ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Fostering Age Inclusive Research (FAIR) Trials for Adolescents and Young Adults

Beate Wulff
F. Hoffmann-La Roche, Ltd.
Ethics Committee Medical Faculty University Duisburg-Essen

ANDREW McDONOUGH B+ FOUNDATION

Why FAIR trials

- Research into teenage and young adults` cancer has made slower progress than for any other age group
- Enrollment of adolescents with cancer in clinical trials is much lower that of pediatric patients
- Many clinical trials exclude patients below 18 yrs of age - without medical justification
- For adolescents with “adult-type” cancers, lack of access to relevant trials
- To confront this problem, the Working Group on Fostering Age Inclusive Research (or FAIR Trials) was established in 2017 by the ACCELERATE Forum

Scientific rationale and medical justification

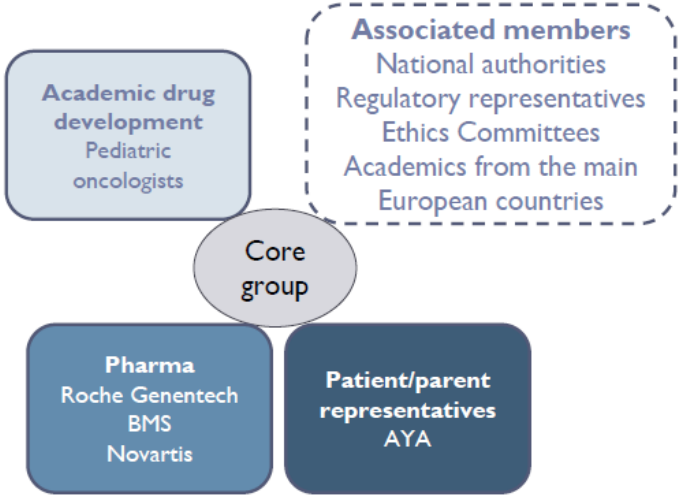
- Similarity of the target disease in adults and adolescents
- Similarity of pharmacokinetics of drugs and therapeutic proteins between adolescents and adults - FDA review of 2013 observed clearance in adolescents averaged 88.6% and 95.1% of the adult clearance for the IV and PO administered drugs
- Adolescents doses may be able to be derived using adult data
- Similarity in safety and tolerabilitty profiles in adults and adolescents

⇒ It can be recommended to include adolescents (ages 12-17) in disease- and target-appropriate adult oncology trials (FDA, EMA, EFGCP)

FAIR Trials Working Group

https://www.accelerate-platform.org/fair-trials/

Fostering Age Inclusive Research



- Raise Awareness
- Gain Endorsement
- Identify Successful Trials
- Develop Tools for Colleagues and Supporters

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ACCELERATE trial strategy for adolescents and young adults

Situations	Solutions	
Similar targets present across the age spectrum	To include adolescents from 12 years in adult phase-I trials	To facilitate regulatory authorization of a given cancer drug for adolescents from 12 years at the same time as adult authorisation
Disease similar in adult and paediatric population e.g. bone sarcoma, Hodgkin disease	To include both paediatric and adult population from phase-II to phase-III trials	
Adult disease rarely present in adolescents e.g. carcinoma, melanoma	To include adolescents from 12 years in adult phase-I to -III trials	
Paediatric disease rarely present in the adult population e.g. medulloblastoma	To include adult patients in paediatric phase-I to -III trials	

Regulatory supports

https://www.accelerate-platform.org/fair-trials/

- Why FAIR trials?
- Multistakeholder supports to FAIR Trial Initiative
- Paediatric and Medical Oncologists
- Patient and Parent advocates
- Industry
- Regulatory

2021 EMA Practical Guidance for industry …

2021 EFGCP Practical Guidance

FDA guidance

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

2019 N-02-RONCAMCE

Clinical Cancer Research

FDA

Enrolling Adolescents in Disease/Target-Appropriate Adult Oncology Clinical Trials of Investigational Agents

Meredith M. Clark*, Jack Mulqueen*, Michelle Roth-Cline*, Nitin Mehrotra*, and Gregory H. Reaman*

we recommend that sponsors consider the inclusion of adolescents [ages 12–17] in disease- and/or target-appropriate adult oncology clinical trials at all stages of development.

ASCO

JOURNAL OF CLINICAL ONCOLOGY

Modernizing Clinical Trial Eligibility: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Minimum Age Working Group

Automatic inclusion of pediatric patients is appropriate in early-phase trials that assess dose, safety, and pharmacokinetics in a variety of tumor types and later phase trials that assess efficacy in a specific disease that spans adult and pediatric populations.

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)

March 2019
Clinical/Medical

EMA letter of support

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2019
EMA/180203/2019
European Medicines Agency
Human Medicines Research and Development Support Division
Paediatric Medicines Office

Prof Gilles Vassal
Chair of Accelerate and President of Innovative Therapies for Children with Cancer in Europe (ITCC)
(Gilles.Vassal@gustaveroussy.fr)

Dr Nathalie Gaspar and Chris Copland (Nathalie.GASPAR@gustaveroussy.fr and chriscopilandatywork@gmail.com)
Co-Chairs of the Accelerate Working Group – Fostering Age Inclusive Research (FAIR)

Dear Dr Gaspar, Professor Vassal and Mr Copland

Ref: Foster Age-Inclusive Research

The EMA and its Paediatric Committee (PDCO) follow closely and with great interest the Accelerate's FAIR (Foster Age-Inclusive Research) initiative, aiming to facilitate timely access of novel therapies for children with cancer. In this respect the EMA and PDCO took also note of the FDA's Draft Guidance for Industry on "Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials" (published in June 2018).

The PDCO reviews Paediatric Investigation Plans (PIPs) for medicines for treatment of children with cancer, as mandated by the EU Paediatric Regulation. With the goal of fostering timely studies in the paediatric population, we generally request early initiation of studies in adolescents, either by inclusion of adolescents in adult trials or by conduct of an adolescent trial in parallel to the adult program, whenever this is scientifically justified. Of course, PIPs are evaluated on a case-by-case basis and thus this strategy is not universally applicable.

Of note, this principle has already been applied and used by the PDCO on a regular basis in discussions during the evaluation of PIPs for paediatric oncology.

Furthermore, the EMA values collaboration and interaction with other medicine regulatory bodies and commits to enhance established frameworks for collaboration with the U.S. FDA's Oncology Centre of Excellence Pediatric Oncology Program, as agreed in the "EMA-EC action plan on paediatrics" published in October 2018, to strengthen collaboration globally on this matter.

We sincerely appreciate your efforts and hope we can all continue to work together to improve the development of medicines for children with cancer.

Kind regards

On behalf of the Paediatric Committee

Dr Dirk Mentzer
Chairman of the Paediatric Committee at the EMA

cc EMA: Dr Enrica Atteri, Dr Ralph Rex

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An agency of the European Union

EFGCP letter of support

EF GCP
where science and ethics meet

29 March 2019

All –

I am very pleased to re-connect and provide an update on activities that have transpired in follow-up to the European Forum for Good Clinical Practice (EFGCP) **'Facilitating Adolescent Inclusion in Adult Research' Kick-Off Meeting** held in October 2018.

On 18 February 2019, the EFGCP Board endorsed the following 'Position Statement' related to adolescent inclusion:

As part of the responsibility to provide better medicines for children, the EFGCP strongly recommends:

- *That researchers, regulators, and members of ethics committees weigh the totality of physiologic, pathologic, and other disease specific evidence to consider adolescent inclusion in adult research and vice versa – young adults as an extension population in paediatric/adolescent studies - when relevant as a trial methodology to facilitate earlier access to investigational and approved medicines for adolescent patients.*

It is our expectation that this statement can be of immediate use to you and the broader pediatric research community when engaging other researchers, regulators, and ethics committees.

In addition, the Children's Medicines Working Party (CMWP) of the EFGCP has completed an analysis of the feedback from the Kick-Off Meeting and has identified 4 priority projects intended to generate meaningful information to be used in further support of this position. The identified priorities include:

1. Meta-analysis for publication on the experience of hybrid trials (adult and adolescents), existing guidance in the EU, and impact on product registration(s)
2. Retrospective analysis of the executed EU paediatric investigation plans (PIPs) to analyze algorithms to identify scenarios where similar safety/efficacy data among adolescents and adults may be used as part of the development considerations for similar mechanisms of action
3. International alignment of approach to facilitate global acceptance of adolescent inclusion in adult research
4. Define pre-requisites/minimum requirements/key criteria for risk-benefit evaluation to support inclusion of adolescents in adult studies (general vs. indication-specific)

To facilitate discussion and accomplish these priorities, the CMWP respectfully requests your continued engagement. **If you or your organization would like to collaborate with us on these priorities, please reply to this communication by EOB (CET) Monday, 08 April 2019**. Upon receipt of affirmative replies, we will provide a Doodle poll of availability to schedule the first planning call.

Thank You for your continued commitment to children. On behalf of the EFGCP CMWP, we look forward to collaborating with you on these next steps!

Warm regards –

Christina Bucci-Rechtweg, MD (on behalf of the EFGCP CMWP)

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Industry support

https://www.accelerate-platform.org/fair-trials/

- Why FAIR trials?
- Multistakeholder supports to FAIR Trial Initiative
  - Paediatric and Medical Oncologists
  - Patient and Parent advocates
  - Industry
  - Regulatory

Industry organisation letter of support

Biotechnology Innovation Organization

EUCOPE European Confederation of Pharmaceutical Entrepreneurs AISBL

efpia European Federation of Pharmaceutical Industries and Associations

June 19, 2020

EuropaBio

PhRMA RESEARCH · PROGRESS · HOPE

- Professor Gilles Vassal, ACCELERATE Chair and Innovative Therapies for Children with Cancer in Europe (ITCC) President
- Dr. Nathalie Gaspar, ACCELERATE Fostering Age Inclusive Research (FAIR) Working Group Co-Chair
- Chris Copland, ACCELERATE Fostering Age Inclusive Research (FAIR) Working Group Co-Chair

RE: Fostering Age-Inclusive Research (FAIR) Trials Initiative

Dear Professor Vassal, Dr. Gaspar, and Mr. Copland,

The Biotechnology Innovation Organization (BIO), European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), European Federation of Pharmaceutical Industries and Associations (EFPIA), EuropaBio – the EuropaBio Association of Bioindustries, the Pharmaceutical Research Manufacturers of America (PhRMA), and our members recognise and value the efforts led by the ACCELERATE'S FAIR Initiative. With the goal of facilitating timely access to novel therapies for children with cancer, we see the FAIR Initiative as an important step to encourage researchers, regulators, ethics committees, and health technology assessment bodies to support and consider the systematic inclusion of adolescents (i.e., individuals from 12 to below 18 years of age), in oncology studies based on the benefit-risk profile of a product, when scientifically, ethically justified and feasible.

Together the Biotechnology Innovation Organization (BIO), European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), European Federation of Pharmaceutical Industries and Associations (EFPIA), EuropaBio – the EuropaBio Association of Bioindustries, Pharmaceutical Research Manufacturers of America (PhRMA), representing the world's leading biotechnology and biopharmaceutical companies and related organisations, we want to bring innovative treatments to all patients that need them and encourage researchers, regulators, ethics committees, and health technology assessment bodies to recognise the use of flexible and practical innovative approaches so that new medicines can reach patients as soon as possible. We encourage an open dialogue between authoritative bodies and companies on timely development strategies for paediatric populations (e.g. inclusion of adolescents in adult studies, or conducting adolescent studies concurrent to adult studies, where scientifically and ethically justified and feasible).

We do appreciate the efforts led by the FAIR Initiative and hope to continue to partner with ACCELERATE to speed up the delivery of innovative therapies to children and adolescents.

Yours sincerely,

E. Cartier Esham, Ph.D.
Executive Vice President, Emerging Companies
Senior Vice President, Science and Regulatory
Biotechnology Innovation Organization (BIO)

Magda Chlebus
Executive Director
Science policy & Regulatory Affairs
EFPIA

Alexander Natz
EUCOPE Secretary General

Chief Medical Officer and Executive Vice President, Science and Regulatory Advocacy
PhRMA

Bernard Grimm
Healthcare Director
EuropaBio

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Patient and Parent advocates

https://www.accelerate-platform.org/fair-trials/

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  - Regulatory

Patient and Parent advocates

Fostering Age Inclusive Research (FAIR) Trials for Adolescents & Young Adults

Patient and parent advocates play a fundamental role for the success of the FAIR trials initiative. Please find below some useful links.

- The patient voice – Clinical trials for adolescents and young adults – video (Institut Gustave Roussy)
- The power of the personal story in spreading our message – article by Debbie Binner
- Mixed media: Childhood and Adolescent Cancer in the UK Press by Max Williamson (09-07-2018)
- Unite2cure fully supports the ACCELERATE FAIR trials initiative – article by Patricia Blanc (Unite2Cure)

"Personally, I have witnessed how devastating it can be for a teenager to receive the news that they can't be helped because they don't meet an age inclusion criteria. A friend of mine, who was diagnosed with rhabdomyosarcoma and was just a few months away from being 18 years old, was denied access to a clinical trial because of his age. I am thrilled to be part of this initiative as a patient advocate and I wish to help shape the dialogue and raise awareness on this very important issue, hoping to encourage the different stakeholders to recognise how not only patients but also the medical and research community can benefit from this more inclusive approach." - **Mariana Coutinho, Portugal**

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FAIR Group Action Points

Increase awareness of tools or information supporting inclusion of AYA patients

helps to

- 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

FAIR for AYA STAMP

https://www.accelerate-platform.org/fair-trials/

- Why FAIR trials?
- Multistakeholder supports to FAIR Trial Initiative
- Early Drug Development for Adolescents: Oncology Protocols Survey
- Resources
  - FAIR Investigations/ Sponsor Toolkit
  - FAIR for AYA Stamp
  - E-learning tools
- Publications
- Who we are

FAIR for AYA Stamp

Fostering Age Inclusive Research (FAIR) Trials for Adolescents & Young Adults

FAIR FOR AYA ACCELERATE

FAIR for AYA STAMP offered for **trials** which actively avoid unnecessary barriers based on age

Structure of confidentiality set up

The First three STAMPS

- Roche: TAPISTRY (Phase II)
- Eli Lilly/Loxo Oncology: LIBRETTO-001 (Phase I –II)
- Eli Lilly and Cie: LIBRETTO-531 (Phase III)

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Germany

Representatives of the German FAIR trial group

Paediatric Oncologist
involved in early drug development

Cornelis van Tilburg, KiTZ Heidelberg
Beate Wulff, EC Essen

- 07/2018: set up of German FAIR special interest group (paed/adult oncologists, parent representative, project manager) including an overall action plan
- 09/2018: preliminary identification of early phase centers pediatric/adult collaboration
- 10/2018: endorsement of German FAIR group by GPOH chairman group

Medical Oncologist
involved in early drug development

Stefan Fröhling NCT Heidelberg

- Identification/contact the adult phase I/II units
- Further actions in collaboration with paediatric oncologists, parent representative

Sites that are able to perform early phase trials in both adult and pediatric oncology

Germany

In total N=58

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

ITCC centres: N=9

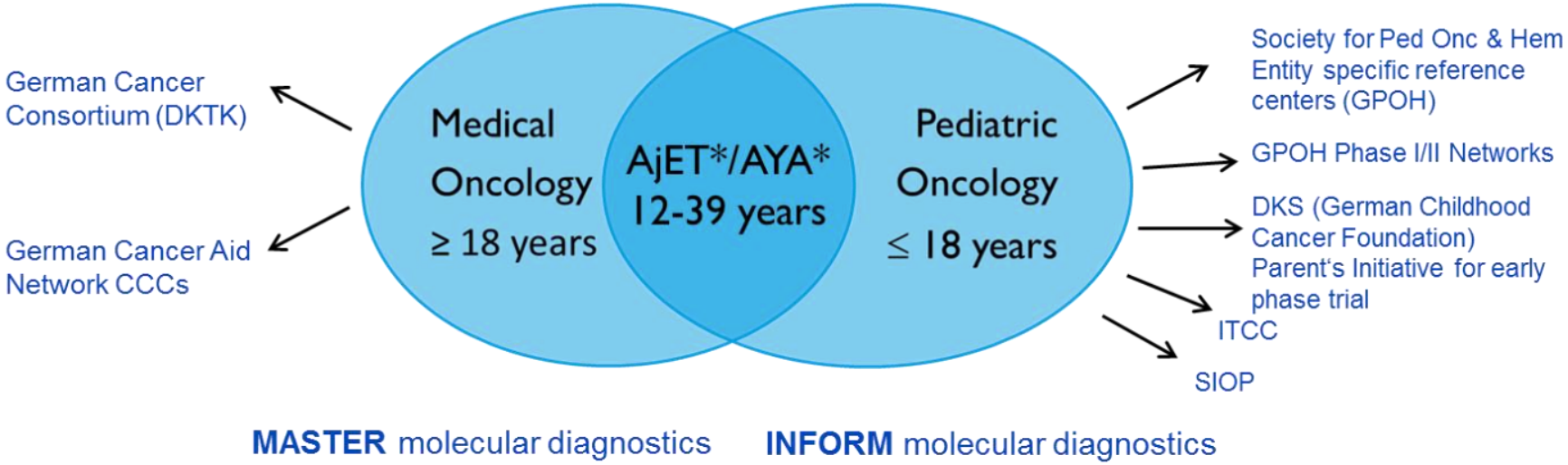
Non ITCC centres N= 49

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

Phase I/II Pediatric and Adults
ITCC Centers

Early phase centers Pediatric+/-Adult Oncology Germany – Preliminary Overview 2019

German Network and Collaboration for FAIR



*AjET adolescents, young adult and transition, AYA adolescents and young adults

What are the hurdles to including adolescents in joint adolescent/adult trials?

A. Limited incidence of the condition in the 12-17 age range
B. Competition for the same patients population (12-17 years of age) from another clinical trial
C. Absence of a pediatric sub-investigator
D. The study protocol was approved in certain institutions/countries only for 18 years old and above
E. No appropriate referral network in place to enable enrollment of adolescents
F. Absence of a pediatric ward or AYA (adolescents young adults) ward/center open for accrual
G. Operational reasons (which one?)

TAPISTRY:

‘Tumor-agnostic precision immuno-oncology and somatic targeting rationale for you - A phase II platform trial’

TAPISTRY

FAIR FOR AYA ACCELERATE

Enrollment via local high quality NGS testing

Central Lab samples required

No minimum - no maximum number of pediatric patients planned for any of the cohorts

ROS1 fusion-positive	✓ Cohort A **Entrectinib**	0+	Solid tumors **including** CNS
NTRK1/2/3 fusion-positive	✓ Cohort B **Entrectinib**	0+	Solid tumors **including** CNS
ALK fusion-positive	✗ Cohort C **Alectinib**		
TMB-high	✓ Cohort D **Atezolizumab**	0+	Solid tumors **including** CNS
AKT1/2/3 mutation positive	✓ Cohort E **Ipatasertib**	≥ 12	Solid tumors - CNS excluded
HER2 mutation positive	✓ Cohort F **Trastuzumab Emtansine**	≥ 12	Solid tumors - CNS excluded
MDM2-amplified, *TP53* wild-type	✗ Cohort G **Idasanutlin**		
PIK3CA multiple mutation-positive	✓ Cohort H **Inavolisib (GDC-0077)**	≥ 12	Solid tumors - CNS excluded
BRAF fusion-positive and mutation positive	✓ Cohort I & J **Belvarafenib**	≥ 12	Solid tumors **including** CNS
RET fusion-positive	✓ Cohort K **Pralsetinib**	≥ 12	Solid tumors **including** CNS

TAPISTRY

A global and extensive pediatric footprint

KEY

- Pediatrics only (n= 21)
- Hybrid (n= 36)

Summary, perspectives - How Ethics Committees could help

- Scientific rationale and medical justification support the inclusion of adolescents (ages 12-17) in disease- and target-appropriate adult oncology trials
- This approach can be expanded to all age groups and to other disease areas
- Age inclusive trials allow earlier access to innovative drugs for children, adolescents and young adults
- Earlier information on safety and efficacy will inform the overall clinical development plan for children and has opportunity to earlier drug approval
- Awareness, knowledge sharing and multistakeholder support are instrumental to promote these activities