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APPLICATION NUMBER:

22-334

MEDICAL REVIEW(S)

CLINICAL REVIEW

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Submission Number 22334
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Reviewer Name Qin Ryan, MD, PhD
Review Completion Date Mar 24, 2009

Established Name Everolimus
(Proposed) Trade Name Afinitor
Therapeutic Class mTor inhibitor
Applicant Novartis

Priority Designation P
Extension 3 months due to major amendment

Formulation Oral
Dosing Regimen 10 mg once daily
Indication Advanced renal cell carcinoma

TABLE OF CONTENTS

LIST OF TABLES.....4

LIST OF FIGURES.....6

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT7

1.1 Recommendation on Regulatory Action.....7

1.2 Risk Benefit Analysis7

1.3 Recommendations for Risk Evaluation and Mitigation Strategies10

1.4 Recommendations on Post Marketing Activities/Phase 4 Commitments.....10

2 INTRODUCTION AND REGULATORY BACKGROUND.....11

2.1 Product Information.....11

2.2 Tables of Currently Available Treatments for Proposed Indications.....11

2.3 Availability of Proposed Active Ingredient in the United States12

2.4 Important Safety Issues with Consideration to Related Drugs12

2.5 Summary of Pre-submission Regulatory Activity Related to Submission12

2.6 Pediatric Waiver12

2.7 Other Relevant Background Information12

3 ETHICS AND GOOD CLINICAL PRACTICES13

3.1 Submission Quality and Integrity13

3.2 Compliance with Good Clinical Practices17

3.3 Financial Disclosures.....17

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES17

4.1 Chemistry Manufacturing and Controls17

4.2 Preclinical Pharmacology/Toxicology.....18

4.3 Clinical Pharmacology18

4.3.1 Mechanism of Action.....19

4.3.2 Pharmacodynamics19

4.3.3 Pharmacokinetics19

5 SOURCES OF CLINICAL DATA21

5.1 Tables of Clinical Studies.....21

5.2 Review Strategy.....21

5.3 Discussion of Individual Studies22

5.3.1 Study C224022

5.3.2 Other Supportive Studies: 2201, 2202, 2207 and 1101.29

6 REVIEW OF EFFICACY29

6.1 Indication.....29

6.1.1 Methods29

6.1.2 Demographics29

6.1.3 Patient Disposition.....32

6.1.4 Analysis of Primary Endpoint(s): PFS.....33

6.1.5 Prespecified Analysis of Secondary Endpoints(s)37

6.1.6 Sensitivity Analyses of the Primary Endpoints: PFS39

6.1.7 Subpopulations52

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

7	REVIEW OF SAFETY	53
7.1	Methods	53
7.2	Adequacy of Safety Assessments	55
7.2.1	Overall Exposure at Appropriate Doses/Durations.....	55
7.2.2	Evaluation for Potential Adverse Events for Other Drugs in this Drug Class	56
7.3	Major Safety Results	57
7.3.1	Deaths	57
7.3.2	Nonfatal Serious Adverse Events	58
7.3.3	Dropouts and/or Discontinuations	60
7.3.4	Dose Interruption and/or Dose Reductions	60
7.3.5	Additional therapy	61
7.3.6	Significant Adverse Events.....	63
7.3.7	Submission Specific Primary Safety Concerns.....	63
7.4	Supportive Safety Results.....	71
7.4.1	Common Adverse Events	71
7.4.2	Laboratory Findings.....	76
8	POSTMARKETING EXPERIENCE	79
9	APPENDICES	79
9.1	Literature Review/References	79
9.2	Labeling Recommendations	82
9.3	Advisory Committee Meeting	82

APPEARS THIS WAY ON ORIGINAL

List of Tables

Table 1: Approved and available therapies for advanced renal cell carcinoma	11
Table 2: Previous everolimus NDA submissions	13
Table 3: NDA 22334 submission and amendments, pre-specified and requested.....	13
Table 4: The clinical review team proposed sites and DSI inspection results.....	16
Table 5: Clinical studies related to the proposed indication	21
Table 6: Dose modification guidelines:	25
Table 7: Toxicity management:	25
Table 8: Study C2240 landmark and amendments	28
Table 9: Study C2240 patient populations.....	30
Table 10: Study C2240 patient demographics (ITT)	30
Table 11: Study C2240 patient characteristics (ITT).....	31
Table 12: Prior therapies on Study C2240 patients (ITT).....	32
Table 13: Study C2240 patient disposition at both cut off dates (Oct 15, 2007 and Feb 28, 2008, ITT)	33
Table 14: Study C2240 primary analysis – PFS (ITT)	34
Table 15: Study C2240 prespecified secondary analysis: OS (ITT).....	37
Table 16: Study C2240 overall response rate (ITT)	39
Table 17: Sensitivity Analyses of PFS in worst case scenario by either IRC or investigator assessment (ITT)	40
Table 18: Analyses of discrepancies of any type in Study C2240 (ITT, Oct 15, 2007 cut-off)..	41
Table 19: Analyses of discrepancies of any type in Study C2240 (ITT, Feb 28, 2008 cut-off)..	42
Table 20: Statistical summary of the time between the censoring date and the Oct 15, 2007 cut-off date in everolimus and placebo arms, based on the independent review	42
Table 21: Statistical summary of the time between the censoring date and the Oct 15, 2007 cut-off date in everolimus and placebo arms based on the investigator review.....	43
Table 22: Statistical summary of the time between the censoring date and the Feb 28, 2008 cut-off date in everolimus and placebo arms based on the independent review	43
Table 23: Statistical summary of the time between the censoring date and the Feb 28, 2008 cut-off date in everolimus and placebo arms based on the investigator review.....	44
Table 24: Summary of the reasons for censoring for PFS based on independent assessments (ITT).....	44
Table 25: Study C2240 PFS options, per protocol and SAP (Feb 1, 2008).....	46
Table 26: PFS sensitivity analyses with difference censoring options (Feb 28 2008 cut-off)	47
Table 27: Reviewer’s summary of discrepancies of disease progression and death events	48
Table 28: Study C2240 TTF (Feb 28, 2008 cut-off).....	49
Table 29: PFS subgroup analysis at Oct 15, 2007 cut-off	50
Table 30: PFS subgroup analysis at Feb 28, 2008 cut-off	51
Table 31: Analysis of PFS based on central radiology review by subgroup (Oct 15, 2007 cut-off)	52

Table 32: Analysis of PFS based on central radiology review by subgroup (Feb 28, 2008 cut-off)	53
Table 33: Key studies reviewed for safety evaluation	54
Table 34: Safety population grouping (SP)	55
Table 35: Study C2240 overall drug exposure (SP, both cut off dates)	56
Table 36: Deaths within 30 days of study treatment (SP)	57
Table 37: Treatment related death (SP)	57
Table 38: Grade 3/4 adverse reactions (SP)	59
Table 39: Adverse reactions that cause treatment termination (SP)	60
Table 40: Adverse reactions that required medical therapy	62
Table 41: Significant adverse reactions observed in Study C2240 (SP)	63
Table 42: Specific adverse reactions in Study C2240 (SP)	63
Table 43: Cytopenia observed in Study C2240 (SP)	64
Table 44: Rash and similar skin reactions observed in Study C2240 (SP)	65
Table 45: Metabolic events with 2 fold increase observed in Study C2240 (SP)	66
Table 46: Renal adverse reactions observed in Study C2240 (SP)	66
Table 47: Pulmonary adverse reactions observed in Study C2240 (SP)	67
Table 48: Coagulation abnormalities and adverse reactions (SP)	68
Table 49: Hepatic adverse reactions observed in Study C2240 patients without co-existing liver disease (SP)	69
Table 50: Infections observed in Study C2240 patients (SP)	69
Table 51: Treatment emergent adverse reaction that occurred in the everolimus arm > 5%	71
Table 52: Investigator determined drug-related adverse reaction* that occurred in the everolimus arm > 5%	72
Table 53: Adverse reaction that occurred in the everolimus arm > 10% by selected broader terms search (Feb 28, 2008 cut-off)	74
Table 54: Comparison on results of treatment emergent, drug-related, and drug-related plus possibly and probably related adverse reactions	75
Table 55: Hematology adverse reactions observed in Study C2240 (SP)	77
Table 56: Chemistry adverse reactions observed in Study C2240 (SP)	78

List of Figures

Figure 1: Study C2240 design.....	23
Figure 2: Kaplan-Meier estimation of PFS per IRC assessments (cut off date: Oct 15, 2007)....	35
Figure 3: Kaplan-Meier estimation of PFS per investigators assessments (cut off date: Oct 15, 2007)	35
Figure 4: Kaplan-Meier estimation of PFS per IRC assessments (cut off date: Feb 25, 2008)....	36
Figure 5: Kaplan-Meier estimation of PFS per investigators assessments (cut off date: Feb 25, 2008)	36
Figure 6: Study C2240 prespecified secondary analysis: OS-Kaplan-Meier Estimation (ITT, Oct 15, 2007 cut-off)	37
Figure 7: Study C2240 prespecified secondary analysis: OS-Kaplan-Meier Estimation (ITT, Feb 28, 2008 cut-off)	38
Figure 8: TTF analysis by Kaplan Meier estimation (Feb 28, 2008 cut-off).....	49

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This review recommends regular approval for everolimus (Afinitor, RAD001) for the indication below:

“Afinitor® is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.”

1.2 Risk Benefit Analysis

The risk benefit analysis to support this recommendation was based on the efficacy and safety results of one randomized, placebo-controlled, double-blind study. Study C2240 was conducted in advanced renal cell carcinoma patients who had received at least one prior anti-VEGFR-TKI (vascular endothelial growth factor receptor tyrosine kinase inhibitor) therapy. Prior to randomization, patients were stratified according to the Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria (favorable vs. intermediate vs. poor risk groups) and prior anticancer therapy (one anti-VEGFR-TKI vs. two). Four hundred sixteen patients, 88%, 77% male, 63% younger than 65 years, and 100% who had received either sunitinib or sorafenib, were randomized in a 2:1 ratio (277 to everolimus, 139 to placebo). Study treatment included continuous oral dosing with everolimus 10 mg daily versus matching placebo. The disease status was assessed every two months (every two 30-day cycles). At the time of disease progression, patients were unblinded. Patients from the placebo arm were given the option of receiving RAD001 in a separate treatment protocol.

The primary endpoint of Study C2240 was progression-free survival (PFS) using a group sequential design with two interim analyses, both of which allowed stopping for lack of efficacy (futility) and for outstanding efficacy. The two interim analyses were planned at 30% and 60% of the required number of PFS events, respectively. Because the second interim analysis result crossed the boundary for outstanding efficacy, the study was stopped and patients on the placebo arm could be all crossed over to receive everolimus regardless the disease status. Although planned enrollment was achieved at the time of study termination, the final PFS analysis was based on a total of 266 PFS events, as per independent central radiological review, instead of the original planned 290 events in the intent-to-treat (ITT) population.

The final PFS analysis of Study C2240 by independent radiological assessment, with a February 28, 2008 data cut-off, was statistically significant in favor of everolimus (HR = 0.33, p value < 0.001). The improvement in median PFS was approximately 3 months (4.9 months versus 1.8 months). This PFS result was consistent with the PFS result from the October 15, 2007 data cut-

off for the second interim analysis (HR = 0.30, p value < 0.001, with median PFS of 4.0 months for everolimus and 1.9 months for the placebo). It was also consistent with the investigator assessments. At the data cut-off time for the final PFS analysis, the difference in overall survival (OS) was not statistically significant in favor of the everolimus arm (HR = 0.82, p value = 0.137). Although the median OS for the everolimus arm had not been reached, the median OS in the placebo arm was 8.8 months (31% deaths for the everolimus arm and 35% for the placebo arm). As a result of the study's crossover design and early termination, 109 of 139 patients from the placebo arm received everolimus either after disease progression or at the time of early termination. Although a longer follow-up for overall survival may not elucidate a survival trend, the applicant should submit the final, per-protocol OS analysis of study C2240, which was to be conducted at 2 years after randomization of the last patient. The overall response rate (ORR = complete response rate + partial response rate) was 1.8% for everolimus and 0% for placebo by independent assessment at the time of final analysis data cut-off. However, there was a trend in favor of everolimus for the percentage of patients with stable disease over the placebo, 67% versus 32%, respectively. This observation is consistent with the PFS data. Although neither OS nor ORR was statistically different between the everolimus and the placebo arms, the subgroup PFS analyses by MSKCC prognostic score and prior anti-VEGFR-TKI therapy were consistent with the result of the primary PFS analyses.

The Study C2240 safety analyses of everolimus compared to the placebo were acceptable in the proposed patient population. Treatment-emergent adverse reactions were observed in 97% of patients who received everolimus and 93% of patients who received placebo. The most common adverse reactions to everolimus were similar to other rapamycin class drugs. The adverse reactions in Study C2240 observed in 20% or more patients were stomatitis (44%), asthenia (33%), diarrhea (30%), cough (30%), rash (29%), nausea (26%), anorexia (25%), peripheral edema (25%), dyspnea (24%), vomiting (20%), and pyrexia (20%). The most common laboratory adverse reactions were anemia (92%), lymphopenia (50%), hypercholesterolemia (77%), hypertriglyceridemia (73%), and hyperglycemia (57%). The grade 3 or 4 adverse reactions observed in more than 4% of patients were lymphopenia (17%), pneumonitis (14%), anemia (13%), dyspnea (8%), fatigue (6%), hyperglycemia (6%), and stomatitis (4%). Deaths due to acute respiratory failure (1.9%), infection (1.1%), and renal failure (0.4%) were observed on the everolimus arm. No deaths due to an adverse reaction were seen in the placebo arm.

The adverse reactions that caused treatment termination were pneumonitis, dyspnea, lung disorders, fatigue and renal failure. Mucositis, pneumonitis and symptoms related to both were the most common reasons for treatment delay or dose reduction. The most common adverse reactions requiring medical interventions during everolimus treatment were anemia, gastrointestinal, respiratory, and skin symptoms.

In terms of laboratory tests, decreases in blood counts, as well as, electrolyte, metabolic, liver and/or renal function test abnormalities occurred more often in the everolimus arm patients. Although less than 4% of patients experienced grade 4 hematological adverse reactions, grade 1-

Clinical Review

Reviewer: Qin Ryan MD, PhD

NDA 22334

Afinitor (everolimus, RAD001)

4 adverse reactions such as anemia (92%), lymphopenia (50%), leukopenia (29%), thrombocytopenia (23%), and neutropenia (14%) were all common. It is noteworthy that 71% of the safety population developed abnormal chemistries and 31% were grade 3 or 4. The most common chemistry abnormalities were hypercholesterolemia (77%), hypertriglyceridemia (73%), hyperglycemia (57%), γ -GT increased (54%), increased creatinine (50%), elevated alkaline phosphatase (44%), hypophosphatemia (37%), hypocalcemia (27%), AST increased (25%), hyponatremia (21%), ALT increased (21%), and hyperkalemia (11%). Therefore, adequate monitoring of blood counts and chemistry analyses, including electrolytes, hepatic function and metabolic profile (glucose and lipids), should be recommended.

The everolimus specific adverse reactions which should be watched and managed appropriately during treatment are as follows.

a. Hyperlipidemia and hyperglycemia, known class effects of rapamycin and its derivatives, were observed in 77% (5% grade 3 or 4) and 57% (16% grade 3 or 4) of patients receiving everolimus in Study C2240, respectively. Two-fold increases in incidence were seen in the everolimus arm compared to the placebo arm. These clinical abnormalities responded to lipid lowering agents such as statins and fibrates in association with dietary recommendations. No treatment discontinuation due to adverse metabolic reactions was observed.

b. Treatment emergent increases in serum creatinine were detected in 50% of patients in the everolimus arm and 34% in the placebo arm by laboratory test. However, treatment related creatinine elevation and renal failure occurred 9% and 2% more, respectively, in the everolimus arm. Carefully monitoring of the serum creatinine and renal function is recommended for patients receiving everolimus treatment. No clinical study of everolimus in renally impaired patients has been conducted.

c. Pneumonitis. The applicant conducted a blinded central radiology review which reported new or worsening CT changes in 48.2% and 14.6% of everolimus and placebo arm patients, respectively. Clinically reported pneumonitis occurred in only 13.5% everolimus patients and 0% placebo patients. Among the everolimus arm patients whose CT suggested pneumonitis, 6.2% (17/274) had clinically confirmed pneumonitis, and 4.1% (11/274) had other lung abnormalities. Among patients in the placebo arm with a CT suggesting pneumonitis, no clinical cases of pneumonitis were reported. Therefore, monitoring everolimus treatment-emergent pneumonitis should combine the clinical presentation and CT results, keeping in mind that the latter is highly sensitive but lacks specificity in the diagnosis of pneumonitis. Of the 37 everolimus arm patients (13.5%) had clinically reported pneumonitis; 18 were grade 2 (6.6%) and 10 were grade 3 (3.6%). There was no grade 4 pneumonitis. Complete resolution was observed in 64% (18/28) of Grade 2 and 3 pneumonitis and 57% (16/28) of patients with grade 2 or 3 pneumonitis required steroid treatment. Everolimus dose reduction was required for 50% (14/28) of grade 2 or 3 cases and treatment discontinuation for 36% (10/28). Therefore, criteria for

dose reduction and discontinuation should be included in the proposed label. This also may be a post marketing safety issue.

d. Increased bleeding events among patients on the everolimus arm (8%) were associated with thrombocytopenia, which occurred in 23% of patients. Adequate platelet count monitoring should be in place throughout everolimus treatment. The number of thromboembolic events was similar between the two arms.

e. Liver function test abnormalities were noted in everolimus treated patients with or without co-existing liver disease, 40% and 4%, respectively. Therefore, adequate liver function monitoring should be considered regardless of co-existing liver disease. No clinical study of everolimus in hepatically impaired patients has been conducted.

f. Mucositis. Significant numbers of patients developed mucositis in the everolimus arm. However, the severity and resolution course appeared to be acceptable with necessary supportive treatment. Treatment discontinuation due to mucositis was infrequent.

g. Infection occurred in 37% of patients on the everolimus arm, which was twice as frequent as in the placebo arm. Seven percent were grade 3 and 3% were grade 4. Three percent required dose reduction or treatment termination. This may be a post marketing safety issue

Additional safety data from other studies in renal cell carcinoma patients or patients with other malignancies were reviewed in support of the safety data from the randomized study. Therefore, this reviewer believes that the clinical efficacy and safety data provided in NDA 22-334 provides a favorable risk/benefit ratio and justifies the approval of everolimus for advanced renal cell carcinoma.

1.3 Recommendations for Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations on Post Marketing Activities/Phase 4 Commitments

1. Develop and propose a 2.5 mg dosing form (tablet) to allow for proper dose reductions when everolimus needs to be co-administered with moderate CYP3A4 inhibitors. The 2.5 mg dose form should be sufficiently distinguishable from the 5 mg and the 10 mg tablets.
2. Conduct a trial in patients with severe hepatic impairment (Child Pugh Class C). This study need not be conducted in patients with cancer and a single dose evaluation will be appropriate. The protocol should be submitted prior to initiation for review and concurrence.

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

3. Submit the final, per-protocol overall survival analysis of study C2240, which was to be conducted at time of 2 years after randomization of the last patient.

2 Introduction and Regulatory Background

2.1 Product Information

Drug Established Name: everolimus

Proposed Trade Name: Afinitor

Drug Class: mTOR inhibitor

Applicant: Novartis
One Health Plaza
East Hanover, New Jersey 07936-1080

Applicant's Proposed Indication: Afinitor is indicated for the treatment of advanced renal cell carcinoma.

Dose and Regimen: 10 mg once daily at the same time every day _____

b(4)

2.2 Tables of Currently Available Treatments for Proposed Indications

The current approved and available therapies for advanced or metastatic renal cell carcinoma patients are summarized below.

Table 1: Approved and available therapies for advanced renal cell carcinoma

Agent	Description
Sorafenib	A VEGFR/Raf TK inhibitor approved for the treatment of patients with advanced renal cell carcinoma based on progression-free survival data.
Sunitinib	A multiple tyrosine kinase receptor inhibitor including VEGFR-2 approved for the treatment of advanced renal cell carcinoma patients who received at least one prior therapy. Approval was based on durable objective response and progression-free survival.
IL-2	High dose interleukin-2 therapy was approved for advanced renal cell carcinoma based on the durable complete response rate.
INF- α	Clinical studies have shown that IFN- α therapy in advanced renal cell carcinoma patients resulted in a 10-15% objective response rate and a statistically-significant overall survival advantage. However, INF- α does not have _____
bevacizumab	Bevacizumab demonstrated a 10% objective response rate and an advantage in progression-free

b(4)

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

Agent	Description
	survival compared to placebo in cytokine refractory renal cell carcinoma patients. It does not have
tensirolimus	Tensirolimus was approved first line therapy for advanced and poor risk renal cell carcinoma patients. It demonstrated a survival advantage compared to INF- α therapy and received FDA approval in 2007.

b(4)

2.3 Availability of Proposed Active Ingredient in the United States

Everolimus, presently, is not marketed in United States.

2.4 Important Safety Issues with Consideration to Related Drugs

The safety issues that should be considered with respect to other rapamycin related drugs are anemia, lymphopenia, hyperlipidemia, hyperglycemia, pneumonitis and renal dysfunction.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Nov 22, 2002: Original IND submission; was allowed to proceed on Dec 19, 2002.

May 17, 2006: EOP2 meeting, discussed indication and study design for the proposed indication.

Sep 15, 2006: Study C2240 protocol was submitted on July 28, 2006 for a special protocol assessment. FDA made recommendations on protocol deficiencies of statistical procedures, CRF contains, PRO tool/analysis, and IRC review procedures. However, the applicant initiated study C2240 before FDA completing the amendment review and, therefore, no SPA agreement was reached.

2.6 Pediatric Waiver

A pediatric waiver request for advanced renal cell carcinoma was included in this NDA submission. Renal cell carcinomas are rarely seen in pediatric patients.

2.7 Other Relevant Background Information

Two NDAs were submitted for everolimus in the past. Neither one received approval, as listed in the table below. The non-approval decision was based on both applications lacking sufficient data to support a safe and effective dosing regimen for everolimus and cyclosporine combination that would minimize renal function impairment or renal toxicity while maintaining adequate

b(4)

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 2: Previous everolimus NDA submissions

NDA numbers	Proposed indication	Status
NDA 21-628	Prophylaxis of organ rejection in allogeneic kidney and heart transplant patients.	Not approved
NDA 21-628		Not approved

b(4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

NDA 22-334 was an electronic submission filed in the FDA electronic Document Room at \CDSESUB1\EVSPROS\NDA022334. The entire NDA and relevant regulatory history were reviewed. No issue was identified that would indicate the need for an ODAC meeting.

Although the original submission was structured according to the outline agreed to by both the applicant and FDA at the time of the pre-NDA meeting, a large amount of pertinent information was missing from the submission. In addition to the pre-specified efficacy and safety update, multiple amendments were made to the original NDA submission, based upon the information requests (IR) from FDA reviewers of various disciplines, as outlined below. Because of the volume and complexity of the clinical and clinical pharmacology amendments that were submitted after Oct 1st, 2008, which was within the last 3 months of the PDUFA date, a 3 month extension was granted to ensure the NDA review process would be adequate and complete.

Table 3: NDA 22334 submission and amendments, pre-specified and requested

Submission Dates	Submitted Items
6-27-08	Original NDA submission
7-29-08	Label in correct format
8-4-08	GCP compliance statements, list of study C2240 principal investigators and contact information, recent investigator brochure, and complete highlights for the clinical pharmacology template.
8-20-08	CMC amendment
8-21-08	Newly derived datasets from the QT study 2118.
8-26-08	60 day pre-specified efficacy update (lack of details, no datasets, 2/28 cut-off)
8-29-08	CMC amendment
09-05-08	CMC amendment
09-09-08	CMC amendment
09-11-08	Clinical amendment for IRC reader concordance
9-29-08	Results of pre-specified and exploratory sensitivity analyses, investigator-assessed best objective tumor response rate for Feb-28-cut off date.
9-30-08	DMPK of study C2101, 2101A and C2102

Clinical Review

Reviewer: Qin Ryan MD, PhD

NDA 22334

Afinitor (everolimus, RAD001)

Submission Dates	Submitted Items
9-30-08	90 day pre-specified safety update (2/28/08 cut-off)
Amendments since Oct 1 st 2008 (3 months before the PDUFA date)	
10-14-08	PK information, datasets from studies C2107 and C2239. Clinical dataset clarification.
10-17-08	Additional datasets for studies 2107 and 2119 PK analyses
10-20-08	Details of central assessments and discrepancies (2300+ pages).
10-21-08	Response to DSI
10-24-08	Dataset update for studies C2101-02, C1101, C2104, C2108, and C2222.
10-24-08	Missing data analyses from both local and central review
10-31-08	Response to Information Request – Chemistry, Manufacturing and Controls
11-11-08	Summary of open label RAD001 treatment and other post study antineoplastic treatments
11-19-08	PK data update
11-26-08	PFS discrepancy analyses and relevant CRFs
12-1-08	Summary of CNS toxicity
12-4-08	Clinical Pharmacology information amendment
12-19-08	PPI revision
01-12-09	Label revision
01-20-09	Applicant response to FDA CMC inspection report
01-30-09	Statistical information to FDA IR regarding post study therapy datasets
02-04-09	Additional information to FDA 2 nd IR regarding post study therapy datasets
02-10-09	Responses to FDA IR regarding patient cross over information.
02-18-09	PFS subgroup analyses based on MSKCC prognostic score (Favorable risk, Intermediate risk, and Poor risk) and Prior VEGFR-TKI therapy (sorafenib only, sunitinib only, and sunitinb and sorafenib)
02-18-09	Discrepancies between the PFS events and patient disposition events at both data cut-offs, subgroup analyses of PFS by sex, age and region for Feb 28, 2008 cut-off.
02-20-09	FDA requested information that would support Tables 2-2 and 2-3 in the 02-18-09 amendment. This reconciled the number of deaths or PD that were in the safety report but not in the efficacy report and vice-versa.
02-23-09	Request data verification for the number of patients revived prior TKI therapy.
2-26-09	Data Monitoring Committee (IDMC) charter for study C2240, IDMC report and meeting minutes for Study C2240 interim analyses. The missing supplement table 4.
3-03-09	Data of patient disposition for ITT population for both data cut-offs.
3-09-09	Applicant-FDA meeting to clarify the differences of PD and death number among the independent, investigator and end of treatment assessments.
3-10-09	Sensitivity analyses on the PFS event definition differences.
3-11-09	Time to treatment failure analysis.
3-18-09	Teleconference regarding safety data to be included in the label.
3-19-09	Treatment emergent adverse reaction analysis under broader terms submitted.
3-23-09	Clarify the incorrect cross reference on safety data.

Source: NDA22334 submission

A single randomized study, RAD001C2240, was submitted to support the assessment of risk versus benefit for approval of everolimus for the treatment of advanced renal cell carcinoma. The following sites were identified as essential to evaluate the study quality and integrity (Table

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

below). The basis of the selection was the number of enrollment of patients and the number of PFS events. As discussed with the Division of Scientific Investigation (DSI), site 604 had been inspected a few years ago and was generally in order. Therefore, inspection was conducted for sites 513, 606 and 756. In addition, DSI also inspected the applicant's central operation for this study at One Health Plaza, East Hanover, New Jersey. The DSI inspection results are summarized in the following table.

**Appears This Way
On Original**

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afimtor (everolimus, RAD001)

Table 4: The clinical review team proposed sites and DSI inspection results

Site Number / PI	Enrollment	Events	Address	Email / Phone Number	Inspection Dates	Final Classification
513 / Robert Motzer	21 (E=12, P=9)	13 (E=5, P=8)	Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10021	motzerr@mskcc.org +1 646 422 4312	10/27 to 10/30/2008	NAI
604 / Bernard Escudier	42 (E=26, P=16)	21 (E=8, P=13)	Institut Gustave Roussy 39 rue Camille Desmoulins Villejuif 94805 France	escudier@igr.fr +33 56 142 4119	A few years ago	Passed
606 / Stephane Oudard	30 (E=24, P=6)	12 (E=7, P=5)	Hôpital Georges Pompidou 20, rue Leblanc Paris 75015 France	stephane.oudard@hop.egp.ap-hop-paris.fr +33 38 811 6344	12/08 to 12/12/2008	VAI
756 / Camillo Porta	24 (E=21, P=3)	12 (E=10, P=2)	Center IRCCS San Matteo University Hospital Piazzale Golgi, 19 Pavia 1-27100 Italy	c.porta@smatteo.pv.it +39 0382 502544	12/15 to 12/19/2008	VAI
Central Operation	Sponsor inspection		Novartis Pharmaceuticals Oncology Business Unit 180 Park Avenue Florham Park, New Jersey 01932	sibylle.jennings@novartis.com +1 862 7781196	10/29 to 11/18/2008	VAI

Key to Classifications

NAI = No deviation from regulations.
 VAI = Deviation(s) from regulations.
 OAI = Significant deviations from regulations. Data are unreliable.
 Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
 EIR has not been received from the field and complete review of EIR is pending.
 E = Everolimus
 P = Placebo
 Source: NDA22334 submission and DSI Clinical Inspection Summary by Dr. Sharon Gershon.

Reviewer: These preliminary results suggest that Study C2240 data are acceptable to use in support of this NDA.

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

3.2 Compliance with Good Clinical Practices

The applicant stated that the studies were conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

3.3 Financial Disclosures

The applicant provided spreadsheets detailing all the clinical investigators participating in studies conducted at US and non-US sites. The disclosure information was tabulated by center, principal investigator, sub-investigators, study facility and address. There were no investigators participating in study CRAD001C2240 who disclosed a conflict of interest.

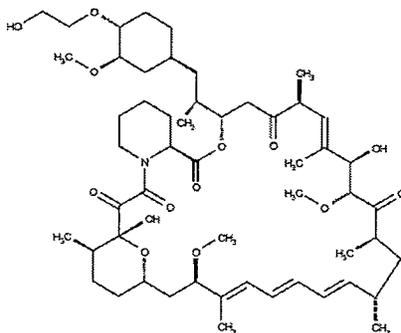
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see the CMC NDA review for details. Briefly, Afinitor (everolimus), an inhibitor of mTOR kinase inhibitor, acts as an antineoplastic agent.

The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-aza-tricyclo[30.3.1.0]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone.

The molecular formula is C₅₃H₈₃NO₁₄ and the molecular weight is 958.2. The structural formula is:



Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

Afinitor is supplied as tablets for oral administration containing 5 mg and 10 mg of everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, lactose anhydrous as inactive ingredients.

4.2 Preclinical Pharmacology/Toxicology

Please see the Pharmacology and Toxicology review for details. Briefly, administration of everolimus for up to 2 years did not indicate oncogenic potential in mice and rats up to the highest doses tested (0.9 mg/kg) corresponding respectively to 4.3 and 0.2 times the estimated clinical exposure (AUC_{0-24h}) at the recommended human dose of 10 mg/day. It should be noted that immunosuppressive agents, including one mTOR inhibitor, are carcinogenic in rodents.

Everolimus was not genotoxic in a battery of *in vitro* assays (Ames mutation test in *Salmonella*, mutation test in L5178Y mouse lymphoma cells and chromosome aberration assay in V79 Chinese hamster cells). Everolimus was not genotoxic in an *in vivo* mouse bone marrow micronucleus test at doses up to 500 mg/kg/day (1500 mg/m²/day, approximately 255-fold the recommended human dose, based on the body surface area), administered as two doses, 24 hours apart.

Based on non-clinical findings, male fertility may be compromised by treatment with everolimus. In a 13-week male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm count, and plasma testosterone levels were diminished at 5 mg/kg, which resulted in infertility at 5 mg/kg. Effects on male fertility occurred at the AUC_{0-24h} values below that of therapeutic exposure (approximately 10%-81% of the AUC_{0-24h} in patients receiving the recommended dose of 10 mg/day). After a 10-13 week non-treatment period, the fertility index increased from zero (infertility) to 65% (13/20 mated females were pregnant). Oral doses of everolimus in female rats at ≥ 0.1 mg/kg (approximately 4% the AUC_{0-24h} in patients receiving the recommended dose of 10 mg/day) resulted in increases in pre-implantation loss, suggesting the drug effect on female fertility. Everolimus crossed the placenta and was toxic to the conceptus. Therefore, men with partners of childbearing potential should use reliable contraception throughout treatment and are recommended to continue this for 3 months after the last dose of Afinitor. Women of childbearing potential should be advised to use an effective method of contraception while receiving everolimus and for up to 8 weeks after ending treatment.

4.3 Clinical Pharmacology

Please see the Clinical Pharmacology review for details.

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

4.3.1 Mechanism of Action

Everolimus is an inhibitor of mTOR (mammalian target of rapamycin), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation and inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP), downstream effectors of mTOR. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g. HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation and angiogenesis when tested by *in vitro* and/or *in vivo* models.

4.3.2 Pharmacodynamics

QT/QTc Prolongation

There is no indication of a QT/QTc prolonging effect of everolimus in single doses up to 50 mg. In a randomized, placebo-controlled, crossover study, 59 healthy subjects were administered a single oral dose of everolimus (20 mg and 50 mg) and placebo. Peak everolimus concentrations for 50 mg dose were approximately 2-fold higher than the steady-state peak concentrations following a 10 mg daily dose.

4.3.3 Pharmacokinetics

Absorption

In patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 to 70 mg everolimus. Following single doses C_{max} is dose-proportional between 5 and 10 mg. At doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady-state was achieved within two weeks following once-daily dosing.

Food effect: Based on data in healthy subjects taking 1 mg everolimus tablets, a high-fat meal reduced C_{max} and AUC by 60% and 16%, respectively. No data are available with everolimus 5 mg and 10 mg tablets.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given everolimus 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Metabolism

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself.

In vitro, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady-state following an oral dose of 10 mg daily is more than 12-fold below the K_i -values of the *in vitro* inhibition. Therefore, an effect of everolimus on the metabolism of CYP3A4 and CYP2D6 substrates is unlikely.

Excretion

No specific excretion studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabelled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces. The mean elimination half-life of everolimus is approximately 30 hours.

Patients with hepatic impairment

The average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in 8 subjects with normal hepatic function. AUC was positively correlated with serum bilirubin concentration and with prolongation of prothrombin time and negatively correlated with serum albumin concentration. The impact of severe hepatic impairment (Child-Pugh class C) has not been assessed. The average AUC of everolimus in eight subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in eight subjects with normal hepatic function. AUC was positively correlated with serum bilirubin concentration and negatively correlated with serum albumin concentration.

Patients with renal impairment

Approximately 5% of total radioactivity was excreted in the urine following a 3-mg dose of [14 C]-labeled everolimus. In a population pharmacokinetic analysis which included 168 patients with advanced cancer, no significant influence of creatinine clearance (25 – 178 mL/min) was detected on oral clearance (CL/F) of everolimus.

Effects of Age and Gender

In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance and patient age or gender.

Ethnicity

Based on a cross-study comparison, Japanese patients (n = 6) had on average exposures that were higher than non-Japanese patients receiving the same dose. Also, oral clearance (CL/F) is on average 20% higher in Black patients than in Caucasians. The significance of these differences on the safety and efficacy of everolimus in Japanese or Black patients has not been established.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The clinical studies relevant to the efficacy and safety of the proposed indication are tabulated below.

Table 5: Clinical studies related to the proposed indication

Study	Study design, objective, and population	Efficacy endpoints	No of patients	
			Everolimus 10 mg	Total
Randomized study				
C2240	Randomized, double-blind, placebo-controlled, efficacy and safety study in patients with mRCC after failure of VEGFr-TKI therapy	Primary: PFS Secondary: ORR, OS, QoL	272	410
Dose selection trials				
C2101 Part 1/ C2102	Phase-I dose-escalation study in patients with advanced solid tumors	ORR	33	92
C2107	Phase-I investigation of safety, tolerability, and molecular pharmacodynamic effects in patients with advanced solid tumors	ORR	12	55
C1101	Phase-I dose-escalation study in Japanese patients with advanced solid tumors	ORR, PFS	3	9

PFS = progression-free survival, ORR = overall response, OS = overall survival, and QoL = quality of life.
 Source: NDA 22334, CTD 2.3.7, section 1.2.

5.2 Review Strategy

This NDA clinical review was primarily based on the efficacy and safety data of study C2240, which are relevant to the proposed indication. Safety data from three other studies were also reviewed. The electronic submission, with the CSRs, and other relevant portions of study C2240 were reviewed and analyzed. The key review materials and activities are outlined below:

- Electronic submission of the NDA;
- Relevant published literature;
- Relevant submissions in response to medical officer's questions;
- Sponsor presentation slides to FDA on July 28, 2008; and
- Major efficacy and safety analyses reproduced or audited using the SAS datasets.

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

5.3 Discussion of Individual Studies

5.3.1 Study C2240

Study C2240 protocol and its amendments are summarized below:

5.3.1.1 Study ID and Title:

C2240: A randomized, double-blind, placebo-controlled, multicenter phase III study to compare the safety and efficacy of RAD001 plus best supportive care (BSC) versus BSC plus placebo in patients with metastatic carcinoma of the kidney which has progressed on VEGF receptor tyrosine kinase inhibitor therapy

5.3.1.2 Study Objective

Primary:

To compare progression-free survival (PFS) in patients who received RAD001 plus best supportive care (BSC) versus patients who received matching placebo plus BSC.

Secondary:

- To compare the overall survival for patients who received RAD001 plus BSC versus matching placebo plus BSC
- To compare the objective response rate and duration in patients who receive RAD001 plus BSC versus matching placebo plus BSC.
- To describe the safety profile of RAD001 when compared to placebo
- To assess disease related symptoms and overall quality of life (QoL) in patients treated with RAD001 plus BSC and to compare these patients reported outcomes to those of the matching placebo plus BSC treatment group.
- To describe the pharmacokinetics of RAD001 in patients with renal cell cancer.
- To explore the relationships between RAD001 blood levels and efficacy/safety endpoints.

5.3.1.3 Protocol Design:

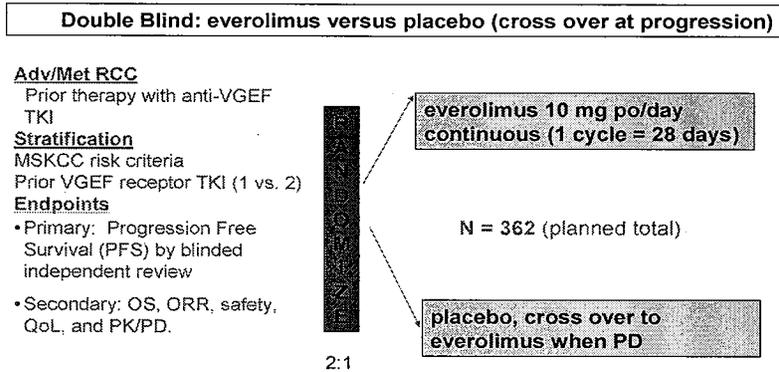
This was a randomized, double-blind, placebo-controlled, multicenter study using a group sequential design with two interim analyses (IAs). The final analysis was to be performed when a total of 290 PFS events (per independent central radiological review) were observed in the intent-to-treat (ITT) population. The first and second interim analyses were planned after observing 30% and 60%, of the required number of PFS events, respectively. Both interim analyses allowed stopping for lack of efficacy (futility) and for outstanding efficacy.

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

Patients were to be randomized in a 2:1 (2 to RAD001, 1 to matching placebo) ratio. Prior to randomization, patients were to be stratified according to the Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria (favorable vs. intermediate vs. poor risk groups) and prior anticancer therapy (one VEGF receptor tyrosine kinase inhibitor vs. two VEGF receptor tyrosine kinase inhibitors).

The disease status was to be assessed every two months (every two 30-day cycles). At the time of disease progression, patients were to be unblinded and the patients on the BSC arm were to be given the choice of receiving RAD001 on a separate treatment protocol.

Figure 1: Study C2240 design



Reviewer: Prior to study initiation, the protocol was submitted to FDA for a special protocol assessment (SPA) and deficiencies were commented to the applicant. Study C2240 started before a SPA agreement was reached.

Although the ideal primary endpoint would be OS, due to no mTor inhibitor being available at the time of the study design, cross over was designed for patients on the placebo arm to have a chance to receive everolimus, which would confound the OS result. Therefore, PFS was the primary endpoint agreed to by FDA.

5.3.1.4 Eligibility Criteria

Inclusion

- Age > 18 years old
- Histologically confirmed metastatic clear cell RCC.

Clinical Review

Reviewer: Qin Ryan MD, PhD

NDA 22334

Afinitor (everolimus, RAD001)

- Progression on or within 6 months of stopping treatment with a VEGF receptor tyrosine kinase inhibitor (sunitinib and/or sorafenib).
- Must have received prior therapy with cytokines and/or VEGF-ligand inhibitors.
- Prior vaccine therapy in the adjuvant setting would be acceptable.
- At least one measurable lesion (PE, CT or MRI) at baseline as per the RECIST criteria.
- Karnofsky Performance Status \geq 70%.
- Adequate bone marrow function: ANC $> 1.5 \times 10^9/L$, Platelets $> 100 \times 10^9/L$, Hb > 9 g/dL.
- Adequate liver function: serum bilirubin: $< 1.5 \times$ ULN, ALT and AST $< 2.5 \times$ ULN. Patients with known liver metastases: AST and ALT $< 5 \times$ ULN.
- Adequate renal function: serum creatinine $< 1.5 \times$ ULN.
- Life expectancy > 6 months.
- Women of childbearing potential must have had a negative serum or urine pregnancy test 48 hours prior to the administration of the first study treatment.
- Patients who provide written informed consent obtained according to local guidelines

Exclusion

- Patients currently receiving chemotherapy, immunotherapy, or radio-therapy or who have received these within 4 weeks of study entry.
- Patients who have previously received mTOR inhibitors.
- Patients with a known hypersensitivity to RAD001 (everolimus) or other rapamycins (sirolimus, temsirolimus) or to its excipients.
- Patients with untreated CNS metastases or who are neurologically unstable despite treatment of the CNS metastases. Patients with treated CNS metastases, who were neurologically stable off of corticosteroids, were eligible to enter study.
- Patients receiving chronic treatment with corticosteroids or another immunosuppressive agent.
- Patients with a known history of HIV seropositivity.
- Patients with an active, bleeding diathesis or on oral anti-vitamin K medication (except low dose coumadin).
- Patients who have any severe and/or uncontrolled medical conditions such as:
 - unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction < 6 months prior to randomization, serious uncontrolled cardiac arrhythmia.
 - uncontrolled diabetes as defined by fasting serum glucose $> 1.5 \times$ ULN.
 - any active or uncontrolled severe infection.
 - cirrhosis, chronic active hepatitis or chronic persistent hepatitis.
 - severely impaired lung function
- Patients who have a history of another primary malignancy < 3 years prior to entry, with the exception of non-melanoma skin cancer, and carcinoma in situ of the uterine cervix.
- Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods.

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

- Patients who are using other investigational agents or who had received investigational drugs < 4 weeks prior to randomization.

5.3.1.5 Treatment Plan

All patients were to be treated with RAD001 10 mg po daily or matching placebo continuously until disease progression (by the RECIST criteria) or unacceptable toxicity, death or discontinuation from the study for any other reason. A treatment cycle was 28 days.

5.3.1.6 Treatment Modifications

The dose reduction schema and indications are summarized in the tables below.

Table 6: Dose modification guidelines:

Dose level	Dose and schedule
0 (starting dose)	10 mg daily
Decrease 1 dose level	5 mg daily
Decrease 2 dose levels	5 mg every other day

Source: Study C2240 protocol

Table 7: Toxicity management:

Toxicity	Actions
Non-hematological toxicity	
Grade 2 (except pneumonitis)*	If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to the patient, interrupt RAD001 until recovery to grade ≤ 1 , then reintroduce RAD001 at the same dose. If the grade 2 event recurs, interrupt RAD001 until recovery to grade ≤ 1 , then reintroduce RAD001 at the lower dose level.
Grade 3 (except hyperlipidemia)	Interrupt RAD001 until recovery to grade ≤ 1 , then reintroduce RAD001 at a lower dose level. For pneumonitis consider the use of a short course of corticosteroids.
Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia)	Should be managed using standard medical therapies.
Grade 4	Discontinue RAD001.
Hematological toxicity	
Grade 2 Thrombocytopenia (platelets < 75, $\geq 50 \times 10^9/L$)	Interrupt RAD001 until recovery to grade ≤ 1 ($>75 \times 10^9/L$), then reintroduce RAD001 at the initial dose. If grade 2 thrombocytopenia recurs, interrupt RAD001 until recovery to grade ≤ 1 , then reintroduce RAD001 at the lower dose level.
Grade 3 Thrombocytopenia (platelets < 50, $> 25 \times 10^9/L$)	Interrupt RAD001 until recovery to grade ≤ 1 (platelets $> 75 \times 10^9/L$). Then resume RAD001 at one dose level lower. If grade 3 thrombocytopenia recurs, discontinue RAD001.
Grade 4 Thrombocytopenia (platelets < $25 \times 10^9/L$)	Discontinue RAD001.
Grade 3 Neutropenia (neutrophils < 1, $> 1.5 \times 10^9/L$)	Interrupt RAD001 until recovery to grade ≤ 1 (neutrophils $> 1.5 \times 10^9/L$).

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Toxicity	Actions
>0.5 x10 ⁹ /L)	10 ⁹ /L), then resume RAD001 at the initial dose. If grade 3 ANC recurs, hold RAD001 until the ANC > 1.5 x 10 ⁹ /L, then resume RAD001 dosing at a lower dose level. Discontinue the patient from study therapy for a third episode of grade 3 neutropenia.
Grade 4 Neutropenia (neutrophils > 0.5 x10 ⁹ /L)	Interrupt RAD001 until recovery to grade ≤ 1 (neutrophils > 1.5 x 10 ⁹ /L). Then resume RAD001 at the lower dose level. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue RAD001.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt RAD001 until resolution of fever and neutropenia to grade ≤ 1. Hold further RAD001 until the ANC > 1,500/mm ³ and fever has resolved, then resume RAD001 at a lower dose level. If febrile neutropenia recurs, discontinue RAD001.
Grade 4 febrile neutropenia (life-threatening)	Discontinue RAD001.
Any hematological or non-hematological toxicity requiring interruption for ~ 3 weeks	Discontinue RAD001

* Both asymptomatic radiological changes (grade 1) and symptomatic non-infectious pneumonitis (grade 2 not interfering with activities of daily living, or grade 3, interfering with activities of daily living and oxygen indicated) have been noted in patients receiving RAD001 therapy. Non-infectious pneumonitis had been associated with RAD001 and other mTOR inhibitors (Atkins 2004). In order to monitor for asymptomatic (grade 1) non-infectious pneumonitis, a chest x-ray or CT scan was required in addition to the bi-monthly CT or MR tumor examinations. Additional chest x-rays or CT scans were to be performed when clinically necessary. If non-infectious pneumonitis developed, a consultation with a pulmonologist was to be considered. If the patient develops grade 3 pneumonitis, treatment with RAD001 was to be interrupted and the patient was to be treated as medically indicated (short course corticosteroids, oxygen, etc).
 Source: Study C2240 protocol

5.3.1.7 Efficacy Assessment

The primary endpoint was PFS, defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause. A patient who had not progressed or died at the date of the analysis cut-off or when he/she received any further anti-cancer therapy was to have his/her PFS censored at the time of the last tumor assessment before the cut-off or the anti-cancer therapy date, whichever is first. For the primary analysis progression-free survival was to be based on independent central radiological data according to the RECIST Criteria.

Reviewer: Potential bias may be introduced if there is an imbalance between the two arms in the numbers of patients who received any further anti-cancer therapy and had their PFS censored at the time of the last tumor assessment before the cut-off or the anti-cancer therapy date.

The primary analysis of PFS was to be based on an independent central radiology review. All CT scans, MRIs and bone scans obtained at baseline, during the treatment period and during the follow-up period were to be sent to the independent Central Radiologist.

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

Patient unblinding information was not to be disclosed to the central radiology reviewers. All patients receiving open-label treatment with RAD001 continued to receive safety and efficacy assessments (as in the blinded portion of the trial).

Secondary efficacy endpoints:

- Overall survival (OS): After discontinuation of RAD001 or matching placebo, all patients were to be followed up every month for survival up to 2 years after the last patient was randomized to the study.
- Objective response rate (ORR): Tumor response and progression were to be assessed using the RECIST Criteria. Tumor measurements by a CT scan or MRI were to be performed at screening and repeated every 2 months (± 1 week) and at discontinuation of the study drug (± 1 week). A partial or a complete response warranted a confirmation no sooner than 4 weeks after its observation. Any patient who discontinued RAD001 or matching placebo for any reason other than disease progression continued to undergo tumor assessments until the patient had documented disease progression.
- Patient reported outcomes (disease-related symptoms): FKSI-DRS questionnaire.
- Patient reported outcome on overall quality of life: EORTC QLQ-C30 questionnaire

IDMC: The Independent Data Monitoring Committee (IDMC) was an independent (external) group consisting of a least 2 clinicians and 1 statistician. The IDMC was to be constituted prior to the randomization of the first patient. Reviews of safety data were to be ongoing and specific reviews of efficacy data were to be performed at the time of interim analyses (IAs).

5.3.1.8 Safety Monitoring

Safety endpoints: Incidence of adverse events (AEs), serious adverse events, changes from baseline in vital signs and laboratory results (hematology, blood chemistry and urinalysis) were all monitored, recorded and managed. All patients were to have a follow-up visit scheduled 28 days after the last dose of the study drug to assess AEs and SAEs that occurred after discontinuation from the study. All AEs and related information were coded using MedDRA version 10.1 terminology.

5.3.1.9 Analytic Plan

A 1-sided sequential log rank score test with a cumulative type I error of $\alpha = 0.025$ and a cumulative power $1 - \beta = 90\%$ was used for the 3-look group sequential plan. Assuming a hazard ratio of 1.5 (corresponding to a median PFS of 3 months for the placebo plus BSC and 4.5

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

months for RAD001 plus BSC), and using a 2:1 randomization to RAD001 vs. placebo, a total of 290 PFS events were required.

Considering a recruitment time of 16 months and an additional follow up of 5 months, a total of 362 patients were to be enrolled. This number included the assumption that about 10% of patients would be lost to follow up during the study.

The final analysis was to be performed when approximately 290 PFS events, as per independent central radiological review, were observed in the intent-to-treat (ITT) population. The first interim analysis was planned after observing 30% and the second after observing 60% of the number of events required for the final statistical analysis of PFS. Both interim analyses allowed stopping for lack of efficacy (futility) or outstanding efficacy.

5.3.1.10 Study C2240 Landmark and Amendments

The landmark and amendment of Study C2240 are listed in the table below. No change of planned analyses occurred.

Table 8: Study C2240 landmark and amendments

Date	Event
April 7, 2006 to July 28, 2006	SPA review, FDA concerns were communicated to the applicant.
Oct 19, 2006 (prior to 1 st patient enrolled)	Amendment 1: Modify the inclusion criterion: "Patients with a life expectancy \geq 6 months. Life expectancy should be judged in relation to other factors determining patient eligibility such as laboratory results, Karnofsky Performance Status etc." to patients with a life expectancy \geq 3 months.
Nov 28, 2006	Study C2240 started and first patient screened
Feb 28, 2007 (when 58 patients, 18%, enrolled, before any unblinding)	Amendment 2: <ul style="list-style-type: none"> • addition of RAD001 pharmacokinetics in Japanese healthy volunteers; • modification of inclusion criteria: patients must have confirmation of clear cell RCC or a component of clear cell RCC; patients with skin lesions reported as target lesions were to have lesions documented by color photography and a measuring device; pregnancy test to be performed within 7 days of first study drug treatment instead of within 48 hours; • modification of exclusion criteria to add information regarding the wash-out period of sunitinib and sorafenib, and to permit entry of patients with treated CNS metastases who were neurologically stable and off of corticosteroids for more than 6 months; • added that if study treatment was interrupted for more than 14 days, for any reason other than toxicities suspected to be related to RAD001, the patient was to discontinue from the study, and tumor evaluations were to be continued until the start of new anticancer therapy; • revision of text regarding treatment blinding: because of the unblinding of a subset of patients at the first occurrence of disease progression, members of the Novartis clinical team will become unblinded to the individual patient's treatment during the conduct of the trial; the independent central radiologists remained blinded to the identity of the treatment assignment; • modification of the study follow-up requirements to allow for collection of tumor assessments (after the local radiologist and investigator declared disease progression) until the time the patient started new anticancer therapy; • addition of procedure for handling Serious Adverse Event (SAE) reports in Japan;

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Date	Event
	<ul style="list-style-type: none"> • clarification that the study consisted of core and extension phases instead of a core and an extension study; • revisions of the statistical methods section of the protocol; • replacement of protocol Post-Text Supplement 1 (RECIST Criteria) with RECIST Criteria Version 2 (18-Jan-2007).
Mar 8, 2007	The amendment of the study C2240 protocol and CRFs, and IRC charter were submitted for a second SPA review.
Apr 18, 2007	FDA stated that the study C2240 was no longer qualifies for a special protocol assessment and potential agreement since the study had already started.
Oct 15, 2007	2 nd interim analysis
Feb 28, 2008	Early termination date (efficacy update cut off date) IDMC advised the applicant that Study C2240 should be stopped and that all placebo arm patients should be permitted to cross over.

Source: NDA 22334 submission

5.3.2 Other Supportive Studies: 2201, 2202, 2207 and 1101.

All these studies were single arm, dose escalation studies conducted in advanced and refractory solid tumor patients. The data only provides supportive information for the safety evaluation.

6 Review of Efficacy

6.1 Indication

Afinitor is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma after disease progression following treatment with sunitinib or sorafenib.

6.1.1 Methods

As described in Sections 5.1 and 5.2, the efficacy review is based on study C2240 data.

6.1.2 Demographics

The study C2240 analysis populations are summarized below.

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 9: Study C2240 patient populations

Analysis population	Oct 15, 2007 cut-off			Feb 28, 2008 cut-off		
	RAD001 N=272 (%)	Placebo N=138 (%)	All patients N=410 (%)	RAD001 N=277 (%)	Placebo N=139 (%)	All patients N=416 (%)
ITT	272 (100)	138 (100)	410 (100)	277 (100)	139 (100)	416 (100)
Safety	269 (98.9)	135 (97.8)	404 (98.5)	274 (98.9)	137 (98.5)	411 (98.8)
Safety (open-label)	1 (0.4)	79 (57.2)	80 (19.5)	-	-	-

Source: Study C2240 report

As shown below, baseline characteristics and demographics of patients enrolled in study C2240 were similar between the two arms.

Table 10: Study C2240 patient demographics (ITT)

Demographics		Cut-off date: Oct 15, 2007			Cut-off date: Feb 28, 2008		
		RAD001 N=272 (%)	Placebo N=138 (%)	All patients N=410 (%)	RAD001 N=277 (%)	Placebo N=139 (%)	All patients N=416 (%)
Gender	Female	60 (22.1)	33 (23.9)	93 (22.7)	61 (22.0)	33 (23.7)	94 (22.6)
	Male	212 (77.9)	105 (76.1)	317 (77.3)	216 (78.0)	106 (76.3)	322 (77.4)
Age (years)	Mean	60.61	59.34	60.18	60.66	59.27	60.20
Age group	< 65	162 (59.6)	97 (70.3)	259 (63.2)	165 (59.6)	98 (70.5)	263 (63.2)
	≥ 65	110 (40.4)	41 (29.7)	151 (36.8)	112 (40.4)	41 (29.5)	153 (36.8)
Race	Asian	11 (4.0)	10 (7.2)	21 (5.1)	16 (5.9)	11 (8.0)	27 (6.6)
	Black	2 (0.7)	3 (2.2)	5 (1.2)	2 (0.7)	3 (2.2)	5 (1.2)
	Caucasian	246 (90.4)	121 (87.7)	367 (89.5)	246 (90.1)	121 (87.7)	367 (88.2)
	Missing	4 (1.5)	1 (0.7)	5 (1.2)	1 (0.4)	0 (0.0)	1 (0.2)
	Native American	1 (0.4)	0 (0.0)	1 (0.2)	8 (2.9)	3 (2.2)	11 (2.7)
	Other	8 (2.9)	3 (2.2)	11 (2.7)	4 (1.4)	1 (0.7)	5 (1.2)
BMI (kg/m ²)	Mean	26.40	26.17	26.32	26.31	26.22	26.28
Karnofsky PS	100	75 (27.6)	40 (29.0)	115 (28.0)	78 (28.2)	41 (29.5)	119 (28.6)
	90	98 (36.0)	53 (38.4)	151 (36.8)	98 (35.4)	53 (38.1)	151 (36.3)
	80	70 (25.7)	30 (21.7)	100 (24.4)	72 (26.0)	30 (21.6)	102 (24.5)
	70	28 (10.3)	15 (10.9)	43 (10.5)	28 (10.1)	15 (10.8)	43 (10.3)
	Missing	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.4)	0 (0.0)	1 (0.2)
MSKCC risk group	Favorable risk	79 (29.0)	39 (28.3)	118 (28.8)	81 (29.2)	39 (28.1)	120 (28.9)
	Intermediate risk	153 (56.3)	78 (56.5)	231 (56.3)	156 (56.3)	79 (56.8)	235 (56.5)
	Poor risk	40 (14.7)	21 (15.2)	61 (14.9)	40 (14.4)	21 (15.1)	61 (14.7)

Source: Study C2240 report

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

Table 11: Study C2240 patient characteristics (ITT)

Characteristics	Cut-off date: Oct 15, 2007			Cut-off date: Feb 28, 2008		
	RAD001 N=272 (%)	Placebo N=138 (%)	All N=410 (%)	RAD001 N=277 (%)	Placebo N=139 (%)	All N=416 (%)
Primary site of cancer						
Kidneys	272 (100)	137 (99.3)	409 (99.8)	277 (100)	138 (99.4)	415 (99.8)
Other	0	1 (0.7)	1 (0.2)	0	1 (0.6)	1 (0.2)
Histology/Cytology						
Clear cell adenocarcinoma	261 (96.0)	132 (95.7)	393 (95.9)	263 (95.9)	131 (95.5)	394 (95.4)
Other	11 (4.0)	6 (4.3)	17 (4.1)	11 (4.0)	6 (4.2)	17 (4.0)
Histological grade						
Well differentiated	21 (7.7)	10 (7.2)	31 (7.6)	22 (8.0)	10 (7.3)	32 (7.8)
Moderately differentiated	56 (20.6)	31 (22.5)	87 (21.2)	57 (20.2)	31 (22.6)	88 (21.4)
Poorly differentiated	83 (30.5)	40 (29.0)	123 (30.0)	83 (30.3)	41 (29.9)	124 (30.2)
Undifferentiated	17 (6.3)	9 (6.5)	26 (6.3)	17 (6.2)	9 (6.5)	26 (6.3)
Unknown	95 (34.9)	48 (34.8)	143 (34.9)	95 (34.7)	46 (33.6)	141 (34.3)
Time since initial diagnosis						
< 6 months	6 (2.2)	3 (2.2)	9 (2.2)	5 (2.0)	3 (2.2)	8 (1.9)
>6 to < 12 months	18 (6.6)	5 (3.6)	23 (5.6)	18 (6.6)	5 (3.7)	23 (5.6)
>12 to <24 months	68 (25.0)	28 (20.3)	96 (23.4)	69 (24.5)	27 (19.4)	94 (22.9)
>24 months	180 (66.2)	98 (71.0)	278 (67.8)	184 (62.7)	102 (73.4)	286 (76.3)
Missing	0	4 (2.9)	4 (1.0)	3 (1.3)	2 (1.3)	5 (1.2)
MSKCC prognostic score						
Favorable risk	79 (29.0)	39 (28.3)	118 (28.8)	81 (29.2)	39 (28.5)	120 (27.1)
Intermediate risk	153 (56.3)	78 (56.5)	231 (56.3)	156 (56.4)	79 (56.7)	235 (55.1)
Poor risk	40 (14.7)	21 (15.2)	61 (14.9)	40 (14.2)	21 (14.3)	61 (24.9)
Most recent secondary sites						
CNS	9 (3.3)	5 (3.6)	14 (3.4)	10 (3.5)	4 (2.8)	14 (3.3)
Bone	101 (37.1)	46 (33.3)	147 (35.9)	104 (37.9)	46 (33.5)	120 (32.6)
Skin	6 (2.2)	5 (3.6)	11 (2.7)	6 (2.1)	5 (3.5)	11 (3.0)
Lung	212 (77.9)	108 (78.3)	320 (78.0)	214 (78.0)	108 (78.6)	322 (78.3)
Pleura	26 (9.6)	16 (11.6)	42 (10.2)	26 (9.4)	15 (10.8)	41 (9.9)
Liver	98 (36.0)	47 (34.1)	145 (35.4)	99 (36.0)	48 (34.9)	137 (35.5)
Lymph node	149 (54.8)	82 (59.4)	231 (56.3)	153 (55.6)	82 (59.7)	235 (57.6)
Retroperitoneal mass	49 (18.0)	15 (10.9)	64 (15.6)	49 (17.8)	15 (10.7)	64 (15.4)
Pleural effusion	17 (6.3)	10 (7.2)	27 (6.6)	17 (6.1)	10 (7.2)	27 (6.9)
Ascites	5 (1.8)	3 (2.2)	8 (2.0)	5 (1.6)	3 (2.0)	8 (1.9)
Other	142 (52.2)	69 (50.0)	211 (51.5)	144 (52.4)	70 (51.0)	214 (51.5)

Source: Study C2240 report

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

The therapies that patients on Study C2240 received prior to the study entry are summarized below.

Table 12: Prior therapies on Study C2240 patients (ITT)

	Cut-off date: Oct 15, 2007		Cut-off date: Feb 28, 2008	
	RAD001 N=272 (%)	Placebo N=138 (%)	RAD001 N=277 (%)	Placebo N=139 (%)
Prior antineoplastic therapies				
Any prior antineoplastic therapy	272 (100)	138 (100)	277 (100)	139 (100)
Any prior radiotherapy	83 (30.5)	38 (27.5)	84 (30.7)	37 (27.0)
Any prior surgery	262 (96.3)	131 (94.9)	266 (97.1)	131 (95.6)
Any prior medication	272 (100)	138 (100)	277 (100)	139 (100)
Systemic therapy type				
Chemotherapy	36 (13.2)	22 (15.9)	36 (13.0)	22 (16.0)
Hormone therapy	5 (1.8)	5 (3.6)	5 (1.7)	5 (3.5)
Immunotherapy	174 (64.0)	91 (65.9)	178 (65.0)	92 (67.2)
Targeted therapy	271 (99.6)	138 (100)	273 (99.5)	136 (99.2)
Other	15 (5.5)	4 (2.9)	15 (5.5)	4 (2.8)
Prior TKIs				
Either	272 (100)	138 (100)	277 (100)	139 (100)
Sorafenib	128 (47.1)	63 (45.7)	81 (29.2)	43 (30.9)
Sunitinib	163 (59.9)	99 (71.7)	124 (44.8)	60 (43.2)
Both	71 (26.1)	36 (26.1)	72 (26.0)	36 (25.9)

Source: Study C2240 report

Reviewer: The patient demographics, characteristics, and exposure to prior therapy appear to be balanced between the two arms.

6.1.3 Patient Disposition

Study C2240 patient disposition, at both cut-off dates, is summarized as below.

**Appears This Way
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Clinical Review
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 NDA 22334
 Afinitor (everolimus, RAD001)

Table 13: Study C2240 patient disposition at both cut off dates (Oct 15, 2007 and Feb 28, 2008, ITT)

Disposition	Second interim analysis Data cut-off: 15-Oct-2007		Safety Update Data cut-off: 28-Feb-2008	
	Everolimus N=272 (%)	Placebo N=138 (%)	Everolimus N=277 (%)	Placebo N=139 (%)
Ongoing	140 (52.0)	29 (21.5)	75 (27.4)	6 (4.4)
Discontinued	132 (48.0)	106 (78.5)	199 (72.6)	131 (95.6)
Cross over	1 (0.4)*	79 (57.2)	3 (1.1)*	106 (76.3)
Main reason for discontinuation				
Disease progression	85 (31.3)	100 (72.5)	137 (49.5)	124 (89.2)
Death	7 (2.6)	3 (2.2)	7 (2.5)	4 (2.9)
Adverse event(s)	26 (9.6)	2 (1.4)	36 (13.0)	2 (1.4)
Patient withdrew consent	7 (2.6)	2 (1.4)	13 (4.7)	2 (1.4)
Lost to follow-up	2 (0.7)	0	4 (1.4)	0
Protocol violation	2 (0.7)	1 (0.7)	2 (0.7)	1 (0.7)
Administrative problems	1 (0.4)	0	2 (0.7)	0
Abnormal laboratory value(s)	0	0	1 (0.4)	0

Patient was randomized to everolimus arm, but received open label drug.

Source: Study C2240 report

Reviewer: The numbers for PD and death in the patient disposition summary are different from the number of PD and death events for the investigator assessed PFS. As per applicant, the patient disposition was based on investigator assessments at the end of the treatment. However, patients could still be on study and the PFS follow up continued until the primary analysis defined event had occurred.

6.1.4 Analysis of Primary Endpoint(s): PFS

The primary analyses using either the Oct 15, 2007 or Feb 28, 2008 cut-off dates are summarized below. The analyses were conducted by the applicant and verified by the FDA statistical reviewer, Dr. Somesh Chattopadhyay.

**Appears This Way
On Original**

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 14: Study C2240 primary analysis – PFS (ITT)

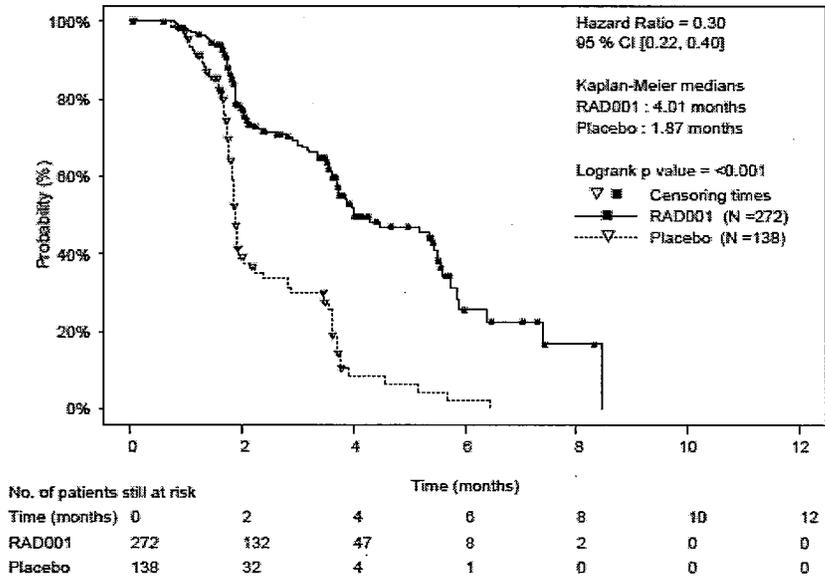
PFS	Oct 15 2007 cut-off N = 410						Feb 25 2008 cut-off N = 416					
	IRC		INV		IRC		INV		IRC		INV	
	R (n=272)	P (n=138)	R (n=272)	P (n=138)	R (n=277)	P (n=139)	R (n=277)	P (n=139)	R (n=277)	P (n=139)	R (n=277)	P (n=139)
Total Events (%)	101 (37)	90 (65)	111 (41)	105 (76)	155 (56)	111 (80)	170 (61)	129 (93)	170 (61)	111 (80)	129 (93)	129 (93)
Death (%)	16 (6)	8 (6)	14 (5)	7 (5)	21 (8)	8 (6)	18 (7)	8 (7)	18 (7)	8 (6)	8 (7)	8 (7)
Progression (%)	85 (31)	82 (59)	97 (36)	98 (71)	134 (48)	103 (74)	152 (55)	121 (87)	152 (55)	103 (74)	121 (87)	121 (87)
Censored (%)	171 (63)	48 (35)	161 (59)	33 (24)	122 (44)	20 (20)	107 (39)	10 (7)	107 (39)	20 (20)	10 (7)	10 (7)
Median PFS, months	4.01	1.87	4.57	1.84	4.90	1.87	5.49	1.87	5.49	1.87	1.87	1.87
Improvement in median PFS	2.14		2.73		3.02		3.62		3.02		3.62	
HR [95% CI]	0.30 [0.23, 0.41]		0.31 [0.24, 0.41]		0.34 [0.26, 0.44]		0.33 [0.26, 0.41]		0.34 [0.26, 0.44]		0.33 [0.26, 0.41]	
p-value	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001	

PFS = Time to Tumor Progression + death, IRC = Independent Reviewer Analysis, INV = Investigators Analysis, R = RAD001, P = Placebo
 Source: Study C2240 report

Reviewer: Although the improvement in PFS by IRC assessment is less than that of the investigators, more subjects were censored in the IRC PFS analysis than in the INV PFS analysis. This suggests that there was missing data in the IRC assessments.

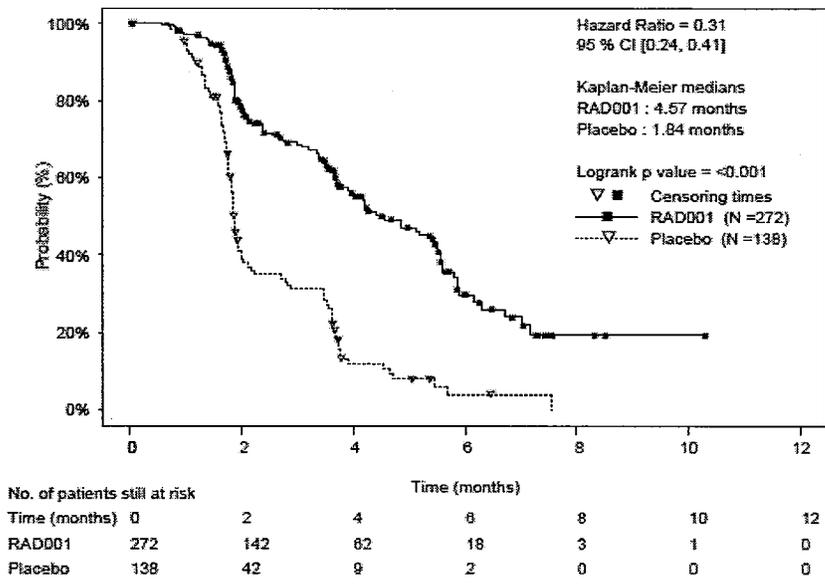
Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Figure 2: Kaplan-Meier estimation of PFS per IRC assessments (cut off date: Oct 15, 2007)



Source: Study C2240 report

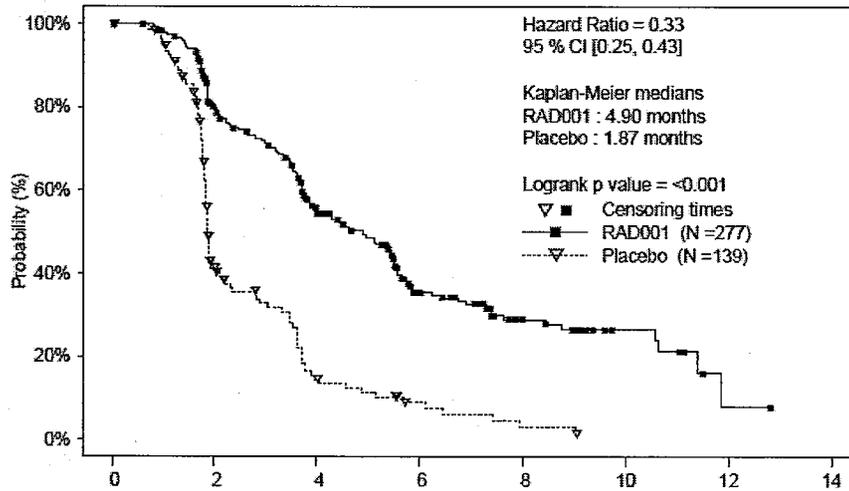
Figure 3: Kaplan-Meier estimation of PFS per investigators assessments (cut off date: Oct 15, 2007)



Source: Study C2240 report

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

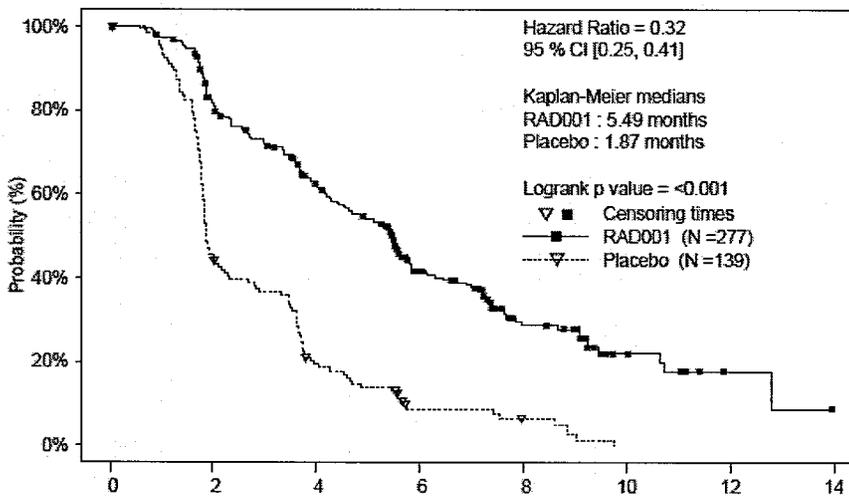
Figure 4: Kaplan-Meier estimation of PFS per IRC assessments (cut off date: Feb 25, 2008)



No. of patients still at risk		Time (months)						
Time (months)	0	2	4	6	8	10	12	14
RAD001	277	192	115	51	26	10	1	0
Placebo	139	47	15	6	2	0	0	0

Source: Study C2240 report

Figure 5: Kaplan-Meier estimation of PFS per investigators assessments (cut off date: Feb 25, 2008)



No. of patients still at risk		Time (months)						
Time (months)	0	2	4	6	8	10	12	14
RAD001	277	210	149	76	33	11	2	0
Placebo	139	62	25	8	5	0	0	0

Source: Study C2240 report

6.1.5 Prespecified Analysis of Secondary Endpoints(s)

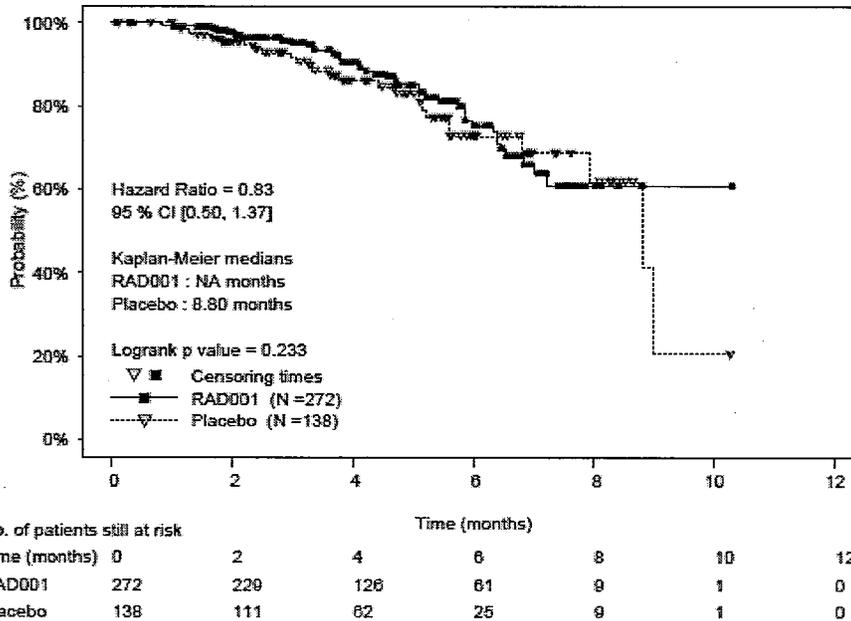
6.1.5.1 Overall Survival (OS)

Table 15: Study C2240 prespecified secondary analysis: OS (ITT)

	Oct 15 2007 cut-off N = 410		Feb 25 2008 cut-off N = 416	
	R (n=272)	P (n=138)	R (n=277)	P (n=139)
Death Events (%)	42 (15.4%)	26 (18.8%)	85 (30.7%)	48 (34.5%)
Censored (%)	230 (84.6)	112 (81.2)	192 (69.3)	91 (65.5)
Median OS, months	n/a	8.8	n/a	13
Improvement in median OS	n/a		n/a	
HR [95% CI]	0.83 [0.50, 1.37]		0.82 [0.57, 1.17]	
p-value	<0.233		<0.137	

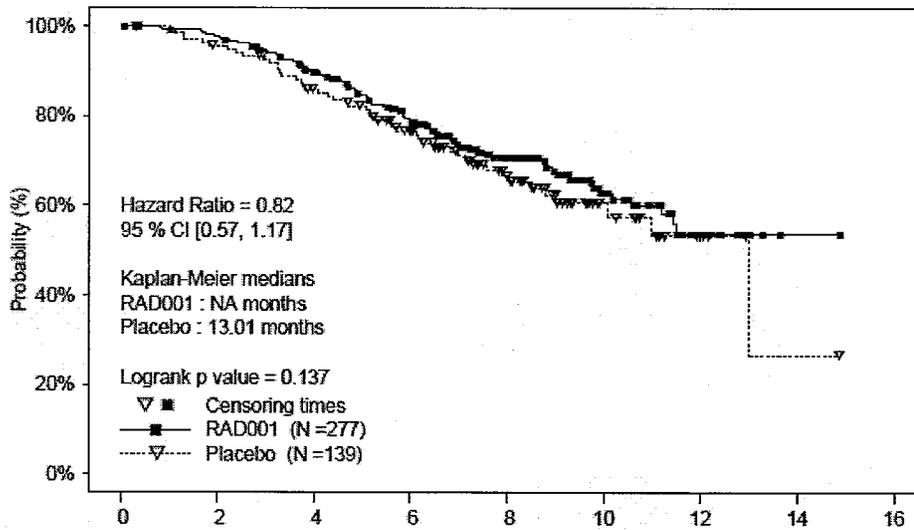
OS = Time from randomization to death, R = RAD001, P = Placebo
 Source: Study C2240 report

Figure 6: Study C2240 prespecified secondary analysis: OS-Kaplan-Meier Estimation (ITT, Oct 15, 2007 cut-off)



Source: Study C2240 report

Figure 7: Study C2240 prespecified secondary analysis: OS-Kaplan-Meier Estimation (ITT, Feb 28, 2008 cut-off)



Time (months)	No. of patients still at risk								
	0	2	4	6	8	10	12	14	16
RAD001	277	267	236	191	108	52	11	1	0
Placebo	139	131	114	91	53	19	6	1	0

Source: Study C2240 report

Reviewer: At the data cut-off for the final PFS analysis, overall survival (OS) was not statistically significantly different in favor of the everolimus arm (HR = 0.82, p value = 0.137). However, the median OS for the everolimus arm had not yet been reached while the median OS and for the placebo arm was 8.8 months. At the time of the analysis, 31% of deaths had occurred on the everolimus arm and 35% on the placebo arm. As a result of the study crossover design and early termination, 109 of 139 patients in the placebo arm received everolimus either after disease progression or after early termination for efficacy. Therefore, a longer overall survival follow up may not further elucidate a survival trend.

6.1.5.2 Overall response rate (ORR)

The Study C2240 overall response rates are summarized below.

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 16: Study C2240 overall response rate (ITT)

PFS	Oct 15 2007 cut-off N = 410				Feb 25 2008 cut-off N = 416			
	IRC		INV		IRC		INV	
	R (n=272)	P (n=138)	R (n=272)	P (n=138)	R (n=277)	P (n=139)	R (n=277)	P (n=139)
ORR (%)	3 (1.1)	0	4 (1.5)	1 (0.7)	5 (1.8)	0	6 (2.2)	1 (0.7)
CR (%)	0	0	0	0	0	0	0	0
PR (%)	3 (1.1)	0	4 (1.5)	1 (0.7)	5 (1.8)	0	6 (2.2)	1 (0.7)
SD (%)	171 (62.9)	44 (31.9)	181 (66.5)	44 (31.9)	185 (66.8)	45 (32.4)	196 (70.8)	48 (34.5)
PD	53 (19.5)	63 (45.7)	55 (20.2)	73 (52.9)	57 (20.6)	74 (53.2)	57 (20.6)	78 (56.1)
Unknown	45 (16.5)	31 (22.5)	32 (11.8)	20 (14.5)	30 (10.8)	20 (14.4)	18 (6.5)	12 (8.6)
95% CI ORR	[0.2; 3.2]	-	[0.4, 3.7]	[0, 4.0]	[0.6; 4.2]	-	[0.8, 4.7]	[0, 3.9]
p-value	0.22		0.51		0.11		0.27	

ORR=CR + PR, IRC=Independent Reviewer Analysis, INV=Investigators Analysis, R=RAD001, P=Placebo
 Source: Study C2240 report

Reviewer: The overall response rate (ORR) was 1.8% for everolimus and 0% for the placebo by independent assessment at the time of the final data cut-off. Therefore, no trend in the rate of objective complete or partial response was noted in favor of everolimus. There was a trend in favor of everolimus in terms of the number of patients with stable disease, 67% for everolimus versus 32% for the placebo. This was consistent with the PFS data.

6.1.5.3 Patient reported outcome (PRO):

The applicant determined that no formal testing of the PRO endpoints could be made because neither OS nor ORR met the criteria for statistical significance.

6.1.6 Sensitivity Analyses of the Primary Endpoints: PFS

Multiple sensitivity analyses were conducted by both applicant and FDA to verify the primary PFS analysis.

6.1.6.1 PFS sensitivity analysis for worst case scenario

This analysis is based on the first occurrence of disease progression by either IRC or investigator assessment. Applicant's worst scenario analysis is summarized below.

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 17: Sensitivity Analyses of PFS in worst case scenario by either IRC or investigator assessment (ITT)

Oct 15, 2007 cut-off	R N=272 (%)	P N=138 (%)
PFS events	139 (51.1)	111 (80.4)
Progression	128 (47.1)	105 (76.1)
Progression assessed first by IRC	45 (16.5)	20 (14.5)
Progression assessed first by INV	48 (17.6)	28 (20.3)
Progression assessed by both INV & IRC	35 (12.9)	57 (41.3)
Death	11 (4.0)	6 (4.3)
Censored	133 (48.9)	27 (19.6)
Median PFS [95% CI] (months)	3.61 [3.19;3.84]	1.84 [1.77;1.87]
p-value	<0.001	
Hazard ratio [95% CI] RAD001 / Placebo	0.34 [0.26,0.45]	

PFS = Time to Tumor Progression + death, IRC = independent review assessments, INV = Investigators Analysis, R = RAD001, P = Placebo

- This sensitivity analysis considers disease progression from both central radiology and the investigator, whichever occurs first.
- P-value is obtained from the Stratified Log-Rank test
- Hazard ratio is obtained using an unadjusted stratified Cox PH model.

Source: Study C2240 report

Reviewer: Based on the applicants summary, 73% (45+48/128) of patients had a disagreement in disease progression date between the IRC and INV assessment for the RAD001 arm, but only 48% (20+28/105) of patients had a disagreement in disease progression dates in the placebo arm.

6.1.6.2 Discrepancy in PFS events and censoring

Arm	INV assessment	IRC assessment		
		Death	PD	Censor
		n=16	n=85	n=171
R (N=272)	Death (n=14)	11	3	0
	PD (n=97)	5	54	38
	Censor (n=161)	0	28	133
		n=8	n=82	n=48
P (N=138)	Death (n=7)	6	1	0
	PD (n=98)	2	75	21
	Censor (n=33)	0	6	27

PD= progression of disease, IRC = independent review assessments, INV = Investigators Analysis, R = RAD001, P = Placebo

Source: Study C2240 report

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Reviewer: The event disagreement is 46.1% $\{[1-(11+54+133)/272] \times 100\%$ for the everolimus arm and 24% $\{[1-(6+75+27)/138] \times 100\%$ for the placebo arm at the time of the Oct 15, 2007 cut-off. FDA statistical reviewer, Dr. Chattopadhyay, conducted detailed analyses of all types of discrepancies between the two assessments, as shown in the table below. This thorough analysis demonstrated discrepancies of any type occurred in 39.3% (100% - 43.8% - 4% - 12.9%) in the everolimus arm and 59.8% (100% - 15.9% - 4.4% - 19.9%) in the placebo at the Oct 15, 2007 cut-off date. For the cut-off date of Feb 28, 2008, discrepancies of any type occurred 55.9% (100% - 22% - 4% - 18.1%) in the everolimus arm and 39.6% (100% - 4.3% - 4.3% - 51.8%) in the placebo arm.

Table 18: Analyses of discrepancies of any type in Study C2240 (ITT, Oct 15, 2007 cut-off)

Oct 15, 2007 cut-off date									
Event Type		RAD001 discrepancy frequency (%)				Placebo discrepancy frequency (%)			
IRC	INV	Same time	IRC after INV	IRC before INV	Total	Same time	IRC after INV	IRC before INV	Total
Censor	PD	27 (9.9)	1 (0.4)	10 (3.7)	38 (14.0)	17 (12.3)	0	4 (2.9)	21 (15.2)
Death	PD	0	5 (1.8)	0	5 (1.8)	0	2 (1.5)	0	2 (1.5)
PD	Censor	13 (4.8)	5 (1.8)	10 (3.7)	28 (10.3)	4 (2.9)	2 (1.5)	0	6 (4.4)
PD	Death	0	0	3 (1.1)	3 (1.1)	0	0	1 (0.7)	1 (0.7)
Censor	Censor	119 (43.8)	4 (1.5)	10 (3.7)	133 (48.9)	22 (15.9)	1 (0.7)	4 (2.9)	27 (19.6)
Death	Death	11 (4.0)	0	0	11 (4.0)	6 (4.4)	0	0	6 (4.4)
PD	PD	35 (12.9)	5 (1.8)	14 (5.2)	54 (19.9)	57 (41.3)	5 (3.6)	13 (9.4)	75 (54.4)
Total		205 (75.4)	20 (7.4)	47 (17.3)	272 (100)	106 (76.8)	10 (7.3)	22 (15.9)	138 (100)

PD = Progression of disease, IRC = independent review, INV = investigator assessment.

Source: Study C2240 report

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 19: Analyses of discrepancies of any type in Study C2240 (ITT, Feb 28, 2008 cut-off)

Feb 28, 2008 cut-off date									
Event Type		RAD001 discrepancy frequency (%)				Placebo discrepancy frequency (%)			
		INV	Same time	IRC	INV	Same time	IRC	INV	Same time
Censor	PD	33 (11.9)	3 (1.1)	13 (4.7)	49 (17.7)	15 (10.8)	4 (2.9)	2 (1.4)	21 (15.1)
Death	PD	0	10 (3.6)	0	10 (3.6)	0	2 (1.4)	0	2 (1.4)
PD	Censor	9 (3.2)	5 (1.8)	20 (7.2)	34 (12.3)	2 (1.4)	0	1 (0.7)	3 (2.2)
PD	Death	0	0	7 (2.5)	7 (2.5)	0	0	2 (1.4)	2 (1.4)
Censor	Censor	61 (22.0)	4 (1.4)	8 (2.9)	73 (26.4)	6 (4.3)	1 (0.7)	0	7 (5.0)
Death	Death	11 (4.0)	0	0	11 (4.0)	6 (4.3)	0	0	6 (4.3)
PD	PD	50 (18.1)	12 (4.3)	31 (11.2)	93 (33.6)	72 (51.8)	5 (3.6)	21 (15.1)	98 (70.5)
Total		164 (59.2)	34 (12.3)	79 (28.5)	277 (100)	101 (72.7)	12 (8.6)	26 (18.7)	139 (100)

PD = Progression of disease, IRC = independent review, INV = investigator assessment.
 Source: Study C2240 report

This also brought the question of whether there are any missing assessments between the cut-off dates and censor dates. The table below is an analysis of the interval between the censored last assessment date of each subject and the clinical cut-off date. Ideally the interval should be similar to the tumor assessment interval.

Table 20: Statistical summary of the time between the censoring date and the Oct 15, 2007 cut-off date in everolimus and placebo arms, based on the independent review

Oct 15, 2007 cut-off date, Independent Review						
Statistic (in days)	Censoring reason					
	Ongoing without event	Lost to follow-up	Withdrew consent	Adequate assessment no longer available	New cancer therapy added	Any
N (R/P)	133/24	2/0	6/0	8/4	22/20	171/48
Mean	38/35	170/-	127/-	160/228	118/104	58/80
SD	25/20	54/-	57/-	25/48	45/60	50/70
Min	2/3	132/-	61/-	132/186	34/14	0/3
Median	39/34	-/-	130/-	163/225	131/103	47/53
Max	111/88	208/-	189/-	189/277	214/237	214/277

R/P = everolimus / placebo
 Source: Study C2240 report

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 21: Statistical summary of the time between the censoring date and the Oct 15, 2007 cut-off date in everolimus and placebo arms based on the investigator review

Oct 15, 2007 cut-off date, Investigator Review							
Statistic (in days)	Censoring reason						
	Ongoing without event	Lost to follow-up	Withdrew consent	Adequate assessment no longer available	New cancer therapy added	Event after ≥ 2 missing assessments	Any
N (R/P)	145/29	2/0	6/0	2/2	5/1	1/1	161/33
Mean	32/30	170/-	127/-	154/225	140/89	224/262	43/50
SD	22/17	54/-	57/-	30/53	69/	-/-	43/64
Min	0/3	132/-	61/-	132/188	63/	-/-	0/6
Q1	13/14	-/-	62/-	-/-	104/	-/-	14/20
Median	34/27	-/-	130/-	-/-	137/	-/-	38/34
Q3	48/38	-/-	187/-	-/-	146/	-/-	53/49
Max	103/66	208/-	189/-	175/262	249/	-/-	249/262

R/P = everolimus / placebo
 Source: Study C2240 report

Table 22: Statistical summary of the time between the censoring date and the Feb 28, 2008 cut-off date in everolimus and placebo arms based on the independent review

Feb 28, 2008 cut-off date, Independent Review							
Statistic (in days)	Censoring reason						
	Ongoing without event	Lost to follow-up	Withdrew consent	Adequate assessment no longer available	New cancer therapy added	Event after ≥ 2 missing assessments	Any
N (R/P)	145/29	2/0	6/0	2/2	5/1	1/1	161/33
Mean	32/30	170/-	127/-	154/225	140/89	224/262	43/50
SD	22/17	54/-	57/-	30/53	69/	-/-	43/64
Min	0/3	132/-	61/-	132/188	63/	-/-	0/6
Median	34/27	-/-	130/-	-/-	137/	-/-	38/34
Max	103/66	208/-	189/-	175/262	249/	-/-	249/262

R/P = everolimus / placebo
 R/P = everolimus / placebo
 Source: Study C2240 report

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 23: Statistical summary of the time between the censoring date and the Feb 28, 2008 cut-off date in everolimus and placebo arms based on the investigator review

Feb 28, 2008 cut-off date, Investigator Review							
Statistic (in days)	Censoring reason						
	Ongoing without event	Lost to follow-up	Withdrew consent	Adequate assessment no longer available	New cancer therapy added	Event after ≥ 2 missing assessments	Any
N (R/P)	71/6	2/0	9/0	10/3	9/1	6/0	107/10
Mean	31/41	198/-	212/-	160/316	198/225	266/-	88/142
SD	19/10	100/-	90/-	43/87	106/	85/-	97/139
Min	1/28	127/-	71/-	128/225	72/	154/-	1/28
Q1	16/35	-/-	148/-	135/225	100/	189/-	21/36
Median	29/39	-/-	198/-	147/324	199/	275/-	43/53
Q3	43/50	-/-	275/-	171/398	273/	344/-	136/225
Max	78/55	268/-	325/-	268/398	385/	360/-	385/398

R/P = everolimus / placebo
 Source: Study C2240 report

Reviewer: Even though there are many discrepancies between the independent and investigator assessments at both cut-off dates, the mean time between the last assessment for censored patients and the cut-off date was within an acceptable time frame (< 2 months). This provides additional assurance that missing data was minimal in Study C2240. Furthermore, PFS analyses by both independent and investigator assessments at each cut-off date have consistently shown an advantage for everolimus over placebo (Section 6.1.4).

6.1.6.3 Reasons for censoring

The reasons for censoring during Study C2240 are summarized below.

Table 24: Summary of the reasons for censoring for PFS based on independent assessments (ITT)

Percentage of total censoring	Oct 15, 2007 cut-off		Feb 28, 2008 cut-off	
	R N=272 (%)	P N=138 (%)	R N = 277 (%)	P N = 139 (%)
Total number of censored patients	171 (62.9)	48 (34.8)	122 (44.0)	28 (20.1)
Reason for Censoring	N = 171 (%)	N = 48 (%)	N = 122 (%)	N = 28 (%)
Ongoing without event	133 (77.8)	24 (50.0)	54 (44.3)	4 (14.3)
Lost to follow-up	2 (1.2)	0	2 (1.6)	0
Withdrew consent	6 (3.5)	0	8 (6.6)	0
Adequate assessment no longer available	8 (4.7)	4 (8.3)	20 (16.4)	4 (14.3)
New cancer therapy added	22 (12.9)	20 (41.7)	34 (27.9)	20 (71.4)
Event after ≥ 2 missing tumor assessments	1 (0.6)	1 (4)	4 (3.3)	0

R = RAD001, P = Placebo
 Source: Study C2240 report

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

Reviewer: About 10% of ITT patients (32% of censored patients) on both arms were censored for reasons other than CR/PR/SD, including lost to follow-up, withdrew consent, adequate assessment no longer available, or event after missing more than 2 tumor assessments.

6.1.6.4 Censoring option analyses

In study C2240 primary PFS analysis, per-protocol and statistical analysis plan (SAP, dated Feb 1, 2008), censoring at the last tumor assessment occurred in the following circumstances and described by the applicant in the table below:

- Absence of an event: Censoring performed at the last adequate tumor assessment (defined as the last tumor assessment with an overall lesion response of CR, PR, or SD) prior to the analysis cut-off or prior to the start of new anticancer therapy, whichever occurred first.
- Event occurred after new anticancer therapy (including open-label everolimus) was given: Censoring performed at the last adequate tumor assessment prior to the initiation of new anticancer therapy.
- Event occurred after two or more missing tumor assessments: Censoring performed at the last adequate tumor assessment before the missing assessments.

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Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 25: Study C2240 PFS options, per protocol and SAP (Feb 1, 2008)

Situation	Options for end-date (event/censoring) ¹	Outcome
A. No baseline assessment	Date of randomization	Censored
B. Progression at or before next scheduled assessment	Date of progression	Progressed
C1. Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
C2. Progression or death after two or more missing assessments	Date of last adequate assessment	Censored
D. No progression	Date of last adequate assessment	Censored
E. Treatment discontinuation due to 'Disease progression' without documented progression, i.e., clinical progression based on investigator claim	N/A	Ignored
F. New anticancer therapy given	Date of last adequate assessment	Censored

¹ Definitions:

Date of death during treatment as recorded on the treatment completion page, or during follow-up as recorded on the study evaluation completion page or the survival follow-up page.

Date of progression was the first assessment date at which the overall lesion response was recorded as progressive disease.

Date of last adequate tumor assessment was the date of the last tumor assessment with an overall lesion response of CR, PR, or SD, made before an event or censoring reason occurred. In this case, the last tumor evaluation date at that assessment was used. If no post-baseline assessments were available (before an event or a censoring reason occurred), the date of randomization/start of treatment was used.

Source: NDA2334 amendment, submitted on Mar 10, 2009.

Per FDA request, the applicant conducted PFS sensitivity analyses under the following criteria:

A. Event occurred after the patient discontinued treatment for toxicity or any other reason (including disease progression): Censoring to be performed at the last adequate tumor assessment before treatment discontinuation.

B. Treatment discontinuation will not be considered as a reason for censoring but will be used to define the last adequate tumor assessment.

The results are shown below:

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Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 26: PFS sensitivity analyses with difference censoring options (Feb 28 2008 cut-off)

	IRC Assessments					
	Per-protocol		A		B	
	R (n=277)	P (n=139)	R (n=277)	P (n=139)	R (n=277)	P (n=139)
Total Events (%)	155 (56)	111 (80)	105 (38)	79 (57)	155 (56)	111 (80)
Death (%)	21 (8)	8 (6)	3 (1)	1 (<1)	21 (8)	8 (6)
Progression (%)	134 (48)	103 (74)	102 (37)	78 (56)	134 (48)	103 (74)
Censored (%)	122 (44)	28 (20)	172 (62)	60 (43)	122 (44)	28 (20)
Median PFS	4.9	1.9	5.6	1.9	4.6	1.9
HR (95%CI) ^a	0.33 (0.25 to 0.43)		0.30 (0.22 to 0.41)		0.33 (0.26 to 0.43)	
P-value	< 0.001		< 0.001		< 0.001	
	INV Assessments					
	Per-protocol		A		B	
	R (n=277)	P (n=139)	R (n=277)	P (n=139)	R (n=277)	P (n=139)
Total Events (%)	170 (61)	129 (93%)	110 (40)	111 (80)	170 (61)	129 (93%)
Death (%)	18 (6.5)	8 (6.8)	3 (1)	8 (5.8)	18 (6.5)	8 (6.8)
Progression (%)	152 (54.9)	121 (87.1)	107 (39)	103 (74.1)	152 (54.9)	121 (87.1)
Censored (%)	107 (39)	10 (7)	167 (60)	45 (32)	107 (39)	10 (7)
Median PFS	5.5	1.9	7.2	2.0	5.5	1.9
HR (95%CI) ^a	0.32 (0.25 to 0.41)		0.28 (0.21 to 0.38)		0.32 (0.25 to 0.41)	
P-value	< 0.001		< 0.001		< 0.001	

a Cox model

b One-sided stratified log-rank test

Source: NDA2334 amendment, submitted on Mar 10, 2009.

Reviewer: Both sensitivity analysis results are consistent with the primary PFS analysis.

6.1.6.5 Time to treatment failure analysis

The applicant reported numbers of disease progression and death events were different between patient disposition and PFS assessment, either by investigator or by independent review, as summarized in the table below.

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 On Original**

Table 27: Reviewer’s summary of discrepancies of disease progression and death events

	Oct 15 2007 cut-off (N = 410)					
	Disposition		IRC		INV	
	R (n=272)	P (n=138)	R (n=272)	P (n=138)	R (n=272)	P (n=138)
Total Events (%)	92 (334)	103 (74)	101 (37)	90 (65)	111 (41)	105 (76)
Death (%)	7 (3)	3 (2)	16 (6)	8 (6)	14 (5)	7 (5)
Progression (%)	85 (31)	100 (73)	85 (31)	82 (59)	97 (37)	98 (71)
	Feb 28 2008 cut-off (N = 416)					
	Disposition		IRC		INV	
	R (n=277)	P (n=139)	R (n=277)	P (n=139)	R (n=277)	P (n=139)
Total Events (%)	144 (52)	128 (93)	155 (56)	111 (80)	170 (61)	129 (93)
Death (%)	7 (3)	4 (3)	21 (8)	8 (6)	18 (7)	8 (7)
Progression (%)	137 (50)	124 (89)	134 (48)	103 (74)	152 (55)	121 (87)

Source: FDA information request on Mar 2, 2009.

The applicant clarified that patient disposition events were counted at the end of the study treatment. Some of the patients, who terminated study treatment for reasons other than a PFS event, were continued for PFS follow up. Therefore, the number of disease progression and death events were different at the time of cut-off dates for investigator determined study treatment termination, investigator assessed PFS, and independent review assessed PFS.

FDA reviewers requested a sensitivity analysis on time to treatment failure (TTF), which is defined as the time from the date of randomization to the earliest date of any of the following:

- death prior to treatment discontinuation
- radiological progression (as per RECIST) assessed by the local investigator prior to treatment discontinuation
- study treatment discontinuation due to:
 - disease progression
 - adverse event(s)
 - abnormal laboratory value(s)
 - abnormal test procedure results
 - subject withdrew consent
 - lost to follow-up
 - death
 - new cancer therapy
 -

Patients who discontinued study treatment for reasons other than those listed above (i.e., as a result of protocol violation, administrative problems, or ‘final primary analysis’) are censored as of the last adequate tumor assessment prior to discontinuation.

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Patients with neither an event nor study treatment discontinuation are censored as of the last adequate tumor assessment.

The result of TTF analysis is shown below.

Table 28: Study C2240 TTF (Feb 28, 2008 cut-off)

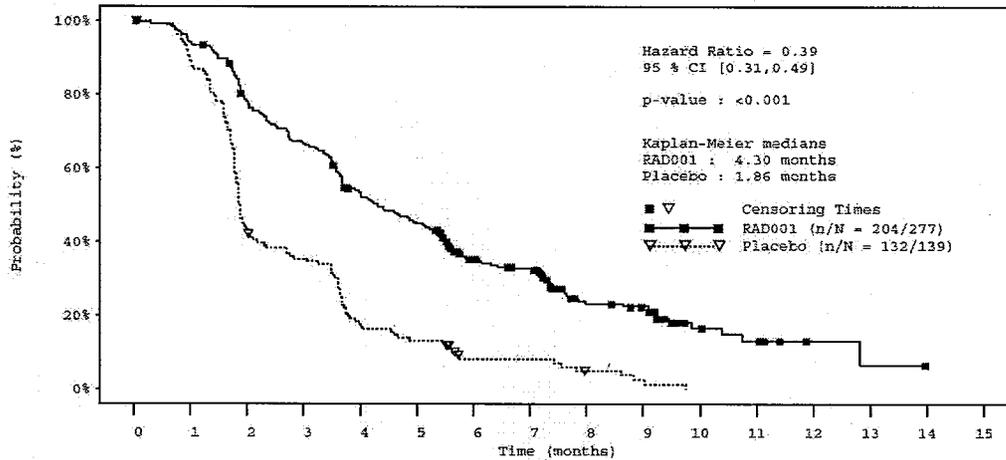
	TTF per investigator	
	R (n=277)	P (n=139)
Total TTF Events (%)	204 (74)	132 (95)
Death (%)	3 (1)	1 (<1)
Disease progression	109 (39)	93 (67)
Treatment discontinuation (%)	92 (33)	38 (27)
Censored (%)	73 (26)	7 (5)
Median TTF	54.3	1.9
HR (95%CI) ^a	0.39 (0.31 to 0.49)	
p-value ^b	< 0.001	

a Cox model

b One-sided stratified log-rank test

Source: NDA2334 amendment, submitted on Mar 12, 2009.

Figure 8: TTF analysis by Kaplan Meier estimation (Feb 28, 2008 cut-off)



No. of patients still at risk																
Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
RAD001	277	259	212	181	141	119	76	68	33	29	11	8	2	1	0	0
Placebo	139	123	60	48	24	18	8	8	4	2	0	0	0	0	0	0

- Cox model and one-sided Log-Rank test stratified by MSKCC risk criteria

Source: NDA2334 amendment, submitted on Mar 12, 2009.

Reviewer: The TTF analysis is consistent with the primary PFS analysis.

6.1.6.6 Post-study antineoplastic therapy

All post study therapies given to Study C2240 patients after the study treatment are summarized below. This excludes crossover after disease progression for placebo arm patients to everolimus treatment.

Arm	Oct 15, 2007 Cut-off			Feb 28, 2008 cut-off		
	Everolimus	Placebo	Total	Everolimus	Placebo	Total
Any subjects*	52	17	69	96	35	131
Missing	6	6	12	18	15	33
Chemotherapy	5	1	6	12	0	12
Hormone therapy	0	0	0	0	1	1
Immunotherapy	3	0	3	8	2	10
Anticonvulsant	11	1	12	11	1	12
Hepatic chemoembolization	0	0	0	14	7	21
Targeted therapy	28	5	33	54	12	66
Other	3	1	4	5	4	9

* Subjects received other post treatment therapies regardless of censored status.
 Source: Study C2240 report

6.1.6.7 Subgroup PFS analyses

PFS analyses in clinically significant subgroups are summarized below.

Table 29: PFS subgroup analysis at Oct 15, 2007 cut-off

Oct 15, 2007 cut-off					
Population	N	Everolimus N=272	Placebo N=138	Hazard Ratio (95%CI)	p-value
		Median progression free survival (months) (95% CI)			
Primary analysis					
All (blinded independent central review)	410	4.0 (3.7 to 5.5)	1.9 (1.8 to 1.9)	0.30 (0.22 to 0.40)	<0.0001
Supportive/sensitivity analyses					
All (local review by investigator)	410	4.6 (3.9 to 5.5)	1.8 (1.8 to 1.9)	0.31 (0.23 to 0.41)	<0.0001
MSKCC prognostic score					
Favorable risk	118	5.5 (3.8 to 5.9)	2.2 (1.9 to 3.6)	0.35 (0.20 to 0.61)	<0.0001
Intermediate risk	231	3.9 (3.6 to 5.5)	1.8 (1.8 to 1.9)	0.25 (0.16 to 0.37)	<0.0001
Poor risk	61	3.6 (1.9 to 5.4)	1.9 (1.7 to 3.6)	0.39 (0.19 to 0.81)	0.009

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Oct 15, 2007 cut-off					
Population	N	Everolimus N=272	Placebo N=138	Hazard Ratio (95%CI)	p-value
		Median progression free survival (months) (95% CI)			
Prior VEGFR-TKI therapy					
Sorafenib only	119	5.5 (3.9 to NA)	3.5 (1.9 to 3.6)	0.29 (0.16 to 0.51)	<0.0001
Sunitinib only	184	3.7 (3.5 to 5.5)	1.8 (1.7 to 1.9)	0.30 (0.20 to 0.47)	<0.0001
Sunitinib and sorafenib	107	3.8 (3.4 to 5.8)	1.8 (1.8 to 1.9)	0.28 (0.16 to 0.52)	<0.0001

Source: Study C2240 report

Table 30: PFS subgroup analysis at Feb 28, 2008 cut-off

Feb 28, 2008 cut-off					
Population	N	Everolimus N=277	Placebo N=139	Hazard Ratio (95%CI)	p-value
		Median progression free survival (months) (95% CI)			
Primary analysis					
All (blinded independent central review)	416	4.9	1.8	0.33 [0.25 to 0.43]	<0.0001
Supportive/sensitivity analyses					
All (local review by investigator)	416	5.5	1.9	0.32 [0.25 to 0.41]	<0.0001
MSKCC prognostic score					
Favorable risk	118	5.8 (4.0 to 7.4)	1.9 (1.9 to 2.8)	0.31 (0.19 to 0.50)	<0.0001
Intermediate risk	231	4.5 (3.6 to 5.5)	1.8 (1.8 to 1.9)	0.32 (0.22 to 0.44)	<0.0001
Poor risk	61	3.6 (1.9 to 4.6)	1.8 (1.8 to 3.6)	0.44 (0.22 to 0.85)	0.0133
Prior VEGFR-TKI therapy					
Sorafenib only	119	5.9 (4.9 to 11.4)	2.8 (1.9 to 3.6)	0.25 (0.16 to 0.42)	<0.0001
Sunitinib only	184	3.9 (3.6 to 5.6)	1.8 (1.8 to 1.9)	0.34 (0.23 to 0.51)	<0.0001
Sunitinib and sorafenib	107	4.0 (3.6 to 5.6)	1.8 (1.8 to 2.0)	0.32 (0.19 to 0.54)	<0.0001

Source: Study C2240 report

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Reviewer: The subgroup analyses based on MSKCC prognostic score (favorable risk, intermediate risk, and poor risk) and Prior VEGFR-TKI therapy with sorafenib only, sunitinib only, and sunitinib and sorafenib) at both data cut-offs were all consistent with the primary PFS analysis.

6.1.7 Subpopulations

As shown in Section 6.1.2, 88% of Study C2240 patients were Caucasian, 77% male, and 63% younger than 65 years. The subgroup PFS analyses by sex, age, and region, using the data from the independent radiology assessments are summarized below.

Table 31: Analysis of PFS based on central radiology review by subgroup (Oct 15, 2007 cut-off)

Oct 15, 2007 cut-off					
Population	N	Everolimus N=272	Placebo N=138	Hazard Ratio (95%CI)	p-value
		Median progression free survival (months) (95% CI)			
Primary analysis					
All (blinded independent central review)	410	4.0 [3.7, 5.5]	1.9 [1.8, 1.9]	0.30 [0.22, 0.40]	<0.0001
Supportive/sensitivity analyses					
All (local review by investigator)	410	4.6 [3.9, 5.5]	1.8 [1.8, 1.9]	0.31 [0.23, 0.41]	<0.0001
Age group					
< 65 years	259	4.0 [3.5, 5.5]	1.8 [1.8, 1.9]	0.32 [0.22, 0.45]	<0.0001
>=65 years	151	5.2 [3.7, 8.4]	2.2 [1.8, 3.5]	0.29 [0.17, 0.49]	<0.0001
Gender					
Male	317	4.0 [3.7, 5.5]	1.8 [1.8, 1.9]	0.29 [0.21, 0.41]	<0.0001
Female	93	5.2 [3.2, 5.9]	1.9 [1.7, 3.6]	0.36 [0.19, 0.70]	0.0016
Region					
US & Canada	130	4.5 [3.7, 6.4]	1.8 [1.8, 1.9]	0.24 [0.14, 0.42]	<0.0001
Europe	251	3.9 [3.6, 5.5]	1.9 [1.8, 2.9]	0.37 [0.25, 0.54]	<0.0001
Australia & Japan	29	n/a [3.8, n/a]	1.8 [1.8, 1.9]	0.10 [0.02, 0.51]	0.0012

Source: Study C2240 report

Table 32: Analysis of PFS based on central radiology review by subgroup (Feb 28, 2008 cut-off)

Feb 28, 2008 cut-off					
Population	N	Everolimus N=272	Placebo N=138	Hazard Ratio (95%CI)	p-value
		Median progression free survival (months) (95% CI)			
Primary analysis					
All (blinded independent central review)	416	4.9 [4.0, 5.5]	1.9 [1.8, 1.9]	0.33 [0.25, 0.43]	<0.0001
Supportive/sensitivity analyses					
All (local review by investigator)	416	5.5 [4.6, 5.8]	1.9 [1.8, 2.2]	0.32 [0.25, 0.41]	<0.0001
Age group					
< 65 years	263	4.3 [3.7, 5.5]	1.9 [1.8, 1.9]	0.34 [0.25, 0.47]	<0.0001
>=65 years	153	5.4 [4.0, 5.9]	2.2 [1.8, 3.5]	0.29 [0.17, 0.49]	<0.0001
Gender					
Male	322	4.0 [4.0, 5.5]	1.9 [1.8, 1.9]	0.29 [0.21, 0.41]	<0.0001
Female	94	5.1 [3.4, 5.9]	1.9 [1.7, 3.6]	0.36 [0.19, 0.70]	0.0004
Region					
US & Canada	130	4.6 [3.7, 5.9]	1.9 [1.8, 2.1]	0.29 [0.19, 0.46]	<0.0001
Europe	251	4.4 [3.7, 5.5]	1.9 [1.8, 2.8]	0.38 [0.27, 0.53]	<0.0001
Australia & Japan	35	10.6 [4.9, n/a]	1.9 [1.8, 3.6]	0.18 [0.07, 0.49]	0.0002

Source: Study C2240 report

7 Review of Safety

7.1 Methods

The safety evaluation of everolimus 10 mg daily, administered as monotherapy, was based on data from 596 patients that received everolimus in applicant conducted studies, shown in the table below. This safety review focused on data from Study C2240, which was the primary

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

support for the indication being sought. Furthermore, this is the only study that allows direct comparison with a placebo control and hence has an ability to discriminate between drug-related and disease-related toxicities. Beyond this comparative study, the focus is primarily on patients receiving the 10 mg daily dose in other monotherapy studies (in various patient populations).

Table 33: Key studies reviewed for safety evaluation

Study	Study design, objectives, and population	Safety endpoints	No of patients received 10-mg Everolimus daily dose regimen
C2240	Double-blind, randomized, placebo controlled study (with open-label extension); Safety and efficacy in patients with mRCC whose disease has progressed despite prior VEGFr-TKI therapy	Toxicity assessment documented by NCI CTCAE, Reporting of AEs, SAEs, Routine laboratory evaluations	Oct 15, 2007 cut-off includes 269 received everolimus in randomized study plus 81 patients who received everolimus in the open-label setting following crossover of 135 placebo patients. Feb 28, 2008 cut-off 274 +109
C2101 Part 1/C2102	Dose-escalation in patients with advanced solid tumors		33
C2107	Phase-Ib study investigating safety, tolerability, and molecular pharmacodynamic effects in patients with advanced solid tumors		12
C1101	Open-label, single-arm, dose-escalation study in Japanese patients with advanced solid tumors		3
C2235	Open-label, single-arm phase-II study of safety and efficacy in patients with advanced NSCLC previously treated with either chemotherapy (CT) only or with CT and an EGFR-TKI		85
C2239	Open-label, stratified phase-II study of safety and efficacy in patients with advanced pNET after the failure of cytotoxic chemotherapy		115 Stratum 1
Total			596

Source: NDA 22334

Other studies provided safety data from an additional 432 subjects (350 patients and 82 healthy volunteers) and also contributed to this evaluation. These include:

- 16 patients from the phase 1 program who were administered 5 mg daily doses
- 95 patients from 3 studies where everolimus monotherapy was administered on a weekly regimen, at doses ranging from 5 mg to 70 mg/week (Study C2101 monotherapy/C2102, Study C2106, and Study C2107)

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

- 239 patients who received treatment with everolimus in combination with other therapies (as part of either a daily or weekly regimen) in 6 studies (Study C2101, Study C2104, Study C2108, Study C2207, Study C2222, and Study C2239)
- 82 healthy subjects from a thorough QT study (assessing the effect of everolimus on cardiac safety) (Study C2118)
- Serious adverse event (SAE) data from ongoing studies, reported prior to the cut-off date of 15-Apr-2008, are also provided in NDA 22-334.

The datasets of the safety population comprised of all patients who received at least one dose of the study drug are summarized below.

Table 34: Safety population grouping (SP)

Dataset	Studies	No of patients	Safety Data and Subgroup analyses
Pivotal phase-III trial: placebo-controlled study	C2240 ^a	269	Data: deaths, SAEs, other significant AEs, all AEs, clinical laboratory results Subgroups: gender, age, race
Pooled dataset: monotherapy safety population	C2240 ^b , C2239, C1101, C2101, monotherapy/C21 02, C2107, C2235	596	Data: deaths, SAEs, other significant AEs, all AEs, clinical laboratory results Subgroups: gender, age, race
QT study – presented individually	C2118	82	QT/QTc prolongation

a Double-blind phase only;

b Double-blind and open-label phases

Source: NDA 22334

Reviewer: All adverse reactions were recorded and analyzed by the applicant using NCI CTCAE (3.0) criteria. This reviewer has re-analyzed the applicant's safety results using applicant-provided datasets with the JMP computer program. This reviewer also sampled 20% of CRFs and all AE narratives for detailed safety assessments. Only the worst adverse reaction per category per patient is included in this safety review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations

As summarized below, the overall drug exposure appears to be adequate.

Table 35: Study C2240 overall drug exposure (SP, both cut off dates)

Exposure	Second Interim Analysis Data cut-off: Oct 15, 2007		Safety Update Data cut-off: Feb 28, 2008	
	Everolimus 10 mg N=269	Placebo N=135	Everolimus 10 mg N=274	Placebo N=137
Exposure categories, n (%)				
<4 weeks	7 (2.6)	8 (5.9)	6 (2.2)	7 (5.1)
4 - <8 weeks	41 (15.2)	42 (31.1)	28 (10.2)	41 (29.9)
8 - <12 weeks	69 (25.7)	41 (30.4)	46 (16.8)	32 (23.4)
12 - <16 weeks	56 (20.8)	12 (8.9)	29 (10.6)	11 (8.0)
16 - <20 weeks	25 (9.3)	18 (13.3)	26 (9.5)	22 (16.1)
20 - <24 weeks	26 (9.7)	8 (5.9)	23 (8.4)	6 (4.4)
24 - <28 weeks	19 (7.1)	4 (3.0)	24 (8.8)	6 (4.4)
28 - <32 weeks	17 (6.3)	1 (0.7)	21 (7.7)	4 (2.9)
≥32 weeks	9 (3.3)	1 (0.7)	71 (25.9)	8 (5.8)
Duration of exposure (days)				
Mean	105.7	75.3	156.1	90.8
Standard deviation	58.5	42.6	94.3	62.5
Median	95.0	57.0	141.0	60.0
Range	12-315	21-237	19-451	21-295
Adjusted everolimus exposure relative to median exposure				
Median	1.0	1.0	1.0	1.0
Range	0.27-2.00	0.76-1.00	0.27-1.00	0.50-2.00
Mean	0.937	0.990	0.918	1.001
Standard deviation	0.163	0.032	0.150	0.133

Source: Study C2240 report

Reviewer: The dosing exposure for both arms appears to be balanced.

7.2.2 Evaluation for Potential Adverse Events for Other Drugs in this Drug Class

Temsirolimus, which is in the same class of drugs, has been previously evaluated and has the following safety profile.

- The most common adverse reactions (incidence $\geq 30\%$) were rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities (incidence $\geq 30\%$) were anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia.
- The most common grade 3/4 adverse reactions (incidence $\geq 5\%$) included asthenia, dyspnea, rash, and pain. The most common grade 3/4 laboratory abnormalities (incidence $\geq 5\%$) included hypertriglyceridemia, anemia, hypophosphatemia, hyperglycemia, lymphopenia, and neutropenia.
- Rare serious adverse reactions associated with temsirolimus included interstitial lung disease, bowel perforation, and acute renal failure.

7.3 Major Safety Results

7.3.1 Deaths

Deaths within 30 days of study treatment are summarized below. Patients who died before receiving the study treatment were not included in this table since they were excluded from the safety population.

Table 36: Deaths within 30 days of study treatment (SP)

Death within 30 day of treatment	Second Interim Analysis 15-Oct-2007 cut-off		Safety Update 28-Feb-2008 cut-off	
	Everolimus N=269 (%)	Placebo N=135 (%)	Everolimus N=274 (%)	Placebo N=137 (%)
Total number of on-treatment deaths	14 (5.2)	6 (4.4)	21 (7.7)	7 (5.1)
AE as primary cause of death	1 (0.4)	1 (0.7)	4 (1.5)	1 (0.7)
AE suspected to be drug-related as primary cause of death	1 (0.4)	0	2 (0.7)	0

Source: Study C2240 report

The deaths on treatment that were likely to be due to an adverse reaction are summarized below.

Table 37: Treatment related death (SP)

Time of death	Second Interim Analysis 15-Oct-2007 cut-off		Safety Update 28-Feb-2008 cut-off	
	Everolimus N=269 (%)	Placebo N=135 (%)	Everolimus N=274 (%)	Placebo N=137 (%)
< 30days	2 (0.8)	1 (0.7)	5 (1.9)	1 (0.7)
45 days	1 (0.4)	0	1 (0.4)	0
112 days	1 (0.4)	0	1 (0.4)	0
145 days	1 (0.4)	0	1 (0.4)	0
Total	5 (2.0)	1 (0.7)	8 (3.0)	1 (0.7)
All cause of death				
Acute renal failure	1 (0.4)	0	1 (0.4)	0
Acute respiratory failure	3 (1.2)	0	4 (1.9)	0
Myocardial infarction	0	1 (0.7)	0	1 (0.7)
Bronchopulmonary aspergillosis	0	0	1 (0.4)	0
Sepsis	1 (0.4)	0	2 (0.7)	0
Cause of death < 30 days				
Acute respiratory failure	2 (0.7)	0	2 (0.7)	0
Sepsis	1 (0.4)	0	2 (0.7)	0
Acute renal failure	1 (0.4)	0	1 (0.4)	0

Source: Study C2240 report

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

Reviewer: Deaths occurring within 30 days of study treatment were caused by acute respiratory failure (0.7%), infection (0.7%), and renal failure (0.4%) on the everolimus arm, whereas no deaths were attributed to these causes on the placebo arm.

7.3.2 Nonfatal Serious Adverse Events

As per the safety update (Feb 28, 2008), the top 5 Grade 3/4 adverse events were anemia (10%), dyspnea (8%), hyperglycemia (6%), fatigue (6%), and lymphopenia (4%), as summarized below.

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 NDA 22334
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Table 38: Grade 3/4 adverse reactions (SP)

	Second Interim Analysis (15-Oct-2007 cut-off)						Safety Update (28-Feb-2008 cut-off)					
	Everolimus N=269 (%)			Placebo N=135 (%)			Everolimus N=274 (%)			Placebo N=137 (%)		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Patients with ≥1 AE	95.5	45.7	8.6	93.3	23.0	4.4	96.7	51.8	13.1	93.4	23.4	5.1
Anemia	28.3	7.1	0.4	14.8	4.4	0.7	37.6	9.5	0.7	14.6	4.4	0.7
Dyspnea	19.3	4.5	1.5	10.4	2.2	0	23.7	6.2	1.5	14.6	2.9	0
Fatigue	27.5	4.5	0	25.9	3.0	0	30.7	5.5	0	27.0	2.9	0.7
Stomatitis	35.7	4.1	0.4	7.4	0	0	37.6	4.0	0.4	6.6	0	0
Hyperglycemia	8.2	4.1	0	2.2	1.5	0	12.0	6.2	0	2.2	1.5	0
Dehydration	4.1	3.0	0.4	3.7	1.5	0	5.1	3.6	0.4	4.4	1.5	0
γ-GT increased	4.8	3.0	0	4.4	1.5	0	5.5	3.6	0	5.8	1.5	0
Pneumonitis	7.1	2.6	0	0	0	0	9.9	2.6	0	0	0	0
Abdominal pain	7.8	2.2	0	3.0	0	0	9.5	3.3	0	4.4	0	0
Pneumonia	3.7	2.2	0	1.5	0	0	5.8	2.2	0.7	1.5	0	0
Asthenia	27.9	1.9	0.4	20.0	3.7	0	33.2	2.6	0.7	22.6	4.4	0
Back pain	9.7	1.5	0.7	10.4	0	0	12.4	1.5	0.7	10.9	0	0
Hypercholesterolemia	14.9	1.9	0	1.5	0	0	20.1	3.3	0	2.2	0	0
Lymphopenia	5.2	1.5	0	2.2	0	0	7.7	4.4	0	1.5	0	0
Vomiting	15.6	1.1	0	10.4	0	0	20.4	2.2	0	11.7	0	0
Hyperuricemia	0.7	0.4	0.4	2.2	2.2	0	0.7	0.4	0.4	3.6	2.2	0

Patients are counted only for the worst grade observed post-baseline
 Source: Study C2240 report

Reviewer: The grade 3 or 4 adverse reactions observed in more than 4% of patients were anemia (10%), dyspnea (8%), fatigue (6%), hyperglycemia (6%), stomatitis (4%) and lymphopenia (4%).

7.3.3 Dropouts and/or Discontinuations

The adverse reactions that caused treatment termination are shown below.

Table 39: Adverse reactions that cause treatment termination (SP)

Reason for treatment termination	Second interim analysis 15-Oct-2007 cut-off		Safety Update 28-Feb-2008 cut-off	
	Everolimus N=269 (%)	Placebo N=135 (%)	Everolimus N=274 (%)	Placebo N=137 (%)
Pneumonitis	7 (2.6)	0	7 (2.6)	0
Dyspnea	5 (1.9)	0	7 (2.6)	0
Lung disorder	4 (1.5)	0	4 (1.4)	0
Fatigue	3 (1.1)	0	3 (1.1)	0
Renal failure	1 (0.4)	0	3 (1.1)	0

Source: Study C2240 report

Reviewer: The five reasons for treatment termination were pneumonitis, dyspnea, lung disorder, fatigue and renal failure.

7.3.4 Dose Interruption and/or Dose Reductions

The adverse reactions that require dose interruption or dose reduction are summarized below.

	Second Interim Analysis Data cut-off: 15-Oct-2007		Safety Update Data cut-off: 28- Feb-2008	
	Everolimus N=269 (%)	Placebo N=135 (%)	Everolimus N=274 (%)	Placebo N=137 (%)
Patients with an AE leading to dose interruption or dose reduction	95 (35.3)	15 (11.1)	122 (44.5)	17 (12.4)
Stomatitis	12 (4.5)	1 (0.7)	13 (4.7)	1 (0.7)
Pneumonitis	9 (3.3)	0	12 (4.4)	0
Dyspnea	8 (3.0)	2 (1.5)	8 (2.9)	1 (0.7)
Mucosal inflammation	8 (3.0)	0	9 (3.3)	0
Asthenia	6 (2.2)	1 (0.7)	7 (2.6)	1 (0.7)
Pneumonia	6 (2.2)	1 (0.7)	6 (2.2)	1 (0.7)
Thrombocytopenia	6 (2.2)	0	6 (2.2)	0
Anemia	5 (1.9)	0	7 (2.6)	0
Diarrhea	5 (1.9)	0	7 (2.6)	0
Rash	4 (1.5)	1 (0.7)	5 (1.8)	1 (0.7)
Pyrexia	4 (1.5)	0	4 (1.5)	0
Vomiting	3 (1.1)	2 (1.5)	7 (2.6)	3 (2.2)
Dehydration	3 (1.1)	1 (0.7)	3 (1.1)	2 (1.5)
Blood creatinine increased	3 (1.1)	0	3 (1.1)	0
Constipation	3 (1.1)	0	2 (0.7)	0
Fatigue	3 (1.1)	0	4 (1.5)	0

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

	Second Interim Analysis Data cut-off: 15-Oct-2007		Safety Update Data cut-off: 28- Feb-2008	
	Everolimus N=269 (%)	Placebo N=135 (%)	Everolimus N=274 (%)	Placebo N=137 (%)
Interstitial lung disease	3 (1.1)	0	4 (1.5)	0
Nausea	3 (1.1)	0	6 (2.2)	1 (0.7)
Abdominal pain	2 (0.7)	0	3 (1.1)	0
Anorexia	2 (0.7)	0	3 (1.1)	0
Arthralgia	2 (0.7)	0	3 (1.1)	0
Edema peripheral	2 (0.7)	0	3 (1.1)	0
Pruritus	2 (0.7)	0	3 (1.1)	0
Pleural effusion	1 (0.4)	0	3 (1.1)	0
Hypercalcemia	0	2 (1.5)	1 (0.4)	2 (1.5)

Source: Study C2240 report

Reviewer: Mucositis, pneumonitis and symptoms related to both events were the most common reasons for treatment delay or dose reduction.

7.3.5 Additional therapy

Adverse reactions that require additional therapy are summarized below.

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Clinical Review
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 NDA 22334
 Afinitor (everolimus, RAD001)

Table 40: Adverse reactions that required medical therapy

	Second Interim Analysis Data cut-off: Oct 15, 2007		Safety Update Data cut-off: Feb 28, 2008	
	Everolimus N=269 (%)	Placebo N=135 (%)	Everolimus N=274 (%)	Placebo N=137 (%)
Patients with AE requiring medical therapy	227 (84.4)	87 (64.4)	247 (90.1)	97 (70.8)
Anemia	51 (19.0)	16 (11.9)	71 (25.9)	15 (10.9)
Stomatitis	44 (16.4)	1 (0.7)	49 (17.9)	1 (0.7)
Constipation	29 (10.8)	16 (11.9)	39 (14.2)	17 (12.4)
Diarrhea	29 (10.8)	2 (1.5)	35 (12.8)	2 (1.5)
Pyrexia	26 (9.7)	5 (3.7)	37 (13.5)	5 (3.6)
Nausea	24 (8.9)	9 (6.7)	36 (13.1)	9 (6.6)
Cough	23 (8.6)	6 (4.4)	35 (12.8)	9 (6.6)
Dyspnea	21 (7.8)	4 (3.0)	24 (8.8)	5 (3.6)
Rash	21 (7.8)	2 (1.5)	26 (9.5)	3 (2.2)
Mucosal inflammation	21 (7.8)	1 (0.7)	29 (10.6)	0
Edema peripheral	18 (6.7)	6 (4.4)	30 (10.9)	6 (4.4)
Insomnia	17 (6.3)	4 (3.0)	21 (7.7)	4 (2.9)
Back pain	15 (5.6)	5 (3.7)	22 (8.0)	4 (2.9)
Anorexia	14 (5.2)	6 (4.4)	17 (6.2)	6 (4.4)
Headache	13 (4.8)	5 (3.7)	18 (6.6)	5 (3.6)
Vomiting	12 (4.5)	8 (5.9)	17 (6.2)	8 (5.8)
Hyperglycemia	12 (4.5)	0	20 (7.3)	1 (0.7)
Abdominal pain	11 (4.1)	2 (1.5)	14 (5.1)	2 (1.5)
Pruritus	10 (3.7)	2 (1.5)	15 (5.5)	3 (2.2)
Pneumonitis	10 (3.7)	0	17 (6.2)	0
Hypercholesterolemia	6 (2.2)	0	17 (6.2)	0
Hypercalcemia	5 (1.9)	6 (4.4)	7 (2.6)	7 (5.1)

Source: Study C2240 report

Reviewer: The most common medical interventions required during everolimus treatment were anemia, gastrointestinal, respiratory, and skin sympt

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

7.3.6 Significant Adverse Events

The significant adverse events are summarized below.

Table 41: Significant adverse reactions observed in Study C2240 (SP)

Adverse Reaction	Listing (%)
Common ($\geq 20\%$)	Stomatitis (38), anemia (38), asthenia (33), diarrhea(30), cough (30), rash (29), nausea (26), anorexia (25), peripheral edema (25), pyrexia (20), vomiting (20), and hypercholesterolemia (20)
Grade 3/4	Anemia (10), dyspnea (8), hyperglycemia (6), fatigue (6), and lymphopenia (4)
Tx termination	Pneumonitis (3), Dyspnea (3), lung disease (1), fatigue (1), renal failure (1)
Death	ARDS (2), Infection (1), ARF (<1)

Source: Study C2240 report

7.3.7 Submission Specific Primary Safety Concerns

Several potential safety concerns were identified in the everolimus studies. These included the following categories of events: stomatitis/oral mucositis/ulcers, hematopoiesis decreased/cytopenias, rash and similar events, metabolic events, renal events, pulmonary events, bleeding and thromboembolic events, hepatic events and CNS events, as shown below.

Table 42: Specific adverse reactions in Study C2240 (SP)

Specific AEs	Second Interim Analysis Data cut-off: 15-Oct-2007		Safety Update Data cut-off: 28-Feb-2008	
	Everolimus N=269 (%)	Placebo N=135 (%)	Everolimus N=274 (%)	Placebo N=137 (%)
Any clinically notable AE	221 (82.2)	53 (39.3)	237 (86.5)	53 (38.7)
Stomatitis / oral mucositis / ulcers	112 (41.6)	11 (8.1)	120 (43.8)	11 (8.0)
Hematopoiesis decreased / cytopenias	103 (38.3)	24 (17.8)	136 (49.6)	25 (18.2)
Rash and similar events	84 (31.2)	9 (6.7)	95 (34.7)	9 (6.6)
Metabolic events	71 (26.4)	11 (8.1)	101 (36.9)	13 (9.5)
Renal events	27 (10.0)	4 (3.0)	36 (13.1)	3 (2.2)
Pulmonary events	24 (8.9)	0	36 (13.1)	0
Bleeding and thromboembolic events	19 (7.1)	6 (4.4)	23 (8.4)	6 (4.4)
Hepatic events	9 (3.3)	1 (0.7)	11 (4.0)	1 (0.7)

Source: Study C2240 report

Reviewer: Specific safety issues from each category were reviewed and described in the sections below.

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

7.3.7.1 Mucositis

Mucositis-related events included aphthous stomatitis, mouth ulcerations or stomatitis. The time to first occurrence of a mucositis related event was within 30 days of receipt of study product. In Study C2240, 12 patients had grade 3 or 4 mucositis and only one patient discontinued treatment. Total incidents are summarized below. Most of the mucositis subsided without dose modification or with minimal treatment, such as non-alcoholic or salt water mouth washes, or topical analgesic mouth treatments.

All Mucositis	Second interim analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus N=269%			Placebo N=135 %			Everolimus N=274 %			Placebo N=137%		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Patients with ≥1 AE	41.6	4.1	0.4	8.1	0	0	43.8	4.0	0.4	8.0	0	0
Stomatitis	35.7	4.1	0.4	7.4	0	0	37.6	4.0	0.4	6.6	0	0
Aphthous stomatitis	7.4	0	0	0	0	0	9.1	0	0	0.7	0	0
Mouth ulceration	1.1	0	0	0.7	0	0	1.5	0	0	0.7	0	0
Tongue ulceration	0	0	0	0	0	0	1.5	0	0	0	0	0

The event with maximum severity is counted for patients who experienced multiple episodes of an event

Reviewer: A significant number of patients with mucositis were observed in the everolimus arm. The severity and resolution appeared to be acceptable. Treatment discontinuation due to mucositis was infrequent.

7.3.7.2 Bone marrow toxicity

As summarized in the table below, 49% of patients had a reduction in blood cell counts. Among them, 42 patients (15%) receiving everolimus therapy required one or more blood transfusions for anemia, compared with 6 patients (4.4%) in the placebo arm.

Table 43: Cytopenia observed in Study C2240 (SP)

Hematological AEs	Second Interim Analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus N=269 %			Placebo N=135 %			Everolimus N=274 %			Placebo N=137 %		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Patients with ≥1 AE	38.3	10.0	0.4	17.8	4.4	0.7	49.6	15.3	0.7	18.2	5.1	0.7
Anemia	28.3	7.1	0.4	14.8	4.4	0.7	37.6	9.5	0.7	14.6	4.4	0.7
Thrombocytopenia	5.6	1.1	0	0	0	0	6.6	1.5	0	0	0	0
Lymphopenia	5.2	1.5	0	2.2	0	0	7.7	4.4	0	1.5	0	0
Leukopenia	1.9	0	0	0	0	0	2.6	0	0	0	0	0
Neutropenia	1.5	0	0	0.7	0	0	1.5	0.4	0	0.7	0	0
Hemoglobin decreased	0.7	0	0	0	0	0	1.5	0	0	1.5	0.7	0
Platelet count decreased	0.7	0.4	0	0	0	0	1.1	0.4	0	0	0	0
Pancytopenia	0.4	0	0	0	0	0	0.4	0	0	0	0	0
Anemia of malignant disease	0	0	0	0.7	0.7	0	0	0	0	0.7	0.7	0
White blood cell count decreased	0	0	0	0.7	0	0	0	0	0	1.5	0	0

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
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Hematological AEs	Second Interim Analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus N=269 %			Placebo N=135 %			Everolimus N=274 %			Placebo N=137 %		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Iron deficiency anemia	0	0	0	0	0	0	0.4	0	0	0	0	0
Microcytic anemia	0	0	0	0	0	0	0.4	0	0	0	0	0
Lymphocyte count decreased	0	0	0	0	0	0	0	0	0	1.5	0	0

The event with maximum severity is counted for patients who experienced multiple episodes of an event
 Source: Study C2240 report

Reviewer: No treatment discontinuation due to cytopenia was observed.

7.3.7.3 Rash and similar events

Rash and similar dermatologic adverse reactions were frequently observed in the everolimus arm, as shown below. In addition to skin rash and related events, palmar-plantar erythrodysesthesia syndrome (PPE) was reported in 14 patients (4.7%), 7 cases were grade 1, 5 were grade 2 and 1 was grade 3.

Table 44: Rash and similar skin reactions observed in Study C2240 (SP)

Dermatologic AEs	Second interim analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus N=269 %			Placebo N=135 %			Everolimus N=274 %			Placebo N=137 %		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Patients with ≥1 AE	31.2	1.9	0	6.7	0	0	34.7	1.5	0	6.6	0	0
Rash	25.7	1.1	0	5.9	0	0	29.2	1.1	0	6.6	0	0
Erythema	4.1	0.7	0	0	0	0	4.4	0.4	0	0	0	0
Rash maculopapular	1.5	0	0	0	0	0	1.5	0	0	0	0	0
Rash erythematous	0.4	0	0	0.7	0	0	0.4	0	0	0	0	0
Generalized erythema	0	0	0	0	0	0	0.4	0	0	0	0	0

The event with maximum severity is counted for patients who experienced multiple episodes of an event
 Source: Study C2240 report

Reviewer: No treatment discontinuation due to adverse skin reactions was observed.

7.3.7.4 Metabolic events

Metabolic adverse reactions were common in the everolimus patients of Study C2240 (see table below). The incidence of events such as hypercholesterolemia, hypertriglyceridemia, hyperglycemia and hyperlipidemia were increased at least a 2-fold compared to placebo.

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 45: Metabolic events with 2 fold increase observed in Study C2240 (SP)

Metabolic AEs	Second Interim Analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus N=269 %			Placebo N=135 %			Everolimus N=274 %			Placebo N=137 %		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Patients with ≥1 AE	26.4	8.2	0.4	8.1	1.5	0	36.9	13.1	0.4	9.5	1.5	0
Hypercholesterolemia	14.9	1.9	0	1.5	0	0	20.1	3.3	0	2.2	0	0
Hypertriglyceridemia	10.0	0.7	0	2.2	0	0	14.6	1.1	0	2.2	0	0
Hyperglycemia	8.2	4.1	0	2.2	1.5	0	12.0	6.2	0	2.2	1.5	0
Hyperlipidemia	2.2	0.4	0	0	0	0	2.2	0.4	0	0	0	0
Blood glucose increased	1.9	0.7	0	0.7	0	0	2.9	1.5	0	0.7	0	0
Blood triglycerides increased	1.5	0.7	0	0	0	0	2.2	0.7	0	0.7	0	0
Diabetes mellitus	1.5	1.1	0	1.5	0	0	1.8	1.5	0	0	0	0
Blood cholesterol increased	0.7	0	0	0	0	0	0.7	0	0	0	0	0
Pancreatitis acute	0.7	0	0.4	0	0	0	0.7	0	0.4	0	0	0
Type 2 diabetes mellitus	0.4	0	0	0	0	0	0.4	0	0	0	0	0
Diabetes mellitus inadequate control	0	0	0	0.7	0	0	0	0	0	2.2	0	0

The event with maximum severity is counted for patients who experienced multiple episodes of an event
 Source: Study C2240 report

Reviewer: Hyperlipidemia, a known class effect of rapamycin and its derivatives, could respond to lipid lowering agents in association with dietary recommendations. Statins and fibrates have been used to effectively control hypercholesterolemia and hypertriglyceridemia in patients receiving everolimus. No treatment discontinuation due to an adverse metabolic reaction was observed.

7.3.7.5 Renal events

As shown in the table below, increased serum creatinine concentration only occurred in everolimus arm patients.

Table 46: Renal adverse reactions observed in Study C2240 (SP)

Renal AEs	Second Interim Analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus N=269 %			Placebo N=135 %			Everolimus N=274 %			Placebo N=137 %		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Patients with ≥1 AE	10.0	1.1	0.4	3.0	2.2	0	13.1	3.3	0.4	2.2	2.2	0
Blood creatinine increased	7.8	0.4	0	0.7	0	0	9.5	1.1	0	0	0	0
Renal failure	1.9	0.7	0	1.5	1.5	0	2.9	1.8	0	1.5	1.5	0
Renal failure acute	0.4	0	0.4	1.5	1.5	0	1.1	0.7	0.4	1.5	1.5	0
Renal failure chronic	0.4	0	0	0.7	0	0	0.7	0.4	0	0.7	0	0
Blood urea increased	0	0	0	0.7	0	0	0.4	0	0	0.7	0	0
Proteinuria	0	0	0	0	0	0	0.4	0	0	0	0	0

The event with maximum severity is counted for patients who experienced multiple episodes of an event
 Source: Study C2240 report

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Reviewer: Treatment-related creatinine elevation and renal failure were 9.5% and 1% more, respectively, in patients receiving everolimus. Carefully monitoring of serum creatinine and renal function should be recommended for patients receiving everolimus treatment.

7.3.7.6 Pulmonary events

The pulmonary toxicities of Study C2240 are summarized below.

Table 47: Pulmonary adverse reactions observed in Study C2240 (SP)

Pulmonary AEs	Second Interim Analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus N=269 %			Placebo N=135 %			Everolimus N=274 %			Placebo N=137 %		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Patients with ≥1 AE	8.9	3.3	0	0	0	0	13.5	3.6	0	0	0	0
Pneumonitis	7.1	2.6	0	0	0	0	9.9	2.6	0	0	0	0
Interstitial lung disease	1.5	0.4	0	0	0	0	2.2	0.7	0	0	0	0
Lung infiltration	1.1	0.7	0	0	0	0	1.5	0.7	0	0	0	0
Pulmonary alveolar hemorrhage	0.4	0.4	0	0	0	0	0.4	0.4	0	0	0	0
Pulmonary toxicity	0.4	0	0	0	0	0	0.4	0	0	0	0	0
Alveolitis	0	0	0	0	0	0	0.4	0	0	0	0	0

The event with maximum severity is counted for patients who experienced multiple episodes of an event
 Source: Study C2240 report

The applicant's analysis by terms listed in the table above summed 36 (13.1%) patients with pulmonary events, all from the everolimus arm. After further reviewing all respiratory AEs, three additional cases of pneumopathy [Patient 0606-00003 and Patient 0606-00024] and non-infectious pneumopathy [Patient 0604-00029] were identified which could represent pneumonitis, making total of 39 cases (14.8%). However, two of the initial 36 cases that had been reported as pneumonitis were of infectious origin (Patient 0429-00007 and Patient 0756-00025) and were therefore discounted. Therefore, the table above shows a 13.5% (37 patients) incidence of pulmonary events in the everolimus arm.

Reviewer: Of 37 patients (13.5%) with a pulmonary event or pneumonitis, 18 were grade 2 (6.6%) and 10 (3.6%) were grade 3. There was no grade 4 pneumonitis. Complete resolution was observed in 64% (18/28) of patients with Grade 2 and 3 pneumonitis and 57% (16/28) of patients with grade 2 or 3 pneumonitis required steroid treatment. Dose reduction was required for 50% (14/28) of grade 2 or 3 cases and treatment discontinuation mandated for 36% (10/28) of grade 2 or 3 cases. Therefore, dose reduction and termination criteria for pneumonitis should be included in the proposed label. In addition this may be a post marketing safety issue

Furthermore, the applicant's blinded central radiology review indicated that new or worsening CT changes were observed in 48.2% and 14.6% of everolimus and placebo arm patients, respectively. Clinically-reported pneumonitis cases occurred in only 13.5% of patients and 0% of patient in the placebo arm. Among patients with a CT suggestive of pneumonitis, only 6.2% (17/274) had clinically confirmed pneumonitis while 4.1% (11/274) had other lung processes.

Therefore, monitoring everolimus treatment-emergent pneumonitis should combine the clinical presentation and CT results, keeping in mind that the latter is highly sensitive but lacks specificity in the diagnosis of pneumonitis.

7.3.7.7 Coagulation abnormalities

As summarized in the table below, coagulation abnormalities that resulted in bleeding events were more frequent in the everolimus arm. In addition, minor bleeding such as epistaxis was reported by 18% (51 of 274) of patients on the everolimus arm versus 0% in the placebo arm. Forty-nine epistaxis cases were grade 1, and two were grade 2.

Table 48: Coagulation abnormalities and adverse reactions (SP)

Coagulation AEs	Second Interim Analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus N=269 %			Placebo N=135 %			Everolimus N=274 %			Placebo N=137%		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Patients with ≥1 AE	7.1	0.4	0	4.4	0.7	0	8.4	0.7	0	4.4	0.7	0
Hemorrhoids	4.5	0	0	0.7	0	0	5.5	0	0	0.7	0	0
Anal hemorrhage	0.4	0	0	0	0	0	0.4	0	0	0	0	0
Angina pectoris	0.4	0	0	0	0	0	0.4	0	0	0	0	0
Cerebral hemorrhage	0.4	0	0	0	0	0	0.4	0	0	0	0	0
Deep vein thrombosis	0.4	0.4	0	0.7	0	0	0.4	0.4	0	0.7	0	0
Gastric hemorrhage	0.4	0	0	0	0	0	0	0	0	0	0	0
Melena	0.4	0	0	0.7	0	0	0.4	0	0	0.7	0	0
Rectal hemorrhage	0.4	0	0	0.7	0	0	0.7	0	0	0.7	0	0
Retinal hemorrhage	0.4	0	0	0	0	0	0.4	0	0	0	0	0
Hematochezia	0	0	0	0.7	0	0	0.4	0.4	0	0.7	0	0
Thrombosis	0	0	0	0	0	0	0	0	0	0.7	0.7	0

Patients are counted only for the worst grade observed post-baseline

Source: Study C2240 report

Reviewer: Increased bleeding events for patients on the everolimus arm were related to the frequency of thrombocytopenia. Therefore, adequate platelet count monitoring should be in place throughout the everolimus treatment course.

The incidences of thromboembolic events were similar between the two arms.

7.3.7.8 Hepatic events

All treatment emergent hepatic function abnormalities are summarized in Section 7.4.2.2 chemistry. Based on the Study C2240 report, changes in liver enzymes in patients without co-existing liver disease were reversible. AST level elevation was the most common hepatic event and was predominantly observed in the everolimus arm (2.9%), with two grade 3 and one grade 4 cases.

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 49: Hepatic adverse reactions observed in Study C2240 patients without co-existing liver disease (SP)

Hepatic AEs	Second Interim Analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus N=269 %			Placebo N=135 %			Everolimus N=274 %			Placebo N=137 %		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Patients with ≥1 AE	3.3	1.1	0	0.7	0	0	4.0	1.1	0.4	0.7	0	0
AST increased	2.6	0.7	0	0.7	0	0	2.9	0.7	0.4	0.7	0	0
ALT increased	1.9	0.4	0	0	0	0	2.9	0.4	0	0	0	0
Hepatic failure	0.4	0.4	0	0	0	0	0.4	0.4	0	0	0	0
LFT abnormal	0.4	0	0	0	0	0	0	0	0	0	0	0

The event with maximum severity is counted for patients who experienced multiple episodes of an event
 Source: Study C2240 report

Reviewer: Adequate liver function monitoring should be considered regardless of co-existing liver disease.

7.3.7.9 Infections

Treatment emergent infections, special infections, and treatment related infections under any organ classes were assessed and summarized below.

Table 50: Infections observed in Study C2240 patients (SP)

Infection and infestations (%)	Second Interim Analysis Data cut-off: 15-Oct-2007		Safety Update Data cut-off: 28-Feb-2008	
	Everolimus N=269 %	Placebo N=135 %	Everolimus N=274 %	Placebo N=137 %
Treatment emergent infections	19 (7)	2 (2)	101 (37)	25 (18)
Pneumonia	4 (12)	1 (<1)	16 (6)	2 (1)
Treatment Termination				
Influenza	3 (1)	0	3 (1)	1 (<1)
Aspergillosis	1 (<1)	0	1 (<1)	0
Bronchopulmonary aspergillosis	1 (<1)	0	2 (<1)	0
Herpes zoster	1 (<1)	0	2 (<1)	2 (1)
Sepsis	0	0	2 (<1)	1 (<1)
Dose Reduction				
Pneumonia	4 (2)	1 (<1)	6 (2)	1 (<1)
Drug-related infections^a	27 (10)	3 (2)	36 (13)	3 (2)
Grade 3	6 (2)	0	6 (2)	0
Grade 4	3 (1)	0	6 (2)	0

a. Includes all preferred terms within the infection and infestation system organ class.

Source: Study C2240 report

Reviewer: Up to 37% treatment-related infections were noted, with 7% grade 3 and 3% grade 4. Three percent required dose reduction or treatment termination. This may be a post marketing safety issue

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

7.3.7.10 Neurological and psychiatric events

Treatment emergent neurological and psychiatric events at the Feb 28, 2009 cut-off date were assessed and summarized below.

	Everolimus N=274 (%)			Placebo N=137 (%)		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Any CNS adverse reaction	106 (39)	7 (3)	2 (<1)	38 (28)	5 (4)	1 (<1)
Headache	51 (19)	2 (<1)	1 (<1)	12 (9)	1 (<1)	0
Dysgeusia	28 (10)	0	0	3 (2)	0	0
Insomnia	25 (9)	1 (<1)	0	7 (5)	0	0
Dizziness	18 (7)	1 (<1)	0	5 (4)	0	0
Paresthesia	13 (5)	0	0	4 (3)	0	0
Anxiety	12 (4)	0	0	4 (3)	0	0
Confusion	4 (2)	3 (2)	0	3 (2)	1 (<1)	0
Sonolence	4 (2)	1 (<1)	0	1 (<1)	0	0
Peripheral sensory neuropathy	2 (<1)	0	0	0	0	0
Lost of consciousness	1 (<1)	1 (<1)	0	0	0	0

Source: Study C2240 report

Reviewer: The neurological and psychological safety profile of everolimus obtained from study C2240 appears to be acceptable.

7.3.7.11 Less frequent but clinically significant events for everolimus

Infrequent but clinically significant adverse reactions observed on the everolimus arm but not on the placebo arm included:

- Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)
- General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%)
- Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)
- Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasia (4%), skin lesion (4%), acneiform dermatitis (3%)
- Metabolism and nutrition disorders: Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (<1%)
- Nervous system disorders: Insomnia (9%), dizziness (7%), paresthesia (5%)
- Eye disorders: Eyelid edema (4%), conjunctivitis (2%)
- Vascular disorders: Hypertension (4%)
- Renal and urinary disorders: Renal failure (3%)
- Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%)
- Musculoskeletal and connective tissue disorders: Jaw pain (3%)

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

- Hematologic disorders: Hemorrhage (8%), Hemorrhoids (5%), Hemorrhage (3%)

Reviewer: This information will be included in the proposed label.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The adverse reactions that occurred in 5% or more of patients in the everolimus arm are listed in the table below with the incidence in the placebo arm as a comparator.

Table 51: Treatment emergent adverse reaction that occurred in the everolimus arm > 5%

MedDRA Preferred terms	Second Interim Analysis 15-Oct-2007 cut-off		Safety Update 28-Feb-2008 cut-off	
	Everolimus N=269 (%)	Placebo N=135 (%)	Everolimus N=274 (%)	Placebo N=137 (%)
Patients with ≥1 AE	257 (95.5)	126 (93.3)	265 (96.7)	128 (93.4)
Stomatitis	96 (35.7)	10 (7.4)	103 (37.6)	9 (6.6)
Anemia	76 (28.3)	20 (14.8)	103 (37.6)	20 (14.6)
Asthenia	75 (27.9)	27 (20.0)	91 (33.2)	31 (22.6)
Fatigue	74 (27.5)	35 (25.9)	84 (30.7)	37 (27.0)
Rash	69 (25.7)	8 (5.9)	80 (29.2)	9 (6.6)
Diarrhea	66 (24.5)	8 (5.9)	81 (29.6)	9 (6.6)
Cough	62 (23.0)	19 (14.1)	82 (29.9)	22 (16.1)
Anorexia	59 (21.9)	17 (12.6)	69 (25.2)	19 (13.9)
Nausea	55 (20.4)	24 (17.8)	72 (26.3)	26 (19.0)
Dyspnea	52 (19.3)	14 (10.4)	65 (23.7)	20 (14.6)
Edema peripheral	48 (17.8)	10 (7.4)	68 (24.8)	11 (8.0)
Pyrexia	43 (16.0)	11 (8.1)	54 (19.7)	12 (8.8)
Constipation	42 (15.6)	23 (17.0)	53 (19.3)	24 (17.5)
Vomiting	42 (15.6)	14 (10.4)	56 (20.4)	16 (11.7)
Mucosal inflammation	41 (15.2)	3 (2.2)	51 (18.6)	2 (1.5)
Hypercholesterolemia	40 (14.9)	2 (1.5)	55 (20.1)	3 (2.2)
Headache	39 (14.5)	11 (8.1)	51 (18.6)	12 (8.8)
Epistaxis	37 (13.8)	0	49 (17.9)	0
Dry skin	29 (10.8)	6 (4.4)	35 (12.8)	7 (5.1)
Pruritus	27 (10.0)	6 (4.4)	37 (13.5)	9 (6.6)
Hypertriglyceridemia	27 (10.0)	3 (2.2)	40 (14.6)	3 (2.2)
Back pain	26 (9.7)	14 (10.4)	34 (12.4)	15 (10.9)
Dysgeusia	23 (8.6)	3 (2.2)	28 (10.2)	3 (2.2)
Hyperglycemia	22 (8.2)	3 (2.2)	33 (12.0)	3 (2.2)
Abdominal pain	21 (7.8)	4 (3.0)	26 (9.5)	6 (4.4)
Blood creatinine increased	21 (7.8)	1 (0.7)	26 (9.5)	0
Arthralgia	20 (7.4)	13 (9.6)	28 (10.2)	14 (10.2)
Insomnia	20 (7.4)	7 (5.2)	25 (9.1)	7 (5.1)

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

MedDRA Preferred terms	Second Interim Analysis 15-Oct-2007 cut-off		Safety Update 28-Feb-2008 cut-off	
	Everolimus N=269 (%)	Placebo N=135 (%)	Everolimus N=274 (%)	Placebo N=137 (%)
Dry mouth	20 (7.4)	6 (4.4)	21 (7.7)	8 (5.8)
Aphthous stomatitis	20 (7.4)	0	25 (9.1)	1 (0.7)
Pneumonitis	19 (7.1)	0	27 (9.9)	0
Pain in extremity	18 (6.7)	7 (5.2)	28 (10.2)	9 (6.6)
Weight decreased	16 (5.9)	5 (3.7)	24 (8.8)	6 (4.4)
Edema	16 (5.9)	2 (1.5)	7 (2.6)	0
Thrombocytopenia	15 (5.6)	0	18 (6.6)	0
Lymphopenia	14 (5.2)	3 (2.2)	21 (7.7)	2 (1.5)
Palmar-plantar erythrodysesthesia syndrome	14 (5.2)	0	13 (4.7)	0
Gamma-glutamyltransferase increased	13 (4.8)	6 (4.4)	15 (5.5)	8 (5.8)
Pleural effusion	12 (4.5)	1 (0.7)	18 (6.6)	1 (0.7)
Hemorrhoids	12 (4.5)	1 (0.7)	15 (5.5)	1 (0.7)
Chest pain	12 (4.5)	1 (0.7)	14 (5.1)	2 (1.5)
Hypophosphatemia	12 (4.5)	1 (0.7)	14 (5.1)	1 (0.7)
Abdominal pain upper	11 (4.1)	7 (5.2)	17 (6.2)	7 (5.1)
Dehydration	11 (4.1)	5 (3.7)	14 (5.1)	6 (4.4)
Musculoskeletal chest pain	11 (4.1)	3 (2.2)	14 (5.1)	4 (2.9)
Hemoptysis	10 (3.7)	7 (5.2)	14 (5.1)	4 (2.9)
Dizziness	10 (3.7)	3 (2.2)	18 (6.6)	5 (3.6)
Pneumonia	10 (3.7)	2 (1.5)	16 (5.8)	2 (1.5)
Hypercalcemia	8 (3.0)	1 (0.7)	17 (6.2)	3 (2.2)
Nasopharyngitis	8 (3.0)	1 (0.7)	17 (6.2)	3 (2.2)
Nail disorder	6 (2.2)	0	14 (5.1)	0

Patients are counted only for the worst grade observed post-baseline
 Source: Study C2240 report

Reviewer: The most common treatment emergent adverse reactions with everolimus were similar to those of other rapamycin class drugs. The adverse reactions observed in more than 20% of patients in study C2240 were stomatitis, anemia, asthenia, rash, diarrhea, cough, anorexia, nausea, dyspnea, peripheral edema, vomiting, pyrexia, and hypercholesterolemia.

The applicant also summarized adverse reactions that investigators suspected to be related to everolimus, as shown below.

Table 52: Investigator determined drug-related adverse reaction* that occurred in the everolimus arm > 5%,

	Second interim analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus N=269 (%)			Placebo N=135 (%)			Everolimus N=274 (%)			Placebo N=137 (%)		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Any adverse reaction	86.6	27.9	1.1	54.8	6.7	0	89.1	35.4	3.3	58.4	6.6	0
Gastrointestinal disorders												
Stomatitis ^a	39.8	3.3	0	8.1	0	0	43.8	4.0	0.4	8.0	0	0
Diarrhea	17.1	1.5	0	3.0	0	0	21.2	1.5	0	3.6	0	0
Nausea	15.2	0	0	8.1	0	0	18.2	0.4	0	8.0	0	0

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

	Second interim analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus N=269 (%)			Placebo N=135 (%)			Everolimus N=274 (%)			Placebo N=137 (%)		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Vomiting	11.9	0	0	3.7	0	0	15.0	0.7	0	3.6	0	0
Dry mouth	6.3	0	0	3.0	0	0	6.2	0	0	4.4	0	0
Constipation	5.9	0	0	5.9	0	0	6.9	0	0	6.6	0	0
Skin and subcutaneous tissue disorders												
Rash	24.5	0.7	0	4.4	0	0	28.1	1.1	0	5.1	0	0
Dry skin	10.8	0.4	0	3.7	0	0	12.0	0.4	0	4.4	0	0
Pruritus	8.9	0.4	0	2.2	0	0	11.7	0.4	0	2.9	0	0
Palmar-plantar erythrodysesthesia syndrome	5.2	0.4	0	0	0	0	4.7	0.4	0	0	0	0
General disorders and administration site conditions												
Fatigue	19.7	3.0	0	16.3	0.7	0	23.0	3.3	0	16.8	0.7	0
Asthenia	17.8	1.5	0	8.1	0.7	0	22.3	1.8	0	9.5	0.7	0
Mucosal inflammation	14.5	1.1	0	2.2	0	0	17.2	1.1	0	1.5	0	0
Edema peripheral	9.7	0	0	3.0	0	0	13.1	0.4	0	3.6	0	0
Pyrexia	4.5	0	0	2.2	0	0	5.5	0	0	2.2	0	0
Blood and lymphatic system disorders												
Anemia	18.2	4.5	0	5.2	0.7	0	25.2	6.2	0.4	4.4	0.7	0
Lymphopenia	4.8	1.5	0	2.2	0	0	6.6	3.3	0	1.5	0	0
Thrombocytopenia	4.5	1.1	0	0	0	0	5.1	1.1	0	0	0	0
Metabolism and nutrition disorders												
Anorexia	16.4	0.4	0	5.9	0	0	18.6	0.4	0	5.8	0	0
Hypercholesterolemia	13.4	1.9	0	1.5	0	0	17.9	2.6	0	1.5	0	0
Hypertriglyceridemia	9.7	0.7	0	2.2	0	0	14.6	1.1	0	2.2	0	0
Hyperglycemia	5.9	2.2	0	0.7	0.7	0	7.7	4.4	0	0.7	0.7	0
Respiratory, thoracic and mediastinal disorders												
Cough	11.9	0	0	3.7	0	0	13.5	0	0	4.4	0	0
Epistaxis	8.6	0	0	0	0	0	12.0	0	0	0	0	0
Pneumonitis ^b	8.2	3.0	0	0	0	0	13.5	3.6	0	0	0	0
Dyspnea	8.2	1.5	0	2.2	0	0	10.2	1.8	0	2.9	0	0
Infections ^c	10.0	2.2	1.1	2.2	0	0	13.1	2.2	2.2	2.2	0	0
Nervous system disorders												
Dysgeusia	8.2	0	0	1.5	0	0	9.9	0	0	1.5	0	0
Headache	7.1	0	0	5.2	0	0	8.8	0	0	5.1	0	0
Investigations												
Blood creatinine increased	0.4	0	0	0	0	0	5.1	0	0	0	0	0
Weight decreased	4.1	0	0	0.7	0	0	5.5	0	0	0.7	0	0

* Search was conducted by broader MedDRA terms

a Includes aphthous stomatitis, mouth ulceration, and stomatitis

b Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, and pulmonary toxicity

c Includes all preferred terms within the 'infections and infestations' system organ class

Source: Study C2240 study report and safety update

Reviewer: The applicant used a selected broader term search by including some more relevant lower level terms to each preferred term group. For example, stomatitis events also included aphthous stomatitis, mouth ulceration, and tongue ulceration. Considering the double blind design of study C2240, the applicant only included investigator determined related adverse reactions for their summary. The everolimus-related stomatitis increased to 44% compared to

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

38% treatment adverse reaction by preferred term only, whereas there was only 1% increase for the placebo arm (8% drug-related versus 7% treatment-emergent). In order to maximally utilize the advantage of double blinding for safety evaluation and also minimize any potential bias, the clinical reviewer recommended that the applicant search all treatment emergent adverse reactions regardless causality by preferred terms and selected broader terms. . This reviewer verified applicant's results in the table below.

The table below only includes adverse reactions that occurred in 10% or more of patients on the everolimus arm at the time of February 28, 2008 cut-off.

Table 53: Adverse reaction that occurred in the everolimus arm > 10% by selected broader terms search (Feb 28, 2008 cut-off)

	Everolimus N=274 (%)			Placebo N=137 (%)		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Any adverse reaction	97	52	13	93	23	5
Gastrointestinal disorders						
Stomatitis ^a	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and infestations^b	37	7	3	18	1	0
General disorders and administration site conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis ^c	14	4	0	0	0	0
Skin and subcutaneous tissue disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and nutrition disorders						
Anorexia	25	1	0	14	<1	0
Nervous system disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	10	1	0	7	0	0
Median duration of treatment (days)	141			60		

^a Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

b Includes all preferred terms within the 'infections and infestations' system organ class including pneumonia, aspergillosis, candidiasis, and sepsis.

c Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Source: Study C2240 study report and safety update

In order to determine which safety assessment would be the best to represent the toxicity profile of everolimus, this review compared all adverse reactions that were more than 10% in the treatment emergent adverse reactions by selected broader terms assessment to the other two assessments. The table below is a comparison of three assessments, treatment-emergent adverse reactions regardless relation to the drug by MedDRA preferred terms (TEPT), investigator determined drug-related adverse reactions by broader terms (DRBT), and treatment-emergent adverse reactions regardless relation to the drug by broader terms (TEBT).

Table 54: Comparison on results of treatment emergent, drug-related, and drug-related plus possibly and probably related adverse reactions

	Everolimus N=274 (%)			Placebo N=137 (%)		
	TEBT	DRBT	TEPT	TEBT	DRBT	TEPT
Any adverse reaction	97	89	97	93	58	93
Gastrointestinal disorders						
Stomatitis ^a	44	44	37	8	8	7
Diarrhea	30	21	30	7	4	7
Nausea	26	18	26	19	8	19
Vomiting	20	15	20	12	4	12
Infections and infestations^b	37	13	37	18	2	19
General disorders and administration site conditions						
Asthenia	33	22	33	23	9	27
Fatigue	31	23	31	27	17	27
Edema peripheral	25	13	25	8	4	11
Pyrexia	20	6	20	9	2	9
Mucosal inflammation	19	17	19	1	2	2
Respiratory, thoracic and mediastinal disorders						
Cough	30	14	30	16	4	16
Dyspnea	24	10	24	15	3	15
Epistaxis	18	12	18	0	0	0
Pneumonitis ^c	14	14	10	0	0	0
Skin and subcutaneous tissue disorders						
Rash	29	28	29	7	5	7
Pruritus	14	12	14	7	3	7
Dry skin	13	12	13	5	4	5
Metabolism and nutrition disorders						
Anorexia	25	19	25	14	6	14
Nervous system disorders						
Headache	19	9	19	9	5	9
Dysgeusia	10	10	12	2	2	2
Musculoskeletal and connective tissue disorders						
Pain in extremity	10	2	10	7	2	7
Median duration of treatment (days)	141			60		

Note: TEPT = treatment emergent adverse reactions regardless relation to the drug by MedDRA preferred terms, DRBT = investigator determined drug related adverse reactions by broader terms, TEBT = treatment emergent adverse reactions by broader terms

Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

Reviewer: As shown in the above safety assessment comparison table, the profiles of adverse reactions which are related to or probably and possibly related to everolimus defined by broader terms (TEBT) were very similar to those of treatment emergent adverse reactions by the preferred terms (TEPT), but highlighted a few clinically significant toxicities, such as stomatitis, and infection. The drug-related adverse reactions by broader terms (DRBT) were obviously less than both TEBT and TEPT. Therefore, this reviewer believes that the TEBT data would best represent the safety profile of everolimus and should be included in the proposed label.

7.4.2 Laboratory Findings

All patients had one or more mild to severe laboratory abnormalities. Grade 3 and 4 laboratory changes, both hematology and chemistry, were observed in approximately 30% of patients.

7.4.2.1 Hematology

Hematologic abnormalities were reported in 98% of patients. Among them, grade 3 or 4 changes were observed in 29% of patients in the everolimus arm and 11% in the placebo arm, as detailed in the table below.

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Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 Afinitor (everolimus, RAD001)

Table 55: Hematology adverse reactions observed in Study C2240 (SP)

Hematology adverse reaction	Second Interim Analysis Data cut-off: 15-Oct-2007				Safety Update Data cut-off: 28-Feb-2008							
	Everolimus N=269		Placebo N=135		Everolimus N=274		Placebo N=137					
	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %	All %	Gr 3 %	Gr 4 %			
Patients with ≥ 1 abnormal laboratory value	97.4	21.9	1.9	81.5	9.6	0.7	97.8	25.5	3.6	84.7	9.5	1.5
Hemoglobin decreased	90.7	8.9	0.4	76.3	5.2	0	92.3	12.0	1.1	78.8	5.1	0.7
Lymphocytes decreased	42.4	14.1	1.5	28.9	5.2	0	50.7	15.7	2.2	28.5	5.1	0
Leukocytes decreased	26.0	0	0	8.1	0	0.7	28.8	0	0	8.8	0	0.7
Platelets decreased	20.4	0.7	0	2.2	0	0.7	23.4	1.1	0	2.2	0	0.7
Neutrophils decreased	10.8	0	0	3.0	0	0	13.5	0	0.4	3.6	0	0

Patients are counted only for the worst grade observed post-baseline
 Source: Study C2240 report

Reviewer: Decreases in blood count, especially a decrease in hemoglobin, occurred more often in everolimus arm patients. Although fewer than 4% of patients experienced grade 4 hematological adverse reactions, anemia, lymphopenia, leukopenia and neutropenia were all common. Adequate monitoring of blood counts is recommended.

7.4.2.2 Chemistry

Chemistry abnormalities were reported in 97% of patients. Among them, grade 3 or 4 changes were observed in 31% of patients in everolimus arm and 4% in the placebo arm.

Clinical Review
 Reviewer: Qin Ryan MD, PhD
 NDA 22334
 A finitor (everolimus, RAD001)

Table 56: Chemistry adverse reactions observed in Study C2240 (SP)

Chemistry adverse reaction	Second Interim Analysis Data cut-off: 15-Oct-2007						Safety Update Data cut-off: 28-Feb-2008					
	Everolimus N=269			Placebo N=135			Everolimus N=274			Placebo N=137		
	All	Gr 3%	Gr 4%	All%	Gr 3%	Gr 4%	All%	Gr 3%	Gr 4%	All%	Gr 3%	Gr 4%
Patients with ≥ 1 abnormal laboratory value	96.3	20.4	0.4	81.5	3.0	0	97.1	28.1	2.6	86.9	3.6	0
Cholesterol increased	76.2	3.3	0	31.9	0	0	77.4	4.4	0	35.0	0	0
Triglycerides increased	71.0	0.7	0	30.4	0	0	73.0	0.7	0	33.6	0	0
γ-GT increased	NR	NR	NR	NR	NR	NR	53.6	12.0	0	35.0	5.8	0
Glucose increased	50.2	11.5	0	23.0	1.5	0	57.3	15.3	0.4	24.8	1.5	0
Creatinine increased	46.5	0.4	0	32.6	0	0	50.0	1.5	0	33.6	0	0
Alkaline phosphatase increased	37.5	0.7	0	29.6	1.5	0	44.2	1.8	0	29.9	1.5	0
Phosphate decreased	32.3	4.5	0	6.7	0	0	37.2	6.2	0	8.0	0	0
AST increased	20.8	0.4	0	6.7	0	0	24.8	0.4	0.4	6.6	0	0
Sodium decreased	18.2	0.4	0	7.4	0	0	20.8	0.4	0.4	7.3	0	0
ALT increased	17.8	0.4	0	3.7	0	0	21.2	1.1	0	3.6	0	0
Calcium decreased	17.1	0	0	5.9	0	0	27.0	0	0	8.0	0	0
Potassium increased	8.2	0	0	11.9	0	0	10.6	0	0	12.4	0	0
Albumin decreased	7.1	0	0	6.7	0	0	9.9	0.4	0	8.8	0	0
Magnesium increased	5.2	0	0	3.0	0	0	5.8	0	0	3.6	0	0
Calcium increased	4.8	0.4	0	8.9	0	0	5.1	0.4	0	10.9	0	0
Potassium decreased	3.0	0	0	0.7	0	0	3.6	0.4	0.4	0.7	0	0
Glucose decreased	2.6	0	0	3.0	0	0	2.6	0	0	3.6	0	0
Magnesium decreased	2.6	0	0	0	0	0	3.3	0	0	0.7	0.7	0
Bilirubin increased	2.2	0.7	0.4	1.5	0	0	2.9	0.7	0.4	2.2	0	0
Sodium increased	1.1	0.4	0	0	0	0	1.8	0.4	0.4	0.7	0	0

Patients are counted only for the worst grade observed post-baseline
 Source: Study C2240 report

Reviewer: More electrolyte, metabolic, liver or renal function test abnormalities occurred in the everolimus arm. Adequate chemistry analyses, including electrolytes, hepatic function and metabolic profile (glucose and lipids), is recommended during everolimus treatment.

8 Postmarketing Experience

None

9 Appendices

9.1 Literature Review/References

This reviewer performed a literature review on the following topics:

- The natural history of renal cell carcinoma,
- Available treatments for RCC, and
- Published studies of RCC using everolimus or other chemotherapies.

No additional information regarding the efficacy or safety of everolimus was obtained via literature review.

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Clinical Review

Reviewer: Qin Ryan MD, PhD

NDA 22334

Afinitor (everolimus, RAD001)

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Clinical Review

Reviewer: Qin Ryan MD, PhD

NDA 22334

Afinitor (everolimus, RAD001)

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Clinical Review
Reviewer: Qin Ryan MD, PhD
NDA 22334
Afinitor (everolimus, RAD001)

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9.2 Labeling Recommendations

See final label.

9.3 Advisory Committee Meeting

NDA 22-334 provided sufficient clinical data to justify a favorable risk/benefit ratio for approval. Therefore, no advisory meeting was requested for NDA 22-334.

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