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.

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Abstract: 8547

Background

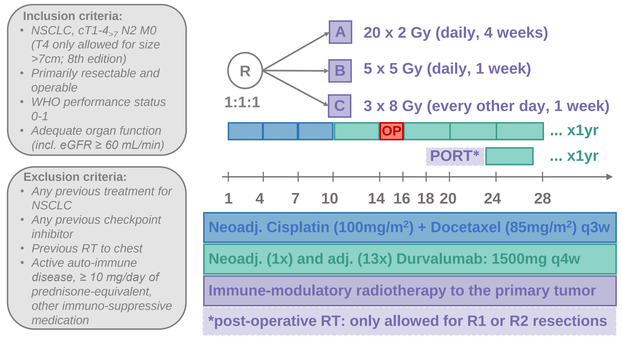
- Neoadjuvant chemo-immunotherapy is a new standard of care for resectable NSCLC stage II-III (based on CheckMate-816).[1]
- SAKK 16/14 demonstrated a major improvement in pathological complete response (pCR), major pathological remission (MPR) and event-free survival (EFS) with the addition of perioperative durvalumab after standard induction chemotherapy (CT) with cisplatin and docetaxel 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).[3]
- The aim of the SAKK 16/18 trial is to evaluate the efficacy and safety of immune-modulatory RT to the primary tumor during neoadj. 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-comparative randomized phase 2 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 1year-EFS.
- Here we report a preplanned interim analysis of the secondary endpoints safety, surgical outcomes and pathological response after resection in 25 pts.

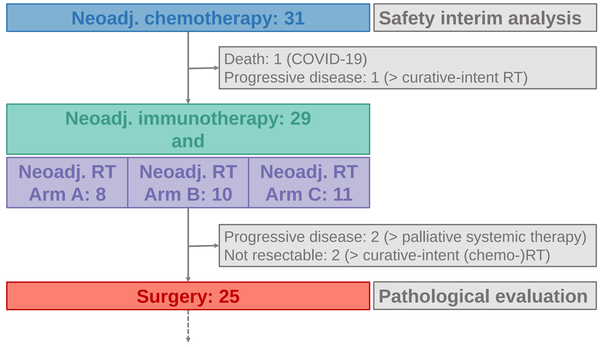
Study design

Figure 1



Consort diagram

Figure 2



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Results

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

Variable	All analyzed patients (N=31) n (%)
. Female / male	10 (32) / 21 (68)
. Current / former / never smoker	15 (48) / 13 (42) / 3 (10)
. WHO performance status 0 / 1	22 (71) / 9 (29)
. Adeno- / squamous cell / large cell carcinoma / NOS	18 (58) / 11 (36) / 1 (3) / 1 (3)
. Tumor stage T1 / T2 / T3 / T4	8 (26) / 8 (26) / 13 (42) / 2 (6)

Table 2 Pathological evaluations

Variable	Arm A (N=7) n (%)	Arm B (N=9) n (%)	Arm C (N=9) n (%)	Total (N=25) n (%)
. MPR (≤10% viable tumor cells)	4 (57)	8 (89)	7 (78)	19 (76)
. pCR (no viable tumor cells)	0 (0)	4 (44)	3 (33)	7 (28)
. Nodal down-staging to <ypN2	3 (43)	6 (67)	6 (67)	15 (60)

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

Highest grade	Neo-adj. CT (N=241) n (%)	Neo-adj. IO (N=12) n (%)	Neo-adj. RT (N=12) n (%)	Surgery (N=21) n (%)	Any trial treatment (N=271) n (%)
1	116 (48)	6 (50)	4 (33)	5 (24)	125 (46)
2	85 (35)	5 (42)	7 (58)	9 (43)	98 (36)
3	34 (14)	1 (9)	0 (0)	6 (29)	41 (15)
4	5 (2)	0 (0)	1 (8)	1 (5)	6 (2)
5	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.4)

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

	Neo-adj. IO (N=29)			Neo-adj. RT (N=29)			Surgery (N=25)		
Highest grade	2	3	4	2	3	4	2	3	4
Anorexia				1					
Arrhythmia								4	
Chylothorax							1		
Dyspnea	1			1			1		
Fatigue	1			1			1		
Gastroparesis				1			1		
Infusion-related reaction	1								
Nausea	1								
Pain				1			3	1	
Pleural effusion							1	1	
Pleural infection						1			1
Pneumonitis	1	1		1					
Pneumothorax							1		
Skin reaction				1					

Note 1: One event may be considered related to more than one treatment.
Note 2: G3-5 AE related to neo-adj. CT were: Neutropenia (3 G3, 3 G4), febrile neutropenia (4 G3), thrombocytopenia (4 G3), lymphopenia (1 G3), dehydration (1 G3), hypokalemia (2 G3), hyponatremia (1 G3), acute kidney injury (3 G3), adrenal insufficiency (1 G3), ALAT elevated (1 G3), colitis (2 G3), oral mucositis (1 G3), nausea/vomiting (2 G3), fatigue (2 G3), pneumonia (2 G3), urinary tract infection (1 G3), infusion-related reaction (1 G3, 1 G4), hearing impairment (1 G3), COVID-19 (1 G5)

Conclusion

- 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 cancellation of surgery due to IO or RT.
- The trial continues to recruit per protocol.
- Preliminary pathological responses are promising.
- At this early timepoint no assumptions with regards to a differential efficacy of the 3 RT regimens can be made.

References [1]Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med. 2022;386(21):1973-1985. [2]S. Rothschild et al., SAKK 16/14: Durvalumab in Addition to Neoadjuvant Chemotherapy in Patients with Stage IIIA(N2) Non-Small-Cell Lung Cancer-A Multicenter Single-Arm Phase II Trial. J Clin Oncol. 2021 Sep 10;39(26):2872-2880. [3]Zhang, Z., Liu, X., Chen, D. et al. Radiotherapy combined with immunotherapy: the dawn of cancer treatment. Sig Transduct Target Ther 7, 258 (2022).

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