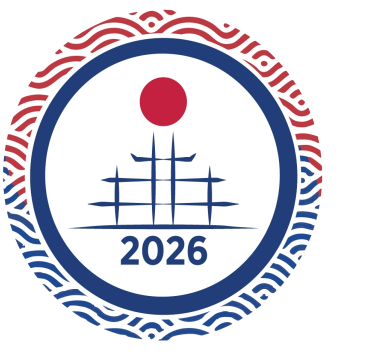




P2.304-390 : MRD-Guided De-escalation of Aumolertinib Maintenance after Induction and MDT-Directed Surgery or Radiotherapy in Unresectable Stage III EGFR-Mutant NSCLC (APPROACH)

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INTRODUCTION

- The current standard therapy for patients with unresectable stage III EGFR-mutated (EGFRm+) non-small cell lung cancer (NSCLC) is definitive chemoradiotherapy followed by epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) therapy (LAURA and POLESTAR)^{1,2}.
- The LungMate007 trial demonstrated the surgical conversion potential of neoadjuvant aumolertinib in this population, with a surgical conversion rate of 45% and a pathological complete response (pCR) rate of 13%³.
- Growing evidence indicates that molecular residual disease (MRD) status can signal disease recurrence or progression earlier than imaging, positioning MRD as a promising biomarker to guide treatment escalation or de-escalation⁴⁻⁸.
- Our study aims to firstly evaluate the efficacy and safety of aumolertinib induction therapy in EGFRm+ patients with unresectable stage III NSCLC and dynamic MRD-guided maintenance therapy with aumolertinib after radical therapy (surgery or chemoradiotherapy) evaluated by multidisciplinary team (MDT) (NCT04841811/CTONG2101).

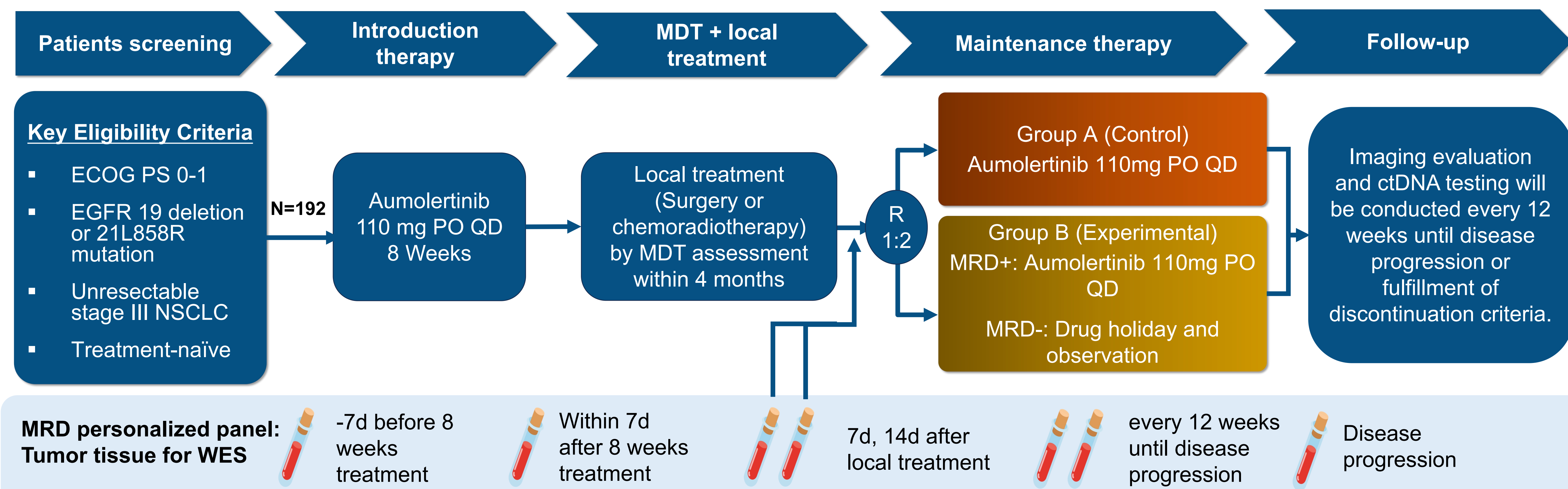
METHODS

- This is an open-label, multi-center, randomized, phase III study. Eligible patients receive aumolertinib 110 mg QD for 8 weeks (2 cycles), followed by local treatment (surgical or chemoradiotherapy) which is evaluated by MDT assessment.
- Patients are randomized (1:2) to group A or B. Stratification factors include EGFR exon 19deletion or 21L858R mutation, shedding or non-shedding ctDNA at baseline, surgery or chemoradiotherapy under MDT.
- Patients in group A receive aumolertinib 110 mg QD. Patients in group B receive aumolertinib 110 mg QD guided by dynamic MRD monitoring: aumolertinib treatment or drug holiday (only observation) in the first cycle is determined by D7 and D14 MRD status after local therapy; after that, when ctDNA positive (MRD+), patients receive aumolertinib 110 mg QD until ctDNA turns to negative (MRD-); at this time, patients stop aumolertinib until ctDNA turns to positive and restart aumolertinib.
- Imaging evaluation and ctDNA testing will be conducted every 12 weeks. The treatment paradigm of group A and B will be continued until disease progression or fulfillment of discontinuation criteria.
- Primary endpoints are objective response rate (ORR) after 8 weeks of aumolertinib induction therapy and 24-month event-free survival (EFS) rate assessed by independent review committee and investigators between group A and B. Secondary endpoints are comparison of 24-months EFS among three cohorts (patients with longitudinal negative MRD in group B vs patients with any positive MRD in group B vs group A), overall survival, EFS, major pathological response rate in patients undergoing surgery, safety and quality of life.

STUDY STATUS

- The trial was initiated in June 2022 and involved 24 participating centers. Patient enrollment has been completed, with a total of 367 patients screened and 193 patients ultimately enrolled.
- The first patient was enrolled on June 24, 2022, and the last patient on February 9, 2026.
- The cutoff dates for the first (data discloses: ORR, frequency of radical surgery, et al.) and second (data discloses: 24-month EFS, et al.) data analyses will be after August 2026 and February 2027, respectively.
- ClinicalTrials.gov: NCT04841811

Figure 1: Key points of study design of CTONG2101/APPROACH



Sample size calculation:

Primary endpoint 1: ORR

Historic control: ORR was 64% (the ORR was 61% and 70% in sequential and concurrent chemoradiotherapy group in RTOG9401 study, respectively). New evidence: ORR was 74% of aumolertinib arm in AENEAS study. A sample size of 192 patients achieves at power 0.8, one-side α 0.025 and a drop-off rate of 10%.

Primary endpoint 2: 24-month EFS rate

Historic control: 24-month EFS rate was 23.3% (95 CI: 14.0%-34.0%) of placebo arm in Gemstone study, 34.0% as historic control group. New evidence: assuming 24-month EFS rate was 50%. A sample size of 80 patients achieves at power 0.8, one-side α 0.025, considering a drop-off rate of 10%.

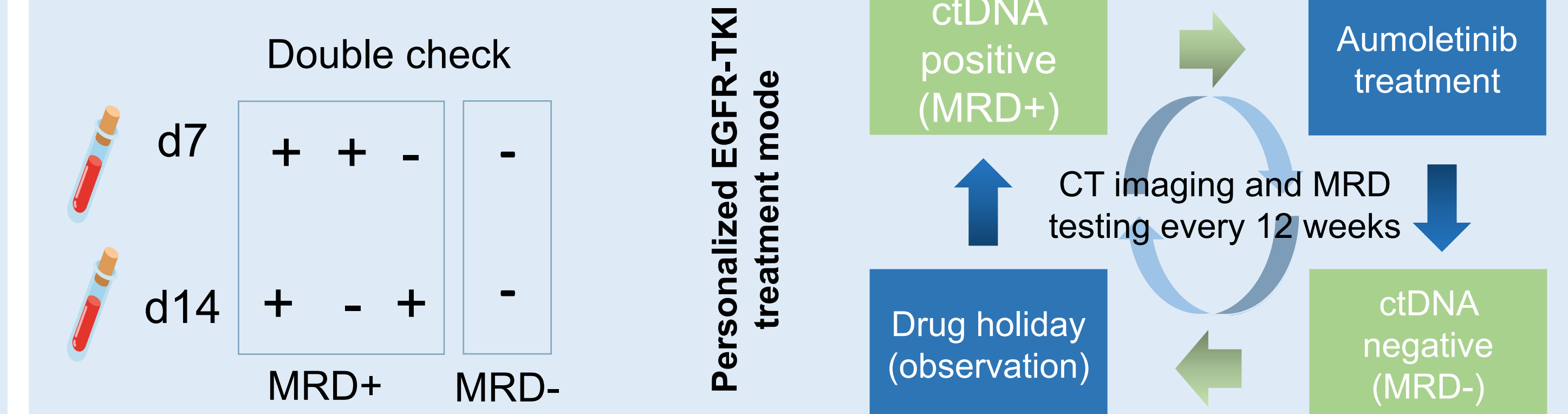
Stratification:

- EGFR mutations: 19del vs 21L858R
- ctDNA status in screening phase: shedding vs non-shedding
- MDT assessment: surgery vs chemoradiotherapy

Primary endpoint:

- ORR after 8 weeks of aumolertinib induction treatment by IRC
- 24-month EFS rate by IRC

Treatment paradigm of group B:



Secondary endpoints:

24-month EFS rate by IRC: patients with persistent MRD- in group A vs patients with any MRD+ in group B vs patients in control group;
ORR after 8 weeks of aumolertinib induction treatment by INV, 24-month EFS rate by INV, EFS, OS, MPR in patients undergoing surgery, safety and quality of life.
Exploratory endpoint :
Dynamic changes of peripheral methylation status before and after aumolertinib treatment and the correlation with efficacy and prognosis

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- We would like to thank all patients and their families for their participation.

