

IFCT-2404 COMET: a phase III trial of tepotinib versus investigator's choice treatment in patients with pre-treated *MET* exon 14 skipping NSCLC



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Background

- MET* exon 14 (*METex14*) skipping mutations occur in 2–3% of NSCLC and mainly affect elderly, frail patients with poor outcomes (median age ~73 yrs; 33% with PS≥2; 32% with brain metastases).
- Tepotinib, a selective MET-TKI, demonstrated meaningful activity in the single-arm phase II VISION trial (ORR 44–50%, median PFS 8.5-11 mo), after platinum-based chemotherapy (CT) and/or anti-PD-(L)1 therapy.
- However randomized data to confirm the superiority of MET-TKIs over standard of care are lacking. The only prior phase III attempt (GeoMETry-III; capmatinib vs docetaxel) closed early after due to slow enrollment. Reimbursement is therefore unavailable in some countries.

Endpoints

Primary Endpoint

- Progression-free survival (PFS) assessed by independent review committee according to RECIST 1.1.

Main secondary endpoints

- Hierarchical analysis #1: Quality of life: change from baseline to week 6 in QLQ-C30 global health status/Quality of life (GHS/QOL) score, using the EORTC QLQ-C30 questionnaire with lung cancer module (QLQ-LC29), tested if the primary endpoint (PFS) shows statistical significance.
- Hierarchical analysis #2: Overall survival, tested if the primary endpoint (PFS) and the first secondary endpoint (QoL) both show statistical significance.

Key points

- IFCT-2404 COMET is a multicenter, open-label, randomized, controlled, phase III study.
- The main objective is to compare the efficacy of tepotinib versus investigator's choice in patients with *METex14* NSCLC following prior treatment with immunotherapy and/or platinum-based chemotherapy.
- Broad inclusion criteria to ensure planned enrollment as well as warrant external validity
- Cross-over allowed in the control arm so PFS is used as the primary endpoint.
- Low intervention trial

Trial design

Randomized, phase 3 trial

- Advanced Non-Small Cell Lung Cancer
- METex14* mutation (local testing)
- No EGFR or ALK/ROS mutation
- Prior progression on platinum-based chemotherapy or anti-PD(L)1 agent
- ≤ 2 prior lines of therapy
- No prior treatment with a MET inhibitor
- PS 0-3
- Brain metastasis allowed

Stratification factors :

- Investigator's choice of control treatment: best supportive care vs other treatment (completed before randomization)
- Presence/absence of brain metastases.

Endpoint: PFS (BICR)

Main eligibility criteria

- Advanced *METex14* NSCLC progressing after ≤2 prior lines
- Patients with ECOG PS ≤ 3
- Active brain metastases allowed

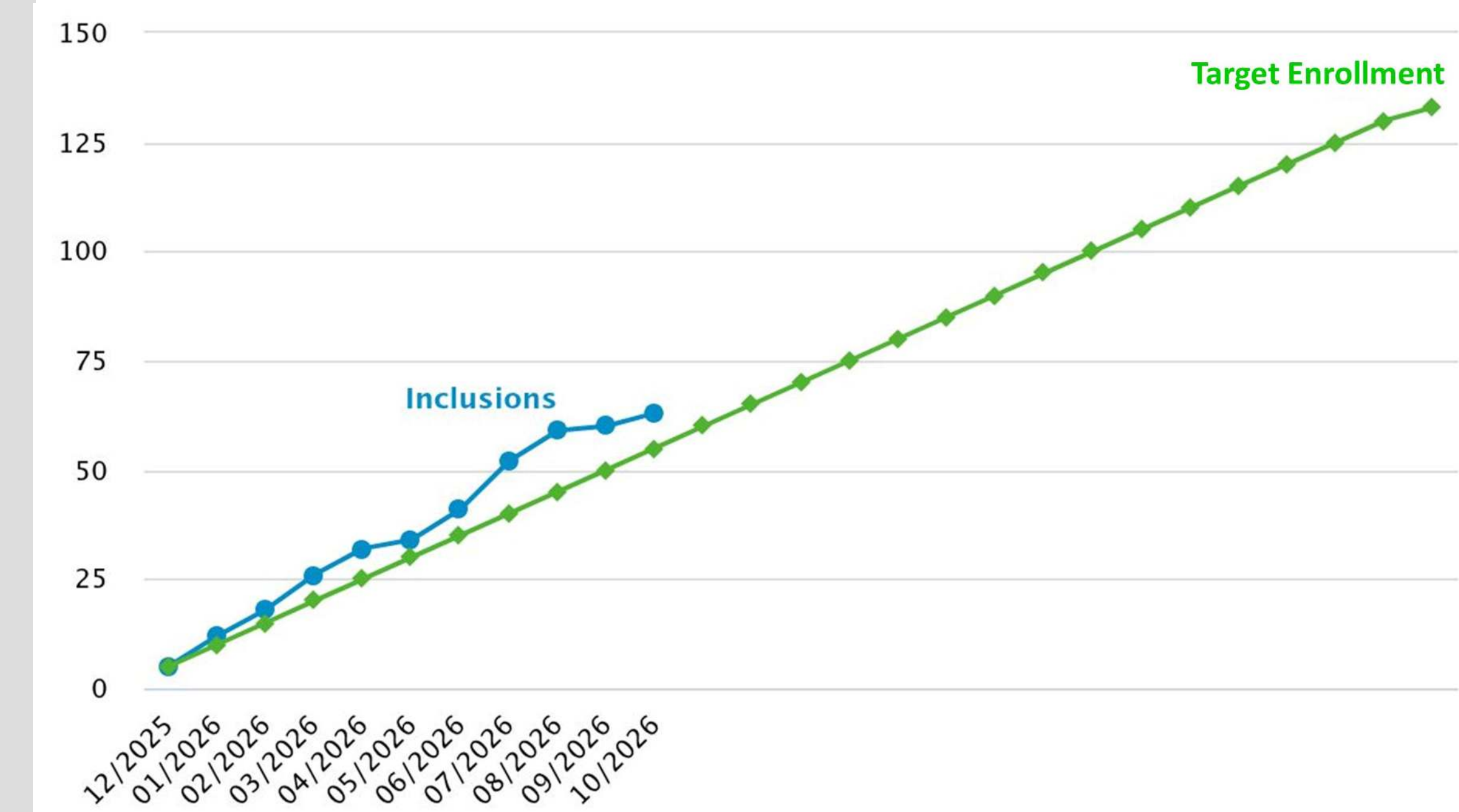
Sample size estimation

- On the basis of a 5 months median PFS in the tepotinib group (based on real-world data), and 2.5 months in control group (based on data from clinical trials with either monotherapy or anti-PD1 agents).
- 104 patients (35 in control arm and 69 in experimental arm) are needed to observe 100 events (34 in control arm and 66 in experimental arm)
- With 90% power to a 5% alpha level (2-sided)
- A total of 133 patients (44 in control arm and 89 in experimental arm) will be included (accounting for patients who failed to start treatment and event-free patients).

Trial progress

As of October 08, 2026: 63 patients randomized in 23 centers.

Inclusion per months



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