response and all stable disease/progressive disease; [c]1 patient discontinued early due to clinical progressive disease, 1 patient discontinued early due to adverse events, and 1 patient discontinued early due to death; [d]Complete response + partial response + stable disease
mITT, modified intent-to-treat.

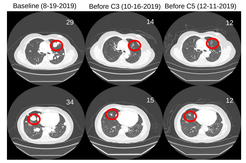
Figure 4. (A) Time on treatment and (B) best percent change from baseline in tumor size



[a]3 patients reduced to rebastinib 25 mg BID due to adverse events.
Waterfall plot excludes 3 patients with early discontinuation for whom no radiological assessments were available
Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for PR and PD, respectively.
ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

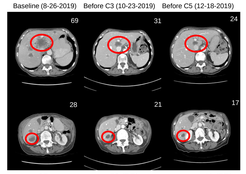
Figure 5. Example case studies

Patient 1: 55-year-old female with stage IV endometrial cancer



Sum of diameters 63 29 (PR) 24 (PR)
Target lesions are marked with red circles
Prior anti-cancer therapy history
1st: Carboplatin/paclitaxel (3 months) – SD
2nd: Carboplatin/paclitaxel (3 months) – SD
3rd: Doxorubicin (15 months) – SD
4th: Bevacizumab/liposomal doxorubicin (12 months) – SD
5th: Everolimus/letrozole (3 months) – SD

Patient 2: 77-year-old female with stage IV endometrial cancer



Sum of diameters 97 52 (PR) 41 (PR)
Target lesions are marked with red circles
Prior anti-cancer therapy history
1st: Carboplatin/paclitaxel/zoledronate (10 months) – PD
2nd: Megestrol acetate/tamoxifen (14 months) – PD
3rd: Liposomal doxorubicin (5 months) – PD

RECIST v1.1 assessment
C, cycle; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease

CONCLUSIONS

- Preliminary activity of rebastinib in combination with paclitaxel was encouraging in heavily pretreated patients
  - 21 patients were treated with rebastinib in combination with paclitaxel with a median duration of 3.7 months
  - All patients received ≥1 prior line of the combination of paclitaxel/carboplatin and 20 (95%) received ≥ 2 prior anti-cancer regimens
  - In 18 patients in the mITT population, the objective response rate was 39% and the clinical benefit rate at 8 weeks was 72%
- Treatment with rebastinib 50 mg BID in combination with paclitaxel was well tolerated
- Enrollment in stage 2 of the endometrial cohort at the rebastinib 50 mg BID dose is near completion and further efficacy and safety evaluation is ongoing

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