EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Histology independent drug development

Regulatory perspective

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Histology-independent indication - concept

The concept has been generally accepted

Guideline on the clinical evaluation of anticancer medicinal products

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.

Basket trials

Basket designs can be used for different purposes with diametrically opposite objectives. They can be used for early phase trials aimed to identify patient populations likely to respond to the treatment for further development. In these cases, the objective is to detect differences in activity between baskets.

When basket trials are intended to serve as pivotal evidence for registration of a histology-independent indication, and when analyses across subpopulations ("pooling of baskets") are performed, there should be reassurance that there is no clear deviation from homogeneity of the treatment effect across baskets. A meaningful assessment of deviation from homogeneity is possible only if a sufficient number of patients from each subpopulation is included. This may not be generally feasible. Therefore, as there are limited possibilities to demonstrate homogeneity of the sub-populations in the baskets, a strong rationale to support a homogeneous treatment effect has to be provided upfront based on mechanistic rationale, pre-clinical data and pharmacodynamics, which need to be supported by the clinical data from the basket study. In particular, sponsors must justify and make it convincingly plausible by clinical and/or pre-clinical data that the interaction with tumour site or histology is negligible and this should also be supported by the final data.

Anticancer GL Rev 6 adopted at ORGAM 05-10-20 clean (europa.eu)

Regulatory requirements/challenges

Non-clinical and clinical pharmacology requirements

- Good understanding of the mechanism of action of the drug
- Strong rationale to support a homogeneous treatment effect based on mechanistic rationale, pre-clinical data and pharmacodynamics (EMA/CHMP/205/95 Rev. 6).
- Biological plausibility of the biomarker: drug targets a specific molecular alteration and/or a driver mutation and/or an essential pathway involved in the cancer pathogenesis
- Good knowledge of potential resistance linked to other oncogenic drivers or mutation
- Convincingly plausible clinical and/or pre-clinical data that the interaction with tumour site or histology is limited should justify the approach e.g tumour growth inhibition similar between different non-clinical xenografts
- Well-defined population

Histology independent development – Study designs

Performing an RCT with patients regardless of tumour site?

- Issue of heterogeneity in terms of e.g. prognosis and optimal comparator
- Low prevalence/rarity of the targeted alteration
- When RCTs per tumour type not feasible and a single RCT across the full histology/tumour type-independent biomarker-positive population not reasonable

  ➔ perform RCT in a subgroup of the wider histology-independent biomarker-positive population

  Complemented with SAT in remaining tumour types

Histology independent development – Study designs

Challenges of SAT based applications:

- Usually acceptable for exploratory purposes
- No contextualisation of the results
- Impact of test agent on time to event endpoints (PFS/OS) cannot be estimated
- Risk of selection bias (selecting responding tumour types/patients)
- External validity of the population?
- Overestimation of ORR?
- High ORR driven by a specific tumour type?

➔ Besides ORR/DOR, data should show consistency of effect across tumour types

Successes and failures?

Successful developments – NTRK inhibitors


Assessment report

VITRAKVI

https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf

Vitrakvi (Larotrectinib)

- Non-clinical data fully compatible with tissue independent activity
- Presence of NTRK fusion was the strongest predictor of response in PK/PD investigations
- Pivotal study NAVIGATE: basket study, 9 different cohorts including previously treated patients who do not have satisfactory treatment options pooled with one paediatric study and one dose escalation/dose expansion study
- 14 tumour types represented with 1 to 21 patients per tumour type for a total of 93 patients
- ORR = 72% (95% CI: 62, 81), response rates ranging from 0 to 100%
- Data not considered comprehensive: CMA* granted in the EU (follow-up data post approval)

*CMA: conditional marketing authorisation

Histology independent development? MSI-H/dMMR

Keytruda (pembrolizumab)

- Developed in tumours with MSI-H/dMMR
- MSI-H not a driver mutation
- High upregulated expression of PD-1/PD-L1 ➔ rationale for PD-L1 blockade
- Application in the EU for 6 tumour types, CRC, endometrial, gastric, small intestine, biliary and pancreatic in previously treated patients based on KEYNOTE-164 (CRC) and KEYNOTE-158 (non-CRC).
- CHMP rejected the pancreatic cancer indication (n=22) with ORR of 18.2% (95% CI: 5.2, 40.3) considered as weak evidence.
- CHMP noted the exploratory nature of data, uncontrolled and post hoc selected.
- Further data in gastric, biliary and small intestine cancers from KEYNOTE-158 requested post approval

Keytruda: INN-pembrolizumab (europa.eu)

HER2/3 as a marker for histology-independent indication?

- Gaps in knowledge:
  - marked diversity and wide distribution of HER2 and HER3 mutations
  - Difficulty of generating preclinical models of these mutations that faithfully recreate their biology in patients
- Response to HER kinase inhibition depends on:
  - the individual mutant variant
  - the tumour types
  - the pattern of co-mutations present

ARTICLE

HER kinase inhibition in patients with HER2- and HER3-mutant cancers

Response to pharmacological inhibition was based on the characteristics of both tumour type and genomic variant to a degree that was not predicted by established preclinical models.

Successful histology independent development

- Requires **in-depth knowledge about the mechanism of action** and at least **strong plausibility of clinical efficacy** across subgroups;
- **Need to explore heterogeneity of effects** (interactions; resistance mechanisms) ;
- **Multiple therapeutic contexts, evidence of positive benefit-risk balance**
  - Higher chances of approval 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

Any questions?