EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Targeting “histology-independent indications” and resulting challenges in the context of orphan designations

Update from EMA workshop and current status

3rd Industry Stakeholder Platform on R&D support

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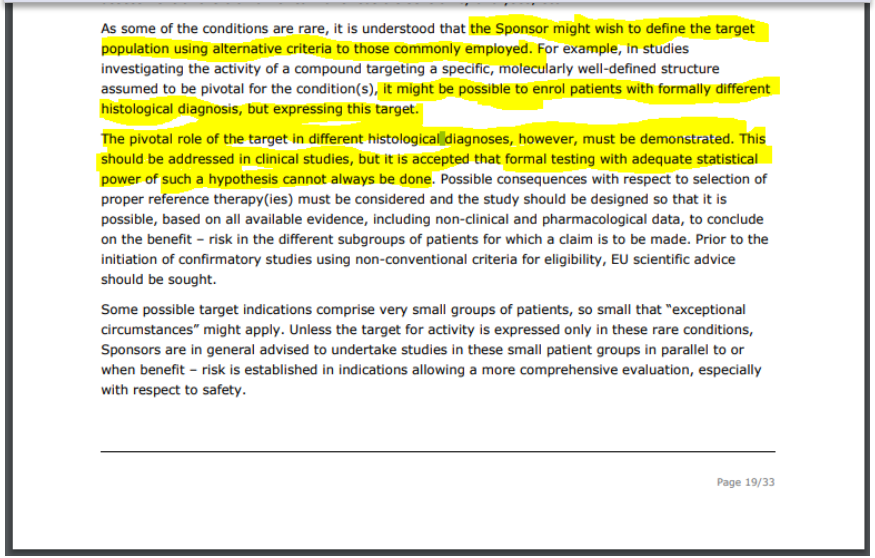
Opportunities: The concept of histology-independent indications

- Pragmatic approach already foreseen in **anticancer guideline**
- Holds great promise especially in **small populations** sharing a **common target**

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/01/WC500137128.pdf



As some of the conditions are rare, it is understood that the Sponsor might wish to define the target population using alternative criteria to those commonly employed. For example, in studies investigating the activity of a compound targeting a specific, molecularly well-defined structure assumed to be pivotal for the condition(s), it might be possible to enrol patients with formally different histological diagnosis, but expressing this target.

The pivotal role of the target in different histological diagnoses, however, must be demonstrated. This should be addressed in clinical studies, but it is accepted that formal testing with adequate statistical power of such a hypothesis cannot always be done. Possible consequences with respect to selection of proper reference therapy(ies) must be considered and the study should be designed so that it is possible, based on all available evidence, including non-clinical and pharmacological data, to conclude on the benefit – risk in the different subgroups of patients for which a claim is to be made. Prior to the initiation of confirmatory studies using non-conventional criteria for eligibility, EU scientific advice should be sought.

Some possible target indications comprise very small groups of patients, so small that "exceptional circumstances" might apply. Unless the target for activity is expressed only in these rare conditions, Sponsors are in general advised to undertake studies in these small patient groups in parallel to or when benefit – risk is established in indications allowing a more comprehensive evaluation, especially with respect to safety.

Page 19/33

Known caveats

- Requires **in-depth knowledge about the mechanism** of action and its **clinical relevance** across tumour types
- Heavily relies on **extrapolation** (plausibility of assumptions)
- **Need to explore heterogeneity** (resistance mechanisms and prognosis) but **lack of power** to detect differences
- Populations with **multiple therapeutic contexts** (available treatments)
  - Challenging for **conditional approval** (requires “unmet medical need or major contribution to patient care”), and **health technology assessment**
- **Lack of historical data** for new biomarkers when randomized trials not possible (rare cancers)

Biostatistics Working Party – key issues with basket trials (work in progress)

- **Type 1 error control in basket trials**
  - If several **independent*** sub-trials **all controlled for type 1 error** relatively to their own design are conducted, **no multiplicity issue**
- **Pooling of sub trials**

* Independence: when the only common points are logistic/ethic/legal aspects and no decision taken for one sub-trial can impact the other ones (e.g. early stop for efficacy)

Current status

- In principle, no regulatory or scientific objection to histology-independent indications.
  - Already contemplated in the anticancer guideline
- In practice though, the concept is challenging
  - Lack of successful examples of marketing authorisation applications in the EU but experience growing in scientific advice
- Reflections ongoing at the level of oncology and biostatistics working parties, possible guidance to be drafted