Up-Front Management of Multiple Myeloma

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## Disclosures

<table>
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<tr>
<th><strong>Consulting Agreements</strong></th>
<th>Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Janssen Biotech Inc, Merck, Takeda Oncology</th>
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<td><strong>Contracted Research</strong></td>
<td>AstraZeneca Pharmaceuticals LP</td>
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</table>
70-year-old woman

- Diagnosis: Stage II t(4;14) multiple myeloma
- Bortezomib/lenalidomide/dexamethasone (VRD), with VGPR
- Patient is willing to receive maintenance therapy but not yet ASCT
84-year-old woman

- Presents with chronic kidney disease and a recent decline in renal function
- Diagnosis: IgG-lambda multiple myeloma, no significant bone disease
- Good performance status, GFR <40
sCR and MRD as a Surrogate Endpoint for PFS and OS

- **Achievement of sCR and MRD negativity after ASCT are associated with better PFS and OS**

  sCR, stringent complete response; MRD, minimal residual disease; OS, overall survival; TTP, time to progression; CR, complete response; nCR, near complete response; ASCT, autologous stem cell transplantation.

  - According to MRD status at the start of maintenance therapy.

Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study

• Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017

D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; QW, weekly; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; PR, partial response; Q8W, every 8 weeks; PD, progressive disease; sCR, stringent complete response; PFS, progression-free survival; MRD, minimal residual disease; CR, complete response; OS, overall survival.

*Dexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1-2 and Days 1 & 2 of Cycles 3-4; 20 mg on Days 6, 9, 15 of Cycles 3-4; 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5-6.
The addition of daratumumab to VTd improved depth of response

**CASSIOPEIA: MRD (Flow Cytometry; 10^{-5})^{a,b}**

**D-VTd superior across all subgroups including high-risk cytogenetics and ISS stage III**

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**Sex**
- Male: VTd 131 (41), D-VTd 192 (61), Odds Ratio (95% CI): 2.22 (1.62–3.05)
- Female: VTd 105 (47), D-VTd 154 (68), Odds Ratio (95% CI): 2.37 (1.62–3.48)

**Age**
- <50 years: VTd 38 (42), D-VTd 56 (68), Odds Ratio (95% CI): 2.84 (1.53–5.28)
- ≥50 years: VTd 198 (44), D-VTd 290 (63), Odds Ratio (95% CI): 2.19 (1.68–2.85)

**Site**
- IFM: VTd 204 (45), D-VTd 287 (64), Odds Ratio (95% CI): 2.16 (1.65–2.81)
- HOVON: VTd 32 (38), D-VTd 59 (65), Odds Ratio (95% CI): 3.05 (1.65–5.65)

**ISS disease stage**
- I: VTd 103 (45), D-VTd 137 (67), Odds Ratio (95% CI): 2.48 (1.68–3.67)
- II: VTd 96 (41), D-VTd 155 (61), Odds Ratio (95% CI): 2.21 (1.54–3.18)
- III: VTd 37 (46), D-VTd 54 (64), Odds Ratio (95% CI): 2.14 (1.15–4.00)

**Cytogenetic profile at trial entry**
- High risk: VTd 36 (44), D-VTd 49 (60), Odds Ratio (95% CI): 1.88 (1.02–3.46)
- Standard risk: VTd 197 (43), D-VTd 296 (64), Odds Ratio (95% CI): 2.35 (1.80–3.07)

**Baseline creatinine clearance**
- >90 ml/min: VTd 139 (44), D-VTd 205 (62), Odds Ratio (95% CI): 2.07 (1.51–2.84)
- ≤90 ml/min: VTd 97 (43), D-VTd 141 (67), Odds Ratio (95% CI): 2.64 (1.79–3.89)

**Baseline hepatic function**
- Normal: VTd 216 (43), D-VTd 310 (65), Odds Ratio (95% CI): 2.40 (1.85–3.10)
- Impaired: VTd 20 (48), D-VTd 36 (57), Odds Ratio (95% CI): 1.47 (0.67–3.21)

**Type of multiple myeloma**
- IgG: VTd 122 (39), D-VTd 201 (61), Odds Ratio (95% CI): 2.43 (1.77–3.34)
- Non-IgG: VTd 59 (49), D-VTd 61 (66), Odds Ratio (95% CI): 2.00 (1.15–3.50)

**Type of multiple myeloma**
- 0: VTd 112 (44), D-VTd 172 (65), Odds Ratio (95% CI): 2.39 (1.68–3.41)
- ≥1: VTd 124 (44), D-VTd 174 (63), Odds Ratio (95% CI): 2.17 (1.55–3.04)

**ECOG performance status**
- 0: VTd 112 (44), D-VTd 172 (65), Odds Ratio (95% CI): 2.39 (1.68–3.41)
- ≥1: VTd 124 (44), D-VTd 174 (63), Odds Ratio (95% CI): 2.17 (1.55–3.04)

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^Based on patients with available cytogenetics results. ^Based on patients with available serum heavy chain disease type only.
CASSIOPEIA: Response Rates Over Time

Responses deepened over time

• Median (range) follow-up: 18.8 (0.0-32.2) months

**18-month PFS**

- **D-VTd (n = 543)**
  - Events, n (%): 45 (8)
  - HR (95% CI): 0.47 (0.33-0.67)
  - *P* value: <0.0001

- **VTd (n = 542)**
  - Events, n (%): 91 (17)
  - HR (95% CI): 1.00 (0.73-1.38)
  - *P* value: 1.00

**53% reduction in the risk of progression or death in the D-VTd arm**

Philippe Moreau, MD

Primary and final PFS analysis of Part 1

**GRiffin (NCT02874742): Randomized Phase 2 study**

- D-RVd vs RVd in transplant-eligible NDMM, 35 sites in US with enrollment from 12/2016 to 4/2018

### Key eligibility criteria:
- Transplant-eligible NDMM
- 18-70 years of age
- ECOG score 0-2
- CrCl ≥30 ml/min

### Induction:
**Cycles 1-4**
- **D-RVd**
  - D: 16 mg/kg IV Days 1, 8, 15
  - R: 25 mg PO Days 1-14
  - V: 1.3 mg/m² SC Days 1, 4, 8, 11
  - d: 20 mg PO Days 1, 2, 8, 9, 15, 16
- **RvD**
  - R: 25 mg PO Days 1-14
  - V: 1.3 mg/m² SC Days 1, 4, 8, 11
  - d: 20 mg PO Days 1, 2, 8, 9, 15, 16

### Consolidation:
**Cycles 5-6c**
- **D-RVd**
  - D: 16 mg/kg IV Day 1
  - R: 25 mg PO Days 1-14
  - V: 1.3 mg/m² SC Days 1, 4, 8, 11
  - d: 20 mg PO Days 1, 2, 8, 9, 15, 16
- **RvD**
  - R: 25 mg PO Days 1-14
  - V: 1.3 mg/m² SC Days 1, 4, 8, 11
  - d: 20 mg PO Days 1, 2, 8, 9, 15, 16

### Maintenance:
**Cycles 7-32d**
- **D-R**
  - D: 16 mg/kg IV Day 1
  - R: 25 mg PO Days 1-14
  - V: 1.3 mg/m² SC Days 1, 4, 8, 11
  - d: 20 mg PO Days 1, 2, 8, 9, 15, 16

### Stem cell mobilization with G-CSF ± plerixaforb

### Endpoints & statistical assumptions

**Primary endpoint:**
- sCR (by end of consolidation); 1-sided alpha of 0.1
- 80% power to detect 15% improvement (50% vs 35%), N = 200

**Secondary endpoints:**
- MRD (NGS 10⁻⁵), CR, ORR, ≥VGPR

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**Key terms and abbreviations:**
- NDMM: newly diagnosed multiple myeloma
- US: United States
- ECOG: Eastern Cooperative Oncology Group
- CrCl: creatinine clearance
- IV: intravenously
- PO: orally
- SC: subcutaneously
- G-CSF: granulocyte colony-stimulating factor
- RVd: lenalidomide/bortezomib/dexamethasone
- D-R: daratumumab-lenalidomide
- Q4W: every 4 weeks
- Q8W: every 8 weeks
- sCR: stringent complete response
- MRD: minimal residual disease
- NGS: next-generation sequencing
- CR, ORR: complete response, overall response rate
- VGPR: very good partial response
- GRIFFIN (NCT02874742): Randomized Phase 2 study
- Transplant-eligible NDMM
- 18-70 years of age
- ECOG score 0-2
- CrCl ≥30 ml/min
- D-RVd, daratumumab-lenalidomib/bortezomib/dexamethasone; RVd, lenalidomib/bortezomib/dexamethasone; NDMM, newly diagnosed multiple myeloma; US, United States; ECOG, Eastern Cooperative Oncology Group; CrCl, creatinine clearance; IV, intravenously; PO, orally; SC, subcutaneously; G-CSF, granulocyte colony-stimulating factor; D-R, daratumumab-lenalidomide; Q4W, every 4 weeks; Q8W, every 8 weeks; sCR, stringent complete response; MRD, minimal residual disease; NGS, next-generation sequencing; CR, complete response; ORR, overall response rate; VGPR, very good partial response.
- Lenalidomide dose adjustments were made for patients with CrCl ≤50 ml/min.
- Cyclophosphamide-based mobilization was permitted if unsuccessful.
- Consolidation was initiated 60-100 days post transplant.
- Patients who complete maintenance cycles 7-32 may continue single-agent lenalidomide thereafter.
- Protocol Amendment 2 allowed for the option to dose daratumumab Q4W, based on pharmacokinetic results from study SMM2001 (NCT02316106).
GRiffin Primary Endpoint: sCR by the End of Consolidation\textsuperscript{a}

- Primary endpoint met at pre-set 1-sided alpha of 0.1
  - sCR by end of consolidation
    - 42.4\% D-RVd vs 32.0\% RVd
    - Odds ratio, 1.57; 95\% CI, 0.87-2.82; 1-sided $P = 0.068$\textsuperscript{b}

Post-consolidation depth of response\textsuperscript{a}

\textsuperscript{a}Included patients in the response-evaluable population (all randomized patients with a confirmed diagnosis of MM, measurable disease at baseline, received $\geq$1 dose of study treatment, and had $\geq$1 post-baseline disease assessment).

\textsuperscript{b}P values were calculated with the use of the Cochran–Mantel–Haenszel chi-square test. A 1-sided $P$ value is reported for sCR; for all other responses, 2-sided $P$ values not adjusted for multiplicity are reported.

GRIFFIN: Responses Deepened Over Time

Response rates and depths were greater for D-RVd at all time points

SD, stable disease; PD, progressive disease; NE, not evaluable.

<table>
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<tr>
<th>MRD-Negative Status (10^{-5})(^a), n (%)</th>
<th>D-RVd</th>
<th>RVd</th>
<th>Odds Ratio (95% CI)</th>
<th>P value(^b)</th>
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<tr>
<td>In ITT population</td>
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<tr>
<td>MRD negative regardless of response</td>
<td>46/104 (44.2)</td>
<td>15/103 (14.6)</td>
<td>4.70 (2.38-9.28)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MRD negative with CR or better</td>
<td>30/104 (28.8)</td>
<td>10/103 (9.7)</td>
<td>3.73 (1.71-8.16)</td>
<td>0.0007</td>
</tr>
<tr>
<td>In patients achieving CR or better</td>
<td>30/51 (58.8)</td>
<td>10/41 (24.4)</td>
<td>4.65 (1.76-12.28)</td>
<td>0.0014</td>
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<tr>
<td>In patients who received ASCT</td>
<td>45/94 (47.9)</td>
<td>14/78 (17.9)</td>
<td>4.31 (2.10-8.85)</td>
<td>&lt;0.0001</td>
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\(^a\)The threshold of MRD negativity was defined as 1 tumor cell per 10^5 white cells. MRD status is based on assessment of bone marrow aspirates by next-generation sequencing in accordance with International Myeloma Working Group criteria. MRD assessments occurred in patients who had both baseline (with clone identified/calibrated) and post-baseline MRD (with negative, positive, or indeterminate result) samples taken (D-RVd, n = 71; RVd, n = 55). Patients with a missing or inconclusive assessment were considered MRD positive. \(^b\)P values were calculated from the Fisher’s exact test.

Ongoing Phase III Studies of Daratumumab Combined with VRd Induction Therapy

• **PERSEUS** (NCT03710603): D-VRd vs VRd in Subjects With Previously Untreated Multiple Myeloma Who Are Eligible for High-dose Therapy (Target N = 690)

• **CEPHEUS** (NCT03652064): D-VRd vs VRd in Subjects With Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy (Target N = 395)

Clinicaltrials.gov, Accessed December 2019
Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma


MAIA Study Design

• Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N = 737)

Key eligibility criteria:
• Transplant- ineligible NDMM
• ECOG 0-2
• Creatinine clearance ≥30 mL/min

Stratification factors
• ISS (I vs II vs III)
• Region (NA vs other)
• Age (<75 vs ≥75 years)

1:1 Randomization

D-Rd (n = 368)
Daratumumab (16 mg/kg IV)<sup>a</sup>
Cycles 1-2: QW
Cycles 3-6: Q2W
Cycles 7+: Q4W until PD
R: 25 mg PO daily on Days 1-21 until PD
d: 40 mg<sup>b</sup> PO or IV weekly until PD

Rd (n = 369)
R: 25 mg PO daily on Days 1-21 until PD
d: 40 mg<sup>b</sup> PO or IV weekly until PD

Primary endpoint:
• PFS

Key secondary endpoints<sup>c</sup>:
• ≥CR rate
• ≥VGPR rate
• MRD-negative rate (NGS; 10<sup>-5</sup>)
• ORR
• OS
• Safety

Cycle: 28 days

<sup>a</sup>On days when daratumumab was administered, dexamethasone was administered to patients in the D-Rd arm and served as the treatment dose of steroid for that day, as well as the required pre-infusion medication.

<sup>b</sup>For patients older than 75 years of age or with BMI <18.5, dexamethasone was administered at a dose of 20 mg weekly.

<sup>c</sup>Efficacy endpoints were sequentially tested in the order shown.

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; NA, North America; IV, intravenously; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; PD, progressive disease; PO, orally; CR, complete response; VGPR, very good partial response; MRD, minimal residual disease; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; BMI, body mass index.
MAIA Primary Endpoint: PFS

Median follow-up: 28 months (range: 0.0-41.4)

44% reduction in the risk of progression or death in patients receiving D-Rd

MAIA: ORR\textsuperscript{a} and MRD\textsuperscript{b} (NGS; 10\textsuperscript{-5} Sensitivity Threshold)

\textsuperscript{a}ITT population. \textsuperscript{b}Assessed at time of suspected CR/sCR; and if confirmed, at 12, 18, 24, and 30 months after first dose. \textsuperscript{c}P < 0.0001; \( P \) values were calculated using the Cochran–Mantel–Haenszel chi-square test.

\[ \text{ORR} = 93\% \]

\[ \text{PR} = 81\% \]

\[ \text{≥CR: 48\%} \]

\[ \text{≥VGPR: 79\%} \]

\[ \text{MRD-negative rate, \( P \) < 0.001; 3.4X} \]

\textbf{Significantly higher ORR, ≥CR rate, ≥VGPR rate, and MRD-negative rate with D-Rd}

MAIA: PFS by MRD Status

- >3-fold higher MRD negativity achieved with D-Rd
- Lower risk of progression or death with MRD negativity