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
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)
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
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
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
# NET: Pathologic Classification

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Grade</th>
<th>Mitotic Count</th>
<th>Ki-67 Index</th>
<th>Tumor Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>Low (G1)</td>
<td>&lt; 2 per 10 HPF</td>
<td>&lt; 3%</td>
<td>Typical carcinoid</td>
<td>Carcinoid morphology, &lt;2 mitoses/2mm², no necrosis</td>
</tr>
<tr>
<td></td>
<td>Intermediate (G2)</td>
<td>2-20 per 10 HPF</td>
<td>3-20%</td>
<td>Atypical carcinoid</td>
<td>Carcinoid morphology, 2-10 mitoses/2mm², foci of necrosis</td>
</tr>
<tr>
<td></td>
<td>High (G3)</td>
<td>&gt; 20 per 10 HPF</td>
<td>&gt;20%</td>
<td>Large cell carcinoma</td>
<td>&gt;10 mitoses/2mm², necrosis cytology resembling NSCLC, IHC positive for NE/granules</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>High (G3)</td>
<td>&gt; 20 per 10 HPF</td>
<td>&gt;20%</td>
<td>Small cell carcinoma</td>
<td>Small cell size, scant cytoplasm, nuclei with finely granular chromatin and absent or faint nucleoli, &gt;11 mitoses/2mm², extensive necrosis</td>
</tr>
</tbody>
</table>

Lloyd RV, Osamura RY, Klöppel G, Rosai J (Eds), WHO Classification of Tumours of Endocrine Organs, 4th ed, IARC Press, Lyon 2017
# NET: Pathologic Classification

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<tr>
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<td>Low (G1)</td>
<td>&lt; 2 per 10 HPF</td>
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Lloyd RV, Osamura RY, Klöppel G, Rosai J (Eds), WHO Classification of Tumours of Endocrine Organs, 4th ed, IARC Press, Lyon 2017
NET Classification by Primary Site

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

Foregut
- Thymus
- Lung
- Esophagus
- Stomach
- Prox. duodenum

Midgut
- Small intestine
- Appendix
- Cecum
- Ascending colon

Hindgut
- Distal colon
- Rectum

Pancreas
Unknown

Kulke and Mayer, NEJM, 2009; Yao, JCO, 2008
Secreted Hormones and Syndromes Vary By Primary Tumor Site

**Foregut**
- Thymus
- Lung
- Esophagus
- Stomach
- Prox. duodenum

**Midgut**
- Small intestine
- Appendix
- Cecum
- Ascending colon

**Hindgut**
- Distal colon
- Rectum

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

**ACTH, histamine, 5-HTP**

**Serotonin (5-HT), tachykinins bradykinins**

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

- Activation of TGFβ signalling pathway
- 5HT2b cardiac valves receptors activation
- Cognitive impairment
- Depletion of tryptophan and niacin
- Carcinoid heart
- Fibrotic reactions: mesenteric, retroperitoneal, skin fibroses
- Diarrhea
- 5HT2a and 5HT4 receptors activation in small and large bowells
- Pellagra
- Serotonin and/or vasoactive substances mass release
- Carcinoid crisis

~ 20-30% of pts have carcinoid syndrome

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Frequency</th>
<th>Mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profound Flushing</td>
<td>85%–90%</td>
<td>Kallikrein, histamine, 5-hydroxytryptamine, prostaglandins, substance P</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>70%</td>
<td>Gastrin, histamine, 5-hydroxytryptamine, prostaglandins, vasoactive Intestinal Peptide</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>35%</td>
<td>Small bowel obstruction due to tumor or tumor products, mesenteric ischemia, hepatomegaly</td>
</tr>
<tr>
<td>Bronchospasms</td>
<td>15%</td>
<td>Histamine, 5-hydroxytryptamine,</td>
</tr>
<tr>
<td>Pellagra</td>
<td>5%</td>
<td>Niacin deficiency</td>
</tr>
<tr>
<td>Hypotension</td>
<td>30%</td>
<td>5-hydroxytryptamine, substance P</td>
</tr>
<tr>
<td>Teleangiectasis</td>
<td>25%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Loughrey et al, Endocrinol Metab Clin N Am, 2018
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
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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# Treatment Options for Advanced NET

<table>
<thead>
<tr>
<th></th>
<th>Pancreatic NET</th>
<th>Carcinoid</th>
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<tbody>
<tr>
<td><strong>Liver-directed therapies</strong></td>
<td>Surgery Hepatic artery embolization</td>
<td>Surgery Hepatic artery embolization</td>
</tr>
<tr>
<td><strong>Systemic Therapy</strong></td>
<td>Lanreotide</td>
<td>Lanreotide Octreotide</td>
</tr>
<tr>
<td></td>
<td>Everolimus</td>
<td>Everolimus (GI, lung)</td>
</tr>
<tr>
<td></td>
<td>Sunitinib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alkylating agents (streptozocin, temozolomide)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$^{177}$Lu-Dotatate</td>
<td>$^{177}$Lu-Dotatate - GI</td>
</tr>
</tbody>
</table>
## Treatment Options for Advanced NET

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<td>Surgery Hepatic artery embolization</td>
<td>Surgery Hepatic artery embolization</td>
</tr>
</tbody>
</table>
| **Systemic Therapy**     | Lanreotide                                          | Lanreotide  
                          |  
                          | Everolimus                                          | Everolimus (GI, lung) |
|                         | Everolimus                                          |                                     |
|                         | Sunitinib                                           |                                     |
|                         | Alkylating agents  
                          (streptozocin, temozolomide)           |                                     |
|                         | $^{177}$Lu-Dotatate                                   | $^{177}$Lu-Dotatate - GI |

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

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\(^4,5\)

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

1° Endpoint: RR
2° Endpoints: PFS, OS, safety and tolerability

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

Chan, ASCO GI, 2017
## Patient Demographics

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

Chan, ASCO GI, 2017
RECISt Response Profiles

Pancreatic NET

<table>
<thead>
<tr>
<th>Response</th>
<th>N=20</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>3</td>
<td>15% (5-36%)</td>
</tr>
<tr>
<td>SD</td>
<td>15</td>
<td>75% (53-89%)</td>
</tr>
<tr>
<td>Unknown*</td>
<td>2</td>
<td>10% (3-30%)</td>
</tr>
</tbody>
</table>

* Treatment stopped prior to restaging.

<table>
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<tr>
<th>Pancreatic NET n=20</th>
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<tr>
<td>Number of treatment cycles completed, median (range)</td>
</tr>
<tr>
<td>Pts on treatment at data analysis 7/2016</td>
</tr>
<tr>
<td>Reason off study</td>
</tr>
<tr>
<td>Disease progression/death</td>
</tr>
<tr>
<td>Adverse event</td>
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<tr>
<td>Withdrawal of consent/investigator decision</td>
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Chan, ASCO GI, 2017
**RECISt Response Profiles**

**Carcinoid**

Prior everolimus

<table>
<thead>
<tr>
<th>Response</th>
<th>N=41</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>6</td>
<td>15% (7-28%)</td>
</tr>
<tr>
<td>SD</td>
<td>26</td>
<td>63% (48-76%)</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>5% (1-16%)</td>
</tr>
<tr>
<td>Unknown*</td>
<td>7</td>
<td>17% (9-31%)</td>
</tr>
</tbody>
</table>

* Treatment stopped prior to restaging.

<table>
<thead>
<tr>
<th>Carcinoid (n=41)</th>
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<td>Number of treatment cycles completed, median (range)</td>
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</table>

Chan, ASCO GI, 2017
Progression-free Survival

Median PFS (95% CI)
- Panc NET: 21.8 mo (8.5-32.0)
- Carcinoid: 31.4 mo (8.5-NR)

% Progression Free

Time (months)

Panc NET: 20 13 5 5 3 1 0 0
Carcinoid: 41 23 14 8 7 6 2 0

Chan, ASCO GI, 2017
## Treatment-Related Adverse Events

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

* 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

Chan, ASCO GI, 2017
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
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.
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)
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
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
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.
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.
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
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
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
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
Data Submission

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

- Available on Alliance and CTSU websites
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.
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
### Study Team

<table>
<thead>
<tr>
<th>Role</th>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Chair</td>
<td>Jennifer Chan (DFCI)</td>
</tr>
<tr>
<td>Protocol Coordinator</td>
<td>Alexandra LeVasseur (Alliance)</td>
</tr>
<tr>
<td>Data Manager</td>
<td>Pamela Fain-Pribyl (Mayo)</td>
</tr>
<tr>
<td>Imaging</td>
<td>Spencer Behr (UCSF), Michael Knopp (IROC Ohio)</td>
</tr>
<tr>
<td>Statistics</td>
<td>Fang-Shu Ou, Michelle Mahoney (Mayo)</td>
</tr>
<tr>
<td>Health Outcomes</td>
<td>Amylou Dueck (Mayo)</td>
</tr>
<tr>
<td>Pathology</td>
<td>Wendy Frankel (OSU)</td>
</tr>
<tr>
<td>Correlative Science</td>
<td>Brian Untch (MSKCC), Federico Innocenti (UNC)</td>
</tr>
<tr>
<td>PK</td>
<td>Jan Beumer (Pitt)</td>
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<tr>
<td>Community Oncology</td>
<td>Jared Acoba (Hawaii Oncology)</td>
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<tr>
<td>ECOG-ACRIN</td>
<td>Efrat Dotan (Fox Chase)</td>
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<tr>
<td>NRG</td>
<td>Arvind Dasari (MDACC)</td>
</tr>
<tr>
<td>SWOG</td>
<td>Jon Strosberg (Moffitt)</td>
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CABINET (A021602): Randomized Double-Blinded Phase III Study of Cabozantinib vs. Placebo in Advanced NET after Progression on Everolimus

**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

**Randomization**
- **Panc NET** n=185
- **Carcinoid** n=210

**Endpoints:**
- **1° Endpoint:** PFS (Central Review)
- **2° Endpoints:** OS, RR, Safety, Tolerability

**Treatment Arms**
- Cabozantinib 60 mg daily
- Placebo daily