FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

NDA 22576
Ridaforolimus (Taltorvic®)
Merck Sharp & Dohme Corp.

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1 Proposed Indication

The applicant is seeking regular approval for the following indication.

Taltorvic (ridaforolimus), a kinase inhibitor of the mammalian target of rapamycin (mTOR), is an antineoplastic agent indicated to treat patients with metastatic soft tissue sarcoma or bone sarcoma whose disease has not progressed after at least 4 cycles of chemotherapy.

2 Executive Summary

The applicant submitted a single Phase 3 study and two Phase 2 trials to support this indication. The Phase 3 study examined the use of ridaforolimus as maintenance therapy in patients with soft tissue or bone sarcoma who had achieved $\geq$ stable disease (SD) with prior chemotherapy. Patients were randomized to ridaforolimus or placebo and imaged every 8 weeks for evidence of progression. Scans were read by an independent review committee. The applicant's analysis of the primary endpoint found that the median progression-free survival (PFS) was 17.7 weeks in the ridaforolimus arm and 14.6 weeks in the placebo arm. The hazard ratio (HR) was 0.72 (95% CI: 0.61, 0.85) with $p = 0.0001$. The FDA analysis found that the median PFS was 16.1 weeks in the ridaforolimus arm and 14.0 weeks in the placebo arm with a HR of 0.74 (95% CI: 0.63, 0.88), $p = 0.0006$. The final analysis of overall survival (OS), showed a median OS of 20.8 months in the ridaforolimus arm and 19.6 months in the placebo arm with a HR of 0.93, $p = 0.46$.

The safety profile of ridaforolimus is similar to that of other mTOR inhibitors. The number of patients who discontinued due to an adverse event (14% ridaforolimus, 2% placebo) is of particular concern in a drug intended for use as maintenance therapy. Likewise, a substantial number of patients experienced grade 3-4 events (64% ridaforolimus, 25% placebo). Grade 1-4 adverse events occurring in > 20% of patients included stomatitis, asthenia/fatigue, infection, rash, cough, diarrhea, nausea, decreased appetite, headache, edema, abdominal pain, dyspnea, and fever. Adverse events of particular concern include pneumonitis, infection, and renal failure/impairment. Laboratory abnormalities included hematologic toxicity (11% gr 3-4 thrombocytopenia), hyperglycemia, hyperlipidemia, and increased ALT (3% gr 3-4).

3 Issues with the Submission

Evaluation of the difference in PFS between arms in light of the toxicity profile of ridaforolimus

4 Background

Ridaforolimus combines with FK506-binding protein to inhibit mTOR complex 1 with an IC_{50} of 12.8 $\pm$ 6.6 nM. Inhibition results in decreased cell growth and proliferation, as well as, a decrease in the production of vascular endothelial growth factor. Ridaforolimus is active in a variety of cell lines, including sarcoma. It appears that the decision to pursue an indication in sarcoma was based on the results of the Phase 1 study. Here, 6 of 7 patients with sarcoma remained progression free for $\geq$ 6 months. Although the decision appears to have been based on clinical findings, in xenograft models, the applicant found that ridaforolimus levels of 2.8-9.4 ng/mL were sufficient to maintain a 56-88% decrease in mTOR signaling.

4.1 Treatment of Sarcoma

The key trial in this application examines the ability of ridaforolimus to extend PFS in patients with either soft tissue or bone sarcomas who have achieved $\geq$ SD with prior chemotherapy. While studies have not been conducted to support this practice, patients with soft tissue and bone sarcomas are often treated to maximum benefit prior to temporary discontinuation of chemotherapy. This is, in part, related to the lifetime limit of doxorubicin, the most active drug in sarcoma. The key trial examines whether ridaforolimus is able to maintain stable disease in this treatment window.

While no products have been approved as maintenance therapy in sarcoma, FDA-approved agents for the treatment of sarcoma include imatinib and sunitinib (gastrointestinal stromal tumor), doxorubicin (bone and soft tissue sarcoma), methotrexate (non-metastatic osteosarcoma), and vincristine (rhabdomyosarcoma). Three agents, erlotinib, pemetrexed, and rituximab, have been approved as maintenance therapy in other indications. The results of these studies are shown below.

Table 1: Products Approved for Maintenance Therapy			
Product	Indicated Population	Trial Design	Findings
Erlotinib	NSCLC w/o progression after 4 cycles of platinum-based therapy	Randomized, placebo-controlled	Median OS: 12.0 vs. 11.0 months Hazard Ratio: 0.81 (0.70, 0.95)
Pemetrexed	Non-squamous NSCLC w/o progression after 4 cycles of platinum-based therapy	Randomized, placebo-controlled	Median OS: 15.5 vs. 10.3 mos Hazard Ratio: 0.47
Rituximab	Follicular CD20+ NHL after CR/PR to rituximab + chemotherapy	Randomized, open label	Hazard Ratio for PFS: 0.54
	Non-progressing low grade CD20+ NHL after 1st line CVP	Randomized, open label	Median PFS: 4.3 vs. 1.3 years Hazard Ratio: 0.40[2]

[1]JCO 2009:1607

4.2 Regulatory History

End-of-Phase 1 and End-of-Phase 2 meetings were held with Ariad Pharmaceuticals in August 2005 and December 2006, respectively. In March and July of 2007, Ariad requested a Special Protocol Assessment (SPA) and no agreement letters were sent. The March 2007 letter stated, “Of note, PFS is not proven to be a surrogate for survival in this disease setting. A statistically significant difference in PFS may not necessarily represent a clinically meaningful difference. Whether PFS supports approval will be a review issue and would depend on the magnitude of the improvement and the risk/benefit ratio.” In July of 2007, Ariad submitted a 3rd request for SPA and an agreement letter was sent in August 2007.

In the agreed to SPA protocol, the applicant estimated that the median time to PFS was 6-9 months and projected a 25% improvement in PFS. This translated into an increase in median PFS from 6 to 8 months or from 9 to 12 months with ridaforolimus. The SPA protocol included 2 interim analyses at approximately 1/3 ($p \leq 0.0001$) and 2/3 ($p \leq 0.006$) of events. Following the 2nd interim analysis, the Data Monitoring Committee stated, “Although the primary endpoint, PFS, technically met the boundary for the secondary interim analysis for efficacy, the overall survival estimates are premature, limited by a 40-week median follow-up time. Therefore, it is not yet clear that overall survival is supportive. The PFS advantage of 7 weeks is not of sufficient clinically meaningful benefit, especially considering the toxicity, and is insufficient to suggest early termination for efficacy without at least a positive trend on overall survival.” The study continued and this NDA was submitted in August 2011.

5 Study Design

5.1 Studies Submitted to Support the Efficacy of Ridaforolimus

1. **P011**: A Pivotal Trial to Determine the Efficacy and Safety of AP23573 when Administered as Maintenance Therapy to Patients with Metastatic Soft-Tissue or Bone Sarcomas

2. **P018**: A Phase II Study of AP23573, an mTOR Inhibitor, in Patients with Advanced Sarcoma

3. **P016**: A Phase I/IIa, Sequential Cohort, Dose Escalation Trial to Determine the Safety, Tolerability, and Maximum Tolerated Dose of AP23573 when Administered Orally in Patients with Refractory or Advanced Malignancies

5.2 P011: Phase 3 Study Design

This study was conducted between October 2007 and October 2010.

Eligibility

1. Patients with metastatic soft tissue or bone sarcoma who have achieved CR, PR, or SD following 4-12 cycles of chemotherapy for metastatic disease. Disease status (≥ SD) must be confirmed by central review of the 2 most recent radiological evaluations.
2. Excluded sarcoma subtypes include:
    a. Alveolar soft-part sarcoma
    b. Clear cell sarcoma
    c. Chondrosarcoma
    d. Chordoma
    e. Desmoid Tumors
    f. Fibrosarcoma (low grade)
    g. Gastrointestinal Stromal Tumor
    h. Hemangioendothelioma (low grade)
    i. Hemangiopericytoma
    j. Liposarcoma (low grade)
    k. Rhabdomyosarcoma (embryonal)
3. 1st, 2nd, or 3rd line chemotherapy for metastatic disease prior to entry
4. Randomization ≤ 13 weeks following prior chemotherapy.
5. Patients with bone sarcoma must have had visceral metastatic disease or have achieved CR following treatment of visceral metastases. Patients with bone or soft tissue sarcoma who achieved PR or SD prior to entry must have measurable disease.
6. Age ≥ 13, patients age 13-17 must weigh ≥ 100 lbs; PS 0-1

7. No active infection requiring systemic therapy; No concomitant immunosuppressive agents; No cholesterol > 350 mg/dL or triglycerides > 400 mg/dL; No creatinine > 1.5xULN
8. Patients with diabetes were eligible for study entry.

Stratification Factors

1. Geographical region per statistical plan
   - North America: US, Brazil, Peru, Mexico, and Chile
   - European Union: France, Great Britain, Germany, Italy, Spain, Australia, Canada, and Sweden.
   - Rest of World: Korea, China, India, Israel, Slovakia, Czech Republic, Poland, New Zealand, South Africa, Greece
2. Tumor histology (soft tissue vs. bone sarcoma)
3. Prior lines of treatment (1st vs. 2nd/3rd line chemotherapy)

   - Patients were randomized 1:1.

Treatment

1. Ridaforolimus 40 mg po qd 5 day/week
2. Placebo

Monitoring

- Routine Laboratories: CBC and chemistries (including triglycerides, cholesterol) were collected at baseline, wks 2 and 4, q 4 wks to wk 16, then q 8 wks until discontinuation, and at 30-day follow up
- Patient reported outcomes: questionnaires concerning pain, cough, and dyspnea were collected q 4 wks x 4, then q 8 wks
- Disease assessment: baseline then q 8 wks ± 1 wk to 18 mos then q 4 mos

5.2.1 Independent Reviews

- Data Monitoring Committee (DMC): The DMC conducted 8 reviews, including 2 interim analyses. The DMC was composed of 3 clinicians and a biostatistician.

- Independent Review Committee (IRC): ICON provided an assessment of progression by 2 radiologists with adjudication by a 3rd radiologist if there was disagreement between the 2 readers on the patient's progression status. The IRC (different reader from the 2 above) also reviewed the 2 scans obtained prior to randomization to determine whether the patient had achieved ≥ SD to prior therapy (entry requirement). RECIST v 1 (minor modification) was used.

- Pathology Review: Samples were to be submitted to ICON central labs within 30 days of randomization. Each patient's slides were reviewed by a single pathologist.

5.2.2 Statistical Analysis Plan

The primary endpoint was PFS defined as the time from the date of randomization to the date of documented progression, recurrence, or death from any cause. The primary analysis utilized IRC-determined progression in the intent-to-treat population. Investigator-determined progression was examined as a supportive analysis. Patients who did not experience a PFS event were censored at the last date the patient was known to be progression-free. Patients who began a new anti-cancer therapy prior to IRC-determined progression were censored at their last tumor assessment. Likewise, patients who missed two or more consecutive tumor assessments prior to the determination of progression were censored at their last tumor assessment. Patients who underwent cancer-related surgery prior to IRC-determined progression were censored at the date of surgery. Patients who died or progressed between scheduled tumor assessments were considered to have had an event. The primary analysis was a stratified (tumor histology, prior lines of therapy) logrank test. A stratified (same strata) Cox proportional hazards model was used to estimate the hazard ratio. The median PFS and survival curves were estimated using the Kaplan-Meier method.

The trial was designed to accrue 650 patients (accrued 711). With 650 patients, it had 90% power to detect a HR of 0.75 with a 1-sided alpha of 0.025. The applicant estimated that ridaforolimus would result in an increase from 6 to 8 months or from 9 to 12 months in median PFS. Two interim analyses, at 1/3 and 2/3 of PFS events, were conducted with alpha-spending of 0.0001 and 0.006. The number of PFS events targeted in the final analysis was 516 (actual # 552). Secondary endpoints included overall survival, best target lesion response, and change in cancer-related symptoms. The study had 64% power to detect a HR for OS of 0.80 (OS improvement 12 to 15 months) and 85% power to detect a HR for OS of 0.75 (OS improvement 12 to 16 months). The secondary endpoint, best target lesion response was defined as the maximum percentage decrease, compared to baseline, in the sum of the longest diameter.

Protocol amendment 3 extended the period between prior chemotherapy and study entry from 8 to 12 weeks. There were no substantive amendments to the statistical analysis plan.

6 Study Results

6.1 Patient Population

Disposition

The table below provides information on patient disposition. Note that while more pts discontinued due to disease progression in the placebo arm (231 vs. 309) that 61

patients in the ridaforolimus arm and 9 in the placebo arm discontinued due to an adverse event.

Table 2: Patient Disposition

	Ridaforolimus N = 347	Placebo N = 364
Not Treated	4	5
Treated	343	359
Ongoing	25	28
Discontinued	318	331
Progressive Disease	231	309
Death	6	2
Adverse Event	61	9
Patient/Investigator Decision	20	8
Protocol Violation	0	3[1]

[1]Excluded sarcoma subtype (2), age not permitted (1)

Data Cutoff 10-25-10

Demographics and Disease Characteristics

Patients were well balanced by age (median 53 vs. 52 years), sex (46% vs. 43% male), and performance status (50% vs. 51% performance status 0) between arms. The majority of patients were White (79% vs. 82%). All comparisons are ridaforolimus vs. placebo. Importantly, 47% of patients in the ridaforolimus arm and 44% in the placebo arm were from the US.

At stratification, there were a number of misclassifications in tumor histology and in the number of lines of prior therapy. As part of the applicant's data collection and monitoring, patients were reclassified based on the source documents. The table below provides information on patient classification during stratification and reclassification based on source documents. For example, 212 patients in the ridaforolimus arm were said to have received 1st line chemotherapy for metastatic disease and were stratified on that basis. However, after monitoring, it was found that 182 patients had received only 1st line chemotherapy. In most instances, reclassification resulted in fewer imbalances between arms. The stratified logrank test used in the primary analysis will be examined using both the stratification and reclassification values for these variables.

Table 3: Stratification Errors				
	Ridaforolimus N = 347		Placebo N = 364	
	Stratum	Actual	Stratum	Actual
Tumor Histology				
Soft Tissue	310	308	332	327
Bone	37	39	32	37
Prior Lines of Chemotherapy				
1st Line	212	182	224	185
2nd/3rd Line	135	165	140	179

Data Cutoff 10-25-10

While the table above provides information on patient reclassification based on information available at the site, the table below compares tumor histology (per source documents available at the site) to that obtained from an independent review. Note that independent review was not a consensus read, but that each patient's slides were read by a single pathologist. There were, however, several pathologists involved in the independent review and, unfortunately, a single grading system was not used. Therefore, subgroup analysis of the HR by grade will not be performed. Importantly, the number of patients with the various sarcoma subtypes and the number with low or high grade disease, by central review, are relatively balanced between arms.

Table 4: Site and Central Review of Tumor Histology				
	Ridaforolimus		Placebo	
	Site N = 347 (%)	Central N = 343 (%)	Site N = 364 (%)	Central N = 356 (%)
Sarcoma Type				
Bone	33 (10)	27 (8)	33 (9)	31 (9)
Osteogenic Sarcoma	29	23	25	24
Ewing's Sarcoma	1	2	5	3
Other	3	2	3	4
Soft Tissue	302 (87)	284 (83)	319 (88)	291 (82)
Leiomyosarcoma	115	102	122	109
Liposarcoma	53	42	55	43
Other	134	140	142	139
Not Sarcoma	0	5	0	11
Missing/Not Done	12	27	12	23
Sarcoma Grade				
2-Scale System				
High	67	37	53	41
Low	5	3	2	4
3-Scale System				
High	91	153	108	154
Intermediate	31	65	30	71
Low	8	10	10	16
4-Scale System				
1	5		8	
2	12		11	
3	15		19	
4	9		13	
Not Graded	102	75	110	70

Data Cutoff 10-25-10

Prior therapy could include surgery or radiation therapy while prior chemotherapy for metastatic disease was an entry requirement. Most patients, 62% in the ridaforolimus arm and 64% in the placebo arm had received 1 prior regimen. An anthracycline or anthracenedione was the most commonly used chemotherapeutic agent. Note that while the median time from last chemotherapy (study permitted up to 91 d) to the first dose of study drug was 42 days in the ridaforolimus and 40 days in the placebo arm that the range of values is wide. It is unknown whether some patients may have progressed between the time of their last regimen and study entry.

Table 5: Prior Therapy		
	Ridaforolimus N = 347 (%)	Placebo N = 364 (%)
Prior Therapy		
Surgery	317 (91)	326 (90)
Radiation Therapy	177 (51)	177 (49)
# Prior Chemotherapy Regimens for Metastases	N = 346	N = 363
1	214 (62)	233 (64)
≥ 2	132 (38)	130 (36)
Prior Chemotherapy		
Anthracycline/Anthracenedione	309 (89)	324 (89)
Ifosfamide	211 (61)	239 (66)
Gemcitabine	118 (34)	126 (35)
Median Time Since Last Chemotherapy[1] (range)	42 days (20-125)	40 days (16-99)

Data Cutoff 10-25-10

Finally, disease status at baseline, by investigator or IRC review, is shown in the table below. Patients in CR could enter with no measurable disease. However, patients with PR or SD were required to have measurable disease. By investigator report, 37 patients were in CR at entry, but (also by investigator report) 74 patients had no target lesions identified at baseline. By IRC review, 173 patients had no measurable disease. Sites of disease and the median sum of the longest diameters at baseline, per IRC, are also shown in the table below. Note that there is a slight imbalance in the number of patients with liver lesions between arms.

Table 6: Disease Status at Baseline		
Investigator Review		
Disease Status at Baseline	N = 341	N = 361
Complete Response	19	18
Partial Response	64	70
Stable Disease	258	273
	N = 320	N = 343
Measurable Disease	291	298
No Measurable Disease	29	45
Median Sum of the Longest Diameter (range)	8.6 cm (1.0-4.9)	7.5 (1.0-5.1)
Independent Review		
	N = 320	N = 344
Measurable Disease	240	251
No Measurable Disease	80	93
Sites of Target and Non-Target Lesions		
Lungs and Pleura	214	216
Abdominal/Retroperitoneal Soft Tissue	76	75
Liver	73	91
Lymph Nodes and Spleen	63	75
Median Sum of the Longest Diameter (range)	8.0 cm (1.0-29.0)	8.0 cm (1.0-5.0)

Data Cutoff 10-25-10

6.2 Efficacy

6.2.1 Primary Endpoint

Three assessments of the primary endpoint, with very similar hazard ratios and highly significant p-values, but with small differences in median PFS are shown in the table below. The ability of this study to precisely (small p-value) detect a small difference in median PFS is due to power of the study (study size). The study was designed to have 90% power to detect a 25% improvement in PFS and with 60-80% power to detect a 20-25% improvement in OS. That is, the study size was increased so that it would have "reasonable" power to detect a difference in OS. The enrollment of 711 patients (rather than 650) further increased the power of this study to detect a small difference in PFS.

The ability of this study to detect a small difference in PFS is also due to inaccuracy in the assessment of median PFS in the control arm. That is, the applicant estimated that PFS would be 6-9 months in the control arm and designed the study to detect a 25% improvement in PFS (1.5-2.25 months). However, the actual PFS in the placebo arm was 3.2 months. With a median of 3.2 months, a 25% improvement in PFS translates into 1.1 months or 33 days.

The difference in PFS between arms should also be considered in the context of the median OS; 20.8 months in the ridaforolimus and 19.6 months in the placebo arm. All of the analyses in the table below use the values for the stratification variables (tumor histology, number of prior therapies) found on site monitoring. Analyses were also performed using the values for the stratification variables identified at the time of randomization. The results of these analyses are very similar to those shown below.

Table 7: Primary Analysis

	FDA		Applicant		Investigator	
	Ridaforolimus	Placebo	Ridaforolimus	Placebo	Ridaforolimus	Placebo
Number of Events						
Event	265	294	261	291	278	319
Censored	82	70	86	73	69	45
Median PFS	16 wks	14 wks	18 wks	15 wks	22 wks	15 wks
Hazard Ratio (p-value)[1]	0.74 (0.0006)		0.72 (0.0001)		0.69 (<0.0001)	

[1]HR-stratified Cox proportional hazards model; p-value-stratified logrank test Data Cutoff 10-25-10

Both the FDA and applicant assessments used IRC-determined progression. The difference between these involves the handling of scans read as new lesion/no progression by the IRC. The applicant analysis did not consider these new lesions as disease progression while the FDA analysis, consistent with the RECIST criteria, considered this to be progressive disease. Review also noted an imbalance in the number of patients read as new lesion/no progression (14 ridaforolimus, 7 placebo). To

fully evaluate whether these lesions did, in fact, represent disease progression, these sites of disease were followed to determine whether they were unchanged, increased, or unevaluable (insufficient number of scans after the identification of the new lesion). The table below provides a by patient breakdown of these new lesions.

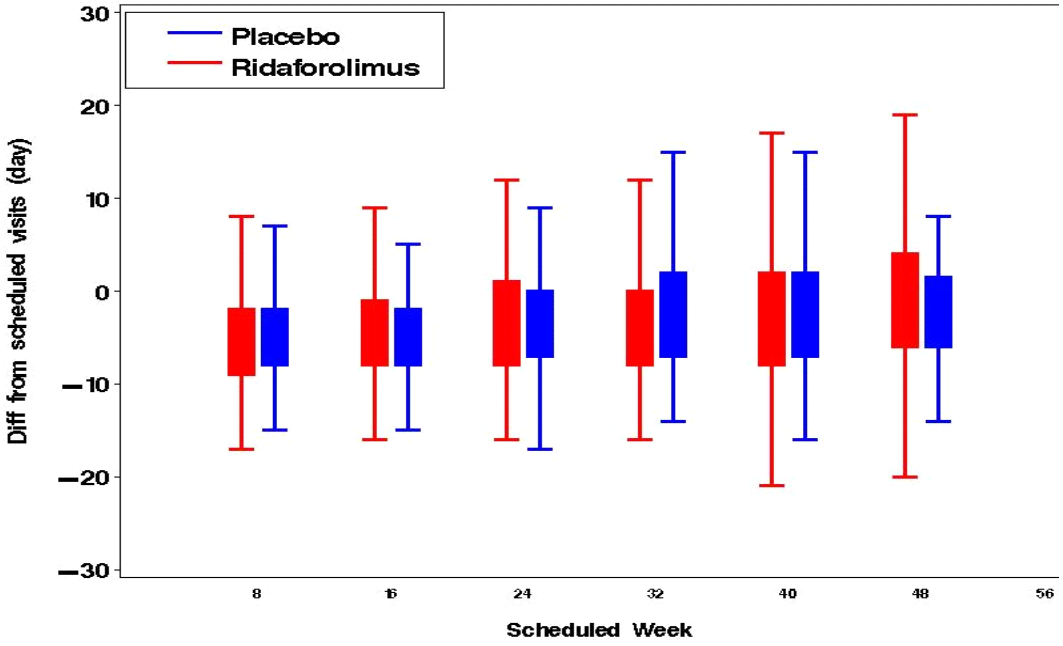
Table 8: Follow Up of New Lesions Read as No Progression

	Ridaforolimus N = 347	Placebo N = 364
Patients with New Lesion/No PD	14	7
Lesion Continued to be Read as Present	10	3
Lesion Increased in Size	3	1
Unevaluable	1	3

Data Cutoff 10-25-10

Given the small difference between in median PFS between arms, time to assessment was examined for systematic differences or substantial outliers that could contribute to this difference. The figure below provides a graphic representation of differences between the actual and scheduled scan date in each arm. The boxes depict the 25%-75% distribution of the data, while outliers are shown by the lines extending from the lower and upper edge of the boxes. Importantly, the difference in the time to scheduled tumor assessment, between arms, was not statistically significant.

Figure 1: Time to Tumor Evaluation between Arms

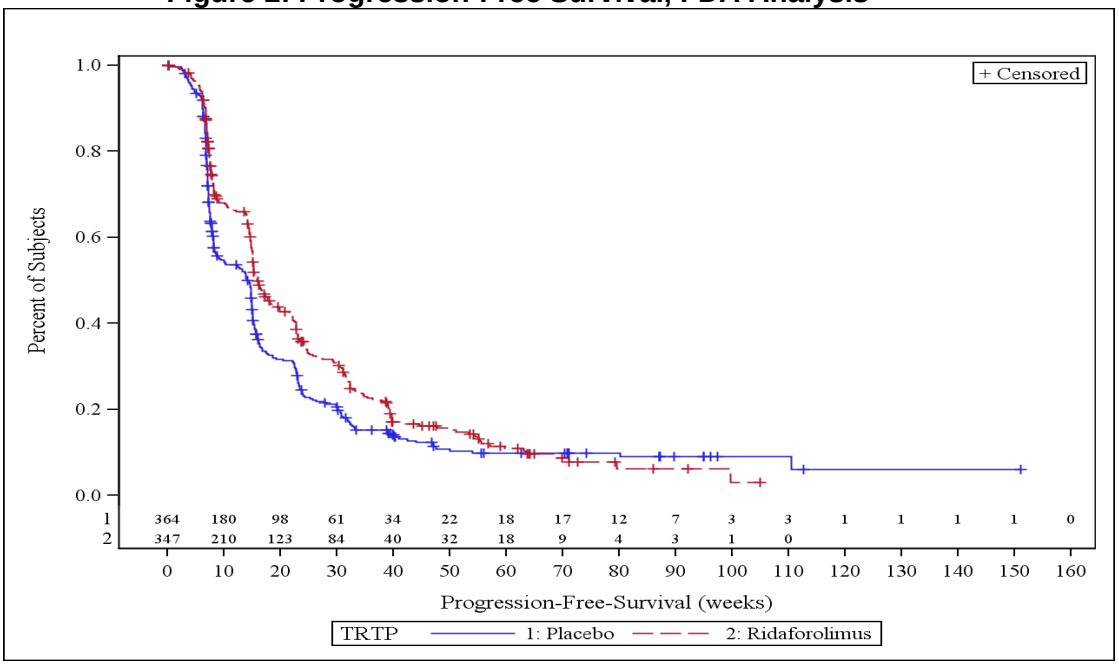


Finally, the discordance between IRC and the INV-assessment of progression was examined. Discordance occurred in 299 (42%) of patients. A difference in event

(progression event vs. censoring) was seen in 107 patients and a difference in the time of progression in 228 patients.

The figure below provides the FDA analysis of PFS. Note the stair-step pattern which suggests that progression was usually identified at the time of the scan, rather than between assessments.

Figure 2: Progression-Free Survival, FDA Analysis



6.2.2 Secondary Endpoints

<u>Overall Survival</u>

The final analysis of OS, using the stratification variables tumor histology and number of prior therapies identified on study monitoring, is shown in the table below.

Table 9: Overall Survival

	Ridaforolimus N = 347	Placebo N = 364
Number of Events		
Deaths	250 (69%)	228 (66%)
Median OS	20.8 months	19.6 months
Hazard Ratio (p-value)[1]	0.93 (p = 0.46)	

[1]HR-stratified Cox proportional hazards model, p-value-stratified logrank test Data Cutoff: 1-21-12

Response Rate

There were no complete responses in either arm. There were 5 partial responses in the ridaforolimus and 2 partial responses in the placebo arm.

6.2.3 Subgroup Analyses

Subgroup analyses are shown in the table below. One concern with the study design is the inclusion of patients with either bone or soft tissue sarcoma. However, subgroup analysis found a very similar HR (0.82 in bone and 0.77 in soft tissue sarcoma) in both groups. An additional concern is the inclusion of patients with variable disease status (CR to SD) and with differences in the number of prior regimens. Subgroup analyses suggest that only the number of prior therapies had an effect on patient outcome. The HR for patients in CR at entry is not included since the number of patients was too small to make an accurate estimate.

Table 10: Subgroup Analysis of PFS

Subgroup	Hazard Ratio (95% CI)
Overall	0.74 (0.63, 0.88)
US	0.85 (0.66, 1.09)
Histology	
Bone Sarcoma	0.82 (0.47, 1.42)
Soft Tissue Sarcoma	0.77 (0.65, 0.92)
Liver Metastases	0.69 (0.46, 1.02)
Response to Prior Therapy	
Partial Response	0.75 (0.51, 1.10)
Stable Disease	0.76 (0.63, 0.93)
Number of Prior Therapies	
1	0.85 (0.69, 1.05)
2	0.61 (0.43, 0.85)
3	0.67 (0.41, 1.12)
Age	
< 65	0.82 (0.68, 0.99)
≥ 65	0.65 (0.45, 0.94)
Sex	
Male	0.70 (0.56, 0.88)
Female	0.89 (0.69, 1.14)
Race	
White	0.82 (0.68, 0.99)
Asian	0.58 (0.36, 0.93)

6.2.4 Other Studies

PO18

P018 was a Phase 2 study examining the effect of ridaforolimus 12.5 mg IV daily for 5 days every 2 weeks in patients with bone sarcoma, leiomyosarcoma, liposarcoma and "other" sarcoma subtypes. A cycle was 28 days and imaging was performed every 2 months. Most patients had received multiple prior chemotherapeutic regimens. The primary endpoint was the percentage of patients, per investigator, with CR, PR, or SD ≥ 102 days using a slight modification to the RECIST criteria. The table below shows the percentage of patients achieving the primary endpoint in each histologic subtype. These results should be interpreted with caution since 36% of patients were recruited from a single site with 46% of patients from that site achieving the primary endpoint.

Table 11: Primary Analysis-Phase 2 Study

	Bone Sarcoma N = 54	Leiomyosarcoma N = 57	Liposarcoma N = 44	Other N = 57
Primary Endpoint[1]	17 (32%)	19 (33%)	13 (30%)	12 (21%)

[1]8 pts unevaluable due to resection

Data Cutoff 8-5-09

P016

P016 was a Phase 1-2 trial designed to assess the maximum tolerated dose of oral ridaforolimus using various doses and schedules and to then examine the recommended Phase 2 dose in patients with sarcoma. The Phase 2 portion of the trial was not carried out. However, the majority of patients accrued to this study had an underlying sarcoma and 24 patients were treated at the dose and schedule chosen for the Phase 3 study. During dose escalation, no DLTs were seen in the patients who received the Phase 3 dose and schedule (40 mg po 5 days/week). The decision to use this dose and schedule for the Phase 3 trial was primarily based on the high AUC achieved with this dose. The AUC of ridaforolimus chosen for the Phase 3 trial is comparable to that of ridaforolimus 12.5 mg IV qd x 5 q 2 wks.

P016 also assessed the percentage of patients achieving, per investigator, a CR, PR, or SD ≥ 4 months. Among the 24 patients treated at the Phase 3 dose and schedule, 3 achieved the primary endpoint. This included 3/13 patients with sarcoma. Among the 45 patients who received 30-50 mg of ridaforolimus daily 5 days/week, 12 achieved the primary endpoint, including 8/26 patients with sarcoma.

6.3 Safety

6.3.1 Safety Population

Approximately 1,500 patients with cancer and 125 volunteers have been exposed to ridaforolimus. The safety information available in this submission includes:

- Phase 3 Study (N = 343 received ridaforolimus) in patients with sarcoma with safety data cutoff September 2011;
- Completed Phase 2 study (N = 212) in patients with sarcoma and completed Phase 1-2 study (N = 147) primarily in patients with sarcoma;
- Completed Phase 1-2 single agent and combination studies (N = 354) in a variety of solid tumors; and
- Serious adverse event reports from ongoing studies (N = 549).

6.3.2 Exposure

The table below provides information on patient exposure to ridaforolimus during the Phase 3 randomized study. Note that 70% of patients required dose reduction and 56% required dose delay on the ridaforolimus arm. Examining the number of patients may under-represent the number of dose reductions required with ridaforolimus. In P011, there were 3,027 dose reductions in 239 patients on the ridaforolimus arm. Median duration of exposure was similar in the two arms.

Table 12: Dose Reduction or Delay on the Phase 3 Study

	Ridaforolimus N = 343	Placebo N = 359
Dose Reductions	239 (70%)	43 (12%)
Dose Delays	191 (56%)	115 (32%)
Median Duration of Exposure (range)	3.5 months (0.03-32)	3.4 months (0.2-44)

Data Cutoff 9-1-11

6.3.3 Deaths and Discontinuations

The table below provides information on the causes of death in the Phase 3 trial. A wide variety of adverse events resulted in death and in many instances it is difficult to determine whether the adverse event was related to disease progression. Note that 1 patient on the ridaforolimus arm died of pneumonitis; an adverse event associated with other rapamycin analogs.

Table 13: Deaths on the Phase 3 Trial Data Cutoff 9-1-11		
	Ridaforolimus N = 343	Placebo N = 359
Within 30 Days	13 (4%)	11 (3%)
Progressive Disease	1	4
General Physical Health Deterioration/ Decreased Performance Status	1	3
Adverse Event	11[1]	4[2]
Pneumonitis	1	0
> 30 Days	8 (2%)	6 (2%)
Progressive Disease	2	2
General Physical Health Deterioration/ Decreased Performance Status	3	2
Adverse Event	2	1
Second Malignancy	1	1

[1]GI hemorrhage (2), 1 each-arrhythmia, dyspnea, hypercalcemia/renal failure (poss infection), pericardial effusion, pleural effusion, pneumonitis, PE, respiratory distress, seizure (CNS mets)
[2]1 each-duodenal perforation, intestinal obstruction, cholangitis, tumor perforation

In the Phase 1-2 study P016, there were 11 (8%) deaths due to an AE within 30 days of study drug while in the Phase 2 study P018, 9 (4%) deaths due to an AE occurred within 30 days.

Discontinuations

The adverse event dataset from the Phase 3 trial includes 48 (14%) patients in the ridaforolimus and 8 (2%) in the placebo arm who discontinued due to an adverse event. This differs from the disposition dataset where 61 (18%) patients in the ridaforolimus and 9 (3%) patients in the placebo arm discontinued due to an adverse event. Examining the patients identified by these two datasets, the increased number of patients in the disposition dataset is primarily due to patients who discontinued due to stomatitis and to patients who discontinued due to an unspecified adverse event. In both of these datasets, the number of patients who discontinued on the ridaforolimus arm was substantially higher than the number who discontinued on the placebo arm. This brings the tolerability of ridaforolimus, as maintenance therapy, into question.

6.3.4 Adverse Events

The table below provides information on grade 1-4 adverse events in > 20% of patients on the ridaforolimus arm. This table does not include laboratories which were reported as adverse events. These are instead included in the laboratory table below.

Table 14: Grade 1-4 Adverse Events in > 20% of Patients Data Cutoff 9-1-11				
	Ridaforolimus N = 343 (%)		Placebo N = 359 (%)	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Any	342 (100)	218 (64)	336 (94)	91 (25)
Gastrointestinal Disorders				
Stomatitis and Mucositis[1]	280 (82)	40 (12)	102 (28)	2 (1)
Diarrhea and Enteritis	110 (32)	10 (3)	67 (19)	0
Nausea	96 (28)	6 (2)	93 (25)	5 (1)
Abdominal Pain and Discomfort[2]	87 (25)	11 (3)	69 (19)	7 (2)
General Disorders				
Asthenia, Fatigue, and Malaise	173 (50)	21 (6)	119 (33)	11 (3)
Edema, Peripheral Edema, and Lymphedema	88 (26)	4 (1)	32 (9)	0
Pyrexia, Hyperpyrexia, and Hyperthermia	83 (24)	1 (0.3)	29 (8)	1 (0.3)
Infections and Infestations				
Any	183 (53)	20 (6)	93 (26)	10 (3)
Metabolism and Nutrition				
Decreased Appetite	93 (27)	2 (0.6)	36 (10)	2 (0.6)
Nervous System Disorders				
Headache and Migraine	94 (27)	4 (1)	53 (15)	2 (0.6)
Respiratory Disorders				
Cough and Productive Cough	113 (33)	2 (0.6)	63 (18)	2 (0.6)
Dyspnea and Exertional Dyspnea	81 (24)	20 (6)	36 (10)	2 (0.6)
Skin Disorders				
Rash[3]	131 (38)	4 (1)	32 (9)	0

[1]Includes aphthous stomatitis, cheilitis, gingival bleeding, pain, and ulceration, glossitis, glossodynia, lip pain and ulceration, mouth ulceration, mucosal inflammation, mucosal hyperemia, oral discomfort, oral mucosal erythema, oral pain, oropharyngeal pain and blistering, stomatitis, tongue blistering, and tongue ulceration
[2]Includes abdominal tenderness, gastrointestinal pain, epigastric discomfort
[3]Includes acne, dermatitis acneiform, dermatitis, exfoliative rash, rash erythematous, and rash generalized, macular, maculo-papular, papular, and pruritic

The most common adverse event was stomatitis occurring in 82% of patients (12% gr 3-4). This was compared to the percentage of patients developing stomatitis on everolimus (44-86% gr 1-4; 4-7% gr 3/4) and temsirolimus (41% gr 1-4; 3% gr 3/4). Surprisingly, given the percentage of patients reporting stomatitis, diarrhea was reported in 32% (3% gr 3-4) of patients while grade 1-4 GI hemorrhage occurred in 7 patients (2 gr 3) in the ridaforolimus arm and 3 patients (2 gr 3/4) in the placebo arm.

Rash, another adverse event commonly reported with rapamycin analogs, was reported in 38% of patients (1% gr 3-4). This was compared to the percentage of patients developing rash on everolimus (29-59% gr 1-4; 0.5-1% gr 3-4) and temsirolimus (47% gr 1-4; 5% gr 3-4). Examining the entire ridaforolimus safety database, there were no reports of toxic epidermal necrolysis or Stevens Johnson syndrome.

Infections and opportunistic infections have also been a concern with rapamycin analogs. While there was an increase in the number of infections with ridaforolimus compared to placebo (53% vs. 26%), in the Phase 3 trial the only infections occurring in > 10% of patients were upper respiratory infection and cystitis/urinary tract infection. Examination of the safety database identified the following opportunistic infections: aspergillosis, bacterial sepsis (burkholderia cepacia), herpes simplex ophthalmic, herpes zoster, nocardiosis, pneumocystis, atypical pneumonia, fungal pneumonia, and systemic fungal infection.

6.3.5 Significant Adverse Events

Pneumonitis

Pneumonitis has been reported with other rapamycin analogs and the ridaforolimus dataset was carefully evaluated for reports of this event. Pneumonitis, interstitial lung disease, pulmonary fibrosis, or allergic alveolitis was reported in the Phase 3 study in 36 (10%) patients in the ridaforolimus arm and 2 (0.6%) patients in the placebo arm. This included 1 death and 7 grade 3 events in the ridaforolimus arm and 1 grade 3 event in the placebo arm. In the safety database, pneumonitis was reported in 6% of patients. Grade 1-4 pneumonitis has been reported in 11-14% of patients on everolimus (gr 3-4 1.6-4%) and in 2% of patients on temsirolimus.

To evaluate the course and risk factors for pneumonitis, the patients in the Phase 3 trial were examined more closely. The median date of onset (1st report) was day 107 (range day 22-638). Among the 32 events that resolved, the median duration was 47 d (range 7-237 days). Consistent with the diagnosis of metastatic sarcoma, 75% of patients with pneumonitis had lung metastases. However, only 2 had received prior radiation to the chest. Among patients with $\geq$ grade 3 pneumonitis, all received steroids and 5/8 received antibiotics. Six patients discontinued ridaforolimus due to pneumonitis.

Renal Failure

In the Phase 3 study, renal failure/impairment was reported in 35 (10%) patients (3% gr 3-4) in the ridaforolimus and 4 (1%) patients (0.3% gr 3) in the placebo arm. While some of these events can be related to dehydration or to multi-organ failure in the setting of sepsis, others remain unexplained and may be due to study drug. Grade 3-4 creatinine was captured in 10 patients in the ridaforolimus and in 6 patients in the placebo arm. In the safety database, gr 1-4 renal failure/impairment was reported in 11% (N = 115) of patients (3% gr 3-4).

Hypersensitivity Reaction

The applicant reported an increase in reactions that may be related to drug hypersensitivity. Including local swelling and localized edema with these terms, 10% of patients in the ridaforolimus arm and 2% in the placebo arm experienced a possible hypersensitivity reaction. While this is clearly increased in the ridaforolimus arm, 8 events were considered definitely (lip swelling, swollen neck, swollen tongue) or probably (eyelid edema (2), face edema (2), swollen face, and nettle rash) related to study drug. The timing of these events was also examined. Two events, eye swelling (ridaforolimus) and hives (placebo) occurred within the first week of exposure. Two events were considered severe (angioedema-ridaforolimus, local swelling-placebo) with 10 patients in the ridaforolimus and 1 in the placebo arm experiencing a grade 2 event.

6.3.6 Laboratory Abnormalities

As shown in the table below, ridaforolimus is associated with hematologic abnormalities (primarily thrombocytopenia), hyperglycemia, and hyperlipidemia. Grade 3-4 lymphocytopenia was also seen in 26% of patients on ridaforolimus (7% placebo). Grade 1-4 elevations in ALT were commonly also noted with ridaforolimus (51% ridaforolimus, 23% placebo). The number of patients with an increase in bilirubin was comparable in the two arms and no patients had both a grade 3 elevation in ALT and a grade 2 elevation in bilirubin. Finally, both hypophosphatemia (gr 1-4 43%; gr 3-4 12%) and hypokalemia (gr 1-4 37%; gr 3-4 6%) were seen in patients on ridaforolimus.

Table 15: Laboratory Abnormalities

	Ridaforolimus				Placebo			
	Baseline		On Study		Baseline		On Study	
Hematology	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4
Neutrophils	10%	0.5%	38%	5%	6%	0.9%	17%	2%
Hemoglobin	57%	0.8%	83%	4%	57%	0.4%	58%	2%
Platelets	8%	0	65%	11%	10%	2%	21%	5%
Chemistry	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4
Glucose	21%	0	73%	12%	22%	0	53%	2%
Cholesterol	31%	0	75%	2%	38%	0	51%	0
Triglyceride	30%	0	74%	3%	33%	0	43%	0
ALT	12%	0	51%	3%	14%	0	23%	0.9%
	Gr 1-4	Gr 2-4	Gr 1-4	Gr 2-4	Gr 1-4	Gr 2-4	Gr 1-4	Gr 2-4
Bilirubin	1%	0.4%	4%	1%	2%	0.7%	6%	2%

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9. Conclusion and Question to ODAC

The Phase 3 study examined the use of ridaforolimus as maintenance therapy in patients with soft tissue or bone sarcoma who had achieved ≥ SD on prior

chemotherapy. Patients were randomized to ridaforolimus or placebo and were imaged every 8 weeks. Scans were read by an independent review committee.

- The FDA analysis of the primary endpoint found that the median PFS was 16.1 weeks in the ridaforolimus arm and 14.0 weeks in the placebo arm with a HR of 0.74, p = 0.0006. In the final analysis of OS, median OS was 20.8 months in the ridaforolimus arm and 19.6 months in the placebo arm with a HR of 0.93, p = 0.46. Both the difference in PFS and the difference in OS should be considered in light of the median OS in the ridaforolimus arm, 20.8 months.

- The safety profile of ridaforolimus is similar to that of other mTOR inhibitors. Adverse events in > 20% of patients included stomatitis, asthenia/fatigue, infection, rash, cough, diarrhea, nausea, decreased appetite, headache, edema, abdominal pain, dyspnea, and fever. Adverse events of particular concern include pneumonitis, infection, and renal failure/impairment. Discontinuation due to an adverse event occurred in 14% of patients in the ridaforolimus arm compared to 2% in the placebo group while a substantial number of patients experienced a grade 3-4 adverse event (64% ridaforolimus, 25% placebo). Laboratory abnormalities include hematologic toxicity, hyperglycemia, hyperlipidemia, and increased ALT.

Draft Question for ODAC: Given the small differences in median PFS and OS between arms, the adverse event profile of ridaforolimus, and its positioning as a maintenance therapy in patients with soft tissue and bone sarcoma, is the risk-benefit assessment favorable for the use of ridaforolimus in the treatment of patients with soft tissue and bone sarcoma who have received prior chemotherapy?