TARGETED INHIBITION OF CHROMOSOMAL MAINTENANCE REGION PROTEIN (CRM1) POTENTLY SUPPRESSES GROWTH OF HUMAN NEUROBLASTOMA CELL LINE MODELS

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BACKGROUND

• Neuroblastoma is the most common extracranial solid tumor of childhood and accounts for a disproportionately high (12%) fraction of deaths from pediatric cancer. Most patients with high-risk neuroblastoma are not cured, and new therapies that rationally target unique vulnerabilities in neuroblastoma cells are urgently needed.

• Although the TP53 gene is rarely mutated in primary neuroblastoma, its protein product is thought to be sequestered in the cytoplasm. Translocation out of the nucleus of p53, FOXO, and IκB are mediated by CRM1 (XPO1), and inhibition of CRM1 is therefore an attractive target in neuroblastoma.

• KPT-330 (Karyopharm Therapeutics) is a Selective Inhibitor of Nuclear Export (SINE) that irreversibly binds CRM1 and inhibits its function. Inhibition of CRM1 results in forced nuclear retention and activation of multiple tumor suppressor proteins; this induces apoptosis in multiple tumor cell types but is tolerated with minimal effect in normal cells.

• KPT-330 is currently in Phase 1 clinical trials in both hematologic and solid adult malignancies.

METHODS

• Cell lines: A panel of 14 well-characterized neuroblastoma cell lines was tested with KPT-330 across a 5-log range. Growth inhibition was measured using CellTiter-Glo viability assays and a real-time growth monitoring system (xCELLigence, Roche).

• Xenograft models: NOD/SCID mice with neuroblastoma xenografts were treated orally with KPT-330 and tumor size was monitored.

• Disseminated models: Neuroblastoma cell lines stably expressing a luciferase construct were tail-vein injected into NGS mice. Treatment started after tumor luminescence exceeded 10^5 photons/s.

• mRNA expression: A well characterized cohort of primary neuroblastoma cases (40 high-risk and 20 low-risk) as well as a panel of cell lines were profiled using Illumina Human 6 expression beadchips.

RESULTS

• Neuroblastomas show sensitivity to CRM1 inhibition both in vitro and in vivo.

• Ongoing work is focused on discovering the cellular and genomic factors responsible for increased sensitivity to nuclear export inhibition.

• With the expected completion of the first in human phase I trials by mid 2013, treatment with KPT-330 has the potential to be rapidly translated into a clinical trial for children with neuroblastoma.

CONCLUSIONS AND FUTURE DIRECTIONS

• Neuroblastomas show sensitivity to CRM1 inhibition both in vitro and in vivo.

• Ongoing work is focused on discovering the cellular and genomic factors responsible for increased sensitivity to nuclear export inhibition.

• The mechanism of apparent drug resistance in vivo is unclear as the cells retain in vitro sensitivity.

• In other studies, higher doses (up to 20 mg/kg) of KPT-330 have been well tolerated and may provide further benefit in these models.

• With the expected completion of the first in human phase I trials by mid 2013, treatment with KPT-330 has the potential to be rapidly translated into a clinical trial for children with neuroblastoma.