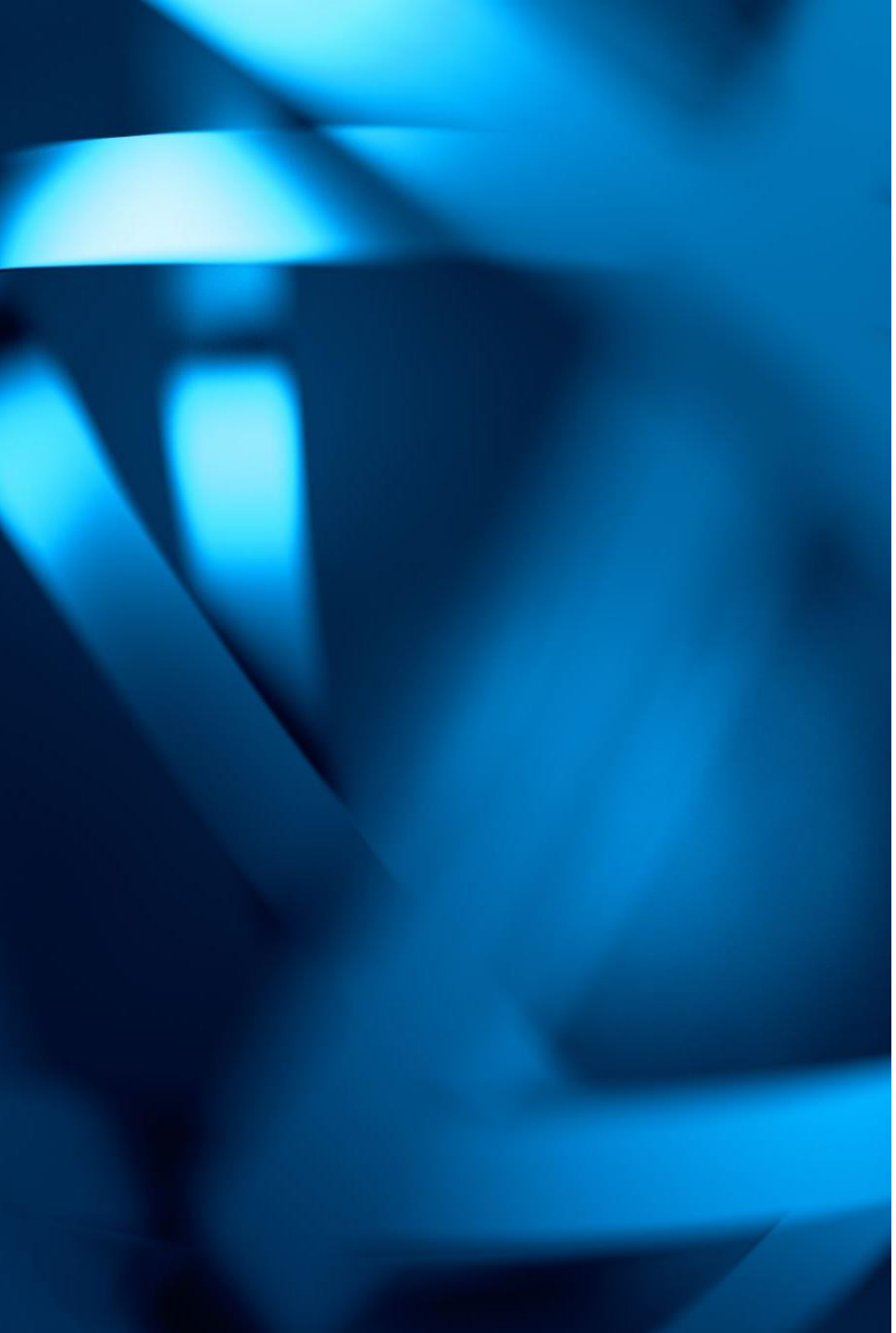

# Mixed Methods Research: Using Embedded Qualitative Interviews to Enhance Interpretation of Clinical Trial Outcomes
# (Recording session April 16; 11am-12noon ET)

Miriam Kimel, PhD, Patient-Centered Research, Evidera, Bethesda, MD, USA
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Carla Dias Barbosa, MSc, Patient-Centered Research, Evidera, London, UK
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# Conflict of Interest Statement

- Miriam Kimel is an employee of and has stocks/shares in Evidera. Funding was not provided for this workshop.
- Naomi Knoble is an employee of the Food and Drug Administration and has no conflict of interest to report. Views expressed are those of the speaker and do not necessarily reflect an official FDA position.
- Carla Dias-Barbosa is an employee of and has stocks/shares in Evidera. This research was funded by Merck Serono.
- Laurie Eliason is an employee of and has stocks/shares in GSK. This research was funded by GSK (205678).

# Background and Purpose

- Conducting embedded interviews within clinical trials is a new research paradigm that can provide a variety of benefits, including understanding treatment benefit and safety/tolerability from the patient perspective, and estimating thresholds for meaningful change.
- Using a mixed method approach, embedded interview data can enrich our understanding of the patients' experience to illuminate and complement the patient-reported outcome (PRO) and biomedical outcomes collected in the trial.
- This workshop will illustrate how embedded interviews can be utilized to generate in-depth and meaningful patient input through the drug development process.

# Agenda

- Introduction to description, uses and value of mixed methods embedded interview research to stakeholders
- Overview of value-added contributions of mixed method embedded interviews to support regulatory inquiries
- Case study on use of mixed methods assessment of patient treatment experience, including disease changes and tolerability in oncology
- Case study of longitudinal mixed methods approach to assess treatment benefit-risk assessment in a rare disease
- Wrap-up

# Key Learning Objectives

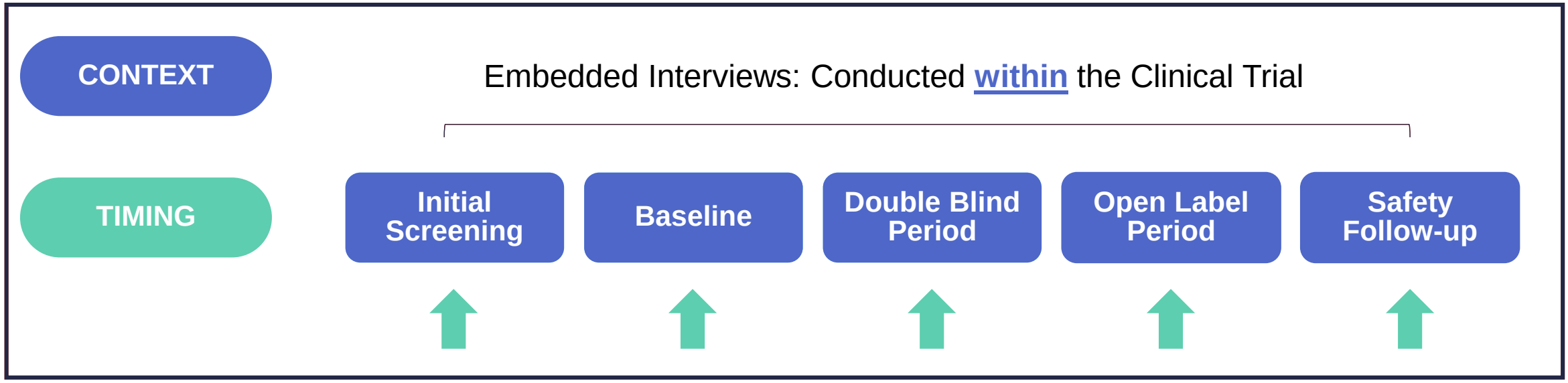
At the end of the workshop, participants will be able to:

- ✓ Identify potential benefits that might be realized from incorporating a mixed methods design within their clinical trials
- ✓ Describe methodology for mixed methods embedded interviews in the context of clinical trials
- ✓ Identify key challenges and solutions for embedding qualitative interviews into clinical trials

# Description, uses and value of mixed methods embedded interview research to stakeholders

Miriam Kimel, PhD, Research Scientist
Evidera, Bethesda, Maryland, United States

# Qualitative Interviews Conducted in Clinical Trials are Defined by Context, Timing, Type, and Design & Analysis




Associated Interviews: Conducted outside the Clinical Trial (i.e., standalone study)

**TYPE**

- Feasibility Interview
- Study Entry Interview
- Repeated (Longitudinal) Interviews
- Early Termination Interviews
- End of Treatment (Exit) Interviews

**DESIGN & ANALYSIS**

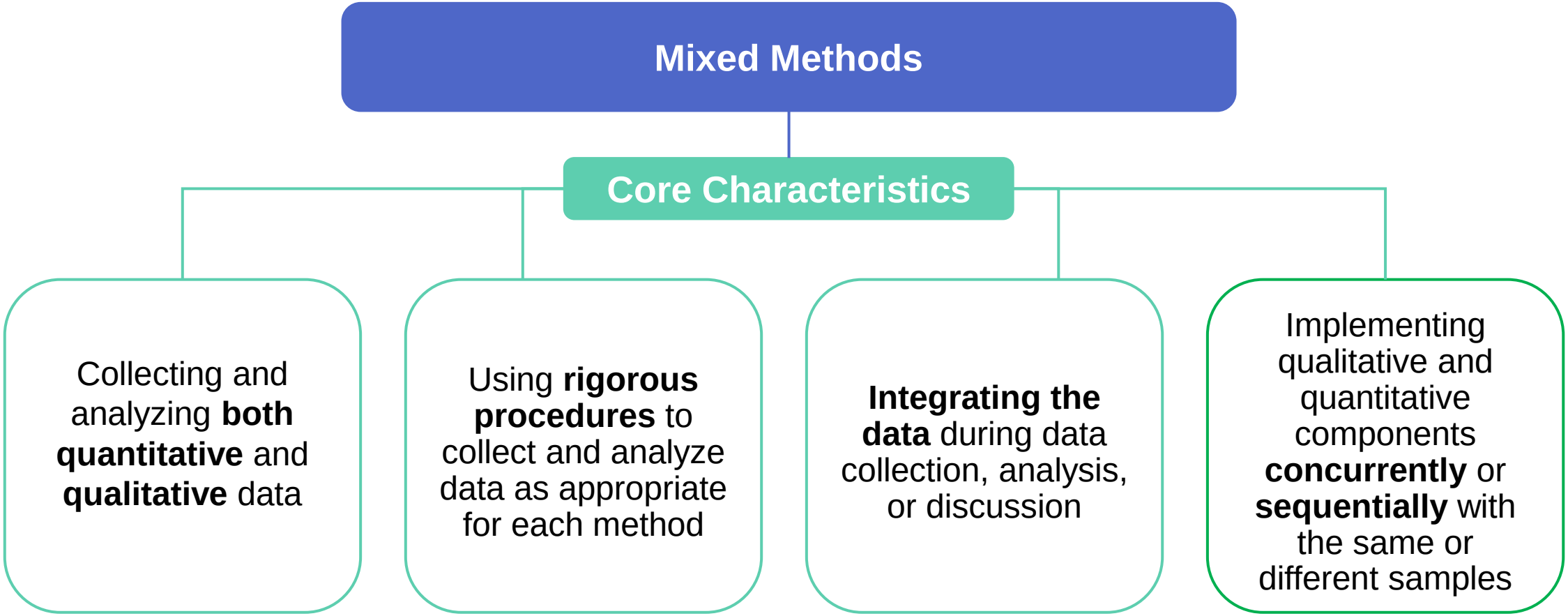
- Sample Size (Total? Sub-sample?)
- Cross-Sectional (When?)
- Longitudinal (How often? When?)
- Mixed-Methods (Timing? What data?)

# Embedded Interview Study Design Based on Objectives

**Possible Objectives of Embedded Interview Study**

| | | | | | |
|---|---|---|---|---|---|
| | • Assess trial materials or procedures<br>• Identify barriers<br>• Test a PRO | • Assess previous treatment experience, expectations, disease burden, or unmet needs | • Assess change over time<br>• Characterize meaningful change | • Understand trial treatment experience<br>• Assess treatment effect (+ or -) | • Assess treatment risk-benefit<br>• Assess long-term experience |
| **Type** | **Feasibility interviews or interviews at screening** | **Study entry interviews** | **Exit or longitudinal interviews** | **Early discontinuation or end of treatment interviews** | **End of follow-up interviews** |
| **Sample** | **Small sample**<br>10 to 30 participants | **Diverse sample**<br>Gender<br>Race/ethnicity<br>Geography<br>Disease severity | **Diverse sample**<br>Across characteristics<br>By subgroups (treatment/placebo) | **Total sample**<br>Attempt to capture all patients treated in study | |

# Mixed-Methods Approach

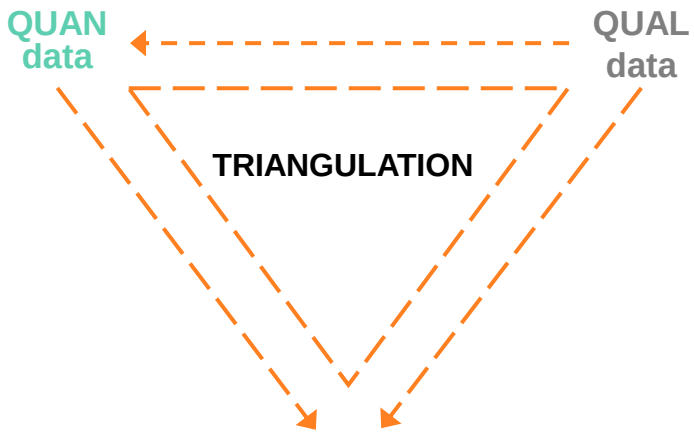


# Mixed Methods Embedded Interviews: Quantitatively Driven Sequential Design

**Embedded Sequential Mixed Methods Design: QUAN → qual***
**(most common design)**

**Quantitative Data**
- **Primary data source**
- Basis of conclusions about efficacy
- Collected at multiple points in trial

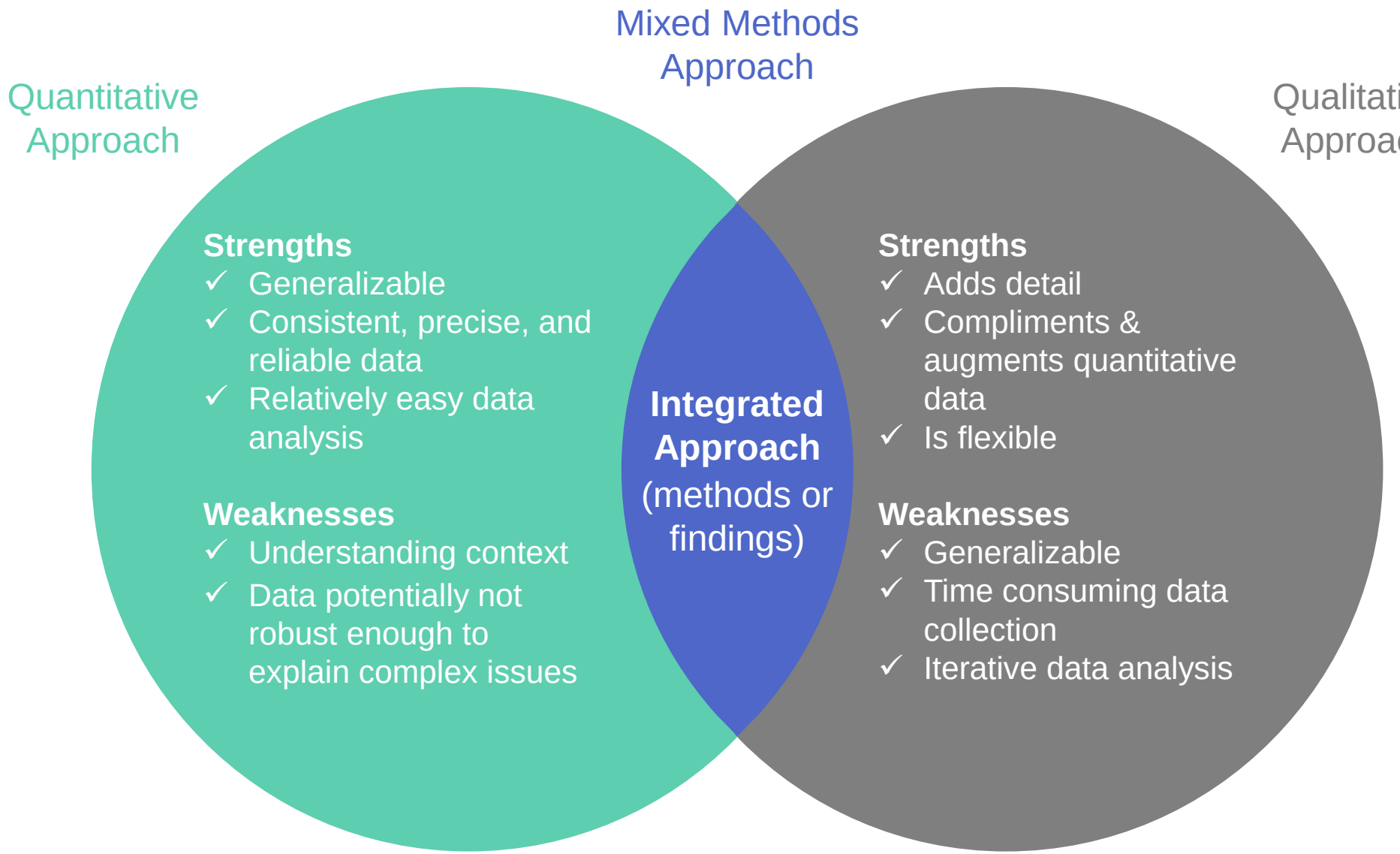
**Qualitative Data**
- **Supportive** of quantitative data
- Collected at end of treatment period (exit interviews)



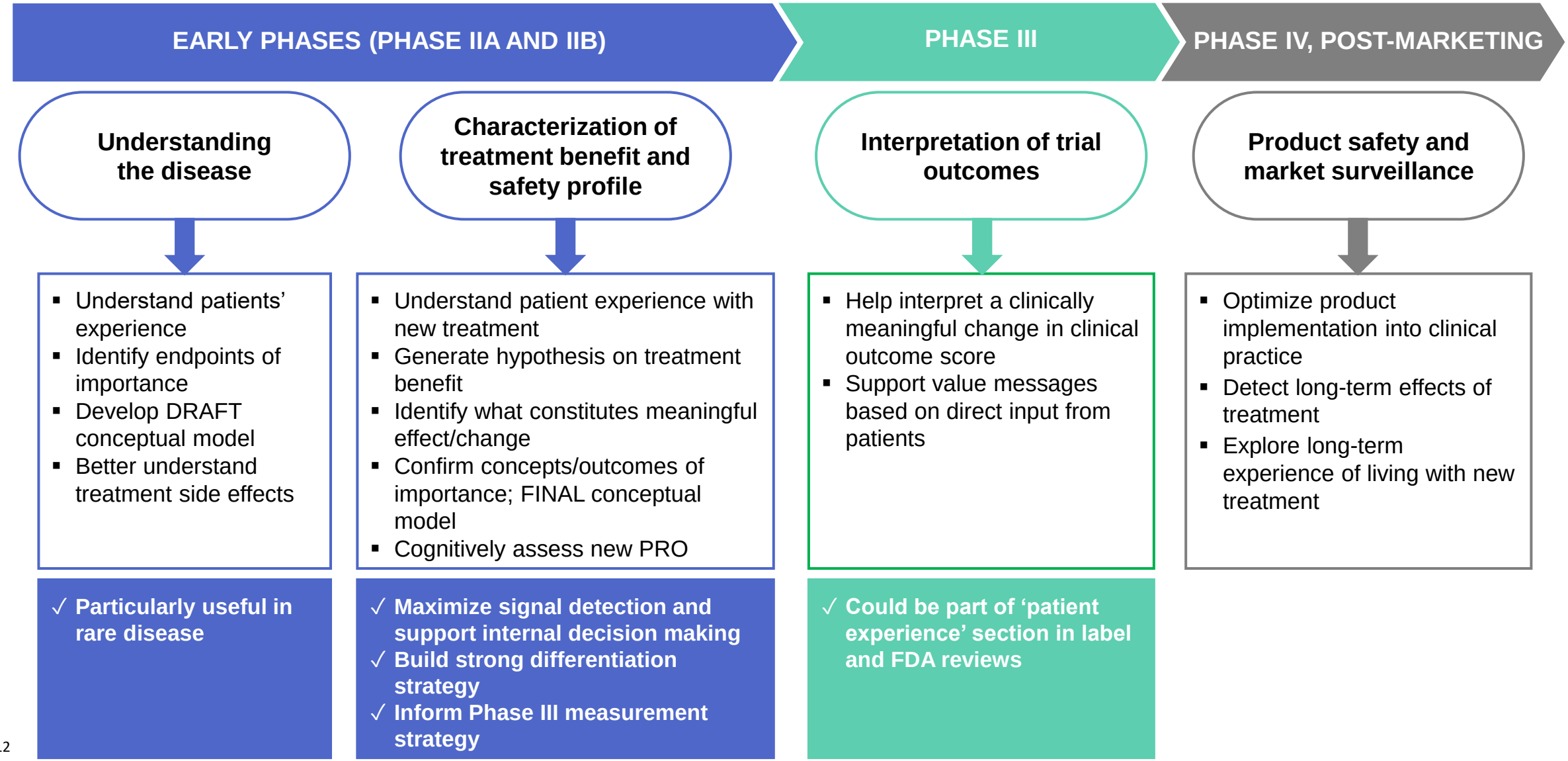

Results compared, integrated and interpreted

**Confirm, Derive, & Interpret Quantitative Results**

# Mixed Methods: Capitalizes on Strengths and Helps Overcome Weaknesses of Both Approaches



# The Patient Voice is Relevant Throughout Drug Development



# The Patient Voice is Relevant to Various Stakeholders

## DRUG MANUFACTURERS

- Design patient-focused measurement strategy
- Refine or establish PRO content validity
- Address regulators' requests/needs
- Optimize future study design(s) and protocols

## REGULATORS

- Interpret findings/PRO scores, inform decision making
- Understand risk-benefit of treatment from patient's perspective
- Include in labeling (patient experience section)

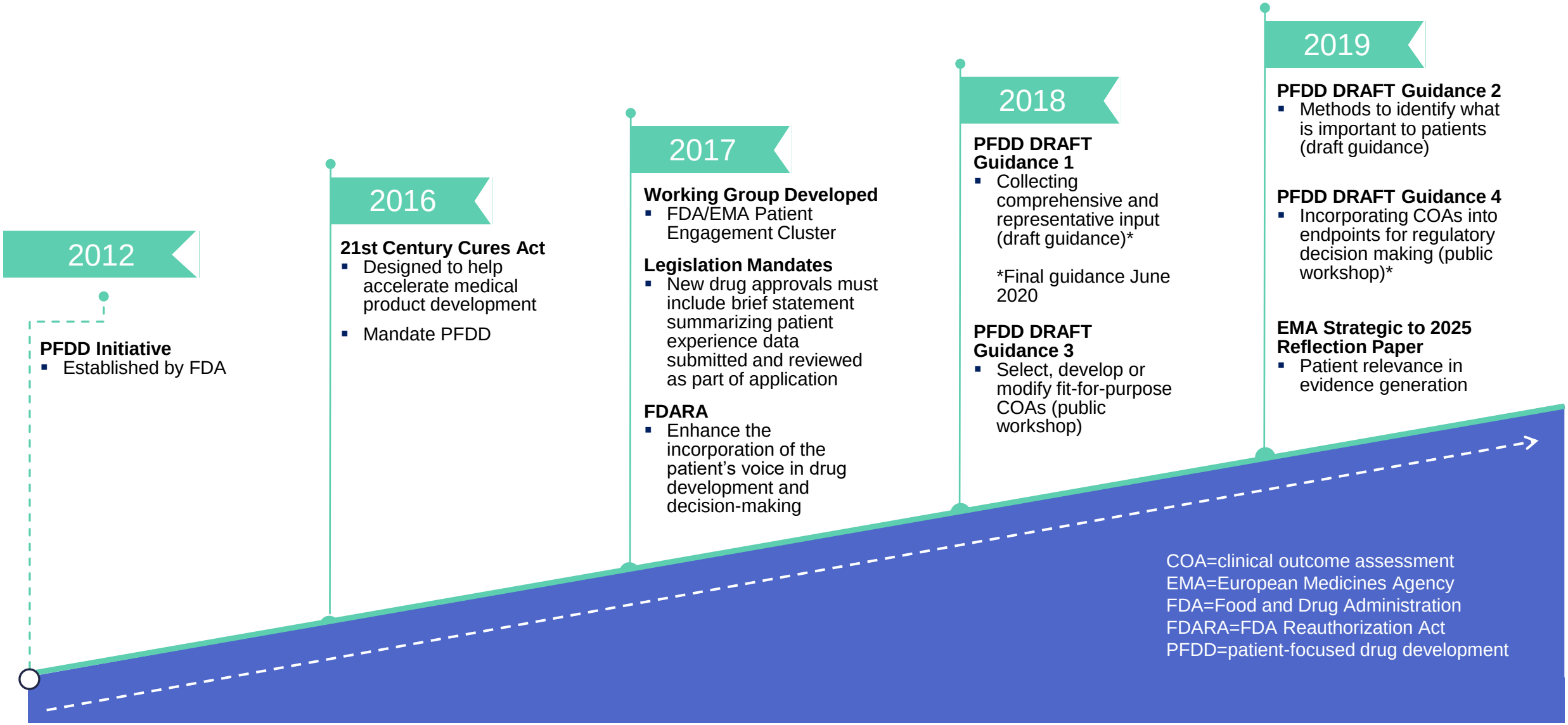
## PAYERS


- Develop better value messages on treatment benefit, treatment satisfaction, and patient/caregiver burden

## PATIENTS

- Generate data that helps future products meet the needs of patients
- Foster drug adoption

# Regulatory Interest in Hearing the Patient Voice Has Increased Over Time




COA=clinical outcome assessment
EMA=European Medicines Agency
FDA=Food and Drug Administration
FDARA=FDA Reauthorization Act
PFDD=patient-focused drug development

# Overview of value-added contributions of mixed method embedded interviews to support regulatory inquiries

Naomi Knoble, PhD, Reviewer, Division of Clinical Outcome Assessment
Food and Drug Administration, Silver Spring, Maryland, United States

# Speaker disclaimer

- The views expressed in this presentation are mine, and do not necessarily represent an official FDA position.

# Science of Patient Input

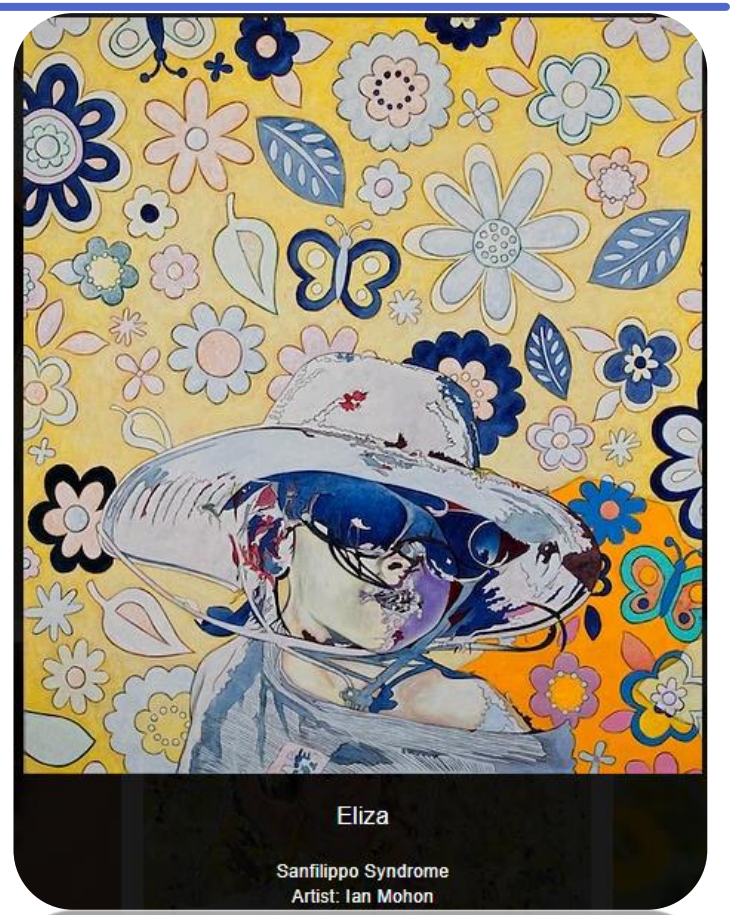
- Patient experience data generation and use is an evolving science
- Multidisciplinary, collaborative approach needed
  - ✓ All three of FDA's medical product centers (CBER, CDER, CDRH) work closely together and draw from each others' expertise
- CDER also engages with *many* external stakeholders
- **Methodological rigor** is essential to ensure evidence is fit for regulatory decision-making
  - ✓ Confidence in the reliability and validity of patient experience data

Slide adapted by permission from Elektra Papadopoulos, MD, Director (Acting), Office of New Drugs, FDA

# Patient-Focused Drug Development (PFDD)

- Systematic approach to help ensure that **patients' experiences, perspectives, needs, and priorities** are captured and meaningfully incorporated into drug development and evaluation

- Recognizes that **patients are experts** in what it is like to live with a disease or condition

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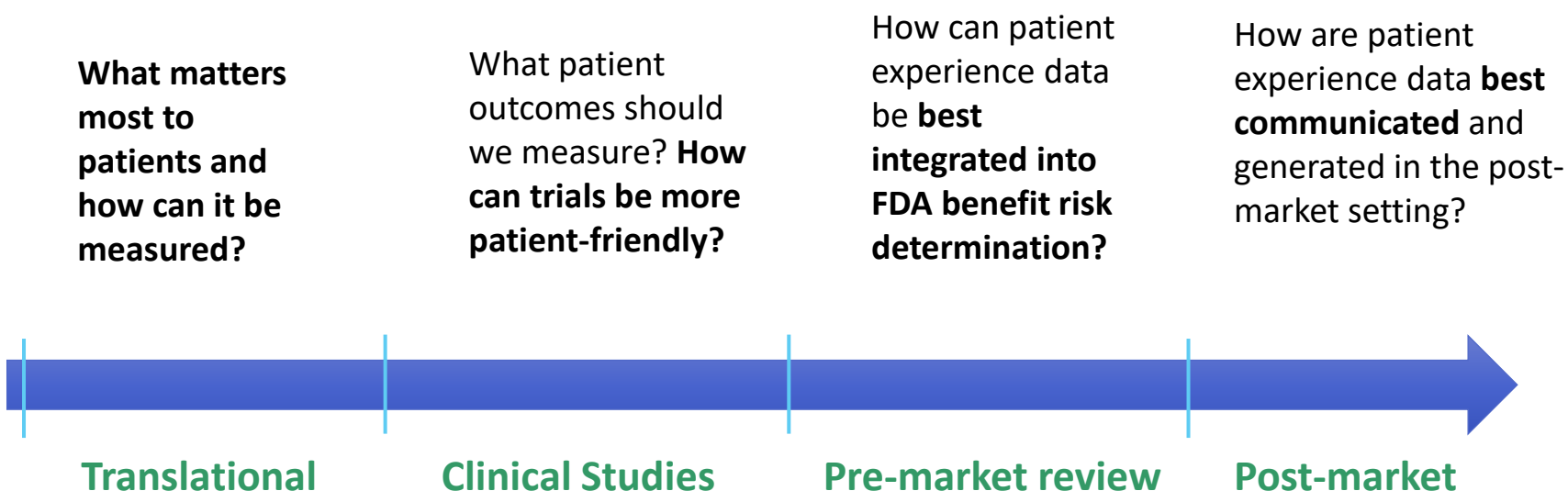
# Patient-Focused Drug Development

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# What is patient experience data?

- **Patient experience data*** is a broad term, it is **not** just *patient-reported outcome*
- Patient experience data are collected by any persons, intended to provide information about *patients' experiences* with a disease or condition.
- Information that captures patients' experiences, perspectives, needs, and priorities related to (but not limited to):
    1) the symptoms of their condition and its natural history
    2) the impact of the conditions on their functioning and quality of life
    3) their experience with treatments
    4) input on which outcomes are important to them
    5) patient preferences for outcomes and treatments
    6) the relative importance of any issue as defined by patients

*Defined in Title III, section 3001 of the 21st Century Cures Act, as amended by section 605 of the FDA Reauthorization Act of 2017 (FDARA)

# Overview of PFDD Guidance Development: 21st Century Cures and PDUFA VI

- **Guidance 1:** Identifying research questions and developing a sampling strategy to collect representative patient input; operationalizing data collection, management and analysis
  - **Final guidance issued**: June 2020
- **Guidance 2:** Methods to elicit detailed, unbiased, and comprehensive input from patients, patient groups, and caregivers; *addresses mixed methods*
  - Draft guidance issued: October 2019
- **Guidance 3:** Using patient input to develop or identify appropriate COAs for use in clinical trials
  - Public Workshop held Oct 15-16, 2018
- **Guidance 4:** Developing COA-related clinical trial endpoints based upon patient input; interpreting those endpoints, including clinically meaningful change
  - Public workshop: Dec. 6, 2019

https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

# Mixed Methods Research and Rare Diseases: Exit Interviews

- Consider the use of exit interviews or exit surveys to understand patient experiences, especially in rare diseases:
  - **Trial measurement:** instrument modification (e.g., add or remove symptoms or impacts), evaluate comprehensiveness of measures
  - **Clinically meaningful change:** gather patient and/or caregiver perspectives on meaningful change (i.e., stability, decline, improvement) in symptoms or impacts from baseline to end of study
  - **Benefits/harms:** patient and/or caregiver perspectives on perceived benefits and harms of the treatment
- **Methodological rigor** is needed to ensure evidence is fit for regulatory decision-making
  - Exit interviews or exit surveys should be planned at the outset of a trial
  - Interviewers should have adequate, documented training
  - Interview guides should be developed without unduly guiding patients, see PFDD Guidance 2

Benjamin K, Vernon MK, Patrick DL, Perfetto E, Nestler-Parr S, Burke L. Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report. *Value Health.* 2017;20(7):838-855.

# Methodological Considerations: Mitigating Risks

1. Longitudinal interviews embedded in a treatment masked study risks unblinding/unmasking patients and/or interfering with trial
   - Consider the clinical trial study design (e.g., open-label single-arm, double-blind placebo-controlled) and how to best integrate patient interview data with the study (e.g., exit interviews)
   - Anticipate and proactively address potential risks through interviewer training, qualitative study protocol procedures
2. Sampling bias
   - Provide a justification and reasonable rationale for participant sampling
3. Participant burden
   - Overtly evaluate patient participation burden and participant engagement
4. Findings from qualitative and quantitative data may appear to conflict
   - Consider methodological approaches that increase the understanding and interpretation of potentially conflicting findings
   - Discovering apparent inconsistencies and/or contradictions can yield new insights into how we understand patient experiences and understand trial results

# Summary and Future Directions

- FDA is committed to working with patients, advocacy groups, commercial sponsors, other agencies, providers, and academics to continue to communicate patient experience data.

- **Methodologically rigorous**, credible patient experience data can support the totality of evidence reviewed for medical product applications

- Patient experience data using mixed methods research is an evolving science

# A mixed method longitudinal approach in the context of treatment benefit-risk assessment within a phase II clinical trial in Merkel cell carcinoma

Carla Dias Barbosa, MSc, Senior Research Scientist
Evidera, London, United Kingdom

- Bharmal, M., Guillemin, I., Marrel, A., Lambert, J., Arnould, B., Fatoumata, F., . . . Dias-Barbosa, C. (2017). PRM6 - Using Convergent Mixed Methods To Evaluate Treatment Risks and Benefits In Rare Disease: An Example From A Phase Ii Registration Trial In Metastatic Merkel Cell Carcinoma. *Value in Health, 20*(9), A731. doi: https://doi.org/10.1016/j.jval.2017.08.1991
- Bharmal, M., Guillemin, I., Marrel, A., Arnould, B., Lambert, J., Hennessy, M., & Fofana, F. (2018). How to address the challenges of evaluating treatment benefits-risks in rare diseases? A convergent mixed methods approach applied within a Merkel cell carcinoma phase 2 clinical trial. *Orphanet journal of rare diseases, 13*(1), 95-95. doi:10.1186/s13023-018-0835-1

# Context and Background

- Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer.
- At the time of the study, limited information was available on the everyday lives of patients with MCC; there were no published qualitative data on how patients feel, function, and survive on everyday basis.
- At the time of the study, no treatment approved by health authorities.*
- Avelumab, a new immunotherapy was tested in phase II clinical trial in metastatic MCC (mMCC).

**Avelumab has shown efficacy and acceptability safety profile in phase 2 clinical trial in metastatic MCC and has been approved in 2017 by both the FDA and the EMA for the treatment of 12 yeas and older with metastatic MCC.*

# The Regulatory Perspective on the Use of PROs and Patient Experience Data in Oncology Trials

- The use of patient-reported outcomes (PRO) in oncology studies is highly recommended by regulators:[1,2]
  - PRO data are reviewed as important supportive data during the benefit-risk determination.
  - PRO data can serve to demonstrate clinical added value and capture the meaningful effect of the new drug.
- PRO data should be considered as important as any other data that supports the safety and efficacy of a treatment .
- Lack of published literature:
  - Rigorous PRO and other clinical outcomes assessment (COA) data should be published contemporaneously with primary efficacy and safety manuscript.

1. Patient-Reported Outcome Measures in U.S. Regulatory Review of Cancer Products (FDA workshop on COAs in Cancer Clinical Trials April 26, 2016 Silver Spring, MD)
2. Appendix 2 to the EMA guideline on the evaluation of anticancer medicinal products in man: The use of patient-reported outcome (PRO) measures in oncology studies

# MCC Phase II Clinical Trial

## Clinical Trial Design

- **Design**: multicenter, international, single-arm, open-label, phase II trial
- **Primary objective**: to assess the clinical activity of avelumab by the objective response rate (ORR)*
- **Population**: subjects with metastatic MCC after failing first-line chemotherapy.
- **Target sample: N=88**

**According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by an Independent Endpoint Review Committee (IERC)*

## Patient-focused Measurement Strategy

**There are no specific questionnaires to assess patient perspective in mMCC.**

- Use of well-known benchmark PRO measures as secondary endpoints:
  - EuroQol-5D (EQ-5D)
  - Functional Assessment of Cancer Therapy (FACT-M) – including the Melanoma module
- Combined with embedded longitudinal interviews with clinical trial participants (optional, exploratory objective)
  - Longitudinal qualitative interviews were conducted at Baseline, week 13 and week 25.
  - **N=9 patients** receiving avelumab were interviewed at baseline prior to receiving study treatment and at weeks 13 and 25.

# Objectives of the Qualitative Interviews

**Baseline interviews:**

**at study entry, prior to treatment initiation**

- To acquire a comprehensive picture of the impact of the disease on patients' lives
- To explore the impact of previous treatment(s) (radiotherapy and chemotherapy) on patients' daily lives independently of the study and the study treatment
- To collect information on patients' expectations of avelumab

**Follow-up interviews:**

**at Week 13 & Week 25**

- To explore patients' experience with avelumab since baseline
- To document the change (improvement, stability or worsening) in disease status following treatment initiation
- To collect information about patients' experience and perception of avelumab compared with previous treatments

# Characteristics of the Qualitative Interviews and Longitudinal Analysis

- Semi-structured
- Phone interviews
- Conducted by psychologists or experienced researchers trained in qualitative research
- Each interview (baseline, week 13, and week 25) was based on a specific interview guide
- Audio recorded
- Transcribed word for word and de-identified
- Longitudinal qualitative analysis using ATLAS.TI software, following **trajectory** and **recurrent cross-sectional** approaches

# Evaluation of Treatment benefits-risks: Use of a Mixed Methods Approach

| Variables | Characterization of change | Description of change category |
|---|---|---|
| **Qualitative variables: Patient interview data** | • Each key concept identified at the baseline analysis was probed during the follow-up interviews.<br>• At each time-point, each concept of interest was assigned a category describing the changes in concepts that occurred between the two time points. | "Improvement"<br>"No change or stable"<br>"Worsening"<br>"Not probed or Not determined" |
| **Quantitative variables: clinical status assessment** | • Patients' overall response was assessed by an Independent Endpoint Review Committee (IERC) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) | Partial or complete response to treatment<br>Stable disease<br>Progressive disease |
| **Quantitative variables: FACT-M assessment** | • For the purpose of the mixed method analysis, a sample of FACT-M items/ scores was selected based on their relevance and similarity with the concepts identified during the baseline interviews.<br>• For each item/ score, the change from baseline to week 25 was calculated and categorized. | Improvement = Positive change in score<br>No change =Null change in score<br>Worsening = Negative change in score<br>Not computed |

# MMR Analysis: Qualitative Findings in Relation to Clinical Status

**Progression trend of the selected concepts of interest since starting avelumab up to Week 25 and its correspondence with clinical status based on overall response by IERC per RECIST**

| Patient # | Clinical status at week 25 | Qualitative variables (change from baseline to week 25) | | | | Concordance of results |
|---|---|---|---|---|---|---|
| | Overall Response by IERC per RECIST* | Overall Change in Patients' Perception of their cancer | Physical Functioning | Fatigue/Energy | Pain | |
| 1 | Partial/Complete Responder | Improvement | Improvement | Still tired since week 13 | No pain | |
| 2 | Partial/Complete Responder | Improvement | Improvement | Improvement | No pain | |
| 3 | Partial/Complete Responder | Improvement | Improvement | Still tired since week 13 | No pain | |
| 4 | Partial/Complete Responder | Improvement | Improvement | Improvement | ND | |
| 5 | Partial/Complete Responder | Improvement | No impact | ND | No pain | |
| 6 | Partial/Complete Responder | Improvement | No impact | Improvement | Improvement | |
| 7 | Partial/Complete Responder | Improvement | No impact | Improvement | Improvement | |
| 8 | Partial/Complete Responder | Improvement | Improvement | ND | Improvement | |
| 9 | Progressive Disease | Still worsened since week 13 | No impact | ND | No pain | |

Abbreviations: IERC = Independent Endpoint Review Committee; ND= Not determined, trend not possible to determined as date was not reported spontaneously by the patient and was not probed at one of the time point
RECIST = Response Evaluation Criteria in Solid Tumors version 1.1
* Overall response by IERC per RECIST identical at both Week 13 and Week 25 for all patients

Green= good concordance between variables
Orange= partial concordance between variables
Red = lack of concordance between variables

# Evaluation of Treatment Benefits-risks: Physical Functioning

**Progression trend of the "physical functioning" concept since starting avelumab up to Week 25 and its correspondence with quantitative assessments.**

| Patient # | Clinical status at week 25 | Change in FACT-M Score Related to Physical Functioning | | Qualitative variable | Concordance of results |
|---|---|---|---|---|---|
| | Overall Response by IERC per RECIST* | Physical Well-being | Functional Well-being | Physical Functioning concept | |
| 1 | Partial/Complete Responder | No change | Improvement | Improvement | |
| 2 | Partial/Complete Responder | Worsening | Worsening | Improvement | |
| 3 | Partial/Complete Responder | No change | Worsening | Improvement | |
| 4 | Partial/Complete Responder | Improvement | Improvement | Improvement | |
| 5 | Partial/Complete Responder | No change | Improvement | No impact | |
| 6 | Partial/Complete Responder | No change | Improvement | No impact | |
| 7 | Partial/Complete Responder | Improvement | Improvement | No impact | |
| 8 | Partial/Complete Responder | Not computed | Not computed | Improvement | |
| 9 | Progressive Disease | Worsening | Improvement | No impact | |

Abbreviations: FACT-M = Functional Assessment of Cancer-Melanoma; IERC = Independent Endpoint Review Committee; NC = not computer; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1

*Overall response by IERC per RECIST identical at both Week 13 and Week 25 for all patients

**Green** = good concordance between variables
**Orange**= partial concordance between variables
**Red** = lack of concordance between variables

# Evaluation of Treatment Benefits-risks: Fatigue

**Progression trend of the "Fatigue" concept since starting avelumab up to Week 25 and its correspondence with quantitative assessments.**

| Patient # | Clinical status at week 25 | Change in FACT-M Score Related to Fatigue | Qualitative variable | Concordance of results |
|---|---|---|---|---|
| | Overall Response by IERC per RECIST* | H17. I feel fatigue | Fatigue / energy concept | |
| 1 | Partial/Complete Responder | No change | Still tired since week 13 |  |
| 2 | Partial/Complete Responder | No change | Improvement |  |
| 3 | Partial/Complete Responder | No change | Still tired since week 13 |  |
| 4 | Partial/Complete Responder | Improvement | Improvement |  |
| 5 | Partial/Complete Responder | No change | ND |  |
| 6 | Partial/Complete Responder | No change | Improvement |  |
| 7 | Partial/Complete Responder | Improvement | Improvement |  |
| 8 | Partial/Complete Responder | Not computed | ND | Not assessed |
| 9 | Progressive Disease | Worsening | ND |  |

Abbreviations: IERC = Independent Endpoint Review Committee; ND= Not determined, trend not possible to determined as date was not reported spontaneously by the patient and was not probed at one of the time point; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1

* Overall response by IERC per RECIST identical at both Week 13 and Week 25 for all patients

**Green** = good concordance between variables
**Orange**= partial concordance between variables
**Red** = lack of concordance between variables

# Patient Quotes Illustrating the Status on the Selected Concepts

## Examples of responders' quotes (n=8)

"I'm doing things that I haven't done in a long time just like being able to go out and walk."

**Week 25, Improved patient on physical functioning**

"I have more energy... I mean, I had energy when I started, but it was more of a forced energy, now it's not a... It's like I forced myself to do things, so that I would keep going. Now I don't need to force myself […] Sometimes I have some fatigue, but it's not bad, I mean, it's just a mild fatigue

**Week 25, Improved patient on fatigue**

"Well, I have, I'm still having some pain in my back, but it has lessened since I started the infusions.

**Week 13, improved patient on pain**

"I feel fine and continue to do what I can. I mean, I am 74 so, you know, I don't do, unlike former President Bush, I don't parachute jumping and stuff like that on my birthday, but, you know, I do not feel limited due to the cancer and what I do in terms of be daily activities

**Week 25, unchanged patient on physical functioning**

## Examples of non-responders' quotes (n=1)

"Physically I'm still fairly strong in what I'm doing, and active as much as I can be […] as this point in time I noticed any drop off in my physical capacities"

**Week 13, unchanged in physical functioning**

"After I received my infusion, **I think it was a day or so after, I'm a little fatigued** […] not very bad, not that I can't' do everything but I'd like to kind of back off that day and take it easy for that day.

**Week 25, worsened patient on fatigue**

"I'm seeing a slow worsening at this point in time. A little bit, like I say, **a little more abdominal pain** […] which I would grade now on a level of one to ten, probably in the 3 range, 4 range, when I have it, it's not a continuous pain, **it's when I'm in certain positions like laying down in bed on my back, it will bother me**

**Week 13, worsened patient on pain**

# Embedded Interview Data Used for Different Purposes

## Document disease burden[1]

- Use of baseline interview data to document the patient experience of the disease prior to the start of the study
- Development of a Conceptual Disease Model of mMCC

## Comparative effectiveness of avelumab versus chemotherapy[2]

- Use of qualitative and quantitative variables analysed following a mixed method approach
  - Qualitative interview data: baseline interview data documenting experience of previous chemotherapy and weeks 13/25 interviews documenting current experience with Avelumab
  - Quantitative PRO data: FACT-M items addressing chemotherapy-impacted concepts at weeks 13/25)

Abbreviations: FACT-M = Functional Assessment of Cancer Therapy – Melanoma; mMCC = metastatic Merkel cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1


1. Kaufman H, Kraemer M, Barbosa CD, Lambert J, Mahnke L, Bharmal M. Patient perspectives on Merkel cell carcinoma (MCC) and its treatment with a novel agent (AVELUMAB): findings from in-depth qualitative patient interviews. Value Health. 2016;19(7):A745.
2. Bharmal, M., Marrel, A., Hennessy, M., Fofana, F., Lambert, J., & Arnould, B. (2018). Comparative effectiveness of avelumab versus chemotherapy in Merkel cell carcinoma: innovative use of patient insights. *J Comp Eff Res, 7*(9), 881-890. doi:10.2217/cer-2018-0048

# Key Learnings and Benefits of Collecting Trial-Embedded Interview Data

## Summary

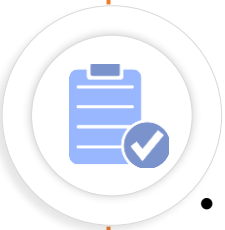
- Patients were very happy to share their experience and were enthusiastic to be interviewed.
- Results suggested a high concordance between clinical between clinical and patient interview data and a moderate concordance between patient interview data and the FACT-M.
- Qualitative interview data collected directly from the patients provided additional evidence not captured by PROs included in the trial.
- Qualitative interview data collected in the Phase II clinical trial in mMCC served different purposes:
  - Understand the patient experience of the disease,
  - Understand the patient experience with the new treatment compared with previous treatments,
  - Provide information about patient perceived meaningful change to support interpretation of clinical trial results,
  - Characterize treatment benefit from a patient perspective.
- Qualitative interview data supported various publications on conferences and clinical and methodological journals.
- Published data contributed to raising awareness on MCC, which is a misdiagnosed disease, among healthcare professionals and patient communities.

# A mixed methods assessment of patient treatment experience, including disease changes and tolerability in oncology

Laurie Eliason, MPH, Director, VEO-Patient Centered Outcomes, Oncology
GSK, Collegeville, Pennsylvania, United States

# Study Background

- Multiple myeloma (MM) is an incurable malignancy and accounts for 1% of all cancers and for 10% of all hematologic malignancies[1]. While almost all patients will respond to first line treatment, most eventually experience progression of disease and need more lines of treatment. Despite large advances in treatment options, most patients with MM will ultimately develop resistance to existing therapies.
- Patients with symptoms and complications of MM, such as fatigue, bone pain, and anemia, have significantly impaired functioning and quality of life, which declines as the disease progresses



DREAMM-2 is a phase II, single-arm, open-label study that is assessing the safety, tolerability, and clinical activity of belantamab mafadotin given in patients with relapsed/refractory multiple myeloma (RRMM)

- Although belantamab mafodotin has demonstrated efficacy and tolerability in this population, some ocular toxicity is common and expected, having other treatments with a similar mechanism.
- Capturing the direct patient perspective about their experience in clinical trials and with experimental treatments has become an important focus in the field of oncological drug development
- Insights from embedded interviews can be used to provide a greater understanding of side effects of new therapies to help complement safety profiles and may also contribute to study design improvements for future clinical trials[2,3]

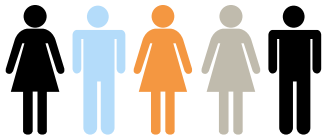

- 1. Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv52-iv61
- 2. Eliason L et al. Presented at the 62nd American Society of Hematology Annual Meeting. 2020;
- 3. Nelson A et al. *Trials*. 2013.

# Objectives of DREAMM-2 Embedded Interviews

This study aimed to use qualitative patient interviews to **understand patient's experiences with belantamab mafodotin** in DREAMM-2, including:

- Changes in MM-related symptoms prior to start of treatment and after study start
- Experience of treatment related symptoms and tolerability, including onset, variability, and resolution of ocular symptoms and vision-related functioning
- Perspectives related to staying on treatment and self risk-benefit evaluations
- Ratings and discussion of overall treatment satisfaction
- Comparison of findings between patients who responded to treatment and those who did not

# DREAMM-2 Study Eligibility and Overall Design[1,2]



**STUDY POPULATION**

**Adult patients ≥18 years**

The DREAMM-2 trial included heavily pre-treated RRMM patients meeting the following criteria:

- Measurable disease
- Previously confirmed MM diagnosis
- ECOG performance status 0-2
- ≥3 prior lines of treatment
- Refractory to PI and an immunomodulatory agent, and failed anti-CD38 antibody

**Patients in both treatment cohorts were invited to interviews at Cycle 4 and end of treatment***

**Interviews averaged 45 minutes and were completed over the telephone in patients' native language by qualitative research interviewers†**

**Questions were open-ended and covered patients' experiences with symptoms, treatment-related burden, and adverse events**

**A scale of 0-10 was used to rate disease and treatment-related symptom severity and overall treatment satisfaction‡**

**Qualitative data from interviews was combined with a mixed methods approach with specific quantitative variables obtained during the interview process§**

*Patients who discontinued treatment before cycle 4 were only interviewed once. The Cycle 4 timepoint was chosen because it represented an interim point at which patients may have experienced a treatment response along with changes in disease- or treatment-related symptoms. Data represents 13-month follow-up analysis.

† Recordings were completed with patient permission and informed consent

‡0=not severe to 10=most severe/0=not at all satisfied to 10=extremely satisfied

§Qualitative data was derived from conversations during the interview and was coded from interview transcripts. The coding process enabled organization of codes in groups by content similarity or theme and then summarized with percentages.

ECOG = Eastern Cooperative Oncology Group; MM = multiple myeloma; PI = proteasome inhibitor;

1. Lonial et al. Lancet Oncol. 2020; 2. Eliason L et al. Presented at the 62nd American Society of Hematology Annual Meeting. 2020.

# DREAMM-2 Baseline Demographics and Patient Characteristics
## *Cycle 4 and End of Treatment Interviews*

| Characteristic | Before or at Cycle 4 Interviews (N=104) | End-of-treatment Interviews (N=26) | Total (N=109) |
|---|---|---|---|
| Median age at time of consent to interview, years (range)* | 66.0 (40–89) | 64.0 (46–89) | 66.0 (40–89) |
| Median time since first diagnosed with MM, years (range) | 6.0 (1.1-12.1) | 4.5 (4.1-9.1) | 5.9 (1.1-12.1) |
| Median prior lines of therapy, n (range) | 6.0 (3-21) | 6.0 (3-21) | 6.0 (3-21) |
| Median time on study treatment, weeks (range)† | 24.9 (3-75) | 40.7 (12-69) | 25.3 (3-75) |
| ORR (sCR+CR+VGPR+PR), n (%) | 59 (56.7) | 22 (84.6) | 62 (56.9) |
| Country of residence, n (%) | | | |
| United States | 69 (66.3) | 19 (73.1) | 72 (66.1) |
| Spain | 7 (6.7) | 3 (11.5) | 9 (8.3) |
| France | 8 (7.7) | 1 (3.8) | 8 (7.3) |
| United Kingdom | 7 (6.7) | 1 (3.8) | 7 (6.4) |
| Germany | 6 (5.8) | 2 (7.7) | 6 (5.5) |
| Canada | 5 (4.8) | -- | 5 (4.6) |
| Australia | 1 (1.0) | -- | 1 (0.9) |
| Italy | 1 (1.0) | -- | 1 (0.9) |
| Race detail, n (%) | | | |
| Black or African American | 17 (16.3) | 5 (19.2) | 18 (16.5) |
| Asian – East Asian Heritage | 1 (1.0) | 0 | 1 (0.9) |
| Asian – South East Asian Heritage | 2 (1.9) | 0 | 2 (1.8) |
| White – Arabic/North African Heritage | 2 (1.9) | 0 | 2 (1.8) |
| White – White/Caucasian/European Heritage | 80 (76.9) | 21 (80.8) | 84 (77.1) |
| Mixed Asian Race | 1 (1.0) | 0 | 1 (0.9) |
| Multiple | 1 (1.0) | 0 | 1 (0.9) |

This chart has been independently created by GSK from original data first presented in Eliason L et al. ASH. 2020.

*Mean (SD) age at time of consent to interview, in years, for cycle 4 interviews = 66.0 (9.1), end-of-treatment interviews = 65.4 (10.0), and total = 65.8 (9.1); †Mean (SD) time on study treatment, in weeks, for cycle 4 interviews = 30.7 (22.4), end-of-treatment interviews = 22 (85), and total = 62 (57.0)
CR = complete response; MM = multiple myeloma; ORR = overall response rate; PR = partial response; PR = partial response; sCR = stringent complete response; VGPR = very good partial response;

\Eliason L et al. Presented at the 62nd American Society of Hematology Annual Meeting. 2020.

# Interview Participants by Treatment Responder Status

## Interview Participant Timing and Treatment Response

| Interview Timepoint†, n | Responders (N = 80) | Non-Responders (N = 50) | Number of Completed Interviews at Each Timepoint (N = 130) |
|---|---|---|---|
| **Before or at Cycle 4 (1st Interview)** | 58 | 46 | 104 |
| **End-of-treatment (1st and only interview)** | 3 | 2 | 5 |
| **End-of-treatment (2nd interview)** | 19 | 2 | 21 |

This chart has been independently created by GSK from original data first presented in Eliason L et al. ASH. 2020.

58 (56%) of the 104 patients who participated in interviews at or before Cycle 4 identified as responders* to treatment

22 (85%) of the 26 patients who participated in end-of-treatment interviews identified as responders to treatment

*Responders had ≥partial response by IMWG criteria.

†For each type of interview, interview windows are 21 days long, starting with cycle 4 or end-of-treatment visit.

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# Patient Report of Disease Symptoms

***Frequency and severity of symptoms by responder status***

## Severity Ratings* for the Most Commonly Reported Disease Symptoms† During Cycle 4 Interviews (n=104)

| Symptom | Frequency (%) | Responders (n=58) | | Non-responders (n=46) | |
|---|---|---|---|---|---|
| | | Mean (SD) severity rating (at start of study) | Mean (SD) severity rating (by Cycle 4 interview) | Mean (SD) severity rating (at start of study) | Mean (SD) severity rating (by Cycle 4 interview) |
| Fatigue | 68 | 4.6 (2.5) | 3.4 (2.4) | 4.4 (2.1) | 4.5 (2.4) |
| Neuropathy | 43 | 4.5 (2.6) | 3.7 (2.5) | 3.9 (1.9) | 2.8 (2.0) |
| Bone pain | 37 | 6.9 (2.1) | 3.6 (3.1) | 4.9 (2.5) | 4.4 (2.3) |
| Back pain | 30 | 5.2 (2.5) | 4.6 (2.9) | 4.7 (2.7) | 4.2 (2.8) |
| Weakness | 22 | 4.4 (2.0) | 4.1 (2.9) | 5.4 (2.1) | 4.8 (1.8) |
| Shortness of Breath | 21 | 4.0 (1.9) | 2.7 (2.9) | 4.1 (2.3) | 4.1 (3.0) |
| Bruising or Bleeding Easily | 16 | 5.2 (2.7) | 2.7 (2.8) | 2.8 (1.2) | 2.6 (1.5) |
| Constipation | 16 | 5.8 (2.2) | 3.7 (2.3) | 3.6 (1.9) | 1.5 (1.8) |

This chart has been independently created by GSK from original data first presented in Eliason L et al. ASH. 2020.

As expected, core MM symptoms of fatigue and pain were frequently reported

Responders generally reported a **decrease in severity of symptoms** from the study start to the time of the interview at Cycle 4

*Disease and treatment-related symptom severity was rated 0–10 (0=not severe;10=most severe);
†Most commonly reported symptoms were reported by >15% of patients.



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# Treatment-Related Ocular Symptoms

***Frequency and severity of ocular symptoms at two interview timepoints***

## Most Commonly Reported Ocular Symptoms*

| Symptom | At Cycle 4 Interviews (n=104) Responders = 58 (56%) | | At End-of-treatment Interviews (n=26) Responders = 22 (85%) | | |
|---|---|---|---|---|---|
| | Frequency n (%) | Mean (SD) severity rating (for symptom "at worst"† during study) | Frequency n (%) | Mean (SD) severity rating (for symptom "at worst" during study) | Mean (SD) severity (by end-of-treatment interview) |
| Visual impairment (includes poor vision, blurred vision, and sensitivity to light) | 59 (57) | 6.6 (2.6) | 17 (65) | 8.5 (1.6) | 2.9 (2.4) |
| Eye irritation (includes irritated eyes, dry eyes, itchy eyes, and feeling that something is in the eye) | 42 (40) | 6.4 (2.0) | 11 (42) | 7.6 (2.0) | 1.6 (2.4) |
| Eye pain (includes painful eyes, sore eyes, and burning) | 12 (12) | 6.6 (2.2) | 4 (15) | 6.6 (2.2) | 0.0 (0.0) |

This chart has been independently created by GSK from original data first presented in Eliason L et al. ASH. 2020.

During end-of-treatment interviews, patients reported **decreased severity of ocular symptoms** between the time when the symptoms were at their worst and the 2-week period prior to the interview

*Disease and treatment-related symptom severity was rated 0–10 (0=not severe to 10=most severe); †Patients were asked to rate the severity of the symptom they thought was the worst for them during their time on the trial.



Eliason L et al. Presented at the 62nd American Society of Hematology Annual Meeting. 2020.

# Evaluation of Impacts During the Study

Interviews revealed themes in treatment's impact on quality of life, physical functioning, and emotional health

## Improved Quality of Life

"Oh yes. I feel it. I mean I haven't felt this good in probably three years."

"I mean it's really helped my quality of life, I'm just really happy with it."

"It's given me some hope for the future, and my general health, I feel like it has improved."

## Physical Functioning/Daily Activities

"I can do things. I can go up and down my steps now without having to sit and rest."

"I can feel my body getting a little stronger… just getting up off the chair without boosting myself up with my arms. I can do that now."

"I feel great. I've got great energy… I was thinking in the beginning I needed to do 1,500 to 2,500, and I've been as high as 10,000 [steps a day]."

## Emotional Health

"…I thought I was at the end of my useful life… in my particular situation I'm probably going to get to walk my daughter down an aisle.… Without your drug that probably wouldn't happen."

"I'm hopeful every day that what I'm in right now is going to propel me toward my goal in life."

"I have noticed that my general health, my general demeanor, my general mindset have definitely improved."

This figure was first presented in Eliason L et al. ASH. 2020.

Eliason L et al. Presented at the 62nd American Society of Hematology Annual Meeting. 2020.

# Weighing the Risks and Benefits of Treatment

Patients had a variety of perspectives on weighing the risks and benefits of treatment

## Staying on Study Treatment Despite New Symptoms

"I make the call usually to push ahead because I'm out of options now. I've been through every standard treatment. So, it would only be trials, that's all I have available."

"I thought seriously about not continuing, and if there had been another drug for me at this point, approved and ready for me to get it, I might have stopped it, but there is not... so I just decided that I would just put up with not being able to see."

"No [never thought of stopping], knowing [side effects] were temporary, they come and go is not bothering—I'm more about staying alive. Except for my eyes I do feel better… so I'm all for it."

"My doctor has worried about the deposits on my eyes, but they don't really bother me.… To me, I never really wanted to get out of the study. I just wanted to keep going because it's just had such a good effect on my numbers."

"It is working on the cancer right now so it seems to be a tradeoff.... Take the drug... put up with blurry vision and reassess down the road."

"So far, the thing that only happened is the blurry eyes, that's all.... No [I didn't think about stopping]. It helps my pain.... It works pretty good on my myeloma."

## Weighing Risks & Benefits

"Aside from the eyes I had no other side effects, and I don't know if the eyes will recur or if they won't but even if they do, that's okay. I'd rather be alive. I'd rather be alive."

"There are side effects to absolutely any treatment you have and some of the treatments I've had have had much worse than this."

"It was either that [side effects] or go through the possibility of… light chains."

This figure was first presented in Eliason L et al. ASH. 2020.

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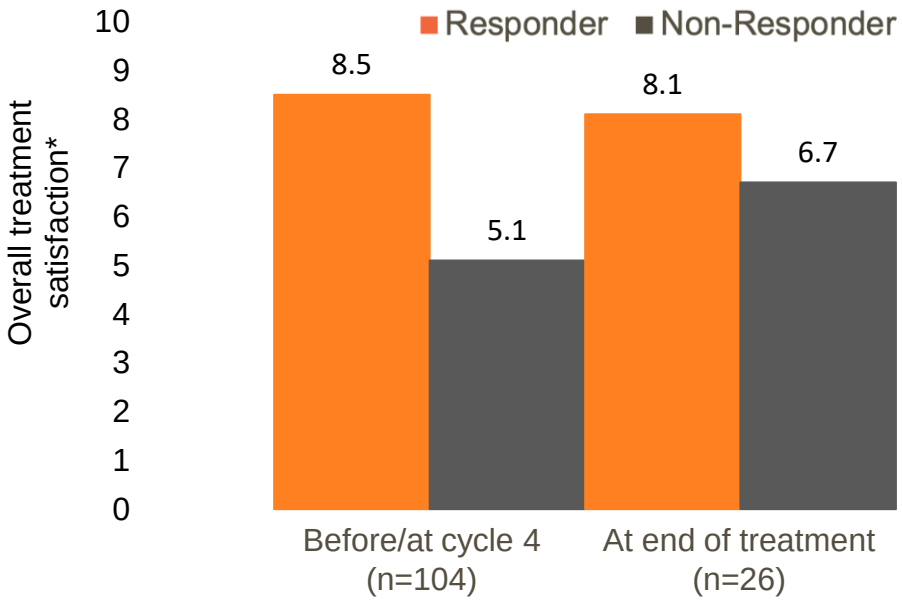
# Treatment Satisfaction

## By treatment responder status

### Patient Treatment Satisfaction*




### Example responder quotes

> I'm tickled to death with what the treatment has done to my cancer. I mean it's dropped my levels tremendously.

> It's worth the side effects that I'm having for the eyes... if I feel that I'm more in control of my body and the myeloma. I feel [as] if I'm in control rather than it being in control of me.

### Example non-responder quotes

> So far I'm satisfied because the doctors are doing everything they can... and I'm hoping for the best.... Not knowing one way or the other, we'd have to go with a five then.

> Yeah, I'd give it a seven or eight or something like that. I mean it didn't work for me, but it might work for other people. Just because it didn't work for me [doesn't] mean it's [not] going to work for somebody else.

Patients were **generally satisfied with treatment** throughout the study, though responders reported higher levels of satisfaction

All patients receiving an interview at the end of treatment (N=26) said **they anticipated the ocular symptoms they experienced**. A total of 6 patients contemplated stopping treatment due to ocular side effects while 3 actually did stop treatment for this reason†

These figures were first presented in Eliason L et al. ASH. 2020.
*Overall treatment satisfaction was rated 0–10 (0=not at all satisfied; 10=extremely satisfied)
†Two patients specifically told their doctor they discontinued treatment due to ocular symptoms

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# Key Findings in Patients from DREAMM-2 Patient Interviews

## Summary of Interviews

- Trial-embedded interviews provided valuable insights into a patient's experience with their disease, the course of treatment-related side effects, and the overall impact on patient satisfaction with treatment
- Overall, responders to treatment reported improvement in key disease symptoms, including bone pain and fatigue
- Many patients reported some type of ocular symptom, but these were shown to improve by end of treatment
- Despite experiencing ocular symptoms, patients reported high satisfaction while on treatment and a desire to remain on treatment, particularly if they were responders

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# Key Learnings and Benefits of Collecting Trial-Embedded Interview Data

## Summary

- Patients often expressed appreciation for the opportunity to share in detail their disease- and treatment-related experiences.
- During the interviews, concept elicitation combined with quantitative ratings and subsequent evaluations by clinical status yielded an informative mixed-methods approach.
- Transcript-level data shared with safety and clinical colleagues provided more patient-level understanding, context, and additional insight into tolerability
- Findings informed the planning of future trial designs and other patient reported endpoints.
- Interviews complemented clinical and patient reported outcomes data in regulatory and payer interactions
- Publication of patient-centered data alongside clinical data increases broader understanding of and demonstrates a focus on the patient perspective.
- Published data have supported patient-focused discussions with healthcare professional and patient advocacy organizations.

# Wrap-Up

**Thank you for attending our workshop!!**

**Please contact us with any questions:**


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