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Review

Accelerating drug development for neuroblastoma: Summary of the Second Neuroblastoma Drug Development Strategy forum from Innovative Therapies for Children with Cancer and International Society of Paediatric Oncology Europe Neuroblastoma



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Abstract Only one class of targeted agents (anti-GD2 antibodies) has been incorporated into front-line therapy for neuroblastoma since the 1980s. The Neuroblastoma New Drug Development Strategy (NDDS) initiative commenced in 2012 to accelerate the development of new drugs for neuroblastoma. Advances have occurred, with eight of nine high-priority targets being evaluated in paediatric trials including anaplastic lymphoma kinase inhibitors being investigated in front-line, but significant challenges remain.

This article reports the conclusions of the second NDDS forum, which expanded across the Atlantic to further develop the initiative. Pre-clinical and clinical data for 40 genetic targets and mechanisms of action were prioritised and drugs were identified for early-phase trials.

Strategies to develop drugs targeting TERT, telomere maintenance, ATRX, alternative lengthening of telomeres (ALT), *BRIP1* and *RRM2* as well as direct targeting of MYCN are high priority and should be championed for drug discovery. Promising pre-clinical data suggest that targeting of ALT by ATM or PARP inhibition may be potential strategies. Drugs targeting CDK2/9, CDK7, ATR and telomere maintenance should enter paediatric clinical development rapidly. Optimising the response to anti-GD2 by combinations with chemotherapy, targeted agents and other immunological targets are crucial.

Delivering this strategy in the face of small patient cohorts, genomically defined subpopulations and a large number of permutations of combination trials, demands even greater international collaboration.

In conclusion, the NDDS provides an internationally agreed, biologically driven selection of prioritised genetic targets and drugs. Improvements in the strategy for conducting trials in neuroblastoma will accelerate bringing these new drugs more rapidly to front-line therapy.

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1. Introduction

Neuroblastoma is the most common extracranial solid tumour in children and a leading cause of death in children. High-risk neuroblastoma accounts for almost 50% of all cases and it mainly comprises children over 18 months with metastatic disease (stage M) or children with tumours harbouring *MYCN* amplification. Despite the very good outcome for children with low/intermediate-risk disease, patients with high-risk neuroblastoma have a poor prognosis as half of them relapse despite intensive multimodal treatment, including standard chemotherapy, surgery, radiotherapy, high-dose chemotherapy, differentiation therapy and immunotherapy with GD2-targeted monoclonal antibody [1,2]. The prognosis at relapse is even more dismal with less than 10% surviving after 5 years [3,4]. Hence, new drugs to improve survival and reduce long-term toxicities are urgently needed to treat high-risk neuroblastoma at diagnosis as well as patients with relapsed or refractory disease [5].

Despite the increased number of promising targets and drugs identified in pre-clinical studies, and an increase in the number of early clinical trials focused on neuroblastoma, the success of drugs becoming the front-line standard of care or even being evaluated in large upfront phase III trials remains extremely limited. To date, the only non-immunological targeted agents in front-line treatment are the anaplastic lymphoma kinase (ALK) inhibitor crizotinib and ¹³¹I-meta-iodobenzylguanidine (¹³¹I-MIBG), which are both currently being evaluated in an ongoing Children's Oncology Group (COG) phase III trial (COG ANBL1531, NCT number NCT03126916).

Several barriers have delayed the development of new drugs in paediatric cancer in general, and in neuroblastoma in particular. Paediatric drug development is still largely centred on adult conditions rather than the biology of the malignancy. The rarity of paediatric tumours and the paucity of novel drugs available for dedicated paediatric early clinical trials have contributed to slow progress [6,7]. Neuroblastoma being essentially only a childhood cancer, in contrast to leukaemia or sarcomas, further complicates drug development efforts. Other factors such as incomplete pre-clinical data on novel drugs and biomarkers and lack of dialogue between academia, regulators and pharmaceutical industries have negatively impacted the prioritisation process in an environment of limited resources. The multi-stakeholder forum, ACCELERATE, which aims to promote innovation in new drug development for children with cancer, has successfully brought together clinicians, academics, patient advocates, representatives of pharmaceutical companies and regulators [8].

In this overall context of paediatric cancer drug development, a concerted international prioritisation

process, anchored in the biology of neuroblastoma, is needed to identify which targets are high priority and which drugs should be taken forward expeditiously into clinical trials for this disease.

The Neuroblastoma New Drug Development Strategy (NDDS) was launched by the Innovative Therapies for Children with Cancer (ITCC) consortium together with the European Network for Cancer Research in Children and Adolescents and the International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) in 2012. The NDDS aims to accelerate the development of new drugs for patients with neuroblastoma by prioritising targets and mechanisms of action and drugs that should be advanced into paediatric clinical trials [5].

The results of the first NDDS meeting (NDDS1) have prioritised resources, informed clinicians designing early- and late-phase clinical studies and highlighted targets, mechanisms of action and drugs of greatest interest to the pharmaceutical industry and regulators [5].

ALK, mitogen-activated protein kinase (MEK), cyclin-dependent kinase (CDK4/6), mouse double minute 2 homolog (MDM2), checkpoint kinase (CHK1), baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5), bromodomain and extra-terminal motif (BET), Aurora A kinase and mammalian target of rapamycin complex (mTORC1/2) (with the three latter targets representing ways of potentially targeting *MYCN*) were the top priority neuroblastoma targets, and their current clinical status is shown in Table 1. Paediatric trials have started for eight of the nine (89%) targets defined as high priority and for which drugs were available; however, their development is well advanced only for the ALK inhibitors. In this field, crizotinib is now being evaluated in a phase III front-line trial (COG ANBL1531, NCT03126916), and ceritinib (NCT01742286) has completed the phase I/II trial (results are awaited). Pre-clinical data relating to lorlatinib, a third-generation ALK inhibitor, have shown more potency compared to other inhibitors and activity against most primary resistant ALK mutations including the F1174L [9,10]. Following this, an NANT phase I trial of lorlatinib (NCT03107988) in relapsed/refractory neuroblastoma is ongoing. The Aurora A kinase inhibitor alisertib has completed a phase II combination trial with irinotecan and temozolomide [11]. Early phase clinical trials including neuroblastoma cohorts have been completed for MEK (trametinib, NCT02124772; results are awaited) and CDK4/6 (ribociclib, NCT01747876) inhibitors, and these are being taken forward in combination studies. Early phase paediatric clinical trials of MDM2, CHK1 and BET inhibitors have just commenced, but have not for BIRC5. BIRC5 was shown to be a target in neuroblastoma with YM155 being an available clinical candidate. However, although YM155 is no longer in development

Table 1

Targets of interest for drug development in patients with neuroblastoma.

Targets	Summary of the development for neuroblastoma
Agents already in paediatric clinical trials	
ALK	<i>Preclinical:</i> Target expressed in tumour samples (protein & mRNA levels), activating mutations and amplification present in tumour tissue. Inhibition of mutant <i>ALK</i> in neuroblastoma is complex and challenging. <i>In vitro</i> and <i>in vivo</i> efficacy data (in xenografts and GEMM) for crizotinib and other inhibitors. <i>Clinical:</i> Crizotinib is currently being evaluated in an ongoing COG phase III trial (COG ANBL1531, NCT number NCT03126916). In the phase I trial of crizotinib, 1/11 <i>ALK</i> mutated or amplified neuroblastoma patients had objective responses (9%). Phase II of single agent and in combination with chemotherapy not reported (NCT00939770 and NCT01606878). The paediatric phase 1/2 trial of ceritinib was recently completed (NCT01742286) with an objective response rate of 20% [76]. A phase 1 trial of crizotinib in combination with temsirolimus (ITCC-CRISP, EudraCT 2015-005437-53) and a phase I/II trial of lorlatinib (NANT, NCT03107988) are ongoing.
Aurora A kinase	<i>Preclinical:</i> Inhibitors act on the <i>MYCN</i> –Aurora complex, but they are also cytotoxic in their own right. Mechanistically, there is evidence that Aurora A kinase inhibitors would synergise with ATR inhibitors, but not with <i>CHK1</i> inhibitors. More potent and selective inhibitors and novel combinations (e.g. ATR inhibitors) should be developed. <i>Clinical:</i> Alisertib completed phase I and II trials as single agent and in combination with irinotecan–temozolomide [11,20]; however, the activity of alisertib was lower in <i>MYCN</i> -amplified neuroblastoma. Partial response rate 31.8% phase I and 21% phase II. AT9283 completed phase I without finding objective responses in three neuroblastoma patients [77]. LY3295668 erbumine (NCT04106219) phase I has just opened.
CDK4/6	<i>Preclinical:</i> Role as a single agent through cyclin D1 and in combination with MEK inhibitors [78]. <i>Clinical:</i> Ribociclib completed phase I single agent [79], demonstrated stable disease as a frequent outcome in neuroblastoma patients (7/15; 47%). Now, being tested in combination in ESMART (NCT02813135) and NEPENTHE (NCT02780128).
WEE1	<i>Pre-clinical:</i> Combinations with gemcitabine and with <i>CHK1</i> inhibitors are active pre-clinically [26]. <i>Clinical:</i> AZD1775 in paediatric phase I trials by COG (NCT02095132) and ITCC (ESMART) in combination with irinotecan and carboplatin.
mTORC1/2	<i>Pre-clinical:</i> mTORC1/2 is a target in <i>MYCN</i> -driven and <i>NRAS</i> -mutated neuroblastoma. There are preclinical data with a number of compounds and combination data with MEK inhibitors [80]. <i>Clinical:</i> AZD2014 included in ESMART (NCT02813135) as single agent and in combination, but drug development discontinued by the company.
CHK1	<i>Preclinical:</i> Neuroblastoma cell lines and transgenic models are very sensitive to <i>CHK1</i> inhibitors [33,81]. Replication stress, but not <i>MYCN</i> amplification, may be predictive of sensitivity to <i>CHK1</i> inhibitors. Gemcitabine is synergistic with <i>CHK1</i> inhibitors as are PARP and WEE1 inhibitors. <i>Clinical:</i> Completed phase I trial of prexasertib (<i>CHK1/2</i> inhibitor) by COG (NCT02808650). Currently, there is no selective <i>CHK1</i> inhibitor being evaluated in paediatrics.
BCL2	<i>Preclinical:</i> BCL-2 is highly expressed in neuroblastoma and plays an important role in oncogenesis. Potential combination with MCL-1 inhibitor should be explored [82,83]. <i>Clinical:</i> Phase I/II study of venetoclax monotherapy and chemotherapy combinations started (NCT03236857) [84]. There is potential for combination studies.
MDM2	<i>Pre-clinical:</i> Targets—p53, MDM2 aberrations, more common at relapse; validated <i>in vitro</i> and <i>in vivo</i> [85]. <i>Clinical:</i> NEPENTHE trial including HDM201 started (NCT02780128), ALRN-6924 and Idasanutlin paediatric studies started (NCT03654716, NCT04029688).
MEK	<i>Pre-clinical:</i> Targets in the RAS-MAPK pathways are frequently mutated in relapsed neuroblastoma [86]. <i>Clinical:</i> Phase I studies of cobimetinib (NCT02639546) and trametinib (including a neuroblastoma cohort, NCT02124772) completed, results pending.
PARP	<i>Pre-clinical:</i> Some neuroblastoma tumours are sensitive to PARP inhibition, resulting in DNA damage and replicative stress [87]. PARP inhibitors may be synergistic with <i>CHK1</i> inhibitors. Loss-of-function of ATRX is synthetically lethal with PARP inhibition [49]. <i>Clinical:</i> Olaparib currently being tested in combination with irinotecan in the ESMART clinical trial (NCT02813135) and as single agent in selected tumours is starting soon.
Polyamine pathway	<i>Pre-clinical:</i> ODC1 is a transcriptional target of MYC, and its encoding gene ODC1 is co-amplified with <i>MYCN</i> in 6% of high-risk neuroblastoma. DFMO is an inhibitor of ODC1 [26,88]. <i>Clinical:</i> Trial reported using lower doses in maintenance adjuvant setting [27]; NANT trial of DFMO with topotecan/cyclophosphamide (NCT02030964); COG ANBL1821 trial will evaluate DFMO added to chemo-immunotherapy in relapsed/refractory neuroblastoma (in development).
BET	<i>Pre-clinical:</i> <i>MYCN</i> amplification strong predictive biomarker. Antitumour effects following down-regulation of <i>MYCN</i> expression and <i>MYCN</i> target genes. <i>Clinical:</i> A paediatric trial with BMS-986158 (NCT03936465) has just commenced. Adult trials including patients older than 12 years are ongoing (NCT02419417).
Priority targets with no agents yet in the paediatric clinic	
ATR	<i>Pre-clinical:</i> Deregulated expression of <i>MYCN</i> activates ATR, and <i>MYCN</i> -driven neuroblastoma is reported to depend on Aurora A kinase to prevent transcription/replication conflicts. The combination of Aurora A kinase and ATR inhibition in <i>MYCN</i> -driven neuroblastoma is currently under investigation. <i>Clinical:</i> Several ATR inhibitors are currently being explored clinically in adults (AZD6738, BAY1895344, VX-970). The combination of AZD6738 is planned in ESMART.

(continued on next page)

Table 1 (continued)

Targets	Summary of the development for neuroblastoma
CDK2/9	<i>Pre-clinical:</i> CDK2/9 inhibition disrupts the interaction between MYCN and pTEFb (CDK9-CyclinT1), resulting in reduced MYCN protein expression and impaired MYCN activity at promoters and enhancers. <i>Clinical:</i> Phase I trials of CYC065 as single agent and in combination with venetoclax for chronic lymphocytic leukaemia are ongoing in adults and planned in paediatrics combined with chemotherapy (ESMART), but have not yet started.
CDK7	<i>Pre-clinical:</i> CDK7 inhibition selectively inhibits growth, induces MYCN down-regulation and affects the transcriptional programs in MYCN-amplified cell lines. <i>Clinical:</i> SY-5609 is a CDK7 inhibitor undergoing clinical evaluation in adults.
Priority targets with no agents yet in the adult or paediatric clinic	
MYCN (direct)	The issues that have impeded traditional medicinal chemistry approaches to drug MYCN oncoproteins include difficulty in crystallisation of the full-length oncoprotein, its variable tertiary structure in solution and relative lack of well-defined docking sites for small-molecule inhibitors. Indirect approaches include that target synthetic lethal interactions, which seek to inhibit defined binding partners of MYCN that modulate specific oncogenic functions of MYCN, inhibitors of proteins that regulate transcriptional output of MYCN and proteins that modulate interaction of MYCN with regulatory enhancer and super enhancers. These include Aurora A kinase, BET, CDK7 or CDK9.
TERT/telomere maintenance	Imetelstat (GRN163L), a potent competitive inhibitor of telomerase enzymatic activity, was evaluated in paediatric trials, but its clinical development has been halted. 6-thio-dG represents a novel drug targeting telomerase activity and has promising preclinical utility against neuroblastoma, but it has not reached clinical development yet.
ALT	No direct therapeutic strategy has been established for cancers with the ALT phenotype. Preclinical studies have suggested that ATR inhibitors, Tetra-Pt (bpy) or ATM inhibitors could be strategies for these patients.
ATR	No published data exist for ATRX, although it has been suggested that it could be targeted via PARP inhibition.
BRIP1	BRIP1 represents a novel target for exploiting replication stress. Direct inhibitors targeting BRIP1 are currently not clinically available, small molecule targeting other components of the replicative stress response machinery are available, such as CHK1, CDC7, ATM and WEE1. RRM2 and FOXM1 have also been identified as potential targets but without direct inhibitors available.
RRM2	RRM2 gene has been identified as a strong dependency gene in high-risk neuroblastoma with overexpression causing remarkable accelerated tumour formation in an MYCN driven neuroblastoma zebra fish model. RRM2 is a component of the ribonucleotide reductase complex involved in dNTP production and located on a highly recurrently gained region on chromosome 2 (2p25.1). Several regulatory pathways control RRM2 expression and protein levels including MYCN itself, E2F1-3, LIN28B as well as ATR, CHK1 and WEE1 cell cycle checkpoint regulators. Therefore, direct RRM2 inactivating drugs may be of benefit to integrate into novel combination therapies aimed to target replicative stress-induced DNA damage response pathways.
BIRC5	<i>Pre-clinical:</i> mRNA and protein over expression described, target validated <i>in vitro</i> with shRNA and <i>in vitro/in vivo</i> efficacy data for YM155. <i>Clinical:</i> Development of YM155 was halted; no clinical candidates are available at the moment.

ALK, anaplastic lymphoma kinase; ALT, alternative lengthening of telomeres; ATM, ataxia telangiectasia mutated; BET, bromodomain and extra-terminal motif; BIRC5, baculoviral inhibitor of apoptosis repeat-containing 5; CDK, cyclin-dependent kinase; CHK, checkpoint kinase; COG, Children's Oncology Group; DFMO, difluoromethylornithine; ESMART, European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumours; ITCC, Innovative Therapies for Children with Cancer; MDM2, mouse double minute 2 homolog; MEK, mitogen-activated protein kinase; mTORC1/2, mammalian target of rapamycin complex; ODC1, ornithine carboxylase; RRM2, ribonucleotide reductase M2.

in view of the negative results of adult trials, the target remains of interest for paediatrics (Table 2).

In 2016, the European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumours (AcSé-ESMART) trial (NCT02813135, EudraCT 2016-000133-40) was launched as the European academic multi-pharma precision medicine trial [12]. This proof-of-concept, phase I/II, multi-centre, prospective basket trial is designed to explore targeted agents, either as a single agent or in combination in a molecularly enriched cancer population. Paediatric patients with relapsed/refractory solid tumours are assigned to one of the multiple arms based on their molecular profile determined by a comprehensive molecular screening within the MAPPYACTS study (NCT02613962) or other advanced molecular profiling programs. In the first version of ESMART, six

of the seven arms included highly relevant drugs for neuroblastoma such as CDK4/6, mTORC1/2, PARP or WEE1. More than 130 patients have already been recruited and amendments are incorporating newer targeted therapies and combinations, thus facilitating the pipeline of drugs and combinations available for further development in neuroblastoma. Despite this progress, challenges remain; for some of these agents, clinical development has been halted or abandoned for reasons not related to their paediatric development, such as vistusertib (AZD2014). For others, attrition has been substantial with a considerable number of single agents, non-biomarker-driven early-phase trials not demonstrating activity and, with the exception of crizotinib, no other compounds reaching front-line evaluation or randomised phase II–III trials. Despite successful examples of multi-arm multi-company trials such as the

Table 2
Status of early paediatric clinical trials of prioritised targets in NDDS.

Target	Agent	Clinical early-phase trials phase I or II and results	Status for neuroblastoma
ALK	Crizotinib	1: completed, RP2D identified 2: completed as single agent, results pending 2: completed in combination with topotecan–cyclophosphamide, results pending	COG study in frontline
Aurora A kinase	Ceritinib	1/2: completed, RP2D identified, results pending	No trials planned
	Lorlatinib	1: ongoing as single agent and in combination	Phase I ongoing
	Alisertib	1: completed as single agent and in combination 2: completed in combination with irinotecan–temozolomide	Not taken forward in paediatrics
CDK4/6	AT9283	1: completed single agent, RP2D identified	Drug discontinued by the company
	LY3295668 Erbumine	1: opening soon for neuroblastoma	Phase I ongoing
	Ribociclib	1: completed single agent 1: evaluated in combination with topotecan–temozolomide and with everolimus in ESMART, results pending	Combination trials planned
BCL2	Venetoclax	1: ongoing as single agent and with chemotherapy	Phase I ongoing
MDM2	HDM201	1: ongoing in NEPENTHE	Phase I ongoing
	ALRN6924	1: ongoing	Phase I ongoing
MEK	Idasanutlin	1: ongoing	Phase I ongoing
	Trametinib	1: completed RP2D identified Expansion cohort completed no results 1: ongoing in NEPENTHE	Phase I combination ongoing
	Cobimetinib Selumetinib	1: ongoing 1: completed 2: completed for plexiform neurofibroma and low-grade glioma	No trials planned in neuroblastoma No trials planned in neuroblastoma
mTORC1/2 WEE1	Vistusertib AZD1775	1: in two arms in ESMART, study suspended 1: ESMART (with carboplatin) and COG (with irinotecan) trial ongoing	Drug discontinued by the company Phase I ongoing
Polyamine pathway	DFMO	1: completed, RP2D identified 2: ongoing chemo-immunotherapy with/without DFMO	Randomised phase II ongoing at relapse
PARP	Olaparib	1: completed, RP2D identified 1: in ESMART with irinotecan	Phase I ongoing
	Talazoparib	1: completed in combination with irinotecan and also temozolomide	No trials planned in neuroblastoma
CHK1	Prexasertib	1: completed by COG	Phase I ongoing
CDK2/9	CYC065	1: to open in ESMART	Phase I awaited
Telomerase	Imetelstat	1: completed, RP2D identified	Drug discontinued by the company
BET	BMS-986158	Phase I ongoing	Phase I ongoing

ALK, anaplastic lymphoma kinase; BET, bromodomain and extra-terminal motif; CDK, cyclin-dependent kinase; CHK, checkpoint kinase; COG, Children's Oncology Group; DFMO, difluoromethylornithine; ESMART, European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumours; MDM2, mouse double minute 2 homolog; MEK, mitogen-activated protein kinase; mTORC1/2, mammalian target of rapamycin complex; NDDS, Neuroblastoma New Drug Development Strategy.

ESMART or Paediatric NCI-MATCH trial, additional challenges ensuring early access to most promising inhibitors remain. With this landscape, a second NDDS forum was convened, and this report summarises the discussions and conclusions from this initiative.

2. Second NDDS

The second NDDS initiative included both North American and European academic researchers to achieve the goal of trans-Atlantic consensus and strengthen collaboration in this rare disease. Patient advocates and regulators were included as key stakeholders. Representatives from pharmaceutical companies enabled a discussion about their early pipeline agents to take

place, but they provided an industry perspective on paediatric cancer early drug development.

The overall aim of the second NDDS forum was to prioritise targets, according to biological rationale and drugs with a strong mechanism of action against those targets. This forum focused on tumour genetic targets or mechanisms of actions and not on microenvironment/immunological targets. The desired outcome was the delivery of early-phase trials with the highest potential to inform decisions about subsequent front-line studies. Within a class of compounds with a specific target, identification of the optimal molecule (i.e. one that specifically has the desired biological effect) is critical. For example, the optimal Aurora A kinase inhibitor to decrease MYCN protein levels is believed to be one

which elicits conformational changes in the MYCN–Aurora complex [13].

The specific objectives of this second forum were to: i) identify strategies to target the telomere pathway and replication stress; ii) prioritise strategies to target MYCN; and iii) prioritise new targets for neuroblastoma and those identified in NDDS1. Drugs relevant to these prioritised targets were to be identified for inclusion in early-phase clinical studies. Given that there is no single genetic driver in neuroblastoma, with the presence of multiple epigenetic events and the role of the immune system, a focus was given to combination strategies, including potential combinations of small molecules with immunotherapy.

For each target, the aim was to review a comprehensive information package including data about the target in neuroblastoma (expression, dependency and validation), pre-clinical results on available drugs, potential combinations and availability of biomarkers. Each delegate provided an overall evaluation for each target.

3. Considerations for neuroblastoma drug development (Table 3)

A coordinated international effort in new drug development in neuroblastoma between Europe, North America and the rest of the world will have substantial benefit, especially in view of the challenge of small patient numbers coupled with a large number of potential permutations of combination trials and genomically defined subpopulations.

Those promising targets that have no drugs at present available for clinical evaluation should be championed for drug discovery by pharmaceutical and biotechnology companies and academic drug discovery units.

There is a need to define the optimal package for a drug to be evaluated pre-clinically in neuroblastoma, as

well as other paediatric tumours. One of the ITCC Paediatric Preclinical Proof-of-concept Platform (ITCC-P4) (www.itccp4.eu) work packages is the development of a consensus for this pre-clinical package. The ITCC-P4 is a European public-private partnership, aiming to establish new, fully characterised patient-derived pre-clinical models of high-risk paediatric solid tumours and to use these models for pre-clinical drug evaluation in a sustainable comprehensive platform.

Early phase (first-in-child) trials that include neuroblastoma expansion cohorts, when appropriate, will provide a preliminary evaluation of therapeutic activity in this entity, enabling the selection of drugs for further randomised multi-arm or umbrella studies. One example of such a study is the SIOPEN-ITCC BEACON trial (NCT02308527), which is a randomised phase II trial evaluating the benefit of the addition of novel drugs, such as the angiogenesis inhibitor bevacizumab, or the anti-GD2 monoclonal antibody dinutuximab beta to the activity of chemotherapy and evaluating backbone chemotherapy regimens for children with relapsed refractory high-risk neuroblastoma. There is a need to define ‘success criteria’ internationally for early clinical trials to warrant further evaluation as a single agent or in combination, particularly for biomarker-driven trials, and drugs should rapidly transition from first-in-child to front-line trials in only three steps—early-phase clinical trials, randomised phase II trials and front-line studies, as shown in Fig. 1.

In parallel, there should be greater emphasis, at a very early stage of drug development, on establishing optimal combinations while clinical development of single-agent molecules should be minimal (Fig. 2 and Fig. 3). Where possible, clinical development of new drugs should commence evaluating combinations or there should be a short ‘run-in’ single-agent phase that leads to early investigation of combinations with other targeted therapies or with backbone chemotherapy regimens.

Table 3
Considerations for neuroblastoma drug development.

Need	Action
Coordinated international effort in new drug development in neuroblastoma	NDDS initiative, third NDDS workshop planned for 2021 Multi-stakeholder and global coordination required
No drugs available for clinical evaluation targeting	Targets championed for drug discovery to pharmaceutical companies
Optimal agreed pre-clinical package for a drug to be evaluated clinically	ITCC-P4 project (www.itccp4.eu) work packages develop a consensus pre-clinical package
Early phase trials include neuroblastoma expansion cohorts	Improved trial design, incorporating neuroblastoma expansion cohorts
Combinations explored at a very early stage of drug development	biomarker enrichment and combinations explored at a very early stage of drug development
First-in-child to front-line trials in only three steps for active drugs	
Lack of long-term outcome data of patients with relapsed disease	INRG initiative has developed a taskforce to incorporate data on relapsed patients from frontline and relapsed trials into the INRG database (www.inrgdb.org)
Define internationally ‘success criteria’ for early clinical trials in neuroblastoma	International consensus—INRG

NDDS, Neuroblastoma New Drug Development Strategy; INRG, International Neuroblastoma Risk Group; ITCC, Innovative Therapies for Children with Cancer.

Despite recent studies reporting data on the outcomes of patients with relapsed neuroblastoma [4,14–16], a more integrated approach including more data on follow-up and biological features is required. Following the meeting, a new International Neuroblastoma Risk Group (INRG) initiative (www.inrgdb.org) has been launched to incorporate this relapse-specific information into the international database.

4. Target prioritisation process

The primary objective of the Second NDDS Forum meeting was to prioritise targets based on tumour biology, with a secondary aim to review the prioritised targets to determine which have clinically developed candidate drugs. Targets were prioritised based on evidence of their dependency for tumour growth and progression, *in vitro* and *in vivo* pre-clinical data and, if available, clinical data in patients following the methodology used in a prior NDDS workshop and other initiatives such as the Paediatric NCI-MATCH [17].

Nevertheless, a reasonable balance between the amount of required pre-clinical data and the clinical urgency to develop treatments for a population with high unmet need was considered as much knowledge is gained from first-in-child studies with integrated

correlative biology studies [6] (www.itccp4.eu). The availability of profiled tumour sample series both at the time of diagnosis and relapse, clinical urgency and availability of paediatric relevant models was considered for this definition.

Before the forum, 40 targets and mechanisms of action were preselected for evaluation based on the most recent available data (Table 1 and Fig. 1).

In view of the limited number of patients available, when several drugs are available for a given target, the drugs need to be considered together in a non-competitive space, for example, in a Paediatric Strategy Forum [18,19]. Given the high attrition rates in anticancer drug development and multiple drugs being developed for a given target, the recommendation is to take two drugs for paediatric clinical development, not just one, because in the future, a second candidate might be needed if the first one is discontinued, or might have more potency or better toxicity profile. Within a class of compounds with a specific target, identification of the optimal molecule (i.e. one that specifically has the desired biological effect) is critical.

Once identified, high-priority targets and mechanisms of action were classified into three categories according to availability of clinical compounds: i) drugs against targets in ongoing paediatric early-phase clinical trials, ii) drugs against targets not in paediatric early-phase

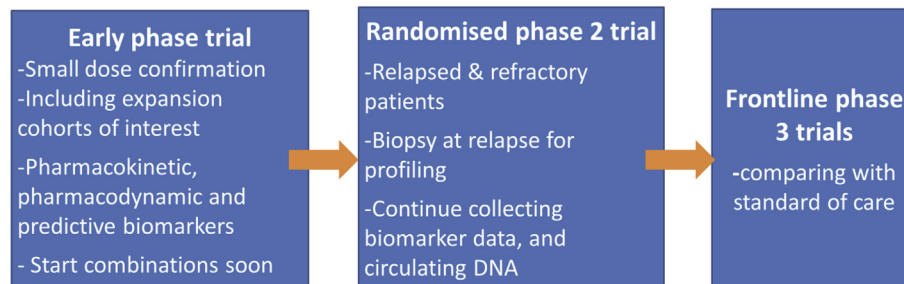


Fig. 1. Schema of clinical drug development for neuroblastoma, from the bench to the clinic.

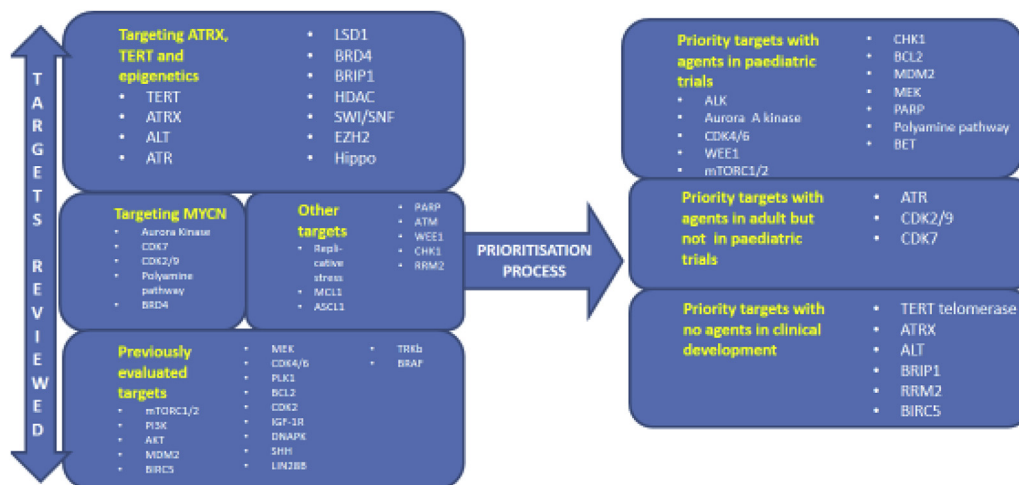


Fig. 2. Summary of targets reviewed and prioritised.

clinical trials and iii) high-priority targets with no drugs at present available in clinical development (Table 1).

5. Priority drugs in paediatric early-phase clinical trials (ALK, Aurora A kinase, CDK4/6, WEE1, mTORC1/2, CHK1, BCL2, MDM2, MEK, PARP, polyamine pathway and BET)

In this forum, high-priority targets were identified for drugs, which are currently in paediatric clinical trials: ALK, Aurora A kinase, CDK4/6, WEE1, mTORC1/2, CHK1, BCL2, MDM2, MEK, PARP, polyamine pathway and BET. Their clinical development status is summarised in Table 1.

ALK is recognised as a high-priority target, with different inhibitors being developed in paediatric trials (crizotinib, ceritinib, entrectinib, lorlatinib) as single agents and in combination. The most advanced ALK inhibitor crizotinib is currently being evaluated in front-line patients with tumours that harbour ALK alterations in the COG ANBL1531 trial (NCT number NCT03126916). The ALK inhibitor in clinical development, which pre-clinically is most potent, lorlatinib, is being tested in an NANT early-phase trial (NCT03107988). ALK inhibitors were not discussed in detail as they had been the focus of a recent Paediatric Strategy Forum [19].

Aurora A kinase inhibitors have completed several steps of paediatric development including up to phase II combination trials in neuroblastoma for alisertib [11,20]. In view of its promising pre-clinical activity and toxicity profile, an international early-phase trial of LY3295668 erbumine specifically in neuroblastoma is about to open (NCT04106219). The CDK4/6 inhibitor ribociclib completed single-agent testing and is now being evaluated in combination in the ESMART (NCT02813135, EudraCT 2016-000133-40) and NEPENTHE trials (NCT02780128). The aim of the NEPENTHE trial is to match genomic aberrations in tumour cells at the time of relapse to rationally designed combinations of molecularly targeted agents: ceritinib (ALK inhibitor), trametinib (MEK inhibitor) and HDM201 (MDM2 inhibitor).

JQ1, a prototypic BET inhibitor, binds the bromo-domain of BET proteins and disrupts BET recruitment to chromatin, downregulating the expression of MYC [21]. *MYCN* amplification was identified as a strong predictive biomarker for response to JQ1 in neuroblastoma cells [22]. Antitumour effects after down-regulation of MYCN expression and *MYCN* target genes were also evident in *MYCN*-amplified neuroblastoma cell lines when treated with other BET inhibitors such as I-BET726 (GSK1324726A) and OTX015 (now MK-8628) [23,24]. Trials in adult cancer patients have started for several of these inhibitors. Although responses have

been demonstrated *in vitro*, in general, *in vivo* evaluation has shown slowing of tumour growth as the best response to monotherapy, with tumour regression being uncommon. Furthermore, myelosuppression is dose limiting to obtain the drug levels that are effective *in vitro*. There is now a dedicated first-in-child trial of the BET inhibitor BMS-986158 (NCT03936465) and adult trials include adolescents [25]. Combination strategies including BET inhibitors, based on biological hypotheses, are particularly relevant.

The polyamine pathway is an emerging target as polyamine metabolism is deregulated in neuroblastoma, ornithine carboxylase (ODC1) is a transcriptional target of *MYCN* and is co-amplified with *MYCN* in 6% of high-risk neuroblastoma. Difluoromethylornithine (DFMO) is an inhibitor of ODC1 and reduces global protein translation by 26–76% in *MYCN*-amplified neuroblastoma [26]. In pre-clinical models, the activity of cyclophosphamide is increased when combined with DFMO. COG will be evaluating DFMO in a randomised study for the first relapse in combination with irinotecan, temozolomide, dinutuximab and GMCSF (COG ANBL1821, NCT03794349). DFMO is also being studied as maintenance therapy at the end of high-risk neuroblastoma therapy [27]. Given the additional risks of bias of evaluating new drugs added at the end of current therapy, evidence from a randomised trial comparing with the standard of care is required.

For WEE1, CHK1, BCL2, mTORC1/2 and MDM2 inhibitors, paediatric trials have recently commenced and no results are yet available. For MEK and PARP, paediatric trials have been conducted, but data from neuroblastoma cohorts are still awaited.

6. Priority drugs not in paediatric early-phase clinical trials (ATR, CDK2/9 and CDK7)

These targets have available clinical candidates in adult development and strong pre-clinical supporting data, but paediatric trials have not yet commenced.

ATR has recently emerged as an attractive therapeutic target as its activation promotes cell survival during DNA damage and replication stress. Several ATR inhibitors are currently being explored clinically. Interestingly, deregulated expression of *MYCN* activates ATR, and *MYCN*-driven neuroblastoma is reported to depend on Aurora A to prevent transcription/replication conflicts [28]. The therapeutic benefit of the combination of Aurora A kinase and ATR inhibition in *MYCN*-driven neuroblastoma is currently under investigation pre-clinically.

CDK2/9 inhibition disrupts the interaction between MYCN and pTEFb (CDK9-CyclinT1), resulting in reduced MYCN protein expression and impaired

Target	Agent	Status		
		Phase 1	Phase 2	Phase 3 - frontline
ALK	Crizotinib	→		
	Ceritinib	■		
	Lorlatinib	→		
Aurora kinase	Alisertib	■		
	AT9283	■		
	LY3295668 Erbumine	→		
CDK4/6	Ribociclib	→		
BCL2	Venetoclax	→	→	
MDM2	HDM201	→		
	ALRN6924	→		
	Idasanutlin	→	→	
MEK	Trametinib	■		
	Cobimetinib	■		
	Selumetinib	■		
mTORC1/2	Vistusertib	■		
WEE1	AZD1775	→		
Polyamine	DFMO	→		
PARP	Olaparib	→		
	Talazoparib	→		
CHK1	Prexasertib	→		
CDK2/9	CYC065	→		
Telomerase	Imetelstat	■		
BET	BMS-986158	→		

Fig. 3. Status of clinical development of high-priority agents that have entered paediatric development. Arrows represent agents currently undergoing clinical trials. Square lines represent agents for which paediatric development has been stopped. Agents coloured in blue are being developed in combination, agents in red have only been developed as a single agent so far. Arrows coloured in white are those where a combination cohort is planned but has not started yet. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

MYCN activity. Phase I trials of the CDK2/9 inhibitor CYC065 are ongoing in adults and in preparation for children within ESMART, but have not currently started.

The transcriptional kinase CDK7 has a role in transcription initiation, but also activates other CDKs namely, CDK1/2/9. CDK7 inhibition selectively inhibits growth, induces MYCN down-regulation and affects the

super-enhancer–driven transcriptional programs in *MYCN*-amplified cell lines [29]. SY-5609 is a clinical candidate.

7. High-priority targets with no drugs currently available (MYCN, TERT mediated/telomere maintenance, ALT, ATRX, BRIP1, RRM2 and BIRC5)

7.1. Targeting MYCN

The association of high-level amplification of *MYCN* with aggressive clinical behaviour in neuroblastoma is well characterised [30]. *MYCN* is therefore a high-priority but nevertheless challenging target for drug development. The issues that have impeded traditional medicinal chemistry approaches to drug *MYC* oncoproteins include difficulty in crystallisation of the full-length oncoprotein, its variable tertiary structure in solution and relative lack of well-defined docking sites for small-molecule inhibitors.

Although strategies to target *MYCN* directly have been elusive, indirect approaches that target synthetic lethal interactions, or which seek to inhibit defined binding partners of *MYCN* that modulate specific oncogenic functions of *MYCN* are gaining ground. Targets of note within this arena include Aurora A kinase, which modulates *MYCN* oncoprotein stability and regulates the transcriptional output of *MYCN*. Alisertib has been evaluated clinically, although little clinical data were generated to confirm selective targeting of *MYCN* [11,20]. More selective Aurora A kinase inhibitors are in development, for example, LY3295668 erbumine (NCT04106219) that may ameliorate these issues [31].

Proteins that regulate the transcriptional output of *MYCN* and proteins that modulate the interaction of *MYCN* with regulatory enhancer and super enhancers are receiving much attention. These include components of the RNA polymerase II complex, such as BET family proteins, amongst these BRD4, for which the toolkit inhibitor JQ1 and clinical compounds GSK525762 and OTX015 were developed [21–23]. Members of the CDK family, in particular CDK7 and CDK9, play a major role in modulating enhancer and super enhancer–dependent transcription of *MYCN* [32]. Finally, a well-characterised synthetic–lethal interaction between expression of checkpoint (CHK) kinases and *MYCN* predicts sensitivity to inhibitors of CHK1/CHK2 (prexasertib LY2606368) or CHK1 (ICR CCT244747, SRA737) [33]. It is envisaged that combinatorial approaches will maximise the efficacy of this approach [34].

A different approach consisting of *MYCN*-specific antigen oligonucleotides has also been proposed, including preclinical candidates such as BGA002, but paediatric clinical development has not yet started [35].

In summary, direct pharmacological inhibition of transcription factors in general, and *MYCN* oncoprotein in particular, have encountered major difficulties. The recent identification of co-factors and *MYCN*-interacting proteins that are essential effectors of oncogenic transformation driven by *MYCN* is leading to a very realistic possibility that indirect *MYCN* inhibitors may enter clinical use in the coming years.

7.2. TERT, telomerase

Over the last few years, TERT-mediated telomere maintenance and alternative lengthening of telomeres (ALT) have been identified as markers of poor prognosis in high-risk neuroblastoma [36–39]. TERT rearrangements, leading to increased telomerase activity, have been identified in a subset of high-risk neuroblastoma tumours [40,41]. In addition, loss-of-function genetic alterations of *ATRX* are associated with ALT, a telomerase-independent mechanism for telomere elongation through homologous recombination.

Targeting telomerase activity and ALT pathways represent a novel therapeutic approach for high-risk neuroblastoma, but no clinical candidates are currently available. Imetelstat (GRN163L), an inhibitor of telomerase enzymatic activity, was evaluated in paediatric trials [42,43], but its clinical development has been halted because of unacceptable toxicity. Nucleoside analogue 6-thio-2'-deoxyguanosine (6-thio-dG) represents a novel drug targeting telomerase activity and has promising preclinical utility against neuroblastoma. 6-thio-dG is recognised by telomerase and is incorporated into *de novo*–synthesised telomeres [44], resulting in modified telomeres, leading to telomere dysfunction, but only in cells expressing telomerase. Clinical trials are awaited.

7.3. Alternative lengthening of telomeres and ATRX

A small number of publications have also reported potential therapeutic strategies for cancers with the ALT phenotype. In osteosarcoma cells, the ALT phenotype confers hypersensitivity to compounds that inhibit the activity of the DNA damage repair response protein ATR [45]. However, these findings have subsequently been refuted by others [46].

A novel cisplatin derivative Tetra-Pt (bpy), which targets the G4 quadruplex, has been developed and shown to selectively inhibit the growth of ALT cells. However, this compound is not currently available for clinical use [47]. Finally, it has recently been shown that ataxia telangiectasia mutated (ATM) is hyperactivated at ALT telomeres, and that the ATM inhibitor AZD0156, which is currently in adult early-phase clinical trials, synergises with conventional chemotherapy in pre-clinical models of ALT neuroblastoma [48].

Genetic alterations in *ATRX* (a tumour suppressor gene) are found in approximately half of ALT

neuroblastoma cases, and may represent another important potential indirect therapeutic target. There are currently no published data for the therapeutic targeting of *ATR* alterations, although preliminary reports have identified that *ATR* loss-of-function is synthetically lethal with PARP inhibition [49]; this is being currently addressed in Arm D of ESMART.

In summary, promising pre-clinical data regarding the therapeutic targeting of TERT and ALT have begun to emerge in recent years. However, there are currently no clinical trials available for these large molecular subgroups of poor outcome patients.

7.4. Replication stress and DNA repair deficiency by *BRIP1* and *RRM2*

Replication stress indicates a series of events that interfere with DNA replication and hinders its progression causing DNA damage [50,51]. Tumours driven by *MYC* are likely to be exposed to high levels of replication stress, but at the same time have efficient mechanisms to overcome otherwise lethal levels of DNA damage thus allowing them to grow [52].

BRIP1 represents a novel target for exploiting replication stress. *BRIP1* exerts multiple functions to protect cells from replicative stress. Firstly, its DNA helicase function has been shown to be critical for unwinding stable G4 structures that occur in single-stranded DNA during replication ensuring timely progression through S-phase [53]. Secondly, *BRIP1* plays a role in stabilising stalled replicative forks and is involved in resolving collapsed forks, as binding partner of *BRCA1* during homologous recombination. Thirdly, and most importantly, *BRIP1* also binds *TOPBP1* to facilitate RPA loading to single-stranded DNA of stalled forks thus providing a crucial upstream trigger for ATR signalling. Although an inhibitor has been identified for the related DNA helicase *WRN*, so far no specific inactivating small molecules for *BRIP1* have been identified [54]. While awaiting such compounds, *in vitro* assays are testing putative synergistic effects of *BRIP1* depletion with inhibition of other replicative stress resistors such as ATR, *CHK1*, *CDC7*, *ATM* and *WEE1* kinases [55] and the ribonucleotide reductase *M2* (*RRM2*) enzyme [56]. *FOXM1* is a key regulator of cell cycle and DNA damage response and also a potential target for replicative stress; however, no drug specifically inhibiting either of these targets is available [34,57].

8. Strategies for combination with immunotherapy

Immunotherapy has become an integral component of therapy for high-risk neuroblastoma following the pivotal publication demonstrating the benefit of a ch14.18 antibody (dinutuximab), targeted to the cell surface GD2 disialoganglioside combined with

cytokines (granulocyte–macrophage colony-stimulating factor and interleukin 2), in addition to isotretinoin [58]. Anti-GD2 antibody ch14.18 is now given alone or with cytokines in both North American and European front-line trials [59,60].

The most recent therapeutic breakthrough for neuroblastoma is the combination of anti-GD2 targeted therapy with chemotherapy [61–63], which demonstrated promising increased objective response rates and progression-free survival in the relapsed and refractory neuroblastoma (COG study ANBL1221 with dinutuximab and St. Jude study with Hu14.18K322A) and front-line settings (St Jude institutional study with Hu14.18K322A) [61,63,64]. This approach is now being explored in a wider multicentre setting in front-line high-risk neuroblastoma (NCT03786783).

Pre-clinical work has recently shown how neutrophils have significant anti-neuroblastoma effects, but only in the presence of dinutuximab. This work also showed enhanced *in vivo* activity for dinutuximab in combination with GM-CSF, topotecan and cyclophosphamide. This further supports the preclinical rationale for the combination of anti-GD2 (14.18) with chemotherapy [65].

Nevertheless, neuroblastoma has not been considered an ‘immunogenic’ tumour as it has a low mutational burden [66] and as a consequence a low number of neoantigens known to promote an immunological antitumour response. This phenotype may in part explain the very poor response of neuroblastoma to immune checkpoint blockade [67,68]. Neuroblastoma cells characteristically have a very low expression of major histocompatibility complex class I [69] and secrete soluble factors that contribute to immune evasion. Furthermore, studies have demonstrated an active immune-suppressing microenvironment in neuroblastoma [70]. Myeloid-derived suppressor cells have been shown to be integral to neuroblastoma tumour growth as demonstrated by a heavy infiltration of myeloid cells found in tumour samples [71,72]. Several strategies are being developed to overcome such inhibitory effects of neuroblastoma aiming to use on-target and off-target effects of small molecules to potentiate both passive and active immunotherapies.

Three approaches to enhance immunotherapy are firstly promoting tumour immunogenicity by pre-treatment with chemotherapy or radiotherapy or combining with anti CTLA4 or MEK inhibitors. Molecular radiotherapy is being used in two ongoing trials evaluating the combination of MIBG therapy with dinutuximab beta and anti-PD1 inhibitors (MINIVAN NCT03332667) and MIBG with dinutuximab (NANT17-01 NCT03332667). Secondly, inhibiting tumour-promoting inflammation, immunomodulatory drugs such as lenalidomide (NANT trial with dinutuximab and lenalidomide, NCT01711554). Thirdly, by increasing innate immunity by an immunomodulatory effect on the tumour microenvironment by increasing NK and T cells, but reducing regulatory T cells by

DFMO, reviewed in Ref. [26]. Alternatively, administering NK cells in conjunction with anti-GD2 antibody or other immunostimulatory approaches may improve antibody-dependent cellular cytotoxicity [73,74]. Other immunological strategies that are being evaluated include vaccines against GD2, CAR T-cells engineered to target neuroblastoma cell surface markers L1-CAM or GD2 have been developed and most recently bispecific antibodies targeting GD2 and CD3. GPC2 has been recently identified as a non-mutated neuroblastoma oncoprotein and candidate immunotherapeutic target that warrants evaluation [75].

As with non-immunotherapy approaches, pre-clinical testing should inform the optimal dose, sequence of drugs to be used in combination and schedule of administration in the clinic. The relative paucity of appropriate pre-clinical immunocompetent models pose a major challenge and will require the development of newer and better immunocompetent models fit for immunotherapeutics (ITCC-P4 Work Package 3). In terms of clinical translation, combinatorial studies exploring immunotherapy agents should be performed with attention to careful safety monitoring as single drug lack of toxicity cannot predict the potential for synergistic adverse effects.

9. Conclusion

Optimal, accelerated drug development for neuroblastoma demands a combination of an efficient strategy and selection of molecules that have the highest potential to lead to front-line studies. A coordinated trans-Atlantic approach is critical to increase the probability of success, especially in view of the relatively small patient numbers and even smaller genomically defined subpopulations. Once this trans-Atlantic strategy has been firmly established, an even more global plan can be initiated.

Presentations from the meeting highlighted the need for an agreed optimal pre-clinical data package [17]. Uniformity of tumour models would advance progress as there would be comparability when results are presented. The ITCC-P4 project will deliver this prerequisite and a consensus of the criteria for drugs to proceed to early clinical evaluation. Neuroblastoma is particularly poised to continue with current collaborations and expansion of those collaborations to cross Atlantic and Pacific trials.

Greater emphasis on establishing optimal combinations at a very early stage of drug development is required. Furthermore, the profiling programs at diagnosis and relapse have confirmed the absence of unique driver events in neuroblastoma. In this setting, models that enable the study of sequential treatments to account for clonal evolution and cellular escape mechanisms are crucial. Also, it is envisaged that high-throughput drug-screening strategies will also contribute to the definition

of effective drug combinations. The number of single-agent early-phase trials should be reduced, combination studies preferred and a small ‘window’ single-agent phase could provide data on the pharmacokinetics and toxicities of a drug.

Early phase trials should include neuroblastoma expansion cohorts, with biomarker enrichment and new active agents should rapidly transition from first-in-child to front-line trials in only three steps—early-phase clinical trials, randomised phase II trials and front-line studies.

Twenty-two of 40 targets reviewed were identified as high priority based on tumour biology. Twelve of these had clinical molecules in paediatric clinical trials, three had molecules that had not reached a paediatric development and seven had no clinical candidates as yet identified. Importance should be given to open studies of the three compounds and those targets with no drugs available should be championed for drug discovery by pharmaceutical companies. Emerging therapies targeting neuroblastoma with *ALT* or *ATRX* alterations should be evaluated rapidly.

In view of the substantial response to immunotherapy for neuroblastoma, integrating immunotherapeutics with targeted drugs is of pivotal importance.

In summary, the development of the prioritised medicinal products should be accelerated by academia and industry. It is envisioned that the ITCC-P4 project work package to develop a consensus pre-clinical package will be a major advance. There should be a trans-Atlantic strategy to evaluate these agents, with the early introduction of combinations and the aim that active drugs are transitioned from first-in-child to front-line trials in only three steps. Collaboration and regular communication are critical to drive forward this approach and increase the number of effective drugs incorporated into front-line therapy.

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Author contributions

AP, GV and LM contributed to the study design and manuscript preparation; AP, LM, GB and SGD contributed to the data acquisition, data analysis and interpretation; all authors contributed to the manuscript editing and review.

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agencies or organisations with which the authors are affiliated.

Conflict of interest statement

LM has participated in advisory boards for Novartis, AstraZeneca, Roche/Genentech, Mundipharma, Bayer and Amgen, has received honoraria from Celgene and Novartis for educational events and travel grants from Mundipharma, Celgene and Amgen, and is a member of the Executive Committee of SIOOPEN, a non-profit organisation that receives royalties for the sales of dinutuximab beta. SGD has received travel expenses from Loxo Oncology, Roche, and Salarius and consulting fee from Loxo Oncology. BG has participated in advisory boards for Roche/Genentech, Bayer, BMS, Celgene, Merck KG, Tesaro and Boehringer Ingelheim. MI provides advice to Bayer Canada. SB is an employee of, and owns shares in, Pfizer Ltd. HC is an employee of, and owns shares in, Hoffman La Roche. SD is an employee of Cyclacel Limited. MM and PM are employees of Astrazeneca. JS is 6-THIO-DG Scientific Founder and MAIA Scientific Advisor. GV provides advice to Roche, BMS, Celgene, Takeda, Aceta Pharma, Merck, Bayer, Servier and Novartis. ADJP provides advice to Novartis, Takeda, Merck, Lilly and Celgene.

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