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

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REVISED 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 (*refer to dose escalation schema*). All pts received everolimus orally at 5 or 10 mg daily. Pts self-administered short-acting pasireotide subcutaneously (sc) for the first 28-day treatment cycle and for 2 wks thereafter. If pasireotide sc was tolerated, pts received the long-acting release (LAR) formulation of pasireotide intramuscularly on day 29 and every 4 wks thereafter. Treatment was continued until tumor progression, unacceptable toxicity, or withdrawal of consent. Dose-limiting toxicity (DLT) was defined as occurring within the first 56 days of therapy.

Results: Among 16 enrolled pts, 15 were evaluable for toxicity. Enrolled pts had the following characteristics: M:F = 10:6; median age 61 (range 38-76); ECOG PS 0/1/2 = 8/7/1; carcinoid/pancreatic NET = 12/4. Pts have received a median of 4 cycles of treatment. No pts in cohorts 1 and 2 experienced DLT. 1 pt in cohort 3 experienced DLT (grade 3 rash); the cohort was expanded to 6 pts with no further observed DLTs. 1 pt in cohort 4 experienced DLT (grade 3 diarrhea). Other ≥ grade 3 treatment-related adverse events included hyperglycemia (n=8), hypophosphatemia (n=3), elevated alkaline phosphatase (n=2), mucositis (n=1), lymphopenia (n=2), and thrombocytopenia (n=1). Insulin was started in 4 pts due to hyperglycemia. Independently-reviewed best objective responses in 13 evaluable pts revealed stable disease in all 13 pts.

Conclusion: Combination therapy with pasireotide and everolimus is safe and feasible. Further enrollment with everolimus 10 mg daily in combination with pasireotide LAR 60 mg monthly is planned.

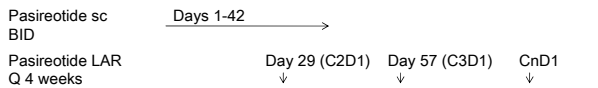
STUDY BACKGROUND

- 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
- 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 determine the pharmacokinetics of pasireotide in combination with everolimus in patients with advanced NET; to make a preliminary assessment of anti-tumor activity of the combination.

STUDY AND DOSE ESCALATION SCHEMA



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

Dose Escalation Schema

Cohort	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

PATIENT CHARACTERISTICS

Characteristic	No. (n = 16)	Percent
Age (years)		
Median	61	
Range	38-76	
Gender		
Male	10	63
Female	6	37
ECOG performance status		
0	8	50
1/2	8	50
Tumor type		
Carcinoid	12	75
Pancreatic NET	4	25

DOSE ESCALATION AND DLT SUMMARY

Cohort	No. pts	DLT	Comment
1	3	None	Insulin started in 1 pt due to hyperglycemia.
2	3	None	
3	7*	1 Gr 3 rash	•Insulin started in 2 pts •1 pt experienced fatal MI, classified as not likely related to therapy, occurring 32 days after last treatment with everolimus and pasireotide LAR.
4	3	1 Gr 3 diarrhea	•Insulin started in 1 pt. •Further dose escalation discontinued at investigator discretion. Additional enrollment at Dose Level 3 (everolimus 10 mg/pasireotide LAR 60 mg) planned.

* 1 pt in Cohort 3 withdrew consent and is not evaluable for toxicity or response

ADVERSE EVENTS

Adverse Event	Maximum Grade (n=15) 1 / 2 No. (%)	3 / 4 No. (%)
Hematologic		
Platelets	9 (60)	1 (7)
Lymphocytes	-	2 (13)
Neutrophils	7 (47)	-
Leukocytes	9 (60)	-
Hemoglobin	10 (67)	-
Non-hematologic		
Hyperglycemia	5 (33)	8 (53)
Hypertriglyceridemia	6 (40)	-
Hypercholesterolemia	5 (33)	-
Elevated alk phosphatase	3 (20)	2 (13)
ALT	7 (47)	-
AST	6 (40)	-
Hypophosphatemia	2 (13)	3 (20)
Other		
Diarrhea	5 (33)	2 (13)
Skin rash	5 (33)	1 (7)
Fatigue	10 (67)	-
Oral mucositis / stomatitis	6 (40)	1 (7)
Nausea	10 (67)	-

TREATMENT RESPONSES

- All 13 patients evaluable for response had stable disease as best response.
- 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.
- Hyperglycemia was observed, requiring initiation of insulin in 4/15 patients.
- Further enrollment with everolimus 10 mg daily in combination with pasireotide LAR 60 mg monthly is planned.