Phase II, Open-label, Single-arm, Multicenter Study to Assess the Activity and Safety of Alectinib as Neoadjuvant Treatment in Surgically Resectable Stage III ALK-positive NSCLC: ALNEO Trial

Phase II, open-label, single-arm, multicenter study to assess the activity and safety of alectinib as neoadjuvant treatment in surgically resectable stage III *ALK*-positive NSCLC: ALNEO trial

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Clinical Practice Points:

- Alectinib is a potent anaplastic lymphoma kinase-tyrosine kinase inhibitor (ALK-TKI) which is currently used in the first-line setting of advanced *ALK*-positive non-small cell lung cancer (NSCLC). Despite favorable results in the metastatic setting, the activity of alectinib in locally-advanced *ALK*-positive NSCLC as a neoadjuvant treatment remains to be assessed.
- We report the case of a patient with stage IIIA *ALK*-positive NSCLC (cT2aN2) who received alectinib as neoadjuvant treatment. Alectinib was well tolerated and successfully granted a major pathological response (MPR) at pathologic examination.
- We designed a phase II, open-label, single-arm, multicenter clinical trial (ALNEO study, EUDRACT number 2020-003432-25) to investigate the activity and safety of alectinib in patients with potentially resectable stage III *ALK*-positive NSCLC. The treatment will consist of neoadjuvant, surgical and adjuvant phases**.** The primary objective is to assess the activity of neoadjuvant alectinib in terms of MPR.
- Our case report supports the feasibility of alectinib as neoadjuvant treatment. Our phase II study will further explore the activity and safety of this novel treatment strategy.

Keywords: neoadjuvant alectinib; ALK-TKI; ALNEO trial; *ALK*-positive NSCLC

1.0 Introduction

The role of neoadjuvant anaplastic lymphoma kinase-tyrosine kinase inhibitors (ALK-TKI) in early stage and locally advanced *ALK*-positive non-small cell lung cancer (NSCLC) is still unclear and poorly explored. Outstanding activity of alectinib has been demonstrated for the treatment of *ALK*-positive NSCLC in the metastatic setting,[1,2] and whether these results could be translated in earlier stages is a matter of debate.

Herein we report the case of a patient with stage IIIA *ALK*-positive NSCLC who received alectinib as neoadjuvant treatment with a major pathological response (MPR). The patient, a former smoker 62 years-old man, had a cytologically proven *ALK*-positive adenocarcinoma of the lung with stage cT2aN2 (IIIA) according to the 8th American Joint Committee on Cancer (AJCC) TNM classification (Figure 1A-B; Figure 2A-B). Neoadjuvant alectinib was offered at the dosage of 600 mg twice daily for two cycles (56 days), achieving a partial response (PR) of disease at the subsequent CT scan (Figure 1C). Collaterally, slight bilateral subpleuric ground-glass opacities appeared, suggestive for SARS-CoV-2 interstitial pneumonia, which was not confirmed at the nasopharyngeal swab. Left upper lobectomy and mediastinal lymphadenectomy were performed one month later, without complications, after resolution of interstitial pneumonia (Figure 1D). At pathologic examination, a MPR was documented, with less than 10% residual viable tumor cells histologically detected only in 4R lymph node station, and tumor was downstaged at ypT0N2 (Figure 2C-D). One month later, after complete recovery from surgery, adjuvant alectinib was started with a pre-planned duration of 24 months.

In clinical practice, neoadjuvant chemotherapy represents the current standard treatment for patients with potentially resectable locally advanced NSCLC. The better activity and safety of ALK-TKIs with regard to chemotherapy in the metastatic setting represent the rationale and the guarantee of their use in early stage *ALK*-positive NSCLC. In particular, alectinib administration before surgery, as in our case, should ensure a better tolerated treatment able to induce a more extensive tumor shrinkage respect to standard chemotherapy. Moreover, alectinib administration after surgery should contribute

to reduce disease recurrence, with a limited risk of toxicity related to the long period of administration. Hence, we designed a phase II study aimed at investigating alectinib in potentially resectable locally advanced stage III *ALK*-positive NSCLC patients (ALNEO trial).

2.0 Materials and methods

2.1 Study design

ALNEO trial is a phase II, open-label, single-arm, multicenter clinical trial to explore the activity and safety of alectinib in patients with potentially resectable locally advanced stage III *ALK*-positive NSCLC who are treatment-naive and eligible for treatment with ALK-TKI. This study performed by *Gruppo Oncologico Italiano di Ricerca Clinica* and supported by Roche (EUDRACT number 2020-003432-25) is planned to recruit approximately 33 subjects in 20 national Italian Centers.

The treatment will consist of neoadjuvant, surgical and adjuvant phases (Figure 3). Eligible patients will be registered to receive oral alectinib 600 mg twice daily for two cycles of 4 weeks each (8 weeks totally) during the neoadjuvant phase. Following the completion of neoadjuvant treatment, patients will undergo a CT scan or a PET-CT scan, after 8 weeks (+/- 1 week) from the starting of neoadjuvant alectinib, to determine the treatment response that will be assessed by the Investigator using RECIST v1.1. If no progressive disease will be documented, candidates will undergo surgery with radical intent within 3 weeks (+/- 1 week) after the completion of neoadjuvant period. After definitive surgery, patients will enter in the adjuvant setting, during which they will receive alectinib 600 mg twice daily for 24 cycles (96 weeks). Adjuvant treatment should begin within 8 weeks from the date of definitive surgery. During the adjuvant phase, radiographic assessments will continue every 12 weeks (+/- 1 week), or until disease recurrence is documented. At the end of adjuvant treatment, radiographic assessments will continue every 24 weeks (+/- 2 weeks) for up to year 3 after surgery or until disease recurrence is documented.

This study will include collection of blood samples for molecular analyses at baseline, 4 and 8 weeks after neoadjuvant treatment, after surgery (within 2 weeks) and at the eventual relapse.

Characterization of *ALK* fusion partner will be performed on diagnostic biopsy and will be assessed on cell-free nucleic acid (cfNA, both cfDNA and cfRNA) extracted from baseline plasma sample. Levels of cfNA *ALK* translocation will be correlated with principal outcome measures. If patients will relapse during or after adjuvant treatment, a study of mechanism of resistance will be performed. The duration of the study is expected to be a maximum of 60 months. The study recruitment period is expected to be approximately 24 months.

2.2 Key Eligibility Criteria

Male and female patients aged ≥ 18 years with Eastern Cooperative Oncology Group (ECOG) performance status (PS) from 0 to 1 who have locally advanced stage III (according to the 8th AJCC TNM edition) *ALK*-positive treatment-naïve NSCLC are eligible. *ALK* rearrangement will be assessed by local laboratory as a part of the screening process according to an FDA-approved and CE-marked test. Tumor must be defined as potentially resectable (any T with N2, T4N0-1), following a multidisciplinary discussion. Other key eligibility criteria include: measurable disease defined by RECIST v1.1 criteria with CT scan; brain magnetic resonance imaging (MRI) or CT scan showing no evidence of metastatic disease; adequate hematological, hepatic and renal function. Key exclusion criteria are: non-resectable stage III and stage IV disease with distant metastases (including malignant pleural effusion) identified on PET-CT scan or biopsy; evidence of severe or uncontrolled systemic diseases.

2.3 Study endpoints

The primary endpoint is MPR, defined as ≤10% residual viable tumor cells histologically detected in the resected primary tumor and all resected lymph nodes after surgery. Secondary endpoints include: pathological complete response (pCR), defined as the absence of residual viable tumor cells in all specimens as evaluated by blinded independent pathological review after surgery; objective response, defined as a complete response or a PR at the pre-surgical radiological evaluation, based on the

Investigator's assessment according to RECIST v1.1; event-free survival, calculated as the interval from the trial inclusion date to either the date of disease recurrence/progression or the date of death; disease-free survival, calculated as the interval from the date of surgical resection to either the date of disease recurrence or the date of death; overall survival, defined as the time from the date of trial inclusion date to the date of death; adverse events graded by Common Terminology Criteria for Adverse Events version 5.0.

2.4 Statistical Design

According to the Simon's two stage mini-max design, the null hypothesis that the MPR rate is ≤ 20% will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are 4 or fewer MPR in these 18 patients, the study will be stopped early for futility. Otherwise, 15 additional patients will be accrued for a total of 33. The null hypothesis will be rejected if 11 or more MPR are observed in 33 patients. This design yields a type I error rate of 0.05 and power of 0.80 when the true MPR rate is 40%.

3.0 Discussion

Neoadjuvant treatment for early stage NSCLC with novel therapeutic agents is an emerging field of investigation, aiming to improve the cure rate. Immune checkpoint inhibitors (ICIs) are being extensively evaluated in the neoadjuvant setting, both as monotherapies, in combination with chemotherapy and as ICIs doublets.[3] The combination of nivolumab plus chemotherapy granted the highest MPR and pCR rates ever reported for neoadjuvant treatment in stage IIIA NSCLC.[4] Moreover, since oncogene addiction is a strong predictor of response to targeted therapies in advanced NSCLC, TKIs constitute an attractive strategy for limited disease.

The vast majority of available data regarding (neo)adjuvant TKIs are limited to *EGFR*-mutated NSCLC patients. Rizvi et al firstly reported the activity of neoadjuvant gefitinib in 50 patients with stage I-II NSCLC enriched for *EGFR* mutations; 21 patients achieved a radiologic tumor shrinkage of ≥ 25%.[5] Further randomized study confirmed the feasibility of neoadjuvant erlotinib, even though

with inconclusive results.[6,7] Studies evaluating neoadjuvant osimertinib in *EGFR*-mutated NSCLC are currently ongoing (NCT03433469, NCT04351555).

Regarding *ALK*-positive tumors, activity of neoadjuvant crizotinib has been reported in 11 pathologically confirmed N2 *ALK*-positive patients, 91% of whom underwent R0 resections with two pathologic complete responses.[8] More recently, Zhang and collaborators reported a clinically successful case involving neoadjuvant alectinib in a stage IIIB *ALK*-positive NSCLC.[9] As in our report, alectinib was given for two cycles (56 days), considering its median response time of 8 weeks in the metastatic disease,[2] in absence of relevant toxicities. Strikingly, alectinib granted a significant downsizing of the tumor, from cT3N2M0 (stage IIIB) to ypT1aN0M0 (stage IB).[2] In this regard, a phase II trial is evaluating different targeted therapies in patients with resectable stage II-III NSCLC that harbour fusions in *ALK, ROS1, NTRK, RET* or the *BRAF V600* mutation, including (neo)adjuvant alectinib for *ALK*-positive cohort (NCT04302025).

In our case, we demonstrated the feasibility and efficacy of neoadjuvant alectinib in a patient with stage IIIA *ALK*-positive NSCLC. Treatment was well tolerated, allowed the patient to avoid a potential pneumonectomy and MPR was achieved at pathological examination. Considering that the main purpose of neoadjuvant treatment is to achieve the best downstaging for surgical resection, we assume that potent new-generation ALK-TKIs, such as alectinib, could be a potential strategy in patients with *ALK*-positive stage III NSCLC.

Apart from neoadjuvant phase, we hypothesize that adjuvant alectinib could successfully eradicate minimal residual disease and prevent brain metastases onset, with the same favorable toxicity profile. The recent practice-changing results of ADAURA trial,[10] comparing osimertinib to placebo in early stage *EGFR*-mutated NSCLC, support the investigation of potent selective TKIs in the adjuvant setting of oncogene-addicted NSCLC. Concerning *ALK*-rearranged NSCLC, no prospective data on adjuvant TKIs is available to date. The ongoing ALCHEMIST study (NCT02194738) is recruiting radically resected stage IB-IIIA NSCLC patients after completion of standard of care chemotherapy and/or radiotherapy. Among these, *ALK*-positive patients are randomized to receive crizotinib 250

mg twice daily versus observation for up to 24 months of treatment. The more recent ALINA trial (NCT03456076) is an ongoing phase III randomized study which compares adjuvant alectinib 600 mg twice daily for 24 months versus adjuvant platinum-based chemotherapy in *ALK*-positive stage IB-IIIA NSCLC after surgical resection.[11]

Our ALNEO study, which will start enrollment in March 2021, will further prospectively explore the role of alectinib as neoadjuvant treatment. The molecular biomarker analyses on baseline tissue/plasma and on following plasma samples will provide new insights into potential early adaptation mechanisms to ALK targeting in this setting.

4.0 Conclusions

Neoadjuvant alectinib was feasible in our case and granted MPR at pathologic examination after surgery. ALNEO study will prospectively assess the activity and safety of alectinib as neoadjuvant treatment in patients with potentially resectable locally advanced stage III *ALK*-positive NSCLC.

Figure legends:

Figure 1: Disease evolution under neoadjuvant alectinib treatment. A) Basal CT scan showed right hilar lesion and upper right paratracheal lymphadenopathy, with occlusion of upper right lobar bronchus and infiltration of principal right pulmonary arteria; **B)** PET-scan demonstrated increased glucose uptake at both the lesions; **C)** After 2 cycles of neoadjuvant alectinib, CT scan revealed partial response of disease and decrease of pulmonary arteria infiltration; **D)** CT scan after one more cycle of neoadjuvant alectinib showed stability of disease.

Figure 2: Histopathological analyses. A) Cytological sample of right hilar lesion at diagnosis: cluster of tumor cells, with high N/C ratio, irregular nuclear membrane, granular chromatin and nucleoli (MGG coloration); **B) FISH for *ALK* on cytological sample of right hilar lesion at diagnosis:** a positive fluorescence in situ break-apart test with split red and green show the presence of an *ALK* rearrangement; **C1-2) Post-surgical histological sample of right hilar lesion:** the predominant histologic changes seen after therapy include fibrosis, acellular necrosis with calcifications, foam cell infiltration and inflammatory cell infiltration; **D) Post-surgical histological sample of 4R lymph node:** the lymph node is replaced mostly by fibrosis post therapy regression. Psammoma bodies and numerous cholesterol crystal clefts surrounding by multinucleated giant cells, epithelioid histiocytes, and foamy macrophages are present (E/E); **E) FISH for *ALK* on post-surgical histological sample of 4R lymph node:** tumor cells show cytoplasmic staining for ALK (D5F3 clone). Some papillary structures with true fibrovascular cores lined by cuboidal to columnar neoplastic cells are still present.

Figure 3: Schema for ALNEO trial.

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