mice, ranging from 0.5 to 1. The plasma clearance of GDC-0941 was similar in the four strains of mice. Exposure following PO dosing was also comparable in the wild type and all knockout mice. Following administration of GDC-0941 to Mdr1a/b(−/−)/Bcrp1(−/−) mice, the PI3K pathway was markedly inhibited in the brain for up to 6 hours post-dose, with a 60% suppression of the pAkt signal, while no effect on the PI3K pathway was detected in the brain of wild type mice. GDC-0941 was efficacious in the U87 glioblastoma orthotopic model that contained compromised blood–brain barriers (BBB) but inactive in a neurosphere-derived model with non-compromised BBB. Additionally, in the Fo1282 breast cancer brain metastasis model, GDC-0941 treatment increased survival benefit and decreased phospho-S6 ribosomal protein levels indicative of PI3K pathway suppression *in vivo*.
Conclusions: These findings show concerted effects of Pgp and Bcrp1 in restricting GDC-0941 access and pathway modulation in the brain of non-tumor bearing mice. Anti-tumor activity of GDC-0941 is observed in orthotopic brain tumor and metastasis models that contain compromised blood–brain barriers.

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Biological characterization of ETP-46321 a potent and selective phosphoinositide-3-kinase inhibitor with antitumor activity

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The phosphoinositide-3-kinase (PI3K) signaling pathway is activated in a variety of solid and non-solid tumors. In many instances this is due to either activating mutations in the catalytic subunit of PI3Kα, p110α or inactivating mutations or deletions of the tumor suppressor PTEN. In addition, the PI3K pathway is activated by mutations in certain receptor tyrosine kinases as well as by mutation of the oncogene KRAS. These data provide a strong rationale for the discovery of PI3K inhibitors for treatment for cancer. Following a rational design strategy, we identified the fused imidazole derivative ETP-46321 as a potent inhibitor of PI3K (e.g., K_i = 2.4 nM *vs.* p110α, K_i = 549 nM *vs*. p110β, K_i = 14 nM *vs.* p110δ, and K_i = 153 nM *vs*. p110γ, respectively). ETP-45321 also inhibits three oncogenc mutants of p110α: p110α E542K K_i = 1.9 nM, p110α E545K K_i = 1.8 nM and p110α H1047R K_i = 2.4 nM. The compound does not significantly inhibit the related PIKK family members such as mTOR, DNA PK or ATR (K_i's >10 μM), or an additional 280 protein kinases that were screened. The compound blocks PI3K signaling, induces cell cycle arrest and inhibits VEGF-dependent sprouting of HUVEC cells. ETP-46321 has a pharmacokinetic profile suitable for oral dosing in mice (%F = 95%, Cl = 0.56 L/hr/kg; Vds = 0.016 L). Analysis of xenograft tumor tissue after acute dosing reveals a reduction in P-Akt levels. Once a day treatment with ETP-46321 of mice with human tumor xenografts with ETP-46321 results in tumor growth delay and is well tolerated. In a mouse model of lung cancer induced by expression of an oncogenic mutant KRAS, treatment with ETP-46321 results in tumor growth delay and a significant PET response. These and combination data will be presented.

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Pediatric Preclinical Testing Program (PPTP) stage 1 evaluation of JNJ-26481585, a second generation histone deacetylase inhibitor

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Background: JNJ-26481585 is a 'second-generation' HDAC inhibitor with prolonged pharmacodynamic response *in vivo*. The agent has demonstrated superior efficacy compared to both standard of care agents and 'first generation' HDAC inhibitors in adult cancer preclinical models. The activity of JNJ-26481585 was evaluated against the *in vitro* and *in vivo* panels of the Pediatric Preclinical testing Program (PPTP).
Methods: JNJ-26481585, which was provided by Johnson & Johnson Pharmaceutical Research and Development, was tested against the PPTP *in vitro* panel (n = 23) at concentrations ranging from 1.0 nM to 10 mM and was tested against the PPTP *in vivo* panel using a dose of 5 mg/kg (solid tumor) or 2.5 mg/kg [acute lymphoblastic leukemia (ALL)] administered by the intraperitoneal route daily for 21 days. Three measures of antitumor activity were used: 1) response criteria modeled after the clinical setting; 2) treated to control (T/C) tumor volume at day 21; and 3) a time to event (4-fold increase in tumor volume) measure based on the median EFS of treated and control lines (intermediate activity required EFS T/C > 2, and high activity additionally required a net reduction in median tumor volume at the end of the experiment).
Results: JNJ-26481585 demonstrated potent cytotoxic activity, with T/C% values approaching 0% for all of the cell lines at the highest concentration tested. The median EC_{50} value for the PPTP cell lines was 2.2 nM, with a range from <1 nM (MOLT-4) to 19 nM (NB-EBc1). JNJ-26481585 was well tolerated and induced significant differences in EFS distribution compared to control in 20 of 31 (65%) of the evaluable solid tumor xenografts and in 5 of 8 (63%) of the evaluable ALL xenografts. JNJ-26481585 induced tumor growth inhibition meeting criteria for intermediate EFS T/C activity (EFS T/C > 2) in 5 of 30 (17%) evaluable solid tumor xenografts. Intermediate activity for the EFS T/C metric occurred most frequently in the glioblastoma panel (2 of 4) and was also observed for one xenograft in the rhabdoid, Ewing, and rhabdomyosarcoma panels. An objective response was observed in 1 of 31 solid tumor xenografts, Rh28 in the rhabdomyosarcoma panel that achieved a maintained complete remission (MCR). For the ALL panel, two xenografts (both T-cell ALL xenografts) achieved CR and MCR, respectively, and a third xenograft achieved stable disease (SD).
Conclusions: The activity signals observed for JNJ-26481585 against the PPTP preclinical models warrant follow-up. *In vivo* activity signals for rhabdomyosarcoma, glioblastoma, and T-cell ALL are particularly noteworthy, with further exploration of the preclinical activity of JNJ26481585 for T-cell ALL being a high priority.

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Activity of the Cdc7 inhibitor NMS-1116354 as single agent and in combination in breast cancer models

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NMS-1116354 is a potent ATP competitive oral inhibitor of the Cdc7 kinase (IC_{50} <3 nM). Consistently with the inhibition of this enzyme, treated cells show inhibition of phosphorylation of serine 40 in the Mcm2 protein and an impairment of DNA replication. While this event leads to apoptotic tumor cell death, in normal cells it induces a reversible cell cycle arrest. In addition, NMS-1116354 induces the down regulation of the pro-survival proteins Mcl-1 and XIAP expression thus exacerbating the effects of the Cdc7 inhibition on tumor growth.
NMS-1116354 has potent antiproliferative activity against a wide panel of tumor cell lines with IC_{50} values ranging between 0.1 and 3 μM. Oral administration of NMS-1116354 demonstrated significant antitumor activity in various tumor animal models as well as in disseminated human leukemia models. Particularly, strong tumor regressions were obtained in breast cancer models. In combination studies, NMS-1116354 exhibited synergistic effects when administered with Irinotecan, Gemcitabine, Erlotinib, Bortezomib and with other approved antineoplastic drugs. The combination with Docetaxel in triple negative breast cancer animal models gave tumor free animals lasting for >4 months.
The phase I clinical trials to evaluate the safety of orally administered NMS-1116354 as single agent with different schedules in cancer patients are ongoing. The results of the combination studies open a possible path for its clinical development in combination with approved drugs.

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Preclinical characterization of ACTB-1010, an orally activity Aurora kinase inhibitor

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Introduction: Aurora Kinases A and B are dysregulated in a number of human cancers and are essential to the regulation and function of mitosis and cytokinesis. ACTB-1010 is an oral kinase inhibitor targeting both Aurora Kinase A and B. ACTB-1010 was selected for development based on the nanamolar potency against targeting Aurora Kinase A and B, without cross reactivity to other major kinases such as VEGF, FGF, KIT and FLT3. We investigated the preclinical efficacy and mechanism of action of ACTB-1010.
Results: ACTB-1010 inhibits both Aurora Kinase A (IC_{50} = 1.6 nM) and Aurora Kinase B (IC_{50} = 9 nM) and is highly active in cell-based mechanistic assays. Human tumor cell lines treated with ACTB-1010 demonstrate a phenotype consistent with Aurora B inhibition including enlarged nuclei