Sviluppo dei farmaci oncologici: punto di vista regolatorio

Convegno monotematico SIF
Development of anticancer drugs
from preclinical testing to clinical practice: quo vadis?

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Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo AIFA o EMA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	■	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	■	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	■	☐	☐	☐ facoltativo
2. Consulenza per una società	■	☐	☐	☐ facoltativo
3. Consulente strategico per una società	■	☐	☐	☐ facoltativo
4. Interessi finanziari	■	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	■	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	■	☐	☐	☐ facoltativo
7. Sperimentatore	■	☐	☐	☐ facoltativo
8. Sovvenzioni o altri fondi finanziari	■	☐	☐	☐ facoltativo
9. Interessi Familiari	■	☐	☐	☐ facoltativo
10. Gravi ragioni di convenienza	■	☐	☐	☐ facoltativo

* Cristina Migali, secondo il Regolamento per la prevenzione e gestione dei conflitti di interessi all'interno dell'Agenzia Italiana del Farmaco approvato con Delibera CdA n.9 del 12 febbraio 2025.

N.B. Per questo intervento non ricevo alcun compenso.

Principle of regulatory assessment

- All new active substances for **cancer** are assessed through the **Centralised Procedure** *(Directive 2001/83/EC - Regulation (EC) No 726/2004)*

- **Benefit/risk** balance should be positive

- Ensure **quality**, **efficacy** and **safety** based on scientific ground

Benefit/Risk balance

ABSOLUTE B/R **(not relative)**

in the target population

Positive B/R: absence of major objections

Negative B/R: presence of major objections

FAVOURABLE EFFECTS

Positive effect on clinical outcomes

UNFAVOURABLE EFFECTS

Mainly related to safety profile

UNCERTAINTIES AND LIMITATIONS about favourable effects

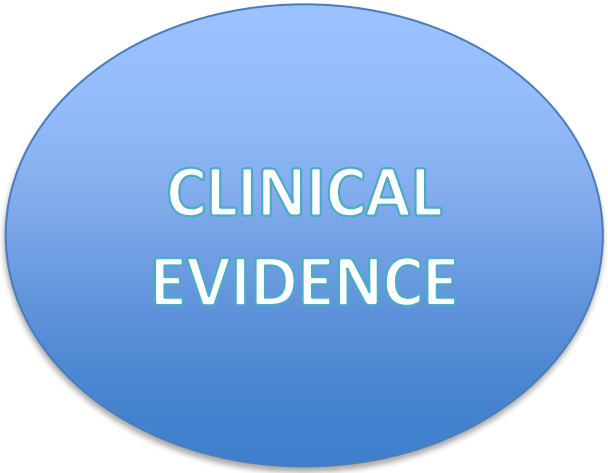
e.g. variation, important sources of bias, methodological flaws or deficiencies (including GCP, compliance, etc.), effects in subgroups etc.

UNCERTAINTIES AND LIMITATIONS about unfavourable effects

Limitations of safety data-base (e.g. sample size, duration of follow-up) and implications in predicting the safety profile of the product

management of uncertainties

Post-marketing commitments



- Regulators → B/R in the target population
- HTA → added value
- Prescribers → individual B/R

HTAR (Regulation EU 2021/2282):

Joint Scientific Consultation

Joint Clinical Assessment

well-informed decisions for developers, regulators, HTA/payers, prescribers

Types of Marketing Authorization

Standard MA	Conditional MA	MA under exceptional circumstances
• MA granting based on *comprehensive* data package • Post approval commitments (studies) *possible* • *5 year validity* • Standard MA at approval	• MA granting based on a *less comprehensive* data package • Comprehensive clinical data *expected within defined timeframe* • Post approval commitments (studies) *always* • *1 year validity* with annual renewal of MA • Switch to standard MA envisaged	• MA granting based on a *less comprehensive* data package • Comprehensive clinical data *not expected* • Post approval commitments (studies) *always* • *5 year validity* with annual reassessment of MA • Standard MA not envisaged

Benefit/risk balance should be always positive!

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AGENZIA ITALIANA DEL FARMACO

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 September 2024
EMA/CHMP/458061/2024
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation application

Considerations on evidence from single-arm trials

The Benefit/Risk Assessment - reality check

Single Arm Trials in Marketing Authorisation

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

Single-arm trials supporting the approval of anticancer medicinal products in the European Union: contextualization of trial results and observed clinical benefit

J. Mulder[1*], S. Teerenstra[1,2], P. B. van Hennik[1], A. M. G. Pasmooij[1], V. Stoyanova-Beninska[1], E. E. Voest[3,4] & A. de Boer[1,5]

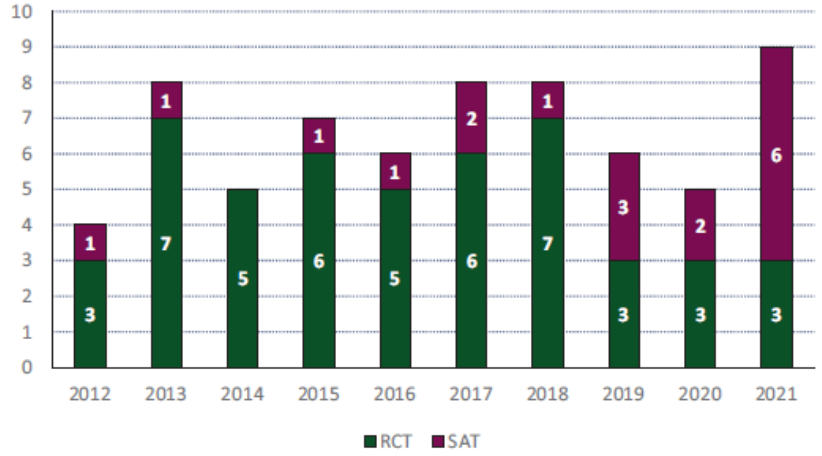
[1]Dutch Medicines Evaluation Board, Utrecht; [2]Department for Health Evidence, Biostatistics Section, Radboud University Medical Center, Nijmegen; [3]The Netherlar Cancer Institute, Amsterdam; [4]Oncode Institute, Amsterdam; [5]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

Available online 11 April 2023

- 18/66 anticancer products approved based on SATs
- 21 therapeutic indications

Observation period: 2012-2021

- Total MA granted in EU: 731
- Anticancer products: 66



Randomised controlled trials (RCTs) are the standard for providing confirmatory evidence on the efficacy and safety of a new treatment

- A randomised clinical study is expected whenever feasible
- Establishing efficacy and a positive B/R based on non-randomized studies might be particularly challenging:
  - lack of features that are instrumental to avoid bias
  - absence of a control arm, and the subsequent need to rely on external (extra-study) information for interpretation of results
  - remaining uncertainties and need for confirmatory comprehensive data to convert CMA into full MA - not always feasible/provided despite agreed SOBs
- Acceptability of SAT as regulatory evidence depends on the clinical context and on the MoA of drug (case-by-case decision) – Scientific advice recommended

Some principles:

- Pre-specify!
- Primary endpoint objectively measurable and able to isolate treatment effects (no time-to event endpoints)
- Selection of adequate population (discuss prognostic and predictive variables) → magnitude of effect should not depend on a favourable selection of the population
- A priori knowledge of the natural course of disease
- High patient or disease heterogeneity → challenge for interpreting a SAT

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SCIENCE MEDICINES HEALTH

24 July 2025
EMA/CHMP/225255/2025
Committee for Medicinal Products for Human Use (CHMP)/Methodology Working Party (MWP)

Draft Concept Paper on the Development of a Reflection Paper on the Use of External Controls for Evidence Generation in Regulatory Decision-Making

- **RCTs are the gold standard of evidence to support causal conclusions on benefits and risks of medicines in regulatory decision making.**
- However, in some situations causal conclusions may be derived from data collected under a clinical trial protocol, while the control arm was not a randomized arm in that same protocol i.e. external control arm (ECA).
- External control may be derived from data from other clinical trials, RWD or other sources.

- Reflection paper planned to be finalized in 2027 → External controls to establish positive B/R??
- Points that will be discussed:
  - Definition of ECA
  - Appropriate clinical and regulatory setting and minimal requirements for external controls
  - Methodology, data quality, source of data

25 July 2024
EMA/CHMP/ICH/295401/2023
Committee for Medicinal Products for Human Use

ICH reflection paper on pursuing opportunities for harmonisation in using real-world data to generate real-world evidence, with a focus on effectiveness of medicines

22 October 2021
EMA/426390/2021
Committee for Human Medicinal Products (CHMP)

Guideline on registry-based studies

17 March 2025
EMA/99865/2025
Committee for Human Medicine Products/Methodology Working Party (CHMP/MWP)

Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence for regulatory purposes

Making greater use of real-world evidence and real-world data can improve the evidence base for benefit-risk decisions

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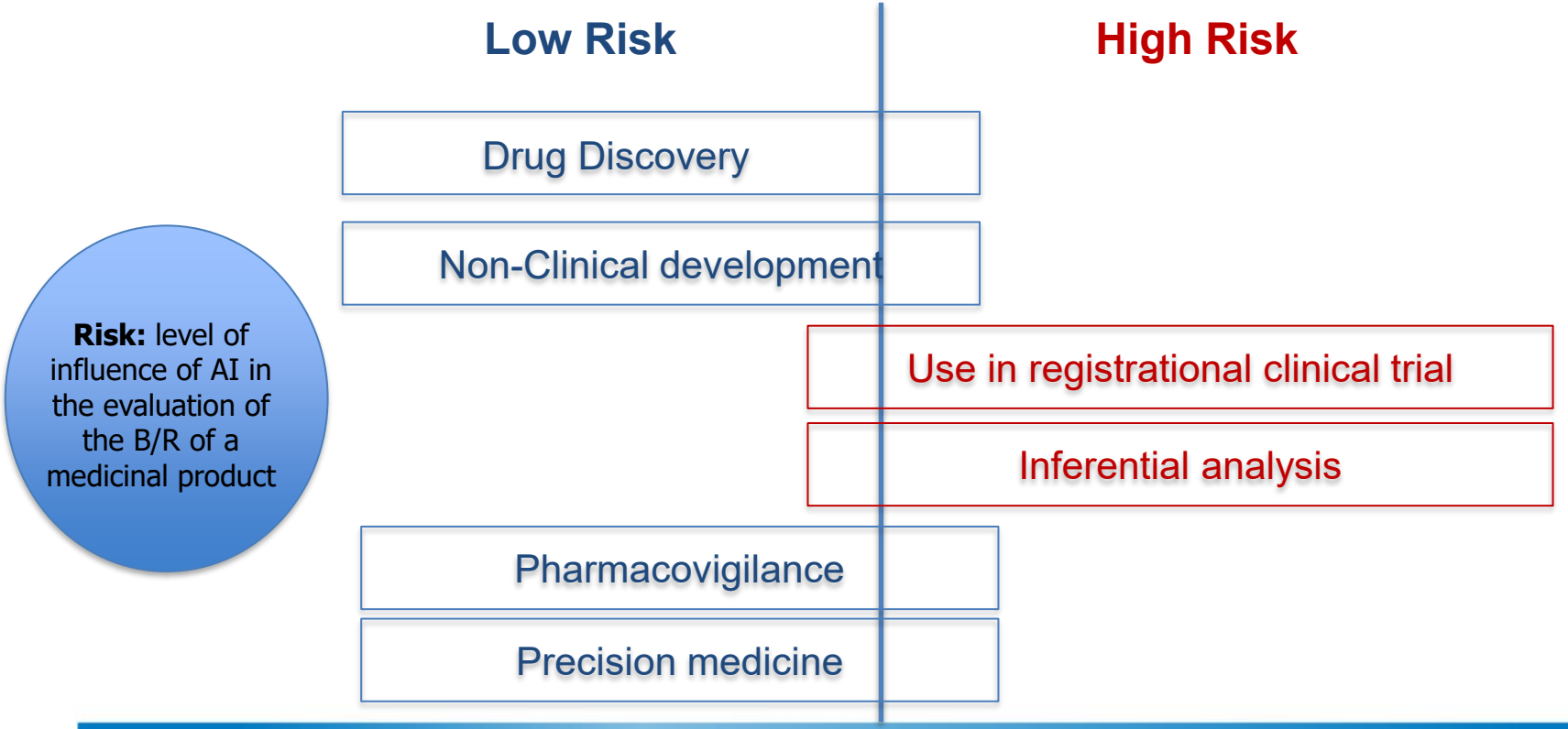
9 September 2024
EMA/CHMP/CVMP/83833/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

EMA reflection paper: risk-based approach



Final considerations (1)

- Positive (absolute) Benefit/Risk in the target population should be demostrated for regulatory approval
- The best possible clinical evidence is key to support regulatory decision and shoud address different questions from different stakeholders
- Regulatory flexibility (e.g. Conditional Marketing Authorization) exists, its use should be justified and only if meeting certain criteria

Final considerations (2)

- RCT is the gold standard to provide confirmatory evidence, and it is expected whenever feasible
- Resorting to non-randomized trials is often justified in rare cancers/rare molecular niches, several examples of successful application based on SAT
- However, acceptability of SAT is a case-by-case decision, establishing a positive B/R on SAT may be challenging

Final considerations (3)

- High-quality RWD/registries may be incorporated in clinical development in rare disease and support decision-making, but need rules
- Regulators should adapt to progress (e.g. AI), but developers should meet regulatory standard → early interaction between regulators and developers (scientific advice)
- Collaboration between regulators, academia/researchers, industry and patients is needed to increase research plan acceptability, evidence generation, scientific rigor, timely decisions

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