Phase II Study of TKIs as Neo(adjuvant) Therapy in Stage II–III Resectable NSCLC with ALK, ROS1, NTRK or BRAF V600 Alterations

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**LEAD AUTHOR DISCLOSURES**

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<tr>
<th>Relationship(s)</th>
<th>Commercial Interest</th>
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<tbody>
<tr>
<td>Speakers bureaus</td>
<td>AstraZeneca, Bristol Myers Squibb, Genentech and Novartis</td>
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<tr>
<td>Advisory boards</td>
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<td>Contracted/supported research grants</td>
<td>UCLA</td>
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*For the disclosures of co-authors, please refer to the abstract*
Introduction and study rationale

• Despite complete surgical resection, disease recurrence remains high in resectable NSCLC\(^1\)
  - Additionally, trials of neoadjuvant and adjuvant chemotherapy have demonstrated a 5-year overall survival benefit of just 5% for patients with resectable disease\(^2,3\)

• TKIs are hypothesised to provide greater clinical benefit and a more favourable safety profile than platinum-based chemotherapy, in patients with resectable lung cancers with oncogenic driver mutations
  - There are several trials investigating adjuvant TKIs for patients with genetic alterations\(^4-6\)
  - Neoadjuvant TKIs are also being evaluated,\(^7,8\) but their role in this setting remains unclear
  - Neoadjuvant trials allow for early treatment of micrometastatic disease and evaluation of surrogate efficacy endpoints,\(^9\) such as pathologic regression
  - Pathologic regression may enable physicians to guide subsequent adjuvant therapy options based on response

NAUTIKA1: study description

- **NAUTIKA1** (NCT04302025) is an ongoing phase II, multicentre, non-randomised study designed to evaluate the efficacy and safety of targeted therapies in patients with resectable stage II–III NSCLC that harbour fusions in ALK, ROS1, NTRK, RET or the BRAF V600 mutation.

- The study consists of:
  1. Neoadjuvant treatment
  2. Surgery
  3. Post-surgery surveillance, which may include adjuvant treatment
  4. Survival follow-up

- We provide a detailed overview of the NAUTIKA1 study, including the study design, study assessments, key eligibility criteria, study endpoints and recruitment information.
NAUTIKA1: study design overview (neoadjuvant treatment)

**Key eligibility criteria**
- Resectable Stage IIA, IIB, IIIA or select IIIB (T3N2) NSCLC
- ALK+, ROS1+, NTRK+, RET+ or BRAF V600 mut+
- ECOG PS 0–1
- No prior therapy for lung cancer within 2 years

**Neoadjuvant treatment and response assessment**
- Patients will be assigned a neoadjuvant therapy based on their driver mutation
  - Patients will receive 8 weeks (2 cycles) of neoadjuvant therapy
  - PET/CT scans will be performed at screening and pre-surgery to determine tumour response
NAUTIKA1: study design overview
(post-surgery surveillance and survival follow-up)

- A surveillance period of up to 3 years will begin for all patients who undergo surgery.
  - Tumour response will be monitored during this time using extended chest CT scans every 3 months for Years 1–2, then every 6 months for Year 3.
  - If PD occurs during this time, the patient will enter survival follow-up.
- Patients who progressed while receiving neoadjuvant therapy but are still able to undergo surgery will enter surveillance and receive standard of care platinum-based chemotherapy only.

Surveillance period (3 years)

Surgery performed (and no PD on neoadjuvant TKI)

- Platinum-based chemotherapy* (up to 4 cycles)
- Cohort-specific adjuvant TKI† (up to 2 years)
- Surveillance only

Survival follow-up (up to 2 years)

No surgery performed

Survival follow-up (up to 5 years)

*At the discretion of the investigator: the following options are permitted for this study: cisplatin + pemetrexed (carboplatin allowed if cisplatin is contraindicated) and carboplatin + paclitaxel (nab-paclitaxel allowed if hypersensitivity occurred). †Patients will receive the same TKI as was given during the neoadjuvant phase.

Post-surgery surveillance and survival follow-up

- A surveillance period of up to 3 years will begin for all patients who undergo surgery.
  - Tumour response will be monitored during this time using extended chest CT scans every 3 months for Years 1–2, then every 6 months for Year 3.
  - If PD occurs during this time, the patient will enter survival follow-up.
- Patients who progressed while receiving neoadjuvant therapy but are still able to undergo surgery will enter surveillance and receive standard of care platinum-based chemotherapy only.
Patients with resectable NSCLC will be assigned to the appropriate cohort based on the driver mutation detected from their most recent tumour biopsy.

- **ALK** fusion detected by FISH or IHC (tissue) or NGS (tissue / blood) → **ALK+ cohort**
- **ROS1** fusion detected by FISH or NGS (tissue / blood) → **ROS1+ cohort**
- **NTRK1/2/3** fusion detected by RT-PCR (tissue) or NGS (tissue / blood) → **NTRK+ cohort**
- **BRAF V600** mut+ detected by RT-PCR or NGS (tissue) → **BRAF cohort**
- **RET** fusion detected by FISH or RT-PCR (tissue) or NGS (tissue / blood) → **RET+ cohort**
NAUTIKA1: study assessments

- This study provides a unique opportunity to obtain longitudinal molecular profiling data from tumour tissue and blood for disease monitoring and to explore potential mechanisms of tumour progression.
**NAUTIKA1: eligibility criteria**

### Neoadjuvant phase

<table>
<thead>
<tr>
<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
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<tbody>
<tr>
<td>Age ≥18 years</td>
<td>NSCLC that is clinically T4 by virtue of mediastinal organ invasion or Stage IIIB by virtue of N3 disease</td>
</tr>
<tr>
<td>Stage IIA, IIB, IIIA or select IIIB (T3N2) NSCLC*</td>
<td>Any prior therapy for lung cancer within 2 years</td>
</tr>
<tr>
<td>ALK+, ROS1+, NTRK+, RET+ or BRAF V600 mut+ determined in a CLIA certified laboratory</td>
<td>Patients with prior lung cancer who have been in remission for &lt;2 years*</td>
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<tr>
<td>Measurable disease, defined by RECIST v1.1</td>
<td>Major surgical procedure within 28 days prior to Cycle 1, Day 1</td>
</tr>
<tr>
<td>Evaluated by attending surgeon prior to enrolment to verify that the primary tumour and any involved lymph nodes are completely resectable</td>
<td>Malignancies other than NSCLC within 3 years prior to enrolment</td>
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<tr>
<td>Adequate pulmonary and cardiac function to be eligible for surgical resection with curative intent</td>
<td>Pregnant or lactating women</td>
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<td>ECOG PS 0–1</td>
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### Adjuvant phase

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<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
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<td>Patients who lack radiographic progression</td>
<td>No general exclusion criteria</td>
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<td>ECOG PS 0–1</td>
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### Key exclusion criteria

- Adequate haematologic and end-organ function

Patients must also meet additional eligibility criteria for individual study cohorts. For example, patients with ALK point mutations, I117N/S or G1202R, will be excluded from the ALK+ cohort.

*Based on the 8th edition of the AJCC NSCLC staging system

RECIST, Response Evaluation Criteria In Solid Tumours
NAUTIKA1: study endpoints

Primary endpoint:
- MPR rate for each targeted therapy, defined as ≤10% residual viable tumour cells, scored by local pathologist

Secondary endpoints:
- MPR rate of resected specimen, scored by a central pathology committee consensus read
- Pathological regression, based on weighted percentage viable tumour cell assessment
- Investigator-assessed ORR per RECIST v1.1
- Pathological complete response rate, defined as a lack of any viable tumour cells following surgery
- Disease-free survival
- Event-free survival
- Overall survival
- Pre-surgery ctDNA clearance rate in patients with detectable ctDNA at the start of neoadjuvant treatment
- Safety

Exploratory endpoints:
- Correlation of blood ctDNA status pre- and post-surgery with clinical outcomes
- Correlation of blood ctDNA profile post-surgery with clinical outcomes

MPR, major pathological response; ORR, objective response rate
NAUTIKA1: recruitment information

- There are several states across the US with planned or confirmed involvement:

Active and planned sites in:

- California
- Florida
- Massachusetts
- Michigan
- Missouri
- New Hampshire
- New Jersey
- New York
- Ohio
- Oregon
- Pennsylvania
- Tennessee
- Texas
- Virginia
- Washington
- Washington, D.C.
- Wisconsin
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