A regulatory perspective on the determination of the clinical value of cancer drugs

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The famous disclaimer of the regulator

- This presentation represents the viewpoint of Filip Josephson and not necessarily that of the Swedish MPA, the EMA or the CHMP
On what endpoints do we approve drugs for the treatment of advanced/metastatic cancer?

- **Overall survival (OS):** time from baseline to death
- **Progression Free Survival (PFS):** time from baseline to death or disease progression by pre-specified criteria (e.g., RECIST). Patients undergo repeat tumour scans/disease evaluation as specified in protocol.
- **Objective Response Rate (ORR):** tumour shrinkage according to specified criteria
- **Duration of Response (DoR):** Time from documentation of tumour response to progression, in responders
What are the designs of the pivotal studies?

• In the general case, randomised controlled trials (RCTs) against a standard-of-care treatment. Relatively often studies are open-label rather than double blind. Decision-making endpoints: PFS and/or OS

• Single arm studies may support approval for highly active drugs in late lines of therapy and/or rare tumours. Decision-making endpoints: ORR and DoR

• The inability to control bias restricts the use of the external controls (e.g., for PFS, OS) to situations where the treatment effect is dramatic
Reflections on PFS and ORR as endpoints for registration

- Direct surrogacy ORR → PFS → OS has in many cases not been established.

- Prolonged PFS as such is considered to be of benefit to the patient. In the general case, at the time of approval based on PFS, available OS data should ensure that the treatment has no detrimental effect on survival.

- Outstanding ORR and DoR data in a single arm study may suffice to establish clinical benefit in settings where the benefit of available therapies is low.
Reflections on survival

• Convincingly demonstrated favorable effects on OS are, from both a clinical and methodological perspective, the most persuasive outcome of a clinical trial

• In case of
  – long anticipated survival after progression
  – considerable influence of next-line therapies on survival
  – cross-over or non-study use of drugs similar to the investigational agents

impractically large and longitudinal studies may be needed to assess the impact of a treatment on OS
What about Patient Reported Outcomes (PRO)?

- Health-related quality of life (HRQL) is an important index of the value of cancer therapies and a complement to PFS
- PRO remains unusual in primary endpoint in registrational studies and are seldom pivotal to approval
- Frequently encountered methodological issues include e.g:
  - potential bias in open-label studies
  - questionable reliability and validity
  - deficiencies in the pre-specified statistical analysis plan (e.g., hypothesis, type 1 error control)
  - high rates of missing data
  - imputation of outcomes due to missing data
  - lack of post-progression data
What are common post-marketing commitments?

• In all cases, general pharmacovigilance activities

• Deliver more mature data from pivotal trials (e.g., OS in case of PFS-based approval)

• Further exploration of biomarkers of response

• In case of a conditional marketing authorisation, efficacy and safety information from an RCT (generally in an earlier line of treatment) may be required to provide ”comprehensive data”

• Post marketing requirements for real-life data on efficacy are unusual
What do HTA assessors tell regulators when we have a chat?

• Comparative studies versus a standard of care are necessary for the HTA evaluation of the value proposition; single arm means no reimbursement!

• HTA evaluations are based on the presumed impact of the treatment on OS and on HRQL

• There is a scepticism towards PFS, ORR/DoR as endpoints to demonstrate clinical benefit

• On the other hand, there is a readiness to use modeling and simulation approaches that are not sufficiently robust for regulatory decisions
Reflections on the interplay between the regulatory and the HTA function

- A Marketing Authorisation can be granted when data suffice to demonstrate that benefits outweigh risks with the proposed use.
- Important information for determining an appropriate price may be missing at the time of approval (e.g. a precise estimate of the impact on OS).
- The approval of a drug impacts the equipoise for its further study in the approved indication.
- Therefore the need to provide timely access to therapies with a demonstrated positive B/R for patients may adversely effect the ability to generate precise estimates of relative efficacy versus other therapies.
- It cannot be ascertained that bias is controlled in non-randomised comparisons of outcomes (e.g., real world data).