FPN:3085

Prognostic and predictive effects of TP53 co-mutations and RET fusion partners in RET-rearranged advanced NSCLC

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BACKGROUND

RET fusions occur in ~1-2% of patients with advanced non small cell lung cancer (aNSCLC).

Selective RET inhibitors (SRIs), such as selpercatinib and pralsetinib, have significantly improved outcomes, but yet ~10% of patients progress in the first 6 months of treatment and ~30% by 12 months (1).

Predictors of response or early progression remain poorly characterized.

(1) Zhou C et al. N Engl J Med. 2023;389:1839–50.

METHODS

A multicenter retrospective analysis (RET-MAP) of RET+ aNSCLC from 47 international centers evaluated clinical and genomic correlates of SRI outcomes.

Multivariable Cox models estimated progression-free (PFS) and overall survival (OS) and tested interactions with first-line (1L) SRI versus chemotherapy ± immunecheckpoint inhibitor (CH±ICI).

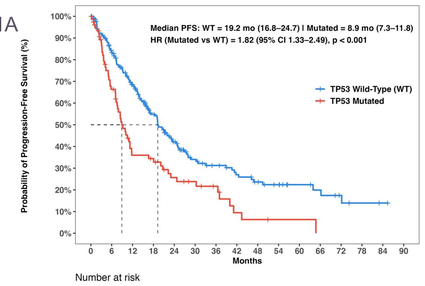
In parallel, genomic and transcriptomic features were characterized in an external Caris Life Sciences (CLS) cohort of patients with RET+ aNSCLC.

RESULTS

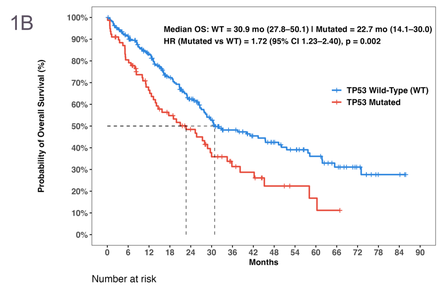
RET-MAP Cohort

- 510 patients with aNSCLC (median age 63; 59% female; 36% ever-smokers; 92% adenocarcinoma).
- SRI any line: 401 patients (1L n=151; later lines n=250) → mFUP (PFS): 29.7 mo (95% CI 26.0–37.0); mFUP (OS): 35.2 mo (95% CI 31.8–40.3).

1A



1B



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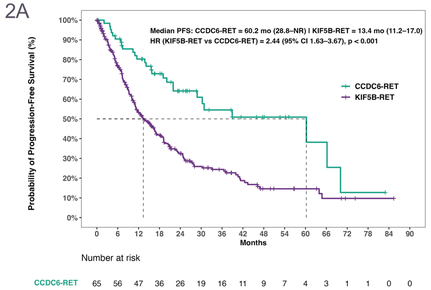

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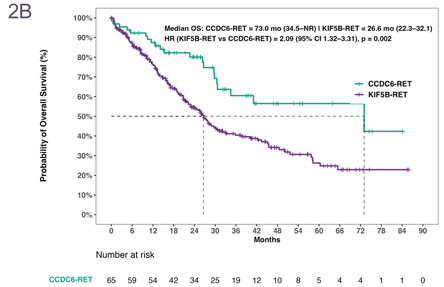


3A

Variable		N	Hazard ratio	p
Age	<70	264	Reference	
	≥70	94	0.87 (0.63, 1.20)	0.392
Sex	Female	210	Reference	
	Male	148	1.09 (0.82, 1.45)	0.547
Smoking	Smoker	124	Reference	
	Never smoker	234	0.88 (0.66, 1.17)	0.371
Histology	Adenocarcinoma	333	Reference	
	Other histologies	25	1.55 (0.93, 2.59)	0.090
Brain metastases	No	268	Reference	
	Yes	90	1.56 (1.14, 2.12)	0.005
ECOG PS	0–1	302	Reference	
	≥2	56	2.25 (1.57, 3.23)	<0.001
TP53	No	199	Reference	
	Yes	72	1.77 (1.27, 2.46)	<0.001
	Unknown	87	1.08 (0.75, 1.55)	0.694
Partner	CCDC6	63	Reference	
	KIF5B	264	2.03 (1.33, 3.10)	0.001
	other	31	1.64 (0.89, 3.00)	0.112
Treatment	Selpercatinib	269	Reference	
	Pralsetinib	89	1.21 (0.89, 1.64)	0.219
Line of treatment	1L	129	Reference	
	≥2L	229	1.27 (0.95, 1.70)	0.113

3B

Variable		N	Hazard ratio	p
Age	<70	265	Reference	
	≥70	94	0.90 (0.63, 1.29)	0.561
Sex	Female	210	Reference	
	Male	149	1.29 (0.94, 1.77)	0.121
Smoking	Smoker	124	Reference	
	Never smoker	235	0.70 (0.51, 0.97)	0.034
Histology	Adenocarcinoma	334	Reference	
	Other histologies	25	1.69 (0.97, 2.93)	0.062
Brain metastases	No	269	Reference	
	Yes	90	1.73 (1.24, 2.43)	0.001
ECOG PS	0–1	303	Reference	
	≥2	56	3.24 (2.21, 4.75)	<0.001
TP53	No	200	Reference	
	Yes	72	1.81 (1.27, 2.58)	0.001
	Unknown	87	1.06 (0.69, 1.63)	0.786
Partner	CCDC6	63	Reference	
	KIF5B	264	1.71 (1.06, 2.75)	0.027
	other	32	1.45 (0.75, 2.79)	0.265
Treatment	Selpercatinib	270	Reference	
	Pralsetinib	89	1.13 (0.80, 1.60)	0.489
Line of treatment	1L	130	Reference	
	≥2L	229	1.50 (1.07, 2.09)	0.017

TP53 co-mutation

- SRI any line: Baseline TP53 co-mutation was associated with shorter PFS (Figure 1A) and OS (Figure 1B).
- 1° Line: No significant treatment-by-TP53 interaction for 1L SRI versus CH±ICI (p=0.22).

Fusion partner

- SRI any line: KIF5B partner had inferior PFS (Figure 2A) and OS (Figure 2B) compared with CCDC6.
- 1° Line: A significant treatment-by-fusion interaction favored SRI over CH±ICI in CCDC6 versus KIF5B partner (p=0.007), suggesting both prognostic and predictive effect.

Multivariate analysis

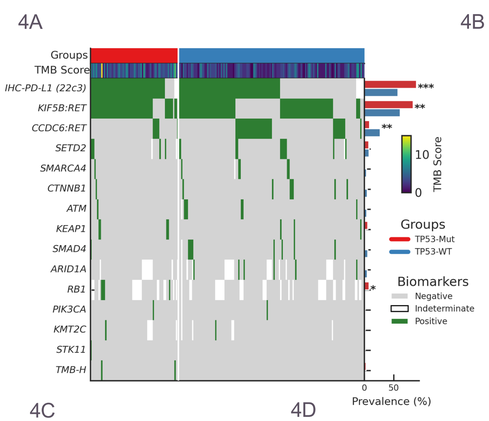
- SRI any line: **shorter PFS and OS were independently associated with TP53 mutation, KIF5B fusion, ECOG ≥2, and brain metastases** (Figure 3A and 3B).

CLS Cohort

TP53-mutant tumors (74/211) were characterized by:

- Enrichment for RB1 mutations and association with KIF5B partner (Figure 4A).
- Higher expression of proliferative pathways in gene set enrichment analysis (Figure 4B).
- Higher PD-L1 expression and tumor mutational burden (TMB) (Figure 4A and 4C).
- Increased M1 macrophages and reduced neutrophils in estimated immune cell fractions derived from transcriptomic data (Figure 4D).

4A



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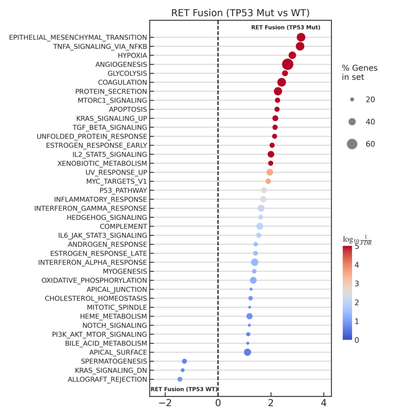

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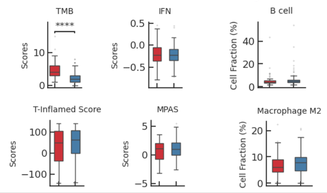

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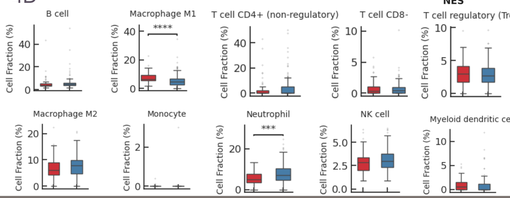

CONCLUSIONS

In RET+ aNSCLC, TP53 mutation is prognostic for inferior outcomes on SRIs but not predictive of differential benefit versus CH±ICI. Fusion partner carries both prognostic and predictive relevance; CCDC6 is associated with a more indolent course and greater relative benefit from SRI. Genomic and transcriptomic profiling supports an inflammatory microenvironment in TP53-mutant disease, reinforcing biologically distinct, and clinically meaningful, subsets within RET-driven lung cancer.

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