PHASE I STUDY OF SORAFENIB IN COMBINATION WITH EVEROLIMUS (RAD001) IN PATIENTS WITH ADVANCED NEUROENDOCRINE TUMORS (NET)

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ABSTRACT

Background: Both sorafenib and everolimus have activity in NETs. We performed a phase I study to evaluate the safety and feasibility of combining sorafenib and everolimus in pts with advanced NETs.

Methods: Patients were treated with everolimus 10 mg daily in combination with sorafenib (dose level 1: 200 mg BID; dose level 2: 200 mg in the morning, 400 mg in the evening) using a standard phase I dose escalation design. Treatment was continued until tumor progression, unacceptable toxicity, or withdrawal of consent.

Results: Enrolled pts had the following characteristics: M:F = 4:5; median age 56 (range 49-68); ECOG PS 0/1 = 5/4. All 9 pts had low-intermediate grade NETs (midgut, n=6; bronchial, n=2; gastric, n=1). Pts received a median of 2 cycles of treatment (range 1-6). One pt in Cohort 1 experienced DLT (grade 3 skin rash); the cohort was expanded to 6 pts with no further DLTs. Other ≥ grade 3 treatment-related adverse events at dose level 1 included grade 3 thrombocytopenia (n=2), grade 3 hypokalemia (n=2), grade 3 hypophosphatemia (n=1), grade 4 hypophosphatemia (n=1), grade 4 hypocalcemia (n=1). One pt treated at dose level 1 with gastric carcinoid tumor experienced fatal gastric perforation occurring after the DLT observation period. In the absence of additional DLT at dose level 1, enrollment to dose level 2 was initiated. All 3 pts in Cohort 2 experienced DLT (grade 3 thrombocytopenia requiring holding treatment for > 14 days, grade 3 hand-foot skin reaction, grade 3 skin rash/allergic reaction). Grade 3 hypophosphatemia (n=1) was also observed at dose level 2. Independently-reviewed best objective responses in 5 evaluable pts in Cohort 1 revealed stable disease in all 5 pts.

Conclusion: Sorafenib 200 mg BID in combination with everolimus 10 mg daily has been established as the MTD in pts with advanced NET. Further enrollment to evaluate safety and antitumor efficacy at this dose level is ongoing.

STUDY BACKGROUND

- Both everolimus and sorafenib have antitumor activity in NETs.
- Phase I study warranted to evaluate the feasibility of combining everolimus and sorafenib.

STUDY DESIGN

- Phase I dose escalation study of cohorts of 3 or 6 patients
- All patients received everolimus orally 10 mg daily in combination with sorafenib orally 200 mg twice daily (Cohort 1) or 200 mg in the morning and 400 mg in the evening (Cohort 2).
- Primary objective: to determine the MTD and DLTs for everolimus in combination with sorafenib in patients with advanced NETs.
- Secondary objectives: to make a preliminary assessment of anti-tumor activity of the combination.

STUDY AND DOSE ESCALATION SCHEMA

	Dose Escalation Schema	
Cohort	**Everolimus**	**Sorafenib**
1	10 mg daily	200 mg twice daily
2	10 mg daily	200 mg in the morning, 400 mg in the evening

- Cycles are repeated every 28 days.
- Restaging scans and biochemical markers repeated after every 2 treatment cycles.

PATIENT CHARACTERISTICS

Characteristic	No. (n=9)	Percent
Age (years)		
Median	56	
Range	49-68	
Gender		
Male	4	44
Female	5	56
ECOG performance status		
0	5	56
1	4	44
Primary site of disease		
midgut	6	67
bronchial	2	22
gastric	1	11

DOSE ESCALATION AND DLT SUMMARY

Cohort	No. pts	DLT	Comment
1	6	1	Grade 3 skin rash Fatal gastric perforation in a patient with gastric carcinoid (occurred after DLT observation period)
2	3	3	Grade 3 thrombocytopenia lasting >14 days Grade 3 hand-foot skin reaction Grade 3 skin rash/allergic reaction

GRADE 3/4 ADVERSE EVENTS

	Adverse Event	Grade	No.
Cohort 1 (n=6)	Skin rash	3	1
	Thrombocytopenia	3	2
	Hypokalemia	3	2
	Hypophosphatemia	3	1
	Hypocalcemia	4	1
	Hypophosphatemia	4	1
Cohort 2 (n=3)	Skin rash/allergic reaction	3	1
	Hand-foot skin reaction	3	1
	Thrombocytopenia	3	1
	Hypophosphatemia	3	1

TREATMENT RESPONSES

- 5 patients in Cohort 1 evaluable for response had stable disease as best response.

CONCLUSIONS

- Sorafenib 200 mg twice daily in combination with everolimus 10 mg daily has been established as the MTD for patients with advanced NET.
- Further enrollment to confirm safety and assess antitumor activity at the MTD dose level is ongoing.