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Original research

First-line immunotherapy for lung cancer with *MET* exon 14 skipping and the relevance of *TP53* mutations

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ABSTRACT

Background: The efficacy of checkpoint inhibitors for non-small cell lung cancer (NSCLC) with *MET* exon 14 skipping (METΔ14ex) remains controversial.
Materials and methods: 110 consecutive METΔ14ex NSCLC patients receiving first-line chemotherapy (CHT) and/or immunotherapy (IO) in 10 German centers between 2016–2022 were analyzed.
Results: Combined CHT-IO was given to 35/110 (32%) patients, IO alone to 43/110 (39%), and CHT to 32/110 (29%) upfront. Compared to CHT, CHT-IO showed longer progression-free survival (median PFS 6 vs. 2.5 months, p = 0.004), more objective responses (ORR 49% vs. 28%, p = 0.086) and numerically longer overall survival (OS 16 vs. 10 months, p = 0.240). For IO monotherapy, OS (14 vs. 16 months) and duration of response (26 vs. 22 months) were comparable to those of CHT-IO. Primary progressive disease (PD) was more frequent with IO compared to CHT-IO (13/43 vs. 3/35, p = 0.018), particularly for never-smokers (p = 0.041). Higher PD-L1 TPS were not associated with better IO outcomes, but *TP53* mutated tumors showed numerically improved ORR (56% vs. 32%, p = 0.088) and PFS (6 vs. 3 months, p = 0.160), as well as longer OS in multivariable analysis (HR=0.54, p = 0.034) compared to their wild-type counterparts. Any second-line treatment was administered to 35/75 (47%) patients, with longer survival for capmatinib or tepotinib compared to crizotinib (PFS 10 vs. 3 months, p = 0.013; OS 16 vs. 13 months, p = 0.270).

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Conclusion: CHT-IO is superior to CHT, and IO alone also effective for METΔ14ex NSCLC, especially in the presence of *TP53* mutations and independent of PD-L1 expression, but never-smokers are at higher risk of primary PD.

Introduction

Mesenchymal epithelial transition factor exon 14 skipping (METΔ14ex) is the driver alteration for approximately 3–4% of non-small cell lung cancers (NSCLC) and target of the recently approved MET inhibitors tepotinib and capmatinib [1,2]. These mutations occur more frequently in older, comorbid patients with a history of smoking and sarcomatoid or adenosquamous tumor histology [3], contrary to *EGFR* and *ALK* alterations which affect mostly never-smokers with younger age and longer life expectancy [4,5]. Although METΔ14ex is generally associated with a higher PD-L1 expression [6,7], the efficacy of immune checkpoint inhibitors (ICI) remains controversial for these patients, as their survival under ICI has been shorter than that of other NSCLC in some reports, which, however, were based on a few patients treated mostly in later lines. This situation is due to both the low incidence and technical difficulties of METΔex14 diagnosis, which frequently requires RNA analysis [8], and has resulted in a lack of robust evidence in the literature. For example, among the 551 patients of the international IMMUNOTARGET which established the ICI-unresponsiveness of oncogene-driven NSCLC, in fact only 23 had METΔex14 [9]. Similarly, the large study by Sabari *et al* with 147 METΔex14 patients, which analyzed PD-L1 expression and tumor mutational burden (TMB), included only 24 response-evaluable cases, of which just 11 had received ICI upfront [6]. For daily clinical practice, the efficacy of ICI already in the first line for METΔ14ex-mutated NSCLC is a matter of major significance, as these patients frequently present with impaired general condition that renders the administration of chemotherapy problematic. The problem is aggravated within the European Medicines Agency (EMA) jurisdiction, which has so far restricted the use of tepotinib and campatinib only for patients after prior immunotherapy and/or platinum-based chemotherapy. Therefore, main aim of the current study was to analyze the efficacy of first-line PD-(L)1 inhibitors alone or combined with chemotherapy in the first line using a large, contemporary and representative real-world cohort of NSCLC patients harboring METΔex14.

Patients and methods

Study population

This multicenter retrospective study included consecutive patients diagnosed with metastatic NSCLC harboring METΔex14 who received first-line PD-(L)1 inhibitors and/or chemotherapy in ten certified German academic lung cancer centers. METΔex14 was detected by

Table 1
Characteristics of study patients.

Variable	All patients	Immunotherapy + CHT PD-L1<50%	Immunotherapy + CHT PD-L1 ≥50%	Immunotherapy PD-L1 ≥50%	CHT All PD-L1	p value
Patients, n (%)	110 (100)	26 (24)	9 (8)	43 (39)	32 (29)	
Age, years						0.279
Median	72.0	72.9	68.1	72.4	72.6	
IQR	65.3-78.1	69.2-77.5	63.4-68.3	65.4-79.2	61.8-77.4	
Gender, n (%)						0.060
Male	56 (51)	18 (73)	4 (44)	21 (48)	20 (62)	
Female	54 (49)	7 (27)	5 (56)	22 (52)	12 (38)	
Histopathology, n (%)						0.366
Adenocarcinoma	86 (78)	19 (73)	7 (78)	35 (81)	25 (78)	
Squamous-cell	9 (8)	5 (19)	0 (0)	2 (5)	2 (6)	
Adenosquamous	9 (8)	1 (4)	1 (11)	4 (10)	3 (10)	
Sarcomatoid	4 (4)	1 (4)	1 (11)	0 (0)	2 (6)	
NOS	2 (2)	0 (0)	0 (0)	2 (5)	0 (0)	
ECOG PS, n (%)						0.371
0	38 (35)	12 (46)	4 (44)	11 (26)	11 (34)	
1	45 (41)	9 (35)	2 (22)	17 (39)	17 (53)	
2	21 (19)	5 (19)	2 (22)	11 (26)	3 (10)	
3	5 (4)	0 (0)	1 (11)	3 (7)	1 (3)	
unknown	1 (1)	0 (0)	0 (0)	1 (2)	0 (0)	
Smoking history, n (%)						0.666
never	36 (33)	11 (42)	2 (22)	12 (27)	11 (34)	
former	49 (45)	11 (42)	5 (56)	21 (49)	12 (38)	
current	18 (16)	4 (16)	1 (11)	5 (12)	8 (25)	
unknown	7 (6)	0 (0)	1 (11)	5 (12)	1 (3)	
Brain metastases, n (%)						0.282
Yes	32 (29)	8 (31)	5 (56)	10 (23)	9 (28)	
No	78 (71)	17 (59)	4 (44)	33 (77)	23 (72)	
TP53 status						0.082
Wild type	55 (50)	11 (42)	4 (44)	19 (44)	21 (66)	
Mutated	37 (34)	11 (42)	4 (44)	17 (40)	5 (15)	
Unknown	18 (16)	4 (16)	1 (12)	7 (16)	6 (19)	
PD-L1 TPS						<0.001
0%	16 (15)	12 (46)	0 (0)	0 (0)	4 (13)	
1-49%	30 (27)	14 (54)	0 (0)	0 (0)	16 (50)	
≥50%	63 (57)	0 (0)	9 (100)	43 (100)	11 (34)	
Unknown	1 (1)	0 (0)	0(0)	0 (0)	1 (3)	

IQR, Interquartile Range; CHT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, Programmed death-ligand 1; TPS, Tumor Proportion Score

Table 2
Outcomes by patient group.

Outcome	All patients	Immunotherapy + CHT PD-L1<50% (n=26)	Immunotherapy + CHT PD-L1 ≥50% (n=9)	Immunotherapy PD-L1 ≥50% (n=43)	CHT All PD-L1 (n=32)	p value
Best response (%)						0.182
PR		12 (48)	5 (56)	15 (35)	9 (28)	
SD		8 (32)	1 (11)	8 (19)	10 (31)	
PD		2 (8)	1 (11)	13 (30)	11 (34)	
Early death		3 (12)	2 (22)	7 (16)	2 (6)	
Median DoR (months)		22	23	26	5	0.006
Median PFS (months)		6	4	3	2.5	0.039
Median OS (months)		16	5	14	10	0.600

CHT, chemotherapy; PD-L1, Programmed death-ligand 1; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression free survival; DoR: duration of response; OS, overall survival

combined RNA and DNA amplicon-based or capture-based next-generation sequencing (NGS), which was performed locally according to the principles of the German national Network for Genomic Medicine, as published [10,11]. Based on the current EMA approval of ICI, 4 patient groups were analyzed: under chemoimmunotherapy (CHT-IO) with PD-L1 < 50% (PD-L1lo); under CHT-IO with PD-L1 TPS ≥ 50% (PD-L1hi); under immunotherapy alone (IO), all of which had tumors with PD-L1 TPS ≥ 50%; and patients under chemotherapy alone (CHT), whose tumors could show any level of PD-L1 expression. Clinicopathologic characteristics were extracted from the medical records. Endpoints included overall response rate (ORR, defined as the sum of complete and partial remissions among all evaluable patients), progression-free survival (PFS, defined as the time from treatment start until disease progression or death) and overall survival (OS, defined as the time from treatment start until death from any cause), with censoring at the time of last follow-up. The study was conducted according to the declaration of Helsinki with institutional review board approval from each participating center. Further details about the Patients and Methods are provided in the Supplements.

Statistical analysis

Continuous and categorical variables were compared using the Wilcoxon and chi-square test, respectively. Survival was calculated according to Kaplan-Meier and compared between groups using log-rank tests. Follow-up time was calculated according to the reverse Kaplan-Meier method. The association between covariates and PFS or OS was analyzed using Cox regression with reporting of Hazard ratios (HR) and 95% confidence intervals (CI). Covariates with p-values < 0.10 in univariable testing were included in multivariable analysis. Statistical analyses were performed using R v4.1.3 (Vienna, Austria).

Results

Clinical characteristics

Overall, 110 consecutive patients treated between 2016–2022 could be enrolled in this study (suppl. Fig. 1). The median age was 72 years (range 49–87), with an equal distribution among sexes (49% or n = 54 female, Table 1). The reported Eastern Cooperative Group (ECOG) performance status (PS) was balanced between 0, 1, and 2 + with 38 (35%), 45 (41%), and 26 (24%) cases, respectively. A positive smoking history was reported in 61% of patients (n = 67 active/former smokers), while brain metastases at initial diagnosis were present in 32 (29%). The most common histologic subtype was adenocarcinoma (n = 86, 78%), followed by squamous cell carcinoma (n = 9, 8%), adenosquamous carcinoma (n = 9, 8%), sarcomatoid carcinoma (n = 4, 4%) and NSCLC, not otherwise specified (NOS, n = 2 or 2%). The PD-L1 TPS was ≥ 1% in 93 patients (85%) and ≥ 50% in 63 patients (57%). The most frequently co-mutated gene was *TP53* (n = 39, 35%). By inclusion criteria, all patients had received some first-line systemic therapy, either ICI (78/110, 71%) alone (43/78, 55%), or ICI in combination with CHT (35/78, 45%), or plain CHT (32/110, 29%). Patient characteristics according to treatment group are summarized in Table 1, while the *MET* and *TP53* mutations of study patients are listed in suppl. Table 1.

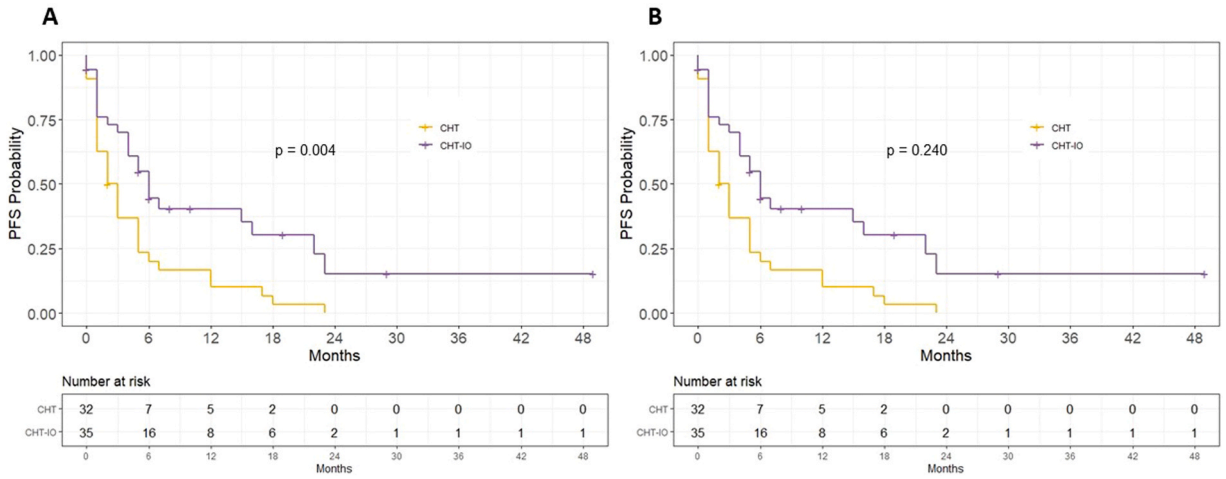

Fig. 1. Progression-free and overall survival of patients with non-small-cell lung cancer harboring METΔex14 by treatment. (A) Median progression-free survival (PFS) was 6 months (95% confidence interval [95% CI] 4–23 [NR]) for CHT-IO vs. 2.5 months (95% CI 1–5) for CHT (logrank p = 0.004). Patients treated with CHT or CHT-IO (n = 67) were included in this analysis. (B) Median overall survival (OS) was 16 months (95% CI 12-NR) for CHT-IO vs. 10 months (95% CI 6–21) for CHT (logrank p = 0.240). Patients treated with CHT or CHT-IO (n = 67) were included in this analysis.

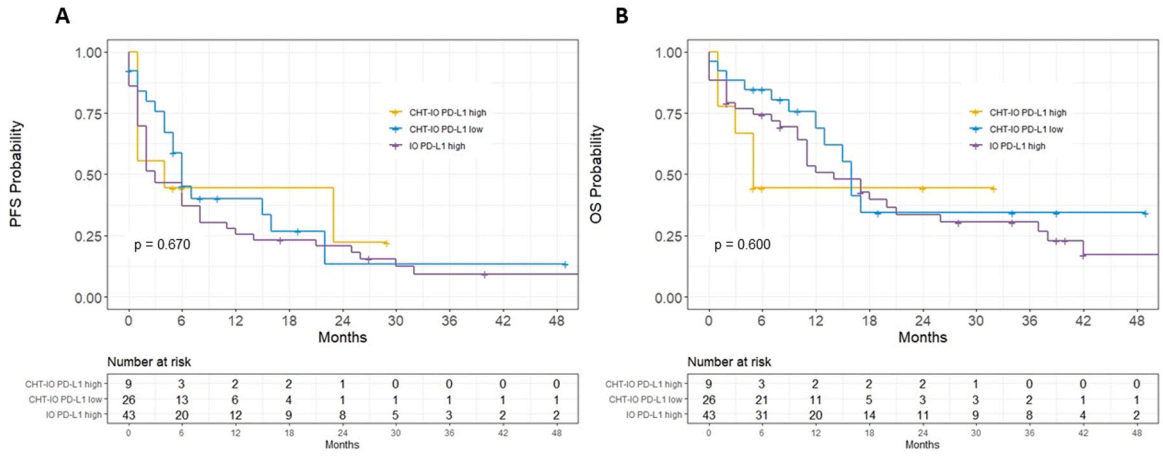

Fig. 2. Progression-free and overall survival of patients with non-small-cell lung cancer harboring METΔex14 by treatment and PD-L1 status. (A) Median progression-free survival (PFS) was 6 months (95% CI 5-Not reached [NR]) for CHT-IO-treated PD-L1^{lo} patients vs. 4 months (95% CI 1-NR) for CHT-IO-treated PD-L1^{hi} patients vs. 3 months (95% CI 2–8) for IO-treated PD-L1^{hi} patients (logrank p = 0.670). All patients treated with first-line PD-(L)1 inhibitors (n = 78) were included in this analysis. (B) Median overall survival (OS) was 16 months (95% CI 13-NR) for CHT-IO-treated PD-L1^{lo} patients vs. 14 months (95% CI 11–26) for CHT-IO-treated PD-L1^{hi} patients vs. 5 months (95% CI 3-NR) for IO-treated PD-L1^{hi} patients (logrank p = 0.600). All patients treated with first-line PD-(L)1 inhibitors (n = 78) were included in this analysis.

Efficacy of first-line chemotherapy with or without immunotherapy

In the overall population (n = 110) the median OS was 15 months (95% CI 10.7–19.3, Table 2) and the median follow-up 34 months (95% CI 28–42). Among patients exposed to chemotherapy, the ORR was 49% (n = 17/35) for CHT-IO vs. 28% (n = 9/32) for CHT (p = 0.086). Furthermore, CHT-IO was associated with significantly longer PFS (median PFS 6 vs. 2.5 months, log-rank p = 0.004), and a trend for longer OS (median OS 16 vs. 10 months, log-rank p = 0.240) compared to CHT (Fig. 1).

Efficacy of first-line immunotherapy alone or combined with chemotherapy

Numerical, but not statistically significant differences were noted between CHT-IO (in PD-L1^{lo} or PD-L1^{hi} patients) and IO monotherapy, in particular for ORR [46% (n = 12/26) or 56% (n = 5/9), vs. 35% (15/43), respectively, p = 0.407] and PFS (median 6 or 4, vs. 3 months, p = 0.670), while the duration of response (DoR, median 22 or 23, vs. 26 months, p = 0.670) and OS (median 16 or 5, vs. 14 months, p = 0.600) appeared comparable (Table 2 and Fig. 2).

Thirteen patients (17%) suffered early death before the first radiologic evaluation, without significant differences between treatment groups (p = 0.825). The best response under therapy was primary progressive disease (PD) for 16 patients (20%), including 30% (13/43) under IO vs. 9% (3/35) under CHT-IO (p = 0.0185). Among patients treated with IO monotherapy, early death or primary PD were significantly associated with smoking status: 8 of the 17 patients with PD as best response or early death were never smokers (47%) and 9 former smokers (53%), while patients with PR or SD were more frequently current (5/21, 24%) or former smokers (12/21, 51%) than never smokers (4/21, 19%, p = 0.041). Trends were also noted in the associations of early death and primary PD with older age (median 76 vs. 70 years, p = 0.165), and a worse ECOG PS ≥ 1 (84% vs. 65%, p = 0.121).

We did not observe better clinical outcomes for tumors with higher compared to lower PD-L1 TPS: the median PFS was 3 months for PD-L1 TPS ≥ 50% under IO monotherapy and 4 months for PD-L1 TPS ≥ 50% under CHT-IO vs. 6 months for PD-L1 TPS 1–49%, and 15 months for PD-L1 negative tumors (p = 0.540, Table 2 and suppl. Fig. 2A); the median

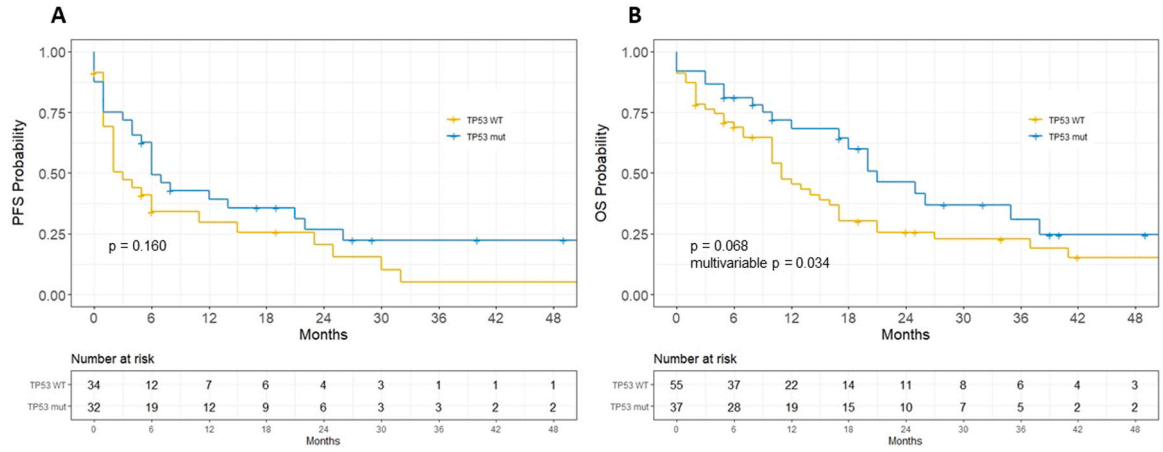

Fig. 3. Progression-free and overall survival of patients with non-small-cell lung cancer harboring METΔex14 by *TP53* mutational status. (A) Median progression-free survival (PFS) was 6 months (95% confidence interval [95% CI] 5–22) for *TP53* mutated vs. 3 months (95% CI 2–15) for *TP53* wild-type tumors (logrank p = 0.160) treated with first-line PD-(L)1 inhibitors (n = 66 patients with available *TP53* status). (B) Median overall survival (OS) was 21 (95% CI 17-NR) for study patients with *TP53* mutated vs. 11 months (95% CI 10–17) for study patients with *TP53* wild-type tumors (p = 0.068 with a logrank test, p = 0.034 in the multivariable analysis).

Table 3
Factors associated with survival.

Variable	OS overall population N=110		PFS CHT N= 32		PFS IO/CHT-IO N= 78	
	HR (univariable)	HR (multivariable)	HR (univariable)	HR (multivariable)	HR (univariable)	HR (multivariable)
Sex						
Male	-		-		-	
Female	0.90 (0.57-1.42, p=0.663)		0.70 (0.32-1.55, p=0.380)		1.08 (0.65-1.79, p=0.779)	
Age						
<70	-	-	-		-	
≥70	**2.31 (1.40-3.81, p=0.001)**	**2.20 (1.23-3.92, p=0.007)**	0.80 (0.38-1.69, p=0.564)		1.41 (0.85-2.35, p=0.181)	
Smoking status						
Current/former	-		-		-	
Never	1.00 (0.60-1.66, p=1.000)		0.82 (0.38-1.78, p=0.616)		1.11 (0.64-1.94, p=0.709)	
Histopathology						
Adeno	-		-	-	-	
Non-adeno	1.08 (0.63-1.85, p=0.784)		**3.12 (1.28-7.62, p=0.012)**	**4.20 (1.62-10.86, p=0.003)**	1.04 (0.56-1.92, p=0.900)	
TP53						
WT	-	-	-		-	
mutated	0.61 (0.35-1.04, p=0.068)	**0.54 (0.31-0.96, p=0.034)**	0.92 (0.31-2.79, p=0.886)		0.67 (0.38-1.17, p=0.161)	
PD-L1 TPS						
<50%	-		-	-	-	
>=50%	1.35 (0.84-2.16, p=0.212)		**3.95 (1.66-9.39, p=0.002)**	**4.77 (1.93-11.80, p=0.001)**	1.28 (0.73-2.26, p=0.387)	
PS ECOG						
0-1	-	-	-		-	
2-3	1.67 (0.99-2.82, p=0.056)	1.75 (0.96-3.22, p=0.069)	2.25 (0.74-6.82, p=0.152)		1.30 (0.74-2.28, p=0.370)	
Brain metastases						
No	-		-		-	
Yes	1.33 (0.82-2.16, p=0.244)		1.28 (0.56-2.88, p=0.558)		1.10 (0.63-1.91, p=0.742)	

OS was 14 months for tumors with PD-L1 TPS ≥ 50% under IO monotherapy and 5 months for tumors with PD-L1 TPS ≥ 50% under CHT-IO vs. 15 months for tumors with PD-L1 TPS 1–49%, and 16 months for PD-L1 negative tumors (p = 0.690, Table 2 and suppl. Figure 2B).

On the other hand, ICI efficacy appeared to be superior for *TP53* mutated compared to wild-type tumors with a trend for higher ORR (18/33 or 56% vs. 11/33 or 32%, respectively, p = 0.083), as well as a trend for longer PFS (median 6 vs. 3 months, respectively, HR 0.67, 95% CI 0.38–1.17, p = 0.160, Fig. 3A). Moreover, in the overall population *TP53* mutated tumors showed longer OS compared to wild-type tumors (median 21 vs. 11 months, respectively, HR 0.61, 95% CI 0.35–1.04, p = 0.034 in the multivariable analysis, Fig. 3B and Table 3). There was no association between the *TP53* status and PD-L1 *TPS* (p = 0.760, suppl. Fig. 3).

Second-line treatment after progression by first-line treatment

Overall, 49/110 patients (45%) received any second-line treatment, among which 22/49 (45%) TKI, 15/49 (31%) CHT, 10/49 (20%) IO, 2/49 (4%) CHT-IO. Among patients who were dead at the time of data cut-off, 40/75 (53%) did not receive any second-line treatment. Among patients receiving a second-line treatment after failure of IO or CHT-IO the outcome appeared comparable between second-line TKI and CHT (overall 29/78 or 37%: 13 TKI [7 crizotinib, 2 capmatinib, 4 tepotinib], 14 chemotherapy [5 as monotherapy and 9 as platinum-based doublet], 2 CHT-IO after progression on pembrolizumab monotherapy): the median PFS was 7 vs. 5 months (p = 0.320) and the median OS 10 vs. 7 months for TKI vs. CHT after failure of (chemo-)immunotherapy, respectively (p = 0.820). Among patients with second-line TKI, tepotinib or capmatinib were associated with a significantly longer PFS compared to crizotinib (10 vs. 3 months, HR 0.17 [95% CI 0.03–0.83], p = 0.013, respectively, suppl. Fig. 4A). There was also a trend in favor of capmatinib/tepotinib for OS, but this did not reach statistical significance (16 vs. 13 months, HR 0.46 [95% CI 0.11–1.89], p = 0.270, suppl. Fig. 4B). Two patients receiving second-line TKI achieved a PR, both treated with tepotinib.

Factors associated with survival

In the overall population, older age≥ 70 years was independently associated with shorter OS [HR 2.24 (95% CI 1.26–3.98), p = 0.006], while there was also a trend for shorter OS with worse ECOG PS 2 + [HR 1.73 (95% CI 0.95–3.15), p = 0.075]. Furthermore, *TP53* mutations were independently associated with longer OS [HR 0.54 (95% CI 0.31–0.93), p = 0.027]. Among patients treated with CHT, non-adenocarcinoma histology and a PD-L1 TPS ≥ 50% were independently associated with worse PFS (HR 4.20 [95% CI 1.62–10.86], p = 0.003 and HR 4.77 (95%bCI 1.93–11.80), p = 0.001, respectively]. The results of univariable and multivariable analyses are shown in Table 3.

Discussion

To our best knowledge, the current study reports the largest cohort of NSCLC patients with METΔex14 NSCLC receiving first-line immunotherapy in the real-world setting so far. The ORR and PFS from combined CHT-IO ware better compared to plain CHT, which is a first sign for clinical utility of PD-(L)1 inhibitors in this setting. Furthermore, IO monotherapy (only for PD-L1^{hi} tumors, according to the EMA label) also conferred substantial clinical benefit, with a somewhat lower ORR of 35% and shorter median PFS of 3 months, but longer DoR at 26 months and OS similar to that of CHT-IO, despite the worse clinical condition of

patients receiving PD-(L)1 inhibitors alone. Overall, the pattern is very similar to that of NSCLC without treatable alterations, for which CHT-IO improves the ORR and PFS, but not OS compared to plain immunotherapy [12,13]. This is important for clinical practice, because many patients with METΔex14-mutated NSCLC present in poor condition, which renders the additional administration of chemotherapy problematic, while at the same time the EMA label does not permit the use of MET TKI upfront. Based on the largest cohort of METΔex14 PD-L1^{hi} tumors reported to date (n = 52), our results demonstrate that IO monotherapy is a reasonable option for these patients and complement previous smaller or equivocal reports on this matter [14,15]. At the same time, caution is warranted in never-smokers, as almost half of the patients (8/17) showing primary PD as best response under IO monotherapy had no history of smoking, while the risk of PD as best response is significantly higher with IO monotherapy compated to CHT-IO (30% vs. 9%, p = 0.0185). It is also worth noting that the efficacy observed for IO monotherapy or CHT-IO in the present study focussing exclusively on the first-line (ORR 35% or 49% and duration of response 26 or 22 months) was generally higher than that reported in other retrospective studies, which included METΔex14 patients receiving immunotherapy mostly in later lines [6].

A further finding was that PD-L1 expression did not correlate with ICI efficacy, as patients with PD-L1 TPS ≥ 50% treated with either CHT-IO or IO monotherapy showed numerically shorter PFS and OS compared to patients with PD-L1 TPS < 50%. This is in contrast to NSCLC patients without actionable alterations, who show longer survival under IO or CHT-IO in case of high PD-L1 TPS ≥ 50% [16,17]. An association between higher PD-L1 expression and worse prognosis has also been described for other oncogene-driven NSCLC, for example ALK-positive tumors [18,19], and may be caused by stronger oncogenic signaling, as PD-L1 is downstream of both MET and ALK [20]. This notion is further supported by the higher PD-L1 expression in ALK-driven tumors with *EML4-ALK* variant 3,[19] which is known to be cause stronger ALK phosphorylation and shorter survival [21,22]. Additional potential links between higher PD-L1 expression and adverse prognosis in MET-driven tumors include the association of PD-L1 with *MET* amplifications [23], and the positive regulation of MET phosphorylation by PD-L1 through the inhibition of PTP1B [24].

Moreover, the current study provides an interesting signal about potentially superior outcome for METΔex14-mutated NSCLC under ICI if *TP53* co-mutations are present, since these patients showed higher ORR and longer OS in multivarlable testing. This echoes the association of *TP53* mutations with better ICI efficacy in *KRAS*-driven NSCLC [25], which is also strongly linked to smoking. Mechanistically, this is probably explained by the higher tumor mutational burden (TMB) of p53-deficient cancers [26], which may be particularly relevant in the low-TMB setting of METΔex14-mutated NSCLC, with a median of 3.8 mut/Mb [6]. On the other hand, *TP53* mutations are associated with impaired benefit from targeted drugs, including EGFR, ALK and MET inhibitors [27–29], and could therefore play a role in the decision between TKI and immunotherapy for METΔex14-positive NSCLC in the future, when more evidence accumulates.

Careful consideration about the first-line choice is especially important for METΔex14 NSCLC, because many patients may not have another chance for antitumor therapy. The rate of second-line treatment after failure of IO or CHT-IO was only 47% in our cohort. The finding of a longer PFS for the newer, MET-selective inhibitors tepotinib and capmatinib compared to crizotinib beyond the first line, underlines the importance of their approval in this setting. However, with the low rates of second-line treatment in METΔex14 NSCLC, many patients eligible for these agents at initial diagnosis may never get them due to deterioration from disease progression or treatment-related toxicity. The observed association between older age and worse ECOG at baseline with shorter OS in the present study underlines this problem.

Main limitations of the current study are the modest number of PD-L1^{hi} patients treated with CHT-IO, as well as its retrospective nature, which cannot exlude confounding. At the same time, main strengths are the largest real-world collection of METΔex14 NSCLC receiving first-line immunotherapy, as well as the homogenous management and high-quality clinical annotation within certified academic thoracic oncology centers. The more frequent use of IO monotherapy compared to CHT-IO in our PD-L1^{hi} cases actually reflects the dire clinical situation of many METΔex14 patients, who cannot tolerate chemotherapy. Pending validation in larger, prospective studies, the presented results provide solid evidence that IO monotherapy is a viable therapeutic option for many METΔex14 patients, especially older and comorbid (ex-) smokers, who cannot tolerate chemotherapy well, resulting in durable tumor responses and survival comparable to that of CHT-IO. Furthermore, PD-L1 expression does not appear to correlate with immunotherapy benefit, while *TP53* mutations emerge as a potential biomarker which may play a role in therapeutic decisions in the future.

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CRediT authorship contribution statement

MB: Conceptualization, Data curation, Investigation, Resources, Supervision, Writing – original draft, Writing – review & editing. JK: Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – review & editing. HL: Investigation, Resources, Writing – review & editing. DM: Investigation, Resources, Writing – review & editing. DiKa: Investigation, Resources, Writing – review & editing. MH: Investigation, Resources, Writing – review & editing. DK: Investigation, Resources, Writing – review & editing. RF: Investigation, Resources, Writing – review & editing. BH: Investigation, Resources, Writing – review & editing. SD: Investigation, Resources, Writing – review & editing. MF: Investigation, Resources, Writing – review & editing. MK: Investigation, Resources, Writing – review & editing. AV: Investigation, Resources, Writing – review & editing. HK: Investigation, Resources, Writing – review & editing. MA: Investigation, Resources, Writing – review & editing. CG: Investigation, Resources, Writing – review & editing. AT: Investigation, Resources, Writing – review & editing. MR: Investigation, Resources, Writing – review & editing. NF: Investigation, Resources, Writing – review & editing. AZ: Investigation, Resources, Writing – review & editing. MT: Conceptualization, Investigation, Supervision, Resources, Writing – review & editing. PC: Conceptualization, Data curation, Investigation, Resources, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

JK: speaker's honoraria from BMS, AstraZeneca and Pfizer, travel grants from Takeda, advisory board honoraria from Takeda, Roche and AstraZeneca.

DM: advisory board/lecture fees from AstraZeneca, BMS, Boehringer Ingelheim, Lilly, MSD, Novartis, Roche, Sanofi and Takeda.

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All other authors have no conflicts of interest to declare.

Data Availability

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

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113556.

References

[1] Assoun S, Theou-Anton N, Nguenang M, Cazes A, Danel C, Abbar B, Pluvy J, Gounant V, Khalil A, Namour C, et al. Association of TP53 mutations with response and longer survival under immune checkpoint inhibitors in advanced non-small-cell lung cancer. Lung Cancer 2019;132:65–71. https://doi.org/10.1016/J.LUNGCAN.2019.04.005.

[2] Hong L, Zhang J, Heymach VJ, Le X. Current and future treatment options for MET exon 14 skipping alterations in non-small cell lung cancer. Ther Adv Med Oncol 2021;13. https://doi.org/10.1177/1758835921992976.

[3] Schrock AB, Li SD, Frampton GM, Suh J, Braun E, Mehra R, Buck SC, Bufill JA, Peled N, Karim NA, et al. Pulmonary sarcomatoid carcinomas commonly harbor either potentially targetable genomic alterations or high tumor mutational burden as observed by comprehensive genomic profiling (In) J Thorac Oncol 2017:932–42.

[4] Vuong HG, Ho ATN, Altibi AM, Nakazawa T, Katoh R, Kondo T. Clinicopathological implications of MET exon 14 mutations in non-small cell lung cancer – a systematic review and meta-analysis. Lung Cancer 2018;123:76–82. https://doi.org/10.1016/j.lungcan.2018.07.006.

[5] Rudin CM, Avila-Tang E, Harris CC, Herman JG, Hirsch FR, Pao W, Schwartz AG, Vahakangas KH, Samet JM. Lung cancer in never smokers: molecular profiles and therapeutic implications. Clin Cancer Res 2009;15:5646–61. https://doi.org/10.1158/1078-0432.CCR-09-0377.

[6] Sabari JK, Leonardi GC, Shu CA, Umeton R, Montecalvo J, Ni A, Chen R, Dienstag J, Mrad C, Bergagnini I, et al. PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. Ann Oncol 2018;29:2085–91. https://doi.org/10.1093/ANNONC/MDY334.

[7] Xu Z, Li H, Dong Y, Cheng P, Luo F, Fu S, Gao M, Kong L, Che N. Incidence and PD-L1 expression of MET 14 skipping in chinese population: a non-selective NSCLC cohort study using RNA-based sequencing. Onco Targets Ther 2020;13:6245. https://doi.org/10.2147/OTT.S241231.

[8] Davies KD, Lomboy A, Lawrence CA, Yourshaw M, Bocsi GT, Camidge DR, Aisner DL. DNA-based versus RNA-based detection of MET exon 14 skipping events in lung cancer. J Thor Oncol 2019;14:737–41. https://doi.org/10.1016/j.jtho.2018.12.020.

[9] Mazieres J, Drilon A, Lusque A, Mhanna L, Cortot AB, Mezquita L, Thai AA, Mascaux C, Couraud S, Veillon R, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: Results from the IMMUNOTARGET registry. Ann Oncol 2019;30:1321–8. https://doi.org/10.1093/ANNONC/MDZ167.

[10] Heydt C, Wölwer CB, Velazquez Camacho O, Wagener-Ryczek S, Pappesch R, Siemanowski J, Rehker J, Haller F, Agaimy A, Worm K, et al. Detection of gene fusions using targeted next-generation sequencing: a comparative evaluation. BMC Med Genom 2021;14(1):14. https://doi.org/10.1186/s12920-021-00909-y.

[11] Volckmar A-L, Leichsenring J, Kirchner M, Christopoulos P, Neumann O, Budczies J, Morais de Oliveira CM, Rempel E, Buchhalter I, Brandt R, et al. Combined targeted DNA and RNA sequencing of advanced NSCLC in routine molecular diagnostics: Analysis of the first 3,000 Heidelberg cases. Int J Cancer 2019;145:649–61. https://doi.org/10.1002/ijc.32133.

[12] Akinboro O, Vallejo JJ, Nakajima EC, Ren Y, Mishra-Kalyani PS, Larkins EA, Vellanki PJ, Drezner NL, Mathieu LN, Donoghue MB, et al. Outcomes of anti–PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non–small cell lung cancer (NSCLC) with PD-L1 score ≥ 50%: FDA pooled analysis. J Clin Oncol 2022;40:9000. https://doi.org/10.1200/JCO.2022.40.16_suppl.9000.

[13] Blasi M, Kuon J, Shah R, Bozorgmehr F, Eichhorn F, Liersch S, Stenzinger A, Heußel CP, Herth FJ, Thomas M, et al. Pembrolizumab alone or with chemotherapy for 70+ year-old lung cancer patients: a retrospective study. Clin Lung Cancer 2023. https://doi.org/10.1016/j.cllc.2023.06.010.

[14] Reis H, Metzenmacher M, Goetz M, Savvidou N, Darwiche K, Aigner C, Herold T, Eberhardt WE, Skiba C, Hense J, et al. MET expression in advanced non-small-cell lung cancer: effect on clinical outcomes of chemotherapy, targeted therapy, and immunotherapy. Clin Lung Cancer 2018;19:e441–63. https://doi.org/10.1016/J.CLLC.2018.03.010.

[15] Guisier F, Descourt R, Babey H, Huchot E, Falchero L, Veillon R, Cortot AB, Tissot C, Chouaid C, Decroisette C. Brief report: first-line pembrolizumab in metastatic non-small cell lung cancer habouring MET Exon 14 skipping mutation and PD-L1 ≥50% (GFPC 01-20 Study). Clin Lung Cancer 2022;23:e545–9. https://doi.org/10.1016/j.cllc.2022.09.002.

[16] Gandhi, Rodríguez-Abreu L, Gadgeel D, Esteban S, Felip E, Angelis E, de F, Domine M, Clingan P, Hochmair MJ, Powell SF, et al. KEYNOTE 189 (adeno): pembrolizumab plus chemotherapy (carbo/pemetrexed) in metastatic non–small-cell lung cancer (adeno). N Engl J Med 2018.

[17] Lopes G, Wu Y-L, Kudaba I, Kowalski D, Cho BC, Castro G, Srimuninnimit V, Bondarenko I, Kubota K, Lubiniecki GM, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. LBA4–LBA4 J Clin Oncol 2018;36. https://doi.org/10.1200/jco.2018.36.18_suppl.lba4.

[18] Zhou Y, Song L, Xu Q, Zeng L, Jiang W, Yang N, Zhang Y. Investigation on the survival implications of PD-L1 expression status in ALK- rearranged advanced non-small cell lung cancer treated with first-line crizotinib. Lung Cancer 2022;167:58–64. https://doi.org/10.1016/J.LUNGCAN.2022.04.002.

[19] Li M, Hou X, Chen J, Zhang B, Wang N, Han H, Chen L. ALK fusion variant 3a/b, concomitant mutations, and high PD-L1 expression were associated with unfavorable clinical response to second-generation ALK TKIs in patients with advanced ALK-rearranged non-small cell lung cancer (GASTO 1061). Lung Cancer 2022;165:54–62. https://doi.org/10.1016/j.lungcan.2022.01.006.

[20] Ota K, Azuma K, Kawahara A, Hattori S, Iwama E, Tanizaki J, Harada T, Matsumoto K, Takayama K, Takamori S, et al. Induction of PD-L1 expression by the EML4-ALK oncoprotein and down stream signaling pathways in non-small cell lung cancer. Clin Cancer Res 2015;21:4014–21. https://doi.org/10.1158/1078-0432.CCR-15-0016/86642/AM/INDUCTION-OF-PD-L1-EXPRESSION-BY-THE-EML4-ALK.

[21] Woo CG, Seo S, Kim SW, Jang SJ, Park KS, Song JY, Lee B, Richards MW, Bayliss R, Lee DH, et al. Differential protein stability and clinical responses of EML4-ALK fusion variants to various ALK inhibitors in advanced ALK-rearranged non-small

cell lung cancer. Ann Oncol 2017;28:791–7. https://doi.org/10.1093/annonc/mdw693.
[22] Christopoulos P, Kirchner M, Endris V, Stenzinger A, Thomas M. EML4-ALK V3, treatment resistance, and survival: refining the diagnosis of ALK+ NSCLC. J Thor Dis 2018;10:S1989–91. https://doi.org/10.21037/jtd.2018.05.61.
[23] Domènech M, Muñoz Marmol AM, Mate JL, Estival A, Moran T, Cucurull M, Saigi M, Hernandez A, Sanz C, Hernandez-Gallego A, et al. Correlation between PD-L1 expression and MET gene amplification in patients with advanced non-small cell lung cancer and no other actionable oncogenic driver. Oncotarget 2021;12. https://doi.org/10.18632/oncotarget.28045.
[24] Lu S, Sun Z, Hu W, Yin S, Zhao C, Hu H. PD-L1 positively regulates MET phosphorylation through inhibiting PTP1B. Cancer Sci 2021;112:1878–87. https://doi.org/10.1111/CAS.14844.
[25] Dong ZY, Zhong WZ, Zhang XC, Su J, Xie Z, Liu SY, Tu HY, Chen HJ, Sun YL, Zhou Q, et al. Potential predictive value of TP53 and KRAS mutation status for response to PD-1 blockade immunotherapy in lung adenocarcinoma. Clin Cancer Res 2017;23:3012–24. https://doi.org/10.1158/1078-0432.CCR-16-2554.
[26] Christopoulos P, Budczies J, Kirchner M, Dietz S, Sültmann H, Thomas M, Stenzinger A. Defining molecular risk in ALK+ NSCLC. Oncotarget 2019;10:3093–103. https://doi.org/10.18632/oncotarget.26886.
[27] Kron A, Alidousty C, Scheffler M, Merkelbach-Bruse S, Seidel D, Riedel R, Ihle MA, Michels S, Nogova L, Fassunke J, et al. Impact of TP53 mutation status on systemic treatment outcome in ALK-rearranged non-small-cell lung cancer. Ann Oncol 2018;29:2068–75. https://doi.org/10.1093/ANNONC/MDY333.
[28] Christopoulos P, Kirchner M, Roeper J, Saalfeld F, Janning M, Bozorgmehr F, Magios N, Kazdal D, Volckmar AL, Brückner LM, et al. Risk stratification of EGFR+ lung cancer diagnosed with panel-based next-generation sequencing. Lung Cancer 2020;148:105–12. https://doi.org/10.1016/j.lungcan.2020.08.007.
[29] Le, X.; Garassino, M.C.; Ahn M.-J.; Felip, E.; Cortot, A.; Sakai, H.; Mazieres, J.; Thomas, M.; Viteri, S.; Hernandez, A.; et al. OA21.06 ctDNA dynamics, prognostic markers and resistance mechanisms in tepotinib treated MET ex14 skipping NSCLC in the VISION trial.