not able to form new tumors and have high expression of CD127 on their T cells, a marker for immunological memory.

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Adding Notch inhibition increases efficacy of standard of care treatment in glioblastoma

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OC-0235
Enhancing stereotactic radiation schedules using the vascular disrupting agent OXi4503

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Purpose or Objective: The novel combretastatin analogue, OXi4503, is a vascular disrupting agent (VDA) that has recently been shown to significantly enhance a stereotactic radiation treatment. This was achieved using an OXi4503 dose of 10 mg/kg combined with a stereotactic treatment of 3 x 15 Gy. The current study was undertaken to determine the OXi4503 dose dependency when using different stereotactic radiation dose schedules.

Materials and Methods: A C3H mammary carcinoma grown in the right rear foot of female CDF1 mice was used in all experiments. Tumour implants were performed percutaneously in anaesthetised animals when tumours had reached 200 cubic mm in size. Tumours were locally irradiated (230 kV x-rays) with 3 fractions of radiation varying from 5-20 Gy (each fraction given with an interval of 2-3 days over a one week period). OXi4503 was dissolved in saline prior to each experiment; once prepared it was kept cold and protected from light. Various doses (5-25 mg/kg) were intraperitoneally injected into mice 1-hour after each irradiation treatment. Three days after the final irradiation the tumours were subjected to a clamped top-up dose which involved giving graded radiation doses with the tumour bearing leg clamped for 5 minutes before and during irradiation. The percentage of mice in each treatment group showing local tumour control 90 days after irradiating was then recorded. Following logit analysis of the clamped top-up radiation dose response curves, the TCD50 values (radiation dose to control 50% of tumours) were estimated. A Chi-squared test (p<0.05) was used to determine significant differences between the TCD50 values.

Results: The clamped top-up TCD50 values (with 95% confidence intervals) obtained following irradiation with 3 treatments of 10, 15 or 20 Gy were found to be 42 Gy (38-47), 30 Gy (23-39) and 0.8 Gy (0.3-2.3), respectively. A plot of the TCD50 values against the stereotactic doses gave rise to a linear response (slope = -4.1; correlation coefficient = 0.97). OXi4503 significantly decreased the clamped radiation top-up TCD50 values and this effect appeared to be independent of both the ambient radiation dose applied with each of the 3 fractions and the VDA dose; the curve showing the TCD50 values against stereotactic radiation dose was similar to that for radiation alone (slope = -4.3; correlation coefficient = 0.94), but the radiation + OXi4503 curve was some 15 Gy lower than the radiation only curve.

Conclusion: OXi4503 is an effective agent for enhancing a stereotactic radiation treatment. But, the enhanced response appeared to be a simple additive effect independent of both the radiation dose applied with each fraction and the VDA dose used.

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OC-0236 DTP-006: a novel, orally bioavailable hypoxia-activated prodrug

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Purpose or Objective: Hypoxia is a common feature of solid tumors. Conventional treatments such as chemotherapeutic and radiotherapy (RT) are less effective against hypoxic tumor cells. Hypoxia-activated prodrugs (HAPs) are specifically activated in hypoxia to target hypoxic cells as well as adjacent oxygenated tumor cells via their bystander effect. DTP-006 is a newly synthesized nitroaromatic HAP with highly favorable properties: 1) activation under hypoxia, 2) high bystander effect, 3) excellent aqueous solubility, 4) murine oral bioavailability and 5) no off-mechanism activation by human hepatic reductases NQO1 and AKR1C3. Here we show the effects of DTP-006 on tumor cell viability, spheroid growth and radiation resistant tumor cells in vivo, and assess its pharmacokinetics and oral bioavailability in mice.

Material and Methods: The one-electron reduction potential (E1) of DTP-006 was determined by pulse and steady state radiolysis. IC50 viability ratios were assessed in 2D cell culture exposed to normoxic or anoxic (5% O2) conditions. H460 murine small cell lung cancer cells were exposed to aerobic (5% CO2, 95% O2) or anoxic (5% CO2, 95% N2) conditions and incubated with DTP-006 for 5 h after which cells were plated for clonogenic survival. H460 spheroids were incubated with DTP-006 upon confirmation of a hypoxic core. NIH-III mice bearing H460 tumors received a single i.p. dose of DTP-006 (781 mg/kg) after irradiation (10 Gy) of tumors. 18 h later, tumors were excised and single cell suspensions were generated and plated for clonogenic survival. Tumor-free female NIH-III mice received a single i.v. or oral dose of DTP-006 (383 mg/kg). Terminal blood samples collected at time points prior to cardiac cannulation were analyzed by LC/MS/MS. Plasma half-life (T1/2) and absolute oral bioavailability (Fabs) were calculated.

Results: DTP-006 has an E1 value of -351 mV, indicating strong oxygen inhibition of nitro radical formation. IC50 were lower in anoxia than normoxia by factors of 293 (MDA-MB-468), 55 (C3A), and 20 (HTC116). In a H460 MCL clonogenic assay, 100 µM DTP-006 caused 99% cell kill under anoxia but exhibited no aerobic cell kill. It caused a concentration-dependent growth delay in spheroids, where 250 µM completely halted growth. A single dose of DTP-006 caused a significant loss of clonogenicity when combined with RT in an in vivo excision assay (log cell kill 2.35 relative to control). T1/2 after oral administration was 0.82 h and bioavailability was 47%.

Conclusion: DTP-006 kills tumor cells only in severe hypoxic conditions in vitro, reduces growth of tumor cell spheroids, and sterilizes radiation resistant tumor cells in vivo. It has clinically relevant bioavailability after oral administration. As such, DTP-006 is a promising new HAP with potentially favorable properties for clinical use. Further studies to determine the antitumor effects of DTP-006 as a monotherapy and in combination with RT in several preclinical tumor models are ongoing.

OC-0237