Accelerating Drug Development for Neuroblastoma - New Drug Development Strategy

An Innovative Therapies for Children with Cancer, European Network for Cancer Research in Children and Adolescents and International Society of Paediatric Oncology Europe Neuroblastoma Project

Running title: New drug development strategy for neuroblastoma

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Abstract (200 words)

Introduction: Neuroblastoma, the commonest paediatric extra-cranial tumour, remains a leading cause of death from cancer in children. There is an urgent need to develop new drugs to improve cure rates and reduce long-term toxicity and to incorporate molecularly targeted therapies into treatment. Many potential drugs are becoming available, but have to be prioritised for clinical trials due to the relatively small numbers of patients.

Areas covered: The current drug development model has been slow, associated with significant attrition, and few new drugs have been developed for neuroblastoma.

The Neuroblastoma New Drug Development Strategy (NDDS) has: 1) established a group with expertise in drug development; 2) prioritised targets and drugs according to tumour biology (target expression, dependency, pre-clinical data; potential combinations; biomarkers), identifying as priority targets ALK, MEK, CDK4/6, MDM2, MYCN (druggable by BET bromodomain, aurora kinase, mTORC1/2) BIRC5 and checkpoint kinase 1; 3) promoted clinical trials with target-prioritised drugs. Drugs showing activity can be rapidly transitioned via parallel randomised trials into front-line studies.

Expert Opinion: The Neuroblastoma NDDS is based on the premise that optimal drug development is reliant on knowledge of tumour biology and prioritisation. This approach will accelerate neuroblastoma drug development and other poor prognosis childhood malignancies.

1. Introduction: The unmet need

Neuroblastoma, the most common extra-cranial solid tumour of childhood, is a leading cause of death in children between 1-4 years [1]. More than forty percent of patients are considered high-risk, including children over the age of 18 months with metastatic disease and those with tumours harbouring *MYCN* amplification [2]. Despite improvements in intensive multi-modal therapy, including chemotherapy, high-dose therapy with autologous hematopoietic stem cell rescue, surgical removal of the primary tumour, radiotherapy, residual disease therapy and immunotherapy with anti-GD2 monoclonal antibodies, long-term survival for children with high-risk neuroblastoma remains below 50% at 5 years [3-6]. The majority of patients experience relapse associated with a dismal prognosis, with five-year overall survival for relapsed metastatic neuroblastoma of 8% in the International Neuroblastoma Risk Group analysis [7]. Approximately one third of patients are refractory to frontline therapy and have a very poor outcome [8, 9]. In addition, survivors face a significant burden of late effects due to the intensity of multimodal therapy [10, 11].

2. Current Paediatric Oncology Drug Development Model for Neuroblastoma

Although genomic aberrations (*MYCN, ALK, TP53, ATRX, TERT* and RAS-MAPK) [12-23], which are molecular drivers for specific subtypes of neuroblastoma, have been described, effective molecularly targeted therapies have not been introduced into current treatment strategies [24]. Furthermore, currently all children with high-risk neuroblastoma receive the same therapeutic approach at presentation and treatment is only modified depending on response - therapy is not personalised. To date, in contrast to adult oncology, progress in paediatric cancers has been slow, with a paucity of molecularly targeted drugs being developed for neuroblastoma.

The availability of drugs for early phase clinical studies for neuroblastoma has been driven predominantly by medicines being developed for adult malignancies. Although the number of early phase clinical trials has increased as a result of the European Paediatric Medicine Regulation, the development of drugs for neuroblastoma is still driven by the adult condition and not the mechanism of action of the drug.

After determining the dose and safety profile in a Phase I study, drugs have been evaluated in Phase II studies with no clear prioritisation to identify those with the greatest potential benefit for front-line randomised trials. Furthermore, there has been a lack of

comprehensive molecular profiling of tumours at presentation or relapse. Finally, there has been no integrated process or a forum for communication and information exchange between biologists and clinicians involved in early and phase clinical trials [25].

This fragmented process has resulted in some drugs being developed with not necessarily the highest biological rationale; multiple phase II studies of the same drug and with the exception of anti-GD2 monoclonal antibodies, no new drugs entering front-line studies for nearly two decades. New therapeutic strategies are therefore needed for these children [24, 26, 27].

3. Neuroblastoma New Drug Development Strategy (NDDS)

The Innovative Therapies for Children with Cancer (ITCC), in conjunction with the European Network for Cancer Research in Children and Adolescents (ENCCA) and the International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN), has established the New Drug Development Strategy (NDDS) project as part of the overall NDDS initiative developed by ITCC and ENCCA. The aim is to accelerate the development of new drugs for patients with neuroblastoma with the ultimate goal of improving survival.

The Neuroblastoma NDDS strategy was designed to encompass all elements of the drug development process, including translational medicine from bench to bedside: molecular profiling to identify new targets and potential predictive (selection) biomarkers, development of relevant drugs, biological and pre-clinical research, first-in-child early phase clinical studies, randomised multi-arm trials and the transition to late-phase trials and the clinic. Central to the approach was the premise that optimal drug development is heavily reliant on understanding tumour biology.

The process was based on the premise that involvement of all stakeholders was critical for delivering an integrated system for drug evaluation and clinical trial methodology in children with neuroblastoma. In view of the large number of potential targets and drugs becoming available for evaluation in children with neuroblastoma, on the one hand, and the genetic heterogeneity of neuroblastoma with few recurrently altered genes on the other, a selection and prioritisation process was required to identify targets and drugs which may be of potential benefit to such children.

This Neuroblastoma NDDS is a dynamic process, which prioritises targets and compounds as new data become available. European experts in neuroblastoma biology and pre-clinical and clinical drug development from fifteen research institutions in seven countries are involved, and members of the European Medicines Agency (EMA) and its Paediatric Committee (PDCO) are observers.

This output of the NDDS (prioritisation and an integrated approach for drug development in neuroblastoma) informs clinicians designing early and late phase clinical studies, highlights targets and drugs of greatest interest to the pharmaceutical industry and regulators, and indicates where resources require the greatest attention from academia and industry. This information would be provided for clinical trials groups and companies preparing Paediatric Investigation Plans for new drugs. This NDDS strategy complements that of the multi-stakeholder Paediatric Platform ACCELERATE, developed by the Cancer Drug Development Forum (CDDF), ITCC, and the European Society for Paediatric Oncology (SIOPE) [26], and with representatives from academia, the pharmaceutical industry, regulators and, very importantly, patient representatives. ACCELERATE has developed a process of mechanism of action and biology driven selection and prioritisation of paediatric drug development, rather than the current process based on adult cancer indications [28]. This process determines, for drugs with a known mechanism of action, if that mechanism is relevant for paediatric malignancy and what is the best match with tumour biology. The NDDS initiative refines this prioritisation further within neuroblastoma.

4. Biology of neuroblastoma

Therapeutic targeting of identified oncogenic drivers in neuroblastoma is a key component of the NDDS. The first pivotal step is to identify the molecular pathways and the tumour biology that are critical drivers in neuroblastoma, focusing on gene/pathway aberrations with proof of "tumour dependence". Information on the incidence of actionable mutations is the most easily obtained data for understanding tumour biology; however, determining the functional dependency of the mutation, if it is an oncogenic driver or whether it drives tumour development or recurrence is a more complicated next stage. Next generation sequencing has demonstrated that neuroblastoma harbour fewer mutations involving recurrently altered genes at diagnosis (mean 10–15 per tumour) than many other, especially adult, tumours [29]. The main oncogenic drivers identified in neuroblastoma include: i) *MYCN* amplification in 25% of patients [12]; ii) anaplastic

lymphoma kinase (*ALK*) mutations and amplification in 10-15% of cases, including those of hereditary neuroblastoma [13-16]; iii) *TP53*, wild-type in the majority of neuroblastoma at diagnosis, with about 2% mutation at presentation, but mutations are acquired during treatment and 15% detected at relapse [17]; iv) RAS-mitogen-activated protein kinase (MAPK) pathway mutations recently described in relapsed neuroblastoma (3% mutations at diagnosis and 78% at relapse) [21]; v) mutations in *ATRX* (9%) reported in older patients [18]; vii) TERT rearrangements reflecting telomerase activation in approximately 30% of high risk cases [19, 20]; and finally vii) *PTPN11* mutations in 2.9% of tumours.[22].

The presence of *MYCN* amplification, its biological role and prognostic relevance were described several decades ago [12]. However, no effective therapeutic strategy demonstrating convincing evidence of MYCN inhibition has yet been translated into the clinic. After incorporating all biological information available to date, a recent classification of five groups of drugs targeting MYC or MYCN at different levels has been reported and will allow prioritisation and development of these agents [30]. The five groups of drugs comprise drugs targeting: DNA-binding functions of MYCN, transcription of MYCN, synthetic-lethal interactions of MYCN, oncogenic stabilisation of MYCN protein and the expression or function of MYCN.

ALK was described in 2008 as an oncogenic driver in neuroblastoma [13-16] and an early clinical trial of crizotinib in children with *ALK* aberrations was rapidly initiated [31]. However, resistance to single therapy agent crizotinib has been described pre-clinically and clinically with moderate response rates (1 complete response, 3 stable disease, and 7 progressive disease of 11 ALK mutated neuroblastoma) in early clinical trials compared to other ALK-driven tumours [32]. Hence, both combinations with chemotherapy or other targeted agents or more potent inhibitors are needed to overcome resistance of some ALK mutations [33].

The tumour suppressor protein p53 is usually nuclear and wild-type at diagnosis (98% of tumours) in neuroblastoma, with intact apoptotic mechanisms, although aberrations in the p53/MDM2/p14^{ARF} pathway are more commonly reported. Interestingly, the p53 gene *TP53* is a direct transcriptional target of MYCN and sensitises cells for MYCN-driven apoptosis [34,35].

The appearance of activating mutations of the RAS/MAPK pathway has also been recently described in a high proportion of neuroblastoma at relapse (up to 78%), some of them are novel whereas others are clonally enriched at relapse [21]. Emerging data highlight the importance of other targets such as the cell cycle regulator CDK4/6 [36,37].

ATRX gene mutations/focal deletions are mutually exclusive with *MYCN* amplification and occur in 9% of high-risk patients at diagnosis [22]. *ATRX* mutations/deletions are also strongly associated with the alternative lengthening of the telomeres phenotype [18, 38]. The clinical features of this group include older age at diagnosis, a chronic progressive course and poor long-term overall survival [18]. However, to date, no novel therapies exist for this important target. In 2015 genomic re-arrangements proximal to *TERT,* which encodes the catalytic subunit of the telomerase enzyme, resulting in its transcriptional up-regulation were described in 23-31% of high-risk cases [19, 20]. *TERT* re-arrangements are also associated with poor prognosis and occur in a mutually exclusive fashion to *MYCN* amplification and *ATRX* alterations. Taken together with evidence that *MYCN* also up-regulates *TERT*, these recent discoveries highlight the importance of active telomere maintenance in neuroblastoma pathogenesis and present a new potential therapeutic target [19].

Molecular profiling of tumour tissues bio-banked at the time of diagnosis has yielded important data, as reported in recent whole exome sequencing (WES)/whole genome sequencing (WGS) publications [22,23]. The European ITCC initiatives are providing data with the aim of discovering novel therapeutics for high-risk disease by routinely molecularly profiling tumours at relapse (MOlecular Screening for CAncer Treatment Optimisation [MOSCATO-01 [39], MoleculAr Profiling for Pediatric and Young Adult Cancer Treatment Stratification [MAPPYACTS], Individualized Therapy for Relapsed Malignancies in Childhood [INFORM] [40], Individualised Therapy [iTHER], and Stratified Medicine – Paediatrics [SM-PAEDS], as is the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) project in the US, which analyses both primary and relapsed neuroblastoma [41,42]. More recently, the appearance of new mutations in individual patients at the time of relapse has been demonstrated for *ALK*, *TP53* and *RAS/MAPK* [17, 21, 43-45]. As has been described for other cancers, these mutations are detected at low levels in diagnostic samples but are enriched at relapse and several of these are potentially important drug targets. Understanding the evolution of mutations in neuroblastoma is of critical importance for drug development [21,43-45]. It underlines

that re-biopsying tumours at the time of relapse, and obtaining snap-frozen tumour and paraffin-embedded material before entering early clinical trials, is increasingly important and should be incorporated into clinical practice. This will provide accurate molecular profiling of neuroblastoma and facilitate access to novel targeted therapies through a personalised medicine approach, as well as improving our understanding of disease biology and mechanisms of resistance to new, targeted therapies. The importance of clonal evolution in neuroblastoma has made it necessary to study sequential samples collected during targeted therapy to understand mechanisms of resistance. As sequential tumour sampling may not be feasible, the role of *liquid* samples has become more important. Emerging technologies allow the detection of actionable mutations in circulating DNA obtained from blood samples, as has been recently shown with the detection of *ALK* mutations in plasma samples [46].

5. Incorporation of biological data: the transition from pre-clinical to clinical development - prioritisation of targets in neuroblastoma

A number of articles and workshop reports have been published without achieving a definitive consensus defining the minimal data package required to provide proof-of-concept and therefore to qualify a target or drug as sufficiently promising to take forward into clinical trials for adult cancers [47-49]. For paediatric cancers, the first step should be to prioritise the targets according to the level of existing evidence, then define whether there are available drugs for the target, and finally establish if they are available for paediatric use and whether early phase clinical trials of these agents should be prioritised.

Targets were pre-selected for evaluation based on the currently available data at that time on molecular pathology, biology, and pre-clinical studies. The decisions to prioritise targets for clinical development were taken by a consensus of clinicians, scientists and academic drug development experts based on specific criteria, which included the robustness of the published evidence that they were oncogenic drivers, the functional dependence in neuroblastoma and whether they were strong candidates for druggable targets.

Targets were ranked as ‘high’ (n=9), ‘intermediate’ (n=5) or ‘low’ (n=7) to enable prioritisation based on target expression, target dependency and validation, availability of pre-clinical data on efficacy, and potential combination and biomarker development. The targets that were given top priority for neuroblastoma based on the available data,

completeness of the data and potentially available inhibitors were ALK, MEK, CDK4/6, MDM2, MYCN (druggable by BET bromodomain, aurora kinase and mTORC1/2 inhibition), BIRC5 and checkpoint Kinase 1 [50,51]. TORC1/2 aurora kinase and BET bromodomain were ranked as high priority targets because of their action on MYCN; however, it was agreed that currently no aurora kinase inhibitor exhibits optimal activity against MYCN [52-54]. LIN28B [55] was identified as an important target but currently no drugs are in development. Table 1 summarises the data available for each target and Table 2 the clinical development of relevant drugs. For all these, the target is expressed in neuroblastoma, has been validated *in vitro* and/or *in vivo* with siRNA functional experiments and shows strong evidence of efficacy *in vitro* and *in vivo*. Research to identify biomarkers, combinations or resistance is less well developed, but nevertheless for these targets it was felt that there was sufficient data to guide initial clinical development. The evidence to date suggests that some of these targets are only relevant to molecular sub-populations, for example, ALK for *ALK* mutated or amplified neuroblastoma. For other agents such as mTORC1/2, aurora kinase or CHK1 inhibitors, evidence suggests that they will be active in MYCN driven neuroblastoma, but they could also have a role in non-MYCN driven tumours.

The critical importance of combinations has been highlighted, as these may enhance efficacy in the majority of instances where dysregulation of more than one biological pathway is responsible for driving the disease and overcome resistance. However, the mechanism of action and cumulative toxicities of additional agents must be carefully considered when designing treatment regimens. A substantial logistical challenge lies in the systematic evaluation of the numerous possible permutations of combinations in a clinical setting [56]. In view of the limited number of children available for early phase studies, a rational approach is needed for the selection of combinations, based on the biology of neuroblastoma and its known biological subsets as well as pathways' data in tumours treated with one agent involved in the combination. Following pre-clinical evaluation of the combinations in a range of well-characterized models derived from patients' tumours or genetically engineered models, a proposed combination should be evaluated clinically. The study of genomic and pharmacodynamic biomarkers during the clinical evaluation will exemplify a "from the bench to the bedside and back again" approach. Finally there must be an awareness of unexpected or greater toxicities with these combinations and extrapolation from adult experience is essential.

6. Drugs relevant to prioritised targets

Paediatric early phase clinical trials are ongoing or have recently closed for ALK and aurora kinase inhibitors [31,57-63].

For neuroblastoma, the responses seen with crizotinib are disappointing and are substantially lower than those seen with tumours driven by ALK translocations - inflammatory myofibroblastic tumour, anaplastic large cell lymphoma and non-small cell lung cancer [31]. The challenge then is to identify more potent drugs or combinations which can overcome the inherent resistant of ALK mutations in neuroblastoma. Currently three ALK inhibitors are marketed for the treatment of ALK driven non-small cell lung cancer (crizotinib, ceritinib and alectinib) and three more are in development in adults (brigatinib, lorlatinib and entrectinib). Paediatric trials of single agents ceritinib (LDK378) and entrectinib, as well as combinations of ALK inhibitors with mTOR or CDK4/6 inhibitors, are ongoing [61-63] and, pre-clinical data relating to lorlatinib is encouraging and a Phase I trial has been activated for ethical/IRB approval [64-66]. The optimal ALK inhibitor for neuroblastoma has yet to be determined clinically, but once identified will be evaluated in front-line studies.

Aurora kinase inhibitors are cytotoxic in their own right, as well as acting on the MYCN-aurora complex. Two aurora kinase inhibitors, alisertib and AT9283 have been evaluated in phase I studies in children with neuroblastoma [58-60]: *AT9283* as a single agent and alisertib as a single agent and in combination with irinotecan and temozolomide. Activity has been observed with alisertib both as single agent and in combination. However, activity of alisertib was lowest in *MYCN* amplified neuroblastoma suggesting that its mechanism of action was by a cytotoxic effect rather than on the MYCN-aurora complex. This further supports the hypothesis that the optimal aurora kinase inhibitor, eliciting conformational changes on the MYCN-aurora complex, has yet to be developed [52-54].

Although mTOR inhibitors - everolimus, temsirolimus and ridaforolimus [67-71] - have been evaluated in clinical trials in children, paediatric trials of the new mTORC1/2 inhibitors have just opened and are a high priority for the paediatric academic community because the dual mTORC1/2 inhibition could overcome resistance to rapalogues.

The first-in-child trial of the CDK4/6 inhibitor ribociclib (LEE011) has been recently completed [72], with stable disease a frequent outcome, demonstrating the importance of

a combination approach, and trials of abemaciclib (LY2835219) and palbociclib are ongoing [73,74]. Early paediatric clinical trials of the MEK inhibitors selumetinib, trametinib and cobimetinib and the pan phosphatidylinositol 3-kinase (PI3K) inhibitor SF1126 [75] are in progress. Additionally, MDM2, BIRC5, CHK1 and BET bromodomain inhibitors are in the early clinical phases of adult development, but paediatric clinical trials have not yet started. Although there is a strong biological, mechanism of action rationale for such development of these inhibitors, the slowness in opening early phase paediatric studies reflects that paediatric drug development is still largely centred on adult conditions and not the mechanism of action based model [28].

7. Transition to clinical development: considerations for early and late clinical trials

Based on the foundation of the Neuroblastoma NDDS, there are four elements for clinical evaluation of new drugs: early phase clinical trials, parallel randomised later-phase clinical trials, molecular profiling and randomised front-line trials. Central to the overall approach is the seamless transition between evaluation of a new drug for a particular molecular sub-type by the Clinical Trials Committee of ITCC and evaluation specifically for relapsed neuroblastoma by the Drug Development Group of SIOPEN.

The objective of an early phase clinical trial is not only to determine the paediatric recommended phase II dose (RP2D), safety profile, pharmacokinetics and pharmacodynamics of a drug, but also to assess preliminary signals of activity. As the paediatric RP2D remains very close to the equivalent adult RP2D and toxicity profiles are class-related and similar to adult drugs [76], for drugs with a wide therapeutic index, it is recommended that the paediatric early phase clinical trial starts at the adult RP2D, corrected for body surface area, and is a dose confirmation study. Using this approach [76], pharmacokinetic profiling is critical and the exposures, clearances and other pharmacokinetic parameters can be confirmed to be similar to those obtained in adults as well as the toxicity profile. Conversely, if the drug has a narrow therapeutic index, then a dose escalation study is required. Existing dose escalation designs such as 3+3 were developed for evaluating chemotherapeutics. For molecularly targeted agents, the use of these conventional dose escalation designs leads to longer study durations, studies remaining closed to recruitment for long periods and more dose levels being tested. New dose escalation designs, such as the Bayesian logistic regression model (BLRM) or continuous reassessment method (CRM), maximise the efficiency of the dose escalation by

leading to a shorter duration of trials and less exposure of patients to doses below the maximum tolerated dose (MTD) [78].

The inclusion of patients with the same molecular sub-type or disease in early phase trials of expansion cohorts will enable a valuable assessment of activity, as well as providing further data on safety and pharmacokinetics. Relatively small sized expansion cohorts can inform statistically go/no-go decisions; for example an Ensign 3-stage design [79], where ten patients are recruited at the RP2D, as used in the European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumours (ESMART)trial (NCT02813135) [80]. If there is no response in the first ten patients, then a further evaluation of the drug is postponed or abandoned. However, if there is a response in the first ten patients, then a further 16 patients are enrolled. Also, the recently presented paediatric study on the BRAF inhibitor dabrafenib included four expansion cohorts with 10 patients each, providing statistically based estimations to guide go/no go decisions [81, 82].

If there is preliminary evidence of activity, then the drug is evaluated further in neuroblastoma-specific, adaptive-design, parallel, randomised or multi-arm, multi-stage studies. Evaluation in randomised trials is essential, as a comparison with historical controls will overestimate the efficacy of the drug [83].

Finally and importantly molecular profiling of the patient's tumour at the time of enrolment on an early phase clinical trial is a critical component of the strategy. Due to clonal evolution and tumour heterogeneity, evaluation of archival tumour is not appropriate. "Liquid biopsies" of circulating free DNA are increasingly being incorporated in both early and randomised trials and will give sequential information about tumour evolution and development of resistance. European ITCC initiatives are providing this information by routine molecular profiling of tumours at relapse (MOSCATO-01 [39], MAPPYACTS, INFORM [40], iTHER, SM-PAEDS).

Currently, the multi-pharma, multi-drug ITCC early phase clinical trial ESMART (NCT02813135) [78] (which includes NDDS prioritised drugs - mTORC1/2, and CDK4/6 inhibitors) and the randomised SIOPEN - ITCC BEACON trial [84] provide a clear pathway for the evaluation of drugs identified in the NDDS to go forward to frontline studies. Single agents or combinations, which show activity in the randomised trial, are then introduced

into front-line therapy and evaluated further - a three-stage process from first-in-child studies to front-line therapy.

By utilising this approach paediatric dose confirmation/finding studies can be conducted rapidly, and activity can be determined more quickly, with meaningful comparators and biological knowledge gained in parallel with prospective molecular profiling.

8. Conclusions and action points

The NDDS initiative, created by ITCC, ENNCA and SIOPEN, aims to accelerate drug development by bringing together biologists, drug developers, regulators, and clinicians leading early and late phase trials, to achieve a consensus. Drug development for neuroblastoma must be driven by biology and knowledge of the molecular pathways, tumour biology and key oncogenic drivers. Targets have been prioritised based on biology, specifically target expression, target dependency and validation, and pre-clinical data on efficacy, potential combinations and availability of biomarkers. Since the start of the NDDS initiative, ITCC and SIOPEN have increased efforts to accelerate the development of the prioritised inhibitors. Furthermore there is a clear continuum incorporating molecular profiling, biological and pre-clinical data, mechanism of action driven strategy for selection and prioritisation, and improved early and late phase clinical trial design to streamline the drug development process (Table 3). A closer dialogue with the pharmaceutical industry will further increase the efficiency of this plan, as will the introduction of a mechanism of action and biology driven selection and prioritisation process in paediatric drug development. This approach will guide scientists, clinicians, pharmaceutical industry and regulators in the immediate future and will enable access to the most promising targeted agents in the hope of improving outcomes for children with neuroblastoma, and potentially other childhood malignancies.

9. Expert Opinion

The existing model of drug development for neuroblastoma is generally reactive and responds to drugs being developed for adult malignancies. Furthermore, in the past there has not been integration and coordination between early and late phase clinical studies. Drug development is not driven by the biology of the tumour and the known genomic drivers. This process results in drugs being evaluated that may not have the greatest

probability of activity in neuroblastoma, and their course of development is interrupted and not planned, and frequently trials compete for small populations. Increased collaboration and data sharing between all stakeholders is needed to avoid regulators and pharma not being aware of developments, and lacking an overview of the landscape of the disease, therapeutic needs and new scientific discoveries.

The approach adopted by the NDDS initiative is integrated, comprehensive, and based on tumour biology, and results in a more efficient and rational process and use of valuable and rare resources. The Neuroblastoma NDDS encompasses all elements of the drug development process, including translational medicine from bench to bedside: molecular profiling to identify new targets and potential predictive (selection) biomarkers, relevant drugs, biological and pre-clinical research, first-in-child early phase clinical studies, randomised multi-arm trials and the transition to late-phase trials and to front-line standard of care. Central to the approach is the premise that optimal drug development is reliant on understanding tumour biology. Selection of drugs should be driven by the aberrant molecular pathways in neuroblastoma [28]. The biological hypotheses relevant to each drug should be tested in the clinic through the use of omic and pharmacodynamic ancillary biomarker studies. This approach is in contrast to the present model, where drug selection is dictated by the adult indication and not necessarily by the probability that the medicine will have the greatest patient benefit in childhood tumours. The major challenge of the proposed model is the availability of drugs. This could be increased by including re-prioritisation of drugs developed for adults, which may not be of high priority for adult cancers, or by incentivising the development of drugs specifically for paediatric cancers. Once this proposed model is incorporated, its results will need to be evaluated prospectively to finally demonstrate that it was fit for purpose and has speeded up drug development for childhood cancers.

A critical feature of the NDDS initiative is bringing together experts in neuroblastoma biology and pre-clinical and clinical drug development and leaders of late-phase studies, with regulators as observers. In this way information can be shared, all participants have a common knowledge and decisions can be made collectively.

The Neuroblastoma NDDS has delivered three outputs:-

1. A multidisciplinary expert group has been established, with participants involved in all aspects of the drug development process, which is able to have a dynamic overview of all new targets and drugs available for the disease.
2. Targets have been prioritised based on target validation and completeness of non-clinical data, including available inhibitors, combinations, resistance mechanisms and biomarkers: ALK, MEK, CDK4/6, MDM2, MYCN (BET, Aurora kinase and mTORC1/2), BIRC5 and CHK1 inhibitors. The process is dynamic, and new targets and drugs are regularly reviewed.
3. Clinical trials of the prioritised targets and drugs have been promoted by liaising with pharma and facilitating investigator-led trials through ITCC.

This output of the NDDS greatly assists clinicians designing early- and late-phase clinical studies and the pharmaceutical industry and regulators who are made aware of targets and drugs of greatest interest. Scientific advice can be sought from regulators at early stages in development. Resources from academia and industry can be directed to areas with greatest potential yield.

As neuroblastoma has different genomic drivers, with clonal evolution and tumour heterogeneity, molecular characterisation with a precision medicine approach will be critical. The ultimate goal is a therapeutic approach comprising: molecular profiling tumour categorisation, molecular targeted therapy for “known” genomic drivers and a strategy for biologically relevant cancer vulnerabilities.

We believe this novel approach will accelerate neuroblastoma drug development and should be applied to other poor prognosis childhood malignancies.

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