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Peter Voorhees, MD
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<td>First Line (1): Smoldering and Transplant-Ineligible Multiple Myeloma</td>
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<td>Relapsed/Refractory: Small Molecules</td>
<td>Suzanne Lentzsch, MD, PhD</td>
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<td>Relapsed/Refractory: CAR Ts</td>
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<td>12.55 PM – 1.00 PM (5 min)</td>
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First Line (1): Smoldering and Transplant-Ineligible Multiple Myeloma

IRENE GHOBRIAL, MD
FIRST LINE (1): SMOLDERING AND TRANSPLANT-INELIGIBLE MULTIPLE MYELOMA – ABSTRACTS

> 57: Longitudinal Immunogenomic Profiling of Tumor and Immune Cells for Minimally-Invasive Monitoring of Smoldering Multiple Myeloma (SMM): The Immunocell Study

> 548: Treatment of High Risk (HR) Smoldering Multiple Myeloma (SMM) with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) Followed By Lenalidomide Maintenance (-R): A Phase 2 Clinical and Correlative Study

> 551: The Phase 3 TOURMALINE-MM2 Trial: Oral Ixazomib, Lenalidomide, and Dexamethasone (IRd) Vs Placebo-Rd for Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma (NDMM)

> 552: Reduction in Absolute Involved Free Light Chain and Difference between Involved and Uninvolved Free Light Chain Is Associated with Prolonged Major Organ Deterioration Progression-Free Survival in Patients with Newly Diagnosed AL Amyloidosis Receiving Bortezomib, Cyclophosphamide, and Dexamethasone with or without Daratumumab: Results from ANDROMEDA
There was general agreement that improvements are needed to identify high-risk patients with smoldering myeloma:

- Additional studies to determine whether genomic changes are driving disease progression or are merely predictive would be beneficial.
- Experts disagreed on whether to treat with curative intent immediately and with a multidrug regimen vs a less aggressive single-agent approach for smoldering disease.
  - Toxicities of the different approaches and potential for developing more-serious disease on the basis of risk-stratification criteria are key considerations.

Experts exercise judgment in risk-assessment and do not universally monitor dynamic disease, especially in patients who have been asymptomatic for longer periods of time.

The TOURMALINE-MM2 data would not change practice approaches for most of the experts:

- The ixazomib toxicity profile is problematic for some of the experts [551].

Some experts are impressed with the data from ANDROMEDA and the use of daratumumab in patients with newly diagnosed amyloidosis [552]:

- Experts speculated on the basis of the ANDROMEDA and MAIA (not presented) trials whether daratumumab should be given as maintenance, acknowledging that there are no data specifically addressing this question.
First Line (2): Induction in Transplant-Eligible Multiple Myeloma

PETER VOORHEES, MD
FIRST LINE (2): INDUCTION IN TRANSPLANT-ELIGIBLE MULTIPLE MYELOMA – ABSTRACTS

> 141: Survival Analysis of Newly Diagnosed Transplant-Eligible Multiple Myeloma Patients in the Randomized Forte Trial

> 142: Upfront Autologous Hematopoietic Stem-Cell Transplantation Improves Overall Survival in Comparison with Bortezomib-Based Intensification Therapy in Newly Diagnosed Multiple Myeloma: Long-Term Follow-up Analysis of the Randomized Phase 3 EMN02/HO95 Study

> 143: Early Versus Late Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma: Long-Term Follow-up Analysis of the IFM 2009 Trial

> 144: A Prospective Phase 2 Study to Assess Minimal Residual Disease after Ixazomib, Lenalidomide and Dexamethasone Treatment for Newly Diagnosed Transplant Eligible Multiple Myeloma Patients
**FIRST LINE (2): INDUCTION IN TRANSPLANT-ELIGIBLE MULTIPLE MYELOMA – KEY TAKEAWAYS**

1. Stem cell transplant remains the “gold standard” for treatment of multiple myeloma (MM).
2. The majority of experts agreed that daratumumab should be part of quadruplet-drug regimens (such as daratumumab + carfilzomib + lenalidomide + dexamethasone [D-KRd]), citing the MAIA and CASSIOPEIA studies (neither presented).
   - Such treatments, however, may be cost-prohibitive for some patients and might not be feasible for elderly or unfit patients.
3. Results of the FORTE trial using KRd upfront impressed several experts.
   - Experts are interested to see results of the 2-drug maintenance in these patients [141].
   - KRd remains a standard of care for these experts.
4. Some experts noted that they will change their treatment approach to trying to induce the deepest remission rather than a “more disease, more treatment” approach.
5. Experts agreed that the best/more-aggressive therapies should be used upfront.
   - Patient benefit cannot “catch up” later if the most effective early line treatments are deferred to later lines.
First Line (3): Maintenance and Prognosis

KEITH STEWART, MB, CHB, MBA
FIRST LINE (3): MAINTENANCE AND PROGNOSIS – ABSTRACTS

> 491: Impact of Minimal Residual Disease (MRD) By Multiparameter Flow Cytometry (MFC) and Next-Generation Sequencing (NGS) on Outcome: Results of Newly Diagnosed Transplant-Eligible Multiple Myeloma (MM) Patients Enrolled in the Forte Trial

> 550: Consolidation Treatment with VRD Followed By Maintenance Therapy Versus Maintenance Alone in Newly Diagnosed, Transplant-Eligible Patients with Multiple Myeloma (MM): A Randomized Phase 3 Trial of the European Myeloma Network (EMN02/HO95)

> 61: High-Dose Melphalan Significantly Increases Mutational Burden in Multiple Myeloma Cells at Relapse: Results from a Randomized Study in Multiple Myeloma

> 549: Daratumumab (DARA) Plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of GRIFFIN after 12 Months of Maintenance Therapy

> 2276: Updated Analysis of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma (NDMM): The Phase 3 MAIA Study
Experts agreed that minimal residual disease (MRD) is an important prognostic marker that could potentially be useful in the future to inform treatment decisions. However, even at the most sensitive level commercially available (10^{-6}), it cannot determine whether the patient is cured.

- Cytogenetic risk is an important consideration across the depths of response.
- MRD-negative results are associated with better outcomes, but there are no trial data supporting treatment decisions that are based on MRD.
  - Some experts stated they would not use MRD to decide whether to continue maintenance therapy.
- MRD status adds to the landscape of prognostic markers and could be an important tool for early detection of relapsing MM before the disease reaches clinically detectable levels.
- A more sensitive MRD assessment (below 10^{-6}) would improve the utility of this marker, allowing early detection and treatment of myeloma cell clonal expansion before overt disease develops.

Experts acknowledged that MRD status is beneficial in guiding the development of maintenance therapies, as emergence of MRD positivity signals that therapy is no longer effective.

- Maintenance therapy with lenalidomide is not optimal and warrants improvement.
  - Experts believe single-agent lenalidomide could drive the emergence of resistant clones.
- A 2-drug maintenance therapy is better than a single drug.
Relapsed/Refractory: Small Molecules

SUZANNE LENTZSCH, MD, PHD
> 415: Randomized Phase 2 Study of Weekly Carfilzomib 70 Mg/m2 and Dexamethasone Plus/Minus Cyclophosphamide in Relapsed and/or Refractory Multiple Myeloma (RRMM) Patients (GEM-KyCyDex)

> 2325: Carfilzomib, Dexamethasone, and Daratumumab Versus Carfilzomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Efficacy and Safety Results of the Phase 3 Candor Study

> 417: ANCHOR (OP-104): Melflufen Plus Dexamethasone (dex) and Daratumumab (dara) or Bortezomib (BTZ) in Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to an IMiD and/or a Proteasome Inhibitor (PI) - Updated Efficacy and Safety

> 726: Selinexor in Combination with Pomalidomide and Dexamethasone (SPd) for Treatment of Patients with Relapsed Refractory Multiple Myeloma (RRMM)
RELAPSED/REFRACTORY: SMALL MOLECULES – ABSTRACTS (2/2)

> 294: Safety and Preliminary Efficacy Results from a Phase II Study Evaluating Combined BRAF and MEK Inhibition in Relapsed/Refractory Multiple Myeloma (rrMM) Patients with Activating BRAF V600E Mutations: The GMMG-Birma Trial

> 295: Safety and Preliminary Efficacy Results from a Phase Ib/II Study of Cobimetinib As a Single Agent and in Combination with Venetoclax with or without Atezolizumab in Patients with Relapsed/Refractory Multiple Myeloma

> 416: Circularly Permuted TRAIL (CPT) Combined with Thalidomide and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study (CPT-MM301)

> 724: First Results of Iberdomide (IBER; CC-220) in Combination with Dexamethasone (DEX) and Daratumumab (DARA) or Bortezomib (BORT) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)
RELAPSED/REFRACTORY: SMALL MOLECULES – KEY TAKEAWAYS

> Experts find the data on the combined inhibition of MEK and BRAF exciting and promising
  - BRAF targeting represents an intriguing approach for future therapeutics
    - Experts would like to see more studies on BRAF inhibition

> Experts noted that “venetoclax is here to stay,” especially in patients with t(11;14)

> Experts initially found the GEM-KyCyDex results in lenalidomide-refractory patients appealing but were disappointed overall, noting the equivalent response rates and deaths in both study arms [415]

> Experts believe the utility of selinexor and melflufen is limited in MM because the agents do not have favorable benefit:risk profiles compared with available agents [417; 726]
> 412: Apollo: Phase 3 Randomized Study of Subcutaneous Daratumumab Plus Pomalidomide and Dexamethasone (D-Pd) Versus Pomalidomide and Dexamethasone (Pd) Alone in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM)

> 413: A Randomized Phase II, Open Label, Study of Daratumumab, Weekly Low-Dose Oral Dexamethasone and Cyclophosphamide with or without Pomalidomide in Patients with Relapsed and Refractory Multiple Myeloma

> 2316: Isatuximab Plus Carfilzomib and Dexamethasone Vs Carfilzomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma (IKEMA): Interim Analysis of a Phase 3, Randomized, Open-Label Study

> 725: Part 1 Results of a Dose Finding Study of Belantamab Mafodotin (GSK2857916) in Combination with Pomalidomide (POM) and Dexamethasone (DEX) for the Treatment of Relapsed/Refractory Multiple Myeloma (RRMM)

> 180: Updated Phase 1 Results of Teclistamab, a B-Cell Maturation Antigen (BCMA) x CD3 Bispecific Antibody, in Relapsed and/or Refractory Multiple Myeloma (RRMM)
290: A Phase 1, First-in-Human Study of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D (GPRC5D) x CD3 Bispecific Antibody, in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)

291: REGN5458, a BCMA x CD3 Bispecific Monoclonal Antibody, Induces Deep and Durable Responses in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

181: A Phase 1 First in Human (FIH) Study of AMG 701, an Anti-B-Cell Maturation Antigen (BCMA) Half-Life Extended (HLE) BiTE® (bispecific T-cell engager) Molecule, in Relapsed/Refractory (RR) Multiple Myeloma (MM)

292: Initial Clinical Activity and Safety of BFCR4350A, a FcRH5/CD3 T-Cell-Engaging Bispecific Antibody, in Relapsed/Refractory Multiple Myeloma

293: Initial Results of a Phase I Study of TNB-383B, a BCMA x CD3 Bispecific T-Cell Redirecting Antibody, in Relapsed/Refractory Multiple Myeloma

3206: Preliminary Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Subcutaneously (SC) Administered PF-06863135, a B-Cell Maturation Antigen (BCMA)-CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)
While bispecifics, antibody-drug conjugates, and emerging antibody therapies such as anti-CD30s represent important treatment options, transplant remains a major player in 2020.

Bispecifics unquestionably will change how physicians treat MM
- Bispecifics may supplant antibody-drug conjugates or other therapies in the treatment of MM
  - Experts believe bispecific antibodies will become a principal treatment option for MM and may even allow patients to obtain a cure in early line treatments
  - Bispecifics and other immunotherapies highlight the growing focus on development of precision medicines in MM

Experts speculated that bispecifics may eventually prove to be an approach that is superior to chimeric antigen receptor T-cell (CAR T) therapies.
Relapsed/Refractory: CAR Ts

SAGAR LONIAL, MD
130: Updated Results from the Phase I CRB-402 Study of Anti-Bcma CAR-T Cell Therapy bb21217 in Patients with Relapsed and Refractory Multiple Myeloma: Correlation of Expansion and Duration of Response with T Cell Phenotypes

131: Idecabtagene Vicleucel (ide-cel, bb2121), a BCMA-Directed CAR T Cell Therapy, in Patients with Relapsed and Refractory Multiple Myeloma: Updated Results from Phase 1 CRB-401 Study

133: Results from Lummicar-2: A Phase 1b/2 Study of Fully Human B-Cell Maturation Antigen-Specific CAR T Cells (CT053) in Patients with Relapsed and/or Refractory Multiple Myeloma

134: Phase 1/2 Study of the Safety and Response of P-BCMA-101 CAR-T Cells in Patients with Relapsed/Refractory (r/r) Multiple Myeloma (MM) (PRIME) with Novel Therapeutic Strategies

177: CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen–Directed Chimeric Antigen Receptor T Cell Therapy, in Relapsed/Refractory Multiple Myeloma

721: Biallelic Loss of BCMA Triggers Resistance to Anti-BCMA CAR T Cell Therapy in Multiple Myeloma
CAR T therapy is still in its infancy in MM, with many questions to be resolved
- Is a second dose of this therapy needed to produce a more sustained response?
- More science is needed on CAR Ts to better understand mechanisms of resistance
- Infection risk is a significant concern or limitation in using CAR T therapy

Experts suggested that CAR T therapy should be given earlier, when there are more functional T cells
- Patients not appropriate for CAR T therapy should see benefit from bispecific antibodies instead
- CAR T therapy is not likely to be an effective option for end-stage MM patients

Allogeneic CAR T therapy does not appear to be as beneficial as autologous CAR T treatments

Various trial data, small patient numbers, and demographics make interpretation of CAR T therapy benefit in MM difficult
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