Poster 74TiP

Dr Yi-Long Wu | syylwu@live.cn

Capmatinib plus Osimertinib versus Platinum-pemetrexed Doublet Chemotherapy as Second-line Therapy in Patients with Stage IIIB/IIIC/IV *EGFR*-mutant, T790M-negative, *MET*-amplified NSCLC

Yi-Long Wu[1], Ji-Youn Han[2], Terufumi Kato[3], Fabrice Barlesi[4], Edward B. Garon[5], Federico Cappuzzo[6], Yuji Shibata[7], Nathalie Smith[8], Sadhvi Khanna[8], Riccardo Belli[8], Alejandro Yovine[8], Daniel Tan[10]

[1]Guangdong Provincial People's Hospital, Guangdong, China; [2]National Cancer Center, Goyang-si Gyeonggi-do, Republic of Korea; [3]Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan; [4]Institut Gustave Roussy, Villejuif, France; [5]David Geffen School of Medicine at UCLA, US; [6]UOC Oncologia Medica 2 Istituto Nazionale Tumori "Regina Elena", Roma, Italy; [7]National Cancer Center Hospital East, Japan; [8]Oncology DU Global Drug Development, Novartis Pharma AG, Basel, Switzerland; [9]Novartis Pharma S.A.S., Paris, France; [10]National Cancer Center Singapore, Singapore.

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SUMMARY

- *MET* amplification is one of the leading mechanism of resistance to EGFR TKIs and occurs in ~5-22% of EGFR TKI resistant *EGFR*-mutant NSCLC
- Preliminary data have demonstrated antitumor activity of capmatinib (METi) in combination with EGFR TKIs in patients with EGFR TKI resistant *EGFR*-mutated, *MET*-amplified NSCLC
- GEOMETRY-E (NCT04816214) evaluates the efficacy and safety of capmatinib + osimertinib versus platinum-pemetrexed doublet chemotherapy as second line therapy in patients with locally advanced/metastatic *EGFR*-mutant, T790M negative, *MET*-amplified NSCLC
- This study is currently recruiting
- This is a 2-part study where part 1 (initial run-in) will confirm the recommended dose for the randomized part 2 and evaluate the safety and tolerability of capmatinib + osimertinib; Part 2 will evaluate the efficacy and safety of the combination vs platinum-pemetrexed
- The primary endpoint for part 1 is the incidence of DLTs during the first 21 days of treatment and part 2 is PFS based on BIRC assessment per RECIST v1.1

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BACKGROUND AND RATIONALE

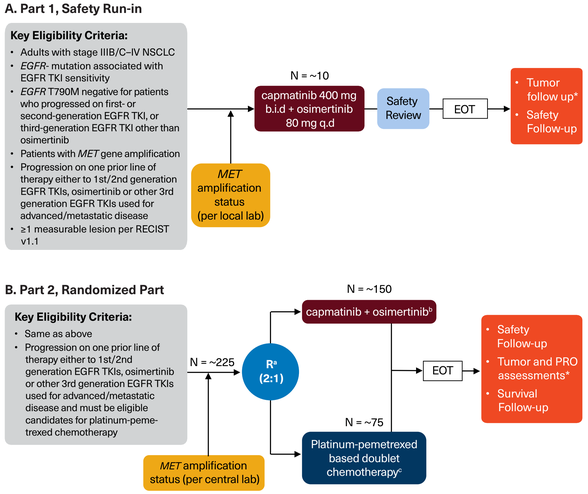
- A majority of patients with epidermal growth factor receptor (*EGFR*)-mutant non-small cell lung cancer (NSCLC) invariably develop resistance to EGFR tyrosine kinase inhibitors (TKIs) within 10–12 months, through the acquisition of *EGFR*-dependent and/or *EGFR*-independent mechanisms[1-3]
- *MET* amplification can arise as a bypass mechanism of resistance to EGFR TKIs occurring in ~5–22% of patients with EGFR TKI resistant *EGFR*-mutant NSCLC[1-8]
- Few treatment options exist for these patients, particularly in the *EGFR* T790M negative setting, representing an unmet medical need
- Capmatinib, a MET inhibitor, is approved in more than 10 countries for the treatment of adult patients with metastatic *MET* exon 14 skipping NSCLC, based on the results from the phase 2, multicohort GEOMETRY mono-1 study[9,10]
- Preliminary clinical data have shown that capmatinib in combination with EGFR TKIs has antitumor activity in patients with EGFR TKI resistant *EGFR*-mutated, *MET*-amplified NSCLC[11,12]
- The GEOMETRY-E trial was designed to evaluate the efficacy and safety of capmatinib + osimertinib vs platinum-pemetrexed doublet chemotherapy as second line treatment in patients with locally advanced/metastatic *EGFR*-mutant, T790M negative, *MET*-amplified NSCLC[13]

METHODS

Study Design[13]

- GEOMETRY-E is a multicenter, open-label, randomized, controlled, global phase III study (NCT04816214)
- This ongoing study is currently recruiting adult patients with *EGFR*-mutant, T790M negative, *MET*-amplified stage IIIB/IIIC/IV NSCLC who have progressed on either first- or second-generation EGFR TKIs, osimertinib or other third-generation EGFR TKIs (**Figure 1**)
- The study consists of an initial run-in part 1 to confirm the recommended dose for the randomized part 2 and to evaluate the safety and tolerability of capmatinib + osimertinib
  - In part 1, ~10 patients will receive dose level 1 (DL1) oral capmatinib 400 mg twice daily + osimertinib 80 mg once daily in 21-day cycles
  - A dose limiting toxicity (DLT) review will be performed to assess if DL1 is tolerated:
    - If yes – DL1 is recommended for part 2
    - If no – a second cohort will be treated with lower dose level (DL-1) (capmatinib 400 mg twice daily + osimertinib 40 mg once daily)
- Patients in part 1 are not eligible to participate in part 2
- The randomized part 2 (~225 patients, randomized 2:1) will evaluate the efficacy and safety of capmatinib + osimertinib vs platinum (cisplatin/carboplatin)-pemetrexed (**Figure 1B**)

Figure 1. Study Design



*Assessments/follow up were performed if EOT is not due to disease progression. [a]Randomization is stratified by presence of brain metastasis (yes/no) and prior treatment with 3rd generation EGFR TKIs (yes/no). [b]Dose will be selected based on the recommendation from run-in part 1. [c]Cisplatin 75 mg/m^2 or carboplatin AUC5 –AUC6; Pemetrexed 500 mg/m^2. B.i.d, twice daily; *EGFR*, epidermal growth factor receptor; EOT, end of treatment; *MET*, mesenchymal–epithelial transition factor; NSCLC, non–small cell lung cancer; PRO, patient-reported outcomes; q.d, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

Patient Eligibility[13]

Key Inclusion Criteria

- Age ≥ 18 years (≥ 20 years in Japan)
- Histologically/cytologically confirmed stage IIIB/IIIC (not amenable to curative surgery, chemoradiation, or radiation) or IV NSCLC at the time of study entry per AJCC 8th edition
- Histologically or cytologically confirmed diagnosis of NSCLC:
  - Patients with *EGFR*-activating mutations (Exon19 del, L858R, either alone or in combination with other *EGFR* mutations) are known to be associated with EGFR TKI sensitivity
  - *EGFR* T790M negative status for patients who have progressed on first- or second-generation EGFR TKIs, or third-generation other than osimertinib[a], as per tissue-based result
- *MET* amplification defined as:
  - Run-in part: IHC 3+* and/or *MET* GCN ≥ 5 per local test in tissue or blood
  - Randomization part: GCN ≥ 5 per central laboratory result from tissue sample test
- Mandatory provision of either a newly obtained tumor tissue sample or archival samples taken after progression on prior line of EGFR TKI
- [#]Progression on one prior line of therapy either to first- or second-generation EGFR TKIs, osimertinib or other third-generation EGFR TKIs used for advanced/metastatic disease and candidates for platinum (cisplatin or carboplatin) - pemetrexed doublet chemotherapy
- Patients with ≥1 measurable lesion per RECIST v1.1
- ECOG PS of 0 or 1

Key Exclusion Criteria

- Prior treatment with any MET inhibitor or HGF-targeting therapy
- Patients with neurologically unstable, symptomatic CNS metastases or those requiring increasing doses of steroids ≤2 weeks prior to study entry to manage CNS symptoms
- Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention)
- Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
- Clinically significant, uncontrolled heart diseases, including history of documented congestive heart failure, Fridericia QT correction formula (QTcF) >470 ms on the screening ECG etc.
- Treatment with a prior first- or second-generation EGFR TKIs, osimertinib or another third-generation EGFR TKIs within 14 days or approximately 5x half-life, whichever is shorter, of the first dose of study treatment
- Patients with known druggable molecular alterations (such as *ROS1* translocation or *BRAF* mutation, *KRAS* mutation) who might be candidates for alternative targeted therapies
- Patients receiving treatment with strong inducers of CYP3A who could not be discontinued >1 week prior to the start of treatment

[a]Patients who received Osimertinib do not require mandatory confirmation of T790M negative status however, patients with a known positive T790M status are excluded from the study. *IHC 3+ is defined as ≥ 50% of cells staining with high intensity.
[#]Acquired resistance to EGFR TKI treatment is defined as documented clinical benefit complete response [any duration], partial response [any duration], or stable disease for at least 6 months) on prior first- or second-generation EGFR TKIs, osimertinib or other third-generation EGFR TKIs and subsequently demonstrated radiological disease progression. Adjuvant osimertinib therapy will count as prior line of EGFR TKI treatment if relapse occurs during this therapy.
AJCC, American Joint Committee on Cancer; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; CNS, central nervous system; CYP3A, cytochrome P4503A; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; GCN, gene copy number; HGF, hepatocyte growth factor; IHC, immunohistochemistry; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *MET*, mesenchymal–epithelial transition factor; NSCLC, non–small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors; *ROS1*, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.

Study Endpoints[13]

Part 1: Run-in Part

Primary

Incidence of DLTs during the first treatment cycle of 21 days

Secondary

- Safety: Incidence, type, and severity of AEs per CTCAE v5 including changes in lab values, vital signs, cardiac and liver assessments
- Tolerability: dose interruptions, reductions, dose intensity, and duration of exposure for all drug components
- PK
- Investigator-assessed ORR, DOR, TTR, DCR, and PFS per RECIST v1.1

Part 2: Randomized Part

Primary

PFS based on BIRC assessment per RECIST v1.1

Key Secondary

- BIRC-assessed ORR per RECIST v1.1
- OIRR by BIRC per RANO-BM

Secondary

- BIRC-assessed DOR, TTR, and DCR per RECIST v1.1
- PFS2 (PFS after next line of treatment) based on local investigator assessment
- OS
- Incidence of AEs and SAEs, change in vital signs, laboratory results, and ECG
- PK
- Change from baseline and time to symptom deterioration in EORTC QLQ-LC13, QLQ-C30, EQ-5D-5L (calculated only for change in baseline), and NCCN Fact Brain symptom index questionnaires
- BIRC-assessed DOIR, TTIR, IDCR per the RANO-BM criteria

AE, adverse event; BIRC, blinded independent review committee; CTCAE, Common Terminology Criteria for Adverse Events; CNS, central nervous system; DCR, disease control rate; DOIR, duration of intracranial response; DOR, duration of response; DLT, dose limiting toxicity; ECG, electrocardiogram; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQOL 5 dimension, 5 level; HRQOL, health-related quality of life; IDCR, intracranial disease control rate; NCCN, national comprehensive cancer network; OIRR, overall intracranial response rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic(s); QLQ-C30, core quality of life questionnaire; QLQ-LC13, quality of life questionnaire lung cancer module; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TTIR, time to intracranial response; TTR, time to response.

Current Study Locations[13]

Enrollment began in September 2021. This trial is currently recruiting in the run-in part.

*The list of countries participating in the 'Randomized part' of the study is currently evolving hence, it is not to be considered as final.

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Presenting Author Disclosures

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