Responses to systemic therapy in metastatic pheochromocytoma/paraganglioma: a retrospective multicenter cohort study

Fischer, Alessa ; Kloos, Simon ; Remde, Hanna ; Dischinger, Ulrich ; Pamporaki, Christina ; Timmers, Henri J L M ; Robledo, Mercedes ; Fliedner, Stephanie M J ; Wang, Katharina ; Maurer, Julian ; Reul, Astrid ; Bechmann, Nicole ; Hantel, Constanze ; Mohr, Hermine ; Pellegata, Natalia S ; Bornstein, Stefan R ; Kroiss, Matthias ; Auernhammer, Christoph J ; Reincke, Martin ; Pacak, Karel ; Grossman, Ashley B ; Beuschlein, Felix ; Nölting, Svenja

DOI: https://doi.org/10.1093/ejendo/lvad146

European Journal of Endocrinology, 2023, **189**, 546–565
https://doi.org/10.1093/ejendo/lvad146
Advance access publication 9 November 2023
Original Research

Responses to systemic therapy in metastatic pheochromocytoma/paraganglioma: a retrospective multicenter cohort study

Alessa Fischer,[1] Simon Kloos,[1] Hanna Remde,[2] Ulrich Dischinger,[2] Christina Pamporaki,[3] Henri J.L.M. Timmers,[4] Mercedes Robledo,[5,6] Stephanie M.J. Fliedner,[7] Katharina Wang,[8] Julian Maurer,[8] Astrid Reul,[1] Nicole Bechmann,[9] Constanze Hantel,[1,3] Hermine Mohr,[10] Natalia S. Pellegata,[10,11] Stefan R. Bornstein,[1,3] Matthias Kroiss,[8] Christoph J. Auernhammer,[8] Martin Reincke,[8] Karel Pacak,[12] Ashley B. Grossman,[13,14] Felix Beuschlein,[1,8] and Svenja Nölting[1,8,*]

[1]Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zurich (USZ) and University of Zurich (UZH), Zurich, Switzerland
[2]Department of Internal Medicine I, Division of Endocrinology and Diabetes, University Hospital, University of Würzburg, Würzburg, Germany
[3]Department of Internal Medicine III, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[4]Division of Endocrinology, Department of Internal Medicine, Radboud University Medical Center, Nijmegen, Netherlands
[5]Hereditary Endocrine Cancer Group, Spanish National Cancer Research Center (CNIO), Madrid, Spain
[6]Centro de Investigación Biomédica en Red de Enfermedades Raras, Institute de Salud Carlos III, Madrid, Spain
[7]First Department of Medicine, University Medical Center Schleswig-Holstein, Lübeck, Germany
[8]Department of Medicine IV, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany
[9]Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Carl Gustav Carus, Medical Faculty Carl Gustav Carus, Technische Universität Dresden, Fetscherstrasse, Dresden, Germany
[10]Institute for Diabetes and Cancer, Helmholtz Zentrum München, Neuherberg, Germany
[11]Department of Biology and Biotechnology, University of Pavia, Pavia, Italy
[12]Eunice Kennedy Shriver NICHD, NIH, Bethesda, MD, United States
[13]Green Templeton College, University of Oxford, Oxford, United Kingdom
[14]NET Unit, ENETS Center of Excellence, Royal Free Hospital, London, United Kingdom

***Corresponding author:** Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zurich (USZ), Raemistrasse 100, Zurich CH-8091, Switzerland. Email: svenja.noelting@usz.ch

Abstract

Objective: The therapeutic options for metastatic pheochromocytomas/paragangliomas (mPPGLs) include chemotherapy with cyclophosphamide/vincristine/dacarbazine (CVD), temozolomide monotherapy, radionuclide therapies, and tyrosine kinase inhibitors such as sunitinib. The objective of this multicenter retrospective study was to evaluate and compare the responses of mPPGLs including those with pathogenic variants in succinate dehydrogenase subunit B (*SDHB*), to different systemic treatments.

Design: This is a retrospective analysis of treatment responses of mPPGL patients ($n = 74$) to systemic therapies.

Methods: Patients with mPPGLs treated at 6 specialized national centers were selected based on participation in the *ENSAT* registry. Survival until detected progression (SDP) and disease-control rates (DCRs) at 3 months were evaluated based on imaging reports.

Results: For the group of patients with progressive disease at baseline (83.8% of 74 patients), the DCR with first-line CVD chemotherapy was 75.0% ($n = 4$, SDP 11 months; *SDHB* [$n = 1$]: DCR 100%, SDP 30 months), with somatostatin peptide receptor-based radionuclide therapy (PPRT) 85.7% ($n = 21$, SDP 17 months; *SDHB* [$n = 10$]: DCR 100%, SDP 14 months), with ^{131}I-meta-iodobenzylguanidine (^{131}I-MIBG) 82.6% ($n = 23$, SDP 43 months; *SDHB* [$n = 4$]: DCR 100%, SDP 24 months), with sunitinib 100% ($n = 7$, SDP 18 months; *SDHB* [$n = 3$]: DCR 100%, SDP 18 months), and with somatostatin analogs 100% ($n = 4$, SDP not reached). The DCR with temozolomide as second-line therapy was 60.0% ($n = 5$, SDP 10 months; *SDHB* [$n = 4$]: DCR 75%, SDP 10 months).

Conclusions: We demonstrate in a real-life clinical setting that all current therapies show reasonable efficacy in preventing disease progression, and this is equally true for patients with germline *SDHB* mutations.

Keywords: metastatic pheochromocytoma, paraganglioma, PRRT, MIBG, CVD, *SDHB*, systemic therapy

Received: April 1, 2023. **Revised:** September 2, 2023. **Editorial Decision:** September 19, 2023. **Accepted:** September 19, 2023

Significance

It is currently unclear which systemic therapies for metastatic pheochromocytomas/paragangliomas (mPPGLs) are effective. We present disease-control rates (DCRs) at 3 months and survival until detected progression for the most common systemic therapies in a multicenter cohort of 74 patients analyzed retrospectively, emphasizing the results in patients with progressive disease and succinate dehydrogenase subunit B (*SDHB*) mutations. The DCR at 3 months for patients progressive at baseline treated with cyclophosphamide/vincristine/dacarbazine (CVD) chemotherapy was 75.0% ($n = 4$), with somatostatin peptide receptor-based radionuclide therapy (PRRT) 85.7% ($n = 21$), with ^{131}I-meta-iodobenzylguanidine (^{131}I-MIBG) 82.6% ($n = 23$), with sunitinib 100% ($n = 7$), and with somatostatin analogs 100% ($n = 4$). In conclusion, we show that all different systemic therapies for mPPGLs including those with pathogenic variants in *SDHB* are effective in the case of progressive disease, justifying their use in treatment programs.

Introduction

Pheochromocytomas (PHEOs) and paragangliomas (PGLs) (together, PPGLs) are a group of relatively rare, clinically heterogeneous endocrine tumors.[1] Pheochromocytomas arise in the adrenal medulla and are metastatic in 10%-15% of cases.[2-4] Paragangliomas are metastatic in 35%-40% of cases and occur either in the paraganglia of the sympathetic (thorax, abdomen, and pelvis) or parasympathetic (head and neck) nervous systems.[2-4] Independent of their initial clinical presentation and histological features, all PPGLs are considered to have metastatic potential. Therefore, the World Health Organization (WHO) defines malignant disease by the presence of metastasis at distant sites where chromaffin cells are physiologically absent.[5] Pheochromocytomas and paragangliomas have a high degree of hereditability with germline pathogenic variants detected in 30%-35% of patients and somatic pathogenic variants in a further 35%-40% of patients with PPGLs.[6-8] Different mutational landscapes are associated with specific clinical features, biochemical phenotypes, location, and long-term prognosis.[3,9] Specifically, patients with succinate dehydrogenase subunit B (*SDHB*) pathogenic variants have a higher risk for metastatic disease.[3,10,11] Succinate dehydrogenase subunit B–related PPGLs not only metastasize more often, but they also have a more extensive vascular supply and locoregional invasive behavior and recurrence.[12-14] Succinate dehydrogenase subunit B pathogenic variants are associated with higher somatostatin receptor 2 (SSTR2) expression.[15,16]

Local or systemic therapies for patients presenting with metastatic PPGL (mPPGL) should be individualized, and, whenever possible, therapy regimens should be chosen based on multidisciplinary endocrine tumor board recommendations.[3,5] Chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD) may be used in patients with rapidly progressive mPPGLs or a high visceral tumor burden where tumor shrinkage is required.[3,17,18] In patients with slow-to-moderate progression and positive SSTR2 or positive meta-iodobenzylguanidine (MIBG) radionuclide imaging, somatostatin peptide receptor-based radionuclide therapy (PRRT), or (high or low specific activity) ^{131}I-MIBG are therapeutic options.[3,5,11,19-22] Peptide receptor-based radionuclide therapy is already an officially approved and highly effective therapy option for patients with advanced midgut and pancreatic neuroendocrine tumors.[23] For slowly to moderately progressing PPGLs that are not eligible for PRRT or MIBG or in the case of progression to first-line therapy, temozolomide (with or without capecitabine), or tyrosine kinase inhibitors (TKIs), such as sunitinib,[3] may be employed.[3] However, apart from high specific activity MIBG in the United States, none of the systemic therapy options is officially Food and Drug Administration (FDA)-approved for the treatment of PPGLs.

Several novel targeted therapies are currently being investigated for patients with metastatic or locally advanced PPGLs.[3,11,17] These include radionuclide therapy with SSTR2 antagonists (NCT 02592707), combination strategies with radiosensitizers, cold SSTR2 analogs (lanreotide; LAMPARA, NCT03946527), poly (ADP-ribose) polymerase (PARP) inhibitors plus temozolomide (NCT04394858, NCT5142241), HIF-2α inhibitors (belzutifan [PT2977]; NCT04924075), immunotherapy (checkpoint inhibitors; NCT02721732), different TKIs (NCT00843037, NCT02302833, NCT03839498, NCT03008369, NCT04860700, NCT05133349), TKIs in combination with immunotherapy (NCT04400474), farnesyltransferase inhibitors (NCT04284774), and therapeutic vaccines (NCT04187404).[3,17] Overall, because of the low patient numbers and diverse treatment options, comparative studies on treatment response are missing.

Therefore, the objective of this multicenter retrospective study was to evaluate and compare the responses of patients with mPPGLs including those with *SDHB* pathogenic variants to different systemic treatments.

Material and methods

Study population

This retrospective study included 74 patients with mPPGLs treated at 6 specialized endocrine tumor centers in Germany (Munich, 12 patients; Dresden, 6 patients; Lübeck, 1 patient; Würzburg, 32 patients), the Netherlands (Nijmegen, 19 patients), and Switzerland (Zurich, 4 patients). Inclusion criteria were the diagnosis of a mPPGL at first diagnosis or follow-up, participation in the "Prospective Monoamine-Producing Tumor study" (PMT study) for patients from Munich, Dresden, Lübeck, and Würzburg and/or in *European Network for the Study of Adrenal Tumors* (ENS@T) for patients from Nijmegen and Zurich, treatment with at least 1 line of systemic therapy, and metastatic disease. Metastatic PPGL was defined by the presence of distant metastases at sites where chromaffin cells are physiologically absent.[5] Further inclusion criteria were the availability of medical records with adequate follow-up data after treatment. The study was conducted in line with the principles of the Declaration of Helsinki and according to the law and regulations of the Ethics Commission of the Canton of Zurich under the reference number BASEC 2017-00771 as part of ENS@T. Written informed consent was obtained from each patient or parental consent in the case of children prior to participation.

Systemic treatments analyzed as part of this study were administered between January 1994 and January 2023.

Clinical data were extracted from medical records, and, when detailed reports were available, treatment responses were evaluated according to *Response Evaluation Criteria In Solid Tumors* (RECIST). When no radiologic reports were available, responses to treatment were used as described in "tumor board" recommendation letters.

The imaging modalities were heterogeneous and included computed tomography (CT) scans; positron emission tomography (PET)/CT scans including gallium-68-labeled-DOTA-somatostatin receptor analog ([^{68}Ga]-DOTA-SSA) PET/CT, ^{18}F-fluoro-l-phenylalanine ([^{18}F]FDOPA) PET/CT, and fluorodeoxyglucose (FDG) PET/CT; iodine-123 MIBG scan; and magnetic resonance imaging (MRI).

Disease burden at the start of systemic therapy and progression at baseline was defined as either indicated in the tumor board recommendation letters or in the imaging reports in the last imaging before start of the systemic therapy. Extensive metastatic disease was defined by more than 5 metastases in 1 organ or metastases in at least 2 organ systems; oligometastatic disease was defined by <5 metastases in 1 organ.

Progression under therapy was defined as progression described in the imaging report or in the tumor board recommendation letter based on imaging results.

The response to PRRT was evaluated at 3 and 6 months after treatment initiation. The response to all other systemic treatments was assessed 3 months after treatment initiation. The disease-control rate (DCR) at 3 months was calculated as the percentage of the sum of patients who achieved a complete response, partial response, or stable disease 3 months after the start of systemic therapy. Response evaluation was purely based on imaging, and a biochemical response was not considered for this calculation. When data on measurement of plasma or urine metanephrine, normetanephrine, or methoxytyramine were available, elevated values or values within the reference range were reported, and classification of catecholamine phenotype was performed as described by Eisenhofer *et al.*[24]

Due to non-standardized follow-up imaging, "survival until detected progression" (abbreviated SDP) was calculated as time from start of the therapy until progression was detected by imaging or as described in the tumor board recommendation letter based on imaging results.

The data on PRRT and somatostatin analogs (SSA) have previously been published in part in Fischer *et al.* (JCEM, 2023).[16] In the current study, we have additionally analyzed the data on PRRT and SSA specifically for the subgroup *SDHB*-related PPGLs; we have included tumor burden and added new follow-up data.

Sequencing

Sequencing was performed by local centers or the *Spanish National Cancer Research Center* (CNIO) in Madrid, Spain, in germline or tumor DNA by next-generation sequencing (NGS), as previously described (Fischer *et al.*, JCEM 2023).[16] When patients agreed to genetic sequencing, they first received genomic sequencing at local centers. Genes covered were *NF1*, *RET*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *VHL*, *TP53*, *TMEM127*, *MAX*, *MET*, and *FH* in Würzburg, Lübeck, Munich, and Zurich. In Nijmegen, patients received germline testing based on clinical evaluation with a NGS panel including *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *TMEM127*, *MAX*, *VHL*, *FH*, *MDH2*, *RET*, and *NF1*. In patients from Dresden, genetic testing for germline pathogenic variants of *SDHx*, *VHL*, *FH*, *MDH2*, *EPAS1*, *TMEM127*, *MAX*, and *RET* was performed using NGS and/or Sanger sequencing as described before.[8] In Dresden, testing of patients also included NGS directed primarily to test tumor tissue for somatic pathogenic variants of *VHL*, *RET*, *SDHB*, *SDHC*, *SDHD*, *MAX*, *TMEM127*, *NF1*, *HRAS*, and *HIF2a* genes. For *NF1*, the diagnosis was based mainly on genetic testing and on clinical manifestations according to established criteria.[25]

Genes covered in the panel at CNIO to detect somatic variants were *VHL*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *SDHAF1*, *MAX*, *HIF1A* (*exon 12*), *HIF2A* (*exon 12*), *TMEM127*, *HRAS*, *KRAS*, *NF1*, *GOT2*, *FH*, *MDH2*, *SLC25A11*, *DNMT3A* (*exon 8*), *DLST* (*exon 14*), *MERTK* (*exon 17*), *IDH1*, *IDH2* (*exon 4*), *CSDE1*, *EGLN1*, *EGLN2*, *BRAF* (*exon 15*), *MET* (*exons 14-21*), *FGFR1* (*exons 12 and 14*), *KIF1B*, *CDKN1B*, *MEN1*, *PTEN*, *H3F3a*, *ATRX*, and the *TERT* promoter region. Pathogenic variants were also assessed in peripheral blood DNA samples when available and confirmed by Sanger sequencing. Multiplex Ligation-dependent Probe Amplification (MLPA) (MRC Holland) was performed for *VHL* and *SDHx* using blood DNA in those with clinical signs but negative NGS results. Classification of identified variants was performed according to standards and guidelines of the *American College of Medical Genetics and Genomics* and the *Association for Molecular Pathology* (ACMG-AMP).[26]

Statistical analysis

The DCR at 3 months was calculated as the percentage of the sum of patients who achieved a complete response, partial response, or stable disease 3 months after the start of therapy. The DCR was calculated for all patients and, separately, for the subgroup of patients progressive at baseline and the subgroup of patients with *SDHB* pathogenic variants. The median time of SDP under therapy and median time between the first surgery and start of first systemic therapy was calculated with the Kaplan–Meier method for patient subgroups. Statistical analyses were performed using *Stata* Statistical Software, Release 16 (StataCorp LLC, College Station, Texas, USA).

Results

Patient characteristics

A total of 74 patients with metastatic PHEO (41 patients) or PGL (33 patients) were included in this study. Patient characteristics and pathogenic variants are summarized in Table 1. Of 74 patients, 47 were male (63.5%). Sequencing data (germline or somatic or both) were available in 64/74 (86.5%) of patients with 24 patients (32.4%) harboring *SDHB* pathogenic variants.

Surgery as first-line therapy before starting systemic therapy was performed in 68/74 (91.9%) patients. The median time from first surgery to start of first systemic therapy was 41 months (minimal 1 month to maximal 409 months) overall and 35 months for the subgroup of *SDHB*-related PPGLs (minimal 1 month to maximal 409 months). In R0-resected

Table 1. Summary of patient characteristics.

	Metastatic PPGL patients with systemic treatment ($n = 74$)
Age at surgery	
Median (range)	48.1 (9-77)
Gender	
Female (%)	27 (36.5%)
Male (%)	47 (63.5%)
Entity at diagnosis	
Pheochromocytoma	41 (55.4%)
Paraganglioma	33 (44.6%)
Tumor diameter	
Mean (+/−SD) in mm	79.6 (+/− 44.0)
Sequencing performed	
Germline	58 (77.0%)
Somatic	2 (2.7%)
Germline and somatic	4 (5.4%)
None	10 (13.5%)
Mutation	
ATRX	1 (1.4%)
HRAS	3 (4.1%)
MAX	1 (1.4%)
RET	1 (1.4%)
SDHA	2 (2.7%)
SDHB	24 (32.4%)
SDHC	1 (1.4%)
SDHD	2 (2.7%)
VHL	2 (2.7%)
No pathogenic variant (germline and somatic)	2 (2.7%)
No pathogenic variant (only germline sequencing)	25 (33.8%)
No sequencing performed	10 (13.5%)

PPGLs without metastases and without pathogenic variants in the *SDHB* gene ($n = 33$), the median time from first surgery to first systemic therapy was 70 months compared with 102 months in *SDHB*-related PPGLs ($n = 11$). In metastatic PPGLs with R1/R0 resection of the primary tumor without pathogenic variants in the *SDHB* gene ($n = 12$), the median time from first surgery to first systemic therapy was 15 months compared with 5 months in *SDHB*-related PPGLs ($n = 8$). The difference between *SDHB* PPGLs and other PPGLs within the group of R0/non-metastatic and R1/metastatic tumors was not statistically significant (*log-rank test*). There were only 4 patients with R1 resection without metastases ($n = 2$ *SDHB* tumors; $n = 2$ non-*SDHB* tumors). The median time from first surgery to first systemic therapy was 9 months compared with 2 months in the *SDHB*-related PPGLs.

In total, 62/74 (83.8%) of patients were progressive at baseline when first-line systemic therapy was started. Of those, 39 (52.7%) had complete tumor resection (R0) without remaining metastases at first surgery. Resection status and time from surgery until start of systemic therapy for individual patients are shown in Table 2 for first-line systemic treatment, in Table 3 for second-line systemic therapy, and in Table 4 for third-line systemic therapy.

Response to different systemic therapies

All 74 patients included in this study were treated with at least 1 line of systemic therapy. Second-line therapy was initiated in 29/74 (39.2%) patients who progressed after first-line systemic treatment. Third-line systemic treatment after progression to second-line therapy was administered in 14 patients (18.9%). The DCR at 3 months for first-, second-, and third-line systemic therapy for patients progressive at baseline is presented in Figure 1 (in detail in Table S1), while the median SDP under first-line therapy in months is presented in Table 5 and under second-line therapy in Table 6. Clinical details on individual patients as well as information on subsequent treatment lines are presented in Tables 2, 3, and 4. Kaplan–Meier survival curves are shown in Figure 2 for first-line systemic therapy and in Figure 3 for second-line systemic therapy for patients progressive at baseline.

Iodine-131 meta-iodobenzylguanidine therapy

In 27 patients treated with first-line ^{131}I-MIBG therapy ($n = 26$ with available information on response to therapy), the DCR at 3 months was 84.6% (*SDHB* [$n = 4$; all progressive at baseline]: DCR 100%). The DCR for patients with progressive disease at baseline ($n = 23$) was 82.6%. The median SDP with ^{131}I-MIBG therapy was 43 months (SDP progressive at baseline: 43 months; *SDHB* [$n = 4$, all progressive at baseline]: SDP 24 months). One patient received second-line ^{131}I-MIBG therapy, showing stable disease (SDP 14 months).

Peptide receptor-based radionuclide therapy

In 22 patients (95.5% progressive at baseline) treated with first-line PRRT ($n = 21$ ^{177}Lu-DOTATATE; $n = 1$ ^{90}Y-DOTATATE; median number of cycles = 4), the DCR at 3 and 6 months was 82.6% (*SDHB* [$n = 11$, $n = 10$ progressive at baseline]: DCR 100%; $n = 1$ *SDHD*, stable disease). The DCR for patients with progressive disease at baseline ($n = 21$) was 85.7%. Overall, the median SDP ($n = 21$) was 18 months (*SDHB* [$n = 12$]: SDP 15 months; *SDHD* [$n = 1$]: SDP 126 months). For patients progressive at baseline, SDP was 17 months ($n = 20$; *SDHB* [$n = 10$]: SDP 14 months).

Six patients received second-line PRRT (after MIBG [$n = 3$], after CVD [$n = 2$], after SSA [$n = 1$]) with a DCR of 83.3% (*SDHB* [$n = 2$]: DCR 50.0%). The median SDP for PRRT as second-line ($n = 6$) was 11 months (*SDHB* [$n = 2$]: SDP 3 months).

Somatostatin analogs

For 6 patients treated with first-line SSA (4/6, 66.7% progressive at baseline), the DCR at 3 months was 100% (*SDHA*-, *SDHB*, *SDHD*-related 1 patient each) overall and for patients progressive at baseline; the median SDP, overall and for patients progressive at baseline, with SSA was not reached, with a cumulative survival of 75.0% at 23 months ($n = 6$, *SDHB* [$n = 1$]: SDP 14 months).

Chemotherapy with CVD

In 5 patients treated with first-line CVD chemotherapy, the DCR at 3 months was 80.0% (*SDHB* [$n = 2$]: DCR 100%), and in 4 patients with progressive disease at baseline, the DCR was 75% (*SDHB* [$n = 1$]: DCR 100%). Patients treated with first-line CVD ($n = 5$) showed a median SDP of 18 months (*SDHB* [$n = 2$]: SDP 18 months). The SDP for patients progressive at baseline ($n = 4$) was 11 months (*SDHB* [$n = 1$]: SDP 30 months). Cyclophosphamide, vincristine, and dacarbazine as second-line was employed in 6 patients with a DCR of 66.7% (*SDHB* [$n = 2$]: DCR 100%). The median SDP under second-line therapy was longest with CVD ($n = 6$), with 21 months (*SDHB* [$n = 2$]: SDP 21 months).

Table 2. Treatment response to first-line systemic therapies and individual patient characteristics.

Pat. #	Genetics	Entity at diagnosis	Surgery (R0 vs R1)	Time surgery to start first-line systemic therapy (in months)	Disease burden before first-line systemic therapy	Progressive disease before systemic therapy	Catecholamines at baseline	Response of catecholamines to therapy	DCR at 3 months	SD at 12 months (yes vs no)	Time in months from start therapy to last imaging showing stable disease (imaging modality)	Time in months until documented progression (imaging modality)	Documented side effect/general remarks
First-line CVD													
2	Not tested	mPheo	No resection	—	EMD (LG, LN)	Yes	Elevated	No	PD	No	None	3 (CT)	Only 2 cycles due to progress/high ECOG
6	*SDHB* (germline)	mPGL	R1m	5	EMD (LG, BN)	Yes	Non-functional	—	SD	Yes	18 (CT)	30 (CT)	At progress restart CVD, stop due to bone marrow toxicity after 2 cycles
43	Negative (germline)	Pheo	R0	175	EMD (LN, LV > 5)	Yes	Elevated (dopaminergic)	Decrease	PR	No	5 (FDG)	11 (FDG)	
54	Negative for *VHL*, *RET*, *SDHB/D*	Pheo	R0 (2001), R1 (2003)	28	Recurrence, OMD (LN)	Yes	Na	na	SD	Yes	na	20 (CT)	
72	*SDHB* (germline)	mPheo	No surgery at diagnosis, neoadjuvant treatment	—	Local infiltration, EMD (LV, BN, LN)	na	Non-functional	—	SD	Yes	14 (FDG)	18 (FDG)	Surgery (liver wedge resection, R1m) 1.5 months after start CVD
First-line TMZ													
39	*SDHB* (germline)	mPGL	No surgery		EMD (BN, LN, LV)	Start at first diagnosis	Elevated (dopaminergic)	na	PR	Yes	34 (FDG)	36 (FDG)	
First-line other chemotherapy													
35	Negative (germline)	HNPGL	R0	78/cisplatin etoposide	EMD (>5 BN)	Yes	Non-functional	—	na	na	na	na	Next therapy line was started 2.5 years later, in between no records
70	Negative (germline)	Pheo	R0	18/streptozotocin and 5FU	EMD (LG [1], BN [2])	Yes	na	na	PD	No	—	3 (CT)	
27	*SDHB* (germline)	PGL	R0m (LG)	GOPH-MET scheme	na	na	na	na	SD	Yes	174 (DOTA)	None	
32	*ARTX* (somatic)	PGL	R0m (LN)	5/6 cycles carboplatin/ etoposide	EMD (>5 LN)	Yes	na	na	PD	No	—	3 (CT)	Patient died 10 months later
First-line MIBG													
1	*VHL* (germline)	Multiple PGL	R1m (2008), R1m (2009)	18	EMD (LN)	Yes	Elevated (noradrenergic)	Decrease by 2/3	SD	Yes	12 years (MRI)	None	—
3	*SDHB* (germline)	PGL	R0	19 years	EMD (LN, BN)	Yes	Slightly elevated	No	SD	Yes	10 years (DOTA)	10 years (DOTA)	—
7	Negative (germline)	Pheo	R0 (98), recurrence R0 (03)	96	Recurrence, OMD (LG)	Yes	Elevated (noradrenergic)	na	SD	Yes	7 years (MIBG scan)	7 years (MIBG scan)	Died of progressive disease 8 years after start MIBG
8	*SDHC* (germline)	PGL	R0	10	EMD (LN >5)	Yes	Elevated (noradrenergic)	Decrease	SD	Yes	16	None	Died of heart failure 2 years after start MIBG
11	Negative (germline)	Pheo	R0 (14), R1 (19)	82	Recurrence, OMD (LN)	Yes	Elevated (noradrenergic)	Decrease (50%)	SD	Yes	24 (CT)	None	
12	*SDHA* (germline)	mPheo	No surgery		na	na	na	na	SD	Yes	10	120 (CT)	
14	Negative (germline)	PGL	R0	10 years	EMD (LN >5 abdominal)	Yes	Non-functional	—	PR	Yes	na	53 (CT)	Died 1 month after imaging showing progress

(*continued*)

Table 2. Continued

Pat. #	Genetics	Entity at diagnosis	Surgery (R0 vs R1)	Time surgery to start first-line systemic therapy (in months)	Disease burden before first-line systemic therapy	Progressive disease before systemic therapy	Catecholamines at baseline	Response of catecholamines to therapy	DCR at 3 months	SD at 12 months (yes vs no)	Time in months from start therapy to last imaging showing stable disease (imaging modality)	Time in months until documented progression (imaging modality)	Documented side effect/general remarks
17	Negative (germline)	Pheo	R0	29 years	EMD (LN, BN, LG)	Yes	Elevated (noradrenergic)	Decrease	SD	Biochemical progression, CT stable	12	Biochemical progression, CT stable	Limited bone marrow reserve, frailty no further MIBG, died 21 months after start treatment
18	na	mPGL	R1m (BN, LN)	12	EMD (LN, BN, LG)	Yes	No clear pattern	—	SD	Yes	12 (MIBG scan)	None	
19	Negative (germline)	mPheo	R0m, 1 remaining LV	29 years	EMD (LN, BN, LG, LV)	Yes	Elevated (adrenergic)	Progress	PD	—	—	3 (MIBG scan)	No follow-up
40	Negative (somatic)	Pheo	R0	8	EMD (LG, BN)	Yes	na	na	PD			2 (CT)	
41	*SDHB* (germline)	PGL	R0, 2 years later recurrence, and LV R0	43	OMD (LG)	Yes	Slightly elevated (noradrenergic)	No clear response	SD	Yes	—	15 (CT)	
42	Negative (germline)	Pheo	R0	23	EMD LN (>5)	Yes	Elevated (adrenergic)	Decrease	PR	Yes	76 (FDG)	88 (FDG)	
44	Negative (germline)	mPheo	R0 incl. hemihepatectomie	1 month	Right after R0 surgery	No	na	na	SD	Yes	—	35 (CT)	
45	Negative (germline)	Pheo	R0 (89), R0 (93)	60	EMD LN (>5)	Yes	na	na	SD	No	na	12 (FDG)	
46	Negative (germline)	Pheo	R0	60	EMD (LG >2, BN, LN)	Yes	na	na	PD	—	None	3	
47	*MAX* (germline)	Pheo	R0 (88), R1 (14), remaining PGLs, BN (2)	316	EMD BN	Yes	Elevated (noradrenergic)	Decrease	SD	Yes	28 (FDG)	37 (DOTA)	
56	Negative (germline)	Pheo	R0 (08), R1 (13)	5 years after first, 1 month after last	Recurrence, OMD (LN)	Yes	Elevate (noradrenergic)	Decrease	PR	Yes	29	None	Aplasia after second MIBG
61	na	Pheo	R0 (07)	10 years	Recurrence, OMD (LN)	Yes	na	na	SD	Yes	12 (FDG)	None	
63	na	Pheo	R0 (14), R1 (17)	48	EMD (BN, LV)	Yes	Non-functional	—	SD	Yes	42 (DOTA)	None	
71	na	mPheo	R0m, LV (3-5 metastasis)	3	OMD (LN)	na	na	na	na	na	na	na	Start CVD 1.5 years later
22	*HRAS* (somatic)	Pheo	R0 (01), R0 (04), R1 (06)	70	EMD (LN >5)	No, right after surgery	Elevated (noradrenergic)	Decrease	SD	Yes	168 (DOTA)	None	
23	na	mPGL	R0m (BN)	3	OMD (BN)	Yes	Elevated (dopaminergic)	Decrease	PR	Yes	37 (CT/MIBG scan)	43 (CT/MIBG scan)	
24	*SDHB* (germline)	Pheo	R0 (96)	204	EMD (BN >5)	Yes	Elevated (noradrenergic	Decrease	SD	Yes	104 (DOTA)	None	
25	*VHL* (germline)	Pheo	R0 (93)	96	EMD (LG, LN)	Yes	Non-functional	—	SD	Yes	9 years (DOPA)	9 years (DOPA)	Received concurrent SSA for 9 years
26	*SDHB* (germline)	mPheo	R0	17	EMD (BN, LN)	Yes	Elevated (noradrenergic)	Decrease	SD	Yes	18 (CT)	24 (FDG)	
28	na	Pheo	R0	188	EMD (LN)	Yes	Elevated	No response	PD	No	—	4 (DOTA)	
First-line PRRT													
4	*SDHB* (germline)	PGL	R0 (98), R0 (09), mR0 (17)	20 years	EMD (LV, BN, LN)	Yes	Elevate (noradrenergic)	Decrease	SD	Yes	6 (DOTA)	18 (DOTA)	No
9	*SDHB* (germline)	mPGL	R0m, BN, LN	4	EMD (BN, LN)	Yes	Non-functional	—	SD	Yes	6 (DOTA)	14 (DOTA)	2 cycles, then thrombopenia, death 18 months later

(*continued*)

Table 2. Continued

Pat. #	Genetics	Entity at diagnosis	Surgery (R0 vs R1)	Time surgery to start first-line systemic therapy (in months)	Disease burden before first-line systemic therapy	Progressive disease before systemic therapy	Catecholamines at baseline	Response of catecholamines to therapy	DCR at 3 months	SD at 12 months (yes vs no)	Time in months from start therapy to last imaging showing stable disease (imaging modality)	Time in months until documented progression (imaging modality)	Documented side effect/general remarks
13	*SDHB* (germline)	mPGL	R1m	6	EMD (BN >5)	Yes	Elevated (noradrenergic)	No response	SD	No	6 (DOTA)	12 (DOTA)	
33	*SDHD* (germline)	HNPGL	R0	6	EMD (BN, LN)	Yes	Elevate (dopaminergic)	Slight reduction	SD	Yes	10 years (DOTA)	None	
36	Negative (germline)	Pheo	R0	17	EMD (BN, LV)	Yes	Elevated (adrenergic)	na	SD	Yes	33 (DOTA)	None	
37	*SDHB* (germline)	PGL	R0m	5	EMD (BN > 5)	No	na	na	SD	Yes	33 (DOTA)	41 (DOTA)	Initially 2 cycles of PRRT, after progression again 2 cycles of PRRT (stable for now)
38	*SDHB* (germline)	PGL	R1	32	EMD (BN, LG, LN)	Yes	Elevated (dopaminergic)	No response	SD	Yes	4 (DOTA)	12 (DOTA)	1 cycle
48	Negative (somatic)	mPheo	R0	11	OMD (LN)	Yes	na	na	PD	No		4 (FDG)	1 cycle PRRT, in addition SSA
49	Negative (somatic)	HNPGL	R0	18 years	OMD (BN < 5)	Yes	na	na	PD	na	na	na	Lost to follow-up
51	*SDHB* (germline)	PGL	R0 (14), R1m (16)	41	EMD (BN)	Yes	Elevated	Slight reduction	SD	Yes	12	17 (DOTA)	
52	*SDHB* (germline)	mPGL	R1 (debulking)	2	EMD (BN, LN)	Yes	Elevate (noradrenergic)	Slight reduction	SD	na	4 (DOTA)	15 (DOTA)	
55	*SDHB* (germline)	PGL	R0 (94), recurrence R0 (06), R1m (2010)	6 years after first, 3 months after last surgery	EMD (BN; LN)	Yes	Non-functional	Not elevated	SD	Yes	6 years (DOTA)	7 years (DOTA)	
57	na	Pheo	R0 (99), R0 (06), R0m (07)	12 years	Recurrence, EMD (LN)	Yes	Elevated (noradrenergic)	Decrease	SD	Yes	9 (DOTA)	None	
62	*SDHB* (germline)	mPheo	No surgery		ED as metastatic disease (LV >5, LN, BN [2])	Start therapy at diagnosis	Elevated (noradrenergic)	—	—	—	—	—	Start TMZ 1 month after PRRT because not enough tracer in the post scan
64	Negative (germline)	mPheo	R0m	15	OMD (BN)	Yes	Elevated (noradrenergic)	No response	SD	Yes	9 (DOTA)	20 (DOTA)	
65	*SDHB* (germline)	PGL	R0	8 years	EMD (BN, LN, LV)	Yes	Elevated (noradrenergic)	Slight reduction	SD	na	6 (MRI)	14 (DOTA)	
66	Negative (germline)	Pheo	R0	6 years	OMD (LN)	Yes	na	na	SD	Yes	na	45 (DOTA)	
68	*RET* (germline)	mPheo	R0m	4	EMD (LN, LG, LV)	Yes	na	na	PD	No	na	3	1 cycle
29	Negative (germline)	PGL	R0 (93), 3× R0 recurrence resection	26 years	EMD LN (>5), LV	Yes	Elevate (noradrenergic)	Decrease	PR	Yes	12 (DOTA)	18 (DOTA)	Anemia (grade 3) and leucopenia/neutropenia (grade 2)
30	Negative (germline)	mHNPGL	R0m	17	EMD (LG, LN, BN)	Yes	Slightly elevated (dopaminergic)	No response	SD	Yes	12 (DOTA)	23 (DOTA)	
20	*SDHB* (germline)	mPGL	R1m	4	OMD (BN)	Yes	Slightly elevated (noradrenergic)	Decrease	SD	Yes	109 (DOTA)	None	
74	*SDHB* (germline)	mPGL	R0m	5	EMD (BN, LN)	Yes	Elevated (noradrenergic)	No response	SD	No		9 (DOTA)	
73	*HRAS* (somatic)	PGL	R0	45	EMD (LN > 5)	Yes	—	—	SD	No	na	9 (DOTA)	
First-line SSA													
10	*SDHD* (germline)	HNPGL	R0	29 years	Recurrence HNPGL, OMD (BN)	Yes	Non-functional	—	SD	Yes	36 (DOTA)	None	SSA stopped after 2 years due to diarrhea

(*continued*)

Table 2. Continued

Pat. #	Genetics	Entity at diagnosis	Surgery (R0 vs R1)	Time surgery to start first-line systemic therapy (in months)	Disease burden before first-line systemic therapy	Progressive disease before systemic therapy	Catecholamines at baseline	Response of catecholamines to therapy	DCR at 3 months	SD at 12 months (yes vs no)	Time in months from start therapy to last imaging showing stable disease (imaging modality)	Time in months until documented progression (imaging modality)	Documented side effect/general remarks
15	Negative (germline)	HNPGL	R1	9	EMD (LG, LN, LV, BN)	Yes	Non-functional	—	SD	Yes	35 (DOTA)	None	
16	Negative (germline)	HNPGL	No surgery	—	EMD (LN, LG, BN)	Yes	Non-functional	—	SD	Yes	18 (DOTA)	None	
34	*HRAS* (somatic)	Pheo	R0	43	OMD (LN)	No	Non-functional	—	SD	Yes	11 years (DOTA)	None	
50	*SDHA* (germline)	HNPGL	R0	83	EMD (BN)	Yes	na	na	SD	Yes	20 (CT)	23 (CT)	New LV and LG under SSA, regressed under continued SSA, since stable
58	*SDHB* (germline)	PGL	R0	39	OMD (BN)	No	na	na	SD	Yes	na	14	
First-line sunitinib													
5	*SDHB* (germline)	mPGL	R0, remaining BN metastasis	65	EMD (BN, LN)	Yes	Elevated (noradrenergic)	No	SD	Yes	15	18 (FDG)	Hypertension, nausea, dry mouth, white hair, cold hands/feet (grades 1-2)
53	na	mPheo	R1m, BN, LV	Right after surgery	EMD (BN, LV)	No, right after surgery	Elevated (noradrenergic)	—	—	—	—	—	Lost to follow-up
59	Negative (germline)	mPheo	R0 (14), R1m (15) debulking LG, LN (>5)	32	EMD (LG, LN)	Yes	Elevated (noradrenergic)	Decrease	SD	Yes	15 (FDG)	21 (FDG)	Mucositis, diarrhea, weight loss
60	No germline mutations in *VHL, RET, SDHx*	mPheo	R0m (LN >10)	23	EMD (LN)	Yes	Elevated (noradrenergic)	Slight reduction	SD	Yes	24 (FDG)	None	AE grade III, stop after 28 months, patient died afterwards
67	*SDHB* (germline)	Pheo	R0	35	EMD (LN, BN, LG)	Yes	Elevated	Slight reduction, no normalization	SD	Yes	31 (FDG)	34 (FDG)	
69	*SDHB* (germline)	Pheo	R0 (87), R0 (04), R1 HNPGLs 07, 15, 20	34 years after first, 12 after last	Recurrence, OMD (BN)	Yes	Elevated (noradrenergic)	No response	SD	No	6 (FDG)	11 (FDG)	
31	Negative (germline)	Pheo	R1	29	EMD (LG; disseminated), LV (1)	yes	Non-functional	—	SD	No	5 (CT)	7 (CT)	
21	na	mPheo	R0m, LG	16	EMD (LN, LG)	Yes	Elevated (noradrenergic)	Decrease	SD	No	3 (CT)	5 (CT)	Dose reduction due to dyspnea and thrombocytopenia (grade II)

Abbreviations: AE, adverse event; BN, bone metastasis; Ctx, chemotherapy; CVD, cyclophosphamide, vincristine, and dacarbazine; CT, computed tomography; DOPA, ^{18}F-fluoro-L-phenylalanine PET/CT; DOTA, gallium-68-labeled-DOTA-somatostatin receptor analog PET/CT; EMD, extensive metastatic disease (at least 5 metastases in 1 organ or metastases in at least 2 organ systems); FDG, fluorodeoxyglucose PET/CT; LG, lung metastasis; LV, liver metastasis; LN, lymph node metastasis; OMD, oligometastatic disease (<5 metastasis in 1 organ); MIBG, ^{131}I-MIBG therapy; MIBG scan, iodine-123 meta-iodobenzylguanidine (MIBG) scan; MRI, magnetic resonance imaging; na, not available; PD, progressive disease; PR, partial response; PRRT, somatostatin peptide receptor-based radionuclide therapy; R0m, R0 surgery with remaining metastases; R1m, R1 surgery with remaining metastases; SD, stable disease; SSA, somatostatin analogs; TMZ, temozolomide; TKI, tyrosine kinase inhibitor.

Table 3. Treatment response to second-line systemic therapies and individual patient characteristics.

Pat. #	Genetics	Entity at diagnosis	Previous treatment	Time start last treatment to start new treatment (in months)	Disease burden before second-line systemic therapy	Progressive disease before systemic therapy	Catecholamines at baseline	Response of catecholamines to therapy	DCR at 3 months	SD at 12 months (yes vs no)	Time in months from start therapy to last imaging showing stable disease (imaging modality)	Time in months until documented progression (imaging modality)	Documented side effect/general remarks
Second-line CVD													
39	*SDHB* (germline)	mPGL	No surgery, TMZ	45	EMD (BN, LN, LV [2]) progress tumor bulk	Yes	Elevated (dopaminergic)	No	SD	na	3 (FDG)	na	No follow-up
45	Negative (germline)	mPheo	MIBG	12	EMD (LN > 5)	Yes	na	na	SD	Yes	na	24 (FDG)	
68	*RET* (germline)	mPheo	1 cycle PRRT	3	EMD (LG, LV, BN)	Yes	na	na	PD	No		3 (FDG)	Cytopenia
71	na	mPheo	MIBG	18	na	na	na	na	PD	—	—	3	
26	*SDHB* (germline)	mPHeo	MIBG	36	EMD (BN, LN abdominal)	Yes	Elevated (noradrenergic)	Small decrease, then rise again	PR	Yes	15 (FDG)	21 (FDG)	12 cycles CVD afterwards TMZ
21	na	mPheo	SUN	5	EMD (LG >5, fast progress)	Yes	Elevate (noradrenergic)	Decrease	PR	Yes	60 (CT)	—	CVD stop after 12 cycles (SD), 5 years later chemotherapy for pancreatic cancer
Second-line TMZ													
4	*SDHB*(germline)	PGL	PRRT	237	EMD (LV, BN, LN)	Yes	Elevated (noradrenergic)	Decrease	SD	No	5 (CT)	10 (CT)	
74	*SDHB* (germline)	mPGL	PRRT	12	EMD (LN)	Yes	Elevated	Reduction, no normalization	PD	No	—	3 (DOTA)	—
13	*SDHB* (germline)	mPGL	PRRT	20	EMD (BN > 5)	Yes	Elevated (noradrenergic)	Decrease	PR	Yes	6 (DOTA)	14	Dose reduction due to thrombopenia
62	*SDHB* (germline)	mPheo	No surgery, 1 cycle PRRT	1	EMD (LV, LN, BN [2])	Yes	Elevated (noradrenergic)	Decrease	SD	Yes	24 (FDG)	None	
66	Negative (germline)	mPheo	PRRT	36	EMD (LN, LV, BN)	Yes	Elevated (noradrenergic)	No response	PD	No	—	3 (FDG)	
Second-line MIBG													
35	Negative (germline)	HNPGL	Chemotherapy	30	EMD (BN > 5)	Yes	Non-functional	—	SD	Yes	na	14	
Second-line PRRT													
44	Negative (germline)	mPheo	MIBG	35	EMD (BN [>5], LN, multiple LV)	yes	Elevated (noradrenergic)	Decrease	SD	na	6 (DOTA)	18 (DOTA)	
54	Negative for *VHL*, *RET*, *SDHB/D*	mPheo	CVD, 1 × Yttrium 90	12	EMD (LN, LV)	Yes	na	na	SD	No	na	11 (DOTA)	
58	*SDHB* (germline)	M PGL (BN < 5)	SSA	20	EMD (BN, LG)	Yes	na	na	PD	No	—	3 (CT)	Only 1 cycle

(*continued*)

Table 3. Continued

Pat. #	Genetics	Entity at diagnosis	Previous treatment	Time start last treatment to start new treatment (in months)	Disease burden before second-line systemic therapy	Progressive disease before systemic therapy	Catecholamines at baseline	Response of catecholamines to therapy	DCR at 3 months	SD at 12 months (yes vs no)	Time in months from start therapy to last imaging showing stable disease (imaging modality)	Time in months until documented progression (imaging modality)	Documented side effect/general remarks
28	na	Pheo	MIBG (1 cycle)	4	EMD (LN)	Yes	Elevated	Slight reduction	SD	Yes	83 (DOTA)	95 (DOTA)	5 cycles
72	*SDHB* (germline)	mPheo	Neoadjuvant CVD, R1 surgery	18	EMD (LV, LN, BN)	Yes	na	na	SD	Yes	17 (FDG)	20 (FDG)	Liver wedge resection twice during treatment
47	*MAX* (germline)	Pheo	MIBG	316	EMD (BN [>5])	Yes	Elevated (noradrenergic)	Decrease	SD	No	3	8 (DOTA)	
Second-line SSA													
29	Negative (germline)	PGL	PRRT	27	EMD (LN, BN)	Yes (minor)	Elevated (noradrenergic)	Slight reduction	SD	No	3 (DOTA)	7 (DOTA)	
Second-line sunitinib													
6	*SDHB* (germline)	mPGL	CVD	30	EMD (BN, LN), growing primarius	Yes	Non-functional	—	PD	No	—	3 (MRI)	Vomiting, weight loss, fatigue Death 4 months after start SUN
12	*SDHA* (germline)	mPheo	MIBG	120	EMD (BN, LN)	Yes	Elevated (noradrenergic)	Initially no, then slight reduction	SD	Yes	6 (CT)	16 (CT)	Sun dose reduced due to fatigue, dizziness, nausea, loss of appetite
46	Negative (germline)	mPheo	MIBG	26	Recurrence, EMD (BN, LN)	Yes	Slightly elevated (adrenergic)	Slight reduction	SD	Yes	84 (FDG)	None	Sun was given for 3.5 years then stopped
48	Negative (germline and somatic)	mPheo	PRRT	10	EMD (LN)	Yes	na	na	PD	—	—	3 (FDG)	
55	*SDHB* (germline)	mPGL	PRRT	78	EMD (BN, LN)	Yes	Not elevated	—	PR	Yes	25	31 (DOTA)	Afterwards active surveillance, high ECOG
30	Negative (germline)	mHNPGL	PRRT	24	EMD (LG, LN, BN)	Yes	Elevated (dopaminergic)	First reduction, then fast rise	PD	No	—	3 (FDG)	
73	*HRAS* (somatic)	mPGL	PRRT	9	EMD (LN)	Yes	—	—	PD	No	—	3 (DOTA)	
Second-line TKI													
51	*SDHB* (germline)	mPGL	PRRT	Cabozantinib; 19	EMD (BN > 5)	Yes	Elevated	No response	PD	—	—	3 (DOTA)	Hand foot syndrome
59	Negative (germline)	mPheo	Sunitinib	Cabozantinib; 28	EMD (LN > 5)	Yes	Elevate (noradrenergic)	No response	SD	No	8	11	

(*continued*)

Table 3. Continued

Pat. #	Genetics	Entity at diagnosis	Previous treatment	Time start last treatment to start new treatment (in months)	Disease burden before second-line systemic therapy	Progressive disease before systemic therapy	Catecholamines at baseline	Response of catecholamines to therapy	DCR at 3 months	SD at 12 months (yes vs no)	Time in months from start therapy to last imaging showing stable disease (imaging modality)	Time in months until documented progression (imaging modality)	Documented side effect/general remarks
25	*VHL* (germline)	mPheo	MIBG and SSA	Sorafenib, 132	EMD (LG, LV, LN)	Yes	Non-functional	—	SD	Yes	4 (CT)	15 (CT)	Dose reduction due to fatigue, painful hands/scalp, diarrhea, stop after 6 months due to side effects, continued Sandostatin, after progression now stable under SSA

Abbreviations: BN, bone metastasis; Ctx, chemotherapy; CT, computed tomography; CVD, cyclophosphamide, vincristine, and dacarbazine; DOTA, gallium-68-labeled-DOTA-somatostatin receptor analog PET/CT; ECOG, Eastern Cooperative Oncology Group; EMD, extensive metastatic disease (at least 5 metastases in 1 organ or metastases in at least 2 organ systems); FDG, fluorodeoxyglucose PET/CT; LG, lung metastasis; LN, lymph node metastasis; LV, liver metastasis; MIBG, ^{131}I-MIBG therapy; MRI, magnetic resonance imaging; na, not available; OMD, oligometastatic disease (<5 metastasis in 1 organ); PD, progressive disease; PR, partial response; PRRT, somatostatin peptide receptor-based radionuclide therapy; R0m, R0 surgery with remaining metastases; R1m, R1 surgery with remaining metastases; SD, stable disease; SSA, somatostatin analogs; SUN, sunitinib; TKI, tyrosine kinase inhibitor; TMZ, temozolomide.

Table 4. Treatment response to third-line systemic therapies and individual patient characteristics.

Pat. #	Genetics	Entity at diagnosis	Previous treatment	Time start last treatment to start new treatment (in months)	Disease burden before third-line systemic therapy	Progressive disease before systemic therapy	Catecholamines at baseline	Response of catecholamines to therapy	DCR at 3 months	SD at 12 months (yes vs no)	Time in months from start therapy to last imaging showing stable disease (imaging modality)	Time in months until documented progression (imaging modality)	Documented side effect/general remarks
Third-line CVD													
58	*SDHB* (germline)	M PGL	SSA, PRRT	6	EMD (BN, LG, LN)	Yes	na	na	SD	Yes	—	17 (CT)	Dose reduction CKD
Third-line TMZ													
48	Negative (germline and somatic)	mPheo	PRRT, sunitinib	4	EMD (LN < 10)	Yes	na	na	SD	No	3 (FDG)	6 (FDG)	Afterwards again 2 × PRRT as fourth-line (PD)
72	*SDHB* (germline)	mPheo	Neoadjuvant CVD, R1 surgery, PRRT	23	EMD (BN, LV, LN)	Yes	na	na	SD	No	6 (FDG)	8 (FDG)	Afterwards 6 cycles of PRRT, PD after 28 months (imaging and biochemistry), then sunitinib PD in imaging after 8 months
29	Negative (germline)	PGL	PRRT, SSA	8	EMD (LN, LV)	Yes	Elevated	Decrease	PR	na	6 (DOTA)	—	Thrombopenia grade 3
47	*MAX* (germline)	Pheo	MIBG, PRRT	8	EMD (BN, LG, LN)	Yes	Elevated (noradrenergic)	Decrease	SD	na	6		
Third-line PRRT													
59	Negative (germline)	mPheo	Sunitinib, cabozantinib	11	EMD (LN, LG)	Yes	Elevated (noradrenergic)	No response	SD	No	na	6 (DOTA)	Afterwards SSA, everolimus, CVD, paclitaxel and docetaxel for <3 months each with PD
73	*HRAS* (somatic)	mPGL	PRRT, sunitinib	5	EMD (LN)	Yes	—	—	SD	No		6 (DOTA)	Second time PRRT here
35	Negative (germline)	HNPGL	Chemotherapy, MIBG	4 years	EMD (massive burden of BN)	Yes	Non-functional	—	SD	Yes	180 (DOTA)	No	Patient died of another cause
Third-line sunitinib													
13	*SDHB* (germline)	mPGL	PRRT, TMZ	16	EMD (BN >5)	Yes	Elevated (noradrenergic)	No response	PD	–	No	3 (CT)	Dose reduction due to elevated CRP and extreme fatigue, died 9 months after start SUN
45	Negative (germline)	mPheo	MIBG, CVD	24	EMD (LN, LV)	Yes	Not elevated	—	PD	—	—	3 (FDG)	Afterwards 1 cycle MIBG with mixed response
66	Negative (germline)	mPheo	PRRT, TMZ	4	EMD (LV, LN, BN)	Yes	Elevated (noradrenergic)	Slight reduction	PD	No	No	3 (FDG)	Afterwards the patient received pembrolizumab, PD and death within 3 months

(*continued*)

Table 4. Continued

Pat. #	Genetics	Entity at diagnosis	Previous treatment	Time start last treatment to start new treatment (in months)	Disease burden before third-line systemic therapy	Progressive disease before systemic therapy	Catecholamines at baseline	Response of catecholamines to therapy	DCR at 3 months	SD at 12 months (yes vs no)	Time in months from start therapy to last imaging showing stable disease (imaging modality)	Time in months until documented progression (imaging modality)	Documented side effect/general remarks
Third-line TKI/other chemotherapy													
54	Negative for *VHL*, *RET*, *SDHB/D*	mPheo	CVD, 1 × yttrium 90, PRRT	Sorafenib + capecitabine after 12	EMD (LG, LV BN)	Yes	na	na	SD	na	9 (FDG)	None	
68	*RET* (germline)	mPheo	1 cycle PRRT, CVD	Selpercatinib	EMD (LG, LV, BN)	na	na	na	na	na	na	na	
71	na	mPheo	MIBG, CVD	Gemcitabine	na	na	na	na	na	na	na	na	

Abbreviations: BN, bone metastasis; Ctx, chemotherapy; CT, computed tomography; CRP, C-reactive protein; CVD, cyclophosphamide, vincristine, and dacarbazine; DOTA, gallium-68-labeled-DOTA-somatostatin receptor analog PET/CT; EMD, extensive metastatic disease (at least 5 metastases in 1 organ or metastases in at least 2 organ systems); FDG, fluorodeoxyglucose PET/CT; LG, lung metastasis; LV, liver metastasis; LN, lymph node metastasis; MIBG, ^{131}I-MIBG therapy; MRI, magnetic resonance imaging; na, not available; OMD, oligometastatic disease (<5 metastasis in 1 organ); PD, progressive disease; PR, partial response; PRRT, somatostatin peptide receptor-based radionuclide therapy; R0m, R0 surgery with remaining metastases; R1m, R1 surgery with remaining metastases; SD, stable disease; SSA, somatostatin analogs; SUN, sunitinib; TKI, tyrosine kinase inhibitor; TMZ, temozolomide.

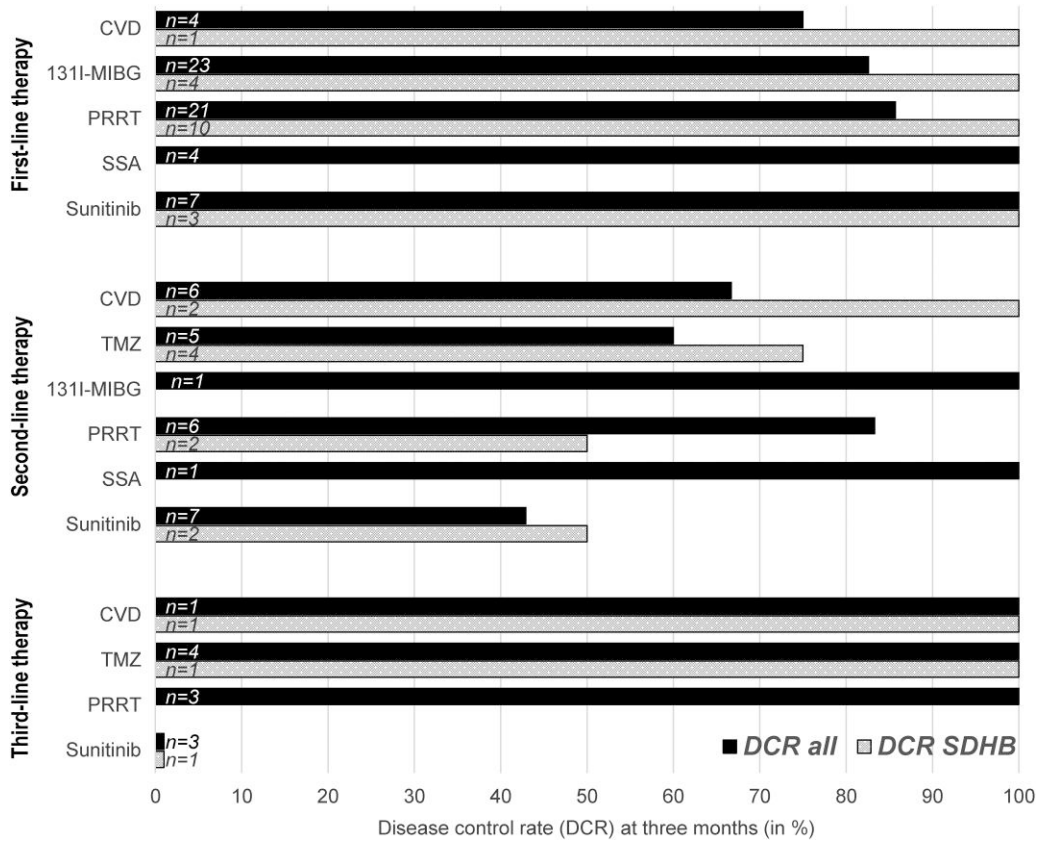

Figure 1. Disease-control rate (DCR) 3 months after start of systemic therapies in mPPGL patients with disease progression at baseline and separately for the subgroup of patients with pathogenic variations in the *SDHB* gene. Abbreviations: CVD, cyclophosphamide, vincristine, and dacarbazine; TMZ, temozolomide; MIBG, ^{131}I-MIBG therapy; PRRT, somatostatin peptide receptor-based radionuclide therapy; SSA, somatostatin analogs.

Table 5. Median survival until detected progression after first-line systemic therapy in mPPGL.

First-line therapy	Median survival until detected progression			Lower limit in months		Upper limit in months		Median survival until detected progression for patients progressive at baseline		
	All	*SDHB*	*SDHA/C/D*	All	*SDHB*	All	*SDHB*	All	*SDHB*	*SDHA/C/D*
CVD	18 ($n=5$)	18 ($n=2$)	—	3	18	30	30	11 ($n=4$)	30 ($n=1$)	—
TMZ	36 ($n=1$)	36 ($n=1$)	—	36	36	36	36	—	—	—
Other Ctx	3 ($n=3$)	NR[a] ($n=1$)	—	3		—		3 ($n=2$)	—	—
^{131}I- MIBG	43 ($n=26$)	24 ($n=4$)	70 ($n=2$)	3	15	168	124	43 ($n=23$)	24 ($n=4$)	70 ($n=2$)
PRRT	18 ($n=21$)	15 ($n=12$)	126 ($n=1$)	3	9	126	109	17 ($n=20$)	14 ($n=10$)	—
SSA	NR[b] ($n=6$)	14 ($n=1$)	30 ($n=2$)	14	14	131	14	NR[b] ($n=4$)	—	30 ($n=2$)
Sunitinib	18 ($n=7$)	18 ($n=3$)	—	5	11	34	34	18 ($n=7$)	18 ($n=3$)	—
Overall	23 ($n=69$)	18 ($n=24$)	—	3	9	168	124	20 ($n=60$)	17 ($n=19$)	—

Abbreviations: Ctx, chemotherapy; CVD, cyclophosphamide, vincristine, and dacarbazine; MIBG, ^{131}I-MIBG therapy; NR, not reached; PRRT, somatostatin peptide receptor-based radionuclide therapy; SSA, somatostatin analogs; TMZ, temozolomide.
[a]Median survival not reached after 174 months.
[b]Median survival not reached, cumulative survival of 75%: 23 months.

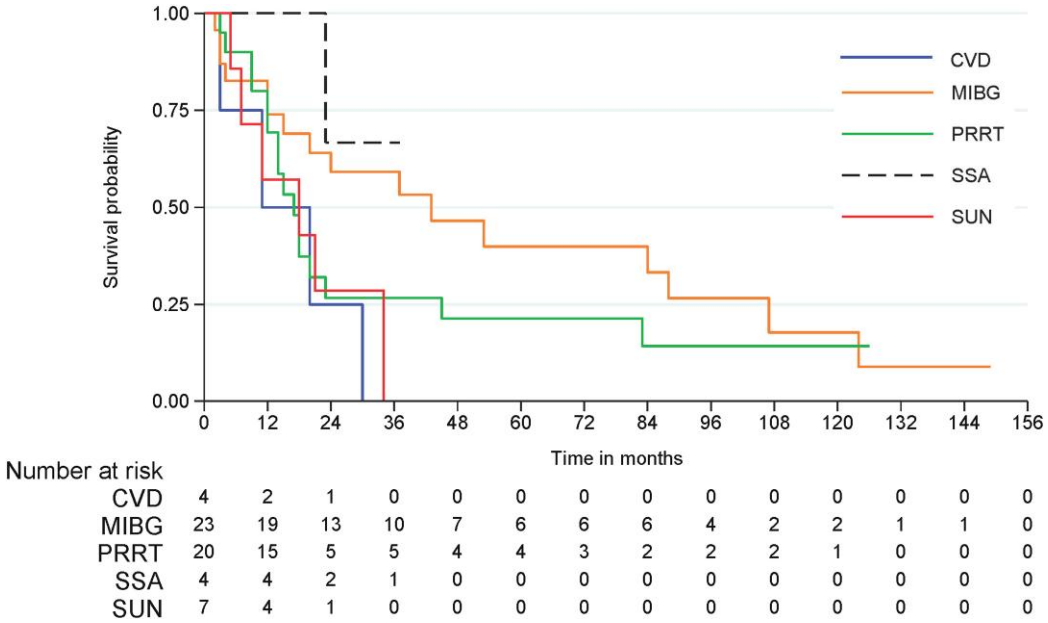

Figure 2. Kaplan–Meier curves for patients with progressive disease at baseline receiving first-line systemic therapies. Abbreviations: CVD, cyclophosphamide, vincristine, and dacarbazine; MIBG, ^{131}I-MIBG therapy; PRRT, somatostatin peptide receptor-based radionuclide therapy; SSA, somatostatin analogs; SUN, sunitinib.

Table 6. Median survival until detected progression after second-line systemic therapy in mPPGL.

Second-line therapy	Median survival until detected progression		Lower limit in months		Upper limit in months	
	All	*SDHB*	All	*SDHB*	All	*SDHB*
CVD	21 ($n=6$)	21 ($n=2$)	3	3	61	21
TMZ	10 ($n=5$)	10 ($n=4$)	3	3	24	24
MIBG	14 ($n=1$)	—	14	—	14	—
PRRT	11 ($n=6$)	3 ($n=2$)	3	3	95	20
SSA	7 ($n=1$)	—	7	—	7	—
Other TKI	11 ($n=3$)	3 ($n=1$)	3	3	15	3
Sunitinib	3 ($n=7$)	3 ($n=2$)	3	3	84	31
Overall	11 ($n=29$)	11 ($n=11$)	3	3	95	31

Other TKIs were cabozantinib ($n=2$) and sorafenib ($n=1$).
Abbreviations: CVD, cyclophosphamide, vincristine, and dacarbazine; MIBG; ^{131}I-MIBG therapy; PRRT, somatostatin peptide receptor-based radionuclide therapy; SSA; somatostatin analogs; TKI, tyrosine kinase inhibitor; TMZ, temozolomide.

Temozolomide

One patient with an *SDHB* mPPGL (not progressive at baseline) received first-line temozolomide and showed a partial response with a SDP of 36 months (cumulative 38 therapy cycles).

Temozolomide as second-line was used to treat 5 patients (all progressive at baseline) with a DCR of 60.0% (*SDHB* [$n=4$]: DCR 75.0%). The median SDP with temozolomide as second-line ($n=5$) was 10 months (*SDHB* [$n=4$]: SDP 10 months).

Other chemotherapies

Other first-line chemotherapies administered included vincristine/ifosfamide/adriamycin/carboplatin according to the GPOH-MET-97 protocol ($n=1$, *SDHB*, stable disease), carboplatin/etoposide ($n=1$, progression), streptozotocin/5-fluorouracil ($n=1$, progression), and cisplatin/etoposide ($n=1$, response not available). The median time until detected progression was short (3 months).

Tyrosine kinase inhibitors

In 8 patients ($n=7$ evaluable, all progressive at baseline) treated with first-line sunitinib, the DCR at 3 months was 100% (*SDHB* [$n=3$]: DCR 100%). The median time until detected progression with sunitinib ($n=7$) was 18 months (*SDHB* [$n=3$]: SDP 18 months).

Sunitinib as second-line was given to 7 patients with a DCR of 42.9% (*SDHB* [$n=2$]: DCR 50%). The median SDP under second-line was shortest with sunitinib ($n=7$: SDP 3 months; *SDHB* [$n=2$]: SDP 3 months).

Three patients received TKIs other than sunitinib as second-line ($n=1$ sorafenib, stable disease, SDP 15 months; $n=2$ cabozantinib: $n=1$ stable disease, SDP 11 months, *SDHB* [$n=1$], progressive disease, SDP 3 months).

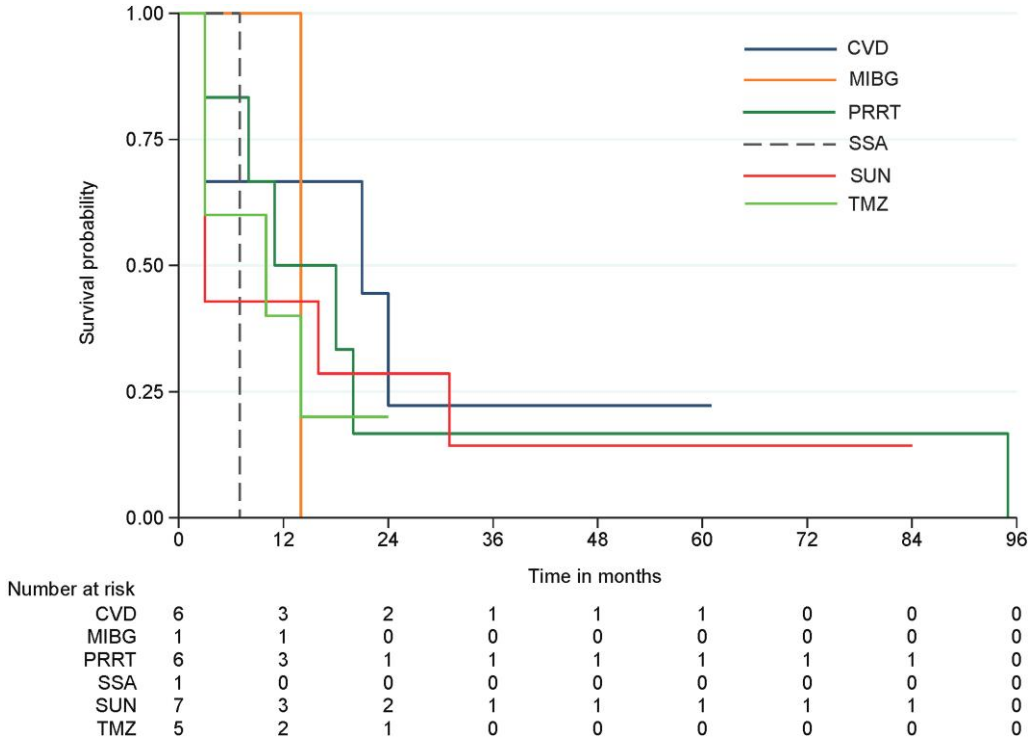

Figure 3. Kaplan–Meier curves for patients with progressive disease at baseline receiving second-line systemic therapies. Abbreviations: CVD, cyclophosphamide, vincristine, and dacarbazine; MIBG, ^{131}I-MIBG therapy; TMZ, temozolomide; PRRT, somatostatin peptide receptor-based radionuclide therapy; SSA, somatostatin analogs; SUN, sunitinib.

Pembrolizumab

One patient with no germline mutation received pembrolizumab as fourth-line systemic therapy and showed disease progression.

Discussion

Prospective or retrospective clinical trials comparing the most commonly applied therapeutic regimens in mPPGLs are very rare. In spite of its retrospective nature, this is the only study that presents data on the DCR and SDP for a variety of systemic treatments, for example, CVD, temozolomide, sunitinib, and "cold" SSTR2 analogs, as well as for radionuclide therapy with ^{131}I-MIBG and PRRT, in a relatively large cohort of mPPGLs, considering the rarity of this tumor entity. Furthermore, we separately present data for the subgroup of *SDHB* tumors and the subgroup of patients progressive at baseline. Interestingly, in a real-life clinical setting, we see a good DCR with all systemic regimens and an especially good DCR in PPGLs with *SDHB* pathogenic variants. Most of the previous studies that included *SDHB* PPGLs did not present data on DCR and SDP for this subgroup separately. A small number of studies have separately reported the response to treatment in *SDHB* tumors for CVD,[27] temozolomide,[28,29] PRRT[30-33], ^{131}I-MIBG therapy,[34,35] TKIs,[36,37] and pembrolizumab.[38]

Radionuclide therapy

Radionuclide therapy with ^{131}I-MIBG or PRRT is a potential first-line therapeutic option for slowly to moderately growing mPPGLs with moderate-to-high tumor burden[3,5,39] ^{131}I-MIBG therapy, including the novel high-specific-activity ^{131}I-MIBG,[35] has shown a DCR of 63%-92% (progression-free survival [PFS] 20.6-28.5 months) in previous studies,[35,40-44] with *SDHB*-related PPGLs being more likely to achieve complete or partial response in 1 study.[35] The DCR was comparable in our study (DCR overall 84.6%, DCR progressive at baseline 82.6%) with a longer median SDP (overall and progressive at baseline 43 months) and an exceptionally high DCR (100%, median SDP 24 months) in the small subgroup of *SDHB*-related mPPGLs.

The DCR with PRRT was ≥80% in most previous studies (PFS 17-39 months).[20,22,31,45-48] In a retrospective study, the DCR after PRRT was longer in *SDHB/SDHD* ($n = 20$) vs wild-type ($n = 16$) mPPGLs (95% vs. 93.8%) with a significantly longer median PFS of the *SDHB/SDHD* group (not reached vs. 51.5 months, $P = .030$).[49] The DCR evaluated at 3 and 6 months after the first cycle of PRRT (DCR overall 82.6%, DCR progressive at baseline 85.7%, *SDHB* 100%) was comparable in our study. However, median SDP (overall 18 months, progressive at baseline 17 months, *SDHB* progressive at baseline 14 months) with PRRT was shorter in our study than in most previous studies. The shorter SDP for PRRT, as compared with ^{131}I-MIBG therapy in our study, might be due to the follow-up with the more sensitive [^{68}Ga]-DOTA-SSA PET/CT in patients treated with PRRT as compared with less sensitive ^{123}I-MIBG imaging. [^{68}Ga]-DOTA-SSA PET/CT was shown to have higher sensitivity to detect tumor growth and new metastases compared with ^{123}I-MIBG imaging, especially in *SDHx* PPGLs.[50,51] In our cohort, 1 patient with an *SDHB* PPGL received standard follow-up imaging with MIBG and was then switched to [^{68}Ga]-DOTA-SSA PET/CT follow-up, where progress of disease was detected. Several prospective clinical trials on PRRT

and ^{131}I-MIBG therapy are currently recruiting (PRRT: NCT03206060, NCT04276597, NCT04711135, NCT04029428; MIBG: NCT00107289, NCT01850888, NCT04770831, NCT00874614 [HSA ^{131}I-MIBG]).

Somatostatin analogs

Data from studies investigating SSA in PPGLs are lacking. However, based on the mechanism of action, PPGLs with high SSTR2 expression (such as *SDHB* PPGLs) might respond well, as previously discussed in Fischer *et al.*[16] and shown in this study, albeit in a small number of patients. A prospective clinical trial (LAMPARA) investigating lanreotide in mPPGL is now recruiting (NCT03946527).

Chemotherapy with CVD and temozolomide

Cyclophosphamide, vincristine, and dacarbazine are frequently applied in rapidly progressive disease with high visceral tumor burden.[5,52] Mostly retrospective studies report a DCR of 48%-100% (PFS 20-40 months) with CVD.[53-56] Cyclophosphamide, vincristine, and dacarbazine have been shown to be specifically effective in the subgroup of PPGLs with *SDHB* pathogenic variants [27] (DCR 100%, PFS 31.2 months). We report a high overall DCR (80.0%, DCR progressive at baseline 75%, *SDHB* 100%). Due to the retrospective nature of our study and missing data, the velocity of progression was not always available. The shorter SDP (overall 18 months, progressive at baseline 11 months, *SDHB* 18 months) in our cohort might be attributed to higher tumor load and progressive disease at baseline.

Temozolomide is an oral alternative to dacarbazine and first- or second-line therapy option for slowly to moderately progressing mPPGLs.[3,52] In a retrospective study, the DCR with temozolomide was 80% (overall PFS 13.3 months, 19.7 months vs 2.9 months in *SDHB* vs non-*SDHB*).[28] Consistent with this, in our study, 1 patient with *SDHB*-related mPPGLs showed a partial response to first-line temozolomide (median SDP 36 months) and in 4 patients with *SDHB*-related disease (all progressive at baseline), the DCR with second-line temozolomide was 75% (median SDP 10 months). Recruiting studies investigating temozolomide vs temozolomide plus olaparib (PARP inhibitor) in mPPGL (NCT04394858) and temozolomide plus talazoparib (another PARP inhibitor) (NCT05142241) are ongoing.

Tyrosine kinase inhibitor

In our study, the TKI sunitinib was mostly used as part of the prospective randomized placebo-controlled FIRST-MAPP study[57]; all other TKIs were used as second- or higher treatment line. According to the results presented at the *ESMO* Congress 2021 of the *FIRST-MAPP* trial investigating sunitinib in progressive PPGLs, the median PFS in the sunitinib group was 8.9 months (33% *SDHB* patients) compared with 3.6 months in the placebo group (23% *SDHB* patients).[57] In another prospective study (SNIPP trial), the DCR with sunitinib was 83% over 3 months (DCR 61% over 6 months) with *SDHx* pathogenic variants showing a DCR of 100% (overall PFS 13.4 months).[37] A retrospective study reported a DCR of 57% with sunitinib over 6 months (PFS 4.1 months).[36] In our study, the DCR with first-line sunitinib (all patients progressive at baseline) was similar to the prospective study (100% over 3 months, median SDP 18 months, *SDHB* [$n = 3$]: DCR over 3 months 100%, median SDP 18 months). Accordingly, in *in vitro* drug testing in human PPGL primary cultures, sunitinib showed best efficacy in *SDHB* tumors.[58] Prospective studies with sunitinib (NCT00843037), cabozantinib (NCT02302833), axitinib (NCT03839498), lenvatinib (NCT03008369), and anlotinib (NCT04860700, NCT05133349) are ongoing.

In order to choose the most appropriate treatment for the patient, not only efficacy but also safety information is important. In Table S2, the most frequent side effects of sunitinib, temozolomide monotherapy, CVD chemotherapy, and SSA are listed. Table S3 presents the side effects observed in the NETTER-1 trial[23] after treatment with PRRT in patients with neuroendocrine tumors and the side effects observed in the study by Pryma *et al.* (2019) evaluating the efficacy and safety of high-specific-activity ^{131}I-MIBG therapy in patients with advanced PHEO or PGL.[19]

Our study has a number of limitations, especially due to its retrospective nature.

The major drawback of our study is the limited number of patients. This makes it difficult to draw general conclusions on the efficacy of the different treatments. One should, however, consider that we investigated treatment modalities in a very rare tumor entity that rarely metastasize and thus require systemic therapy. Due to the scarcity of the tumor entity investigated, prospective trials are extremely hard to conduct and take considerable time to complete. Therefore, multinational retrospective studies, such as ours, are in most cases the only available resource to better understand and assess the different treatment modalities applied in a real-world setting.

However, there are variations in terms of treatment response analysis and follow-up between the centers from 3 different countries, as well as site-to-site variations in choice of first-line treatment based on the experience/availability of certain treatment modalities. Meta-iodobenzylguanidine therapy and PRRT are not strictly comparable as different follow-up protocols were used. Follow-up protocols in published studies on PRRT are also not consistent,[31,32,45,47] which makes comparison of DCR especially difficult. Due to the retrospective nature of this study, several patients were lost to follow-up, some data were incomplete, and newer treatment options such as PRRT or TKIs were not in use at the time of treatment start for some of the patients.

The data based on a limited number of patients do not allow the identification of any single systemic therapy as superior to another for treatment of mPPGLs, including metastatic disease due to *SDHB* pathogenic variants. Furthermore, recommendations on possible treatment sequences are not possible with our data. Our cohort did not include sufficient number of patients with pathogenic variants other than *SDHB* to allow for subgroup analysis. For systemic treatment suggestions for PPGLs harboring germline *SDHD* pathogenic variants, we refer to the recent published guidelines by Taieb and colleagues.[59]

In conclusion, we show in a real-life clinical setting that all currently applied systemic therapies seem to be effective in the case of progressive disease and also in patients with *SDHB* tumors. However, the optimal sequencing of treatments for these patients remains unclear.

Acknowledgments

We thank Prof. Graeme Eisenhofer for reviewing and editing the manuscript.

Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

Funding

This work was in part supported by the German Research Foundation (Deutsche Forschungsgemeinschaft [DFG]) within the CRC/Transregio 205/2, project number: 314061271 – TRR 205 "The Adrenal: Central Relay in Health and Disease" and the Immuno-TargET project under the umbrella of University Medicine Zurich.

Conflict of interest: None declared.

Data availability

Some or all data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Dahia PLM. Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. *Nat Rev Cancer*. 2014;14(2):108-119. https://doi.org/10.1038/nrc3648
2. Patel D, Phay JE, Yen TWF, *et al*. Update on pheochromocytoma and paraganglioma from the SSO endocrine and head and neck disease site working group, part 2 of 2: perioperative management and outcomes of pheochromocytoma and paraganglioma. *Ann Surg Oncol*. 2020;27(5):1338-1347. https://doi.org/10.1245/s10434-020-08221-2
3. Nölting S, Bechmann N, Taieb D, *et al*. Personalized management of pheochromocytoma and paraganglioma. *Endocr Rev*. 2021;43(2):199-239. https://doi.org/10.1210/endrev/bnab019
4. Hescot S, Curras-Freixes M, Deutschbein T, *et al*. Prognosis of malignant pheochromocytoma and paraganglioma (MAPP-Prono study): a European Network for the Study of Adrenal Tumors retrospective study. *J Clin Endocrinol Metab*. 2019;104(6):2367-2374. https://doi.org/10.1210/jc.2018-01968
5. Lenders JWM, Kerstens MN, Amar L, *et al*. Genetics, diagnosis, management and future directions of research of phaeochromocytoma and paraganglioma: a position statement and consensus of the working group on endocrine hypertension of the European Society of Hypertension. *J Hypertens*. 2020;38(8):1443-1456. https://doi.org/10.1097/HJH.0000000000002438
6. Fishbein L, Leshchiner I, Walter V, *et al*. Comprehensive molecular characterization of pheochromocytoma and paraganglioma. *Cancer Cell*. 2017;31(2):181-193. https://doi.org/10.1016/j.ccell.2017.01.001
7. Luchetti A, Walsh D, Rodger F, *et al*. Profiling of somatic mutations in phaeochromocytoma and paraganglioma by targeted next generation sequencing analysis. *Int J Endocrinol*. 2015;2015:1-8. https://doi.org/10.1155/2015/138573
8. Jiang J, Zhang J, Pang Y, *et al*. Sino-European differences in the genetic landscape and clinical presentation of pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab*. 2020;105(10):3295-3307. https://doi.org/10.1210/clinem/dgaa502
9. Wachtel H, Fishbein L. Genetics of pheochromocytoma and paraganglioma. *Curr Opin Endocrinol Diabetes Obes*. 2021;28(3):283-290. https://doi.org/10.1097/MED.0000000000000634
10. Crona J, Lamarca A, Ghosal S, Welin S, Skogseid B, Pacak K. Genotype–phenotype correlations in pheochromocytoma and paraganglioma: a systematic review and individual patient meta-analysis. *Endocr Relat Cancer*. 2019;26(5):539-550. https://doi.org/10.1530/ERC-19-0024
11. Taïeb D, Jha A, Treglia G, Pacak K. Molecular imaging and radionuclide therapy of pheochromocytoma and paraganglioma in the era of genomic characterization of disease subgroups. *Endocr Relat Cancer*. 2019;26(11):R627-R652. https://doi.org/10.1530/ERC-19-0165
12. Loriot C, Burnichon N, Gadessaud N, *et al*. Epithelial to mesenchymal transition is activated in metastatic pheochromocytomas and paragangliomas caused by SDHB gene mutations. *J Clin Endocrinol Metab*. 2012;97(6):E954-E962. https://doi.org/10.1210/jc.2011-3437
13. Letouzé E, Martinelli C, Loriot C, *et al*. SDH mutations establish a hypermethylator phenotype in paraganglioma. *Cancer Cell*. 2013;23(6):739-752. https://doi.org/10.1016/j.ccr.2013.04.018
14. Zethoven M, Martelotto L, Pattison A, *et al*. Single-nuclei and bulk-tissue gene-expression analysis of pheochromocytoma and paraganglioma links disease subtypes with tumor microenvironment. *Nat Commun*. 2022;13(1):6262. https://doi.org/10.1038/s41467-022-34011-3
15. Elston MS, Meyer-Rochow GY, Conaglen HM, *et al*. Increased SSTR2A and SSTR3 expression in succinate dehydrogenase–deficient pheochromocytomas and paragangliomas. *Hum Pathol*. 2015;46(3):390-396. https://doi.org/10.1016/j.humpath.2014.11.012
16. Fischer A, Kloos S, Maccio U, *et al*. Metastatic pheochromocytoma and paraganglioma: somatostatin receptor 2 expression, genetics and therapeutic responses. *J Clin Endocrinol Metab*. 2023;108(10):2676-2685. https://doi.org/10.1210/clinem/dgad166
17. Wang K, Crona J, Beuschlein F, Grossman AB, Pacak K, Nölting S. Targeted therapies in pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab*. 2022;107(11):2963-2972. https://doi.org/10.1210/clinem/dgac471
18. Fishbein L, Del Rivero J, Else T, *et al*. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and management of metastatic and/or unresectable pheochromocytoma and paraganglioma. *Pancreas*. 2021;50(4):469-493. https://doi.org/10.1097/MPA.0000000000001792
19. Pryma DA, Chin BB, Noto RB, *et al*. Efficacy and safety of high-specific-activity ^{131}I-MIBG therapy in patients with advanced pheochromocytoma or paraganglioma. *J Nucl Med*. 2019;60(5):623-630. https://doi.org/10.2967/jnumed.118.217463
20. Kong G, Grozinsky-Glasberg S, Hofman MS, *et al*. Efficacy of peptide receptor radionuclide therapy for functional metastatic paraganglioma and pheochromocytoma. *J Clin Endocrinol Metab*. 2017;102(9):3278-3287. https://doi.org/10.1210/jc.2017-00816
21. Taïeb D, Hicks RJ, Hindié E, *et al*. European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of phaeochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging*. 2019;46(10):2112-2137. https://doi.org/10.1007/s00259-019-04398-1
22. Van Essen M, Krenning EP, De Jong M, Valkema R, Kwekkeboom DJ. Peptide receptor radionuclide therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor positive tumours. *Acta Oncol*. 2007;46(6):723-734. https://doi.org/10.1080/02841860701441848
23. Strosberg J, El-Haddad G, Wolin E, *et al*. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376(2):125-135. https://doi.org/10.1056/NEJMoa1607427
24. Eisenhofer G, Deutschbein T, Constantinescu G, *et al*. Plasma metanephrines and prospective prediction of tumor location, size and mutation type in patients with pheochromocytoma and paraganglioma. *Clin Chem Lab Med CCLM*. 2021;59(2):353-363. https://doi.org/10.1515/cclm-2020-0904
25. Tonsgard JH. Clinical manifestations and management of neurofibromatosis type 1. *Semin Pediatr Neurol*. 2006;13(1):2-7. https://doi.org/10.1016/j.spen.2006.01.005
26. Richards S, Aziz N, Bale S, *et al*. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424. https://doi.org/10.1038/gim.2015.30

27. Jawed I, Velarde M, Därr R, *et al*. Continued tumor reduction of metastatic pheochromocytoma/paraganglioma harboring succinate dehydrogenase subunit B mutations with cyclical chemotherapy. *Cell Mol Neurobiol*. 2018;38(5):1099-1106. https://doi.org/10.1007/s10571-018-0579-4
28. Hadoux J, Favier J, Scoazec JY, *et al*. *SDHB* mutations are associated with response to temozolomide in patients with metastatic pheochromocytoma or paraganglioma: temozolomide for malignant pheochromocytoma/paraganglioma. *Int J Cancer*. 2014;135(11):2711-2720. https://doi.org/10.1002/ijc.28913
29. Perez K, Jacene H, Hornick JL, *et al*. SDHx mutations and temozolomide in malignant pheochromocytoma and paraganglioma. *Endocr Relat Cancer*. 2022;29(9):533-544. https://doi.org/10.1530/ERC-21-0392
30. Pinato DJ, Black JRM, Ramaswami R, Tan TM, Adjogatse D, Sharma R. Peptide receptor radionuclide therapy for metastatic paragangliomas. *Med Oncol*. 2016;33(5):47. https://doi.org/10.1007/s12032-016-0737-9
31. Vyakaranam AR, Crona J, Norlén O, *et al*. Favorable outcome in patients with pheochromocytoma and paraganglioma treated with 177Lu-DOTATATE. *Cancers (Basel)*. 2019;11(7):909. https://doi.org/10.3390/cancers11070909
32. Zandee WT, Feelders RA, Smit Duijzentkunst DA, *et al*. Treatment of inoperable or metastatic paragangliomas and pheochromocytomas with peptide receptor radionuclide therapy using 177Lu-DOTATATE. *Eur J Endocrinol*. 2019;181(1):45-53. https://doi.org/10.1530/EJE-18-0901
33. Kolasinska-Ćwikła A, Pęczkowska M, Ćwikła J, *et al*. A clinical efficacy of PRRT in patients with advanced, nonresectable, paraganglioma-pheochromocytoma, related to SDHx gene mutation. *J Clin Med*. 2019;8(7):952. https://doi.org/10.3390/jcm8070952
34. Fishbein L, Bonner L, Torigian D, *et al*. External beam radiation therapy (EBRT) for patients with malignant pheochromocytoma and non-head and -neck paraganglioma: combination with ^{131}I-MIBG. *Horm Metab Res*. 2012;44(05):405-410. https://doi.org/10.1055/s-0032-1308992
35. Gonias S, Goldsby R, Matthay KK, *et al*. Phase II study of high-dose [^{131}I]metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma. *J Clin Oncol*. 2009;27(25):4162-4168. https://doi.org/10.1200/JCO.2008.21.3496
36. Ayala-Ramirez M, Chougnet CN, Habra MA, *et al*. Treatment with sunitinib for patients with progressive metastatic pheochromocytomas and sympathetic paragangliomas. *J Clin Endocrinol Metab*. 2012;97(11):4040-4050. https://doi.org/10.1210/jc.2012-2356
37. O'Kane GM, Ezzat S, Joshua AM, *et al*. A phase 2 trial of sunitinib in patients with progressive paraganglioma or pheochromocytoma: the SNIPP trial. *Br J Cancer*. 2019;120(12):1113-1119. https://doi.org/10.1038/s41416-019-0474-x
38. Jimenez C, Subbiah V, Stephen B, *et al*. Phase II clinical trial of pembrolizumab in patients with progressive metastatic pheochromocytomas and paragangliomas. *Cancers (Basel)*. 2020;12(8):2307. https://doi.org/10.3390/cancers12082307
39. Nölting S, Ullrich M, Pietzsch J, *et al*. Current management of pheochromocytoma/paraganglioma: a guide for the practicing clinician in the era of precision medicine. *Cancers (Basel)*. 2019;11(10):1505. https://doi.org/10.3390/cancers11101505
40. van Hulsteijn LT, Niemeijer ND, Dekkers OM, Corssmit EPM. ^{131} I-MIBG therapy for malignant paraganglioma and phaeochromocytoma: systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2014;80(4):487-501. https://doi.org/10.1111/cen.12341
41. Nastos K, Cheung VTF, Toumpanakis C, *et al*. Peptide receptor radionuclide treatment and (131)I-MIBG in the management of patients with metastatic/progressive phaeochromocytomas and paragangliomas. *J Surg Oncol*. 2017;115(4):425-434. https://doi.org/10.1002/jso.24553
42. Loh KC, Fitzgerald PA, Matthay KK, Yeo PPB, Price DC. The treatment of malignant pheochromocytoma with iodine-131 metaiodobenzylguanidine (131I-MIBG): a comprehensive review of 116 reported patients. *J Endocrinol Invest*. 1997;20(11):648-658. https://doi.org/10.1007/BF03348026
43. Thorpe MP, Kane A, Zhu J, Morse MA, Wong T, Borges-Neto S. Long-term outcomes of 125 patients with metastatic pheochromocytoma or paraganglioma treated with 131-I MIBG. *J Clin Endocrinol Metab*. 2020;105(3):e494-e501. https://doi.org/10.1210/clinem/dgz074
44. Wakabayashi H, Inaki A, Yoshimura K, *et al*. A phase I clinical trial for [131I]meta-iodobenzylguanidine therapy in patients with refractory pheochromocytoma and paraganglioma. *Sci Rep*. 2019;9(1):7625. https://doi.org/10.1038/s41598-019-43880-6
45. Forrer F, Riedweg I, Maecke HR, Mueller-Brand J. Radiolabeled DOTATOC in patients with advanced paraganglioma and pheochromocytoma. *Q J Nucl Med Mol Imaging*. 2008;52(4):334-340.
46. Satapathy S, Mittal BR, Bhansali A. Peptide receptor radionuclide therapy in the management of advanced pheochromocytoma and paraganglioma: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2019;91(6):718-727. https://doi.org/10.1111/cen.14106
47. Jaiswal SK, Sarathi V, Memon SS, *et al*. 177Lu-DOTATATE therapy in metastatic/inoperable pheochromocytoma-paraganglioma. *Endocr Connect*. 2020;9(9):864-873. https://doi.org/10.1530/EC-20-0292
48. Roll W, Müther M, Sporns PB, *et al*. Somatostatin receptor–targeted radioligand therapy in head and neck paraganglioma. *World Neurosurg*. 2020;143:e391-e399. https://doi.org/10.1016/j.wneu.2020.07.165
49. Severi S, Bongiovanni A, Ferrara M, *et al*. Peptide receptor radionuclide therapy in patients with metastatic progressive pheochromocytoma and paraganglioma: long-term toxicity, efficacy and prognostic biomarker data of phase II clinical trials. *ESMO Open*. 2021;6(4):100171. https://doi.org/10.1016/j.esmoop.2021.100171
50. Fonte JS, Robles JF, Chen CC, *et al*. False-negative 123I-MIBG SPECT is most commonly found in SDHB-related pheochromocytoma or paraganglioma with high frequency to develop metastatic disease. *Endocr Relat Cancer*. 2012;19(1):83-93. https://doi.org/10.1530/ERC-11-0243
51. Petenuci J, Fagundes GFC, Benedetti AFF, *et al*. SDHB large deletions are associated with absence of MIBG uptake in metastatic lesions of malignant paragangliomas. *Endocrine*. 2021;72(2):586-590. https://doi.org/10.1007/s12020-020-02594-w
52. Fassnacht M, Assie G, Baudin E, *et al*. Adrenocortical carcinomas and malignant phaeochromocytomas: ESMO–EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(11):1476-1490. https://doi.org/10.1016/j.annonc.2020.08.2099
53. Niemeijer ND, Alblas G, van Hulsteijn LT, Dekkers OM, Corssmit EPM. Chemotherapy with cyclophosphamide, vincristine and dacarbazine for malignant paraganglioma and pheochromocytoma: systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2014;81(5):642-651. https://doi.org/10.1111/cen.12542
54. Ayala-Ramirez M, Feng L, Habra MA, *et al*. Clinical benefits of systemic chemotherapy for patients with metastatic pheochromocytomas or sympathetic extra-adrenal paragangliomas: insights from the largest single-institutional experience. *Cancer*. 2012;118(11):2804-2812. https://doi.org/10.1002/cncr.26577
55. Deutschbein T, Fassnacht M, Weismann D, Reincke M, Mann K, Petersenn S. Treatment of malignant phaeochromocytoma with a combination of cyclophosphamide, vincristine and dacarbazine: own experience and overview of the contemporary literature. *Clin Endocrinol (Oxf)*. 2015;82(1):84-90. https://doi.org/10.1111/cen.12590
56. Averbuch SD. Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. *Ann Intern Med*. 1988;109(4):267. https://doi.org/10.7326/0003-4819-109-4-267

57. Baudin E, Goichot B, Berruti A, *et al*. First international randomized study in malignant progressive pheochromocytoma and paragangliomas (FIRSTMAPPP): an academic double-blind trial investigating sunitinib. *Ann Oncol*. 2021;32(suppl_5):S621-S625. https://doi.org/10.1016/j.annonc.2021.08.702
58. Wang K, Schütze I, Gulde S, *et al*. Personalized drug testing in human pheochromocytoma/paraganglioma primary cultures. *Endocr Relat Cancer*. 2022;29(6):285-306. https://doi.org/10.1530/ERC-21-0355
59. Taïeb D, Wanna GB, Ahmad M, *et al*. Clinical consensus guideline on the management of phaeochromocytoma and paraganglioma in patients harbouring germline SDHD pathogenic variants. *Lancet Diabetes Endocrinol*. 2023;11(5):345-361. https://doi.org/10.1016/S2213-8587(23)00038-4