Debio 0123, an oral, brain-penetrant and highly selective inhibitor of the WEE1 kinase:

- WEE1, a DNA damage-activated kinase, governs the G2/M cell cycle checkpoint, arresting the cell cycle to allow for DNA repair (Fig. 1). Cells often rely on WEE1 to avoid excess DNA damage accumulation.
- WEE1 is an attractive therapeutic target, as its inhibition, combined with mounting DNA damage, can induce mitotic catastrophe and apoptosis.

Debio 0123 is a selective, potent, orally available ATP-competitive, brain-penetrant WEE1 inhibitor that has previously shown a proportional increase in target engagement in 150 mg in patient skin biopsies.

METHODS

Debio 0123 is a Phase 1 dose-escalation study of Debio 0123 in patients (pts) with advanced solid tumors that recurred or progressed after platinum-containing therapy, where no standard therapy of proven benefit is available.

- Approximately 60 pts were planned to be treated in this dose-escalation study.
- In Arm A, Debio 0123 monotherapy is given in Cycle (C) 1 (Day D-3 and D1 to D3), then in combination with carboplatin (CP) from C2 (D1 to D3) until end of treatment (EOT).
- In Arm B, Debio 0123 is given with CP (D1 to D3 and D8 to D10) from EOT.

RESULTS

- Patient demographics:
  - Arm A data with a cut-off date of April 30th 2023 is presented.
  - Overall, 38 pts were treated in Arm A. 2 pts continue treatment.
  - Most (78.9%) pts were female and the mean age was 59 years.
  - The most common primary solid tumor location was ovary (21%).

Debio 0123 combined with CP was well tolerated in Arm A:

- The worst grade of Debio 0123-related treatment-emergent adverse events (TEAEs) were grade 1/2 in most pts.
- Debio 0123-related TEAEs occurred in 68.4% of pts over all dose levels.
- The worst grade of Debio 0123-related treatment-emergent adverse events (TEAEs) in Arm A was grade 2/3.
- Serious Debio 0123-related TEAEs occurred in 10.5% of pts over all dose levels tested.

The maximum tolerated dose (MTD) of Debio 0123 was 520 mg:

- Debio 0123 doses tested (mg):
  - Debio 0123 doses levels: 100, 200, 300, 400, 500, 520 mg.
  - Debio 0123 doses tested in Arm A: 100, 200, 300, 400, 500 mg.
  - Debio 0123 doses tested in Arm B: 100, 200, 300, 400, 500 mg.

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Debio 0123 is administered on D1, D2 and D3 of each cycle in a fasted state

- Debio 0123 is administered on D1, D2 and D3 of each cycle in a fasted state.
- Debio 0123 + CP combination
  - Debio 0123 is given on D1, D2 and D3 of each cycle in a fasted state.
  - CP is given on D1 of each 21-day cycle in both arms.

- DLT period = C1 and C2
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The maximum tolerated dose (MTD) of Debio 0123 was 520 mg

Debio 0123 shows antitumor activity when combined with CP in pts with solid tumors who progressed with prior platinum-based chemotherapy:

- 4/12 pts with platinum-resistant ovarian cancer had a PR. 1 pt is ongoing.
- Median duration of response was 10.9 months.

Debio 0123 is in Phase I clinical investigation as a monotherapy (NCT05109975), in combination with CP (NCT03968653), and in combination with temozolomide + radiotherapy (NCT08356291).

CONCLUSIONS

- Debio 0123, in combination with CP, is well tolerated up to 520 mg and demonstrates a manageable safety profile like that for CP monotherapy.
- Debio 0123 shows dose-proportional increases in exposure and evident target engagement from 150 mg that became more pronounced with higher doses.
- The Debio 0123 CP combination led to antitumor activity in pts with cancers who had progressed with previous platinum-based chemotherapy, including confirmed responses in pts with platinum-resistant ovarian cancer.
- Further evaluation of therapeutic Debio 0123 is warranted and dose escalation with a more intense schedule (Arm B) is currently ongoing.

REFERENCE

1. Squire CJ, et al. DEBIO 0123-101, A PHASE 1 TRIAL OF DEBIO 0123 IN COMBINATION WITH CARBOPLATIN IN ADVANCED SOLID TUMORS: SAFETY, PHARMACOKINETIC, AND PRELIMINARY ANTITUMOR ACTIVITY DATA. ABSTRACT #3012