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Review

Bromodomain and extra-terminal inhibitors—A consensus prioritisation after the Paediatric Strategy Forum for medicinal product development of epigenetic modifiers in children—ACCELERATE

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Abstract Based on biology and pre-clinical data, bromodomain and extra-terminal (BET) inhibitors have at least three potential roles in paediatric malignancies: NUT (nuclear protein in testis) carcinomas, *MYC*/*MYCN*-driven cancers and fusion-driven malignancies. However, there are now at least 10 BET inhibitors in development, with a limited relevant paediatric population in which to evaluate these medicinal products. Therefore, a meeting was convened with the specific aim to develop a consensus among relevant biopharmaceutical companies, academic researchers, as well as patient and family advocates, about the development of BET inhibitors, including prioritisation and their specific roles in children.

Although BET inhibitors have been in clinical trials in adults since 2012, the first-in-child study (BMS-986158) only opened in 2019. In the future, when there is strong mechanistic rationale or pre-clinical activity of a class of medicinal product in paediatrics, early clinical evaluation with embedded correlative studies of a member of the class should be prioritised and rapidly executed in paediatric populations.

There is a strong mechanistic and biological rationale to evaluate BET inhibitors in paediatrics, underpinned by substantial, but not universal, pre-clinical data. However, most pan-BET inhibitors have been challenging to administer in adults, since monotherapy results in only modest anti-tumour activity and provides a narrow therapeutic index due to thrombocytopenia. It was concluded that it is neither scientifically justified nor feasible to undertake simultaneously early clinical trials in paediatrics of all pan-BET inhibitors.

However, there is a clinical need for global access to BET inhibitors for patients with NUT carcinoma, a very rare malignancy driven by bromodomain fusions, with proof of concept of clinical benefit in a subset of patients treated with BET inhibitors. Development and regulatory pathway in this indication should include children and adolescents as well as adults.

Beyond NUT carcinoma, it was proposed that further clinical development of other pan-BET inhibitors in children should await the results of the first paediatric clinical trial of BMS-986158, unless there is compelling rationale based on the specific agent of interest. BDII-selective inhibitors, central nervous system–penetrant BET inhibitors (e.g. CC-90010), and those dual-targeting BET/p300 bromodomain are of particular interest and warrant further pre-clinical investigation.

This meeting emphasised the value of a coordinated and integrated strategy to drug development in paediatric oncology. A multi-stakeholder approach with multiple companies developing a consensus with academic investigators early in the development of a class of compounds, and then engaging regulatory agencies would improve efficiency, productivity, conserve resources and maximise potential benefit for children with cancer.

1. Introduction

The fifth multi-stakeholder Paediatric Strategy Forum on epigenetic modifiers, organised by ACCELERATE [1] in collaboration with the European Medicines Agency (EMA) with participation of the US Food and Drug Administration (FDA), agreed that there was a need for a dedicated meeting focused on prioritising the multiple bromodomain and extra-terminal (BET) inhibitors in clinical development that could potentially be evaluated in children with cancer [2].

The BET family of proteins consists of four members (BRD2, BRD3, BRD4 and BRDT) that regulate chromatin structure and gene expression through binding to acetylated lysine residues on histone tails, which is critical in regulating transcription [3]. Each

BET protein contains tandem dual bromodomains (BDs), which are structurally similar between all four family members. The BET family is one of the most prominent transcriptional vulnerabilities in human cancer and therefore is an attractive epigenetic therapeutic target.

Based on biology and pre-clinical data, BET inhibitors have at least three roles in paediatric malignancies: NUT (nuclear protein in testis) carcinomas [4], *MYC*/*MYCN*-driven malignancies [5–8] and fusion-driven cancers [9–13]. NUT carcinomas are the archetype of a BET-driven malignancy, with *BRD4* and *BRD3* fusions characteristic of this disease. There is controversy relating to the role of BET inhibitors in malignancies other than those driven by *BRD3*/*BRD4* fusions [14–16]. It is uncertain if the concentrations necessary to achieve a biological effect *in vivo* in other cancers can be achieved in clinical practice due to toxicity, notably thrombocytopenia. As a result, in clinical trials, in adults to date, pan-BET inhibitors have been challenging to administer and monotherapy has generally resulted in only modest anti-tumour activity [14–23].

Although BET inhibitors have been in clinical trials in adults since 2012, the first-in-child study only opened in 2019 [24]. In July 2020, there were at least 10 pan-BET inhibitors in clinical development (a number of others have been discontinued), and the relevant paediatric population is not large enough to accommodate clinical trials of all these BET medicinal products.

The consensus of the broader Paediatric Strategy Forum on epigenetic modifiers was that the future focus should be on BET inhibitors with a broader therapeutic index (facilitating combination treatment strategies), BET inhibitors with improved blood–brain barrier penetrance, and second-generation BET inhibitors with selective inhibition of the BDII bromodomain [2]. The aim of this follow-up meeting dedicated solely to BET inhibitors was to develop further a consensus, between biopharmaceutical companies with publicly recognised BET inhibitor development plans, academic researchers and patient advocates, about the development of BET inhibitors including prioritisation and their specific roles.

The meeting was held virtually over 4 h on 10th July 2020. As an introduction, an overview of the biological rationale for BET inhibitors in paediatric malignancies, relevant pre-clinical data and early clinical studies were presented. This introduction was followed by presentations by invited companies of their adult and paediatric plans, pharmacological and clinical information on nine compounds being developed as BET inhibitors. This provided a basis for a strategic discussion, overall conclusions and final consensus recommendations.

There were 47 participants: 15 academic experts; 20 representatives from eight companies with publicly recognised BET inhibitor development plans (BMS/Celgene, Boehringer Ingelheim, Constellation Pharmaceuticals, AstraZeneca, Incyte, Plexxikon, Developmental Therapeutics Consortium and Abbvie); four patient advocates (Andrew McDonough B+ Positive Foundation, Children's Cancer Cause, Coalition Against Childhood Cancer, Solving Kids' Cancer); six regulators from the FDA and EMA as observers; and two organisers. GlaxoSmithKline was initially intending to participate, but their product (molibresib) has been discontinued. Zenith Epigenetics did not respond to invitations.

2. Paediatric cancer biology relevant to BET inhibitors

NUT carcinoma is considered the prototype of a BET family-driven cancer in which the fusion of *BRD4* or *BRD3* with *NUTM1* yields a *bona fide* oncogenic driver blocking differentiation through activation of *MYC* [4,25–27]. These rare aggressive tumours can arise in children, adolescents and adults. BET inhibitors were first demonstrated to have pre-clinical activity in *BRD4*-rearranged NUT carcinoma [4] and then were shown to downregulate *MYC* and *MYCN* [5]. *MYCN*-amplified neuroblastoma was shown to be highly sensitive *in vitro* and *in vivo* to BET inhibitors, through downregulation of *MYCN* [6] resulting in enhanced survival in these models [6,28]. Furthermore, *MYCN* overexpression partially reversed the effects of a BET inhibitor on growth inhibition [28], and BET inhibition downregulates the expression of *MYCN* target genes in neuroblastoma [7]. However, not all *MYCN*-amplified neuroblastoma models are responsive *in vivo* [29]. BET inhibitor treatment also represses *MYC*/*MYCN* and enhances survival in certain medulloblastoma models [30,31]. In addition, pre-clinical activity has been shown in paediatric Ewing sarcoma [11], osteosarcoma [32], rhabdomyosarcoma [10], diffuse intrinsic pontine glioma [13], Mixed lineage leukemia (MLL)-rearranged leukaemia [12], acute myeloid leukaemia [33] and acute lymphoblastic leukaemia models [34,35]. Based on the molecular driver, some sub-types of acute myeloid leukaemia [36] should be susceptible to BET inhibition [12,37,38]. A report showing that BET inhibition leads to the reversible disruption of the GATA1-dependent transcription of genes that promote erythropoiesis and thrombopoiesis provides an explanation of the thrombocytopenia observed in clinical trials of BET inhibitors [39].

In adult malignancies, there are data for combinations with BET inhibitors in pre-clinical models and the optimal agent may be disease specific [39–41]; however, there are only modest pre-clinical data available to suggest potential combination partners with BET inhibitors in paediatric cancers. There is pre-clinical synergy between BET inhibitors and PI3K inhibitors in

neuroblastoma [42,43] and in some adult tumours [44], and with CDK4/6 inhibitors in medulloblastoma [45].

3. Clinical trials of BET inhibitors in adults

As a result of their mechanism of action, the main downstream targets of BET inhibition are enriched in haematological malignancies. Therefore, BET inhibitors have been evaluated predominantly in myelofibrosis, acute myeloid leukaemia and adult lymphoma [15–23,46–49]. Toxicity, notably thrombocytopenia, has been described in clinical trials, which has been the dose-limiting feature. In myelofibrosis, combinations with ruxolitinib and other JAK Inhibitors are being explored [50,51].

Beyond haematological malignancies, another focus of adult clinical development has been on NUT carcinoma. As described earlier, NUT carcinoma is a very rare, squamous cell carcinoma defined most commonly by rearrangement of the *NUTM1* gene with either the *BRD4* or *BRD3* genes [51–56]. Although the exact incidence is unknown as it is very frequently misdiagnosed, it is estimated that there are approximately 1000 new cases per year in the United States of America; however, the majority are not diagnosed. Biologically, there are no differences in NUT carcinomas occurring in different ages. The malignancy is associated with a very poor prognosis with a 70% mortality rate 1 year from diagnosis, 4% 5-year overall survival and a median survival of 6.5 months [57]. There is no established therapeutic approach, although some success has been achieved using a multimodal approach including early surgical resection and adjuvant chemotherapy and radiotherapy [49–55]. BET inhibitors are active in NUT carcinoma, resulting in a partial response rate of 20–33%, although described responses have often been short-lived with only 10% of patients having responses lasting for longer than 2 months. In a phase I/II trial of molibresib, 19 patients with NUT carcinoma enrolled on the phase I arm [16] with two confirmed partial responses (12%) treated at doses of 60 mg and higher, and there also were two unconfirmed partial responses (confirmed and unconfirmed = 21%). A phase I study of birabresib (previously OTX-015) enrolled nine patients with NUT carcinoma with three partial responses, but only one of which had a response duration exceeding 2 months [15] (Table 1).

4. First-in-child trial of a BET inhibitor

The first dedicated paediatric trial of a BET inhibitor is now actively accruing patients. This trial is evaluating BMS-986158 (NCT03936465) [24]. The primary aims of this trial are to: (i) define paediatric recommended phase II dose of BMS-986158 and (ii) describe toxicities of this agent in a paediatric population. The secondary aims are to: (i) describe the anti-tumour activity of BMS-986158; (ii) describe the pharmacokinetics of BMS-986158 in paediatrics and (iii) evaluate potential pharmacodynamic and predictive biomarkers. The eligibility criteria are age ≤21 years, ability to swallow intact pills, relapsed or refractory solid tumour or lymphoma (central nervous tumours only if biomarker selected). In one cohort, there is a biomarker enrichment strategy for any of the following features, with a novel continual reassessment method design to allow patients with these features to enrol into a separate cohort even if the main dosing cohort is temporarily full: *MYCN* amplification/high copy gain; *MYC* amplification/high copy gain; translocation involving *MYC* or *MYCN; BRD4* amplification; translocation involving *BRD3* or *BRD4;* or histologic diagnosis of NUT carcinoma. The study is rich in embedded correlative biology. The trial opened in June 2019, with an estimated completion of July 2022 and 34 participants anticipated.

Table 1
Phase I clinical trials with BET inhibitors in NUT carcinoma.

	Molibresib (GSK525762) [15]	Birabresib [16] (OTX-015, MK-8628)
n	19	9
CR (%)	0 (0)	0 (0)
PR (%)	4 (21)	3 (33)
SD (%)	7 (36)	3 (33)
PD (%)	4 (21)	2 (22)
NE (%)	3 (16)	1 (11)
AEs in all solid tumours on the trial		
Evaluable patients	65	19
DLT (%)	5 (6)	4 (21)
SAE (%)	31 (48)	7 (35)
G3-4 Thrombocytopenia (N/%)	24 (37)	5 (25)
Median PFS (months)	2.5	1.3

AE, adverse event; BET, bromodomain and extra-terminal; CR, complete response; DLT, dose-limiting toxicity; NE, not evaluable; NUT, nuclear protein in testis; PD, progressive disease; PFS, progression-free survival; PR, partial response; SAE, severe adverse event; SD, stable disease.
*2 unconfirmed.

5. BET inhibitors presented

BMS-986158, CC-90010, BI 894999, CPI-0610, AZD5153, INCB57643, PLX2853 and ABBV-075 (all pan-BET inhibitors), ABBV-744 targeting BDII of the BET family and NEO2734 targeting BET/p300 bromodomain were presented (Table 2).

6. Distinguishing features of BET inhibitors presented

There appeared to be very strong pre-clinical data in NUT carcinoma using NEO2734 as a combined BET and p300/CBP inhibitor to cooperatively deplete *MYC* [58]. There was considerable interest in ABBV-744 as this was the only BDII-selective BET inhibitor presented [59–61]. Pre-clinical data in rats suggest that ABBV-744 could be associated with less thrombocytopenia [59–61] and pre-clinical data of other BDII-selective inhibitors indicate that BDII inhibition could be more effective in *MYC*-driven malignancies [62]. In addition, there was interest in CC-90010 because it has greater central nervous system penetrance [63] and in PLX2853 because of its pharmacokinetics, which may result in less thrombocytopenia.

7. Discussion

The average number of non-synonymous coding mutations in childhood tumours is on average about a hundred-fold lower than in adult malignancies [64,65]. However, as most mutations in paediatric malignancies influence chromatin-associated proteins or transcription, and paediatric cancers are driven by developmental gene expression programs, targeting epigenetic mechanisms, such as inhibition of BET, has the potential to be a very important therapeutic approach in paediatric cancer.

There are many targets relevant to BET inhibitors on the FDA Relevant Paediatric Molecular Targets List [66], including BRD3-NUTM1, BRD4-NUTM1, ETS gene fusion, EWSR1-FLI1, MYC, NFkappaB, NSD3-NUTM1 and PAX-FOXO1. Therefore, the FDA Reauthorization Act of 2017, section 504, which incorporates the Research to Accelerate Cures and Equity (RACE) for Children Act [67], mandates clinical investigation of this class of agents in children unless the required investigations are waived or deferred.

It was agreed that it is not scientifically justified or feasible to undertake simultaneously early clinical trials in paediatrics of all pan-BET inhibitors currently in clinical development.

Table 2
BET inhibitors discussed at the meeting.

	Pan-BET	CNS	Toxicity	Adult development	Paediatric development	Combination	Comments
BMS-986158	√	Low	Thrombocytopenia	Phase I/IIa	Phase I		
CC-90010	√	√	Thrombocytopenia	Phase I			Long half-life
BI-894999	√	No supportive data	Thrombocytopenia	Phase I (focus on NUT carcinoma)	Planned (focus on NUT carcinoma; adolescents)		One paediatric dosage formulation planned
CPI-0610	√	TBD	Thrombocytopenia	Phase I/II (monotherapy and ruxolitinib combination) Phase III − ruxolitinib + CPI-0610 vs ruxolitinib + placebo in myelofibrosis		Ruxolitinib	Wide therapeutic index
AZD5153	√	Low	Thrombocytopenia	Phase I/II	? AML	Olaparib Venetoclax	Unique bivalent binding mode
INCB57643	√		Thrombocytopenia	Phase I myelofibrosis			
PLX2853	√	No	Less thrombocytopenia	Phase Ib/IIa	Planned		Very interesting pharmacokinetics high maximum serum concentration but with short half-life
NEO2734	BET/p300 bromodomain			About to enter clinical development			Promising pre-clinical data in NUT carcinoma
ABBV-075	√	No data	Thrombocytopenia	Phase I → Phase I myelofibrosis			
ABBV-744	BDII	No data	Pre-clinical Less thrombocytopenia	Phase I AML → phase I myelofibrosis			

CNS—CNS penetration.
AML, acute myelogenous leukaemia; BET, bromodomain and extra-terminal; CNS, central nervous system; NUT, nuclear protein in testis; TBD, To be determined.

Pan-BET inhibitors have been under investigation in clinical trials in adults since 2012 and have been challenging to administer in adults. Monotherapy has resulted in modest anti-tumour activity, and there appears to be a narrow therapeutic index due to thrombocytopenia. It was agreed that there is a disconnect between the *in vitro* activity of BET inhibitors and their clinical activity in adults. The pre-clinical *in vivo* activity observed has most commonly, but not exclusively [41], been a slowing of tumour growth without tumour regression, mirroring but not exclusively [41], the clinical findings for most adult cancers against which BET inhibitors have been evaluated. Dating from 2010, there is a strong pre-clinical evidence of activity in NUT carcinoma [4], *MYCN, MYC* and fusion-driven malignancies (in most studies), which was first published in 2013 [6]. Therefore, this drug class remains of broad interest for evaluation in a range of paediatric cancers.

There is a clear genomic rationale for evaluating BET inhibitors in NUT carcinoma, as these drugs target the initiating fusion and the clinical need is great. In view of these features, it was agreed that clinical development of BET inhibitors for NUT carcinomas needs to be considered separately from development in other diseases impacting children. Owing to the rarity of these tumours and the fact that BET inhibitors have antitumor activity in patients with NUT carcinoma, there is a need for a global approach and access to this class of compounds. The development and regulatory pathway for NUT carcinomas should include children, adolescents and adults, with clinical trials designed to identify ways to increase the proportion of patients responding to BET inhibitors and increasing the duration of response among responding patients. To achieve the goal children, adolescents and adults should be included in the pivotal registration studies, augmented through extrapolation and pharmacokinetic modelled dosing.

Data from the first paediatric trial of a BET inhibitor, BMS-986158, will be highly informative as 'proof of concept' in tumours beyond NUT carcinoma, and this trial should clarify the role of pan-BET inhibitors in children. Moreover, the clinical experience should yield important information as to whether a clinically meaningful biological effect can be achieved despite thrombocytopenia as a common toxicity of this drug class. If a patient population can be identified in which clinical activity is observed, then further development of pan-BET inhibitors in this group can be planned, including development of a paediatric appropriate formulation. In the future, the potential evaluation of BET inhibitors together with thrombopoietin mimetics (e.g. romiplostim) can be considered to overcome the dose-limiting toxicity of thrombocytopenia and potentially improve the therapeutic window of these agents. However, as a prelude to clinical evaluation of this combination, extensive pre-clinical research will be required.

It was proposed that further clinical development of other pan-BET inhibitors in children, apart from those with NUT carcinoma, should be postponed until the early results of the paediatric clinical trial of BMS-986158 are known, unless there is compelling rationale based on the specific agent of interest. This proposal is based on the adult experience of BET inhibitors for which there are substantial pre-clinical data indicating *in vitro* and *in vivo* activity in a range of adult malignancies, which has not yet translated to clinical activity, with the exception of myelofibrosis, some advanced sarcomas and diffuse large B-cell lymphomas. The preliminary results of the BMS-986158 trial will first be required to demonstrate proof of concept that pan-BET inhibitors can be effective in *MYC*/*MYCN*-driven tumours. The trial design allows enrichment for patients with *MYC*/*MYCN*-amplified tumours.

Further pre-clinical evaluation of BDII-selective inhibitors, BET/p300 bromodomain dual inhibitors (e.g. NEO2734) and PLX2853 should be prioritised in view of their promising pre-clinical data [68,69] and if confirmed, early clinical studies prioritised. There is an unmet need for clinically active BET inhibitors in central nervous system tumours driven by *MYC*/*MYCN*, and there is interest in further paediatric evaluation of BET inhibitors with improved central nervous system penetrance such as CC-90010.

The clinical evaluation of combinations including BET inhibitors should be based on a strong biological rationale and robust pre-clinical studies, especially since thrombocytopenia has to date appeared to be a key dose-limiting toxicity and appears to be an on-target class effect of BET inhibitors [38]. Understanding how BET inhibitors and other epigenetic modifiers might impact expression of other therapeutic targets may indicate potential novel combinations to evaluate in paediatrics. Attention should be paid to avoid drug combinations where the second agent also has thrombocytopenia as a significant overlapping toxicity.

The general proposed regulatory strategy, where there are multiple products of the same class, is that there is a consolidated agreement by all involved (industry and academia) regarding which product, based on current evidence, is considered to have the highest potential to address unmet medical needs. This product should then be advanced into paediatric development and submitted for regulatory approval, without delay (i.e. without a deferral). Part of this prioritisation discussion, however, also includes the need to decide on the sequence in which (any) other available (or emerging) products should be developed in reference to the one decided to move forward into development. This should be based on scientific arguments. The development of these products should be deferred in sequence and in dependency, so that as soon as a development is completed (either due to futility or efficacy) others are already prepared for evaluation. Such consolidated

prioritisation strategies allow fulfilment of the respective regulatory requirements, improves efficiency and is of benefit to children with malignancy. Any remaining level of uncertainty can be managed through modifications which might be needed to contextualise subsequent development relative to any emerging evidence.

Regulators only participated as observers and no regulatory decisions were made at the meeting. However, it was highlighted that early interactions with regulatory agencies (e.g. through the request of Paediatric Investigation Plan (PIP) and initial Paediatric Study Plan (iPSP) pre-submission meetings), concurrent submission of individual PIPs and iPSPs to the EMA/Paediatric Commitee (PDCO) and FDA, respectively, including importantly a request for discussion at cluster calls [70].

The patient advocates emphasised the critical value of considering the needs of children and adolescents early in the drug development process. For the 126 agents first approved by the FDA for any oncology indication from 1997 to 2017, there was an unacceptable delay (median 6.5 years) from the initiation of first-in-human trials to the start of the first-in-child trial [71]. BET inhibitors clearly exemplify this issue as the first clinical trial of a BET inhibitor in adults opened in 2012; however, the first-in-child study opened in 2019, 7 years later. This delay occurred despite a strong mechanistic rationale and pre-clinical evidence for the activity of BET inhibitors in paediatric malignancies.

In the future, when there is strong pre-clinical evidence for the activity of a class of medicinal product, or when there is strong mechanistic rationale [72], but uncertainty about the potential utility in paediatrics, early clinical evaluation, with detailed embedded correlative biology of a member of the class in paediatrics, should be prioritised and rapidly executed. To achieve this goal, there should be measures to facilitate and incentivise paediatric anticancer drug development: there are opportunities for this to occur in Europe with the European Commission current evaluation of the EU Paediatric and Orphan Regulations [73] and the new EU Pharmaceutical Strategy [74].

This meeting emphasised the value of a coordinated and integrated strategy to drug development in paediatric malignancy. An approach with multiple companies developing a consensus with clinicians, based on strong scientific rationale and/or proof of principle, early in the development of a class of compound, and then engaging regulatory agencies would improve efficiency, productivity conserve resources and benefit children with cancer.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as

Box 1. Key conclusions of the meeting.

- Based on biology and pre-clinical data, BET inhibitors have at least three potential roles in paediatrics: nuclear protein in testis (NUT) carcinomas, MYC/MYCN-driven malignancies and fusion-driven cancers.
- Although BET inhibitors have been in clinical trials in adults since 2012, the first-in-child study (BMS-986158) only opened in 2019.
- As many targets relevant to BET inhibitors are on the FDA Paediatric Molecular Targets List, clinical investigation of this class is mandated unless the required investigations are waived or deferred.
- As there are at least 10 BET inhibitors in development with a limited relevant paediatric population in which to evaluate these medicinal products, prioritisation is required. It was concluded that it is not scientifically justified or feasible to undertake simultaneously early clinical trials in paediatrics of all pan-BET inhibitors.
- There is a strong mechanistic and biological rationale to evaluate BET inhibitors in paediatrics, underpinned by substantial, but not universal, pre-clinical data. However, pan-BET inhibitors have been challenging to administer in adults, monotherapy has resulted in modest anti-tumour activity, and there may be a relatively narrow therapeutic index due to thrombocytopenia.
- There is a very clear biological rationale for BET inhibitors in NUT carcinoma, and there is a clinical need for global access to BET inhibitors for patients with this malignancy. Development and regulatory pathway should include children, adolescents and adults.
- Further clinical development of other pan-BET inhibitors in children with tumours other than NUT carcinoma should be postponed until the results of the paediatric clinical trial of BMS-986158 are known, unless there is compelling rationale based on the specific agent of interest.
- BDII-selective medicinal products and those targeting BET/p300 bromodomain are of interest and warrant further pre-clinical investigation.
- The clinical evaluation of combinations including BET inhibitors should be based on a strong biological rationale and robust pre-clinical studies.
- Understanding how BET inhibitors and other epigenetic modifiers might impact expression of other therapeutic targets may indicate potential novel combinations to evaluate in paediatrics.
- When there is strong mechanistic rationale or pre-clinical evidence for the activity of a class of medicinal product, early clinical evaluation, with embedded correlative biology of a member of the class in paediatrics should be prioritised and rapidly executed.
- A coordinated and integrated approach to paediatric cancer drug development is of great value. A multi-stakeholder approach with multiple companies developing a consensus with clinicians early in the development of a class of compound and then engaging regulatory agencies in a consolidated effort would improve efficiency, productivity, conserve resources and benefit children with cancer.

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being made on behalf of, or reflecting the position of, the agencies or organisations with which the authors are affiliated.

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Conflict of interest statement

KS has consulted for Kronos Bio and Auron Therapeutics, receives grant funding from Novartis for an unrelated project, holds stock options with Auron Therapeutics, and has given a sponsored presentation for Bristol Meyers Squibb. MK is an employee of Bristol Myers Squibb. KB is an employee of AbbVie. EG is an employee of Boehringer Ingelheim Pharma GmbH & Co KG. FG has consulted for Epigene Therapeutics. MH is an employee of Astra-Zeneca. KL is an employee of Constellation Pharmaceuticals. ZN is an employee of Celgene/Bristol Myers Squibb. AT is an employee of Plexxikon. FZ is an employee of Incyte. ADJP has participated in advisory boards for Novartis, Takeda, Merck, Lilly and Celgene. SGD has received fees for consulting and advisory board roles from Bayer and Loxo Oncology and has received travel expenses from Loxo Oncology, Roche/Genentech, and Salarius Pharmaceuticals. All remaining authors have declared no conflicts of interest.

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References

[1] Vassal G, Rousseau R, Blanc P, Moreno L, Bode G, Schwoch S, et al. Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. Eur J Cancer 2015;51:218–24.

[2] Pearson AD, Stegmaier K, Bourdeaut F, Reaman G, Heenen D, Meyers ML, et al. Paediatric Strategy Forum for medicinal product development of epigenetic modifiers for children: ACCELERATE in collaboration with the European Medicines Agency with participation of the Food and Drug Administration. Eur J Cancer 2020;139:135–48.

[3] Loven J, Hoke HA, Lin CY, Lau A, Orlando DA, Vakoc CR, et al. Selective inhibition of tumor oncogenes by disruption of super-enhancers. Cell 2013;153:320–34.

[4] Filippakopoulos P, Qi J, Picaud S, Shen Y, Smith WB, Fedorov O, et al. Selective inhibition of BET bromodomains. Nature 2010;468:1067–73.

[5] Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, Jacobs HM, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 2011;146:904–17.

[6] Puissant A, Frumm SM, Alexe G, Bassil CF, Qi J, Chanthery YH, et al. Targeting MYCN in neuroblastoma by BET bromodomain inhibition. Cancer Discov 2013;3:308–23.

[7] Henssen A, Althoff K, Odersky A, Beckers A, Koche R, Speleman F, et al. Targeting MYCN-driven transcription by BET-bromodomain inhibition. Clin Cancer Res 2016;22:2470–81.
[8] Mertz JA, Conery AR, Bryant BM, Sandy P, Balasubramanian S, Mele DA, et al. Targeting MYC dependence in cancer by inhibiting BET bromodomains. Proc Natl Acad Sci U S A 2011;108:16669–74.
[9] Gollavilli PN, Pawar A, Wilder-Romans K, Natesan R, Engelke CG, Dommeti VL, et al. EWS/ETS-Driven ewing sarcoma requires BET bromodomain proteins. Cancer Res 2018;78:4760–73.
[10] Gryder BE, Yohe ME, Chou H-C, Zhang X, Marques J, Wachtel M, et al. PAX3-FOXO1 establishes myogenic super enhancers and confers BET bromodomain vulnerability. Cancer Discov 2017;7:884–99.
[11] Hensel T, Giorgi C, Schmidt O, Calzada-Wack J, Neff F, Buch T, et al. Targeting the EWS-ETS transcriptional program by BET bromodomain inhibition in Ewing sarcoma. Oncotarget 2016;7:1451–63.
[12] Dawson MA, Prinjha RK, Dittmann A, Giotopoulos G, Bantscheff M, Chan WI, et al. Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. Nature 2011;478:529–33.
[13] Piunti A, HashizumeR, Morgan MA, Bartom ET, Horbinski CM, Marshall SA, et al. Therapeutic targeting of polycomb and BET bromodomain proteins in diffuse intrinsic pontine gliomas. Nat Med 2017;23:493–500.
[14] Martin-Romano P, Baldini C, Postel-Vinay S. How much can we bet on activity of BET inhibitors beyond NUT-midline carcinoma? JNCI Cancer Spectr 2019;4:pkz092. https://doi.org/10.1093/jncics/pkz092.
[15] Piha-Paul SA, Hann CL, French CA, Cousin S, Braña I, Cassier PA, et al. Phase 1 study of molibresib (GSK525762), a bromodomain and extra-terminal domain protein inhibitor, in NUT carcinoma and other solid tumors. JNCI Cancer Spectr 2019;4:pkz093.
[16] Lewin J, Soria JC, Stathis A, Delord JP, Peters S, Awada A, et al. Ib trial with birabresib, a small-molecule inhibitor of bromodomain and extraterminal proteins, in patients with selected advanced solid tumors. J Clin Oncol 2018;36:3007–14.
[17] Patnaik A, Carvajal RD, Komatsubara KM, Britten CD, Wesolowski R, Michelson M, et al. Phase Ib/2a study of PLX51107, a small molecule BET inhibitor, in subjects with advanced hematological malignancies and solid tumors. J Clin Oncol 2018;36 (suppl; abstr 2550).
[18] Falchook G, Rosen S, LoRusso P, et al. Development of 2 Bromodomain and Extraterminal inhibitors with distinct pharmacokinetic and pharmacodynamic profiles for the treatment of advanced malignancies. Clin Cancer Res 2019;26:1247–57.
[19] Aftimos PG, Aftimos P, Awada A, et al. Phase I dose-finding study of a novel bromodomain and extra-terminal domain (BET) inhibitor (BI 894999) in patients with advanced malignancies. In: ENA annual meeting; 2018.
[20] Hilton J, Cristea MC, Voskoboynik M, et al. Initial results from a phase I/IIa trial evaluating BMS-986158, an inhibitor of the bromodomain and extra-terminal (BET) proteins, in patients with advanced cancer. Ann Oncol 2018;29. viii134.
[21] Postel-Vinay S, Herbschleb K, Massard C, et al. First-in-human phase I study of the bromodomain and extraterminal motif inhibitor BAY 1238097: emerging pharmacokinetic/pharmacodynamic relationship and early termination due to unexpected toxicity. Eur J Cancer 2019;109:103–10.
[22] Stathis A, Zucca E, Bekradda M, et al. Clinical response of carcinomas harbouring the BRD4-NUT oncoprotein to the targeted bromodomain inhibitor OTX015/MK-8628. Cancer Discov 2016;6:492–500.
[23] Amorim S, Stathis A, Gleeson M, et al. Bromodomain inhibitor OTX015 in patients with lymphoma or multiple myeloma: a dose-escalation, open-label, pharmacokinetic, phase 1 study. Lancet Haematol 2016;3:e196–204.
[24] https://clinicaltrials.gov/ct2/show/NCT03936465.
[25] Grayson AR, Walsh EM, Cameron MJ, Godec J, Ashworth T, Ambrose ME, et al. MYC, a downstream target of BRD-NUT, is necessary and sufficient for the blockade of differentiation in NUT midline carcinoma. Oncogene 2014;33:1736–42.
[26] Alekseyenko AA, Walsh EM, Wang X, Grayson AR, Hsi PT, Kharchenko PV, et al. The oncogenic BRD4-NUT chromatin regulator drives aberrant transcription within large topological domains. Genes Dev 2015;29:1507–23.
[27] French CA, Ramirez CL, Kolmakova J, Hickman TT, Cameron MJ, Thyne ME, et al. BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells. Oncogene 2008;27:2237–42.
[28] Wyce A, Ganji G, Smitheman KN, Chung CW, Korenchuk S, Bai Y, et al. BET inhibition silences expression of MYCN and BCL2 and induces cytotoxicity in neuroblastoma tumor models. PloS One 2013;8:e72967.
[29] Healy JR, Hart LS, Shazad AL, Gagliardi ME, Tsang M, Elias J, et al. Limited antitumor activity of combined BET and MEK inhibition in neuroblastoma. Pediatr Blood Cancer 2020;67:e28267. https://doi.org/10.1002/pbc.28267.
[30] Bandopadhayay P, Bergthold G, Nguyen B, Schubert S, Gholamin S, Tang Y, et al. BET bromodomain inhibition of MYC-amplified medulloblastoma. Clin Cancer Res 2014;20:912–25.
[31] Henssen A, Thor T, Odersky A, Heukamp L, El-Hindy N, Beckers A, et al. BET bromodomain protein inhibition is a therapeutic option for medulloblastoma. Oncotarget 2013;4:2080–95.
[32] Shi C, Zhang H, Wang P, Wang K, Xu D, Wang H, et al. PROTAC induced-BET protein degradation exhibits potent anti-osteosarcoma activity by triggering apoptosis. Cell Death Dis 2019;10:815. https://doi.org/10.1038/s41419-019-2022-2.
[33] Da Costa D, Agathanggelou A, Perry T, Weston V, Petermann E. Zlatanou A et alBET inhibition as a single or combined therapeutic approach in primary paediatric B-precursor acute lymphoblastic leukaemia. Blood Cancer J 2013;3:e126. https://doi.org/10.1038/bcj.2013.
[34] Rhyasen GW, Hattersley MM, Yao Y, Dulak A, Wang W, Petteruti P, et al. AZD5153: a novel Bivalent BET bromodomain inhibitor highly active against hematologic malignancies. Mol Cancer Ther 2016;15:2563–74.
[35] Massé A, Roulin L, Pasanisi J, Penneroux J, Gachet S, Delord M, et al. BET inhibitors impair leukemic stem cell function only in defined oncogenic subgroups of acute myeloid leukaemias. Leuk Res 2019;87:106269. https://doi.org/10.1016/j.leukres.2019.106269.
[36] Dawson MA, Gudgin EJ, Horton SJ, Giotopoulos G, Meduri E, Robson S, et al. Recurrent mutations, including NPM1c, activate a BRD4-dependent core transcriptional program in acute myeloid leukemia. Leukemia 2014;28:311–20.
[37] Braun T, Gardin C. Investigational BET bromodomain protein inhibitors in early stage clinical trials for acute myelogenous leukemia (AML). Expert Opin Investig Drugs 2017;26:803–11.
[38] Zhang C, Xu K, Panzica-Kelly J, Price J, Bounous D, Coker S, et al. Inhibition of BET signaling leads to reversible GATA1-associated repression of hematopoietic progenitors: translation from preclinical assessment to clinical development. Cancer Res 2020;80(16 Suppl). Abstract 1742.
[39] Ramadoss M, Mahadevan V. Targeting the cancer epigenome: synergistic therapy with bromodomain inhibitors. Drug Discov Today 2018;23:76–89.

[40] Stathis A, Bertoni F. BET proteins as targets for anticancer cancer treatment. Cancer Discov 2018;8:24–36.
[41] Moreno V, Braña I, Sepulveda JM, Vieito M, Hernández-GuerreroM, Doger B, et al. CC-90010, a reversible, oral bromodomain and extra-terminal (BET) inhibitor in patients with advanced solid tumors and relapsed/refractory non-Hodgkin lymphoma: updated results of a phase 1 study. In: ESMO conference 2020 Sept; 2020. Madrid, Spain Presentation Number 3052.
[42] Iniguez AB, Alexe G, Wang EJ, Roti G, Patel S, Chen L, et al. Resistance to epigenetic-targeted therapy engenders tumor cell vulnerabilities associated with enhancer remodeling. Cancer Cell 2018;34:922–38.
[43] Claeys S, Denecker G, Durinck K, Decaesteker B, Mus LM, Loontiens S, et al. ALK positively regulates MYCN activity through repression of HBP1 expression. Oncogene 2019;38:2690–705.
[44] Stratikopoulos EE, Dendy M, Szabolcs M, Khaykin AJ, Lefebvre C, Zhou M-M, et al. Kinase and BET inhibitors together clamp inhibition of PI3K signaling and overcome resistance to therapy. Cancer Cell 2015;27:837–51.
[45] Bandopadhayay P, Piccioni F, O'Rourke R, Ho P, Gonzalez EM, Buchan G, et al. Neuronal differentiation and cell-cycle programs mediate response to BET-bromodomain inhibition in MYC-driven medulloblastoma. Nat Commun 2019;10:2400. https://doi.org/10.1038/s41467-019-10307-9.
[46] Ameratunga M, Braña I, Bono P, Postel-Vinay S, Plummer R, Aspegren J, et al. First-in-human Phase 1 open label study of the BET inhibitor ODM-207 in patients with selected solid tumours. Br J Cancer 2020. https://doi.org/10.1038/s41416-020-01077-z.
[47] Piha-Paul SA, Sachdev JC, Barve M, LoRusso P, Szmulewitz R, Patel SP, et al. First-in-Human study of Mivebresib (ABBV-075), an oral pan-inhibitor of bromodomain and extra terminal proteins, in patients with relapsed/refractory solid tumors. Clin Cancer Res 2019;25:6309–19.
[48] Berthon C, Raffoux E, Thomas X, Vey N, Gomez-Roca C, Yee K, et al. Bromodomain inhibitor OTX015 in patients with acute leukaemia: a dose-escalation, phase 1 study. Lancet Haematol 2016;3:e186–95.
[49] Odore E, Lokiec F, Cvitkovic E, Bekradda M, Herait P, Bourdel F, et al. Phase I population pharmacokinetic assessment of the oral bromodomain inhibitor OTX015 in patients with haematologic malignancies. Clin Pharmacokinet 2016;55:397–405.
[50] Verstovsek S, MesaRA, Gotlib M, Levy RS, Gupta V, DiPersio JF, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366:799–807.
[51] Kleppe M, Koche R, Zou L, van Galen P, Hill CE, Dong L, et al. Dual targeting of oncogenic activation and inflammatory signaling increases therapeutic efficacy in myeloproliferative neoplasms. Cancer Cell 2018;33:785–7.
[52] French CA, Miyoshi I, Kubonishi I, Grier HE, Perez-Atayde AR, Fletcher JA. BRD4-NUT fusion oncogene: a novel mechanism in aggressive carcinoma. Cancer Res 2003;63:304–7.
[53] French CA, Kutok JL, Faquin WC, et al. Midline carcinoma of children and young adults with NUT rearrangement. J Clin Oncol 2004;22:4135–9.
[54] French CA, Ramirez CL, Kolmakova J, et al. BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells. Oncogene 2008;27:2237–42.
[55] French C. NUT midline carcinoma. Nat Rev Cancer 2014;14:149–50.
[56] French CA. NUT carcinoma: clinicopathologic features, pathogenesis, and treatment. Pathol Int 2018;68:583–95.
[57] Chau NG, Ma C, Danga K, Al-Sayegh H, Nardi V, Barrette R, et al. An anatomical site and genetic-based prognostic model for patients with nuclear protein in testis (NUT) midline carcinoma: analysis of 124 patients. JNCI Cancer Spectr 2019;4(2):pkz094.
[58] Morrison-Smith CD, Knox TM, Filic I, Soroko KM, Eschle BK, Wilkens MK, et al. Combined targeting of the BRD4-NUT-p300 Axis in NUT midline carcinoma by dual selective bromodomain inhibitor, NEO2734. Mol Cancer Ther 2020;19:1406–14.
[59] Sheppard GS, Wang L, Fidanze SD, Hasvold LA, Liu D, Pratt JK, et al. Discovery of N-Ethyl-4-[2-(4-fluoro-2,6-dimethylphenoxy)-5-(1-hydroxy-1-methyl-ethyl)phenyl]-6-methyl-7-oxo-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (ABBV-744), a BET bromodomain inhibitor with selectivity for the second bromodomain. J Med Chem 2020;63:5585–623.
[60] Chen J, Li Y, Zhang J, Zhang M, Wei A, Liu H, et al. Discovery of selective HDAC/BRD4 dual inhibitors as epigenetic probes. Eur J Med Chem 2020:112868. https://doi.org/10.1016/j.ejmech.2020.112868.
[61] Faivre EJ, McDaniel KF, Albert DH, Mantena SR, Plotnik JP, Wilcox D, et al. Selective inhibition of the BD2 bromodomain of BET proteins in prostate cancer. Nature 2020;578:306–10.
[62] Slavish PJ, Chi L, Yun MK, Tsurkan L, Martinez NE, Jonchere B, et al. Bromodomain-selective BET inhibitors are potent antitumor agents against MYC-driven pediatric cancer. Cancer Res 2020;80:3507–18.
[63] Moreno V, Sepulveda JM, Vieito M, Hernández-Guerrero T, Doger B, Saavedra O, et al. Phase I study of CC-90010, a reversible, oral BET inhibitor in patients with advanced solid tumors and relapsed/refractory non-Hodgkin's lymphoma. Ann Oncol 2020. https://doi.org/10.1016/j.annonc.2020.03.294. S0923-S7534(20)36381-X.
[64] Grobner SN, Worst BC, Weischenfeldt J, Buchhalter I, Kleinheinz K, RudnevaVA, et al. The landscape of genomic alterations across childhood cancers. Nature 2018;555:321e7.
[65] Ma X, Liu Y, Liu Y, Alexandrov LB, Edmonson MN, Gawad C, et al. Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. Nature 2018;555:371e6.
[66] https://www.fda.gov/media/120331/download.
[67] https://www.congress.gov/115/plaws/publ52/PLAW-115publ52.pd (Accessed 13 November 2020).
[68] Spriano F, Gaudio E, Cascione L, Tarantelli C, Melle F, Motta G, et al. Antitumor activity of the dual BET and CBP/EP300 inhibitor NEO2734. Blood Adv 2020;4:4124–35.
[69] Yan Y, Ma J, Wang D, Lin D, Pang X, Wang S, et al. The novel BET-CBP/p300 dual inhibitor NEO2734 is active in SPOP mutant and wild-type prostate cancer. EMBO Mol Med 2019;11:e10659.
[70] Reaman G, Karres D, Ligas F, Lesa G, Casey D, Ehrlich L, et al. Accelerating the global development of pediatric cancer drugs: a call to coordinate the submissions of pediatric investigation plans and pediatric study plans to the European Medicines Agency and US Food and Drug Administration. J Clin Oncol 2020;38:4227–30.
[71] Neel DV, Shulman DS, DuBois SG. Timing of first-in-child trials of FDA-approved oncology drugs. Eur J Cancer 2019;112:49–56.
[72] Pearson ADJ, Pfister SM, Baruchel A, Bourquin JP, Casanova M, Chesler L, et al. From class waivers to precision medicine in paediatric oncology. Lancet Oncol 2017;18:30442–4.
[73] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Revision-of-the-EU-legislation-on-medicines-for-children-and-rare-diseases.
[74] https://ec.europa.eu/health/human-use/strategy_en.