The Oncologist®

Clinical Trial Results

Phase II Study of Everolimus in Metastatic Malignant Melanoma (NCCTG-N0377, Alliance)

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT00098553
- **Sponsor(s)**: National Cancer Institute (NIH Award Numbers U10CA180821, U10CA180882 [to the Alliance for Clinical Trials in Oncology], and U10CA180790)
- **Principal Investigator**: Svetomir Markovic
- **IRB Approved**: Yes

Lessons Learned

- Everolimus does not have sufficient activity to justify its use as single agent in metastatic melanoma.
- Patients treated with 10 mg per day dose were most likely to require dose reductions.
- Everolimus appeared to reduce the numbers of regulatory T cells in approximately half of the treated patients; unfortunately, these effects were not correlated with clinical outcomes.

Abstract

Background. Everolimus (RAD-001) is an orally active rapamycin analogue shown in preclinical data to produce cytostatic cell inhibition, which may be potentially beneficial in treating melanoma. We conducted a phase II study to evaluate the efficacy and safety of everolimus in patients with unresectable metastatic melanoma (MM).

Methods. This study included two cohorts; cohort 1 received 30 mg of everolimus by mouth (PO) weekly, and cohort 2 was dosed with 10 mg of everolimus PO daily. The endpoints of the study were safety, 16-week progression-free survival (PFS), overall survival (OS), and measures of immunomodulatory/antiangiogenic properties with therapy. Tumor samples before therapy and at week 8 of treatment were analyzed. Peripheral blood plasma or mononuclear cell isolates collected prior to therapy and at weeks 8 and 16 and at time of tumor progression were analyzed for vascular endothelial growth factor and regulatory T-cell (Treg) measurements.

Results. A total of 53 patients were enrolled in cohort 1 ($n = 24$) and cohort 2 ($n = 29$). Only 2 patients of the first 20 patients enrolled in cohort 2 had treatment responses (25%; 95% confidence interval, 8.6%–49.1%); this result did not allow full accrual to cohort 2, as the study was terminated for futility. Median OS was 12.2 months for cohort 1 versus 8.1 months in cohort 2; no PFS advantage was seen in either group (2.1 months vs. 1.8 months). Dose-limiting toxicities included grade 4 myocardial ischemia (3.4%); grade 3 fatigue, mucositis, and hyperglycemia (10.3%); and anorexia and anemia (6.9%). Everolimus significantly reduced the number of Tregs in approximately half of the treated patients; however, these effects were not correlated with clinical outcomes.

Conclusion. Everolimus does not have sufficient single-agent activity in MM; however, we have identified evidence of biological activity to provide a potential rationale for future combination studies. ***The Oncologist*** 2018;23:887–e94

Discussion

Melanoma is the most malignant form of skin cancer, the fifth most common cancer in men and sixth in women in the U.S., with its highest incidence in the white population [1–3].

In preclinical studies by our group, inhibitors of mammalian target of rapamycin (mTOR) demonstrated a potent inhibitory effect on tumor growth, improved survival, an inhibitory effect of rapamycin on angiogenesis, and significant decrease in the number of capillaries perfusing the tumor [4–6]. The results of the current study demonstrate that single-agent therapy with RAD-001 does not have sufficient activity to justify its use as a single agent in the treatment of metastatic melanoma. Our

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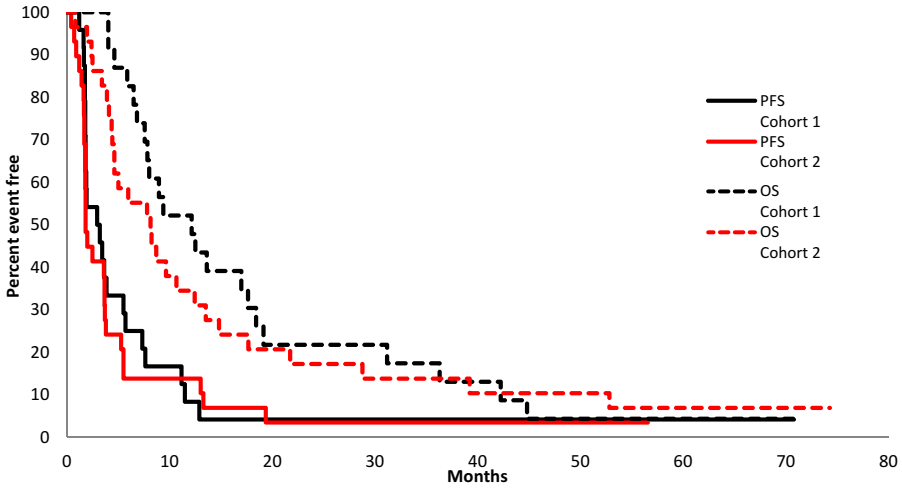

Figure 1. Kaplan-Meier plot. Overall survival (OS) and PFS comparing cohort 1, 30 mg by mouth (PO) weekly ($n = 24$), with cohort 2, 10 mg PO daily ($n = 9$). Median OS was 12.2 months versus 8.1 months, respectively; no PFS advantage was seen in either group (2.1 months vs. 1.8 months).

Abbreviation: PFS, progression-free survival.

data also suggest that patients treated with the 10 mg per day dose were most likely to require dose reductions. The treatment did appear to modulate aspects of both immunity and angiogenesis; however, in view of the insufficient clinical efficacy of treatment, these findings can only be viewed as exploratory and illustrative of the potential utility of everolimus in combination with other agents. Everolimus significantly reduced the numbers of Tregs in approximately half of the treated patients; unfortunately, these effects were not correlated with clinical outcomes.

Investigating the benefits of everolimus as a single agent is the first step toward incorporating this agent into a combination regimen to treat melanoma. Because the 10 mg per day dose appeared to be excessively toxic in this population, future studies will need to use a lower dose. The toxicity profile of everolimus does not overlap with other melanoma therapies.

Trial Information	
Disease	Melanoma
Stage of Disease/Treatment	Metastatic/Advanced
Prior Therapy	No designated number of regimens
Type of Study - 1	Phase I/II
Type of Study - 2	Phase II study
Primary Endpoint	Safety
Secondary Endpoint	Overall response rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Correlative endpoint

Additional Details of Endpoints or Study Design

The primary endpoint of this trial was the proportion of patients that were failure-free (FF) at 16 weeks. A patient was defined as FF if the patient was progression-free and still receiving study treatment at 16 weeks. The study utilized a two-stage Simon design to test that the true 16-week FF rate was at most 30% versus the alternative, which was at least 50%. This design had a significance level of 0.10 with a power of 90%. To test this hypothesis, a maximum of 55 evaluable patients were to be accrued. After the first 20 evaluable patients were enrolled, accrual was stopped. If, after the first 20 evaluable patients, there were at most 6 patients who remained FF, no more patients were to be accrued. Otherwise, an additional 25 evaluable patients were to be accrued. In order for the trial to be declared successful, a minimum of 17 patients were to be declared FF at 16 weeks (of the first 45 evaluable patients).

The results of the interim analysis performed on the first 20 patients enrolled allowed accrual to continue; however, clinical studies in renal cell carcinoma demonstrated early positive results with a slightly higher dose of therapy (10 mg/day). Considering these new observations and in consultation with the National Cancer Institute, a decision was made to restart the trial at the 10 mg/day dose of RAD-001 and plan to enroll another cohort of 55 patients, using the same two-stage design and eligibility and decision rules for efficacy.

Secondary endpoints included overall survival (OS, defined as the time from study registration until death), progression-free survival (PFS, defined as the time from study entry until disease progression or death when patients died without documentation of disease progression), confirmed response rate (a confirmed response was defined as a CR or PR on consecutive cycles at least 8 weeks apart), LDH (testing LDH's influence on PFS, OS, and treatment response), and correlative laboratory studies (effects of therapy on PET/CT imaging, mTOR inhibition, and immune homeostasis parameters).

Progression-free survival at 16 weeks was not achieved. Secondary endpoints, including OS (defined as the time from study registration until death), PFS (defined as the time from study entry until disease progression or death if patients died without

documentation of disease progression), and confirmed response rate (a confirmed response was defined as a complete response [CR] or partial response [PR] on consecutive cycles at least 8 weeks apart), were not achieved.

Investigator's Analysis
Inactive because results did not meet primary endpoint

Drug Information

Generic/Working Name	Everolimus (RAD-001)
Company Name	Novartis
Drug Type	Small molecule
Drug Class	mTOR
Dose	30 milligrams (mg) per flat dose
Route	PO
Schedule of Administration	Doses: Cohort 1 received 30 mg of everolimus PO weekly, and cohort 2 was dosed with 10 mg of everolimus PO daily.

Patient Characteristics

Number of Patients, Male	37
Number of Patients, Female	16
Stage	IV
Age	Median (range): 61 years (21.0-81.0)
Performance Status: ECOG	0 — 31 1 — 20 2 — 2 3 — Unknown —
Cancer Types or Histologic Subtypes	Malignant melanoma

Primary Assessment Method for Phase I Control

Title	Total Patient Population
Number of Patients Enrolled	53
Number of Patients Evaluable for Toxicity	53
Evaluation method	RECIST, version 1.0
Response assessment CR	$n = 0$
Response assessment PR	$n = 1$
Response assessment SD	$n = 0$
Response assessment PD	$n = 52$

Adverse Events

	Cohort 1, *n* (%)			Cohort 2, *n* (%)		
Adverse event	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**
Fatigue	6 (25)	0	0	9 (31)	3 (10)	0
Anorexia	1 (4)	0	0	5 (17)	2 (7)	0
Leukopenia	2 (8)	0	0	4 (14)	1 (3)	0
Oral mucositis	0	0	0	4 (14)	2 (7)	0
Anemia	2 (8)	0	0	2 (7)	2 (7)	0
Hyperglycemia	1 (4)	0	0	1 (3)	3 (10)	0
Peripheral sensory neuropathy	0	0	0	5 (17)	0	0

Dose-Limiting Toxicities

Dose level	Dose of everolimus (RAD-001)	Number enrolled	Total number of cycles	Number with a dose-limiting toxicity	Dose-limiting toxicity information
Cohort 1	30 mg per week	24	55	0	
Cohort 2	10 mg per day	29	65	2	Mucositis; thrombocytopenia

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Inactive because results did not meet primary endpoint

Although the inhibition of PI3K/mammalian target of rapamycin (mTOR)/AKT pathway is a therapeutic strategy for several cancer types, the current study demonstrates that single-agent therapy with everolimus does not have sufficient activity to justify its use in the treatment of metastatic melanoma. This was our conclusion, despite literature showing that the mTOR pathway is activated in malignant melanoma as opposed to benign nevi [7]. Efforts to evaluate the efficacy of everolimus with other regimens have been performed by different groups; for example, the use of everolimus in combination with temozolamide was evaluated in a single-arm phase II multi-institution trial; although the regimen was well tolerated, it failed to meet or exceed the study threshold for promising clinical activity in patients with metastatic melanoma [8]. A subsequent phase II trial combining paclitaxel, carboplatin, and everolimus showed activity in the first-line treatment of metastatic melanoma; unfortunately, the duration of benefit was brief for most patients [7]. A recent study evaluated the addition of everolimus to carboplatin, paclitaxel, and bevacizumab; this combination was found to be ineffective in metastatic melanoma because of inability to give the full dose of everolimus, predominantly because of cytopenias [9]. Although it was a negative study, the investigators reported that the everolimus combination arm performed exceptionally well, receiving >30 cycles of therapy [9].

Interestingly, the use of everolimus in a preclinical model demonstrated increased programmed death-ligand 1(PD-L1) expression in renal cell carcinoma, and the addition of everolimus to anti-PD-L1 significantly reduced tumor burden compared with everolimus alone; [10] the use of immunotherapy in combination with everolimus in patients with melanoma warrants further investigation.

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Disclosures

Val J. Lowe: GE Healthcare, AVID Radiopharmaceuticals (RF), Celgene, AMAG Pharma, Alexion Inc., Exelixis Inc. (OI). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

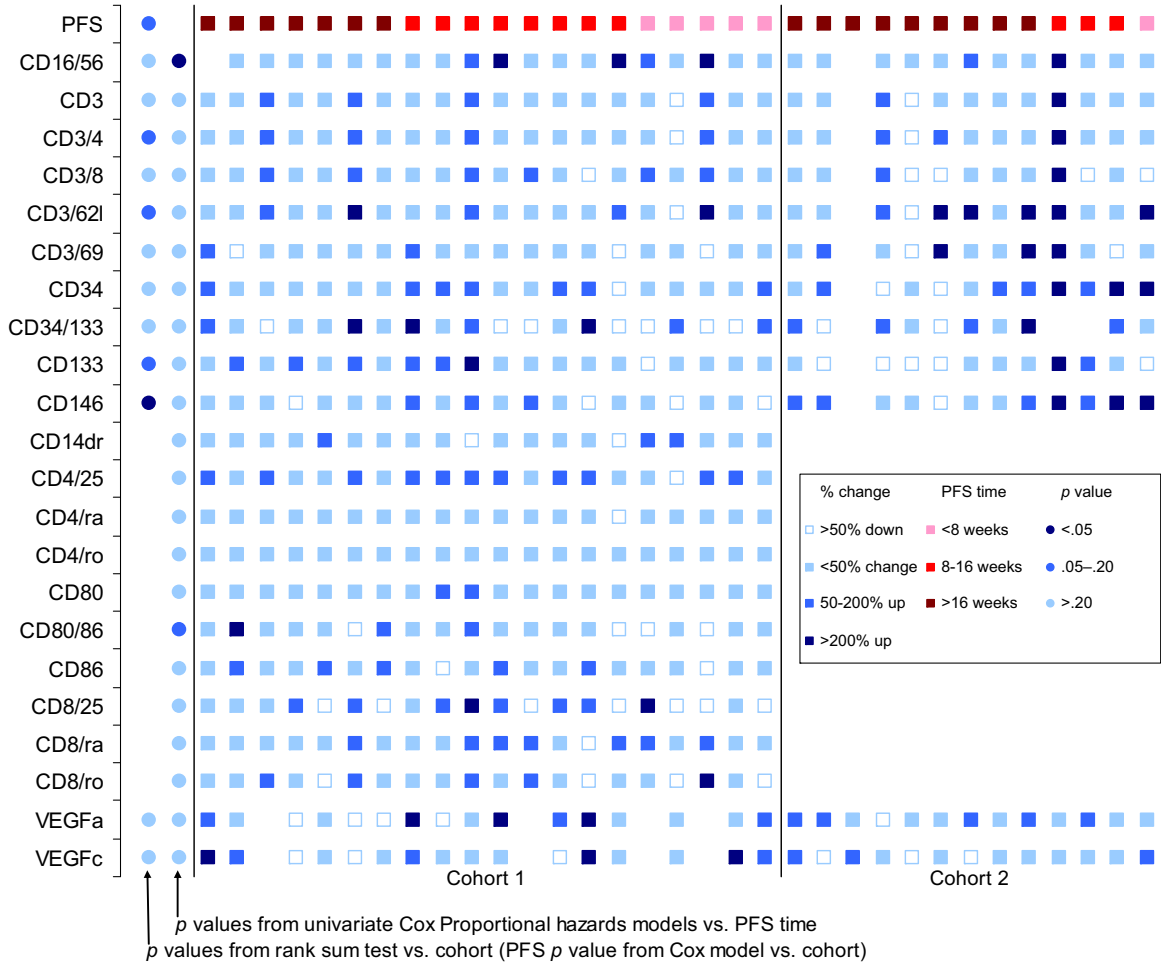

Figure 2. Summary of correlative studies. Effects of RAD-001 therapy on peripheral blood-derived parameters of immune homeostasis. Peripheral blood plasma or mononuclear cell isolates collected prior to therapy, at weeks 8 and 16 of therapy as well as at the time of tumor progression, were analyzed. For most measured parameters, RAD-001 therapy did not appear to significantly influence the measurements; however, therapy did appear to significantly reduce the numbers of regulatory T cells (Treg) in approximately half of the treated patients. These effects were not correlated with clinical outcomes.

Abbreviation: PFS, progression-free survival.

Table 1. Patient characteristics

Characteristic	Cohort 1 ($n = 24$), *n* (%)	Cohort 2 ($n = 29$), *n* (%)	Total ($n = 53$), *n* (%)
Age, years			
Mean (standard deviation)	58.4 (13.8)	61.9 (13.8)	60.3 (13.8)
Median	57.5	63.0	61.0
Gender			
Female	8 (33.3)	8 (27.6)	16 (30.2)
Male	16 (66.7)	21 (72.4)	37 (69.8)
Race			
White	24 (100.0)	28 (96.6)	52 (98.1)
Black or African American	0 (0.0)	1 (3.4)	1 (1.9)
Performance score			
0	14 (58.3)	17 (58.6)	31 (58.5)
1	9 (37.5)	11 (37.9)	20 (37.7)
2	1 (4.2)	1 (3.4)	2 (3.8)
Metastatic disease			
M1a	3 (12.5)	4 (13.8)	7 (13.2)
M1b	3 (12.5)	7 (24.1)	10 (18.9)
M1c	18 (75.0)	18 (62.1)	36 (67.9)
Ulcerative lesions			
Missing data	8 (33.3)	11 (37.9)	19 (35.8)
Yes	5 (20.8)	6 (20.7)	11 (20.8)
No	7 (29.2)	5 (17.2)	12 (22.6)
Unknown	4 (16.7)	7 (24.1)	11 (20.8)
Brain metastases			
Yes	1 (4.2)	0 (0.0)	1 (1.9)
No	23 (95.8)	29 (100.0)	52 (98.1)