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Targeting Tumor Hypoxia in Patient-Derived Pancreatic Xenografts Using TH-302. Ines Lohse, Joanna Rasowski, PinJiang Cao, Emin Ibrahimov, Melania Pintille, Ming S. Tsao, Richard Hill, David W. Hedley. Ontario Cancer Institute / Princess Margaret Hospital, Toronto, ON, Canada.

All solid tumors independent of their origin contain areas of low oxygen tension. It is well established that tumor hypoxia induces an epigenetic selection for cancer cells that survive the hostile tumor microenvironment. Tumors resistant to hypoxia are generally more aggressive and less responsive to cancer therapy than hypoxia-sensitive tumors. We have recently shown that high levels of hypoxia in patient-derived pancreatic cancer xenografts correlate with both increased metastatic potential and high proliferation. The tumor selective hypoxia-activated cytotoxic prodrug TH-302 specifically and selectively targets extreme hypoxia found in solid tumors and is therefore believed to not only increase the treatment response of the primary tumor but also prevent tumor recurrence and metastasis. The clinically validated warhead functions as an alkylator that kills dividing as well as non-dividing tumor cells while designed to be inactive and non-toxic in normal tissues. Several clinical trials are currently ongoing to investigate the effect of TH-302 on various cancers in combination with established chemotherapeutics. We used 7 patient-derived xenograft models to examine the efficiency of the hypoxia-activated drug TH-302 in pancreatic tumors. Mice received a chronic treatment with TH-302 alone, IR alone or the combination treatment; where TH-302 treated mice received 3 doses of 50mg/kg TH-302 and ionizing radiation (IR) treated mice received 2Gy on 3 consecutive days. TH-302 specifically targeted the hypoxic zone in the xenograft models. Additionally, TH-302 treatment induced DNA damage in tumor tissue adjacent to the hypoxic zone which is consistent with the previously demonstrated bystander effect of TH-302. In the primary patient-derived xenograft models treatment with TH-302 in combination with IR reduced tumor growth in high and medium hypoxic xenograft models, while having little impact on tumor growth in low or non hypoxic models. Furthermore, our results showed that TH-302 treatment efficiency depended on the extent of tumor hypoxia and the tumor growth rate. While showing high treatment efficiency even as a single agent in fast-growing hypoxic models, TH-302 treatment had little effect on tumor growth in a hypoxic model that displayed slow growth rates. Together, these findings demonstrate that the combination of radiation therapy and TH-302 may provide an effective treatment strategy for pancreatic cancer patients.