Exploratory Analysis of Potential Predictive Markers to Identify Sensitive/Responder Sarcoma Patients with Ridaforolimus in the Phase 3 Randomized Placebo-controlled Trial (SUCCEED)

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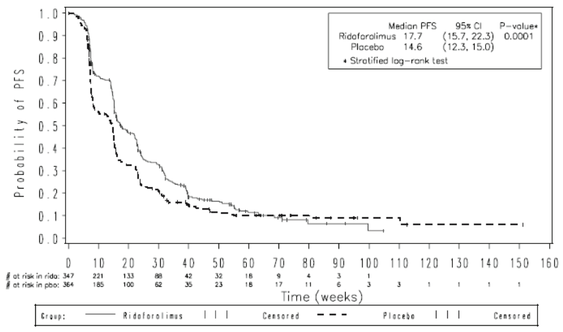
Background

- The PI3K-AKT-mTOR signaling pathway plays an important role in growth and proliferation of many types of sarcomas.
- Activation of mammalian target of rapamycin (mTOR), downstream of several signaling pathways, results in abnormal angiogenesis, metabolism, cell growth and proliferation, which contributes to the malignant phenotype.
- Ridaforolimus is a rapamycin analog mTOR inhibitor that was recently shown in a pivotal phase III trial (N=711) to induce a statistically significant improvement in progression free survival (hazard ratio 0.72; p<0.0001) compared to placebo control as maintenance therapy for patients with metastatic sarcoma who had achieved clinical benefit from prior conventional chemotherapy **(Figure 1)**.[1]
- To assess whether a subset of patients who are particularly responsive to the benefits of ridaforolimus might be identified, we have performed exploratory analyses of efficacy by patient baseline demographic characteristics or specific histologic subtypes of sarcoma.

[1] Presented at ASCO 2011, Chicago, IL

Figure 1. Kaplan-Meier plot of progression-free survival by independent radiological assessment (ITT population) (primary endpoint)



Methods

Study Design

- Double-blind, randomized, parallel study comparing ridaforolimus and placebo in metastatic sarcoma.
- Ridaforolimus given at 40 mg/day for 5 days weekly
- Primary endpoint: progression free survival (PFS)
  - Disease status confirmed by independent radiological review

Patients

- Age ≥13
- Histologically confirmed metastatic sarcoma of soft tissue or bone (excluding certain subtypes such as GIST, ASPS, others)
- Complete remission (CR), partial remission (PR), or stable disease (SD) after 1st, 2nd, or 3rd line chemotherapy
- Adequate hematology and end-organ function

Analyses

- Prespecified subgroup PFS analysis by baseline characteristics, including bone vs. soft tissue sarcoma
- Additional, exploratory post-hoc PFS analysis by:
  - Sarcoma histologic subtype
  - Occurrence of grade 2+ stomatitis within 28 days
  - Segmentation of "stable" or responding disease at study entry: differential assessment of patients with different percent changes in measurable target lesion size immediately prior to study entry on screening eligibility CT scans (performed ≥6 and <12 weeks apart)
    - Tumor ***shrinkage*** ≥ 10% ("stable" [minor response] subgroup)
    - Tumor ***shrinkage*** < 10% to tumor ***growth*** < 10% ("stable" [truly stable] subgroup)
    - Tumor ***growth*** ≥ 10% ("stable" [growing] subgroup)
- Descriptive analyses; not adjusted for multiplicity

Results

Patients

- Baseline characteristics were similar across treatment groups **(Table 1)**. Histologic subtypes determined by central pathology review are shown in **Table 2**.

Table 1. Baseline patient characteristics

	Ridaforolimus N=347 n (%)	Placebo N=364 n (%)	P-Value*
Age, mean (SD)	52.0 (16.0)	50.6 (15.0)	0.2360
Gender			0.4969
Male	158 (45.5)	156 (42.9)	
Female	189 (54.5)	208 (57.1)	
ECOG			1.0000
0	174 (50.1)	184 (50.5)	
1	172 (49.6)	180 (49.5)	
Missing	1 (0.2)	0 (0.0)	
Sarcoma Histotype			0.4476
Soft Tissue	310 (89.3)	332 (91.2)	
Bone	37 (10.7)	32 (8.8)	
Prior Most Recent Chemotherapy†			0.9386
1st Line	212 (61.1)	224 (61.5)	
2nd/3rd Line	135 (38.9)	140 (38.5)	
Tumor Grade per central pathology review			0.7152
Low	13 (3.7)	20 (5.5)	
High	256 (73.8)	266 (73.1)	
Cannot be assessed	30 (8.6)	28 (7.7)	
Missing	40 (11.5)	41 (11.3)	

*Nominal 2-sided p-value based on the Fisher's Exact test or Wilcoxon Rank Sum test, as applicable
†From stratification

Table 2. Baseline sarcoma histology based on independent pathology review (ITT population)*

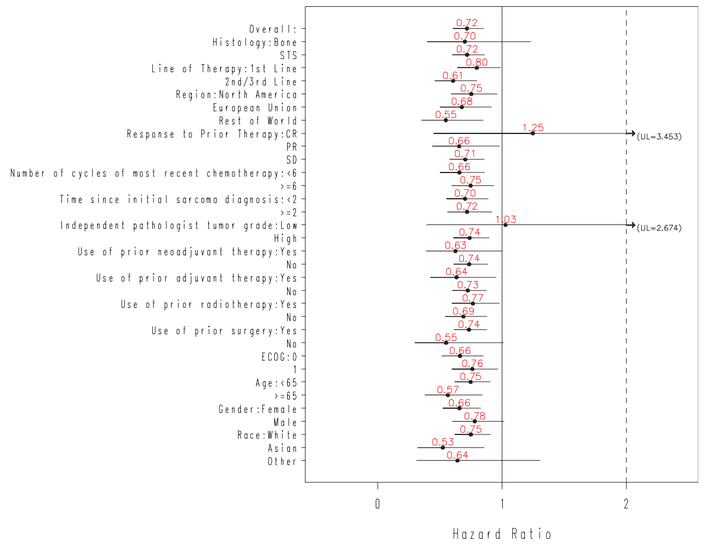
		Ridaforolimus (N=347)	Placebo (N=364)	Overall (N=711)
Bone Sarcoma				
	Osteosarcoma	25 (7.2%)	25 (6.9%)	50 (7.0%)
	Other Bone Sarcoma†	5 (1.4%)	8 (2.2%)	13 (1.8%)
Soft Tissue Sarcoma				
Leiomyosarcoma	Leiomyosarcoma	113 (32.6%)	118 (32.4%)	231 (32.5%)
Liposarcoma	Liposarcoma	51 (14.7%)	48 (13.2%)	99 (13.9%)
Other Soft Tissue Sarcoma	Angiosarcoma	7 (2.0%)	5 (1.4%)	12 (1.7%)
	Desmoplastic Small Round Cell Tumor	7 (2.0%)	4 (1.1%)	11 (1.5%)
	Malignant Peripheral Nerve Sheath Tumor	7 (2.0%)	9 (2.5%)	16 (2.3%)
	Myxofibrosarcoma	9 (2.6%)	6 (1.6%)	15 (2.1%)
	Rhabdomyosarcoma	5 (1.4%)	8 (2.2%)	13 (1.8%)
	Solitary Fibrous Tumor	8 (2.3%)	2 (0.5%)	10 (1.4%)
	Spindle Cell Sarcoma	9 (2.6%)	7 (1.9%)	16 (2.3%)
	Synovial Sarcoma	23 (6.6%)	37 (10.2%)	60 (8.4%)
	Undifferentiated Pleiomorphic Sarcoma	27 (7.8%)	28 (7.7%)	55 (7.7%)
	Other†	43 (12.4%)	46 (12.6%)	89 (12.5%)
Other Cancer				
	Other†	5 (1.4%)	12 (3.3%)	17 (2.4%)
Unknown				
	Unknown	3 (0.9%)	1 (0.3%)	4 (0.6%)

*Independent pathology review was available in >90% of patients; when unavailable, local diagnosis was used
† The Other Categories include specific diagnoses in fewer than 10 patients each.

Prespecified Subgroup Analysis: PFS by demographic features (Figure 2)

- The beneficial effect of ridaforolimus on PFS relative to placebo is highly consistent across subgroups, with most HRs ranging from 0.53 to 0.78.
- There was a trend toward greater improvement in PFS for patients receiving ridaforolimus after benefit from prior 2nd/3rd line chemotherapy (HR 0.61) compared to those patients receiving ridaforolimus after 1st line therapy (HR 0.80), although the CIs for the two subgroups are overlapping

Figure 2. Prespecified subgroup analysis of the primary endpoint

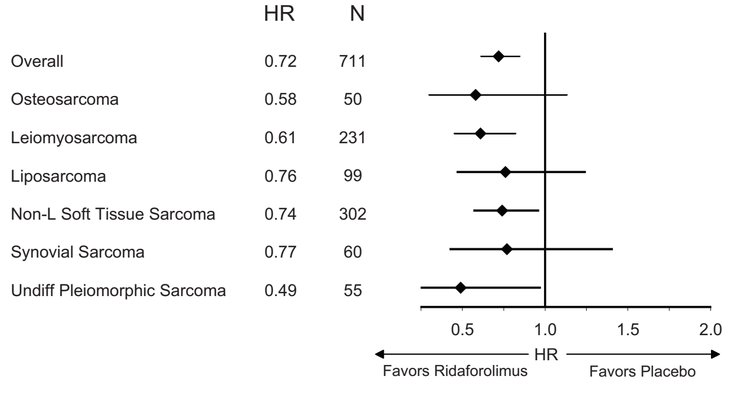


Post-hoc Analyses

PFS by histologic subtype (**Figure 3**)

- The beneficial effect of ridaforolimus relative to placebo appears consistent across all histologic subtypes, although the sample sizes and number of events are too small to draw meaningful conclusions from this post-hoc analysis.

Figure 3. PFS analysis by sarcoma subtypes based on independent pathology review



PFS by grade 2+ stomatitis within 28 days (**Table 3**)

- Ridaforolimus had significantly greater PFS than placebo in both patients with and without grade 2+ stomatitis, however the effect was substantially larger in patients with grade 2+ stomatitis.

Table 3. Progression-free survival in patients with and without grade 2+ stomatitis within 28 days

	N	Number of PFS Events	Number Censored	PFS (weeks) Median (95% CI)	Hazard Ratio @ (95% CI) Compared to placebo
Ridaforolimus, *with* grade 2+ stomatitis	137	100	37	18.7 (12.1, 21.7)	0.66 (0.53, 0.84)
Ridaforolimus *without* grade 2+ stomatitis	189	154	35	13.1 (11.3, 18.0)	0.78 (0.63, 0.95)
Placebo	364	291	73	10.9 (9.7, 11.1)	

PFS measured starting day 29 in both groups

PFS by differential segmentation of "stable" disease at study entry (**Table 4**)

- There was improved PFS in all 3 defined subgroups, but there was a tendency in patients in the "stable" [growing] and "stable" (truly stable) subgroups to derive greater benefit from ridaforolimus, compared to the "stable" [minor response] subset.
- The median PFS was relatively consistent among all 3 subgroups for patients receiving ridaforolimus (15.3 - 19.7 weeks), whereas in patients receiving placebo, median PFS was considerably lower in the "stable" [growing] subgroup (7.4 weeks) compared to the "stable" [minor response] and "stable" [truly stable] subgroups (14.4 - 14.9 weeks)

Table 4. Progression-free survival based on segmentation of "stable" disease group at study entry (pre-study tumor size change on pre-study eligibility CT scans*)

	N	Number of PFS Events	Number Censored	PFS (weeks) Median (95% CI)	Hazard Ratio† (95% CI)
No target lesion					
Ridaforolimus	80	49	31	23.4 (16.4, 29.3)	0.71 (0.49, 1.04)
Placebo	85	66	19	15.1 (9.4, 20.4)	
Total	165	115	50		
Tumor shrinkage ≥ 10%					
Ridaforolimus	93	74	19	15.3 (14.9, 19.9)	0.77 (0.55, 1.07)
Placebo	92	75	17	14.4 (8.9, 15.3)	
Total	185	149	36		
Tumor shrinkage < 10% to tumor growth < 10%					
Ridaforolimus	152	118	34	19.7 (14.9, 23.0)	0.69 (0.53, 0.90)
Placebo	153	119	34	14.9 (8.3, 15.4)	
Total	305	237	68		
Tumor growth ≥ 10% but stable					
Ridaforolimus	22	20	2	15.9 (10.6, 22.7)	0.55 (0.30, 1.00)
Placebo	34	31	3	7.4 (7.1, 10.3)	
Total	56	51	5		

*Eligibility scans performed at ≥6 and <12 week apart
†Based on a stratified[1] Cox Proportional Hazards Model with treatment as a covariate (ridaforolimus relative to placebo)

Conclusions

- Ridaforolimus demonstrates meaningful and statistically significant beneficial impact to prolong PFS as maintenance therapy in patients with a variety of soft tissue and bone sarcoma subtypes following benefit from prior 1st, 2nd, or 3rd line chemotherapy.
- The efficacy of ridaforolimus is highly consistent across patient demographic characteristics and sarcoma subtypes.
- The efficacy of ridaforolimus may be greater in patients with rapid onset of grade 2+ stomatitis, suggesting the possibility that stomatitis is a functional biomarker of mTOR target engagement and, thus, of ridaforolimus activity. This is consistent with Phase I data showing a correlation between grade 2+ stomatitis and ridaforolimus exposure (based on average blood concentration).
- Patients who qualified as "stable" at study entry with evidence of early growth or true disease stability (as opposed to minor response) appeared to exhibit somewhat greater benefit from ridaforolimus. This may be due to residual activity of prior therapy in patients with minor response classified as "stable disease" at study entry.