Alliance A021602: Randomized, Double-blinded Phase III Study of Cabozantinib versus Placebo in Patients with Advanced Neuroendocrine Tumors after Progression on Everolimus (CABINET)

Jennifer Chan, MD, MPH
Dana-Farber Cancer Institute

Alliance CRP Education Session
November 2, 2018

Disclosures

- Consulting/Advisory Board Participation
  - Ipsen, Lexicon, Novartis

- Stock Ownership
  - Merck

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Objectives

- Describe the treatment landscape for advanced neuroendocrine tumors
- Understand the results of a phase II trial of cabozantinib in patients with advanced neuroendocrine tumors
- Discuss the trial design and objectives of A021602 (CABINET)

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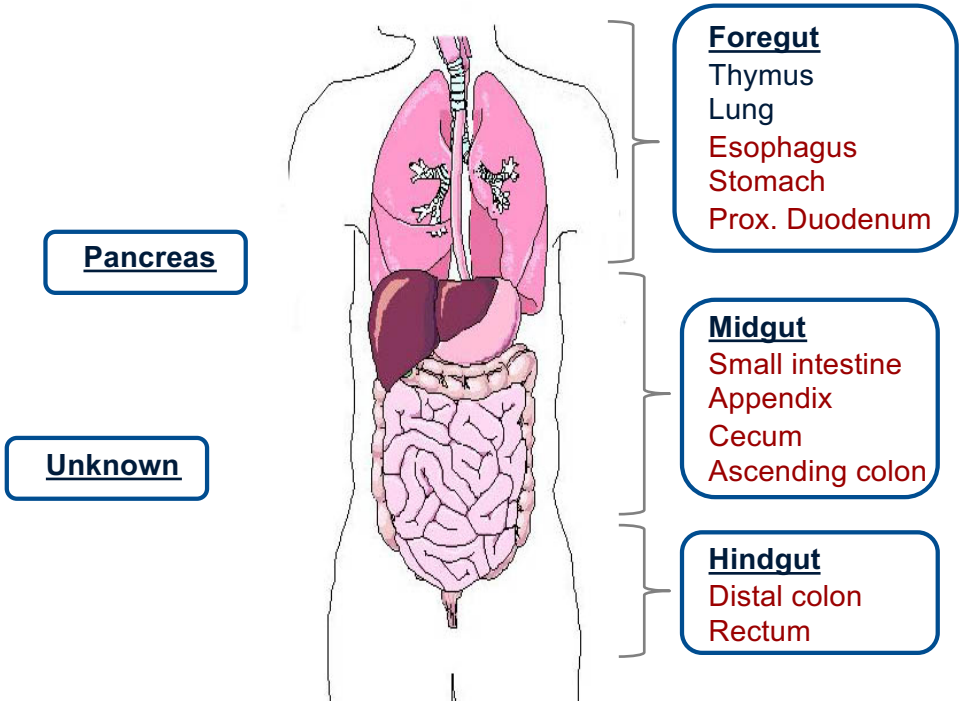
Neuroendocrine Tumors (NETs)

- Arise from cells in the diffuse neuroendocrine system
- May pursue more indolent clinical course than other malignancies
- Can secrete peptides leading to symptoms of hormone excess



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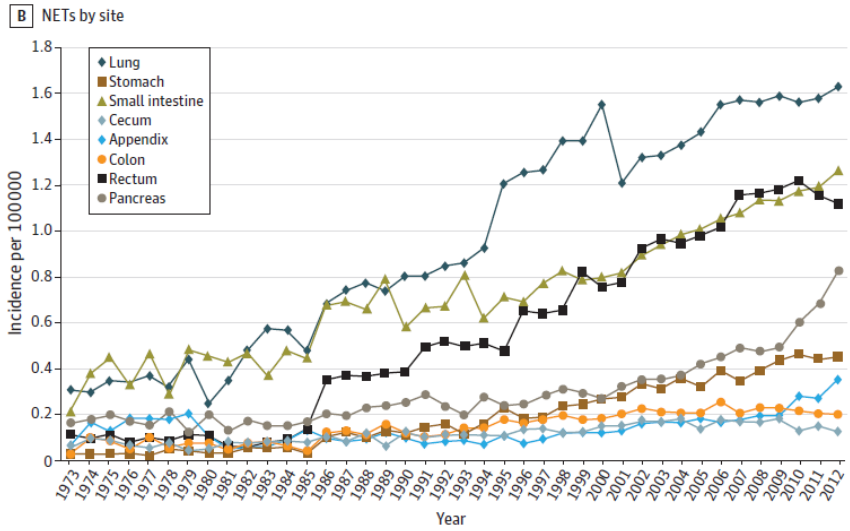
Epidemiology of NET

- Incidence has increased to 7/100,000
- Projected prevalence in the US in 2014 was 171,321
- Increasing incidence likely due to improved awareness, classification, and diagnostic modalities



Dasari A, et al. *JAMA Oncol* 2017

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Key Features of NET

- Pathologic features
  - Grade
  - Differentiation
- Primary site
  - Pancreatic NET
  - “Carcinoid”: GI, lung, thymus
- Functional status
  - Presence of clinical symptoms related to hormone secretion

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NET: Pathologic Classification

	GI/Panc (WHO)			Lung NET (WHO 2015)	
Differentiation	**Grade**	**Mitotic Count**	**Ki-67 Index**	**Tumor Type**	**Features**
Well differentiated	Low (G1)	< 2 per 10 HPF	< 3%	Typical carcinoid	Carcinoid morphology, <2 mitoses/2mm^2, no necrosis
	Intermediate (G2)	2-20 per 10 HPF	3-20%		
	High (G3)	> 20 per 10 HPF	>20%	Atypical carcinoid	Carcinoid morphology, 2-10 mitoses/2mm^2, foci of necrosis
Poorly differentiated	High (G3)	> 20 per 10 HPF	>20%	Large cell carcinoma	>10mitoses/2mm^2, necrosis cytology resembling NSCLC, IHC positive for NE/granules
				Small cell carcinoma	Small cell size, scant cytoplasm, nuclei with finely granular chromatin and absent or faint nucleoli, >11 mitoses/2mm^2, extensive necrosis

Lloyd RV, Osamura RY, Klöppel G, Rosai J (Eds), WHO Classification of Tumours of Endocrine Organs, 4th ed, IARC Press, Lyon 2017
Travis WD, Brambilla EW, Burke AP, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus, and Heart, IARC Press, Lyon 2015.

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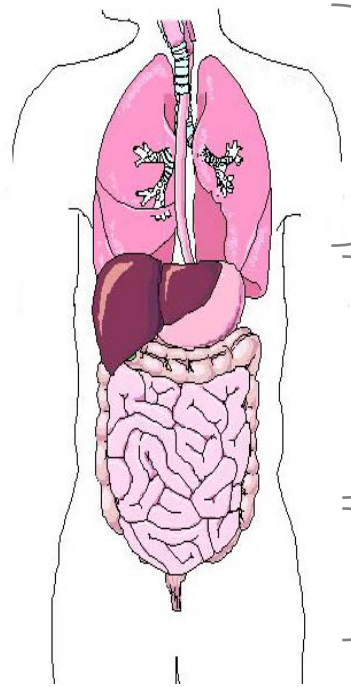
NET Classification by Primary Site



Foregut
Thymus
Lung
Esophagus
Stomach
Prox. duodenum

Midgut
Small intestine
Appendix
Cecum
Ascending colon

Hindgut
Distal colon
Rectum

GI-NET

Pancreas

Unknown

- More favorable biology and prognosis for midgut NET
- Treatment sensitivity varies according to primary site

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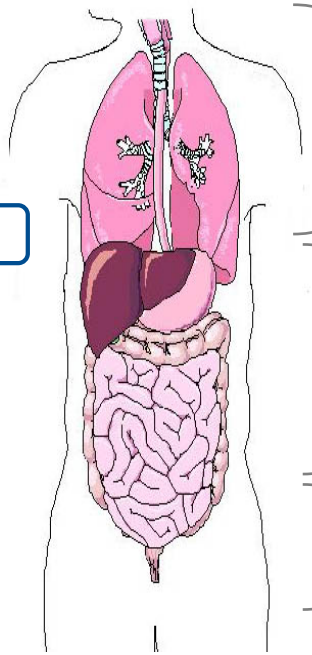
Kulke and Mayer, NEJM, 2009; Yao, JCO, 2008

Secreted Hormones and Syndromes Vary By Primary Tumor Site

Insulin
Gastrin
Glucagon
VIP
Somatostatin
GRF
ACTH
Serotonin,
PTHrP
Other rare hormones*

* LH, renin, GLP-1, IGF-2, erythropoietin, CCK, enteroglucagon

Pancreas



Foregut
Thymus
Lung
Esophagus
Stomach
Prox. duodenum

ACTH, histamine, 5-HTP

Midgut
Small intestine
Appendix
Cecum
Ascending colon

Serotonin (5-HT), tachykinins bradykinins

Hindgut
Distal colon
Rectum

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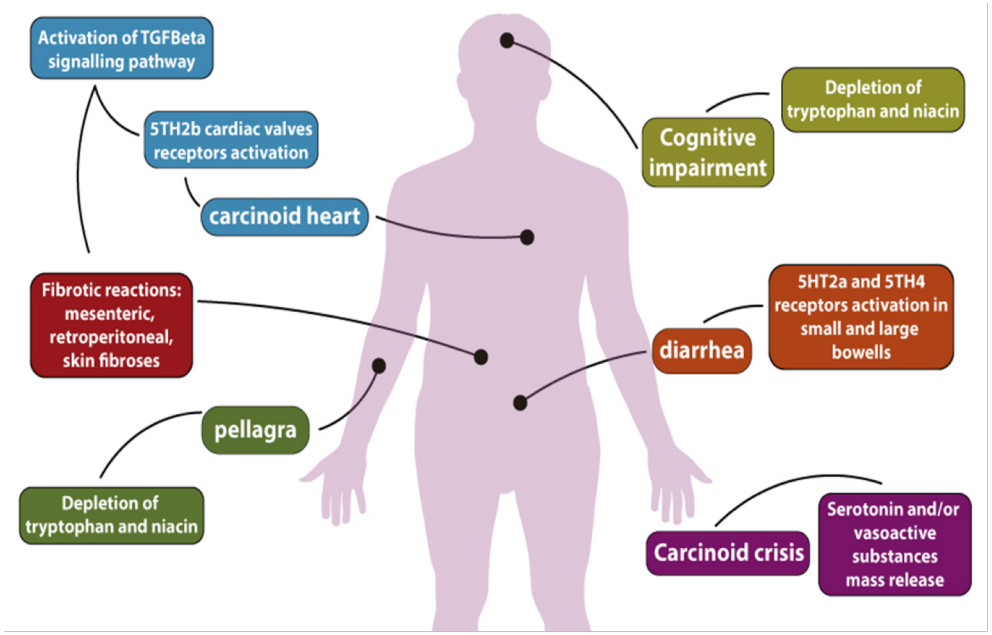
Classic Carcinoid Syndrome



Symptoms	Frequency	Mediators
Profound Flushing	85%–90%	Kallikrein, histamine, 5-hydroxtryptamine, prostaglandins, substance P
Diarrhea	70%	Gastrin, histamine, 5-hydroxtryptamine, prostaglandins, vasoactive intestinal peptide
Abdominal Pain	35%	Small bowel obstruction due to tumor or tumor products, mesenteric ischemia, hepatomegaly
Bronchospasm	15%	Histamine, 5-hydroxtryptamine,
Pellagra	5%	Niacin deficiency
Hypotension	30%	5-hydroxtryptamine, substance P
Teleangiectasis	25%	N/A

~ 20-30% of pts have carcinoid syndrome

Loughrey et al, Endocrinol Metab Clin N Am, 2018

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Neuroendocrine Tumors: Management Principles

- Resection of localized and limited metastatic disease
- Advanced disease
  - Control of hormone secretion for functional tumors
  - Control of growth of disease

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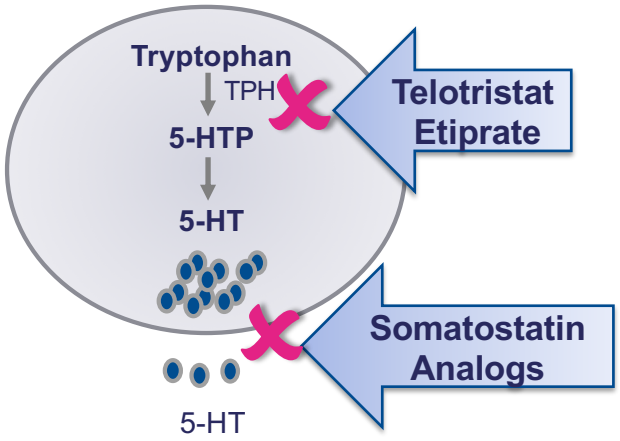
Treatment for Carcinoid Syndrome



- Somatostatin analogs (Octreotide, Lanreotide)
  - First line therapy for carcinoid syndrome (CS)
  - Can improve hormone-mediated symptoms by reducing hormone secretion
- Telotristat
  - Inhibits production of serotonin
  - Improves diarrhea from CS not well controlled with SSA
- Liver-directed therapies (embolization)

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Kvols et al, NEJM, 1986; Moertel CG. *J Clin Oncol*, 1987.
Rubin et al, *J Clin Oncol*, 1999; Khan et al, *Aliment Pharmacol Ther*, 2011; Vinik et al, Endocr Pract 2016;
Kulke et al, *J Clin Oncol* 2017

Treatment Options for Advanced NET

	Pancreatic NET	Carcinoid
Liver-directed therapies	Surgery Hepatic artery embolization	Surgery Hepatic artery embolization
Systemic Therapy	Lanreotide	Lanreotide Octreotide } GI
	Everolimus	Everolimus (GI, lung)
	Sunitinib	
	Alkylating agents (streptozocin, temozolomide)	
	^{177}Lu-Dotatate	^{177}Lu-Dotatate - GI

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Treatment Options for Advanced NET

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Effective treatments are needed for pancreatic NET and carcinoid after progression on everolimus

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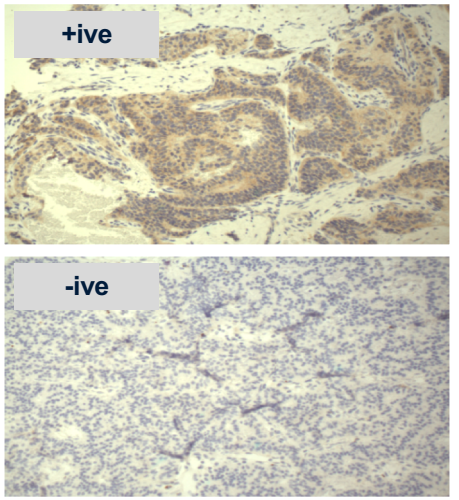
Treatment Targets in NET

- VEGF pathway inhibitors have activity in advanced neuroendocrine tumors (NET)[1,2,3]

- Recent studies have suggested that MET activation may also play a role in NET growth[4]



DFCI: 7/11 (64%) of panc NET with pos. staining for MET

1.Raymond et al., NEJM 2011; 364: 501-13. 2. Grande et al., Ann Oncol 2015; 26: 1987-93. 3. Phan et al., Lancet Oncol 2015; 16: 695-703. 4. Krampitz et al., PNAS 2016: 113: 4464-69.

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Cabozantinib

- TKI targeting VEGF receptors, MET, AXL, RET
- FDA-approved for patients with advanced renal cell carcinoma (RCC) and medullary thyroid carcinoma (MTC)[1,2,3]
- In preclinical NET models, cabozantinib inhibits cell viability and decreases metastases and invasion[4,5]

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1. Choueiri et al., J Clin Oncol 2017; 35:591-597. 2. Choueiri et al., NEJM 2015; 373: 1814–1823. 3. Elisei et al., J Clin Oncol 2013; 31: 3639–3646. 4. Reuther et al., Neuroendocrinology; 103: 383-401. 5. Sennino et al., Cancer Discovery 2012; 2: 270-287.

Phase II: Cabozantinib in Progressive NET (MGH, DFCI)

Key inclusion criteria:

- Well-differentiated NET
- Unresectable or metastatic
- Radiographic progression within 12 months of entry
- No prior cabozantinib; other anti-VEGF treatment allowed
- Concurrent somatostatin analog allowed if stable dose for 2 months

→ **Cabozantinib 60 mg p.o. daily** →

Enrolled 7/2012-11/2015

- Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent
- Cycle length: 28 days
- Restaging every 2 cycles for the first 6 cycles, then every 3 cycles

1° Endpoint : RR

2° Endpoints: PFS, OS, safety and tolerability

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Chan, ASCO GI, 2017

Patient Demographics

	Pancreatic NET (n=20)		Carcinoid (n=41)	
Time from dx, median (range)	37 (4-152) mo		59 (5-192) mo	
Median age (yrs)	55		63	
Male	12 (60%)		18 (44%)	
ECOG PS 0/1 (%)	40/60		51/49	
Primary Tumor	-		Small Intestine Lung Unknown Other (rectum, thymus, kidney)	29 (71%) 5 (12%) 3 (7%) 4 (10%)
# Prior Therapies, median (range)	3 (0-8)		1 (0-6)	
Prior Therapy	Sunitinib Everolimus Temozolomide	12 (60%) 13 (65%) 11 (55%)	Everolimus Bevacizumab IFN Temozolomide	12 (29%) 6 (15%) 4 (10%) 3 (7%)
Prior Somatostatin Analog	15 (75%)		40 (98%)	

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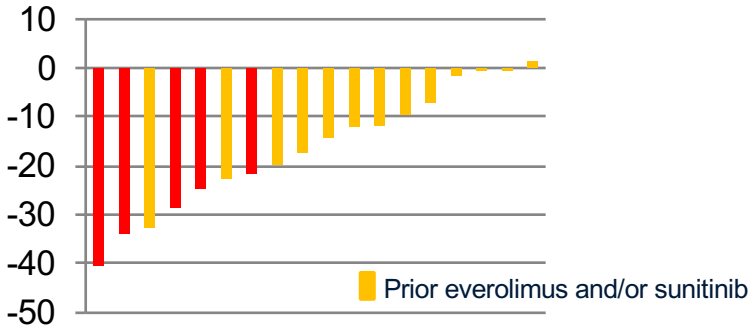
RECIST Response Profiles

Pancreatic NET



Response	N=20	% (95% CI)
PR	3	15% (5-36%)
SD	15	75% (53-89%)
Unknown*	2	10% (3-30%)

	Pancreatic NET n=20
Number of treatment cycles completed, median (range)	10 (0-35)
Pts on treatment at data analysis 7/2016	5 (25%)
Reason off study Disease progression/death Adverse event Withdrawal of consent/investigator decision	 10 (50%) 3 (15%) 2 (10%)

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* Treatment stopped prior to restaging.

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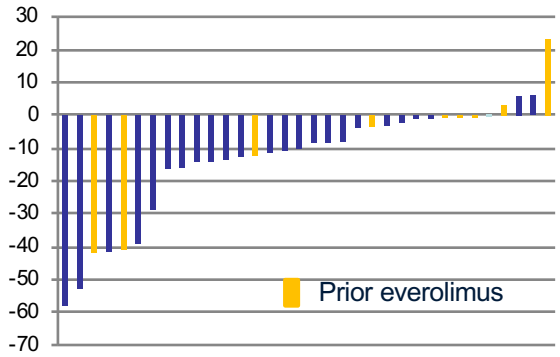
RECIST Response Profiles

Carcinoid



Response	N=41	% (95% CI)
PR	6	15% (7-28%)
SD	26	63% (48-76%)
PD	2	5% (1-16%)
Unknown*	7	17% (9-31%)

* Treatment stopped prior to restaging.

	Carcinoid (n=41)
Number of treatment cycles completed, median (range)	8 (0-44)
Pts on treatment at data analysis 7/2016	9 (22%)
Reason off study Disease progression/death Adverse event Withdrawal of consent/investigator decision	 14 (34%) 7 (17%) 11 (27%)

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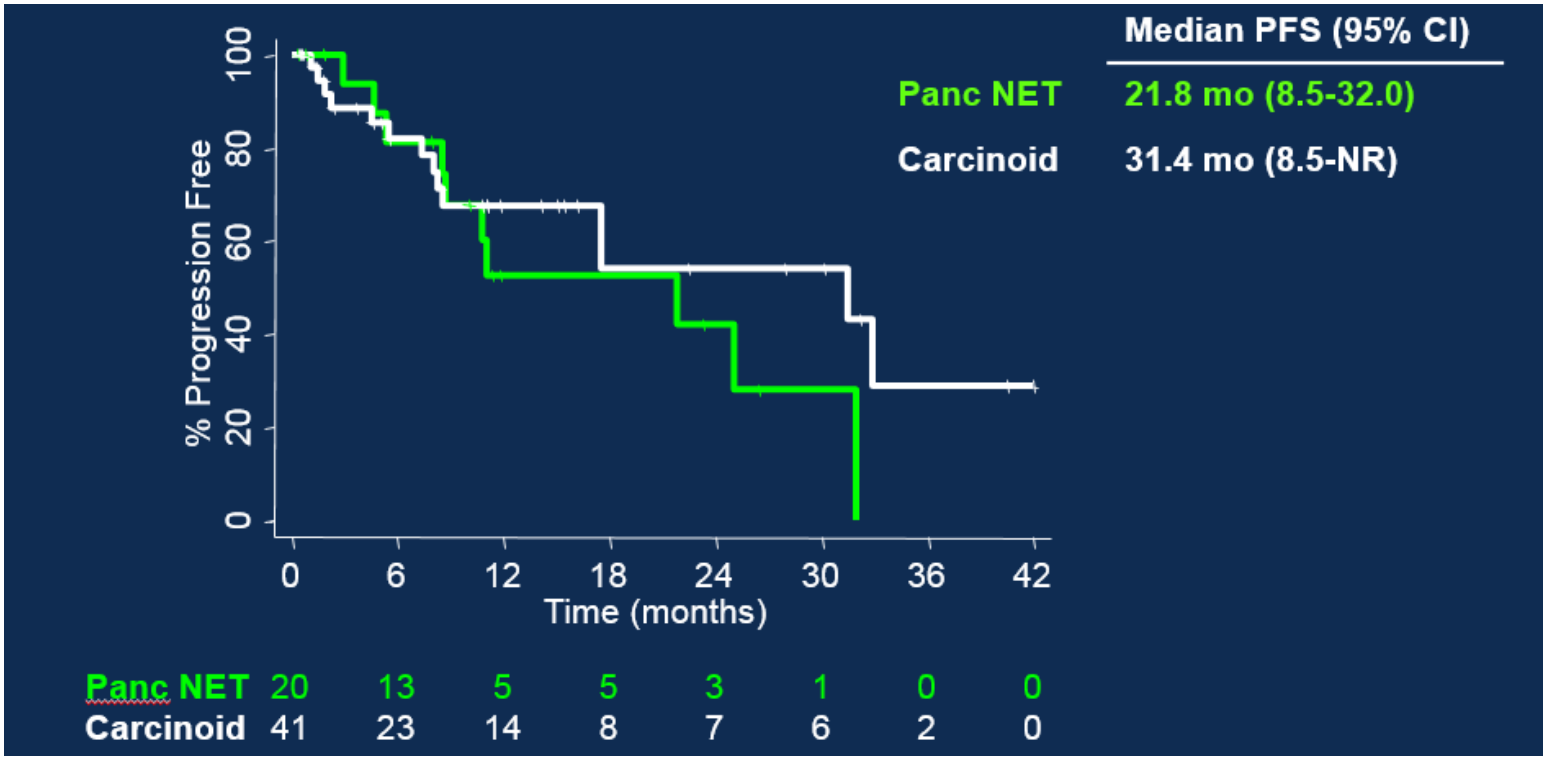
Progression-free Survival



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Treatment-Related Adverse Events

Adverse Event (n=61)	All Grades*	Grade 3/4**
Fatigue	41 (67%)	3 (5%)
AST increase	36 (59%)	1 (2%)
Diarrhea	33 (54%)	6 (10%)
Thrombocytopenia	27 (44%)	3 (5%)
Hypertension	25 (41%)	8 (13%)
ALT increase	24 (39%)	1 (2%)
Anemia	24 (39%)	1 (2%)
WBC decrease	24 (39%)	1 (2%)
Alk phos increase	20 (33%)	-
Nausea	19 (31%)	1 (2%)
Mucositis	19 (31%)	-
Hypophosphatemia	15 (25%)	7 (11%)
Lipase or amylase increase	13 (21%)	4 (7%)
Lymphocyte decrease	7 (11%)	4 (7%)

* Events reported in at least 30% of patients

** Events reported in >1 patient. Other notable Gr 3/4 AE: heart failure, hemolytic anemia, bowel perforation, acute kidney injury

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Adverse Events and Dose Modification

- Toxicity profile of cabozantinib in NET is consistent with data in other disease settings

- 43/53 (81%) of patients completing at least 1 cycle underwent dose reduction

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Alliance A021602: Randomized, Double-blinded Phase III Study of Cabozantinib versus Placebo in Patients with Advanced Neuroendocrine Tumors after Progression on Everolimus (CABINET)

This is an FDA Registration Study.

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Study Objectives

- Primary Objectives:
  - To determine whether cabozantinib can significantly improve PFS compared with placebo in patients with pancreatic NET whose disease has progressed on everolimus
  - To determine whether cabozantinib can significantly improve PFS compared with placebo in patients with carcinoid tumor whose disease has progressed on everolimus

- Secondary Endpoints:
  - OS, Radiographic RR
  - Safety, tolerability (CTCAE, PRO-CTCAE)

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Eligibility Criteria

- Documentation of Disease:
  - Local pathology report must state one of the following:
    - Well- or moderately-differentiated neuroendocrine tumor
    - Low- or intermediate-grade neuroendocrine tumor
    - Carcinoid tumor or atypical carcinoid tumor
  - Histologic documentation of neuroendocrine tumor of pancreatic, gastrointestinal, lung, or unknown primary site
    - GI, lung, unknown primary will enroll in carcinoid cohort
  - Locally advanced/unresectable or metastatic disease
  - Target lesions must have shown evidence of disease progression by RECIST v1.1 criteria in the 12 months prior to registration
  - Measurable disease per RECIST v1.1 by CT scan or MRI

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Eligibility Criteria (continued)

- Prior Treatment:
  - Must have failed at least one prior systemic therapy that included everolimus.
  - Prior treatment must be completed at least 28 days prior to registration.
    - Prior treatment with somatostatin analogs allowed; continuation of somatostatin analogs allowed.
- Age ≥ 18 years
- ECOG Performance Status: 0-2

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Treatment Plan

- Administration Schedule:
  - Cabozantinib/placebo 60 mg PO QD on Days 1-28
    - Protocol therapy administered as three 20 mg tablets

- Additional Drug Dosing Information:
  - Do not eat 2 hours before or 1 hour after taking cabozantinib/placebo

- Crossover from placebo to cabozantinib at the time of disease progression will not occur.

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Treatment Plan (continued)

- Treatment is to begin within 14 days of registration.
- One cycle is defined as 28 days of treatment.
  - Up to 28 days are allowed if delays occur due to toxicity
- Chemotherapy and imaging must be performed at the registering institution.
  - After cessation of therapy, imaging may be performed at a non-registering institution.

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Study Calendar

- In general, the following items are required on Day 1 of each cycle:
  - H&P, PS, vital signs, CBC with differential, platelets, creatinine, chemistry panel, and electrolytes
    - ECG, TSH, urine protein & creatinine, serum chromogranin A, and 24-hour urine 5-HIAA are also required at varying intervals per Section 5.0
- CT (or MRI) is required every 12 +/1 weeks until evidence of progression
  - Imaging modality used at baseline must be used for all subsequent imaging time points
  - Imaging scans are to be submitted to IROC Ohio for Central Review per Section 6.3 of the protocol

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Study Evaluations for PFS

- Real-time central review of scans with local determination of progressive disease to confirm progression (24-72 hours)
  - Patients continue cabozantinib/placebo while central review results are pending, unless the treating investigator believes a change in therapy is medically necessary

- Retrospective blinded central radiology review of all scans

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Correlative Studies/Biobanking

- Quality of Life (A021602-HO1): Amylou Dueck (Mayo)
  - EORTC QLQ-30 and GI.NET 21
  - At baseline, every 12 weeks, end of treatment

- Blood/Tissue Banking (A021602 Biobanking): Brian Untch (MSKCC)
  - At baseline, C2D1, at progression
  - Submit to Alliance Biorepository at OSU

- Pharmacokinetic Substudy (A021602-PP1): Jan Beumer (Pitt)
  - At C1D1, C1D15, C2D1, C2D15, C3D1
  - Submit to Alliance PK Lab at the University of Pittsburgh

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Data Entry

- Data entry for this trial is via Medidata Rave®
- Treatment Form requires “Reason interval ended”
  - Footnote 5 includes a definition for each option

Line #	Start date[1] *(dd MMM yyyy)*	Stop date[2] *(dd MMM yyyy)*	Total daily dose (mg)[3]	If Other, specify[4]	Reason interval ended[5]	If Other, specify[6]
	__-___-____	__-___-____	☐60 ☐40 ☐20 ☐0 ☐Other		☐End of cycle ☐Permanent treatment discontinuation ☐Adverse event ☐Subject non-compliance other than AE ☐Site/Logistical error ☐Treatment resumed ☐Other	
(add a log line for each constant dose level)						

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Data Submission

- Data Submission Schedule (DSS)
  - Pages 1-3
  - Page 4: Source documentation requirements for monitoring

- Available on Alliance and CTSU websites

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Follow-up

Folder Name in the Data Entry System	Follow-Up	
	Clinical Follow-Up	Survival and Disease Status Follow-Up
Supporting Documentation[13]	X	
Laboratory Tests and Results[14]		
Specimen Submission: Biobanking[15]		
Specimen Submission: Blood (A021602-PP1)[16]		
Patient Status: Treatment (Intervention)		
Off Treatment[17]		
Patient Status: Clinical Follow-Up/Observation	X	
Patient Status: Survival and Disease Status Follow Up		X
Late Adverse Events[18]		X
Late Expedited Reporting Evaluation[19]		X
Notice of New Primary[20]		
Consent Withdrawal[21]		
Consent Withdrawal: All Follow-Up[22]		
Consent Withdrawal: Clinical Follow-Up Only[23]		
Consent Withdrawal: Specimen Only[24]		
Consent Withdrawal: QOL Only[25]		
First Non-protocol Treatment[26]	X	X

Follow-up/Survival forms are required in Rave every 6 months up to 8 years after registration.

Patients will be followed for survival and progression every 12 weeks until progression or start of new anticancer therapy, and then for survival every 6 months until 8 years after registration or until death, whichever comes first.

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Central Monitoring

- A021602 will utilize central monitoring in order to ensure complete and consistent data collection.
- Centralized data monitoring with source data verification (SDV) will be performed for all patients for key eligibility and response/disease outcomes.
  - Please refer to Data Submission Schedule (DSS), page 4 for required items

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Study Team

Study Chair	Jennifer Chan (DFCI)
Protocol Coordinator	Alexandra LeVasseur (Alliance)
Data Manager	Pamela Fain-Pribyl (Mayo)
Imaging	Spencer Behr (UCSF), Michael Knopp (IROC Ohio)
Statistics	Fang-Shu Ou, Michelle Mahoney (Mayo)
Health Outcomes	Amylou Dueck (Mayo)
Pathology	Wendy Frankel (OSU)
Correlative Science	Brian Untch (MSKCC), Federico Innocenti (UNC)
PK	Jan Beumer (Pitt)
Community Oncology	Jared Acoba (Hawaii Oncology)
ECOG-ACRIN	Efrat Dotan (Fox Chase)
NRG	Arvind Dasari (MDACC)
SWOG	Jon Strosberg (Moffitt)

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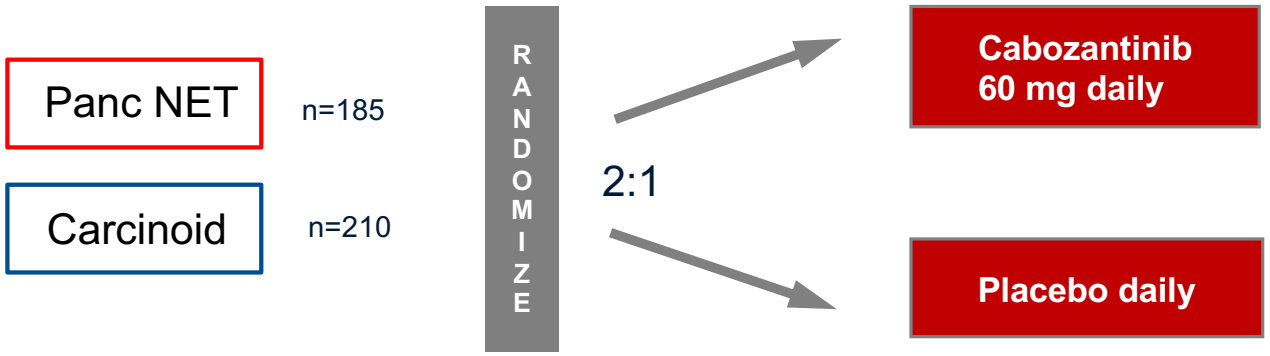
CABINET (A021602): Randomized Double-Blinded Phase III Study of Cabozantinib vs. Placebo in Advanced NET after Progression on Everolimus



1° Endpoint : PFS (Central Review)

2° Endpoints: OS, RR, Safety, Tolerability

Key inclusion criteria:

- **Well- to moderately differentiated NET, functional and nonfunctional**
- **Disease progression by RECIST within 12 months prior to randomization**
- **Failure of at least 1 prior systemic therapy including everolimus**
- **Concurrent SSA allowed provided stable dose for ≥ 2 mo**

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