Real-world outcomes in patients with resected non-small cell lung cancer (NSCLC) receiving (neo)adjuvant treatment in Germany: an I-O Optimise analysis

EPH82

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Background

- Lung cancer is the second most common cancer in Europe[1]; population-based data from Germany reported a lung cancer incidence of 67.1 to 71.3 per 100,000 individuals from 2010 to 2019[2]
- Approximately 40%-50% of patients with non-small cell lung cancer (NSCLC) are diagnosed with non-metastatic disease (stage I-III)[3-5]
- More than 30% of patients with NSCLC who undergo a complete resection experience disease recurrence[6]
- Adjuvant and neoadjuvant chemotherapy have demonstrated modest clinical benefit in patients with non-metastatic NSCLC, with an increase of 4%-5% in 5-year overall survival (OS) compared with surgery alone[7,8]
- Only recently, immunotherapy-based regimens have been approved in the adjuvant and neoadjuvant settings for non-metastatic NSCLC
  - Atezolizumab and nivolumab + chemotherapy were approved by the European Medicines Agency in June 2022[9] and June 2023[10], respectively
- Immunotherapy-based regimens in the adjuvant and neoadjuvant settings have shown improved patient outcomes in several trials[11-13]
- Once sufficient real-world data are available, assessment of the real-world effectiveness of these new treatments will be required, including country-specific data due to specificities in approval and clinical practice
- The purpose of this analysis was to provide a pre-immunotherapy baseline with which outcomes with newer immunotherapy-based regimens could be compared
- Using data from 4 German population-based cancer registries, we aimed to assess OS from the start of treatment and its associated baseline factors in resected patients with non-metastatic NSCLC receiving adjuvant, neoadjuvant, or perioperative systemic anticancer treatment (SACT) before the availability of immunotherapy in these settings in Germany

Methods

- This analysis was part of a retrospective cohort study based on the Versorgungsforschung in der Onkologie database (VONKOdb), which is made up of 4 federal state cancer registries providing data on a total of > 70,000 patients with lung cancer
- Inclusion criteria for the retrospective cohort were as follows:
  - Aged ≥ 18 years
  - Newly diagnosed non-metastatic NSCLC (tumour, node, metastasis stages I-IIIC) per the study periods defined by region (**Table 1**)
- A treatment decision algorithm was used to identify a cohort of patients with stage IB-IIIA non-metastatic NSCLC who received surgery with adjuvant, neoadjuvant, or perioperative SACT
- Resected patients who received SACT were categorised as receiving:
  - Adjuvant SACT ± radiotherapy (RT), or neoadjuvant SACT ± RT or perioperative SACT
    - Resected patients receiving neoadjuvant SACT ± RT or perioperative SACT were recategorised into a single group because of small numbers
  - Adjuvant SACT ± RT, or neoadjuvant SACT ± RT or perioperative SACT with cisplatin or carboplatin
- Patients were followed from their date of diagnosis until death or end of follow-up (**Table 1**)

Table 1. Study period for the analysis

VONKOdb registry	Diagnosis inclusion period	End of follow-up[a]
Hamburg	1 Jan 2016 to 31 Dec 2018	31 Dec 2019
Baden-Württemberg	1 Jan 2016 to 31 Dec 2019	31 Dec 2020
North Rhine-Westphalia	1 Jan 2016 to 31 Dec 2019	31 Jul 2021
Schleswig-Holstein	1 May 2016 to 31 Dec 2019	31 Mar 2022

[a]Patients were followed from their initial NSCLC diagnosis until the earliest date of death or censoring (known exit from the data source or end of study period).

- OS outcomes with cisplatin and carboplatin could not be compared in our analyses due to the inherent differences in patient population characteristics that determine administration of each treatment[14]
- OS was defined as the time from start of initial adjuvant SACT ± RT, or neoadjuvant SACT ± RT or perioperative SACT until the earliest date of death or censoring (known exit from the data source or end of study period)
- Median OS and OS at 6, 12, 18, 24, 36, and 48 months, and every year after this until the maximum follow-up, were assessed using the Kaplan-Meier method
- Multivariate Cox regression analyses were performed to identify patient demographic and clinical characteristics associated with OS
- Primary data masking was performed if patient counts were < 5

Results

Analysis population

- 2039 resected patients with stage IB-IIIA NSCLC were included in the analysis
  - 1716 (84.2%) received adjuvant SACT ± RT
  - 323 (15.8%) received neoadjuvant SACT ± RT or perioperative SACT (of this population, 69 [21.4%] received perioperative SACT)
- Median (interquartile range [IQR]) follow-up was 15.0 (6.0-29.1) months

Baseline characteristics

- Key baseline characteristics were generally similar among treatment groups (**Table 2**)
- Most patients had stage II or IIIA NSCLC and a higher proportion of patients who received neoadjuvant SACT ± RT or perioperative SACT were stage IIIA compared with patients who received adjuvant SACT ± RT

Table 2. Baseline characteristics by treatment

Stage	Adjuvant SACT ± RT (n = 1716)	Neoadjuvant SACT ± RT or perioperative SACT (n = 323)
Median age (IQR), years	64 (52-76)	64 (52-76)
Age ≥ 75 years, n (%)	181 (10.5)	38 (11.8)
Sex, n (%)		
Male	1053 (61.4)	204 (63.2)
Female	663 (38.6)	119 (36.8)
Year of diagnosis, n (%)		
2016	435 (25.3)	83 (25.7)
2017	491 (28.6)	71 (22.0)
2018	389 (22.7)	96 (29.7)
2019	401 (23.4)	73 (22.6)
Stage, n (%)		
IB	72 (4.2)	8 (2.5)
II	807 (47.0)	65 (20.1)
IIIA	837 (48.8)	250 (77.4)
Histology, n (%)		
NSQ	934 (54.4)	167 (51.7)
SQ	639 (37.2)	126 (39.0)
NSCLC NOS	67 (3.9)	22 (6.8)
Other specified NSCLC	76 (4.4)	8 (2.5)
SACT only, n (%)	1335 (77.8)	255 (78.9)[a]
SACT + RT, n (%)	381 (22.2)	68 (21.1)
Cisplatin,[b] n (%)	976 (56.9)	164 (50.8)
Carboplatin,[b] n (%)	488 (28.4)	94 (29.1)

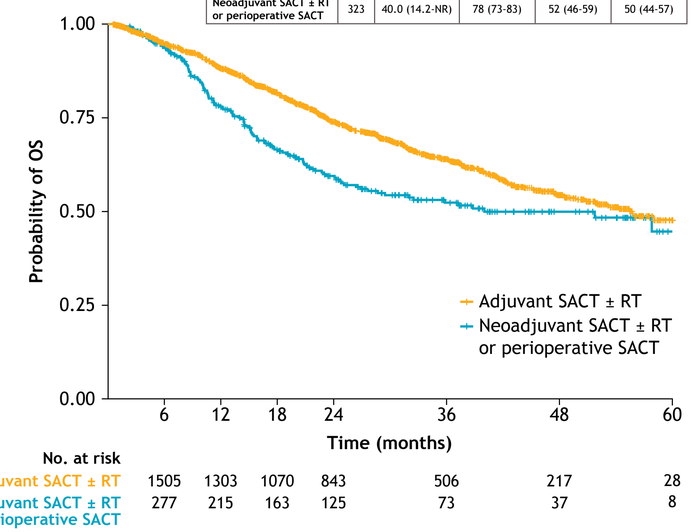
[a]Includes resected patients receiving perioperative SACT (n = 69). [b]Relates to receipt of these treatments as part of surgery plus adjuvant or neoadjuvant SACT either alone or as part of doublet or triplet chemotherapy.
NOS, not otherwise specified; NSQ, non-squamous; SQ, squamous.

OS outcomes

- Resected patients receiving adjuvant SACT ± RT had numerically higher median OS (55.8 months) compared with those receiving neoadjuvant SACT ± RT or perioperative SACT (40.0 months) (**Figure 1**)
- The 4-year OS rates in patients receiving adjuvant SACT ± RT and neoadjuvant SACT ± RT or perioperative SACT were 54% and 50%, respectively

Figure 1. OS in resected patients with stage IB-IIIA NSCLC receiving adjuvant SACT ± RT, or neoadjuvant SACT ± RT or perioperative SACT

Treatment	n	Median OS (IQR), months	1-year OS probability (95% CI), %	3-year OS probability (95% CI), %	4-year OS probability (95% CI), %
Adjuvant SACT ± RT	1716	55.8 (23.2-NR)	88 (87-90)	64 (61-67)	54 (51-58)
Neoadjuvant SACT ± RT or perioperative SACT	323	40.0 (14.2-NR)	78 (73-83)	52 (46-59)	50 (44-57)



No. at risk							
Adjuvant SACT ± RT	1505	1303	1070	843	506	217	28
Neoadjuvant SACT ± RT or perioperative SACT	277	215	163	125	73	37	8

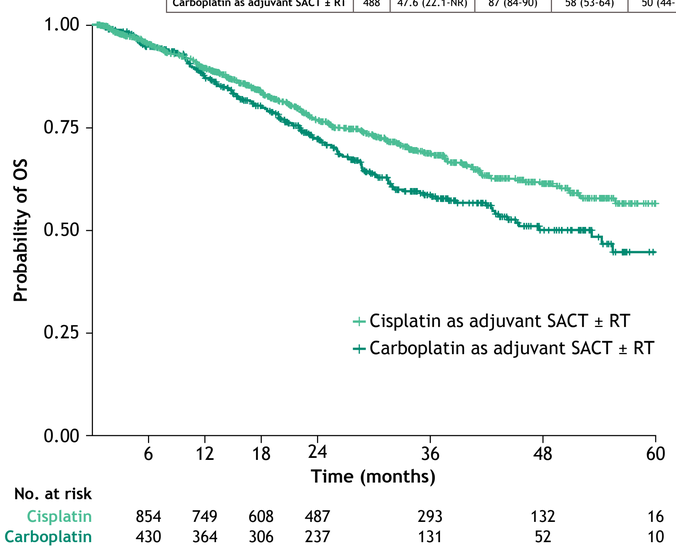
CI, confidence interval; NR, not reached.

- Median OS was numerically longer in resected patients receiving cisplatin as adjuvant SACT ± RT (NR) compared with resected patients receiving carboplatin as adjuvant SACT ± RT (47.6 months) (**Figure 2A**)
- Median OS was comparable in resected patients receiving cisplatin as neoadjuvant SACT ± RT or perioperative SACT (57.8 months) and resected patients receiving carboplatin as neoadjuvant SACT ± RT or perioperative SACT (60.9 months) (**Figure 2B**)

Figure 2. OS in resected patients with stage IB-IIIA NSCLC receiving cisplatin or carboplatin as A) adjuvant SACT ± RT and B) neoadjuvant SACT ± RT or perioperative SACT

A

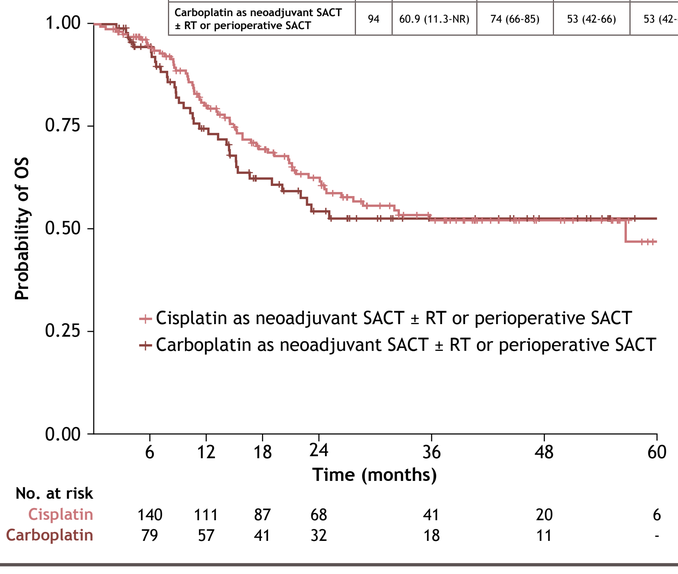
Treatment	n	Median OS (IQR), months	1-year OS probability (95% CI), %	3-year OS probability (95% CI), %	4-year OS probability (95% CI), %
Cisplatin as adjuvant SACT ± RT	976	NR (25.5-NR)	89 (87-91)	69 (65-72)	61 (57-65)
Carboplatin as adjuvant SACT ± RT	488	47.6 (22.1-NR)	87 (84-90)	58 (53-64)	50 (44-57)



No. at risk							
Cisplatin	854	749	608	487	293	132	16
Carboplatin	430	364	306	237	131	52	10

B

Treatment	n	Median OS (IQR), months	1-year OS probability (95% CI), %	3-year OS probability (95% CI), %	4-year OS probability (95% CI), %
Cisplatin as neoadjuvant SACT ± RT or perioperative SACT	164	57.8 (15.0-NR)	80 (74-87)	52 (44-62)	52 (44-62)
Carboplatin as neoadjuvant SACT ± RT or perioperative SACT	94	60.9 (11.3-NR)	74 (66-85)	53 (42-66)	53 (42-66)

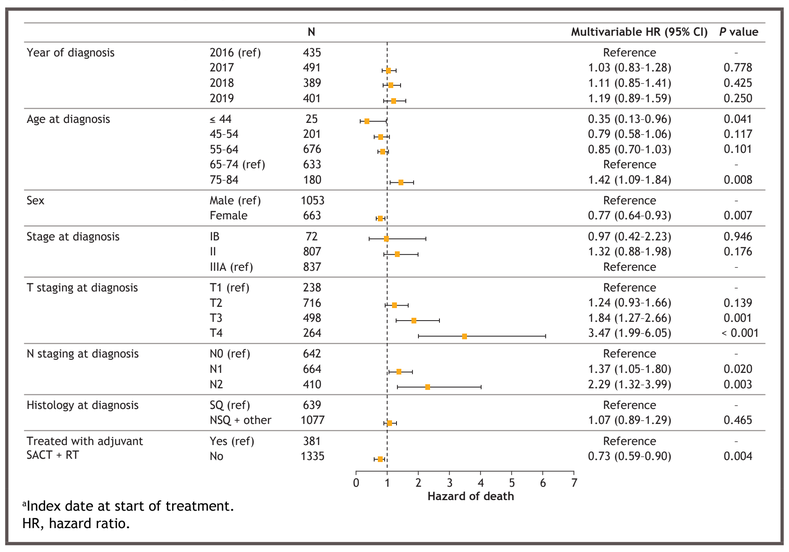


No. at risk							
Cisplatin	140	111	87	68	41	20	6
Carboplatin	79	57	41	32	18	11	-

Factors associated with OS

- In 1716 resected patients receiving adjuvant SACT ± RT, factors significantly associated with worse prognosis were (**Figure 3**):
  - Age 75-84 vs 65-74 years
  - Tumour stages T3 and T4 vs T1
  - Node stages N1 and N2 vs N0
  - Male vs female sex
  - Adjuvant SACT + RT vs no adjuvant SACT + RT

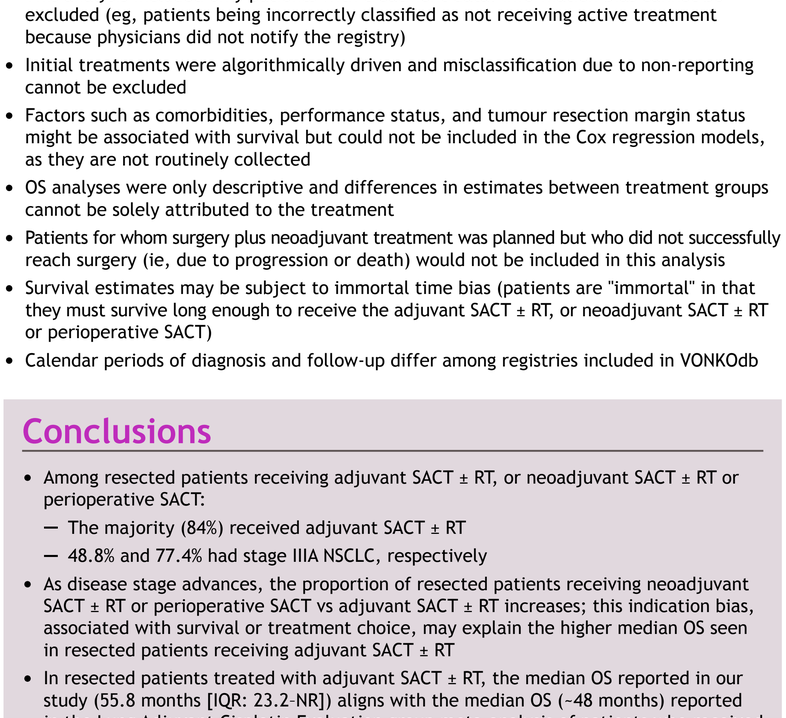
Figure 3. Association between key characteristics and OS in resected patients receiving adjuvant SACT ± RT[a]



[a]Index date at start of treatment.
HR, hazard ratio.

- In 323 resected patients receiving neoadjuvant SACT ± RT or perioperative SACT, factors significantly associated with worse prognosis were (**Figure 4**):
  - Age 65-74 vs 55-64 years
  - Neoadjuvant SACT + RT vs no neoadjuvant SACT + RT

Figure 4. Association between key characteristics and OS in resected patients receiving neoadjuvant SACT ± RT or perioperative SACT[a]



[a]Index date at start of treatment.

Strengths

- Data were derived from the VONKOdb, including > 70,000 patients with NSCLC (all Union for International Cancer Control stages) from the cancer registries of the Hamburg, Baden-Württemberg, North Rhine-Westphalia, and Schleswig-Holstein federal states in Germany, representing ~40% of the German population; the study therefore provides considerable real-world coverage, rather than only including data from referred cancer patients
- Patients were treated in clinics/hospitals and in private practices; these data reflect the heterogeneous treatment landscape in Germany
- There was no loss of patients to follow-up due to regular data linkage to registration offices

Limitations

- This analysis included only patients with treatment data. Information bias cannot be excluded (eg, patients being incorrectly classified as not receiving active treatment because physicians did not notify the registry)
- Initial treatments were algorithmically driven and misclassification due to non-reporting cannot be excluded
- Factors such as comorbidities, performance status, and tumour resection margin status might be associated with survival but could not be included in the Cox regression models, as they are not routinely collected
- OS analyses were only descriptive and differences in estimates between treatment groups cannot be solely attributed to the treatment
- Patients for whom surgery plus neoadjuvant treatment was planned but who did not successfully reach surgery (ie, due to progression or death) would not be included in this analysis
- Survival estimates may be subject to immortal time bias (patients are "immortal" in that they must survive long enough to receive the adjuvant SACT ± RT, or neoadjuvant SACT ± RT or perioperative SACT)
- Calendar periods of diagnosis and follow-up differ among registries included in VONKOdb

Conclusions

- Among resected patients receiving adjuvant SACT ± RT, or neoadjuvant SACT ± RT or perioperative SACT:
  - The majority (84%) received adjuvant SACT ± RT
  - 48.8% and 77.4% had stage IIIA NSCLC, respectively
- As disease stage advances, the proportion of resected patients receiving neoadjuvant SACT ± RT or perioperative SACT vs adjuvant SACT ± RT increases; this indication bias, associated with survival or treatment choice, may explain the higher median OS seen in resected patients receiving adjuvant SACT ± RT
- In resected patients treated with adjuvant SACT ± RT, the median OS reported in our study (55.8 months [IQR: 23.2-NR]) aligns with the median OS (~48 months) reported in the Lung Adjuvant Cisplatin Evaluation group meta-analysis of patients who received adjuvant chemotherapy[15]
- In resected patients treated with neoadjuvant SACT ± RT or perioperative SACT, the median OS reported in our study (40.0 months [IQR: 14.2-NR]) aligns with the median OS (26.2-93.6 months) reported in clinical trials of neoadjuvant chemotherapy[16-18]
- In resected patients receiving adjuvant SACT ± RT, multivariate analyses showed a trend towards associations between older age, male sex, more advanced disease (higher tumour or nodal stage), or administration of adjuvant SACT + RT and worse prognosis
- In resected patients receiving neoadjuvant SACT ± RT or perioperative SACT, multivariate analyses showed a trend towards associations between older age or administration of neoadjuvant SACT + RT and worse prognosis
- These data represent a useful baseline against which future changes in patient management and clinical outcomes can be compared

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