Innovation and access in rare cancers

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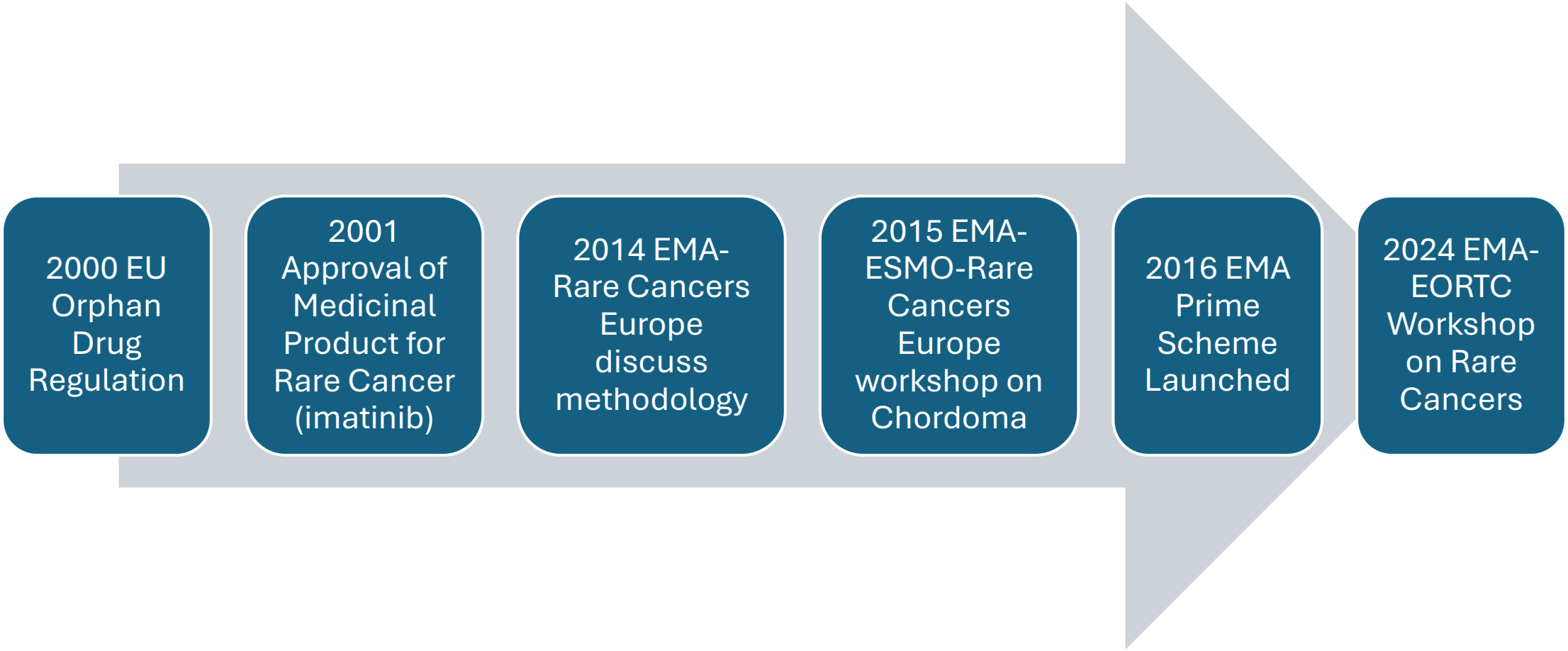
(Disclaimer: The views presented are personal and not those of EMA)

EMA's Rare Cancers Timeline



Key Challenges in Rare Cancers and Innovation Pathways

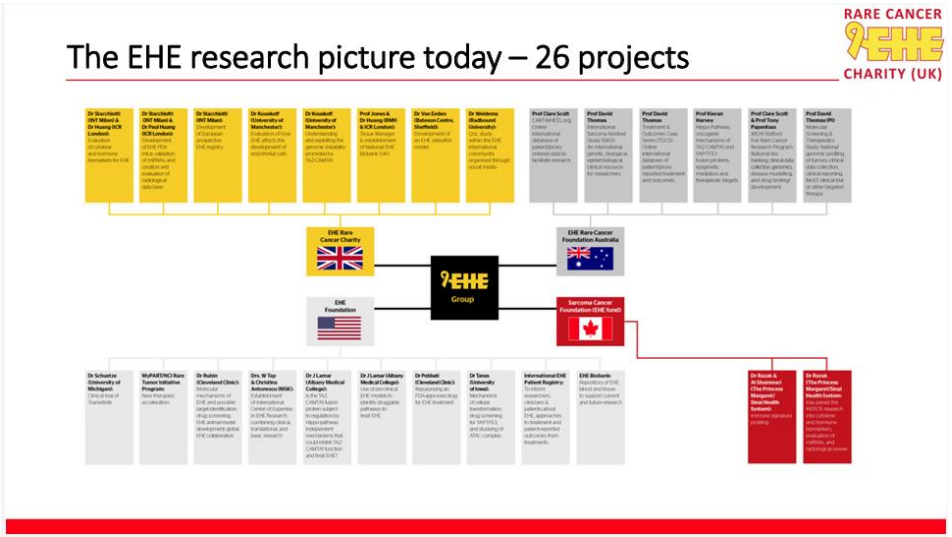
- **Challenges in Rare Cancers**
  - **Rarity of Patient Populations**: Small patient groups make recruitment for clinical trials difficult
  - **Limited Knowledge**: Fewer studies on rare cancers lead to gaps in understanding disease mechanisms and treatments
  - **Regulatory Hurdles**: Approvals often require high levels of evidence, but standard randomized trials may be impractical
  - **High Development Costs**: Limited market potential and higher development costs
- **Innovation Pathways**
  - **Expedited Regulatory Approvals**: Use of mechanisms like conditional marketing authorization (CMA) and accelerated approval processes
  - **Benefit-risk Communication**: Structured frameworks for communication
  - **Use of Real-World Data (RWD)**: Incorporating data from patient registries, observational studies, and electronic health records to support clinical evidence
  - **Patient engagement**: Interest in patient preferences, outcome research
  - **Collaborative Research Networks**: Partnerships to share knowledge and resources

“To the people who have them, rare cancers are not just ‘rare’ – They are very frightening!”

H. Leonard (2024)

EMA-EORTC workshop on ultra-rare cancers

“Patients have a huge part to play,
in research, funding, and much more
(‘momentum building’),
but we need solutions. Urgently!”



Key Challenges in Advanced Cancers with High Unmet Need That Affect Small Populations

- **High Unmet Medical Need**
  - **Lack of Effective Therapies for Advanced Disease:** Many rare cancers are diagnosed at advanced stages due to non-specific symptoms and limited awareness
- **Additional Challenges Due To Small Populations**
  - **Rarity of Patient Populations**: Small patient groups make recruitment for clinical trials difficult
  - **Limited Knowledge**: Fewer studies on rare cancers lead to gaps in understanding disease mechanisms and treatments
  - **Regulatory Hurdles**: Approvals often require high levels of evidence, but standard randomized trials may be impractical
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Urgency To Address High Unmet Medical Needs (HUMN)

- HUMN justify different risk attitudes
  - E.g., expedited approval like “conditional approval” or “accelerated approval”
- Rarity per se does not justify different evidentiary standards
  - E.g., Orphan Drug legislation to support development

L. Fields (1891), “The Doctor”, Tate Gallery, London

Risk Attitudes and Decisions

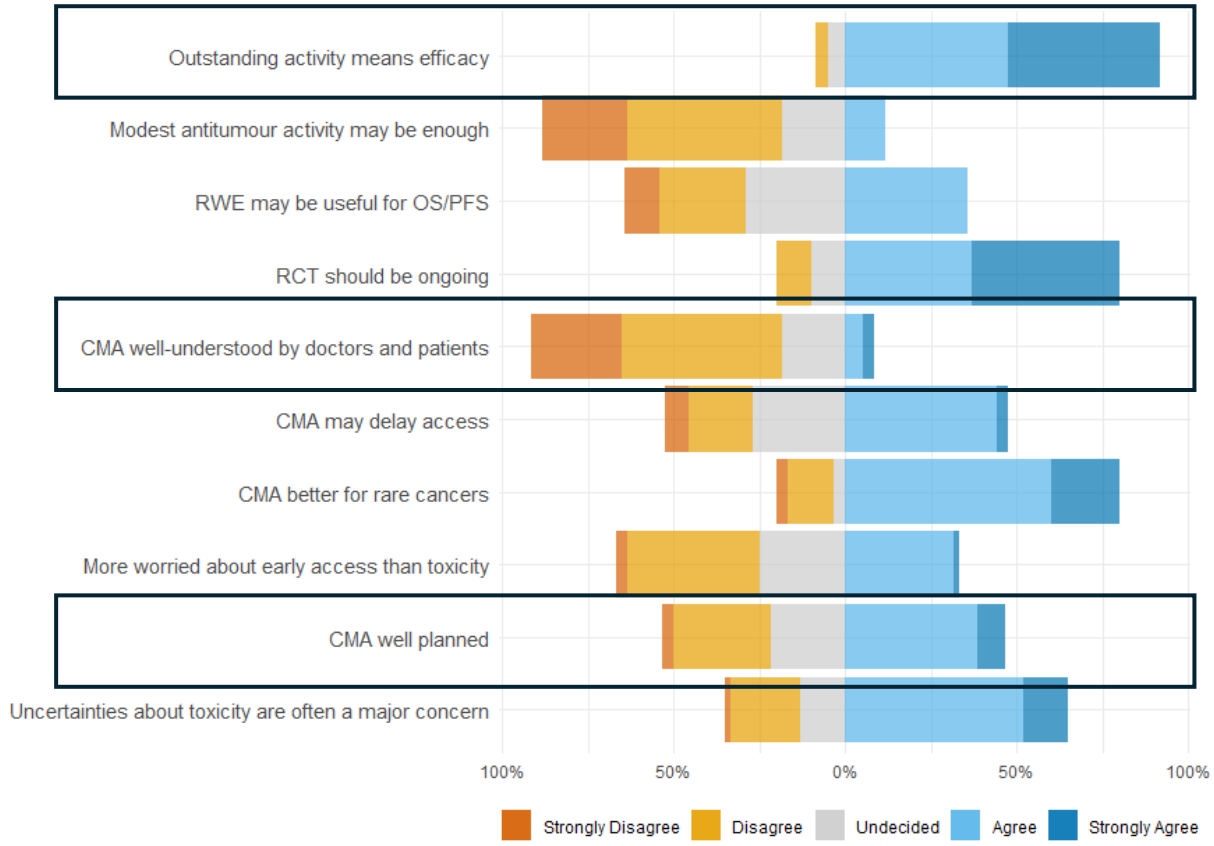
- Full approval
  - Decision under “certainty”: Effects are quantified at population level with measurable precision
  - Positive benefit-risk: “How much do I value this treatment’s effects? Is this treatment more useful than placebo?”
    - A question of value judgments
- Expedited approval
  - Decision under “uncertainty”: likelihoods of effects often not precise, large uncertainties
  - Positive benefit-risk: “How likely will this treatment improve my quality of life or survival, and what are the risks of harm or no benefit? Would I find such likelihoods and risks acceptable?”
    - A question of risk attitudes

Patients’ different attitudes to risk should be respected (…) Healthy persons’ fear of risk cannot block access to experimental drugs

B. Ryll (2015) EMA-RCE Chordoma Workshop

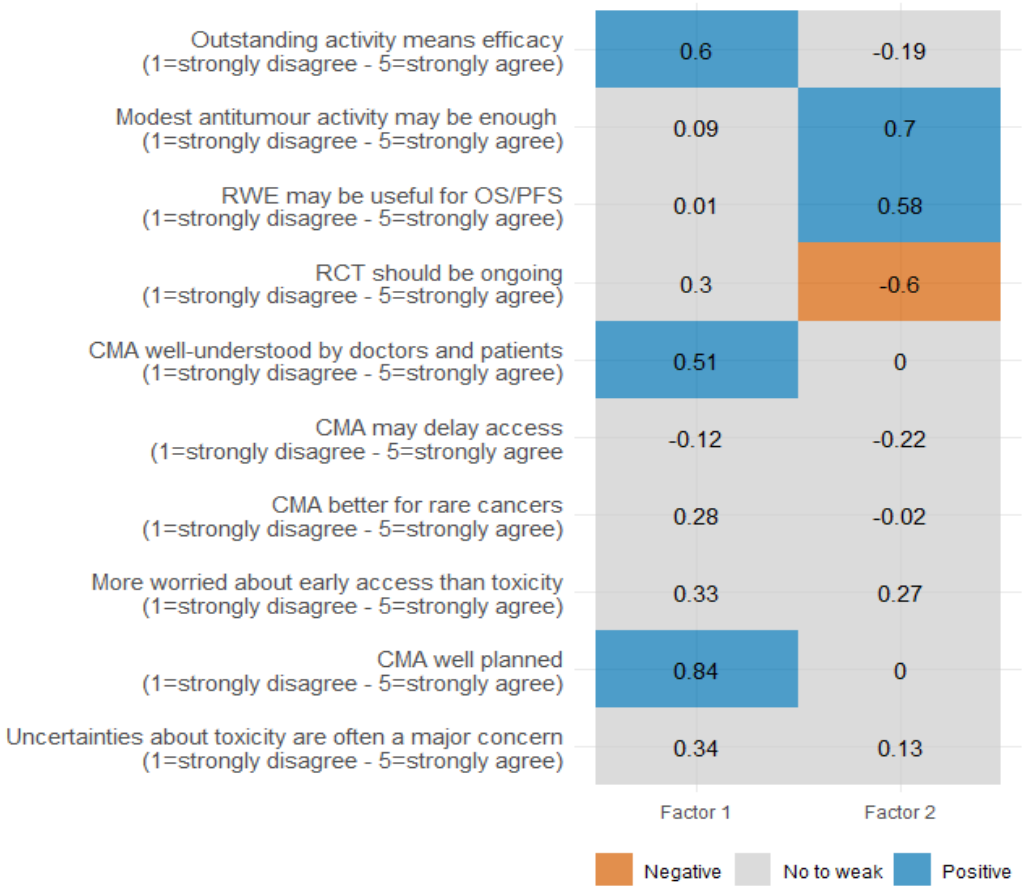
EU Regulators' Attitudes abut Expedited Approval

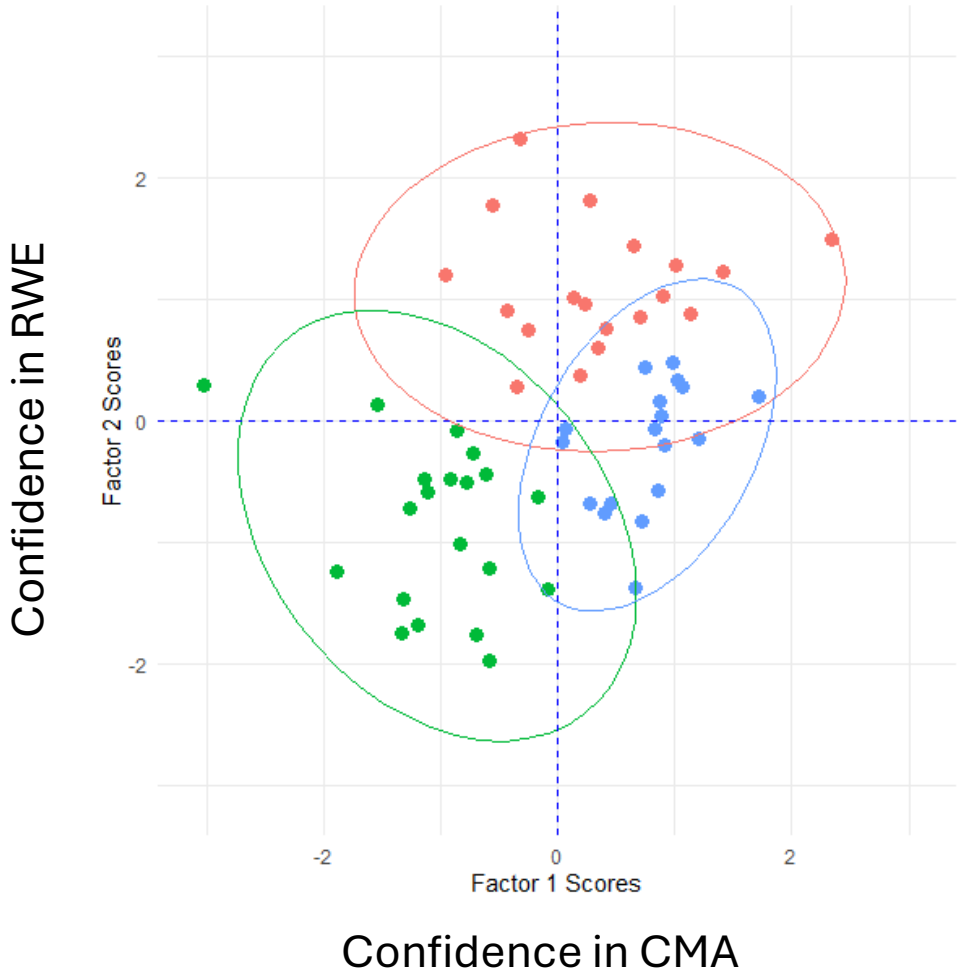
- High antitumour activity convincing
- Submission needs to be part of a comprehensive evidence generation plan (efficacy, toxicity)
- Need to communicate uncertainties effectively to doctors and patients



Attitudes about expedited approval
D. Postmus (2024) DIA Europe

Different Groups Based on Confidence in CMA and RWE





Summary of EMA CMA Survey

- In situations of high unmet medical needs
  - The value of high **antitumour activity**
  - Developing Comprehensive **Communication**
  - Role of evidence other than randomized clinical trials (**RWD**)

The Value of High Antitumour Activity

- An endpoint generally considered not to measure clinical benefit
  - Effects on PFS/OS/HRQoL can only be assumed
- In situations of HUMN (rapidly progressive disease, no other treatments), a new treatment that leads to tumour shrinkage is **considered useful by many patients and doctors, even if effects on other endpoints cannot be easily expected**
  - **A useful effect in specific situations?**
  - **Study patient preferences**

P. Rubens (1611-1612), "Prometheus Bound", Philadelphia Museum of Art

Developing Comprehensive Communication

- Need a decision framework that ensures timely evidence generation and efficient communication

1.Likelihood of Effects: What are the expected benefits and harms? What are levels of uncertainty and assumptions over time?
2.Timeframes for Confirmation: What confirmatory studies or data collection (e.g., post-marketing trials); what delay is justified?
3.Conditions for Reassessment: How the decision will be reassessed, what is the hypothesis? What if it is not met? What if the data re not clear?
4.Risk Management and "coping strategies": How to monitor and mitigate risks?
5.Transparency and Communication: How to fully inform patients and doctors about the uncertainty and any updates.

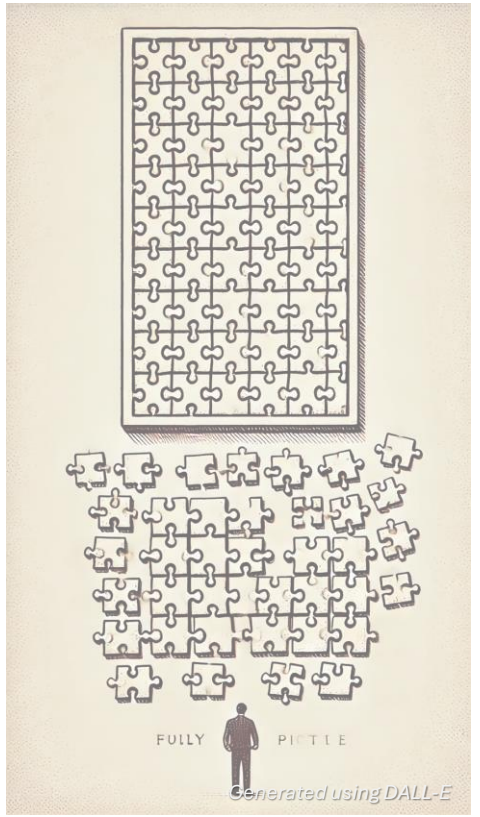
What Evidence When Populations are Small?

- Trade-off between statistical precision and clinically interpretable results
- How to strengthen the evidence adequate for decision context? EMA Small Population Guidance
  - Corroboration: Combine data from multiple sources (e.g., RWD, patient registries, multiple centres/cohorts)
  - Triangulation: Use various methodologies (different estimands; indirect comparisons) to gather complementary evidence
  - Sensitivity analyses: Check whether results hold under different assumptions

Raphael (1509–1511), “The School of Athens”, Apostolic Palace, Vatican City

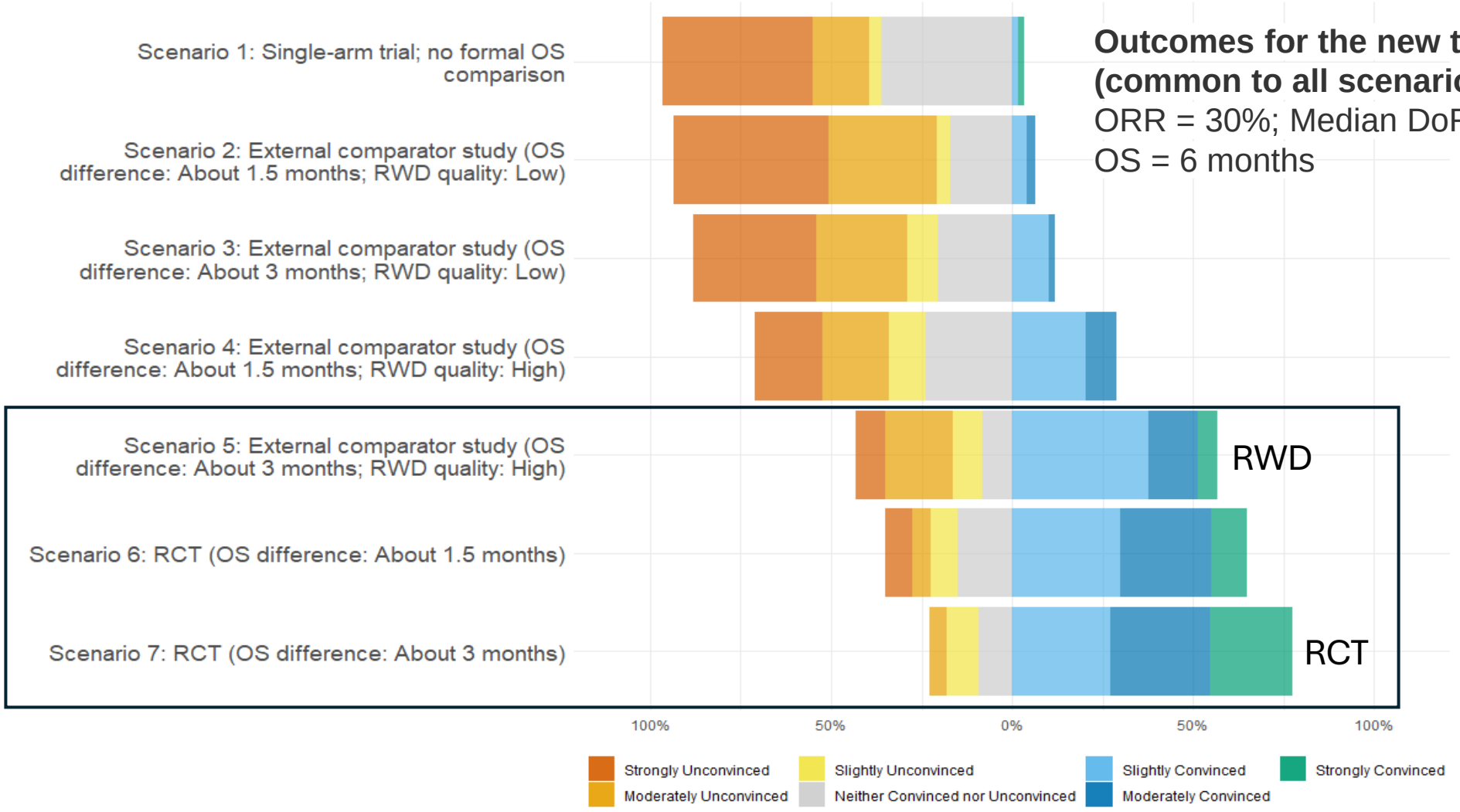
Designing “Tailored” Trials

- In some situations, it may be justified to address **multiple questions** to maximise likelihood to observe an effect even if contribution of different elements unclear
  - E.g., novel/novel; combinations
  - Optimisation v timely access v innovation: Need for systematic approach based on unmet need, innovation, etc.
- Good Clinical Practice: **Study standards have to be proportional to the objectives**
  - EMA framework for collaboration with academia; **avoid overinterpretation of regulatory requirements**



Conquer first and optimise later

Role of External Controls Based on RWD



Outcomes for the new treatment (common to all scenarios)
ORR = 30%; Median DoR = 6 months;
OS = 6 months

High quality RWD almost as convincing as RCT in some situations

D. Postmus (2024), Results of a survey among hematologists and regulators, DIA Global.

Finding a Path Forward

- **Patient preferences and risk attitudes** in situations of high unmet medical need
  - Value of durable **antitumor response** in specific settings; uncertainty decision framework
- Use **different approaches to evidence generation** to overcome the challenges of small populations
  - Evidence development plan: Corroboration; triangulation; high quality **external controls based on RWD**
- **Communicate** uncertainties effectively to doctors and patients
  - Develop a structured **framework for communicating uncertainties**

V. van Gogh (1889), "The Starry Night", The Museum of Modern Art, New York.