SAKK 16/18: Immune-modulatory radiotherapy to enhance the effects of neoadjuvant PD-L1 blockade after neoadjuvant chemotherapy in patients with resectable stage III(N2) non-small cell lung cancer (NSCLC). A multicenter phase II trial.

Laetitia A. Mauli, Tobias Finazzi, Lisa Hole, Adrienne Bettini, David König, Martin Fröh, Simon Haefiger, Alfredo Addo, Michael Mark, Martin Buess, Patrizia Froeschli, Wolf-Dieter Janthur, Christine Wabel, Christoph J. Ackermann, Miklos Pless, Bernhard Scheib, Patrick Dorn, Matthias Guckenberiger, Spasenija Savic Prince, Sacha I. Rothchild for the Swiss Group for Clinical Cancer Research (SAKK)

Background

Neoadjuvant chemo-immunotherapy is a new standard of care for resectable NSCLC stage III-N2 (based on CheckMate-816). 1 SAKK 16/14 demonstrated a major improvement in pathological complete response (pCR), major pathological remission (MPR) and event-free survival (EFS) with the addition of perioperative durvalumab after standard induction chemotherapy (CT) with cisplatin doublet in patients (pts) with resectable stage III (N2) NSCLC.2

Radiotherapy (RT) has the potential to act synergistically with immunotherapy (IO) through release of tumor antigens and modulation of the local immune microenvironment in favor of a better (systemic) anti-tumor immune response (abscopal effect).

The aim of the SAKK 16/18 trial is to evaluate the efficacy and safety of immune-modulatory RT to the primary tumor during neoad. IO.

Due to the lack of evidence for an optimal RT regimen for an "in-situ vaccination" effect three different RT regimens are being tested.

Methods

SAKK 16/18 is a prospective non-randomized phase II trial in 14 cancer centers in Switzerland.

The SAKK 16/18 study design is presented in Fig. 1.

- 90 pts are randomized to three RT arms (30 per arm): 20 x 2 Gy (Arm A: over 4 weeks), 5 x 5 Gy (Arm B: over 1 week), 3 x 8 Gy (Arm C: every other day, over 1 week).
- Arms A and B: Homogeneous dose prescription, Arm C: inhomogeneous dose prescription (to the 65%-80% isodose).
- Intensity-modulated RT (IMRT) to the primary tumor only, with strict sparing of mediastinal lymph nodes and thoracic organs at risk (OAR) being prioritised over target volume coverage.
- The primary endpoint is 1yFS.
- Here we report a preplanned interim analysis of the secondary endpoints safety, surgical outcomes and pathological response after resection in 25 pts.

Study design

Figure 1

Consort diagram

Figure 2

Table 1 Patient and tumor characteristics

Table 2 Pathological evaluations

Table 3 Treatment-related adverse events (AEs) – total number of events (CTCAE v5.0)

Table 4 AEs related to neo-adj, IO-RT and surgery grade 2

Data cut-off: On October 8, 2022 25 pts have reached post-operative day 30 and a total of 31 pts were included in the safety analysis (Figure 2). For non-resected pts safety follow-up was at least 90 days after the last trial treatment. Trial start: July 2020

Table 1 Patient and tumor characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All analyzed patients (N=31)</th>
<th>n (%)</th>
</tr>
</thead>
</table>

Table 2 Pathological evaluations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arm A (N=12)</th>
<th>Arm B (N=12)</th>
<th>Arm C (N=15)</th>
<th>Total (N=39)</th>
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</thead>
</table>

Table 3 Treatment-related adverse events (AEs) – total number of events (CTCAE v5.0)

<table>
<thead>
<tr>
<th>Highest grade</th>
<th>Neoad-adj (N=241)</th>
<th>Neoad-adj (N=12)</th>
<th>Surgery (N=21)</th>
<th>Any trial treatment (N=271)</th>
</tr>
</thead>
</table>

Table 4 AEs related to neo-adj, IO-RT and surgery grade 2

<table>
<thead>
<tr>
<th>Highest grade</th>
<th>Neoad-adj (N=28)</th>
<th>Neoad-adj (N=4)</th>
<th>Surgery (N=25)</th>
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Conclusions

- At the preplanned interim analysis, safety outcomes were as expected. There was no relevant increase in TRAE due to IO or RT and no delay or cancer recurrence due to surgery.
- The trial continues to recruit per protocol.
- Preliminary pathological responses are promising.
- At this early timepoint the authors present with regards to a differential efficacy of the 3 RT regimens can be made.

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References


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The Swiss Oncology Research Network