Harmonization of Cohorts, Adjustment Methods, and Endpoint Assessments for the Development of ECAs

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Disclosure

- Qiufei Ma is an employee and shareholder of Regeneron Pharmaceuticals, Inc.
- The views and recommendations are the employee's own and not to be attributed to the employer, Regeneron

Recent ECA Developments in Hematology Oncology: Industry Examples

ECA name	Disease	Multiple data sources
ReCORD-FL (Salles et al, 2022)	FL	10 **clinical centers** in 5 countries (US, Canada, Spain, UK, Germany)
SCHOLAR-5 (Ghione et al, 2022)	FL	7 clinical centers in 5 countries (US, Canada, Spain, UK, Portugal) pooled with **post-trial** data
SCHOLAR-2 (Hess et al 2022)	MCL	14 centers in UK, France, Germany, Spain, Italy, Sweden, and Denmark
NDS-NHL-001 (Van Le et al, 2023)	DLBCL	11 clinical sites (2 in North America and 9 in Europe) pooled with 3 US **EHR**
KarMMa-RW (Jagannath et al, 2021)	MM	Data sources from North America and Europe: < 30 clinical sites, **registry**, 4 EHR
ORCHID / FLORA (Thieblemont et al, 2022; Bachy et al, 2022)	DLBCL / FL	About 30 global clinical sites (North America, Europe, Asia)

DLBCL: diffuse large B cell lymphoma; ECA: external control arm; EHR: electronic health record; FL: follicular lymphoma; MCL: mantle cell lymphoma; MM: multiple myeloma.

Limitations Raised by Regulator / HTA Reviewers That Impact the Interpretability of the ECA Results

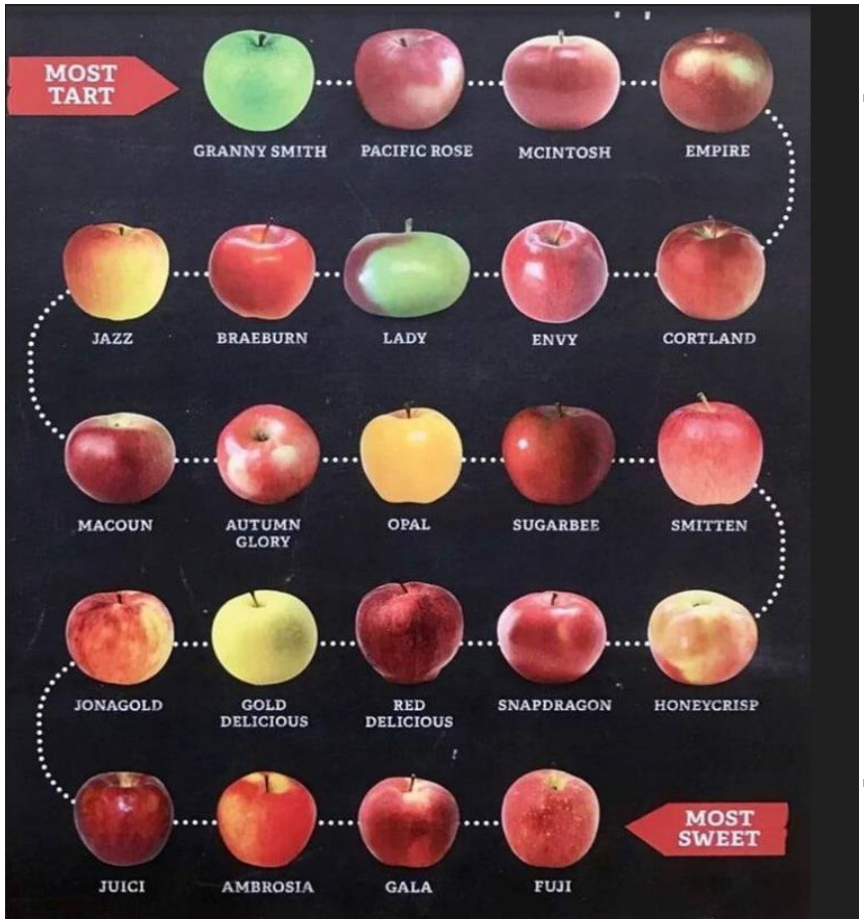
Today's focus is on the following challenges (and potential solutions):

1. Heterogeneity of **data collection / capture** across multiple data sources
2. Selection of **prognostic** variables for matching / weighting in comparative analyses
3. Lack of standardized assessment criteria and timing of real-world **response**

ECA: external control arm; HTA, health technology assessment.

One Cohort Needs To Be Drawn From Multiple Sources

Selecting similar patients to those in a target trial to create an ECA cohort



ECA **versus** **Target trial**

ECA: external control arm.

Identifying an ECA Cohort Comparable to the Trial Arm

- Conducting a **feasibility** assessment of target trial I/E criteria used in real-world (RW) settings
  - With clinical expert input, site- / data-manager interview, literature review
- Documenting **similarities and differences** in I/E criteria between ECA and target trial
  - Explaining why some trial criteria are not applicable in RW settings
- Developing a **systematic** approach to applying the trial I/E criteria across real-world data sources
  - Aim to use majority of the trial I/E criteria (e.g., 50%-70%). Limitation: excluding those with missing values for I/E will reduce sample size
  - May modify key inclusion criteria to exclusion instead (e.g., convert inclusion requirement ECOG=0/1 to exclusion criteria [i.e., exclude those with ECOG>=2])
  - For criteria not existing in RW, appropriate algorithm/imputation can be leveraged with clinical judgment
    - Example: how to apply “life expectancy > 6 month” in ECA? Development of de novo life expectancy (LE) prediction models, incorporating known predictors for LE and clinical expert opinion, to allow for the application of the minimum LE clinical trial criterion in RW studies

I/E: inclusion and exclusion; ECA: external control arm; ECOG: Eastern Cooperative Oncology Group; RW: real-world

How to Select Prognostic Factors for Matching/Weighting in Comparative Analyses?

- *To avoid a results-driven analysis, the relevant factors of the adjustment in the analysis must be prespecified*
- *Ranking importance of factors is also essential for actual variable use and imputation for missing values in ECA*

Challenge	Solution
Lack of consensus on important prognostic factors ▪ How to prespecify prognostic factors for adjustment?	**Conduct a systematic literature review and survey of physician experts**

ECA: external control arm.

Key Prognostic Factors: Myeloma Example

Step 1: To conduct an SLR of prognostic factors associated with objective response rate, overall survival, progression-free survival, complete response, partial response, and duration of response in patients with relapsed / refractory multiple myeloma[1]

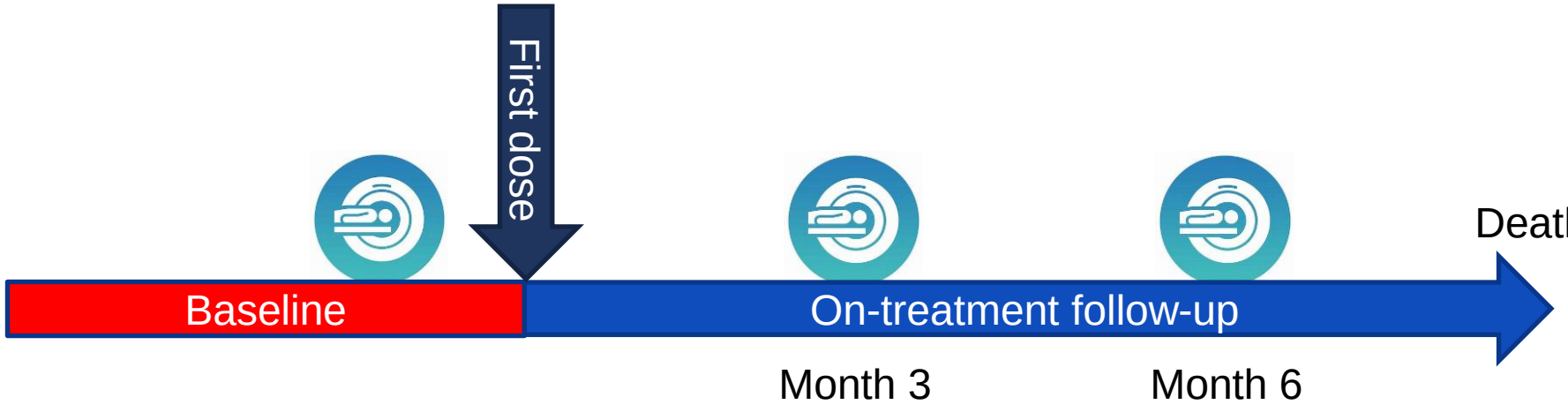
Step 2: Ranking importance of prognostic factors for MM—international physician panel consensus following an SLR[1]

- Included international MM clinical experts from France, Germany, the UK, and the US
- The objective of the panel was to confirm the variables identified in the SLR and to **rank** the prognostic factors by level of importance:
  - Pooled rankings calculated by averaging across the experts' individual rankings
  - Presented to the panel for discussion; rounds of panel voting to obtain agreement

[1]Kumar et al., *Hemasphere*. 2023a; IMS, 2023b.
MM: multiple myeloma; SLR: systematic literature review.

Clinical Trial Response Determination had a Fixed Schedule With Prespecified Classification Criteria

- In oncology trials, and unlike in the real-world, response is generally assessed according to a fixed schedule.



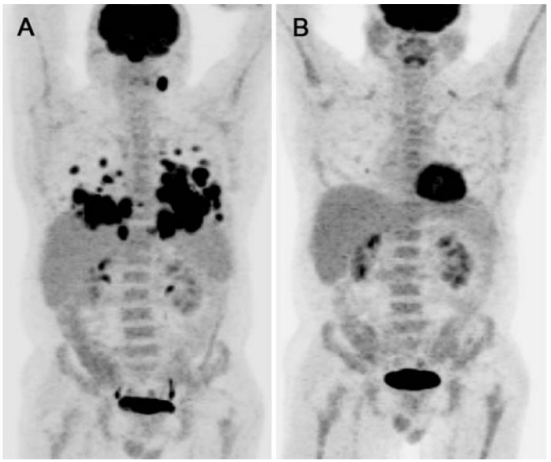


Image: Schöder, 2006.

- Single-arm trial, DLBCL, regular imaging schedule to ascertain treatment response: according to the **Lugano** classification of malignant lymphoma and as assessed by **independent central review (ICR)**
- Similar considerations apply to cancers with laboratory-based responses, e.g., multiple myeloma

DLBCL: diffuse large B cell lymphoma.

Variability in RW Response Assessment

Situation

Differences in **response assessment** approach and schedule of subjects from **RW sources** may impact the interpretability of the ECA study results

DLBCL Example

- Target trial: Response assessment based on Lugano according to ICR
- ECA RW response criteria: May also include IWG Response Criteria and Revised Response Criteria for Malignant Lymphoma, in addition to Lugano
  - Certain sites (e.g., Germany) do not systematically undertake PET-CT scans for patients. Some patients cannot be classified per Lugano due to the lack of required underlying information (PET-CT)

DLBCL: diffuse large B cell lymphoma; ECA: external control arm; ICR: Independent central review; IWG: International Working Group; PET-CT: positron emission tomography-computed tomography; RW: real-world.

Improve Ascertainment of ECA Treatment Response

When a trial primary endpoint is **response** and timeline / budget allow, there are 2 options for consideration:

1. Collect scans for all patients
   (Thieblemont et al, 2022; Bachy et al, 2022)

- **ICR** of baseline and follow-up scans, per Lugano, as **primary** analysis of response:
  - Pros: may harmonize RW response determination; mimics target clinical trial's endpoint
  - Cons: cost and timeline implications; need a larger pool of patients to yield adequately sized subsample of patients with available scans
- **Sensitivity** analysis: **treating physician**-assessed response comparison from ECA vs trial

Note that ICR does not improve on data availability nor fully resolve assessment schedule difference

2. Collect scans in a subset of patients
   (Zinzani et al, 2021)

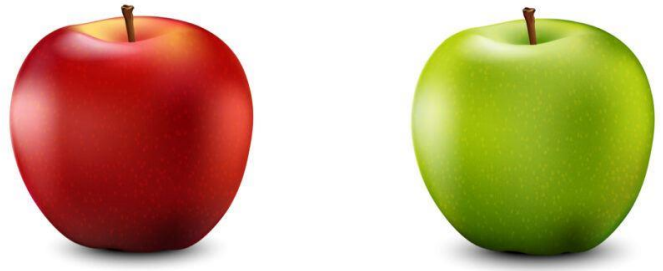
- **Validation** of response assessments can be performed on 20% of patients from an ECA:
  - Available scans before baseline and ≥ 1 postbaseline scan, physician recorded tumor-response assessment, and relevant available clinical data
  - Response assessments from the physician-reported and the independently reviewed/validated can be subjected to a concordance analysis
    - Pros: validate RW response
    - Cons: subset may not be representative of all patients

ECA: external control arm; ICR: Independent central review; RW: real-world.

Summary

Harmonization of cohorts, adjustment methods, and endpoint assessments for the development of ECAs:

1. Develop a systematic approach to applying the trial inclusion / exclusion criteria across RW data sources
2. Conduct an SLR and survey of physician experts to define prognostic factors a priori in the SAP, for matching / weighting in comparative analyses
3. Use independent central review (ICR) or validate response in a subset of patients to enhance the comparability of outcomes



ECA: external control arm; ICR: Independent central review; RW: real-world; SAP: statistical analysis plan; SLR: systematic literature review.

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