### 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 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 the formation of sarcoma subtypes of sarcoma.

### Study Design

**Double-blind, randomized, parallel study comparing ridaforolimus and placebo in metastatic sarcoma.**

1. **Ridaforolimus given at 40 mg/d for 5 days weekly**
2. **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**
- **Performing certain subtypes such as GIST, GIST, and other sarcoma**
- **Completed rest of therapy with 14 days of the last dose of irinotecan**
- **No prior anti-mTOR therapy**

**Methodology**

**Analytics**

- 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” vs. responding disease at 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) and <10% (stable) subgroup**
- **Tumor growth >10% (stable) subgroup**

**Results**

**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 1st line therapy (HR = 0.81) compared to those patients receiving ridaforolimus after 1st line therapy (HR = 0.90), although the CI’s for the two subgroups are overlapping.

**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.

**Conclusions**

- Ridaforolimus demonstrates meaningful and statistically significant benefit for 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 activity 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 determined by imaging) had a significant improvement in PFS compared to patients classified as “stable in the absence of clinical disease progression” at study entry.