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

4th Industry Stakeholder Platform on R&D support

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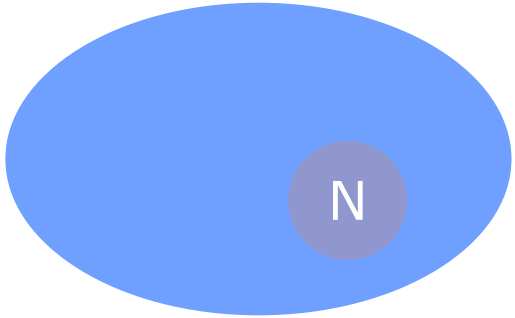
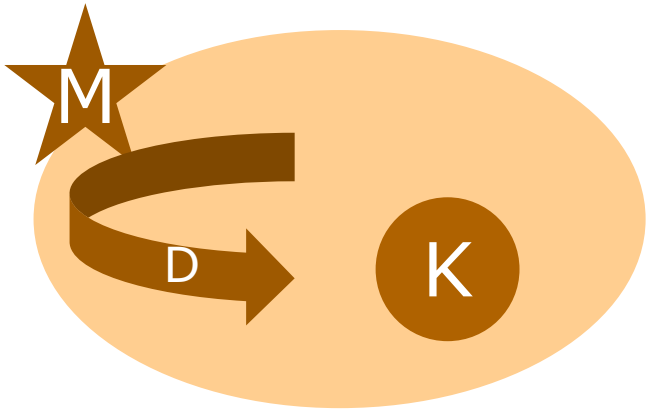
Markers and Drivers



Normal cell

Oncogenic process or survival pathway
(resistance) : efficient malignant cell (clone)

Marker = biological revelator
Driver = chain of events leading to malignancy

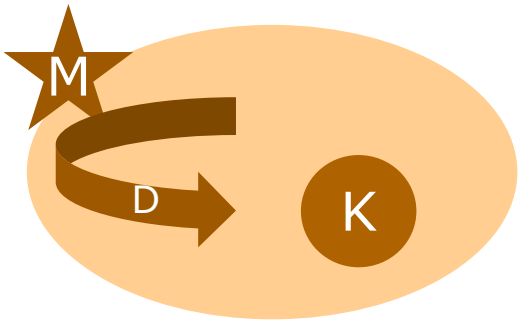


Markers and Drivers Examples

Survival or oncogenic pathway : double BRCAm

Marker = Germinal mutation or somatic mutation,
or platinum sensitivity.

Driver = DNA repair deficiency



Easy story

One marker detects
One driver
Sensitivity to **one** specific therapeutic approach

Let's use that therapeutic approach
As soon as a tumour expresses the marker
Histology, anatomy, age, line do not matter any longer

IN OTHER TERMS : THE MARKER IS THE BEST (the only relevant) PREDICTOR OF SUCCESS

The story is not always that simple

Multiple drivers (BRAFm and colorectal cancer)

New drivers (loss of Pt sensitivity)

Tumour heterogeneity (within tumours, between sites)

Proof of concept

Importance of non-clinical models

Should (could) we keep all fruits ?

Rare cancers

Prognosis ?

Comparative data ?

Extrapolations ?

- across diseases
- across lines
- across ages

Extrapolation starting point ?

The concept of histology-independent indications

- Requires **in-depth knowledge about the mechanism** of 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

The concept of histology-independent indications : 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

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