Harnessing the Anticancer Activity of the Stapled Peptide ALRN-6924, a Dual Inhibitor of MDMX and MDM2, Using Rational Combination Strategies for Breast Cancer and Other Malignancies

Allen Annis1, Jian-Guo Ren1, Luis A. Carvajal1, Solimar Santiago1, Narayana Narasimhan1, David Sutton1, Seyed Saeed Fairaway2, Vincent Guerlavais3, Funda Meric-Bernstam4, Manuel Aivado1

1Aileron Therapeutics Inc, Watertown, MA 02472 USA; 2NIH Advanced Cancer Center Institutes, TX, USA

Background
The purpose was to identify rational anticancer drug combinations with ALRN-6924.

Material and Methods
ALRN-6924 is a cell-permeating, stabilized α-helical peptide that mimics the p53 tumor suppressor protein to disrupt its interactions with both its endogenous inhibitors, MDMX and MDM2. For p53 wild-type tumors, ALRN-6924 can reverse p53-dependent tumor suppression leading to antitumor efficacy. ALRN-6924 was tested in combination with 39 drugs for synergistic in vitro anticancer activity. Select agents were further evaluated in vivo. Drugs listed in Table 1 were assayed in combination with ALRN-6924 using WST-1 and clonogenic assays in immortalized T47D and Caki-1 cell lines. Synergy was quantified by the Chou-Talalay method using CompuSyn. Mouse xenograft models were treated with ALRN-6924, and combinations were evaluated using the mammary tumor model. Combination studies were approved as described in Table 1. Positive expression of p16/p14/ARF biomarkers demonstratingforcing energy of the antitumor activity of single agents and combination.

Results
All drugs evaluated except demethylazene were additive or synergistic with ALRN-6924 in vitro; no antagonism was observed. Pharmacodynamic biomarkers indicated co- medication activity. In MCF-7 xenografts, tumor growth inhibition was improved when ALRN-6924 was given in combination with palbociclib, abemaciclib, or nab-paclitaxel compared to single-agent therapy. Wt p53 burdens and mortality data suggest ALRN-6924 and combinations with paclitaxel and palbociclib were tolerated at the doses tested.

Conclusions
ALRN-6924 is a first-in-class clinical stage MDMXα dual inhibitor displaying promising anticancer activity in patients. Recently, ALRN-6924 was shown to display strong co- mechanism anti-tumor activity in preclinical models of MMU and FTCU. In the current study, we demonstrate that ALRN-6924 can be rationalized by combined pathway-selective and chemotherapeutic agents. These results, plus promising ALRN-6924 safety and antitumor activity as a monotherapy, support the development of combination regimens for breast cancer and other malignancies.

References