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Patient-derived organoids (PDOs) as a companion tool to understand drug responses in the DKTK-funded SORATRAM IIT trial

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Class-III BRAF mutations are increasingly identified across all tumor entities. They render the kinase inactive and - contrary to what one might expect –can lead to strong upregulation of the MAPK pathway through dimerization and strong allosteric activation of other Raf kinases such as RAF1 (c-RAF). Due to the inactivity of the kinase, selective BRAF inhibitors such as Vemurafenib or Dabrafenib are ineffective. Hence, the pan-Raf inhibitor Sorafenib comes into play. To enhance its inhibitory effect on the MAPK pathway and to counteract paradoxical activation at low concentrations, Sorafenib is combined with the MEK inhibitor Trametinib. The DKTK-funded IIT SORATRAM is a basket trial investigating the efficacy of Sorafenib and Trametinib in cancer with kinase inactive BRAF mutations. For this study, biopsies from patients that were eligible for enrollment in the SORATRAM clinical trial were processed and patient-derived-organoids (PDOs) from their various tumor entities were established. Several SORATRAM drug tests were carried out to determine the responsiveness of the patients *in-vitro*. Through Western Blots and RNA-sequencing of PDOs, we gained a deeper insight into the mechanisms of the SORATRAM combination for each patient individually. Importantly, we could show that it is possible to confirm drug responses in PDOs while the patient is still receiving guideline therapies. We expect that this approach will guide therapeutic decisions in individual patients and will be invaluable to interpret the clinical data of SORATRAM.

Preferred type of presentation

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