Multiple Myeloma
New Trials and New Drugs

Rafat Abonour, M.D.
Treatment Combinations Then and Now

OLD

Induction
Thal/Dex
VAD
DEX

Consolidation

Post consolidation
SCT
Nothing
Prednisone
Thalidomide

Rescue
Few options

NEW

Front line treatment
VD
Rev/Dex
CyBorD
VTD
VRD
VD/VRD

Consolidation

Post consolidation
SCT
Lenalidomide
Bortezomib

Maintenance

Relapsed
Bortezomib
Lenalidomide
Thalidomide
Carfilzomib
Pomalidomide
Dratumumab
Elotuzumab
HDAC
Bendamustine

Thalidomide
Carfilzomib
Pomalidomide
Dratumumab
Elotuzumab
HDAC
Bendamustine
Achieving Great cytoreduction (≥ VGPR/CR) = Better Outcomes

Achieving ≥ VGPR\(^1\)

\[ P = .0017 \]

CR + VGPR (n = 445)

PR (n = 288)

Achieving CR\(^2\)

CR or better

VGPR

PR

PD

SD

0 0.2 0.4 0.6 0.8 1.0

0 1 2 3 4 5 6 7 8

Time Since Transplantation, years

Time Since Transplantation, years

Probability of OS

Probability of OS

Depth of Response Influence Time to Progression

- Presentation
- PR
- VGPR
- CR
- stringent CR

**Total number of tumor cells**

- Presentation
- PR
- VGPR
- CR
- stringent CR

**MRD**

- Quiescent or controlled levels of detectable MRD
- Late relapse on patients with undetectable MRD
- Long-term disease control in patients with undetectable MRD

**Operational cure**

- Diagnosis
- End of therapy
- Time to progression
Is three better than two?

**SWOG S0777 Study Design (continued)**

- **VRd**

- **Rd**

### After induction

- **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 325 mg/day

### VRd patients received HSV prophylaxis

Dorie et al, ASH 2015
Progression-Free Survival By Assigned Treatment Arm

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

<table>
<thead>
<tr>
<th></th>
<th>Events / N</th>
<th>Median in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRd</td>
<td>137 / 242</td>
<td>43 (39, 52)</td>
</tr>
<tr>
<td>Rd</td>
<td>166 / 229</td>
<td>30 (25, 39)</td>
</tr>
</tbody>
</table>
Overall Survival By Assigned Treatment Arm

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

Deaths / N
VRd  76 / 242
Rd   100 / 229

Median in Months
VRd  75 (66, .)
Rd   64 (56, .)

Durie et al, ASH 2015
The New Kid on the Block: Carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX)

AJ Jakubowiak,1 K Griffith,2 D Dytfeld,3 DH Vesole,4 S Jagannath,5 T Anderson,2 B Nordgren,2 K Detweiler-Short,2 D Lebovic,2 K Stockerl-Goldstein,6 T Jobkar,2 S Wear,7 A Al-Zoubi,2 A Ahmed,2 M Mietzel,2 D Couriel,2 M Kaminski,2 M Hussein,8 H Yeganegi,9 R Vij6

1University of Chicago, Chicago, IL; 2University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; 3Poznan University of Medical Sciences, Poznan, Poland; 4John Theurer Cancer Center, Hackensack, NJ; 5Mount Sinai Medical Center, New York, NY; 6Washington University School of Medicine, St. Louis, MO; 7Multiple Myeloma Research Consortium, Norwalk, CT; 8Celgene, Inc, Summit, NJ; 9Onyx Pharmaceuticals, South San Francisco, CA
Treatment Roadmap

**Transplant-eligible and -ineligible patients**

- CRd Cycles 1–4
- CRd Cycles 5–8
- CRd Cycles 9–24
- LEN Cycles 25+

1. Assessments on D1 and 15 of C1 and D1 thereafter using modified IMWG Criteria with nCR
2. Cycles 1–8
   - CFZ Days 1–2, 8–9, 15–16 at assigned doses
   - LEN 25 mg Days 1–21
   - DEX 40 mg weekly Cycles 1–4, 20 mg weekly Cycles 5–8
3. Cycles 9–24
   - CFZ on Days 1–2 and 15–16 only
   - CFZ, LEN, DEX at last best tolerated doses
   - After Cycle 4, pts could undergo stem cell collection and then continue CRd with the option to proceed to ASCT

KRD for newly diagnosed Myeloma

K Rd w/o ASCT

- 4 cycles n=49: ≥VGPR 69%, ≥nCR 43%, ≥CR 18%, sCR 8%
- 8 cycles n=44: ≥VGPR 89%, ≥nCR 66%, ≥CR 34%, sCR 30%
- 18 cycles n=41: ≥VGPR 90%, ≥nCR 80%, ≥CR 51%

K Rd + ASCT

- 4 cycles n=73: ≥VGPR 73%, ≥nCR 22%, ≥CR 16%, sCR 11%
- 8 cycles n=52: ≥VGPR 96%, ≥nCR 85%, ≥CR 73%, sCR 69%
- 18 cycles n=28: ≥VGPR 93%, ≥nCR 93%, ≥CR 82%, sCR 82%

Response after ASCT (n=64)
- ≥VGPR: 92%
- ≥nCR: 45%
- ≥CR: 27%
- sCR: 20%

nCR, near complete response; VGPR, very good partial response
MRD Evaluation

- Multiparameter Flow Cytometry (MFC)
  - 10 color
  - Sensitivity: $10^{-4} - 10^{-5}$

- Next generation sequencing (NGS)
  - Adaptive Biotechnologies
  - Sensitivity: $10^{-6}$

KRd w/o ASCT
At CR

- MRD negative, %
  - n=26: 51*
  - n=16: 39†

KRd + ASCT‡
At landmark time points

- n=33 (8 cycles): 82
- n=29: 66
- n=20 (18 cycles): 89
- n=16: 71

*Estimated rate based on 23 of 26 evaluated pts assessed for MRD by flow cytometry at CR/ suspected CR
†Estimated rate based on percentage of 13 pts in CR/sCR negative by NGS
‡Actual MRD rates in subgroup of pts evaluated for MRD at the end of 8 and 18 cycles as per new IMWG MRD criteria (pts were considered MRD – negative only if in CR/sCR)
Multiple Myeloma

Treatment of Relapse Patients
First Oral PI: IXAZOMIB
TOURMALINE-MM1 Study Design

28-day cycles

Randomization
N=722
Stratification:
• Number of prior therapies
• PI exposure
• ISS stage

IRd
Ixazomib 4 mg Days 1, 8, 15
Lenalidomide 25 mg Days 1–21
Dexamethasone 40 mg Days 1, 8, 15, 22

Rd
Lenalidomide 25 mg Days 1–21
Dexamethasone 40 mg Days 1, 8, 15, 22

LEN NAÏVE OR LEN SENSITIVE

TOURMALINE-MM1 Results

<table>
<thead>
<tr>
<th></th>
<th>I-Rd (n=360)</th>
<th>Rd (n=362)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>20.6</td>
<td>14.7</td>
<td>0.742</td>
<td>0.012</td>
</tr>
<tr>
<td>ORR, %</td>
<td>78.3</td>
<td>71.5</td>
<td>—</td>
<td>0.035</td>
</tr>
<tr>
<td>≥VGPR, %</td>
<td>48.1</td>
<td>39.0</td>
<td>—</td>
<td>0.014</td>
</tr>
<tr>
<td>AEs, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥G3 Diarrhea</td>
<td>6</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>≥G3 PN</td>
<td>2</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Benefit with IRd was also noted in pts with high-risk cytogenetics.

Phase 3 study of weekly oral ixazomib plus lenalidomide-dex: final PFS analysis

- **35% improvement in PFS with IRd vs Rd** (data cut-off 30 October 2014)

**Graph**: Median follow-up:
- IRd 14.8 months
- Rd 14.6 months

**Median PFS**:
- IRd 20.6 months, Rd 14.7 months
- Log-rank test p=0.012
- Hazard ratio (95% CI): 0.742 (0.587, 0.939)
- Number of events: IRd 129; Rd 157

**Number of patients at risk**:
- IRd: 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
- Rd: 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

A subsequent exploratory analysis of PFS was conducted (median follow-up 23.3 and 22.9 months in the IRd and Rd arms); median PFS 20 vs 15.9 months
Daratumumab Anti-CD 38 MoAb

modulation of enzymatic activation

apoptosis after cross-linking

induction of CDC

cADPR

NAD

effector cell

induction of ADCC and ADCP

18 of 29 patients in phase I benefit (5PR, 4MR, 9SD)

DeWeers et al, J Immunol 2011; 186: 1840
Daratumumab - Single Agent Efficacy in Combined Analysis

- ORR = 31%

- 18% ORR
- 10% VGPR or better
- 2% CR or better
- 1% sCR

- ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function
**Daratumumab Combination: Study Design**
Multicenter, randomized (1:1), open-label, active-controlled, phase 3 study

**DRd (n = 286)**
- Daratumumab 16 mg/kg IV
  - Qw in Cycles 1 to 2, q2w in Cycles 3 to 6, then q4w until PD
  - R 25 mg PO
    - Days 1 to 21 of each cycle until PD
  - d 40 mg PO
    - 40 mg weekly until PD

**Rd (n = 283)**
- R 25 mg PO
  - Days 1 to 21 of each cycle until PD
  - d 40 mg PO
    - 40 mg weekly until PD

**Primary endpoint**
- PFS

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

**Stratification factors**
- No. of prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide exposure, but not refractory
- Creatinine clearance ≥30 mL/min

**Key eligibility criteria**
- RRMM
- ≥1 prior line of therapy
- Prior lenalidomide exposure, but not refractory
- Creatinine clearance ≥30 mL/min

**Statistical analyses**
- Primary analysis: ~177 PFS events

Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg, acetaminophen, and an antihistamine

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ISS, international staging system; DRd, daratumumab/lenalidomide/dexamethasone; IV, intravenous; qw, weekly; q2w, every 2 weeks; q4w, every 4 weeks; PD, progressive disease; R, lenalidomide; PO, oral; d, dexamethasone; Rd, lenalidomide/dexamethasone; PFS, progression-free survival; TTP, time to progression; OS, overall survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease.

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a On daratumumab dosing days, dexamethasone 20 mg was administered as pre-medication on Day 1 and Day 2.
Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DRd (n = 286)</th>
<th>Rd (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>65 (34-89)</td>
<td>65 (42-87)</td>
</tr>
<tr>
<td>≥75, %</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>ISS stage, %&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>II</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>III</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Median (range) time from diagnosis, y</td>
<td>3.48 (0.4-27.0)</td>
<td>3.95 (0.4-21.7)</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min), %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>279</td>
<td>281</td>
</tr>
<tr>
<td>&gt;30-60</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>&gt;60</td>
<td>71</td>
<td>77</td>
</tr>
<tr>
<td>Cytogenetic profile, (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>161</td>
<td>150</td>
</tr>
<tr>
<td>Standard risk</td>
<td>83</td>
<td>75</td>
</tr>
<tr>
<td>High risk</td>
<td>17</td>
<td>25</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DRd (n = 286)</th>
<th>Rd (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior lines of therapy, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>1 (1-11)</td>
<td>1 (1-8)</td>
</tr>
<tr>
<td>1</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>&gt;3</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>1-3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>Prior ASCT, %</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>Prior PI, %</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>Prior bortezomib, %</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>Prior IMiD, %</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Prior lenalidomide, %</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Prior PI + IMiD, %</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Refractory to bortezomib, %</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Refractory to last line of therapy, %</td>
<td>28</td>
<td>27</td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug.

<sup>a</sup>ISS staging is derived based on the combination of serum β2-microglobulin and albumin.

<sup>b</sup>Central next-generation sequencing. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities.

<sup>c</sup>Exploratory.
Updated Efficacy

- **Median (range) follow-up: 17.3 (0-24.5) months**

Responses continue to deepen in the DRd group with longer follow-up

HR, hazard ratio; CI, confidence interval; sCR, stringent complete response; PR, partial response.
Note: PFS = ITT population; ORR = response-evaluable population.

\(^a\)Kaplan-Meier estimate;
\(^b\)P <0.0001 for DRd vs Rd.
MRD-negative Rate

MRD-negative rates were >3-fold higher at all thresholds

*P < 0.0001.

Intent-to-treat population.

P values are calculated using likelihood-ratio chi-square test.

31.8

24.8

11.9

2.5
PFS: Cytogenetic Risk in All Evaluable Patients

- Comparable results in 1 to 3 prior lines population

<table>
<thead>
<tr>
<th></th>
<th>DRd</th>
<th>Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>NR</td>
<td>10.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.44 (0.19-1.03)</td>
<td>0.0475</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>DRd</th>
<th>Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>NR</td>
<td>17.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.30 (0.18-0.49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR, not reached; NS, not significant.

*ITT/Biomarker risk–evaluable analysis set. High-risk patients had any of t(4;14), t(14;16), or del17p. Standard-risk patients had an absence of high-risk abnormalities.

DRd improves outcomes regardless of cytogenetic risk
Intent-to-treat population. Median OS was not reached; results did not cross the prespecified stopping boundary.

**OS**

- OS events^a^
  - 40 (14%) in DRd
  - 56 (20%) in Rd

Curves are beginning to separate, but OS data are immature
CAR – T Immune Therapy
T cells are white blood cells that attack and kill viruses and cancer cells.

Chimeric antigen receptors (CARs) help T-cells recognize and destroy cancer cells.

1. T cells are collected from the patient. A machine removes the desired cells from the blood, then returns the rest back to the patient.

2. A modified virus (blue) is used to transfer DNA to the patient’s T cells so they will produce CAR proteins.

3. CARs have two ends: a binding site (blue) specific to the tumor cells, and a signaling engine that activates the T cell to kill the tumor it binds to.

4. Once designed, millions of engineered CAR T cells are grown in the laboratory.

5. The expanded population of CAR T cells is infused into the patient through a standard blood transfusion.
MM Patient #1: Response to CD19 CAR Therapy

- IgA (mg/dl)
- MEL 200
- LEN
- LEN/BTZ
- DEX/CLR
- CY
- MEL 140
- CTL019

Additional regimens including:
- carfilzomib
- pomalidomide
- vorinostat
- elotuzumab

sCR, MRD neg
Now d +307
TTP after ASCT #1 d190
Remission inversion

Garfall et al, NEJM 2015; 373: 1040-7
CAR-BCMA T Cells in Myeloma: Background

- T cells can be genetically modified to express chimeric antigen receptors (CARs) specific for malignancy-associated antigens.

- B-cell maturation antigen (BCMA) is expressed by normal and malignant plasma cells.
  - BCMA is a potential target for CAR T-cell therapy for MM.

- The patient’s own T-cells were stimulated, transduced with CAR-BCMA retroviruses, and cultured for 9 days before infusion.

- Study presented ASH 2015 evaluated CAR-BCMA T cell infusion for treatment of advanced MM.

CAR-BCMA T Cells in Myeloma: Study Design

• First-in-human phase I trial

- Pts with advanced relapsed/ refractory MM
- More than 3 prior lines of therapy;
- BCMA expression on myeloma cells
- 12 patients enrolled

Cyclophosphamide 300 mg/m²
Fludarabine 30 mg/m²
QD for 3 days

CAR-BCMA T cells*
Single infusion

*Dose escalation of CAR+ T cells/kg
0.3 x 10⁶
1.0 x 10⁶
3.0 x 10⁶
9.0 x 10⁶

**CAR-BCMA T Cells in Myeloma: Response to therapy**

<table>
<thead>
<tr>
<th>Response to Therapy</th>
<th>Number of Patients (total 12 treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stringent complete response(sCR)</td>
<td>1</td>
</tr>
<tr>
<td>Very good partial response VGPR</td>
<td>1</td>
</tr>
<tr>
<td>Partial response</td>
<td>2</td>
</tr>
<tr>
<td>Stable disease</td>
<td>8</td>
</tr>
</tbody>
</table>
BCMA-BiTE-based Immunotherapies

- CD3
- BCMA
- Cytotoxic granule

T cell proliferation

BCMA-BiTE

MM cell lysis

Tai et al 2016
Bortezomib + AIDS drug (Nelfinavir)

- St Gallen team from Switzerland.
- 34 patients resistant to Bortezomib (velcade).
- Nelfinavir and oral (HIV protease inhibitor)
- Nelfinavir and bortezomib was well tolerated
- Overall response rate was 65%. Four patients achieved very good partial response.

- ASH 2016 abstract 487.
Venetoclax Monotherapy for Relapsed/Refractory Multiple Myeloma: Safety and Efficacy Results From a Phase I Study

Shaji Kumar, Ravi Vij, Jonathan L Kaufman, Joseph Mikhael, Thierry Facon, Brigitte Pegourie, Lofti Benboubker, Cristina Gasparetto, Martine Amiot, Philippe Moreau, Stefanie Alzate, Jeremy Ross, Martin Dunbar, Tu Xu, Suresh Agarwal, Joel Levenson, Paulo Maciag, Maria Verdugo, Cyrille Touzeau

1Mayo Clinic, Rochester, MN, USA; 2Washington University School of Medicine, St. Louis, MO, USA; 3Winship Cancer Institute of Emory University, Atlanta, GA, USA; 4Mayo Clinic, Scottsdale, AZ, USA; 5CHRU Lille, Hopital Huriez, France; 6CHU Grenoble, France; 7CHRU Tours, France; 8Duke University, Hematologic Malignancies & Cellular Therapy, Durham, NC, USA; 9CHU de Nantes, Hotel Dieu–HME, France; 10AbbVie Inc., North Chicago, IL, USA
Background

- Anti-apoptotic proteins BCL-2 and MCL-1 promote multiple myeloma (MM) cell survival\(^1\)
- Venetoclax induces cell death in multiple myeloma (MM) cell lines and primary samples, particularly those positive for the translocation t(11;14), which correlates with higher ratios of \(BCL2\) to \(MCL1\) and \(BCL2\) to \(BCL2L1\) (BCL-X\(_L\)) mRNA\(^1,2\)

1. Touzeau C et al. Leukemia 2014
2. Punnoose E et al. Mol Cancer Ther 2016

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# Patient Disposition

<table>
<thead>
<tr>
<th>Enrolled</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>66</td>
</tr>
<tr>
<td>Time on study, median (range), months</td>
<td>3.3 (0.2–27)</td>
</tr>
<tr>
<td>Time on venetoclax monotherapy, median (range), months</td>
<td>2.5 (0.2–25)</td>
</tr>
<tr>
<td>Time on venetoclax + dexamethasone,(^a) median (range), months</td>
<td>1.4 (0.1–13)</td>
</tr>
<tr>
<td>Active, n (%)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Discontinued, n (%)</td>
<td>55 (83)</td>
</tr>
<tr>
<td>Primary reason for discontinuation, n (%)</td>
<td></td>
</tr>
<tr>
<td>Related to disease progression</td>
<td>41 (62)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>5(^b) (8)</td>
</tr>
<tr>
<td>Withdrawn consent</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Reason not specified</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>8(^c) (12)</td>
</tr>
</tbody>
</table>

\(^a\)\(n=17\) received combination therapy; dexamethasone was added after disease progression.

\(^b\)Renal failure (2), worsening pulmonary disorder (1), paralyzing sciatica (1), and shortness of breath and pain (1).

\(^c\)Data cutoff of 19 Aug 2016.
Objective Response Rates in all Patients and by t(11;14) Status

- **All Patients**:
  - ORR 21%
  - ORR 6%

- **t(11;14)**:
  - ORR 40%

- **non-t(11;14)**:
  - ORR 6%

Data cutoff of 19 Aug 2016
Current Status on Study

- **ORR**
  - sCR/Cr
  - VGPR
  - PR
  - MR
  - SD
  - PD

- **t(11;14)**
  - Venetoclax monotherapy (t[11;14])
  - Venetoclax monotherapy (non-t[11;14])
  - Venetoclax + Dexamethasone

*Patient discontinued with no response data; *Patient discontinuation was related to progression.

Data cutoff of 19Aug2016
Responses by $BCL2:BCL2L1$ Ratio Among $t(11;14)$-Positive Patients

**Gene expression ratio among $t(11;14)$ patients**

- **High $BCL2:BCL2L1$**
  - ORR 88% (n=9)
  - 11% sCR
  - 33% CR
  - 11% VGPR
  - 33% PR

- **Low $BCL2:BCL2L1$**
  - ORR 20% (n=15)
  - 33% sCR
  - 13% CR
  - 7% VGPR

$BCL2$ and $BCL2L1$ ($BCL\cdot X_L$) quantitation using droplet digital PCR performed on CD138-selected bone marrow mononuclear cells collected at baseline. Bootstrapping and Aggregating Thresholds from Trees (BATTing) used to estimate threshold $BCL2:BCL2L1$ for selection of patients likely to have a clinical response vs non-response.

Data cutoff of 19Aug2016
Nivolumab + donor lymphocyte infusion
Conclusions

• Survival is improving due to better combinations and leading to robust eradication of myeloma burden.
• Combination therapy provide higher rates of negative minimal residual disease results and improve survival.
• Immune therapy is very promising.
• Newer drugs are very encouraging.