Common and uncommon mutations in NSCLC: differences in response to treatment with tyrosine kinase inhibitors

A single-center retrospective analysis

Carolina Sciortino[1*], Benedetta Bovolenta[1], Giovanni Antonio Marrocco[1], Greta Martino[1], Alessio Neri[1], Massimo Nucci[1], Laura Pappalardo[1], Mariam Grazia Polito[1], Valentina Viglialoro[1], Enrico Cortesi[2], Salvatore Caponnetto[2]

Department of Radiology, Oncology and Pathology, Policlinico Umberto I, Sapienza University of Rome, Italy.

[2] Medical Oncology Unit B, Department of Radiology, Oncology and Pathology, Policlinico Umberto, I Sapienza University of Rome, Italy

INTRODUCTION

Uncommon EGFR mutations are a heterogeneous group, discovered in ~10% of the population with EGFR-positive non-small cell lung cancer (NSCLC), whose sensitivity to tyrosine-kinase inhibitors is not yet widely demonstrated. Several studies show a reduced response in patients harboring uncommon mutations, however, due to their heterogeneity and lack of data it is still uncertain which treatment is best for these patients.

PATIENTS AND METHODS

48 patients with EGFR-positive NSCLC, treated with TKIs, were identified and divided into subgroups by mutation.
Progression-free survival (PFS) and overall survival (OS) were evaluated for the entire cohort while time to treatment failure (TTF) was evaluated only in patients treated with Afatinib (Giotrif®).

Survival assessment was calculated using the Kaplan-Meier method.

Subgroups were compared using the log-rank test and a multivariate analysis was performed.

OBJECTIVES

We propose to retrospectively analyze how patients with various EGFR mutations respond differently to treatment with tyrosine-kinase inhibitors.

Mutation	No	Frequency	PFS (months)	OS (months)
Del19	18	37.5%	15.5 (9-33)	31 (22-51)
L858R	18	37.5%	10 (6-22)	23 (6-33)
Complex mutations	2	4.1%	8.25 (0.5-16)	8.25 (0.5-16)
DelIns19	4	8.3%	11 (2-30)	21.5 (2-43)
Exon 18-21	4	8.3%	2.5 (1-4)	6.5 (4-30)
Exon 20	2	4.1%	4.5 (4-5)	3 (2-4)

RESULTS

In the different subgroups, there were no significant differences in smoking status (ex-smokers, smokers, nonsmokers) and sex, respectively, with a P value of 0.35 and 0.15.

In patients with common mutations, the median age was 65.5 years, whereas in patients with uncommon mutations, the median age was higher (74.5 years).

Patients with common mutations, deletion in exon 19 and L85R in exon 21, had a median OS of 31 months (95% CI: 22-51) and 23 months (95% CI: 6-33) and a median PFS of 16 months (95% CI: 9-33) and 10 months (95% CI: 6-22), respectively.

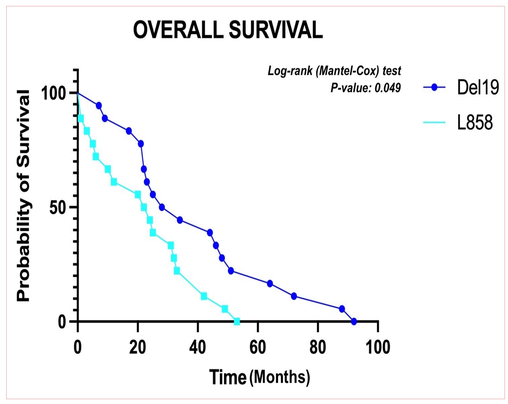
OS and PFS, in patients with common mutations, were superior to those with an uncommon mutation with a *P-value* of 0.003 and 0.0001.

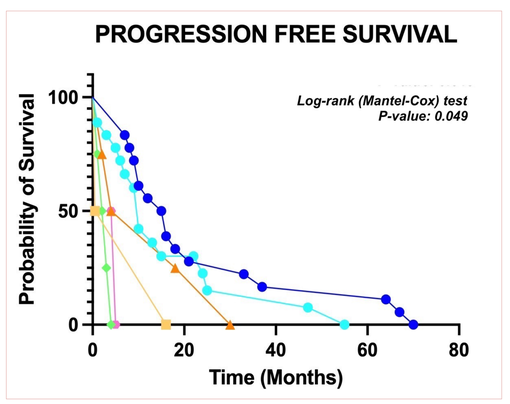
Patients with mutations in exon 18 and 21 and patients with mutations in exon 20 had the worst outcome with an OS of 6.5 months (95% CI: 4-30) a PFS of 2.5 months (95% CI: 1-4) and an OS of 3 months (95% CI: 2-4) and a PFS of 4.5 (95% CI: 4-5), respectively.

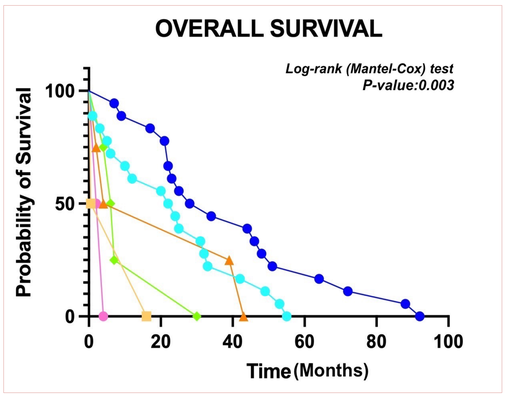
Patients with these mutations also had significantly lower TTF.

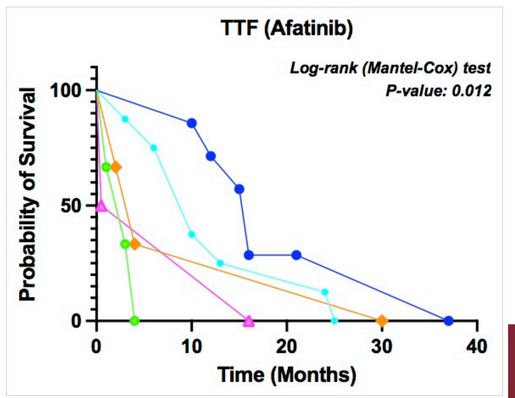
Multivariate analysis confirmed the results: patients with point mutations in exon 19-21 and mutations in exon 20 had the highest risk of death (HR 6.01 CI: 1.02-35.46 P-*value* 0.001 and HR 12.81 CI: 2.46-62.19 P-*value* 0.004).

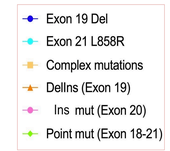
Characteristics	Uncommon m. N=12	Common m. N=36	P-*value*
Median age (years)			
Median	74,5	65,5	
Range	50-85	35-84	
Sex			
Male	3	17	0.15
Female	9	19	
Smoking history			
Current or past smoker	8	14	0.35
Non-smoker	4	15	
Hystological type			
Adenocarcinoma	12	36	
Other NSCLC	0	0	











CONCLUSIONS

Patients with uncommon mutations respond heterogeneously to tyrosine-kinase inhibitor treatments.
Patients with deletion-insertion or complex mutations are sensitive to treatment, whereas patients with insertion in exon 20 or mutations in exons 18 and 21 respond very poorly.

1000P