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The ITCC-P4 consortium: Deep molecular characterization of pediatric cancer xenograft PDX models enable prediction of novel personalized combination treatment options for patients with childhood cancer

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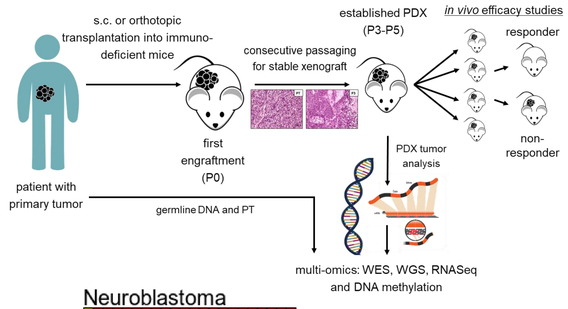
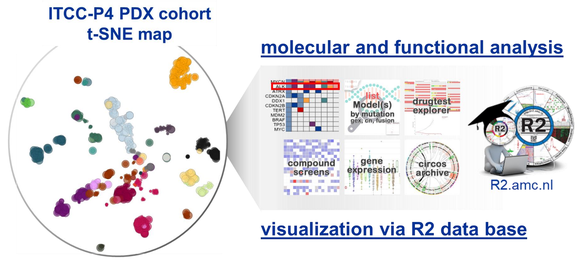
Background

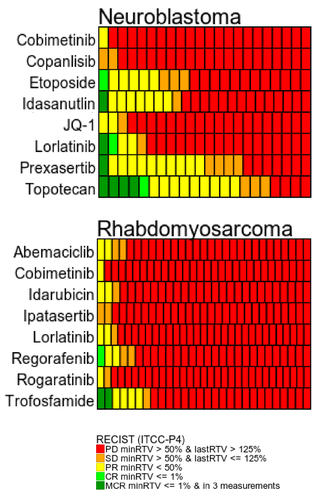
Childhood cancer oncogenesis occur from developing cells and consequently result in high tumor heterogeneity and low mutational burden. These molecular characteristics of pediatric cancer lead to highly variable clinical outcomes in patients. Clinical trials for pediatric cancers fail to provide groundbreaking progress, especially not in relapse or high-risk entities. Molecular and genetic data on pediatric tumors for preclinical applications, in particular from relapsed patients, are limited. Recent clinical trials in pediatric oncology utilizing targeted therapies did not outperform cytotoxic chemotherapy regime. Re-thinking of preclinical filtering and drug testing is needed to overcome lack of translation into new treatment strategies for children with cancer.

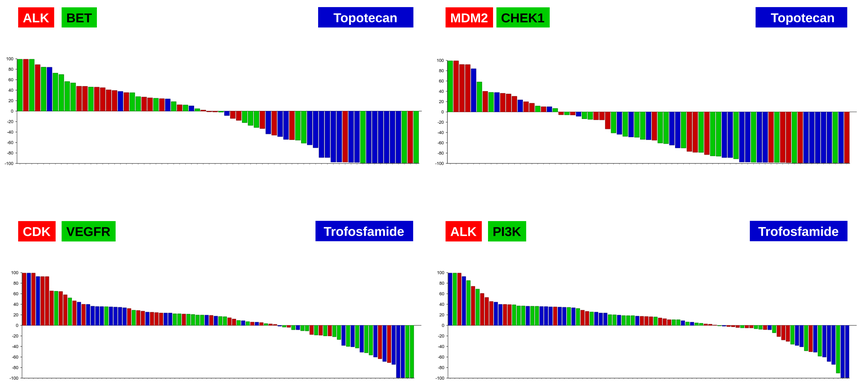
Aim and Methods

We performed preclinical drug screening experiments in 23 neuroblastoma and 28 rhabdomyosarcoma PDX models with the objective to characterize their individual drug response profiles. In these single mouse trials targeted therapies show low response rates compared to cytotoxic chemotherapy (AACR, abstract #2199). Therefore, we filtered molecular data of our complete cohort of ITCC-P4 NB and RS models for prediction of potential drug candidates. Together with clinical experts from the ITCC-P4 program, a pipeline list of compounds was established for the combination testing of selected targeted drugs in 10 NB and RS PDX models.







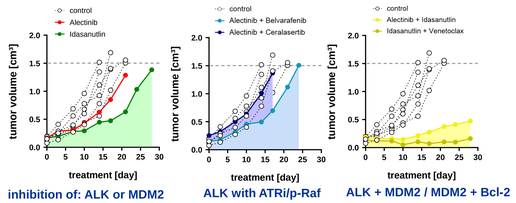


less than 20% response of single targeted agent!

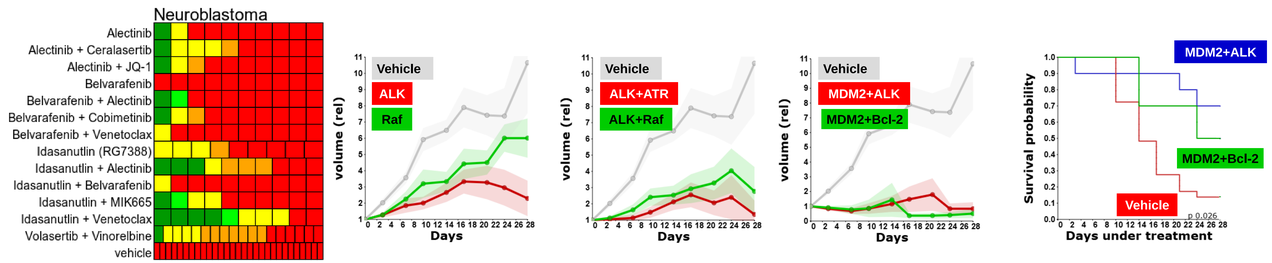
Results

Analysis of NB and RS molecular phenotypes identified ALK (Alectinib), MDM2 (Idasanutlin), Bcl-2 (Venetoclax) and Raf-signaling (Belvarafenib) as potential targets for initial combination testing strategy. Approved or clinical phase II/III drug candidates were selected accordingly. Final drug combinations were planned based on actual clinical trials or bioinformatic analysis. Identical to previous testing, ALK inhibition alone was not able to substantially suppress tumor progression (<20% response). Only minimal synergistic effect of ALK-inhibitor in combination with ATR-/ or Raf-inhibitor (<40% of PDX) were detected in both entities. Interestingly, in combinations of ALK and Bcl-2 targeting with MDM2 blockade, a significant and strong antitumoral synergism was noticed leading to 70-80% response rates in both, neuroblastoma and rhabdomyosarcoma PDX models.

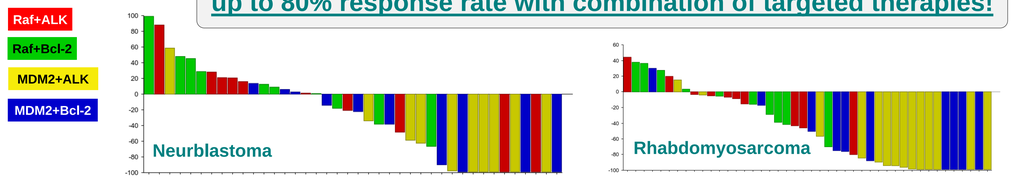
Neurblastoma PDX ITCC-P4_s16_NB0617

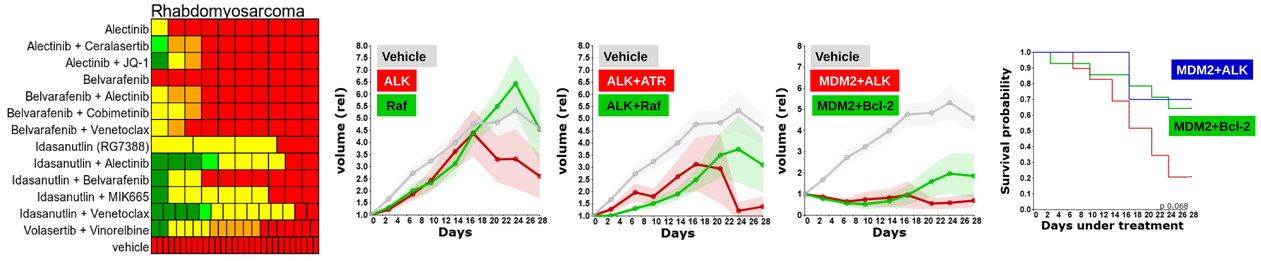


Results for combination testing in ITCC-P4 PDX models

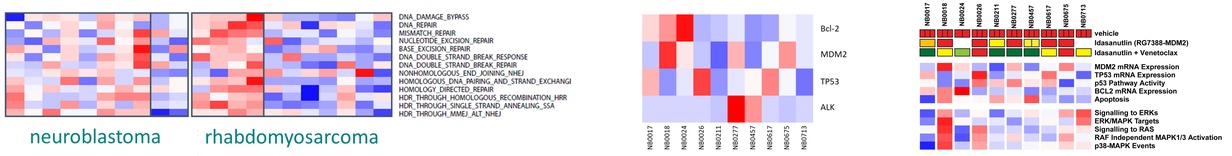


up to 80% response rate with combination of targeted therapies!





Molecular target and biomarker analysis



Based on drug response in drug testing studies we aimed to analyze molecular data focussing on re-sponder and non-responder PDX models. With our current bioinformatics analysis in progress we identified several DNA repair and inflammatory pathways clustering in subsets of NB and RS upon testing with the combination therapy. We will utilize Cancer Hallmark pathways and genes to identify differentially regulated genes for consideration of potential biomarkers. Specific target activation provide a rational for prediction of response in combination trials of solid pediatric PDX models.

Summary and Outlook

Deep molecular characterization enable prediction of highly effective combination treatment therapy in NB and RS PDX models. Highest response rates were achieved with combination of MDM2 with ALK-/or Bcl-2-inhibitor. In RS, also the second tested Bcl-2 inhibitor MIK665 together with MDM2 achieved best response which was significantly lower in tested NB PDX (40% response). Our successful combination treatment approach with pediatric ITCC-P4 PDX cohort is a valuable add-on to the preclinical toolbox. With our ongoing biomarker analysis we aim to identify molecular mechanism in order to enable prediction efficiency of distinct drug candidates based on their molecular mode of action. In the future, novel pipeline candidates can be easily tested with already approved or newly identified drugs for fast translation into new treatment approaches for childhood cancer.

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