DATA COMPASS

KEY RESULTS IN MULTIPLE MYELOMA & AL AMYLOIDOSIS

ASH 2024 PRE-MEETING REPORT

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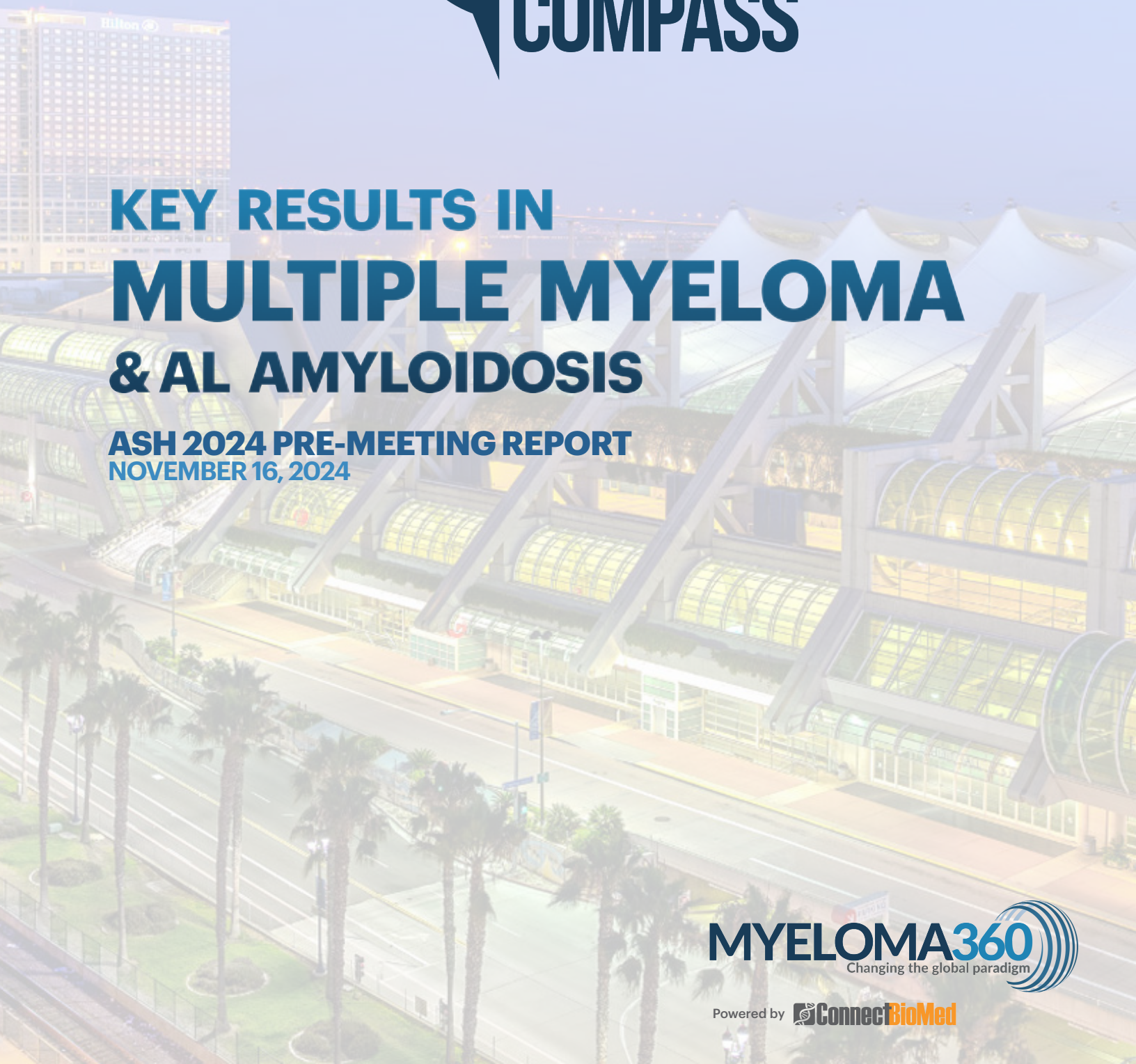

MYELOMA360
Changing the global paradigm

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EXECUTIVE SUMMARY

The upcoming ASH meeting will present significant advances across multiple areas of myeloma management, with several potentially practice-changing findings:

CAR T-Cell Therapy

- Novel products demonstrate high response rates, including anitocabtagene autoleucel (95% ORR) [Abstract 1031] and academic-developed HBI0101 (92% ORR) [Abstract 1030]
- First use of CAR T in smoldering myeloma shows promise [Abstract 1027]
- Real-world data suggests superior outcomes with cilta-cel versus ide-cel [Abstract 936]

Bispecific Antibodies

- Successful implementation in community settings demonstrated [Abstract 933]
- Effective in elderly populations with manageable toxicity [Abstract 934]
- Novel combinations show promise, particularly with standard myeloma agents [Abstract 1024]
- Emerging role as bridging therapy to CAR T [Abstract 931]

Novel Therapeutics

- New drug classes show promise: BCL-2 inhibitor (lisaftoclax) [Abstract 1022], p300/CBP inhibitor (inobrodib) [Abstract 1023], and CELMoD agent (mezigdomide) [Abstract 1025]
- Novel combinations demonstrate improved outcomes across various disease settings

Early/High-Risk Disease

- Daratumumab monotherapy shows significant benefit in high-risk smoldering myeloma [Abstract 773]
- Improved risk stratification models incorporating biomarker trajectories [Abstract 1017]
- Evidence supporting earlier intervention in high-risk disease states

Patient Care and Assessment

- Patient preferences and frailty-adjusted approaches demonstrate importance in treatment decisions [Abstracts 706, 673]
- Novel monitoring approaches including ctDNA and mass spectrometry show promise [Abstracts 252, 489]
- MRD assessment continues to demonstrate prognostic value across multiple settings [Abstracts 889, 1032]

AL Amyloidosis

- Daratumumab-VCd demonstrates superior outcomes with significant improvement in cardiac responses [Abstract 891]
- Novel combinations (IsaPd) show rapid and deep responses [Abstract 892]
- Targeted approaches with venetoclax in t(11;14) disease show promise [Abstract 893]
- First evidence of CAR T-cell therapy efficacy with high response rates [Abstract 894]

These advances collectively suggest continued rapid evolution in both multiple myeloma and AL amyloidosis therapy, with trends toward more personalized approaches, earlier intervention in high-risk disease, and improved methods for monitoring and assessing response.

The field appears to be moving toward more precise, patient-centered care while maintaining focus on deep and durable responses across the disease spectrum.

CAR T-CELL THERAPY

Several key studies will present significant advances in CAR T-cell therapy, demonstrating continued evolution in both product development and clinical application.

New Products and Constructs

The phase 2 registrational iMMagine-1 trial of anitocabtagene autoleucel will show promising results with a 95% overall response rate and 62% complete/stringent complete response rate in relapsed/refractory patients [Abstract 1031]. Notable is the manageable safety profile with no delayed neurotoxicity reported.

In academic development, HBI0101, a novel anti-BCMA CAR T, demonstrates a 92% overall response rate with 55% achieving complete response in a heavily pretreated population [Abstract 1030]. This study highlights the potential for academic centers to successfully develop effective CAR T products.

Real-World Outcomes:

A comprehensive comparison of ciltacabtagene autoleucel (cilta-cel) versus idecabtagene vicleucel (ide-cel) in real-world settings demonstrates superior efficacy for cilta-cel, though with slightly higher toxicity rates [Abstract 936]. The study provides valuable insights for product selection in clinical practice.

Novel Approaches

In a groundbreaking study, cilta-cel is evaluated in high-risk smoldering myeloma, representing the first use of CAR T therapy in precursor disease [Abstract 1027]. Early results show promising safety and efficacy, potentially opening new treatment paradigms for early intervention.

The CARTITUDE-4 trial demonstrates superior outcomes with cilta-cel compared to standard care in lenalidomide-refractory patients, achieving significantly higher MRD-negativity rates (62% vs 18%) [Abstract 1032]. This data supports the use of CAR T therapy in earlier treatment lines.

A novel dual-targeting approach using anti-BCMA/GPRC5D bispecific CAR T-cells shows promise in treating extramedullary disease, with a 100% overall response rate in evaluable patients [Abstract 1028], addressing an important unmet need in myeloma treatment.

Special Populations

Phase 1/2 study of BCMA/CD19 dual-targeting CAR T shows promise, including in extramedullary disease [Abstract 923]

Summary

These advances collectively demonstrate the rapid evolution of CAR T-cell therapy in multiple myeloma, with improvements in efficacy, earlier line use, and novel targeting strategies. The field continues to move toward more personalized approaches while maintaining manageable safety profiles.

BISPECIFIC ANTIBODIES

Several important studies will present data on bispecific antibodies, highlighting their growing role in myeloma treatment.

Novel Agents and Combinations

Elranatamab combined with carfilzomib and dexamethasone demonstrates promising early efficacy in the Phase 1b MagnetisMM-20 trial, with a 100% unconfirmed overall response rate and 83.3% confirmed response rate [Abstract 1024]. The combination shows a manageable safety profile with no dose-limiting toxicities observed.

Real-World Experience

An analysis of teclistamab in academic versus community settings reveals important insights into real-world implementation. The study demonstrates higher response rates in community settings (81%) compared to academic centers (62%), despite treating an older population [Abstract 933]. This data suggests teclistamab can be effectively administered in community settings.

Special Populations

In elderly patients (≥75 years) treated with teclistamab, outcomes appear comparable to younger patients, with similar safety profiles and response rates [Abstract 934]. Notably, the median progression-free survival is longer in the elderly cohort (10.7 months versus 5.2 months), though this may reflect patient selection.

Bridging Strategies

Talquetamab shows promise as a bridging therapy to BCMA CAR T-cell therapy, with 95% of patients successfully proceeding to CAR T infusion [Abstract 931]. The strategy demonstrates an overall response rate of 62% during bridging, suggesting effective disease control while awaiting definitive therapy.

Novel Combinations

The combination of teclistamab with pomalidomide and dexamethasone in heavily pretreated patients demonstrates early efficacy, with particular benefit seen in pomalidomide-refractory patients [Abstract 495], suggesting potential synergy between these agents.

Long-Term Follow-Up

Initial results from a first-in-human study of ISB 2001, a BCMAxCD38xCD3 trispecific antibody [Abstract 1026]

Safety Considerations

Real-world data across studies continues to show manageable safety profiles for bispecific antibodies, with predominantly low-grade cytokine release syndrome and manageable hematologic toxicities [Abstracts 933, 934, 495]. The implementation of step-up dosing and prophylactic measures appears effective in mitigating severe adverse events.

Summary

These studies collectively demonstrate the growing utility of bispecific antibodies across various clinical settings and patient populations, while providing practical insights into their optimal use and sequencing.

NOVEL THERAPEUTIC APPROACHES

Several innovative therapeutic strategies and combinations will be presented, highlighting continued evolution in myeloma treatment approaches.

Novel Agents

Lisaftoclax, a novel BCL-2 inhibitor, combined with standard regimens demonstrates promising activity with an overall response rate of 61.3% when combined with pomalidomide-dexamethasone and higher rates with daratumumab-lenalidomide-dexamethasone [Abstract 1022]. The safety profile appears manageable with primarily hematologic toxicities.

Inobrodib, a first-in-class p300/CBP inhibitor, combined with pomalidomide and dexamethasone shows encouraging early efficacy in heavily pretreated patients, with best response rates of 75% in the highest dose cohort [Abstract 1023]. The combination demonstrates tolerability with primarily manageable hematologic adverse events.

Mezigdomide, a novel CELMoD agent, in combination with proteasome inhibitors shows promising activity. When combined with bortezomib or carfilzomib plus dexamethasone, overall response rates of 75-85% are achieved [Abstract 1025]. The 1.0 mg dose demonstrates optimal pharmacodynamic effects.

Novel Combinations

The addition of isatuximab to bortezomib-lenalidomide-dexamethasone significantly improves progression-free survival in newly diagnosed transplant-eligible patients [Abstract 769], suggesting potential benefit of quadruplet therapy in this setting.

GEM2017Fit trial evaluating daratumumab at induction and/or consolidation in fit elderly patients [Abstract 678]

Phase 3 study of daratumumab-VRd versus VRd alone in transplant-ineligible NDMM [Abstract 362]

Innovative Treatment Strategies

The GEM2017Fit trial evaluates different approaches for fit elderly patients, comparing various combinations including daratumumab-based regimens. The study demonstrates improved MRD-negative rates with novel combinations [Abstract 678], providing important insights for treating this specific population.

Early Disease Treatment

A phase 2 randomized trial comparing carfilzomib-lenalidomide-dexamethasone versus lenalidomide-dexamethasone in high-risk smoldering myeloma demonstrates superior outcomes with the triplet regimen [Abstract 676], suggesting potential benefit of more intensive therapy in high-risk precursor disease.

Consolidation/Maintenance Strategies

Important studies redefine post-transplant approaches, with the EMN02/HOVON95 trial showing improved 10-year overall survival with VRD consolidation (64% vs 50%) [Abstract 674].

MRD-guided maintenance discontinuation shows feasibility, with 86% maintaining MRD negativity three years after stopping lenalidomide [Abstract 361].

The addition of daratumumab to lenalidomide maintenance demonstrates superior outcomes with higher MRD-negative conversion rates [Abstract 675].

These findings support personalized post-transplant approaches based on patient characteristics and response.

Summary

These studies highlight the continued innovation in myeloma therapeutics, with novel mechanisms of action and combinations showing promise across various disease settings. The field continues to move toward more targeted and personalized approaches while maintaining acceptable safety profiles.

HIGH-RISK AND EARLY DISEASE MANAGEMENT

Several key studies will present important advances in managing high-risk and early disease states, potentially reshaping treatment approaches.

Smoldering Myeloma

A groundbreaking phase 3 study of daratumumab monotherapy versus active monitoring in high-risk smoldering multiple myeloma (SMM) demonstrates significant improvement in progression-free survival with daratumumab (HR 0.49) [Abstract 773]. The trial shows high response rates (63.4%) with manageable toxicity, potentially establishing a new standard of care for high-risk SMM.

Venetoclax plus dexamethasone as first-line treatment for t(11;14) SMM shows promise in a phase II study, with early data demonstrating a complete/very good partial response rate of 62.9% [Abstract 893]. This targeted approach highlights the potential for biomarker-driven therapy in early disease.

Risk Assessment

The PANGEA 2.0 model introduces an improved risk stratification approach for SMM by incorporating biomarker trajectories. This model demonstrates superior predictive accuracy compared to the current 20/2/20 model, with C-statistics of 0.86 in the training cohort [Abstract 1017].

A comprehensive genomic analysis distinguishing MM-like SMM from non-progressor SMM reveals distinct molecular patterns that could guide treatment decisions [Abstract 1018]. The study identifies key genomic features associated with progression risk.

Early Intervention Strategies

The first trial of CAR T-cell therapy in SMM demonstrates promising early results with ciltacabtagene autoleucel, showing manageable safety and high rates of MRD negativity [Abstract 1027]. This represents a potential paradigm shift in treating precursor disease.

A phase II study of carfilzomib-lenalidomide-dexamethasone versus lenalidomide-dexamethasone in high-risk SMM shows superior outcomes with the triplet regimen, including higher MRD negativity rates [Abstract 676], supporting more intensive early intervention in selected patients.

High-Risk Disease Management

A European Myeloma Network analysis of early relapse patterns in over 10,000 patients identifies key prognostic factors and demonstrates the impact of double-hit high-risk cytogenetic abnormalities, particularly those involving del(17p) [Abstract 898]. This data provides valuable insights for risk-adapted treatment approaches.

Summary

These studies collectively demonstrate significant progress in identifying and managing high-risk disease states, with potential implications for earlier intervention and more personalized treatment approaches. The

field appears to be moving toward more aggressive management of high-risk precursor states while refining risk stratification methods.

CLINICAL PRACTICE PATTERNS AND PATIENT CARE

Multiple studies will present important insights into real-world practice patterns and patient-centered care approaches.

Treatment Decision-Making

A novel analysis of patient decision-making reveals that side effect severity significantly influences treatment autonomy. Patients who consider side effects highly influential demonstrate greater engagement in treatment decisions and are more likely to make final treatment choices themselves [Abstract 706]. This highlights the importance of shared decision-making and comprehensive patient education.

Frailty-Adjusted Therapy

The UK Myeloma Research Alliance FiTNEss trial demonstrates that International Myeloma Working Group frailty score-adjusted therapy delivery reduces early mortality risk in newly diagnosed transplant-ineligible patients [Abstract 673]. While not reducing early treatment cessation rates, frailty-adjusted dosing shows improved one-year overall survival (88.7% vs 83.2%).

Management of Elderly Patients

Real-world outcomes of teclistamab in elderly patients (≥75 years) demonstrate comparable efficacy to younger patients, with potentially better progression-free survival, challenging assumptions about age-based treatment restrictions [Abstract 934].

Treatment-Free Intervals

A significant study examining patient preferences reveals that 49% of multiple myeloma patients highly value extended treatment-free intervals, with implications for quality of life and treatment planning [Abstract 284]. The study emphasizes the importance of incorporating patient preferences into treatment strategies.

Treatment Sequencing

Impact of previous HDM/ASCT on BCMA-directed CAR T-cell therapy outcomes [Abstract 79]. Genomic determinants of resistance to anti-BCMA CAR T-cell therapies [Abstract 247]

Community vs Academic Settings

Analysis of teclistamab administration in community versus academic settings shows comparable or better outcomes in community settings, with an overall response rate of 81% versus 62% [Abstract 933]. This data supports broader implementation of novel therapies across different practice settings.

Summary

These findings collectively emphasize the importance of personalized approaches to treatment, considering patient preferences, frailty status, and practice setting. The data supports more nuanced decision-making in multiple myeloma care, with particular attention to quality of life considerations.

RESPONSE ASSESSMENT AND MONITORING

Several important studies will present advances in disease monitoring and response assessment, potentially influencing future clinical practice.

MRD Assessment Evolution

A critical analysis of minimal residual disease (MRD) in light-chain amyloidosis demonstrates that MRD negativity significantly correlates with improved outcomes, supporting its use as a prognostic marker in this setting [Abstract 889]. The study shows a 59% reduction in risk of progression/death for MRD-negative patients.

The CARTITUDE-4 trial provides compelling evidence for the prognostic value of MRD assessment, with significantly higher MRD-negativity rates in cilta-cel treated patients (62% vs 18%) compared to standard of care [Abstract 1032]. The study demonstrates the importance of deep responses in predicting outcomes.

Novel Monitoring Approaches

Circulating tumor DNA (ctDNA) analysis emerges as a promising non-invasive predictor of early relapse, with detection preceding clinical progression by a median of 252 days [Abstract 252]. This approach may overcome limitations of traditional bone marrow-based assessments.

A novel approach to MRD assessment using mass spectrometry demonstrates superior performance compared to traditional methods, potentially redefining complete response criteria [Abstract 489]. The study suggests that MS-based response categories could reduce the need for bone marrow assessments.

Risk Assessment Tools

A comprehensive study of circulating tumor cells (CTCs) presents a novel prognostic system for newly diagnosed multiple myeloma [Abstract 490]. The integration of CTC assessment with existing staging systems provides improved risk stratification.

Treatment Response Evaluation

The relationship between MRD status and long-term outcomes is further validated in several studies, with sustained MRD negativity emerging as a key therapeutic goal [Abstracts 361, 362]. These findings support the use of MRD as a treatment endpoint and guide for therapy duration.

Summary

These advances in response assessment and monitoring techniques may lead to more precise and less invasive methods for tracking disease status and predicting outcomes. The integration of novel technologies with traditional approaches appears to enhance the ability to make informed treatment decisions.

AL AMYLOIDOSIS: EMERGING THERAPEUTIC APPROACHES

Several important studies will present significant advances in the treatment of AL amyloidosis, demonstrating evolution across multiple therapeutic platforms.

Anti-CD38 Based Therapy

The phase 3 ANDROMEDA study demonstrates that subcutaneous daratumumab plus VCd significantly improves hematologic complete response rates (59.5% vs 19.2%) compared to VCd alone [Abstract 891]. Notably, cardiac complete response rates are substantially higher with daratumumab-VCd (40.7% vs 13.7%), with a manageable safety profile.

Isatuximab combined with pomalidomide and dexamethasone (IsaPd) shows promising efficacy in relapsed AL amyloidosis, with an overall response rate of 80% after 6 cycles [Abstract 892]. The study demonstrates rapid responses, with 38.5% achieving ≥VGPR by day 8, suggesting potential utility in this challenging setting.

Targeted Therapy

A phase II study of venetoclax plus dexamethasone as first-line treatment for t(11;14) AL amyloidosis demonstrates early efficacy with a CR+VGPR rate of 58.6% at three months [Abstract 893]. This biomarker-driven approach highlights the potential for personalized therapy in AL amyloidosis.

Cellular Therapy

In a pioneering study, anti-BCMA CAR T-cell therapy shows efficacy in relapsed/refractory AL amyloidosis with a 94% overall hematologic response rate and 75% complete response rate [Abstract 894]. The therapy demonstrates manageable safety with no treatment-related deaths, potentially opening a new therapeutic avenue for resistant disease.

Summary

These studies collectively demonstrate significant progress in AL amyloidosis treatment, with particular advances in targeted approaches and the successful translation of myeloma therapies to this challenging disease. The field appears to be moving toward more personalized approaches while maintaining focus on both hematologic and organ responses.