i^2TEAMM Presentation to Support MRD as Accelerated Approval Endpoint

Oncologic Drugs Advisory Committee (ODAC)

April 12, 2024
Introduction

Brian G.M. Durie, MD

Chief Scientific Officer, International Myeloma Foundation
Cedars-Sinai Outpatient Cancer Center
International Independent Team for Endpoint Approval of Myeloma Minimal Residual Disease (i²TEAMM)

Academic Sites
International Independent Team for Endpoint Approval of Myeloma Minimal Residual Disease (i²TEAMM) Academic Sites and Industry Global Trials
Unique Time in Progress of Myeloma Therapy

19 drugs approved in the last 20 years

Significant prolongation of survival outcomes

Multiple new drugs and combinations under evaluation

Patients will have to wait for longer and longer periods for documented PFS benefit
Unmet Need in 2024

- Early endpoint that can reliably predict Progression Free Survival (PFS)

Minimal residual disease (MRD) testing fulfills this unmet need
Depth of Response Predicts Longer PFS and OS

Depth of Response Matters

The deeper the response, the longer the PFS and OS.

MRD significantly improves upon use of ORR and CR alone for response assessment.

- **Diagnosis**
  - ORR
  - CR
  - CR Level: <10 - 5
  - MRD Level: 1/100,000
    - 1/10,000
    - 1/1,000,000
    - 1/1,000,000
Advantages of MRD as Early Endpoint

- Earlier readouts: 9-12 months versus ≥5 years
- Timely approval of life saving therapies / combinations
- Major positive impact for patients
**In Pursuit of MRD Endpoint Approval Goal, Multiple FDA Interactions Occurred**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Initial Discussions/Planning</td>
</tr>
<tr>
<td>2016</td>
<td><strong>MAR 2017 FDA meeting</strong></td>
</tr>
<tr>
<td>2017</td>
<td><strong>DEC 2018 FDA meeting:</strong> review PFS as true endpoint</td>
</tr>
<tr>
<td>2018</td>
<td><strong>JUL 2020 FDA meeting:</strong> Proposed SAP</td>
</tr>
<tr>
<td>2019</td>
<td>SAP finalized with FDA feedback</td>
</tr>
<tr>
<td>2020</td>
<td><strong>MAR 2022 FDA meeting:</strong> Results per SAP [v3.1]</td>
</tr>
<tr>
<td>2021</td>
<td></td>
</tr>
<tr>
<td>2022</td>
<td></td>
</tr>
<tr>
<td>2023</td>
<td><strong>MAR 2023 Data submission to FDA</strong></td>
</tr>
</tbody>
</table>
Seeking approval for the use of MRD negative CR as an early endpoint for accelerated drug approval in multiple myeloma
### Upcoming Presentation Agenda

| The Need for MRD Assessment | Bruno Paiva, PhD  
|                           | Director of Flow Cytometry CIMALAB Diagnostics  
|                           | Department of Hematology  
|                           | Clinica Universidad de Navarra, SPAIN  
| Meta-Analysis and Key Results | Qian Shi, PhD  
|                             | Professor of Biostatistics and Oncology  
|                             | Mayo Clinic  
| Conclusions                | Kenneth C. Anderson, MD  
|                            | Kraft Family Professor of Medicine  
|                            | Dana-Farber Cancer Institute and Harvard Medical School  

The Need for MRD Assessment

Bruno Paiva, PhD,
Director of Flow Cytometry CIMALAB Diagnostics
Department of Hematology
Clinica Universidad de Navarra, SPAIN
Overall Response Rates (ORR) Are Nearing 100% with Standards of Care

- Newly diagnosed transplant-eligible (NDTE) ~97%\textsuperscript{a}
- Newly diagnosed transplant-ineligible (NDTinE) ~93%\textsuperscript{b}
- Relapsed/refractory (RRMM) >63–85%\textsuperscript{c-i}

\textsuperscript{a}: PERSEUS (Sonneveld, \textit{N Engl J Med} 2023); \textsuperscript{b}: MAIA (Facon, \textit{Lancet Oncol} 2021); \textsuperscript{c}: ICARIA (Moreau, \textit{Lancet Oncol} 2021); \textsuperscript{d}: CANDOR (Usmani, \textit{Lancet Oncol} 2022); \textsuperscript{e}: APOLLO (Dimopoulos, \textit{Lancet Oncol} 2021); \textsuperscript{f}: Talquetamab (Chari \textit{N Engl J Med} 2022); \textsuperscript{g}: Teclistamab (Moreau \textit{N Engl J Med} 2022); \textsuperscript{h}: KarMMa-3 (Rodriguez-Otero, \textit{N Engl J Med} 2023); \textsuperscript{i}: CARTITUDE-4 (San-Miguel, \textit{N Engl J Med} 2023)
MRD is the Most Accurate Response Criterion to Measure Treatment Efficacy and Predict Longer Survival\(^1\)

**Progression-free Survival (PFS)**

- MRDpos
- MRDneg

**Overall Survival (OS)**

- MRDneg
- MRDpos

---

MRD is the Most Accurate Response Criterion to Measure Treatment Efficacy and Predict Longer Survival

MRD negativity is the new CR

Progression-free Survival (PFS)

Overall Survival (OS)

Two Next-Generation MRD Methods Detect MRD at $10^{-5}$ Threshold

Next-generation Flow Cytometry (NGF)

Next-generation Sequencing (NGS)

Progression-free Survival (%)

Time Since First Randomization (months)

Best MRD ITT: Neg vs. Pos
HR (95% CI) = 0.29 (0.20, 0.40)
p < 0.0001

Best MRD ITT: Neg vs. Pos
HR (95% CI) = 0.27 (0.18, 0.39)
p < 0.0001

MRD Assessment is Feasible in Clinical Trials

458 NDTE Patients and 1119 Assessments

<table>
<thead>
<tr>
<th>MRD DATA OBTAINED IN</th>
<th>THE MEDIAN LIMIT OF DETECTION WAS</th>
<th>10^{-5} SENSITIVITY ACHIEVED IN</th>
</tr>
</thead>
<tbody>
<tr>
<td>99.6% of samples</td>
<td>2.9 \times 10^{-6}</td>
<td>99.9% of samples</td>
</tr>
</tbody>
</table>
The More Sensitive the MRD Assessment, the Better the Prediction of Clinical Benefit

<table>
<thead>
<tr>
<th>MRD Sensitivity Threshold</th>
<th>N</th>
<th>PFS Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-4}$</td>
<td>2127</td>
<td>0.38 (0.32-0.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$10^{-5}$</td>
<td>5361</td>
<td>0.31 (0.27-0.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$10^{-6}$</td>
<td>1469</td>
<td>0.22 (0.16-0.29)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

MRD is a Key Prognostic Factor in All Disease Settings

Association of MRD Negativity with PFS by Disease Settings

- **MRDneg**
  - NDMM-transplant-eligible
  - NDMM-transplant-ineligible
  - RRMM

- **MRDpos**
  - NDMM-transplant-eligible
  - NDMM-transplant-ineligible
  - RRMM

p<0.01 vs MRD+ for all groups

Large Meta-analysis Using Published Data

- 93 publications
- 8098 patients

MRD Negative Rates Predict Clinical Benefit

Phase 3 Trials Investigating Anti-CD38 Antibodies

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Disease Setting</th>
<th>Randomization</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASSIOPEIA</td>
<td>NDTE</td>
<td>D-VTD vs VTD</td>
<td>D-VTD</td>
</tr>
<tr>
<td>ALCYONE</td>
<td>NDTinE</td>
<td>D-VMP vs VMP</td>
<td>D-VMP</td>
</tr>
<tr>
<td>MAIA</td>
<td>NDTinE</td>
<td>D-Rd vs Rd</td>
<td>D-Rd</td>
</tr>
<tr>
<td>CASTOR</td>
<td>RRMM</td>
<td>D-Vd vs Vd</td>
<td>D-Vd</td>
</tr>
<tr>
<td>IKEMA</td>
<td>RRMM</td>
<td>I-Kd vs Kd</td>
<td>I-Kd</td>
</tr>
<tr>
<td>POLLUX</td>
<td>RRMM</td>
<td>D-Rd vs Rd</td>
<td>D-Rd</td>
</tr>
</tbody>
</table>

Significantly higher MRD negative rates preceded significant differences in PFS

Increased Rates of MRD Negativity Are Associated With Prolonged PFS


**MRD Negativity (10^-5)**

- P<0.0001
- Odds Ratio (95% CI): 3.40 (2.47-4.69)

**PERSEUS Phase 3 Trial**

**MRD assessment**

**48-Month PFS**

- D-VRd: 84.3%
- VRd: 67.7%

**HR (95% CI): 0.42 (0.30-0.59)**

**P<0.0001**

**% Surviving Without Progression**

- D-VRd vs VRd: 84.3% vs 67.7%

**PERSEUS Phase 3 Trial**

**MRD assessment**

- D-VRd: 84.3%
- VRd: 67.7%

**HR (95% CI): 0.42 (0.30-0.59)**

**P<0.0001**

**% Surviving Without Progression**

- D-VRd vs VRd: 84.3% vs 67.7%

**PERSEUS Phase 3 Trial**

**MRD assessment**

- D-VRd: 84.3%
- VRd: 67.7%

**HR (95% CI): 0.42 (0.30-0.59)**

**P<0.0001**

**% Surviving Without Progression**

- D-VRd vs VRd: 84.3% vs 67.7%
MRD Negativity is Associated with Longer PFS/OS in All Treatment Modalities Including Novel Immunotherapies

CAR T cells and TCE

Progression-Free Survival

Overall Survival

Ongoing RCT investigating CAR T cells or TCE are using MRD as co-primary endpoint

HR (95% CI): 0.12 (0.085-0.17)  
p<0.001

HR (95% CI): 0.16 (0.105-0.241)  
p<0.001

CAR T = chimeric antigen receptor; TCE = T cell engager therapies
Summary of MRD Assessment in Multiple Myeloma

- ORR are becoming universal in MM
  - Treatment efficacy must be measured with higher sensitivity
- MRD is evaluated with state-of-the-art and uniform technology
  - Provides results and achieves 10-5 sensitivity in virtually all samples
  - More sensitive than CR criterion
- MRD assessment has shown to be prognostic in all disease settings and treatment scenarios
  - Confirmed in a large meta-analysis based on published data¹
  - Yet to be confirmed in a large meta-analysis based on individual patient data
- Virtually all phase 3 trials leading to drug approvals in MM have shown superior MRD negative rates in the investigational arm
  - Confirmed in a meta-analysis based on published data²
  - Yet to be confirmed in a large meta-analysis based on individual patient data

Meta-Analysis and Key Results

Qian Shi, PhD

Professor of Biostatistics and Oncology
Department of Quantitative Health Sciences
Mayo Clinic, Rochester MN, USA
Overview

• **Initial Objective**
  – To validate minimal residual disease (MRD) as a full surrogate endpoint of **PFS** in multiple myeloma (MM) clinical trials using individual patient data (IPD) from a large collection of randomized clinical trials

• **Revised Objective**
  – To evaluate if current available data can support MRD as an **Early Endpoint** that is reasonably likely to predict clinical benefit in future MM clinical trials
  – Two-level meta-analytic evaluation:
    • **Primary Evaluation**: Individual-patient-level correlation by **Global Odds Ratio** (OR)
    • Supplemental evaluation: Trial-level correlation by $R^2_{WLS}$ and $R^2_{Copula}$
Prespecified Study Selection Criteria

**Inclusion Criteria**
- Multi-center, randomized clinical trial
- Previously untreated patients with NDTE, NDTinE or RR multiple myeloma (MM)
- >100 patients
- Published after 2006

**Exclusion Criteria**
- Evidence that MRD testing with $10^{-4}$ or higher sensitivity level was never performed
- Uncertain/insufficient MRD data quantity and quality

NDTE=Newly Diagnosed Transplant-eligible
NDTinE= Newly Diagnosed Transplant-ineligible
RR=Relapsed/Refractory

Unprecedented Data Sharing in Multiple Myeloma

143 references were identified*

29 study owners were contacted

Individual Patient Data (IPD) from 12,316 patients provided from 20 studies

**NDTE MM**
- 10 trials; 6,084 patients†
  - $10^{-4}$: 7 trials
  - $10^{-5}$: 7 trials
  - $10^{-6}$: 5 trials

**NDTinE MM**
- 7 trials; 4,411 patients†
  - $10^{-4}$: 5 trials
  - $10^{-5}$: 4 trials
  - $10^{-6}$: 2 trials

**RR MM**
- 4 trials; 1,821 patients†
  - $10^{-4}$: 4 trials
  - $10^{-5}$: 4 trials
  - $10^{-6}$: 4 trials

Note: one trial enrolled patients in both NDTE and NDTinE populations

*Identified March 2020, Medline database search for publications and conference abstracts using the strategy of the MeSH terms “multiple myeloma” AND “neoplasm, residual” AND the nonMeSH terms “MRD”, “myeloma”, AND “minimal residual disease”.
†Unique patients indicated in the transferred datasets who were randomized.

EXCLUDED
- 114 did not meet inclusion criteria
- 9 not able to share IPD
Measuring the correlation between MRD and PFS/OS endpoints at individual-patient level

- **Interpretation:** Ratio of odds that a patient remaining progression-free and alive beyond any timepoint for patients who achieved MRD negativity compared to those who remained MRD positive
- **Statistical Significance:** 95% confidence interval (CI) excluding 1.0
- Estimated via Bivariate Plackett Copula Model\(^1\)

Supplemental analysis:
- Landmark log-rank test comparing PFS/OS between patients who achieved MRD negativity compared to those who remained MRD positive

\(^1\)Burzykowski et al. *J Royal Statist Soc.* 2004
Supplemental: Trial-level Correlation – $R^2_{WLS}$ and $R^2_{Copula}$

- Measures how precisely treatment effect on the true endpoint may be predicted based on observed treatment effect on the surrogate endpoint
  - **Interpretation:** closer to 1.0, stronger the trial-level correlation
  - Estimated via two-stage models
    - **$R^2_{WLS}$**: Coefficient of determination of weighted linear regression\(^1\)
      - Paired data: $\log(OR_{MRD})$ via Logistic model and $\log(HR_{PFS})$ via Cox model
    - **$R^2_{Copula}$**: Coefficient of determination of random effect model\(^2\)
      - Paired data: $\log(OR_{MRD})$ & $\log(HR_{PFS})$ estimated by Bivariate Plackett Copula Model
  - **Require sufficient number of trials (2-arm comparisons) to provide robust estimations\(^3\)**

---

1. Sarget et al. *JCO 2005 & 2007*
3. Shi et al. *CSDA 2011*
Supplemental: Trial-level Correlation – $R^2_{WLS}$ and $R^2_{Copula}$

Inclusion of 2-arm comparison:
- $\geq 80\%$ of patients’ MRDneg-CR status can be determined & $\geq 50$ patients
- $>0\%$ MRDneg-CR rate in all arms

Among included 2-arm comparisons, patients with missing MRD were
- excluded (Primary)
- imputed as MRD positive (Sensitivity)

Pre-defined and endorsed by FDA

Analytic Units: Trials (2-arm comparisons)
Data Values: ORs comparing MRD, HRs comparing PFS

Object size is proportional to sample size
MRD Early Endpoint Candidates

- **Primary: 9 months MRDneg-CR**
  - Defined as % of patients with MRD negative status observed at 9 months (+/-3 months) after the date of randomization

- **Secondary: 12 months MRDneg-CR**
  - Defined as % of patients with MRD negative status observed at 12 months (+/-3 months) after the date of randomization

- MRD negativity required ≥1 confirmed CR/sCR during evaluation period
- Pre-defined based on clinical justifications and data availabilities before formal meta-analyses and endorsed by FDA (July of 2020)
9 Months MRDneg-CR Rate

Primary surrogate endpoint candidate for PFS and OS
Data Availability for 9 Months MRDneg-CR Status

20 studies; 12,316 patients

10^-4
26 2-arm comparisons*  
7,466 (61%) unique pts
Excluding 12: <80% pts with MRD data  
1: with 0 MRDneg rate
NDTE: 6 comparisons  
NDTinE: 4 comparisons  
RR: 3 comparisons

10^-5
21 2-arm comparisons*  
6,325 (51%) unique pts
Excluding 8: <80% pts with MRD data  
1: with 0 MRDneg rate
NDTinE: 5 comparisons
NDTinE: 4 comparisons  
RR: 3 comparisons

10^-6
16 2-arm comparisons*  
4,613 (37%) unique pts
Excluding 7: <80% pts with MRD data  
4: with 0 MRDneg rate
NDTE: 3 comparisons  
NDTinE: 1 comparisons  
RR: 1 comparisons

Landmark Analyses
Individual Level (Global OR)
Trial level ($R^2_{WLS}$ & $R^2_{Copula}$)

*Multiple 2-arm comparisons were formed for trials with either 1) > 1 experimental arms or 2) > 1 randomization; NDTE, newly diagnosed transplant eligible; MM, multiple myeloma; NDTinE, newly diagnosed transplant ineligible; RR, relapsed or refractory
Data Availability for 9 Months MRDneg-CR Status

20 studies; 12,316 patients

10^-4
26 2-arm comparisons*
7,466 (61%) unique pts
Excluding
12: <80% pts with MRD data
1: with 0 MRDneg rate
NDTE: 6 comparisons
NDTinE: 4 comparisons
RR: 3 comparisons

10^-5
21 2-arm comparisons*
6,325 (51%) unique pts
Excluding
8: <80% pts with MRD data
1: with 0 MRDneg rate
NDTE: 5 comparisons
NDTinE: 4 comparisons
RR: 3 comparisons

10^-6
16 2-arm comparisons*
4,613 (37%) unique pts
Excluding
7: <80% pts with MRD data
4: with 0 MRDneg rate
NDTE: 3 comparisons
NDTinE: 1 comparisons
RR: 1 comparisons

Landmark Analyses

Individual Level (Global OR)

Trial level ($R^2_{WLS}$ & $R^2_{Copula}$)

*Multiple 2-arm comparisons were formed for trials with either 1) > 1 experimental arms or 2) > 1 randomization;
NDTE, newly diagnosed transplant eligible; MM, multiple myeloma; NDTinE, newly diagnosed transplant ineligible; RR, relapsed or refractory
## Clinical Endpoint: Progression-Free Survival

<table>
<thead>
<tr>
<th>Disease Population</th>
<th>Excluded Patients with Missing MRD</th>
<th>Imputed Missing MRD as Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDTE</td>
<td>N Comp. (N Pts)</td>
<td>Global OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>5 (1,430)</td>
<td>3.06 (2.09-4.03)</td>
</tr>
<tr>
<td>NDTinE</td>
<td>4 (2,235)</td>
<td>9.80 (5.14-14.46)</td>
</tr>
<tr>
<td>RR</td>
<td>3 (1,378)</td>
<td>8.24 (4.41-12.07)</td>
</tr>
</tbody>
</table>
# Strong Individual-Patient-Level Correlation by Population

9 months MRDneg-CR Status, Classified at $10^{-5}$ Threshold

## Clinical Endpoint: Overall Survival

<table>
<thead>
<tr>
<th>Disease Population</th>
<th>Excluded Patients with Missing MRD</th>
<th>Imputed Missing MRD as Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Comp. (N Pts)</td>
<td>Global OR (95% CI)</td>
</tr>
<tr>
<td>NDTE</td>
<td>5 (1,430)</td>
<td>2.81 (1.54-4.08)</td>
</tr>
<tr>
<td>NDTinE</td>
<td>4 (2,235)</td>
<td>10.34 (0.97-19.72)</td>
</tr>
<tr>
<td>RR</td>
<td>3 (1,378)</td>
<td>6.60 (2.36-10.85)</td>
</tr>
</tbody>
</table>
MRD Negativity Strongly Associated with Longer PFS in all 3 Populations
9 months MRDneg-CR Status, Classified at $10^{-5}$ Threshold

Clinical Endpoint: Progression-Free Survival

**NDTE MM**

- **MRDneg**
- **MRDpos**

Stratified Log-rank P-value < 0.0001

% Alive and Progression-Free vs. Months

Patients at Risk
- **MRDneg**: 533
- **MRDpos**: 1412

HR = 0.29 (0.24-0.37)

**NDTinE MM**

- **MRDneg**
- **MRDpos**

Stratified Log-rank P-value < 0.0001

% Alive and Progression-Free vs. Months

Patients at Risk
- **MRDneg**: 133
- **MRDpos**: 1585

HR = 0.24 (0.16-0.36)

**RR MM**

- **MRDneg**
- **MRDpos**

Stratified Log-rank P-value < 0.0001

% Alive and Progression-Free vs. Months

Patients at Risk
- **MRDneg**: 104
- **MRDpos**: 845

HR = 0.31 (0.20-0.46)

Stratified by studies
MRD Negativity Strongly Associated with Longer OS in all 3 Populations
9 months MRDneg-CR Status, Classified at 10^{-5} Threshold

Clinical Endpoint: Overall Survival

NDTE MM

<table>
<thead>
<tr>
<th>Months</th>
<th>Patients at Risk MRDneg</th>
<th>Patients at Risk MRDpos</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>403</td>
<td>1441</td>
</tr>
<tr>
<td>12</td>
<td>357</td>
<td>1234</td>
</tr>
<tr>
<td>24</td>
<td>239</td>
<td>897</td>
</tr>
<tr>
<td>36</td>
<td>161</td>
<td>523</td>
</tr>
<tr>
<td>48</td>
<td>64</td>
<td>218</td>
</tr>
<tr>
<td>60</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>72</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>80</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NDTinE MM

<table>
<thead>
<tr>
<th>Months</th>
<th>Patients at Risk MRDneg</th>
<th>Patients at Risk MRDpos</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>133</td>
<td>1890</td>
</tr>
<tr>
<td>12</td>
<td>115</td>
<td>1431</td>
</tr>
<tr>
<td>24</td>
<td>54</td>
<td>571</td>
</tr>
<tr>
<td>36</td>
<td>21</td>
<td>145</td>
</tr>
<tr>
<td>48</td>
<td>11</td>
<td>70</td>
</tr>
<tr>
<td>60</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>72</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>84</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

RR MM

<table>
<thead>
<tr>
<th>Months</th>
<th>Patients at Risk MRDneg</th>
<th>Patients at Risk MRDpos</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>133</td>
<td>1890</td>
</tr>
<tr>
<td>12</td>
<td>115</td>
<td>1431</td>
</tr>
<tr>
<td>24</td>
<td>54</td>
<td>571</td>
</tr>
<tr>
<td>36</td>
<td>21</td>
<td>145</td>
</tr>
<tr>
<td>48</td>
<td>11</td>
<td>70</td>
</tr>
<tr>
<td>60</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>72</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>84</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR=0.38 (0.27-0.56)
HR=0.16 (0.07-0.38)
HR=0.25 (0.14-0.46)

Stratified by studies
Trial-Level Correlation Between 9 Months MRDneg-CR Rate and PFS – Pooling 3 Populations

Clinical Endpoint: Progression-Free Survival

Excluding pts with missing MRD status

<table>
<thead>
<tr>
<th></th>
<th>12 comparisons; 5,043 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>R²_WLS (95% CI)</td>
<td>0.70 (0.47, 0.92)</td>
</tr>
<tr>
<td>R²_Copula (95% CI)</td>
<td>0.66 (0.36, 0.97)</td>
</tr>
</tbody>
</table>

Imputing missing MRD status as MRD+

<table>
<thead>
<tr>
<th></th>
<th>12 comparisons; 5,741 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>R²_WLS (95% CI)</td>
<td>0.73 (0.53, 0.93)</td>
</tr>
<tr>
<td>R²_Copula (95% CI)</td>
<td>0.71 (0.43, 0.99)</td>
</tr>
</tbody>
</table>

Note: size of dot is proportional to sample size
Trial-Level Correlation Between 9 Months MRDneg-CR Rate and OS – Pooling 3 Populations

Clinical Endpoint: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Excluding pts with missing MRD status</th>
<th>Imputing missing MRD status as MRD+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 comparisons; 5,043 patients</td>
<td>12 comparisons; 5,741 patients</td>
</tr>
<tr>
<td>(R^2_{WLS}) (95% CI)</td>
<td>0.69 (0.51, 0.87)</td>
<td>0.71 (0.50, 0.93)</td>
</tr>
<tr>
<td>(R^2_{Copula}) (95% CI)</td>
<td>0.64 (0.31, 0.96)</td>
<td>0.64 (0.31, 0.97)</td>
</tr>
</tbody>
</table>

Note: size of dot is proportional to sample size.
### Trial-Level Correlation Between 9 Months MRDneg-CR Rate and PFS/OS – Pooling NDTE and NDTinE Populations

**Corresponding to U. of Miami Analysis**

<table>
<thead>
<tr>
<th>Missing MRD</th>
<th>N Comp. (N Pts)</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( R^2_{WLS} ) (95% CI)</td>
<td>( R^2_{Copula} ) (95% CI)</td>
</tr>
<tr>
<td>Excluded</td>
<td>9 (3,665)</td>
<td>0.73 (0.39, 1.00)</td>
<td>0.67 (0.31, 1.00)</td>
</tr>
<tr>
<td>Imputed as MRD Positive</td>
<td>9 (4,227)</td>
<td>0.77 (0.49, 1.00)</td>
<td>0.73 (0.42, 1.00)</td>
</tr>
</tbody>
</table>
12 Months MRDneg-CR Rate

Secondary surrogate endpoint candidate for PFS and OS
Data Availability for 12 Months MRDneg-CR Status

20 studies; 12,316 patients

10^-4
26 2-arm comparisons’ 7,170 (58%) unique pts

Excluding
14: <80% pts with MRD data
1: with 0 MRDneg rate

NDTE: 4 comparisons
NDTinE: 4 comparisons
RR: 3 comparisons

10^-5
21 2-arm comparisons’ 6,241 (51%) unique pts

Excluding
9: <80% pts with MRD data
2: with 0 MRDneg rate

NDTE: 4 comparisons
NDTinE: 4 comparisons
RR: 2 comparisons

10^-6
16 2-arm comparisons’ 4,428 (36%) unique pts

Excluding
6: <80% pts with MRD data
3: with 0 MRDneg rate

NDTE: 4 comparisons
NDTinE: 2 comparisons
RR: 1 comparisons

Landmark Analyses

Individual Level (Global OR)

Trial level ($R^2_{WLS}$ & $R^2_{Copula}$)

*Multiple 2-arm comparisons were formed for trials with either 1) > 1 experimental arms or 2) > 1 randomization; NDTE, newly diagnosed transplant eligible; MM, multiple myeloma; NDTinE, newly diagnosed transplant ineligible; RR, relapsed or refractory
Data Availability for 12 Months MRDneg-CR Status

20 studies; 12,316 patients

10^-4
26 2-arm comparisons
7,170 (58%) unique pts
Excluding 14: <80% pts with MRD data
1: with 0 MRDneg rate
NDTE: 4 comparisons
NDTinE: 4 comparisons
RR: 3 comparisons

10^-5
21 2-arm comparisons
6,241 (51%) unique pts
Excluding 9: <80% pts with MRD data
2: with 0 MRDneg rate
NDTE: 4 comparisons
NDTinE: 4 comparisons
RR: 2 comparisons

10^-6
16 2-arm comparisons
4,428 (36%) unique pts
Excluding 6: <80% pts with MRD data
3: with 0 MRDneg rate
NDTE: 4 comparisons
NDTinE: 2 comparisons
RR: 1 comparisons

Landmark Analyses

Individual Level
(Global OR)

Trial level
($R^2_{WLS}$ & $R^2_{Copula}$)

*Multiple 2-arm comparisons were formed for trials with either 1) > 1 experimental arms or 2) > 1 randomization; NDTE, newly diagnosed transplant eligible; MM, multiple myeloma; NDTinE, newly diagnosed transplant ineligible; RR, relapsed or refractory
## Strong Individual-Patient-Level Correlation by Population

**12 months** MRDneg-CR Status, Classified at $10^{-5}$ Threshold

### Clinical Endpoint: Progression-Free Survival

<table>
<thead>
<tr>
<th>Disease Population</th>
<th>Excluded Patients with Missing MRD</th>
<th>Imputed Missing MRD as Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Comp. (N Pts)</td>
<td>Global OR (95% CI)</td>
</tr>
<tr>
<td>NDTE</td>
<td>4 (1,285)</td>
<td>4.45 (3.19-5.70)</td>
</tr>
<tr>
<td>NDTinE</td>
<td>4 (2,281)</td>
<td>11.95 (7.32-16.58)</td>
</tr>
<tr>
<td>RR</td>
<td>2 (863)</td>
<td>16.24 (5.77-26.71)</td>
</tr>
</tbody>
</table>
### Clinical Endpoint: Overall Survival

<table>
<thead>
<tr>
<th>Disease Population</th>
<th>Excluded Patients with Missing MRD</th>
<th>Imputed Missing MRD as Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Comp. (N Pts)</td>
<td>Global OR (95% CI)</td>
</tr>
<tr>
<td>NDTE</td>
<td>4 (1,285)</td>
<td>5.16 (2.80-7.53)</td>
</tr>
<tr>
<td>NDTinE</td>
<td>4 (2,281)</td>
<td>7.08 (2.84-11.31)</td>
</tr>
<tr>
<td>RR</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
MRD Negativity Strongly Associated with Longer PFS in all 3 Populations

Clinical Endpoint: Progression-Free Survival

MRD Negativity Strongly Associated with Longer PFS in all 3 Populations

12 months MRDneg-CR Status, Classified at 10^{-5} Threshold

Clinical Endpoint: Progression-Free Survival

HR=0.37 (0.29-0.47)  
HR=0.22 (0.16-0.31)  
HR=0.30 (0.20-0.45)
MRD Negativity Strongly Associated with Longer OS in all 3 Populations

12 months MRDneg-CR Status, Classified at 10^{-5} Threshold

Clinical Endpoint: Overall Survival

HR=0.34 (0.22-0.54)  
HR=0.26 (0.14-0.46)  
HR=0.25 (0.13-0.45)
Trial-Level Correlation Between 12 Months MRDneg-CR Rate and PFS – Pooling 3 Populations

Clinical Endpoint: Progression-Free Survival

Excluding pts with missing MRD status

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 comparisons; 4,429 patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( R^2_{WLS} ) (95% CI)</td>
<td>( R^2_{Copula} ) (95% CI)</td>
</tr>
<tr>
<td></td>
<td>0.66 (0.34, 0.98)</td>
<td>0.61 (0.23, 0.99)</td>
</tr>
</tbody>
</table>

Imputing missing MRD status as MRD+

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 comparisons; 4,960 patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( R^2_{WLS} ) (95% CI)</td>
<td>( R^2_{Copula} ) (95% CI)</td>
</tr>
<tr>
<td></td>
<td>0.72 (0.46, 0.99)</td>
<td>0.69 (0.38, 1.00)</td>
</tr>
</tbody>
</table>

Note: size of dot is proportional to sample size
Trial-Level Correlation Between 12 Months MRDneg-CR Rate and OS – Pooling 3 Populations

Clinical Endpoint: Overall Survival

Excluding pts with missing MRD status

<table>
<thead>
<tr>
<th></th>
<th>10 comparisons; 4,429 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2_{WLS}$ (95% CI)</td>
</tr>
<tr>
<td></td>
<td>0.60 (0.29, 0.92)</td>
</tr>
</tbody>
</table>

Imputing missing MRD status as MRD+

<table>
<thead>
<tr>
<th></th>
<th>10 comparisons; 4,960 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2_{WLS}$ (95% CI)</td>
</tr>
<tr>
<td></td>
<td>0.69 (0.45, 0.94)</td>
</tr>
</tbody>
</table>

Note: size of dot is proportional to sample size
Trial-Level Correlation Between 12 Months MRDneg-CR Rate and PFS/OS – Pooling NDTE and NDTinE Populations

Corresponding to U. of Miami Analysis

<table>
<thead>
<tr>
<th>Missing MRD</th>
<th>N Comp. (N Pts)</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$R^2_{WLS}$ (95% CI)</td>
<td>$R^2_{Copula}$ (95% CI)</td>
</tr>
<tr>
<td>Excluded</td>
<td>8 (3,566)</td>
<td>0.78 (0.49, 1.00)</td>
<td>0.71 (0.36, 1.00)</td>
</tr>
<tr>
<td>Imputed as MRD Positive</td>
<td>8 (4,010)</td>
<td>0.85 (0.70, 1.00)</td>
<td>0.82 (0.60, 1.00)</td>
</tr>
</tbody>
</table>
High Individual-Patient-Level Correlation Supports Consideration of Early Endpoint For Accelerated Approval

- Consistent high individual-patient-level correlations provide strong evidence that 9 months MRDneg-CR rate at $10^{-5}$ threshold reasonably likely predicts clinical benefit of PFS in NDTE, NDTinE and RR MM populations
  - Promising trial-level correlations pooling 3 populations provide supportive evidence
  - Similar results were seen for 12 months MRDneg-CR rate at $10^{-5}$ threshold
  - Similar results were seen for OS, except in the scenarios with low events

MRDneg-CR rate classified at $10^{-5}$ threshold at 9 and 12 months IS reasonably likely to predict clinical benefit in NDTE, NDTinE, and RR MM settings
Summary and Conclusions

Kenneth C. Anderson, MD
Kraft Family Professor of Medicine
Harvard Medical School
Clear Rationale to Seek Endpoint Measuring Earlier Response

• Therapeutic landscape in myeloma has greatly expanded
  ‒ ORR near 100% and CR >70%
  ‒ Median PFS >6 years and median OS >10 years

• Urgent need to develop alternative endpoints that provide sensitive earlier read out allowing patients timely access to newer treatment options
MRD Determination Provides for Reproducible Assessment of Residual Disease and Predicts Outcome

- Technological advances allow reproducible assessment of MRD
- Large number of studies have confirmed significant impact of MRD on PFS and OS
- Trial-level analyses correlating an MRD sensitivity $10^{-5}$ or better with PFS and OS

i²TEAMM Study: Heterogeneity is a Strength

- Trial-level meta-analysis of 20 robust, randomized, controlled Phase 3 clinical trials with mature PFS data and large sample sizes
- Enrolled patients from US, Europe, Middle East, Africa, and Asia
- Varied in design, lines of therapy, treatment strategies, MRD testing methods, timing and/or number of assessments, and sensitivity levels

Results are largely representative of a wide spectrum of treatment options and clinical practice
• Although chimeric antigen receptor (CAR) T cell therapy and T cell engager therapies are not represented, MRD is correlated with PFS after CAR T cell therapy

Strength of Results: Consistent in 2 Independent Studies

- Two independent analyses with differences in methodologies, but overlapping studies
- BOTH show a similar strong association between MRD negative CR and PFS at individual-patient-level
- Re-analysis by i²TEAMM using similar inclusion criteria (e.g. missingness of data) shows consistent results
i²TEAMM Study: Consistent Results of Trial and Patient Level Analyses

Trial-level association

• MRD negative CR and PFS is promising at $10^{-5}$ MRD sensitivity level

Individual patient level

• Bivariate association analysis and landmark analysis showed strong association between MRD negative CR (at 9 and 12 months) and PFS
Conclusion

• Combined results of individual patient-level and trial-level surrogacy support the use of MRD negative CR as an early endpoint reasonably likely to predict clinical benefit

Results support the use of MRD negative CR as an early endpoint for accelerated drug approval in multiple myeloma
i²TEAMM Presentation to Support MRD as Accelerated Approval Endpoint

Oncologic Drugs Advisory Committee (ODAC)

April 12, 2024