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# Real-world multicentre analysis of neoadjuvant immunotherapy and chemotherapy in localized or oligometastatic non-small cell lung cancer (KOMPASSneoOP)

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***Abstract***

**Background:** Recent clinical trials demonstrate the feasibility of neoadjuvant immuno(chemo) therapy and report high rates of pathological remission, a surrogate marker for overall survival.

**Patients and methods:** This is a retrospective multicentre real-world analysis of patients with locally resectable NSCLC, including oligometastatic disease, who received neoadjuvant immuno(chemo)therapy and resection. Consolidating immunotherapy was applied following multidisciplinary board recommendation. Primary endpoint was the rate of complete pathological response (pCR, no residual vital tumour cells) or major pathological response (MPR, ⩽ 10% residual vital tumour cells). Secondary endpoints included the radiological response and survival.

**Results:** Seven centres contributed 59 patients (56% stage IIB–IIIC, 44% in stage IVA–IVB with up to four oligometastatic sites). MPR was found in 68% including 53% with pCR. There were no radiological progressions. Median follow-up was 24.3 months. At 12 and 24 months, progression-free survival was 82.6% and 68.1%, and overall survival was 89.5% and 87.2%, respectively.

**Conclusion:** To our knowledge, this study encompassed the largest NSCLC real-world cohort treated with neoadjuvant immuno(chemo)therapy to date. In routine clinical practice, resection after neoadjuvant immuno(chemo)therapy is feasible in patients with locally resectable NSCLC, including oligometastatic disease. In line with clinical trials, we found MPR in more than two-thirds of patients. Early data show encouraging survival.

***Keywords:*** checkpoint inhibitor, NSCLC, pathological response, real world, survival

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## Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer death.[1,2] In locally advanced NSCLC, recommended treatment options include resection after neoadjuvant chemotherapy or radical chemoradiotherapy followed by consolidation immunotherapy with durvalumab.[3,4] Oligometastatic NSCLC may be treated radically by induction chemotherapy, followed by debulking surgery.[5] For clarity and readability, we subsume 'induction' therapy into 'neoadjuvant' therapy, and 'debulking surgery' into 'resection' throughout the text. Despite curative intent, 60–80% of treated patients will have a recurrence with no further curative treatment option.

Recent phase II–III trials have reported the feasibility of neoadjuvant immuno(chemo)therapy in

**Table 1.** Prospective trials in neoadjuvant immuno(chemo)therapy.

| Trial | Stage | Neoadjuvant treatment | Duration (cycles) | *n* | Resected | MPR (%) | cPR (%) |
|---|---|---|---|---|---|---|---|
| Phase II | | | | | | | |
| CheckMate-159[6,7] | I-IIIA | Nivolumab | 2 | 22 | 20 | 45 | 15 |
| LCMC3[8] | IB-IIIB | Atezolizumab | 2 | 93 | 82 | 18 | 5 |
| IONESCO[9] | IB-IIB | Durvalumab | 3 biweekly | 50 | 43[a] | 19 | 7 |
| NEOMUN[10] | II-IIIA | Pembrolizumab | 2 | 15 | 15 | 27 | 18 |
| Reuss[11] | IB-IIIA | Ipilimumab and nivolumab | 3 biweekly | 9 | 6[b] | NA | 33 |
| NEOSTAR[12] | I-IIIA | Ipilimumab and nivolumab *versus* nivolumab | 3 biweekly | 44 | 34 | 29 *versus* 17 | 19 *versus* 9 |
| Shu[13] | IB-IIIA | Atezolizumab, carboplatin, and nab-paclitaxel | 4 | 30 | 29 | 57 | 33 |
| NADIM[14,15] | | Nivolumab, carboplatin, and paclitaxel | 3 | 46 | 41 | 80 | 63 |
| Phase III: | | | | | | | |
| CheckMate-816[16,17] | IB-IIIA | Platinum-doublet and nivolumab *versus* platinum-doublet | 3 | $2 \times 158$ | 149 *versus* 135 | 36.9 *versus* 8.9% | 24.2% *versus* 2.2% |

MPR, major pathological response.
[a]Early termination because of five post-operative deaths.
[b]Terminated early due to toxicity.

resectable stage III NSCLC (Table 1).[18,19] These studies have also reported high rates of pathological response, which is regarded as a surrogate marker of overall survival (OS) after neoadjuvant chemotherapy.[20–22] Two cycles of nivolumab (CheckMate-159) induced major pathological response (⩽10% residual viable tumour, MPR) in 45% of patients ($n=20$), including 15% of pathological complete response (no residual viable tumour, pCR).[7] In a study of neoadjuvant combination immuno-oncological treatment with nivolumab and ipilimumab, two complete responses were observed in six resected patients without recurrence at 24 months. However, the study was terminated early due to toxicity.[11] In contrast, the NEOSTAR trial was feasible and safe with the same strategy.[12] Furthermore, studies of neoadjuvant immuno(chemo)therapy have provided early evidence of efficacy with acceptable toxicity and no delays in surgery. Up to four cycles of chemo-immunotherapy with atezolizumab, carboplatin, and nanoparticle albumin-bound paclitaxel (nab-paclitaxel) resulted in successful R0-resection in 87% of the patients, of whom 57% had MPR.[13] In the Spanish NADIM trial, neoadjuvant chemo-immunotherapy with three cycles of nivolumab, carboplatin, and paclitaxel resulted in an MPR rate of 80% in patients with resection, including 63% with pCR.[15] However, resection following neoadjuvant treatment was not performed in 5 of the 46 patients. Among patients with tumour resection, the progression-free survival (PFS) at 24 months was significantly greater in patients with pCR (96%) than in patients with MPR but no pCR (88%) or no MPR (57%), supporting the negative predictive value of pathological response for recurrence. Taken together, the phase II studies reported MPR and cPR rates of 18–45% and 5–15%, respectively, for mono-immunotherapy, of 29%

and 19–33% for combination immunotherapy, and of 57–80% and 33–63% for immunochemotherapy. The ongoing phase III trial CheckMate-816 of neoadjuvant chemotherapy with three cycles of nivolumab or chemotherapy alone recently reported significantly higher pathological response rates with chemoimmunotherapy compared to chemotherapy (MPR 36.9% *versus* 8.9%, pCR 24.2% *versus* 2.2%, respectively).[16,17] Furthermore, co-primary EFS endpoint has been reached, but the magnitude of benefit is unknown.[23] Since these trials used from one to four cycles of neoadjuvant immuno(chemo)therapy, the question of how many cycles are necessary remains unanswered (Table 1).

Oligometastatic patients were excluded from the prospective randomized trials. Recently, we reported pathological response rates and outcome in a prospective monocentric cohort of immuno(chemo) therapy prior to definitive therapy, including 11 patients with complete resection.[24] Of these, eight (73%) had MPR including seven (64%) with pCR. Among the patients with pCR, three had oligometastatic disease. On ESMO 2021, a recent Chinese retrospective study of neoadjuvant immunochemotherapy ($n=45$) was presented reporting MPR of 69% and pCR of 40%.[25] Furthermore, 'real-world evidence' on neoadjuvant immuno(chemo)therapy in oligometastatic patients is restricted to few cases reporting encouraging outcome.[26–28]

To assess the efficacy of neoadjuvant immuno(chemo)therapy in a broad real-world NSCLC population, we performed a multicentre retrospective analysis (KOMPASSneoOP) of pathological and radiological response and survival after resection following neoadjuvant immuno(chemo)therapy in patients with stage IIB–IVB NSCLC (oligometastatic).[5] Furthermore, we addressed the open question of the necessary number of cycles of neoadjuvant therapy.

## Material and methods

### *Study design and participants*

This multicentre retrospective real-world analysis (KOMPASSneoOP) was conducted at seven experienced lung cancer centres, five of which are certified by the German Cancer Society (DKG). Each centre included consecutive patients with localized or oligometastatic NSCLC (stage IIB–IVB)[5] who received neoadjuvant immuno(chemo) therapy and subsequent resection. Briefly, all patients had histologically confirmed NSCLC and complete tumour staging, including positron emission tomography and computed tomography (PET-CT) and contrast-enhanced magnetic resonance imaging (MRI) of brain at baseline. Involvement of PET-positive mediastinal lymph nodes (N2 or N3 disease) was confirmed cytologically or histologically by endobronchial ultrasound guided biopsy. Staging was performed according to the International Association for the Study of Lung Cancer (IASLC) 8th edition.[29] In stage IVA or IVB patients, the metastatic sites had to be amenable to local curative treatment, either by resection or stereotactic ablative radiotherapy (SABR).

### *Pathology*

PD-L1 expression levels were determined locally based on tumour samples obtained at diagnosis of NSCLC. All pathologists had successfully passed the German PD-L1 proficiency testing.[30] In accordance with clinical routine, the following PD-L1 antibodies were used: SP263 (47%), Cal10 (23%), 28-8 (13%), ZR3 (11%), and 22c3 (6%). No centre used the less sensitive antibody SP142.[31] Since there has so far been no approved neoadjuvant targeted treatment in the curative setting of NSCLC, patients were not routinely tested for oncogenic drivers.

Objective pathological response was assessed by the measurement of the percentage of residual viable tumour in resected primary tumours following IASLC recommendations.[32] pCR was defined as tumours with no viable tumour cells in the resected lung cancer specimen and in none of the sampled regional lymph nodes. MPR was defined as the presence of 10% or fewer viable tumour cells in the primary tumour and by definition includes the patients with pCR.[21,33]

### *Procedures*

Treatment followed the recommendation of the local multidisciplinary tumour board (MDB) taking into account the evidence available at the time. Following the presentation of Forde's first data on neoadjuvant nivolumab monotherapy ($n=15$, MPR in six patients) in 2016,[6] the initial patients were treated with neoadjuvant immuno-monotherapy. Following the presentation of first results of the NADIM trial on neoadjuvant immunochemotherapy ($n=13$, cPR in nine patients) in 2018,[14]

most subsequent patients were treated with neoadjuvant immunochemotherapy. The pembrolizumab-containing protocols were selected since they had resulted in the highest response rates reported so far in the relevant phase III-NSCLC trials. Moreover, the response rates were significantly higher compared to chemotherapy (KEYNOTE-024: 44.8% *versus* 27.8%; KEYNOTE-189: 47.6% *versus* 18.9%; KEYNOTE-407: 57.9% *versus* 38.4%).[34–36] This was deemed to improve resectability (e.g. by lobectomy instead of pneumonectomy). Thus, patients with non-squamous histology received pembrolizumab, pemetrexed, and carboplatin or cisplatin (KEYNOTE-189 protocol).[35] Patients with squamous histology received pembrolizumab, paclitaxel or nab-paclitaxel, and carboplatin (KEYNOTE-407 protocol).[36] Alternatively, patients could receive immuno-monotherapy with pembrolizumab (if PD-L1 TPS was ⩾50%, KEYNOTE-024 protocol)[34] or nivolumab (240 mg) on Day 1 of each 14-day cycle.[7] Patients received immuno-oncological treatment as clinical routine either in label (stage IV patients) or off-label as an individual 'Heilversuch' (healing attempt) according to German law (stage II–III patients). Patients gave written informed consent in the off-label use. Resection of the primary tumour and systematic lymph node dissection were performed according to institutional standards. Consolidating pembrolizumab was given if recommended by the MDB. In oligometastatic patients, all metastatic sites were treated locally in curative intent, either by resection or SABR. Following recurrence, patients were treated according to current guidelines, with continued follow-up of survival.

### Outcomes

As primary endpoint, we assessed the proportion of patients with pCR or MPR. As secondary endpoints, we assessed the proportion of patients who achieved complete or partial radiologic response (RECIST1.1),[1] PFS, defined as time from diagnosis to date of recurrence or death, and OS, defined as time from diagnosis to date of death. The database was locked on 15 November 2021. Data from patients who were still alive were censored at the date of last contact. The swimmer plot and Kaplan–Meier plots were generated using GraphPad Prism 9. Significances were calculated using the unpaired *t*-test for parametric data and the Mann–Whitney U-test for non-parametric data (GraphPad Software, San Diego, California, USA).

## Results

In total, 59 patients diagnosed with NSCLC from 28 December 2017 until 21 December 2020 were included. At baseline, 33 (55.9%) of the patients were Union for International Cancer Control (UICC) stage IIB–IIIC, and 26 (44.1%) had stage IVA–IVB disease with up to four metastases (oligometastatic).[5] Baseline characteristics, treatment, and outcome are shown in Table 2. The patients had higher PD-L1 TPS than an unselected real-world population (Tables 3–5). The PD-L1 TPS was similarly distributed in patients with localized and with oligometastatic disease and in patients with non-squamous and squamous histology. The swimmer plot shows the characteristics and progression of each patient (Figure 1). The PET-CT scans in Figure 2 show representative morphologic and metabolic responses to neoadjuvant immuno(chemo)therapy. Neoadjuvant treatment was well tolerated with no new safety signals.

From a surgical perspective, neoadjuvant immuno-oncological treatment resulted in firm adhesions particularly of hilar and mediastinal lymph nodes, and in areas of lymphadenopathy around the bronchial and vascular structures making the separation of the perivascular and peribronchial tissue layers more difficult than in patients treated with neoadjuvant chemotherapy alone. A minimally invasive approach (VATS) was used in 13% of resections. Complete resection was achieved in 56 patients (95%). There was one perioperative death due to aspiration pneumonia in a comorbid patient with coexisting Parkinson's disease. Adjuvant immunotherapy with pembrolizumab was administered in 4 of 33 stage IIB–III patients (12%) and in 12 of 26 stage IV patients (46%). Apart from more advanced stage, all other major prognostic markers, including age (median 59 *versus* 65 years), performance status at baseline (ECOG 0 in 63% *versus* 35%), histology (non-squamous 94% *versus* 58%), PD-L1 TPS (>50% in 67% *versus* 41%), response rate to immuno(chemo)therapy (complete or partial response in 100% *versus* 77%) and pathological responses (cPR in 69% *versus* 47%), were biased in favour of patients with consolidation immunotherapy. From the fact, that stage IV patients and patients with adenocarcinoma (14/16) are overrepresented, it may be speculated, that the perceived need to control distant disease has guided the treatment decision.

With respect to the primary endpoint pathological response, 40 patients (67.8%) had MPR, including

**Table 2.** Baseline characteristics (A), Treatment (B), and Outcome (C), according to pathological response.

| *n* | All patients | Patients with pCR | Patients with MPR but without pCR | Patients without MPR |
|---|---|---|---|---|
| | 59 | 31 (53%) | 9 (15%) | 19 (32%) |
| A Baseline characteristics | | | | |
| Age (mean, range) | 63.6 (47.5–84.5) | 64.7 (50.6–84.5) | 63.0 (55.0–69.7) | 62.2 (47.5–83.8) |
| Gender | | | | |
| Male | 30 (51%) | 19 (61%) | 1 (11%) | 10 (53%) |
| Female | 29 (49%) | 12 (39%) | 8 (89%) | 9 (47%) |
| Performance status | NA 1 (2%) | NA 1 (3%) | | |
| ECOG 0 | 25 (43%) | 14 (47%) | 2 (22%) | 9 (47%) |
| ECOG 1 | 32 (55%) | 15 (50%) | 7 (78%) | 10 (53%) |
| ECOG 2 | 1 (2%) | 1 (3%) | 0 | 0 |
| Smoking status | NA 3 (5%) | NA 2 (6%) | NA 1 (11%) | |
| Never smoker | 3 (5%) | 1 (3%) | 1 (13%) | 1 (5%) |
| Ever smoker | 53 (95%) | 28 (97%) | 7 (88%) | 18 (95%) |
| Histology | | | | |
| Adenocarcinoma | 36 (61%) | 16 (52%) | 6 (67%) | 14 (74%) |
| Squamous cell carcinoma | 19 (32%) | 14 (45%) | 2 (22%) | 3 (16%) |
| Adenosquamous carcinoma | 2 (3%) | 0 | 0 | 2 (11%) |
| LCNEC | 1 (2%) | 0 | 1 (11%) | 0 |
| NOS | 1 (2%) | 1 (3%) | 0 | 0 |
| PD-L1 (TPS)[a] | NA 3 (5%) | NA 2 (6%) | | NA 1 (5%) |
| 0% | 4 (7%) | 1 (3%) | 1 (11%) | 2 (11%) |
| 1–49% | 25 (45%) | 12 (41%) | 4 (44%) | 9 (50%) |
| 50–100% | 27 (48%) | 16 (55%) | 4 (44%) | 7 (39%) |
| Stage (UICC 8) | | | | |
| IIB | 1 (2%) | 0 | 1 (11%) | 0 |
| IIIA | 17 (29%) | 11 (35%) | 2 (22%) | 4 (21%) |
| IIIB | 11 (19%) | 5 (16%) | 1 (11%) | 5 (26%) |
| IIIC | 4 (7%) | 3 (10%) | 0 | 1 (5%) |
| IVA | 22 (37%) | 11 (35%) | 4 (44%) | 7 (37%) |
| M1b (BRA) | 11 | 6 | 2 | 3 |
| M1b (ADR) | 3 | 1 | 0 | 2 |

*(Continued)*

**Table 2.** (Continued)

| *n* | All patients | Patients with pCR | Patients with MPR but without pCR | Patients without MPR |
|---|---|---|---|---|
| | 59 | 31 (53%) | 9 (15%) | 19 (32%) |
| M1b (HEP) | 1 | 0 | 1[b] | 0 |
| M1b (OSS) | 2 | 2 | 0 | 0 |
| M1b (LYM) | 1 | 1 | 0 | 0 |
| M1b (PLE) | 2 | 0 | 1[c] | 0 |
| M1b (PUL) | 2 | 0 | 0 | 2 |
| IVB | 4 (7%) | 1 (3%) | 1 (11%) | 2 (11%) |
| M1c (BRA) | 3 | 1 | 1 | 1 |
| M1c (ADR) | 1 | 0 | 1 | 0 |
| M1c (LYM) | 2 | 0 | 0 | 2 |
| M1a (PUL) | 1 | 1 | 0 | 0 |
| B Treatment | | | | |
| Neoadjuvant immuno(chemo)therapy | | | | |
| Completed per protocol | 58 (98%) | 31 (100%) | 9 (100%) | 18 (95%) |
| irAE as reason for not completing | 1 (2%) | - | - | 1 (6%) |
| Pembrolizumab/pemetrexed/cisplatin | 13 (22%) | 3 (10%) | 2 (22%) | 8 (44%) |
| Pembrolizumab/pemetrexed/carboplatin | 20 (34%) | 11 (35%) | 4 (44%) | 5 (28%) |
| Pembrolizumab/paclitaxel/carboplatin | 6 (10%) | 4 (13%) | 0 | 2 (11%) |
| Pembrolizumab/nab-paclitaxel/carboplatin | 14 (24%) | 10 (32%) | 2 (22%) | 2 (11%) |
| Pembrolizumab mono | 4 (7%) | 2 (6%) | 1 (11%) | 1 (6%) |
| Nivolumab mono | 2 (3%) | 1 (3%) | 0 | 1 (6%) |
| Consolidating immunotherapy | | | | |
| Pembrolizumab | 16 (27%) | 11 (36%) | 2 (22%) | 3 (17%) |
| Resection of oligometastatic sites[d] | | | | |
| Brain (followed by radiotherapy) | 11 | 6 | 2 | 3 |
| Adrenal | 4 | 1 | 1 | 2 |
| Liver | 1 | 0 | 0 | 1 |
| Soft tissue/skin | 1 | 0 | 0 | 1 |
| Lung | 1 | 1 | 0 | 0 |
| SABR of oligometastatic sites (not resected) | | | | |
| Brain | 3 | 1 | 0 | 2 |

*(Continued)*

**Table 2.** (Continued)

| *n* | All patients | Patients with pCR | Patients with MPR but without pCR | Patients without MPR |
|---|---|---|---|---|
| | 59 | 31 (53%) | 9 (15%) | 19 (32%) |
| Bone | 1 | 0 | 0 | 1 |
| C Outcome | | | | |
| Response to IO (RECIST)[e] | | | | |
| Complete response (CR) | 3 (6%) | 3 (10%) | 0 | 0 |
| Partial response (PR) | 47 (76%) | 25 (81%) | 9 (100%) | 13 (68%) |
| Stable disease (SD) | 9 (18%) | 3 (10%) | 0 | 6 (32%) |
| Progression (PD) | 0 | 0 | 0 | 0 |
| Current status | | | | |
| Recurrences | 12 (20%) | 4 (13%) | 1 (11%) | 7 (37%) |
| Local recurrence/mediastinal lymph nodes | 2 | 0 | 0 | 2 |
| Pleura | 2 | 0 | 0 | 2 |
| Lung | 0 | 0 | 0 | 0 |
| Brain | 4 | 2 | 1 | 1 |
| Adrenal | 1 | 1 | 0 | 0 |
| Liver | 2 | 1 | 0 | 1 |
| Bone | 0 | 0 | 0 | 0 |
| Soft tissue | 1 | 0 | 0 | 1 |
| Deaths | 8 (14%) | 3 (10%)[f] | 1 (11%)[g] | 4 (21%)[h] |
| Follow-up of living patients [median, range (months)] | 24.3 (5.5–46.6) | 25.3 (9.2–46.6) | 18.7 (5.5–43.5) | 25.0 (13.8–44.5) |

CRT, chemo-radiotherapy; ECOG, Eastern cooperative oncology group; irAE, immune-related adverse event; LCNEC, large-cell neuroendocrine carcinoma; MPR, major pathological response; NA, not assessed; nab-paclitaxel, nanoparticle albumin-bound paclitaxel; NOS, not otherwise specified; pCR, pathological complete response; PD-L1, programmed-death ligand 1; RECIST, response evaluation criteria in solid tumours; SABR, stereotactic ablative radiotherapy; TPS, tumour-proportion score.

[a]PD-L1 TPS of patients with pCR was significantly higher than PD-L1 of patients without pCR or MPR ($p = 0.030$). PD-L1 of patients with pCR or MPR was significantly higher than PD-L1 of patients without pCR or MPR ($p = 0.047$).

[b]Following IO, the hepatic metastasis was no longer detectable. Therefore, no local treatment was applied.

[c]Cytologically malignant cells in pleural effusion. Following IO, the pleural effusion was completely resolved, and no local treatment was applied.

[d]In seven oligometastatic patients (IVA: two with pleural effusion containing malignant cells, two with solitary bone lesions, one each with metastasis to the contralateral lung, liver, and lymph node), the metastasis did not receive local ablative therapy since the metastatic site was no longer detectable after neoadjuvant immuno(chemo)therapy. In the resected primary lung tumour, four of these patients had pCR, two had MPR, and one had an incomplete response.

[e]Patients with pCR had significantly better responses to IO than patients without pCR or MPR ($p = 0.031$, Mann–Whitney). Patients with pCR or MPR had significantly better responses to IO than patients without pCR or MPR ($p = 0.013$, Mann–Whitney).

[f]One death due to progressive disease, two deaths due to COVID-19 infection without evidence of recurrence.

[g]Death at home of uncertain cause with no evidence of recurrence at last visit.

[h]Two deaths due to progressive disease and two deaths due to pneumonia.

**Table 3.** PD-L1 TPS in the study cohort presented.

| Study cohort | | PD-L1 TPS | | |
|---|---|---|---|---|
| **Stage** | ***n*** | **⩾50%** | **1–49%** | **0** |
| IIB–IIIC | 33 (NA 2) | 16 (52%) | 14 (45%) | 1 (3%) |
| IVA–IVB | 26 (NA 1) | 11 (44%) | 11 (44%) | 3 (12%) |
| Histology | | | | |
| Non-squamous | 40 (NA 2) | 18 (47%) | 17 (45%) | 3 (8%) |
| Squamous | 19 (NA 1) | 9 (50%) | 8 (44%) | 1 (6%) |
| All study patients | **59 (NA 3)** | **27 (48%)** | **25 (45%)** | **4 (7%)** |

PD-L1, programmed-death ligand 1; TPS, tumour-proportion score.

**Table 4.** PD-L1 TPS in an unselected German NSCLC cohort with adenocarcinoma or squamous-cell carcinoma and stage IIB-IVA. Unpublished data for comparison from the Esslingen Cancer registry (KOMPASS).

| Esslingen cohort | | PD-L1 TPS | | |
|---|---|---|---|---|
| **Histology** | ***n*** | **⩾50%** | **1–49%** | **0** |
| Adenocarcinoma | 73 | 21 (29%) | 22 (30%) | 30 (41%) |
| Squamous cell carcinoma | 101 | 18 (18%) | 43 (43%) | 40 (40%) |
| Both histologies | **173** | **39 (22%)** | **65 (37%)** | **70 (40%)** |

PD-L1, programmed-death ligand 1; TPS, tumour-proportion score.

**Table 5.** Pathological response in patients of the study cohort with different PD-L1 TPS.

| Study cohort | | Pathological response | |
|---|---|---|---|
| **PD-L1 TPS (NA 3)** | ***n*** | **MPR** | **pCR** |
| ⩾50% | 27 | 20 (74%) | 16 (59%) |
| 1–49% | 25 | 16 (64%) | 12 (48%) |
| 0% | 4 | 2 (50%) | 1 (25%) |

MPR, major pathological response; pCR, complete pathological response, PD-L1, programmed-death ligand 1; TPS, tumour-proportion score.

31 patients (52.5%) with pCR. Patients with higher PD-L1 TPS had higher rates of pathological response. However, responses were seen in patients with low or negative PD-L1 TPS (Table 5). Patients with MPR had significantly higher PD-L1 TPS than patients without MPR (mean PD-L1 TPS 52% *versus* 31%, $p=0.047$). In patients with PD-L1 TPS ⩾ 50%, pathological response rates in patients receiving neoadjuvant mono-immunotherapy ($n=6$, MPR 84% including pCR 67%) and in patients receiving neoadjuvant immunochemotherapy ($n=21$, MPR 76% including pCR 62%) were similar. No patient with PD-L1 TPS < 50% received mono-immunotherapy.

The pathological response tended to be stronger in patients with localized disease (MPR 73.3% including pCR 63.3%) than in patients with oligometastatic disease (MPR 62.5% including pCR 45.8%). Moreover, in patients with localized disease, the pathological response increased with the number of cycles of neoadjuvant immuno(chemo) therapy. With one or two cycles ($n=8$), 37.5% of patients had MPR, including 12.5% pCR. With three or more cycles ($n=25$), MPR was found in 80%, including 72% pCR ($p=0.0016$ for ⩽ 2 *versus* ⩾ 3 cycles). The investigators assumed that a longer treatment duration was required in patients with advanced disease and opted for at least four cycles in most oligometastatic patients (68.0%), while only 23.5% of patients with localized disease received four cycles (median number of cycles 4.1 and 3.0, respectively, $p=0.0033$). In oligometastatic patients, pCR was found in 50% of patients with ⩾ 4 cycles compared with 37.5% with ⩽ 3 cycles. There was no bias towards more cycles in patients with higher PD-L1 TPS. Patients with 1–3 cycles ($n=32$) had a mean PD-L1 TPS of 43.4%, compared to a mean PD-L1 TPS of 43.1% in patients with ⩾ 4 cycles ($n=24$).

Radiologically, neoadjuvant immuno(chemo) therapy resulted in complete remission (CR) in three patients (5%), partial remission (PR) in 46 (78%), and stable disease (SD) in 10 patients (17%). There was no disease progression. Patients with CR or PR had received more cycles of neoadjuvant immuno(chemo)therapy than patients with SD (3.6 *versus* 2.7 cycles, $p=0.056$). Patients with radiological CR or PR had significantly higher PD-L1 TPS than patients with SD (mean PD-L1 TPS 78% *versus* 47%, $p=0.025$).

Recurrences occurred in 7 of the 33 patients with localized disease (21.2%) and in 5 of the 26 oligometastatic patients (19.2%, n.s.). Significantly, fewer recurrences occurred in patients who had MPR (5/40, 12.5%) than in patients without MPR (7/19, 36.8%, $p=0.042$). There were 2

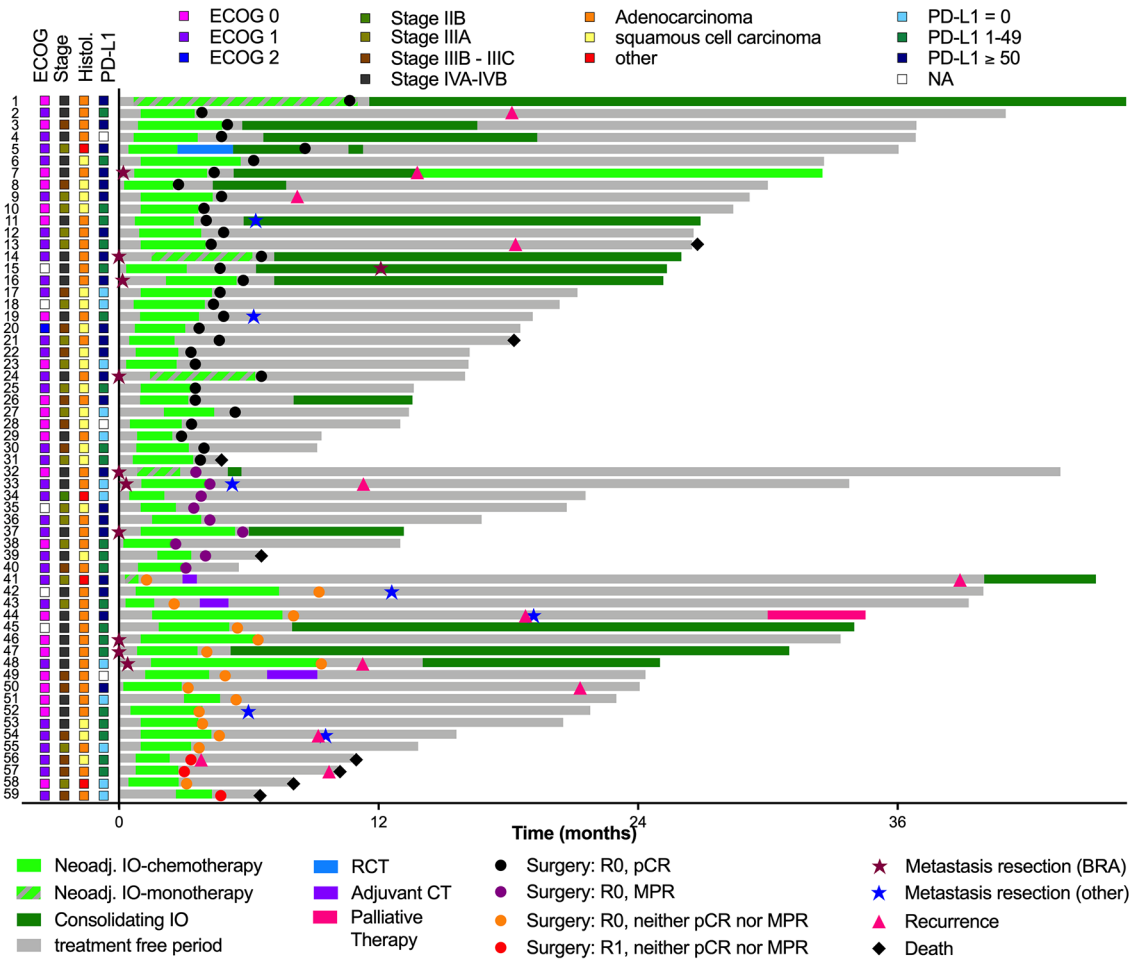


**Figure 1.** Swimmer plot of treatment and survival.
Each bar represents one patient. The left column shows clinical and histological characteristics. Patients 1 – 31 had a pCR. Patients 32 - 40 had MPR, and patients 41 – 59 had an incomplete pathological response. Patients 20 and 31 died of a COVID-19 infection with no evidence of tumour recurrence.
BRA, brain metastasis; consolidating IO, consolidating mono-immunotherapy; CRT, chemo-radiotherapy; CT, chemotherapy; ECOG, Eastern cooperative oncology group performance score; IO-monotherapy, mono-immunotherapy; IO-chemotherapy, immuno-chemotherapy; MPR, major pathological response; NA, not assessed; pCR, pathological complete response; PD-L1, programmed-death ligand 1; TPS, tumour proportion score.

recurrences among the 16 patients who received consolidating immunotherapy (12.5%) compared with 10 recurrences among the 43 patients who did not receive consolidating immunotherapy (23.3%, $p = 0.042$).

After a median follow-up of 24.3 months, PFS at 12 and 24 months was 82.6% and 68.1%, respectively. At these time points, OS was 89.5% and 87.2%, respectively (Figure 3). Two patients with tumour resection (#21 and #31 in the swimmer plot Figure 1) died of COVID-19 at five, respectively, 12 months postoperatively with no evidence of recurrence. With few non-survival events so far, subgroup analysis by pathological response, histology, or PD-L1 TPS did not reveal significant differences in survival (Figure 4). However, patients with oligometastatic disease had better OS. Compared to patients with localized disease, patients with oligometastatic disease had more favourable baseline characteristics with respect to age, performance state, and histology, and their local thoracic stage was less advanced (Table 6). Similarly, a higher number of cycles of neoadjuvant immuno(chemo)therapy was associated with significantly improved OS. Again, compared to patients with $\leqslant 3$ cycles, patients with $\geqslant 4$ cycles had more favourable baseline characteristics with respect to age, performance state, and histology (Table 7), reflecting the ability to tolerate a

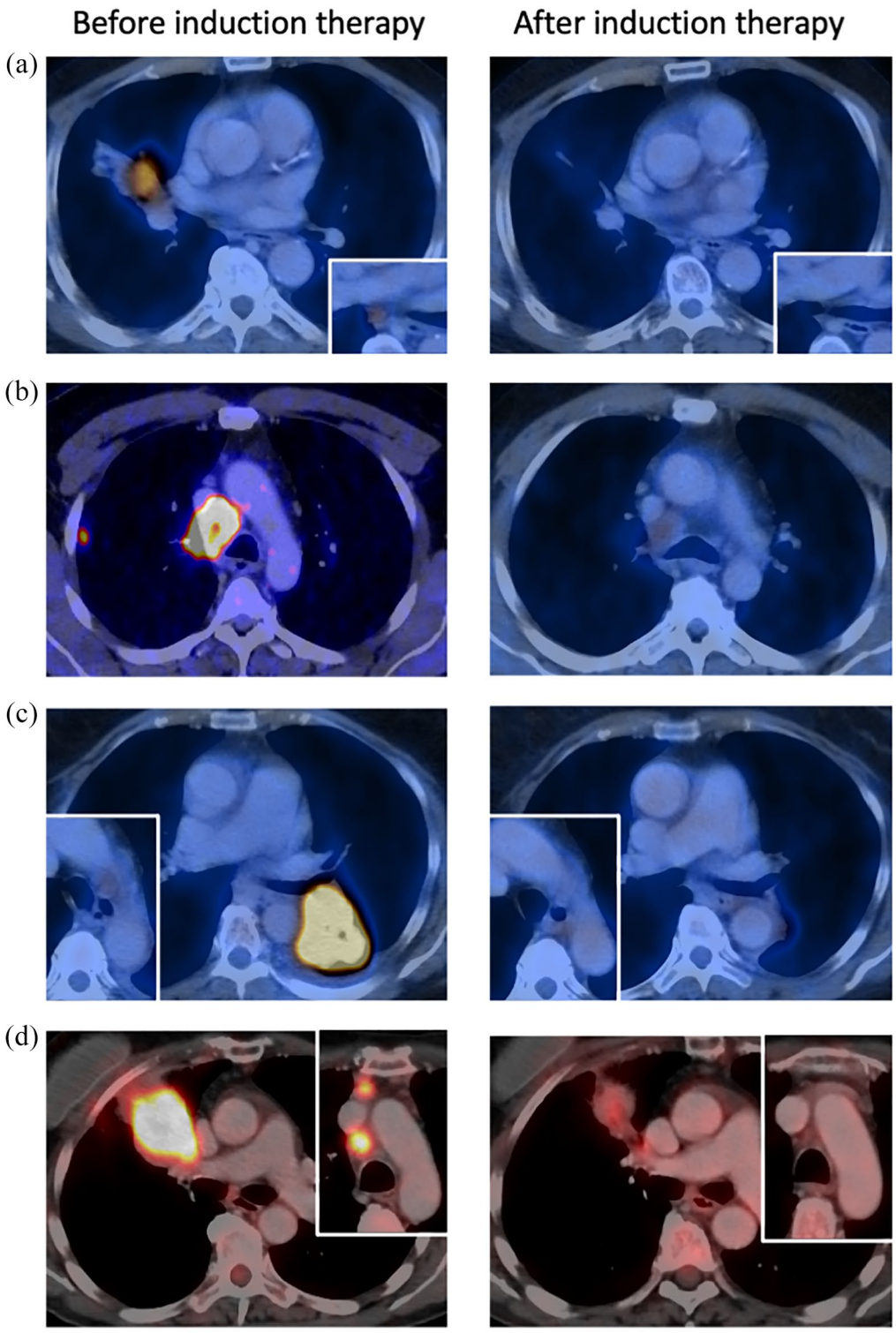


**Figure 2.** Representative examples of PET-CT scans before and after neoadjuvant immuno(chemo)therapy.

prolonged neoadjuvant treatment. However, patients with ⩾4 cycles also had more advanced stage than those with ⩽3 cycles (67% stage IV and 24% stage IV, respectively).

## Discussion

We present a multicentre national retrospective study in a large real-world cohort of patients with localized or oligometastatic NSCLC treated with

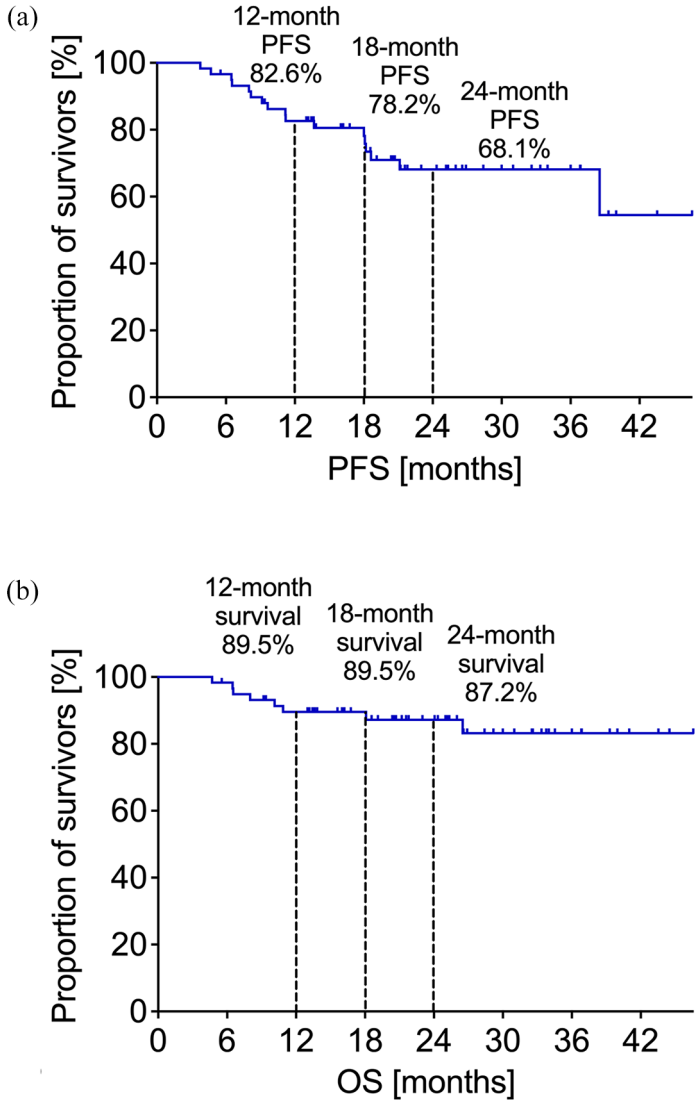


**Figure 3.** Survival: Kaplan-Meier curves of progression-free survival (A) and overall survival (B).

neoadjuvant immuno(chemo)therapy and resection. To our knowledge, ours is the largest cohort of this type reported to date. Of special interest is our sizable cohort of oligometastatic patients ($n=24$), a group of NSCLC patients, for whom to date only few case reports are available.

We found MPR in two-thirds of the patients. The similar pathological responses on neoadjuvant mono-immunotherapy and on neoadjuvant immunochemotherapy in patients with PD-L1 TPS $\geqslant 50\%$ underline the major role of immunotherapy in achieving pathological remission. Although the pathological response rates were numerically slightly lower in oligometastatic patients than in patients with localized disease, in both cohorts they were similar to those reported in recent prospective trials for stage III patients.[7,13,15,16] Interestingly, in our cohort, OS was better in oligometastatic patients than in patients with localized disease. Improved survival may be partly accounted for by better prognostic baseline characteristics, including less advanced local thoracic tumour stage. Furthermore, the abscopal effect of radiotherapy to the oligometastatic sites on immunotherapy, which has recently been confirmed for pembrolizumab in NSCLC, may have contributed to improved survival in oligometastatic disease.[37] Thus, our multicentre real-world data support the use of neoadjuvant immuno(chemo)therapy in the important subgroup of oligometastatic

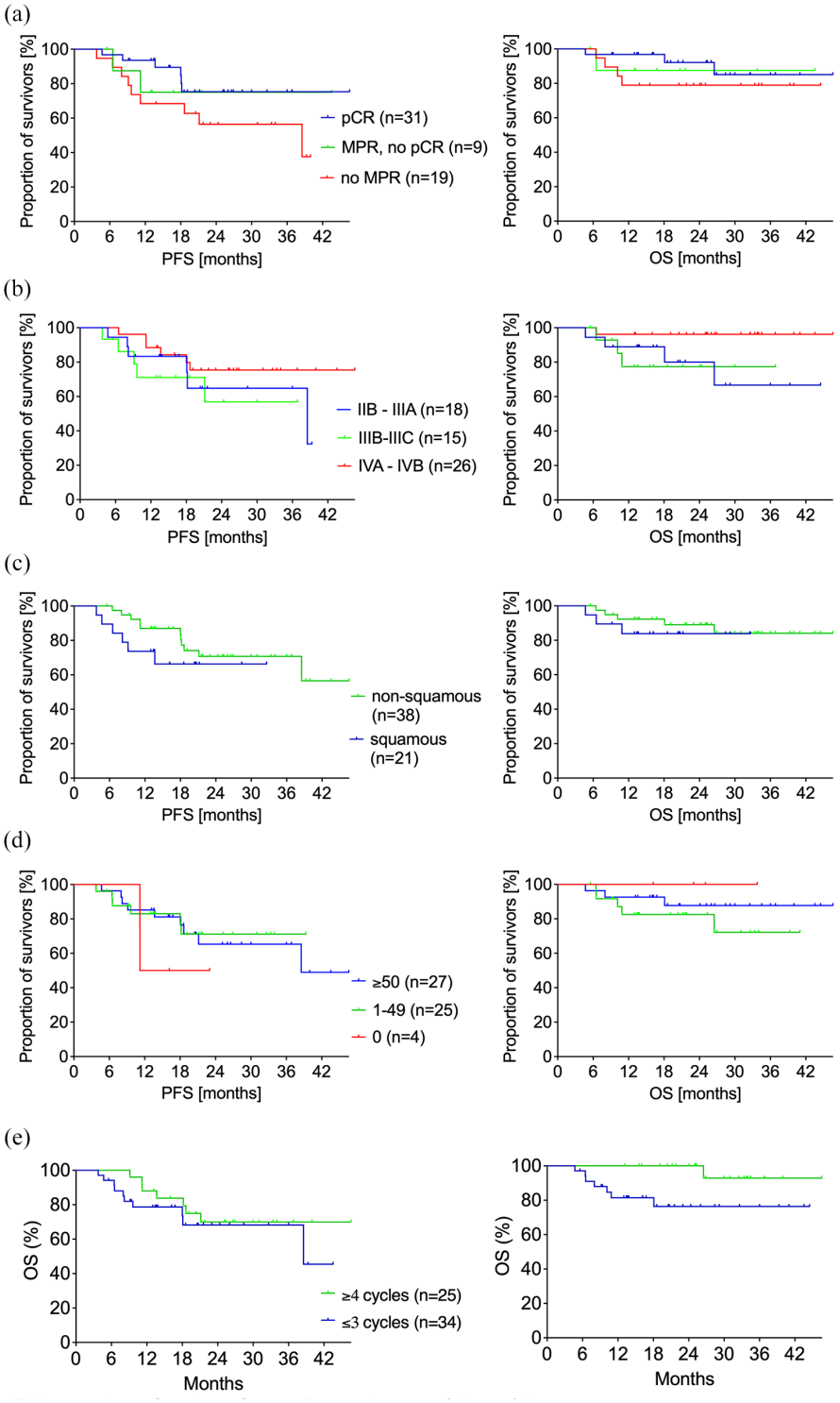


**Figure 4.** Subgroup analysis: Kaplan-Meier curves of progression-free survival (left column) and overall survival (right column).
A. Survival by pathological response. B. Survival by stage. Overall survival was significantly improved in patients with stage IV (oligometastatic) compared to localized patients (HR 0.22, CI 0.054 to 0.88, p=0.032). C. Survival by histology. Patients with adeno-squamous histology were assigned to the squamous subgroup. D. Survival by PD-L1 TPS. E. Survival by number of cycles of neoadjuvant immuno(chemo)therapy. Overall survival was significantly improved in patients receiving ↗4 cycles compared to those receiving ↖3 cycles (HR 0.22, CI 0.055 to 0.90, p=0.035). There were no other significant differences in survival.
MPR: major pathological response; pCR: pathological complete response; PD-L1: programmed-death ligand 1; TPS tumour proportion score.

**Table 6.** Baseline characteristics according to stage.

| | All patients | Patients with localized NSCLC | Patients with oligometastatic NSCLC |
|---|---|---|---|
| ***n*** | **59** | **33 (56%)** | **26 (44%)** |
| Mean number of cycles | 3.4 | 2.9 | 4.1 |
| Age (mean, range)[a] | 63.6 (47.5–84.5) | 65.7 (47.5–84.5) | 61.0 (50.6–69.0) |
| Gender | | | |
| Male | 30 (51%) | 18 (55%) | 12 (46%) |
| Female | 29 (49%) | 15 (45%) | 14 (54%) |
| Performance status | NA 1 (2%) | | NA 1 (4%) |
| ECOG 0 | 25 (43%) | 11 (33%) | 14 (56%) |
| ECOG 1 | 32 (55%) | 21 (64%) | 11 (44%) |
| ECOG 2 | 1 (2%) | 1 (3%) | 0 |
| Smoking status | NA 3 (5%) | NA 1 (3%) | NA 2 (8%) |
| Never smoker | 3 (5%) | 2 (6%) | 1 (4%) |
| Ever smoker | 53 (95%) | 30 (94%) | 23 (96%) |
| Histology | | | |
| Adenocarcinoma | 36 (61%) | 14 (42%) | 22 (85%) |
| Squamous cell carcinoma | 19 (32%) | 15 (45%) | 4 (15%) |
| Adenosquamous carcinoma | 2 (3%) | 2 (6%) | 0 |
| LCNEC | 1 (2%) | 1 (3%) | 0 |
| NOS | 1 (2%) | 1 (3%) | 0 |
| PD-L1 (TPS) | NA 3 (5%) | NA 2 (6%) | NA 1 (4%) |
| 0% | 4 (7%) | 1 (3%) | 3 (12%) |
| 1–49% | 25 (45%) | 14 (45%) | 11 (44%) |
| 50–100% | 27 (48%) | 16 (52%) | 11 (44%) |
| Stage (UICC 8) | | | Local thoracic stage (NA 2, 8%) |
| IIB | 1 (2%) | 1 (3%) | (IB–IIB) 8 (33%) |
| IIIA | 17 (29%) | 17 (52%) | 8 (33%) |
| IIIB | 11 (19%) | 11 (33%) | 6 (25%) |
| IIIC | 4 (7%) | 4 (12%) | 2 (8%) |
| IVA | 22 (37%) | 0 | 22 (85%) |
| IVB | 4 (7%) | 0 | 4 (15%) |

ECOG, Eastern cooperative oncology group; LCNEC, large-cell neuroendocrine carcinoma; NA, not assessed; NOS, not otherwise specified; PD-L1, programmed-death ligand 1; TPS, tumour-proportion score.
[a]Patients with oligometastatic disease were significantly younger than patients with localized disease ($p = 0.025$).

**Table 7.** Baseline characteristics according to number of cycles of neoadjuvant immuno(chemo)therapy.

| | All patients | Patients with ⩽3 cycles | Patients with ⩾4 cycles |
|---|---|---|---|
| ***n*** | **59** | **34 (58%)** | **25 (42%)** |
| Mean number of cycles | 3.4 | 2.6 | 4.6[a] |
| Age (mean, range)[b] | 63.6 (47.5–84.5) | 65.5 (47.5–84.5) | 61.0 (50.9–73.6) |
| Gender | | | |
| Male | 30 (51%) | 16 (47%) | 14 (56%) |
| Female | 29 (49%) | 18 (53%) | 11 (44%) |
| Performance status | NA 1 (2%) | NA 1 (3%) | |
| ECOG 0 | 25 (43%) | 11 (33%) | 14 (56%) |
| ECOG 1 | 32 (55%) | 21 (64%) | 11 (44%) |
| ECOG 2 | 1 (2%) | 1 (3%) | 0 |
| Smoking status | NA 3 (5%) | | NA 3 (11%) |
| Never smoker | 3 (5%) | 3 (9%) | 0 |
| Ever smoker | 53 (95%) | 31 (91%) | 22 (100%) |
| Histology | | | |
| Adenocarcinoma | 36 (61%) | 15 (44%) | 21 (84%) |
| Squamous cell carcinoma | 19 (32%) | 15 (44%) | 4 (16%) |
| Adenosquamous carcinoma | 2 (3%) | 2 (6%) | 0 |
| LCNEC | 1 (2%) | 1 (3%) | 0 |
| NOS | 1 (2%) | 1 (3%) | 0 |
| PD-L1 (TPS) | NA 3 (5%) | NA 2 (6%) | NA 1 (3%) |
| 0% | 4 (7%) | 2 (6%) | 2 (8%) |
| 1–49% | 25 (45%) | 15 (47%) | 10 (42%) |
| 50–100% | 27 (48%) | 15 (47%) | 12 (50%) |
| Stage (UICC 8) | | | |
| IIB | 1 (2%) | 1 (3%) | 0 |
| IIIA | 17 (29%) | 15 (44%) | 2 (8%) |
| IIIB | 11 (19%) | 8 (24%) | 3 (12%) |
| IIIC | 4 (7%) | 2 (6%) | 2 (8%) |
| IVA | 22 (37%) | 8 (24%) | 14 (56%) |
| IVB | 4 (7%) | 0 | 4 (11%) |

ECOG, Eastern cooperative oncology group; LCNEC, large-cell neuroendocrine carcinoma; NA, not assessed; NOS, not otherwise specified; PD-L1, programmed-death ligand 1; TPS, tumour-proportion score.
[a]22 patients received 4 cycles, only 3 patients received more than 4 cycles.
[b]Patients with ⩾4 cycles were significantly younger than patients with ⩽3 cycles ($p = 0.038$).

NSCLC as part of curative-intent treatment and confirm the data from prospective studies in patients with localized disease (Table 1) and also our own monocentre prospective data.[24]

The lack of an effect of pathological response or PD-L1 on survival is likely due to immature data and to deaths due to COVID-19 infection. However, patients with MPR had fewer recurrences supporting the role of pathological response as surrogate marker of survival. The association of higher PD-L1 TPS with both radiological response and pathological response supports the role of PD-L1 as biomarker for immunotherapy in NSCLC. The higher PD-L1 scores in the population presented here compared to unselected real-world NSCLC patients shows that PD-L1 TPS was used for the selection of patients for neoadjuvant immuno(chemo)therapy. However, a high PD-L1 TPS was not required for inclusion. Relevant pathological responses were also seen in patients with PD-L1 TPS below 50% who represent more than half of the patients analysed in our cohort. The selection is likely due to the fact that PD-L1 TPS is an established biomarker in metastasized NSCLC which in a real-world setting was assumed to predict response to immunotherapy in localized disease as well. Our result shows similar responses in localized and oligometastasized stages and thus supports this hypothesis.

With respect to duration of neoadjuvant treatment, our data on pathological response, on radiological response, and on OS suggest that four cycles of neoadjuvant may be given. In patients with localized disease, and in patients with squamous histology or poorer performance state, three cycles might be appropriate. In our cohort, the occurrence of significantly fewer recurrences in patients who received consolidating immunotherapy is likely due to an important selection bias, although it is in line with the beneficial effect of consolidating immunotherapy after definitive chemoradiotherapy (PACIFIC)[4] and resection (IMPOWER 110).[38]

Of note, only 5% of patients achieved a radiological complete response after neoadjuvant (chemo) immunotherapy. This contrasts with the pCR of 52.5%. The discrepancy between radiological and histopathological response was also observed in earlier studies.[15,39] However, it is important to point out, that the predictive value of CT is low, and that better staging strategies are urgently needed. Whether PET scan might be helpful or whether circulating tumour DNA (ctDNA) analysis from peripheral blood is more sensitive should be investigated in future trials.[40–43]

Strengths of our study include the systematic multicentre analysis of the largest cohort of real-world NSCLC patients with neoadjuvant immuno(chemo)therapy and the inclusion of the largest cohort with oligometastatic NSCLC in this setting to date. Limitations of our study include the small sample size, the short follow-up period in a potentially curative setting with few non-survival events, the inherent patient heterogeneity, the lack of a central assessment of PD-L1 TPS, the selection bias towards NSCLC with high PD-L1 TPS, and the lack of a randomized control group. Because of the heterogeneity, no firm conclusions with respect to the optimal number of cycles of neoadjuvant treatment can be drawn. However, due to the heterogeneity, particularly in oligometastatic patients, a randomized confirmation may not be realistic. This emphasizes the value of our real-world data, which require confirmation with larger patient numbers and longer follow-up. Of note, all treatments were performed in a real-world setting. Therefore, our findings may be translated into routine clinical care offering the chance of better curative-intent treatment to a relevant subgroup of patients with NSCLC, including oligometastatic disease.

## Conclusion

In routine clinical practice, resection after neoadjuvant immuno(chemo)therapy in localized or oligometastatic NSCLC is feasible, with high rates of pCR or MPR similar to those in clinical trials. A higher PD-L1 TPS and longer neoadjuvant immuno(chemo)therapy were associated with improved pathological response rates. Patients with MPR had fewer recurrences than those without MPR. The early survival data are encouraging.

## Author contributions

**Martin Faehling:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

**Hanno Witte:** Data curation; Writing – review & editing.

**Martin Sebastian:** Conceptualization; Data curation; Writing – review & editing.

**Matthias Ulmer:** Data curation; Writing – review & editing.

**Rainer Sätzler:** Data curation; Writing – original draft; Writing – review & editing.

**Konrad Steinestel:** Data curation; Investigation; Writing – review & editing.

**Wolfgang M. Brückl:** Conceptualization; Data curation; Writing – review & editing.

**Georg Evers:** Data curation; Writing – review & editing.

**Christian Meyer zum Büschenfelde:** Conceptualization; Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

**Annalen Bleckmann:** Conceptualization; Data curation; Investigation; Writing – original draft; Writing – review & editing.

## Conflict of interest statement

M.F. has received honoraria for lectures and participated as PI in clinical trials of AstraZeneca, Roche, MSD, and BMS. M.U. has received honoraria for consulting from AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Lilly, MSD, Pfizer, and Roche. M.S. reports honoraria and lecture fees by Novartis, BMS, Roche, Lilly, Boehringer Ingelheim, Pfizer, AstraZeneca, Takeda, Sanofi, MSD, Amgen, Sanofi, Janssen-Cilag, Tesaro, BionTech, CureVac, Sanofi, and Amgen. W.M.B. has received honoraria for consulting from AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Lilly, MSD, Pfizer Roche Pharma, and Sanofi. C.M.z.B. has received honoraria for consulting from AstraZeneca, BMS, Pfizer, Amgen, Boehringer Ingelheim, MSD, and Celgene and has received research funding from AstraZeneca, GSK, and Roche. A.B. has received honoraria for consulting and lectures from AstraZeneca, BMS, Boehringer Ingelheim, MSD, Celgene, Merck, Alexion, Gilead, Novartis, Servier, Roche Takeda, AstraZeneca, Lilly, and BeiGene. H.W., M.S., R.S., K.S., and G.E. report no competing interests.

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## Ethics approval and consent to participate

The study was approved by the ethics committee of the Baden-Württemberg Medical Association (Landesärztekammer Baden-Württemberg) (F-2017-004, F-2019-092) and ethics committee of the Westphalia-Lippe Medical Association (Ärztekammer Westphalen Lippe und University Münster) (2020-964-b-S). All patients gave written informed consent for the collection of clinical data for research purposes. The study was performed in accordance with the Declaration of Helsinki.

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## Data availability

The original data are available upon reasonable request as far as legally and ethically possible.

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