Supplementary Appendix 'Clinical guideline on the management of pheochromocytoma and paraganglioma in patients harboring germline pathogenic variants in the succinate dehydrogenase subunit D gene'

Supplemental Table 1. Transient and permanent side effects after stereotactic radiosurgery

Side effects	CK (transient)	CK (permanent)	LINAC (transient)	LINAC (permanent)	Gamma Knife Surgery (transient)	Gamma Knife Surgery (permanent)
N, V	0%	0%	46.2%	0%	2.1%	0%
CN V	0%	0%	0%	0%	6.5%	0%
CN VII	0%	0%	38.5%	0.1%	10.8%	0.57%
CN VIII (hearing loss)	0%	0%	0%	0.1%	2.1%	1.28%
CN X	0%	0%	0%	0%	6.5%	0.57%
CN XII	0%	0%	15.3%	0%	0%	0%
Total % of side effects	0.9%	0.1%	4.8%	0.7%	6.7%	3%

Side effects of stereotactic radiosurgery noted specifically for HNPGLs – adapted from Fatima et al., 2021.[1]

Supplemental Table 2. Summary of clinical studies investigating systemic therapies

Author	Therapy (retrospective study if not indicated otherwise)	Patient number (n) (disease status at treatment start)	Complete response	Partial response	Stable disease	Median overall survival (OS)/ progression free survival (PFS)/time to progression (TTP)
Nastos et al., 2017[2]	[^{90}Y]/[^{177}Lu]-DOTATATE (PRRT) (2 patients with PGLs [^{177}Lu]-DOTATATE) vs. [^{131}I]-MIBG	N=22 patients, n=7 PHEOs, n=15 PGLs (n=5 *SDHB*, no *SDHD*) n=9 [^{90}Y]/[^{177}Lu]-DOTATATE (n=1 PHEO, n=8 PGLs) n=11 [^{131}I]-MIBG (n=6 PHEOs, n=5 PGLs), n=2 combination (n=2 PGLs) (not all progressive)		Disease control rate (response plus stable disease) to several cycles of treatment: [^{90}Y]/[^{177}Lu]-DOTATATE 100% (13/13) vs. [^{131}I]-MIBG: 63% (10/16) Sub-group PGLs: [^{90}Y]/[^{177}Lu]-DOTATATE 100% (13/13) vs. [^{131}I]-MIBG 50% (4/8)		OS/PFS [^{90}Y]/[^{177}Lu]-DOTATATE 60.8/38.5 months vs. OS/PFS ^{131}I]-MIBG 41.2/20.6 months Sub-group PGLs: OS/PFS [^{90}Y]/[^{177}Lu]-DOTATATE 60.8/38.5 months vs. OS/PFS [^{131}I]-MIBG 22.8/14.4 months (p<0,05)
Imhof et al. 2011[3]	[^{90}Y] DOTATOC (phase II, prospective)	N=39 (n=11 PHEOs, n=28 PGLs) (all progressive disease), genetic results not provided	ns	18%	ns	Mean OS in PHEO/PGL 32/82 months
Puranik et al., 2015[4]	[^{90}Y]-DOTATOC n=4 combined with ^{177}[Lu]-DOTATATE (prospective)	N=9 HNPGLs (n=4 solitary tumor, n=4 multiple tumors, n=1 metastatic disease) Genetic results not provided	0%	0%	100% (including 44% minor/minimal response)	-
Kolasinska-Cwikla et al., 2019[5]	[^{90}Y]-DOTATATE (prospective) (3.3GBq/cycle and 9.9GBq cumulative)	N=13 (n=5 *SDHB*, n=8 *SDHD*) (all progressive disease)	0%	8% (6 months)	75% (6 months)	PFS/OS total 35/68 months (*SDHB* subgroup 12/25 months, *SDHD* subgroup not reached/not reached)
Taieb et al., 2019[6]	[^{90}Y]/ ^{177}[Lu]-DOTATATE	Meta-analysis from 13 studies n= 234 (n=166 (71%) with progressive disease), n=21 *SDHB,* n=24 *SDHD*			Disease control rate (partial response plus stable disease): 90%	
Satapathy et al., 2019[7]	^{177}[Lu]/[^{90}Y]-DOTATATE, [^{90}Y]-DOTATOC	Meta-analysis from 12 studies: n= 201, n=22 *SDHB*, n=12 *SDHD*		Overall response rate 25% (n=179)	Disease control rate 84% (n=151)	-
Zovato et al., 2012[8]	[^{177}Lu]-DOTATATE	N=4 PGLs (all with *SDHD* PV) (n=2 thoracic PGLs, n=2 HNPGLs) (all progressive disease at baseline) (non-metastatic)	0%	50%	50%	-
Jaiswal et al., 2020[9]	^{177}[Lu]-DOTATATE	N=15 [n=4 PHEOs, n=4 sympathetic PGLs (n=1 *SDHB*), n=5 HNPGLs, n= 1 PHEO + sympathetic PGL, n=1 HNPGL +	0%	7%	73%	PFS/OS not reached after 27 months; very good response of the *SDHD*-mutated HNPGL

		sympathetic PGL (*SDHD*)] (not all progressive)				
Zandee et al., 2019[10]	^{177}[Lu]-DOTATATE 7.4GBq x 4 but up to 11 cycles	N=30 (n=17 parasympathetic PGLs with n=11 *SDHD*, n=10 sympathetic PGLs with n=5 *SDHB*, n=3 PHEOs) (not all progressive)	0%	23%	67%	PFS total 30 months, PFS in parasympathetic (65% *SDHD*) PGLs/sympathetic PGLs (50% *SDHB*)/PHEOs 91/13/10 months, respectively
Van Essen et al., 2006[11]	[^{177}Lu] DOTATATE	N=12 (n=11 evaluable) (n=1 PHEO, n=5 HNPGLs, n=6 other PGLs) (not all progressive), genetics not provided	0%	18% (2/11)	55% (5/11)	TTP 11 and 15 months, respectively in 2 patients, median TTP to progression not reached in PGL patients
Severi et al., 2021[12]	[^{177}Lu] DOTATATE (cumulative 24.4GBq) [^{90}Y] DOTATATE (cumulative 9.2 GBq) prospective	N=46 (n=16 no PV/n=20 *SDHB*/*SDHD*) (n=16 sympathetic and n=30 parasympathetic). [may not have had progression]	0% overall 0% ^{90}Y 0%^{177}Lu	8.7% 8.3% 8.9%	71.7% 66.7% 73.5%	OS 142 months, PFS not reached. ^{90}Y OS 92 months ^{177}Lu OS 143 months
Forrer et al., 2008[13]	[^{90}Y] DOTATOC, 3 combined with [^{177}Lu] DOTATATE	N=28 (n=9 PHEO, n=19 PGL) (all progressive disease at baseline) genetics not provided	0%	7%	64%	TTP 3 to > 42 months, median TTP 18+/- 14 (6-44) months
Kong et al., 2017[14]	[^{177}Lu]-DOTATATE, 9 combined with radiosensitizing chemotherapy	N=20 (n=8 PHEO, n=5 HNPGLs, n=5 abd. PGLs, n=2 HN plus abd. PGLs) (n=7 *SDHB,* n=1 *SDHD*, n=2 no PV, n=10 unknown) (not all progressive)	0%	29%	57%	PFS 39 months, OS not reached
Pinato et al., 2016[15]	^{177}[Lu]-DOTATATE	N=5 abd. PGLs (n=5 *SDHB*, no *SDHD*) (all progressive disease at baseline)	0%	20%	60%	PFS 17 (0-78) months/mean OS 53 months (median OS not reached)
Yadav et al., 2019[16]	^{177}[Lu]-DOTATATE plus capecitabine	N=25 PGLs (not all progressive) genetics not provided	0%	28%	56%	PFS 32 months, OS not reached
Vyakaranam et al., 2019[17]	^{177}[Lu]-DOTATATE 7.4GBq x 4	N=22 (n=11 sympathetic PGLs, n= 2 HNPGLs, n=9 PHEOs) (n=4 *SDHB*, no *SDHD*, n=9 not tested) (not all disease progression)	0%	9%	91%	PFS 21.6 months/OS 49.6 (Ki-67 > 15%: negative predictive factor for PFS/OS)
Hamiditabar et al., 2017[18]	^{177}[Lu]-DOTATATE (prospective)	N=5 [not reported if progressive], genetics not provided			Disease control rate/stable disease 80% (n=4/5)	
Garske-Roman et al., 2018[19]	^{177}[Lu]-DOTATATE (prospective)	N=5 [not all progressive], genetics not provided			Disease control rate/stable disease 100% (n=5/5)	PFS 14 months, OS 37 months

Demirci et al., 2018[20]	^{177}[Lu]-DOTATATE	N=12 [not reported if progressive], genetics not provided	0%	50%	25%	PFS (mean): 31.4 months OS (mean): 51.8 months
Parghane et al., 2020	[^{177}Lu] DOTATATE 5.5-7.4 GBq/cycle, mean 24.4 GBq cumulative	N=9 PGL (all MIBG neg), n=5 HNPGLs, n=4 other PGLs [not all progressive] genetics not provided	0%	11%	56% (including 22% with minor/minimal response)	OS or PFS median not reached at 40 months, 63% PFS at 40 months/65% OS at 40 months
Roll et al., 2020	^{177}[Lu]-DOTATATE	N=7, n=1 *SDHB,* no *SDHD* [not all progressive]		57%	43% (disease control rate 100%)	
Gonias et al., 2009[21]	[^{131}I]-MIBG (phase II, prospective)	N=50 (n=49 evaluable, n=15 PHEOs, n=34 PGLs), n=12 *SDHB* PV (predictive for partial or complete response), *SDHD* status not available (not stated if progressive disease)	8%	14%	43%	5-year OS 64%, predictors of poor OS: Prior chemotherapy, female sex
Fishbein et al, 2012[22]	EBRT and [^{131}I]-MIBG, retrospective	n=5 EBRT and I-131 MIBG. (n=3 *SDHB,* n=2 not tested, no known *SDHD*) [not stated if progressive disease]	0	0	0	PFS *SDHB* 3.6-21.5 m OS *SDHB* 17.7-23.5
Van Hulsteijn et al., 2014[23]	[^{131}I]-MIBG	Meta-analysis from 17 studies: n= 243 (n=99 PHEOs, n=47 PGLs, n=2 HNPGLs), no *SDHD*, n=15 *SDHB* PV	3% [slightly larger pooled proportions of complete response for PGLs (4%) than for PHEOs (1%)]	27% [slightly larger pooled proportions of partial response for PGLs (30%) than for PHEOs (28%)]	52%	PFS in 2 studies 23.1 and 28.5 months, respectively
Loh et al., 1997[24]	[^{131}I]-MIBG	Meta-analysis n=116 (n=86 documented tumor site, n=66 PHEOs, n=18 PGLs, n=2 PHEO plus PGL) genetics not provided	4%	26%	57%	OS responders/non-responders: 22/13 months
Thorpe et al., 2020[25]	[^{131}I]-MIBG	N=125 (n=88 evaluable, n=73 PHEOs, n=52 PGLs), (all progressive) genetics not provided	1%	33%	53%	PFS 2 years, OS responders vs. non-responders 6.3/2.4 years
Wakabayashi et al., 2019[26]	[^{131}I]-MIBG (phase I, prospective)	N=20 (n=13 PHEOs, n=7 PGLs), best overall response for PGL: stable disease (not all disease progression) genetics not provided	10%		65%	6-months OS/PFS 100%/80%
Noto et al., 2018[27]	HSA [^{131}I]-MIBG (phase I, prospective)	N=21 (n=10 PHEOs, n=11 PGLs) (not all disease progression) genetics not provided		19%	61.9%	2-year OS 62%
Pryma et al. 2019[28]	HSA [^{131}I]-MIBG (phase II, prospective)	N=68 (evaluable n=64) patients (n=53 PHEOs, n=21 PGLs) (not all disease progression) genetics not provided	0%	23%	69%	OS 36.7 months: 18 months after one cycle / 44 months after two cycles
Averbuch et al., 1988[29]	CVD chemotherapy (prospective)	N=14 genetics not provided		57% (complete plus partial response)		PFS 21 months (7 to >34 months)
Huang et al., 2008[30]	CVD chemotherapy (prospective)	N=18 (n=3 *SDHB*, n=2 possible *SDHB*, n=4 *SDHB* or *SDHD*, n=1 *SDHD*)	11%	44%	44% (including 16% with minor/mini	OS responders/non-responders 3.8/1.8 years

					mal response)	
Niemeijer et al, 2014[31]	CVD chemotherapy	Meta-analysis from 4 studies: n=50 (n=3 *SDHB*, n=2 possible *SDHB*, n=4 *SDHB* or *SDHD*, n=1 *SDHD*)	4% (0-11%)	37% (24-50%)	14% (0-24%)	PFS in 2 studies 20 and 40 months, respectively
Asai et al., 2017[32]	CVD chemotherapy	N=23 genetics not provided	4%	22%	22%	OS/PFS responders vs. non-responders 4.6 vs. 2 years/1.7 vs. 0.3 years, respectively
Deutschbein et al., 2015[33]	CVD chemotherapy	N=8 genetics not provided	0%	25%	38%	PFS 5.4 months (2.5-26.8 months)
Tanabe et al., 2013[34]	CVD chemotherapy	N=17 genetics not provided	0%	24%	47% (including 23% with minor/minimal response)	PFS responders 40 months (31-60 months), 50% survival: Responders (n=8) 6 years, stable disease (n=4) 4 years, progressive disease (n=5) 3 years
Jawed et al., 2018[35]	Prolonged CVD chemotherapy (median 20,5 cycles, 4-41 cycles)	N=12 (all with *SDHB* PV, all metastatic), tumor shrinkage in all patients (12%-100% by RECIST)	16,7% (2/12)	66.7% (8/12)	16,7% (2/12) (minor/minimal response)	OS/PFS 3.3/2.6 years (1190/930 days)
Ayala-Ramirez et al., 2012[36]	Different chemotherapy regimens	N=54 (n=52 evaluable, n=4 *SDHB*, n=1 *SDHC*, no known *SDHD)* (all progressive disease at baseline), 100% of responders: schemes included cyclophosphamide and dacarbazine, 82% of responders: schemes included vincristine		33% (17/52) symptomatic or morphological response, 25% (13/52) morphological response, none of the *SDHB*-mutated patients in the group of responders		OS responders/non-responders 6.4/3.7 years
Hadoux et al., 2014[37]	Temozolomide monotherapy	N=15 (n=14 evaluable) (n=10 with *SDHB* PV, no *SDHD*), all metastatic, all responders *SDHB*-mutated	0%	33% (5/14) (RECIST plus PERCIST)	47% (7/14) (RECIST plus PERCIST)	PFS 13.3 months, significantly longer in patients with *SDHB* pathogenic variant (19.7 vs. 2.9 months)
Tena et al., 2018[38]	Metronomic low dose temozolomide plus high dose Lanreotide Autogel (pre-treated with CVD)	N=2 (n=2 *SDHB*, no *SDHD*) (case reports)	0%	0%	100%	OS (n=2) not reached, PFS 13 months (n=1), PFS not reached after 27 months (n=1)
Baudin et al, 2021, (ESMO 2021, abstract)[39]	TKI sunitinib (FIRST-MAPP study), first randomized placebo-controlled clinical trial in PPGL	N=78 (50% PHEO, 50% PGL), all metastatic and progressive at baseline, 32% (n=22) *SDHB:* 33% (n=13) sunitinib group, 23% (n=9) placebo group, *SDHC*: 3% (n=1) sunitinib group, no *SDHD*			35.9% (partial response or stable disease after 12 months)	PFS 8.9 months (sunitinib) vs. 3.6 (placebo), PFS 12 months: 35.9% sunitinib group vs. 18.9% placebo group
O`Kane et al., 2019[40]	TKI sunitinib, SNIPP (phase II, prospective),	N=25 (n=14 PHEOs, n=11 PGLs, n=5 *SDHB*, n=1 *SDHA*,	0%	13% (3/23) (2/3 *SDHA/B* PV) >	70% (16/23) > 12 weeks	PFS 13.4 months

	sunitinib 50 mg for 4 weeks, 2 weeks off treatment (50% requiring dose reduction)	n=1 *SDHC,* no known *SDHD*, n=23 evaluable) (all patients with *SDHx* PV partial response or stable disease)		12 weeks/3 months	(disease control rate after 24 weeks/6 months 61%)	
Ayala-Ramirez et al., 2012[41]	TKI sunitinib (retrospective) (n=1 sunitinib plus rapamycin in reduced doses with PFS not reached)	N=17 (n=14 evaluable, n=8 *SDHB* PV, no *SDHD*), all metastatic, all rapidly progressive at baseline	0%	21% (3/14) (1/3 *SDHB* PV) > 4 months	36% (5/14) (4/5 *SDHB* PV) > 6 months	PFS 4.1 months (62.5% (5/8) with stable disease or partial response *SDHB* carriers)
Jimenez et al. 2017 (5th International Symposium on Pheochromocytoma and Paraganglioma 2017, abstract)	TKI cabozantinib (phase II, prospective) 60/40/20 mg cabozantinib	N=10 (n=5 *SDHB* PV, no *SDHD*)		40% > 3 months, all *SDHB*-mutated PPGLs partial/minor response (partial/minor response > 3 months 90%, partial/minor response > 6 months 70%, partial/minor response >12 months 30%)	50% > 3 months, all minor response	PFS 11.1 months (0.9-28 months)
NCT01967576 (completed, preliminary data)	TKI axitinib (phase II, prospective), axitinib 5 mg 2x/d, 28-day-cycles	N=14 (n=12 evaluable) genetics not provided	0%	41.7%	41.7%	PFS 7.7 months (3.3.-16.8 months)
Jasim et al., 2017[42]	TKI pazopanib (phase II, prospective) cycle 1: 400 mg daily d 1-14, cycle 2: 800 mg daily d 1-14, and then cycle 2 +: 800 mg daily on all days	N=7 (6 evaluable) genetics not provided		17% (1/6) over 2.4 years		PFS/OS 6.5/14.8 months
Oh et al., 2012[43]	MTORC1 inhibitor everolimus (phase II, prospective)	N=7 (n=5 PHEOs, n=2 PGLs) genetics not provided	0%	0%	71% (5/7)	PFS 3.8 months
Druce et al., 2009[44]	MTORC1 inhibitor everolimus (10 mg/d)	N=4 (n=2 no *SDHx* PV, n=2 not tested, no known *SDHD*)	0%	0%	25% (1/4) (stable disease for 3 months)	PFS 3 months (n=1)
Naing et al., 2020[45]	Pembrolizumab (phase II, prospective)	N=9 (n=8 evaluable) genetics not provided	0%	0%	75%	27-weeks PFS 43%
Jimenez et al., 2020[46]	Pembrolizumab (phase II, prospective)	N=11 (n=2 *SDHB*, n=1 *SDHD*)		9%	64% (≥ 4 months)	PFS 5.7 months (4.37 months - not reached) (n=1 *SDHD* stable disease for 24 months, n=1 *SDHB* tumor shrinkage >30%)

Reported minor/minimal response is included in "Stable disease"; For each study, it is indicated if HNPGL and *SDHD*- or *SDHB*-mutated tumors have been included and if data are given separately for this group, or if genetic data was not provided. *SDHx*: pathogenic germline variant in one of the genes encoding for the four subunits of the SDH enzyme. PV for pathogenic variant.

Supplemental Table 3: Adverse effects of targeted internal radiotherapy

Conventional low-specific-activity (LSA) MIBG, high-dose (>12 mCi/kg), meta-analysis [6,23]	87% grade 3/4 neutropenia (required growth factor), 83% grade 3/4 thrombocytopenia (required platelet transfusion), myelodysplastic syndrome 4% (especially together with chemotherapy), hypothyroidism (11-20%), acute respiratory distress syndrome, bronchiolitis obliterans, hypertension, hypogonadism, rarely: renal failure, hypertensive crisis (despite alpha-blockade), hepatotoxicity.	
Conventional low-specific-activity (LSA) MIBG, low-dose (149 mCi total dose) [6]	well-tolerated, hypothyroidism (11-20%), hypogonadism	
High-specific-activity (HSA) MIBG [28]	Prolonged myelosuppression, 90% hematologic adverse events - with grade 3/4 adverse events or other severe adverse events in 72% of patients, 25% required hematological supportive care, 19% hematologic toxicity serious adverse events, 3% lung embolism, 4% myelodysplastic syndrome, AML 1.5%, ALL 1.5%	
PRRT	Adverse events in one meta-analysis (n=234): [6] Myelodysplastic syndrome (MDS) 1.4-2.2%, nephrotoxicity 0-1.5%, grade 3/4 hematologic toxicity 9.5-11.3%. Incidence for PRRT-related myelodysplastic syndrome from NET studies: 2%.[47,48]	Adverse events in another meta-analysis (n=201) [7]: Nephrotoxicity 4%, grade 3/4 neutropenia, thrombocytopenia, lymphopenia in 3%, 9% and 11% of the patients, respectively.

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