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A Phase 2 Trial of Everolimus and Pasireotide Long Acting Release in Patients with Metastatic Uveal Melanoma

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Abstract

Objectives—Test the hypothesis that inhibiting mammalian target of rapamycin (mTOR) and Insulin Growth Factor-1 Receptor would be efficacious in metastatic uveal melanoma.

Methods—Phase 2 trial of everolimus 10mg daily plus pasireotide long-acting release 60mg every 28 days enrolling patients with progressive, metastatic uveal melanoma to treatment until progression by RECIST 1.1 or unacceptable toxicity. The primary endpoint was clinical benefit rate (CBR), defined as any objective response or RECIST 1.1 stable disease at 16 weeks. A subset of patients underwent baseline Indium-111 octreotide scans.

Results—14 patients were enrolled, of which 13 were evaluable for the primary endpoint, before the study was terminated due to poor accrual. Three of 13 (26%) patients obtained clinical benefit. Seven of 13 (54%) had stable disease lasting a median of 8 weeks (range: 8–16 weeks). Grade 3 adverse events deemed at least possibly related to study drugs were hyperglycemia (n=7), oral mucositis (n=2), diarrhea (n=1), hypophosphatemia (n=1), and anemia (n=1). Seven of 14 patients (50%) required at least 1 dose reduction due to toxicity. Seven of 8 patients (88%) with baseline In^{111} octreotide scans had at least 1 avid lesion, with significant intrapatient heterogeneity. There was a trend toward an association between octreotide avidity and cytostatic response to therapy (p=0.078).

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Conclusions—The combination of everolimus and pasireotide has limited clinical benefit in this small metastatic uveal melanoma cohort. Dose reductions for side effects were common. Further investigation into the relationship between somatostatin receptor expression and cytostatic activity of somatostatin analogues is warranted.

Keywords

uveal melanoma; everolimus; mTOR; somatostatin; pasireotide; insulin growth factor; octreotide

Background

Uveal melanoma is the most common primary intraocular malignancy in adults, with an incidence of 4–5 cases per million [1]. Approximately half of all patients with uveal melanoma will eventually develop metastatic disease, and their prognosis remains poor [2]. Over the past several years, studies have identified activating mutations in the G alpha protein subunits GNAQ and GNA11 in the vast majority of uveal melanomas that lead to downstream activation of multiple signaling pathways, including mitogen-activated protein kinase (MAPK), Protein Kinase C (PKC), and Phosphoinositol-3-Kinase (PI3K)/Akt/mammalian target of Rapamycin (mTOR) [3–6]. Recently, a randomized Phase 2 trial of the MEK inhibitor selumetinib demonstrated a progression-free survival (PFS) benefit versus investigator's choice chemotherapy (median 16 vs 8 weeks) [7]. This has provided proof of concept that targeted inhibition of growth signals in uveal melanoma can lead to clinical benefit. Recently, a Phase 3 trial of dacarbazine versus dacarbazine plus selumetinib failed to demonstrate an improvement in progression free survival, suggesting combined inhibition of multiple signaling pathways may be required for sustained clinical benefit.

PI3K/Akt/mTOR signaling is dysregulated in a variety of human cancers [8]. In uveal melanoma, 60% of metastatic tumors display loss of PTEN, a tumor suppressor that inhibits this pathway [9]. As a result, mTOR represents an attractive therapeutic target in uveal melanomas. Clinical resistance to mTOR monotherapy is a frequent occurrence, however, and combination therapeutic strategies may be required for sustained clinical benefit. One potential mechanism of resistance to mTOR inhibition is rebound activation of insulin-like growth factor-1 receptor (IGF1R) pathway signaling [10]. In uveal melanoma, tumor IGF1R expression has been associated with disease progression and in vitro inhibition of IGF1R causes uveal melanoma tumor regression [11, 12].

IGF1 ligand levels in plasma are increased by somatostatin signaling, and in one study of 25 uveal melanoma specimens, 100% expressed somatostatin receptor (SSTR)-2A, 56% expressed SSTR-5, and 28% expressed SSTR-3 [13]. This suggests that nuclear imaging with an octreotide analog such as Indium-111 octreotide (Octreoscan) that binds to SSTR-2A may be used to select for patients with advanced uveal melanoma that may be more likely to respond to IGF1R pathway inhibition. A recent report by Valsecchi and colleagues [14] demonstrated In^{111} octreotide avidity in 14/30 patients (44%) with advanced uveal melanoma. In their cohort, 7 patients with positive In^{111} octreotide scans received Sandostatin long-acting release (LAR) outside of a formal clinical trial, and two patients had clinically stable disease for over 5 months [14].

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Combination IGF1R and mTOR inhibition therefore may provide clinical benefit in uveal melanoma. To investigate this, we launched a single-arm Phase 2 trial of combined mTOR and IGF1R inhibition with everolimus and pasireotide LAR in patients with metastatic uveal melanoma. Correlative analysis was performed by measuring plasma levels of IGF1 and baseline Indium-111 (In^{111}) octreotide scans. We hypothesized that plasma IGF1 levels would decrease while receiving pasireotide LAR, consistent with IGF1R pathway inhibition, and patients with positive In^{111} octreotide uptake in their tumors would derive more benefit from the study combination than those whose tumors did not take up In^{111} octreotide.

Methods

Trial Design

This is an open-label, single-arm Phase II trial in which patients with metastatic uveal melanoma received everolimus (RAD001) 10mg orally daily plus pasireotide LAR (SOM230) 60mg intramuscularly (IM) once every 28 days until progression by RECIST 1.1 or unacceptable toxicity. Up to two dose reductions for both everolimus and pasireotide LAR were allowed to accommodate for toxicities. This protocol (NCT01252251) was approved by the Memorial Sloan Kettering Cancer Center Institutional Review Board.

Key inclusion criteria were age >18 years, histologically confirmed metastatic UM with measurable disease per RECIST 1.1, progression on prior therapy in the opinion of the treating physician, ECOG performance status (PS) 0–1, and adequate end-organ function. Key exclusion criteria included brain metastases with stability <2 months, prior therapy with an mTOR inhibitor, or uncontrolled hyperglycemia or hypertriglyceridemia. Patients were evaluated via cross-sectional imaging at baseline and then every 8 weeks, corresponding to the end of even numbered cycles. Adverse events were coded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The primary endpoint was clinical benefit rate (CBR), defined as RECIST 1.1 stable disease at 16 weeks or any objective response. Secondary endpoints included PFS and overall survival (OS). Patients who did not complete 1 cycle (28 days) due to toxicity were considered replaceable for purposes of the primary endpoint.

Imaging and Plasma Correlates

Optional In^{111} octreotide scans were performed prior to starting therapy using planar imaging done at 4 hrs and 24 hours post injection of radiotracer. SPECT or SPECT/CT of the abdomen was performed at 4 hours post injection, and SPECT or SPECT/CT of the chest at 24 hours post injection. All scans were retrospectively reviewed by a board certified nuclear medicine physician on a Hermes workstation (Hermes Medical Solutions, Stockholm, Sweden). A 1cm 3D spherical region of interest was placed over all malignant lesions noted by the study radiologist, and 3Dmax and mean counts were recorded. Max and mean counts from normal liver and aortic arch (for blood pool) were recorded to serve as reference regions. Mean background counts were used in determining tumor to liver and tumor to blood pool ratios. Ratios of uptake in lesions versus background were used to

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derive semiquantitative assessment of uptake intensity, and any lesion with a ratio >2 above background aortic arch uptake at either 4 or 24 hours was considered avid.

Serum insulin-like growth factor-1 (IGF1) levels were assayed at baseline and after every 4 weeks using a commercial liquid chromatography-mass spectrometry assay (Quest Diagnostics, San Juan Capistrano, CA) to assess changes in the IGF1R signaling axis.

Statistical Methods

A Simon two-stage design was utilized to evaluate the CBR. In order to evaluate a promising CBR of 30% versus non-promising CBR of 10% with 90% power at an alpha of 0.10, ≥5 of 25 total patients would have to achieve clinical benefit. The trial was designed to terminate for futility if ≤1 of the first 16 patients achieved clinical benefit.

To explore the association between study drug response and In^{111} octreotide avidity, each RECIST 1.1 target lesion was assessed from baseline to first follow up CT scan and classified as an In^{111} octreotide avid or non-avid lesion. Since multiple lesions were measured within each patient, a generalized estimating equation model was utilized to assess association between In^{111} octreotide avidity of the lesion and percentage changes in size by RECIST. P values <0.05 were considered significant.

Results

Demographics

Between 1/1/2011 and 4/31/2014, 21 patients were consented, of which 14 enrolled on study. The clinical characteristics of these 14 patients are listed in Table 1. Median age was 61 (range: 41–83). Median ECOG PS was 0 (range: 0–1). The majority of patients had M1b or M1c disease (64 and 14%, respectively) by AJCC 7^{th} edition staging guidelines for uveal melanoma [15]. Median number of prior systemic therapy was 2 (range: 1–5), with 9/14 (64%) having progressed on a prior MEK inhibitor. Six patients also received at least 1 prior locoregional therapy. GNAQ/11 Exon 5 mutational status was assessed in 12/14 patients. 10 of these 12 patients had Q209 mutations (GNAQ n=5, GNA11 n=5). Of the two Exon 5 wild-type samples, 1 had a GNA11 Exon 4 R183Q mutation and 1 was not tested further.

Efficacy

The study was terminated early due to poor accrual. Thirteen of 14 patients were evaluable for the primary endpoint; one patient withdrew consent after less than one week on study. See Table 2 for efficacy for each patient on study. Three of 13 patients (23%) had stable disease for at least 16 weeks and were considered to have derived clinical benefit. Overall, SD was the best objective outcome in 7 of 13 patients. Median duration of SD in these patients was 8 weeks (range: 8–16 weeks). Six of 13 patients had PD on first assessment. Two patients had disease regression (−10% and −28%), both of which had tumors that were wild-type for GNAQ/11 Exon 5 mutations. Median time on treatment was 8 weeks (range: 1–23 weeks); see Figure 1. Reasons for stopping therapy were disease progression (n=9), toxicity (n=3), or a switch to attempt a newly available alternate therapy (n=2). Median PFS from first date of treatment for the 13 evaluable patients was 16 weeks (range: 7–23 weeks);

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see Figure 2. Median OS from first day of study treatment was 11 months (range: 4.5–28.5 months); see Figure 3.

Toxicity

Table 3 depicts all adverse events (AEs) occurring in >1 patient and Grade 3 AEs occurring in ≥1 patient deemed at least possibly related to study drugs. All 14 patients experienced at least 1 possibly related AE. The most frequently identified AEs were metabolic (hyperglycemia, hypertriglyceridemia, hypercholesterolemia), gastrointestinal (diarrhea, oral mucositis), or hematologic (leukopenia, thrombocytopenia, neutropenia) in nature. The Grade 3 AEs deemed at least possibly related were hyperglycemia (n=7), oral mucositis (n=2), diarrhea (n=1), hypophosphatemia (n=1), and anemia (n=1). There were no Grade 4 or 5 AEs.

Seven of 14 patients (50%) had at least 1 dose reduction of everolimus. The reasons for dose reduction were mucositis (n=6) and anemia (n=1). Three patients discontinued study treatment due to toxicity: 2 for Grade 2 mucositis and 1 for Grade 3 diarrhea.

Indium^{111} Octreotide Scans, Plasma IGF1R Levels, and Outcomes

8 patients who were evaluable for response underwent baseline Indium-111 octreotide scans, of which 7 of 8 (88%) had positive uptake in ≥1 metastatic lesion. There was heterogeneous uptake in most patients (Table 2 and Figure 4). Five of 7 patients with >1 assessable lesion had both In^{111} octreotide avid and non-avid tumors. Overall, 14 of 28 lesions (50%) were In^{111} octreotide avid. Among the 26 lesions that had been labeled prospectively as RECIST 1.1 target lesions, 12 were avid. There was a trend toward In^{111} avidity and lower percent growth in lesion size on therapy that did not meet statistical significance (p=0.078).

In the 13 evaluable patients, plasma IGF1 levels after 1 cycle of therapy were decreased a median of 54% compared to baseline (range: 7–75%), which was statistically significant ($p<0.001$, paired t test). This reduction in IGF1 levels was sustained for patients who remained on therapy (data not shown). There was no association between IGF1 plasma levels and clinical benefit.

Discussion

Metastatic uveal melanoma remains a disease with poor prognosis, with most patients surviving 6–12 months following diagnosis of metastasis [16, 17]. Multiple ongoing clinical trials are investigating the clinical benefit of inhibiting MEK, PKC, and/or PI3K, and there is a critical need to identify relevant therapeutic targets in this disease [18].

In this highly-pretreated cohort of patients with metastatic uveal melanoma, there was preliminary evidence of clinical benefit with combined IGF-1R and mTOR inhibition. Although the trial did not complete accrual, the fact that 3 patients obtained >16 weeks of stable disease suggests certain patients with advanced uveal melanoma may benefit from this therapy. Interestingly, all 3 of these patients had previously progressed on MEK inhibitors (selumetinib, n=2; trametinib, n=1). Recent work has identified that Akt upregulation is common in MEK-resistant cell lines and showed HRAS signaling is an important upstream

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mediator [19]. The possibility that mTOR and/or IGF-1 signaling plays some additional role in progression to MEK inhibitors requires further investigation. There were no on-treatment biopsies to assess the pharmacodynamic effect of everolimus in this study. The decrease in serum IGF-1 levels, however, suggests pasireotide LAR inhibited signaling of the IGF-1 axis to varying extents.

Of the 8 evaluable patients with an In^{111}-octreotide scan, 7 (88%) had at least 1 octreotide-avid metastasis. This rate is somewhat higher than the 44% rate described by Valsecchi et al despite using the same cutoff for positivity of two-fold increase above background [14]. Our study is the first, to our knowledge, to describe intrapatient heterogeneity in In^{111} octreotide avidity between multiple tumors and suggests there is intrapatient heterogeneity in tumor expression of SSTR-2A. In this small sample size, there was a trend between In^{111} octreotide avidity and stability of disease with combined anti-IGF1R plus mTOR therapy that did not reach statistical significance. This suggests that, while the routine use of In^{111}-octreotide scans in this disease cannot be recommended to document extent of metastatic disease, there may be a biologically relevant relationship between In^{111} octreotide avidity and cytostatic effect of somatostatin analogues in uveal melanoma. This should be investigated in a larger cohort of patients, potentially utilizing more sensitive nuclear imaging modalities such as Gallium-68 octreotate positron emission tomography [20].

As our understanding of uveal melanoma biology increases and more clinical trials utilize targeted inhibitors of growth signals, it will become increasingly important to identify rational strategies to combine antineoplastic agents. This study is the first to our knowledge to combine targeted inhibition in uveal melanoma. Combination therapy with mTOR and IGF1-R inhibitors led to a relatively high rate of AEs, most commonly metabolic, GI, and hematologic in nature. Dose reductions, largely for mucositis, may have limited the long-term tolerability of this combination and slowed accrual of this trial. Nonetheless, given the presence of prolonged stable disease in select patients refractory to multiple therapies, future trials investigating the role of mTOR and/or IGF1-R inhibition in uveal melanoma are warranted.

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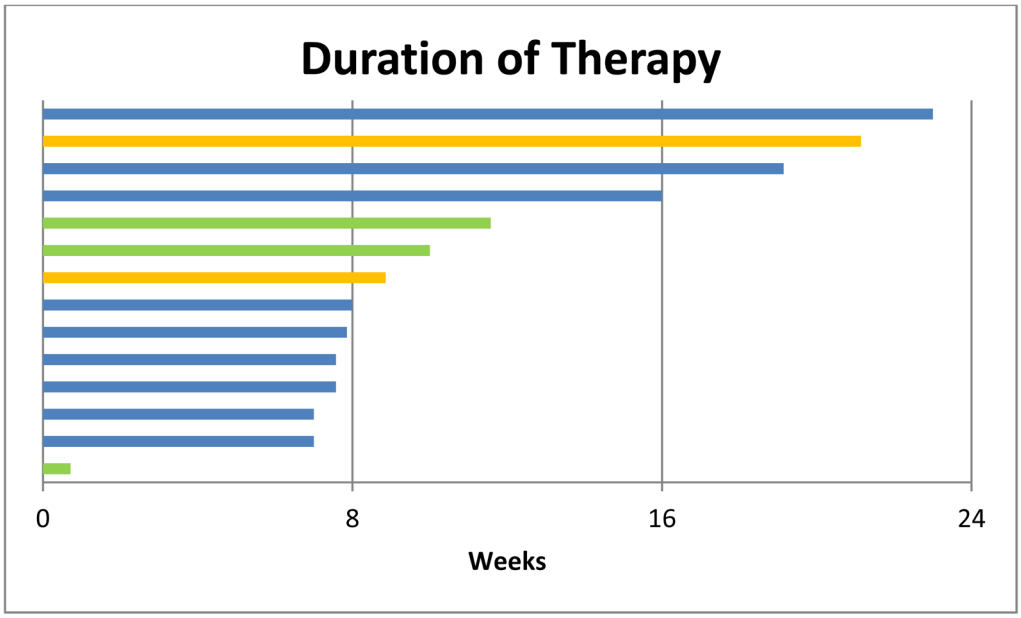

Figure 1.

Swim plot of treatment duration on study and reasons for discontinuation. Three patients obtained >16 weeks of clinical benefit. Patients came off for either POD (blue; n=9), toxicity (green; n=3), or pursuing immune-based therapy (orange; n=2).

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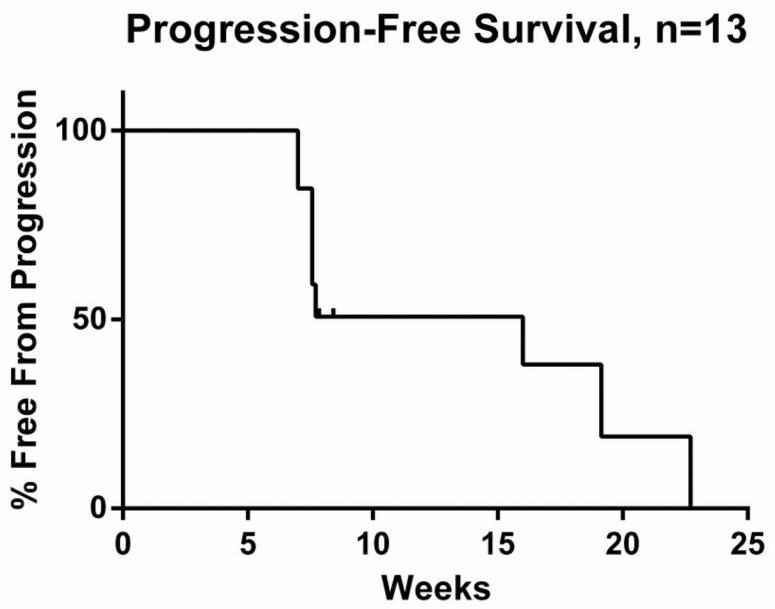

Figure 2.
Kaplan-Meier curve of progression-free survival. Median PFS was 16 weeks.

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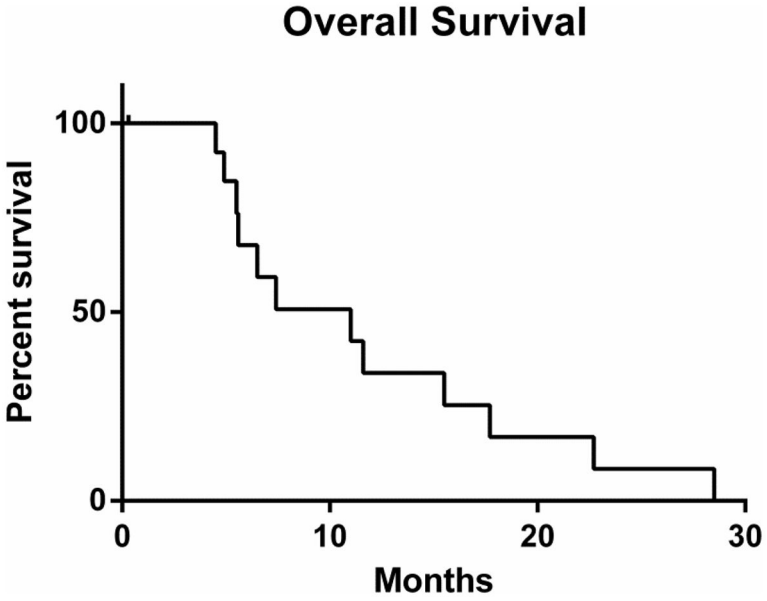

Figure 3.
Kaplan-Meier curve of overall survival. Median OS was 11 months (range: 4.5 – 28.5 months).

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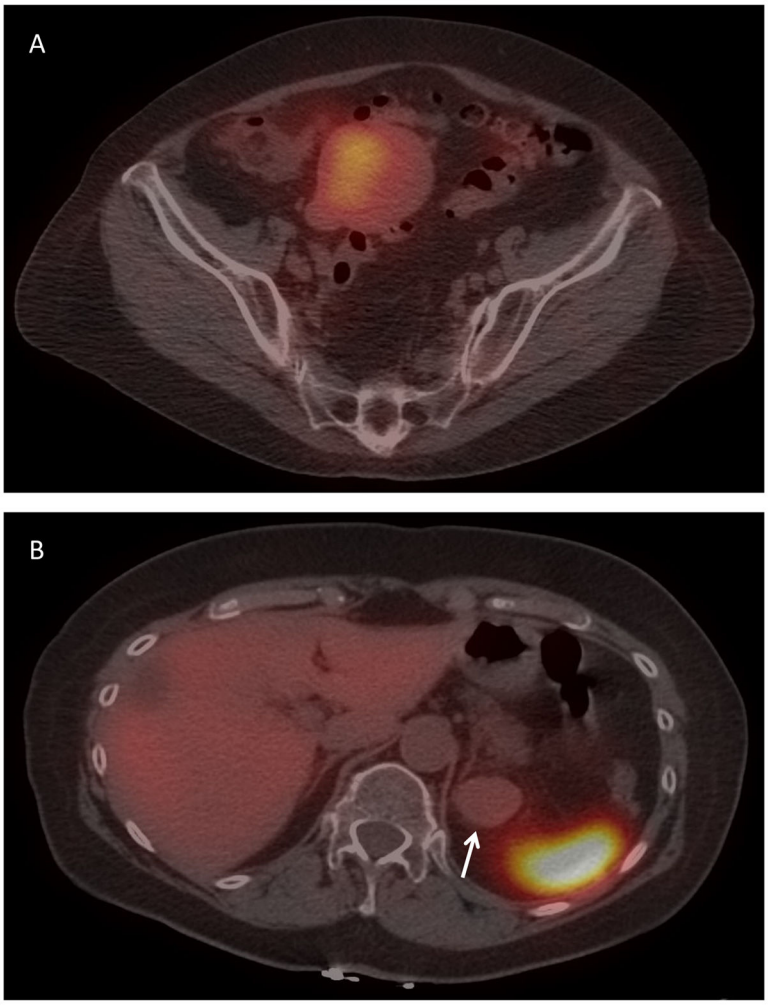

Figure 4.

Heterogeneous In^{111} octreotide pre-treatment uptake in a patient with metastatic uveal melanoma. (A) Pelvic metastasis with In^{111} octreotide avidity. (B) Left perinephric metastasis (arrow) without In^{111} octreotide avidity (with adjacent normal avid spleen visible).

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Table 1

Patient Demographics

Patient #	Sex	Age	Uveal Stage	Cutaneous Stage	LDH*	ECOG	# Prior Systemic Therapies	Prior MEK Inhibitor?	# Prior Local Therapies	GNAQ/11	Codon
1	F	61	M1b	M1c	High	0	3	Yes	1	GNAQ	Q209L
2	M	66	M1b	M1c	High	0	2	Yes	1	GNAQ	Q209P
3	M	55	M1b	M1c	Normal	0	2	Yes	0	GNAQ	Q209L
4	F	63	M1b	M1c	Normal	0	2	Yes	0	GNA11	Q209L
5	M	61	M1b	M1c	Normal	1	2	Yes	0	GNA11	Q209L
6	F	52	M1a	M1b	Normal	0	1	Yes	0	GNAQ	Q209L
7	F	72	M1c	M1c	High	0	2	Yes	0	not done	not done
8	F	42	M1b	M1c	High	0	1	No	1	unknown	Ex5 wt
9	F	72	M1b	M1c	High	0	1	Yes	0	GNA11	Q209L
10	F	74	M1a	M1c	High	0	5	Yes	0	GNA11	R183Q
11	F	60	M1a	M1c	High	1	4	No	5	GNA11	Q209L
12	M	56	M1b	M1c	High	0	3	No	0	GNA11	Q209L
13	M	83	M1b	M1c	High	0	1	No	1	not done	not done
14	M	58	M1c	M1c	High	0	3	No	3	GNAQ	Q209R

*High refers to a value above the upper limit of normal

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Table 2

Efficacy outcomes, IGF1 suppression, and In^{111} octreotide results

Patient #	RECIST Best Response	Best % Change in Tumor Burden	Duration of SD (weeks)	Time on Study (weeks)	Clinical Benefit?	IGF1 Suppression after 1 Cycle	Octreotide Avidity (+/ total lesions)
1	POD	+20.3	N/A	8	No	57%	Yes (1/3)
2	SD	+3	16.0	21	Yes	56%	Yes (3/4)
3	POD	+6.5	N/A	7	No	23%	Yes (1/4)
4	N/A	N/A	N/A	0.7	N/A	N/A	N/A
5	SD	+14	8.4	12	No	7%	Yes (3/6)
6	SD	+3	7.0	10	No	39%	Yes (2/2)
7	SD	+4	15.0	19	Yes	51%	Yes (3/6)
8	SD	−28	7.9	16	No	42%	N/A
9	POD	+53	N/A	8	No	63%	N/A
10	SD	−10	15.4	23	Yes	74%	N/A
11	POD	+20	N/A	8	No	26%	N/A
12	SD	+16	7.9	9	No	54%	N/A
13	POD	+35	N/A	8	No	75%	Yes (1/1)
14	POD	+35	N/A	7	No	69%	No (0/2)

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Table 3

Select CTCAE v4.0 Adverse Events at least Possibly Related to Study Drugs

Adverse Event	Grade 1	Grade 2	Grade 3
Hyperglycemia	1 (7%)	4 (29%)	7 (50%)
Hypertriglyceridemia	8 (57%)	2 (14%)	0
Diarrhea	8 (57%)	0	1 (7%)
Leukopenia	5 (36%)	4 (29%)	0
Hypercholesterolemia	4 (29%)	4 (29%)	0
Mucositis	4 (29%)	2 (14%)	2 (14%)
Thrombocytopenia	7 (50%)	0	0
Neutropenia	0	5 (36%)	0
Elevated CPK	4 (29%)	0	0
Hypophosphatemia	0	2 (14%)	1 (7%)
Nausea	3 (21%)	0	0
Rash	2 (14%)	1 (7%)	0
Dyspnea	1 (7%)	1 (7%)	0
Fatigue	2 (14%)	0	0
Anemia	0	0	1 (7%)

All AEs occurring in >1 patient regardless of severity or any Grade 3 or higher AEs at least possibly related to study drugs are depicted. There were no Grade 4 or 5 toxicities related to study drugs.