Early CgA response as predictor of outcome following everolimus therapy among patients with low- to intermediate-grade neuroendocrine carcinoma: Analyses of a single institution phase II study

Carmen B. Jacobs,[1] Alexandria T. Phan,[1] Robert A. Wolff,[1] Funda Meric-Bernstam,[2] James C. Yao[1]

Departments of Gastrointestinal Medical Oncology,[1] and Surgical Oncology,[2] The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, United States

THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER *Making Cancer History®*

Abstract

Background
Everolimus with or without octreotide LAR has demonstrated promising antitumor activity in advanced low- to intermediate- grade neuroendocrine carcinoma. In a multi-national phase II study (RADIANT-1), early Chromogranin A (CgA) response correlated with improved progression free survival (PFS) (Yao et al, WCGI 2009). In this analysis, we confirm early CgA response as markers of outcome in an independent single institution phase II study.
Methods
Treatment consisted of everolimus 5 mg/day (30 patients) or 10 mg/day (30 patients) and octreotide LAR 30 mg every 28 days. Thirty carcinoid and 30 islet cell patients were enrolled. CgA was assessed at baseline, week 4 and every 3rd cycle. Early CgA response was defined as a 30% decrease at week-4.
Results
Intent-to-treat response rate was 20%. Per protocol, among 30 carcinoid patients, there were 5 (17%) confirmed PRs, 24 (80%) SDs, and 1 (3%) PD. Among 30 islet cell patients, there were 8 (27%) PRs, 18 (60%) SDs, and 4 (13%) PDs. Median PFS of patients with carcinoid and islet cell tumors were 63 and 50 weeks. Median OS has not been reached. Early CgA responders had a higher response rate (32% vs. 10%; P=.046). Early CgA responders also had longer PFS (72 vs 39 weeks; P=0.04) and OS (45 vs 31 months; P=0.12). Within subgroups, early CgA response correlated with PFS and OS among patient with islet cell (median PFS, 73 vs. 21 weeks, P<.001; median OS, 24 months vs. not reached, P<0.001), but not among patients with carcinoid. Interestingly, trends toward improved response rate, PFS, OS were observed among patients with normal CgA at protocol entry who achieve 30% decrease at week-4.
Conclusion
Daily everolimus with concomitant octreotide LAR, demonstrates antitumor activity. Patients with an early CgA response have clinical outcome. Early CgA response is a promising biomarker of everolimus activity.

Introduction

Low grade neuroendocrine carcinoma consists of carcinoid, and islet cell carcinoma. Effective systemic therapy options are lacking. While often slow growing, they are nonetheless incurable and lethal when advanced.

We conducted a phase II study octreotide LAR and everolimus in 60 patients with NETs. A promising intent-to-treat response rate of 20% was observed. Median PFS duration was 60 weeks.

In a follow-up, multi-national phase II study of everolimus in advanced pancreatic NETs with progression following chemotherapy (RADIANT-1), 160 patients were treated in 2 strata, with everolimus (N=115) or everolimus (N=45) plus octreotide based on whether patients were on octreotide at study entry. The median PFS for patients receiving everolimus or everolimus plus octreotide were 9.7 and 16.7 months respectively. Early biomarker response with either a 30% decrease or normalization of CgA or NSE at week 4 correlated with superior PFS.

Objectives

The goal of these analyses is to confirm early CgA response as markers of outcome in a single institution phase II study conducted independently of the RADIANT-1 study.

- Assess whether 30% decrease in CgA at week 4 following initiation of everolimus was associated with RECIST response rate, PFS, and OS
- Assess whether 30% decrease in CgA at week 4 following initiation of everolimus among patients with baseline CgA within laboratory normal range was associated with RECIST response rate, PFS, and OS

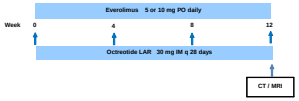
Method

Additional analyses were carried out in our previously published single institution phase II study of octreotide plus everolimus using CgA values collected during the study.

Study design:

Single-arm phase 2 study among patients with metastatic well-differentiated NET (30 carcinoid and 30 islet cell)

- Cohort 1 (N=30): everolimus 5 mg po daily
- Cohort 2 (N=30): everolimus 10 mg po daily



- Treatment duration was for 1 year in absence of progression. Treatment could continue beyond 1 year if there was continued response or clinical benefit.
- Protocol response was evaluated according to RECIST
- PFS and overall survival (OS) were measured from the date of study entry using the Kaplan-Meier method.
- Differences were considered significant when the two-sided P value was ≤ 0.05.
- All statistical calculations were performed using SPSS 17.0 (SPSS Inc., Chicago, Illinois).

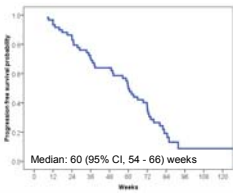
Results

Overall study results:
Intent to treat response rate is 20%. Per-protocol response rate was 22%. Response and median PFS are included in Table 1.

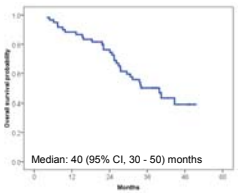
Per-protocol of RECIST response rates and median PFS durations.

Per protocol	Overall n = 60	Carcinoid n = 30	Islet Cell n = 30
PR	13 (22%)	5 (17%)	8 (27%)
SD	42 (70%)	24 (80%)	18 (60%)
PD	5 (8%)	1 (3%)	4 (13%)
PFS (median)	60 wks	63 wks	50 wks
OS (median)	40 months	40 months	34 months

PFS



OS



Early CgA response among patients with normal baseline CgA:

The significance of further CgA decrease among patient with normal baseline CgA is not known. Week 4 among patients with normal baseline CgA was associated with therefore evaluate whether a treatment emergent 30% decrease in CgA at improved outcome.

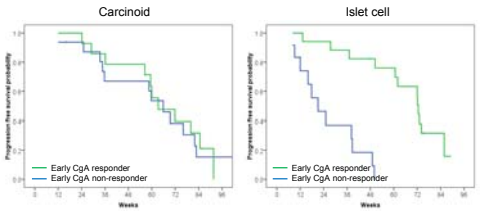
- 22 patients with normal CgA at baseline.
- 9 (41%) achieved early CgA response.
- PR were observed among 3/9 (33%) early CgA responders and 1/13 (8%) early CgA non-responders.
- Median PFS was 80 (95% CI, 66 – 94) weeks among early CgA responders and 39 (95% CI, 20 – 57) weeks among early CgA non-responders.
- Median OS was 34 (95% CI, 19 – 49) months among early CgA non-responders. Median OS among early CgA responders have not been reached.

The differences in response rates, PFS and OS did not reach statistical significance due to the smaller number of patients. However, results suggest early CgA response is a promising biomarker among patients with normal CgA at baseline and that patients with normal baseline CgA can be included in analyses of early CgA response.

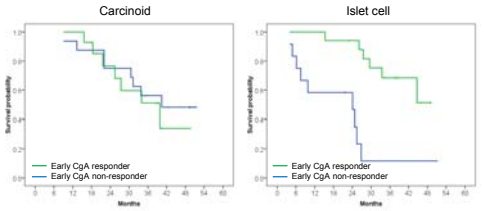
Early CgA response and RECIST response

	All		Carcinoid		Islet cell	
	CgA resp n = 31	CgA non-resp n = 28	CgA resp n = 14	CgA non-resp n = 16	CgA resp n = 17	CgA non-resp n = 12
Response						
PR	10 (32%)	3 (11%)	5 (36%)	1 (6%)	5 (29%)	2 (17%)
SD/PD	21 (68%)	25 (89%)	9 (64%)	15 (94%)	12 (71%)	10 (83%)
	P = .046		P = .04		P = .43	
PFS	72 wks	39 wks	63 wks	66 wks	73 wks	21 wks
(median)	P = .04		P = .88		P < .001	
OS	45 months	31 months	40 months	40 months	Not reached	24 months
(median)	P = .12		P = .58		P < .001	

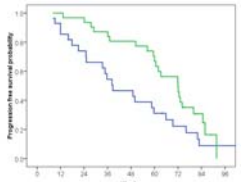
Progression free survival by early CgA response separated by group



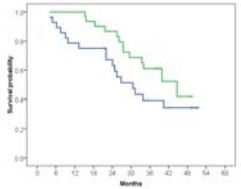
Overall survival by early CgA response separated by group



Progression free survival by early CgA response



Overall survival by early CgA response



Conclusion

- Daily everolimus with concomitant octreotide LAR, demonstrates antitumor activity.
- Early CgA response was associated with higher response rate among carcinoid patients.
- Early CgA response was associated with longer PFS and OS among patients with islet cell.
- The limited treatment duration in this study may have precluded observation of difference by early CgA response among patients with carcinoid.
- Confirmatory Phase III studies have completed accrual.

References

1. Yao JC, Phan AT, Chang DZ, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: Results of a phase II study. Journal of Clinical Oncology 26(26):4311-4318, 9/2008.
2. Kulke MH, Bergsland EK, Yao JC. Glycemic Control in Patients with Insulinoma Treated with Everolimus. New England Journal of Medicine 360(2):195-197, 1/2009.
3. Yao JC, Lombard-Bohas C, Baudin E, et al. Daily Oral Everolimus Activity in Patients with Metastatic Pancreatic Neuroendocrine Tumors After Failure of Cytotoxic Chemotherapy: A Phase II Trial. Journal of Clinical Oncology *In Press 2009*