Cancer remains the leading cause of disease-related death in children after the first year of life. For the ~25% of children whose tumor relapse, usually after intensive first-line therapy, curative treatment options are scarce. Preclinical drug testing to identify promising treatment options that match tumor biology is hampered by the fact that i) molecular genetic data on pediatric solid tumors from relapsed
patients and thus our understanding of tumor evolution and therapy resistance are very limited and ii) for many of the high-risk entities, no appropriate and molecularly characterized patient-derived models and/or genetic mouse models are available. Thus, quality-assured upfront preclinical testing of novel molecularly targeted compounds in a (saturated) repertoire of well-characterized models will increase therapeutic successes of drugs in children with cancer. Since these tumors are overall genetically much less complex than their adult counterparts, it is anticipated that it will be easier to identify powerful predictive biomarkers to aid drug selection.

To address the significant preclinical gap in identifying promising molecules to fight paediatric cancer, the main objectives for this preclinical platform are the following:

• To establish a representative collection of patient-derived in vitro and in vivo models (~420) as well as genetic mouse models of the most common paediatric solid high-risk entities (including relapsed tumors), and liquid tumors.
• To molecularly characterize and to quality-assess the models and the matching primary tumor samples/germline controls with state-of-the-art molecular diagnostic tools.
• To enable regulatory filings in the EU through the development of comprehensive preclinical data packages necessary to move drugs into clinical trials for children with cancer.
• To prioritize paediatric drug development using existing collections of molecular data for systematic target reports, followed by in vivo drug testing in disease models, including at least three standards-of-care regimens for all models as a baseline for comparisons.
• To build an international consensus on preclinical data packages for paediatric cancer to enable clinical development.
• To identify suitable biomarkers for future clinical stratification of patients.

Ultimately, the establishment of the ITCC-P4 will overcome a long-standing gap by enabling thorough molecular characterization of high-risk paediatric malignancies coupled with standardized preclinical testing procedures and will thus greatly expedite the development of more precise and efficacious drugs.

Progress was made despite the COVID-19 pandemic, and excellent cooperation continues between academia and European Federation of Pharmaceutical Industries and Associations (EFPIA) in all WPs and project management. In terms of digital communication and awareness, the ITCC-P4 website (re-launched in 2021) and our LinkedIn account continue to allow facile connection with the community, and are consistently being updated. At year’s end, we had 230 fully established patient derived xenograft (PDX) models from 220 unique patients. All models are available at the testing sites for drug testing. Another 330 models are in early development. Of the 230 established models, 92 have been fully molecularly characterized, along with matching patient tumors and blood. Molecular characterization of the remaining 138 models is expected to be completed by the end of Q1 2021 with a publication anticipated by the summer of '21. At Bayer, full imaging proof-of-concept evaluation was performed on several tumor cell derived brain tumor models, which led to the conclusion to use luciferase imaging for in vivo response assessment. At Roche, several fully humanized neuroblastoma models were successfully generated and immunologically profiled, though they did not recapitulate the immune compartment observed in humans. Regarding in vitro organoid model development,
neuroblastoma organoids and models from several other solid tumors were established, while medulloblastoma organoid establishment remains challenging. Drug testing in PDX models started in Q4, 2020. Information technology advances have continued as evidenced by an enhanced and evolving mouse tumor barcoding system and continued development of the R2 platform (https://hgserver1.amc.nl/cgi-bin/r2/main.cgi). To support selection, prioritization and planning of targeted molecule efficacy testing, the methodology required for the determination of “target actionability” was established and was accepted for publication in Q1, 2020. Four additional target actionability reviews are currently being conducted. As part of our outreach to the greater pediatric community, we presented at the American Association for Cancer Research and American Society of Clinical Oncology Meeting as well as the inaugural meeting of the Foundation for the National Institutes of Health initiative for a pediatric preclinical testing platform in North America. A white paper following from the multi-stakeholder meeting in 2018 which included representation from major EU and US paediatric research centers, Pediatric Preclinical Testing Consortium leadership, Food and Drug Administration leadership, patient advocacy and concerned EU citizens was accepted for publication in Q1, 2021. This document, the first of its kind for global paediatric research, will serve as the basis for a guidance document to be submitted to regulatory authorities for qualification to improve prioritization and effectiveness of paediatric drug development in cancer. Numerous disclosures from members of the Leadership Team were given across the globe as part of our ongoing effort to inform the worldwide paediatric community of the development and importance of the ITCC-P4 platform. Finally, WP7 discussions are well under way with multiple potential scenarios to develop a viable solution for the sustainability platform. Indeed, the survey of the needs of both academia and industry helped identify the key criteria for the platform to satisfy its customers and to define the platform offer. The market sizing was performed and considered the changes in the regulatory environment that will generate an increased need for preclinical testing of anticancer drugs on pediatric tumor models. Two scenarios have been explored in depth for the sustainable platform: a platform managed by the 3 testing sites and a platform with a one stop shop entry implemented with the 3 testing sites.

In addition to the rapid generation of PDX models, where we expect to reach 420 established models even before the end of the funding period, we were successful in attracting two additional EFPIA partners. This, along with an additional contribution from Roche, has enabled the addition of liquid tumors. Additionally, we are in advanced discussions with two additional EFPIA companies to join (2021). If successful, this would support additional combination testing in vivo, showcasing the platform. The sustainability solution is developing quickly, and an advanced discussion occurred near the end of 2020. International visibility has been astonishing as evidenced by invitations to numerous major cancer meetings. Based on the work done during the period in WP7, the final arbitrage on the business model for the sustainable platform will conducted with the consortium partners for an expected final validation during the 2021 General Assembly.
There are no “Summary for Publication" images.