



Thank you for invitation to join you today.

Talking from perspective of parents of a child who had cancer AND as funders of paediatric research.

Kevin and Karen are dual stakeholders – parents and funders of paediatric research

## Christopher

- Diagnosed with medulloblastoma at 4<sup>1</sup>/<sub>4</sub>
- Treated with chemotherapy/high dose chemotherapy with stem cell rescue
- Immediate post therapy prognosis good
- Relapse 4 months post therapy
- Died 21 months after diagnosis



Christopher's  
Smile  
our kids get cancer too

**Almost 7 yrs to the day Christopher died. He was 5 years old.**

We should have been **celebrating** Christopher's birthday as a family on Sunday – our family has been ripped apart and we are a couple again. There was not much to celebrate – only memories of a short life.

**Almost 2 years of our son's life were spent fighting an aggressive brain tumour.**

**Each day of 21 months** from diagnosis we lived in **fear**, in **pain** BUT with **HOPE**. HOPE that the aggressive drugs which damaged his hearing, immune system, his development would save his life. **THEY DIDN'T.**

**We saw how much a helpless little body can tolerate** – day after day, month after month being battered with the harsh drugs we hoped would save him from this equally harsh and cruel disease which was ravaging his body.

Can't be much **harder & cruel experience for any parent** than to sit **beside your child & watch them suffer** – see them unable to move, unable to eat, unable to function independently. Our son reverted to being baby-like in his abilities – this was consequence of treatment, not the cancer.

**The situation looked brighter** for a few short months, **then time and the treatment options ran out.**

**We could only wait for our son to die.**

## Paediatric Oncology Current Treatments

First line treatment options: surgery, and/or cytotoxic chemotherapy and/or radiotherapy

- Surgery: Neurosurgery – high risk, amputated limbs do not grow back
- Chemotherapy: vast majority is used 'off label' and often leaves a legacy of issues
- Radiotherapy: devastates a developing brain



We were **thrust** into a new world - a **parallel existence** to “normal” life. We were faced with very **limited choices** in terms of available treatment - **confronted with decisions no parent should have to make.**

Yes, of course we wanted our son to live but there was a high price to pay in the way of side effects.

**Neuro surgery** always comes with a risk of damage to the brain.

**Take chemotherapy** – Mostly used off label – each time more drugs were offered we had to sign a consent form. We hoped to save our child’s life but there appeared to be numerous pay offs - loss of hearing, possible heart issues, kidney problems, weak immune system, cancer later in life.

**Radiotherapy** – we were told our son’s level of radio would need to be so high he would never be able to lead an independent life afterwards.

**Often the child who goes into treatment is not the same child afterwards.**

**Those of you in the room who have children may want to reflect upon this for a moment.**

## Commonly used drugs to treat children with cancer:

- include known carcinogens
- are not approved for use on children and have an average age of 40-50 years



*Is this the best that is available in 2015  
after 8 years of the Paediatric  
Regulation?*

Christopher's  
Smile  
coz kids get cancer too



Let's take a **closer look at chemotherapy....**

Many of these **drugs are known to cause cancers** in later life – children (if they survive) have lives ahead of them therefore good chance of being subjected to a second cancer

**When Christopher died, “targeted therapy development” was in early stages.** Science & technology have progressed at a fast pace since 2008 and we frequently hear about new drugs for *adults* coming through pipelines into frontline use.

**Not for children though.**

**It was hard enough having to accept our son was going to die** because there simply were no drugs anywhere which could save his life.

**What must it feel like today** to sit beside your child waiting for them to die – in the knowledge there could be potentially life saving treatments to save them? **Treatments which are not being made available for children?**

**Should we allow this to continue?**

**Current Treatments – Legacy of Issues**

- Survival plateaued in last 10 years
- Children still dying from decades old toxic treatments
- Unacceptable side effects
- Ongoing late effects
- Cost burden of survival
- 7 years since Christopher's death, 8 years of the Paediatric Regulation – **what has changed?**

Christopher's Smile  
may kids get cancer too



From our perspective the concerns are NOT ONLY about “whilst a family is going through treatment” . **The challenges for a family are ongoing.**

There has been recent “**headline news**” in UK about **improvements in cancer survival**. For **children there has been a PLATEAU for the past 10 yrs**. Any increase in children’s survival has been in the most common leukaemia but in many cancers there SIMPLY HASN’T BEEN IMPROVEMENT.

**We are STILL dealing with a KILLER DISEASE.**

Children not only die from the **disease –there’s worse....** Children are still **dying from the treatments** . **In 2015 should we be hearing about children’s deaths resulting from treatment side effects? WE DO.**

Living **life in the “main stream”** for some children will never be a reality again as their needs are so great.

Then we have the **issue of late effects....**We may be talking about “survival success” for young patients treated for leukaemia now, but what about in the next 5-10 years or later? We now know cancer treatment at a young age can mean increased chances of 2<sup>nd</sup> cancers due to chemotherapy.

And what about the cost to society of all of this?

I think if **we** ask ourselves honestly what has changed **since our son died; since the introduction of the Paediatric Regulation**. The answer is ..... **VERY LITTLE.**

**We believe we are failing our children with cancer.**



**The Parent community are extremely disappointed with the rate of introduction of new drugs.**

We **are** in a position to make changes - knowledge is there – drugs are there – we need the willingness to act to provide new safe and effective treatments for children which surely is the objective of the Paediatric Regulation.

## New treatments for children - Challenges

- Pharma focus their R&D on adult conditions
- Too easy for Pharma to obtain a waiver for potential new life saving treatments for children
- Years may pass between initial adult trial and agent availability for paediatric pre clinical testing



The pharmaceutical industry focus their development activities towards adult cancers as these present a very large market.

Currently waivers to develop a drug in the paediatric population are issued based on whether an adult disease occurs in children. Modern targeted oncology drugs are designed to target specific abnormalities that could occur in a range of cancers.

Once a waiver to develop a drug in the paediatric population is granted there is no obligation for the drug's manufacturer to supply the drug to paediatric researchers so the potential use in children is not explored.

### Current Implementation of the Paediatric Regulation - Oncology

- More waivers are issued for oncology drugs than any other clinical area despite cancer being the principal cause of death by disease in children in Europe
- In the implementation of Article 43 for Oncology drugs, the EMA have drawn up an inventory which includes highly cytotoxic agents decades old and drugs for which the EMA have granted waivers




We believe the current implementation of the Paediatric Regulation with respect to the issuance of waivers is not complementary with the objectives of the Paediatric Regulation.

The implementation of Article 43 – the production of an inventory by the EMA of paediatric drugs – contains drugs which have known life threatening side effects and drugs that are currently the subject of a waiver.



Can anyone explain this?




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23 September 2014  
EMA/POC/161720/2014  
Human Medicines Research & Development Support Division

Draft inventory of paediatric therapeutic needs  
Paediatric oncology

Contains the following drugs that ALL have a waiver

Axitinib	Crizotinib
Bortezomib	Ruxolinitib
Cabazitaxel	Sorafenib

Christopher's Smile   
For kids get cancer free

The 6 drugs shown here have been granted a waiver by the EMA. At the same time they are listed on the EMAs inventory of drugs in everyday paediatric use.

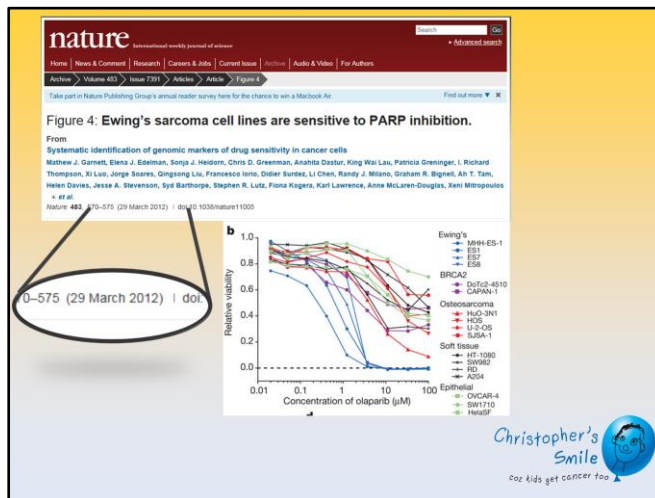
This does not make sense and begs the question “why?”

VI Discussion on the applicability of class waiver				
Active substance	Proposed indication	Condition	Outcome	Potential paediatric interest of this medicine suggested by PDCO
<sup>177</sup> Lu-DOTA <sup>1</sup> -Tyr <sup>3</sup> -Octreotate	Treatment of metastatic or unresectable, well differentiated, midgut neuroendocrine tumours, which overexpress somatostatin receptors	Treatment of gastroenteropancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglioblastoma, pheochromocytoma)	Positive	Neuroblastomas, Medulloblastomas and Ewing sarcomas
Ramucirumab	<ul style="list-style-type: none"> <li>Cyramza in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy; Cyramza monotherapy is indicated for the</li> </ul>	<ul style="list-style-type: none"> <li>Treatment of lung carcinoma (small and non-small cell carcinoma);</li> <li>Treatment of liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma);</li> <li>Treatment of gastric adenocarcinoma;</li> <li>Treatment of adenocarcinoma of the colon and rectum;</li> <li>Treatment of ureter and bladder carcinoma.</li> </ul>	Positive	Paediatric solid tumours





If we look at the Paediatric Committee minutes from Jan 2015

Two drugs have been identified as having potential paediatric use yet waivers were issued for both products



The drug Olaparib was the subject of a published article in March 2012 stating that Olaparib could potentially be of therapeutic use for Ewings Sarcoma

<div>              EUROPEAN MEDICINES AGENCY             <small>SCIENCE MEDICINES HEALTH</small> </div> <div>           09 January 2012            EMA/538304/2008            Human Medicines Development and Evaluation         </div> <div>           Paediatric Committee (PDCO)            Minutes of the 05-07 December 2012 meeting         </div> <table> <tr> <th>Class waiver number</th><th>Active substance</th><th>Proposed indication</th><th>Condition</th><th>Outcome (confirmed / not confirmed)</th></tr> <tr> <td>EMA-42-2012</td><td>Olaparib (AZD2281, K12-0059436)</td><td>Maintenance monotherapy for the treatment of patients with gBRCA mutation positive Platinum Sensitive Relapse (PSR) ovarian cancer who have responded (complete response or partial response) to platinum-based chemotherapy.  Maintenance monotherapy for the treatment of patients with gBRCA mutation positive first line ovarian cancer who have responded (complete response or partial response) to first-line platinum-based chemotherapy.</td><td>Treatment of ovarian carcinoma</td><td>Confirmed</td></tr> </table> <div>              Christopher's Smile             <small>so kids get cancer too</small> </div>					Class waiver number	Active substance	Proposed indication	Condition	Outcome (confirmed / not confirmed)	EMA-42-2012	Olaparib (AZD2281, K12-0059436)	Maintenance monotherapy for the treatment of patients with gBRCA mutation positive Platinum Sensitive Relapse (PSR) ovarian cancer who have responded (complete response or partial response) to platinum-based chemotherapy.  Maintenance monotherapy for the treatment of patients with gBRCA mutation positive first line ovarian cancer who have responded (complete response or partial response) to first-line platinum-based chemotherapy.	Treatment of ovarian carcinoma	Confirmed
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In the following December (2012) the PDCO granted a waiver for Olaparib. Was this in keeping with the objectives of the Paediatric Regulation with regards to ‘facilitating the development and availability of medicines for children aged 0 to 17 years’?

This means that children with the deadly childhood cancer Ewings Sarcoma are being denied a potential drug that could extend or save their lives.

## Paediatric Regulation Chapter 2 Article 11

1. Production of the information referred to in point (a) of Article 7(1) shall be waived for specific medicinal products or for classes of medicinal products, if there is evidence showing any of the following:
  - (a) that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;
  - (b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations;
  - (c) that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.



The implementation of Article 11 is defined in:

EMA document

Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver)

This document specifies at which level in a hierarchical classification the adult condition is defined. We want this level to change to reflect a genetic or biological abnormality.

### What needs to change

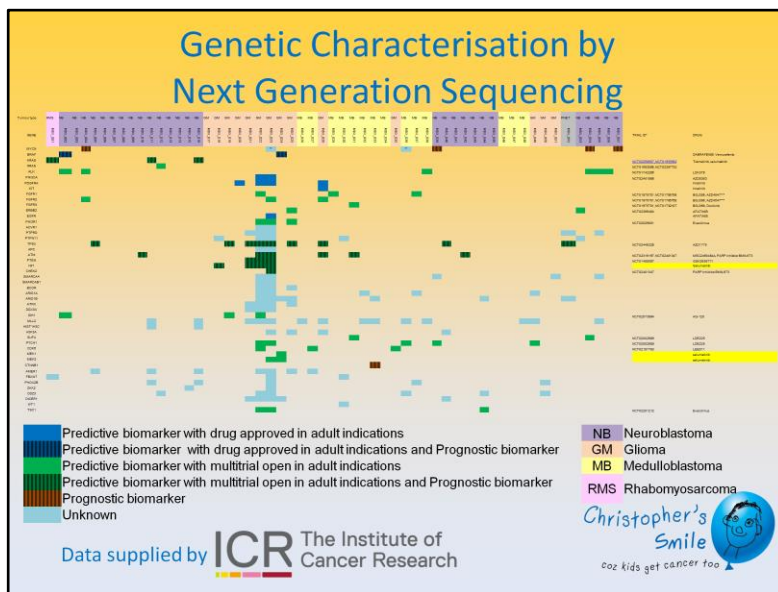
- The original objectives of the Paediatric Regulation need to be implemented for the area of oncology.
- The current implementation of Article 11(b) for oncology drugs is failing children with cancer (MedDRA HLT vs PT)



**We believe the Paediatric Regulation's objective is to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0 to 17 years.**

**This still has to be delivered for children with cancer.**

**The EMA use the MedDRA classification system for defining the term 'condition' for the granting of waivers. The current classification in our opinion is outdated and needs to change to reflect current scientific advancement especially in the area of genetic classification using Next Generation Sequencing.**



Christopher's Smile has recently funded Genetic Sequencing work and this slide shows the output from Next Generation Sequencing on 57 tissue samples.

These samples are from 4 tumour types but they show an amazing difference in genetic abnormalities.

The coloured blocks show genetic abnormalities by sample. On the left is a list of genes and on the right, current trials that are open in adults for either drugs or biomarkers.

## Genetic Characterisation by Next Generation Sequencing

From 57 patients 35 (~60%) could potentially be eligible for novel trials using target specific therapies, either as predictive biomarkers into clinical practice or prognostic biomarkers for treatment decision.



Unless we change the implementation of Article 11 (b) this, and subsequent data will not be taken into account by the EMA thereby denying children access to potentially life saving drugs.





Genetic Abnormalities are terms used in the mass media. Thanks to Angelina Jolie – the world knows about BRCA-1 and BRCA-2 mutations that increases a ladies chance of developing breast and/or ovarian cancer.

Same two genetic faults – two completely different cancers

Yet the EMA still uses a single adult disease as the basis for granting a waiver.

The time has come for us to use the genetic abnormality that a drug targets as the basis for a waiver. Certainly for Paediatric Oncology.

## Paediatric Regulation Recital (13)

(13) In order to ensure that research in the paediatric population is only conducted to meet their therapeutic needs, there is a need to establish procedures for the Agency to waive the requirement referred to in Recital (11) for specific products or for classes or part of classes of medicinal products, these waivers being then made public by the Agency. **As knowledge of science and medicine evolves over time, provision should be made for the lists of waivers to be amended.** However, if a waiver is revoked, that requirement should not apply for a given period in order to allow time for at least a paediatric investigation plan to be agreed and studies in the paediatric population to be initiated before an application for marketing authorisation is submitted.



This sentence was obviously a prediction for what needs to happen with drugs for Paediatric Oncology.

**We have**

The technology - Next Generation Sequencing

**We have**

An area of unmet need (EMA description of paediatric oncology)

**We have**

Children dying every day (cancer is the biggest killer of children by disease in Europe)

**We have**

A Paediatric Regulation whose implementation can be changed

**Do we have**

The will to change?

## Actions – not just talk

- What & Who
  - EC to instruct EMA Paediatric Committee to implement Article 11(b) to issue waivers based upon 'Condition' where 'Condition' is defined by a biological or genetic abnormality (change to MedDRA PT-level)
  - For oncology, EMA should review class list and remove all diseases where biological or genetic mutation occurs in the paediatric population.
  - MEPs to work with the Commission to ensure necessary changes are implemented with all speed.
- When
  - Agree timescales *at this meeting*

Children with cancer do not have time on their side

Christopher's Smile  
For kids get cancer too





To summarise – We want to see actions as a result of today. Actions speak louder than words!

We want to have answers to WHAT, WHO & WHEN with regard to the 3 points on this slide.

Let us not over-complicate what can be done thereby losing precious time. Want to see the following actions:

**We want** the European Commission to instruct the EMA & the PDCO to implement Article 11 (b) to issue waivers based on Condition where Condition is defined by biological or genetic abnormality;

**We want** a full review of the Class waiver list & removal of all diseases where biological or genetic mutation occurs in the paediatric oncology population (not just a cosmetic change currently under consideration)

**We want** MEPS to work with the Commission to ensure these changes are made at earliest opportunity.

Let's not forget that cancer is still the biggest killer by disease of children in Europe. One thing these children do not have is....time. The time for talk is over.

**The call for change has been made many times – but with no success. We now have a REAL CHOICE: Make CHANGES or HAVE a Paediatric Regulation which does NOT meet its original objectives.**

**Our son would have been 13 years old on Sunday. There wasn't much for us to celebrate.**

**We want something to celebrate for other children and their families. We believe they deserve this.**