



Advances in PPGL

Wednesday, 28 January 2026, 18:00 – 19:10 CET

Disclosure Statement

Ashley GROSSMAN (Moderator) has no potential conflicts of interest to report.

The Aim and Concept

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- ✓ Webinars are free of charge and can be accessed by all.
- ✓ All webinars will be recorded and made available on the ENETS website after the event.
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Live poll question: Getting to know the audience

In which medical discipline are you trained or currently working?

Tonight's faculty



Ashley GROSSMAN

Royal Free Hospital
London, UK
Endocrinology



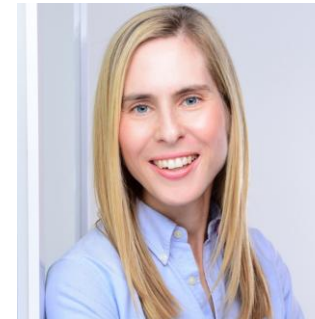
Jaydira DEL RIVERO

National Cancer Institute /
National Institutes of Health
Bethesda, Maryland, USA
Oncology



Camilo JIMENEZ

University of Texas
MD Anderson Cancer Center
Houston, Texas, USA
Endocrinology



Svenja NÖLTING

University Hospital Zürich,
Switzerland
Endocrinology

Tonight's agenda

- | | |
|---------------|---|
| 18:00 – 18:05 | Opening comments
<i>Ashley GROSSMAN, GBR</i> |
| 18:05 – 18:20 | Update in the genetics and diagnostic approach of PPGL:
what the clinician should know
<i>Jaydira DEL RIVERO, USA</i> |
| 18:20 – 18:35 | Treatment of advanced PPGL
<i>Camilo JIMENEZ, USA</i> |
| 18:35 – 18:50 | Bench-bedside-back - patient tissue as key for personalised medicine
<i>Svenja NÖLTING, SUI</i> |
| 18:50 – 19:05 | Discussion |
| 19:05 – 19:10 | Closing comments
<i>Ashley GROSSMAN, GBR</i> |

Update in the Genetics and Diagnostic Approach of PPGL: What the Clinicians Should Know

Jaydira Del Rivero, MD

Associate Research Physician

Developmental Therapeutics Branch

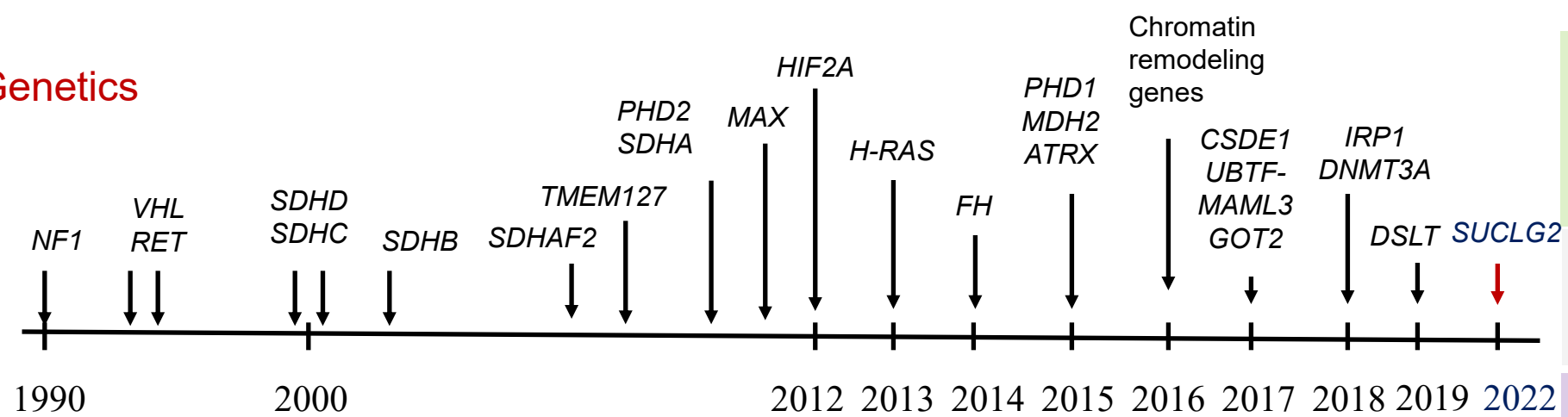
National Cancer Institute/National Institutes of Health

Disclosure Information

- I have no personal or professional conflicts of interests.
- I have no financial disclosures

PPGL: Continuing Progress

Genetics



Cluster I: Pseudohypoxia group

DHA, SDHB, SDHC, SDHD, SDHAF2, FH, VHL, IDH1/2, MHD2, PHD1/2, and HIF2/EPAS1

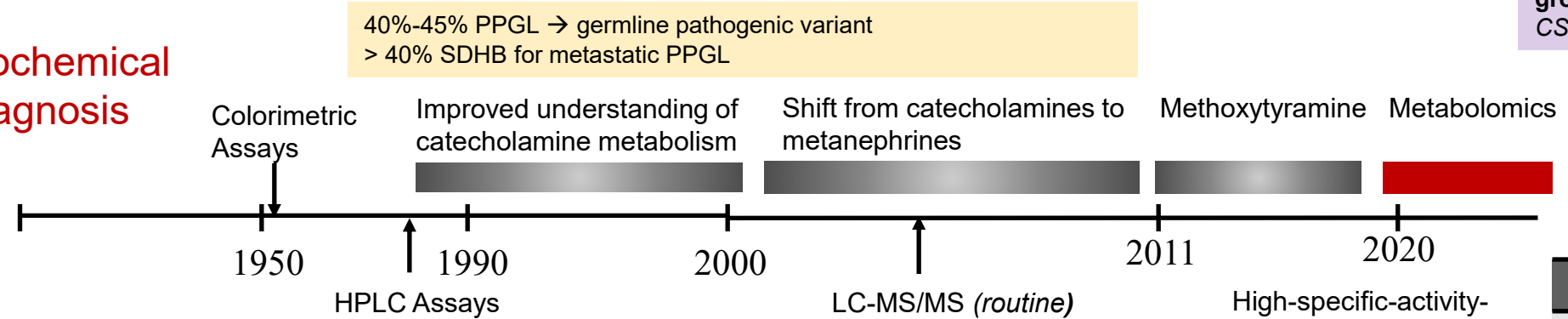
Cluster II: Kinase signaling group

RET, NF1, TMEM127, MAX, and HRAS

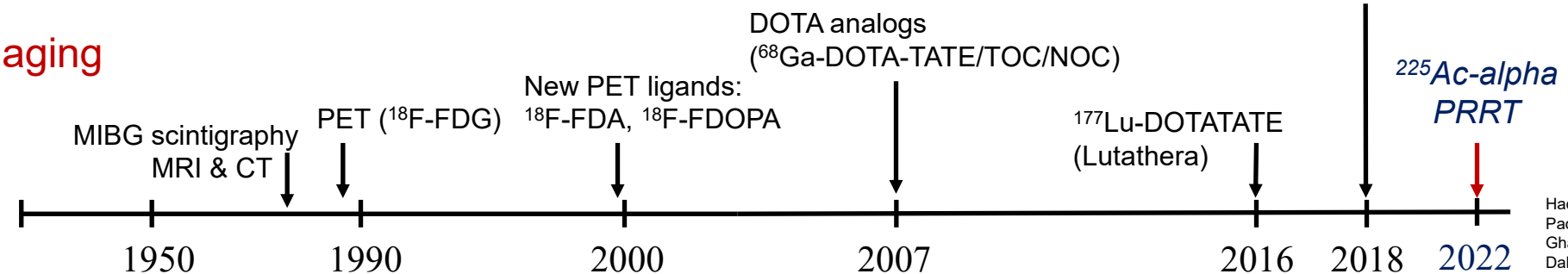
Cluster III: Wnt signaling group

CSDE1 and MAML3

Biochemical Diagnosis



Imaging



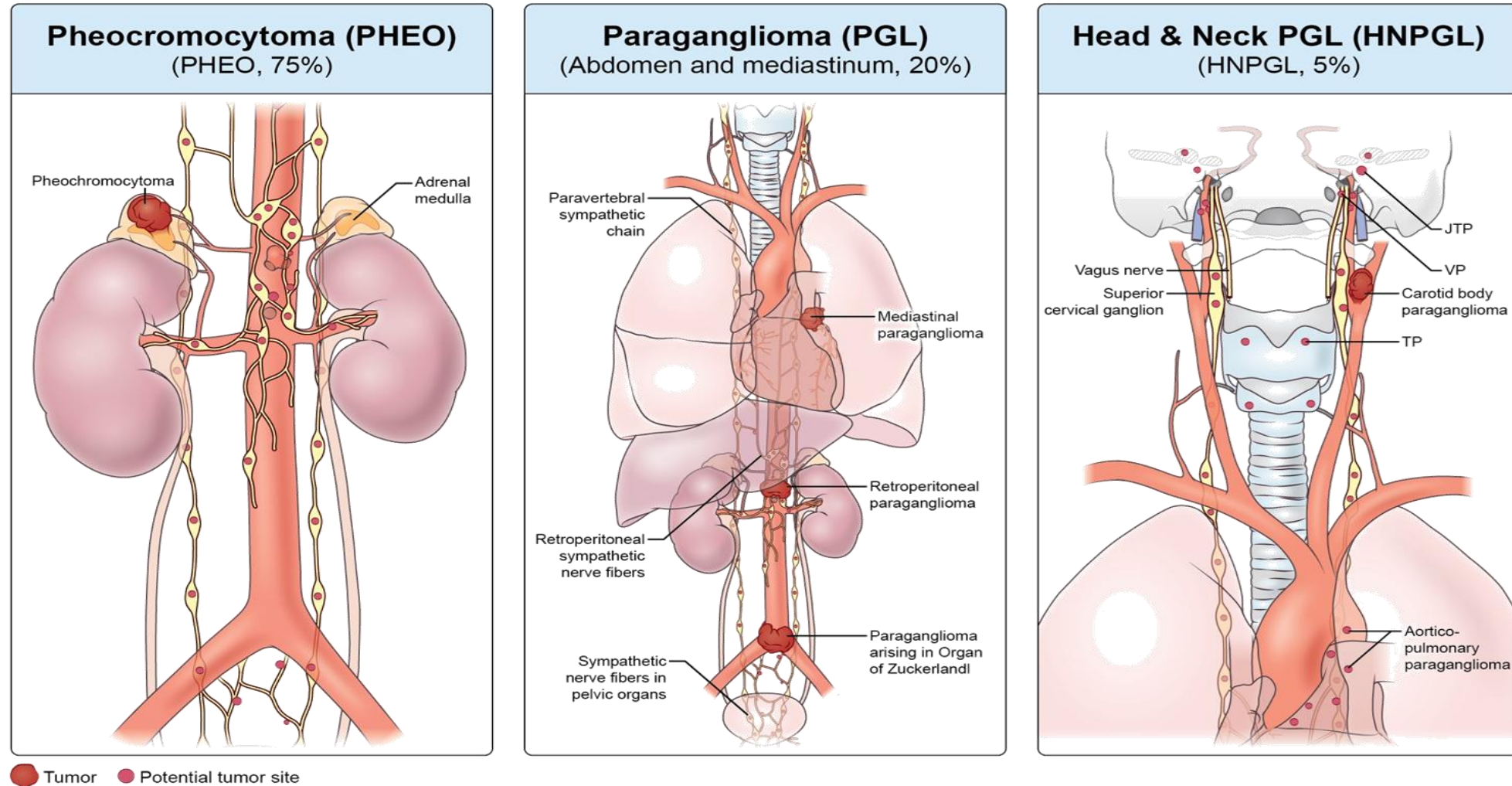
Sensitivities mPPGL

¹²³ I-MIBG	50-60%
⁶⁸ Ga-Dotatate	98-99%
¹⁸ F-FDG	68-92%

Hadrava Vanova JNCI 2021; in press
Pacak et al. Nat. Rev. Endocrinol. 2020; 16:621
Ghayee et al. Metabolism 2020; 110:154297
Dahia et al. Endocr. Relat. Cancer 2020; 27:T41
Jimenez et al. Cancers 2019; 11:1018
Fishbein et al. Cancer Cell 2017; 31:181

Adapted Courtesy of K. Pacak and G Eisenhofer

Pheochromocytoma/Paraganglioma (PPGL)



Lenders et al. *Clin Endocrinol Metab.* 2014;99(6):1915-1942.

PPGLs Genetics

Cluster I: Pseudohypoxia group

DHA, SDHB, SDHC, SDHD, SDHAF2, FH, VHL IDH1/2, MHD2, PHD1/2, and HIF2/EPAS1

Cluster II: Kinase signaling group

RET, NF1, TMEM127, MAX, and HRAS

Cluster III: Wnt signaling group

CSDE1 and MAML3

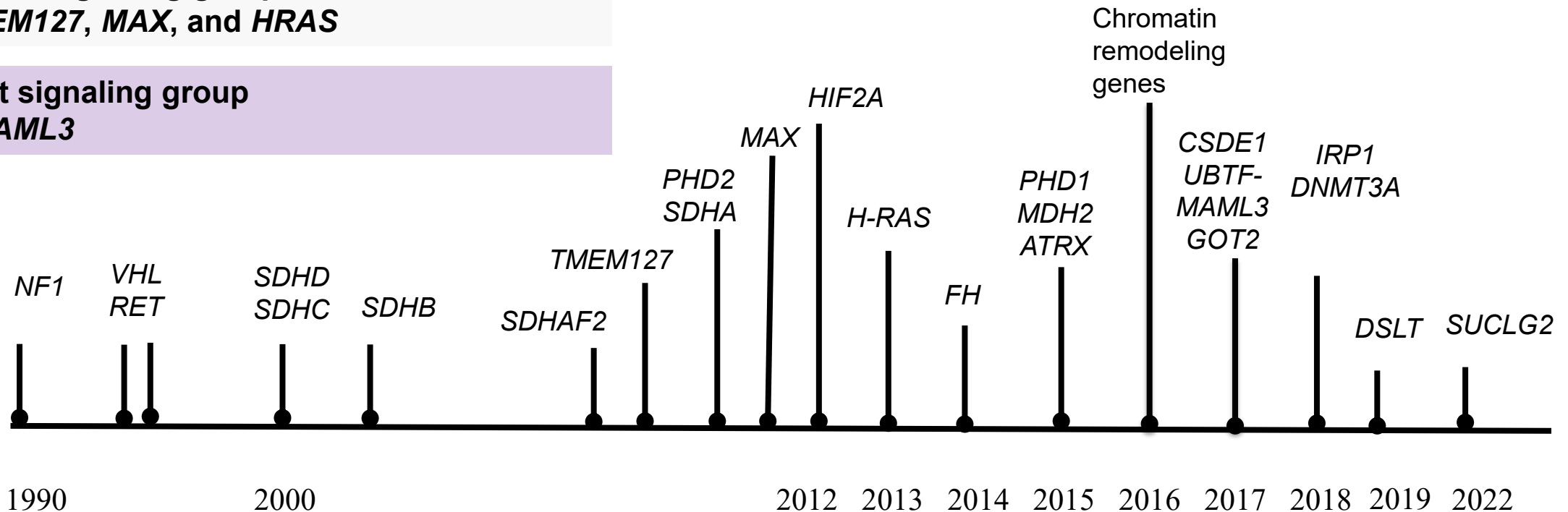
SDHx-mutated tumors →
PARP
inhibitors with
TMZ

Cluster I
PPGLs →
HIF2-alpha
inhibitors

Cluster II
PPGLs →
Tyrosine
Kinase
Inhibitors

SSTR
expression →
177Lu
DOTATATE

NE transporter
system
expression →
¹³¹I-MIBG
therapy



- **35%-40% PPGL → germline pathogenic variant**
- **About 40% of metastatic PPGL has SDHx pathogenic variant**

Adapted. Courtesy of K. Pacak
Fishbein et al. Cancer Cell 2017; 31:181
Crona et al. Endocr. Rev. 2017; 38:489
Dahia et al. Nat. Rev. Cancer 2014; 14:108
Fischbein, Del Rivero...Jimenez, NANETS Consensus Guidelines 2021

Parasympathetic paragangliomas:
Most often found in the head and neck

95% casos: non-functional/non-secreting

Sympathetic paragangliomas:
Located in the sympathetic paravertebral ganglia of thorax, abdomen, and pelvis

Functional/secreting

Pheochromocytomas
Adrenal medulla

Functional/secreting

Paraganglioma

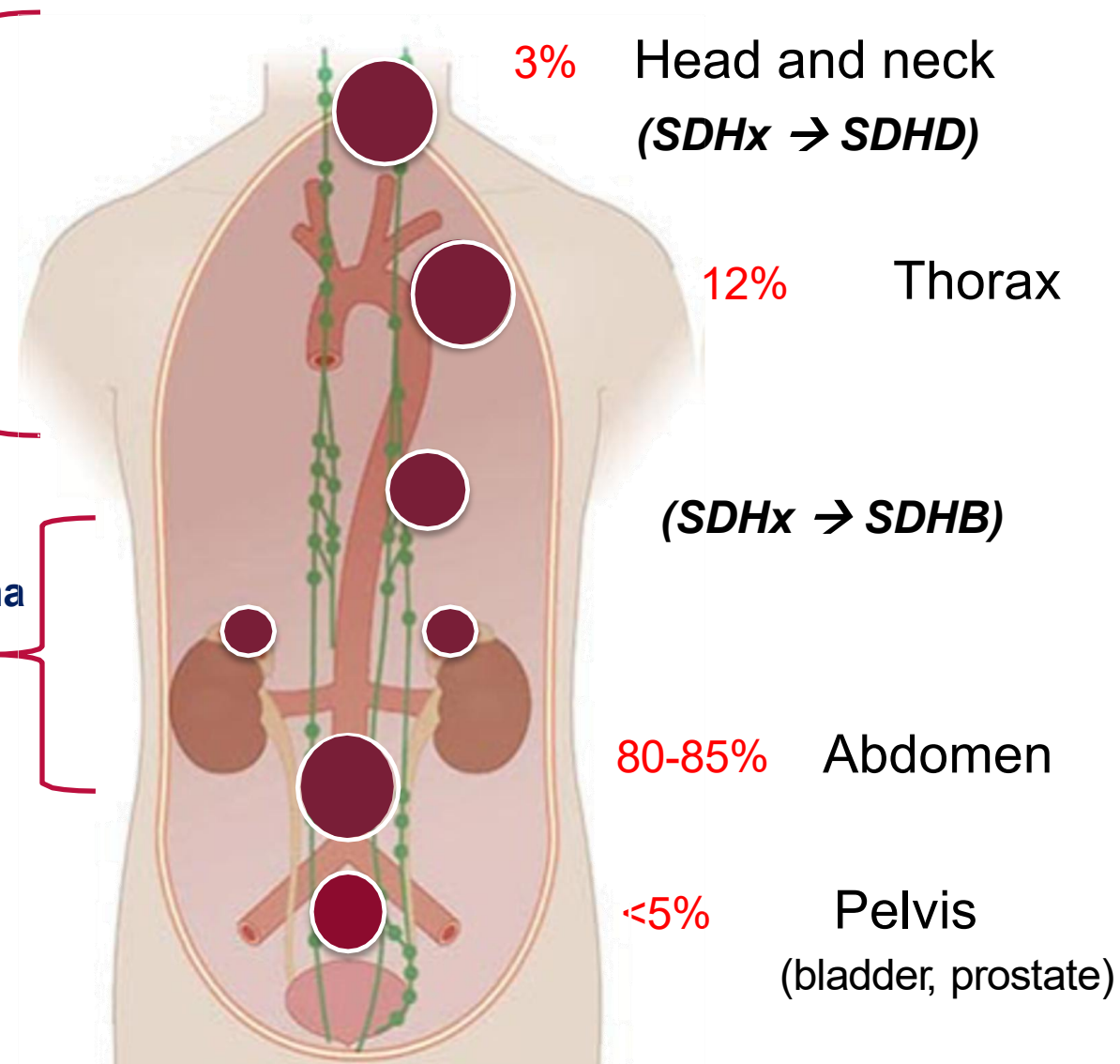
Extra-adrenal

15-20% of cases

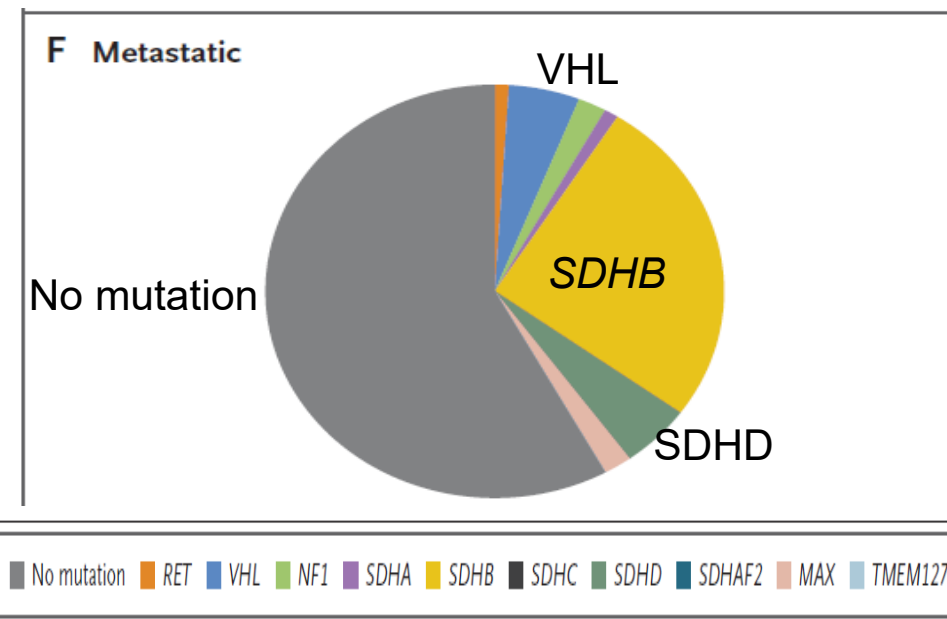
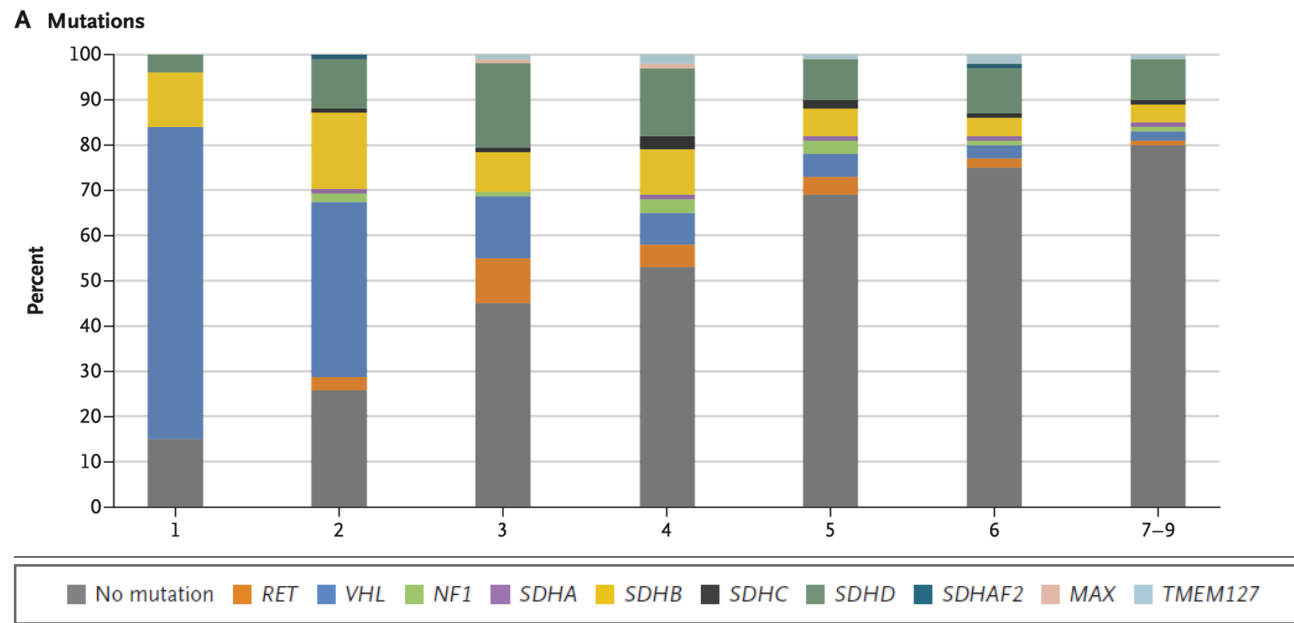
Pheochromocytoma

Adrenal

80-85% of cases



Genetic Counseling and Testing



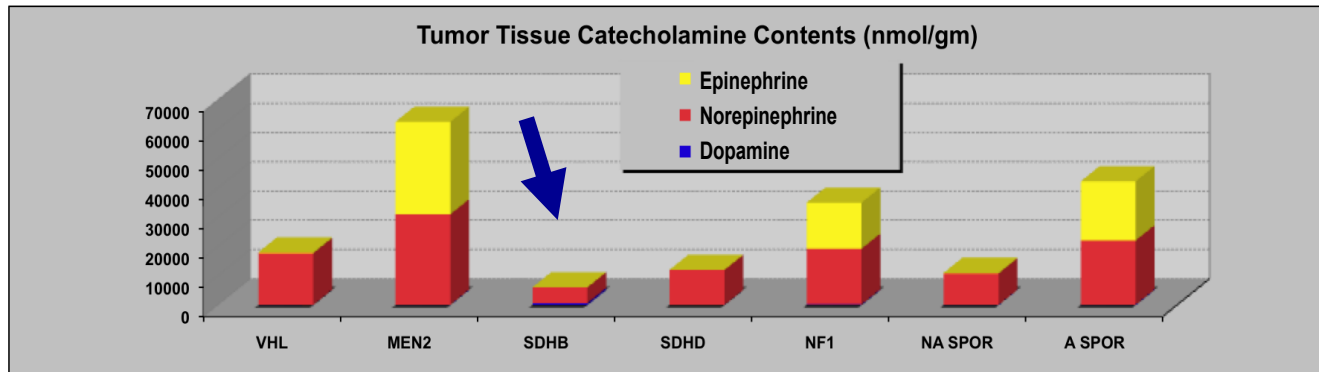
Recommendation

We recommend that all patients with primary PPGL or metastatic PPGL have clinical germline genetic testing and recommend family cascade testing if the patient carries a susceptibility gene pathogenic variant.

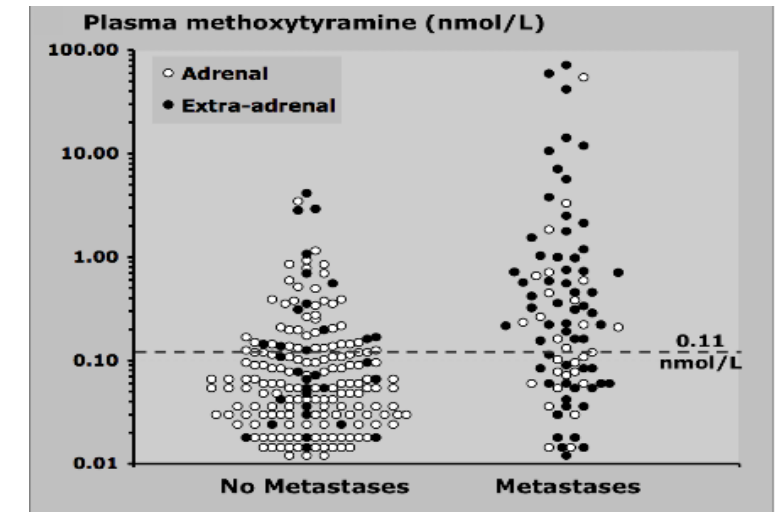
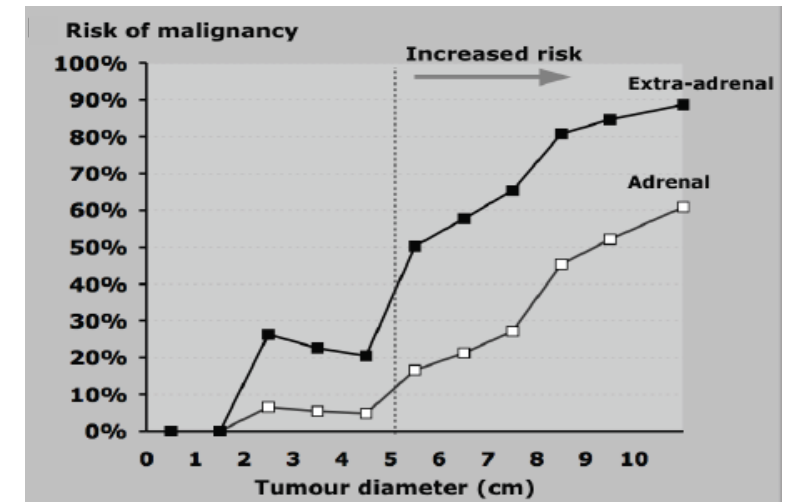
Fischbein, Del Rivero...Jimenez, NANETS Consensus Guidelines 2021
N Engl J Med 2019;381:552-65. DOI: 10.1056/NEJMra1806651

Predictors of Hereditary Disease

- Family history of PPGL
- Age <40 years at diagnosis
- Multiple or bilateral tumors
- Extra-adrenal location (especially head-and-neck paragangliomas)
- Metastatic disease
- Associated syndromic features



Eisenhofer et al. Endocr. Relat. Cancer 2011; 18:97
Fischbein, Del Rivero...Jimenez, NANETS Consensus Guidelines 2021



Zelinka et al. Eur.J. Clin. Invest.; 2011; 41:1121
Eisenhofer et al. Eur. J. Cancer; 2012; 48:1739

Genotype-Phenotype Correlations in Hereditary PPGL

Gene	Typical Tumor Location & Pattern	Metastatic Risk / Penetrance	Key Phenotypic Features	Inheritance / Surveillance
SDHD	Predominantly head-and-neck paragangliomas; often multifocal	Low–moderate metastatic risk; high penetrance	Multiple tumors common	Paternal inheritance ; screen only if variant inherited from father
SDHB	Extra-adrenal paragangliomas (abdomen, thorax, pelvis)	Highest metastatic risk (~30–70%)	Aggressive behavior, dopamine secretion	Early, intensive lifelong surveillance (start ~6–10 years)
SDHC	Mainly head-and-neck paragangliomas	Low penetrance; low metastatic risk	Usually solitary tumors	Later onset; less intensive surveillance
SDHA	Abdominal paragangliomas ± pheochromocytoma	Moderate metastatic risk	Variable phenotype	Lower penetrance but surveillance required
SDHAF2	Head-and-neck paragangliomas, often multiple	Very low metastatic risk	Early onset	Paternal inheritance , similar to SDHD

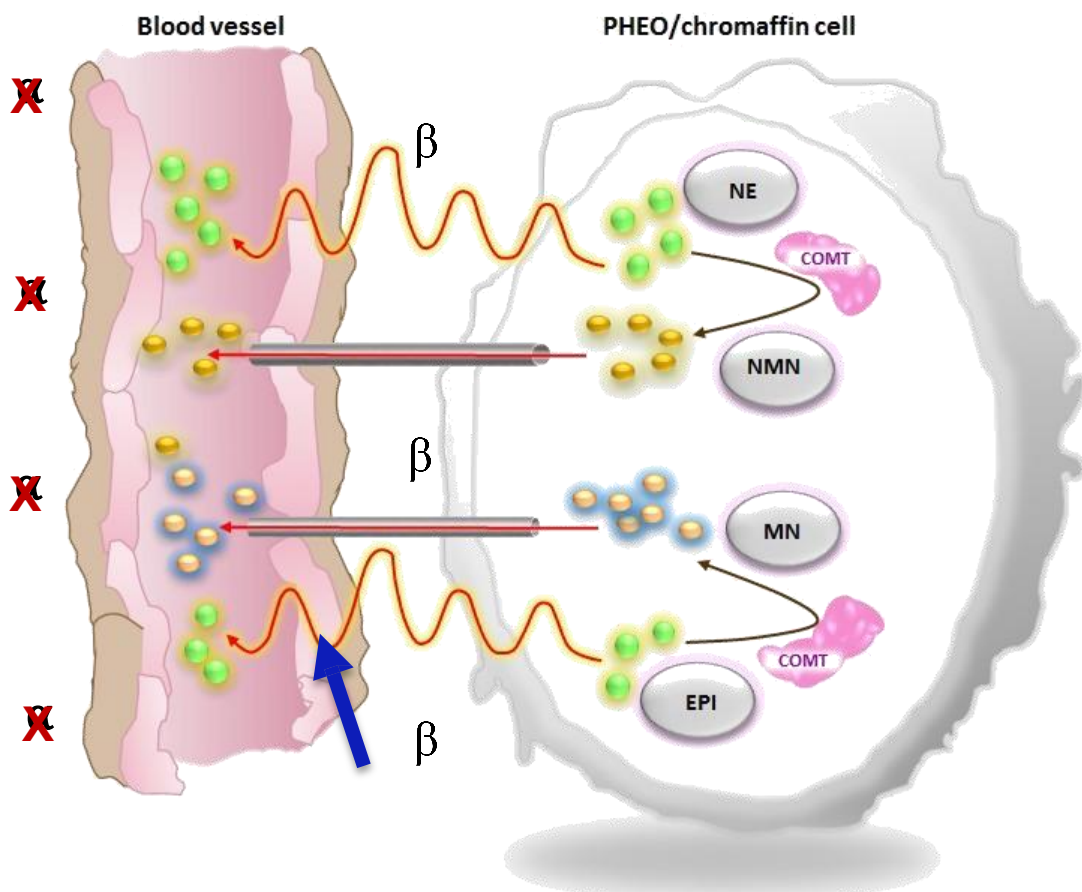
Amar L et al. *Nat Rev Endocrinol*. 2021 Jul;17(7):435-444
Casey, RT et al. *Nat Rev Endocrinol* 20, 729–748 (2024)
Lussey-Lepoutre C. *Best Pract Res Clin Endocrinol Metab*. 2025 Jan;39(1):101938.

Genotype-Phenotype Correlations in Hereditary PPGL

Gene / Syndrome	Typical Tumor Location & Pattern	Metastatic Risk	Key Associated Features	Surveillance
VHL disease	Bilateral adrenal pheochromocytomas (type 2)	Low	Renal cell carcinoma, CNS hemangioblastomas, pancreatic NETs	Youngest age at diagnosis ; multisystem surveillance essential
MEN2 (RET mutations)	Bilateral adrenal pheochromocytomas (up to 50%)	Low	Medullary thyroid carcinoma ($\leq 98\%$), hyperparathyroidism (MEN2A)	PCC screening guided by RET risk category
NF1	Usually unilateral pheochromocytoma (~3%)	Low	Café-au-lait spots, neurofibromas, Lisch nodules	Diagnosis often clinical; PPGL screening symptom-driven

Amar L et al. *Nat Rev Endocrinol*. 2021 Jul;17(7):435-444
 Casey, RT et al. *Nat Rev Endocrinol* 20, 729–748 (2024)
 Lussey-Lepoutre C. *Best Pract Res Clin Endocrinol Metab*. 2025 Jan;39(1):101938.

Clinical Features: "The Great Mimic"



α blockers: doxazosin, phenoxybenzamine
prazosin, terazosin

*α blockers is recommended before any procedure,
ablative or systemic therapies

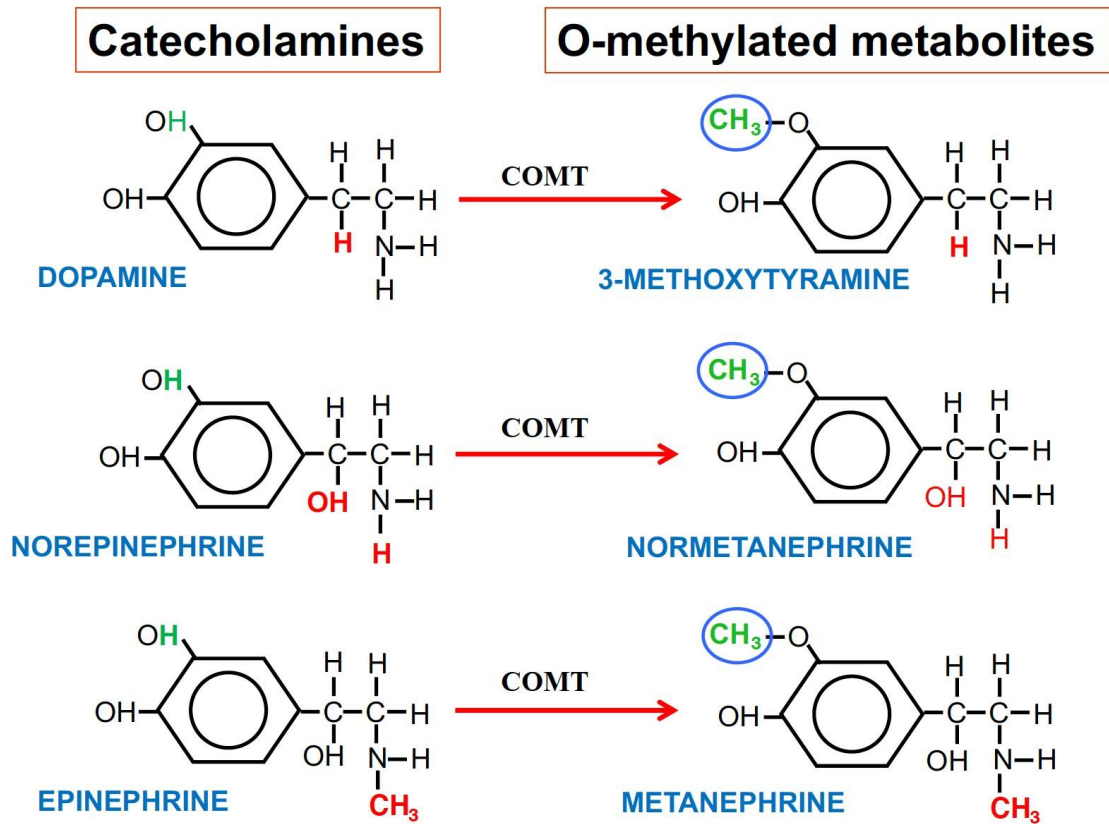
Symptoms	Incidence	Signs	Incidence
Headaches	++	Hypertension	++++
Palpitations	+++	Tachycardia or reflex bradycardia	+++
Diaphoresis	+++	Postural hypotension	++
Anxiety/nervousness	++	Hypertension, paroxysmal	++
Tremulousness	++		
Nausea/emesis	++	Weight loss	++
Pain in chest/abdomen	++	Pallor	++
		Hypermetabolism	++
Weakness/fatigue	+++	Fasting hyperglycemia	++
Dizziness	+	Tremor	++
Heat intolerance	+	Increased respiratory rate	++
Paresthesias	+	Decreased gastrointestinal motility	++
Constipation	++	Psychosis (rare)	very rare
Dyspnea	+	Flushing, paroxysmal (rare)	+
Visual disturbances	+		
Seizures, grand mal	very rare		

Fischbein, Del Rivero...Jimenez, NANETS Consensus Guidelines 2021

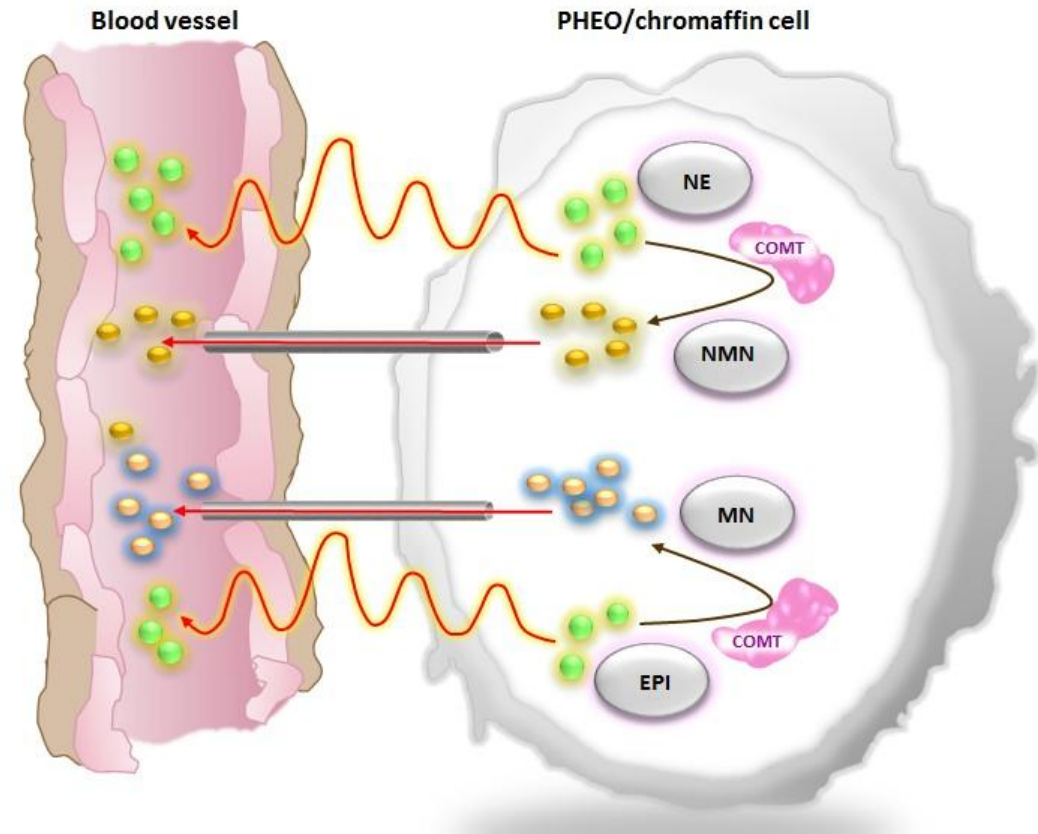
Pacak et al. DeGroot Endocrinology Textbook, 2021

Lenders et al. J. Hypertens. 2020; 38:1443 Eisenhofer et al. Eur. J. Cancer 2012; 48:1739

Diagnostic Approach: Biochemical Testing



- Plasma free metanephrines or 24-hour urine fractionated metanephrines are the cornerstone of biochemical diagnosis, with **97% sensitivity and 93% specificity**
- Elevations **>3 times the upper limit of normal** are diagnostic.

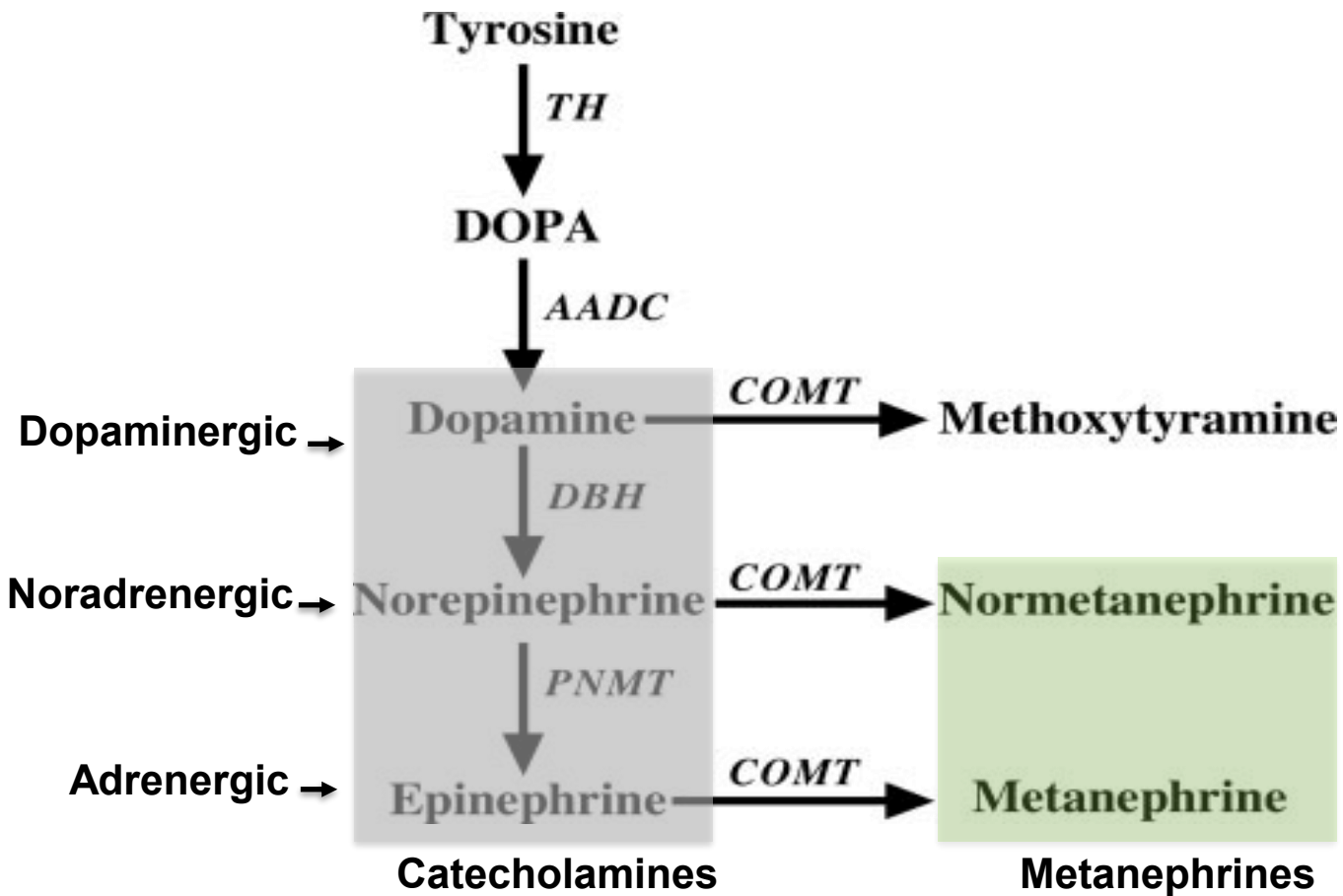


Metanephrines are produced and released continuously independent of pulsatile catecholamine secretion

COMT: catechol-O-methyl transferase

Lenders et al. JAMA 2002; 287:1427
Darr et al. Endocrine 2017; 56:495
Eisenhofer et al. Eur. J. Cancer 2012; 48:1739
& adapted from Lenders and Eisenhofer

Biochemical Diagnosis of PPGL



PHENOTYPE: Adrenergic: produces MN or EPI

MEN, NF-1



**Always adrenergic
(assess syndromic and
familial presentation)**

PHENOTYPE: Noradrenergic: produces NMN or NE

VHL, SDHx



**Assess syndromic and
familial presentation**

**PHENOTYPE: Noradrenergic & dopaminergic: produces also
DA or MTY**

SDHx



**See location: e.g.
head/neck:
SDHD**

Lenders et al. JAMA 2002; 287:1427

Darr et al. Endocrine 2017; 56:495

Eisenhofer et al. Eur. J. Cancer 2012; 48:1739

& adapted from Lenders and Eisenhofer

Important Preanalytical Considerations

- Discontinue interfering medications (tricyclic antidepressants, psychoactive agents) → 2 weeks before testing
- Plasma samples should be drawn in the supine position
- Clinical circumstances (acute illness) can cause false positives

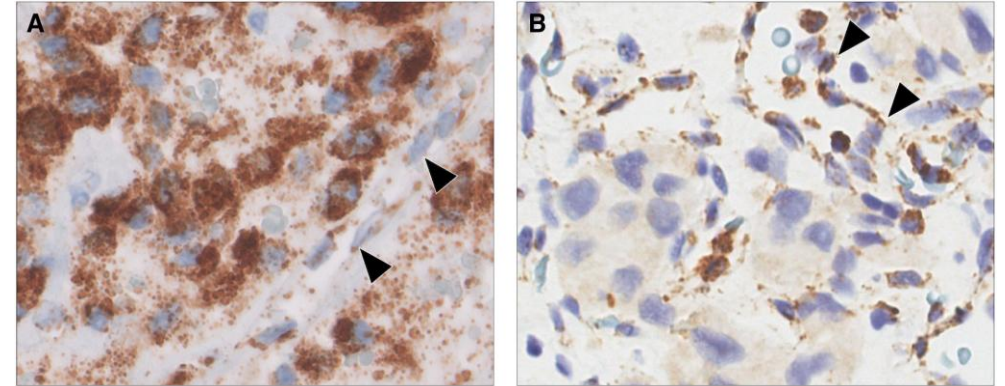
	Plasma		Urine	
	NMN	MN	NMN	MN
Acetaminophen	++	-	++	-
Labetalol	-	-	++	++
Sotalol	-	-	++	++
Buspirone	-	++	-	++
TCA	++	-	++	-
Phenoxybenzamine	++	-	++	-
Sulphasalazine	++	-	++	-
Levodopa	+	+	++	+

Acetaminophen: stop: 3-5 days; interferes with HPLC method

Eisenhofer & Pacak, Harrison's Textbook online, 2004
Lenders et al. Endocrine Society Guideline. JCEM 2014, 99(6):1915-1942

Role of SDHB Immunohistochemistry

- Sensitivity: ~95% for detection of SDHx-related tumors
- Specificity: ~82–92%, depending on tumor type and clinical setting
- Positive predictive value (PPV):
 - Head-and-neck paragangliomas: ~100%
 - Pheochromocytomas: ~25%



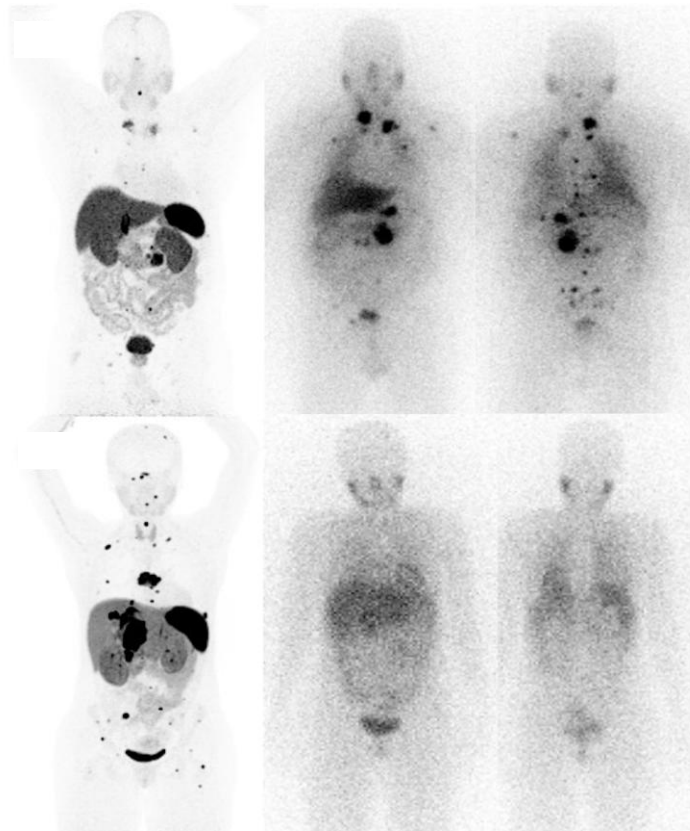
Loss of SDHB by IHC

Clinical Utility

- Guides genetic testing
 - SDHB loss → prioritize SDHx germline testing
- Prognostic information
 - Independent association with shorter disease-free survival and higher metastatic risk, especially relevant in SDHB-related disease
- Context-dependent interpretation
 - Must be integrated with tumor site, biochemistry, and family

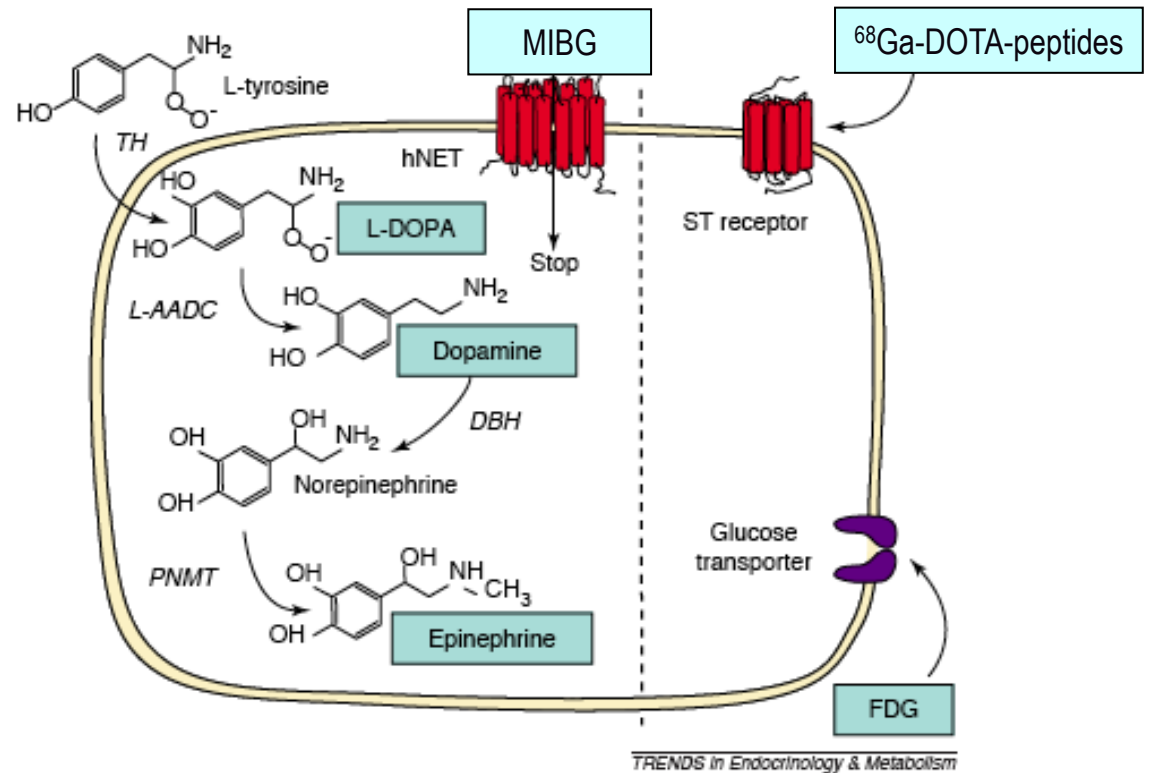
Molecular Imaging PPGL → Theranostics

- Diagnosis, staging, follow up of PPGL
- Selection for targeted molecular radiotherapy



⁶⁸Ga-Dotatate

¹²³I-MIBG



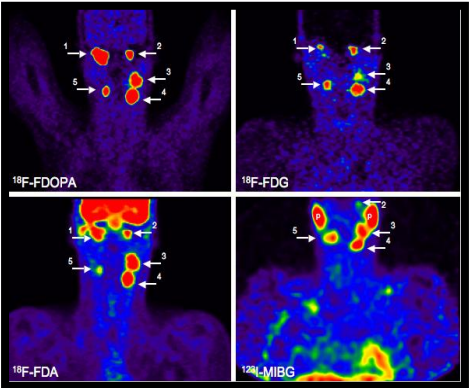
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⁶⁸ Ga-Dotatate	98-99%
¹⁸ F-FDG	68-92%

Taieb et al. J. Nucl. Med. 2012; 53:264

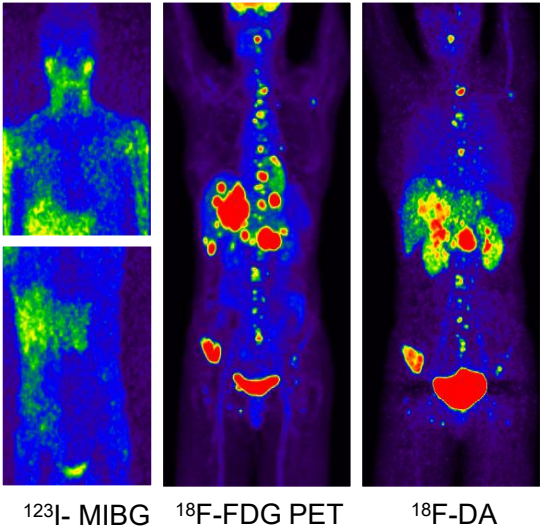
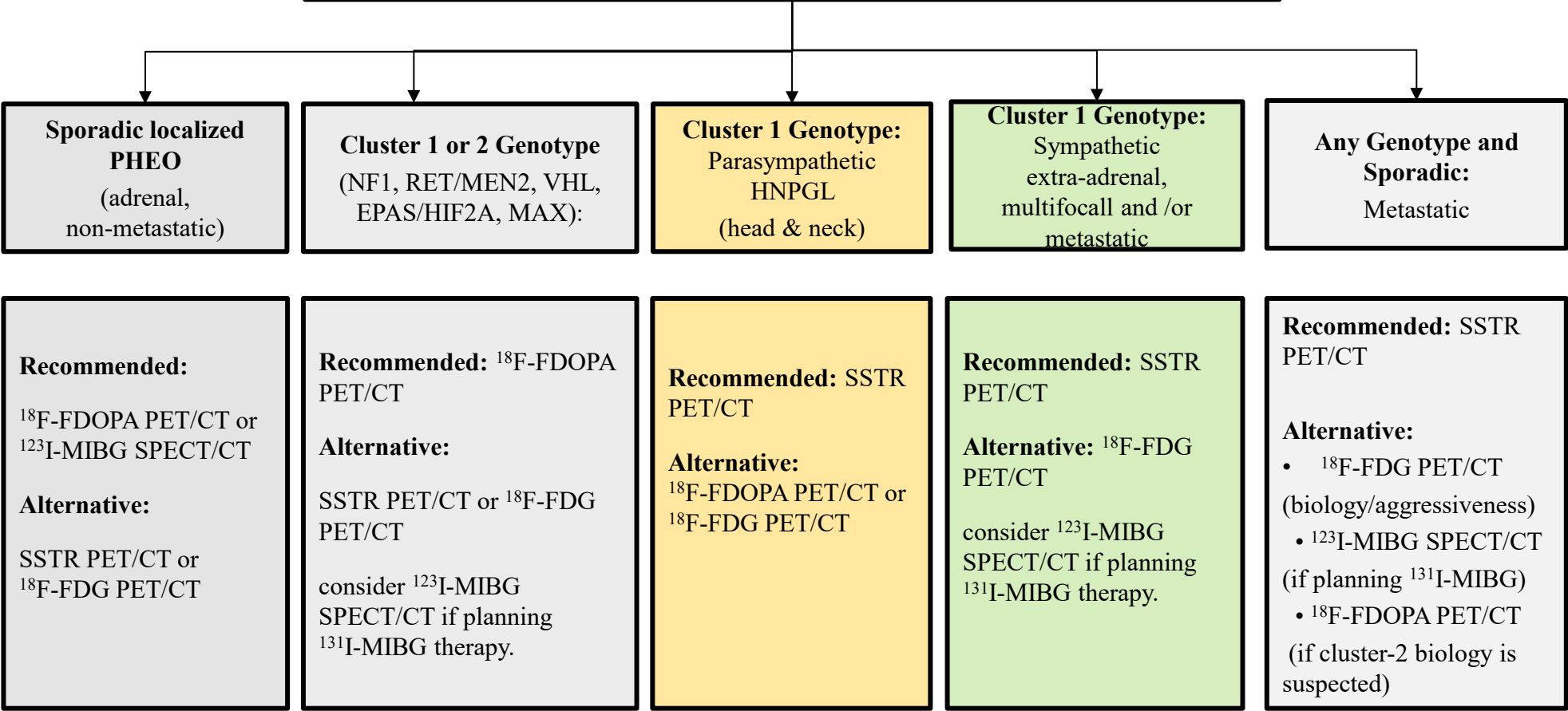
PET Imaging Algorithm for PPGLs

Head and neck PGLs:
¹⁸F-FDOPA: 100% (9 pts)



Kign et al. JCEM 2010; 95:481
King et al. JCEM 2011; 96:2779

Nuclear Imaging Algorithm for Pheochromocytoma / Paraganglioma (PPGL) *Radiotracer selection guided by tumor location, genotype, and metastatic status.*



Taïeb D et al. Eur J Nucl Med Mol Imaging. 2019 Sep;46(10):2112-2137
Hernandez et al. Radioligand Therapies for PPGL. Submitted for publication

Cluster-Based and General Systemic Therapies for Metastatic PPGL

Clinical Context	Preferred Therapeutic Options	Rationale
Cluster 1 – Pseudohypoxia (SDHx, VHL, EPAS1)	Belzutifan (VHL / EPAS1) Temozolomide or CVD (especially SDHB)	HIF stabilization, angiogenesis, and DNA repair vulnerability dominate biology
Cluster 2 – Kinase signaling (RET, NF1, TMEM127, MAX)	Anti-angiogenic TKIs (sunitinib, cabozantinib) Selpercatinib (RET-driven disease)	Kinase pathway activation; targetable oncogenic drivers
SSTR-positive disease	PRRT (¹⁷⁷Lu-DOTATATE)	High somatostatin receptor expression on functional imaging
MIBG-avid disease (any cluster)	High-specific-activity ¹³¹I-MIBG	NET expression enables targeted radiotherapy

Conclusions

- ✓ PPGLs have the highest heritability of all tumors, with approximately 40% of cases harboring germline mutations in over 20 susceptibility genes
- ✓ All patients with PPGL should receive genetic counseling and testing
- ✓ SDHB mutations confer the highest metastatic risk and require the most intensive surveillance starting in childhood
- ✓ Lifelong surveillance is required for all PPGL patients due to risk of recurrence and metastasis
- ✓ Plasma metanephrines are the preferred biochemical test with high sensitivity and specificity
- ✓ SDHB immunohistochemistry can guide genetic testing and provides independent prognostic information
- ✓ Functional imaging → recommended to be cluster-specific
- ✓ Three main molecular clusters: Cluster 1 (Pseudohypoxia/Krebs Cycle), Cluster 2 (Kinase signaling), Cluster 3 (Wnt Signaling)
- ✓ Molecular cluster classification guides biochemical testing, imaging selection, surveillance intensity, and therapeutic options
- ✓ Multidisciplinary management with tumor boards is essential for optimal outcomes

Thank You for Your Attention!

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[@JaydiDelRivero](https://www.instagram.com/JaydiDelRivero)

Treatment of Advanced Pheochromocytoma and Paraganglioma

Camilo Jimenez, MD

Professor

Department of Endocrine Neoplasia and Hormonal Disorders

The University of Texas MD Anderson Cancer Center

Houston, Texas, USA

DISCLOSURE INFORMATION

*Research support provided by MERCK, EXELIXIS, LANTHEUS
PHARMACEUTICALS, PROGENICS*

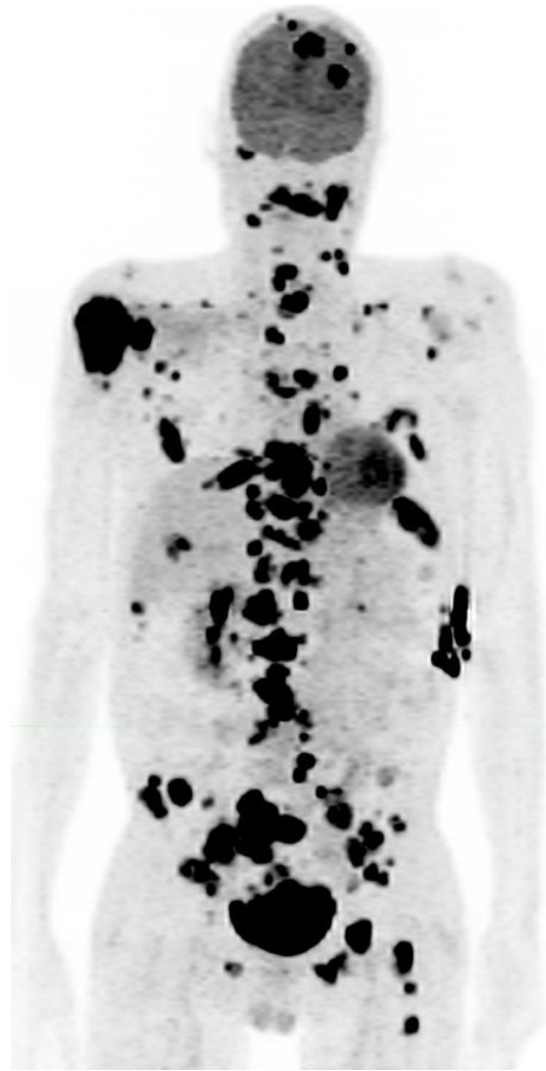
DISCLOSURE SLIDE

- *Advisory Board: MERCK*
- *The University of Texas MD Anderson Cancer Center has received research financial support from MERCK, EXELIXIS, LANTHEUS PHARMACEUTICALS, PROGENICS*

Outline

- ✓ Introduction
 - ✓ Pheochromocytomas and Paragangliomas are tumors with heterogeneous behavior
- ✓ Clinical Trials with Definitive Results:
- ✓ Active and/or effective systemic therapies that target hallmarks of cancer irrespective of genotype
 - ✓ Cabozantinib
 - ✓ Sunitinib
- ✓ Systemic therapies that represent examples of precision medicine
 - ✓ Belzutifan

Metastatic Pheochromocytomas and Paragangliomas

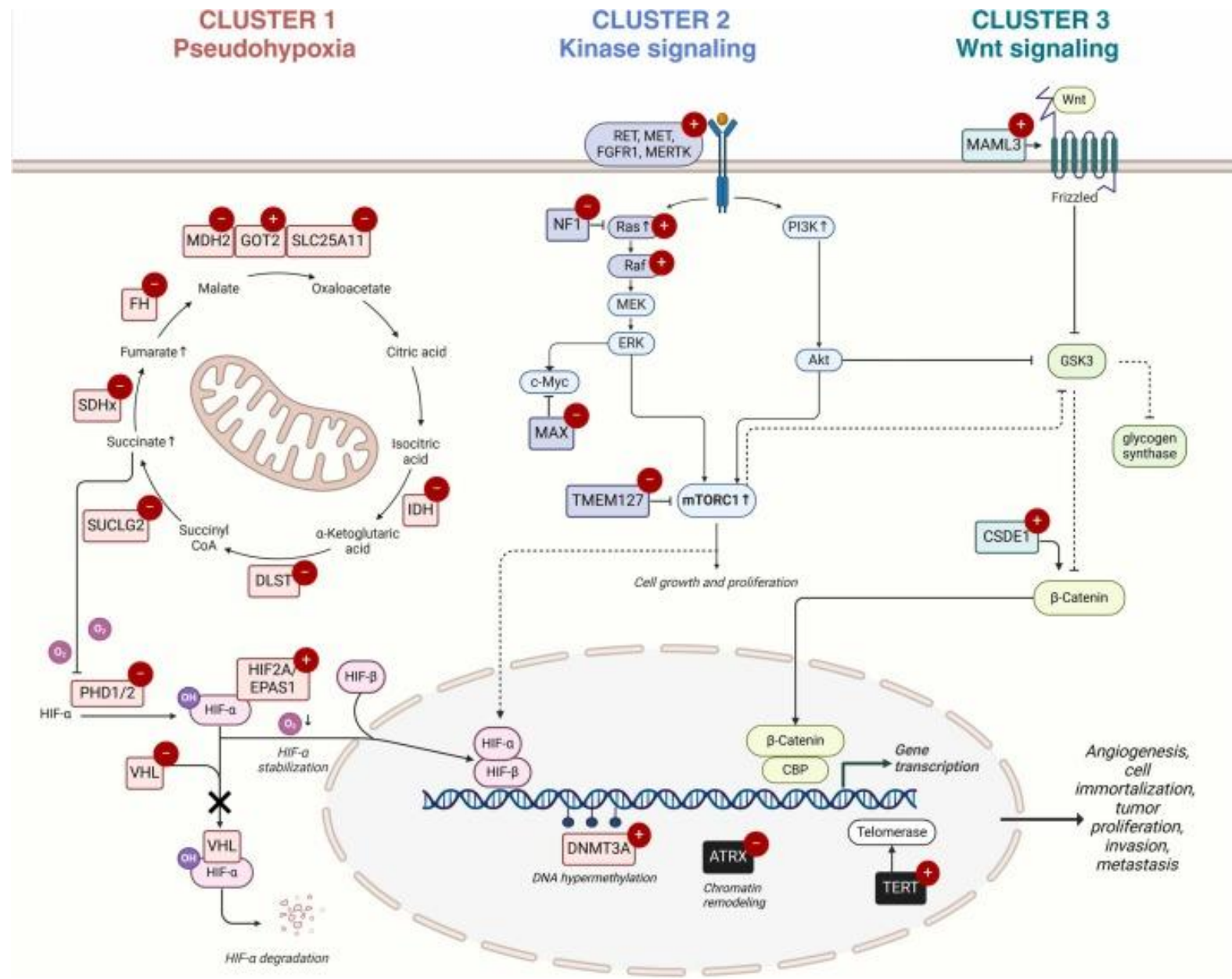


Up to 25% of pheochromocytomas and paragangliomas are metastatic (MPPGLs)

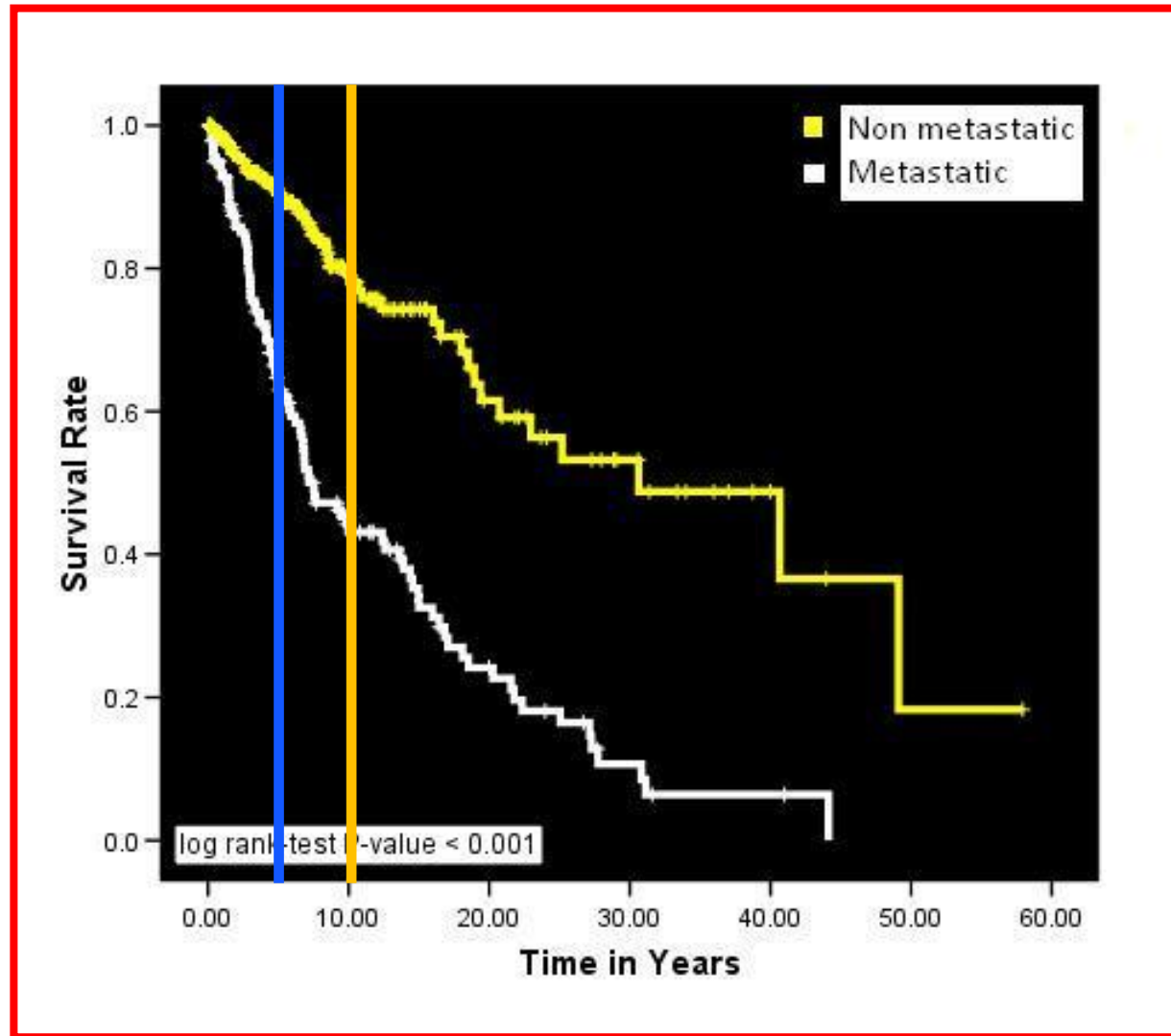
- ✓ MPPGLs may or may not be hormonally active
- ✓ Up to 50% of MPPGLs are associated with germline *SDHB* pathogenic variants (Cluster 1-Pseudohypoxia)
- ✓ Metastases happen more commonly in lymph nodes, bones, liver, and lungs
- ✓ 50% are synchronous, 50% are metachronous
- ✓ 50-60% express the noradrenaline transporter and are MIBG-avid and >90% express the somatostatin receptors (DOTATATE positive)

Molecular phenotype of
Metastatic
pheochromocytomas and
paragangliomas:

Cluster 1: 80-85%
Cluster 2: 5-10%
Cluster 3: 5-7%



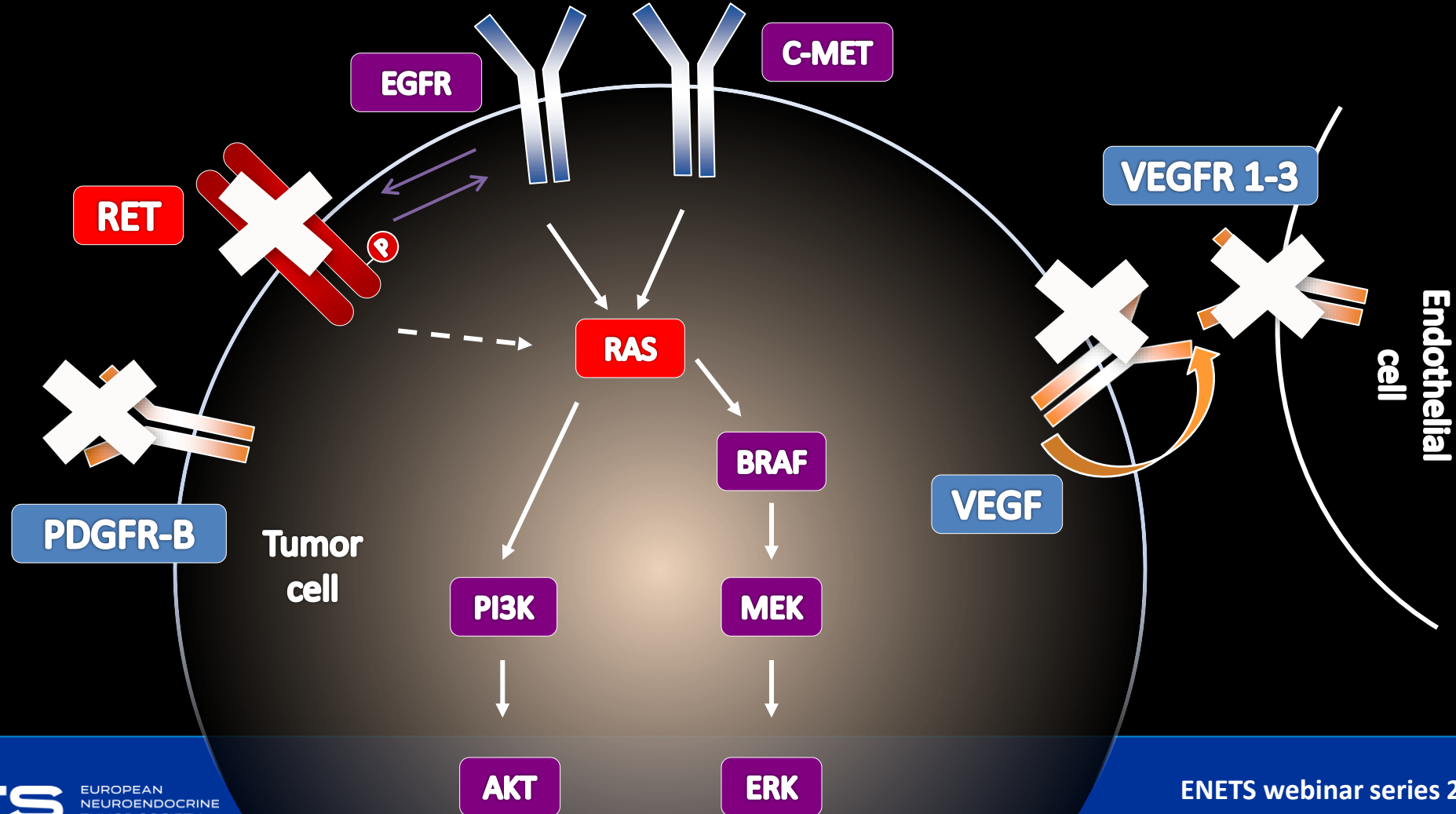
Overall Survival MPPGLs vs. Non-metastatic PPGLs



Morbidity and survival are determined by:

1. Hormonal activity
2. Tumor burden
3. Speed of progression

Sunitinib



Sunitinib for metastatic progressive phaeochromocytomas and paragangliomas: results from FIRSTMAPPP, an academic, multicentre, international, randomised, placebo-controlled, double-blind, phase 2 trial

Eric Baudin, Bernard Goichot, Alfredo Berruti, Julien Hadoux, Salma Moalla, Sandrine Laboureau, Svenja Nölting, Christelle de la Fouchardière, Tina Kienitz, Timo Deutschbein, Stefania Zovato, Laurence Amar, Magalie Haissaguerre, Henri Timmers, Patricia Niccoli, Antongiulio Faggiano, Moussa Angokai, Livia Lamartina, Florina Luca, Deborah Cosentini, Stefanie Hahner, Felix Beuschlein, Marie Attard, Matthieu Texier, Martin Fassnacht*; on behalf of the ENDOCAN-COMETE and ENSAT Networks*

THE LANCET

Baudin E, et al. Lancet. 2024 Mar 16;403(10431):1061-1070.

FIRSTMAPPP: Double-blind Randomized Phase II Trial

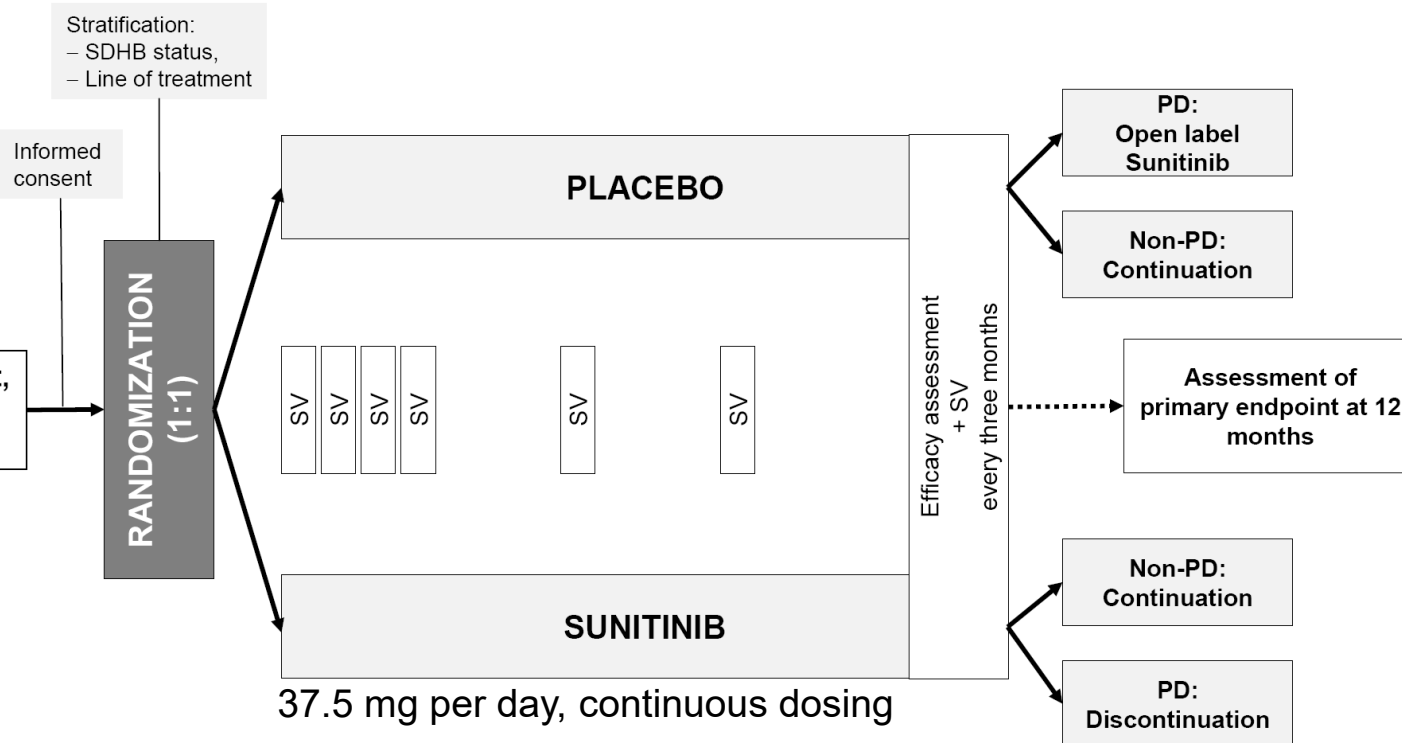
Main inclusion criteria

- Metastatic disease
- Pre-treated or not
- Evaluable, RECIST 1.1 criteria
- Progressive disease within 18 months according to RECIST

Main exclusion criteria

- Hypertension that cannot be controlled
- Abnormal cardiac function
- Prior tyrosine kinase inhibitors or anti-VEGF inhibitors.

Patient with malignant, non-resectable, progressive PPGL

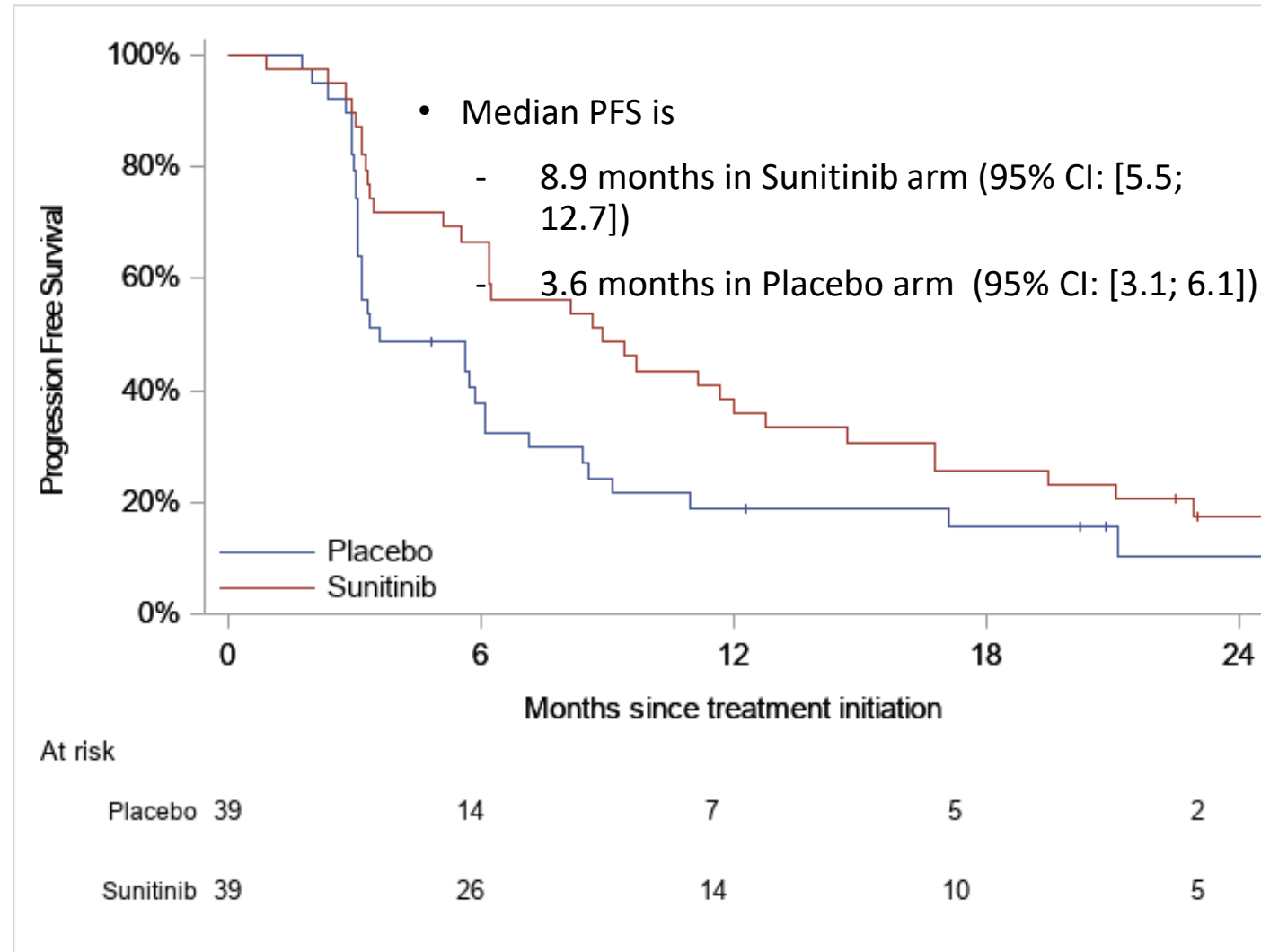


RECIST 1.1/12 weeks
Real time central review

Sunitinib dose 37.5 mg daily (continuous dosing)

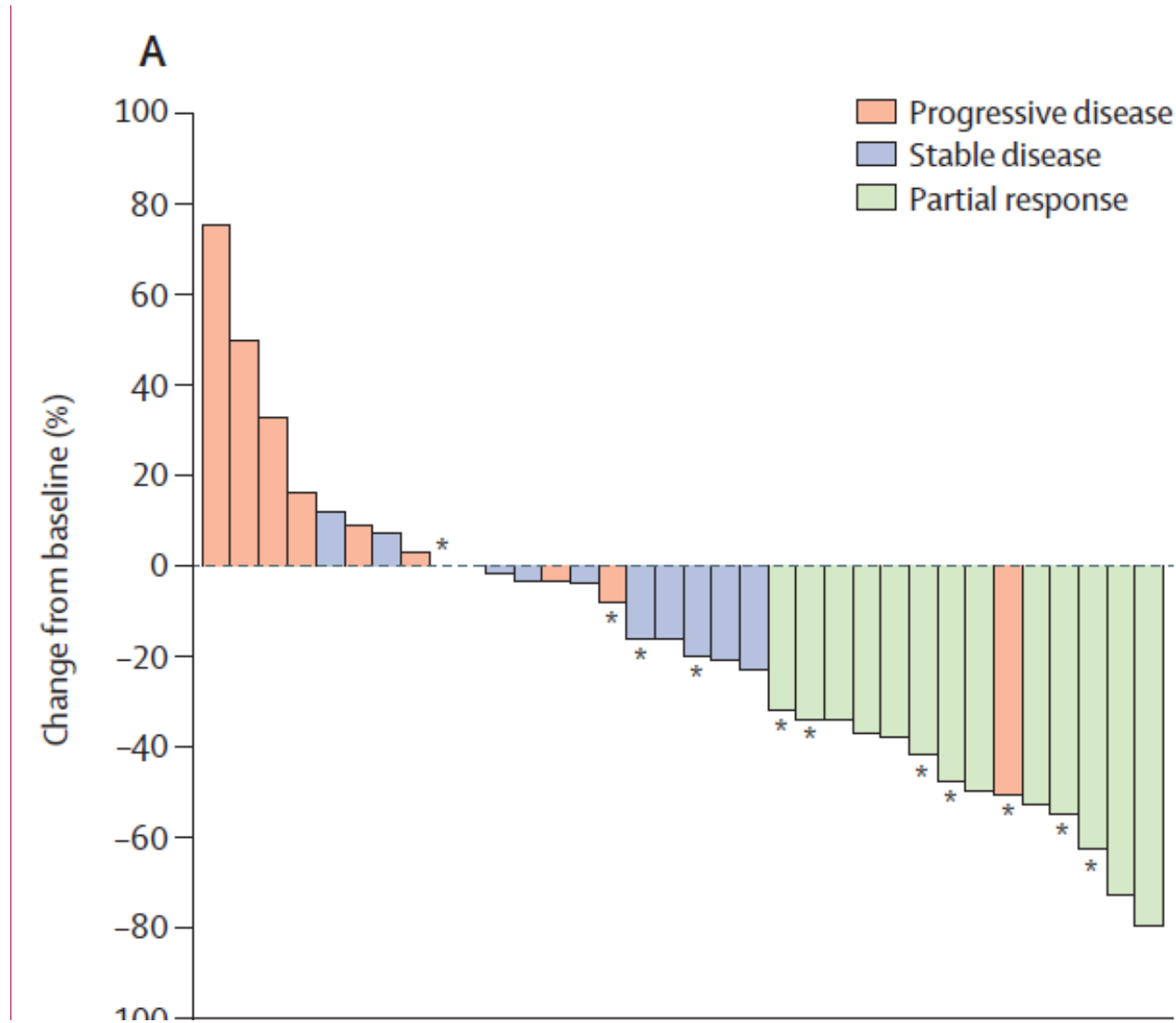
Baudin E, et al. Lancet. 2024 Mar 16;403(10431):1061-1070.

Progression Free Survival



Baudin E, et al. Lancet. 2024 Mar 16;403(10431):1061-1070.

FIRSTMAPPP: Objective Response Rate 36%

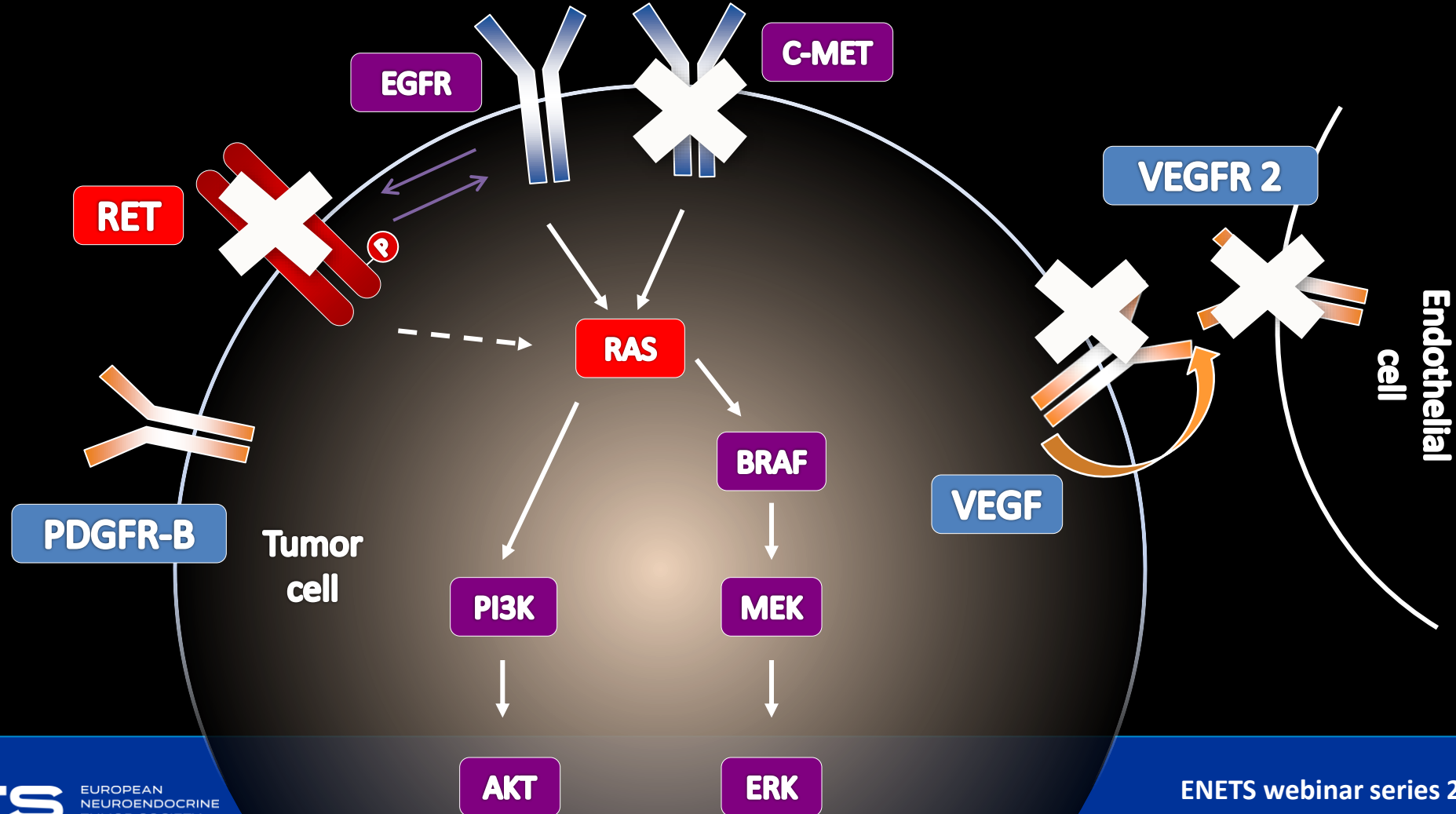


ORR 36%
DCR 72%

SDHB (+)
ORR 50%

Baudin et al, Lancet, 2024

Cabozantinib



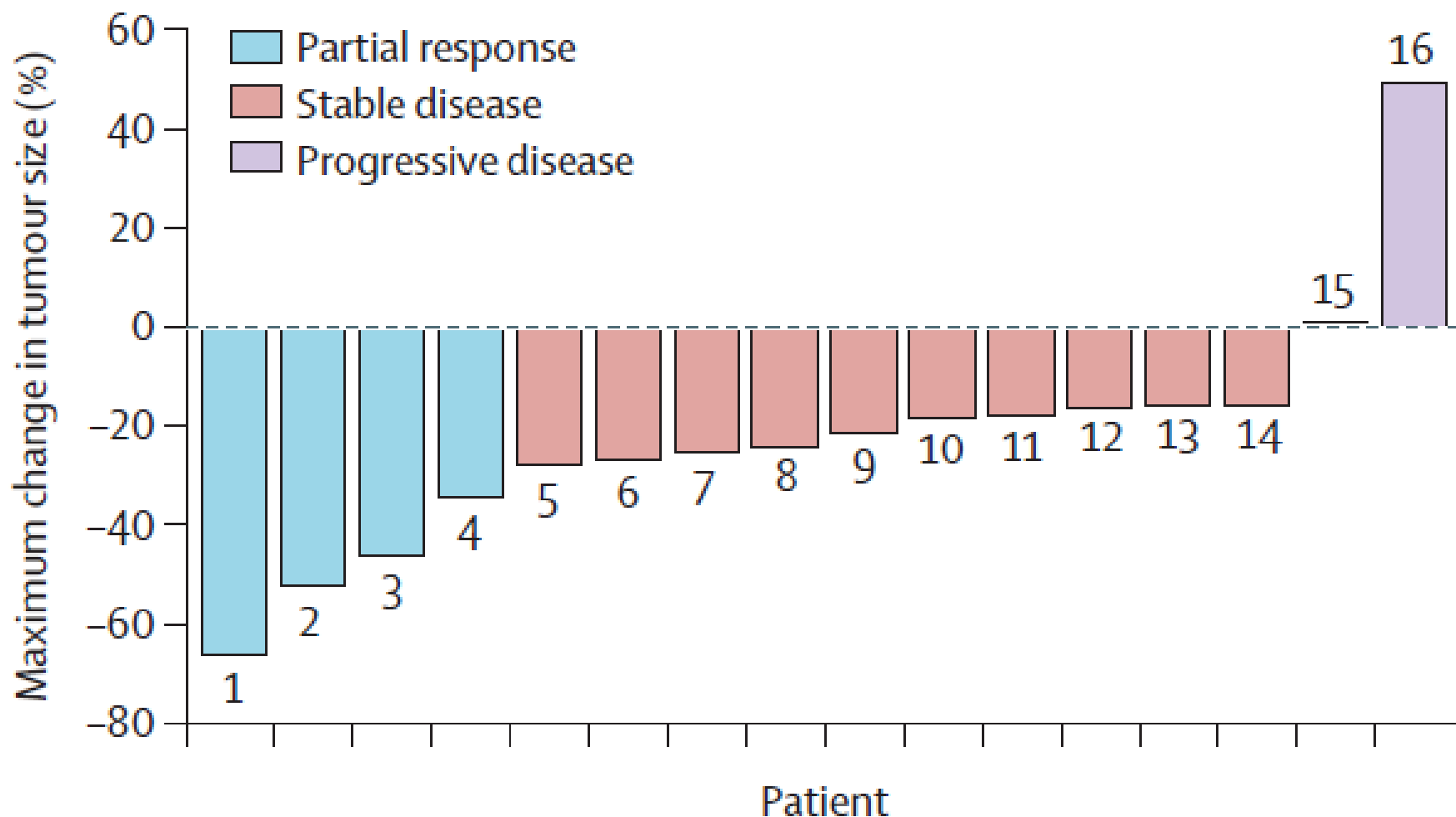
Cabozantinib in patients with unresectable and progressive metastatic phaeochromocytoma or paraganglioma (the Natalie Trial): a single-arm, phase 2 trial

Camilo Jimenez, Mouhammed Amir Habra, Matthew T Campbell, Gina Tamsen, Damaris Cruz-Goldberg, James Long, Roland Bassett, Robert Dantzer, Vania Balderrama-Brondani, Jeena Varghese, Yang Lu

THE LANCET
Oncology

Jimenez C et al. Lancet Oncol. 2024 Apr 9:S1470-2045(24)00133-5.

NATALIE: Objective Response Rate 25%

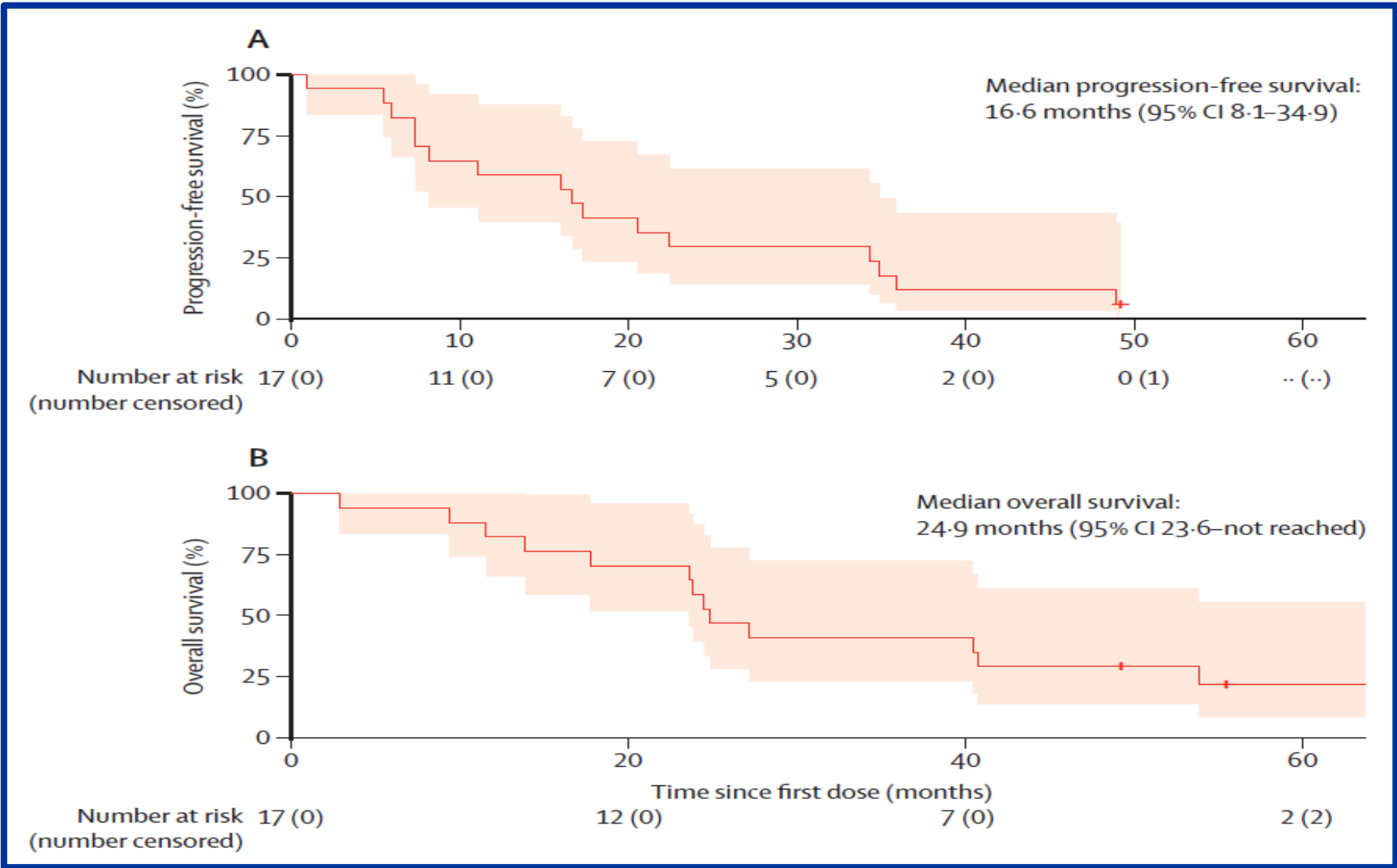


ORR 25%
DCR 93%

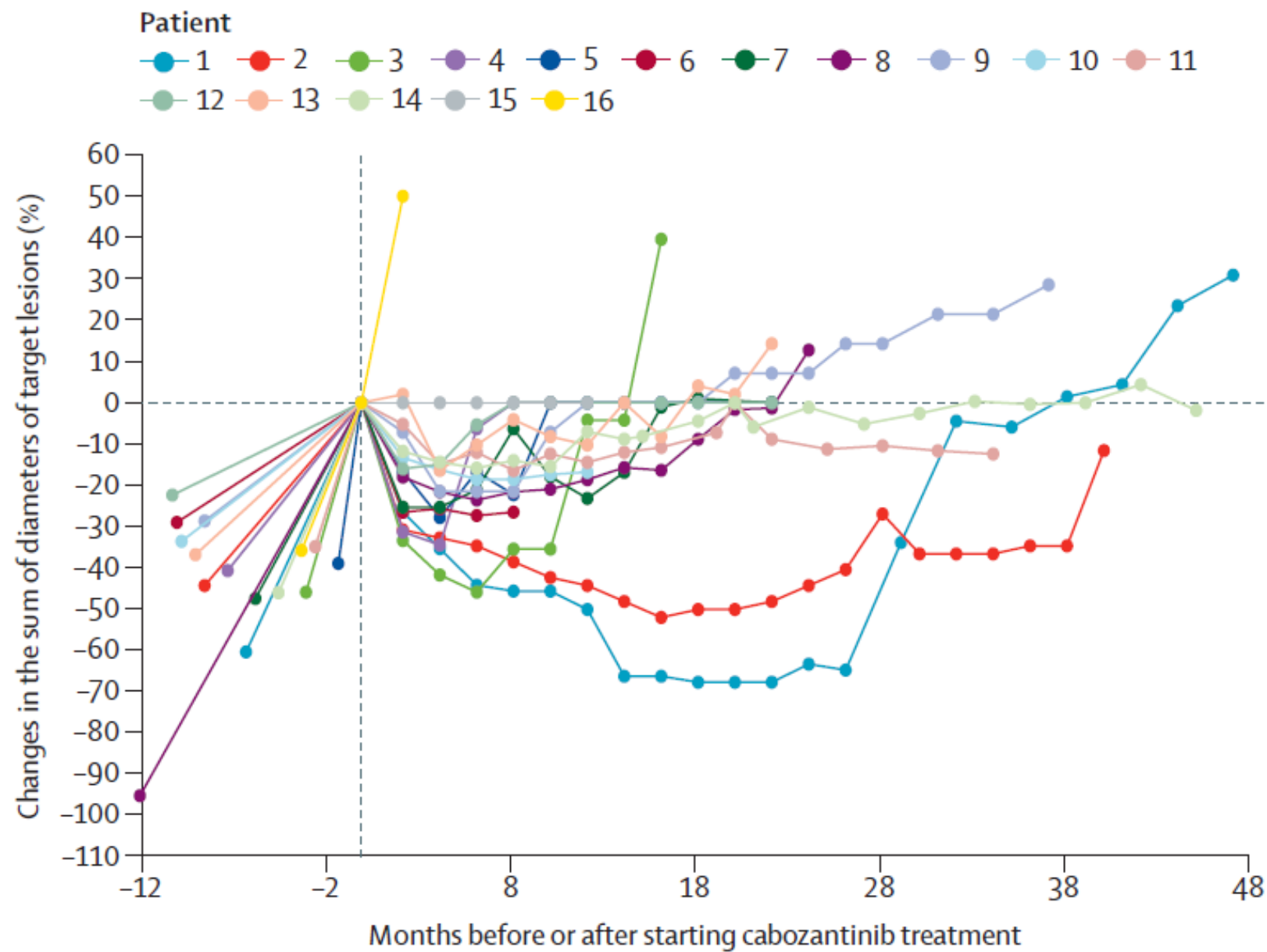
SDHB (+):
ORR 60%
DCR 100%

Jimenez C et al. Lancet Oncol. 2024
Apr 9:S1470-2045(24)00133-5.

Median Progression Free Survival and Median Overall Survival



Jimenez C et al. Lancet Oncol. 2024
Apr 9:S1470-2045(24)00133-5.



Jimenez C et al. Lancet Oncol. 2024 Apr
9:S1470-2045(24)00133-5.

Adverse events

	Grade 1	Grade 2	Grade 3
Laboratory abnormalities			
Increased ALT or AST	15 (88%)	0	0
Increased alkaline phosphatase	7 (41%)	2 (12%)	0
Increased amylase or lipase	2 (12%)	1 (6%)	2 (12%)
Increased creatinine	6 (35%)	1 (6%)	0
Hypomagnesaemia	3 (18%)	0	1 (6%)
General disorders			
Dysgeusia	12 (71%)	0	0
Hand-and-foot syndrome	7 (41%)	3 (18%)	1 (6%)
Mucositis	8 (47%)	2 (12%)	0
Fatigue	7 (41%)	9 (53%)	0
Weight loss	8 (47%)	2 (12%)	0
Hypertension	4 (24%)	11 (65%)	1 (6%)
Diarrhoea	7 (41%)	0	0
Nausea	8 (47%)	0	0
Arthralgia or myalgia	6 (35%)	0	0
Primary hypothyroidism	4 (24%)	8 (47%)	0
Anorexia	7 (41%)	4 (24%)	0
Hoarseness	4 (24%)	0	0
Rectal fistula	0	0	1 (6%)
QT interval prolongation	0	0	1 (6%)
Grey hair or skin hypopigmentation	7 (41%)	0	0
Peripheral oedema	2 (12%)	0	0

Jimenez C et al. Lancet Oncol. 2024 Apr 9:S1470-2045(24)00133-5.

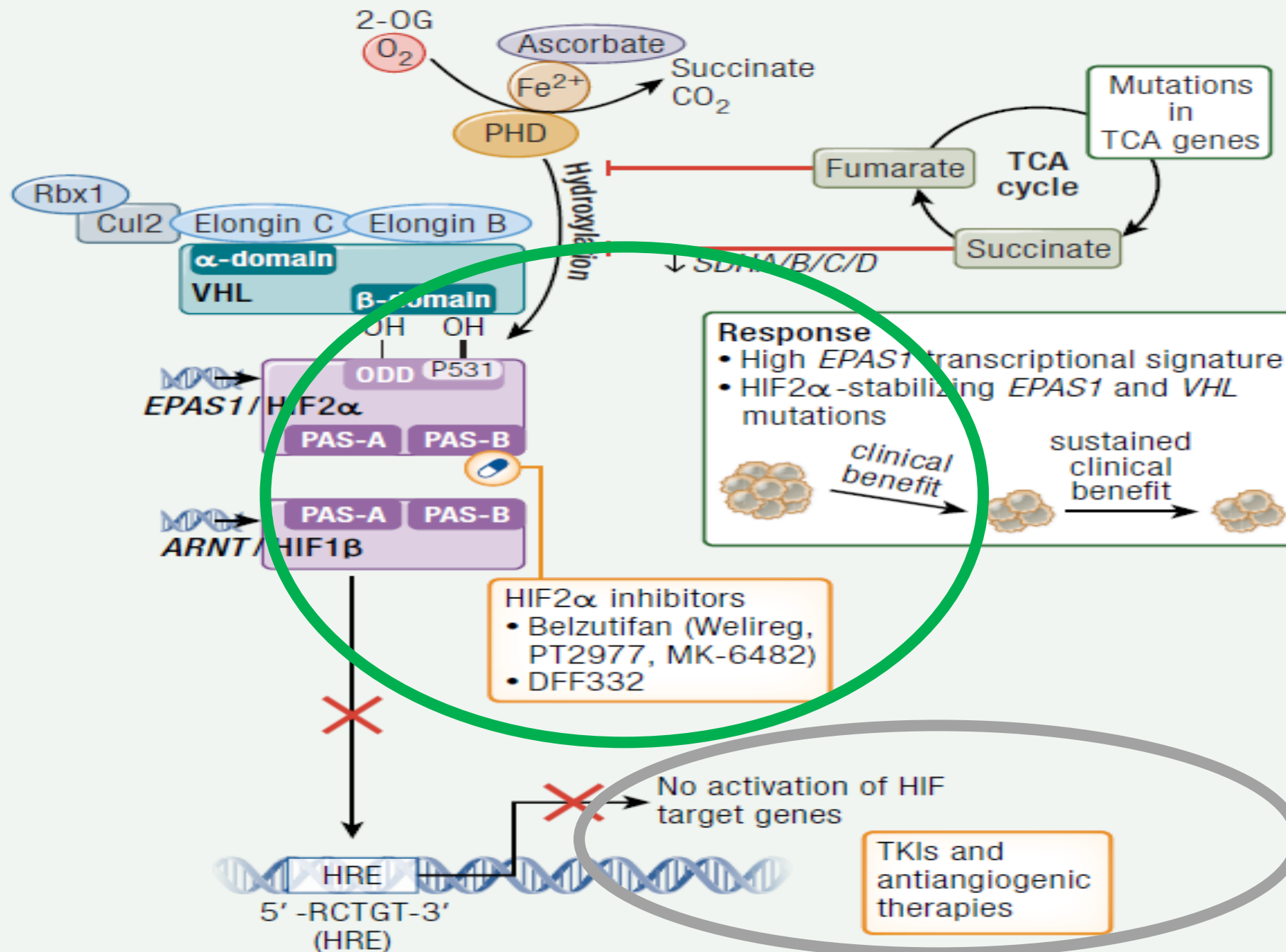
NATALIE Trial: Oncomine Analysis

Solid Tumor Genomic Assay-DNA Report

- ✓ A next-generation sequencing (NGS)–based analysis was performed to detect somatic mutations in the coding sequence of 136 genes and selected copy number variations (amplifications) in 47 genes in the DNA extracted from the sample
- ✓ There were no c-met pathogenic variants/amplifications
- ✓ There were 5 cases with paraganglioma syndrome type 4.
- ✓ There were no somatic pathogenic variants.
- ✓ Oncomine did not test for cluster 3 pathogenic variants

Jimenez C et al. Lancet Oncol. 2024 Apr 9:S1470-2045(24)00133-5.

Sensitive tumors



ORIGINAL ARTICLE

Belzutifan for Advanced Pheochromocytoma or Paraganglioma

Camilo Jimenez, M.D.,¹ Mikkel Andreassen, M.D., Ph.D.,² Alice Durand, M.D.,³
Sophie Moog, M.D., Ph.D.,⁴ Andrew Hendifar, M.D.,⁵ Staffan Welin, M.D.,⁶
Francesca Spada, M.D., Ph.D.,^{7,8} Rohini Sharma, M.B., B.S., Ph.D.,⁹
Edward Wolin, M.D.,¹⁰ Joseph Ruether, M.D.,¹¹ Rocio Garcia-Carbonero, M.D.,¹²
Martin Fassnacht, M.D.,^{13,14} Jaume Capdevila, M.D., Ph.D.,¹⁵
Jaydira Del Rivero, M.D.,¹⁶ Othon Iliopoulos, M.D.,¹⁷ Olivier Huillard, M.D.,¹⁸
Raymond Jang, M.D.,¹⁹ Knut Mai, M.D.,^{20,21} Elena Artamonova, M.D., Ph.D.,²²
Andreas Hallqvist, M.D.,²³ Tobias Else, M.D.,²⁴ Amos Odeleye-Ajakaye, M.S.,²⁵
Alexander Gozman, M.D.,²⁵ Girish S. Naik, M.D., M.M.Sc.,²⁵ and
Alfredo Berruti, M.D.,²⁶ for the LITESPARK-015 Investigators*

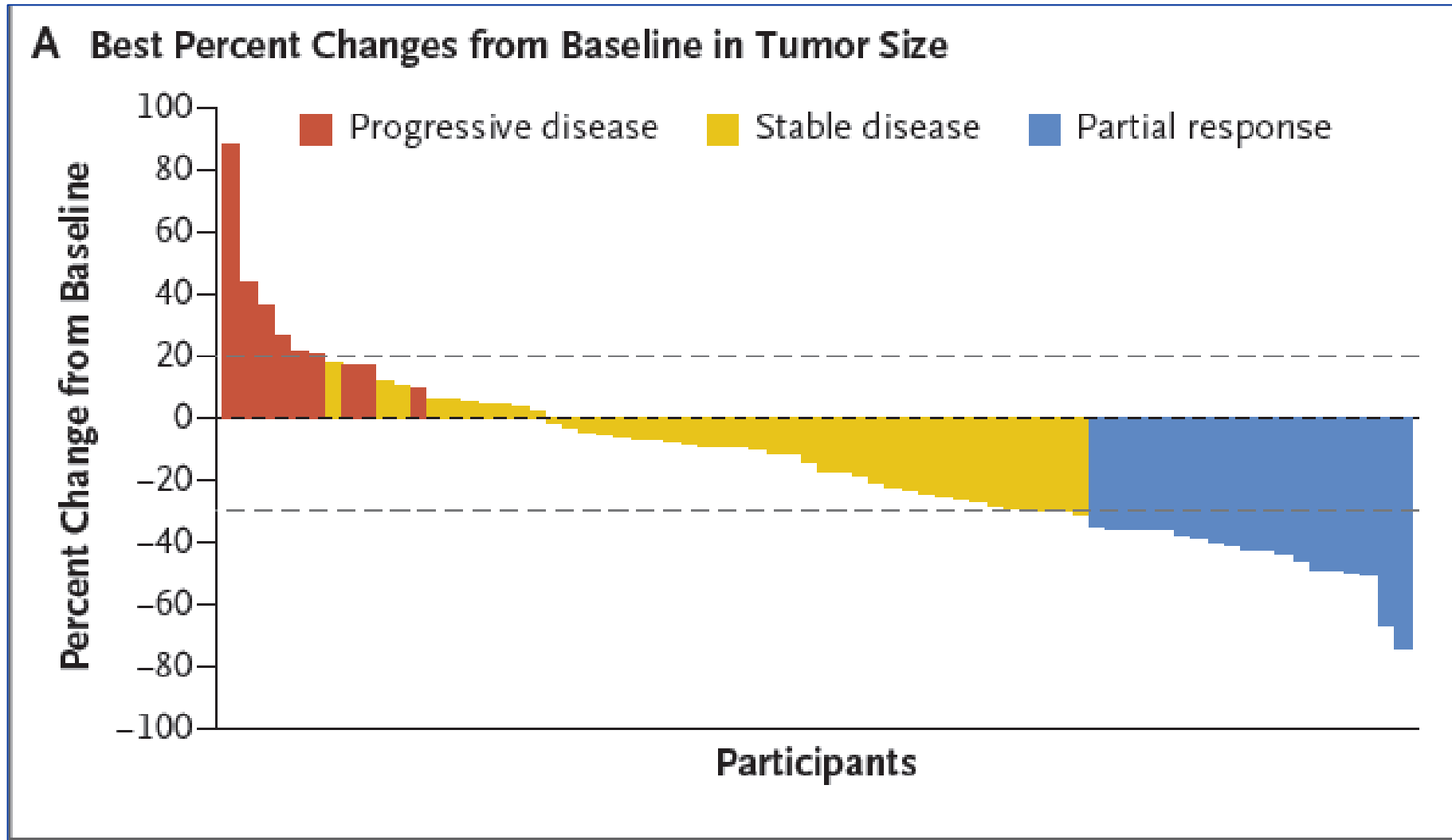
Baseline Characteristics

Demographic or characteristic	PPGL N = 72
Median age, (range)	51.5 (22-77)
≥ 65	9 (13%)
Sex	
Male	42 (58%)
Female	30 (42%)
Geographical region	
North America	21 (29%)
Western Europe	46 (64%)
Rest of the World	5 (7%)
ECOG performance status	
0	39 (54%)
1	33 (46%)
Prior lines of therapy^a	
Median (range)	1 (0 ^a ,5)
≥1 prior line of systemic therapy	54 (75%)
Prior therapy	
Chemotherapy	36 (50%)
Radiopharmaceutical	32 (44%)
VEGF tyrosine kinase inhibitor	18 (25%)
Other anti-cancer therapy	5 (7%)
Somatostatin analog	10 (14%)
Disease presentation type	
Locally advanced	2 (3%)
Metastatic	70 (97%)

Demographic or characteristic	PPGL N = 72
Medical history of hypertension	
Yes	60 (83%)
No	2 (17%)
Genetic syndrome history	
Yes	28 (39%)
SDHA-related tumor predisposition syndrome	2 (3%)
SDHB-related tumor predisposition syndrome	24 (33%)
SDHD-related tumor predisposition syndrome	2 (3%)
No	20 (28%)
Unknown	24 (33%)
Diagnosis	
Pheochromocytoma	24 (33%)
Paraganglioma	45 (63%)
Both	3 (4%)
Baseline tumor burden (mm)	
Median (range)	84.5 (10-261)
Baseline site of disease or metastasis	
Lymph node	48 (67%)
Bone	41 (57%)
Liver	23 (32%)
Lung	19 (26%)
Peritoneum	10 (14%)
Other	57 (79%)

Jimenez C et al. NEJM, 2025, Nov. 20, 2012-2022

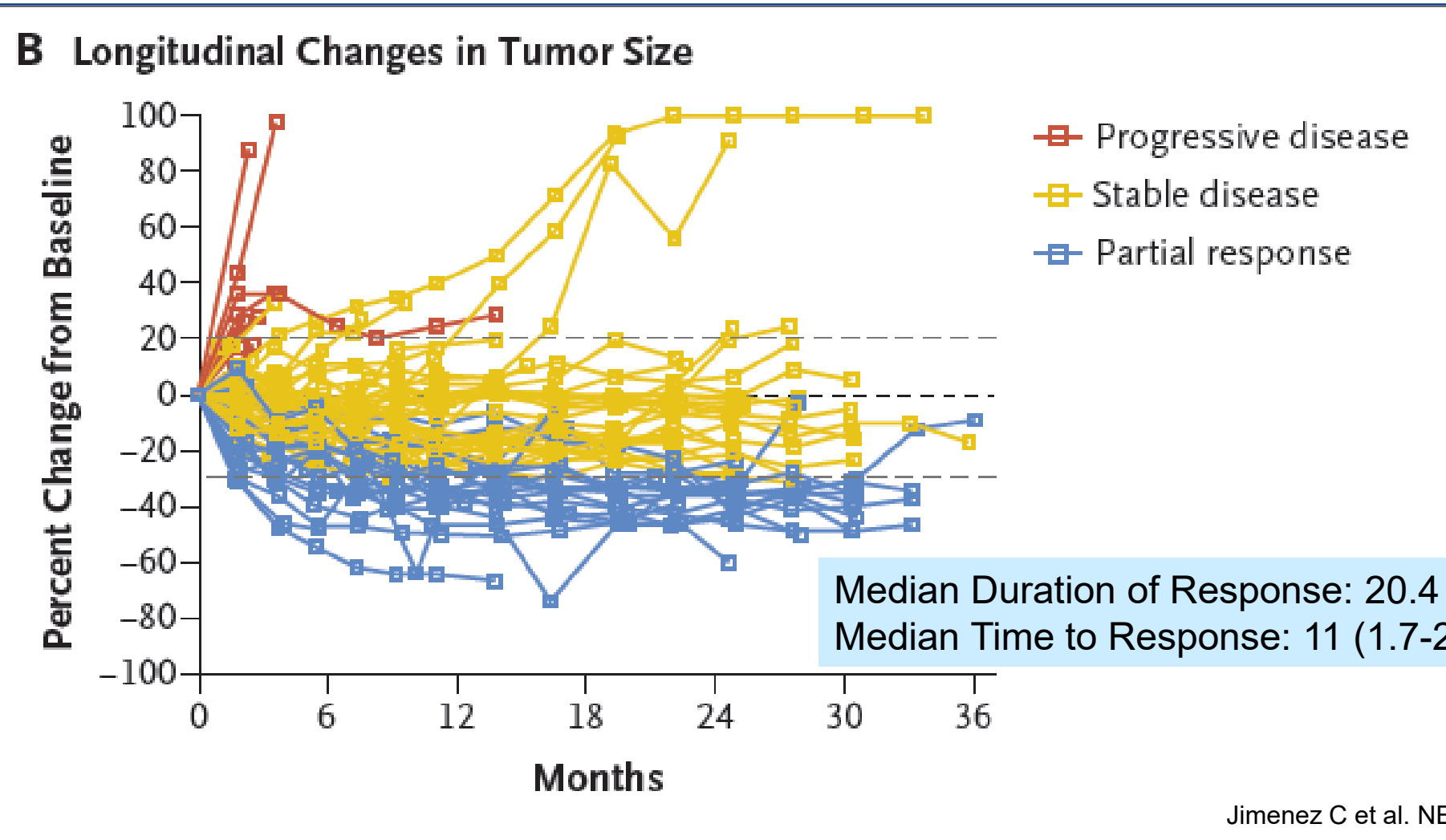
LITESPARK 015: ORR



ORR: 19 (26%)
DCR: 61 (85%)
CR: 0
PR: 19 (26.4%)
SD: 42 (58.3%)

Jimenez C et al. NEJM, 2025, Nov. 20, 2012-2022

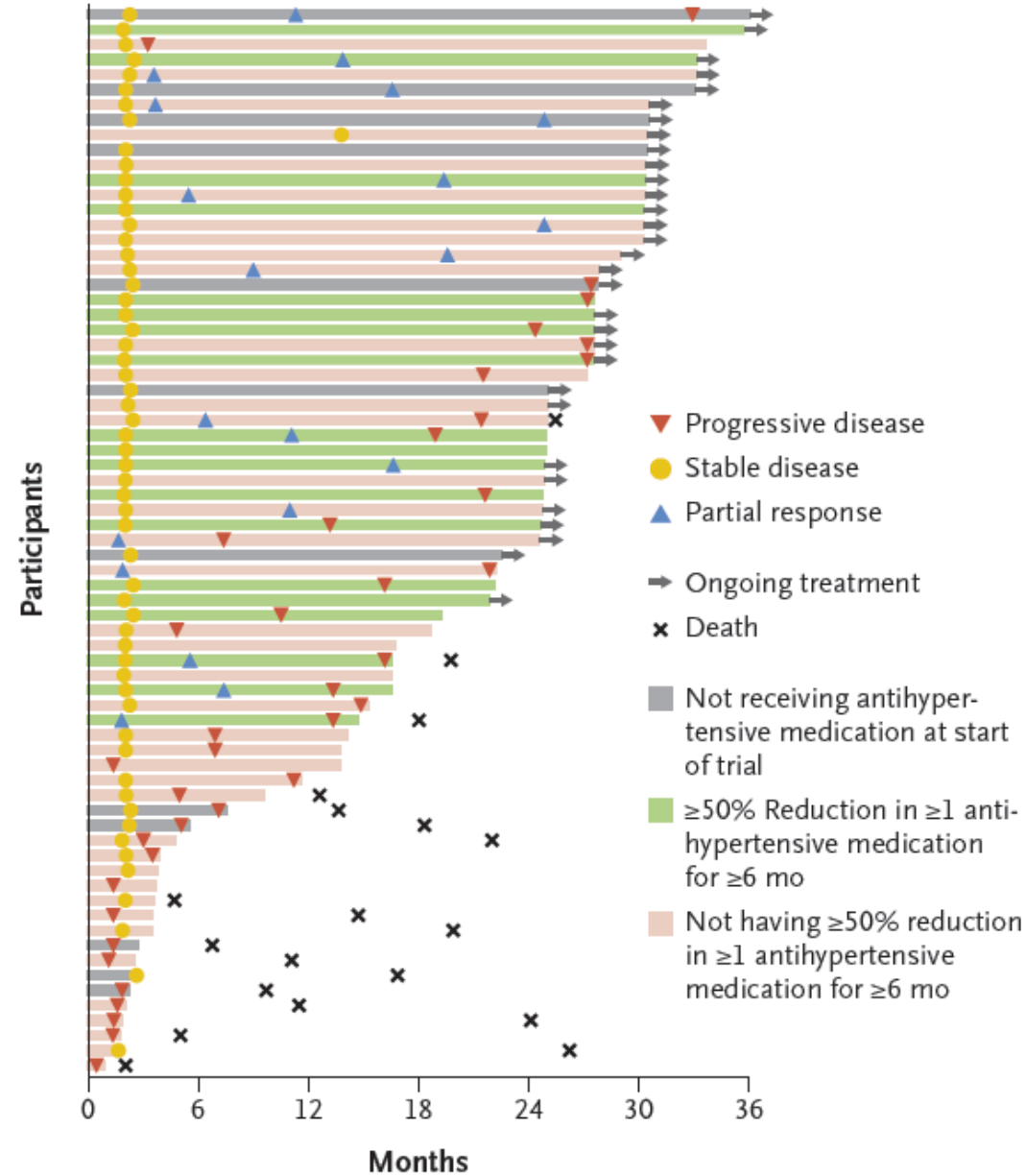
LITESPARK 015: Duration of Response



Jimenez C et al. NEJM, 2025, Nov.20, 2012-2022

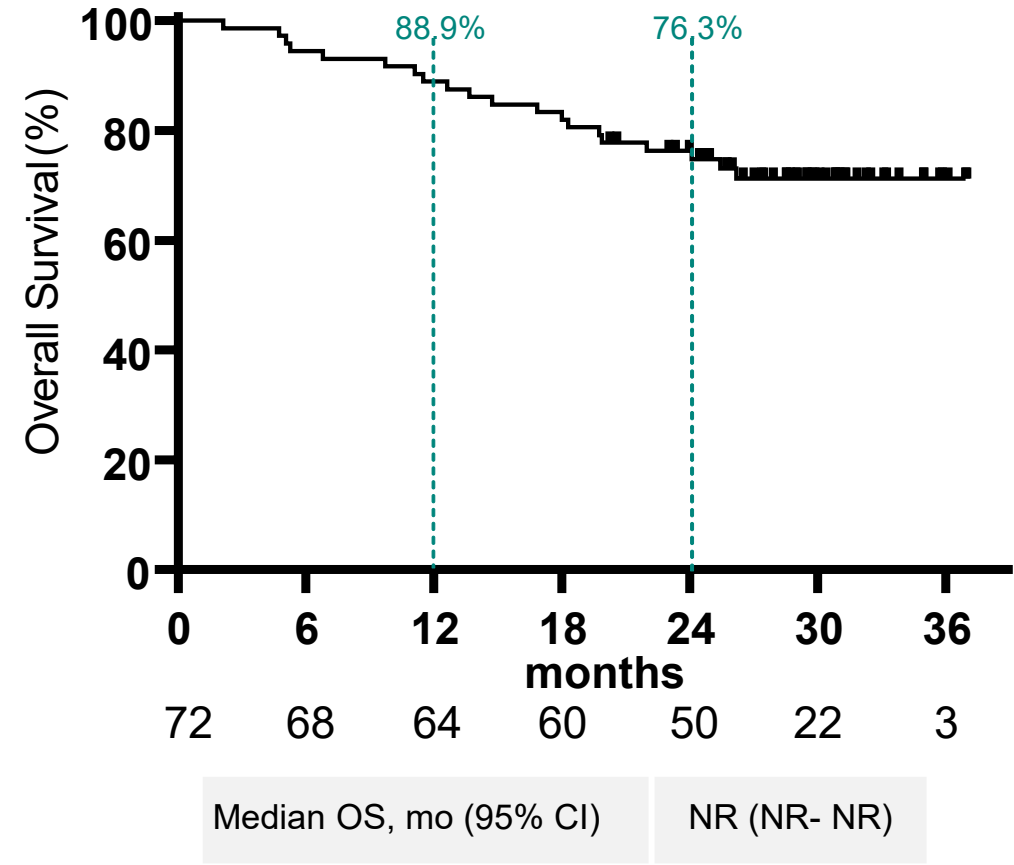
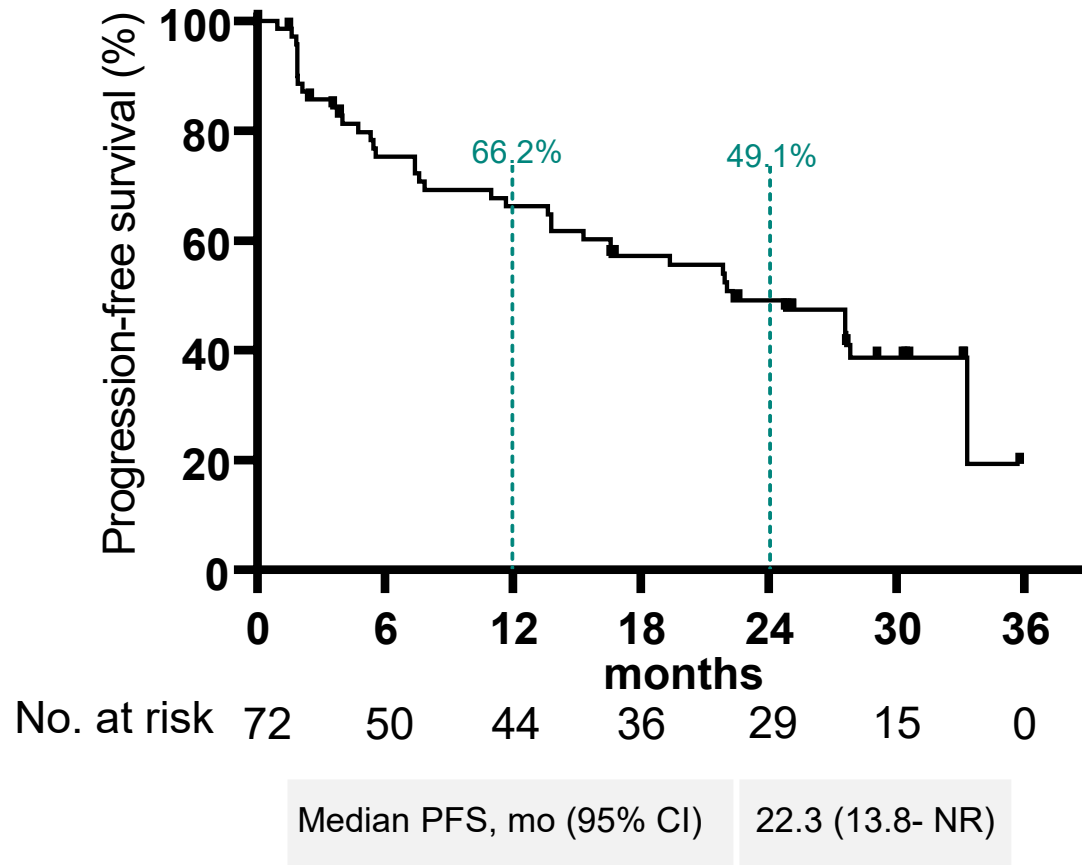
LITESPARK 015: Duration of Trial Treatment and Time to Response

C Duration of Trial Treatment and Time to Response



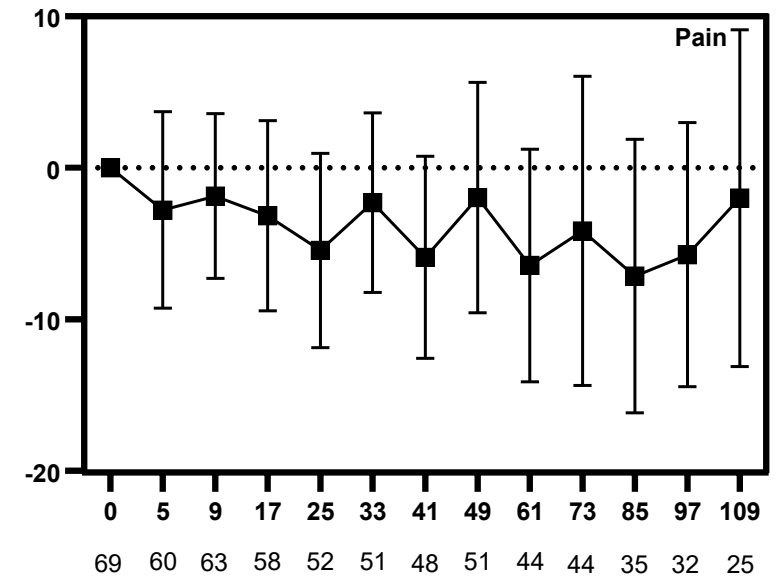
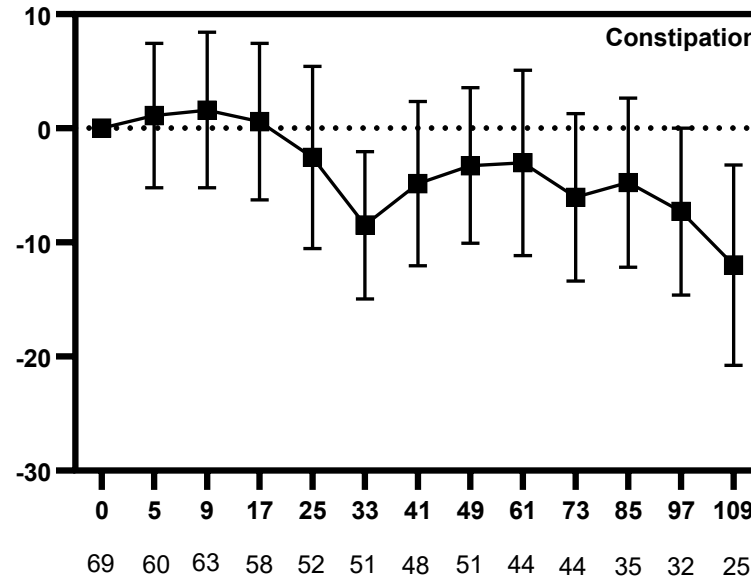
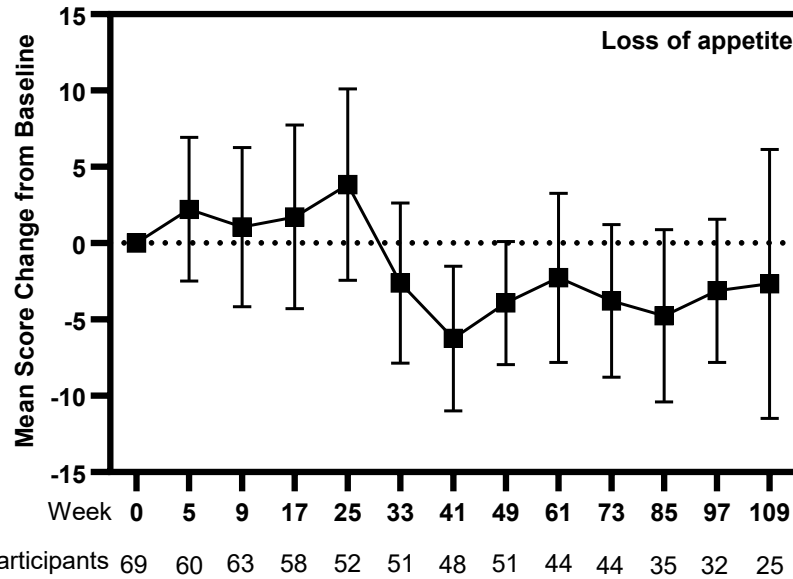
Jimenez C et al. NEJM, 2025, Nov. 20, 2012-2022

Survival Outcomes



Jimenez C et al. NEJM, 2025, Nov. 20, 2012-2022

Global Health Status and Quality of Life



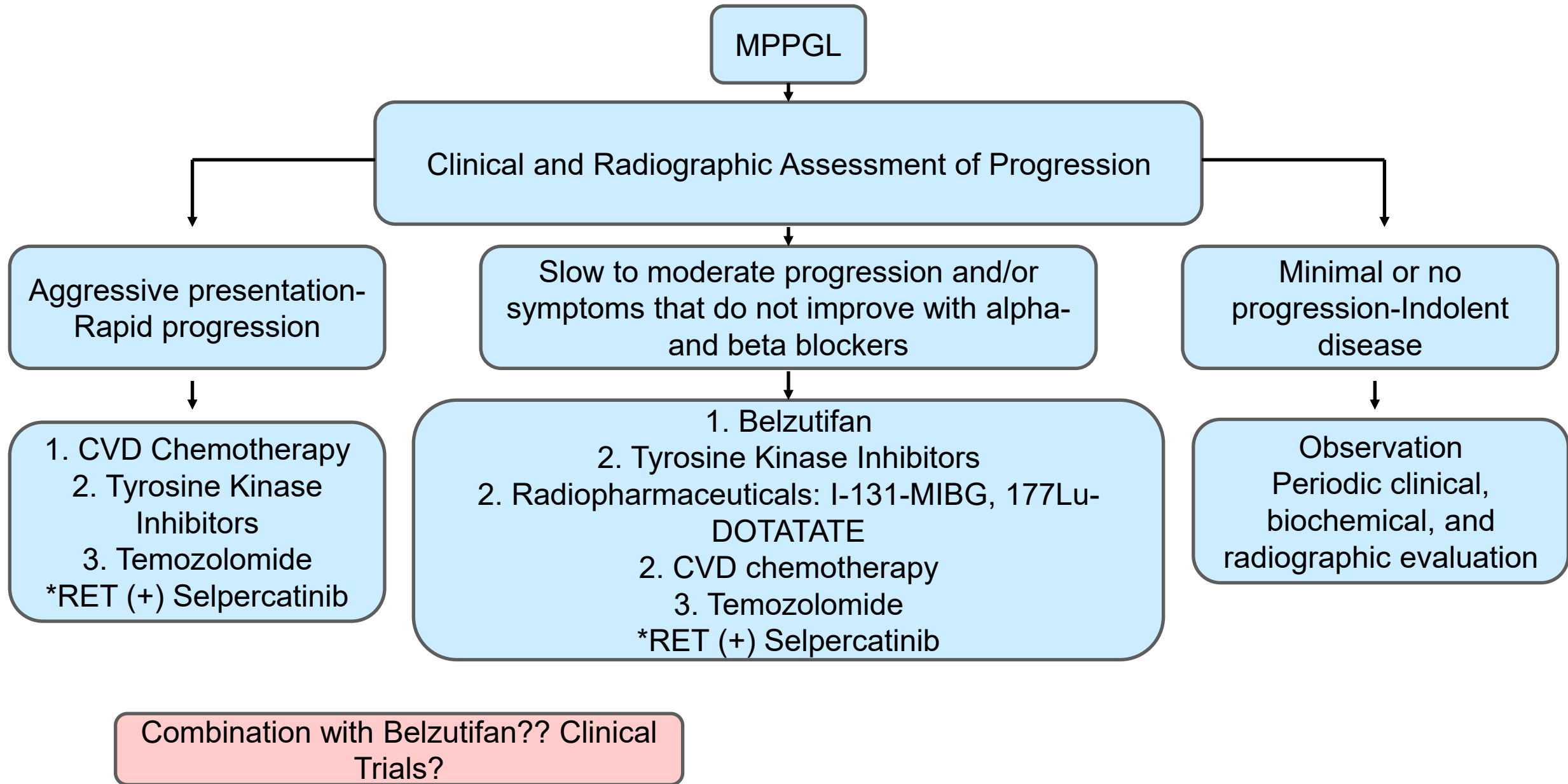
	PPGL PRO population N = 69	
	Global Health Status/QoL	Physical functioning
Improved, n (%) [95% CI]	15 (21.7) [12.7 - 33.3]	14 (20.3) [11.6 - 31.7]
Stable	36 (52.2) [39.8 - 64.4]	40 (58.0) [45.5 - 69.8]
Improved + Stable	51 (73.9) [61.9 - 83.7]	54 (78.3) [66.7 - 87.3]
Deteriorated	17 (24.6) [15.1 - 36.5]	12 (17.4) [9.3 - 28.4]
Unconfirmed	1 (1.4) [0 - 7.8]	3 (4.3) [0.9 - 12.2]

Jimenez C et al. NEJM, 2025, Nov. 20 2012-2022

Treatment Related Adverse Events

Adverse Events, n (%)	PPGL N = 72	
Any grade	71 (99)	
Grade 3-4	33 (46)	
Serious adverse events	8 (11)	
Led to death (Grade 5)	0	
Led to discontinuation	2 (3)	
Led to dose reduction	9 (13%)	
Treatment-related AEs occurring in $\geq 10\%$ of participants	Any	Grade ≥ 3
Anemia	63 (88)	16 (22)
Fatigue	23 (32)	3 (4)
Dyspnea	15 (21)	0
Hypoxia	10 (14)	7 (10)
Asthenia	10 (14)	0
Nausea	9 (13)	1 (1)
Edema peripheral	9 (13)	0
Headache	8 (11)	0

Jimenez C et al. NEJM, 2025, Nov. 2012-2022





cjimenez@mdanderson.org

Bench-Bedside-Back – patient tissue as key for personalised medicine

Prof. Dr. Svenja Nölting

University Hospital Zurich, USZ, University of Zurich, UZH

DISCLOSURE SLIDE

I have no conflicts/disclosures to declare

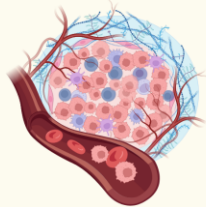
Overview

- Background: Genetics
- (Personalized) Therapy overview
- Research rational
- Patient-derived PPGL platform for next-generation personalized drug testing
- Patient-derived PPGL platform for next-generation personalized risk assessment
- Transferability to GEP-NET
- Summary

Background: Genetics and Overview

CLUSTER 1 Pseudohypoxia

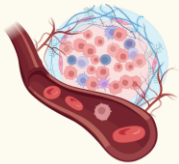
Cluster 1A: **SDHx**, *FH*, *MDH2*, *GOT2*, *SLC25A11*, *IDH*, *DLST*
Cluster 1B: **VHL**, *EPAS1 (HIF2A)*, *PHD1/2*, *IRP1*



- Mostly extra-adrenal (PGL)
- Metastatic risk up to 75%
- Norepinephrine, dopamine

CLUSTER 2 Kinase signaling

Cluster 2: **NF1**, **RET**, *MAX*, *TMEM127*, *HRAS*, *BRAF*, *MET*, *MERTK*, *FGFR1*, *NGFR*

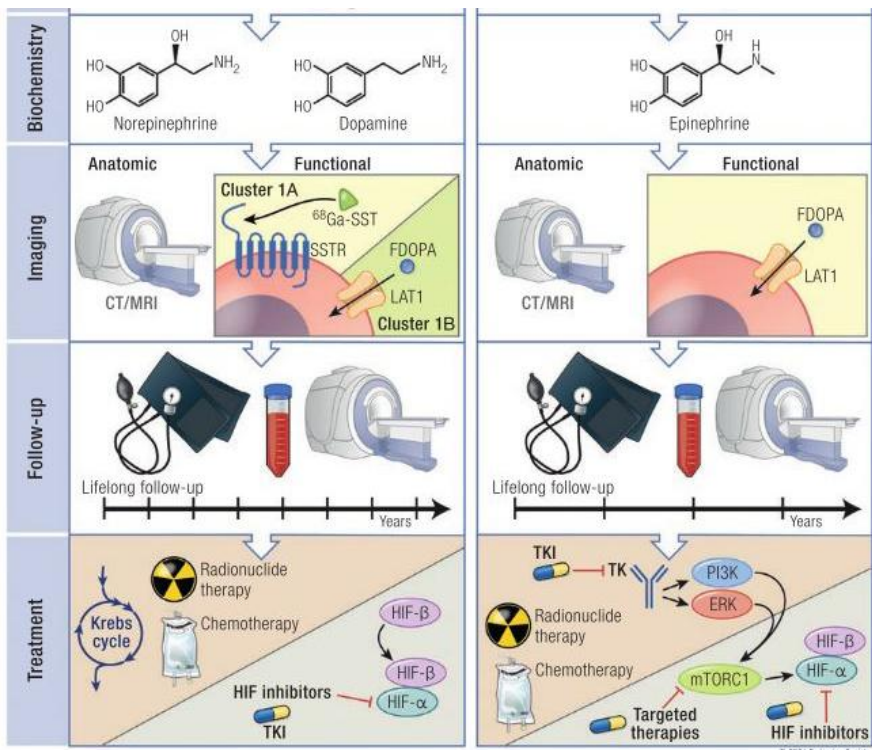


- Mostly adrenal (PCC)
- Metastatic risk 2-12%
- Epinephrine

CLUSTER 3 Wnt signaling

- PPGLs highest heritability among all cancers
- 65-80% of PPGLs assigned to one of 3 molecular clusters
- Consensus: Germline testing of *all* patients
- Diagnostics: Biochemistry: Plasma(nor)metanephrines (LC-MS/MS)
- Diagnostics: Personalized functional imaging
- Personalized follow-up

➤ (Personalized genetically tailored) therapy?



Nölting, Syllabus 28.
Intensivkurs
Endokrinologie der DGE
2025;
Nölting et al., *Endocrine Reviews* 2021

Background: *SDHB* & *SDHD* PPGL consensus statements

nature reviews endocrinology

<https://doi.org/10.1038/s41574-023-00926-0>

Consensus statement



Management of pheochromocytoma and paraganglioma in patients with germline *SDHB* pathogenic variants: an international expert Consensus statement

David Taïeb¹, Svenja Nölting^{2,3}, Nancy D. Perrier⁴, Martin Fassnacht⁵, Jorge A. Carrasquillo⁶, Ashley B. Grossman^{7,8}, Roderick Clifton-Bligh⁹, George B. Wanner¹⁰, Zachary G. Schwam¹⁰, Laurence Amar^{11,12}, Isabelle Bourdeau¹³, Ruth T. Casey¹⁴, Joakim Crona¹⁵, Cheri L. Deal¹⁶, Jaydara Del Rivero¹⁷, Quan-Yang Duh¹⁸, Graeme Eisenhofer¹⁹, Tito Fojo^{20,21}, Hans K. Ghayee^{22,23}, Anne-Paule Gimenez-Roqueplo^{11,24}, Antony J. Gill^{25,26}, Rodney Hicks²⁷, Alessio Imperiale²⁸, Abhishek Jha²⁹, Michiel N. Kerstens³⁰, Ronald R. de Krijger^{31,32}, André Lacroix³³, Ivica Lazurova³⁴, Frank I. Lin³⁵, Charlotte Lussey-Lepoutre^{11,36}, Eamonn R. Maher¹⁴, Ozgur Mete³⁷, Mitsuhide Naruse^{38,39}, Naris Nilubol⁴⁰, Mercedes Robledo^{41,42}, Frédéric Sebag⁴³, Nalini S. Shah⁴⁴, Akiyo Tanabe⁴⁵, Geoffrey B. Thompson⁴⁶, Henri J. L. M. Timmers⁴⁷, Jiri Widimsky⁴⁸, William J. Young Jr⁴⁹, Leah Meuter⁵⁰, Jacques W. M. Lenders⁴⁷ & Karel Pacak²⁹ ✉

Novel PPGL guideline in preparation

Nature Reviews Endocrinology 2024

THE LANCET
Diabetes & Endocrinology



Volume 11, Issue 5, May 2023, Pages 345-361

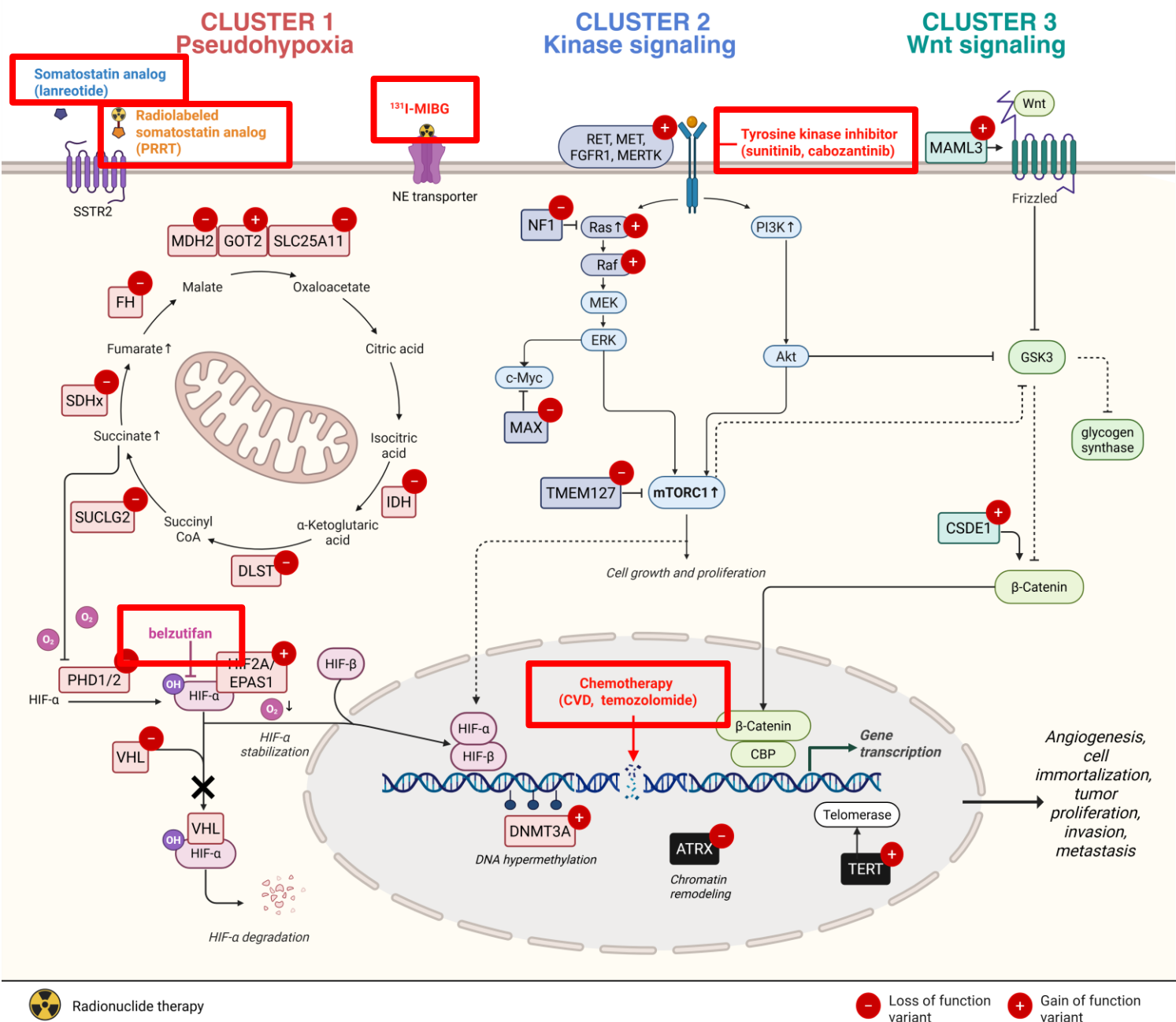
Review

Clinical consensus guideline on the management of pheochromocytoma and paraganglioma in patients harbouring germline *SDHD* pathogenic variants

Prof David Taïeb MD^{ap}, Prof George B Wanner MD^{ar}, Maleeha Ahmad MD^a, Prof Charlotte Lussey-Lepoutre MD^{d ad}, Prof Nancy D Perrier MD^{ak}, Prof Svenja Nölting MD^{aj}, Prof Laurence Amar MD^{d e}, Prof Henri J L M Timmers MD^{aa}, Zachary G Schwam MD^{ar}, Prof Anthony L Estrera MD^t, Prof Michael Lim MD^a, Erqi Liu Pollom MD^c, Lucas Vitzthum MD^c, Prof Isabelle Bourdeau MD^g, Ruth T Casey PhD^h, Prof Frédéric Castinetti MD^{am ao}, Prof Roderick Clifton-Bligh PhD^{ij}, Eleonora P M Corssmit MD^k, Ronald R de Krijger MD^{m n}, Jaydara Del Rivero MD^o, Prof Graeme Eisenhofer PhD^r, Hans K Ghayee DO^u, Prof Anne-Paule Gimenez-Roqueplo MD^{d f}, Prof Ashley Grossman FmedSci^{v w}, Prof Alessio Imperiale MD^x, Prof Jeroen C Jansen MDⁱ, Abhishek Jha MBBS^p, Michiel N Kerstens MD^y, Prof Henricus P M Kunst MD^{z ab}, Prof James K Liu MD^{ac}, Prof Eamonn R Maher MD^h, Prof Daniele Marchioni MD^{ae}, Prof Leilani B Mercado-Asis MD^{af}, Prof Ozgur Mete MD^{ag ah}, Mitsuhide Naruse MD^{ai}, Naris Nilubol MD^q, Prof Neeta Pandit-Taskar MD^{al}, Prof Frédéric Sebag MD^{an}, Akiyo Tanabe MD^{aq}, Prof Jiri Widimsky MD^{as}, Leah Meuter BS^b, Prof Jacques W M Lenders MD^{s aa}, Prof Karel Pacak MD^p ✉

Lancet Diabetes Endocrinol. 2023

(Personalized genetically tailored) Therapy Overview



Fischer*, Del Rivero*,...Nölting*, Jimenez*,
*contributed equally,
Best Pract Res Clin Endocrinol Metab 2025

(Personalized genetically tailored) Therapy Overview: Phase 2 Studies

What's new (including genetics)?

Prospective Phase 2 studies 2024 & 2025:

- Only one FDA-approved drug (May 2025) HIF-2 α inh. belzutifan (LITESPARK-015, molecular-genetic analysis pending, *SDHB*>sporadic), n=72
- TKI sunitinib (FIRSTMAPPP, first and only RCT, Objective Response Rate (ORR) *SDHB*>others), n=78
- TKI cabozantinib (NATALIE, ORR *SDHB*>others), n=17
- PRRT (long Progression Free Survival (PFS)/Overall Survival (OS) sporadic>*SDHX*), n=36
- Ctx high tumor burden, fast-growing, *SDHB* maybe better response
- LAMPARA (lanreotid) ongoing (ASCO 2025: PFS > 2J, disease stabilising) (n=14/18 *SDHX*)

Fischer*, Del Rivero*,...,Nölting*, Jimenez*, *contributed equally, *Best Pract Res Clin Endocrinol Metab* 2025

Baudinet al., *Lancet* 2024

Jimenez et al., *Lancet Oncol* 2024

Jimenez et al., *N Engl J Med* 2025

FDA (www.fda.gov) approval for belzutifan (May 2025)

Lin et al., *J Clin Oncol* 2025

Rational for my translational research

Rarity of disease: Lack of prospective randomized placebo-controlled therapy studies (RCT) (only one RCT: FIRSTMAPPP (sunitinib))



Performance of randomized prospective clinical trials exceptionally challenging

Baudin et al.,
Lancet. 2024

Solution?



Aims

Personalized therapies

Genetically tailored therapies

Problem: No reliable human cell lines available

Patient-derived PPGL platform for next-generation personalized drug testing

Endocrine-Related
Cancer

K Wang, I Schütze *et al.*

Human pheochromocytoma
primary cultures

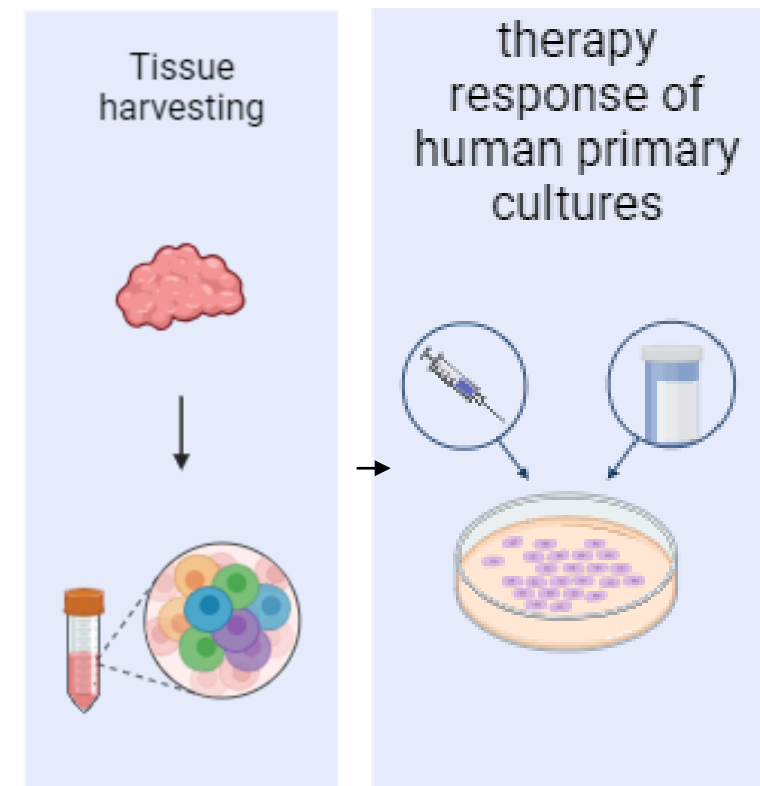
29:6

285–306

RESEARCH

Personalized drug testing in human pheochromocytoma/paraganglioma primary cultures

Katharina Wang^{ID1,*}, Ina Schütze^{2,*}, Sebastian Gulde³, Nicole Bechmann^{ID4,5}, Susan Richter^{ID4}, Jana Helm⁵, Michael Lauseker⁶, Julian Maurer¹, Astrid Reul², Gerald Spoettl¹, Barbara Klink^{7,8,9}, Doreen William⁹, Thomas Knösel¹⁰, Juliane Friemel¹¹, Michel Bihl^{ID11}, Achim Weber¹¹, Maria Fankhauser¹, Laura Schober¹, Diana Vetter¹², Martina Broglie Däppen¹³, Christian G Ziegler^{ID5}, Martin Ullrich^{ID14}, Jens Pietzsch^{14,15}, Stefan R Bornstein⁵, Christian Lottspeich¹, Matthias Kroiss^{ID1,16}, Martin Fassnacht¹⁶, Vera Ursula Julia Wenter^{ID17}, Roland Ladurner¹⁸, Constanze Hantel^{2,5}, Martin Reincke¹, Graeme Eisenhofer^{4,5}, Ashley B Grossman^{19,20}, Karel Pacak^{ID21}, Felix Beuschlein^{1,2}, Christoph J Auernhammer¹, Natalia S Pellegata³ and Svenja Nölting^{ID1,2}

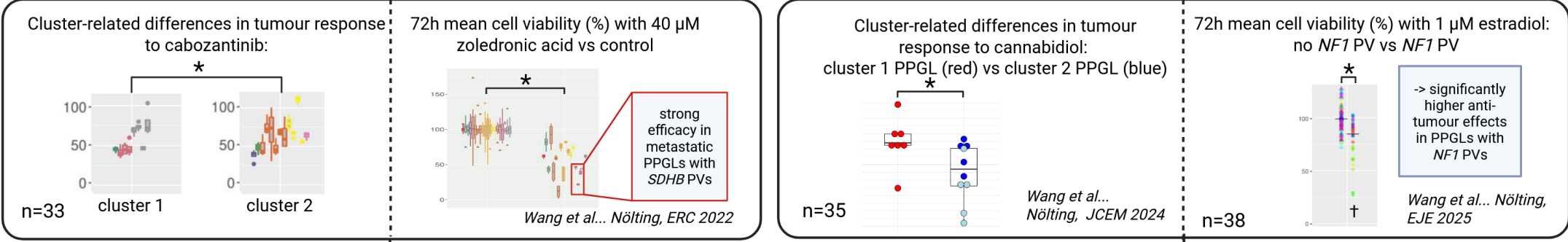


Wang, ..., Nölting,
Endocr Relat Cancer 2022

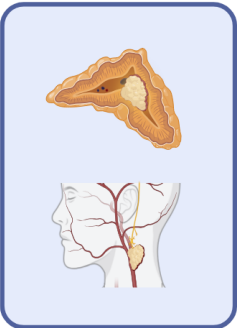
Created by BioRender

Patient-derived PPGL platform – personalized drug testing & risk assessment

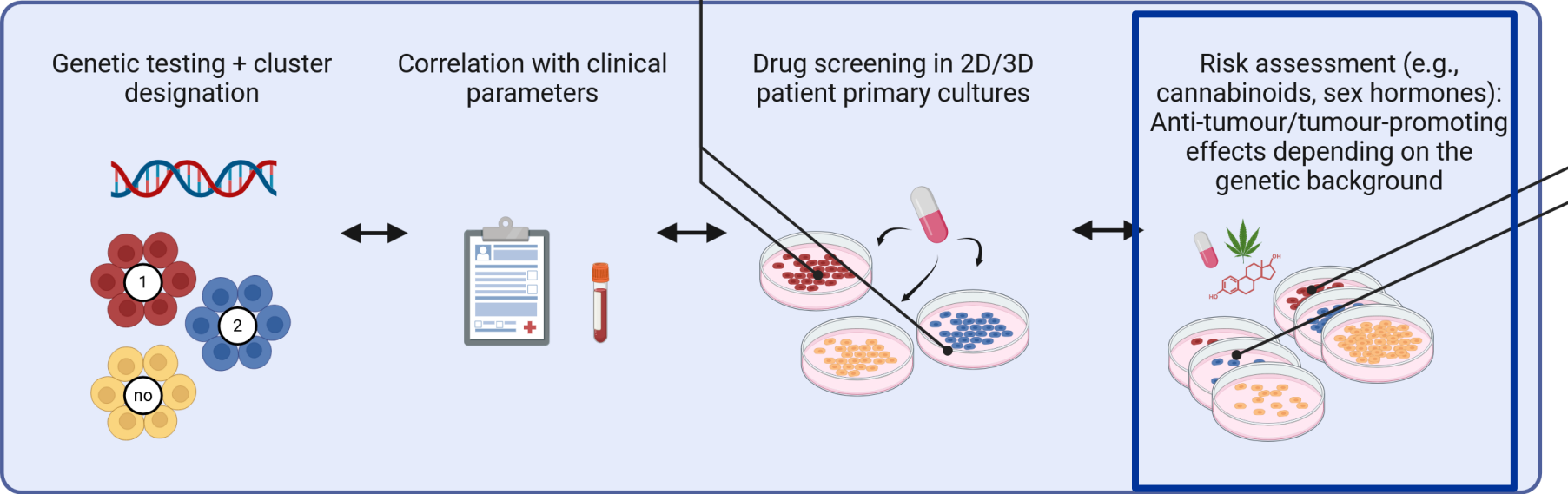
NATALIE trial cabozantinib: ORR overall 25% vs. *SDHB* 60% (Jimenez, *Lancet Oncol* 2024)
Case report: Complete response of a *SDHB* mPPGL to zoledronic acid (Schutte, *BMJ Case Rep* 2024)



Patient-derived PPGL (n=15-20 per year)



>110 fresh surgery-derived PPGL
>50 drugs



Wang,..., Nölting, *Endocr Relat Cancer* 2022 Wang,...Zitzmann*, Nölting*, *JCEM* 2024 Wang,..., Nölting, *Eur J Endocrinol.* 2025 Wang,..., Nölting *Best Pract Res Clin Endocrinol Metab* 2025

*contributed equally



Efficacy and risk: Cannabidiol (CBD) in PPGL & GEP-NET

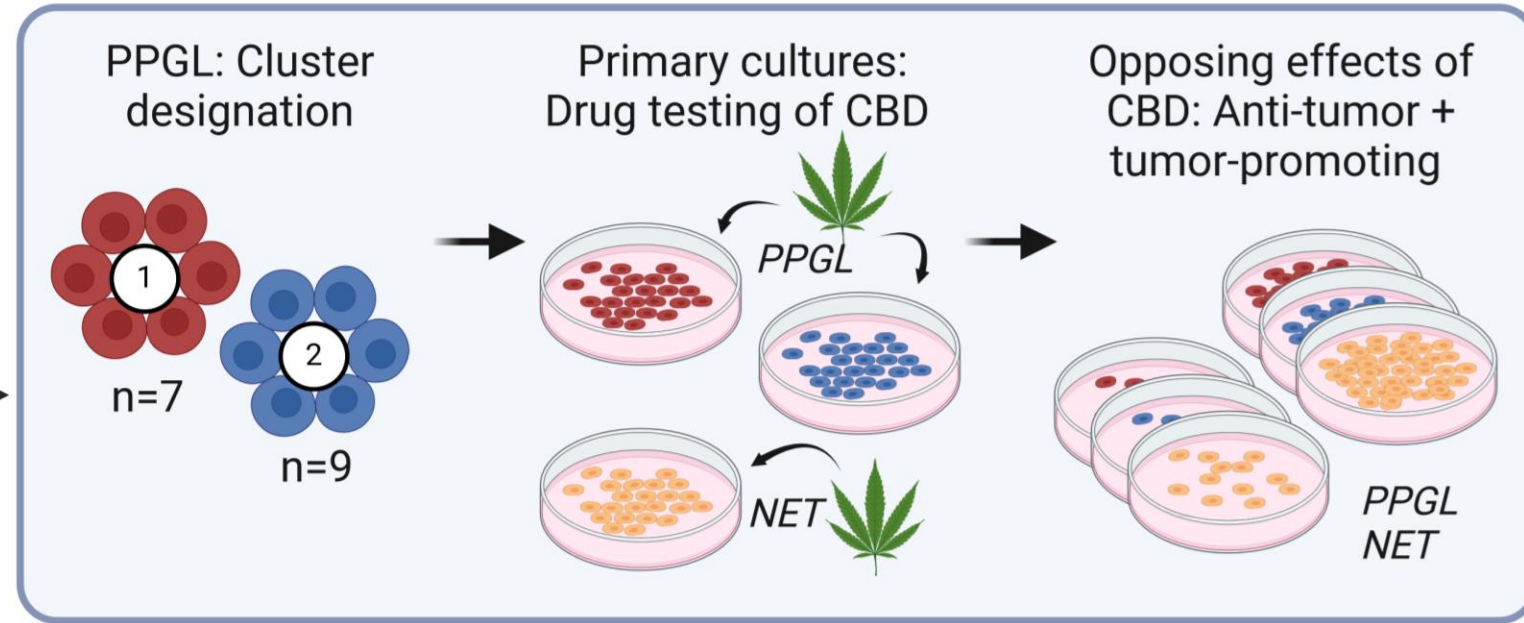
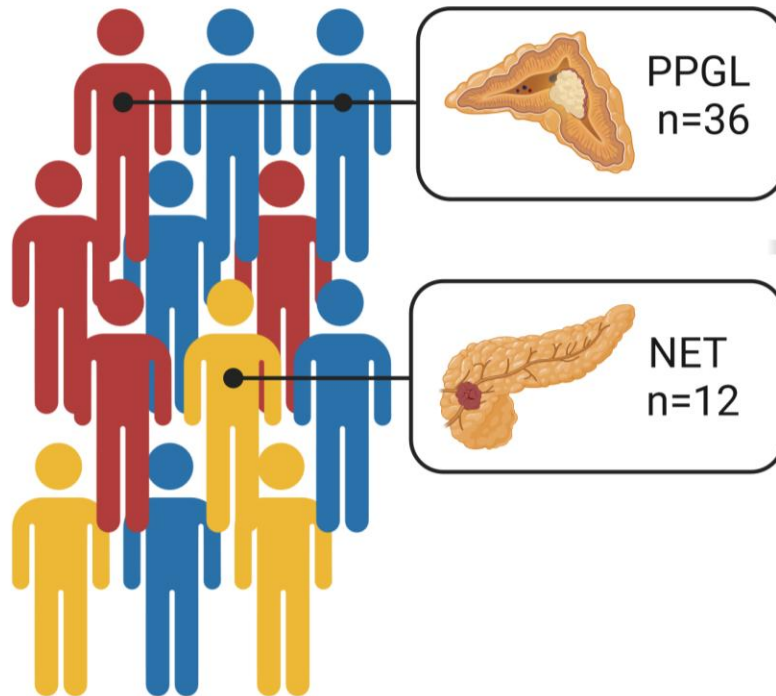
JCEM
THE JOURNAL
OF CLINICAL
ENDOCRINOLOGY
& METABOLISM



Opposing Effects of Cannabidiol in Patient-derived Neuroendocrine Tumor, Pheochromocytoma/Paraganglioma Primary Cultures

Katharina Wang ✉, Laura Schober, Alessa Fischer, Nicole Bechmann, Julian Maurer, Lea Peischer, Astrid Reul, Constanze Hantel, Martin Reincke, Felix Beuschlein, Mercedes Robledo, Hermine Mohr, Natalia S Pellegata, Katharina Schilbach, Thomas Knösel, Matthias Ilmer, Martin Angele, Matthias Kroiss, Umberto Maccio, Martina Broglie-Däppen, Diana Vetter, Kuno Lehmann, Karel Pacak, Ashley B Grossman, Christoph J Auernhammer, Kathrin Zitzmann, Svenja Nölting

Patient-derived tumors n=48
from 46 different patients



CBD: Cannabidiol

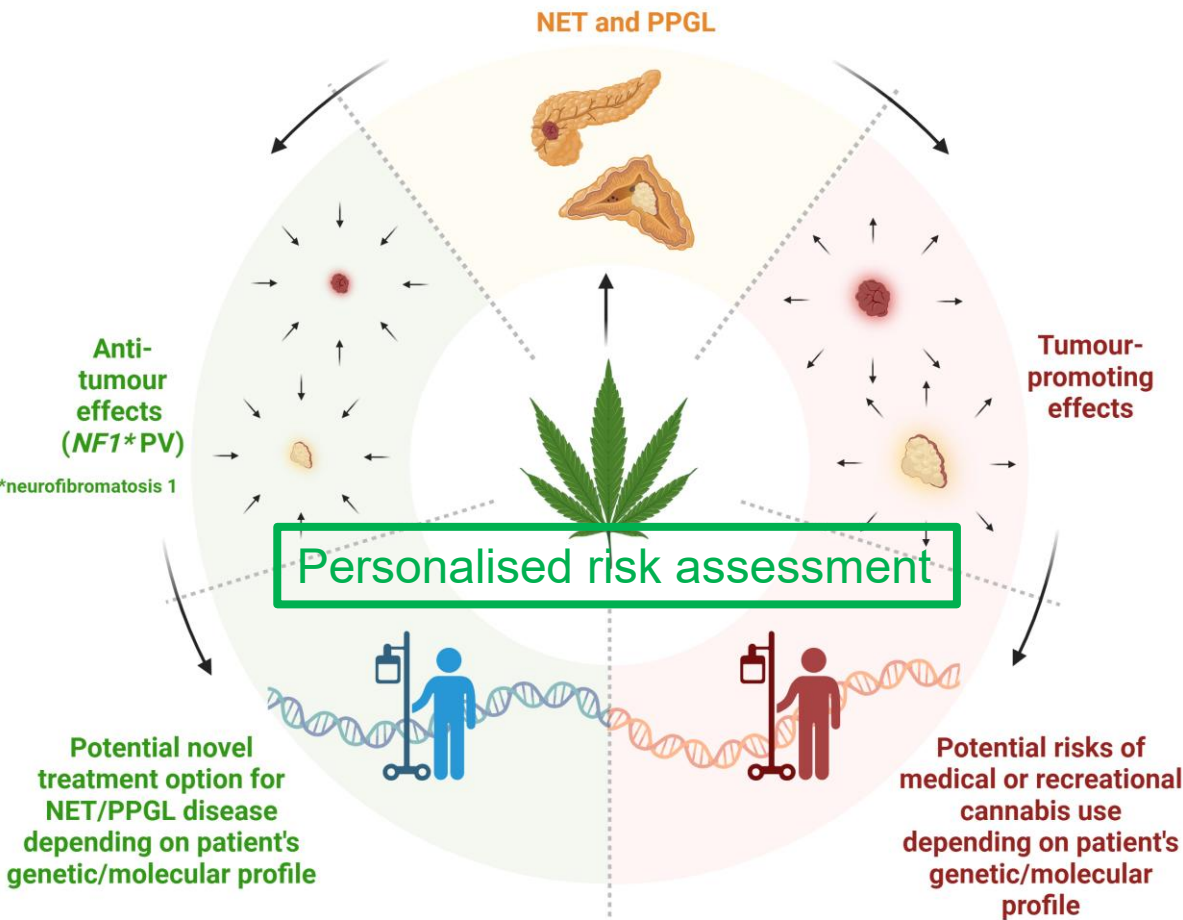
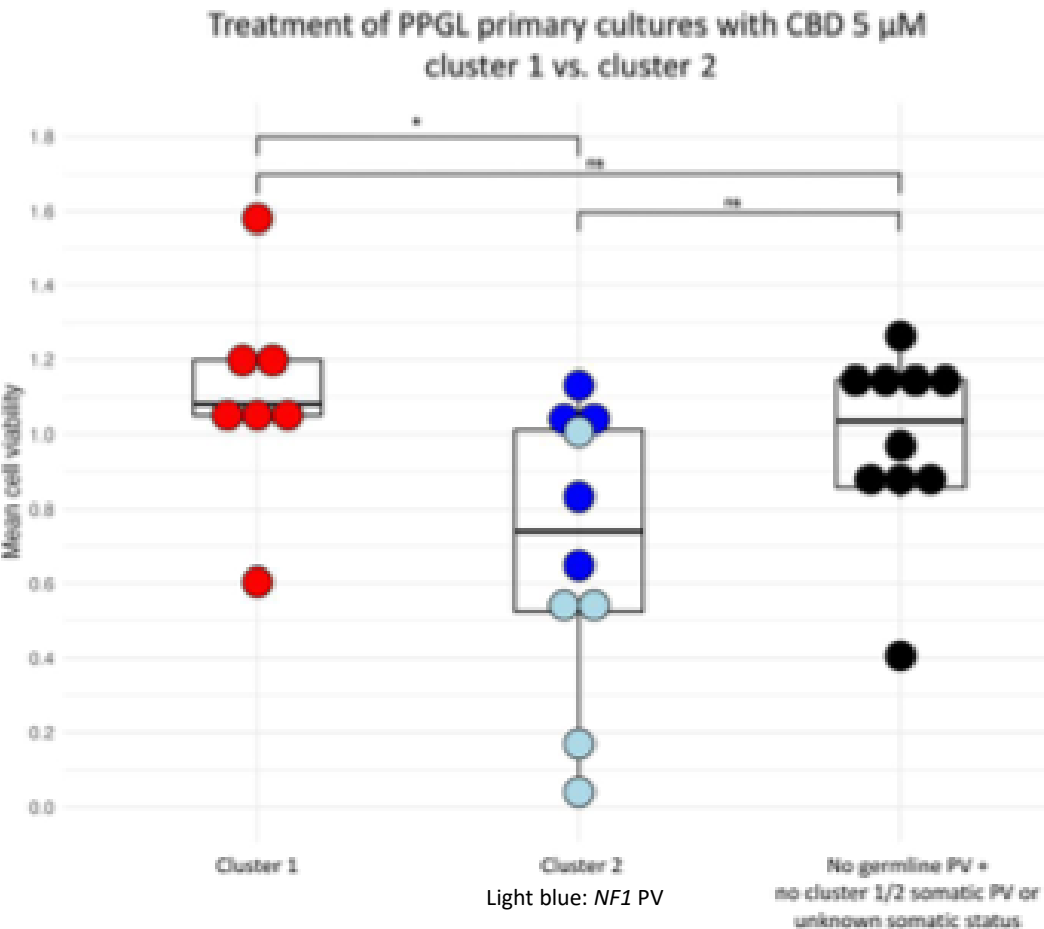
Genetic testing

Correlation of drug responsivity with
genetic status and clinical data

Efficacy and risk: Cannabidiol (CBD) in PPGL & GEP-NET: Opposing effects

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Potential effects of cannabinoids on neuroendocrine tumours and phaeochromocytomas/paragangliomas

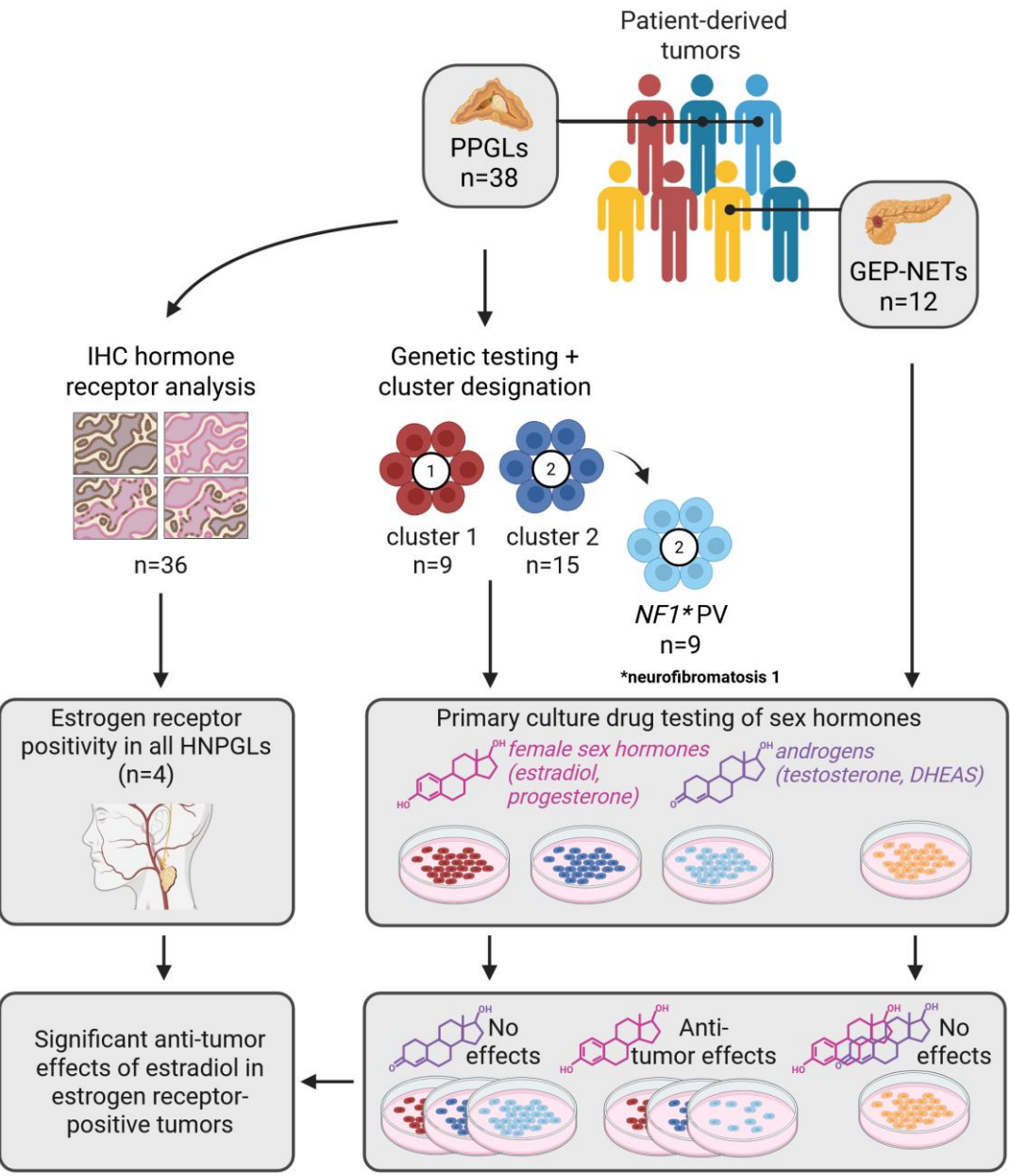


Wang,... Zitzmann*, Nölting*, *JCEM* 2024
*contributed equally

Efficacy or risk? Sex hormones in PPGL & GEP-NET: Female sex hormones anti-tumor effects

EJE Impact of sex hormones on pheochromocytomas, paragangliomas, and gastroenteropancreatic neuroendocrine tumors

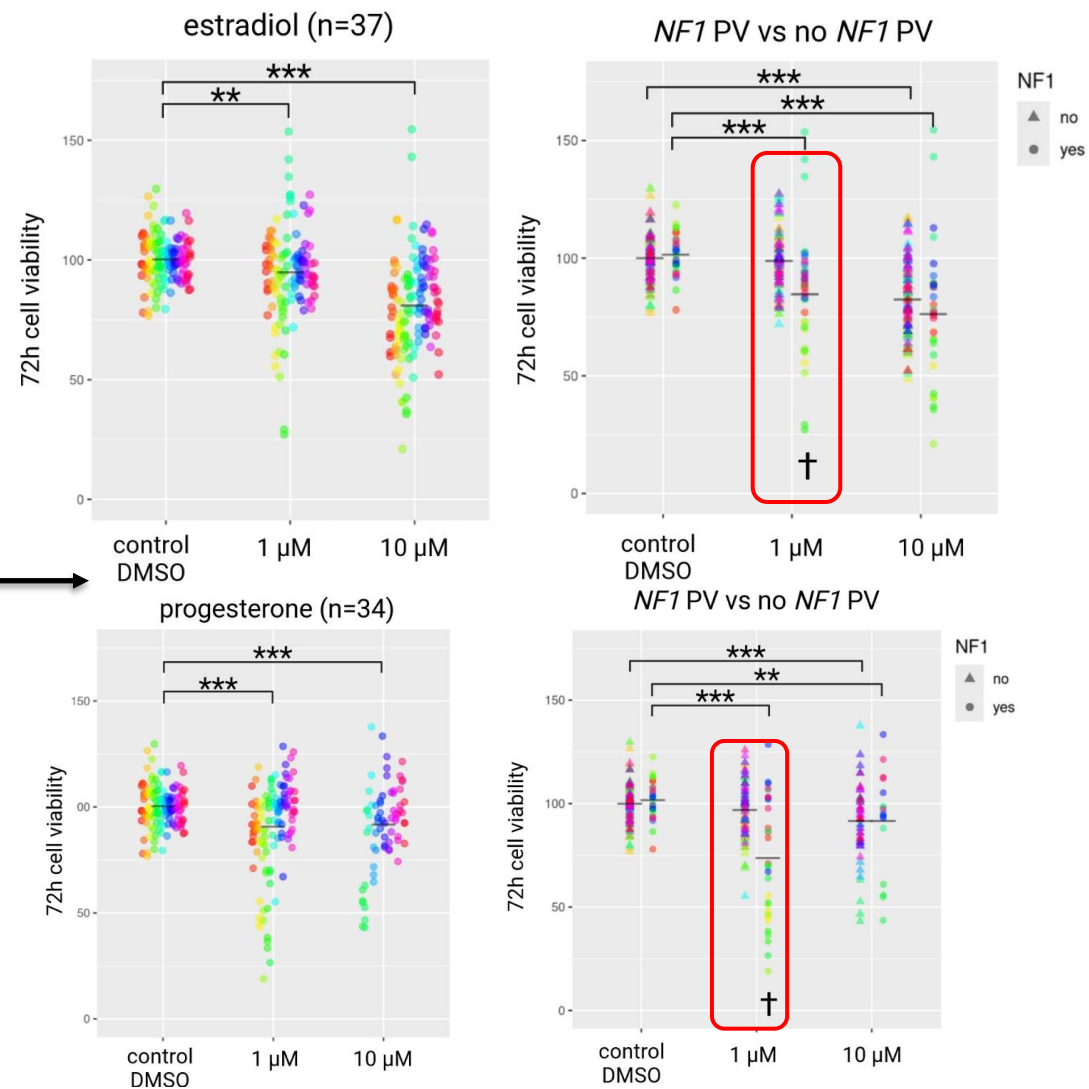
Katharina Wang, Alessa Fischer, Umberto Maccio, Kathrin Zitzmann, Mercedes Robledo, Michael Lauseker, Jana Bauer, Nicole Bechmann, Simon Gahr, Julian Maurer, Lea Peischer, Astrid Reul, Hanno Nieß, Petra Zimmermann, Matthias Ilmer, Katharina Schilbach, Thomas Knösel, Matthias Kroiss, Martin Fassnacht, Simon A Müller, Gregoire B Morand, Alexander Huber, Diana Vetter, Kuno Lehmann, Zsolt Kulcsar, Hermine Mohr, Natalia S Pellegata, Constanze Hantel, Martin Reincke, Felix Beuschlein, Karel Parak, Ashlev R Grossman, Christoph J Auernhammer, Svenja Nölting



patient

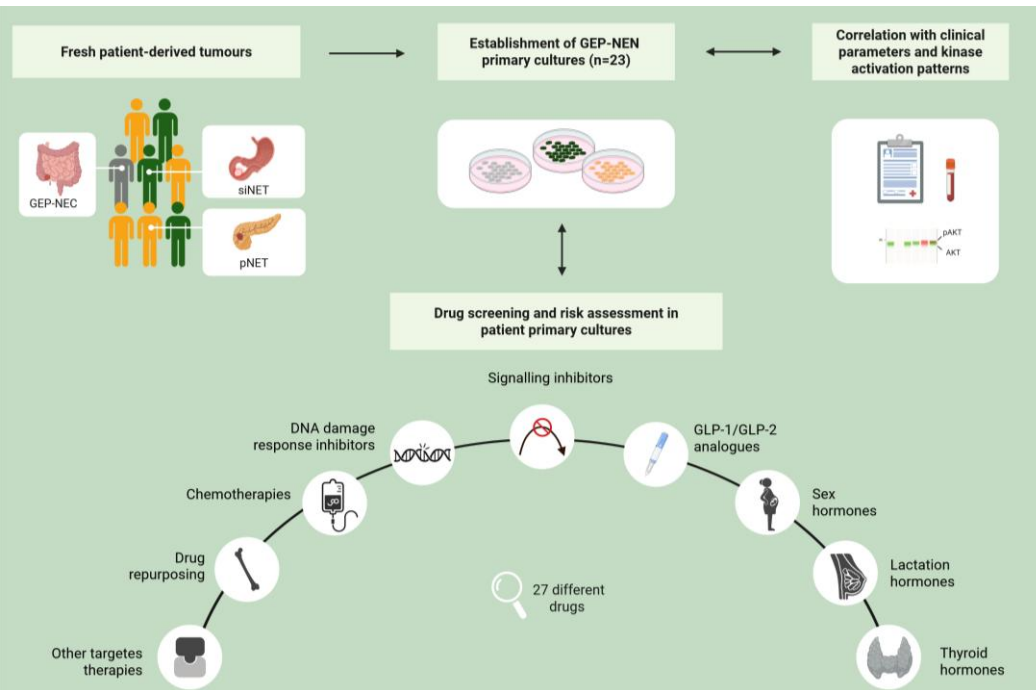
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Wang, ...Nölting, Eur J Endocrinol. 2025

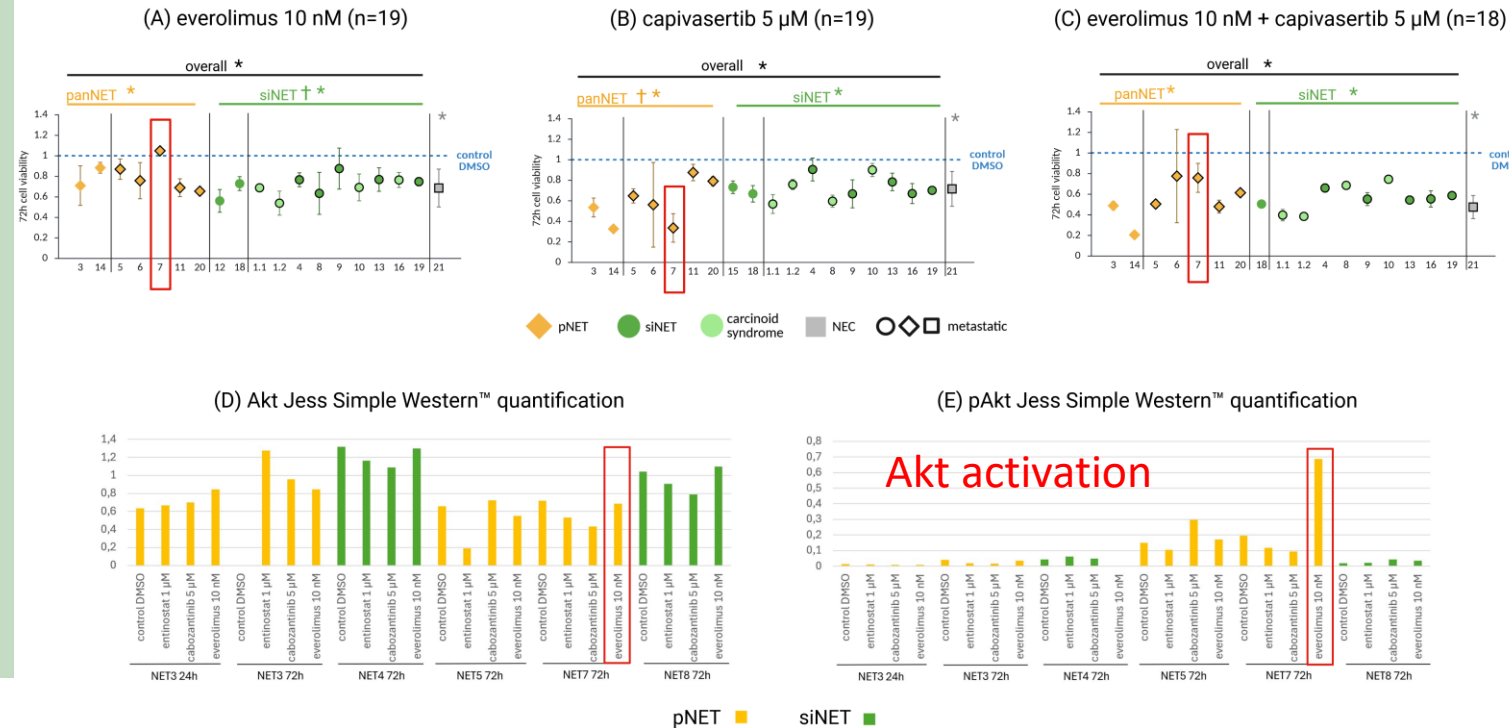


Transferability: Patient-derived GEP-NET platform – personalized drug testing

JCEM THE JOURNAL
OF CLINICAL
ENDOCRINOLOGY
& METABOLISM



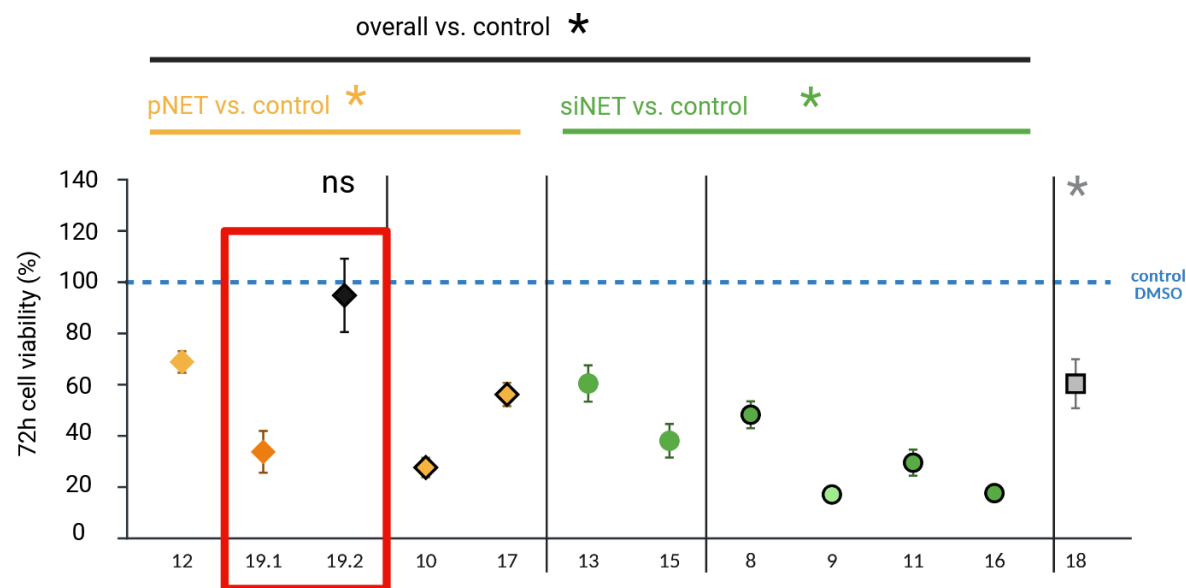
Targeted (combination) therapies:
mTORi everolimus and AKTi capivasertib



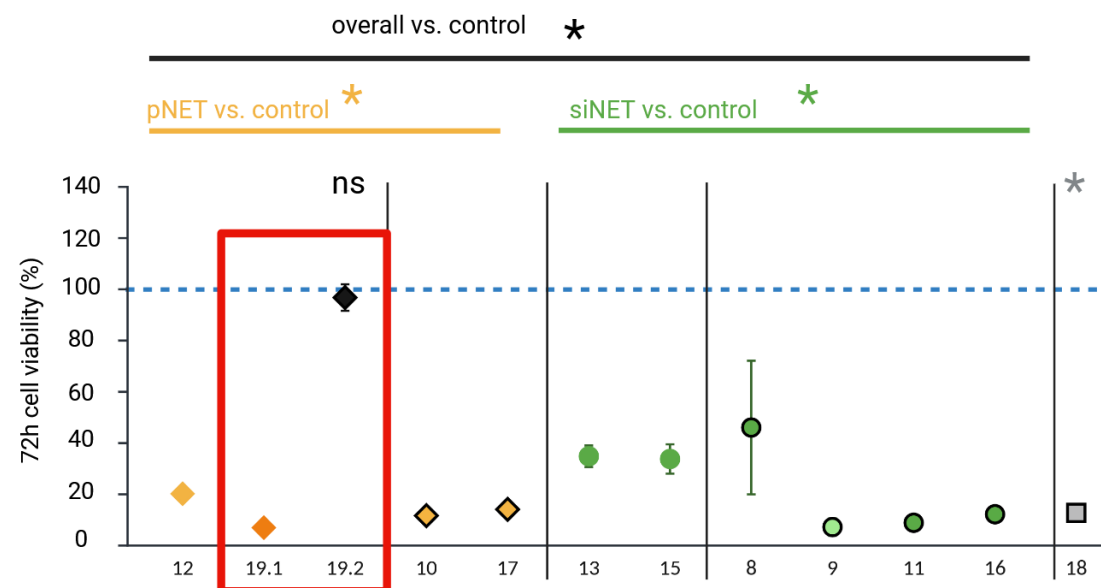
Auernhammer*, Wang*...Nölting,
*contributed equally,
JCEM 2026

Transferability: Patient-derived GEP-NET platform and 3D spheroids

(C) metformin 10 mM (n=12)



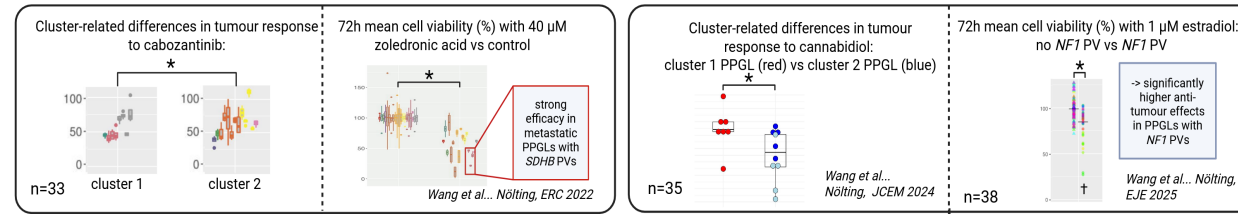
(D) metformin 50 mM (n=12)



Nölting*, Luca*,...Hantel,
*contributed equally,
Endocr Relat Cancer 2025

Summary

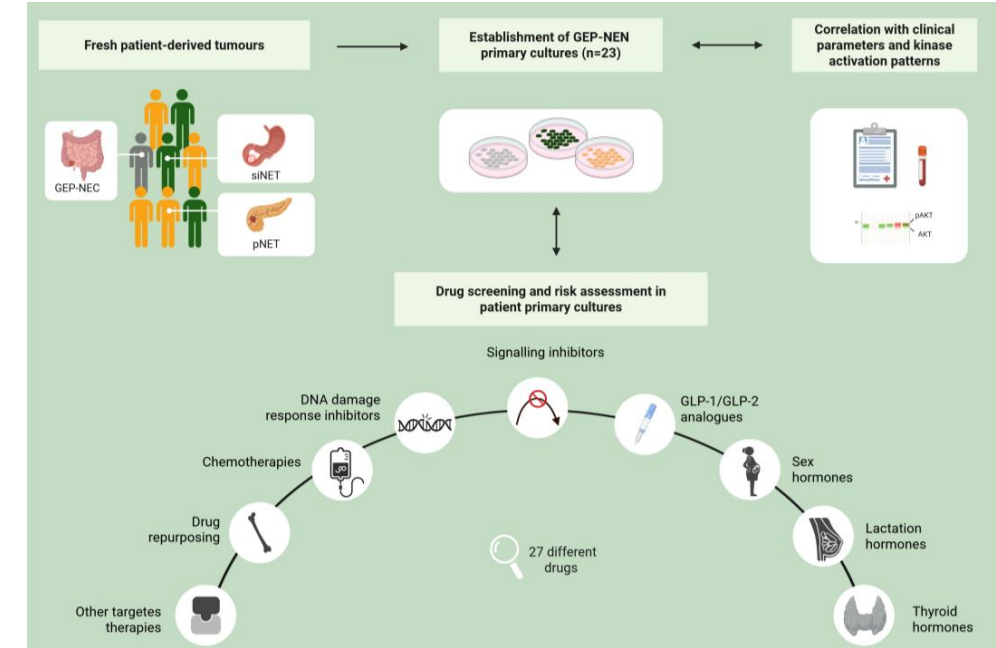
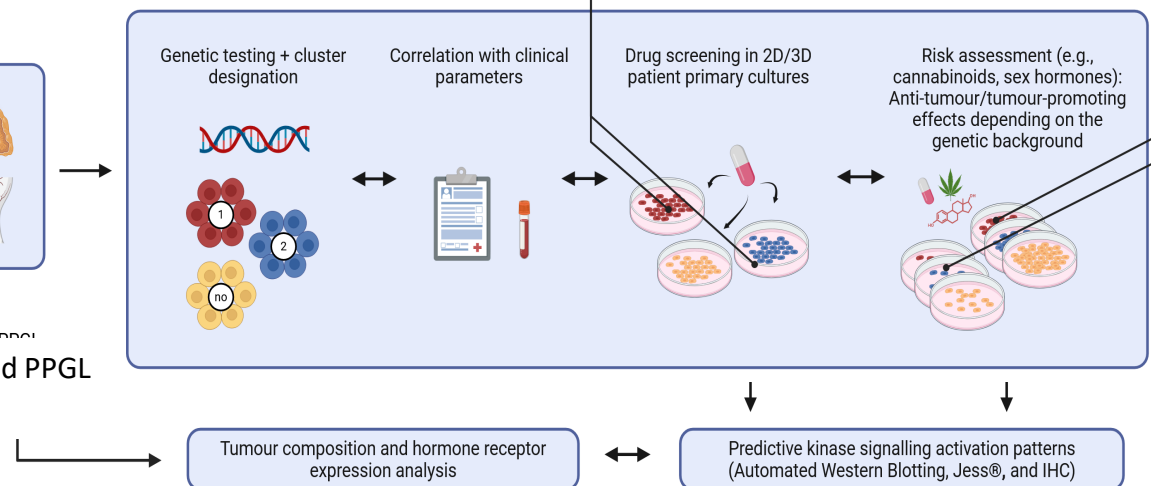
- Rational: Prospective clinical studies extremely challenging in PPGL, no reliable human cell lines
- Patient-derived PPGL platform for next-generation personalized drug testing & risk assessment
- Direct clinical relevance for the individual patient
- Identification of genetically tailored therapies or risk factors for tumor-promoting effects
- Transferability of the PPGL patient-derived tumor platform to other (neuro)endocrine tumors



Patient-derived PPGL (n=15-20 per year)

>110 fresh surgery-derived PPGL

>50 drugs



Auernhammer...Nölting, JCEM, 2026

Wang,...Nölting, *Endocr Relat Cancer* 2022; Wang,...Zitzmann*, Nölting*, *JCEM* 2024; Wang,...Nölting, *Eur J Endocrinol.* 2025; Wang,...Nölting, *Best Pract Res Clin Endocrinol Metab* 2025; Auernhammer*, Wang*,...Nölting, *JCEM* 2026, *contributed equally



Thank you!

Questions?

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Comprehensive Cancer Center Zürich



Discussion



Closing comments

Take-home messages

- Germline genetic analysis is essential for all pheochromocytomas and especially paragangliomas.
- Targeted therapies now play a significant role in treatment.
- Molecular agents such as TKIs, belzutifan and PRRT need individualisation.
- Patient-derived tumour platforms may help personalise therapy.
- Therapy sequencing remains unclear: guideline assist, MDTs essential.

A BIG "Thank You" to

- ✓ Our speakers and moderators
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- ✓ The ENETS Education Group
- ✓ YOU, our valued participants

The ENETS Education Group

- **Simona GLASBERG (Lead)** | Endocrinology | Israel
- **Mairéad McNAMARA (Lead)** | Oncology | United Kingdom
- Eric BAUDIN | Endocrinology | France
- Emanuel CHRIST | Endocrinology | Switzerland
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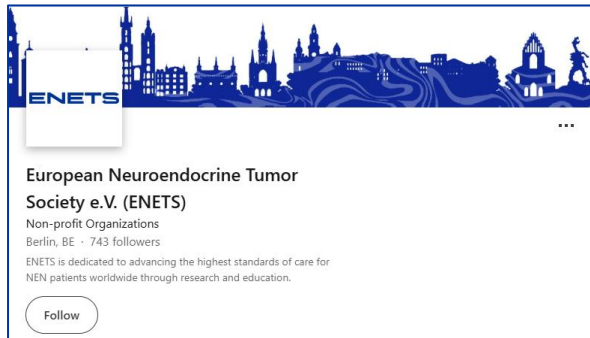
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