European Journal of Cancer 127 (2020) 52–66

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

ACCELERATE and European Medicines Agency Paediatric Strategy Forum for medicinal product development of checkpoint inhibitors for use in combination therapy in paediatric patients

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https://doi.org/10.1016/j.ejca.2019.12.029

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Received 17 December 2019; accepted 23 December 2019
Available online 24 January 2020

KEYWORDS
Paediatric oncology;
Immune checkpoint inhibitors;
Medicinal product development

Abstract The third multistakeholder Paediatric Strategy Forum organised by ACCELERATE and the European Medicines Agency focused on immune checkpoint inhibitors for use in combination therapy in children and adolescents. As immune checkpoint inhibitors, both as monotherapy and in combinations have shown impressive success in some adult malignancies and early phase trials in children of single agent checkpoint inhibitors have now been completed, it seemed an appropriate time to consider opportunities for paediatric studies of checkpoint inhibitors used in combination.

Among paediatric patients, early clinical studies of checkpoint inhibitors used as monotherapy have demonstrated a high rate of activity, including complete responses, in Hodgkin lymphoma and hypermutant paediatric tumours. Activity has been very limited, however, in more common malignancies of childhood and adolescence. Furthermore, apart from tumour mutational burden, no other predictive biomarker for monotherapy activity in paediatric tumours has been identified. Based on these observations, there is collective agreement that there is no scientific rationale for children to be enrolled in new monotherapy trials of additional checkpoint inhibitors with the *same* mechanism of action of agents already studied (e.g. anti-PD1, anti-PDL1 anti-CTLA-4) unless additional scientific knowledge supporting a different approach becomes available. This shared perspective, based on scientific evidence and supported by paediatric oncology cooperative groups, should inform companies on whether a paediatric development plan is justified. This could then be proposed to regulators through the available regulatory tools. Generally, an academic-industry consensus on the scientific merits of a proposal before submission of a paediatric investigational plan would be of great benefit to determine which studies have the highest probability of generating new insights.

There is already a rationale for the evaluation of combinations of checkpoint inhibitors with other agents in paediatric Hodgkin lymphoma and hypermutated tumours in view of the activity shown as single agents. In paediatric tumours where no single agent activity has been observed in multiple clinical trials of anti-PD1, anti-PDL1 and anti-CTLA-4 agents as monotherapy, combinations of checkpoint inhibitors with other treatment modalities should be explored when a scientific rationale indicates that they could be efficacious in paediatric cancers and not because these combinations are being evaluated in adults.

Immunotherapy in the form of engineered proteins (e.g. monoclonal antibodies and T cell engaging agents) and cellular products (e.g. CAR T cells) has great therapeutic potential for benefit in paediatric cancer. The major challenge for developing checkpoint inhibitors for paediatric cancers is the lack of neoantigens (based on mutations) and corresponding antigen-specific T cells. Progress critically depends on understanding the immune macroenvironment and microenvironment and the ability of the adaptive immune system to recognise paediatric cancers in the absence of high neoantigen burden. Future clinical studies of checkpoint inhibitors in children need to build upon strong biological hypotheses that take into account the distinctive immunobiology of childhood cancers in comparison to that of checkpoint inhibitor responsive adult cancers.

1. Introduction

The third multistakeholder Paediatric Strategy Forum held in September 2018 and jointly organised by ACCELERATE [1] and the European Medicines Agency (EMA) focused on checkpoint inhibitors used in combination therapy in children and adolescents. Paediatric Strategy Forums have been created to evaluate science, facilitate dialogue and provide an opportunity for constructive interactions between relevant stakeholders (patients/patient advocates, clinicians, academics, biotechnology/pharmaceutical companies and regulators) on specific topics requiring open discussion on development of medicines in the best interests of children and adolescents with cancer [2]. The goal of this Forum was to share information and to facilitate the development of innovative medicines.

The first two Paediatric Strategy Forums held in January and November 2017 focused on medicinal product development for anaplastic lymphoma kinase inhibition and mature B-cell malignancies, respectively [3,4].

Immune checkpoint inhibitors have shown impressive success in some adult malignancies, in particular, monoclonal antibodies that block the interaction between programmed death ligand 1 (PD-L1) on the surface of tumour or antigen-presenting cells and programmed death 1 (PD-1) on the surface of lymphocytes [5–7]. Many of these products have now been licensed as first or second-line treatments for adult malignancies. Furthermore, the combination of antibodies targeting PD-1 with those targeting the immune checkpoint molecule CTLA-4 has shown particularly high response rates in adult patients with several malignancies, including metastatic melanoma [8]. In addition, the combination of PD1 inhibitors with chemotherapy for first-line therapy of non–small-cell lung cancer has been a notable success [9–11]. Early phase trials of single agent checkpoint inhibitors in children have now been completed [12–14] and antitumour responses have been observed in some cancers common to children and adults, for example in Hodgkin lymphoma and hypermutated tumours in the context of Constitutional Mismatch Repair Deficiency (CMMRD) [15]. However, these results appear not to be reflected in typical paediatric malignancies such as neuroblastoma and rhabdomyosarcoma. Some combination studies are in progress, and others are planned. It therefore seemed opportune to review the results of these early phase trials in children and consider opportunities for paediatric studies in which checkpoint inhibitors are used in combination with other medicinal products, including also possible other approaches (e.g. radiotherapy, chemotherapy and targeted therapies).

2. Format of the Paediatric Strategy Forum

The Paediatric Strategy Forum was held over 2 days at the EMA, with an emphasis on facilitating discussion amongst the participants. The Forum was structured so that there was first an overview by academic experts on the present understanding of the immunological environment and immunotherapeutic challenges of paediatric malignancy and on the available strategies to combine checkpoint inhibitors with other treatment modalities and alternative immunotherapies. This was followed by a review of paediatric investigation plans (PIPs) of checkpoint inhibitors, and then, the results of the completed early phase trials of single agent checkpoint inhibitors in children were presented and formed a basis for a discussion of the implications of these trials and the way forward in hypermutated tumours, Hodgkin lymphoma, primary mediastinal B cell lymphoma and anaplastic lymphoma kinase–positive anaplastic large cell lymphoma. This gave context to the subsequent presentation by pharmaceutical companies of open or planned trials of checkpoint inhibitors in combination; these were grouped by the mechanism of action of the drugs. Finally, overall conclusions were made by all participants.

The Forum was advertised, and expressions of interest were sought from the pharmaceutical industry (if

they wished to present data on relevant medicinal products, a condition for their participation), academic clinicians and patient advocates.

There were 75 participants present and an additional 25 joined by remote access, including European and North American experts in immunotherapy and drug development in children; representatives from 16 pharmaceutical companies (chosen from 32 submitted expressions of interest); patient advocates (from Unite2Cure, Imagine for Margo and Children's Cause for Cancer Advocacy); regulators from EU national competent authorities, the EMA (including Paediatric Committee), Committee for Medicinal Products for Human Use and Scientific Advice Working Party members and the US Food and Drug Administration (FDA).

Key conclusions of the Paediatric Strategy Forum

- High rate of activity of monotherapy checkpoint inhibitors, including complete responses, in Hodgkin lymphoma and hypermutant tumours.
- Very limited activity of checkpoint inhibitors as single agents in other paediatric tumours (overall response rate−2.8% with Hodgkin's lymphoma excluded).
- Except for hypermutation, there is no other predictive biomarker.
- There is no benefit to children to be included in new monotherapy trials of other checkpoint inhibitors with the *same* mechanism of action unless there is more scientific knowledge.
- In the European Union, product-specific waivers may be proposed when supported by oncology paediatric cooperative groups on the basis of robust scientific evidence, using the appropriate regulatory tools.
- Academic-industry consensus on the scientific merits of a proposal before submission of a paediatric investigation plan would be of great benefit to regulators.
- In view of the activity shown as single agents, combinations of checkpoint inhibitors with other agents should be evaluated in lymphomas and hypermutated tumours.
- In immunologically 'cold' childhood cancers, there appears to be a lack of neoantigens and naturally occurring tumour-reactive effector lymphocytes.
- Synthetic immunotherapy (e.g. CAR T cells and engineered antibody-based proteins) may be an effective combination with an immune checkpoint agent in some paediatric cancers.
- In paediatric tumours where there is no single agent activity, combinations of checkpoint inhibitors with other treatment modalities could be explored based on *hypotheses, preclinical evidence and scientific data relevant to paediatric cancers with their low neoantigen burden and not only because these combinations are being evaluated in adults.*
- There is a critical need for enhanced understanding of the immune microenvironment and immune subtypes for paediatric cancers and also for enhanced understanding of the ability of the adaptive immune system to recognise paediatric cancers in the absence of high neoantigen burden.
- Substantial benefits of conducting academic sponsored exploratory proof-of-concept protocols with adaptive design including drugs from multiple companies which can generate data on which further studies can be based. These trials should be designed with 'intent to file', i.e. with the potential to provide data of a quality suitable to support licensing procedures, with early input from regulators.

3. Immunological environment and immunotherapeutic challenges of paediatric malignancy

Immune checkpoint blockade acts primarily by invigoration of preexisting cytolytic T cells with native specificity for tumour-associated antigens in the tumour microenvironment. Broadly, the function of PD-1 checkpoint inhibitors depends on (i) availability of actionable tumour-associated (neo) antigens, (ii) endogenous T cell infiltrate and (iii) PD-L1/PD-1 expression [16–18]. Some tumours in adults have multiple non-synonymous somatic mutations which may give rise to aberrant proteins that can be recognised by the immune system; in contrast, the majority of paediatric tumours have a low mutational burden [19]. Children with CMMRD syndrome have higher levels of neoantigens [15], which are associated with responsiveness to checkpoint inhibitors, while even at relapse the tumour mutational burden in most paediatric cancers appears to remain well below that associated with response to checkpoint inhibitors in adults [20].

The immune landscape of tumours can be divided into three types—(i) T cell-inflamed with chemokines, $CD8^+$ T cells and type I IFN signature (so-called "hot" tumours); (ii) T cell exclusion with a low inflammatory signature, where T cells have accumulated at the periphery of tumour sites but are not efficiently infiltrating the tumour microenvironment and (iii) T cell deserted, where there are no tumour reactive lymphocytes ("cold tumours') [21,22]. The presence of immune-modulatory/immuno-inhibitory cells such as Tregs and myeloid derived suppressor cells (MDSC) or inhibitory pathways such as PD-L1, IDO and TGF-beta are associated with the T cell-inflamed signature and $CD8^+$ T cell infiltrate [23]. Activity of anti-PD1/PD-L1 checkpoint inhibitors in many adult cancers is associated with a T cell-inflamed tumour microenvironment signature at baseline [24]. Primary resistance to PD-L1 inhibitors is hypothesised to be a consequence of a lack of T cell-inflamed tumour microenvironment. The type of immune microenvironment may be determined by such factors as (i) somatic differences at the level of tumour

cells (mutational landscape and oncogenic pathways determining interaction with host immunity); (ii) germ line genetic differences at the level of the host (polymorphisms in immune regulatory genes) and (iii) environmental differences (commensal microbiota or immunologic/pathogen exposure history of patients).

In neuroblastoma, the number of infiltrating T cells has been correlated with International Neuroblastoma Risk Group and outcome [25] and transcriptomic analyses (by RNAseq) of tumours at diagnosis show an association of immune signatures with outcome [26]. However, tumour-associated leucocytes of most paediatric tumours contain few T cells, substantially lower numbers than tumours in adults [27]. Furthermore, PD-L1 expression is absent in the majority of tumours except Hodgkin lymphoma [28,29]—therefore, most paediatric malignancies are considered immunologically 'cold' [30]. Instead, they normally contain higher proportions of myeloid cells, which can be broadly considered within the categories of macrophages and MDSC [26] contributing to tumour growth and immune evasion [31,32].

4. Completed early phase trials of single agent checkpoint inhibitors in children

Two hundred and fifty-one patients have been recruited into three early phase trials of single agent immune checkpoint inhibitors which have been completed, including the PD-1 inhibitors pembrolizumab (155 enrolled, 154 treated) [12] and nivolumab (20 enrolled and treated) [13] and the PD-L1 inhibitor atezolizumab (90 enrolled, 87 treated) [14].

For these three trials, the recommended phase II doses (RP2D) in children (aged 2 to <18 years) were generally equal to those determined in adults [12–14]. The incidence (6–11%) of grade III-V adverse events in the paediatric population and the safety profile were consistent with that demonstrated in adults, and no new safety signals were identified in the paediatric trials. The most common grade III-V adverse events were rash, hepatitis, hypothyroidism, infusion-related reactions, pneumonitis, lymphocytopenia, anaemia, increased AST, colitis, gastric ulcer, neutropenia, pleural effusion, pruritus and pulmonary oedema and were at a similar frequency to those documented in adults. No major untoward effects were documented on the developing immune system.

In the trial of pembrolizumab, tumours were 'screened' and only children with PD-L1 positive cancers above a certain predefined threshold (≥1% except for melanoma) were enrolled (796 tumours were evaluable for assessment of PD-L1 expression, of these, 278 [34.9%] were PD-L1 positive). In the other two trials, most paediatric solid tumours exhibited low PD-L1 expression and low CD3/CD8 T cell infiltration, based on analyses performed retrospectively, and the assays differed between the trials.

For all 251 patients enrolled in these studies [12–14], the overall response rate (ORR) (complete [CR] and partial [PR]) was 6.8% (17/251). In Hodgkin lymphoma, there were two patients with a CR and seven patients with a PR producing an ORR of 42.9% (9/21). In the remaining patients, the ORR was 3.5% (8/230) with PR in two patients with adrenocortical carcinoma and individual patients with non-Hodgkin lymphoma, malignant ganglioglioma, rhabdoid tumour, lymphoepithelial carcinoma, mesothelioma and epithelioid sarcoma.

Owing to the lack of tumour material obtained directly before entry on to these trials and lack of re-biopsies during or after therapy, meaningful analyses of the immune environment and correlative biological studies were not (and will not be) possible.

The single agent phase I study of ipilimumab (anti-CTLA-4) in children and adolescents with treatment-resistant cancer (NCT01445379) recruited 31 patients [33]. It demonstrated that the spectrum of immune-related adverse events is similar to those described in adults; however, many of the paediatric toxicities were evident after a single dose. Although no objective tumour regressions were observed with ipilimumab as a single agent, subjects with immune-related toxicities had an increased overall survival compared with those who showed no evidence of breaking tolerance. Six subjects with melanoma, osteosarcoma, clear cell sarcoma and synovial sarcoma had stable disease. The phase II study of ipilimumab in adolescents with unresectable stage III or stage IV malignant melanoma showed that ipilimumab had activity in melanoma patients aged 12 to <18 years, with an objective response rate of 2 of 12 patients (17%). Furthermore, the safety profile was similar to that seen in adults [34]. Studies are ongoing combining ipilimumab with nivolumab in paediatric recurrent or refractory solid tumours or sarcomas (NCT02304458) [35] and high-grade primary central nervous system malignancies (NCT03130959) [36].

5. Hypermutant tumours

Following the observation that tumours in children arising in the context of CMMRD have the highest mutational load of any other paediatric malignancy [37] and can respond to immune checkpoint inhibitors [15], the International Replication Repair Deficiency Consortium has collected data on the response in other hypermutant tumours. With a definition of hypermutation of >10 mut/Mb [38] and the extension of causes of hypermutation to tumours driven by other genes in the replication repair machinery such as *DNA Polymerase Epsilon, Catalytic Subunit* and *polymerase*

delta 1, data accumulated by the consortium registry study on more than 50 patients are now maturing. Objective responses have been observed across gastrointestinal, genitourinary and brain tumours and overall survival, observed across cancers, at 3 years is 50%. These results are restricted to replication repair-deficient hypermutant cancers, and data are still lacking on childhood cancers caused by hypermutation because of other mechanisms, such as other DNA damage repair dysfunction and chemotherapy-induced tumours. Although mutational load is positively associated with clinical benefit from immune checkpoint inhibitors, it is clear that other parameters are important for immune response to such therapy.

Table 1
Details of monotherapy early clinical trials of checkpoint inhibitors in children.

Disease	Number of patients evaluated	Response		
		CR	PR	NE/ Missing
CNS tumours	**37**			
High-grade astrocytoma	16			
Ependymoma, NOS	4			
Atypical teratoid rhabdoid tumour	4			
Medulloblastoma	2			
Pilocytic astrocytoma	2			
Malignant ganglioglioma	1		1	
Other	8			
Non-CNS solid tumours	**102**			
Neuroblastoma	21			1
Melanoma	8			
Adrenocortical carcinoma	5		2	
Hepatoblastoma	4			
Myofibroblastic tumour	4			
Chordoma	3			
Hepatocellular carcinoma	4			1
Wilms tumour	13			2
Atypical teratoid rhabdoid tumour	3			1
Rhabdoid tumour	3		1	1
Lymphoepithelial carcinoma	2		1	
Mesothelioma	2		1	
Germ cell tumour	2			
Myoepithelial carcinoma	2			
Neuroendocrine	3			
Renal cell carcinoma	3			
Renal medullary carcinoma	2			
Other	18			
Sarcoma	**84**			
Osteosarcoma	40			
Rhabdomyosarcoma	16			1
Non-rhabdomyosarcoma soft tissue sarcoma	10			2
Ewings	31			
Epithelioid sarcoma	1		1	
Other	6			
Lymphoma	**28**			
Hodgkin lymphoma	21	2	7	
Other	5		1	1

CR, complete response; PR, partial response; NE, not evaluable

6. Activity of checkpoint inhibitors as monotherapy in children

Responses to checkpoint inhibitor monotherapy in children have only been observed in lymphomas (Hodgkin lymphoma and exceptionally others), hypermutant tumours and individual rare paediatric tumours. There has been a striking lack of activity of monotherapy in common paediatric tumours, for example neuroblastoma (0/21), osteosarcoma (0/40) rhabdomyosarcoma (0/16) and Wilms tumour (0/13) (Table 1). However, the activity in acute leukaemia, the most common category of paediatric malignancy, has not been investigated extensively.

Apart from hypermutation, there have been no identified predictive biomarkers. Greater than 1% positivity PD-L1 expression not being defined as a predictive biomarker in children might have been influenced by a predefined threshold of PD-L1 positivity being a prerequisite for enrolment in the pembrolizumab trial. Furthermore, there were differences in assays/thresholds assessing PD-L1 positive expression. It appears that the mechanism of response in Hodgkin lymphoma may be different [39,40].

Any insight into the mechanism of responses to checkpoint inhibitors in the three paediatric single agent trials is thwarted by the lack of informative tumour material (tumour material obtained before entry on to the trial) for the study of predictive biomarkers. Thus, in future studies material from paediatric tumours should be collected at study entry.

7. The way forward for checkpoint inhibitors in lymphomas—Hodgkin lymphoma

Consistent with results in adults [41], checkpoint inhibitors are active in paediatric Hodgkin lymphoma with an ORR of 42.9% (9/21) (Table 1). A number of studies are open or planned to evaluate the role of these products in combination in Hodgkin lymphoma. These include combining nivolumab with brentuximab vedotin for patients in relapse (NCT 02927769) (AHOD1721) [42]; nivolumab and brentuximab with or without ipilumumab in adolescents and young adults with relapsed disease (ECOG/ACRIN E4412) (NCT03407144) [43]; pembrolizumab in combination with chemotherapy in children, adolescents and young adults who have an inadequate response (NCT03407144) [44] and the proposed trial of doxorubicin, vinblastine and dacarbazine with nivolumab or brentuximab for high-risk patients. The participants of the Forum considered that randomised studies are very valuable scientifically and should always be taken into account, as single-arm study comparisons with historical controls are often inconclusive. They also strongly encouraged the inclusion of adolescents in relevant adult trials. The

results of ongoing studies will inform further development. Encouraged by responses to monotherapy, combination therapies should be evaluated in an attempt to further improve response. Furthermore, the concept that the addition of checkpoint inhibitors to standard of care may replace other more toxic components of therapy, for example radiotherapy, and thereby prevent late effects of current curative treatment should be explored.

8. The way forward for checkpoint inhibitors in lymphomas—primary mediastinal B cell lymphoma

As the spectrum, biology, clinical behaviour and response to therapy of primary mediastinal B cell lymphoma is similar in children compared with adults, the published experience of the efficacy of anti-PD1 immune checkpoint inhibitors in primary mediastinal B cell lymphoma, with an ORR of 41% [45] may be extrapolated to patients aged below 18 years. Owing to the rarity of the disease in the paediatric population, a randomised international paediatric and adult trial of a checkpoint inhibitor in combination with standard backbones with children and adults would be a rational investigational approach.

9. The way forward for checkpoint inhibitors in lymphomas—anaplastic large cell lymphoma

Although clinical experience with checkpoint inhibitors in anaplastic large cell lymphoma is limited to individual case reports [46,47] there is a strong biological rationale for their use based on the observed expression of cell-surface PD-L1 in anaplastic lymphoma kinase translocated cell lines and tumour samples [48]. Therefore, nivolumab is being evaluated in a phase II trial in paediatric and adult relapsing/refractory anaplastic lymphoma kinase−translocated anaplastic large cell lymphoma [49].

10. The way forward for checkpoint inhibitors in hypermutant tumours

To gain maximum information, patients with hypermutant tumours and replication repair−deficient cancers receiving therapy with checkpoint inhibitors should be enrolled in studies which specifically assess hypermutation and defects in DNA replication repair. Examples of these studies include the International Replication Repair Deficiency Consortium monotherapy (nivolumab) trial for hypermutant cancers (tumour mutational burden >10 mut/Mb or tumour mutational burden 5−10 mut/Mb) open in US, Canada, Europe and Israel and soon in Australia and some developing countries (NCT02992964 [50], INFORM2 NCT03838042 [51], KEYNOTE-051 NCT02332668 [52] and NCT02813135) [53].

A combination trial initially with nivolumab and ipilumumab is opening soon in North America as a part of the Stand up to Cancer Initiative effort. As there is a high incidence of mutations of the RAS-MAPK

Table 2
Medicinal products being or proposed to be combined with checkpoint inhibitors presented and discussed at the Forum.

Class of combinational medicinal product	Combination	Company
Chemotherapy/anti angiogenics:	Pembrolizumab and chemotherapy—Hodgkin lymphoma	Merck & Co., Inc., Kenilworth, NJ, USA
	Avelumab and standard of care	Pfizer and Merck KgaA
	Avelumab and axitinib	Pfizer and Merck KgaA
Radiotherapy	Pembrolizumab, I^{131}-MIBG, and anti-GD2—Minivan-	Academic
	Cemiplimab and radiotherapy	Regeneron
PARP Inhibitors	Pembrolizumab/dostarlimab and niraparib	Tesaro
	Tislelizumab and pamiparib	BeiGene Inc. and Celgene
HDAC inhibitor	Nivolumab and entinostat -INFORM2 NivEnt	Syndax Pharmaceuticals Academic—KiTZ sponsor
Checkpoint inhibitors—CTLA-4	Durvalumab and tremelimumab	AstraZeneca
	Nivolumab and ipilimumab	BMS and academic—COG
	Nivolumab and ipilimumab in CNS malignancies	BMS
	Nivolumab, ipilimumab and relatlimab (anti-LAG-3)	BMS
	Nivolumab ipilimumab and NKTR-214	BMS
Anti-LAG-3	BI 754091(anti-PD-1) and BI 754111 (anti-LAG-3) monoclonal	Boehringer Ingelheim
	Anti-PD-1 and TSR-033 (TSR-033)	Tesaro
Monoclonal antibodies	Cemiplimab and bispecific CD20xCD3 antibody	Regeneron
	Anti-PD-1 and iisatuximab (CD38 monoclonal antibody)	Sanofi
Other immuno-oncology products	Nivolumab and brentuximab bendamutisne, ipilimumab	BMS
	M7824 (bifunctional fusion protein combining a PD-L1 antibody and the extracellular domain of TGFβRII neutralising TGFβ)	EMD Serono
	Anti-PD-1 TSR 022 (anti-TIM-3)	Tesaro
	Cemiplimab and SAR439459 (anti TGF beta)	Sanofi
Cell therapy	Pembrolizumab and allogeneic cell therapy ilixadencel, ATMP	Immunicum AB
	Pembrolizumab/Atezolizumab and ATIMP	Autolus Ltd

PD-L1, programmed death ligand 1; PD-1, programmed death 1.

pathway [54] in hypermutated tumours, combinations of checkpoint and MEK inhibitors may also be considered. Studies to evaluate hypermutation at relapse in the absence of CMMRD should continue although hypermutation at relapse appears to be restricted to select populations (e.g. glioma patients treated with temozolomide whose tumours develop loss of mismatch repair as a resistance mechanism) [55,56]. The lack of activity in paediatric phase II trials of checkpoint inhibitors to date in relapsed patients suggests that clinically relevant hypermutation is uncommon in paediatric cancers.

11. Combinations

The range of combination studies presented and discussed at the Forum are shown in Table 2 grouped according to the class of the combination agent.

An overarching principle for immunologically 'cold' childhood cancers is that there appears to be a lack of naturally occurring tumour-reactive effector lymphocytes. As a result, incorporation of synthetic immunotherapy (e.g. CAR T cells and engineered antibody-based proteins) is a logical step forward, perhaps in combination with an immune checkpoint agent.

There are a number of studies in adults combining radiotherapy with checkpoint inhibitors, and some have shown a significant effect. In addition to a direct cytotoxic effect, radiotherapy can enhance anti-tumour immunity by inducing DNA mutations and releasing chemokines that recruit inflammatory cells into the tumour microenvironment, including antigen-presenting cells that activate cytotoxic T cell function, but also with the potential to induce or inhibit immunosuppressive responses [57,72]. Systemic immune-mediated effects of radiotherapy are supported by the observation that in some circumstances, the anti-tumour effect of radiotherapy extends outside the radiation field, a phenomenon known as the abscopal effect [58]. The MiNivAN trial combines PD-1 inhibition with radiotherapy and GD2 antibody targeting, based on pre-clinical data that (i) PD1 blockade augments the anti-GD2–mediated response by natural killer (NK) cells in neuroblastoma; (ii) radiation and an anti-GD2 monoclonal antibody induce a tumour-specific T cell response with 'epitope spread' and (iii) combined radiation and anti-GD2 monoclonal antibody augment the local and systemic response to checkpoint inhibition [59–61]. Combining radiotherapy, including hypo-fractionated radiotherapy, with a checkpoint inhibitor is an approach worthy of exploration [62]. However, it must be remembered that in most adult tumours, the role of radiotherapy with checkpoint inhibitors is being considered when activity from a single agent checkpoint inhibitor and a high level of neoantigens and antigen-specific T cells has been observed, which is not the case for most paediatric tumours.

Combinations of PARP inhibitors with anti-PD-1 agents may warrant evaluation in paediatric tumours with high prevalence of homologous recombination defects as determined by a BRCAness signature [19,63,64]. The rationale is supported by pre-clinical evidence [65] from several independent laboratories and early clinical data with PARP and anti-PD-1 inhibitors [66,67]. The mechanism of the combination is based on the increased immunogenicity of tumours, via release of neoantigens and increased tumour mutational burden and increased antigen-presenting cells activity after exposure to PARP inhibitors [68]. The effect is probably mediated through activation of the STING pathway, induction of the expression of ligands for NKG2D [69] and induction of tumour inflammation/immunologic memory.

Combinations of checkpoint inhibitors with T cell-engaging antibodies and CAR T cells which target surface antigens overexpressed in paediatric cancers warrant evaluation because they overcome the lack of effector cells currently preventing the mechanism of action of immune checkpoint inhibitors [70,71]. To what extent the combination with PD-1 antagonists can amplify the anti-cancer efficacy of these agents is being studied in ongoing clinical trials in both adults and children.

Ongoing trials in paediatrics are exploring if radiotherapy and chemotherapy can increase the number of neoantigens expressed, for example, the NIVOGLIO trial combining nivolumab, radiotherapy and temozolomide in paediatric high-grade gliomas (EudraCT No: 2018-002688-24) [72]. Also, the early-phase trial of nivolumab and ipilimumab in paediatric brain tumours included a stratum for radiation therapy in newly diagnosed diffuse intrinsic pontine gliomas followed by adjuvant nivolumab or nivolumab and ipilimumab (NCT03130959) [36]. The role of epigenetic modifiers [73] in increasing tumour-associated antigens [74] and in leading to broader immunological effects, e.g. down-regulation of immune suppressor cells including MDSCs and Tregs, is being investigated in the biomarker-enriched stratified combination trial of an HDAC inhibitor and a checkpoint inhibitor (INFORM2 NivEnt: NCT03838042) [51,75].

Furthermore, as PD1 blockade can also augment some NK cell responses, combinations with tumour reactive monoclonal antibodies (such as rituximab or anti-GD2 monoclonal antibodies) to augment antibody-dependent cell-mediated tumour cytotoxicity (ADCC) are underway [60,76].

12. Discussion

Studies of anti-PD-1/PD-L1 agents to date have demonstrated activity in few tumour types that are relevant for the paediatric population: Hodgkin lymphoma, primary mediastinal B cell lymphoma,

anaplastic large cell lymphoma and hypermutated tumours. In these malignancies, combinations should be evaluated in an attempt to further improve response rates.

Apart from these tumour types, early clinical studies with checkpoint inhibitors have demonstrated very limited activity in paediatric cancers (although the activity in acute leukaemia has not been studied extensively), and there are no biomarkers apart from hypermutation, defined as >10mut/Mb [38]. Based on these observations, the academic clinicians, biopharmaceutical companies and parent advocates concluded that no benefit would be expected from additional monotherapy trials employing other checkpoint inhibitors with the *same* mechanism of action (e.g. anti-PD1, anti-PDL1 and anti-CTLA-4) until more scientific knowledge becomes available. This shared perspective can inform companies when deciding whether a paediatric development plan is justified for any of the checkpoint inhibitors acting with the same mechanism of action as above and used as monotherapy. The outcome of these discussions could then be proposed to regulators through the available regulatory tools [77].

Similarly, a modification of an existing PIP could be submitted to adjust previously agreed commitments based on emerging evidence. Discussions among clinicians, cooperative groups and pharmaceutical companies should take place before PIP submission to decide which compounds are most likely to be relevant for evaluation in children. Given the number of same in class products, the disappointing clinical experience in children to date and the insufficient biologic rationale for adaptive intervention of the immune system in children, sponsors may also exercise the option to include a planned request for waiver of required studies of single agent checkpoint inhibitors in their initial Paediatric Study Plans (iPSPs) submitted to the FDA. It was generally agreed that scientific discussions leading to an academic-industry consensus would be of great interest to all stakeholders.

Many proposed combination studies in paediatrics are based on combinations being studied in adults to boost anti-PD-1/PD-L1 response to tumour neoantigens. These combinations have limited applicability in the paediatric setting as there is no baseline response on which to build, and therefore, an underlying scientific rationale is absent. However, combinations that result in an increased neoantigen burden that facilitate intratumoural localisation of antigen-specific T cells or that are expected to increase the effect of checkpoint inhibitors in paediatric cancers should be explored in children. They should be based on paediatric-relevant hypotheses and scientific data and not only because these combinations are being evaluated in adults. Specifically, proposed combination strategies should take into account the immunological landscape of the individual tumour and follow a rational development strategy. In the situation where intra-tumour–reactive T cells are present, checkpoint inhibitors could be combined with medicinal products to overcome additional mechanisms of immune suppression. For tumours with excluded tumour-reactive T cells, checkpoint inhibitors could be combined with agents to improve tumour entry of T cells and to activate tumour-reactive T cells within the tumour to the endogenous recognisable antigens (embryonic, differentiation and neoantigens) on the tumour. This concept has been likened to starting the engine and giving it some gas before releasing the brakes [78].

If there are no tumour-reactive T cells in the tumour, the situation is more challenging; as in this case, antigen-specific T cells need to be generated and adoptively transferred into the tumour. In principle, antigen-specific T cells can be activated *in vivo* by bispecific T cell engagers [79] or generated by CAR T cells [80–83] and TCR gene-modified T cells [84]. The choice of immune agent in this setting may be influenced heavily by the presence or absence of MHC-I on the tumour cells, thus emphasising the need for evaluating tumour phenotype before initiating this form of therapy. The activity of bispecific T cell engager and CAR T cell therapy in non-lymphoid solid tumours has yet to be demonstrated.

Checkpoint inhibitors could be an adequate combination partner for preventing functional inactivation in the hostile microenvironment. The abundance of myeloid cells in paediatric solid tumours may require additional measures to overcome immunoinhibitory barriers, for example by blocking CSF-1R signalling in macrophages [85,86]. Overcoming the inadequate, heterogeneous expression of most known tumour-associated antigens [74], for example by epigenetic modifiers [73], is a further strategy being evaluated in the paediatric biomarker-specific stratified combination trial of an HDAC inhibitor and a checkpoint inhibitor (INFORM2 NivEnt: NCT03838042)[51,76], where one of the arms is for hypermutant tumours. An additional role for checkpoint inhibitors is augmenting NK responses, combined with tumour-reactive monoclonal antibodies and thereby amplifying ADCC.

For therapeutic strategies to be based on the immunological environment, there is a need to understand the immune landscape of paediatric cancers at the different stages of treatment in more detail, as at present, there is a lack of knowledge. This is highlighted by the relative lack of informative tumour material from the three single agent early phase studies of checkpoint inhibitors. In future early phase clinical trials of immuno-oncology products (including checkpoint inhibitors), biopsy of the tumour at the time of enrolment should be considered as a prerequisite, particularly as the immune microenvironment (including PD-1/PD-L1 expression) may change significantly during the course of disease and treatment. Should this be the case, the results of the

biopsy could potentially benefit the patient. These biopsies will form the basis of studies of the immune microenvironment which should be standardised, harmonised and integrated across all histologies, in a similar way to the program being developed by the Innovative Therapies for Children with Cancer (ITCC) Biology Group. In this way, the maximal amount of scientific knowledge will be gained from these studies, as informative correlative biological studies could be carried out. Furthermore, the participants of the Forum strongly encouraged combining and making available the biological data of the three early phase studies of checkpoint inhibitors with the aim that this may yield valuable information for future studies.

Detailed analysis of individual immune gene and protein signatures as well as signalling networks, along with quantifications of different immune cell subpopulations have grouped adult cancers into six different immune subtypes, from highly inflammatory, wound healing phenotypes to lymphocyte-depleted and entirely quiet types [87]. Some of these immune subtypes may also be found in children, and alternative signatures specific for cancers in the paediatric age group may be found and inform more effective studies in the near future. A similar analysis in paediatric cancers should be carried out to identify immune signatures amenable to combination strategies either with or without transfer of T cells [26].

There is a scientific rationale for adult cancers with high neoantigen burden for combinations of checkpoint inhibitors with radiotherapy, and 'immunogenic' chemotherapy [88], though the relevance of these combination approaches to paediatric cancers appears limited based on current understanding. More relevant to paediatric cancers appear to be combinations of checkpoint inhibitors with T cell engaging antibodies, CAR T cells, TCR-engineered T cells and tumour-reactive monoclonal antibodies. Clinical trials of these combinations will be difficult to interpret without randomised studies and appropriate control groups.

Development of new checkpoint inhibitors in paediatrics should be considered early in the drug development process, and if there is a scientific rationale for development in paediatrics, this should be pursued. Data (including pre-clinical investigations and potentially early clinical proof of concept data from adolescents included into adult trials) should be generated early before full development in paediatrics. Trials containing two or more investigational agents, contributing to separate PIPs for each of the products but based on the same trial, could be foreseen.

The value of academic sponsored, industry supported, exploratory proof of concept protocols, including drugs from multiple companies which can generate data on which further studies can be based, such as the ITCC European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumours [89], the NCI-COG Paediatric MATCH trial [90] and INFORM2[51,76] were highlighted. Such basket or umbrella protocols should be global and trans-Atlantic in view of the rare populations. These trials should be designed on an 'intent to file' basis, i.e. with the potential to provide data of a quality suitable to support licensing procedures, when appropriate. These protocols could be part of a regulatory package in Europe (i.e. included in a PIP) and fulfil FDA regulatory requirements in response to Paediatric Research Equity Act (including planned amendments in 2020) and/or Best Pharmaceuticals for Children Act (BPCA). Data generated by proof-of-concept protocols could be part of *early* development (dose finding and signal seeking) and included in PIPs for the individual drugs. As PIPs require, in addition, studies generating pivotal evidence, a 'placeholder' study of a 'pivotal trial' with all the relevant details needs to be part of each of the individual PIPs, iPSPs, Proposed Paediatric Study Request. Companies should consider requesting a Common Commentary from EMA and FDA at the time of PIP/iPSP submission.

There were concerns that relatively infrequent late adverse effects of checkpoint inhibitors in children may not be detected early enough and appropriately. Therefore, it was proposed that there should be an international inter-company registry of early and late adverse effects of immuno-oncology products including checkpoint inhibitors. To this end, ACCELERATE has convened a working group to create an international data repository to collect information on long-term health in children who have received these modalities of anticancer treatment.

13. Conclusion

Early clinical studies of checkpoint inhibitors used as monotherapy have demonstrated activity in Hodgkin lymphoma, hypermutant tumours and some rare paediatric tumours, but not the more common in paediatric and adolescent cancers; no predictive biomarkers other than tumour mutational burden have been identified. Based on these observations, it was concluded that there is no benefit for children to be included in new monotherapy trials with additional checkpoint inhibitors displaying the same mechanism of action of those tested in monotherapy trials until we have a better understanding of the immune microenvironment and macroenvironment and of how the immune system could recognise paediatric cancers as foreign in the absence of high neoantigen burden.

As immune checkpoint blockade acts primarily by invigoration of pre-existing cytolytic T cells with native specificity for tumour-associated antigens, the major challenge for developing checkpoint inhibitors for paediatric cancers is the lack of neoantigens and corresponding naturally occurring tumour-reactive effector lymphocytes. Thus, the majority of paediatric tumours are immunologically 'cold'. As a result, incorporation of synthetic

immunotherapy (e.g. CAR T cells and engineered antibody-based proteins) is a logical step forward, perhaps in combination with an immune checkpoint agent.

To make progress in the rational development of immuno-oncology products, the immune microenvironment of paediatric cancers and how it changes in response to therapy needs to be investigated in detail, and there needs to be a greater understanding of the extent to which the immune system is able to recognise paediatric cancers as different from normal. There is rationale for the evaluation of combinations involving multiple immune checkpoint inhibitors in Hodgkin lymphoma and hypermutated tumours in view of the single agent activity of checkpoint inhibitors observed in these settings. In paediatric tumours for which there is no single agent activity, combinations of checkpoint inhibitors with drug products other than checkpoint inhibitors and/or other treatment modalities should be explored only on the grounds of well-supported hypotheses and paediatric-relevant scientific data and in well-designed informative clinical trials and not only because these combinations are being evaluated in adults. For the foreseeable future, it is likely that the primary role of immunotherapy for childhood cancers will involve engineered proteins (e.g. monoclonal antibodies and T cell engaging agents) and cellular products (e.g. CAR T cells and T cell receptor-engineered T cells). The evaluation of checkpoint inhibitors when added to these modalities is justified by pre-clinical data, and clinical assessment of these concepts is now in progress. Thus, the role of currently available checkpoint inhibitors in the paediatric setting will likely remain limited as monotherapy and expanded use will likely be dependent upon investigation of their activity in combination with engineered products and upon enhanced understanding of the ability of the adaptive immune system to recognise paediatric cancers in the absence of high neoantigen burden.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of, or reflecting the position of the agencies or organisations with which the authors are affiliated.

Contribution

Study concepts was designed by A.D.J.P., G.V., K.N., D.K., G.L. and F.L. Manuscript preparation was carried out by A.D.J.P., G.V., L.V.M., C.R., J.G., G.L., B.G., J.A., P.S. and V.M.C. Study design, data acquisition, quality control of data analysis and algorithms, data analysis and interpretation, manuscript editing and manuscript review was carried out by all authors.

Conflict of interest

J.A. is medical and scientific director for TC Biopharm and holds stock and share options in TC Biopharm and Autolus Ltd; M.B. is an employee of Merck Group; CB. is an employee of Tesaro; EB. is an employee of Pfizer; R.C. is an employee of Novartis; H.C. is an employee of Roche; S.J.D. is an employee of Merck & Co; M.E. is an employee of Boehringer-Ingelheimm Pharma GmbH; B.G. attended at a Roche sponsored advisory board for atezolizumab; R.I. is an employee of Celgene; M.K. is an employee and owns stock in Bristol-Myers Squibb; I.L. is an employee of Regeneron; L.V.M. has participated in advisory boards for AstraZeneca, Merck, Tesaro, Bayer and Celgene; M.M. is an employee of Syndax Pharmaceuticals; C.O. is an employee of Sanofi; A.D.J.P. has participated in advisory boards for Novartis, Taked, Merck, Lilly and Celgene; V.G.R.P. is an employee and shareholder of Autolus Ltd; C.R. attended advisory boards for Amgen, Celgen, EUSA Pharma, Genentch, Novartis and Roche, speaker honaria for Bristol Myers Squibb, Pfizer and Roche; P.K.S. is an employee of AstraZeneka; P.S. is an employee of Immunicum AB; C.v.T. participated in advisory boards for Novartis and Bayer; T.Y. is an employee of Beigene.

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Acknowledgements

The authors thank Elena Botanina for her dedication and very substantial work in preparation of the Forum, Samira Essiaf and Isabel Perez their pivotal roles in organising the Forum and Gynette Cook for preparation of the manuscript.

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