SAKK 16/14: Anti-PD-L1 Antibody Durvalumab in Addition to Neoadjuvant Chemotherapy in Patients with Stage IIIA(N2) Non-Small Cell Lung Cancer (NSCLC) — A Multicenter Single-arm Phase II Trial

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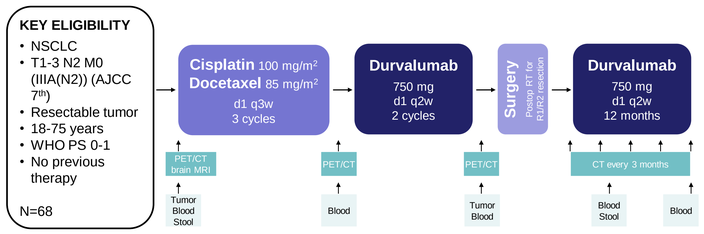
Background

- Approximately 15-20% of non-small cell lung cancer (NSCLC) patients initially present with locally advanced stage IIIA(N2) disease
- Platinum-based chemotherapy in addition to surgery (neoadjuvant or adjuvant) improves survival by about 4% in stage IB-III NSCLC[1]
- Surgery after neoadjuvant therapy is feasible in selected patients with N2 disease at experienced centers with recorded low perioperative mortality[2-4]
- Previous SAKK trials established a standard of care for stage IIIA(N2):
  - 3 cycles of neoadjuvant chemotherapy with cisplatin and docetaxel followed by surgery (SAKK 16/96 and SAKK 16/00)[3,4]
  - Addition of neoadjuvant radiotherapy does not improve outcome[4]
- Neoadjuvant PD-1/PD-L1 blockade in early stage NSCLC is feasible and associated with high pathological response rates[5-8]

Trial Design

- Multicenter, single-arm, phase II trial



- Lifelong follow-up with optional re-biopsy at progression

Study Endpoints

- ***Primary endpoint***
  - Event-free survival (EFS) at 12 months
- ***Secondary endpoints***
  - EFS, OS, Objective response (OR)
  - Pathological complete response (pCR)
  - Major pathological response (MPR) (≤10% viable tumor)
  - Rate of nodal down-staging to < ypN2
  - Complete resection, Pattern of recurrence
  - Adverse events (AEs), Postoperative 30-day mortality

Statistical Considerations

- Improve EFS at 12 months from ≤ 48%[4] to ≥ 65%

Patient Demographics

	N=67	%
Age, median (range)	61 (41-74)	
Gender		
- Male / Female	35 / 32	52.2% / 47.8%
WHO PS		
- 0 / 1	52 / 15	77.6% / 22.4%
Histology		
- Adenocarcinoma	37	55.2%
- Squamous cell carcinoma	22	32.8%
- Large cell carcinoma	1	1.5%
- NOS	7	10.4%
T stage		
- T1 / T2 / T3	15 / 33 / 19	22.4% / 49.3% / 28.4%

Treatment

	N	%
Neoadjuvant Chemotherapy	67	
- Completed / Not completed[1]	60 / 7	89.6% / 10.4%
Neoadjuvant Immunotherapy	62	
- Completed / Not completed[2]	58 / 4	86.6% / 13.4%
Surgery	55	
- Pneumonectomy	5	9.1%
- Bilobectomy	7	12.7%
- Lobectomy	43	78.2%
- R0/R1/R2	50/3/2	90.9%/5.5%/3.6%
Postoperative Radiotherapy	6	10.9%
Adjuvant Immunotherapy	50	
- Completed	25	50.0%
- Still on treatment	5	10.0%
- Not completed[3]	20	40.0%

[1]Reasons for discontinuation: tox. (n=2), physicians decision (n=2), PD (n=2), patient refusal (n=1)
[2]Reasons for discontinuation: PD (n=2), respiratory insufficiency (n=1), patient refusal (n=1)
[3]Reasons for discontinuation: PD (n=10), tox. (n=5), patient refusal (n=3), treatment delay (n=2)

Results

Radiographic response

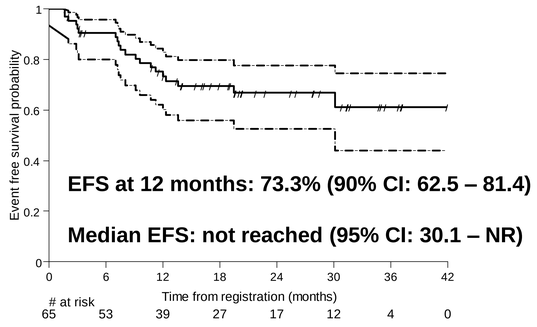
Response	Total (N=62) N (%)
CR	4 (6.5%)
PR	32 (51.6%)
SD	16 (25.8%)
PD	4 (6.5%)
NE	4 (6.5%)
Missing[1]	2 (3.2%)

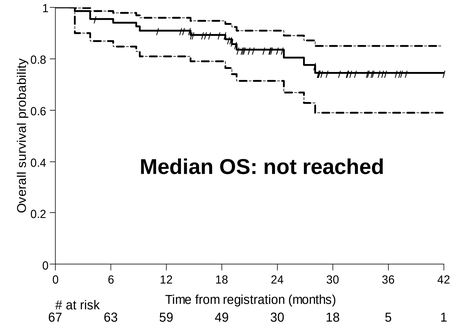
[1] Tumor assessment not done (N=2)

Pathologic response

Response	Total (N=55) N (%)
pCR	10 (18.2%)
MPR	33 (60.0%)
Nodal downstaging	37 (67.3%)
- ypN0	26 (47.3%)
- ypN1	11 (20.0%)

- Median follow-up: 28 months. Time point of analysis: January 15, 2020





Adverse events (highest grade per patient)

Highest grade	AEs overall (N=67)	AEs neoadj. chemo (N=67)	AEs neoadj. Durva (N=62)	AEs surgery (N=58)	AEs adj. Durva (N=50)
No AES	0 (0.0%)	0 (0.0%)	12 (19.4%)	10 (17.2%)	1 (2.0%)
1	1 (1.5%)	3 (4.5%)	21 (33.9%)	18 (31.0%)	8 (16.0%)
2	7 (10.4%)	19 (28.4%)	21 (33.9%)	13 (22.4%)	16 (32.0%)
3	32 (47.8%)	26 (38.8%)	6 (9.7%)	12 (20.7%)	20 (40.0%)
4	25 (37.3%)	18 (26.9%)	2 (3.2%)	4 (6.9%)	5 (10.0%)
5	2 (3.0%)	1 (1.5%)	0 (0.0%)	1 (1.7%)	0 (0.0%)

- 2 fatal AEs (Respiratory failure during neoadjuvant chemo; Bronchopulmonary hemorrhage after surgery)
- 30-day postoperative mortality: n=1 (1.8%)

Pattern of recurrence

Site of recurrence	Total (N=14) N (%)
Local	2 (14.3%)
Loco-regional	3 (21.4%)
Distant	8 (57.1%)
Local & distant	1 (7.1%)

Conclusions

- **This is to our knowledge the largest cohort of patients with resectable stage IIIA(N2) NSCLC receiving perioperative immune checkpoint inhibitor therapy**
- **The addition of perioperative durvalumab to standard of care cisplatin/docetaxel**
  - **is safe**
  - **results in a very encouraging 1-year EFS rate that exceeds historical data of chemotherapy alone**
  - **leads to high major pathological response rate and rate of nodal downstaging**
- **Perioperative PD-L1 inhibition in addition to standard neoadjuvant chemotherapy forms the backbone of our next study investigating the additional benefit of neoadjuvant immune-modulatory radiotherapy (SAKK 16/18; NCT04245514)**

References

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