54P Efficacy of first-line immunotherapy for non-small cell lung cancer with MET exon 14 skipping according to PD-L1 expression [Abstract]

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53P MET exon 14 skipping mutations in non-small cell lung cancer: Real-world data from the Italian biomarker ATLAS database

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Background: MET exon 14 skipping mutation (METex14) is a rare alteration in non-small cell lung cancer (NSCLC). Here we report disease and patients characteristics, efficacy and tolerability of MET inhibitors among advanced METex14 NSCLC patients from the Italian real-world registry ATLAS.

Methods: Clinical, pathological and molecular data, treatment efficacy/tolerability outcomes were retrospectively collected from patients' medical charts and electronic healthcare records from the ATLAS registry.

Results: From July 2020 to July 2023 a total of 146 METex14 advanced NSCLC patients were included across 27 Italian centers. Median age was 74 years old (range 46-92). Most patients were male (52%), with ECOG- PS <2 (72%) and adenocarcinoma subtype (83%). 24% had brain metastases. Overall, 56 (38%) patients were treated with capmatinib and 34 (23%) with tepotinib. Among patients treated with MET inhibitors, 29% and 52% of them received targeted treatment in 1st and 2nd line, respectively. Response rate (RR) was 37% (33% in previously treated and 46% in treatment-naïve patients) with a disease control rate of 62%. With a median follow up of 10.8 months, progression free survival (PFS) was 6.6 months (95% CI: 4.3-8.3). In patients receiving MET inhibitor in 1st, 2nd and further lines, PFS was 7.2 (95% CI: 4.3-10.4), 6.6 months (95% CI: 5.1-11.2) and 3.9 months (95% CI: 2.7-8.7), respectively. Overall survival was 10.7 months (95% CI: 7.2-19.3). In patients with measurable brain metastases (17 cases), the intracranial RR was 41%. Grade 3-4 treatment-related adverse events (TRAEs) occurred in 12% of patients with grade 3 peripheral edema in 7% of cases. A fatal adverse reaction occurred in one patient due to pneumonitis. TRAEs-related dose reduction and discontinuation were reported in 6% and 8% of cases.

Conclusions: Capmatinib and tepotinib represent an effective treatment option in NSCLC patients with MET exon 14 skipping mutation. Real-world efficacy outcomes are worse than those reported in prospective clinical trials. MET inhibitor activity is more pronounced in the treatment-naïve population, suggesting that this is the right setting in the METex14 therapeutic strategy management.

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54P Efficacy of first-line immunotherapy for non-small cell lung cancer with MET exon 14 skipping according to PD-L1 expression

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Background: METΔ14ex is the driver alteration for approximately 3% of non-small cell lung cancers (NSCLC) and associated with a higher PD-L1 expression, but unclear benefit from immunotherapy (IO).

Methods: Seventy-eight consecutive patients with metastatic NSCLC harboring METΔex14 who received first-line IO as monotherapy or chemoimmunotherapy (CHT+IO) in 10 German academic lung cancer centers were analyzed.

Results: The median age was 72 years (range 49-86), 34 patients (44%) were female, 47 (60%) were active or former smokers, and 23 (29%) presented with brain metastases. The Eastern Cooperative Group (ECOG) performance status was 0, 1, 2 and 3 in 27 (35%), 28 (36%), 18 (23%) and 4 (5%) cases, respectively. The most common histology was adenocarcinoma (n=61, 78%). IO was given to 43 (55%) patients as monotherapy, and to 35 (45%) combined with CHT. For patients with PD-L1 tumor proportion score (TPS) ≥50% (n=52, 67%), 1-49% (n=14, 18%) and <1% (n=12, 15%), disease control rates (DCR) were 56%, 57% and 100% (p=0.015), respectively. Other efficacy parameters including overall response rate (ORR), median progression-free survival (mPFS) and median overall survival (mOS) by PD-L1 tumor proportion score (TPS) and type of treatment are summarized in the table. Primary progressive disease/early death (before radiologic reassessment) under IO monotherapy, but not under CHT+IO, was significantly associated with never-smoker status (p=0.041). No significant correlations were found between smoking status and PD-L1 TPS (p=0.595).

Table: 54P

	TPS≥50% / IO n=43	TPS≥50% / CHT+IO n=9	TPS 1-49% / CHT+IO n=14	TPS 0% / CHT+IO n=12	p-value
ORR (%)	35	56	43	50	0.599
DCR (%)	54	67	57	100	0.030
mPFS (mo)	3	4	6	15	0.520
mOS (mo)	14	5	15	16	0.690

Conclusions: Our exploratory analysis suggests an association between higher PD-L1 TPS and worse clinical outcomes under IO in patients with NSCLC harboring METΔ14ex. Although these results should be interpreted with caution, they contrast the favorable effect of PD-L1 expression for IO efficacy in other NSCLC and underline the need for alternative biomarkers for IO in this patient population.

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55P Differences in response to immune treatment between KRAS G12C and KRAS non-G12C mutated non-small cell lung cancer

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Background: Non-small cell lung cancer (NSCLC) can harbor different KRAS mutations. Although targeted therapy is available for KRAS G12C-mutant (mt) NSCLC, immune checkpoint inhibitors (ICIs) are still the first line treatment (tx) for these patients (pts). Here we aimed to assess the outcomes on ICIs for KRAS G12C compared to KRAS non-G12C-mt pts.

Methods: This is an updated observational, retrospective, multicenter study of pts with KRAS-mt NSCLC treated with ICIs between January 2017 and October 2023. 14 pts received anti-KRAS G12C tx. Targeted sequencing was performed in 59% cases and polymerase chain reaction in the rest. Clinicopathological and molecular data were collected. We evaluated the characteristics, tx response and survival outcomes on ICIs of pts with KRAS G12C vs non-G12C-mt tumors.

Results: 189 pts were included with a median follow-up of 34.3 months (m). STK11 and TP53 were the most frequent co-mutated genes present in 4.3%/18.5% G12C/non-G12C and 21.3%/44.7% G12C/non-G12C, respectively. In all KRAS mt tumors, harboring a TP53 co-mutation was associated to a positive PD-L1 and a better ECOG ($p < 0.001$ and $p=0.006$, respectively). In addition, a trend to a better overall survival (OS) was seen in TP53 vs STK11 tumors (14.7 vs 6.1m, respectively, $p = 0.195$). No differences were seen in the median duration of response or progression free survival between G12C/non-G12C (10.7 vs 9.5m $p=0.202$ and 8 vs 5m $p= 0.554$, respectively). KRAS G12C tumors were associated with a better median OS compared with non-G12C tumors (16.2 vs 9.2m $p=0.024$). In the multivariate analysis for OS, PD-L1 negative tumors and ECOG ≥ 1 were independently associated with worse OS ($p=0.004$ and $p<0.001$, respectively).

Table: 55P

N (%)	G12C (n=92)	Non-G12C (n=97)	p-value
Median age (range)	62.9 (61.8-64.9)	65 (63-66.3)	
Sex			0.237
Male	36 (39.1)	67 (69.1)	
Female	56 (60.9)	30 (30.9)	
Tobacco			0.866
Former	47 (51.1)	49 (50.5)	
Current	44 (47.8)	46 (47.4)	
Stage			0.530
I-III	18 (19.6)	23 (23.7)	
IV	74 (80.4)	74 (76.3)	
M1 CNS	17 (18.5)	26 (26.8)	0.172
M1 liver	16 (17.4)	19 (19.6)	0.698
ICIs treatment line			0.466
1	72 (78.3)	80 (82.5)	
≥2	20 (21.7)	17 (17.5)	
PD-L1			0.234
Negative (0%)	22 (23.9)	32 (33)	
Positive (≥1%)	64 (69.6)	63 (65)	
ECOG			0.241
0	34 (37)	44 (45.4)	
≥1	58 (63)	53 (54.6)	

Conclusions: Our work shows that pts with KRAS G12C tumors are associated with better OS on ICIs tx when compared with pts with KRAS non-G12C tumors. Harboring a TP53 co-mutation associated to a KRAS mutation might determine a different tumor microenvironment and therefore a better response to ICI tx.

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56P Prevalence, clinical characteristics, and treatment outcomes of patients with KRAS-mutated non-squamous NSCLC and PD-L1 expression: Real-life data analysis

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Background: Lung adenocarcinoma is a complex and heterogeneous disease characterized by diverse molecular alterations. Programmed death-ligand 1 (PD-L1) expression is a crucial biomarker in treatment algorithms, yet its clinico-pathological correlations with other mutations remain unclear. This study aims to investigate the impact of PD-L1 expression on outcomes in patients with KRAS mutations.

Methods: A single-center retrospective cohort study included patients diagnosed with non-squamous NSCLC between January 2018 and July 2022. A targeted next-generation sequencing (NGS) analysis by Ion Torrent® (ThermoFisher Scientific) (Ion AmpliSeq CLv2 panel) was performed. PD-L1 expression was assessed by Immunohistochemistry (ab SP263), and patients were categorized into PD-L1 <1% (negative), 1-49% (intermediate), and ≥ 50% (high).

Results: Clinical data from 464 patients were collected, revealing KRAS mutations in 179 patients (38.6%). 77 (43%) had a co-mutation, most frequently TP53 (74%) and STK11 (14.3%). Others co-mutations (24.7%) include MET, BRAF, FGFR2, SMAD4, ERBB4, PTEN, CTNNB1, PIK3CA, FBXW7. PD-L1 expression in KRAS mut cohort was negative in 59 (33,7%), intermediate in 61 (34.8%) and high in 55 pts (31,4%); in KRAS WildType: negative in 109 (39.9%), intermediate in 105 (38.4%) and high in 59 pts (21,6%); in patients with KRAS and a co-mutation was: negative in 22 (29%), intermediate in 22 (29%) and high in 33 pts (43,4%). Our data shows a higher incidence of PD-L1 expression in KRAS-mutated patients compared to KRAS wild-type ($p=0.02$), especially when presenting a co-mutation ($p=0.003$). Analysis of progression-free