

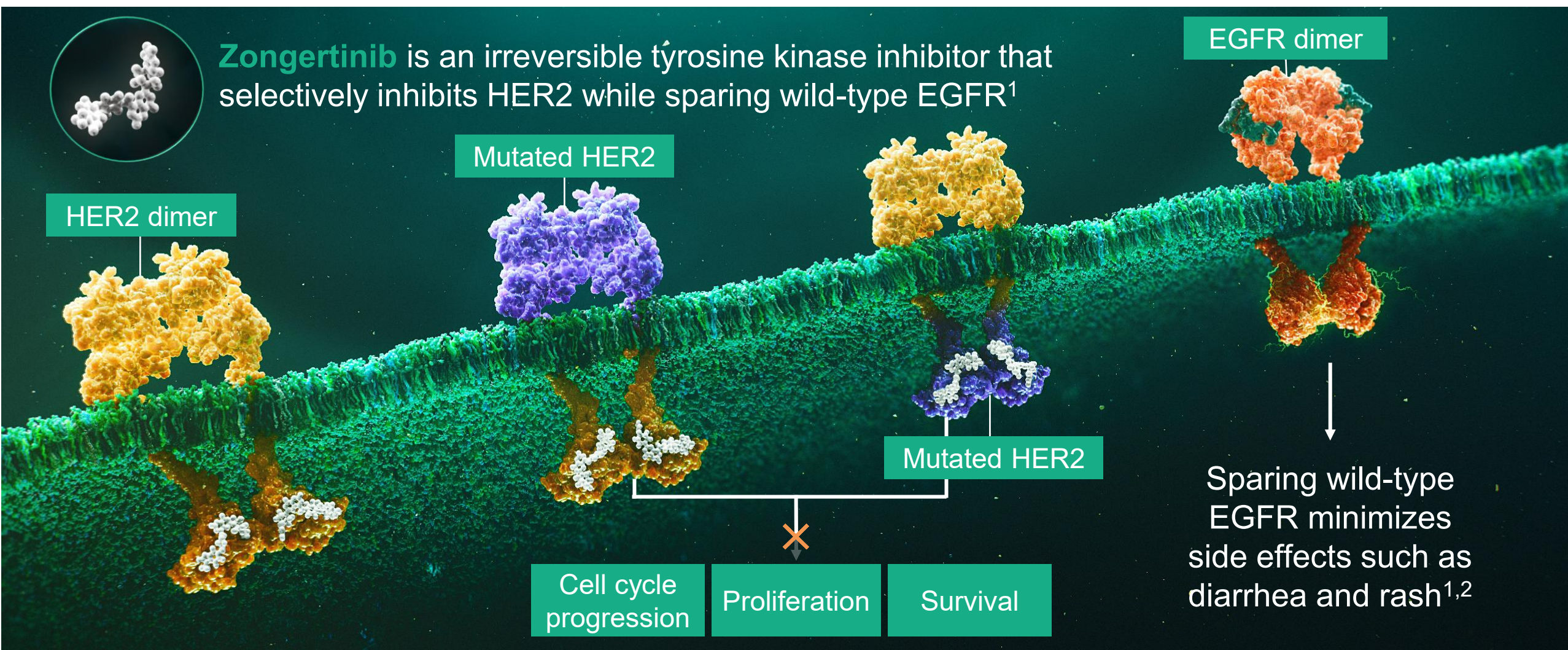
Zongertinib Plus Platinum-Pemetrexed Chemotherapy ± Pembrolizumab in Treatment-Naïve *HER2*-Mutant NSCLC: Phase IIa Platform Study

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Introduction

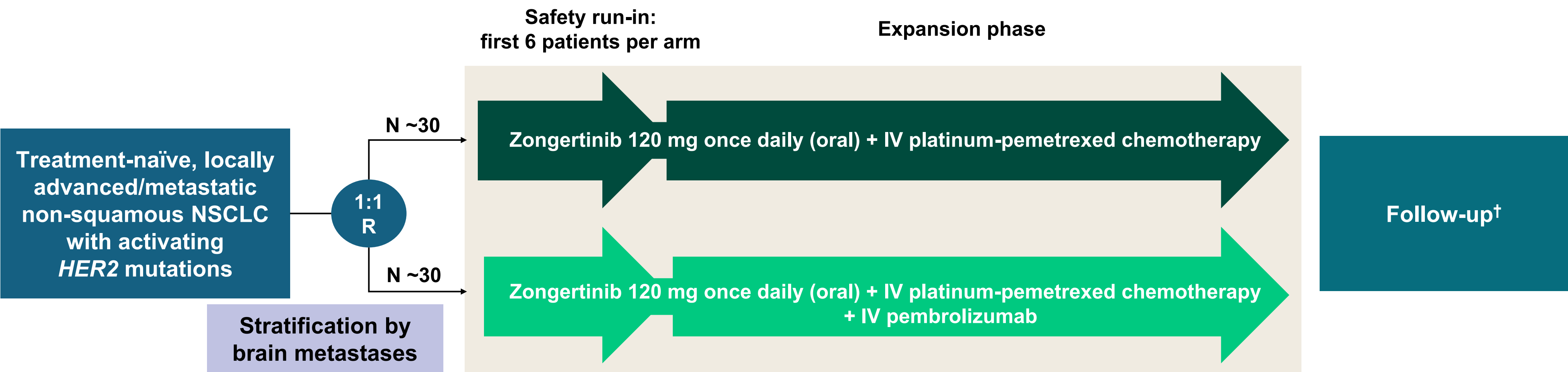
- Zongertinib is an irreversible TKI that selectively inhibits *HER2* while sparing wild-type *EGFR*, thereby minimizing associated toxicities^{1,2}
- Prior to the availability of zongertinib, first-line standard of care in advanced/metastatic *HER2*-mutant NSCLC typically consisted of platinum-based chemotherapy with or without immunotherapy³
- Combining zongertinib with platinum-pemetrexed chemotherapy ± immunotherapy may further enhance first-line outcomes in patients with *HER2*-mutant NSCLC



EGFR, epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

Trial Design

- Beamion 44 (NCT07486817) is a randomized, open-label, multicenter, Phase IIa platform trial that is evaluating the safety, tolerability, and early efficacy signals of zongertinib plus platinum-pemetrexed chemotherapy ± pembrolizumab, in treatment-naïve patients with locally advanced/metastatic non-squamous NSCLC with activating *HER2* mutations
- HER2* mutation status will be determined locally, preferably by tissue next-generation sequencing or PCR (circulating tumor DNA analysis is also acceptable); archival tumor tissue will be submitted after randomization for retrospective central confirmation of *HER2* mutation status
- Patients will receive oral zongertinib 120 mg once daily plus intravenous carboplatin AUC 5 or cisplatin 75 mg/m² and pemetrexed 500 mg/m² ± intravenous pembrolizumab 200 mg, in 3-week cycles



- The first six patients in each arm will be monitored closely during a safety run-in phase, during which early tolerability will be evaluated. Enrollment will continue seamlessly into the expansion phase unless prespecified stopping rules are met
- Zongertinib will be continued until documented disease progression (by RECIST v1.1), unacceptable toxicity, or other protocol-defined discontinuation criteria are met. After up to four cycles of platinum-pemetrexed (± pembrolizumab) chemotherapy, pemetrexed (± pembrolizumab) may continue for a maximum of 35 cycles in total from the start of the trial, or until stopping criteria are met
- Primary endpoint analysis will be conducted after all patients have completed two cycles. No statistical comparisons will be made between treatment arms, and all endpoints will be summarized descriptively

†Visits will continue until disease progression, introduction of a new anti-cancer therapy, death, loss to follow up, withdrawal of consent, or the end of the trial. AUC, area under the curve; IV, intravenous; PCR, polymerase chain reaction; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1

Plain Language Summary

- Until recently, most patients with *HER2*-mutant NSCLC were initially treated with chemotherapy, with or without immunotherapy
- Zongertinib is a medicine designed to target *HER2* that is taken once daily. It has shown good antitumor activity and is generally well tolerated, with manageable and predictable side effects. It is possible that combining zongertinib with chemotherapy and immunotherapy might further improve treatment outcomes in patients with advanced *HER2*-mutant NSCLC
- The Beamion 44 clinical trial is investigating zongertinib in combination with standard treatments in patients with advanced *HER2*-mutant NSCLC. The trial will primarily assess the safety and tolerability of these treatment combinations

Key Points

- Beamion 44 is the first trial to evaluate the safety and tolerability of zongertinib in combination with platinum-pemetrexed chemotherapy, with or without immunotherapy (pembrolizumab)
- Results will inform the further development of zongertinib-based combination regimens in patients with treatment-naïve advanced NSCLC with activating *HER2* mutations

Key Inclusion and Exclusion Criteria

Key inclusion criteria	Key exclusion criteria
Aged ≥18 years	Prior <i>HER2</i> -directed therapy
Histologically/cytologically confirmed, locally advanced/metastatic non-squamous NSCLC with a documented activating <i>HER2</i> mutation, within or outside the tyrosine kinase domain	Tumors with targetable alterations with approved available therapy
Treatment-naïve for unresectable locally advanced/metastatic disease, and not eligible for curative therapy	Radiotherapy within 4 weeks prior to treatment start, [‡] or major surgery within 4 weeks of randomization or planned within 6 months after screening
At least one measurable non-CNS lesion (by RECIST v1.1); asymptomatic brain metastases allowed if neurologically stable for ≥14 days	Ongoing treatment for brain metastases which may interfere with safety and/or endpoint assessment
Eligible for platinum-pemetrexed and pembrolizumab	Presence or history of leptomeningeal disease
Adequate organ function	Active or history of non-infectious ILD/pneumonitis or a history of grade ≥2 immune-related hepatitis, or other unresolved immune-related AEs requiring systemic immunosuppression
Eastern Cooperative Oncology Group performance status of 0 or 1	Uncontrolled gastrointestinal disorders, significant cardiovascular disease, or other conditions that could compromise protocol compliance or trial participation

[‡]With the exception of palliative radiotherapy under certain conditions. AE, adverse event; CNS, central nervous system; ILD, interstitial lung disease

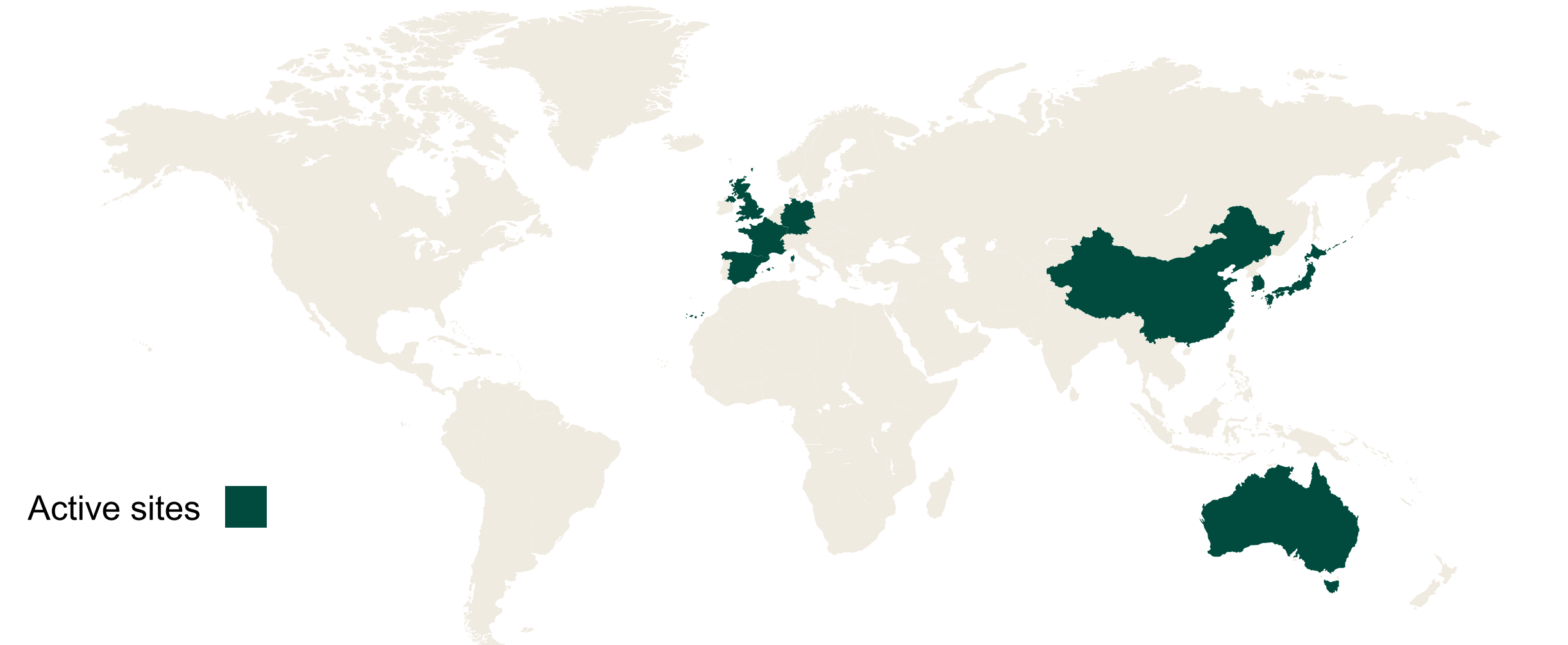
Endpoints

Primary endpoint	
Occurrence of discontinuation and/or prolonged interruption (>7 days) of zongertinib due to treatment-related AEs during the first 2 treatment cycles	
Secondary endpoints [§]	
Discontinuation and/or prolonged interruption (>7 days) of zongertinib due to treatment-related AEs during the on-treatment period	CLTs during the on-treatment period
SAEs during the on-treatment period	OR (investigator-assessed, RECIST v1.1), time to OR, and duration of OR
Dose reductions of zongertinib	PFS (investigator-assessed, RECIST v1.1)
Grade ≥3 non-hematologic AEs during the on-treatment period	Time on treatment (from first dose until zongertinib discontinuation or death)

[§]All safety-related secondary endpoints will be assessed during the on-treatment period and through the safety follow-up, defined as at least 30 days after end of treatment; unresolved AEs are followed until resolution or stabilization. CLT, combination-limiting toxicity; OR, objective response; PFS, progression-free survival; SAE, serious adverse event

Current Status

- The trial is being conducted at approximately 20 sites in 8 countries: Australia, China, France, Germany, Japan, South Korea, Spain, and the UK
- Approximately 60 patients will be enrolled
- Recruitment started in June 2026



References

- Wilding B, et al. Cancer Discov 2025;15:119–38; 2. Heymach JV, et al. N Engl J Med 2025;392:2321–33; 3. Muscolino P, et al. Int J Mol Sci 2026;27:2334



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