**Beamion LUNG-1, an ongoing Phase Ia/lb trial of the HER2 TKI, zongertinib (BI 1801631) in patients with advanced solid tumours with HER2 aberrations: latest data**

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**Introduction**

- Activating mutations in the HER2 gene drive many solid tumours, including NSCLC, where HER2 mutations are present in 2–4% of cases. Generally, 50% of NSCLC patients with HER2 mutations have TKD mutations.
- There is an unmet need for effective targeted therapy against HER2 mutated solid tumours. Historically, HER2 TKD mutations have responded poorly to TKIs. Moreover, TKIs that inhibit both EGFR and HER2 are typically limited by toxicities associated with inhibition of wild-type EGFR.
- Zongertinib (BI 1801631), a novel TKI that covalently and selectively binds to the TKD of HER2 while sparing wild-type EGFR, is under investigation as an oral treatment for NSCLC mutations harboring HER2 TKD TKO mutations, including ex vivo studies (Beamion LUNG-1: NCCTN88664).

**Methods**

- In Cohort 1 of Phase Ia, patients were being randomised to either 240 mg or 120 mg OD in 3-week cycles.
- In Phase Ib, patients with TKD mutations were enrolled in a 2:1 ratio (patients with TKD mutations: all comers).
- The planned futility analysis was passed, and the trial is continuing, with recruitment into all cohorts ongoing.
- Currently, patient numbers in Phase Ib are small and investigator-assessed tumour responses are reported without the requirement of confirmation by a second review.

**Key findings and conclusions**

- In Phase Ia, the MTD of zongertinib was not reached.
- Doses taken into optimisation are 240 mg and 120 mg QD.
- Zongertinib was well tolerated with low rates of EGFR-mediated adverse events and no discontinuations in Phase Ia.
- The planned futility analysis was passed, and the trial is continuing, with recruitment into all cohorts ongoing.
- Currently, patient numbers in Phase Ib are small and investigator-assessed tumour responses are reported without the requirement of confirmation by a second review.
- Nevertheless, initial efficacy results in patients with HER2 TKD mutation-positive NSCLC are encouraging.

**Phase Ia: dose escalation and safety**

- Dose levels taken into optimisation: 240 mg QD and 120 mg QD.
- 3 patients with DLTs during the on-treatment period:
  - 60 mg BID, grade 2 oedema
  - 120 mg BID, grade 2 diarrhoea
  - 240 mg QD, grade 3 elevated ALT, grade 2 blood dyscrasias
- TRAE led to discontinuation: Grade 3 ALT increased.

**Phase Ia: efficacy**

- Patients included in the efficacy analysis had completed 2–5 cycles of treatment at data cut-off.
- Median number of cycles (range): 7.5 (1–24)
- Median percentage change from baseline in target lesions: -41.2%

**Phase Ib: baseline characteristics**

- 42 patients entered Phase Ib.
- 26 patients (61.9%) had HER2 TKD mutations.
- Overall (N=42): ORR: 41.3%; DCR: 91.7%.
- Patients with noted treatments (with or without EGFR TKI) included investigational drug combinations (n=3), targeted combination chemotherapy (n=1), and ruxtecan with a hedgehog inhibitor (n=1).

**Phase Ib: TRAEs**

- Discontinuations due to adverse events:
  - 2 patients had DLTs in MTD evaluation period: 240 mg QD, grade 4 immune thrombocytopenia
  - 1 patient had DLTs during the on-treatment period: 240 mg QD, grade 3 ALT and AST increased, and grade 4 neutrophil count decreased
  - 1 patient with TRAEs that led to dose reduction: Grade 3 neutrophil and grade 3 neutrophil count decreased

**Phase Ib: access to SMART**

- The first pre-planned interim analysis in Cohort 1 was passed and the trial is ongoing.

**References**


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