IMPROVING AYA ACCESS TO INNOVATIVE THERAPIES BY BREAKING THE 18 YEARS DOGMA

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THE CURRENT LANDSCAPE AN URGENT NEED IN NEW DRUGS FOR ADOLESCENTS AND YOUNG ADULTS

Rare disease

Wide range of histologies
from paediatric type to adult type cancers
and cancer with a peak incidence at adolescence

TYA 15-24 years in Europe
~20,000 new cases per year


Cancer is the third cause of death in the adolescents and young adults

Persistent problems for AYA survival
Acute leukaemia, soft tissue and bone sarcoma, some brain tumours
Some metastatic or relapsing cancer forms

Cancer in Adolescents and Young Adults (AYA) Working Group
INCLUSION OF AYA IN THERAPEUTIC TRIALS MIGHT IMPROVE SURVIVAL OF AYA WITH CANCER

Lower AYA survival gains over years paralleled under-representation of AYA in therapeutic trials

Mean = 1.5% / year

Access to innovative therapies might improve AYA survival (e.g. imatinib plus chemotherapy in Philadelphia chromosome-positive acute lymphoid leukaemia more often seen in AYA)


AYA INCLUSION RATES ARE HIGHER IN AYA DISEASES WHERE JOINT PAEDIATRIC/ADULT PHASE III TRIALS ARE AVAILABLE

Good example: Bone sarcomas (osteosarcomas and Ewing sarcomas)

Efforts to reach a consensus for JOINT paediatric/adult phase III trial is ongoing in germ cell tumours, rhabdomyosarcoma while more discussion is required in lymphomas and soft tissue sarcomas
INAPPROPRIATE AGE INCLUSION CRITERIA IN RELAPSE PHASE II TRIALS BY INSUFFICIENT AYA ACCESS TO NEW DRUGS

Age inclusion criteria in osteosarcoma phase II trials 2003-2014

Osteosarcoma

Cancer epidemiology in older adolescents and young adults 15 to 29 years of age including SEER incidence and survival 1975-2000

Only 30% of phase II trial was age adapted to osteosarcoma relapse epidemiology (Worse for targeted therapies than for chemotherapeutic agents)

One alleged cause is the absence of available paediatric recommended dose issued from paediatric phase 1 trial


Cancer in Adolescents and Young Adults (AYA) Working Group
THE CURRENT LANDSCAPE

Early drug development for adolescents and young adults

The impressive progress recently observed in adult cancers through the introduction of new drugs has not yet been translated to adolescents 12–17 years of age [defined according to the International Conference on Harmonization (ICH) E11].

The current drug development landscape separates adult and paediatric drug development (see next slide). Adolescents are grouped with children, leading to a mismatch with a lack of trials for adolescents with relapsed cancer and delayed access to new, effective drugs already available for adults.
EUROPEAN REGULATION AND CURRENT LANDSCAPE IN NEW EARLY DRUG DEVELOPMENT FOR ADOLESCENTS

Table 1. European regulation and current drug development landscape for adolescents

European regulation
- The Regulation mandated the establishment of the European Medicines Agency (EMA)’s Paediatric Committee (PDCO), coordinating the Agency’s work on the development of medicines for children and agreeing to the studies that pharmaceutical companies must carry out as part of Paediatric Investigation Plans (PIPs).
- The Regulation comprises a system of requirements, obligations, incentives and rewards for completed PIPs, and also waivers and deferrals which provide the framework for either obviating or postponing the institution or completion of studies in some or all of the paediatric population (age < 18 years).
- The Clinical Trials Regulation (EU) No 536/2014 has further improved the environment for clinical research in the paediatric population, now legally recognising their assent or agreement to clinical trial participation at the European level [25]. This is amongst other provisions to facilitate international research and to ensure quicker access to new, innovative treatments [26].

Consequences on current drug development landscape for adolescents
- The possibility for PIP requirements beyond studies proposed by companies is limited by the adult condition (cancer type), and cannot be mandated on the basis of the drug’s-MoA. However, as PIPs must specify how research and development is done in patients from all age cohorts < 18 years, sponsors usually include adolescents 12–17 years in paediatric separate studies, rather than including them in relevant adult trials (which cannot be mandated). Adult studies generally recruit patients ≥ 18 years, while paediatric studies often cease recruitment at 18–21 years.
- As paediatric studies generally start later than studies in adults, there are delays in evaluating new drugs for adolescents, and adult patients with ‘typical paediatric cancers’ are not included in disease-specific ‘paediatric’ trials. Such studies can be proposed by companies, and some have been agreed as part of PIPs (e.g. larotrectinib in an osteosarcoma phase II trial, NCT02432274), while others are executed without being part of a PIP (e.g. ruxolitinib phase III trial in GVHD, NCT02913261).

The European Paediatric Medicine Regulation [(EC)-No1901/2006)] has dramatically improved the European regulatory environment for the development of paediatric medicines in the EU and has had an international impact [27].

In some cancer types with identical drug targets in the paediatric and adult populations, adult phase II trials have demonstrated efficacy, but paediatric clinical development commenced much later:

- **Significantly delayed introduction of beneficial drugs to adolescents**

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**Brentuximab vedotin**

- Adult Phase I trial ≥ 18 years
  - Relapsed or refractory CD30 positive HL
  - NCT00430846
  - Published Nov 2011

- **Approved for adult relapsed or refractory HL (2012)**

- **Successful trial of BV + Chemotherapy in Adults Stage II-IV HIV- HL, first line TT**
  - NCT01771107
  - March 2013- 2017

- **Approved by FDA for front line tt of high risk HL (2018)**

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**Paediatric Phase-I/II trial of BV < 18 years for R/R HL NCT01492088**

Randomized Phase 3 Study of BV for Newly Diagnosed High-Risk HL in Children and Young Adults (<21 y)

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**TYA disease**

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**Cancer in Adolescents and Young Adults (AYA) Working Group**

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NON-VIABLE ADOLESCENT SPECIFIC TRIALS IN ADULT DISEASE RARELY PRESENT IN ADOLESCENTS E.G. MELANOMA

In diseases too rare in adolescents to allow completion of paediatric trials within a reasonable timeframe, even with worldwide accrual over several years, a very low (but not non-existent) incidence of a condition in adolescents has triggered the regulatory requirement for an adolescent study, while waivers have been granted, based on the absence of the condition, for studies in children < 12 years.

- ‘Unfeasible’ adolescent-specific phase I/II trials, using a drug already demonstrated effective in adults with the same disease

Vemurafenib
- Approved for adult melanoma V600E
- PDCO request for Melanoma V600E trial for 12-18 years

Recruiting
BRIM-P: A Study of Vemurafenib in Pediatric Patients With Stage IIIIC or Stage IV Melanoma Harboring BRAFV600 Mutations

Condition: Malignant Melanoma
Intervention: Drug: vemurafenib

- Unsufficient accrual worldwide
- Drug prescribed off label to ado with no data collected
- Adult studies: combination of Vemurafenib with MEK inhibitors = better therapeutic option than single agent Vemurafenib

Ipilimumab, Same story
- Paediatric trial prematurely closed
- Standard care in adult are the combinations*

OFF-LABEL USE IN ADOLESCENTS OF NEW EFFICIENT DRUGS APPROVED IN ADULT INDICATIONS

Efficient drug in adult phase I/II trial in a same disease present in adolescent + Delayed paediatric trial

Off-label use of the drug with an already marketed authorisation in adults

No Protection of the adolescents through the research

No data collection in the adolescent population on safety, efficacy, and biology
For marketing authorisation in this population

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LOSS OF BIOLOGICAL INFORMATION FOR THE ADOLESCENTS AND THE DRUG ACTION/RESISTANCE
E.g. medulloblastoma, SHH pathway inhibitor

No efficacy of SHH inhibitors if TP53 mutation presents
Mutations are age-dependant
=> The drug development can not be done in adults only

Vismodegib

Adult Phase-I trial ≥ 18 years
NCT00607724
run 01/2007-12/2008
Response in a 26y-old MB
Published Nov 2010

Adult Phase-II
NCT00939484
ended in Dec 2012
Published 2015

Paed Phase-I trial 3-21 years
NCT00822458
01/2009-09/2013
Published 2013

Paed Phase-II
NCT01239316
ended in March 2015
Published 2015

Good example of joint development from early phase trial

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YOUNG ADULTS MIGHT BENEFIT OF DISEASE-SPECIFIC ‘PAEDIATRIC’ PHASE 1 TO 3 TRIALS

When they suffer from paediatric cancer

Paediatric inspired protocols might increase AYA but also older adult survival (e.g. leukaemia)\(^1\)

Such studies can be proposed by companies and there are concrete examples where such studies have been agreed as part of PIPs (e.g. lenvatinib in an osteosarcoma phase II trial, NCT02432274), and others executed without being part of a PIP (e.g. ruxolitinib phase III trial in GVHD, NCT02913261)\(^2\)

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**Crizotinib**
- Approved only for adult NSCLC with either ALK or ROS fusion
- Waiver below 18 years as NSCLC does not exist in children
- No authorisation in ALCL with NPM-ALK fusion while Crizotinib is efficient in this rare AYA disease

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**ALCL an AYA disease**

<table>
<thead>
<tr>
<th>Age at Diagnosis (Years)</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-19</td>
<td>100</td>
</tr>
<tr>
<td>20-24</td>
<td>200</td>
</tr>
<tr>
<td>25-29</td>
<td>300</td>
</tr>
</tbody>
</table>

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**Huge efficacy of crizotinib in ALCL**

- Crizotinibb 165mg/m²/d ORR 83%  
- Crizotinibb 280mg/m²/d ORR 90%  


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A paediatric Phase 3 trial of ALK inhibitors in ALCL is in discussion with pharma. Inclusion criteria are intended to include young adult up to 25 years to match the epidemiology of the disease.

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HOW TO CHANGE THE CURRENT LANDSCAPE?
A rational, rapid and safe solution
To include adolescents in « adults » trials from early phases (phase I/II)

A rational approach to drug development based on the mechanism of action (MoA) of the drug, the therapeutic need and disease epidemiology in adolescents; and similarity between adolescents and adults disease, physiology and drug exposure.

Enrolment of adolescents of 12 years and over in adult early phase clinical drug trials, even in phase I first-in-human trials, may represent a safe and more efficient alternative compared with the current unsatisfactory situation.

This approach is complementary to existing paediatric and adult drug development approaches and should not replace, or delay them; it rather increases opportunities for adolescents to be included in early-phase trials.
TO INCLUDE ADOLESCENTS IN « ADULTS » TRIALS FROM EARLY PHASE (PHASE I/II)

An agreement of all multi-stakeholders involved in early drug development in Europe

Joint adolescent–adult early phase clinical trials to improve access to new drugs for adolescents with cancer: proposals from the multi-stakeholder platform—ACCELERATE


Published: 16 January 2018


Cancer in Adolescents and Young Adults (AYA) Working Group
NO INCREASED RISK FOR ADOLESCENTS COMPARED TO ADULTS

Under cover of pharmacokinetic assessment in the adolescent population

*In vitro* and *in vivo* studies have shown that most elimination pathways are mature and reach adult levels by the age of 12 years¹

Clearance of drugs and many therapeutic proteins have been shown to be similar between adolescents and adults once the effect of body size on pharmacokinetics is taken into account²

The nearly identical doses in patients aged 12 to 17 and adults provide a scientific rationale and biologic justification from a pharmacokinetics perspective that adolescents aged 12 to 17 can be included in selected adult trials³

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NO INCREASED RISK FOR ADOLESCENTS COMPARED TO ADULTS

Similar paediatric and adult phase I trial parameters and acute toxicities – For chemotherapeutic agents, targeted therapies and immunotherapies

Maximal tolerated dose (MTD)
Paediatric MTD strongly correlated to adult MTD
- Either for cytotoxic agents: paediatric MTD = 70-160% of adult MTD in 75% of the trials
- And molecular targeted agents: Paediatric RPIID = 90-130% of the BSA-adjusted approved dose in adults for 70% of the trials and 75% of compounds

Pharmacokinetic
High plasma drug clearance correlation in children and adults (r 0.97)
Median ratio paediatric/adult clearance = 0.95 (range 0.06-2.2)

Acute toxicity profiles
Toxicities types experienced by children enrolled into phase I trials were, with few exceptions, the same as those experienced by adult patients
- Either with cytotoxic agents
- Or with molecular targeted agents

NO LEGAL ISSUE AT EUROPEAN LEVEL

Either to include adolescents in adult trial or young adult population in PIP trial. Joint paediatric /adult trials can be considered…

... If the prerequisites to protect children in research are respected

European Paediatric Medicine Regulation [(EC) No 1901/2006)] on 26 /01/2007: objective of ‘improving the health of children in Europe by facilitating the development and availability of medicines for children (between birth and 18 years)

International ICH E11 guideline for the conduct of paediatric clinical trials updated in 2016: recommendation to initiate paediatric studies with medicines that may represent an important advance in treatment for serious and life-threatening diseases with limited treatment options, earlier in the medicine’s development

Clinical Trials Regulation (EU) No 536/2014, legally recognising adolescent assent or agreement to clinical trial participation at the European level.

... In Paediatric Investigation Plan (PIP) proposals

PIPs define datasets to be submitted and although in most cases specific trials are proposed, the data may be collected in different ways (e.g. data from adolescent patients included within adult trials, despite the fact that the adult trial could not be changed by the PDCO, as agreeing adult trials is beyond the remit of the PDCO and the trial is often underway/advanced by the time the PIP is submitted/under consideration).
Efficacy in adolescents cannot be fully extrapolated from adult data, including for:
- A same disease
- A similar therapeutic target

Distinct gene expression patterns between adult and paediatric tumours of the same histology


No legal issue at European level to include adolescents in adult trial

1. A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:
   (f) the clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;
   (g) there are scientific grounds for expecting that participation in the clinical trial will produce:
      (i) a direct benefit for the minor concerned outweighing the risks and burdens involved; or
      (ii) some benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor’s condition.

Possible benefit for younger children

Adolescent inclusion in early adult trials might give signal of activity in paediatric cancers usually not included in adult trials.

Expected individual benefit

For these adolescents with severe and life-threatening disease without cure hope.


NO ARBITRARY AGE LIMIT IN CLINICAL TRIALS

A concept already integrated in the health care policy of some countries …

*Panel: Statements in regulatory and health-care policies about age eligibility*

- **UK Cancer Reform Strategy**
  “The use of age as an exclusion criterion in cancer clinical trials is avoided wherever possible”

- **Japanese Health Policy Bureau**
  “It is inappropriate to establish an arbitrary age limitation in clinical trial protocols”

- **US FDA guideline for industry**
  “Protocols should not ordinarily include arbitrary upper age cutoffs”

- **International Conference on Harmonisation of Technical Requirements for registration of pharmaceuticals for human use studies in support of special populations: geriatrics E7**
  “Drugs should be studied in all age groups”; “protocols should not include arbitrary upper age cutoffs”

- **US FDA guideline for industry E11, clinical investigation of medicinal products in the paediatric population**
  “The identification of which ages to study should be medicinal product specific and justified”

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NO OPPOSITION FROM THE INDUSTRY…

…Which might give some advantages to joint adolescent/adult early trials

This JOINT adolescent and adult trial from early drug development

- Did not jeopardise the outcomes of adult trials
- Might increase the likelihood of achieving proof of concept/proof of principle for drugs with brand new mechanisms of action
- Might increase biology knowledge in drug efficacy/resistance mechanisms, given rational for further development of molecular driven trial and personalised medicine
  - Might positively influence adult drug development of a given drug
  - Shorten and orientate the full paediatric drug development time
- Might accelerate marketing authorisations of an effective drug in adolescent population at the same time of adult approval
PATIENT AND PARENTS SUPPORT
As trials are the safest way to access new drugs for these adolescents

Adolescent patients and their parents are leading co-drivers of this initiative and support it strongly, as do several AYA associations across Europe.

The need to have early access to more new drugs and to be proactively informed about which trials are available has been highlighted by adolescents and parents as priorities.

Adolescents, who have defined themselves as ‘people who have to live with the disease without current chance of cure’, claim to be able to understand and freely choose whether or not to participate in a trial once they have had clear explanations of expected adverse effects and uncertainties about drug efficacy, and enough time to discuss with their parents and others. They are more than willing to participate in adult trials to increase the chance of their own disease responding, as well as for altruistic reasons i.e. to help future patients, as long as they can still be treated in an age-appropriate environment for their adolescent condition (such as paediatric or AYA units), and maintain the established relationship of trust with their referring doctor. These factors are also considered very important for trial compliance and retention, and thus, ultimately, data quality.

https://imagineformargo.org/en/minimum-age-for-adult-clinical-trials-why-it-should-change/
https://unite2cure.org/news/
A RATIONAL, RAPID AND SAFE SOLUTION

To include adolescents in « adults » trials from early phases (phase I/II)

No increased risk for the adolescents

Comparison of ped and adult phase I showed for adolescents ≥ 12 years and adults
- Similar PK
- Similar recommended dose
- Less acute toxicity

No legal issue at European level

If the prerequisites to protect children in research are respected

No opposition from the industry

How to do it in practice?

Patient and parents support

As trials are the safest way to access new drugs for the adolescents
A RATIONAL, RAPID AND SAFE SOLUTION …

To include adolescents from early phase « adults » trials (phase I/II) …
But not at all cost

Not all drugs but based on a scientific rational (same disease, same therapeutic target)
Paediatric oncologists should be involved from the trial concept to adapt it at best to adolescents
To respect the requirements of the regulation for paediatric clinical trial
First patient on a phase I/II trial should not be an adolescent
Use dose adapted to body weight or body surface area without exceeding adult dose
To perform PK and toxicity monitoring in the adolescent population, even in phase II or III trials, if the adolescent population is included in adult trial without previous paediatric phase I trial
The adolescent care should continue to be given in an age appropriate care unit (paediatric or TYA units) authorised for phase I/II trials
1. In adult early-phase anticancer drug studies, the age of entry into clinical trials should be lowered to 12 years where the agent has an MoA relevant to adolescents’ unmet treatment needs, especially when the disease is rarely present in adolescents (making separate studies unlikely), unless there are well justifiable medical and/or scientific reasons not to do so.

2. There should be no set upper or lower age limit criteria for phases II and III trials for adolescent and young adult (AYA) cancers that are present in both paediatric and adult populations with similar biology. Adolescents over 12 years of age should be included from the onset of the cancer drug development process in adults. Additional adolescent PK and toxicity studies should be undertaken in phase II studies. Children < 12 years should be studied as soon as the pRP2D is determined.

3. Trials enrolling adolescents should always be conducted in an age-appropriate setting with clinical care provided by expert paediatric or AYA oncologists, to ensure best safety, care and compliance. This could be facilitated by having coprincipal investigators, with separate responsibilities for adults and adolescents.

4. Adolescents should be included in paediatric phase I, II and III trials where relevant (e.g. adolescents with paediatric cancers type or biological targets).

5. Young adults with paediatric cancer types should be offered to participate in paediatric phase II/III trials.

6. This approach should yield adequate data to support an adolescent indication at the time of the initial marketing authorisation application for a given anticancer drug, particularly where the disease crosses the age spectrum and has similar biological and clinical behaviour, or when diseases are histologically different but have similar targets present across the age spectrum. Adolescent PK/safety data collected in adult trials, even within trials for different diseases, might support extrapolation of activity between diseases if the targets are the same.

**BENEFITS**

Including adolescents in adult phase I/II trials without the need for prior paediatric phase I/II trials

- Improved and earlier access of adolescents to new cancer drugs
- Reduce off-label use in the paediatric population
- Increased innovative trial available for the AYA population
- Accelerate marketing authorisations of an effective drug in the adolescent population at the same time of adult approval
- Increase the likelihood of achieving proof of concept/proof of principle for drugs with brand new mechanisms of action
- Shorten and orientate the full paediatric drug development time
- Might positively influence adult drug development of a given drug
- Increase knowledge in AYA tumour biology and drug efficacy/resistance mechanisms, given rational for further development of molecular driven trial and personalised medicine

Cancer in Adolescents and Young Adults (AYA) Working Group
PROPOSED CHANGES
OF THE EUROPEAN PAEDIATRIC PLATFORM

ACCELERATE trial strategy for adolescents and young adults

**Situations**
- Similar targets present across the age spectrum
- Disease similar in adult and paediatric population e.g. bone sarcoma, Hodgkin disease
- Adult disease rarely present in adolescents e.g. carcinoma, melanoma
- Paediatric disease rarely present in the adult population e.g. medulloblastoma

**Solutions**
- To include adolescents from 12 years in adult phase-I trials
- To include both paediatric and adult population from phase-II to phase-III trials
- To include adolescents from 12 years in adult phase-I to -III trials
- To include adult patients in pediatric phase-II to -III trials
- In a AYA environment

Adolescents inclusion in adult trial when appropriate, even in phase I trial, as soon as some adult PK and toxicity data are available and under cover of adolescent PK/PD studies


Cancer in Adolescents and Young Adults (AYA) Working Group
FAIR TRIALS WORKING GROUP
Fostering Age Inclusive Research

Objective 1
To identify successful trials

Objective 2
Raising awareness to the professional 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

https://www.accelerate-platform.eu/work-programme/ongoing/working-group-fair/why-fair-trials/
A UNIVERSAL CHANGE OF PRACTICE

Enrolling Adolescents in Disease/Target-Appropriate Adult Oncology Clinical Trials of Investigational Agents
Meredith K. Chuk1, Yeruk Mulugeta2, Michelle Roth-Cline5, Nitin Mehrotra2, and Gregory H. Reaman1

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.

Modernizing Clinical Trial Eligibility: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Minimum Age Working Group
Lia Gore, S. Percy Ivy, Frank M. Balis, Eric Rubin, Katherine Thornton, Martha Donoghue, Samantha Roberts, Suanna Bruinooge, Jennifer Ersek, Nancy Goodman, Caroline Schenkel, and Gregory Reaman

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.

Cancer in Adolescents and Young Adults (AYA) Working Group
A SUCCESSFUL EXAMPLE

An “age- and tumour-agnostic” drug development e.g. rare NTRK fusion positive tumours (<1% of all tumours)

**Larotrectinib**

- A quick co-development
- A common publication
- Biology knowledge

**FDA designations**
- Sep 2015: Orphan drug
- Jun 2016: Rare pediatric disease
- Jul 2016: Breakthrough therapy
- May 2018: Priority Review for the treatment of adult and pediatric patients (at the same time) with locally advanced or metastatic solid tumors with NTRK fusion

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**Adolescents and adults phase 2 “basket” study**
- Age ≥12 years
- Without previous paed data
- NCT02576431
- Oct 2015

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**Adult phase 1**
- Age ≥18 years
- NCT02122913
- May 2014

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**Dec 2015**
- Paediatric phase 1–2 study
  - Age <21 years
  - NCT02637687

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**Jul 2017**
- LOXO-195 common phase 1–2 study
  - Age ≥1 month
  - NCT03215511
  - Specifically designed to address the acquired kinase domain mutations issue
CONCLUSION

Breaking the 18 years dogma in haemato-oncology through JOINT adolescent and adult clinical trials from early drug development is safe and might speed up

- Early drug access of adolescents and young adults (AYA)
- General drug development for both adult and paediatric population

Requirements

- Changing minds
- Increasing collaboration between paediatric and « adult » oncologists
- Increasing collaboration among all the multistakeholders of drug development
THANK YOU FOR YOUR ATTENTION

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