PHASE I STUDY OF PASIREOTIDE (SOM230) IN COMBINATION WITH EVEROLIMUS (RAD0001) IN PATIENTS WITH ADVANCED NEUROENDOCRINE TUMORS (NET)

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ABSTRACT

Background: Octreotide has demonstrated antiproliferative effects in carcinoid tumors. The mTOR inhibitor everolimus also has antitumor activity in NETs. Pasireotide is a novel somatostatin analog with binding affinity to a broader range of somatostatin receptor subtypes than octreotide. We performed a phase I study to evaluate the safety and feasibility of combining pasireotide and everolimus for pts with advanced carcinoid and pancreatic NETs.

Methods: Pts received escalating doses of pasireotide and everolimus (see dose escalation schema). Treatment was continued until tumor progression, unacceptable toxicity, or withdrawal of consent. Dose-limiting toxicity (DLT) was defined within the first 56 days of therapy.

Results: Among 22 enrolled pts, 21 were evaluable for toxicity. Enrolled pts had the following characteristics: M/F = 14/8; median age 60 (range 35-76); ECOG PS 0/1/2 = 16/5/1; carcinoid/pancreatic NET = 18/4. Pts have received a median of 6 cycles of treatment (range 1-29). No pts at dose level (DL) 1 and DL 2 experienced DLT. DLT was experienced by 1 pt at DL 3 (gr 3 rash) and 1 pt at DL 4 (gr 3 diarrhea). Dose escalation was halted at DL 4 to further assess safety and toxicity at DL 3; no further DLT was observed in 6 additional patients treated at DL3.

Other gr 3 or higher treatment-related adverse events across all cycles included hyperglycemia (n=8; 1 at DL1, 1 at DL2, 4 at DL3, 2 at DL4), hypophosphatemia (n=6; 1 at DL1, 1 at DL2, 3 at DL3, 1 at DL4), thrombocytopenia (n=3; 2 at DL3, 1 at DL4), lymphopenia (n=2; 1 at DL1, 1 at DL3), elevated alkaline phosphatase (n=2; 1 at DL2, 1 at DL3), mucositis (n=1 at DL3), prolonged QTc (n=1 at DL3), and joint pain (n=1 at DL4). Independently-reviewed best objective responses in 21 evaluable pts revealed partial response in 1 pt, stable disease in 19 pts, and progressive disease in 1 pt.

Conclusion: Combination therapy with pasireotide and everolimus is safe and feasible and is associated with preliminary evidence of antitumor activity in NET. Pasireotide 60 mg IM monthly combined with everolimus 10 mg daily should be further investigated in future NET studies.

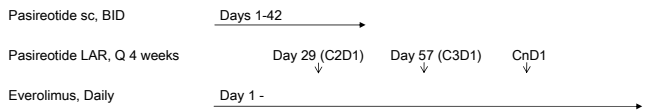
STUDY BACKGROUND

- Both everolimus and octreotide have antitumor activity in NETs.
- Pasireotide has broader affinity for somatostatin receptors than octreotide.
- Phase I study warranted to evaluate the feasibility of combining everolimus and pasireotide.

STUDY DESIGN

- Phase I dose escalation study of cohorts of 3 or 6 patients with low- or intermediate-grade NET.
- All patients received everolimus orally at 5 or 10 mg daily.
- Patients self-administered short-acting pasireotide subcutaneously (sc) for the first 28-day treatment cycle and for 2 weeks thereafter. If pasireotide sc was tolerated, patients received the long-acting release (LAR) formulation of pasireotide intramuscularly on day 29 and every 4 weeks thereafter.
- Primary objective: to determine the MTD and DLTs for pasireotide in combination with everolimus in patients with advanced NETs.
- Secondary objectives: to make a preliminary assessment of the anti-tumor activity of pasireotide in combination with everolimus in patients with advanced NET.
- DLT defined as drug-related toxicity (NCI CTC v. 3.0) during the first 2 cycles leading to:
  - Grade ≥3 non-hematologic toxicity (excluding nausea, vomiting, hyperlipidemia, hyperglycemia, alopecia, isolated ≥ grade 3 lab abnormalities deemed not clinically significant by the treating investigator).
  - Grade ≥ 3 nausea, vomiting uncontrolled by aggressive antiemetic support.
  - Grade ≥ 3 hematologic toxicity lasting ≥ 7 days.
  - Inability to take >75% of the planned treatment dose during the DLT observation period or inability to start subsequent cycle within 7 days of planned date.
- MTD defined as highest dose level at which less than 33% of patients experienced a DLT.

STUDY SCHEMA



- Cycles (pasireotide LAR and everolimus) are repeated every 28 days.
- Restaging scans and biochemical markers repeated after every 2 cycles.

DOSE ESCALATION SCHEMA

Dose Level	Pasireotide sc	Pasireotide LAR	Everolimus
1	600 mcg	40 mg	5 mg
2	900 mcg	60 mg	5 mg
3	900 mcg	60 mg	10 mg
4	1200 mcg	80 mg *	10 mg

- DL4 was discontinued at investigator and sponsor discretion to further evaluate safety and toxicity of DL3.
- Patients enrolled at DL4 received 60 mg of pasireotide LAR .

PATIENT CHARACTERISTICS

Characteristic	No. (n = 22)	Percent
Age (years)		
Median (range)	60 (35-76)	
Gender		
Male	14	64
Female	8	36
ECOG performance status		
0	16	73
1/2	6	27
Tumor type		
Carcinoid	18	82
Pancreatic NET	4	18
Prior octreotide	18	82

DOSE ESCALATION AND DLT SUMMARY

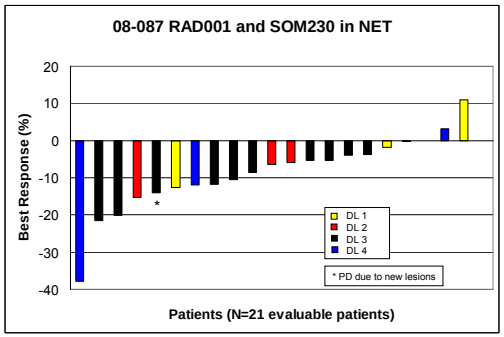
Dose Level	No. pts	DLT	Comment
1	3	None	
2	3	None	
3	7* + 6	1 Gr 3 rash	•1 pt not evaluable for toxicity or response. •1 pt experienced DLT; the cohort was expanded to 6 pts with no further DLT observed. • 1 pt experienced fatal MI, classified as not likely related to therapy, occurring 32 days after last treatment with everolimus and pasireotide LAR. • 6 additional patients treated at DL3 to further assess safety and toxicity.
4	3	1 Gr 3 diarrhea	• DL4 was discontinued at investigator and sponsor discretion to further evaluate safety and toxicity of DL3. Patients enrolled at DL4 received 60 mg pasireotide LAR.

GRADE 3-4 ADVERSE EVENTS ACROSS ALL CYCLES

Dose Level	No. evaluable patients	Toxicity	
1	3	Hyperglycemia (n=1) Hypophosphatemia (n=1) Lymphopenia (n=1)	
2	3	Alkaline phos elevation (n=1) Hyperglycemia (n=1) Hypophosphatemia (n=1)	
3	12	Alkaline phos elevation (n=1) Hyperglycemia (n=4) Hypophosphatemia (n=3) Lymphopenia (n=1)	Mucositis (n=1) Thrombocytopenia (n=2) QTc prolongation (n=1) Rash (n=1)
4	3	Diarrhea (n=1) Hyperglycemia (n=2) Hypophosphatemia (n=1)	Joint pain (n=1) Thrombocytopenia (n=1)

TREATMENT RESPONSES

- Among 21 evaluable patients, 1 had PR, 19 had SD, 1 had PD (new lesions) as best response to treatment using RECIST 1.0 criteria.



- Progressive disease not required prior to study entry.

CONCLUSIONS

- Treatment with everolimus 10 mg daily in combination with pasireotide LAR 60 mg monthly is feasible and is associated with preliminary evidence of antitumor activity in NET.
- Pasireotide 60 mg IM monthly combined with everolimus 10 mg daily should be further investigated in future NET studies.