EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Considerations related to dosage optimisation of new drug and biological products for paediatric patients with cancer – European regulatory perspective –

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Overview

General reflections

Current approach and practical considerations – case examples

- Early at Paediatric Investigation Plan (PIP) development discussions
- At time of marketing authorisation and along the medicines lifecycle

Conclusions

References

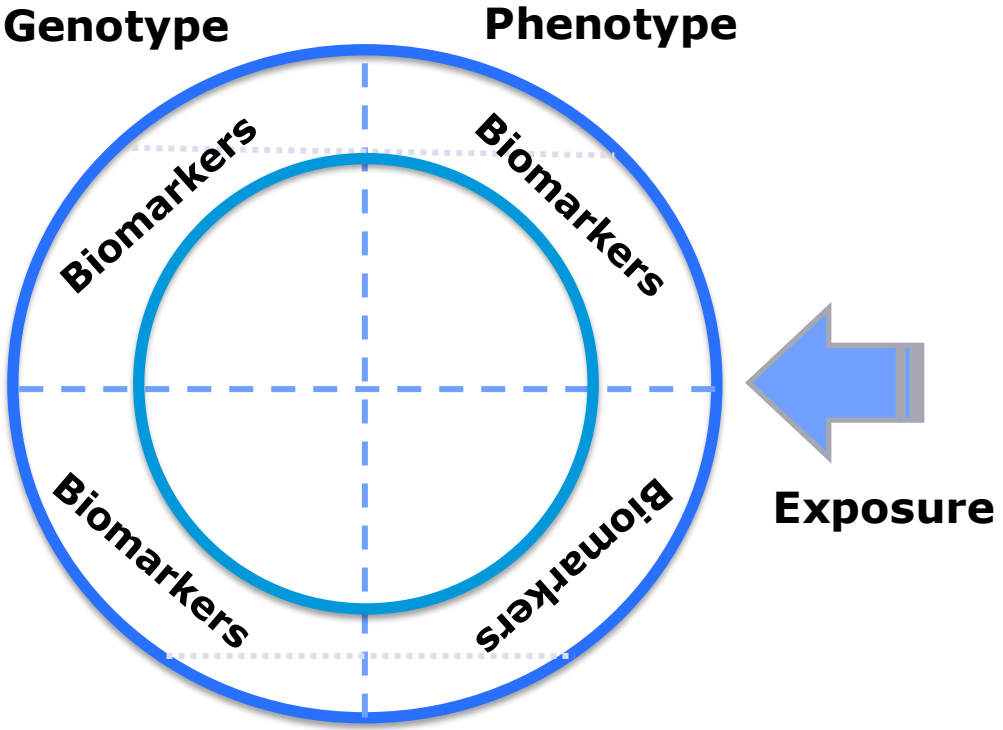
General reflections for paediatric development

- Key to consider early in the development to maximise success with the most optimal dosage based on totality of data
  - based on and supported by all available evidence (quality, pre-clinical, clinical) and relevant methodologies (e.g. pharmacometrics)
- Non-availability of adult data is not an argument to delay planning and initiation of paediatric development
- Context dependent: medicinal product, biology/disease specific, target population, age subsets under (e.g. first-in-child) development, combination therapies, availability of prior evidence (e.g. adults, relevant non-clinical data)

General reflections related to dosage selection and optimisation

Patient/participant characteristics

Disease/tumour characteristics



General reflections related to dosage selection and optimisation

- Safety and pharmacokinetics characterisation remain key objectives for initial exploratory trials

- Acknowledgment that safety is only one of determinants for dosage selection, historically used for cytotoxic compounds, differences with e.g. small molecule molecularly targeted agents, monoclonal antibodies
  - often continuous and prolonged administrations, safety profiles differ, clinically relevant toxicities may occur with a later onset

- Regulatory support to timely determine optimised dosage, including effect on biomarker(s) and outcomes

General reflections related to **paediatric** dosage selection and optimisation

- Expectation that the pharmacological rationale behind proposed dosing regimen and potential combination development takes into consideration, as relevant, existing non-clinical and/or clinical data in adults in support of a development in the indented target population (including all relevant age subsets)

- If sound prior data in adults are lacking or not relevant, general guideline considerations for stand alone developments are commonly followed for paediatric developments

General reflections related to **paediatric** dosage selection and optimisation

- When clinically and scientifically justified, relevant approaches are applied:
  - allometric scaling based on body weight or body surface area (BSA)
  - systemic exposure matching, considering allometric scaling, maturation
  - use of the recommended Phase 2 dose (RP2D) in adults (e.g. 70-80% of the adult RP2D as adjusted starting dose in a paediatric dose-finding trial)

- Considerations towards within-patient dose (de-)escalation/titration (e.g. based on exposure, pharmacodynamics [PD], activity, safety) may be appropriate when sound, adequately justified and pre-defined

Current approach and practical considerations – general case examples from PIP development discussions I

- Different dosage approaches (flat, body weight/size-based, with cut off by body-weight/size or age, hybrid)

- Important that BSA or body weight – based approaches account for variability in exposure characterised through and supported by modelling & simulation [M&S] with available adult data and using relevant pre-defined cut offs (e.g. age, weight)

- Ensuring M&S models fit also ontogeny/maturation considerations, e.g. for children under 2 years of age (in case included as an age subset)

Current approach and practical considerations – general case examples from PIP development discussions II

- (Potential) higher toxicities in children limiting achievement of the target exposure
  - Reflections on potential drug-drug interactions (for different combinations) that might increase drug toxicity
- Considerations related to binding affinity and kinetics of target engagement, target occupancy, early assessment and validation of biomarkers
- Anti-tumour activity data from early phase studies expected to form the basis for go/no-go decisions moving forward into pivotal development
- Increasing use of different designs to support dosage finding, beyond rule-based designs and/or beyond considering only toxicity, such as model-based (e.g. continual reassessment method) and model-assisted (e.g. Bayesian optimal interval) designs

Current approach and practical considerations – general case examples from PIP development discussions III

Generally, considering all available knowledge

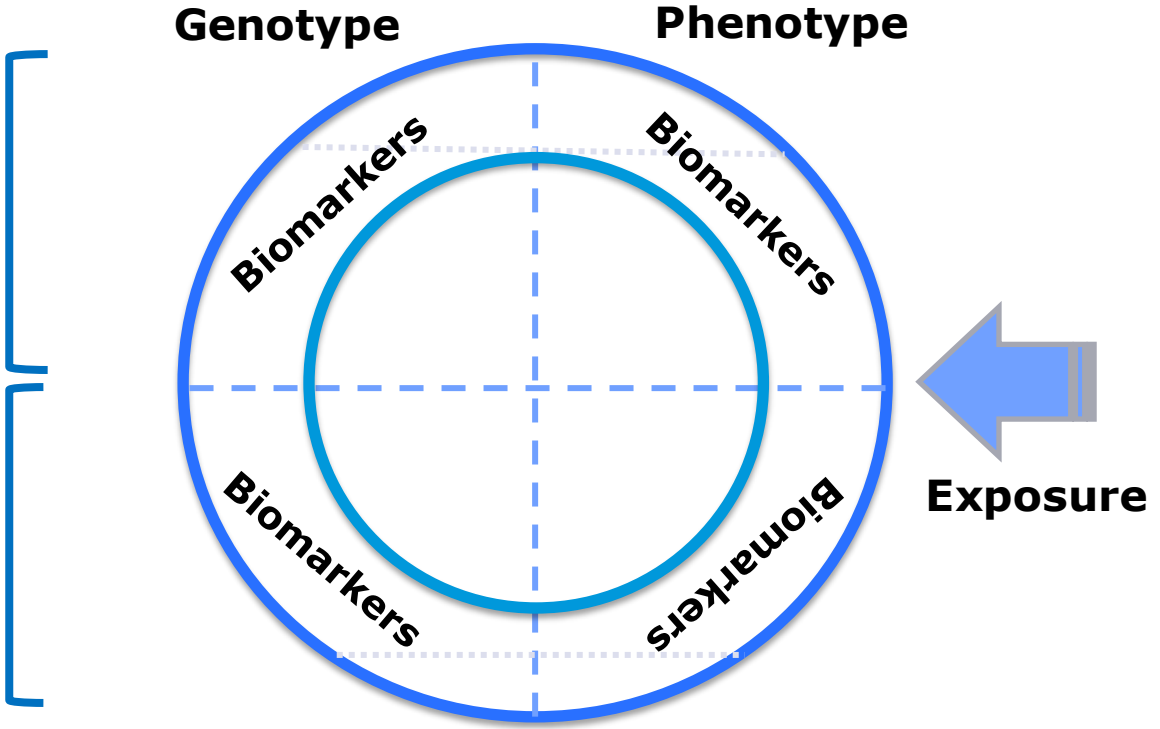
- challenging developers on how the totality of paediatric data (planned to be) generated in an early phase studies, including pharmacokinetics [PK], PD, safety, activity/efficacy, patient reported outcomes can/should inform appropriate dose finding, particularly in cases of expected longer term use

→ Ensuring the totality of evidence approach is used while progressively moving forward into a pivotal development

Current approach and practical considerations – case examples at time of marketing authorisation and along the lifecycle

Patient/participant characteristics

Disease/tumour characteristics



Case examples at time of marketing authorisation – primarily/predominant paediatric development

- **Pegaspargase** - *as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients*
- Intramuscular (IM) injection or intravenous (IV) infusion
- Body surface area (BSA)-based dosing with age cut off in young adults:
  - 2,500 U /m^2 every 14 days ≤21 years of age and ≥0.6 m^2
  - 2,000 U /m^2 every 14 days for adults aged >21 years
- **Treatment may be monitored** based on the trough serum asparaginase activity measured before the next administration. Development of specific antibodies may result in hypersensitivity reactions, reducing efficacy was also recorded.

Case examples at time of marketing authorisation – primarily/predominant paediatric development

- **Selumetinib** - *selective small molecule kinase inhibitor (MEK1/2), indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above*
- Oral use, capsules 10 mg and 25 mg, different strengths can be combined
- BSA-based dosing: among 3 doses evaluated (20, 25, 30 mg/m^2 orally twice daily) one dose (25 mg/m^2 twice daily) was selected. Dosing is rounded to the nearest achievable 5 mg or 10 mg dose (up to a maximum single dose of 50 mg).
- Pooled population PK (popPK) model (adult and paediatric data): BSA – impact on PK
- **Post-marketing** (PIP measure): to **evaluate PK and tolerability of the age-appropriate formulation** in paediatric patients 1-7 years of age, to evaluate PK and tolerability of low-fat meal in adolescents

Case examples at time of marketing authorisation – simultaneous paediatric development

- **Larotrectinib** - *selective small molecule kinase inhibitor (TRK family), for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options*
- Oral use, capsules 25 mg and 100 mg; BSA-based dosing: 100 mg/m^2 twice daily with a maximum of 100 mg per dose
- PopPK: C_{max} higher, AUC similar from 3 months to 12 years of old; both similar in adolescents; both higher in <3 months old; <6 years old: higher exposure
- **Post-marketing** commitment to **collect more PK data** in children and **to revise the dosing recommendation if needed**; development of a new age-appropriate solution 2% 50ml for oral use, study for nasogastric tubes

Case examples at time of marketing authorisation – paediatric development following initial adult development

- **Selpercatinib** - *selective small molecule kinase inhibitor (RET), for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer*
- Oral use, capsules 40 mg and 80 mg, different strengths can be combined
- Dose-finding study: algorithm/rule-based 3+3 design considering toxicity
- PopPK: dose and body weight - significant covariates for PK variability; relevance for adolescents, exposure matching; exposure-safety analyses: no clear relationship;
- **Flat dosing**: 120 mg twice daily if < 50 kg, 160 mg twice daily if ≥ 50 kg
- **Mainly metabolised by CYP3A4** (adolescents as adults), open growth plates in adolescents should be monitored, juvenile animal toxicity studies

Case examples at time of marketing authorisation– paediatric development following initial adult development

- **Rituximab -** *monoclonal antibody, biomarker-defined, treatment in combination with chemotherapy of paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma, Burkitt lymphoma/Burkitt leukaemia (mature B-cell acute leukaemia) or Burkitt-like lymphoma*
- IV infusion with premedication, BSA-based dosing 375 mg/m^2, no other dose adjustments in paediatric patients, the same dose as in adults
- Later paediatric approval, extension of indication in 2020
- **PopPK model updated,** inclusion of a maturation factor to the constant clearance component to account for the effect of the neonatal Fc receptor (FcRn) variation with age

Case examples at time of marketing authorisation – paediatric development following initial adult development

- **Blinatumomab**, *bispecific T-cell engager, CD19 on target cells and CD3 on T-cells, monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative (Ph-) CD19 positive B-precursor ALL*

➢ *refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation*

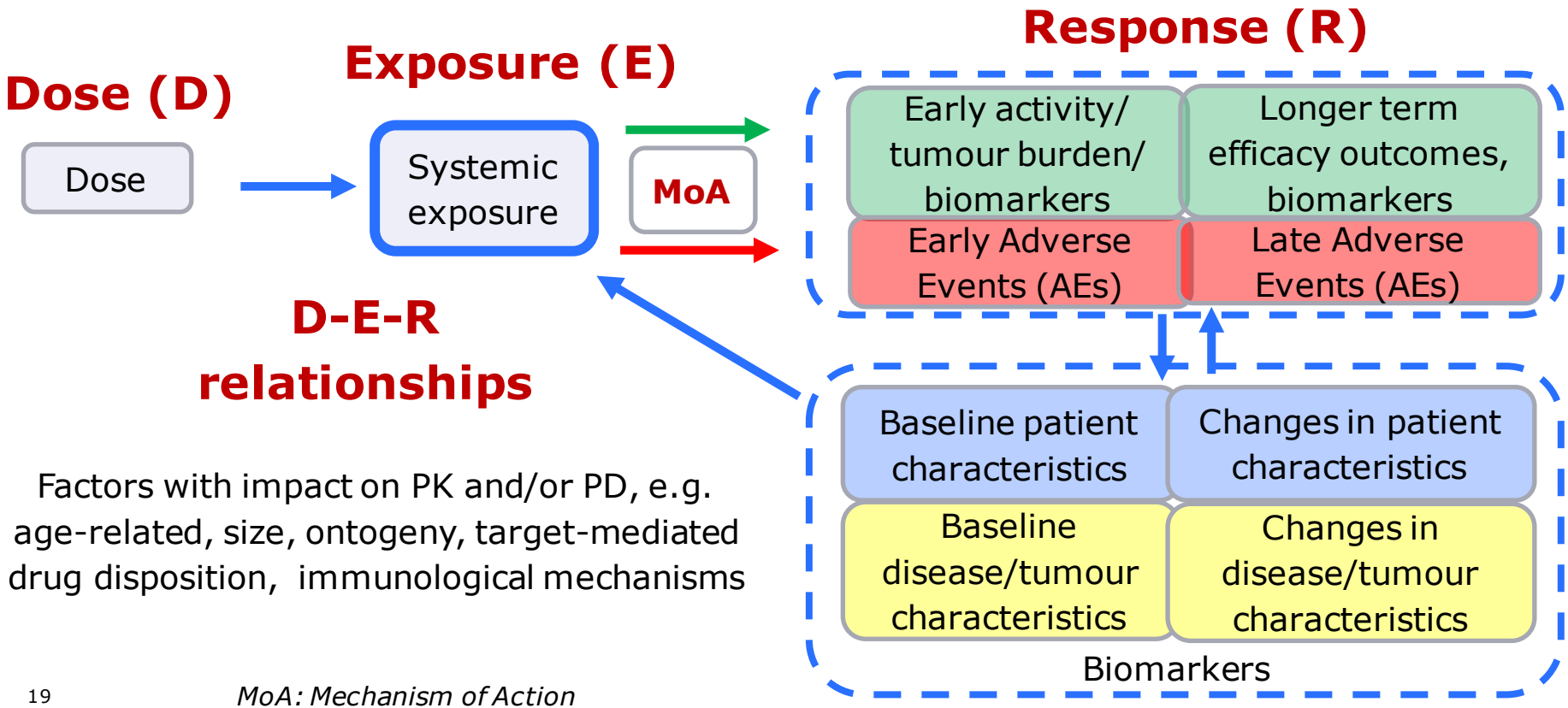
➢ *high-risk first relapsed, as part of the consolidation therapy*

- Fixed dose if ≥45 kg, BSA-based dosing if <45kg, step-up dosing for the 1st indication
- PopPK – BSA influences the PK
- According to the PIP – extension of indication to high-risk first relapsed patients, **dosing regimen should have been guided by PK/PD modelling**

Case examples at time of marketing authorisation – simultaneous paediatric development

- **Nivolumab and relatlimab**, *fixed dose combination of monoclonal antibodies (Anti-PD-1 and anti-LAG-3), first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%*
- **Flat dosing**: 480 mg nivolumab and 160 mg relatlimab every 4 weeks administered as an IV infusion. This dose is established for adolescent patients weighing at least 30 kg, expected to result in similar safety and efficacy to that of adults
- Nivolumab clearance and volume of distribution in adolescents were 36% and 16% lower, respectively, of those in adult reference patients (unknown for relatlimab)
- 30 min infusion duration is recommended as 60 min duration was predicted to produce similar (< 1% different) exposures

Clinical pharmacology of monoclonal antibody-based medicines



Factors with impact on PK and/or PD, e.g. age-related, size, ontogeny, target-mediated drug disposition, immunological mechanisms

MoA: Mechanism of Action

D-E-R relationships for dosage selection and optimisation

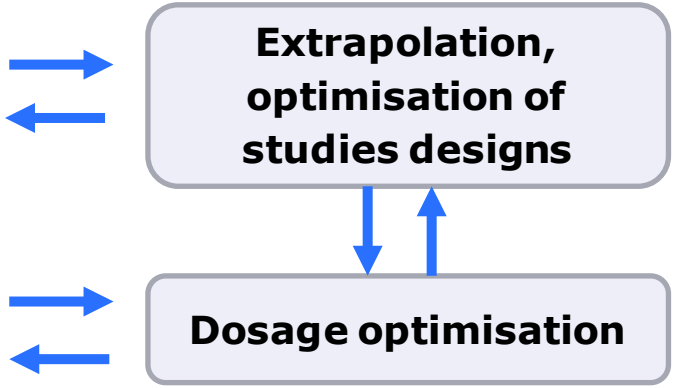
Dosage selection

-initial in target paediatric population, monotherapy or combination therapy

-in new population (age group, disease entity, line)

-new formulation or route of administration

-changes in dose/schedule, including duration, dosage approach (flat, body weight/size-based, with cut-off by body-weight/size or age, hybrid)



Prior knowledge and assumptions from non-clinical, adult clinical data, similar products

Paediatric considerations (disposition mechanisms, ontogeny, long-term toxicity, etc.),

Pharmacometrics approaches: PopPK, PK/PD, physiologically based PK (PBPK) modelling, quantitative systems pharmacology (QSP) modelling, hybrid/multi-model, etc

Conclusions

- Context is essential, need to ensure all available and relevant evidence is used to inform early dosage finding
  - Non-availability of adult data is not an argument to delay paediatric developments
- Key to ensure maximising data generation (i.e. collecting all relevant data)
  - Use of novel methodological approaches
  - In case initial dosage based on simulations, a paediatric study to confirm the simulated dose recommendation expected
  - Consider including the patient voice more in the totality of data
- Early and continuous interactions with regulators is key, supported through evolutionary, stepwise PIP framework
  - Use of mechanisms in place for close collaboration between EMA and FDA

References

- Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6) and related documents - https://www.ema.europa.eu/en/evaluation-anticancer-medicinal-products-man-scientific-guideline#current-version---under-revision--section
- https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics
- https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1901
- https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans#joint-ema-/-fda-guidance-on-cancer-medicines-for-use-in-children-section
- https://www.ema.europa.eu/en/documents/scientific-guideline/structured-guidance-use-extrapolation_.pdf
- https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans#stepwise-pip-pilot-supporting-authorisation-of-innovative-medicines-(new)-section

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EU Paediatric Regulation - REGULATION (EC) No 1901/2006

Background – EU Paediatric Regulation

Objective:

- Improve the health of children:
  - Increase high quality, ethical **research** into medicines for children
  - Increase **availability** of authorised medicines for children
  - Increase **information** on medicines
- Achieve the above:
  - As **timely** as possible
  - Without unnecessary studies in children
  - Without delaying authorization for adults

Pillars:

- EMA and its Paediatric Committee (PDCO)
- Paediatric Investigation Plan (PIP)
- A system of **obligations** and **rewards**

Paediatric Investigation Plan (PIP)

Research and development programme framed around concept of **condition**

Quality
Pre-clinical
Clinical
} Marketing Authorisation

Tools like **deferrals, modifications** and **waivers** in place, intended to ensuring:

- timely evidence generation

while allowing:

- (re) focus of development efforts based on emerging evidence and potential changing needs over time

Pediatric Oncology Drug Development: Dose and Dose Optimization

PedsODAC: June 16, 2023

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Disclosure Information
Pediatric Oncology Subcommittee, Oncology Drugs Advisory Committee
June 16, 2023

Elizabeth Fox, MD

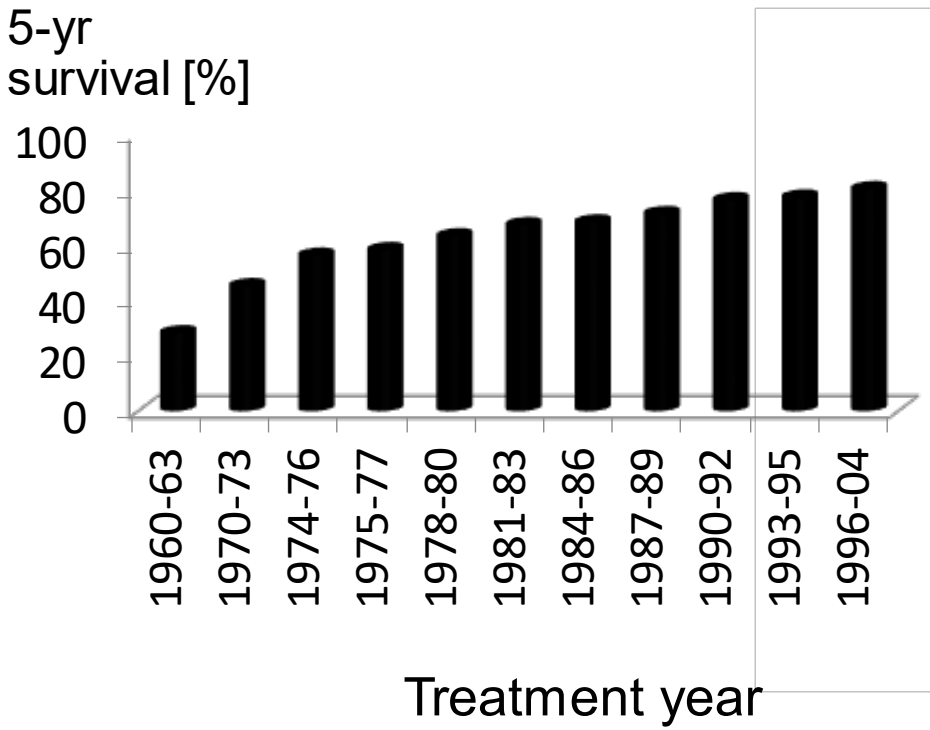
Disclosures: none

I will discuss the following off label use or investigational use:
Cabozantinib, Crizotinib, Entrectinib, Larotrectinib, Trametinib

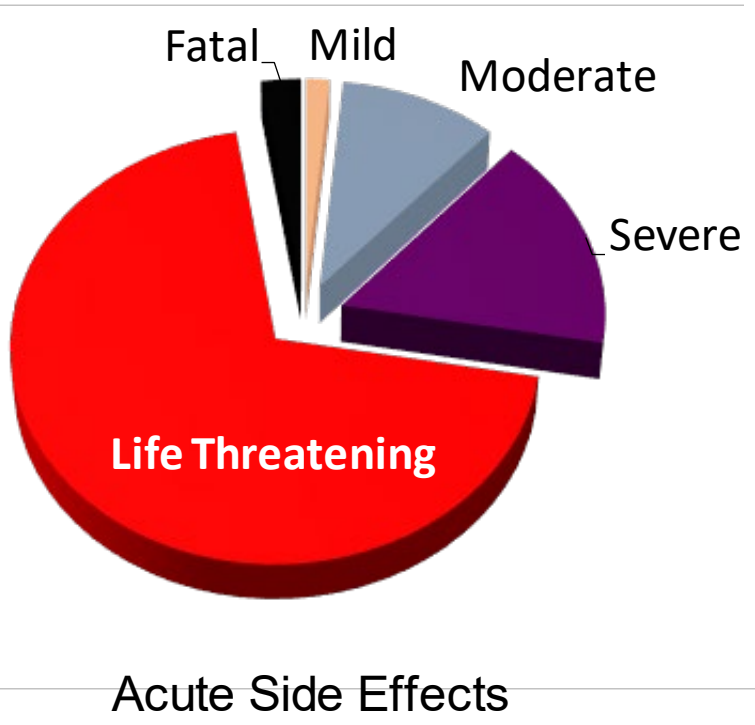
This presentation reflects my opinion, based on referenced data available in the public domain, and does not reflect the opinion of the institutions, sponsors, cooperative groups or consortia with whom I am affiliated.

Unifying Goal of Childhood Cancer Drug Development

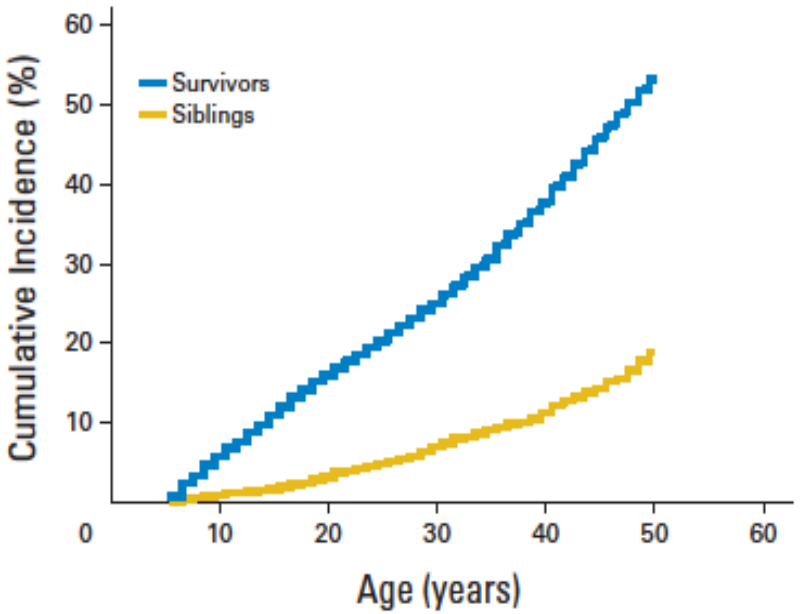
Improve cure rates.



Diminish acute toxicity.



Eliminate late effects.



Grade 3 to 5 chronic health conditions in Survivors of Childhood Cancer

Armstrong et al JCO 2014

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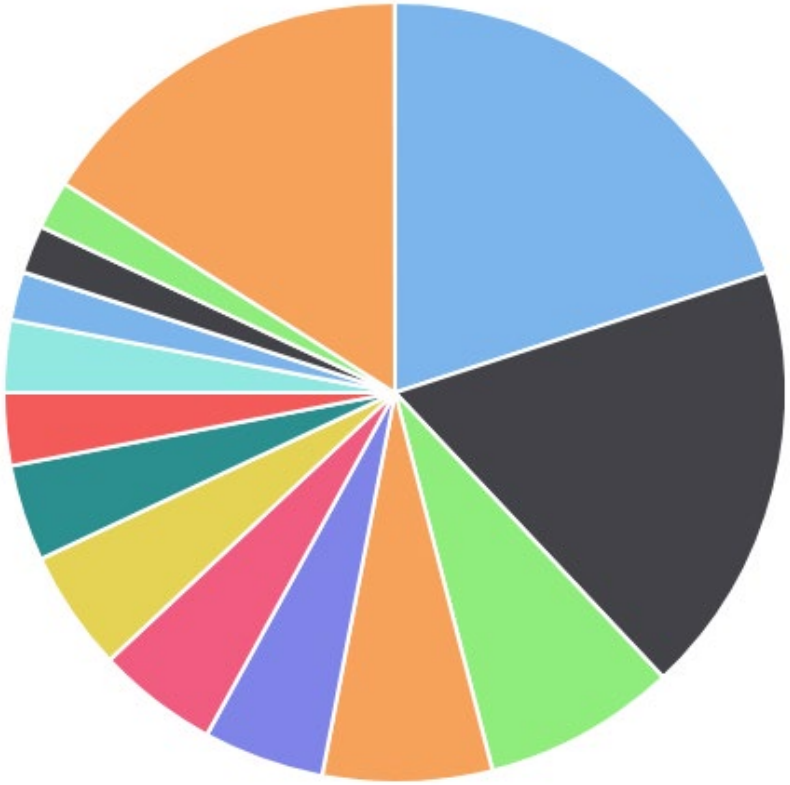
Childhood Cancer Diagnosis (%)	Common Age Range
Acute Lymphoblastic Leukemia (20%)	< 8 y
Brain/ CNS Tumors (18%)	0-19 y
Hodgkin Lymphoma (8%)	10-19y
Non-Hodgkin Lymphoma (7%)	0-19 y
Acute Myeloid Leukemia (5%)	<2y; >12y
Neuroblastoma (5%)	<4 y
Bone: Osteosarcoma+Ewing Sarcoma (5%)	10-19y
Thyroid Carcinoma (4%)	15-19y
Wilms/Kidney (3%)	<5 y
Germ Cell Tumors (3%)	15-19y
Rhabdomyosarcoma (2%)	0-19 y
Retinoblastoma (2%)	< 1 y
Melanoma (2%)	>12y
Other (16%)	

Adapted from Siegel et al CA Cancer J Clin 2017

Each year **15,780 Children** in the US are diagnosed with **Cancer**



Objective

Illustrate why rationale dose determination is a prerequisite for optimization in drug development for infants, children, and adolescents with cancer

- Dosing Methods in Children
- Dose Determination
- Impact of Formulations

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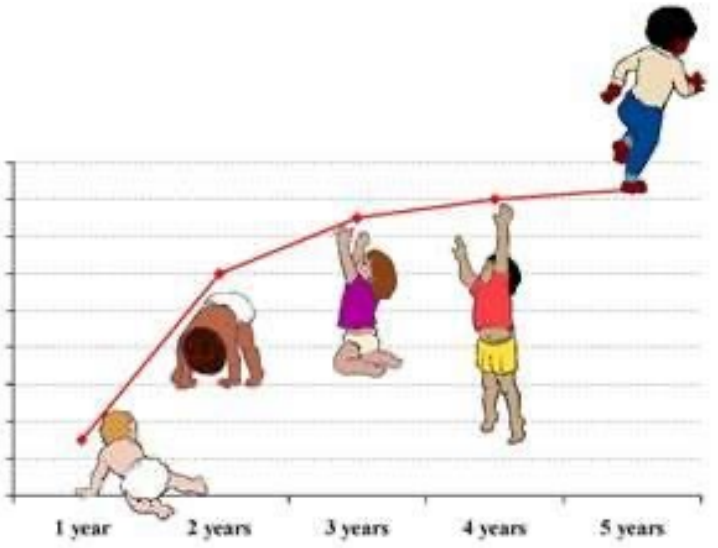
Impact of Ontogeny on Drug Dosing in Children

Weight change

- 10-fold increase from birth to 10 years. (3.5 kg to 32 kg)
- 2-fold increase from 10 years to adulthood (32 kg to 70 kg)



https://www.who.int/tools/child-growth-standards

Excretory organ **growth rate** proportional to body weight

Greatest changes in **renal and hepatic function** occur in the first year of life

Aspects of normal growth & development may be inhibited by targeted anticancer drugs

Comparison of Dosing Methods

Example Monoclonal Antibody with Adult Dose 600 mg IV

	Units	Advantages	Disadvantages	Patient 5y	Patient 6y	Patient 12y
Weight Based	mg/kg	Continuous variable Patient specific Easily measured	Actual vs Ideal Impact of con-meds Fluctuates Constraints with oral formulations Systematic dose reduction in infants	144	162	306
Body Surface Area Based	mg/m^2	Continuous variable Patient specific Limited range (0.23-2.5m^2)	Height is primary driver Calculations; Multiple formulas Constraints with oral formulations	246	267	416
Age based	years	Categorical variable Easily measured	Changes with birthdays not physiology/ontogeny	300	400	400
Fixed dose	mg	Convenient in Adults	Does not account for 10x weight change in childhood	600	600	600

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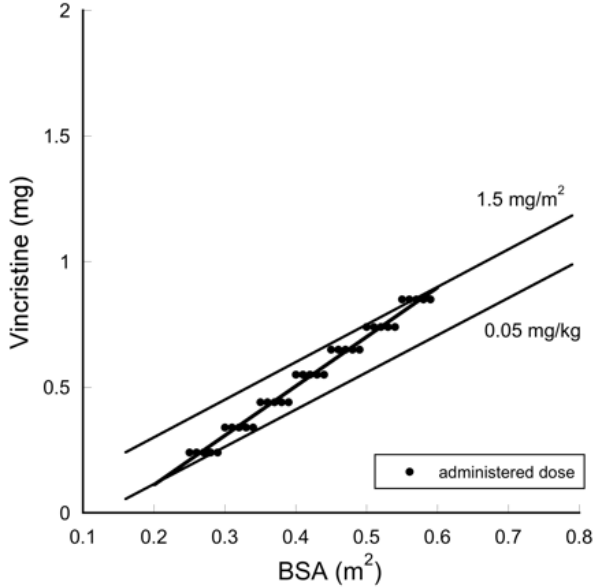
Children's Oncology Group Strategies for Dosing

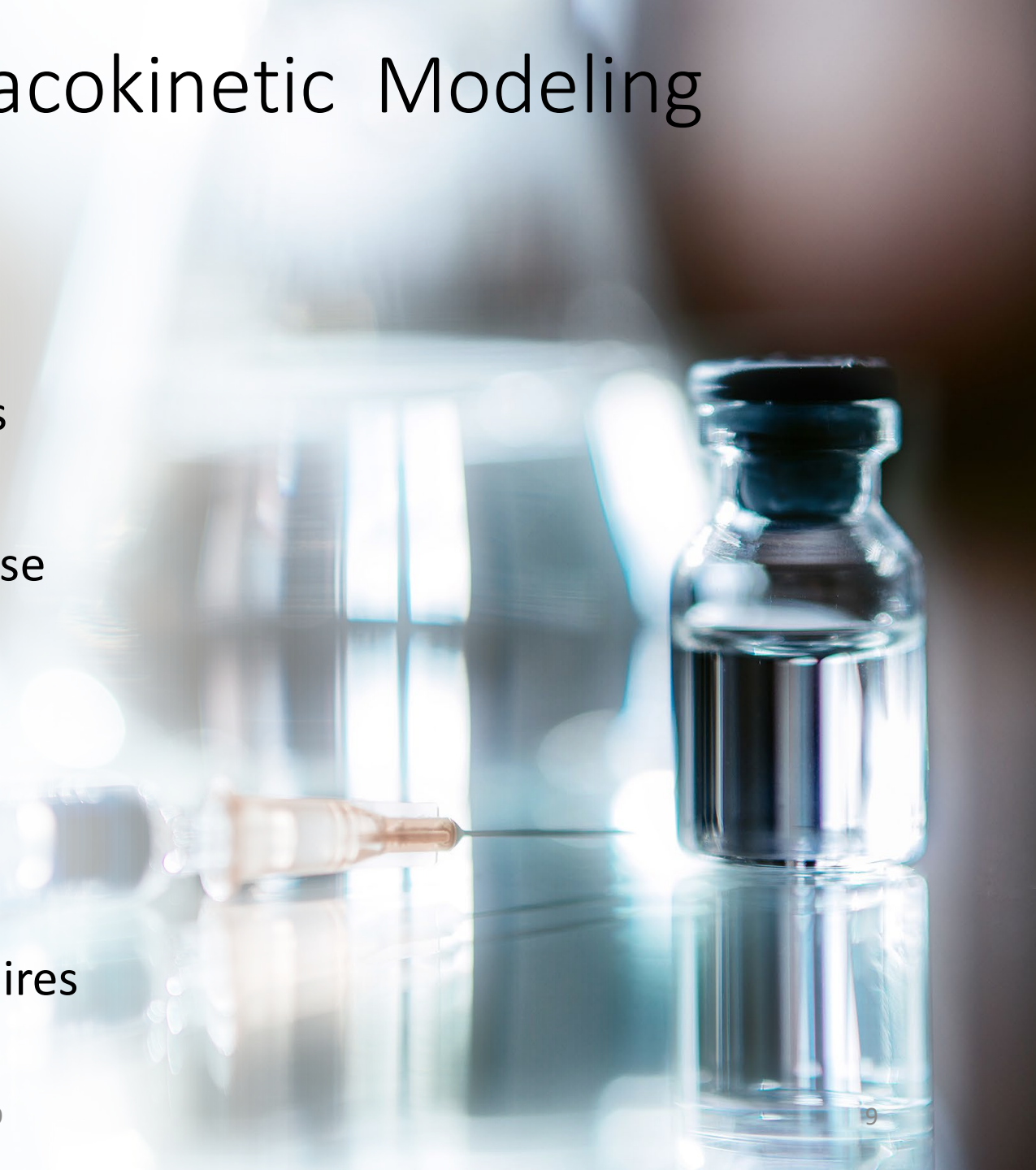
- Infant Dosing Tables for many cytotoxic drugs
  - Eliminates "Quantum Leap" at age/weight thresholds for transition for mg/kg to mg/m^2
  - Gradually reduces the systematic mg/kg dose reduction
- Dosing Nomograms for Oral Agents
  - Standardizes dose by BSA bands
  - Permits adequate dose reductions, if necessary
  - Ensures discrete dose levels
- Limited number of dose levels for dose exploration



VINCRISTINE 1.5 mg/m^2/dose Dose Level	
BSA (m2)	Dose (mg)
0.25-0.29	0.24
0.3-0.34	0.34
0.35-0.39	0.44
0.4-0.44	0.55
0.45-0.49	0.65
0.5-0.54	0.74
0.55-0.59	0.85
≥ 0.6	1.5 mg/m^2
Max Dose 2 mg	

Pharmacokinetics and Pharmacokinetic Modeling

- Critical to understanding pediatric dose, tolerability and response
- Extrapolation from adult data often neglects dramatic weight change during childhood
- Inclusion of detailed PK data from limited dose escalation trials in children could validate assumptions of extrapolated PK models
- Categorical dosing methods will increase variability in exposure
- Determining plateau of dose-response or exposure-response curves or thresholds requires responses.



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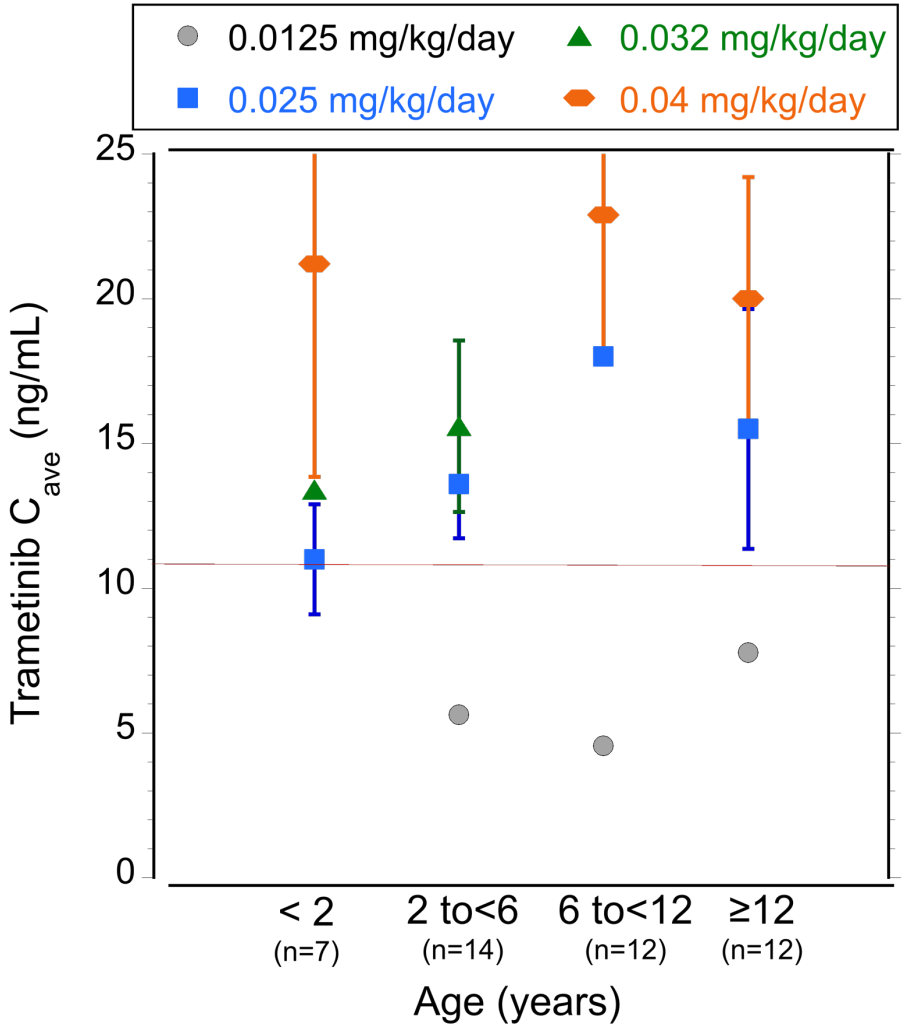
Trametinib Dosing in Children



Age Based Recommended Dose

- <2 years : 0.032 mg/kg
- ≥2 to 17 years : 0.025 mg/kg
- ≥18 years: 2 mg (0.028 mg/kg)

Formulations

- Oral Liquid: 0.05 mg/mL
- Tablets: 0.5 mg, 2 mg

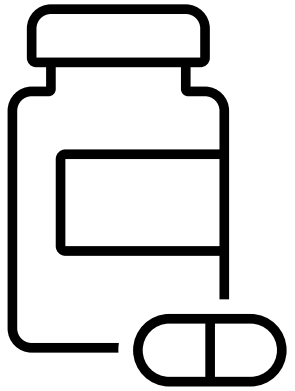
Dose	n	C_{ave} (ng/mL)	CL/F (L/h)
0.025 mg/kg	18	14.4 (CV= 26%)	1.79 (58%)
0.032 mg/kg	9	15.9 (CV=25%)	1.27 (24%)
2 mg (Adult, 57 years)	493	12.1 (CV=19%)	4.91 (61%)

Is age-based dosing necessary if we dose according to size?

Bouffet et al JCO (2023) 41: 664-674.
Ouellet et al Cancer Chemother Pharmacol (2016) 77:807–817

FDA Approval of Trametinib in Children

Body weight	Recommended dosage total volume of oral solution once daily (trametinib content)
8 kg	6 mL (0.3 mg)
9 kg	7 mL (0.35 mg)
10 kg	7 mL (0.35 mg)
11 kg	8 mL (0.4 mg)
12 to 13 kg	9 mL (0.45 mg)
14 to 17 kg	11 mL (0.55 mg)
18 to 21 kg	14 mL (0.7 mg)
22 to 25 kg	17 mL (0.85 mg)
26 to 29 kg	18 mL (0.9 mg)
30 to 33 kg	20 mL (1 mg)
34 to 37 kg	23 mL (1.15 mg)
38 to 41 kg	25 mL (1.25 mg)
42 to 45 kg	28 mL (1.4 mg)
46 to 50 kg	32 mL (1.6 mg)
≥ 51 kg	40 mL (2 mg)



Body weight	Recommended dosage
26 to 37 kg	1 mg orally once daily
38 to 50 kg	1.5 mg orally once daily
51 kg or greater	2 mg orally once daily

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204114s025lbl.pdf

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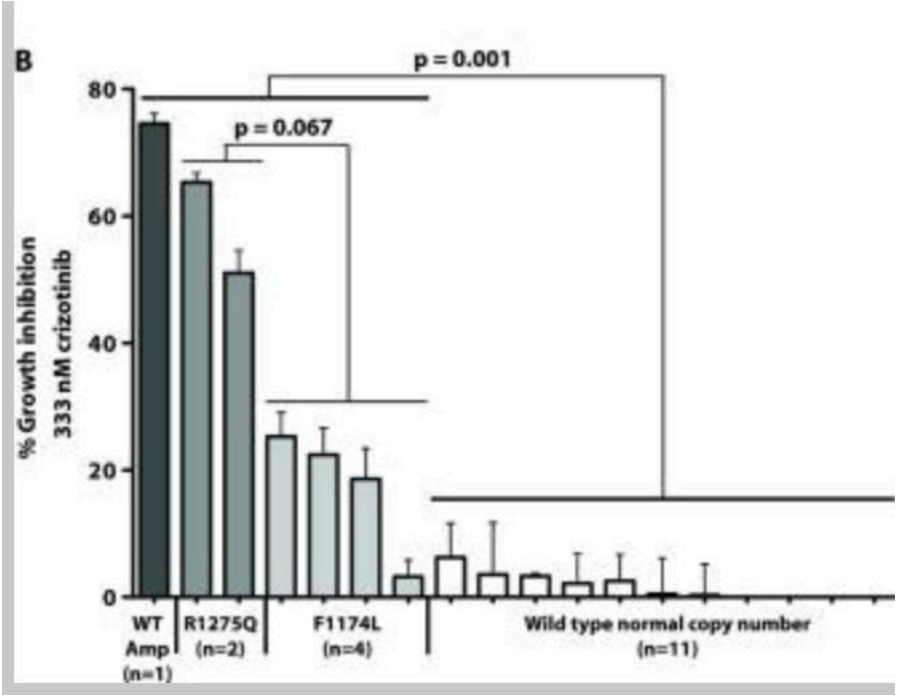
Phase 1/2 Trial of Crizotinib in Children

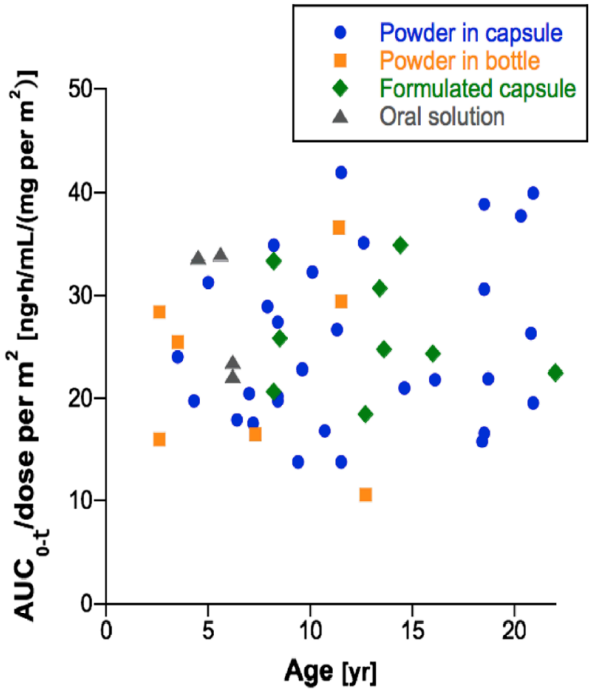
Crizotinib oral Anaplastic Lymphoma Kinase (ALK) inhibitor:
Adults with ROS1 (c-ros oncogene) or ALK+ Non-Small Cell Lung Cancer: 250 mg BID (145 mg/m^2 BID)
FDA Approved Maximum Tolerated Dose/Recommended Dose in children: 280 mg/m^2 BID



Pre-clinical Evaluation

Phase 1 Dose Escalation in Children			
Dose Level	**Crizotinib mg/m^2/dose BID**	**Evaluable/ DLT**	**Cycle 1 DLT**
1	100	3/0	
2	130	4/0	
3	165	6/0	
4	215	7/2	Dizziness, Hemorrhage
5	**280**	**5/0**	
6	365	6/2	LFTs ANC

Phase 1 Dose Escalation

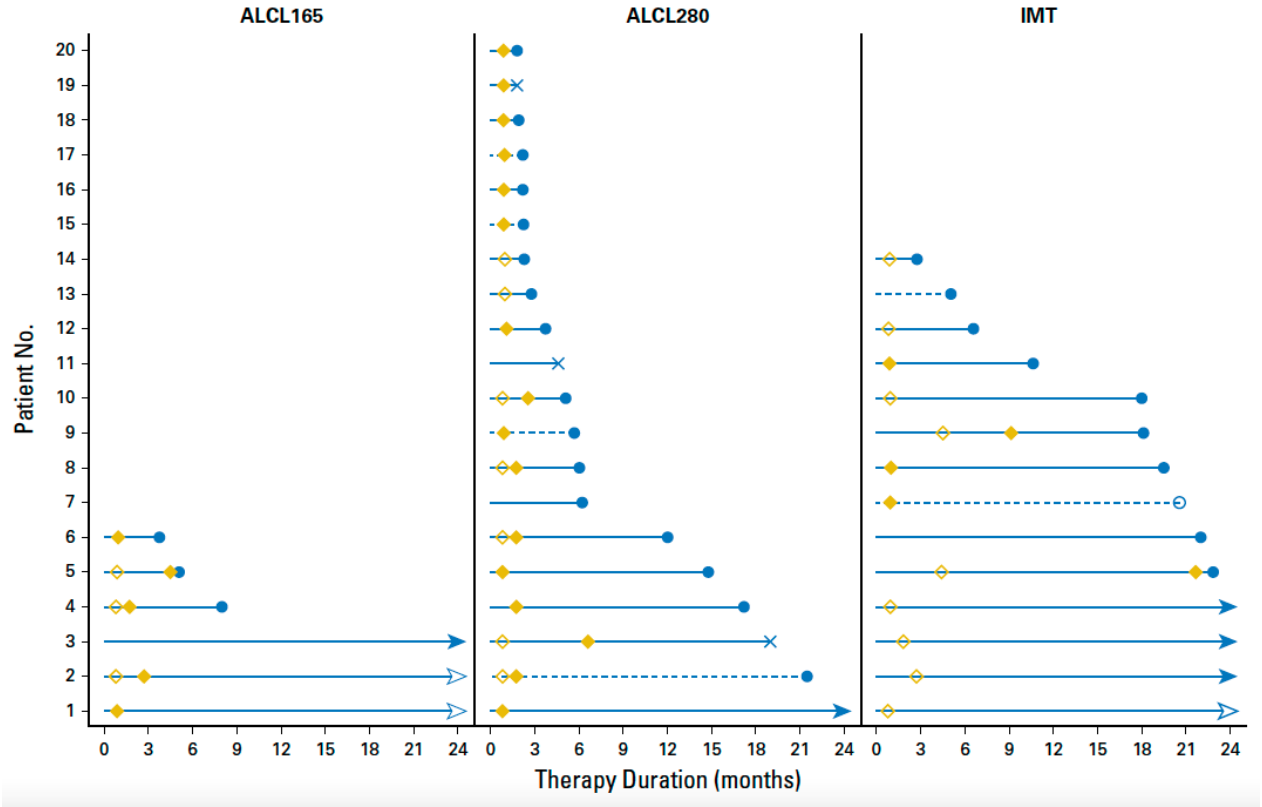


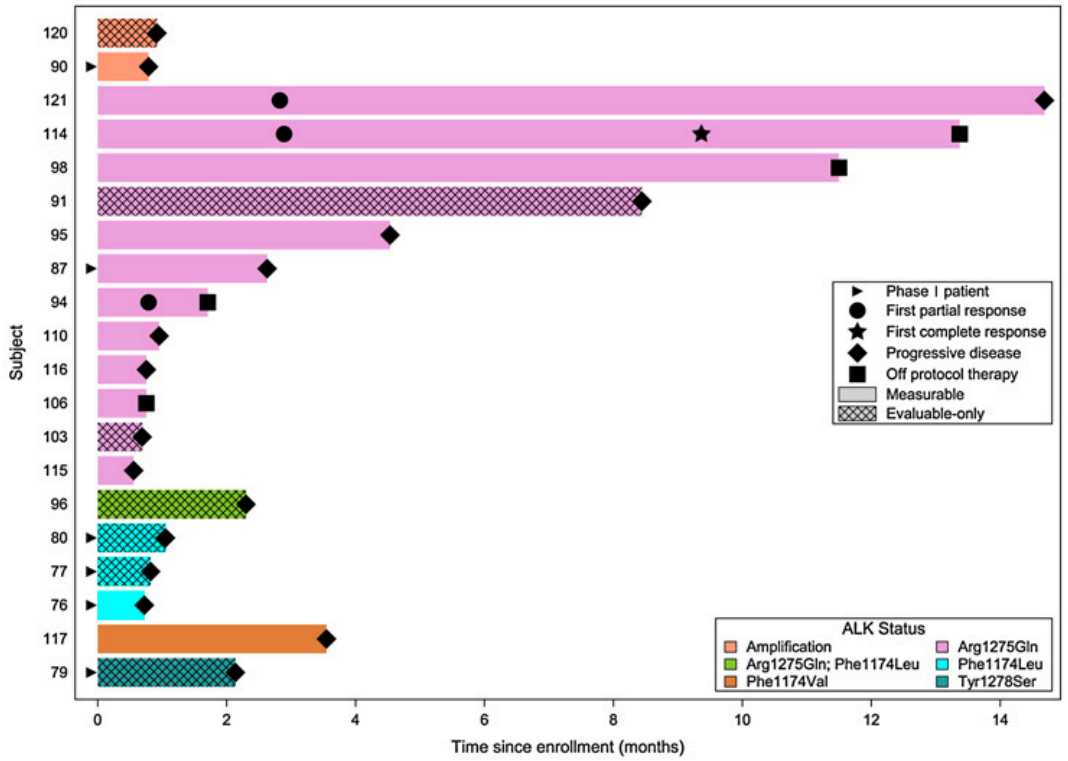
Pharmacokinetics and Formulation

Mosse et al Lancet Oncology 2013
Balis et al Cancer Chemoth Pharmacol 2017

NCI Pediatric Early Phase Clinical Trials Network
A program funded by the National Cancer Institute of the National Institutes of Health

Response to Crizotinib in Children





- Crizotinib (165 mg/m^2 and 280 mg/m^2) is active in patients with Anaplastic Large Cell Lymphoma.
- In patients with Inflammatory Myofibroblastic Tumor toxicity and response were similar at doses 100 mg/m^2- 280 mg/m^2

- Crizotinib is active against a subset of Arg1275Gln ALK–mutated neuroblastoma.
- Crizotinib had no activity inpatients with neuroblastomas harboring other hotspot ALK mutations or amplification.

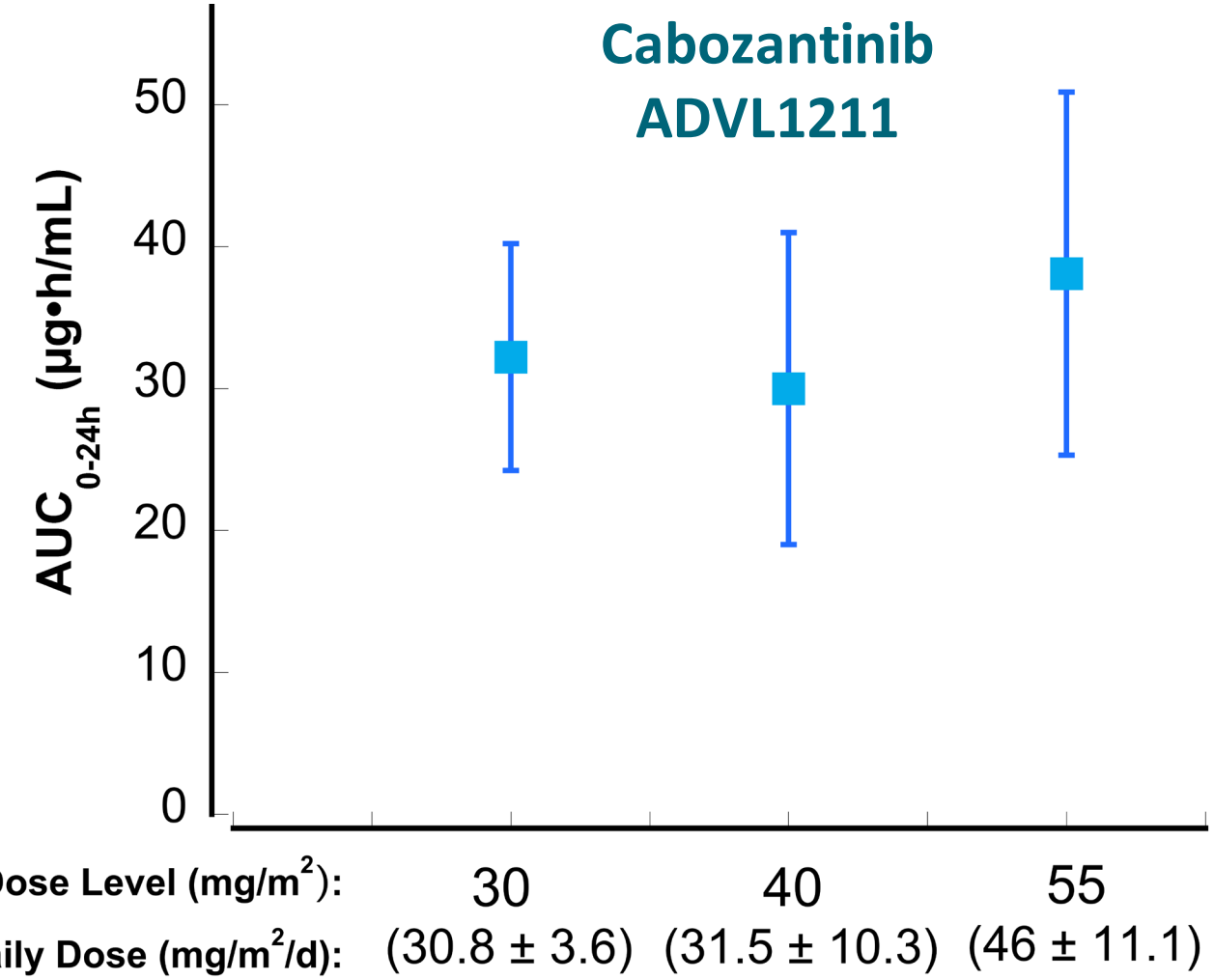
Is optimization of Crizotinib FDA approved dose necessary in children with ALCL or IMT?

Mosse et al J Clin Oncol 2017
Foster et al Clin Cancer Res 2021

NCI Pediatric Early Phase Clinical Trials Network
A program funded by the National Cancer Institute of the National Institutes of Health

Pediatric Appropriate Formulation

- Bioavailability
- Taste
- Palatability
- Concentration (volume)
- Stability
- Preparation
- Administration



Impact of Formulation

	Larotrectinib	Entrectinib
Reference	Laetsch et al Lancet Oncology 2018	Desai et al J NeuroOnc 2022
Population	Biomarker enriched/selected	Solid tumor Dose Escalation; biomarker expansion
N	24 (17 fusion positive)	16 (3 fusion positive)
Median Age (years)	4.5	10
Dose Limiting Toxicity	increased Alanine Transaminase (ALT)	pulmonary edema, fatigue, dysguesia, elevated creatinine
Max Tolerated Dose	No	Yes
Pediatric Dose	100 mg/m^2 BID (max 100 mg/dose)	MTD 550 mg/m^2 Daily
Adult Dose	100 mg BID	600 mg/day (~350 mg/m^2)
Objective Response	14/15 patients with fusion positive tumors	3/3 patients with fusion positive tumors
Formulations	25 or 100 mg capsules; 20 mg/mL oral solution	100 and 200 mg capsules
FDA Approval	2018 age and histology agnostic approval	2019 adults and children ≥ 12y BSA > 1.50 m2 : 600 mg once daily BSA 1.11 to 1.50 m^2 : 500 mg once daily BSA 0.91 to 1.10 m^2 : 400 mg once daily

Summary

- Maximum Tolerated Dose is not an appropriate endpoint for many targeted agents; variability and formulation impact the utility of Pharmacokinetics as an endpoint
- Pharmacokinetics and age-related toxicity data are essential
- Accurate dosing across the age spectrum, limited dose exploration, and detailed pharmacology are needed for pharmacokinetic modeling in children
- Dose optimization in children requires drug specific considerations
  - Formulation
  - Pharmacokinetics variability
  - Target exposure in pediatric cancer
- Optimization of dose in children requires defining the dose-response relationship, not randomization of doses.
- Clinical trials in children cannot wait for optimized dosing in adults.

DOSE

“There is only a quantitative difference between a drug and a poison”

Walter Staub

Thank You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Dosage Optimization of New Drug and Biological Products for Pediatric Patients with Cancer: A Perspective from The Biopharmaceutical Industry

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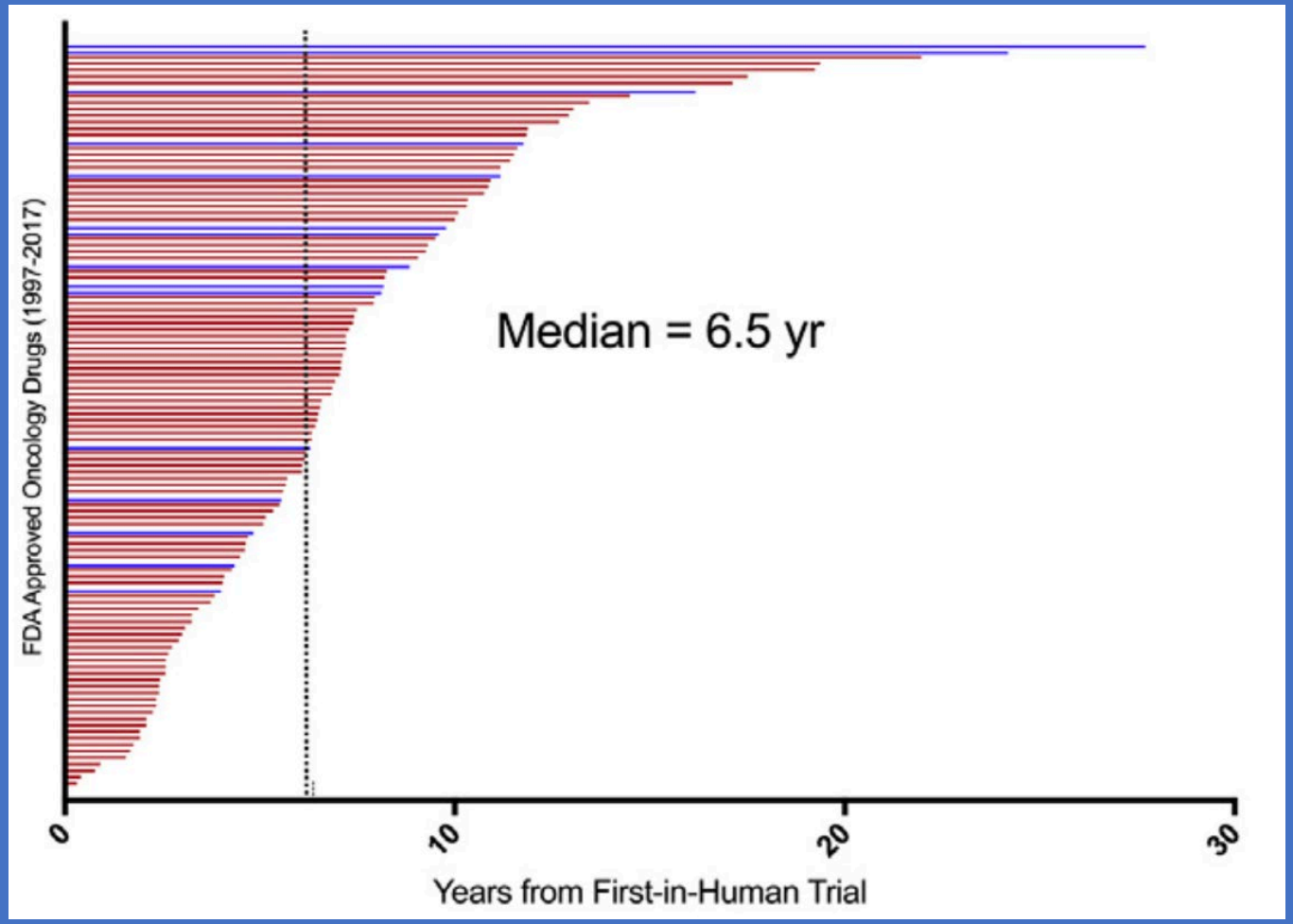
Disclaimer

- I am speaking as an individual.
- My comments reflect my personal perspectives on this topic, and the publicly-available data that I cite, and do not represent the views of Day One Biopharmaceuticals.
- I am not speaking on behalf of the biopharmaceutical industry.
- I am a full-time employee of, and have an equity position in, Day One Biopharmaceuticals, Inc.

Despite US/EU incentives and requirements, the pace of pediatric oncology drug development continues to lag that of adults



Neel et al., Eur. J Cancer, 2019

Structural and cultural challenges can lead to friction that can slow pediatric development efforts

- Regulatory requirements (PIPs, iPSPs)
- Internal champions
- Improvements in trial design
- Advances in PK modeling
- Regulatory incentives
- Advocacy
- Moral/social imperative

Motivation

Friction

- Cost (time, dollars, opportunity)
- Limited preclinical models
- Risk aversion
- Capital demands (esp. biotech)
- Insufficient target validation
- Time to peds formulation development
- Regulatory requirements (CDx, dose optimization)
- Limited # of patients and need to evaluate across age ranges
- Herd effect
- Limited system capacity
- Need for combination therapy in many indications

PIP = Paediatric Investigation Plan; iPSP = initial Pediatric Study Plan; PK = pharmacokinetic; CDx = companion diagnostic

Innovation in drug development is coming from biotech, but these companies have been under significant financial pressure of late

BIOTECH

Four in 10 biotechs trading below cash

Roughly four out of every 10 biotechs are worth less on the stock market than the amount of cash they have in the bank, and nearly half are worth less than $100 million.

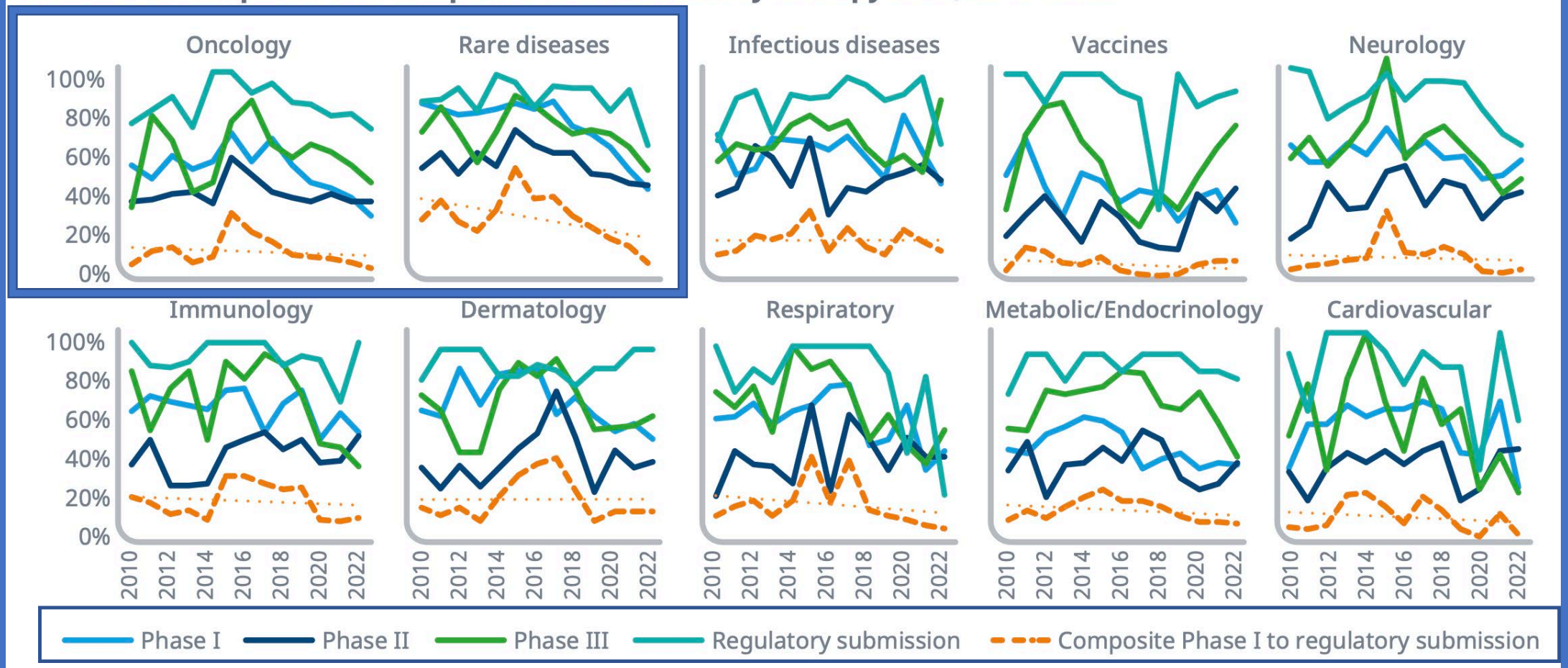
That's from the latest BIO investment data, which were presented at the conference late Tuesday. The organization reported that 39% of small biotechs — that is, companies with fewer than 500 employees — were trading below their cash holdings, compared to 33% in the second quarter of 2022. That rate has been on the rise since mid-2022, rising as the public and private investment markets have dried up.

Drug companies are limping to the R&D finish line, though: The number of new drugs getting approved is pacing ahead of those launched in 2022, and 65% have come from small biotechs. As of June 1, 26 drugs had been approved and reached the commercial markets, compared to 42 in all of 2022 and 54 in the year prior.

STAT News
6/7/2023

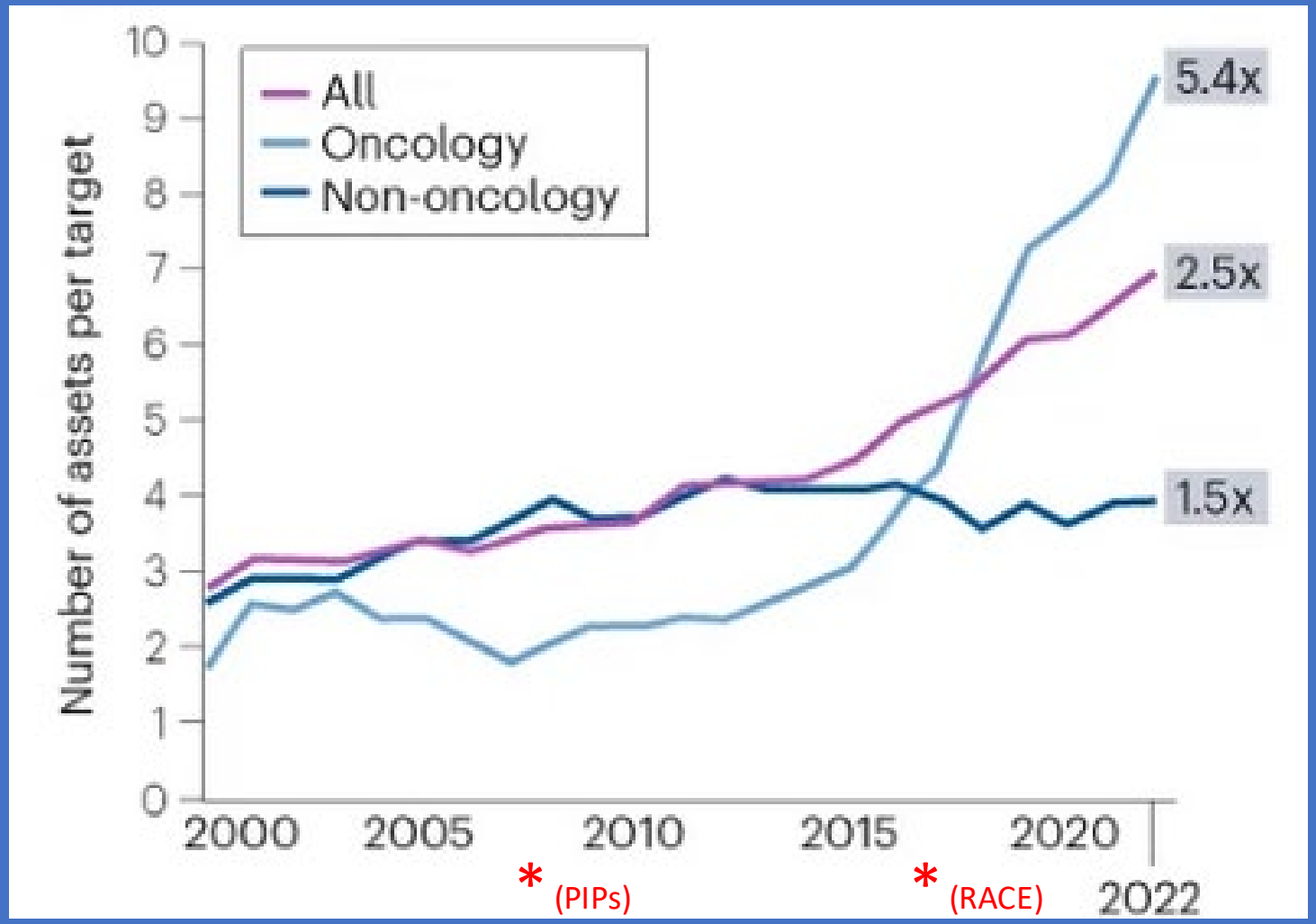
Success rates for new oncology therapeutics are lower than in recent years as the low-hanging fruit has been picked. Development risk for innovation is high.

Exhibit 36: R&D phase and composite success rates by therapy area, 2010–2022



Source: IQVIA Pipeline Intelligence, Dec 2022; IQVIA Institute, Jan 2023.

There is a herd effect in oncology drug development leading to the creation of multiple programs against validated oncology targets



Fougner et al. Nat Rev Drug Discov (2023)

Regulatory requirements for pediatric development pre-dated the inflection point; **prioritization remains a challenge for the pediatric oncology ecosystem**.

Multiple programs for targets in rare indications (e.g. ALK in neuroblastoma, CD19 in B-cell malignancies) lead to requirement for clinical trial subjects that may **exceed the available trial-eligible population**.

ALK = anaplastic lymphoma kinase; RACE = RACE for Children Act, or Title V of the FDA Reauthorization Act (FDARA) (21 USC 355c)

Per-patient drug development costs in industry are high, and capital must be allocated appropriately

- **For company-sponsored trials, per-patient trial costs for Phase 1 or Phase 2 oncology studies are typically budgeted at $200-250K per patient**
  - Internal resources
  - Contract research organizations (CROs)
  - Imaging CRO costs
  - Data management
  - Pharmacovigilance
  - Site-costs
  - External lab costs (PK assay development and validation, pharmacodynamic (PD) assay development and validation)
  - Formulation development
- **Particularly for small companies, there is an incentive to defer investment in pediatric drug development until there's high confidence that the lead indication has a path to POC or registration**

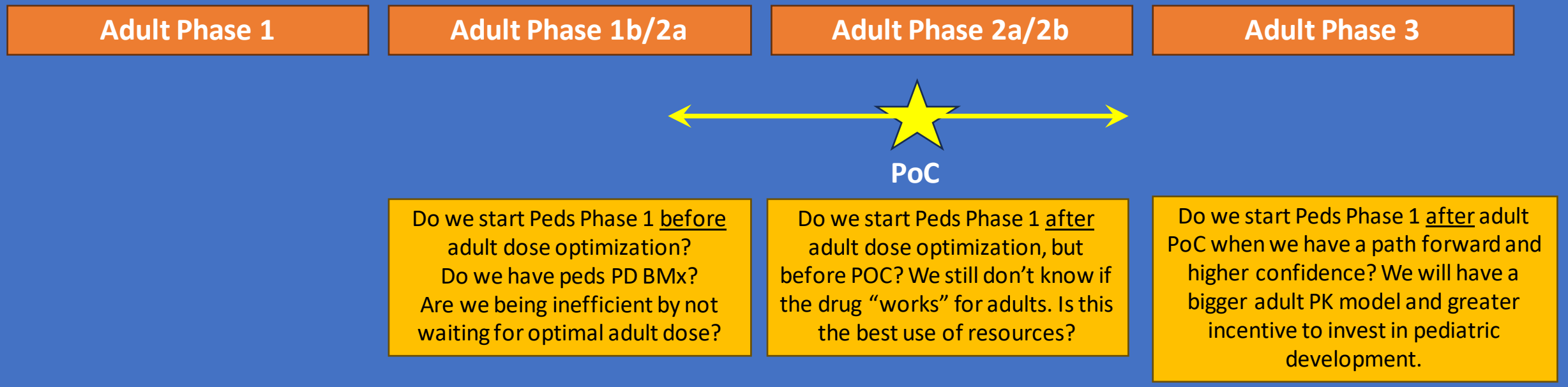
Inflation Reduction Act (IRA) disincentivizes small molecule development and the pursuit of rare indications as a lead indication

- Small molecule medicines are disadvantaged by the law by allowing Medicare to negotiate prices after just nine years, compared with the 13 years afforded to large molecule, or biologic, treatments.

- The “IRA clock” starts running after the first approval, so the strategy of pursuing approval in smaller indications first (i.e. smaller, biomarker-defined subsets) is disfavored. There will be less of an incentive to pursue a pediatric indication as a lead indication with which to file.

- **For many small biotech companies, limitations to a return on investment for small molecules in rare indications will make it more difficult to raise capital and will shift development focus to larger indications and/or biologics.**

Challenges already exist in determining the best time to start pediatric dose escalation/confirmation studies – they increase if you require greater precision around the optimal dose at the time of approval



- Companies have historically been reticent to start pediatric phase 1 without adult proof of concept (PoC), which conflicts with PIP guidance that pediatric phase 1 should start at end of adult phase 1
- Low incentive to invest in pediatric formulation development before adult POC due to a high risk of program failure
- "Infrastructure" for needed for pediatric dose optimization may not be fully in place until later in development (pediatric-specific PD biomarkers, population PK (popPK), identification of pediatric responder population, sufficient anti-tumor activity to enable exposure/response modeling)

Aspects of selecting an optimal dose are different for children compared to adults

- Translational models for pediatric cancers are far less abundant, making pre-clinical dose optimization work a challenge.
- Obtaining samples for PD biomarkers is far easier in adults compared to children. Liquid biopsies may be useful for hematologic malignanices or some solid tumors, but may be insufficient for brain tumors (the most common solid tumor of childhood)
- The broad population recommended for dose optimization studies in adults would need to be even broader for pediatric oncology, owing to differences in age and development.
- Optimizing dose for near-term safety/tolerability in advanced adult cancers makes sense, but safety for children is more than just near-term, and requires long-term follow-up data.
- Some new therapies being developed for children will likely be studied as combinations with existing chemotherapy backbones. Monotherapy dose-optimization early in development may not be the right place to invest the required time and effort.

Dose optimization for pediatric oncology is not a question of “if”, but one of “when”

- **The MTD may (or may not) be the optimal dose for targeted therapies. Dose optimization is important to maximize efficacy and maximize both short-term and long-term safety in children.**
- Accurate dosing across the age spectrum, limited dose exploration, and **detailed PK are needed for PK modeling in children**
- Dose optimization in children requires **drug-specific considerations** (formulation, PK variability, target exposure in peds cancers)
- Optimization of dose in children **requires defining the dose-response relationship**, not randomization of doses
- **Clinical trials in children cannot wait for optimized dosing in adults**

All of these points argue for an approach to pediatric dose optimization that doesn’t see approval as the deadline, but rather, as a milestone or benchmark, especially given time and cost pressures on drug development activities

Potential solutions to achieve a common goal

- **Remove the illusion of precision**
  - Is randomizing an additional 6-12 pediatric patients (of various ages/sizes) between two dose level pre-POC going to lead to an optimal dose if there isn't a reliable PD biomarker or efficacy data upon which to base a choice?
  - Should we, instead, be collecting more extensive (larger n) pediatric PK over the longer time frame of pediatric development, and utilize modeling and extrapolation wherever possible to learn from adult PK/PD and PK/efficacy?

Potential solutions to achieve a common goal

- **Remove artificial time pressure**
  - To achieve more rapid development of novel for pediatric populations, it may be necessary to accept that initial dose optimization is based on safety, while additional optimization for efficacy, or long-term safety, comes later (post-approval).
  - If there is a path to approval in a pediatric indication, is delaying review of an active drug for a pediatric indication due to lack of pediatric dose optimization at the time of approval going to benefit patients, especially in indications where patients are harder to find?
  - Can we make optimization a post-marketing committment linked to confirmatory trials or collection and submission of long-term follow-up data by including PK data?
  - Pediatric oncologists have a long history of pursuing dose optimization and combination development. How can we best encourage collaborations between industry and academia via investigator-sponsored trials (ISTs), cooperative group studies, registries, etc. to ensure that this important work done, and done to regulatory standards, and ensure those data become a part of labeling?

Potential solutions to achieve a common goal

- **Use existing incentives**
  - Can we link dose optimization to pediatric exclusivity through pediatric preclinical study requests (PPSRs)/written requests(WRs) and PIPs?
- **Work together**
  - Can we collect sparse PK on post-approval studies or as part of registries for long-term safety studies?
  - Can companies fund the transfer validated PK assays to a central location (NCI, CTEP) to ensure they are available for long-term PK data collection and dose optimization studies.
  - PIPs are considered "living documents" because the time-course of pedaitric development is long, and we learn many new things along the way. Can labeling for pediatric uses be seen the same way?

> Richard Pazdur, director of the FDA Oncology Center of Excellence, has noted that the drug label "is a living document. Many people have the misconception that the history of the drug ends with the approval of the drug. Really, that is just the beginning….We have to keep that in mind and also have a process of updating these labels."

Balogh et al, Oncologist. 2020 Mar; 25(3): e405–e411

"Dans ses écrits, un sage Italien. Dit que le mieux est l'ennemi du bien" (In his writings, a wise Italian says that the best is the enemy of the good)

- *Voltaire, Questions sur l'Encyclopédie (1770)*

Thank you for your time.