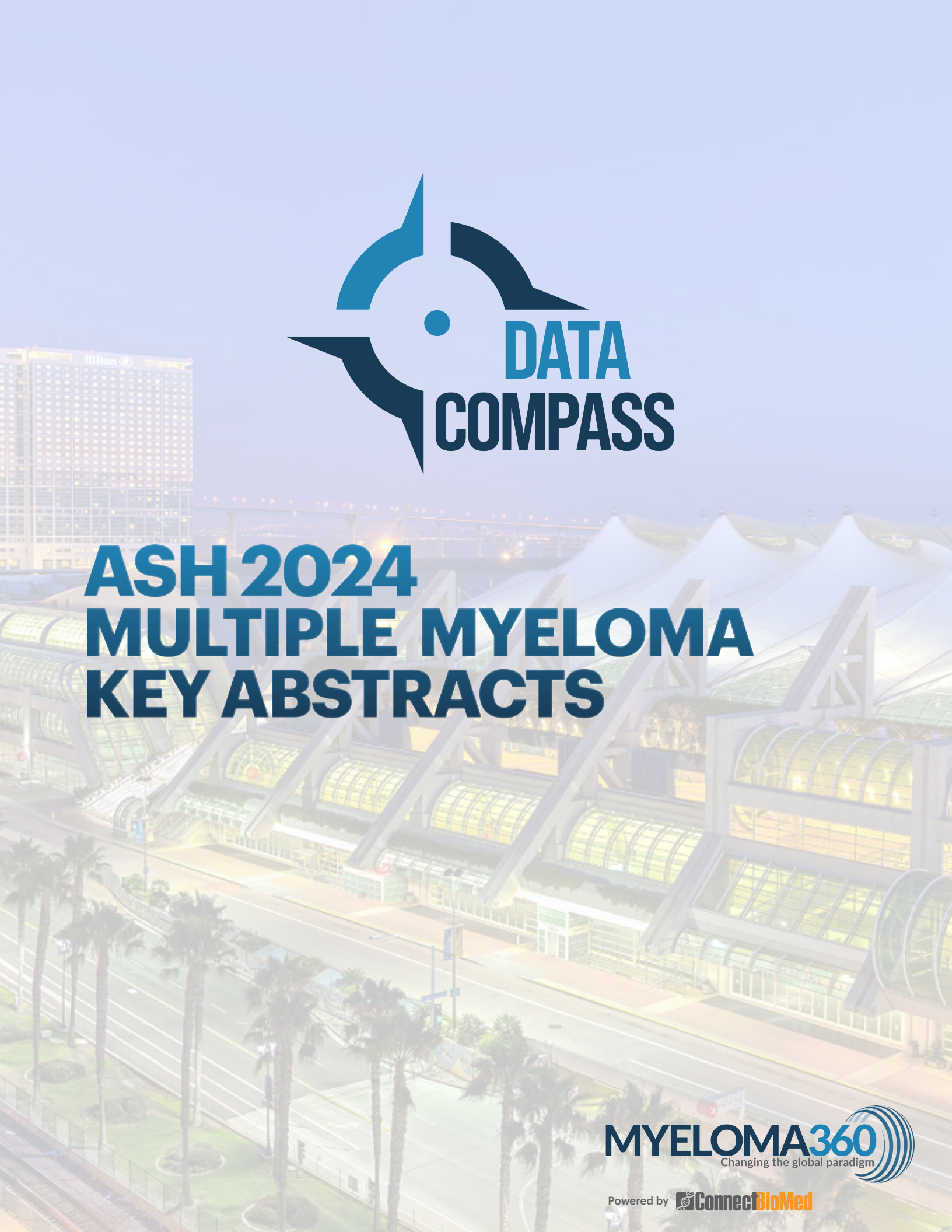

DATA COMPASS

ASH 2024 MULTIPLE MYELOMA KEY ABSTRACTS

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Abstract Number: 258

Daratumumab-Based Quadruplet Versus Triplet Induction Regimens in Frontline Transplant-Eligible Newly Diagnosed Multiple Myeloma: A Systematic Review and Meta-Analysis

Presenter: Joao Tadeu Damian Souto Filho, MD, PhD
Session: 653. Multiple Myeloma: Clinical and Epidemiological: Addressing Hematologic and Immune Toxicities and the Status of Quad Therapies
Date & Time: Saturday, December 7, 2024 3:15 PM–3:30 PM
Location: Pacific Ballroom Salons 21-22 (Marriott Marquis San Diego Marina)

Abstract Summary:

- The addition of daratumumab to triplet induction regimens significantly improves overall survival (OS) in transplant-eligible newly diagnosed multiple myeloma (TE-NDMM) patients, with a pooled hazard ratio (HR) of 0.60 (95% CI 0.48-0.75; p < 0.00001).
- Progression-free survival (PFS) is also significantly enhanced with daratumumab-based quadruplet regimens, showing a pooled HR of 0.49 (95% CI 0.37-0.65; p < 0.00001).
- Subgroup analysis of D-VRD versus VRD regimens indicates that daratumumab significantly extends both OS (pooled HR 0.68; 95% CI 0.48-0.97; p = 0.03) and PFS (pooled HR 0.41; 95% CI 0.31-0.54; p < 0.00001).
- The meta-analysis supports the use of daratumumab-based quadruplet regimens as a superior frontline treatment option for TE-NDMM, potentially guiding clinical decision-making in the absence of long-term data from ongoing trials.

Clinical relevance: Practice Changing

Rationale:

1. Strength and Reliability of Data:

- The meta-analysis includes data from four studies, three of which are randomized controlled trials (RCTs), providing a high level of evidence. The inclusion of a large sample size (3,327 patients) enhances the reliability of the findings.
- The systematic review and meta-analysis were conducted following Cochrane Collaboration and PRISMA guidelines, ensuring methodological rigor.
- The statistical significance of the results is strong, with pooled hazard ratios indicating a substantial improvement in both overall survival (OS) and progression-free survival (PFS) with daratumumab-based regimens.

2. Comparison to Current Standard-of-Care:

- The current standard induction therapy for TE-NDMM patients typically involves triplet regimens. The addition of daratumumab to these regimens (forming quadruplet regimens) has shown significant improvements in survival outcomes.

- The pooled hazard ratios for OS (0.60) and PFS (0.49) suggest a meaningful clinical benefit over existing triplet regimens, indicating a potential shift in the standard of care.

3. Clinical Relevance and Feasibility:

- The findings are clinically relevant as they provide evidence supporting the use of daratumumab-based quadruplet regimens as a superior first-line treatment option for TE-NDMM patients.
- The feasibility of incorporating daratumumab into existing regimens is supported by previous studies demonstrating its safety and efficacy in combination with other agents.
- Given the robust evidence from multiple RCTs, the significant improvement in survival outcomes, and the feasibility of integrating daratumumab into current treatment protocols, these findings are strong enough to warrant a change in clinical practice for the treatment of transplant-eligible newly diagnosed multiple myeloma patients.

LINK TO ABSTRACT

Abstract Number: 362

Phase 3 Randomized Study of Daratumumab (DARA) + Bortezomib, Lenalidomide and Dexamethasone (VRd) Versus Alone in Patients with Transplant-Ineligible Newly Diagnosed Multiple Myeloma or for Whom Transplant Is Not Planned As Initial Therapy: Analysis of Minimal Residual Disease in the Cepheus Trial

Presenter: Sonja Zweegman, MD, PhD
Session: 653. Multiple Myeloma: Clinical and Epidemiological: Advancing Minimal Residual Disease (MRD): Detection, Impact on Prognosis and Treatment Decisions
Date & Time: Saturday, December 7, 2024 4:15 PM–4:30 PM
Location: San Diego Ballroom AB (Marriott Marquis San Diego Marina)

Abstract Summary:

- D-VRd significantly increased overall and sustained MRD negativity rates at both 10^{-5} and 10^{-6} sensitivity thresholds compared to VRd in transplant-ineligible and transplant-deferred NDMM patients.
- Prespecified subgroup analyses showed consistent MRD benefits with D-VRd across most subgroups, except for those with high cytogenetic risk.
- D-VRd improved progression-free survival (PFS) compared to VRd, with a 54-month PFS rate of 81.0% in MRD-negative patients versus 69.5% for VRd.
- Patients achieving MRD-negativity with D-VRd had a higher likelihood of being alive and progression-free at 54 months, supporting D-VRd as a potential new standard of care for NDMM patients who are transplant-ineligible or have deferred transplant.

Clinical relevance: Practice Changing

Rationale:

1. Strength and Reliability of Data:

- The CEPHEUS study is a multicenter, open-label, randomized, phase 3 trial, which provides a high level of evidence due to its robust design.
- The sample size is substantial, with 395 patients randomized, ensuring adequate power to detect differences between the treatment groups.
- The statistical significance of the findings is strong, with P-values <0.0001 for MRD-negativity rates and sustained MRD negativity, indicating a high level of confidence in the results.

2. Comparison to Current Standard-of-Care:

- The study compares D-VRd (Daratumumab with VRd) to the current standard VRd regimen in transplant-ineligible or deferred patients with newly diagnosed multiple myeloma (NDMM).
- D-VRd demonstrated superior outcomes in terms of MRD-negativity rates and progression-free survival (PFS), with a hazard ratio of 0.57 for PFS, indicating a 43% reduction in the risk of progression or death compared to VRd.
- The improvement in MRD-negativity rates at both 10^{–5} and 10^{–6} thresholds suggests a deeper and more durable response, which is associated with better long-term outcomes.

3. Clinical Relevance and Feasibility:

- The findings are clinically relevant as they provide evidence for a new standard of care in a specific patient population (transplant-ineligible or deferred NDMM patients).
- The use of Daratumumab in combination with VRd is feasible in clinical practice, given its established use and manageable safety profile.
- The significant improvement in PFS and MRD-negativity rates supports the immediate incorporation of D-VRd into clinical practice for the specified patient group.

Overall, the study's results are compelling and provide strong evidence for the adoption of D-VRd as a new standard of care, making it practice changing for the treatment of transplant-ineligible or deferred NDMM patients.

LINK TO ABSTRACT

Abstract Number: 675

Daratumumab Plus Lenalidomide (D-R) Versus Lenalidomide (R) Alone As Maintenance Therapy in Newly Diagnosed Multiple Myeloma (NDMM) after Transplant: Analysis of the Phase 3 Auriga Study Among Clinically Relevant Subgroups

Presenter: Laahn Foster, MD
Session: 654. Multiple Myeloma: Pharmacologic Therapies: Optimizing Therapy in Newly Diagnosed Myeloma and Beyond
Date & Time:
Location: Pacific Ballroom Salons 21-22 (Marriott Marquis San Diego Marina)

Abstract Summary:

- The addition of daratumumab (DARA) to lenalidomide (R) maintenance therapy significantly improved the MRD-negative conversion rate by 12 months across all subgroups compared to R alone, with notable improvements in patients <65 years, ≥65 years, Black, White, ISS stage III, and those with high cytogenetic risk.
- Progression-free survival (PFS) hazard ratios consistently favored the D-R combination over R alone across all subgroups, indicating a potential benefit in delaying disease progression.
- The incidence of grade 3/4 treatment-emergent adverse events (TEAEs) was higher in the D-R group compared to the R group, particularly among Black and White patients and those <65 years.
- Grade 3/4 infection rates were similar between D-R and R groups across most subgroups, with slight variations.
- The study supports the benefit of adding DARA to R maintenance in improving outcomes for anti-CD38 naive NDMM patients who are MRD-positive post-ASCT, despite an increased risk of TEAEs.

Clinical relevance: Important but Not Practice Changing

Rationale:

1. Strength and Reliability of the Data:

- The study is a phase 3 randomized controlled trial, which is a strong study design for evaluating the efficacy of a treatment. The sample size of 200 patients is reasonable, but not large, which may limit the generalizability of the findings.
- The primary endpoint, MRD-negative conversion rate, is a relevant and increasingly recognized surrogate marker for progression-free survival (PFS) in multiple myeloma.
- The statistical significance of the MRD-negative conversion rates across various subgroups is compelling, with odds ratios indicating a clear benefit of the D-R combination over R alone.

2. Comparison to Current Standard-of-Care:

- The current standard of care for transplant-eligible newly diagnosed multiple myeloma (NDMM) patients includes induction/consolidation therapy followed by maintenance therapy with lenalidomide (R).
- The addition of daratumumab (DARA) to R maintenance shows improved MRD-negative conversion rates and favorable PFS hazard ratios.
- However, while the MRD-negative conversion rates are promising, the PFS hazard ratios, although favoring D-R, do not reach statistical significance in most subgroups, which is a critical factor for practice-changing recommendations.

3. Clinical Relevance and Feasibility:

- The findings are clinically relevant as they suggest a potential benefit of adding DARA to R maintenance therapy in improving MRD-negative rates and possibly PFS in certain subgroups of patients.
- The increased incidence of grade 3/4 treatment-emergent adverse events (TEAEs) with D-R, particularly in younger patients and across racial groups, raises concerns about the safety and tolerability of this regimen, which may limit its immediate adoption in clinical practice.

In summary, while the study provides valuable insights and suggests a potential benefit of adding DARA to R maintenance therapy, the lack of statistically significant improvement in PFS and the increased incidence of adverse events suggest that these findings are not yet strong enough to change current clinical practice. Further studies with larger sample sizes and longer follow-up are needed to confirm these results and assess the long-term impact on overall survival and quality of life.

LINK TO ABSTRACT

Abstract Number: 771

Final Analysis of the Randomised UK MRA Myeloma XI+ Trial Examining Krdc (carfilzomib, lenalidomide, dexamethasone and cyclophosphamide) As Induction Therapy for Newly Diagnosed Multiple Myeloma Patients

Presenter: Charlotte Pawlyn, PhD
Session: 654. Multiple Myeloma: Pharmacologic Therapies: Refining the Evidence: Randomized Trials in Multiple Myeloma
Date & Time: Monday, December 9, 2024 11:00 AM–11:15 AM
Location: Pacific Ballroom Salons 21-22 (Marriott Marquis San Diego Marina)

Abstract Summary:

- The KRdc regimen (carfilzomib, lenalidomide, dexamethasone, cyclophosphamide) significantly improved progression-free survival (PFS) compared to triplet therapies (CRd/CTd), with a median PFS of 56 months versus 37 months (HR 0.69, p<0.001).

- KRdc demonstrated improved PFS across all cytogenetic risk groups, including standard risk (SR), high risk (HiR), and ultra-high risk (UHiR), with the most pronounced benefit in UHiR patients.
- Minimal residual disease (MRD) negativity was more frequently achieved with KRdc, both after induction (38.5%) and post-ASCT (57.0%), correlating with improved PFS.
- Overall survival (OS) analysis showed a significant benefit for KRdc when including all randomized patients, with a 60-month OS of 76% versus 68% for CTd/CRd (HR 0.80, p=0.011), particularly benefiting patients with ISS stage 3 and HiR/UHiR disease.
- The study underscores the clinical advantage of early combination therapy with proteasome inhibitors and immunomodulatory drugs, especially for patients with aggressive myeloma.

Clinical relevance: Practice Changing

Rationale:

1. Strength and Reliability of the Data:

- The study is a phase III randomized trial, which is a robust design for evaluating the efficacy of new treatments.
- The sample size is substantial, with 1056 patients undergoing induction randomization, providing a strong basis for statistical analysis.
- The study reports a significant improvement in progression-free survival (PFS) with a hazard ratio (HR) of 0.69 (95% CI 0.60, 0.80, p<0.001) for the KRdc group compared to the triplet therapies, indicating a strong effect size.
- The overall survival (OS) analysis, although initially underpowered due to early trial closure, was adjusted for temporal changes and still showed a significant improvement (HR 0.80, 95% CI 0.67, 0.95, p=0.011).

2. Comparison to Current Standard-of-Care:

- The current standard-of-care for newly diagnosed multiple myeloma (NDMM) often involves triplet regimens. The addition of carfilzomib to a triplet regimen (KRdc) represents an intensified induction approach.
- The study demonstrates that KRdc not only improves PFS but also shows a significant OS benefit when adjusted for temporal trends, which is a critical endpoint in oncology.
- The achievement of minimal residual disease (MRD) negativity was higher in the KRdc group, which is increasingly recognized as an important prognostic marker in multiple myeloma.

3. Clinical Relevance and Feasibility:

- The findings are clinically relevant as they suggest a new standard for induction therapy in NDMM, particularly for patients with high-risk cytogenetic profiles.
- The regimen is feasible in clinical practice, as carfilzomib is already an approved drug for multiple myeloma, and the combination with lenalidomide, dexamethasone, and cyclophosphamide is manageable in terms of administration and toxicity.

- The study emphasizes the importance of early and aggressive treatment, which could lead to changes in treatment guidelines, especially for high-risk patients.

Overall, the evidence from this trial is strong enough to support a change in clinical practice, particularly for patients with high-risk or ultra-high-risk multiple myeloma, making it a practice-changing study.

LINK TO ABSTRACT

Abstract Number: 772

Belantamab Mafodotin, Bortezomib, and Dexamethasone Vs Daratumumab, Bortezomib, and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Overall Survival Analysis and Updated Efficacy Outcomes of the Phase 3 Dreamm-7 Trial

Presenter: Vania Hungria, MD, PhD
Session: 654. Multiple Myeloma: Pharmacologic Therapies: Refining the Evidence: Randomized Trials in Multiple Myeloma
Date & Time: Monday, December 9, 2024 11:15 AM–11:30 AM
Location: Pacific Ballroom Salons 21-22 (Marriott Marquis San Diego Marina)

Abstract Summary:

- The DREAMM-7 trial demonstrated that the triplet regimen of belantamab mafodotin, bortezomib, and dexamethasone (BVd) significantly improved progression-free survival (PFS) compared to daratumumab, bortezomib, and dexamethasone (DVd) in patients with relapsed/refractory multiple myeloma (MM) after at least one prior line of therapy.
- BVd showed a median PFS of 36.6 months versus 13.4 months for DVd, with a hazard ratio (HR) of 0.41, indicating a substantial reduction in the risk of disease progression or death.
- BVd was associated with higher rates of complete response or better plus minimal residual disease (MRD) negativity (25% vs 10%) and a longer duration of response (DOR) compared to DVd.
- Although median overall survival (OS) was not reached in either arm at the first interim analysis, there was a strong trend favoring BVd, with an HR of 0.57, suggesting a potential OS benefit.
- These findings suggest that BVd could become a new standard of care for MM at first relapse or later, with updated OS results anticipated at ASH 2024.

Clinical relevance: Practice Changing

Rationale:

1. Strength and Reliability of the Data:

- The DREAMM-7 trial is a global, randomized, open-label, phase 3 study, which provides a high level of evidence due to its robust design.
- The study included a substantial sample size of 494 patients, ensuring adequate power to detect differences between the treatment arms.
- The primary endpoint of progression-free survival (PFS) was met with a highly statistically significant hazard ratio (HR) of 0.41 (95% CI, 0.31-0.53; P<.00001), indicating a strong treatment effect favoring the belantamab mafodotin, bortezomib, and dexamethasone (BVd) regimen over the daratumumab, bortezomib, and dexamethasone (DVd) regimen.

2. Comparison to Current Standard-of-Care:

- The BVd regimen demonstrated a median PFS of 36.6 months compared to 13.4 months with DVd, which is a substantial improvement over the current standard-of-care.
- BVd also showed higher rates of complete response or better plus minimal residual disease (MRD) negativity (25% vs 10%) and a more favorable duration of response (DOR) than DVd.
- The observed trend towards improved overall survival (OS) with BVd, with an HR of 0.57 (95% CI, 0.40-0.80), further supports its potential superiority.

3. Clinical Relevance and Feasibility:

- The findings suggest that BVd could become a new standard of care for patients with relapsed/refractory multiple myeloma (MM) after at least one prior line of therapy, given its significant efficacy benefits.
- The study's results are clinically meaningful, showing not only improved PFS but also a trend towards better OS, which is crucial for patient outcomes.
- The anticipated presentation of updated OS data at ASH 2024 is expected to further solidify the practice-changing potential of the BVd regimen.

Overall, the DREAMM-7 trial provides compelling evidence that supports the incorporation of the BVd regimen into clinical practice for the treatment of relapsed/refractory MM, marking it as a practice-changing development.

LINK TO ABSTRACT

Abstract Number: 773

Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients with High-Risk Smoldering Multiple Myeloma: Primary Results of the Aquila Study

Presenter: Meletios-Athanasios Dimopoulos
Session: 654. Multiple Myeloma: Pharmacologic Therapies: Refining the Evidence: Randomized Trials in Multiple Myeloma
Date & Time: Monday, December 9, 2024 11:30 AM–11:45 AM
Location: **Pacific Ballroom Salons 21-22 (Marriott Marquis San Diego Marina)**

Abstract Summary:

- Daratumumab (DARA) significantly improved progression-free survival (PFS) in high-risk smoldering multiple myeloma (SMM) patients compared to active monitoring, with a hazard ratio (HR) of 0.49 and a median PFS not reached in the DARA group versus 41.5 months for active monitoring.
- The overall response rate (ORR) was markedly higher with DARA (63.4%) compared to active monitoring (2.0%), and the time to first-line multiple myeloma (MM) treatment was significantly prolonged with DARA.
- Positive trends were observed for PFS on first-line MM treatment (PFS2) and overall survival (OS) in favor of DARA, with 60-month OS rates of 93.0% for DARA versus 86.9% for active monitoring.
- Grade 3/4 treatment-emergent adverse events (TEAEs) were more frequent in the DARA group (40.4%) compared to active monitoring (30.1%), but the incidence of fatal TEAEs was low in both groups.
- The study supports early intervention with DARA monotherapy as a beneficial strategy for delaying progression to active MM in high-risk SMM patients, compared to the current standard of care of active monitoring.

Clinical relevance: Practice Changing

Rationale:

1. Strength and Reliability of the Data:

- The study is a phase 3 randomized controlled trial (RCT), which is the gold standard for clinical research, providing high-quality evidence.
- A substantial sample size of 390 patients was randomized, ensuring adequate power to detect differences between the treatment and control groups.
- The statistical significance of the primary endpoint, progression-free survival (PFS), was robust (HR, 0.49; 95% CI, 0.36-0.67; P < 0.0001), indicating a strong effect of daratumumab (DARA) in delaying progression to multiple myeloma (MM).
- Secondary endpoints, such as overall response rate (ORR) and time to first-line MM treatment, also showed significant improvements with DARA, further supporting the primary findings.

2. Comparison to Current Standard-of-Care:

- Currently, high-risk smoldering multiple myeloma (SMM) is managed with active monitoring, with no approved treatments to delay progression to MM.
- The study demonstrates that DARA monotherapy significantly prolongs PFS compared to active monitoring, with a median PFS not reached in the DARA group versus 41.5 months in the control group.
- The ORR was markedly higher in the DARA group (63.4% vs. 2.0%), indicating a substantial therapeutic benefit.
- These results suggest a paradigm shift in the management of high-risk SMM, providing a proactive treatment option that could alter the disease course.

3. Clinical Relevance and Feasibility:

- DARA is already approved for use in other stages of MM, suggesting that its safety profile is well understood and manageable.
- The treatment regimen (subcutaneous administration) is feasible and aligns with existing clinical practices for MM, facilitating integration into current healthcare settings.
- The low incidence of grade 3/4 treatment-emergent adverse events (TEAEs) and treatment discontinuations due to adverse events supports the tolerability of DARA in this patient population.

Overall, the findings from the AQUILA study provide compelling evidence that DARA monotherapy can significantly delay progression to active MM in patients with high-risk SMM, offering a new therapeutic strategy that could be immediately incorporated into clinical practice.

LINK TO ABSTRACT

Abstract Number: 774

The IFM2017-03 Phase 3 Trial: A Dexamethasone Sparing-Regimen with Daratumumab and Lenalidomide for Frail Patients with Newly-Diagnosed Multiple Myeloma

Presenter: Salomon Manier, MD, PhD
Session: 654. Multiple Myeloma: Pharmacologic Therapies: Refining the Evidence: Randomized Trials in Multiple Myeloma
Date & Time: Monday, December 9, 2024 11:45 AM–12:00 PM
Location: Pacific Ballroom Salons 21-22 (Marriott Marquis San Diego Marina)

Abstract Summary:

- The IFM2017-03 trial demonstrated that the daratumumab lenalidomide (DR) regimen significantly improved progression-free survival (PFS) compared to lenalidomide dexamethasone (Rd) in frail elderly patients with newly diagnosed multiple myeloma, with a median PFS of 48.5 months for DR versus 21.5 months for Rd (HR 0.51, p<0.0001).

- Overall response rates were higher in the DR arm (92%) compared to the Rd arm (85%, p=0.025), and the median overall survival (OS) was not reached in the DR arm versus 36.0 months in the Rd arm (HR 0.46, p=0.0001).
- The DR regimen was associated with a higher incidence of grade ≥3 hematologic adverse events, particularly neutropenia (62% in DR vs. 33% in Rd), but similar rates of grade ≥3 infections and pneumonia.
- Discontinuation rates due to adverse events were comparable between the two arms (28% in DR vs. 34% in Rd).
- The DR group experienced significantly shorter times to clinically meaningful improvement in health-related quality of life across all QLQ-C30 domains compared to the Rd group.

Clinical relevance: Practice Changing

Rationale:

1. Strength and Reliability of the Data:

- The IFM2017-03 trial is a phase 3, prospective, randomized, open-label study, which is a robust design for evaluating the efficacy and safety of new treatment regimens.
- The sample size of 295 patients is adequate, and the study includes a well-defined frail elderly population with NDMM, which is often underrepresented in clinical trials.
- The primary endpoint, progression-free survival (PFS), showed a statistically significant improvement with a hazard ratio (HR) of 0.51 and a p-value of <0.0001, indicating a strong reduction in the risk of progression or death with the DR regimen compared to Rd.
- Secondary endpoints, including overall survival (OS) and overall response rate, also demonstrated significant benefits for the DR arm, with a HR for OS of 0.46 and a p-value of 0.0001.

2. Comparison to Current Standard-of-Care:

- The current standard-of-care for elderly frail patients with NDMM often includes lenalidomide and dexamethasone (Rd). However, long-term dexamethasone use is associated with significant side effects, particularly in frail patients.
- The DR regimen, which reduces dexamethasone exposure, not only improves PFS and OS but also maintains a favorable safety profile, addressing a critical need for safer treatment options in this population.
- The study demonstrates that the DR regimen provides superior outcomes compared to the standard Rd regimen, with a significant reduction in the risk of progression or death and improved health-related quality of life (HRQoL).

3. Clinical Relevance and Feasibility:

- The findings are highly relevant for clinical practice, particularly for the management of frail elderly patients with NDMM, who are at higher risk of adverse events and treatment discontinuation.
- The DR regimen is feasible for implementation in clinical settings, as it involves the use of daratumumab, which is already an approved agent for multiple myeloma, and lenalidomide, a standard treatment.

- The improved HRQoL and reduced dexamethasone-related side effects make the DR regimen an attractive option for this vulnerable patient population.

Overall, the IFM2017-03 trial provides compelling evidence that the DR regimen is superior to the standard Rd regimen for frail elderly patients with NDMM, with significant improvements in efficacy, safety, and quality of life. These findings are strong enough to warrant immediate incorporation into clinical practice, making this study practice changing.

LINK TO ABSTRACT

Abstract Number: 936

Comparative Safety and Efficacy of Ciltacabtagene Autoleucel and Idecabtagene Vicleucel CAR T-Cell Therapies in Relapsed or Refractory Multiple Myeloma

Presenter: Doris K. Hansen, MD
Session: 907. Outcomes Research: Plasma Cell Disorders: Bispecific Antibodies and CAR-T Therapies in Myeloma-The Yin and Yang of Powerful Therapies
Date & Time:
Location: San Diego Ballroom AB (Marriott Marquis San Diego Marina)

Abstract Summary:

- Cilta-cel demonstrated superior efficacy compared to ide-cel, with higher rates of complete and partial responses, and longer progression-free survival (PFS) and overall survival (OS).
- Patients treated with cilta-cel experienced a higher incidence of grade ≥3 cytokine release syndrome (CRS), infections, and delayed neurotoxicity (NT) compared to those treated with ide-cel.
- There was no significant association between therapy type and the occurrence of second primary malignancies (SPMs), severe immune effector cell-associated neurotoxicity syndrome, any CRS, severe cytopenias, or non-relapse mortality.
- In a propensity-matched analysis, cilta-cel maintained superior PFS across various subgroups, including those with extramedullary disease, high-risk cytogenetics, and elevated baseline ferritin.
- The study highlights the need for further validation through large-scale real-world experiences or prospective studies to confirm these findings and guide CAR T-cell therapy selection.

Clinical relevance: Important but Not Practice Changing

Rationale:

1. Strength and Reliability of the Data:

- The study is a retrospective chart review, which inherently has limitations compared to prospective randomized controlled trials (RCTs). While the use of inverse probability of treatment weighting (IPTW) and propensity score matching helps balance covariates and reduce bias, these methods cannot fully account for all potential confounders.
- The sample size is relatively large (641 patients leukapheresed, 586 infused), which adds robustness to the findings. However, the retrospective nature and potential for selection bias remain concerns.
- The statistical significance of the findings, particularly the superior progression-free survival (PFS) and overall survival (OS) for cilta-cel, is compelling (e.g., PFS HR=0.47, $p<0.001$; OS HR=0.63, $p=0.02$).

2. Comparison to Current Standard-of-Care:

- Both cilta-cel and ide-cel are already approved CAR T-cell therapies for relapsed/refractory multiple myeloma (RRMM), and this study provides a direct comparison in a real-world setting.
- The study suggests cilta-cel may offer superior efficacy in terms of response rates and survival outcomes compared to ide-cel. However, this comes with a higher incidence of certain toxicities, such as grade ≥ 3 cytokine release syndrome (CRS) and delayed neurotoxicity (NT).
  - The findings are valuable for informing treatment decisions and patient counseling, particularly in weighing the benefits of improved efficacy against the risks of increased toxicity.

3. Clinical Relevance and Feasibility:

- The study's results are clinically relevant as they provide insights into the comparative effectiveness and safety profiles of two CAR T-cell therapies in a real-world setting.
- However, the increased toxicity associated with cilta-cel may limit its applicability to certain patient populations, and careful patient selection and monitoring would be necessary.
- The conclusion emphasizes the need for further validation through prospective studies or additional real-world data to confirm these findings and enhance their applicability in clinical practice.

In summary, while the study provides important insights into the comparative efficacy and safety of cilta-cel and ide-cel, the retrospective design and need for further validation mean that the findings are not yet strong enough to warrant immediate changes to clinical practice. However, they are valuable for guiding treatment decisions and patient counseling in the context of RRMM.

LINK TO ABSTRACT

Abstract Number: 1031

Phase 2 Registrational Study of Anitocabtagene Autoleucel for the Treatment of Patients with Relapsed and/or Refractory Multiple Myeloma: Preliminary Results from the IMMagine-1 Trial

Presenter: Ciara Louise Freeman, PhD, MSc, FRCPC, MRCP
Session: 655. Multiple Myeloma: Cellular Therapies: Unleashing Cell Therapies Against Myeloma
Date & Time:
Location: Pacific Ballroom Salons 24-26 (Marriott Marquis San Diego Marina)

Abstract Summary:

- In the Phase 2 iMMagine-1 trial, anitocabtagene autoleucel (anito-cel) demonstrated a high overall response rate (ORR) of 95% in patients with relapsed/refractory multiple myeloma (RRMM), with a complete/stringent complete response (CR/sCR) rate of 62%.
- Minimal residual disease (MRD) negativity was achieved in 92% of evaluable patients, indicating deep responses.
- The estimated 6-month progression-free survival (PFS) and overall survival (OS) rates were 90% and 95%, respectively, with median PFS and OS not yet reached.
- Safety profile showed manageable adverse events: 84% experienced cytokine release syndrome (CRS), mostly Grade 1, with only one Grade 5 event; immune effector cell-associated neurotoxicity syndrome (ICANS) was observed in 9% of patients, all resolving without sequelae.
- The study reported no delayed neurotoxicity or other severe neurological events, and the treatment was deemed effective and manageable in a high-risk RRMM population.

Clinical relevance: Important but Not Practice Changing

Rationale:

1. Strength and Reliability of the Data:

- The study is a Phase 2 trial, which provides a moderate level of evidence. While promising, Phase 2 trials are generally not sufficient alone to change clinical practice without further validation in larger Phase 3 trials.
- The sample size of 58 patients is relatively small, which limits the generalizability of the findings.
- The follow-up period is relatively short (median of 10.3 months), which may not fully capture long-term efficacy and safety outcomes.
- The reported outcomes, such as the overall response rate (ORR) of 95% and a complete response/ stringent complete response (CR/sCR) rate of 62%, are impressive, but longer follow-up is needed to confirm durability.

2. Comparison to Current Standard-of-Care Treatments:

- The results are promising, especially in a heavily pre-treated, high-risk population (triple- and penta-class refractory multiple myeloma), where treatment options are limited.
- The high ORR and MRD negativity rates suggest that anito-cel could be a potent option for patients with relapsed/refractory multiple myeloma.
- However, current standard-of-care treatments for multiple myeloma are well-established, and new therapies typically require robust evidence from Phase 3 trials to demonstrate superiority or significant benefit over existing options.

3. Clinical Relevance and Feasibility:

- The safety profile appears manageable, with most cytokine release syndrome (CRS) events being Grade 1, and a low incidence of immune effector cell-associated neurotoxicity syndrome (ICANS).
- The occurrence of Grade 5 CRS and treatment-emergent adverse events leading to death highlight the need for careful patient monitoring and management.
- The feasibility of implementing CAR T-cell therapies like anito-cel in clinical practice involves considerations of cost, manufacturing time, and infrastructure, which are not addressed in the abstract.

In summary, while the preliminary results of the iMMagine-1 Phase 2 trial are encouraging and suggest potential for anito-cel in treating relapsed/refractory multiple myeloma, the evidence is not yet strong enough to warrant a change in clinical practice. Further data from ongoing trials, particularly Phase 3 studies, will be necessary to confirm these findings and establish anito-cel as a new standard of care.

LINK TO ABSTRACT

Abstract Number: 1032

Ciltacabtagene Autoleucel (Cilta-cel) Vs Standard of Care (SoC) in Patients with Lenalidomide (Len)-Refractory Multiple Myeloma (MM) after 1–3 Lines of Therapy: Minimal Residual Disease (MRD) Negativity in the Phase 3 Cartitude-4 Trial

Presenter: Rakesh Popat, MBBS, PhD
Session: 655. Multiple Myeloma: Cellular Therapies: Unleashing Cell Therapies Against Myeloma
Date & Time: Monday, December 9, 2024
Location: Pacific Ballroom Salons 24-26 (Marriott Marquis San Diego Marina)

Abstract Summary:

- Cilta-cel significantly improved overall MRD-negativity rates compared to standard of care (SoC), with rates over three times higher in the intent-to-treat (ITT) set (62% vs 18%) and among MRD-evaluable patients (89% vs 38%) at the 10^{-5} threshold.
- At the 12-month mark, 44% of patients in the cilta-cel arm achieved MRD-negative complete response (≥CR) compared to 8% in the SoC arm, highlighting the rapid achievement of MRD negativity post-cilta-cel infusion.
- Sustained MRD-negativity rates were significantly higher with cilta-cel, with 40% in the ITT set achieving sustained MRD negativity compared to 6% with SoC.
- Median progression-free survival (PFS) was not reached in patients with MRD-negative ≥CR at 12 months in the cilta-cel arm, indicating a strong prognostic value for MRD negativity.
- The study underscores the benefit of cilta-cel in achieving deep and sustained MRD negativity in len-refractory multiple myeloma, even as early as the first relapse.

Clinical relevance: Practice Changing

Rationale:

1. Strength and Reliability of the Data:

- The study is a randomized, phase 3 trial (CARTITUDE-4), which is a robust design for evaluating clinical interventions.
- The sample size is substantial, with 419 patients randomized, providing a strong basis for statistical analysis.
- The results show statistically significant improvements in both progression-free survival (PFS) and overall survival (OS) with cilta-cel compared to standard of care (SoC), with hazard ratios of 0.26 for PFS and 0.55 for OS, both with highly significant p-values (<0.0001 and 0.0009, respectively).

2. Comparison to Current Standard-of-Care Treatments:

- Cilta-cel demonstrated a significant improvement in MRD-negativity rates compared to SoC, with a more than threefold increase in MRD-negativity rates at both the 10^-5 and 10^-6 thresholds.
- The achievement of MRD-negative complete response (≥CR) at 12 months was significantly higher in the cilta-cel arm (44% vs 8% in the SoC arm), which is a strong prognostic marker for prolonged survival.
- The sustained MRD-negativity rates were also significantly higher with cilta-cel, indicating a durable response.

3. Clinical Relevance and Feasibility:

- The findings are clinically relevant as they demonstrate that cilta-cel can achieve deeper and more sustained responses in patients with lenalidomide-refractory multiple myeloma, a population with limited treatment options.

- The treatment regimen, involving a single infusion of cilta-cel after apheresis and lymphodepletion, is feasible and represents a significant advancement over existing therapies.
- The improvement in both PFS and OS, along with the high rates of MRD negativity, suggests that cilta-cel could become a new standard of care for this patient population.

Overall, the data from the CARTITUDE-4 trial provide compelling evidence that cilta-cel offers significant clinical benefits over current standard treatments for len-refractory multiple myeloma, warranting its incorporation into clinical practice.

LINK TO ABSTRACT

Abstract Number: 2002

Long-Term Benefits in Patient-Reported Outcomes and Time to Next Anti-Myeloma Therapy of Ciltacabtagene Autoleucel (Cilta-cel) Versus Standard of Care for Patients with Lenalidomide-Refractory Multiple Myeloma: Results from the Phase 3 Cartitude-4 Clinical Trial

Presenter: Noffar Bar, MD
Session: 655. Multiple Myeloma: Cellular Therapies: Poster I
Date & Time: Saturday, December 7, 2024 5:30 PM–7:30 PM
Location: Halls G-H (San Diego Convention Center)

Abstract Summary:

- Ciltacabtagene autoleucel (cilta-cel) significantly improved progression-free survival (PFS) and overall survival compared to standard of care (SOC) in lenalidomide-refractory multiple myeloma patients, with a hazard ratio (HR) of 0.26 for PFS and 0.55 for overall survival.
- Patient-reported outcomes (PROs) indicated that cilta-cel significantly delayed the time to worsening (TTW) of symptoms and functional impacts, with HRs of 0.38 and 0.42, respectively, compared to SOC.
- By 30 months, 77% of cilta-cel patients had not experienced symptom worsening, and 83% had not experienced functional impact worsening, compared to 63% and 69% in the SOC group.
- Cilta-cel also significantly delayed the time to worsening of global health status/quality of life (GHS/QoL), with an HR of 0.40, and 79% of cilta-cel patients had not experienced GHS/QoL worsening by The time to next anti-myeloma therapy (TTNT) was significantly delayed by 66% with cilta-cel, with a median TTNT not reached, compared to 13.37 months for SOC, supporting cilta-cel as a new standard of care for this patient population.

Clinical relevance: Practice Changing

Rationale:

1. Strength and Reliability of Data:

- The study is a phase 3 randomized controlled trial (RCT), which is the gold standard for clinical research, providing high-quality evidence.
- A substantial sample size of 419 patients enhances the reliability of the findings.
- The statistical significance of the results is robust, with hazard ratios (HR) indicating a strong reduction in risk for progression-free survival (PFS), overall survival (OS), and time to next treatment (TTNT) compared to standard of care (SOC).

2. Comparison to Current Standard-of-Care:

- Cilta-cel demonstrated superior outcomes in terms of PFS and OS compared to SOC regimens, which include pomalidomide, bortezomib, dexamethasone, and daratumumab.
- The hazard ratio for PFS (0.26) and OS (0.55) indicates a significant improvement over existing treatments, suggesting a meaningful advancement in therapeutic options for lenalidomide-refractory multiple myeloma.

3. Clinical Relevance and Feasibility:

- The findings are clinically relevant as they address a critical need for effective treatments in lenalidomide-refractory multiple myeloma patients who have limited options after 1-3 prior lines of therapy.
- The single infusion of cilta-cel offers a practical and potentially more convenient treatment option compared to continuous SOC regimens.
- The significant delay in TTNT and improvement in patient-reported outcomes (PROs) such as symptom control and quality of life further support its clinical applicability and benefit to patients.

Overall, the evidence from the CARTITUDE-4 trial is compelling enough to consider cilta-cel as a new standard of care for this patient population, warranting immediate incorporation into clinical practice.

LINK TO ABSTRACT

Abstract Number: 2005

Efficacy of Carvykti in Cartitude-4 Versus Other Conventional Treatment Regimens for Lenalidomide-Refractory Multiple Myeloma Patients Using Inverse Probability of Treatment Weighting

Presenter: Rafael Fonseca, MD
Session: 655. Multiple Myeloma: Cellular Therapies: Poster I
Date & Time: Saturday, December 7, 2024 5:30 PM–7:30 PM
Location: Halls G-H (San Diego Convention Center)

Abstract Summary:

- Cilta-cel demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS) compared to all comparator regimens (DVd, DKd, Kd, Pd) in patients with relapsed and refractory multiple myeloma (RRMM), with hazard ratios (HRs) for PFS ranging from 0.21 to 0.58 and for OS from 0.31 to 0.55.
- The overall response rate (ORR) and very good partial response (VGPR) rates were consistent with previous findings, but cilta-cel showed a marked increase in complete response (CR) rates, with response rate ratios (RRs) for ≥CR ranging from 2.71 to 31.47 compared to other regimens.
- DKd was the most effective comparator regimen, yet cilta-cel still showed superior efficacy.
- Sensitivity analyses confirmed the robustness of cilta-cel's benefits across various statistical approaches.
- The study supports cilta-cel as a highly effective treatment option for RRMM patients who have received 1-3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

Clinical relevance: Practice Changing

Rationale:

1. Strength and Reliability of Data:

- The study is a phase 3 randomized controlled trial (RCT), which is the gold standard for clinical research, providing high-quality evidence.
- The analysis included a substantial sample size with 155 patients in the cilta-cel arm and a total of 280 patients across comparator arms, ensuring robust statistical power.
- The use of inverse probability of treatment weighting (IPTW) to adjust for key prognostic baseline covariates enhances the reliability of the comparative efficacy results.

2. Comparison to Current Standard-of-Care:

- Cilta-cel demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS) compared to standard regimens (DVd, DKd, Kd, Pd), with hazard ratios indicating a substantial reduction in risk of progression or death.

- The response rates, particularly the complete response (CR) rates, were markedly higher for cilta-cel, with adjusted response rate ratios showing a significant advantage over all comparator regimens.
- These results suggest cilta-cel offers a superior therapeutic option for patients with relapsed and refractory multiple myeloma (RRMM) who have received 1-3 prior lines of therapy.

3. Clinical Relevance and Feasibility:

- The findings are clinically relevant as they provide a new, highly effective treatment option for a challenging patient population (RRMM refractory to lenalidomide).
- The significant OS benefit and high response rates support the incorporation of cilta-cel into clinical practice, particularly in settings where current standard regimens are less effective.
- The study's results are consistent across sensitivity analyses, reinforcing the robustness and applicability of the findings.

Overall, the evidence from the CARTITUDE-4 trial is compelling enough to consider cilta-cel as a practice-changing treatment for RRMM, offering significant improvements in survival and response outcomes over existing therapies.

LINK TO ABSTRACT

Abstract Number: 3354

Extended Intensified Consolidation and Maintenance Improve Ultra High-Risk Multiple Myeloma Patient Outcome – Long-Term Follow-up of the Ukmra Optimum/Muknine Trial

Presenter: Martin F Kaiser, MD
Session: 654. Multiple Myeloma: Pharmacologic Therapies: Poster II
Date & Time: Sunday, December 8, 2024 6:00 PM–8:00 PM
Location: Halls G-H (San Diego Convention Center)

Abstract Summary:

- The OPTIMUM trial demonstrated significantly improved progression-free survival (PFS) and overall survival (OS) for ultra-high risk (UHiR) multiple myeloma (MM) patients compared to the Myeloma XI (MyXI) trial, with a hazard ratio for PFS of 0.325 and for OS of 0.467.
- At 60 months, PFS for OPTIMUM was 61.4% compared to 23% for MyXI, and OS was 71.1% versus 43.5%, indicating a substantial benefit of the tailored treatment approach in OPTIMUM.
- Patients with plasma cell leukemia (PCL) in OPTIMUM had poorer outcomes, highlighting an unmet need in this subgroup, with a hazard ratio of 4.01 compared to UHiR MM.

- Genetic characteristics strongly influenced outcomes; patients with 2 high-risk cytogenetic abnormalities (HRCA) and no gene expression profile (GEP) risk had a 60-month PFS of 95%, while those with 2 HRCA plus GEP risk had a PFS of 46.9%.
- The study supports the integration of GEP with genetic testing in MM and suggests that the OPTIMUM treatment regimen, including quintuplet induction and extended consolidation, offers significant benefits for UHiR MM patients.

Clinical relevance: Practice Changing

Rationale:

1. Strength and Reliability of the Data:

- The OPTIMUM/MUKnine trial is a well-designed, prospective study with a substantial sample size of 107 ultra-high risk (UHiR) multiple myeloma (MM) patients, including 9 with plasma cell leukemia (PCL). The study's follow-up period of over 5 years provides robust long-term data.
- The statistical significance of the findings is strong, with a hazard ratio (HR) of 0.325 for progression-free survival (PFS) and 0.467 for overall survival (OS) compared to the Myeloma XI (MyXI) trial, both with highly significant p-values ($p<0.0001$ and $p=0.0006$, respectively).

2. Comparison to Current Standard-of-Care:

- The OPTIMUM trial demonstrates superior outcomes compared to the MyXI trial, which represents a current standard-of-care approach for UHiR MM. The PFS and OS improvements are substantial, with PFS estimates at 60 months being 61.4% for OPTIMUM versus 23% for MyXI.
- The trial's tailored approach, including quintuplet induction therapy and extended consolidation and maintenance phases, shows a marked improvement over existing treatments, particularly for patients with ≥2 high-risk cytogenetic abnormalities (HRCA).

3. Clinical Relevance and Feasibility:

- The findings are clinically relevant as they address a significant unmet need in the treatment of UHiR MM, a group with historically poor outcomes.
- The integration of genetic and gene expression profiling (GEP) to stratify patients and tailor treatment regimens is feasible and aligns with precision medicine approaches increasingly adopted in oncology.
- The study identifies subgroups of patients who benefit exceptionally from the OPTIMUM regimen, as well as those with ongoing unmet needs, such as PCL patients, guiding future research and treatment strategies.

Overall, the OPTIMUM trial's results provide compelling evidence for a new standard of care in UHiR MM, demonstrating significant improvements in survival outcomes and supporting the integration of genetic and GEP risk stratification in clinical practice.

LINK TO ABSTRACT