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Phase 2 study of berzosertib (M6620) + topotecan in patients with relapsed platinum-resistant SCLC: DDRiver SCLC 250

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DDRiver™ SCLC 250

STUDY STATUS

- **This Phase 2 study is open and currently recruiting**
- **Sites open to enrollment in the USA, France, Spain, Italy, Belgium, and China for the primary cohort**
- **Sites in Japan open to enrollment in the safety run-in**

BACKGROUND

- Small-cell lung cancer (SCLC), characterized by high genomic instability and limited treatment options, comprises 14% of lung cancers worldwide.[1–4]
- Targeting key proteins of the cellular DNA damage response involved in maintaining genomic stability, such as ataxia telangiectasia and Rad3-related (ATR) protein kinase and topoisomerase I, may be a rational treatment strategy for SCLC.
- Berzosertib (M6620) is an intravenous (i.v.), highly potent, and selective first-in-class ATR inhibitor.[5]
- In a single-arm Phase 1/2 study, the combination of berzosertib + topotecan showed antitumor activity and was well tolerated in patients with advanced solid tumors, including platinum-resistant and platinum-sensitive SCLC.[6,7]
- The DDRiver SCLC 250 study (NCT04768296) aims to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of berzosertib + topotecan in patients with relapsed, platinum-resistant SCLC.
- Berzosertib + DNA damage-inducing chemotherapy is currently being investigated in numerous solid tumor types, including platinum-resistant high-grade serous ovarian cancer (NCT02595892) and small-cell carcinomas (NCT03896503).[8–10]

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TRIAL DESIGN

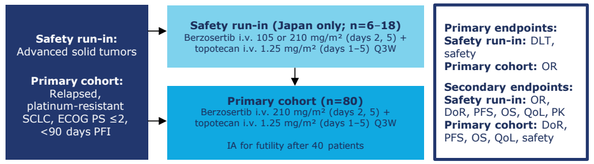
Primary cohort

- Patients with relapsed, platinum-resistant SCLC (n~80) will receive berzosertib 210 mg/m² (days 2, 5) + topotecan 1.25 mg/m² (days 1–5) i.v. in 21-day cycles until disease progression or unacceptable toxicity.
- Primary/secondary prophylactic granulocyte-colony stimulating factor is highly recommended and can be administered according to local practice.

Safety run-in (Japan only)

- Japanese patients (n=3–9) with advanced solid tumors will receive dose level (DL) 1: berzosertib 105 mg/m² (days 2, 5) + topotecan 1.25 mg/m² (days 1–5) (i.v.) in 21-day cycles until disease progression or unacceptable toxicity.
- If DL1 is tolerated, Japanese patients with relapsed, platinum-resistant SCLC (n=3–9) will be enrolled to the DL2 arm (same dose as primary cohort).
- If DL2 is tolerated, Japanese patients with relapsed, platinum-resistant SCLC will be enrolled to the primary cohort.

Figure 1. Trial design



DLT, dose-limiting toxicity; **DoR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **IA**, interim analysis; **i.v.**, intravenous; **OR**, overall response; **OS**, overall survival; **PFI**, platinum-free treatment interval; **PFS**, progression-free survival; **PK**, pharmacokinetics; **Q3W**, every 3 weeks; **QoL**, quality of life; **SCLC**, small-cell lung cancer.

ELIGIBILITY, OBJECTIVES, AND ENDPOINTS

Table 1. Key eligibility criteria

Key inclusion criteria

Primary cohort + safety run-in (DL2)

- Histologically confirmed SCLC, with disease progression on/after first-line platinum-based treatment or chemoradiation, with or without immunotherapy, with a PFI* <90 days
- Measurable disease per RECIST version 1.1
- ECOG PS ≤2 and Karnofsky Scale ≥60%

Safety run-in (DL1)

- Histologically confirmed advanced solid tumors for which no effective standard therapy exists, or standard therapy has failed or cannot be tolerated
- ECOG PS ≤1 and Karnofsky Scale ≥70%

Key exclusion criteria

Primary cohort + safety run-in

- Prior treatment with ATR inhibitor
- Prior treatment with TOP1 inhibitor
- Unstable brain metastases

*PFI is defined as the time from the last day of a platinum-based treatment regimen to documented disease progression.
ATR, ataxia telangiectasia and Rad3-related; **DL**, dose level; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **PFI**, platinum-free treatment interval; **RECIST**, Response Evaluation Criteria in Solid Tumors; **SCLC**, small-cell lung cancer; **TOP1**, topoisomerase I.

Table 2. Objectives and endpoints criteria

Objectives	Endpoints
Primary cohort	
To assess efficacy of berzosertib + topotecan in patients with relapsed, platinum-resistant SCLC (**primary objective**)	OR by RECIST version 1.1
Safety run-in	
To confirm whether the RP2D of berzosertib + topotecan applies to Japanese patients (**primary objective**)	Occurrence of DLTs, AEs, TEAEs, and changes in vital signs, clinical laboratory parameters, and ECGs
To characterize the PK profile of berzosertib in Japanese patients	PK parameters in plasma by NCA
Both parts	
To evaluate the efficacy of berzosertib + topotecan	OR, DoR, PFS, by RECIST version 1.1, OS, and QoL
To evaluate the safety and tolerability of berzosertib + topotecan	Occurrence of AEs, and changes in vital signs, clinical laboratory parameters, and ECGs

AE, adverse event; **DLT**, dose-limiting toxicity; **DoR**, duration of response; **ECG**, electrocardiogram; **NCA**, non-compartmental analysis; **OR**, overall response; **OS**, overall survival; **PFS**, progression-free survival; **PK**, pharmacokinetics; **QoL**, quality of life; **RECIST**, Response Evaluation Criteria in Solid Tumors; **RP2D**, recommended Phase 2 dose; **SCLC**, small-cell lung cancer; **TEAE**, treatment-emergent adverse event.

STATISTICAL ANALYSES

- An interim analysis for futility is planned after 40 patients.
- Objective response rate (ORR) will be calculated with a two-sided 95% confidence interval using the Clopper–Pearson method; the treatment effect assumption is an ORR of 30%.
- Adverse events will be classified according to the Medical Dictionary for Regulatory Activities and will be graded according to Common Terminology Criteria for Adverse Events version 5.0.
- The safety run-in will follow a Bayesian Optimal Interval Design.
- PK parameters will be calculated or estimated using non-compartmental or population PK analysis.

STUDY CONTACT

- The corresponding author of this presentation is Dr. Anish Thomas, MBBS, M.D (Anish.Thomas@nih.gov).
- For further information, please visit www.ClinicalTrials.gov (NCT04768296) or www.merckgroup.com.

AUTHOR DISCLOSURES

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