El sistema inmune en las hemopatías malignas:
Inmunoterapia aplicada al mieloma múltiple

Joan Bladé
Hospital Clínic, Barcelona
Miércoles, 22 de junio de 2016
Four major targets for cancer immunotherapy

- Direct targeting of surface tumor antigens: *Monoclonal antibodies*
- Boosting immune effectors: Adoptive cell therapy
- Activating tumor specific immunity: *Vaccins*
- Overcoming inhibitory immune supression: *Immunomodulators: IMIDs, Checkpoint inh*
Monoclonal antibodies

- Direct targeting of surface tumor antigens: **Monoclonal antibodies**
- Boosting immune effectors:
  - Adoptive cell therapy

- Activating tumor specific immunity: **Vaccins**
- Overcoming inhibitory immune suppression:
  - Immunomodulators: IMIDs, Checkpoint inh
Elotuzumab: Immunostimulatory Mechanism of Action

- Elotuzumab is an immunostimulatory monoclonal antibody that recognizes SLAMF7, a protein highly expressed by myeloma and natural killer cells\(^1\)
- Elotuzumab causes myeloma cell death via a dual mechanism of action\(^2\)


ADCC=antibody-dependent cell-mediated cytotoxicity; SLAMF7=signaling lymphocytic activation molecule F7
ELOQUENT-2 demonstrated clinical benefits of E-Ld compared with lenalidomide and dexamethasone (Ld) alone\textsuperscript{1}

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Co-primary endpoint:} & \textbf{E-Ld} & \textbf{Ld} \\
\hline
\textbf{ORR} & 79 & 66 \\
\textbf{95\% CI} & 74, 83 & 60, 71 \\
\hline
\end{tabular}
\end{table}

Study Design

- **ELOQUENT-2** is an open-label, randomized, multicenter, phase 3 trial

**Patients**
- RRMM
- 1–3 prior lines of therapy
- Prior Len permitted in 10% of patients (if sensitive)

**Elotuzumab plus Ld (E-Ld): n=321**
- Elo: Cycles 1 and 2 weekly, then every other week, 10 mg/kg IV
- Len: D1–21, 25 mg PO
- Dex: weekly equivalent, 40 mg

**Len/Dex (Ld): n=325**
- Len: D1–21, 25 mg PO
- Dex: weekly, 40 mg PO

**Endpoints**

- Co-primary
  - PFS
  - ORR
- Others
  - OS
  - Safety
  - Duration of response
  - Quality of life

- Statistical analysis
  - Threshold for interim OS significance was 0.014 based on 295/427 events required for final analysis

**Database lock:**
- September 2014 (ASCO/EHA 2015)
- Primary analysis
- August 2015 (ASH 2015)
- Extended follow-up
### Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>E-Ld (n=321)</th>
<th>Ld (n=325)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>International Staging System (ISS) disease stage,</strong> n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>141 (44)</td>
<td>138 (42)</td>
</tr>
<tr>
<td>II</td>
<td>102 (32)</td>
<td>105 (32)</td>
</tr>
<tr>
<td>III</td>
<td>66 (21)</td>
<td>68 (21)</td>
</tr>
<tr>
<td><strong>Cytogenetics (FISH),</strong> n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(17p)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>102 (32)</td>
<td>104 (32)</td>
</tr>
<tr>
<td>No</td>
<td>213 (66)</td>
<td>218 (67)</td>
</tr>
<tr>
<td>t(4;14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (9)</td>
<td>31 (10)</td>
</tr>
<tr>
<td>No</td>
<td>285 (89)</td>
<td>290 (89)</td>
</tr>
<tr>
<td><strong>Prior regimens, median (range)</strong></td>
<td>2 (1–4)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td><strong>Prior therapies, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>219 (68)</td>
<td>231 (71)</td>
</tr>
<tr>
<td>Melphalan (PO or IV)</td>
<td>220 (69)</td>
<td>197 (61)</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>153 (48)</td>
<td>157 (48)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>16 (5)</td>
<td>21 (6)</td>
</tr>
<tr>
<td><strong>Response to most recent line of therapy,</strong> n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory</td>
<td>113 (35)</td>
<td>114 (35)</td>
</tr>
<tr>
<td>Relapsed</td>
<td>207 (65)</td>
<td>211 (65)</td>
</tr>
<tr>
<td><strong>Prior stem cell transplantation, n (%)</strong></td>
<td>167 (52)</td>
<td>185 (57)</td>
</tr>
</tbody>
</table>

*Not reported’ not shown. †No minimum cut-off for del(17p) positivity. ‡Response for 1 E-Ld patient unknown. FISH=fluorescence in situ hybridization.

ELOQUENT-2 Update: A Phase 3, Randomized, Open-Label Study of Elotuzumab in Combination with Lenalidomide/Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma – 3-Year Safety and Efficacy Follow-up

Meletios Dimopoulos,1 Sagar Lonial,2 Darrell White,3 Philippe Moreau,4 Antonio Palumbo,5 Jesus San Miguel,6 Ofer Shpilberg,7 Kenneth Anderson,8 Sebastian Grosicki,9 Ivan Spicka,10 Adam Walter-Croneck,11 Hila Magen-Nativ,12 Maria-Victoria Mateos,13 Andrew Belch,14 Donna Reece,15 Meral Beksac,16 Eric Bleickardt,17 Valerie Poulart,18 Jessica Katz,19 Anil Singhal,20 Paul Richardson8

1National and Kapodistrian University of Athens, Athens, Greece; 2Winship Cancer Institute, Emory University School of Medicine, Atlanta, USA; 3QEII Health Science Center and Dalhousie University, Halifax, Canada; 4University Hospital, Nantes, France; 5A.O.U. San Giovanni Battista di Torino - Ospedale Molinette, Torino, Italy; 6Clinical Universidad de Navarra, Pamplona, Spain; 7Assuta Medical Centers, Tel-Aviv, Israel; 8Dana-Farber Cancer Institute, Boston, MA; 9Silesian Medical University, Katowice, Poland; 10Charles University Hospital, Prague, Czech Republic; 11Medical University of Lublin, Lublin, Poland; 12Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, and Tel Aviv University, Ramat Aviv, Israel; 13University Hospital of Salamanca-IBSAL, Salamanca, Spain; 14Cross Cancer Institute and University of Alberta, Edmonton, Canada; 15Princess Margaret Cancer Center, Toronto, Canada; 16Ankara University, Ankara, Turkey; 17Bristol-Myers Squibb, Wallingford, CT; 18Bristol-Myers Squibb, Braine-l'Alleud, Belgium; 19Bristol-Myers Squibb, Princeton, NJ; 20AbbVie Biotherapeutics Inc. (ABR), Redwood City, CA

American Society of Hematology (ASH) Annual Meeting & Exposition; December 5–8, 2015; Orlando, Florida
Extended Progression-Free Survival

**PFS benefit with E-Ld was maintained over time (vs Ld):**
- Overall 27% reduction in the risk of disease progression or death
- Relative improvement in PFS of 44% at 3 years

**HR 0.73 (95% CI 0.60, 0.89); p=0.0014**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-Ld</td>
<td>19.4 mos (16.6, 22.2)</td>
</tr>
<tr>
<td>Ld</td>
<td>14.9 mos (12.1, 17.2)</td>
</tr>
</tbody>
</table>

**No. of patients at risk**

<table>
<thead>
<tr>
<th>PFS (months)</th>
<th>E-Ld</th>
<th>Ld</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>321</td>
<td>325</td>
</tr>
<tr>
<td>2</td>
<td>293</td>
<td>266</td>
</tr>
<tr>
<td>3</td>
<td>259</td>
<td>215</td>
</tr>
<tr>
<td>6</td>
<td>227</td>
<td>181</td>
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<tr>
<td>9</td>
<td>195</td>
<td>157</td>
</tr>
<tr>
<td>12</td>
<td>171</td>
<td>130</td>
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<td>15</td>
<td>144</td>
<td>106</td>
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<td>18</td>
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<td>21</td>
<td>107</td>
<td>67</td>
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<tr>
<td>24</td>
<td>94</td>
<td>60</td>
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<td>27</td>
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<td>30</td>
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<td>33</td>
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<td>36</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>39</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>42</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>45</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Probability progression free**

- **1-year PFS:** 68% (E-Ld), 57% (Ld)
- **2-year PFS:** 41% (E-Ld), 27% (Ld)
- **3-year PFS:** 26% (E-Ld), 18% (Ld)
E-Ld-treated patients had a median delay of 1 year in the time to next treatment vs Ld-treated patients.
## Progression-Free Survival: Predefined Subgroups

<table>
<thead>
<tr>
<th>Subgroup Description</th>
<th>Number of Events (Number of Patients)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;75 years)</td>
<td>E-Ld 169 (253) Ld 178 (264)</td>
<td>0.76 (0.62–0.94)</td>
</tr>
<tr>
<td>Age (≥75 years)</td>
<td>E-Ld 39 (68) Ld 42 (61)</td>
<td>0.59 (0.38–0.91)</td>
</tr>
<tr>
<td>Age (&lt;65 years)</td>
<td>E-Ld 86 (134) Ld 96 (142)</td>
<td>0.74 (0.55–0.99)</td>
</tr>
<tr>
<td>Age (≥65 years)</td>
<td>E-Ld 122 (187) Ld 124 (183)</td>
<td>0.72 (0.56–0.92)</td>
</tr>
<tr>
<td>ISS stage at enrollment (I)</td>
<td>E-Ld 83 (141) Ld 86 (138)</td>
<td>0.70 (0.52–0.95)</td>
</tr>
<tr>
<td>ISS stage at enrollment (II)</td>
<td>E-Ld 69 (102) Ld 72 (105)</td>
<td>0.90 (0.64–1.25)</td>
</tr>
<tr>
<td>ISS stage at enrollment (III)</td>
<td>E-Ld 52 (66) Ld 51 (68)</td>
<td>0.72 (0.49–1.06)</td>
</tr>
<tr>
<td>Response to most recent line of therapy (refractory)</td>
<td>E-Ld 76 (113) Ld 83 (114)</td>
<td>0.57 (0.41–0.78)</td>
</tr>
<tr>
<td>Response to most recent line of therapy (relapsed)</td>
<td>E-Ld 131 (206) Ld 137 (211)</td>
<td>0.82 (0.65–1.05)</td>
</tr>
<tr>
<td>No. of lines of prior therapy (1)</td>
<td>E-Ld 98 (151) Ld 107 (159)</td>
<td>0.79 (0.60–1.05)</td>
</tr>
<tr>
<td>No. of lines of prior therapy (2 or 3)</td>
<td>E-Ld 110 (170) Ld 113 (166)</td>
<td>0.68 (0.52–0.88)</td>
</tr>
<tr>
<td>Prior IMiD therapy (prior thalidomide only)</td>
<td>E-Ld 100 (150) Ld 108 (153)</td>
<td>0.68 (0.52–0.90)</td>
</tr>
<tr>
<td>Prior IMiD therapy (other)</td>
<td>E-Ld 10 (16) Ld 14 (21)</td>
<td>0.55 (0.24–1.25)</td>
</tr>
<tr>
<td>Prior bortezomib (yes)</td>
<td>E-Ld 151 (219) Ld 163 (231)</td>
<td>0.68 (0.55–0.85)</td>
</tr>
<tr>
<td>Prior bortezomib (no)</td>
<td>E-Ld 57 (102) Ld 57 (94)</td>
<td>0.83 (0.58–1.21)</td>
</tr>
<tr>
<td>Prior stem cell transplant (yes)</td>
<td>E-Ld 112 (167) Ld 129 (185)</td>
<td>0.73 (0.57–0.94)</td>
</tr>
<tr>
<td>Prior stem cell transplant (no)</td>
<td>E-Ld 96 (154) Ld 91 (140)</td>
<td>0.74 (0.55–0.98)</td>
</tr>
<tr>
<td>del(17p) (yes)</td>
<td>E-Ld 61 (102) Ld 67 (104)</td>
<td>0.70 (0.49–0.99)</td>
</tr>
<tr>
<td>t(4;14) (yes)</td>
<td>E-Ld 24 (30) Ld 26 (31)</td>
<td>0.52 (0.29–0.93)</td>
</tr>
</tbody>
</table>
Co-Primary Endpoint: Overall Response Rate

Overall response rate

- **E-Ld**: 79%
- **Ld**: 66%

Combined response (VGPR or better)

- **E-Ld**: 34%
- **Ld**: 29%

Complete response (sCR + CR)

- **E-Ld**: 5%
- **Ld**: 9%

Very good partial response

- **E-Ld**: 29%
- **Ld**: 20%

Partial response

- **E-Ld**: 45%
- **Ld**: 37%

*Defined as partial response or better

†Complete response rates in the E-Ld group may be underestimated due to interference from therapeutic antibody in immunofixation and serum protein electrophoresis assay
## Progression-Free Survival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>E-Ld</th>
<th>Ld</th>
<th>Relative difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>19.4</td>
<td>14.9</td>
<td></td>
</tr>
<tr>
<td>1-year PFS (%)</td>
<td>68</td>
<td>57</td>
<td>19</td>
</tr>
<tr>
<td>2-year PFS (%)</td>
<td>41</td>
<td>28</td>
<td>52</td>
</tr>
<tr>
<td>3-year PFS (%)</td>
<td>26</td>
<td>18</td>
<td>44</td>
</tr>
<tr>
<td>Primary analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.70 (0.57, 0.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.0004</td>
</tr>
<tr>
<td>3-year follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.73 (0.60, 0.89)</td>
<td></td>
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</tbody>
</table>
Prespecified interim analysis for overall survival indicates a strong trend (p=0.0257) with early separation sustained over time for E-Ld vs Ld
Elotuzumab, a novel immunostimulatory monoclonal antibody, in combination with Ld, demonstrated a durable and clinically relevant improvement in PFS and ORR.

- Extended follow-up demonstrated a 27% reduction in the risk of progression or death compared with Ld alone (HR 0.73; p=0.0014)
- 38% fewer patients in the E-Ld vs Ld arm started a subsequent line of therapy during the follow-up period
- PFS benefits with E-Ld were consistent across key subgroups

Interim overall survival analysis demonstrated a strong trend in favor of E-Ld vs Ld (HR 0.77; p=0.0257)

Updated safety and tolerability data are consistent with previous findings, confirming that there is minimal incremental toxicity associated with the addition of elotuzumab to Ld.

FDA recently granted approval for the use of elotuzumab in combination with Ld in patients with multiple myeloma who have received one to three prior therapies.
Elotuzumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma: 2-year follow-up

Antonio Palumbo,1 Massimo Offidani,2 Brigitte Pégourie,3 Javier De La Rubia,4 Laurent Garderet,5 Kamel Laribi,6 Alberto Bosi,7 Roberto Marasca,8 Jacob Laubach,9 Ann Mohrbacher,10 Angelo Michele Carella,11 Anil K Singhal,12 Mark Lynch,13 Ying-Ming Jou,14 Andrzej Jakubowiak15

1A.O.U. San Giovanni Battista di Torino–Ospedale Molinette, Torino, Italy; 2A.O.U Ospedali Riuniti di Ancona, Ancona, Italy; 3C.H.U. de Grenoble–Hôpital Albert Michallon, Grenoble, France; 4H.U.P. La Fe, Valencia, Spain; 5Hôpital Saint Antoine, Paris, France; 6Centre Hospitalier, Le Mans, France; 7A.O.U. Careggi, Florence, Italy; 8A.O.U–Policlinico di Modena, Modena, Italy; 9Dana-Farber Cancer Institute, Boston, MA; 10University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; 11IRCCS San Martino–IST, Genoa, Italy; 12AbbVie Biotherapeutics Inc., Redwood City, CA; 13Bristol-Myers Squibb, Wallingford, CT; 14Bristol-Myers Squibb, Hopewell, NJ; 15University of Chicago Medical Center, Chicago, IL

Presented at the 57th American Society of Hematology (ASH) Annual Meeting and Exposition; December 5–8, 2015; Orlando, FL
Rationale

- In preclinical studies, elotuzumab activity was enhanced when combined with lenalidomide or bortezomib\(^1,2\).

- Clinical studies have shown synergy between bortezomib and dexamethasone (Bd) for the treatment of patients with relapsed/refractory MM\(^3,4\).

- A proof-of concept study was designed to evaluate efficacy and safety of elotuzumab combined with Bd vs Bd alone.

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**Study Design**

- **Phase 2, open-label, randomized, multicenter trial**

  **Elotuzumab IV** administered over ~2–3 hours; gradual escalation to 5 mL/min permitted.

  **Patients**
  - (N=152)
  - RRMM
  - 1–3 prior therapies
  - ECOG PS ≤2
  - Prior PI (if not refractory)

  **Stratification:**
  - Prior PI therapy
  - FcγRIIIa V allele
  - Lines of therapy

  **Endpoints**
  - Primary
    - PFS (ITT population)
  - Secondary/other
    - ORR
    - OS
    - Safety

  **Premedication regimen given to mitigate infusion reactions**

  **Elotuzumab 10 mg/kg IV:**
  - C1-2: D1,8,15; C3-8: D1,11; C9+ Q2W

  **Bortezomib 1.3 mg/m² IV or SC:**
  - C1-8 D1,4,8,11; C9+ D1,8,15

  **Dexamethasone 20 mg PO:**
  - 8 mg PO + 8 mg IV on elotuzumab dosing days C1 and 2 D1,8,15; C3-8 D1,11; C9+ Q2W

  **Bortezomib 1.3 mg/m² IV or SC:**
  - C1-8 D1,4,8,11; C9+ D1,8,15

  **Dexamethasone 20 mg PO:**
  - C1-8 D1,2,4,5,8,9,11,12; C9+ D1,2,8,9,15,16

**2-sided 0.30 significance level specified to test for PFS difference between arms**

**Study had 80% power to detect a hazard ratio of 0.69 with 103 events**
Progression-Free Survival (September 2014 data cut-off)

1-year PFS

HR 0.72 (70% CI, 0.59–0.88; 95% CI, 0.49–1.06); stratified log-rank p=0.09

Median PFS
EBd: 9.7 mo (95% CI, 7.4–12.2)
Bd: 6.9 mo (95% CI, 5.1–10.2)

Number of patients at risk
EBd: 77 69 58 47 41 32 26 22 14 11 5 3 2 1 0
Bd: 75 61 50 37 32 25 21 14 11 9 5 3 1 0 0

Primary endpoint met: EBd-treated patients had a 28% reduction in the risk of disease progression or death

Jakubowiak A et al. EHA 2015 [Oral S103]
EBd-treated patients had a 24% reduction in the risk of disease progression or death.

Stratified by prognostic factors, EBd-treated patients had a 38% reduction.
Median time to response: 1.4 months (EBd) vs 1.5 months (Bd)
Stable disease: 13 (17%) patients (EBd) vs 14 (19%) patients (Bd)
Progressive disease: 4 (5%) patients in each group

*Partial response or better (International Myeloma Working Group criteria); †Complete response rates in the EBd group may be underestimated due to interference from therapeutic antibody in immunofixation
At 2 years, EBd-treated patients had a 25% reduction in the risk of death.

At time of analysis, 60/85 deaths have occurred (EBd 28; Bd 32)
  - Majority due to disease progression

NE = not estimable
Summary

- At 2 year follow-up elotuzumab in combination with Bd continues to show durable efficacy (PFS) vs Bd alone
  - 24% reduction in risk of disease progression/death

- In overall survival analysis, the trend is in favor of elotuzumab in combination with Bd
  - 25% reduction in risk of death

- Safety profile of elotuzumab in combination Bd is comparable with Bd alone
Future Directions

• Newly diagnosed patients with MM
  – ELOQUENT-1: elotuzumab in combination with lenalidomide and dexamethasone

• Combination with other novel therapies in advanced MM
  – Elotuzumab in combination with pomalidomide and dexamethasone in patients with RRMM

• Combination with other Immuno-Oncology (I-O) agents
  – Elotuzumab in combination with nivolumab in patients with RRMM

• Exploratory studies in smoldering MM
Phase III Study of Lenalidomide and Dexamethasone with or without Elotuzumab to Treat Newly Diagnosed, Previously Untreated Multiple Myeloma (ELOQUENT-1) (CA204-006 / NCT01335399)

**Purpose**
- Determine whether the addition of elotuzumab to lenalidomide/low-dose dexamethasone increases PFS.

**Primary Endpoint**
- PFS

**Secondary Endpoints**
- ORR
- OS

**Study Specific Eligibility Criteria**
- Newly diagnosed, symptomatic multiple myeloma
- No prior systemic therapy for multiple myeloma
- Measurable disease
- Not a candidate for high-dose therapy plus stem-cell transplantation because aged ≥65 years or comorbidity preventing stem-cell transplantation if <65 years
- No non-secretory or oligo-secretory or free light-chain only myeloma
- No smoldering multiple myeloma, defined as asymptomatic multiple myeloma with absence of lytic bone lesions
- No monoclonal gammopathy of undetermined significance
- No active plasma cell leukemia

**Study Start Date:** May 2011  
**Estimated Study Completion Date:** July 2020  
**Estimated Primary Completion Date:** April 2018  
**Primary Investigator:** Bristol-Myers Squibb  
**ORR=objective response rate; OS=overall survival; PFS=progression-free survival.**
Daratumumab-Len-Dex (DRd) vs Len-Dex (Rd) in Relapsed MM - Phase III POLLUX trial

Phase III POLLUX trial

Study population (N = 569)
• Relapsed progressive MM after 1 prior line of therapya
• ECOG PS 0-2
• Len Sensitive

Primary endpoint: PFS
Secondary endpoints: TTP, ORR, VGPR or better, MRD neg rate, OS, DOR, Time to response, safety.

Both arms to receive 28 day cycles until progression

DRd
Daratumumab 16mg/kg IV
C1 & C2: days 1, 8, 15, 22. C3-C6 on days 1 and 15. C7 and beyond: day 1
Lenalidomide 25 mg
Days 1-21
Dexamethasone 40 mg weekly
Once weekly days 1, 8, 15, and 22

Rd
Lenalidomide 25 mg
Days 1-21
Dexamethasone 40 mg
Once weekly days 1, 8, 15, and 22

Patients characteristics:
Median number of prior lines: 1 (1 – 11). 19% patients received ≥3 prior lines.
86% prior bortezomib. 55% prior IMID and 18% prior Lenalidomide.
27% refractory to last line.

Daratumumab-Len-Dex (DRd) vs Len-Dex (Rd) in Relapsed MM - *Phase III POLLUX trial* (569 Patients)

<table>
<thead>
<tr>
<th>Metric</th>
<th>DRd vs Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>93% vs 76%</td>
</tr>
<tr>
<td>CR</td>
<td>43% vs 19%</td>
</tr>
<tr>
<td>TTP</td>
<td>NR vs 18.4</td>
</tr>
<tr>
<td>DOR</td>
<td>NR vs 17.4 m</td>
</tr>
</tbody>
</table>

Median Follow-up: 13.5 m

Daratumumab significantly improved median PFS (63% reduction in risk of progression/death) for DRd vs Rd

# Daratumumab-Velcade-Dex (DVd) vs Velcade-Dex (Vd) in Relapsed MM - *Phase III CASTOR trial*

## Phase III CASTOR trial

**Study population (N = 569)**
- ≥1 prior line of therapy and achieved PR on prior therapy
- Documented progressive disease by International Myeloma Working Group (IMWG) criteria on or after their last regimen
- Documented relapsed MM with measurable disease
- Excluded patients refractory or intolerant to bortezomib, refractory to another PI
- Excluded patients with grade ≥2 peripheral neuropathy or neuropathic pain

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DVd (n=252)</strong></td>
<td></td>
</tr>
</tbody>
</table>
Daratumumab 16mg/kg IV Qw in Cycles 1-3, Day 1 of Cycles 4-8, then q4w until PD
Bortezomib 1.3 mg/m² s.c. Days 1, 4, 8, 11 8 cycles
Dexamethasone 20 mg weekly Once weekly days 1, 2, 4, 5, 8, 9, 11, 12, 8 Cycles |
| **Vd (n= 247)** | 
Bortezomib 1.3 mg/m² s.c. Days 1, 4, 8, 11 8 cycles
Dexamethasone 20 mg weekly Once weekly days 1, 2, 4, 5, 8, 9, 11, 12, 8 Cycles |

Cycles 1-8: 21-day cycles; Cycles 9+: 28-day cycles

**Primary endpoint: PFS**

Planned prespecified interim analysis, greater than 177 PFS events

**DVd vs Vd in Relapsed MM - Phase III CASTOR trial**

**Efficacy data: ORR, PFS and TTP**

**ORR (DVd vs Vd): 83% vs 63%**

**CR (DVd vs Vd): 20% vs 9%**

**PFS**

- Median PFS: NR
- Median PFS: 7.2 months
- HR: 0.39 (95% CI, 0.28-0.53); \( P < 0.0001 \)

**TTP**

- Median TTP: NR
- Median TTP: 7.3 months
- HR: 0.30 (95% CI, 0.21-0.43); \( P < 0.0001 \)

**No. at risk**

<table>
<thead>
<tr>
<th></th>
<th>Vd</th>
<th>DVd</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>247</td>
<td>251</td>
</tr>
<tr>
<td>3</td>
<td>215</td>
<td>214</td>
</tr>
<tr>
<td>6</td>
<td>146</td>
<td>145</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>12</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

MMY-1001: Daratumumab + Pomalidomide + Dex
Overall response rate

<table>
<thead>
<tr>
<th></th>
<th>DARA + POM-D (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) 95% CI</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>53 (71) 59.0-80.6</td>
</tr>
<tr>
<td>(sCR+CR+VGPR+PR)</td>
<td></td>
</tr>
<tr>
<td>Best response</td>
<td></td>
</tr>
<tr>
<td>sCR</td>
<td>4 (5) 1.5-13.1</td>
</tr>
<tr>
<td>CR</td>
<td>3 (4) 0.8-11.2</td>
</tr>
<tr>
<td>VGPR</td>
<td>25 (33) 22.9-45.2</td>
</tr>
<tr>
<td>PR</td>
<td>21 (28) 18.2-39.6</td>
</tr>
<tr>
<td>MR</td>
<td>2 (3) 0.3-9.3</td>
</tr>
<tr>
<td>SD</td>
<td>17 (23) 13.8-33.8</td>
</tr>
<tr>
<td>PD</td>
<td>3 (4) 0.8-11.2</td>
</tr>
<tr>
<td>VGPR or better (sCR+CR+VGPR)</td>
<td>32 (43) 31.3-54.6</td>
</tr>
<tr>
<td>CR or better (sCR+CR)</td>
<td>7 (9) 3.8-18.3</td>
</tr>
</tbody>
</table>

- ORR = 71%
- ORR in double-refractory patients = 67%
- Clinical benefit rate (ORR + minimal response) = 73%
- Rates of grade ≥3 AEs were similar to those observed with POM-D alone
Checkpoint inhibitors: Overcoming tumor immune suppression

- Direct targeting of surface tumor antigens:
  - Monoclonal antibodies

- Activating tumor specific immunity:
  - Vaccins

- Boosting immune effectors:
  - Adoptive cell therapy

- Overcoming inhibitory immune suppression:
  - Immunomodulators: IMIDs, Checkpoint inh
Under normal physiological conditions, immune checkpoints are crucial for:

- Maintenance of self-tolerance (prevent autoimmunity)
- Protect tissues from damage

Activation of T-cell is a two-step process:

1. Interaction of TCR with a specific antigenic peptide-containing complex on APC/tumor cells.
2. Co-stimulatory signal, that induces activation and expansion of T-cells. In the absence of this signal, T-cells fail to respond and are inactivated.

Overcoming tumor immune suppression

THE AIM IS TO AMPLIFY THE T CELL RESPONSE
Monoclonal antibodies targeting immune checkpoints

**CTLA-4 INHIBITORS:**
- Ipilimumab

**PD-1 INHIBITORS**
- Nivolumab
- Pembrolizumab
- Pidilizumab

**PD-L1 INHIBITORS**
- Durvalumab
- BMS-936559
- MPDL3280A
# Pembrolizumab treatment in RRMM

<table>
<thead>
<tr>
<th></th>
<th>KEYNOTE-023 (PhI): PEMBRO-LEN-DEX&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Ph I/II: PEMBRO – POMA –DEX&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>PEMBRO 200mg/2QW LEN 25mg 1-21 DEX 40mg weekly</td>
<td>PEMBRO 200mg/2QW POMA 4mg 1-21 DEX 40mg weekly</td>
</tr>
<tr>
<td><strong>Patient population</strong></td>
<td>- &gt; 2 prior lines - PI &amp; IMID exposure</td>
<td>- &gt;2 prior lines - RRMM - PI &amp; IMID exposure</td>
</tr>
<tr>
<td><strong>Refractory status</strong></td>
<td>76% Len-refractory 30% Bort-refractory 50% double/triple/cuadruple refractory</td>
<td>89% Len-refractory 82% Bort-refractory 70% double-refractory</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>ITT population (n=51): 39% Efficacy populat. (n=40): 50% Len-refr (n=29): 38%</td>
<td>Total (n=38): ORR: 66% Double refractory (n=31): 65% Median PFS 14m</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>AEs consistent with individual drug safety profiles for approved indications IRAEs: no pneumonitis. No colitis. 65% AEs grade 3-5, 33% neutropenia</td>
<td>Good safety profile irAEs: 38% Pneumonitis: 14%</td>
</tr>
</tbody>
</table>

<sup>1</sup>San Miguel JF, ASH 2015 oral presentation 505; <sup>2</sup>Badros A, ASH oral presentation 585
Pembrolizumab in Combination With Lenalidomide and Low-Dose Dexamethasone for Relapsed/Refractory Multiple Myeloma: Final Efficacy and Safety Analysis

Maria-Victoria Mateos,1 Robert Orlowski,2 David Siegel,3 Donna Reece,4 Philippe Moreau,5 Enrique Ocio,1 Jatin Shah,2 Paula Rodríguez-Otero,6 Nihkil Munshi,7 David Avigan,8 Razi Ghori,9 Patricia Marinello,9 Jesus San Miguel6

1Complejo Asistencial Universitario de Salamanca/IBSAL, Salamanca, Spain; 2The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 3Hackensack University Medical Center, Hackensack, NJ, USA; 4Princess Margaret Cancer Centre, Toronto, ON, Canada; 5University Hospital Hotel-Dieu, Nantes, France; 6Clinica Universidad de Navarra, Pamplona, Spain; 7Dana-Farber Cancer Institute, Boston, MA; 8Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, USA; 9Merck & Co, Inc, Kenilworth, NJ, USA
Are IMiDs and PD-1 Inhibitors Synergistic in Multiple Myeloma?

Image courtesy of Paula Rodríguez-Otero
KEYNOTE-023: Phase 1 Trial of Pembrolizumab + Lenalidomide and Low-Dose Dexamethasone in RRMM

• Primary end points: Safety and tolerability
• Secondary end points: ORR, DOR, PFS, OS

†TPI = Toxicity Probability Interval (Ji Y et al. Clin Trials. 2007;4:235-244)
Maximum Change from Baseline in M Protein or Free Light Chains (Efficacy Population)

35/40 (88%) of patients with a decrease
## Antitumor Activity
### Central Review (IMWG 2006)

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Efficacy Population† (n = 40)</th>
<th>Len-Refractory (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>20 (50)</td>
<td>11 (38)</td>
</tr>
<tr>
<td>Stringent complete response (sCR)</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
<td>5 (13)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>14 (35)</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>19 (48)</td>
<td>17 (59)</td>
</tr>
<tr>
<td>Disease control rate (CR+PR+SD)</td>
<td>39 (98)</td>
<td>28 (97)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

†11 patients NE by central review

3 discontinued within cycle 1 for reasons other than PD (2 no treatment assessments and 1 SD by investigator)
8 inadequate myeloma data for response assessment (5 PD and 3 SD by investigator)
Patient Case 1: Triple Refractory

- 49 years, Male
- Diagnosed in 2010
  - MM IgGκ
- Initial treatment
  - BD + PLD: MR
  - ASCT: refractory
  - Len/Dex: refractory
Patient Case 2: Double Refractory With EMD Disease: sCR After Two Cycles, Response Still Ongoing Since June 2015

PRIOR THERAPIES:

• 1st line:
  • Bort-Dex-Adrya + ASCT
  • Response: CR (DOR 3 y)

• 2nd line:
  • Len-Dex
  • Refractory

• 3rd line:
  • VMP
  • Refractory

• 4th line:
  • Pembro + Len-Dex
  • Response: sCR after 2 cycles