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Use of an independent data review committee to promote best practices for external control arms: A case study in relapsed/refractory multiple myeloma

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Background

Regulatory landscape and ECA studies

- External control arm (ECA) studies using patient-level real-world data (RWD) may be used as comparators for single-arm clinical trials
- The FDA acknowledges the potential of real-world evidence (RWE) in assessing treatment benefits, provided that the data are both relevant and reliable to address the specific research question[1]

Unmet need

- However, variability in RWD sources, differences in patient populations and the absence of random assignment in ECA studies can make ensuring data quality, relevance, and cohort comparability a challenge

IDRC use and strengths

- Use of an Independent Data Review Committee (IDRC) can mitigate these limitations by providing impartial evaluation of data quality, examination of data relevance and endpoint-blinded assessment of the suitability of comparing clinical trial and RW standard-of-care (SOC) cohorts
- Furthermore, IDRC involvement strengthens regulatory and Health Technology Assessment (HTA) submissions by providing an additional layer of scientific rigor and transparency to ensure that data analysis plans are aligned with health authority requirements for RW studies

Objective

- To describe our experience leveraging an IDRC to assess data quality, relevance, and cohort comparability in an ECA study for relapsed/refractory multiple myeloma (RRMM)

Involvement

Regeneron (sponsor): devised concept of IDRC; reviewed IDRC charter; contracted IDRC members;
EVERSANA (third-party vendor): developed IDRC charter; identified potential IDRC members; analyzed data; organized and prepared IDRC meeting materials; presented data at IDRC meetings;
IDRC Chair: endorsed IDRC charter; moderated discussions during IDRC meetings; compiled IDRC recommendations;
IDRC members: attended IDRC meetings; assessed data quality, relevancy, and comparability of cohorts; provided recommendations; voted on formal statistical comparisons of study endpoints and study continuation.

Abbreviations

BCMA, B-cell maturation antigen; ECA, external control arm; GRN, Guardian Research Network; HTA, health technology assessment; IDRC, Independent Data Review Committee; I/E, inclusion/exclusion; IMF, International Myeloma Foundation; IMWG, International Myeloma Working Group; IPTW, inverse probability of treatment weighting; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; RW, real-world; RWD, real-world data; RWE, real-world evidence; SOC, standard-of-care; TTNT, time to next treatment.

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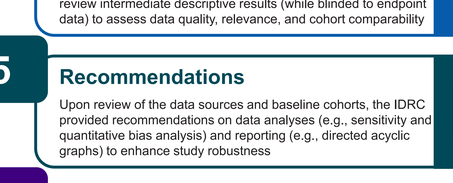
An external control arm study for RRMM

- **R5458-ONC-21101 (NCT05673967)**[2,3] is a global, non-interventional ECA study examining RWD from patients with triple-class–exposed RRMM initiating SOC treatment to contextualize results from the linvoseltamab (anti-B-cell maturation antigen [BCMA]×CD3 antibody) 200 mg cohort of the LINKER-MM1 phase 1/2 single-arm clinical trial (NCT03761108)[4]
- **RWD sources:** Two SOC cohorts were derived: one from chart reviews at participating International Myeloma Foundation (IMF) International Myeloma Working Group (IMWG) sites and one from two US-based oncology electronic health record databases (COTA and Guardian Research Network [GRN])
- **Data analysis:** Comparative analysis between cohorts required adjustment for baseline covariates using inverse probability of treatment weighting (IPTW); covariates were identified using a systematic literature review and ranked by clinical importance by an independent expert panel



Committee methodology and procedures

- The following methodology and procedures were employed to institute an IDRC in the R5458-ONC-21101 ECA study:

1 Development of committee charter
A committee charter was established *a priori* to define the committee's scope, responsibilities, and procedures to ensure transparency and consistency in the decision-making process

2 Selection of committee
The IDRC was composed of five committee members: two hematologists and three epidemiologists / health decisions scientists, including the committee Chair

3 Introductory meeting
An introductory meeting was held on October 10, 2023, to familiarize committee members with the committee charter and the study design of the REGN-ONC-21101 ECA study

4 Data-review meetings
Three data-review meetings (COTA/GRN: November 17, 2023; IMF: June 27 and July 17, 2024) were held for the IDRC to review intermediate descriptive results (while blinded to endpoint data) to assess data quality, relevance, and cohort comparability

5 Recommendations
Upon review of the data sources and baseline cohorts, the IDRC provided recommendations on data analyses (e.g., sensitivity and quantitative bias analysis) and reporting (e.g., directed acyclic graphs) to enhance study robustness

6 Voting and endorsement
Per study protocol, conduct of comparative analyses was contingent on IDRC approval. The IDRC voted to endorse formal statistical comparisons of study endpoints for the COTA/GRN cohort on November 17, 2023, and IMF cohort on July 17, 2024

Committee assessments and data review

Areas of assessment	Methods and data reviewed
Data relevance	• Fitness of **data sources** for the research question • Study populations and similarity of **inclusion/exclusion (I/E) criteria applied** in RW SOC cohorts and the LINKER-MM1 clinical trial • **Intervention** (linvoseltamab) and the ability to identify relevant **comparators** (treatments received) in the RW SOC cohorts • Similarity and completeness of **endpoint definitions**, including methods used to ascertain the objective response rate (independent central review, database algorithms) and variables used to derive time-to-event endpoints (progression-free survival [PFS], time to next treatment [TTNT], overall survival) • Appropriateness of the **study design** and approach, based on the target trial emulation framework
Data quality	• Procedures to **identify errors in data collection** and approach to address concerns • Availability and **completeness** of **baseline variables** and impact of missingness on proposed data analysis • Approach to **handling missing data**
Comparability of cohorts	• The distribution of estimated propensity scores, after IPTW adjustment, was assessed for overlap using **density plots** • The degree of balance as measured by **standardized mean differences** before and after weighting • The **number of clinically important factors** included in estimation of the weights • **Distribution** of patient **weights** and degree of extreme weights • **Effective sample size** after IPTW • Maturity of clinical trial data (i.e., having reached median event-free time)

Committee recommendations

Select recommendations for data analysis and reporting

Data analysis – IMF IMWG site cohort

- Perform a **quantitative bias analysis** to estimate potential bias due to residual confounding, given that cytogenetic risk (top-ranked factor) cannot be adjusted for in the primary analysis due to the high level of missing information
- Consider conducting a subgroup analysis and stratifying baseline characteristics and treatment regimens by geographic region

Data analysis – COTA/GRN cohort

- Conduct the following sensitivity analyses:
  I. Impute variables with more than 30% missingness using a substantially higher threshold or no threshold for missingness
  II. Generate double-robust comparative effectiveness estimates
- Measures to enrich the model should be listed and considered. For example, adjustment for a more complete set of potential confounders (e.g., prior line of therapy)

Reporting

- Describe study data quality procedures in more detail
- If certain I/E criteria cannot be applied, document the reason
- Describe the characteristics of patients excluded from a sample based on insufficient measurable disease, prior anti-BCMA treatment, and inadequate renal function or inadequate hematologic function
- Incorporate differences in regional care practices (notably in China) into the discussion of study results
- Consider TTNT as a more appropriate real-world endpoint compared with PFS
- Include directed acyclic graph to represent the data-generation process

Best practices and learnings for successful implementation of IDRCS in ECA and RW studies

Committee charter

- **Committee procedures:** Develop a pre-defined committee charter that outlines the IDRC's roles, responsibilities, scope of review, and decision-making processes
- **Disagreement resolution:** Develop a process for resolving disagreements within the committee, ensuring that data-review decisions remain objective and are based on scientific evidence

Committee selection

- **Expertise**: Choose members with relevant expertise in the disease area, data analysis, and statistical and causal inference methods; a diverse committee with various specialties can provide well-rounded reviews and recommendations
- **Independence**: Ensure that all members are independent and have no direct involvement with the study design, data collection, analysis, or study sponsorship to prevent any bias in the data evaluation

Logistics

- **Planning:** Schedule meetings 3–4 months in advance; consider convening virtually to allow for flexibility
- **Onboarding:** Hold an introductory meeting to ensure that committee members understand the study's objectives, methodology, and committee responsibilities; send biographical sketches to all committee members prior to the meeting to facilitate introductions
- **Documentation:** Maintain thorough documentation of the IDRC's activities, including meeting minutes, recommendations, decisions, and any actions taken in response to findings

Data review

- **Blinding:** Ensure that the committee members are blinded to outcome data (when applicable for study design) to prevent any potential bias during the data-review process
- **Review criteria:** Apply standardized review criteria, and data integrity checks, to ensure that the data review process is consistent across all stages of the study
- **Adaptability:** The IDRC should be able to adapt to changes in the study protocol, and unanticipated issues in their reviews, while maintaining consistency in their approach

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