ACCELERATE Annual Conference 2022

Topic: Accelerating development of combination regimens in frontline therapy

Executive summary

During the 2022 Annual ACCELERATE conference, participants were split in small groups to work on four topics related to the development of innovative therapies for children and adolescents with cancer in order to identify issues and propose solutions. An executive summary has been prepared for each topic.

Proposals were discussed thereafter in the Plenary Session of the Annual Conference to define actions. The ACCELERATE 2022 work plan describes the objectives of ACCELERATE on this topic.

Disclaimer: The views expressed in this Executive Summary are the personal views of the participants of the Breakout Session and may not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organizations, including ACCELERATE, with which the authors are affiliated.

Chairs: Steven DuBois (Dana-Farber Cancer Institute), Martha Donoghue (U.S. Food and Drug Administration), Nicole Scobie (Zoe4life), Hubert Caron (Roche)

1. Rationale

Curing more children and adolescents with cancer will be achieved by introducing new safe and effective anticancer agents in combinations. Empiric experience strongly suggests that multiple agents are likely to be more active than monotherapy. Furthermore, there is a higher likelihood of activity with agents with non-cross resistant mechanisms of action (MOAs).

Combination therapies also offer opportunities for synergy and synthetic lethality, as well as opportunities to build upon existing standards of care (SoC).

Broadly two types of combinations can be considered: “Novel/Novel”, combining two different novel targeted therapies, and “Novel/SoC”, combining a novel therapy with a well-established treatment.

The main differences between initial trials for these two types are reflected on the following table:

<table>
<thead>
<tr>
<th>Novel-Novel</th>
<th>Novel-SoC</th>
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<tbody>
<tr>
<td>- Usually early phase trials</td>
<td>- Usually later phase</td>
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<tr>
<td>- Often relapsed/refractory population with no established standard of care (SOC)</td>
<td>- Often frontline population or a population with active relapse regimen</td>
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<tr>
<td>- Treatment with therapeutic intent but not given together with standard curative therapies</td>
<td>- Often population treated with curative intent</td>
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2. **Topics discussed**

a) **How to best to identify and prioritise relevant combinations?**

Three key themes arose from the issues raised by the discussants: biological rationale; paediatric differences; and complexity of the topic:

**Key Theme #1: Biologic rationale should drive decision-making**
- High threshold to enter pediatric clinic given rarity of paediatric malignancies
- Preclinical testing often leverages academic collaborations (rather than in-house testing in industry)
- Concern that some decisions are made for pragmatic (e.g., drug supply) rather than scientific reasons

**Key Theme #2: Children have unique considerations**
- Expect that many combinations will be “paediatric only” rather than following on from adult combination.
- Development paths will be different for new combinations tested only in children compared to moving adult combinations into younger patients
- Different standards of care - Even early phase trials must have an eye towards ultimate context of frontline standard of care

**Key Theme #3: Topic is complex**
- Highly complex topic with more questions than answers after 90-minute session
- We need agreement upon guiding principles to help prioritize combinations
- Importance of multi-stakeholder collaboration to provide infrastructure for decision-making / prioritization

b) **What are the current limitations to the rapid clinical evaluation of combinations?**
Pre-clinical combination testing is challenging
- Multi-arm experiments for efficacy and toxicity are large and expensive
- Challenges in isolating effect of each combination partner
- Assessing impact on developing organs

**Trial Design**
Trial designs should limit monotherapy testing to minimum required scientifically
- Large numbers of patients receiving monotherapy may have ethical challenges, depending upon agent and mechanism of action
- Limit lead-in phase with monotherapy to days/weeks/single cycle to obtain initial pharmacokinetic and safety data. If patients progress on monotherapy, patients can still access the combination
- Limited monotherapy data may make isolating effect of new agent more difficult

**Engaging Industry Partners**
Mixed experience combining drugs from different industry partners
- Some groups have been able to do this well and we should try to learn from these successes, e.g., eSMART trial (NCT02813135), ComboMATCH
- Other groups have had major delays and/or funding issues due to this issue. Some have moved forward with an agent because it is what was available, while some have considered purchasing one of the agents directly, but with a high cost

**Filing**
Characterizing contribution of each component of combination is important for regulatory authorities, but this is challenging
- Regulators and Health Technology Agencies may require comparison to standard of care, which can be challenging depending on trial design and combination being tested
- Complexity of developing data packages that provide contribution of each component to treatment effect observed

### c) What solutions could accelerate the development of combinations?

**Pre-clinical**
Advances in computational biology approaches
- Leverage preclinical platforms for prioritization – algorithmic modeling systems that can be used to inform synergy/antagonism/additive effect
- “Biosimulation”

**Trial Design**
Novel statistical approaches
- Role of small randomized phase 2 trials to get initial signal. OLIE trial is a good example (ifosfamide and etoposide compared to lenvatinib with ifosfamide and etoposide for relapsed osteosarcoma - NCT04154189)
- Data sharing to provide use of real-world evidence for comparator
- Hybrid comparator groups using blend of historic and contemporary comparators
- Seamless designs with go / no-go gates within a single protocol

**Engaging Industry Partners**
Potential role for government agencies
- Incentives vs. mandates for combination testing
- Hosting “across company platforms” (e.g., ComboMATCH, [https://childrensoncologygroup.org/combomatchcog](https://childrensoncologygroup.org/combomatchcog))
- Prioritize funding for combination testing (preclinical and clinical)
| Filing | All of our combination trials need to have an eye towards ultimate regulatory filing  
- Harmonize standards between academic and industry-sponsored trials  
- Engage regulatory bodies early in the development process to maximize likelihood of successful combination development program |

3. Next steps & Output

The main proposal is to have a dedicated Paediatric Strategy Forum – a multi-stakeholder workshop focused on:

- When and how much single agent testing is appropriate
- Framework for prioritizing combinations relevant to children
- Guiding principles governing early and late-phase combination testing, addressing trial design and regulatory requirements.