A phase 1/2a, open-label, dose-finding study of the safety, pharmacokinetics, and preliminary efficacy of iza-bren (BL-B01D1) combinations in patients with advanced solid tumors

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Background

- Lung cancer is the leading cause of cancer-related death worldwide, and ~90% of lung cancer cases are attributed to non-small cell lung cancer (NSCLC)[1,2]
- *EGFR* gene mutations leading to constitutive activation are known to drive tumor progression in many solid tumors, such as NSCLC[3,4]
- Iza-bren is a potential first-in-class antibody-drug conjugate consisting of an EGFR × HER3 bispecific antibody conjugated to a novel topoisomerase-I inhibitor (Ed-04) payload via a stable tetrapeptide-based cleavable linker
- Iza-bren has shown promising clinical activity and a manageable safety profile, both as monotherapy and in combination regimens, in studies of patients with locally advanced or metastatic solid tumors, including those with NSCLC[5,6]
  - Iza-bren monotherapy was recently granted breakthrough therapy designation by the US Food and Drug Administration for patients with previously treated *EGFR*-mutated advanced NSCLC[7]
- The current study (CA244-001; NCT06618287) is designed to assess iza-bren combinations in patients with advanced solid tumors, with initial enrollment of patients with either *EGFR*-mutated or *EGFR*-wild-type NSCLC

Study design

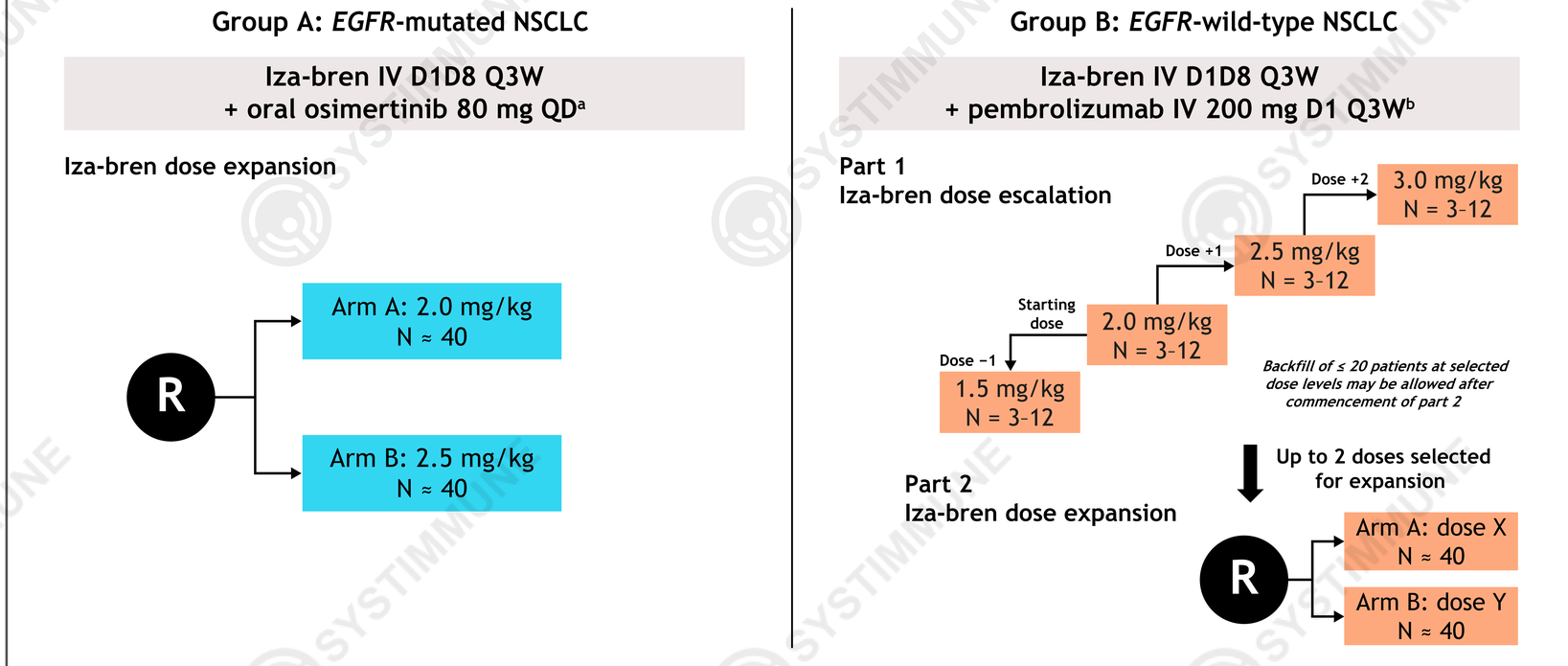
- This is a global phase 1/2a, open-label study enrolling patients with either *EGFR*-mutated NSCLC (group A; dose expansion phase only) or *EGFR*-wild-type NSCLC (group B; dose escalation and dose expansion phases) (**Figure 1**)
- Key inclusion criteria for all patients are age ≥ 18 years, pathologically confirmed locally advanced or metastatic NSCLC, measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and an Eastern Cooperative Oncology Group performance status of 0-1
- Key exclusion criteria for all patients are mixed NSCLC/small cell lung cancer histology; grade 3 lung disease or a history of interstitial lung disease or pneumonitis; a history of serious recurrent infections; and spinal cord compression, symptomatic central nervous system (CNS) metastases, or progression of existing CNS metastases (untreated CNS metastases may be eligible if they are asymptomatic, stable, and do not require immediate treatment in the opinion of the investigator)
  - **Table 1** shows eligibility criteria specific to groups A and B

Table 1. Specific eligibility criteria for groups A and B

Group A	Group B
A known *EGFR* mutation[a]	No *EGFR* or other select mutations[b,c]
Suitability for receipt of first-line osimertinib treatment	Documented radiographic progression on/after the most recent therapy (part 1)
No prior systemic therapy for locally advanced or metastatic NSCLC (including TKIs)	If received prior pembrolizumab, must have received ≥ 3 cycles, with no evidence of disease progression (part 1)
	No prior systemic therapy for locally advanced or metastatic NSCLC (part 2)
	Available tumor cell PD-L1 expression data prior to randomization (part 2)

[a]An *EGFR* exon 19 deletion or L858R mutation in exon 21, either alone or in combination with other *EGFR* mutations, which may include T790M in exon 20. Patients with other *EGFR* mutations (eg, exon 21 L861Q, exon 18 G719X, and exon 20 S768I mutations) are also allowed, although patients with a known *EGFR* exon 20 insertion will be excluded. [b]For part 1, patients with known actionable mutations and/or translocations in any of the following genes will be excluded unless they have received and progressed on or were intolerant to available approved SOC AGA targeted therapies: *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, *RET*, and *HER2*. [c]For part 2, patients with known actionable mutations and/or translocations in any of the following genes will be excluded as approved SOC AGA targeted therapies are available for such patients: *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, *RET*, and *HER2*. AGA, actionable genomic alteration; PD-L1, programmed death ligand 1; SOC, standard of care; TKI, tyrosine kinase inhibitor.

Figure 1. Study design



[a]For group A, the presence or absence of CNS metastases will be used as a stratification factor. [b]For group B part 2, PD-L1 expression will be used as a stratification factor.
D1 Q3W, day 1 every 3 weeks dosing; D1D8 Q3W, day 1 and day 8 every 3 weeks dosing; IV, intravenous; QD, once daily; R, randomization.

- **Table 2** shows key study endpoints

Table 2. Key study endpoints

Primary endpoints
• Incidence of AEs, SAEs, AEs meeting protocol-defined DLT criteria, AEs leading to discontinuation, and death (groups A and B)
• Incidence of DLTs during the DLT evaluation period (group B, part 1)
Secondary endpoints
• PK profile of iza-bren (and constituent parts) including concentrations and parameters such as C_{max}, T_{max}, $AUC_{(0-T)}$, and $AUC_{(TAU)}$ (groups A and B)
• ORR and BOR assessed by investigator per RECIST v1.1 (groups A and B)

AE, adverse event; AUC, area under the concentration-time curve; BOR, best overall response; C_{max}, maximum observed concentration; DLT, dose-limiting toxicity; ORR, objective response rate; PK, pharmacokinetic; SAE, serious adverse event; T_{max}, time of maximum observed concentration.

Recruitment

- Enrollment is ongoing with actively recruiting sites in the following countries:
  - Australia
  - Canada
  - The Netherlands
  - Spain
  - United Kingdom
  - United States of America

References

1. Bray F, et al. *CA Cancer J Clin* 2024;74:229-263.
2. Zhang Y, et al. *Lancet Oncol* 2023;24:1206-1218.
3. Wieduwilt MJ, Moasser MM. *Cell Mol Life Sci* 2008;65:1566-1584.
4. Arteaga CL, Engelman JA. *Cancer Cell* 2014;25:282-303.
5. Ma Y, et al. *Lancet Oncol* 2024;25:901-911.
6. Zhou F, et al. Oral presentation at IASLC 2025 World Conference on Lung Cancer; September 6-9; Barcelona, Spain. Abstract 2114.
7. Bristol Myers Squibb press release. Izalontamab brengitecan (EGFRxHER3 ADC) granted breakthrough therapy designation by U.S. FDA for patients with previously treated advanced EGFR-mutated non-small cell lung cancer. August 18, 2025.

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Declaration of interests

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