# Phase 1b/2 study of rebastinib (DCC-2036) in combination with paclitaxel: Preliminary safety, efficacy, pharmacokinetics, and pharmacodynamics in patients with advanced or metastatic solid tumors


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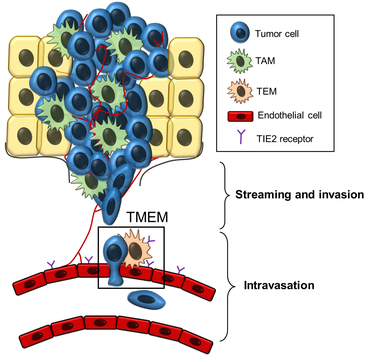
**Abstract: B055**


## INTRODUCTION

- Tunica interna endothelial cell kinase (TIE2) is a cell-surface receptor tyrosine kinase that is expressed in endothelial cells and a subset of macrophages, called TIE2-expressing tumor-associated macrophages (TEMs)[1,2]
- In endothelial cells, the angiopoietin (Ang)/TIE2 signaling axis is a key regulator of angiogenesis and vascular remodeling[1,3]
- TEMs are pro-angiogenic and immunosuppressive and are involved in tumor intravasation and metastasis (**Figure 1**)[2,4]
  - Intravasation occurs at microanatomical vascular sites called the tumor microenvironment of metastasis (TMEM), which are composed of a dedicated tumor cell, a TEM, and an endothelial cell (**Figure 1**)[2,4]
- Chemotherapy, despite decreasing tumor size, may increase the risk of metastasis through promoting TMEM assembly and increasing the dissemination of tumor cells[5]

### Figure 1. Metastasis-mediated tumor cell intravasation



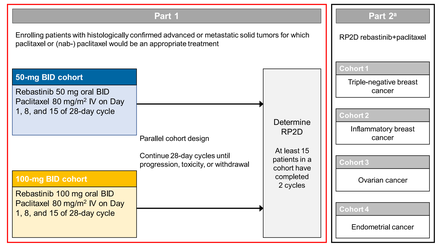

TAM, tumor-associated macrophage; TEM, TIE2-expressing tumor-associated macrophage; TIE2, tunica interna endothelial cell kinase; TMEM, tumor microenvironment of metastasis.

- Rebastinib (DCC-2036) is a novel tyrosine kinase switch control inhibitor that is a potent and selective picomolar inhibitor of TIE2 kinase activity
  - In preclinical studies, rebastinib blocked the recruitment and function of TEMs and reversed chemotherapy-induced TMEM activity[5,6]
- Rebastinib blocked primary tumor growth, inhibited metastatic growth, and extended survival in combination with paclitaxel or eribulin in a murine breast tumor model[5]
- An investigator-initiated phase 1 study (NCT02824575) of rebastinib in combination with paclitaxel or eribulin mesylate in metastatic breast cancer began in 2016 and is ongoing; rebastinib 100 mg twice daily (BID) was selected as the recommended phase 2 dose (RP2D)[7]
- Two Deciphera-sponsored phase 1b/2 studies are further assessing the safety, tolerability, antitumor activity, and pharmacokinetics of rebastinib in combination with paclitaxel (NCT03601897) or carboplatin (NCT03717415) in patients with advanced or metastatic solid tumors
  - Here, we present data from the dose-escalation phase (Part 1) of the study of rebastinib in combination with paclitaxel

## 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) using a parallel cohort design (**Figure 2; Table 1** and **2**)

### Figure 2. Overall study design




**ClinicalTrials.gov: NCT03601897**

[a]Part 2 uses a Simon 2-stage design. If >4 responses are seen in a cohort, additional patients will be enrolled for a total of up to 33 patients. If <4 responses are seen in a cohort, the cohort will be terminated.
BID, twice daily; IV, intravenous infusion; RP2D, recommended phase 2 dose.

### Table 1. Key inclusion and exclusion criteria for Part 1

**Inclusion criteria**

- ≥18 years old
- Histologically confirmed diagnosis of locally advanced or metastatic solid tumor for which paclitaxel is considered an 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 performed ≤14 days of first dose of study drug

**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

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricle ejection fraction; RECIST, response evaluation criteria in solid tumors.

### Table 2. Study objectives for Part 1

**Primary objectives**

- Safety and tolerability
- RP2D

**Secondary objectives**

- Antitumor activity
- Pharmacokinetics of rebastinib

**Relevant exploratory objectives**

- Biomarker changes in the tumor microenvironment, blood cells, and fluids such as plasma and ascites

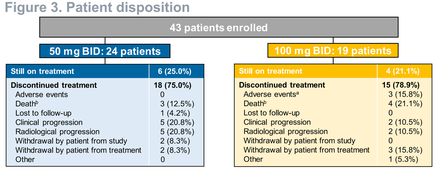
RP2D, recommended phase 2 dose.

## RESULTS

### Patient demographics and disposition

- As of August 9, 2019, 43 patients with advanced solid tumors were enrolled and treated with rebastinib 50 mg BID or 100 mg BID in combination with paclitaxel, of which 10 (23.3%) are still on treatment (**Figure 3**)

### Figure 3. Patient disposition




| Still on treatment | 6 (25.0%) |
|---|---|
| **Discontinued treatment** | **18 (75.0%)** |
| Adverse events | 0 |
| Death[b] | 3 (12.5%) |
| Lost to follow-up | 1 (4.2%) |
| Clinical progression | 5 (20.8%) |
| Radiological progression | 5 (20.8%) |
| Withdrawal by patient from study | 2 (8.3%) |
| Withdrawal by patient from treatment | 2 (8.3%) |
| Other | 0 |

| Still on treatment | 4 (21.1%) |
|---|---|
| **Discontinued treatment** | **15 (78.9%)** |
| Adverse events[a] | 3 (15.8%) |
| Death[b] | 4 (21.1%) |
| Lost to follow-up | 0 |
| Clinical progression | 2 (10.5%) |
| Radiological progression | 2 (10.5%) |
| Withdrawal by patient from study | 0 |
| Withdrawal by patient from treatment | 3 (15.8%) |
| Other | 1 (5.3%) |

[a]Adverse events leading to discontinuation of treatment: Grade 2 muscular weakness and dizziness (n = 1; possibly related to rebastinib), Grade 3 atrial fibrillation (n = 1; not related), and Grade 4 tubulointerstitial nephritis (n = 1; not related). [b]All death cases reported as not or unlikely related to study treatment.
BID, twice daily.

- The most frequent diagnoses were ovarian cancer, breast cancer, and endometrial adenocarcinomas (**Table 3**)

### Table 3. Patient demographics and clinical characteristics

| | 50 mg BID (n = 24) | 100 mg BID (n = 19) | Total (n = 43) |
|---|---|---|---|
| **Age**, years, median (min, max) | 61 (35, 78) | 61 (31, 74) | 61 (31, 78) |
| **Female**, n (%) | 19 (79.2) | 15 (78.9) | 34 (79.1) |
| **Cancer Type**, n (%) | | | |
| Ovarian cancer[a] | 5 (20.8) | 5 (26.3) | 10 (23.3) |
| Breast cancer | 5 (20.8) | 3 (15.8) | 8 (18.6) |
| Endometrial adenocarcinoma | 4 (16.7) | 3 (15.8) | 7 (16.3) |
| Melanoma | 1 (4.2) | 2 (10.5) | 3 (7.0) |
| Adenocarcinoma of the pancreas | 0 | 2 (10.5) | 2 (4.7) |
| Carcinosarcoma[b] | 2 (8.3) | 0 | 2 (4.7) |
| HNSCC | 2 (8.3) | 0 | 2 (4.7) |
| Cervical cancer | 1 (4.2) | 0 | 1 (2.3) |
| Thyroid cancer | 1 (4.2) | 0 | 1 (2.3) |
| Mesothelioma, malignant peritoneal | 1 (4.2) | 0 | 1 (2.3) |
| Urothelial tract/bladder cancer | 0 | 1 (5.3) | 1 (2.3) |
| Other[c] | 2 (8.3) | 3 (15.8) | 5 (11.6) |

[a]Epithelial, fallopian tube, or primary peritoneal; [b]Uterine and ovarian; [c]Other: rectal cancer, adrenocortical carcinoma, squamous cell carcinoma of esophageal, cholangiocarcinoma, and carcinoma of anus.
BID, twice daily; mAB, monoclonal antibody; HNSCC, head and neck squamous cell carcinoma.

- The majority of patients (55.8%) received >3 prior therapies; the median number of prior therapies was 4.5 (**Table 4**)

### Table 4. Prior therapy

| | 50 mg BID (n = 24) | 100 mg BID (n = 19) | Total (n = 43) |
|---|---|---|---|
| **Prior regimens**, median (min, max) | 4.0 (1, 13) | 5.0 (1, 10) | 4.5 (1, 13) |
| 1 prior regimen, n (%) | 2 (8.3) | 1 (5.3) | 3 (7.0) |
| 2–3 prior regimens, n (%) | 8 (33.3) | 5 (26.3) | 13 (30.2) |
| >3 prior regimens, n (%) | 12 (50.0) | 12 (63.2) | 24 (55.8) |
| **Prior treatment**, n (%) | | | |
| Chemotherapy | 21 (87.5) | 17 (89.5) | 38 (88.4) |
| Taxane | 17 (70.8) | 15 (78.9) | 32 (74.4) |
| Paclitaxel | 13 (54.2) | 13 (68.4) | 26 (60.5) |
| Immunotherapy | 11 (45.8) | 6 (31.6) | 17 (39.5) |
| mAB (excluding immunotherapy) | 9 (37.5) | 8 (42.1) | 17 (39.5) |
| Targeted therapy (TKIs) | 2 (8.3) | 4 (21.1) | 6 (14.0) |
| Targeted therapy (other) | 3 (12.5) | 3 (15.8) | 6 (14.0) |
| Antibody-drug conjugates | 3 (12.5) | 0 | 3 (7.0) |
| Other | 5 (20.8) | 5 (26.3) | 10 (23.3) |

BID, twice daily; mAB, monoclonal antibody; TKI, tyrosine kinase inhibitor.

### Safety

- Commonly reported treatment-emergent adverse events (TEAEs) (≥10% of total) regardless of relatedness are shown in **Table 5**
  - Frequencies of TEAEs were similar between 50 mg and 100 mg BID
- One patient experienced a rebastinib-related serious AE (SAE) (grade 2 muscular weakness), and 4 patients had an SAE related to paclitaxel and rebastinib (5 events: grade 3 pneumonia [n = 2], grade 3 nausea [n = 1], grade 3 vomiting [n = 1], and grade 2 myocardial ischemia [n = 1])
- Two patients in Part 1 experienced muscular weakness (one grade 1 at 50 mg BID and remains on treatment, and one grade 2 at 100 mg BID resulted in discontinuation of treatment), a lower frequency of muscular weakness compared with the first-in-human study of rebastinib alone (21/57 [36.8%] patients)[8]
- 100 mg BID dose was chosen as the initial RP2D. Based on a higher observed frequency of muscular weakness in preliminary data from the ongoing Part 2 portion of the study, the RP2D was changed to 50 mg BID

### Table 5. Common (≥10%) TEAEs regardless of relatedness

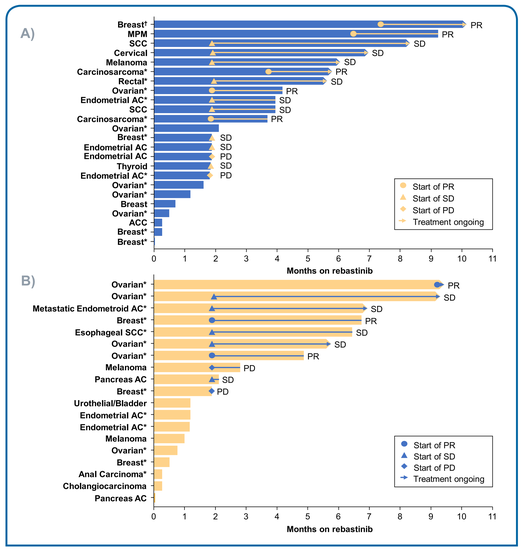
| | 50 mg BID (n = 24) | | 100 mg BID (n = 19) | | Total (n = 43) | |
|---|---|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Fatigue | 8 (33.3) | 1 (4.2) | 5 (26.3) | 0 | 13 (30.2) | 1 (2.3) |
| Constipation | 3 (12.5) | 0 | 6 (31.6) | 0 | 9 (20.9) | 0 |
| Diarrhea | 2 (8.3) | 0 | 7 (36.8) | 0 | 9 (20.9) | 0 |
| Dry mouth | 6 (25.0) | 0 | 3 (15.8) | 0 | 9 (20.9) | 0 |
| Alopecia | 4 (16.7) | 0 | 4 (21.1) | 0 | 8 (18.6) | 0 |
| Anemia | 4 (16.7) | 2 (8.3) | 4 (21.1) | 2 (10.5) | 8 (18.6) | 4 (9.3) |
| Dyspnea | 4 (16.7) | 0 | 4 (21.1) | 0 | 8 (18.6) | 0 |
| Nausea | 6 (25.0) | 1 (4.2) | 2 (10.5) | 0 | 8 (18.6) | 1 (2.3) |
| Peripheral sensory neuropathy | 2 (8.3) | 0 | 6 (31.6) | 0 | 8 (18.6) | 0 |
| Dizziness | 3 (12.5) | 0 | 4 (21.1) | 0 | 7 (16.3) | 0 |
| Hypokalemia | 4 (16.7) | 1 (4.2) | 3 (15.8) | 0 | 7 (16.3) | 1 (2.3) |
| Urinary tract infection | 3 (12.5) | 1 (4.2) | 4 (21.1) | 0 | 7 (16.3) | 1 (2.3) |
| Hypomagnesemia | 3 (12.5) | 0 | 3 (15.8) | 0 | 6 (14.0) | 0 |
| Onychomadesis | 3 (12.5) | 0 | 3 (15.8) | 0 | 6 (14.0) | 0 |
| Sepsis | 2 (8.3) | 2 (8.3) | 4 (21.1) | 4 (21.1) | 6 (14.0) | 6 (14.0) |
| ALT increased | 5 (20.8) | 0 | 0 | 0 | 5 (11.6) | 0 |
| Decreased appetite | 3 (12.5) | 0 | 2 (10.5) | 0 | 5 (11.6) | 0 |
| Dysgeusia | 3 (12.5) | 0 | 2 (10.5) | 0 | 5 (11.6) | 0 |
| Headache | 1 (4.2) | 1 (4.2) | 4 (21.1) | 0 | 5 (11.6) | 1 (2.3) |
| Rash | 3 (12.5) | 0 | 2 (10.5) | 0 | 5 (11.6) | 0 |
| Stomatitis | 4 (16.7) | 1 (4.2) | 1 (5.3) | 0 | 5 (11.6) | 1 (2.3) |
| Vomiting | 4 (16.7) | 1 (4.2) | 1 (5.3) | 0 | 5 (11.6) | 1 (2.3) |

ALT, alanine aminotransferase; BID, twice daily; TEAE, treatment-emergent adverse events.

### Antitumor activity

- The median duration of treatment was 56 (range 1–309) days
- A best response of partial response (PR) was observed in 5/24 patients in the 50-mg BID dose cohort and 3/19 in the 100-mg BID dose cohort (**Figure 4**)
  - 7/8 patients with a PR had prior therapy with paclitaxel or docetaxel

### Figure 4. Time on treatment and best response for the (A) 50-mg BID and (B) 100-mg BID dose cohorts

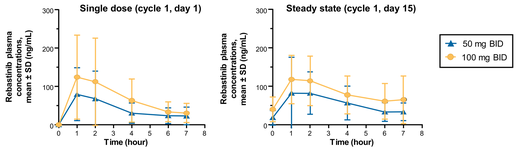



*Prior paclitaxel therapy; †Patient did not receive prior paclitaxel, but did receive prior docetaxel
Magnetic resonance imaging or computed tomography scans of the chest, abdomen, and pelvis were evaluated for tumor response by the investigator according to RECIST v1.1 criteria.
AC, adenocarcinoma; ACC, adrenocortical carcinoma; BID, twice daily; MPM, malignant peritoneal mesothelioma; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SCC, squamous cell carcinoma; SD, stable disease.

### Pharmacokinetics and pharmacodynamics

- Rebastinib exposure was dose proportional from 50 mg BID to 100 mg BID (**Figure 5**)

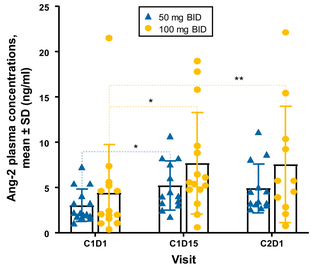
### Figure 5. Rebastinib concentration vs time profiles for the 50-mg BID and 100-mg BID dose cohorts




Pharmacokinetics of rebastinib were determined from blood samples drawn on cycle 1, day 1 and cycle 1, day 15 before paclitaxel infusion; and at approximately 1, 2, 4, and 6 hours post-rebastinib administration.
BID, twice daily; SD, standard deviation.

- Circulating Ang-2 significantly increased in both dose cohorts (50 and 100 mg BID) by treatment with rebastinib in combination with paclitaxel (**Figure 6**)

### Figure 6. Angiopoietin-2 induction during rebastinib treatment




*P<0.05; **P<0.001. P-values are based on Wilcoxon signed-rank test.
The Ang-2 level in rebastinib-treated patients was assessed by standard Luminex methods. Plasma samples were collected from patients on the first dose of rebastinib (cycle 1 day 1), cycle 1 day 15, and cycle 2 day 1.
The top of the column represents the mean, error bars indicate the standard deviation, and circles and triangles are individual measurements.
Ang-2, angiopoietin-2; BID, twice daily; C, cycle; D, day; SD, standard deviation.

## CONCLUSIONS

- Rebastinib in combination with paclitaxel was generally well tolerated
- There were no apparent initial differences in safety between the 50-mg BID and 100-mg BID dose cohorts in Part 1
- Preliminary antitumor activity is encouraging in both treatment arms; in a heavily pretreated heterogeneous patient population including prior therapy with paclitaxel, objective responses were seen in patients with ovarian cancer, breast cancer, carcinosarcoma, and peritoneal mesothelioma
- Exposure to rebastinib was dose proportional at the 50-mg BID and 100-mg BID doses when given in combination with paclitaxel
- Mean circulating Ang-2 levels increased with exposure to higher doses of rebastinib in combination with paclitaxel, indicating TIE2 inhibition[6]
- The RP2D for rebastinib is 50 mg BID in combination with paclitaxel
- The safety and tolerability of rebastinib+paclitaxel will continue to be evaluated in Part 2 in patients with triple-negative breast cancer, inflammatory breast cancer, ovarian cancer, and endometrial cancer (NCT03601897)
- A phase 1b/2 study evaluating rebastinib in combination with carboplatin in patients with advanced or metastatic solid tumors is also ongoing (NCT03717415)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