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Global Accelerator for Paediatric formulations
WHO Hosted Network

World Health Organization

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All external experts submitted to WHO a declaration of interest disclosing potential conflicts of interest that might affect, or might reasonably be perceived to affect, their objectivity and independence in relation to the subject matter of the PADO–cancer process. WHO reviewed each of the declarations and concluded that none could give rise to a potential or reasonably perceived conflict of interest related to the subjects discussed at the meeting(s) or covered by the report.

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# Abbreviations

| | |
|---|---|
| **ALL** | acute lymphoblastic leukaemia |
| **APL** | acute promyelocytic leukaemia |
| **CML** | chronic myeloid leukaemia |
| **CNS** | central nervous system |
| **DNA** | deoxyribonucleic acid |
| **EMA** | European Medicines Agency |
| **EMLc** | WHO Model List of Essential Medicines for Children |
| **GAP-f** | Global Accelerator for Paediatric Formulations Network |
| **GICC** | Global Initiative for Childhood Cancer |
| **GPACCM** | Global Platform for Access to Childhood Cancer Medicines |
| **HIV** | human immunodeficiency virus |
| **ICTRP** | International Clinical Trials Registry Platform |
| **IT** | intrathecal |
| **IV** | intravenous |
| **LGG** | low-grade glioma |
| **LMICs** | low- and middle-income countries |
| **MPP** | Medicines Patent Pool |
| **NTD** | neglected tropical disease |
| **PADO** | paediatric drug optimization |
| **PO** | per oral (administration) |
| **RNA** | ribonucleic acid |
| **SQ** | subcutaneous |
| **TB** | tuberculosis |
| **tRNA** | transfer RNA |
| **US FDA** | United States Food and Drug Administration |
| **WHO** | World Health Organization |

# Introduction

## The need for paediatric drug optimization

The development of medicines for children lags unacceptably behind that for adults, typically by around a decade *(1)*. Since 2016, following the World Health Assembly's adoption of a resolution on *Promoting innovation and access to quality, safe, efficacious and affordable medicines for children*, the World Health Organization (WHO) and its partners have intensified their efforts to fulfil this global commitment. They have expanded activities to ensure that age-appropriate formulations of essential medicines are available in child-friendly forms *(2)*.

The Global Accelerator for Paediatric Formulations Network (GAP-f), a WHO-hosted network, works across the life cycle of drug development to accelerate the investigation, development and introduction of optimal formulations for children *(3)*. Setting priorities is the first step in enabling a targeted approach to research and development. Creating a priority drug portfolio of the most needed formulations for children is essential. This approach helps streamline the efforts and resources of researchers and suppliers, focusing on specific dosage forms and formulations that address the most urgent needs of children. This is particularly important given that the market for medicines for children is often small and/or fragmented, resulting in limited volumes with potential market failures.

Paediatric drug optimization (PADO) identifies key priority products and their preferred product characteristics have for research and development. Related activities have been successfully undertaken for human immunodeficiency virus (HIV), hepatitis C, tuberculosis (TB), antibiotics, and neglected tropical diseases (NTDs), demonstrating impact on accelerated access to optimal formulations in the context of fragmented, small markets for medicines for children. To provide further guidance to support similar processes for optimizing drugs for children in other disease areas, GAP-f has published guidance for undertaking a PADO process and adapt it to the specific needs of each disease area *(4)*.

## PADO for cancer medicines

Each year, an estimated 400 000 children and adolescents of 0–19 years old develop cancer *(5,39)*. Globally, acute lymphoblastic leukaemia (ALL) is the most common malignancy accounting for an estimated 19% of the total childhood cancer incidence, followed by non-Hodgkin lymphoma, Burkitt lymphoma (5%), Wilms tumour (nephroblastoma) (5%), and retinoblastoma (5%) *(6,39)*. Inadequate data availability in low- and middle-income countries (LMICs) does not allow for an accurate assessment of the paediatric cancer burden. Weak cancer registries for childhood cancer, particularly in LMICs, limit ability to accurately assess the disease burden. In 2022, it was

estimated that globally more than 105 000 children died of cancer *(7,38)*. The likelihood of surviving a diagnosis of childhood cancer depends on the country in which the child lives: in high-income countries, more than 80% of children with cancer are cured, but in many LMICs less than 30% are cured. This survival gap is one of the greatest inequalities in cancer and child health. Improving access to childhood cancer care, including to essential medicines and technologies, is highly cost effective, feasible and can improve survival in all settings.

To improve outcomes for children and adolescents with cancer, the Global Initiative for Childhood Cancer (GICC) was launched in 2018 by St. Jude Children's Research Hospital and WHO, along with other leading global partners *(8)*. Working together, the goal is to achieve a global survival rate of at least 60% and to reduce the suffering of all children with cancer by 2030, saving the lives of 1 million children. The GICC focuses on these highly curable and prevalent cancers as tracers for implementing programmes and monitoring progress: ALL, Burkitt lymphoma, Hodgkin lymphoma, retinoblastoma, Wilms tumour, and low-grade glioma (LGG).

Following a systematic assessment of the age-appropriateness of formulations listed in the WHO Model List of Essential Medicines for Children (EMLc), numerous entries – including those for cancer medicines – were modified, added or removed in the revised EMLc published in July 2023 *(9)*. This assessment identified formulations gaps that were brought to the attention of WHO and GAP-f for consideration and further prioritization.

The PADO–cancer exercise and related meetings, considered the above mentioned EMLc assessment outcomes but also selected and assessed medicines from a recent landscape and pipeline analysis of all cancer drugs used in paediatric cancer clinical trials registered in the International Clinical Trials Registry Platform (ICTRP) database between 2007 and 2022. A total of 440 unique drugs were identified and subsequently characterized by mechanism of action, molecular target, phase of development, available formulations with specific storage requirements, specific malignancies for use, and status of United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) regulatory approvals *(10)*.

The PADO for childhood cancer medicines was therefore designed with the overall goal of better targeting research and development efforts towards those paediatric formulations and medicines that address current needs for GICC index cancers and anticipate future advances in the management of childhood cancers.

## Objectives

The purposes of the PADO–cancer founding meeting(s) were to:

- review cancer formulations currently recommended and in use, and their appropriateness for paediatric populations;
- identify cancer formulations from the pipeline analysis to be further prioritized for investigation and development for use in children and adolescents;
- develop a clear research agenda to support and enable future cancer drug optimization for children, with the goal of ensuring that the unique needs of children are effectively addressed.

Overall, the goal of the PADO-cancer exercise was to develop a PADO priority list of formulations to be prioritized with a time horizon of 3–5 years, and a PADO 'watch list' containing promising candidates for investigation and development for children with a time horizon of 5–10 years. The PADO–cancer exercise enables alignment between funders, procurers, market-coordination entities, researchers, innovators, generics manufacturers, product development partnerships and regulators on priority products to be investigated and developed, as well as increasing efforts to tackle challenges in access to cancer medicines in LMICs.

# Methodology

## Scope

The overall scope of the exercise was to prioritize cancer medicines that are relevant to the GICC index cancers: ALL, Burkitt lymphoma, Hodgkin lymphoma, retinoblastoma, Wilms tumour, and LGG.

Two distinct selection approaches were identified:

a. Cancer medicines shortlisted for prioritization from the WHO EMLc *(9)* and flagged for having a gap in the availability of age-appropriate formulations (i.e. identified in the context of previous work undertaken by the WHO and GAP-f).

- 35 cytotoxic medicines and 10 targeted therapies in the WHO EMLc list were considered.
- Paediatric quality target profile tool *(11)* was applied to the 45 medicines, in relation to:
  - target population, dose and dose flexibility, patient acceptability, excipient safety, administration considerations, stability, storage conditions, primary packaging material, and registration status (regulatory approval).
- A dedicated expert group was formed to review and produce recommendations for formulations in the EMLc for 11 cytotoxic medicines and three targeted therapies. For eight cytotoxic medicines and two targeted *(9)* medicines a gap in age-appropriate formulations was clearly identified.
- Of the 10 medications flagged, eight were considered relevant to the GICC, establishing the basis for the prioritization exercise.

b. Cancer medicines shortlisted for prioritization from a landscape and pipeline analysis undertaken to catalogue all medicines used as standard of care (or currently under investigation) for paediatric cancer.

- Landscape and pipeline analysis of childhood cancer medicines identified 440 medicines *(10)*.
- Medicines that were marketed or in Phase 3 of clinical development were selected for consideration.
- The prioritization exercise focused on those with oral (PO) or subcutaneous (SQ) routes of administration and indications including at least one of the GICC index cancers.

## Preparatory work

Before the meeting(s), two dedicated frameworks were developed (Table 1) by a team of technical experts comprising selected meeting participants who were invited to complete pre-meeting survey ranking the attributes in each framework to facilitate subsequent priority-setting decisions.

**Table 1. Cancer medicine attributes used in selection approaches**

| Cancer medicines from the EMLc | Cancer medicines from the landscape/pipeline analysis (marketed/Phase III) |
|---|---|
| Public health relevance | Efficacy |
| Indication for multiple malignancies and/or part of multiple treatment regimens | Safety and toxicity profile |
| Essential role for specific malignancy | Public health relevance |
| Frontline treatment | Indication for multiple malignancies and/or part of multiple treatment regimens |
| Relapse/refractory treatment | Essential role for specific malignancy |
| Palliative treatment | Frontline treatment |
| Suitability of current formulations | Relapse/refractory treatment |
| Toxicity (benefit/risk) | Palliative treatment |
| Administration requirements (monitoring, training, etc.) | Suitability of current formulations |
| Diagnostic testing availability | Administration requirements (monitoring, training, etc.) |
| Storage requirements | Diagnostic testing availability |
| Supportive care needs | Storage requirements |
| | Supportive care needs |

These attributes were used to select specific cancer medicines, for consideration of their relative importance and for the purpose of facilitating participants' discussions during the prioritization exercises.

## PADO–cancer meetings

The PADO–cancer meetings were held online on: 12th January 2024 (introductory meeting), 17th January 2024 (cancer medicines on the EMLc) and 18th January 2024 (pipeline analysis cancer medicines: marketed/Phase III), and brought together academics, researchers, clinical experts, paediatricians, regulators, funders, and other key stakeholders involved in research and development for cancer medicines.

Over the course of the meetings, participants engaged in a systematic review and prioritization of cancer medications. Organized into groups based on cancer types (i.e. leukaemias and lymphomas, solid tumours, and brain tumours), they evaluated existing and pipeline medicines using predefined attributes. Supported by technical experts, the groups analysed and discussed each medicine's attributes, shared insights, and raised research questions (Table 1).

Consensus on priority cancer medicines to be further investigated and/or developed for infants, children and adolescents was reached through working group discussions informed by the pre-populated frameworks. The final PADO priority and watch lists for cancer medicines were agreed upon by consensus during the closing plenary session. Additionally, research priorities were identified, and medicines facing access challenges were highlighted.

Conflict-of-interest declarations were collected for all participants and closely reviewed. Five participants with relevant conflicts were asked to participate as observers.

At the end of day 3 prioritization of all medicines were reviewed with all participants in both exercises to gain consensus on the six-priority cancer medicines, two watch-list medicines, and two medicines flagged for access challenges.

# Summary of discussions

## Overview of epidemiology and clinical management

Childhood cancer is a public health priority as it constitutes one of the leading causes of death for children in three of the six WHO regions and is progressively increasing as a problem in the other three regions. Incidence rates are similar between regions and countries but there are minor variations given over 50 unique types of cancer, adding to the complexities of monitoring, treating and managing the condition *(12)*. One of the main challenges is that childhood cancer is a non-preventable complex disease that requires a multifaceted response across the health system. Among conditions causing death and disability among people under 20 years of age, least global progress has been made for childhood cancer *(12)*. In HICs, cancer survival rates have been increased to as high as 80–90% due to improvements in access to and quality of care, as well as strengthening of health systems during the decades prior to introduction of molecularly targeted immunotherapies and other more recent innovations. An opportunity now exists to decrease the gap between HICs and LMICs with achievable targets to make substantial impact, supported by several World Health Assembly resolutions that elevate childhood cancer as a priority public health issue *(13–17)*, and the strong backing of the global cancer community and key stakeholders.

The GICC Cure*All* Framework *(18)* is an operational approach to guide policy-makers and cancer control managers to assess their cancer control capacities, identify priority actions, formulate and cost cancer control plans, and monitor for improvements. It supports the establishment of quality childhood cancer programmes around the world.

In 2021, building from the successful GICC collaboration, WHO and St Jude Children's Research Hospital launched the Global Platform for Access to Childhood Cancer Medicines (GPACCM) *(19)*. The platform has the goal of providing greater access to cancer medicines for more than 120 000 children in 50 countries in the next five years. It creates a unique mechanism for the cancer community to prioritize children with cancer and adds to the dynamic landscape of GICC. The GPACCM fully complements the GICC in accelerating progress toward the target of achieving an overall child cancer survival rate of 60% by 2030. These endeavours, along with the PADO–cancer exercise, align with the WHO mandates and resolutions that will help shape research agendas and product pipeline development towards the unique needs of children with cancer.

A broad range of challenges contribute to insufficient access to essential childhood cancer medicines for the majority of children with cancer around the world. The market for purchasing medicines for children is extremely fragmented. In LMICs, demand-side barriers include inadequate public sector financing, constraints with facility-based purchasing, and weak infrastructure and forecasting mechanisms. Supply-side barriers include small markets for medications with high entry barriers, and limited manufacturers that can impact product quality. Pipelines for cancer medicines are heavily skewed towards markets supplying adult-appropriate products in high-resource settings.

Many LMICs do not have national or regional guidelines or standards of care for the different types of cancers, hindering the forecasting, selection and procurement of essential childhood cancer medicines. However, as part of the Cure*All* implementation – particularly through its pillar three: 'Regimens optimized for

the delivery of quality diagnostic and treatment services' – countries are receiving technical support to develop or adapt national standards contributing to improvements in care quality. Standards and resource-adapted guidelines for the management of GICC index cancers are used as a reference for reviewing the prioritized medicines in resource-constrained settings.

## Pipeline challenges and impact on current practice

Timely access to the most promising cancer medicines is a challenge for children in HICs as well as LMICs settings. Only a small proportion of medicines approved in adults undergo regulatory approval in children. Even if they do, there is a significant time delay between adult and paediatric approvals *(20)*. One of the biggest challenges for children in LMICs is that new agents for cancer in common use (or development) in HIC settings are either molecularly targeted agents or immunotherapies *(10)*. These effective and often less toxic drugs are revolutionizing some cancer treatments in HIC contexts.

For children in LMICs, these medicines are often out of reach due to lack of required diagnostics, access to clinical trials and regulatory approvals, high up-front costs and administration challenges that are faced in low-resource settings.

Access to improved formulations for the paediatric population in LMICs settings would lower toxicity and require fewer supportive care needs, leading to lower treatment-related morbidity/mortality and improved disease response, as well as less need for relapse/refractory disease care and laboratory monitoring.

Cancer medicines that are given orally have less specialized pharmacy needs and are more easily administered in outpatient settings, reducing resource needs such as hospital beds, nursing care and additional equipment. Most importantly, many of these agents represent the best chance of cure for many children. Therefore, it is imperative to enable access to these medicines for children in LMICs as rapidly as possible.

## The need for better formulations

The challenges with formulating paediatric medicines that address relative ability to swallow, palatability, and dose flexibility are well-known. Traditionally, ready-to-dispense liquid dosage forms were considered preferred for ease of use, despite drawbacks in relation to stability and shelf life. These issues become even more difficult to counteract in resource-constrained settings, where environmental controls such as consistent refrigeration are more difficult to achieve. As a result, novel paediatric formulations such as dispersible tablets, 'mini' tablets and sprinkle dosage forms are increasingly the goal.

Cancer medicines have a high toxicity profile, and formulating medicines that promote safe and accurate use is essential. There are several oral dosage forms of chemotherapy with known activity in paediatric cancer, but whose practical use are limited due to administration and dosing challenges with currently available adult-marketed dosage formulations. In other settings, tablets or capsules may be split or crushed to achieve paediatric dosing or flexible administration methods. However, the paediatric cancer population comes with an additional layer of complexity, as the medicines used are often classified as hazardous and should not be manipulated without appropriate precautions, including personal protective equipment. This requires manipulation by trained staff in a health care setting and/or considerable education to caregivers regarding appropriate technique and health risks of accidental exposure. Clinicians and pharmacists have successfully constituted oral liquid formulations to achieve dosing and administration amenable to paediatric patients *(21)*. However, even these formulations are limited to settings where hazardous non-sterile compounding can be performed, and they come with limited stability and pharmacokinetic data to support their routine use.

Furthermore, chemotherapy medicines often require titration for toxicity and 'on-and-off' scheduling, which create additional risks for dosing errors. When formulations marketed for adults are used, the potential impact of these risks are intensified. This makes flexible formulations, packaging and education essential components of paediatric cancer drug development.

These challenges underscore the need for medicines development in the area of paediatric oncology to support access to clinically important medicines in formulations and dosages that can be feasibly and safely administered to children with cancer.

## Priority-setting and watch lists

The priority-setting process was conducted for both cancer medicines that are already included in WHO EMLc with indications for children, and for cancer medicines identified from the landscape/pipeline analysis but not yet on the EMLc.

Eight priority cancer medicines for children were flagged as potential priority compounds during the **WHO EMLc review**:

- Calcium folinate (leucovorin calcium)
- Cyclophosphamide (oral administration: PO)
- Etoposide (PO)
- Mercaptopurine
- Methotrexate (PO/intrathecal (IT))
- Procarbazine
- Rituximab
- Tioguanine

Ten cancer medicines for children were flagged as potential priority compounds during the **landscape/pipeline analysis** (i.e. marketed/ Phase III + PO/SQ + not included in EMLc):

- Dabrafenib [b (BRAF)]
- Fludarabine
- Lomustine (CCNU) [b]
- Ruxolitinib [a,b (JAK1/JAK2)]
- Selumetinib [a,b (MEK1/MEK2)]
- Sirolimus [b (mTOR)]
- Topotecan
- Temozolomide [a]
- Trametinib [b (MEK1/MEK2)]
- Venetoclax [(BCL2)]

Medicines identified during the landscape/ pipeline analysis were approved for paediatric use by the European Medicines Agency[a] and/or by the United States Food and Drug Administration.[b] Molecular targets for each medicine are noted in brackets.

## Priority-setting drug choices and rationale

The PADO–cancer process recommended prioritization of six childhood cancer medicines (Fig. 1):

**a. Cyclophosphamide (PO)**

**b. Etoposide (PO)**

**c. Mercaptopurine**

**d. Methotrexate (PO/IT)**

**e. Procarbazine**

**f. Temozolomide**

**a. Cyclophosphamide** is a cytotoxic nitrogen mustard derivative widely used in cancer chemotherapy that works by cross-linking genetic material in cancer cells, preventing DNA from uncoiling and replicating, thus preventing cell division *(22,23)*. At certain doses, cyclophosphamide can also enhance anti-tumour immune responses through T cell-mediated mechanisms. The WHO EMLc includes a large range of indications for use of cyclophosphamide, including: ALL, anaplastic large cell lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, Ewing sarcoma, Hodgkin lymphoma, LGG, Wilms tumour, and rhabdomyosarcoma *(9)*. The oral formulation, which was the focus of this exercise, is typically used for palliative intent in the treatment of solid tumours or for immunosuppression. The oral capsules and tablets can be administered at home and stored at room temperature. Available tablet/capsule sizes (25 mg, 50 mg) vary in some markets. This offers a range of doses that can be easily rounded or adjusted to achieve paediatric dosing with whole capsules/tablets (typical dosing is 2.5 mg/kg, capped at 100 mg). However, the tablet/capsule size (8mm/11mm) has been flagged as difficult for young children to swallow. Notably, the capsules and tablets should not be manipulated by caregivers of patients due to risk of hazardous exposure. There have also been publications to support a compounded oral suspension extemporaneously prepared from the intravenous formulation *(24,25);* however, this formulation is limited by stability, palatability and ability to compound.

The recommendation from the exercise was to develop and investigate a more age-appropriate formulation in a non-liquid oral dosage formulation (e.g. coated sprinkles, minitabs, dispersible tablets). A lower strength, age-appropriate formulation would be more easily titratable for dose adjustment. Such an oral formulation would also allow for more flexibility in procurement, which would be useful in LMICs where there is significant cyclophosphamide usage in palliative and metronomic treatment (latter involves administering lower doses of chemotherapy drugs more frequently and for longer periods, without extended breaks between treatments).

**b. Etoposide** is cytotoxic agent that is a semi-synthetic derivative of podophyllotoxin, which binds to topoisomerase II and ligates cleaved DNA molecules causing single- and double-stranded DNA breaks and inhibiting DNA replication and transcription. It targets the G2 and S phases of the cell cycle, ultimately leading to apoptotic cell death *(26)*. The WHO EMLc includes a large range of indications for use of etoposide, including: ALL, acute myeloid leukaemia (AML), anaplastic large cell leukaemia, Burkitt lymphoma, Ewing sarcoma, Hodgkin lymphoma, Wilms tumour, osteosarcoma, ovarian germ cell tumour, retinoblastoma, and testicular germ cell tumours *(9)*. The oral formulation, which was the focus of this exercise, is typically used for palliative intent in the treatment of solid tumours or forms of leukaemia.

The capsules can be administered at home, but some dosage forms have specific storage requirements (i.e. refrigeration). The available capsule sizes (50 mg, 100 mg) represent a limited range of doses that can be difficult to adjust within recommended range for paediatric patients. This sometimes results in alternate day-of-week schedules to achieve an average daily dose (e.g. 50 mg MWF/100 mg TRSS), which can be challenging for caregivers and presents risk for error. Notably, capsules should not be manipulated by caregivers of patients due to hazardous exposure risk. An oral solution can be extemporaneously compounded from the intravenous formulation, but it requires challenging off-label, at-home dilution instructions *(27)*.

**Fig. 1. PADO–cancer medicines list of priority products**

| | |
|---|---|
| **Cyclophosphamide (PO)** | • Multiple EMLc indications for cancer (GICC: ALL, Burkitt lymphoma, Hodgkin lymphoma, LGG, Wilms tumour)<br>• Opportunity to reduce toxicity with a more titratable lower strength non-liquid oral dosage formulation<br>• Develop an oral dosage form more acceptable for younger patients which would also allow for greater flexibility in procurement |
| **Etoposide (PO)** | • Multiple EMLc indications for cancer (GICC: ALL, Burkitt lymphoma, Hodgkin lymphoma, Wilms tumour, retinoblastoma)<br>• Opportunity to reduce toxicity with a more easily titratable non-liquid oral dosage formulation |
| **Mercaptopurine** | • Frontline and essential treatment, also used in relapse/refractory treatment (GICC: ALL)<br>• Improve existing liquid formulation to preservative-free to increase shelf life<br>• Opportunity to reduce toxicity with a more easily titratable non-liquid oral dosage formulation |
| **Methotrexate (PO/IT)** | • Frontline and essential treatment, also used in relapse/refractory and palliative treatment (GICC: ALL, Burkitt lymphoma)<br>• Improve existing liquid formulation to preservative-free to increase shelf life<br>• Opportunity to reduce toxicity with a more easily titratable non-liquid oral dosage formulation |
| **Procarbazine** | • Component of frontline treatment, also in relapse/refractory treatment (GICC: Hodgkin lymphoma)<br>• Opportunity to reduce toxicity with a more easily titratable non-liquid oral dosage formulation<br>• Lower strength would increase dose flexibility |
| **Temozolomide** | • CNS Tumours (GICC: LGG); component of first line for glioblastoma multiforme<br>• Opportunity to reduce toxicity with a more easily titratable non-liquid oral dosage formulation |

This off-label formulation is also limited by stability, palatability and ability to compound.

The recommendation from the exercise was to develop and investigate a more age-appropriate formulation in a non-liquid oral dosage formulation (e.g. coated sprinkles, minitabs, dispersible tablets). This would provide a more easily titratable age-appropriate formulation to allow for safe administration to paediatric patients.

**c. Mercaptopurine (6MP)** is a thiopurine-derivative antimetabolite that blocks the formation of purine nucleotides and inhibits DNA synthesis, when incorporated into the DNA, it disrupts DNA replication *(28)*. The WHO EMLc indications for mercaptopurine include: ALL, acute promyelocytic leukaemia (APL), and Langerhans cell histiocytosis *(9)*. This medication is used as a frontline treatment and is considered essential in treatment plans. It can also be used for relapse/refractory treatment. Mercaptopurine has a side-effect profile that includes, but is not limited to neutropenia, hepatotoxicity and gastrointestinal issues, so routine laboratory monitoring is required.

The available capsule form of 50 mg at a size of 10 mm was flagged to be harder to swallow for younger children. While the oral liquid suspension is available it can be costly and is only found in some markets with a short shelf-life. Given access issues, it is more common to crush tablets or give alternate day-of-week dosing schedules. Studies have shown that strict adherence to restrictions may not influence outcome and therefore crushing tablets and alternate dosing schedules may be acceptable *(29,30)*.

The recommendation from the exercise was to develop and investigate a more age-appropriate formulation in a non-liquid oral dosage formulation (e.g. coated sprinkles, minitabs, dispersible tablets) that is more easily titratable. Improving the existing liquid formulation with excipient of concern and shorter shelf life with a preservative-free formulation would be ideal in LMIC settings.

**d. Methotrexate** is a folate antagonist that is cytotoxic through inhibition of dihydrofolate reductase (DHFR), inhibition of thymidylate, and an alteration of the transport of reduced folates *(31)*. This results in a decrease in DNA synthesis, repair and cellular replication (highly effective for rapidly dividing cells in the S phase of cell cycle) *(31)*. The WHO EMLc indications for methotrexate include: ALL, APL, anaplastic large cell lymphoma, Burkitt lymphoma, Langerhans cell histiocytosis, and osteosarcoma *(9)*. This medication is used as a frontline treatment and is considered essential in many treatment plans. It can also be used for relapse/refractory treatment and in palliative care settings. Methotrexate has a side-effect profile that includes but is not limited to myelosuppression and liver toxicity; and the intrathecal form has a risk of neurotoxicity. Methotrexate requires routine laboratory monitoring.

The 2.5 mg tablet sizes are generally amenable with doses used in paediatric oncology and an oral liquid formulation does exist (not currently on EMLc), though with limited availability and stability (refrigeration required) with storage requirements. Access to a preservative-free methotrexate for IT use may also be limited in some areas.

The recommendation from the exercise was to develop and investigate a more age-appropriate formulation in a non-liquid oral dosage formulation (e.g. coated sprinkles, minitabs, dispersible tablets) that is more easily titratable. Consideration for improving the existing liquid formulation with excipient of concern and shorter shelf life with a preservative-free formulation would be ideal in LMIC settings.

**e. Procarbazine** is a cytotoxic methylating agent with mutagenic activity – after metabolic activation it appears to inhibit the trans-methylation of methionine into transfer RNA (tRNA), thereby preventing protein synthesis disrupting DNA and RNA synthesis *(32)*. Procarbazine is a component of treatment regimen for the listed indication of Hodgkin Lymphoma in the WHO EMLc *(9)*. It is also used in the treatment of central nervous system (CNS) tumours. It can be used in frontline treatment, depending on local standards of care, and can also be used in the relapse/refractory setting.

The formulation is available in an oral capsule (50 mg) that caters to adult dosage (typical paediatric dose 50–100 mg/m$^2$ body surface area). Paediatric doses often require alternating schedules to achieve an average daily dose. There are directions from the manufacturer to extemporaneously compound an oral suspension; this suspension is only stable for seven days, but this may be acceptable for some regimens where procarbazine is given for seven days (or four doses). Use of this practice is limited by the ability to compound and ability of families to access and give the medicine within the appropriate time frame for stability.

The recommendation from the exercise was to develop and investigate a more age-appropriate formulation in a non-liquid oral dosage formulation (e.g. coated sprinkles, minitabs, dispersible tablets) that is titratable with a lower dosing strength that is amenable to paediatric dosing.

**f. Temozolomide** is a cytotoxic imidazotetrazine second-generation alkylating agent that damages the DNA and triggers apoptosis *(33)*. It is unique in that it enters the cerebrospinal fluid and does not require hepatic metabolism. For paediatric use, it is currently approved by the EMA but not by the US FDA. The indications of use for temozolomide are CNS tumours, including LGG and glioblastoma multiforme (GBM), sarcomas, advanced stage retinoblastoma with CNS infiltration, other solid tumours, and T-cell lymphomas. It is a component of first line therapy for GBM and is otherwise commonly used in the treatment of relapsed solid tumours.

This formulation is available in various oral capsules (5, 20, 100, 140, 180, 250 mg) that can be given at home and stored at room temperature. Paediatric dosages (usually 100–200 mg/m$^2$/dose) are typically achievable with the available range of capsules sizes without imposing an extensive number of capsules. However, its use can be limited by the ability to swallow capsules whole. There are publications to support stability of off-label extemporaneous compounded oral suspension from capsules or oral solution from intravenous (IV) powder for reconstitution, which must be refrigerated. An oral liquid formulation is currently under development.

The recommendation from the exercise was to develop and investigate a more age-appropriate formulation in a non-liquid oral dosage formulation (e.g. coated sprinkles, minitabs, dispersible tablets) predominantly in the relapse/refractory setting.

## Watch list drug choices and rationale

The PADO–cancer process also identified two compounds for placing on a watch list:

a. **Rituximab (SQ)**

b. **Venetoclax**

**a. Rituximab** is a recombinant chimeric murine/human antibody directed against the CD20 antigen; binding causes a host cytotoxic immune response (complement- and cell-mediated) against CD20-positive cells causing apoptosis, structural changes, and the sensitization of cancer cells *(34)*. It improves outcomes on CD20+ lymphoma when added to treatment regimens and is frontline for the WHO EMLc indications of Burkitt lymphoma and diffuse large B-cell lymphoma. It can also be used for relapse/refractory treatment. It requires facility administration with observation for allergic reactions, and the risk of immunosuppression, infusion reactions, hepatitis B reactivation, and progressive multifocal leukoencephalopathy. There is a limited availability of CD20 testing in many LMIC settings.

The intravenous (IV) formulation is amenable to a range of paediatric dosages and at a usually acceptable concentration for paediatric administration (typically less than maintenance IV fluid rate unless giving rapid infusion); and it contains acceptable excipients. There is some potential for waste with existing vial sizes, however, and consideration could be given to development of an intermediate vial size (e.g. 250 mg) to minimize waste.

**Fig. 2. PADO–cancer watch list medicines**

| | |
|---|---|
| **Rituximab SQ** | • Efficacy and safety research specifically on rituximab SQ in standard Burkitt lymphoma regimens<br>• Review previous submission to EMLc |
| **Venetoclax** | • Emerging use in ALL; currently used in AML and CML<br>• Further research on bioavailability and bioequivalence studies on adapted peadiatric formulation in ALL<br>• Opportunity to reduce toxicity with a more easily titratable non-liquid oral dosage formulation |

Recognizing the existence of biosimilar intravenous formulations that are still not accessible in many LMIC settings, the consensus of the participants was that rituximab should not be highlighted as facing a challenge of access but rather constrained due to lack of availability and affordability. Considering the demonstrated benefits of including rituximab into low-intensity regimens for the treatment of Burkitt lymphoma – to improve overall survival and reduce treatment-related morbidity and mortality – greater efforts should be made to increase the availability of rituximab formulations in LMIC settings. Due to the limited experience in terms of efficacy and safety of the subcutaneous form of rituximab when added to standard chemotherapy regimens for the treatment of Burkitt lymphoma, further research is needed.

**b. Venetoclax** is a selective small molecule inhibitor of the anti-apoptotic protein BCL2 with potential antineoplastic activity that is currently in Phase III of clinical development for paediatrics *(35)*. It is approved in adults for AML and chronic myeloid leukaemia (CML) but is not approved by the EMA or the US FDA for paediatric use. Nevertheless, there is reported emerging use in children for treatment of relapse/refractory ALL, AML and neuroblastoma. The challenges noted are in preparation and in administering the oral solution as well as the need for inpatient monitoring for tumour-lysis syndrome in high-risk patients. The molecular targeted medicine does require BCL2 testing. The available doses are 10, 50 and 100 mg, with oral suspension under development. Multiple doses are required, due to the need to titrate up or down depending on toxicity and to prevent tumour lysis syndrome.

Venetoclax was flagged in the exercise for inclusion in the watch list for its emerging use in ALL and the need for developing and investigating a more age-appropriate optimal formulation in a non-liquid oral dosage formulation (e.g. coated sprinkles, minitabs, dispersible tablets), as the current sachet and size of pills are not ideal. Specifically, there is a need to investigate further if the crushed or powder forms are effective and establish its role in treatment of ALL. Also, a consideration for innovation in developing one dose or having a consensus globally on one to two preparations would increase accessibility in LMICs.

## Access to childhood cancer medicines: Call to action

The access list generated by the PADO–cancer process includes two medicines (Fig. 3):

**a. Dabrafenib**

**b. Trametinib**

Two medicines were included in the PADO–cancer access list. Both are targeted agents approved for the treatment of LGG and other solid tumours with BRAF V600E mutations. Both compounds are approved for use in combination for this indication, but also may be used as monotherapy for other tumours with aberrations of the mitogen-activated protein kinase (MAPK) pathway.

**a. Dabrafenib** is an inhibitor of the B-raf (BRAF) protein with potential antineoplastic activity blocking the action of an abnormal protein that signals the cancer cells to multiply *(36)*. This medication is indicated, in combination with trametinib, as a frontline treatment for BRAF-mutated LGG and other solid tumours, which can replace the need for traditional cytotoxic drugs in this setting. Dabrafenib can also be used in relapsed/refractory BRAF solid tumours. It does have US FDA approval for paediatric use, but not EMA approval. Its use in LMICs may be limited by the requirement for BRAF V600E or V600K testing. Dabrafenib also has the risk of gastrointestinal (vomiting and diarrhoea) and dermatologic (rash) side-effects, both of which may be treatment-limiting. Patients also require active monitoring for myelosuppression, cardiomyopathy and ocular toxicity.

Dabrafenib is available as an oral capsule (50 mg, 75 mg) and (more recently) as a soluble oral tablet for paediatric use (10 mg), from which an oral suspension is prepared immediately prior to administration. The liquid formulation must be stored at 4°C. With typical dosing, this is usually 2–6 tablets for small children. The dose is dissolved in water – which takes three or more minutes to dissolve for multiple tablets – then administered orally via syringe. Education must be provided to patients/caregivers for dissolution with water (5 mL volume for 1–4 tablets and 10 mL for more tablets).

**b. Trametinib** is a reversible, highly selective, allosteric inhibitor of MEK1 and MEK2. Once bound to the unphosphorylated MEK1 and MEK2 enzymes with high affinity, it blocks their catalytic activity and decreases cell proliferation, G1 cell cycle arrest, and finally apoptosis *(37)*. This medication is indicated, in combination with dabrafenib, as frontline treatment for BRAF-mutated LGG and other solid tumours, which can replace the need for traditional cytotoxic drugs. Trametinib also has emerging use as in other malignancies with aberrations of the MAPK pathway. It does have US FDA approval, but not EMA approval for paediatric use. Its use in LMICs may be limited by the requirement for BRAF and other MEK-pathway testing. Trametinib also has the risk of gastrointestinal toxicity (diarrhoea) and or dermatologic side-effects, both of which can be treatment-limiting. Hypertension, hyperglycaemia, myelosuppression, cardiomyopathy and ocular toxicity can also occur and require regular laboratory monitoring, ocular screening and echocardiograms.

**Fig. 3. PADO–cancer access list medicines**

| | |
|---|---|
| **Dabrafenib** | • Targeted agent for low-grade glioma<br>• Explore licensing possibilities |
| **Trametinib** | • Targeted agent for low-grade glioma<br>• Explore licensing possibilities |

There is an acceptable paediatric formulation available on the market in oral tablets (0.5, 2 mg) and recently an oral solution (0.05 mg/mL), which comes as an oral powder for reconstitution. The liquid formulation must be stored at 4°C. It is dispensed with an oral dosing syringe for administration at home.

The access list includes two cancer medicines that already have suitable formulations approved, but there would be a great benefit from introducing a generic and more affordable version that would need to be developed to ensure global access for children with LGG. For these products, models such as the one implemented by the Medicines Patent Pool (MPP) for anti-HIV medicines could facilitate affordable access to essential medicines through the negotiation of public health-oriented licences with patent holders allowing generic manufacture and supply of medicines in LMICs. As part of the PADO–cancer process, MPP was asked to further explore licensing possibilities for dabrafenib and trametinib.

## Research gaps

Following the priority-setting exercise, each group considered some of the relevant research gaps for cancer medicines in children, and noted areas of clinical research where the case for innovation in formulations could be strengthened and where significant challenges in access persist (Box 1).

Alignment between the US FDA and the EMA on study design, inclusion criteria and regulatory requirements for studies of cancer medicines for paediatric use is clearly needed in the future.

**Box 1. Research priorities identified by the PADO–cancer process**

## Pharmacokinetic and safety studies

Further research is needed to determine whether rituximab (SQ) is better than the IV formulation in terms of efficacy and safety when used in combination with standard chemotherapy regimens for Burkitt lymphoma. This question is raised because of the need to improve access to rituximab in LMICs where availability of IV biosimilars is still limited.

Bioavailability/bioequivalence of venetoclax formulation adapted to children (role in ALL):

- focus on minimizing handling ie. coated granules (toxicity/safety).
- Compare oral suspension formulations to sprinkle/dispersible/minitab preparations.

## Diagnostics and stewardship

Development and availability of adequate priority biomarker testing for molecular targeted medicines and immunotherapies suitable for LMIC settings.

## Optimizing clinical use

- How to make patented medicines that are approved in HICs accessible in LMICs in a generic form.
- Further investigation to establish role of venetoclax in ALL, AML and neuroblastoma.
- Further investigation on usage of non-liquid oral formulations for temozolomide.
- Explore alternative forms of topotecan for intraocular administration for retinoblastoma.
- Development of a cyclophosphamide + mesna combination formulation.
- Research transit delays and shelf-life of cytotoxic medicines.
- Creation of an optimal formulation of calcium folinate (delivery via patch).
- Studying non-inferiority of oral vs IV formulation for cure protocols and for metronomic or palliative care.
- Will new formulations improve home medication compliance with administering mercaptopurine and methotrexate during the maintenance phase of treatment?

## Study design and regulation

- Investigating heat-stable technology (e.g. cold chain or innovative mechanisms for temperature maintenance), and formulations suitable for room temperature that are labelled appropriately.
- Review of toxicity domains (there are many dimensions and considerations that affect practice).

## Others

- Expansion of indication for priority formulations to include brain tumours.
- How to make compassionate use available in LMICs.

## Noteworthy cancer medicine in the pipeline

While not one the focus medications for this PADO session because of its current development stage, **blinatumomab** was discussed in the general session as an important cancer medicine for future consideration. Blinatumomab is a bispecific T-cell engager (BITE) CD3/CD19 monoclonal antibody, which has been approved by the EMA and US FDA for relapsed/refractory ALL in adults and children and is currently in Phase III clinical trials in HICs for first line childhood ALL treatment. In addition to its high cost, there are significant administration challenges for blinatumomab in low-resource settings, including the requirement that it be infused intravenously over 24 hours for 28 consecutive days. However, there is a new subcutaneous formulation currently in Phase I/II trial development in adults. This medicine is a potential game-changer for children with ALL in LMICs. Including the needs of children living in all resource settings early in the blinatumomab subcutaneous formulation development process is crucial to expedite availability and access to those children who will most benefit.

# Moving forward and next steps

The results of the PADO–cancer process will be widely shared with GAP-f partners and relevant stakeholders to guide actions aimed at speeding up the product life cycle for prioritized products. GAP-f will facilitate scoping work to understand the feasibility of formulating priority cancer medicines in child-friendly dosage forms, as well as supporting development of a clear target product profile for all priority and watch list products. The GAP-f Product Development and Regulatory Affairs Working Group will examine opportunities to facilitate the development and regulatory approval of cancer medicines that already have indications for children. All prioritized medicines will be considered for inclusion in the WHO Prequalification Expression of interest list once a clear target product profile is available. The medicines that have been flagged with access challenges will also be reviewed by the Medicines Patent Pool and community organizations to facilitate collective interventions and highlight potential downstream changes that could be made in the near future.

A second round of prioritization is anticipated in 2025 for pipeline products in Phase II and III, including consideration of IV formulations, with the goal of shaping future drug optimization in childhood cancers therapies. To ensure appropriate dissemination – and promote alignment among key stakeholders in the global cancer community – an advocacy brief and peer-reviewed outputs will be developed to highlight PADO outcomes at forthcoming global cancer meetings and as part of private sector dialogues.

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# Annex 1. Meeting agenda

## **Day 1** January 12th 2024 (15.00–16.30 Cet)

**Introductory meeting**

| Topic | Speaker | Time |
|---|---|---|
| Welcome | Bente Mikkelsen (WHO/NCD Director) | 15.00–15.10 |
| Meeting objectives | Martina Penazzato (GAP-f/WHO) | 15.10–15.20 |
| Epidemiological background and WHO programme of work in cancer | André Ilbawi (WHO) | 15.20–15.30 |
| Global Platform for Access to Childhood Cancer Medicines | Carlos Rodriguez-Galindo (St. Jude) | 15:30–15:40 |
| Regional perspectives | Roberta Ortiz (WHO), Bishnu Giri (WHO South-East Asia Regional Office), Liliana Vásquez (NCD/PAHO, WHO) | 15:40–16:05 |
| Ongoing efforts to accelerate approval of cancer medicines | Gilles Vassal (SIOP EURO, Accelerate) | 16.05–16.15 |
| PADO for cancer – an overview | Anjali Srivastava (WHO) | 16.15–16.20 |
| Q&A | All | 16.20–16.30 |

## **Day 2** January 17th 2024 (13.00–17.00 CET)

**Prioritization of EMLc cancer medicines**

| Topic | Speaker | Time |
|---|---|---|
| Welcome and review Day 2 objectives | Martina Penazzato (GAP-f/WHO) | 13.00–13.05 |
| Summary of EMLc work to inform the PADO exercise | Bernadette Cappello (WHO) | 13.05–13.25 |
| Methodology of PADO for existing cancer formulations | Anjali Srivastava (WHO) | 13.25–13.35 |

## **Day 2** Continued...

| | | |
|---|---|---|
| Breakout sessions (3 groups) (Prioritization and research agenda) | Facilitated by Lilliana Vásquez (NCD/PAHO, WHO), Roberta Ortiz (WHO), Jennifer Pauley (St. Jude) | 13.35–15.15 |
| BREAK | | 15:15–15:30 |
| Report back | Rapporteurs: Mae Dolendo (Davao Medical Centre), Gilles Vassel (SIOP EURO), Carmen Auste (Childhood Cancer Institute) | 15.30–16.00 |
| Plenary discussion | Facilitated by André Ilbawi (WHO) | 16.00–16.50 |
| Wrap up | André Ilbawi (WHO) | 16.50–17.00 |

## **Day 3** January 18th 2024 (14.00–18.00 CET)

**Cancer medicines of interest for global use from pipeline analysis**

| **Topic** | **Speaker** | **Time** |
|---|---|---|
| Welcome and review Day 3 objectives | Martina Penazzato (GAP-f/WHO) | 14.00–14.05 |
| Cancer medicines overview | Jessica Boklan (WHO) | 14.05–14.25 |
| Methodology of PADO for cancer formulations for consideration | Anjali Srivastava (WHO) | 14.25–14.35 |
| Breakout sessions (3 groups) (Prioritization and research agenda) | Facilitated by Lilliana Vásquez (NCD/ PAHO,WHO), Roberta Ortiz (WHO), Jennifer Pauley (St. Jude) | 14.35–16.00 |
| BREAK | | 16:00–16:15 |
| Report back | Rapporteurs: Avram Denburg (Sick Kids) | 15:15–15:30 |
| Jennifer Pauley (St. Jude) Gilles Vassel (SIOP EURO) | 16.15–16.30 | 15:30–16:15 |
| Plenary discussion | Facilitated by Jennifer Pauley (St. Jude) | 16.30–17.15 |
| Review of overall PADO outcomes | Roberta Ortiz (WHO) | 17.15–17.45 |
| Wrap up and next steps | André Ilbawi & Martina Penazzato (WHO) | 17.45–18.00 |

# Annex 2. List of meeting participants

**Aizhan Aidarbekova,** Regulatory Affair Services, Kyrgyzstan

**Aala Ansari,** Cankids, India

**Ramandeep Arora,** SIOP Asia, India

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**Eric Bouffet,** The Hospital for Sick Children, Canada

**Guillermo Chantada,** SIOP, Switzerland

**Tim Cressey,** PENTA Foundation, Italy

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**Mae Dolendo,** Davao Medical Centre, Philippines

**Martha Donoghue,** Food and Drug Administration (FDA), United States

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