Paediatric Cancer Medicines -

Urgent need to speed up life-saving innovation

Proposal by the Stakeholders

27 January 2016

CALL TO ACTION

WE, UNITED STAKEHOLDERS IN CHILDHOOD CANCER DRUG DEVELOPMENT, PROPOSE THE EU PAEDIATRIC MEDICINES REGULATION BE AMENDED TO SUPPORT:

1. **Mandatory** paediatric investigation of drugs based on **'mechanism of action'** rather than adult disease,
2. **Prioritisation of drugs** in order to preserve and match rare and frail children with cancer to the best available therapies,
3. **More effective and flexible rewards** to drive early clinical development of drugs for childhood cancers and specifically for those cancers which only occur in children.

THE ISSUE

Each year, 6,000 young people die of cancer in Europe, and cancer remains the first cause of death by disease beyond one year of age.

There is a need to increase and accelerate cancer drug development for children and adolescents. In 2007 the EU Paediatric Medicine Regulation was launched and benefited many childhood diseases but not cancer.

In the eight years since the EU Paediatric Medicine Regulation, the landscape of therapeutic innovations for cancer has changed with many more new drugs in development but still very few reaching children.

Less than 10% of children in relapse with a terminal cancer have access to new, experimental drugs from which they could benefit.

► **There is an urgent need to change the EU Paediatric Medicine Regulation to ensure it can be effectively implemented to the benefit of children and adolescents with cancer and to accelerate therapeutic innovations which will lead to more lives being saved.**

THE MULTI-STAKEHOLDER PLATFORM & UNITE2CURE

In December 2013, within the EU-funded programme *ENCCA*, *SIOPE*, *ITCC* and *CDDF* created a *multistakeholder platform to improve new oncology drug development for children and adolescents*. In this forum, all stakeholders - parents, academia, industry and regulators - work together to analyse the current situation, identify bottlenecks and design solutions to be proposed to decision makers.

Parents and patient advocates have created *Unite2Cure*, a successful awareness campaign. Under the banner "Unite Against Childhood and Teenage Cancer", they aim to build upon a growing desire for change so that more young people with cancer can be given access to new drugs that are better tolerated and more effective.

WHY THE PAEDIATRIC MEDICINE REGULATION DOES NOT ADEQUATELY ADDRESS THE NEEDS OF CHILDREN AND ADOLESCENTS WITH CANCER

1. **The legal requirements for paediatric drug development are often waived** because the treatment being researched is for a disease which does not occur in children. This is despite the fact that many cancers in children do not occur in adults. Furthermore, the way the drug works (its *mechanism of action*) in an adult type of cancer may be relevant to a cancer type that only occurs in children (see example 1)
2. **There are major delays** in starting clinical trials of oncology drugs for children while waiting for the drug to show promise in adult cancer patients without regard to whether they could benefit children. Financial incentives to develop drugs for a cancer which only occurs in childhood often come too late for pharmaceutical companies to consider investing in research & development in the paediatric oncology space (see example 2)
3. When eventually mandated, **Paediatric Investigation Plans are approved following lengthy negotiations** with health authorities and too often prove unfeasible because they focus on the rare occurrence of an adult cancer in a child rather than the potentially wider use of the new drug in other relevant children's cancers (see example 3)

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SELECTED EXAMPLES

Example 1: Unjustified waiver: crizotinib

- Crizotinib is a targeted anticancer drug for the treatment of ALK+ lung cancer.
- Lung cancer does not exist in children and the drug has been class waived for its development in the paediatric population.
- ALK rearrangements are observed in several paediatric malignancies: anaplastic lymphoma, soft tissue sarcoma, neuroblastoma, making crizotinib a relevant and important drug to evaluate in children based on its mechanism of action.

Consequences:

- The paediatric development of crizotinib started in the US in December 2009 and showed high level of activity in children and adolescents with lymphoma and sarcoma as well as some activity in children with neuroblastoma.
- In Europe, children and adolescents with ALK+ relapsed malignancies have been denied access to an ALK inhibitor until ceritinib, another ALK inhibitor, has been voluntarily developed in children (February 2013).
- Currently, there are major inequalities in Europe for children accessing crizotinib as: i)very few academia-driven trials are ongoing; ii) the drug is prescribed off label in some countries; iii) most children with an ALK+ malignancy do not have access to an ALK inhibitor.

Example 2: Major Delays – Pembrolizumab and Nivolumab

- Pembrolizumab and Nivolumab are the first PD1 inhibitors approved for the treatment of melanoma in September and December 2014 in the US, respectively, and in July 2015 in Europe.
- These immunotherapy medicines have also a significant activity in several other adult cancers, such as lung cancer, kidney cancer, bladder cancer, Hodgkin disease and a very large portfolio of trials explores currently several PD1 and PDL1 inhibitors in all adult malignancies.
- The paediatric development of Nivolumab and Pembrolizumab started in early 2015 i.e. after they were granted a marketed approval in the US.
- The effective development of PD1 inhibitors in children has been delayed and we are unaware if this class of drugs will benefit children.

Example 3: Unfeasible PIPs – Vemurafenib

Vemurafenib is a targeted anticancer drug for the treatment of B-RAF mutated melanoma, approved in the US in 2011 and in Europe in 2012.

- B-RAF metastatic melanoma is extremely rare in adolescents and B-RAF mutations are found in several paediatric malignancies, such as brain tumours (high grade and low grade gliomas) and histiocytosis.
- Thus, the adult indication (melanoma) is extremely rare in adolescents but the mechanism of action is relevant for several paediatric malignancies.
- A PIP was granted in April 2011 to study vemurafenib in B-RAF advanced metastatic melanoma in patients aged 12 to 18, only.
- The paediatric clinical trial started in January 2011 and is open in 26 investigating sites in 10 countries and 4 continents. As of December 2015 and with the drug now being commercially available and because of the limited focused of the paediatric development plan, only 6 adolescents have been recruited on trial.

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ANNEX: ABOUT THE STAKEHOLDERS

Unite2Cure

Unite2Cure (www.unite2cure.org) is a network of parents, parent organisations and patient advocates from across Europe, which is calling for better treatment and better access to treatment for children and young people with cancer.
This network is supported by many doctors, paediatric oncologists and researchers from all over Europe.

SIOPE

SIOPE, the European Society for Paediatric Oncology (www.siope.eu), is the only pan-European organisation representing all professionals working in the field of childhood cancers in close cooperation with parents, patients and survivors. With more than 1,500 members across 31 European countries, today SIOPE is leading the way to ensure the best possible care and outcomes for all children and adolescents with cancer across Europe.
The SIOPE Strategic Plan - endorsed by all partners in the field - aims to a future where no child dies of cancer and survivors live to the fullest. As a 'European Childhood Cancer Plan', it is based on 7 key objectives and will inspire all future initiatives in this field.

ITCC

ITCC, the Innovative Therapies for Children with Cancer (www.itcc-consortium.org) Consortium was created in 2003. It is a non-profit organisation under the French Law. ITCC gathers 49 European Paediatric Oncology Departments with expertise in conducting early phase trials in children and adolescents, and 9 European research laboratories. The aim of this organisation is to **develop novel therapies for the treatment of paediatric and adolescent cancers** in cooperation with regulatory bodies, pharmaceutical enterprises, parents and patients.
In January 2011 ITCC was established as a European Category 1 Network for Paediatric Research at the European Medicines Agency (EnprEMA). Its structure comprises several Committees which take care and contribute to a particular issue in the development of novel therapeutic strategies in paediatric oncology.

CDDF

The Cancer Drug Development Forum (CDDF) is a not-for-profit association providing a unique platform to facilitate interactions between all stakeholders to improve the efficiency of cancer drug development: www.cddf.org.

ENCCA

ENCCA – the European Network for Cancer Research in Children and Adolescents (www.encca.eu) is a 5 years' project (2011-2015) funded via the European Union's Seventh Framework Programme under the Health topic "Structuring clinical research in paediatric and adolescent oncology in Europe". The mission of ENCCA is to efficiently structure and enhance collaboration within the field of paediatric oncology research in Europe. Among its important deliverables, ENCCA ensured the integration of a large number of European investigator-driven research networks to accelerate drug development and quality of care and cure for children and adolescents with cancer via the creation of the 'SIOPE Clinical Research Council for Paediatric Oncology' (SIOPE CRC).

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