PHASE I/II STUDY OF EVEROLIMUS (RAD001) IN COMBINATION WITH TEMOZOLOMIDE IN PATIENTS WITH ADVANCED PANCREATIC NEUROENDOCRINE TUMORS

M.H. Kulke[1], L. Blaszkowsky[2], A.X. Zhu[2], S. Florio[1], E. Regan[1], D.P. Ryan[2], J.A. Chan[1]

[1]Dana-Farber Cancer Institute, Boston, MA, [2]Massachusetts General Hospital, Boston, MA

REVISED ABSTRACT

Background: Both the mTOR inhibitor RAD001 and temozolomide (TMZ) have been shown to have antitumor activity in neuroendocrine tumors (NET). We performed a phase I/II study to evaluate the tolerability and efficacy of RAD001 in combination with TMZ in pts with advanced pancreatic NETs.

Methods: Pts were enrolled at 2 dose levels: TMZ 150 mg/m^2 po qd, administered for 7 consecutive days every other week, in combination with RAD001 5 mg po qd (Cohort 1) or RAD001 10 mg po qd (Cohort 2). TMZ with RAD001 10 mg po qd was established as the phase II dose. TMZ was administered in combination with RAD001 for a maximum of six 4-week treatment cycles, at which point pts with response or stable disease continued treatment with RAD001 alone. Pts received prophylaxis with trimethoprim-sulfamethoxazole by mouth 3 times weekly. Treatment was continued until tumor progression, unacceptable toxicity, or withdrawal of consent.

Results: In Phase I, 1 pt in cohort 1 experienced dose-limiting toxicity (DLT) consisting of grade 4 thrombocytopenia, and the cohort was expanded to 6 pts. No further DLTs have been observed. A total of 27 pts have been enrolled; 7 in cohort 1 (6 evaluable) and 20 in cohort 2 (19 evaluable). Enrolled pts have the following characteristics: M:F =15:12 ; median age 52 (range 29-87); ECOG PS 0/1= 13/14. Pts have received a median of 5 cycles of treatment. The most common observed grade 3 or 4 toxicities were anticipated hematologic effects and included thrombocytopenia (n=5), lymphopenia (n=7), and neutropenia (n=2). Grade 3 or 4 non-hematologic toxicities included diarrhea (n=1), hyperglycemia (n=1), elevated transaminases (n=2), elevated triglycerides (n=2) skin rash (n=1), fatigue (n=1), hyper/hypokalemia (n=1/1), and hyponatremia (n=1). 22 pts are evaluable for response (by RECIST). Observed responses include 7 pts with partial responses (32%), 13 with stable disease (59%), and 2 with progressive disease (9%). 17/22 pts had elevated CGA levels (>225 ng/ml) at baseline; 5 (29%) experienced CGA decreases of >50% from baseline on 2 consecutive assessments.

Conclusions: The combination of RAD001 and TMZ can be safely administered and shows promising activity in pts with advanced pancreatic NET. Further enrollment is planned.

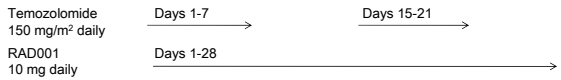
STUDY BACKGROUND

- Both temozolomide and RAD001 have demonstrated antitumor activity in patients with advanced pancreatic NETs
- Given the single-agent activity demonstrated with both temozolomide and RAD001 in patients with pancreatic NETs, evaluation of the combination of these two agents is warranted.

STUDY DESIGN

- Phase I dose escalation study of cohorts of 3 or 6 patients treated with TMZ 150 mg/m^2 daily, administered for 7 consecutive days every other week, in combination with RAD001 5 mg daily (Cohort 1) or RAD001 10 mg daily (Cohort 2)
- Two-stage phase II study of temozolomide and RAD001 at the maximum tolerated dose established in Phase I.
- Primary endpoint: response rate, evaluated by RECIST using independent radiologic review
- Secondary endpoints: safety, progression-free survival, overall survival, biochemical response as measured by chromogranin A

STUDY SCHEMA



- Cycles are repeated every 28 days.
- Patients received prophylaxis with trimethoprim-sulfamethoxazole 3 times weekly.
- Temozolomide discontinued after Cycle 6 to minimize risk of immunosuppression.
- Restaging scans and biochemical markers repeated after every 2 treatment cycles.

DOSE ESCALATION RESULTS

- One patient in Cohort 1 experienced protocol-defined DLT consisting of grade 4 thrombocytopenia. The cohort was expanded to 6 patients without further DLT.
- No DLT was observed in Cohort 2.
- Temozolomide, 150 mg/m^2 administered daily for 7 consecutive days every other week, with RAD001 10 mg daily has been established as the phase II dose. A total of 20 patients have been treated at this dose level.

PATIENT CHARACTERISTICS

Characteristic	No. (n = 27)	Percent
Age (years)		
Median	52	
Range	39 – 87	
Gender		
Male	15	56
Female	12	44
ECOG performance status		
0	13	48
1	14	52
Chromogranin A (ng/ml)		
Median	660	
Range	14 – 56,500	

TREATMENT RESPONSES

Response	No.*	Percent
Partial response	7	32
Stable Disease	13	59
Progressive disease	2	9

* 3 patients have not undergone restaging studies. 2 enrolled patients (one in each cohort) withdrew consent and are not evaluable for response or toxicity.

17 patients had an elevation in chromogranin A (>225 ng/ml) at baseline. 5 patients (29%) experienced a drop in chromogranin A by >50% on two or more consecutive measurements.

ADVERSE EVENTS

Adverse Event	Maximum Grade (n=25)	
	1 / 2 No. (%)	3 / 4 No. (%)
Hematologic		
Platelets	10 (40)	5 (20)
Lymphocytes	4 (15)	7 (28)
Neutrophils	13 (52)	2 (8)
Leukocytes	12 (48)	1 (4)
Hemoglobin	17 (68)	-
Non-hematologic		
Hyperglycemia	18 (72)	1 (4)
Hypertriglyceridemia	13 (52)	2 (8)
Hypercholesterolemia	11 (44)	-
AST (SGOT)	15 (60)	1 (4)
ALT (SGPT)	7 (28)	1 (4)
Hypokalemia	1 (4)	1 (4)
Hyperkalemia	3 (12)	1 (4)
Hyponatremia	3 (12)	1 (3)
Hypophosphatemia	5 (20)	-
Elevated alk phosphatase	7 (28)	-
Creatinine	7 (28)	
Other		
Diarrhea	12 (48)	1 (4)
Skin rash	10 (40)	1 (4)
Fatigue	18 (72)	1 (4)
Oral mucositis / stomatitis	14 (48)	-
Nausea	17 (68)	-
Vomiting	9 (36)	-
Pneumonitis	1 (4)	-

CONCLUSIONS

- In patients with unresectable or metastatic pancreatic NET, RAD001 can be safely administered in combination with temozolomide.
- The combination of RAD001 and temozolomide shows promising activity in patients with advanced pancreatic NET.
- Further enrollment to assess antitumor efficacy is ongoing.