OPTIMIZING THE USE OF STEM CELL TRANSPLANT IN MYELOMA

Controversial cases presented by local physicians with emphasis on local practice
CASE REPORT: Syngeneic SCT in MM

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Clinical Center of Serbia, University of Belgrade
DIAGNOSIS AND STAGING
- December 2011.
- Accidental fracture of the left humerus.
- Osteolytic lesions.
- SE 18/; Ø RI,
- Total serum protein 91 gr/l; M protein IgG lambda 29.6 gr/l;
- Kappa/lambda 0.04; B2 2.91 gr/l;
- LDH 600mU/L (≤350mU/L)

Patient:
V.M. male, 53 yrs
Patient: V.M. male, 53 yrs

- X-Ray: diffuse multiple osteolytic lesions
- MRI of the spine and pelvis: multiple infiltrative lesions Th3-Th7, Th12-L3
- BM biopsy: 25% PL CD38, CD138, lambda+, Ki 67 5%
- FISH: del13q without t(4,14); t(14,16); del17p
ISS for Multiple Myeloma.
Greipp PR et al. JCO, 2005
R-ISS for MM: An IMWG Report
Palumbo et al. JCO, 2015

- MM IgG lambda
- IIIA CS ISS1
- R-ISS 2
- CTD VI cycles
- ASCT

IMID based

Overall Survival (probability)

Time (months)

Median OS

- R-ISS 1
- R-ISS 2 86 months
- R-ISS III 42 months

NR
- HLA identical TWIN brother – Syngeneic SCT Ø – personal attitude of patient
- Tandem ASCT
  + local Rx during 4m period between ASCT1 and ASCT2

Bone Marrow Transplantation; 52, 191-6, 2017.
Course of treatment:

- **June 2012:**
  Mobilization CAD (1-4d) + G-CSF (09-15d)
  10μg/day
  Collection on 15d
  19x10^6/kgBW
  CD34+ cells

- **July 2012 ASCT1:**
  Mel200 – recovery +12d

- **November 2012:**
  **ACT2:** Mel 200 – recovery +18d
- **June 2012:** After CTD induction - VGPR
- **October 2012**
  - **ASCT1:** VGPR (IgG ∧ by IEF; 5% PL CD38, ∧+)
- **March 2013 ACT2:**
  - CR (IgG ∧ Ø; κ/λ 0,26; Ø PL in biopsy; PET-CT Ø activity)

**Treatment response (IMWG criteria):**
- **Maintenance:**
  Thalidomide
  100mg/d x12m
- **Visits in 3m periods**
- **January 2015:**
  Persistently febrile (38-39°C) without proven infective etiology - Relapse?
1. RELAPSE
Jan, 2015:
- SE 75/
- O RI, Hb 90gr/l, total serum protein 102gr/l
- M protein IgG lambda 32.0gr/l
- kappa/lambda 0.02; B2 7.22 gr/l
- CRP 45 gr/l, LDH 1478 mU/l, (≤350 mU/l)

Patient:
V.M. Male, 57 yrs
X-Ray:
Ø progression of bone disease

BM biopsy:
39% PL CD38, CD 138, lambda+, Ki 67 20%

Control FISH: del 1p21 (25% nuclei); del 17p13.1 (10% nuclei)

H. Chang et al. 1p21 deletion in myeloma. Bone Marrow Transplantation 2010.
TREATMENT AND COURSE OF DISEASE
- MM IgG lambda in relapse IIIA CS ISS3; R-ISS3
- PFS 25m
- PAD VI cycles
- Salvage HSCT
- Syngeneic SCT

Course of treatment:

- **July 2015:** After VI cycles of PAD – PR (IMWG criteria)
- **August 2015:** BuMel + Syngeneic SCT with engraftment + 25d
- **November 2015:** VGPR + 100d (IgGλ by IEF; k/λ 0.10; in biopsy ≈5% PL CD38, λ+)
- **Maintenance:** Thalidomide
  100mg/d x12m
- Visits in 3m periods
- **December 2016:**
  Fatigue, bone pain
- Relapse?

**FOLLOW-UP:**
2. RELAPSE
December 2016:
- SE 90/; Hb 77 gr/l; Ø RI, total serum protein 91 gr/l; M protein
- IgG lambda 26.0 gr/l;
- kappa/lambda 0.08; ß2 13.0 gr/l;
- CRP 12 gr/l; LDH 890 mU/L
(≤350 mU/L)

Patient:
V.M. male, 59 yrs
Patient: V.M. male, 59 yrs

- X-Ray:
  - Ø progression of bone disease

- BM biopsy:
  - 20% PL CD38, CD 138, lambda+, Ki 67 28%

- Control FISH:
  - del 1p21 (25% nuclei)
  - del 17p13.1 (30% nuclei)
  - + 1q21 (10% nuclei)
TREATMENT AND OUTCOME
Course of treatment and outcome:

- MM IgG lambda in 2. relapse IIIA CS ISS3; R-ISS3
- PFS 14m
- CVD III cycles
- PD with lethal outcome
- OS 64m
Position of salvage SCT in the era of new drugs

Recommended FISH panel
- At diagnosis
- In relapse

Optimal induction
Bz based 3-drug combo

Position of syngeneic SCT
After 1. ASCT
Optimizing the use of stem cell transplant in myeloma
(Albanian case)

Arben Ivanaj
UMT of Tirana, Albania
Me disclaim

• I received disbursement from Novartis, Roche, Pfizer, etc..
### Distribution by age  MM in 100 000

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Car</th>
<th>Population by age</th>
<th>Incidence /100 000 people</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>25-34 years</td>
<td>2</td>
<td>426 325</td>
<td>0.47</td>
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<tr>
<td>3</td>
<td>35-44 years</td>
<td>14</td>
<td>432 708</td>
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<td>4</td>
<td>45-54 years</td>
<td>39</td>
<td>350 491</td>
<td>11.13</td>
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<tr>
<td>5</td>
<td>55-64 years</td>
<td>62</td>
<td>240 683</td>
<td>25.76</td>
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<tr>
<td>6</td>
<td>&gt; 65 years</td>
<td>49</td>
<td>256 857</td>
<td>19.08</td>
</tr>
<tr>
<td></td>
<td>TOTALI</td>
<td>166</td>
<td>1 707 064</td>
<td>9.72</td>
</tr>
</tbody>
</table>

T. Caja, A Ivanaj, and al. EPIDEMIOLOGICAL DATA OF MULTIPLE MYELOMA IN ALBANIA, Haematologica, June 2013, abstract, B1542
The Good News

Overall survival from diagnosis

- Outcomes for patients are clearly improved
- The use of HDT or melphalan based novel agent inductions have doubled median survival for nearly all patients

Suggested Approach to the Treatment of Newly Diagnosed Multiple Myeloma

Patient with newly diagnosed multiple myeloma

Transplantation-eligible patient

Three-drug induction

Bortezomib–dexamethasone plus cyclophosphamide or doxorubicin or lenalidomide or thalidomide for 3–6 cycles

Two-drug induction

Bortezomib–dexamethasone for 3–6 cycles or Lenalidomide–dexamethasone for 4 cycles

Autologous stem-cell transplantation

Maintenance with thalidomide or lenalidomide until progression or intolerance

Transplantation-ineligible patient

Three-drug induction

Melphalan–prednisone–thalidomide for 6–12 cycles or Melphalan–prednisone–bortezomib for 9 cycles or Melphalan–prednisone–lenalidomide for 9 cycles followed by maintenance with lenalidomide until progression or intolerance

Two-drug induction

Bortezomib–dexamethasone for 8 cycles or Lenalidomide–dexamethasone until progression or intolerance

Scoring factors and maximum points of the R-MCI as compared to the IMWG frailty index, CCI, HCT-CI, KFI and R-ISS.

Progression-free Survival.

![Graph showing progression-free survival rates for Daratumumab and Control groups.]

- **No. of Patients**
  - Daratumumab: 350
  - Control: 356

- **Median Progression-free Survival**
  - Daratumumab: NE
  - Control: 18.1 months

- **No. at Risk**

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Daratumumab</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>350</td>
<td>356</td>
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<tr>
<td>3</td>
<td>322</td>
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<td>9</td>
<td>298</td>
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<td>12</td>
<td>285</td>
<td>231</td>
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<td>15</td>
<td>179</td>
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<tr>
<td>18</td>
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<td>21</td>
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<tr>
<td>24</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Hazard ratio for disease progression or death, 0.50 (95% CI, 0.38–0.65) P<0.001

Proposed guidelines for management of younger MM patients.

Newly-diagnosed younger patients with MM

- ISS, R-ISS, comorbidity assessment
- No comorbidities
- Renal impairment
- Peripheral neuropathy

Consider clinical trials

- RVD
  - KRD
- Consider CyBorD
- Favor KRD if no cardiovascular risk factors
  - IRD if feasible

Stem cell collection – consider ASCT followed by consolidation

Induction

- Continuous therapy/Maintenance
  - Lenalidomide – based maintenance
    - Consider adding bortezomib
  - Lenalidomide – based maintenance if renal function recovered
    - Consider adding bortezomib
  - Lenalidomide – based maintenance
    - Consider adding ixazomib
    - Consider bortezomib, if PN recovered.

Supportive care and bisphosphonates

Sara Gandolfi et al. Blood 2018;132:1114-1124
What is the goal of treatment in elderly multiple myeloma patients?

- Prolong survival
- Delay disease progression
- Ensure good quality of life

What is needed to achieve this?

Maximal eradication of tumor clone through achievement of best possible response balanced with acceptable toxicity
Case pts 1

• Hommen 57 y
• MM stage III A

• VAD if CR/PR (no pain, cytologic and serologic PR/ CR) stop the treatment to progression.

• Second line VED, +/- Alkeran
Albania frontline therapy in MM....

- VAD
- VED
- Cyclophosphamide + dexamethasone
- Alkerane + prednisone
- ....
Case pts 2.....Albanian pts treated in London

• Hommen 61 year

• 2005 MM st III A

• VED + SCBT x 2 + lenalidomide

• After 13 y .... progression ....what treatment ??
Case pts 2

• We have 5-8 pts like this that we follow-up per year,
• We don’t have choices

• The first choice

• Phase I or II study ...

• New drugs, CAR T cell, immunotherapy etc .....
phase III ARROW trial

- The study randomly assigned participants to receive either a 30-minute infusion of once-weekly carfilzomib 70 mg/m² with dexamethasone or a 10-minute infusion of twice-weekly carfilzomib 27 mg/m² with dexamethasone.

- Patients receiving the once-weekly treatment had longer progression-free survival compared with the twice-weekly cohort (11.2 months vs. 7.6 months, respectively; p=0.0014). The overall response rates were 62.9 percent and 40.8 percent in the once-weekly and twice-weekly arms, respectively (p<0.0001).

LANCET, VOL 19, 7, P953-964, JULY 01, 2018
….case pts 1 vs case pts 2

• ...big difference .... We know, but ?

• How to reduce the difference....

• The change came from in inside ...

• ...why not a collaboration..;

• ... a project
Conclusion

• In real world there exists a big difference for treatment of the pts with MM

• Only with work we can retrieve the lost time

• Solidarity from the EHA....
Thank you
Myeloma

Case study
Ibricevic Balic Lejla
Case Study

SA, female, born 1952., 58 age

Patients was referred to hematologist due to elevated SE
Rutne laboratory showed elevated SE in march 2010. , no comorbidities

Check up in december lab results deteriorated
decembar 2010.godine
SE 57/− >150,
Hgb 134–124 g/L
Creatinin 82 (45–90) umol/L, kreatinin kliren 1.9 (1.36–2.43) ml/s
Ca −2.68 mmol/L
Proteins 74.0–104.0/ serum albumin 39.0–39.0
Serum protein electroforesis: alfa1 glob0,03 alfa2 globulini 0,08 beta globulini 0,28 paraprotein gana globulini 0,10
Bence Jonce : present in urin , kappa 6,7 lambda 153,0 k/lamb. 0.04 /rv 0,75–4,5

IgG 5.4 IgA 13.1  IgM 0.3.
LDH 306 U/L normalan ( rv 230–460)
beta 2mcroglobulin 4.0 – 4.9 umol
Bone marrow citology; infiltration with plasma cells 26%-28%
Bone marrow biopsy: atipic plasma cells 30%;CD38+,CD117+,lambda*,kapa+,MUM-1 +.
Cytogenetics: 46 XX FISH: negative for delp53, t(4;14), t(14;16),
Radiogram:without osteoltic lesions
Diagnosis: Myeloma Multiplex IgA lambda CS IIA ISS II/R-ISS II
**Treatment**

- **First line:** VTD (Velcade, Thalidomid, Dexamethason)
  - 2 cycles + biphophonates (zolendronic acid)
- Evaluation after 2 cycles: Hgb 128, urea 7.9, creatinin 86, Ca 2.56 mmol/L, serum protein 57.0 g/L /alb.30,0
  - paraprotein in serum electoforesis and Bence Jonce: negative, IgG 3.6, IgA 2.3, IgM 0.2, LDH 306 U/L
- Bone marrow smear: 6% plasma cells
- Very good partial response
- Toxicity—polyneuropathy
1. ASCT 13.06.2011.

- mobilisation with cyclophosphamide conditioning with Melfalan 200 mg/m2 13.06.2011.
- no maintenance therapy – biphosphonates
December 2014.

  Se 34, proteins 80,0/alb.40,0 no paraproteins
  Hgb 141 g/L, IgG 10.8 IgA 3.56 IgM 0.48
  Ig kappa 12.77 Ig lambda 76.33 (5.7–26.3 mg/l
  light chains in urine lambda 116.97 mg/l
  light chains in serum: kappa 3.63 (1.7–3.7) g/l, lambda 2.16 (0.9–2.1) g/L kappa/lambda 1.68 (1.35–2.65)
- Immunofixation of urine Ig lambda 37.95
  LDH 295 U/L
  Bone marrow smear: 2% plasma cells,
  Bone marrow flow cytometry– no monoclonal plasma cells
  MRI – lesions in pubic bone,
  PET/CT metabolic active lesions in pubic and ischiadic bone, sternum, biopsy of te lesions in pubic bone– verified relapse od myeloma extramedulary
• First late relapse / extramedulary: January 2015.
• Therapy 2 cycles of VTD
• Evaluation after 2 VTD:
• SE 55, renal function: normal, LDH 448 elevated
  Serum proteins 63.1 albumins 56.4, no paraprotein
  Immunofixation:
  Serum IgG 6.2, IgA 0.63, IgM 0.55, IgKappa 5.26 Ig-lambda 7.17 Ig-Lambda lanci 1.36
  Urin: kappa lanci 11.73 (0.012–32.71 mg/L)
  Bone marrow biopsy i flow cytometry: normal,
  PET-CT: VGPR
2. ASCT 21.05.2015.

- Second autologus stem cell transplant
  - Melfalan 140mg/m² 21.05.2015.
  - 6,0x10⁸/kg body weight
  - Engraftment +11 day
August–October 2015.

- Evaluation within 100 days of PBSCT: FISH shows 10% cells with del p53
- PET–CT in August 2015 shows deposits in left pubic bone
- October 2015. Palliative radiation TD 30Gy of left pubic bone
- Maintenance therapy Lenalidomide 10 mg for 2 years
2016

- June 2016 – evaluation
- PET/CT discrete progression of lesions in ischiadic bone,
- Elevated light chains in serum (IgLambda 242.37 mg/l and Ig kappa 225.25 mg/l)
- Lenalidomide 20 mg/day 1-4 day
- August 2016 – suprarenals insufficiency
- Dexamethasone discontinued
August 2016

- August 2016. PET-regresion of lesions –left pubic bone, ishiadic bone –complete regresion
December 2016

- Progression– CT showed tumor mass in sternum 48 mm x 30 mm
- Irradiation in January 2017. TD 20Gy/10f
2017.

- Therapy continued with Revlimid 25 mg from January 2017.
- Deterioration of lab. results in August 2017. Anemia, trombocytopenia, IgA 3.86
- Both: Ig kappa and Ig lambda elevated,
- Revlimid reduced to 15 mg/day for 21 days
- Stable disease
2018

- In may 2018 evaluation showed stable disease
- In october 2018 progression – tumor mass in sternum has enlarged
- Elevated IgA in serum, Bence Jonce: poz
- Therapy: cyclophosphamide/lenalidomide/dexa
Conclusion

- Myeloma Multiplex IgA lambda CS IIA ISS II/RISS II
- First line: VTD 2 cycles + HDT+ASCT
- First late relapse after I ASCT extramedullary (osis pubis, ossis ishiadici et sternum)
- Second line: VTD 2 cycles and II HDT+ASCT
- FISH after II ASCT: del p53
- Maintenance therapy: Lenalidomid mono
- Progression of lesions after 5 months: extramedullary (osis pubis, ossis et sternum) radiotherapy + Lenalidomid/Dexamethason
- Complications: Mb.Adison,
- Lenalidomid mono: Thrombocythopenia
- Lenalidomid reduced to 15 mg/day
- Partial remission up till October 2018: tumor mass in sternum enlarged with propagation in soft tissues – radiotherapy, Ixazomib?
Current approach to the treatment for the elderly myeloma patients

Thierry Facon, MD
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Service des Maladies du Sang
University of Lille
Lille, France
Disclosures

• Member of the speaker’s bureau of Celgene and Janssen

• Advisory boards for Celgene, Janssen, BMS, Takeda, Amgen, Novartis, Karyopharm

This presentation will discuss off-label use of myeloma drugs
Multiple Myeloma affects primarily elderly patients

- **Changing demographics:**
  - Increase in life expectancy
  - Aging of the population
  - Increase in the number of elderly

- **Myeloma is most frequently diagnosed among people aged 65-74**
  - Median age at diagnosis is 69

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Continuing evolution of multiple myeloma treatment: selected new classes and targets 2017-2018

IMiD, immunomodulatory drug; HDAC, histone deacetylase
*Not yet FDA-approved for MM; available in clinical trials

Adapted from Richardson PG. et al ASH 2015, MMRF 2016
Front-line therapy: ESMO guidelines

Induction: 3-drug regimens
- VTD
- VCD
- RVD
- PAD

200 mg/m² melphalan followed by ASCT

Lenalidomide maintenance

Eligibility for ASCT

Yes

First option: VMP, Rd, RVD
Second option: VCD, MPT
Other options: BP, CTD, MP

No

Note: high-risk patients not categorized. ASCT, autologous stem cell transplant; BP, bendamustine + prednisone; CTD, cyclophosphamide + thalidomide + dexamethasone; MP, melphalan + prednisone; MPT, melphalan + prednisone + thalidomide; PAD, bortezomib + doxorubicin + dexamethasone; Rd, lenalidomide + low-dose dexamethasone; RVD, lenalidomide + bortezomib + dexamethasone; VCD, bortezomib + cyclophosphamide + dexamethasone; VMP, bortezomib + melphalan + prednisone; VRd, lenalidomide + low-dose dexamethasone + bortezomib; VTD, bortezomib + thalidomide + dexamethasone.

MPT Becomes a Standard of Care

Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99–06): a randomised trial


Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials

Peter M. Fayers, Antonio Palumbo, Cyrille Hulin, Anders Waage, Pierre Wijermans, Meral Beksaç, Sara Bringhen, Jean-Yves Mary, Peter Ginsing, Fabian Termorshuizen, Rauf Haznedar, Tommaso Caravita, Philippe Moreau, Ingemar Turesson, Pellegrino Musto, Lotfi Benboubker, Martijn Schaafsma, Pieter Sonneveld, Thierry Facon and on behalf of the Nordic Myeloma Study Group, Italian Multiple Myeloma Network, Turkish Myeloma Study Group, Hemato-Oncologie voor Volwassenen Nederland, Intergroupe Francophone du Myélome, and European Myeloma Network

VMP Becomes a Standard of Care

Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma

Jesús F. San Miguel, M.D., Ph.D., Rudolf Schlag, M.D., Nuriet K. Khugeva, M.D., Ph.D., Meletios A. Dimopoulos, M.D., Ofer Shpilberg, M.D., Ph.D., Martin Kropff, M.D., Ivan Spicka, M.D., Ph.D., Maria T. Petrucci, M.D., Antonio Palumbo, M.D., Olga S. Samoilova, M.D., Ph.D., Anna Dmoszynska, M.D., Ph.D., Kudrat M. Abdulkadyrov, M.D., Ph.D., Rik Schots, M.D., Ph.D., Bin Jiang, M.D., Maria-Victoria Mateos, M.D., Ph.D., Kenneth C. Anderson, M.D., Dixie L. Esseltine, M.D., Kevin Liu, Ph.D., Andrew Cakana, M.D., Helgi van de Velde, M.D., Ph.D., and Paul G. Richardson, M.D., for the VISTA Trial Investigators*

VISTA Trial: MP + Bortezomib (VMP) vs. MP

Bortezomib twice a week x 4 cycles + weekly x 5 cycles

RR (CR) (%): 71(30) vs. 35(4)

TTP

Patients without event (%)

VMP: 24.0 months
MP: 16.6 months, P < 0.000001

OS

Patients without event (%)

Median follow-up 60 months
Median OS:
- VMP: 56m
- MP: 43m, P = 0.0008

CLARION study KMP vs VMP
Progression-Free Survival and Response rates

- Median follow-up time: 22.2 months for KMP and 21.6 months for VMP
- The absence of PFS difference was consistent across subgroups

<table>
<thead>
<tr>
<th>Disease progression or death – n (%)</th>
<th>KMP (n=478)</th>
<th>VMP (n=477)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR; 84.3% KMP vs. 78.8% VMP</td>
<td>207 (43.3)</td>
<td>214 (44.9)</td>
</tr>
<tr>
<td>CR; 25.9% KMP vs. 23.1% VMP</td>
<td>22.3</td>
<td>22.1</td>
</tr>
</tbody>
</table>

HR for KMP vs VMP (95% CI)

- 0.91 (0.75–1.10)
- 1-sided P=0.16

Facon et al, IMW meeting 2017, oral presentation
# ALCYONE Study Design

## Key eligibility criteria:
- Transplant-ineligible NDMM
- ECOG 0-2
- Creatinine clearance ≥40 mL/min
- No peripheral neuropathy grade ≥2

## Stratification factors
- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

## D-VMP × 9 cycles (n = 350)
- Bortezomib: 1.3 mg/m² SC
  - Cycle 1: twice weekly
  - Cycles 2-9: once weekly
- Melphalan: 9 mg/m² PO on Days 1-4
- Prednisone: 60 mg/m² PO on Days 1-4
- Daratumumab: 16 mg/kg IV
  - Cycle 1: once weekly
  - Cycles 2-9: every 3 weeks

Same VMP schedule

## VMP × 9 cycles (n = 356)
- Daratumumab: 16 mg/kg IV
  - Cycles 1-9: 6-week cycles

## D-Cycles 10+
- Daratumumab: 16 mg/kg IV
  - Every 4 weeks: until PD

## Follow-up for PD and survival

## Primary endpoint:
- PFS

## Secondary endpoints:
- ORR
- ≥VGPR rate
- ≥CR rate
- MRD (NGS; 10⁻⁵)
- OS
- Safety

## Statistical analyses
- 360 PFS events: 85% power for 8-month PFS improvement
- Interim analysis: ~216 PFS events

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ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; EU, European Union; SC, subcutaneously; PO, orally; D, daratumumab; IV, intravenously; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; OS, overall survival.

*8-month PFS improvement over 21-month median PFS of VMP.*
Efficacy: PFS

- Median (range) follow-up: 16.5 (0.1-28.1) months

50% reduction in the risk of progression or death in patients receiving D-VMP.

HR, 0.50 (95% CI, 0.38-0.65; P <0.0001)

Mateos et al. NEJM 2017;378:318-21
Efficacy: ORR<sup>a</sup>

- Median duration of response: 21.3 months in VMP versus not reached in D-VMP

Significantly higher ORR, ≥VGPR rate, and ≥CR rate with D-VMP; >2-fold increase in rate of sCR with D-VMP

PR, partial response; sCR, stringent complete response. *ITT population. ** <0.0001; P value was calculated with the use of the Cochran–Mantel–Haenszel chi-square test. "Responders in response-evaluable population.

Mateos et al. NEJM 2017;378:318-21
### Safety: Most Common TEAEs

<table>
<thead>
<tr>
<th></th>
<th>VMP (n = 354)</th>
<th>D-VMP (n = 346)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Hematologic, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>186 (53)</td>
<td>137 (39)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>190 (54)</td>
<td>133 (38)</td>
</tr>
<tr>
<td>Anemia</td>
<td>133 (38)</td>
<td>70 (20)</td>
</tr>
<tr>
<td>Nonhematologic, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>121 (34)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>49 (14)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>87 (25)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>74 (21)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>76 (22)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17 (5)</td>
<td>14 (4)</td>
</tr>
</tbody>
</table>

- 1 patient in each arm discontinued treatment due to pneumonia
- 1.4% and 0.9% of patients receiving VMP and D-VMP, respectively, discontinued treatment due to infection.

**Deaths due to TEAEs, n (%):**

<table>
<thead>
<tr>
<th></th>
<th>VMP (n = 354)</th>
<th>D-VMP (n = 346)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19 (5)</td>
<td>19 (6)</td>
</tr>
</tbody>
</table>

TEAE, treatment-emergent adverse event.

a Any grade TEAEs in ≥20% of patients and grade 3 or 4 TEAEs in ≥10% of patients in either treatment group.
FIRST (IFM2007-01-MM-020): Study Design

- Stratification: Age (≤ 75 vs > 75 yrs), country, and ISS stage (I/II vs III)
- Thromboprophylaxis was mandatory
- Data cutoff: January 21, 2016

**Screening**

- Arm A: Rd Continuous (n = 535)
- Arm B: Rd18 (n = 541)
- Arm C: MPT (n = 547)

**Active Tx + PFS Follow-Up Phase**

- Arm A: LEN + LoDEX: Continuously
  - LENALIDOMIDE: 25 mg days 1-21/28
  - LoDEX: 40 mg days 1, 8, 15, 22/28
- Arm B: LEN + LoDEX: 18 Cycles (72 weeks)
  - LENALIDOMIDE: 25 mg days 1-21/28
  - LoDEX: 40 mg days 1, 8, 15, 22/28
- Arm C: MEL + PRED + THAL 12 Cycles (72 weeks)
  - MELPHALAN: 0.25 mg/kg days 1-4/42
  - PREDNISONE: 2 mg/kg days 1-4/42
  - THALIDOMIDE: 200 mg days 1-42/42

- Pt aged > 75 yrs: LoDEX 20 mg days 1, 8, 15, 22/28; THAL 100 mg days 1-42/42; MEL 0.2 mg/kg days 1-4

**LT Follow-Up**

- PD or Unacceptable Toxicity
- Active Tx + PFS Follow-Up Phase
- PD, OS, and Subsequent anti-MM Tx

**FIRST, Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide; ISS, International Staging System; LoDex, low-dose dexamethasone; LT, long-term; MM, multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; pts, patients; Tx, treatment.**

FIRST Study: PFS\(^a\) and OS

**Survival Probability**

**Progression-Free Survival (months)**

**Median PFS, 4-yr PFS, mo %**

<table>
<thead>
<tr>
<th></th>
<th>Rd cont</th>
<th>Rd18</th>
<th>MPT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rd cont</strong></td>
<td>26.0</td>
<td>21.0</td>
<td>21.9</td>
</tr>
<tr>
<td><strong>Rd18</strong></td>
<td>21.0</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td><strong>MPT</strong></td>
<td>21.9</td>
<td>13.6</td>
<td></td>
</tr>
</tbody>
</table>

**Overall Survival (months)**

<table>
<thead>
<tr>
<th></th>
<th>Rd cont</th>
<th>Rd18</th>
<th>MPT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rd cont</strong></td>
<td>59.1</td>
<td>62.3</td>
<td>49.1</td>
</tr>
<tr>
<td><strong>Rd18</strong></td>
<td>59.0</td>
<td>58.0</td>
<td></td>
</tr>
<tr>
<td><strong>MPT</strong></td>
<td>51.7</td>
<td>51.7</td>
<td></td>
</tr>
</tbody>
</table>

- The pre-specified final OS analysis for the primary comparison showed that Rd continuous significantly extended OS vs MPT

* PFS is based on investigator assessment of IMWG criteria; data cutoff: January 21, 2016.
cont, continuous; FIRST, Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide; HR, hazard ratio; IMWG, International Myeloma Working Group; MPT, melphalan, prednisone, thalidomide; OS, overall survival; PFS, progression-free survival; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

Facon T, et al Blood 2018;130:301-10
IFM 2007-01-MM-020- FIRST;Response - ITT population

- **Rd Cont (n=535)**:
  - PR: 33%
  - VGPR: 27%
  - CR: 21%
  - Total: 81%

- **Rd18 (n=541)**:
  - PR: 31%
  - VGPR: 27%
  - CR: 20%
  - Total: 79%

- **MPT (n=547)**:
  - PR: 37%
  - VGPR: 18%
  - CR: 12%
  - Total: 67%

Patients (%)

Facon et al. Blood 2018;130:301-10
Age Analysis: Grade 3/4 Nonhematologic TEAEs

<table>
<thead>
<tr>
<th>Grade 3/4 TEAEs, %</th>
<th>Age ≤ 75 Years</th>
<th>Age &gt; 75 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rd Continuous (n = 347)</td>
<td>Rd18 (n = 348)</td>
</tr>
<tr>
<td>Infections</td>
<td>30</td>
<td>21</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Back pain</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TEAEs of special interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>DVT</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>PE</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

DVT, deep vein thrombosis; MPT, melphalan, prednisone, thalidomide; PE, pulmonary embolism; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; TEAE, treatment-emergent adverse event.
Myeloma XI - trial outline

Induction 1

- CTD
- CRD

Max. response:
- PD
- SD
- MR
- PR
- VGPR
- CR

Induction 2

- CVD
- No CVD

Maintenance

- ASCT (if TE)
- Observation
- Lenalidomide

R

R 1:1
Transplant non-eligible pathway
Lenalidomide improved PFS from 11 to 26 months, hazard ratio of 0.44

<table>
<thead>
<tr>
<th></th>
<th>Median PFS [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide (n=407)</td>
<td>26.0m [21.8, 30.7]</td>
</tr>
<tr>
<td>Observation (n=316)</td>
<td>11.0m [5.2, 23]</td>
</tr>
</tbody>
</table>

HR: 0.44 95% CI [0.37, 0.53]
Log-Rank P < 0.0001

PFS: progression-free survival
Transplant non-eligible pathway
Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Median OS [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide (n=407)</td>
<td>50.8m [46.8, 65.2]</td>
</tr>
<tr>
<td>Observation (n=316)</td>
<td>57.2m [47.0, 63.6]</td>
</tr>
</tbody>
</table>

HR: 1.02 95% CI [0.8, 1.29]
Log-Rank P = 0.8773

OS: overall survival
SWOG S0777: Study Design

Randomization
N = 525
Stratification:
• ISS (I, II, III)
• Intent to transplant @ progression (yes/no)

Eight 21-day Cycles of VRd
Bortezomib 1.3/mg² IV
Days 1, 4, 8, and 11
Lenalidomide 25 mg/day PO
Days 1-14
Dexamethasone 20 mg/day PO
Days 1, 2, 4, 5, 8, 9, 11, 12

Six 28-day Cycles of Rd
Lenalidomide 25 mg/day PO
Days 1-21
Dexamethasone 40 mg/day PO
Days 1, 2, 4, 5, 8, 11, 12

Rd Maintenance Until PD, Toxicity or Withdrawal
Lenalidomide 25 mg PO days 1-21
Dexamethasone 40 mg PO days 1, 8, 15, 22

• All patients received aspirin 325mg/day
• VRd patients received HSV prophylaxis

HSV, herpes simplex virus; ISS, international staging system; PD, progressive disease; Rd, lenalidomide plus low dose dexamethasone; VRd, bortezomib, lenalidomide and dexamethasone.

Durie et al. Lancet 2017;389:517-527
<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Patients given bortezomib with lenalidomide and dexamethasone (VRd group)</th>
<th>Patients given lenalidomide and dexamethasone (Rd group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG performance status &gt; 1</td>
<td>64/471 (14%)</td>
<td>28/242 (12%)</td>
<td>36/229 (16%)</td>
</tr>
<tr>
<td>Serum beta 2 microglobulin concentration ≥3.5 mg/L</td>
<td>282/459 (61%)</td>
<td>141/235 (60%)</td>
<td>141/224 (63%)</td>
</tr>
<tr>
<td>C-reactive protein concentration ≥8 mg/L</td>
<td>104/444 (23%)</td>
<td>48/225 (21%)</td>
<td>56/219 (26%)</td>
</tr>
<tr>
<td>Creatinine concentration ≥2 mg/dL</td>
<td>22/471 (5%)</td>
<td>11/242 (5%)</td>
<td>11/229 (5%)</td>
</tr>
<tr>
<td>Lactate dehydrogenase concentration ≥190 U/L</td>
<td>166/462 (36%)</td>
<td>84/236 (36%)</td>
<td>82/226 (36%)</td>
</tr>
<tr>
<td>Albumin concentration &lt;3.5 g/dL</td>
<td>197/466 (42%)</td>
<td>98/239 (41%)</td>
<td>99/227 (44%)</td>
</tr>
<tr>
<td>Haemoglobin concentration &lt;10 g/dL</td>
<td>151/471 (32%)</td>
<td>79/242 (33%)</td>
<td>72/229 (31%)</td>
</tr>
<tr>
<td>Platelet count &lt;150 x 10^9/L</td>
<td>21/469 (4%)</td>
<td>11/241 (5%)</td>
<td>10/228 (4%)</td>
</tr>
<tr>
<td>International Staging System stage III</td>
<td>157/471 (33%)</td>
<td>78/242 (32%)</td>
<td>79/229 (34%)</td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>202/471 (43%)</td>
<td>93/242 (38%)</td>
<td>109/229 (48%)</td>
</tr>
<tr>
<td>Women</td>
<td>196/471 (42%)</td>
<td>89/242 (37%)</td>
<td>107/229 (47%)</td>
</tr>
<tr>
<td>Intent to transplant</td>
<td>324/471 (69%)</td>
<td>168/242 (69%)</td>
<td>156/229 (68%)</td>
</tr>
</tbody>
</table>

Data are n/N (%). ECOG = Eastern Cooperative Oncology Group.

**Table 1: Baseline characteristics**
SWOG S0777: PFS and OS by Assigned Treatment Arm

PFS by assigned treatment arm

VRd 137/242 43 (39, 52)
Rd 166/229 30 (25, 39)

HR = 0.712 (0.560, 0.906)*
Log-rank P value = 0.0018 (one sided)*

OS by assigned treatment arm

VRd 76/242 75 (66, -)
Rd 100/229 64 (56, -)

HR = 0.709 (0.516, 0.973)*
Log-rank P value = 0.0250 (two sided)*

* Stratified
HR, hazard ratio; OS, overall survival; PFS progression free survival; Rd, lenalidomide plus low dose dexamethasone; VRd, bortezomib, lenalidomide and dexamethasone.

Durie et al. Lancet 2017;389:517-527
Modified RVD (RVD-lite) in transplant-ineligible MM

**Patient population:** NDMM ≥ 65 years and/or ineligible for ASCT

<table>
<thead>
<tr>
<th>Baseline characteristics, %</th>
<th>N = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>73 (65–91)</td>
</tr>
<tr>
<td>ISS stage at diagnosis</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>38</td>
</tr>
<tr>
<td>II</td>
<td>34</td>
</tr>
<tr>
<td>III</td>
<td>28</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
</tr>
</tbody>
</table>

*The first 10 patients received bortezomib IV for Cycle 1 only followed by SC administration. Subsequent patients received bortezomib SC; aD1, 2, 8, 9, 15, 16, 22, 23 for patients ≤ 75 years; D1, 8, 15, 22 for patients > 75 years; b Or last tolerated dose as of Cycle 9; cOptional.
RVD-lite: efficacy

- ≥ CR was 44% (ITT population, N = 50)
- ORR was 86%, ≥ VGPR was 66% for patients evaluable for response\(^a\) after 4 cycles (n = 46)
- Median TTR was 1.1 months

\(^a\)Six percent of patients received < 4 cycles of therapy and were therefore not evaluable.

CR, complete response; ITT, intention to treat; MR, minimal response; ORR, overall response rate; PR, partial response; RVD, lenalidomide, bortezomib and dexamethasone; sCR stringent complete response; SD, stable disease; TTR, time to response; VGPR, very good partial response.

ENDURANCE (ECOG E1A11): Phase 3 Trial of RVd vs CRd → LEN Maintenance

**Primary Endpoints:**
- OS (maintenance)

**Secondary Endpoints:**
- PFS (maintenance), OS (induction), ORR, TTP, DoR, safety, HRQoL

**INDUCTION**

**RVd**
- BORT SQ or IV
  - C1–8: D1, 4, 8, 11; C9–12: D1, 8
  - LEN PO D1–14
  - Dex PO
    - C1–8: D1, 2, 4, 5, 8, 9, 11, 12
    - C9–12: D1, 2, 8, 9
  - 12 × 21-day cycles

**CRd**
- CFZ IV
  - C1, D1 + 2
  - C1–9: D1, 2, 8, 9, 15, 16
  - LEN D1–21
  - Dex PO
    - C1–9: D1, 8, 15, 22
  - 9 × 28-day cycles

**MAINTENANCE**

**LEN 24**
- LEN PO D1–21
  - 24 × 28-day cycles

**Continuous LEN**
- LEN PO D1–21
  - 28-day cycles
  - Until PD or excessive toxicity

**NDMM, standard risk**
- N = 756

Study start date:
- November 2013

NCT01863550

Phase 3 Rd-based Continuous Studies for Elderly Patients

- **Primary endpoint for all studies is PFS**

1. NCT01335399
2. NCT01850524
3. NCT02252172
EFC12522 study design

- **Population:**
  - 440 NDMM patients who are not eligible for HDT-ASCT
  - Stratification: age threshold 70 yrs; R-ISS stage 1 and 2 vs stage 3 vs UNK

- **Primary endpoint:** PFS (40 mo vs 62.5 mo)
- **Secondary endpoints:** OS, PFS2, ORR, CR, Safety, QoL, MRD negativity
Asessment of fitness and frailty is relevant for optimal treatment selection
“New” Stratification of Elderly Myeloma Patients

IMWG frailty score

**PATIENT STATUS ASSESSMENT**

<table>
<thead>
<tr>
<th>Age (score 0 - 1 - 2)</th>
<th>Charlson (score 0 - 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL (score 0 - 1)</td>
<td>IADL (score 0 - 1)</td>
</tr>
</tbody>
</table>

**FIT**
- Additive total score = 0
- Full-dose
  - TRIPLET REGIMENS
    - VMP
    - MPT
  - DOUBLET REGIMENS
    - Rd
    - Vd

**INTERMEDIATE**
- Additive total score = 1
- Full-dose
  - TRIPLET REGIMENS
    - VMP
    - MPT
  - DOUBLET REGIMENS
    - Rd
    - Vd

**FRAIL**
- Additive total score ≥ 2
- Reduced dose
  - Doublet regimens
    - rd
    - vd

MM Frailty Score: long-term outcome

Overall Survival

- Fit: 84% @ 3 yrs
- Intermediate: 76% @ 3 yrs (P = 0.042)
- Frail: 57% @ 3 yrs (P < 0.001)

Progression-free Survival

- Fit: 48% @ 3 yrs
- Intermediate: 41% @ 3 yrs (P = 0.211)
- Frail: 33% @ 3 yrs (P < 0.001)

Cumulative Incidence Non-hematologic AEs

- Fit: 22% @ 12 mo
- Intermediate: 26% @ 12 mo (P = 0.217)
- Frail: 34% @ 12 mo (P < 0.001)

Cumulative Incidence Drug Discontinuation

- Fit: 16% @ 12 mo
- Intermediate: 21% @ 12 mo (P = 0.026)
- Frail: 31% @ 12 mo (P < 0.001)

**R-MCI German Frailty Score - Practical Use**

Website: [www.myelomacomorbidityindex.org](http://www.myelomacomorbidityindex.org)

### Data entry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Categorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR ml/min /1.73m²</td>
<td>&lt; 60</td>
</tr>
<tr>
<td>Lung dysfunction</td>
<td>No/mild</td>
</tr>
<tr>
<td>Karnofsky Index</td>
<td>≤70%</td>
</tr>
<tr>
<td>Frailty</td>
<td>No/Mild</td>
</tr>
<tr>
<td>Age in years</td>
<td>&lt; 60</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Favorable</td>
</tr>
</tbody>
</table>

**Pt-specific survival probability (blue graph)**

Engelhardt M. Haematologica 101:1110-9, 2016
Engelhardt M. Haematologica 102:910-921, 2017
Engelhardt M. Dtsch Med Wochenschr. 142:e51-e60, 2017
Gay F, Engelhardt M, ...Haematologica 103:197-211, 2018
Ludwig H, .....Engelhardt M, ...Leukemia  doi: 10.1038/leu.2017.353, 2018
## Revised Frailty Algorithm with ECOG

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\leq 75 ) years</td>
<td>0</td>
</tr>
<tr>
<td>76-80 years</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 80 years</td>
<td>2</td>
</tr>
<tr>
<td>Charlson (\leq 1)</td>
<td>0</td>
</tr>
<tr>
<td>Charlson &gt; 1</td>
<td>1</td>
</tr>
<tr>
<td>ECOG = 0</td>
<td>0</td>
</tr>
<tr>
<td>ECOG = 1</td>
<td>1</td>
</tr>
<tr>
<td>ECOG (\geq 2)</td>
<td>2</td>
</tr>
</tbody>
</table>

Sum of Scores = 0 or 1 → NON-FRAIL
Sum of Scores \(\geq 2\) → FRAIL
### PFS and OS by Frailty Level in the FIRST study

**Product-limit survival estimates with number of subjects at risk**

<table>
<thead>
<tr>
<th></th>
<th>Subjects</th>
<th>Events</th>
<th>Censored</th>
<th>Survival</th>
<th>95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-frail</td>
<td>828</td>
<td>560</td>
<td>268</td>
<td>23.95</td>
<td>22.34–25.56</td>
</tr>
<tr>
<td>Frail</td>
<td>790</td>
<td>586</td>
<td>224</td>
<td>19.35</td>
<td>18.17–20.57</td>
</tr>
</tbody>
</table>

**Log rank P<0.001**

- **Non-frail**
  - PFS INV (months) 2016: 828, 558, 414, 252, 176, 133, 107, 52, 12, 0
  - OS (months) 2016: 828, 764, 693, 628, 551, 479, 406, 195, 45, 0
- **Frail**
  - PFS INV (months) 2016: 790, 458, 292, 187, 117, 76, 50, 17, 2, 0
  - OS (months) 2016: 790, 645, 547, 443, 370, 302, 248, 115, 15, 0

+ censored
Myeloma XIV: FITNESS trial
PI: Prof Gordon Cook and Prof Graham Jackson

Elderly +/- Frail patients

- Non-frailty adjusted induction
  - IxaRd

- Frailty Index-adjusted induction
  - Fit: IxaRd No dose reduction
  - Intermediate: IxaRd Dose reduction 1
  - Frail: IxaRd Dose reduction 2

Maintenance: R vs IxaR

- New research being conducted in this population

FITNESS, Frailty Adjusted therapy In Transplant Non-Eligible patientS with Symptomatic myeloma; IxRd, ixazomib, lenalidomide and dexamethasone; PI, principal investigator; R, lenalidomide.

Slide courtesy of Myeloma UK.
A french study for frail elderly NDMM patients; IFM 2018-01
A dexamethasone sparing study

Randomization will be stratified by International Staging System (I vs II vs III) and age (<80 vs ≥80)

In Arm A Low Dose Dex (20mg/week) during Cycle 1 and 2 then Methylprednisolone (with SC Dara)
A Spanish study for fit elderly NDMM patients; GEMFIT2016

Primary endpoint: Immunophenotypic complete response
Secondary exploratory outcome: PFS
Treatment of MM in Elderly Patients – Landscape and Perspectives

MP, melphalan and prednisone; MPR, melphalan, prednisone, and lenalidomide; MPT, melphalan, prednisone, and thalidomide; Rd, lenalidomide plus low-dose dexamethasone; T, thalidomide; Vd, bortezomib plus dexamethasone; VMP, bortezomib, melphalan and prednisone; VRD, bortezomib, lenalidomide and dexamethasone

MM Remains Incurable Despite Improvements

Survival Probability for MM Patients (N=7139) Vs Non-MM Population by year

Fonseca et al. Leukemia 2017, Jan20 Epub ahead of print
Patient populations with high unmet medical need

Extra-Medullary (PCL, CNS)

1st Line
- Induction: High risk, Standard risk
- Maintenance: High risk, Standard risk

TE NDMM patients
- High risk
- Standard risk

TNE NDMM patients
- High risk
- Standard risk

HDM/ASCT Alternative
- Frail patients
- Fit patients

2nd Line
- High risk (1-3 prior lines)
- Standard Risk (1-3 prior lines)

3rd Line
- Early PD following ASCT
- Non early PD following ASCT

4th Line
- Double exposed (PI and IM compound)
- Triple exposed (PI, IM compound and anti-CD38)

≥5th Line
- Molecularly predicted as pomalidomide refractory

Smoldering MM

Higher Unmet Need
Lower Unmet Need

Active MM

NDMM

RRMM

Smoldering MM
**Efficacy: MRD<sup>a</sup> (NGS; 10<sup>-5</sup> Sensitivity Threshold)**

- Median (range) follow-up: 16.5 (0.1-28.1) months

\[ P < 0.0001 \]

\[ 3.6X \]

>3-fold higher MRD-negative rate with D-VMP;

Lower risk of progression or death in all MRD-negative patients

---

<sup>a</sup>Assessed at time of confirmation of CR/sCR and, if confirmed, at 12, 18, 24, and 30 months after first dose.
mSMART guidelines for NDMM - transplant eligible

mSMART – Off-Study
Transplant Eligible

**t(11;14), t(6;14), Trisomies**

- 4 cycles of VRd
- Collect Stem Cells
- Autologous stem cell transplant (preferred)
- Len maintenance for at least 2 years

**Del 17p**

- VRd x 4 cycles
- Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT
- Carfilzomib or Bortezomib-based maintenance till progression

**t(4;14), t(14;16), t(14;20), Double or Triple Hit Myeloma**

- 4 cycles of VRd or KRd
- 4 cycles of KRd
- Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT
- Carfilzomib or Bortezomib-based maintenance till progression

---

*a If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor
*b Duration based on tolerance; consider risks and benefits for treatment beyond 3 years
*c Continuing Rd for patients responding to Rd and with low toxicities

MANAGEMENT OF MULTIPLE MYELOMA IN A PATIENT INELIGIBLE FOR ASCT
CASE REPORT

Sorina Badelita
Fundeni Clinical Institute Bucharest
Medical history

G.V.
75 years old
Male
Smoker 150 packs/year
VHC infection

Disease onset
April 2014

ECOG 3
Fatigue
Palour
Confused
Cutaneous prurit
Pain and paresthesia on lower limbs
Lower back pain
Hb 10 g/dl; Plt 49.000/mmc; WBC 7600/mmc; MCV 98 fl;
Erythrocytes in rouleaux; Macrocytosis; Hypersegmented granulocytes
Vit B12 = 85 pg/ml (211-911 pg/ml);
Parietal Cell and Intrinsec Factor antibodies-negative;
Superior Endoscopy - no abnormalities (performed in an other department, without gastric biopsy)
Creatinine 1.84 mg/dl; creatinine clearance 35 ml/min (C.G)
Proteinuria - absent
Calcium 12.2 mg/dl;
GGT 391 U/l (0-55 U/l); AP 155 U/l (42-128 U/l); AST 53 U/l; ALT 52 U/l;
b2M 7 mg/dl; albumin 3 g/dl;
LDH 57 U/l (105-248 U/l);
IgA 21.14 g/l (0.7-4.0 g/l); IgG 0.35 g/l (7.0-16.0 g/l); IgM 0.42 g/l; (0.4-2.3 g/l)
Free kappa 147 mg/l (3.3-19.4 mg/l); free lambda 16 mg/l (5.7-26.3 mg/l);
kappa/lambda 9.18; difference 131;
M spike 1.5 g/dl;
Immunofixation: IgA kappa
Bone marrow biopsy:
20-30% plasma cells;
megaloblastic changes in the erythroid precursors
megaloblastic metamyelocytes
hypersegmented enlarged granulocytes;
scarce megacaryocytes with low platelet production;

Abdominal fat biopsy:
Congo Red stain positive in polarised light
EMG:
Peripheral sensory-motor polineuropathy
Bilateral carpal tunnel syndrome

Echocardiography:
diastolic dysfunction, EF 65%; IVS 11 mm

Skeletal Xray:
osteolytic lesions T8, T9, L3

FibroScan:
11.8 kPa, F3
Diagnosis

IgA kappa Multiple Myeloma stage IIIB, ISS III

Systemic AL Amyloidosis with peripheral nervous system and hepatic involvement

Cholestasis

Moderate Anemia – vit B12 deficiency (malabsorption ??) and chronic disease

Sensitive- motor polyneuropathy grade II

Bilateral Carpal tunnel syndrome

Stage III Chronic Kidney Disease


Chronic VHC infection
Vitamin B12 im with cytopenia resolution

Mel Dex* x 6
Melphalan iv 15 mg/sqm every 28 days
Dexamethasone 20 mg day 1-4

Bisphosphonates
* Bortezomib could not be associated due to peripheral sensory-motor neuropathy

Disease assessment

ECOG 1
Free kappa 83.4 mg/l; M spike: 0.4 g/dl -> PR

M spike 0.9 g/dl; Free kappa 518 mg/l;

Amyloid vasculopathy
Cutaneous prurit with elevated bilirubin levels
Proteinuria 3.9 g/ 24 hours (albuminuria)
Fish exam-negative for del17p, t(4;14), t(14;16)

Fig 1,2 Vasculitic lesions of forearms
CyBorD x5 (28 days cycle)
Bortezomib 0.7 mg/sqm sc weekly
Cyclophosphamide 500 mg iv weekly
DXM 16 mg weekly

Disease assessment
M spike 0.2 g/dl; free kappa 102 mg/l; ->PR
proteinuria 0.87 g/24h

Echocardiography:
EF 60%; IV septum 11 mm, Diastolic dysfunction
Orthostatic hypotension
Involuntary weight loss 7 kg/3 months
Progressive neuropathy
Fibroscan F4 metavir 13.8 kPa
Proteinuria 4.45 g/24 hours
M spike 1.2 g/dl; free kappa 907 mg/l;

LenDex x2 (Lenalidomide from India)
Disease assessment
M spike 0.2 g/dl free kappa 174 mg/dl;->PR

STOP Dexamethasone due to corticosteroid-induced myopathy

Lenalidomide maintenance x4
10 mg/day 1-21
Bradylalia
Cephalic edema,
Hyponatremia (131 mmol/l)

Cerebral CT:
vascular degenerative lesions

EEG:
hypoxic-metabolic encephalopathy

Doppler-US:
55% left carotid stenosis

Treatment
Syptomatic + Aspenter
Stop Lenalidomide

Fig 1,2 Cephalic edema, periorbital edema
February 2018

Emergency admission
Fever 39.3°C, Chills
Confusional syndrome, Hypotension
Bradylalia, Periorbital edema

Hb 7.5 g/dl
TSH 108 U/ml fT3 0 ng/ml fT4 0.13 ng/ml
ATPO- negative; Anti Tg ab-negative

Thyroid US:
without abnormalities

Endocrinology exam:

*mixedema probably due to amyloid infiltration of the thyroid*

Treatment:
Euthirox - Favorable clinical outcome
Restart Lenalidomide
**February 2018**

**Echocardiography**
- EF 40%; IVS 14 mm;
- Moderate systolic dysfunction;
- Severe diastolic dysfunction
- NT proBNP 2463 ng/ml;

**March 2018**

- Proteinuria 3.3 g/24 h
- M spike 0.8 g/l; free kappa 789 mg/l

Stop Lenalidomide

What’s next treatment? Carfilzomib??

Symptomatic and palliative therapy
Angor pectoris
NT proBNP 5428 ng/ml;
ECG:
T wave inversion; ST segment depression

Coronary stent implantation (LAD, LCA, LCx)

June 2018

August 2018

Sudden cardiac death at home, 4 years after diagnosis
A case presentation with MM

Prof. RODICA MIHAESCU, Ph.D,
University of Medicine of Timisoara and
Oncohelpe Hospital, Timisoara

Athens, 2018
Disclosure

• Nothing to declare
T.R.- 65 years old male

July, 2007

Clinic status: - chest pain,
- weakness and fatigue,
- weight loss,
- pallor

Rx: spinal compression to T10
08 2007 Neurosurgery
Emergency Hospital, Timisoara

- chest pain
- superficial hyperesthesia skin band – T10-T11 appropriate bilateral
- spastic paraparesis gait

MRI – tumor at T 10 level with spinal cord compression and three secondary vertebral lesions at lumbar spine level

Intervention: decompressive laminectomy and biopsy from the tumor

HP: Plasmacytoma
Clinical:

- asthenia,
- pallor,
- back and chest pain
- postoperative scars
Laboratory tests

- **ESR** – 38 mm/h
- **WBC**: 5800/ mm$^3$
- **Hb**: 11,5g/dl, **Ht**: 39%
- **Plt**: 220.000/ mm$^3$
- **Electrophoresis:**
  - TP-8,7g/dl:
    - Alb 42.6 (alfa 1-7,6%);
    - alfa 2-8,8%; beta –7,9%;
    - gamma-33,1%)
    - monoclonal aspect
- **Immunofixation**: Ig G kappa light chains
- **Beta 2 microglobulin** – 2,3 mg/L
- **C- reactive protein** – 30g/dl
- **BM aspiration** – 42% plasmocytes
Laboratory tests 2

- Bence Jones urine paraprotein – positive
- Creatinine - 1.2 mg/dl
- Serum calcium - 9.9 mg/dl
- MRI: osteolytic lesions and extramedullary plasmacytoma
- HP Dg. of tumor: plasmacytoma
Treatment

• Dg. MM, IgG kappa light chains, Stage IIA. Extramedullary Plasmacytoma
  IP ECOG: 1

• 6 x VAD (VCR+ADR+DEXA)
• Bisphosphonate Therapy
• Antalgic therapy
January – November 2008

- **ASCT tandem** in “Louis Turcanu” Hospital of Timisoara conditioning by Melphalan 200 mg/mp in June and in November 2008, conditioning by Melphalan 140 mg/mp).
- After 2 months he began a consolidation therapy with
- 12 cycles of Velcade - 1,3 mg/m 2, IV, weekly (donation)
Nov 2009 medical examination in “Louis Turcanu” Hospital

Clinical status: generally good condition

LABORATORY INVESTIGATIONS:

- HLG: Hb = 11.9 g/dl; Thrombocytes = 83,000/mm³
- WBC = 3900 /mm³
- ESR = 2 mm/h
- Beta 2 microglobulin - 1.1 mg/l
- Immune status: a slight decrease in total LyT accompanied by a moderate increase in LyB (normally after ASCT)
- Absolute values: moderate lymphopenia with moderate LyT CD4+ and CD8+ decrease; NK cells slightly below the lower limit of normal. Low CD4/CD8 ratio.
- Immunofixation: normal
- No treatment
2010 - medical examination
“Louis Turcanu” Hospital

Feb: - Immunofixation – normal
- beta 2 microglobulin - 1,32mg/l
- hematologic - normal

April:
• Immunofixation - IgG Kappa light chains positive
• Beta 2 microglobulin - 1,17 mg/l
April 2010  First relapse
Oncohelp Hospital

ESR - 43 mm³
Serum calcium - 10, 5mg/dl
Creatinine - 1,17mg/dl
HB - 10, 8g/dl
RBC - 3100000/mm³
WBC - 3400/mm³
PLT - 120 000/mm³
LDH - 302UI/l
TP - 8,6g/l
ALB - 3,2 g/d
IgG - 4,5g/dl
Beta 2M - 1,17mg/l

BM aspiration - plasmocytes - 12%
No - Rx, CT, MRI
No cytogenetics, no FISH
Dg: MM Ig G kappa light chains, stage IIA

PI: ECOG 1

- April 2010 treatment –
  - Vel/Dex – (Velcade 1mg/m² sc weekly = 1,9
  - Dexamethazone 20 mg – 6 Cycles of 4 applications
- Bisphosphonate – monthly
- Later - without maintenance treatment
- No approval for Velcade or IMiDs in Romania
2012 - 2013
medical examination and laboratory tests

- Hb = 12.7 g/dl
- Red blood cells = 3,870,000 /mm³
- Thrombocytes = 149,000 /mm³
- Leucocytes = 5400 /mm³;
  Neu = 57.7 %; Mon = 9.7%; Limf = 28.7%; Eoz = 3.5%; Bazo = 0.4%
- Serum calcium level - 9mg/dl
- ESR - 20/mm/h
- Imunofixation – normal
- No urinary light chains
January 2014

• Biopsy for an interscapular tumor with irregular surface
  HP: Basal cell carcinoma

• Biopsy for a tumor on the medial face of the left arm
  HP: keratoacanthoma

There is no treatment
04 2014  Second relapse !!!
Oncohelp

Clinical status:
- Asthenia
- Anemia
- Back pain

Laboratory tests:
- Hb - 9g/dl
- WBC – 2940/mm³ (gr-52%, Ba-3,5%, Mo.7,5% Ly-34%, Eo-3%)
- Plt – 184 000/mm³
- Serum Calcium – 7,31mg/dl
-Creatinine - 2,80mg/dl
- ESR – 43 mm/h
- TP – 8,5 g/l with the range gamma globulin of 29%
- Alb – 5,7mg/l
- Immunofixation - IgG – kappa light chains
- BM aspiration - 11% plasma cells
- Beta 2 M – 5,6mg/l
## ESMO guidelines – updated

### MM ESMO Clinical Practice Guidelines

### Table 2. International staging system for MM

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum β2M &lt; 3.5 mg/mL and serum albumin ≥ 3.5 g/dL</td>
</tr>
<tr>
<td>II</td>
<td>Not stage I or III*</td>
</tr>
<tr>
<td>III</td>
<td>Serum β2M ≥ 5.5 mg/mL</td>
</tr>
</tbody>
</table>

*There are two possibilities for stage II:
- Serum β2M < 3.5 mg/L but serum albumin < 3.5 g/dL;
- Serum β2M 3.5-5.5 mg/L irrespective of the serum albumin.
β2M, β2 microglobulin; MM, multiple myeloma.

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### Table 3. Standard risk factors for MM and the revised ISS

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS stage</td>
<td>Serum β2M &lt; 3.5 mg/L, serum albumin ≥ 3.5 g/dL</td>
</tr>
<tr>
<td></td>
<td>Not ISS stage I or II</td>
</tr>
<tr>
<td></td>
<td>Serum β2M ≥ 5.5 mg/L</td>
</tr>
<tr>
<td>CA by iFISH</td>
<td>Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)</td>
</tr>
<tr>
<td>High risk</td>
<td>No high-risk CA</td>
</tr>
<tr>
<td>LDH</td>
<td>Serum LDH &gt; the upper limit of normal</td>
</tr>
<tr>
<td></td>
<td>Serum LDH &lt; the upper limit of normal</td>
</tr>
</tbody>
</table>

A new model for risk stratification for MM

<table>
<thead>
<tr>
<th>R-ISS stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ISS stage I and standard-risk CA by iFISH and normal LDH</td>
</tr>
<tr>
<td>II</td>
<td>Not R-ISS stage I or III</td>
</tr>
<tr>
<td>III</td>
<td>ISS stage III and either high-risk CA by iFISH or high LDH</td>
</tr>
</tbody>
</table>

β2M, β2 microglobulin; CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridisation; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

Reprinted from [2], with permission © 2015 American Society of Clinical Oncology. All rights reserved.
Dg. MM Ig G kappa light chains stage III B
Extramedullary plasmacytoma
PI: ECOG 2

EKG, ECHO cardiography with assessment of diastolic function and measurement of interventricular septal thickness - normal for his age

Treatment

- **Caelyx (40mg/mp)**
- **Thal (100mg)**
- **Dex (40mg x 4 days)**

**4 cycles**

- Maintenance therapy-only **Thalidomide 100 mg/day**
- Acenocumarol – prophylactic Deep Vein Thrombosis
September 2015 medical examination

- Clinical – relatively normal

Laboratory tests:

- ESR - 6 mm/h
- Immunofixation - normal
- TP - 7,4 g/l...Range G -16,2%
- Creatinine – 0,83 mg/dl
- Calcium - 9,3 mg/dl
- Hb -14 g/dl,
- WBC - 5300/ mm³
- Plt - 134000/mm³
Medical examination
March and June 2016

- ESR - 4 mm/h... ... ... ... ... ... ... 12mm/h
- Creatinine - 0,93mg/dl... ... ... ... ... 0,91mg/dl
- Serum calcium - 9,1mg/dl... ... ... ... 9,2mg/dl
- PT - 7,1g/dl... ... ... ... ... ... ... ... ... 7,3mg/dl
- gamma G - 20,5%..........................21%
- Hb. - 14,6 g/dl... ... ... ... ... ... ... ... ... 14,1g/dl
- WBC - 5790 /mm³... ... ... ... ... ... 4980/mm³
- Plt - 121000/mm³... ... ... ... ... ... ... ... ... 117000/mm³
- Serum Immunofixation - normal
- No Rx, No TC
August 2016 - 3th relapse!!!
ONCOHELP

• Chest pain
• Gait disturbance
• Marked asthenia

• CT:
  • left paravertebral tumor mass that causes osteolysis of T3 and T4 with invasion into the medullary cavity. Multiple osteolytic lesions

• MRI
  • left paravertebral tumor mass that causes osteolysis to T3 and T4 with invasion into the medullary cavity, with pleura extension. Multiple osteolytic lesions
Treatment - Oncohelp

• 6 cycles x MPR - well tolerated
• Continue with Lenalidomide - 21 days/month
• November and December 2016 - external radiotherapy to linear accelerator
  • up to the total dose 30Gy, from 2nd to 5th thoracic level
  • good tolerance
• MRI December - tumor disappearance but still osteolytic lesions persistance
• It remains on Lenalidomide 21 days/month
2017 - Oncohelp

- Medical examination at 2 months with good overall condition

- Under treatment with **Lenalidomide**
  - 21 days/month

- Ig G – 12,1 g/l (N: 07-16 g/l)

- Kappa light chains – 0,31g/l (N: 1,7 – 3,7)

- Hematologic – moderate thrombocytopenia
August 2017 - evolution under Len
Left hip fracture on pathological bone
Orthopedics - County Hospital of Timisoara

- Left Hemiarthroplasty with Cemented Bipolar Prothesis
- Biopsy - HP: plasmacytoma
- Continue with Len
- Antalgic treatment
- No radiotherapy
February 2018 - ONCOHELP

- Clinical: chest pain radiating to the anterior chest yielding to opiates, headache, dizziness, balance disorder
- Laboratory:
  - ESR - 45mm/h
  - Serum calcium - 8,1mg/dl
  - Serum creatinine – 0,65mg/dl
  - Hb. - 10,6g/l
  - WBC – 3540/mm³
  - Plt – 93000/mm³
  - BM aspiration: plasma cells 3%
  - Immunofixation: monoclonal aspect – IgG presence with kappa light chains
Computer Tomography (CT):

- Progressive disease:
  - a spontaneous hyperdensity, round, diameter of about 11 mm located in the pontocerebellar right angle and new osteolytic lesions at the vertebral level
Kd for the Treatment of RRMM who Have Received 1-3 prior Lines of Therapy

BEST FOR

• Patients who progress on lenalidomide
• Patients who are candidates for bortezomib retreatment
• Very good results as 2nd line therapy
• Very good results for elderly patients (>75 years of age)
Therapy - MM high risk - KD

- **Kyprolis** 56mg/mp, 100mg IV + **Dexamethasone** 20 mg / cure – from February 2018 until to this date
- Slight thrombocytopenia and anemia
- Non antalgic treatment
- Associated treatment: Acyclovir 200 mg. 2x1 capsule /day, Ca-D3 1 g/day, Allopurinol 100 mg/day, Aspirin 75 mg/day
Medical examination + Computer Tomography (CT) in September 2018

The disappearance of the ponto-cerebellar tumor and the reduction of bone osteolytic lesions
Clinical status: fever, chills, myalgia, anemia

- Hb. – 9,2 g/dl
- WBC - 3180/mm³
- Plt – 89.000/mm³
- Creatinine – 1,17mg/dl
- Serum calcium – 8,7mg/dl
- ESR – 56mm/h
- Blood culture - sepsis with Klebsiella pneumoniae
- Supportive treatment, antibiotics, antifungal, hydration, urolytic, calcium, aspirin
- Timing the cystostatic cure until October
- Now under KD
- Generally good condition
Discussions

• Old patient diagnosed in 2007 with multiple myeloma IgG kappa II A, extramedullary plasmacytoma, chemotreated and with ASCT tandem
• Periodic follow-up but no maintenance treatment until relapse, when switched to III B stage
• He was followed in several hematology departments
• With numerous relapses - 5 - all of them, type extramedular plasmacytoma, always with multiple osteolytic lesions
Negative points:

- There is no cytogenetic analysis and no FISH
- Relapse after ASCT tandem + Velcade after 17 months
- There is no continuous follow up with Rx, CT, MRI
- Lack of approval in Romania for maintenance treatment at the time of 1st relapse - the patient agreed to buy thalidomide and late lenalidomide
• Although with repeated relapses, the patient has an evolution of 11 years without significant comorbidities, now with a very good response to the treatment with Kyprolis - Dexamethasone (10 cycles)
• We try to do until 16 cycles
• We must have a cytogenetic test
• For a new relapse - Daratumumab anti CD38 - it was approved in Romania for patients with refractory MM
A Patient With Deep Vein Thrombosis And Pulmonary Thromboembolism As An Initial Presentation Of Multiple Myeloma

Milena Dapcevic
Clinical centre of Montenegro
No disclosures
Multiple myeloma (MM) is clonal plasma cell disorder and leading indication for autologous stem cell transplantation worldwide.

- Second most prevalent hematological malignancy
- Median age at diagnosis is 70 years
- Survival is increasing but no modality with the possible exception of allogeneic stem cell transplantation is curative in multiple myeloma
- Diverse hemostatic abnormalities have been reported in patients with myeloma which predispose to bleeding and also thrombosis.
Thrombosis

1. The first description of thrombosis pathogenesis was given by Rudolf Virchow in 1856. Virchow-triad
2. Disease is multifactorial:
   - Endothelial injury
   - Stasis of the blood flow
   - Hypercogulability
Vein thromboembolism

Vein thromboembolism comprises deep vein thrombosis and pulmonary embolism.

Vein thromboembolism constitutes the third most common cardiovascular disease.

Common risk factors with atherothrombosis and coronary disease are obesity, hypertension, diabetes mellitus, cigarette smoking, hypercholesterolemia and metabolic syndrome.
Vein thromboembolism

The most important inherited risk factors are major thrombophilias - factor V Leiden and prothrombin 20210 mutations, deficiencies of protein C, protein S and antithrombin III

The most important acquired risk factors are advanced age, immobility, recent trauma, surgery, inflammation, hospitalization and cancer (neoplasm)
Multiple myeloma (MM) is one of the neoplasms that exhibit a high incidence of thromboembolic events (TEs), and approximately 10% patients with MM develop TEs during their clinical courses.
There are no adequate scoring systems for thrombosis in haematological malignacies

- Wells scoring system, Ottawa scoring system

### Wells Scoring System for Diagnosing DVT

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing, within, 6 months or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremity</td>
<td>1</td>
</tr>
<tr>
<td>Bedridden for &gt;3 days or major surgery with general/regional anaesthesia within previous 12 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema confined to symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose)</td>
<td>1</td>
</tr>
<tr>
<td>Previous documented DVT</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as DVT e.g (Popliteal (Baker) cyst, superficial thrombophlebitis, muscle pulls/tears, chronic venous insufficiency, and others)</td>
<td>-2</td>
</tr>
</tbody>
</table>

**Clinical probability simplified score**

- **DVT likely**: 2 points or more
- **DVT unlikely**: 1 point or less
Venous thromboembolism (VTE) is also an increasingly recognized problem in the post-hematopoietic stem cell transplantation (HSCT) setting.

Autologous stem cell transplantation is not curative in multiple myeloma, however, event-free survival and overall survival is improved by approximately one year after autologous hematopoietic stem cell transplantation compared to conventional chemotherapy.

All patients younger than 65-70 years should be considered for high-dose chemo with autologous stem cell transplantation.
A 54 years old man was hospitalized in our department due to high fever, severe anemia, haemoptysis and pleural effusion.

He had no significant past medical history.
Markedly elevated level of Immunoglobulin G/lambda monoclonal component was detected (IgG 47 g/l)

Greater than 60 percent of monoclonal plasma cells, CD138 positive, MUM-1 negative, lambda positive, CD20 negative, CD3 negative were found by bone marrow biopsy

Serum creatinin, calcium, albumin and beta2-microglobulin levels were normal
The skeletal survey X-ray was showed only calvarial osteolytic lesions, but computed tomography (CT) scan was performed showing few more lesions in lumbo-sacral bone structures.

No renal impairment
Diagnosis of Multiple myeloma IgG/lambda type clinical stage III A was established
- D dimer elevation *(over 35 µg/ml)* suggested presence of thrombosis, levels of troponine and natriuretic peptid type B were normal
- Color Doppler ultrasonography of low limbs was performed and it showed signs of deep vein thrombosis
- On Multislice Computed Tomography (MSCT) scan of pulmonary arteries subsegmental pulmonary embolism was detected
- Echocardiography: no right ventricle dilatation, no pulmonary hypertension
Multidisciplinary Team

- The patient was stratified as a “low risk and good prognosis”
- Multidisciplinary approach
- No inherited risk factors
• Chemotherapy strategies in addition to thalidomide were safely performed with anticoagulant therapy

• Patient recived six cycles of CTD protocol (cyclophosphamide, thalidomide, dexamethasone) and achieved at least very good partial remission

• Maintenance monotherapy with thalidomide was obtained for another six months
• Vitamin- K dependent oral antikoagulant profilaxis was continued for next 12 months

• The patient was considered not to be candidate for autologous stem cell transplantation at the time

• Hematologic remission has been maintained over two years
Now he receives only bisphosphonates (zolendronic acid) with calcium and vitamin D supplements and 100 mg of acetil salyc acid, and has no signs of disease progression.

- He is planned for the secondary autologous haematological stem cell transplantation (HSCT) in the relaps.
There is a higher risk for thromboembolic event in multiple myeloma because of cancer status, intrinsic risk factors and exposure to prothrombotic therapies, first of all immunomodulatory agents and steroids.

Many diverse hemostatic abnormalities have been reported: presence of lupus anticoagulant (LA), increased levels of factor VIII and fibrinogen, activated protein C resistance, significantly higher endogenous thrombin potential, elevated interleukin 6 (IL6) level, paraprotein interference with fibrin structure and endothelial damage.
There is an increased tendency for thrombosis, which may lead to deep vein thrombosis and pulmonary embolism in about 5% of patients with multiple myeloma, and treatment including steroids and thalidomide, can increase this risk to between 10% to 15%.

Primary thromboprophylaxis in cancer patients is challenging, as the risk of VTE is not equal in all patients and as anticoagulation in those patients is associated with increased bleeding complications compared with patients without cancer.
Discussion- emphasys on clinical practice

- Thrombotic events (TEs) are increasingly recognized problem in the post- hematopoetic stem cell transplantation setting
- Concomitant risk for bleeding complications
- Prior thrombotic event is an additional risk for thrombosis after stem cell transplantation
- Anticoagulant and antiagregation therapy demand more then 50x10^9/l platelets in the blood count
- Autologous HSCT is not curative in myeloma
Autologous stem cell transplantation

Risc factors before TE

Previous thrombosis

Present Risc faktors

Previous thrombosis
Thrombogenic therapy
Longtherm immobillisation
Hospitalization
Possibile infections
Indwelling catheters
Posttransplant maintenance therapy
Active disease
Dilemas

There are lots of open questions in this area!

- Should secondary autologous transplantation be performed?
- Which protocol for mobilization of progenitor cells should be used?
- Which protocol for maintenance therapy after autologous stem cell transplantation is the most safe one?
- Risc/benefit of autologous stem cell transplantation in the high risc of thrombosis?
- Duration of thromboprofilaxis after TEs in myeloma?
CONCLUSION

WE NEED MORE “BEST CLINICAL PRACTICE” RECOMMENDATIONS AND ADEQUATE SCORING SYSTEM FOR THROMBOSIS RISC IN MYELOMA
THANK YOU FOR YOUR ATTENTION!
Treatment of Early Relapses in Multiple Myeloma

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## Disclosures: Meletios A. Dimopoulos

<table>
<thead>
<tr>
<th>Research Support/P.I.</th>
<th>Janssen, Genesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honoraria, Consulting fees, Lecture fees</td>
<td>Celgene, Janssen, Amgen, Takeda, BMS</td>
</tr>
</tbody>
</table>
New criteria for response evaluation during follow-up to check if patient is relapsing/progressing

<table>
<thead>
<tr>
<th>Relapse category</th>
<th>Response criteria</th>
</tr>
</thead>
</table>
| **Progressive disease**<sup>*,†</sup> | Any one or more of the following criteria:  
  • Increase of 25% from lowest confirmed response value in one or more of the following criteria:  
    - serum M-protein (absolute increase must be ≥ 0.5 g/dL)  
    - serum M-protein increase ≥ 1g/dL, if the lowest M component was ≥ 5 g/dL  
    - urine M-protein (absolute increase must be ≥ 200 mg/24h)  
    - in patients without measurable disease in serum and urine, the difference between involved and uninvolved FLC levels (absolute increase must be ≥ 10 mg/dL)  
    - in patients without measurable disease in serum, urine and sFLC, bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be ≥ 10%)  
    - appearance of new lesion(s), ≥ 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1cm in short axis  
    - ≥ 50% increase in circulating plasma cells (minimum of 200 cells per ul) if this is the only measure of disease |
| **Clinical relapse** | One or more of the following criteria:  
  • direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder  
  • development of new soft tissue plasmacytomas or bone lesions (not osteoporotic fractures)  
  • definite increase in the size of existing plasmacytomas or bone lesions  
  • hypercalcaemia (> 11 mg/dL)  
  • decrease in haemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions  
  • rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma  
  • hyperviscosity related to serum paraprotein |
| **Relapse from complete response (to be used only if the end point is DFS)** | Any one or more of the following criteria:  
  • reappearance of serum or urine M-protein by immunofixation or electrophoresis  
  • development of ≥ 5% plasma cells in the bone marrow  
  • appearance of any other sign of progression (i.e. new plasmacytoma, lytic bone lesion or hypercalcaemia) |
| **Relapse from MRD negative (to be used only if the end point is DFS)** | Any one or more of the following criteria:  
  • loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma)  
  • reappearance of serum or urine M-protein by immunofixation or electrophoresis  
  • development of ≥ 5% clonal plasma cells in the bone marrow  
  • appearance of any other sign of progression (i.e. new plasmacytoma, lytic bone lesion or hypercalcaemia) |

Footnote information available in the slide notes.  
CRAB, calcium, renal failure, anaemia, bone lesions; DFS, disease-free survival; FLC, free light chain; MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing, sFLC, serum free light chain; SPD, sum of the products of maximal diameters.

Recommended work-up at relapse

- Medical history and physical examination
- Haemogram
- Biochemistry: creatinine and calcium values*
- Protein studies
  - Total serum protein and serum electrophoresis (serum M-protein)
  - 24-hour urine protein electrophoresis (urine M-protein)
  - Serum and urine immunofixation
- Bone marrow aspirate ± biopsy: non-secretory/myelodysplasia/clinical trial†
- Imaging techniques

*B₂₉-microglobulin or ISS stage not clear at the moment of relapse; †FISH analysis is usually performed at relapse if not available or normal at diagnosis.

FISH, fluorescence in situ hybridization; ISS, International Staging System.

Work-up at relapse

• **Clonal evolution**\(^1\)
  - At relapse, mutational burden was unchanged
  - There are different scenarios: **selection** of very rare subclones present at diagnosis, **appearance/disappearance** of mutations, **stability**
  - Chemo resistance at relapse could be induced by newly acquired mutations in myeloma drivers or pre-existing subclonal mutations

• **Immune profiling**\(^2\)
  - Some studies show associations between MRD status and immune profiling
  - Further studies are needed to determine whether immune profiling can be used to predict outcomes

• **Use of PET-CT/ WBLD-CT/CT at relapse**\(^3–5\)
  - More sensitive assessments
  - Non-invasive monitoring during follow-up

---


CT, computed tomography; MRD, minimal residual disease; PET-CT, positron emission tomography–computed tomography; WBLD-CT, whole-body low-dose computed tomography.
Multiple Myeloma: Patient Outcomes in Real-World Practice

*Treatment Duration and Treatment-Free Interval by Line of Therapy*

Data from 4997 patient charts in Belgium, France, Germany, Italy, Spain, Switzerland, and the UK. The proportion of patients who had received each line are from the cross-sectional review; data on durations of treatment and treatment-free intervals are from the retrospective review.

1L-5L = first line-fifth line treatment; CI = confidence interval; m = month.

Factors to Consider When Selecting Treatment at Relapse

**Goals of Treatment**

- Maximize response and maintain disease control\(^4,5\)
- Delay or prevent disease progression
- Balance efficacy with tolerability and QoL\(^4,5\)
- **Prolong survival\(^5\)**
- Stable disease may be beneficial

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**Disease-Related Factors\(^1,2\)**
- Type and risk status of disease
- Presence of refractory disease
- Aggressiveness of current relapse

**Treatment-Related Factors\(^1,2\)**
- Type of prior Txs and prior response
- Prior Tx-related toxicity
- Bone marrow reserve
- Expected efficacy and toxicity of proposed Tx
- Expectations of the patient

**Patient-Related Factors\(^1,2,3\)**
- Age, frailty, and performance status
- Comorbidities
- Renal insufficiency/hepatic impairment
- Preference on mode of administration

QoL = quality of life.

Should biochemical/asymptomatic relapse be treated?

Clinical trials include patients with asymptomatic relapse; however, in clinical practice the approach is sometimes different, and current recommendations state that treatment can be delayed in the case of asymptomatic relapse.

Analysis of the characteristics of relapse in 211 patients after ASCT

For patients with asymptomatic relapse:

• Median time to treatment requirement of 5.6 months
  › (10 months in a recent Spanish trial)

• 26% of patients (n = 12) did not require treatment in 2 years
  › ISS I or II at diagnosis (n = 12)
  › IgG type (58%)
  › No extramedullary disease (n = 11)
  › Clinical features of aggressiveness at diagnosis were rare
    › Renal failure, n = 1; hypercalcemia, n = 1; anaemia, n = 3

• Consider early treatment if
  › Previous aggressive presentation/clinical behaviour
  › Clearly increasing M-protein, particularly light chains in urine
  › Decreasing Hb level

ASCT, autologous stem cell transplantation; Hb, haemoglobin; IgG, immunoglobulin G; ISS, International Staging System.

How Has Treatment Developed in Patients Who Have Received 1-3 Prior Lines of Therapy?
## Therapies Using Rd as Backbone

### Proteasome Inhibitors

<table>
<thead>
<tr>
<th>Epoxyketone PI</th>
<th>Boronate PI</th>
<th>Anti-CD38</th>
<th>Anti-SLAMF7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carfilzomib</strong>&lt;sup&gt;1-6&lt;/sup&gt;</td>
<td><strong>Ixazomib</strong>&lt;sup&gt;7-9&lt;/sup&gt;</td>
<td><strong>Daratumumab</strong>&lt;sup&gt;10-12&lt;/sup&gt;</td>
<td><strong>Elotuzumab</strong>&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Belongs to the epoxyketone class that is structurally different from boronate PIs</td>
<td>• Like bortezomib, belongs to the boronic acid class</td>
<td>• Broad-spectrum killing activity of CD38-expressing tumor cells</td>
<td>• Binds with SLAMF7 on plasma cells, marking them for activation by NK cells</td>
</tr>
<tr>
<td>• Selectively and irreversibly binds to the N-threonine active sites of the constitutive proteasome and the immunoproteasome</td>
<td>• Reversibly Inhibits (β1) caspase-like and (β2) trypsin-like sites of 20S proteasome, but preferentially inhibits (β5) chymotrypsin-like site</td>
<td>• Exerts anti-tumor activity via ADCC, ADCP, CDC, and apoptosis</td>
<td>• Binds with SLAMF7 on NK cells and activates them directly</td>
</tr>
</tbody>
</table>

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**ASPIRE: Study Design**

**Patient with relapsed multiple myeloma**

**Randomization**

1:1

N = 792

**Stratification:**

- β₂-microglobulin
- Prior bortezomib
- Prior lenalidomide

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**28-day cycles**

**KRd**

Carfilzomib 27 mg/m² IV (10 minutes)

*Days 1, 2, 8, 9, 15, 16 (20 mg/m² days 1, 2, cycle 1 only)*

Lenalidomide 25 mg *days 1–21*

Dexamethasone 40 mg *days 1, 8, 15, 22*

After cycle 12, carfilzomib given on *days 1, 2, 15, 16*

*After cycle 18, carfilzomib discontinued*

---

**Rd**

Lenalidomide 25 mg *days 1–21*

Dexamethasone 40 mg *days 1, 8, 15, 22*

---

*All patients received Rd until disease progression, withdrawal of consent, or toxicity.*

ASPIRE: KRd Extended Median Progression-Free Survival (PFS) by 8.7 Months

KRd-treated patients had a 31% reduction in the risk of disease progression or death in comparison with Rd

- Median follow-up was 32.3 months for KRd and 31.5 months for Rd

ASPIRE: Progression-Free Survival Subgroup Analyses

one vs 2-3 prior lines of therapy

Prior bortezomib or no bortezomib therapy

ASPIRE: K Rd Extended Overall Survival (OS) by 7.9 Months

- Carfilzomib discontinued after 18 cycles
- Events at 18 months: K Rd, 71 (17.9%); Rd, 97 (24.5%); HR (95% CI) = 0.69 (0.51–0.93)²

Using a piecewise Cox model, the 18-month OS HR was estimated as 0.69 (95% CI, 0.51–0.93)

**POLLUX: Study Design**

Comparison of daratumumab (D) + lenalidomide + dexamethasone (Rd) vs Rd

Aims: compare the efficacy and safety of D in combination with Rd vs Rd alone in patients with RRMM in a randomized, open-label, multicenter, phase 3 study

Primary endpoint: PFS

Selected secondary endpoints: TTP, ORR, ≥ VGPR, minimal residual disease-negative rate, OS, duration of response, time to response, safety

*Patients were given the treatment until PD.

D = daratumumab; PO = oral; TTP = time to progression.

POLLUX: PFS

DRd Reduced Risk of Progression or Death by 56%

- 56% reduction in risk of progression/death for DRd vs Rd

NR = not reached; DRd = daratumumab, lenalidomide, and dexamethasone.

POLLUX: PFS by prior lines of therapy

**DRd Reduced Risk of Progression or Death by 59% in Patients With 1 Prior Line of Therapy**

- Median follow-up: months
- 22.5
- HR: 0.41 (0.27 - 0.63)
- P = 0.004

**DRd Reduced Risk of Progression or Death by 62% in Patients With 2 Prior Lines of Therapy**

- Median follow-up: months
- 22.9
- HR: 0.47 (0.29 - 0.77)
- P = 0.004

**POLLUX: DRd Extended PFS by 9.8 Months in Patients With 3 Prior Lines of Therapy**

- Median follow-up: months
- 22.0
- HR: 0.47 (0.23 - 0.90)
- P = 0.031
In the total evaluable population, MRD negative rates were more than 3-fold higher with DRd versus Rd at all sensitivity thresholds. MRD negative patients (identified at the $10^{-5}$ sensitivity threshold) accumulated more rapidly with DRd versus Rd.

MRD = minimal residual disease.
TOURMALINE-MM1: Study Design

Global, double-blind, randomised, placebo-controlled study design

N = 722

Randomization 1:1

**Ixazomib + Lenalidomide + Dexamethasone (all oral)**
- Ixazomib: 4 mg on days 1, 8, and 15
- Lenalidomide: 25 mg* on days 1–21
- Dexamethasone: 40 mg on days 1, 8, 15, 22

Repeat every 28 days until progression, or unacceptable toxicity

**Placebo + Lenalidomide + Dexamethasone (all oral)**
- Placebo: on days 1, 8, and 15
- Lenalidomide: 25 mg* on days 1–21
- Dexamethasone: 40 mg on days 1, 8, 15, 22

**Stratification:**
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

**Primary endpoint:**
- PFS

**Key secondary endpoints:**
- OS
- OS in patients with del(17p)

*10 mg for patients with creatinine clearance $\leq 50$ or $\leq 60$ mL/min, depending on local label/practice.

ISS = International Staging System.

TOURMALINE-MM1: Ixazomib Extended Progression-Free Survival by 5.9 Months

Table:

<table>
<thead>
<tr>
<th></th>
<th>IRd (n = 360)</th>
<th>Rd (n = 360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, months</td>
<td>~ 15</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>20.6</td>
<td>14.7</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.74 (0.59–0.94)</td>
<td>Log-rank test $P = 0.01$</td>
</tr>
</tbody>
</table>

Figure:

- IRd
- Placebo-Rd

Number of patients at risk:

<table>
<thead>
<tr>
<th>IRd</th>
<th>Placebo-Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>360 345 332 315 298 283 270 248 233 224 206 182 145 119 111 95 72 58 44 34 26 14 9 1 0</td>
<td>362 340 325 308 288 274 254 237 218 208 188 157 130 101 85 71 58 46 31 22 15 5 3 0 0</td>
</tr>
</tbody>
</table>

TOURMALINE-MM1: PFS according to the number of prior lines of therapy

Pts with 2 or 3 PL or 1PL without trx seemed to have greater benefit than pts after 1PL and trx

ELOQUENT-2: Study Design

Relapsed andor Refractory MM
1–3 Prior lines
N = 646

R 1:1

ERd (n = 321)
Elotuzumab 10 mg/kg IV, Cycles 1 and 2 weekly (days 1, 8, 15, 22), then every other week (days 1, 15)
Lenalidomide days 1–21, 25 mg PO
Dexamethasone 40 mg PO, weekly

Mandatory pre-medication 30 to 90 min before infusion: diphenhydramine (25–50 mg PO or IV) or equivalent, ranitidine (50 mg IV) or equivalent and acetaminophen (650–1000 mg PO)

Until progression or unacceptable toxicity

Rd (n=325)
Lenalidomide days 1–21, 25 mg PO
Dexamethasone 40 mg PO, weekly

Primary endpoint: PFS, ORR

Selected secondary endpoints: OS, severity of pain or interference with daily life
ELOQUENT-2: Elotuzumab Extended PFS by 4.5 Months at the 4-Year Follow-Up

- At 4 years, ELOQUENT-2 has the longest follow-up for PFS in RRMM
- 29% reduction in the risk of progression or death (sustained over time)
- 50% relative improvement in the PFS rate at 4 years (21% vs 14%) in favor of ERd

ELOQUENT-2: Median Time Since Diagnosis and Prior Lines of Therapy

Dimopoulos MA, et al. EHA 2017; Abstract S456
Lenalidomide-Based Studies in RRMM

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>ASPIRE(^1) K Rd vs Rd</th>
<th>POLLUX(^2,3) DRd vs Rd</th>
<th>TOURMALINE-MM1(^4) IRd vs Rd</th>
<th>ELOQUENT-2(^5,6) ERd vs Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS HR (95% CI)</td>
<td>Crizluzomib given for 18 cycles; Rd until progression</td>
<td>Until progression</td>
<td>Until progression</td>
<td>Until progression</td>
</tr>
<tr>
<td></td>
<td>0.69 (0.57–0.83)</td>
<td>0.37 (0.27–0.52)</td>
<td>0.74 (0.59–0.94)</td>
<td>0.73 (0.60–0.89)</td>
</tr>
<tr>
<td>ORR</td>
<td>87%</td>
<td>93%</td>
<td>78%</td>
<td>79%</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>70%</td>
<td>76%</td>
<td>48%</td>
<td>33%</td>
</tr>
<tr>
<td>≥ CR</td>
<td>32%</td>
<td>43%</td>
<td>14%</td>
<td>4%</td>
</tr>
<tr>
<td>DoR (months)</td>
<td>28.6</td>
<td>NE</td>
<td>20.5</td>
<td>20.7</td>
</tr>
<tr>
<td>OS HR (95% CI)</td>
<td>0.79 (0.63–0.99)</td>
<td>NA</td>
<td>NE</td>
<td>0.78 (0.63–0.96)</td>
</tr>
</tbody>
</table>

DoR = duration of response; NA = not available; NE = not evaluated.

This table is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

Rd Backbone Treatments in Patients With High-Risk Cytogenetics
New Agents for RRMM Efficacy: PFS by Cytogenetic Risk

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New Agents for RRMM Efficacy: PFS by Cytogenetic Risk

This graph is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

Treatment With Non-Rd Backbones
**ENDEAVOR: Carfilzomib-Dex vs Bortezomib-Dex**

**Study Design**

**Kd**
- Carfilzomib 56 mg/m² IV
  - Days 1, 2, 8, 9, 15, 16 (20 mg/m² days 1, 2, cycle 1 only)
  - Infusion duration: **30 minutes for all doses**
- Dexamethasone 20 mg
  - Days 1, 2, 8, 9, 15, 16, 22, 23
- 28-day cycles until PD or unacceptable toxicity

**Vd**
- Bortezomib 1.3 mg/m² (IV bolus or subcutaneous injection)
  - Days 1, 4, 8, 11
- Dexamethasone 20 mg
  - Days 1, 2, 4, 5, 8, 9, 11, 12
- 21-day cycles until PD or unacceptable toxicity

**ENDEAVOR: Kd Extended Progression-Free Survival by 8.2 Months**

**ENDEAVOR Updated PFS**

<table>
<thead>
<tr>
<th></th>
<th>Initial Analysis²</th>
<th>Updated Analysis¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kd (n = 464)</strong></td>
<td><strong>Vd (n = 465)</strong></td>
<td><strong>Kd (n = 464)</strong></td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>11.9</td>
<td>11.1</td>
</tr>
<tr>
<td>Median treatment duration, months</td>
<td>9.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>18.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.53 (0.44–0.65; P &lt; 0.0001)</td>
<td>0.53 (0.44–0.63; P &lt; 0.0001)</td>
</tr>
</tbody>
</table>

¹Treatment duration in the safety population: Kd (n = 463), Vd (n = 456).

ENDEAVOR: Kd Extended Overall Survival by 7.6 Months

ENDEAVOR: Progression-Free Survival according to prior lines of therapy

CASTOR: Study Design

**Multicenter, randomized, open-label, active-controlled phase 3 study**

**Key eligibility criteria**
- RRMM
- ≥ 1 prior line of therapy
- Prior bortezomib exposure, but not refractory

**DVd (n = 251)**
- Daratumumab (16 mg/kg IV) Every week - cycles 1–3
- Every 3 weeks - cycles 4–8
- Every 4 weeks - cycles 9+
- Vel: 1.3 mg/m² SC, days 1, 4, 8, 11 - cycles 1–8
- Dex: 20 mg PO–IV, days 1, 2, 4, 5, 8, 9, 11, 12 - cycles 1–8

**Vd (n = 247)**
- Vel: 1.3 mg/m² SC, days 1, 4, 8, 11 - cycles 1–8
- Dex: 20 mg PO–IV, days 1, 2, 4, 5, 8, 9, 11, 12 - cycles 1–8

**Primary Endpoint**
- PFS

**Secondary Endpoints**
- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

**Statistical analyses**
- 295 PFS events: 85% power for 4.3 month PFS improvement
- Interim analysis: ~ 177 PFS events

**Daratumumab IV administered in 1000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/hour permitted**

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dex = Dexamethasone; DVd = daratumumab/bortezomib/dexamethasone; SC = subcutaneous; Vel = bortezomib; Vd = bortezomib/dexamethasone.

CASTOR Update: DVd Improved Progression-Free Survival by 9.6 Months

- Median follow up: 26.9 months

CASTOR: Response Rate and MRD Negativity

Response Rate, %

- **ORR = 85%**
  - Dvd: CR = 30, VGPR = 33, PR = 22
  - Vd: CR = 10, VGPR = 19, PR = 34

- **ORR = 63%**

MRD Negative Rate, %

- **5**
  - Dvd: MRD-ve = 5
  - Vd: MRD-ve = 1

<table>
<thead>
<tr>
<th>Complete Response Rate</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Dvd (n = 240)</td>
<td>Vd (n = 234)</td>
</tr>
<tr>
<td>( \geq CR, % )</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>( P ) value</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>CR ratio*</td>
<td>3.0</td>
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<table>
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<tr>
<th>MRD Negative Rate (10^-6)</th>
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<tbody>
<tr>
<td></td>
<td>Dvd (n = 251)</td>
<td>Vd (n = 247)</td>
</tr>
<tr>
<td>MRD-ve, %</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>( P ) value</td>
<td>( P &lt; 0.005 )</td>
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Non-Rd Backbone Treatments in Patients With High-Risk Cytogenetics
# Progression-Free Survival in Patients With High-Risk Cytogenetics

<table>
<thead>
<tr>
<th></th>
<th>Carfilzomib&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Daratumumab&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kd (n = 177)</td>
<td>Vd (n = 177)</td>
</tr>
<tr>
<td>Median follow-up in ITT, months</td>
<td>11.9</td>
<td>11.1</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>8.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.65</td>
<td>(0.45–0.92; P = 0.0075)</td>
</tr>
</tbody>
</table>

This table is provided for ease of viewing information from multiple trials. Direct comparison between trials is not intended and should not be inferred.

Patients with Early Relapse (≤12 months from previous therapy)
In ASPIRE, KRd vs Rd extended PFS in RRMM patients regardless of whether they experienced early or late relapse.

In both arms, patients with early relapse had worse PFS outcomes than those with late relapse.
ENDEAVOR: Kd Effects on PFS in Early and Late Relapse Patients

- In ENDEAVOR, Kd vs Vd extended PFS in RRMM patients regardless of whether they experienced early or late relapse.
- In both arms, patients with early relapse had worse PFS outcomes than those with late relapse.

<table>
<thead>
<tr>
<th></th>
<th>Kd (n = 123)</th>
<th>Vd (n = 116)</th>
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</thead>
<tbody>
<tr>
<td>Progression/Death, n (%)</td>
<td>58 (47.2%)</td>
<td>73 (62.9%)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>13.9</td>
<td>5.7</td>
</tr>
<tr>
<td>HR (Kd/Vd) (95% CI)</td>
<td>0.598 (0.423, 0.846)</td>
<td></td>
</tr>
<tr>
<td>P value (1-sided)</td>
<td>0.0017</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Kd (n = 335)</th>
<th>Vd (n = 340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression/Death, n (%)</td>
<td>111 (33.1%)</td>
<td>167 (49.1%)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>22.2</td>
<td>10.2</td>
</tr>
<tr>
<td>HR (Kd/Vd) (95% CI)</td>
<td>0.486 (0.382, 0.620)</td>
<td></td>
</tr>
<tr>
<td>P value (1-sided)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

# Regimens for RRMM After 1-3 Prior Lines

Based on previous exposure or refractoriness to bortezomib or lenalidomide (according inclusion/exclusion criteria of respective studies)

<table>
<thead>
<tr>
<th></th>
<th>KRD</th>
<th>KD</th>
<th>Elo-RD</th>
<th>IRD</th>
<th>DRd</th>
<th>DVd</th>
<th>Pom-VD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bortezomib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Refractoriness</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Lenalidomide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Refractoriness</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
# Lenalidomide refractoriness

<table>
<thead>
<tr>
<th>Lenalidomide-Refractory</th>
<th>DVd (n = 45)</th>
<th>Vd (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up in ITT, months</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>10.3</td>
<td>4.4</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.37 (0.21–0.65; P = 0.0004)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lenalidomide-Refractory</th>
<th>Kd (n = 113)</th>
<th>Vd (n = 122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.9</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>8.6</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>0.80 (0.57–1.11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


OPTIMISMM Phase 3 study design

**RRMM patients N = 559**
- 1-3 prior regimens
- Prior-LEN
- Prior-BORT allowed, no PD

**Randomization 1:1**

**PVd**
- **POM**: 4 mg D1–14,
- **BORT**: 1.3 mg/m² cy 1–8: D1, 4, 8, 11; cy 9 onwards: D1, 8
- **LoDEx**: 20 mg (10mg >75 yrs) DEX cy 1–8: D1–2, 4–5, 8–9, 11–12; cy 9 onwards: D1–2, 8–9
- 21 day cycles

**Vd**
- **BORT**: 1.3 mg/m² cy 1–8: D1, 4, 8, 11; cy 9 onwards: D1, 8
- **LoDEx**: 20 mg (10mg >75 yrs) DEX cy 1–8: D1–2, 4–5, 8–9, 11–12; cy 9 onwards: D1–2, 8–9
- 21 day cycles

**Endpoints**
- Primary: PFS
- Secondary: OS, ORR, duration of response
- Exploratory: TTR, PFS2, MRD, HRQoL

**Stratification Factors**
- Age (≤ 75 vs. > 75 yrs)
- Number of prior anti MM regimens (1 vs. > 1)
- β2M at screening (< 3.5 mg/L vs. ≥ 3.5 mg/L; ≤ 5.5 mg/L vs. > 5.5 mg/L)

**Follow-Up for OS**
- Ongoing evaluation
  - Every 21 (± 3) days

**Tx D/C due to PD**
- PFS follow-up
  - Every 21 (± 3) days

**Tx D/C prior to PD**
- PD

Richardson P, et al. ASCO 2018
**CONTEXTUALIZING THE PATIENT POPULATION:**

OPTIMISMM: 70% of patients were len refractory

% **Len-exposed, Len-refractory and non-Len exposed patients in early-RRMM* combination trials**

- Len-exposed, non-refractory
- Len-refractory
- Non-Len-exposed

**OPTIMISMM/ Pvd**

Median 2 prior lines

- 71%
- 29%

**ASPIRE/ Rd+K**

- Median # prior lines: 2
- 13% Len-refractory
- 7% Non-Len-exposed
- 80% Non-Len-exposed

**TOURMALINE/ Rd+I**

- 2 prior lines
- 12% Len-refractory
- 95% Non-Len-exposed
- 88% Non-Len-exposed

**ELOQUENT Rd+E**

- 2 prior lines
- 5% Len-refractory
- 95% Non-Len-exposed
- 95% Non-Len-exposed

**POLLUX/ Rd+D**

- Median 1 prior line
- 18% Len-refractory
- 83% Non-Len-exposed
- 83% Non-Len-exposed

**CASTOR/ Vd+D**

- 2 prior lines
- 12% Len-refractory
- 64% Non-Len-exposed
- 64% Non-Len-exposed

**ENDEAVOUR/ Kd**

- 2 prior lines
- 14% Len-refractory
- 24% Non-Len-exposed
- 24% Non-Len-exposed

**PANORAMA***/ Vd+P

- NR
- 19%*** Len-refractory
- 81% Non-Len-exposed

* Median 1-2 prior lines
**Len refractory data not reported
***IMiD exposed data – will include previous thalidomide

Richardson P, et al. ASCO 2018
Progression-Free Survival (ITT)

PVd reduced the risk of progression and death by 39% compared with Vd

<table>
<thead>
<tr>
<th></th>
<th>Events/N</th>
<th>Median PFS, months</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVd</td>
<td>154/281</td>
<td>11.20</td>
<td>0.61 (0.49-0.77)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Vd</td>
<td>162/278</td>
<td>7.10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Richardson P, et al. ASCO 2018
Progression-Free Survival by len refractoriness

- PFS was improved with PVd regardless of LEN refractoriness

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PFS</th>
<th>PVd</th>
<th>Vd</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEN-refractory&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n/N</td>
<td>120/200</td>
<td>118/191</td>
</tr>
<tr>
<td></td>
<td>Median, months</td>
<td>9.53</td>
<td>5.59</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>0.65 (0.50-0.84)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>P Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEN-nonrefractory</td>
<td>n/N</td>
<td>34/81</td>
<td>44/87</td>
</tr>
<tr>
<td></td>
<td>Median, months</td>
<td>22.01</td>
<td>11.63</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>0.48 (0.30-0.75)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>P Value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Refractory: failure to achieve minimal response or development of progressive disease during therapy, or progression within 60 days of last dose, inclusive.

LEN-refractory: refractoriness to the last LEN-containing regimen, LEN-nonrefractory: nonrefractory to LEN in last LEN-containing regimen
Progression-Free Survival (1 Prior Line of Therapy)

- In patients with 1 prior line, PVD reduced the risk of progression and death by 46% compared with VD.
- 57.7% of patients treated with PVD and 56.5% treated with VD were refractory to LEN.

<table>
<thead>
<tr>
<th></th>
<th>Events/N</th>
<th>Median PFS, months</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVD</td>
<td>45/111</td>
<td>20.73</td>
<td>0.54 (0.36-0.82)</td>
<td>.0027</td>
</tr>
<tr>
<td>VD</td>
<td>52/115</td>
<td>11.63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Richardson P, et al. ASCO 2018
Progression free survival in ITT and subgroups

**Progression Free Survival, months**

- **ITT**: N = 281, n = 200, 0.61 (0.49-0.77) < .0001
- **ITT, LEN-refractory**: N = 278, n = 191, 0.65 (0.50-0.84) < .001
- **ITT, LEN non refractory**: N = 81, n = 87, 0.48 (0.30-0.75) .001
- **1st relapse**: N = 111, n = 115, 0.54 (0.36-0.82) .0027
- **1st relapse, LEN-refractory**: N = 64, n = 65, 0.55*

Abstract 8001: OPTIMISM — Paul Richardson

* Verbal Communication during EHA; unpublished data
Progression-Free Survival in Patient subgroups

- PFS was improved with PVd vs Vd across all patient subgroups

### Table: Progression-Free Survival in Patient subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PVd</th>
<th>Vd</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 75 y</td>
<td>126/235</td>
<td>134/231</td>
<td>0.59 (0.46–0.76)</td>
</tr>
<tr>
<td>&gt; 75 y</td>
<td>28/46</td>
<td>28/47</td>
<td>0.78 (0.46–1.32)</td>
</tr>
<tr>
<td>≤ 65 y</td>
<td>60/123</td>
<td>67/120</td>
<td>0.58 (0.41–0.83)</td>
</tr>
<tr>
<td>&gt; 65 y</td>
<td>94/158</td>
<td>95/158</td>
<td>0.64 (0.48–0.86)</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>69/149</td>
<td>71/137</td>
<td>0.62 (0.45–0.87)</td>
</tr>
<tr>
<td>&gt; 0</td>
<td>85/132</td>
<td>91/141</td>
<td>0.60 (0.45–0.82)</td>
</tr>
<tr>
<td><strong>High risk cytogenetics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37/61</td>
<td>34/49</td>
<td>0.56 (0.35–0.90)</td>
</tr>
<tr>
<td>No</td>
<td>73/137</td>
<td>80/132</td>
<td>0.56 (0.41–0.77)</td>
</tr>
<tr>
<td><strong>No. of lines of prior therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>45/111</td>
<td>52/115</td>
<td>0.54 (0.36–0.82)</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>109/170</td>
<td>110/163</td>
<td>0.63 (0.48–0.83)</td>
</tr>
<tr>
<td>2</td>
<td>74/117</td>
<td>67/104</td>
<td>0.67 (0.48–0.94)</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>35/53</td>
<td>43/59</td>
<td>0.60 (0.38–0.95)</td>
</tr>
</tbody>
</table>

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Abstract 8001: OPTIMISM—Paul Richardson, MD
Response

- ORR was significantly higher with PVd vs Vd in the ITT population \( (P < .001) \) and in patients with 1 prior line of therapy \( (P < .001) \)
  - PVd led to deeper responses with higher sCR/CR and \( \geq \) VGPR rates vs Vd
- Median TTR was 0.9 vs 1.4 months, and median DOR was 13.7 vs 10.9 months (ITT)

![Bar chart showing response rates for PVd and Vd in ITT and 1 Prior Line of Therapy groups]
Relapsed/refractory multiple myeloma
ESMO guidelines 2017

First relapse after IMiD-based induction

Doublets
Kd/Vd

Triplets based on BORT
DARA Vd or PANO Vd or ELO Vd or VCD

First relapse after BORT-based induction

Rd

Triplets based on Rd
DARA Rd or KRd or IXA Rd or ELO Rd

2L, second line; 3L, third line; BORT, bortezomib; CYCLO, cyclophosphamide; DEX, dexamethasone; DARA, daratumumab; ELO, elotuzumab; IMiD, immunomodulatory drug; IXA, ixazomib; Kd, carfilzomib and DEX; KRd, carfilzomib, lenalidomide and DEX; POM, pomalidomide; Rd, lenalidomide and DEX; Vd, bortezomib and DEX.

Mayo Guidelines for the Relapsed Patients
Mayo Risk Adapted Groups

Therapy at first relapse (off study)

Receiving maintenance
- Fit patient
  - Receiving lenalidomide
    - KPd
    - DVd
  - Receiving bortezomib
    - DRd
- Indolent relapse or frail patient
  - Receiving lenalidomide
    - DVd
    - ICd
  - Receiving bortezomib
    - IRd
    - DRd

Discontinued therapy/unmaintained
- Fit patient
- Indolent relapse or frail patient
  - KRd
  - DRd
  - IRd
  - ERd

\(^a\) ASCT is an option for select patients.

Consensus guidelines for salvage ASCT in RRMM  
(ASBMT, EBMT, BMT CTN, and IMWG)

1. In transplantation-eligible patients relapsing after primary therapy that did NOT include an autologous HCT, high-dose therapy with autologous HCT as part of salvage therapy should be considered standard.

2. High-dose therapy and autologous HCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HCT with initial remission duration of >18 months.

3. High-dose therapy and autologous HCT can be used as a bridging strategy to allogeneic HCT.
Conclusions for patients with early realapses

- Patients who received bortezomib-based regimens may be given RD-based triplets
  - For standard-risk patients: DaraRd shows the best results to-date
  - For high-risk patients: KRd, IRd, DaraRd
  - For bortezomib refractory patients: DaraRd, EloRd
  - For lenalidomide refractory patients: PomVd, DaraVd, Kd
  - For early relapsing patients: KRd but still not satisfactory for young patients; UNMET NEED

- Lenalidomide refractoriness is a considerable problem: PomVd gives the best results in this setting

- Salvage transplant maybe considered for patients with EFS >2 years after previous transplant; however this maybe >3 years for patients who receive lenalidomide maintenance

- Optimal sequencing is an important consideration for individual patient care
Thank you
Treatment of Patients Refractory to PIs and Lenalidomide

Jean Luc Harousseau
Institut de Cancérologie de l’Ouest
Intergroupe Francophone du Myélome
General considerations

- At each relapse remission duration decreases
- At each therapy a more resistant clone occurs
- BTZ/PI and Len are now used in frontline therapy: RVd, KRd, Rd, maintenance..
- BTZ/PI and Len refractory relapses occur earlier
- Cytotoxic combinations (DCEP, DT PACE, bendamustine-based) remain possible treatments in this situation

Keats JJ Blood 2012;120:1067
DEFINITION

- No response or Progressive disease during therapy or within 60 days after completion of last therapy \(^1\)

**BUT some questions**

- **For lenalidomide:** the dose of lenalidomide if progression (10mg as in maintenance or 25 mg as in induction)

- **For Bortezomib:** if no response when treatment is stopped for toxicity

- This information is not always available in reported results of treatment of RRMM

\(^1\) Rajkumar SV Blood 2011;117:4691
Clonal Evolution in MM

- During the evolution expansion of resistant clones that either existed before treatment or result of new alterations gained during therapy

- Branching model may explain the re-emergence of subclones that possibly retained sensitivity to previously used therapies

- **Refractory to a drug as last treatment**

Double Refractory Multiple Myeloma

- Retrospective analysis of 286 patients refractory to BTZ and were relapsed from, refractory to, or ineligible for IMiDs₁

- Initial response after relapsed/refractory criteria was met: **24%**
  - Response, including all subsequent therapies, was **32%**

- Median OS = **9 months**
- Median EFS = **5 months**
- These endpoints have been used as benchmarks for clinical trials for novel agents in this setting

Survival Outcomes

- Median (range), Months:
  - Overall survival 170/286, 9(7-11)
  - Event-free survival 217/286, 5(4-6)

Kumar et al, Leukemia 2012
Double refractory MM

- At least 3 lines of treatment
- Ref to Len or Pom and to Bort or Car (last 2 lines)
- 462 pts (who received at least 1 treatment after)
- RR to first treatment 12%
- 35 % if Pom or Car
- Med PFS 5m
- Med OS 15m

Kumar S Leukemia 2017
Can efficacy of Lenalidomide be restored in synergistic combinations? The REP regimen

- Len 25mg/D D1-21
- Cyclo 50mg/D
- PDN 20mg/d

<table>
<thead>
<tr>
<th></th>
<th>L-ref</th>
<th>L and B-ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>66</td>
<td>42</td>
</tr>
<tr>
<td>≥ PR</td>
<td>67%</td>
<td>60%</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>23%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Median PFS 12m OS 29m

Nijhoff S Blood 2016 :128 :2297
Can Bortezomib efficacy be restored in synergistic combinations

The role of Nelfinavir

Six 21 days cycles
Nelfinavir 2500mg D1-14
BTZ 1.3mg/m2 D1,4,8,11
Dex 20mg/D D 1-2, 4-5,8-9,11-12

- 34 BTZ-refractory patients
- Median number or prior lines 5
- 38% high-risk cytogenetic abnormalities
- Median PFS **12 weeks** (≥ PR)

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>11 (32%)</td>
<td>12 (36%)</td>
<td>10 (29%)</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (3%)</td>
<td>3 (9%)</td>
<td>2 (6%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (24%)</td>
<td>5 (15%)</td>
<td>6 (20%)</td>
<td>7 (23%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infections</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung infection</td>
<td>7 (21%)</td>
<td>1 (3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (3%)</td>
<td>3 (9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-hematological</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>8 (24%)</td>
<td>8 (10%)</td>
<td>2 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>4 (12%)</td>
<td>4 (12%)</td>
<td>8 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (9%)</td>
<td>5 (18%)</td>
<td>8 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>7 (21%)</td>
<td>3 (9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (12%)</td>
<td>8 (24%)</td>
<td>4 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>6 (18%)</td>
<td>5 (15%)</td>
<td>1 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (3%)</td>
<td></td>
<td></td>
<td></td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Driessen C Blood 2018 online
In pivotal randomized studies comparing Rd or Vd to triplets with one of these new agents patients refractory to Len or Bort were not included.
Is pomalidomide active in Len-refractory patients?
Randomized study comparing Pom-dex versus high-dose dex (MM003)

San Miguel JF et al Haematologica 2015;100:1334
Efficacy of Pomalidomide-Low dose Dexamethasone in refractory patients Stratus-MM010

- Median PFS in pts refractory to Len and Bort 4.2 months

Dimopoulos MA et al Blood 2016;128:497
## Pomalidomide-dex in RRMM
### The IFM experience (IFM 2009-02)

<table>
<thead>
<tr>
<th>Ref to LEN</th>
<th>N</th>
<th>RR(%)</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref to LEN last line</td>
<td>75</td>
<td>6</td>
<td>4.4</td>
</tr>
<tr>
<td>Ref to Bort</td>
<td>68</td>
<td>20</td>
<td>3.8</td>
</tr>
<tr>
<td>Double Ref</td>
<td>64</td>
<td>20</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Is Carfilzomib active in BTZ-refractory patients?

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>RR %</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (75% Bort-ref)</td>
<td>257</td>
<td>23.7</td>
<td>7.8m</td>
</tr>
<tr>
<td>Ref/or intol to B and L</td>
<td>214</td>
<td>20.1</td>
<td>7.4m</td>
</tr>
<tr>
<td>Ref to B and L</td>
<td>169</td>
<td>15.4</td>
<td><strong>7.8m</strong></td>
</tr>
</tbody>
</table>

Siegel  Blood 2012;120:2817
**Daratumumab monotherapy in RRMM**

- 148 pts treated in the GEN 501 and in the Sirius trials at the dose of 16mg/kg

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>RR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>148</td>
<td>31.1%</td>
</tr>
<tr>
<td>Ref to B and L</td>
<td>114</td>
<td>29.8%</td>
</tr>
<tr>
<td>Ref to B-L and P</td>
<td>70</td>
<td>27.1%</td>
</tr>
<tr>
<td>Ref to B-L and K</td>
<td>49</td>
<td>22.4%</td>
</tr>
</tbody>
</table>

Usmani SZ 2016;128:37
Pom-dex combinations

- + chemotherapy
  - cyclophosphamide
  - bendamustine
- + PI
  - Bortezomib
  - Carfilzomib
  - Ixazomib
- + antibodies
  - Daratumumab
  - Isatuximab
  - Elotuzumab
**Pomalidomide Cyclophosphamamide dex**

<table>
<thead>
<tr>
<th>Pom-dex</th>
<th>Pom-Cy-dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=36</td>
<td>N=34</td>
</tr>
<tr>
<td>Len-ref</td>
<td>100%</td>
</tr>
<tr>
<td>Bort-ref</td>
<td>78%</td>
</tr>
<tr>
<td>Carf-ref</td>
<td>44%</td>
</tr>
<tr>
<td>RR</td>
<td>39%</td>
</tr>
<tr>
<td>Med PFS</td>
<td>4.4m</td>
</tr>
</tbody>
</table>

**Phase ½ study**
- Pom 1-2.5 mg/d D1-21 Cyclo and PDN 50 mg every other day
- 69 pts (22 pts ref to L and B)
- MTD Pom 2.5 mg
- At the MTD
  - All pts (55) B and L ref (16)
  - ORR 51% 50%
  - Med PFS 10.4m (all pts)

Baz RC Blood 2016;27:2561
Larocca A Blood 2013;122:2799
Pomalidomide Bortezomib dex

PHASE 3 OPTIMISMM STUDY DESIGN

21-day cycles

RRMM
• 1-3 prior regimens, ≥2 cycles of LEN
• ECOG PS ≤ 2
• Prior BORT allowed (PD with 1.3 mg/m² twice weekly dose excluded)*
N = 559

Stratification
• Age (≤ 75 y vs > 75 y)
• Prior regimens (1 vs > 1)
• β2-microglobulin at screening
(<3.5 mg/L vs ≥3.5 to ≤5.5 mg/L vs >5.5 mg/L)

PVd (n = 281)
• POM
  4 mg D 1-14
• BORT
  1.3 mg/m² SC
  cycles 1-8: D 1, 4, 8, 11
  cycles 9+: D 1 and 8
  20 mg (<75 y) or 10 mg (>75 y)
  day of and day after BORT

LoDEX
• BORT
  1.3 mg/m² SC
  cycles 1-8: D 1, 4, 8, 11
  cycle 9+: D 1 and 8
• LoDEX
  20 mg (<75 y) or 10 mg (≥75 y)
  day of and day after BORT

Follow-up visit
28 days after Tx discontinuation
Tx discontinued due to PD
Tx discontinued prior to PD
Enter PFS follow-up period

PD or unacceptable toxicity

PD, subsequent antmyeloma Tx, and survival

LT follow-up

Study endpoints
• Primary: PFS
• Secondary: OS, ORR by IMWG criteria, DOR, safety
• Key exploratory: TTR, PFS2, efficacy analysis in subgroups

Data cutoff: October 26, 2017

* Patients with PD during therapy or within 60 days of the last dose of a prior corticosteroid therapy under the approved dosing schedule of 1.3 mg/m² twice weekly dose excluded. ** Primary evaluation every 71 days; 14 days until PD.

Richardson P ASCO 2018
PRIOR THERAPY (ITT)

- As per protocol, 100% of patients received prior treatment with LEN

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PVd (n = 281)</th>
<th>Vd (n = 278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median no. of prior lines of therapy (range)</td>
<td>2 (1-3)</td>
<td>2 (1-4)*</td>
</tr>
<tr>
<td>1 prior line, %</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>2 prior lines, %</td>
<td>42</td>
<td>37</td>
</tr>
<tr>
<td>≥ 3 prior lines, %</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Prior SCT, %</td>
<td>57</td>
<td>59</td>
</tr>
<tr>
<td>Prior LEN, %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>LEN-refractory, %</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>Refractory to LEN in last prior regimen, %</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>Prior PI, %</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>PI-refractory, %</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Prior BORT, %</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>BORT-refractory, %</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Refractory to last prior regimen, %</td>
<td>70</td>
<td>66</td>
</tr>
</tbody>
</table>

*One patient in the Vd arm received > 3 prior lines of therapy.
Pomalidomide Carfilzomib dex

Carf 27mg/M2 D1,2;8,9;15,16
Pom 4mg D 1-21 Dex 40mg/w

- 32 pts all refractory to L including 30 pts also ref to B

<table>
<thead>
<tr>
<th>Response category, n (%)</th>
<th>All evaluable patients, N = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>16 (50)</td>
</tr>
<tr>
<td>VGPR</td>
<td>5 (16)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (34)</td>
</tr>
<tr>
<td>MR</td>
<td>5 (16)</td>
</tr>
</tbody>
</table>

- 57 pts
  - MTD Carf 27mg/m2
  - In pts refractory to L and B
    - 71% ≥PR
    - 19% ≥ VGPR

- PFS 10.3 m

Shah JJ Blood 2015;126:2294
S Bringhen Leukemia 2018;32:1803

Med PFS 7.2 m
Pomalidomide Ixazomib Dex

Phase ½ Ixa 3mg or 4mg D1,8,15 28-d cycles
Pomalidomide 4mg D1-21
Dexamethasone (40mg D1,8 15, 22)

- 32 pts
  100% Len-ref (but 17 ≤ 15mg/d)
  59 % Bort-ref (Double-refractory 59%)
- 4mg recommended Phase 2 dose
- At this dose (25 pts) 48% ≥ PR and 20% VGPR
  but only 29% for 14 double-refractory pts
Dara Pom dex

- **Dara 16-mg/kg**
- **Pom 4mg D1-21**
- **Dex 40mg/W**

- 103 Pts Prior lines of therapy
- Median 3
- 71% refractory to both B and L

**Chari A Blood 2017;130:974**
Daratumumab-Carfilzomib-dexamethasone

- 85 pts (1-3 lines of Tt including B and L)
- 51 L-ref (60%)
- 25 PI and IMID ref (29%)

Dosing schedule (28-day cycles)

DARA:
- **Split first dose**: 8 mg/kg Days 1-2 of Cycle 1
- Single first dose: 16 mg/kg on C1D1
- 16 mg/kg IV QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter until PD

Carfilzomib:
- 20 mg/m² IV Cycle 1 Day 1
- Escalated to 70 mg/m² Cycle 1 Day 8+; **weekly (Days 1, 8, 15)** until PD

Dexamethasone:
- 40 mg/week (Days 1, 8, 15, 22) IV or PO until PD
Dara-Kd
Preliminary results (12 months f-up)

RR

PFS
An international, open-label, randomized, phase 2 trial (NCT02654132), with a 2-sided $\alpha=0.2$ and 85% power to detect a true HR of 0.57

ELOQUENT-3 Study Design

Primary
- PFS by investigator

Secondary
- Overall response rate (ORR)
- Overall survival (OS)

Exploratory
- Safety
- Duration of response (DOR)

Endpoints
Primary
- PFS by investigator

Secondary
- Overall response rate (ORR)
- Overall survival (OS)

Exploratory
- Safety
- Duration of response (DOR)

Cycles are 28 days

• 2 prior lines of therapy
• Refractory to last therapy
• Refractory or relapsed and refractory to lenalidomide and a proteasome inhibitor
• Prior pomalidomide

Follow-up every 4 weeks

Cycles 1-2
- Elotuzumab 10 mg/kg IV Weekly
- Pomalidomide 4 mg orally; Days 1–21
- Dexamethasone 40 mg$^a$ equivalent$^b$; weekly

Cycles 3+
- Elotuzumab 20 mg/kg IV Every 4
- Pomalidomide 4 mg orally; Days 1–21
- Dexamethasone 40 mg$^a$ orally; weekly

Cycles are 28 days

$^a$20 mg in patients aged >75 years (8 mg) doses on days with elotuzumab
$^b$Dexamethasone was split between oral (28 or 8 mg in patients aged ≤75 or >75 years) and IV
$^c$Follow-up continued until disease progression; follow-up for survival occurred at least every 12 weeks

HR, hazard ratio
ELOQUENT-3 Results

**Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EPd (n=60)</th>
<th>Pd (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>69 (43–81)</td>
<td>66 (36–81)</td>
</tr>
<tr>
<td>Prior lines of therapy, median (range)</td>
<td>3 (2–8)</td>
<td>3 (2–8)</td>
</tr>
<tr>
<td>Refractory to lenalidomide, n (%)</td>
<td>54 (90)</td>
<td>48 (84)</td>
</tr>
<tr>
<td>Refractory to a proteasome inhibitor, n (%)</td>
<td>47 (78)</td>
<td>47 (82)</td>
</tr>
<tr>
<td>Refractory to lenalidomide and a proteasome inhibitor, n (%)</td>
<td>41 (68)</td>
<td>41 (72)</td>
</tr>
</tbody>
</table>

**Graphs and Charts**

- **Bar Chart**: ORR and CR or sCR
  - ORR: 53% (Odds ratio: 3.25, 95% CI 1.49, 7.11, p=0.0029)
  - CR or sCR: 26%
  - CR: 8%
  - sCR: 2%

- **Survival Analysis**: Comparison of EPd and Pd with median PFS:
  - EPd: 10.3 mo
  - Pd: 4.7 mo

- **Log-Rank Test**: Comparison of ORR and CR or sCR between EPd and Pd

---

Dimopoulos MA EHA 2018
Triple combinations with Approved drugs in Dual-refractory MM

<table>
<thead>
<tr>
<th></th>
<th>Pom-dex</th>
<th>Pom-Cd</th>
<th>Pom-Kd</th>
<th>Dara-Pd</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ PR</td>
<td>20-35%</td>
<td>50%</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>7-8%</td>
<td>16%</td>
<td>17%</td>
<td>Med PFS</td>
</tr>
<tr>
<td>4m</td>
<td>9m ?</td>
<td>7m</td>
<td>8m</td>
<td></td>
</tr>
</tbody>
</table>

- With **Dara K-dex** and **Elo Pom-dex**
  median PFS of 10 to 12 m ?
- The choice depends on other relapse/patient characteristics **but mostly on drug availability**
Treatment of relapsed MM
What are the newer agents?

- Melflufen*
- Selinexor*
- Venetoclax*
- Nelfinavir*
- Anti PD1-PDL1
- Anti BCMA BITe Antibody drug conjugate
- Anttibody drug conjugate
- CAR-T*
- Vaccines*

Legend:
- IMiD, immunomodulatory drug
- HDAC inhibitor
- Monoclonal antibody
- Vaccines
- Checkpoint inhibitors
- IMiD: immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein; SiNE, selective inhibitor of nuclear export.
- *Not yet FDA-approved for MM; only available in clinical trials.
- †Treatments studied in MMRC trials.
Isatuximab Carfilzomib dex

- Phase 1b
- Increasing doses of Isa
- Car 27mg/m2
- 33 pts

Refractory disease at enrollment, %

<table>
<thead>
<tr>
<th>Refractory to IMiD</th>
<th>91%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Len (%)</td>
<td>82%</td>
</tr>
<tr>
<td>Pom (%)</td>
<td>52%</td>
</tr>
<tr>
<td>Refractory to Proteasome Inh (%)</td>
<td>85%</td>
</tr>
<tr>
<td>Bor/txaz (%)</td>
<td>64%</td>
</tr>
<tr>
<td>CFL (%)</td>
<td>30%</td>
</tr>
<tr>
<td>Double refractory (%)</td>
<td>79%</td>
</tr>
</tbody>
</table>

- Median PFS 10.3m

- ORR = 60.6%, CBR 84.6%; N = 33 - all patients
- ORR = 58% in double refractory; N = 26
- ORR = 71% in high risk cytogenetics/fish; N = 7
- ORR = 50% in CFL refractory; N = 10

Chari A ASCO 2018 Abs
Randomized Phase III studies with Isatuximab in RRMM

**Ph III Study of Isa + Pom/Dex in RRMM**

- **Patients with RRMM**: 82 prior lines of anti-myeloma therapy, which must include 82 consecutive cycles of Len and PI.
- **Randomization**: 1:1, N=600
- **Treatment**: Until progression or unacceptable toxicities
- **Primary endpoint**: PFS
- **Key secondary endpoints**: ORR, OS

**Ph III Study of Isa + Carfil/Dex in RRMM**

- **Patients with RRMM**: 1-3 prior lines of anti-myeloma therapy
- **Randomization**: 3:2, N=320
- **Treatment**: Until progression or unacceptable toxicities
- **Primary endpoint**: PFS
- **Key secondary endpoints**: ORR, OS

**Drug Details**

- **Isatuximab**: 10 mg/kg QW cycle 1 then QOW
- **Carfilzomib**: 20 mg/m² on Days 1 and 2 then 56 mg/m² on Days 8, 9, 16, and 16 of cycle 1 then 56 mg/m² on Days 1, 2, 8, 9, 15, and 18
- **Pomalidomide**: 4 mg on Days 1-21 of a 21-day cycle
- **Dexamethasone**: 40 mg (20 mg for 27.5 kg) on Day 1, 8, 15 and 22
Selinexor is the first-in-class of the Selective Inhibitor of Nuclear Export (SINE) which are XPO1 inhibitors.

XPO1 transport tumor-suppressor genes from the nucleus to the cytoplasm.
SELINEXOR
INITIAL RESULTS

Sd
Sel 80 mg po D 1,3,8,9,15,17
Dex 20mg same days
28-D cycles
- 79 pts
- med number of prior lines 7
- HR cytogenetics 50%

Quad Ref (B,K,L,P)
ORR 21%

Penta Ref (+Dara)
ORR 20%

Median duration of response 5m

Phase 1/2 SVd
Sel 100 mg po W
Bort 1.3 mg/m2 W
Dex 40 mg/W
- 40 pts including 19 pts refractory to PI and IMIDs

In PI and IMID ref pts
43% ORR 21%≥ VGPR

Vogl JCO 2018;36:859
Bahlis NJ Blood 2018, in press
<table>
<thead>
<tr>
<th></th>
<th>Sd</th>
<th></th>
<th></th>
<th>SVd</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>66%</td>
<td>8%</td>
<td>57%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>40%</td>
<td>4%</td>
<td>28%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38%</td>
<td>5%</td>
<td>36%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>48%</td>
<td>15%</td>
<td>45%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Appetite</td>
<td>47%</td>
<td>3%</td>
<td>57%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Thrombo</td>
<td>14%</td>
<td>59%</td>
<td>4%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>Cytopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stop Treatment</td>
<td>18%</td>
<td></td>
<td>19%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to AE</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Venetoclax

- Targets MM with high levels of BCL-2

- Sensitivity is restricted to t(11.14)

- However rationale for combining Venetoclax and PI (which target MCL-1)

- Encouraging results in combination with Bort and Carf in Bort-ref and double-ref

Moreau P Blood 2017;130:239  Costa L ASCO 2018
Venetoclax in t(11;14) MM

The response rate is the same in B-L refractory patients harboring t(11.14)

Touzeau Leukemia 2014;28:210
Kumar S Blood 2017;130:2401
Efficacy of Venetoclax is related to the BCL-2/BCL2L1 ratio

Kumar S Blood 2018
Targeting BCMA in MM

- B-cell Maturation antigen
- Is expressed on normal and MM PC
- New anti-BCMA Immunotherapies
  - Bispecific T-cell engagers (BiTE)
  - Antibody Drug Conjugate
  - Anti BCMA CAR T-cells
Anti BCMA Antibody Drug Conjugate

GSK-ADC: DREAMM1 Phase 2 Part 2:
- Results at 3.4 mg/kg IV Q3 Wk

ORR = 21/35 (60%; 95% CI: 42.1%, 76.1%)
* 1 sCR, 2 CR, 15 VGPR, 3 PR

89% Double refractory; 34% double + Dara refractory; Cyto High-risk 29%

Trudel et al. Ash 2017
bb2121 Anti-BCMA CAR T Cell Therapy in Patients With Relapsed/Refractory Multiple Myeloma: Updated Results From a Multicenter Phase I Study

**Tumor Response By Dose**

- sCR/CR: 33.3% (mDOR=1.9 mo)
- VGPR: 42.9
- PR: 7.1

- ORR=57.1%
- mDOR=10.8 mo

**Cytokine Release Syndrome By Dose Level**

- Maximum Toxicity Grade
- Dose Level

- 150 x 10^6 (n=18) 82%
- >150 x 10^6 (n=22) 50.0
- 150 x 10^6 (n=18) 22.7
- >150 x 10^6 (n=22) 22.2

- 150 x 10^6 (n=18) 82%
- >150 x 10^6 (n=22) 50.0
- 150 x 10^6 (n=18) 22.7
- >150 x 10^6 (n=22) 22.2

N Raje ASCO 2018
PROGRESSION-FREE SURVIVAL

- mPFS of 11.8 months at active doses (≥150 x 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

PFS at Inactive (50 x 10^6) and Active (150–800 x 10^6) Dose Levels

- mPFS = 11.8 mo
- mPFS = 2.7 mo

PFS in MRD-Negative Patients

- mPFS = 17.7 mo
- (5.8–NE)

Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. mPFS in dose escalation cohort.
Conclusions

- MM refractory to both Len and Bort occur earlier in the course of the disease
- Pomalidomide and Daratumumab-based combinations offer new possibilities
- The incidence of MM refractory to all IMIDs and PIs (quadri-refractory: Len, Bort, Pom, Carf) and even of penta-refractory (+ Dara) is increasing
- New approaches such as Selinexor, Venetoclax and anti-BCMA immunotherapy including CAR-T cells are being rapidly developed
Management of Side Effects
IMS Athens October 2018

Irit Avivi, Tel Aviv Medical center, TA
Agenda

Importance of recognizing and managing adverse events

Therapy related side effects

Management of therapy related adverse events
Introduction

During the last years, options for multiple myeloma have increased substantially, including IMiDs, PIs & MoABs.

The new drugs differ not only in their mode of action, but also in their toxicity profile, from previous standard treatments.
Adverse events profile

How does it affect our clinical decisions?

The treatment of Myeloma has currently become a "continues, non-ending therapy", a policy which requires the achievement of high tolerance to therapy.

Many drugs are oral and high tolerability is associated with better compliance, which results in improved outcome.

Recognition of AEs helps in choosing the right treatment to the right patient.

Recognition and early detection of AEs, would translate into an improved outcome.
Adverse Events
Case 1 (IMiDs)

A 55 yr old lady.

Prior Medical history

Obesity,

Breast Ca, 4 yrs earlier, treated with lumpectomy + radiotherapy and is currently receiving tamoxifen.

Treatment plan

VRD followed by ASCT and Lenalidomide maintenance.
Lenalidomide

IMiDs

“Real life Practice”
What do you tell your patient?

Decreased blood counts – 100%
Thrombosis – 100%
GI (Diarrhea) – 40%
SPMs – 30%
Fatigue – 20%
Rash – 20%
Infections – 10%
Lenalidomide

Less likely then thalidomide to cause Neuropathy, constipation and somnolence

First Trial

Grade ≥3 neutropenia - 26% with Rd18; 28% with continuous Rd
Grade ≥3 thrombocytopenia -8% of patients in either arm.

Non-hematological grade ≥3 AEs with Rd18:
Infections (22%),
Fatigue (9%),
Cardiac disorders (7%),
VTE (6%)

Facon T, Blood 2018
How are you going to thrombo-prophylax this patient?

A 65 year old lady.
Prior Medical history of breast Ca (currently in remission), Obesity.
Planned for VRD.

What would be your thromboprophylaxis?

Thromboprophylactic options
LMWH - 10%
LMWH during the first few cycles (disease control), followed by Aspirin -30%
Aspirin - 60%
Thrombosis prophylaxis (Palumbo A, 2008; Trepos 2017)

Thromboembolic events occur more frequently during the initial phase of treatment, less commonly in well-controlled disease or at relapse.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Patient and MM Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Related</strong></td>
<td>1 RF- Aspirin (81-325 mg/d)</td>
</tr>
<tr>
<td>Obesity</td>
<td>≥2 RF – LMWH (40/d; CCT&gt;30ml/min)</td>
</tr>
<tr>
<td>S/P VTE</td>
<td>Drug Related</td>
</tr>
<tr>
<td>Central Catheter or pacemaker</td>
<td>LMWH (CCT&gt;30ml/min)/ warfarin</td>
</tr>
<tr>
<td>Comorbidities: diabetes, infections, cardiac diseases, CRD, immobilization</td>
<td></td>
</tr>
<tr>
<td>Inherited thrombophilia</td>
<td>Myeloma related</td>
</tr>
<tr>
<td></td>
<td>Uncontrolled disease</td>
</tr>
</tbody>
</table>

**Drug Related**

- EPO, IMiDs, Doxo, MultiChemo,

New oral anticoagulants (NOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban, have been shown to be useful for initial and extended VTE treatment [48].
The patient was treated with RVD followed by ASCT, achieving VGPR.

She is considered now for lenalidomide maintenance therapy.

She is in complete remission of her breast CA for the last 4 years.

Would you give her lenalidomide maintenance?

Yes - 30%
No - 70%
Lenalidomide- Related SPMs

- An increase of hematologic plus solid tumor SPMs, notably AML and MDS, have been observed.
- A higher incidence of invasive SPM was not observed with LEN treatment until PD vs fixed-duration LEN.

<table>
<thead>
<tr>
<th>SPMs, %</th>
<th>NDMM</th>
<th>Following HDM/ASCT</th>
<th>RRMM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LEN + MEL</td>
<td>MEL</td>
<td>LEN Maint</td>
</tr>
<tr>
<td>Hematologic(^a)</td>
<td>5.3</td>
<td>1.3</td>
<td>7.5</td>
</tr>
<tr>
<td>AML and MDS</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hematologic + solid tumors(^b)</td>
<td>—</td>
<td>—</td>
<td>14.9</td>
</tr>
<tr>
<td>Nonmelanoma skin cancer(^c)</td>
<td>—</td>
<td>—</td>
<td>3.9</td>
</tr>
</tbody>
</table>
SPMs following HD Melphalan & transplantation

Attal, M JCO 2017; Attal NEJM 2012; McCarthy NEJM 2012; Palumbo NEJM 2014
LEN MAINTENANCE AFTER ASCT IN NDMM
META-ANALYSIS: SECOND PRIMARY MALIGNANCIES

- Time to PD or second-line therapy was longer with LEN maintenance vs placebo/observation
- The risk of developing PD was higher than the risk of developing an invasive SPM in both groups
Lenalidomid amd SPM - Unsorted Questions

No data regarding the risk of recurrence of prior malignancy in receiving lenalidomide

No data on risk of developing a cancer in a patients with a

No guidelines how to manage a patient that was diagnosed with cancer while being treated with lenalidomide
The patient was treated with lenalidomide maintenance therapy, 10 mg/day.

She felt very well, with almost no side effects for almost 24 months. However, she started to suffer from “diarrhea attacks” which significant impaired her quality of life.
Diarrhea

• Diarrhea is most frequently observed with bortezomib, ixazomib and lenalidomide.

• Diarrhea in general was rare in patients exposed to C-Rd (4%) or Rd18 (3%). (Facon T, Blood 2018).

• However, long-term therapy with lenalidomide may induce a specific form of diarrhea:

  **Bile salt malabsorption syndrome,**
  resulting from damage of the intestinal mucosa due to increased accumulation of bile acids in the small bowel [Pawlyn C, Blood 2014].
Diarrhea - Diagnosis and Management

Stool cultures + C Diff, ruling out infection

Diagnosis of bile salt malabsorption syndrome can be established by non-invasive selenium homocholic acid taurine (SeHCAT) scanning or supported by an improvement to treatment with bile acid binders such as colesevelam (Westergaad H, Gastroentrol 2007).

Treatment of bile salt malabsorption syndrome:
Reduced fat intake diet ( <20% of calories) and/or bile acid sequestrant, (colesevelam, up to 6×625mg in split doses with food) (Westergaad H, Gastroentrol 2007).

Supportive:
Active opioids, such as loperamide, deodorized tincture of opium, and a combination of diphenoxylate plus atropine (Andreyev HJ Gut 2012; Benson AB, JCO 2004).
Case 2
A 73 yr old man. Prior medical history of NIDDM, HT, IHD. Recently diagnosed with MM, planned for VCD

“Real life Practice”: What do you tell patients?
Bortezomib; Grade 3-4 AEs

APEX trial, Richardson P, 2005
Case 2 cont.

The patient has already completed 3 cycles of VCD, achieving a VGPR.

However, he is currently complaining on bilateral eye swelling and discomfort.

In addition, he developed a progressing burning pain in his legs. “On the other hand”, he is happy to report a significant improvement in his blood pressure that used to be high despite taking pills. “Sometimes, the blood pressure is even too low, resulting in lightheadness.”
**Bortezomib- Induced PNP**

- Among PIs, bortezomib was shown to induce severe PNP.
- Neurodegeneration occurs via a proteasome-independent mechanism, therefore not considered a class effect (Arastu –Kapur S, Clin Cancer Reserechm, 2011)

- BiPN is predominantly sensory, with prominent small fiber involvement

- May involve the autonomic nervous system, including orthostatic hypotension, suppressed heart rate variability, and delayed gastric emptying.

- IV administration of bortezomib leads to 10-fold higher peak plasma levels and to higher rates of BiPNP than subcutaneous administration.
- Subcutaneous administration, though preferable, still results in PNP

Ludwig H Leukemia 2018
Management of Bortezomib Induced PNP

BiPNP grade 1 with pain, or grade 2 - Bortezomib should be reduced to 1.0mg/m2 twice weekly or 1.3mg/m2 once per week.

BiPNP grade 2 with pain, or grade 3 - Withhold Tx until symptoms resolved. Treatment can be re-initiated at a dose of 0.7mg/m2 once per week.

Grade 4 - Treatment must be discontinued [30,31].
Treatment of Polyneuropathy

Still unsatisfactory

Painful polyneuropathy
Anti-convulsive agents (gabapentin and pergabalin), Antidepressants and Opioids (Palumbo A JCO 2014; Ludwig H, Leukemia 2014)

Topical pain medications include lidocaine and capsaicin (Stacey BR 2005).

Orthostatic dysregulation
Vasoconstrictor drugs, volume expansion, compression garments, and postural adjustment, together with reduction or discontinuation of any concomitant blood pressure lowering medication. Drugs such as midodrine, pyridostigmine, and fludrocortisone can be administered, and physical inactivity should be avoided (Figueroa JJ 2010)
Bortezomib induced Blepharitis

- Reported in up to 15% of Bortezomib treated patients
- Improves after stopping therapy
- Responds to local eye drops; AB in combination with steroids and/or oral doxycycline
Case 3 (Cont)

Bortezomib dose was reduced and the patient was treated with weekly bortezomib, 1mg/m², with no further deterioration in his neuropathy.

He felt generally well and stopped taking all pills you prescribed him when he started therapy.

He attend your clinic, complaining on a “new back pain”
Physical examination revealed a rash:
Herpes Zoster Prevention

Post-herpetic neuralgia is the most common morbidity associated with herpes zoster reactivation.

Herpes zoster infection reported in 3–13% of patients receiving bortezomib monotherapy [EPAR 2016].

Herpetic infections have also been patients receiving daratumumab, therefore, prevention of HZ in patients receiving PIs or daratumumab is mandatory [NCCN, Dec 2017].
**Prevention & Treatment of Herpes Zoster Infection**

- Present herpes zoster vaccines are live vaccines and controversy exists whether they can be offered to patients with well-controlled disease.
- As an alternative to live attenuated vaccines, which are contraindicated for immunocompromised individuals are heat-inactivated varicella zoster vaccines and recombinant subunit vaccines, both are being currently studied [Aaoro MS Eur J cancer 2011; Trepos Ehaematologica 2015;Anderson KC J Nat Comr Cancer Net 201664–66].

- In patients with HZ, Valaciclovir and penciclovir have greater bioavailability than acyclovir, making them preferable for outpatient treatment [Sampathkumar P, Mayo Clin Proc 2009].

- Valaciclovir was shown to significantly reduce the incidence of post-herpetic neuralgia in patients that experience HZ, [MacFarlane LL, JANFP 1998], though, randomized controlled trials comparing various agents are not available.
Case 3

A 55 year old lady,

Started pomalidomide dexamethasone quite recently due to relapsed myeloma. Attended clinic due to the development of mild rash on her arms.
Severe Skin Reactions [Van de Donk, Cancer Mang res 2012].

- Severe skin reactions are most common with all IMiDs or ixazomib.

- **Limited, localized rash** - antihistamines or topical steroids are recommended.

- **Mild but extensive rash** - a short course of low-dose prednisone

- **Grade 2/3 skin rash** - treatment should be discontinued and reinstated in case of complete resolution.

- Rarely, severe skin reactions such as Steven–Johnson syndrome or even TDN

- In such severe cases, treatment should be permanently discontinued.
  - [EPAR 2015; EPAR 2017; FDA 2016].

- For lenalidomide, desensitization with progressively increased doses and dosing frequencies to reach a target dose of 10mg/day has been proposed [Lee MJBH 2014].

- Patients experiencing skin reactions during thalidomide should not receive lenalidomide or in case of limited alternatives, should be started at a low dose [EPAR Oct 2017; FDA 2017].
Case 4

A 76 year old
MM since 2011
Treated with VCD followed by ASCT, achieving durable response, lasting for almost 5 years.
He was then treated with Rd, but has recently developed disease relapse, for which was started on carfilzomib-cytoxan and dexamethasone.

Prior Medical history is unremarkable except of hypertension
Carfilzomib
“Real life Practice”
What do you tell your patient?

Thrombocytopenia - 100%
HZ reactivation
Cardiac Toxicity - 80%
HT - 60%
GI (Diarrhea)
Fatigue
Infections
Dyspnea
Carfilzomib

Carfilzomib is generally well tolerated.

The most commonly reported ADRs are Anemia, Fatigue, Diarrhea, Thrombocytopenia, Nausea, Pyrexia, Dyspnea, Respiratory tract infection, Cough, Peripheral edema
## Carfilzomib related Cardio Vascular Toxicity

### Eligibility and Cardiovascular Risk Factors in Phase 3, R/R MM Studies

|        | ASPIRE (N = 792)
|--------|----------------|
|        | KRd vs Rd      | ENDEAVOR (N = 929)
|        | Kd56 vs Vd    | FOCUS (N = 315)
|        | K vs BSC      |

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>Uncontrolled hypertension excluded</th>
<th>Uncontrolled hypertension not excluded</th>
<th>Randomized K vs BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF not specified</td>
<td>LVEF ≥ 40%</td>
<td>LVEF ≥ 40%</td>
<td></td>
</tr>
</tbody>
</table>

### EXCLUSIONS

- MI within 4 months prior to randomization
- NYHA Class III or IV heart failure
- Uncontrolled angina or history of severe CAD
- SSS, uncontrolled V arrhythmias, conduction abnormalities
- MI in the previous 4 months
- NYHA Class III or IV heart failure
- Symptomatic ischemia or uncontrolled conduction abnormalities
- MI in the previous 3 months
- NYHA Class III or IV heart failure
- Congestive heart failure

<table>
<thead>
<tr>
<th>Renal function</th>
<th>CrCl ≥ 50 mL/min</th>
<th>CrCl ≥ 15 mL/min</th>
<th>CrCl ≥ 15 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>20/27 mg/m2 infused over 10 min</td>
<td>20/56 mg/m2 infused over 30 min</td>
<td>20/27 mg/m2 infused , 10 min</td>
</tr>
<tr>
<td>Duration</td>
<td>K fixed: up to 18 cycles Rd to progression or toxicity</td>
<td>Kd to progression or toxicity</td>
<td>K to progression or toxicity</td>
</tr>
</tbody>
</table>
## Carfilzomib -Related Cardiac Toxicities

<table>
<thead>
<tr>
<th>Carfilzomib Dose (mg/m²)*</th>
<th>ASPIRE&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ENDEAVOR&lt;sup&gt;2&lt;/sup&gt;</th>
<th>FOCUS&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20/27</td>
<td>20/56</td>
<td>20/27</td>
</tr>
<tr>
<td>Safety Population</td>
<td>KRd n = 396</td>
<td>Rd n = 389</td>
<td>Kd56 n = 463</td>
</tr>
<tr>
<td></td>
<td>Vd n = 456</td>
<td></td>
<td>Vd n = 456</td>
</tr>
<tr>
<td></td>
<td>K n = 157</td>
<td></td>
<td>Control n = 153</td>
</tr>
<tr>
<td>Duration, median weeks</td>
<td>72</td>
<td>57</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Relative dose intensity for proteasome inhibitor</td>
<td>94%</td>
<td>NA</td>
<td>91%</td>
</tr>
<tr>
<td><strong>AEs of interest†, any grade, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>7.1</td>
<td>4.1</td>
<td>10.8</td>
</tr>
<tr>
<td></td>
<td>3.3</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17.1</td>
<td>8.7</td>
<td>32.2</td>
</tr>
<tr>
<td></td>
<td>14.5</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>6.9</td>
<td>4.6</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>AEs of interest†, grade ≥ 3, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>4.3</td>
<td>2.1</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.4</td>
<td>2.3</td>
<td>14.5</td>
</tr>
<tr>
<td></td>
<td>3.3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>3.8</td>
<td>2.3</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
The patient, a 76 year old gentleman, was started on Carfilzomib 20/27+ dexamethasone 20 mg/w, after being refractory to both bortezomib & lenalidomide-based combinations.

He completed 1 cycle of therapy, achieving a very good response, before being admitted to E.R, complaining on shortness of breath. Physical examination revealed an increased BP (160/85), dyspnea (26 breaths/min) and wet crepitation on both lungs. Echocardiogram showed globally decreased LVEF ≈40%. Blood count was normal (HB-12) and chemistry was also within the normal range.

What would do next?
- Stop and restart therapy if EF has improved
- Stop and switch to other drugs
Cardiac Toxicity

• Hypertension – Most common cardiac AE. Mostly after infusion.

• Mechanism is not fully defined.
• Carfilzomib affects endothelial cells and is associated with an acute rise in NT-proBNP [Pawlyn C Blood 2014].

• Reductions in left ventricular ejection fraction were mostly reversible.

• The utility of echocardiography and blood cardiac markers as a predictive tool for cardiac events are limited [Chari A Blood 2016, abst 2142].
How to reduce the Risk of CardioVascular Events?

**Prior to Treatment**

Identify patients at greater risk for CHF: Age>75

A known pre-existing cardiac disease

Risk minimization measures:
- Control hypertension prior to starting carfilzomib treatment (<140)

Plan fluid management:
- Oral: 30 mL fluid per kg at least 48 hours before Cycle 1, Day 1
- IV: 250–500mL fluid prior to each dose in Cycle 1
- Adjust total fluid intake as clinically appropriate in patients with baseline or risk of cardiac failure

**During Treatment**

Monitor blood pressure:
- Regular blood pressure measured in all patients

Monitor for evidence of volume overload:
- Monitor patients for evidence of volume overload and adjust as clinically appropriate, especially patients at risk for cardiac failure
How to reduce the Risk of CardioVascular Events and how to manage them ?(II)

• Before administration, BP should be tightly controlled: <140mmHg.
• Adherence to 30-min infusion time is recommended.
• Shortening infusion time after 1/2 cycle to 10min can be considered [Nijhof IS Blood 2016].
• In case of grade 3-4 cardiac events, carfilzomib should be interrupted until recovery.
• Carfilzomib may be restarted >2 weeks after patient recovery (with a complete resolution of cardiac complication), employing a reduced dose after a thorough benefit/risk assessment [Tacchetti P Am J Hem 2011; Dimopoulos MA Eur J Hematol 2011].
• The patient should be assessed for fluid overload [Nijhof IS Blood 2016].

• Currently, no clear dose effect on cardiac toxicity was demonstrated
• Starting with a lower dose in patients aged >75 years and in those with a history of mild cardiac disease is recommended.
Case 6

A 76 year old gentleman, planned for single agent Daratumumab, being already refractory now to Lenalidomide, bortezomib and Carfilzomib.

Planned for single agent daratumumab
### Daratumumab
**ALCYONE (MMY3007) Safety: Most Common TEAEs**

<table>
<thead>
<tr>
<th></th>
<th>VMP (n = 354)</th>
<th>D-VMP (n = 346)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td><strong>Hematologic, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>186 (53)</td>
<td>137 (39)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>190 (54)</td>
<td>133 (38)</td>
</tr>
<tr>
<td>Anemia</td>
<td>133 (38)</td>
<td>70 (20)</td>
</tr>
<tr>
<td><strong>Nonhematologic, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>121 (34)</td>
<td>14 (4)</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>URTI</td>
<td>170 (48)</td>
<td>52 (15)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>49 (14)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>87 (25)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>74 (21)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>76 (22)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17 (5)</td>
<td>14 (4)</td>
</tr>
<tr>
<td>Second primary cancer</td>
<td>9 (2.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Any infusion-related reaction</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

- IRR- in 50%
- Mostly in 1\textsuperscript{st} infusion
- Grade 3-4 IRR to D – 5%
- 1.4% and 0.9% of patients receiving VMP and D-VMP, respectively, discontinued treatment due to infection
- 5 (1.4%) patients discontinued daratumumab due to IRRs
## Incidence of IRRs in Patients Treated with Daratumumab IV and SC

### Patients
<table>
<thead>
<tr>
<th>IV Dose</th>
<th>SC Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEN501¹</td>
<td>GEN503²</td>
</tr>
<tr>
<td>N=42</td>
<td>N=32</td>
</tr>
<tr>
<td>POLLUX³</td>
<td>CASTOR⁴</td>
</tr>
<tr>
<td>N=283</td>
<td>N=243</td>
</tr>
<tr>
<td>SIRIUS⁵</td>
<td>PAVO⁶</td>
</tr>
<tr>
<td>N=106</td>
<td>N=25</td>
</tr>
</tbody>
</table>

### Patient Population
- R/R to ≥2 prior therapies
- R/R to ≥1 prior therapy

### Dose
- Daratumumab 16 mg/kg IV
- Daratumumab 1,800 mg SC

### Incidence of Infusion Related Reactions

<table>
<thead>
<tr>
<th>Daratumumab Studies</th>
<th>Incidence of Infusion Related Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEN501</td>
<td>71%</td>
</tr>
<tr>
<td>GEN503</td>
<td>56%</td>
</tr>
<tr>
<td>POLLUX</td>
<td>48%</td>
</tr>
<tr>
<td>CASTOR</td>
<td>45%</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>42%</td>
</tr>
<tr>
<td>PAVO</td>
<td>16%</td>
</tr>
</tbody>
</table>

Daratumumab (Cont)

Daratumumab interferes with blood group serological testing, it binds to CD38 on RBC and results in a positive indirect antiglobulin test.

Being an IgGk Ab, it may interfere with M protein assessment in patients with an IgGk.

It may also with interfere with EUROFLOW MRD assessment, as it binds to CD38-positive residual MM cells.
Management of IRR

Elotuzumab and daratumumab, are both IgG1κ isotype Abs. IRR – reported in 10% of patients receiving 20mg/kg of elotuzumab, all grade 1-2 [89].

Single-agent daratumumab resulted in IRR in 45%, with only few grade 3 [90].

For both drugs, prophylactic measures are recommended:
• IV 100mg methylprednisolone, ~1h before daratumumab infusion,
• Oral antipyretic (paracetamol 650–1000mg),
• Oral or IV antihistamine (diphenhydramine 25–50mg).
• Post-infusion treatment with 20mg methylprednisolone for 2 days following infusion.

• Special precautions need to be taken in patients with pre-existing COPD.
• Premedication with 10mg montelukast, an oral leukotriene receptor antagonist, 30min before daratumumab should be considered as well as post-infusion
Management of IRR (Cont)

- The infusion should be interrupted at any grade/severity.
- If grade 1–2 IRR occurs, the infusion may be resumed at half the rate at which it occurred, provided the patient is stabilized;
- In case of no recurrence of IRR, escalation can be resumed.
- If grade 3 IRR occurs, once IRR decreases to grade ≤2, the infusion may be restarted at no more than half the rate at which the IRR occurred.
- If no recurrence of IRR, escalation can be resumed.
- Patients have to discontinue daratumumab therapy in case of grade 4 (life threatening) IRRs at first or subsequent infusion.
Case 7

A 66 year old lady, followed in the hematology division since 2015, due to SMM
Recently diagnosed with MM, and is currently receiving VRD.

She attended day care due to fever, cough and shortness of breath, reporting runny nose and cough which started 4 days earlier
CXR showed lobar pneumonia.
**Vaccines**

What do you recommend a newly diagnosed pt with HR SMM?

- No recommendations unless planned to start Anti MM Tx shortly - 30%
- Anti -Herpes Zoster vaccine only - 0%
- Anti Flu vaccine only - 50%
- Anti Flu vaccine to the pt and her caregivers - 10%
- Anti Pneumococcal (1?/2?) vaccine only - 0%
- Anti Flu+ Anti Pneumococcal - 10%
Recommendations for Vaccination

- Patients should be vaccinated against influenza virus, pneumococci, and haemophilus influenzae.

- A trivalent/ quadrivalent influenza vaccine should be used in patients and caregivers.

- Vaccination against pneumococci should be started with a 13-valent vaccine (PCV13) and followed at least 8 weeks later by a dose of PCV23 (23 valent polysaccharide conjugate) [Musto P, NJH 1995].

- Response to vaccines frequently is suboptimal

- Repeated vaccinations with the same influenza vaccine may enhance anti-vaccine Ab [CDC 2016].

- Ideally, patients should already be vaccinated in the premalignant state; MGUS or SMM or, when feasible, during periods of optimal disease control.
Case 7

A 32 year old lady, 27th week first pregnancy

Diagnosed with Myeloma, presenting with lytic lesions in her ribs and sternum, in the presence of 60% PCs in BM.
Teratogenicity

Almost all novel agents and backbone agents showed a certain embryo-fetal risk, especially the thalidomide analogs of the IMiD group, but also Pis.

Pregnancy must be excluded before start of treatment. Women of reproductive potential and their partners should be informed about the embryo-fetal risk of the respective drugs and about adequate contraceptive measures.

In case of diagnosis of MM during pregnancy, steroids or Cytoxan-steroids, or VAD are all optional.
Conclusions

- A number of novel drugs have recently been introduced in the treatment of multiple myeloma.

- These drugs differ in their mode of action and their side effect and safety profile.

- Knowledge of their potential risks and of established measures to prevent occurrence of complications is essential for preventing severe symptoms, dose reductions, and/or treatment discontinuations.
Thanks and best wishes for good health!
IMS – Educational Workshop Athens

How to make the right choices in the relapsed patients?

Case report

Josip Batinić; MD
University Hospital Centre Zagreb, Croatia
Patient born in 1953, male

- medical history: at 20 years of age - vertebral fracture Th12-L4
- August 2008 diagnosed with multiple myeloma kappa light chains
- Osteolytic lesions of lumbar vertebra
- DS IIIA, ISS II
- Induction therapy: 4 cycles of VAD (vincristine, adriamycin, dexamethasone)
- March 2009 autologus HSCT
- Response: CR

- Hb 112 g/L
- L 5.3x10e9/L
- Creatinin 93 µmol/L
- Ca 2.3 mmol/L
- sFLC: kappa 5300 mg/L; lambda 350 mg/L
- Kappa/lambda 15.14
- IgG 6.3; IgA 2.7; IgM 0.6 g/L
- Albumin 33 g/L
- Beta2 microglobulin 4.8 mg/L
- Bone marrow: 48% plasma cells
- X-ray: multiple osteolyses
Patient born in 1953, male – MM kappa light chains

- December 2012 - biochemical relapse: sFLC kappa 800 mg/L
- No end organ damage
- Maintenance therapy with dexamethasone 40 mg weekly
- February 2013 – IFE: hypogammaglobulinemia, sFLC kappa 92.0 mg/L

- December 2015 - neck pain and pain in left hip, no neurological deficite
  - sFLC (mg/L): kappa 664.0, lambda 8.87; kappa/lambda 74.86
- Bone marrow: no plasma cell infiltration
- Soft tissue tumor in the right clavicular region - cytology: plasma and proplasma cells – extramedullary relaps
Patient born in 1953, male – MM kappa light chains

MSCT: pathological fracture of atlas, with soft tissue tumor paravertebrally, lytic lesions of right condile of occipital bone
Patient born in 1953, male – MM kappa light chains

- 2\textsuperscript{nd} line therapy: CyBorDex (cyclophosphamide 500 mg weekly, dexamethasone 40 mg iv weekly, bortezomib 1.6 mg/m\textsuperscript{2} weekly) + local irradiation (30 Gy /10 fractions)
- Reevaluation after 4 cycles – partial regression of soft tissue lesions on CT scan
- Continued with chemotherapy with 4 cycles of CyBorDex protocol

- sFLC(mg/L): kappa 160.00; lambda 8.24; kappa/lambda 19.4; sIF: monoclonal light chain kappa
- Adverse effects: peripheral neuropathy (gr. I-II)

- 2\textsuperscript{nd} autologous HSCT recommended – patient refused at that time
Patient born in 1953, male – MM kappa light chains

- January 2017 – sFLC (mg/L): kappa 1470.00, lambda 14.20 kappa/lambda 103.52
- IF (serum and urin) monoclonal light chains kappa

- MSCT (Feb 2017): anterior mediastinum, paravertebraly 2 nodal soft tissue lesions: 2.3x1.4cm and 3x1.2cm; posterior mediastinum soft tissue tumor 5.6 x 1.3 cm; accidental finding: subacute pulmonary embolism

- 3rd line therapy: IRd (ixazomib, lenalidomide, dexamethasone) + local radiotherapy: TD 30Gy/10 fractions
- September 2017 – sFLC (mg/L): kappa 60.5, lambda 16.6; kappa/lambda 3.64
- IF (serum and urine): normal (hypogammaglobulinemia)
- Received 16 cycles IRd; adverse effect: worsening of peripheral neuropathy (gr. II-III)
Patient born in 1953, male – MM kappa light chains

- August 2018 MSCT: no change in the size of preexisting soft tissue tumors BUT new soft tissue tumors (VII rib right 5x3cm; VIII rib left 6x4cm)
- sFLC (mg/L): kappa 63.0, lambda 15.4; kappa/lambda 4.09; IF (serum and urine): normal (hypogammaglobulinemia)
- Progression!? 

- What to do next?
  - Rd + cyclophosphamide?
  - Pomalidomide? – available
  - MP +/- PI or IMID?
  - 2nd autologous HSCT – after/if acheive response…
Thank You for Your attention
Controversial cases with emphasis on local practice
Case presentation

Dr Eirini Katodritou
Hematologist, Director,
Theagenion Cancer Hospital,
Thessaloniki Greece
Real-world data on OS in the era of novel agents

Overall survival: 4 periods

- Median OS
- 5-year OS

4 Periods
- <2000
- 2001-2005
- 2006-2010
- 2011-2017

Cumulative survival

p < 0.001

no = 827

Katodritou E, et al. Theagenion database
Case 1: a success story

- **Diagnosis October 2010**
  - 61 year old female, IgA\(\lambda\) symptomatic MM (advanced bone disease, moderate anemia), standard risk MM (FISH), ISS1, RISS1, Bence Jones (-), 45% BM monoclonal plasma cells, absence of clonal PCs in the peripheral blood

- **1st line therapy:** VD+ ASCT: response CR.
- **Maintenance:** dexamethasone 20mg x 2 years
- Zoledronic acid 4mg/mo x 2 years

- **Relapse April 2017**

- **2nd line treatment:** DRd: CR documented in 8 months. Currently at cycle 14, in CR
  - PFS: 79 mo
  - OS: 93 months

Theagenion Database: standard risk pts who underwent ASCT (34%): median PFS: 52mo
Median OS: 124 mo
Case 2: The dark side of the moon...

- **Diagnosis November 2014**
  - 64 year old male
  - IgAκ MM, standard risk (FISH including 1q+), normal karyotype, ISS1, RISS1, LDH normal
  - anemia (Hb: 9.5g/dL)
  - WBXR: lytic lesion right femur, 11th thoracic vertebra collapse
  - 48% BM monoclonal plasma cells, no PCs in the peripheral blood

- **1st line treatment:**
  - VCD + ASCT

**Response:**

- vgPR
- MRD (MFC): 0.36%, CD45 dim/-, CD38/138 (+), CD19 (-), CD56(+)

- **Maintenance:** Dexamethasone 20mg/wk
  (Len maintenance was not approved at that time)

- Zoledronic acid 4mg/mo
Case 2

- **Relapse May 2017 (PFS: 31mo)**
  - Gradual increase of M-Component (4.5g/dL), moderate anemia (Hb: 11g/dL)
  - Bence Jones (-)
  - Repeat FISH for Del 17p and 1q+: both neg
  - Spine and pelvis MRI were normal

Bone marrow biopsy: 90% clonal PCs CD38/CD138+, CD19(-), CD56+, c-myc (-)

MFC:
1) old clone CD45dim/-, CD19-, CD56+
2) new clone CD45(+)bright, CD19+, CD56+

A. Papanikolaou with permission
Case 2

- **2nd line therapy (May 2017)**
  - KRd
    - M-component after 1 cycle 80% reduction
    - CR documented after 6 months. MRD (-)
    - Continue treatment
    - side effects (bradycardia, no signs of cardiac failure)
  - **After 13 cycles (June 2018)**
    - He presented complaining about strong pain in the hip joint and the pelvis.
    - A CT scan and an MRI of the hip and pelvis revealed a large soft tissue mass surrounding the iliac bone without evidence of cortical disruption

- **A restaging was performed**
  - Bone marrow aspiration and trephine: negative
  - SPE/IFE: inconspicuous M-component/ IgA, FLCR: normal, Bence Jones (+) (κ light chain: 0.3g/24h)
Case 2

MFC 2018: 1% Polyclonal PCs in the bone marrow
PET-CT at relapse

Multiple hypermetabolic foci throughout the skeleton, most of them without corresponding bone lysis (medullary lesions).

Extramedullary foci involving the liver, lungs, pleura, lymph nodes (thoracic and abdominal), peritoneum and carvenous sinus

Large gluteal mass (surrounding the iliac bone without cortical erosion) (Suv_max 21.2)
Gluteal mass biopsy*

H&E

CD138

C-myc (+) > 50%

Clgκ+

MIB-1 ~100%

*CD56 (-) CD19/20 (-)

A. Papanikolaou with permission
Iliac bone biopsy

H&E

C-MYC -> 30%

CD138

MYC 8q24 break apart (FISH)

A. Papanikolaou with permission
Case summary

- Extramedullary relapse
- Absence of BM infiltration (bone marrow aspiration, MFC, and biopsy)
- Recognition of at least 3 different subclones during the course of the disease (clonal evolution):
  - In the bone marrow
    - A typical CD45dim/CD138/38+, CD19-/CD56+ clone
    - An additional CD45bright/CD19+/CD56+ clone at relapse (c-myc expression: negative)
  - In the soft tissue and iliac biopsy
    - CD138/38+, CD19-/CD56- (MIB-1 100%, c-myc expression >50%)

What would be the best treatment option for a patient relapsing with aggressive extramedullary disease who is Len and PI refractory?
- PomDex?
- Daratumumab-monotherapy_clinical trial (DaraPomDex)?
- Conventional chemo?
Case 2 outcome

- The patient was treated with
  - PomDex 1 cycle and 1 cycle DCEP: no response, disease progressed rapidly
- He deceased 3 months after relapse from disease progression and multiorgan failure
- OS: 45mo
Discussion

- The incidence of extramedullary relapse ranges from 6-20% (inconsistencies in the definition that confuse the true incidence)
- The most common sides of EMD at relapse: liver and pleura (Infiltration was evident in 40% of post mortal liver autopsy)
- Soft tissues may have different origins:
  1) Direct growth from bone lesions by disrupting the cortical bone
  2) hematogenous dissemination (escape phenomenon)
  3) triggered by previous surgical procedures.
- EMD is associated with shorter survival

### Biological characteristics of extramedullary myeloma

<table>
<thead>
<tr>
<th>Biologic mechanism</th>
<th>Characteristics of extramedullary multiple myeloma lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>High plasma cell proliferation</td>
<td>Overexpression of MIB-1</td>
</tr>
<tr>
<td>Compromise of production of heavy chains</td>
<td>Light chain escape</td>
</tr>
<tr>
<td>Adhesion molecules</td>
<td>Down regulation of CD56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genetic changes</th>
<th>Genetic mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overexpression of CD44</td>
<td>P53 deletion</td>
</tr>
<tr>
<td>CCND1 overexpression</td>
<td>RAS mutations</td>
</tr>
<tr>
<td>Deletion of chromosome 13</td>
<td>Overexpression of angiopoietin 1, notch 3, fibronectin 1</td>
</tr>
<tr>
<td>Increased CD31 and endoglin protein expression</td>
<td></td>
</tr>
</tbody>
</table>

Has the incidence of extramedullary disease increased in the modern therapeutic era?

Different patterns of relapse after autologous peripheral blood stem cell transplantation in multiple myeloma: clinical results of 280 cases from the Spanish Registry

EMD: 7.5%

EMD: 14%

EMD in 9 patients treated with Thal-based regimens: PCs detected in the soft tissue displayed anaplastic morphology and were CD56 (-)

Has the incidence of extramedullary disease increased in the modern therapeutic era?

Incidence and clinical features of extramedullary multiple myeloma in patients who underwent stem cell transplantation

Development of extramedullary myeloma in the era of novel agents: no evidence of increased risk with lenalidomide–bortezomib combinations

Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients

C-myc in MM

- C-myc is expressed in about 2/3 of MM patients but not in MGUS
- Its activation is involved in secondary genetic events leading to the transition from MGUS to MM
- C-myc overexpression correlates with high PC proliferative rate (high Ki67 expression) and shorter OS
1) The combination of novel agents lead to suppression of more benign clones and the emergence of highly aggressive drug resistant clones that have the capacity to migrate outside BM microenvironment.

2) Novel drugs induce better disease control and prolong OS leading indirectly to high risk progressive disease (i.e. extramedullary disease).

3) Increased use of advanced imaging allows higher sensitivity in detecting extramedullary masses.

4) EMD at diagnosis is a strong predictor for EMD at relapse suggesting that Inherent disease characteristics (preexisting aggressive subclones) may lead to the development of extramedullary disease rather than the exposition to novel agents.
Questions

- Do next generation novel agents correlate with the development of extramedullary disease?
- Are there any reliable biomarkers that could predict extramedullary disease?
- Could monitoring with advanced imaging be helpful for early recognition of extramedullary relapse?
- What are the exact mechanisms of hematogenous spread?
- What is the best treatment approach for these patients?
Thank you
Multiple extramedullary plasmacytoma (?)

Artur Jurczyszyn  MD, PhD, Assoc. Prof.
Department of Hematology
Jagiellonian University Medical College

ATHENES, October 26-27 2018
CASE REPORT

- 54 y old woman
- **no medical history**
- **medications**: iron supplements 2x 0,5y in the past
- **PMH**:
  - mild anemia
  - tuberculosis (1992)- TB treatment completed
- **allergies**: tramadol, penicillin
- **addictives**: cigarettes- av. 5/d yet; 10/d overall
- **FH**
  - mother: G-B disease
  - sister: G-B disease
  - son: asthma, atopic dermatitis, food allergy
- **gynecologic history**: regular cycles; periods 4-5d, moderate blood loss; G3, P3
- **occupation**: nurse
CC/HPI

[01/2016] **sacral region**: small pea-sized cohesive **lump** with red aerola

[05/2016] hospital in Dębica – **surgical removal** of skin lump

**hist-pat**: diffused infiltration with plasma-cell line cells,

- CD3(-), CD20(-), kappa(-), lambda(+), CD138(+), CD56(+), CD30(-),
- CD123(-), ALK(-), Ki67-50%

**EXTRAOSSEUS PLASMACYTOMA**

[05/07/2016] Department of Hematology, University Hospital in Krakow
IHC - lambda
Fot. Grzegorz Dyduch MD, PhD
### Lab tests

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>2.32 mmol/l</td>
<td>[2.15 - 2.55]</td>
</tr>
<tr>
<td>Iron</td>
<td>4.00 umol/l</td>
<td>[5.83 - 34.50]</td>
</tr>
<tr>
<td>Ferritin</td>
<td>5 ug/l</td>
<td>[13 - 400]</td>
</tr>
<tr>
<td>TIBC</td>
<td>85.80 umol/l</td>
<td>[40.80 - 76.60]</td>
</tr>
<tr>
<td>Creatinin</td>
<td>64.0 umol/l</td>
<td>[44 - 80]</td>
</tr>
<tr>
<td>eGFR (MDRD)</td>
<td>&gt; 60 ml/min/1.73m²</td>
<td>&gt; 60</td>
</tr>
<tr>
<td>Protein</td>
<td>70.0 g/l</td>
<td>[66.0 - 87.0]</td>
</tr>
<tr>
<td>Albumin</td>
<td>43.00 g/l</td>
<td>[35.00 - 52.00]</td>
</tr>
<tr>
<td>LDH</td>
<td>392 U/l</td>
<td>[240 - 480]</td>
</tr>
<tr>
<td>APTT</td>
<td>34.2 sec</td>
<td>[26.0 - 36.0]</td>
</tr>
<tr>
<td>INR</td>
<td>1.01</td>
<td>[0.90 - 1.20]</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>3.7 g/l</td>
<td>[1.8 - 3.5]</td>
</tr>
<tr>
<td>CRP</td>
<td>2.33 mg/l</td>
<td>&lt; 5.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunofixacja</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA</td>
<td>3.87 g/l</td>
<td>[0.70 - 4.00]</td>
</tr>
<tr>
<td>IgG</td>
<td>8.09 g/l</td>
<td>[6.38 - 17.00]</td>
</tr>
<tr>
<td>IgM</td>
<td>1.16 g/l</td>
<td>[0.40 - 2.30]</td>
</tr>
<tr>
<td>κ</td>
<td>12.90 mg/l</td>
<td>[6.70 - 22.40]</td>
</tr>
<tr>
<td>λ</td>
<td>19.20 mg/l</td>
<td>[8.30 - 27.00]</td>
</tr>
<tr>
<td>κ/λ</td>
<td>0.6719</td>
<td>[0.31 - 1.56]</td>
</tr>
<tr>
<td>β2m</td>
<td>2.03 mg/L</td>
<td>[1.09 - 2.53]</td>
</tr>
</tbody>
</table>

**IFE:** poorly isolated monoclonal IgAλ with triple zone- 1 in β fraction, other in γ fraction
## Lab tests

<table>
<thead>
<tr>
<th>SPE</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumins %</td>
<td>50,30 % [60,00 - 71,00]</td>
</tr>
<tr>
<td>α-1 globulins %</td>
<td>3,60 % [1,40 - 2,90]</td>
</tr>
<tr>
<td>α-2 globulins %</td>
<td>14,80 % [7,00 - 11,00]</td>
</tr>
<tr>
<td>β-globulins %</td>
<td>15,50 % [8,00 - 13,00]</td>
</tr>
<tr>
<td>γ-globulins %</td>
<td>15,80 % [9,00 - 16,00]</td>
</tr>
<tr>
<td>Albumins</td>
<td>35,21 g/l [35,00 - 55,00]</td>
</tr>
<tr>
<td>α-1 globulins</td>
<td>2,52 g/l [0,90 - 2,10]</td>
</tr>
<tr>
<td>α-2 globulins</td>
<td>10,36 g/l [5,00 - 7,90]</td>
</tr>
<tr>
<td>β-globulins</td>
<td>10,85 g/l [5,70 - 7,90]</td>
</tr>
<tr>
<td>γ-globulins</td>
<td>11,06 g/l [6,50 - 11,50]</td>
</tr>
<tr>
<td>A/G</td>
<td>1,01</td>
</tr>
</tbody>
</table>

## Cytogenetics

- plasma cells: 3,3%
- no CD138 positive segregation

## Myelogram

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metamyelocytes</td>
<td>5,3%</td>
<td>8,0 - 25,0</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>24,5%</td>
<td>11,0 - 20,0</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0,0%</td>
<td>0,4 - 1,0</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>18,3%</td>
<td>3,0 - 12,0</td>
</tr>
<tr>
<td>Plasmablasts</td>
<td>0,0%</td>
<td>0,0</td>
</tr>
<tr>
<td>Plasma cells</td>
<td>3,3%</td>
<td>0,2 - 2,0</td>
</tr>
<tr>
<td>Megakaryocytes</td>
<td>0,0%</td>
<td>0,01 - 0,40</td>
</tr>
<tr>
<td>Granulocytes/Erythrocytes</td>
<td>3,4:1</td>
<td>3:1 - 4:1</td>
</tr>
</tbody>
</table>

## Trephine biopsy

- cellularity: 40-60%
- IHC: CD138(+), kappa(+), lambda(+) – 4-5%
- no histological evidence of neoplastic plasma cells
IHC – lambda
Fot. Łukasz Chmura MD
[27/07/2016] Department of Nuclear Medicine, Oncology Centre in Bydgoszcz

PET/CT

- **right sciatic tuber**: osteolytic lesion 9mm; *SUV 2.9*
- **ascending colon**: mass-like lesion infiltrating the colon wall 39x13x42 mm; *SUV 4.12*

**EXTRAOSSEUS FOCUS**
or **SIMULTANEOUS PRIMARY COLON MALIGNANCY ???**
Fot. Bodan Małkowski MD, PhD
THERAPY & results

[08/09/2016] Hospital in Dębica; General Surgery Ward – right hemicolecotomy

hist-pat: EXTRAOSSTEUS PLASMACYTOMA infiltrating the muscular layer of the colon wall, focally- serous membrane; no angioinvasion; surgical margins clear

[11-12/2016] rth VMAT - total dose of 50 Gy/25 fractions

[02/2017] hematological CR

| Calcium   | 2,34 mmol/l | [2,15 - 2,55] |
| Iron      | 25,30 umol/l | [5,83 - 34,50] |
| Ferritin  | 30 ug/l     | [13 - 400]    |
| Creatinin | 70,0 umol/l | [44 - 80]     |
| Protein   | 63,0 g/l    | [66,0 - 87,0] |
| Albumin   | 44,00 g/l   | [35,00 - 52,00] |
| LDH       | 302 U/l     | [240 - 480]   |
| CRP       | <1 mg/l     | [< 5,00]      |

IgA        | 2,79 g/l | [0,70 - 4,00] |
IgG        | 8,34 g/l | [6,38 - 17,00] |
IgM        | 1,34 g/l | [0,40 - 2,30] |
K          | 19,20 mg/l | [6,70 - 22,40] |
L          | 17,10 mg/l | [8,30 - 27,00] |
K/λ        | 1,1228 | [0,31 - 1,56] |
K urine    | 7,570 mg/l | [< 7,300] |
L urine    | < 3,690 mg/l | [< 4,000] |
## THERAPY & results

<table>
<thead>
<tr>
<th>SPE</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Albumins %</td>
<td>54,60 %</td>
<td>[60,00 - 71,00]</td>
</tr>
<tr>
<td>α-1 globulins %</td>
<td>2,90 %</td>
<td>[1,40 - 2,90]</td>
</tr>
<tr>
<td>α-2 globulins %</td>
<td>13,20 %</td>
<td>[7,00 - 11,00]</td>
</tr>
<tr>
<td>β-globulins %</td>
<td>13,40 %</td>
<td>[8,00 - 13,00]</td>
</tr>
<tr>
<td>γ-globulins %</td>
<td>15,90 %</td>
<td>[9,00 - 16,00]</td>
</tr>
<tr>
<td>Albumins</td>
<td>37,13 g/l</td>
<td>[35,00 - 55,00]</td>
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<tr>
<td>α-1 globulins</td>
<td>1,97 g/l</td>
<td>[0,90 - 2,10]</td>
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<tr>
<td>α-2 globulins</td>
<td>8,98 g/l</td>
<td>[5,00 - 7,90]</td>
</tr>
<tr>
<td>β-globulins</td>
<td>9,11 g/l</td>
<td>[5,70 - 7,90]</td>
</tr>
<tr>
<td>γ-globulins</td>
<td>10,81 g/l</td>
<td>[6,50 - 11,50]</td>
</tr>
<tr>
<td>A/G</td>
<td>1,2</td>
<td></td>
</tr>
</tbody>
</table>

[02/2017] **disqualification from auto-PBSCT**

return to work
PET/CT

- **sternum**: inferior part, left side, at the level of 4th rib attachment increased 18F-FET uptake sized 11x9mm; *SUV 3,64*

- **left 4th rib**: *SUV 2,94*

- **right sciatic tuber**: osteolytic lesion 16x17mm; *SUV 2,27 (↓activity)*

**RECURRENCE**
Fot. Bodan Małkowski MD, PhD
F, 54Y
CURRENT STUDY 2017-03-01
CT WB 3.0 eFoV [3] | PET WB
--> AQ1:A1 | AQ1:F1
PET*PETCT_WB_FET (Adult)
2017-03-01 | 2017-03-01
15:08:56 | 15:10:03
IMA ~126 | IMA ~168
SP H538,3 | SP H538,3

Fot. Bodan Małkowski MD, PhD
Fot. Bodan Małkowski MD, PhD
THERAPY & results

[20/03/2017] start of chemotherapy VTD (She received 6 cycles) + LMWH + biphosphonate + antiviral prophylaxis

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
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<tbody>
<tr>
<td>IgA</td>
<td>2.88 g/l</td>
<td>[0.70 - 4.00]</td>
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<tr>
<td>IgG</td>
<td>9.05 g/l</td>
<td>[6.38 - 17.00]</td>
</tr>
<tr>
<td>IgM</td>
<td>1.21 g/l</td>
<td>[0.40 - 2.30]</td>
</tr>
<tr>
<td>κ FLC</td>
<td>21.70 mg/l</td>
<td>[3.30 - 19.40]</td>
</tr>
<tr>
<td>λ FLC</td>
<td>27.00 mg/l</td>
<td>[5.71 - 26.30]</td>
</tr>
<tr>
<td>κ/λ</td>
<td>0.8037</td>
<td>[0.26 - 1.65]</td>
</tr>
<tr>
<td>β2m</td>
<td>1.84 mg/l</td>
<td>[1.09 - 2.53]</td>
</tr>
</tbody>
</table>

IFE: trace of IgA

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>κ urine</td>
<td>&lt; 6,690 mg/l</td>
<td>[ &lt; 7,300]</td>
</tr>
<tr>
<td>λ urine</td>
<td>&lt; 3,690 mg/l</td>
<td>[ &lt; 4,000]</td>
</tr>
</tbody>
</table>

SPE

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
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<tbody>
<tr>
<td>Albumins %</td>
<td>59.40 %</td>
<td>[60.00 - 71.00]</td>
</tr>
<tr>
<td>α-1 globulins %</td>
<td>2.60 %</td>
<td>[1.40 - 2.90]</td>
</tr>
<tr>
<td>α-2 globulins %</td>
<td>12.20 %</td>
<td>[7.00 - 11.00]</td>
</tr>
<tr>
<td>β-globulins %</td>
<td>11.60 %</td>
<td>[8.00 - 13.00]</td>
</tr>
<tr>
<td>γ-globulins %</td>
<td>14.20 %</td>
<td>[9.00 - 16.00]</td>
</tr>
<tr>
<td>Albumins</td>
<td>43.48 g/l</td>
<td>[35.00 - 55.00]</td>
</tr>
<tr>
<td>α-1 globulins</td>
<td>1.90 g/l</td>
<td>[0.90 - 2.10]</td>
</tr>
<tr>
<td>α-2 globulins</td>
<td>8.93 g/l</td>
<td>[5.00 - 7.90]</td>
</tr>
<tr>
<td>β-globulins</td>
<td>8.49 g/l</td>
<td>[5.70 - 7.90]</td>
</tr>
<tr>
<td>γ-globulins</td>
<td>10.39 g/l</td>
<td>[6.50 - 11.50]</td>
</tr>
<tr>
<td>A/G</td>
<td>1.46</td>
<td></td>
</tr>
</tbody>
</table>
THERAPY & results

[10/04/2017] signs of peripheral polyneuropathy → pregabalin

| IgA   | 1,07 g/l | [0,70 - 4,00] |
| IgG   | 6,21 g/l | [6,38 - 17,00] |
| IgM   | 0,88 g/l | [0,40 - 2,30] |
| κ FLC | 20,10 mg/l | [3,30 - 19,40] |
| λ FLC | 14,20 mg/l | [5,71 - 26,30] |
| κ/λ   | 1,4155   | [0,26 - 1,65] |

IFE: negative

[05/07/2017] Department of Nuclear Medicine, Oncology Centre in Bydgoszcz

PET/CT

- 4th rib: moderately increased 18F-FET uptake sized 11mm; SUV 2,43 (↓)
- right sciatic tuber: osteolytic lesion 16x17mm; SUV 1,8 (↓)

WITHOUT ACTIVE PROLIFERATIVE PROCESS

[> 09/2017] preparation for auto-PBSCT; after 6 cycles VTD

Tandem auto-PBSCT - November 2017 and April 2018
July 2018 - consolidation 1 cycle VDT-PACE; October 2018 - CR
Fot. Bodan Małkowski MD, PhD
F, 54Y
CURRENT STUDY 2017-03-01
CT WB 3.0 eFoV [3] | PET WB
PET*PETCT,WB,FET (Adult)
2017-03-01 | 2017-03-01
15:08:56 | 15:10:03
3 IMA - 165 | 4 IMA - 219
SP H384,9 | SP H384,9

Fot. Bodan Małkowski MD, PhD
DISCUSSION

What is the exact diagnosis?
Multiple extramedullary plasmacytomas or...?

What is the best treatment?
Combination chemotherapy was started with melphalan, dexamethasone, and thalidomide. The patient has shown a very good response to chemotherapy even after 2 cycles. A total of 12 cycles were given. Currently the patient is maintaining well.
High Dose Therapy with Autologous Stem Cell Transplantation for Solitary Bone Plasmacytoma Complicated by Local Relapse or Isolated Distant Recurrence

MELETIOS A. DIMOPOULOS\textsuperscript{a,}\textsuperscript{*}, CHRISTOS PAPADIMITRIOU\textsuperscript{a}, ATHANASSIOS ANAGNOSTOPOULOS\textsuperscript{a}, DIMITRIOS MITSIBOUNAS\textsuperscript{a} and JEAN-PAUL FERMAND\textsuperscript{b}

\textsuperscript{a}Department of Clinical Therapeutics, University of Athens, School of Medicine, Athens, Greece; \textsuperscript{b}Department of Immuno-Hematology, Hospital Saint-Louis, Paris, France

(Received 10 July 2002)

We report three patients with solitary bone plasmacytoma (SBP) who developed either local recurrence within the radiotherapy field or an isolated distal recurrence and who were treated with high dose therapy supported by autologous stem cell transplantation. All patients remain without evidence of disease for 4–10 years after the procedure. High dose therapy may be of value and require further study in patients with SBP who develop local or distant failure.
Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma

Most patients with plasma cell neoplasia have generalized disease at diagnosis, i.e. multiple myeloma (MM). However, a minority (<5%) of patients with plasma cell malignancies present with either a single bone lesion, or less commonly, a soft tissue mass, of monoclonal plasma cells: solitary bone plasmacytoma (SBP) or extramedullary plasmacytoma (SEP). SBP has a high risk of progression to MM and on magnetic resonance imaging (MRI) examination at least 25% of patients

**Solitary bone plasmacytoma**

**Context**

Epidemiology and clinical features. Solitary bone plasmacytoma has a male:female ratio of 2:1, with a median age of 55 years and primarily affects the axial skeleton especially the vertebrae (see Table II) (Dimopoulos et al, 2000). Malignant bone

- It is recommended that SBP is treated with **radical radiotherapy** with a margin of at least 2 cm and treating to a dose of 40 Gy in 20 fractions. (grade B recommendation, level III evidence)

- Patients not responding to radiotherapy should be treated with **chemotherapy**. A suggested approach is to follow guidelines for the treatment of MM. In younger patients, this would include **high dose therapy and ASCT** (grade C, level IV)

- Surgery is contra-indicated in the absence of structural compromise or neurological compromise (grade C, level IV evidence).

Soutar et al., Br J Haematol. 2004; 124(6)
Waldenström’s Macroglobulinemia

Steve Treon MD, PhD
Bing Center for Waldenstrom’s Macroglobulinemia
Dana Farber Cancer Institute
Harvard Medical School
17th International Workshop on MM
Boston, USA - September 12-14, 2018
www.imw2019boston.org
Manifestations of WM Disease

≤20% at diagnosis; 50-60% at relapse.

Bone Marrow
↓Hb>>> ↓PLT> ↓WBC

Bing Neel Syndrome

Hyperviscosity Syndrome:
Epistaxis, Headaches
Impaired vision
>6,000 mg/dL or >4.0 CP

Cold Agglutinemia (5%)
Cryoglobulinemia (10%)
IgM Neuropathy (22%)
Amyloidosis (10-15%)

Hepcidin
↓Fe Anemia

NCCN Guidelines for Initiation of Therapy in WM

- Hb ≤10 g/dL on basis of disease
- PLT <100,000 mm³ on basis of disease
- Symptomatic hyperviscosity
- Moderate/severe peripheral neuropathy
- Symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, amyloid.

# Primary Therapy of WM with Rituximab

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR</th>
<th>VGPR/CR</th>
<th>TTP (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab x 4</td>
<td>25-30%</td>
<td>0-5%</td>
<td>13</td>
</tr>
<tr>
<td>Rituximab x 8</td>
<td>40-45%</td>
<td>5-10%</td>
<td>16-22</td>
</tr>
<tr>
<td>Rituximab/thalidomide</td>
<td>70%</td>
<td>10%</td>
<td>30</td>
</tr>
<tr>
<td>Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, CDR</td>
<td>70-80%</td>
<td>20-25%</td>
<td>30-36</td>
</tr>
<tr>
<td>Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R</td>
<td>70-90%</td>
<td>20-30%</td>
<td>36-62</td>
</tr>
<tr>
<td>Rituximab/Proteasome Inhibitor i.e. BDR, VR, CaRD</td>
<td>70-90%</td>
<td>20-40%</td>
<td>42-66</td>
</tr>
<tr>
<td>Rituximab/bendamustine</td>
<td>90%</td>
<td>30-40%</td>
<td>69</td>
</tr>
</tbody>
</table>

Reviewed in Dimopoulos et al, Blood 2014; 124(9):1404-11; Treon et al, Blood 2015; How I Treat WM
I don’t know what the references for this are.

tristin.abair, 6/6/2011
Rituximab induced IgM Flare in WM Patients

*P* denotes patient-required plasmapheresis for hyperviscosity.

Nucleoside Analogues in WM

- Risk of Transformation or MDS/AML is 10-15%;
- Risk of secondary malignant events in 1/3 patients with FCR;
- Stem cell collection impacted by nucleoside analogues: avoid in ASCT candidates;
- Consider Impact on future therapy (Bendamustine);
- **Role in CNS Disease (Bing Neel Syndrome)**

Cyclophosphamide-Based Therapy

- CDR (Cyclophosphamide, Dex, Rituximab) widely used.
- Adriamycin and vincristine may be dispensed as they not appear to impact response rates or PFS and are associated with more toxicity.
- ORR to CDR is 83%; Major RR 74%.
- Median PFS is 3 years. (Without maintenance)

Bendamustine-R in WM

- German STiL Study

![Graph showing survival rates]

- Prolonged cytopenias >4 cycles
- Secondary MDS/AML 5-8%

- Mayo Study: 2 yr PFS 88% vs. 61% for Benda-R vs. CDR

# Proteasome Inhibitor Therapy in Frontline WM

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>ORR</th>
<th>Major RR</th>
<th>PFS</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>VR</td>
<td>88%</td>
<td>66%</td>
<td>75% PFS at 1 yr.</td>
<td>No</td>
</tr>
<tr>
<td>BDR</td>
<td>96%</td>
<td>83%</td>
<td>66 mos</td>
<td>Yes</td>
</tr>
<tr>
<td>BORT ➔ BDR</td>
<td>85%</td>
<td>68%</td>
<td>42 mos</td>
<td>No</td>
</tr>
<tr>
<td>CaRD</td>
<td>81%</td>
<td>71%</td>
<td>46 mos.</td>
<td>Yes</td>
</tr>
<tr>
<td>IDR</td>
<td>96%</td>
<td>77%</td>
<td>&gt;22 mos.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>GRADE 1,2</th>
<th>GRADE ≥3</th>
<th>PI-DISCONTINUED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2X WEEK BORT</strong></td>
<td>40-70%</td>
<td>20-30%*</td>
<td>20-30%</td>
</tr>
<tr>
<td><strong>1X WEEK BORT</strong></td>
<td>20-40%</td>
<td>5-20%</td>
<td>10-20%</td>
</tr>
<tr>
<td><strong>CaRD</strong></td>
<td>20%</td>
<td>0%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td><strong>IDR</strong></td>
<td>15%</td>
<td>3%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

Discovery of the MYD88 Mutation in WM -2012-
## MYD88 L265P in WM/IGM MGUS
>50 confirmatory studies

<table>
<thead>
<tr>
<th>Study</th>
<th>METHOD</th>
<th>TISSUE</th>
<th>WM</th>
<th>IGM MGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treon</td>
<td>WGS/Sanger</td>
<td>BM CD19⁺</td>
<td>91%</td>
<td>10%</td>
</tr>
<tr>
<td>Xu</td>
<td>AS-PCR</td>
<td>BM CD19⁺</td>
<td>93%</td>
<td>54%</td>
</tr>
<tr>
<td>Gachard</td>
<td>PCR</td>
<td>BM</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>Varettoni</td>
<td>AS-PCR</td>
<td>BM</td>
<td>100%</td>
<td>47%</td>
</tr>
<tr>
<td>Landgren</td>
<td>Sanger</td>
<td>BM</td>
<td></td>
<td>54%</td>
</tr>
<tr>
<td>Jiminez</td>
<td>AS-PCR</td>
<td>BM</td>
<td>86%</td>
<td>87%</td>
</tr>
<tr>
<td>Poulain</td>
<td>PCR</td>
<td>BM CD19⁺</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Argentou</td>
<td>PCR-RFLP</td>
<td>BM</td>
<td>92%</td>
<td>1/1 MGUS</td>
</tr>
<tr>
<td>Willenbacher</td>
<td>Sanger</td>
<td>BM</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>Mori</td>
<td>AS-PCR/BSiE1</td>
<td>BM</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Ondrejka</td>
<td>AS-PCR</td>
<td>BM</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Ansell</td>
<td>WES/AS-PCR</td>
<td>BM</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>Patkar</td>
<td>AS-PCR</td>
<td>BM</td>
<td>85%</td>
<td></td>
</tr>
</tbody>
</table>
MYD88 L265P by AS-PCR can help distinguish WM from overlapping entities

Xu et al, Blood 2013
Pro-Survival Signaling Driven by Mutated MYD88 in Waldenström's Macroglobulinemia

Yang et al, Blood 2013
Yang et al, Blood 2016
Hunter et al, Blood 2014
Hunter et al, J CO 2017
Guerrera et al, Haematologica 2018
LYMPHOID NEOPLASIA

The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis

Zachary R. Hunter,1,2 Lian Xu,1 Guang Yang,1 Yangsheng Zhou,1 Xia Liu,1 Yang Cao,1 Robert J. Manning,1 Christina Tripas,1 Christopher J. Patterson,1 Patricia Sheehy,1 and Steven P. Treon1,3

1Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; 2Department of Pathology and Laboratory Medicine, Boston University School of Graduate Medical Sciences, Boston, MA; and 3Harvard Medical School, Boston, MA

Key Points

- Highly recurring mutations are present in WM, including MYD88 L265P, warts, hypogammaglobulinemia, infection, and myelokathexis-syndrome–like mutations in CXCR4, and ARID1A.
- Small, previously undetected CNAs affecting B-cell regulatory genes are highly prevalent in WM.

The genetic basis for Waldenström macroglobulinemia (WM) remains to be clarified. Although 6q losses are commonly present, recurring gene losses in this region remain to be defined. We therefore performed whole genome sequencing (WGS) in 30 WM patients, which included germline/tumor sequencing for 10 patients. Validated somatic mutations occurring in >10% of patients included MYD88, CXCR4, and ARID1A that were present in 90%, 27%, and 17% of patients, respectively, and included the activating mutation L265P in MYD88 and warts, hypogammaglobulinemia, infection, and myelokathexis-syndrome–like mutations in CXCR4 that previously have only been described in the germline. WGS also delineated copy number alterations (CNAs) and structural variants in the 10 paired patients. The CXCR4 and CNA findings were validated in independent expansion cohorts of 147 and 30 WM patients, respectively. Validated gene losses due to CNAs involved PRDM2 (93%), BTG1 (87%), HIVEP2 (77%), MKL1 (77%), PLEKHG1 (70%), LYN (60%), ARID1B (50%), and FOXP1 (37%). Losses in PLEKHG1, HIVEP2, ARID1B, and BCLAF1 constituted the most common deletions within chromosome 6. Although no recurrent translocations were observed, in 2 patients deletions in 6q corresponded with translocation events. These studies evidence highly recurring somatic events, and provide a genomic basis for understanding the pathogenesis of WM. (Blood. 2014;123(11):1637-1646)
WHIM-like CXCR4 mutations in Waldenstrom’s Macroglobulinemia

- 25-40% of WM patients
- Receptor for CXCL12
- Higher incidence in MYD88 mutated patients
- > 40 types of Nonsense and Frameshift Mutations
- Nonsense mutations associated with high serum IgM levels.
- Promotes in vitro drug resistance through AKT and ERK activation.

Multicenter study of Ibrutinib in Relapsed/Refractory WM (≥1 prior therapy)

Screening

Registration

420 mg po qD Ibrutinib

Progressive Disease (PD) or Unacceptable Toxicity

Stop Ibrutinib

Event Monitoring

Stable Disease or Response Continue

Event Monitoring

✔ MYD88, CXCR4 Mutation Status

NCT01614821
## Baseline Characteristics for Study Participants (n=63)

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>63</td>
<td>44-86</td>
</tr>
<tr>
<td><strong>Prior therapies</strong></td>
<td>2</td>
<td>1-9</td>
</tr>
<tr>
<td><strong>Refractory to prior therapy</strong></td>
<td>25 (40%)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Hemoglobin (mg/dL)</strong></td>
<td>10.5</td>
<td>8.2-13.8</td>
</tr>
<tr>
<td><strong>Serum IgM (mg/dL)</strong></td>
<td>3,520</td>
<td>724-8,390</td>
</tr>
<tr>
<td><strong>B₂M (mg/dL)</strong></td>
<td>3.9</td>
<td>1.3-14.2</td>
</tr>
<tr>
<td><strong>BM Involvement (%)</strong></td>
<td>60</td>
<td>3-95</td>
</tr>
<tr>
<td><strong>Adenopathy &gt;1.5 cm</strong></td>
<td>37 (59%)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Splenomegaly &gt;15 cm</strong></td>
<td>7 (11%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Treon et al, NEJM 372: 1430, 2015
# Updated Clinical Responses to Ibrutinib

ORR: 91% (No change)  Major RR ($\geq$ PR): 73→78%

<table>
<thead>
<tr>
<th></th>
<th>(N=)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VGPR</strong></td>
<td>10→18</td>
<td>16%→29%</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>36→31</td>
<td>57%→49%</td>
</tr>
<tr>
<td><strong>MR</strong></td>
<td>11→8</td>
<td>17%→13%</td>
</tr>
</tbody>
</table>

Median time to $\geq$ MR: 4 weeks  
Median time to $\geq$ PR or better: 8 weeks  

Data cutoff: December, 2017  
Median time on treatment: 47 months  

Treon et al, N Engl J Med. 2015; EHA 2018
Responses to ibrutinib are impacted by MYD88 (L265P and non-L265P) and CXCR4 mutations.

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>MYD88\textsuperscript{Mut}</th>
<th>MYD88\textsuperscript{Mut}</th>
<th>MYD88\textsuperscript{WT}</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=</td>
<td>63</td>
<td>36</td>
<td>21</td>
<td>5*</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>91%</td>
<td>100%</td>
<td>85.7%</td>
<td>60%</td>
<td>0.005</td>
</tr>
<tr>
<td>Major (&gt;PR)</td>
<td>78%</td>
<td>97%</td>
<td>67%</td>
<td>0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VGPR</td>
<td>29%</td>
<td>44%</td>
<td>10%</td>
<td>0%</td>
<td>0.007</td>
</tr>
<tr>
<td>Time to Minor Response</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Time to Major Response</td>
<td>2.0</td>
<td>2.0</td>
<td>6.0</td>
<td>N/A</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*2 patients at initial reporting with major responses were discovered subsequently to have MYD88 mutated disease (S243N, L265P). One patient at initial reporting was subsequently found to CXCR4 mutated disease upon genotyping of CD19-selected WM cells.
Ibrutinib in Previously Treated WM: Updated PFS

5 year PFS: 60% (95% CI 46-71%).

Data cutoff: December, 2017
Ibrutinib Related Adverse Events in previously treated WM patients

Original Study

Toxicities >1 patient; N=63

- Neutropenia
- Anemia
- Thrombocytopenia
- Arrhythmia
- Lung Infection
- Skin Infection
- Diarrhea
- Post-procedure bleed
- Epistaxis
- Dehydration
- Pre/Syncope
- Hypertension
- Mucositis

Update on Adverse Events (Grade >2) in >5% of patients: Neutropenia (22%); Thrombocytopenia (14%), Pneumonia (9%); GERD (8%); Hypertension (8%); anemia (6%); and skin infection (5%). Seven patients (11%) had atrial arrhythmia [Grade 1 (n=1); Grade 2 (n=5); Grade 3 (n=1)], and 6 continued ibrutinib following medical management.
Ibrutinib Monotherapy in Symptomatic Treatment Naive WM

Screening
Registration
420 mg po qD Ibrutinib

Progressive Disease (PD) or Unacceptable Toxicity
Stop Ibrutinib
Event Monitoring

Stable Disease or Response Continue
Event Monitoring

✔ MYD88, CXCR4 Mutation Status

NCT02604511
Treon et al, JCO 2018
Time to and depth of response to ibrutinib are impacted by CXCR4 mutations.

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>MYD88\textsuperscript{MUT} CXCR4\textsuperscript{WT}</th>
<th>MYD88\textsuperscript{MUT} CXCR4\textsuperscript{MUT}</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=</td>
<td>30</td>
<td>16</td>
<td>14</td>
<td>N/A</td>
</tr>
<tr>
<td>Overall Response Rate-no. (%)</td>
<td>30 (100%)</td>
<td>16 (100%)</td>
<td>14 (100%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Major Response Rate-no. (%)</td>
<td>25 (83%)</td>
<td>15 (94%)</td>
<td>10 (71%)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**Categorical responses**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>MYD88\textsuperscript{MUT} CXCR4\textsuperscript{WT}</th>
<th>MYD88\textsuperscript{MUT} CXCR4\textsuperscript{MUT}</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor responses-no. (%)</td>
<td>5 (17%)</td>
<td>1 (6%)</td>
<td>4 (29%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Partial responses-no. (%)</td>
<td>19 (63%)</td>
<td>10 (63%)</td>
<td>9 (64%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Very good partial responses-no. (%)</td>
<td>6 (20%)</td>
<td>5 (31%)</td>
<td>1 (7%)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

**Median time to response (months)**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>MYD88\textsuperscript{MUT} CXCR4\textsuperscript{WT}</th>
<th>MYD88\textsuperscript{MUT} CXCR4\textsuperscript{MUT}</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor response (≥Minor response)</td>
<td>1.0</td>
<td>0.9</td>
<td>1.7</td>
<td>0.07</td>
</tr>
<tr>
<td>Major response (≥Partial response)</td>
<td>1.9</td>
<td>1.8</td>
<td>7.3</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data cutoff: Jan. 22, 2018  Median f/u: 14.6 (range 1.8-21.6 months)
## Adverse Events (>5%)

<table>
<thead>
<tr>
<th>Event or Abnormality</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total Grades 2-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Bruising</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (7%)</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>

- Minimal hematological toxicity
- Median serum IgA levels decreased from 62 to 39 mg/dL; p=0.04
- Median serum IgG levels declined from 563 to 462; p=0.003
- Afib medically managed in 2 patients who continue on treatment; cardiac ablation for one patient with left atrial enlargement off treatment.
Ibrutinib Monotherapy in Frontline WM: PFS

18 mo: PFS 92%; All patients alive.

PD patients were both CXCR4 mutated.

Data cutoff: Jan. 22, 2018

Median f/u: 14.6 (range 1.8-21.6 months)
Ibrutinib (560 mg/day) induced response in a WM patient with Bing Neel Syndrome

Mason et al, BJH 2016
Other BTK Inhibitors

• **Acalabrutinib:** BID dosed; Phase II Study Reported.

• **Zanubrutinib:** BID dosed; Phase I/II Study Reported, Phase III randomized study is ongoing.

• **Vecabrutinib:** Non-covalent inhibitor that binds to a different site from other BTK inhibitors; use in resistant disease due to BTK mutations; study ongoing.
Strategies to Enhance BTK Inhibitors in WM
ARM B: Placebo + Rituximab 375mg/m² x 8 infusions (weeks 1, 2, 3, 4, 17, 18, 19, and 20)

ARM A: ibrutinib 420mg + Rituximab 375mg/m² x 8 infusions (weeks 1, 2, 3, 4, 17, 18, 19, and 20)

ARM C: ibrutinib 420mg
Subjects considered refractory to prior rituximab

ABC patients genotyped for MYD88 and CXCR4
Response rates in Innovate A/B

- **Proportion of patients with genetic subtype†, ibrutinib-RTX vs placebo-RTX:**
  - MYD88<sup>L265P</sup>/CXCR4<sup>WT</sup>: 46% vs 52%
  - MYD88<sup>L265P</sup>/CXCR4<sup>WHIM</sup>: 38% vs 34%
  - MYD88<sup>WT</sup>/CXCR4<sup>WT</sup>: 16% vs 13%

*Following modified 6<sup>th</sup> IWWM Response Criteria (NCCN 2014); required two consecutive assessments.
†Proportion of patients calculated after excluding patients for whom data were missing or unknown (ibrutinib-RTX: n = 6; placebo-RTX: n = 8).

Dimopoulos et al, EHA 2018; NEJM 2018
Progression-Free Survival for Innovate A/B

Progression-Free Survival by IRC for all patients

- Hazard ratio: 0.20 (95% CI, 0.11–0.38), P < 0.0001
- Placebo-RTX: Median (mo) 20.3, NR

Progression-Free Survival by Genotype

- Median follow-up 26.5 months
- Dimopoulos et al, EHA 2018; NEJM 2018
What is still unknown after iNNOVATE?

- Is IR better than Ibrutinib alone??
- Is IR a better choice vs. other chemo-R regimens such as Benda-R?
- Are there other ways to improve outcome ibrutinib outcome in WM beside combining with rituximab?
Phase I/II Trial of Ulocuplumab and Ibrutinib in CXCR4 mutated patients with symptomatic WM

**Schema**

**Ibrutinib**
- Weekly Ulo
  - 4 weeks
- Biweekly Ulo
  - 20 weeks

**Dose Level**
- Level 1 – Starting dose
  - Ibrutinib: 420mg PO DQ
  - Ulocuplumab Cycle 1: 400 mg weekly
  - Ulocuplumab Cycles 2-6: 800 mg every other week
- Level 2
  - Ibrutinib: 420mg PO DQ
  - Ulocuplumab Cycle 1: 800 mg weekly
  - Ulocuplumab Cycles 2-6: 1200 mg every other week
- Level 3
  - Ibrutinib: 420mg PO DQ
  - Ulocuplumab Cycle 1: 800 mg weekly
  - Ulocuplumab Cycles 2-6: 1600 mg every other week

ClinicalTrials.gov Identifier: NCT03225716
BCL-2 is overexpressed in primary WM patient cells by transcriptome analysis in MYD88 mutated patients regardless of CXCR4 mutation status.

\[ p<0.001 \text{ for healthy donor samples versus any MYD88}^{L265P} \text{CXCR4}^{WT} \text{ or WHIM} \]

Hunter et al, BLOOD 2016
Phase II Study of Venetoclax in Previously Treated WM

Selected inclusion criteria:
- Clinicopathological diagnosis of WM
- Serum IgM >2 x ULN
- Previously treated
- Age ≥18 years
- Good performance
- Normal organ and marrow function

Selected exclusion criteria:
- Serious medical condition
- Concurrent anti-cancer agent
- Known CNS lymphoma
- Active HIV, HBV, HCV infection
- Lactating or pregnant women

Screening

Informed Consent and Registration

Venetoclax
200 mg PO QD
800 mg PO QD

Progressive Disease or Unacceptable Toxicity

Stop ABT-199

SD or Response → Continue for 2 years

Event Monitoring

www.clinicaltrials.gov: NCT02677324

Castillo et al. EHA 2018
## Phase II Study of Venetoclax in Previously Treated WM

<table>
<thead>
<tr>
<th>Response</th>
<th>No prior ibrutinib (n=15)</th>
<th>Prior ibrutinib (n=15)</th>
<th>CXCR4 WT (n=14)</th>
<th>CXCR4 MUT (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>14 (93%)</td>
<td>12 (80%)</td>
<td>12 (86%)</td>
<td>14 (87%)</td>
</tr>
<tr>
<td>Major</td>
<td>13 (87%)</td>
<td>9 (60%)</td>
<td>9 (86%)</td>
<td>13 (63%)</td>
</tr>
<tr>
<td>Very good</td>
<td>4 (27%)</td>
<td>1 (7%)</td>
<td>4 (29%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Partial</td>
<td>9 (60%)</td>
<td>8 (53%)</td>
<td>8 (57%)</td>
<td>9 (56%)</td>
</tr>
<tr>
<td>Minor</td>
<td>1 (7%)</td>
<td>3 (20%)</td>
<td>0 (0%)</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Stable</td>
<td>1 (7%)</td>
<td>3 (20%)</td>
<td>2 (14%)</td>
<td>2 (13%)</td>
</tr>
</tbody>
</table>

Median follow-up: 11 months

1 patient had progressive disease at 9 months (MYD88, CXCR4, TP53)

Castillo et al. EHA 2018
Addition of Venetoclax (ABT-199) augments ibrutinib triggered apoptosis in CXCR4 WT and mutated WM Cells.

Cao et al, BJH 2015
Ibrutinib and Venetoclax in Treatment Naïve WM

24 months

Ibrutinib
420 mg/day
x 4 weeks

Add Venetoclax
100 mg/day week 5
200 mg/day week 6
400 mg/day weeks 7,8

Ibrutinib
420 mg/day
And
Venetoclax
400 mg/day

Observation

Follow to PD
or off study

Jorge Castillo, PI (DFCI)
Approach to Frontline Therapy of Symptomatic WM

**Hyperviscosity, Severe Cryos, CAGG, PN ➔ Plasmapheresis**

**MYD88 Mutated/No CXCR4 mutation**
- No bulky disease, no contraindications ➔ Ibrutinib (if available)
- Bulky disease ➔ Benda-R
- Amyloidosis ➔ Bortezomib/Dex/Rituximab (BDR)
- IgM Peripheral Neuropathy ➔ Rituximab ± Alkylator

**MYD88 Mutated/CXCR4 mutation** ➔ +Ibrutinib and Rituximab
- Same caveats as above
- If immediate response needed, either BDR or Benda-R

**MYD88 Wild-Type**
- ✓ non-L265P MYD88 mutations
- BDR > Benda-R

- Hold Rituximab until IgM <4000 mg/dL or empiric pheresis is performed.
- Consider Maintenance Rituximab
- Consider Ofatumumab if R intolerant.

Hunter et al, JCO 2017; LeBlond IWWM10
Salvage Therapy of Symptomatic WM

Consider repeat primary therapy if response >2 years

**MYD88 Mutated/No CXCR4 mutation**
Same caveats as primary therapy

**MYD88 Mutated/CXCR4 mutation**
Same caveats as primary therapy
If immediate response needed, either BDR or Benda-R

**MYD88 Wild-Type**
Same caveats as primary therapy
✓ non-L265P MYD88 mutations

- Everolimus >2 prior therapies
- Nucleoside analogues (non-ASCT candidates)
- ASCT in multiple relapses, chemosensitive disease

Hunter et al, JCO 2017

+ Venetoclax for pts previously exposed to IB
Amyloidosis: “Under-diagnosed disorder”

Giampaolo Merlini

Amyloidosis Research and Treatment Center
IRCCS Policlinico San Matteo and
Department of Molecular Medicine
University of Pavia, Italy
OUTLINE

- Diagnosis red flags
- Early diagnosis ➔ Biomarkers
- Risk assessment ➔ Treatment selection
- Treatment outline
Patients referred to the Pavia Center for Amyloidosis

2240 patients (1998-2012)

- ApoA1: 8%
- ATTRm: 11%
- ATTRwt: 3%
- Other: 2%
- AL: 70%

895 patients (2013-2017)

- ApoA1: 8%
- ATTRm: 9%
- ATTRwt: 13%
- Other: 2%
- AL: 62%

Wild-type TTR could be the most frequent form of cardiac amyloidosis, affecting mostly males (>80%) in the late 70s. ~25% of patients have a monoclonal protein (Geller et al, Mayo Clin Proc. 2017)
Outcomes in 1065 patients with AL amyloidosis

**Patient survival**

- **No heart involvement (18%)**
  - P<0.001
- **Asymptomatic heart inv. (22%)**¹ Med. Surv. 54 month
- **Symptomatic heart involvement (60%)**
  - median survival 15 months

**Renal survival**

- **Nephrotic syndrome**
  - dialysis: 20% @2y; 28% @5y
  - P<0.001
- **Asymptomatic (proteinuria <3 g/24h)**
  - dialysis: 4% @2y; 8% @5y

**EARLY DIAGNOSIS IS VITAL**

1. Basset et al, EHA23 PS 1335
There were 223 hematologists that missed making the diagnosis.
When should an hematologist think about amyloidosis?

In a patient with a monoclonal protein

- Severe fatigue, unexplained weight loss
- Exertional dyspnea (very late symptom!)
- Leg swelling (proteinuria)
- Carpal tunnel syndrome (bilateral)
- Peripheral neuropathy
- Autonomic neuropathy (postural hypotension, erectile /bladder / bowel dysfunction)
- Hepatomegaly with normal imaging
- Macroglossia and/or periorbital purpura
EARLY DIAGNOSIS

Biomarkers
- sFLC
- NT-proBNP
- u. Albumin

Imaging
- Echocardiography (SVI)
- CMR
- DPD/PYP scintigraphy
- $^{18}$F-florbetapir PET/CT
Diagnosis: imaging cardiac amyloidosis

Mainstay: Echocardiography

Strain Doppler imaging “bulls eye” (apical sparing) Courtesy Martha Grogan

Stroke volume index (Milani et al, Circ Cardiovasc Img. 2018)

Cardiac MRI - T1 map - LGE

Maceira et al, Circulation 2005
Banypersad et al, Circ Cardiovasc Img. 2013
Fontana et al, J ACC Cardiovasc Img. 2017
Martinez-Naharro et al, ISA 2018 PA060
Knight et al, J ACC Cardiovasc Img. 2018

$^{18}$F-florbetapir
$^{18}$F-florbetaben
$^{11}$C-Pittsburgh compound B

Dorbala et al, EJ NMMI 2014
Park et al, Circ Cardiov Img. 2015
Pilebro et al, J Nucl Cardiol. 2017
Manwani et al, ISA 2018 PB054
Predicting outcomes in AL amyloidosis

**Mayo Clinic / European staging system**

- **Stage I (18%)**
  - Median 5 months
- **Stage II (44%)**
  - Median 49 months
- **Stage IIIa (20%)**
  - Median 14 months
- **Stage IIIb (18%)**
  - Median 5 months

Staging is based on **NT-proBNP** (cutoff 332 ng/L) and **troponin I** (cutoff 0.1 ng/mL). Very high (>8500 ng/L) NT-proBNP identifies patients with advanced cardiac dysfunction (Stage IIIb).

**Revised Mayo Clinic staging system**

- **Stage I (23%)**
- **Stage II (24%)**
  - Median 57 months
- **Stage III (27%)**
  - Median 18 months
- **Stage IV (26%)**
  - Median 6 months

Staging is based on **NT-proBNP** (cutoff 1800 ng/L), **troponin I** (cutoff 0.07 ng/mL), and **dFLC** (cutoff 180 mg/L).

Kumar et al, J CO 2012

**Renal staging system**

- **Stage III (15%)**
  - Dialysis 48% @ 2y
- **Stage II (42%)**
  - Dialysis 12% @ 2y
- **Stage I (43%)**
  - Dialysis 1% @ 2y

Staging is based on **proteinuria** (cutoff 5g/24h) and **eGFR** (cutoff 50 mL/min per 1.73 m²).


- **P=0.040**


- **GDF-15** is a strong predictor for renal outcomes
- **GDF-15** reduction after therapy is associated with better outcome

Kastritis et al, Blood 2018
**Diagnostic algorithm for systemic amyloidosis**

**Suspect systemic amyloidosis**
- Heart failure & preserved ejection fraction, low ECG voltage
- Proteinuria (Leg swelling) – Fatigue & weight loss
- Axonal sensorimotor polyneuropathy (carpal tunnel synd. 50%)
- Hepatomegaly, non-infectious diarrhea
- MGUS with abnormal FLC ratio and elevated NT-proBNP and/or proteinuria

**Serum and urine immunofixation electrophoreses + sFLC**
Add cardiac PYP or DPD scan\(^1\) if heart symptoms/suggestive echo

Abdominal fat aspirate: (underutilised):\(^2\) sensitivity 81-84\(^{\%}^{3,4}\)
Possible lip/minor salivary gland biopsy for Congo red

**Negative**
- Cardiac MRI

**Positive**
- Type amyloid deposits
  - Proteomics-MS\(^5,6\)
  - Immuno-EM\(^7\)
  - Immunohistochemistry\(^8\)

---

Characterization of the amyloidogenic clone

Serum and urine immunofixation and FLC measurement (mass spectrometry) (Palladini et al, Clin Chem. 2009)

- Poor prognosis if BMPC>10% (AL+MM) overcome by Bortez/Len (Rodriguez-Lobato et al, EHA23 PS1314)
- High PC proliferative index (Sidiqi et al, Haematol)
- t(11;14) translocation (~40-60% vs 17% in MM): lower benefit from bortezomib and IMiDs than from M-Dex and HDM (Bochtler et al, J Clin Oncol. 2015 - Muchtar et al, Leukemia 2016)
- Gain of 1q21 (~25%): poor outcome with M-Dex (Bochtler et al, Amyloid 2014) overcome by HDM and bortezomib (Bochtler et al J Clin Oncol 2015, Blood 2016)
Venetoclax induced a complete response in a patient with immunoglobulin light chain amyloidosis plateaued on cyclophosphamide, bortezomib and dexamethasone.

Leung et al, Haematologica 2018
<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
</table>
| **Hematologic** | **CR**: negative s&u IFE + normal FLCR  
**VGPR**: dFLC <40 mg/L  
**PR**: dFLC decrease >50%  
**Low-dFLC response**: dFLC <10 mg/L |
| **Cardiac** | NT-proBNP decrease >30% & >300 ng/L |
| **Renal** | Proteinuria decrease >30% |

Validated criteria for **early (3 & 6 months)** assessment of response

**Hematologic CR** → 54% **Cardiac response**  
→ 68% **Renal response**

**Health-related QoL** McCausland et al. EHA23 S147

**Grading of cardiac response (215 patients)**

Minimal residual disease in AL amyloidosis

Patients who achieved CR

- Improvement in **cardiac response**
  - 33% in mPC- vs 15% in mPC+ (p = 0.003)
- **Renal response**
  - 19% in mPC- vs 3% in mPC+ (p = 0.02).

34 patients in CR
21 (62%) MRD negative

Compared to the time of aCR achievement, further renal response was obtained in 9 of 13 evaluable MRD negative patients (69%) and in 2 of 11 MRD positive patients (18%, P=0.034)

Palladini et al, ASH 2016, Abstract #3261 updated
Kastritis et al, EHA23 PS 1304

Patients who do not achieve organ response despite sustained complete hematologic response should be tested for MRD by NGF.

Further treatment may be considered in MRD positive patients if risk assessment allows

Sidana et al, Leukemia 2018
ASCT in AL amyloidosis

- 1,536 patients at 134 centers from 1995 to 2012
- HR/CR 61/33%, TRM 4% (2007-2012)
- Renal response 30%

Fit patients: ~20%
age < 70 years, ECOG PS≤2, BP >90 mmHg,
cTnT < 0.06 ng/mL, Creatinine clear. >30 mL/min,
NYHA I or II, ≤ 2 organs involved

- CyBorD indu
- BDex if < CR

1. Tandon et al, BMT 2017
2. Sidiqi et al, JCO 2018
4. Scharman et al, ASH 2017 Abstr .4552
5. Landau et al, Leukemia 2017
**Treatment of intermediate-risk patients (~60%)**
(ineligible for ASCT, stages I-IIla)

Standard of care: Bortezomib-based regimens → VGPR/CR~50%
(BDex, CyBorD, BMDex) → VGPR/CR ~40-20% in Stage IIIa/IIlb


**Phase I/II study of ixazomib in relapsed refractory AL amyloidosis**

27 patients - Overall hematologic response rate: 52%, ≥VGPR 43%
Cardiac response 45%, renal response 45%

Phase III study of ixazomib vs. physician’s best choice in rel/ref AL amyloidosis ongoing (NCT01659658)
A phase III trial of BMDex vs. MDex in newly-diagnosed AL

<table>
<thead>
<tr>
<th>Response</th>
<th>MDex (56 pts)</th>
<th>BMDex (53 pts)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Hem.</td>
<td>32 (57%)</td>
<td>43 (81%)</td>
<td>0.005</td>
</tr>
<tr>
<td>CR</td>
<td>11 (20%)</td>
<td>12 (23%)</td>
<td>0.440</td>
</tr>
<tr>
<td>VGPR</td>
<td>11 (20%)</td>
<td>22 (%)</td>
<td>0.007</td>
</tr>
<tr>
<td>PR</td>
<td>10 (17%)</td>
<td>9 (%)</td>
<td>0.454</td>
</tr>
<tr>
<td>Heart</td>
<td>10/36 (28%)</td>
<td>10/26 (38%)</td>
<td>0.195</td>
</tr>
<tr>
<td>Kidney</td>
<td>15/35 (43%)</td>
<td>16/36 (44%)</td>
<td>0.448</td>
</tr>
</tbody>
</table>

Hematologic response at 3 months prolongs survival in frail patients with advanced heart involvement.

Stage IIIb: NT-proBNP > 8500 ng/L (~20%)

Heart transplantation

- age < 65 yrs,
- no significant extra-cardiac amyloidosis
- ASCT after HTx very effective¹-⁴
- outcomes comparable to non-amyloid⁵

Bortezomib-based regimens


Interfering with cardiac toxicity in AL amyloidosis

30 patients treated with doxycycline (100 mg bid) + CT
73 matched controls CT

Survival of patients treated with an upfront bortezomib-based regime

Doxycycline

Controls

P = 0.012

An international Phase III trial is ongoing

Wechalekar et al, *Blood Cancer J* 2017
Newer (and older) chemotherapy approaches - bendamustine

Hematologic response
- 35% (CR 2%, VGPR 8%)
- 55-59% in patients with IgM-AL (CR 8-11%, VGPR 25-37%)

Treatment of relapsing/refractory patients

IMiDs are effective rescue agents (increase in NT-proBNP, Len potential nephrotoxicity)

Pomalidomide produces rapid and profound responses
Daratumumab in AL amyloidosis

Kaufman et al, Blood 2017 & Kaufman et al, EHA23 PS1305

Abeykoon et al, Leukemia 2018

Phase III international study of CyBorD vs CyBorD+Dara upfront (ANDROMEDA) - Safety run-in results: Merlini et al, EHA23 PS1318

<table>
<thead>
<tr>
<th>Prior lines of therapy, n (range)</th>
<th>ORR n (%)</th>
<th>CR n (%)</th>
<th>VGPR n (%)</th>
<th>PR n (%)</th>
<th>Time to 1st/ best response, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>25 (83)</td>
<td>5 (17)</td>
<td>19 (63)</td>
<td>1 (3)</td>
<td>2.2 (1.7–4.8) / 5.7(3.4-7.7)</td>
</tr>
</tbody>
</table>

Kaul et al, Jaccard et al, EHA23 S851

- CR 5%
- VGPR 43%
- PR 10%
- 58%
**Anti-SAP antibodies**

1. CPHPC to deplete circulating SAP
2. monoclonal IgG1 anti-SAP antibody

Most patients receiving > 200 mg of anti-SAP antibody had manageable infusion reaction

**Fibril-reactive antibody 11-1F4**

**Phase 1a 8 patients**
- Single IV infusion 0.5 to 500 mg/m² Week 1

**Phase 1b 19 patients**
- Weekly IV infusion for 4 weeks

SAE ≥3 in 5 patients (diarrhea, pain, pruritus, pleural/pericardial effusion)

Wall et al, Blood 2010

Richards et al, NEJM 2015;373:1106-14
Edwards et al, Amyloid 2017 and ASH 2017 Abstr.509
Conclusions

• Early diagnosis, novel agents, biomarker-guided treatment strategy are improving the outcome of patients with amyloidosis

• Advanced cardiac AL amyloidosis remains an unmet need: improve the understanding of the mechanisms of cardiac damage

• In the near future the treatment of systemic amyloidosis will include the combination of agents targeting critical steps of the amyloid cascade increasing efficacy, but raising concerns about sustainability and access to drugs

• Novel collaborative models are necessary to tackle these challenges. Pharma companies, patients’ advocacy groups and scientific societies, regulatory and funding agencies and academia are all essential for progress and hope
CAR-T cells and the Immune System in Multiple Myeloma

Nikhil C. Munshi, MD
Professor of Medicine
Harvard Medical School
Director Basic and Correlative Sciences
Dana-Farber Cancer Institute
Boston VA Healthcare System
Origin of the Disease

- Chronic antigenic stimulation of the plasma cell
- Repeated infections
- Chronic inflammation
- Autoimmune disorders
- A Patient with a prior therapy with horse anti-serum against tetanus
  - Developed MGUS
  - Stable for 30 years then progressed to MM.
  - The serum IgG component was found to react specifically against horse α-2 macroglobulin.
Clonal Immunoglobulin Against Lysolipids in The Origin of Myeloma

• MGUS developing during the course of Gaucher’s disease are reactive against lyso-glucosylceramide (LGL1), which is elevated as a consequence of the metabolic defect.

• Binding to this antigen was noted in one third of sporadic human monoclonal gammopathies.

Nair et al. NEJM 2016
Evolution of Multiple Myeloma - Genomic Changes

Normal Plasma Cells  MGUS Cells  Myeloma Cells  Extramedullary Disease

Spontaneous Evolution
- Inherent
- Microenvironmental
- Immune effects

Spontaneous Evolution
- Inherent
- Microenvironmental
- Immune effects

Therapy Effects
- Clonal selection
- Clonal induction
- Mutation promotion
- Effect on repair

WGS at diagnosis
WGS at relapse
WGS at diagnosis and relapse - Significant increase in complexity

Rise of Immunotherapy !!
Targeting Growth, Survival, and Drug Resistance of MM in BM Microenvironment

Growth promoting
- Stromal cells
- Osteoclast
- Adipocytes
- Endothelial cells
- Immune cells

Cytokines
- IL-6, VEGF
- IGF-1, SDF-1α
- BAFF, APRIL
- BSF-3

Adhesion
- BMSC
- SC
- CD40
- FGFR3
- CS1
- BAFF-R
- VEGFR

Cytokines
- TNFα
- TGFβ
- VEGF

Cell surface targets
- CD40
- JAK/STAT3
- RAF
- MEK/ERK
- PI3-K
- NF-κB

Survival
- Anti-apoptosis
- Cell cycle

Survival
- Anti-apoptosis
- Cell cycle

Survival
- Anti-apoptosis
- Proliferation

Proliferation
- Anti-apoptosis

Migration
- GSK-3β
- FKHR
- Caspase-9
- NF-κB
- Mcl-1
- Bcl-xL
- IAP
- Cyclin-D
- MEK/ERK

Protein Kinase C (PKC)
- Akt
- Bad

Raf
- MEK/ERK
- p27Kip1

Survival
- Anti-apoptosis

Cell cycle
- MEK/ERK

Hideshima T and Anderson KC. Nat Rev Cancer 2007,
Fundamental immune Consequence in Myeloma

- Augmentation of myeloma promoting immune responses
  - Plasmacytoid Dendritic cells (pDC)
  - Myeloid Derived suppressor cells (MDSC)
  - T Helper 17 and 22 cells (Th17, Th22)

- Suppression of myeloma protecting immune responses
  - B cell, NK and NKT cell, T cell - Treg, Th17, Th9, Tfh Cell dysfunction
Plasmacytoid DCs Promote Growth, Survival, and Drug-Resistance in Myeloma

Chauhan et al: Cancer Cell 2009
Elevated Th17 supports MM cell growth

Elevated Th17 cells in Myeloma

IL-17A increases Myeloma Growth

Prabhala RH et al Blood 2011
Reduced Myeloma Growth by Anti-IL-17A mAb Secukinumab in Vitro and in vivo

Prabhala RH et al Leukemia 2016
Antibodies and Small molecules Targeting Pro-inflammatory Pathways

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17</td>
<td>AIN457</td>
<td>Novartis</td>
</tr>
<tr>
<td>IL-17</td>
<td>LY2439821</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>IL-17R</td>
<td>AMG 827</td>
<td>Amgen</td>
</tr>
<tr>
<td>IL-20</td>
<td>Anti-IL-20</td>
<td>NovoNordisk</td>
</tr>
<tr>
<td>IL-22</td>
<td>ILV094</td>
<td>Pfizer</td>
</tr>
<tr>
<td>JAK3</td>
<td>CP-690,550</td>
<td>Pfizer</td>
</tr>
<tr>
<td>IL-23</td>
<td>LY2525623</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>IL-23</td>
<td>CNTO1959</td>
<td>Jansen</td>
</tr>
<tr>
<td>IL23p19</td>
<td>SCH 900222</td>
<td>Scheringh/Merck</td>
</tr>
<tr>
<td>IL-23+IL6</td>
<td>AZ17</td>
<td>Allozyne</td>
</tr>
</tbody>
</table>
Suppressed Myeloma Protecting Immune Responses

- **B cell defect**
  - Suppression of uninvolved immunoglobulins
- **T cell dysfunction**
- **NK cell activity** - relatively preserved
- **NKT cell dysfunction** that can recover following in vitro culture
Time course of Ulg recovery

IgG Myeloma

IgA Myeloma

Light Chain disease

Munshi et al Blood 2000
Normalization of IgM Post-Transplant Predicts for Better Survival
Reduction of immunosuppression

IMIDs
Thalidomide, Lenalidomide, Pomalidomide

Checkpoint blockers
PD-L1/PD-1 inhibitors

Immune adjuvants
CpG ODNs, TLR-7/9 agonists

Vaccines
Native idiotype protein, PVX-410, CD138, MM-DC

CAR T cells
anti-Kappa, CD138, BCMA, NKG2D

Tumor promoting cells
- MDSCs
- Tregs cells
- pDC

Induction of anti-MM activity
- NK cells
- DC
- Cytotoxic T cells

Anti-tumor cellular immunity
- B cells
- Th cells
- Cytotoxic T cells
- CAR T cells
Immune-therapies under investigation in Myeloma

Immunotherapy\textsuperscript{1,2}

**Active**
(Designed to act on the immune system itself)

- I-O therapies
  - Immune effector cell modulators
  - Checkpoint Inhibitors
  - Co-stimulatory agonists
- Therapeutic cancer vaccines
  - Cell-based
  - DC-based cancer vaccines
  - Single antigen/peptide-based
- Unspecific
  - Cytokines
  - Interleukins
  - Interferons
  - IMiDs

**Passive**
(Designed to act on the tumor)

- Antitumor mAbs
- Adoptive
  - Tumor-directed mAbs
  - Ab-drug Conjugates (ADC)
  - Cell therapies
  - Adoptive T-cell therapy

---

DC, dendritic cell; IMiD, immunomodulatory agent; I-O, immuno-oncology; mAb, monoclonal antibody.

Peptide-based Vaccination

- Single Antigen Targeting Peptides
  - Bae et al Blood 2006
  - Bae et al Blood 2007
  - Bae et al CCR 2010

- Vaccination Using Cocktail of Peptides

Clinical Study of Multi-peptide Vaccination in Smoldering Myeloma
With Lenalidomide

On Going study with PD1 and PD-L1 antibodies
Vaccines Targeting MM Specific Peptides in Smoldering Multiple Myeloma

Goal is to prevent evolution of smoldering to active myeloma

- Cocktails of immunogenic HLA-A2-specific XBP1, CD138, CS1 peptides to induce MM-specific and HLA-restricted CTL responses

Clinical trials (LLS TAP Program):
Immune responses to vaccine in all patients including tetramer positive cells and type I cytokines

Lenalidomide with vaccine augments these immune response

Lenalidomide and PDL-1, HDAC 6i 241 with vaccine to induce memory immune response against myeloma

Bae et al, Leukemia 2015

MM/DC Vaccination following Autologous PBSCT for Myeloma

Immune-therapies under investigation in Myeloma

Immunotherapy

Active (Designed to act on the immune system itself)

- I-O therapies
  - Immune effector cell modulators
    - Checkpoint Inhibitors
    - Co-stimulatory agonists
- Therapeutic cancer vaccines
  - Cell-based
    - DC-based cancer vaccines
  - Single antigen/peptide-based
- Unspecific
  - Cytokines
    - Interleukins
    - Interferons
  - IMiDs

Passive (Designed to act on the tumor)

- Antitumor mAbs
  - Tumor-directed mAbs
  - Ab-drug Conjugates (ADC)
- Adoptive
  - Cell therapies
    - Adoptive T-cell therapy

DC, dendritic cell; IMiD, immunomodulatory agent; I-O, immuno-oncology; mAb, monoclonal antibody.

MAb Based Therapeutic Targeting of MM

Antibody-dependent Cellular Cytotoxicity (ADCC)

Effector cells:
- NK cell
- macrophage
- neutrophil...

ADCC

- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1)
- Daratumumab (CD38)
- XmAb®5592 (HM1.24)
- Isatuximab (CD38)

Complement-dependent Cytotoxicity (CDC)

- Daratumumab (CD38)
- Isatuximab (CD38)

CDC

- huN901-DM1* (CD56)
- nBT062-maytansinoid/DM4* (CD138)
- 1339 (IL-6)
- BHQ880 (DKK)
- RAP-011 (activin A)
- Daratumumab (CD38)
- Isatuximab (CD38)
- J 6M0-MMAF* (BCMA)

* Ab drug conjugate

Apoptosis/growth arrest via intracellular signaling pathways
Explosion in Adoptive Cellular Therapies!

- Antigen-Directed T cells
  - Engineered T-cell Receptors
  - Anti-viral or tumor-peptide Cytotoxic T Lymphocytes
  - Chimeric Antigen Receptor T cells
Chimeric Antigen Receptor T cells (CAR T Cells)

- These T cells exploit native antibody or T cell recognition and signaling pathways.
- Introduction of unique genes through viral vectors to allow recognition of tumor cells.
- Dramatic expansion after infusion, and effective tumor cell killing.
- After initial trials proving the efficacy in B cell malignancies, other targets, cancers and molecular constructs are being explored.

Image courtesy of Stephan Grupp, UPenn.
“Classic” CAR T-cell construct

- scFv and other Ab-related
  - Specifically targeting myeloma
  - CD19, anti-kappa, CS1, CD138, CD38, BCMA
## Target Antigens for Multiple Myeloma CAR-T Cell Therapy

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Expression in nonmalignant cells</th>
<th>Expression in MM</th>
<th>Clinical trial of CAR-Ts in myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD44v6</td>
<td>Activated T cells, activated monocytes, keratinocytes</td>
<td>Reported to be expressed by 43% of advanced MM cases</td>
<td>No</td>
</tr>
<tr>
<td>CD70</td>
<td>Activated lymphoid cells</td>
<td>Only a portion of the myeloma cells express CD70 in most cases</td>
<td>No</td>
</tr>
<tr>
<td>CD56</td>
<td>NK cells, T cells, neuronal cells</td>
<td>Strongly expressed in 70% of patients with myeloma</td>
<td>No</td>
</tr>
<tr>
<td>CD38</td>
<td>Precursor B cells, <strong>plasma cells</strong>, T cells, NK cells, myeloid precursors, prostate cells, nervous system, osteoclasts, muscle cells</td>
<td>Strong, uniform expression on myeloma cells</td>
<td>No</td>
</tr>
<tr>
<td>CD138</td>
<td><strong>Plasma cells</strong>, salivary glands, liver, skin</td>
<td>Expressed on MM cells</td>
<td>Yes</td>
</tr>
<tr>
<td>CD19</td>
<td>B cells</td>
<td>Minimal expression on MM cell surface. CD19+ cells may represent cancer stem cell in MM</td>
<td>Yes</td>
</tr>
<tr>
<td>Immunoglobulin κ light chain</td>
<td>Mature B cells</td>
<td>Potential target on B cells that represent MM stem cells and that express surface immunoglobulins</td>
<td>Yes</td>
</tr>
<tr>
<td>SLAMF7</td>
<td><strong>Plasma cells</strong>, NK cells, CD8+ cells, activated monocytes and B cells, dendritic cells</td>
<td>Strongly expressed by MM cells</td>
<td>No</td>
</tr>
<tr>
<td>BCMA</td>
<td><strong>Plasma cells</strong>, small subset of B cells</td>
<td>Expressed on MM cells</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Mikkilineni et al Blood 2017
# Clinical trials of CAR-Ts for MM with published results

<table>
<thead>
<tr>
<th>Target</th>
<th>Institution</th>
<th>CAR construct</th>
<th>Conditioning chemotherapy</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD138</td>
<td>Chinese People’s Liberation Army Hospital</td>
<td>Lentivirus; CD28 murine scFv</td>
<td>Varied chemotherapy shortly before cell infusion</td>
<td>5 patients treated; best responses: 4 SD, 1 PD</td>
</tr>
<tr>
<td>CD19</td>
<td>University of Pennsylvania</td>
<td>Lentivirus 4-1BB murine scFv</td>
<td>Melphalan 140-200 mg/m² prior to ASCT</td>
<td>10 patients treated; median PFS 185 d (range, 42-479 d)</td>
</tr>
<tr>
<td>Immunoglobulin κ light chain</td>
<td>Baylor College of Medicine</td>
<td>γ-retrovirus; CD28 murine scFv</td>
<td>Salvage chemotherapy or cyclophosphamide 4 days</td>
<td>7 patients treated: 4 SD, 3 no response</td>
</tr>
<tr>
<td>BCMA</td>
<td>National Cancer Institute</td>
<td>γ-retrovirus; CD28 murine scFv</td>
<td>Fludarabine/Cyclophosphamide</td>
<td>12 patients treated ORR – 4 (1 sCR); 8 SD</td>
</tr>
<tr>
<td>BCMA</td>
<td>Multicenter; Bluebird Bio</td>
<td>Lentivirus; 4-1BB murine scFv</td>
<td>Fludarabine/Cyclophosphamide</td>
<td>18 patients treated ORR – 17 (94%); 10 CR (56%) and 9/10 MRD-. negative</td>
</tr>
<tr>
<td>BCMA</td>
<td>University of Pennsylvania</td>
<td>Lentivirus; 4-1BB human scFv</td>
<td>None</td>
<td>6 patients treated; 1 sCR; 1 VGPR; 4 with minimal or no response</td>
</tr>
<tr>
<td>BCMA</td>
<td>The 2nd Affiliated Hospital of Xi’an Jiaotong University</td>
<td>Not published</td>
<td>Not published</td>
<td>19 patients treated ORR 100%; 18 patients obtaining sCR or VGPR</td>
</tr>
</tbody>
</table>
BCMA - A Promising Target in Multiple Myeloma

- **BCMA** is member of the TNF receptor superfamily
  - Expressed nearly universally on MM cells
  - Expression largely restricted to plasma cells and some mature B cells

**BCMA Is A Selective Plasma Cell Antigen**

- Membrane BAFF
- Soluble BAFF
- HSPG-bound APRIL trimer
- BAFF-R
- Cell membrane
- Signal transduction
- B cell survival
- Long-lived Plasma cell survival
- B cell Maturation (class switch to IgA, IgG)
- Ligands by neutrophil, myeloid cell, DC, osteoclasts, tumor cell
  - Affinity to BCMA: APRIL (nM) >> BAFF (μM)
  - Elevated in sera of MM patients

- Receptors on B cells
- BCMA >> TACI
  - by ~2-100-fold in MM (loss of BAFF-R in MM)

BCMA CAR T Studies
Low level BCMA expression sufficient to activate bb2121

BCMA Receptor Density and bb2121 Activity

BCMA Receptor Density on Human Myeloma Cells

Range 387 - 4268

All human MM expected to express levels of BCMA sufficient to trigger bb2121 killing activity

222 BCMA molecules per cell
CRB-401 PHASE 1 STUDY DESIGN

≥50% BCMA expression

Dose Escalation (N=21)

- 50 x 10^6
- 150 x 10^6
- 450 x 10^6
- 800 x 10^6

Dose Expansion (N=22)

<50% BCMA expression (n=10)
≥50% BCMA expression (n=12)
Dose range: 150-450 x 10^6 CAR+ cells

Screening

Leukapheresis

bb2121 manufacturing
Manufacturing (10 days) + release

bb2121 infusion

1st Response Assessment (Wk 4)

Flu 30 m/m^2
Cy 300 mg/m^2

Day 0

BM BX (Wk 2)
BM BX (Wk 4)

Sample collections for T cell expansion & cytokines
## TREATMENT HISTORY

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Escalation (N=21)</th>
<th>Expansion (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (min, max) prior regimens</td>
<td>7 (3, 14)</td>
<td>8 (3, 23)</td>
</tr>
<tr>
<td>Prior autologous SCT, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21 (100)</td>
<td>19 (86)</td>
</tr>
<tr>
<td>1</td>
<td>15 (71)</td>
<td>14 (64)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>6 (29)</td>
<td>5 (23)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Escalation (N=21)</th>
<th>Expansion (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior therapies, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>21 (100)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>19 (91)</td>
<td>21 (96)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>21 (100)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>19 (91)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>15 (71)</td>
<td>19 (86)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Escalation (N=21)</th>
<th>Expansion (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative exposure, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bort/Len</td>
<td>21 (100)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Bort/Len/Car/Pom/Dara</td>
<td>15 (71)</td>
<td>21 (96)</td>
</tr>
</tbody>
</table>

Data cutoff: March 29, 2018. SCT, stem cell transplant.
ADVERSE EVENTS OF SPECIAL INTEREST

<table>
<thead>
<tr>
<th>CAR T Treatment-Emergent Adverse Events</th>
<th>All Infused Patients (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE, n (%)</td>
<td>Overall</td>
</tr>
<tr>
<td>Cytokine release syndrome(^{a})</td>
<td>27 (63)</td>
</tr>
<tr>
<td>Neurotoxicity(^{b})</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35 (81)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26 (61)</td>
</tr>
<tr>
<td>Anemia</td>
<td>24 (56)</td>
</tr>
<tr>
<td>Infection(^{c})</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>26 (61)</td>
</tr>
<tr>
<td>First Month</td>
<td>10 (23)</td>
</tr>
</tbody>
</table>

- No grade 4 CRS events
- No fatal CRS or neurotoxicity events

Data cutoff: March 29, 2018. NE, not estimable. \(^{a}\)CRS uniformly graded per Lee DW, et al. Blood. 2014;124(2):188-195. \(^{b}\)Events occurring in first 28 d and including dizziness, bradypnea, somnolence, confusional state, nystagmus, insomnia, memory impairment, depressed level of consciousness, neurotoxicity, lethargy, tremor and hallucination. \(^{c}\)Includes the SOC Infections and Infestations. Events observed in >10% include upper respiratory tract infection and pneumonia. \(^{d}\)Includes patients treated with active doses (150–800 × 10⁶ CAR+ T cells; N=40). Median and 95% CI from Kaplan-Meier estimate. \(^{e}\)Time from first bb2121 infusion to the first grade ≤2 event after day 32.

- 31/40 (78%) recovered ANC to ≥1000/µL by Day 32
- 22/40 (55%) recovered PLT to ≥50,000/µL by Day 32
CYTOKINE RELEASE SYNDROME

Cytokine Release Syndrome Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dosed Patients (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a CRS event, n (%)</td>
<td>27 (63)</td>
</tr>
<tr>
<td>Maximum CRS grade&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>16 (37)</td>
</tr>
<tr>
<td>1</td>
<td>16 (37)</td>
</tr>
<tr>
<td>2</td>
<td>9 (21)</td>
</tr>
<tr>
<td>3</td>
<td>2 (5)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Median (min, max) time to onset, d</td>
<td>2 (1, 25)</td>
</tr>
<tr>
<td>Median (min, max) duration, d</td>
<td>6 (1, 32)</td>
</tr>
<tr>
<td>Tocilizumab use, n (%)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Corticosteroid use, n (%)</td>
<td>4 (9)</td>
</tr>
</tbody>
</table>

Cytokine Release Syndrome By Dose Level

Data cutoff: March 29, 2018. *CRS uniformly graded according to Lee DW, et al. Blood. 2014;124(2):188-195. <sup>3</sup>3 patients were treated at the 50 x 10⁶ dose level for a total of 43 patients.
ROBUST bb2121 CAR+ T CELL EXPANSION WITH LONG-TERM PERSISTENCE

**Median (Q1, Q3) Vector Copies in CD3-Enriched Peripheral Blood by Dose Cohorts**

<table>
<thead>
<tr>
<th>Time After bb2121 Infusion, months</th>
<th>Dose Level</th>
<th>50 × 10⁶ (n=3)</th>
<th>150 × 10⁶ (n=12)</th>
<th>450 × 10⁶ (n=19)</th>
<th>800 × 10⁶ (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>LLOQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
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<tr>
<td>4</td>
<td></td>
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<tr>
<td>5</td>
<td></td>
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<td></td>
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<tr>
<td>6</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
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<tr>
<td>8</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients with a post-baseline vector copy value were included. One patient was dosed at 205 × 10⁶ CAR+ T cells instead of the planned 450 × 10⁶ and was included in the 450 × 10⁶ dose group.

<table>
<thead>
<tr>
<th>Month</th>
<th>At risk, n</th>
<th>With detectable vector, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>31 (97)</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>22 (85)</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>7 (44)</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>2 (20)</td>
</tr>
</tbody>
</table>

Data cutoff: March 29, 2018. C_{max}, maximum serum concentration; LLOQ, lower limit of quantitation.

**Peak bb2121 Vector Copies in Responders vs Nonresponders**

- Comparable C_{max} in active dose cohorts (≥150 × 10⁶ CAR+ T cells)
- Durable bb2121 persistence (≥6 months) in 44%
- Higher peak expansion in patients with response

Patients with ≥2 months of response data and 1 month of vector copy data (N=36). P value based on a 2-sided Wilcoxon rank sum test.
**TUMOR RESPONSE: DOSE-RELATED; INDEPENDENT OF TUMOR BCMA EXPRESSION**

![Tumor Response By Dose]  
Objective Response Rate, %

<table>
<thead>
<tr>
<th>Dose</th>
<th>ORR (%)</th>
<th>mDOR (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 x 10^6</td>
<td>33.3</td>
<td>1.9</td>
</tr>
<tr>
<td>150 x 10^6</td>
<td>42.9</td>
<td>NE</td>
</tr>
<tr>
<td>&gt;150 x 10^6</td>
<td>50.0</td>
<td>10.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median follow-up (min, max), d</th>
</tr>
</thead>
<tbody>
<tr>
<td>84 (59, 94)</td>
</tr>
<tr>
<td>87 (36, 638)</td>
</tr>
<tr>
<td>194 (46, 556)</td>
</tr>
</tbody>
</table>

![Tumor Response By BCMA Expression]  
Objective Response Rate, %

<table>
<thead>
<tr>
<th>BCMA Expression</th>
<th>ORR (%)</th>
<th>mDOR (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low BCMA</td>
<td>100%</td>
<td>10.8</td>
</tr>
<tr>
<td>High BCMA</td>
<td>91%</td>
<td>3.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median follow-up (min, max), d</th>
</tr>
</thead>
<tbody>
<tr>
<td>168 (121, 184)</td>
</tr>
<tr>
<td>311 (46, 556)</td>
</tr>
</tbody>
</table>

Data cutoff: March 29, 2018. CR, complete response; mDOR, median duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; VGPR, very good partial response. aPatients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Low BCMA is <50% bone marrow plasma cells expression of BCMA; high BCMA is defined as ≥50%.
TUMOR RESPONSE: DEEP MRD-NEGATIVE RESPONSES OBSERVED

<table>
<thead>
<tr>
<th>Response</th>
<th>50 × 10^6</th>
<th>150 × 10^6</th>
<th>450 × 10^6</th>
<th>800 × 10^6</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD-evaluable responders</td>
<td>0</td>
<td>4</td>
<td>11</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>MRD-neg^a</td>
<td>0</td>
<td>4 (100)</td>
<td>11 (100)</td>
<td>1 (100)</td>
<td>16 (100)</td>
</tr>
</tbody>
</table>

Data cutoff: March 29, 2018. ^aOf 16 MRD-negative responses: 4 at 10^-6, 11 at 10^-5, 1 at 10^-4 sensitivity by Adaptive next-generation sequencing assay.

- All responding patients evaluated for MRD were MRD negative at 1 or more time points
- 2 nonresponders evaluated for MRD were MRD positive at month 1
PROGRESSION-FREE SURVIVAL

- mPFS of 11.8 months at active doses (≥150 × 10^6 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. *PFS in dose escalation cohort.
A LCAR-B38M is based on a bispecific antibody platform with potent target selectivity.

Engineered to optimize the CAR target–binding mechanism and subsequent CAR signal transduction.

Pilot I/II study in 35 patients who received at least 3 prior lines of therapy, 19 with > 4 months f/p.

High response rate > 100%
  - sCR - 74%

Well tolerated – CRS in 83% of 35 patients.
  - Grade 1 in 17 patients,
  - Grade 2 in 10 patients
  - Grade 3 in 2 patients with no grade 4 events.
  - Tocilizumab - 40% of patients
Future directions in BCMA Cellular Therapies

- Novel constructs, vectors (SynNotch-binding to one Ag drives expression of CAR for second Ag)
Universal SLAMF7-Specific CAR T (abs 502)

- “Off-the-shelf”
- Normal healthy PB donors
- Inactivation of the \( TCR\alpha \) constant (\( TRAC \)) gene using gene-editing technology to prevent GVHD and expression of T cell SLAMF7.

- Campath MoAb targeting CD 52 can be used if needed to prevent host rejection of normal donor CAR T cells
BCMA Growth, Survival, Drug Resistance Signaling in MM

Ligands
by neutrophil, myeloid cell, DC, osteoclasts, tumor cell

Affinity to BCMA:
APRIL (nM) >> BAFF (μM)
Elevated in sera of MM patients

Receptors
on B cells

BCMA >> TACI
by ~2-100-fold in MM
(loss of BAFF-R in MM)

Tai & Anderson
GSK2857916 Aurostatin Immunotoxin Targeting BCMA in Relapsed/Refractory Multiple Myeloma

- BCMA Selectively expressed on MM/plasma cells
- BCMA MoAb linked to aurostatin immunotoxin
- Median follow-up 6.6 months
- ORR of 60% in heavily pre-treated MM
- Median PFS 7.9 months
- Well tolerated and side effects manageable
  - Thrombocytopenia and corneal events most frequent AEs
  - IRRs occurred in only 23% of patients without pre-medications; no IRRs occurred on subsequent infusions
- Additional monotherapy and combination studies are planned

Trudel et al ASH 2017

DOR, duration of response; IRR, infusion-related reaction; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; VGPR, very good partial response
Targeting APRIL in MM

Conclusion

• Immune-based therapies are achieving impressive responses
• Adoptive Transfer of CAR-T cells has great promise
• Task for us is to sustain/maintain the great responses achieved with CAR-T cell infusion
  – Newer generation of CAR-T cells
  – Combination with conventional agents
  – Reinfusion of CAR-T cells – maintenance dosage
  – Develop more convenient CAR-T generation methods and process
Climb To Cure Multiple Myeloma
BCMA-BiTE-Based Immunotherapies

CD3
BCMA
Cytotoxic granule

T cell proliferation

MM cell lysis

bb2121 at active doses (≥150 × 10⁶ CAR+ T cells) induces deep and durable responses in a heavily pretreated population with R/R MM

• Median PFS of 11.8 months for patients in the dose escalation cohort
• MRD-negative results in 100% of 16 evaluable responding patients; median PFS of 17.7 months
• Mostly grade 1/2 CRS observed with infrequent tocilizumab and corticosteroid use
• Ongoing trial for FDA approval.

Checkpoint Blockade Induces Effector Cell Mediated MM Cytotoxicity

**Effector:** Autologous effector cells (CD3T cells, NK cells)

**Target:** CD138⁺ MM cells from Rel/Ref MM-BM

Anti-PDL1 Ab Induces MM-Specific CD8+ CTLs and NK cell-Mediated Cytotoxicity in Presence of pDCs

Ray et al, Leukemia, in press
**bb2121: Anti-BCMA Chimeric Antigen Receptor T-Cell in Multiple Myeloma**

Responses to bb2121 Infusion

**Bone marrow response and tumor burden reduction**

*All patients treated at doses > 5x10⁷ with bone marrow involvement at baseline have had no detectable bone marrow disease on Day 14 or beyond.*

**IHC**

- **Baseline**
- **Day 14**

**PET**

- **Baseline**
- **Month 1**

*Patient 6*

*Patient 8*
Lenalidomide Reduces PD1 and PD-L1 Expression on RR-MM Bone Marrow Cells

CD138\(^+\) MM cells

\(\%\) of PD-L1 expression on MM cells

Untreated

Lenalidomide

\(p<0.04\)

mMDSC

% Expression of PD-L1 on mMDSC

\(\%\) of PD-L1 expression on mMDSC

Untreated

Lenalidomide

T cells CD14\(^+\) Myeloid cells

PD-1

PD-L1

Untreated

Lenalidomide

Pembrolizumab Plus Lenalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Overall Response

Change From Baseline in M Protein or Free Light Chain

- Overall Population
  - 41 (85.4%) patients experienced a reduction from baseline

- Lenalidomide-Refractory Population
  - 31 (86.1%) lenalidomide-refractory patients experienced a reduction from baseline

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Rodríguez-Otero et al EHA 2017

*12 patients were not included because they did not have ≥2 postbaseline efficacy assessments or they had major protocol violations.

*DCR = sCR + CR + VGPR + PR + SD.

*Assessments were not available for 2 (4%) patients who recently enrolled in the study.

Data cutoff: March 10, 2017.
Pembrolizumab, Pomalidomide and Dex in RR Myeloma: Summary of Responses

**Depth of Response**

**Overall response – no. (%)**
- Double refractory: 29 (65)
- High risk cytogenetics: 22 (68)

**Clinical benefit – no. (%)**
- Double refractory: 23 (69)
- High risk cytogenetics: 16 (60)

**Best response – no. (%)**
- sCR: 3 (7)
- CR: 1 (2)
- VGPR: 9 (20)
- PR: 16 (36)
- MR: 3 (7)
- SD: 11 (23)
- PD: 2 (5)

29% 24% 15%

Badros et al ASH 2016
Role of NK and NKT cells in Myeloma

Cancer Therapy: Preclinical

Generation of Antitumor Invariant Natural Killer T Cell Lines in Multiple Myeloma and Promotion of Their Functions via Lenalidomide: A Strategy for Immunotherapy

Weihua Song,¹ Hans J.J. van der Vliet,² Yu-Tzu Tai,¹ Rao Prabhala,¹,³ Ruojie Wang,² Klaus Podar,¹ Laurence Catley,¹ Masood A. Shammas,³ Kenneth C. Anderson,¹ Steven P. Balk,² Mark A. Exley,² and Nikhil C. Munshi¹,³

MHC class I chain-related protein A antibodies and shedding are associated with the progression of multiple myeloma


*Department of Medical Oncology and Cancer Vaccine Center, Dana–Farber Cancer Institute and Department of Medicine, and †Department of Pathology, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA 02115; and *Department of Biostatistics and Computational Biology, Dana–Farber Cancer Institute, Harvard Medical School, Boston, MA 02115
Immune Cells Contribute to Genomic Instability in Myeloma

U266 (co-cultured with pDC)

U266 (co-cultured with iDC)

U266 + IFN-α (4 days)
Targeting pDC-MM Interaction By pDC cytotoxicity OR pDC Maturation

IL-3R
SL-401

TLR-7
GS4369869

Chauhan et al: Cancer Cell 2009
Plasmacytoid DCs Promote Growth, Survival, and Drug-Resistance in Myeloma

Chauhan et al: Cancer Cell 2009
Suppressed Virus-Specific T cells in Myeloma Responsive to in vitro Stimulation

Healthy Donor

Day 0

Day 11

Myeloma Patient

Day 0

Day 11

EBV tetramer

Inf A

CD8
Development of T lymphocyte helper Subsets

Naïve CD4

Th1
- IFN-γ
- Protection against infectious agents, anti-tumor immunity

Th2
- IL-4
- Antibodies/Allergy

Th17
- TH-17 assoc cytokines

Treg
- TGF-β
- IL-10
- Control immune responses

Th9
- IL-9
- Protection against parasites

Tfh
- Participate antigen-specific B cell responses

IL-12, T-bet

IL-4, GATA-3

TGF-β, IL-6, ROR-γt

TGF-β, FOXP3

TGF-β, IL-4

Autoimmunity
Protection against parasites & fungal infections

Inflammation
Protection against parasites

Participate antigen-specific B cell responses
Immune Suppressive Microenvironment in MM

- Immune suppression by pDC, MDSC
- IL-6, IL-10, TGFβ, PGE, ARG1, NO, ROS, COX2
- Depletion of cysteine
- Tumor promotion and induction of PD-L1 expression

Increased PD1 Expression on Effector cells in MM

CD4⁺T cells

% Expression of CD279 in CD4⁺T cells

CD8⁺T cells

% Expression of CD279 in CD8⁺T cells

NK cells

% Expression of CD279 in NK cells

NKT cells

% Expression of CD279 in NKT cells

*p<0.05

High PDL1 Expression on MM Cells, pDCs and MDSCs in Myeloma

Ray et al, Leukemia, in press
BM Microenvironment Triggers Proteasome Activity in MM Cells

Key role of protein homeostasis and protein degradation pathway in myeloma

Chauhan et al., 2006
Abnormal B cell-subsets in Myeloma

![Flow cytometry charts showing abnormal B cell subsets in normal blood (N=9) and myeloma blood (N=5).](image)

- **B1b** and **B1a**
- **B2** and Breg

**Bone Marrow**

- **B1b** and **B1a**
- **B2** and Breg

**Graphs showing**

- % of CD19 positive cells in normal blood (N=17) vs. myeloma blood (N=7)
- % of CD5 positive cells in NBM (N=9) vs. MMBM (N=5)
T Cell Immunity Against SOX2 At Baseline Correlates With Reduced Risk Of Progression To Symptomatic MM

Events / N

<table>
<thead>
<tr>
<th>Condition</th>
<th>Events</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-SOX2 T cells absent</td>
<td>36</td>
<td>145</td>
</tr>
<tr>
<td>Anti-SOX2 T cells present</td>
<td>12</td>
<td>142</td>
</tr>
</tbody>
</table>

24-month Estimate

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-SOX2 T cells absent</td>
<td>21.1%</td>
</tr>
<tr>
<td>Anti-SOX2 T cells present</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

$p = 0.0003$

Dhodapkar et al, Blood 2015