TP53 co-mutation and survival outcomes in non-small cell lung cancer (NSCLC) with rare driver mutations

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Introduction

TP53 variants are common in non small cell lung cancer (NSCLC) and have been reported as predictive of response and prognostic of poor outcome in EGFR-mutant NSCLC[1]. The impact of *TP53* co-mutation in NSCLCs carrying rarer driver mutations with approved targeted treatments is unclear.

Methods

Records of 319 patients with rare driver mutation positive NSCLC at Princess Margaret Cancer Centre were reviewed. Associations between *TP53* status, baseline demographics and outcomes (response [ORR], survival [OS], recurrence-free survival [RFS] for stage I-III patients, progression-free survival [PFS] for stage IV patients), were investigated. ORR (to first-line targeted therapy only) was compared via Fisher's exact test. OS and PFS were compared by Kaplan-Meier estimates, and Cox regression adjusted for stage at diagnosis with wildtype (WT) as reference.

Results

TP53 variants were found in 123/319 (38.6%; Table 1) with >1 driver mutations in 33 (10.3%). The only significant demographic difference between *TP53*-mutated (MUT) and WT was a higher percentage of smokers in the WT (56% *TP53-MUT v* 68% *TP53*-WT, p=0.001).

Table 1. Baseline characteristics

	All patients (n=319) N (%)	*TP53*-WT (n=148) N (%)	*TP53*-MUT (n=123) N (%)	p value
Median age (range)	64.2 (22.0, 96.0)	63.0 (31.8, 91.0)	65 (22, 96)	0.38
Female sex	195 (61%)	124 (63%)	71 (58%)	0.38
Never smoker	191 (64%)	125 (68%)	66 (56%)	0.001
Adenocarcinoma	302 (95)	186 (95)	116 (94)	0.73
Stage at diagnosis				0.44
I	65 (21%)	45 (23%)	20 (16%)	
II	18 (6%)	10 (5%)	8 (7%)	
III	54 (17%)	34 (18%)	20 (16%)	
IV	180 (57%)	105 (54%)	75 (61%)	
PD-L1 >50%	111 (40%)	60 (36%)	51 (47%)	0.16
Brain metastases at diagnosis	57 (19%)	37 (21%)	20 (17%)	0.56
Brain metastases at any time	105 (35%)	62 (34%)	43 (37%)	0.64
Driver mutations *				
ALK	68	56	12	
BRAF V600E	29	17	12	
EGFR exon 20 ins	29	16	13	
EGFR (Uncommon)	40	25	15	
Fusion (*ALK, ROS, RET, NRG1*)	121	87	34	
HER2 exon 20 ins	50	27	23	
HER2 oncogenic SNV	12	6	6	
KIT	2	0	2	
MET exon 14 skip	44	24	20	
NRG1	4	2	2	
RET	21	13	8	
ROS1	28	16	12	

* 33 patients carried >1 driver mutation and may be double counted in different cohorts

Results cont.

ORR to *first-line* targeted treatment was 58% vs 68% in the *TP53*-MUT and WT cohorts, respectively (p=0.28; Table 2). More patients with *TP53*-MUT cancer had progressive disease (PD) as best response (28% *v* 11%, p=0.02).

Table 2. Response to first-line targeted treatment in the entire cohort

	TP53-WT N (%)	*TP53*-MUT N (%)	p value
Response to therapy	n=120	n=60	0.02
Complete Response (CR)	1 (1%)	1 (2%)	
Partial Response (PR)	72 (67%)	28 (56%)	
Stable Disease (SD)	22 (20%)	7 (14%)	
Progressive Diease (PD)	12 (11%)	14 (28%)	
Non-evaluable	13	10	

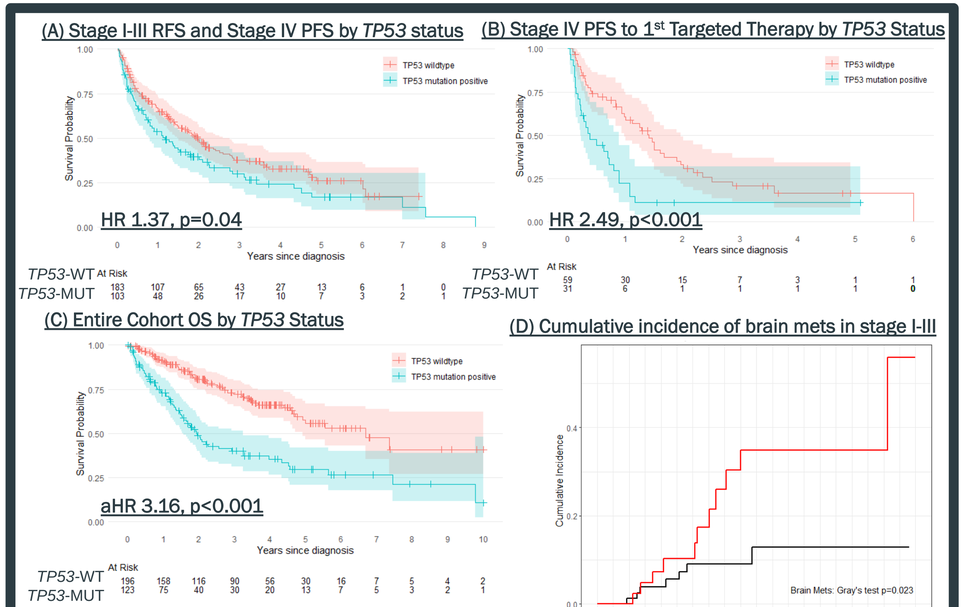

Fig 1. Kaplan-Meier estimates of *TP53*-MUT and *TP53*-WT rare driver mutation positive lung cancers (A) stage I-III RFS and stage IV PFS, (B) PFS to 1st palliative intent targeted therapy, (C) OS in the entire cohort and (D) cumulative incidence of brain mets in stage I-III patients.

mPFS (Fig 1B) to 1st line/instance of targeted therapy was 4.6m for *TP53*-MUT (95% CI 2.7-10.7) *v* 16.9m for WT (CI 11.7-23.5) (hazard ratio [HR] 2.49, CI 1.49-4.14; p<0.001). Similar findings were seen in mRFS (early stage) and mPFS (late stage) by *TP53* status (Fig 1A).

Median OS (Fig 1C) was significantly shorter in the *TP53*-MUT cohort at 23.4m (CI 18.7-38.9) compared to 80.1m (CI 58.9-not reached) (HR 2.63, CI 1.86-3.72; p<0.001).

There was a significantly higher incidence of brain metastases in stage I-III patients with *TP53*-MUT (Fig 1D). This was not seen in stage IV patients (not shown, Gray's test p=0.8).

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Table 3. Survival outcomes and response to 1st line targeted therapy (*TP53*-MUT vs WT)

	Overall survival	PFS in stage IV (any therapy)	Response to 1st line of palliative targeted therapy
Entire cohort	**23.4m *v* 80.1m** aHR 3.16, CI 2.21-4.50; p<0.001, n=319	**4.6m *v* 11.2m** HR 1.89, CI 1.31-2.75; p<0.001, n=149	PD rate **28% *v* 11%** p=0.02, n=157
HER2	**24.3m *v* 56.5m** aHR 2.39, CI 1.20-4.76; p=0.01, n=70	**4.8m *v* 7.5m** HR 1.60, CI 0.82-3.14; p=0.17, n=42	PD rate **56% *v* 22%** p=0.04, n=39
Fusion (*ALK, ROS1, RET, NRG1*)	**20.0m *v* 80.1m** aHR 5.78, CI 2.84-11.75; p<0.001, n=121	**3.0m *v* 16.9m** HR 2.69, CI 1.41-5.14; p=0.003, n=62	PD rate **31% *v* 4%** p=0.005, n=71
ALK	**14.4m *v* 80.1m** aHR 6.06, CI 2.08-17.60; p<0.001, n=64	**3.7m *v* 22.1m** HR 2.68, CI 1.05-6.84; p=0.04, n=39	PD rate **38% *v* 5%** p=0.03, n=45
MET exon 14 skipping	**22.8m *v* 26.4m** aHR 1.92, CI 0.77-4.79; p=0.16, n=44	**3.7m *v* 3.4m** HR 0.96, CI 0.36-2.56; p=0.93, n=19	PD rate **0% *v* 2%** p=0.50, n=18
BRAF V600E	**11.0m *v* 41.2m** aHR 3.35, CI 1.08-10.36; p=0.04, n=29	**1.5m *v* 4.4m** HR 2.01, CI 0.47-8.56; p=0.35, n=10	PD rate **0% *v* 0%** n=8
EGFR uncommon	**67.7m *v* NR** aHR 1.61, CI 0.56-4.65; p=0.38, n=40	**12.9m *v* 14.9m** n=14*	PD rate **11% *v* 30%** p=0.58, n=19
EGFR exon 20 ins	**17.4m *v* NR** aHR 4.91, CI 1.44-16.80; p=0.01, n=29	**6.7m *v* 4.2m** n=8*	PD rate **0% *v* 50%** p=0.46, n=8

* p-values not provided if it could not be reliably estimated

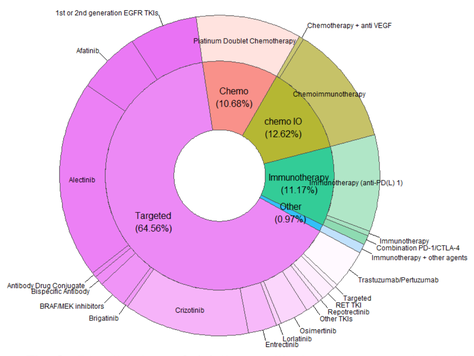

Fig 2. Distribution of 1st line palliative treatment including targeted therapy, chemotherapy and/or immunotherapy.

Discussion

- Our retrospective cohort demonstrates poorer outcomes in *TP53*-MUT oncogene-addicted NSCLC
- *TP53*-MUT had a tendency to have progression as best response which may explain the shortened survival
- Currently there is no targeted intervention or change in treatment for lung cancers with TP53 mutations, but many novel agents are in development [2]

TP53 co-mutation with multiple rare driver mutations is predictive of poor response to targeted treatments and prognostic of shorter OS and PFS in NSCLC.