Overall Survival and Progression-free Survival by Treatment Duration With Daratumumab + Lenalidomide/Dexamethasone in Transplant-ineligible Newly Diagnosed Multiple Myeloma: Phase 3 MAIA Study*

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**Advisory boards:** Amgen, Celgene/Bristol Myers Squibb, Janssen, Oncopeptides, and Sanofi

**Honoraria:** Amgen, Celgene/Bristol Myers Squibb, Janssen, Oncopeptides, and Sanofi
Introduction

- The PFS benefit of daratumumab in combination with standard of care versus standard of care alone in patients with NDMM was established in the phase 3 ALCYONE, MAIA, and CASSIOPEIA studies\textsuperscript{1-3}; the OS benefit of a daratumumab-based regimen in patients with NDMM was also established in the ALCYONE study\textsuperscript{4}

- VRd was established as a standard-of-care regimen for elderly patients based on results of the phase 3 SWOG S0777 study in patients with NDMM without intent for immediate transplant (69% of whom were intended for eventual transplant)\textsuperscript{5}
  - At a median follow-up of 84 months, the median PFS was 41 months for VRd and 29 months for Rd (HR, 0.742); median OS was not reached versus 69 months, respectively (HR, 0.709)\textsuperscript{6}
  - 43% of patients in SWOG S0777 were ≥65 years of age (compared with 99% in MAIA); however, a significant OS benefit was not observed in this subgroup for VRd versus Rd (median, 65 months vs 56 months; HR, 0.769; \( P = 0.168 \))\textsuperscript{6}

- Real-world data indicate that >50% of transplant-ineligible elderly patients with NDMM do not receive any subsequent therapy; this suggests that the most effective therapy should be used upfront and not saved for relapse,\textsuperscript{7} at which time additional genetic mutations conferring resistance may have been acquired\textsuperscript{8}

- In a previous MAIA update (Kumar SK, et al. ASH 2020), D-Rd prolonged PFS and PFS2 versus Rd alone in transplant-ineligible patients with NDMM; OS data were not yet mature\textsuperscript{9}

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Here, we report updated efficacy and safety results from a pre-specified interim OS analysis of MAIA and a post hoc analysis of PFS by treatment duration after a median follow-up of approximately 56 months

PFS, progression-free survival; NDMM, newly diagnosed multiple myeloma; OS, overall survival; VRd, bortezomib/lenalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; HR, hazard ratio; D-Rd, daratumumab plus lenalidomide/dexamethasone; PFS2, progression-free survival on the next subsequent line of therapy.

MAIA Study Design

• Patients were enrolled in MAIA from March 2015 through January 2017

Key eligibility criteria
• TIE NDMM
• ECOG PS score 0-2
• CrCl ≥30 mL/min

1:1 randomization

D-Rd

D: 16 mg/kg IV
  QW Cycles 1-2, Q2W Cycles 3-6,
  then Q4W thereafter until PD
R: 25 mg PO
  Days 1-21 until PD
da: 40 mg PO or IV
  Days 1, 8, 15, 22 until PD

Rd

R: 25 mg PO Days 1-21 until PD
da: 40 mg PO
  Days 1, 8, 15, 22 until PD

Cycles: 28 days

End-of-treatment visit (30 days after last dose)

Long-term follow-up

Primary endpoint
• PFS

Key secondary endpoints
• OS
• PFS2
• ORR
• CR/sCR rate
• MRD (NGS; 10^-5)

MAIA is a multicenter, randomized, open-label, active-controlled, phase 3 study of D-Rd versus Rd alone in patients with NDMM who are transplant ineligible

TIE, transplant-ineligible; ECOG PS, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; IV, intravenous; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; PD, progressive disease; PO, oral; ORR, overall response rate; CR, complete response; sCR, stringent complete response; MRD, minimal residual disease; NGS, next-generation sequencing; BMI, body mass index.

\(^{4}\)On days when daratumumab is administered, dexamethasone will be administered to patients in the D-Rd arm and will serve as the treatment dose of steroid for that day, as well as the required pre-infusion medication. \(^{4}\)For patients >75 years of age or with BMI <18.5 kg/m\(^2\), dexamethasone was administered at a dose of 20 mg QW.
### Demographics and Baseline Characteristics (ITT)

<table>
<thead>
<tr>
<th>Age Distribution, n (%)</th>
<th>D-Rd (n = 368)</th>
<th>Rd (n = 369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 y</td>
<td>4 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>65-&lt;70 y</td>
<td>74 (20)</td>
<td>73 (20)</td>
</tr>
<tr>
<td>70-&lt;75 y</td>
<td>130 (35)</td>
<td>131 (36)</td>
</tr>
<tr>
<td>≥75 y</td>
<td>160 (43)</td>
<td>161 (44)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG PS score, a n (%)</th>
<th>D-Rd (n = 368)</th>
<th>Rd (n = 369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>127 (35)</td>
<td>123 (33)</td>
</tr>
<tr>
<td>1</td>
<td>178 (48)</td>
<td>187 (51)</td>
</tr>
<tr>
<td>2 b</td>
<td>63 (17)</td>
<td>59 (16)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ISS stage, c n (%)</th>
<th>D-Rd (n = 368)</th>
<th>Rd (n = 369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>98 (27)</td>
<td>103 (28)</td>
</tr>
<tr>
<td>II</td>
<td>163 (44)</td>
<td>156 (42)</td>
</tr>
<tr>
<td>III</td>
<td>107 (29)</td>
<td>110 (30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of measurable disease, n (%)</th>
<th>D-Rd (n = 368)</th>
<th>Rd (n = 369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>225 (61)</td>
<td>231 (63)</td>
</tr>
<tr>
<td>IgA</td>
<td>65 (18)</td>
<td>66 (18)</td>
</tr>
<tr>
<td>Other d</td>
<td>9 (2)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Detected in urine only</td>
<td>40 (11)</td>
<td>34 (9)</td>
</tr>
<tr>
<td>Detected as serum-free light chain only</td>
<td>29 (8)</td>
<td>28 (8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytogenetic profile, e n/total n (%)</th>
<th>D-Rd (n = 368)</th>
<th>Rd (n = 369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard risk</td>
<td>271/319 (85)</td>
<td>279/323 (86)</td>
</tr>
<tr>
<td>High risk</td>
<td>48/319 (15)</td>
<td>44/323 (14)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median time since initial diagnosis of MM (range), months</th>
<th>D-Rd (n = 368)</th>
<th>Rd (n = 369)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.95 (0.1-13.3)</td>
<td>0.89 (0-14.5)</td>
</tr>
</tbody>
</table>

Demographics and baseline characteristics were well balanced between arms.

ITT, intention-to-treat.

*ECOG PS is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. **Two patients had an ECOG PS score >2 (1 patient each with an ECOG PS score of 3 and 4). *ISS stage is derived based on the combination of serum β₂-microglobulin and albumin; higher stages indicate more severe disease. **Includes IgD, IgE, IgM, and biclonal. *Cytogenetic abnormalities were identified by fluorescence in situ hybridization or karyotype testing; high risk was defined as having a t(4;14), t(14;16), and/or del17p abnormality. Note: percentages may not add up to 100% due to rounding.
## Treatment Exposure and Patient Disposition

Median duration of follow-up: 56.2 months

<table>
<thead>
<tr>
<th>Safety population (received ≥1 dose of study treatment)</th>
<th>D-Rd (n = 364)</th>
<th>Rd (n = 365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of study treatment, months (range)</td>
<td>47.5 (0.10-69.26)</td>
<td>22.6 (0.03-69.22)</td>
</tr>
<tr>
<td>Lenalidomide median RDI, % (range)</td>
<td>66 (8-206)</td>
<td>86 (5-239)</td>
</tr>
<tr>
<td>Discontinued lenalidomide only while continuing other study treatment, n (%)</td>
<td>33 (9)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>IV daratumumab median RDI, % (range)</td>
<td>98 (3-107)</td>
<td>–</td>
</tr>
<tr>
<td>Discontinued daratumumab only while continuing other study treatment, n (%)</td>
<td>5 (1)</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ITT population</th>
<th>D-Rd (n = 368)</th>
<th>Rd (n = 369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remaining on study treatment, %</td>
<td>42</td>
<td>18</td>
</tr>
<tr>
<td>Discontinued study treatment, %</td>
<td>57</td>
<td>81</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>27</td>
<td>34</td>
</tr>
<tr>
<td>Adverse event</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Death</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Noncompliance with study drug</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Physician decision</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Patient withdrawal</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

42% of patients in the D-Rd arm and 18% of patients in the Rd arm remained on treatment; more patients in the Rd arm than in the D-Rd arm discontinued due to AEs

RDI, relative dose intensity; AE, adverse event.
Note: percentages may not add up to 100% due to rounding.
• D-Rd induced deeper responses, with significantly higher rates of ≥CR and ≥VGPR, compared with Rd

• With >28 months of additional follow-up, responses deepened with continued daratumumab therapy

ORRa

VGPR, very good partial response; PR, partial response; OR, odds ratio.

*ITT population. bP < 0.0001; P values were calculated from the Cochran–Mantel–Haenszel chi-squared test.


Note: percentages may not add up to the total due to rounding.
Updated PFS

Median follow-up: 56.2 months

- D-Rd continued to demonstrate a significant PFS benefit, with median PFS not reached with D-Rd
- These data provide a new PFS benchmark in patients with NDMM who are transplant ineligible

NR, not reached; CI, confidence interval.

HR, 0.53; 95% CI, 0.43-0.66; \( P < 0.0001 \)

No. at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at risk</th>
<th>Rd</th>
<th>D-Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>369</td>
<td>368</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>333</td>
<td>347</td>
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<tr>
<td>6</td>
<td>307</td>
<td>335</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>280</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>255</td>
<td>290</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>237</td>
<td>276</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>220</td>
<td>266</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>205</td>
<td>256</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>196</td>
<td>246</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>179</td>
<td>237</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>172</td>
<td>232</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>155</td>
<td>222</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>146</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>133</td>
<td>199</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>123</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>113</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>105</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>94</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>63</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>36</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>12</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>66</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>69</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
D-Rd showed a robust PFS benefit among patients treated for ≥18 months, with a 43% reduction in the risk of disease progression or death and a 20% increase in PFS rate at 60 months

*Post hoc analysis.*
D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible.

*P = 0.0013 is statistically significant, crossing the pre-specified stopping boundary of P = 0.0414.
Subgroup Analysis of OS

<table>
<thead>
<tr>
<th>Sex</th>
<th>No. of deaths/total no.</th>
<th>D-Rd Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>71/189</td>
<td>88/195</td>
<td>NE 57.2</td>
</tr>
<tr>
<td>Female</td>
<td>46/179</td>
<td>68/174</td>
<td>NE NE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of deaths/total no.</th>
<th>D-Rd Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75 years</td>
<td>52/208</td>
<td>80/208</td>
<td>NE NE</td>
</tr>
<tr>
<td>≥75 years</td>
<td>65/160</td>
<td>76/161</td>
<td>NE 55.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>No. of deaths/total no.</th>
<th>D-Rd Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>106/336</td>
<td>138/339</td>
<td>NE NE</td>
</tr>
<tr>
<td>Other</td>
<td>11/32</td>
<td>18/30</td>
<td>NE 49.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>No. of deaths/total no.</th>
<th>D-Rd Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>33/101</td>
<td>46/102</td>
<td>NE 55.7</td>
</tr>
<tr>
<td>Other</td>
<td>84/267</td>
<td>110/267</td>
<td>NE NE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline renal function (CrCl)</th>
<th>No. of deaths/total no.</th>
<th>D-Rd Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 mL/min</td>
<td>59/206</td>
<td>89/227</td>
<td>NE NE</td>
</tr>
<tr>
<td>≤60 mL/min</td>
<td>58/162</td>
<td>67/142</td>
<td>NE 54.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline hepatic function</th>
<th>No. of deaths/total no.</th>
<th>D-Rd Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>104/335</td>
<td>144/340</td>
<td>NE NE</td>
</tr>
<tr>
<td>Impaired</td>
<td>13/31</td>
<td>12/29</td>
<td>NE NE</td>
</tr>
</tbody>
</table>

OS benefit with D-Rd was generally consistent across patient subgroups

ISS disease stage

<table>
<thead>
<tr>
<th>ISS disease stage</th>
<th>No. of deaths/total no.</th>
<th>D-Rd Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>19/98</td>
<td>24/103</td>
<td>NE NE</td>
</tr>
<tr>
<td>II</td>
<td>50/163</td>
<td>69/156</td>
<td>NE NE</td>
</tr>
<tr>
<td>III</td>
<td>48/107</td>
<td>63/110</td>
<td>62.8 47.3</td>
</tr>
</tbody>
</table>

Type of MM

<table>
<thead>
<tr>
<th>Type of MM</th>
<th>No. of deaths/total no.</th>
<th>D-Rd Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>74/225</td>
<td>90/231</td>
<td>NE NE</td>
</tr>
<tr>
<td>Non-IgG</td>
<td>22/74</td>
<td>37/76</td>
<td>NE 53.7</td>
</tr>
</tbody>
</table>

Cytogenetic risk at study entry

<table>
<thead>
<tr>
<th>Cytogenetic risk at study entry</th>
<th>No. of deaths/total no.</th>
<th>D-Rd Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>25/48</td>
<td>26/44</td>
<td>55.6 42.5</td>
</tr>
<tr>
<td>Standard risk</td>
<td>80/271</td>
<td>116/279</td>
<td>NE NE</td>
</tr>
</tbody>
</table>

ECOG PS score

<table>
<thead>
<tr>
<th>ECOG PS score</th>
<th>No. of deaths/total no.</th>
<th>D-Rd Median OS (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>24/127</td>
<td>36/123</td>
<td>NE NE</td>
</tr>
<tr>
<td>1</td>
<td>64/178</td>
<td>82/187</td>
<td>NE 58.3</td>
</tr>
<tr>
<td>≥2</td>
<td>29/63</td>
<td>38/59</td>
<td>62.8 39.0</td>
</tr>
</tbody>
</table>

NE, not estimable.
Subsequent Therapy

• Median time to next treatment was not reached with D-Rd versus 42.4 months with Rd (HR, 0.47; 95% CI, 0.37-0.59; \( P < 0.0001 \))

• 114 patients in the D-Rd arm and 186 patients in the Rd arm received subsequent therapy; of these:
  – A PI-containing regimen without an IMiD was the most common first subsequent therapy (53% vs 54% with D-Rd and Rd, respectively)
  – 15% of patients in the D-Rd arm and 46% of patients in the Rd arm received a daratumumab-containing regimen as any subsequent line of therapy

PI, proteasome inhibitor; IMiD, immunomodulatory drug.
Most Common (>5%) Grade 3/4 TEAEs (Safety Population)\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th><strong>D-Rd</strong> (n = 364)</th>
<th><strong>Rd</strong> (n = 365)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic, n (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Neutropenia</td>
<td>197 (54)</td>
<td>135 (37)</td>
</tr>
<tr>
<td>Anemia</td>
<td>61 (17)</td>
<td>79 (22)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>60 (16)</td>
<td>41 (11)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>42 (12)</td>
<td>23 (6)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>32 (9)</td>
<td>34 (9)</td>
</tr>
<tr>
<td><strong>Nonhematologic, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>70 (19)</td>
<td>39 (11)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>46 (13)</td>
<td>36 (10)</td>
</tr>
<tr>
<td>Cataract</td>
<td>40 (11)</td>
<td>39 (11)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32 (9)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 (9)</td>
<td>17 (5)</td>
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<tr>
<td>Hypertension</td>
<td>31 (9)</td>
<td>16 (4)</td>
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<tr>
<td>Hyperglycemia</td>
<td>28 (8)</td>
<td>14 (4)</td>
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<tr>
<td>Pulmonary embolism</td>
<td>26 (7)</td>
<td>19 (5)</td>
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<tr>
<td>Asthenia</td>
<td>19 (5)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>19 (5)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>19 (5)</td>
<td>10 (3)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Median duration of study treatment was 47.5 months in the D-Rd arm and 22.6 months in the Rd arm. Data are not exposure adjusted.

No new safety concerns were identified with longer follow-up
Conclusions

• After almost 5 years of follow-up, a significant OS benefit of D-Rd versus Rd given to progression was demonstrated in patients with transplant-ineligible NDMM, representing a 32% reduction in the risk of death
  – The estimated 5-year OS rate was 66.3% with D-Rd and 53.1% with Rd, which will likely lead to a substantial improvement of median OS in this patient population

• The significant PFS benefit of D-Rd versus Rd was maintained, with a 47% reduction in the risk of disease progression or death (median PFS for D-Rd, not reached)
  – The estimated 5-year PFS rate was 52.5% with D-Rd and 28.7% with Rd
  – These data provide a new PFS benchmark in patients with NDMM who are transplant ineligible
  – In a post hoc analysis, D-Rd showed a robust PFS benefit versus Rd among patients treated for ≥18 months

• These PFS and OS results have been achieved in a study population with 44% of patients aged 75 to 90 years

• No new safety concerns were identified with continuous therapy and longer follow-up

These results strongly support upfront D-Rd as a new standard of care for patients with transplant-ineligible NDMM
Acknowledgments

• Patients who participated in this study
• All investigators who contributed to the study
  – Intergroupe Francophone du Myélome
• Staff members at the study sites
• Data and safety monitoring committee
• Staff members involved in data collection and analyses

• Other ongoing frontline registration daratumumab studies include:
  – Transplant ineligible: CEPHEUS (D-VRd)
  – Transplant eligible: PERSEUS (D-VRd)

D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone.
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