**INTRODUCTION**

- Worldwide, 1.6 million people are diagnosed annually with lung cancer, with an estimated 224,210 new diagnoses in 2014 in the US.8
- Approximately 80% of all lung cancer diagnoses are non-small cell lung cancer (NSCLC), and 40% are adenocarcinoma.1
- In China, lung cancer has increased by 465% in the past 30 years and has become the second leading cause of cancer-related death, with a World Health Organization-estimated 1 million diagnoses annually by 2025.6
- Standard first-line treatment options for Chinese patients with adenocarcinoma is chemotherapy (e.g., bevacizumab), with Chinese State Food and Drug Administration (CFDA)-approved targeted therapies for patients with epidermal growth factor receptor (EGFR)-mutated NSCLC.5

**Study rationale**

- Genomic analyses have now identified a number of genetically altered signaling pathways in NSCLC, particularly in adenocarcinoma (Figure 1).
- As a result, a number of targeted treatment options are now potentially available, and advanced NSCLC management has evolved toward individual patient subtyping based on targetable oncogenic drivers.1,8
- Most patients with molecularly characterized lung adenocarcinoma could potentially benefit from targeted treatment, and there is a need for new study designs that select patients based on targetable oncogenic genetic alterations.3

- This study investigates the innovative paradigm of allocating patients to specific treatment arms based on their genetic profile.
- The five agents studied target specific known molecular alterations in adenocarcinoma (Table 1).

**METHODS**

**Study design**

- This study is a Phase II, multiple-arm, open-label study that will enroll patients with advanced (stage IIIb/IV) lung adenocarcinoma who have failed prior treatment or are unsuitable for chemotherapy, and have received ≥2 prior lines of therapy.6
- A total of 30-35 independent and treatment arms comprising AUY922, BYL719, INC280, ceritinib (LDK378), and MEK162 treatment groups according to their tumor’s confirmed molecular alterations, in an innovative study design (Figure 2).

**Key inclusion criteria**

- Symptomatic central nervous system metastases that are neurologically unsalvageable or requiring increasing doses of steroids ≥4 weeks prior to study entry.
- Radiation therapy ≤4 weeks prior to study entry, with the exception of limited-field palliative radiotherapy for bone pain relief.
- Any other malignancies within the last 5 years before study entry, except for adequately treated carcinoma in situ of cervix, basal, or skin, and melanoma ≤1 cm in diameter.
- Major surgery ≤2 weeks prior to study entry or who have not recovered from side effects of such therapy.
- Previous anticancer therapy ≤4 weeks prior to the first dose of study treatment (except ≤6 weeks for nitrosourea and mitomycin) and have not recovered from the side effects of such treatment prior to the first dose of study treatment, except for alopecia.

**Key exclusion criteria**

- PK blood tests in Chinese patients.
- Serial blood samples collected from ≤6 patients in each arm for PK analysis (non-compartmental approach).
- Sparse blood samples from all other patients to assess PK (population PK approach).
- Optional biomarkers to study resistance mechanisms in each arm. Advise events will be assessed according to Common Terminology Criteria for Adverse Events version 4.03.
- Follow-up:

  - All patients will be followed up for safety 30 days after the last dose of the study treatment.
  - Patients who discontinue study treatment for any reason other than disease progression will be followed up for progression of disease.

- All patients will be followed up for survival.

**Statistics**

- Sample size was calculated based on a Bayesian approach using either a minimally informative prior (AUY922, INCY280, and binimetinib [MEK162]; n=20 for each) or an informative prior using relevant historical data (AUY922 [n=30] and ceritinib [LDK378]; n=25).
- The sample sizes will allow detection with high likelihood of statistically and clinically relevant antitumor activity.

- Each treatment arm is independent from another and will be analyzed separately.
- A Bayesian approach will be used to estimate overall response rate and to provide inferential statements for each treatment arm.
- Bayesian decision rules will be used to define clinically and statistically significant antitumor activity.
- At the time of analysis each treatment arm the respective prior distribution will be updated with all available data from patients in respective full-analysis set.
- An early futility analysis is planned for the AUY922 and binimetinib (MEK162) arms.

**REFERENCES**


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