ACCELERATE Annual Conference 2021

Topic: Histology-agnostic evaluation of compounds in rare subgroups

Executive Summary

During the 2021 Annual ACCELERATE conference, participants were split in small groups to work on five topics related to the development of innovative therapies for children and adolescents with cancer in order to identify issues and propose solutions. Proposals were discussed thereafter in plenary sessions to define actions. An executive summary has been prepared for each topic.

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1. Rationale

Histology-agnostic cancer drugs treat cancers based on specific markers (e.g., genomic aberrations/target mutations) that they display, instead of the tissue type, organ or anatomical location in which they arise, i.e., they are “histology-independent” (of note: “histology-agnostic”, “tissue-agnostic” and “tumor-agnostic” can be considered synonyms in this context). These drugs may be expected to be active in cancers arising anywhere in the body if the relevant marker is present.

Histology-agnostic agents are also often age-agnostic, so should be effective in adult and paediatric cancers if the relevant marker is present. There may be some variability in the level of drug activity depending on disease context. Development of the drug and marketing authorisation are based on the mechanism of action of the drug rather than the (usually adult cancer) condition/indication. To date, three anticancer medicines have been approved with a histology-agnostic indication in the US and Europe (see Annex).

The objectives of this breakout session were:

1) To discuss lessons learnt from recently approved medicines for histology- (and therefore usually also age-) agnostic indications
2) To propose an optimal, efficient, future approach agreed by stakeholders for the agnostic evaluation of innovative drugs for children and adolescents.

2. Topics discussed

- Operational issues with age-agnostic studies spanning children and adults
- Evolving role for companion diagnostics in the era of more routine clinical sequencing
- Interface between rare molecular subsets and orphan drug regulations
- Regulatory and third-party payor review of histology-agnostic agents
- How to ensure that a child with a given molecular alteration gets access to the “right” agent

3. Conclusions

1. **Histology-agnostic equals age-agnostic**

   - It is broadly agreed that histology-agnostic evaluation of drugs should lead to an age-agnostic approach. However, the level of evidence needed to include children in histology-agnostic drug development programs remains as yet undefined and further discussion and consideration is required.
   - Some proposals as to how to operationalize drug development across the age spectrum may include:
     - Inclusion of children early on in drug development programs
       - Step-wise approaches (if needed) to include children in clinical trials should be well-designed, with a carefully considered dose selection process for the first children enrolled, ensuring a balance between safety and at least some chance of clinical benefit
     - The development of agnostic drugs can be conducted in separate trials (pediatric vs adult), combined trials including patients >12 yo, or truly age-agnostic trials
       - Separate trials may be less efficient but are more likely to ensure children are actually enrolled.
       - Specific pediatric slots in combined trials could help to reduce the risk of not enrolling children due to competition for slots. However, reserving specific pediatric slots should not delay the adult development. For very rare diseases, there is a real risk of that if the number of pediatric cases is truly very low - there may be no pediatric patients available. The role of master protocols with pediatric modules could be explored, as could statistical designs where a minimum number of pediatric patients is not specifically mandated, but where they are enrolled. Additional sub-analysis could be undertaken on the pediatric patient cohort to assess for any impact of age on outcomes.
     - Trials including >12 yo patients, which are an important step in pediatric development, but data are also still needed in younger patients
     - Combined trials may be best suited to specific centers with integrated experimental therapeutics programs. One way to include more pediatric centers could be achieved by implementing “satellite site” or “remote access” models. Pediatric patients should always receive their care in age-appropriate settings, by clinicians with age-appropriate expertise.

2. **Access to testing**

   - The role of advocacy groups in educating patients/families and advocating for coverage of testing is key. Some EU countries and Canada are attempting to get molecular tumor profiling covered by government health plans. The US may require a multipronged approach, with the...
involvement of advocates and academia, demonstrating cost-effectiveness and including recommendations for sequencing in national guidelines

- There are emerging issues related to companion diagnostics. The role for narrow tests is questionable in a time when more comprehensive sequencing is extending to more centers and patients, and is increasingly more time and cost-efficient, and likely to open more clinical treatment options more quickly. Moreover, it is increasingly understood that fusion type may be atypical in some tumors (e.g., NTRK1 fusion in inflammatory myofibroblastic tumor or ALK fusion in medullary thyroid carcinoma). As such, sequencing to identify only the “typical” fusion is not in the best interest of the patient. The cost to develop a specific test that few patients may use is unjustified. Furthermore, tissue scarcity for validation studies poses challenges.
  - Therefore, the group questioned the role for the need to develop companion diagnostics and proposed that new drugs should not be requested to be filed with a companion diagnostic test.
- There is growing complexity of interpreting data from newer tests and the quality of clinical curation remains understudied.

3. Regulatory issues

- Histology-agnostic trials are often relatively small and non-randomized.
- There is a need to define to what extent sponsors must demonstrate that activity is similar across the age spectrum and across histologies. It might be necessary to define a minimum number of children to include in order to support pediatric authorization, but extrapolation from adults should be used where this is possible. Trials designed with specific strata defined by histology could play a role but are generally discouraged as they are contrary to the principle of a histology-agnostic drug development paradigm.
- While pooled analysis of separate trials may be a valid approach in rare molecular subsets, it is important to prespecify the plan for a joint analysis.
- There is lack of regulatory uniformity in how agnostic drugs interface with orphan drug incentive programs, specifically with regard to whether rare subtypes of a less rare tumor type may be regarded as orphan and attract the orphan incentives for drug development, and this differs on each side of the Atlantic. The European orphan legislation is currently under review, so it is an ideal time to consider aligning perspectives.
- Overall, aligned regulatory guidance for sponsors would be helpful for the field, given the novelty of this drug development approach.

4. Real-World Data

- The opportunity for the use of real word data and real world evidence from various sources other than randomized controlled clinical trials was recognized as something that could support tumor agnostic drug development.
- The role of data from compassionate access programs needs to be elucidated. These data may help to inform dose selection for children, particularly if PK data are included. While serious adverse events (SAEs) must be reported, more data, such as efficacy or lack of efficacy, could be collected, perhaps through a centralized data warehouse.
- Post-marketing studies are difficult to conduct since they often involve small populations and low incidence events. Furthermore, academic sites may be more likely to prioritize resources
to phase 1 rather than phase 4 studies. Nonetheless, these studies will be critical to understand late effects in young patients treated early in age-agnostic drug development programs. Real-world data collection could complement post-marketing studies.

### 4. Next steps & Output

- Regulatory guidance for sponsors and investigators developing histology-agnostic agents is needed from both FDA and EMA
- Creative solutions from cooperative groups are needed in order to overcome the logistic challenges of histology-agnostic, combined (pediatric and adult) trials
- It is paramount to ensure that data derived from histology-agnostic trials are appropriate for regulatory and HTA purposes
- ACCELERATE will support the necessary framework to move these ideas forward

### 5. Annex

**Anticancer drugs approved with a histology-agnostic indication, as of February 2021**

- Pembrolizumab (US 2017)
- Larotrectinib (US 2018; EU 2019)
- Entrectinib (US 2019; EU 2020)

*The first US approval (FDA) for an agnostic drug was pembrolizumab in 2017 for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or Mismatch Repair Deficient cancer. The first agnostic drug to be approved both in the US (2018) and Europe (2019) was Larotrectinib, indicated for the treatment of adult and pediatric patients with solid tumors that display an NTRK gene fusion, who have disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no other satisfactory treatment options. TRK fusions are found in diverse cancer histologies. It has been shown that larotrectinib is effective regardless of tumor type, age, NTRK fusion gene or partner. The same has been observed for entrectinib, which also achieved agnostic approval in the US (2019) and Europe (2020).*