Background
ALRN-6924 is a stapled alpha-helical peptide that mimics the p53 tumor suppressor protein to disrupt p53X's interactions with its endogenous inhibitors, MDM2 and MDM4 (Figure 1A). ALRN-6924 has been evaluated in >175 cancer patients and demonstrated single agent activity and a well-tolerated single-agent safety profile.1,2
MDM2 amplification is an oncogenic event found in up to 4% of all cancers. Co-amplification of MDM2 and cyclin-dependent kinase 4 (CDK4), which are co-located on chromosome 12p13 (Figure 1B), provides the rationale for combined use of the MDM2 inhibitor ALRN-6924 and the CDK4 inhibitor palbociclib in this population, and is further supported by enhanced combination activity in preclinical models (Figure 1C).

Figure 1: The Dual MDM2/MDM4 Inhibitor ALRN-6924 Activates p53 to Induce Cell Cycle Arrest and Apoptosis, and Synergizes with the CDK4/6 Inhibitor Palbociclib

Methods
This is a multicenter, open-label, Phase 2a expansion cohort of an ongoing Phase 1 clinical trial that is enrolling MDM2 amplified or MDM2/CDK4 co-amplified cancer patients (NCT02025643). This Phase 2a trial is designed to enroll 25 patients with solid tumors harboring wild-type p53 and MDM2 amplification or MDM2/CDK4 co-amplifications. Patients have exhausted or are not eligible for other treatment options. ALRN-6924 is given at a dose of 3.1 mg/kg IV infusion on Days 1, 8, and 15, and palbociclib is given as an oral dose of 100 mg/day on Days 1-21 of every 28-day treatment cycle. The first nine patients enrolled were evaluated for safety and tolerability prior to completion of one treatment cycle (safety/roll-in). Anti-tumor activity is evaluated with imaging every 8 weeks.

Figure 2: Duration of Exposure for All Enrolled Patients (N=26)

Conclusions
• This interim analysis shows the combination of ALRN-6924 and palbociclib is well tolerated and has a good safety profile in patients with MDM2 amplified or MDM2/CDK4 co-amplified tumors
• Preliminary efficacy was observed in patients with locally advanced or metastatic liposarcomas, supporting the hypothesis that dual targeting MDM2/CDK4 co-amplified patients with ALRN-6924 + palbociclib may result in clinical activity
• Further development of this combination in liposarcoma patients is warranted

References


Table 1: Demographic and Clinical Characteristics

Table 2: Adverse Events and Serious Adverse Events

Table 3: Best Percentage Change in Sum of Diameters From Baseline

Figure 3: Activity in Liposarcoma Patients (N=17)**

Figure 4: Liposarcoma Patients PPS

Figure 5: All Patients PFS