



Precision Oncology in Rare Endocrine and Neuroendocrine Neoplasms: Experiences and Challenges of the CCCMunich^{LMU} Molecular Tumor Board

Klara Dorman^{1,2} · Christoph J. Auernhammer^{3,11} · Christine Spitzweg^{3,11} · Ralf Schmidmaier^{3,12} · Svenja Nölting^{3,14} · Matthias Kroiss^{3,12} · Martin Reincke^{3,12} · Christian Schulz^{4,11} · Martin Angele^{5,11} · Jens Werner^{5,11} · Christine Schmid-Tannwald^{6,11,12} · Josefine Rauch^{7,11} · Mathias Zacherl^{8,11} · Thomas Knösel^{2,9,11} · Jörg Kumbrink^{2,9} · Andreas Jung^{2,9} · Frederick Klauschen^{2,9} · Amanda Tufman¹³ · Danmei Zhang^{1,2} · Lena Weiss¹ · Stefan Böck^{1,2,10} · Michael von Bergwelt-Baildon^{1,2,11} · Volker Heinemann^{1,2} · C. Benedikt Westphalen^{1,2,11} · Kathrin Heinrich^{1,2,11} 

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Abstract

Background Comprehensive genomic profiling (CGP) has become more generally accessible to patients with rare cancer, but data on the results and benefits are limited.

Objective Our objective was to gain a real-world understanding of the molecular landscape and targeted treatment options in neuroendocrine tumors, neuroendocrine carcinomas, adrenocortical carcinomas, pheochromocytomas, and carcinoids.

Patients and Methods In this retrospective cohort study, we analyzed CGP results and clinical data from patients with neuroendocrine tumors, neuroendocrine carcinomas, adrenocortical carcinomas, pheochromocytomas, and carcinoids who were discussed in the CCCMunich^{LMU} Molecular Tumor Board (MTB) between May 2017 and April 2023.

Results In total, 104 patients with endocrine and neuroendocrine neoplasms were discussed in the MTB. CGP was technically successful in 99 patients. The most commonly mutated genes were *TP53* (29.3%), *RBI* (11.1%), and *KRAS* (10.1%). The highest overall prevalence of pathogenic alterations was detected in neuroendocrine carcinomas (76.9%) and carcinoids (83.3%), and the lowest prevalence of pathogenic alterations was seen in adrenocortical carcinoma (37.5%). Of the 99 patients with successful CGP, 35 received a treatment recommendation from the MTB based on the CGP results. Of these, ten patients ultimately received the recommended treatment. Of the ten treated patients, four experienced a longer progression-free survival under the targeted treatment than under their previous treatment.

Conclusions One-third of patients with rare endocrine and neuroendocrine neoplasms who underwent CGP had a druggable alteration and received a treatment recommendation from the MTB. However, only 28.6% of these patients were treated accordingly. Our experience highlights the unmet medical need for targeted treatment options in patients with rare cancers.

1 Introduction

Neuroendocrine neoplasms (NENs) are a rare and heterogeneous subset of tumors that originate from cells with a neuroendocrine phenotype and can occur at many different anatomical sites [1]. The International Agency for Research on Cancer and World Health Organization expert consensus proposal recommends a uniform classification for NENs. Depending on their differentiation, NENs can be divided

into neuroendocrine tumors (NETs, well-differentiated) and neuroendocrine carcinomas (NECs, poorly differentiated). Furthermore, NETs should be graded as low grade, intermediate grade, and high grade (G1, G2, and G3, respectively), depending on mitotic count, ki67, and presence of necrosis, whereas NECs are always high grade [2]. Pheochromocytomas are another subgroup of NETs that originate in the adrenal medulla and can produce catecholamines [3]. The most frequent anatomical site for NENs is the digestive system, followed by the lung [4]. Along with the profound heterogeneity of NENs, oncogenic molecular drivers and epigenetic profiles also vary greatly [5, 6].

Extended author information available on the last page of the article

Key Points

The spectrum of molecular alterations in rare endocrine and neuroendocrine malignancies is broad. The most common pathogenic alterations found in our cohort of patients with neuroendocrine tumors, neuroendocrine carcinomas, adrenocortical carcinomas, pheochromocytomas, and carcinoids were *TP53* (29%), *RBI* (11%), and *KRAS* (10%) mutations.

The most frequent treatment recommendation by the Molecular Tumor Board was immune checkpoint inhibition. Although 35 of 99 patients received a molecularly informed treatment recommendation from the Molecular Tumor Board, only one-third of these received the recommended targeted treatment, resulting in a survival benefit in four of ten of these patients.

Therapeutic options of chemotherapy and immunotherapy in metastatic extrapulmonary NECs of gastroenteropancreatic and other rare primary tumor locations are limited [4, 7, 8]. In contrast, treatment of gastroenteropancreatic NETs encompasses somatostatin analogs, peptide receptor radionuclide therapy, chemotherapy in NETs of pancreatic origin, mammalian target of rapamycin inhibitors, and tyrosine kinase inhibitors [4, 6, 9, 10]. Treatment of metastatic pheochromocytoma involves chemotherapy, radionuclide therapies, and tyrosine kinase inhibitors [11]. Treatment strategies for lung typical and atypical carcinoids are similar to those for NETs but with specific guideline recommendations [12].

Although some of these approaches are targeted therapies, the treatment decisions are usually not based on the molecular pathology of the tumors, but rather the anatomical site, grading, growth dynamics, and somatostatin receptor status assessed by imaging of the NEN, as well as the patient's comorbidities and preferences [6].

In some tumor entities, such as cholangiocarcinoma and lung adenocarcinoma, comprehensive genomic profiling (CGP) is routinely recommended to detect targetable alterations [13, 14]. Although CGP is not routinely recommended in NENs, European Society of Medical Oncology (ESMO) recommendations include determining the tumor mutational burden (TMB) in well-to-moderately differentiated NETs [13].

To gain a better understanding of the molecular profiles, therapeutic options, and potential differences within

the heterogeneous group of NENs, we collected real-world data from our Molecular Tumor Board (MTB) from 2017 to 2023. Although adrenocortical carcinoma (ACC) is a rare endocrine neoplasm and treatment also differs [15, 16], we included this entity in our analysis because of the high therapeutic need and rarity. We report the retrospective analysis of CGP results and medical charts of 104 patients with rare endocrine tumors and NETs, including NET, NEC, pheochromocytoma, carcinoids, and ACC. Hereafter, we collectively refer to these tumor entities as NENs to improve readability.

2 Material and Methods

2.1 Molecular Tumor Board

The University Hospital Munich's interdisciplinary MTB consists of clinicians, pathologists, tumor geneticists, and experts for precision oncology and takes place weekly. It is a platform to discuss patients' CGP results and targeted treatment options [17]. Treatment recommendations are based on CGP results, the clinical situation and medical history of the patient, and literature research. After the interdisciplinary discussion, recommended treatments include approved targeted therapies, available clinical trials, and off-label treatments. Recommendations are annotated with the evidence level according to the ESMO Scale for Clinical Actionability of molecular Targets and the National Center for Tumor Diseases. The treating physician then discusses the results of the MTB, and the decision whether to follow the recommendations is ultimately made by the physician and the patient.

2.2 Patient Population

In this retrospective cohort study, patients with NET, NEC, ACC, pheochromocytoma, and carcinoids who were discussed in the University Hospital Munich's MTB between May 29, 2017, and April 3, 2023, were included in the analysis (Fig. 1). During this period, 2587 cases of various tumor entities were discussed in the MTB. The study was approved by the local ethics committee of the Ludwig-Maximilians-University Munich (project number 21-0869). Median follow-up was 20.8 months (range 0.3–158.7). Molecular testing had been recommended beforehand, either by the entity-specific tumor board or by the coordinator of the precision oncology program, or patients already had CGP results and had been referred by external physicians for discussion.

2.3 Sequencing Assays

The various sequencing assays performed at the accredited pathology of the University Hospital Munich have been described in a previous report [17]. With the addition of broader panels and the analysis of the TMB, the number of assays for molecular testing has increased over recent years. Since December 2021, the most frequently used panel at our center has become the *TruSightOncology500* assay, covering 523 genes for assessment of DNA and RNA variants, TMB, and microsatellite instability [18]. Other sequencing assays that were used in this analysis are OncoPrint, OncoPrint Comprehensive, OncoPrint Comprehensive TMB, OncoPrint Comprehensive Assay v3, FoundationOne, Archer FUSIONPlex, and the AmpliSeq for Illumina BRCA panel. The allele frequency threshold for inclusion in the analysis was set at 5%.

2.4 Follow-Up

We retrospectively reviewed patients' medical charts, pathologist reports, and MTB statements to collect baseline characteristics, treatment outcomes, results of molecular testing, and MTB treatment recommendations. We also collected whether the recommendations were put into practice and/or which other treatments the patients received after the MTB.

2.5 Statistical Analysis

We used IBM SPSS Statistics version 29.0 and Microsoft Excel version 16.84 to perform descriptive and statistical analysis and generate graphs and tables. We calculated the survival time from the date of initial diagnosis to the date of death or last contact. We used the Kaplan–Meier method to estimate survival curves and statistically compared them

using the Log-rank test. Statistical significance was determined as p -values < 0.05 . To evaluate the clinical benefit of targeted therapies, we calculated the progression-free survival (PFS) ratio by dividing the PFS during targeted treatment by the PFS of the last prior systemic therapy [19]. We used a cut-off of > 1.3 as an indicator of clinical benefit, in accordance with previous studies [20, 21].

3 Results

3.1 Patient Characteristics

During the study period, 104 patients with NEN were discussed in the MTB. Most patients had NECs ($n = 52$), followed by NETs ($n = 36$). The median age of all patients at initial diagnosis was 54.2 years (range 19–82), and the patients with pheochromocytoma and ACC were youngest at initial diagnosis (37.1 and 36.0 years, respectively). The most common location of the primary tumor was the pancreas (32.7%). Of all patients, 67.3% presented with synchronous metastatic disease. The median time between initial diagnosis and diagnosis of metastatic disease was 4.8 months (range 0.0–78.0), and patients were discussed in the MTB a median of 24.5 months (range 1.0–158.0) after initial diagnosis. The included patients with NEC of the lung had large-cell NEC in six cases and small-cell lung cancer in one case. Of the six patients with carcinoid tumor, five had an atypical carcinoid. Baseline characteristics of the 104 included patients are presented in Table 1. Testing was done with liquid biopsy in only two cases. In all other patients, testing was performed on tissue from the primary tumor (27.9%) or metastatic tissue (68.3%). CGP was successful in 91.3% of cases; the reason for unsuccessful testing was insufficient quality of tumor material. In some cases, testing

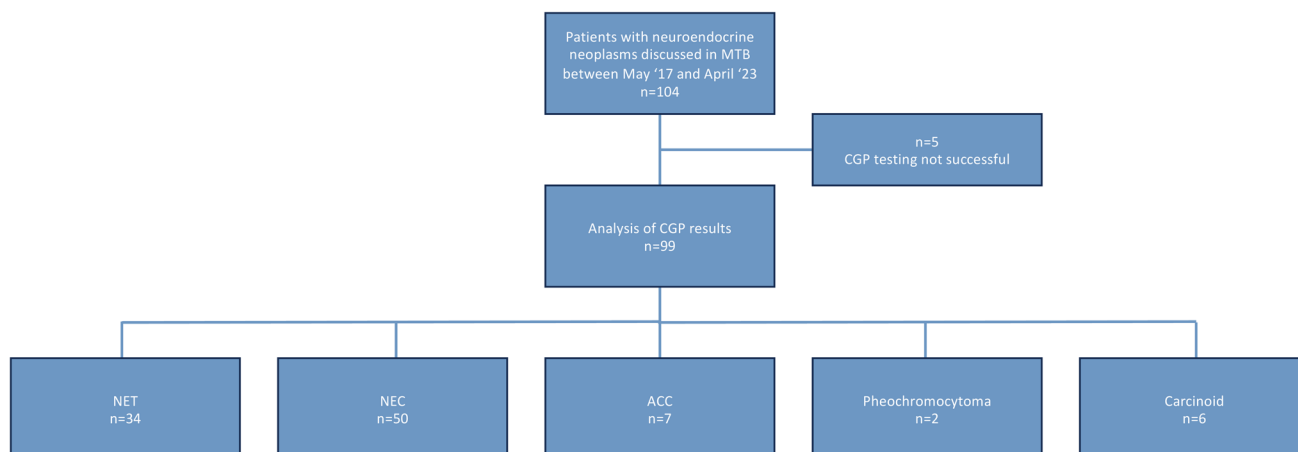


Fig. 1 Flowchart of included patients. ACC adrenocortical carcinoma, CGP comprehensive genomic profiling, MTB Molecular Tumor Board, NEC neuroendocrine carcinoma, NET neuroendocrine tumor

was repeated with different material, and—ultimately—CGP results from 99 patients (95.2%) were obtained.

3.2 Molecular Alterations

Of the 99 patients with technically successful CGP, a pathogenic alteration was found in 71 patients (71.7%). A median of one pathogenic alteration was detected (range 0–12). Figure 2 shows an oncoplot of the altered genes among all patients with technically successful CGP. The most commonly mutated genes in this population were *TP53* (29.3%), *RBI* (11.1%), and *KRAS* (10.1%). In total, 31.3% of tumors harbored alterations that were not present in any other case in the study population. The highest prevalence of pathogenic alterations was detected in NEC (76.9%) and carcinoids (83.3%), whereas the lowest prevalence of pathogenic alterations was seen in ACC (37.5%). Targetable molecular alterations were found in 40.0% of NEC cases, 33.3% of NET G1 cases, 42.9% of NET G2 cases, and 52.9% of NET G3 cases.

3.3 Targeted Treatment Recommendations

Of the 99 patients with successful CGP, 35 (35.4%) received a treatment recommendation from the MTB (19 with NEC, 13 with NET, three with atypical carcinoids). Of these, ten ultimately received the recommended treatment (Table 2). The most frequently proposed treatment option was checkpoint inhibition in patients with either high TMB or pathogenic molecular alterations that have been described as associated with sensitivity to checkpoint inhibition [22, 23]. Four of the treated patients experienced a clinical benefit under the targeted treatment (PFS ratio > 1.3), four patients were lost to follow-up, and two patients had a PFS ratio of 0.19 and 1.14. One patient with atypical carcinoid with high TMB reached a PFS ratio of 8.16 during checkpoint inhibition and was still receiving treatment at data cut-off. The reasons that the remaining patients did not receive the recommended targeted treatment options included rapid deterioration of the patient or death before the recommendation could be implemented, refusal of cost coverage by the insurance company,

Table 1 Baseline characteristics of patients included in the study (n=104)

Characteristic	All pts (n = 104)	NET ^a (n = 36)	NEC (n = 52)	Pheochr. (n = 2)	ACC (n = 8)	Carcinoid ^b (n = 6)
Age (years)	54.2 (19–82)	53.5 (23–78)	59.1 (27–82)	37.1 (26–47)	36.0 (19–59)	61.9 (27–69)
Sex						
Male	60 (57.7)	22 (61.1)	32 (61.5)	1 (50)	3 (37.5)	2 (33.3)
Female	44 (42.3)	14 (38.9)	20 (38.5)	1 (50)	5 (62.5)	4 (66.7)
Status at last follow up						
Deceased	54 (51.9)	14 (38.9)	32 (61.5)	2 (100)	4 (50)	2 (33.3)
Alive	50 (48.1)	22 (61.1)	20 (38.5)	–	4 (50)	4 (66.7)
Tumor stage at initial diagnosis						
Locally limited	34 (32.7)	9 (25.0)	16 (30.8)	2 (100)	5 (62.5)	2 (33.3)
Metastatic	70 (67.3)	27 (75.0)	36 (69.2)	–	3 (37.5)	4 (66.7)
Tumor stage at time of MTB						
Locally limited	10 (9.6)	3 (8.3)	7 (13.5)	–	–	–
Metastatic	94 (90.4)	33 (91.7)	45 (86.5)	2 (100)	8 (100)	6 (100)
Location of primary tumor						
Adrenal glands	10 (9.6)	–	–	2 (100)	8 (100)	–
Colorectal	11 (10.6)	2 (5.6)	9 (17.3)	–	–	–
Lung	12 (11.5)	–	7 (13.5) ^c	–	–	4 (66.7)
Pancreas	34 (32.7)	23 (63.9)	11 (21.2)	–	–	–
Small intestine	4 (3.8)	3 (8.3)	1 (1.9)	–	–	–
Unknown	13 (12.5)	4 (11.1)	9 (17.3)	–	–	1 (16.7)
Other	20 (19.2)	4 (11.1)	15 (28.8)	–	–	1 (16.7)

Data are presented as median (range) or n (%)

ACC adrenocortical carcinoma, MTB Molecular Tumor Board, NEC neuroendocrine carcinoma, NET neuroendocrine tumor, Pheochr. Pheochromocytoma, pt(s) patient(s)

^aThree pts with low-grade NET, 15 pts with intermediate-grade NET, 18 pts with high-grade NET

^bFive pts with atypical carcinoid, one pt with typical carcinoid

^cSix pts with large-cell NEC, one pt with small-cell lung cancer

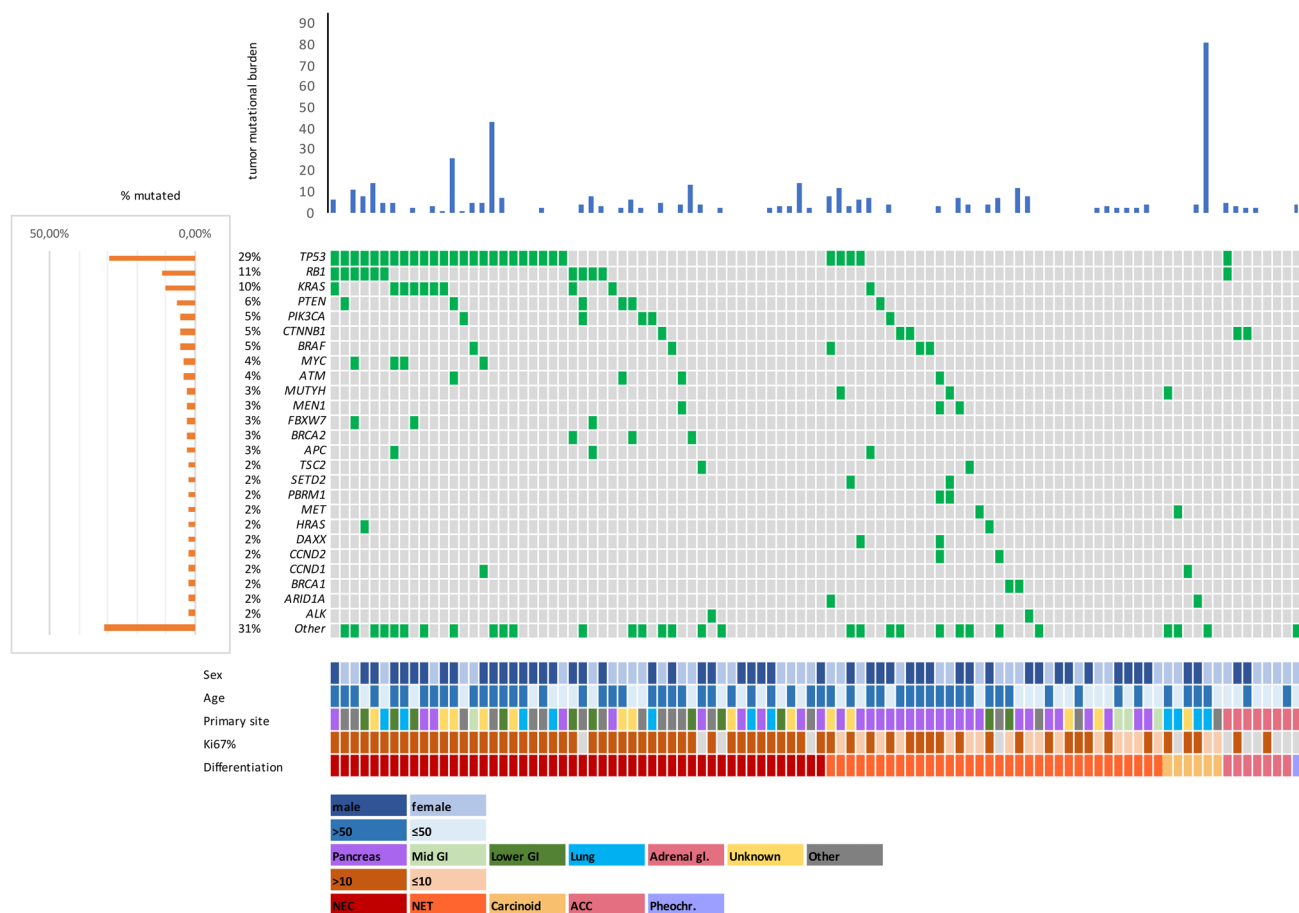


Fig. 2 OncoPrint of molecular alterations in patients with neuroendocrine neoplasm (NEN). The oncoPrint shows altered genes (rows) among 99 patients with NEN (columns). Genes altered in at least two cases are depicted separately; genes altered in only one case are summarized as “other”. The tumor mutational burden is depicted in

the upper panel; the lower panel shows a heatmap of the patients’ sex, age, primary site, Ki67%, and differentiation of the tumor. *ACC* adrenocortical carcinoma, *Adrenal gl.* adrenal glands, *GI* gastrointestinal tract, *NEC* neuroendocrine carcinoma, *NET* neuroendocrine tumor, *Pheochr.* pheochromocytoma

and treating physician’s choice; however, in many cases the specific reason was not known.

3.4 Outcome

Median overall survival (mOS) across all included patients was 45.6 months (95% confidence interval [CI] 26.8–64.5). Although patients who received a recommended targeted treatment had a numerically longer mOS than patients who received a treatment recommendation but were not treated accordingly (102.0 vs. 44.6 months, respectively; Fig. 3), this difference was not statistically significant ($p = 0.232$). In patients with NEC, mOS was 19.3 months (95% CI 11.9–26.7). Female patients with NEC had a numerically longer mOS than male patients (43.1 vs. 18.9 months, respectively); however, this difference was also not statistically significant ($p = 0.156$). Patients with NET had an mOS of 82.0 months (95% CI 28.1–135.9).

4 Discussion

This retrospective cohort study analyzed patients with NET, NEC, ACC, pheochromocytoma, and carcinoids whose CGP results were discussed in the University Hospital Munich MTB. Patients with pheochromocytoma or ACC had a lower median age at diagnosis (37.1 and 36.0 years, respectively) than those in the other subgroups. As only a few patients with pheochromocytoma, ACC, or carcinoids were included in the analysis, this limits the representability of these subgroups; however, a median age < 50 years at diagnosis has been reported previously for pheochromocytoma and ACC [24, 25].

The most common pathogenic alterations found in our cohort of patients with NENs were *TP53* (29%), *RB1* (11%), and *KRAS* (10%) mutations. A different study of patients discussed in an MTB included 114 patients with NET or NEC and also found *TP53* and *RB1* mutations to be common, but *KRAS* mutations were markedly less frequent;

Table 2 Treatments recommended by the Molecular Tumor Board (MTB)

Recommendation ^a	NEC	NET	Carcinoid
Checkpoint inhibition			
ARID1A mutation	–	2	1
PBRM1 mutation	–	2	–
High TMB	6 (3 pts treated, LTFU)	2	1 (treated, PFS ratio 8.16)
Crizotinib, cabozantinib			
MET amplification		–	1
MET mutation		1	
Crizotinib			
ROS1 mutation	1		
BRAF inhibitor			
BRAF V600E mutation	2 (treated, PFS ratios 2.33 and 1.14)	1	
BRAF V600R mutation	–	1	
BRAF fusion	–	1	
ALK inhibitor			
ALK fusion	1	1	
Sotorasib			
KRAS G12C mutation	1 (treated, PFS ratio 0.19)		
PARP inhibitor			
ATM mutation	1	–	
BRCA1 mutation	–	2	
BRCA2 mutation	2 (1 pt treated, LTFU)		
Alpelisib			
PIK3CA mutation	2	1	
Neratinib			
ERBB2 mutation	1		
Osimertinib			
EGFR mutation	1 (treated, PFS ratio 1.43)		
CDK4/6 inhibitor			
CDK4 amplification	1		
Everolimus			
PTEN mutation		1 (treated, PFS ratio 1.43)	
Pralsetinib, selpercatinib			
RET fusion		1	
Erdaftinib			
FGFR3 fusion		1	
Fulvestrant after ER IHC			
ESR1 mutation	1		
Regorafenib			
FLT3 amplification	1		

EGFR epidermal growth factor receptor, ER IHC estrogen receptor immunohistochemistry, LTFU long-term follow-up, NEC neuroendocrine carcinoma, NET neuroendocrine tumor, PFS progression-free survival, pt(s) patient(s), TMB tumor mutational burden

^aDepending on the exact MTB recommendation, either a drug class or a specific drug is indicated

instead, *MEN1* mutations were more common than in our cohort [26]. The rate of cases in which no pathogenic alteration was identified by CGP was comparable, with 72% in our cohort and 74% in the cohort from Boilève et al. [26].

The mutational spectrum of gastroenteropancreatic NEC and NET differs from, for example, *MEN1*, *DAXX*, and *ATRX* mutations, which are frequently found in pancreatic NETs but rarely in gastroenteropancreatic NECs [27]. In

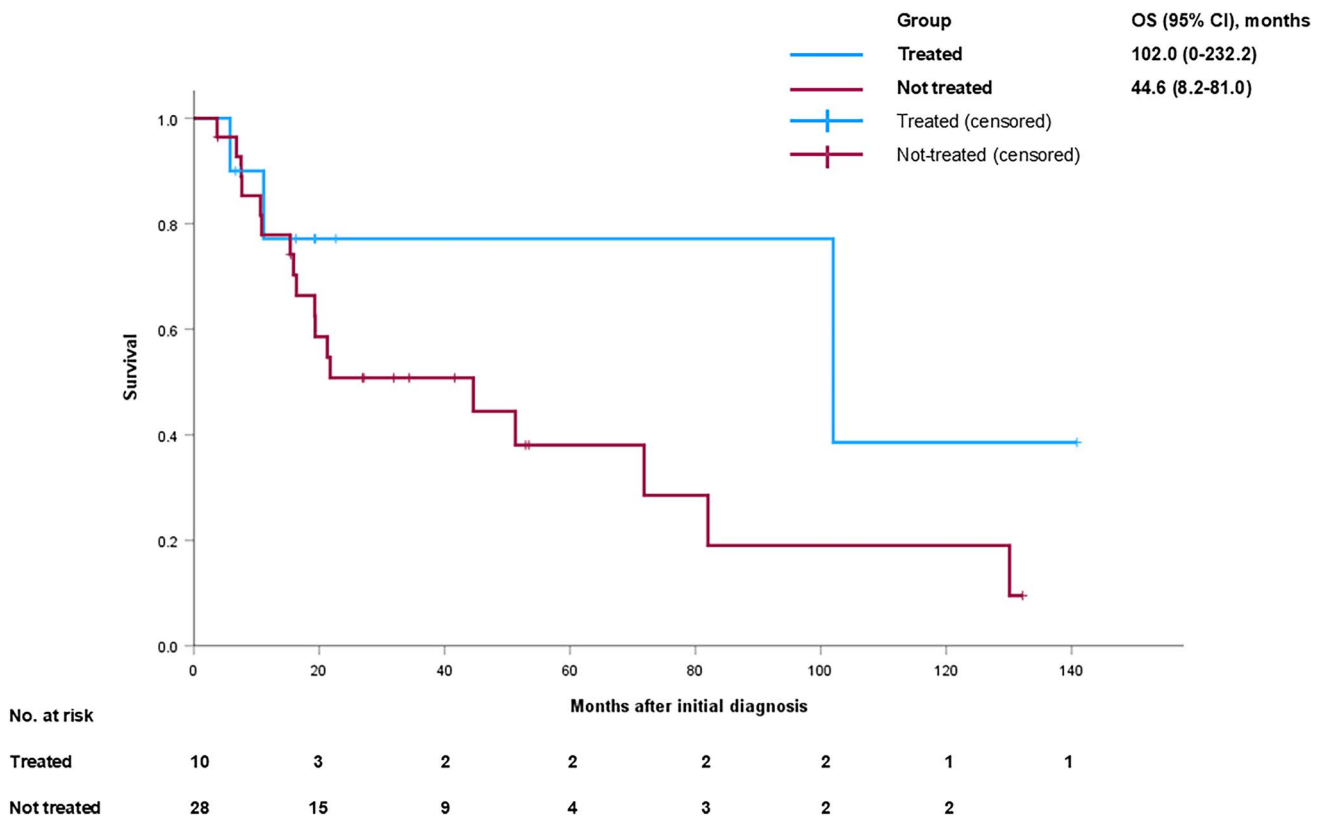


Fig. 3 Survival curves of patients who received the treatment recommended by the Molecular Tumor Board and patients who were given a treatment recommendation but were not treated accordingly

our cohort, no *ATRX* mutations were found, whereas *MEN1* mutations were found in NET and NEC, and *DAXX* mutations were only detected in pancreatic NET.

After receiving a treatment recommendation from the MTB, only 28.6% of patients (10/35) received the recommended targeted therapy. In most cases, the reasons for not initiating the recommended treatment were not known, but possible reasons could be deterioration of the patient's clinical state before treatment initiation, patient wishes, treating physician's choice, or denial of cost reimbursement by the health insurance provider. Patients with other entities discussed in the MTB, such as pancreatic cancer (3.2%), cholangiocellular carcinoma (19.4%), cancer of unknown primary (14%), and gynecological cancers including cervical, vaginal, and vulvar cancer (7%), received recommended targeted treatments even less frequently, possibly due to a more aggressive tumor biology and therefore faster clinical deterioration of patients [28–31]. Boilève et al. [26] described an implementation rate of 35% in patients with NET or NEC, which is slightly higher than in our patient cohort. Patients treated according to MTB recommendations in the cohort from Boilève et al. [26] mostly had NETs, whereas most of the patients in our cohort who received the targeted treatment had NECs; however, the proportion

of all NECs in the cohort was higher in our analysis. In the future, the implementation rate could possibly be improved upon with the implementation of standardized follow-up of patients after MTB.

Encouragingly, four of the ten patients who received the recommended targeted treatment benefitted in terms of the PFS ratio. ESMO recommendations include testing of TMB in well-to-moderately differentiated NETs [13]; however, in our cohort, high TMB was detected in six patients with NEC and one patient with atypical carcinoid, who ultimately benefitted by far the most, with a PFS ratio of 8.16 during checkpoint inhibition. However, ESMO recommendations also include testing for tumor-agnostic alterations, including TMB, in patients with metastatic cancers when access to matched therapies is available [13, 14], and our study highlights the relevance of this. Neither patients with ACC nor those with pheochromocytoma received treatment recommendations from our MTB. This may be due to the low patient numbers in our cohort but emphasizes the need for ongoing research to identify targeted treatment options for these rare tumor entities.

Patients who received a recommended targeted treatment had a numerically longer mOS than those who received a treatment recommendation but were not treated accordingly;

however, this difference was not statistically significant, and larger patient numbers would most likely be needed to show possible significant differences in survival. Nevertheless, considering the survival curves and the PFS ratios, CGP followed by MTB discussion can lead to meaningful clinical benefit in a few selected patients with NENs.

As this was a retrospective single-center study, this analysis has limitations. The inclusion of NET, NEC, ACC, pheochromocytoma, and carcinoids means that the analyzed patients represent a heterogeneous cohort with partially very small subgroups that can only be examined descriptively. Furthermore, given the low implementation rate of the recommended treatments, many patients need to receive CGP testing and subsequent MTB discussion for some to ultimately benefit. As described in previous publications from our center, the structured follow-up of patients discussed in the MTB is currently being improved upon and will facilitate future analysis, especially of patient outcomes [17].

5 Conclusion

This analysis showed that CGP can be a useful addition to current treatment options for certain patients with NENs. It shows the need for concepts to improve the implementation rate of treatments recommended after MTB, for example with structured follow-up, support with the application process for cost reimbursement from health insurance providers, and close communication with clinical trial units. Since the overall survival of patients with NET is relatively long, especially compared with patients with the more aggressive NECs, these patients often receive multiple therapy lines and would likely benefit from more targeted treatment options. However, as our and others' analyses have shown, pathological alterations in NENs are very diverse, which complicates the development of targeted treatments suitable for a broader range of patients.

Declarations

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Ethics Approval This retrospective chart review study involving human participants was undertaken in accordance with the principles of the Declaration of Helsinki and its later amendments. The study was approved by the local ethics committee of the Ludwig-Maximilians-University Munich (project number 21-0869).

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Data Availability The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Code Availability Not applicable.

Author Contributions All authors contributed to the study conception and design. Klara Dorman and Kathrin Heinrich prepared the material collected and analyzed the data. Klara Dorman wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Authors and Affiliations

Klara Dorman^{1,2} · Christoph J. Auernhammer^{3,11} · Christine Spitzweg^{3,11} · Ralf Schmidmaier^{3,12} · Svenja Nölting^{3,14} · Matthias Kroiss^{3,12} · Martin Reincke^{3,12} · Christian Schulz^{4,11} · Martin Angele^{5,11} · Jens Werner^{5,11} · Christine Schmid-Tannwald^{6,11,12} · Josefine Rauch^{7,11} · Mathias Zacherl^{8,11} · Thomas Knösel^{2,9,11} · Jörg Kumbrink^{2,9} · Andreas Jung^{2,9} · Frederick Klauschen^{2,9} · Amanda Tufman¹³ · Danmei Zhang^{1,2} · Lena Weiss¹ · Stefan Böck^{1,2,10} · Michael von Bergwelt-Baildon^{1,2,11} · Volker Heinemann^{1,2} · C. Benedikt Westphalen^{1,2,11} · Kathrin Heinrich^{1,2,11} 

✉ Kathrin Heinrich
Kathrin.heinrich@med.uni-muenchen.de

¹ Department of Medicine III and Comprehensive Cancer Center, LMU University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany

² German Cancer Consortium (DKTK), Partner Site Munich, Munich, Germany

³ Department of Medicine IV, LMU University Hospital, LMU Munich, Munich, Germany

⁴ Department of Medicine II, LMU University Hospital, LMU Munich, Munich, Germany

⁵ Department of General, Visceral and Transplant Surgery, LMU University Hospital, LMU Munich, Munich, Germany

⁶ Department of Radiology, LMU University Hospital, LMU Munich, Munich, Germany

⁷ Department of Radiation Oncology, LMU University Hospital, LMU Munich, Munich, Germany

⁸ Department of Nuclear Medicine, LMU University Hospital, LMU Munich, Munich, Germany

⁹ Institute of Pathology, Faculty of Medicine, LMU Munich, Munich, Germany

¹⁰ Department of Hematology and Oncology, Munich Municipal Hospital Neuperlach, Munich, Germany

¹¹ Interdisciplinary Center of Neuroendocrine Tumors of the GastroEnteroPancreatic System (GEPNET-KUM, ENETS certified Center of Excellence), LMU University Hospital, LMU Munich, Munich, Germany

¹² Interdisciplinary Center of Endocrine Tumors (ZET), LMU University Hospital, LMU Munich, Munich, Germany

¹³ Department of Medicine V, LMU University Hospital, LMU Munich, Munich, Germany

¹⁴ Department of Endocrinology, Diabetes and Clinical Nutrition, University Hospital Zurich, USZ, UZH, Zurich, Switzerland