Abstract 3524

Pharmacological characterization of pediatric brain tumor PDX models in a single mouse trial format

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Abstract

Cancer remains the leading cause of disease-related death in children. Preclinical drug testing to identify promising treatment options for relapsed patients or those with poor prognosis is hindered by the lack of well characterized and annotated preclinical models. In the framework of the ITCCP4 consortium (www.ITCCP4.eu) our group determined the pharmacological profile of 47 orthotopically implanted pediatric brain PDX models. The panel comprised 21 high grade glioma (HGG), 13 medulloblastoma (MB), eight ependymoma (EP), three non-classified brain tumors (XT), one atypical teratoid/rhabdoid tumor (AT/RT) and one neuroblastoma (NB). Depending on the tumor type the models were screened in an eleven or twelve arms single mouse trial study layout. Three treatment arms comprised standard of care cytotoxic compounds and radiation, whereas the other arms covered targeted therapies, mostly small molecules. Tumor load was determined using a fluorescent based in vivo imaging technology based on the lentiviral transient transduction of the PDX cells with iRFP713 prior to implantation into the brain. In addition, body weight and neurological scoring was applied to determine the overall condition of the animals. At the end of the study brain tissue was harvested and tumor load confirmed by immunohistochemistry. The mean overall survival of the orthotopic implanted animals on study was 48 days with a minimum of 7 days and a maximum of 132 days. Overall, the treatment was well tolerated in the tumor bearing animals as determined by body weight measurement. However, the combination of two cytotoxic drugs in some of the arms needed dose adjustments due to increased toxicity. Across all tumor types at least one of the cytotoxic arms improved overall survival of the tumor bearing animals markedly: Temozolomide and Lomustine for HGG (43d and 50d, respectively vs 28d in the control arm), Lomustine and Endoxan for MB (99d and 73d, respectively vs 61d in the control arm), and Actinomycin D for EP (64d vs 52d). However, several of the targeted agents showed a distinct efficacy profile: Cobimetinib was efficacious in 50% of the HGG (47d vs 28d in the sensitive subset) and Idanasutlin in 80% of the EP models (79d in the sensitive subset vs 52d). The optical imaging signal over time confirmed tumor engraftment at the start of treatment. The most efficacious treatment arms induced growth delay or partial remission. This preclinical validation set gains even more importance using the accompanying molecular profiling data that are available not only for the PDX but also for the donor patient. Together with the breadth and depth of the still growing PDX collection, a unique preclinical platform for the development of drugs as well as companion diagnostics specifically for pediatric brain cancers is now available to the scientific community.