PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

The NeoTRACK Trial - Neoadjuvant TiRagolumab, Atezolizumab and Chemotherapy – Dissection of IO efficacy in NSCLC by longitudinal tracKing: protocol of a non-randomized, open-label, single arm phase II study

Authors

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Greystoke , Alastair**
Affiliation	**Newcastle University**
Date	**17-Dec-2024**
COI	**None**

The rational for giving only adjuvant immunotherapy in patients with pathological CR is not outlined

What is the rational for 2 cycles of chemotherapy with immunotherapies? Large Phase 3 use either 3 or 4 cycles. Please outline

The rationale for following patients up for 30 Months is not defined. Why this time period.

Background

Please include Keynote 671 and Aegean studies for balance.

Also in adjuvant setting PEARLS and BR.31

Exclusion Criteria. What happens with patients with known HER2 and RET abnormalities , are they eligible?

There is no details as to planned hypothesis or analysis for the translational research, this should be outlined even if briefly including potential uses of donated tumour and blood

It is not appropriate to not involve Patents and Public in design and conduct of research

Discussion “First clinical data from the CITYSCAPE trial [15] showed promising results for dual immune checkpoint inhibition with tiragolumab”

If stating this consider discussing that SKYSCRAPER 1 and KEY-VIBE studies are negative on press release.

Reviewer	**2**
Name	**Bilgin, Burak**
Affiliation Hospital	**Department of Medical Oncology, Ankara Bilkent City**
Date	**22-Dec-2024**
COI	**None**

It is an interesting study on perioperative treatment of NSCLC, which has become very popular in recent years, and I am eagerly awaiting the results.

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1(Dr. Alastair Greystoke , Newcastle University)

Comments to the Author:

The rationale for giving only adjuvant immunotherapy in patients with pathological CR is not outlined

Dear Dr. Alastair, thank you to address that question. Meta-analysis of all relevant IO/CHT trials in neoadjuvant and perioperative setting by Marinelli et al. showed comparable event-free survival in patients with pCR irrespective of the treatment regimen (neoadjuvant only vs. perioperative). Based on the results of their analysis, the authors recommended individual discussion of adjuvant treatment in pCR patients depending on their physical status, treatment toxicity and immune-system related comorbidities. Marinelli et al. remained in favor for adjuvant treatment in patients without pCR given the high likelihood of disease recurrence (*J Thorac Oncol. 2024 Oct 9: S1556-0864(24)02374-8*).

To date, there is no prospective trial stratifying neoadjuvant only versus perioperative treatment depending on pathologic response rate. Of note, the results of the Marinelli metaanalysis were not available when the neoTRACK-trial was planned. The neoTRACK investigators believe that continuous adjuvant treatment with immunotherapy for a limited time frame may consolidate anti-tumority by fostering the patient’s immune-response thus helping to avoid disease recurrence.

We hypothesize that the effect of complete pathologic response after only two cycles of dual IO / CHT is more likely related to the immunotherapy component rather than chemotherapy, and therefore decided to stratify patients towards their depth of postoperative pathologic remission and to not further expose complete pathologic responders to dual immunotherapy only without additional chemotherapy.

What is the rationale for 2 cycles of chemotherapy with immunotherapies? Large Phase 3 use either 3 or 4 cycles. Please outline.

Thank you for your valuable comment. NeoTRACK-patients have primary technically operable lung cancer. Surgery within the NeoTRACK trial is planed after two cycles of neoadjuvant chemotherapy with dual immunotherapy.
While SOC neoadjuvant therapy consists of chemotherapy in combination with mono-immunotherapy, the neoTRACK regimens uses chemotherapy combined with dual immunotherapy, therefore both concepts are not directly comparable. The reduced number of cycles before surgery may lead to an expected better general

condition at the time of resection and a lower likelihood of progression under induction therapy, while achieving comparable responses due to dual immunotherapy.

Our strategy of restaging after 2 cycles of neoadjuvant dual-immunotherapy with chemotherapy allows for confirmation of continued technical operability and scheduling surgery 4 weeks afterwards. This strategy of continuous radiologic follow-up enables local therapy without any delay in patients who have responded. This strategy does not further increase preoperative toxicity that can be of significant relevance when 3 or 4 cycles are administered neoadjuvantly. In non-responders (visible during restaging after two cycles), on the other hand, further escalation of the assumed "ineffective" induction therapy can then be dispensed. 4 cycles of neoadjuvant CHT-IO can be considered problematic, as the same agents without tiragolumab (azetolizumab/platinumbased chemotherapy) had resulted in an R1-resection rate of 13% in Shu et al. (Lancet Oncol 2020; 21: 786-95) due to local or systemic progression on therapy. Published data from the CM816 trial (NCT02998528) show an R1-resection rate close to 20% in both treatment arms (CHT vs. CHT-IO) and a pneumonectomy rate of 17-25%, which are both considered unacceptable. We claimed that an interval of 2x3 weeks of neoadjuvant dual immunochemotherapy plus 4 weeks of recovery until surgery is therefore justified to avoid relevant toxicity as well as unnecessary extended and/or incomplete resections in a setting where primary surgery is still competing alternative therapy.

The rationale for following patients up for 30 Months is not defined. Why this time period.
All patients undergo institutional SOC follow up as long as possible. A time frame of 30 months was on the one hand chosen to increase the chance to detect recurrence after multimodal treatment. Second, an in-trial follow up of 30 months seemed as well adequate not to miss late toxicities related to adjuvant dual immunotherapy treatment.

There is no details as to planned hypothesis or analysis for the translational research, this should be outlined even if briefly including potential uses of donated tumour and blood:

Dear Dr. Alaistair, thank you for that comment and reasonable request. The effect of perioperative Immunotherapy is influenced by a variety of parameters located within the tumor microenviroment. The translational research program therefore aims to characterize the peritumoral milieu by analysis of the patient blood and tumor-accompanying tissue. We included a separate section to briefly describe the the main aims and underlying mechanisms in the revised manuscript describing the planned investigations on tissue and blood samples.

Data obtained through the translational analysis will be correlated with the clinical course. The aim is to elucidate immune-related mechanisms underlying the potentially synergistic, immune-stimulating effect of the combination of PD-L1 and TIGIT blockade in order to identify new biomarkers for predicting treatment response and for therapy control.

It is not appropriate to not involve Patents and Public in design and conduct of research

Thank you for that important issue. The study was planned and officially set up in 2020. At this timepoint patient patents and Public in design and conduct of research involvement was not requested by the regulatory authorities.

Background
Please include Keynote 671 and Aegean studies for balance.
Also in adjuvant setting PEARLS and BR.31
We agree with your valuable recommendation and included the trials within the manuscript.

Exclusion Criteria. What happens with patients with known HER2 and RET abnormalities , are they eligible?
After careful consideration with the regulatory authorities and in line with the then in current approval situation, we decided to exclude patients with activating EGFR-mutations, ROS1-mutations and ALK-fusions. Upfront NGS-testing is obligate as a screening procedure. Due to lack of evidence from neoadjuvant/perioperative phase III trials patients with HER2 and RET abnormalities will not be excluded from trial participation.

Discussion "First clinical data from the CITYSCAPE trial [15] showed promising results for dual immune checkpoint inhibition with tiragolumab"If stating this consider discussing that SKYSCRAPER 1 and KEY-VIBE studies are negative on press release.
Thank you for that important issue. We have also noticed the press release in SKYSCRAPER 01 that was published more or less simultaneously when we were planning the publication of our protocol. We are aware of the informative content of the press release however have not noticed any full publication on other tiragolumab data during the review process of our planned publication. SKYSCRAPER 01 as well as most of the KEYVIBE

trials aim to treat patients with stage IV. SKYSCRAPER 01-Inclusion criteria were NSCLC with non squamous histology and high PD-L1 expression. They differ from the neoTRACK- population that consist of an all-comer PD-L1 surgical cohort with different NSCLC histologies. Our research therefore has the potential to further investigate the relevance of dual anti PD-L1 anti TIGIT plus chemotherapy in a neoadjuvant setting in a broad subset of lung cancer patient.

Reviewer: 2 **Dr. Burak Bilgin, Department of Medical Oncology, Ankara Bilkent City Hospital**

Comments to the Author:It is an interesting study on perioperative treatment of NSCLC, which has become very popular in recent years, and I am eagerly awaiting the results.
Dear Dr. Bilgin, thank you for your time reviewing the manuscript of our trial protocol.

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Greystoke , Alastair**
Affiliation	**Newcastle University**
Date	**16-Feb-2025**
COI	

Thank you for addressing fully my previous comments in your updated manuscript