ISP and PPGL Update

April 2023

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SDHB PHEOPARACOALITION

Highly heritable, multiple genes…..

Table 1 | Genes and diseases

Disease (phenotype MIM numbers)	Genes	Mutation rate (%)*	Main features
Neurofibromatosis type 1 (162200)	*NF1*	3	Café-au-lait spots, neurofibromas, axillary and inguinal freckling, Lisch nodules, osseous lesions, optic gliomas, mainly phaeochromocytomas
Multiple endocrine neoplasia type 2 (171400; 162300)	*RET*	6	2A: Medullary thyroid cancer, primary hyperparathyroidism, PPGL 2B: Medullary thyroid cancer, PPGL, Marfanoid habitus, mucocutaneous neuromas, gastrointestinal ganglioneuromatosis
von Hippel–Lindau disease (193300)	*VHL*	7	Central nervous system or retinal haemangioblastomas, renal cell carcinoma, PPGL, pancreatic neuroendocrine tumours and cysts, endolymphatic sac tumours, papillary cystadenoma of the epididymis and broad ligament
Hereditary paragangliomas (168000; 605373; 115310; 601650; 614165)	SDHx genes:		
	SDHB	10	PPGL, rare renal cancers, GIST
	SDHD	9	PPGL, rare renal cancers, GIST
	SDHC	1	PPGL, rare renal cancers, GIST
	SDHA	<1	PPGL, GIST
	SDHAF2	<0.1	Head and neck paraganglioma
Familial phaeochromocytomas (173300; 613403; 154950)	*TMEM127*	1	Mainly phaeochromocytomas, rare renal cancers
	MAX	1	Mainly PPGL
Polycythemia paraganglioma syndrome (603349)	*EPAS1*	1	Polycythemia, PPGL, somatostatinoma
Leiomyomatosis and renal cell cancer (150800)	*FH*	1	Cutaneous and uterine leiomyomas, type 2 papillary renal carcinoma, rare PPGL

*The mutation rate is the percentage of patients with PPGL with mutations in the gene concerned. Abbreviations: GIST, gastric stromal tumours; MIM, Mendelian Inheritance in Man; PPGL, paraganglioma and/or phaeochromocytoma.

Gene	Inheritance	Locus	Associated tumors/ features
DNMT3A	Autosomal dominant	2p23.3	Gain-of-function mutations: H&N PGL
DLST	Autosomal dominant	14q24.3	PGL (multiple) >> PCC
SUCLG2[a]	ND	3p14.1	PCC >>>> pPGL
MAML3 fusions	Sporadic	4q31.1	PCC
RET fusions	Sporadic	10q11.21	PCC

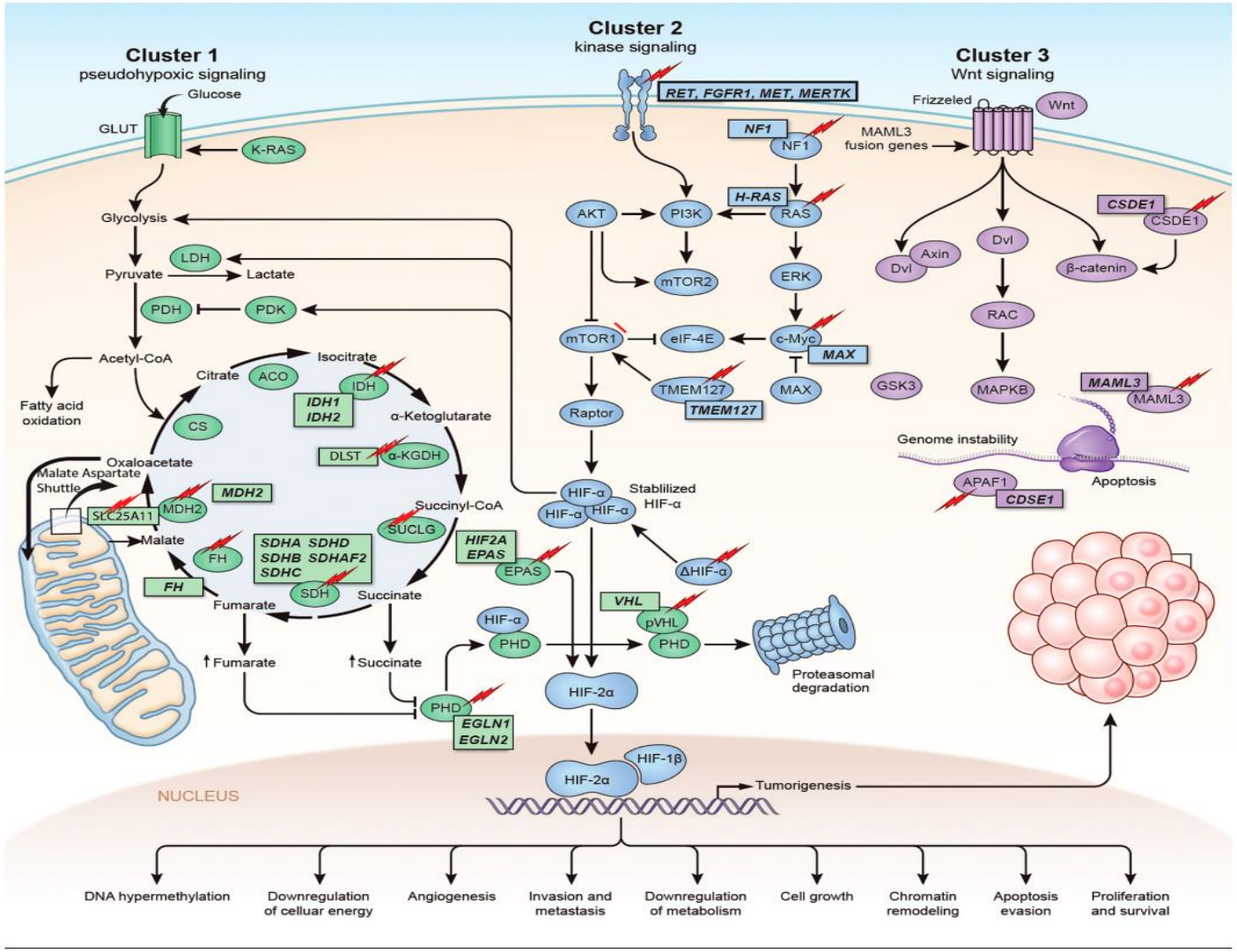
[a]More evidence are needed before considering it as a susceptibility gene.

- PHEO/PGL has the highest rate of underlying genetic susceptibility of any tumor type
  - ~30% overall
  - ~40% in paragangliomas
  - ~50% in metastatic disease
- Genetic testing is considered standard of care for all patients with PHEO or PGL

Favier et al., *Nat Rev Endo* 2014; Gimenez-Roqueplo et al., *Endocr Relat Cancer*, 2022

Clinically tested genes

- *VHL*
- *RET*
- *NF1*
- *SDHA*
- *SDHB*
- *SDHD*
- *SDHC*
- *TMEM127*
- *SDHAF2*
- *MAX*
- *FH*
- *EPAS1*
- *EGLN1*
- *KIF1B*

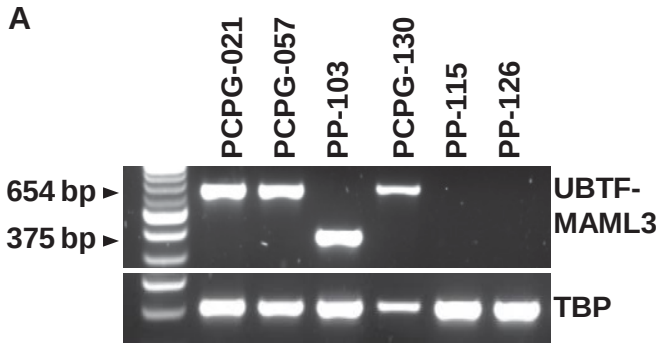


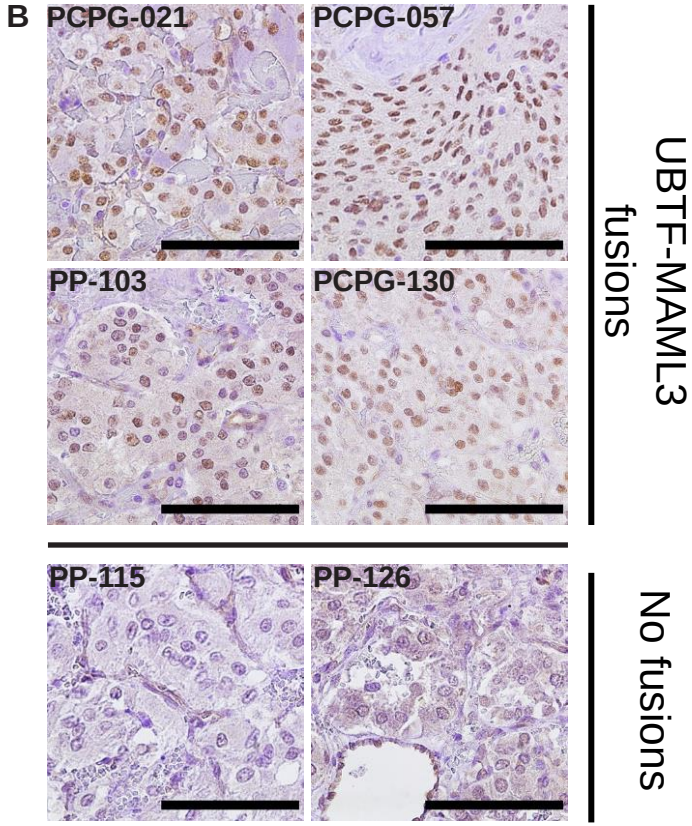
DLST variant is likely pathogenic

- DLST mutated tumors are pseudohypoxic but not hypermethylated
- Succinylation is highly dependent on DLST
- DLST tumors – hyposuccination – which is a new mechanisms underlying development of PPGL

DLST - dihydrolipoamide S-succinyltransferase

Confirmed *UBTF~MAML3* fusions in 7% PCC/PGL and associated with metastatic disease
MAML3 overexpression is tumorigenic
Overexpressed MAML3 increases and interacts with β-catenin to activate WNT signaling





29% of sporadic mPPGL have *UBTF-MAML3* fusion

Alzofon, Koc et al Mol Cancer Res 2021

Cyanotic Congenital Heart Disease & PPGL

- Improved management for patients with cyanotic congenital heart disease (CCHD) has led to prolonged lifespan but also increased prevalence of PPGL
- PPGL susceptibility genes including *VHL, SDH(x), FH, and EPAS1* have been connected to a common signaling pathway that activates hypoxia-inducible factors
- Hypothesis: hypoxic environment selects for gain-of-function mutations (EPAS1) predisposing patients to develop PPGL even when environment is no longer hypoxic
- Increase incidence of PPGL in CCHD patients
- Possible that similar etiology for PPGL in patients with sickle cell disease

INTRODUCTION: *EPAS1* mutations and CCHD-PPGL Association

> N Engl J Med. 2018 Mar 29;378(13):1259-1261. doi: 10.1056/NEJMc1716652.

EPAS1 Mutations and Paragangliomas in Cyanotic Congenital Heart Disease

Anand Vaidya [1], Shahida K Flores [2], Zi-Ming Cheng [2], Marlo Nicolas [2], Yilun Deng [2], Alexander R Opotowsky [3], Delmar M Lourenço Jr [4], Justine A Barletta [1], Huma Q Rana [5], M Adelaide Pereira [4], Rodrigo A Toledo [6], Patricia L M Dahia [7]

EPAS1 mutations in 4/6 PPGL tumors of 5 CCHD patients.

> J Clin Endocrinol Metab. 2022 Aug 18;107(9):2545-2555. doi: 10.1210/clinem/dgac362.

Genetic Analysis of Pheochromocytoma and Paraganglioma Complicating Cyanotic Congenital Heart Disease

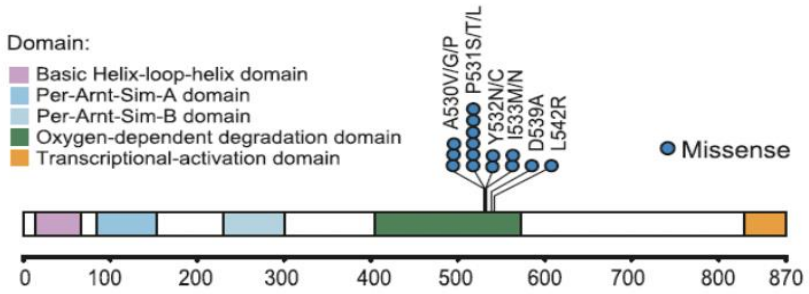
Tatsuki Ogasawara [1 2], Yoichi Fujii [1 2], Nobuyuki Kakiuchi [1 3 4], Yusuke Shiozawa [1], Ryuichi Sakamoto [5], Yoshihiro Ogawa [5], Katsuki Ootani [6], Etsuro Ito [6], Tomoaki Tanaka [7], Kenichiro Watanabe [8], Yusaku Yoshida [9], Noriko Kimura [10], Yuichi Shiraishi [11], Kenichi Chiba [11], Hiroko Tanaka [12], Satoru Miyano [12], Seishi Ogawa [1 2 13]

EPAS1 mutations in 15/16 PPGL/AMH tumors of 7 CCHD patients.

*AMH: Adrenal Medullary Hyperplasia

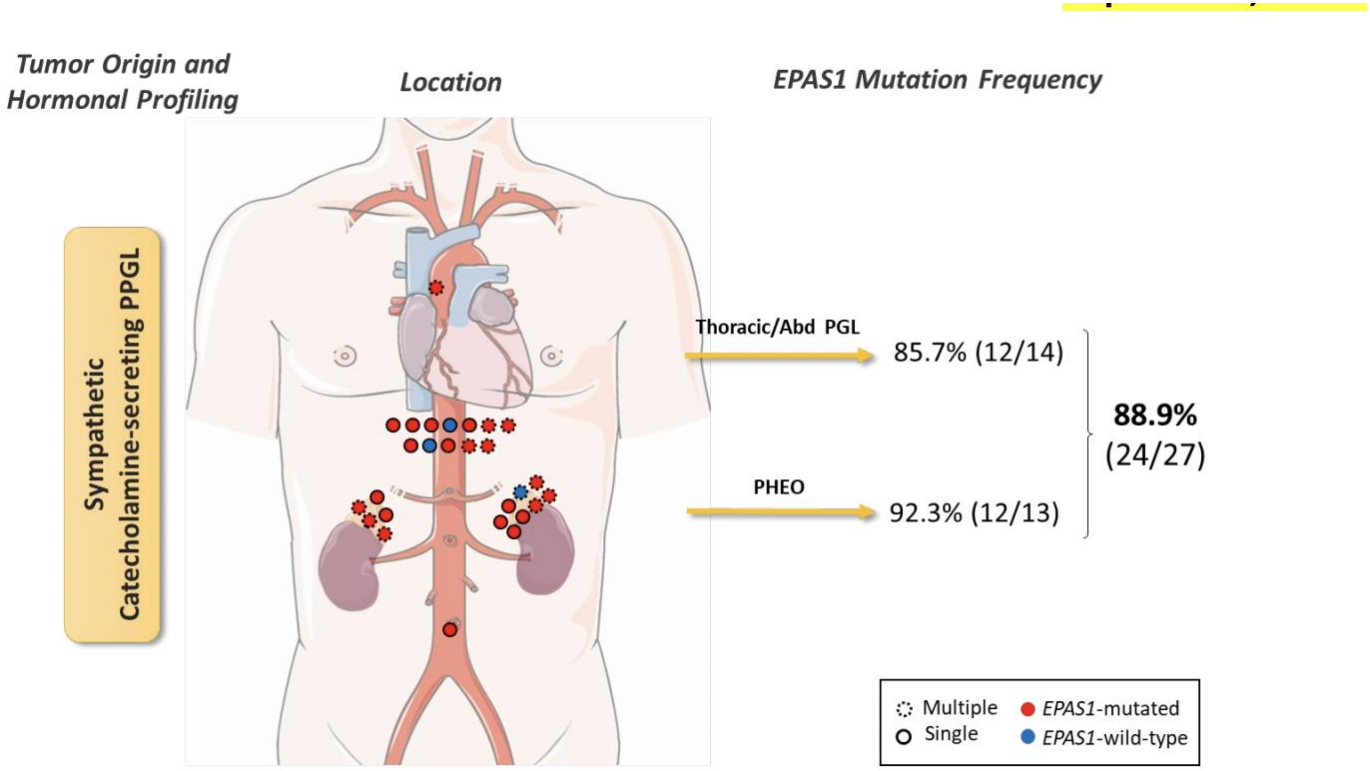
Congenital Cyanotic Heart Disease - CCHD

Typical missense gain-of-function **somatic mutations** of ***EPAS1* gene** (HIF2A) in PPGL tumors



Ogasawara et al. JCEM 2022
MJPercy, et al. NEJM 2008
Lorenzo V, et al. Blood 2012
Comino-Méndez I, et al. Hum Mol Gen 2013
Toledo RA. ERC 2017
Tarade D, et al. Nat Commun 2018

Highly frequent and convergent EPAS1 gain-of-function in sympathetic CCHD-PPGLs



39/43 (91%) CCHD-sPPGLs described so far carry a EPAS1 gain-of-function mutation (Dahia P, Toledo Rodrigo)

Summary of data

Characteristic	Notes
Demographics	4 of 9 patients are female
Surgeries to correct CCHD	Most within days of life, latest was age 12 years, one had heart transplant
Avg age of PPGL dx	30.7 years (SD: 9.6 years, range: 15-47 years)
PPGL Symptoms	Hot flashes (5), arrhythmias (4), hypertension (4), abdominal pain (2), headaches (1), none (1)
Multiple/metastatic	3 had multiple PPGL, 2 had metastatic or recurrent PPGL
Location	Mediastinal and abdominal (6), head and neck (5), pheo (3)
Size	Range from 9-65mm
Genetics	3 patients: SDHB heterozygous (c.137G>A, p.Arg46Gln), SDHA variant of unknown significance, BARD1 (c.448C>T, p.Arg150*)

Biomarkers to predict metastatic disease
EDTA Plasma from PPGL and SDHx Carriers

- Measured succinate and succinate/fumarate levels in PPGL and SDHx carriers

Predictors variable for SDHx positive status	Cut off (uM)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sample #
succinate	4.94	64	91	58	93	140
succinate/fumarate	1.66	68	88	52	94	140
fumarate	3.18	50	66	22	88	140

- Succinate and succinate/fumarate – shown to be valuable diagnostic biomarkers in predicting SDHx genetic status prior to surgery

Biomarkers to predict metastatic disease

- Tumoral and circulation mRNA
- Telomerase reactivation
- Methylation analysis of TERT promotor

Future biomarkers for symptomatic PPGL

- Plasma succinate – SDHx/IHC
- Circ miR_483 – methyl TERT promotor

Functional Imaging algorithm according to genetic status

- Cluster 1a – SDHx (SDHA, SDHB, SDHC, SDHD< SDHAF2) - ***Gallium-68 dotatate***
- Cluster 1b – vHL/EPAS1- Fluoro-dopamine PET
- Cluster 2 (RET/NF1/MAX/MAPK/TMEM127) – Flouro-dopamine PET

Sporadic (no mutation)

- Primary pheo - Flouro-dopamine PET
- Metastatic - Gallium-68 dotatate

Personalized Treatment Approach Options for mPPGL

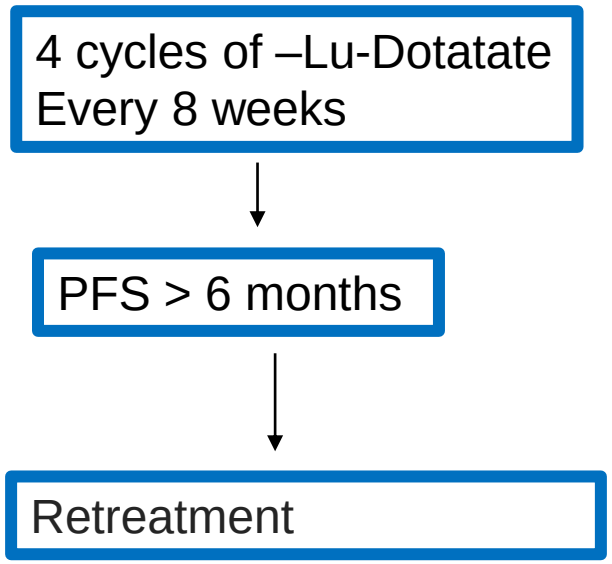
- SDHx mutated tumors – PARP inhibitors with temozolamide
- Cluster 1 PPGLs – HIF2-alpha inhibitors
- Cluster II PPGLs – Tyrosine kinase inhibitors
- SSTR expression in PPGL – ^{177} Lu DOTATATE
- Norepinephrine transporter system expression (^{123}MIBG) - ^{131} MIBG

Current clinical Trials

- 177 Lu-DOTATATE in MPPGL/inoperable PPGL - PFS
- Randomaized phase II trial: TMZ vs TMZ + Olaparib in PPGL - PFS
- Belzutifan in Advanced PPGL or pNET
- Lanreotide in MPPGL (Lampara) – rate of tumor growth
- Axitinib and Lenvatinib -ORR

PRRT in inoperable PPGL (NIH)

- Phase II study
- Age > 18 years
- Metastatic or inoperable PPGL
- SSTR + disease documented by Ga-68 DOTATATE PET



Primary Objective

- PFS

Secondary Objective

- OS
- ORR
- Changes in plasma biochemistries
- QOL
- Decrease in BP meds

Immunotherapy

- PPGL are immunologically cold tumors
- Low amount of neoantigens, low somatic mutation burden, no/minimal leucocyte infiltration

Clinical Trials

- NCT 02834013 – nivolumab/ipilimumab – active, closed to PPGL
- NCT 02721732 – pembrolizumab – active/not recruiting
- NCT03333616 – nivolumab/ipilimumab – recruiting
- NCT04187404 – E02401 peptide therapeutic vaccine + nivolumab – recruiting

Therapeutics for Pheo/PGL

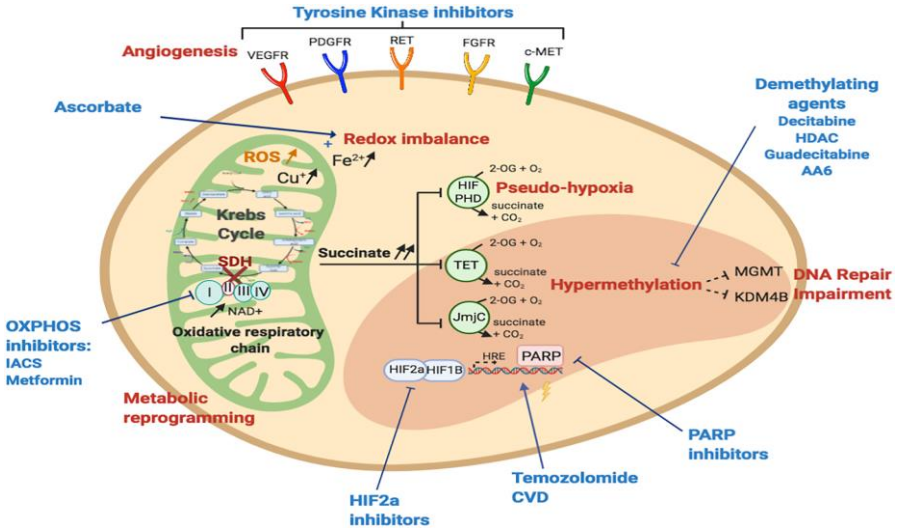
Clinical Trials 2022

Table 7. Ongoing clinical therapy studies for metastatic PPGLs

Ongoing studies	Therapy	Patient number (n)	Status
NCT04394858	PARP inhibitor olaparib plus temozolomide (phase II, prospective)		Recruiting
NCT01850888	[^{131}I]-MIBG		Recruiting
NCT00107289	[^{131}I]-MIBG (phase II, prospective)		Recruiting
NCT04029428	[^{177}Lu] DOTATATE vs [^{90}Y] DOTATATE vs mix each of 50% (PRRT) (phase II, prospective)		Recruiting
NCT03206060	[^{177}Lu] DOTATATE (Lutathera) (PRRT) (phase II, prospective)		Recruiting (SDHx-related and sporadic PPGLs)
NCT04276597	^{177}Lu] DOTATOC (PRRT) (phase II, prospective)		Recruiting
NCT04711135	[^{177}Lu] DOTATATE (Lutathera) (PRRT) in adolescents (phase II, prospective)		Not yet recruiting
NCT03923257	[^{177}Lu] DOTATATE (PRRT) in children and adolescents (phase I/II, prospective)		Recruiting
LAMPARA NCT03946527	Lanreotide (cold somatostatin analog) (phase II, prospective)		Not yet recruiting
NCT03034200	Dopamine receptor D2 and caseinolytic protease P (ClpP) agonist ONC201(phase II, prospective)		Recruiting
NCT04284774	Farnesyltransferase inhibitor tipifarnib (RAS inactivation) (phase II, prospective)		Recruiting
FIRST-MAPP Study, NCT01371201	TKI sunitinib (phase II, prospective, first randomized placebo-controlled study)	N = 74 (closed)	Data arriving soon
NCT03839498	TKI Axitinib (AG-013736) (phase II, prospective)		Recruiting
NCT03008369	TKI lenvatinib (phase II, prospective)		Active, not recruiting
NCT02302833	TKI cabozantinib (phase II, prospective)	N = 10	Recruiting (preliminary data from n = 10, partial response 40%, PFS 11.2)
NCT04400474	Cabozantinib plus atezolizumab (CABATEN) (phase II, prospective)		Recruiting
NCT02834013	Nivolumab plus ipilimumab (phase II, prospective)		Recruiting
NCT02721732	Pembrolizumab (phase II, prospective)		Recruiting
NCT02923466	VSV-IFNβ-NIS and avelumab(phase II, prospective)		Recruiting
NCT04187404	Novel Therapeutic Vaccine (EO2401) (phase I/II, prospective)		Recruiting

Black letters: potentially specifically interesting for cluster 1; gray letters: potentially specifically interesting for cluster 2.
Abbreviations: MIBG, meta-iodobenzylguanidine; PARP, poly(ADP-ribose) polymerase; PPGL, pheochromocytoma/paraganglioma; PRRT, peptide receptor radionuclide therapy; SDHx, succinate dehydrogenase subunit x; TKI, tyrosine kinase inhibitor;

Potential targets



Belzutifan (Welirig)

- *Participated in clinical trial leading to FDA approval*
- *Large experience treating patients*
- *Response to pheo/pgl has been observed*
- *May be a therapeutic for patients with SDHx mutations*

Nolting et al., *Endocr Review*, 2022; Kaelin, *JCI*, 2022

MPPGL: Baseline Patient Characteristics

- Retrospective cohort study
- 133 patients with PPGL were diagnosed with metastatic disease
- Penn – 107, Colorado – 26

Baseline Clinical Characteristic	
Synchronous Metastases	N = 40 (30.1%)
Male	50.4%
Median Age at Metastasis	50.2 years (IQR 36.7 – 61.9)

Primary Tumor Location	% (N=133)
Adrenal	31.6%
Extra-Adrenal	38.3%
Head/Neck	23.3%
Multiple Primary Tumors	6.8%

- Median time between initial PPGL diagnosis and metastasis was 5.7 yrs (IQR 0.1 – 7.8)

Genetic status

Germline genetic status was assessed in 110 pts (82.7%)

Germline Variant	% of total Patient Coh0ort (N=133)	% of those patients who had genetic testing (110)
SDHB	33.1%	**40%**
SDHD	4.5%	**5.5%**
SDHA	1.5%	**1.8%**
NF1	1.5%	1.8%
SDHC	0.8%	**0.9%**
Other Mutation (MSH2, FH, BRCA2)	2.3%	2.7%
Negative Genetic Testing	39.1%	47.3%

48% had a ***SDH*** mutation

Treatments for Metastatic Disease

Local Debulking / Palliative Treatments were the most commonly utilized modalities

Local Therapy Modality	% (N=133)
Debulking Surgery	63.2%
≥ 2 Debulking Surgeries	22.2%
Palliative Radiation	43.6% (range 1 – 9 total RT courses per patient)

Systemic Therapies for Metastatic PPGL

Patients received a median of 1.9 systemic treatment lines (range 0 – 8)

- 28.5% of pts received CVD chemotherapy
  - median treatment duration was 6.2 months (IQR 2.3 – 13)
- CVD treatment durations were numerically longer among ***SDHB*-positive pts (N=14) vs. *SDHB*-negative pts (N=17)**
  - Median treatment duration of **12.5 months** (SDHB-positive) vs. **3.1 months** (SDHB-negative)
- ***This may indicate greater clinical benefit and more durable disease control in SDHB-related disease.***

Fishbein L, Ben-Maimon S, Keefe S, Cengel K, Pryma DA, Loaiza-Bonilla A, Fraker DL, Nathanson KL, Cohen DL. *SDHB* mutation carriers with malignant pheochromocytoma respond better to CVD. Endocr Relat Cancer. 2017 Aug;24(8):L51-L55. doi: 10.1530/ERC-17-0086. Epub 2017 May 31. PMID: 28566531.

Other Systemic Therapies

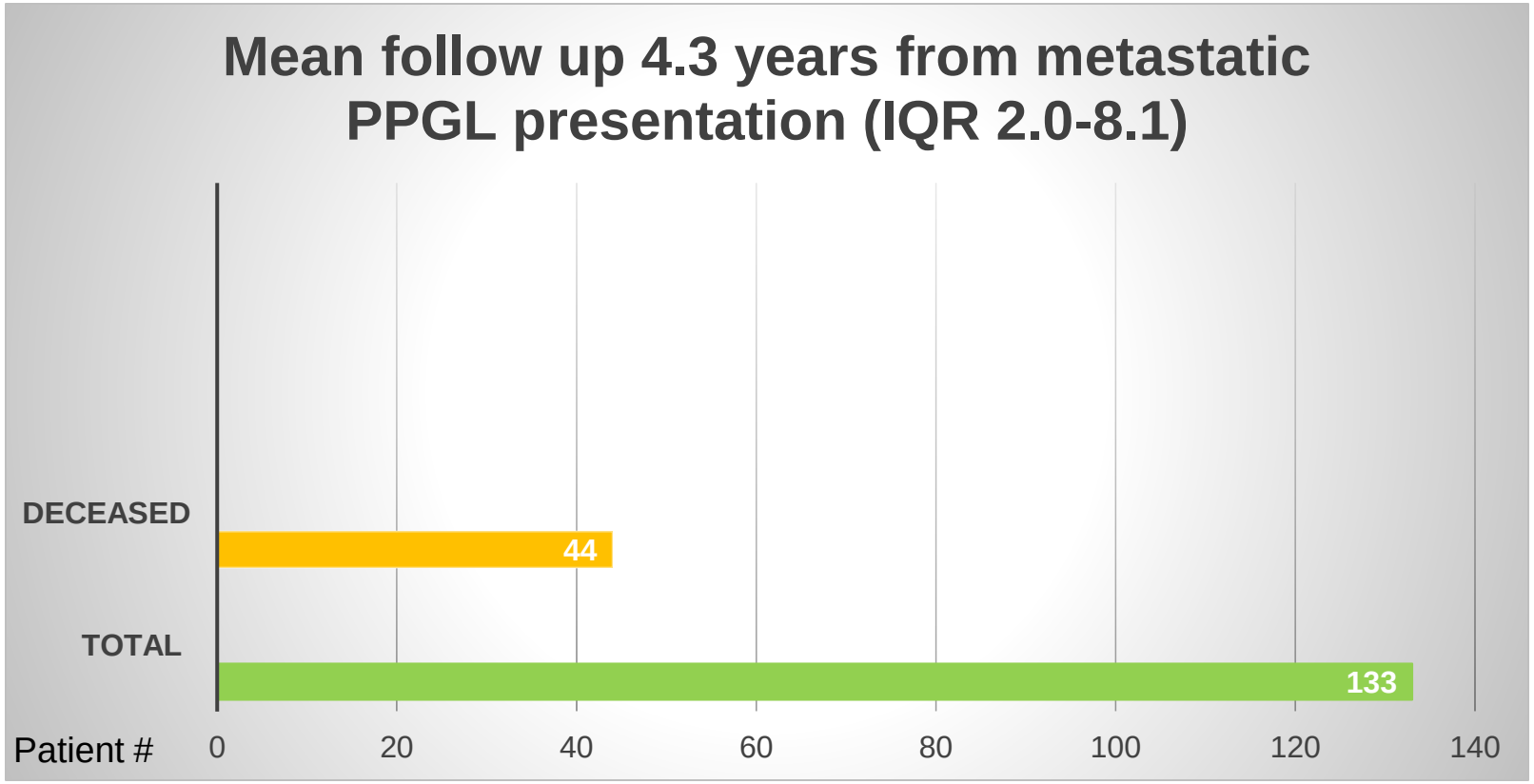
MIBG based therapies

- 33.1% received MIBG (range 1-4 cycles)
- 15.5% received Azedra (range 1-3 cycles)

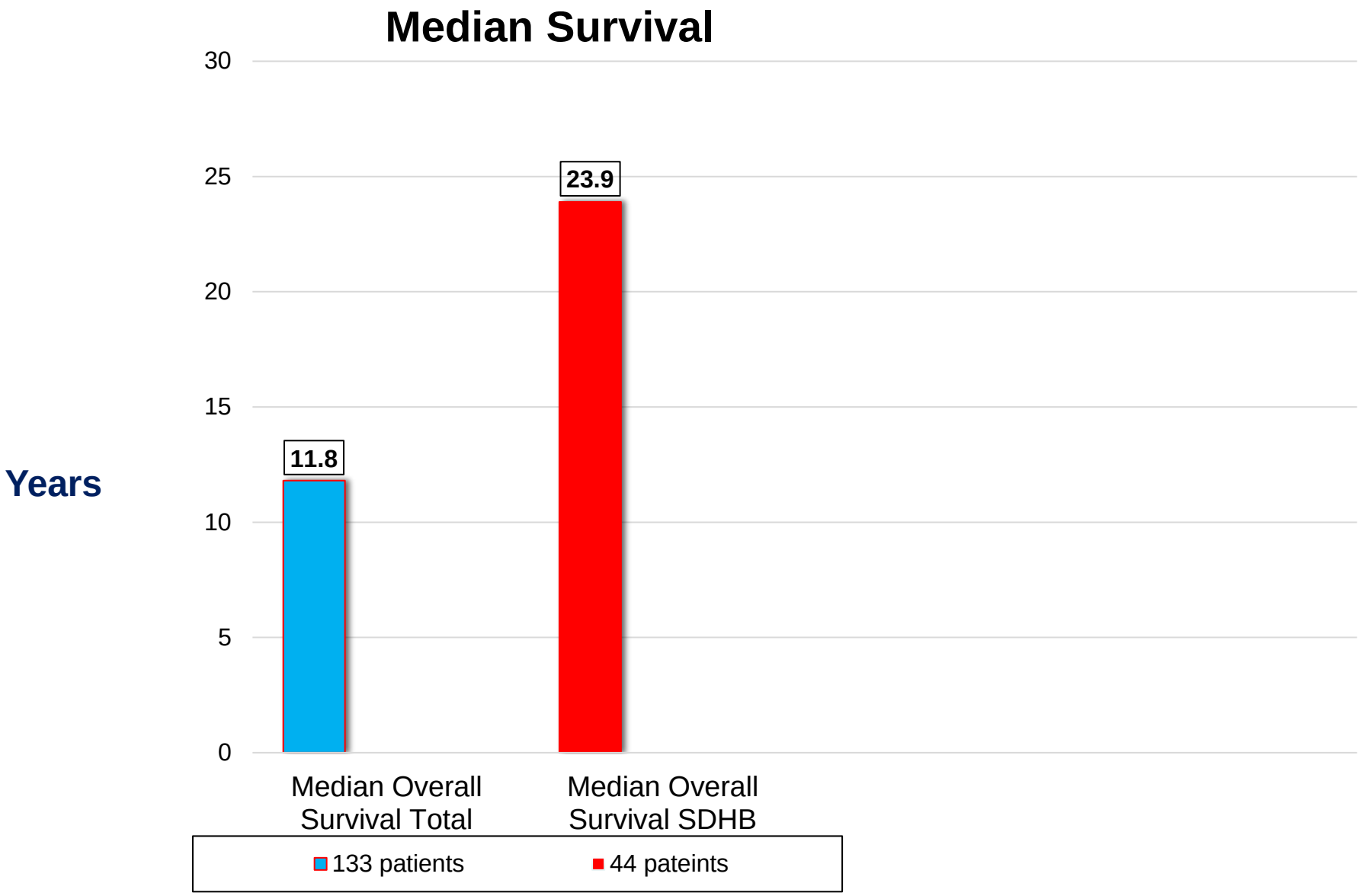
Other

- 30% patients received other systemic therapies (including temodar-based chemotherapy; SSA therapy)

Survival Data for MPPGL



44 (33%) of patients died from total of 133


Median Survival
Years
30
25
20
15
10
5
0
23.9
11.8
Median Overall Survival Total
Median Overall Survival SDHB
133 patients
44 pateints

SDHB
PHEOPARACOALITION

the PARADIFFERENCE foundation

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PHEO PARA ppa ALLIANCE
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