7TH ACCELERATE PAEDIATRIC ONCOLOGY CONFERENCE

14-15 FEBRUARY 2019 | BRUSSELS, BELGIUM

ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Welcome and Introduction to the Conference

Gilles Vassal, *ACCELERATE Chair*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Improving new drug development for children and adolescents with cancer

The value of working together

Working together : a journey……

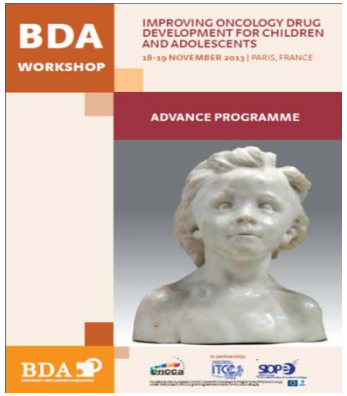
A FP7-NoE

2011
London

Where to go?

2013
Paris

Improving



P L A T F O R M

2015
Vienna

Prioritising

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

2016
Brussels

Accelerating

CDDF ITCC SIOPE

Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer

Eur J Cancer 2015;51:218.

EJC

Gilles Vassal[a,*], Raphaël Rousseau[b], Patricia Blanc[c], Lucas Moreno[d], Gerlind Bode[e], Stefan Schwoch[f], Martin Schrappe[g], Jeffrey Skolnik[h], Lothar Bergman[i], Mary Brigid Bradley-Garelik[j], Vaskar Saha[k], Andy Pearson[l], Heinz Zwierzina[m]

2018

2017


ACCELERATE
7TH ACCELERATE PAEDIATRIC ONCOLOGY CONFERENCE
14-15 FEBRUARY 2019 | BRUSSELS, BELGIUM
In partnership with:
ITCC
SIOPE
UNITE 2 CURE

ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Improving new drug development for children and adolescents with cancer

A global endeavour

In 2018 ACCELERATE INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER became

An international platform

ACCELERATE Steering Committee

ITCC President / ACCELERATE Chair

Gilles Vassal

SIOP Europe CEO

Samira Essiaf

Academia

Peter Adamson

Pam Kearns

Lynley Marshall

Andy Pearson

Industry

Elly Barry

Hubert Caron

Rosanna Ricafort

Darshan Wariabharaj

Patients Advocacy

Leona Knox

Patricia Blanc

Susan Weiner

Nicole Scobie

Regulatory Bodies

Koen Norga

Dominik Karres

Gregory Reaman

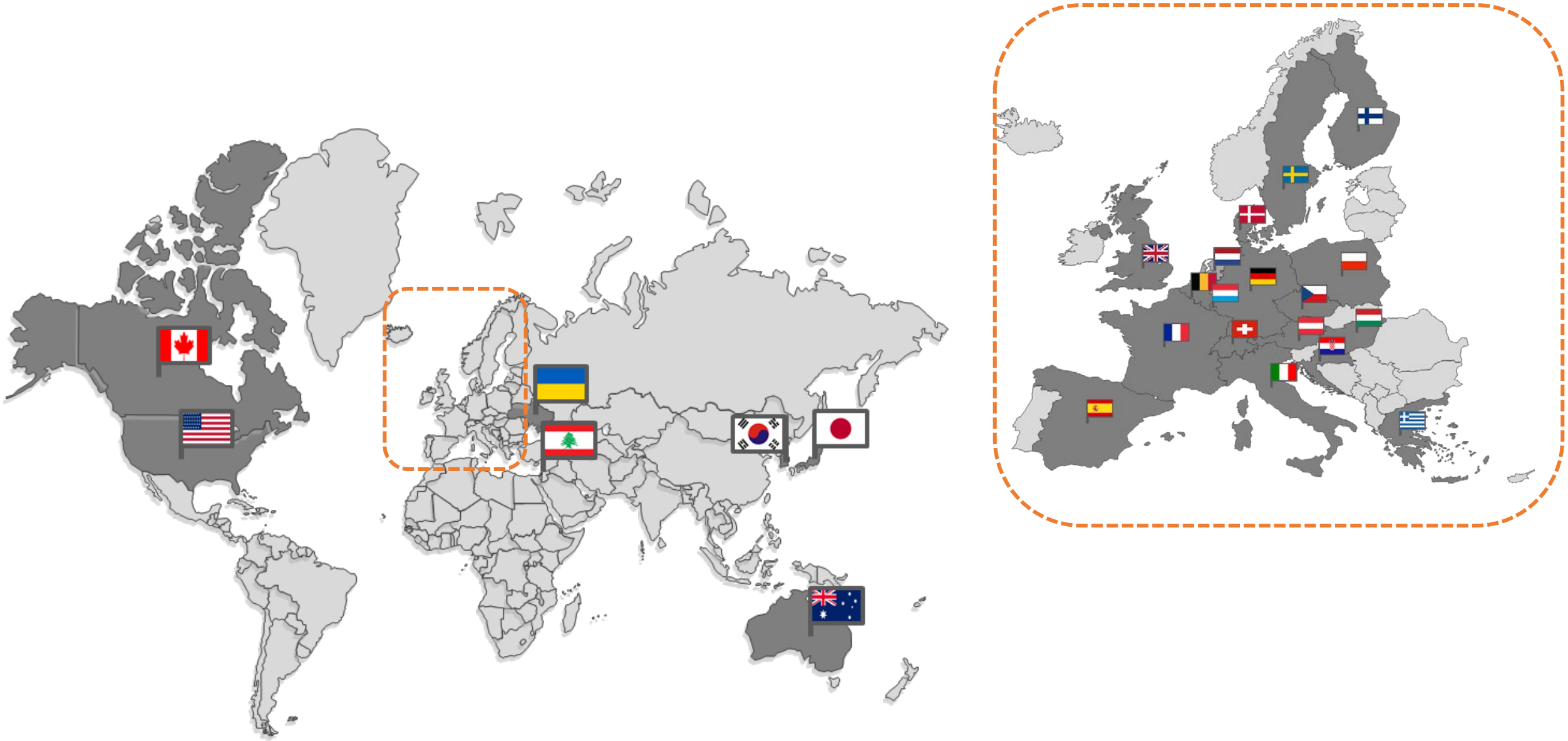
Alberto Pappo

In tuitu personae

Jeffrey Skolnik

Raphael Rousseau

A truly International Conference



ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

is supported by :

CDDF

Cancer Drug Development Forum

Innovative Therapies for Children with Cancer

ITCC

European consortium

SIOPE

SIOP Europe

ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Steering Committee

Administrative support by SIOPE and ITCC

Projet Management Team

WG

WG

WG

WG

Pediatric Strategy Forums

Annual Conference

Terms of reference

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

AACR American Association for Cancer Research
FINDING CURES TOGETHER®

ATLANTA
April, 2
10:30am

ACCELERATE-ing Pediatric Oncology Drug Discovery and Development

www.accelerate-platform.eu

The oncology paradoxe in 2018

Many drugs in adults
Adult disease – based pediatric developments

- Waived or delayed pediatric developments
- Poor access to pediatric patients

Rare patients

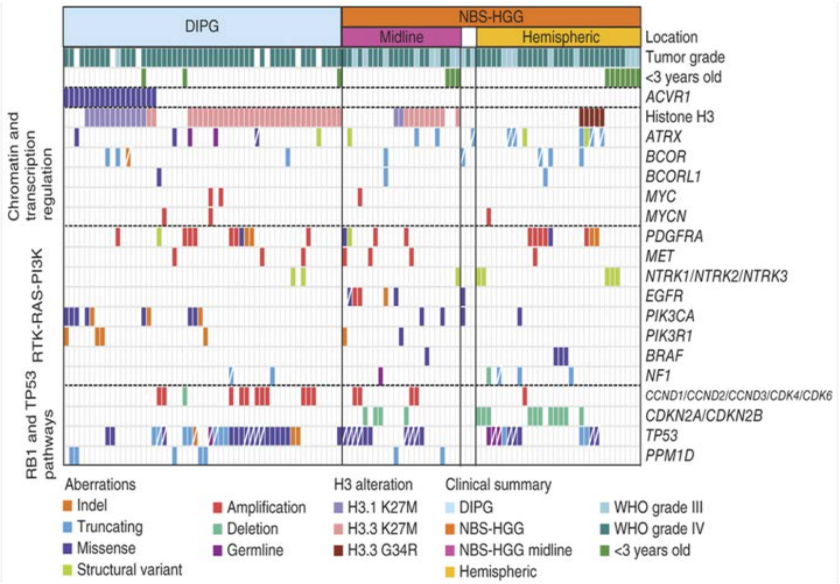
- Poor access to innovation

New oncology drug development for children : the goal

Many drugs in adults

SCIENCE

MOA* – based development



Nat Genet. 2014 May;46(5):444-450.

PRIORITISATION

Specific pediatric drugs

NEEDS

Improved access

*Mechanism of action

Better Medicines for Children From Concept to Reality

PROGRESS REPORT ON THE PAEDIATRIC REGULATION (EC) N°1901/2006

COM (2013) 445
FINAL

ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

The value of working together

No blame! No shame!

Generate data and find solutions

CDDF - ITCC - SIOPE 4th Paediatric Oncology Conference

ACCELERATING THE DEVELOPMENT OF NEW ONCOLOGY DRUGS FOR CHILDREN AND ADOLESCENTS

20-21 January 2016
Brussels, Belgium

1. Pediatric development should be based on drug **mechanism of action** instead of adult indication
2. **Prioritisation** should be set up to choose compounds to be evaluated or not in children
   - Based on MOA, needs, feasibility
   - Using stonger biological and preclinical data
3. **Reduce delays in starting pediatric development**
4. **Break the 18 years dogma**
5. **New incentives and rewards**

CDDF - ITCC - SIOPE 4th Paediatric Oncology Conference

ACCELERATING THE DEVELOPMENT OF NEW ONCOLOGY DRUGS FOR CHILDREN AND ADOLESCENTS

20-21 January 2016
Brussels, Belgium

1. **Mechanism of action** based developments

FDA

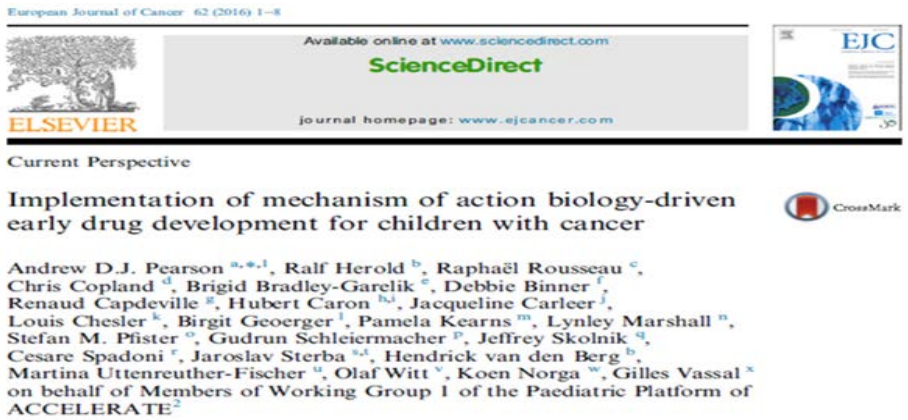
FDARA2017

RACE for Children

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA decision (CW/0001/2015) of 23 July 2015 on class waivers, in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

Revised Class Waiver List
Enters into force July 28, 2018



European Journal of Cancer 62 (2016) 1–8

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com

ELSEVIER

EJC

Current Perspective

Implementation of mechanism of action biology-driven early drug development for children with cancer

CrossMark

Andrew D.J. Pearson [a,*,1], Ralf Herold [b], Raphaël Rousseau [c], Chris Copland [d], Brigid Bradley-Garelik [e], Debbie Binner [f], Renaud Capdeville [g], Hubert Caron [h,i], Jacqueline Carleer [j], Louis Chesler [k], Birgit Geoerger [l], Pamela Kearns [m], Lynley Marshall [n], Stefan M. Pfister [o], Gudrun Schleiermacher [p], Jeffrey Skolnik [q], Cesare Spadoni [r], Jaroslav Sterba [s,t], Hendrick van den Berg [b], Martina Uttenreuther-Fischer [u], Olaf Witt [v], Koen Norga [w], Gilles Vassal [x] on behalf of Members of Working Group 1 of the Paediatric Platform of ACCELERATE[2]

CDDF - ITCC - SIOPE 4th Paediatric Oncology Conference

ACCELERATING THE DEVELOPMENT OF NEW ONCOLOGY DRUGS FOR CHILDREN AND ADOLESCENTS

20-21 January 2016
Brussels, Belgium

Pediatric Strategy Forums

ACCELERATE in partnership with EMA and FDA

Prioritisation

Based on MOA, needs and feasibility

Using stonger biological and preclinical data

ITCC P4 PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM

imi innovative medicines initiative

efpia

CDDF - ITCC - SIOPE 4th Paediatric Oncology Conference

ACCELERATING THE DEVELOPMENT OF NEW ONCOLOGY DRUGS FOR CHILDREN AND ADOLESCENTS

20-21 January 2016
Brussels, Belgium

Break the 18 years dogma

Fostering Age Inclusive Research

ANNALS OF ONCOLOGY

Joint Adolescent - Adult Early Phase Clinical Trials to Improve Access to New Drugs for Adolescents with Cancer Proposals from the Multi-stakeholder Platform - ACCELERATE

N Gaspar ✉, L V Marshall, D Binner, R Herold, R Rousseau, P Blanc, R Capdeville, J Carleer, C Copland, Y Kerloeguen K Norga, L Pacaud, M-A Sevaux, C Spadoni, J Sterba, F Ligas, T Taube, M Uttenreuther-Fischer, S Chioato, M A O'Connell, B Geoerger, J-Y Blay, J C Soria, S Kaye, B Wulff, L Brugières, G Vassal, A D J Pearson,
on behalf of Members of Working Group 1 of the Paediatric Platform of ACCELERATE

WG5
Fostering Age Inclusive Research (FAIR trials)

Nathalie Gaspar

Chris Copland

CDDF - ITCC - SIOPE 4th Paediatric Oncology Conference

ACCELERATING THE DEVELOPMENT OF NEW ONCOLOGY DRUGS FOR CHILDREN AND ADOLESCENTS

20-21 January 2016
Brussels, Belgium

New incentives and rewards

New models for development

WG4

Setting Up New Business Models and Ways to Invest in Paediatric Oncology Research and Drug Development

Delphine Heenen

Sam Blackman

CDDF - ITCC - SIOPE 4th Paediatric Oncology Conference

ACCELERATING THE DEVELOPMENT OF NEW ONCOLOGY DRUGS FOR CHILDREN AND ADOLESCENTS

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5. **New incentives and rewards**

~~12h45~~	
Breakout 1	**Further Development of Paediatric Strategy Forums** **Co-chairs: Andy Pearson,** *ACCELERATE* **Darshan Wariabharaj,** *Janssen Research & Development*
Breakout 2	**How to implement Mechanism of Action and Biology-driven Developments of Oncology Drugs for Children and Adolescents in the new Regulatory Environment?** **Co-chairs: Peter Adamson,** *Children Hospital of Philadelphia* **Patricia Blanc,** *Imagine for Margo*
Breakout 3	**How to strengthen International Cooperation?** **Co-chairs: Greg Reaman,** *Food and Drug Administration* **Nicole Scobie,** *Zoé4life*
Breakout 4	**Readdressing the Needs for long-term Follow up** **Co-chairs: Mark Kieran,** *Bristol-Myers Squibb* **Danielle Horton Taylor,** *Unite2Cure*
Breakout 5	**Designing and conducting Investigator-initiated Clinical Trials of new Drugs to meet the regulatory Requirements for Approval by Health Authorities** **Co-chairs: Pam Kearns,** *University of Birmingham* **Elly Barry,** *Pfizer*

SESSION 7 - Wrap-up and 2019 Action Plan		
15h00	Defining the 2019 ACCELERATE Action Plan	*All participants*
16h15	Conclusions	*Gilles Vassal, ACCELERATE Chair*
16h30	End of Conference	

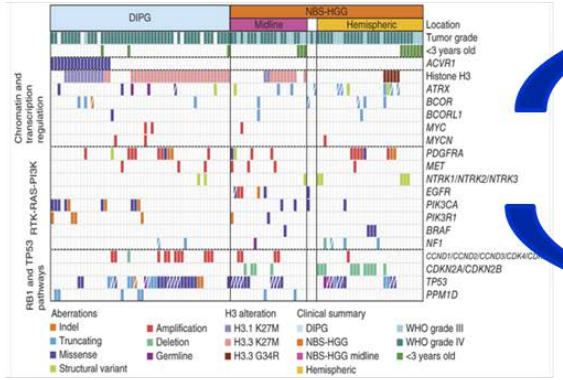
2019 WORKPLAN

New oncology drug development for children :
an international collaboration

SCIENCE **NEEDS**

Many drugs in adults

MOA* – based development and prioritisation



PRIORITISATION

Specific pediatric drugs

Improve access

Work together (all stakeholders)

In a favorable regulatory environment

Thank you

Andy Pearson

The ACCELERATE Conference Team

SIOP Europe
the European Society for Paediatric Oncology

Andrea Demadonna

Elena Botanina

Jackie Mellese

Marta Kania

Innovative Therapies for Children with Cancer
ITCC
European consortium

Carole Lecinse

Jerome Ducroq

Thanks to

Childhood Cancer International

WILTCHER'S
STEIGENBERGER

visit.brussels

Thanks to you

International Chilhood Cancer Day

Session 1 – Launching the new ACCELERATE Platform

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Goals and Projects of ACCELERATE

Gilles Vassal, *ACCELERATE Chair*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Session 2 – Immunotherapy for Paediatric Malignancies

Co-Chairs:
Greg Reaman, *Food and Drug Administration*
Pam Kearns, *University of Birmingham*

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INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Future Development of CAR-T Cells for Paediatric Malignancies

Crystal Mackall, *Stanford Medicine Cancer Institute*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Stanford MEDICINE

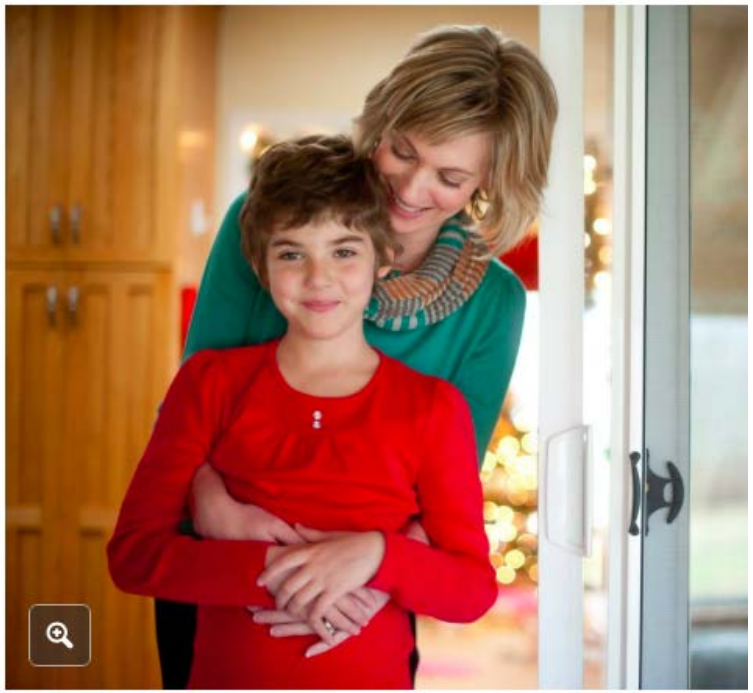
Future Development of CAR T Cells for Pediatric Malignancies

7th *ACCELERATE* Pediatric Oncology Conference
Feb 2019, Brussels

Crystal L Mackall MD
Ernest and Amelia Gallo Family Professor of Pediatrics and Medicine, Stanford University
Director, Stanford Center for Cancer Cell Therapy
Director, Parker Institute for Cancer Immunotherapy @ Stanford
Associate Director, Stanford Cancer Institute

CD19-CAR Therapy (CTL019, tisagenlecleucel, KYMRIAH): *A Watershed Moment*

Spring 2012



Emily Received CD19-CAR T Cells
Age: 6 yrs

August 2017

HEALTH

F.D.A. Panel Recommends Approval for Gene-Altering

By DENISE GRADY JULY 12, 2017

Emily Whitehead, 12, and her parents, Tom and Kari Whitehead, appeared at an F.D.A. hearing on Tuesday about a treatment for leukemia that had saved Emily's life. T.J. Kirkpatrick for The New York Times

- ✓ First FDA approved cell therapy for the treatment of cancer
- ✓ First gene therapy approved in the United States
- ✓ Unusual developmental path: approval in children prior to adults: Still no CD19-CAR therapy approved in US for adults >26 years of ago
- ✓ First therapy with an outcome based payment model
- ✓ Trial soon to launch to test Kymriah for MRD+ disease following consolidation in HR-ALL

Watershed (Oxford): An event or period marking a turning point in a situation

Pre-CD19-CAR

- ✓ Cell therapy will never work, how could you commercialize it?
- ✓ Bispecific antibodies do the same thing, why do we need cells?
- ✓ Autologous products from cancer patients won't work, they're too immunosuppressed…
- ✓ It will take too long to make the product, these are aggressive diseases
- ✓ It's too darn expensive

Present Day

- ✓ It's too darn expensive, how can we lower the price?
  - $475,000 USD for Kymriah/B-ALL: Highest "sticker price" of any cancer therapy
  - $373,000 USD for Yescarta/DLBCL
  - $373,000 USD for Kymriah/DLBCL
- ✓ How can we scale up to make products for all patients who need it?
- ✓ Autologous or allogeneic?
- ✓ Could it really work for solid tumors?

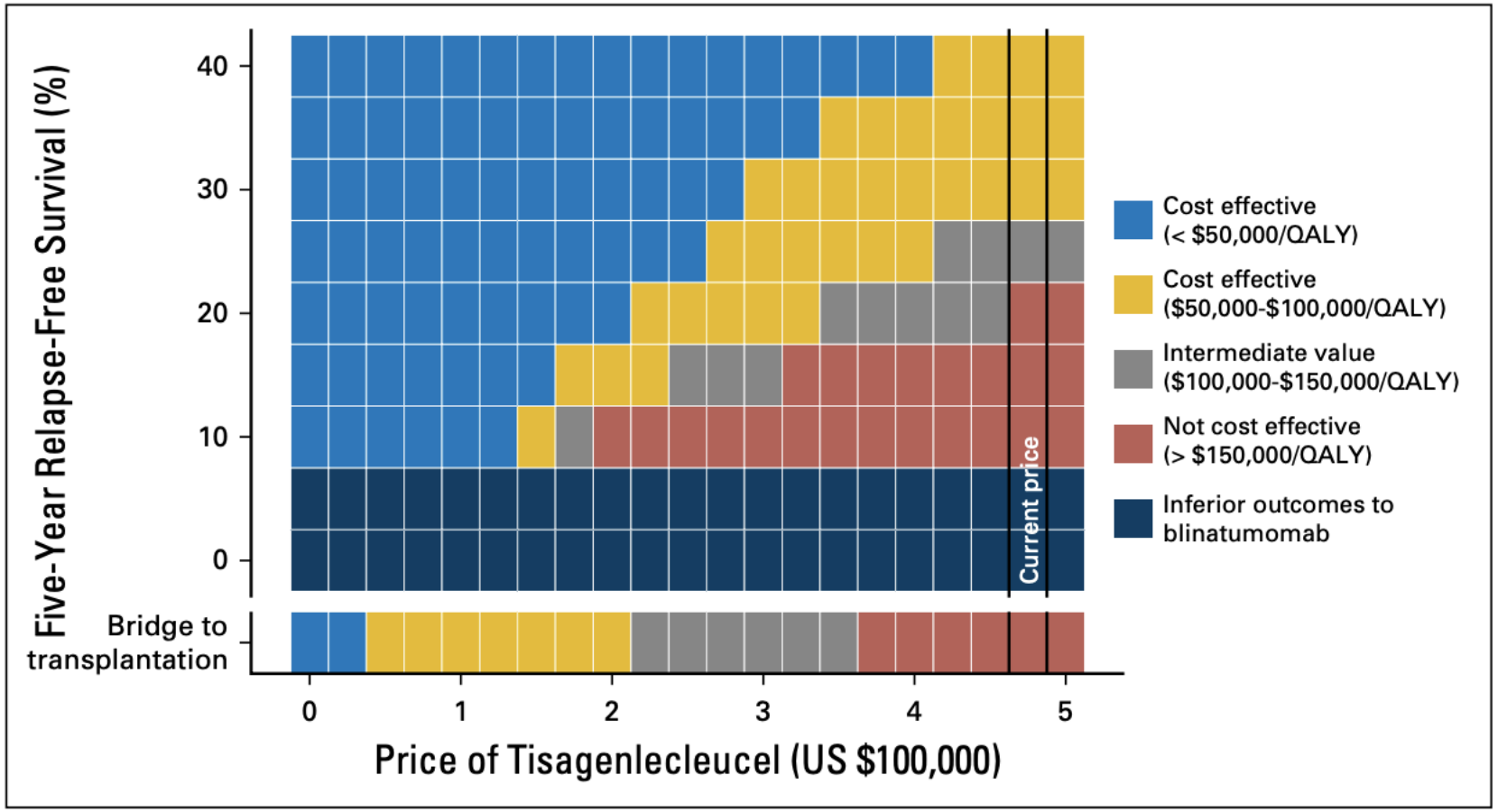
VOLUME 36 · NUMBER 32 · NOVEMBER 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Relapsed or Refractory Pediatric B-Cell Acute Lymphoblastic Leukemia

John K. Lin, Benjamin J. Lerman, James I. Barnes, Brian C. Boursiquot, Yuan Jin Tan, Alex Q.L. Robinson, Kara L. Davis, Douglas K. Owens, and Jeremy D. Goldhaber-Fiebert

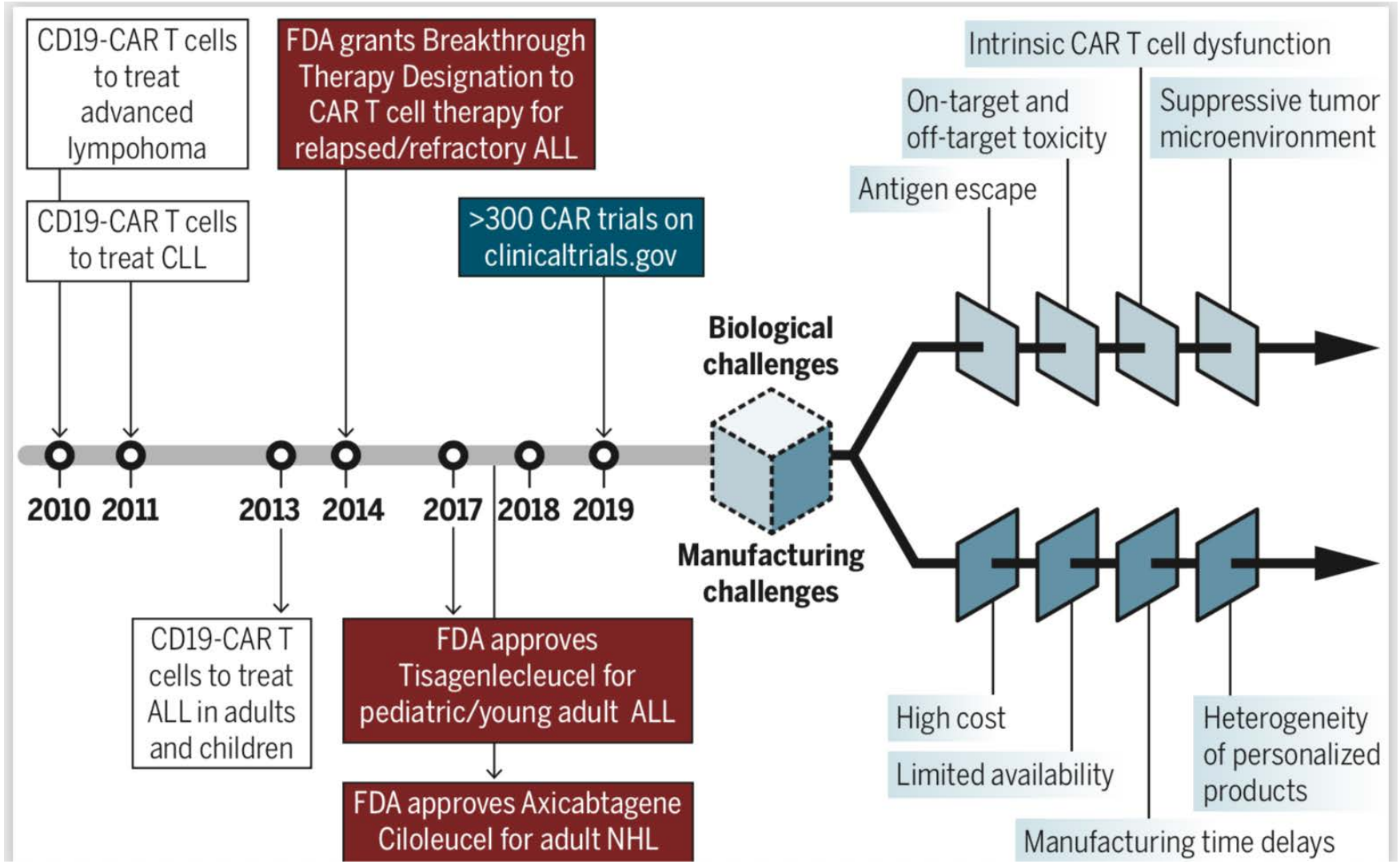


Bottom line:

At current cost (~$600K), CD19-CAR is “cost effective” if it provides long-term transplantation free survival in at least 40%

If the price dropped to $200-$350K cost effectiveness could be achieved even with transplant.

Future Challenges to Developing CAR Therapies: *Scientific and Manufacturing Hurdles*



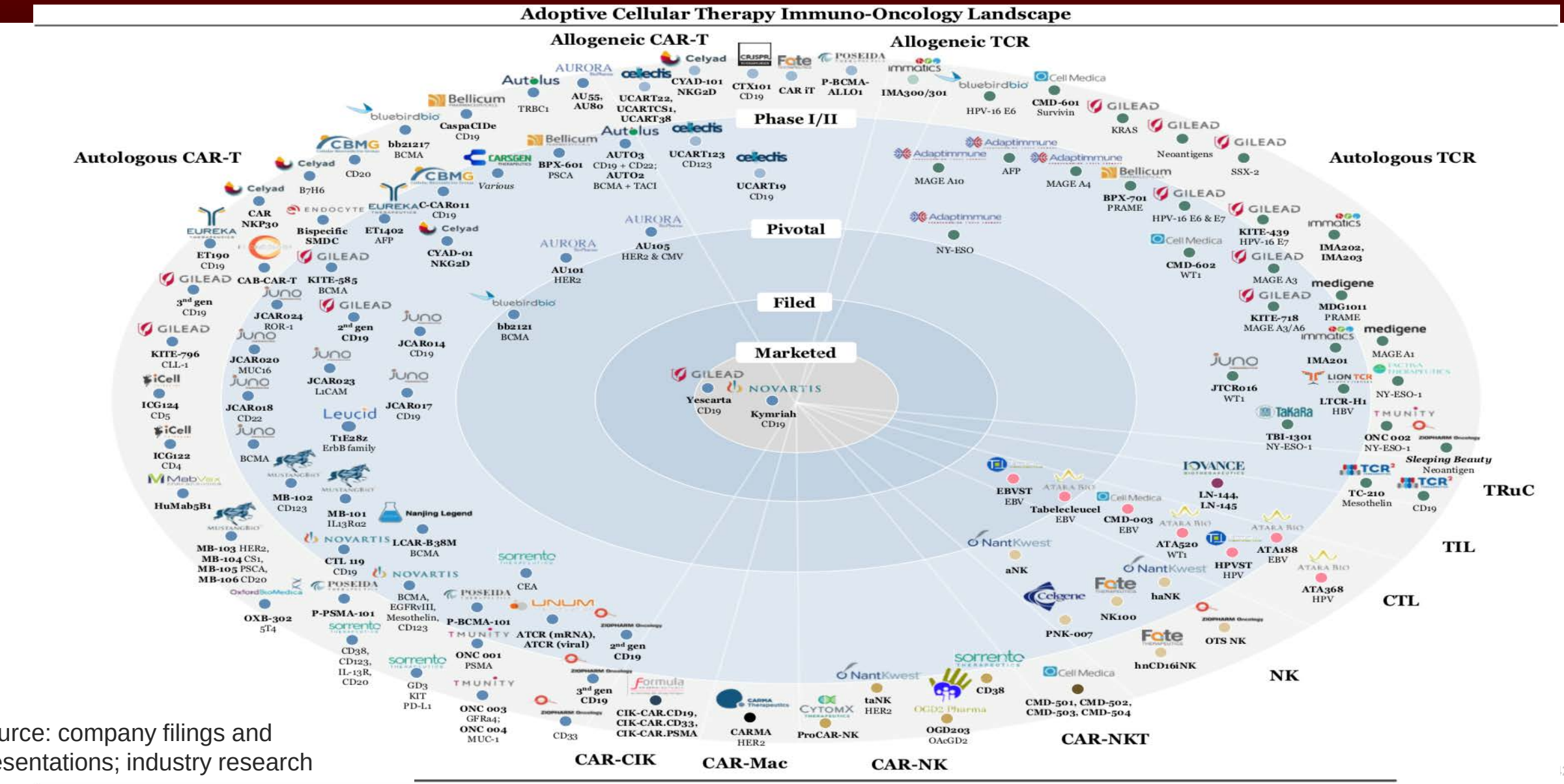
Shultz and Mackall, Sci Trans Med, In Press, 2019

Nonetheless….,*Cancer Cell Therapy (and non-Cancer) Is Experiencing an Inflection Point*

- FDA Approvals: 3 in 2017/2018
  - ✓ Kymriah for Pediatric/Young Adult B-ALL
  - ✓ YesCarta for Adult Large B Cell Lymphoma
  - ✓ Kymriah for Adult Large B Cell Lymphoma
- Tang, Nature Reviews Drug Discovery, May 2018 and highlighted by the Cancer Research Institute
  - ✓ 753 cancer cell therapy in the global development pipieline
  - ✓ 375 cancer cell therapies in clinical studies
  - ✓ 350 cancer cell therapy entered the pipeline since September 2017 (87% increase)
  - ✓ 113 targets pursued in 7 different classes
- FDA Statement: January 15, 2019

  "….We anticipate that by 2020 we will be receiving more than 200 INDs per year, building upon our total of more than 800 active cell-based or directly administered gene therapy INDs currently on file with the FDA. And by 2025, we predict that the FDA will be approving 10 to 20 cell and gene therapy products a year based on an assessment of the current pipeline and the clinical success rates of these products…."

2019: Adoptive Cell Therapy Immuno-Oncology Landscape



Source: company filings and presentations; industry research

Rapidly Evolving Technologies for Manufacturing

"Miltenyi Prodigy" distributed manufacturing model could enable production within hospitals

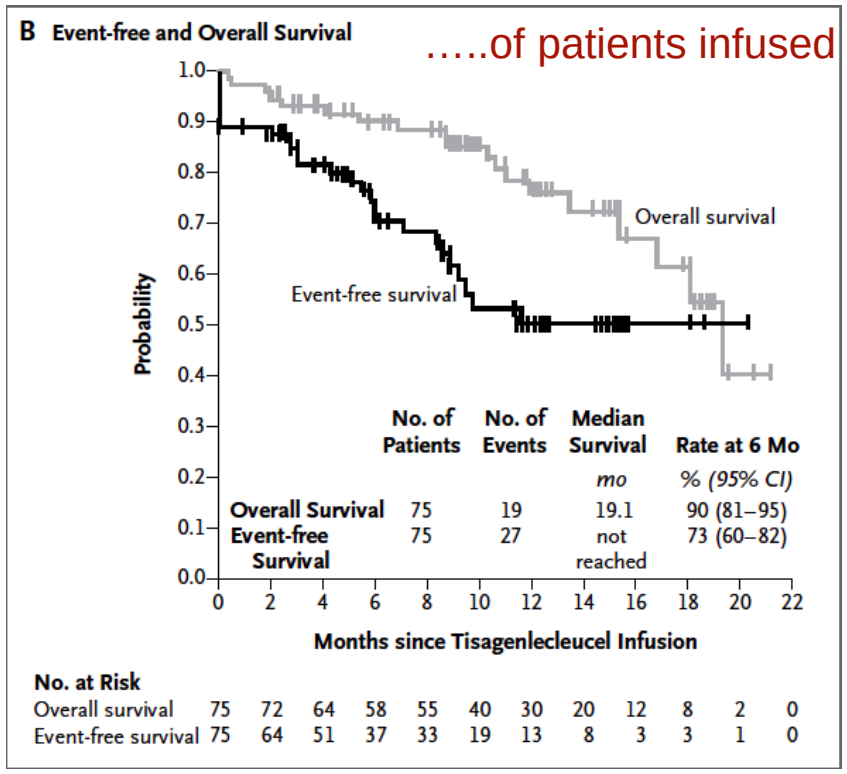
"Lonza's" cocoon closed manufacturing system could allow for unprecedented scale-up

Evolving Models for Manufacturing: Centralized vs. Distributed

- Centralized Manufacturing
  - ✓ Current FDA and EMA approved CAR T cell products are manufactured in a centralized commercial manufacturing plant.
  - ✓ Centralized manufacturing is very costly and limits what companies will develop to products with high profit margins
  - ✓ Cost will likely come down in the future but with tighter margins, it seems unlikely the private sector develop these for rare indications, such as pediatric cancers
  - ✓ Off-the-shelf would prove the most cost effective but still much work to do
- Distributed manufacturing
  - ✓ model would enable hospitals to manufacture individualized products using automated platforms
  - ✓ In some ways akin to bone marrow transplantation at specialized medical centers

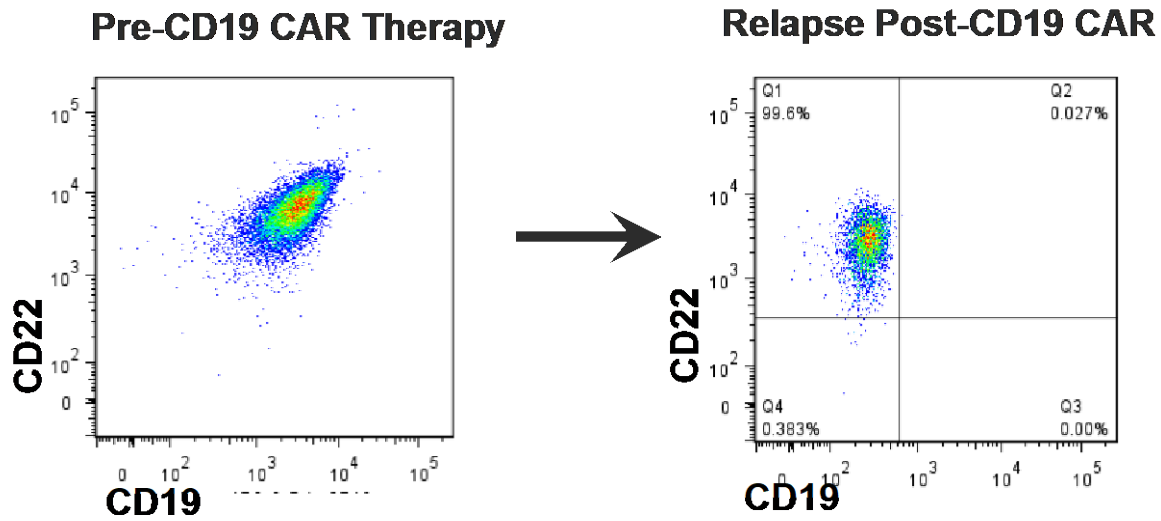
Scientific Challenges Revealed by Experience in B-ALL:
Intent-to-treat CR 66%, CR after infusion 81% with ~50% EFS, Sustained Remission Intent-to-Treat ~30%

Maude et al, NEJM 2018



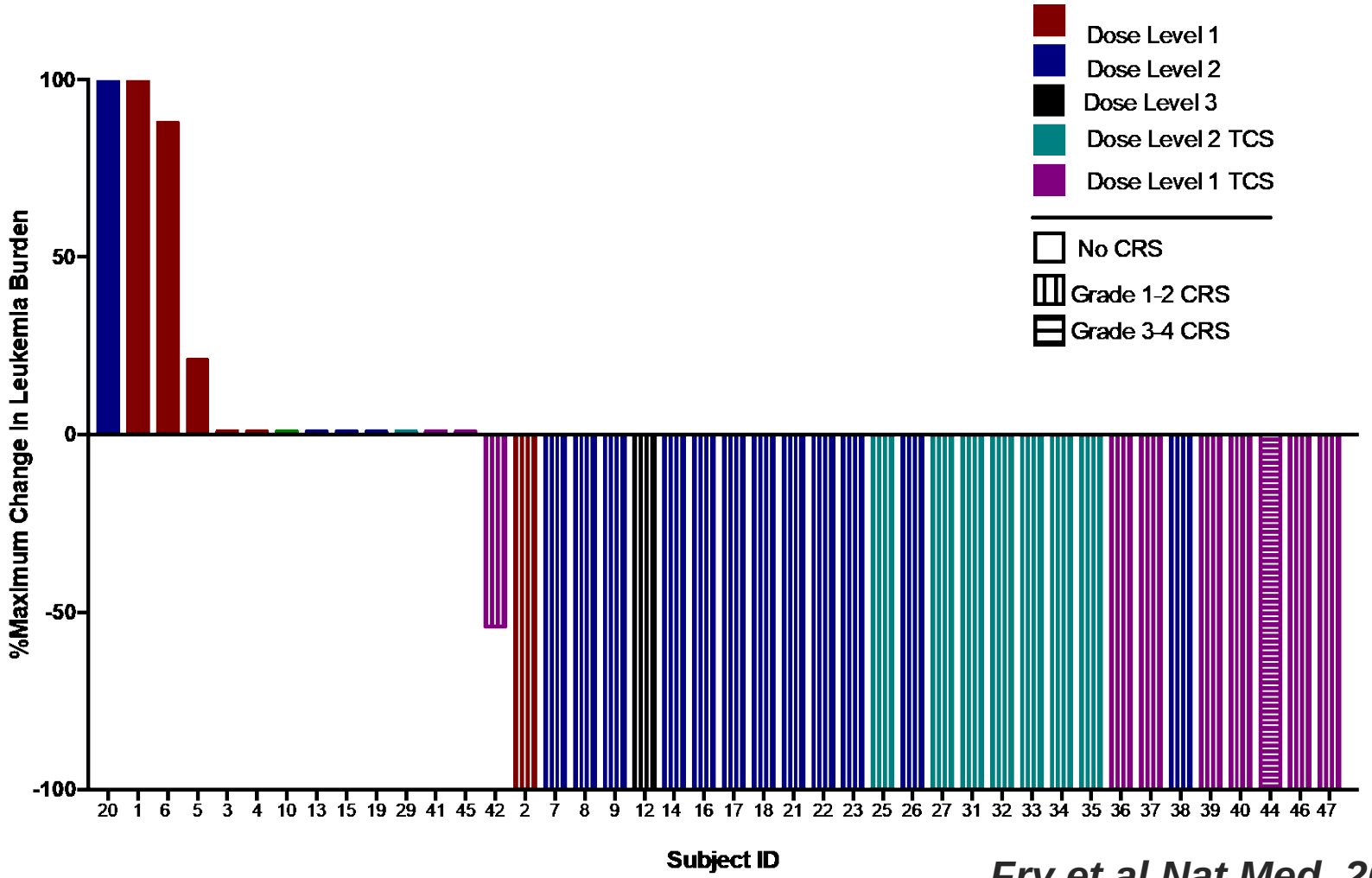
Major Challenges:

- ✓ Manufacturing issues (delays, failures)
- ✓ Toxicity: supportive care improving
- ✓ Acquired Resistance: Antigen loss escape
  - 15/16 relapses tested were CD19neg



Stanford MEDICINE | Center for Cancer Cell Therapy

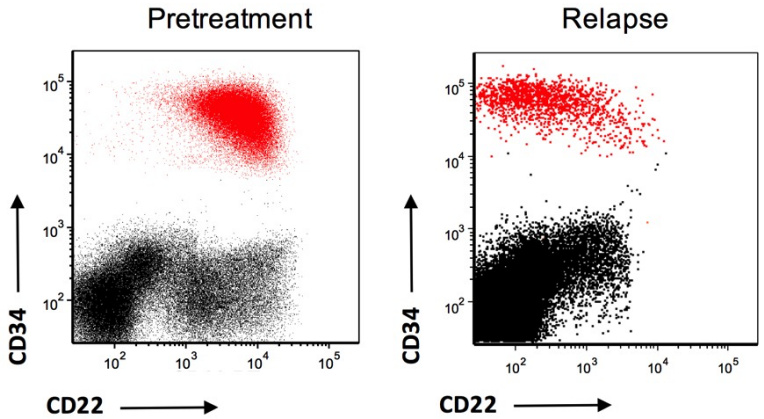
CD22-CAR Induces a Similarly High Response Rate in B-ALL as CD19-CAR….. First evidence that CD19 is not a unique target for CAR efficacy

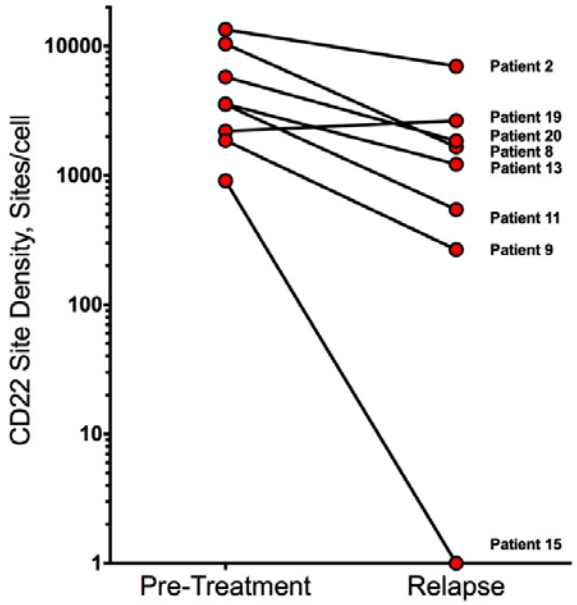


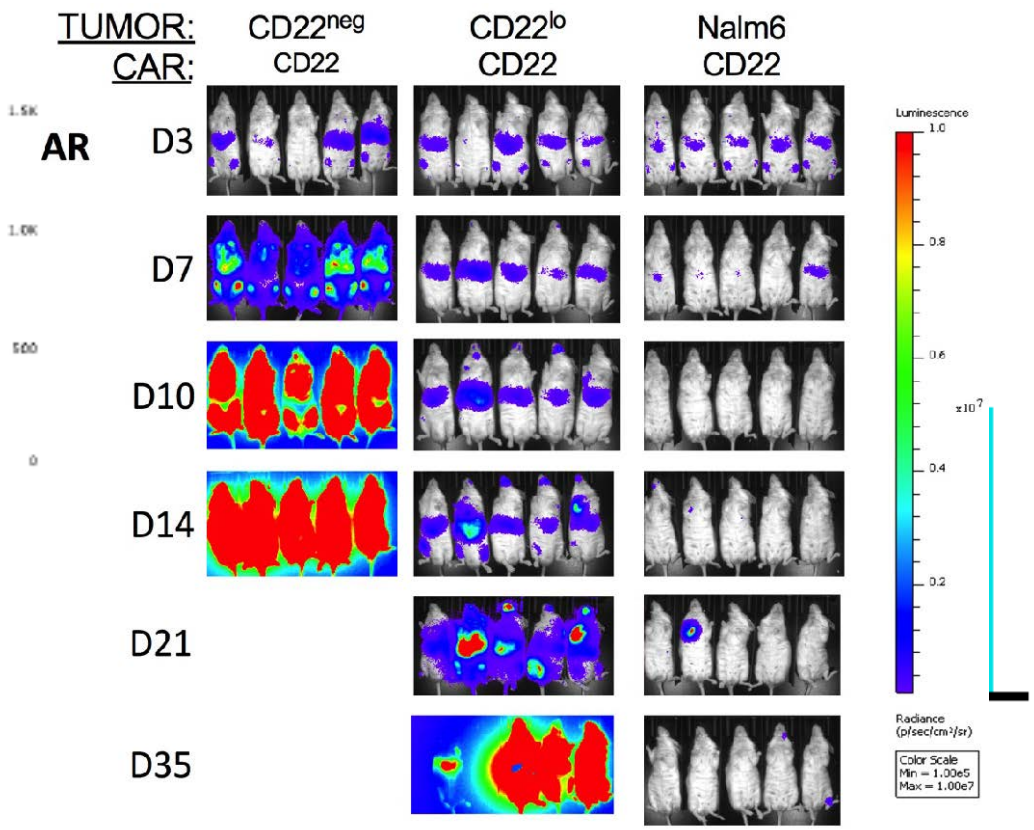
Stanford MEDICINE | Center for Cancer Cell Therapy

Fry et al Nat Med, 2018 plus updated data
Courtesy Nirali Shah, NCI

Like CD19-CAR, *Antigen Lo* Relapse Limits Efficacy

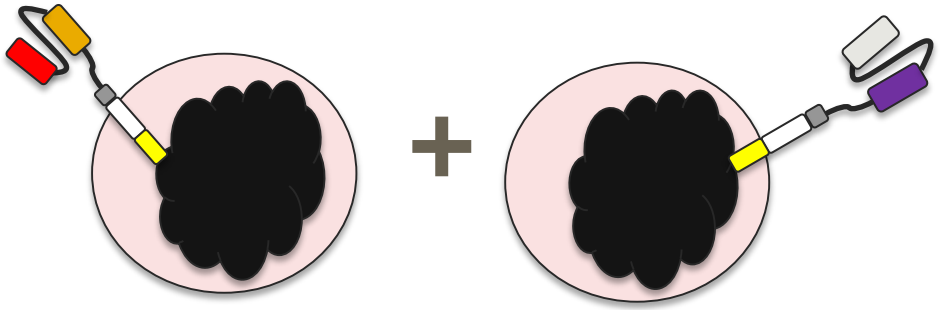






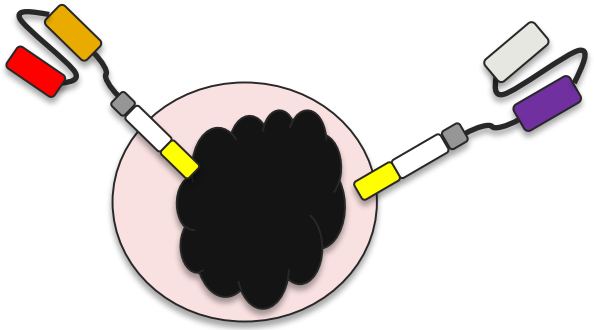
Fry et al, Nat Med, 2018

Options for Simultaneous Targeting of Two Antigens by CAR-T cells



Co-administration

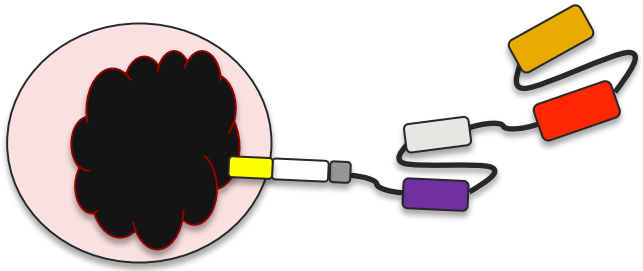
Under study at Seattle Children's



Co-expression

- ✓ ***Two vectors (Cotransduction)***
- ✓ ***One Bicistronic vector***

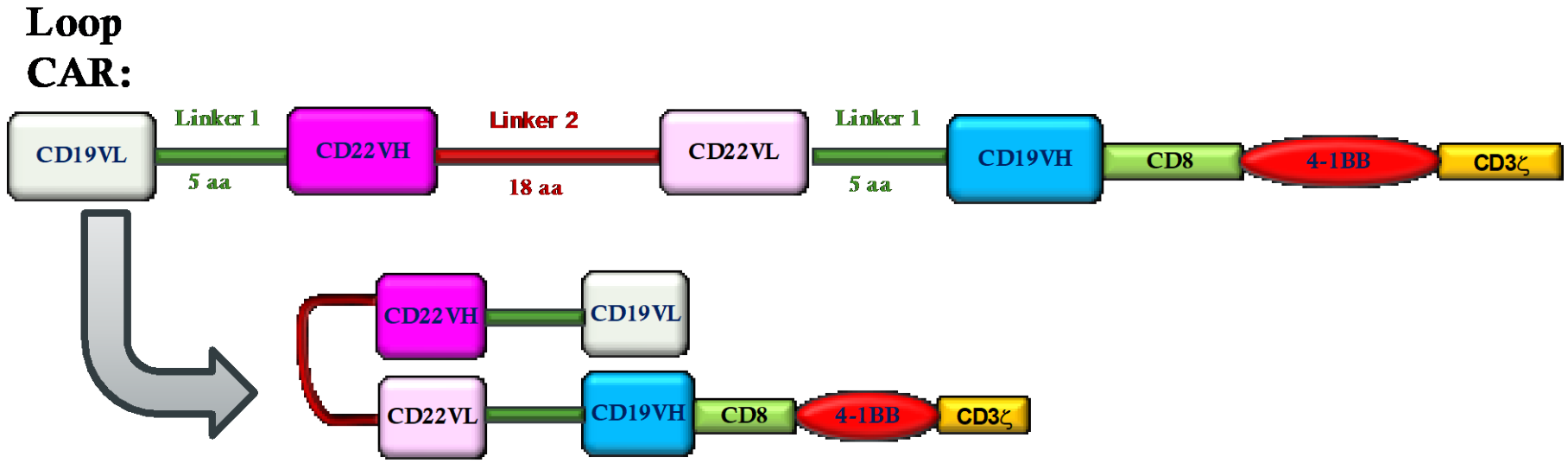
Soon to open at NCI and Children's Colorado

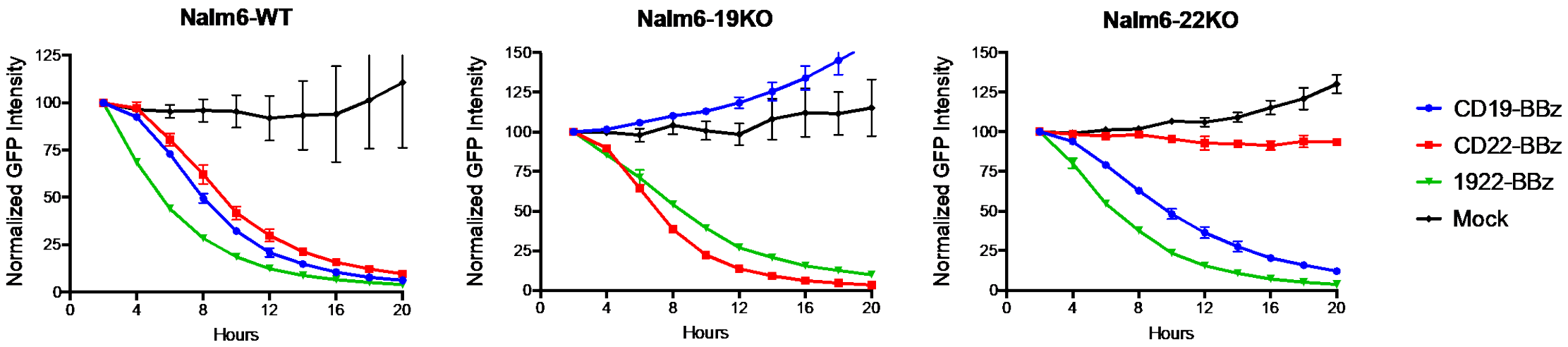


Bivalent-Bispecific Receptor (aka TanCAR)

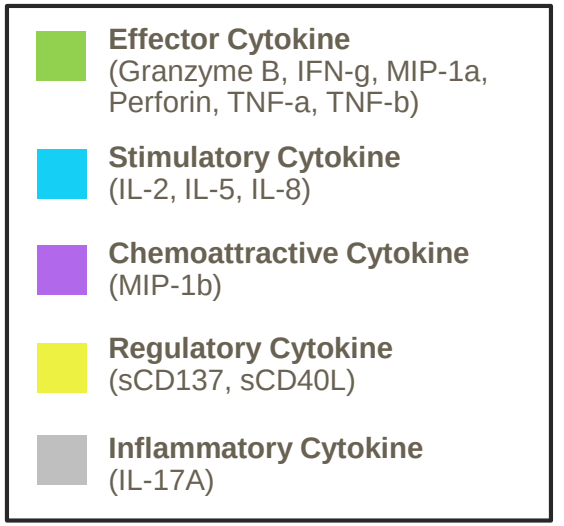
Open at Stanford and NCI for Children and Stanford for adults

Bivalent “Loop” CAR Provides a CD19/22 OR GATE





Manufactured CD19/22-CAR Products Demonstrate Cytokine secretion following stimulation with CD19, CD22 or both CD19 and CD22



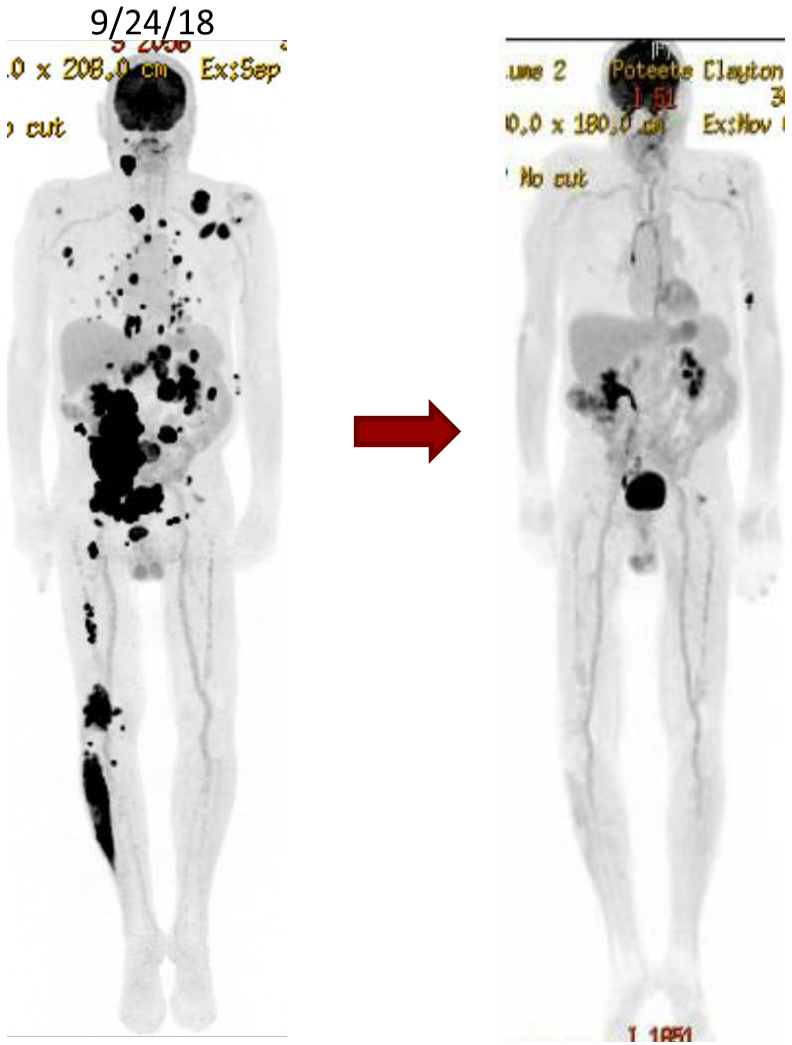
Predominance of effector cytokines;

- Granyzme B
- Perforin
- IL-2

NGFR CD19 CD22 CD19/ CD22 NGFR CD19 CD22 CD19/ CD22 NGFR CD19 CD22 CD19/ CD22

Impressive Response in Lymphomatous B-ALL Following Bispecific CD19/22 CAR Infusion

- Two trials of CD19/22-bispecific CAR at Stanford underway: Pediatric and Adult
- Relapsed refractory B cell malignancies
  - ✓ Primary objectives: Safety and Feasibility
  - ✓ Secondary objectives:
    - o Response rate
    - o Does CD19 and/or CD22 site density impact response to therapy in DLBCL?
    - o Can we distinguish recurrence due to antigen downmodulation from recurrence due to T cell failure?
- Dose escalation continuing
- Twelve patients treated (10 at DL1, 2 at DL2)
  - ✓ Maximum CRS Grade 2, Maximum neurotoxicity Grade 2
  - ✓ Of 5 patients with DLBCL: 1CR, 2PR, 2PD
  - ✓ Of 6 patients with B-ALL: 5 CR



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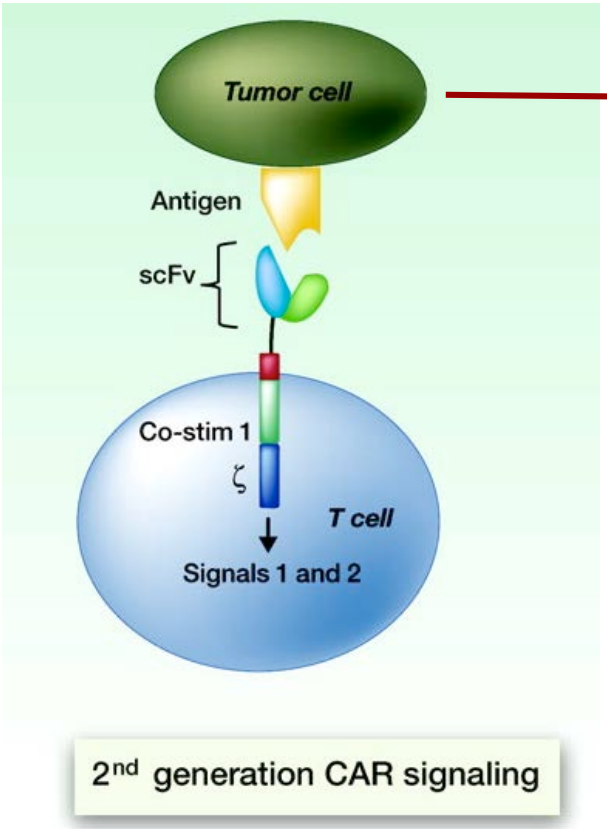
CAR-T Cell Prototype: 2019

Anticipate clinical testing of more complex and sophisticated CARs in the next 5 years



In clinical trials

CD19
CD22
19/22
GD2
BCMA
CD123
CD33
B7H3
Mesothelin
EGFRViii
IL13Ra2
Her2
PSMA
ROR1
....

- ***recognize intact cell surface antigens***
- ***non- MHC restricted***
- ***costimulatory signal provided coincident with antigen recognition***

- ✓ Bispecific CARs (OR gates)
- ✓ Trispecific CARs (OR gates)
- ✓ Quad-specific CARs (OR gates)
- ✓ Regulatable CARs (small molecule on or off)
- ✓ "Universal" CARs
  - Antibody or other protein administered activates CAR
  - Switch antibody in event of antigen escape
- ✓ AND Gate CARs (increase specificity for antigen groups)
- ✓ Switch Receptor CARs
  - Turns an inhibitory signal in the tumor microenvironment into an activating signal
- ✓ Exhaustion-resistant CARs
- ✓ CARs engineered to recognized low antigen density
- ✓ CARs that make their own growth factors
  - No lymphodepletion, better persistence?
- ✓ Allogeneic off-the-shelf CAR
- ✓ γδ-CAR, NKT-CAR
- ✓ ……..

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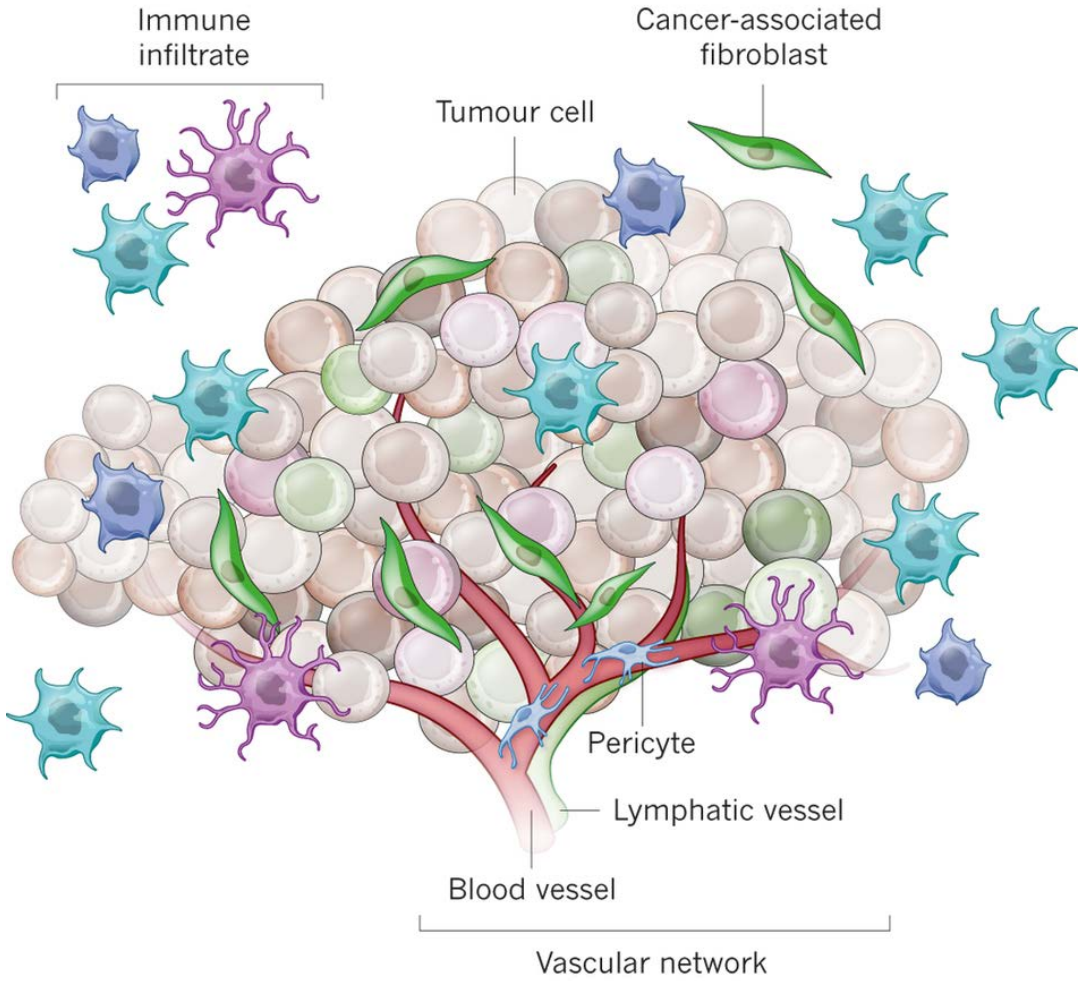
Challenges and Opportunities Facing CAR-T Cell Therapy for Solid Tumors



Juntilla, Nature, 2013

Challenges

- ✓ Low/Heterogeneous Antigen Expression
- ✓ T cell exhaustion (intrinsic T cell dysfunction)
- ✓ Suppressive microenvironment (extrinsic T cell dysfunction)
- ✓ Insufficient tumor trafficking?

Opportunity?

- Epitope spreading could be robust in tumors with high neoantigen levels

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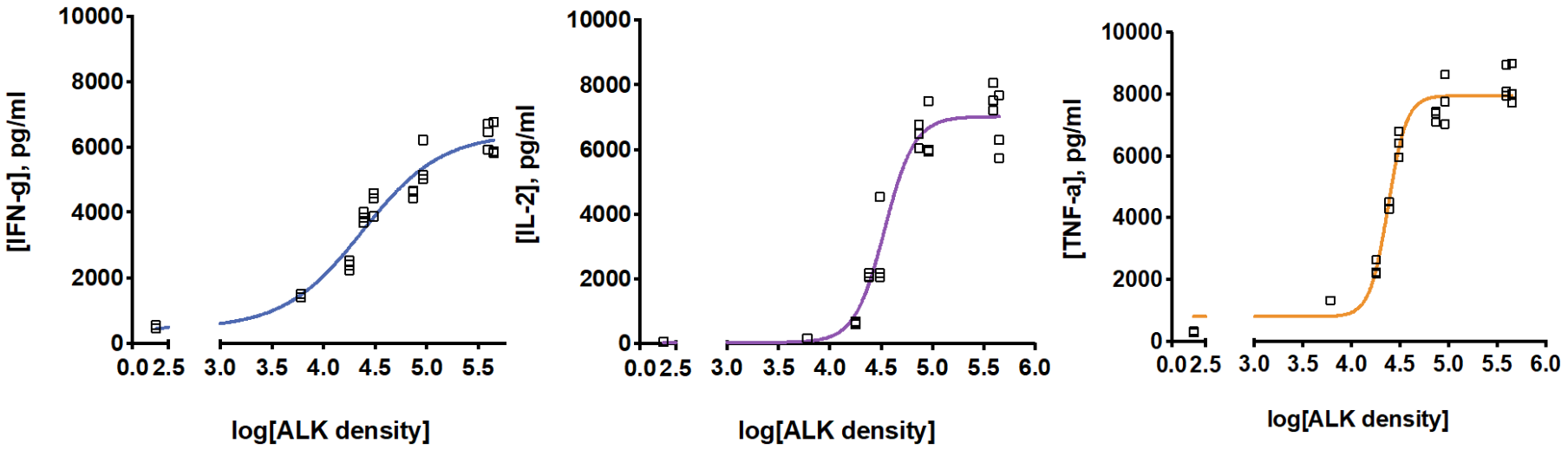
Target Antigen Density Exerts a Major Impact on ALK-CAR T Cell Cytokine Production: Quality and Quantity



= *Range of densities on ALK Expressing Cell Lines*

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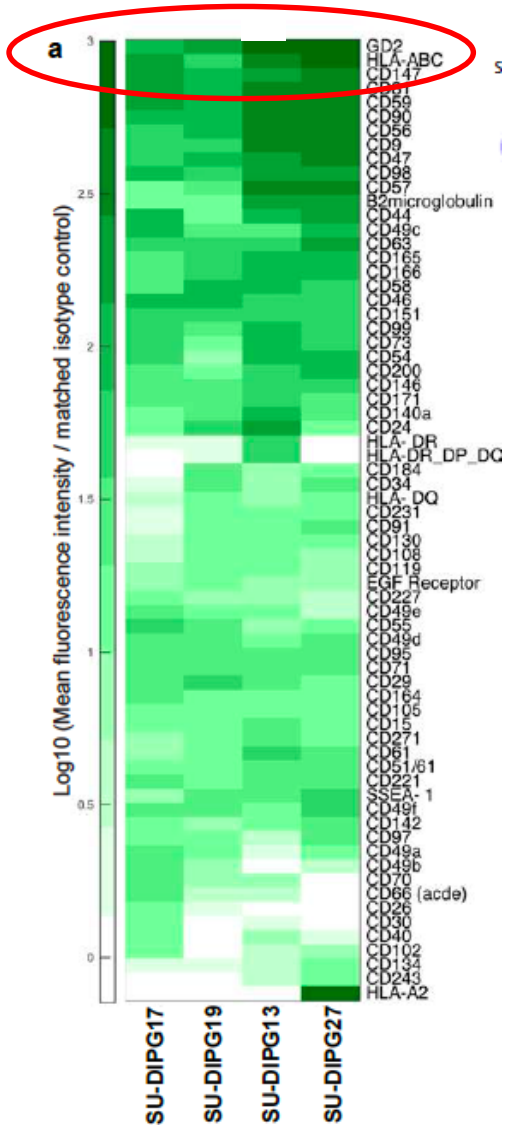
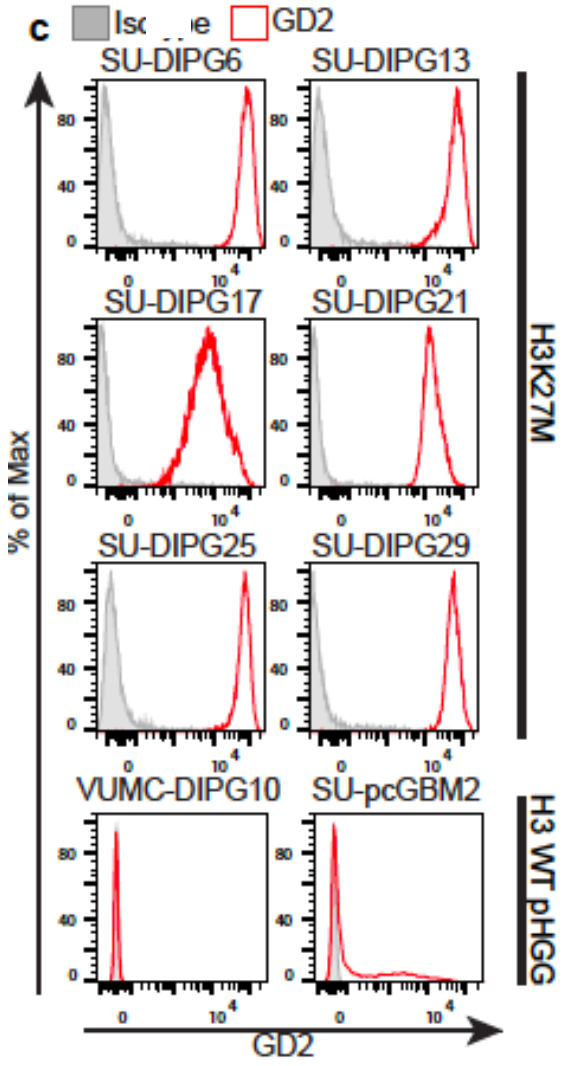
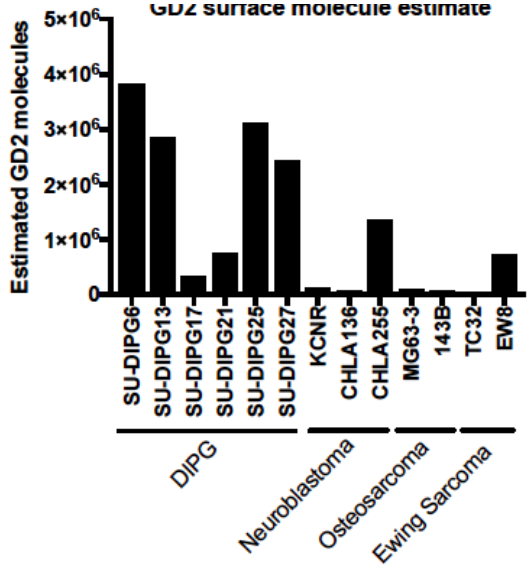
Walker/Majzner et al, 2017, Mol Therapy

GD2 Appears as the Highest Differentially Expressed Surface Antigen on K27M DIPG Early Passage Lines *Mount/Majzner, Nat Med, 2018*



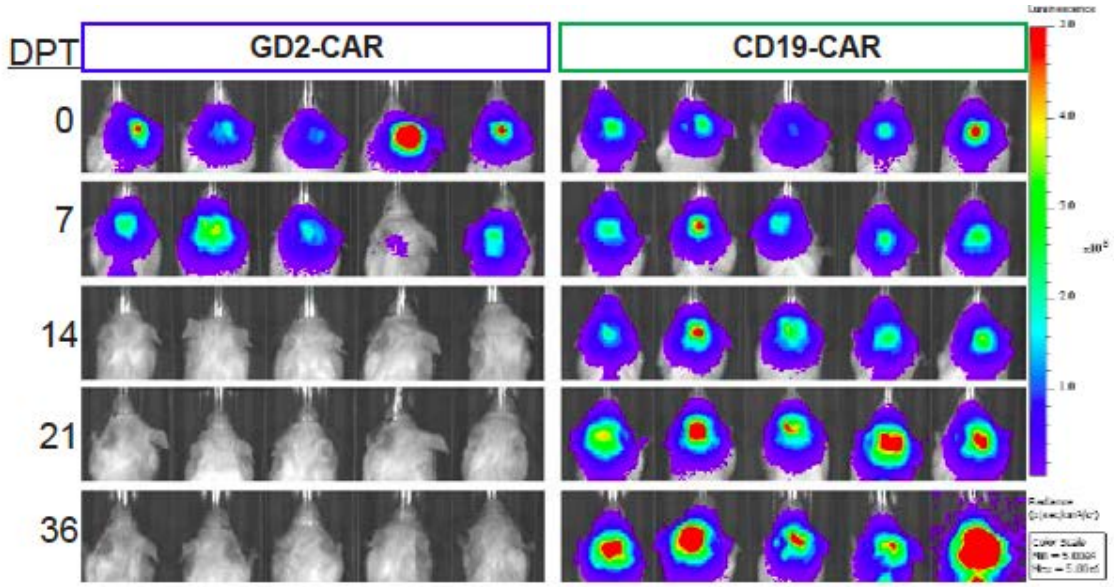


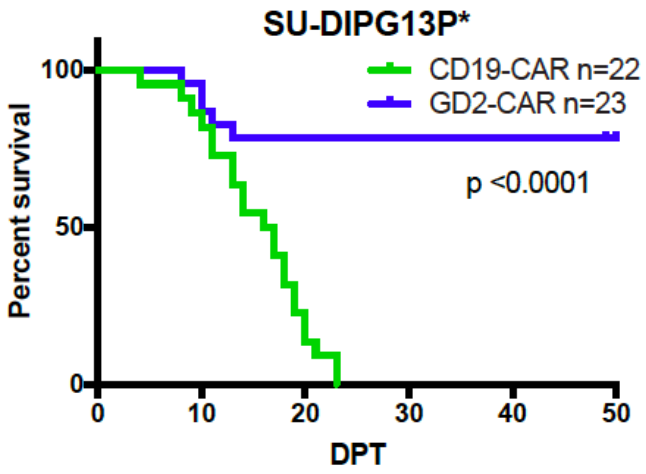
K27M DMG Lines express more GD2 than any other pediatric tumor analyzed



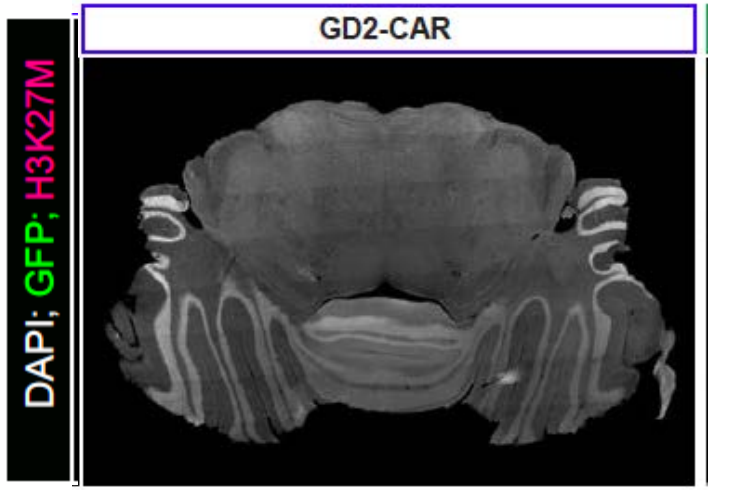
Michelle Monje MD, PhD *Chris Mount, MSTP* *Robbie Majzner, MD*

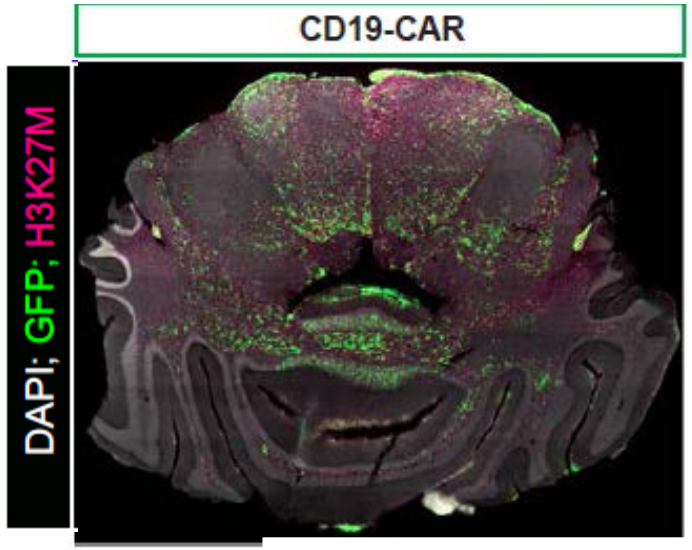
Intravenous Administration of An “Optimized” GD2.BB.z-CAR Shows Potent Activity in Murine Models of K27M DIPG and Spares Normal Brain Tissue





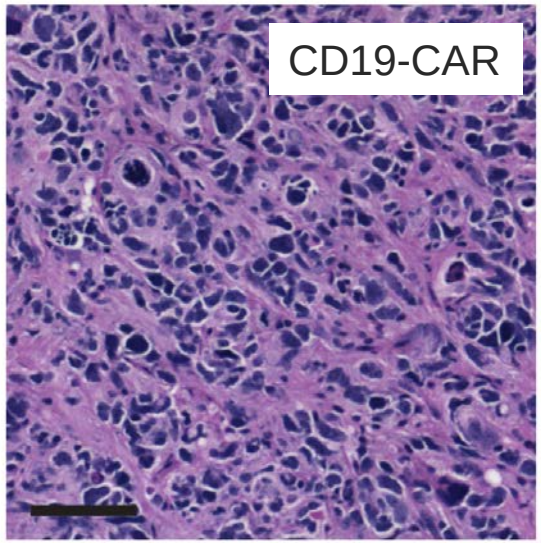
Early deaths in a small fraction associated with ventricular enlargement, likely due to tumor swelling

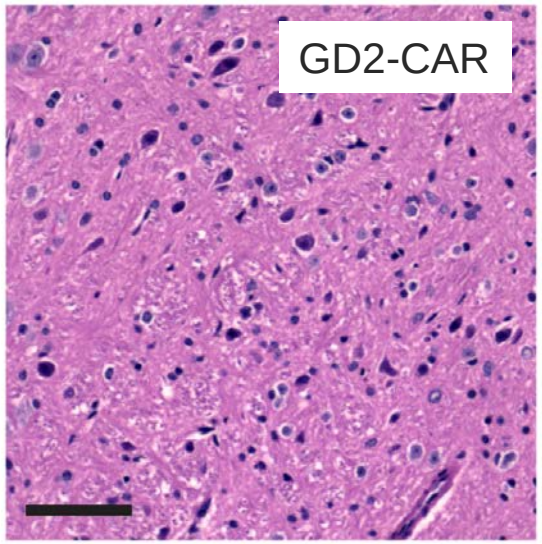


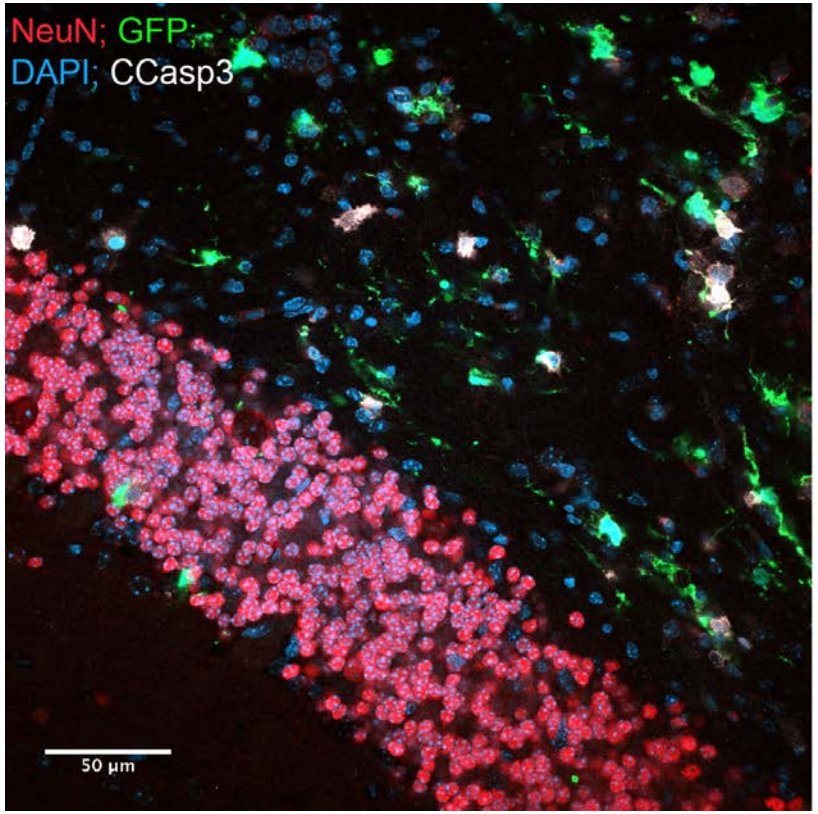


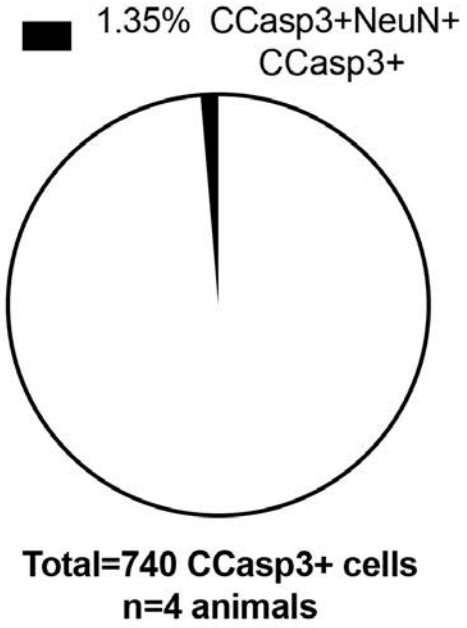
Mount/Majzner, Nature Med, 2018

Neurons in the Tumor Microenvironment are Spared by the GD2-CAR T Cells









Mount/Majzner, Nature Med, 2018

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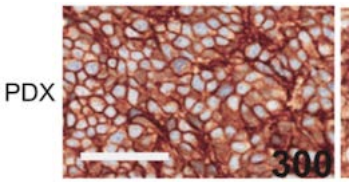
Clinical Trial of GD2-CAR T cells for Diffuse Intrinsic Pontine Glioma

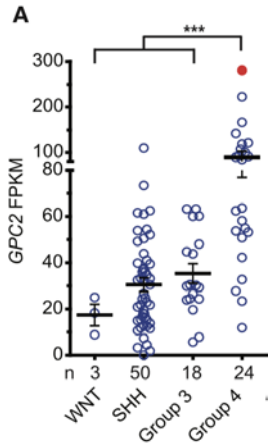
- Single institution, investigator-initiated trial
- Eligibility: 3 months from completion of upfront XRT or earlier recurrence, no corticosteroids, no thalamic/cerebellar involvement, no bulky disease
- Autologous GD2.BBz.iCasp9-CAR T cells (1e6/kg, 3e6/kg, 1e7/kg) following cyclophosphamide/fludarabine conditioning regimen
- Careful monitoring for increased intracerebral pressure
- In the event of unacceptable toxicity
  - ✓ Supportive care for elevated ICP
  - ✓ Consider dasatinib to reversibly suppress CARs
  - ✓ Consider AP1903 to activate the suicide switch

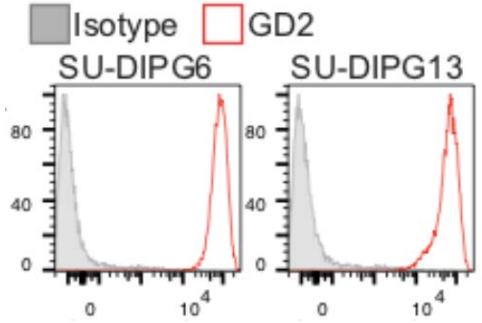
Candidate Cell Surface Targets on Pediatric Solid Tumors With High Differential Expression

Medulloblastoma Group 3, 4
Neuroblastoma



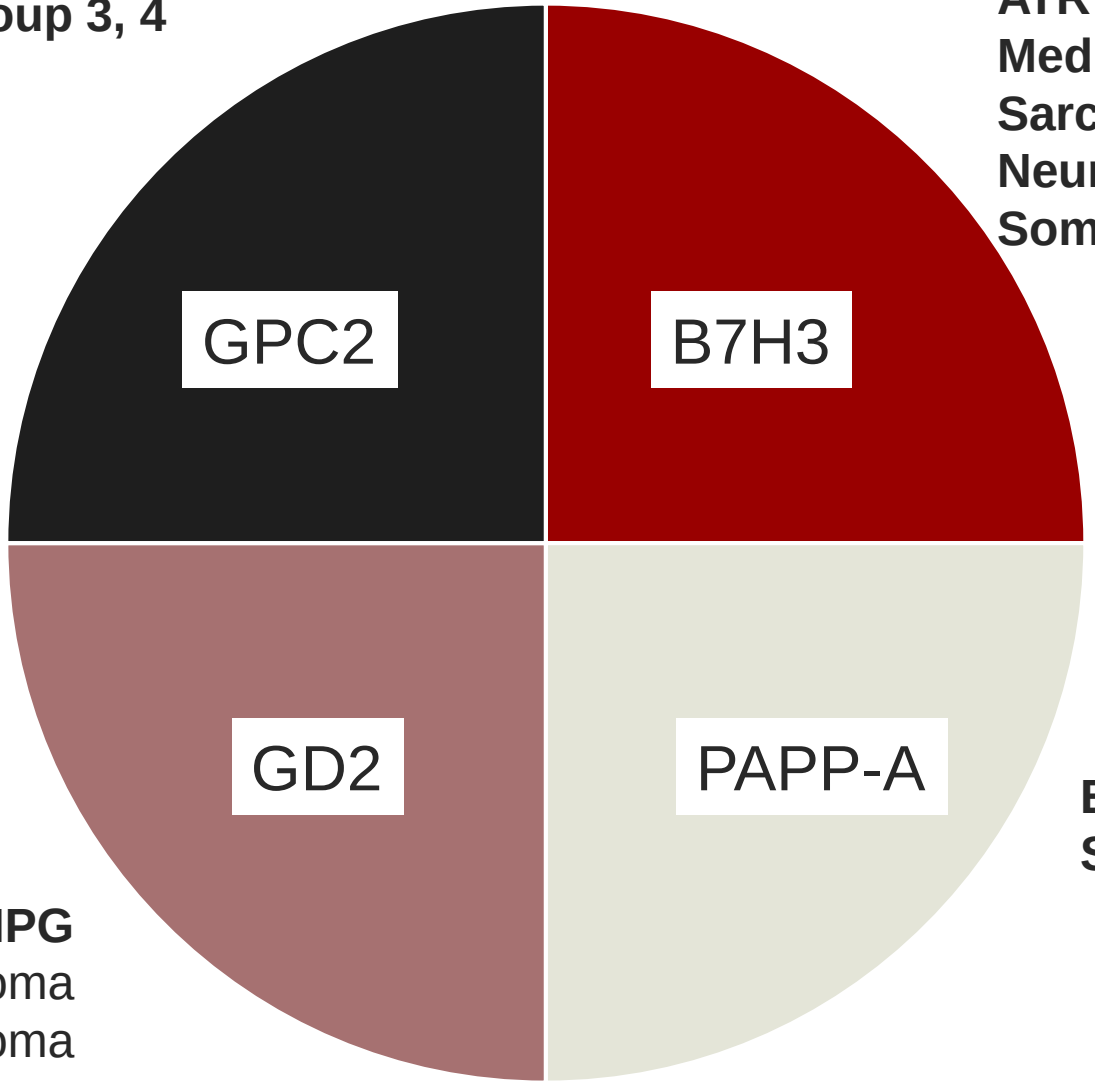
Bosse, Cancer Cell, 2017



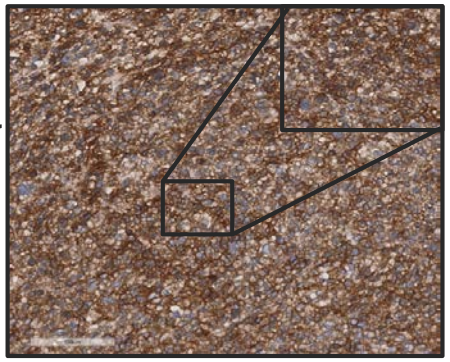


Mount, Nat Med 2018

DIPG
Neuroblastoma
Osteosarcoma

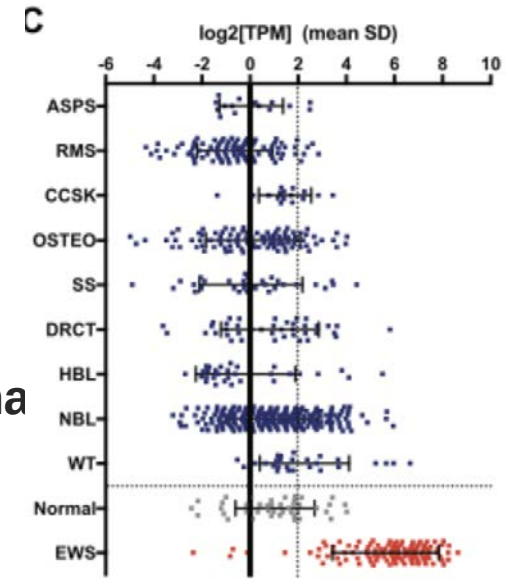


ATRT
Medulloblastoma
Sarcomas
Neuroblastoma
Some AML



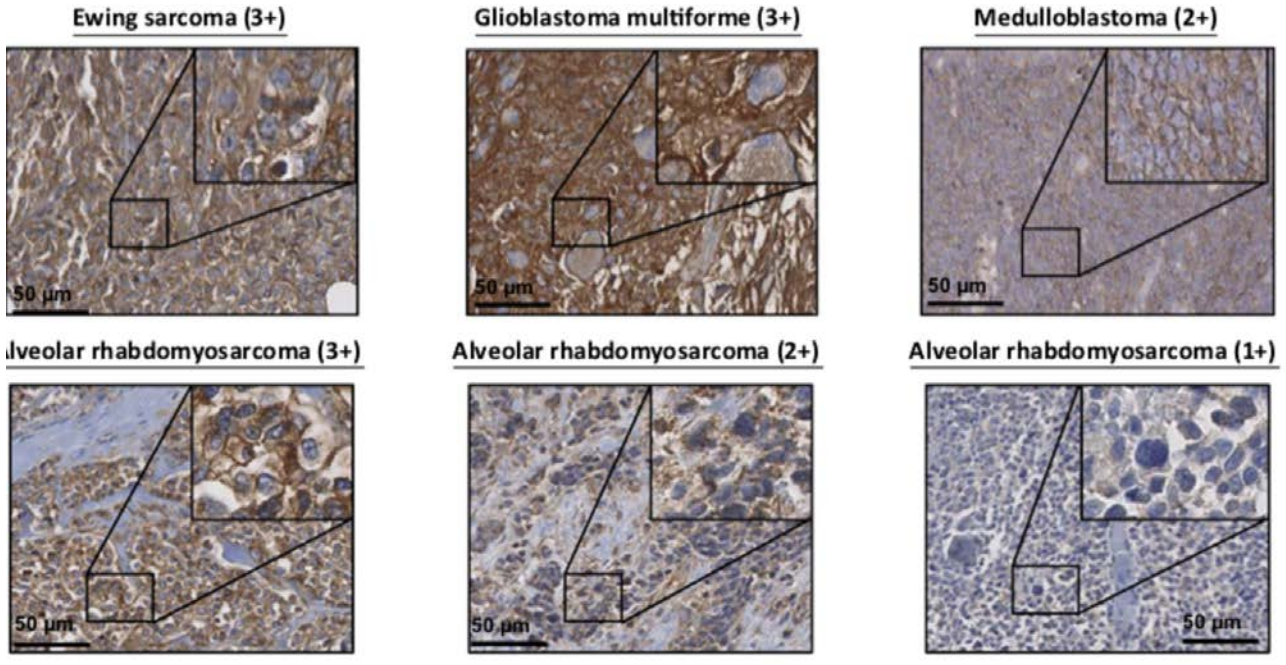
Majzner, CCR, 2019
Theruvath, In preparation

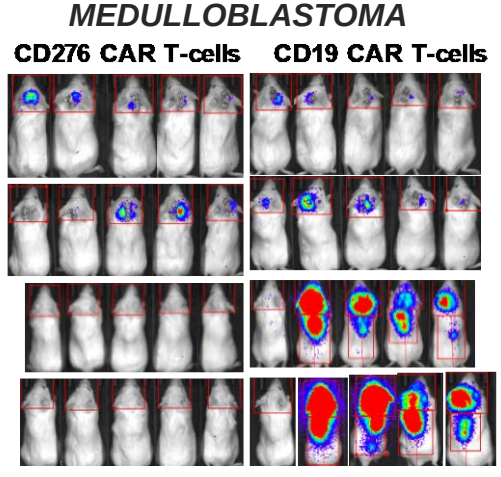
Ewing Sarcoma

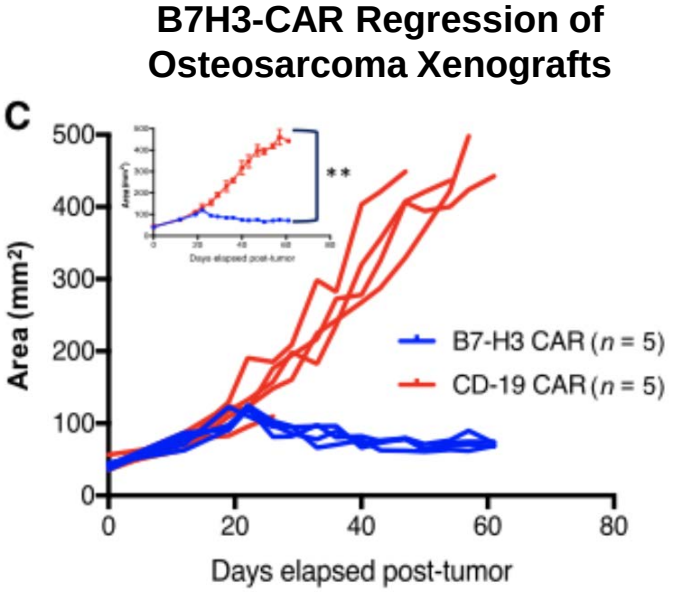


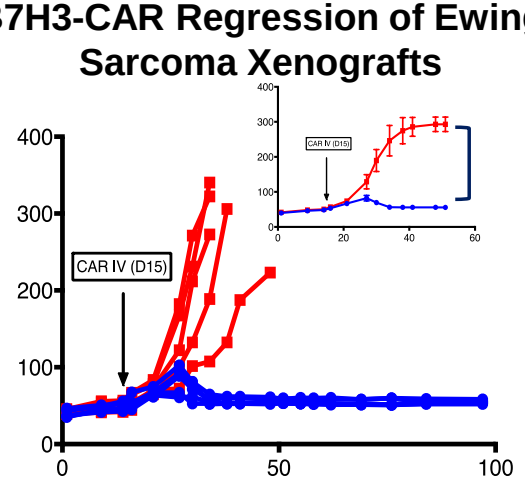
Heitzeneder, JNCI, 2019

Many Pediatric Solid Tumors Overexpress B7H3 and Regress Following B7H3-CAR T cells in Preclinical Models (*Majzner, Clin Can Res 2019*)









Conclusions

- CAR T cells made their debut in pediatric oncology and drove a paradigm-shift in the field of cancer cell therapy and gene therapy
- Many manufacturing challenges and scientific challenges remain. But, the science and emerging technology in the field is very robust.
- FDA, academic medical centers and private sector are betting that this field that will grow dramatically in the next 5-10 years
- Continued positive clinical results will continue to drive technological advances and decreased cost of goods which will, in turn, drive costs down and increase accessibility in coming years.
- Pediatric oncology could continue to benefit from these advances, especially if the distributed manufacturing model is adopted by regulatory agencies and leading medical centers.

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ALLIANCE FOR CANCER GENE THERAPY
Discovering new ways to treat and defeat cancer

PARKER INSTITUTE
for CANCER IMMUNOTHERAPY

OBSIDIAN THERAPEUTICS

LUDWIG CANCER RESEARCH

STAND UP TO CANCER

CIRM
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Dinutuximab: a newly approved Immunotherapy for the Treatment of Neuroblastoma

Nick Bird, *Solving Kid's Cancer*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Dinutuximab: a newly approved immunotherapy for the treatment of neuroblastoma

7TH ACCELERATE PAEDIATRIC ONCOLOGY CONFERENCE

14-15 FEBRUARY 2019 | BRUSSELS, BELGIUM

Nick Bird

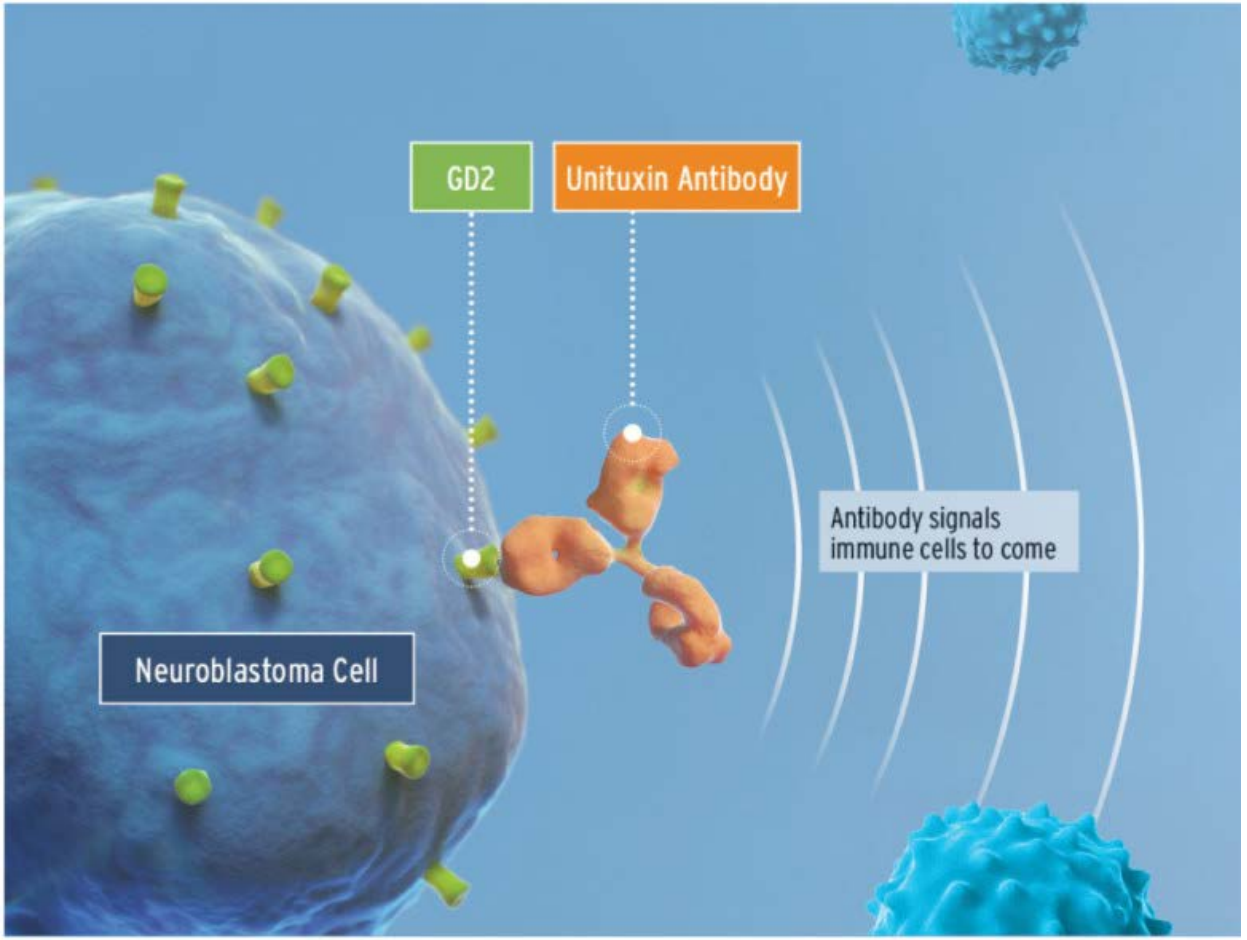
- Adam’s Dad
- Chair & Research Trustee/Director, Solving Kids’ Cancer Europe
- Consumer Member, UK NCRI Children’s Cancer Clinical Studies Group & Neuroblastoma Group
- Patient Expert NICE, dinutuximab & dinutuximab beta

- Diagnosed high-risk neuroblastoma, July 2009
- 4-years of continuous treatment in UK, Germany, and America
- Died July 2013 at 9-years old

Scope

- GD2 as a target antigen in cancer
- Anti-GD2 monoclonal antibodies
- Dinutuximab and dinutuximab beta
  - Early development
  - Major clinical trials
  - Approval & reimbursement
- Other anti-GD2 antibodies
- Reflections on anti-GD2 antibodies & HTAs
- Anti-GD2 – where next?

Ganglioside GD2

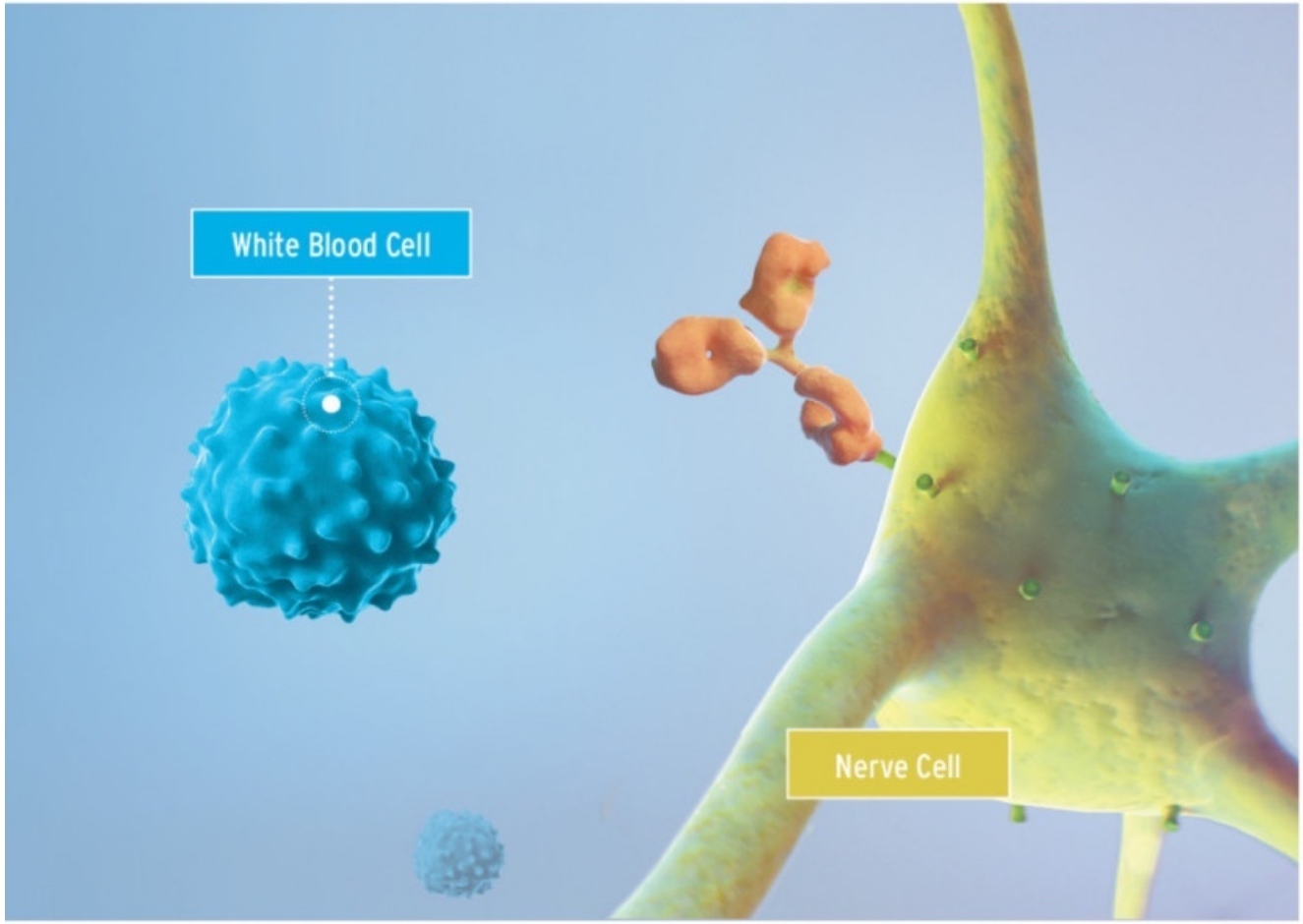


- Gangliosides first discovered in 1942
- GD2 is a cell surface molecule
- Highly expressed on a variety of human cancers including neuroblastoma
- Tumour associated antigen
- Anti-GD2 antibodies bind to GD2 and recruit the immune system to attack and kill the cell

Source: How Unituxin Works (http://www.unituxin.com/about-unituxin/mechanism-of-action/antibody-therapy/)

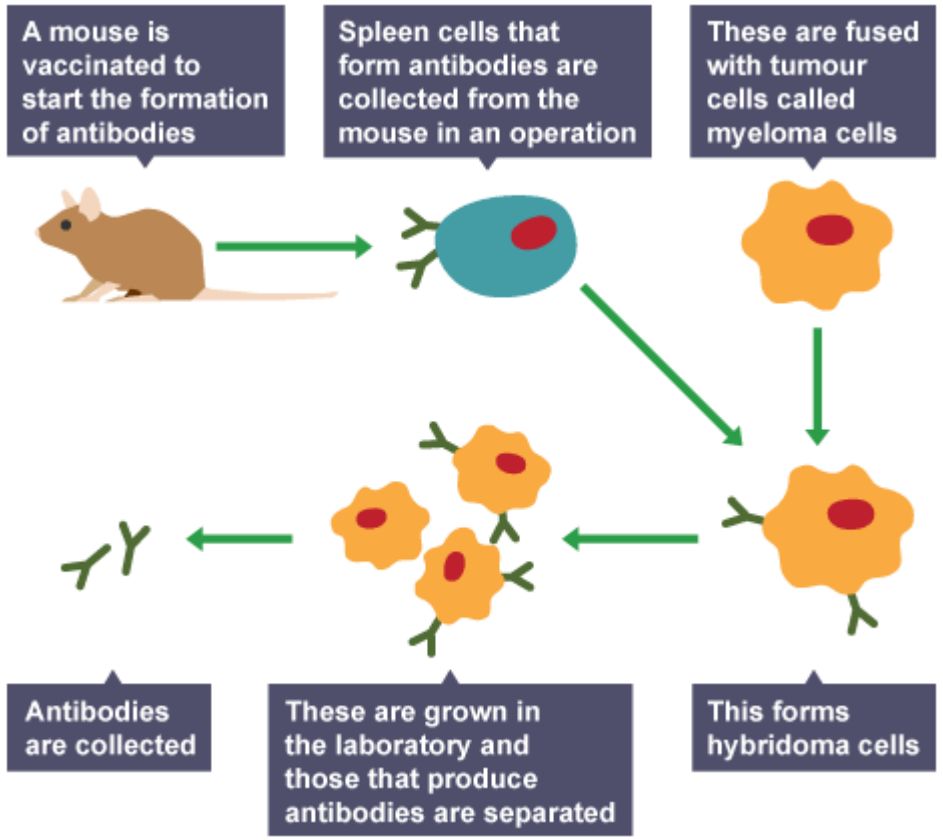
Ganglioside GD2

- GD2 is also found on normal cells
- Expressed in CNS
- Expressed on peripheral nerve fibers
- Major toxicity of anti-GD2 antibodies is neuropathic pain requiring large doses of analgesia
- Anti-GD2 antibodies do not cross blood-brain barrier



Source: How Unituxin Works (http://www.unituxin.com/about-unituxin/mechanism-of-action/antibody-therapy/)

Anti-GD2 Monoclonal Antibodies



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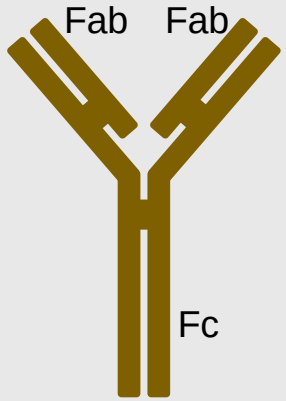
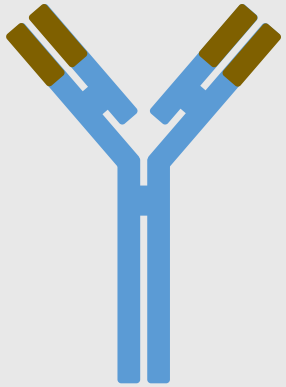
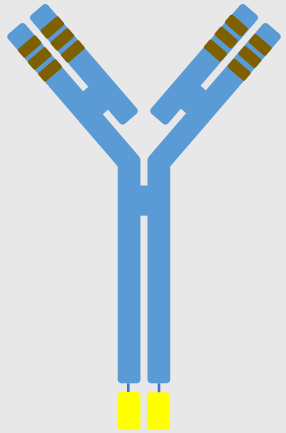
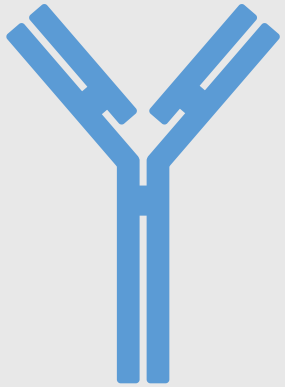
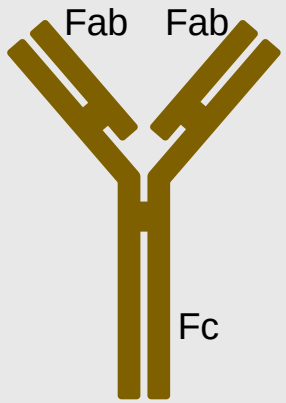
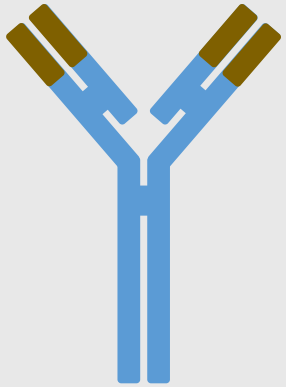
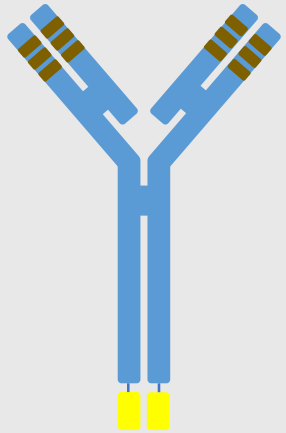
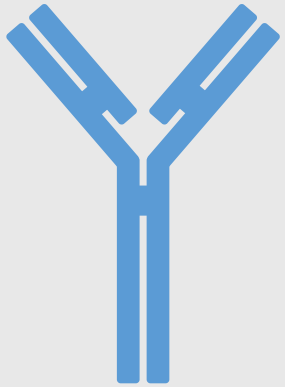
Mouse Sequence %	100%	33%	10%	0%
				
	3F8 14.18 14.G2a	ch14.18/SP2/0 ch14.18/CHO	hu14.18-IL2 hu14.18K322A hu3F8	
Year*	**1985/1986/1989**	**1990/2004**	**2004/2012/2012**	

*Year is earliest reference to antibody in a published paper according to search of pubmed

Anti-GD2 Monoclonal Antibodies

- Passive Immunotherapy
- +Cytokines – IL-2, GM-CSF
- Minimal Residual Disease

Type	Mouse	Chimeric	Humanized	Human
Mouse Sequence %	100%	33%	10%	0%
				
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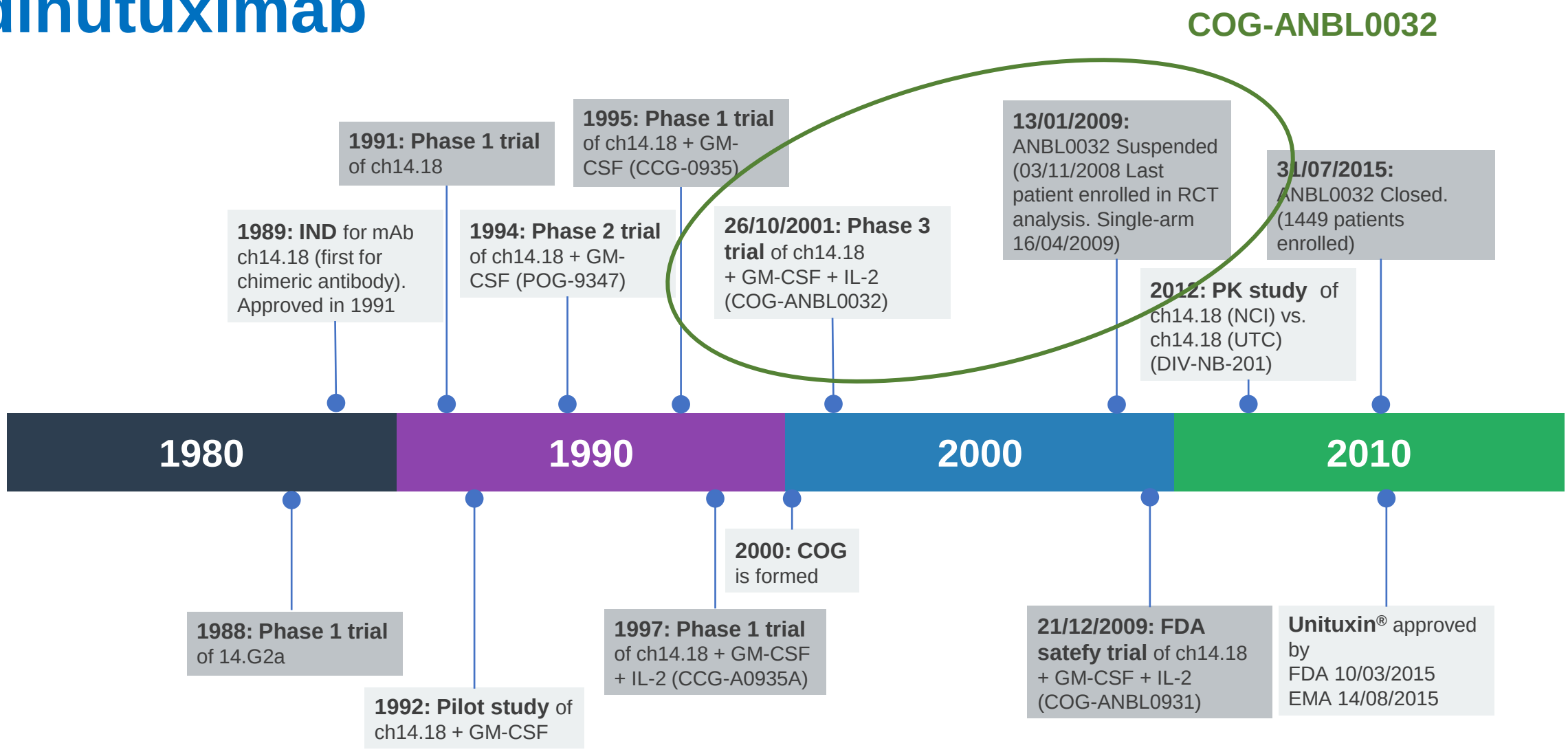
Year*	**1985/1986/1989**	**1990/2004**	**2004/2012/2012**	

*Year is earliest reference to antibody in a published paper according to search of pubmed

ch14.18/SP2/0 dinutuximab



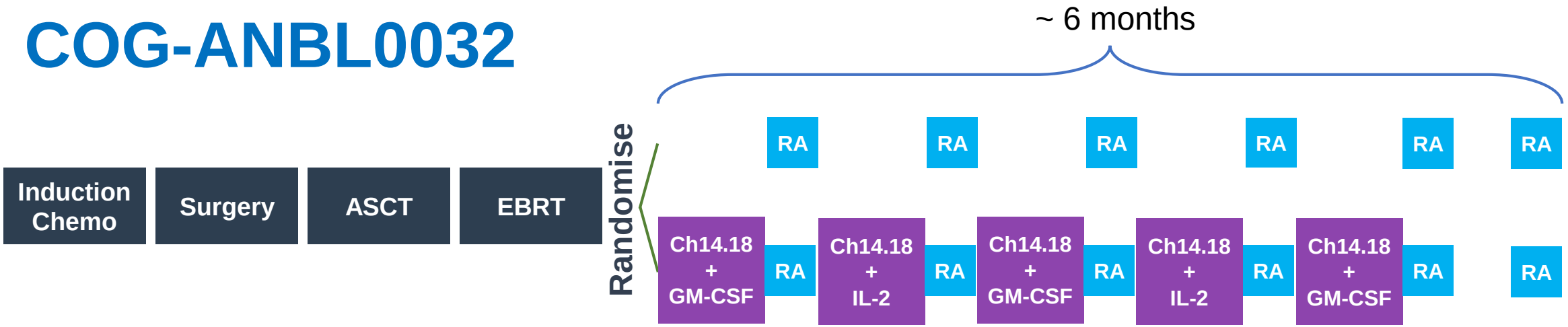
ch14.18/SP2/0
dinutuximab

Unituxin®
(dinutuximab)
Injection

- New Brunswick Biotech ➠ Damon ➠ Repligen ➠ Abbott ➠ ⊖
- 1996 : Alice Yu travelled to DNC (Decision Network Committee) at NCI to review imaging studies etc.
- Biopharmaceutical Resource Branch to produce ch14.18 at NCI-at-Frederick located at Fort Detrick ➠ ANBL0032
- July 2010 : NCI Cooperative Research and Development Agreement with United Therapeutics Corporation (UTC)
- April 2014 : United Therapeutics submitted Biologics Licensing Application (BLA) for Unituxin®

Dr. Alice Yu

COG-ANBL0032

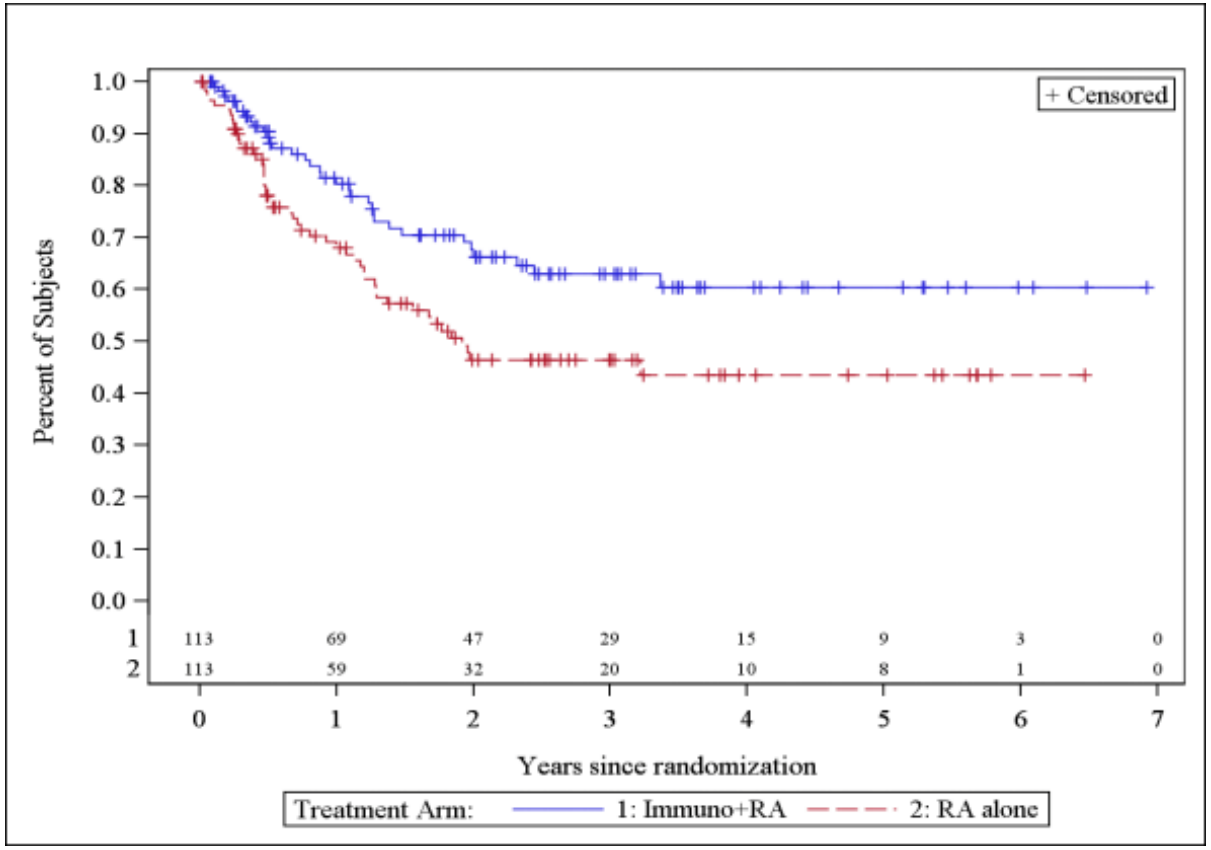


- Opened in **166** institutions across USA, Canada, and Australia
- Planned accrual 386 patients to detect 15% difference in 3yr EFS (50% vs. 65%) over < 5 years
- Dose of 25 mg/m^2/d as minimum 10-hour infusion for 4 consecutive days
- Terminated for superior EFS after **226** (58%) patients accrued between **2001** and **2008**
- EFS at 2yrs ch14.18 arm (66% ± 5%) vs. standard arm (46% ± 5%) (p=0.01)

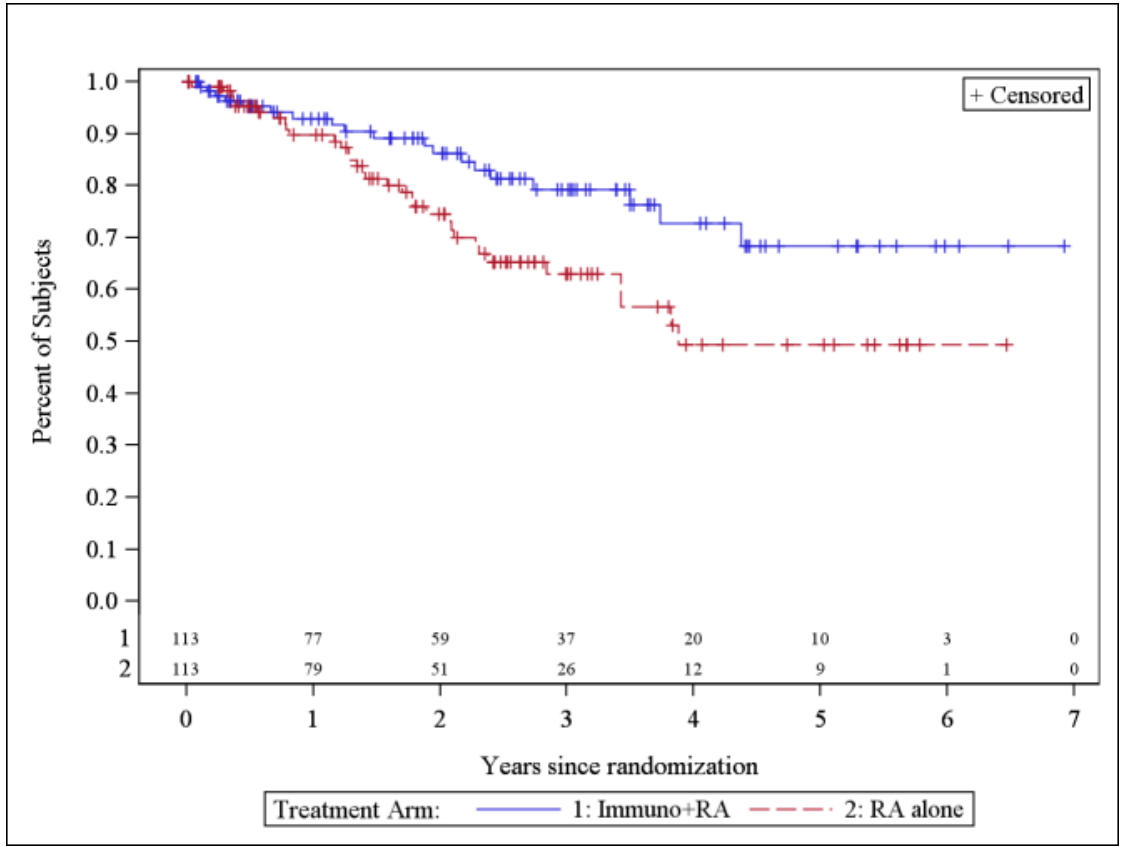
ASCT=Autologous Stem Cell Transplantation; EBRT=Radiotherapy; RA=13-cis-retinoic acid/isotretinoin

COG-ANBL0032

Kaplan-Meier Curve of EFS 13 Jan 2009



Kaplan-Meier Curve of OS 13 Jan 2009



FDA Review | Unituxin®

Company: United Therapeutics Corporation
Application No.: 125516
Approval Date: 3/10/2015

- Approval Letter(s) (PDF)
- Printed Labeling (PDF)
- Summary Review (PDF)
- Officer/Employee List (PDF)
- Office Director Memo (PDF)
- Cross Discipline Team Leader Review (PDF)
- Medical Review(s) (PDF)
- Chemistry Review(s) (PDF)
- Pharmacology Review(s) (PDF)
- Statistical Review(s) (PDF)
- Microbiology Review(s) (PDF)
- Clinical Pharmacology Biopharmaceutics Review(s) (PDF)
- Risk Assessment and Risk Mitigation Review(s) (PDF)
- Proprietary Name Review(s) (PDF)
- Other Review(s) (PDF)
- Administrative Document(s) & Correspondence (PDF)

Date created: April 8, 2015

- Raw dataset for 13 Jan 2009 data analysis was corrupted and not available
- 30 June 2009 data used for ‘confirmatory analysis’ (2yr EFS: 65.6% vs. 48.1%, p=0.033)
- 30 June 2012 data used for ‘supportive analysis’ (3yr EFS: 62.8% vs. 50.9%, p=0.099)
- Observed p-value on 7th interim assessment did not cross alpha boundary (Nominal α=0.0108, p-value=0.0115)
- Study design not statistically powered for overall survival
- 77% of ANBL0931 patients completed treatment. Neuropathic pain (51%) , pyrexia (40%), infusion-related reactions (25%), capillary leak syndrome (23%), hypotension (16%), sepsis (16%)

EMA Review | Unituxin®

- Additional data analysis requested – overall survival as at March 2014
- Increase in EFS in 13-cis RA arm between Jan/June 2009 data due to data corrections
- Overall survival analyses unequivocally demonstrate benefit of immunotherapy – statistically and clinically significant
- August 2015 : EMA marketing authorisation granted for the European Union

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

NICE Appraisal | Unituxin®

NICE National Institute for Health and Care Excellence

- October 2015 : Single Technology Appraisal (STA)
  - All supporting evidence apart from ANBL0032 dismissed
  - Requested updated EFS data analysis as at March 2014
  - Critical of ANBL0032 early stopping + use of single study data with immature follow-up
  - No special dispensation within “methods guidance” for very young patient population

- Three appraisal meetings (two public) ➠ simple discount patient access scheme ➠ still not cost-effective

- July 2016 : Decision not to recommend dinutuximab (ICER = £ per QALY too high)
  - March 2014 analysis should be basis for decision-making
  - Cure threshold of 10 years ➠ approx. 50% of patients considered cured regardless of treatment
  - Uncaptured health-related benefits and impact on parents and families not captured by models
  - Company highlighted significant cost of administration in economic models over and above drug cost

QALY=Quality Adjusted Life Year; ICER=Incremental Cost Effectiveness Ratio

NICE Appraisal | Unituxin®

Figure 1: Event-free survival in ANBL0032 trial (March 2014 data)

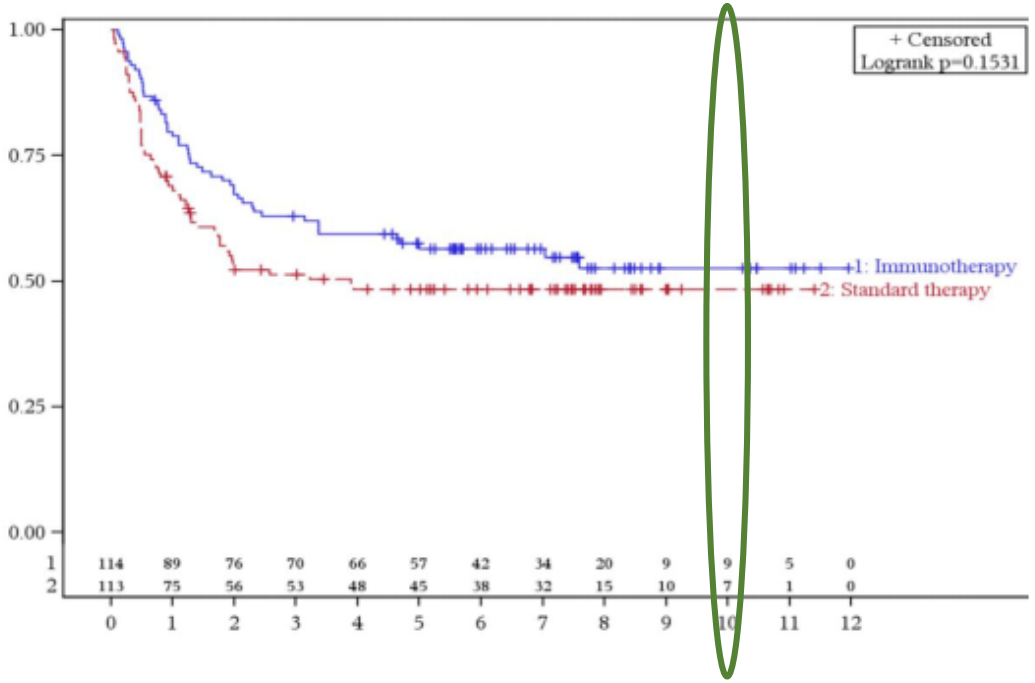
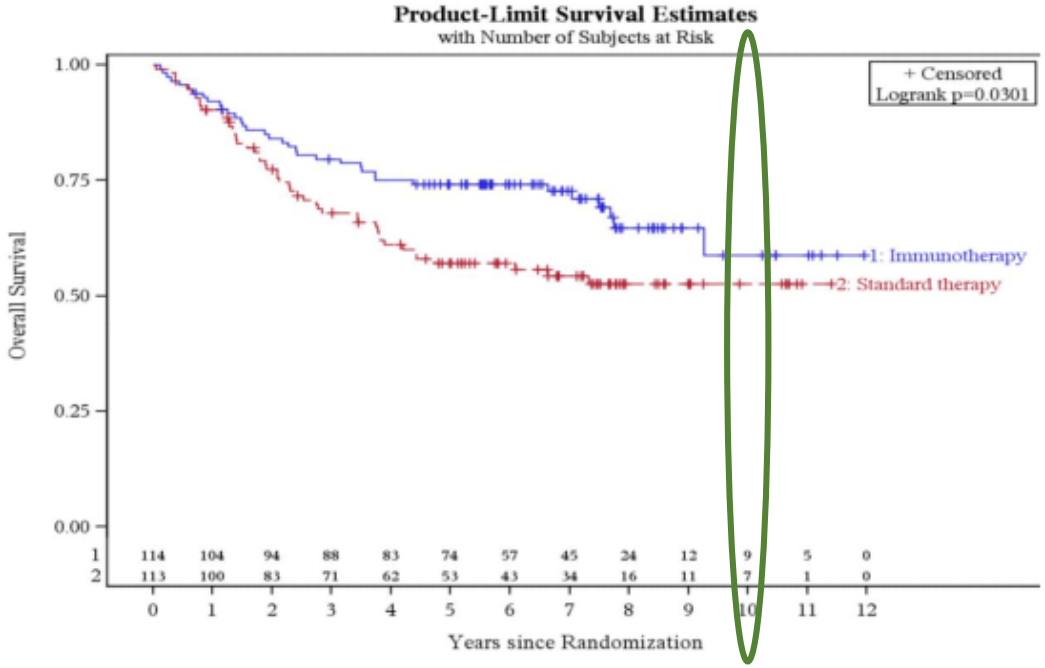


Figure 2: Overall survival in ANBL0032 trial (March 2014 data)



Solving Kids' Cancer Appeal

NICE National Institute for Health and Care Excellence

Solving Kids' Cancer Europe appealed decision unilaterally without support from United Therapeutics

- First time any organisation had launched appeal without pharmaceutical company involvement
- Pro-bono support from Covington & Burling LLP in London

Appeal permitted on two grounds.

1. NICE has exceeded its powers:
    - Breach of Children Act 2004 and UN Convention on the Rights of the Child

2. The recommendation is unreasonable in light of the evidence submitted to NICE:
    - It was unreasonable for the Institute to use a 10-year cure point given the evidence before it

Appeal on 10-year cure point accepted as valid after expert input from Dr. Wendy London, COG statistician

Solving Kids' Cancer

COVINGTON

Solving Kids' Cancer Appeal

NICE National Institute for Health and Care Excellence

- September 2016 : Appeal Panel Hearing – quasi-judicial process
  - Written and oral submissions
  - No evidence in committee papers that the Committee had considered the special position of children
  - 11 of 114 patients censored prior to 5 years but 58 from 5-10 years ➠ wide 95% CI ± 25% at 10 years

- November 2016 : Appeal Panel Decision – both appeal points upheld
  - Committee should consider whether there is anything particular to this patient group as children that should be taken into account in the appraisal, if so take it into account, if not say so with reasons
  - Committee directed to review range of cure points and associated ICERs between 5 and 10 years and FAD should contain balanced reasoning for their choice

- February 2017 : Appraisal is suspended as UTC withdraw drug supply outside USA

- EMA marketing authorisation withdrawn

Solving Kids' Cancer

COVINGTON

United Therapeutics CORPORATION

Unituxin®

HEALTH NEWS AUGUST 19, 2015 / 3:47 PM / 3 YEARS AGO

AbbVie buys special review voucher for $350 million

(Reuters) - AbbVie Inc has bought a priority review voucher from United Therapeutics Corp for $350 million that will allow it to accelerate the review process for one of its drugs.

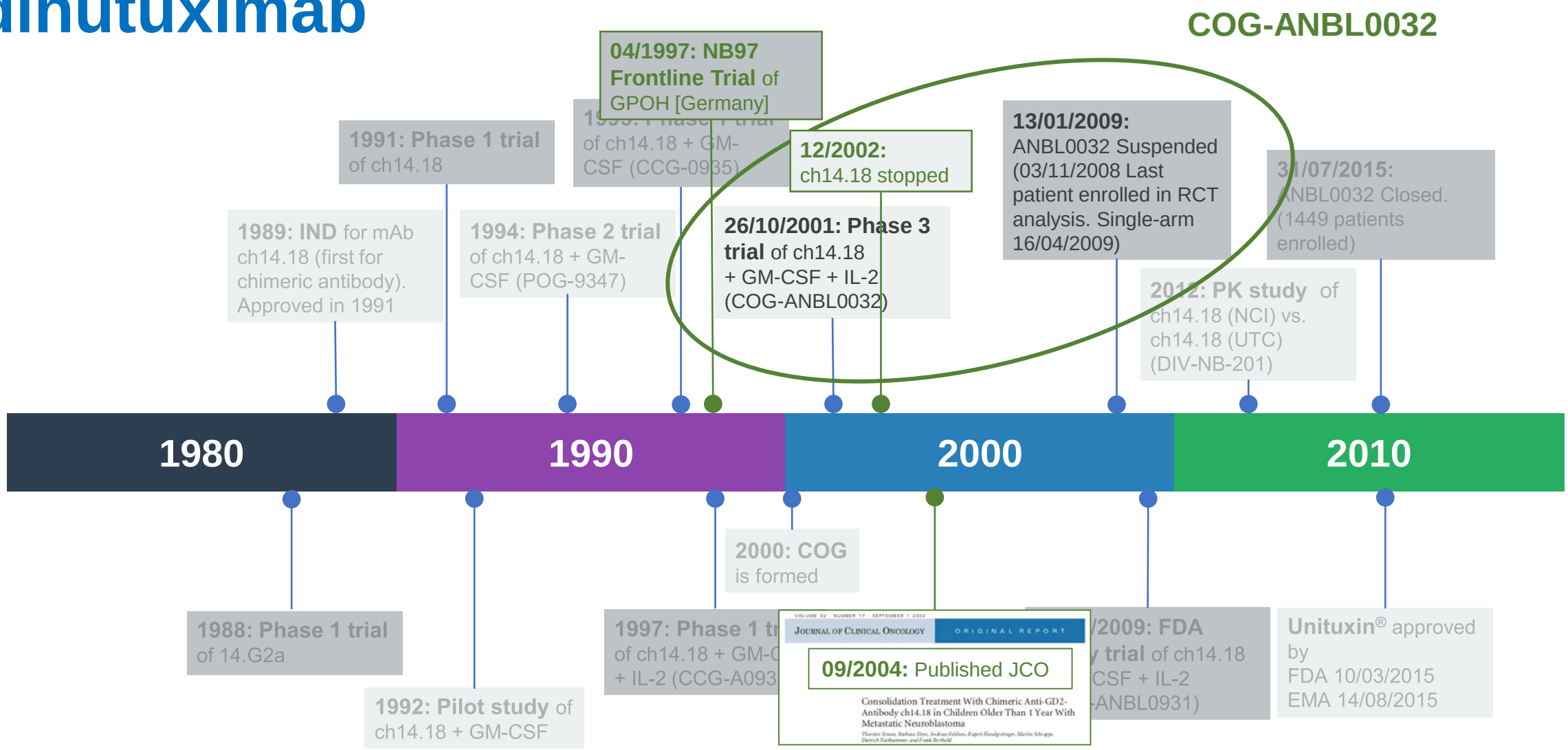
after its drug, Unituxin, was approved by the U.S. Food and Drug Administration to treat neuroblastoma, the company said on Wednesday.

	Remodulin	Tyvaso	Adcirca	Orenitram	Unituxin	Total
Year Ended December 31, 2017						
Net product sales	$670.9	$372.9	$419.7	$185.8	$76.0	$1,725.3
Cost of product sales	15.9	18.5	43.1	15.3	12.9	105.7
Gross profit	$655.0	$354.4	$376.6	$170.5	$63.1	$1,619.6
Year Ended December 31, 2016						
Net product sales	$602.3	$404.6	$372.2	$157.2	$62.5	$1,598.8
Cost of product sales	10.5	19.6	21.4	13.7	7.5	72.7
Gross profit	$591.8	$385.0	$350.8	$143.5	$55.0	$1,526.1
Year Ended December 31, 2015(1)						
Net product sales	$572.8	$470.1	$278.8	$118.4	$20.5	$1,460.6
Cost of product sales	12.4	23.9	16.5	12.5	3.7	69.0
Gross profit	$560.4	$446.2	$262.3	$105.9	$16.8	$1,391.6

- $500m gross profit since launch in Q3 2015
- Annual contribution to profit is just 4%
- Construction of new cell culture and purification facility started in 2017 – online 2021
- No plans to re-enter market in Europe
- CADTH pan-Canadian Oncology Drug Review (pCODR) submitted 1st October 2018[1] – frontline approved indication only?
- Australia/New Zealand – supply incl. for future COG trials?

Source: [1]https://www.cadth.ca/unituxin-neuroblastoma-details

ch14.18/SP2/0 dinutuximab



VOLUME 22 · NUMBER 17 · SEPTEMBER 1 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Consolidation Treatment With Chimeric Anti-GD2-Antibody ch14.18 in Children Older Than 1 Year With Metastatic Neuroblastoma

Thorsten Simon, Barbara Hero, Andreas Faldum, Rupert Handgretinger, Martin Schrappe, Dietrich Niethammer, and Frank Berthold

From the Children's Hospital, University of Cologne, Cologne; Institute for Medical Biostatistics, Epidemiology, and Informatics, University of Mainz, Mainz; Children's Hospital, Medical School of Hanover, Hanover; Children's Hospital, University of Tübingen, Tübingen, Germany; St Jude Children's Research Hospital, Memphis, TN.

Submitted September 21, 2003; accepted June 7, 2004.

The neuroblastoma trials were supported by Deutsche Krebshilfe. The antibody production was sponsored by Deutsche Leukämieforschungshilfe and Merck.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Thorsten Simon, MD, Children's Hospital, Department of Pediatric Oncology and Hematology, University of Cologne, Joseph-Stelzmann-Straße 9, 50924 Köln, Germany; e-mail: thorsten.simon@uk-koeln.de.

0732-183X/04/2217-3549/$20.00

DOI: 10.1200/JCO.2004.08.143

ABSTRACT

Purpose
Antibody treatment is considered tolerable and potentially effective in the therapy of neuroblastoma. We have analyzed stage 4 neuroblastoma patients older than 1 year who underwent consolidation treatment with the chimeric monoclonal anti-GD2-antibody ch14.18.

Patients and Methods
Stage 4 patients older than 1 year who completed initial treatment without event were eligible. ch14.18 was scheduled in a dose of 20 mg/m^2/d during 5 days in six cycles every 2 months. Patients who did not receive ch14.18 served as controls.

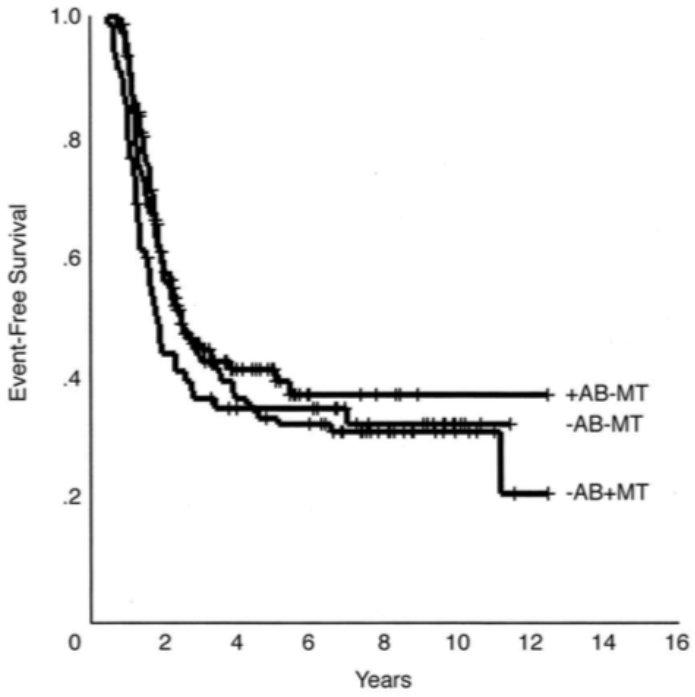
Results
Of 334 assessable patients, 166 received ch14.18, 99 received a 12-month low-dose maintenance chemotherapy (MT) instead, and 69 had no additional treatment. During 695 ch14.18 cycles, fever (55% of cycles), abnormal C-reactive protein without infection (35%), cough (24%), rash (22%), and pain (16%) were the main side effects. Univariate analysis found similar event-free survival (EFS) for the three groups (3-year EFS, 46.5% ± 4.1%, 44.4% ± 4.9%, 37.1% ± 5.9% for patients treated with antibody ch14.18, MT, and no additional therapy, respectively; log-rank test, $P = .314$). For overall survival (OS), ch14.18 treatment (3-year OS, 68.5% ± 3.9%) was superior to MT (3-year OS, 56.6% ± 5.0%) or no additional therapy (3-year OS, 46.8% ± 6.2%; log-rank test, $P = .018$). Separate univariate analysis of patients with autologous stem-cell transplantation revealed no difference between patients with ch14.18 treatment and no additional consolidation. Multivariate analysis failed to demonstrate an advantage of antibody treatment for EFS and OS.

Conclusion
Consolidation treatment of stage 4 neuroblastoma with ch14.18 was associated with considerable but manageable side effects. Compared with oral maintenance chemotherapy and no consolidation treatment, ch14.18 had no clear impact on the outcome of patients.

J Clin Oncol 22:3549-3557. © 2004 by American Society of Clinical Oncology

GPOH | mAb ch14.18

- ch14.18 produced by BioInvent in Sweden
- 20 mg/m^2/d over 8-12 hour for 5 days
- 6 cycles – every 2 months for one year
- Non-randomised study design
- Published September 2004



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GPOH | mAb ch14.18

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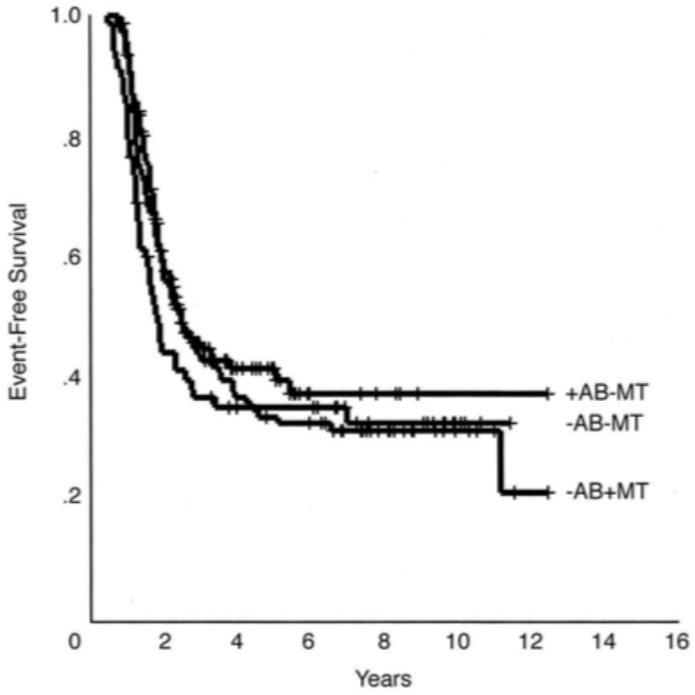
- ch14.18 produced by BioInvent in Sweden
- 20 mg/m^2/d over 8-12 hour for 5 days
- 6 cycles – every 2 months for one year
- Non-randomised study design
- Published September 2004

"In conclusion, this retrospective analysis demonstrated a considerable but manageable toxicity of MAB ch14.18 treatment. Univariate analysis found an advantage of ch14.18 treatment for overall survival but not for EFS in stage 4 neuroblastoma. Multivariate analysis did not confirm such a benefit. Because of these results, the MAB ch14.18 treatment is not continued in the current German neuroblastoma trial."

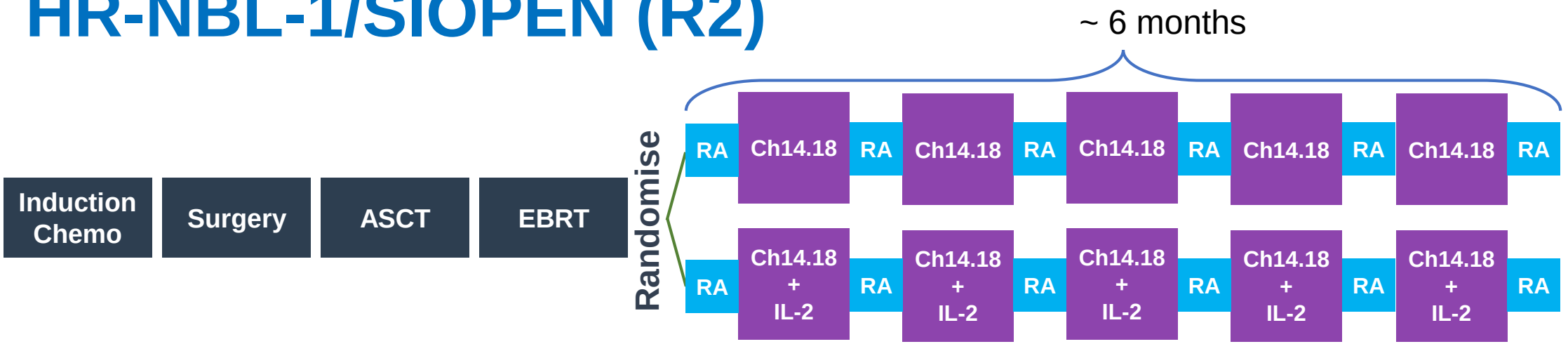


ch14.18/CHO
dinutuximab beta

- Design of GPOH study + observed improvement in 3-yr OS
  ➠ rationale for randomisation in SIOPEN HR-NBL-1 trial
- R2 randomisation (13-cis RA ± ch14.18)
- 2004 : Antibody recloned into Chinese hamster ovary cells
- 2005 : Phase 1 ch14.18/CHO in 15 R/R patients
- 2007 : R2 activated 11/2006 – 33 patients randomised
- 2009 : R2 amended to 13-cis RA + ch14.18/CHO ± s/c IL-2
  ➠ unacceptable to randomise to no antibody

Prof. Dr. med. Holger Lode

HR-NBL-1/SIOPEN (R2)



- HR-NBL-1/SIOPEN trial opened in **128** SIOPEN member institutions across **18** countries
- Randomised **406** patients between 22/10/2009 and 12/08/2013
- Dose of 20 mg/m^2/d as minimum 8-hour infusion for 5 consecutive days
- EFS at 3yrs – 56% (49-63) for dinutuximab beta vs. 60% (53-66) for dinutuximab beta + s/c IL-2 (p=0.76)
- 87% of patients on dinutuximab beta alone received all treatment vs. 62% for dinutuximab beta + s/c IL-2

ASCT=Autologous Stem Cell Transplantation; EBRT=Radiotherapy; RA=13-cis-retinoic acid/isotretinoin

ch14.18/CHO
dinutuximab beta

- June 2011 : Apeiron Biologics acquired rights to ch14.18/CHO
- Dec 2011 : LTI (Long-term infusion) study – dose schedule of 10mg/m^2/d + s/c IL-2 given over 10 days
  ➠ favourable toxicity profile of antibody plus IL-2 and ~30% response rate
- HR-NBL-1 R2 results suggested patients who received all doses of ch14.18/CHO + IL-2 might do better
- April 2014 : R4 randomisation of ch14.18/CHO (cont. inf.) ± half-dose s/c IL-2
  ➠ LTI study amended to same randomised question in relapsed, refractory and non-R4 eligible patients
- May 2015 : Apeiron submitted dinutuximab beta (APN311/ISQETTE) to EMA for marketing authorisation
- October 2016 : EUSA Pharma, UK purchase exclusive global commercialisation rights to dinutuximab beta
- May 2017 : EMA marketing authorisation granted under exceptional circumstances (with IL-2 for R/R pts)

CHMP=Committee for Medicinal Products for Human Use

NICE Review | Qarziba®

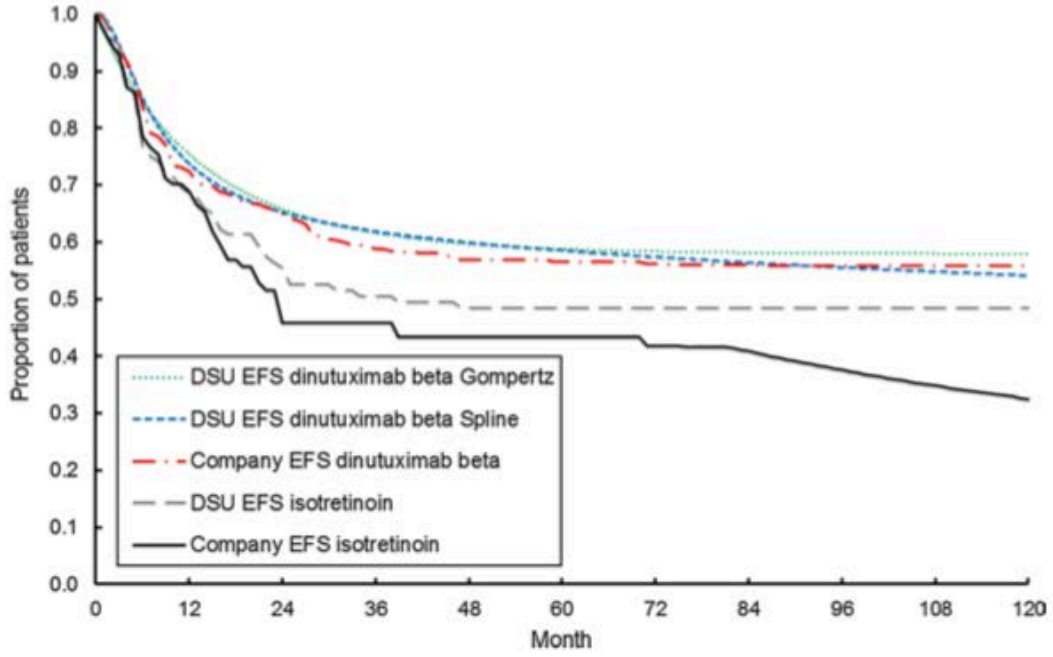
NICE National Institute for Health and Care Excellence

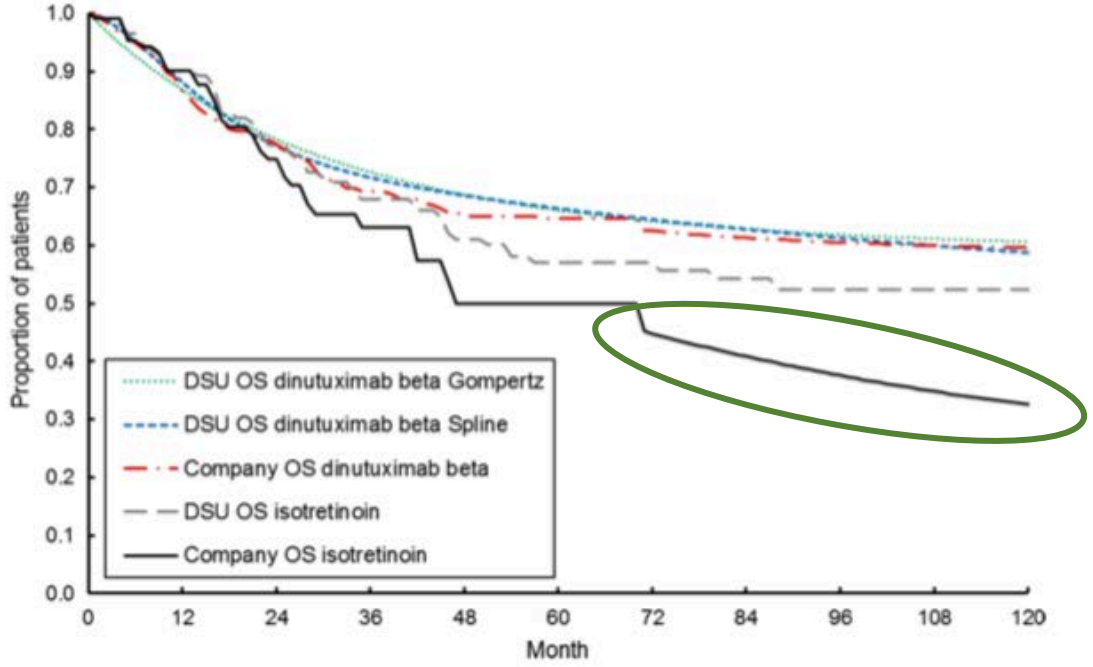
- November 2017 : Single Technology Appraisal (STA)
  - Slide on Solving Kids' Cancer appeal in dinutuximab appraisal
  - Clear appreciation of potential sensitivities around this kind of appraisal
  - No director comparator evidence – use of R1 (BuMel vs. CEM ASCT) not fit for purpose
  - R/R not considered further – evidence 'unfit for purpose' + patients in studies had no prior anti-GD2
- April 2018 : Second (public) appraisal committee meeting
  - MAIC comparison with isotretinoin arm of COG-ANBL0032 as required by Committee
- May 2018 : Decision not to recommend dinutuximab beta
- June 2018 : Third (public) appraisal committee meeting
- July 2018 : Dinutuximab beta recommended on commercial-in-confidence discount scheme
  - ICER more than £40,000 – above upper threshold normally accepted by NICE for STAs
- 10-day continuous infusion of dinutuximab beta is now standard of care without any (R4) results

MAIC=Matching Adjusted Indirect Comparison; STC=Simulated Treatment Comparison

NICE Review | Qarziba®

NICE National Institute for Health and Care Excellence





- Highlights the issue and danger of relying on pure data analysis and model-fitting
- Company submission supports a lower ICER at later time points for cure threshold ➠ winner!
- Implausible and not supported by clinical experience not appropriate/relevant ➠ dismissed!

NICE Highly Specialized Technologies (HST)

- Department of Health and Social Care (DHSC) provides list of evaluation topics
- Higher upper ICER threshold (~£100,000) and total annual cost to NHS must be < £20m

28. Topics evaluated through the HST programme will be formally referred to NICE by Ministers. HSTs are selected using the following criteria, **all** of which have to apply:

- The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS;
- The target patient group is distinct for clinical reasons;
- The condition is chronic and severely disabling;
- The technology is expected to be used exclusively in the context of a highly specialised service;
- The technology is likely to have a very high acquisition cost;
- The technology has the potential for life long use;
- The need for national commissioning of the technology is significant.

"The HST guidance recognises the particular circumstances of these very rare conditions – the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for manufacturers in making a reasonable return on their investment because of the very small populations treated.

In evaluating these drugs, NICE takes into account a greater range of criteria about the benefits and costs of highly specialised technologies than is the case with its appraisals of mainstream drugs and treatments. We do this because applying our standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair."

Sir Andrew Dillon, NICE Chief Executive, 2015

Source: Interim Process and Methods of the Highly Specialised Technologies Programme [NICE]

NICE National Institute for Health and Care Excellence

Qarziba®

- **England & Wales & NI** : Approved for patients with no prior anti-GD2 incl. refractory (PR + ASCT)
- **Scotland** : Approved by SMC for frontline high-risk, relapsed and refractory patients

- **Ireland** : Submissions to NCPE and NCCP – negotiations ongoing since late 2018

- **Germany** : “NUB” status – as per routine procedures reimbursement negotiated separately by hospitals ➠ available mainly in university hospitals. Normally “NUB” evolves to “ZE” ➠ available in all hospitals

- **France** : HTA (HAS) / Pricing (CEPS) separate bodies. HAS clinical assessment ASMR IV (minor) for frontline high-risk and ASMR V (none) for relapse/refractory ➠ generally ASMR I to III reimbursed
  - Health ministry reimbursement of EUR 4m to Dec 2019 for frontline (only product with such funding)

- **Spain** : National scientific/technical review ➠ Ministry of Health/17 regional health systems/company negotiate price ➠ interim each hospital/regional health system decisions on patient-by-patient basis ➠ could still become available in some regions/hospitals and not others (40+ paediatric centres in Spain)

- Biologics Licence Application (BLA) to the FDA in the U.S. expected – not a biosimilar?

SMC=Scottish Medicines Consortium; NCPE=National Centre for Pharmacoeconomics; NCCP= National Cancer Control Programme; NUB=neue Untersuchungs- und Behandlungsverfahren (new diagnostics and treatments); HAS=Haute Autorité de Santé;ASMR=Amélioraation du service medical rendu (improvement of clinical situation); CEPS=Economic Committee for Health Products

hu3F8 | naxitamab

- 3F8 is a mouse developed by Dr. Nai-Kong Cheung in 1980s and used extensively at MSKCC
- HAMA response – neutralising anti-mouse antibodies produced by immune system to ‘foreign’ 3F8
- Used as high-risk neuroblastoma maintenance therapy in combination with GM-CSF
- hu3F8 developed to overcome HAMA and modify Fc portion for enhanced effector function – Phase 1 study in 2011
- Licensed to Y-mAbs Therapeutics in 2015
- Outpatient treatment – 35 minute infusion of hu3F8 on day 1, 3, 5 with s/c GM-CSF day -4 to 0 and day 1 to 5
- 2019 : International study of hu3F8 + GM-CSF in R/R with plans to submit a BLA in the U.S.

Dr. Nai-Kong Cheung

hu14.18-IL2 | APN301

- Developed and owned by Apeiron Biologics
- Fusion protein of humanized antibody (hu14.18) and IL-2
- “Immunocytokine”
- Tested in Phase I/II clinical trials through Children’s Oncology Group
- Responses in patients with residual disease but none in patients with bulky tumours measurable by MRI/CT
- Current clinical trial of hu14.18-IL2 in combination with haploidentical NK cells by Paul Sondel’s group at University of Wisconsin–Madison (UW)

hu14.18K322A

- Developed at St Jude Children’s Research Hospital
- Produced in rat myeloma cell lines which reduces fucosylation ➠ potentially enhancing ADCC
- 98% human to reduce allergic reactions
- Single “point-mutation” (small structural change) to reduce compliment activation (CDC) ➠ reduce pain ➠ increase dose?
- Used in several Phase I/II studies at St Jude
- Ongoing Phase pilot II study combining hu14.18K322A with induction chemotherapy for frontline patients

The Proposal For an EU HTA Regulation

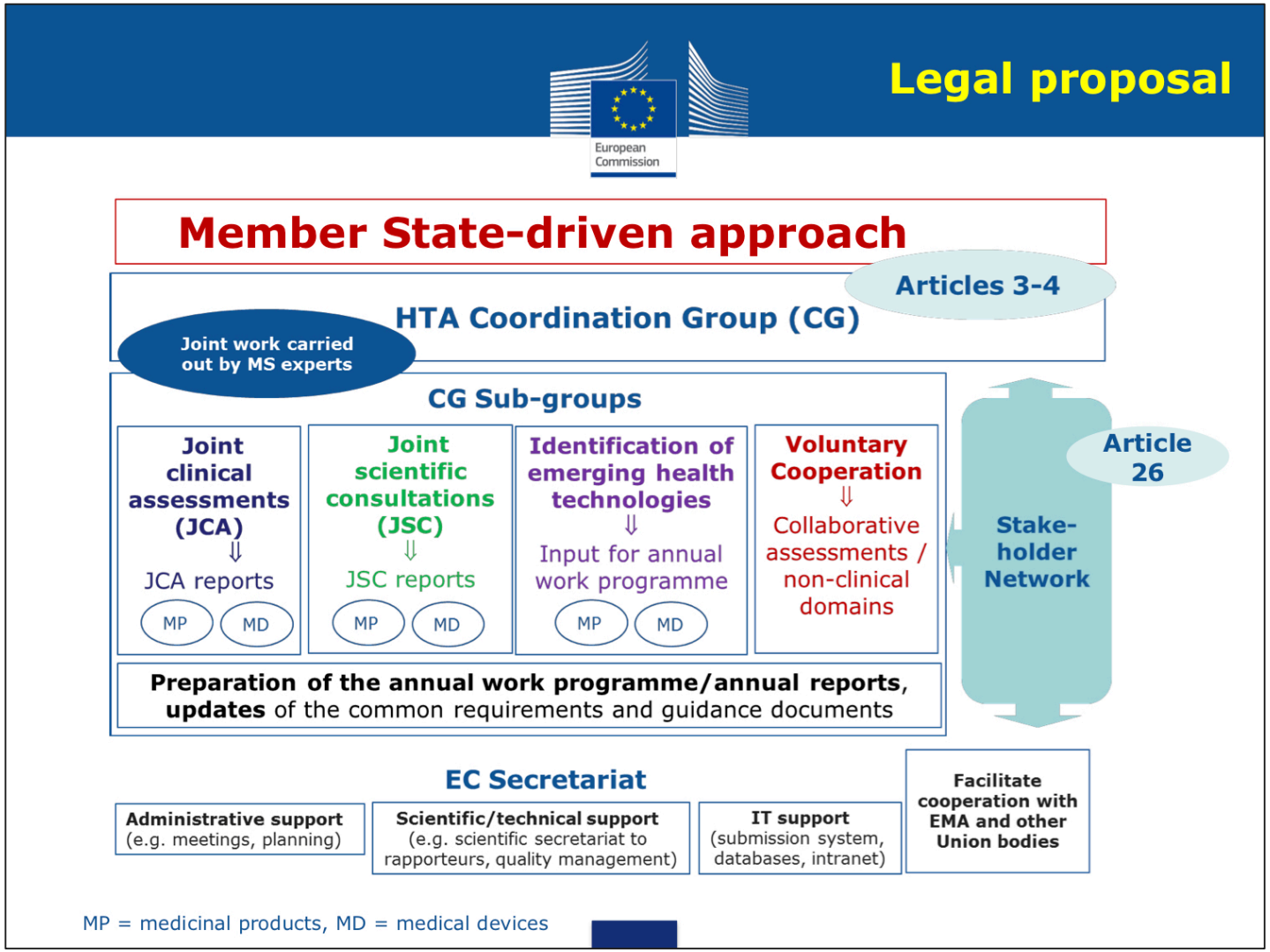
The Proposal For an EU HTA Regulation

- Reasons for proposal
  - National processes = multiple data and evidence requests = higher costs and effects on innovation
  - Duplication of work – repeated clinical assessments with potentially different outcomes/conclusions
  - Unsustainability of Union-level HTA cooperation – project-based with short-term funding

- Objectives
  - Improve availability of innovative health technologies for EU patients
  - Ensure efficient use of resources and strengthen quality of HTA across the EU
  - Improve business predictability
  - Promote convergence in HTA tools, procedures and methodologies
  - Reduce duplication of efforts for HTA bodies and industry
  - Ensure the use of joint outputs in Member States
  - Ensure the long-term sustainability of EU HTA cooperation

- Medicinal products undergoing the central marketing authorisation procedure, new active substances and existing products for which the marketing authorisation is extended to a new therapeutic indication

The Proposal For an EU HTA Regulation



Source: Proposal for Regulation on HTA, HTA Network Stakeholder Pool Meeting (Brussels, 16 January 2019)

CADTH | NICE

NICE National Institute for Health and Care Excellence

Improving health and social care through evidence-based guidance

CADTH Evidence Driven.

ACMTS Preuves à l'appui.

06 February 2019

Share

NICE collaborates with the Canadian Agency for Drugs and Technology in Health to offer parallel scientific advice

NICE and the Canadian Agency for Drugs and Technology in Health (CADTH) have launched a new collaboration to offer parallel scientific advice to the life sciences industry.

Scientific advice helps companies develop the evidence that can demonstrate the value of a new treatment. It does so by using expert opinion from a range of contributors including clinicians, health economists and patient representatives to provide detailed feedback on companies' plans to generate clinical and economic evidence.

Reflections | anti-GD2 antibodies

- Hindsight is always a wonderful thing
- Life is often messy and complicated … situations evolve … navigating isn't easy
- Competition between researchers and institutions … drives innovation … and duplication
- 5 anti-GD2 antibodies in ongoing clinical research studies in the same rare paediatric cancer
- Lack of approval and reimbursement may have stalled or even ended development?
- Licensed drugs may be a barrier to further innovation ➠ revenue streams to protect?
- What now for other anti-GD2 antibodies, anti-idiotype antibodies, *O*-acetyl-GD2?

Reflections | HTAs

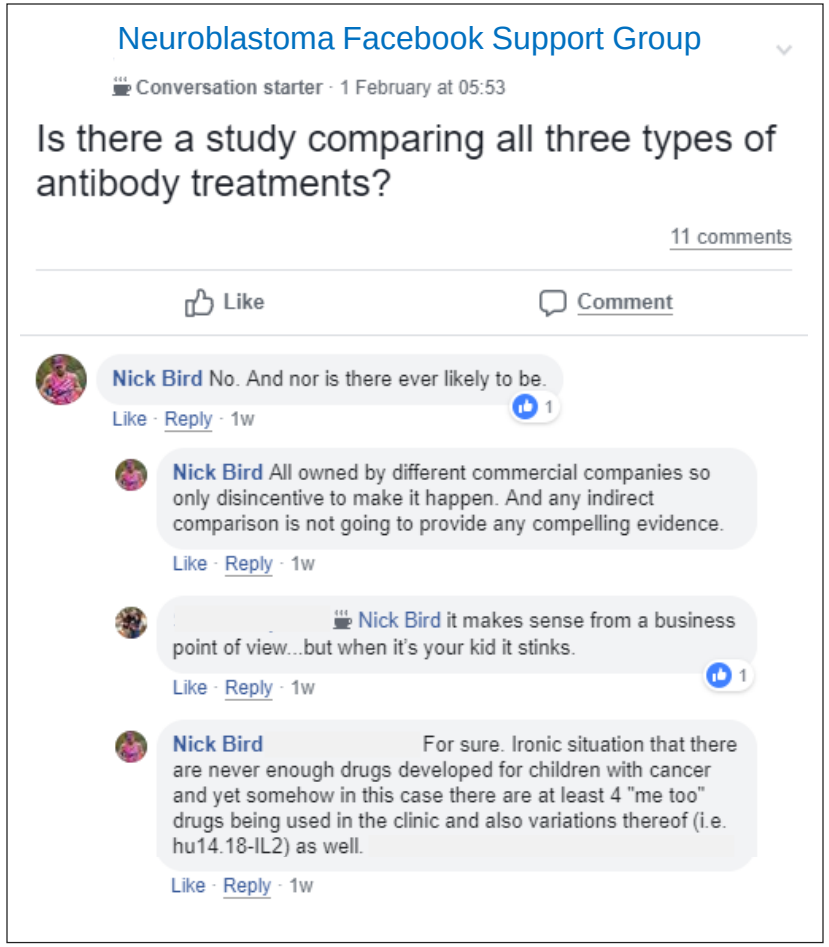
- USA simpler market/model ➠ FDA vs. Europe ➠ EMA ➠ national HTAs ➠ national price negotiations?
- Lack of HTA experience (and thus flexibility) in assessing drugs for rare orphan diseases in children?
- No premium placed on children – adding 2 years of life to a 2-year old or a 72-year old is equivalent?
- No allowances for nature and scale of task in developing and testing drugs to treat children with cancer
  - Patient population small and limited ➠ need for cooperative group trials across many institutions
  - Phase 3 trials take a long time, confirmatory trials are infeasible (unethical?)
  - Lack of options/approved drugs not relevant and no joined-up assessment of impact on innovation
- Children + Cancer + mobilised parent/advocate community ➠ powerful movement and force for change
- Political pressure, media storm, public sympathy and support ➠ not normal conditions for HTAs
- Parents and advocates act for children directly … but for manufacturers indirectly

Reflections | HTAs

- Late involvement of pharma, sub-licensing adds complexity, disjointedness and lack of ‘ownership’
- Companies seeking approvals across multiple similar but distinct HTAs “learning on the job”
- Drugs are marketed at very high prices (£150,000+ per child) ➠ always likely to be a challenge
- Paediatric-only indications / rare diseases patient population is small and limited ➠ poor revenue growth
  - Growth depends on additional markets or finding and pursuing adult indication
- Absolute cost to healthcare systems relative to total spend is very small
  - Estimated total NHS spending on medicines in England in 2016/17 was £17.4bn[1]
  - Acquisition cost of Qarziba® for all eligible high-risk patients < £5m?
- Academic trial designs, execution, and data management should be with principle of filing intent

Source: [1]The Kings Fund – The rising cost of medicines to the NHS: what’s the story?

Parents just want the best for their children



Anti-GD2 | The Next Chapter

- [2017] Irinotecan–temozolomide with temsirolimus or dinutuximab in children with R/R neuroblastoma (COG ANBL1221) – 5CR, 4 PR (9/17 pts) in dinutuximab arm
- [2018] Plus expansion cohort – total 11 CR, 10 PR (40% RR, 21/53 pts, 9/21 prior anti-GD2)
- [2017] hu14.18K22A + NK cells in R/R – 4 CR, 1 VGPR, 3 PR (8/13 pts. 9/13 with prior anti-GD2 therapy)
- [2017] hu14.18K22A + GM-CSF + IL-2 concomitantly with Cyclo/Topo in newly diagnosed pts. 32/42 pts (≥ PR) vs. 12/30 in COG pilot study of Cyclo/Topo alone
- [NCT03794349] Irinotecan Hydrochloride, Temozolomide, and Dinutuximab With or Without Eflornithine in Treating Patients With R/R Neuroblastoma (not yet open)
- [NCT03786783] Dinutuximab, Sargramostim, and Combination Chemotherapy in Treating Patients With Newly Diagnosed High-Risk Neuroblastoma (Phase II pilot study - recruiting)
- +++

- BEACON Amendment (BEACON Immuno) – Chemotherapy ± dinutuximab beta in R/R Neuroblastoma (funded)

ACCELERATE

Lessons learnt from the Development of Blinatunomab for the Treatment of acute Lymphoblastic Leukemia in Children and Adolescents

Gerhard Zugmaier, *AMGEN*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

LESSONS LEARNT FROM THE DEVELOPMENT OF BLINATUMOMAB FOR THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN AND ADOLESCENTS

GERHARD ZUGMAIER

AMGEN®

AGENDA

- **Presentation of 1st child treated with blinatumomab**
- Mechanism of action of blinatumomab
- Clinical Development plan of blinatumomab in B cell acute lymphoblastic leukemia (ALL)
- Selected data from the Phase 1 and 2 trials
- Overall summary

FIRST PEDIATRIC PATIENT TREATED WITH BLINATUMOMAB IN 2008

Handgretinger R., Zugmaier, G., et al.

Leukemia advance online publication, 14 October 2010;
doi:10.1038/leu.2010.239

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FIRST PEDIATRIC PATIENT TREATED WITH BLINATUMOMAB IN 2008

- Patient was a 7-year-old boy in 2008
- First diagnosis high-risk B-precursor ALL in 2004
- First bone marrow relapse in 2006
  - Persistent disease
  - Second complete remission after three courses of clofarabine
  - Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) in 2007
- Second bone marrow relapse in 2008
  - Persistent disease with 3% Blasts in bone marrow
  - Treatment with blinatumomab at 15 mg/m2/day by continuous intravenous infusion – no GvHD- for 5 weeks in 2008
  - Second allogeneic HSCT in 2008
- Alive and well in 2019

Handgretinger R., Zugmaier, G., et al.

Leukemia advance online publication, 14 October 2010; doi:10.1038/leu.2010.239

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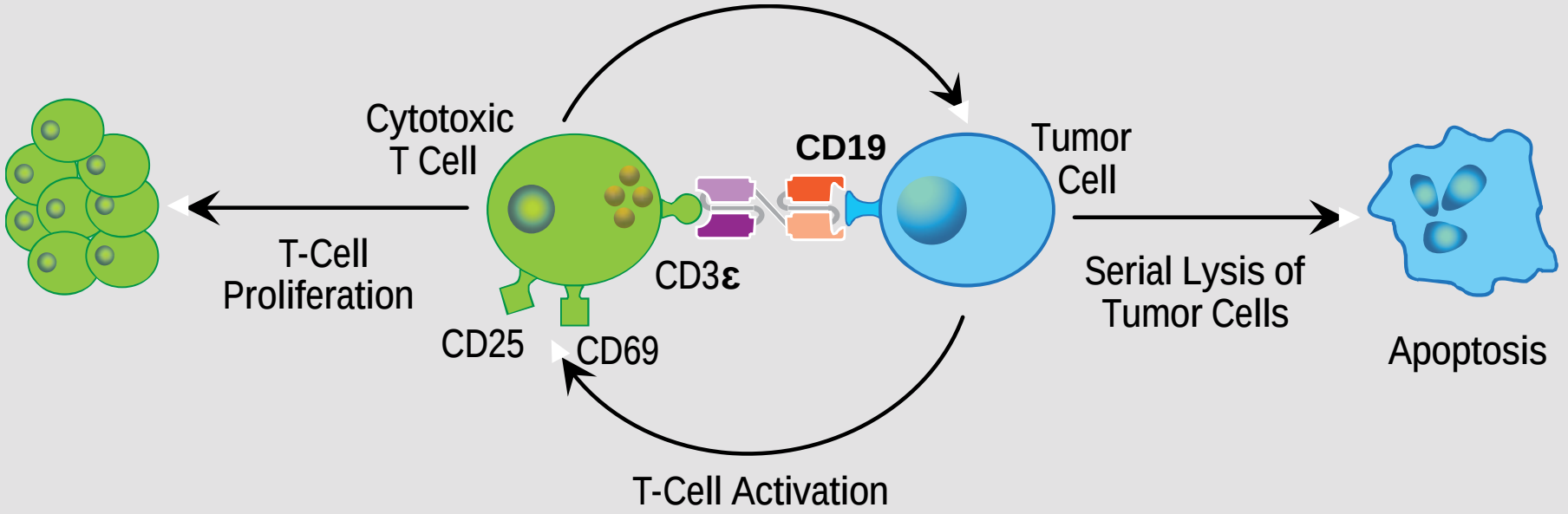
BLINATUMOMAB: A BISPECIFIC T-CELL ENGAGER (BITE®) ANTIBODY CONSTRUCT



- **Blinatumomab redirects CD3-positive cytotoxic T cells to lyse CD19-positive B cells[1]**

1. Bargou R, et al. *Leuk Lymphoma*. 2011;52:1098-1107

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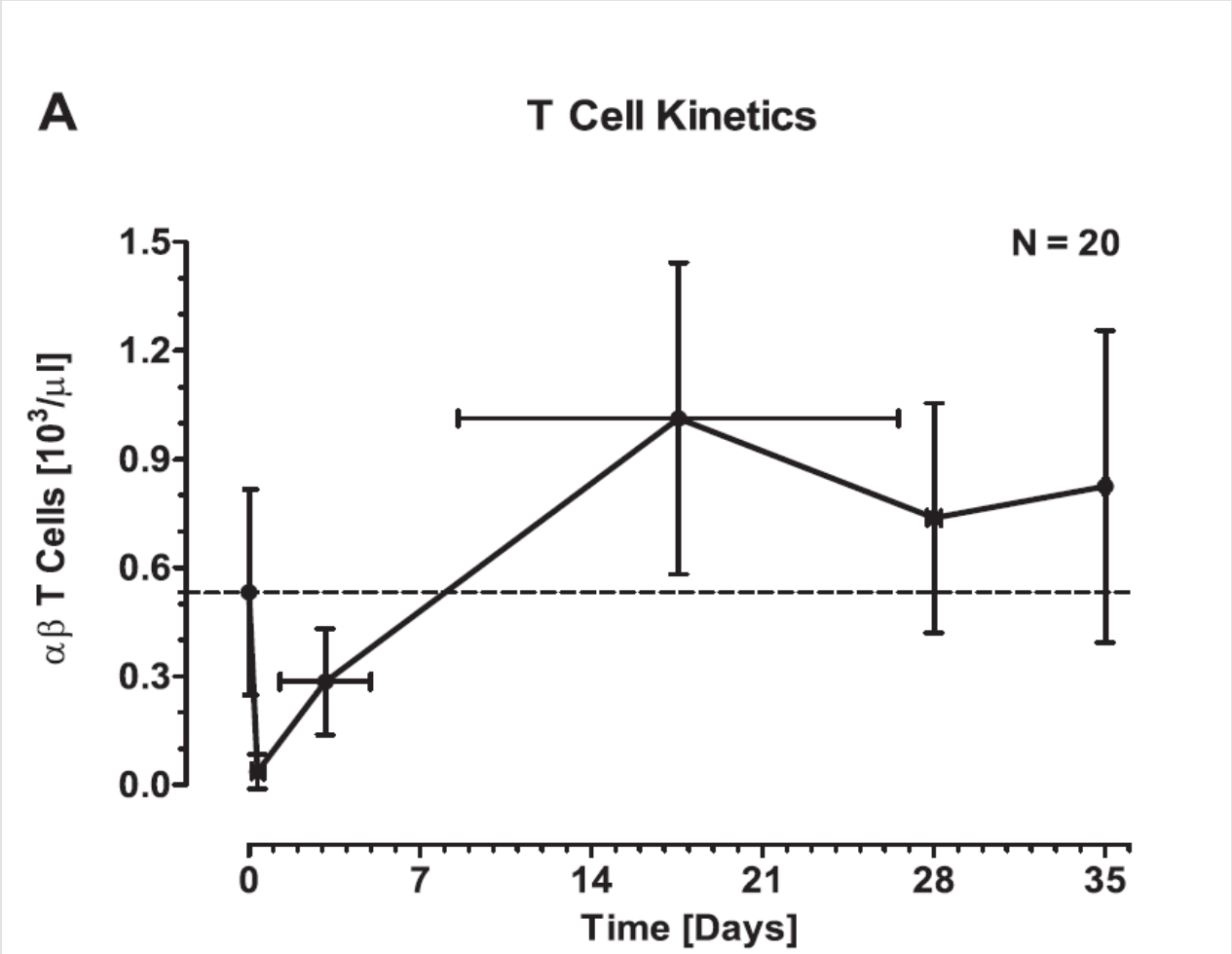
MEAN T CELL COUNTS OF 20 PATIENTS, ERROR BARS = STANDARD DEVIATION
BASELINE, MEAN NADIR, MEAN TIME POINT OF 50% RECOVERY TO BASELINE, MEAN TIME POINT OF MAXIMAL EXPANSION, END OF THE 4-WEEK TREATMENT PERIOD, ONE WEEK AFTER THE END OF INFUSION



Klinger et al. BLOOD, 2012 VOLUME 119; 26: 6226 - 6233

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AGENDA

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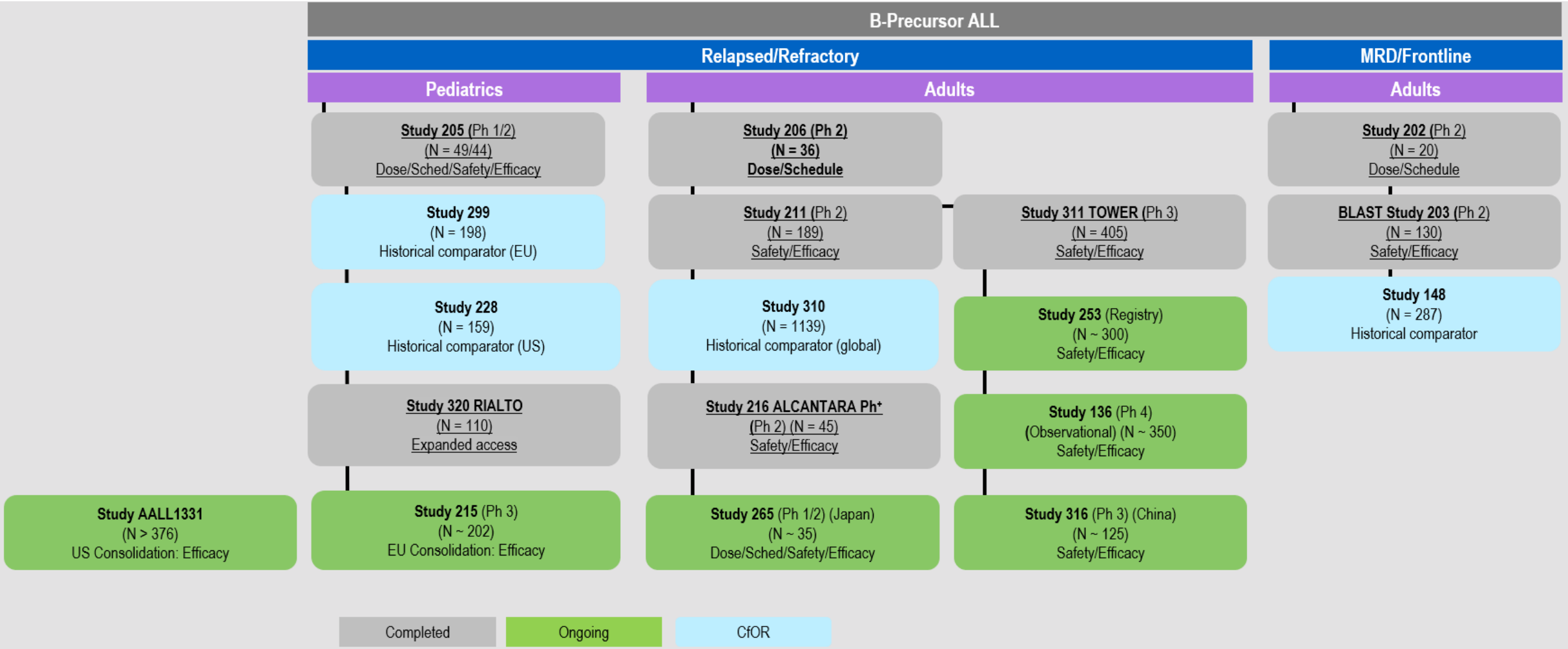
BLINATUMOMAB CLINICAL DEVELOPMENT PROGRAM OVERVIEW IN B CELL ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)



- ALL, acute lymphoblastic leukemia; CfOR, Center for Observational Research; EU, European Union; MRD, minimal residual disease; NHL, Ph, phase; US, United States.
- Data on file, Amgen.

AGENDA

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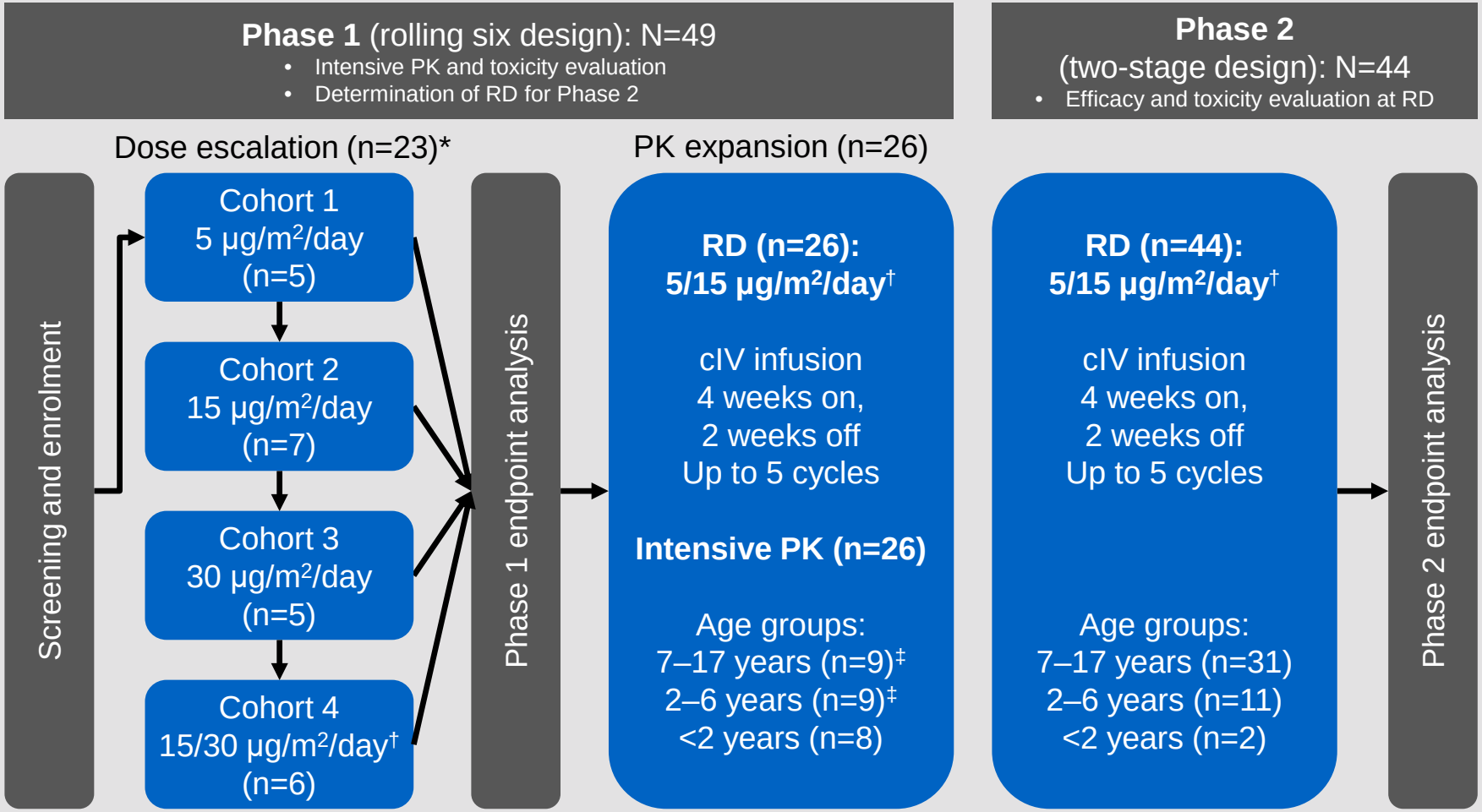
OPEN-LABEL, SINGLE-ARM, MULTICENTRE PHASE 1/2 STUDY OF BLINATUMOMAB IN PAEDIATRIC PATIENTS WITH RELAPSED/REFRACTORY B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA

Study 205 NCT01471782

OPEN-LABEL, SINGLE-ARM, MULTICENTRE PHASE 1/2 STUDY OF BLINATUMOMAB IN PAEDIATRIC PATIENTS WITH R/R B-CELL PRECURSOR ALL



- *Only patients 2–17 years were enrolled; †Stepwise dosing (5 or 15 µg/m²/day on Days 1–7, 15 or 30 µg/m²/day thereafter)
  ‡Patients ≥2 years were evaluated before enrolment of patients <2 years
  RD, recommended dose; PK, pharmacokinetics
- https://clinicaltrials.gov/ct2/show/NCT01471782 accessed August 2016;
  von Stackelberg A, et al. J Clin Oncol VOLUME 34 • NUMBER 36 • DECEMBER 20, 2016

KEY ELIGIBILITY CRITERIA

Inclusion

- B-cell precursor ALL with >25% BM blasts (M3) at study enrolment
- Age <18 years at study enrolment
  - Patients <2 years not enrolled in Phase 1 until RD established and assessed in patients ≥2 years
- Relapsed/refractory disease:
  - Primary refractory
  - 1st relapse after full salvage induction regimen
  - ≥2nd relapse or any relapse after alloSCT

Exclusion

- Active acute or extensive chronic GvHD
- Active CNS or testicular involvement
- Current or history of relevant CNS pathology

https://clinicaltrials.gov/ct2/show/NCT01471782 accessed August 2016;
von Stackelberg A, et al. J Clin Oncol VOLUME 34 • NUMBER 36 • DECEMBER 20, 2016

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DEMOGRAPHIC AND BASELINE CHARACTERISTICS

			All patients at Recommended Dose* (N=70)
Male, n (%)			47 (67)
Median age, years (range)			8 (<1–17)
Age group, n (%) <2 years 2–6 years 7–17 years			 10 (14) 20 (29) 40 (57)
Genetic abnormalities, n (%) *MLL* total *MLL*-AF4 Other *MLL* *BCR-ABL* Hypodiploidy Constitutional trisomy 21			 10 (14)† 8 (11) 2 (3) 2 (3) 4 (9) 2 (3)
BM blast count <50%, n (%) BM blast count ≥50%, n (%)			18 (26) 52 (74)
Number of prior relapses, n (%) 0 1 2 ≥3			 2 (3) 31 (44) 29 (41) 8 (11)
Refractory disease, n (%)			39 (56)
Previous alloSCT, n (%) No prior alloSCT, n (%)			40 (57) 30 (43)
Median time between last relapse and first blinatumomab infusion, months (range)			2.9 (0.4–49.8)
Relapse within 6 months of last prior therapy, n (%)	–	–	50 (71)

*Relapse within 6 months of last prior therapy in Phase 1 or Phase 2
†8 patients with *MLL* translocations were <2 years old: 6 had *MLL*-AF4, 2 had other *MLL* abnormalities

von Stackelberg A, et al. J Clin Oncol VOLUME 34 • NUMBER 36 • DECEMBER 20, 2016

SUMMARY OF RESPONSE TO BLINATUMOMAB

			All patients at Recommended Dose* (N=70)	
Hematological Response			**n/N (%)**	**95% CI**
Complete Remission (CR) achieved within first 2 cycles Patients with <50% BM blasts at baseline Patients with ≥50% BM blasts at baseline			27 (39) 10/18 (56) 17/52 (33)	27–51 31–79 20–47
Minimal Residual Disease (MRD) response in patients achieving CR				
Achieved MRD response Complete MRD response			14 (52) 14 (52)	32–71 32–71
No MRD response			12 (44)	
No data available			1 (4)	

*All patients treated at the stepwise dose of 5/15 µg/m^2/day in Phase 1 or Phase 2

von Stackelberg A, et al. J Clin Oncol VOLUME 34 • NUMBER 36 • DECEMBER 20, 2016

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RESPONSE TO BLINATUMOMAB IN PATIENTS <2 YEARS

	Patients <2 years at Recommended Dose (N=10)*	
Hematological Response	**n/N (%)**	**95% CI**
CR achieved within first 2 cycles Patients with <50% BM blasts at baseline Patients with ≥50% BM blasts at baseline	6 (60) 2/2 (100) 4/8 (50)	26–88 16–100 16–84
Minimal Residual Disease (MRD) response in patients achieving CR		
Achieved MRD response Complete MRD response	3/6 (50) 3/6 (50)	12–88
No MRD response	3/6 (50)	
No data available	0 (0)	

*All patients treated at the stepwise dose of 5/15 µg/m^2/day in Phase 1 or Phase 2

von Stackelberg A, et al. J Clin Oncol VOLUME 34 • NUMBER 36 • DECEMBER 20, 2016

HIGH MOLECULAR REMISSION RATE IN PEDIATRIC PATIENTS WITH RELAPSED/REFRACTORY B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH BLINATUMOMAB: RIALTO, AN OPEN-LABEL, MULTICENTER, EXPANDED ACCESS STUDY

Franco Locatelli[1], Gerhard Zugmaier[2], Peter Bader[3], Sima Jeha[4], Paul-Gerhardt Schlegel[5], Jean-Pierre Bourquin[6], Rupert Handgretinger[7], Benoit Brethon[8], Claudia Rossig[9], Christiane Chen-Santel[10]

[1]Department of Hematology and Oncology, IRCCS Bambino Gesù Children's Hospital, Rome, Italy; [2]Amgen Research (Munich) GmbH, Munich, Germany; [3]Department for Children and Adolescents, University Hospital Frankfurt, Frankfurt, Germany; [4]St Jude Children's Research Hospital, Memphis, TN, USA; [5]University Children's Hospital Wuerzburg, Wuerzburg, Germany; [6]Department of Pediatric Oncology, Children's Research Centre, University Children's Hospital Zurich, Zurich, Switzerland; [7]Department of Hematology and Oncology, University Children's Hospital Tuebingen, Tuebingen, Germany; [8]Pediatric Hematology and Immunology Department, Robert Debre Hospital, APHP, Paris, France; [9]University Children's Hospital Muenster, Muenster, Germany; [10]Charité University Medicine Berlin, Berlin, Germany

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METHODS

Table 1. Patient Eligibility

Key Inclusion Criteria	• Age > 28 days and < 18 years • CD19-positive Bcp-ALL with ≥ 5% blasts in the bone marrow or < 5% blasts and MRD level ≥ 10^{-3} • Relapsed/refractory disease defined as – Second or greater bone marrow relapse – Any relapse after allogeneic (allo) HSCT; or – Refractory to other treatments (chemotherapy/alloHSCT)
Key Exclusion Criteria	• Active acute or extensive chronic GvHD • Active CNS or testicular involvement • Current or history of relevant CNS pathology

- This analysis focuses on the first 98 pediatric and adolescent patients enrolled into the expanded access study
- Data cutoff was March 9, 2018

CD, cluster of differentiation; CNS, central nervous system; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease

Locatelli F, et al. Poster presented at: 60th ASH Annual Meeting & Exposition of the American Society of Hematology; December 1-4, 2018; San Diego, CA.

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RESULTS

Table 6. Best Response During the First 2 Cycles of Blinatumomab

	n (%)
All patients (N=98)	
CR during the first 2 cycles	59 (60)
CR with full recovery of peripheral blood counts	39 (40)
CR without full recovery of peripheral blood counts	20 (20)
Non-CR	
Hypoplastic or acellular bone marrow	1 (1)
Partial remission	1 (1)
Stable disease	4 (4)
Progressive disease	16 (16)
No response data or non-evaluable	17 (17)
Patients who achieved CR during first 2 cycles (N=59)	
MRD response during the first 2 cycles[a]	47 (80)
Proceeded to alloHSCT	27 (46)

alloHSCT, allogeneic hematopoietic stem cell transplantation; CR, complete response; MRD, minimal residual disease

Locatelli F, et al. Poster presented at: 60th ASH Annual Meeting & Exposition of the American Society of Hematology; December 1-4, 2018; San Diego, CA.

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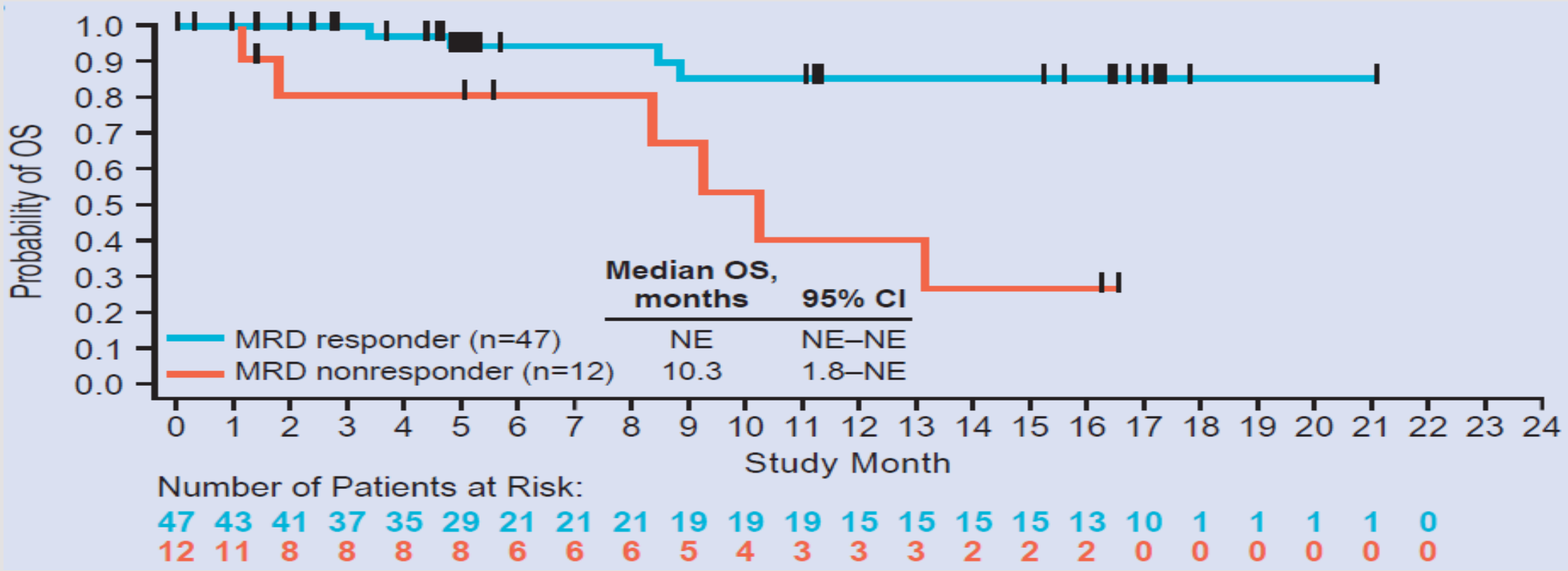
RESULTS – OVERALL SURVIVAL ESTIMATE BY THE KAPLAN - MEIER METHOD

Figure 4B. Overall Survival by MRD Response



OS by MRD response is based only on responders and calculated from time of CR by Kaplan-Meier method.
CI, confidence interval; MRD, minimal residual disease; NE, not evaluable; OS, overall survival; RFS, relapse-free survival
Locatelli F, et al. Poster presented at: 60th ASH Annual Meeting & Exposition of the American Society of Hematology; December 1-4, 2018; San Diego, CA.

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OVERALL SUMMARY

- **Development program Trans - Atlantic from beginning**
  - Two Phase 1 and Phase 2 trials in relapsed or refractory disease
  - Two randomized controlled Phase 3 trials
- **Protocol development**
  - All protocols and the Pediatric Investigational Plan were developed in close collaboration with the Regulatory Agencies and the Cooperative Groups
- **Treatment regimen**
  - Robust regimen manageable also by sites with less experience
  - Short half life helps with mitigation of toxicity
  - More than 6000 patients with B-Cell Precursor Acute Lymphoblastic Leukemia treated by now

- **The success of blinatumomab was mainly based on close collaboration and communication with Regulatory Agencies and Cooperative Groups**

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Conclusions of the Paediatric Strategy Forum on Checkpoint Inhibitors in Combination

Andy Pearson, *ACCELERATE Steering Committee Member*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Conclusions of the Paediatric Strategy Forum on checkpoint inhibitors in combination

ACCELERATE-EMA-FDA Paediatric Strategy Forums

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

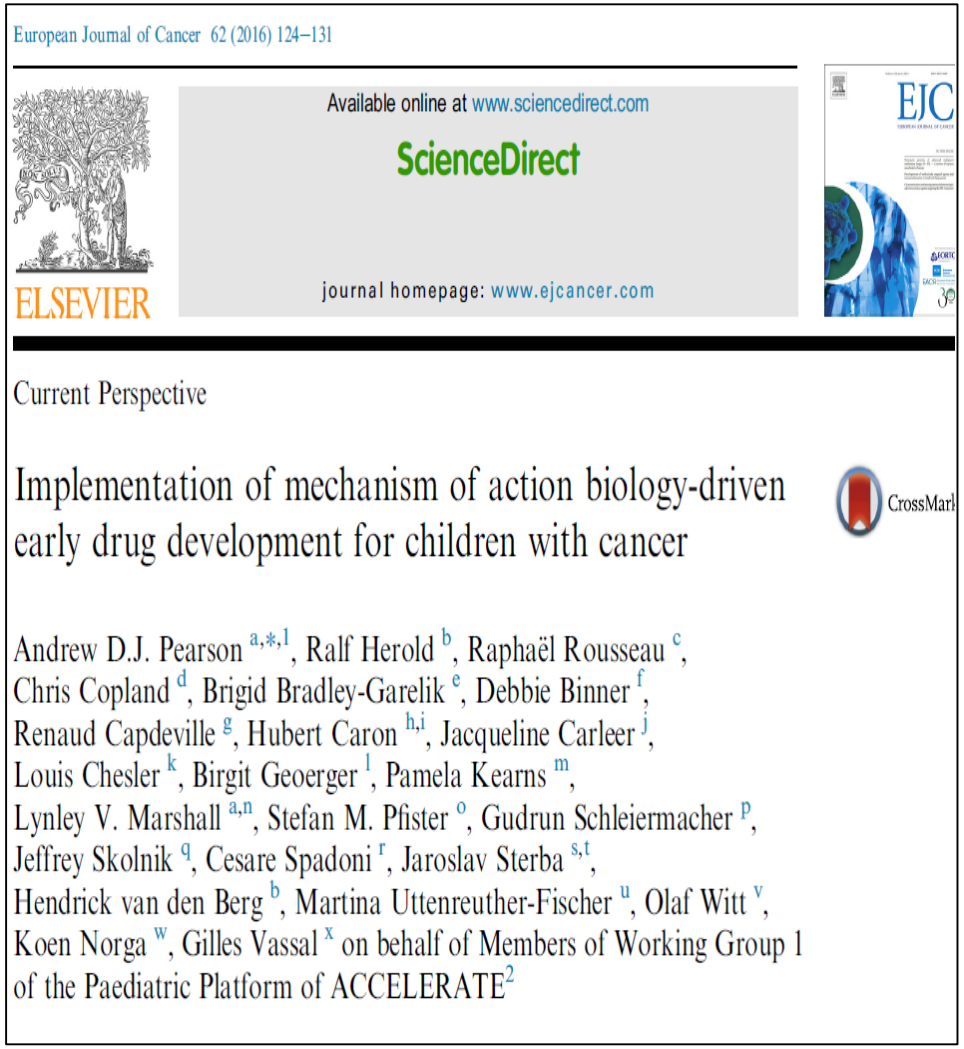
Paediatric Strategy Forum on checkpoint inhibitors in combination

- Paediatric Strategy Forums
- Format of Forum on checkpoint inhibitors in combination
- Overview of monotherapy trials of checkpoint inhibitors
- The Way Forward - Checkpoint inhibitors in lymphomas and hypermutant malignancies
- Checkpoint inhibitors in combination
- Conclusions

ACCELERATE-EMA-FDA Paediatric Strategy Forums

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

- **Specific issue**
- **Goal -** To ***share*** information between all stakeholders, in a pre-competitive setting, to ***inform*** paediatric drug development strategies and *subsequent* decisions
- **This will be achieved by** providing a unique opportunity to facilitate *dialogue* and enable constructive interactions between *all* stakeholders on ***topics*** *requiring discussion in drug development* in children and adolescents with malignancy



European Journal of Cancer 62 (2016) 124–131

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Current Perspective

Implementation of mechanism of action biology-driven early drug development for children with cancer

Andrew D.J. Pearson [a,*,1], Ralf Herold [b], Raphaël Rousseau [c], Chris Copland [d], Brigid Bradley-Garelik [e], Debbie Binner [f], Renaud Capdeville [g], Hubert Caron [h,i], Jacqueline Carleer [j], Louis Chesler [k], Birgit Geoerger [l], Pamela Kearns [m], Lynley V. Marshall [a,n], Stefan M. Pfister [o], Gudrun Schleiermacher [p], Jeffrey Skolnik [q], Cesare Spadoni [r], Jaroslav Sterba [s,t], Hendrick van den Berg [b], Martina Uttenreuther-Fischer [u], Olaf Witt [v], Koen Norga [w], Gilles Vassal [x] on behalf of Members of Working Group 1 of the Paediatric Platform of ACCELERATE[2]

ACCELERATE-EMA-FDA Paediatric Strategy Forums

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

- **First Forum** for ALK Inhibition in Paediatric Malignancies - EMA - January 2017 - 6 products; 5 companies
- **Second Forum** - Medicinal Product Development for Mature B cell Malignancies in Children - EMA - November 2017 - 20 products; 14 companies
- ➢ **Third Forum** - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies - EMA - September 2018 - 20 products; 16 companies (32 EOI)
- **Fourth Forum** - Medicinal Product Development for Acute Myeloid Leukaemia in Children - Rotterdam - 11-12 April 2019 28 products; 18 companies

Target or disease focussed

Continually developing and adapting to needs

Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

- Immune checkpoint inhibitors have shown impressive success in some adult malignancies
- Results of early phase trials in children of single agent checkpoint inhibitors are now available
- Some combination studies are in progress and others are planned

➢ Opportune to review early results of early phase trials in children and consider opportunities for paediatric studies of check-point inhibitors in combination


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

5 September 2018
EMA/242738/2018

Paediatric Strategy Forum for Medicinal Product Development of Checkpoint inhibitors for use in combination therapy in paediatric patients
5-6 September 2018

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

EMA
September
2018

73 Participants at the EMA and 25 by remote access

- 20 Medicinal products discussed
- 16 Pharmaceutical companies (29 EOI)
- European and North American experts in paediatric immunotherapy and drug development
- Patient representatives from Unite2Cure (Europe) and Children's Cause for Cancer Advocacy (US)
- Regulators from EU national competent authorities, EMA & US FDA
- NCI

Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Companies - Participated in the Forum

- AstraZeneca
- Autolus Ltd
- BeiGene Inc.
- Boehringer Ingelheim
- BMS
- Celgene
- Immunicum AB
- Merck KgaA
- Merck, Sharp & Dohme (MSD)
- Novartis
- Pfizer inc
- Regeneron Ireland U.C
- Roche
- Sanofi
- Syndax Pharmaceuticals
- Tesaro Bio GmbH

Companies - Expressed an interest but did not participate

- Bayer AG
- CATS Ergomed
- Faron Pharmaceuticals Ltd.
- GlaxoSmithKline R&D
- Incyte Biosciences
- IPSEN
- Janssen Research & Development, LLC
- Kinesys
- Les Laboratoires Servier
- MedImmune
- MSD
- PPD
- PsiOxus Therapeutics Limited

Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Programme

- Immunological environment and immunotherapeutic challenge of paediatric malignancy
- Rational design of clinical immunotherapy combination trials for maximum benefit and information
- Review of Paediatric Investigation Plans of Checkpoint inhibitors
- Results of Checkpoint inhibitors in early phase clinical studies
- The Way Forward - Checkpoint inhibitors in lymphomas and hypermutant malignancies
- Presentation by pharma of Checkpoint inhibitor combinations

Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Medicinal Products Presented at the Forum

- Pembrolizumab
- Atezolizumab
- Nivolumab
- Ipilimumab
- Pembrolizumab and chemotherapy
- Nivolumab and brentuximab
- Avelumab and standard of care and axitinib
- Cemiplimab and radiotherapy
- Niraparib
- Tislelizumab
- Entinostat
- CTLA- 4
- Nivolumab and ipilimumab

- Tremelimumab and durvalumab
- Anti - LAG 3
- Anti-LAG-3 mAb - Boehringer Ingelheim
- TSR-033
- NKTR
- Bispecific CD20xCD3 antibody
- Isatuximab
- M7824
- TSR 022
- Anti TGF beta – Sanofi
- Ilixadence
- ATMP
- ATIMP

ACCELERATE-EMA-FDA Paediatric Strategy Forums

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Paediatric Strategy Forum on checkpoint inhibitors in combination

- Paediatric Strategy Forums
- Format of Forum on checkpoint inhibitors in combination
- ➢ Overview of monotherapy trials of checkpoint inhibitors
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Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Overview of monotherapy trials of checkpoint inhibitors

317 Patients recruited into early phase studies of three checkpoint inhibitors

- RP2D and safety profile essentially the same as adults
- Low toxicity
- No major untoward effects on the developing immune system
- Limited informative tumour material

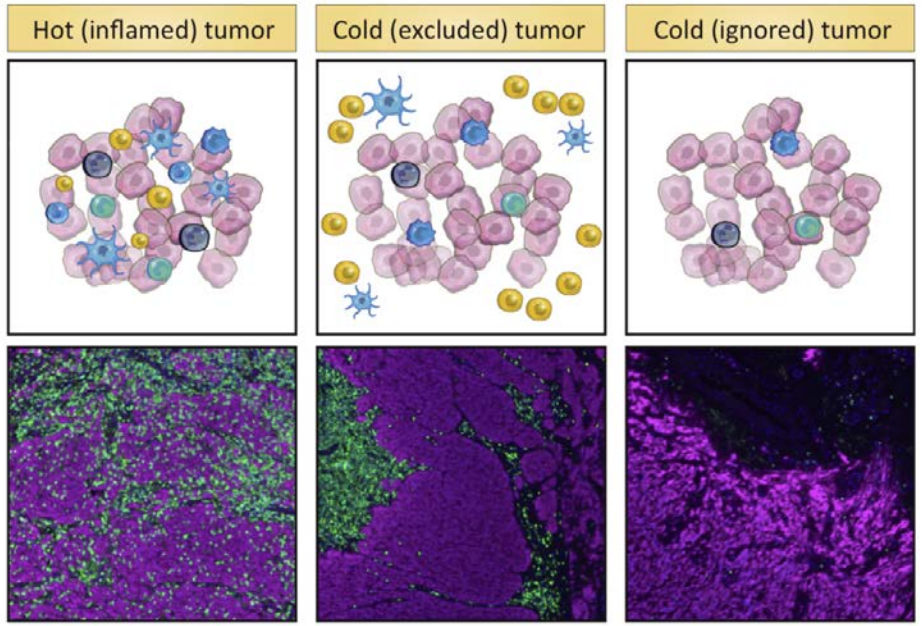
Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Malignancy	Enrolled	CR	PR
Hodgkin's lymphoma	33	3	9
Adrenocortical carcinoma	5		2
Non-Hodgkins lymphoma	5		1
Non-rhabdomyosarcoma soft tissue	13		1
Malignant ganglioglioma	1		1
Lymphoepithelial carcinoma	2		1
Mesothelioma	2		1
Epithelioid sarcoma	1		1
Neuroblastoma	43		

ORR - All - 14% (20/317); Hodgkin's 36% (12/33); Excluding Hodgkin's 2.8% (8/284)

Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Activity of checkpoint Inhibitors as monotherapy in children



van der Woude LL, *et al*. Trends Cancer 2017;3:797-808

Lack of clarity of the mechanism of action of checkpoint inhibitors in children

- Lack of biomarkers
- Majority of paediatric tumours – cold(ignored tumours)
- Hodgkin's Disease - different mechanism infiltrate of T4 cells - histological subtype specific

Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Activity of checkpoint Inhibitors as monotherapy in children

Conclusions

- Priority - to understand the immune microenvironment of paediatric cancers at the different stages of treatment by standardised, harmonised and integrated studies *across* histologies
- Tumour biopsy at the time of enrolment, should be considered as a prerequisite of entering early clinical trials of checkpoint inhibitors; however the results of the biopsy should potentially benefit the patient
- High priority should be given to considering combining biological data of 3 early phase studies of checkpoint inhibitors

Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Activity of checkpoint Inhibitors as monotherapy in children

Conclusions

No benefit to children with malignancy to have more trials of other checkpoint inhibitors with the **same** mechanism of action until there is more scientific knowledge

In the EU a product specific waiver could be submitted supported by academia based on scientific evidence of lack of therapeutic benefit for other checkpoint inhibitors

Similar a modification of an existing Paediatric Investigational Plan could be submitted

ACCELERATE-EMA-FDA Paediatric Strategy Forums

ACCELERATE
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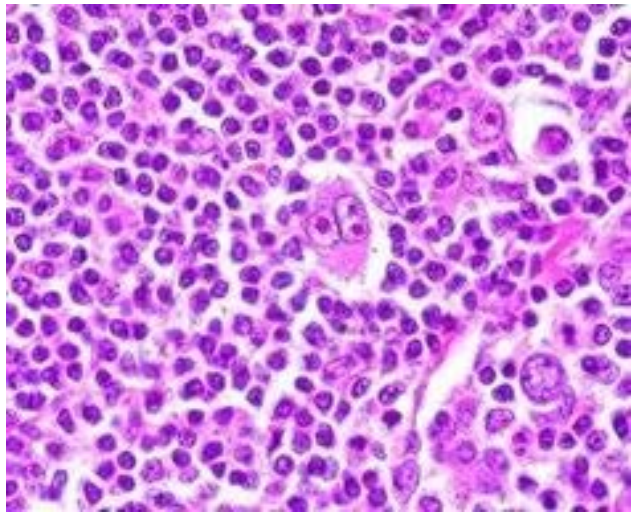
Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

The way forward for checkpoint Inhibitors in lymphomas

Hodgkin's Disease



- ORR -36%
- Await the results of ongoing studies which evaluate role of checkpoint inhibitors in Hodgkin's Disease
- Randomised studies are very valuable scientifically and should be always considered
- As the response to monotherapy with checkpoint inhibitors should be improved, combinations should be developed
- Checkpoint inhibitors might allow other components of therapy to be replaced

Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

The way forward for checkpoint inhibitors in lymphomas

Primary Mediastinal B Lymphoma

- ORR of checkpoint inhibitors 41%
- Need for randomized trials with international and adult collaboration evaluating anti-PD1 combination with standard backbones
- Consider enrolling children on adult studies - separate cohort

Anaplastic Large Cell Lymphoma

- Limited clinical experiences but strong biological background
- Phase II trial of nivolumab for paediatric and adult relapsing/refractory ALK+ ALCL

Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

The way forward for checkpoint inhibitors in hypermutated tumours

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

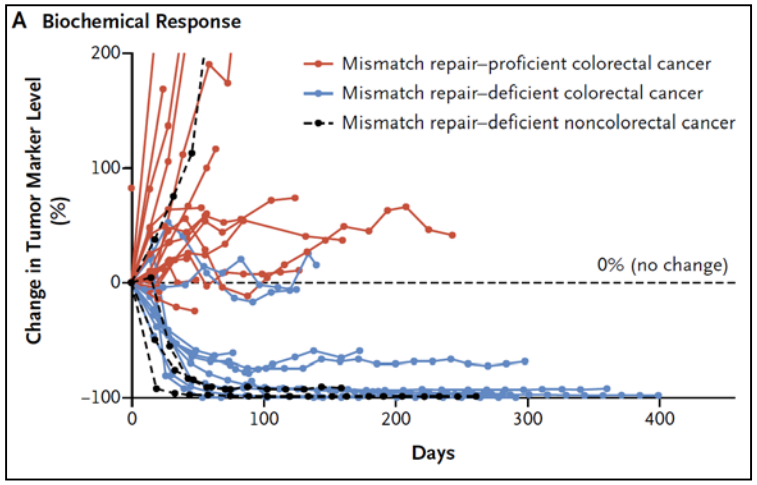
Le DT et al N Engl J Med 2015; 372:2509-2520

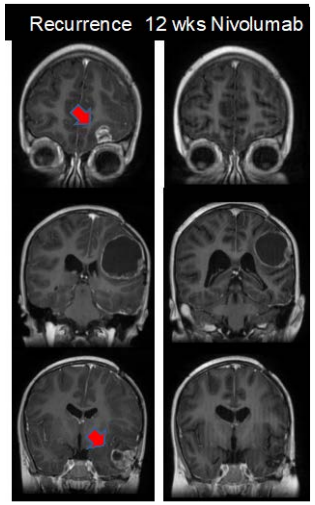
VOLUME 34 · NUMBER 19 · JULY 1, 2016

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency

Eric Bouffet, Valérie Larouche, Brittany B. Campbell, Daniele Merico, Richard de Borja, Melyssa Aronson, Carol Durno, Joerg Krueger, Vanja Cabric, Vijay Ramaswamy, Nataliya Zhukova, Gary Mason, Roula Farah, Samina Afzal, Michal Yalon, Gideon Rechavi, Vanan Magimairajan, Michael F. Walsh, Shlomi Constantini, Rina Dvir, Ronit Elhasid, Alyssa Reddy, Michael Osborn, Michael Sullivan, Jordan Hansford, Andrew Dodgshun, Nancy Klauber-Demore, Lindsay Peterson, Sunil Patel, Scott Lindhorst, Jeffrey Atkinson, Zane Cohen, Rachel Laframboise, Peter Dirks, Michael Taylor, David Malkin, Steffen Albrecht, Roy W.R. Dudley, Nada Jabado, Cynthia E. Hawkins, Adam Shlien, and Uri Tabori





Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

The way forward for checkpoint inhibitors in hypermutated tumours

- Response rate **ORR 69**% in hypermutated tumours (International Biallelic Mismatch Repair Deficiency Consortium trial)
- Definition - hypermutated tumours >10/mb and ultrahypermutation as >100/MB (Campbell et al, Cell (2017), https://doi.org/ 10.1016/j.cell.2017.09.048)

Conclusions

- Consolidate data through global entry on International Biallelic Mismatch Repair Deficiency Consortium trial
- Evaluate combinations
- Evaluate hypermutation at relapse – however lack of activity in paediatric phase II trials of checkpoint inhibitors to date suggests that “clinically relevant” hypermutation is uncommon"

ACCELERATE-EMA-FDA Paediatric Strategy Forums

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

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Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Combinations presented at the Forum

In the region of 20 very recently opened or soon to open studies of checkpoint inhibitors in combination

- Chemotherapy/anti angiogenics
- Radiotherapy

  Concept of addition of checkpoint inhibitor to established therapy
- PARP Inhibitors

  Design – enrichment based on "BRCA" signature
- HDAC inhibitors
- Other checkpoint Inhibitors
  - Anti-CTLA-4
  - Anti-LAG-3

Other immunoncology products

- Monoclonal antibodies directly targeting tumour antigens.
- Combined checkpoint inhibitor and anti-TGF-beta
- Anti-TIM-3
- Anti-TGF-beta
- Cell therapy

Third Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Combinations

How to identify the best choices of combinations for the treatment of children with cancer?

- **Combinations need to be based on strong scientific rationale in paediatrics**
- **Combinations being studied in adults to boost anti-PD-1/PD-L1 response** to tumour neoantigens have limited paediatric applicability - absent additional scientific rationale

Third Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Combinations

- Strategies should be **based on immunological landscape**
  - Intra-tumoural reactive T cell cells
  - Excluded reactive T cell cells
  - No tumour reactive lymphocytes

- Development in paediatrics should be ***considered*** EARLY
- Immune checkpoint inhibitor combinations should be evaluated in hypermutated tumours and lymphomas to improve response rates
- Combinations in which checkpoint inhibitors are “added” to established therapy - very difficult to interpret without randomised studies and “controls”

Third Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Combinations

- Global industry supported, academic sponsored studies with compounds from different pharmaceutical companies using a master protocol in rare populations have considerable merit
- These protocols should be designed with “intent to file”

Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Conclusions

- Monotherapy with checkpoint Inhibitors in children - very limited activity in children except for lymphomas, hypermutant tumours and rare paediatric tumours
- Except for hypermutation there are no clearly defined biomarkers
- The immune microenvironment of paediatric cancers needs to investigated
- Immune Checkpoint Inhibitor Combinations should be evaluated in lymphomas and hypermutated tumours
- Combinations of checkpoint inhibitors should be explored in paediatrics based on **hypotheses and scientific data** and not only because these combinations are being evaluated in adults
- Need for international inter-company registry of early and late adverse effects

Roundtable Discussion: Immunotherapy for Children with Cancer: current Challenges and where to go?

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

See you at 16h30!

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Session 3 – New Initiatives to accelerate Paediatric Oncology Drug Development

Co-Chairs:
Rosanna Ricafort, *Bristol-Myers Squibb*
Susan Weiner, *Children's Cause for Cancer Advocacy*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Fostering Age Inclusive Research (FAIR)

Nathalie Gaspar, *Gustave Roussy*
Chris Copland, *University of York*

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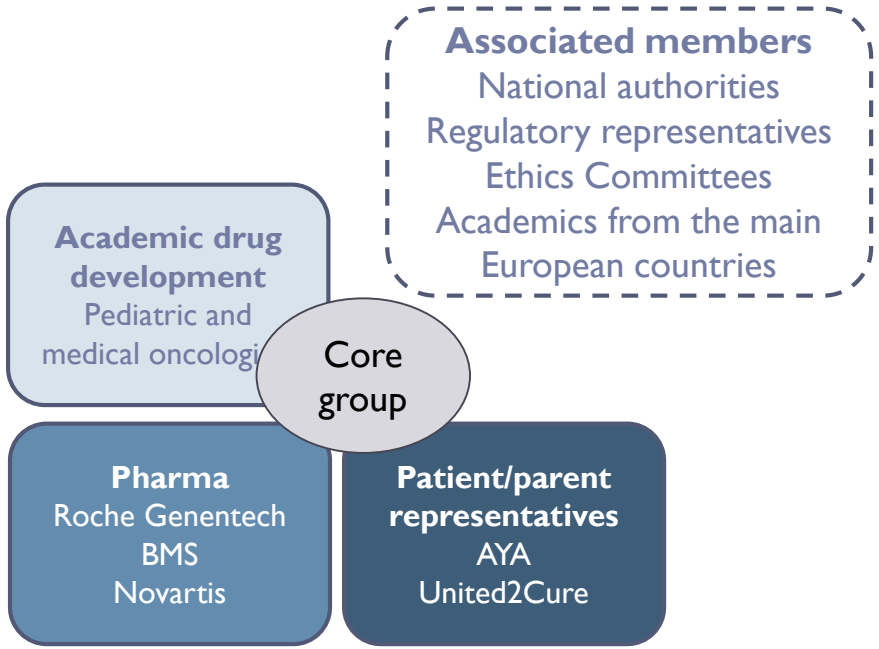
Fostering Age Inclusive Research

https://www.accelerate-platform.eu/work-programme/ongoing/working-group-fair/why-fair-trials/



Objective 1
To identify successful trials

Objective 2
Awareness Raising to the professionals involved in trial design and approval and the general public

Objective 3
Tools ready to use to facilitate the understanding of the problem and the initiation of trial

Objective 4
Endorsement of the adolescent strategy

FAIR Group Action Points

Objective 1

The Survey:

- *Early phase 1/2 trials*
- *Intended for academic PIs for academic trials through ITCC*
- *Intended for ACCELERATE pharma partners for pharma trials*

2017

Responses
Academia 2 | 17 trials | Pharma 9

Phase 3: 7
Trials open<2017: 8
Insufficient info: 1

No trials:
- Academia: 5
- Pharma: 3

4 Trials open

Academic trials: 1 Pharma trials: 3

Trial phase	Ped. Trial with YA	Adult trial with Ado.
Phase 1 / 1b	1	0
Phase 2	3	0

2018

Responses
Academia 13 | 29 trials | Pharma 8

Phase 3: 3
Trials open<2018: 14
Duplication: 1

No trials:
- Academia: 4
- Pharma: 3

7 Trials open

Academic trials: 2 Pharma trials: 5 (+ 3 confidential)

Trial phase	Ped. Trial with YA	Adult trial with Ado.
Phase 1 / 1b	2	1
Phase 2	4	0

FAIR Group Action Points

Objective 1

The Survey:

- *Early phase 1/2 trials*
- *Intended for academic PIs for academic trials through ITCC*
- *Intended for ACCELERATE pharma partners for pharma trials*

Adult early phase trial including adolescents

*An Open-label phase 1b study of the safety, tolerability, and preliminary antitumor activity of INCB059872 in participants with relapsed or refractory Ewing sarcoma
(Sponsor: Incyte Corporation)

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

FAIR Group Action Points

Objective 2

European networks

Paediatric oncology

EF GCP
Guidelines
Position paper 2019

Paediatric oncologists
SIOP 2017, 2018
ITCC 2018

SIOP Europe
Education book 2018
Website 2019
Article 2019

Innovative Therapies for Children with Cancer
ITCC European Consortium

Medical oncology

Medical oncologists
ESMO 2017 et 2018

ESMO
Education book 2018
E-learning 2018

EORTC European Organisation for Research and Treatment of Cancer
Meta-analysis
Submitted JNCI
TAT-ESMO conf
TAT 2019

National networks

Representatives of the main EU countries ….
Meeting and cancer societies

FAIR Group Action Points

Objective 3

National initiatives through ITCC contacts

Contact with paediatric oncologists involved in early drug development and AYA friendly

Carole Lecinse

Objectives = to have …
An overview of national situation on the topic
An action plan to promote adolescent inclusion in early phase adult clinical trial

To identify paediatric and medical oncologists involved in early drug and parent/patient representatives who might be supportive and proactive

To provide contacts and action plan towards ethics committees and competent national authorities

Paper in 2019?

To expand communication and awareness across their own country

To identify places where both adolescent and adult early phase trials could be run (same center or paediatic/adult centers collaborating)

N.Gaspar **France**

L.Marshall **UK**

K. Nysom **Denmark**

AJ.Ribelles **Spain**

B.Wulff **Germany**

M.Casanova **Italy**

Austria, Belgium, Finland, Ireland, the NL, Sweden, Switzerland

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INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

FAIR Group Action Points

Objective 2

European networks

Paediatric oncology

EF GCP
Guidelines
Position paper 2019

Paediatric oncologists
SIOP 2017, 2018
ITCC 2018

SIOP Europe
Education book 2018
Website 2019
Article 2019

Innovative Therapies for Children with Cancer
ITCC
European Consortium

Medical oncology

Medical oncologists
ESMO 2017 et 2018

ESMO
Education book 2018
E-learning 2018

EORTC
European Organisation for Research and Treatment of Cancer
Meta-analysis
Submitted JNCI
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TAT 2019

National networks

Representatives of the main EU countries ….
Meeting and cancer societies

General public

Online
Broadcast media
Face 2 face

UNITE 2 CURE

FAIR Group Action Points

Objective 2

Raising Awareness

ACCELERATE front page

FAIR Group Action Points

Objective 2

Raising Awareness / Use of Media

Web page

- from list of objectives to set of resources for awareness raising
- engaging different audiences – plain language /info. depth
- promotion of Toolkit and Gold Ribbon

Unite2Cure video

Mainstream media

- Horizon (BBC TV)
- National press

Emulating this example

FAIR Group Action Points

Objective 3

- When safe and justified the design or amendment of clinical protocols targeting both AYA (adolescents & young adults) and adult patients in the same clinical research study can be considered

- Limited awareness on requirements and clinical-protocol specificities to enable AYA inclusion in adult trials can unnecessarily obstruct the inclusion of the AYA population in adult trials.

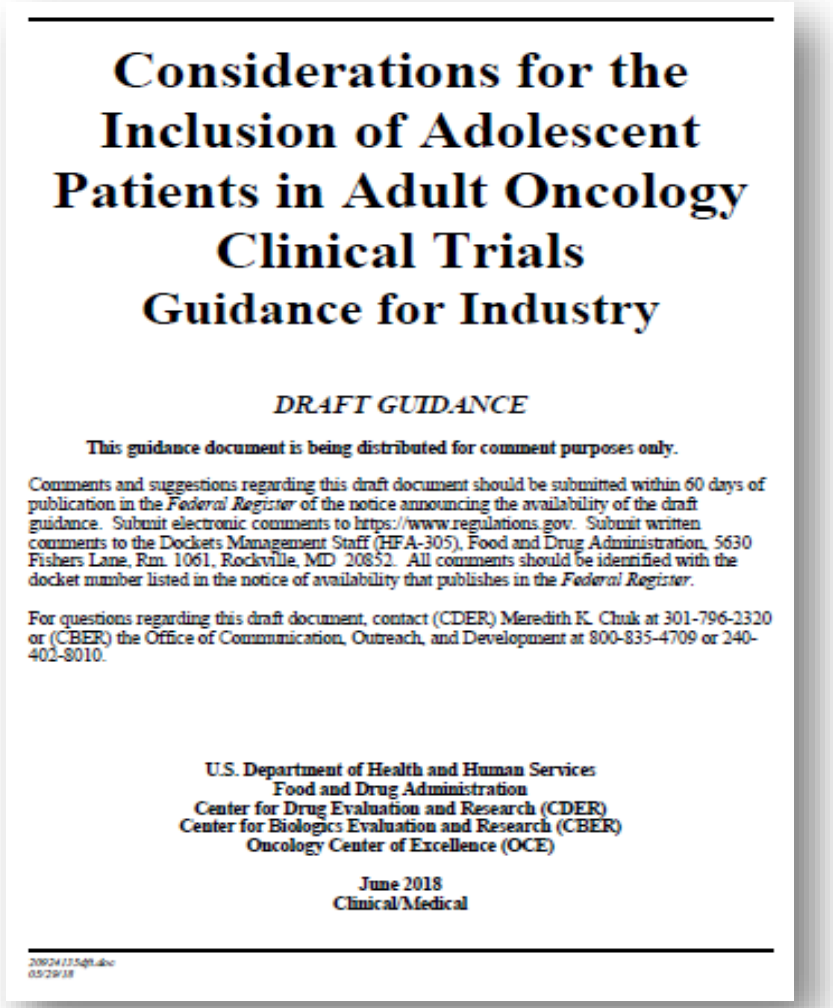
- **The AYA toolkit** is intended as a resource to support and guide design of AYA-inclusive clinical studies

FAIR Group Action Points

Objective 3

- **Regulators** increasingly recognize the need of considering inclusion of adolescents in adult oncology trials to ensure timely access of these populations to innovative medicines

- FDA released **draft guidance** in 2018 providing recommendations to industry on inclusion of adolescent patients, ages 12 to 17 in adult oncology clinical trials.



Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Meredith K. Chuk at 301-796-2320 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

June 2018
Clinical/Medical

FAIR Group Action Points

Objective 3

Increase awareness of tools or information supporting inclusion of AYA patients can:

- positively influence decision making in consideration of trials including AYA patients
- address scientific-knowledge gaps impacting AYA inclusion in adult trials
- Ensure minimum requirements are in place

AYA Toolkit

- Regulatory aspects
- Protocol elements
- Assent guidance
- Other protocol tools (e.g. PROs)
- List of ongoing AYA friendly trials
- AYA-friendly clinical sites

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INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

FAIR Group Action Points

Objective 3

Example 1

Tool Name:
Assent requirements

Description:

The Assent is a form of agreement of someone not able to give legal consent to participate in an activity/clinical research study. The Assent does not substitute the informed consent which is required to be signed by the parent or legal guardian and constitutes the legal documentation of understanding of the implications of taking part in the research , and agreement to take part to it.

Content example:

- Protocol sections wording referring to assent requirements
- ENPR-EMA country specific guidance for Informed Consents/Assent in Pediatric Clinical Trials
- List of Lay Terms compiled by EC
- Assent template resources

FAIR Group Action Points

Objective 3

Example 2

Tool Name:
Patient Reported Outcomes for AYA (PROs)

Description:

PROs have been defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." In other words, PRO tools measure what patients are able to do and how they feel by asking questions. These tools enable assessment of patient–reported health status for physical, mental, and social well–being.

Content example:

Example of Oncology PROs with versions suitable for AYA patients

Adolescent-Ready PRO Assessment	Matching Adult PRO Assessment	Description
Pediatric MDASI	MDASI	Pediatric MD Anderson Symptom Inventory
Pediatric PRO-CTCAE	PRO-CTCAE	Pediatric Patient-Reported Outcomes Common Toxicity Criteria for Adverse Events
EQ-5D-Y	EQ-5D-5L	A EuroQoL health status measure
Peds FACIT-F	FACIT-F	A fatigue measure
Peds FACT-Br	FACT-FBrSI	A brain cancer symptom measure
Peds-FAACT	FAACT	Anorexia and cachexia measure
…	…	…

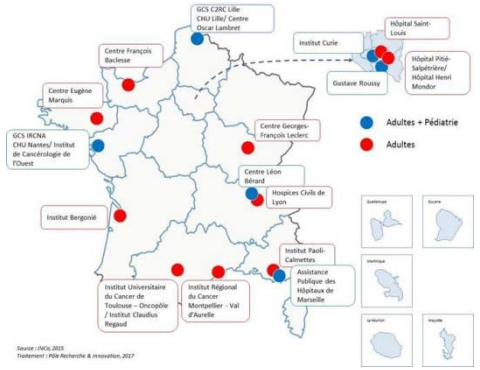
EuroQoL=European quality of life; FACT(-Br), (-F)=Functional Assessment of Chronic Illness Therapy (−Brain Cancer (−Fatigue); FAACT=Functional Assessment of Anorexia and Cachexia Therapy

FAIR Group Action Points

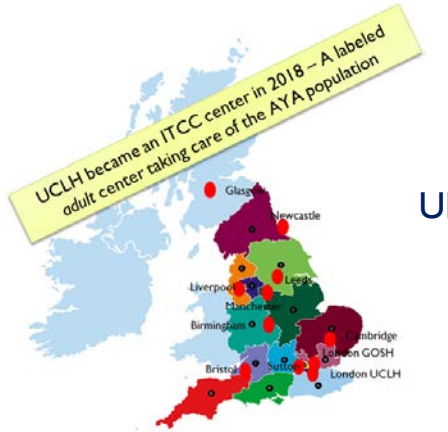
Objective 3

National initiatives through ITCC contacts

Pediatric and Adult sites

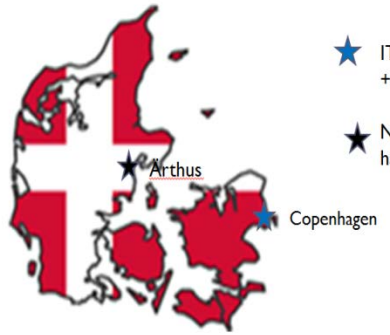


FRANCE



UK

ITCC centres



★ ITCC centre + adult haematology + adult oncology

★ Non-ITCC centre + adult haematology + adult oncology

DENMARK

SPAIN

Spanish centres with pediatric oncology units

5 ITCC centres

Both paediatric and adult early drug development

FAIR Group Action Points

Objective 3

National initiatives through ITCC contacts

Pediatric and Adult sites

GERMANY

- Phase I/II Pediatric and Adults
- ITCC Centers

In total N=58

Paediatric oncology centres accredited according to German Federal Joint Committee (G-BA)

ITCC centres: N=9

Non ITCC centres N= 49

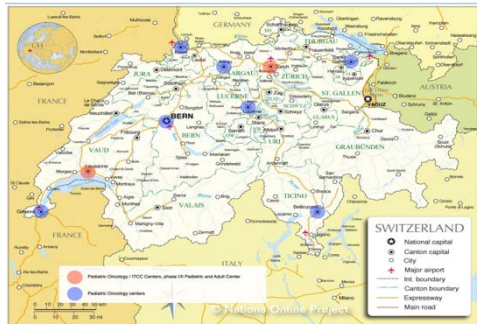
Epidemiology:
1800 new diagnoses per year
ca. 360-400 relapses,
ca. 40 – 50 of these will be cured,
> 300 children with poor prognosis

Milano INT : phase I program for all ages (ped + adults : unified SOPs, PK lab etc)

Roma Gemelli and Bologna same hospital but 2 different programs for phase I

Monza FBB and Torino Different locations but in close collaboration

ITALY



SWITZERLAND

Adult & Pediatric Oncology units: Umeå, Uppsala, Stockholm, Linköping, Lund, Göteborg

ITCC Units: Göteborg, Stockholm

SWEDEN

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INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

FAIR Group Action Points

Objective 4

EMA, PDCO

On a regular basis the Paediatric Committee (PDCO) is challenging companies to include adolescents into the adult development programs whenever scientifically justified. This holds true for all therapeutic areas, not only for oncology.

The EMA's Committee for Medicinal Products for Human Use (CHMP) has expanded the concept of age inclusive research to age inclusive marketing authorisation, again whenever there is sound scientific evidence supporting this. A recent example is Mylotarg, for which adolescents have been included into the initial marketing authorisation.

Overall, from our regulatory perspective, fostering age inclusive research whenever scientifically justified is implemented in our procedural routine from the research and development stage to the licensing stage.

05/11/2018

Official statement?

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

FAIR Group Action Points

Objectives 2019

- ❑ Survey: to be modified to include the number of adolescents really included in the trials — 1 month
- ❑ Tool kit: to have it on the website/ advertised on the different networks — 2 months
- ❑ Website redesign : lively and friendly user site with all the documents we produced — 3-4 months
- ❑ Country by country action
  - Document plan — 1 month
  - Paper of the current situation — 12 months
- ❑ EMA official endorsement — ?????????

ACCELERATE FAIR trial group

We are ready to jump
Waht about you ?

Innovative Models for Paediatric Oncology Drug Development

Delphine Heenen, *KickCancer*
Sam Blackman, *Mavupharma, Inc.*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

WORKING GROUP 4: Setting Up New Business Models and Ways to Invest in Paediatric Oncology Research and Drug Development

WG4 team: patients advocates

Patricia Blanc
Imagine for Margo, FR
Unite2Cure, EU

Sam Daems
Waterland, BE-GER-POL

Delphine Heenen
KickCancer, BE
Unite2Cure, EU

Jean-Charles van den Branden
Bain & Company, WW
KickCancer, BE

Working Group 4 team: industry and academics

Sam Blackman
MavuPharma, USA
CureSearch, USA
Accelerate, EU

Gilles Vassal
Gustave Roussy, FR
ITCC, EU
SIOPE, EU
Accelerate, EU

Raphaël Rousseau
Gristone, USA
CureSearch, USA
Accelerate, EU

Andy Pearson
Ex-Institute of Cancer Research, UK
Ex-Royal Marsden Hospital NHS, UK
ITCC, EU
Accelerate, EU

Drug development in paediatric oncology is frequently deemed not profitable

Too long!

Complex with different age groups

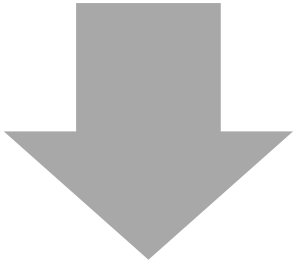
Expensive and not profitable

Regulatory issues and uncertainties on reimbursement

Small population…

We need a new model for paediatric oncology

New drug development is driven by adult diseases and targets
(vs. paediatric diseases and targets)



Let’s think differently and start from the children’s needs

Innovation is booming but delayed not for children

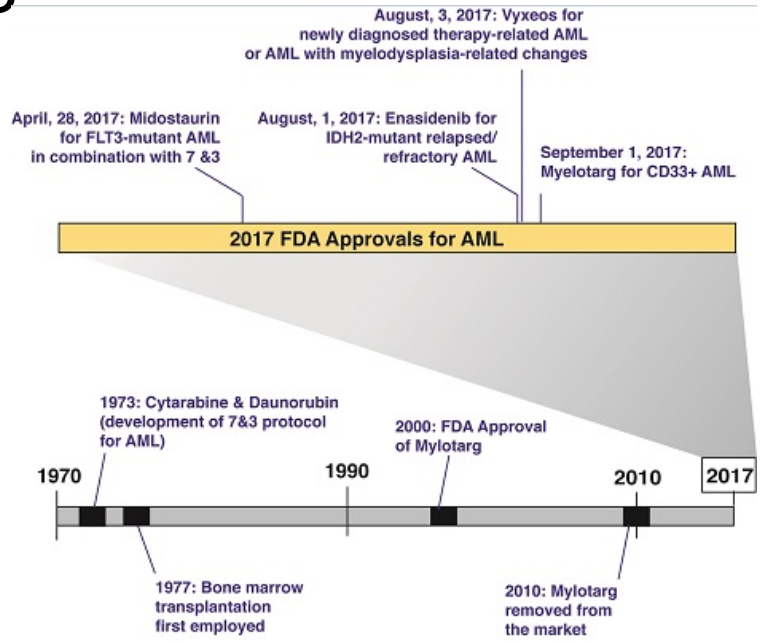
Kinase inhibitors (targeted therapies)	**48** approved for use in adults	**3** approved for use in children
Checkpoint inhibitors	**7** approved for use in adults	**1** approved for use in children
Antibody-drug conjugates	**6** approved for use in adults	**2** approved for use in children
CAR-T cells & BiTEs	**3** approved for use in adults	**2** approved for use in children

When it comes to innovation in paediatric oncology, ***children (usually) come last***

Source: IMS Health, MIDAS, Lifecycle, R&D Focus, IMS Institute for Healthcare Informatics, Dec 2015; US FDA; Blue Ridge Institute for Medical Research

Explosion of new therapies for AML but few approvals for paediatric patients

- **Gilteritinib** (2018): adult patients with r/r AML with FLT3 mutation
- **Glasdegib** (2018): patients ≥ 75y ineligible for induction chemotherapy
- **Ivosidenib** (2018): adult patients with r/r AML with IDH1 mutation
- **Enasidenib** (2017): adult patients with r/r AML with IDH2 mutation
- **Midostaurin** (2017): adult patients with AML and FLT3 mutation
- **Gemtuzumab ozogamicin** (2017): CD33+ AML in adults and children ≥ 2



FLT mutations occur in 15% of pediatric AML
(versus 20-35% of adult AML)

IDH mutations occur in 3.5% of pediatric AML
[10% with normal karyotype]
(versus 16% of adult AML)

CALL TO ACTION

Stars are aligned to do better…

Strong international networks of professionals

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

SIOPE
SIOP Europe
the European Society for Paediatric Oncology

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA

CHILDREN'S ONCOLOGY GROUP

Innovative Therapies for Children with Cancer
ITCC
European Consortium

UNITE 2 CURE

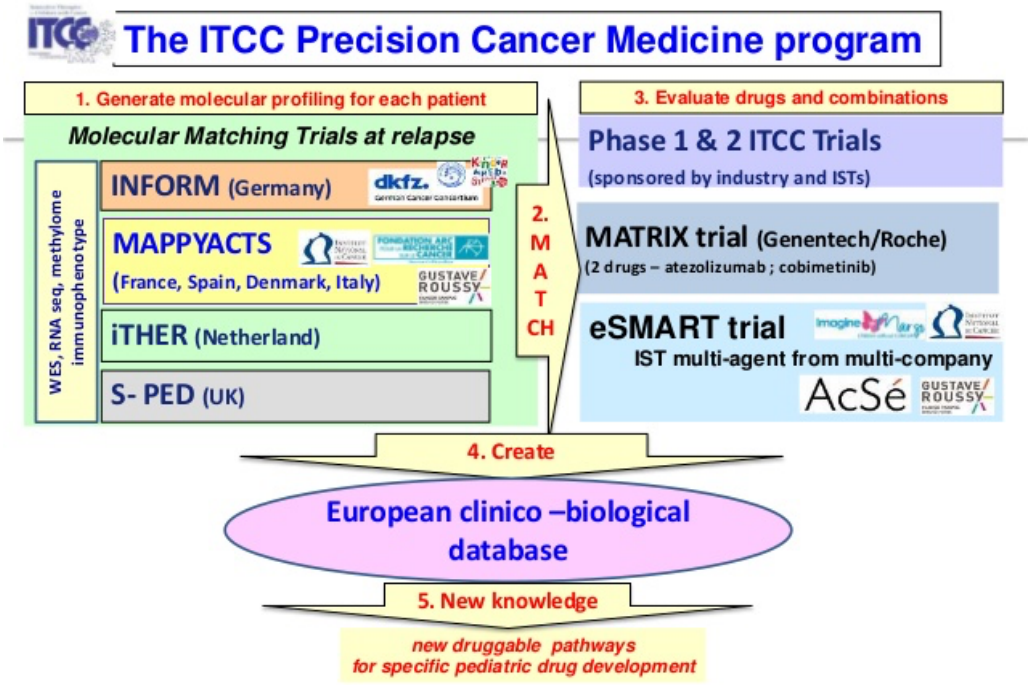
Parents, academics, pharma industry and regulators already work together to accelerate innovation

Improvements in our understanding of paediatric cancer biology has led to the development of new clinical trial infrastructure

International precision medicine strategy

Whole genome and whole exome sequencing (WES/WGS)

Immune profiling (e.g. MSI-H)



THE ACCELERATOR

Multiple ways to bring innovation to children

The goal: Identify scientifically relevant drugs for paediatric indications and make them:

- **available for children**
- **approved on label for paediatric indications**

Accelerating testing of new adult drugs in children

Make sure that clinical trials lead to market authorisation for paediatric use of new drugs earlier

Develop de novo drugs for children for validated targets

Develop drugs where the target is predominant in paediatric tumor biology (e.g. EWS-FLI1)

Retargeting existing or discontinued drugs

Repurpose abandoned molecules in adult oncology based on emerging paediatric cancer biology data

A ”portfolio” model for pediatric oncology

JAMA Oncology | Review

New Business Models to Accelerate Innovation in Pediatric Oncology Therapeutics
A Review

Sonya Das; Raphaël Rousseau, MD, PhD; Peter C. Adamson, MD; Andrew W. Lo, PhD

OBSERVATIONS Review of published studies of pediatric oncology research and the cost of drug development, as well as clinical trials of pediatric oncology therapeutics at ClinicalTrials.gov, identified 77 potential drug development projects to be included in a hypothetical portfolio. The returns of this portfolio were simulated so as to compute the financial returns and risk. Simulated business strategies include combining projects at different clinical phases of development, obtaining partial funding from philanthropic grants, and obtaining government guarantees to reduce risk. The purely private-sector portfolio exhibited expected returns ranging from −24.2% to 10.2%, depending on the model variables assumed. This finding suggests significant financial disincentives for pursuing pediatric oncology therapeutics and implies that financial support from the public and philanthropic sectors is essential. Phase diversification increases the likelihood of a successful drug and yielded expected returns of −5.3% to 50.1%. Standard philanthropic grants had a marginal association with expected returns, and government guarantees had a greater association by reducing downside exposure. An assessment of a proposed venture philanthropy fund demonstrated stronger performance than the purely private-sector–funded portfolio or those with traditional amounts of philanthropic support.

CLINICAL RELEVANCE A combination of financial and business strategies has the potential to maximize expected return while eliminating some downside risk—in certain cases enabling expected returns as high as 50.1%—that can overcome current financial disincentives and accelerate the development of pediatric oncology therapeutics.

Added value of the Accelerator

1 Covers the whole value chain of development

Develop and maintain a list of eligible, prioritized compounds to be developed in children

Definition of an integrated development plan for each compound including regulatory, strategy, clinical trial plan & dev costs

Execute / project manage / delegate integrated development plan: from drug selection to MA filing

2 Starts from the patients' needs by target and by disease

3 Focuses development strategy to reach MA faster

4 Helps the industry in paediatric development by acting as strategic partner

5 Cost effective due to expertise in paediatric oncology development

A specific set of criteria will help determine the first candidate molecules

Demonstrated unmet need

Goal is to **help children not helped today**

- Size of patient population
- Low survival rates
- Low QoL from current standard-of-care
- Limited progress/interest to date for target/disease

Probability of launch

Goal is to demonstrate capability to **bring product to the market**

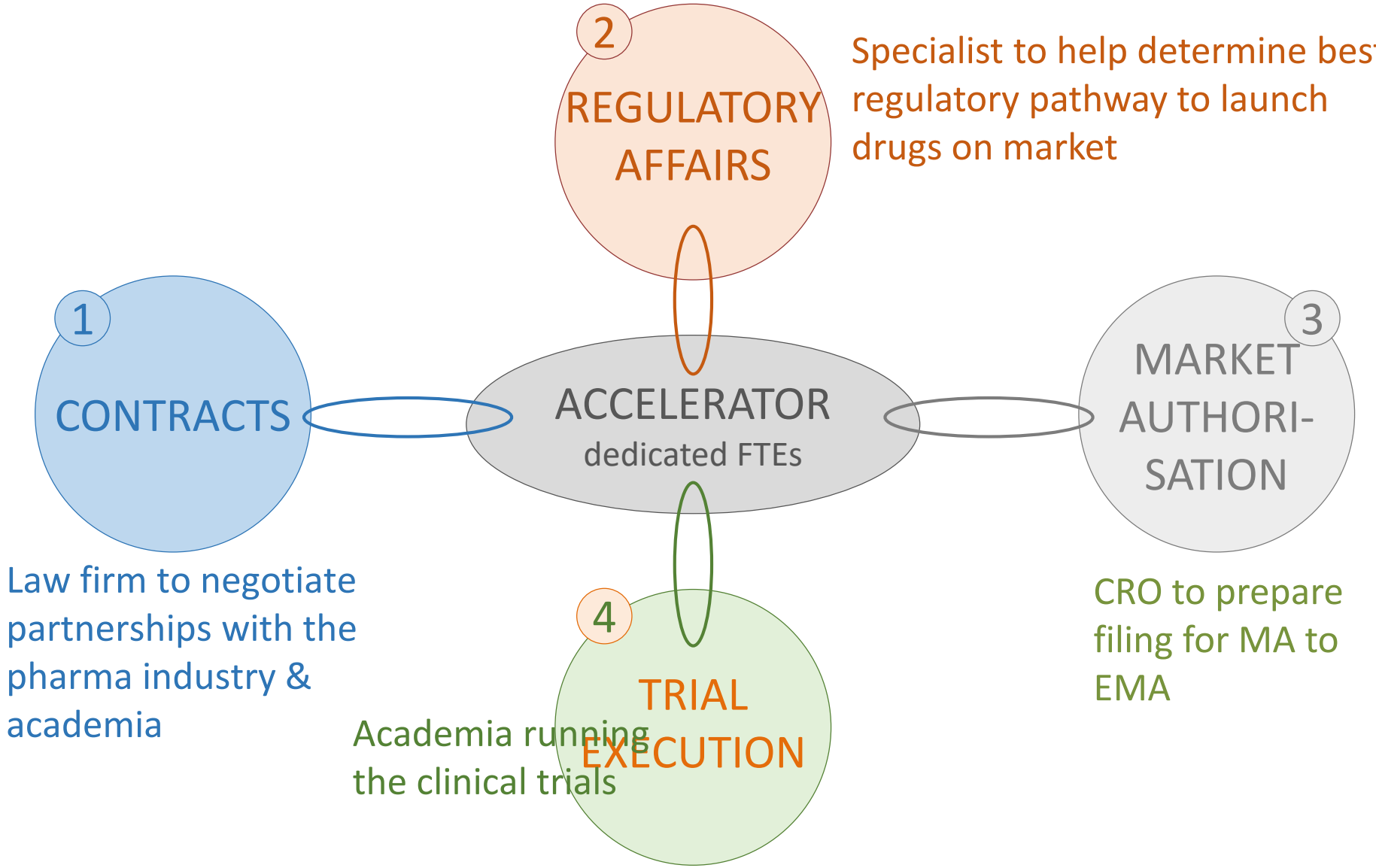
- Strong pre-clinical data
- Success in other studies
- Adult data available
- Success in agents in same class
- Promising results from previous phase
- Diagnostic data / Proof of mechanism in humans
- Clear regulatory pathway

Time to value inflection

Goal is to achieve **rapid proof-of-concept**

- Technically/statistically feasible to prove beneficial impact on short-term endpoints
- Substantial patient pool for trial recruitment
- Limited competing trials
- Dismal survival rate in the near-term

The Accelerator will operate through a delegated model, with specialized team to manage projects



Building a viable new company requires solving these problems

Employees	⟺	Capital & Molecule
Access to molecule (license)	⟺	Capital & Team
Capital (investors)	⟺	Team & Molecule & Clinical dev path

KEY FINDINGS

Full-time expert team is critical for success

Individuals with significant industry experience

- **Target/program hunting**
- **Getting in the door** business development/licensing groups
- **Structuring, financing, and executing complex deals**
- **Designing and executing focused trials**
- **Agility**: If successful, team will need to rapidly initiate clinical development, manufacturing, regulatory interactions

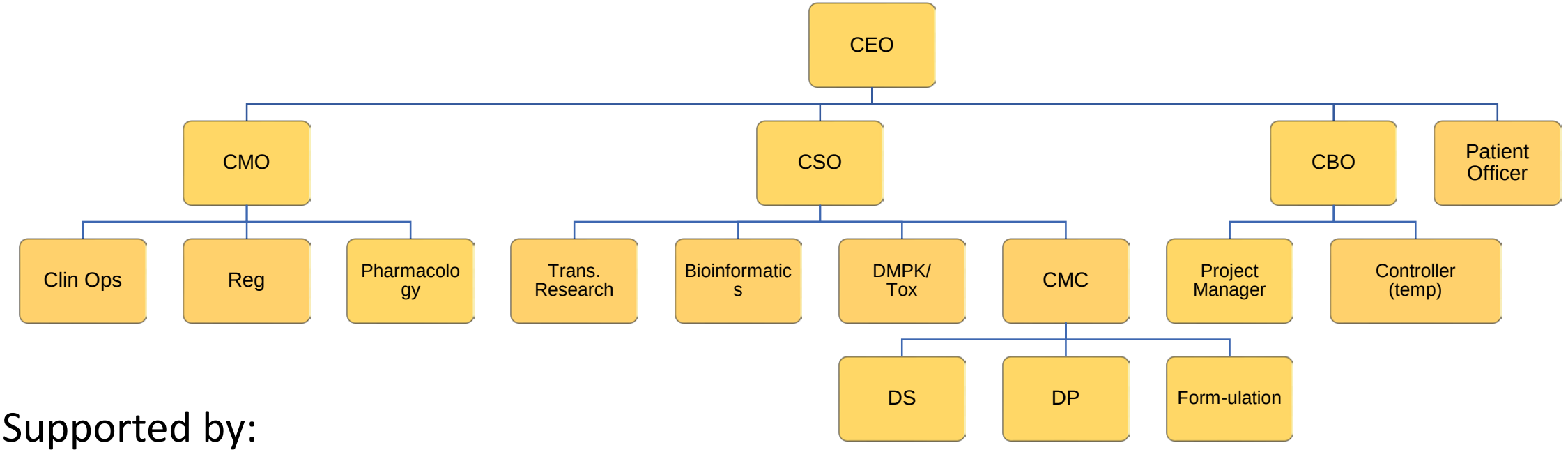
Broad Network

- **Global clinical development partners**
- **Access to sources of capital and programs**: VCs/institutional investors, family foundations/HNW individuals; biopharmaceutic BD/L teams

Compensation

- **Market for oncology biopharma talent is extremely competitive**:
- Salary, benefits, and equity required to recruit top talent away from other companies or compete against funded startups

Proposed minimal viable team for development stage execution



Supported by:

- Corporate board (BOD)
- Clinical/scientific advisors
- Parent/patient advisors

Initial team

Second-wave hires

What patient/parent representative can bring to the project

Political network

- Contact with politicians at national and international levels
- Agenda to improve the regulatory environment in favor of children with cancer

Patients' network

- Access to patients can improve recruitment to trials
- Expert patients can contribute to improved trial design (compliance, tolerability)

Access to executives

- Long-standing relationship with several pharmaceutical companies
- Mostly with the top executives, who may help gain access to programs despite BD group's priorities

Access to pipelines is **harder than expected**

Companies often do **not have large efforts dedicated to out-licensing**

- Information around discontinued programs is usually not publicly available
- Pharma business development/licensing efforts are laser-focused on **in-licensing**
- High cost for out-licensing assets, including opportunity cost

Most out-licensing/partnering deals to date are **front-ended** (large upfront cash payment)

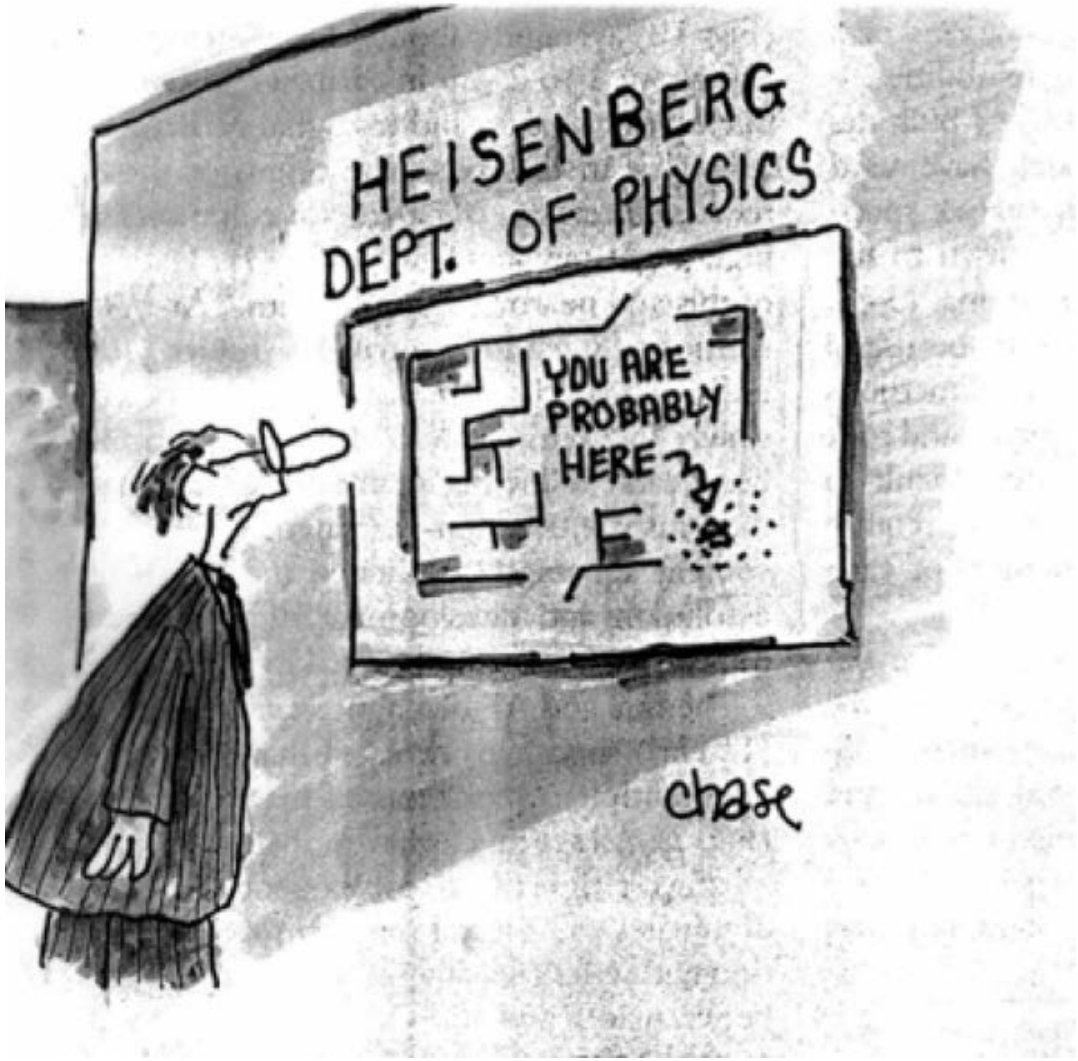
A new company without capital can usually only do back-ended deals (equity, royalties)

Terminal elimination half-life of discontinued programs is **very short**

- Loss of institutional knowledge
- Loss of manufacturing capability, existing API

Even if successful, new translational/validation data in appropriate models may be required to de-risk hypotheses (e.g. CSF1R)

Unintended consequences: Heisenberg's Uncertainty Principle



Sharing a new hypothesis about a discontinued program may impact a company's perception of the value of the program.

Unintended consequences: LOXO FOMO

BIOTECH AND PHARMACEUTICALS

HEALTH | HOSPITALS | BIOTECH AND PHARMA | HEALTH INSURANCE | MODERN MEDICINE

Eli Lilly to buy Loxo Oncology for about $8 billion in cancer drug bet

Access to significant capital/financing is required

- Capital demands for development more than what private donors can raise
  - $20-50M to value inflection
  - Commercialization/manufacturing
- **Venture returns** are expected by VCs for an ongoing company.
- Competition for investment dollars with **many other high-risk/high-reward opportunities**.

Buying and selling at the same time

- Negotiating for assets and planning clinical development without having capital in hand
- Fundraising without having a full team and/or assets in place.

Conclusions of WG4 and Next Steps

- WG4 concludes that a **novel biotechnology company** is the business model with the highest probability of success across all domains (retaining talent, access to pipelines, ability to raise capital).
- Multiple emerging biotech companies are using this model, but none are focused either primarily or exclusively on new therapeutics for **pediatric oncology**:

- There are **ongoing efforts** to bring forward **not-for-profit** and **for-profit** companies focused on pediatric cancer.
- Time will tell which model will succeed. Most importantly: **the experiment has started.**

Multiple efforts of all types should be encouraged/supported until the problem is solved

Session 4 – Widening the ACCELERATE Initiative

Co-Chairs:
Alberto Pappo, *Paediatric sub-committee ODAC*
Dominik Karres, *European Medicines Agency*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

The Asian Initiative

Eunkyung Kim, *Bristol-Myers Squibb*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Passion for Pediatric Oncology : Asian Approach

Eunkyung Kim, M.D., Ph.D.
Pediatric Oncology Lead, Japan/Korea/Taiwan
Bristol-Myers-Squibb

Feb 14th, 2019
The 7th ACCELERATE Conference

ONCBE19NP00293

BMS Commitment for Pediatric Oncology

Mission

BMS is committed to discover, develop and deliver safe and effective innovative medicines that help pediatric patients prevail over cancer

Priorities

1. Advance the strategic development of early assets across multiple pediatric cancers and advance preclinical research (translational medicine and biomarker)

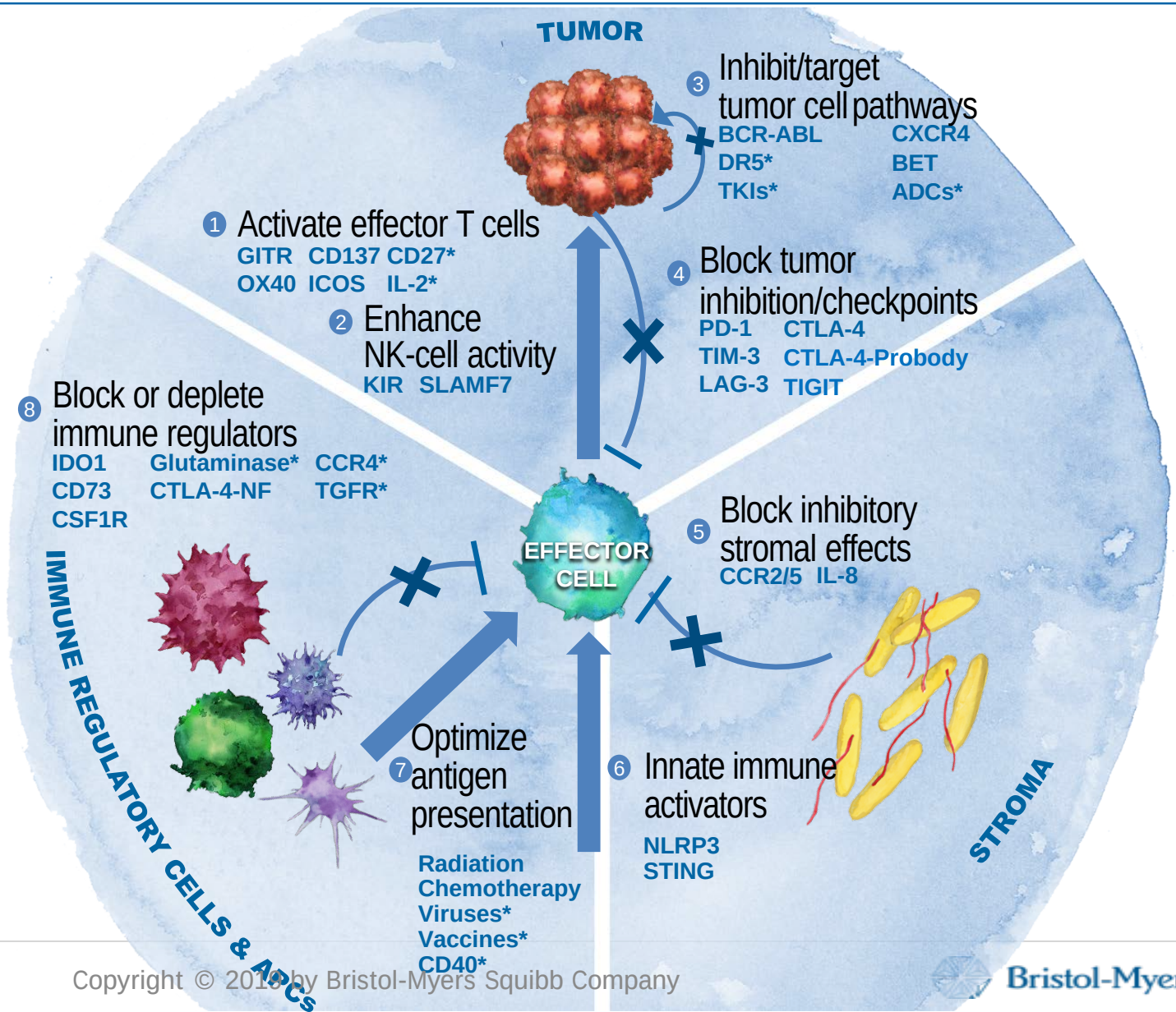
2. Advance clinical research of IO/IO, IO/non-IO combinations and other cutting-edge technologies in pediatric cancer patients

3. Effectively address key issues that affect pediatric cancer survivors

BMS Pediatric Oncology Team

BMS deep Portfolio under Investigation

BMS is developing a deep portfolio of novel clinical-stage therapies with the potential to provide transformational clinical benefits*

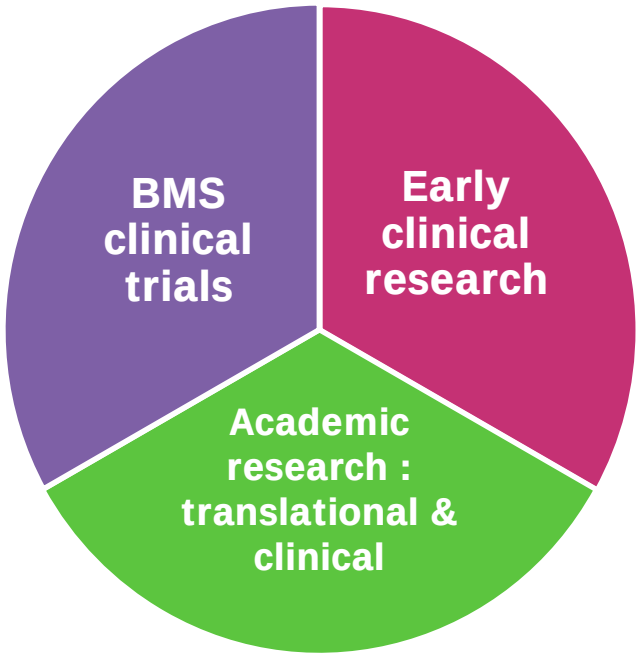


*Includes clinical collaborations.

BMS in FRANCE

Scientific Pillar

Cure



Societal Pillar

Care

U-LINK

Access to treatment equity

Quality of Life

VIK-e

Franco-African Pediatric Oncology Group collaboration

gfaop

Mobilize

TIME TO ENGAGE

Engage BMS employees to Patient advocacy groups activities

Raise awareness & federate all stakeholders to make public politic evolve in France/EU with innovative collaboration

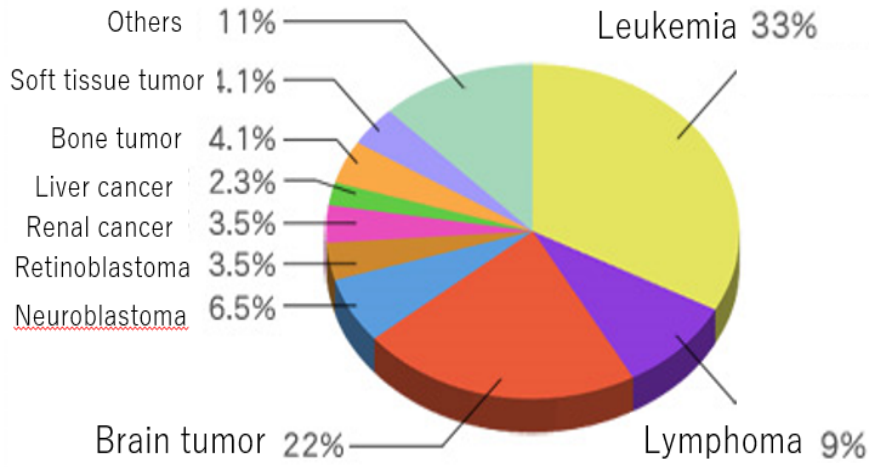
Industry + Institutional & Politics + PAGs + Public + HCP

BMS foundation is a part of Gravir collective/ National cause

Japan, Korea and Taiwan: Pediatric Cancer

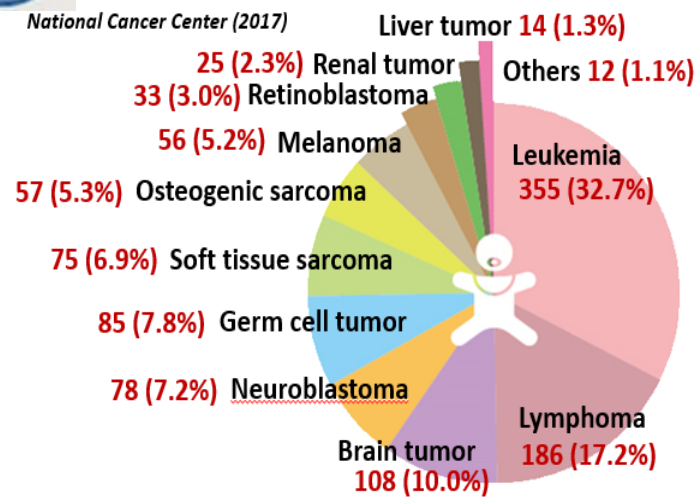
JCCG

Japan Children's Cancer Group



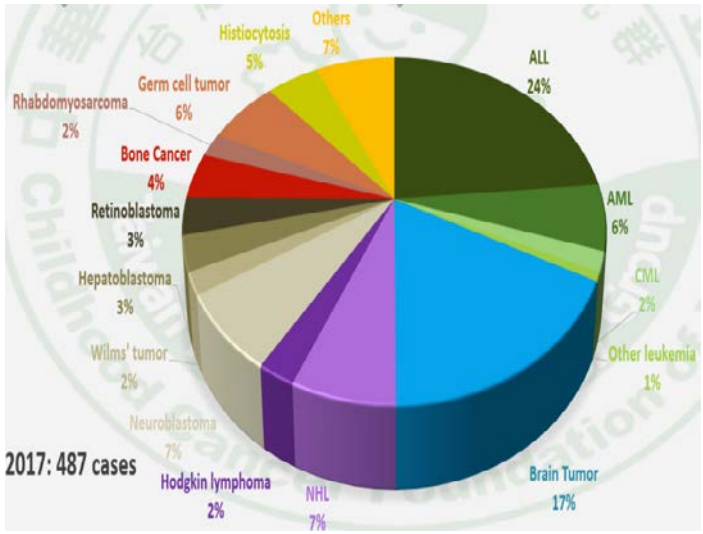
(from pediatric cancer information service by National Cancer Center)

Korea Society of Pediatric Hematology-Oncology



(from 2018 BMS pediatric oncology meeting)

Taiwan Pediatric Oncology Group



(from2018 BMS pediatric oncology meeting)

Pediatric Cancer Incidence in Japan Korea Taiwan

- Japan: around 2,000-2,500 /year
  (based on multiple publications)
- Total yearly childhood cancer patients in JKT
  : Around 4,000 pts/year

(total population: JP 127 million, South KR 51 million, TW 23 million)

Common Unmet Needs from Asian Leaders

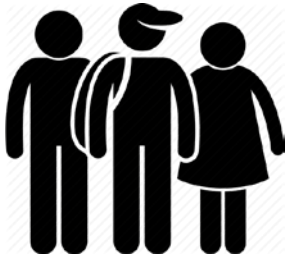
- Development of new medicines for pediatric cancer patients in Asia working with pharmaceutical company
  - ✓ Considerable number of patients even for the rare tumors
  - ✓ fairly-uniform ethnic background
  - ✓ qualified institutions in each country

Social Program for Children/AYA with Cancer

Social Support Program

For Young adult cancer survivors & Child cancer patients

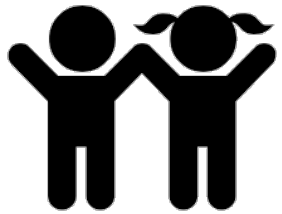
to return to school and society



Reboot

RebooTeen

for the future of children with cancer



	Reboot	RebooTeen
Partner	MILAL Welfare Foundation	Korean Association for Children with Leukemia and Cancer
Target	Cancer survivors aged 19-39 years	Pediatric cancer patients under the age of 24 years
Program	Provide tailored support programs upon the patients' need - such as training for job, schooling, emergency financial support	Provide economic support for treatment and various programs to grow up as active and productive members of society

*Both programs are owned by the respective independent organizations and BMS provided grant for the activities

Photo source: KACLC

Commitment for Pediatric Drug Development

Japan, Korea and Taiwan

1. Social Aspect
   - Child death is socially unacceptable in Asia like US and European countries.
   - Cancer is the leading cause of death in childhood (1-9 years old).
   - Even those that survive suffer significant long-term morbidity and thus less toxic therapies are needed.

2. Regulatory Aspect
   - There is no regulatory obligation to develop medicines for pediatric patients.

3. Medical Aspect
   - When cancer progresses after standard of care, clinical trials are the best way to help patients with innovative medicines.
   - Unlike US and European countries, there is limited access to innovative investigational medicines in Asia, and very few clinical trials for pediatric cancer patients.
   - So there is an urgent need to access innovative investigational medicines through clinical trial

BMS is committed to translating our success in adult oncology into
creating innovative solutions for pediatric cancer patients.

Becoming a Frontier in Pediatric Drug Development

Japan, Korea and Taiwan

Our Goals are:

- **Joining global pediatric trials** to accelerate pediatric drug development and access to innovative medicines in Asia
- **Building stronger partnerships** with pediatric medical societies for research collaboration
- **Leveraging advanced technology** and infrastructure of Japan, Korea and Taiwan for innovative drug development in the pediatric population

Bridging key components across regions and partnership for pediatric cancer patients

Thank You

The French IMPACT Platform

Patricia Blanc, *Imagine for Margo*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Widening the ACCELERATE initiative

The French IMPACT platform

2007

the European Paediatric Medicine Regulation

<u>to improve</u> the health of children in Europe by facilitating:

the development and availability of medicines

2017

Significant changes, but not in pediatric oncology

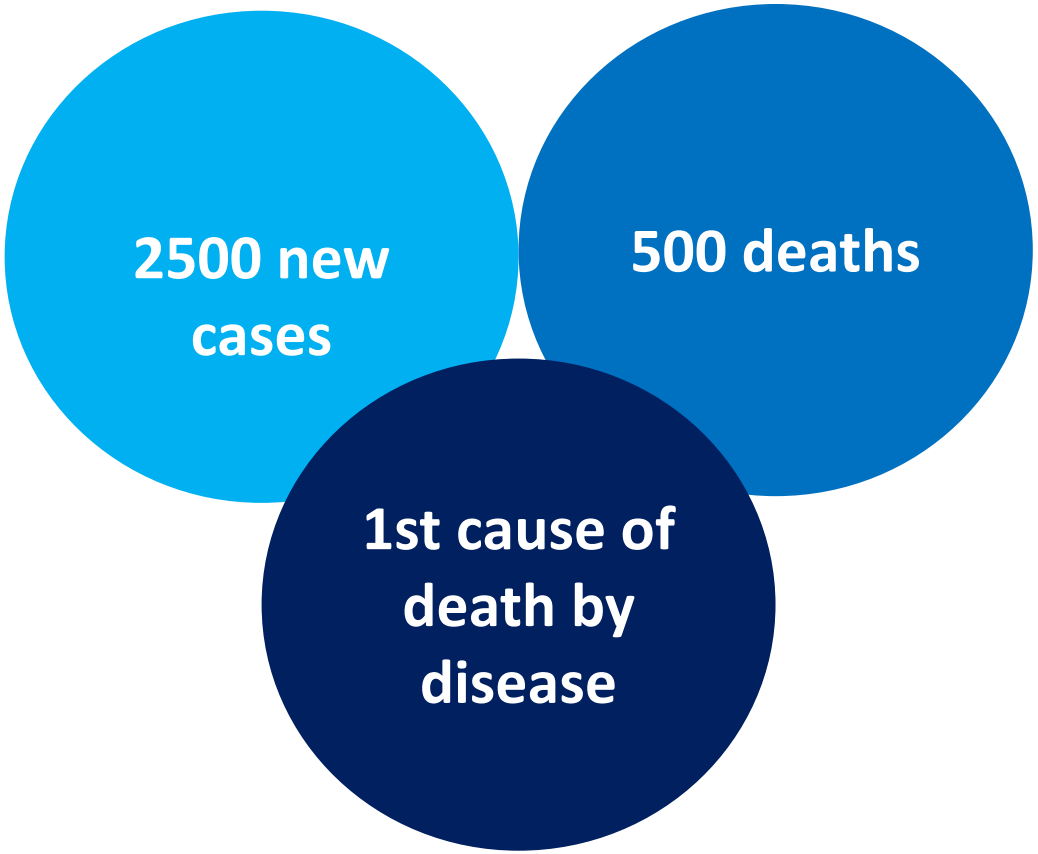
NEED

to accelerate

Development and Access to innovative therapies

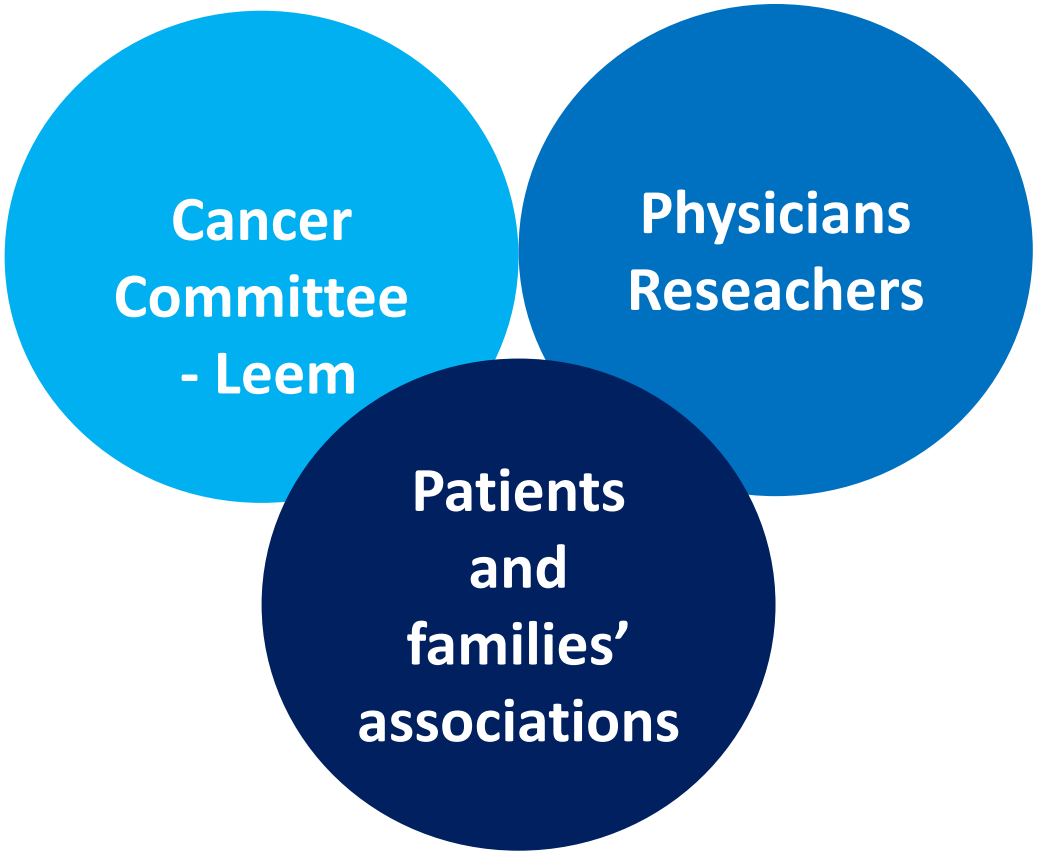
WHY?

Each year, in France



HOW?

Using a collaborative approach



Laurette Fugain
Contre les leucémies, soutenons la vie

leem
LES ENTREPRISES DU MÉDICAMENT

IMAGINE FOR Margo
Children without CANCER

UNAPECLE
Avec les enfants atteints de cancer ou de leucémie

Société Française de lutte contre les Cancers et les leucémies de l'Enfant et de l'adolescent
SFCE

enfance & CANCER
ASSOCIATION HUBERT GOUIN

Innovative Therapies for Children with Cancer
ITCC
European Consortium

IMPACT

AGIR AUTREMENT POUR VAINCRE LES CANCERS DES ENFANTS ET DES JEUNES ADULTES

Introduction: A collaborative approach

Phase 1…

09/2016: LEEM Cancer committee : PRIORITY 2017 = PEDIATRIC CANCERS

01-02/2017: Collect needs from academics and parents charities

07/2017: Action plan with 3 work priorities

1. Enhance new drugs development
2. Facilitate access to treatment
3. Improve the quality of life for patient and their family

…phase 2

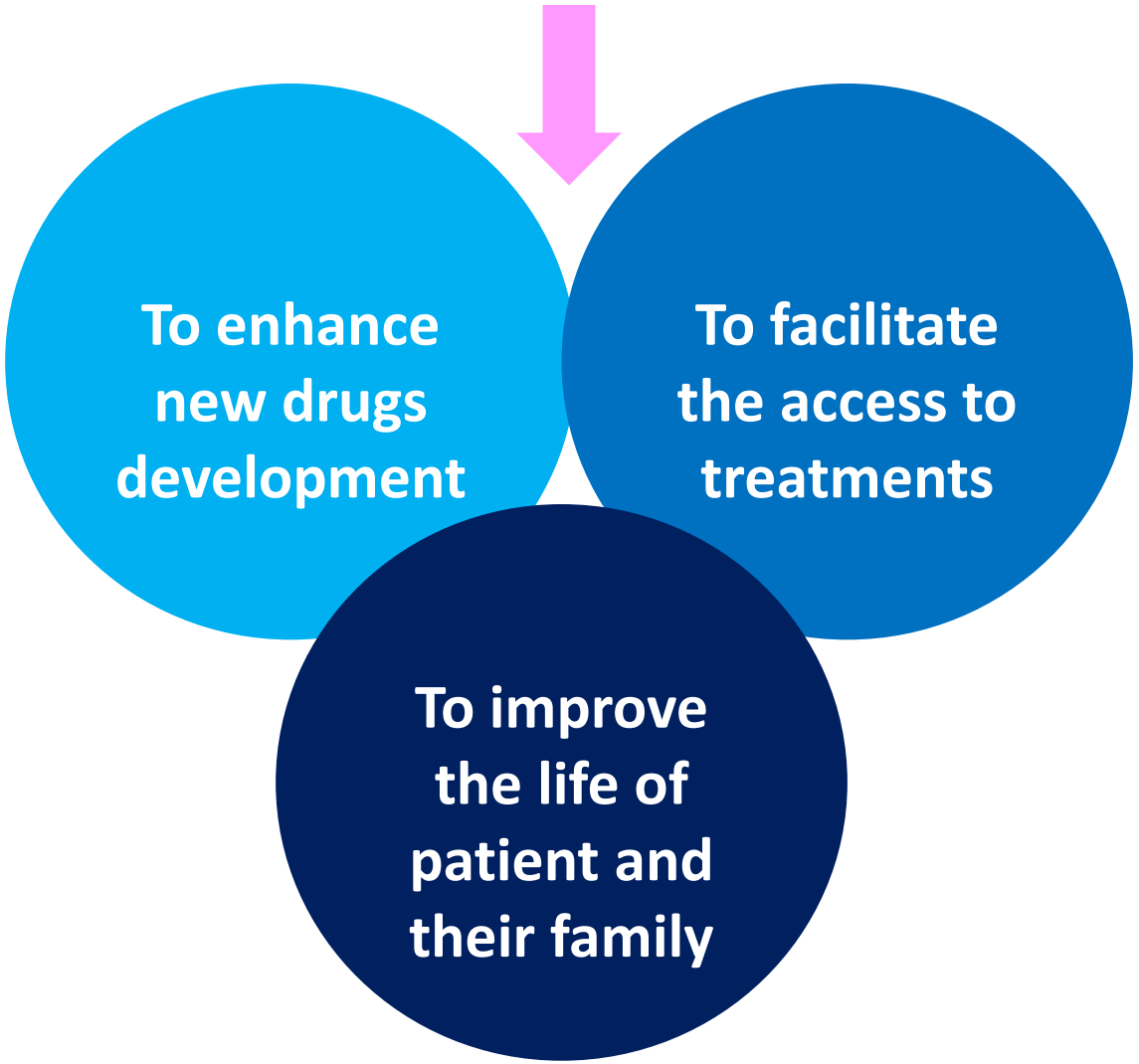
Working groups:

- Regular meetings
- Synthesis by action

global meeting :

- Validate actions
- Define Next steps

SPECIFIC OBJECTIVES?



Action Plan

Impact 1: Enhance new drugs development

- Elaborate a dynamic analysis of all molecules being developed in oncology : Horizon Scanning
- Ensure fast and qualitative evaluation of Clinical trial autorization requests in pediatric oncology
- *Train young researchers and doctors in pediatric oncology*
- *Mobilize for FAIR trials (include 12-18 years old in adults clinical trials)*

Plan d'actions

Impact 2 : Facilitate access to treatments

- Inventory of off-label used in children drugs and drugs with the temporary use authorizations (ATU) mechanism
- Reduce inequalities in getting access to treatments and clinical trials (U-Link project)
- *Strengthening the Pediatric Oncology Nurse Coordination System*
- *Improve conditions for the implementation of clinical trials for children*

Action plan

Impact 3: Improve the quality of life of patient and their family

- Mobilize drug companies around “gifts of live” (platelets, bone marrow, umbilical cords, organs…)
- *Reduce pain and anxiety related to care*
- *Expand sports practice during care*

2018 status : where are we ?

- Elaborate a dynamic analysis of all molecules being developed in oncology : Horizon Scanning
- Ensure fast and qualitative evaluation of Clinical trial autorization requests in pediatric oncology
- Inventory of off-label used in children drugs and drugs with the temporary use authorizations (ATU) mechanism
- Reduce inegalities in getting access to treatments and clinical trials (U-Link project)
- Mobilize drug companies around blood donation

1-Elaborate a dynamic analysis of all molecules being developed in oncology : Horizon Scanning

The Horizon scanning tool

- Goal: develop a tool to select potentially efficient molecules against childhood cancer
- How : Match **FDA** target list (Raceforchildren Act) and molecules being developed by pharma (source : LEEM INNOVATION tool)

Pediatric Molecular Target List (source **FDA**)

X

Site Internet **GeneCards**

X

BDD INNOVATION (Leem)

Ensure fast and qualitative evaluation of Clinical trial autorization requests in pediatric oncology

ANSM reorganization

Fast track process implemented

Early discussion meeting

- reduction of delay from 63 days average in December 2017 to 45 days in September 2018

Ethical committees : reorganization

New law : october 2018

selection according to competency and availability

3-Inventory of all off-label used in children drugs and drugs with the temporary use authorizations (ATU) mechanism

SACHA project

- **Secured Access to innovative medicines for CHildren with cAncer**

- Collect full information about prescription of off-label used in children drugs and drugs with the temporary use authorizations (ATU) mechanism, given to children in relapse who can not have access to a clinical trial.

- 450 patients, 30 centers

4-Reduce inegalities in getting access to treatments and clinical trials (U-Link project)

Part 1 Clinical trial database

1er bilan

101 CT on academics side

67 CT on family side (easy reading for families)

Part 2 logistic and financial support for families

- **Transportation and accommodation costs for families (routine care and clinical trials)**
- **1st results :** 156 files - budget 70 000 €

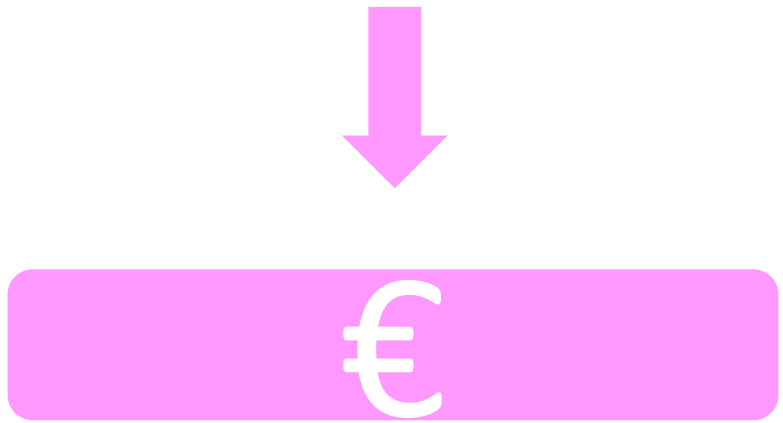
5-Mobilize drug companies around blood donation

Promote « gifts of live » donation : the SRE challenge

- Label creation « drug company supporting “gifts of life” donation (platelets, bone marrow, umbilical cords, organs…)

- Trophy event planned for **december 2019**

NEXT STEP?



LEEM Foundation main priority
Fighting kids cancer

- Call for projects launched in Jan 2019
- to support NGO acting in pediatric oncology

https://www.leem.org/fondation-des-entreprises-du-medicament-pour-lacces-aux-soins

The Canada Initiative

Patrick Sullivan, *Ac2orn and Coast to Coast Against Cancer Foundation*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

The Canadian Initiative

Improving Outcomes for Canadian Children, Adolescents, and Young Adults with Cancer:

A proposal for a working relationship with Health Canada

June 1, 2018

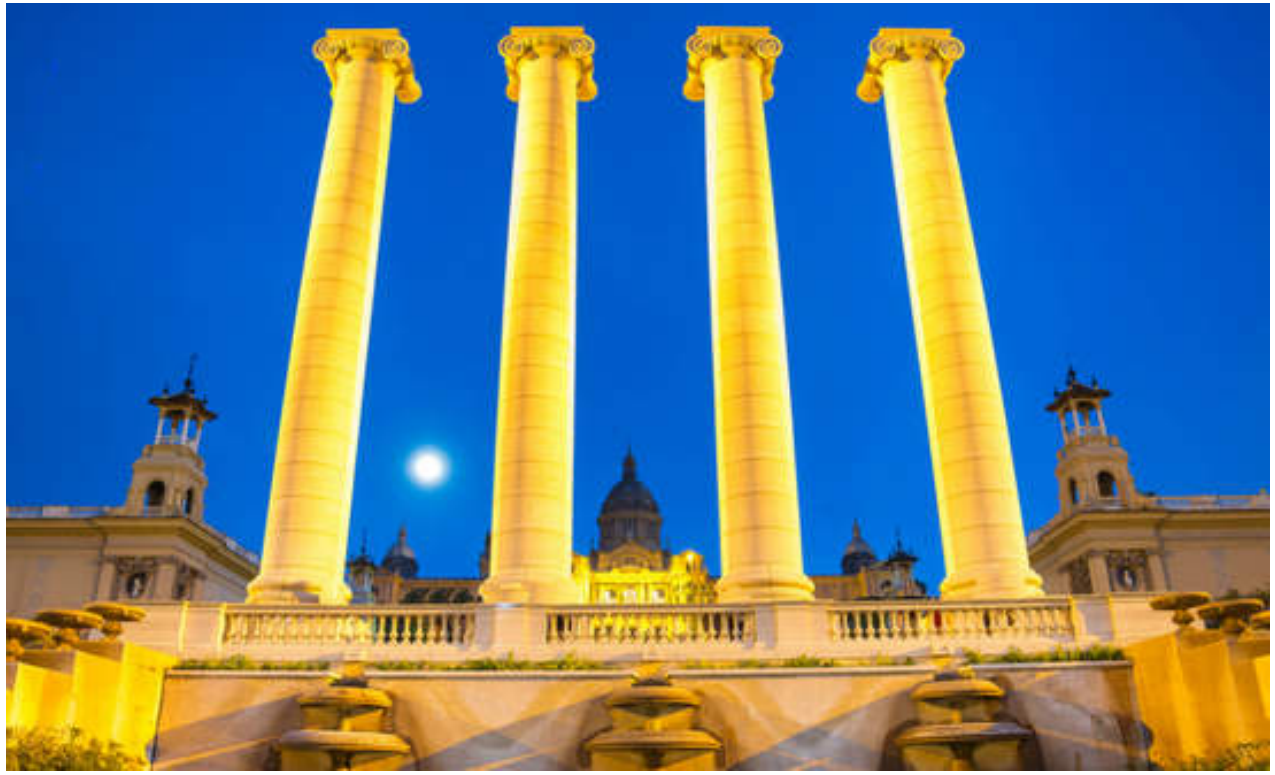
Supporters/Signatories:

For more information, please contact Patrick Sullivan (patrick@ac2orn.com) or Antonia Palmer (antonia@ac2orn.com).

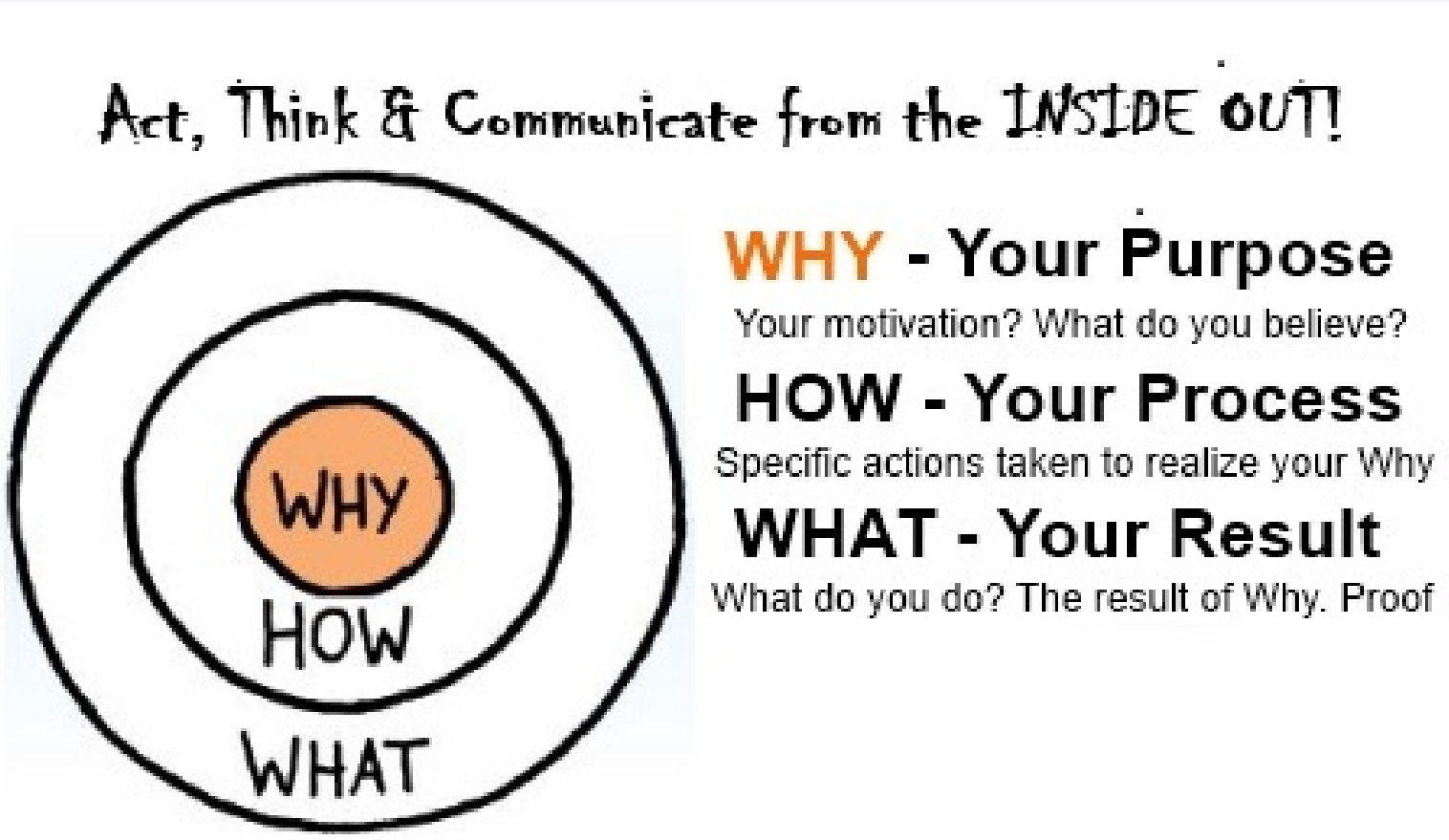
Canada: A Primer

My Journey to This Place

Four Central Pillars:
One Advocates Perspective



1. Do Not Confuse How With Why



2. Success Complicates Progress

3. Apart Will Not Work

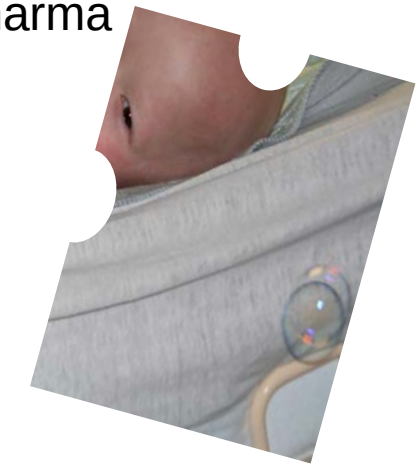
International Collaboration

Payors

Advocates/ Patients

Regulators

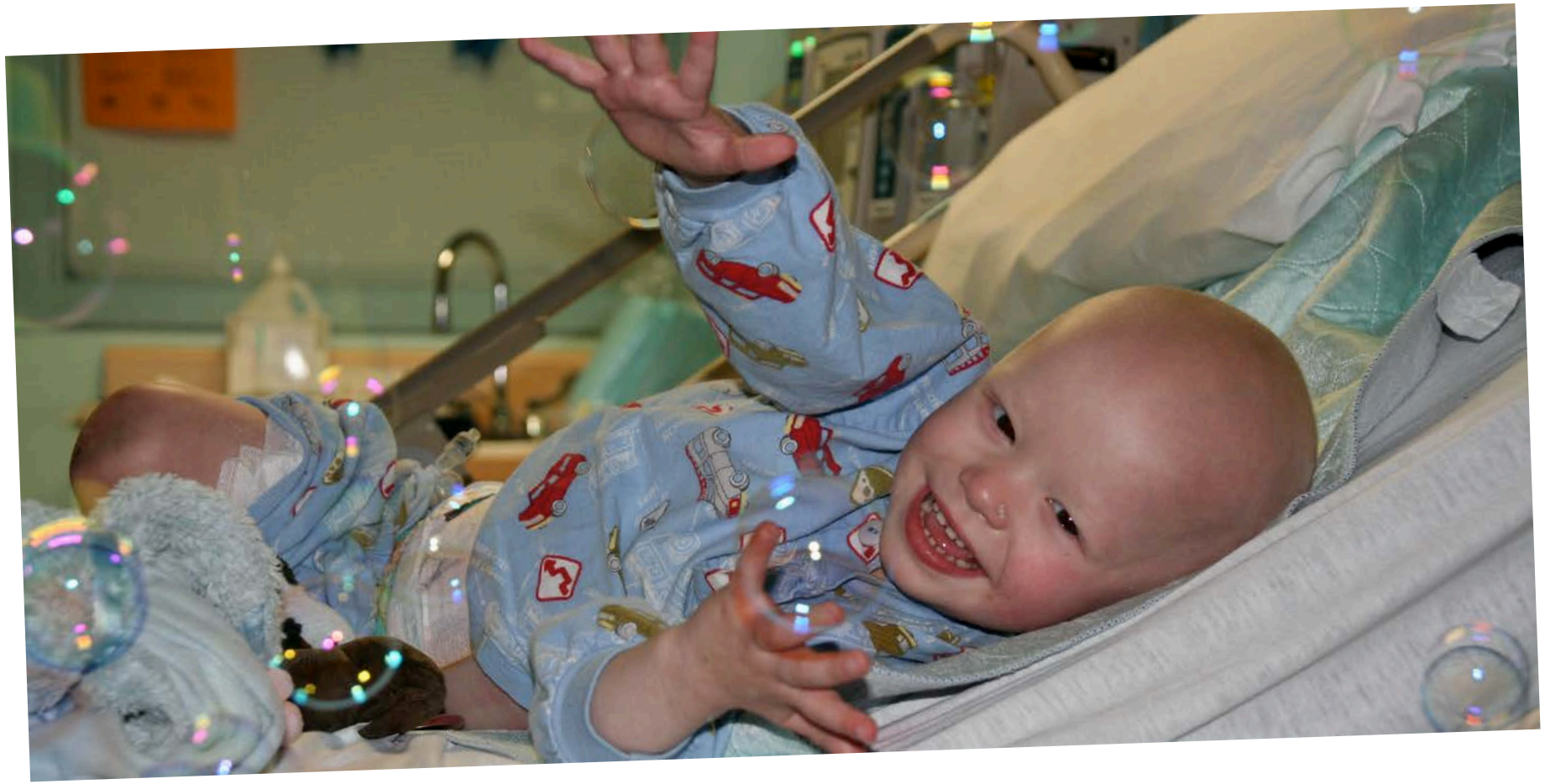
Industry/Pharma



Clinicians/ Scientists

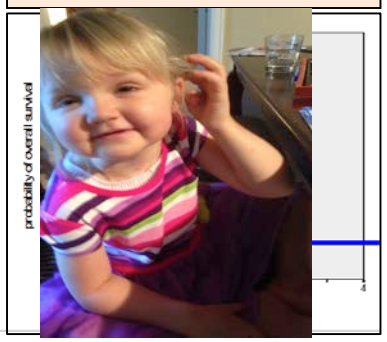
Payors

4. We Need To Start With Why



Why

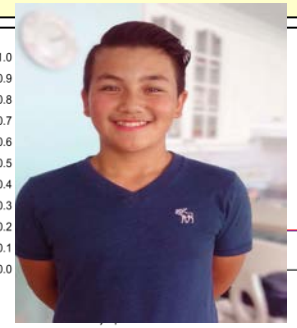
ALL-HR
Phoebe



Post-Transplant
Eric

AML
Zach

Rare Pediatric Cancers
Mateo



Brain Tumors
Derek

Ewing Sarcoma
Brenden

Osteosarcoma
Katie

Neuroblastoma
Oscar, Erik,

Rhabdomyosarcoma
Sean

Back To The Canadian Initiative

Overview

Despite gains in childhood, adolescent and young adult (CAYA) cancer research and treatment, Canadian children continue to die. This will improve only if our health care system identifies and implements innovative models of care for CAYA with cancer. We have a plan that has been built over time and on the basis of collaboration: a plan for a coordinated Canadian effort to ensure that survival rates continue to increase, quality of life continues to improve through treatment and beyond, that research capacity is strengthened, and that Canada continues to lead in CAYA oncology.

Our plan starts with two initiatives:

1. **Enabling equitable access to early phase cancer clinical trials**

   Currently, no coordinated system exists to allow Canadian children with cancer to access promising treatments outside of their home province or outside of Canada. Families without treatment options in their home province are forced to advocate for early phase clinical trial access and must often pay extraordinary out of pocket costs. The Canadian healthcare system needs to support families and help them access potentially life-saving clinical trials for their children – no matter where they live. Therefore, we need new ways to effectively reallocate resources[2] from futile "standard" treatment to promising and effective new treatments. We are proposing a program to address these problems.

2. **CAYA Oncology Patient Engagement Collaborative**

   We are asking a Health Canada Secretariat to create a collaborative Working Group to address health system issues related to CAYA cancer. This Working Group will be a forum to create a Report to discuss the allocation of an additional federal commitment to solve problems such as inadequate supports for pediatric oncology research, the lack of a formalized CAYA cancer drug discovery program, the need for a clinical trial pipeline and potential opportunities to incentivize industry to support CAYA oncology. Together with Health Canada, we would like to meaningfully address these and many other issues.

Ac2orn, Advocacy for Canadian Childhood Oncology Research Network, was founded in 2012 as a national

December Health Canada Meeting

1. Terry Fox Profyle

2. Use of Off-Label Drugs in Context of Clinical Trials

3. Accelerate

Never Underestimate What This Community Can Offer

"The pediatric oncology research community through extensive collaboration worldwide has been at the forefront of exploiting next-generation sequencing technologies to gain better insight into tumour biology" *Implementation of mechanism of action biology-driven early drug development for children with cancer"* Working Group 1 Accelerate

Never Underestimate What This Community Can Offer

"The pediatric oncology research community through extensive collaboration worldwide has been at the forefront ~~of exploiting next-generation sequencing technologies to gain better insight into tumour biology"~~ ~~*Implementation of mechanism of action biology-driven early drug development for children with cancer"*~~ ~~Working Group 1 Accelerate~~

Take-A-Ways

1. Canadians Need Your Help and Canadians Want to Help You

2. Sustained Success is Complicated

1. We All Control Different Parts of the Puzzle

1.Always Start With Why

1. Advocates Can Work From The Outside or from the Inside

1. Success Will Only Come From Working Together

1. We Can Lead

1. We Should Lead

Discussion

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Thank you for participating!

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Networking Cocktail: 19h30 – 20h00

Where: **Library room**

Social Dinner: 20h00 – 22h30

Where: **Ballroom A**

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

7TH ACCELERATE PAEDIATRIC ONCOLOGY CONFERENCE

14-15 FEBRUARY 2019 | BRUSSELS, BELGIUM

ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Session 5 – The new Regulatory Landscape and relevant Initiatives

Co-Chairs:
Brenda Weigel, *University of Minnesota*
Davy Chiodin, *Acerta-Pharma*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

The 2018 EMA action plan to improve the implementation of the Paediatric Medicine Regulation

Ralph Bax, *European Medicines Agency*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The 2018 EMA-EC action plan to improve the implementation of the Paediatric Regulation

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

7th ACCELERATE Paediatric Oncology Conference
Brussels, 14-15 February 2019

Presented by Ralph Bax
Head of Paediatric Medicines, Product Development Scientific Support Department, European Medicines Agency

1 More medicines authorised for children

2 Better product information

3 More paediatric trials and research

goals

analysis


EUROPEAN COMMISSION

Brussels, 26.10.2017
COM(2017) 626 final

REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL

State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation

Workshop 3/2018

Next steps

Paediatric Committee

Paediatric Investigation Plans - Waivers

Paediatric Network

Information – Transparency

EU Paediatric Regulation 2006


European Commission

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Medicines Agency and European Commission (DG Health and Food Safety) action plan on paediatrics

Introduction

The EU's regulatory framework for paediatric medicines, the Paediatric Regulation[1], came into force in 2007. In 2017, the European Commission's (EC) issued their ten-year report[2] on the implementation of the Regulation, which showed that the number of medicines developed for children increased during this period. However, it also revealed specific challenges, like developing medicines for diseases that only affect children or for diseases that manifest differently in adults and children. The report also highlighted that the development and later availability at patients' bedside of paediatric medicines is often delayed when compared with adult medicines.

Action plan 10/2018

Workshop to improve implementation of Paediatric Regulation

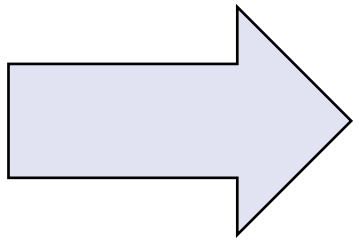
- Date: 20 March 2018
- Multi-stakeholder meeting (~160 participants present + remote access):
  - Patients/carers
  - Academia (incl. networks)
  - Health Care Professionals
  - Industry
  - FDA
  - CTFG
  - WHO
  - Ethics committees
  - EMA/PDCO/EC

EMA-EC action plan 2019-2020

Needs	• Identifying paediatric medical needs
Decision makers	• Strengthening cooperation between decision makers
Timely PIP completion	• Ensuring timely completion of PIPs
Handling of PIPs	• Improving the handling of PIP applications
Transparency	• Increasing transparency around paediatric medicines

Identifying paediatric medical needs

- Raise awareness for paediatric medical needs
  - Input from all stakeholders
  - Multi-stakeholder focus groups and workshops
  - 'Paediatric Landscape Reports'
- Structured assessment in PIPs



3	Establish framework for collaboration of EMA/PDCO with the U.S. FDA's Oncology Center of Excellence Pediatric Oncology Program regarding the assessment of relevant molecular targets in paediatric cancers.	To maximise synergies and share expertise in the assessment of relevant molecular targets and to address medical needs with a global perspective.	In progress.	12/2019

Strengthening of international cooperation

- Initiatives to further increase regulatory paediatric cluster interactions

- Contribution of investigators and other stakeholders
  - Clinical Trial Facilitation Group
  - Regulatory paediatric cluster activities (enhanced integration and transparency)
  - Increase global interactions between EMA/PDCO and other stakeholders including networks.

Ensuring timely completion of PIPs

- Optimisation of development programmes from early stages onwards:
  - Knowledge/information sharing between all relevant stakeholders (patients, academia/research, networks, industry)
  - Consideration and early regulatory discussions of trial designs and methodologies
  - Optimisation of the estimation of patient availability
  - Involvement of patients and young people along the drug development process
- Clinical trials:
  - Recommendations for planning clinical trials
  - Sustainable infrastructure and funding
- Training and exchange of information between assessors of clinical trials (NCAs), ethics committees and regulators (involved in PIP-process and marketing authorisation).

Improving the handling of PIP applications

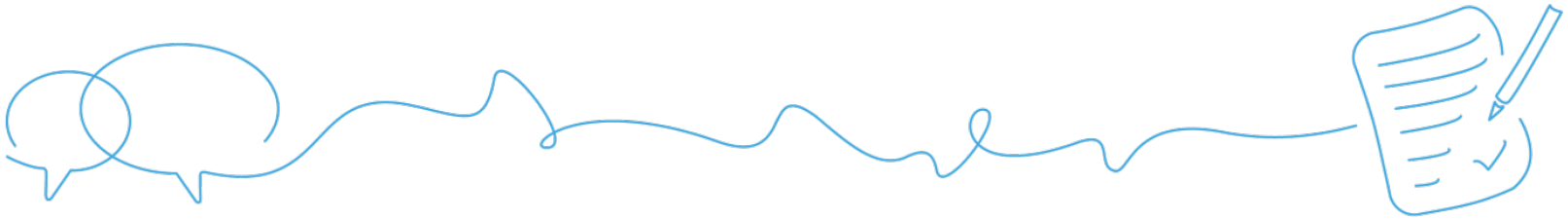
- Exploring ways of adapting PIPs to the evolution of scientific knowledge
- Enhance possibilities of communication with PIP applicants
- Improvement of guidance, administrative requirements

Work is ongoing!

EC/EMA Action plan to cover period until 2020

- Time lines for action items according to priority
- Working groups with stakeholders have already started

Follow-up and outcome



Thank you for your attention

Further information

Ralph.Bax@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Follow us on **@EMA_News**

Implementation of the Race for Children ACT

Greg Reaman, *Food and Drug Administration*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Implementation of FDARA Title V: Evolving U.S. Regulatory Framework for Pediatric Assessment of New Oncology Products

Gregory H. Reaman, M.D.
Associate Director, Oncology Sciences
Office of Hematology and Oncology Products, CDER
Associate Director for Pediatric Oncology
Oncology Center of Excellence, OC

RACE for Children Act: Changing the Paradigm

- Incorporated as Title V Sec. 504 of the **FDA Reauthorization Act (FDARA),** enacted August 18, 2017
- **Requires** evaluation of new molecularly targeted drugs and biologics "intended for the treatment of adult cancers and directed at a **molecular target** substantially relevant to the growth or progression of a pediatric cancer."
- Amends PREA: requirement for pediatric assessment based on MoA rather than clinical indication.
- **Molecularly targeted pediatric cancer investigation**: dosing, safety and **preliminary** efficacy to inform potential pediatric labeling."
- Elimination of **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets.

Molecular Target Definition

- A molecule in human cells (normal or malignant) that is intrinsically associated with a particular disease process such as etiology, progression, and/or drug resistance. To be referred to as a target, there must be evidence that by addressing the target with a small molecule, biologic product, or other intervention, a desired therapeutic effect is produced resulting in the alteration of the disease process

Statutory Requirements for FDA

- Establish with NCI, update regularly, and post on FDA website a **list of "relevant" targets** (1 year)
- Establish and post a **list of targets (non-relevant) leading to waivers** of pediatric studies (1 year)
- Work with NCI, Pediatric Subcommittee of ODAC, PeRC, investigators, sponsors, experts, and advocates on implementation and required studies
- Convene an open public meeting to generate/finalize lists (1 year)
- Issue guidance on implementation (2 years)

Current FDA Efforts: Implementation

- Open Public meetings:
  1)**April 20, 2018 at FDA - Review candidate molecular target lists.**
  2) **Pediatric Subcommittee of ODAC, June 20, 2018** - finalize lists; considerations for **application of target lists**; process for **prioritization** including same in class agents- working with external constituents (multi-stakeholder); a process to support **international collaboration/coordination-** Global Drug Development and non-alignment of regulatory requirements/timelines
- Planning and implementation coordinated with internal FDA programs- OHOP/OCE, OPT, OCP, DPMH, ORP, and OCC
- **Focus on accelerating initial pediatric evaluations early in development timeline of appropriate drugs not increasing number of pediatric phase 1 studies**
- Lists posted on OCE website Pediatric Oncology Program (https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/default.htm)
- Advising sponsors of new conditions and requirements for iPSPs for **new** applications with planned submission dates after 8/18/2020

Framework* for Defining Relevance

- Presence of target in one or more pediatric cancers- not prevalence-dependent
- Target function- etiology, drug resistance, lethality
- Non-clinical evidence- general and pediatric-specific
- Adult clinical experience
- Predictive/response biomarkers availability
- Accessibility for immunotherapy-directed targets
- Therapeutic agent available/in development
- **Focus on facilitating appropriate initial pediatric evaluations early in development timeline not increasing number of pediatric phase 1 studies**

*Multi-stakeholder workshop sponsored by FoCR

Target Lists

- Statutory requirement to address regulatory uncertainty for Industry and **guide (not dictate)** decision-making re. early evaluation of a specific agent as an amended PREA requirement through the iPSP process
- **Designation as relevant neither an absolute nor exclusive requirement for decisions related to pediatric evaluation:** studies of new products may be required if directed at a target **not** on the list and waivers may be justified for products directed at targets considered relevant
- **Not envisioned to restrict authority or flexibility**
- Relevant molecular targets- independent of agent and/or biomarker availability
- **Candidate** Target List constructed by OCE with NCI and input from international content experts; reviewed in a open public meeting
- Published, peer-reviewed literature, abstracts, public databases
- No pre-specified **minimum evidence base**
- Further recommendations received via NCI RFI through May 30, 2018

Targets Associated with Specific Gene Abnormalities

Target Symbol	Gene Abnormality
ABL1/2 *	ABL1/2 gene fusions (BCR-ABL1, etc.)
ACVR1	ACVR1
ALK *	ALK and ALK gene fusions
ASCL1	ASCL1 gene
BRAF *	BRAF
BRD3-NUTM1	BRD3-NUTM1
BRD4-NUTM1	BRD4-NUTM1
CCND1,2	CCND1,2
CDK12	EWSR1-FLI1
c-KIT or KIT *	c-KIT or KIT
CSF1R	CSF1R gene fusions
CTNNB1 (β-catenin)	CTNNB1

Target Symbol	Gene Abnormality
DDX3X	DDX3X
DOT1L	MLL gene fusions
EGFR *	EGFR
ERK *	BRAF, MAP2K1
ETS gene fusions	ETS fusions (ERG, FLI1, ETV1)
EWSR1-FLI1	EWSR1-FLI1
EZH2 *	SMARCB1, SMARCA4
FGFR *	FGFR and FGFR gene fusions
FLT3 *	FLK2, STK1, CD135
Gamma secretase	NOTCH1 and FBXW7
GFI1	GFI1
GFI1B	GFI1B

Targets Associated with Specific Gene Abnormalities

Target Symbol		Gene Abnormality
Histone 3 G34R/V		Histone 3 G34R/V
Histone 3 K27M	*	Histone 3 K27M
IDH1 and IHD2	*	IDH1 and IDH2
JAK1, 2, and 3		JAK1, 2, and 3
LIN28B		LIN28B
MDM2	*	MDM2, TP53
MEK	*	BRAF and BRAF gene fusions, MAP2K1, NF1
Menin		MLL gene fusions
MET		MET
MLL		MLL gene fusions (MLL-AF4/AF9/AF10/ENL/ELL/AF1p/AFX/FKHRL1/SEPT6/GAS7/EEN/CBP/PTD)
mTOR	*	TSC1, TSC2
MYC		MYC translocations and amplification

Target Symbol		Gene Abnormality
MYCN		MYCN amplification
Neoantigens		MSH2, MLH1, MSH6, PMS2 POLE, and POLD1
NFkappaB		RELA fusion
NOTCH1		NOTCH1, FBXW7
NSD3-NUTM1		NSD3-NUTM1
NT5C2		NT5C2
NTRK	*	NTRK gene fusions
ODC1		MYC target gene
PARP	*	BRCA1/2, PALB2, ATM, BRIP1, CHEK2, RAD51, etc.
PAX-FOXO1		PAX-FOXO1
PDGFRA/B	*	PDGFRA/B gene fusions
PI3Kα	*	PIK3CA

Targets Associated with Specific Gene Abnormalities

Target Symbol	Gene Abnormality
PPM1D (WIP1)	PPM1D (WIP1)
RAS	RAS
RET *	RET
SH2B3	SH2B3
SHP2	SHP2
Smoothened *	PATCH1, SMO
STAT2,3	STAT2,3

Target Symbol	Gene Abnormality
SYT-SSX	SYT-SSX
TERT	TERT
TORC1/2 as distinct from mTOR	TORC1/2
TrkB	TrkB
TP53	TP53
TYK2	TYK2
ZNF532-NUTM1	ZNF532-NUTM1

Targets Associated with Cell Lineage Determinants

Target Symbol (1)	Target Symbol (2)	Target Symbol (3)	Target Symbol (4)
AKR1C3	CD70	GPNMB	PTEN
BCOR	CD79b	ERBB2 (HER2/Neu) *	SYK
BTK *	CD123/IL3RA	IL6	WT1
CD7	CD276 (B7-H3)	IL13RA2	YAP1
CD19 *	Cereblon CBL (E3 Ubiquitine protein ligase)	LRRC15	
CD20	DLL3	MAGE-A3	
CD22 *	DLK1	MSLN (mesothelin)	
CD30 *	EGFRvIII *	NR5A1 (Steroidogenic factor-1)	
CD33 *	EPHA2	NY-ESO-1 *	
CD37	GD2	Olig2	
CD38	GPC2	PIK3CD (PI3 kinase delta)	
CD56	GPC3	PRAME	

Targets on Immune Cells and Cellular Components of the Tumor Microenvironment

Target Symbol (1)	
B7H3	
CD40	
CD47	
CD52	
CXCR4	
CXCL10	
CTLA4	*
GM-CSF	
IDO1	*
IFN-gamma	
IL-2	
LAG3	

Target Symbol (2)	
OX40	
PD-1/PD-L1	*
RELA	
RIG-I	
STEAP1	
STING	
TIM3/TIM4	
VEGF	*
VEGFR	*

Other Targets:Pathways and Functional Mechanisms

Target Symbol (1)	Target Symbol (2)	Target Symbol (3)	Target Symbol (4)
AKT *	BMPR	DNA-PK	LSD1
ATM *	Brd1	DNMT (DNA methyl transferase)	MCL1
ATR	Brd4	FAK	MCT1 (monocarboxylate transporter 1)
ATRX	CDK4/6 *	FOLR1 (folate receptor 1)	MEK *
AURKA (Aurora kinase A)	CHK1	GSK-3	MIZ1
AURKB (Aurora kinase B)	CDK2	HDAC	MGMT
AXL	CDK7	HIF1A	MLL5
A1/BFL	CDK9	Hippo pathway (YAP, TAZ, TEADs)	MYST3 (MYST histone acetyltransferase (monocytic leukemia)
BAK	CK1	Hsp90 *	NAMPT
BAX	CK2 (casein kinase 2)	IAPs (inhibitor-of-apoptosis)	NEDD8 activating enzyme (NAE)
BCL2 family members (Bcl-2, Bcl-XL, Mcl-1, A1/BFL, BAK, BAX) *	CREBBP/EP300	IGFR-1 *	PARP *
BET bromodomain family *	DNA (alkylators)	KDM4A	PDK-1 (3-phosphoinositide-dependent protein kinase 1)

Other Targets:Pathways and Functional Mechanisms

Target Symbol (5)	
PI3Kdelta	
PIM1	
PKA	
PKC	
PLK1	
POL1	*
PRDM1	
PRDM8	
PRDM10	
PRMT2	
PRMT5	
Proteasome	*

Target Symbol (6)	
PTPN (protein tyrosine phosphatase)	
RPA3	
SHP2	
SMYD3	
Somatostatin Receptor	
Survivin (BIRC5)	
SUZ12	
SWI/SNF	*
TET2	
TGF-beta	
Thymidylate synthase	
Topoisomerase I/II	*

Target Symbol (7)	
TRAIL	*
Tubulin	*
XPO1 (Exportin)	
WDR5	
WEE1	

Non-Relevant Targets Leading to Waivers

Target Symbol
AR
ESR1
ESR2
GnRHR
PSA/PSCA/PSMA

Deferrral Considerations for Agents Directed at Relevant Targets

- Insufficient data to define relevance until such time that evidence provides a biologic rationale for study in children
- Lack of reasonable evidence of clinical activity associated with inhibition of target or pathway
- Uncertainty re. single agent activity until one or more biologically rational combinations demonstrate treatment effect
- Appropriate formulation development

Waiver Considerations for Agents Directed at Relevant Targets

- Serious developmental toxicity- consideration for full or age dependent partial waivers
- Second or third “in class” product (**single agent**) without compelling evidence of substantial differences in efficacy, safety, PK profiles, or formulation to warrant additional pediatric studies
- Age group-specific partial waivers for formulation concerns
- Feasibility and practicability due to small study populations potentially addressed by limited study requirements and innovative study design and conduct: embedded pediatric trials, expansion cohorts, histology-agnostic development

Publishing and Updating Lists

- Semi-annual public workshops
- Enabling on-going recommendations for addition/deletion
- Opened FDA docket for comments on existing targets and suggestions for additions/deletions
- Planned review of “Immune/Tumor Micro-environment” targets, June 2019 at Pediatric Subcommittee of ODAC meeting

Addressing Challenges

- Opportunities for uniform international **master protocols** for biomarker-directed studies- efficient and high quality data
- Expanding opportunities for early pre-clinical development in **pediatric model systems**
- Increasing **extramural** input while respecting proprietary considerations
- **Early** pipeline presentations; possible pre-competitive Industry collaboration
- Industry-initiated Public Private Partnership

Successful Implementation

- Transparency among all stakeholders
- Address anticipated, potentially adverse consequences
- **Initiate early pediatric pre-clinical testing initiatives - effective Industry-Academic collaboration when necessary (Public-Private Partnerships)**
- Recognize emerging scientific discovery
- Robust, publicly shared, datasets-genomic, proteomic, pre-clinical testing- all require support and expansion
- Global coordination and international collaboration- Pediatric Cluster calls and expansion of ACCELERATE Platform

Discussion

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

International Consensus for Preclinical Testing: a joint Initiative by ITCC-P4 and PPTC

Louis Stancato, *Eli Lilly Company*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

ITCC P4 PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM

NCI PPTC Pediatric Preclinical Testing Consortium

International consensus for preclinical testing: a joint initiative by ITCC-P4 and the PPTC

ACCELERATE 2019

Louis Stancato, Eli Lilly and Company

ACCELERATE INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

imi innovative medicines initiative

IMI2 Grant Agreement No 116064 ITCC-P4

The regulatory environment is changing…

ITCC P4 PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM

FDA REAUTHORIZATION OF 2017

SEC. 504. DEVELOPMENT OF DRUGS AND BIOLOGICAL PRODUCTS FOR PEDIATRIC CANCERS: molecular targets regarding cancer drugs and biological products..... if the drug or biological product is .....

"(i) **intended for the treatment of an adult cancer**;

and

"(ii) **directed at a molecular target that the Secretary determines to be substantially relevant to the growth or progression of a pediatric cancer**."

EUROPEAN MEDICINES AGENCY

SCIENCE MEDICINES HEALTH

EMA decision (CW/0001/2015) of 23 July 2015 on class waivers, in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

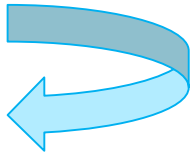
Revised Class Waiver List
Enters into force July 28, 2018

Target date: August 2019

imi innovative medicines initiative

…and the paediatric community must make the most of these changes!

- A supportive regulatory environment will
  - Spur investment in paediatric research
  - Result in the “right” clinical trials
  - Ultimately save lives

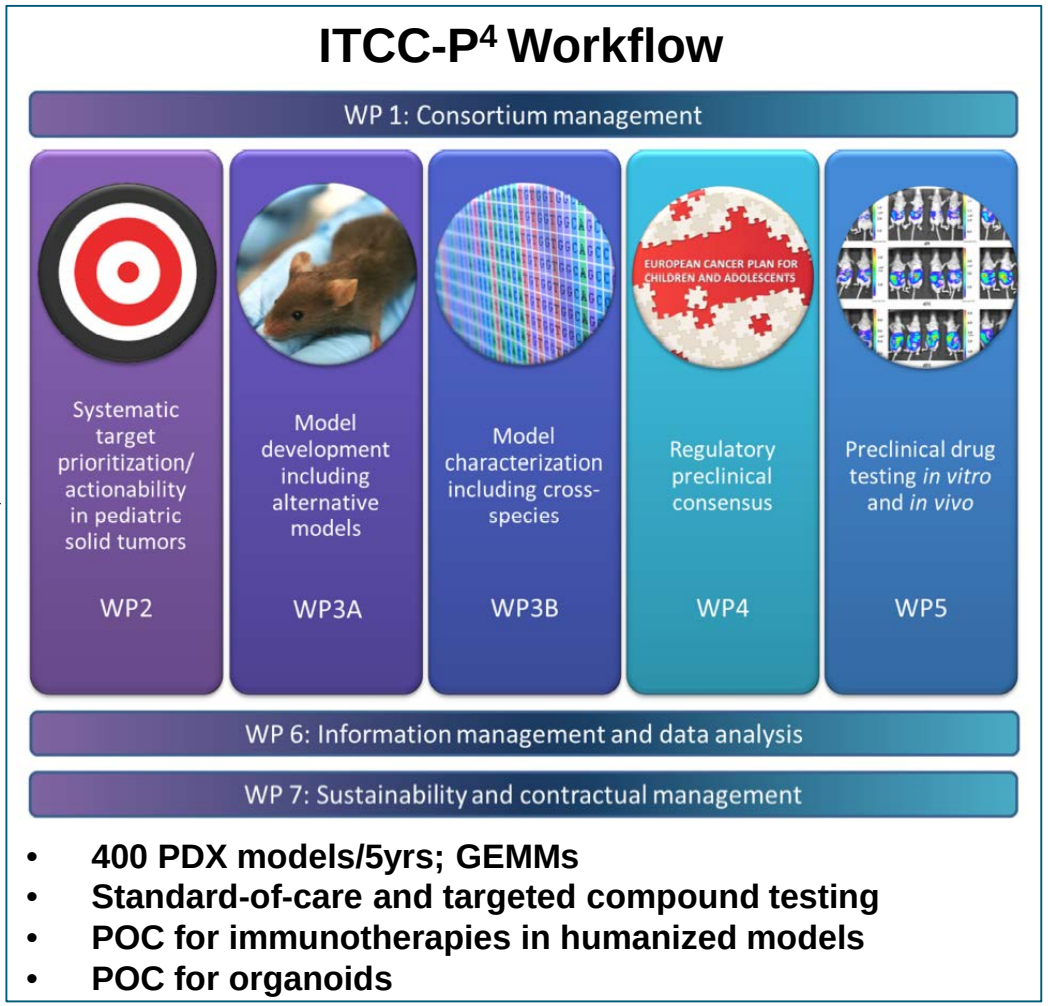


But how?

- Build preclinical research platforms
- Harmonize preclinical methods to identify promising drugs
- Test drugs for paediatric and adult efficacy in *parallel*
- Ultimately, *prioritize* drugs for clinical testing

ITCC-P4: The platform

ITCC PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM



- **400 PDX models/5yrs; GEMMs**
- **Standard-of-care and targeted compound testing**
- **POC for immunotherapies in humanized models**
- **POC for organoids**

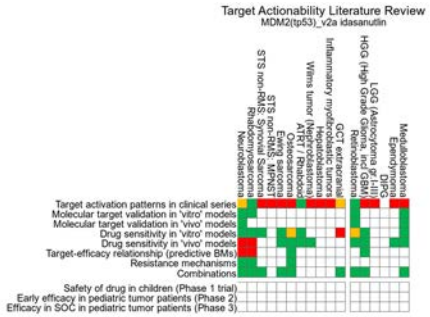
Initial compound testing begins mid ‘19

imi innovative medicines initiative

What did ITCC-P4 accomplish in 2018?

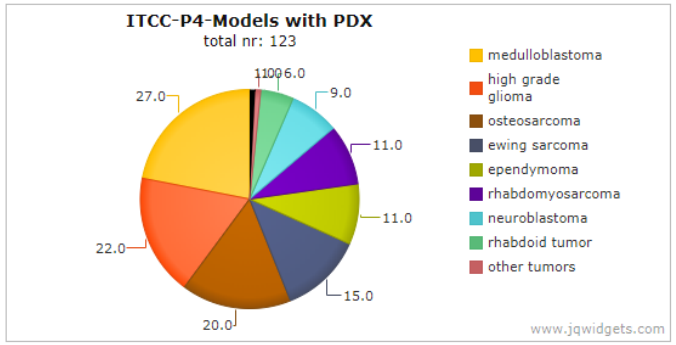
ITCC P4 PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM

Established Target Actionability Review Methodology

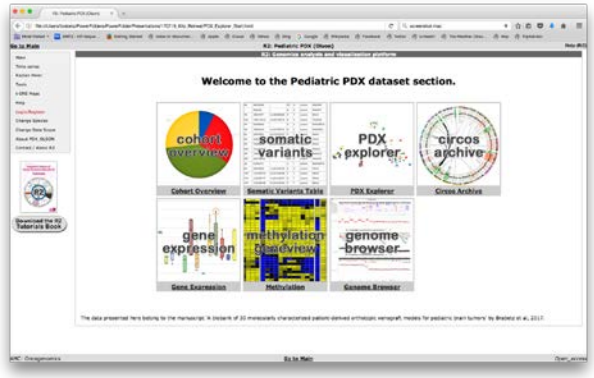


Target Actionability = Matched Targeted Therapy

Model establishment well underway



R2 informatics portal enhancements



Test drugs selected; SOPs developed

platform tumor indications	SoC 1	SoC 2	SoC 3	two-SoC combination	ID 1	ID 2	ID 3	ID 4	ID 5	ID 6
Medulloblastoma (MB)	E	CPA	L	CP + E	SHI-I	BET/BRD4	CHK1	CDK4/6	Akt-I	TGFBI
High Grade Glioma (HGG) (including DIPG)	TZ	L	RT	TZ + RT	MEK-I	PI3K-I	BET/Brd4	AKT-I	Regorafenib	CHK1
Ependymoma (EPN)	RT	CPA	AD	RT + CP	MDM2-I	PI3K-IR1	AKT-I	CDK4/6	FGFRI	PI3K-IR2
Atypical Teratoid / Rhabdoid Tumor (ATRT)	DR	CP	E	DR + CPA	CDK4/6I	SMOI	FGFR-I	MKI1	AKT-I	MKI2
Neuroblastoma (NB)	CPA	E	TT	CPA + CP	MDM2-I	BET/BRD4	CHK1	MEK-I	ALK	PI3K
Rhabdomyosarcoma (RMS)	VC	TF	ID	AD + VC	MEK-I	FGFR-I	Regorafenib	ALK-I	CDK4/6	AKT-I
Non-RMS soft tissue sarcoma	E	ID	TF	AD + VC	MEK-I	FGFR1	BET/Brd4	MTOR	ALKI	CDK4/6
Osteosarcoma (OS)	DR	RT	CIP	DR + M	FGFR-I	MDM2-I	Regorafenib	CDK4/6	Bevacizumab	
Ewing sarcoma (EWS)	DR	VC	AD	DR + CPA	Regorafenib	BET/Brd4	PI3K-I	CDK4/6	MDM2	FGFR-I
all GEMMs	entity-specific SoC drugs				immune checkpoint inhibitor					

ITCC-P4 International Workshop

IMPROVING PEDIATRIC ONCOLOGY DRUG DEVELOPMENT THROUGH PRECLINICAL RESEARCH

September 27th and 28th, 2018 // Amsterdam, NL

ITCC P4 PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM

imi innovative medicines initiative

NCI – Preclinical Pediatric Testing Consortium (leader – M. Smith)

http://www.ncipptc.org/

ITCC P4 PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM + NCI PPTC Pediatric Preclinical Testing Consortium

Goal

International scientific consensus on the role and place of preclinical evaluation of paediatric tumor models to improve prioritization and effectiveness of drug development for children and adolescents with cancer

Output

Peer-reviewed ‘white paper’ serving as a basis for a guidance to be submitted to competent authorities for qualification

Who was there?

- ITCC-P4 & PPTC leadership
- Leaders from academia (33/18) & industry (19/11), FDA, advocacy (4/3)
- Concerned citizens

Topics - Current state of preclinical research

- Models
- Evaluation of brain tumors
- Evaluation of IO drugs
- Methodology
- Data and reporting standards

→ Minimal / Optimal preclinical package

imi innovative medicines initiative

Findings: Defining the need

- Accelerating and improving the development of new drugs for children with cancer
- Prioritizing drugs in adult development to encourage the development of drugs targeting alterations specific to paediatrics
- Relevant preclinical data to support science-driven decisions
- An international, multi stakeholder consensus for preclinical testing

Findings: Current state of preclinical paediatric drug research

- ‘Catch-as-catch-can” – haphazard preclinical evaluation; not systematic

- Scarcity of models
  - mainly academic
  - few in pharma; lacks access
  - no quality process for regulatory use

- The most comprehensive program over the past ten years = The Preclinical Pediatric Testing Program → many lessons to be learned

Findings: what are the “best” preclinical paediatric models?

- Patient derived xenografts preferred
- Metastatic models should be used for drugs with an anti-metastatic MOA →very few metastatic pediatric tumor models
- Paediatric organoids →improve *in vitro* screening (replacing 2D)? Prelude to *in vivo* for drugs targeting tumors?
- Other models (e.g., drosophila, zebrafish) of lesser value?

Inherent in all of our findings is a critical role in harmonizing methodology, data and reporting standards

Streamlining the preclinical process – an example from PPTC

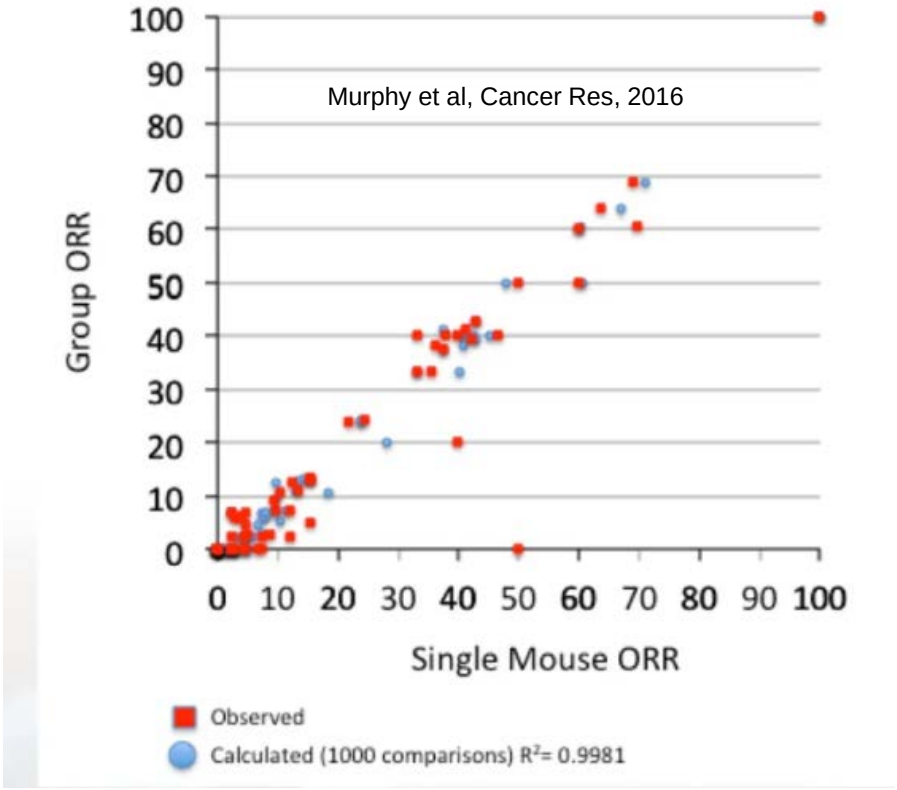
Subtitle: making it affordable

Question: Are large (& expensive) preclinical mouse model studies necessary?

Answer: No

Why this matters
- Capacity limitations
- Simple economics

Example four-arm study savings
- ~ 23 000 €/study (n=8 vs n=1)
- Across *single* ITCC-P4 disease entity = 920 000 € (40 PDX/entity)



Comparison of *objective response rates* of studies w/ n=8-10 vs n = 1
(2106 studies)

Thank you Pete Houghton!

Findings: Brain tumors require different approaches

- Orthotopic preferred
- Subcutaneous models as a screening tool prior to orthotopic evaluation?
- Defining efficacy: survival vs imaging approaches → comparison studies needed

Findings: The next frontier – preclinical immuno oncology research

- Reminder: children with cancer are *not* little adults with cancer; even “truer” for IO

- E*xtremely limited* availability of relevant *in vivo* paediatric tumor models for IO compound testing

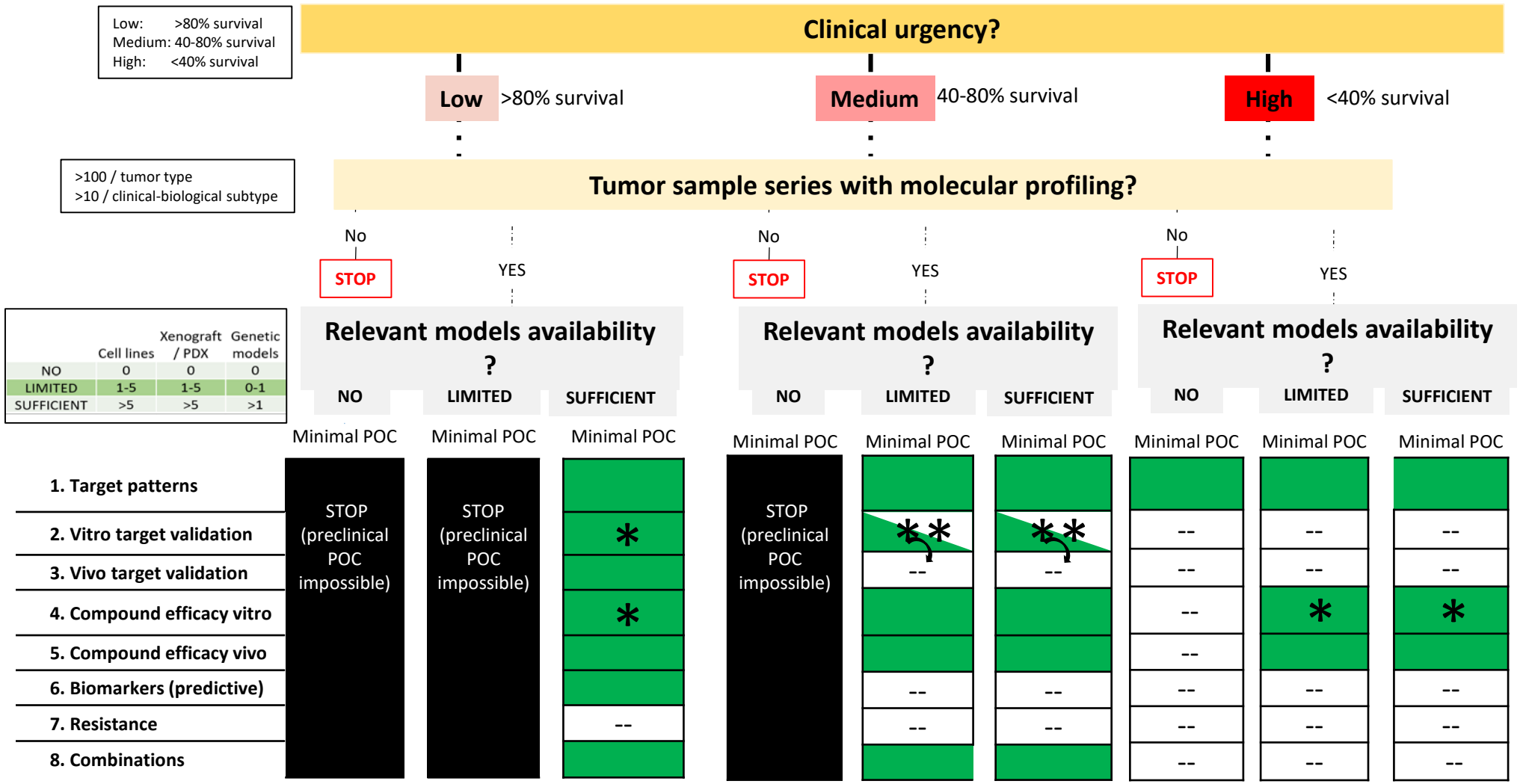
- Critical need for humanized mouse models of paediatric cancer

- Sharing expression databases & establishing a paediatric tumor immune atlas will shed light on relevance of antigens and targets

Findings: Let's not forget the importance of patient advocacy

- Maintain *patient* need as the driver of all activities
- Bridge b/w all stakeholders
- Insist on the avoidance of any unjustified delays
- Vigilance

A DRAFT *proposal* for defining a minimally-required preclinical paediatric dataset



	Cell lines	Xenograft / PDX	Genetic models
NO	0	0	0
LIMITED	1-5	1-5	0-1
SUFFICIENT	>5	>5	>1

* If no cell lines available than vitro validation and efficacy not possible, ** If validation vitro not possible, than replace by vivo validation

Thank you Hubert Caron!

What next?

- Submit white paper
- Regulatory interaction
  - EMA – submit a document for qualification process later this year
    - Contacts w/EMA delayed due to Business Continuity Plan (i.e., BREXIT)
  - FDA – no qualification process. « The published article will be used » Greg Reaman, 09/2018

Thanks to ALL Workshop participants

Thanks to those actively writing the white paper:

Hubert Caron
Sara Colombetti
Peter Houghton
Xiaonan Li
Stefan Pfister
Julia Schuler
David Shields
Malcolm Smith
Gilles Vassal
Olaf Witt

Thanks to:

Horizon Scanning of global Paediatric Oncology Drug Developments

Gilles Vassal, *Gustave Roussy*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Horizon Scanning of global pediatric oncology development

Preliminary results

Gilles Vassal

Brussels, February 15, 2019

IMPACT

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

leem LES ENTREPRISES DU MÉDICAMENT

Care Factory

The French Multi-stakeholder IMPACT Platform

Gustave Roussy
Comprehensive Cancer Center

LEEM – Les Entreprises du Médicament
Professional organization of pharmaceutical companies operating in France.

Care Factory
French consulting company specialized in healthcare.

Need for Horizon Scanning

*Horizon scanning aims to **spot changes** in the world around us before they become 'old news', so that decision makers can plan on **how to exploit or mitigate these changes**, securing the most positive outcome for their organization.*

- **Science driven new oncology drug development for children**
- **The FDA Target lists will help making decisions**
- **Prioritization will be key to meet the needs of patients**

Need to generate regularly updated information about drugs in development that target the FDA list to facilitate decision making

The INNOVATION database, a Horizon Scanning tool developed by LEEM and Care Factory

The INNOVATION database is a Horizon Scanning Tool which lists all the interventional clinical studies about pharmaceutical compounds in progress or completed during the last 3 years.
This database has been developed since 2016 by LEEM and Care Factory

Several databases have been combined **to ensure the completeness** of this Horizon Scanning Tool. Among these databases, 4 of them are particularly important

1

ClinicalTrial.gov

A database of privately and publicly funded clinical studies conducted around the world.

2

AdisInsight

A database for drug R&D, disease treatment and decision making, based on trusted, scientifically sound data.

3

EMA / FDA / ANSM

European, American and French medicines agencies.

4

MeshTerms TreeMap

National Library of Medicine's controlled vocabulary thesaurus.

The design of the INNOVATION database allows a three-fold approach:

- *1. By molecule*
- *2. By indication*
- *3. By mechanism of action*

Objectives

OBJECTIVES

1. To describe ongoing global development of new oncology drugs in the pediatric population
2. To define how many drugs in development since 2007* target the FDA pediatric targets list

*launch of EU Pediatric Medicine Regulation

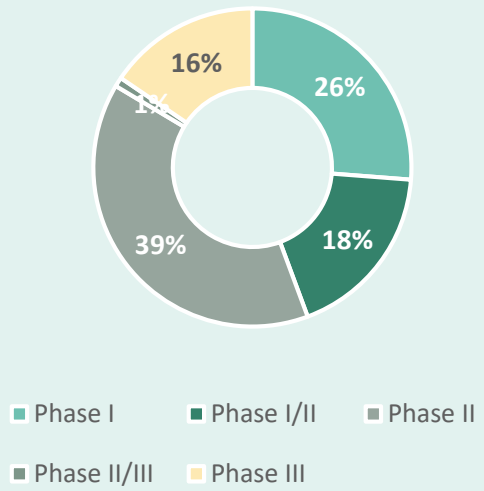
Pediatric oncology trials

Investigated perimeter (INNOVATION Database):

- Pathology: Oncology
- Sponsorship: **Industry only and IIT with Industry partner**
- Status: Recruiting, Active, not recruiting, Completed since less than 3 years
- Start date: ≥ 01/01/2013

3 382 clinical trials are currently active *(February 2019)*

% of current active clinical trials

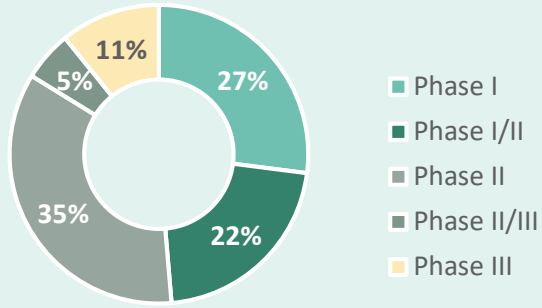


1.1 %

of the current active trials are targeting a pediatric population (children only)

37 pediatric (children only) clinical trials are currently active *(February 2019)*

% of current active clinical trials

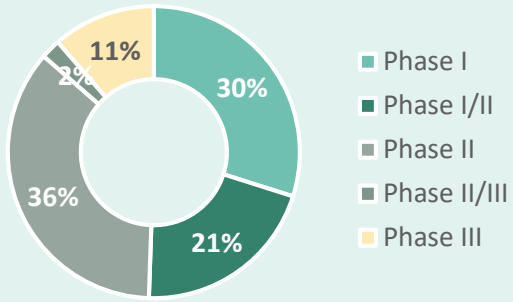


5.4 %

of the current active trials are targeting a pediatric population (children + adults)

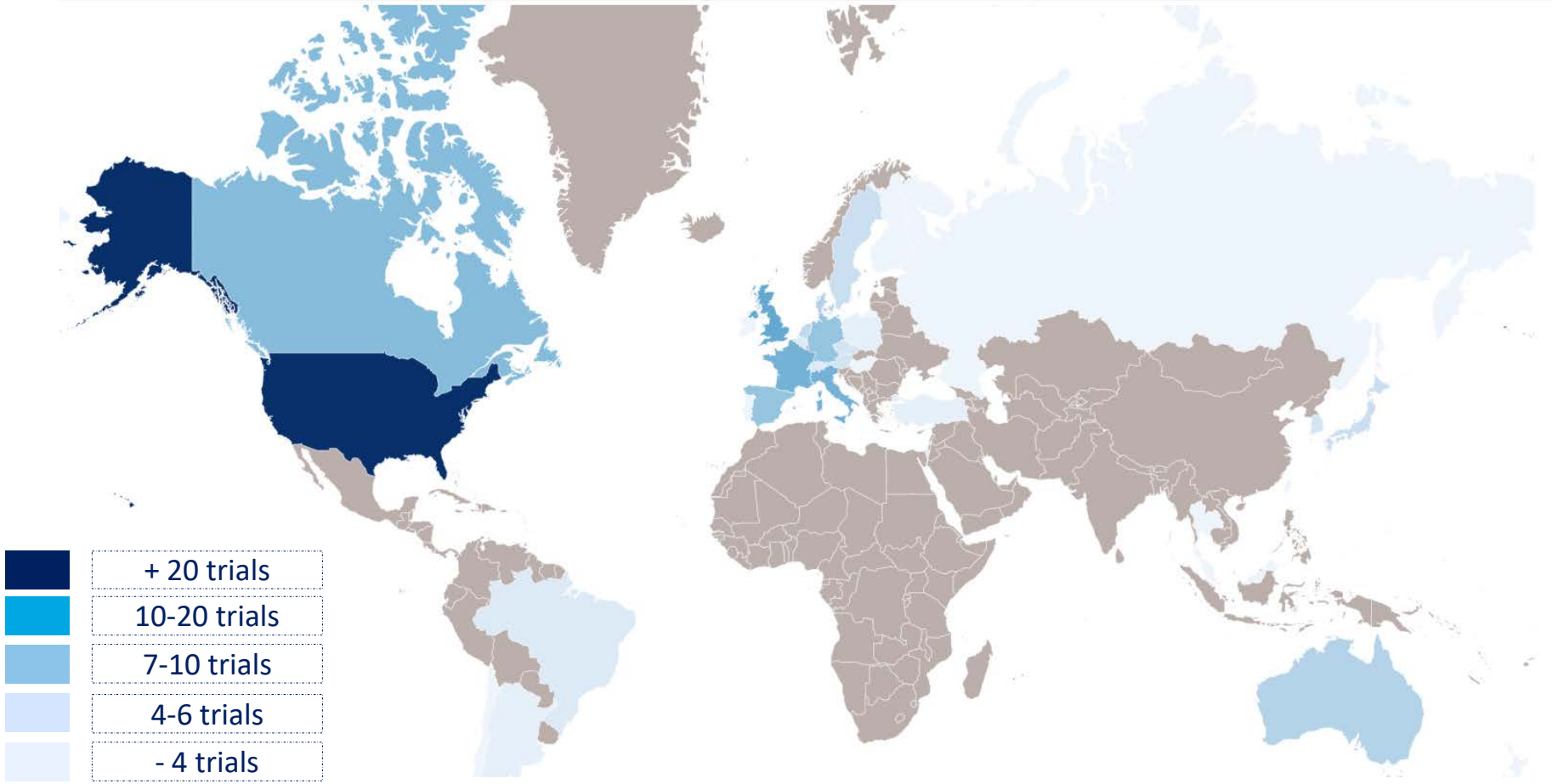
184 pediatric (children + adults) clinical trials are currently active *(February 2019)*

% of current active clinical trials



Global development through industry trials

Mapping of clinical centers currently testing oncology drugs on pediatric population
(children only)



Composition of the FDA Pediatric Molecular Target List

The FDA Pediatric Molecular Target List has been released in 2018

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/UCM616597.pdf

The FDA suggested a distribution of the targets in 5 families

Some targets can be found in several families

Gene Abnormality *(62 targets)*	Others *(77 targets)*	Cell Lineage *(40 targets)*	Tumor Microenvironment & immunotherapy *(21 targets)*	Automatic Waivers *(5 targets)*
Examples of targets				
FLT3 NT5C2 ODC1	AXL FAK SWI/SNF	CD20 BTK SYK	CXCR4 STING VEGFR	AR ESR1/2 GnRHR

A total of 205 targets have been referenced by the FDA

Methodology

A matching between the FDA Pediatric Molecular Target List and the Genecards database allowed us to identify the relations between genes and drugs. The results were then treated following a 4 steps methodology :

Pediatric Molecular Target List (**FDA**) **X** Public database referencing more than **148,000 genes** and the drugs that target them

Methodology

1. **Exclusion of couples Princeps /INN** *(International Non-proprietary Name)*
2. **Exclusion of laboratory chimic compounds**
3. **Study of the MA status (FDA/EMA/ANSM)**
4. **Distinction before/after 2007**

6 554 « Drug/Gene » interactions

↓

5 859 « Drug/Gene » interactions

↓

2 602 « Drug/Gene » interactions

- **« Drug/Gene » interactions with a MA :**
  - 893
  - 912
- **« Drug/Gene » interactions without a MA**
  - 1709
  - 1690

- **« Drug/Gene » interactions with a MA anterior to 2007**
  - 512
  - 471
- **« Drug/Gene » interactions with a MA posterior or equal to 2007:**
  - 381
  - 441

Not all FDA targets have a compound in development

205 | **205 targets** in the **Pediatric Molecular Target List**

X 1,5

309 | **309 genes** in **GeneCards** (Subunits, etc.)

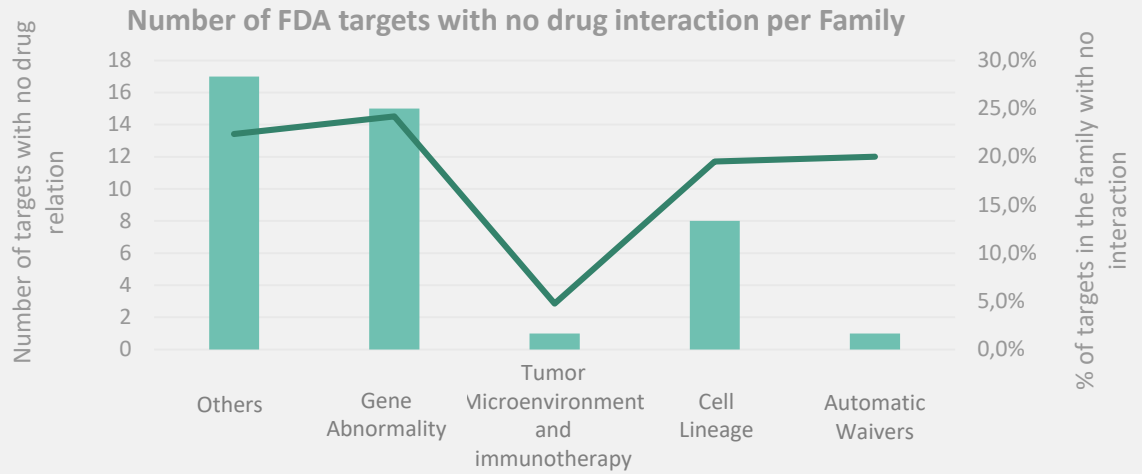
Targets and Genes

20% | For **41** pediatric molecular targets (20%), **no interaction with a molecule is referenced** in GeneCards

26% | **53 pediatric molecular targets** with a compound which is **not under development**

Compounds in development

Targets without compounds



Examples of target without compounds:

- ATRX
- DDX3X
- SUZ12
- MYCN

64

Summary: Number of molecules targeting the list *(after cleaning)*

1 169 compounds interact with, at least, one of the pediatric molecular target identified by the FDA

In average, one drug is related to 2.2 FDA targets

With a MA < 2007	With a MA > 2007	With no MA
211 compounds	97 compounds	861 compounds
191 compounds	115 compounds	863 compounds
18%	8%	74%

1 169 compounds target the FDA targets list

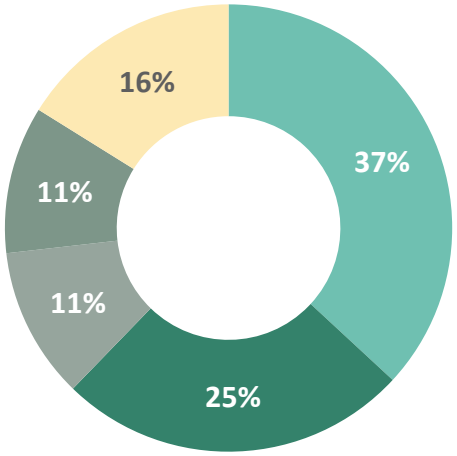
EMA MA

MA <2007

211

compounds present an interaction with a FDA target and benefit from a MA anterior to 2007

Number of compounds (MA<2007) presenting, at least, one interaction with a FDA family

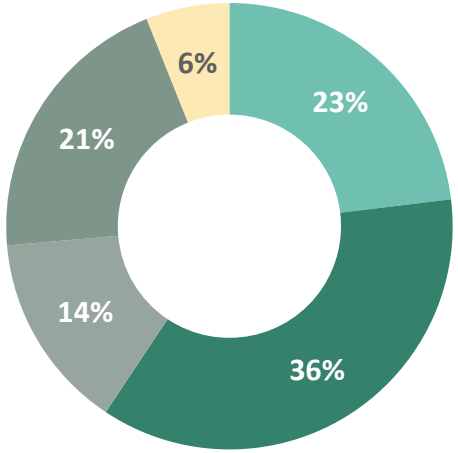


MA ⩾ 2007

97

compounds present an interaction with a FDA target and benefit from a MA posterior or equal to 2007

Number of compounds (MA>2007) presenting, at least, one interaction with a FDA family

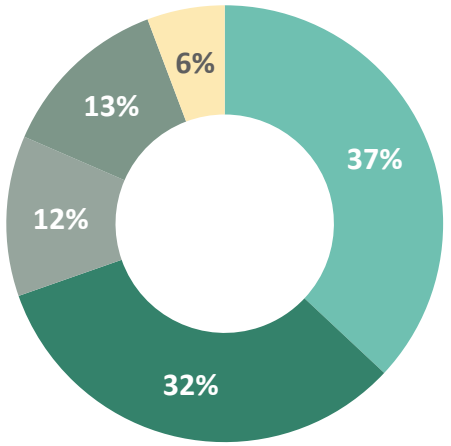


No MA

861

compounds present an interaction with a FDA target but do not have a MA

Number of compounds (no MA) presenting, at least, one interaction with a FDA family



Others | Gene Abnormality | Tumor Microenvironment and Immunotherapy | Cell lineage | Automatic Waivers

Drugs without Marketing Authorization

EMA MA

861 drugs do not have a Marketing Authorization

Two possibilities:

1. Drugs can be **currently under development**
2. **Clinical development** can be **stopped**

Methodology employed to distinguish these two categories

If the drug can be found in the INNOVATION Database *(as the experimental treatment and not as a comparator)*	If the drug is missing can not be found in the INNOVATION Database *(as the experimental treatment and not as a comparator)*
Ongoing development	**Stopped development**

The following **filters** were **applied to build the INNOVATION Database**

- ***Sponsorship**: Industrial sponsorship and co-sponsorship*
- ***Start date**: ≥ 01/01/2013*
- ***Objective:** Interventional*
- ***Status**: Recruiting, Active, not recruiting, Completed since less than 3 years*
- ***Localization**: At least one center out of Asia and sub-Saharan Africa*
- ***Studied compound:** Drug or Biological*

Results

27% **230** **Drugs may be currently in a active clinical development**

73% **631** **Drugs may have a stopped clinical development**

Number of drugs without Marketing Authorization

Drugs currently under development versus stopped development

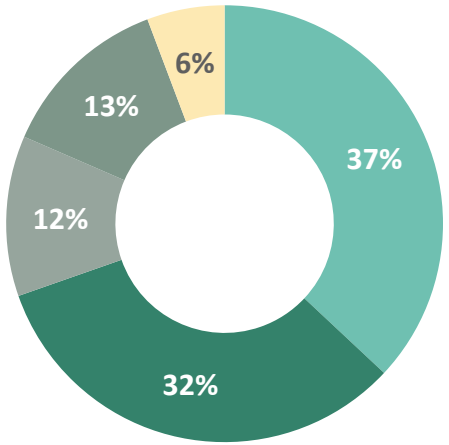
EMA MA

No MA

861

compounds present an interaction with a FDA target but do not have a MA

Number of compounds (no MA) presenting, at least, one interaction with a FDA family

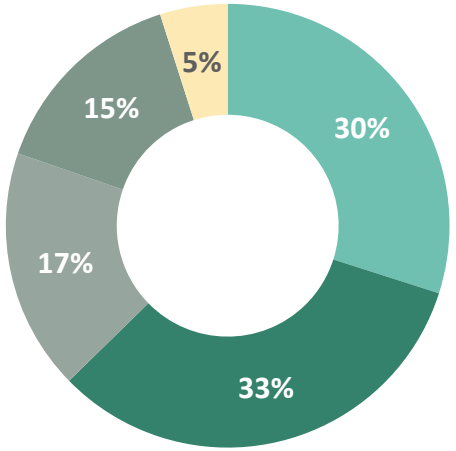


Under dev.

230

compounds present an interaction with a FDA target, do not have a MA but are currently under development

Number of compounds (no MA but under dev.) presenting, at least, one interaction with a FDA family

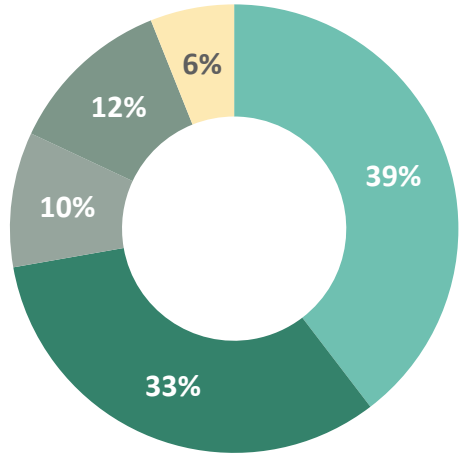


Stopped dev.

631

compounds present an interaction with a FDA target, do not have a MA and are no longer under development

Number of compounds (no MA and no longer under dev.) presenting, at least, one interaction with a FDA family



Others | Gene Abnormality | Tumor Microenvironment and Immunotherapy | Cell lineage | Automatic Waivers

Written Requests (WRs) and Pediatric Investigation Plans (PIPs)

EMA MA

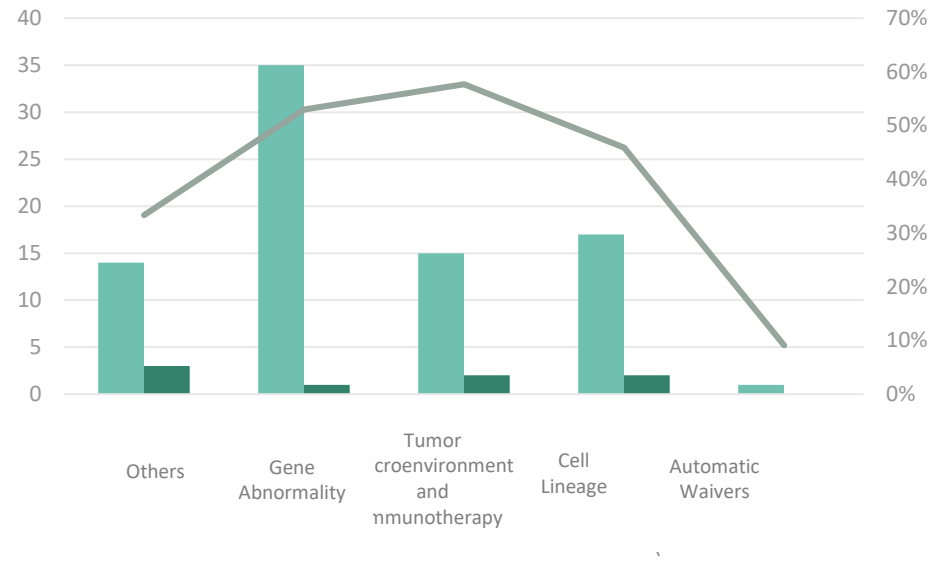
Drugs which benefit from a MA > 2007

Total number of drugs	97	
Number of drugs with a **WR***	5	5%
Number of drugs with a **PIP**	46	47%
Number of drugs with a **Waiver**	15	15%

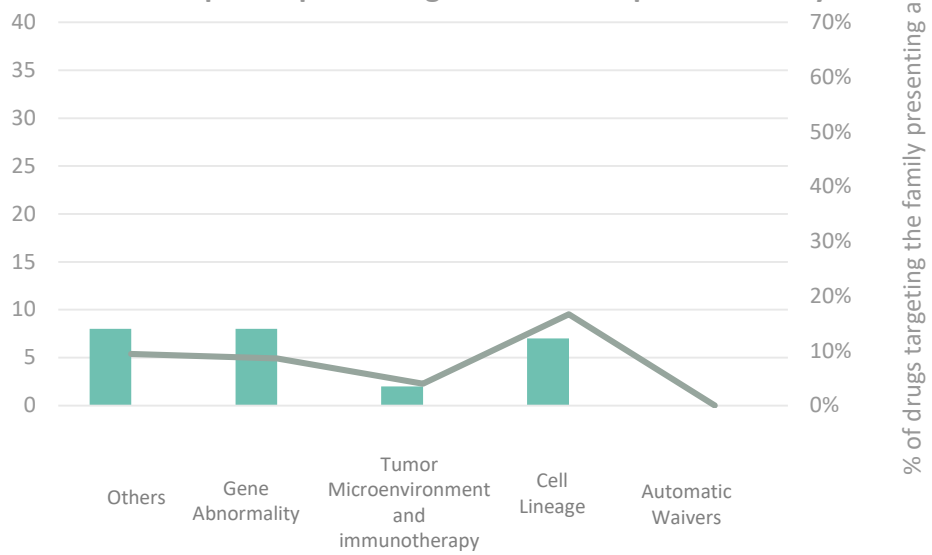
Drugs without MA under development

Total number of compounds	230	
Number of compounds with a **WR***	0	0%
Number of compounds with a **PIP**	20	9%
Number of compounds with a **Waiver**	14	6%

Number of compounds with a MA>2007 presenting a PIP or a WR per FDA family



Number of compounds without a MA under development presenting a PIP or a WR per FDA family



Number of compounds with a PIP | Number of compounds with a WR | % of the family presenting a PIP

*Information about Pediatric Study Plans are not publicly provided by the FDA

FLT3 in pediatric acute myeloid leukemia (AML)

FLT3

- FMS-like tyrosine kinase-3 receptor
- Same family as c-KIT, CSF1R, PDGFR
- Mutated in 25% AML

Acute myeloid leukemia

- ~ 500 children and ~20,000 adults per year in the US and in Europe
- 65% 5 yr DFS in children with intensive treatment
- Worse prognosis for children with a mt-FLT3 AML

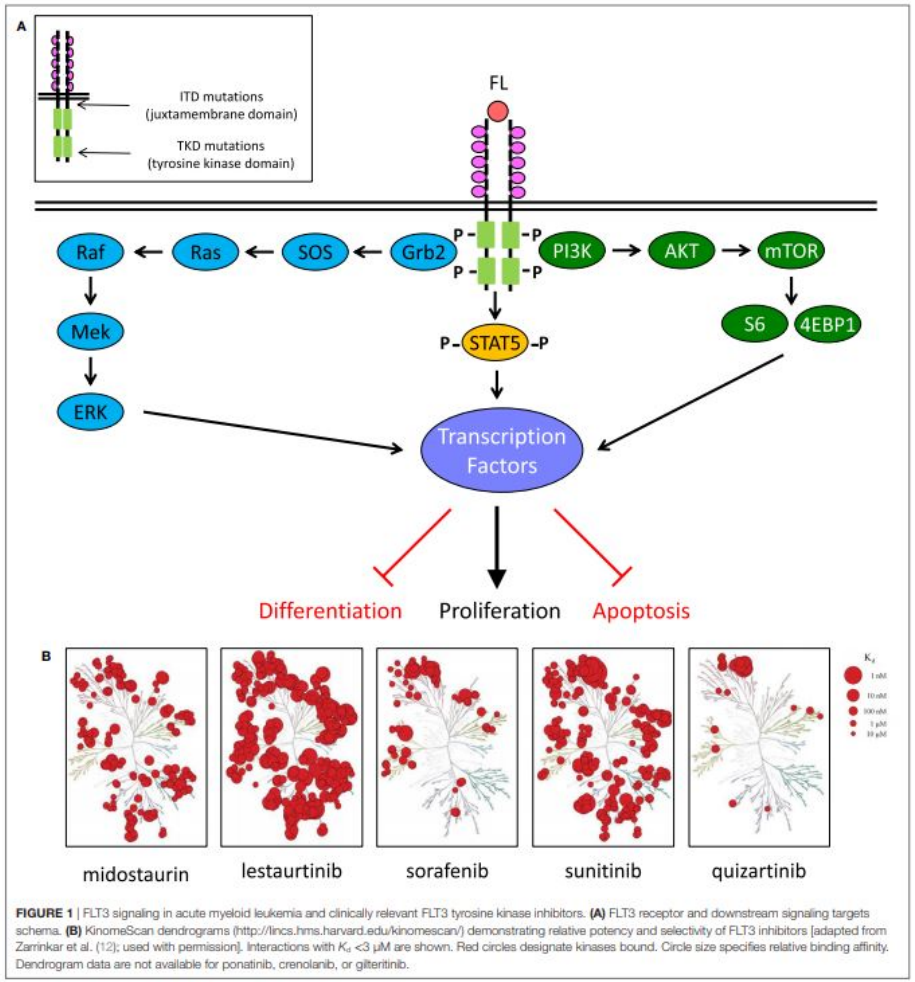
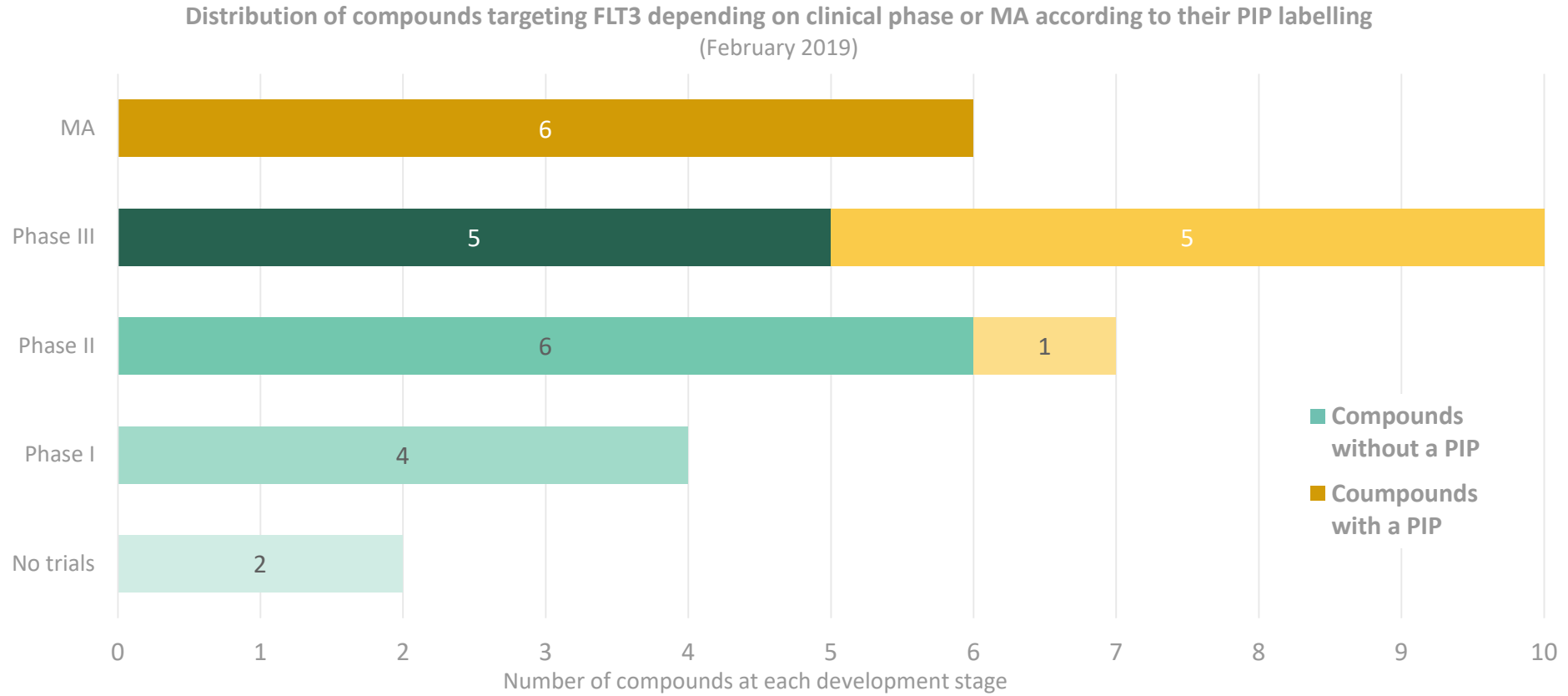


FIGURE 1 | FLT3 signaling in acute myeloid leukemia and clinically relevant FLT3 tyrosine kinase inhibitors. **(A)** FLT3 receptor and downstream signaling targets schema. **(B)** KinomeScan dendrograms (http://lincs.hms.harvard.edu/kinomescan/) demonstrating relative potency and selectivity of FLT3 inhibitors [adapted from Zarrinkar et al. (12); used with permission]. Interactions with K_d <3 μM are shown. Red circles designate kinases bound. Circle size specifies relative binding affinity. Dendrogram data are not available for ponatinib, crenolanib, or gilteritinib.

Sexauer *et al* in Frontiers in Pediatrics, 2017, 5: 248

29 drugs target FLT3

EMA MA



Number of compounds targeting FLT3 who have undergone a pediatric clinical trial *(all sponsorship)*	**10**	**34%**
Number of FLT3 compounds who currently undergone a pediatric clinical trial *(all sponsorship)*	**6**	**21%**

Mean duration between the start date of the 1st trial and the start date of the 1st pediatric trial

4 years & 11 months

Min	**7 months**
Max	**9 years & 6 months**

List of current active pediatric trials related to drugs targeting FLT3 *(all sponsorship)*

Drug	Phase	Disease	NCT Id	Age
Crenolanib	NA	Cancers With PDGFRa Mutations or FLT3 Mutations	NCT03620318	NA
Quizartinib	I/II	Relapsed/Refractory AML	NCT03793478	1mo to 21yo
Cabozantinib	I	Relapsed or Refractory Solid Tumors	NCT03611595	2yo to 21yo
	II	Recurrent or Progressive High-Grade Glioma	NCT02885324	2yo to 21yo
	I	Recurrent or Refractory Solid Tumors	NCT01709435	2yo to 18yo
	II	Refractory Sarcomas, Wilms Tumor, and Other Rare Tumors	NCT02867592	2yo to 30yo
	II	Neurofibromatosis Type 1	NCT02101736	3yo and +
Ponatinib	II/III	Post-transplants on Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia	NCT03624530	14yo to 65yo
Midostaurin	II	FLT3-mutated AML	NCT03591510	3mo to 17yo
Sorafenib	II	Relapsed/Recurrent/Refractory Solid Tumors	NCT02747537	2yo to 21yo
	And 22 more			

70% of the trials currently testing drugs targeting FLT3 are being conducted by academic organizations

Key findings

- 46% of FDA listed targets have no compound or no compound in development

- 1169 drugs target the FDA list:
  - 18% had a marketed authorisation before 2007
  - 8% had a marketed authorisation after 2007
  - 74% have no marketed authorisation

- 73% of drugs with no marketed authorisation are suspected to be no longer in development

Lessons and further development

- Horizon scanning is limited by the content and quality of publicly available databases

- The tool needs to be improved:
  - to be fully automated for updates
  - to include all academic oncology trials

Conclusion

- The FDA target list is a tool and a trigger to think early of pediatric malignancies and generate bioglogical and preclinical data
- There are many compounds outthere which may be worth to consider
- Value of horizon scanning

THANKS

Charles Toussaint

Elodie Lheman

Daniel Szeftel

Ariane Galaup-Paci

Fabrice Meillier

Groupe Cartogaphie:
Jérôme Krulik, Bruno Schoentes, Romain , François

Future-proofing academic Clinical Trials to adapt for regulatory Use

Andrew Embleton, *University College London*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Future-Proofing Academic Clinical Trials To Adapt For Regulatory Use

Andrew Embleton

15-Feb-2019

Outline

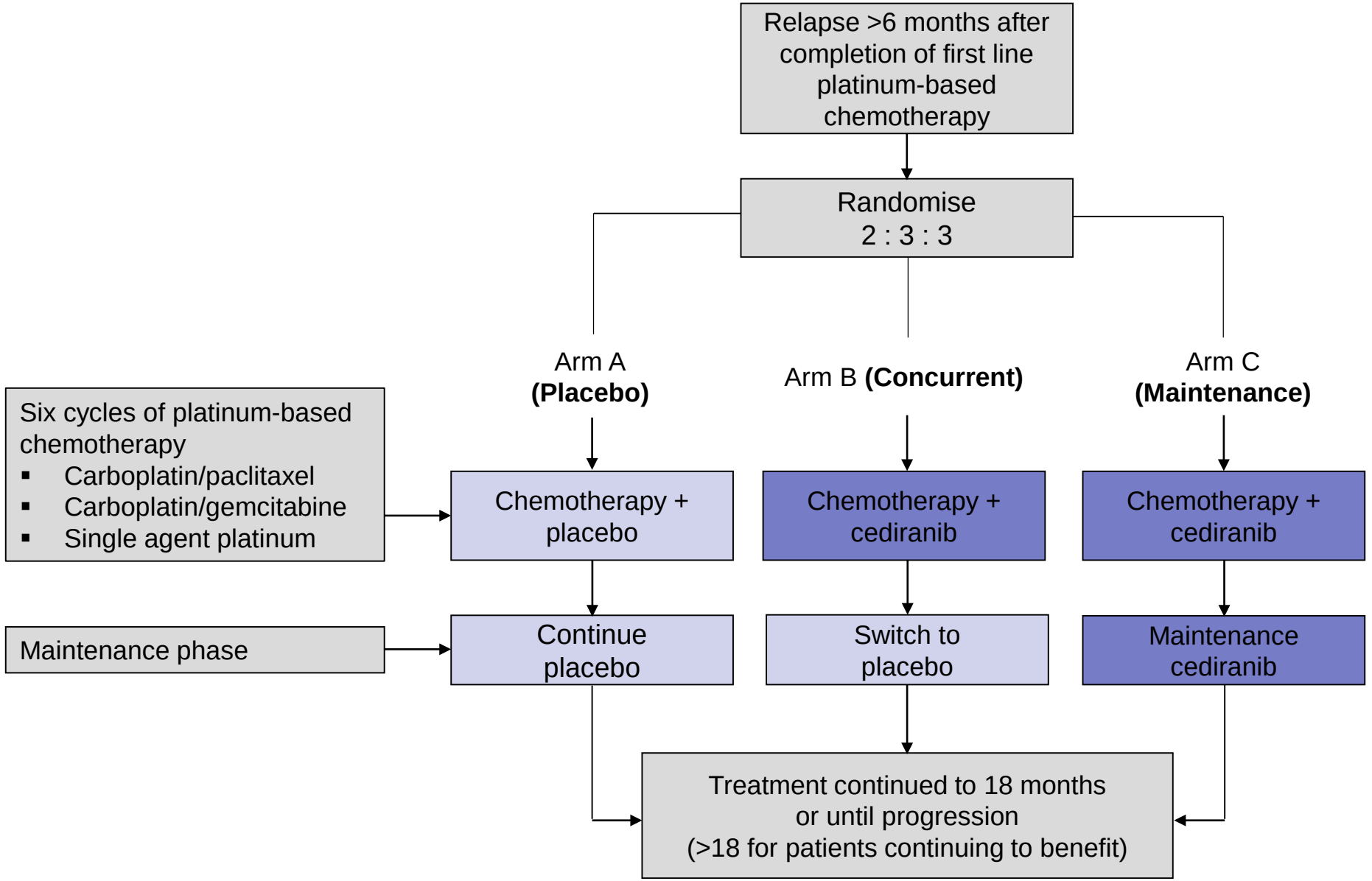
ICON6 regulatory submission

Rationale

EMA submission review

Draft recommendations

The ICOn6 Experience


Relapse >6 months after completion of first line platinum-based chemotherapy
Randomise 2 : 3 : 3
Arm A (Placebo)
Arm B (Concurrent)
Arm C (Maintenance)
Six cycles of platinum-based chemotherapy
Carboplatin/paclitaxel
Carboplatin/gemcitabine
Single agent platinum
Chemotherapy + placebo
Chemotherapy + cediranib
Chemotherapy + cediranib
Maintenance phase
Continue placebo
Switch to placebo
Maintenance cediranib
Treatment continued to 18 months or until progression (>18 for patients continuing to benefit)

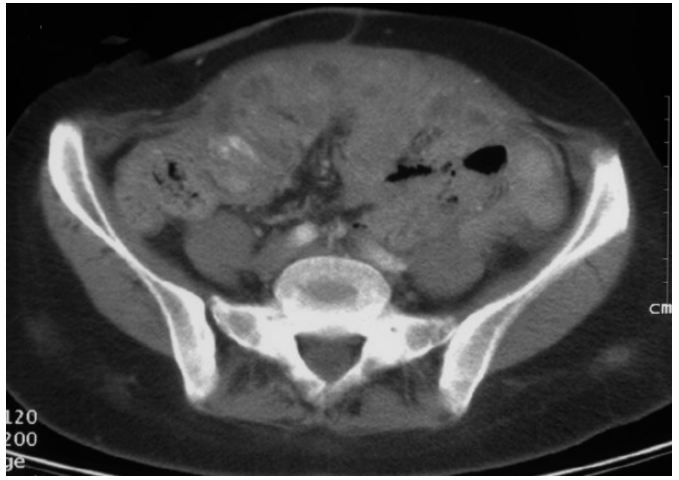
Hazard Ratio 0.57 (0.45–0.74)
Log-rank p=0.00001

ECC 2013 Press Release: Biological Therapy with Cediranib Improves Survival in Women with Recurrent Ovarian Cancer

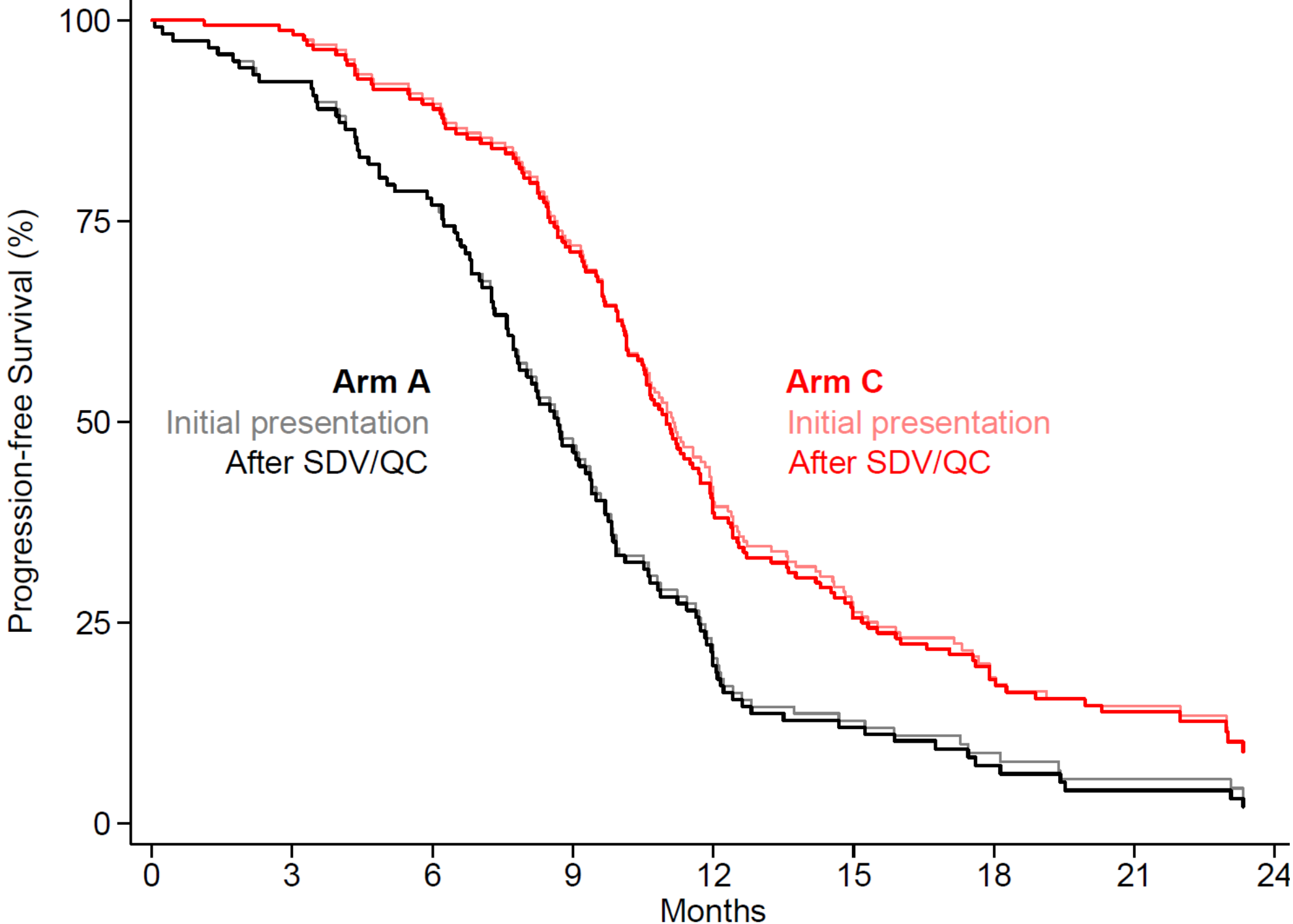
Women with ovarian cancer that has recurred after chemotherapy have survived for longer after treatment with a biological therapy called cediranib, according to new results to be presented Monday at the 2013 European Cancer Congress (ECC2013) [1].

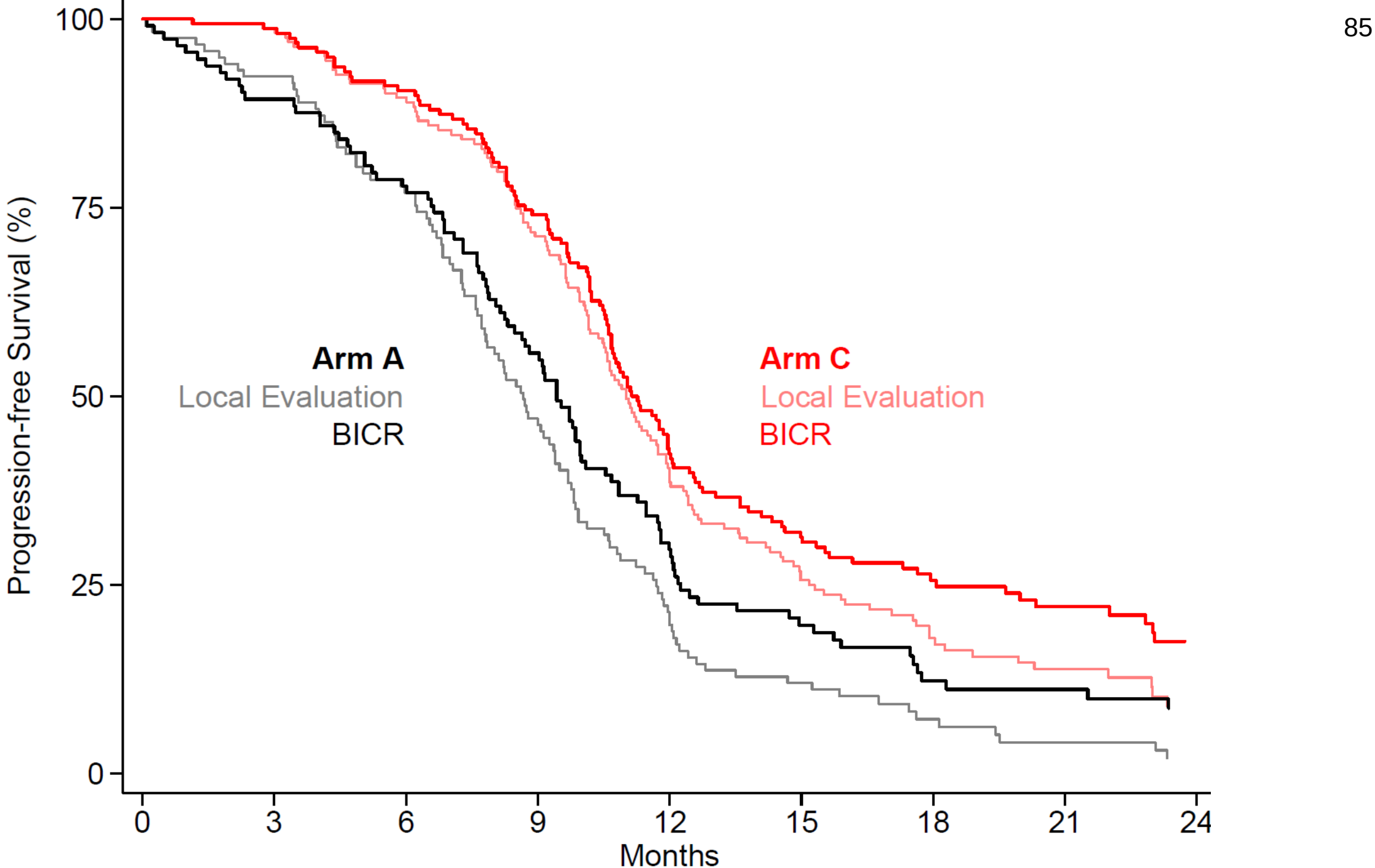
Source Data Verification

Quality Checking



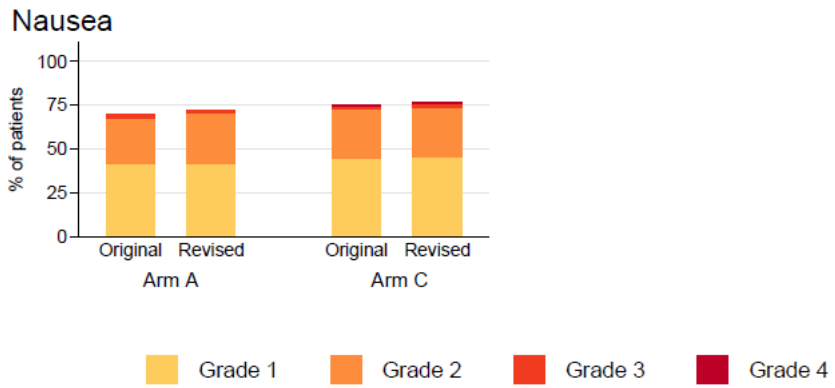
Blinded Independent Central Review


Progression-free Survival (%)
100
75
50
25
0
0
3
6
9
12
15
18
21
24
Months
Arm A
Initial presentation
After SDV/QC
Arm C
Initial presentation
After SDV/QC


Progression-free Survival (%)
100
75
50
25
0
0
3
6
9
12
15
18
21
24
Months
Arm A
Local Evaluation
BICR
Arm C
Local Evaluation
BICR

Chemotherapy phase

Maintenance phase



Submission

EMA following retrospective verification

Opinion within 210 days

With a couple of opportunities for pauses where AZ answer questions

Opinion was negative at interim

GCP inspection was requested

GCP inspection

2.4. General comments on compliance with GMP, GLP, GCP

A request for GCP inspection has been adopted for the following clinical study D8480C0037. This was a routine GCP inspection. No specific concerns were known to have been identified by the assessment at the time of adoption of the inspection request. However, in this particular case, the fact that a national inspection conducted at one site in UK revealed critical findings in relation to safety and data integrity has been considered.

A total of four study sites were inspected (of 62 participating study centers). The inspections revealed several GCP findings. The main issues were related to:

- Oversight by the study sponsor which resulted in non-uniform conduct and reporting of data.
- The impact of post-unblinding activities on the reported data
- Lack of available documentation of the appearance of test and control product meant the blinding process is not verifiable.
- The safety profile was considered incomplete.

The Telegraph

AstraZeneca withdraws cancer drug after 'differences of opinion' with regulator

Rationale

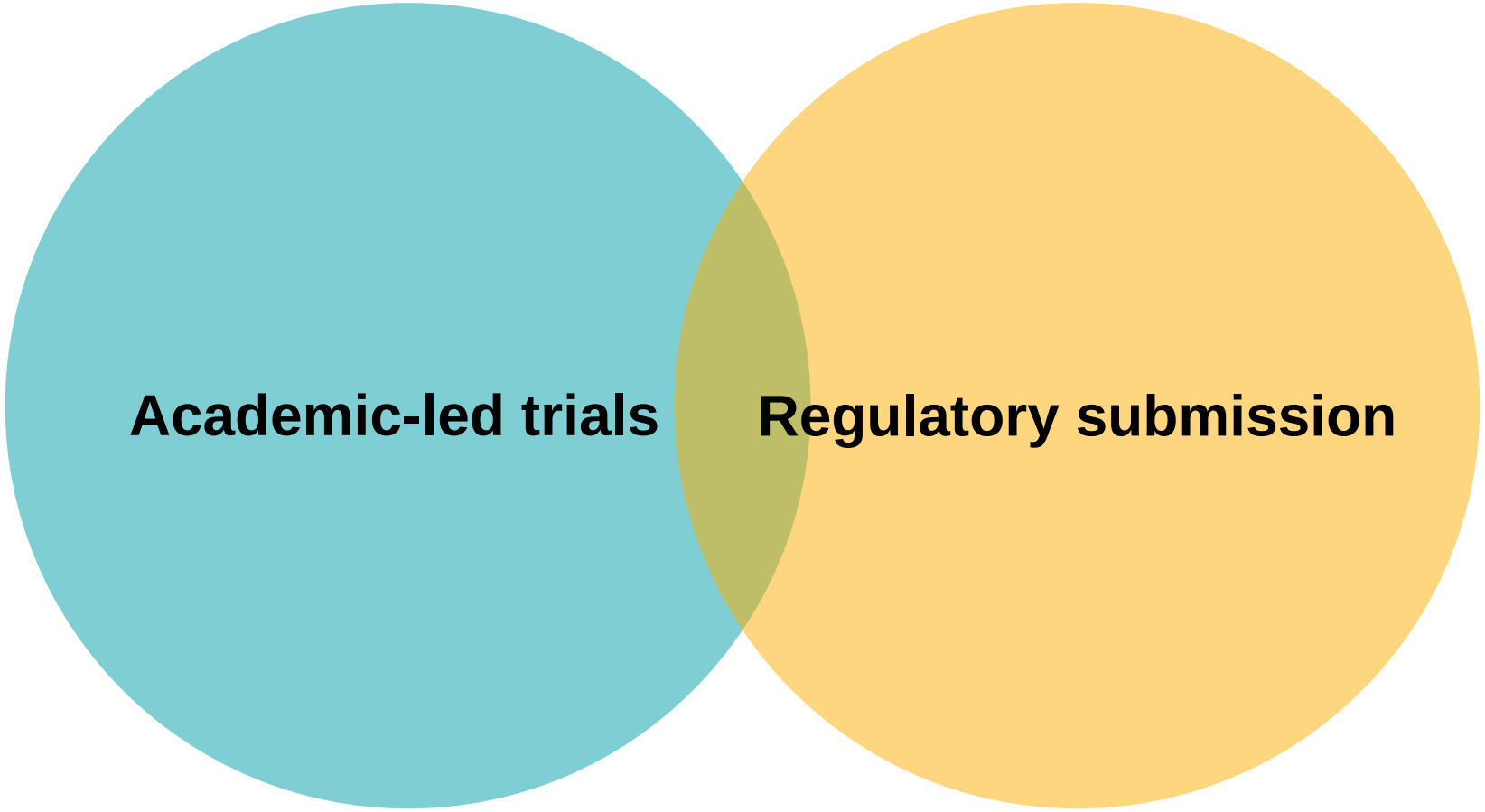
Academic research needed because industry…

1. Cannot explore all options
2. Rarely investigate less common diseases
3. Prefers short-term outcomes

The most obvious differences to me are in terms of purpose and cost

Literature review

Looking for the interaction of two broad themes



Regional regulatory approval (1)

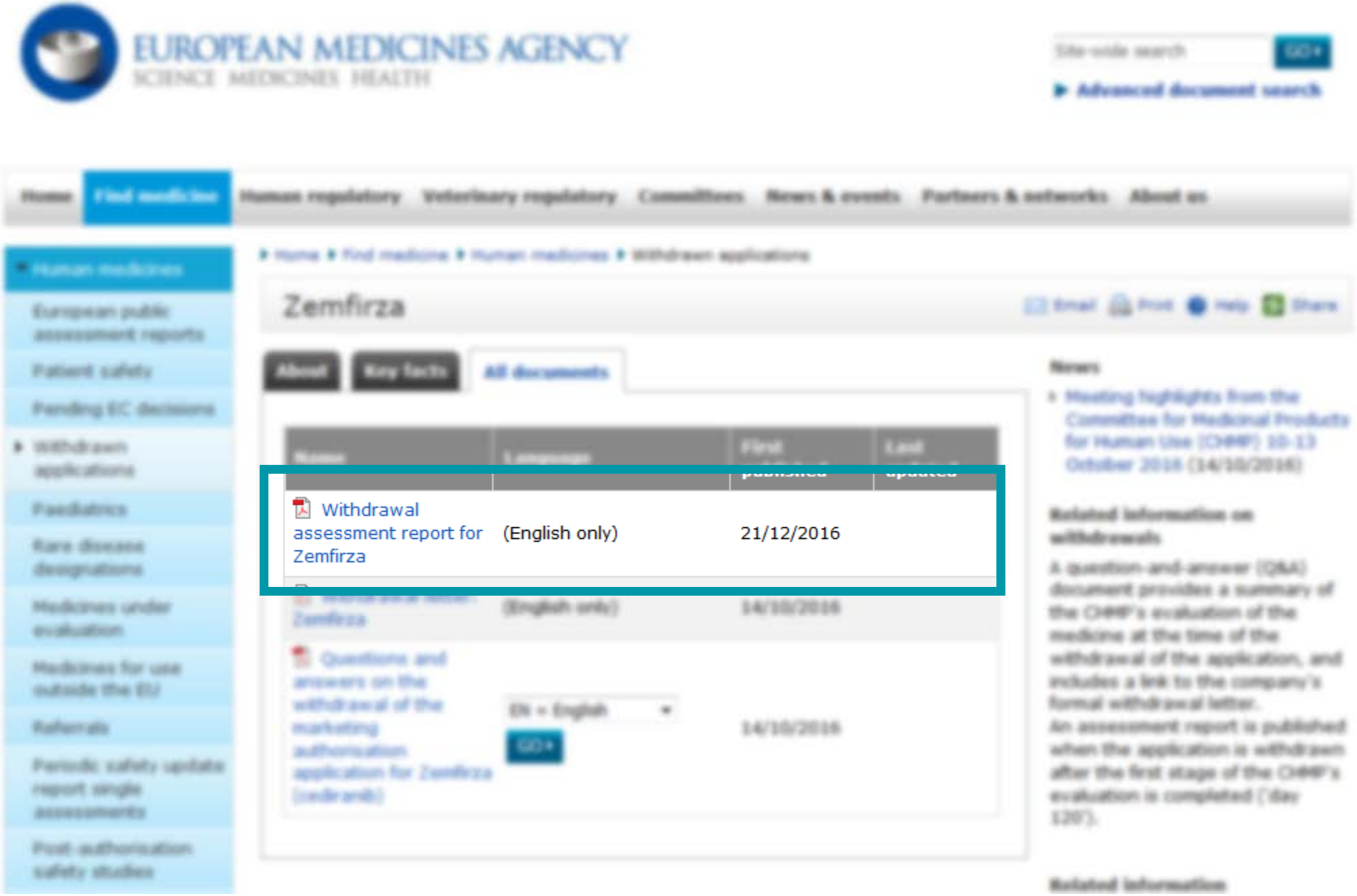
Industry-academia interactions (4)

Academic drug discovery (2)

Trial conduct (2)

Data standards (2)

Review of EMA Licence Submissions


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
Site-wide search
GO
Advanced document search
Home
Find medicine
Human regulatory
Veterinary regulatory
Committees
News & events
Partners & networks
About us
Human medicines
European public assessment reports
Patient safety
Pending EC decisions
Withdrawn applications
Paediatrics
Rare disease designations
Medicines under evaluation
Medicines for use outside the EU
Referrals
Periodic safety update report single assessments
Post-authorisation safety studies
Home
Find medicine
Human medicines
Withdrawn applications
Zemfirza
Email
Print
Help
Share
About
Key facts
All documents
Name
Language
First published
Last updated
Withdrawal assessment report for Zemfirza
(English only)
21/12/2016
Zemfirza
(English only)
14/10/2016
Questions and answers on the withdrawal of the marketing authorisation application for Zemfirza (cediranib)
EN - English
GO
14/10/2016
News
Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 10-13 October 2016 (14/10/2016)
Related information on withdrawals
A question-and-answer (Q&A) document provides a summary of the CHMP's evaluation of the medicine at the time of the withdrawal of the application, and includes a link to the company's formal withdrawal letter.
An assessment report is published when the application is withdrawn after the first stage of the CHMP's evaluation is completed ('day 120').
Related information

EPAR review

Understand the problem

Retrieval

Search process

Results

1141 medicines processed > 386 results > **109 relevant**

Categorised as **major**, **minor** or **micro** involvement

25 (23%) major examples of academic involvement,
42 (39%) minor and also **42 (39%) micro**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Name	INN	Status	Indication	Therapeutic area	Trial use	Main issue
Zometa	zoledronic acid	Withdrawn	Extension	Breast cancer	Pivotal	Lack of activity Choice of reference arm Trial conduct
Firazyr	icatibant acetate	Withdrawn	Extension	Hereditary Angioedemas	Pivotal	Trial conduct
Strimvelis	autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	Approved	Initial	Severe Combined Immunodeficiency	Pivotal	-
Zemfirza	cediranib maleate	Withdrawn	Initial	Ovarian cancer	Pivotal	Size of effect Trial conduct
Lutathera	lutetium (177Lu) oxodotreotide	Approved	Initial	Neuroendocrine tumors	Supportive	-

Approved

Majority

Approval rate comparable

Larger proportion that anticipated initial applications

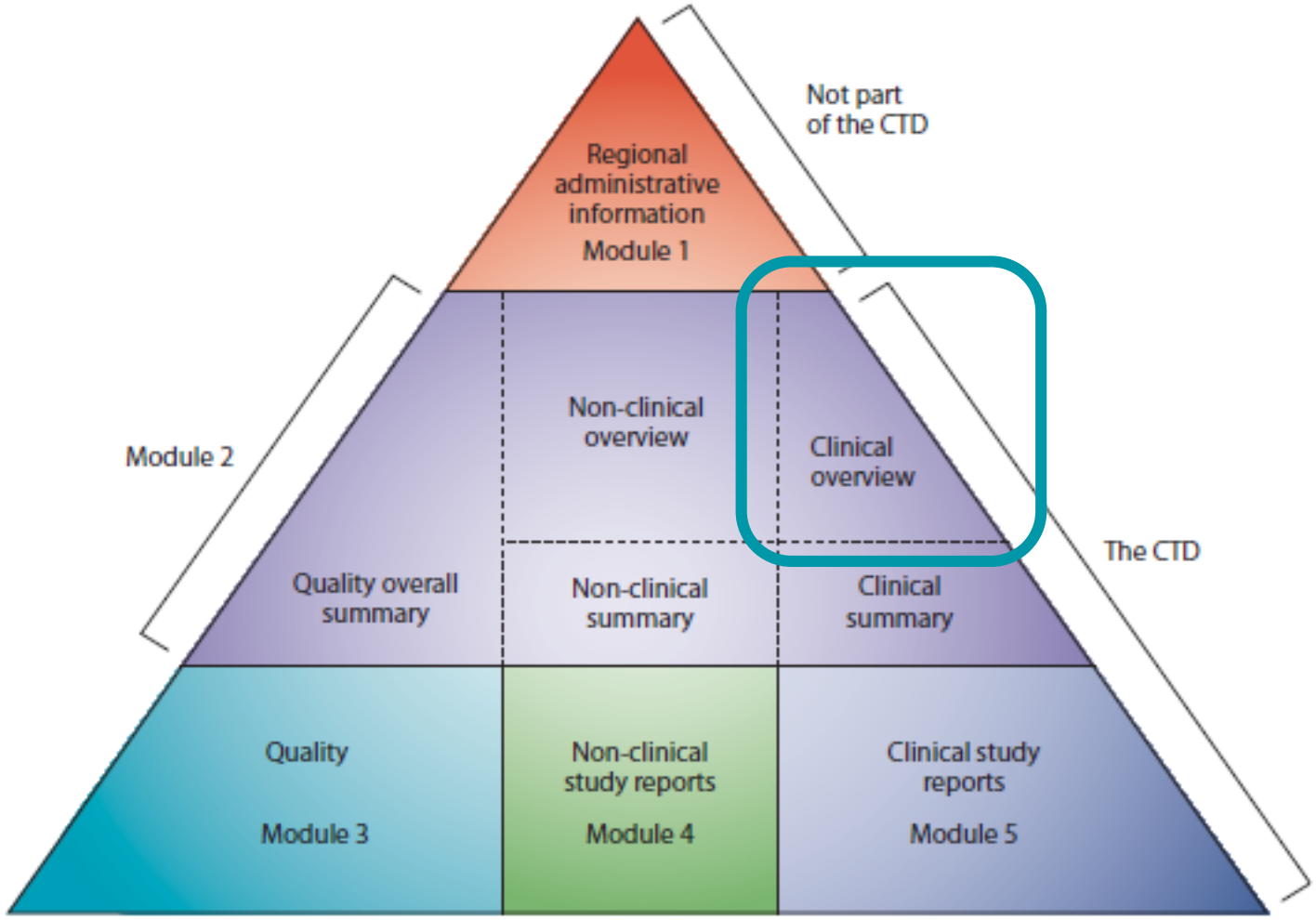
Rare diseases – much more common, commercial interest?

Withdrawn

Split initial/extensions

Majority not rare

All had major objections due to GCP


Not part
of the CTD
Regional
administrative
information
Module 1
Module 2
Non-clinical
overview
Clinical
overview
The CTD
Quality overall
summary
Non-clinical
summary
Clinical
summary
Quality
Module 3
Non-clinical
study reports
Module 4
Clinical study
reports
Module 5

Mylotarg (gemtuzumab ozogamicin, EMEA/H/C/004204)

ALFA-0701, conducted and sponsored by the Acute Leukemia French Association (ALFA) group

Also 5 non-commercial trials in supporting meta-analysis

- ALFA-0701
- SWOG-S0106
- MRC AML15
- NCRI AML16
- GOELAMS AML2006IR

For the treatment of acute myeloid leukaemia in patients above 15 years of age

Some retrospective safety data collection needed

Approved

Draft recommendations

5

ICON6

Regional, co-operative sponsors

Lead group oversight

Versioning of scales

Only enrol patients with Ethic’s approved, fully translated, consent forms

Formal IB communication

Whether these can be generalised to most trials or not is yet to be determined

More broadly

Academic-led trial use is possible

Gain more experience in collaboration on complex matters

Engage with the EMA – Scientific Advice

Awareness of potential issues – GCP inspection

Goal

Illustrate it is possible for successful submission of academic-led trials

Ultimately aiming to create a CONSORT-style framework of points to consider

Future-Proofing Academic Clinical Trials To Adapt For Regulatory Use

Andrew Embleton

15-Feb-2019

Session 6 – Breakout Sessions

1. **Further development of Paediatric Strategy Forums**
   Andy Pearson, *ACCELERATE*
   Darshan Wariabharaj, *Janssen Research & Development*
2. **How to implement Mechanism of Action and Biology-driven Developments of Oncology Drugs for Children and Adolescents in the new Regulatory Environment?**
   Peter Adamson, *Children Hospital of Philadelphia*
   Patricia Blanc, *Imagine for Margo*
3. **How to strengthen International Cooperation?**
   Greg Reaman, *Food and Drug Administration*
   Nicole Scobie, *Zoé4life*
4. **Readdressing the Needs for long-term Follow-up**
   Mark Kieran, *Bristol-Myers Squibb*
   Danielle Horton Taylor, *Unite2Cure*
5. **Designing and conducting Investigator-initiated Clinical Trials of new Drugs to meet the regulatory Requirements for Approval by Health Authorities**
   Pam Kearns, *University of Birmingham*
   Elly Barry, *Pfizer*

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

BO 1 - Further development of Pediatric Strategy Forums (PSFs)

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BO 1: Further development of Pediatric Strategy Forums (PSFs)

Chairs: Andy Pearson and Darshan Wariabharaj

BO 1: Chairs Objectives

1. Facilitate break-out session
2. Level setting stakeholders on Paediatric Strategy Forums
   - What? Why? How?
   - Paediatric Strategy Forums - an evolutionary concept
3. Share chair's perspectives:
   1. From the inside
   2. From the outside
4. Stakeholder engagement
5. Deliverables
   - Feedback – further development of Paediatric Strategy Forums
6. Incorporate following (topics identified by conference participants):
   1. Better design of clinical trials to maximize chances of success and avoid predictable failure and unnecessary patient burden
   2. How to speed up evolution of frontline trials, and get new drugs into newly diagnosed?

BO 1: Paediatric Strategy Forums

- **ACCELERATE-EMA-FDA**
- Specific issue (Target or Disease)
- *Continually developing and adapting to needs*

- **Goal -** To ***share*** information between all stakeholders, in a pre-competitive setting, to ***inform*** paediatric drug development strategies and *subsequent* decisions

- **This will be achieved by** providing a unique opportunity to facilitate *dialogue* and enable constructive interactions between *all* stakeholders on ***topics*** *requiring discussion in drug development* in children and adolescents with malignancy

Informing NOT decision-making

BO 1: Paediatric Strategy Forums

- **First Forum** for ALK Inhibition in Paediatric Malignancies - EMA - January 2017 - 6 products; 5 companies
- **Second Forum** - Medicinal Product Development for Mature B cell Malignancies in Children - EMA - November 2017 - 20 products; 14 companies
- **Third Forum** - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies - EMA - September 2018 - 20 products; 16 companies (32 EOI)
- **Fourth Forum** - Medicinal Product Development for Acute Myeloid Leukaemia in Children - Rotterdam - 11-12 April 2019 28 products; 18 companies
- **Fifth Forum** - in US

BO 1: Paediatric Strategy Forums

European Journal of Cancer 110 (2019) 74–85

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

ACCELERATE and European Medicine Agency Paediatric Strategy Forum for medicinal product development for mature B-cell malignancies in children

Andrew D.J. Pearson [a,*,1], Nicole Scobie [b], Koenraad Norga [c], Franca Ligas [d], Davy Chiodin [e], Amos Burke [f], Veronique Minard-Colin [g], Peter Adamson [h], Lynley V. Marshall [i,am], Arun Balakumaran [j,2], Bouchra Benettaib [k], Pankaj Bhargava [l], Catherine M. Bollard [m], Ellen Bolotin [n], Simon Bomken [o], Jochen Buechner [p], Birgit Burkhardt [q], Hubert Caron [r], Christopher Copland [s], Pierre Demolis [t], Anton Egorov [u], Mahdi Farhan [v], Gerhard Zugmaier [w], Thomas Gross [x], Danielle Horton-Taylor [y], Wolfram Klapper [z], Giovanni Lesa [d], Robert Marcus [aa], Rodney R. Miles [ab], Kerri Nottage [ac], Lida Pacaud [ad], Rosanna Ricafort [ae], Martin Schrappe [af], Jaroslav Sterba [ag], Remus Vezan [ah], Susan Weiner [ai], Su Young Kim [aj], Gregory Reaman [ak], Gilles Vassal [al]

BO Session Outputs (1): Stakeholder Engagement How to move forward?

1. What works? What does not”? Learnings for future Forums e.g. formal feedback process?
2. Forum Steering Committee(s)/Stakeholder Gap Analysis: Goal International + Diverse
3. Forum Agenda - finding right balance: Data review vs discussion
4. Expand “pre forum preparatory work”:
   - Issue identification (including stakeholder alignment)
   - 1:1 phone calls with regulators, academics and industry
5. Ensure sustainability – Forum follow-up and/or Action Plan
6. Timely/Optimal communication(s)
   - Options beyond publishing in journal?
7. Process for deciding forum topics?

BO Session Outputs (2): Stakeholder Engagement Future Forum Topics?

8. Next Forum - early pediatric oncology development:
    - Optimal format/focus for influencing implementation of FDARA?
9. Other potential forum topics:
    - Disease Focused: High Grade Glioma
    - Target focused: DNA Repair, BET inhibitors, CSF1 inhibitors
10. Forums continually developing and adapting to needs:
    - Innovative Immunotherapies in pediatric oncology
    - Pediatric rare diseases – Registries/Real World Evidence
    - Pediatric master protocols – barriers to implementation

Let’s Discuss !!!!!!!!!!!!!!

BO 1: Paediatric Strategy Forums

European Journal of Cancer 110 (2019) 74–85

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

ACCELERATE and European Medicine Agency Paediatric Strategy Forum for medicinal product development for mature B-cell malignancies in children

Andrew D.J. Pearson [a,*,1], Nicole Scobie [b], Koenraad Norga [c], Franca Ligas [d], Davy Chiodin [e], Amos Burke [f], Veronique Minard-Colin [g], Peter Adamson [h], Lynley V. Marshall [i,am], Arun Balakumaran [j,2], Bouchra Benettaib [k], Pankaj Bhargava [l], Catherine M. Bollard [m], Ellen Bolotin [n], Simon Bomken [o], Jochen Buechner [p], Birgit Burkhardt [q], Hubert Caron [r], Christopher Copland [s], Pierre Demolis [t], Anton Egorov [u], Mahdi Farhan [v], Gerhard Zugmaier [w], Thomas Gross [x], Danielle Horton-Taylor [y], Wolfram Klapper [z], Giovanni Lesa [d], Robert Marcus [aa], Rodney R. Miles [ab], Kerri Nottage [ac], Lida Pacaud [ad], Rosanna Ricafort [ae], Martin Schrappe [af], Jaroslav Sterba [ag], Remus Vezan [ah], Susan Weiner [ai], Su Young Kim [aj], Gregory Reaman [ak], Gilles Vassal [al]

BO 1: Further development of Pediatric Strategy Forums (PSFs)

1. PFS strengths:

- 6 months planning (invite international experts; insights of collaborative groups; Industry participation condition (present data).
- Tone + culture: comfort zone for stakeholders; trust + common purpose; outputs

2. PSF outputs available as planning tools – for future PSFs (guide potential deliverables) – on ACCELERATE websites
3. PSF weakness – **inadequate time for discussion**
4. Institute democratic process for topic selection
5. Timely Forum follow-up: Efficient application of recommendations:

- Industry/Investigator/Academia alignment: Cleaning drug development landscape
- Modifications of PIPs e.g. BTK inhibitors

5. Future stakeholder participation: HTAs
6. Ensure topics are key issues are what US and EU ped oncologist want to discuss.
7. Future consideration: Need more Forums

BO 1: Further development of Pediatric Strategy Forums (PSFs)

1. 5th forum in US:

- Explore early paediatric oncology drug development (target list of FDA and preclinical testing program) – BET inhibitors

2. Disease PSFs:

- Really hard – pick disease biggest killers. Need alignment with cooperative groups to avoid redundancy
- Sarcomas, brain tumors

3. Tumor-agnostic approaches
4. Ped rare disease: registry; tissue collection; industry commitments; minimal data package for approval
5. PIPS: Shift from very specified detailed PIP to early stage development – evolutionary pip based on list of unmet medial needs
6. PSF in I-O space problematic due to lack of pre-clin testing program (no models).

BO 1: Paediatric Strategy Forums

- Fourth ACCELERATE - EMA – *FDA* Paediatric Strategy Forum - Medicinal Product Development for Acute Myeloid Leukaemia in Children
- 11 -12 April 2019 – Rotterdam
- FDA on Organising Committee
- Disease experts on Organising Committee
- Linking with Leukaemia Lymphoma Society
- Organising Committee

  ACCELERATE - Gilles Vassal, Andy Pearson

  EMA - Franca Ligas, Dominik Karres, Giovanni Lesa

  PDCO - Koen Norga

  FDA - Greg Reaman

  AML - Michel Zwaan, Andy Kolb, Henrik Hasle

BO 2 - How to implement Mechanism of Action and Biology-driven Developments of Oncology Drugs for Children and Adolescents in the new Regulatory Environment?

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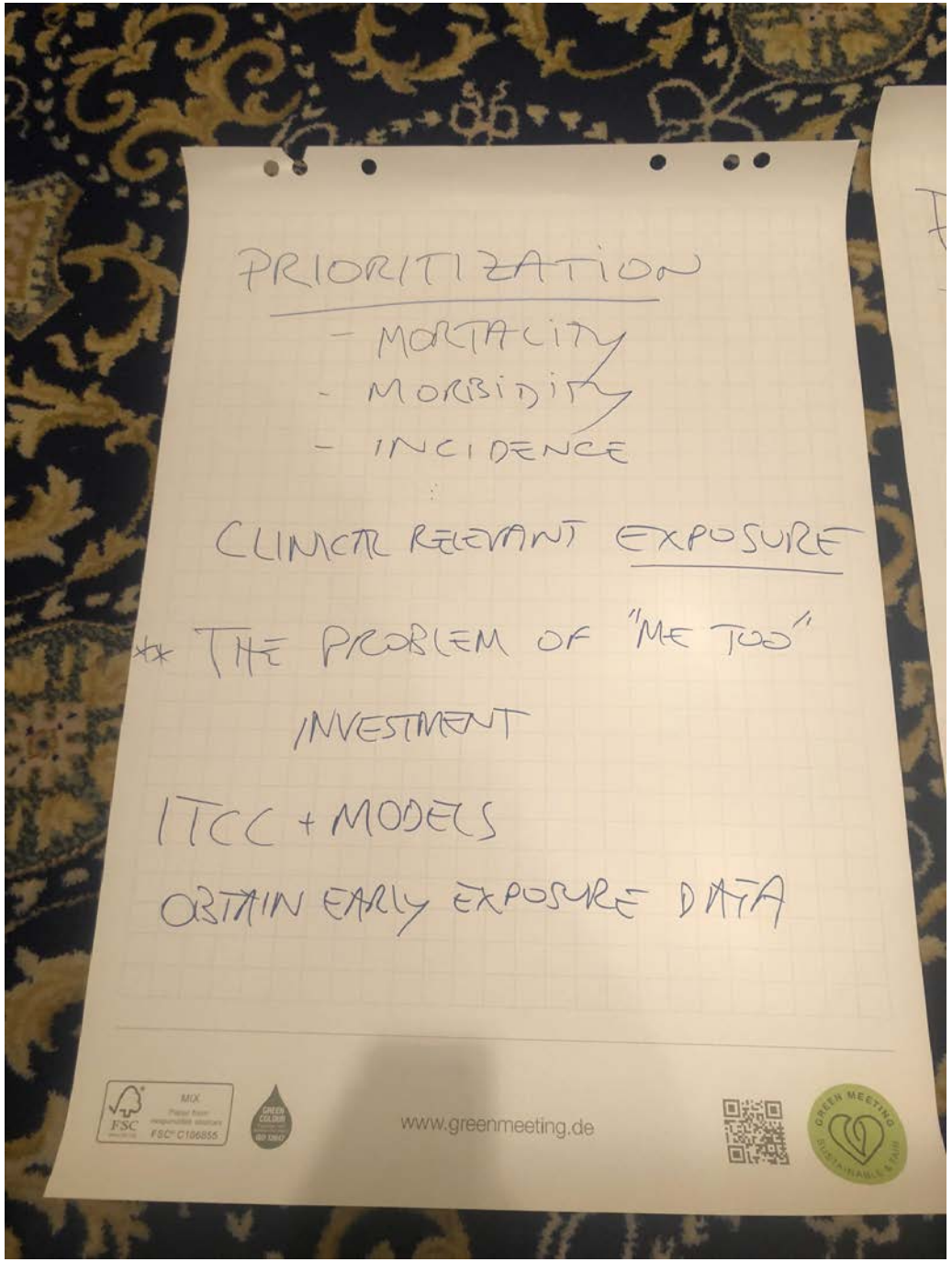

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INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

PRIORITIZATION

UNMET NEED?

RELEVANT TARGET

ME TOO vs INNOVATION

PHARMA - ACADEMIA PARTNERSHIPS

NOT INDUSTRY

ADVOCACY ROLE

www.greenmeeting.de

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

COORDINATION

SINGLE PLAN

HOW?

PARALLEL SUBMISSION

ALIGN TIMING

TWO SYSTEMS

APPROACH TO DIALOGUE

www.greenmeeting.de

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

BO 3 - How to Strengthen International Collaboration

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ACCELERATE

INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

How to Strengthen International Collaboration

Accelerate Conference

14/15 February 2019 Brussels, Belgium

Together, we can make a difference

WHY

- Childhood cancer is a global problem
- Small patient population(s) and getting smaller (biology, molecular subgroups)
- We all share some similar issues/problems but also have local differences
- Avoid duplication
- Advocacy → united voice is important
- To ACCELERATE!
- Widen access to treatment and information globally to save lives
- WHY NOT??

WHO

- EVERYONE!
- Also outside of the paediatric/oncology community
- Reach out to ‘other groups’ like ethics communities, HTAs, payers, policy makers, funders (government, private groups, small charities)
- Connecting high income and low-middle income countries

WHAT needs changing, WHAT do you want more of?

- Lack of harmonization
- Need an entity on an international level
- Streamline and modify regulatory requirements – create the environment to harmonize?
- Be open to new and different approaches
- Focus on paediatric-specific discovery without losing our ability to leverage adult discovery
- Facilitate efficiency in innovation process
- Create and expand a pre-competitive environment wherever and whenever possible

HOW (challenges, priorities)

- Think outside the box
- Get buy-in from key opinion leaders that this is a huge priority
- Learn from other disease types/models and industries
- The dream: create studies that satisfy multiple national regulatory requirements
- Define the players – identify influencers and roadblocks (legislators)
- As groups of advocates/parents/ funders DEMAND that this happens
- Ensure that stakeholders are transparent and specific about roadblocks so that advocates and campaigners have clear understanding of the issues
- Make patient level clinical and biological data available for free and open exploration – open source?
- Create systems to access publicly available data
- Capture compassionate use/n of 1 data? OR create platform trials to facilitate new drug development
- Create a position statement, white paper on importance of international collaboration
- Define priorities
- Regular communication – more opportunity for face-to-face meetings

SUMMARY

- Focus on the WHY
- HONESTY AND TRANSPARENCY BETWEEN STAKEHOLDERS IS KEY
- RECOMMENDATION – create a working group to deal with international collaboration which can meet outside of regular Accelerate meetings

BO 4 - Readdressing the need for long-term follow up

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Readdressing the need for long-term follow up

Danielle Horton-Taylor

Mark W. Kieran

Vision

Create an international data repository with ACCELERATE to collect information on long-term health in children who have received new modalities of anticancer treatment to facilitate an open sustainable resource to allow for the evaluation and optimization of follow up care

History of the long-term follow up committee

Lessons learned

- Focused
- Achievable

Path forward

Subcommittee formation

1) Infrastructure
2) Data
3) Sustainability
4) Governance

Timeline

Subcommittee output review in two months
Committee report in six months
Initiation of platform creation by the end of 2019

BO 5 - Designing and conducting Investigator-initiated Clinical Trials of new Drugs to meet the regulatory Requirements for Approval by Health Authorities

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Designing and conducting investigator-initiated clinical trials of new drugs to meet the regulatory requirements for approval by health authorities

Pamela Kearns, MD (University of Birmingham, UK)
Elly Barry, MD (Pfizer, Inc.)

Industry perspective: Advantages of Collaborating with Academic Groups and Utilizing Academic Study Data

- Collaboration with experts in the disease
  - Advance medicine/patient care in a meaningful way
  - Vast experience in pediatric oncology clinical research
- Access to networks of centers
  - Faster recruitment
  - Utilize existing research infrastructure
- Collaborators provide an informed perspective helpful in regulatory interactions
- Cost

Industry perspective: Challenges with Utilizing Academic Study Data

- Study design
  - Research objectives may not always align (e.g. endpoints, comparator arms)
- Timing
  - Sequencing of studies relative to regulatory submission timelines
- Less control of study time lines
- Operational/documentation challenges (next slide)
  - Particularly if the use of data for regulatory submissions was not foreseen prospectively
  - May be seen as burdensome by academic centers/cooperative groups

Industry perspective: Challenges with Utilizing Academic Study Data

- Operational:
  - Independent confirmation of tumor response, duration of response
  - Monitoring of data – how much?
  - Database specs (ICH part 11 compliance, audit trail)
  - Dataset transfer
    - Electronic vs. paper data
    - Data mapping can be time consuming, iterative…resource intensive for all

- Documentation to support regulatory dossier: ICH-compliant CSR
    - Collection of comprehensive AE and lab data, vitals, ECGs
    - Collection of drugs given, doses, interruptions on CRF pages
    - Development of a SAP to prospectively document all analyses planned
    - Financial disclosures
    - Investigator CVs
    - 1572s
    - Completed CRFs
    - Record of protocol deviations
    - GCP compliance/attestation

Questions discussed
How to better bridge data from academic trials to regulatory submissions?

- When should a study be industry-sponsored vs. academic group sponsored?
  - What are the real and perceived differences?
- Do regulators view data generated by academic investigators differently than industry-sponsored studies?
  - What are the barriers to using academic trial data for regulatory submissions?
- How can pharma better assist/provide support?
  - What should the partnership look like ?

Fit for Filing WG

Aim:

To develop best principles on how the design and deliver a trial with a dataset that can be included in a package for filing

- Define the barriers and propose solutions to ensure academic trial datasets are usable for regulatory submissions?
- Define how industry can pharma support academic/healthcare institutions to deliver fit for filing trials?

Fit for Filing WG

Tasks

- Produce best principles guidelines including
  - Defining elements of a data package for filing
  - Defining roles and responsibilities in collaborative studies
- Develop a education programme to support investigators and academic sponsors understand the needs for ‘fit for filing ‘ trials
- Define the resource needs to operationalise and deliver these types of trials

But before…group picture outside the hotel!

See you at 11h00!

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See you at 13h45!

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Session 7 – Wrap-up and 2019 Action Plan

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Defining the 2019 ACCELERATE Action Plan

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Conclusions

Gilles Vassal, *ACCELERATE Chair*

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Thank you for participating
and
see you on 6th and 7th of February 2019 in Brussels!

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7TH ACCELERATE PAEDIATRIC ONCOLOGY CONFERENCE

14-15 FEBRUARY 2019 | BRUSSELS, BELGIUM

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