PLEURAL EFFUSION IS A NEGATIVE PROGNOSTIC FACTOR FOR IMMUNE CHECKPOINT INHIBITOR (ICI) IN NON SMALL CELL LUNG CANCER (NSCLC): THE PLUIE STUDY.

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INTRODUCTION

- ICI represent a major therapeutic class in NSCLC as they are the first-line treatment , in absence of actionable molecular alteration combined or not with chemotherapy depending on PD-L1 status.
- Pleura is a common site of metastatic involvement in patients with NSCLC.
- Pleural cavity is a natural permeable barrier that can limit the penetration of cancer therapies in case of effusion.
- Very few data is available regarding implications of pleural effusion (PE) in NSCLC patients treated with ICI

OBJECTIVE

- We aimed to assess the clinical outcome of pleural effusion in NSCLC treated with ICI.

METHODS

- Multicenter international retrospective study of patients with related to NSCLC treated with ICI included between 2012 and 2019.
- We stratified the population according to the presence of pleural effusion at ICI baseline (PE vs. Non-PE).
- Primary endpoints were overall survival (OS) and early death rate (EDR).
- Secondary outcomes were progression free survival (PFS) and disease control rate (DCR).
- Association between response endpoints and PE was evaluated with logistic regression.
- Univariate and multivariate Cox models were performed for OS and PFS.

Baseline characteristics

Characteristics		Global (n=538)	Non-PE (n=342)	PE (n=196)	p-value
Age	> 65	228 (42.5%)	135 (39.7%)	93 (47.4%)	0.01
Gender	Female	186 (34.6%)	124 (36.3%)	62 (31.6%)	0.28
Smoking history	Current	175 (33.1%)	118 (35.2%)	57 (29.4%)	0.13
Histology	Non squamous	407 (75.7%)	255 (74.6%)	152 (77.6%)	0.44
PD-L1 status	Positive	179 (65.3%)	112 (67.1%)	67 (62.6%)	0.45
EGFR mutation	Yes	25 (5.8%)	16 (6.0%)	9 (5.5%)	0.82
ALK rearrangement	Yes	7 (1.6%)	4 (1.5%)	3 (1.8%)	1
ICI line	median [IQR]	2.6 [2;3]	2.6 [2;3]	2.6 [2;3]	0.88
ICI	Nivolumab	362 (67.3%)	222 (64.9%)	140 (71.4%)	<0.001
	Pembrolizumab	140 (26.0%)	94 (27.5%)	42 (23.5%)	
	Atezolizumab	32 (5.9%)	23 (6.7%)	9 (4.6%)	
	Other	4 (0.8%)	1 (0.3%)	0 (0%)	
ECOG-PS at ICI start	0-1	83 (15.7%)	65 (19.5%)	18 (9.2%)	0.002
	2 or more	445 (84.3%)	268 (80.5%)	177 (90.8%)	
Appearance of PE on ICI	Yes	-	-	31 (16.4%)	-
Therapeutic pl. intervention	Yes	-	-	73 (38.2%)	-

Table 1: Baseline characteristics of the overall cohort and according to the presence or absence of Pleural effusion.

RESULTS

- A total of 538 were included: 196 in the PE group and 342 in the non-PE group.
- In the PE group, median age was 64.4 years, 31.6% were female, 29.4% were current smokers and 77.6% presented a non-squamous NSCLC.
- PE was associated with higher number of metastatic sites (median 3.5 vs. 2.7), and worse performance status (PS≥2, 90.8% and 80.5% in non-PE).
- In the PE group, there were appearance of a PE in 31 patients (16.4%) and a therapeutic pleural intervention for 73 (38.2%)

Response endpoints
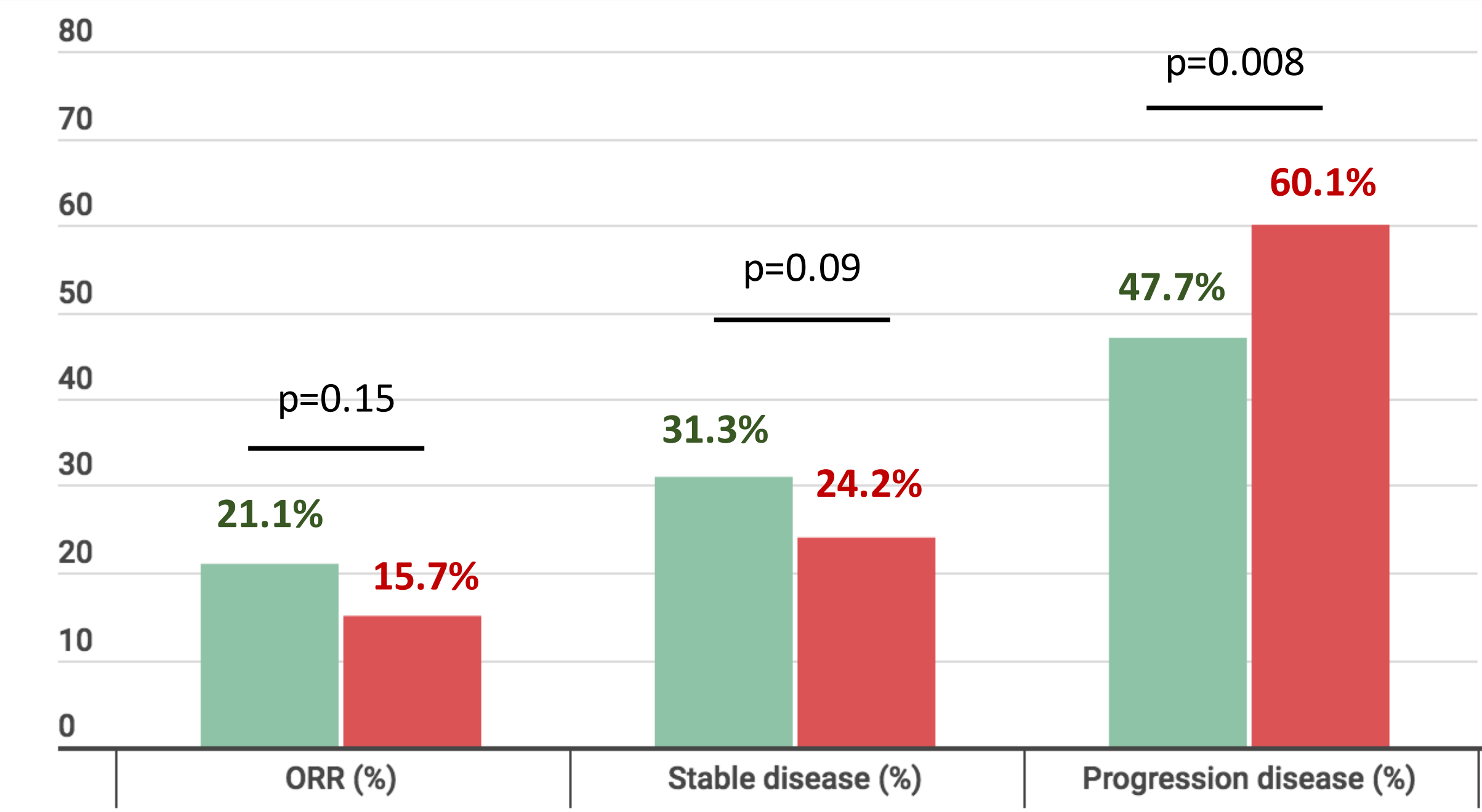
ORR was higher in the non PE group (21.1 vs. 15.7%, p=0.15) as well as SD rate (31.3 vs. 24.2%, p=0.09).

PD rate was higher in the PE group (60.1 vs. 47.7%, p=0.008).

Figure 1: Response endpoints according to the presence of pleural effusion.
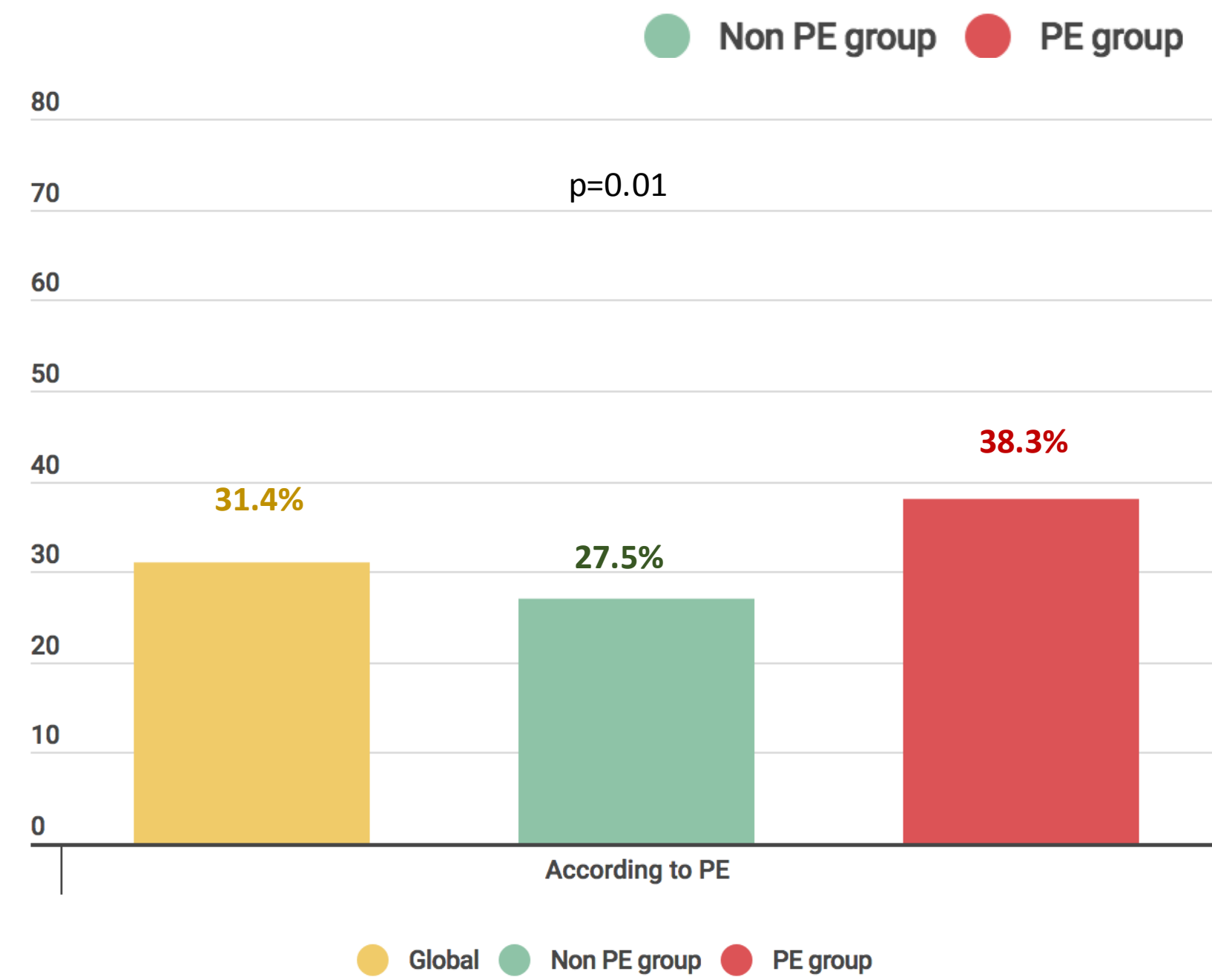

Figure 2A: Early death rate according to pleural effusion
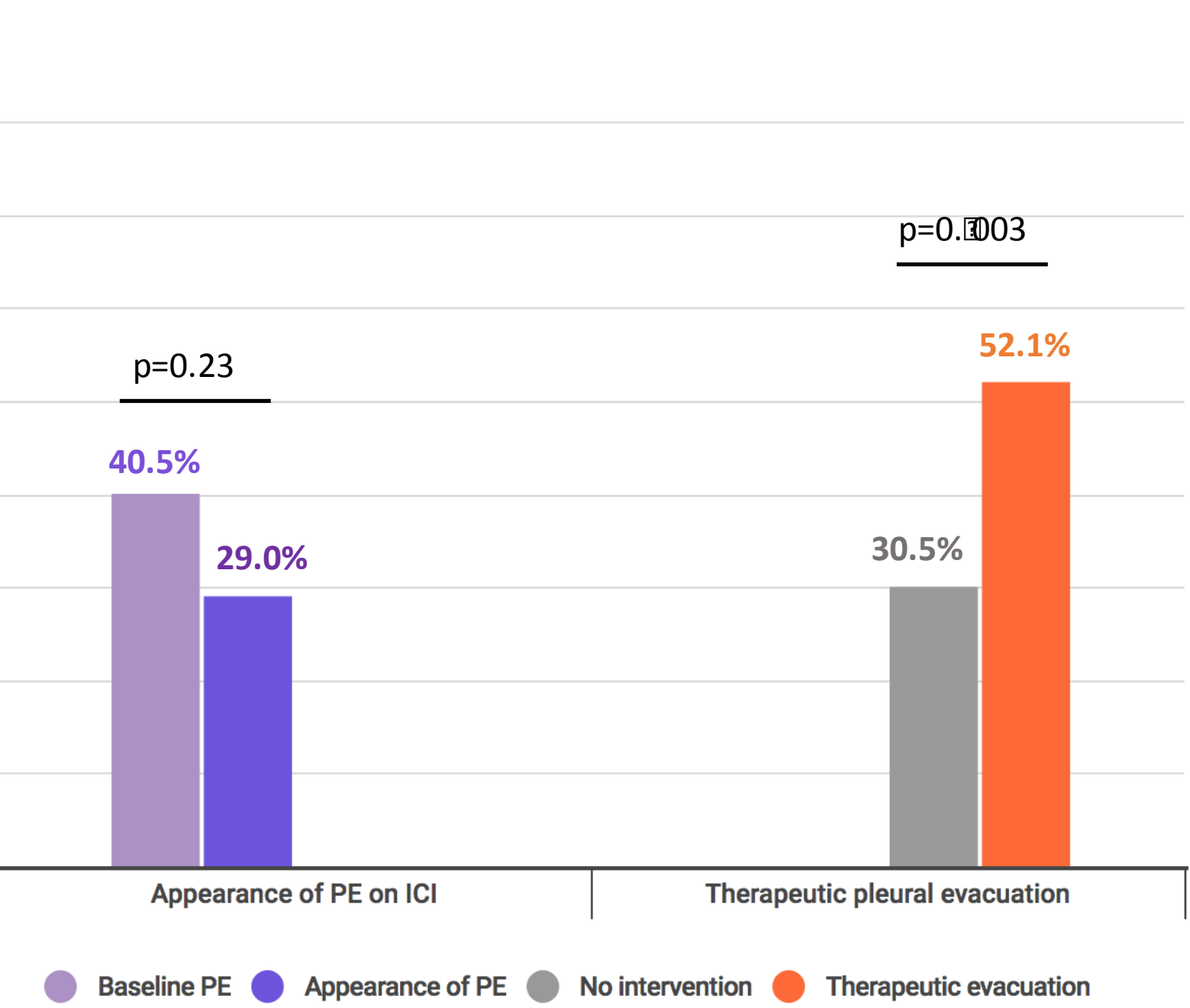

Figure 2B: Early death rate according to the appearance of PE or not and to therapeutic pleural evacuation or not

EDR was higher in the PE group (38.3% vs. 27.5%, p=0.01.

There was a trend to lower EDR in the group appearance of PE (29.0% vs 40.5%, p=0.23).

Therapeutic pleural evacuation was also correlated with more early death (52.1% vs 30.5% p=0.003)

Survival

Overall survival
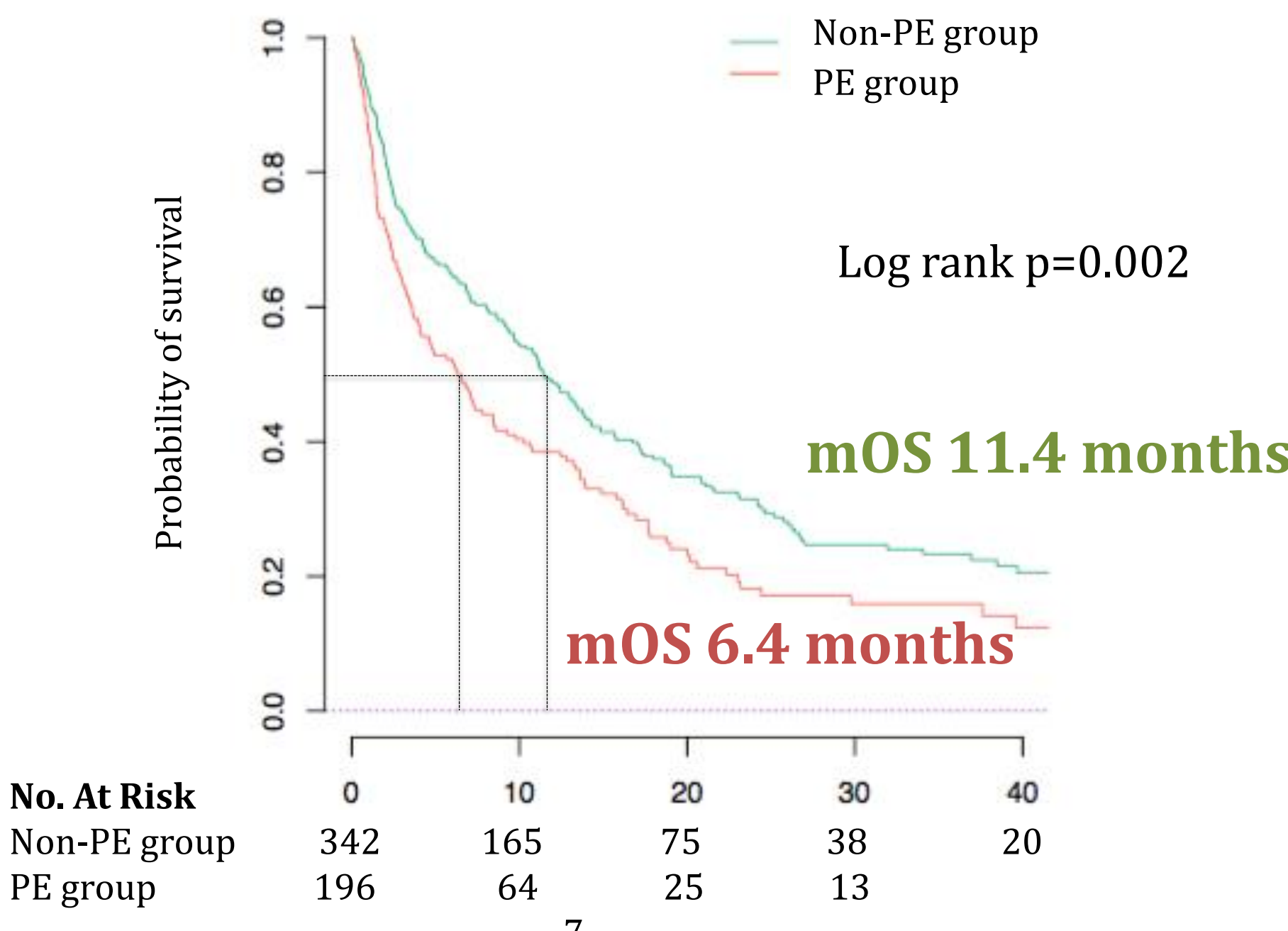
Overall, median OS was 9.7 months (95%CI, 22.1 to 31)

Log rank p=0.002

mOS 11.4 months

mOS 6.4 months

No. At Risk					
Non-PE group	342	165	75	38	20
PE group	196	64	25	13	
		7			

Figure 3: Overall survival

Progression free survival

Overall, median PFS was 2.1 months (95%CI, 1.8 to 2.7)

Log rank p=0.04

mPFS 2.3 months

mPFS 1.8 months

No. At Risk					
Non-PE group	340	78	34	19	
PE group	193	32	12	7	
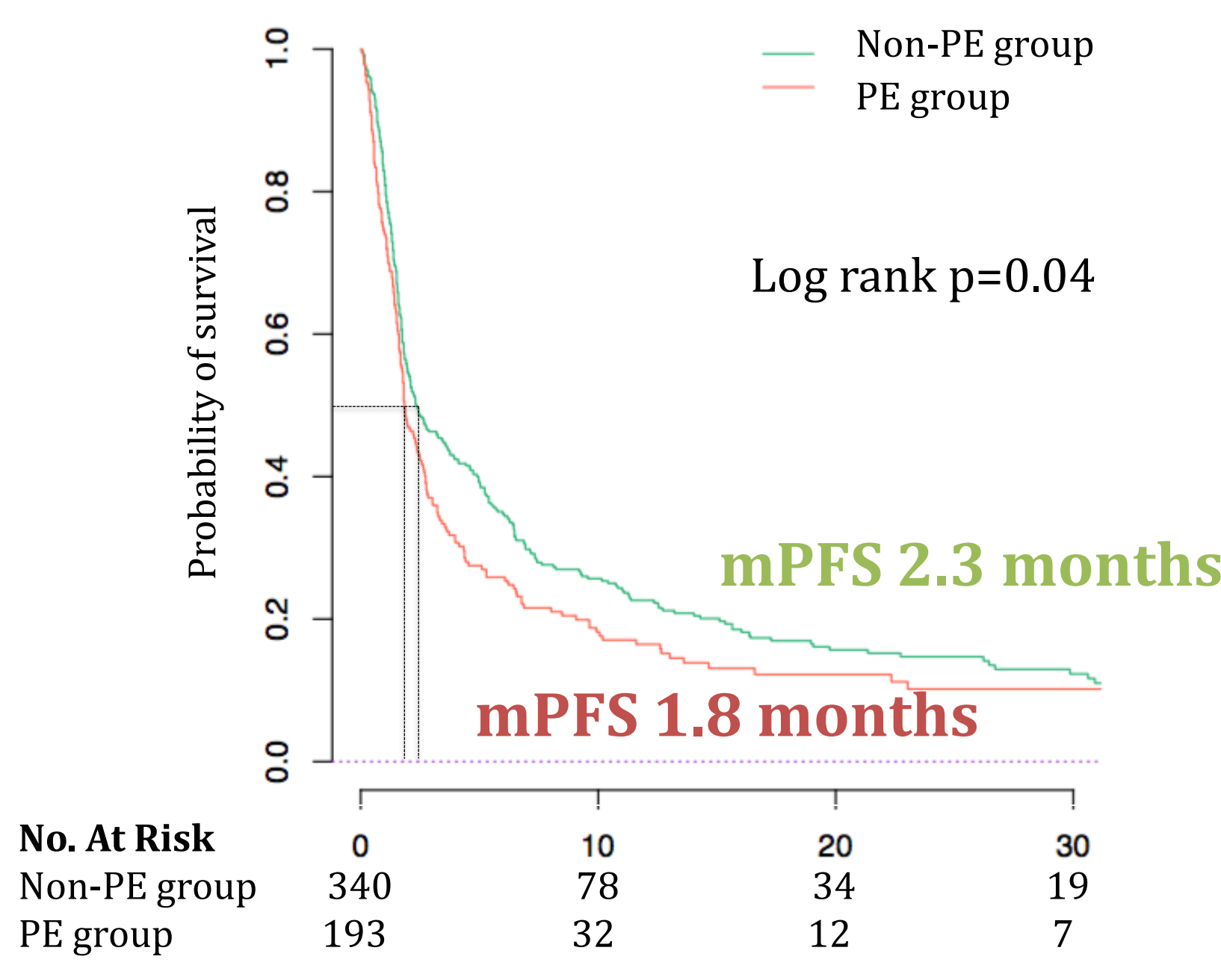
Figure 4: Progression free survival

Multivariate Cox model

	Overall survival		Progression free survival	
	HR (95%CI)	p	HR (95%CI)	p
Age >65 years	1.2 (1.0-1.6)	0.07	1.0 (0.8-1.2)	0.6
ICI line ≥2	1.1 (0.9-1.4)	0.5	1.3 (1.0-1.6)	0.02
Pleural M. before ICI	**1.4 (1.1-1.7)**	**0.007**	**1.6 (1.1-1.7)**	**0.006**
Bone M. before ICI	1.5 (1.2-1.9)	0.001	1.6 (1.3-2.0)	0
Liver M. before ICI	1.5 (1.2-2.0)	0.001	1.2 (1.0-1.5)	0.1
PS ≥2	1.7 (1.2-2.4)	0.003	1.1 (0.8-1.5)	0.4
dNLR ≥ 3	1.9 (1.5-2.3)	0	1.6 (1.3-1.9)	0

Table 2: Multivariate Cox model analysis for overall and progression free survivals

Pleural metastasis was an independent prognostic factor for poorer OS and PFS.

A sensitivity analysis with multiple imputation of PDL1 status data found that PE was still an independent prognostic factor for both OS and PFS.

CONCLUSION

- Pleural effusion confers worse prognosis and lower responses in NSCLC treated with ICI :
  - Median Overall Survival was higher in the PE group than in the non PE group : 11.4 vs. 6.4 months (p=0.002),
  - EDR was higher in the PE group than in the non PEgroup (38.3% vs. 27.5%, p=0.01).
- Appearance of PE was associated with more early death (29.0% vs 40.5%, p=0.23) such as therapeutic pleural evacuation (52.1% vs 30.5% p=0.003).
- Thus, a combination chemotherapy-ICI appears to be indicated in this population in which predictive markers of ICI efficacy should be searched.