ASH Draft Recommendations for Guidelines on Treatment of AL Amyloidosis

INTRODUCTION

American Society of Hematology (ASH) guidelines are based on a systematic review of available evidence. Through a structured process, a guideline panel makes judgments about the evidence and forms recommendations.

The public comment period occurs after recommendations are formed but before ASH organizational approval of the guidelines. Comments collected during the open comment period are provided to the guideline panel for review prior to finalizing the guidelines.

These draft recommendations are not final and therefore are not intended for use or citation.

To submit comments on the draft recommendations, please email **guidelines@hematology.org**. Evidence Profiles and Evidence to Decision Frameworks are available via links below. If you are unable to access these links, please email Rachel Cohen at rcohen@hematology.org.

The public comment period for these draft recommendations is open until **July 7th, 2026**.

Overarching Good Practice Statements

- Timely Treatment decisions should involve an experienced multidisciplinary team — including hematology and relevant specialists (e.g., cardiology, nephrology, neurology)—to ensure individualized assessment of risk, benefit, and treatment eligibility.
- The goals of therapy in AL amyloidosis are to achieve the most rapid and deepest hematologic response in order to maximize organ response.
- Treatment decisions should actively engage individuals in shared decision-making to ensure that management aligns with individual values, goals, and preferences.
- Cytogenetic evaluation, including evaluating for t(11;14), should be performed at diagnosis in individuals with AL amyloidosis, as cytogenetic abnormalities may influence prognosis, likelihood of response to specific therapies, and treatment selection.
- Individuals with newly diagnosed AL amyloidosis should undergo comprehensive evaluation of organ involvement and transplant eligibility at an experienced amyloidosis center, with particular attention to cardiac staging, performance status, and risk of treatment-related toxicity.
- Individuals receiving treatment for AL amyloidosis should undergo serial monitoring of hematologic response and organ function at regular intervals throughout therapy and during long-term follow-up.
- When organ progression occurs without confirmed hematological progression, clinicians should first exclude alternative causes-including treatment-related adverse effects-before reinitiating therapy.
- Enrollment in clinical trials should be encouraged whenever possible to improve therapeutic strategies, survival outcomes, response-adapted approaches, and organ-specific endpoints in AL amyloidosis.

Recommendations

Frontline Therapy

- **Question 1:** Should transplant eligible individuals with a new diagnosis of AL amyloidosis without concurrent Myeloma undergo ASCT without induction vs induction with Dara-based regimen then transplant vs induction with non-Dara-based regimen then transplant vs Dara VCD without transplant (6 months then 18 months)?
    - **Recommendation 1**: The ASH AL Amyloidosis Treatment Guideline Panel suggests that, in transplant-eligible individuals with newly diagnosed AL amyloidosis without concurrent multiple myeloma, ***suggests either*** daratumumab plus VCd (Daratumumab-VCd) without upfront autologous stem cell transplantation (ASCT) or daratumumab-based induction therapy followed by ASCT, rather than proceeding directly to ASCT without induction or using non–daratumumab-based induction regimens. (Conditional recommendation based on very low certainty of evidence.)
        - **Remarks:**

- Treatment selection should be individualized based on disease burden, treatment-related risks, extent of organ involvement (particularly cardiac stage), depth of hematologic response to induction therapy, available resources and cost considerations, and individual preferences and goals of care.
- Daratumumab-VCd without upfront ASCT, as evaluated in the ANDROMEDA trial, represents an appropriate frontline treatment option for transplant-eligible individuals with newly diagnosed AL amyloidosis.
- In settings where daratumumab is not available, non–daratumumab-based induction followed by ASCT is preferred over upfront ASCT without induction. Higher bone marrow plasma cell burden may further inform this decision.
- The evidence base supporting these recommendations is derived exclusively from studies evaluating daratumumab-containing regimens. Recommendations specify daratumumab rather than anti-CD38 antibodies as a class, as daratumumab is currently the only agent in this category with frontline data in AL amyloidosis.

- **Good Practice Statement.** In transplant-eligible individuals, timely initiation of therapy aimed at rapid hematologic response is essential with reassessment of transplant candidacy following induction therapy.

➢ Evidence Profile and Evidence-to-Decision (EtD) Framework

STEM CELL TRANSPLANT (ASCT)

Background: The following recommendations apply to transplant-eligible individuals with newly diagnosed AL amyloidosis without concurrent multiple myeloma. "Initial therapy" refers to frontline systemic combination therapy administered prior to the ASCT decision point. Hematologic response should be assessed using standard consensus criteria see accompanying manuscript). "Preplanned treatment strategy" refers to the continuation of intended therapy based on individual clinical circumstances. “Persistent clonal disease burden" is defined in the accompanying manuscript.

➢ **Question 2:** Should transplant eligible individuals with new diagnosis AL amyloidosis without concurrent Myeloma undergo ASCT or not based on hematological response?

- **Recommendation 2:** For transplant-eligible individuals with AL amyloidosis without concomitant myeloma who achieve hematologic CR after initial therapy, the ASH AL Amyloidosis Treatment Guideline Panel ***suggests*** continuing preplanned therapy rather than proceeding with ASCT. (Conditional recommendation based on very low certainty evidence)
  - **Remarks:**
    - Individuals who do not proceed to ASCT should be managed with a preplanned treatment strategy with serial hematologic and organ response monitoring.

        - Shared decision-making is essential, as some individuals may reasonably choose to proceed with ASCT based on individual risk profiles, initial disease burden, and preferences.
    - **Recommendation 3:** For transplant-eligible individuals with AL amyloidosis without concomitant myeloma who achieve VGPR after initial therapy, the ASH AL Amyloidosis Treatment Guideline Panel ***suggests*** proceeding with ASCT in individuals who have not achieved organ response and have evidence of persistent clonal disease burden (conditional recommendation based on very low certainty evidence)
        - **Remarks:**
            - Individuals with VGPR accompanied by organ response may reasonably continue a preplanned treatment strategy without proceeding to ASCT, with close serial monitoring of dFLC and organ biomarkers.
            - Shared decision-making between physicians and individuals is essential, as some individuals may reasonably defer ASCT based on their individual risk profile, predicted transplant-related mortality, organ response trajectory, and preferences.
    - **Recommendation 4:** For transplant-eligible individuals with AL amyloidosis without concomitant myeloma who achieve less than VGPR (<VGPR) after initial therapy, the ASH AL Amyloidosis Treatment Guideline Panel ***suggests*** proceeding with ASCT (conditional recommendation based on very low certainty evidence)
        - **Remarks:**
            - Individuals with no hematologic response or hematologic progression during initial therapy should be considered to have refractory disease, prompting a switch to alternative therapy, as further addressed in Questions 3 and 5.
            - For individuals in whom ASCT is ultimately not pursued, alternative treatment intensification strategies should be considered, preferably through clinical trial enrollment or referral to a center of excellence.

- Evidence Profile and Evidence-to-Decision (EtD) Framework

Switching vs Continuing

- **Question 3:** Should individuals with Al amyloidosis who achieve VGPR or PR continue treatment at VGPR, or should they switch therapy to achieve a CR?

No Hematological Response

- **Recommendation 3:** For individuals with AL amyloidosis without concomitant myeloma and undergoing treatment, the ASH AL Amyloidosis Treatment Guideline Panel ***recommends*** switching treatment regimen rather than continuing the same regimen in individuals achieving no hematologic response

after 2 to 4 cycles of treatment (Strong recommendation based on very low certainty of evidence).

- **Remarks:**
  - Early switching of therapy is appropriate after two cycles, when individuals are not showing any significant decrease in hematologic light chain parameters/assays, especially when potent upfront regimens are being used.
  - Switching therapy is warranted even when organs appear stable, as hematologic non-response carries ongoing risk of progressive major organ injury.
  - The kinetics of hematologic response may vary across biologic subgroups, particularly in individuals with t(11;14), and according to the therapeutic regimen used.

Partial Response (PR)

- **Recommendation 4A (Partial Response after 2 cycles):** For individuals with AL amyloidosis without concomitant myeloma and undergoing treatment, the ASH AL Amyloidosis Treatment Guideline Panel ***suggests*** continuing therapy with close hematologic and organ response monitoring, rather than switching to an alternative regimen in individuals achieving PR after 2 cycles (conditional recommendation based on very low certainty of evidence).
- **Recommendation 4B (Partial Response after 4-6 cycles):** For individuals with AL amyloidosis without concomitant myeloma and undergoing treatment, the ASH AL Amyloidosis Treatment Guideline Panel ***recommends*** switching therapy rather than continuing the same regimen in individuals achieving only PR after 4 to 6 cycles (strong recommendation, very low certainty of evidence).
  - **Remarks:**
    - Early PR (≤2 cycles) is reasonably considered an acceptable interim milestone, supporting continuation of therapy with close monitoring; however, reassessment at cycles 4–6 is critical, with continuation only if VGPR or better response is achieved.
    - The recommendations acknowledge heterogeneity in disease biology, including cases with low baseline difference in involved and uninvolved free light chains (dFLC) or intact monoclonal protein, where conventional PR criteria may be less informative.

Very Good Partial Response (VGPR)

- **Recommendation 5 (Very Good Partial Response (VGPR):** For individuals with AL amyloidosis without concomitant myeloma and undergoing treatment, the ASH AL Amyloidosis Treatment Guideline Panel ***suggests*** continuing therapy in individuals with VGPR. (Conditional recommendation based on very low certainty of evidence).

- **Remark:** For individuals who achieve VGPR as best hematologic response but continue to have organ progression please refer to recommendation 7B (Question 4).

Complete Response (CR)

- **Recommendation 6:** For individuals with AL amyloidosis without concomitant myeloma who achieve complete response, the ASH Guideline Panel ***recommends*** continuing therapy as planned rather than switching therapy (Strong recommendation based on very low certainty of evidence).
  - **Remarks:**
    - Organ responses frequently lag behind hematologic response, and early organ progression may reflect delayed recovery or intercurrent conditions rather than true relapse. Careful longitudinal interpretation and exclusion of alternative etiologies are therefore essential.
    - Current hematologic response criteria may lack sensitivity; emerging evidence supports the prognostic value of deeper responses defined by very low difference in involved and uninvolved free light chains (dFLC) and/or low involved free light chain levels (iFLC), although such thresholds are not yet standardized.

➢ Evidence-to-Decision (EtD) Framework

Progression

➢ **Question 4:** Should individuals with AL amyloidosis without Myeloma with hematological response of VGPR or better be treated when there is evidence of organ progression vs treatment on biochemical relapse?

- **Recommendation 7A:** For individuals with AL amyloidosis without concomitant myeloma who previously achieved a VGPR or better, the ASH AL Amyloidosis Treatment Guideline Panel ***recommends*** reinitiating or modifying treatment upon hematological progression* in the absence of organ progression. (Strong recommendation based on very low certainty of evidence.)
  - **Remarks:**
    - Upon hematological progression, clinicians should not delay treatment initiation pending evidence of concurrent organ progression, in order to avoid the development of irreversible organ damage.
    - Standard progression thresholds may not apply for individuals with low levels of FLC* at diagnosis; individualized lower thresholds should be used.

    * For the definition of low FLC levels please see the definition section.

* For the definition of hematological progression please see the definitions section.

- **Recommendation 7B:** For individuals with AL amyloidosis without concomitant myeloma who previously achieved a VGPR or better, the ASH AL Amyloidosis Treatment Guideline Panel ***suggests*** reinitiating or modifying treatment upon organ progres sion^ in the absence of hematological progression*.(Conditional recommendation based on very low certainty of evidence.)
  - **Remarks:**
    - When organ progression occurs without confirmed hematological progression, clinicians should first exclude alternative causes-including treatment-related adverse effects-before reinitiating therapy.
    - The timing of organ progression in relation to hematologic response should be considered when determining whether organ deterioration reflects new or ongoing amyloid deposition versus residual damage from prior disease.
    - Early organ worsening after hematologic response is more likely related to prior damage or, depending on the organ, treatment related toxicity, whereas late deterioration raises concern for ongoing amyloid deposition.

  * For the definition of hematological progression please see the definition section.

  * For the definition of Organ Progression please see the definitions section.
- **Recommendation 8:** For individuals with AL amyloidosis without concomitant myeloma who previously achieved a VGPR or better, the ASH AL Amyloidosis Treatment Guideline Panel ***recommends*** prompt reinitiating or modifying of treatment at concurrent hematological and organ progression. (Strong recommendation based on very low certainty of evidence.)
  - **Remark:** Upon hematological progression, clinicians should not delay treatment initiation pending evidence of concurrent organ progression, in order to avoid the development of irreversible organ damage.
- **Recommendation 9:** The ASH AL Amyloidosis Treatment Guideline Panel ***suggests against*** routine reinitiation or modification of therapy in individuals with AL amyloidosis without concomitant myeloma who have achieved a VGPR or better in the absence of confirmed hematologic or organ progression. (Conditional recommendation based on very low certainty of evidence.)
  - **Remarks:**
    - Clinical suspicion of disease recurrence alone should generally prompt closer monitoring and reassessment rather than immediate

treatment modification, particularly when progression criteria are not yet met.
    - In individuals in whom standard biomarker-based progression criteria are difficult to interpret, including those with low baseline FLC levels*, fluctuating biomarkers, or frailty, additional diagnostic tools (e.g., advanced imaging assessment) may help characterize disease status.
    - Organ biomarker fluctuations should be interpreted cautiously, as non–amyloid-related comorbidities and intercurrent clinical events may influence laboratory or imaging findings in the absence of true disease progression.

  * For the definition of low FLC levels please see the definitions section.

- Evidence Profile and Evidence-to-Decision (EtD) Framework

Relapsed Refractory

- **Question 5:** In individuals with relapsed/refractory (heme response based) and not t(11;14) AL amyloidosis without concurrent Myeloma should they receive second-line treatment with IMids vs PI vs Anti CD38 vs ASCT vs Combination therapy?
    - **Recommendation 10:** For individuals with relapsed/refractory AL amyloidosis without concomitant myeloma, the ASH AL Amyloidosis Treatment Guideline Panel ***suggests*** treatment with an anti-CD38 antibody–based regimen rather than PI-based therapy or autologous stem cell transplant (ASCT) and suggests against IMiD-based therapy. This is a conditional recommendation based on very low certainty in the evidence of effects.
        - **Remarks:**
            - This recommendation may not apply to individuals who were previously treated with anti-CD38 therapy.
            - Limited evidence exists to suggest a difference in outcomes between ASCT and PI based therapy in relapsed disease
            - Treatment with a non-transplant modality may be initiated while discerning whether to proceed with ASCT.
            - When anti-CD38–based therapy, PI-based therapy, and ASCT are not acceptable, available, or feasible for the clinician or patient, treatment with an IMiD-based regimen remains a reasonable option.
            - BCL-2 inhibitors, namely Venetoclax, are effective in individuals with t(11;14).
- Evidence Profile and Evidence-to-Decision (EtD) Framework

Definitions

- Definitions for Public Comment