Autologous Stem Cell Transplantation and Cellular Therapy In Multiple Myeloma

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Multiple Myeloma originates from a malignant clone of plasma cells, terminally differentiated B-lymphocytes.
Cause of Relapse: Suboptimal Depth of Response

Total Therapy Clinical Trials

MRD - Flow - NGS

1. Induction
2. Transplant
3. Consolidation
4. Maintenance

Therapies:
- Thalidomide
- Bortezomib
- Carfilzomib
- Daratumumab

Risk Levels:
- Low Risk
- High Risk

Previous Treatments:
- Higher Risk, Bortezomib (A)
- High Risk, Daratumumab (B)
- Previously Treated

Cure:
- Presentation
- VGPR
- CR
- Relapse
- TT1
- TT2
- TT3
- TT4
- TT5A/B
- TT6
- TT7
Role of Upfront Autologous Stem Cell Transplant
## Trials comparing high-dose chemotherapy and ASCT with novel agent–based regimens without ASCT

<table>
<thead>
<tr>
<th>Trials</th>
<th>Study Design</th>
<th>PFS, Median</th>
<th>OS, Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV-MM-209</td>
<td>MPR x 6 cycles vs HDC ASCT x2</td>
<td>43m vs 22 m (p&lt;0.001)</td>
<td>4y 82% vs 65% (p=0.02)</td>
</tr>
<tr>
<td>EMN 442</td>
<td>CRD x 6 cycles vs HDC ASCT x2</td>
<td>43 vs 29 m (p&lt;0.001)</td>
<td>4y 86% vs 73% (p=0.004)</td>
</tr>
<tr>
<td>EMN02/HO99</td>
<td>VMP x 4 cycles vs HDC ASCT (1 vs 2)</td>
<td>56·7m vs 41·9m (p=0·0001)</td>
<td>5y 75.1% vs 71.6% (p=0.35)</td>
</tr>
<tr>
<td>IFM 2009</td>
<td>RVD x 5 cycles vs HDC ASCT x1 + RVD 2 cycles</td>
<td>50m vs 36m (p&lt;0.001)</td>
<td>8y 62.2% (ASCT) % vs 60.2% (RVD) p=NS</td>
</tr>
</tbody>
</table>

Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma: IFM 2009

Stratified by ISS stage and cytogenetics

- Pts 65 yrs old of age or younger with symptomatic NDMM; ECOG PS < 2 with organ damage and measurable disease*; treated with 1 cycle RVD† (N = 700)

- RVD† Cycles 2, 3 PBSC collection
  - Cyclophosphamide 3 g/m² + G-CSF
- RVD† Cycles 4-8 (n = 350)

- RVD† Cycles 2, 3 PBSC collection
  - Cyclophosphamide 3 g/m² + G-CSF
- ASCT with MEL200
- RVD† Cycles 4, 5 (n = 350)

- Lenalidomide Maintenance 10-15 mg/day for 12 mos

*Serum M-protein > 10 g/L and/or urine M-protein > 200 mg/24 hrs and/or serum FLC > 100 mg/L if serum FLC ratio is abnormal.

†Lenalidomide 25 mg/day on Days 1-14; bortezomib 1.3 mg/m² on Days 1, 4, 8, 11; dexamethasone 20 mg/day on Days 1, 2, 4, 5, 8, 9, 11, 12.


Slide credit: clinicaloptions.com
High-dose chemotherapy plus transplantation was associated with significantly longer progression free survival

Attal M, et al. NEJM 2017
Carfilzomib-based induction/consolidation with or without autologous transplant (ASCT) followed by lenalidomide (R) or carfilzomib-lenalidomide (KR) maintenance FORTE Trial

- Multicenter, randomized, open-label phase II study

Induction
4 x 28-Day Cycles

- Arm A: KCd (n = 159)
- Arm B: KRd (n = 158)
- Arm C: KRd (n = 157)

Consolidation
4 x 28-Day Cycles

- Arm A: KCd (n = 159)
- Arm B: KRd (n = 158)
- Arm C: KRd (n = 157)

Mobilization

Single ASCT

Second Randomization

Patients with NDMM, eligible for ASCT and < 65 yrs of age (N = 474)

Dosing in slide notes.

Endpoint 1: postinduction VGPR

Endpoint 2: premaintenance VGPR, sCR, MRD negativity, safety, rate of early relapse

PFS from R1

PFS from R2

Gay et al ASH 2020
Role of Delayed Autologous Stem Cell Transplant
Early Versus Late Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma: Long-Term Follow-up Analysis of the IFM 2009 Trial

8-year OS 62.2% (ASCT) % vs 60.2% (RVD)

- Transplant significantly reduced the risk of progression or death by 30% compared to RVd alone
- 35% of patients in the transplant arm didn't relapse until after 8 years
- More patients achieved MRD negativity with transplant
# Early versus Delayed ASCT

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Study type</th>
<th>Induction regimen (early ASCT vs delayed ASCT)</th>
<th>Response (early vs delayed ASCT)</th>
<th>PFS (early vs delayed ASCT)</th>
<th>OS (early vs delayed ASCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fermand et al</td>
<td>1998</td>
<td>P</td>
<td>VAMP × 3-4 cycles and ASCT vs VMCP until plateau and ASCT at relapse</td>
<td>85.7% vs 55.5%</td>
<td>39 mo vs 13 mo</td>
<td>64.6 mo vs 64 mo (P = .92)</td>
</tr>
<tr>
<td>Attai et al</td>
<td>2017</td>
<td>P</td>
<td>VRD × 3 cycles and ASCT + VRD × 2 cycles vs VRD × 8 cycles and ASCT at relapse</td>
<td>CR: 59% vs 48% (P = .03)</td>
<td>50 mo vs 36 mo (P &lt; .01)</td>
<td>4 y: 81% vs 82%</td>
</tr>
<tr>
<td>Kumar et al</td>
<td>2012</td>
<td>r</td>
<td>TD or RD × 4-6 cycles followed by early or delayed ASCT</td>
<td></td>
<td>20 mo vs 16 mo (P = NS)</td>
<td>4 y: 73% vs 73% (P = .3)</td>
</tr>
<tr>
<td>Dunavin et al</td>
<td>2013</td>
<td>r</td>
<td>T-, R-, or V-based induction followed by early or delayed ASCT</td>
<td>≥VGPR: 77% vs 55% (P &lt; .01)</td>
<td>28 mo vs 18 mo (P = .11)</td>
<td>NR vs 83 mo (P = .45)</td>
</tr>
<tr>
<td>Remenyi et al</td>
<td>2016</td>
<td>r</td>
<td>57% in early ASCT and 53.2% in delayed ASCT group received novel therapies</td>
<td>CR: 58.1% vs 46.8% (P = .016)</td>
<td>30.2 mo vs 23.3 mo (P = .36)</td>
<td>97.2 mo vs 99.1 mo (P = .77)</td>
</tr>
</tbody>
</table>
Outcome of patients who have sub-optimal pre ASCT response

- Additional pretransplant chemotherapy resulted in deepening responses
- There was no impact of pretransplant salvage chemotherapy on treatment-related mortality, risk for relapse, progression-free survival, or overall survival
- Transplant-eligible patients who achieve a suboptimal response to initial induction therapy should move on to planned ASCT
OS was inferior among patients with the top-tertile reduction in serum-free light chain compared with the rest of the patients when the response was measured before ASCT (2-year OS, 79% vs 92%; HR, 3.31; P < .001). Patients with early MRD negativity experienced a shorter time to MRD conversion (P <0.0001).

Early attainment of MRD negativity (within 6 months from start of therapy) was associated with a higher risk of MRD conversion (57%, 24/42 vs. 38%, 200/526; P = 0.02) and IMWG relapse (50%, 21/42 vs. 29%, 156/526; P = 0.009).
Role of Tandem Autologous Stem Cell Transplant
## Studies Comparing Single and Double ASCT

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>PFS, Median</th>
<th>OS, Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attal 2003</td>
<td>Mel at 140 mg/m$^2$ + TBI at 8 Gy + ASCT vs Mel at 140 mg/m$^2$ + TBI at 8</td>
<td>25 vs 36 mo</td>
<td>48 vs 58 mo</td>
</tr>
<tr>
<td></td>
<td>Gy + ASCT2</td>
<td>$P = .03$</td>
<td>$P = .1$</td>
</tr>
<tr>
<td>Fermand 2003</td>
<td>Mel at 140 mg/m$^2$ + ASCT vs Mel at 140 mg/m$^2$ + ASCT1 → Mel at 140 mg/m$^2$ + VP16 + TBI at 12 Gy + ASCT2</td>
<td>31 vs 33 mo</td>
<td>—</td>
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<tr>
<td>Cavo 2007</td>
<td>Mel at 200 mg/m$^2$ + ASCT vs Mel at 200 mg/m$^2$ ASCT1 → Mel at 140 mg/m$^2$</td>
<td>25 vs 35 mo</td>
<td>65 vs 71 mo</td>
</tr>
<tr>
<td></td>
<td>+ Bu at 1 mg/kg + ASCT2</td>
<td>$P = .01$</td>
<td>$P = .9$</td>
</tr>
<tr>
<td>Mai 2016</td>
<td>Mel at 200 mg/m$^2$ + ASCT × 1 vs Mel at 200 mg/m$^2$ + ASCT × 2</td>
<td>25 vs 29 mo</td>
<td>75 vs 79 mo</td>
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<tr>
<td></td>
<td></td>
<td>$P = NS$</td>
<td>$P = NS$</td>
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<tr>
<td>Cavo 2016</td>
<td>Mel at 200 mg/m$^2$ + ASCT × 1 vs Mel at 200 mg/m$^2$ + ASCT1 × 2</td>
<td>45 mo vs NR</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td>3 y: 60% vs 73%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P = .03$</td>
<td>—</td>
</tr>
<tr>
<td>Stadtmauer 2016</td>
<td>Mel at 200 mg/m$^2$ + ASCT1 → lenalidomide maintenance vs Mel at 200 mg/m$^2$</td>
<td>38 mo: 57% vs 52%</td>
<td>38 mo: 82% vs 83%</td>
</tr>
<tr>
<td></td>
<td>+ ASCT × 2 → lenalidomide maintenance</td>
<td>$P = NS$</td>
<td>$P = NS$</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; ASCT1, first autologous stem cell transplantation; ASCT2, second autologous stem cell transplantation; Bu, busulphan; Mel, melphalan; NR, not reported; NS, not significant; OS, overall survival; PFS, progression-free survival; TBI, total body irradiation; VP16, etoposide.
STaMINA: Study Design

Randomized, open-label phase III trial

Stratified by risk group (high vs standard)

ASCT-eligible patients ≤ 70 yrs with symptomatic MM and ≥ 2 cycles systemic tx initiated in past 12 mos; no prior progression; adequate organ function; (N = 758)

secondary endpoints: OS, ORR, CR conversion rate, safety, infections, tx-related mortality, QoL

Current analysis assessed long-term efficacy, safety in patients with no PD at 38 mos

ASCT/Maintenance Group
Lenalidomide maintenance until PD
10 mg/day for 3 cycles, then 15 mg/day* (n = 257)

ASCT/RVD Group
Bortezomib 1.3 mg/m² IV Days 1, 4, 8, 11
Lenalidomide 15 mg Days 1-15
Dexamethasone 40 mg IV Days 1, 8, 15
Four 28-day cycles (n = 254)

ASCT/ASCT Group
Melphalan 200 mg/m² IV + Second ASCT (n = 247)

ASCT/Maintenance Group
Lenalidomide Maintenance until PD
10 mg/day for 3 cycles, then 15 mg/day*
STaMINA Long-term Follow-up: PFS and OS with Tandem ASCT

PFS benefit for ASCT/ASCT cohort, most notably in high-risk group

- **5-Yr PFS, % (Range)**
  - **High risk**: ASCT/ASCT 43.7 (33-58), ASCT/RVD 37.3 (26-48), ASCT/Maint 32 (24-40), P Value .03
  - **Standard risk**: ASCT/ASCT 58.1 (48-67), ASCT/RVD 48.2 (40-56), ASCT/Maint 47.7 (41-54), P Value .196

- **PFS, % (Range)**
  - **5 yrs**: ASCT/ASCT 53.6 (46-61), ASCT/RVD 44.1 (37-50), ASCT/Maint 42.3 (37-47)
  - **6 yrs**: ASCT/ASCT 49.4 (41-57), ASCT/RVD 39.7 (33-46), ASCT/Maint 38.6 (33-43)

**OS difference between treatment groups**


Slide credit: clinicaloptions.com
EMN02/HO95

Pts with ND MM who received VCD induction x 3-4 cycles + PBSC collection (N = 1192)

First randomization

- VMP* for 4 cycles (n = 497)
- HDM* + single/double ASCT (n = 695)

Second randomization

- VRD x 2 Consolidation
- No Consolidation
- Maintenance lenalidomide

Centers with single ASCT policy
- VMP (n = 294)
- Single ASCT (n = 280)

Centers with double ASCT policy
- VMP (n = 203)
- Single ASCT (n = 208)
- Double ASCT (n = 207)

Key secondary endpoint for this analysis: PFS from first randomization for ASCT-1 vs ASCT-2


Slide credit: clinicaloptions.com
Tandem ASCT in high-risk cytogenetics

Double HSCT significantly improved 5-year progression-free survival (53·5%) compared with single HSCT (44·9%; HR 0·74, p=0·036) and 5-year overall survival (80·3% [74·5–86·4]) than single HSCT (72·6% [66·5–79·3]; HR 0·62, 95% CI 0·41–0·93; adjusted p=0·022)
Role of Consolidation therapy
STaMINA: Study Design

Randomized, open-label phase III trial

Stratified by risk group (high vs standard)

ASCT-eligible patients ≤ 70 yrs with symptomatic MM and ≥ 2 cycles systemic tx initiated in past 12 mos; no prior progression; adequate organ function; (N = 758)

Melphalan 200 mg/m² IV + ASCT

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Four 28-day cycles
(n = 254)

ASCT/ASCT Group
Melphalan 200 mg/m² IV + Second ASCT
(n = 247)

Lenalidomide Maintenance until PD
10 mg/day for 3 cycles, then 15 mg/day*

*Originally given for 3 yrs only but amended to until PD in 2014.
Autologous Transplantation, Consolidation, and Maintenance Therapy in Multiple Myeloma: Results of the BMT CTN 0702 Trial

No difference between study arms for PFS and OS

No difference between study arms in incidence of SPM by 6 yrs ($P = .745$); no difference observed between hematologic vs solid cancers between study arms
Role of Consolidation: EMN02/HO95

Sonneveld et al. JCO 2021
Role of Maintenance therapy
<table>
<thead>
<tr>
<th>Maintenance Study</th>
<th>Comparison</th>
<th>Planned Length of Maintenance</th>
<th>Progression free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>McCarthy et al (CALGB 100104)</strong></td>
<td>Lenalidomide vs. placebo</td>
<td>Until progression</td>
<td>Median PFS (46 vs. 27 months; ( p &lt; .001 ))</td>
<td>3-year OS (88% vs. 80%; ( p = .03 ))</td>
</tr>
<tr>
<td><strong>Attal et al (IFM 0502)</strong></td>
<td>Lenalidomide vs. placebo after 2 months lenalidomide consolidation</td>
<td>Until progression, but terminated early for SPM</td>
<td>Median PFS (41 vs. 23 months; ( p &lt; .001 ))</td>
<td>4-year OS (73% vs. 75%; ( p = \text{NS} ))</td>
</tr>
<tr>
<td><strong>Palumbo et al</strong></td>
<td>MPR vs. tandem ASCT followed by lenalidomide vs. placebo</td>
<td>Until progression</td>
<td>Median PFS 41.9 vs. 21.6 months; ( p &lt; .001 ))</td>
<td>3-year OS (88% vs. 79.2%; ( p = .14 ))</td>
</tr>
</tbody>
</table>
Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis
Role of Salvage Autologous Stem Cell Transplant
Salvage Second Transplantation in Relapsed Multiple Myeloma

1-year PFS = 50%
3-year PFS = 13%

1-year OS = 94%
3-year OS = 68%

Patients relapsed ≥36 months after first AHCT had significantly better PFS and OS than those relapsing earlier
Triple class refractory and Penta refractory MM is associated with poor outcome

Retrospective study of 275 MM patients refractory to anti-CD38 mAbs

<table>
<thead>
<tr>
<th>MAMMOTH</th>
<th>Median OS</th>
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<tbody>
<tr>
<td>Triple class refractory (PI, IMiD, anti-CD38)</td>
<td>8.6 months</td>
</tr>
<tr>
<td>Penta refractory (2 PIs, 2 IMiDs, anti-CD38)</td>
<td>5.6 months</td>
</tr>
</tbody>
</table>

Non-triple refractory: refractory to 1 CD38 mAb, and not both PI and IMiD
Triple and quad refractory: refractory to 1 CD38 mAb + 1 IMiD + 1 PI; or 3 CD38 mAb + 1 PI + 1 or 2 IMiDs; or 1 CD38 mAb + 1 or 2 PIs + 1 IMiD
Penta refractory: refractory to 1 CD38 mAb + 2 PIs + 2 IMiD compounds

OS According to Refractoriness

- Non-triple refractory (n = 57): 11.2 mo
- Triple and quad refractory (n = 148): 9.2 mo
- Penta refractory (n = 70): 5.6 mo

Proportion Surviving

\[ P = .002 \]
What is The Role of Salvage ASCT in Triple Class Refractory MM?

Factors associated with poor outcome:
1. Increasing age
2. Poor performance status
3. High GEP70 risk score at diagnosis

An increased time interval from initial ASCT to salvage ASCT showed an improved outcome but was only significant for PFS.

Ide-cel clinical outcomes:
- Median PFS: 8.8 months
- Median OS: 19.4 months
BCMA Targeted therapy
BCMA Is Potentially One of the Best Targets in MM, With High Specificity and Expression on MM Cells

**BCMA is member of the TNF receptor superfamily**

- Expressed nearly universally on MM cells
- Expression largely restricted to plasma cells and some mature B-cell
- Expression of BCMA increases as disease progresses from MGUS to advanced myeloma

**Initial proof of anti-BCMA activity demonstrated (NCI CAR construct)**

- T-cells transduced with a gamma-retroviral vector encoding anti-BCMA CAR with CD28 costimulatory domain
- Significant CRS occurred in patients with high disease burden treated at highest dose (9 x 10^6 CAR T-cells/kg)
- Deep MM responses (VGPR, sCR) observed at highest dose
Mechanism of Action for Novel BCMA-Targeted Therapies

Antibody–Drug Conjugates
- Cytotoxic payload released into cell

CAR T-Cells
- Bispecific Antibodies
- Signaling domain
- Cytotoxic cytokines

Idecabtagene vicleucel: BCMA-directed genetically modified autologous CAR T-cell therapy
Phase II KarMMa: Pivotal Study of Idecabtagene Vicleucel in Relapsed Refractory MM

Phase II trial of ide-cel in R/R MM; including double- and triple-refractory patients (IMiD, PI, and an anti-CD38 mAb)

MRD-negative status achieved in 26% of treated patients
Phase Ib/II CARTITUDE-1: Anti-BCMA CAR T-Cell, Ciltacabtagene Autoleucel, in RR MM After ≥3 Prior Tx

Patients with R/R MM, ≥ 3 prior therapies including PI, IMiD, and anti-CD38 therapy, or double refractory to PI and IMiD

Screening, enrollment, leukapheresis

Lymphodepletion
FLU 30 mg/m² + CY 300 mg/m² x 3 days

Ciltacabtagene autoleucel infusion
0.5 x 10⁶ - 1.0 x 10⁶ CAR T-cells/kg (target: 0.75 x 10⁶)

Post-infusion assessments

± Bridging chemotherapy

Day -5 to -3

Follow up

12 month 77%

12 month 89%

CAR T-Cell Related AEs

<table>
<thead>
<tr>
<th>AEs of Interest, n (%)</th>
<th>All Patients (N = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade</td>
</tr>
<tr>
<td>CRS</td>
<td>92 (94.8)</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>20 (20.6)</td>
</tr>
</tbody>
</table>
Pathophysiology of CAR T Toxicities

A: CRS; B: ICANS; C: on target off tumor effects
Clinical Manifestations of CRS

- High Fevers
- Myalgia Arthralgias
- Nausea Vomiting Anorexia
- Fatigue
- Headache
- Hypotension Tachycardia
- Neurologic Change
- Dyspnea Tachypnea, Hypoxia

Clinical Symptoms/Findings
Immune effector cell associated neurotoxicity syndrome (ICANS)

- Confusion
- Delirium
- Transient aphasia
- Encephalopathy
- Bradyphrenia
- Agitation
- Hallucination
- Seizures
- Nerve palsy and peripheral neuropathy
- Dizziness
- Vertigo

**Ide-cel**
- grade 3 parkinsonism
- grade 3 myelitis

**Cita-cel**
- Delayed neurotoxicity is a concern
- Median onset: 27 (11-108) days
- Movement/neurocognitive changes
- Nerve palsy and peripheral neuropathy
Managing Cytokine-Release Syndrome

<table>
<thead>
<tr>
<th>Grade</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
</table>
| 1     | **Tocilizumab**: Onset ≥72 hr after infusion, treat symptomatically; onset <72 hr after infusion, consider tocilizumab 8 mg/kg IV over 1 hr  
**Corticosteroids**: Consider dexamethasone 10 mg IV every 24 hr | |
| 2-3   | **Tocilizumab** 8 mg/kg IV over 1 hr, repeat every 8 hr as needed if not responsive to IV fluids or supplemental O₂  
**Corticosteroids**: Dexamethasone 10 mg IV every 12-24 hr  
If no improvement in 24 hr or rapid progression, repeat tocilizumab and escalate to dexamethasone 20 mg IV every 6-12 hr  
If no improvement in 24 hr or continued rapid progression, repeat tocilizumab and switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times/day | |
| 4 (ICU/critical care required) | **Tocilizumab** 8 mg/kg IV over 1 hr, repeat every 8 hr as needed if not responsive to IV fluids or supplemental O₂  
**Corticosteroids**: Dexamethasone 20 mg IV every 6 hr  
If no improvement in 24 hr, consider methylprednisolone (1-2 g, repeat every 24 hr if needed; taper as clinically indicated) or other anti–T-cell therapies | |

After 2 doses of tocilizumab, consider alternative anticytokine agents; do not exceed 3 doses of tocilizumab in 24 hr, or 4 doses total.
Humoral immune reconstitution after anti-BCMA CAR-T cell therapy in relapse/refractory multiple myeloma

Anti-BCMA CAR-T cells caused a 7-month aplasia of bone marrow normal plasma cells and a longer period of hypogammaglobulinemia.

A prolonged hypogammaglobulinemia suggests a profound and lasting humoral immune deficiency after anti-BCMA CAR-T cell therapy.
The cumulative incidence of infection with bsAb and CAR-T were 25 and 5 (p=0.012), respectively, with 41.2% of patients experiencing at least one episode of infection with bsAb and 23.1% with CAR-T (p=0.141)
<table>
<thead>
<tr>
<th>Antibody–Drug Conjugate</th>
<th>CAR T-cells</th>
<th>Bispecific Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-the-shelf</td>
<td>Personalized</td>
<td>Off the shelf</td>
</tr>
<tr>
<td>Targeted cytotoxicity</td>
<td>Targeted immuno-cytotoxicity: Unprecedented ORR incl. MRD-neg in heavily pretreated pts</td>
<td>Targeted immuno-cytotoxicity; rapid and deep responses in ongoing trials</td>
</tr>
<tr>
<td>Not dependent on T-cell health</td>
<td></td>
<td></td>
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<tr>
<td>Encouraging responses in triple class exposed pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lymphodepletion</td>
<td>Single infusion (“one and done”); long “chemo holiday”</td>
<td>No lymphodepletion</td>
</tr>
<tr>
<td>No steroids</td>
<td></td>
<td>Minimal steroids</td>
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<tr>
<td>Outpatient administration; Can be given in the community</td>
<td>Potentially persistent</td>
<td>Can be given in the community after 1st cycle (once approved)</td>
</tr>
<tr>
<td>Currently requires REMS/close collaboration with Ophthalmology</td>
<td>Manufacturing time makes impractical for pts with rapidly progressive disease</td>
<td>Dosing/schedule/combinations to be determined</td>
</tr>
<tr>
<td>Modest ORR and PFS in TCR pts</td>
<td>FACT-accredited center, with required infrastructure</td>
<td>Initial hospitalization required until low CRS risk</td>
</tr>
<tr>
<td>Requires continuous treatment until progression or intolerance</td>
<td>CRS and ICANS - hospitalization likely required; Safety in frail elderly?</td>
<td>CRS and neurotoxicity possible but low risk; limited severe cases</td>
</tr>
<tr>
<td></td>
<td>Dependent on T-cell health (manufacturing failures)</td>
<td>Dependent on T-cell health (T-cell exhaustion)</td>
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<tr>
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<td>Requires significant social support – caregiver required</td>
<td>Requires continuous treatment</td>
</tr>
</tbody>
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Concerns with current CAR T data

- No survival plateau so far
- CRS occurs virtually in all patients (grade 3 CRS in 5-10%)
- Neurotoxicity can be seen in up to 20%, delayed neurotoxicity with Cita-cel
- Good renal function (upto 45%) mandated for effective LD chemotherapy
- Multiple Myeloma control is necessary before CAR
- Unknown efficacy in CNS disease and plasma cell leukemia

Mechanisms of Relapses
- Loss of antigen
- T cell exhaustion
- Lack of CAR T persistence

Management of Adverse Effects
- CRS
- ICANS
- Infections

Major hurdle is Access to CAR T therapy

Novel Non BCMA approaches
- GRPC5D, FCRH5
- Sequencing of BCMA targeting therapies
Conclusions

• ASCT in MM is here to stay
• ASCT is the unbeaten standard of care for every eligible NDMM
• CAR T therapy have unprecedented responses but no plateau
• CRS/ICANS are manageable
• New unmet need “BCMA refractory population”
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Our Patients and Families

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