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

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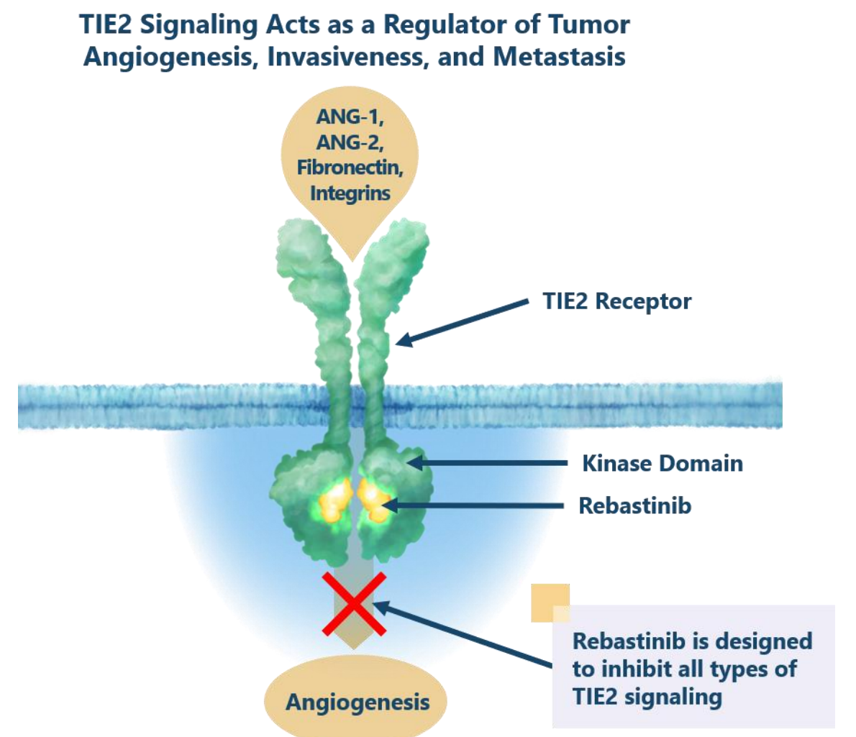
INTRODUCTION

- Rebastinib is a first-in-class investigational, orally administered, potent, and selective inhibitor of the tunica interna endothelial cell kinase 2 (TIE2) kinase[1]
- TIE2 is the receptor for angiopoietins (ANG) 1 and 2, an important family of vascular growth factors, and 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 tumour angiogenesis, invasiveness, and metastasis (**Figure 1**)[2,3]
- Rebastinib binds potently into the switch pocket of TIE2, stabilising the inhibitory switch and displacing the activation switch to block TIE2 signaling[1]
- There is a high unmet need for an effective therapy for heavily pretreated patients with advanced or metastatic platinum-resistant ovarian cancer (PROC); in this setting, single-agent weekly paclitaxel provides a median progression-free survival (PFS) of approximately 3–4 months[4,5]
- This study is a 2-part open-label, phase 1b/2, multicentre study of rebastinib orally administered in combination with paclitaxel
- In Part 1, we observed encouraging antitumour 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[6]
- Here, we summarise preliminary results of rebastinib in combination with paclitaxel in patients with PROC from Part 2 of the study

Figure 1. Rebastinib mechanism of action

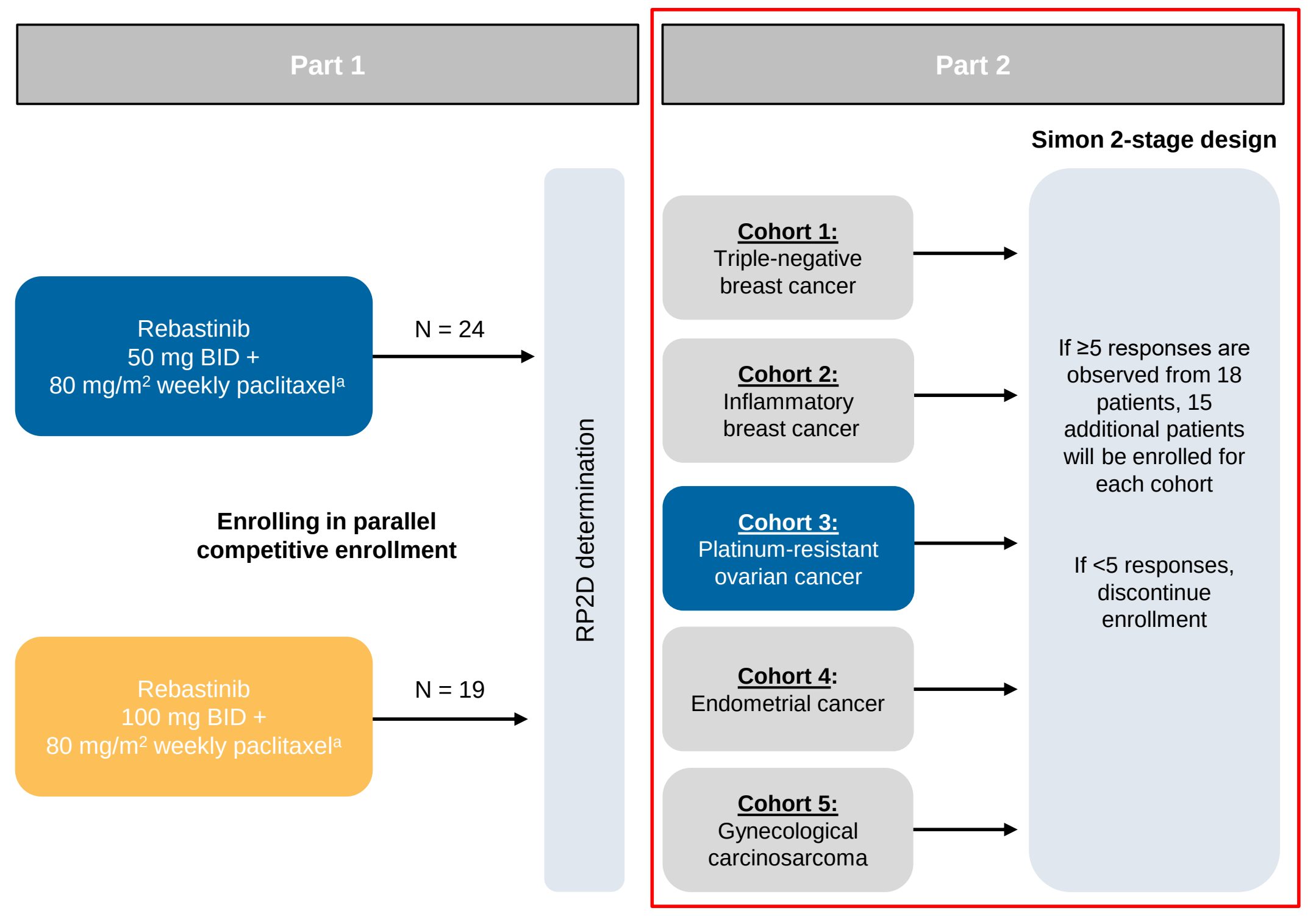


ANG-1, angiopoietin 1; ANG-2, angiopoietin 2; TIE2, tunica interna endothelial cell kinase 2.

METHODS

- Part 1 enrolled adults with locally advanced/metastatic solid tumours into 1 of 2 rebastinib dose cohorts (50 or 100 mg BID) in combination with paclitaxel using a parallel cohort design to determine recommended dose for part 2 (**Figure 2**)
- Part 2 of this study has 5 disease-specific cohorts (triple-negative breast cancer, inflammatory breast cancer, PROC, 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)
- In this presentation, results are reported for patients with PROC with a data cut-off of June 22, 2021
- Patients were evaluated for safety according to CTCAE v5.0, tumour response according to RECIST v1.1, and cancer antigen-125 (CA-125) response (at least 50% reduction of CA-125 levels confirmed and maintained for at least 28 days) according to Gynecological Cancer Intergroup criteria

Figure 2. Overall study design



Part 1

Rebastinib
50 mg BID +
80 mg/m^2 weekly paclitaxel[a]
N = 24

Enrolling in parallel
competitive enrollment

Rebastinib
100 mg BID +
80 mg/m^2 weekly paclitaxel[a]
N = 19

RP2D determination

Part 2

Simon 2-stage design

Cohort 1: Triple-negative breast cancer

Cohort 2: Inflammatory breast cancer

Cohort 3: Platinum-resistant ovarian cancer

Cohort 4: Endometrial cancer

Cohort 5: Gynecological carcinosarcoma

If ≥5 responses are observed from 18 patients, 15 additional patients will be enrolled for each cohort

If <5 responses, discontinue enrollment

ClinicalTrials.gov: NCT03601897
[a]Paclitaxel was administered weekly for 3 weeks followed by 1 week off treatment
BID, twice daily; RP2D, recommended phase 2 dose.

Table 1. Key inclusion and exclusion criteria for PROC cohort

Inclusion criteria

- ≥18 years old
- Histologically confirmed, recurrent epithelial ovarian, peritoneal or fallopian tube carcinoma
- Progressed or relapsed within 6 months after the completion of a platinum-containing chemotherapy regimen
  - Patients who progressed during treatment or ≤1 month after the completion of the first platinum-containing chemotherapy regimen (primary platinum refractory) are excluded
- ≤5 prior lines of systemic anticancer therapy
- If BRCA 1 or 2 alteration (germline or somatic), must have received prior PARP inhibitor
- Measurable disease per RECIST v1.1
- ECOG Performance Status of ≤2
- Adequate organ function, bone marrow reserve, and cardiac function

Exclusion criteria

- Prior anticancer therapy or other investigational therapy ≤28 days or 5x half-life prior to the first dose of study drug, whichever is shorter
- Not recovered from toxicities from prior therapy to Grade 1 (or baseline)
- Grade >1 peripheral neuropathy (any etiology)
- Known active CNS metastases
- History or presence of clinically relevant cardiovascular abnormalities
- Known retinal neovascularisation, macular oedema, or macular degeneration

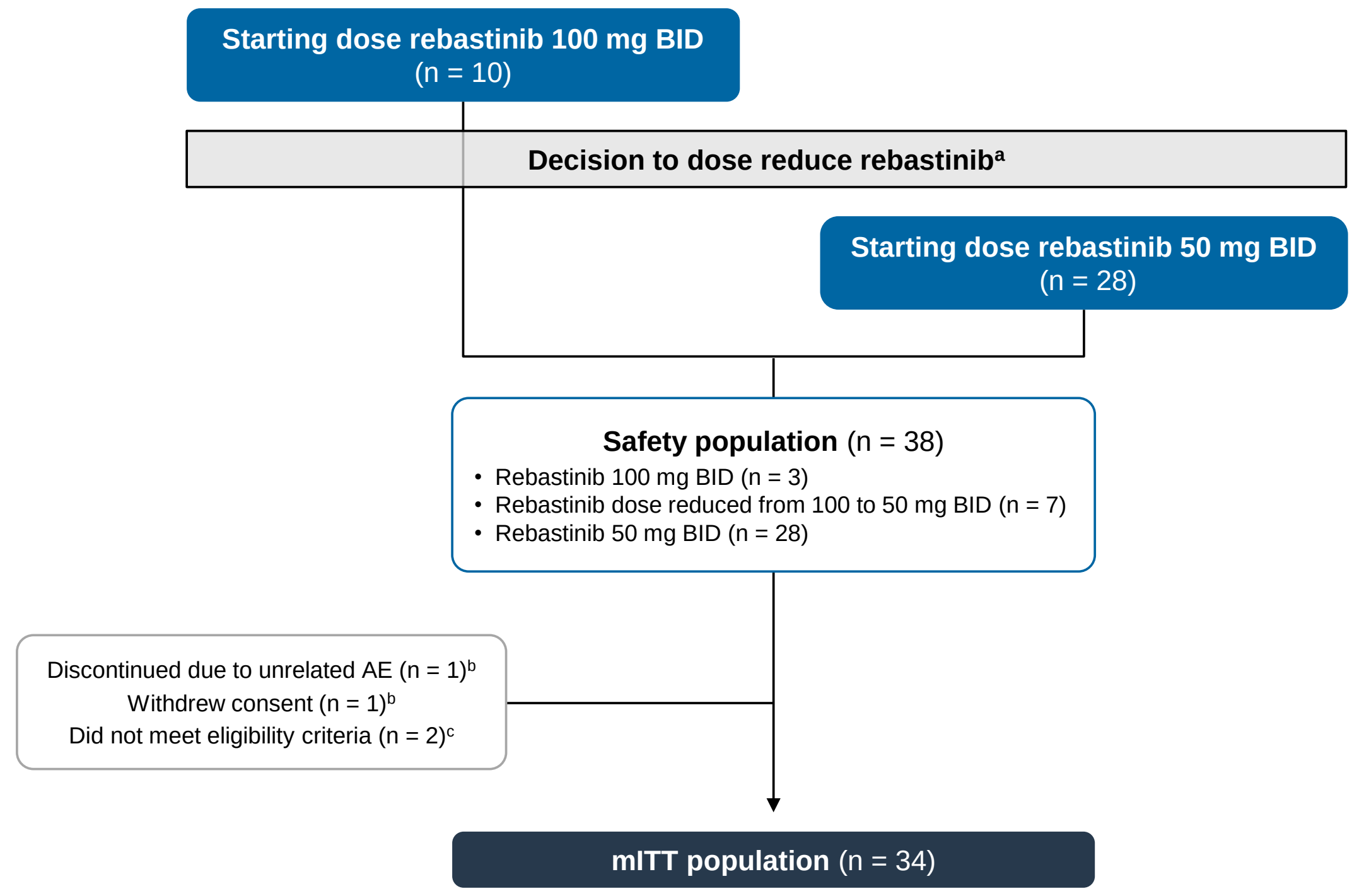
BRCA, breast cancer gene, CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; PARP, poly adenosine diphosphate-ribose polymerase; PROC, platinum resistant ovarian cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

RESULTS

Patient demographics and disposition

- In this analysis, 38 patients with PROC have initiated treatment with rebastinib and are in the safety population; 4 patients did not meet the criteria to be in the modified intent-to-treat population (mITT), resulting in 34 patients in the mITT population (**Figure 3**)
  - Of 38 patients, 10 patients were treated with rebastinib starting dose of 100 mg BID (7 patients reduced to 50 mg BID) and 28 patients with rebastinib starting dose of 50 mg BID in combination with weekly paclitaxel 80 mg/m^2
- As of June 22, 2021, there were 6 patients on active treatment (**Figure 4B**)

Figure 3. Patient disposition in PROC cohort



Starting dose rebastinib 100 mg BID
(n = 10)

Decision to dose reduce rebastinib[a]

Starting dose rebastinib 50 mg BID
(n = 28)

Safety population (n = 38)
- Rebastinib 100 mg BID (n = 3)
- Rebastinib dose reduced from 100 to 50 mg BID (n = 7)
- Rebastinib 50 mg BID (n = 28)

Discontinued due to unrelated AE (n = 1)[b]
Withdrew consent (n = 1)[b]
Did not meet eligibility criteria (n = 2)[c]

mITT population (n = 34)

[a]Decision to dose reduce to 50 mg BID due to observed reversible muscular weakness.
[b]Patients who discontinued due to withdrawal of consent or an unrelated AE were excluded because they did not have a postbaseline assessment.
[c]Of the 2 patients who did not meet eligibility criteria, 1 had non-measurable disease at baseline and the other did not have ovarian cancer.
AE, adverse event; BID, twice daily; mITT, modified intent-to-treat; PROC, platinum resistant ovarian cancer.

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

	PROC cohort (N = 38)
Age, years, median (min, max)	59.5 (36, 76)
Histology	
High-grade serous	34 (89)[a]
Mixed	2 (5)
Endometrioid	1 (3)
Seromucinous	1 (3)
BRCA+	8 (21)
Median number of prior regimens (min, max)	4 (2, 7)
2–3 regimens	15 (39)
≥4 regimens	23 (61)
Prior therapy	
Paclitaxel	38 (100)
Bevacizumab	33 (87)
Anti-PARP	26 (68)
Other	8 (21)
Prior surgery	37 (97)
Prior radiation	1 (3)

[a]Includes one patient whose histology was classified as “Other, high-grade serous”.
Data shown as n (%) unless indicated otherwise.
BRCA, breast cancer gene; PARP, poly adenosine diphosphate-ribose polymerase; PROC, platinum resistant ovarian cancer.

- In this analysis, 100% of patients received ≥2 lines of therapy; 61% of patients received ≥4 lines of therapy (**Table 2**)
- All patients received prior platinum/taxane chemotherapy and 87% of patients received bevacizumab (**Table 2**)

Antitumour activity

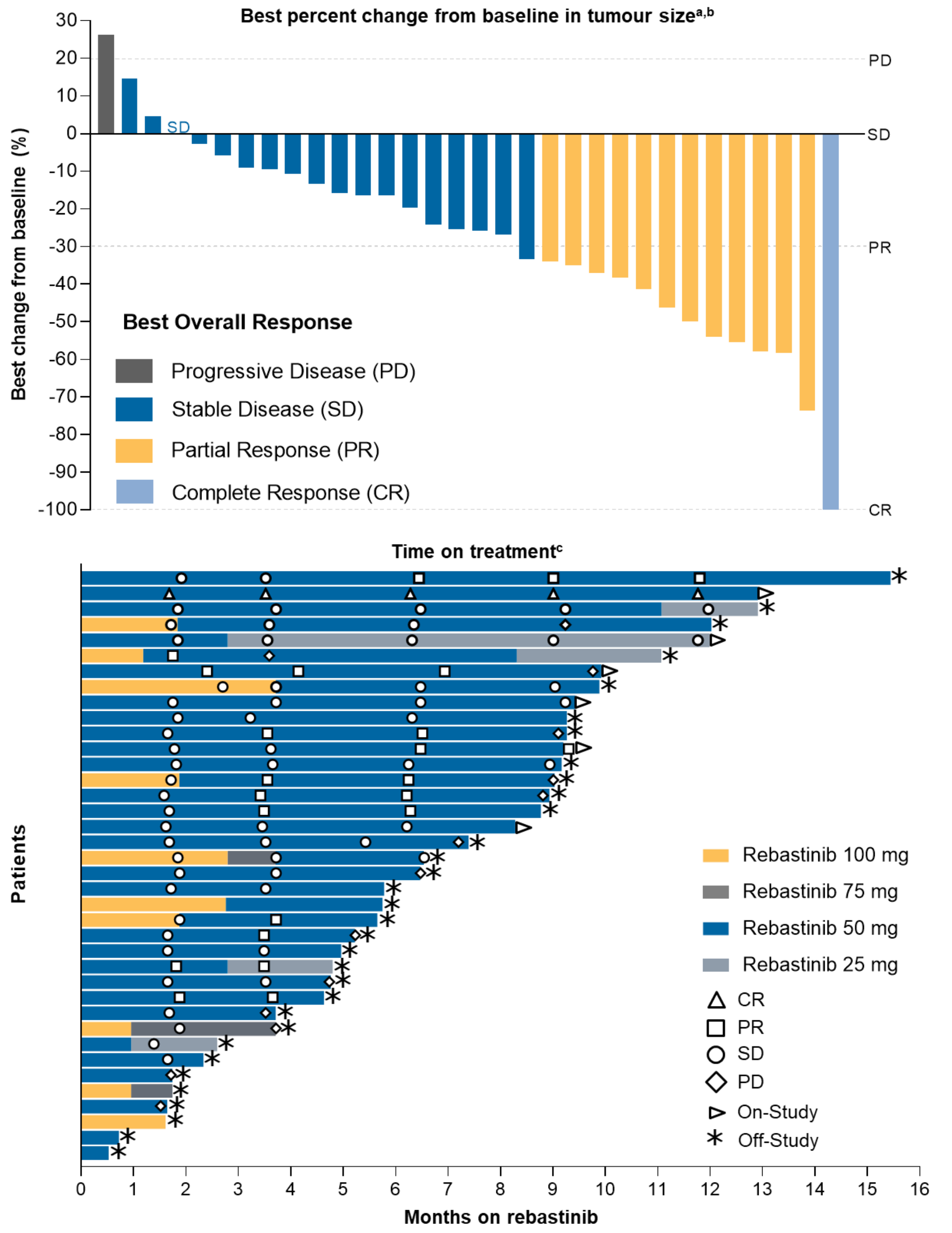
- The ORR (confirmed + unconfirmed) was 38%; the clinical benefit rate (CBR) at 16 weeks was 76% (**Table 3**)
- CA-125 was evaluated in 26 patients; 19 (73%) had a CA-125 response
- The median PFS was 9.1 months (90% confidence interval, 6.5–NE; **Figure 5**)

Table 3. Best overall response from PROC cohort (mITT)

	PROC cohort (N = 34)
Objective response rate	13 (38)
Confirmed objective response rate	10 (29)
Best overall response	
CR	1 (3)
PR	12 (35)
SD	18 (53)
PD	1 (3)
No follow-up radiological assessment	2 (6)
Duration of response, months[a]	
Median	5.5
90% CI	2.6, 7.4
Clinical benefit rate[b] (8 weeks)	30 (88)
Clinical benefit rate[b] (16 weeks)	26 (76)

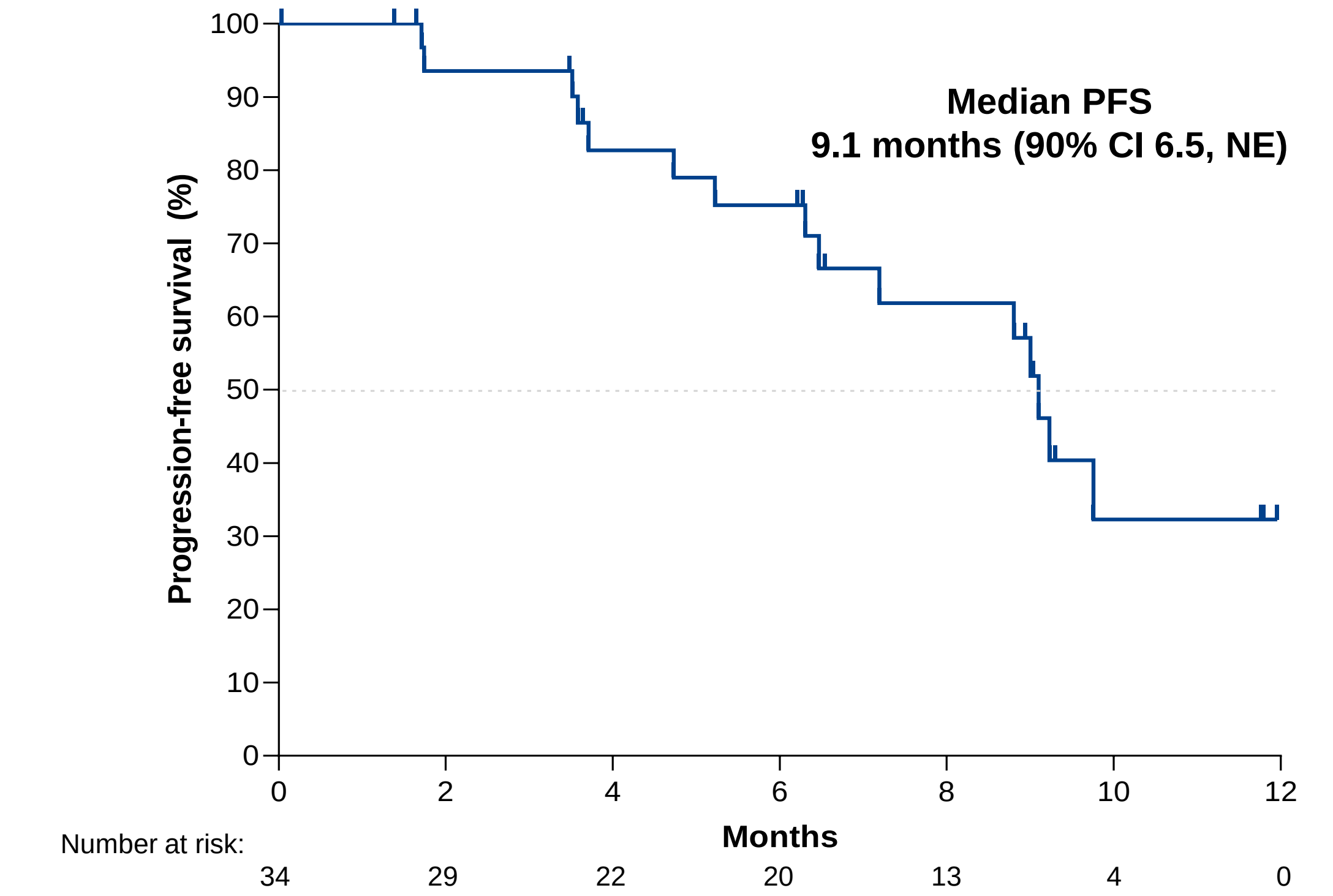
One patient had a best response of SD at day 42 (6 weeks) and is not counted as having clinical benefit at 8 weeks.
[a]Estimated using Kaplan-Meier methods among 13 patients with objective response. Among 10 patients with confirmed objective responses, the median duration of response was 5.6 months (90% CI: 5.4–NE).
[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.
Data shown as n (%) unless indicated otherwise.
CI, confidence interval; CR, complete response, mITT, modified intent-to-treat; PD, progressive disease; PR, partial response; PROC, platinum resistant ovarian cancer; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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



[a]Patients with ≥1 postbaseline radiological assessment are shown (N = 32); plot includes confirmed and unconfirmed responses.
[b]Dotted lines denote 30% decrease and 20% increase in tumour size cutoffs for PR and PD, respectively.
[c]Overall, 13 patients (34%) discontinued due to radiological PD, 9 patients (24%) discontinued due to an AE, 7 patients (18%) discontinued due to clinical PD, 2 patients (5%) chose to withdraw, and 1 patient (3%) died due to causes unrelated to rebastinib.
AE, adverse event; CR, complete response; mITT, modified intent-to-treat; PD, progressive disease; PR, partial response; PROC, platinum resistant ovarian cancer; SD, stable disease.

Figure 5. PFS Kaplan-Meier curve for patients in the PROC cohort (mITT)



Number of events (%): 15 (44%)
CI, confidence interval; mITT, modified intent-to-treat; NE, non-estimable; PFS, progression-free survival; PROC, platinum resistant ovarian cancer.

Safety

- Most AEs reported were Grade ≤2 (**Table 5**)
- Four patients (11%) experienced 5 serious AEs at least possibly related to rebastinib: Grade 3 reversible muscular weakness (n = 2 [5%], occurred at 50 mg and 75 mg BID), Grade 2 constipation (n = 1; 3%), Grade 3 fatigue (n = 1; 3%), Grade 3 urinary tract infection (n = 1; 3%)

Table 4. Treatment duration and dose modifications in the PROC cohort

	PROC cohort (N = 38)
Treatment duration (months), median (min, max)	6.5 (0.5, 15.4)
Interruption due to AE	
Rebastinib	28 (74)
Rebastinib (related)	16 (42)
Paclitaxel	23 (61)
Dose reduction due to AE	
Rebastinib	8 (21)
Rebastinib (related)	8 (21)
Paclitaxel	3 (8)
Discontinuation of rebastinib due to AE	9 (24)
Discontinuation of rebastinib due to AE (related)[a]	7 (18)

[a]Rebastinib-related AEs leading to discontinuation, at least possibly related to rebastinib: Grade 3 muscular weakness and Grade 3 fatigue (n = 1), Grade 1 muscular weakness (n=1), Grade 2 vulvitis and Grade 2 priapism (n = 1), Grade 1 oedema peripheral (n = 2), Grade 2 oedema peripheral (n = 1), and retinal vein occlusion (n=1).
Data shown as n (%) unless indicated otherwise.
AE, adverse event; max, maximum; min, minimum; PROC, platinum resistant ovarian cancer.

Table 5. Summary of treatment-emergent AEs ≥15% regardless of relatedness (N = 38)

Preferred term	Any grade	Grade 3
Fatigue	22 (58)	3 (8)
Alopaecia	16 (42)	1 (3)[a]
Oedema peripheral	15 (39)	2 (5)
Dry mouth	14 (37)	0
Nausea	14 (37)	1 (3)
Peripheral sensory neuropathy	14 (37)	0
Constipation	12 (32)	0
Diarrhoea	12 (32)	2 (5)
Hypertension	12 (32)	3 (8)
Abdominal pain	11 (29)	2 (5)
Muscular weakness	10 (26)	3 (8)[b]
Stomatitis	10 (26)	0
Dyspnoea	9 (24)	1 (3)
Dizziness	8 (21)	0
Hypomagnesaemia	8 (21)	0
Urinary tract infection	8 (21)	1 (3)
Abdominal distension	7 (18)	0
Anaemia	7 (18)	1 (3)
Decreased appetite	7 (18)	0
Hypokalaemia	7 (18)	1 (3)
Vomiting	7 (18)	1 (3)
Arthralgia	6 (16)	0
Cough	6 (16)	0
Dry eye	6 (16)	0
Headache	6 (16)	0
Nail discolouration	6 (16)	0
Pain in extremity	6 (16)	1 (3)

[a]Grade 3 alopecia is not in CTCAE, site queried and updated to Grade 2.
[b]One patient had Grade 3 muscular weakness that was considered related to rebastinib but was not entered as an SAE. This event occurred at 100 mg BID.
AE, adverse event; BID, twice daily; CTCAE, common terminology criteria for adverse events; SAE, serious AE.

CONCLUSIONS

- Rebastinib demonstrated encouraging preliminary antitumour activity in combination with paclitaxel in heavily pretreated patients with advanced/metastatic PROC (all receiving platinum/taxane, 61% ≥4 prior anticancer regimens, 87% prior bevacizumab):
  - The median PFS was 9.1 months
  - The ORR was 38% (confirmed + unconfirmed) and 29% (confirmed); the median duration of response was 5.5 months
  - The clinical benefit rate at 16 weeks (confirmed + unconfirmed) was 76%
  - A CA-125 response occurred in 19 of 26 patients (73%)
- The safety profile of rebastinib 50 mg BID in combination with paclitaxel was generally well tolerated
- The median PFS was promising when considering previously reported data for weekly paclitaxel monotherapy in the PROC setting (median PFS 3–4 months)[4,5]
- This updated safety and efficacy analysis supports further development of rebastinib 50 mg BID in combination with paclitaxel in previously treated patients with PROC

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Dr. Hamilton is employed by Sarah Cannon Research Institute, Tennessee Oncology, LLC; acts in an advisory/consultancy role for AstraZeneca, Black Diamond, Boehringer Ingelheim, Daiichi Sankyo, Genentech/Roche, Lilly, Mersana, Novartis, Pfizer, Puma Biotechnology, and Silverback; receives accommodations from AstraZeneca, Clovis Oncology, Eisai, EMD Serono, Genentech/Roche, Lilly, Novartis, Pfizer, Tesaro, Amgen, Bayer, Bristol-Myers Squibb, Foundation Medicine, Genzyme, Guardant Health, Helsinn Therapeutics, HERON, Lexicon, Medivation, Merck, and Sysmex. Dr. Hamilton's institution receives funding from AstraZeneca, Black Diamond, Boehringer Ingelheim, AbbVie, Acerta Pharma, Aravive, ArQule, Arvinas, BerGenBio, 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, Orinove, Pfizer, Puma Biotechnology, Radius Health, Regeneron, Rgenix, Seattle Genetics, Sermonix Pharmaceuticals, Silverback, Stem CentRx, Syros Pharmaceuticals, Taiho Pharmaceutical, Takeda, Tapimmune Inc., Tesaro, Unum Therapeutics, Verastem, Zenith Epigenetics, and Zymeworks.

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