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Impact of KRAS/TP53 and KEAP1/STK11 Co-mutations on Immune Checkpoint Inhibitor Outcomes for metastatic NSCLC patients: Insights from Real-World Data

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Background

- Immune checkpoint inhibitors (ICIs), alone or in combination with chemotherapy (ICI+CTx), are standard 1st-line treatments for mNSCLC.
- However, PD-L1, the only biomarker currently guiding therapy, has limited predictive power, and clinical outcomes remain heterogeneous.
- We evaluated the impact of KRAS/TP53 and KEAP1/STK11 alterations on the clinical benefit of ICI/ICI+CTx therapy using data from the Baden-Wuerttemberg Cancer Registry (BWCR), Germany.

Methods

- mNSCLC patients with no targetable genetic alterations, available KEAP1/STK11 status, and treated with first-line ICI/ICI+CTx (Table 1).
- Multivariate Cox proportional hazards models were adjusted for age, PD-L1 status, ECOG, metastatic stage, and all four studied biomarkers
- Median overall survival (mOS) was assessed using Kaplan-Meier statistics

Tab 1: Baseline characteristics of stage IV NSCLC patients treated with ICI/ICI-chemotherapy by KEAP1/STK11 co-mutation status.

		KEAP1 /STK11						
	Overall	WT/WT	WT/Mut	Mut/WT	Mut/Mut	Mut/ unknown	p-value	SMD
	805	530	67	91	84	33		
Age, Mean (SD)	61.61 (9.50)	62.06 (9.51)	61.19 (9.13)	60.00 (9.78)	60.60 (9.36)	62.42 (9.36)	0.276	0.133
KRAS – no. (%)								
WT	399 (55.6)	274 (60.0)	33 (50.0)	51 (58.0)	31 (39.2)	10 (35.7)	0.017	0.284
Mut (not G12C)	175 (24.4)	97 (21.2)	18 (27.3)	21 (23.9)	29 (36.7)	10 (35.7)		
G12C	144 (20.1)	86 (18.8)	15 (22.7)	16 (18.2)	19 (24.1)	8 (28.6)		
PDL – no. (%)								
<1	106 (13.2)	64 (12.1)	12 (17.9)	8 (8.8)	14 (16.7)	8 (24.2)	0.043	0.369
1-50	249 (30.9)	163 (30.8)	17 (25.4)	29 (31.9)	31 (36.9)	9 (27.3)		
>50	132 (16.4)	97 (18.3)	9 (13.4)	20 (22.0)	4 (4.8)	2 (6.1)		
unknown	318 (39.5)	206 (38.9)	29 (43.3)	34 (37.4)	35 (41.7)	14 (42.4)		
TP53– no. (%)								
WT	224 (32.9)	137 (30.9)	23 (37.7)	33 (38.4)	30 (41.7)	1 (5.9)	0.029	0.399
Mut	456 (67.1)	307 (69.1)	38 (62.3)	53 (61.6)	42 (58.3)	16 (94.1)		
Type of Treatment								
ICI	106 (13.2)	78 (14.7)	4 (6.0)	13 (14.3)	6 (7.1)	5 (15.2)	0.134	0.170
ICI+CTx	699 (86.8)	452 (85.3)	63 (94.0)	78 (85.7)	78 (92.9)	28 (84.8)		
Sex– no. (%)								
Male	512 (63.6)	339 (64.0)	44 (65.7)	61 (67.0)	47 (56.0)	21 (63.6)	0.602	0.100
Female	293 (36.4)	191 (36.0)	23 (34.3)	30 (33.0)	37 (44.0)	12 (36.4)		
Histology– no. (%)								
LUAD/ASC	614 (76.3)	376 (70.9)	60 (89.6)	72 (79.1)	75 (89.3)	31 (93.9)	<0.001	0.386
LUSC	121 (15.0)	101 (19.1)	6 (9.0)	10 (11.0)	3 (3.6)	1 (3.0)		
others	70 (8.7)	53 (10.0)	1 (1.5)	9 (9.9)	6 (7.1)	1 (3.0)		
ECOG – no. (%)								
0-1	554 (68.8)	367 (69.2)	49 (73.1)	58 (63.7)	57 (67.9)	23 (69.7)	0.846	0.161
2+	76 (9.4)	46 (8.7)	6 (9.0)	11 (12.1)	8 (9.5)	5 (15.2)		
unknown	175 (21.7)	117 (22.1)	12 (17.9)	22 (24.2)	19 (22.6)	5 (15.2)		
Stage – no. (%)								
IVa	500 (62.1)	341 (64.3)	43 (64.2)	44 (48.4)	46 (54.8)	26 (78.8)	0.006	0.302
IVb	305 (37.9)	189 (35.7)	24 (35.8)	47 (51.6)	38 (45.2)	7 (21.2)		

Table 2 Multivariate Cox Regression Analysis of OS in patients with mNSCLC receiving ICI/ICI-CHx therapy

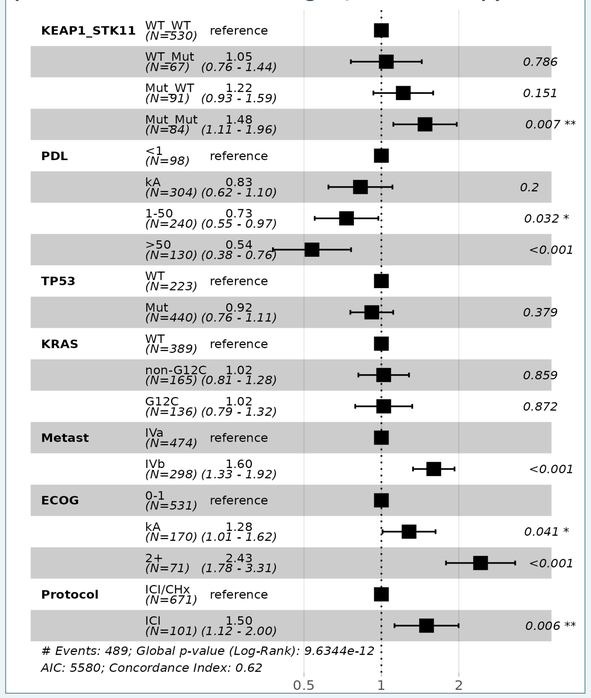


Fig. 1 Distribution of co-mutation groups in the study population:
KEAP1/STK11 subgroups (outer layer) within KRAS/TP53 co-mutation groups (inner layer)

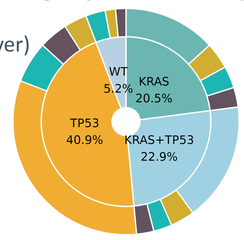
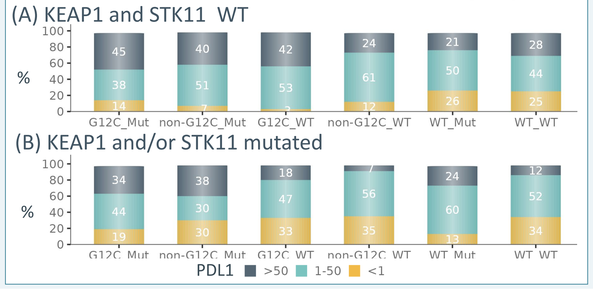


Fig. 2 PD-L1 expression status in KRAS/TP53 subgroups:



Results

- In multivariate analysis, KEAP1 mutation and KEAP1/STK11 co-mutation were associated with poorer therapeutic outcomes (p = 0.007; Table 2), together with stage IVb disease, PD-L1 status, ECOG ≥ 2, and treatment with ICI+CTx versus ICI alone.
- Higher PD-L1 expression was observed in the KRAS/TP53 co-mutation groups (Fig. 2).
- In the absence of KEAP1/STK11 alterations, the longest mOS was observed in the KRAS (non-G12C)/TP53 (mut) subgroup (19.8 months), compared with 11.2 months in the KRAS (wt)/TP53 (wt) subgroup (Fig. 3A, 4A).
- In contrast, KEAP1 and/or STK11 mutations were associated with reduced mOS across all subgroups, except KRAS (wt)/TP53 (wt).
- The most pronounced loss of benefit from ICI/ICI+CTx therapy in the case of KEAP1/STK11 mutation (~11-month reduction in mOS; Fig. 3) occurred in the KRAS (non-G12C)/TP53 (mut) subgroup (p = 0.04; Table 3).

Table 3 Multivariate Cox Regression analysis of OS in patients with KEAP1/STK11 Mut vs WT in KRAS/TP53 co-mutation group (adjusted for age, PD-L1 status, ECOG, metastatic stage, and all for studied biomarkers)

KRAS	TP53	N: KEP1/STK11 (WT/Mut)	HR OS (0.95LCL-0.95UCL)	P-value
WT	WT	68/31	0.76 (0.47-1.22)	0.29
WT	Mut	193/87	1.03 (0.78-1.4)	0.80
G12C	WT	28/19	1.50 (0.78-2.96)	0.38
G12C	Mut	46/22	1.52 (0.83-2.78)	0.16
Non-G12C	WT	40/37	1.62 (1.0-2.62)	0.16
Non-G12C	Mut	48/32	1.74 (1.0-2.98)	0.04

Fig. 3 Comparison of mOS in co-mutation groups: KEAP1/STK11 WT vs Mut

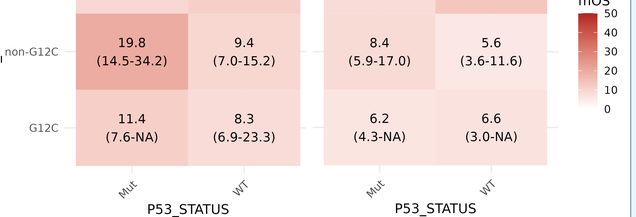
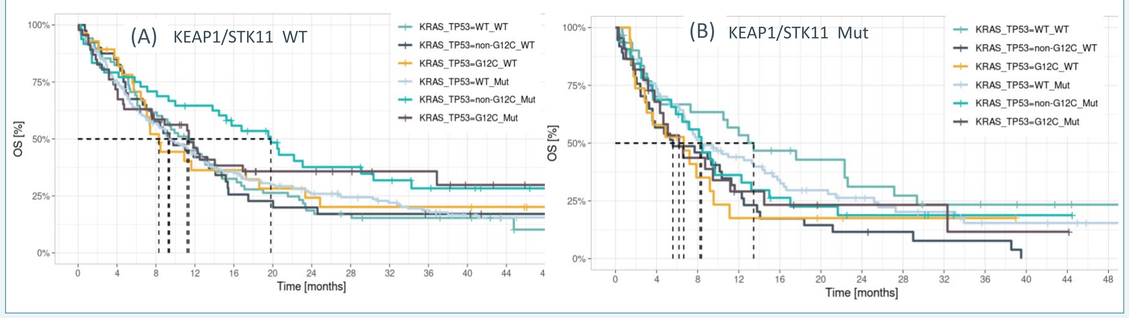


Fig. 4: Kaplan–Meier plots of OS stratified by biomarker status for KRAS and TP53: (A) KEAP1 and STK11 WT and (B) KEAP1 and/or STK11 mutated.



Conclusions

- The benefit of ICI/ICI+CTx therapy is strongly influenced by the mutational status of KEAP1, STK11, KRAS, and TP53.
- The greatest impact of KEAP1/STK11 alterations on mOS was observed in patients harboring KRAS(non-G12C) together with TP53 mutations
- These findings highlight the potential for improved therapeutic stratification of patients with metastatic NSCLC based using these molecular biomarkers.

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