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Original Research

Prognosis of *ALK*-rearranged non-small-cell lung cancer patients carrying *TP53* mutations

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ABSTRACT

Non-small-cell lung cancer (NSCLC) is the primary cause of cancer-related death. Gene rearrangements involving the anaplastic lymphoma kinase (*ALK*) tyrosine kinase identify a clinical and molecular subset of NSCLC patients, who benefit from the monotherapy with *ALK* tyrosine kinase inhibitors. Nonetheless, responsiveness to TKIs and prognosis of these patients are influenced by several factors, including resistance mechanisms and mutations affecting genes involved in key molecular pathways of cancer cells. In a cohort of 98 NSCLC patients with *ALK* gene rearrangements, we investigated the role of Tumor Protein (*TP53*) gene mutations in predicting patients prognosis. *TP53* mutations were evaluated in relation to disease control rate (DCR), objective response rate (ORR), progression-free survival (PFS) and overall survival (OS).Results: In patients with available clinical and *TP53* mutation information, we found that 13 patients (20.3%) were affected by *TP53* mutations. Considered together, even though showing a trend, *TP53* mutations were not associated with PFS and OS. Considering the different *TP53* mutations by functionality in terms of disruptive and non-disruptive mutations, we observed that *TP53* non-disruptive mutations were able to predict worse OS in the overall case series. Moreover, a worse PFS was seen in the subgroup of patients with *TP53* non-disruptive mutation, in first-, second-, and third line of treatment. Our results show that mutations affecting *TP53* gene, especially non-disruptive mutations, are able to affect prognosis of *ALK*-rearranged NSCLC patients.

Introduction

Non-small-cell lung cancer (NSCLC) is the most commonly diagnosed cancer and the major cause of cancer-related death worldwide [1]. The anaplastic lymphoma kinase (*ALK*) gene is located in chromosome 2p23.2, and encodes for a single-pass membrane tyrosine kinase receptor, member of the insulin receptor superfamily. Binding of the ligand leads to receptor dimerization, auto-phosphorylation and signal transduction through JAK-STAT, PI3KCA-AKT, mTOR and MAPK pathways, resulting in cellular responses such as cell growth and resistance to apoptosis [2]; *ALK* rearrangements constitutively activate protein tyrosine kinase domain, leading to transforming downstream pathways [3].

A small inversion involving the echinoderm microtubule-associated protein-like 4 (EML4) and *ALK* was firstly reported in NSCLC in 2007 [4], and even though to date more than 20 genes have been identified as

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ALK fusion partners, the most frequent genomic variants are represented by different potential breakpoints affecting the EML4 gene, while the majority of fusion breakpoints for *ALK* falls before exon 20 of the gene, preserving the entire kinase domain [5,6]. Depending on the fusion partner and the genomic variant, the tyrosine kinase domain of *ALK* is constitutively activated through mechanisms affecting gene expression (the promoter region of the partner gene induces a constitutive transcription of the *ALK* mRNA), subcellular localization (mediated by partner domains) and ligand-independent phosphorylation (mediated by functional domains of the partner, e.g. coiled-coil) [5].

ALK rearrangements are usually mutually exclusive with respect to other driver mutations (e.g. EGFR, ROS1, RET), and characterize a specific subtype of oncogene-addicted NSCLC; these gene fusions occur in up to 8% of patients, and are mainly associated with clinical features such as adenocarcinoma histology, never or light-smoking history and young age [7–9].

Initially designed as a c-Met-tyrosine kinase inhibitor (TKI), crizotinib received FDA approval for *ALK* positive NSCLC patients after strong clinical results of a phase I/II study, later established as a first-line therapy for this subset of patients [10–12]. Thereafter, several second generation TKIs demonstrated a benefit in progression-free survival (PFS) and overall survival (OS) in crizotinib *ALK*-pretreated patients [13–16], until the displacement of crizotinib as a first-line therapy by brigatinib and alectinib [17–18].

Since the discovery of the first therapeutic agents for *ALK* positive patients, acquired resistance mechanisms have been highlighted, mainly classified as on-target or off-target mechanisms. On-target resistance mechanisms include *ALK* secondary mutations affecting the kinase domain, or *ALK* gene amplification, while the off-target ones involve signaling pathways that bypass the *ALK* tumor dependency, with the activation of alternative pathways, as HER2, EGFR overexpression, c-MET amplification or phenotypic changes guided by epithelial-mesenchymal transition (EMT) of cancer cells [19].

Beyond the cellular and molecular mechanisms induced by TKIs, response and prognosis of patients is affected by several pathways, which the most important probably is represented by Tumor Protein 53 (*TP53*) gene mutations. Mutations affecting *TP53* demonstrated to play a pivotal role in influencing response to TKIs and prognosis of oncogene-addicted NSCLC patients, and it has been reported that different *TP53* mutations could confer different functions to p53 protein, in particular those affecting exons 5–8 of the gene coding region: in particular, categorizing *TP53* mutations in disruptive and non-disruptive mutations, basing on differences of protein structure and function of protein alterations, showed to predict different cellular functions, and an association with patient clinical outcome [20,21]. Basing on these results, the rationale to investigate the role of *TP53* mutations in oncogene-addicted NSCLC is an emerging field of investigation to identify new prognostic and predictive biomarkers for this malignancy.

We previously showed that *TP53* mutations, especially those affecting the exon 8 of the gene, affect response to first-line TKIs and prognosis of two independent cohorts of EGFR-mutated NSCLC patients [22,23]. At this regard, a recent article highlighted that specific *TP53* mutations are involved in primary and acquired resistance to EGFR-TKIs. In particular, it has been demonstrated that exon 8 R273H mutations are able to guide primary and acquired resistance to EGFR-TKIs inducing epithelial-mesenchymal transition (EMT) effectors in an EGFR L858R/T790M cell line model, while this effect was not observed in an EGFR exon 19 deletion and *TP53* R248Q model [24]. Moreover, another study found that *TP53* mutations arise during resistance to osimertinib in EGFR-mutated patients, suggesting a role in guiding molecular pathways for resistance to TKIs [25]. In this study, we evaluated the role of *TP53* mutations in predicting response to therapy and prognosis of *ALK*-positive NSCLC patients treated with TKIs.

Materials and methods

Data from all consecutive *ALK*-positive advanced NSCLC patients from July 2003 to February 2018 treated at the Medical Oncology Units of the Romagna catchment area (Area Vasta Romagna, AVR) and at the S. Maria della Misericordia Hospital of Perugia, Italy, were retrospectively retrieved. Medical and radiographic records were reviewed to obtain demographic and clinical features of patients, including tumor histology, age, gender, smoking history and information about treatments received, responses and clinical follow-up. *ALK* rearrangements were routinely assessed at the Pathological Anatomy Units of the centers involved in the study, by immunohistochemistry (IHC), Fluorescent in-situ hybridization (FISH), or both. A total of 98 records were obtained for this study; of these, 76 had available clinical and follow-up information and were considered for *TP53* mutation and statistical analyses.

All patients provided a written informed consent, and the study was approved by the CEROM Ethical Committee (study code IRST-B087).

TP53 mutation analysis

TP53 mutation analyses were performed on the same formalin-fixed paraffin embedded (FFPE) samples used for *ALK* rearrangement diagnosis, using the NM_000546.6 as a reference sequence. A dedicated expert pathologist from each Center accurately selected a tumor containing at least 50% of tumor cells for DNA extraction.

Following macro-dissection, cells were lysed in 50 mmol/L KCl, 10 mmol/L Tris–HCl pH 8.0, 2.5 mmol/L MgCl2, and Tween-20 0.45% digestion buffer. Proteinase K at 1.25 mg/mL were added and incubated overnight at 56 °C. Proteinase K was inactivated at 95 °C for 10 min, samples were centrifuged twice to eliminate debris and DNA quantity and quality in the supernatant was evaluated by Nanodrop (Celbio).

TP53 mutation status was determined for the exons 5–8 by PCR amplification and Direct Sequencing using 3130 Genetic Analyzer (Applied Biosystems, Monza, Italy) or Next-Generation Sequencing (NGS) Ion S5 platform (Thermofisher Scientific, Monza, Italy). NGS libraries were manually prepared starting from 10 ng of genomic DNA, using the AmpliSeq™ Library kit 2.0 and Ion AmpliSeq™ Colon and Lung Cancer Research Panel v2 (Thermofisher Scientific, Monza, Italy). Template preparation and enrichment were performed on a Ion Chef™ system with the Ion PGM Hi-Q View Chef kit. Sequencing was performed on the Ion PGM System using the Ion 316™ Chip v2. (Thermofisher Scientific, Monza, Italy). Signal processing and base calling were carried with the default base-caller parameters of Torrent Suite. Variants with <30 calls were filtered out. NGS analysis was performed using Ion Reporter software (v5.10). Limit of detection (LOD) for single nucleotide variants (SNV), insertions/deletions and splice site mutations was $>3\%$ mutant allele frequency (MAF) with a minimum depth of 500x. Frequencies of each single mutant were recorded and amplicon reads were reviewed with the Integrative Genomics Viewer (IGV), allowing visual inspection of the coverage of the regions of interest. Alignment and variant calling were performed using human reference genome 19 (hg 19). *TP53* mutations were qualitatively classified as disruptive and non-disruptive mutations, as previously described [22,23]. Any mutation resulting in a stop codon, missense mutations occurring outside the L2 or L3 protein loops, and in-frame deletions within the L2 or L3 loops were categorized as disruptive mutations. Non-disruptive mutations were identified as missense mutation and in-frame deletions occurring outside the L2 or L3 loops and missense mutations within the L2 or L3 loops resulting in a substitution of one amino-acidic residue with another of the same polarity/charge.

Response evaluation

Best clinical responses to treatment to TKIs were evaluated on the basis of interval CT scans using standard Response Evaluation Criteria in Solid Tumors criteria (RECIST) version 1.1. In particular, responses to

treatments were classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Patients with both diagnostic and at least one repeated evaluation after *ALK*-TKI monotherapy were considered for the study. All centers involved in the study used the same criteria for response evaluation.

Statistical analyses

Data were summarized by mean ± standard deviation (SD) for continuous variables and through natural frequencies and percentages for categorical ones. The association between categorical variables was tested by the Pearson's χ 2 test or Fisher exact test, when appropriate, whereas those between a continuous variable and a categorical one was tested by means of the Student *t*-test or analogous non-parametric Wilcoxon-Mann Whitney test, when appropriate. Treatment responses were reported as objective response rate (ORR) and disease control rate (DCR). Objective response rate (ORR) was calculated as the ratio between complete response (CR) and partial response (PR), and the total number of patients evaluable, while Disease Control Rate (DCR) was calculated as the ratio between CR, PR and stable disease (SD) and the total number of evaluable patients.

The time-to-event endpoints examined were progression-free survival (PFS) and overall survival (OS). With regard to treatment response and PFS, separate analyses for each line of treatment were performed. PFS was defined as the time from start of treatment to disease progression or death for any cause, whichever occurred first. Patients who were alive and progression-free at December 31, 2018, the last follow-up update, were censored at that date. With regard to PFS, separate analyses for line of treatment were performed. With regard to OS, the analysis was done on all patients. OS was defined as the time from date of diagnosis of advanced cancer to death for any cause. Alive patients were censored at the date of the last follow-up update. PFS and OS functions were estimated using the Kaplan–Meier method, and the log-rank test was used to assess differences between groups. Median PFS and OS were reported as point estimates and 95% confidence intervals (CI) in round brackets. The Cox proportional hazards regression model was used to quantify the association between specific covariates and the time-to-event endpoints. Results are reported as hazard ratio (HR) and 95% CI in round brackets. As the main study objective was to investigate an association between the presence of *TP53* mutation or the type of *TP53* mutation and PFS or OS, potential confounders (demographic or clinical covariates) of such relationship were studied comparing non-adjusted HR and adjusted one, that is including in the model other covariates other than the one related to *TP53*. If the percent-age difference between the two estimates was greater than10%, confounding was considered present. Overall and when not otherwise specified, a two-sided p-value (p) <0.05 was considered statistically significant. All statistical analyses were performed using STATA 15.0 software (College Station, TX, USA).

Results

Clinico-pathologic and molecular features of patients

Retrospective data on 98 *ALK*-translocated NSCLC patients were obtained through medical chart review. Of these, 22 patients had no information on the clinical outcomes as well as on the treatment received; for this reason, analyses focused on 76 patients. Patients characteristics, including methodology for *ALK* assessment and *TP53* mutations are reported in Table 1.

Of patients with available information on smoking history, 28 patients were never smokers (47.5%), 22 were former smokers (37.3%) and 9 were currently smokers (9%). *TP53* mutation status was evaluated on 64 patients with tissue availability for molecular testing; of these, 13 (20.3%) were affected by mutations: 4 in exon 5 (30.8%), 5 in exon 6 (38.5%), 1 in exon 7 (7.7%) and 3 in exon 8 (23%), while 51 patients (79.7%) had wild-type *TP53*. Accordingly to our previous works [22, 23], we qualitatively classified *TP53* mutation into disruptive and non-disruptive mutations, finding that 7 patients had a disruptive mutation (53.8%) and 6 had a non-disruptive mutation (46.2%) (Table S1).

Table 1
Patients' characteristics ($n = 76$).

	N	%
Gender		
female	44	57.9
male	32	42.1
Age at diagnosis (yrs), mean ± ds	57.3 ± 13.0	
missing	10	
Smoking habit		
never	28	47.5
former	22	37.3
current	9	15.3
missing	17	
ALK rearrangment detection		
FISH	31	40.8
IHC	8	10.5
FISH + IHC	37	48.7
TP53 mutation status		
wt	51	79.7
exon 5	4	6.3
exon 6	5	7.8
exon 7	1	1.6
exon 8	3	4.7
missing	12	
Type of *TP53* mutation		
Wt	51	79.7
Disruptive	7	10.9
Non-disruptive	6	9.4
missing	12	

FISH: Fluorescence in-situ hybridization; IHC: immunohistochemistry.

In the present study, 21 patients received an *ALK*-TKI agent as a first-line treatment, 57 as a second-line, and 28 patients as a third-line treatment. The type of *ALK*-TKIs received in each line is reported in Table S2. The total does not add up to 76 as some patients were treated with an *ALK*-TKI agent in more than one line. To investigate the association between *TP53* mutations and response to treatment as well as progression-free survival, separate analyses for each line of treatment were performed. That is, on 76 *ALK*-translocated patients treated in first-line, on 67 patients in second-line, and on 36 patients in third-line.

Impact of TP53 mutations on response to treatment and progression-free survival

Response to treatment was evaluated as objective response rate (ORR) and disease control rate (DCR). In any line of treatment, no statistically significant association was found between *TP53* mutations and ORR or DCR (Table S3). *TP53* mutations were not correlated with ORR or DCR neither if classified as disruptive and non-disruptive mutations (Table S4).

In first-, second- and third-line treatment, median PFS was 4.59 (95% CI: 0.95-NA), 4.14 (95% CI: 0.59–12.98) and 3.55 months (95% CI: 0.16-NA) for *TP53*-mutated patients, respectively, while it was equals to 7.59 (95% CI: 4.93–11.14), 8.74 (95% CI: 5.42–12.42) and 11.76 months (95% CI: 2.99–19.97) for wt *TP53* patients, respectively (Figure S1). No statistically significant associations were found in any line of treatment (log-rank test p-value equal to 0.203, 0.321 and 0.501, respectively).

When considering the different *TP53* mutations in terms of disruptive and non-disruptive mutations, patients with non-disruptive mutations showed a worse prognosis. In first-, second and third line treatment, median PFS was 1.41 (0.82-NA), 3.91 (0.72-NA) and 1.91 (0.16-NA) for *TP53* non-disruptive mutations, and 5.72 (95% CI: 0.76-NA), 4.14 (0.59-NA) and 34.17 (5.55-NA) for patients with *TP53* disruptive mutations, respectively (Fig. 1).

Table 2 shows the results from Cox regression. At univariate Cox

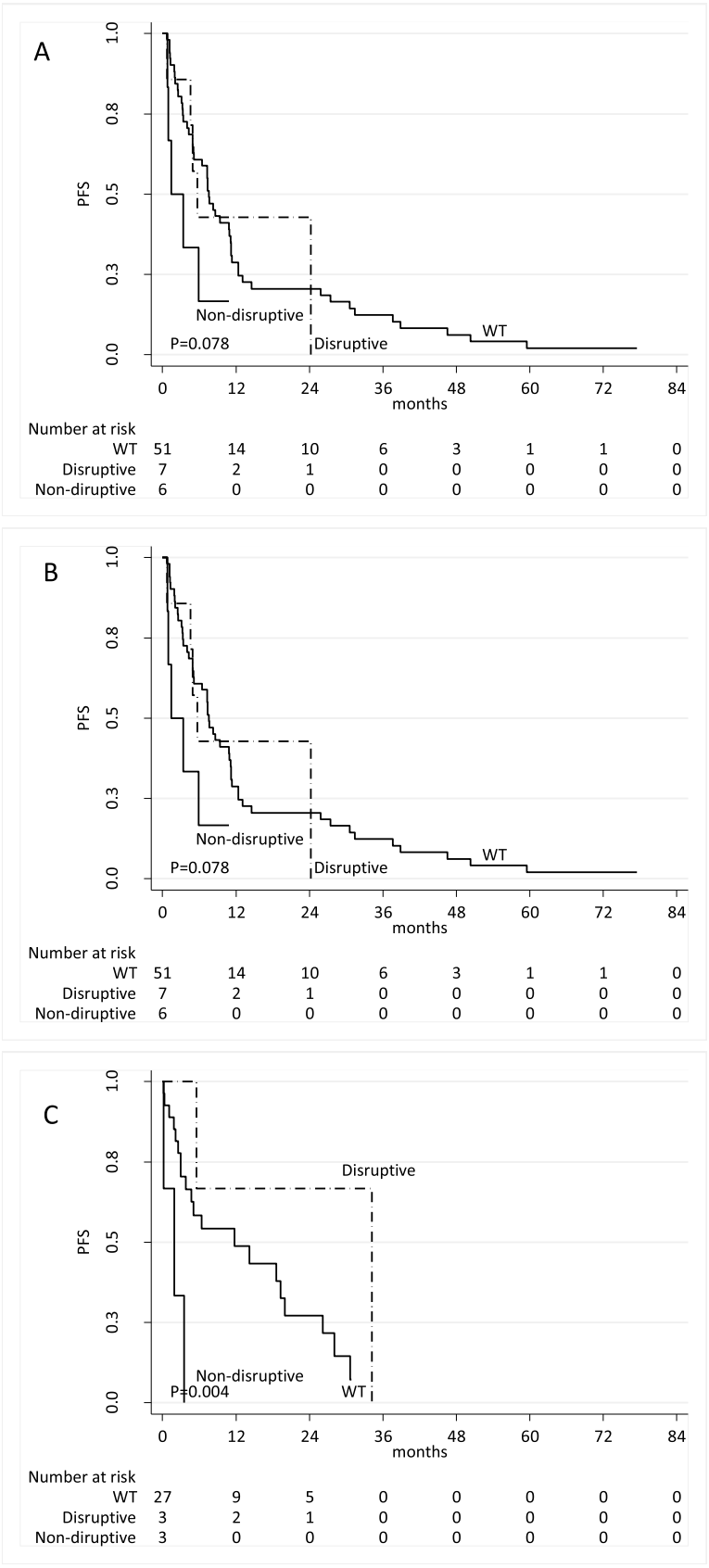

Fig. 1. Impact of disruptive and non-disruptive *TP53* mutations on Progression-free survival (PFS) of patients in first- (A), second- (B) and third-line of treatment (C).

Table 2
Results from univariate Cox proportional hazards models for Progression-Free Survival for each line of treatment.

	First line		Second line		Third-line	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
wt *TP53*	1		1		1	
TP53 Disruptive mutation	0.96 (0.38–2.43)	0.927	1.05 (0.36–3.07)	0.926	0.28 (0.04–2.08)	0.212
TP53 Non-disruptive mutation	2.49 (0.96–6.43)	0.059	2.02 (0.78–5.21)	0.146	5.85 (1.53–22.38)	0.010

analyses, patients carrying a *TP53* disruptive mutation compared to wt *TP53* patients were associated with a shorter PFS, especially in first- and third-line of treatment (HR=2.49, 95% CI: 0.96–6.43, $p = 0.059$; HR=2.02, 95% CI: 0.78–5.1, $p = 0.146$; HR=5.85, 95% CI: 1.53–22.38, $p = 0.010$ for first-, second-, and third-line, respectively). No confounding effect by demographic and clinical covariates was observed.

Impact of TP53 mutations on overall survival

Median OS was 57.03 months (26.38-NA). Considering the patients by *TP53* mutations, median OS was 48.88 months (2.99-NA) for *TP53*-mutated patients and 67.77 (53.32-NA) for wt *TP53* patients (Figure S2); *TP53* mutations were also analyzed in terms of disruptive and non-disruptive mutations, and we confirmed that non-disruptive mutations are able to negatively affect OS (Fig. 2). At univariate analysis, the hazard ratio for patients with *TP53* non-disruptive mutations as compared to wild type patients was 4.49 (95% CI: 1.49–13.58, $p = 0.008$), while it was 1.05 (95% CI: 0.25–4.53, $p = 0.943$) for patients with *TP53* disruptive mutations as compared to wild type patients. No confounding effect by demo-graphic and clinical covariates was observed.

Discussion

Following our previous results in two independent cohorts of EGFR-mutated NSCLC patients, in this study we analyzed the effect of *TP53* gene mutations on clinical outcomes of *ALK*-rearranged NSCLC patients. Our results show that *TP53* non-disruptive mutations predict worse clinical outcome of patients [22,23].

TP53 mutations are the most frequent in human cancers, promoting survival and resistance to apoptosis of cancer cells, with association to worse prognosis of cancer patients and resistance to systemic therapies [26,27]. Moreover, *TP53* germinal are associated to Li-Fraumeni syndrome, confirming its role as a master regulator in human cancer [28].

TP53 is the most frequently mutated gene also in NSCLC, with mutation rates up to 55%, a predominant clonal expression [29–31]. On the other hand, in *ALK*-rearranged NSCLC patients, *TP53* mutation rates range between 26% and 33% [32].

The prognostic role of *TP53* mutations have been widely investigated in NSCLC, and several data showed that mutations affecting this gene are associated with worse patients prognosis [30,33-35], also affecting responsiveness to TKIs in the subset of EGFR-mutated patients [36–37].

In recent years, several studies investigated the role of *TP53* mutations in predicting prognosis and responsiveness to TKIs in the subset of *ALK*-rearranged NSCLC patients.

Strong evidences and a recent meta-analysis indicate that *TP53* mutations are strong indicators of worse prognosis in *ALK*-rearranged NSCLC patients [32,38-40]; furthermore, longitudinal assessment highlighted that these gene mutations are able to guide patients prognosis, and that the acquisition of *TP53* mutation addressed patients to a

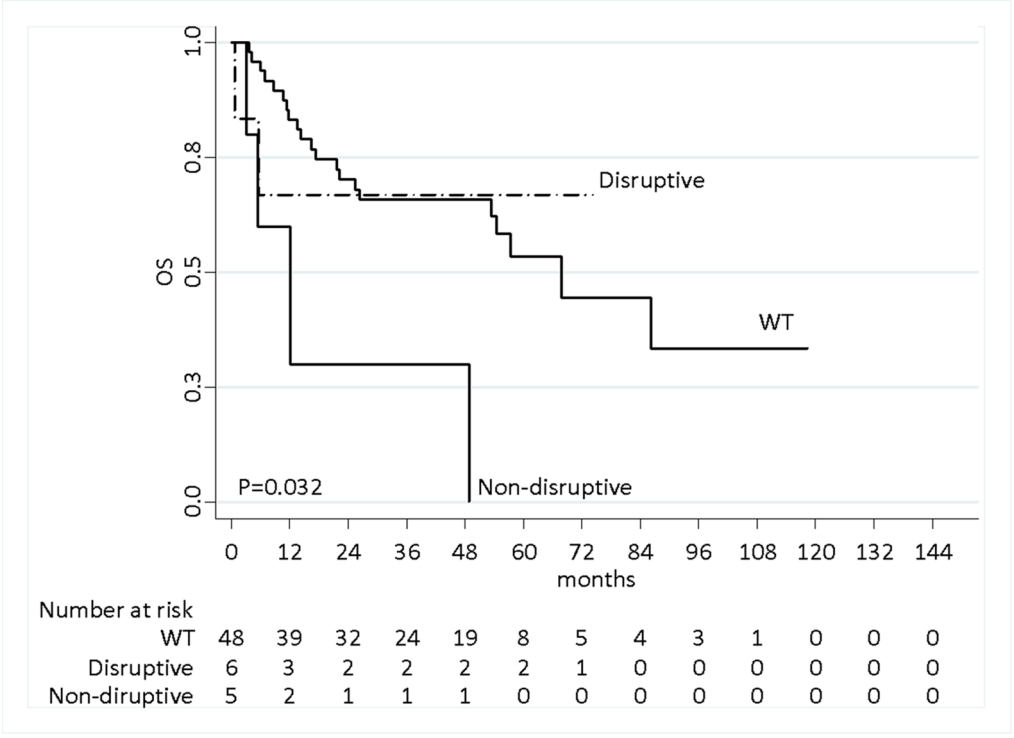

Fig. 2. Overall survival (OS) of patients in relation to TP53 disruptive and non-disruptive mutations. Median follow-up were 55.72 months (95% CI: 41.39–59.82), 19.55 months (95% CI: 9.4 - Not reached) and Not Reached for wt patients, patients with a disruptive mutation and patients with a non-disruptive mutation, respectively.

worse prognosis and shorter PFS following TKI treatment [41]. Robust data by Kron and colleagues confirmed that *ALK*-rearranged and *TP53* co-mutations are predictive of both shorter PFS to *ALK*-TKIs, and shorter OS [41]; same evidence arose from three independent studies carried out in Asian patients, demonstrating that *TP53* mutations predict low responsiveness to alectinib and crizotinib, and worsen OS [42–45].

Taken together, these evidences clearly indicate as *TP53* mutations could negatively influence prognosis of patients, and even responsiveness to anti-*ALK* therapy. At this regard, and extensive recent review shed new light on *ALK* rearrangement variants and *TP53* mutations with the response to *ALK*-TKIs [46]. On the other hand, the characterization of *TP53* mutations could add significant and qualitative indications.

Great interest has been focused on the type of *TP53* mutations, as several data highlighted that different mutations confer different functions of p53 protein. At this regard, several classification systems for *TP53* mutations have been proposed, in order to assess the impact of the type of mutation on cellular machinery [47].

The p53 protein is a 53 kDa protein mainly divided in three portions: the transactivation domain (exon 2–4), the DNA binding domain (DBD, exon 5–8) and the oligomerization domain (exons 9–11) [48]. The 80% of *TP53* gene mutations have been found in the 200 aminoacids of the DBD, suggesting that exons 5–8 represent the crucial portion for protein activities [49].

In-vivo studies demonstrated that part of the mutations within the DBD domain are associated to loss of protein function (LOF), acting like to a null allele [50,51]. Interestingly, specific p53 mutants could be associated with acquired oncogenic gain of function (GOF) [52].

These mutants are able to achieve pro-tumorigenic activity, enhancing cellular growth, resistance to induced cell death and provoking genomic instability and invasiveness [49]. Mechanistically, GOF include the independent activation of transcription factors and co-factors, activation of signaling cascades and alteration of chromatin epigenetic pathways [49,53-55]. At this regard, on the basis of the functional effect on the protein, it has been proposed a categorization of *TP53* alterations into disruptive and non-disruptive mutations, for which disruptive mutations lead to partial or complete inactivation of the p53 protein, and non-disruptive mutations, even though retaining some activities of wt p53 protein, are majorly associated to acquired oncogenic GOF [21,56]. Following this classification, non-disruptive mutations were reported to negatively affect prognosis in NSCLC patients [20].

In this study, we found that non-disruptive *TP53* mutations are strongly associated with worse OS, and also showed an association with shorter PFS.

No differences in terms of overall survival between patients with non-disruptive vs disruptive mutations were observed.

Consistent with our data, Song et al. reported that *TP53* non-disruptive mutations distinguish a subgroup of *ALK* rearranged patients with worse PFS, finding a non-statistically significant trend in prognosis of patients [57]. These are the first evidences that specific *TP53* mutations affect differently prognosis and responsiveness o NSCLC *ALK* rearranged patients. Considering that similar evidences have been highlighted for EGFR-mutated patients, further studies are needed to better understand the molecular mechanisms standing at the basis of the p53 GOF in cancer cells.

A major limitation of the present study is its retrospective nature. Although all consecutive patients tested for *ALK*-translocation in the study centers were considered, missing information were present for some clinical and biological information, potentially introducing some selection bias in the analyses. Another limitation relates to the study size that, in presence of not so common mutations such as those in *TP53* gene, may preclude the observation of significant associations.

Nonetheless, the role of *TP53* mutations in predicting response to TKIs and prognosis of patients is supported by several evidences, and a study with a larger case series is needed to better understand the emerging role of these gene mutations in *ALK* rearranged NSCLC patients.

Conclusions

In this study, we found that mutations affecting *TP53* gene, especially non-disruptive mutations, are able to affect prognosis of *ALK*-rearranged NSCLC patients.

Data availability statement

The datasets generated for this study can be found by the Corresponding Author upon reasonable request.

Funding

This research received no external funding.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee Comitato Etico della Romagna (C.E.ROM.), protocol code IRST-B087, date of approval 06 March 2019.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

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Supplementary materials

Figure S1: Impact of *TP53* mutations on Progression-free survival (PFS) of patients in first- (A), second- (B) and third-line of treatment (C). Figure S2: Overall survival (OS) of patients in relation to *TP53* mutations. Table S1: *TP53* mutations of the patients case series. Table S2: *ALK*-TKIs admistration across the different lines of treatment. Table S3: Objective response rate (ORR) and disease control rate (DCR) according to *TP53* mutations. Table S4: Objective response rate (ORR) and disease control rate (DCR) according to disruptive and non-disruptive *TP53* mutations.

CRediT authorship contribution statement

Matteo Canale: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Elisabetta Petracci:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Paola Cravero:** Writing – review & editing, Investigation, Data curation. **Marita Mariotti:** Writing – review & editing, Investigation, Data curation. **Gabriele Minuti:** Writing – review & editing, Investigation, Data curation. **Giulio Metro:** Writing – review & editing, Investigation, Data curation. **Vienna Ludovini:** Writing – review & editing, Investigation, Data curation. **Sara Baglivo:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation. **Maurizio Puccetti:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Alessandra Dubini:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Giovanni Martinelli:** Writing – review & editing, Project administration, Investigation. **Angelo Delmonte:** Writing – review & editing, Visualization, Supervision, Resources,

Project administration, Investigation, Funding acquisition, Conceptualization. **Lucio Crinò:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Paola Ulivi:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2022.101471.

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