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First-line *nab*-paclitaxel plus carboplatin for patients with advanced non-small cell lung cancer: Final results of the NEPTUN study

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Abstract

Real-world data on the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) are still limited. The NEPTUN study evaluated effectiveness and safety of first-line *nab*-paclitaxel (Abraxane) plus carboplatin (*nab*-P/C) in patients with advanced NSCLC in routine clinical practice in Germany. Patients included in our study were aged ≥18 years, diagnosed with locally advanced or metastatic NSCLC and with decision for first-line *nab*-P/C in routine clinical practice. Primary objective was 6-month progression-free survival rate (PFS6), secondary objectives included overall survival (OS), overall response rate (ORR) and safety. From 2016 to 2019, 408 patients from 75 sites were enrolled. PFS6 was 39.5% (95% CI: 34.2-44.8), median PFS was 5.1 months (95% CI: 4.6-5.6), ORR was 42.9% (95% CI: 37.7-48.2). Median OS was 10.5 months (95% CI: 9.2-11.6). In subgroup analyses, median OS for squamous vs non-squamous histology was 11.5 months (95% CI: 9.2-13.8) vs 9.8 months (95% CI: 8.1-11.3) and for patients aged ≥70 vs <70 years median OS was 12.4 months (95% CI: 9.8-15.1) vs 9.6 months (95% CI: 7.7-11.1). Adverse events (AEs) related to *nab*-paclitaxel were reported in 247 (66.4%) patients, while carboplatin-related AEs were documented in 224 (60.2%) patients. Most frequently related AEs were leukopenia (22.3%) for *nab*-paclitaxel and anemia (20.2%) for carboplatin. *Nab*-P/C-related deaths were reported in 2 (0.5%) patients (sepsis and neutropenic sepsis). No new or unexpected safety signals emerged.

Abbreviations: ADR, adverse drug reaction; AE, adverse event; ALK, anaplastic lymphoma kinase; ASCO, American Society of Clinical Oncology; BRAF, proto-oncogene B-raf; CI, confidence interval; CR, complete response; CrCl, creatinine clearance; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EOS, end of study; EOT, end of treatment; EQ-5D-5L, EuroQoL 5-dimension 5-level; ESMO, European Society for Medical Oncology; EWB, Emotional Well-Being; FACT-G, functional assessment of cancer therapy—general; FACT-L, functional assessment of cancer therapy—lung; FAS, full analysis set; FWB, functional well-being; HR, hazard ratio; HRQoL, health-related quality of life; ICI, immune checkpoint inhibitor; LCS, lung cancer subscale; max, maximum; MedDRA, Medical Dictionary for Regulatory Activities; min, minimum; *nab*-P/C, *nab*-paclitaxel/carboplatin; NIS, non-interventional study; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; OS12, 12-month overall survival rate; PD, progressive disease; PD1, programmed cell death 1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PFS6, 6-month progression-free survival rate; PR, partial response; PRO, patient-reported outcome; PS, performance status; PWB, physical well-being; QoL, quality of life; RI, renal impairment; ROS1, proto-oncogene ROS1; RWD, real-world data; RWE, real-world evidence; SAF, safety analysis set; SD, stable disease, standard deviation; SmPC, summary of product characteristics; SWB, social/family well-being; TEAE, treatment emergent adverse event; TOI, trial outcome index; VAS, visual analogue scale.

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These results support the effectiveness and safety of first-line *nab*-P/C in patients with advanced NSCLC reported in the pivotal trial and highlight the clinical value of this regimen in the real-world setting.

KEYWORDS
carboplatin, first-line, *nab*-paclitaxel, non-small cell lung carcinoma, real-world

What's new?

Non-small cell lung cancer (NSCLC) patients often are diagnosed in advanced stages of disease, at which point, in cases without targetable mutations, first-line therapy typically entails platinum-based chemotherapy. A recommended therapy is albumin-bound paclitaxel plus carboplatin combination (*nab*-P/C). Here, the authors evaluated the use of first-line *nab*-P/C therapy in a real-world setting in patients with locally advanced or metastatic NSCLC. Results show that survival was improved among *nab*-P/C-treated patients, with better outcomes observed particularly among patients age 70 and older and in those with mild to moderate renal impairment. Improvements in tumor response, independent of histological subtype, were also observed.

1 | INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) accounts for 85% to 90% of all lung cancer cases.[1] Histologically, NSCLC is characterized as squamous cell carcinoma or non-squamous cell carcinoma (adenocarcinoma and large-cell carcinoma).[2,3] Overall prognosis is poor.[4] The majority of patients is diagnosed with advanced, unresectable or metastatic disease. For stage IVA and IVB NSCLC (hereafter referred to as metastatic NSCLC), the 5-year survival rate is ~10% and <1%, respectively.[5] Despite improvement over time, median OS is < 2 years and mortality remains high during the first year after diagnosis.

Systemic therapy for advanced NSCLC consists of chemotherapy, targeted therapy, immunotherapy or a combination of these.[6] Treatment options for patients with genetic aberrations have markedly improved following development of tyrosine kinase inhibitors. However, only a small proportion of patients currently benefits from targeted therapies against disease-evoking alterations in genes like epidermal growth factor (EGFR), anaplastic lymphoma kinase (ALK), proto-oncogene ROS1 or BRAF due to the relatively low mutation frequency of NSCLC.[7,8] In recent years, immunotherapy has become the standard of care for NSCLC patients, especially for patients with elevated (≥50%) PD-L1 expression (pembrolizumab monotherapy[9,10]) or independent of PD-L1 expression level in combination with supportive chemotherapy as described in pivotal phase 3 trials.[11] Even though more recent treatments based on histology and molecular alterations including immune checkpoint inhibitors (ICI) are preferred as they are beneficial for patients with specific molecular subtypes,[12,13] chemotherapeutic combinations still play a major role in first-line treatment. In general, the first-line therapy for patients with advanced NSCLC without any targetable mutations is platinum-based chemotherapy. The American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) recommend an albumin-bound paclitaxel plus carboplatin combination (*nab*-P/C) for patients with advanced NSCLC without druggable alteration and independent of PD-(L)1 expression.[14,15] For patients with high PD-L1 expression (TPS ≥50%) and absence of contraindications to immune checkpoint therapies, single-agent pembrolizumab (Keytruda) is recommended, while for patients with either negative (0%) or low positive (1%-49%) PD-L1 expression, pembrolizumab/carboplatin/pemetrexed, atezolizumab/carboplatin/nab-paclitaxel or atezolizumab/carboplatin/paclitaxel/bevacizumab is recommended. *Nab*-P/C was approved for first-line treatment of advanced NSCLC in 2012. In a pivotal phase 3 trial comparing solvent-based paclitaxel/carboplatin with *nab*-P/C, *nab*-P/C showed an increased overall response rate (ORR) mainly observed in patients with squamous NSCLC while at the same time patients suffered less from neuropathy and arthralgia.[16] The reduction of neuropathy symptoms observed in patients treated with *nab*-P/C led to a significant improvement in quality of life (QoL). The ABOUND studies examining patients who are elderly or with poor performance status treated with *nab*-P/C reported improved PFS and ORR when patients aged ≥70 years were allowed a 1-week break between *nab*-P/C treatment doses and showed favorable tolerability both in elderly patients as well as patients with ECOG performance status (PS) 2.[17,18] However, real-world data on effectiveness and patient-reported outcomes for the *nab*-P/C regimen in patients with advanced NSCLC in Germany are scarce.

Thus, the NEPTUN study was designed to evaluate effectiveness, safety and health-related and overall QoL (HRQoL) of NSCLC patients receiving first-line *nab*-P/C in routine clinical practice in Germany.

2 | PATIENTS AND METHODS

2.1 | Study design and patient eligibility

NEPTUN was a non-interventional, prospective, observational study conducted in Germany. The study was designed to assess effectiveness, safety and patient-reported outcomes (PROs) on HRQoL in patients

receiving first-line *nab*-P/C for advanced/metastatic NSCLC in routine clinical practice.

Eligible patients were aged ≥18 years and diagnosed with locally advanced and unresectable or metastatic NSCLC. The decision for *nab*-P/C prescription was clearly separated from and prior to the decision to include patients into the study. A retrospective inclusion for up to 4 weeks following start of study treatment was permitted. Between August 2016 and June 2019, 408 patients were enrolled in 75 practices and hospitals, of these, 372 patients were treated first-line with *nab*-P/C according to Summary of Product Characteristics (SmPC) of Abraxane in routine clinical practice.

2.2 | Primary and secondary study objectives

Primary objective was 6-month progression-free survival rate (PFS6). Secondary objectives were progression-free survival (PFS), overall survival (OS) and overall response rate (ORR). Additionally, the occurrence of adverse events (AEs) and PROs on HRQoL using the EQ-5D-5L and FACT-L questionnaires were evaluated.

2.3 | Observational period

The treatment observation period lasted from the first until the last dose of *nab*-paclitaxel (ie, end of treatment, EOT). The follow-up period comprised a 30-day safety follow-up period (except for severe AEs [SAEs], which were to be followed until recovered, recovered with sequelae, not recovered [death due to another cause] or death due to the SAE) and documentation of survival status until death or end of study (EOS, 24 months after last-patient-in).

2.4 | Treatment and study procedures

Patients received study treatment according to routine clinical practice and current German SmPC of Abraxane. The decision for first-line *nab*-P/C treatment was at the discretion of the respective treating physician and was clearly separated from and prior to the decision to include patients in the study.

Tumor response was assessed by the respective treating physician according to local standards and routine clinical practice. Documentation of tumor response continued in the follow-up period for patients who had not progressed at EOT and lasted until progression or start of next antineoplastic therapy.

AEs were to be reported from day of first administration of *nab*-paclitaxel until 30 days after the last administration of *nab*-paclitaxel.

2.5 | Evaluation of PROs on HRQoL

Patients had to provide separate consent for participation in the questionnaire project. HRQoL was assessed at baseline before start of therapy, at week 6, week 12 and then every 3 months until progressive disease (PD) or start of next antineoplastic therapy (only for patients who had not progressed at EOT) by PRO using the questionnaires EQ-5D-5L and FACT-L. Additionally, patients were also asked to complete the questionnaires at EOT and at PD.

The EQ-5D-5L questionnaire is a standardized measure of health comprising questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each rated on a 5-level Likert-type scale (no problems, slight problems, moderate problems, severe problems, extreme problems).[19] Additionally, the EQ visual analogue scale (VAS) records the patient's health status on a vertical 20-cm-visual analogue scale calibrated from "the worst health you can imagine" (score 0) to "the best health you can imagine" (score 100). The EQ-5D-5L health states can also be converted into a single index value which reflects the overall health state according to the preferences of the general population of a country/region. The FACT-L questionnaire covers four general QoL domains (physical well-being [PWB], social/family well-being [SWB], emotional well-being [EWB] and functional well-being [FWB]) based on the FACT-G questionnaire and a lung cancer subscale (LCS; symptoms, cognitive function and regret of smoking).[20] Subscale scores are added to obtain total scores, that is, FACT-G (sum of PWB, SWB, EWB and FWB) and FACT-L (sum of PWB, SWB, EWB, FWB and LCS). Alternative scoring includes the Trial Outcome Index (TOI), which is the sum of PWB, FWB and LCS.

2.6 | Statistical analyses

Descriptive statistical analyses were performed for all parameters and were explorative in nature. Effectiveness was evaluated in all patients who had received at least one dose of *nab*-P/C and for whom at least one information for assessing effectiveness (defined as documented tumor assessment including documentation of PD in follow-up or EOT/EOS with reason "tumor progression" or documented death) after the first application is documented. Pre-defined clinically relevant subgroups within the FAS were: ECOG PS score at baseline (ECOG PS 0/1 [n = 258] vs ECOG PS ≥2 [n = 71]), age at date of informed consent (≥70 years [n = 133] vs <70 years [n = 226]), histology of primary tumor at initial diagnosis (squamous [n = 146] vs non-squamous cell carcinoma [n = 213]) and renal impairment (RI) at baseline (normal kidney function; [CrCl ≥90 mL/min; n = 132] vs mild RI [CrCl ≥60 to <90 mL/min; n = 133] vs moderate RI [CrCl ≥30 to <60 mL/min; n = 62] vs severe RI [CrCl <30 mL/min; n = 1]). Time-to-event analysis variables (PFS and OS) and their fixed-time estimators (PFS6 and 12-month OS rate [OS12]) were analyzed for the whole patient population and aforementioned subgroups using the Kaplan-Meier method. PFS was defined as the time from start of therapy to date of documented PD or death due to any cause, whichever came first. Patients with no event were censored at the date of last contact or at the date of start of the subsequent systemic antineoplastic therapy, whichever occurred first. Patients having started a subsequent systemic therapy before documented PD were censored at the start date of the subsequent therapy. Treatment with subsequent

carboplatin monotherapy after end of treatment with *nab*-paclitaxel was not considered for censoring. OS was defined as the time from start of therapy to date of death due to any cause. Patients with no documented date of death were censored at the last date known to be alive. For PFS and OS, hazard ratios (HRs) for predefined prognostic covariates were estimated using a multivariable Cox regression analysis. ORR was defined as proportion of patients with complete response (CR) or partial response (PR) as best response. DCR was defined as proportion of CR, PR or stable disease (SD) or non-PD/non-CR. The safety analysis set comprised all patients who had received at least one dose of *nab*-paclitaxel and for whom at least one post-baseline safety assessment (ie, AEs, safety laboratory, vital signs, physical examination) had been documented after first application. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 and severity was graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.[21] An AE was classified as treatment-emergent AE (TEAE) if it was temporarily related to the study treatment, that is, having emerged or worsened in the on-treatment period defined as the time from day of first dose of *nab*-paclitaxel to 30 days after last dose of *nab*-paclitaxel. Only AEs classified as TEAEs were included in the analysis. Relative dose intensity was calculated based on the recommended dose according to SmPC. Treatment duration was calculated as the time from first application of study medication to the treatment end date (last application date plus 21 days for carboplatin or last application date plus 7 days for *nab*-paclitaxel). Scores for scales, subscales and single items of the HRQoL questionnaires EQ-5D-5L and FACT-L were calculated according to respective manuals.

3 | RESULTS

3.1 | Patients

Between August 2016 and June 2019, 408 patients had been enrolled. Of those, 372 patients treated first-line with *nab*-P/C according to SmPC were evaluated for safety (safety analysis set—SAF). Exactly 359 patients qualified for effectiveness analysis (full analysis set—FAS) since they had at least one documented effectiveness assessment (Figure 1).

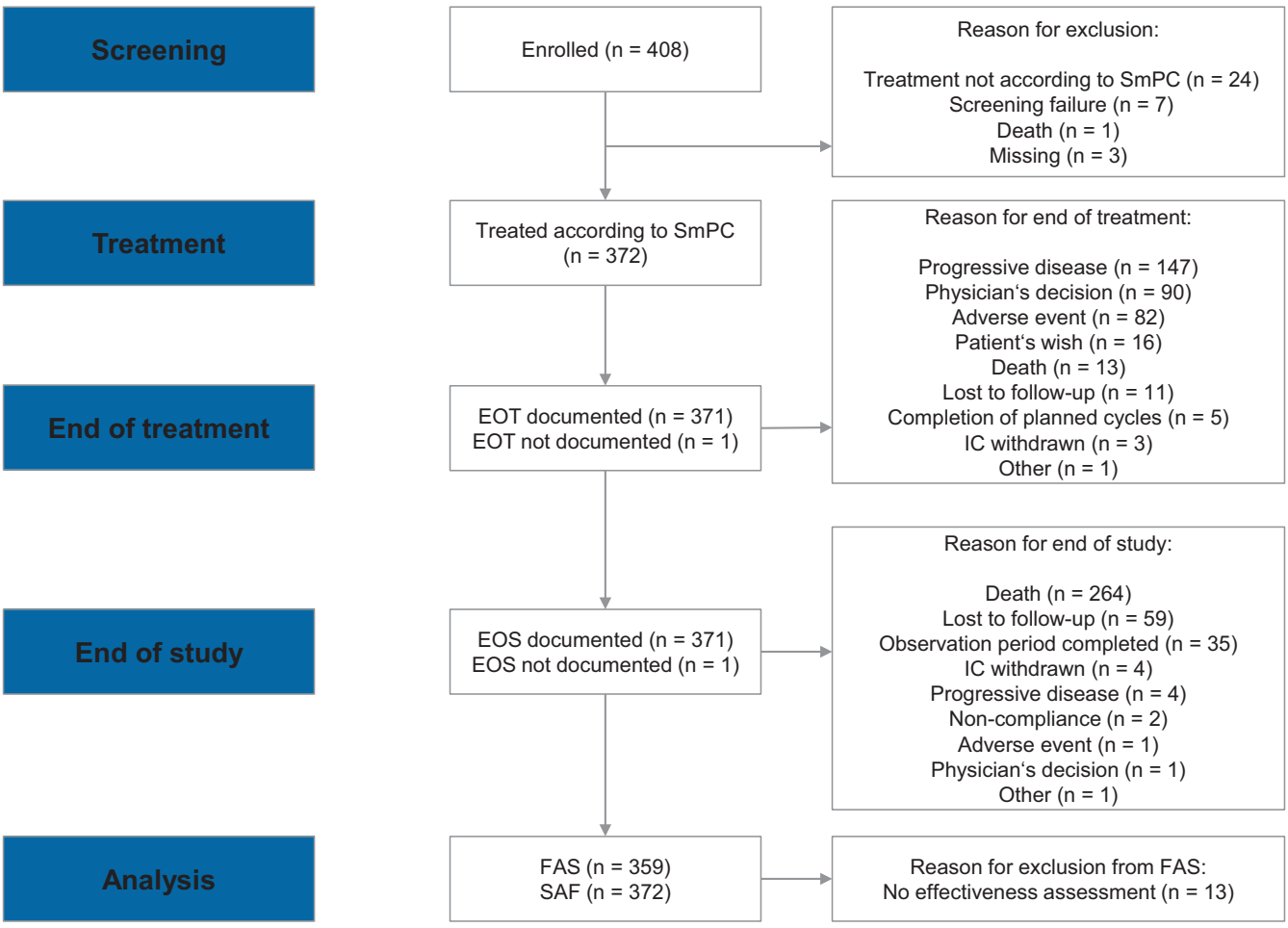


FIGURE 1 Patient disposition–CONSORT diagram. EOS, end of study; EOT, end of treatment; FAS, full analysis set; IC, informed consent; n, number; SAF, safety analysis set; SmPC, summary of product characteristics. "EOT/EOS not documented" or reason for exclusion "missing": study site was closed before documentation of patients had been completed.

TABLE 1 Baseline patient and tumor characteristics.

Characteristic	Total (N = 359) n	%
Age at date of informed consent [years]		
Median	67.6	
Range	44-87	
<70	226	63.0%
≥70	133	37.0%
Sex		
Male	255	71.0%
Female	104	29.0%
ECOG PS, n (%)		
0	92	25.6%
1	166	46.2%
2	62	17.3%
3	9	2.5%
Missing	30	8.4%
Histology of primary tumor		
Adenocarcinoma	177	49.3%
Squamous cell carcinoma	146	40.7%
Large cell carcinoma	20	5.6%
Other	16	4.5%
Locally advanced disease[a]		
Yes	298	83.0%
No	61	17.0%
Distant metastases[b]		
Yes	300	83.6%
No	59	16.4%
Number of metastatic sites, n (%)		
0	59	16.4%
1	155	43.2%
2-3	126	35.1%
≥4	19	5.3%
Localization of metastases (>5% of patients)		
Lymph nodes, distal	93	25.9%
Bones	91	25.3%
Liver	64	17.8%
Brain	56	15.6%
Lung, contralateral lobe	56	15.6%
Adrenal gland	33	9.2%
Pleural effusion	25	7.0%
Renal impairment (RI)		
No RI	132	36.8%
Mild RI	133	37.0%
Moderate RI	62	17.3%
Severe RI	1	0.3%
Smoking status		
Former smoker	176	49.0%
Current smoker	112	31.2%
Never smoker	70	19.5%
Missing	1	0.3%

Note: Renal impairment (RI) at baseline; no RI: CrCl ≥90 mL/min; mild RI: CrCl ≥60 to <90 mL/min; moderate RI: CrCl ≥30 to <60 mL/min; severe RI: CrCl <30 mL/min. Thirty-one patients were excluded due to missing values for creatinine clearance.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N/n, number; PS, performance status; RI, renal impairment.

[a]Displayed are the answers to the question "Does the patient present locally advanced/inoperable disease at baseline?"

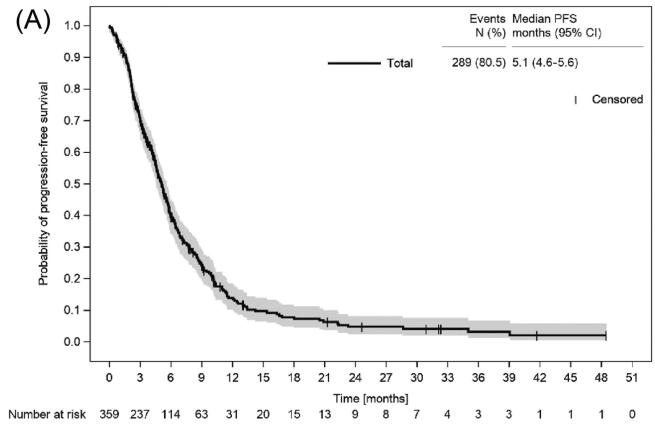
[b]Displayed are the answers to the question "Does the patient present metastases at baseline?"

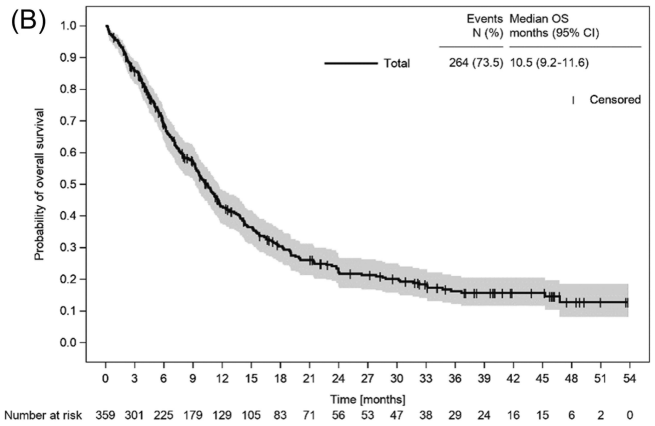
The median age of patients was 67.6 years (min 44, max 87 years) and the majority (63.0%) was younger than 70 years. Patients were predominantly male (71.0%), current or former smokers (80.2%) and presented with an ECOG PS ≤1 (71.8%). The most common histology was adenocarcinoma (49.3%) followed by squamous cell carcinoma (40.7%). A total of 300 patients (83.6%) had distant metastases at baseline, with distal lymph nodes and bones most frequently affected (25.9% and 25.3%), followed by liver (17.8%) and brain (15.6%). The patient characteristics and demographics at baseline are summarized in Table 1.

3.2 | Effectiveness

3.2.1 | Progression-free survival

PFS6 was 39.5% (95% CI: 34.2-44.8), median PFS was 5.1 months (95% CI: 4.6-5.6) (Figure 2A). PFS was further evaluated in clinically relevant subgroups. In patients with ECOG PS 0/1 at baseline, PFS was markedly longer (median: 5.7 months [95% CI: 5.2-6.3]; PFS6: 45.0% [95% CI: 38.4-51.4]) as compared to patients with ECOG PS ≥2 at baseline (median: 3.2 months [95% CI: 2.3-4.6]; PFS6: 24.1% [95% CI: 14.7-34.8]). For patients aged ≥70 years PFS6 was higher with 47.7% (95% CI: 38.6-56.2) than for patients <70 years (34.6% [95% CI: 28.0-41.2]), though with slightly overlapping 95% CIs. The median PFS for patients aged ≥70 years was 5.8 months (95% CI: 4.8-6.9) compared to 4.6 months (95% CI: 4.1-5.3) for patients <70 years of age. Patients with squamous cell histology had a PFS6 of 40.6% (95% CI: 32.1-48.9) and median PFS of 5.5 months (95% CI: 4.6-5.9), similar to patients with non-squamous histology with PFS6 of 38.9% (95% CI: 31.9-45.7) and median PFS of 4.9 months (95% CI: 4.2-5.4). Patients with mild and moderate RI showed comparable PFS6 (41.6% [95% CI: 32.8-50.2] and 43.1% [95% CI: 30.2-55.4]) and PFS of 5.3 months each (95% CI: 4.6-6.2 and 95% CI: 3.8-7.2) compared to PFS6 (33.6% [95% CI: 24.9-42.5]) and PFS of 4.1 months (95% CI: 3.2-5.1) in patients without RI, although the 95% CIs are wide and overlap distinctly.





Patients (N)	359
Events n (%)	289 (80.5%)
Censored n (%)	70 (19.5%)
25% quantile (95% CI)	2.5 (2.2-3.0)
Median (95% CI)	5.1 (4.6-5.6)
75% quantile (95% CI)	8.8 (7.7-10.1)
6-month rate (95% CI)	**39.5% (34.2-44.8)**
6-month rate (95% CI) by ECOG	
PFS6 (95% CI) ECOG PS = 0/1 (n = 258)	45.0% (38.4-51.4)
PFS6 (95% CI) ECOG PS≥2 (n = 71)	24.1% (14.7-34.8)

Patients (N)	359
Events n (%)	264 (73.5%)
Censored n (%)	95 (26.5%)
25% quantile (95% CI)	5.0 (4.3-5.9)
Median (95% CI)	10.5 (9.2-11.6)
75% quantile (95% CI)	21.5 (18.3-28.8)
12-month rate (95% CI)	**43.0% (37.5-48.3)**
12-month rate (95% CI) by ECOG	
OS12 (95% CI) ECOG PS = 0/1 (n = 258)	49.8% (43.3-56.0)
OS12 (95% CI) ECOG PS≥2 (n = 71)	15.3% (7.7-25.4)

FIGURE 2 Effectiveness. PFS and PFS6 (A), OS and OS12 (B). CI, confidence interval; CR, complete remission; N/n, number; OS, overall survival; PFS, progression-free survival.

A multivariable Cox regression analysis was conducted to identify predefined covariates with a potential impact on PFS. This analysis showed that ECOG PS score at baseline (≥2 vs 0/1) was most likely to have an impact on PFS (HR 1.60 [95% CI: 1.18-2.17]) (Table 2A), with shorter PFS for patients having an ECOG PS ≥2 (see paragraph above).

3.2.2 | Overall survival

Median OS was 10.5 months (95% CI: 9.2-11.6) and the 12-months OS rate (OS12) was 43.0% (95% CI: 37.5-48.3) (Figure 2B). OS was further evaluated in clinically relevant subgroups. In patients with ECOG PS 0/1 at baseline, OS was markedly longer (median: 11.8 months [95% CI: 10.5-14.3]; OS12: 49.8% [95% CI: 43.3-56.0]) as compared to patients with ECOG PS ≥2 at baseline (median: 4.9 months [95% CI: 3.8-6.9]; OS12: 15.3% [95% CI: 7.7-25.4]). Median OS for patients ≥70 years was 2.8 months longer compared to patients <70 years (12.4 months [95% CI: 9.8-15.1] vs 9.6 months [95% CI: 7.7-11.1]), however, with wide and overlapping 95% CIs. Patients with squamous or non-squamous histology showed comparable OS (median OS: 11.5 months [95% CI: 9.2-13.8] vs 9.8 months [95% CI: 8.1-11.3]). The median OS was comparable between the subgroup of patients with no RI (9.0 months [95% CI: 6.8-11.2]), with mild RI (10.5 months [95% CI: 8.7-13.8]) or with moderate RI (10.2 months [95% CI: 7.5-14.3]) at baseline. Also, the 12-month OSR was similar in RI-subgroups (35.5% [95% CI: 26.8-44.2] vs 46.6% [95% CI: 37.5-55.2] vs 45.8% [95% CI: 32.7-57.9]). The 95% CIs are wide and overlap markedly.

A multivariable Cox regression analysis revealed that only ECOG PS score at baseline (≥2 vs 0/1) was likely to affect OS (HR 2.37 [95% CI: 1.73-3.25]), with shorter OS for patients having an ECOG PS ≥2 (see paragraph above).

3.2.3 | Tumor response

ORR and DCR were 42.9% (95% CI: 37.7-48.2) and 64.1% (95% CI: 58.9-69.0), respectively (Table 2B). Elderly patients ≥70 years showed a higher ORR with 48.9% and DCR of 70.7% (95% CI: 40.1-57.7 and 95% CI: 62.2-78.2) than patients <70 years with 39.4% and 60.2% (95% CI: 33.0-46.1 and 95% CI: 52.5-66.6), respectively, though with wide and overlapping 95% CIs. The ORR for patients with squamous histology was higher (47.3% [95% CI: 38.9-55.7]) than for patients with non-squamous histology (39.5% [95% CI: 33.3-46.8]), however, with wide and overlapping 95% CIs. In patients with mild and moderate RI (47.4% [95% CI: 38.7-56.2] and 33.9% [95% CI: 22.3-47.0]), the ORR was comparable to patients with no RI (38.6% [95% CI: 30.3-47.5]). The 95% CIs are wide and overlap markedly. The DCR was higher in patients with mild RI (72.2% [95% CI: 63.7-79.6]) than in patients with no RI (53.0% [95% CI: 44.2-61.8]) with non-overlapping 95% CIs and comparable to patients with moderate RI (61.3% [95% CI: 48.1-73.4]) with markedly overlapping 95% CIs.

TABLE 2 Effectiveness: multivariable cox regression analysis—Hazard ratios for PFS (A) and tumor response (B).

A		
Covariate	**Hazard ratio**	**95% CI**
ECOG performance status score at baseline		
≥2 vs 0/1	1.60	[1.18-2.17]
Histology of primary tumor		
Squamous vs non-squamous	0.81	[0.62-1.06]
Age subgroups [years]		
≥70 vs <70	0.80	[0.59-1.07]
Renal impairment (RI) at baseline		
Mild RI vs no RI	0.84	[0.63-1.14]
Moderate RI vs no RI	0.77	[0.52-1.14]
Severe RI vs no RI	0.00	[0.00-NA]
Smoking status at baseline		
Current smoker vs never smoker	0.97	[0.65-1.46]
Former smoker vs never smoker	1.09	[0.76-1.56]

B	**Total (N = 359)**	
	n	**% (95% CI)**
Best response		
Complete response	6	1.7
Partial response	148	41.2
Stable disease	74	20.6
Non-CR, Non-PD	2	0.6
Progressive disease	92	25.6
Not evaluable	4	1.1
No tumor assessment available	33	9.2
Overall response rate	154	42.9 (37.7-48.2)
Disease control rate	230	64.1 (58.9-69.0)

Note: (A) Renal Impairment (RI) at baseline; no RI: CrCl ≥90 mL/min; mild RI: CrCl ≥60 to <90 mL/min; moderate RI: CrCl ≥30 to <60 mL/min; severe RI: CrCl <30 mL/min. N = 299; thereof 63 (21.1%) censored cases. Sixty observations were excluded due to missing values in covariates. (B) Overall response rate was defined as the proportion of patients with complete response or partial response as best documented tumor response related to all patients. Disease control rate was defined as the proportion of patients with complete response, partial response or non-CR/non-PD as best documented tumor response compared to total patient number.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N/n, number; NA, not available; PD, progressive disease; RI, renal impairment.

3.3 | Therapy details

The median treatment duration was 3.2 months (95% CI: 0.2-22.6) for *nab*-paclitaxel and 3.4 months (95% CI: 0.7-15.5) for carboplatin. Mean relative dose intensity was 74.1% (SD 17.92) for *nab*-paclitaxel and 75.1% (SD 17.49) for carboplatin. *Nab*-paclitaxel therapy interruptions were reported in 83.1% of the patients while carboplatin dose interruptions were observed less frequently (64.8%). Reasons for therapy interruptions were most often AEs (*nab*-paclitaxel: 65.1%; carboplatin: 39.2%) followed by organizational reasons (*nab*-paclitaxel: 47.6%; carboplatin 40.1%). Dose reductions were documented in 31.5% of patients for *nab*-paclitaxel and 57.0% for carboplatin. Permanent therapy withdrawal of *nab*-P/C occurred in 22.3% of patients. Reasons for therapy withdrawals were most frequently AEs (*nab*-paclitaxel: 66 [17.7%]; carboplatin: 13 [3.5%]).

3.4 | Safety

AEs of any grade were reported in 349 patients (93.8%), with anemia (27.4%) and leukopenia (26.1%) being the most common (Table 2). SAEs were documented in 180 patients (48.4%); pneumonia (5.6%) and general physical health deterioration (5.1%) were the most frequent events. AEs related to *nab*-paclitaxel occurred in 247 patients (66.4%), while carboplatin-related AEs were reported in 224 patients (60.2%). SAEs related to *nab*-paclitaxel were reported in 48 (12.9%) patients and carboplatin related SAEs in 42 (11.3%) patients. AEs of CTCAE grade 3/4 were documented in 206 patients (55.4%); most frequently reported events were leukopenia (10.2%), anemia (8.9%) and pneumonia (5.6%). AEs of grade 3/4 related to *nab*-paclitaxel (n = 105; 28.2%) and/or carboplatin (n = 92; 24.7%) were most commonly anemia (21.2%, 20.2%) and leukopenia (22.3%, 18.8%). Permanent treatment discontinuation of *nab*-paclitaxel due to an AE was documented in 81 patients (21.8%), *nab*-paclitaxel related AEs were reported in 39 (10.5%) patients and carboplatin related AEs in 31 (8.3%) patients. A fatal AE was reported in 51 patients (13.7%). Six patients died from pneumonia and/or sepsis (including sepsis, neutropenic sepsis and pulmonary sepsis), deterioration of general condition was given as reason for death in seven patients and two patients were documented with death due to comorbidity (blood pressure decreased, general physical health deterioration). Fatal AEs related to study treatment comprised in total three patients. Two patients were reported with a fatal event related to both *nab*-paclitaxel and carboplatin (sepsis, neutropenic sepsis). One patient was documented with a fatal event related to carboplatin only (pulmonary sepsis). Table 3 summarizes the most frequently (≥5% of patients) reported AEs and selected AEs of interest including severity and causality to study treatment.

3.5 | PROs on HRQoL

In total, 227 patients participated in the HRQoL questionnaire project. FACT-L and EQ-5D-5L questionnaires were answered throughout the entire observation period. At baseline, the questionnaire return rate was 90.6% and decreased markedly at most subsequent timepoints. The mean/median EQ-5D-5L VAS score and index value were slightly lower at EOT compared to baseline, though with large standard deviations (Figure 3A,B). The median total scores (FACT-L TOI, FACT-G

TABLE 3 Most frequent (≥5.0% of patients) adverse events.

	Patients (N = 372)			
Adverse events	**Any grade, n (%)**	**Grade 3/4, n (%)**	**Related to *nab*-paclitaxel, n (%)**	**Related to carboplatin, n (%)**
Patients with any event	349 (93.8)	206 (55.4)	247 (66.4)	224 (60.2)
Hematological				
Anemia	102 (27.4)	33 (8.9)	79 (21.2)	75 (20.2)
Leukopenia	97 (26.1)	38 (10.2)	83 (22.3)	70 (18.8)
Thromobocytopenia	65 (17.5)	16 (4.3)	48 (12.9)	48 (12.9)
Neutropenia	32 (8.6)	18 (4.8)	23 (6.2)	23 (6.2)
Non-hematological				
Nausea	61 (16.4)	5 (1.3)	44 (11.8)	44 (11.8)
Fatigue	53 (14.2)	6 (1.6)	34 (9.1)	26 (7.0)
Polyneuropathy	41 (11.0)	8 (2.2)	33 (8.9)	11 (3.0)
General physical health deterioration	43 (11.6)	19 (5.1)	16 (4.3)	13 (3.5)
Diarrhea	42 (11.3)	6 (1.6)	25 (6.7)	19 (5.1)
Dyspnea	42 (11.3)	12 (3.2)	1 (0.3)	1 (0.3)
Constipation	31 (8.3)	1 (0.3)	14 (3.8)	9 (2.4)
Pneumonia	28 (7.5)	21 (5.6)	8 (2.2)	8 (2.2)
Alopecia	25 (6.7)	1 (0.3)	24 (6.5)	20 (5.4)
Decreased appetite	21 (5.6)	3 (0.8)	10 (2.7)	9 (2.4)
C-reactive protein increased	20 (5.4)	5 (1.3)		

Note: Displayed are AEs documented in ≥5.0% of patients. Adverse events were coded using MedDRA version 21.0. AEs were to be documented from first administration of *nab*-paclitaxel until at least 30 days after *nab*-paclitaxel discontinuation. More than one reported preferred term per patient within a system organ class was possible.
Abbreviation: N/n, number.

total score and FACT-L total score) at baseline and EOT were comparable (Figure 3C).

4 | DISCUSSION

The NEPTUN study shows favorable safety, tolerability and effectiveness of first-line *nab*-P/C in patients with unresectable advanced or metastatic NSCLC in a real-world setting, supporting the results of previous studies. Real-world data (RWD) from large, prospective, observational cohort studies with longitudinal follow-up data makes it feasible to both complement and corroborate clinical trial data. Here, NEPTUN contributes significantly by presenting RWD and real-word evidence (RWE) in the total population and in predefined clinically relevant subgroups. The strength of RWE is found in the potential of inclusion of high patient numbers and thus the generation of evidence for rare subgroups, elderly and frail patients as well as patients with multiple comorbidities and concomitant medications, the potential to include patients commonly treated in the daily oncologic care; however, underrepresented in randomized clinical trials, the description of longitudinal treatment patterns, real-world effectiveness, safety within more vulnerable patient populations and their health-related and overall QoL and long-term safety. Thus, our study provides a wide range of important RWE in patients with advanced or metastatic NSCLC treated with first-line nab-P/C.

The effectiveness results in our study with a median PFS and OS of 5.1 and 10.5 months, respectively, are in line with the pivotal phase 3 trial in 2012 by Socinski et al (6.3 and 12.1 months, respectively). It should be considered that NEPTUN included patients with more comorbidities (19.8% of patients with ECOG PS ≥2). The ORR in our study was slightly higher, although in the same range compared to Socinski et al (42.9% vs 33%).[16] In NEPTUN, 1.7% of patients achieved a complete remission and 41.2% a partial remission, whereas Socinski et al reported 33% partial remission (no CR). These differences might be due to differences in patient characteristics and study settings including inclusion and exclusion criteria. Furthermore, in this NIS, tumor assessment was conducted according to routine clinical practice, whereas in the pivotal study it was performed and evaluated as per RECIST.

Our study shows that ECOG PS score at baseline (≥2 vs 0/1) seems to be the most influencing factor for PFS and OS. PFS6 was nearly twice as high in patients with ECOG PS 0/1 (45.0%) compared to patients with ECOG PS ≥2 at baseline (24.1%). A favorable outcome for the former subgroup was also observed for OS12 (49.8% vs 15.3%). The fact that 20% of patients in this NIS had an ECOG PS ≥2 at baseline may account for the shorter PFS/OS observed in our study compared to the pivotal trial. The proportion of patients

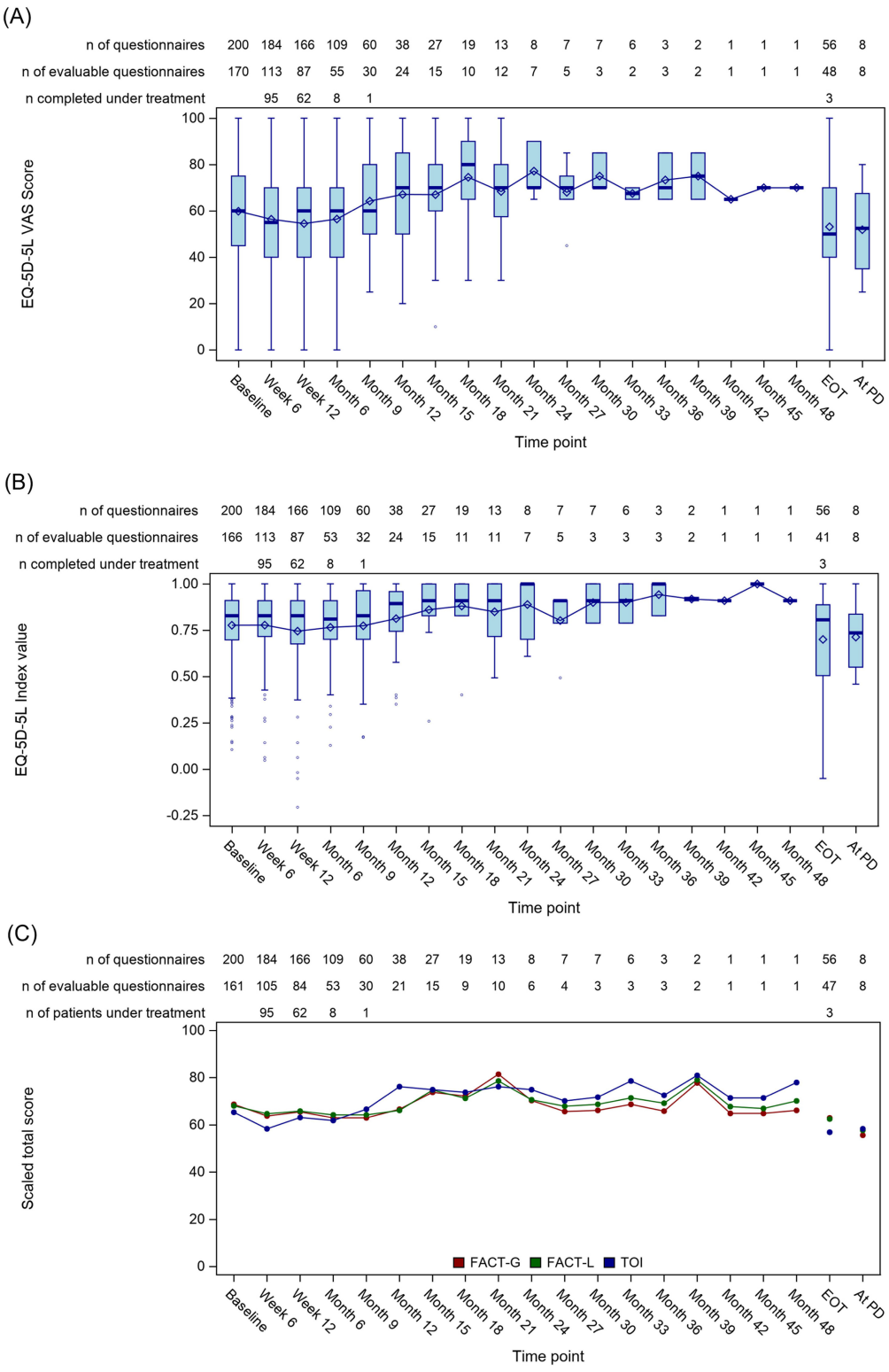


FIGURE 3 Patient-reported outcome-Quality of life. Patient-reported QoL according to EQ-5D-5L-VAS score at baseline and over time (A), EQ-5D-5L-Index value at baseline and over time (B), Scaled total score at baseline and over time (C). EOT, end of treatment; FACT-G, functional assessment of cancer therapy-general; FACT-L, functional assessment of cancer therapy-lung; N/n, number; PD, progressive disease; TOI, trial outcome index. The respective questionnaire was considered evaluable if the displayed scale/score was evaluable according to the definition in the respective manual (ie, a sufficient number of items composing the scale/score have been answered). An item was considered as "evaluable" if not more than one answer had been selected. Higher scores indicate better quality of life. The individual time points "EOT" and "At PD" could not be put into the general chronological order. They are therefore displayed separately. Box: lower to upper quartile, horizontal line inside box: median, diamond inside box: mean, whisker: minimum/maximum value within lower quartile minus ×1.5 IQR/upper quartile plus ×1.5 IQR, respectively, circles: outliers outside of lower quartile minus ×1.5 IQR/upper quartile plus ×1.5 IQR, respectively (IQR, interquartile range).

regarding ECOG PS at baseline was well balanced between the subgroups of patients aged <70 years and the patients aged ≥70 years. For the other covariates in our study (histology of primary tumor, age subgroups, RI at baseline and smoking status), the 95% CI for the HR comprised 1.0. A HR = 1.0 implies equal hazard in the two groups compared. Therefore, one may stress with certainty that ECOG PS score at baseline had an impact on PFS/OS in this NIS, while the other covariates may show a tendency towards an influence on PFS/OS based on the results from the Cox regression analysis. Median PFS and OS were shorter in the subgroup of patients with no RI than in the subgroup of patients with mild RI or moderate RI, though the 95% CIs were wide and overlapped markedly. The DCR was lower in patients with no RI than in patients with mild RI, while it was similar to the DCR of patients with moderate RI. However, the differences observed in effectiveness outcomes between subgroups may be down to differences in baseline patient characteristics as well as in therapy duration and modifications including duration of interruption and in incidence of AEs. Prolonged survival in elderly patients has been observed earlier in the pivotal trial with a median OS of 19.9 months (vs 11.4 months for patients <70 years).[16] A further study centering elderly patients (aged ≥70 years) revealed a median OS of 14.5 months.[18] So far, no survival benefit for patients with squamous histology has been reported, rather, Socinski et al reported shorter median OS times for patients with squamous compared to patients with non-squamous histology (10.7 vs 13.1 months).[16,22] Nevertheless, consistent with the pivotal study by Socinski et al, the results of the NEPTUN study support the effectiveness of first-line therapy with *nab*-P/C in a real-world setting independent of histologic subtype.

The older patient collective with more comorbidities in the NEPTUN study as compared to the pivotal trial may account for the shorter median treatment duration observed (3.2 vs 4.5 months). In this NIS, therapy with *nab*-P/C was permanently withdrawn due to an AE in 22.3% of patients. For both *nab*-paclitaxel (17.7%) and carboplatin (3.5%), therapy was most frequently withdrawn due to an AE. This would suggest that therapy management and management of adverse drug reactions is important so that more patients could benefit longer from *nab*-P/C combination therapy. Instead of permanent discontinuation of *nab*-P/C therapy, dose modification as well as temporary interruption of therapy may be an option to address *nab*-paclitaxel/carboplatin-related AEs. *Nab*-paclitaxel dose reductions were more frequent in the pivotal phase 3 trial compared to NEPTUN (46% vs 31.5%), whereas carboplatin doses were more frequently reduced in NEPTUN (57% vs 46%). In this NIS, therapy interruptions were documented in 309 patients for *nab*-paclitaxel (83.1%) and 241 patients for carboplatin (64.8%)—however, no data is available on the duration of therapy interruption. Nevertheless, the results provide important RWD indicating that *nab*-paclitaxel therapy may be temporarily interrupted for a time period long enough to allow management of AEs with subsequent resumption of *nab*-paclitaxel therapy.

QoL is an important factor to consider when choosing an optimal treatment regimen for a patient. As chemotherapy not only serves as a backbone for several targeted therapies but also remains the standard of care for many patients with NSCLC, HRQoL data for chemotherapeutic agents can be a useful source of information to decide for the best regimen. In NEPTUN, the EQ-5D-5L and FACT-L questionnaires were used to assess PROs on HRQoL. No major differences were observed at baseline and over time for both questionnaires. The results of PROs do not indicate a significant worsening of HRQoL with first-line *nab*-paclitaxel and carboplatin combination therapy. However, the data need to be interpreted with caution as the number of returned/evaluable questionnaires decreased over time, which may partly be a consequence of patients with poor QoL dropping out earlier, though this is of speculative nature as the QoL of patients having dropped out of the study for various reasons was not further assessed. Furthermore, only a small number of patients or no patient had completed the questionnaires under treatment at later timepoints (month 6 and subsequent timepoints), further limiting the interpretability of these data. Thomas et al reported improved QoL over the first four cycles of *nab*-P/C treatment in patients with squamous NSCLC.[23] At the end of treatment cycle four, QoL seemed to drop in patients responding and not-responding to the treatment but was no longer recorded after completion of the last treatment cycle.[23]

Immunotherapies yield the best results for patients with stage IIIB to IV NSCLC.[24,25] The approval of pembrolizumab for PD-L1-positive NSCLC in 2017 and the approval of atezolizumab plus bevacizumab and chemotherapy for patients with advanced NSCLC in 2019 have changed the type of first-line treatments since the start of NEPTUN. Recent studies investigating the combination of PD-1/PD-L1 blockade together with chemotherapy revealed significantly improved PFS and OS upon treatment with pembrolizumab and *nab*-P/C.[26,27] Also treatment with atezolizumab in combination with *nab*-P/C led to improved PFS.[28,29] Additionally, CTLA-4 checkpoint inhibitors like ipilimumab may be used together with PD-1 blockade and chemotherapy for patients with limited performance status or comorbidities.[30] For patients with newly diagnosed metastatic squamous PD-L1-negative NSCLC, the KEYNOTE-407 regimen (pembrolizumab plus carboplatin and paclitaxel/*nab*-paclitaxel) may be considered, particularly for older patients and those who have pre-existing comorbidities given the relative toxicities of *nab*-paclitaxel vs paclitaxel. The choice of therapy comes down to patient's performance status/comorbidities and perhaps tumor burden. The proportion of PD-L1 positive tumor cells serves as an established biomarker for selecting patients for first-line anti-PD-L1 monotherapy.[9,31] However, although it has been reported that greater PD-L1 expression leads to longer PFS in the KEYNOTE-407 trial and in KEYNOTE-189 using pembrolizumab plus pemetrexed and a platinum-based drug,[26] it has been shown that combination treatments improve outcomes over chemotherapy across a wide range of PD-L1 tumor proportion scores far below 50% PD-L1 expression. Nevertheless, combination approaches may lead to increased side effects compared to chemotherapy alone; the chemotherapeutic agent should therefore be chosen with caution to reduce the risk of undesirable effects for the patient. The results of the NEPTUN study are in line with the known side effects of *nab*-P/C treatment and no new or unexpected events were reported. Also, the frequency of fatal *nab*-paclitaxel-related AEs was low (0.5%). In the pivotal phase 3 trial and the study by Langer et al on elderly patients ≥70 years, a higher frequency of grade 3/4 events

were reported than in the whole patient population of NEPTUN.[16,18] As data were collected in routine clinical practice within the current applicable version of the SmPC of Abraxane, bias in patient selection, treatment and reporting cannot be ruled out (eg, underreporting of AEs). However, a reasonable number of sites was selected for participation in our study to represent the patient population.

Major strengths of the NEPTUN study are its prospective design and the unselected patient population recruited in multiple study sites (n = 75) compared to phase 3 trials. Accordingly, this NIS provides real-world data on treatment of patients with advanced and unresectable or metastasized NSCLC in routine clinical practice comprising patients with *nab*-paclitaxel-related (0.5%) and carboplatin-related (0.8%) fatal events. Nevertheless, there are also limitations associated with our study. As subgroup analyses are exploratory in nature, the interpretability and generalizability of the results are limited. Across all subgroup categories, the distribution of strata was unbalanced, limiting the comparability between these subgroups. With regards to the RI subgroups, 31 patients were excluded due to missing values for creatinine clearance. The subgroup of severe RI comprised only one patient, therefore, data of this subgroup are not interpretable. The PRO data on HRQoL are limited in interpretability since the number of returned and evaluable questionnaires decreased over time.

However, the data obtained in our study provide an important and valuable estimate of how clinical efficacy documented in controlled, randomized studies translates into effectiveness in routine clinical practice in Germany. The regimen *nab*-paclitaxel and carboplatin are still frequently used either without or in combination with other substances. This makes *nab*-P/C an important standard treatment option for many patients and the data obtained in our study may help in choosing the appropriate therapy regimen for patients with advanced NSCLC.

During the follow-up period (7 June 2019 to 6 June 2021) of the NEPTUN study, the SARS-CoV-2 was spread worldwide. On 22 March 2020, a nationwide lockdown was imposed in Germany, which had an impact on the conduct of interventional and non-interventional studies. The SARS-Cov-2 pandemic had virtually no impact on the conduct of the NEPTUN study. Only the monitoring was affected by the pandemic situation as on-site visits could not be carried out or only to a very limited extent, especially at the beginning of the pandemic. This was managed by partially replacing on-site visits with remote calls. No patient was documented with an AE related to SARS-CoV-2. All study objectives could be addressed and evaluated as planned and defined in the study protocol. No protocol amendment was required due to the SARS-Cov-2 pandemic.

5 | CONCLUSION

The data obtained in our study underline the effectiveness and safety of first-line *nab*-P/C treatment of patients with locally advanced or metastatic NSCLC who are not candidates for potentially curative surgery or radiation therapy in routine clinical practice in Germany. Elderly patients aged ≥70 years and patients with mild/moderate RI showed a tendency towards better outcome in terms of survival and tumor response independent of histologic subtype. The safety information documented in the NEPTUN study reflect the known safety profile of Abraxane. No new or unexpected safety signals were identified.

AUTHOR CONTRIBUTIONS

The work reported in the article has been performed by the authors, unless clearly specified in the text. All authors reviewed the article and approved the final version of the article. Further author contributions were as follows: **Tobias Dechow:** Data collection; principal investigator. **Jorge Riera-Knorrenschild:** Data collection. **Björn Hackanson:** Data collection. **Jan Janssen:** Data collection. **Holger Schulz:** Data collection. **Ursula Oppermann:** Study conduct, analysis and interpretation of the data. **Marco Chiabudini:** Preparation of the statistical analysis plan, statistical analyses and interpretation of the data. **Ludwig Fischer von Weikersthal:** Data collection. **Stephan Budweiser:** Data collection. **Axel Nacke:** Data collection. **Dagmar Taeuscher:** Data collection. **Manfred Welslau:** Data collection. **Karin Potthoff:** Conception and design of the study, analysis and interpretation of the data.

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CONFLICT OF INTEREST STATEMENT

T. Dechow received remuneration as principal investigator and for the documentation of patient data. J. Riera-Knorrenschild, B. Hackanson, J. Janssen, H. Schulz, L. Fischer von Weikersthal, S. Budweiser, A. Nacke, D. Taeuscher and M. Welslau received remuneration for the documentation of patient data. L. Fischer von Weikersthal received honoraria for lectures from Lilly, Novartis, Pierre-Fabre. All the other authors declare no conflict of interest concerning the topic of this publication.

DATA AVAILABILITY STATEMENT

Clinical data were documented in electronic Case Report Forms and are the property of iOMEDICO. Further information is available upon request to Dr. Potthoff, Email: manuscript@iomedico.com.

ETHICS STATEMENT

The NEPTUN study (NCT02799862) was approved by the responsible ethics committees and written informed consent was obtained from

each patient prior to enrollment. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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