

Search for Biomarkers to Personalize Treatment with Streptozotocin plus 5-Fluorouracil or Everolimus in Patients with Advanced Pancreatic Neuroendocrine Tumors: The Randomized Phase III SEQTOR Trial (GETNE-1206)

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INTRODUCTION

Streptozotocin (STZ) plus 5-Fluorouracil (5-FU) and everolimus are standard treatment options for pancreatic neuroendocrine tumors (panNET).^{1,2}

The SEQTOR trial is the first prospective, randomized phase III study that aimed to determine the optimal sequence for these treatments in patients with advanced panNET (Fig.1).

Genes involved in transcription and chromatin remodeling (i.e. *DAXX* and *ATRX*), and tumor suppression (i.e. *MEN1* and *PTEN*) are commonly mutated in patients with pancreatic neuroendocrine tumors (panNETs).^{3,4} Here we report the translational results from the SEQTOR trial that evaluated treatment sequence in panNETs.

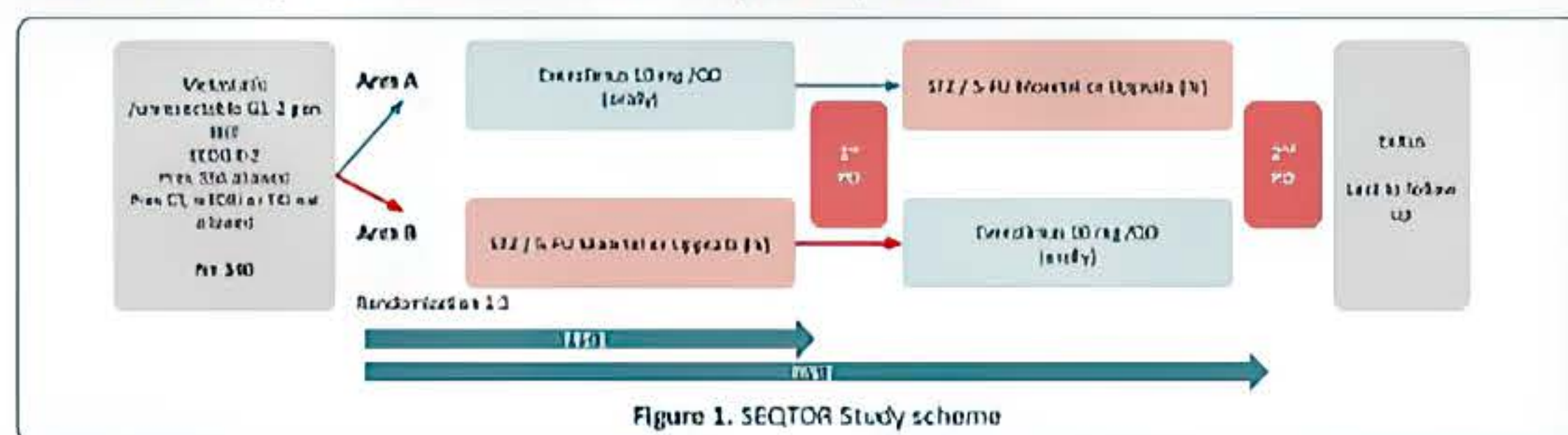


Figure 1. SEQTOR Study scheme

METHODS

Patients with grade 1/2 advanced panNETs, were randomized to receive everolimus (10 mg per day) at first line, followed by STZ/5-FU at second line (Arm A) or the reverse sequence (Arm B).

Paraffin embedded tumor tissue underwent DNA sequencing, using NanoString digital hybridization-detection system. TempOSeq multiomic profile including more than 22,533 genes was performed for 27 patients to classify patients in gene expression subtypes. Primary endpoint, 12-months progression-free survival (PFS) rate, and secondary endpoints, objective response rate (ORR) and overall survival (OS), were correlated with biomarkers

Table 1. Baseline characteristics

		Arm A N = 72	Arm B N = 69	p-value
Sex, n (%)	Male	41 (56.9)	44 (63.8)	0.403
	Female	31 (43.1)	25 (36.2)	
ECOG, n (%)	1	20 (27.8)	22 (31.9)	0.557
	2	2 (2.8)	0 (0)	
Tumor grade, WHO, n (%)	G1	12 (16.7)	8 (11.6)	0.609
	G2	56 (77.8)	57 (82.6)	
	UK	4 (5.6)	4 (5.8)	
CI 67, n (%)	≤ 2	10 (13.9)	19 (27.5)	0.045
	3-70	62 (86.1)	50 (72.5)	
Tumor burden, n (%)	≤ 99.5 mm	36 (50.0)	30 (43.5)	0.485
	> 99.5 mm	32 (44.4)	34 (49.3)	
	UK	4 (5.6)	5 (7.2)	
Previous treatments, n (%)	0	36 (50.0)	43 (62.3)	0.301
	1	32 (44.4)	22 (31.9)	
	≥ 2	4 (5.6)	4 (5.8)	

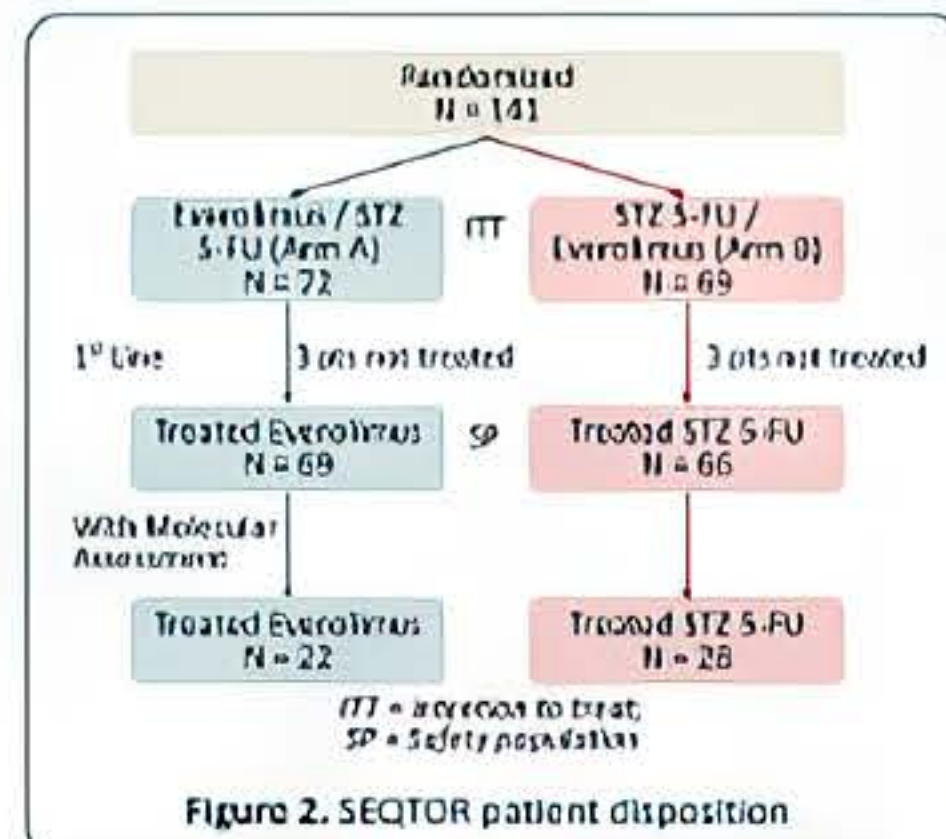


Figure 2. SEQTOR patient disposition

From June 2014 to July 2021, 141 patients were randomized to receive everolimus followed by STZ/5-FU (Arm A; n=72) or the reverse sequence (Arm B; n=69) (Fig.2). Patient characteristics in overall population are depicted in Table 1.

Mutational analysis was performed in 50 out of 141 patients (Fig.2). *MEN1* was mutated in 13 (59.1%) and 12 (42.9%) in arms A / B, respectively, *ATRX* in 5 (22.7%) and 6 (21.4%), *DAXX* in 5 (22.7%) and 6 (21.4%), and *PTEN* in 3 (13.6%) and 3 (10.7%) (Fig.3)

Four panNETs gene expression subtypes were obtained from TempOSeq profiling: Insulinoma-like (19%), metastases-like primary (MLP-1; 15%), MLP-2 (33%) and intermediate (33%) (Fig 3). Insulinoma subtype had lower risk of PD than other genetic subtypes (Fig.4). *DAXX* was associated with the risk of PD in Arm B (Fig.5). OS was not influenced by tumor genetic alterations (Fig.5 & 6).

RESULTS

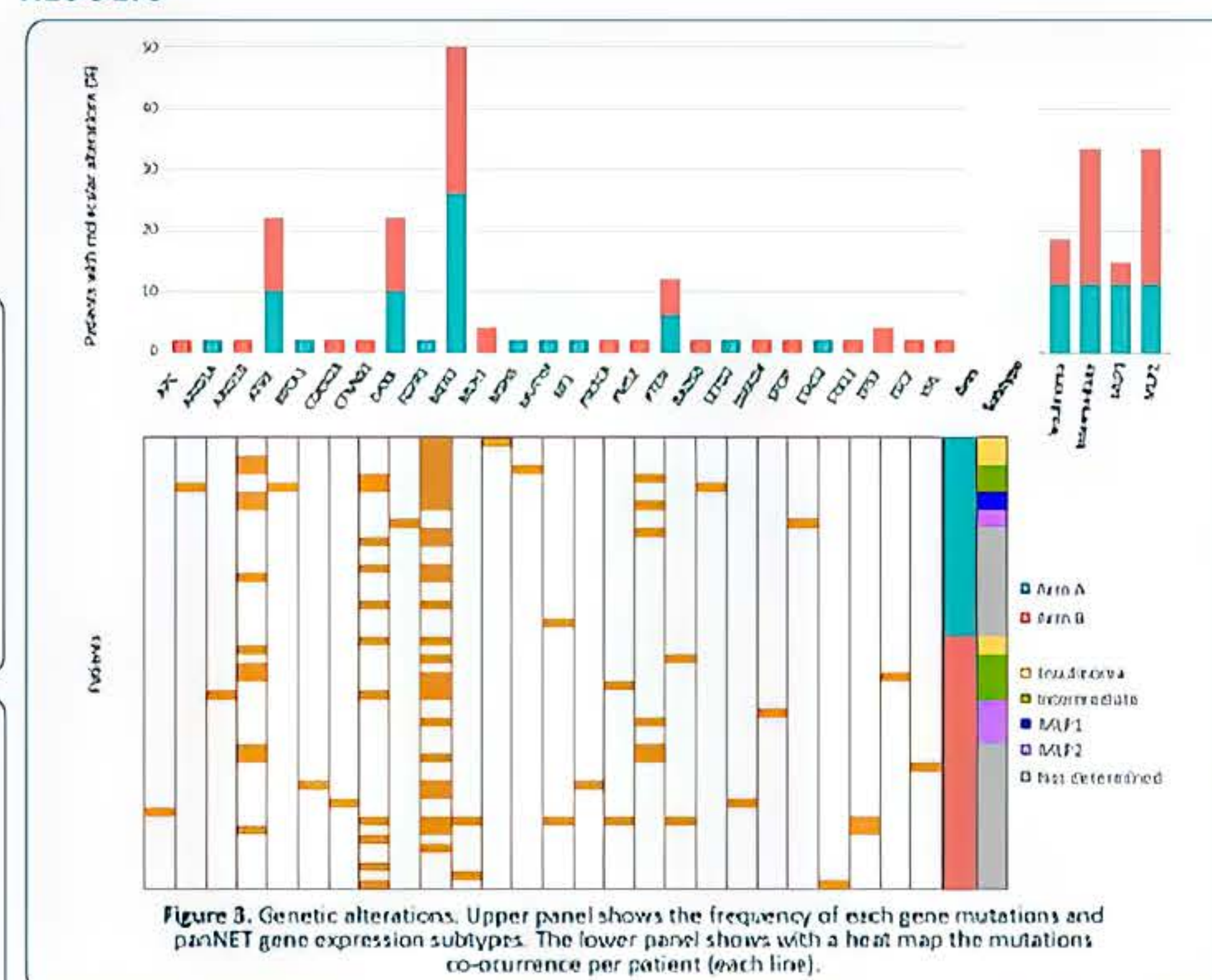


Figure 3. Genetic alterations. Upper panel shows the frequency of each gene mutations and panNET gene expression subtypes. The lower panel shows with a heat map the mutations co-occurrence per patient (each line).

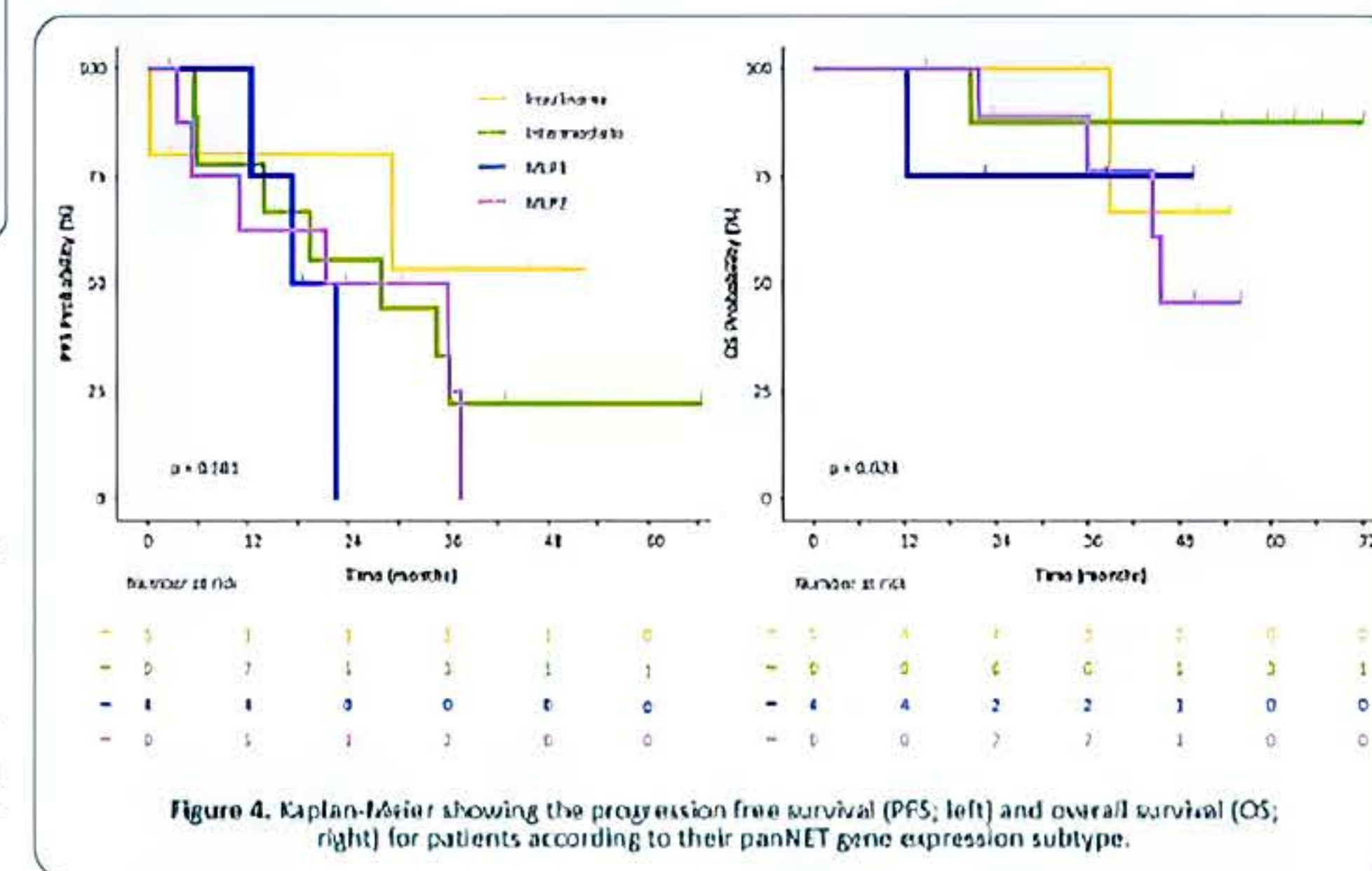


Figure 4. Kaplan-Meier showing the progression free survival (PFS; left) and overall survival (OS; right) for patients according to their panNET gene expression subtype.

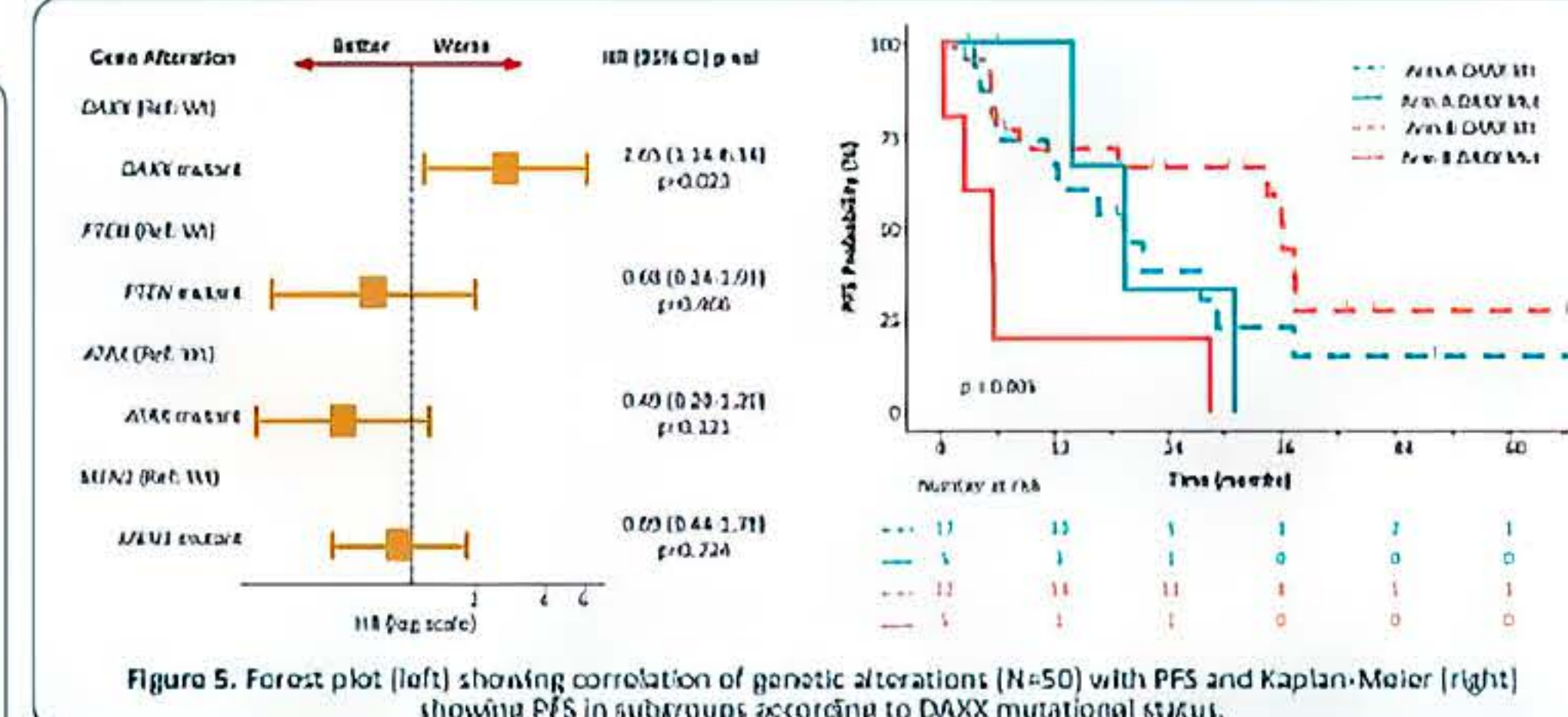


Figure 5. Forest plot (left) showing correlation of genetic alterations (N=50) with PFS and Kaplan-Meier (right) showing PFS in subgroups according to *DAXX* mutational status.

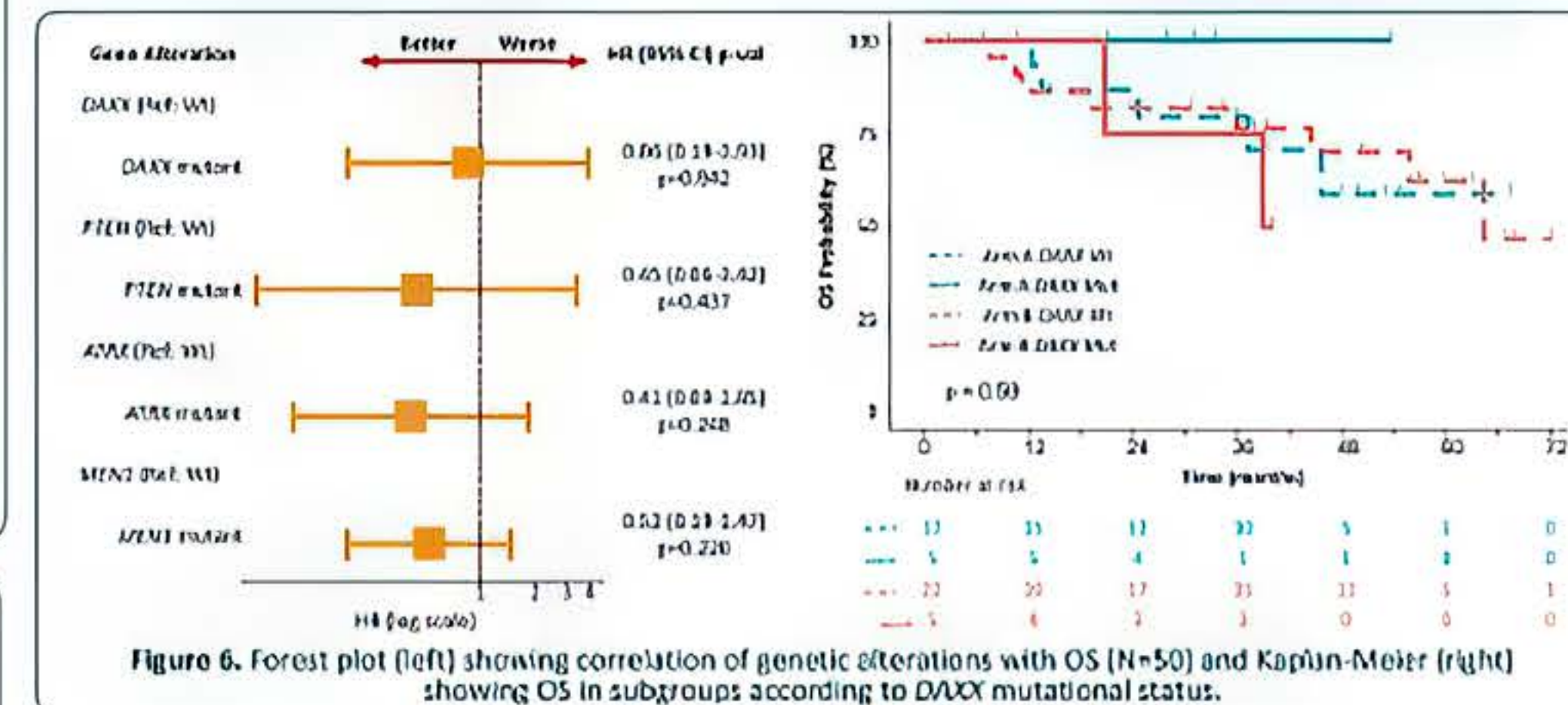


Figure 6. Forest plot (left) showing correlation of genetic alterations with OS (N=50) and Kaplan-Meier (right) showing OS in subgroups according to *DAXX* mutational status.

CONCLUSIONS

- Genetic alterations in the SEQTOR study had similar prevalence than previous reports in patients with panNETs, the most frequent ones being *MEN1*, *DAXX*, *ATRX* and *PTEN*.
- DAXX* mutation was associated with worse PFS₁₂ of STZ / 5-FU. No other treatment interactions have been observed probably due to limited sample size and tissue availability.
- Patients with Insulinoma-like gene expression subtype seem to have lower risk of PD in line with previous observations of good prognosis in this patient subgroup and a watch and wait strategy or less aggressive strategies could be considered for them. No treatment interactions were observed in this limited analysis.

EudraCT: 2013-000726-66 | Clinicaltrials.gov: NCT02246127

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