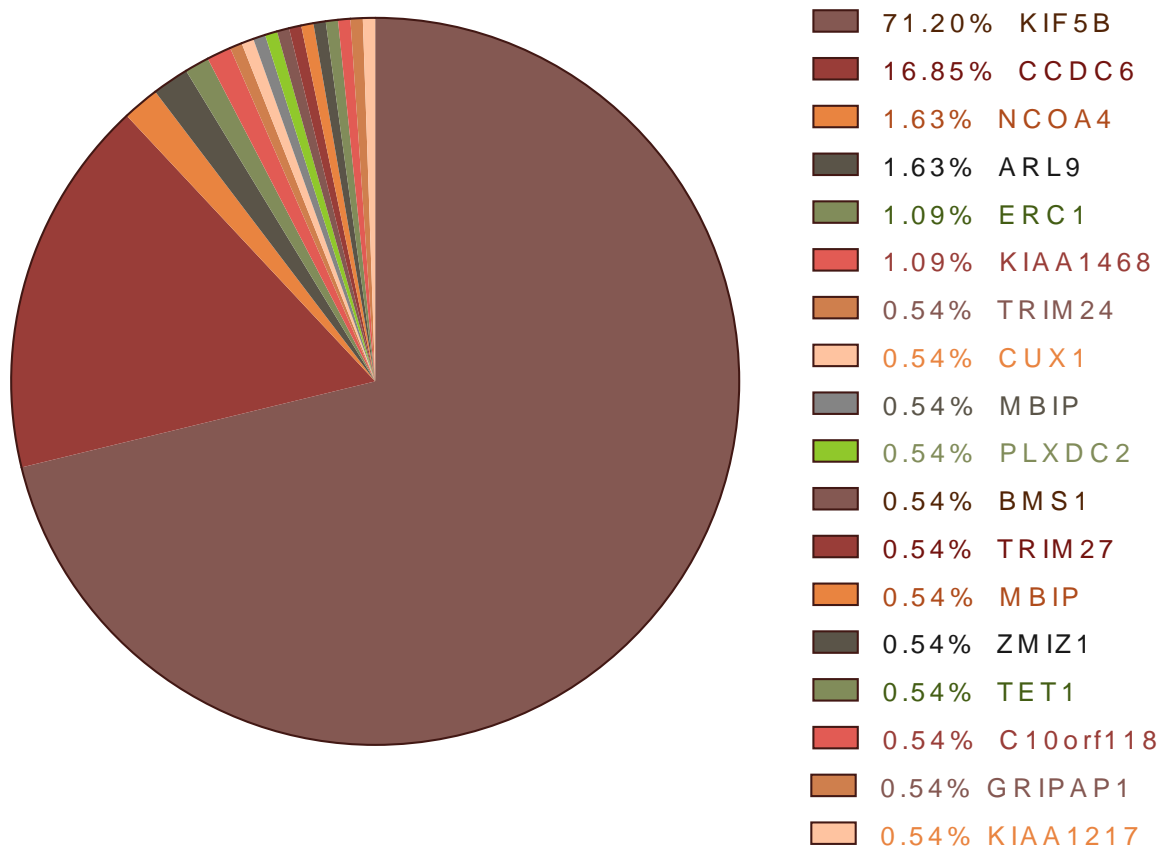
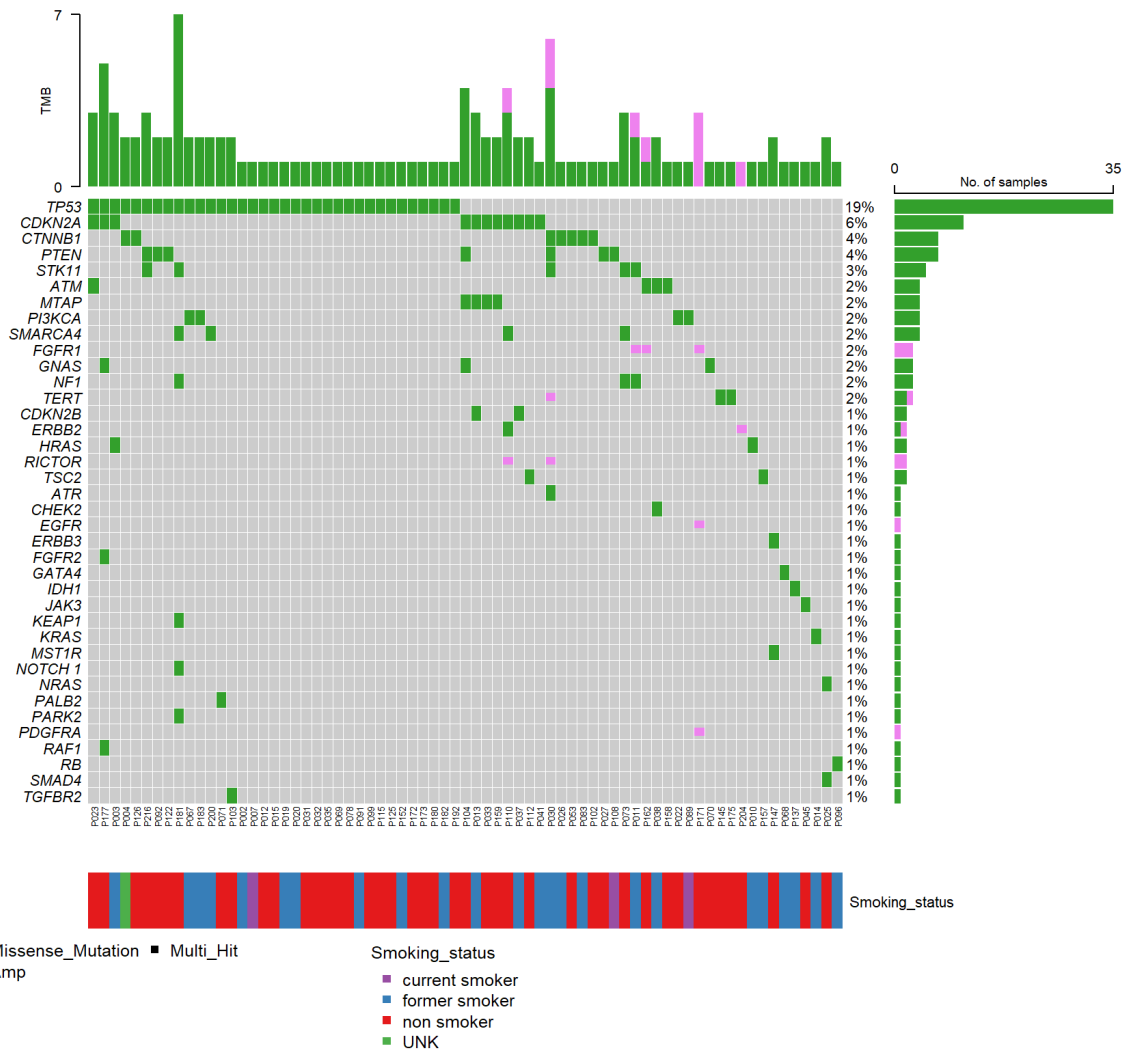


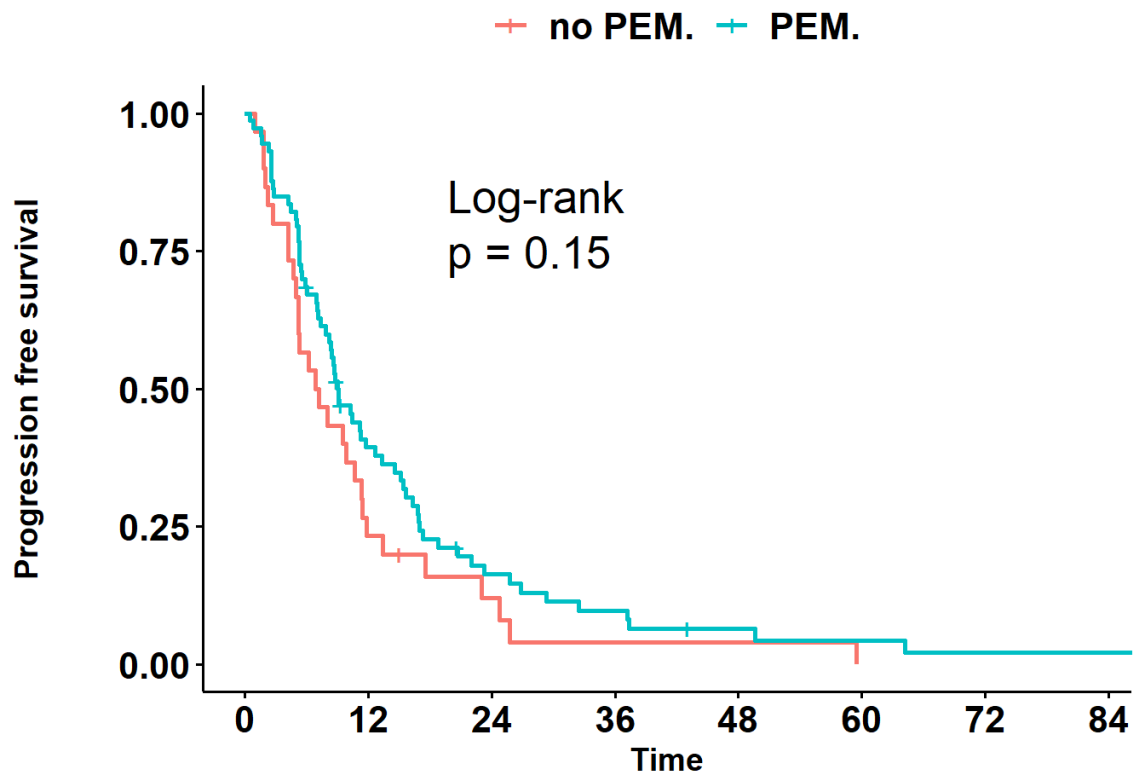
## Supplementary Figures



**Supplementary Figure 1.** Frequency of *RET* fusions according to the fusion partner.



**Supplementary Figure 2.** Genomic alterations concurrent with *RET* fusions in baseline tumor samples were identified in a total of 38% samples. Amp: amplification.



Number at risk

no PEM.	30	7	3	1	1	0	0	0
PEM.	73	26	10	6	3	2	1	1

**Supplementary Figure 3.** Progression-free survival (PFS) in patients treated with platinum-pemetrexed treatment versus other platinum-based doublets. PEM: pemetrexed.



**Supplementary Table 1.** Progression-free survival to various systemic treatments according to the type of the *RET* fusion partner in patients with a known *RET* fusion partner

	<b>Doublet CT (N=77)</b>	<b>Single agent CT (N=19)</b>	<b>CT-ICB (N=32)</b>	<b>ICB (N=41)</b>	<b>MTKi (N=13)</b>	<b>RETi (N=110)</b>
<b><i>KIF5B-RET</i></b>	9 [8-16.3]	3.9 [2-8.9]	7.3 [4.5-13.8]	3.1 [2-8.6]	5.3 [2.8-NR]	15 [11.1-23.2]
<b>Non-<i>KIF5B-RET</i></b>	10.7 [8.3-20.7]	8.9 [2.4-NR]	10.8 [2.7-NR]	2.9 [2.4-NR]	5.4 [3.8-NR]	43.2 [11.5-NR]
<b><i>P value</i></b>	0.91	0.08	0.29	0.33	0.77	0.07

PFS expressed in months [95%CI]. NR, not reached.

**Supplementary Table 2.** Baseline characteristics at time of advanced disease in patients treated with RETi versus those without RETi

<b>Characteristics</b>	<b>RETi N=145</b>	<b>No RETi N=60</b>	<b><i>P value</i></b>
Sex, N (%) Female	85 (59%)	32 (53%)	0.5
Age at time of advanced disease , median [IQR]	63 [55-71]	62 [52-68]	0.2
ECOG performance status, N (%) PS ≤1 PS >1 Unknown	124 (87%) 19 (13%) 2	50 (86%) 8 (14%) 2	0.5
Smoking status, N (%) Former or current smoker Non-smoker Unknown	61 (43%) 82 (57%) 2	22 (37%) 37 (63%) 1	0.1
Histology, N (%) Adenocarcinoma Non-adenocarcinoma	137 (94%) 8 (6%)	53 (92%) 7 (8%)	0.1
Stage at diagnosis according AJCC 8 <sup>th</sup> edition I II III IV	6 (4.1%) 9 (6.2%) 19 (13%) 111 (77%)	2 (3.3%) 2 (3.3%) 4 (6.7%) 52 (87%)	0.4
Total N of metastatic sites 1 site ≥ 2 sites	46 (32%) 99 (68%)	24 (40%) 36 (60%)	0.6

N, number.

**Supplementary Table 3.** Adverse events leading to permanent treatment discontinuation

Adverse events	Chemotherapy- ICB N=41	ICB N=51	RETi N=145
Pneumonitis	1	1 <sup>€</sup>	2 <sup>£</sup> + 1
Acute hypertension			2
Hematologic toxicity	2 <sup>€</sup>		3
Pericardial effusion	1		
Renal failure	4		1+1 <sup>£</sup>
Colitis	1 <sup>€</sup> + 1	2 <sup>€</sup>	1 <sup>£</sup>
Increased liver enzymes		1 <sup>€</sup>	1+1 <sup>£</sup>
Increased CPK			1+1 <sup>£</sup>
Pancreatitis			1
Gastrointestinal bleeding			1
Arthritis		1 <sup>€</sup>	
Asthenia			1
Neuropathy			1
Proteinuria			1 <sup>£</sup>
Toxidermia			1 <sup>£</sup>

ICB, immune checkpoint blockade; <sup>€</sup>immune-

related; RETi, RET inhibitor

<sup>€</sup>immune-related; <sup>£</sup> prior ICB anytime before RETi.