National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Systemic Light Chain Amyloidosis

Version 1.2026 — June 11, 2025

NCCN.org

**NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.**

Continue

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2026
# Systemic Light Chain Amyloidosis

NCCN Guidelines Index
Table of Contents
Discussion

***Shaji K. Kumar, MD/Chair ‡**
Mayo Clinic Comprehensive Cancer Center

***Natalie S. Callander, MD/Vice Chair ‡ ξ**
University of Wisconsin
Carbone Cancer Center

**Kehinde Adekola, MD, MSCI ‡**
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

**Larry D. Anderson, Jr., MD, PhD ‡**
UT Southwestern Simmons Comprehensive Cancer Center

***Muhamed Baljevic, MD ‡ Þ ξ**
Vanderbilt-Ingram Cancer Center

**Rachid Baz, MD ‡**
Moffitt Cancer Center

**Erica Campagnaro, MD ‡**
University of Michigan Rogel Cancer Center

**Caitlin Costello, MD ‡ Þ ξ**
UC San Diego Moores Cancer Center

**Christopher D'Angelo, MD ‡**
Fred & Pamela Buffett Cancer Center

**Benjamin Derman, MD † ‡**
The UChicago Medicine Comprehensive Cancer Center

**Srinivas Devarakonda, MD ‡**
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

**Noura Elsedawy, MD †**
St. Jude Children's Research Hospital/ The University of Tennessee Health Science Center

**Amandeep Godara, MD ‡**
Huntsman Cancer Institute at the University of Utah

**Kelly Godby, MD ‡**
O'Neal Comprehensive Cancer Center at UAB

**Jens Hillengass, MD, PhD ‡**
Roswell Park Comprehensive Cancer Center

**Leona Holmberg, MD, PhD ‡ ξ**
Fred Hutchinson Cancer Center

**Myo Htut, MD ‡ Þ**
City of Hope National Medical Center

**Carol Ann Huff, MD † ‡**
Johns Hopkins Kimmel Cancer Center

**Malin Hultcrantz, MD, PhD ‡**
Memorial Sloan Kettering Cancer Center

**Yubin Kang, MD ‡ † ξ**
Duke Cancer Institute

**Sarah Larson, MD † ‡**
UCLA Jonsson Comprehensive Cancer Center

**Hans C. Lee, MD ‡ ‡**
The University of Texas MD Anderson Cancer Center

**Michaela Liedtke, MD ‡**
Stanford Cancer Institute

**Thomas Martin, MD ‡**
UCSF Helen Diller Family Comprehensive Cancer Center

**James Omel, MD ¥**
Patient Advocate

**Timothy J. Robinson, MD, PhD §**
Yale Cancer Center/Smilow Cancer Hospital

**Aaron Rosenberg, MD ‡ ξ**
UC Davis Comprehensive Cancer Center

**Shayna Sarosiek, MD ‡**
Dana-Farber/Brigham and Women's Cancer Center

**Mark A. Schroeder, MD ‡**
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

**Daniel Sherbenou, MD, PhD †**
University of Colorado Cancer Center

**Attaya Suvannasankha, MD ‡**
Indiana University Melvin and Bren Simon Comprehensive Cancer Center

**Jason Valent, MD ‡**
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

**Asya Nina Varshavsky-Yanovsky, MD, PhD † ‡**
Fox Chase Cancer Center

**Dan Vogl, MD ‡**
Abramson Cancer Center at the University of Pennsylvania

**NCCN**
**Emily Kovach**
**Rashmi Kumar, PhD**

[NCCN Guidelines Panel Disclosures]

Continue

ξ Bone marrow transplantation
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
¥ Patient advocacy
§ Radiation oncology
* Discussion section writing committee

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2026
# Systemic Light Chain Amyloidosis

NCCN Guidelines Index
Table of Contents
Discussion



Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

**NCCN Categories of Preference:** All recommendations are considered appropriate.

See NCCN Categories of Preference.

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2026
# Systemic Light Chain Amyloidosis

NCCN Guidelines Index
Table of Contents
Discussion

**Updates in Version 1.2026 of the NCCN Guidelines for Systemic Light Chain Amyloidosis from Version 2.2025 include:**

AMYL-1
- Clinical and amyloid-related assessment, bullet 6 added: 6-minute walk test.
- Footnote c added: The 6-minute walk test is used to assess aerobic capacity and endurance and serves as a predictor of cardiac function. Cohen OC, et al. Heart 2022;108:1616-1622.
- Footnote d modified: It is essential to confirm that patients have primary SLCA rather than hereditary amyloidosis, wild-type transthyretin-related (amyloid transthyretin [ATTR]) cardiac amyloidosis, or secondary amyloidosis. The amyloid deposits should be confirmed to be composed of light chains using immunohistochemistry or MS. Immunohistochemistry for transthyretin or serum amyloid A component should be performed if kappa and lambda stains are negative. *In the absence of monoclonal protein or elevated light chains*, 99mTc-pyrophosphate *(PYP)* scan can help *diagnose* ~~distinguish cardiac involvement with SLCA from~~ ATTR.
- Footnote e modified: Identification of light chains in the serum or urine without confirmation of the amyloid *deposition* ~~composition~~ in tissue is not adequate, as patients with other forms of amyloidosis may have an unrelated monoclonal gammopathy of undetermined significance (MGUS). Lachmann HJ, et al. N Engl J Med 2002;346:1786-1791.

AMYL-4
- Column 4, clinical finding added: ...protein *or elevated FLC with abnormal ratio* present.
- Footnote v added: Previous tissue biopsy (within last 1-2 years) can be stained with Congo red.

AMYL-B (1 of 6)
- Bullet 3 modified: *Modification of treatment should be considered* ~~*I*~~*if* hematologic (biochemical) response *is* < very good partial response (VGPR) by cycle 3 or < partial response (PR) by cycle 2 of initial therapy*, or* ~~*and*~~ *no complete response (CR) and persistent organ dysfunction.* ~~eventually organ response, consider treatment modification.~~
- Bullet 4 added: Typically, light-chain normalization precedes organ response.
- Sub-header added: Supportive Care.
- Supportive Care, bullet added: There are several supportive care measures that should be considered. See Table 1 in Maroun BZ, et al. Blood Res 2022;57:106-116.

AMYL-B (2 of 6)
- Significant neuropathy, All stages, Melphalan/Dexamethasone (if ineligible for HCT) moved from Preferred to Useful in Certain Circumstances.
- Footnote c added: Patients with IgM paraprotein may require different therapy. If there is underlying plasma cell clone, follow suggested therapies. For lymphoma or LPL, see NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma.

AMYL-B (4 of 6)
- Useful in Certain Circumstances, regimen added: Venetoclax t(11;14) + Daratumumab.

AMYL-B (6 of 6)
- Reference added for Venetoclax/Daratumumab.

## INITIAL DIAGNOSTIC WORKUP[a]

**Clinical and amyloid-related assessment**
- History and physical (H&P)
- Orthostatic vital signs
- Whole-body low-dose CT[b] or FDG-PET/CT
- Electrocardiogram (ECG)
- Echocardiogram with global longitudinal strain assessment
- 6-minute walk test[c]

**Pathologic evaluation**[d,e]
- Bone marrow aspirate + biopsy[f]
- Plasma cell fluorescence in situ hybridization (FISH) on bone marrow aspirate
- Abdominal fat pad sampling[g] and/or involved organ biopsy as clinically indicated
- Amyloid tissue subtyping with mass spectrometry (MS)
- If lymphoplasmacytic clone is present, then test for *MYD88* L265P mutation

**Laboratory evaluation for systemic light chain amyloidosis (SLCA)**
- To assess plasma cell markers:
  - Complete blood count (CBC), differential, platelet count
  - Peripheral blood smear
  - Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), and serum immunofixation electrophoresis (SIFE)
  - Serum free light chain (FLC) assay
- To assess organ involvement:
  - Heart
    - ◊ NT-proBNP/BNP,[h] troponin T (TnT)[h]
    - ◊ Lipid panel
  - Kidney
    - ◊ 24-h urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE)
    - ◊ Serum blood urea nitrogen (BUN)/creatinine, electrolytes, albumin, calcium, serum uric acid, serum lactate dehydrogenase (LDH), and beta-2 microglobulin
    - ◊ Creatinine clearance (calculated or measured directly)
  - Liver
    - ◊ Alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin
  - Coagulation system
    - ◊ Comprehensive coagulation studies if indicated
    - ◊ Prothrombin time (PT), partial thromboplastin time (PTT), and Factor X

→ Organ involvement (AMYL-2)

**Clinical suspicion of localized amyloidosis** → AMYL-3

**Clinical suspicion of isolated cardiac amyloidosis** → AMYL-4

[a] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[b] Skeletal survey is acceptable in certain circumstances. However, it is significantly less sensitive than whole-body low-dose CT and FDG-PET/CT. If FDG-PET/CT or whole-body low-dose CT has been performed, then skeletal survey is not needed. Refer to NCCN Guidelines for Multiple Myeloma for Principles of Imaging.
[c] The 6-minute walk test is used to assess aerobic capacity and endurance and serves as a predictor of cardiac function. Cohen OC, et al. Heart 2022;108:1616-1622.
[d] It is essential to confirm that patients have primary SLCA rather than hereditary amyloidosis, wild-type transthyretin-related (amyloid transthyretin [ATTR]) cardiac amyloidosis, or secondary amyloidosis. The amyloid deposits should be confirmed to be composed of light chains using immunohistochemistry or MS. Immunohistochemistry for transthyretin or serum amyloid A component should be performed if kappa and lambda stains are negative. In the absence of monoclonal protein or elevated light chains, 99mTc-pyrophosphate (pyrophosphate scintigraphy [PYP]) scan can help diagnose ATTR.
[e] Identification of light chains in the serum or urine without confirmation of the amyloid deposition in tissue is not adequate, as patients with other forms of amyloidosis may have an unrelated monoclonal gammopathy of undetermined significance (MGUS). Lachmann HJ, et al. N Engl J Med 2002;346:1786-1791.
[f] Congo red staining for amyloid. Congo stain does not differentiate between types of amyloid.
[g] Alternate sites could include rectal or minor salivary gland biopsy.
[h] If N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) is not available, B-type natriuretic peptide (BNP) can be performed. If TnT is not available, then troponin I is acceptable.

**Note: All recommendations are category 2A unless otherwise indicated.**

## DIAGNOSTIC WORKUP[i]

**Special testing based on organ system involvement**

- Cardiac
  - Cardiovascular magnetic resonance (CMR)[j] imaging (in certain circumstances)[k]
    - ◊ Cardiac MRI with and without contrast
- Liver and gastrointestinal (GI) tract
  - Gastric emptying scan (if gastroparesis present)
  - Abdominal ultrasound or abdominal CT to document craniocaudal liver span as clinically indicated
  - Upper and lower endoscopies if symptoms suggestive of GI involvement
- Peripheral nervous system
  - Electromyography (EMG) (if clinically significant peripheral neuropathy)/nerve conduction studies
- Other
  - Endocrine testing: thyroid-stimulating hormone (TSH), cortisol
  - Pulmonary testing: pulmonary function tests
  - Chest CT without contrast as indicated

→

## CLINICAL FINDINGS

If there is organ involvement based on amyloidosis consensus criteria[l]
- Evaluate for hematopoietic cell transplant (HCT) candidacy[m,n]

→

## TREATMENT OF NEWLY DIAGNOSED SLCA[i,l,o]

Clinical trial

or

Therapy for newly diagnosed disease[p] (AMYL-B)

and

Best supportive care
(See NCCN Guidelines for Palliative Care and NCCN Guidelines for Survivorship)

→

## RELAPSED/ REFRACTORY SLCA

Therapy for relapsed/ refractory disease (AMYL-B)

and

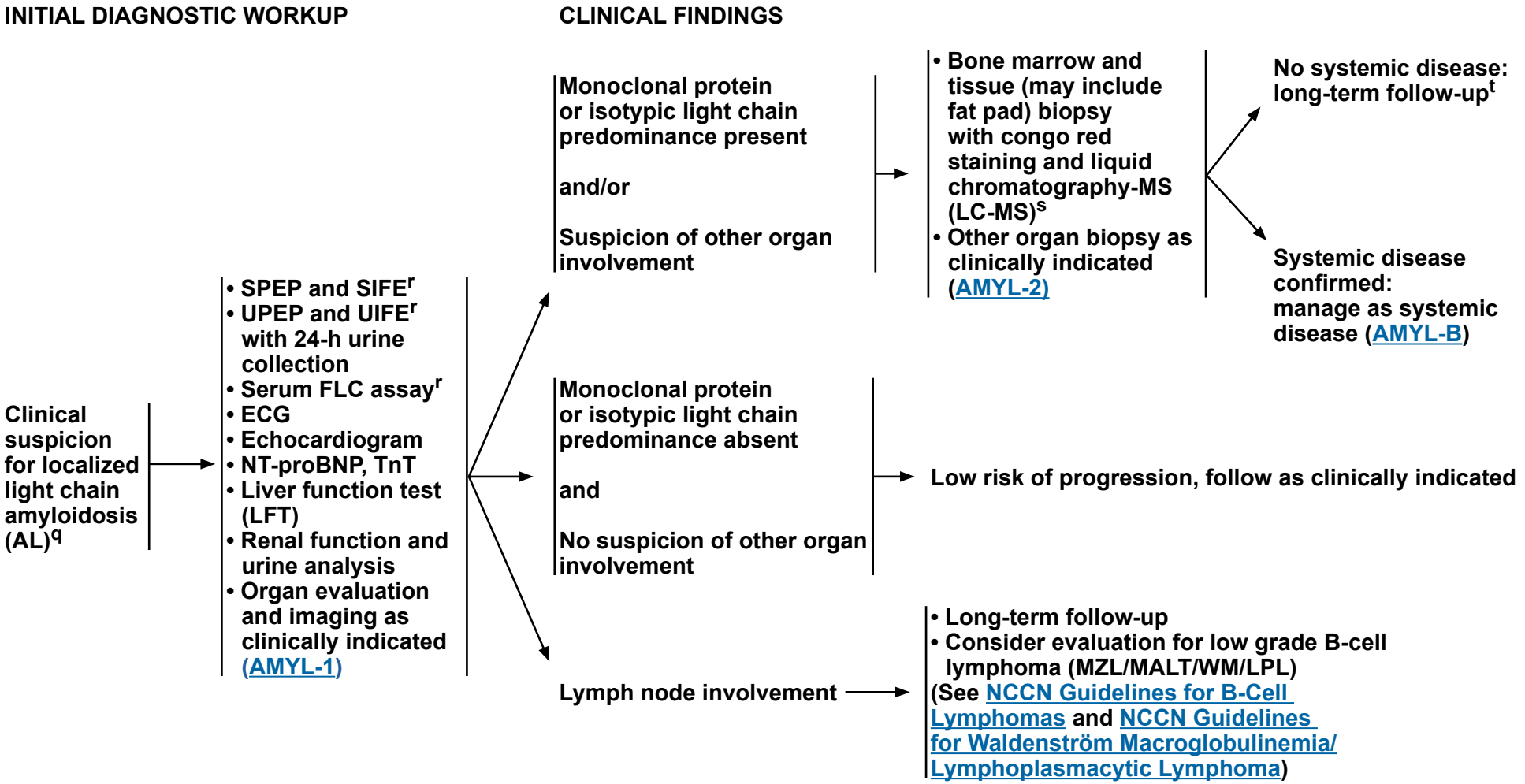
Best supportive care
(See NCCN Guidelines for Palliative Care)

[i] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[j] Transthoracic echocardiogram with global longitudinal strain imaging in patients where CMR is not feasible/optimal.
[k] Characteristic findings on cardiac MRI: global subendocardial late gadolinium enhancement (subendocardial or transmural involvement) with abnormal myocardial and blood-pool gadolinium kinetics. When appropriate, imaging should be done with contrast unless contraindicated.
[l] Definition of Organ Involvement Based on Amyloidosis Consensus Criteria (AMYL-C).
[m] In those patients with very low tumor burden, induction therapy may not be required. If not a candidate for HCT at initial diagnosis, reassess after initiating systemic therapy.
[n] Patients eligible for HCT can elect to collect stem cells and delay transplant to a later line of therapy.
[o] Definition of Organ and Hematologic Response and Progression Criteria (AMYL-D).
[p] Organ transplant, as clinically indicated.

**Note: All recommendations are category 2A unless otherwise indicated.**

# NCCN Guidelines Version 1.2026
# Systemic Light Chain Amyloidosis

NCCN Guidelines Index
Table of Contents
Discussion

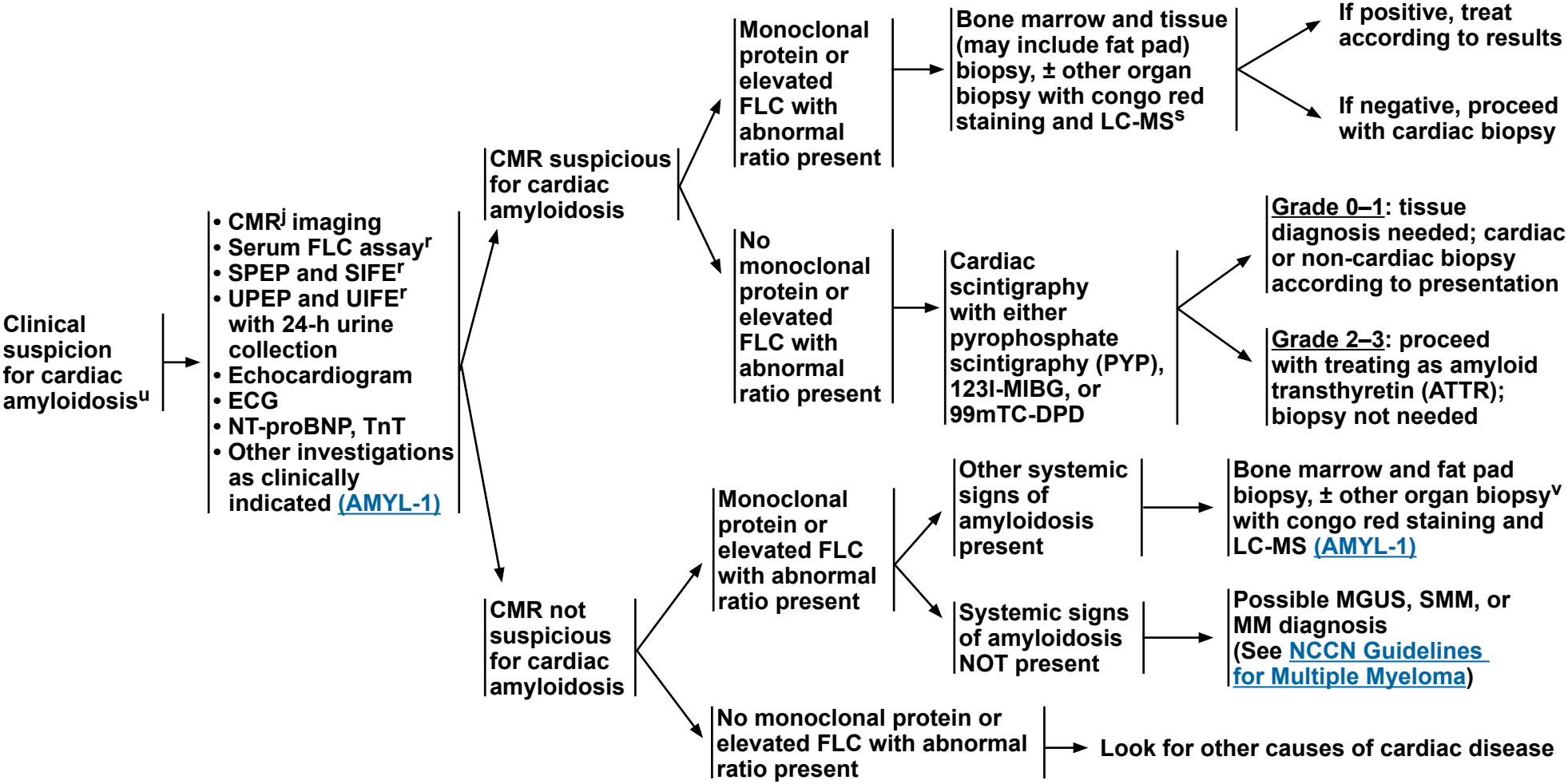



[q] Confirmed by MS.
[r] Screening for monoclonal protein must include immunofixation studies in both urine and serum for greatest sensitivity. Using electrophoresis alone without immunofixation or testing in serum alone has low sensitivity.
[s] Immunohistochemistry or immunofluorescence can be considered if MS is not available.
[t] Surgical approaches may be appropriate for symptomatic or cosmetic reasons (eg, skin lesions).

**Note: All recommendations are category 2A unless otherwise indicated.**

## CARDIAC AMYLOIDOSIS

### CLINICAL FINDINGS




[j] Transthoracic echocardiogram with global longitudinal strain imaging in patients where CMR is not feasible/optimal.
[r] Screening for monoclonal protein must include immunofixation studies in both urine and serum for greatest sensitivity. Using electrophoresis alone without immunofixation or testing in serum alone has low sensitivity.
[s] Immunohistochemistry or immunofluorescence can be considered if MS is not available.
[u] Syncope/presyncope/arrhythmia, unexplained left ventricular hypertrophy, voltage complex lower than expected for the left ventricular thickness, thick ventricular septum, persistent or unexplained elevation of NT-proBNP or TnT, and right heart failure symptoms.
[v] Previous tissue biopsy (within last 1–2 years) can be stained with Congo red.

**Note: All recommendations are category 2A unless otherwise indicated.**

## STAGING SYSTEMS FOR LIGHT CHAIN AMYLOIDOSIS

### Mayo 2012 Staging System[1]

| Prognostic Risk Variables | | Value | Prognostic Variable Risk Score | Stage Based on the Prognostic Variable Risk Scores |
|---|---|---|---|---|
| Troponin[a] | cTnT | ≥0.025 µg/L | 1 | Stage I (Risk Score = 0) |
| | hs-cTnT | ≥40 pg/mL | | Stage II (Risk Score = 1) |
| | cTnI | ≥0.1 µg/L | | |
| BNP | NT-ProBNP | ≥1800 ng/L | 1 | Stage III (Risk Score = 2) |
| | BNP | ≥400 ng/L | | |
| dFLC | dFLC | ≥18 mg/dL (180 mg/L) | 1 | Stage IV (Risk Score = 3) |

### Mayo 2004 Staging System with European Modifications[2]

| Risk Factors | | Value | Stage Based on Risk Factors |
|---|---|---|---|
| Troponin[a] | cTnT | ≥0.035 µg/L | Stage I (No risk factors) |
| | hs-cTnT | ≥50 ng/L | Stage II (1 risk factor) |
| | cTnI | ≥0.1 µg/L | |
| BNP | NT-ProBNP | ≥332 ng/L | Stage IIIA (2 risk factors: NT-proBNP 332 to <8500 ng/L or BNP 81 to <700 ng/L) |
| | BNP | ≥400 ng/L | |
| | | | Stage IIIB (2 risk factors: NT-proBNP ≥8500 ng/L or BNP ≥700 ng/L ) |

[a] High-sensitivity, troponin assays are increasingly used and replacing cTnI and cTNT in practice.

[1] Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol 2012;30:989-995.
[2] Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood 2015;126:612-615.

**Note: All recommendations are category 2A unless otherwise indicated.**

## GENERAL CONSIDERATIONS FOR SYSTEMIC THERAPY FOR SLCA

### General Considerations
- The goal of treatment is to achieve a complete hematologic response.
- Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
- Modification of treatment should be considered if hematologic (biochemical) response is < very good partial response (VGPR) by cycle 3 or < partial response (PR) by cycle 2 of initial therapy, or no complete response (CR) and persistent organ dysfunction.[1]
- Typically, light-chain normalization precedes organ response.
- For SLCA with an underlying lymphoplasmacytic clone, treat underlying Waldenström macroglobulinemia (WM)/lymphoplasmacytic lymphoma (LPL) as outlined in the NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma.

### Supportive Care
- There are several supportive care measures that should be considered. See Table 1 in Maroun BZ, et al. Blood Res 2022;57:106-116.

### Screening and Prophylaxis Recommendations
- Screen for HIV, hepatitis B, and hepatitis C, as clinically indicated.
- Recommend herpes zoster prophylaxis for patients treated with proteasome inhibitors or Daratumumab.

### Side Effects and Lab Tests
- Regimens containing Bortezomib are associated with a higher risk of treatment-related peripheral and autonomic neuropathy, especially in those with disease-related baseline neuropathy. Close monitoring or alternative therapies should be considered in some patients.
- Carfilzomib can potentially cause cardiac and pulmonary toxicity, especially in older patients.
- Treatment with immunomodulatory drugs is associated with transient elevation of cardiac biomarkers. Patients with cardiac amyloid should be carefully monitored while on therapy with immunomodulatory drugs.
- For patients with cardiac amyloidosis or nephrotic syndrome who are taking corticosteroids, close monitoring for volume overload is necessary. A dose reduction or elimination may be required.
- Renal function should be continuously monitored while on Lenalidomide to ensure appropriate dosing.
- Type and screen should be performed before using Daratumumab. Daratumumab may interfere with serologic testing and cause a false-positive indirect Coombs test.
- Daratumumab can produce a false-positive serum immunofixation if the monoclonal protein is IgG kappa and special interference testing or MS-based assessment can differentiate between the two.

### Dosing and Administration
- Proteasome inhibitors:
  - Subcutaneous Bortezomib is the preferred method of administration.
  - Weekly dosing schedules of Bortezomib are recommended.
  - Carfilzomib may be used once (preferred) or twice weekly and at different doses.
  - For any regimen that includes Daratumumab, this could be Daratumumab for intravenous infusion or Daratumumab and Hyaluronidase-fihj for subcutaneous injection. Daratumumab and Hyaluronidase-fihj for subcutaneous injection has different dosing and administration instructions compared to Daratumumab for intravenous injection.

**Note: All recommendations are category 2A unless otherwise indicated.**

References

| PRIMARY THERAPY FOR HCT-ELIGIBLE AND NON-ELIGIBLE PATIENTS WITH SLCA[1,2,a,b,c] | | | |
|---|---|---|---|
| (Note: If not a candidate for HCT at initial diagnosis, reassess after initiating systemic therapy based on improvements in functional status and/or organ response.) | | | |
| **Patient Characteristics** | **Mayo 2004 Staging** | **Preferred** | **Useful in Certain Circumstances** |
| **No significant neuropathy** | **Stage I–IIIa** | • Daratumumab/Bortezomib/Cyclophosphamide/ Dexamethasone[f,g,h] (category 1)<br>• Autologous HCT (if eligible[i]) | • Bortezomib/Cyclophosphamide/Dexamethasone[f,g]<br>• Bortezomib/Melphalan/Dexamethasone (if ineligible for HCT)[g] |
| | **Stage IIIb[d]** | • Dose-modified Daratumumab/Bortezomib/ Cyclophosphamide/Dexamethasone[f,g,h]<br>• Single-agent Daratumumab | • Dose-modified Bortezomib/Cyclophosphamide/ Dexamethasone[g]<br>• Bortezomib/Melphalan/Dexamethasone (if ineligible for HCT)[g] |
| **Significant neuropathy** | **All stages[e]** | • Daratumumab/Bortezomib/Cyclophosphamide/ Dexemathasone[f,g,h] | • Lenalidomide[j]/Dexamethasone<br>• Carfilzomib/Dexamethasone<br>• Melphalan/Dexamethasone (if ineligible for HCT) |

[a] General Considerations for Systemic Therapy for SLCA (AMYL-B 1 of 6).
[b] For autologous HCT eligibility and Melphalan dosing, see (AMYL-B 3 of 6).
[c] Patients with IgM paraprotein may require different therapy. If there is underlying plasma cell clone, follow suggested therapies. For lymphoma or LPL, see NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma.
[d] Stage IIIB patients were excluded at screening from the ANDROMEDA trial according to the protocol. Retrospective trials have demonstrated acceptable efficacy and safety profile of Daratumumab/Cyclophosphamide/Bortezomib/ Dexamethasone in stage IIIb SLCA.
[e] Dose modification and adjustments are mandatory in patients with advanced end organ damage (cardiac or other).
[f] Dexamethasone dosing can be considered at the 20 mg weekly dose, per physician discretion, in those who are >70 years of age, had underweight (body mass index <18.5), or had hypervolemia, poorly controlled diabetes mellitus, or previous unacceptable side effects associated with glucocorticoid therapy. Cyclophosphamide is capped at a 500 mg maximum weekly dose.
[g] Dose reduce or discontinue Bortezomib if significant neuropathy.
[h] Single-agent Daratumumab was given as maintenance therapy in the ANDROMEDA trial.
[i] Patients with single organ involvement, <10% marrow plasma cell involvement, and good performance status.
[j] Lenalidomide therapy is associated with increased toxicities, particularly in newly diagnosed patients with untested cardiac functional impairment. Lenalidomide should not be used in patients with advanced heart or autonomic nerve involvement. Consider a lower starting dose (10–15 mg) of Lenalidomide in patients with SLCA than is used in multiple myeloma (MM) even in those with normal renal function. See NCCN Guidelines for Multiple Myeloma.

[1] Wechalekar AD, Cibeira MT, Gibbs SD, et al. Guidelines for non-transplant chemotherapy for treatment of systemic AL amyloidosis: EHA-ISA working group. Amyloid 2023;30:3-17.
[2] Sanchorawala V, Boccadoro M, Gertz M, et al. Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines. Amyloid 2022;29:1-7.

**Note: All recommendations are category 2A unless otherwise indicated.**

## TREATMENT CONSIDERATIONS FOR NEWLY DIAGNOSED SLCA

**Considerations for Autologous HCT[2,3]**

- Careful patient selection is critical for the success of autologous HCT in AL amyloidosis. Enrollment of patient in a clinical trial is encouraged.
- Autologous HCT could be deferred if complete hematologic response is achieved with induction therapy.
- Prior to HCT: Consider induction therapy (AMYL-B [2 of 6])
- Post HCT: Consolidation and maintenance therapy are not routinely recommended in SLCA.[k]

**Definite Exclusions for Autologous HCT[2]**

- Symptomatic and/or medically refractory:
  - Ventricular and atrial arrhythmias
  - Pleural effusions
- Uncompensated heart failure
- Orthostatic hypotension refractory to medical therapy
- Factor X deficiency with factor X level of <25% and/or evidence of active bleeding
- Extensive GI involvement with evidence of active GI bleeding or risk of bleeding

**Melphalan Dosing Considerations:**

- The dose of Melphalan can be adjusted based on factors such as age, renal function, presence/absence of cardiac involvement, and number of organs involved (see table below). These risk-adapted approaches have not been evaluated in randomized studies.

| | Melphalan 200[l] | Melphalan 200[m] | Melphalan 140 |
|---|---|---|---|
| **Age** | ≤65 | >65 | |
| **Cardiac stage** | I or II | II or III | |
| **eGFR (mL/min/m²)** | >50 | 30–50 | <30[n] |

[k] In patients with overt concurrent MM, bone marrow plasma cells ≥20%, or high-risk FISH changes [del(17p), t(4;14), t(14;16), and t(14;20), 1q gain/amplification], consideration can be given to extended duration therapy, including forms of maintenance used in myeloma. Also, consolidation treatment may be considered for patients with VGPR or complete hematologic response with persistent minimal residual disease and no organ response.

[l] Patient must meet all criteria to receive Melphalan 200.

[m] Multidisciplinary discussion of using Melphalan 200 for autologous HCT versus Daratumumab and Bortezomib-based induction regimen is recommended for this patient group.

[n] Increased risk of acute kidney injury and end-stage renal disease during peri-autologous HCT period, can consider if on a stable chronic dialysis schedule.

[2] Sanchorawala V, Boccadoro M, Gertz M, et al. Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines. Amyloid 2022;29:1-7.

[3] Baljevic M. Evolving role of autologous stem cell transplantation for light chain amyloidosis in the modern era. Oncology (Williston Park) 2021;35:474-475.

**Note: All recommendations are category 2A unless otherwise indicated.**

| THERAPY FOR PREVIOUSLY TREATED DISEASE[a,o] |
|---|
| **Consider repeating initial therapy, especially if relapse-free for several years[p]**<br>• Bortezomib<br>• Bortezomib/Dexamethasone<br>• Bortezomib/Cyclophosphamide/Dexamethasone<br>• Bortezomib/Melphalan/Dexamethasone<br>• Daratumumab<br>• Ixazomib/Cyclophosphamide/Dexamethasone<br>• Ixazomib/Dexamethasone<br>• Ixazomib/Lenalidomide/Dexamethasone[q]<br>• Lenalidomide/Cyclophosphamide/Dexamethasone[q]<br>• Lenalidomide/Dexamethasone[q]<br>• High-dose Melphalan with HCT<br>• Melphalan/Dexamethasone<br>• Pomalidomide/Dexamethasone |
| **Useful in Certain Circumstances**<br>• Bendamustine/Dexamethasone<br>• For non-cardiac amyloidosis<br>▸ Carfilzomib<br>▸ Carfilzomib/Dexamethasone<br>• Daratumumab/Lenalidomide/Dexamethasone[q]<br>• Venetoclax t(11;14)[r]<br>• Venetoclax t(11;14)[r]/Dexamethasone<br>• Venetoclax t(11;14)[r] + Daratumumab |

[a] General Considerations for Systemic Therapy for SLCA (AMYL-B 1 of 6).
[o] Consider collection of hematopoietic stem cells, if appropriate.
[p] Recommend Daratumumab-based therapy for those who did not receive it as primary therapy.
[q] Recommended starting dose of Lenalidomide is 10–15 mg.
[r] Since a majority of patients with AL have t(11;14), consideration for BCL-2 targeting agents eg, Venetoclax should be a strong consideration in the relapse setting.

**Note: All recommendations are category 2A unless otherwise indicated.**

## SYSTEMIC LIGHT CHAIN AMYLOIDOSIS THERAPY: REFERENCES FOR TREATMENT OPTIONS

**• Bendamustine/Dexamethasone**
- Lentzsch S, Lagos GG, Comenzo RL, et al. Bendamustine with dexamethasone in relapsed/refractory systemic light-chain amyloidosis: Results of a phase II study. J Clin Oncol 2020;38:1455-1462.

**• Bortezomib/Cyclophosphamide/Dexamethasone**
- Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood 2012;119:4387-4390.
- Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood 2012;119:4391-4394.

**• Bortezomib ± Dexamethasone**
- Reece DE, Hegenbart U, Sanchorawala V, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: Results of a phase 1/2 study. Blood 2011;118:865-873.
- Kastritis E, Wechalekar AD, Dimopoulos MA, et al. Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis. J Clin Oncol 2010;28:1031-1037.
- Singh V, Saad A, Palmer J, et al. Response to bortezomib based induction therapy in newly diagnosed light chain (AL) amyloidosis [abstract]. Blood 2009;114 (Suppl):Abstract 1867.
- Lamm W, Willenbacher W, Lang A, et al. Efficacy of the combination of bortezomib and dexamethasone in systemic AL amyloidosis. Ann Hematol 2011;90:201-206.
- Reece DE, Sanchorawala V, Hegenbart U, et al. Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of a phase 1 dose-escalation study. Blood 2009;114:1489-1497.

**• Bortezomib/Lenalidomide/Dexamethasone**
- Kastritis E, Dialoupi I, Gavriatopoulou M, et al. Primary treatment of light-chain amyloidosis with bortezomib, lenalidomide, and dexamethasone. Blood Adv 2019;3:3002-3009.

**• Bortezomib/Melphalan/Dexamethasone**
- Gasparetto C, Sanchorawala V, Snyder RM, et al. Use of melphalan (M)/dexamethasone (D)/bortezomib in AL amyloidosis [abstract]. J Clin Oncol 2010;28 (Suppl):Abstract 8024.

**• Carfilzomib/Dexamethasone**
- Manwani R, Mahmood S, Sachchithanantham S, et al. Carfilzomib is an effective upfront treatment in AL amyloidosis patients with peripheral and autonomic neuropathy. Br J Haematol 2019;187:638-641.

**• Daratumumab**
- Kaufman GP, Schrier SL, Lafayette RA, et al. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood 2017;130:900-902.
- Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. N Engl J Med 2021;385:46-58.

**• Daratumumab/Bortezomib/Cyclophosphamide/Dexamethasone**
- Palladini G, Kastritis E, Maurer MS, et al. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. Blood 2020;136:71-80.
- Chakraborty R, Rosenbaum C, Kaur G, et al. First report of outcomes in patients with stage IIIb AL amyloidosis treated with Dara-VCD front-line therapy. Br J Haematol 2023;201:913-916.

**• Daratumumab/Lenalidomide/Dexamethasone**
- Kawano Y, Hata H, Takashio S, et al. Daratumumab, lenalidomide and dexamethasone in newly diagnosed systemic light chain amyloidosis patients associated with multiple myeloma. B J Haematol 2022;198:e38-e41.

**• High-dose Melphalan with HCT**
- Skinner M, Sanchorawala V, Seldin D, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med 2004;140:85-93.
- Gertz MA, Lacy MQ, Dispenzieri A, et al. Risk-adjusted manipulation of melphalan dose before stem cell transplantation in patients with amyloidosis is associated with a lower response rate. Bone Marrow Transplant 2004;34:1025-1031.
- Perfetti V, Siena S, Palladini G, et al. Long-term results of a risk-adapted approach to melphalan conditioning in autologous peripheral blood stem cell transplantation for primary (AL) amyloidosis. Haematologica 2006;91:1635-1643.
- D'Souza A, Dispenzieri A, Wirk B, et al. Improved outcomes after autologous hematopoietic cell transplantation for light chain amyloidosis: A center for international blood and marrow transplant research study. J Clin Oncol 2015;33:3741-3749.
- Dispenzieri A, Seenithamby K, Lacy MQ, et al. Patients with immunoglobulin light chain amyloidosis undergoing autologous stem cell transplantation have superior outcomes compared with patients with multiple myeloma: a retrospective review from a tertiary referral center. Bone Marrow Transplant 2013;48:1302-1307.

**• Ixazomib/Dexamethasone**
- Sanchorawala V, Palladini G, Kukreti V, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. Blood 2017;130:597-605.

Continued

**Note: All recommendations are category 2A unless otherwise indicated.**

## SYSTEMIC LIGHT CHAIN AMYLOIDOSIS THERAPY: REFERENCES FOR TREATMENT OPTIONS

**• Ixazomib/Cyclophosphamide/Dexamethasone**
- Muchtar E, Gertz MA, LaPlant BR, et al. Phase 2 trial of ixazomib, cyclophosphamide, and dexamethasone for previously untreated light chain amyloidosis. Blood Adv 2022;6:5429-5435.

**• Ixazomib/Lenalidomide/Dexamethasone**
- Cohen OC, Sharpley F, Gilmore JD, et al. Use of ixazomib, lenalidomide and dexamethasone in patients with relapsed amyloid light-chain amyloidosis. Br J Haematol 2020;189:643-649.

**• Lenalidomide/Cyclophosphamide/Dexamethasone**
- Kumar SK, Hayman SR, Buadi FK, et al. Lenalidomide, cyclophosphamide, and dexamethasone (CRd) for light-chain amyloidosis: long-term results from a phase 2 trial. Blood 2012;119:4860-4867.
- Palladini G, Russo P, Milani P, et al. A phase II trial of cyclophosphamide, lenalidomide and dexamethasone in previously treated patients with AL amyloidosis. Haematologica 2013;98:433-436.

**• Lenalidomide/Dexamethasone**
- Sanchorawala V, Wright D, Rosenzweig M, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. Blood 2007;109:492-496.
- Dispenzieri A, Lacy M, Zeldenrust S, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. Blood 2007;109:465-470.
- Dispenzieri A, Lacy M, Zeldenrust S, et al. Long term follow-up of patients with immunoglobulin light chain amyloidosis treated with lenalidomide and dexamethasone [abstract] Blood 2008;112: Abstract 1737.

**• Oral Melphalan/Dexamethasone**
- Palladini G, Russo P, Nuvolone M, et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. Blood 2007;110:787-788.
- Jaccard A, Leblond V, Royer B, et al. Autologous stem cell transplantation (ASCT) versus oral melphalan and high-dose dexamethasone in patients with AL (primary) amyloidosis: long term follow-up of the French multicentric randomized trial [abstract]. Blood 2010;116: Abstract 1344.

**• Pomalidomide/Dexamethasone**
- Dispenzieri A, Buadi F, Laumann K, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. Blood 2012;119:5397-5404.
- Sanchorawala V, Shelton A, Lo S, et al. Pomalidomide and dexamethasone in the treatment of AL amyloidosis: Results of a phase 1 and 2 trial. Blood 2016;128:1059-1062.

**• Venetoclax ± Dexamethasone**
- Premkumar VJ, Lentzsch, Pan S, et al. Venetoclax induces deep hematologic remissions in t(11;14) relapsed/refractory AL amyloidosis. Blood Cancer J 2021;11:10.

**• Venetoclax/Daratumumab**
- Lebel E, Kastritis E, Palladini G, et al. Venetoclax in relapse/refractory AL amyloidosis-a multicenter international retrospective real-world study. Cancers (Basel) 2023;15:1710.

**Note: All recommendations are category 2A unless otherwise indicated.**

## DEFINITION OF ORGAN INVOLVEMENT BASED ON AMYLOIDOSIS CONSENSUS CRITERIA[1,2]

**Organ Involvement**

| | |
|---|---|
| **Kidney** | • 24-h urine protein >0.5 g/d, predominantly albumin |
| **Heart**[a] | • Echo:<br>▸ Mean wall thickness >12 mm<br>▸ No other cardiac cause or an elevated NT-proBNP (>332 ng/L) in the absence of renal failure or atrial fibrillation |
| **Liver** | • Total liver span >15 cm in the absence of heart failure or alkaline phosphatase >1.5 times institutional upper limit of normal |
| **Nerve** | • Peripheral: clinical;<br>▸ Symmetric lower extremity sensorimotor peripheral neuropathy<br>• Autonomic:<br>▸ Gastric-emptying disorder,<br>▸ Pseudo-obstruction,<br>▸ Voiding dysfunction not related to direct organ infiltration |
| **Gastrointestinal tract** | • Direct biopsy verification when GI tract specific symptoms are present |
| **Lung** | • Direct biopsy verification when lung specific symptoms are present<br>• Interstitial radiographic pattern |
| **Soft tissue** | • Tongue enlargement, clinical<br>• Arthropathy<br>• Claudication, presumed vascular amyloid<br>• Skin<br>• Myopathy by biopsy or pseudohypertrophy<br>• Lymph node (may be localized)<br>• Carpal tunnel syndrome |

[a] Characteristic findings on cardiac MRI: global subendocardial late gadolinium enhancement (subendocardial or transmural involvement) with abnormal myocardial and blood-pool gadolinium kinetics. Transthoracic echocardiogram with global abnormal strain imaging in patients where CMR is not feasible/optimal. Note: This is not part of the consensus criteria.

[1] Adapted with permission from John Wiley and Sons, Inc. Gertz M, Comenzo R, Fermand JP, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France,18-22 April 2004. Am J Hematol 2005;79:319-328. Copyright (2005).

[2] Gertz MA, Merlini G. Definition of organ involvement and response to treatment in AL amyloidosis: an updated consensus opinion. Amyloid 2010;17(Suppl 1):48-49.

**Note: All recommendations are category 2A unless otherwise indicated.**

## DEFINITION OF ORGAN AND HEMATOLOGIC RESPONSE AND PROGRESSION CRITERIA

### Hematologic Response and Progression Criteria[1]

| Response Category | Criteria |
|---|---|
| **Complete** | Normalization of the FLC levels and ratio,[a] negative serum and urine immunofixation |
| **Very good partial** | Reduction in the dFLC to <40 mg/L |
| **Partial** | A greater than 50% reduction in the dFLC |
| **No response** | Less than a PR |
| **Progression** | • From CR, any detectable monoclonal protein or abnormal FLC ratio (light chain must double)<br>• From PR, 50% increase in serum M protein to >0.5 g/dL or 50% increase in urine M protein to >200 mg/d (a visible peak must be present)<br>• Serum-FLC increase of 50% to >100 mg/L |

### Organ Response and Progression Criteria

| Organ | Response | Progression |
|---|---|---|
| **Heart[1]** | NT-proBNP response (>30% and >300 ng/L decrease in patients with baseline NT-proBNP ≥650 ng/L) or NYHA class response (≥2 class decrease in subjects with baseline NYHA class 3 or 4) | NT-proBNP progression (>30% and >300 ng/L increase)[b] or cTnT progression (≥33% increase) or ejection fraction progression (≥10% decrease) |
| **Kidney[2]** | ≥30% decrease in proteinuria or drop of proteinuria below 0.5 g/24 h in the absence of renal progression | ≥25% decrease in eGFR |
| **Liver[1]** | • 50% decrease in abnormal alkaline phosphatase value<br>• Decrease in liver size radiographically at least 2 cm | 50% increase of alkaline phosphatase above the lowest value |
| **Peripheral nervous system[a]** | Improvement in electromyogram nerve conduction velocity (rare) | Progressive neuropathy by electromyography or nerve conduction velocity |

[a] When FLC ratio is not within the reference range, the uninvolved FLC concentration must be greater than the involved FLC concentration. Palladini G, Schonland SO, Sanchorawala, et al. Clarification on the definition of complete haematologic response in light-chain (AL) amyloidosis. Amyloid 2021;28:1-2.
[b] Patients with progressively worsening renal function cannot be scored for NT-proBNP progression.
[1] Reproduced with permission from Springer Nature: Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia 2012;26:2317-2325. Copyright (2012).
[2] Adapted with permission from the American Society of Hematology: Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood 2014;124:2325-2332.

**Note: All recommendations are category 2A unless otherwise indicated.**

## ABBREVIATIONS

| | |
|---|---|
| AL | light chain amyloidosis |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| ATTR | amyloid transthyretin |
| BNP | B-type natriuretic peptide |
| BUN | blood urea nitrogen |
| CBC | complete blood count |
| CR | complete response |
| CMR | cardiovascular magnetic resonance |
| cTnI | cardiac troponin I |
| cTnT | cardiac troponin T |
| dFLC | difference between involved FLC and uninvolved FLC |
| ECG | electrocardiogram |
| eGFR | estimated glomerular filtration rate |
| EMG | electromyogram |
| FDG | fluorodeoxyglucose |
| FISH | fluorescence in situ hybridization |
| FLC | free light chain |
| GI | gastrointestinal |
| H&P | history and physical |
| HCT | hematopoietic cell transplant |
| HIV | human immunodeficiency virus |
| hs-cTnT | high sensitivity cardiac troponin T |
| LC-MS | liquid chromatography-mass spectrometry |
| LDH | lactate dehydrogenase |
| LFT | liver function test |
| LPL | Lymphoplasmacytic Lymphoma |
| MALT | mucosa-associated lymphoid tissue |
| MGUS | monoclonal gammopathy of undetermined significance |
| MM | multiple myeloma |
| MS | mass spectrometry |
| MZL | marginal zone lymphoma |
| NT-proBNP | N-terminal prohormone of B-type natriuretic peptide |
| PR | partial response |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| PYP | pyrophosphate scintigraphy |
| SIFE | serum immunofixation electrophoresis |
| SLCA | systemic light chain amyloidosis |
| SMM | smoldering multiple myeloma |
| SPEP | serum protein electrophoresis |
| TnT | troponin T |
| TSH | thyroid-stimulating hormone |
| UIFE | urine immunofixation electrophoresis |
| UPEP | urine protein electrophoresis |
| VGPR | very good partial response |
| WM | Waldenström macroglobulinemia |
| 99mTc | technetium-99m |

| NCCN Categories of Evidence and Consensus | |
|---|---|
| **Category 1** | Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate. |
| **Category 2A** | Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate. |
| **Category 2B** | Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate. |
| **Category 3** | Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |

All recommendations are category 2A unless otherwise indicated.

| NCCN Categories of Preference | |
|---|---|
| **Preferred** | Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability. |
| **Other recommended** | Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes. |
| **Useful in certain circumstances** | Other interventions that may be used for selected patient populations (defined with recommendation). |

All recommendations are considered appropriate.

**Note: All recommendations are category 2A unless otherwise indicated.**

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2026
# Systemic Light Chain Amyloidosis

## Discussion

This discussion corresponds to the NCCN Guidelines for Systemic Light Chain Amyloidosis (Last updated: March 12, 2025)

### Table of Contents

# NCCN Guidelines Version 1.2026
# Systemic Light Chain Amyloidosis

## Overview

Primary systemic light chain amyloidosis (SLCA), in contrast to multiple myeloma, is typically characterized by a low burden of monoclonal plasma cells in the bone marrow. The abnormal plasma cells produce light chains that get converted to amyloid fibrils with an affinity for visceral organs (such as the kidney, heart, gastrointestinal [GI] tract, liver, spleen, and nervous system) and cause end-organ dysfunction.[1]

Major principles of management in SLCA are to rapidly and sustainably reduce the production, as well as harmful deposition, of causative amyloidogenic amyloid fibrils through individualized therapy based on the extent of disease and organ involvement, type and the extent of symptom burden, as well as anticipated treatment-related toxicity. Throughout the management, organ-specific supportive care is extended, preferentially in the context of experienced multidisciplinary subspecialty care teams, to maximize treatment efficacy, minimize disease and treatment-related complications, optimize quality of life, and ultimately recover the function of the affected organs and reduce the risk of death.

Around 69% of newly diagnosed patients have more than one organ involved at the time of diagnosis.[2] According to data from the U.S. claims database, the incidence of amyloidosis seems to range from 9 to 14 cases per million person-years.[3] Due to earlier diagnosis, newer therapies that provide deeper responses, and better selection of candidate patients for autologous hematopoietic cell transplant (HCT) consolidation, the early mortality rates (including transplant-related mortality) of patients with SLCA have decreased, and survival has improved.

## Literature Search Criteria

Prior to the update of this version of the NCCN Clinical Practice Guidelines (NCCN Guidelines®) for Systemic Light Chain Amyloidosis, an electronic search of the PubMed database was performed to obtain key literature in SLCA, using the following search terms: Systemic Light Chain Amyloidosis and Amyloidosis. The PubMed database was chosen as it is the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[4]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline, Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The results of the PubMed search were examined for their potential relevance. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the Panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

## Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[5] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-

biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

## Initial Diagnostic Workup

The workup of patients with suspected amyloidosis is geared towards demonstration of the amyloid fibrils in tissue, identification of the protein of origin, and in the setting of light chain amyloidosis demonstration of the monoclonal plasma cell disorder. Subsequent workup is geared towards identifying the organs involved and the severity of organ involvement and assessment of the feasibility and safety of different treatment approaches.

### Clinical and Amyloid-Related Assessment

The initial diagnostic workup includes a detailed history and physical (H&P) examination, evaluation of orthostatic vital signs, and careful evaluation for the pathognomonic signs of amyloidosis. In the setting of a monoclonal process, imaging with whole-body low-dose CT scan or FDG-PET/CT can detect osteolytic bone lesions. A skeletal survey is acceptable in certain circumstances (ie, limited access to health care resources), but it is significantly less sensitive than whole-body low-dose CT and FDG-PET/CT. If FDG-PET/CT or whole-body low-dose CT has been performed, then a skeletal survey is not needed. Electrocardiogram (ECG) may demonstrate low voltages and rhythm abnormalities, especially in the setting of cardiac amyloidosis.

### Laboratory Evaluation

The laboratory evaluation begins with a complete blood count (CBC) with differential, including platelet counts, and peripheral blood smear. Screening for monoclonal protein by serum and urine protein electrophoresis (SPEP and UPEP) alone may not be adequate, as it does not show a monoclonal spike in nearly 50% of cases. Therefore, serum immunofixation electrophoresis (SIPE) and 24-hour urine immunofixation electrophoresis (UIPE) is essential along with serum free light chain (FLC) analysis. The measurement of serum FLC is a diagnostic necessity, as the majority of patients with light chain amyloidosis will have abnormalities of the kappa or lambda chains with an abnormal kappa/lambda ratio.[6,7]

To assess organ involvement, the workup should include urinalysis with quantification of proteinuria by 24-hour urine collection and measurement of creatinine clearance (calculated or measured directly). FLCs are cleared by the kidney; therefore, renal insufficiency increases the concentrations of FLC. In that case, the kappa/lambda ratio or the difference between involved and uninvolved FLCs should be monitored.[6] Tests to assess renal function such as serum blood urea nitrogen (BUN) content and serum creatinine, electrolytes, albumin, calcium, serum uric acid, serum lactate dehydrogenase (LDH), and beta-2 microglobulin are also recommended by the NCCN Panel. Recommended liver function evaluation tests (LFTs) include alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin. Cardiac biomarkers in the serum

provide a quantitative assessment of cardiac dysfunction (troponin I or T), and cardiac stress brain natriuretic peptide (BNP) or N-terminal prohormone of brain natriuretic peptide (NT-proBNP) are important predictors of outcome in amyloidosis as well as part of the cardiac response criteria.[8,9] BNP evaluation can be performed if NT-proBNP assessment is unavailable. Similarly, if troponin T (TnT) is unavailable, then troponin I is acceptable. A lipid panel is also recommended.

The Panel recommends comprehensive coagulation studies if indicated, including prothrombin time (PT), partial thromboplastin (PTT), and Factor X. Patients with SLCA are at risk of developing acquired factor X deficiency due to binding of factor X to amyloid fibrils.[10-12] This deficiency typically responds to treatment of the underlying amyloidosis. To determine if factor X is involved, prolonged thromboplastin time (PT) and activated prolonged partial thromboplastin time (PTT) tests may be performed. The amyloid deposits should be confirmed to be composed of light chains using immunohistochemistry or mass spectrometry. Immunohistochemistry for transthyretin or serum amyloid A component should be performed if kappa and lambda stains are negative.

**Pathologic Evaluation**

The diagnosis of amyloidosis requires the identification of amyloid deposits in tissues either by aspiration of abdominal subcutaneous fat and/or biopsy of the organs involved. Characterization of amyloidosis as a systemic light chain type requires the demonstration of the underlying plasma cell clone. Therefore, identification of FLCs in the serum or urine must be followed by confirmation of amyloid in the tissue by pathologic evaluation.

Congo red staining of the subcutaneous fat aspirate is a reliable and noninvasive test reported to identify amyloid deposits in approximately 85% of patients.[12-14] Amyloid deposits can be identified by bone marrow aspiration and biopsy followed by Congo red staining. The monoclonal plasma cell population can be detected in bone marrow aspirates by immunohistochemical staining of kappa and lambda chains. Immunohistochemistry for transthyretin or the serum amyloid A component should be performed if kappa and lambda stains are negative. The stroma or blood vessels have been reported to be positive for amyloid in 60% of patients.[15] Plasma cell fluorescence in situ hybridization (FISH) studies can be performed on bone marrow aspirates. FISH studies can be used to identify genetic aberrations, which can be prognostic in SCLA.[16]

Identification of FLCs in the serum or urine without confirmation of the amyloid composition in tissue is not adequate, as patients with other forms of amyloidosis may have an unrelated monoclonal gammopathy of undetermined significance (MGUS).[17] Therefore, it is essential to confirm that the amyloid deposits are composed of light chains by immunohistochemical methods, electron microscopy, or mass spectrometry.[18-20] Mass spectroscopy has a higher diagnostic accuracy compared to immunohistochemistry in identifying the protein subunit and is considered the gold standard to confirm light chain amyloid (AL) subtype.[21]

If fat pad aspirate and bone marrow biopsy are negative and amyloidosis is still suspected, then the affected organs (eg, kidney, liver, heart) should be evaluated.

A non-invasive nuclear imaging test, 99mTc-pyrophosphate (PYP) scans can help distinguish cardiac involvement with AL from amyloid transthyretin (ATTR). In individuals with cardiac involvement from AL, a PYP scan is much less likely to be abnormal when compared to individuals with ATTR.[22,23]

Since the treatment is different in the various types of amyloidosis, it is essential to confirm that patients have light chain amyloidosis (AL)

rather than hereditary amyloidosis, senile amyloidosis, or secondary amyloidosis.

**Specialized Testing Based on Organ Involvement**

The majority of patients present with one or more organs affected by amyloidosis.

Cardiac involvement is diagnosed by imaging techniques such as cardiovascular magnetic resonance (CMR) imaging in certain circumstances. Transthoracic echocardiogram with global longitudinal strain imaging is also an option in patients where CMR is not feasible/optimal. Low voltages and rhythm abnormalities can also be captured on ECG in individuals with cardiac amyloid involvement. Cardiovascular MRI has been successfully used for the diagnosis and prognosis of amyloid cardiomyopathy.[24,25] Characteristic findings on cardiac MRI include global subendocardial late gadolinium enhancement (subendocardial or transmural involvement) with abnormal myocardial and blood-pool gadolinium kinetics. When appropriate, imaging should be done with contrast unless contraindicated.

Liver and GI involvement may be confirmed by performing a gastric emptying scan if gastroparesis is present; and abdominal ultrasound or CT scan as clinically indicated to determine craniocaudal liver span. Upper and lower endoscopies with random biopsies of suspected affected portions to confirm AL involvement of the GI tract can be extremely helpful in establishing the presence of deposits.

An electromyogram (EMG) or nerve conduction testing can be performed if the patient has significant peripheral neuropathy to confirm peripheral nervous system involvement.

Endocrine tests (thyroid-stimulating hormone and cortisol levels) and pulmonary function tests may be performed if involvement of the endocrine system or lungs is suspected. Chest CT without contrast may be performed, if clinically indicated.

## Localized Amyloidosis

Localized amyloidosis (LA) is a rare, self-limiting disorder, caused by the production of immunoglobulin-free light chains locally from plasma cells or plasmacytic B-cells, typically affecting a single organ.[26] Unlike SLCA, LA frequently has no circulating monoclonal immunoglobulin light chains. The most common organs affected in LA are the larynx, trachea, lung, skin, or urinary tract, and account for approximately 7% to 12% of all amyloidosis diagnoses.[26,27] Because of the confined nature of this disorder, and low propensity to develop generalized involvement, individuals with LA typically have an excellent prognosis and overall survival (OS) comparable to that of the general population.[26]

If LA is suspected, it should first be confirmed by mass spectrometry. Once confirmed, SPEP and SIFE, and UPEP and UIFE with 24-hour urine collection are recommended as part of the workup. Serum FLC assay, ECG, echocardiogram, NT-proBNP, TnT, LFTs, renal function and urinalysis, and organ evaluation and imaging as clinically indicated (see *Laboratory Evaluation* above) are also included as part of the initial diagnostic workup.

If monoclonal protein or isotypic light chain predominance is present and/or there is suspicion of other organ involvement, bone marrow and tissue biopsy with congo red staining and any identified amyloid deposit be subjected to liquid chromatography-mass spectrometry (LC-MS). Immunohistochemistry or immunofluorescence can be considered if mass spectrometry is not available. If clinically indicated, biopsy of other organs can be considered. If SLCA is confirmed, see *Treatment of*

*Newly Diagnosed SCLA* below. If no systemic disease is found, long-term follow-up is recommended. Surgical approaches can be considered for symptomatic or cosmetic reasons. A retrospective case series evaluated the efficacy of surgical management in localized laryngeal amyloidosis in 18 patients.[28] Eleven patients (61.1%) required surgical intervention due to progression, dysphonia/aphonia, dyspnea, dysphagia, and to rule out malignancy. No patients developed systemic amyloidosis.

If monoclonal protein or isotypic light chain predominance is absent and there is no suspicion of other organ involvement, patients can be followed as clinically indicated due to low risk of progression. However, if there is lymph node involvement, evaluation for low grade B-cell lymphoma can be considered (marginal zone lymphoma, mucosa-associated lymphoid tissue [MALT] lymphoma, Waldenström macroglobulinemia, or lymphoplasmacytic lymphoma). See the NCCN Guidelines for B-Cell Lymphomas and NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma (available at www.NCCN.org). Long-term follow-up is also required.

## Cardiac Amyloidosis

If cardiac amyloidosis is suspected, workup includes SPEP and SIFE, UPEP and UIFE with 24-hour urine collection. Imaging techniques for cardiac involvement should also be included as well as cardiac biomarkers discussed in the *Laboratory Evaluation* section above.

If CMR is suspicious for cardiac amyloidosis and monoclonal protein is present, bone marrow and tissue biopsy with or without other organ biopsy with congo red staining and LC-MS on any identified amyloid deposit should be performed. If results indicate SLCA, treat accordingly. If results are negative for SLCA, a cardiac biopsy is warranted.[29] If no monoclonal protein is present, the NCCN Panel recommends cardiac scintigraphy with either PYP scintigraphy 123I-MIBG, or 99mTC-DPD followed by treatment according to semiquantitative grade.[30]

If CMR is not suspicious for cardiac amyloidosis and monoclonal protein is present with other signs of SLCA, a bone marrow and fat pad biopsy with or without other organ biopsy with congo red staining and LC-MS should be performed. If systemic signs of amyloidosis are not present, the patient should be worked up for other diagnoses such as monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), or multiple myeloma (MM). See the NCCN Guidelines for Multiple Myeloma (available at www.NCCN.org). If no monoclonal protein is present, other causes of cardiac disease should be investigated.

## Staging

While multiple prognostic models have been proposed for patients with amyloidosis, the NCCN Panel recommends using the Mayo 2012 Staging System or the Mayo 2004 Staging System with European Modifications.[31,32] The Mayo 2012 Staging System incorporates NT-proBNP ≥1800 ng/L (or BNP ≥400 ng/L), cTnT ≥0.025 µ/L (or cardiac troponin I [cTnI] ≥ 0.1 µ/L or high-sensitivity cTnT [hs-cTnT] ≥40 pg/mL), and the difference between involved and uninvolved serum free light chains (dFLC) ≥18 mg/dL as risk factors.[31,33]

Patients with no risk factors are classified as stage I, those with one elevated risk factor as stage II, those with two elevated risk factors as stage III, and those with three elevated risk factors as stage IV. For patients classified as having stage I, II, III, or IV disease, the median OS from diagnosis is 94, 40, 14, and 6 months, respectively.[31]

The Mayo 2004 Staging System with European Modifications is similar to the Mayo 2012 Staging System, however, does not include dFLC.[32] Some of the risk factor values also vary slightly, including cTNT ≥0.035

µg/L, hs-cTnT ≥50 ng/L, and NT-ProBNP ≥332 ng/L, while the cutoff for cTnI and BNP are the same.

Patients with no, or one risk factor are classified as stage I or II, respectively.[32] Stage IIIA and IIIB include two risk factors are divided based on NT-proBNP and BNP levels (Stage IIIA: NT-proBNP 332 to <8500 ng/L or BNP 81 to <700 ng/dL and Stage IIIB: NT-proBNP ≥8500 ng/L or BNP ≥700 ng/dL.

## Organ Involvement and Response to Treatment

The first international consensus opinion for the definition of organ involvement and response to treatment for SLCA was published in 2005.[34] These criteria have since been updated,[35,36] and the tables with definitions for hematologic and organ involvement and criteria for response to treatment are included in the NCCN Guidelines algorithms. It is important to note that the definition of complete response (CR) has been updated to highlight that beyond the need for having negative amyloidogenic light chains (either free and/or as part of a complete immunoglobulin) in immunofixation electrophoresis of both serum and urine, either an FLC ratio within the reference range or the uninvolved FLC concentration greater than involved FLC concentration with or without an abnormal FLC ratio is acceptable.[37]

## Treatment of Newly Diagnosed SLCA

All patients with newly diagnosed SLCA with organ involvement should be assessed to determine eligibility for autologous HCT.[38-40] Only a small proportion of patients with AL are typically considered eligible for autologous HCT based on the number and severity of organs involved. Those with low tumor burden can proceed to receive HCT immediately. Those who are not eligible for HCT due to high tumor burden may receive systemic therapy first, and their eligibility for transplant may be assessed after initiating systemic therapy based on improvements in functional status and/or organ response. The NCCN Panel members recommend that treatment of SLCA should be in the context of a clinical trial when possible because data are insufficient to identify optimal treatment of the underlying plasma cell disorder.

All current strategies include systemic therapy to destroy the plasma cells responsible for the synthesis of immunoglobulin light chains. Several active regimens are available for the treatment of SLCA. Most are derived from the treatment of multiple myeloma. The goals of therapy include eliminating the misfolded amyloid light chains as promptly as possible, minimizing treatment toxicity, and supporting the function of the damaged organs. The consensus criteria for hematologic and organ response were updated at the 12th International Symposium on Amyloidosis.[35]

The preferred primary treatment for patients with SLCA is in a clinical trial, and participation in clinical trials should be encouraged.

### Primary Therapy for SLCA

***Preferred Regimens for Primary Treatment of SLCA***

*Daratumumab in Combination with Bortezomib/Cyclophosphamide/Dexamethasone*

For Mayo 2004 stages I–IIIa, with no significant neuropathy, data supporting the use of this regimen come from a phase 3 trial (ANDROMEDA) in which patients (n = 388) with newly diagnosed amyloidosis were randomized to receive six cycles of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) with or without subcutaneous daratumumab (daratumumab and hyaluronidase).[41,42]

Those receiving subcutaneous daratumumab as part of their regimen received single-agent daratumumab monthly as maintenance therapy

for up to 2 years. After a median follow-up of 11.4 months, the addition of daratumumab to CyBorD resulted in higher rates of hematologic CR (53% vs. 18%), cardiac response (42% vs. 22%), and renal response (53% vs. 24%). The addition of daratumumab also delayed major organ deterioration, hematologic progression, and death (hazard ratio [HR], 0.58; 95% CI, 0.36–0.93).[42] The most common grade 3 or 4 adverse events in the daratumumab arm compared with the control arm were lymphopenia (13.0% vs. 10.1%), pneumonia (7.8% vs. 4.3%), cardiac failure (6.2% vs. 4.8%), and diarrhea (5.7% vs. 3.7%).[42] The U.S. Food and Drug Administration (FDA) has approved this regimen for patients with SLCA.

The NCCN Panel has included daratumumab in combination with CyBorD as a category 1, preferred therapy option for patients with stage I-IIIa SLCA and no significant neuropathy. For patients with significant neuropathy, regardless of stage, this regimen is a category 2A, preferred option.

For patients with no significant neuropathy and Mayo 2004 stage IIIb disease, dose-modified daratumumab + CyBorD is a preferred regimen. Because the ANDROMEDA trial excluded those with IIIb disease during the screening process, only retrospective trials are available for review. A multicenter retrospective cohort study evaluated the outcomes of 19 individuals with stage IIIb SLCA.[43] Overall response rate was 100%, with 17 patients achieving a very good partial response (VGPR). At a median follow-up of 12 months, estimated overall survival was 67.5% (95% CI, 43.8–84.7).

*Autologous Hematopoietic Stem Cell Transplant*

The role and timing of HCT for patients with AL amyloidosis is evolving, especially with the availability of new systemic therapy options, including daratumumab-containing regimens. Careful patient selection is critical for the success of HCT in AL amyloidosis due to the increased risk of treatment-related mortality from compromised organs from amyloid deposits. Autologous HCT is a preferred option for only carefully selected patients who meet all the following criteria: single vital organ involvement, <10% marrow plasma cell involvement, and good performance status (PS).[40] It is important to keep in mind notable exclusions for autologous HCT candidacy (see AMYL-B).[40] Of note, the SWOG phase III, randomized study comparing CyBorD induction, followed by autologous HCT or CyBorD consolidation with daratumumab maintenance in individuals with newly diagnosed AL is currently recruiting participants. (NCT06022939)

*Daratumumab*

Single agent daratumumab is a preferred option for patients with no significant neuropathy and stage IIIb disease. Daratumumab may be administered subcutaneously (daratumumab 1800 mg with hyaluronidase 30,000 units) or intravenously (daratumumab 16 mg/kg). Subcutaneous administration has fewer infusion-related reactions and a faster administration time. Single-agent daratumumab has been associated with high rates of overall hematologic response (66.6%–90%).[44-46] The toxicity profile is similar to that seen in patients with multiple myeloma; however, the rates of infection are more common in patients with SLCA.[47]

*Oral Melphalan/Dexamethasone (if ineligible for HCT)*

The melphalan/dexamethasone regimen has also been used in the management of SLCA. It has shown promising results in patients with primary amyloidosis who are ineligible for HCT. A small study reported hematologic response in 67% (n = 31), and complete remission in 33% (n = 15) of patients treated with melphalan and high-dose dexamethasone in a median of 4.5 months.[48] Improvement in organ function was seen in 48% (n = 22) of patients. The updated results reported that the CR induced by melphalan and high-dose

dexamethasone was maintained in 70% of patients for up to 3 years, and survival at a median follow-up of 5 years was about 50%.[49]

A long-term follow-up study evaluated the hematologic response rates of oral melphalan with full-dose dexamethasone and an attenuated dexamethasone schedule.[50] Of the 259 patients, 76% in the full-dose group (n = 119) had a hematologic response rate versus 51% in the attenuated-dose group. Median OS was 7.4 years and 20 months in the full-dose and attenuated dose, respectively.

The French Myeloma Collaborative Group compared melphalan and dexamethasone to high-dose melphalan followed by HCT in a randomized trial and found no significant differences for hematologic or organ responses.[51] With a longer follow-up, the authors found that neither survival nor remission duration were statistically different between melphalan and dexamethasone versus high-dose melphalan followed by HCT even after eliminating treatment-related mortality from the HCT arm.[50,52] The NCCN Panel has included oral melphalan/dexamethasone as a preferred option for patients with SLCA of all stages, and with significant neuropathy, who are not candidates for HCT.

***Regimens Useful in Certain Circumstances for Primary Treatment of SLCA***

*Bortezomib/Cyclophosphamide/Dexamethasone*

The CyBorD regimen was reported to have high hematologic response rates and CR in two independent studies.[53,54] In one study, 17 patients (including 10 who received no prior therapy) treated with CyBorD achieved a hematologic response of 94% and a CR rate of 71%.[53] The median duration of response was 22 months. Organ response was observed in 50% of the patients with renal involvement. Three patients originally ineligible for autologous HCT became eligible after treatment with CyBorD.[53] In another study, 43 patients (including 20 who received no prior therapy) were treated with biweekly administration of CyBorD.[54] The hematologic response rate was 81.4% with a CR rate of 41.9%. A small retrospective study of patients newly diagnosed with systemic amyloidosis and multiple myeloma treated with the CyBorD regimen containing subcutaneous bortezomib reported a high response rate and minimal toxicity.[55]

A European collaborative study evaluated the efficacy of CyBorD as a first-line treatment for systemic amyloidosis in 230 patients using the Mayo 2004 Staging System with European Modifications.[32] Of the 201 patients with measurable disease, overall response was 77% in stage I (n = 30), 64% in stage II (n = 67), 69% in Stage IIIA (n = 61), and 42% in stage IIIB (n = 43). There was no significant difference in cumulative proportion survival between stage II and stage IIIA ($P$ = .613), however, average survival of patients with stage IIIA disease was 7 months ($P$ < .001 when compared to stage I, II, and IIIA).

The NCCN Panel has included CyBorD as a treatment option for individuals with no significant neuropathy and stages I–IIIa. Dose-modified cyclophosphamide, bortezomib and dexamethasone is an option for patients with no significant neuropathy and stage IIIb disease. This regimen is also an option if daratumumab is not available.

*Bortezomib/Melphalan/Dexamethasone (if ineligible for HCT)*

Combining weekly bortezomib with melphalan in a small series of patients has yielded hematologic response rates of 94%.[56] Bortezomib in combination with melphalan and dexamethasone was evaluated in a small phase II trial, and resulted in a best-response rate of over 80% and a CR rate of 42%.[57]

Data supporting the use of this regimen are from a phase III trial of patients ineligible for transplant (n = 109) with SLCA who were

randomly assigned to receive primary therapy with bortezomib/melphalan/dexamethasone versus melphalan/dexamethasone.[58] Hematologic response at 3 months was 79% versus 52%; VGPR plus CR rate (64% vs. 39%) and superior OS (median OS not reached vs. 34 months; HR, 0.50; 95% CI, 0.27–0.90). The rates of peripheral neuropathy were lower with subcutaneous bortezomib compared with intravenous bortezomib.[58]

The NCCN Panel has included bortezomib/melphalan/dexamethasone as an option for those with no significant neuropathy and all stages, and ineligible for HCT.

*Lenalidomide/Dexamethasone*

A pooled analysis of three phase II trials evaluated the efficacy of immunomodulatory agents in SLCA, which included dexamethasone with either lenalidomide (Len-Dex), cyclophosphamide and lenalidomide, or pomalidomide (n = 101).[59] The Len-Dex cohort (n = 37) included individuals who were newly diagnosed or had relapsed/refractory disease. Five-year OS was 32% (95% CI, 11.7–59.6) and 3 participants (8%) died.

A phase 2 trial evaluated the efficacy and toxicity of lenalidomide in newly diagnosed, and previously treated, patients (n = 23) with SLCA. [60] Dexamethasone was added if no hematologic response was seen. Of the patients who received lenalidomide/dexamethasone, a hematologic response rate of 75% was achieved. The NCCN Panel recommends lenalidomide with dexamethasone as a primary treatment option in patients with SLCA and significant neuropathy, regardless of stage. Dose modification and adjustments are mandatory in patients with advanced end organ damage (cardiac or renal).

*Carfilzomib/Dexamethasone*

Carfilzomib, a second-generation proteasome inhibitor (PI) may be used in combination with dexamethasone as a primary treatment option in patients with SLCA, regardless of stage, and in those with significant neuropathy. However, data on the use of carfilzomib as a primary treatment option in SLCA is limited and prospective data is needed. A small cohort study of five patients with newly diagnosed SLCA, all of whom had cardiac involvement and neuropathy, received IV carfilzomib and corticosteroids (methylprednisolone or dexamethasone) for a median number of three cycles.[61] After one cycle, rapid hematological response was reported with an 80.6% reduction in median dFLC. Three patients achieved CR and VGPR was induced in the remaining two patients. No decline in cardiac function or worsening neuropathy was reported in any of the five patients.

## Therapy for Previously Treated SLCA

There are no clinical trial data to determine the appropriate regimens for previously treated SLCA. Treatment depends on prior therapy received, patient preferences, and toxicity profile. The NCCN Panel recommends considering repeating the initial therapy, especially if the patient has no relapse of disease for several years.

*Bortezomib with or without Dexamethasone*

Clinical studies have reported bortezomib with or without dexamethasone to be active as primary treatment as well as for relapsed amyloidosis.[13,62-64]

In a study comparing two doses of bortezomib, it was seen that bortezomib is well tolerated at doses up to 1.6 mg/m$^2$ on a once-weekly schedule and 1.3 mg/m$^2$ on a twice-weekly schedule.[65] Although once-weekly and twice-weekly bortezomib were seen to be generally well tolerated, those on the once-weekly bortezomib regimen had lower

neurotoxicity.[65] After 51.8 months of median follow-up, the median OS for all patients was 62.7 months,[66] suggesting that achievement of organ response has a positive impact on OS.

Data from three international centers from 94 patients (18 previously untreated) treated with bortezomib reported a 71% (67 out of 93 patients) overall response rate with CR in 25% of patients (47% CR was in previously untreated patients).[13] In another study, 26 patients (18 who received no prior therapy) were treated with the combination of bortezomib/dexamethasone. The overall response rate was 54%, with a 31% CR rate.[63]

The combination of bortezomib and dexamethasone was studied as consolidation therapy in patients after HCT to see whether depth of response can be improved. At 24 months, greater than 60% had a partial response (PR), 40% had a CR, and organ responses were seen in 70% of patients.[67] The OS at 12 months was 88% and 82% at 24 months.[67]

In the relapsed setting only, a small study of patients (n = 18) with relapsed or progressive amyloidosis on prior therapies showed hematologic response in 94% (n = 14) including CR in 44% (n = 7)[68] when treated with bortezomib/dexamethasone. The National Amyloidosis Center in Britain conducted a study of patients (n = 20) with relapsed or refractory SLCA treated with bortezomib, and reported a hematologic response in 80% (n = 16), of which 15% (n = 3) achieved a CR and 65% (n = 13) achieved a PR.[62] In another multicenter phase I/II dose-escalation study of bortezomib, hematologic responses were seen in 50% of patients (15 out of 30 evaluable pretreated patients) with a CR rate of 20% (n = 6).[69]

The NCCN Panel recommends bortezomib with or without dexamethasone as a therapy option for previously treated disease.

*Bortezomib/Cyclophosphamide/Dexamethasone*

Studies of CyBorD in patients with SLCA have included newly diagnosed and relapsed/refractory patients.[32,53,54]

The NCCN Panel notes that patients on regimens containing bortezomib are associated with a higher risk of treatment-related peripheral and autonomic neuropathy, especially in those with disease-related baseline neuropathy. Therefore, close monitoring, judicious dosing, or alternative therapies should be considered in some patients.

*Bortezomib/Melphalan/Dexamethasone*

While bortezomib, melphalan and dexamethasone is recommended by the NCCN Panel as a primary therapy option regardless of stage, it is also included as a therapy option for previously treated disease.[58] See *Primary Therapy for SLCA.*

*Daratumumab*

While single-agent daratumumab is a preferred primary therapy option for certain patients, the NCCN Panel also recommends it as an option for patients with previously treated disease (if they have not received daratumumab-based therapy as a primary treatment). A retrospective analysis evaluated the efficacy of daratumumab in 25 patients with SLCA who had received a median of 3 prior lines of therapy.[44] Overall hematologic response rate was 76%, which included a CR and VGPR of 36% and 24%, respectively. Results also showed that daratumumab was well tolerated, as only grade 1 and 2 infusion reactions were observed.

*Ixazomib/Cyclophosphamide/Dexamethasone*

A single-arm, phase II trial evaluated the efficacy of ixazomib, cyclophosphamide, and dexamethasone, followed by ixazomib maintenance therapy in newly diagnosed patients with AL.[70] Thirty-five patients were included in the study, with a median age of 67 years. The primary objective was hematologic response, which was induced in 63% of patients. Complete response and VGPR was achieved in 11.4% and 37.1% of patients, respectively. Two-year PFS was 74% and OS was 78% at median follow-up of 29.7 months. (NCT01864018)

*Ixazomib/Dexamethasone*

A phase III trial (TOURMALINE-AL1) studied patients (n = 168) with relapsed or refractory SLCA randomized to either ixazomib/dexamethasone or to physician's choice of a non-proteasome inhibitor-containing regimen following 1 to 2 prior lines of therapy.[71] Hematologic response rate was the same, and occurred in 53% of patients treated with ixazomib/dexamethasone and in 51% with physician's choice ($P$ = .76). The CR rate was 26% with ixazomib versus 18% ($P$ = .22). Median time to vital organ deterioration or mortality was longer with ixazomib at 34.8 versus 26.1 months (HR, 0.53; 95% CI, 0.32–0.87; $P$ = .01). Importantly, median treatment duration of patients treated with ixazomib was longer at 11.7 versus 5.0 months. Adverse events included diarrhea (34% vs. 30%), rash (33% vs. 20%), cardiac arrhythmias (26% vs. 15%), and nausea (24% vs. 14%).

*Ixazomib/Lenalidomide/Dexamethasone*

A phase I/II trial evaluated the outcomes of patients (n = 40) with relapsed SLCA treated with ixazomib/lenalidomide/dexamethasone. Hematologic responses were seen at 3 months in 57.9% of patients. Median progression-free survival (PFS) was 17 months in the overall study patients. In those achieving CR/VGPR, the PFS was further improved to 28.8 months. Serious adverse events were infection (40%), fluid overload (33.3%), cardiac arrhythmia (13.3%), renal dysfunction (6.6%), and anemia (6.6%).[72]

*Lenalidomide/Cyclophosphamide/Dexamethasone*

In previously treated patients with relapsed SLCA, treatment with lenalidomide/cyclophosphamide/dexamethasone has been shown to produce a response rate of 62%.[73-75]

*Lenalidomide/Dexamethasone*

A retrospective analysis investigated the efficacy and toxicity of lenalidomide and dexamethasone in a large cohort of patients (n = 260) with relapsed/refractory SLCA.[76] Participants had received an average of two prior lines of therapy and after 3 months of treatment, hematological response rate was 31%. Median OS and hematologic event-free survival was 32 months and 9 months, respectively after follow-up at 56.5 months.

The results of another phase 2 trial (n = 34 and 91% of patients had prior therapy) demonstrated that the reduced dose of lenalidomide at 15 mg per day had acceptable toxicity and good hematologic responses.[77] Of the 24 evaluable patients, reduced dose of lenalidomide along with dexamethasone showed an overall hematologic response rate of 67% (29% CR and 38% PR).[77]

In a more recent study, patients (n = 84) previously treated with thalidomide and/or bortezomib were treated with lenalidomide and dexamethasone. The overall hematologic response rate was 61%, including a 20% CR rate. The 2-year OS and PFS rates were reported as 84% and 73%, respectively.[78]

*High-Dose Melphalan Followed by HCT*

High-dose melphalan followed by HCT is one of the therapeutic options listed in the NCCN Guidelines for Systemic Light Chain Amyloidosis® (available at www.NCCN.org). This treatment modality is associated with significant treatment-related mortality[79-85]; therefore, careful evaluation of patients who are potential candidates is key. The extent of organ involvement is considered a predictor of outcome.[82,83,86]

In eligible patients, high-dose chemotherapy along with HCT has been associated with higher response rates and improved OS than standard chemotherapy.[86] The best outcomes following HCT have been reported in patients who achieve a CR to high-dose primary chemotherapy,[87] including improvement of organ-related disease.[88] The most significant indicator of treatment benefit is the depth of the response to therapy measured by the lowest level of serum FLCs post-transplantation.[89]

A number of groups have evaluated dose adjustment of high-dose melphalan during a transplant based on factors such as age, number of organs involved, and presence or absence of cardiac involvement.[88,90,91] The reported toxicity of reduced-dose melphalan is substantially less than that of high-dose melphalan.[90] Older studies indicated that higher doses of melphalan were associated with a higher CR rate, and improved OS and event-free survival, but these publications occurred during an era where patients received transplant as primary therapy, and those receiving lower doses of melphalan typically had more advanced AL, and thus were destined for inferior outcomes.[92] Over the past decade, transplant-related mortality rates have decreased from 40% to about 7%.[93-95]

A long-term single-center study of the outcomes of patients who underwent treatment with high-dose melphalan followed by HCT reported survival of up to 20 years in 28.6% of patients.[94] While the survival was strongly dependent on achievement of a hematologic CR, those who do not achieve a CR and/or who relapsed after CR also had a survival benefit with HCT.[77]

*Melphalan/Dexamethasone*

The NCCN Panel recommends melphalan and dexamethasone as a therapeutic option for previously treated disease. Data has shown CR rates ranging from 13% to 33% and average OS from 10.5 to 61.2 months.[96] See *Primary Therapy for SLCA.*

*Pomalidomide/Dexamethasone*

The safety and efficacy of pomalidomide and dexamethasone were studied in a prospective phase II study.[97] Patients with previously treated SLCA (n = 33) were enrolled in the trial and upon treatment with pomalidomide and dexamethasone, confirmed response was reported in 48% (n = 16) with a median time to response of 1.9 months. The median OS rate was 28 months and PFS rate was 14 months; the OS and PFS rates at 1 year were 76% and 59%, respectively.

***Useful in Certain Circumstances for Previously Treated SLCA***

*Bendamustine/Dexamethasone*

Bendamustine/dexamethasone is an option for patients who have received multiple prior regimens. A multicenter phase 2 trial evaluated this regimen in patients with persistent or progressive SLCA after at least one prior therapy.[98] Responses (PR or better) were seen in 57% of patients. Seven out of 24 patients with organ involvement had overall organ response. The median PFS and OS were 11.3 months and 18.2 months, respectively. OS was better among those with a hematologic response. The most common adverse events were myelosuppression, fatigue, nausea, and vomiting.[98]

*Carfilzomib for Non-cardiac Amyloidosis with or without Dexamethasone*

Data from a phase 1/2 study of carfilzomib with patients with relapsed/refractory SLCA showed the maximum tolerated dose to be 36 mg/m$^2$ twice weekly (after initial 20 mg/m$^2$ dosing).[99]

Patients in this trial had a hematologic response rate of 63%. Grade 3 or 4 adverse events occurred in 71% of patients with multiple cardiac events, including hypotension, hypertension, decreased ejection fraction, and symptomatic ventricular tachycardia. Eleven patients had worsening of NT-proBNP on carfilzomib, with five of those patients developing progressive cardiac dysfunction. Therefore, the NCCN Panel has listed carfilzomib as an option for treatment of relapsed/refractory SLCA in select patients with no cardiac involvement.

*Daratumumab/Lenalidomide/Dexamethasone*

A retrospective cohort study investigated the hematological and organ response of daratumumab, lenalidomide, and dexamethasone (DRd) in 10 patients with multiple myeloma and concurrent SLCA.[100] Eight patients were considered stage III or IV according to the Mayo 2012 staging system. Nine patients had cardiac involvement, and three patients had renal amyloidosis. At 6 months, overall hematological response was 90%, with >50% achieving a VGPR. Four of eight patients with a baseline BNP of ≥150 pg/ml saw a >30% decrease. Renal response was induced in two of the three patients with amyloidosis and kidney involvement. The NCCN Panel recommends DRd as a “Useful in Certain Circumstances” option for previously treated disease and for those who did not receive a daratumumab-based regimen as a primary therapy.

*Venetoclax t(11;14) with or without Dexamethasone*

Given the high prevalence of t(11;14) (~50%) and the efficacy of the bcl2 inhibitor venetoclax in t(11;14) myeloma, there has been interest in exploring this drug in AL. A multicenter, international, retrospective cohort study reported on outcomes of patients (n = 43) with relapsed/refractory SLCA treated with venetoclax-containing regimens.[101] The overall PFS and OS at 12 months were 78% and 93%, respectively. However, in patients (n = 30) harboring t(11;14), median PFS and OS were not reached and 12-month PFS and OS were 90% and 97%, respectively. In comparison, among patients without t(11;14) (n = 11), 12-month PFS and OS were 45% and 82%, respectively. Also, 81% (22 out of 27) of patients with t(11;14) achieved at least a PR and 78% (21 out of 27) achieved a VGPR/CR.[101]

**Treatments Targeting Amyloid Fibrils**

While prior small studies demonstrated a potential role doxycycline may have in reducing early mortality in cardiac patients when used prophylactically in combination with plasma cell-directed therapy,[102,103] a recent randomized controlled study in China failed to demonstrate a benefit of doxycycline with standard-of-care therapy.[104] A trial of doxycycline versus standard supportive therapy in newly diagnosed cardiac AL amyloidosis patients undergoing bortezomib-based therapy has also recently been terminated due to difficulty in recruitment (NCT03474458). Therefore, the Panel at present cannot recommend the use of amyloid-targeting agents outside the setting of clinical trials.[105]

Data on a definitive impact of several anti-fibril monoclonal antibodies added to the standard of care anti-plasma cell therapy is currently the subject of ongoing, phase 3, multicenter, global, randomized, double-blind, placebo-controlled trials in patients with newly diagnosed SLCA Mayo 2004 stage IIIa (NCT04512235), Mayo 2004 stage IIIb (NCT04504825), and Mayo 2012 stage IV (NCT04973137) disease.

## Summary

Successful management of SLCA remains a challenge due to delayed recognition of patients who often experience significant lag in timely diagnosis. The clinical manifestations are diverse and diagnosing it accurately and at an early stage are key to improved outcomes. Treatment of patients with SLCA has improved significantly over the years, and therapeutic options have expanded significantly with newer therapies, which have demonstrated capability in inducing rapid and deep responses, that in turn translate into high rates of organ response. Whenever possible, patients should be evaluated in the context of experienced amyloid multidisciplinary programs, and considered for participation and treatment on clinical trials.

## References

1. Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. N Engl J Med 1997;337:898-909. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9302305.

2. Al Hamed R, Bazarbachi AH, Bazarbachi A, et al. Comprehensive Review of AL amyloidosis: some practical recommendations. Blood Cancer J 2021;11:97. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34006856.

3. Quock TP, Yan T, Chang E, et al. Epidemiology of AL amyloidosis: a real-world study using US claims data. Blood Adv 2018;2:1046-1053. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29748430.

4. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.

5. Freedman-Cass DA, Fischer T, Alpert AB, et al. The Value and Process of Inclusion: Using Sensitive, Respectful, and Inclusive Language and Images in NCCN Content. J Natl Compr Canc Netw 2023;21:434-441. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37156485.

6. Dispenzieri A, Kyle R, Merlini G, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia 2009;23:215-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19020545.

7. Baker KR. Light Chain Amyloidosis: Epidemiology, Staging, and Prognostication. Methodist Debakey Cardiovasc J 2022;18:27-35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35414848.

8. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol 2004;22:3751-3757. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15365071.

9. Palladini G, Campana C, Klersy C, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. Circulation 2003;107:2440-2445. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12719281.

10. Choufani EB, Sanchorawala V, Ernst T, et al. Acquired factor X deficiency in patients with amyloid light-chain amyloidosis: incidence, bleeding manifestations, and response to high-dose chemotherapy. Blood 2001;97:1885-1887. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11238135.

11. Thompson CA, Kyle R, Gertz M, et al. Systemic AL amyloidosis with acquired factor X deficiency: A study of perioperative bleeding risk and treatment outcomes in 60 patients. Am J Hematol 2010;85:171-173. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20052750.

12. Abdallah N, Muchtar E, Dispenzieri A, et al. Coagulation Abnormalities in Light Chain Amyloidosis. Mayo Clin Proc 2021;96:377-387. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33549257.

13. Kastritis E, Wechalekar AD, Dimopoulos MA, et al. Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis. J Clin Oncol 2010;28:1031-1037. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20085941.

14. Yakupova EI, Bobyleva LG, Vikhlyantsev IM, Bobylev AG. Congo Red and amyloids: history and relationship. Biosci Rep 2019;39. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30567726.

15. Swan N, Skinner M, O'Hara CJ. Bone marrow core biopsy specimens in AL (primary) amyloidosis. A morphologic and immunohistochemical study of 100 cases. Am J Clin Pathol 2003;120:610-616. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14560572.

16. Gertz MA, Dispenzieri A, Muchtar E. Importance of FISH genetics in light chain amyloidosis. Oncotarget 2017;8:81735-81736. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29137218.

17. Lachmann HJ, Wechalekar AD, Gillmore JD. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J

Med 2008;358:91-92; author reply 92-93. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18175386.

18. Lavatelli F, Perlman DH, Spencer B, et al. Amyloidogenic and associated proteins in systemic amyloidosis proteome of adipose tissue. Mol Cell Proteomics 2008;7:1570-1583. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18474516.

19. Vrana JA, Gamez JD, Madden BJ, et al. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood 2009;114:4957-4959. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19797517.

20. Brambilla F, Lavatelli F, Di Silvestre D, et al. Reliable typing of systemic amyloidoses through proteomic analysis of subcutaneous adipose tissue. Blood 2012;119:1844-1847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21917755.

21. Gilbertson JA, Theis JD, Vrana JA, et al. A comparison of immunohistochemistry and mass spectrometry for determining the amyloid fibril protein from formalin-fixed biopsy tissue. J Clin Pathol 2015;68:314-317. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25637636.

22. Dorbala S, Falk R. Imaging cardiac amyloidosis: Patient page. J Nucl Cardiol 2019;26:217-221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30515743.

23. Dower J, Dima D, Lalla M, et al. The use of PYP scan for evaluation of ATTR cardiac amyloidosis at a tertiary medical centre. Br J Cardiol 2022;29:19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36212788.

24. Maceira AM, Joshi J, Prasad SK, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 2005;111:186-193. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15630027.

25. Martinez-Naharro A, Patel R, Kotecha T, et al. Cardiovascular magnetic resonance in light-chain amyloidosis to guide treatment. Eur Heart J 2022;43:4722-4735. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36239754.

26. Martinez JC, Lichtman EI. Localized light chain amyloidosis: A self-limited plasmacytic B-cell lymphoproliferative disorder. Front Oncol 2022;12:1002253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36457485.

27. Schmid SE, Nesbitt NB, Snitchler AN, et al. Localized Amyloidosis Involving Palatine Tonsils: A Case Report and Literature Review. Head Neck Pathol 2020;14:1036-1040. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32451875.

28. Hazenberg AJ, Hazenberg BP, Dikkers FG. Long-term follow-up after surgery in localized laryngeal amyloidosis. Eur Arch Otorhinolaryngol 2016;273:2613-2620. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27156084.

29. Aguilera C, Oteo Dominguez JFOD, Garcia Izquierdo Jaen EGIJ, et al. Patients with suspected cardiac amyloidosis. Role of endomyocardial biopsy. European Heart Journal 2021;42. Available at: https://doi.org/10.1093/eurheartj/ehab724.0857.

30. Schockling EJ, Farrell MB, Embry-Dierson M, et al. Cardiac Amyloidosis Imaging, Part 2: Quantification and Technical Considerations. J Nucl Med Technol 2023;51:90-98. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37268318.

31. Kumar S, Dispenzieri A, Lacy MQ, et al. Revised Prognostic Staging System for Light Chain Amyloidosis Incorporating Cardiac Biomarkers and Serum Free Light Chain Measurements. Journal of Clinical Oncology 2012;30:989-995. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22331953.

32. Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood 2015;126:612-615. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25987656.

33. Muchtar E, Kumar SK, Gertz MA, et al. Staging systems use for risk stratification of systemic amyloidosis in the era of high-sensitivity troponin T assay. Blood 2019;133:763-766. Available at: https://www.sciencedirect.com/science/article/pii/S0006497120428009.

34. Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol 2005;79:319-328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16044444.

35. Gertz M, Merlini G. Definition of organ involvement and response to treatment in AL amyloidosis: an updated consensus opinion [abstract]. Amyloid 2010 17(Suppl 1):48-49.

36. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol 2012;30:4541-4549. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23091105.

37. Palladini G, Schönland SO, Sanchorawala V, et al. Clarification on the definition of complete haematologic response in light-chain (AL) amyloidosis. Amyloid 2021;28:1-2. Available at: https://www.tandfonline.com/doi/full/10.1080/13506129.2020.1868810.

38. Sidiqi MH, Aljama MA, Muchtar E, et al. Autologous stem cell transplant for immunoglobulin light chain amyloidosis patients aged 70 to 75. Biol Blood Marrow Transplant 2018;24:2157-2159. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29933071.

39. Al Saleh AS, Sidiqi MH, Muchtar E, et al. Outcomes of patients with light chain amyloidosis who had autologous stem cell transplantation with 3 or more organs involved. Biol Blood Marrow Transplant 2019;25:1520-1525. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31054986.

40. Sanchorawala V, Boccadoro M, Gertz M, et al. Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines. Amyloid 2022;29:1-7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34783272.

41. Palladini G, Kastritis E, Maurer MS, et al. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. Blood 2020;136:71-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32244252.

42. Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. N Engl J Med 2021;385:46-58. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34192431.

43. Chakraborty R, Rosenbaum C, Kaur G, et al. First report of outcomes in patients with stage IIIb AL amyloidosis treated with Dara-VCD front-line therapy. Br J Haematol 2023;201:913-916. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36896578.

44. Kaufman GP, Schrier SL, Lafayette RA, et al. Daratumumab yields rapid and deep hematologic responses in patients with heavily pretreated AL amyloidosis. Blood 2017;130:900-902. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28615223.

45. Schwotzer R, Manz MG, Pederiva S, et al. Daratumumab for relapsed or refractory AL amyloidosis with high plasma cell burden. Hematol Oncol 2019;37:595-600. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31486522.

46. Roussel M, Merlini G, Chevret S, et al. A prospective phase 2 trial of daratumumab in patients with previously treated systemic light-chain amyloidosis. Blood 2020;135:1531-1540. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32108228.

47. Van de Wyngaert Z, Carpentier B, Pascal L, et al. Daratumumab is effective in the relapsed or refractory systemic light-chain amyloidosis but associated with high infection burden in a frail real-life population. Br

J Haematol 2020;188:e24-e27. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31742668.

48. Palladini G, Perfetti V, Obici L, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. Blood 2004;103:2936-2938. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15070667.

49. Palladini G, Russo P, Nuvolone M, et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. Blood 2007;110:787-788. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17606766.

50. Palladini G, Milani P, Foli A, et al. Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach. Haematologica 2014;99:743-750. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24213149.

51. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med 2007;357:1083-1093. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17855669.

52. Jaccard A, Leblond V, Royer B, et al. Autologous stem cell transplantation (ASCT) versus oral melphalan and high-dose dexamethasone in patients with AL (primary) amyloidosis: long term follow-up of the French multicentric randomized trial [abstract]. Blood 2010;116:Abstract 1344. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/1344.

53. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood 2012;119:4391-4394. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22331188.

54. Venner CP, Lane T, Foard D, et al. Cyclophosphamide, bortezomib, and dexamethasone therapy in AL amyloidosis is associated with high clonal response rates and prolonged progression-free survival. Blood 2012;119:4387-4390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22331187.

55. Shah GL, Kaul E, Fallo S, et al. Subcutaneous bortezomib in combination regimens in newly diagnosed patients with myeloma or systemic AL amyloidosis: High response rates and minimal toxicity [abstract]. Blood 2012;120:Abstract 2968. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;120/21/2968.

56. Gasparetto C, Sanchorawala V, Snyder RM, et al. Use of melphalan (M)/dexamethasone (D)/bortezomib in AL amyloidosis [abstract]. j Clin Oncol 2010;28:Abstract 8024. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/8024.

57. Zonder J, Sanchorawala V, Snyder R. Rapid haematologic and organ responses in patients with AL amyloid treated with bortezomib plus melphalan and dexamethasone [abstract]. Amyloid 2010;17(s1):86.

58. Kastritis E, Leleu X, Arnulf B, et al. Bortezomib, melphalan, and dexamethasone for light-chain amyloidosis. J Clin Oncol 2020;38:3252-3260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32730181.

59. Warsame R, LaPlant B, Kumar SK, et al. Long-term outcomes of IMiD-based trials in patients with immunoglobulin light-chain amyloidosis: a pooled analysis. Blood Cancer J 2020;10:4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31913261.

60. Dispenzieri A, Lacy M, Zeldenrust S, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. Blood 2007;109:465-470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17008538.

61. Manwani R, Mahmood S, Sachchithanantham S, et al. Carfilzomib is an effective upfront treatment in AL amyloidosis patients with

peripheral and autonomic neuropathy. Br J Haematol 2019;187:638-641. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31388995.

62. Wechalekar AD, Lachmann HJ, Offer M, et al. Efficacy of bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease. Haematologica 2008;93:295-298. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18245653.

63. Lamm W, Willenbacher W, Lang A, et al. Efficacy of the combination of bortezomib and dexamethasone in systemic AL amyloidosis. Ann Hematol 2011;90:201-206. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20821326.

64. Singh V, Saad A, Palmer J, et al. Response to bortezomib based induction therapy in newly diagnosed light chain (AL) amyloidosis [abstract]. Blood 2009;114:Asbtract 1867. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/114/22/1867.

65. Reece DE, Hegenbart U, Sanchorawala V, et al. Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study. Blood 2011;118:865-873. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21562045.

66. Reece DE, Hegenbart U, Sanchorawala V, et al. Long-term follow-up from a phase 1/2 study of single-agent bortezomib in relapsed systemic AL amyloidosis. Blood 2014;124:2498-2506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25202139.

67. Landau H, Hassoun H, Rosenzweig MA, et al. Bortezomib and dexamethasone consolidation following risk-adapted melphalan and stem cell transplantation for patients with newly diagnosed light-chain amyloidosis. Leukemia 2013;27:823-828. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23014566.

68. Kastritis E, Anagnostopoulos A, Roussou M, et al. Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone. Haematologica 2007;92:1351-1358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024372.

69. Reece DE, Sanchorawala V, Hegenbart U, et al. Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of a phase 1 dose-escalation study. Blood 2009;114:1489-1497. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19498019.

70. Muchtar E, Gertz MA, LaPlant BR, et al. Phase 2 trial of ixazomib, cyclophosphamide, and dexamethasone for previously untreated light chain amyloidosis. Blood Adv 2022;6:5429-5435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35737873.

71. Dispenzieri A, Kastritis E, Wechalekar AD, et al. Primary results from the phase 3 Tourmaline-AL1 trial of ixazomib-dexamethasone versus physician's choice of therapy in patients (Pts) with relapsed/refractory primary systemic AL amyloidosis (RRAL). Blood 2019;134:139-139. Available at: https://doi.org/10.1182/blood-2019-124409.

72. Cohen OC, Sharpley F, Gillmore JD, et al. Use of ixazomib, lenalidomide and dexamethasone in patients with relapsed amyloid light-chain amyloidosis. Br J Haematol 2020;189:643-649. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31984481.

73. Kastritis E, Terpos E, Roussou M, et al. A phase 1/2 study of lenalidomide with low-dose oral cyclophosphamide and low-dose dexamethasone (RdC) in AL amyloidosis. Blood 2012;119:5384-5390. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22517904.

74. Kumar SK, Hayman SR, Buadi FK, et al. Lenalidomide, cyclophosphamide, and dexamethasone (CRd) for light-chain amyloidosis: long-term results from a phase 2 trial. Blood 2012;119:4860-4867. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22504925.

75. Palladini G, Russo P, Milani P, et al. A phase II trial of cyclophosphamide, lenalidomide and dexamethasone in previously treated patients with AL amyloidosis. Haematologica 2013;98:433-436. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22983583.

76. Basset M, Kimmich CR, Schreck N, et al. Lenalidomide and dexamethasone in relapsed/refractory immunoglobulin light chain (AL) amyloidosis: results from a large cohort of patients with long follow-up. Br J Haematol 2021;195:230-243. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34341985.

77. Sanchorawala V, Wright D, Rosenzweig M, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. Blood 2007;109:492-496. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16960148.

78. Mahmood S, Venner CP, Sachchithanantham S, et al. Lenalidomide and dexamethasone for systemic AL amyloidosis following prior treatment with thalidomide or bortezomib regimens. Br J Haematol 2014;166:842-848. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24930361.

79. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. Blood 2002;99:4276-4282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12036853.

80. Gertz MA, Lacy MQ, Dispenzieri A, et al. Stem cell transplantation for the management of primary systemic amyloidosis. Am J Med 2002;113:549-555. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12459400.

81. Goodman HJ, Gillmore JD, Lachmann HJ, et al. Outcome of autologous stem cell transplantation for AL amyloidosis in the UK. Br J Haematol 2006;134:417-425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16822290.

82. Jimenez-Zepeda VH, Franke N, Delgado D, et al. High-dose melphalan for AL amyloidosis: The importance of case selection to improve clinical outcomes [abstract]. Blood 2010;116:Abstract 2403. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/2403.

83. Wechalekar AD, Schonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood 2013;121:3420-3427. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23479568.

84. Sanchorawala V. Role of high-dose melphalan and autologous peripheral blood stem cell transplantation in AL amyloidosis. Am J Blood Res 2012;2:9-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22432083.

85. Cordes S, Dispenzieri A, Lacy MQ, et al. Ten-year survival after autologous stem cell transplantation for immunoglobulin light chain amyloidosis. Cancer 2012;118:6105-6109. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22707405.

86. Dispenzieri A, Kyle RA, Lacy MQ, et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. Blood 2004;103:3960-3963. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14739213.

87. Gertz MA, Lacy MQ, Dispenzieri A, et al. Effect of hematologic response on outcome of patients undergoing transplantation for primary amyloidosis: importance of achieving a complete response. Haematologica 2007;92:1415-1418. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17768110.

88. Skinner M, Sanchorawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med 2004;140:85-93. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14734330.

89. Kumar SK, Dispenzieri A, Lacy MQ, et al. Changes in serum-free light chain rather than intact monoclonal immunoglobulin levels predicts outcome following therapy in primary amyloidosis. Am J Hematol 2011;86:251-255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21328431.

90. Gertz MA, Lacy MQ, Dispenzieri A, et al. Risk-adjusted manipulation of melphalan dose before stem cell transplantation in patients with amyloidosis is associated with a lower response rate. Bone Marrow

Transplant 2004;34:1025-1031. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15516945.

91. Perfetti V, Siena S, Palladini G, et al. Long-term results of a risk-adapted approach to melphalan conditioning in autologous peripheral blood stem cell transplantation for primary (AL) amyloidosis. Haematologica 2006;91:1635-1643. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17145600.

92. Cibeira MT, Sanchorawala V, Seldin DC, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. Blood 2011;118:4346-4352. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21828140.

93. Gertz MA, Lacy MQ, Dispenzieri A, et al. Trends in day 100 and 2-year survival after auto-SCT for AL amyloidosis: outcomes before and after 2006. Bone Marrow Transplant 2011;46:970-975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20935685.

94. Sanchorawala V, Sun F, Quillen K, et al. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem cell transplantation: 20-year experience. Blood 2015;126:2345-2347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26443620.

95. Tsai SB, Seldin DC, Quillen K, et al. High-dose melphalan and stem cell transplantation for patients with AL amyloidosis: trends in treatment-related mortality over the past 17 years at a single referral center. Blood 2012;120:4445-4446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23175664.

96. Sanchorawala V, Patel JM, Sloan JM, et al. Melphalan, lenalidomide and dexamethasone for the treatment of immunoglobulin light chain amyloidosis: results of a phase II trial. Haematologica 2013;98:789-792. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23144200.

97. Dispenzieri A, Buadi F, Laumann K, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. Blood 2012;119:5397-5404. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22493299.

98. Lentzsch S, Lagos GG, Comenzo RL, et al. Bendamustine with dexamethasone in relapsed/refractory systemic light-chain amyloidosis: Results of a phase II study. J Clin Oncol 2020;38:1455-1462. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32083996.

99. Cohen AD, Landau H, Scott EC, et al. Safety and efficacy of carfilzomib (CFZ) in previously-treated systemic light-chain (AL) amyloidosis. Blood 2016;128:645-645. Available at: https://www.sciencedirect.com/science/article/pii/S0006497119306469.

100. Kawano Y, Hata H, Takashio S, et al. Daratumumab, lenalidomide and dexamethasone in newly diagnosed systemic light chain amyloidosis patients associated with multiple myeloma. Br J Haematol 2022;198:e38-e41. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35524546.

101. Premkumar VJ, Lentzsch S, Pan S, et al. Venetoclax induces deep hematologic remissions in t(11;14) relapsed/refractory AL amyloidosis. Blood Cancer Journal 2021;11:10. Available at: https://doi.org/10.1038/s41408-020-00397-w

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7801694/pdf/41408_2020_Article_397.pdf.

102. Wechalekar AD, Whelan C. Encouraging impact of doxycycline on early mortality in cardiac light chain (AL) amyloidosis. Blood Cancer J 2017;7:e546. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28338670.

103. D'Souza A, Flynn K, Chhabra S, et al. Rationale and design of DUAL study: Doxycycline to Upgrade response in light chain (AL) amyloidosis (DUAL): A phase 2 pilot study of a two-pronged approach of prolonged doxycycline with plasma cell-directed therapy in the treatment of AL amyloidosis. Contemp Clin Trials Commun 2017;8:33-38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29696194.

104. Shen KN, Fu WJ, Wu Y, et al. Doxycycline combined with bortezomib-cyclophosphamide-dexamethasone chemotherapy for newly diagnosed cardiac light-chain amyloidosis: A multicenter randomized controlled trial. Circulation 2022;145:8-17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34503349.

105. Wechalekar AD, Cibeira MT, Gibbs SD, et al. Guidelines for non-transplant chemotherapy for treatment of systemic AL amyloidosis: EHA-ISA working group. Amyloid 2023;30:3-17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35838162.