ORIGINAL ARTICLE

Checkpoint Inhibitor Monotherapy in Potentially Trial-Eligible or Trial-Ineligible Patients With Metastatic NSCLC in the German Prospective CRISP Registry Real-World Cohort (AIO-TRK-0315)

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ABSTRACT

Introduction: Patients with metastatic NSCLC (mNSCLC) treated with immune checkpoint inhibitors in clinical practice may often not meet the strict inclusion criteria of clinical trials. Our aim was to assess the trial eligibility of patients with mNSCLC treated with pembrolizumab monotherapy in real-world and to compare the outcome of "trial-ineligible" and "potentially trial-eligible" patients.

Methods: Data from the prospective, clinical research platform CRISP were used to compare patient characteristics, treatment, and outcome of patients with programmed cell death-ligand 1 tumor proportion score greater than or equal to 50% tumors treated with pembrolizumab monotherapy who are deemed either "potentially trial-eligible" or "trial-ineligible" according to inclusion and exclusion criteria of the registrational studies (KEYNOTE-024 and -042).

Results: Of 746 patients included, 343 patients (46.0%) were classified as "trial-ineligible" and had significantly worse outcomes compared with "potentially trial-eligible" patients (n = 403, 54.0%): median progression-free survival: 6.2 (95% confidence interval [CI]: 5.2–8.4) versus 10.3 (95% CI: 8.4–13.8) months, hazard ratio (trial-ineligible versus potentially trial-eligible) of 1.43 (95% CI: 1.19–1.72), *p* less than 0.001; median overall survival: 15.9 (95% CI: 11.4–20.3) versus 25.3 (95% CI: 19.8–30.4) months, hazard ratio of 1.36 (95% CI: 1.10–1.67), *p* equals 0.004.

Conclusions: Our data reveal that a considerable proportion of patients with mNSCLC are not eligible to participate in a clinical trial and were found to have worse outcomes than potentially trial-eligible patients, whose outcomes were comparable with those obtained from pivotal clinical trials. This is of substantial clinical relevance for physicians discussing outcomes to be expected with their patients and stresses the need for real-world effectiveness analyses.

Keywords: Non–small cell lung carcinoma; Prospective studies; Immune checkpoint inhibitors; Pembrolizumab

Introduction

NSCLC, accounting for 80% to 90% of all lung cancers,[1] is often diagnosed at metastatic or an advanced, unresectable disease stage not amenable to curative treatment.[2] Until the advent of immunotherapies in recent years, treatment of patients with metastatic or advanced NSCLC without oncogenic driver mutations was limited to chemotherapy associated with poor survival times and toxicity profile.[3] As such, the availability of immunotherapeutic options caused a paradigm shift in the treatment landscape of NSCLC opening new perspectives for a number of patients.[1] Results from pivotal clinical studies revealed marked improvements in survival with immune checkpoint inhibitors (CPIs) as compared with standard chemotherapy and led to the approval of various CPIs for the treatment of metastatic NSCLC (mNSCLC).[4–7] In the frontline setting, pembrolizumab, a monoclonal antibody targeting programmed cell death protein 1, received approval in 2016 after having superiority over chemotherapy in all efficacy analyses of the pivotal KEYNOTE-024 trial, including overall response rate, progression-free survival (PFS), and overall survival (OS).[8] In an updated analysis after prolonged follow-up, pembrolizumab monotherapy continued to have superior survival times as compared with chemotherapy (26.3 mo [95% confidence interval (CI): 18.3–40.4] versus 13.4 mo [95% CI: 9.4–18.3]).[9] In a subsequent phase 3 trial of pembrolizumab monotherapy versus chemotherapy as first-line treatment (KEYNOTE-042),[10] the patient population was expanded compared with KEYNOTE-024 in that also patients with a programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) of 1% and greater (instead ≥50%) were included. Again, a significant survival benefit was found in patients with PD-L1–positive tumors, which was driven by patients with a TPS of greater than or equal to 50%.

Following these promising results, pembrolizumab replaced chemotherapy as a first-line standard for patients with mNSCLC with a TPS for PD-L1 of greater than or equal to 50% without the presence of EGFR or ALK genetic aberrations.[1]

Although randomized controlled clinical trials (RCTs) are considered the accepted standard of proving the efficacy of new therapies,[11] it is also known that a considerable number of patients in everyday clinical practice would not be eligible to participate in a clinical trial owing to strict inclusion and exclusion criteria.[12] This was also found for patients with mNSCLC treated with immune-based therapies in both first line[13] and second line.[14] Both retrospective studies revealed differences in outcomes of trial-eligible and ineligible patients,[13,14] suggesting a gap between patients treated in RCTs and those treated in everyday practice. To add knowledge on the effectiveness of immune therapies in routine care, particularly in the frontline setting, the objective of the present work was to compare patient characteristics, treatment, and outcome of potentially trial-eligible and trial-ineligible patients with PD-L1 TPS greater than or equal to 50% tumors.

Patients and Methods

Study Design and Patients

CRISP (NCT02622581) is an open, noninterventional, prospective, multicenter, clinical registry, which collects

data of patients with lung cancer at more than 170 cancer sites in Germany. Eligible patients for the present analysis are aged above or equal to 18 years with histologically confirmed diagnosis of mNSCLC (stage IV), with PD-L1 TPS greater than or equal to 50% and no EGFR or ALK mutation who have signed informed consent no later than 4 weeks after start of first-line treatment and who are able to understand and complete the patient-reported outcome (PRO) assessment questionnaires. Further details on the data collection in CRISP have been published previously.[15–17]

Definition of Trial Ineligibility and Eligibility

Following inclusion and exclusion criteria of the clinical trials KEYNOTE-024 and -042,[8,10,18] patients were classified as potentially trial eligible, when the following inclusion criteria were met and had been documented: Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, no known history of human immunodeficiency virus or second tumor, no prior (neo-)adjuvant therapies less than 6 months before diagnosis of first metastasis, no brain metastases at inclusion. Because data in CRISP do not capture whether patients with documented brain metastases have stable or active metastases, we excluded patients with brain metastases from the potentially trial-eligible patient population. When at least one of the above-mentioned four criteria was not met, patients were defined as trial ineligible.

Patient-Reported Outcome

To assess PROs, the 36-item Functional Assessment of Cancer Therapy—Lung (FACT-L) version 4 questionnaire, which has been validated for assessment of various aspects of health-related quality of life in patients with lung cancer undergoing cancer therapy[19] was used. The FACT-L questionnaire includes the 27-item FACT-G core questionnaire, covering the four domains physical, social and family, emotional, and functional well-being, including a nine-item lung cancer-specific (LCS) module. The FACT-L items are rated on a five-level Likert-type scale. The FACT-L has a possible total score range of 0 to 136. Change from baseline was calculated as mean of the individual difference between baseline and the respective time point for all patients with data available at baseline and the respective time points. In addition, anxiety and depression were assessed using the PHQ-4 ultra-brief four-item questionnaire including the subscales PHQ-2 for depression and the Generalized Anxiety Disorder Scale-2 (GAD-2).[20,21] The PHQ-4 has a possible score range of 0 to 12. Probable cases of depression (PHQ-2) or anxiety (GAD-2) were defined as a score greater than or equal to three on the respective scale at the respective time point.

Patients were asked to fill out the questionnaires at the time of recruitment (baseline), every 2 months until month 12, and thereafter every 3 months for up to 36 months. For the present analysis, questionnaires until month 15 were evaluated and analyzed according to their respective manuals.

Statistical Analysis

Patient and clinical characteristics for the total patient population and by trial eligibility were presented using descriptive statistics.

Time to events was estimated using the Kaplan-Meier method.[22] PFS was defined as the interval between start of first-line treatment and the date of progression or death. Patients without such an event before start of second-line treatment were censored at start of second-line treatment or at last contact. In CRISP, there are no strict specifications as to the timing, frequency, or criteria of tumor assessment as in clinical trials (e.g., Response Evaluation Criteria in Solid Tumors), and thus registry-PFS data should be considered as the best clinical approximation and might not be identical to the PFS determined in clinical trials. OS was defined as the interval between start of first-line treatment and the date of death from any cause. Patients alive or lost to follow-up at data cutoff (June 30, 2022) were censored at last contact. Time to next treatment was defined as the time between start of first-line treatment and start of second treatment line or death, whichever occurred first. Patients without start of subsequent treatment line or death were censored at the last contact.

Association of the trial eligibility status with PFS and OS was estimated using Cox modeling, adjusted for potential covariates (age at inclusion, body mass index, sex, Charlson Comorbidity score, smoking status, histological classification, and number of affected organ systems). Hazard ratios (HRs) and 95% confidence intervals (CIs) of the trial eligibility status and potential covariates were displayed as forest plots. All analyses were calculated using R software, version 4.0.5, and SAS software, version 9.4, of the SAS System for Windows.

Results

Cohort Definition and Trial Eligibility

From December 2015 to June 2022, 7774 assessable patients with advanced stage IIIB/C or metastatic stage IV NSCLC have been prospectively recruited into the CRISP Registry. Data cutoff for this interim analysis was on June 30, 2022. A total of 746 stage IV patients with high PD-L1 expression (TPS $\geq$ 50%) and without EGFR/ALK alteration, who received first-line pembrolizumab

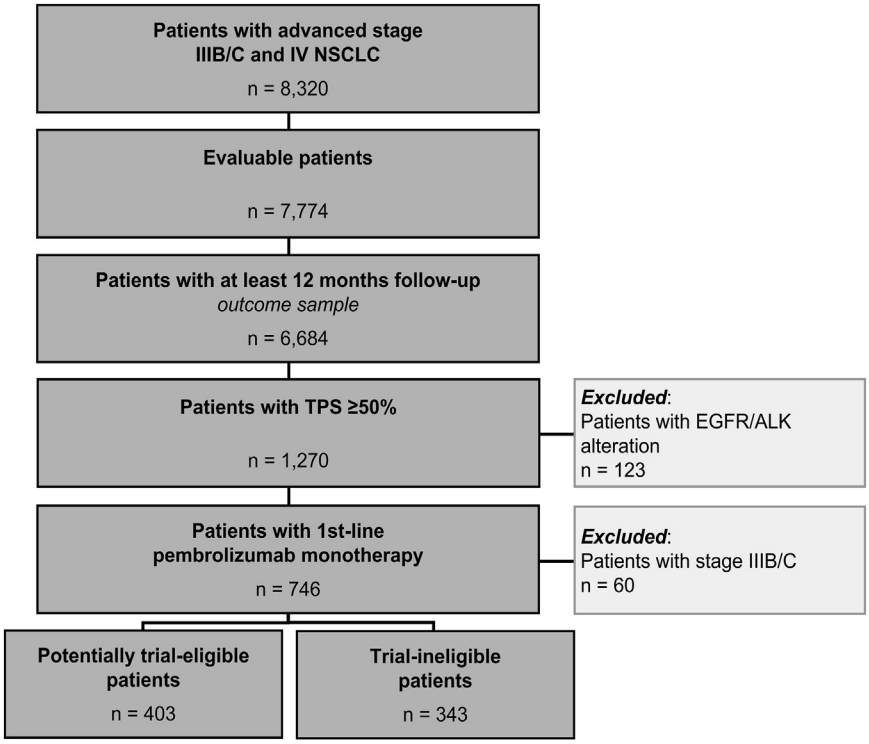


Figure 1. Flow chart. Patient flow chart of all patients with metastatic stage IV NSCLC included in this analysis, starting from the total number of patients recruited into the CRISP registry from December 2015 to June 2022. Patients with TPS greater than or equal to 50% and first-line pembrolizumab monotherapy who had been followed-up for at least 12 months were classified as potentially trial-eligible when all the following criteria were met: ECOG performance status = 0 or 1, no brain metastases at inclusion, no HIV or second tumor, no prior (neo-)adjuvant therapies less than 6 months before diagnosis of first metastasis. Otherwise, patients were classified as trial-ineligible. ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; TPS, tumor proportion score.

monotherapy and who had been followed up for at least 12 months, were included in this analysis. Thereof, 403 patients (54.0%) were classified as potentially trial eligible and 343 (46.0%) as trial ineligible (Fig. 1). Most patients (n = 283, 82.5%) were excluded owing to one exclusion criterion, whereas 58 patients (16.9%) met two and two patients (0.6%) met three exclusion criteria. None of the patients met all four exclusion criteria. The most common reason for trial ineligibility was ECOG performance status greater than or equal to 2, unknown or missing (60.9%); followed by the presence of brain metastases at inclusion (49.3%). There were 11 patients (3.2%) documented with a known human immunodeficiency virus infection.

Patient and Tumor Characteristics

Patient and tumor characteristics for the total study cohort and stratified according to study eligibility are presented in Table 1.[23] Most patients were men in both study groups. Median age at start of first-line treatment was 70 years in potentially trial-eligible patients and 67 years in trial-ineligible patients. Current smoking was documented for 28.0% of both, potentially trial-eligible and trial-ineligible patients. Although all patients in the potentially trial-eligible group had an ECOG of 0 (31.8%) or 1 (68.2%) as per definition, less than half (39.1%) of trial-ineligible patients had an ECOG less than or equal to 1 and a proportion of 34.1% had an ECOG greater than or equal to 2. For 26.8% of trial-ineligible patients, their ECOG status was unknown or missing. Proportions of 73.4% and 82.8% of patients with nonsquamous histology and proportions of 26.6% and 17.2% of patients with squamous NSCLC histology were documented among potentially trial-eligible patients and trial-ineligible patients, respectively. The proportions of patients with more than one metastatic site were 34.2% among potentially trial-eligible patients and 47.5% among trial-ineligible patients.

Treatment and Response to Therapy

First-line treatment characteristics and patients' response to therapy are presented in Table 2. Proportions of 82.4% and 88.6% of potentially trial-eligible and trial-ineligible patients, respectively, were documented with completed first-line treatments. The duration of first-line treatment was longer for

Table 1. Patient and Tumor Characteristics of Potentially Trial-Eligible and Trial-Ineligible Patients at First-Line Treatment

Characteristics at Start of First-Line Treatment[a]	Total N = 746	Potentially Trial Eligible n = 403	Trial Ineligible n = 343
Age, median (25%-75% quantile)	68.2 (61.8-75.4)	69.5 (62.7-76.3)	66.8 (60.5-73.6)
<65 y	280 (37.5)	134 (33.3)	146 (42.6)
≥65 y	466 (62.5)	269 (66.7)	197 (57.4)
Sex			
Female	309 (41.4)	161 (40.0)	148 (43.1)
Male	437 (58.6)	242 (60.0)	195 (56.9)
BMI (kg/m^2), mean (±SD)	24.8 (5.1)	25.1 (5.0)	24.5 (5.2)
Patients with any comorbidity	671 (89.9)	368 (91.3)	303 (88.3)
Comorbidities according to the CCI[b]			
CCI = 0	348 (46.6)	188 (46.7)	160 (46.6)
CCI = 1-2	322 (43.2)	175 (43.4)	147 (42.9)
CCI = 3-4	59 (7.9)	36 (8.9)	23 (6.7)
CCI ≥ 5	16 (2.1)	4 (1.0)	12 (3.5)
Missing	1 (0.1)	0 (0.0)	1 (0.3)
Performance status			
ECOG 0	176 (23.6)	128 (31.8)	48 (14.0)
ECOG 1	361 (48.4)	275 (68.2)	86 (25.1)
ECOG ≥ 2	117 (15.7)	0 (0.0)	117 (34.1)
Unknown	91 (12.2)	0 (0.0)	91 (26.5)
Missing	1 (0.1)	0 (0.0)	1 (0.3)
Smoking status			
Current smoker	210 (28.2)	113 (28.0)	97 (28.3)
Former smoker (heavy)	291 (39.0)	160 (39.7)	131 (38.2)
Former smoker (intensity unknown)	82 (11.0)	42 (10.4)	40 (11.7)
Former smoker (light)	63 (8.4)	34 (8.4)	29 (8.5)
Never smoker	54 (7.2)	29 (7.2)	25 (7.3)
Unknown	45 (6.0)	25 (6.2)	20 (5.8)
Missing	1 (0.1)	0 (0.0)	1 (0.3)
Histology			
Nonsquamous	580 (77.7)	296 (73.4)	284 (82.8)
Adenocarcinoma	531 (91.6)	268 (90.5)	263 (92.6)
Large cell carcinoma	11 (1.9)	6 (2.0)	5 (1.8)
Others	38 (6.5)	22 (7.4)	16 (5.6)
Squamous	166 (22.3)	107 (26.6)	59 (17.2)
Metastatic stage			
M1a	199 (26.7)	143 (35.5)	56 (16.3)
M1b/M1c	547 (73.3)	260 (64.5)	287 (83.7)
MX	0 (0.0)	0 (0.0)	0 (0.0)
Number of metastatic sites (at inclusion)			
0	0 (0.0)	0 (0.0)	0 (0.0)
1	445 (59.7)	265 (65.8)	180 (52.5)
2	170 (22.8)	81 (20.1)	89 (25.9)
3	84 (11.3)	39 (9.7)	45 (13.1)
≥4	47 (6.3)	18 (4.5)	29 (8.5)
Selected metastatic sites (at inclusion)[c]			
Adrenal gland	167 (22.4)	85 (21.1)	82 (23.9)
Bone	228 (30.6)	126 (31.3)	102 (29.7)
Brain	169 (22.7)	0 (0.0)	169 (49.3)
Extrathoracic lymph nodes	114 (15.3)	64 (15.9)	50 (14.6)
Liver	109 (14.6)	62 (15.4)	47 (13.7)
Lung (contralateral)	199 (26.7)	129 (32.0)	70 (20.4)
Pleura	108 (14.5)	60 (14.9)	48 (14.0)
KRAS mutation status (at inclusion)			
Alteration (druggable, unknown druggability)	83 (11.1)	43 (10.7)	40 (11.7)
Wild-type/non-druggable alteration	286 (38.3)	148 (36.7)	138 (40.2)
Unknown/no testing	377 (50.5)	212 (52.6)	165 (48.1)

(continued)

Table 1. Continued

Characteristics at Start of First-Line Treatment[a]	Total N = 746	Potentially Trial Eligible n = 403	Trial Ineligible n = 343
ROS mutation status (at inclusion)			
Alteration (druggable, unknown druggability)	7 (1.0)	4 (1.0)	3 (0.9)
Wild-type/non-druggable alteration	471 (63.1)	238 (59.1)	233 (67.9)
Unknown/no testing	268 (35.9)	161 (40.0)	107 (31.2)
BRAF mutation status (at inclusion)			
Alteration (druggable, unknown druggability)	11 (1.5)	5 (1.2)	6 (1.7)
Wild-type/non-druggable alteration	452 (60.6)	236 (58.6)	216 (63.0)
Unknown/no testing	283 (37.9)	162 (40.2)	121 (35.3)

Note: Data are number (%), unless otherwise indicated. Some percentages might not add up to 100% owing to rounding.
[a]Unless otherwise indicated.
[b]CCI according to Quan et al.[23]
[c]Multiple answers possible.
BMI, body mass index; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group.

potentially trial-eligible than for trial-ineligible patients (4.9 versus 3.0 mo in median). Besides reasons not further specified, the most common reason for end of treatment was disease progression, both among potentially trial-eligible patients (39.5%) and trial-ineligible patients (33.2%). Further reasons were toxicity related (13.3% and 8.9%, respectively) and related to treatment plan/guidelines (8.4% and 6.6%, respectively). In addition, 28.5% and 24.5% of potentially trial-eligible and trial-ineligible patients, respectively, received second-line treatment; thereof, most patients received chemotherapy (69.9% and 72.6%, respectively).

Similar proportions of patients among potentially trial-eligible and trial-ineligible patients achieved a complete response (2.7% and 2.6%), whereas 26.8% and 23.0%, respectively, were documented with partial response and 25.3% and 20.1% with stable disease. For 21.4% and 17.8%, respectively, progressive disease was documented as best response. For 23.8% and 36.5% of potentially trial-eligible and trial ineligible patients, best response to treatment was unknown. Median time to next treatment (range) was 13.7 (11.0, 18.0) months for potentially trial-eligible and 8.3 months (6.2, 11.3) for trial-ineligible patients.

Clinical Outcome

Kaplan-Meier estimates for PFS and OS are presented in Fig. 2 and Cox proportional hazards models in Fig. 3. PFS and OS of the total patient population were 8.5 months (95% CI: 7.3–10.0) and 20.0 months (95% CI: 16.8–24.8). The clinical outcome of patients classified as trial-ineligible was significantly worse than that of potentially trial-eligible patients (median PFS: 6.2 (95% CI: 5.2–8.4) versus 10.3 (95% CI: 8.4–13.8) mo [Fig. 2*A*], HR [trial-ineligible versus potentially trial-eligible] of 1.43 (95% CI: 1.19–1.72), $p < 0.001$ [Fig. 3*A*]; median OS: 15.9 (95% CI: 11.4–20.3) versus 25.3 (95% CI: 19.8–30.4) mo [Fig. 2*B*], HR of 1.36 (95% CI: 1.10–1.67), $p = 0.004$ [Fig. 3*B*]).

Patient-Reported Outcome

PRO data were documented for 311 (77.2%) potentially trial-eligible patients and for 250 (72.9%) ineligible patients. The return rate of questionnaires was higher for potentially trial-eligible patients at early time points (Table 2).

The mean (±StD) baseline total scores for FACT-G and FACT-L were higher for potentially trial-eligible than trial-ineligible patients (72.6 (±16.2) versus 68.1 (±17.8) and 90.9 (±19.5) versus 86.0 (±21.5), Table 2, Fig. 4*F*). The mean baseline total scores for LCS were almost identical between both groups (18.3 for potentially trial-eligible patients versus 18.0 for trial-ineligible patients) (Table 2, Fig. 4*E*). Subscale baseline scores for physical well-being and functional well-being were slightly higher for potentially trial-eligible patients than for trial-ineligible patients (Fig. 4*A* and *D*), but the differences were not clinically relevant. There were no substantial differences in the mean change from baseline plots between potentially trial-eligible and trial-ineligible patients (Fig. 4*A–F*). The mean baseline total scores for PHQ-4 were almost identical between both groups (3.6 for potentially trial-eligible patients versus 3.9 for trial-ineligible patients, Table 2). In both study groups, approximately 15% to 20% of patients reported anxiety, approximately 25% signs of depression (Fig. 4*G* and *H*).

Discussion

In the present study, we evaluated the impact of trial eligibility on treatment, clinical, and PRO of patients with mNSCLC treated with first-line pembrolizumab monotherapy in routine care. To our knowledge, this is the first large, multicenter study using prospectively collected data in this context. Our results suggest that

Table 2. Treatment Characteristics, Response to Therapy, and PRO Assessment

Treatment and PRO Parameters	Total N = 746	Potentially Trial Eligible n = 403	Trial Ineligible n = 343
Start of treatment			
2016-2018	348 (46.6)	183 (45.4)	165 (48.1)
2019	177 (23.7)	92 (22.8)	85 (24.8)
2020	154 (20.6)	89 (22.1)	65 (19.0)
2021	67 (9.0)	39 (9.7)	28 (8.2)
Length of treatment cycle, d			
≤14	26 (3.5)	12 (3.0)	14 (4.1)
21-28	698 (93.6)	381 (94.5)	317 (92.4)
42	13 (1.7)	4 (1.0)	9 (2.6)
Missing	9 (1.2)	6 (1.5)	3 (0.9)
Start dose of pembrolizumab			
200 mg	695 (93.2)	383 (95.0)	312 (91.0)
400 mg	10 (1.3)	4 (1.0)	6 (1.7)
Other	35 (4.7)	11 (2.7)	24 (7.0)
Missing	6 (0.8)	5 (1.2)	1 (0.3)
TTNT			
Events[a]	455 (61.0)	238 (59.1)	217 (63.3)
TTNT in months, median (95% CI)	11.1 (9.2-13.4)	13.7 (11.0-18.0)	8.3 (6.2-11.3)
Prior systemic treatment (curative)			
Yes (platin-based chemotherapy)	33 (4.4)	8 (2.0)	25 (7.3)
No	703 (94.2)	390 (96.8)	313 (91.3)
Unknown	8 (1.1)	3 (0.7)	5 (1.5)
Missing	2 (0.3)	2 (0.5)	0 (0.0)
Any palliative surgery (during the course of the project)			
Yes	59 (7.9)	28 (6.9)	31 (9.0)
Potential[b]	202 (27.1)	118 (29.3)	84 (24.5)
No	483 (64.7)	256 (63.5)	227 (66.2)
Missing	2 (0.3)	1 (0.2)	1 (0.3)
Any palliative radiotherapy (during the course of the project)			
Yes	313 (42.0)	129 (32.0)	184 (53.6)
Potential[b]	132 (17.7)	96 (23.8)	36 (10.5)
No	299 (40.1)	177 (43.9)	122 (35.6)
Missing	2 (0.3)	1 (0.2)	1 (0.3)
Patients with documented PRO data			
Return rate			
T0 at baseline	561 (75.2)	311 (77.2)	250 (72.9)
T1 after 2 mo	396 (53.1)	233 (57.8)	163 (47.5)
T2 after 4 mo	364 (48.8)	220 (54.6)	144 (42.0)
PRO total scores at T0, mean (±SD)			
FACT-G	70.1 (17.1)	72.6 (16.2)	68.1 (17.8)
LCS	18.2 (5.4)	18.3 (5.1)	18.0 (5.8)
PHQ-4	3.7 (2.9)	3.6 (2.8)	3.9 (2.9)
Patients with completed first-line treatments	636 (85.3)	332 (82.4)	304 (88.6)
Treatment duration in months, median (25%-75% quartile)	3.8 (1.4-15.5)	4.9 (1.6-12.4)	3.0 (0.7-8.5)
Reason for end of treatment[c]			
Toxicity	71 (11.2)	44 (13.3)	27 (8.9)
Progression	232 (36.5)	131 (39.5)	101 (33.2)
According to treatment plan/guidelines	48 (7.5)	28 (8.4)	20 (6.6)
Other	278 (43.7)	124 (37.3)	154 (50.7)
Missing	7 (1.1)	5 (1.5)	2 (0.7)
Registry best response[d]			
Complete response	17 (2.7)	9 (2.7)	8 (2.6)
Partial response	159 (25.0)	89 (26.8)	70 (23.0)
Stable disease	145 (22.8)	84 (25.3)	61 (20.1)
Progressive disease	125 (19.7)	71 (21.4)	54 (17.8)
Unknown	190 (29.9)	79 (23.8)	111 (36.5)

(continued)

Table 2. Continued

Treatment and PRO Parameters	Total N = 746	Potentially Trial Eligible n = 403	Trial Ineligible n = 343
Patients with second-line treatment	199 (26.7)	115 (28.5)	84 (24.5)
Second-line treatment strategy[e]			
CT	141 (70.9)	80 (69.6)	61 (72.6)
CPI mono	19 (9.5)	11 (9.6)	8 (9.5)
CPI+CT	16 (8.0)	8 (6.9)	8 (9.5)
Tyrosine kinase inhibitor	7 (3.5)	7 (6.1)	0 (0.0)
RAM/NIN + DOC	10 (5.0)	8 (6.9)	2 (2.4)
Other	6 (3.0)	1 (1.0)	5 (9.5)
Patients with potential for second line[f]			
First-line treatment ongoing	104 (13.9)	65 (16.1)	39 (11.4)
First-line completed, but no new therapy line documented	81 (10.9)	44 (10.9)	37 (10.8)

Note: Data are number (%), unless otherwise indicated. Some percentages might not add up to 100% owing to rounding.
[a]TTNT was defined as the time between start of first-line treatment and start of second treatment line or death, whichever occurred first. Patients without start of subsequent treatment line or death were censored at last contact.
[b]Potential: patients whose current treatment is ongoing and who could still receive surgery/radiotherapy. "No palliative radiotherapy given" can only be documented at completion of documentation for the respective patient.
[c]Percentages relate only to patients with completed first-line treatments.
[d]There are no specifications as to the timing, frequency or criteria of tumor assessment, thus registry response data should be considered as the best clinical approximation and might not be identical to the response determined in clinical trials.
[e]Percentages relate only to patients with second-line treatment.
[f]Potential: patients whose line of treatment is ongoing or for whom data on a new line of treatment have not yet been documented could still have the option of receiving or not receiving second-line therapy during the course of the project.
CI, confidence interval; CPI, checkpoint inhibitor; CT, chemotherapy; DOC, docetaxel; FACT-G, Functional Assessment of Cancer Therapy-General; LCS; lung cancer subscale; NIN, nintedanib; PHQ, Patient Health Questionnaire; PRO, patient-reported outcome; rw, real-world; RAM, ramucirumab; TTNT, time to next treatment.

close to 50% of patients with mNSCLC treated in everyday clinical practice in German lung cancer-specified institutions would not have met the eligibility criteria for registrational trials of immunotherapy and as such are treated without clear evidence from clinical trials. Interestingly, this finding has similarly been reported from a recently published retrospective study from Germany evaluating real-world pembrolizumab therapy in patients with advanced or mNSCLC.[24] It is of substantial clinical relevance for physicians discussing outcomes to be expected with their patients as it implies that published outcome data from clinical trials may not be transferred to a significant proportion of their patients. In our study, trial ineligibility was associated with a significantly worse clinical outcome in multivariable Cox regression models with HR (trial-ineligible versus potentially eligible patients) for disease progression of 1.43 (95% CI: 1.19–1.72) and a HR for death of 1.36

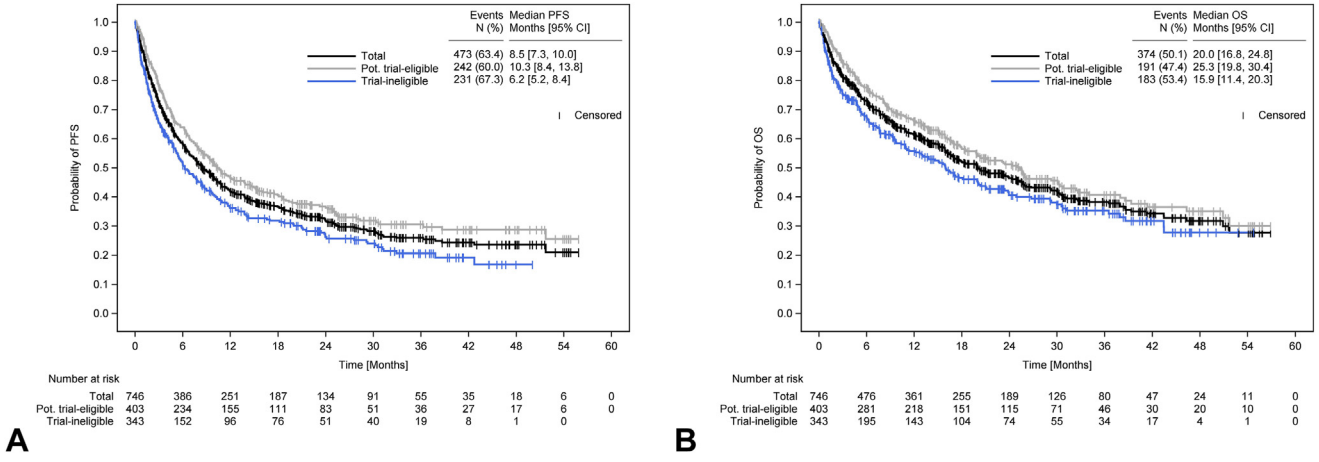
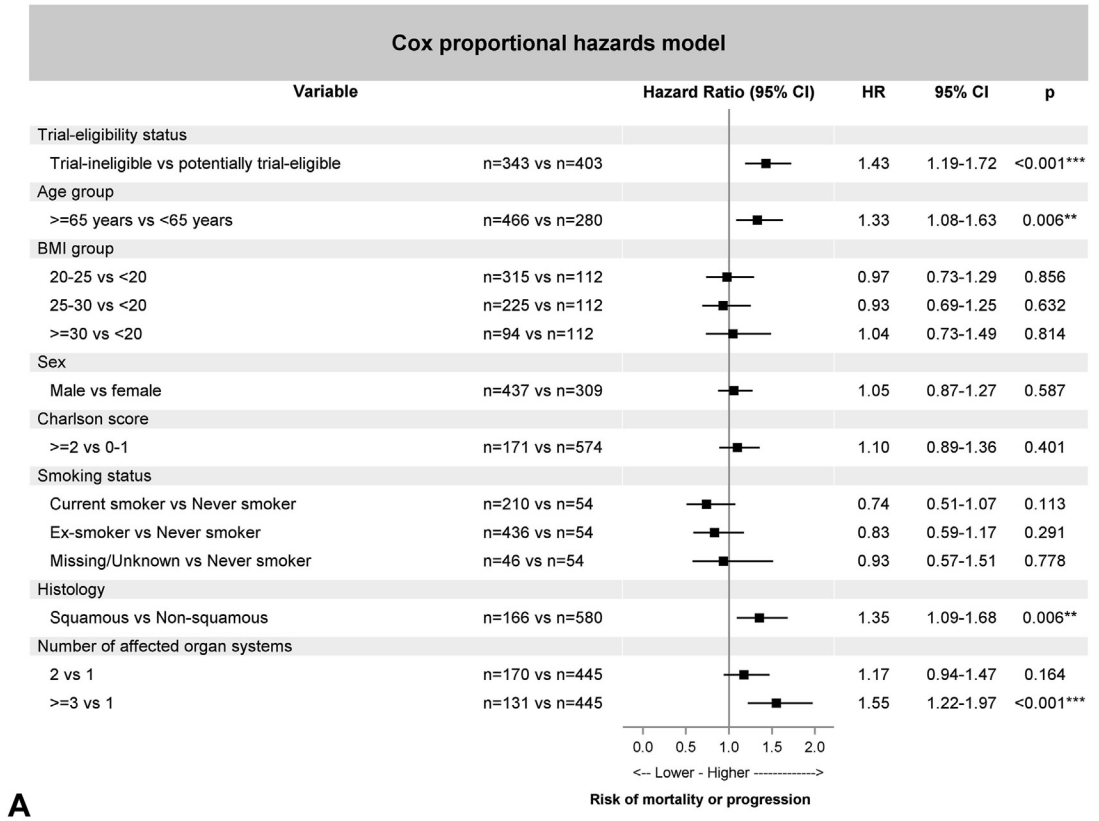
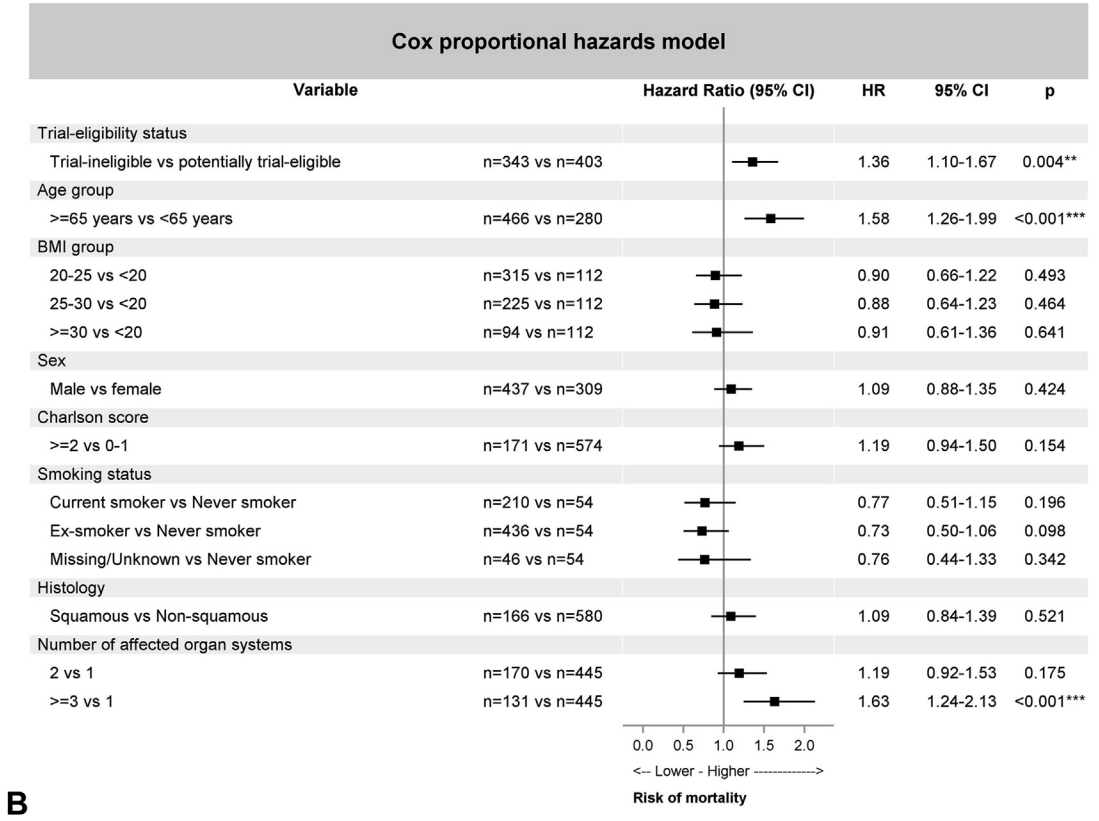


Figure 2. Survival analysis. (*A*) First-line registry-PFS and (*B*) first-line OS in all patients with metastatic NSCLC with TPS greater than or equal to 50% and first-line pembrolizumab monotherapy who had been followed-up for at least 12 months (total) and classified by trial-eligibility status. OS, overall survival; PFS, progression-free survival; Pot., potentially; TPS, tumor proportion score.



A



B

Figure 3. Regression analysis. Cox proportional hazards model for (*A*) PFS and (*B*) OS, respectively. OS, overall survival; PFS, progression-free survival.

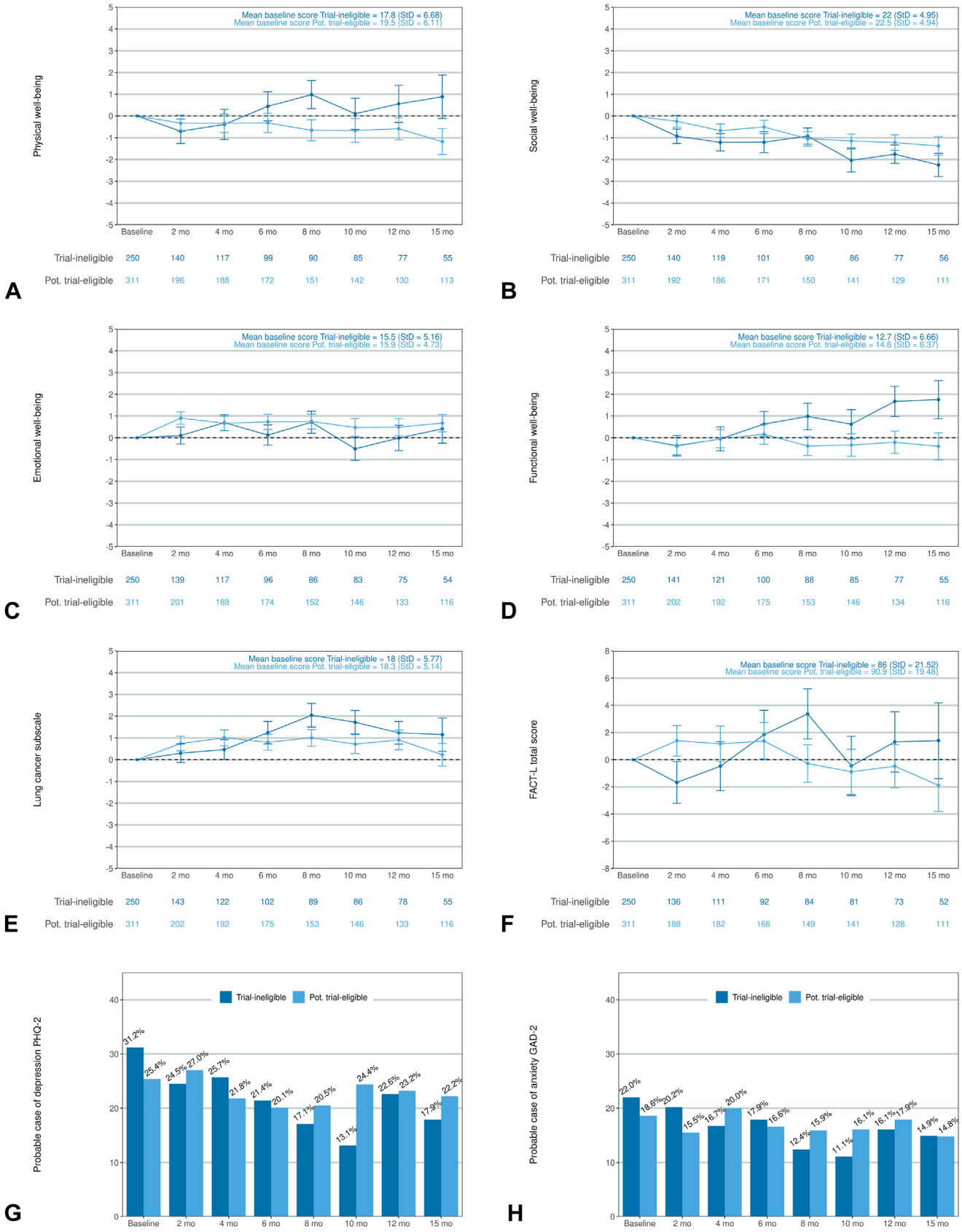


Figure 4. Change in health-related quality of life and reported anxiety/depression from baseline to month 15. Mean change from baseline plots (mean ± 95% CI) for the FACT-G subscales (*A*) physical well-being, (*B*) social well-being, (*C*) emotional

(95% CI: 1.10–1.67). Of note, outcomes of patients who would have met the eligibility criteria of pivotal clinical trials (KEYNOTE-024 and -042)[8–10,18] were comparable to published outcomes of the respective studies: PFS: 10.3 months (95% CI: 8.4–13.8) versus 7.7 months (95% CI: 6.1–10.2) in the updated analysis of KEYNOTE-024 and 7.1 months (95% CI: 5.9–9.0) in KEYNOTE-042; OS: 25.3 months (95% CI: 19.8–30.4) versus 26.3 months (95% CI: 18.3–40.4) in the updated analysis of KEYNOTE-024 and 20.0 months (95% CI: 15.4–24.9) in KEYNOTE-042. This finding is in line with previous study results among patients with advanced or mNSCLC receiving pembrolizumab monotherapy, in which effectiveness in real-world was well comparable to clinical trial efficacy provided that patients were comparable to each other with regard to baseline characteristics.[24,25] Remarkably, outcomes of trial-eligible patients in our study were comparable to trial results, although patients in our study were notably older (median age 70 y versus 65 y in KEYNOTE-024 and 63 y in KEYNOTE-042).[8,10,18] Although older age was associated with worse survival in our analysis, it was not found to have an influence on OS in previous real-world studies including older patients.[26,27] In contrast, patients with advanced or mNSCLC and a poor performance status were consistently found to have clearly worse outcomes in several previously published purely retrospective studies evaluating pembrolizumab monotherapy, including a recent meta-analysis of real-world data.[26,28–33] As patients with an ECOG greater than 1 were excluded from most RCTs evaluating immune CPI therapy in mNSCLC, there is little evidence about the efficacy of immune therapy in this patient population. To date, only two small, single-arm phase 2 trials evaluated pembrolizumab in patients with advanced or mNSCLC and an ECOG status of greater than or equal to 2 and similarly revealed worse outcomes compared with those obtained in the registrational studies.[34,35] Accordingly, another phase 2 trial evaluating nivolumab as second-line therapy revealed worse outcomes among patients with an ECOG status of 2.[36]

In the present study, poor performance status (ECOG status $>$ 1) was a main reason for patients to be classified as trial-ineligible. Likewise, poor ECOG status was the most common reason for trial-ineligibility in two previously published retrospective studies evaluating the impact of trial eligibility on CPI treatment outcomes in patients with advanced or mNSCLC.[13,14] In the study of Gan et al.[13] from Canada, outcomes of trial-ineligible patients with advanced NSCLC were inferior to those of trial-eligible patients (HR for death trial-ineligible versus trial-eligible: 2.21 (95% CI: 1.58–3.11)), and a considerable proportion of patients (39%) were classified as trial-ineligible, consistent with our results. Besides similar criteria as applied in our study (ECOG $>$ 1 and presence of brain metastases), patients were further classified as trial-ineligible if they exceeded a defined threshold of laboratory parameters (estimated glomerular filtration rate, hemoglobin, and neutrophils). Unlike in our study, also patients with a TPS for PD-L1 of less than 50% and patients receiving pembrolizumab in combination with chemotherapy were included; however, most patients had a TPS for PD-L1 of greater than or equal to 50% (86% trial-ineligible and 80% trial-eligible patients) and were treated with pembrolizumab monotherapy (89% trial-ineligible and 85% trial-eligible patients). Yoo et al.[14] suggested a huge gap between phase 3 trials on immune CPIs and the general population, as in their study an even higher number of patients with advanced or mNSCLC were classified as trial-ineligible (approximately 70%) and were found to have inferior outcomes as compared with those of trial-eligible patients. Notably, the low number of included patients receiving CPIs as routine practice (n = 53) limits the comparability with our data. Furthermore, the study differed from our study in that patients treated with second-line CPIs (either nivolumab or pembrolizumab) were included and compared with RCTs in that setting.[14]

Despite the limited comparability between the studies, the findings overall suggest that the outcomes of patients with mNSCLC receiving pembrolizumab monotherapy obtained in clinical trials within a selected patient population should not generally be translated to patients treated in routine practice but only to those fulfilling the inclusion criteria of the studies. Especially patients with a poor performance status, representing a considerable proportion of patients in routine practice (20%–30%),[37] may have clearly worse outcomes. Inferior survival was also reported for patients with mNSCLC and symptomatic brain metastases,[24] whereas not consistently.[38] These results point toward a need to

well-being, (*D*) functional well-being, and the (*E*) lung cancer subscale LCS, and for the (*F*) FACT-L total scale. For better readability, a line graph format was chosen; however, individual data points are found and not a change over time. Proportion of probable cases of (*G*) depression and (*H*) anxiety for potentially trial-eligible and ineligible patients. Change from baseline is calculated as mean of the individual difference between baseline and respective time point for all patients with data available at baseline and the respective time points. Probable cases of depression (PHQ-2) or anxiety (GAD-2) are defined as a score greater than or equal to 3 on the respective scale at the respective time point. CI, confidence interval; FACT-G/-L Functional Assessment of Cancer Therapy-General/-Lung; GAD-2, Generalized Anxiety Disorder Scale-2; LCS, lung cancer subscale; PHQ-2, Patient Health Questionnaire-2; pot., potentially.

extend the inclusion criteria of clinical trials to obtain evidence about the efficacy of new therapy options within a broader patient population.

Besides further evidence on patients' clinical outcome, more evidence on PROs would also be of interest to evaluate quality of life and symptom burden experienced by more comorbid mNSCLC patients with worse performance status receiving immunotherapy, whose treatment tolerability may differ and who might need a closer monitoring of health-related quality of life and symptom burden as suggested in a previous study.[39] In the present analysis of PRO data, only the subscale baseline scores for physical well-being and functional well-being slightly differed between the groups and were—as it might be expected—higher for potentially trial-eligible patients than for trial-ineligible patients. Nevertheless, we did not observe any clinically relevant differences in mean change to baseline in the subscale scores during the course of first-line treatment.

Although our findings are important to be considered by physicians discussing outcome expectations with their patients, they are not meant to guide treatment decisions. Although patients with mNSCLC frequently excluded from clinical trials may have worse outcomes as compared with selected patients usually presenting at a more favorable risk profile, they may still benefit from treatment with pembrolizumab, as it was also suggested from the referenced phase 2 trials, in which good tolerability of pembrolizumab was reported among patients with a poor performance status.[34,35] Notwithstanding the above-mentioned discussion, the subjectivity and variability of measurement of patients' performance status is an important point to consider when interpreting outcome data according to performance status and has been suggested to result in large heterogeneity.[29] In our study, there was a considerable proportion of patients with unknown ECOG status (26.5%), who were classified as trial-ineligible, which may further limit the interpretation of data on patients' performance status. Nevertheless, sensitivity analyses excluding all patients with unknown ECOG status were performed, which did not reveal substantial differences from the primary analysis. As there might be differences other than those described between patients classified as trial-ineligible and potentially trial-eligible, no causal relations can be drawn. Furthermore, the proportion of patients classified as trial-ineligible might be underestimated as there are additional exclusion criteria frequently defined from clinical trials (e.g., sufficient life expectancy, history of autoimmune condition, steroid use) which were not captured in the present study. Along with these limitations, the study has important strengths as the analysis of data from a large real-world cohort and the prospective design, thereby adding valuable evidence to the limited data from mainly modest-sized retrospective studies published to date.

In conclusion, the results of the present study suggest that a considerable proportion of patients in German routine practice would be ineligible to participate in a clinical trial. Although outcomes of potentially trial-eligible patients were comparable to outcomes obtained in the registrational studies, patients classified as trial-ineligible had significantly worse outcomes. These findings are of substantial clinical relevance for physicians discussing outcomes to be expected with their patients. Moreover, they point toward the need to extend inclusion criteria of clinical trials investigating immunotherapy for patients with mNSCLC to generate evidence for patients usually excluded from clinical trials, such as patients with a poor performance status or relevant medical history.

CRediT Authorship Contribution Statement

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Martin Sebastian: Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Writing—original draft.

Wolfgang M. Brueckl: Investigation, Resources, Writing—review and editing.

Horst-Dieter Hummel: Investigation, Resources, Writing—review and editing.

Bastian Jaeschke: Investigation, Resources, Writing—review and editing.

Jens Kern: Investigation, Resources, Writing—review and editing.

Claas Wesseler: Investigation, Resources, Writing—review and editing.

Martina Jänicke: Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing—original draft.

Annette Fleitz: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Visualization, Writing—original draft.

Stefan Zacharias: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing—original draft.

Annette Hipper: Funding acquisition, Project administration, Supervision, Writing—original draft.

Annika Groth: Project administration, Writing—review and editing.

Wilko Weichert: Investigation, Resources, Writing—review and editing.

Steffen Dörfel: Investigation, Resources, Writing—review and editing.

Volker Petersen: Investigation, Resources, Writing—review and editing.

Jan Schröder: Investigation, Resources, Writing—review and editing.

Jochen Wilke: Investigation, Resources, Writing—review and editing.

Wilfried E.E. Eberhardt: Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Writing—original draft.

Michael Thomas: Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Writing—original draft.

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Ethics Statement

The CRISP Registry was approved by the responsible ethics committee and is registered at ClinicalTrials.gov (NCT02622581). Written informed consent was obtained from all patients.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

Appendix

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