SELINEXOR

- Selinexor is an orally bioavailable Selective Inhibitor of Nuclear Export (SINE).
- Selinexor binds covalently to the nuclear export protein XPO1 at Cys528 resulting in irreversible inactivation.
- XPO1 exports over 200 proteins with specific nuclear export sequences.
- Cargo proteins include tumor suppressor proteins such as FOXO, IκB, pRb, p53, p73, p21 and p27.
- Selinexor is in clinical trials for adults with cancer.

SELINEXOR IN VIVO ACTIVITY

- Selinexor was tested against the PPT/P in vivo xenograft panels administered orally at a dose of 10 mg/kg (3 times per week) for 4 weeks.
- For collection of specimens for pharmacodynamic testing, KT-10 tumors that regressed rapidly after treatment with selinexor were harvested 24 hours after a single dose of drug (10 mg/kg). Other, less responsive tumors, were harvested 2 hours after dose (MWF dosing) at 10 mg/kg/dose.
- Immunoblots were probed for p53, p21, PARP and cleaved PARP and XPO1/CRM1.
- IHC analysis was performed for a comparable set of proteins to assess nuclear localization.
- For exome sequencing, all mutations were verified and assessed as somatic using a virtual normal subtraction algorithm.

SELINEXOR INDUCES NUCLEAR ACCUMULATION OF XPO1 CARGO PROTEINS IN PEDIATRIC CANCER MODELS

- Sections from vehicle and selinexor treated KT-10 were analyzed by immunohistochemistry (IHC). XPO1 cargo proteins were blocked in the nucleus and the expression of signaling proteins that are associated with cell proliferation was reduced. Cells from tumors that were treated with selinexor showed increased nuclear accumulation of FOXO1, IκBα, NFB, pRb, ERK and Survivin. In addition the IHC slides show reduction in Mcl-1 protein.

SELINEXOR INDUCES TP53 PATHWAY GENES

- For three TP53 wildtype xenografts that showed significant tumor growth delay to selinexor (CHLA-258, RH28, and RH30), p21 induction was noted after 6 doses of selinexor. The TP53 mutated xenograft SK-NEP-1 showed no pTP3 or p21 induction.

SELINEXOR INDUCES TP53 PATHWAY GENES IN PEDIATRIC CANCER MODELS

- Gene mutation profiles were examined for five models with objective responses (KT-10, BT-45, BT-50, ALL-8, and ALL-19).
- Two genes were mutated in two models: FBXW7 and SMARCA4.
- For FBXW7, known oncogenic mutations were identified for both BT-50 (R465H) and ALL-8 (R465C). BT-50 also had a SUFU mutation (D182G), consistent with SHH pathway medulloblastoma.
- For SMARCA4, the R119Q mutation, which is predicted to be deleterious by both SIFT and PolyPhen, was observed in BT-45 and ALL-8.
- KT-10 and BT-45 also showed objective responses to cisplatin. KT-10 has a PALB2 mutation that leads to defective homologous recombination and to sensitivity to PARP inhibitors as well as to cisplatin. BT-45 has a mutation profile consistent with WNT pathway medulloblastoma (CTNNB1 and TP53 mutation).
- Further preclinical research and clinical experience will be required to determine if any of the mutated genes noted above are able to predict response to selinexor.

MUTATIONS IN RESPONDING XENOGRAFTS

- For RH28, which showed limited tumor growth inhibition to selinexor, there was only partial FOXO3 nuclear accumulation with much cytoplasmic stain. In addition, there was minimal reduction of p-catenin and almost no reduction in Mcl-1 protein.