FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting
April 12, 2011

NDA 22334
Afinitor® (everolimus)
Applicant: Novartis Pharmaceuticals

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought everolimus to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

ODAC Briefing Document

1. Introduction

Novartis Pharmaceuticals submitted a supplemental new drug application for everolimus in the treatment of patients with advanced neuroendocrine tumors of gastrointestinal, lung, or pancreatic origin. The application is supported by 2 randomized Phase 3 studies in 2 subgroups of patients with neuroendocrine tumors; pancreatic neuroendocrine tumors (PNET) and carcinoid tumors. Data from a single arm Phase 2 study in patients with PNET has also been included in this submission. Issues in the review of this application include:

- The impact of informative censoring on both studies;
- The impact of everolimus on overall survival (OS);
- The inability of these two trials, both in neuroendocrine tumors, to support each other; and
- The use of progression-free survival to establish clinical benefit and its impact on overall survival.

2. Background

Everolimus is approved for the treatment of advanced renal cell carcinoma in patients who have received prior treatment with sunitinib or sorafenib and for the treatment of subependymal giant cell astrocytoma. Everolimus, marketed under the name Zortress, is also approved for prophylaxis of organ rejection in adults at low-moderate immunologic risk who are receiving a kidney transplant. Everolimus is a multi-kinase inhibitor that forms an inhibitory complex with the mammalian target of rapamycin (mTOR). The mTOR complex is important in cell proliferation and may have additional importance in neuroendocrine cells which are able to undergo autocrine regulation through the actions of insulin-like growth factor 1 (IGF-1) on this pathway. Everolimus has been shown to block the action of IGF-1 in neuroendocrine cells (Cancer Res 2000 60:4573).

This application examines the role of everolimus in the treatment of PNET and carcinoid tumors. Pancreatic neuroendocrine tumors include both functional (gastrinomas, insulinoma, etc.) and non-functional tumors arising in the pancreas. Carcinoid tumors are usually categorized as arising from the foregut, midgut, or hindgut. However, carcinoid is also used as a more general term for all neuroendocrine tumors. Both PNET and carcinoid tumors may be of low, intermediate, or high grade. This submission includes only patients with low and intermediate grade tumors. An examination of the prognosis of patients with low and intermediate grade PNETs using SEER data from 1973 to 2000 found a median survival of 17 months for patients with distant metastases and 69 months for patients with regionally advanced disease. The relatively prolonged survival of patients with PNET and carcinoid

tumors should be kept in mind when evaluating changes in progression-free survival. Prognostic factors in patients with PNET included functional tumor status (when corrected for stage), age, stage, sex (females did better), and grade (Ann Oncol 2008 19:1727). The prognosis of patients with carcinoid tumors was examined in another study using SEER data from 1973 to 2004. This analysis included a small number of patients with pancreatic carcinoids, but the majority of patients had tumors of GI or tracheobronchial origin. Median survival in patients with grade 1-2 disease who presented with distant metastases was 33 months while patients with regional spread had a median survival of 111 months. Prognostic factors included stage, grade, sex (females did better), age, and primary tumor site. This study noted that median survival in the years 1988-2004 was improved when compared to survival in 1973-1987 and that somatostatin analogs were introduced in 1987 (JCO 2008 26:3063). It is unclear whether this represents an improvement in imaging and in medical care or the effect of somatostatin analogs.

While a large number of drugs have been studied in patients with neuroendocrine tumors only streptozocin is approved for the treatment of metastatic islet cell carcinoma of the pancreas. The streptozocin indication statement goes on to say that use of streptozocin should be limited to patients with symptomatic or progressive metastatic disease. Octreotide is approved only for the symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease. Octreotide is also indicated for the treatment of the profuse watery diarrhea associated with vasoactive intestinal polypeptide-secreting tumors.

A major aspect of this application involves differences in radiologic assessment by the investigator (INV) and by central radiological review (IRC) (see Study Design). To fully evaluate this, it is helpful to examine other trials in which documented differences between INV and IRC review have been documented. The table below provides information on the percentage of patients whose progression event differed between INV and IRC review. Differences in the type and timing of the progression events are also shown. The bullets below provide examples of differences in the type and timing of events.

- Type of Event: INV-determined progressive disease (PD) at cycle 7; IRC does not detect PD and censors the patient

- Timing of Event: INV-determined PD at cycle 7; IRC detects PD at cycle 4

- Type and Timing of Event: INV-determined PD at cycle 7; IRC did not detect progression, but includes the patient’s death at day 218 as a PFS event

Patients in whom there was a disagreement in both the type and timing of an event are included among those with a difference in the type of event.

Table 1: Discordance Between INV and IRC-Determined Progression Free Survival						
	Experimental			Control		
	Type	Timing	Total	Type	Timing	Total
Lapatinib (breast)[1]	14.7%	24.6%	39.3%	15.2%	23.2%	38.4%
Bevacizumab (breast)[2]	24.4%	26.4%	50.8%	23.7%	27.4%	51.1%
Everolimus (renal cell)[3]	36.1%	19.9%	56.0%	20.1%	19.4%	39.5%
Trabectedin[4]	18.9%	25.6%	44.5%	20.5%	24.6%	45.1%
Liposomal Doxorubicin (breast)[5]			55.3%			53.4%

[1] www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022059s000_MedR_P1.pdf
[2] www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4332b1-01-FDA.pdf
[3] www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022334s000_StatR.pdf
[4] www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM121149.pdf
[5] www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM176243.pdf

Dodd et al examined discordance in INV-determined and IRC-determined PFS. This article includes information on discordance in 2 additional studies of bevacizumab (JCO 2008 26:3791). Multiple examinations of CT and MR scanning and inter- and intra-observer variability among radiologist have been published. In 1 of the best examples, Erasmus et al examined inter and intra-observer variability among 5 thoracic radiologists in 33 patients with NSCLC (40 tumors). Tumors varied from 1.8 to 8 cm. The intra-observer variability in the use of the RECIST criteria for progression resulted in misclassifications in a median of 4 tumors. Inter-observer pair variability in the use of the RECIST criteria for progression resulted in misclassifications in a median of 10.5 tumors. Given this level of variability in the same target lesions, the level of discordance between INV and IRC (who choose different target lesions) is not surprising. Further, neuroendocrine tumors are particularly difficult to image and imaging during the correct contrast phase is essential since these tumors can appear isodense with the liver in uniphasic scans (Hematol Oncol Clin N Am 2007 21:409).

Regulatory History

An end of phase 2 meeting was held in January 2006 to discuss the development program for everolimus in the treatment of neuroendocrine tumors. After extensive discussion of single arm trial designs, the two Phase 3 trials included in this application were submitted for Special Protocol Assessment (SPA). Both trials used progression-free survival (PFS) as determined by an Independent Radiology Committee (IRC) as the primary endpoint. A SPA agreement was reached for both protocols in 2007. In the Phase 3 trial of patients with PNET, the applicant proposed an increase from 6 (control) to 9 months with everolimus. In the Phase 3 trial of patients with carcinoid tumor an improvement in PFS from 9 (control) to 13.5 months with everolimus was proposed. In the SPA approval letter for the PNET trial, FDA stated, "Progression-free survival is acceptable in principle as the primary endpoint for this study. As previously communicated, whether a given PFS result will support approval is a review issue." In October of 2009, Novartis and FDA met to discuss the discordant evaluations of PFS by the local investigator and the IRC in the carcinoid study during the 2nd interim analysis. This finding resulted in amendments to the protocols changing the primary endpoint of:

- Study 2324 (PNET) to PFS as determined by the local investigator; and
- Study 2325 (Carcinoid) to PFS as determined by a Central Adjudication Committee.

During a pre-NDA meeting in August of 2010, FDA noted that both SPA agreements had been invalidated by this change in primary endpoint and that the acceptability of the revised statistical plans would be a review issue.

3. Clinical/Statistical - Efficacy

Phase 3 trials submitted in this application include:

- **PNET**: A randomized double-blind phase III study of RAD001 10 mg/d plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor
- **Carcinoid**: A randomized, double-blind, placebo-controlled, multicenter phase III study in patients with advanced carcinoid tumor receiving Sandostatin LAR® Depot and RAD001 10 mg/d or Sandostatin LAR® Depot and placebo

Study Design

Table 2: Study Design

	PNET	Carcinoid
Eligibility Criteria	1. Unresectable or metastatic PNET 2. Low or intermediate-grade neuroendocrine carcinoma 3. Disease progression ≤ 12 mos prior to entry 4. Measurable disease per RECIST 5. No hepatic embolization ≤ 6 mo prior to entry (1 mo if other sites of measurable disease) 6. No cryoablation/radiofrequency ablation ≤ 4 wks prior to entry 7. Performance status 0-2	1. Unresectable or metastatic carcinoid tumor 2. Low or intermediate-grade neuroendocrine carcinoma 3. Disease progression ≤ 12 mos prior to entry 4. Measurable disease per RECIST 5. No hepatic embolization ≤ 6 mo prior to entry (1 mo if other sites of measurable disease 6. No cryoablation/radiofrequency ablation ≤ 4 wks prior to entry 7. Performance status 0-2 8. History of diarrhea/flushing or both; Symptoms not required at entry
Stratification Factors	Prior cytotoxic chemotherapy (Y/N) Performance status (0 vs. 1-2)	None
Treatment	1. Everolimus 10 mg/d 2. Placebo daily • Placebo patients could crossover to open label everolimus on investigator-determined progression	1. Everolimus 10 mg/d + Octreotide 30 mg IM q 28 d 2. Placebo daily + Octreotide 30 mg IM q 28 d • Placebo patients could crossover to open label everolimus on investigator-determined progression.
Monitoring	Imaging: baseline then q 12 weeks until investigator-determined progression or start of a new cancer therapy CBC, Chemistries: baseline, C1D1 and 15, then q cycle Lipids: baseline, then q 3 cycles. Baseline screening for hepatitis	Imaging: baseline then q 12 weeks until investigator-determined progression or initiation of a new cancer therapy CBC, Chemistries: baseline, C1D1 and 15, then q cycle Lipids: baseline, then every 3 cycles Baseline screening for hepatitis
Independent Radiology Committee	Both studies included a central radiology review of all scans by 2 radiologists. Discrepancies between the 2 radiologists were adjudicated by a 3rd radiologist. The radiologists determined only radiologic progression and had no clinical information.	
Primary Endpoint	PFS by Investigator	PFS by Adjudicated Review
Secondary Endpoints	Overall survival Response rate by investigator Duration of response	Overall survival Response rate by adjudicated review Duration of response

Statistical Plan	In both studies, PFS was defined as the time from entry until radiologic progression or death due to any cause. In the PNET study, the hazard ratio for the primary endpoint was estimated with a Cox proportional hazard model using the stratification factors at randomization and unadjusted for other covariates. A logrank test stratified by the same factors was used to obtain the p-value. In the Carcinoid study, the hazard ratio for the primary endpoint was estimated using an unstratified, unadjusted Cox proportional hazards model and the p-value obtained from an unstratified logrank test. Both studies used identical criteria for censoring in the estimation of PFS. Patients were censored if they: • Were ongoing without a PFS event; • Were lost to follow up or withdrew consent; • Did not have a tumor assessment available. This includes patients who discontinued without a PFS event; • Began a new cancer therapy (including crossover to everolimus) in the absence of a PFS event; and • Had a PFS event which occurred after $\geq$ 2 missing tumor assessments (26 weeks). These patients were censored at their last adequate tumor assessment. Patients with no measurable disease at baseline were not censored. No interim analyses were included in the PNET study. The Carcinoid study was to conduct 2 interim analyses (at ~ 20% and ~ 60% of events) and a final analysis at 287 events. Both studies planned to perform an interim analysis of overall survival at the time of the final PFS analysis. On both studies, the final analysis of overall survival (OS) would occur when ~ 60% of events had occurred. Both studies will have 80% power to demonstrate a 30% improvement in overall survival compared to control using a one sided p=0.025.

Changes in Study Conduct

Both studies were designed to use IRC-determined PFS as the primary endpoint. Following the 2nd interim analysis of the Carcinoid study, both trials were amended to utilize the primary endpoints listed in Table 2. At the 2nd interim analysis of the Carcinoid study:

- IRC-determined PFS crossed the futility boundary of p = 0.175 with a p-value of 0.233; and
- INV-determined PFS crossed the efficacy boundary of p = 0.010 with a p-value of 0.003.

Following the 2nd interim analysis of the Carcinoid study, both protocols were amended to include review by an Adjudication Committee (AC). The AC included a radiologist and an oncologist who jointly examined:

- All patients in which there was a difference in the type of INV- and IRC-determined progression. For example, a patient with PD by the INV and Censored by the IRC would undergo adjudication; and
- All patients in which there was a difference in the timing of INV- and IRC-determined progression $\geq$ 126 days (1.5 evaluation periods with tumor imaging q 12 weeks). Patients with a smaller difference in the timing were assigned the date and type of the event determined by the IRC.

The AC was asked to choose either INV- or IRC-determined progression. The AC was unaware of the study arm or origin of the evaluation (INV or IRC). However, the AC was able to communicate with Novartis personnel to obtain patient history and some Novartis personnel were aware of the findings of the 2nd interim analysis.

Following the 2nd interim analysis of the Carcinoid study, the applicant chose to:

- Amend the PNET study to utilize INV-determined PFS; and
- Amend the Carcinoid study to utilize AC-determined PFS in the primary analysis.

The Carcinoid study was also amended to use a cutoff date, April 2, 2010, rather than the number of events (originally 287 events) in the final analysis. With this cutoff date, if 200 adjudicated events were available, the final analysis had 80% power to detect a 33% improvement in PFS using an alpha of 0.0249.

Additional Change in Study Conduct

After 49 patients were accrued, the Carcinoid study was amended to enroll only patients with a history of flushing and/or diarrhea. These symptoms were not required at study entry, but all patients must have had a history of carcinoid syndrome. At this point, the stratification factor (site of tumor origin) was removed from the randomization and the primary analysis. It was thought that patients with functional tumors would have a similar prognosis and that this eligibility criterion would ensure a homogenous population in the absence of stratification.

Patient Disposition

The table below provides information on patient disposition during the randomized phase. In the PNET study, 4 patients discontinued due to a protocol violation. These violations include ineligible histology, unblinded without progressive disease, withdrew consent prior to the 1st dose, and ineligible primary tumor site. In the PNET study, 148/203 (72.9%) patients in the placebo arm crossed over to everolimus upon INV-determined progression. In the Carcinoid study, 3 patients on the everolimus and 4 patients on the placebo arm discontinued due to a protocol violation. These violations included non-compliance (2), unblinded without progressive disease (2), ineligible histology (2), and patient ineligible (1). In the Carcinoid study, 124/213 (58.2%) patients in the placebo arm crossed over to everolimus upon INV-determined progression.

Note that in the Carcinoid study, the number of patients who are ongoing, without INV-determined progression, is similar between arms and that a substantial number of patients discontinued due to an adverse event or patient decision.

Table 3: Patient Disposition During the Randomized Phase

	PNET (Cutoff Date 2-28-10)		Carcinoid (Cutoff Date 4-2-10)	
	Everolimus	Placebo	Everolimus	Placebo
Randomized	207	203	216	213
Treated	204	203	215	211
Ongoing	66	26	37	34
Discontinued	141	177	179	179
Progressive Disease/Death due to Disease	92/1	163/2	95/1	146/0
Adverse Event/Death due to Adverse Event	36/3	7/1	57/5[1]	14/2
Patient Decision	4	4	17	11
Lost to Follow Up	1	0	0	1
Protocol Violation	4	0	3	4
New Cancer Therapy	0	0	1	1

[1]One cause of death listed as unknown. Review of the narrative suggests progressive disease.

Patient Demographics and Disease Characteristics

PNET

The PNET study was conducted at 82 centers in 18 countries with 40.2% of patients coming from the US. Demographic characteristics were similar between arms. Median ages were 58 and 57 years in the everolimus and placebo arm respectively. Both arms enrolled more male patients; 53.1% everolimus and 57.6% placebo. The majority of patients on both arms were Caucasian (76.3% everolimus and 81.8% placebo). The remaining patients were Asian with few Black or Hispanic patients entered in the trial. Performance status was 0-1 in 97.1% of patients on the everolimus and 97.0% on the placebo arm. The table below provides information on the baseline disease characteristics in each arm. Here, percentage refers to the percentage of patients enrolled. Only sites of target and non-target lesions in > 10% of patients are included in the table below. A single site of disease was identified in 11 patients.

Table 4: Baseline Disease Characteristics (Cutoff Date 2-28-10)

	Everolimus N = 207	Placebo N = 203
Primary Site		
Pancreas	97.1%	98.5%
Unknown	1.9%	1.0%
Other[1]	1.0%	0.5%
Histological Grade		
Well Differentiated	82.1%	84.2%
Moderately Differentiated	16.9%	14.8%
Poorly Differentiated	0	0
Unknown	1.0%	1.0%
Median Time Since Diagnosis (25-75)	2.5 years (1.1-5.6)	2.9 years (1.1-4.9)
Prior Therapy		
Surgery (including biopsy)	100%	100%
Radiation Therapy	22.7%	19.7%
Chemotherapy	57.5%	58.1%
Somatostatin Analog at Entry	48.8%	50.2%
Sites of Target/Non-Target Lesions[2]		
Liver	92.2%	92.1%
Pancreas	44.4%	41.4%
Lymph Node/Spleen	33.8%	36.5%
Lung/Pleura	15.5%	16.7%
Bone	6.3%	14.3%
Sum of the Longest Diameters		
INV-Median (25-75)	12.5 cm (7.2-20.8)	11.6 cm (7.6-19.8)
IRC-Median (25-75)	18.5 cm (10.6-25.4)	15.8 cm (10.8-26.7)

[1]Root of mesentery, para-duodenal, liver
[2]Sites of target and non-target lesion per INV assessment, list is not inclusive

Carcinoid

The Carcinoid study was conducted in 93 centers in 15 countries with 43.6% of patients coming from the US. Some demographic characteristics varied between arms and these are included in the table below. The median age on both arms was 60 and the majority of patients (95.8% everolimus, 93.9% placebo) were Caucasian. Only sites of target and non-target lesions in > 10% of patients are included in the table below.

In their analysis of overall survival, the applicant has commented on imbalances in baseline characteristics between arms. This study did not use stratification factors, but pre-defined the following subgroups: gender, performance status, primary tumor site, and histological grade. The applicant has examined imbalances in these as well as in the number of organs involved with tumor and in the prior use of chemotherapy. Each of these is examined in the lengthy table below.

- Gender: There were more females in the everolimus arm. Females have a slightly better prognosis than males with carcinoid tumors (JCO 2008 26:3063).

- Performance Status: More patients had a PS of 0 in the placebo arm. However, the number of patients with a performance status of 0-1 is comparable (93.5% everolimus, 94.8% placebo).

- Primary Site: More patients had a primary site in the lung in the everolimus arm and in the appendix in the placebo arm. Among patients with distant metastatic disease, those with primary sites in the small intestine, cecum, and thymus have a better prognosis while tumors originating in the colon, liver, stomach, or lung have a worse prognosis (JCO 2008 26:3063).

- Histological Grade: More patients in the placebo arm had a well differentiated tumor. Grade was the result of local review and was not evaluated centrally.

- Number of Organs: More patients in the everolimus arm had $\geq$ 4 organs involved with tumor. This data was obtained from the sites of INV-determined target and non-target lesions. If the sites of IRC-determined target and non-target lesions are used, the number of patients with $\geq$ 4 organs involved with tumor (17.6% everolimus, 15.0% placebo) is similar.

- Prior Chemotherapy: More patients in the everolimus arm received prior chemotherapy. The table below includes only systemic chemotherapy (targeted, cytotoxic and investigational) and does not include chemoembolization.

Table 5: Demographics and Baseline Disease Characteristics (Cutoff Date 4-2-10)		
	Everolimus N[1] = 216	Placebo N[1] = 213
Age		
< 65/ ≥ 65	66.2%/ 33.8%	67.1%/ 32.9%
Gender		
Male/Female	44.9%/55.1%	58.2%/ 41.8%
Performance Status.		
0	54.6%	65.7%
1	38.9%	29.1%
2	6.5%	4.7%
Unknown	0	0.5%
Primary Site[2]		
Small Intestine	51.4%	53.3%
Lung	15.3%	5.2%
Unknown Primary Site/Other	12.0%/0	9.4%/3.3%
Colon	6.5%	6.6%
Pancreas	5.1%	7.1%
Liver	3.2%	5.2%
Rectum	2.3%	2.8%
Stomach	1.9%	2.8%
Thymus	1.4%	0
Peritoneum/Omentum	0.5%	1.4%
Appendix	0	1.9%
Histological Grade		
Well Differentiated	76.9%	82.2%
Moderately Differentiated	17.6%	14.1%
Poorly Differentiated	0.5%	0.5%
Unknown/Missing	5.1%	3.3%
Median Time Since Diagnosis (25-75)	3.6 years (1.8-7.6)	3.5 years (1.3-6.9)
Prior Therapy		
Surgery (including biopsy)	100%	99.5%
Radiation Therapy	24.1%	27.6%
Chemotherapy	43.2%	35.9%
Number of Organs Involved[3]		
1-3	76.7%	85.8%
≥ 4	23.3%	14.2%
Sites of Target/Non-Target Lesions[3]	215	211
Liver	92.1 %	92.9%
Lymph Node/Spleen	42.3%	44.1%
Lung/Pleura	32.6%	26.5%
Bone	17.2%	11.4%
Pelvic/Abdominal Mass	14.0%	10.9%
Peritoneum/Omentum	13.0%	15.2%
Median SLD INV	13.1 cm (7.7-20.5)	12.9 (6.8-19.0)
Median SLD IRC	15.7 cm (10.6-25.5)	15.7 (9.1-22.7)
History of Flushing and/or Diarrhea	95.4%	96.7%
Flushing and/or Diarrhea at Entry	78.7%	81.1%
Somatostatin Use at Entry	80.1%	77.9%

[1]N varies with up to 4 missing patients per arm
[2]One patient each with a primary site in the head and neck, kidney, and spinal cord
[3]Based on sites of target and non-target lesions per investigator

Protocol Violations

In the PNET study, 72.9% of patients in the everolimus and 62.65% of patients in the placebo arm had a protocol violation of some kind. However, major protocol violations occurred in 11.1% in the everolimus and 5.4% in the placebo arm. In the Carcinoid study, 79.6% of patients in the everolimus and 84.0% of patients in the placebo arm had a protocol violation while 13.0% in the everolimus and 9.4% in the placebo arm had a major protocol violation. The method used to categorize major and minor protocol violations differs from that of the applicant. No protocol violations are recorded for missing or delayed scans. Tumor imaging occurred every 12 $\pm$ 6 weeks, making delayed scanning an unlikely protocol violation. The results of inspection of clinical sites by the Division of Scientific Investigations are pending at this time.

Primary Endpoint

The tables below provide information on INV-, IRC-, and AC-determined PFS. The primary analysis for each study is shaded.

PNET

The applicant changed their primary endpoint to INV-determined PFS. In the initial protocol, IRC-determined progression was the primary endpoint. Here, analyses of PFS that use INV-, IRC-, and AC-determined progression all have similar hazard ratios and highly significant p-values.

Table 6: PNET Primary Analysis (Cutoff Date 2-28-10)

	INV		IRC		Adjudication	
	Everolimus	Placebo	Everolimus	Placebo	Everolimus	Placebo
# PFS Events	109	165	87	112	95	142
# Censored Events	98	38	120	91	112	61
Median PFS	11.0	4.6	13.7	5.7	11.4	5.4
Hazard Ratio[1]	0.35		0.38		0.34	
p-value[2]	< 0.001		< 0.001		< 0.001	

[1] Stratified (prior cytotoxic chemotherapy and performance status), unadjusted Cox proportional hazards model
[2]Stratified logrank test, 1-sided p-value

In the PNET study, 133 patients were adjudicated (58 everolimus, 75 placebo). This included patients in which there was a difference in the type and/or timing (if the timing differed by $\geq$ 126 days) of progression. Patients with a smaller difference in the timing were assigned the date and type of event determined by the IRC. The AC assigned INV-determined progression to 24 (41.4%) patients in the everolimus and 36 (48.0%) of patients in the placebo arm.

Carcinoid

The applicant changed their primary endpoint to AC-determined PFS. In the initial protocol, IRC-determined progression was the primary endpoint. The applicant has treated this as their final analysis and assigned all remaining alpha (remaining after the 2nd interim analysis) to the analysis of AC-determined PFS. Using this approach, the alpha available for this analysis is 0.0246. FDA considers this a 3rd interim analysis with, using the Lan-DeMets alpha spending function, an available alpha of 0.0098. In either assessment, the p-value does not achieve statistical significance.

In the original statistical plan, the final analysis of PFS was to occur at 287 IRC-determined PFS events. The number of PFS events in these analyses ranges from 208 to 284 events. Based on the IRC data at the 2nd interim analysis, the predicted probability of seeing a significant result (HR < 0.67) if the applicant had continued this study and recruited more patients is 13.0%. Studies are typically conducted with a predicted probability > 20%.

Table 7: Carcinoid Primary Analysis (Cutoff Date 4-2-10)

	Adjudication		IRC		INV	
	Everolimus	Placebo	Everolimus	Placebo	Everolimus	Placebo
# PFS Events	103	120	105	103	128	156
# Censored Events	113	93	111	110	88	57
Median PFS	16.4	11.3	14.9	13.9	12.0	8.6
Hazard Ratio[1]	0.77		0.93		0.78	
p-value[2]	0.026		0.298		0.018	

[1]Unstratified, unadjusted Cox proportional hazards model
[2]Unstratified logrank test, 1-sided p-value

Adjudication was conducted in 169 patients (77 everolimus, 92 placebo). The adjudication committee assigned INV-determined progression to 25 (32.5%) patients in the everolimus and 37 (40.2%) of patients in the placebo arm.

Concordance-Discordance in the Type and Timing of PFS Events

The marked discordance in INV and IRC events has led to difficulties in the analysis of the Carcinoid study. To further characterize the issue and to understand the relationship between studies (1 with and 1 without a significant p-value), we examined both the PNET and Carcinoid studies. The table below provides information on the number of patients in which the INV and IRC disagreed and on the type or timing of the patient's PFS event. This table includes all disagreements and is not limited to patients who were reviewed by the AC.

Note that the percentage of patients with INV-IRC discordance in the PNET study is lower than that in the Carcinoid study (41.0% PNET, 52.0% Carcinoid). However, in both studies, there is an increase in the number of discordant patients in the placebo arm when compared to the everolimus arm.

Table 8: Discrepancies Between INV and IRC Assessment of PFS Events in Both Studies (Cutoff Dates 2-10 and 4-10)

	Everolimus			Placebo		
	Type	Timing	Total	Type	Timing	Total
PNET	25.6%	12.1%	37.7%	36.4%	7.9%	44.3%
Carcinoid	32.4%	16.2%	48.6%	40.8%	14.4%	55.4%

The table below provides additional information on the types of progression events in which there was discordance between the INV and IRC. Information of the number of patients in which there was a difference in timing of PD is also included. In both arms, patients with INV-determined PD (55 patients in the everolimus arm of Table 9) were most often censored by the IRC (35 patients in the everolimus arm of Table 9). That is, the IRC did not detect a progression event and informative censoring occurred. Further, informative censoring was more likely to occur in the placebo arm than in the everolimus group (Table 9 35 patient

everolimus, 61 patients placebo). This suggests bias in the determination of PD in the placebo arm. This pattern is seen in both studies with a larger number of discordant patients in the Carcinoid study.

Table 9: PNET-Discordance in PFS Events (Cutoff Date (2-28-10)								
	Everolimus				Placebo			
	INV-Death	INV-PD	INV-Censored	Timing	INV-Death	INV-PD	INV-Censored	Timing
IRC-Death	0	1	0		0	4	0	
IRC-PD	4	19	13	15	1	13	8	16
IRC-Censored	0	35	6		0	61	3	

Table 10: Carcinoid-Discordance in PFS Events (Cutoff Date 4-2-10)								
	Everolimus				Placebo			
	INV-Death	INV-PD	INV-Censored	Timing	INV-Death	INV-PD	INV-Censored	Timing
IRC-Death	0	10	1	0	0	1	0	0
IRC-PD	3	26	16	35	5	28	14	31
IRC-Censored	0	40	9	0	0	67	3	0

We examined a number of factors that may have affected INV-IRC discordance.

- Prior Embolization: We were concerned that the investigators, but not the IRC may be aware that a lesion had been embolized (if contrast timing was poor) and that this may have led to discordance. In the PNET study, among the 85 patients who had undergone embolization, 31 were among the 168 patients with INV-IRC discordance. In the Carcinoid study, among the 61 patients had undergone embolization, 30 were among the 223 patients with INV-IRC discordance. Since these make up only a small proportion of discordant patients, it seems unlikely that they contributed markedly to INV-IRC discordance.

- Scan Quality: Issues related to scan quality were identified by the IRC in 87 patients in the PNET and 107 in the Carcinoid study. Thirty-nine patients in the PNET study were among the 168 with INV-IRC discordance. Fifty-eight patients in the Carcinoid study were among the 223 patients with INV-IRC discordance.

- Disease Burden: Disease burden was not related to INV-IRC discordance.

- Region and Center: Region was unrelated to INV-IRC discordance. Site appears to be unrelated to INV-IRC discordance. However, the percentage of discordant patients (in sites with > 3 patients) varied from 0-100%.

Finally, we examined discordance between Reviewer 1 and Reviewer 2 in the IRC. In both studies, all scans in the same patient were reviewed by the same 2 radiologists. When there was a disagreement, this was adjudicated by a 3rd radiologist who selected either Reviewer 1's or Reviewer 2's findings. It is particularly valuable to examine the level of disagreement between these 2 reviewers since both have the same level of information (scans only) available, but may choose different target lesions. In the Carcinoid study, there was discordance between Reviewer 1 and Reviewer 2 at the final assessment in 159/429 (37.1%) patients. Among these 159 patients, there was INV-IRC discordance in 104 patients.

All of this suggests that difficulties in imaging neuroendocrine tumors combined with the long imaging interval, and possible bias contributed to the difficulties in assessing the primary analysis of the Carcinoid study.

Sensitivity Analyses

The applicant provided an additional analysis (IPCW) of the data in the Carcinoid study which examines the effect of informative censoring on PFS. In this analysis, patients in which (in the applicant's assessment) informative censoring occurred are replaced by patients in which informative censoring did not occur. However, in the applicant's analysis, the algorithm used to select patients who had undergone informative censoring included INV-determined progression. The use of INV-determined progression, in our opinion, may bias the results of this analysis making it uninterpretable since potential investigator bias was ignored. When INV-determined progression was removed from this analysis, the hazard ratio (HR) for this analysis was 0.88 (95% CI; 0.64-1.20).

The applicant assessed the impact of missing scans by using approaches they refer to as 'actual event' and 'backdating'. The 'actual event' analysis use the PFS event date irrespective of whether it was preceded by missing scans. In the 'backdating' analysis, PFS events that occurred after missing scans were 'backdated' so that the event would occur on the date of the first missing scan. In the PNET study, the results of both of these analyses, in terms of the hazard ratio and the median PFS, are consistent with the primary analysis. In the Carcinoid study, the 'actual event' analysis resulted in a HR of 0.80 (95% CI; 0.62, 1.02) while the 'backdating' analysis resulted in a HR of 0.84 (95% CI; 0.65, 1.07). In the Carcinoid study, the small increase in HR when compared to the applicant's primary analysis suggests that missing scans did impact the outcome of this study.

Since many patients with PNET or Carcinoid tumors have undergone prior embolic therapy, we assessed the impact of this on PFS. When these patients were excluded from the PNET study (N = 325), the HR using IRC-determined PFS was 0.42 (95% CI; 0.30, 0.59). When these patients were excluded from the Carcinoid study, (N = 368), the HR using the IRC-determined PFS was 1.02 (95% CI; 0.76, 1.36). In both these studies, these patients may be impacting outcome.

In the PNET study, 34 patients had major protocol violations. When these patients were removed (N = 376), the HR for IRC-determined PFS increased from 0.38 to 0.40 (95% CI; 0.29, 0.54). In the Carcinoid study, 48 patients had major protocol violations. When these patients were removed (N = 381), the HR for IRC-determined PFS increased from 0.93 to 0.94 (95% CI; 0.71, 1.24). It is unlikely that the small number of patients with major protocol violations contributed to the outcome of this study.

Finally, there were 20 patients, 10 in the PNET and 10 in the Carcinoid study, in whom the timing of their progression event changed after application of the RECIST and censoring rules by the FDA. When the new progression dates are used in the analysis of the PNET study, the

IRC-determined HR increases to 0.41. When the new dates are used in the Carcinoid study, the IRC-determined HR remains 0.93.

Subgroup Analyses

PNET
Analyses of the effect of everolimus among various subgroups supported the primary analysis. The HR in the US population was 0.36 (95% CI; 0.25, 0.52).

Carcinoid
The HR for the effect of everolimus on AC-determined PFS in various subgroups was similar to that in the primary analysis. In subgroup analyses, patients with a baseline performance status of 0 had a HR of 0.67 (95% CI; 0.47, 0.97) while those with well differentiated tumor had a HR of 0.74 (95% CI; 0.55, 0.99). Notably, the 44 patients with a lung as the primary site of disease had a HR of 0.72 (95% CI; 0.31, 1.68). The HR in the US population was 0.68 (95% CI; 0.45, 1.04).

Overall Survival

PNET
An interim analysis of OS, at the time of the final PFS analysis, is shown in the table below. At the time of the interim analysis of OS, 148 (72.9%) placebo patients had crossed over from placebo to everolimus. Following the unadjusted analysis, the statistical plan provided for an additional adjusted analysis of OS (adjusted for the covariates age (<65, ≥ 65), gender, region (Europe, America, Asia), prior use of long acting somatostatin (Y/N)). The hazard ratio for the adjusted analysis was 1.03 (95% CI; 0.70, 1.53). The final analysis of OS will take place when 250 events have occurred.

Table 11: PNET-Interim Analysis of Overall Survival (Cutoff Date 2-28-10)

	Everolimus N = 207	Placebo N = 203
Deaths	51 (24.6%)	50 (24.6%)
Median OS	NR	NR
Hazard Ratio		
Unadjusted Analysis (95% CI)	1.05 (0.71, 1.55)	

The applicant also provided an unplanned analysis (submitted with the Safety Update) of OS at 27.6% of events. Here, the unadjusted HR was 0.99 (95% CI; 0.68, 1.43) and the adjusted HR 0.97 (95% CI; 0.66, 1.41).

Information on the use of anti-cancer therapy following discontinuation of the double-blind or open-label portion of the PNET study is shown in the table below. The effect of these agents on OS is unknown.

Table 12: PNET Anti-Neoplastic Therapy After Discontinuation of Double-Blind or Open-Label Study Drug (Cutoff Date 2-28-10)		
	Everolimus N = 207	Placebo N = 203
Any	78 (37.7%)	58 (28.6%)
Cytotoxic Chemotherapy	34 (16.4%)	28 (13.8%)
Local Therapy[1]	13 (6.3%)	11 (5.4%)
Sunitinib/Everolimus	11 (5.3%)	9 (4.4%)
Somatostatin Analog	5 (2.4%)	4 (2.0%)
Other	25 (12.1%)	20 (9.9%)

[1]Includes embolization, chemoembolization, radiofrequency ablation, external beam radiation and surgery

Carcinoid

An interim analysis of OS, at the time of the final PFS analysis, is shown in the table below. Note that at the time of the analysis 124 (58.2%) of patients had crossed over to everolimus from placebo. Following the unadjusted analysis, the statistical plan provided for an additional adjusted analysis of OS (adjusted for the covariates age (<65, ≥ 65), gender, race (Caucasian/non-Caucasian), performance status (0 vs. 1-2), prior use of long acting somatostatin analog (Y/N)). The hazard ratio for the adjusted analysis was 1.06 (95% CI; 0.79, 1.43). The final analysis of OS will take place when 252 events have occurred.

Table 13: Carcinoid-Interim Analysis of Overall Survival (Cutoff Date 4-2-10)		
	Everolimus N = 216	Placebo N = 213
Deaths	100 (46.3%)	85 (39.9%)
Median OS	26.3 months	33.2 months
Hazard Ratio		
Unadjusted Analysis (95% CI)	1.22 (0.91, 1.62)	

The applicant also provided an unplanned analysis of OS at 47.3% of events. Here, the unadjusted HR was 1.17 (95% CI; 0.89, 1.54) and the adjusted HR 1.05 (95% CI; 0.79, 1.39).

Information on the use of anti-cancer therapy following discontinuation of the double-blind or open-label portion of the Carcinoid study is shown in the table below. The applicant has noted that patients on the placebo arm who crossed over to everolimus continued to receive a long acting somatostatin analog while only 2.9% of patients on the everolimus arm received a somatostatin analog. At present, it is unclear whether somatostatin analogs impact OS. It should be noted that while a small percentage of patients in the table below reported the use of somatostatin analogs ~ 80% of patients reported somatostatin use at study entry. This suggests that somatostatin analogs may not have been considered an additional anti-neoplastic therapy by many investigators.

Table 14: Carcinoid Anti-Neoplastic Therapy After Discontinuation of Double-Blind or Open-Label Study Drug (Cutoff Date 4-2-10)		
	Everolimus N = 173	Placebo N = 139
Any	69 (39.9%)	33 (23.7%)
Cytotoxic Chemotherapy	35 (20.2%)	10 (7.2%)
Local Therapy[1]	11 (6.4%)	9 (6.5%)
Sunitinib/Everolimus	2 (11.6%)	1 (0.7%)
Somatostatin Analog	5 (2.9%)	4 (2.9%)
Other	33 (19.1%)	12 (8.6%)

[1]Includes embolization, chemoembolization, radiofrequency ablation, external beam radiation and surgery

A HR greater than 1 in these analyses of OS is of great concern since this cannot be explained by the crossover of 58.2% of patients or by the use of additional therapy after the completion of study drug. The imbalance in baseline prognostic factors could potentially explain this difference. However, it is unclear whether there was a substantial imbalance in patients with poor prognostic factors in the everolimus arm.

Response Rate

PNET

The INV-determined response rate was 4.8% in the everolimus arm and 2.0% in the placebo arm. The IRC-determined response rate was 2.4% in the everolimus arm and 0.5% in the placebo arm. In both assessments, all responses were partial.

Carcinoid

The INV-determined response rate was 3.2% in the everolimus arm and 2.3% in the placebo arm. The IRC-determined response rate was 1.9% in the everolimus arm and 1.4% in the placebo arm. In both assessments, all responses were partial.

Supportive Study

The applicant conducted an open label Phase 2 study of the effect of everolimus on patients with PNET. Patients were divided into those who had progressive disease on or after an adequate course of cytotoxic chemotherapy, but had not received a long acting somatostatin analog within the 2 months prior to entry (Stratum 1) and those who had received at least 3 months of a long acting somatostatin analog (Stratum 2). Other eligibility criteria were similar to those on the PNET study. The primary endpoint was response rate by independent review. Among the 115 patients enrolled in Stratum 1, RR was 9.6% with a median duration of 10.6 months. Among the 45 patients enrolled in Stratum 2, RR was 4.4%. There was insufficient data for assessment of the duration of response in Stratum 2. All responses were partial.

A published article from an investigator conducted Phase 2 study was also provided (JCO 2008 26:4311). The study design and the number of patients actually included in the analysis and the arms is complex, but the study suggested that both patients with islet cell tumors and those with carcinoid tumors responded to everolimus and that 10 mg of everolimus may be more active than 5 mg (RR 13% vs. 30%).

4. Safety

Safety Database

The table below provides information on the safety database available in patients with neuroendocrine tumors. All studies initiated treatment with 10 mg/d of everolimus.

Table 15: Safety Database (Cutoff Dates 6-10 and 7-10)		
Study	Population	Number of Patients Exposed to Everolimus
C2324 Phase 3	PNET	356
C2325 Phase 3	Carcinoid	342
C2239 Phase 2	PNET	160
Total		858

Exposure

The table below provides information on exposure to everolimus or placebo during the double-blind portion of the PNET and the Carcinoid study. The median duration of dosing in the everolimus arm of the PNET study is similar to that in the Carcinoid study. This is surprising given the adverse event profile of these 2 studies (see below). In addition, the percentage of patients undergoing dose reduction or interruption is similar in the 2 studies. Note the number of patients who require at least 2 dose interruptions or reductions. In the PNET study, the duration of exposure to placebo is markedly shorter than the exposure to everolimus. This suggests that patients progressed more rapidly on the placebo arm. In contrast, in the Carcinoid study, the duration of exposure to everolimus or placebo is similar.

Table 16: Exposure to Study Drug (Cutoff Dates 6-10 and 7-10)				
	PNET		Carcinoid	
	Everolimus N = 204	Placebo N = 203	Everolimus N = 215	Placebo N = 211
Median Duration of Exposure (range)	37.3 weeks (1.1-129.9)	16.1 weeks (0.4-146.0)	37.0 weeks (0.6-175.6)	36.6 weeks (0.4-165.1)
Dose Interruption or Reduction	61.3%	29.1%	67.0%	37.0%
1 Dose Interruption or Reduction	15.2%	14.3%	15.3%	20.9%
$\geq$ 2 Dose Interruptions or Reductions	45.1%	14.8%	51.6%	16.6%

Safety Overview

The tables below provide an overview of the safety findings of the PNET and Carcinoid studies. In general, the adverse event profile of everolimus is similar to that described in the package insert. Table 17 provides information on number of events that occurred in each of the major safety categories. The incidence of adverse events in each of the major safety categories was increased in the Carcinoid study when compared to the PNET study. The reason for this finding is unclear. Exposure to everolimus was similar in the two studies and the studies were comparable in terms of patient performance status and median SLD at baseline. Octreotide was administered to patients in both arms of the Carcinoid study. However, the adverse event profile of octreotide is unlikely to explain these findings. Octreotide is associated with inhibition in gall bladder contractility, hypo/hyperglycemia, hypothyroidism, bradycardia, conduction abnormalities, diarrhea, and abdominal discomfort. In addition to the increase in events in the Carcinoid study; note that the number of deaths, discontinuations due to an adverse event, and grade 3-4 adverse events are all increased in the everolimus arm.

Table 17: Incidence of Major Safety Categories				
	PNET (Cutoff Date 6-3-10)		Carcinoid (Cutoff Date 7-2-10)	
	Everolimus N = 204	Placebo N = 203	Everolimus + Octreotide N = 215	Placebo + Octreotide N = 211
Deaths	3.4%	0.5%	5.6%	2.4%
Discontinuations	20.1%	5.9%	28.3%	20.9%
SAEs	40.7%	25.6%	58.6%	34.6%
Grade 3-4 AEs	61.8%	40.4%	74.9%	51.7%
Grade 1-4 AEs	99.5%	97.5%	100%	96.2%

The following tables provide an overview of the adverse events seen in the everolimus arm of the PNET study during the double-blind phase. This is followed by a table that provides information on grade 1-4 adverse events which occurred in at least 30% of patients. The incidence of grade 3-4 events for each of these terms is also included.

Table 18: PNET-Overview of Adverse Events in the Everolimus Arm (Cutoff Date 6-3-10)	
Deaths	Renal Failure, Acute Respiratory Distress Syndrome, Cardiac Arrest, Hepatic Failure, Pneumonia, Sepsis, Unknown
Discontinuations $\geq$ 2%	Pneumonitis
SAEs $\geq$ 5%	None
Grade 3-4 AEs $\geq$ 5%	Anemia, Hyperglycemia, Somatitis, Hypophosphatemia, Diarrhea, Fatigue
Grade 1-4 AEs $\geq$ 30%	Stomatitis, Rash, Diarrhea, Fatigue, Edema, Abdominal Pain, Nausea, Fever, Headache

Table 19: PNET-Grade 1-4 Adverse Events in $\geq$ 30% of Patients (Cutoff Date 6-3-10)				
	Everolimus N = 204		Placebo N = 203	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Stomatitis[1]	69.6%	6.9%	19.7%	0
Rash[2]	59.3%	0.5%	18.7%	0
Diarrhea[3]	49.5%	5.4%	9.9%	2.5%
Fatigue/Malaise	44.6%	5.4%	27.1%	5.4%
Edema	39.2%	2.0%	11.8%	1.0%
Abdominal Pain	36.3%	3.9%	31.9%	7.4%
Nausea	31.9%	2.5%	32.5%	2.0%
Pyrexia	30.9%	1.0%	12.8%	0.5%
Headache/Migraine	30.4%	0.5%	14.8%	1.0%

[1]Also includes aphthous stomatitis, gingival pain, gingival swelling, gingival ulceration, glossitis, glossodynia, lip, mouth and tongue ulceration
[2]Also includes dermatitis, dermatitis acneiform, exfoliative rash, and rash papular, pruritic, erythematous, generalized, and maculo-papular
[3]Also includes defecation urgency, enteritis, enterocolitis, streatorrhea

The table below provides an overview of the adverse events in the Carcinoid study followed by a table listing the grade 1-4 adverse events that occurred in at least 30% of patients. The incidence of grade 3-4 events for each of these terms is also included. Although the toxicity of everolimus is well-described, it should be noted that everolimus is associated with considerable toxicity. For example, 8.0% of patients in the placebo arm of the Carcinoid study reported grade 3-4 diarrhea (despite the use of octreotide) while 15.3% of those in the everolimus arm reported grade 3-4 diarrhea (an known adverse event of everolimus).

Table 20: Carcinoid-Overview of Adverse Events in the Everolimus Arm (Cutoff Date 7-2-10)	
Deaths	Acute Respiratory Failure, Heart Failure, Cardiac Arrest, Hepatic Failure, Pneumonia, Pulmonary Embolism, Sepsis, Unknown
Discontinuations ≥ 2%	Pneumonitis, Asthenia, Pneumonia, Fatigue
SAEs ≥ 5%	Abdominal Pain, Diarrhea, Pneumonia, Intestinal Obstruction
Grade 3-4 AEs ≥ 5%	Diarrhea, Fatigue, Abdominal Pain, Hyperglycemia, Cardiac Valve Disease, Pneumonia, Stomatitis, Tachycardia, Asthenia
Grade 1-4 AEs ≥ 30%	Stomatitis, Diarrhea, Fatigue, Edema, Nausea, Abdominal Pain, Vomiting, Dyspnea, Headache, Cough

Table 21: Grade 1-4 Adverse Events in ≥ 30% of Patients (Cutoff Date 7-2-10)				
	Everolimus + Octreotide N = 215		Placebo + Octreotide N = 213	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Stomatitis[1]	66.0%	5.6%	6.1%	0.5%
Diarrhea[2]	53.5%	15.3%	38.5%	8.0%
Fatigue/Malaise	49.3%	11.2%	45.5%	3.8%
Rash[3]	43.7%	1.4%	18.3%	0
Generalized/Peripheral Edema	43.3%	2.3%	23.0%	1.9%
Nausea	42.8%	4.2%	30.0%	2.8%
Abdominal Pain	39.5%	10.7%	43.7%	12.2%
Vomiting	33.0%	4.2%	20.2%	2.8%
Dyspnea	32.1%	5.6%	13.6%	0.5%
Headache/Migraine	31.6%	0	23.9%	1.4%
Cough/Productive Cough	30.7%	1.4%	16.0%	0
Anemia[4]	30.7%	6.0%	11.7%	1.4%

[1]Also includes aphthous stomatitis, gingival pain, gingival swelling, gingival ulceration, glossitis, glossodynia, and lip, mouth, and tongue ulceration
[2]Also includes defecation urgency, enteritis, enterocolitis, streatorrhea
[3]Also includes dermatitis, dermatitis acneiform, exfoliative rash, and rash papular, pruritic, erythematous, follicular, generalized, macular, and maculo-papular
[4]Also includes hemoglobin decreased, iron deficiency anemia and microcytic anemia

Significant Adverse Events

Pneumonitis

The PNET and Carcinoid studies collected information on the incidence of pneumonitis as detected by CXR or CT scan. By this method, 5.9% of patients were detected to have pneumonitis at baseline. These patients were removed from subsequent analyses. We found that the number of patients in the PNET and Carcinoid studies who were reported, in post-baseline evaluations, to have pneumonitis was 135/381 (35.4%) in the everolimus arm and 54/381 (14.2%) in the placebo arm. Among these 135 patients, 39 (28.9%) were reported to have the adverse event pneumonitis. Given this finding along with the number of patients with evidence of pneumonitis in the placebo arms, CXR/CT Scans (done for tumor imaging) appears to over estimate the number of patients with pneumonitis.

The table below summarizes the information available from the safety database concerning the patients who were reported to have the adverse event pneumonitis. The median age in patients with pneumonitis is slightly greater than that of the population as a whole (57.4 years). Note that while 8% of patients in the safety database are Asian, Asians make up 14.0% of the patients with the adverse event pneumonitis. No risk factors for pneumonitis were clearly identified.

Table 22: Pneumonitis in the Safety Database (Cutoff Dates 11-08 and 6/7-10)	
Incidence by Adverse Event Report[1]	93/858 (10.8%)
Grade 4	1
Grade 3	14
Grade 2	46
Grade 1	32
Characteristics of Patients with an Adverse Event	
Median Age	61 years
Gender	
Male	47/93 (50.5%)
Female	46/93(49.5%)
Race	
Caucasian	75/93 (80.6%)
Asian	13/93 (14.0%)
Median Day of Onset	Day 198
Median Duration[2]	38.5 Days

[1]Preferred terms pneumonitis, interstitial lung disease, lung disorder (investigator terms reticular opacities), lung infiltration (investigator term bibasal interstitial infiltrates), pulmonary fibrosis, and restrictive pulmonary disease in Studies C2239, C2324, and C2325.
[2]End dates are available for 100 of 151 events

Recorded interventions include oxygen, antibiotics, steroids, or both antibiotics and steroids. The median duration of pneumonitis was 38.5 days. Everolimus was permanently discontinued in 21 patients.

Opportunistic Infections

Since everolimus is immunosuppressive, we examined the incidence of opportunistic infections in the safety database and were able to identify 3 patients with mycobacterium infections, 2 with an aspergillus infection, and 1 patient with reactivation of hepatitis B. The risk of reactivation of hepatitis has already been added to the label by the applicant.

Renal Failure

The table below provides information on the reports of renal failure during the double-blind period on the PNET and Carcinoid studies. The imbalance between the experimental and control arms was of concern and we examined the patients in the everolimus arms more closely. Many of these were associated with dehydration due to stomatitis or diarrhea while others occurred in the setting of multi-organ failure. However, some of these events could not be readily explained and we will examine this further.

Table 23: Renal Failure During Double-Blind Therapy (Cutoff Dates 6-10 and 7-10)				
	PNET		Carcinoid	
	Everolimus N = 204	Placebo N = 203	Everolimus N = 215	Placebo N = 211
Grade 3-4 Renal Failure[1]	6	3	8	1

[1] Preferred terms azotemia, nephritis, renal atrophy, renal failure, renal failure acute, renal failure chronic, renal impairment, renal tubular acidosis, renal tubular necrosis

Hyperglycemia

Since hyperglycemia has been associated with the use of everolimus while both hypo and hyperglycemia have been associated with the use of octreotide, we further examined the incidence of poor glucose control in the PNET and Carcinoid studies. Unfortunately, we cannot determine who, among the PNET patients, had an insulinoma and examine these patients further. The table below provides information on both adverse events and abnormal laboratory values. Overall, the incidence of high grade hyper- or hypoglycemia was low. Hyperglycemia does not appear to be increased with the addition of octreotide in the Carcinoid study. However, 3 patients in the Carcinoid study did have grade 3-4 hypoglycemia (glucose < 40 mg/dL).

Table 24: Hyperglycemia During Double-Blind Therapy (Cutoff Dates 6-10 and 7-10)

	PNET		Carcinoid	
	Everolimus N = 204	Placebo N = 203	Everolimus N = 215	Placebo N = 211
Adverse Events				
Grade 3-4 Hyperglycemia[1]	25	8	16	2
Grade 3-4 Hypoglycemia	2	2	2	4
Laboratories				
Grade 3-4 Hyperglycemia	37	12	28	3
Grade 3-4 Hypoglycemia	0	0	2	1

[1]Preferred terms blood glucose increased, diabetes mellitus, glucose urine present, type 2 diabetes mellitus.

5. Issues for ODAC

The effect of everolimus on progression-free survival in patients with neuroendocrine tumors was examined in both the PNET and the Carcinoid study. The effect of everolimus on progression-free survival should be considered in the context of its adverse event profile, the natural history of this disease, and the impact of everolimus on overall survival.

Issues for ODAC include:

- The impact of informative censoring on both studies;
- The impact of everolimus on OS (particularly in the carcinoid study);
- The inability of these two trials, in similar tumor types, to support each other; and
- The use of PFS to establish clinical benefit and its impact on OS.