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CONGRESS
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**KRAS G12C VS NON-G12C:
DIVERGENT IMMUNOTHERAPY OUTCOMES IN
NON-SMALL CELL LUNG CANCER**

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Background

- *KRAS* mutations are among the most prevalent oncogenic drivers in non-small cell lung cancer (NSCLC)¹.
- The most frequent subtypes are *G12C* (33.6%), *G12D* (23.9%) and *G12V* (22.1%)².
- Presence of co-mutations is frequent in *KRAS*-mutated tumors and impacts their biological behaviour³.
- *KRAS* allele mutation types have also been correlated to different PD-L1 expression⁴.
- Emerging evidence suggests differential responses to immune checkpoint inhibitors (ICI) between tumors harboring *KRAS G12C* and *non-G12C* mutations.

This study aimed to evaluate the impact of **distinct *KRAS* mutation** subtypes in the clinicopathological characteristics and outcomes of patients treated with **ICI-based regimens**

Patients and Methods

Descriptive analysis

- Observational, retrospective, multicenter study.
- **Study population:** NSCLC harbouring *KRAS* mutations and treated with ICI-based regimens, from January 2017 to January 2023, in 3 Spanish hospitals (n = 207).
- ***KRAS* detection:**
 - Real-time polymerase chain reaction (RT-PCR) (n = 77).
 - Next generation sequencing (NGS) (n = 130).
 - * *Oncomine focus assay, oncomine-solid tumor DNA assay, oncoDNA assay, Ion PGM, Ion GeneStudio S5, Ion Torrent Genexus system and TELMA trial screening platforms.*
- **PD-L1 detection:** by immunohistochemistry.
 - * *22C3 pharmDx kit, Roche's SPS263 Ventana.*

Patients and Methods

Statistical Analysis

- Two groups based on **KRAS mutation**: G12C and non-G12C.

Statistical Analysis:

- Baseline characteristics: Chi-square and Fisher's exact test.
- Distribution PD-L1 expression levels between subgroups: Mann-Whitney U test (2 groups) and Kruskal-Wallis test (multiple independent groups).
- Survival analysis: Kaplan-Meier model.
- Multivariate models to identify independent predictors of survival outcomes.

Results

Baseline characteristics

N (%)	G12C (n=98)	Non-G12C (n=100)	p-value
Median age	64 (41 – 80)	65 (45 – 83)	0.406
Sex			
Male	60 (61%)	69 (69%)	0.251
Female	38 (39%)	31 (31%)	
Tobacco			
Never smoker	1 (1%)	3 (3%)	0.606
Former smoker	51 (52%)	50 (50%)	
Current smoker	46 (47%)	47 (47%)	
Pack-year history	40 (15 – 180)	40 (0 – 250)	0.892
ECOG			
0	39 (40%)	45 (45%)	0.459
≥ 1	59 (60%)	55 (55%)	
M1 CNS	17 (17%)	28 (28%)	0.074
M1 liver	16 (16%)	19 (19%)	0.536
Histology			
Adenocarcinoma	95 (97%)	94 (94%)	0.321
Other	3 (3%)	6 (6%)	
PD-L1 levels			
< 1%	23 (23%)	33 (33%)	0.304
1 - 49%	26 (27%)	29 (29%)	
≥ 50%	43 (44%)	36 (36%)	
Unknown	6 (6%)	2 (2%)	
Stage at diagnosis			
Stage I-III	20 (20%)	23 (23%)	0.658
Stage IV	78 (80%)	77 (77%)	

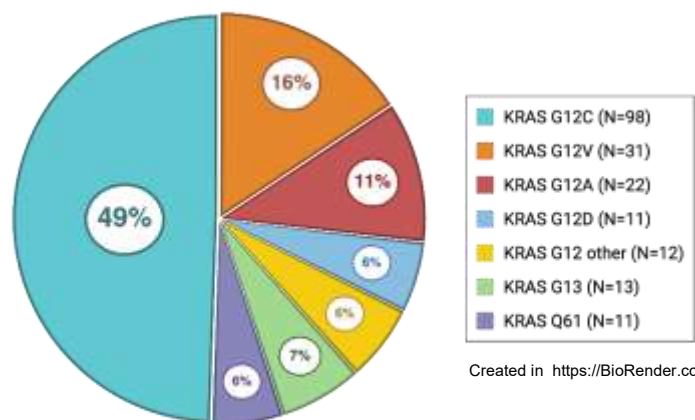
Baseline patient characteristics.

N (%)	G12C (n=98)	Non-G12C (n=100)	p-value
Immunotherapy treatment modality			
Monotherapy	57 (58%)	52 (52%)	0.530
CT-ICI	38 (39%)	45 (45%)	
ICI-ICI combination	2 (2%)	1 (1%)	
Others	1 (1%)	2 (2%)	
Treatment line			
1st line	78 (80%)	83 (83%)	0.538
≥ 2nd line	20 (20%)	17 (17%)	
KRAS G12C inhibitors at progression to immunotherapy			
Sotorasib	11 (11%)		NA
Adagrasib	7 (7%)		
None	80 (82%)	100 (100%)	

Type of treatment received by KRAS mutation.

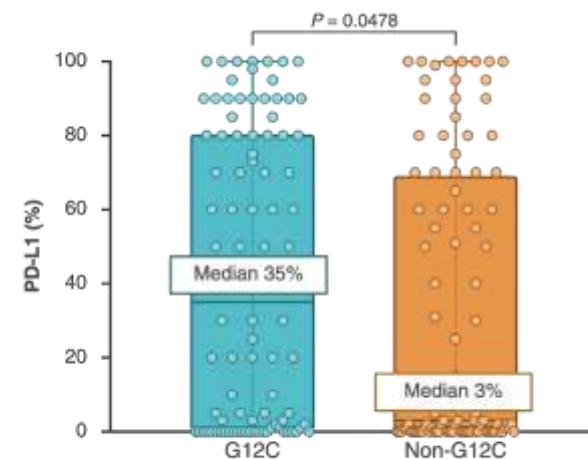
Results

Baseline characteristics



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KRAS allele mutation distribution (n = 198).



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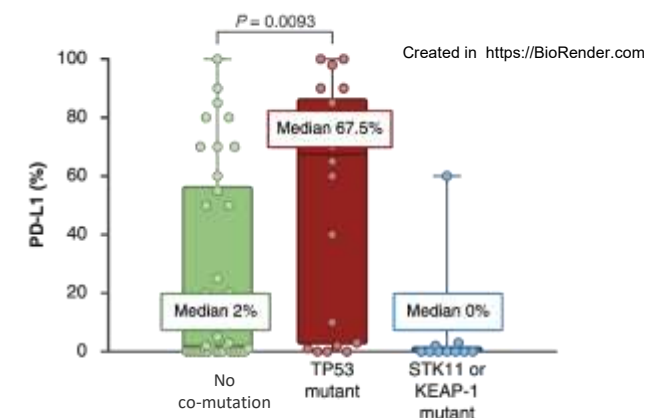
PD-L1 levels according to KRAS subgroups.

	KRAS G12C (n = 98)	KRAS non-G12C (n = 100)	P value
TP53			
Tested	51 (52%)	67 (67%)	-
Mutated	10 (20%)	23 (34%)	0.022
STK11/LKB1			
Tested	26 (27%)	46 (46%)	-
Mutated	2 (8%)	11 (24%)	0.004

Co-mutational status according to tested patients and KRAS allele mutation subtype

N (%)	TP53 and STK11 wild type (n = 36)	TP53 mutated (n = 21)	STK11 or KEAP-1 mutated (n = 10)
PD-L1 levels			
0 - 49%	24 (67%)	9 (43%)	9 (90%)
≥ 50%	12 (33%)	12 (57%)	1 (10%)

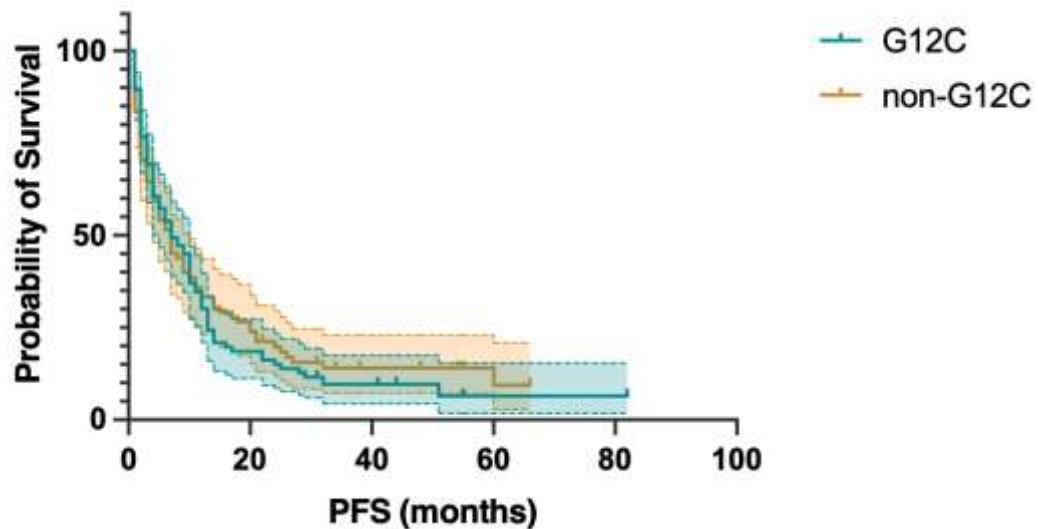
PD-L1 levels according to co-mutation status. Only patients with at least a known TP53 and STK11 mutation and known PD-L1 levels were included (n = 67).



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Results

Survival outcomes with ICI-based regimen



N° at risk

— (98)

17

6

2

2

-

— (100)

20

7

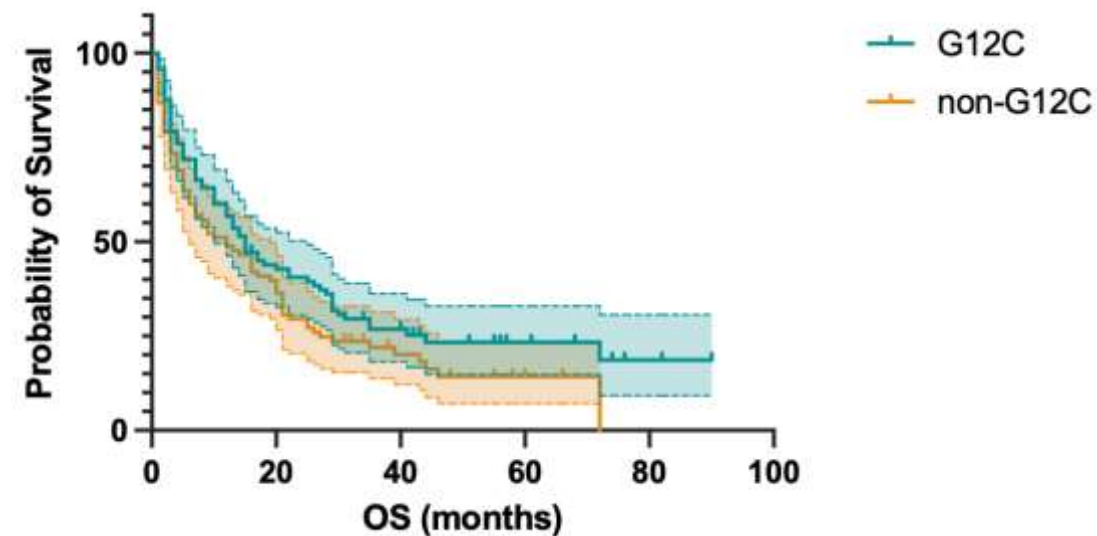
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	Median PFS (95% CI)	HR (95% CI)	p value
G12C	7 months (4 – 10)	0.93 (0.66 – 1.30)	0.765
Non-G12C	7 months (4 – 10)		

Progression-free survival outcomes from the beginning of immunotherapy treatment according to *KRAS* allele mutation subtype (G12C vs non-G12C, n = 198).



N° at risk

— (98)

40

19

8

3

-

— (100)

35

12

4

0

-

	Median OS (95% CI)	HR (95% CI)	p value
G12C	15 months (10 – 25)	0.77 (0.55 – 1.06)	0.119
Non-G12C	12 months (6 – 20)		

Overall survival outcomes from the beginning of immunotherapy treatment according to *KRAS* allele mutation subtype (G12C vs non-G12C, n = 198).

Results

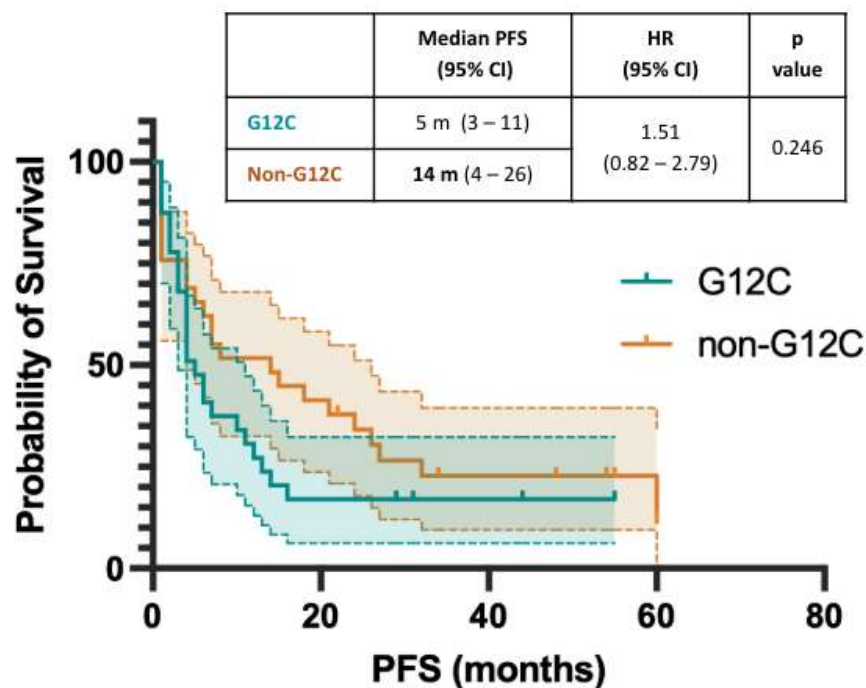
Multivariate study

Multivariate	Overall survival		Progression-free survival	
	HR (95% CI)	p value	HR (95% CI)	p-value
Sex				
Female vs. Male	0.86 (0.60 - 1.23)	0.441	0.92 (0.65 - 1.29)	0.615
ECOG				
≥ 1 vs. 0	2.13 (1.47 - 3.09)	< 0.001	1.78 (1.26 - 2.52)	0.001
KRAS allele mutation				
Non-G12C or V vs. G12C	1.17 (0.54 - 2.51)	0.691	1.07 (0.52 - 2.20)	0.864
G12V vs. G12C	1.96 (0.86 - 4.48)	0.111	1.89 (0.85 - 3.52)	0.119
PD-L1 levels				
≥50% vs. 0-49%	0.46 (0.31 - 0.70)	< 0.001	0.55 (0.37 - 0.82)	0.004
Central nervous system metastasis at diagnosis				
Yes vs. No	1.47 (0.99 - 2.19)	0.056	1.77 (1.21 - 2.58)	0.003
Anti-KRAS G12C at progression				
Yes vs No	0.41 (0.20 - 0.83)	0.014	NA	NA
Treatment type				
CT-IO vs. IO	1.03 (0.69 - 1.53)	0.893	0.88 (0.60 - 1.30)	0.526
Treatment line				
2nd vs. 1st line	1.36 (0.85 - 2.18)	0.197	1.83 (1.16 - 2.89)	0.009
Immune-mediated toxicity				
Yes vs. No	0.39 (0.27 - 0.56)	< 0.001	0.44 (0.32 - 0.63)	< 0.001

Multivariate analysis for overall and progression-free survival outcomes on immunotherapy.

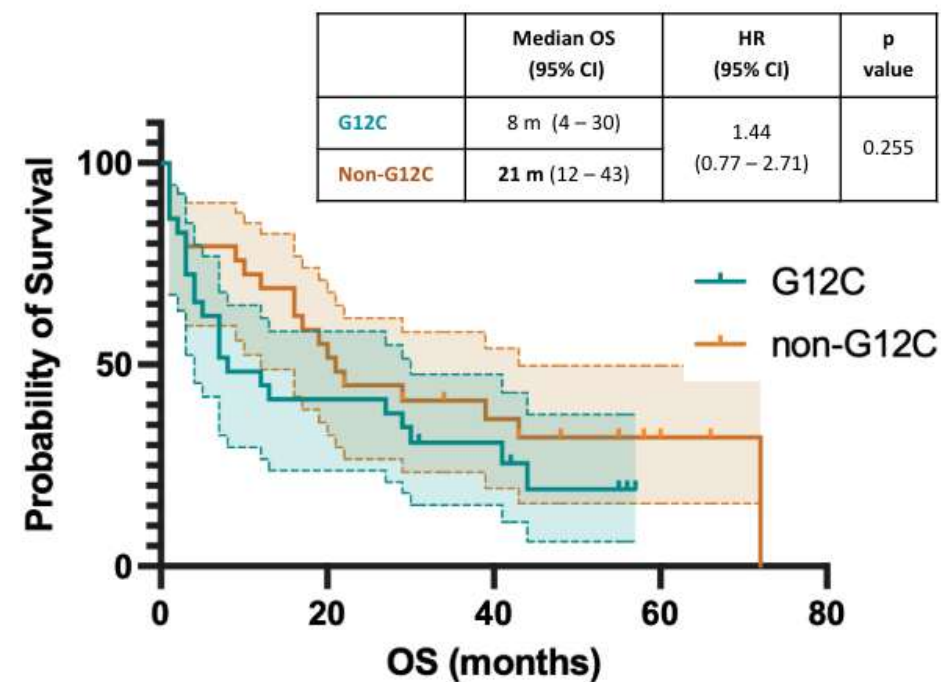
Results

Survival outcomes with ICI monotherapy in PD-L1 ≥ 50%



N° at risk

	0	20	40	60
— (32)	32	6	4	0
— (29)	29	13	6	2



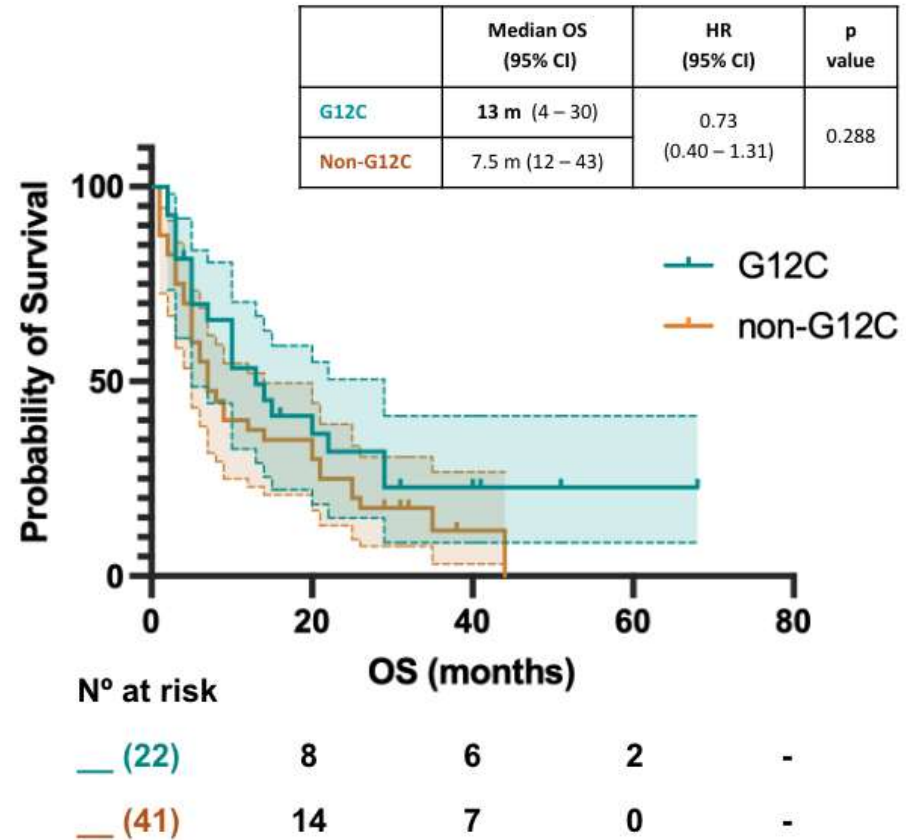
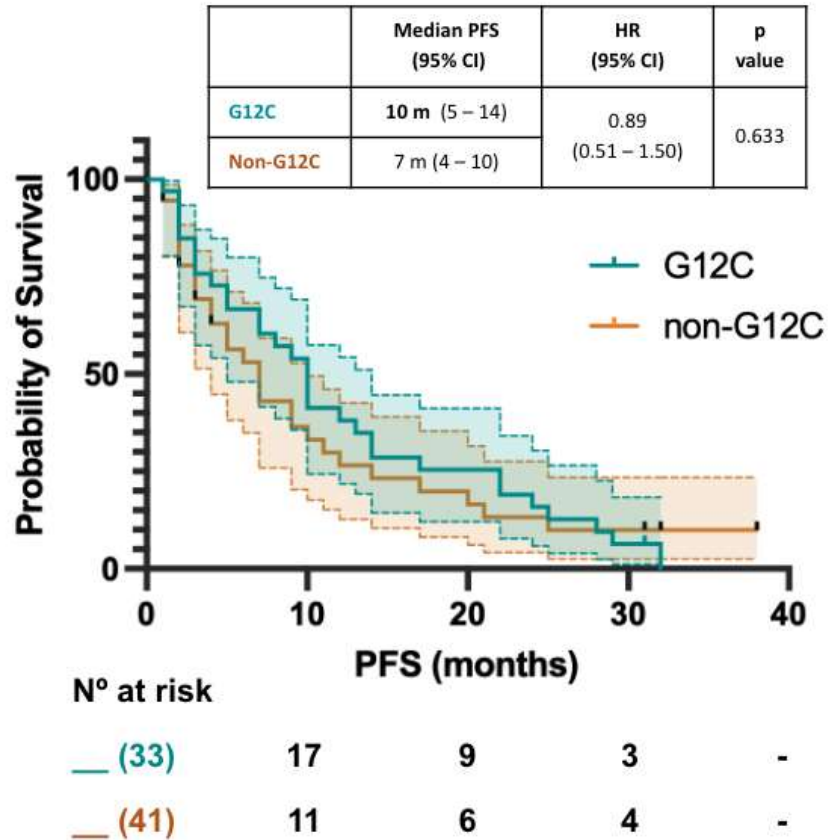
N° at risk

	0	20	40	60
— (29)	29	13	8	1
— (29)	29	16	9	4

Survival outcomes from the beginning of first-line immunotherapy in monotherapy in patients with PD-L1 ≥ 50% according to mutation status (G12C vs non-G12C, n = 61):
 A) Progression-free survival; B) Overall survival excluding KRAS G12C patients who were treated at progression with KRAS G12C inhibitors (n = 58).

Results

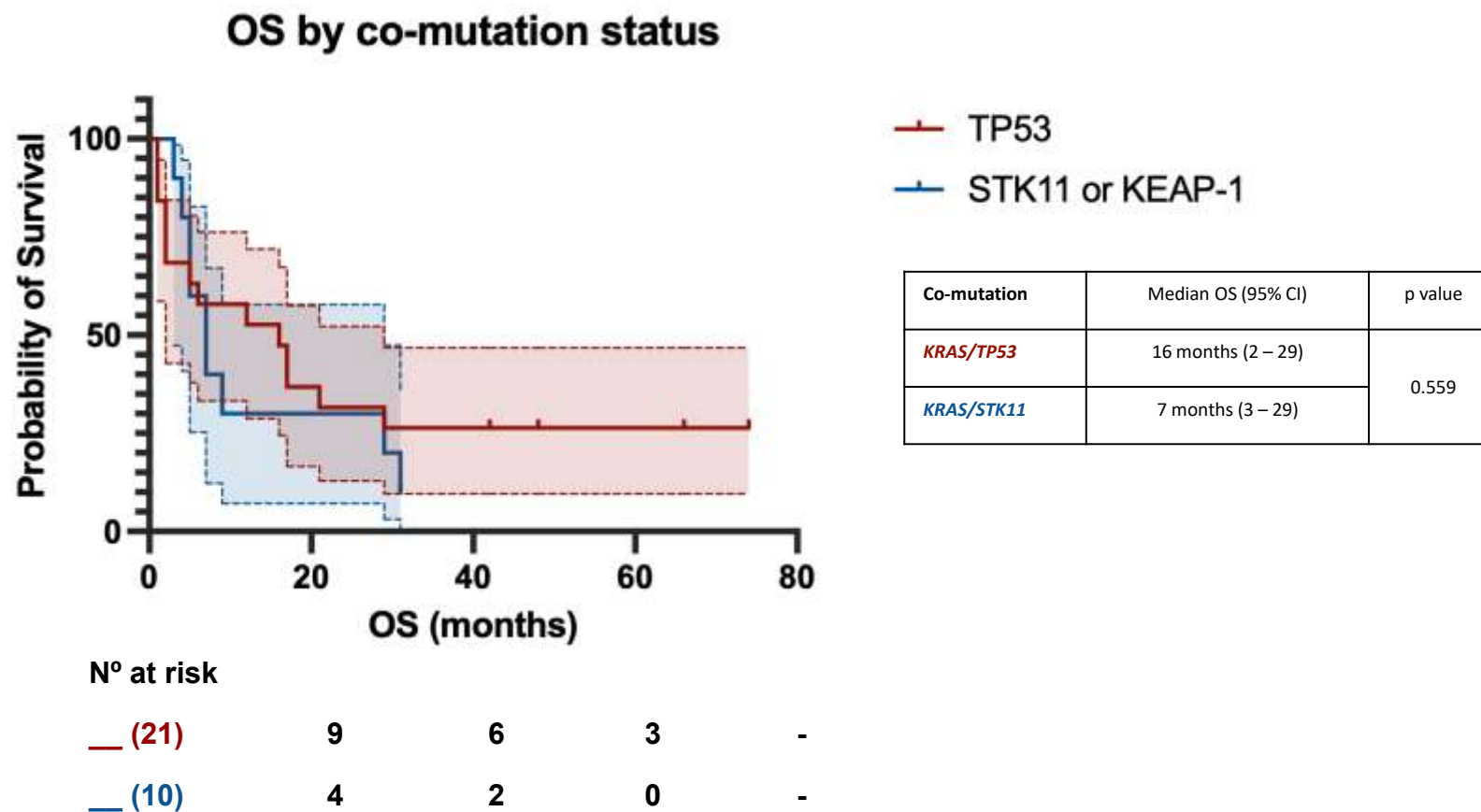
Survival outcomes with ICI-chemotherapy combination in PD-L1 < 50%



Survival outcomes from the beginning of first-line immunotherapy in combination with chemotherapy in patients with PD-L1 < 50% according to mutation status (G12C vs non-G12C, n = 74): A) Progression-free survival; B) Overall survival excluding KRAS G12C patients who were treated at progression with KRAS G12C inhibitors (n = 63).

Results

Overall survival with ICI-based regimen depending on co-mutation status



Overall survival outcomes from the beginning of immunotherapy treatment according to co-mutation status.

Conclusion

- The molecular profile of *KRAS non-G12C* subgroup (higher burden of co-mutations *STK11/KEAP-1*, lower PD-L1 expression) appears to contribute to a comparatively “colder” tumor microenvironment.
- PD-L1 expression remains regarded as the strongest predictor of response to immunotherapy.
- Co-mutations, especially *TP53* and *STK11*, appear to further modulate treatment outcomes.
- *KRAS G12C* inhibitor therapy acts as an independent determinant of overall survival in *KRAS G12C* subgroup.
- Specific *KRAS* mutation subtypes probably have distinct biological characteristics; however, these differences remain insufficiently explored due to limited sample size.
- Prospective validation is needed to confirm these observations and guide therapy selection.

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