Cabozantinib Versus Placebo for Advanced Neuroendocrine Tumors after Progression on Prior Therapy (CABINET Trial/Alliance A021602)

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Background

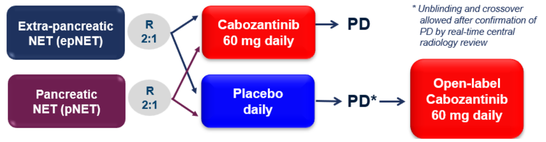
- New therapeutic options are needed for patients with advanced NETs
- Drugs targeting the vascular endothelial growth factor (VEGF) pathway have activity in NETs
- Inhibition of MET can impede resistance that develops to VEGF pathway inhibitors
- Cabozantinib is a multi kinase inhibitor targeting VEGF, c-MET, AXL, and RET
- Alliance A021602 (CABINET) was a Phase III trial designed to evaluate the efficacy of cabozantinib in patients with advanced extra-pancreatic (epNET) and pancreatic NET (pNET) who had received at least 1 line of prior FDA approved therapy, not including somatostatin analogs (SSAs)

Key Eligibility Criteria

- Well-to moderately differentiated NET
- Grades 1-3, functional or nonfunctional NET
- Disease progression by RECIST 1.1 within 12 months prior to randomization
- Progression or intolerance of at least 1 prior FDA-approved systemic therapy, not including SSA
  - Includes everolimus, sunitinib and Lu-177 DOTATATE PRRT for pNETs
  - Includes everolimus for lung NETs
  - Includes everolimus and Lu-177 DOTATATE PRRT for GI NETs

Study Design and Endpoints

Study Design: Randomized Double-blind Phase III Trial



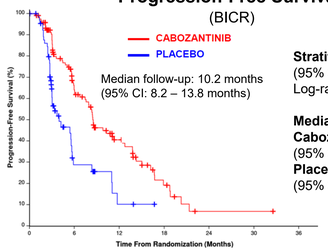
- Primary Endpoint per cohort: Progression-free survival (PFS) by blinded independent central review (BICR)
- Secondary Endpoint per cohort: Objective response rate (ORR), safety and tolerability, overall survival

Baseline Characteristics and Results - Efficacy

Extrapancreatic NETs

	Cabozantinib (N=134)	Placebo (N=69)
Age, years (range)	66 (28-86)	66 (30-82)
Female	55%	31%
ECOG PS 0/1	33%/63%	46%/52%
Grade (G1/G2/G3)	28%/64%/6%	22%/70%/7%
Primary (GI/Lung/unknown/other)	52%/20%/16%/12%	67%/17%/3%/13%
Functional tumor	31%	36%
Concurrent/prior SSA	69%/93%	70%/93%
Prior systemic therapy (median)	2	2
• Everolimus	72%	64%
• Lu-177 DOTATATE	60%	59%
• Temozolomide-based	32%	29%
• Platinum-based	8%	12%

Progression-Free Survival (BICR)

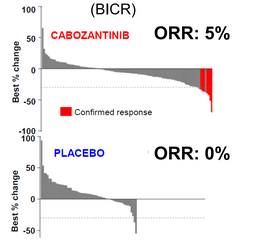


Median follow-up: 10.2 months (95% CI: 8.2 – 13.8 months)

Stratified HR = 0.38 (95% CI: 0.25 – 0.59) Log-rank p<0.0001

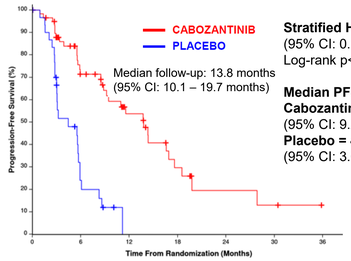
Median PFS
Cabozantinib = 8.4 months (95% CI: 7.6 – 12.7 months)
Placebo = 3.9 months (95% CI: 3.0 – 5.7 months)

Objective Response Rate (BICR)



Pancreatic NETs

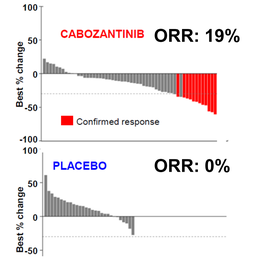
	Cabozantinib (N=64)	Placebo (N=31)
Age (range)	60 (29-79)	64 (39-79)
Female	42%	42%
ECOG PS 0/1	55%/44%	48%/52%
Grade (G1/G2/G3)	22%/61%/13%	23%/61%/10%
Functional tumor	17%	16%
Concurrent/prior SSA	55%/98%	55%/97%
Prior systemic therapy (median)	3	2
• Everolimus	88%	81%
• Lu-177 DOTATATE	59%	58%
• Temozolomide-based	67%	52%
• Sunitinib	28%	23%



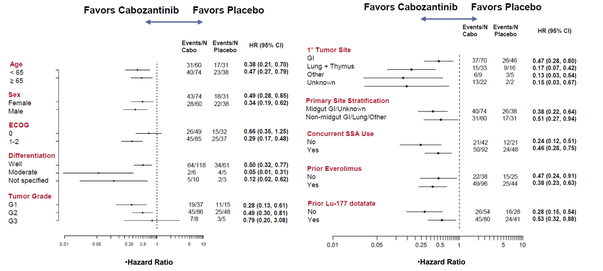
Median follow-up: 13.8 months (95% CI: 10.1 – 19.7 months)

Stratified HR = 0.23 (95% CI: 0.12 – 0.42) Log-rank p<0.0001

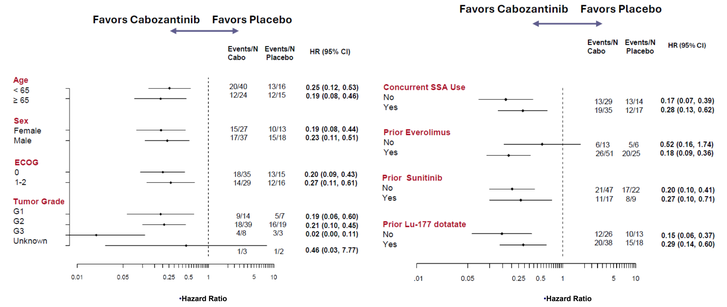
Median PFS
Cabozantinib = 13.8 months (95% CI: 9.2 – 18.5 months)
Placebo = 4.4 months (95% CI: 3.0 – 5.9 months)



Extrapancreatic NETs



Pancreatic NETs



Results – Treatment Exposure

Treatment exposure	epNETs		pNETs	
	Cabo	Placebo	Cabo	Placebo
Median duration of therapy (months)	5.5	2.8	8.3	2.9
• Range (months)	0.2 – 32.4	0.6 – 21.4	0.5 – 39.6	0.5 – 11.2
Dose reduction needed	66%	10%	68%	19%
Average daily dose	38.4 mg	59.0 mg	37.9 mg	56.9 mg
Off therapy (%)	111 (84%)	60 (90%)	49 (78%)	29 (94%)
• Progression	52 (47%)	38 (63%)	28 (57)	23 (79)
• AEs	34 (31%)	9 (15%)	10 (20%)	0 (0%)

Results – Adverse Events

Selected Grade 3 and 4 Adverse Events	epNETs (%)		pNETs (%)	
	Cabo	Placebo	Cabo	Placebo
Any AE	62	27	65	23
Fatigue	62	8	11	3
Diarrhea	11	5	6	0
Hypertension	21	3	22	10
Mucositis	4	0	8	0
PPE	3	0	10	0
VTE	0	0	11	0

PPE: Palmar-plantar erythrodysesthesia; VTE: Venous thromboembolism

Conclusions

- Cabozantinib significantly improves PFS in patients with previously treated, progressive extra-pancreatic or pancreatic NET
- Benefits of cabozantinib were observed among all subgroups
- Adverse events are consistent with previously reported safety profile of cabozantinib
- Overall survival data are not mature yet
- CABINET is one of the first prospective, randomized trials to evaluate the efficacy of therapy following PRRT, chemotherapy, and targeted therapy
- Cabozantinib is an effective therapy option for previously treated extrapancreatic and pancreatic NETs