Table 3: Summary of NDDS Strategy

Molecular profiling	• Molecular profiling at diagnosis and at the time of relapse is highly encouraged
Pre-clinical data evaluation should comprise (adapted depending on specifics of each target)	• Target status in clinical series • Target validation (tumour dependence of the target) • *In vitro* activity • *In vivo* activity • Biomarkers (pharmacodynamic and predictive) • Information about resistance mechanisms and how to overcome those • Data on the rational combinations
Prioritisation of targets and drugs	• ALK, MEK, CDK4/6, MDM2, BET bromodomain, aurora kinase, mTORC1/2, BIRC5 and checkpoint Kinase 1 given top priority for pursuing in early clinical trials.
Population for early clinical trials in neuroblastoma should include	• Patients showing early progressive disease • Refractory patients after induction and second line chemotherapy (INRC2 criteria) • Patients with early relapse - during therapy and ≤1 year after diagnosis • Patients with late relapses - 1 year after diagnosis. Relapses >1 year after diagnosis have longer progression free survival, although survival is still extremely poor so new therapies should be offered
Mechanism of action biology driven drug development	• Goal is to match the biology of tumours with existing drugs (with known mechanism of action) as early as possible in the drug development process • Strategy for selection and prioritization of potential paediatric indications rather than the current process based on adult cancer indications.
Early phase clinical trial designs	• Early phase clinical trials should incorporate expansion cohorts in the tumour of interest to obtain proof-of-concept • Start at 100% of the adult body surface area adjusted equivalent RP2D, with attention paid to very young children with immature organs • Bayesian or continuous reassessment method dose escalation design should be used • It is necessary to incorporate biomarkers into early clinical trials in order to accelerate and improve the efficiency of the drug development process by molecular pre-selection
Parallel randomised trials	• Single arm Phase II studies should be abandoned • Randomised parallel trials should be performed based on molecular pre-selection • More efficient adaptive Phase II designs should be incorporated (Bayesian, pick-the-winner, drop-the-loser, octopus, multi-arm multi-stage [MAMS]).

Abbreviations: INRC2: International Neuroblastoma Response Criteria task force to update the initial INRC published in the 1990s (Brodeur J Clin Oncol 1993); PIP: Paediatric Investigation Plan; ITCC: Innovative Therapies for Children with Cancer European consortium