Clinical Trials (Open and Recruiting) for Pheochromocytomas and Paragangliomas

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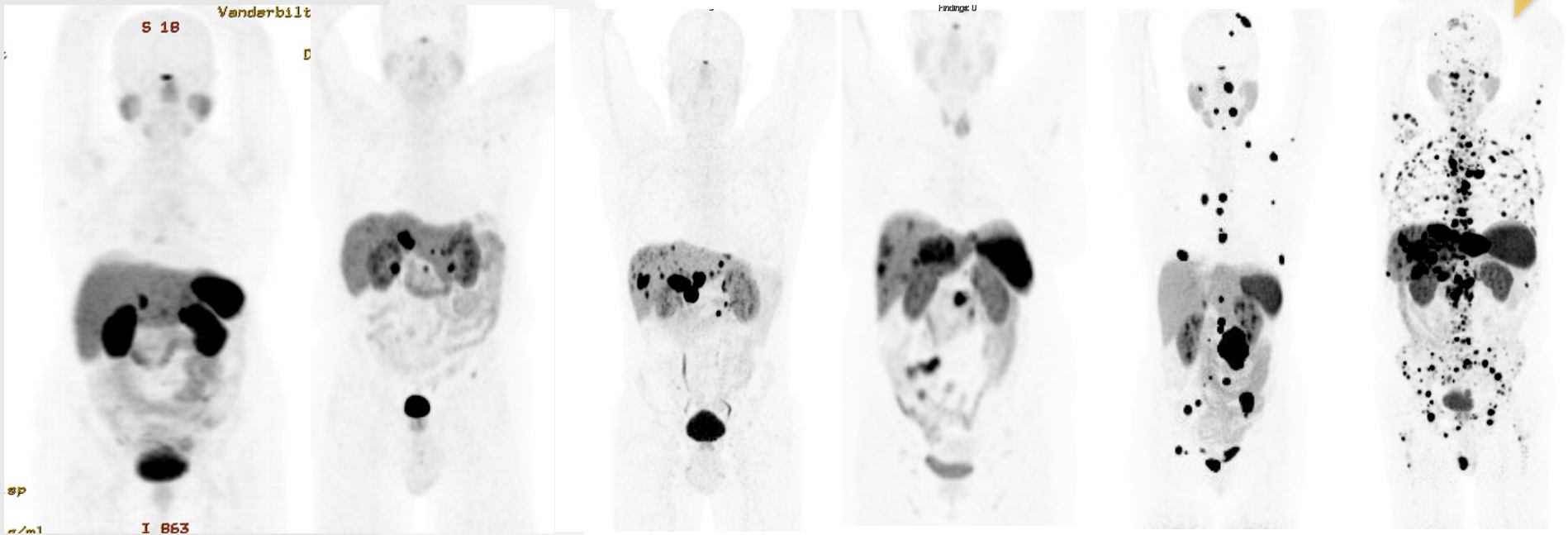
Treatment Options- Customized Approaches for Individual Needs

Low tumor burden **Intermediate tumor burden** **High tumor burden**



Liver tumor volume/total liver volume by CT or MRI **Rapid progression: growth of more than 30% within 3 months**

Low tumor burden (25%) **Intermediate tumor burden (25-50%)** **High tumor burden (>50%)**

Treatments for Tumor/Hormonal Control for Advanced PPGL

Peptide Receptor Radionuclide Therapy (PRRT)

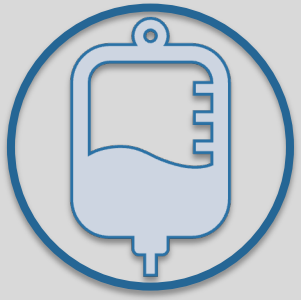
- ^{177}Lu DOTATATE

Somatostatin Analogues

- Octreotide LAR
- Lanreotide

Targeted Therapies

- Sunitinib
- Cabozantinib
- Axitinib

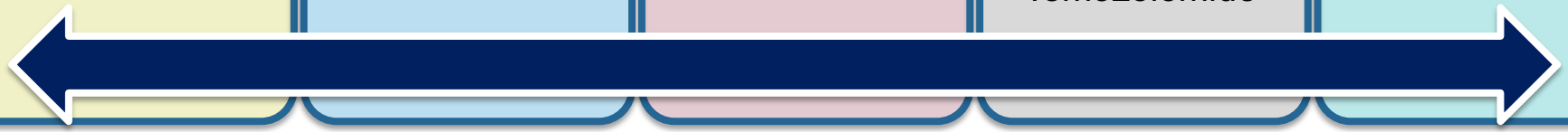


Cytotoxic Chemotherapies

- **C**yclophosphamide, **V**incristine and **D**acarbazine (CVD)
- Temozolomide

Surgery /LDT

- Cytoreductive surgery
- Ablation/ embolization



Management of Advanced/Metastatic PPGLs

Alpha-blockade
Doxazosin, phenoxybenzamine

↓

Beta blocker
Calcium channel blocker
Metyrosine

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

FDA approves iobenguane I 131 for rare adrenal gland tumors

On July 30, 2018, the Food and Drug Administration approved iobenguane I 131 (AZEDRA, Progenics Pharmaceuticals, Inc.) for adult and pediatric patients (12 years and older) with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) who require systemic anticancer therapy.

Locally unresectable

- Observation
- Cytoreductive surgery
- TKI (sunitinib, cabozantinib, axitinib)
- ^{131}I-MIBG
- PRRT with ^{177}Lu-DOTATATE**
- Clinical trials

Distant metastasis

- Observation
- Cytoreductive surgery
- Systemic chemotherapy(CVD/TMZ)
- TKI (sunitinib, cabozantinib, axitinib)
- ^{131}I-MIBG
- PRRT with ^{177}Lu-DOTATATE
- Clinical trials

Fischbein, Del Rivero…Jimenez, NANETS Consensus Guidelines 2021
NCCN Guidelines 2022[4]

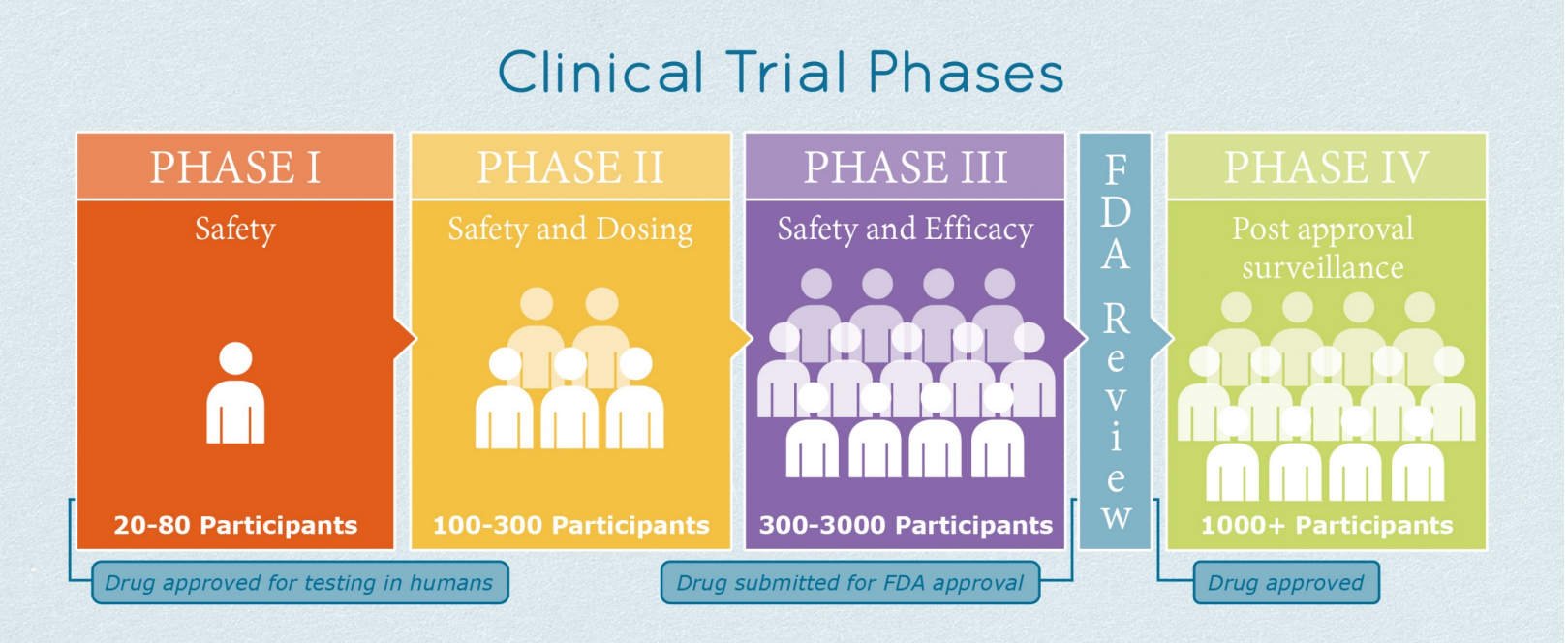
What are Clinical Trials?

BASIC RESEARCH ≠ CLINICAL TRIALS

- Clinical trials are research studies that test how well new medical approaches in people
- Each study tries to find better ways to prevent, screen for, diagnose, or treat a disease.
- Clinical trials may also compare a new treatment to a treatment that is already available
- The goal of clinical trials is to determine if these treatments approaches are safe and effective.

Clinical Trials

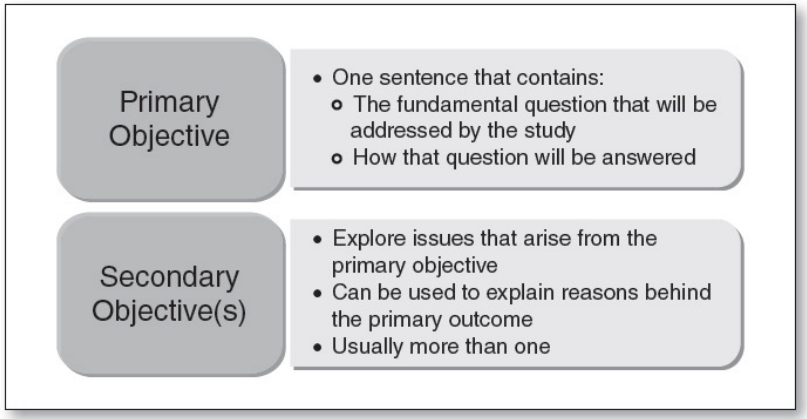
- **Clinical trials are research studies that test how well new medical approaches work in people**



https://www.cancer.gov/about-cancer/treatment/clinical-trials/questions

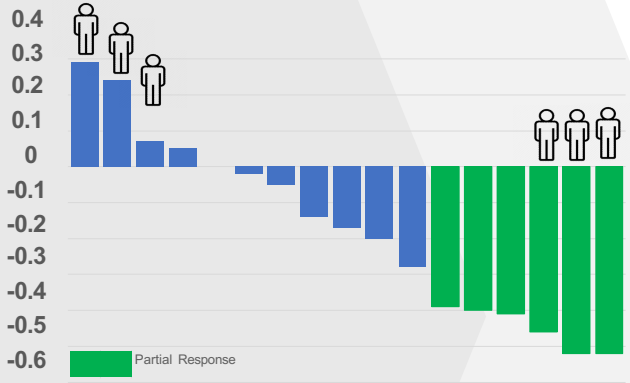
Objectives in Clinical Trials

- **Primary Objectives:** measure outcomes that will answer the primary or most important question being asked by a clinical trial
  - whether a new treatment is better at reducing tumor size than the standard therapy
- **Secondary Objectives:** answer other relevant questions about the same study
  - whether there is also a reduction in disease measures, or outcomes rated by patients such as quality of life

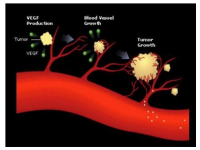


Tyrosine Kinase Inhibitor (TKI) Therapy

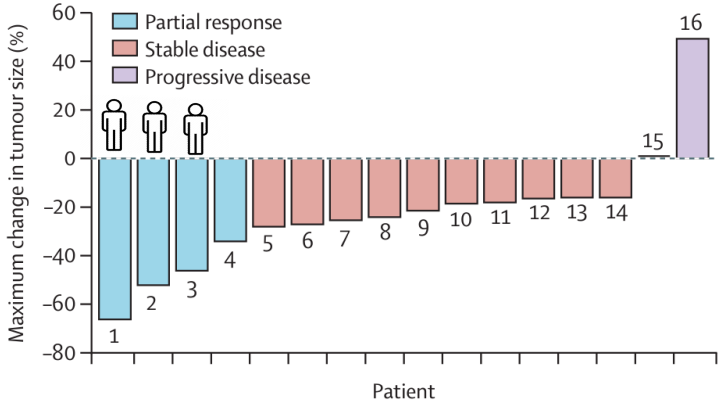
Phase II Clinical Trial with Axitinib



ASCO 2024



Phase II Clinical Trial with Cabozantinib



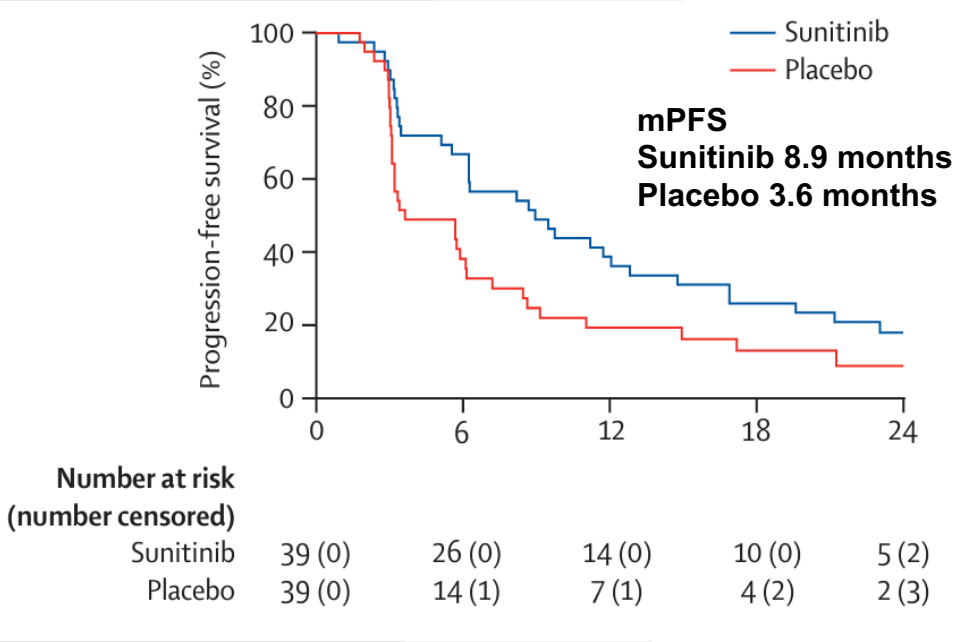
Jimenez et al. Lancet Oncology. 2024 May;25(5):658-667

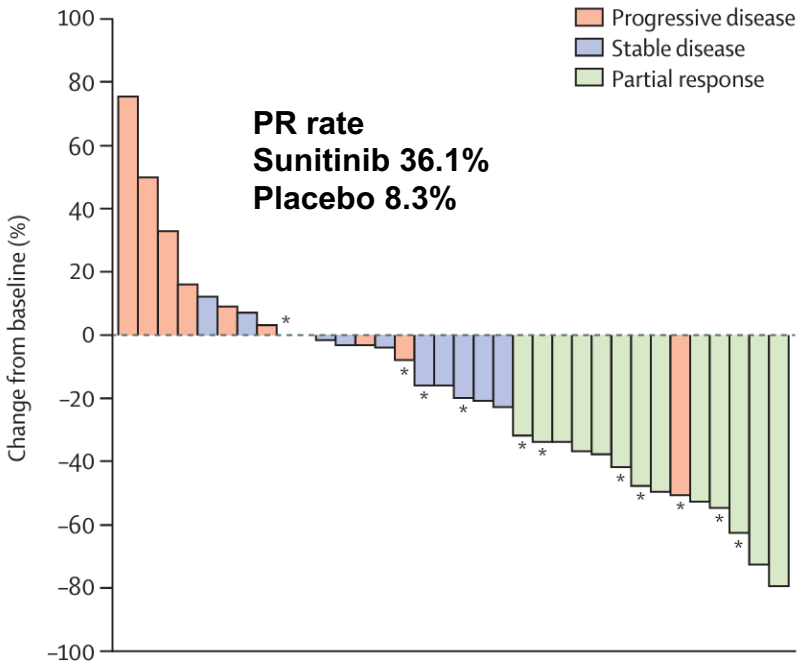
Recommendation by NANETS Guidelines

The TKIs could be a therapeutic option for patients with metastatic PPGLs, especially for those with tumors non-avid on MIBG, mixed tumors, and patients with contraindications for MIBG therapy (i.e, bone marrow suppression due to bone metastases) or for any patients with rapid progression.

Fischbein, Del Rivero…Jimenez, NANETS Consensus Guidelines 2021

First International Randomized Study in Malignant Progressive Pheochromocytoma and Paraganglioma (FIRSTMAPPP)





36% of patients [90% CI 23–50]) showed no progression of disease at 12 months

Baudin et al. Lancet 2024; 403: 1061–70

Natural History Studies

- Researchers follow people with cancer over a long period of time
- As part of the study, researchers will collect details about the patient's medical history, tissue (such as blood and saliva) and tumor samples, and other data.
- Researchers who conduct natural history studies use this information to study questions such as:
  - How do specific cancers form, grow, and spread?
  - What genes cause cancer to develop at a high rate in certain families?
  - Can we learn clues to help prevent cancer?
  - Can we learn clues to help develop new treatments?

Tissue Procurement and Natural History Study of Neuroendocrine Neoplasms (NENs) (NCT05237934)

Primary Objective:
Characterize the natural history of neuroendocrine neoplasms (NENs). Data will include patient demographics, clinical characteristics, patterns of disease progression, response or lack of response to therapeutic interventions, disease recurrence and overall survival

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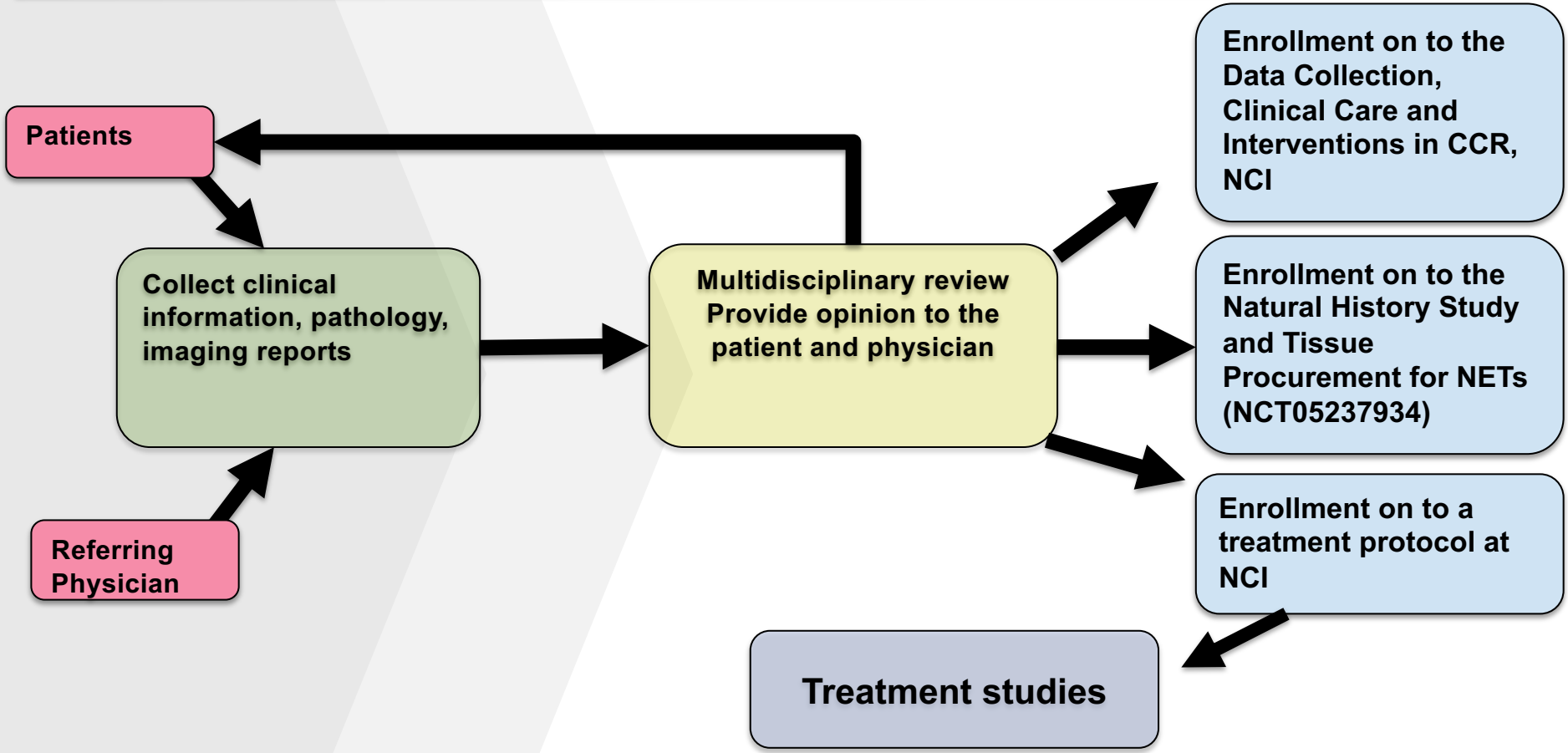
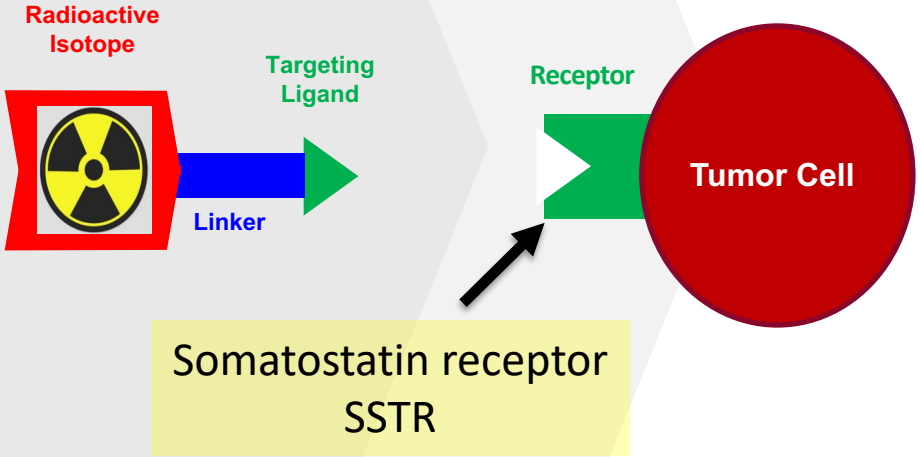
August 5, 2024

Clinical Trials at the NCI



Theranostics-PRRT Basics



- Theranostics is a combination of the terms **thera**peutics and diag**nostics**

Theranostics

^{68}Ga-DOTATATE or ^{64}Cu-DOTATATE PET/CT

PRRT ^{177}Lu-DOTATATE

- Peptide Receptor Radionuclide Therapy (PRRT) is radiation that is theranostic and can be given systemically to treat metastatic disease

Phase II Lu-177-DOTATATE (Lutathera) in Therapy of Inoperable Pheochromocytoma/Paraganglioma (NCT03206060)

Phase II Study

- **Patients >18 years-old**
- Patients with metastatic or inoperable Pheochromocytoma/ Paraganglioma
  - SSTR+ disease as documented by positive ^{68}Ga-DOTATATE or ^{64}Cu-DOTATATE PET/CT

4 cycles of ^{177}Lu-Dotatate every 2 months

Dose 1	Dose 2	Dose 3	Dose 4

Secondary Objectives:

- Overall Survival (OS): The amount of time the patient is alive after start of this treatment
- Objective response rate (ORR): The percentage of patients whose cancer shrinks or disappears after treatment
- Determine changes in plasma biochemical markers
- Evaluate Quality of Life (QoL)
- Determine ability to decrease anti-hypertensive medication

Primary Objective
Progression-free survival (PFS)
The percentage of people who did not have new tumor growth or cancer spread during or after treatment.
This means the cancer is still there but not growing or spreading.

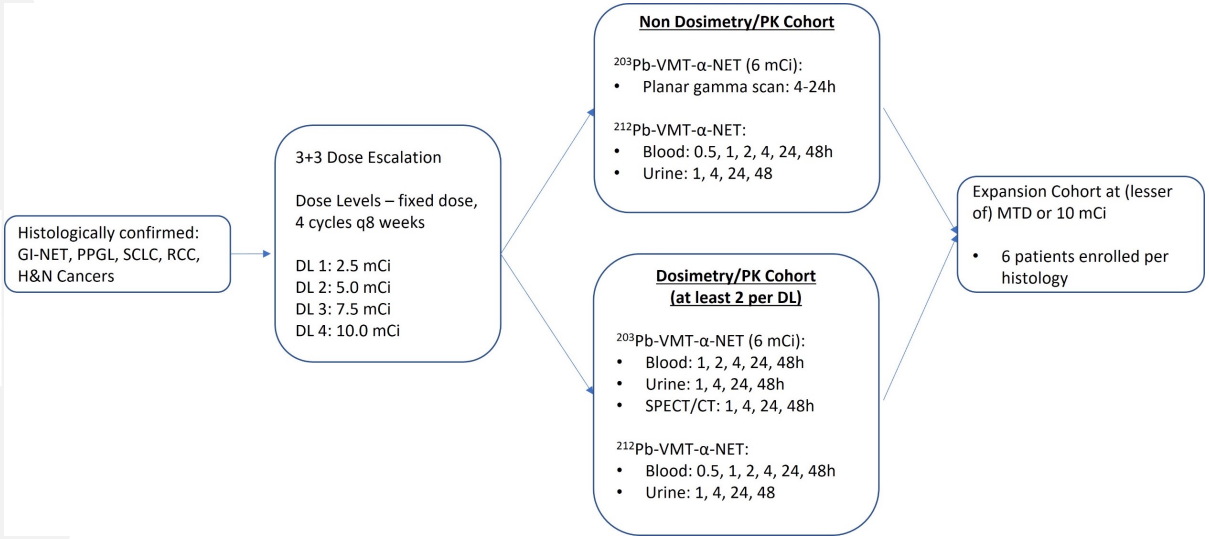
Dr. Frank Lin

[212Pb]VMT-Alpha-NET in Metastatic or Inoperable Somatostatin-Receptor Positive Gastrointestinal Neuroendocrine Tumors, Pheochromocytoma/Paragangliomas, Small Cell Lung, Renal Cell, and Head and Neck Cancers (NCT06479811)

- **Patients >18 years- old**
- SSTR+ disease as documented by positive ^{68}Ga-DOTATATE or ^{64}Cu-DOTATATE PET/CT

4 cycles of every 2 months [212Pb]VMT-Alpha-NET

Dose 1 | Dose 2 | Dose 3 | Dose 4



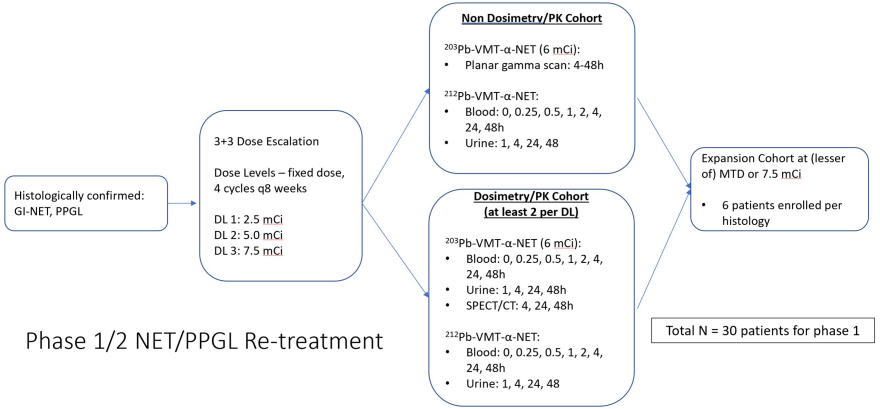
Primary Objective:

Phase 1: Safety profile and tolerability of the [212Pb]VMT-Alpha-NET, determine the maximum tolerated dose and assess safety

Dr. Frank Lin

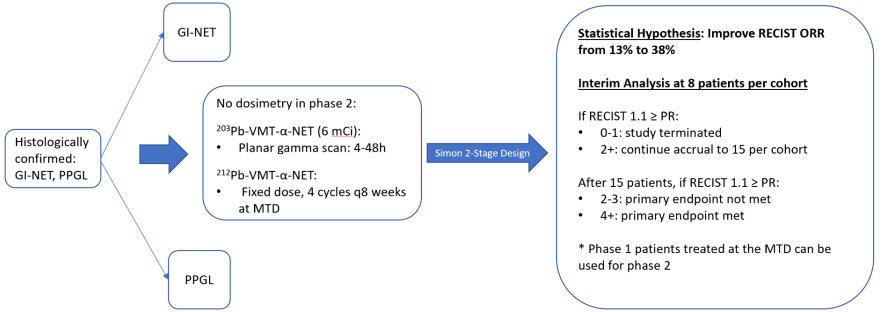
Somatostatin-Receptors (SSTR)-Agonist [212Pb]VMT-alpha-NET in Metastatic or Inoperable SSTR+ GEP-NETs and Pheochromocytoma/Paraganglioma Previously Treated With Systemic Targeted Radioligand Therapy (NCT06427798)

Schema – Retreatment Phase 1



Phase 1/2 NET/PPGL Re-treatment

Schema – Retreatment Phase 2



Phase 1/2 NET/PPGL Re-treatment

Additional Phase 2 N = 18 (9 per cohort)

Total N = 53 (with 10% loss included)

- **Patients >18 years- old**
- SSTR+ disease as documented by positive ^{68}Ga-DOTATATE or ^{64}Cu-DOTATATE PET/CT

4 cycles of every 2 months [212Pb]VMT-Alpha-NET

Dose 1	Dose 2	Dose 3	Dose 4

Dr. Frank Lin

A021804: Randomized Phase II Trial: Temozolomide vs. Temozolomide + Olaparib in PHEO/PARA (NCT04394858)

Phase II study

Primary Objective

- Compare the progression-free survival (PFS) of patients with advanced PHEO/PARA receiving temozolomide and olaparib to that of patients receiving temozolomide alone

Secondary Objective

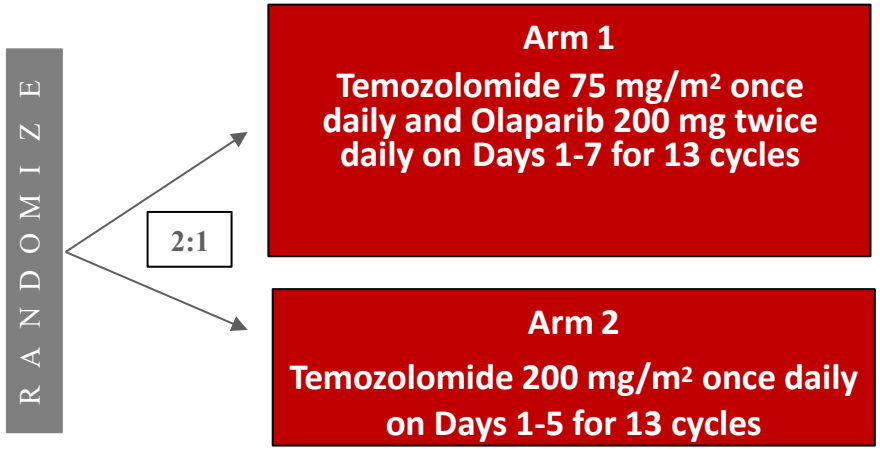
- To compare the overall survival (OS) of patients with PHEO/PARA receiving temozolomide and olaparib vs. temozolomide alone.
- To compare the objective response rate (ORR) associated with temozolomide and olaparib vs. temozolomide alone
- To evaluate and compare the toxicity profile of temozolomide-based combinations and olaparib vs. temozolomide

Dr. Kim Perez

Schema

For Arm 1: One Cycle = 21 Days

For Arm 2: One Cycle = 28 Days



- Radiologic assessment every 8 weeks (+/- 1 week)
- Treatment is to continue for 13 cycles or until disease progression, unacceptable adverse event, or withdrawal of consent

Phase II Study Belzutifan/MK-6482 for the Treatment of Advanced Pheochromocytoma/Paraganglioma or Pancreatic Neuroendocrine Tumor (NCT04924075)

Phase II Study

12 years and older
Patients with advaced or metastatic Pheochromcoytoma/ Paraganglioma and Pancreatic Neuroendocrine Tumors

Multicenter International Study
Cedars-Sinai Medical Center
University of Iowa
Johns Hopkins Hospital
Icahn School of Medicine at Mount Sinai
Vanderbilt University Medical Center
MD Anderson
National Cancer Institute*

- **Pheochromcoytoma/ Paraganglioma**
- **Pancreatic Neuroendocrine Tumors**
- **vHL Pheochromocytoma and paraganglioma**
- **HIF2 Alpha Related-Tumors**
- **Gastrointestinal Stromal Tumors (GIST)**

Primary Objective:

Objective Response Rate (ORR): The percentage of patients whose cancer shrinks or disappears after treatment

Secondary Objectives:

Duration of Response (DOR)

Time to Response (TTR)

Disease Control Rate (DCR)

Progressive Free Survival (PFS)

Overall Survival (OS)

Phase II Study of Axitinib in Treating Patients With Metastatic Pheochromocytomas or Paragangliomas (NCT03839498)

Phase II Study

- Patients with advaced or metastatic Pheochromcoytoma/ paraganglioma

→ **Axitinib** orally twice a day every 12 hours →

Primary Objective
Objective response rate (ORR): The percentage of patients whose cancer shrinks or disappears after treatment,

Secondary Objectives
Progression-free survival (PFS): The percentage of people who did not have new tumor growth or cancer spread during or after treatment.

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Phase II Study of LAnreotide in Metastatic Pheochromocytoma / PARAganglioma (LAMPARA) (NCT03946527)

Phase II Study

- Patients with advaced or metastatic Pheochromcoytoma/ paraganglioma

Lanreotide 120 mg deep subcutaneous injection every 4 weeks (±7 days) for 52 weeks, followed by an extension phase

Primary Objective
Rate of tumor growth: Tumor growth measured by a CT or MRI scan in pre-treatment, and minimum of three scans (prior to every 3rd visit, or every 12 weeks) in post-treatment.

Secondary Objective:
- Overall survival (OS)
- Overall Response Rate (ORR)
- Progression-free survival (PFS)

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A Novel Therapeutic Vaccine (EO2401) in Metastatic Adrenocortical Carcinoma or Malignant Pheochromocytoma/Paraganglioma (NCT04187404)

Phase I/II Study

- Patients with advaced or metastatic Pheochromcoytoma/ Paraganglioma and
- Adrenocortical cancers

Cohort 1: Phase I: Safety
patients with adrenal carcinoma or progressive malignant pheochromocytoma/paraganglioma
EO2401 in combination with nivolumab

Cohort 2: Phase II
Patients with pheochromocytoma and paraganglioma previously treated or untreated patients
EO2401 in combination with nivolumab

Primary Objective:
Adverse events assessment

Multicenter International Study
MD Anderson

Active Treatment Studies for PPGL

NCTN	Phase	Intervention	Key Eligibility	Primary end point	Where
NCT00107289	II	**Iodine I 131 Metaiodobenzylguanidine** (recurrent, progressive neuroblastoma or PPGL)	>1 year and older Positive MIBG	The objective response rate (ORR)	MSKCC
NCT05636618	I/IIa	First-in-Human Study of **[212Pb]VMT-α-NET** Targeted Alpha-Particle Therapy for Advanced SSTR2 Positive NET	>18 years-old STR2 expression by PET imaging agent, i.e.[68Ga]DOTATATE, [64Cu]DOTATATE	Dose Escalation to determine phase II dose and Determination of the overall response rate (ORR)	Multicenter in the US
NCT05885399	II	The Efficacy and Safety of **Penpulimab** in the Treatment of Metastatic PPGL Patients Who Fail to Other Systemic Treatment	>18 years-old Previously treated with anti-PD1, anti-PD-L1, or anti-PD-L2 medications were excluded from this trial.	The objective response rate (ORR)	Beijing, China
NCT06429397	II	First-line **Anlotinib** Combined With **Penpulimab** for Advanced PPGL	>18 years-old Previously treated with anti-PD1, anti-PD-L1, or anti-PD-L2 medications were excluded from this trial.	The objective response rate (ORR)	Multicenter in China
NCT05883085	II	A Study on the Safety and Effectiveness of **Anlotinib** for Neoadjuvant Treatment of PPGL	>18 years-old Patients who have previously used other anti-vascular targeted drugs, such as sunitinib	The objective response rate (ORR), the disease control rate (DCR)	Beijing, China
NCT05885386	II	A Study on the Safety and Effectiveness of **Temozolomide** for Neoadjuvant Treatment of PPGL	>10 years-old	The proportion of patients whose tumor change from unresectable to resectable tumor	Beijing, China

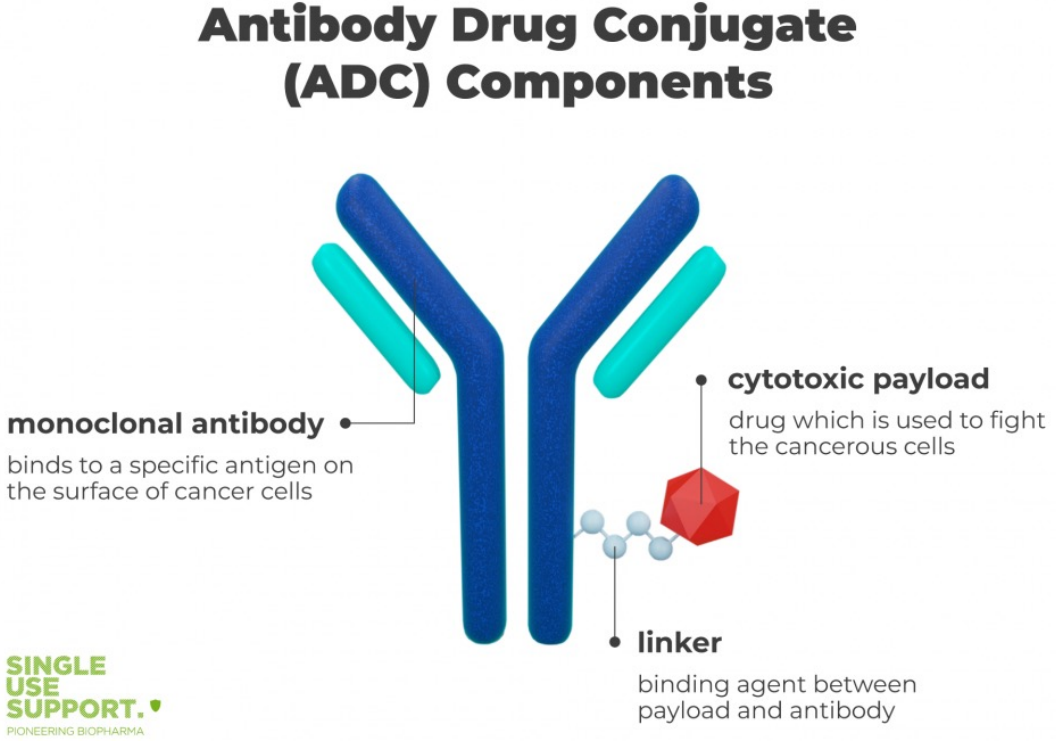
A First-in-Human Phase I Trial with Antibody Drug Conjugate ADCT-701 in Neuroendocrine Tumors and Carcinomas

NIH NATIONAL CANCER INSTITUTE

August 5, 2024

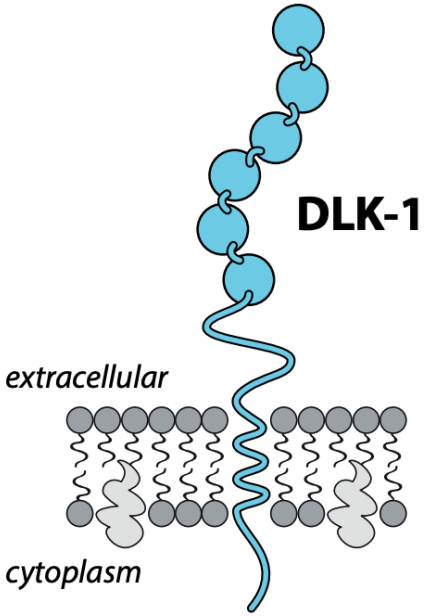
What is an Antibody Drug Conjugated?

Antibody-drug conjugates (ADCs) are a class of therapeutic agents that combine the target specificity of a monoclonal antibody with the lethality of cytotoxic cellular poison



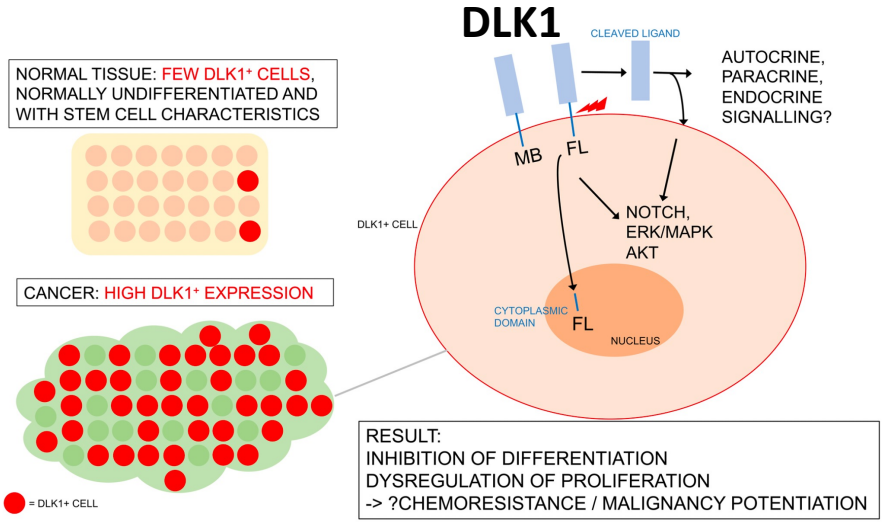
To Which Antigen Does the Antibody Bind?

- It binds to Delta Like Non-Canonical Notch Ligand 1 (DLK1)
- DLK1 is strongly expressed during fetal development, while its expression is highly restricted in adult tissues
- DLK1 is expressed in neuroendocrine cancers, neuroblastoma, adrenal cortical carcinoma and other cancers

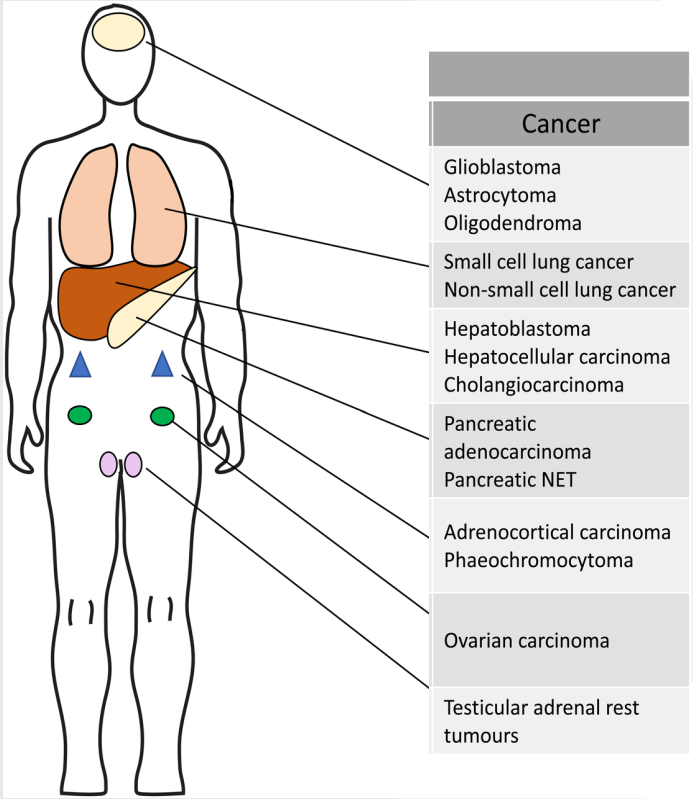


DLK1 is Mostly Restricted in Neuroendocrine Tissues

- DLK1 is expressed in many human tissues during embryonic development but in adults expression is low and is mostly restricted to (neuro) endocrine tissues.
- DLK1 is expressed at a high frequency in many common and more recently, high levels of expression have been identified in (neuro) endocrine-related cancers DLK1 expression in cancer is associated with worse prognosis
- DLK1 may be important in driving chemoresistance and potentiating malignancy in cancers



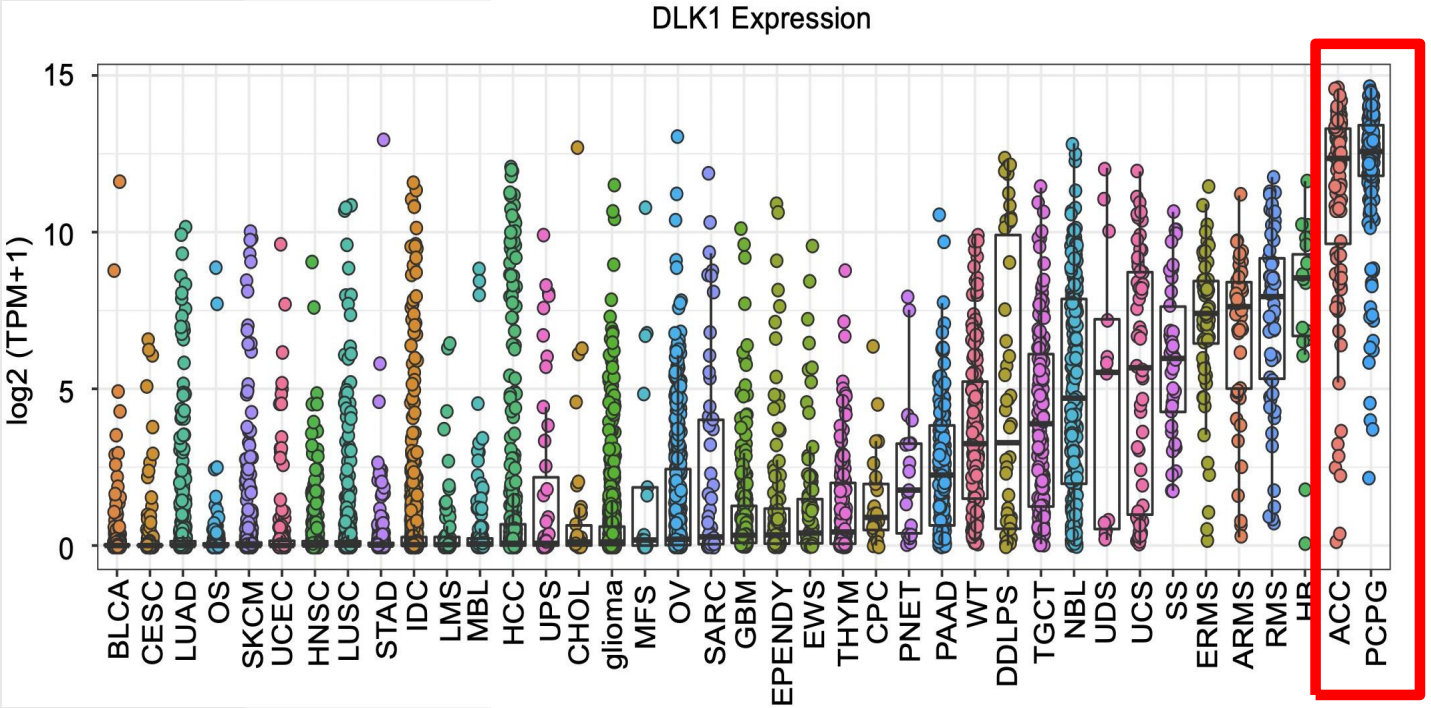
DLK1 Tumor Expression



Indication	# Cases	% Positive	Method	# Studies
HCC	200/624	32%	IHC	5
Hepatoblastoma	87/92	95%	IHC	2
Non-Small Cell Lung Cancer (NSCLC)	5/56	9%	IHC	2
SCLC	21/40	53%	IHC	2
Colon	34/58	59%	IHC	1
Breast	23/59	39%	IHC	1
Gastric	9/68	13%	IHC	1
Pancreatic	16/51	31%	IHC	1
Neuroblastoma	0/10	0% (neuroblastic)	IHC	1
	7/10	70% (endothelial)		
Adrenal Gland	37/37	100%	IHC	1
Pheochromocytoma	13/13	100%	IHC	1
Paraganglioma	4/4	100%	IHC	1
Thyroid Medullary	5/11	45%	IHC	1
Skeletal Muscle	18/21	86%	IHC	1
Liposarcoma	5/19	26%	IHC	1
Glioma	10/31	32%	mRNA	1
Wilms Tumour	12/30	40%	mRNA	1

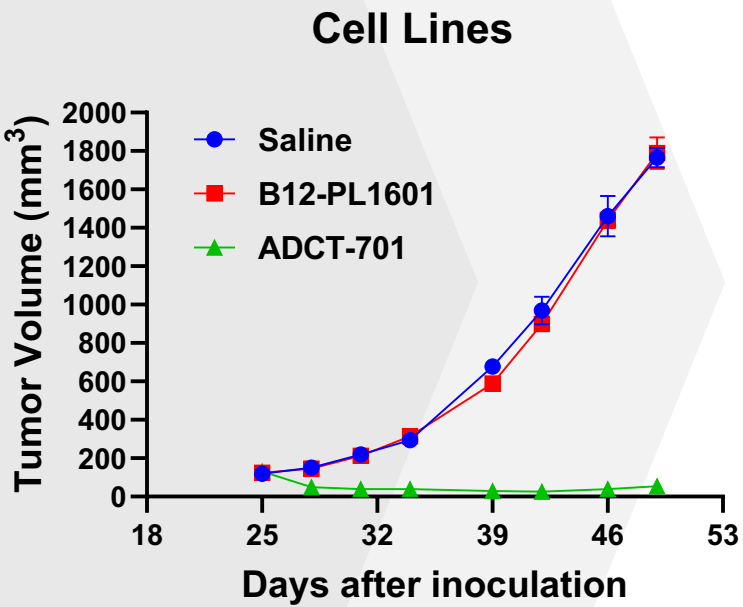
Pittaway et al. Endocrine-Related Cancer, 2021. 28(12

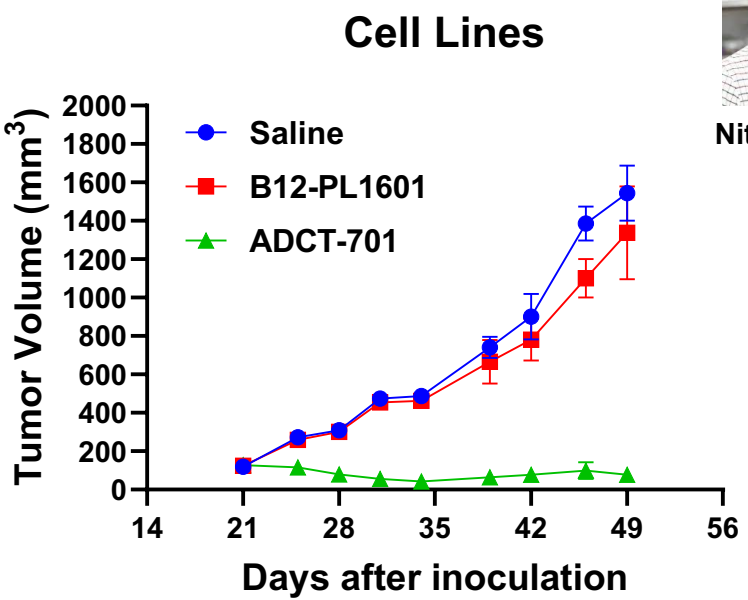
Across Cancers, Adrenal Tumors have Highest Expression of DLK1



TCGA & TARGET database

ADCT-701 has Potent Anti-Tumor Activity





Nitin Roper

Unpublished data

ADCT-701 First in Human Phase 1 Trial Design

- Safety and tolerability of ADCT-701 in adult patients with ACC, NB, PPGL, NEC, NET and SCLC
- Phase 1 open-label study with dose escalation

Dose Escalation

3+3

Dose level	ADCT-701 (µg/Kg), Q3W*
1	2 µg/Kg
2	4 µg/Kg
3	8 µg/Kg
4	16 µg/kg
5	32 µg/kg
6	64 µg/kg
7	96 µg/Kg
8	144 µg/Kg
9	192 µg/Kg
10	255 µg/Kg

Patient Eligibility

- Patients >18 years
- Evaluable disease
- ECOG ≤ 2

Up to 70 evaluable participants

Primary Objective

- MTD of ADCT-701

Secondary Objective

- Safety
- Primary anti-tumor activity
- PK

Exploratory Objectives

- NOTCH and DLKI expression by IHC

Questions to Ask Your Doctor About Clinical Trials

Questions about the trial:

- What is the purpose of the study?
- Why do researchers think the approach may be better than the one being use now?
- How long will I be in the trial?
- What kinds of tests and treatments are involved?
- Who can I speak with about questions I have during and after the trial?
- Who will be in charge of my care?

Questions about risk and benefits

- What are the possible side effects or risks of the new treatment?
- What are the possible benefits?

https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics
https://www.cancer.gov/about-cancer/treatment/clinical-trials/questions

Questions to Ask Your Doctor About Clinical Trials

Questions about your rights

- How will my health information be kept private?
- What happens if I decide to leave the trial?

Questions about cost

- Which costs do I have to pay if I take part in the trial?
- What costs will my health insurance cover?
- Who can help answer questions from my insurance company?

Questions about daily life

- How could the trial affect my daily life?
- How often will I have to come to the hospital or clinic?
- How far will I need to travel to take part in the trial?
- Will I have check-ups after the trial?

https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics
https://www.cancer.gov/about-cancer/treatment/clinical-trials/questions

Tips for Asking Your Doctor About Trials

- Consider taking a family member or friend along for support and for help in asking questions or recording answers
- Plan what to ask and don't hesitate to ask any new questions
- Write down questions in advance to remember them all
- Write down the answers so that they’re available when needed

https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics

Clinical Trials at the NCI

Center for Cancer Research

jaydira.delrivero@nih.gov

Office: 240-858-3851

Direct: 240-805-2888

@JaydiDelRivero

- Patients can contact us directly
- Call the CCR referral coordinator at 1-888-NCI-1937

How to Take Part

- Have your diagnosis confirmed by your own doctor.
- Have an illness that is being studied in a clinical trial that is accepting patients
- The research team for the trial you are interested in will review patient's records. Depending on the results of this review, they may invite you to the Clinical Center for a screening visit.

Once enrolled in a clinical trial, care at the clinical center is free

https://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials/where/clinical-center

Contact Us for Help

Call 1-800-4-CANCER

(1-800-422-6237)
Mon - Fri
9 a.m. to 9 p.m. ET

Live Chat

LiveHelp
Mon - Fri
9 a.m. to 9 p.m. ET

Email Us

NCIinfo@nih.gov

jaydira.delrivero@nih.gov

The Cancer Information Service (CIS)

Information specialists at NCI's Cancer Information Service (CIS), NCI's contact center, are available to help answer your cancer-related questions whether you are a patient, family member or friend, health care provider, or researcher. Our service is available in English and Spanish.

We provide accurate, up-to-date, and reliable information that is easy to understand and free of charge. Our trained information specialists provide personalized responses to a range of cancer questions, including:

- tailored clinical trials searches
- cancer research
- how to find cancer treatment centers
- cancer prevention and early detection
- risk factors
- symptoms
- diagnosis and treatment
- living with cancer
- tissue donation
- questions about NCI and its programs

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MyPART

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“Cancer cannot cripple love, it cannot shatter hope, it cannot conquer the spirit.” — Unknown.

“To all our brave patients, compassionate caregivers, and devoted families, we are eternally grateful for your selflessness, courage, and unwavering strength. Without your participation and unwavering support, none of these studies would be possible””

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ALLIANCE