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Molecular profiling and target actionability for precision medicine in neuroendocrine neoplasms: real-world data

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Key word : Neuroendocrine tumours; Neuroendocrine carcinomas; Molecular profile; Molecularly matched treatment; Precision medicine

Abstract Background: Key molecular alterations (MA) of neuroendocrine neoplasm (NEN) of various grade/primaries have been described but the applicability of molecular profiling (MP) for precision medicine in NEN remains to be demonstrated.

Methods: We conducted a retrospective study of all patients with metastatic NEN who had MP on tumour tissue at Gustave Roussy. The primary objective was to assess the clinical applicability of MP by evaluating the growth modulator index (GMI) as the primary end-point.

Results: MPs were obtained in 114 out of 156 eligible patients, including 12% NET-G1, 42% NET-G2, 13% NET-G3 and 35% neuroendocrine carcinoma (NEC). Primary sites were lung/ thymus (40%), pancreas (19%), gastrointestinal (16%), head&neck (10%), unknown (10%) and others (10%) with synchronous metastases in 61% of the patients. Most frequent MA were: *MEN1* (25%), *PTEN* (13%), *TP53* (11%) and *TSC2* (9%), in neuroendocrine tumour (NET), and *TP53* (50%) and *RBI* (18%) in NEC. ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) classification of these MA were: I(5%), III(20%), IV(23%), X (27%); a putative actionable MA was identified in 48% patients. Median TMB was 5.7 Mut/ Mb, with 3 TMB > 10 and 1 MSI NET. No MA was found in 26% patients. Molecularly matched treatment was administered to 19 patients (4 NEC, 15 NET): immunotherapy (n = 3), tipifarnib (n = 1), NOTCHi (n = 1), EGFRi (n = 2), HER2i (n = 1) and everolimus (n = 11). Overall, 67% of patients had a clinical benefit defined as a GMI over 1.3 with a 78% disease control rate.

Conclusion: We report 48% of NEN with a putative actionable MA of which 35% received molecularly matched treatment, with a clinical benefit in 67% of the cases.

Introduction

Neuroendocrine neoplasms (NEN) include a heterogeneous group of tumours [1], characterised by various prognosis, from indolent to very aggressive, with diverse treatment responses. The initial pathological diagnosis of NEN relies on the distinction between well-differentiated neuroendocrine tumour (NET) and poorly differentiated neuroendocrine carcinoma (NEC) and on grade according to the ki67 index [1]. Molecular profiles of these neoplasms are very diverse and reflect this heterogeneity, especially according to grading and primary location [2–9].

The recent years have shown the development of new treatments, with multi-kinase inhibitors, mTOR inhibitors and Peptide Receptor Radionuclide Therapy (PRRT) [10,11]. In most of the cases, treatment decisions are largely based on the primary, tumour stage, grading [10,11], tumour volume and slope and Somatostatin receptor (SSTR) expression. Biology-informed treatments in NEN remain at the margin and the use of approved targeted therapies such as everolimus or sunitinib is not based on molecular alterations. Whether molecular profiling (MP) could improve treatment decision-making is still to be demonstrated for NEN patients.

Several prospective studies tried to evaluate the feasibility and clinical benefit derived from MP by next-generation sequencing (NGS) in patients with a various range of advanced solid tumours [12–15]. A large range of actionable MA per patient was described, ranging from 40% to more than 90%. Nevertheless, only 10–25% of patients in these studies received a molecularly matched (MMT) treatment informed by MP [12–17]. Moreover, two randomised clinical trials designed to evaluate the precision-medicine strategy found no improvement in progression-free survival (PFS) for patients receiving MMT [12,13]. Recently, a prospective randomised precision medicine trial reported that clinically targeted therapies matched to genomics improved PFS only when MA were classified as level I/II according to the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) (HR 0.41, $P < 0.001$) [15].

This was confirmed in data from the precision medicine programme at Gustave Roussy [18]. Altogether, these results confirm the need to get more data on the clinical benefit of MMT, especially in rare cancers.

In this study, we aimed to report the clinical applicability of precision medicine in NEN. We analysed the MPs obtained in our patients through our institutional precision medicine programmes along with their clinical outcomes under MMT by using the GMI as a primary end-point.

1. Patients and methods

Patients with NEN were identified from 2010 to 2021. Inclusion criteria were: metastatic NEN followed in our centre, with a MP report from an NGS analysis of a tumoural tissue available. Exclusion criteria were: non-contributive MP, MP obtained by liquid biopsy only.

Clinical characteristics and treatment-related outcomes were retrospectively collected by hospital chart review. Pathological samples were reviewed by our expert pathologist (JYS) and tumour grading was performed for all patients according to the common classification framework [1].

This retrospective study complies with the French MR004 methodology regarding general data protection regulation for non-interventional retrospective health research (Délibération n° 2018–155 du 3 mai 2018) and was approved by our institutional review board (CSET N° 2022–121), in compliance with Helsinki declaration. All patients gave signed informed consent for NGS analyses.

1.1. Clinical sequencing

Unselected NEN patients were offered MP as part of their routine clinical management through inclusion into two institutional personalised medicine programmes at Gustave Roussy: MOSCATO (NCT01566019)

and STING (NCT04932525) in an attempt to identify actionable MA. Inclusion criteria for these programmes were neither restricted to specific patient population nor to specific lines of treatment. Therefore, patients were included in various stages of their clinical management.

The different molecular panels included:

- in-house panel of 75 oncogenes and tumour suppressor genes (Supplementary 1, [12])
- Foundation Medicine ® panel including 324 oncogenes, tumour suppressor genes or gene rearrangement (Supplementary 1) as well as microsatellite stability status and tumour mutational burden.

1.2. End-points and evaluation

For all patients, a weekly multidisciplinary precision medicine tumour board reviewed, interpreted, and discussed MP. Classification of actionability of MA was performed based on ESCAT classification [19]. Considerations for MMT were based on variant annotation databases such as OncoKB, CIViC, My Cancer Genome, and literature as well as EMA approval, ClinicalTrials.gov and clinical trials available in our institution. The retrospective review of each case identified the NEN patients with MA and who received an MMT at any time during their disease time course.

Primary objective was to assess the clinical applicability of NEN MP in clinical practice, and primary end-point was the proportion of patients who derived a clinical benefit from this precision medicine approach, defined as the proportion of patient with growth modulator index (GMI) ≥ 1.3 . GMI is defined as the ratio of time to progression (TTP) under the MMT (TTP_N, e.g. oriented treatment line) to TTP under the treatment received prior to MMT (TTP_{N-1}). A GMI ≥ 1.3 is considered as relevant clinical benefit, meaning TTP_N is at least superior by 30% as compared to TTP_{N-1} [20].

Secondary end-points included the disease control rate (DCR, addition of patients with stable disease (SD), partial response (PR) or complete response (CR) under MMT), PFS and overall survival (OS). Disease progression was defined using RECIST1.1 criteria.

1.3. Statistics

All variables were summarised as median [Interquartile range (IQR)] or number and percentages. Quantitative variables were compared using a Student t-test or Wilcoxon test. Qualitative variables were compared using a Fisher exact test or Chi² test depending on applicability conditions. Kaplan-Meier method was used for survival analyses with log-rank test for comparisons. A *p*-value < 0.05 was considered statistically significant and all the tests were bilateral. All statistical analyses were done using the R-4.0.2 (The R-Core-Team 2020, Vienna, Austria).

2. Results

2.1. Clinical characteristics

Out of 156 identified patients with a NEN and an MP performed on tumour tissue, 114 patients with contributive samples were included in our study (Fig. 1). Seventy-six patients (67%) had a well-differentiated NET and 38 patients (33%) a poorly differentiated neuroendocrine carcinoma (NEC) (Fig. 1). NETs were classified as grade 1 (G1) (12%), grade 2 (G2) (42%) and grade 3 (G3) (13%) (Table 1). NEC were classified as small-cell NEC in 37% (five lungs) and large-cell NEC in 63% of the cases, with a mean Ki67 of 75% (range 40–100).

Primary sites were: Lung/thymus (*n* = 45, 39%), pancreas (*n* = 22, 19%), gastro-intestinal (GI) (*n* = 18, 16%), unknown primitive (UK) (*n* = 11, 10%), head & neck (*n* = 6, 5%) and others (*n* = 12, 11%, with three cervix, two bladder, two prostate, one skin and one node). Other patients' characteristics are summarised in Table 1

2.2. Molecular characteristics

MPs were performed on primary or metastatic tumoural sites (20% and 80%, respectively). MP was performed after a median of two lines of systemic treatment in patients with unresectable/metastatic disease. Twenty-three (20%) MPs were performed with in-house panel and 91 MPs (80%) with Foundation medicine® panel. MA were found in 74% of patients. Most frequent MA were: *MEN1* (25%), *PTEN* (13%), *TP53* (11%) and *TSC2* (9%), in NET, and *TP53* (50%) and *RBI* (18%) in NEC (Supplementary Table 3, Fig. 2A). Of the 26% with no identified MA despite contributive analyses, there were ten NEC and 20 NET. We then classified MA considering molecular pathway altered, and found that mTOR pathway was the most frequently altered (24%), followed by MEN1 pathway (18%), cellular cycle pathway (6%), Rb pathway (9%), DAXX/ATRAX pathway (5%), RAS pathway (6%) and chromatin re-modelling pathway (7%) (Supplementary Table 3). NEC carried a higher frequency of alterations of the Rb pathway ($P = 0.015$) and NET a higher frequency of alterations of the MEN1 pathway ($P = 0.003$) (Supplementary Table 2).

According to primary, the most frequent MA in NETs were *MEN1* (45%), *TSC2* (30%) and *PTEN* (30%) for pancreatic NET, *PTEN* (18%) for GI NET and *MEN1* (33%) and *ARID1A* (7%) for lung NET (Fig. 2B). Interestingly, *HRAS* mutation was identified in four out of four (100%) Head&Neck Grade 2 NET. In NEC, the most frequent MAs were *TP53* (53%), *KRAS* (20%) and *RBI* (20%) in lung, and *TP53* (43%), *HRAS* (29%) and *RBI* (29%) in GI NEC (Fig. 2B).

Regarding actionability, these alterations were classified as ESCAT I (MSI or TMB-high tumours, $n = 6$, 5%), III (*HRAS*, *EGFR*, *ROS1*, *TSC2*, *FLT3*, *EGFR*, *PI3K*, *KRAS G12C*, *HER2*, *ATM*, $n = 23$, 20%), IV (*PTEN*, *ARID1A*, *KRAS*, *NRAS*, *CDKN2A/B*, *BRAF*, *NOTCH*, *CDK6*, *CCND1*, $n = 26$, 23%), X (27%) for the overall cohort. ESCAT (I, III, IV and X) proportions were 3%, 21%, 29%, 29% in NET and 8%, 20%, 21%, 26% in NEC. A putative actionable alteration (ESCAT I to IV) was therefore identified in 55 patients (48%) of patients. TMB was available in 58 patients and median TMB was 2.52 Mut/Mb, slightly higher in NEC than NET (3.78 versus 2.52 Mut/Mb, $P = \text{NS}$). Overall, three patients had a TMB over 10 (1 grade 1 and 1 grade 2 pancreatic NET and 1 head&neck NEC) and 1 patient had an MSI (NET) tumour.

2.3. Outcome and clinical benefit

Median overall survival from metastatic diagnosis was 152 months (95% CI: 104-NR) in NET and 21 months (95% CI: 16–38) in NEC (Fig. 4A). Out of the 55 patients with an actionable MA, an MMT was administered to 19 patients (35%) (NEC $n = 4$, NET $n = 15$): immunotherapy ($n = 3$), tipifarnib ($n = 1$), NOTCHi ($n = 1$), EGFRi ($n = 2$), HER2i ($n = 1$) and everolimus ($n = 11$) (of them 2 NET grade 3), (Supplementary Table 2)). All patients who had an MMT as first-line were treated with everolimus according to guidelines.

Clinical benefit ($\text{GMI} \geq 1.3$), was observed in 67% of those patients (Fig. 3). The median number of prior lines before MMT was two (range 0–9) with no difference in terms of clinical benefit if MMT was received after 0–1 line or > 1 line. All patients were progressive at time of MMT. RECIST 1.1 evaluation revealed 1CR, 3 PR, 12 SD and 3 PD for a DCR of 84%. Median OS of patients who received an MMT (immunotherapy, everolimus, NOTCH inhibitor, HER2 inhibitor, VEGFR or FGFR inhibitor, PI3KCA inhibitor, tipifarnib, PARP inhibitor, or EGFR inhibitor) was higher than those who did not (Fig. 4B) ($P < 0.0001$).

Regardless of MP, OS of NET patients who received everolimus tended to be higher than those who did not ($P = \text{NS}$, Fig. 4C). Median PFS under everolimus was not different between mTOR-altered patients and non-altered patients (Fig. 4D). For NET patients, we investigated the differential PFS under the most used therapeutic options (somatostatin-analogs (SSA), everolimus, sunitinib and alkylating-based chemotherapy) according to the presence or absence of alterations in the MEN1, PI3K/AKT/mTOR and DAXX/ATRAX pathways (Table 2). We found no differences in PFS suggestive of a better clinical

efficacy with one treatment or the other according to this molecular classification.

Regarding immunotherapy, one patient with a head & neck NEC (Ki-67 = 50%) in progression after platinum/etoposide, FOLFIRI and 5Fu/dacarbazine (PR, 18 cycles) exhibited a dramatic response to durvalumab, administered after identification of a high TMB (380 mutations/megabase) on a biopsy performed after dacarbazine administration. Another patient with MSI head&neck NET (Grade II, Ki-67 = 15%) received anti-PD-1 and is still in complete metabolic response, 36 months after the end of immunotherapy. The third patient received anti-PD-L1 because of a high-TMB metastatic pancreatic NET during 16 months with stable disease. Of the two other patients that experienced PR under MMT, one received everolimus (for more than 8 months) and the other tipifarnib targeting *HRAS* mutation (more than 21 months).

3. Discussion

Here we report real-world data of the clinical applicability of MP and precision medicine for the therapeutic management of NEN in routine clinical practice of an expert tertiary centre. MP with targeted NGS in NEN is feasible in a routine clinical practice setting. However, with this approach, only 35% of all patients received an MMT. For these patients, we report a clinical benefit ($GMI \geq 1.3$) in 67% of cases, mostly represented by NETs patients who received everolimus ($n = 11$). The choice of clinically meaningful standardised end-points is difficult. Von Hoff described in 1998 an approach based on an inpatient comparison of successive TTP intervals [20]. In this setting, each couple of tumour/patient is its own control. Since the successive TTPs tend to be shorter in subsequent treatment lines, it was suggested that GMI over 1.3 is a clinically meaningful threshold.

We report that the most frequent MAs were: *MEN1* (25%), *PTEN* (13%), *TP53* (11%) and *TSC2* (9%), in NET, and *TP53* (50%) and *RB1* (18%) in NEC.

Classically, in NEN, mutations in *MEN1*, *DAXX*, and *ATRX* are found more frequently in well-differentiated NETs, whereas NECs usually have *TP53* or *RB1* mutations [21]. We found less frequent MA in *TP53* and *RB1* in NEC and *DAXX*/*ATRX* in NET as compared to what is reported in the literature. Nevertheless, it is important to keep in mind that this MP were performed prospectively during the clinical management of each patient with various targeted panels and not retrospectively by whole genome or whole exome sequencing. Our in-house panel MOSCATO did not analyse *DAXX*/*ATRX* genes that are frequently mutated in NEN and our NEC cohort presented a majority of LCNEC (large cell NEC) which are known to harbour fewer *RB1* gene alterations. Interestingly, all head&neck NET patients ($n = 4$) exhibited *HRAS* mutation, that may be targetable by tipifarnib [22]. Therefore, these rare NEN should be systematically screened for MP, even if more data are needed to validate these findings. We found that the most frequent MMT was everolimus. However, everolimus is approved whatever the mutational status in GEP and lung NET [23] and, therefore, molecular profiling did not really change patients' therapeutic options when mTOR pathway alterations were found. We were not able to demonstrate a better PFS/OS when everolimus was administered in NETs patient with an mTOR pathway alteration. This was consistent with previous work from RADIANT trials [24]. The second most frequent MMT in our cohort was immunotherapy (three patients), for high-TMB or MSI tumour. To date, the results of immune checkpoint inhibitors targeting the PD-1/PD-L1 axis have been disappointing in NEN [25,26]. In our cohort, a dramatic response to anti-PDL1 therapy was observed in a patient with a head & neck NEC, administered after identification of alkylating chemotherapy-induced high-TMB. Whether dacarbazine-induced high-TMB is a suitable molecular selection mark of immunotherapy is yet to precise as conflicting data have emerged from glioblastoma and colon cancers [27,28].

Overall, we found that 48% of patients presented an actionable MA, of which 35% received MMT, with a clinical benefit in 67% of patients. However, on overall population MMT could be offered to only 19

(14%) patients in our cohort and only eight of those had mutations in pathways different from the mTOR pathway. In the NET cohort of MASTER precision medicine trial in rare cancers [29], a higher proportion (31%) of NEN patients with MP could be treated according to molecular tumour board recommendations, with 32% ORR and 71% DCR, in line with other advanced rare cancers included in the study. We observed a similar DCR of 84%.

Although only 14% of our patients received MMT, this result is similar to previous large precision medicine studies which enrolled various cancers [12,30], and therefore one could conclude that NEN have no more and no less targetable alterations than other types of tumours. Other reasons for this low clinical applicability in NEN might be proposed. First, accessibility to treatments is not easy, especially accessibility of early phase I targeted therapy trials or in case of not commercially available drugs. Second, MP is sometimes performed after several treatment lines, and the patient might exhibit a poorer general status that may prevent clinical benefit from MMT and a poorer tolerance. Third, NEN and especially NETS have a high frequency of alterations in epigenetics-involved genes which are still currently hard to properly target [8,31].

There are several limits to our study. First, this is a monocentric and retrospective study. However, we address the question of precision medicine in a real-life setting, in the largest cohort of NEN reported so far. Second, patients were heterogeneous regarding clinical characteristics, pathology, grading and primaries which reflects the very high heterogeneity of NEN and the bias of a referral centre treating all NEN whatever grading and primaries. Third, MP was performed on either primary and metastatic lesions and we may have not captured the evolution of MP through the metastatic disease course for those 20% of the patients who had MP on their primary. This reflects real-life practice where available tissues (archived tissue or specific biopsy) are chosen in the best interest and less risk for the patient. Fourth, although used in personalised medicine trials, GMI may not be a clinical-friendly end-point for assessing the clinical benefit provided by MMT in routine clinical practice as compared to disease control rate, PFS and overall response rate. Finally, we do not explore the impact of liquid biopsy which is a non-invasive effective molecular profiling tool that is rapidly developing [32]. Further exploration of the clinical utility of liquid biopsy will be needed for NEN patients.

When molecular profiling should be done in patients with NENs? Taking our results and their limitations into consideration, MP cannot guide upfront treatment in NET nor in NEC but may provide some molecular information to guide treatment after first-line treatment for NEC and second to third line for NET. Offering molecular profiling later may prevent MMT access, especially in the setting of clinical trials, due to more advanced disease and less fit patients. We also believe that MP after alkylating-based chemotherapy might help to identify chemo-induced high TMB for discussing immunotherapy. However, it is important to clearly inform the patients of the expected clinical value of MP which might be limited to no more than 14–35% of the cases. Our results shed lights on the unmet needs in NEN: better molecular screening, better basic science and better-targeted treatment will be needed in the future to achieve the goals of an effective personalised medicine in these patients.

Conclusion

Our retrospective monocentric study reports real-world data of the clinical applicability of precision medicine in NEN patients with 48% of patients presenting a putative actionable alteration, of which 35% only (14% of overall cohort) received molecularly matched treatment, with 67% clinical benefit. Molecular profiling cannot guide upfront treatment of NEN patients but may be offered after failure of standard therapies. Further studies on molecular screening, basic science and new targeted treatment will be needed to achieve the goals of an effective personalised medicine in these patients.

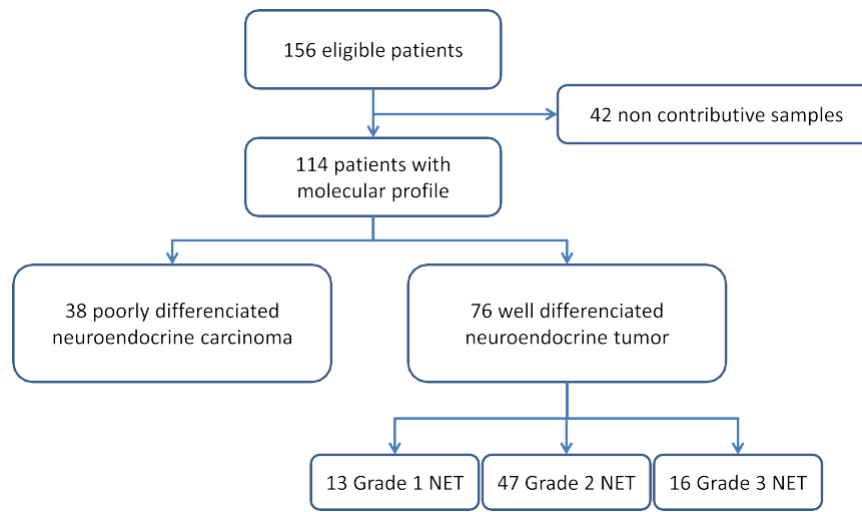


Fig. 1. Study flow chart. NET = neuroendocrine tumour.

Table 1

Patients' and tumours' characteristics (n = 114).

Variables (n,%)	All patients (n = 114) ^a		NEC (n = 38) ^a		NET (n = 76) ^a	
Age at diagnosis (years, IQR)	55	(41, 64)	56	(45, 65)	54	(41, 64)
Sex						
Female	57	50%	18	47%	39	51%
Male	57	50%	20	53%	37	49%
ECOG performance status						
0–1	96	93%	32	89%	64	96%
2–4	7	7%	4	11%	3	4%
Unknown	11		2		9	
Stage at diagnosis						
Localised	21	18%	6	16%	15	20%
Locoregional	21	18%	9	24%	12	16%
Metastatic	70	62%	23	61%	47	64%
Unknown	2		0		2	
Grade						
Grade 1	-		-		13	12%
Grade 2	-		-		47	42%
Grade 3	-		38	100%	16	21%
Primary sites						
Lung/thymus	45	39%	15	39%	30	39%
Pancreas	22	19%	2	5%	20	26%
Intestinal tract	18	16%	7	18%	11	14%
Unknown primitive	11	10%	3	9%	8	11%
Head & Neck	6	5%	2	5%	4	5%
Other	12	11%	9	24%	3	4%

Metastatic sites at metastatic diagnosis

Liver	70	61%	17	45%	53	70%
Nodes	70	61%	22	58%	48	63%
Bone	50	44%	12	32%	38	50%
Lung	29	25%	12	32%	17	22%
Brain	16	14%	11	29%	5	7%
Peritoneum	14	12%	4	11%	10	13%
Cutaneous	11	10%	3	8%	8	11%
Pleura	6	5%	2	5%	4	5%
Other	26	23%	13	34%	13	17%
Metastatic status						
Synchronous	70	61%	23	61%	47	64%
Metachronous	44	39%	15	37%	29	38%
Number of metastatic organs						
0	1	1%	0		1	1%
1	23	20%	11	29%	12	16%
2	33	29%	10	26%	12	16%
> 2	57	50%	17	45%	23	30%
Functioning syndrome at diagnosis	25	22%				
Carcinoid syndrome	14	12%				
Other	13	11%				
Prior treatments						
Surgery of primitive tumour	55	44%	5	13%	45	59%
Vectorized internal radiotherapy	16	14%	0	0%	19	25%
Somatostatin-analogs	52	46%	1	2.6%	51	67%
Chemotherapy	84	74%	36	95%	48	63%
Sunitinib	19	17%	0	0%	19	25%
Everolimus	48	42%	3	8%	45	49%
Immune checkpoint inhibitor	18	16%	9	24%	9	12%

NEC, neuroendocrine carcinoma; IQR, Interquartile range.^a n (%); Median (IQR) **P*-value < 0.05.

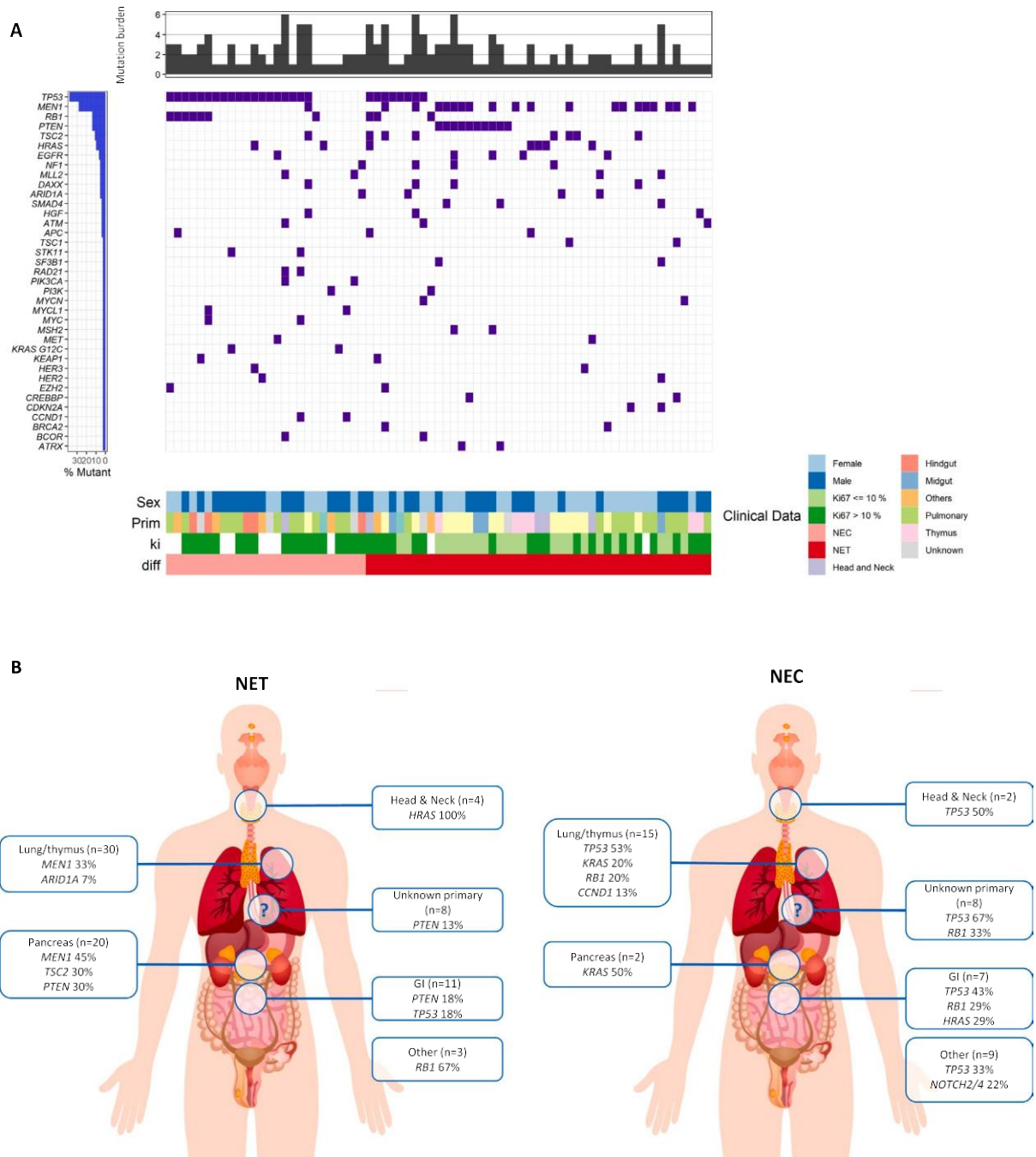


Fig. 2. Summary of molecular alterations in NEN patients. A: Oncoplot showing the top 50 most frequently altered genes (rows) among 114 NEN patients (columns). Upper panel shows the mutational burden per sample. The panel under the oncoplot area is composed of four single row heatmaps showing primary tumour site (prim), Ki67% (ki), gender (sex) and differentiation (diff). B: Main molecular alterations according to the primary and the NET/NEC classification. NEN = neuroendocrine neoplasm, NET = neuroendocrine tumour, NEC = neuroendocrine carcinoma, GI = Gastro-intestinal primary.

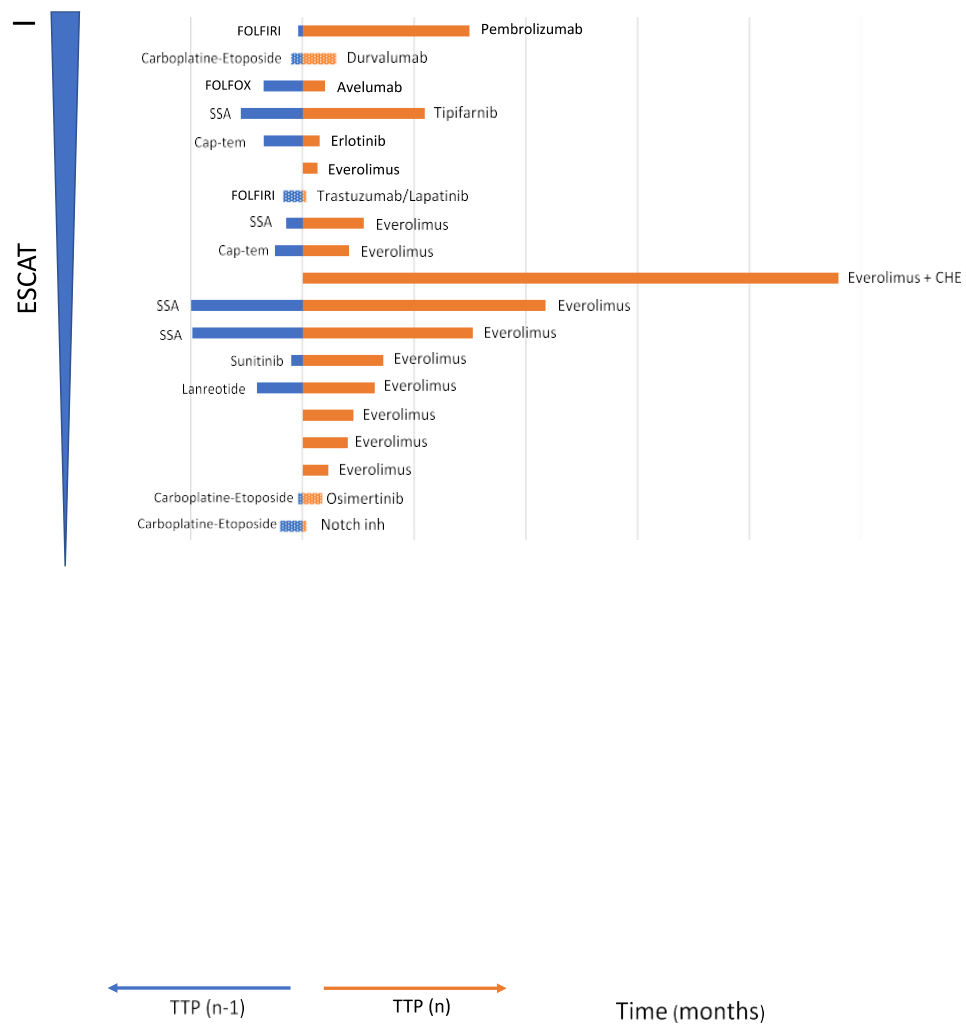


Fig. 3. Individual clinical benefit for each of the 19 patients who received a molecularly matched treatment (MMT). TTPn-1 = Time to progression under the treatment received prior to the MMT (blue bar) and TTPn = Time to progression under the MMT (orange bar). Evero = everolimus, CHE = chemoembolisation. (Hemstitch: neuroendocrine carcinoma (NEC)).

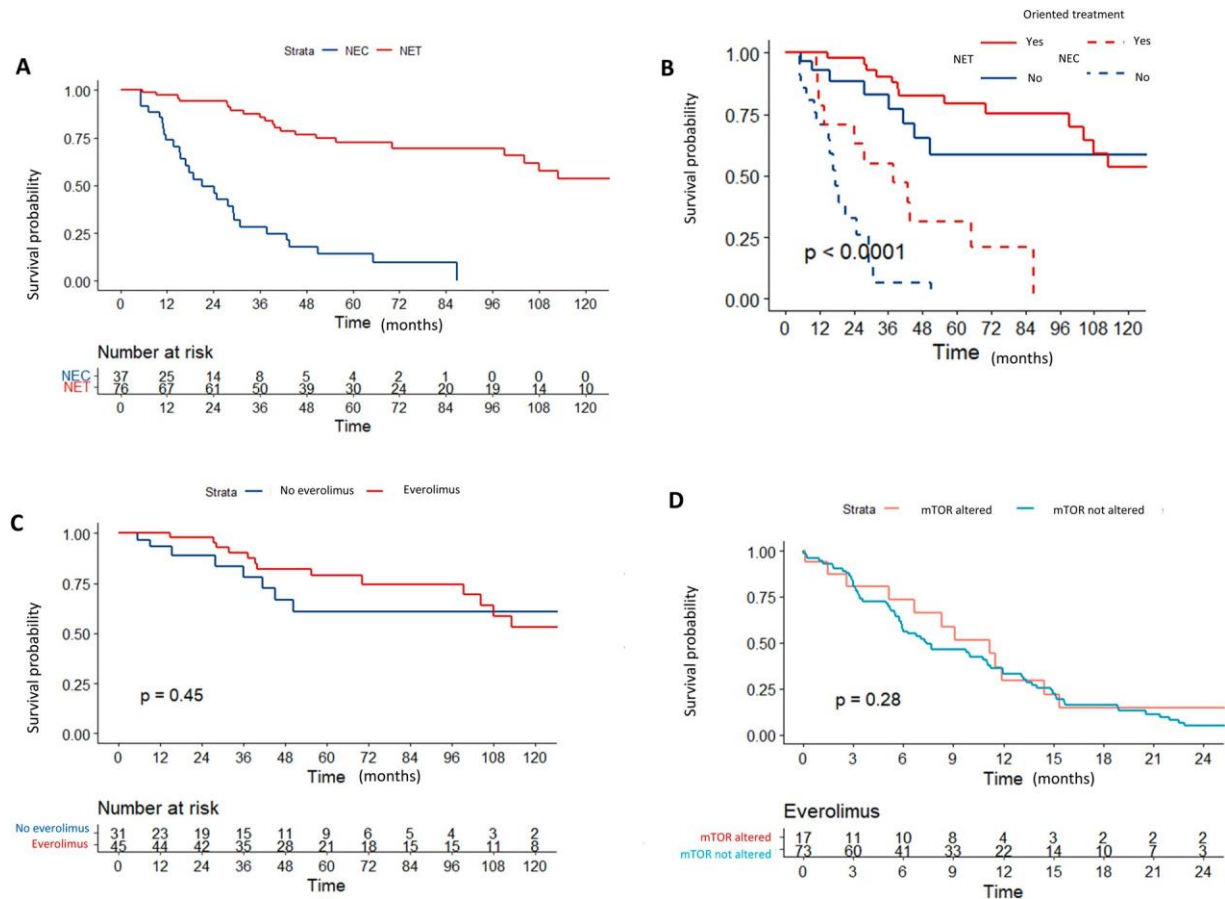


Fig. 4. Kaplan-Meier survival curves. A: Overall survival from metastatic diagnostic depending on the NET/NEC classification. B: Overall survival from metastatic diagnostic in patients who received MMT according to the NET/NEC classification. MMT = molecularly matched treatment. C: Overall survival from metastatic diagnostic in NET patients according to whether they received everolimus or not. D: Progression-free survival under everolimus depending on mTOR status in NET patients. NET = neuroendocrine tumour, NEC = neuroendocrine carcinoma.

Table 2

Median progression-free survivals of treatments depending on molecular pathway altered.

Treatments/ Molecular pathways	Everolimus (n = 90)	SSA (n = 111)	Sunitinib (n = 32)	Alkylating-based chemotherapy (n = 99)
PI3K/AKT/mTOR				
Altered	11 (6.7, 43)	20 (5.2, —)	6.5 (3.2, —)	5.0 (2.9, 23)
Non-altered	7.4 (5.9, 11)	9.5 (8.0, 13)	5.7 (3.0, 8.0)	5.0 (3.1, 7.0)
DAXX ATRX				
Altered	5.8 (2.6, —)	26 (5.2, —)	4.1 (3.2, —)	6.8 (5.4, —)
Non-altered	7.7 (6.0, 11)	9.5 (8.0, 13)	4.1 (3.2, —)	5.0 (3.1, 6.0)
MEN1				
Altered	11 (5.5, —)	4.8 (3.0, —)	4.1 (3.2, —)	5.5 (4.0, 24)
Non-altered	7.7 (5.9, 11)	10 (8.0, 13)	6.8 (3.0, 8.6)	4.8 (3.1, 6.0)

SSA: Somatostatin-analogs.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: EB received honorarium for board participation and grants from HRA. TSL: consultant:GE, Terumo, quantum surgical (none related to this paper)

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