Histology-independent indications
Regulatory aspects

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What is an indication?

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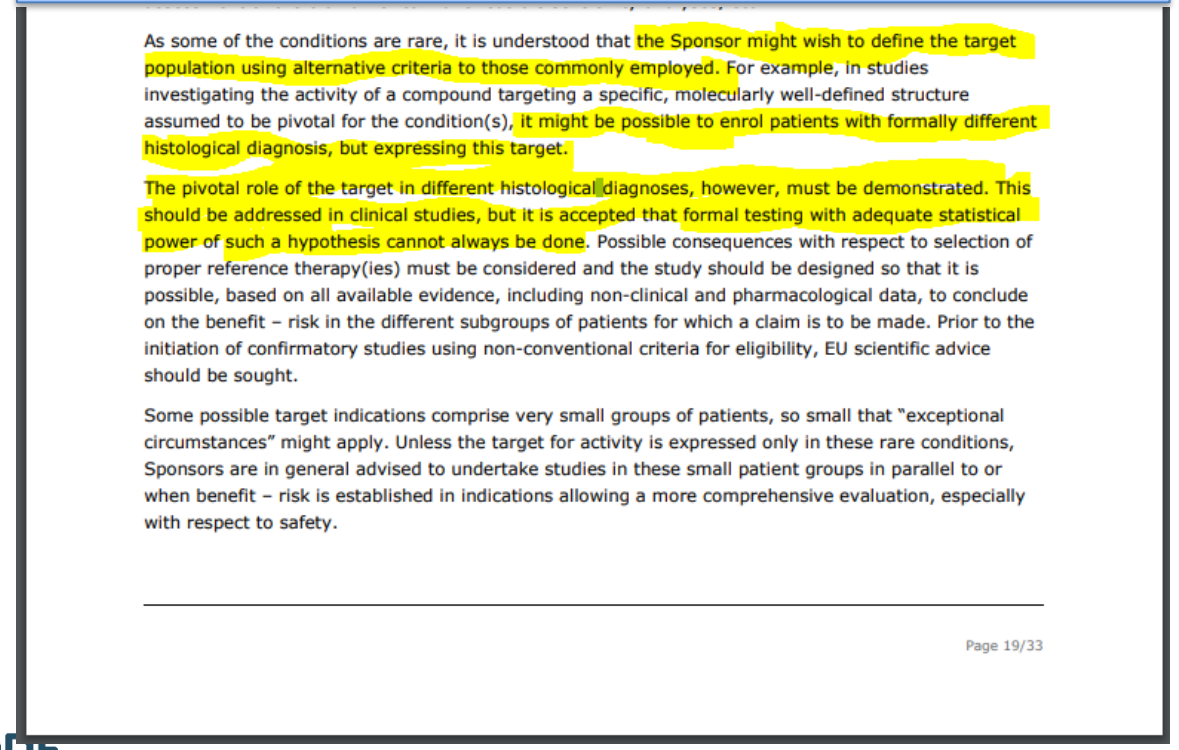
- A description of patient, disease and treatment characteristics that describe a population in whom the balance of benefits and harms has been established to be positive.
- **Is tumour type/tissue or histology necessary?**
- **Is biomarker presence sufficient?**

Histology-independent indication - concept

- The concept has been generally endorsed/encouraged
- Biomarker-driven approach already foreseen in **guidelines**

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.

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Regulatory requirements/challenges

The concept of histology-independent indications

- Requires **in-depth knowledge about the mechanism** of action and at least **strong plausibility** across subgroups;
- **Need to explore heterogeneity of effects** (interactions; resistance mechanisms) ;
- **Multiple therapeutic contexts, evidence of positive benefit-risk balance**
  - Easier when high unmet need across subgroups
  - Challenging when competing against available options with established clinical utility (e.g. survival) in some subgroups; indirect comparisons (rare diseases; lack of historical data); extrapolation

Benefit/risk considerations

B/R assessment is absolute but…

➔ How to contextualise benefit/risk in histology-independent setting?

Is RCT feasible?

If not, how to address the issue in an uncontrolled trial?

- Historical controls?
- Registries?

Some limits

- **'Orphanization'**: one unique marker artificially selected to justify ultra-orphan development despite the drug (or the marker) not being that specific of the driver/disease.
- Is the medical need the same across indications ?
  - e.g., colorectal cancer, first line, established treatments with OS benefit

Experience in the EU

Vitrakvi – Larotrectinib

- CHMP adopted a positive opinion in July 2019
- Scientific advisory group
- Oral explanation
- Indication applied:

Treatment of adult and paediatric patients with locally advanced or metastatic solid tumours (excluding primary CNS tumours) with a NTRK gene fusion after prior standard therapy or as initial therapy when there is no adequate treatment option

Vitrakvi – initial phases of assessment

Some level of scepticism on histology-independent effect

- Use of hypothesis-generating study as pivotal evidence
- Lack of representation of all tumour types, small number of patients in certain tumour types
- Tissue or histology-specific bypass mechanisms

Divergent views within the CHMP on what the outcome could be

Vitrakvi – Scientific Advisory Group - Oncology (SAG-O)

During MAA – CHMP requested expert input on scientific issues

1. Based on available data, are NTRK gene mutations driver mutations? Is the mechanism of action independent of tumour type/histology? and does larotrectinib have clinically relevant activity regardless of tissue of origin?

Outcome: Data available do not support NTRK gene fusions as universal oncogenic "drivers" and data insufficient to establish activity regardless of tumour type

2. Prognostic impact of NTRK fusion proteins?

Outcome: Association between the NTRK-fusions and prognosis in terms of long-term clinical outcomes not well-understood

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3. Indication reflecting population where treatment with larotrectinib clinically reasonable

Outcome: evidence-based clinical decisions to use larotrectinib only justified for a few conditions in situations where established alternatives are lacking or where available alternatives are associated with high morbidity and mortality

4. What additional data would be relevant

Outcome: Collect biological and clinical evidence to understand the resistance mechanisms involved, role of concomitant biological and other characteristics explaining observed heterogeneity or lack of activity, and to confirm extrapolations using reasonably powered studies to detect sufficient activity in different tumour types.

How the CHMP reached its conclusion

- **High and durable clinical activity** shown in a number of tumour types
- Thinking of the majority evolved to consider histology as effect modifier
- Histology-independent indication but restricted only to **patients with no satisfactory treatment option**
- Data not considered comprehensive → **Conditional MA**: major uncertainties on the Benefit/Risk to be addressed post authorisation and reviewed annually

Indication adopted

Treatment of adult and paediatric patients with solid tumours that display a 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

Uncertainties and limitations of favourable effects

• Importance of the histology and/or concomitant genetic alterations • Small efficacy sample size	• the extent to which tissue of tumour origin or concomitant genetic alterations impact efficacy is in need of further clarification • Issues with regard to the representativeness in relation to the indication sought • efficacy estimates imprecise • possibility to draw conclusions regarding efficacy in subgroups hampered **➔Warning in product information** **➔Specific obligation: pooled analysis for the increased sample size including the final report of study LOXO-TRK-15002 (NAVIGATE)**

Source: Vitrakvi EPAR

Summary and current status

- Concept generally agreed, some challenges remain
- Important to **consider EU scientific advice for development strategy**
- Implementation will require different approach to patient selection (repeated biopsy and whole genome/exome sequencing) and evidence generation
- Role of Registries to support benefit/risk evaluation?
- Ongoing dialogue with CHMP biostatistics and oncology working parties, FDA (international cluster; workshops), EUNetHTA, EFPIA.

Thank you for your attention