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Antitumor activity of PLX4032, a selective V600EB-Raf inhibitor, as monotherapy and in combination with capecitabine±bevacizumab in a colorectal cancer xenograft model

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The Ras-Raf-MEK-ERK signaling pathway plays a critical role in human tumorigenesis. B-Raf mutations occur in over 7% of human cancers (melanoma 70%, papillary thyroid 35–70%, ovarian 35% and colorectal 12–30%). A majority of the B-Raf mutations involve a single amino acid substitution, V600E, resulting in constitutive activation of the MEK-ERK signaling pathway. PLX4032 is a first-in-class, V600EB-Raf-selective small molecule inhibitor. PLX4032 dose-dependently inhibits tumor growth in mutant V600EB-Raf-carrying colorectal tumor xenografts in monotherapy; in vitro cell-based combination study demonstrated that PLX4032 had additive/synergistic effect in combination with 5-FU [Yang H, et al. EORTC-NCI-AACR 2007; A252]. The present study evaluated the activity of PLX4032 in combination with capecitabine±bevacizumab in the HT29 colorectal cancer xenograft model. The anti-tumor activity of PLX4032 monotherapy was superior to that of bevacizumab and capecitabine 14+/7− schedule monotherapy, but not capecitabine 7+/7−/7+ monotherapy; the survival observed with PLX4032 monotherapy was better than all other monotherapies. Anti-tumor activity and survival with capecitabine 7/7 + PLX4032 doublet was superior to all monotherapies and capecitabine 14/7 + PLX4032 doublet. Anti-tumor activity of capecitabine 14/7 + PLX4032 + bevacizumab triplet was significantly superior to all monotherapies and doublets except capecitabine 7/7 + PLX4032; however, survival was significantly better than all monotherapy and doublet groups. Anti-tumor activity and survival of capecitabine 7/7 + PLX4032 + bevacizumab was significantly better than all monotherapy and doublet groups. Anti-tumor activity of the capecitabine 7/7 + PLX4032 + bevacizumab was significantly superior to capecitabine 14/7 + PLX4032 + bevacizumab; however, survival was equivalent. Therefore the study concluded that survival was superior with PLX4032 monotherapy than with capecitabine or bevacizumab monotherapy. For doublet therapy, capecitabine 7/7 + PLX4032 was the better regimen. Both capecitabine + PLX4032 + bevacizumab triplet regimens had statistically significantly improved survival compared with all monotherapy and doublet regimens.

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Obatoclax (GX17–070), a small molecule pan-bcl-2 inhibitor, in combination with docetaxel in a phase I/II trial enrolling patients with relapsed non-small cell lung cancer (NSCLC)

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Background: Overexpression of bcl-2 family proteins is common in NSCLC, and the BH-3 mimetic obatoclax (O) induces apoptosis in a subset of NSCLC where it synergizes with cisplatin (Li et al., Cancer Chemother. Pharmacol., 2008). In this trial combining O with a cytotoxic, docetaxel (D), safety and efficacy were evaluated.
Materials and Methods: Eligibility criteria included advanced stage IIIB/IV NSCLC, prior paclitaxel (but not D) allowed, measurable disease, ECOG PS $\leqslant$1, disease progression, adequate hematological, renal and hepatic function. D was given as a 1 h infusion on day1 followed by flat dose O given as a 24 h continuous infusion on days 1 and 2, every 3 wk for up to 8 cycles. Dose Level 1: D 55 mg/m^2 and O 30 mg X 2; Dose Level 2: D 75 mg/m^2 and O 30 mg X 2; Dose Level 3: D 75 mg/m^2 and O 45 mg X 2; Dose Level 4: D 75 mg/m^2 and O 60 mg X 2. PK samples were obtained at 1, 3, 24, 47, and 49 h after start of O infusion.
Results: 18 patients were enrolled in Phase I (3, 3, 6 and 6 in consecutive Dose Levels). Phase I patient characteristics: 11 male, median age = 62 (range 44−81), PS = 0 in 12 and PS = 1 in 6, median prior regimens = 1 (range 1–6). A median of 4 cycles were administered in Phase I (range 1–10). Phase I Grade (Gr) 3−4 adverse events (AEs) included 3 Gr 3 febrile neutropenia (DL2, 3 & 4), 1 Gr 3 vomiting (DL1), 1 Gr 3 hypoxia (DL2), 1 Gr 3 DVT (DL3), and 2 Gr 4 pulmonary embolism (DL3&4). Known AEs of O were infrequent in Phase I: ataxia in 3 pts (DL1, 3 & 4); euphoria in 1 each in DL2&3 and 2 in DL4; somnolence only in 1 at DL4. Mean±SD plasma concentrations of O at 1, 3, 24, 47, and 49 h time-points from the start of infusion in the 60 mg dose level were 5.03±4.61, 8.16±3.17, 10.34±7.34, 12.44±9.42 and 5.45±2.25, respectively. There were 2 PRs (11%) in Phase I patients. 30 evaluable patients have been enrolled in the Phase II portion of the study in which D 75 mg/m^2 and O 60 mg $\times$2 were administered. Phase II patient characteristics: 17 male, median age = 62 (range 31−81), PS = 0 in 9 and PS = 1 in 21, limited to 1 prior chemo +/− EGFR inhibitors. Preliminary data indicate 2 PRs, with additional patients too early for analysis. Full efficacy results will be presented.
Conclusions: The BH3-mimetic O can be safely administered with D with no increase in neutropenia. The regimen described by DL4 has been evaluated in a phase II trial in relapsed NSCLC and has been well tolerated. Final efficacy results will be presented.

Topoisomerase inhibitors

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Rational design of effective therapy combining irinotecan and rapamycin to target mTOR/HIF-1 alpha axis in colon cancer

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Background: Despite recent progress, colon cancer is often resistant to combination chemotherapy, highlighting the need for development of novel therapeutic approaches. Here we investigated how colon tumor response to irinotecan could be improved by combination with mTOR inhibitors. This association was rationally designed based on gene-expression profiling of patient-derived colon xenograft tumors following treatment with irinotecan alone.
Material and Methods: Irinotecan was first tested on 7 subcutaneous colon xenografts and its gene expression signature was determined using Affymetrix micro arrays. Based on these results, xenografts were treated with low doses of irinotecan alone, rapamycin alone or combination of both drugs. Cellular effects of irinotecan and rapamycine were further characterized for HT-29 and HCT-116 colon cancer cells in vitro in hypoxic conditions.
Results: Gene expression analysis in xenografted tumors showed that two-third of the down-regulated genes after treatment with irinotecan alone are HIF-1 alpha target genes. This signature correlated with a complete inhibition of HIF-1 alpha protein accumulation. Since this effect appeared independent of mTOR pathway inhibition, we rationally hypothesized that rapamycin, a potent mTOR inhibitor, could synergize at low doses with irinotecan.
Xenografted tumors treated with the combined treatment showed a dramatic reduction in tumor volume which was accompanied by a synergestic inhibition of the mTOR/HIF-1 alpha axis. In vitro experiments showed that exposure to both drugs at low concentrations resulted in massive HT-29 cell death under hypoxic conditions and pointed to a cytotoxic effect mediated through HIF-1 alpha inhibition. Experiments using siRNA targeting specifically HIF-1 alpha are on going to confirm this result. HCT-116 cells were less sensitive to the combined treatment due to constitutive activation of PI3K/Akt and Ras/MAPK pathway. However, sensitivity in these cells could be rescued by combining irinotecan with selective agents targeting activated Akt (LY294002) or K-Ras (salirasib).
Conclusions: These results identify HIF-1 alpha as a promising target and provide a rationale for clinical trials of low dose irinotecan and rapamycin combination toward colon cancer. Given that HIF-1 alpha regulates the expression of many genes implicated in epithelial-mesenchymal transition and metastasis, we are currently investigating the impact of HIF-1 alpha modulation on cancer cell invasion.