Review

Discovery Medicine 2024; 36(188): 1761–1771
https://doi.org/10.24976/Discov.Med.202436188.162

Current and Emerging Immunotherapies for Systemic AL Amyloidosis

Valeria Moreno[1], Ludovic Saba[1], Sara Tama-Shekan[2], Chakra P. Chaulagain[1,*]

[1]Department of Hematology-Oncology, Myeloma and Amyloidosis Program, Maroone Cancer Center, Cleveland Clinic Florida, Weston, FL 33331, USA
[2]Medical University of the Americas, Devens, MA 01434, USA
*Correspondence: chaulac@ccf.org (Chakra P. Chaulagain)
Published: 20 September 2024

Systemic light-chain (AL) amyloidosis is a rare and complex clonal plasma cell neoplasm characterized by the production of misfolded and unstable immunoglobulin light-chains leading to multisystem amyloid deposition, which progresses to organ dysfunction and eventual failure. The importance and urgency of AL amyloidosis depends on its potential to induce significant organ impairment, progressive course, risk of life-threatening complications, and the limited treatment options available. Treatment options and prognosis depend on the number and severity of organ involvement at the time of diagnosis with cardiac involvement carrying the worst outcomes. The treatments aim to target eliminating the underlying clonal plasma cell neoplasm and prevent the production and deposition of amyloid precursor immunoglobulin light-chain protein in the affected vital organs. Strategies for treating systemic AL amyloidosis have incorporated anti-plasma cell therapies approved in the management of multiple myeloma due to their shared cellular derivation. Quadruplet therapy of cyclophosphamide, bortezomib, dexamethasone and daratumumab (DaraCyborD) is the currently approved first-line induction therapy for systemic AL amyloidosis. Some patients need upfront autologous hematopoietic stem cell transplantation (HSCT) after high-dose melphalan conditioning particularly if DaraCyborD is not able to achieve complete hematologic response (CHR). Additionally, a promising treatment option involves disassembling amyloid deposits from the vital organs using monoclonal antibodies such as CAEL 101 or Birtamimab with the expectation of restoring damaged tissues of the vital organs affected thereby improving or reversing patients' symptoms. Both CAEL 101 and Birtamimab are currently being tested in phase 3 clinical trials for systemic AL amyloidosis patients with advanced cardiac involvement. This comprehensive review provides an up-to-date overview of AL amyloidosis therapy, with a particular focus on recent advances and future directions of immunotherapeutic strategies.

Keywords: AL amyloidosis; immunoglobulin light-chain; plasma cell dyscrasia; monoclonal antibodies; immunotherapy

Introduction

Immunoglobulin light-chain amyloidosis (AL amyloidosis), also known as primary amyloidosis is a rare hematologic malignancy caused by plasma cell dyscrasia characterized by deposition of insoluble amyloid fibrils comprised of fragments of misfolded monoclonal light-chains κ or λ type leading to organ dysfunction and failure [1,2]. AL amyloidosis stands as the most prevalent and serious type of systemic amyloidosis. In the United States, it is estimated to affect around 9 to 14 individuals per million persons-years. This type of amyloidosis primarily affects older individuals with a median age at diagnosis of 64 years and male predominance [3].

AL amyloidosis is usually observed concurrently with other plasma cell disorders such as multiple myeloma, smoldering myeloma or monoclonal gammopathy of undetermined significance (MGUS) and less commonly with lymphoproliferative disorders such as Waldenström's macroglobulinemia (lymphoplasmacytic lymphoma), non-Hodgkin lymphoma, or Chronic Lymphocytic Leukemia. The clinical manifestations of systemic AL amyloidosis vary based on both the quantity and specific organs impacted. The kidneys and heart experience the highest incidence of involvement, following the liver, the gastrointestinal (GI) tract, and the peripheral and autonomic nervous system [4]. A single organ can be affected as well for example as a solitary or multiple lung nodules or isolated GI involvement in the form of a polypoid growth. However, it can also accumulate in various tissues of vital organs, leading to multi-organ failure. Approximately 80% of the patients have reported fatigue as the most common symptom [1]. Additionally, exertional dyspnea, peripheral edema, paresthesia, weight loss, purpura, dysgeusia, macroglossia, hepatosplenomegaly, and heavy proteinuria can be present [5].

The absence of specific symptoms and the wide range of presentations make the diagnosis of AL amyloidosis a complex challenge. The typical duration between the onset of symptoms and the confirmation of a diagnosis ranges

from approximately 6 to 12 months [1]. In general, the initial assessment of a patient suspected of having AL amyloidosis should include serum and urine protein electrophoresis with immunofixation, analysis of the serum-free light-chain levels and ratio, as well as obtaining an abdominal fat pad aspirate and conducting a bone marrow aspiration and biopsy [6]. The definitive method for diagnosing AL amyloidosis is a tissue biopsy of the involved organ. Congo Red ("Gold Standard") and Thioflavin S are the primary histological stains employed to identify any form of amyloid from the tissue biopsy specimen. The classification of amyloid is essential since treatment approaches depend on identifying the specific precursor protein, and this can be assessed using methods such as the gold standard technique of laser microdissection mass spectrometry (MS) or, less desirable but quicker and easily available techniques such as immunofluorescence, immunohistochemistry, or immunogold [1].

In systemic AL amyloidosis, the precursor protein consists of monoclonal immunoglobulin light-chains (either kappa or lambda) derived from clonal bone marrow plasma cells, and the primary focus of treatment lies in clearing the plasma cell clone out of the bone marrow and decreasing (and ideally eliminating) the amyloid precursor light-chain production. This will prevent further amyloid deposits in the vital organs and provide a break for recovery of the organs from both amyloid toxicity and light-chain toxicity. The management of this condition is typically a collaborative, multidisciplinary effort that often requires the involvement of specialists in various fields [7].

Autologous hematopoietic stem cell transplantation (HSCT) after high-dose melphalan conditioning has been an important therapeutic regimen in AL amyloidosis management in eligible patients. Subcutaneous daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone is the only US Food and Drug Administration (FDA)-approved therapy for patients with newly diagnosed AL amyloidosis. Daratumumab monotherapy is associated with deep and rapid hematological responses in previously treated AL patients, with an excellent safety profile. Proteasome inhibitors, such as bortezomib and Ixazomib, have been used based on their demonstrated efficacy. Bortezomib has shown overall response rates of 70–80% in the relapsed setting [7,8]. Lenalidomide has been administered at lower doses than multiple myeloma and Venetoclax has also been used with promising results. Monoclonal antibodies, due to their high selectivity and low toxicity, have been introduced in several clinical trials with the aim of improving and enhancing the treatment approach for AL by eliminating preexisting amyloid fibrils through the enhancement of the immune system [2]. Birtamimab (NEOD001-301) has been considered an effective treatment in the most advanced patients (Mayo stage IV) in the phase 3 VITAL clinical trial. This data will be confirmed with the current confirmatory ongoing phase 3 clinical trial, AFFIRM-AL [9] and CAEL-101, which showed tolerability and biomarker improvement within 3 weeks after the first infusion confirmed by a phase 1a/b study [10].

In this manuscript, we will conduct a review of the therapeutic approach directed towards the current immunotherapies and investigational drugs for systemic AL amyloidosis patients to delve into the forthcoming outlooks.

Standard Systemic Approach

In patients diagnosed with AL amyloidosis, treatment aims to target clonal plasma cells, thereby reducing (ideally eliminating) amyloidogenic light-chain production leading to immediate reduction in clonal light-chain toxicity to the involved organs and eventual reduction in the amyloid formation and deposition thereby curbing further organ damage. While this approach doesn't rapidly reverse pre-existing amyloid deposits or heal previously affected organs, it can effectively halt additional harm. For this reason, it's imperative to initiate treatment for systemic AL amyloidosis upon diagnosis before critical irreversible organ damage occurs. While conventional treatments don't yet cure systemic AL amyloidosis, earlier diagnosis and optimal treatments have reduced early mortality and improved survival [11].

Autologous hematopoietic stem cell transplantation (HSCT) after high-dose melphalan conditioning has been a fundamental pillar in AL amyloidosis management in eligible patients but unfortunately, most of the patients are not eligible for this therapy due to frailty from multiple organ involvement, particularly advanced cardiac involvement which makes them ineligible for this intervention. As such, assessing HSCT eligibility is essential for every patient with systemic AL amyloidosis at the time of diagnosis [12]. With the approval and availability of quadruplet therapy of subcutaneous cyclophosphamide, bortezomib, dexamethasone and daratumumab (DaraCyborD), the role of upfront HSCT has become less urgent but should still be considered for all eligible patients. Most patients with systemic AL amyloidosis are ineligible for HSCT at the time of diagnosis and hence should be treated with DaraCyborD (Fig. 1).

First-Line Treatment for Newly Diagnosed Systemic AL Amyloidosis

Determination of HSCT Eligibility

In addressing the importance of patient stratification and the assessment of eligibility for autologous HSCT in AL amyloidosis, it's crucial to outline the specific eligibility criteria guiding this decision-making process. These criteria serve as a fundamental framework for determining whether a patient is a suitable candidate for HSCT, ensuring that the procedure is both safe and efficacious for the individual.

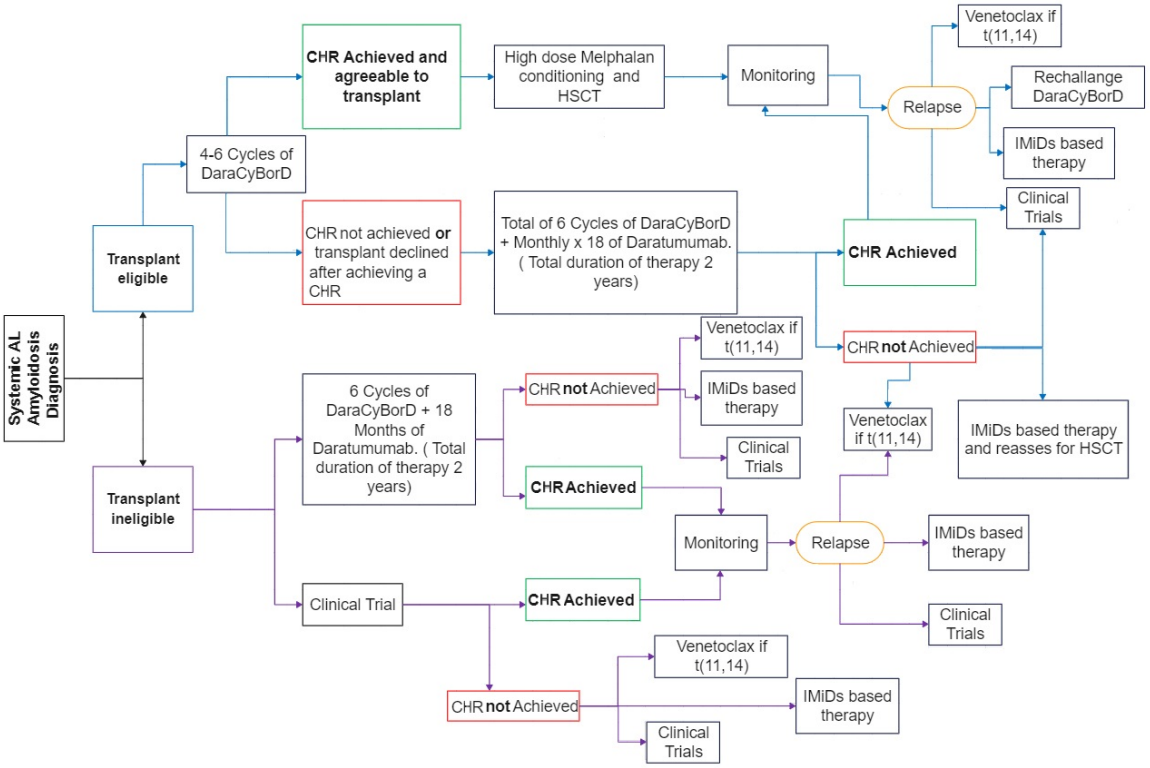

Fig. 1. Overview of treatment pathways. Fig. 1 was created using Edrawmax (EdrawMax for Windows, version 13.50, Shenzhen, China). IMiDs, immunomodulatory drugs; CHR, complete hematologic response.

Age and Physiological Status

Patients aged over 18 years with a "physiological age" of less than 70 years are typically considered eligible for HSCT. However, chronological age alone does not serve as an absolute cutoff, with decisions made on a case-by-case basis, considering overall health status and physiological age.

Diagnostic Confirmation

Eligible candidates must have confirmed tissue diagnosis of AL amyloidosis with appropriate typing, ensuring accurate classification of the disease subtype.

Evidence of Clonal Plasma Cell Dyscrasia

The presence of clonal plasma cell dyscrasia confirms the underlying pathology driving AL amyloidosis, substantiating the rationale for HSCT intervention.

Organ Involvement

Candidates must exhibit at least one major vital organ involvement, excluding solitary amyloid deposition in bone marrow or soft tissues. However, no more than two vital organs should be significantly involved, encompassing the heart, autonomic nervous system, kidney, or liver.

Performance Status and Functional Assessment

Eastern Cooperative Oncology Group (ECOG) performance status should be $\leq$2, with exceptions considered if peripheral neuropathy contributes to an advanced ECOG status.

New York Heart Association (NYHA) functional status class should be I or II, indicating mild or moderate symptoms of heart failure.

Physiological Parameters

Vital physiological parameters, including a room air blood oxygen saturation $\geq$95%, a diffusion lung capacity for carbon monoxide (DLCO) $>$50%, and a supine systolic blood pressure $\geq$90 mmHg, should be within acceptable ranges.

Exclusion of Complications

Absence of orthostatic hypotension refractory to medical therapy, decompensated heart failure, significant gastrointestinal tract involvement with active or increased risk of bleeding, symptomatic or medically refractory arrhythmias, and pleural effusions is imperative for HSCT eligibility.

Biochemical Markers

Several biochemical markers serve as indicators of organ function and disease severity, including conjugated

Table 1. Comprehensive evaluation framework for assessing hematopoietic stem cell transplantation (HSCT) benefits in systemic light-chain amyloidosis.

Aspect of evaluation	Description
Clonal immunoglobulin assessment [17,18]	relies on serum-free light chains (FLCs) approximately 20% of patients may have FLC levels below quantifiable thresholds normalization in FLC concentration a robust predictor for prolonged survival
Early hematologic response [19]	essential in mitigating prolonged exposure of vital organs to toxic FLCs timely intervention is crucial for improving patient outcomes post-HSCT
Minimal residual disease (MRD) assessment [20,21]	facilitated by sensitive methodologies like next-generation flow (NGF) and sequencing (NGS) offers insights into treatment response at a molecular level
Organ response evaluation [22,23]	encompasses heart, kidney, and liver function assessment biomarker-based assessment: cardiac response: N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP) and Troponin T renal response: Proteinuria and eGFR liver response: Alkaline Phosphatase level (ALP)
Future directions [24]	development of graded criteria for response evaluation integration of biomarker-response assessments with functional tests

bilirubin <2 mg/dL, N-terminal pro-B-type natriuretic peptide (NT-proBNP) <5000 pg/mL, Troponin I <0.1 ng/mL, Troponin T <60 ng/mL, and hs-Troponin <75 ng/mL.

Renal Function and Coagulation Status

Adequate renal function, with an estimated glomerular filtration rate (eGFR) >30 mL/min/m^2, is essential. Patients with severe factor X deficiency (<25%) are at increased transplant-related mortality risk and may require splenectomy to increase factor X levels prior to HSCT.

These eligibility criteria represent a comprehensive assessment of patient suitability for hematopoietic cell transplantation (HCT), considering various physiological, biochemical, and functional parameters. The stringent criteria aim to maximize the likelihood of successful transplant outcomes while minimizing the risks associated with the procedure [4,13].

Patients Eligible for HSCT

For systemic AL amyloidosis patients who are eligible for HSCT, clinical trials are recommended (when available) due to the uncertainty of optimal management particularly in the context of newly approved quadruplet therapy of DaraCyborD. Patients who achieve complete hematologic response (CHR) after initial 4–6 cycles of DaraCyborD therapy can undergo high-dose melphalan conditioning and HSCT. For HSCT-eligible patients who achieve a CHR and decline to undergo HSCT, we treat them with 6 cycles of DaraCyborD followed by monthly daratumumab for 18 months with a total duration of therapy of two years per ANDROMEDA protocol [9]. The goal of HSCT is to further cytoreduce clonal plasma cell neoplasm stop amyloid precursor light-chain production and prevent the production and deposition of more amyloid fibrils, leading to improved organ function, quality of life and survival of patients [14]. However, patient selection is essential due to the risk of treatment-related mortality from compromised organs. Patients with renal dysfunction need to have a reduced dose of melphalan at the time of conditioning. Patients with advanced cardiac involvement who are initially ineligible for HSCT may become eligible due to improved performance status after 4–6 cycles of DaraCyborD therapy and therefore need to be reassessed for HSCT at that point. Maintenance therapy post-HSCT may also be indicated especially for patients who achieve a very good partial response (VGPR) but not CHR after the HSCT. Melphalan (MEL) at a dose of 200 mg/m^2 is the standard for HSCT in AL amyloidosis, with reduced doses showing less efficacy [15,16]. However, in renal dysfunction, MEL 140 mg/m^2 is used to avoid morbidity without significant compromise in the efficacy.

In the assessment of HSCT benefits in AL amyloidosis, a multifaceted evaluation framework is employed. Table 1 (Ref. [17–24]) below is a comprehensive overview of the key aspects involved in the evaluation of HSCT benefits in AL amyloidosis, highlighting the assessment of clonal immunoglobulins, early hematologic response, minimal residual disease (MRD) assessment, and organ response evaluation, including specific biomarkers used for cardiac, renal, and liver function assessment. Finally, the phase 3 ANDROMEDA study did not include patients with stage IIIB cardiac amyloidosis patients and patients with glomerular filtration rate (GFR) <20 mL/min/1.73 m^2 and with Eastern Cooperative Oncology Group (ECOG) performance status of >2, systolic blood pressure of <90 mmHg, New York Heart Association (NYHA) stage IIIB or IV at screening. The treatment of this very sick subgroup ac-

counts for a significant portion of newly diagnosed cases and the standard of care for this group remains to be determined.

Patients Ineligible for HSCT

A significant number of patients may not qualify for HSCT due to factors such as comorbidities, advanced age, frailty, advanced heart, or renal failure, autonomic dysfunction, or extensive organ involvement. However, more may qualify after successful initial induction treatment [25]. However, the quadruplet therapy of DaraCyborD has been approved by the Food and Drug Administration (FDA and represents the current standard of care for induction therapy in newly diagnosed patients). While various regimens such as melphalan and prednisone, melphalan and dexamethasone, and CyborD were standard for AL amyloidosis patients ineligible for transplant in the past, combination therapy of cyclophosphamide, bortezomib, dexamethasone and daratumumab (DaraCyborD) [26], is the current standard of care. The triplets such as CyBorD [27,28] or bortezomib, melphalan, and dexamethasone (BMD) [29] are recommended in resource-poor settings where daratumumab is not available. The phase 3 randomized ANDROMEDA trial showed that the addition of daratumumab to CyBorD enhanced treatment outcomes with minimal to none added toxicity or burden to the patients [26].

Daratumumab is a human IgGκ1 monoclonal antibody with a high affinity for CD38, an antigen that is widely expressed by all plasma cells, leading to cell death through different pathways. Several prospective and retrospective trials have shown good tolerability and high response rates in patients with AL amyloidosis [30].

In the phase 3 ANDROMEDA study, subcutaneous administration of daratumumab in combination with bortezomib/cyclophosphamide/dexamethasone (VCD) regimen was compared to 6 cycles of standard VCD (CyBorD) therapy in newly diagnosed stage I–IIIA patients. Following the initial 6 cycles, daratumumab was continued for up to 18 months in the daratumumab-VCD arm. The primary endpoint of the study was the achievement of complete response (CR) rates, which were notably higher in the daratumumab-VCD group at 53% compared to 18% in the VCD group. Overall hematologic response rates were notably increased in the daratumumab-VCD arm at 92% compared to 77% in the VCD group, with very good partial response (VGPR) rates also notably improved (79% vs. 49%). At the 6-month mark, organ response rates, particularly cardiac (42% vs. 22%) and renal (53% vs. 24%), were higher in the daratumumab-VCD arm, with further improvements observed at the 18-month follow-up (53% and 58%, respectively) compared to no change in the control arm. Major Organ Deterioration-progression-free survival (MOD-PFS), defined as a combination of cardiac or renal failure, hematologic progression, or death, was enhanced in the daratumumab-VCD arm due to lower rates of hematologic progression during the follow-up period. Regarding the safety profile of this novel combination therapy, there was a noted increase in infection rates, while no clear evidence of cardiac toxicity was observed [4,30].

The BMD's efficacy was supported by a phase 3 trial showing improved outcomes compared to melphalan plus dexamethasone [29]. All bortezomib-containing regimens require antiviral prophylaxis against varicella zoster virus during treatment and for one year after the last dose of bortezomib. Care should also be given to the risk of peripheral neuropathy in patients receiving bortezomib. Subcutaneous administration of bortezomib is associated with a lower risk of neuropathy and therefore we recommend against intravenous bortezomib. Finally, the continual quest for better treatments remains crucial, especially for those with advanced symptomatic cardiac involvement. Patients should undergo close follow-up and monitoring to evaluate the effectiveness of their therapy and decide if a change in treatment is necessary either due to suboptimal response or due to toxicity.

Relapsed or Refractory Disease

For patients with relapsed or refractory disease after initial treatments, multiple therapeutic options are available, but they should be considered for participation in clinical trials if available. The choice of therapy depends on what drugs were given at the time of previous treatment and whether the disease was still sensitive or refractory to that regimen. Anti-CD38 monoclonal antibodies such as daratumumab, proteasome inhibitor (bortezomib or carfilzomib), and immunomodulatory drugs (lenalidomide and dexamethasone)-based regimens are all possible alternatives. The best regimen depends on multiple factors. For instance, daratumumab and bortezomib combination suits patients with severe cardiac issues. For very frail patients where tolerability of multiple drug combinations is a concern, one can even consider single-agent therapy. For example, retrospective studies have indicated a high response rate with single-agent daratumumab [17,18]. However, when combined with other treatments like, lenalidomide, pomalidomide, or bortezomib, enhanced effectiveness has been reported [31,32]. Some phase 2 trials also revealed improved progression-free survival (PFS) [33,34]. The daratumumab monotherapy is well tolerated in patients with relapsed systemic AL amyloidosis (including relapsed after HSCT) and leads to rapid and deep hematologic responses (~86% very good partial response-VGPR or better) and organ responses which was demonstrated in a prospective phase 2 trial [19]. In another phase 2 prospective multicenter study of daratumumab monotherapy, 40 previously treated AL patients were included and ~48% of patients had VGPR or better. Daratumumab monotherapy is associated with deep and rapid hematological responses in previously treated AL patients, with an excellent safety profile. Hence, a daratumumab naïve patient who relapses should be treated

Table 2. Current clinical trials that are actively recruiting participants and include a monoclonal antibody as part of their AL amyloidosis therapy are available at www.clinicaltrials.gov.

Phase/Title	Brief description	Study type	Study design	Study arms	Clinicaltrials.gov ID
Phase 2 Study Evaluating Maintenance in Light-chain Amyloidosis (EMILIA).	Daratumumab Maintenance Therapy for Improving Survival in Patients with Light-chain Amyloidosis, EMILIA Trial after 3–6 versus 18 cycles of daratumumab maintenance following 6 cycles induction of daratumumab-CyBorD in newly diagnosed AL amyloidosis.	interventional targeting of the plasma cell clone	randomized, Open-label.	*Experimental: Arm I* (6 cycles of daratumumab) *Active Comparator: Arm II* (18 cycles of daratumumab)	NCT05898646
Phase 1/Slow-Go Strategy for High-Risk AL amyloidosis: Isatuximab for Upfront Therapy.	Evaluate the effectiveness of Isatuximab in the treatment of individuals diagnosed with high-risk immunoglobulin light-chain amyloidosis (AL amyloidosis). Isatuximab, in combination with weekly Dexamethasone, will be administered, and based on tolerance, Velcade and cyclophosphamide may be added.	interventional targeting of the plasma cell clone	single group assignment; Open-label; Treatment.	*Experimental: Treatment* (Isatuximab, chemotherapy)	NCT04754945
A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Birtamimab Plus Standard of Care vs. Placebo Plus Standard of Care in Mayo Stage IV Subjects with Light-chain (AL) amyloidosis.	Evaluate Birtamimab efficacy in newly diagnosed Mayo Stage IV patients. Birtamimab/Placebo will be administered every 28 days plus Standard of Care chemotherapy (Bortezomib-containing chemotherapy regimen).	interventional targeting of the amyloid deposits	randomized; Quadruple (Participant, Care provider, Investigator, Outcomes Assessor) masking; Treatment.	*Experimental*: Birtamimab plus Standard of Care Chemotherapy *Placebo Comparator*: Placebo plus Standard of Care Chemotherapy	NCT04973137

at least with a daratumumab monotherapy with the option to combine with another agent such as bortezomib or lenalidomide if less than optimal response to therapy is noted after a few months of daratumumab monotherapy.

Proteasome inhibitors, such as bortezomib and Ixazomib, have been used based on their demonstrated efficacy. A phase 3 trial showed that patients treated with Ixazomib and dexamethasone had delayed organ damage or mortality compared to other treatments [35]. Meanwhile, bortezomib showed overall response rates of 70–80% in the relapsed setting [7,8].

Lastly, immunomodulatory derivatives, like lenalidomide, have also been effective, though they are administered at lower doses than for multiple myeloma due to tolerability issues in patients with renal and cardiac dysfunction. A new agent Venetoclax (a BCL2 inhibitor) is being investigated with promising preliminary results in patients with AL amyloidosis who have t(11;14) translocation in the clonal plasma cells by fluorescent in situ hybridization (FISH) testing. About 50% of AL amyloid patients have this specific translocation and therefore can be considered for off-label treatment in combination with dexamethasone (VenDex). Though not yet FDA approved, VenDex is supported by National Comprehensive Cancer Network (NCCN) guidelines to be used in relapsed systemic AL amyloidosis with t(11;14).

Role of Maintenance Therapy

The role of maintenance therapy in AL amyloidosis post-HSCT or after achieving a CHR in a non-HSCT candidate is not fully defined. The decision to prescribe maintenance therapy and its duration is left to the discretion of the treating physician in clinical practice. Daratumumab maintenance is being currently investigated in a phase 2 Clinical trial (Table 2). The "Daratumumab Maintenance Therapy for Improving Survival in Patients with Light-chain Amyloidosis, Evaluating Maintenance in Light-chain Amyloidosis (EMILIA) Trial" is testing 3–6 versus 18 cycles of daratumumab maintenance following 6 cycles induction of DaraCyborD in newly diagnosed AL amyloidosis. Consolidation therapy (usually bortezomib-based) is often offered to patients who do not achieve a CHR after HSCT.

Immunomodulatory Drugs (IMiDs)

When combined with dexamethasone, immunomodulatory drugs such as lenalidomide demonstrate enhanced anti-tumor activity. However, they exhibit a slower clonal clearance in AL amyloidosis patients in contrast with multiple myeloma patients' response. Immunomodulatory drugs (IMiDs) were linked to elevated rates of toxicity in patients with AL amyloidosis. Neurological and gastrointestinal toxicity were linked with Thalidomide [36]. Lenalidomide should start with a lower dose with an escalation based on tolerance. Common lenalidomide-related adverse effects in AL amyloidosis patients include skin rashes, thromboembolic complications, infections, fatigue, and renal failure [37]. Pomalidomide presents a more favorable renal profile and may be better tolerated in AL amyloidosis patients compared to lenalidomide. Both lenalidomide and pomalidomide in combination with dexamethasone, have also demonstrated high hematologic response rates among patients with relapsed/refractory systemic AL amyloidosis [38,39]. NT-proBNP may be elevated temporarily while using IMiDs, making it challenging to assess the cardiac response. Nowadays, IMidD therapy is considered a secondary treatment option in AL amyloidosis due to the availability of more effective and tolerable daratumumab and bortezomib combinations. Additionally, they can be considered as part of maintenance therapy after achieving CHR or VGPR if patients and families find injections of daratumumab and bortezomib inconvenient. Thromboprophylaxis (usually aspirin 81 mg daily) is a common practice while using lenalidomide or pomalidomide in systemic AL amyloidosis due to the increased risk of arterial and venous thrombosis.

Prognosis

The prognosis and response to treatment depend on the extent of cardiac involvement at initial diagnosis, which is determined through the evaluation of biomarkers NT-pro-BNP and troponin T. The Mayo 2004 staging system, established to classify AL amyloidosis patients based on their risk profile and overall survival, relies on the levels of troponin T and NT pro-BNP elevation, categorizing them into a three-stage model [4]. However, in the European 2016 modification of the Mayo 2004 staging system, stage III is further subdivided into two sub-stages (IIIA with NT-proBNP $<$8500 pg/mL and IIIB with NT-proBNP $>$8500 pg/mL) based on the severity of NT-proBNP elevation. The prognosis for stage IIIB is drastically dismal with median overall survival of 4 months compared to median overall survival of 36 months for stage IIIA. The revised Mayo Staging system (2012) is based on cardiac and clonal biomarkers, while European modification is based solely on cardiac biomarkers [1]. When detected at a late stage, AL amyloidosis has a poor long-term prognosis with most deaths attributed to advanced heart failure. Median survival can be as short as 6 months and therefore early diagnosis and prompt anti-plasma cell therapy is the only way to prevent deaths in this dreadful disease. Both hematologic and organ responses are associated with improved survival in systemic AL amyloidosis and therefore any therapies that improve these two clinical bottom lines can greatly impact prognosis.

New Advances in Systemic AL Amyloidosis

Currently, the treatment plan primarily targets the plasma cell clone responsible for generating the immunoglobulin light-chain protein that misfolds to form the

amyloid fibrils. There is a shift in pharmaceutical research towards a more focused effort on selectively removing or dissolving the amyloid fibrils, which leads to the reversal of organ dysfunction triggered by amyloid deposition, ultimately enhancing rapid recovery of vital organ function and ultimately improving overall survival. The dual-targeted therapy aims to clear the plasma cell clone in the bone marrow by anti-plasma cell therapy and at the same time facilitates dissolving the amyloid deposits from the organs. This modern visionary framework of anti-AL amyloidosis treatment can become a reality in the near future. Monoclonal antibodies, due to their high selectivity and low toxicity, have been introduced in several clinical trials with the aim of improving and enhancing the treatment approach for AL. Monoclonal antibodies exert various mechanisms to eliminate tumor cells, including direct tumor cell cytotoxicity, apoptosis, immune-mediated tumor cell eradication (Antibody-Dependent Cellular cytotoxicity (ADCC) and Complement-Dependent Cytotoxicity-CDC), and vascular and stromal ablation. In AL amyloidosis patients, organ damage significantly affects patient survival. This underscores the need for innovative strategies that, when combined with earlier diagnosis and multidisciplinary management, can achieve a faster and deeper remission and rapid reversal of organ dysfunctions and ultimately improve overall survival [40].

This brings us to the concept of "*Antifibril agents*". These drugs work by eliminating preexisting amyloid fibrils through the enhancement of the immune system, which induces a chemical and enzymatic breakdown, as well as antibody-dependent phagocytosis of these fibrils [2]. Currently, there are clinical trials investigating this new treatment approach in AL amyloidosis, which includes two monoclonal antibodies: Birtamimab (NEOD001-301) and CAEL-101.

Birtamimab (NEOD001) is a humanized IgG1 immunoglobulin that interacts with both amyloid fibrils present in the bloodstream and those already deposited in tissues. It specifically targets a hidden epitope on serum-free light-chain proteins, leading to an enhanced elimination of amyloid fibrils through phagocytosis. This activation of macrophages facilitates the breakdown and removal of light-chain-derived amyloid fibrils [40].

In 2018, the VITAL Study, a Phase 3, Randomized, Multicenter, Double-Blind trial, investigated the Efficacy and Safety of NEOD001 (Birtamimab) Plus Standard of Care versus Placebo Plus Standard of Care in Individuals with Light-chain (AL) amyloidosis. Out of the 260 participants, 77 met the Mayo 2012 Stage IV criteria; 38 were allocated to Birtamimab plus Standard of Care (SOC) and 39 to placebo plus SOC, with a median age of 64 years. Following an analysis, the independent data monitoring committee advised halting the trial early due to a numerical trend favoring Birtamimab in the primary endpoint for the entire cohort, likely influenced by its impact on the most advanced patients (Mayo stage IV). Subsequent analyses focused on patients with Mayo stage IV AL amyloidosis suggested a potential benefit of Birtamimab on mortality in those at the highest risk of early mortality, along with significant improvements in quality of life (QoL) and cardiac function. Adverse event frequencies, including Fatigue, Nausea, Peripheral edema, Constipation, Diarrhea, Dyspnea, Insomnia, Cough, Hypokalemia, Dizziness, Cardiac failure, and Hypotension, were comparable between treatment groups. However, administration of multiple IV infusions of Birtamimab was generally well tolerated without significant volume overload, particularly in patients with Mayo stage IV AL amyloidosis [4,9].

The AFFIRM-AL study, a phase 3, randomized, multicenter, double-blind, placebo-controlled trial (NEOD001 - NCT04973137), is currently underway to validate the findings of the VITAL study in patients with Mayo Stage IV AL amyloidosis and assess the efficacy of Birtamimab by evaluating time to all-cause mortality. Approximately 150 newly diagnosed Mayo Stage IV patients with AL amyloidosis are anticipated to be enrolled and randomized in a 2:1 ratio to receive Birtamimab or placebo [9].

CAEL-101 is an immunoglobulin G1 monoclonal antibody specifically designed to target amyloid fibrils (NCT04512235 - NCT04504825). It possesses a high affinity for both kappa and lambda light chains, derived from monoclonal plasma cells. CAEL-101 is a chimeric monoclonal antibody that homes in on a concealed epitope within immunoglobulin light chains. This epitope becomes accessible when these light chains misfold, whether they are free in the bloodstream or deposited in various organs. By binding to these serum-free immunoglobulin light chains, CAEL-101 enhances opsonization and activates neutrophils and macrophages. These immune cells, in turn, break down the complex through phagocytosis and/or enzymatic and chemical proteolysis decreasing the light-chain load on organs and improving overall organ response to AL amyloidosis treatment [41] (Fig. 2).

CAEL-101 was assessed in a phase 1a/b trial enrolling patients with symptomatic AL amyloidosis. In phase 1a, individual patient cohorts received escalating doses of mAb CAEL-101 as a one-time treatment (starting at 0.5 mg/m^2, with doses increased as tolerated up to 5, 10, 50, 100, 250, and 500 mg/m^2). In phase 1b, the first patient received 4 weekly infusions of mAb CAEL-101 at 0.5 mg/m^2, with subsequent dose escalation as tolerated up to 5, 10, 50, 100, 250, and 500 mg/m^2. No dose-limiting toxicity was observed up to 500 mg/m^2 in either phase 1a or 1b. Predominant treatment-related adverse events in phase 1a included mild nausea, diarrhea, rash, pruritus, and hyperuricemia. No grade 4 or 5 drug-related events or dose-limiting toxicities were reported. Outcomes from the phase 1a/1b investigation confirm the well-tolerated nature of mAb CAEL-101 therapy, with the potential to enhance biomarkers associated with organ dysfunction in AL amyloidosis patients.

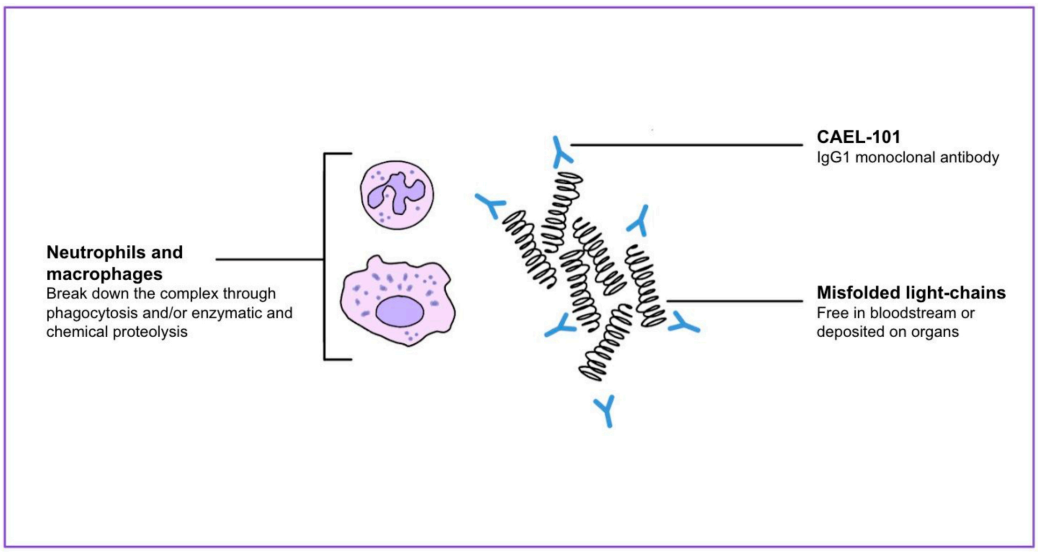

Fig. 2. Mechanism of action of a monoclonal antibody (CAEL-101). Fig. 2 was created using Notability (Verison 11.8.9, Ginger Labs LLC, San Francisco, CA, USA).

In phase 1a, 63% of evaluable patients exhibited an organ response following the initial infusion, while 61% demonstrated such a response in phase 1b. The median onset of response occurred at 2 weeks post-treatment initiation, with faster responses observed at higher doses. The organ response appeared independent of the light-chain type [10,37].

Two phase 3 placebo-controlled double-blind clinical trials of CAEL-101 (Caelum CARES 301 and 302 study) in combination with DaraCyborD have been completed and the results are currently awaited. CAEL-101 and Birtamimab, both in combination with the standard of care in comparison to the standard of care alone (DaraCyborD $\pm$ CAEL-101 or DaraCyborD $\pm$ Birtamimab), are part of two-Phase 3 clinical trials for cardiac AL amyloidosis. These trials have been enrolling patients at various sites and different cardiac stages of the disease. Both studies have DaraCyborD as a comparator for the standard of care based on the high efficacy of the 4 drug regimen in the landmark phase 3 ANDROMEDA study [42]. Recent advancements also feature AT-02, an all-encompassing panamyloid removal agent. AT-02 is a humanized and recombinant IgG1 monoclonal antibody fusion protein with a subnanomolar binding affinity currently being tested in phase 1 clinical trials in systemic AL amyloidosis [40]. Table 2 summarizes the current clinical trial testing monoclonal antibodies in systemic AL amyloidosis.

Conclusion

AL amyloidosis presents a formidable challenge in the field of hematologic malignancies but daratumumab-based therapy has revolutionized the modern treatment landscape. DaraCyborD is the mainstay of induction therapy for newly diagnosed patients but single-agent daratumumab can also induce rapid and deep responses in frail patients either as upfront therapy or at the time of relapse. HSCT remains the therapy with the most experience in systemic AL amyloidosis and confers excellent long-term PFS and Overall Survival benefits in eligible patients. The defining characteristic of systemic AL amyloidosis is the deposition of misfolded immunoglobulin light chains in tissues, resulting in progressive organ failure with high morbidity and mortality particularly from advanced cardiac involvement. The key is early diagnosis and prompt therapy to eliminate the clonal plasma cell neoplasm and allow supportive care and potential utilization of amyloid-clearing immunotherapies to the damaged organs in the near future. To confront this complex challenge, ‘Antifibril agents’ have been developed and incorporated into numerous clinical trials. These agents aim to dissolve the deposited amyloid proteins from the vital organs, potentially reversing organ damage and debilitating symptoms. The final goal is to improve the quality of life and survival rates and extend periods of remission. The concurrent administration of a dual-targeted immunotherapy-based approach to the clonal plasma cells and the amyloid deposits may provide rapid recovery of organ functions needed in very sick patients particularly those with advanced cardiac involvement and refractory heart failure.

Availability of Data and Materials

Not applicable.

Author Contributions

CPC conceived this manuscript. VM conceptualized the review’s structure, data collection, and drafting of the

manuscript. LS and STS contributed to the acquisition of data. STS created Fig. 2 within the manuscript. CPC contributed valuable intellectual insights, reviewed the final draft, and actively participated in the discussion. All authors were involved in the drafting and critical revision of the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Muchtar E, Dispenzieri A, Gertz MA, Kumar SK, Buadi FK, Leung N, *et al*. Treatment of AL Amyloidosis: Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Statement 2020 Update. Mayo Clinic Proceedings. 2021; 96: 1546–1577.

[2] Fontana M. Cardiac amyloidosis: Epidemiology, clinical manifestations, and diagnosis - UpToDate. 2024. Available at: https://www.uptodate.com/contents/cardiac-amyloidosis-epidemiology-clinical-manifestations-and-diagnosis?search=al%20amyloidosis%20&source=search_result&selectedTitle=6~94&usage_type=default&display_rank=6 (Accessed: 4 September 2023).

[3] Dispenzieri A. Clinical presentation, laboratory manifestations, and diagnosis of immunoglobulin light chain (AL) amyloidosis - UpToDate. 2024. Available at: https://www.uptodate.com/contents/clinical-presentation-laboratory-manifestations-and-diagnosis-of-immunoglobulin-light-chain-al-amyloidosis?search=al%20amyloidosis%20treatment&source=search_result&selectedTitle=2~91&usage_type=default&display_rank=2 (Accessed: 4 September 2023).

[4] Bou Zerdan M, Nasr L, Khalid F, Allam S, Bouferraa Y, Batool S, *et al*. Systemic AL amyloidosis: current approach and future direction. Oncotarget. 2023; 14: 384–394.

[5] Gorevic PD. Overview of amyloidosis - UpToDate. 2024. Available at: https://www.uptodate.com/contents/overview-of-amyloidosis?sectionName=CLINICAL%20MANIFESTATIONS&search=al%20amyloidosis%20&topicRef=6668&anchor=H10&source=see_link#H755478005 (Accessed: 4 September 2023).

[6] Dispenzieri A. Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis - UpToDate. 2024. Available at: https://www.uptodate.com/contents/treatment-and-prognosis-of-immunoglobulin-light-chain-al-amyloidosis?sectionName=PRETREATMENT%20EVALUATION&topicRef=6668&anchor=H15768474&source=see_link#H15768474 (Accessed: 7 September 2023).

[7] Reece DE, Hegenbart U, Sanchorawala V, Merlini G, Palladini G, Bladé J, *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.

[8] Reece DE, Hegenbart U, Sanchorawala V, Merlini G, Palladini G, Bladé J, *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.

[9] Gertz MA, Cohen AD, Comenzo RL, Kastritis E, Landau HJ, Libby EN, *et al*. Birtamimab plus standard of care in light-chain amyloidosis: the phase 3 randomized placebo-controlled VITAL trial. Blood. 2023; 142: 1208–1218.

[10] Edwards CV, Rao N, Bhutani D, Mapara M, Radhakrishnan J, Shames S, *et al*. Phase 1a/b study of monoclonal antibody CAEL-101 (11-1F4) in patients with AL amyloidosis. Blood. 2021; 138: 2632–2641.

[11] Muchtar E, Gertz MA, Kumar SK, Lacy MQ, Dingli D, Buadi FK, *et al*. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. Blood. 2017; 129: 2111–2119.

[12] Dispenzieri A, Seenithamby K, Lacy MQ, Kumar SK, Buadi FK, Hayman SR, *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 Transplantation. 2013; 48: 1302–1307.

[13] Sanchorawala V, Boccadoro M, Gertz M, Hegenbart U, Kastritis E, Landau H, *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.

[14] Seldin DC, Anderson JJ, Sanchorawala V, Malek K, Wright DG, Quillen K, *et al*. Improvement in quality of life of patients with AL amyloidosis treated with high-dose melphalan and autologous stem cell transplantation. Blood. 2004; 104: 1888–1893.

[15] Gertz MA, Lacy MQ, Dispenzieri A, Ansell SM, Elliott MA, Gastineau DA, *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 Transplantation. 2004; 34: 1025–1031.

[16] Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. Blood. 2002; 99: 4276–4282.

[17] Palladini G, Dispenzieri A, Gertz MA, Kumar S, Wechalekar A, Hawkins PN, *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. Journal of Clinical Oncology. 2012; 30: 4541–4549.

[18] Palladini G, Jaccard A, Milani P, Lavergne D, Foli A, Bender S, *et al*. Circulating free light chain measurement in the diagnosis, prognostic assessment and evaluation of response of AL amyloidosis: comparison of Freelite and N latex FLC assays. Clinical Chemistry and Laboratory Medicine. 2017; 55: 1734–1743.

[19] Dittrich T, Bochtler T, Kimmich C, Becker N, Jauch A, Goldschmidt H, *et al*. AL amyloidosis patients with low amyloidogenic free light chain levels at first diagnosis have an excellent prognosis. Blood. 2017; 130: 632–642.

[20] Sidana S, Muchtar E, Sidiqi MH, Jevremovic D, Dispenzieri A, Gonsalves W, *et al*. Impact of minimal residual negativity using next generation flow cytometry on outcomes in light chain amyloidosis. American Journal of Hematology. 2020; 95: 497–502.

[21] Kastritis E, Kostopoulos IV, Terpos E, Paiva B, Fotiou D, Gavriatopoulou M, *et al*. Evaluation of minimal residual disease using next-generation flow cytometry in patients with AL amyloidosis. Blood Cancer Journal. 2018; 8: 46.

[22] Palladini G, Hegenbart U, Milani P, Kimmich C, Foli A, Ho AD, *et al*. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood. 2014; 124: 2325–2332.

[23] Gertz MA, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PN, *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. American Journal of Hematology. 2005; 79: 319–328.

[24] Muchtar E, Dispenzieri A, Leung N, Lacy MQ, Buadi FK, Dingli D, *et al*. Depth of organ response in AL amyloidosis is associated with improved survival: grading the organ response criteria. Leukemia. 2018; 32: 2240–2249.

[25] Cornell RF, Hari P, Goodman S, Costa LJ, Fraser R, Estrada-Merly N, *et al*. Bortezomib induction prior to autologous hematopoietic cell transplantation (AHCT) for newly diagnosed light chain amyloidosis (AL): A study of 426 patients. Journal of Clinical Oncology. 2020. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.8515 (Accessed: 27 October 2023).

[26] Kastritis E, Palladini G, Minnema MC, Wechalekar AD, Jaccard A, Lee HC, *et al*. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. The New England Journal of Medicine. 2021; 385: 46–58.

[27] Manwani R, Cohen O, Sharpley F, Mahmood S, Sachchithanantham S, Foard D, *et al*. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. Blood. 2019; 134: 2271–2280.

[28] Palladini G, Sachchithanantham S, Milani P, Gillmore J, Foli A, Lachmann H, *et al*. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood. 2015; 126: 612–615.

[29] Kastritis E, Leleu X, Arnulf B, Zamagni E, Cibeira MT, Kwok F, *et al*. Bortezomib, Melphalan, and Dexamethasone for Light-Chain Amyloidosis. Journal of Clinical Oncology. 2020; 38: 3252–3260.

[30] Wechalekar AD, Sanchorawala V. Daratumumab in AL amyloidosis. Blood. 2022; 140: 2317–2322.

[31] Kimmich CR, Terzer T, Benner A, Dittrich T, Veelken K, Carpinteiro A, *et al*. Daratumumab for systemic AL amyloidosis: prognostic factors and adverse outcome with nephrotic-range albuminuria. Blood. 2020; 135: 1517–1530.

[32] Abeykoon JP, Zanwar S, Dispenzieri A, Gertz MA, Leung N, Kourelis T, *et al*. Daratumumab-based therapy in patients with heavily-pretreated AL amyloidosis. Leukemia. 2019; 33: 531–536.

[33] Sanchorawala V, Sarosiek S, Schulman A, Mistark M, Migre ME, Cruz R, *et al*. Safety, tolerability, and response rates of daratumumab in relapsed AL amyloidosis: results of a phase 2 study. Blood. 2020; 135: 1541–1547.

[34] Roussel M, Merlini G, Chevret S, Arnulf B, Stoppa AM, Perrot A, *et al*. A prospective phase 2 trial of daratumumab in patients with previously treated systemic light-chain amyloidosis. Blood. 2020; 135: 1531–1540.

[35] Dispenzieri A, Kastritis E, Wechalekar AD, Schönland SO, Kim K, Sanchorawala V, *et al*. A randomized phase 3 study of ixazomib–dexamethasone versus physician's choice in relapsed or refractory AL amyloidosis. Leukemia. 2022; 36: 225–235.

[36] Hideshima T, Chauhan D, Shima Y, Raje N, Davies FE, Tai YT, *et al*. Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood. 2000; 96: 2943–2950.

[37] Guidelines for non-transplant chemotherapy for treatment of systemic AL amyloidosis: EHA-ISA working group. 2023. Available at: https://www.tandfonline.com/doi/epub/10.1080/13506129.2022.2093635 (Accessed: 18 September 2023).

[38] Basset M, Kimmich CR, Schreck N, Krzykalla J, Dittrich T, Veelken K, *et al*. Lenalidomide and dexamethasone in relapsed/refractory immunoglobulin light chain (AL) amyloidosis: results from a large cohort of patients with long follow-up. British Journal of Haematology. 2021; 195: 230–243.

[39] Palladini G, Milani P, Foli A, Basset M, Russo F, Perlini S, *et al*. A phase 2 trial of pomalidomide and dexamethasone rescue treatment in patients with AL amyloidosis. Blood. 2017; 129: 2120–2123.

[40] Popkova T, Hajek R, Jelinek T. Monoclonal antibodies in the treatment of AL amyloidosis: co-targetting the plasma cell clone and amyloid deposits. British Journal of Haematology. 2020; 189: 228–238.

[41] Wechalekar AD, Fontana M, Quarta CC, Liedtke M. AL Amyloidosis for Cardiologists: Awareness, Diagnosis, and Future Prospects: *JACC: CardioOncology* State-of-the-Art Review. JACC. CardioOncology. 2022; 4: 427–441.

[42] Khouri J, Anwer F, Samaras CJ, Mejia Garcia AV, Koc ON, Faiman BM, *et al*. Safety, Tolerability and Efficacy of Cael-101 in AL Amyloidosis Patients Treated on a Phase 2, Open-Label, Dose Selection Study to Evaluate the Safety and Tolerability of Cael-101 in Patients with AL Amyloidosis. Blood. 2020; 136: 21.