A phase I–III platform study evaluating the safety and efficacy of multiple therapies in patients with biomarker-defined locally advanced, unresctable, stage III non-small cell lung cancer (NSCLC)

Luis Paz-Ares,1 Carl M. Gay,2 Caicong Zhao,1 Tenifura Kato,1 Luis Corrales,1 Karl Rodenhiser,2 Ahmadur Rahman,1 Denise Bradley,1 Elisabeth Theogar,1 Katherine E. Hutchinson,1 Sharon M. Shagam,1 Benjamin J. Solomon7

BACKGROUND
• Oncogetic driver alterations may arise to consitutively activate kinases capable of driving cancer development across a range of tumour types, including NSCLC.1
• Therapies targeting actionable alternatives, such as ALK, neurotrophic receptor and paxilastin (for ALK, ROS1 and RET alterations, respectively), have demonstrated efficacy and safety in patients with advanced NSCLC,2–4 evaluation of these therapies in unresectable, stage III NSCLC is warranted.
• Characteristic therapy (CRT) selected by the biomarker through liquid biopsy is a standard of care for patients with locally advanced, unresectable, stage III NSCLC; however, there remains an unmet need for improved therapeutic options among these patients, including those with drive-mutated tumours.5,6

METHODS
• Patients with locally advanced, unresectable, stage III NSCLC who have previously received concurrent or sequential CRT have not had histologic progression, and whose tumours harbour a fusion (or rearrangement in the ALK, ROS1, or RET genes, are enrolled (Figure 1).
– Biomarker eligibility is determined through central tissue-based testing within the BIOSTART master screening study, NCT05419375) master screening study, or through local tissue-based testing.
– Eligible patients are randomised 1:1:1 to receive durvalumab or targetted therapy, based on the biomarker detected in the tissue sample.
– Patients are stratified according to disease staging (stage IIIA vs. stage IIIB or IIIC), type of prior CRT (sCRT vs. cCRT), and with biomarker-defined eligibility.

Table 1: Key inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aged ≥18 years</strong></td>
<td>Any history of previous NSCLC (including NSCLC with known or likely oncogenic driver(s) and prior NSCLC treatment or evidence of disease progression)</td>
</tr>
<tr>
<td><strong>Newly diagnosed, histologically/cytologically confirmed locally advanced, unresectable stage III NSCLC with an oncogenic-specific hybridisation, reverse transcription polymerase chain reaction, or NanoString; Oral</strong></td>
<td>Prior treatment with inhibitors specific to the biomarker of each cohort.</td>
</tr>
<tr>
<td><strong>Blood sample</strong></td>
<td>NSCLC treatment with a prohibited medication.</td>
</tr>
<tr>
<td><strong>Telephone assessment</strong></td>
<td><strong>Total duration of study treatment for each cohort is presented in Table 1.</strong></td>
</tr>
</tbody>
</table>
| **Treatment with a prohibited medication** | **Inclusion criteria:**

Secondary and exploratory endpoints
• **Secondary endpoints include time to CNS progression, objective response rate, duration of response, and distant metastasis-free survival.** At BICR and investigator assessment per RECIST v1.1, investigator-assessed PFS, overall survival, brain confirmation determination, maintenance or meaningful improvement in patient-reported outcomes (PROs), and safety.
• **Safety** will be assessed in all patients receiving ≥1 dose of study treatment in addition to the incidence, type, and severity of adverse events as graded by the investigator in accordance with the NCI CTCAE v5.0.
• Exploratory objectives include additional assessments of PROs and safety endpoints, as well as biomarker, pharmacokinetic, and health status utility analyses.

Assessment schedule
• Before and during treatment, blood samples and tumour biopsies (some optional) will be collected for biomarker assessment (Figure 2).
• Tumour responses will be assessed by computed tomography or magnetic resonance imaging at screening and then every 5 weeks for the first 48 weeks post-treatment initiation, followed by every 12 weeks thereafter.7

Figure 1. HORIZON-1 study design

Figure 2. Assessment schedule

Table 2: Study treatment and dosages

<table>
<thead>
<tr>
<th>Therapeutics</th>
<th>Administration</th>
<th>Dosea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectinib</td>
<td>Oral</td>
<td>600 mg BID for 28-day cycles for ≤3 years</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>Oral</td>
<td>600 mg QD for 28-day cycles for ≤3 years</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>IV infusion</td>
<td>1300 mg QD for 28-day cycles for 1 year</td>
</tr>
</tbody>
</table>

b Corticals may be added/closed independently from one another

At the end of 14 March 2022, seven patients have been randomized.b

1. Alectinib
2. Ategravir
3. Atezolizumab
4. BIRB-796
5. Durvalumab
6. Entrectinib
7. Nintedanib
8. Pembrolizumab
9. Sunitinib
10. Vemurafenib
11. Votrient
12. Votrient
13. Xolcorin
14. Zanivimab

Disclosures
• Writing assistance, under the direction of the authors, was provided by TL and AL, with funding from Genentech Inc. South San Francisco, California, USA; and Roche Products Ltd, Welwyn Hatfield, Hertfordshire, UK.

Acknowledgements
• The DFCI Lung Cancer Imaging and Translational Research Core, the DFCI Interventional Radiology Core, the DFCI Pathology Core, the Dana-Farber Cancer Institute Imaging Core, and the Dana-Farber Cancer Institute Biostatistics and Bioinformatics Core.

References