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Daratumumab Plus CyBorD for Patients With Newly Diagnosed AL Amyloidosis: Safety Run-in Results of ANDROMEDA

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Abstract:
Although no therapies are currently approved for light chain (AL) amyloidosis, cyclophosphamide, bortezomib, and dexamethasone (CyBorD) is considered a standard treatment for newly diagnosed patients. Based on safety and efficacy of the anti-CD38 antibody daratumumab in multiple myeloma (MM), the phase 3 ANDROMEDA study is evaluating daratumumab-CyBorD versus CyBorD in newly diagnosed AL amyloidosis. We report results of the 28-patient safety run-in. Patients received subcutaneous daratumumab (DARA SC) QW Cycles 1-2 (28 days/cycle), Q2W Cycles 3-6, and Q4W thereafter for up to 2 years. CyBorD was given weekly for 6 four-week cycles. Median age was 67.5 (range, 35-83) years; median time from diagnosis was 59.5 (range, 15-501) days. Patients had a median of 2 (range, 1-4) involved organs; kidney and cardiac involvement affected 68% and 61% of patients, respectively. Patients received a median of 16 (range, 1-23) treatment cycles. The most common any-grade treatment-emergent adverse events were diarrhea (68%), fatigue (54%), and peripheral edema (50%), consistent with DARA SC in MM and the CyBorD safety profile. Infusion-related reactions occurred in 1 patient (grade 1). No grade 5 TEAEs were reported; 5 patients died, 3 following autologous transplant. Overall hematologic response rate was 96%, with ≥very good partial response in 23 (82%) patients and complete hematologic response in 15 (54%) patients; ≥partial response occurred in 20, 22, and 17 patients at 1, 3, and 6 months, respectively. The organ response rate was 64% (median follow-up 17.6 months). Renal response occurred in 6/16, 7/15, and 10/15 patients, and cardiac response occurred in 6/16, 6/13, and 8/13 patients at 3, 6, and 12 months, respectively. Hepatic response occurred in 2/3 patients at 12 months. Daratumumab-CyBorD was well tolerated, with no new safety concerns compared with the intravenous formulation, and demonstrated robust hematologic and organ responses. http://ClinicalTrials.gov NCT03201965.

Conflict of interest: COI declared - see note

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Clinical trial registration information (if any): ClinicalTrials.gov NCT03201965

Title **Daratumumab Plus CyBorD for Patients With Newly Diagnosed AL Amyloidosis: Safety Run-in Results of ANDROMEDA**

Running Head **Daratumumab-CyBorD in AL Amyloidosis**

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Key Points

- Daratumumab subcutaneous (DARA SC)-CyBorD was well tolerated in patients (excluded Mayo Stage IIIb) with newly diagnosed AL amyloidosis
- DARA SC-CyBorD elicited robust hematologic and organ responses in these patients

Abstract

Although no therapies are currently approved for light chain (AL) amyloidosis, cyclophosphamide, bortezomib, and dexamethasone (CyBorD) is considered a standard treatment for newly diagnosed patients. Based on safety and efficacy of the anti-CD38 antibody daratumumab in multiple myeloma (MM), the phase 3 ANDROMEDA study is evaluating daratumumab-CyBorD versus CyBorD in newly diagnosed AL amyloidosis. We report results of the 28-patient safety run-in. Patients received subcutaneous daratumumab (DARA SC) QW Cycles 1-2 (28 days/cycle), Q2W Cycles 3-6, and Q4W thereafter for up to 2 years. CyBorD was given weekly for 6 four-week cycles. Median age was 67.5 (range, 35-83) years; median time from diagnosis was 59.5 (range, 15-501) days. Patients had a median of 2 (range, 1-4) involved organs; kidney and cardiac involvement affected 68% and 61% of patients, respectively. Patients received a median of 16 (range, 1-23) treatment cycles. The most common any-grade treatment-emergent adverse events were diarrhea (68%), fatigue (54%), and peripheral edema (50%), consistent with DARA SC in MM and the CyBorD safety profile. Infusion-related reactions occurred in 1 patient (grade 1). No grade 5 TEAEs were reported; 5 patients died, 3 following autologous transplant. Overall hematologic response rate was 96%, with ≥very good partial response in 23 (82%) patients and complete hematologic response in 15 (54%) patients; ≥partial response occurred in 20, 22, and 17 patients at 1, 3, and 6 months, respectively. The organ response rate was 64% (median follow-up 17.6 months). Renal response occurred in 6/16, 7/15, and 10/15 patients, and cardiac response occurred in 6/16, 6/13, and 8/13 patients at 3, 6, and 12 months, respectively. Hepatic response occurred in 2/3 patients at 12 months. Daratumumab-CyBorD was well tolerated, with no new safety concerns compared with the intravenous

formulation, and demonstrated robust hematologic and organ responses. http://ClinicalTrials.gov NCT03201965.

Introduction

Systemic amyloid light-chain (AL) amyloidosis is a rare plasma cell disorder primarily affecting older adults. In the United States, the unadjusted incidence is approximately 10 to 14 cases per million person-years,[1] which is likely underestimated due to delayed or missed diagnosis. AL amyloidosis is characterized by deposition of insoluble amyloid fibrils into tissues and organs, resulting in progressive organ damage. Affected organs most frequently include the heart, kidney, and liver, but soft tissues and the nervous system may be involved.[2,3]

Application of novel drugs developed for multiple myeloma (MM), in particular bortezomib, have improved AL amyloidosis outcomes.[4,5] Among patients at the Mayo Clinic in the United States, the 2-year overall survival (OS) rate increased from 42% among those diagnosed from 2000-2004 to 60% in patients diagnosed from 2010-2014.[5] In a population-based Swedish study, the 2-year OS rate improved from 42% to 61% between 2000-2004 and 2010-2013.[6] Outcomes in both studies suggested that early diagnosis and treatment with more effective antiplasma cell therapy could decrease early mortality.

Despite these promising findings, antiplasma cell therapy remains suboptimal for most patients with AL amyloidosis. Hematologic complete response (CR) rates in newly diagnosed patients receiving commonly used drug regimens such as cyclophosphamide, bortezomib, and dexamethasone (CyBorD) range from 23%-47%.[7,8] Similar or higher CR rates are achievable with high-dose melphalan treatment and autologous stem cell transplant (ASCT), but this therapy is only feasible in a minority of patients.[9-11] Additionally, AL patients experience more frequent

and severe toxicity compared to MM patients receiving the same regimens.[12,13] Thus, an unmet need remains for more tolerable and effective therapies for AL amyloidosis.

Depth of hematologic response is strongly associated with organ response and improved survival in AL amyloidosis.[14] Antiplasma cell regimens that induce rapid, deep, and durable hematologic responses can ameliorate organ dysfunction and ultimately increase OS. Daratumumab is a human IgGκ monoclonal antibody targeting CD38 that is uniformly expressed on clonal plasma cells and has a direct on-tumor and immunomodulatory mechanism of action.[15-21] In MM, daratumumab (16mg/kg intravenous [IV]) has demonstrated efficacy as monotherapy and in combination with standard regimens in newly diagnosed and relapsed MM.[22-28] Daratumumab combination regimens have shown remarkable rates of undetectable minimal residual disease, a predictable and manageable safety profile,[26-30] and have not been associated with cardiac or renal toxicities, which are of particular concern to AL amyloidosis patients.[22-26]

AL amyloidosis plasma cells have been shown to express CD38.[31,32] Additionally, preliminary results of 2 prospective studies of daratumumab monotherapy in relapsed AL amyloidosis have shown promising hematologic responses without cardiac, renal, or other notable toxicities and overall hematologic response rates ≥59%.[33-35] These promising results and favorable attributes make daratumumab ideally suited for study in the AL population with compromised organ function.

Here we present for the first time the use of the subcutaneous formulation of daratumumab (DARA SC) in AL amyloidosis in the safety run-in cohort of the phase 3 ANDROMEDA study

(AMY3001; ClinicalTrials.gov Identifier: NCT03201965). This study is investigating DARA SC in combination with CyBorD in patients with newly diagnosed AL amyloidosis.

Methods

Study design

ANDROMEDA is a randomized, open-label, active-controlled, multicenter, phase 3 study with a safety run-in phase. Here we report the results of the safety run-in phase, which was conducted to determine the safety and tolerability of DARA SC plus CyBorD in ≥10 patients with newly diagnosed AL amyloidosis. If no safety signals were observed after ≥1 cycle of treatment, the randomized portion of the study would begin with approximately 360 patients being randomized 1:1 to receive CyBorD with or without DARA SC. All patients in the safety run-in cohort received DARA SC (1,800 mg in 15mL) with recombinant human hyaluronidase PH20 (rHuPH20; 30,000 U; ENHANZE® drug delivery technology, Halozyme, Inc).

DARA SC was administered in a single, pre-mixed vial, given by manual subcutaneous injection over 3-5 minutes weekly in Cycles 1-2, every 2 weeks in Cycles 3-6, and every 4 weeks thereafter as monotherapy for a maximum of 2 years from study start (all cycles were 28 days). Cyclophosphamide 300 mg/m^2 orally or intravenously and bortezomib 1.3 mg/m^2 subcutaneously were given on Days 1, 8, 15, and 22 of each cycle for up to 6 cycles. Dexamethasone 40 mg (starting dose) was given orally or intravenously weekly for each cycle for up to 6 cycles. For patients who were >70 years of age, underweight (body mass index <18.5 kg/m^2), had hypervolemia (including heart failure), poorly controlled diabetes mellitus, or prior intolerance to

steroid therapy, dexamethasone could be administered at 20 mg weekly per investigator discretion.

Patients

Eligible patients were ≥18 years of age with a histopathologic diagnosis of systemic AL amyloidosis and measurable hematologic disease without prior therapy. Histopathologic diagnosis of amyloidosis was based on detection by immunohistochemistry and polarizing light microscopy of green birefringent material in tissue specimens stained with Congo red in an organ other than bone marrow, or characteristic electron microscopy appearance (unbranched 10 nm-thick fibrils). Subjects whose only evidence of amyloid deposition was in the bone marrow were excluded. Age-related amyloidosis and hereditary amyloidosis were ruled out, respectively, in male patients ≥70 years of age with cardiac involvement only and in patients of African descent, using mass spectrometry typing of amyloid deposits in a tissue biopsy.

Measurable disease was defined by either: (1) a serum free light-chain (FLC) level ≥50 mg/L with an abnormal kappa to lambda ratio or the difference between involved (amyloidogenic) FLC (iFLC) and uninvolved FLC (uFLC) ≥50 mg/L; or (2) a serum monoclonal protein level ≥5.0 g/L. During the study screening phase, patients must have had an absolute neutrophil count ≥1.0 x 10^9/L, hemoglobin levels ≥80 g/L, platelet count ≥50 × 10^9/L, aspartate and alanine aminotransferase levels ≤2.5 times the upper limit of normal (ULN), and total bilirubin levels ≤1.5 times ULN. Estimated glomerular filtration rate as determined by the Chronic Kidney Disease Epidemiology Collaboration equation was required to be ≥20 mL/min/1.73 m^2. Eligible patients had ≥1 impacted organ according to consensus criteria for the organ involved[36,37] and an

Eastern Cooperative Oncology Group[38] performance status score ≤2. Eligible patients were classified by cardiac stage at screening based on the European Modification of the Mayo Clinical Cardiac Staging system.[39] This system categorizes patients by the presence of 2 risk factors defined by elevated levels of the biomarkers N-terminal pro-brain natriuretic peptide (NT-proBNP: >332 ng/L) and high sensitivity cardiac troponin (>54 ng/L).[40] Stage I patients had neither risk factor, stage II patients had 1 risk factor, stage IIIa patients had both risk factors with NT-proBNP levels ≤8,500 ng/L, and stage IIIb patients had NT-proBNP levels >8,500 ng/L.[41]

Patients were not eligible if they had prior therapy for AL amyloidosis or MM (including CD38-targeted agents) or had a previous or current diagnosis of symptomatic MM. Patients with significant cardiovascular conditions as evidenced by NT-proBNP levels >8,500 ng/L, New York Heart Association classification IIIb or IV heart failure,[42] ischemic heart disease or uncorrected valvular disease unrelated to AL amyloid cardiomyopathy, sustained ventricular tachycardia, aborted ventricular fibrillation, atrioventricular nodal or sinoatrial nodal dysfunction with no pacemaker, QT interval as corrected by Fridericia's formula >500 msec without pacemaker, supine systolic blood pressure <90 mm Hg, or symptomatic orthostatic hypotension (a decrease in systolic blood pressure upon standing of >20 mmHg despite medical management [eg, midodrine, fludrocortisones] in the absence of volume depletion) were excluded. Patients with a history of malignancy (other than AL amyloidosis), chronic obstructive pulmonary disease, moderate or severe persistent asthma, current uncontrolled asthma, positivity for human immunodeficiency virus, active hepatitis B or C infection, grade 2 sensory or grade 1 painful peripheral neuropathy, any form of non-AL amyloidosis, or any concurrent medical condition or disease that would likely interfere with study procedures or results were excluded.

Study endpoints

In the safety-run in phase, absence of a safety signal (particularly with regard to volume overload) was required for the randomized portion of the study to begin. The primary endpoint of the randomized portion of ANDROMEDA is overall complete hematologic response rate (CR) based on International Amyloidosis Consensus Criteria (ICC) guidelines.[14,43,44] Amyloidosis CR (aCR) criteria require normalization of FLC levels and ratio, and negative serum and urine immunofixation (IFE). Patients who demonstrated negative serum and urine IFE but did not achieve a normalized FLC ratio due to suppression of uFLC below the lower limit of normal (FLC ratio abnormal or normal), and achieved normalized iFLC levels could not be formally categorized as achieving aCR and were classified as having a modified CR (mCR). Among patients with measurable difference between involved and uninvolved FLC (dFLC: ≥50 mg/L), VGPR was defined as a reduction of dFLC to <40 mg/L, and a PR by a decrease in dFLC by >50%.

A secondary endpoint was major organ deterioration progression-free survival (MOD-PFS), a composite of endpoints occurring from randomization to whichever of the following occurs first: death, clinical manifestation of cardiac or renal failure, or hematologic progressive disease per consensus guidelines. Cardiac failure was defined as development of dyspnea at rest for ≥3 consecutive days due solely to amyloidosis cardiac deterioration, or need for left ventricular assist device, intra-aortic balloon pump, or cardiac transplant. Renal failure was defined as development of end-stage renal disease requiring hemodialysis or renal transplant. Hematologic progression was defined based on ICC: starting from CR, a change to abnormal FLC ratio

[involved free light chain must double and be above ULN] or reappearance of the involved monoclonal protein on IFE; or starting from CR/very good partial response (VGPR)/partial response (PR), a 50% increase in serum M-protein to >0.5 g/dL or a 50% increase in urine M-protein to >200 mg/day [visible peak must be present]; or FLC increase of 50% to >100 mg/L.

Other secondary endpoints included organ response rate (assessed by biomarkers), PFS, OS, improvement in patient-reported fatigue according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, time to next treatment, rate of hematologic VGPR or better, time to hematologic and organ response, and duration of organ response. Cardiac response was defined as >30% and >300 ng/L decreases in NT-proBNP levels in patients with baseline levels ≥650 ng/L.[14] Cardiac progression was defined as >30% and >300 ng/L increase in NT-proBNP levels, ≥33% increase in cardiac troponin levels, or ≥10% decrease in left ventricular ejection fraction. Renal response was characterized by a ≥30% decrease in proteinuria or decrease in proteinuria below 0.5 g in 24 hours without renal progression. Renal progression was defined as a ≥25% decrease in estimated glomerular filtration rate. Hepatic responses were defined as a 50% decrease in abnormal alkaline phosphatase values; progression of liver disease was considered a 50% increase in alkaline phosphatase level above the lowest value.[14]

Study analyses

In the safety run-in, safety was evaluated after ≥10 patients received ≥1 treatment cycle. Treatment-emergent adverse events (TEAEs) were coded using the Medical Dictionary for Regulatory Activities. Dosing was staggered ≥48 hours between patients to assess infusion

related reactions (IRRs). Preliminary overall best hematologic response rates were also evaluated. All continuous variables were summarized using descriptive statistics, while categorical variables were summarized using frequency and percentage, unless stated otherwise.

Hematologic responses were evaluated weekly for Cycle 1, every 4 weeks for Cycles 2-6, and every other month thereafter until MOD-PFS, death, withdrawal of consent to participate, or end of the study. Organ responses were categorized by increased functionality measured by organ-specific serum and urine assays[14,45] and were assessed according to the same schedule as hematologic responses. Cardiac response was evaluated at a central laboratory.

Study oversight

The study was registered at ClinicalTrials.gov (NCT03201965) and was sponsored by Janssen Research & Development, LLC. Institutional review boards or independent ethics committees at study sites approved this study. Each patient provided written consent according to local requirements. The investigators and sponsor devised the study design and analysis. Study data were collected by investigators and their research teams. Janssen conducted the final data analysis and verified data accuracy. Investigators were not restricted by confidentiality agreements and had full accessibility to all data. Writing assistance was funded by Janssen Global Services, LLC.

Data sharing statement

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access

to the study data can be submitted through the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Results

Patients and treatment

A total of 28 patients received ≥1 treatment cycle in the safety run-in portion of the study. Patient demographics and baseline characteristics are presented in **Table 1**. Median age was 67.5 (range, 35-83) years, with more than half (n = 16 [57%]) of patients ≥65 years of age. Median time from diagnosis was 59.5 (range, 15-501) days. Twenty-two (79%) patients had measurable disease as indicated by serum FLC levels only, and 3 (11%) patients each had disease as measured by serum M-protein levels only and by both serum M-protein and FLC levels. FLC isotypes were lambda (75%) and kappa (25%). Immunoglobulin heavy chain expression was observed in 10 patients (8 [30%] IgG and 2 [7%] IgA). More than 50% of patients had ≥2 organs involved, with 61% and 68% with heart and kidney involvement, respectively. The majority (n = 22 [79%]) of patients were classified as cardiac stage II or higher per the modified Mayo staging system.[39] One patient with values corresponding to stage IIIa during screening subsequently increased to IIIb on Cycle 1 Day 1.

Patients received a median of 16 (range, 1-23) treatment cycles with a median duration of treatment of 15.1 (range, 0.2-20.1) months. Median dose intensities were 80% (range, 62%-99%) for cyclophosphamide, 96% (range 56%-101%) for bortezomib, 97% (range, 52%-102%) for dexamethasone, and 100% (range, 85%-100%) for DARA SC. The median duration of the first DARA SC injection was 5 (range, 3-17) minutes; second and subsequent injections also had a

median duration of 5 minutes (respective ranges, 4-9 and 1-15 minutes). The median duration of follow-up was 17.6 (range, 1.3-20.4) months. A total of 25 (89%) patients have received ≥6 cycles of treatment; 3 patients received all 6 planned cycles of DARA SC plus CyBorD without subsequent DARA SC maintenance, and 22 (67%) patients received DARA SC maintenance monotherapy (>6 treatment cycles). At the time of clinical cutoff (July 23, 2019), a total of 13 (46%) patients had discontinued treatment.

A total of 9 (32%) patients underwent elective ASCT (**Figure 1**). These patients received a median of 7 (range, 6-16) cycles of DARA SC plus CyBorD or DARA SC monotherapy. All patients were able to mobilize adequate numbers of $CD34^+$ cells (median 7×10^6/kg, range 3-14 $\times 10^6$/kg), all were mobilized with granulocyte colony-stimulating factor or equivalent, and 6 were also given plerixafor. One patient required a second mobilization attempt.

Safety

The most common any-grade and grade 3/4 TEAEs are reported in **Table 2**. Twenty-six (93%) patients experienced TEAEs considered related to study treatment; TEAEs in 21 (75%) patients were considered related to daratumumab. A total of 14% of patients experienced any-grade peripheral sensory neuropathy with DARA SC plus CyBorD (no grade 3/4 events). Grade 3/4 infections included pneumonia (n = 3 [11%]), cellulitis (n = 2 [7%]), and peritonitis, upper respiratory tract infection, and vascular device infection (n = 1 each [4%]).

All-grade cardiac TEAEs included palpitations (n = 2 [7%]) and arrhythmia, atrial fibrillation, atrial flutter, and congestive cardiac failure (n = 1 each [4%]; atrial fibrillation and cardiac failure

were considered treatment-related). Congestive cardiac failure was the only grade 3/4 cardiac TEAE. All-grade renal/urinary disorder TEAEs included pollakiuria (n = 4 [14%]), acute kidney injury (n = 3 [11%]; 1 [4%] treatment-related), hematuria, renal impairment, urinary retention (n = 2 each [7%]; 1 [4%] renal impairment considered treatment-related), and chronic kidney disease, dysuria, nephrolithiasis, nocturia, urinary incontinence, and urinary tract pain (n = 1 each [4%]; incontinence and pain were considered treatment-related). The only grade 3/4 renal/urinary disorder TEAE was acute kidney injury (n = 2 [7%]).

Serious TEAEs occurred in 12 (43%) patients and included fall and acute kidney injury (11% each), and pneumonia and cellulitis (7% each; cellulitis not related to injection site). A total of 5 (18%) patients died: 3 (11%) due to complications of high-dose melphalan and ASCT (septic shock and multiorgan system failure, recurrent infections, and septic shock, respectively), and 2 (7%) due to progression of amyloidosis-related organ dysfunction.

An IRR occurred in 1 (4%) patient, comprised of chest discomfort, cough, hypotension, oropharyngeal pain, and sneezing, all of which were grade 1. All occurred on Cycle 1 Day 1 except hypotension (Cycle 1, Day 8; considered probably related to DARA SC), and all resolved. A total of 6 injection-site reactions occurred in 3 (11%) patients. All injection-site reactions were grade 1 and included erythema, bruising, and skin discoloration; none led to changes in treatment.

Efficacy

The ORR (best response) to therapy with DARA SC plus CyBorD was 96% at a median follow-up of 17.6 months. A total of 15 (54%) patients achieved CR or mCR; 10 (36%) patients achieved CR based on consensus criteria, and 5 (18%) patients achieved CR based on all criteria except normalization of the FLC ratio (mCR; **Figure 2A**; **Supplementary Appendix**). Twenty-three (82%) patients achieved VGPR or better. PR or better was achieved by 20 (71%) patients at 1 month, 22 (79%) patients at 3 months, and 17 (61%) patients at 6 months. The number of patients achieving deep hematologic responses as measured by dFLC <10 mg/L[44] and iFLC ≤20 mg/L[43] were 19 (68%; **Figure 3**) and 20 (71%), respectively.

In responders, the median time to first response (PR or better) was 9 (range, 7-85) days, median time to VGPR was 19 (range, 7-339) days, and median time to aCR+mCR was 85 (range, 29-179) days. The median duration of aCR+mCR has not been reached, and responses deepened with time (**Figure 1**). At a median follow-up of 17.6 months, all patients achieving aCR+mCR remained in hematologic remission (only 1 patient underwent ASCT for consolidation of CR). Among 9 patients who proceeded to ASCT, only 1 was in CR prior to transplant. Of the 7 patients with measurable organ involvement at baseline, 5 (71%) patients had an organ response prior to ASCT (2 cardiac and 3 renal). There are currently 6 patients evaluable for post-ASCT hematologic response, of whom 4 (67%) deepened their response. Three of 9 patients died of transplant related complications; their clinical courses are summarized in the **Supplementary Appendix**.

The overall organ response rate (any evaluable organ[s]; heart, kidney, and/or liver) was 64% at a median follow-up of 17.6 months. Responses for specific organs are shown in **Figure 2B**. In patients with cardiac involvement, responses were seen in 9 of 17 (53%) patients, with 6 of 16 (38%) evaluable patients having a response at 3 months, 6 of 13 (46%) evaluable patients having a response at 6 months, and 8 of 13 (62%) evaluable patients with a response at 12 months. Among those with renal involvement, responses were observed in 15 of 18 (83%) patients: in 6 of 16 (38%) evaluable patients at 3 months, 7 of 15 (47%) evaluable patients at 6 months, and 10 of 15 (67%) patients at 12 months. Among the 4 patients with hepatic involvement, 2 showed a response; in 0 of 2 evaluable patients at 3 months, 0 of 3 evaluable patients at 6 months, and 2 of 3 evaluable patients at 12 months. The median time to response in cardiac responders was 114 (range, 29-561) days; for renal responders, 57 (range, 29-449) days; and for hepatic responders, 330 (range, 321-338) days.

Discussion

In the safety run-in cohort of the phase 3 ANDROMEDA study, DARA SC plus CyBorD was well tolerated in patients with previously untreated AL amyloidosis. No new safety concerns were identified with DARA SC plus CyBorD compared with daratumumab monotherapy (IV or SC) or CyBorD alone.[46-50] DARA SC is associated with low rates of IRRs, few injection-site reactions, and reduced administration times compared with DARA IV.[48] The advantages of DARA SC as reported in the phase 3 COLUMBA study in MM,[48] particularly the small administration volume, are relevant to AL amyloidosis patients for whom volume overload is a concern due to cardiac involvement. The safety profile of DARA SC plus CyBorD compared to that of CyBorD alone will be examined further in the randomized portion of the ANDROMEDA study.

The depth and rapidity of hematologic response to DARA SC plus CyBorD were notable. Additionally, the majority of patients achieved an absolute dFLC level <10 mg/L or an iFLC level <20 mg/L.[43,44] These stringent hematologic responses induced substantial organ responses; an overall organ response rate of 64% for the heart, kidney, and/or liver demonstrates clinically relevant functional improvement in organs most frequently affected by AL amyloidosis.

Criteria for defining hematologic response in AL amyloidosis have evolved in parallel with diagnostic and therapeutic advances[37] (**Table 3**). Development of assays to detect serum FLC levels allows measurement of hematologic responses in most patients, and the absolute depth of FLC response is now known to impact patient outcomes.[43,44] Although negative serum and urine IFE remain requirements for achievement of aCR, investigators have begun to consider the absolute dFLC or iFLC levels a more relevant measure of hematologic response. Importantly, Muchtar et al demonstrated that normalization of FLC has no impact on OS or organ response rate compared to an abnormal FLC ratio. These investigators also showed that an absolute iFLC level ≤20 mg/L is associated with improved survival.[43] Manwani et al recently reported outcomes of newly diagnosed AL patients (N = 915) treated with bortezomib-based therapy (95% received CyBorD) using a dFLC level <10 mg/L as a "stringent dFLC response." Achieving a stringent dFLC response was associated with improved OS and time to next treatment compared with less deep responses. Cardiac and renal responses were significantly higher among those achieving a stringent dFLC response.[44] These findings strongly support the concept that the absolute reduction of the amyloidogenic light chain is the most physiologically relevant measure of hematologic response and outcomes in AL amyloidosis, and that the current

international consensus criteria should be re-evaluated. An additional methodologic advance to assess and manage patients with AL amyloidosis is evaluation of minimal residual disease (MRD), as the absence of MRD may be associated with deeper organ response.[51]

In this trial, we assessed 5 patients as achieving mCR defined as a negative serum and urine IFE and iFLC less than the upper limit of normal, regardless of the uFLC level or FLC ratio. Of the 4 patients reaching mCR who had baseline cardiac, renal, or hepatic involvement, 3 achieved organ responses for each of the respective involved organs; the fourth achieved a response for 1 of 4 involved organs. More than half of patients in the ANDROMEDA safety run-in cohort achieved either aCR or mCR. Notably, these promising hematologic responses were durable, as all 15 patients achieving aCR+mCR remained in remission at a median follow-up of 17.6 months.

No therapies have been approved for AL amyloidosis. Currently, the most commonly used front-line regimens for this disease are CyBorD,[7] melphalan with dexamethasone (MDex),[52] and high-dose melphalan (HDM) with ASCT, although the latter is not feasible for many AL amyloidosis patients.[9-11] In patients with newly diagnosed AL amyloidosis receiving CyBorD,[7] MDex,[52] and HDM with ASCT,[9-11] hematologic CR rates were 23%, 12%, and 34%-48%, respectively. DARA SC plus CyBorD achieved a stringent dFLC response in 68% of patients compared with 30% with bortezomib-based combinations (95% received CyBorD).[44] Hematologic responses in the safety run-in cohort of ANDROMEDA compare favorably to all commonly used frontline regimens, including HDM and ASCT. Cardiac and renal response rates in the ANDROMEDA safety run-in cohort were 53% and 83%, respectively, and compare favorably with the current

standard nontransplant regimens above. Respective cardiac and renal response rates were 17% and 25% for CyBorD, and 20% and 17% for MDex.[7,52] Among patients who achieved CR with HDM and ASCT, the organ response rate was 79%.[9]

In summary, this is the first report on the use of daratumumab in combination with CyBorD in patients with newly diagnosed AL amyloidosis, and the first report of DARA SC treatment for a disease other than MM. DARA SC plus CyBorD was well tolerated in the safety run-in portion of the phase 3 ANDROMEDA study. No new safety concerns were identified compared with intravenous or subcutaneous daratumumab monotherapy or CyBorD alone, and low rates of IRRs were observed. Preliminary efficacy was robust, with high rates of deep and durable hematologic responses, and importantly, organ responses elicited by DARA SC plus CyBorD. These results indicate that DARA SC plus CyBorD is a promising treatment for AL amyloidosis, and support the ongoing randomized portion of ANDROMEDA.

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Authorship

Contributions: All authors drafted and reviewed the manuscript, approved the final version, decided to publish this report, and vouch for data accuracy and completeness.

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Table 1. Demographics and baseline characteristics

Characteristic	Patients (n = 28)
Age	
Median (range), years	67.5 (35-83)
Category, n (%)	
<65 years	12 (42.9)
≥65 years	16 (57.1)
Male, n (%)	16 (57.1)
Race, n (%)	
White	25 (89.3)
Black/African American	2 (7.1)
Unknown	1 (3.6)
ECOG performance status,* n (%)	
0	7 (25.0)
1	18 (64.3)
2	3 (10.7)
Time from diagnosis	
Median (range), days	59.5 (15-501)
Involved organs, n (%)	
Median, n (range)	2 (1-4)
≥2 organs	19 (67.9)
Kidney	19 (67.9)
Heart	17 (60.7)
Nerve	6 (21.4)
Gastrointestinal tract	5 (17.9)
Peripheral nervous system	5 (17.9)
Liver	4 (14.3)
Soft tissue	4 (14.3)
Autonomic nervous system	1 (3.6)
FLC isotype, n (%)	
Lambda	21 (75.0)
Kappa	7 (25.0)
Immunoglobin heavy chain isotype, n (%)	N = 27
Any heavy chain expression	10 (37.0)
IgG	8 (29.6)
IgA	2 (7.4)
Mayo Clinic cardiac stage, † n (%)	
I	6 (21.4)
II	16 (57.1)
IIIa	5 (17.9)
IIIb‡	1 (3.6)
NYHA class, § n (%)	

I	17 (60.7)
II	10 (35.7)
IIIA	1 (3.6)
Baseline creatinine clearance, n (%)	
n	27
≥60 mL/minute	20 (74.1)
<60 mL/minute	7 (25.9)

ECOG indicates Eastern Cooperative Oncology Group; and NYHA, New York Heart Association.
*ECOG performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.
†Based on the European Modification of the Mayo Staging system;[39] cardiac stage was based on 2 biomarker risk factors: NT-proBNP and high sensitivity cardiac troponin.
‡One patient with values corresponding to IIIa during screening subsequently increased to IIIb on Cycle 1 Day 1.
§NYHA classification class I patients have no limitation during ordinary physical activity; class II patients have slight limitation during ordinary physical activity; class IIIA patients have symptoms with less than ordinary physical activity; class IIIb patients have symptoms with daily living activities, and class IV patients have symptoms at rest.[42] Patients with class IIb or IV disease were excluded from the study.

Table 2. Most common all-grade TEAEs and grade 3/4 TEAEs

	Patients (n = 28)	
	All-grade TEAEs (≥25%), n (%)	**Grade 3/4 TEAEs (>1 patient), n (%)**
Overall	28 (100)	20 (71.4)
Diarrhea	19 (67.9)	4 (14.3)
Fatigue	15 (53.6)	6 (21.4)
Peripheral edema	14 (50.0)	4 (14.3)
Anemia	13 (46.4)	4 (14.3)
Constipation	13 (46.4)	0
Dizziness	13 (46.4)	0
Lymphopenia	12 (42.9)	5 (17.9)
Nausea	12 (42.9)	0
Upper respiratory tract infection	11 (39.3)	1 (3.6)
Hyperglycemia	10 (35.7)	0
Insomnia	9 (32.1)	2 (7.1)
Dyspnea	9 (32.1)	0
Cough	8 (28.6)	0
Hypoalbuminemia	7 (25.0)	2 (7.1)
Hyponatremia	7 (25.0)	2 (7.1)
Hypokalemia	7 (25.0)	1 (3.6)
Aspartate aminotransferase increased	7 (25.0)	0
Thrombocytopenia	7 (25.0)	0
Fall	6 (21.4)	3 (10.7)
Cellulitis	4 (14.3)	2 (7.1)
Acute kidney injury	3 (10.7)	2 (7.1)
Pneumonia	3 (10.7)	3 (10.7)
Hypertension	2 (7.1)	2 (7.1)
Syncope	2 (7.1)	2 (7.1)

TEAE, treatment-emergent adverse event.

Table 3. Definitions of deep hematologic responses in AL Amyloidosis are evolving

	Complete response			Modified CR*	Stringent dFLC response*	Absolute iFLC response*
Parameter	**Gertz 2005[37]**	**Comenzo 2012[14]**	**Palladini 2012[53]**	**AMY3001 2019**	**Manwani 2019[44]**	**Muchtar 2019[43]**
Negative serum IFE	✓	✓	✓	✓	✓	✓
Negative urine IFE	✓	✓	✓	✓	✓	✓
Bone marrow plasma cells <5%	✓	Not required	Not required	Not required	Not required	Not required
FLC	Normal levels	Normal levels	Not required	iFLC <ULN	dFLC <10 mg/L	iFLC ≤20 mg/L
FLC ratio (normal)	✓	✓	✓	Not required	Not required	Not required

*Pending validation and international consensus agreement.

Figure legends

Figure 1. Swim lane plot of patients enrolled in the safety run-in portion of ANDROMEDA.

Patient disposition by hematologic response is shown for the 28 patients enrolled in the safety run-in portion of the study. Black ovals indicate partial response, light gray ovals indicate very good partial response, and white ovals indicate complete response. Dark gray rectangles indicate autologous stem cell transplant, and X indicates death. PR, partial response. VGPR, very good partial response. CR, complete response. A, autologous stem cell transplant. D, death.

Figure 2. Summary of overall best hematologic and organ responses.

Overall best response for hematologic responses **(A)** and organ responses **(B)**. Patients who met VGPR criteria and also had negative serum and urine immunofixation and normalization of involved FLC but with uninvolved FLC below the lower limit of normal (FLC ratio abnormal or normal) who therefore did not meet the criteria for CR were included in the mCR group. PR, partial response. VGPR, very good partial response. aCR, amyloidosis complete response. mCR, modified complete response. CR, complete response.

Figure 3. Reduction in dFLC levels.

Lowest dFLC level achieved while on the study.

Figure 1

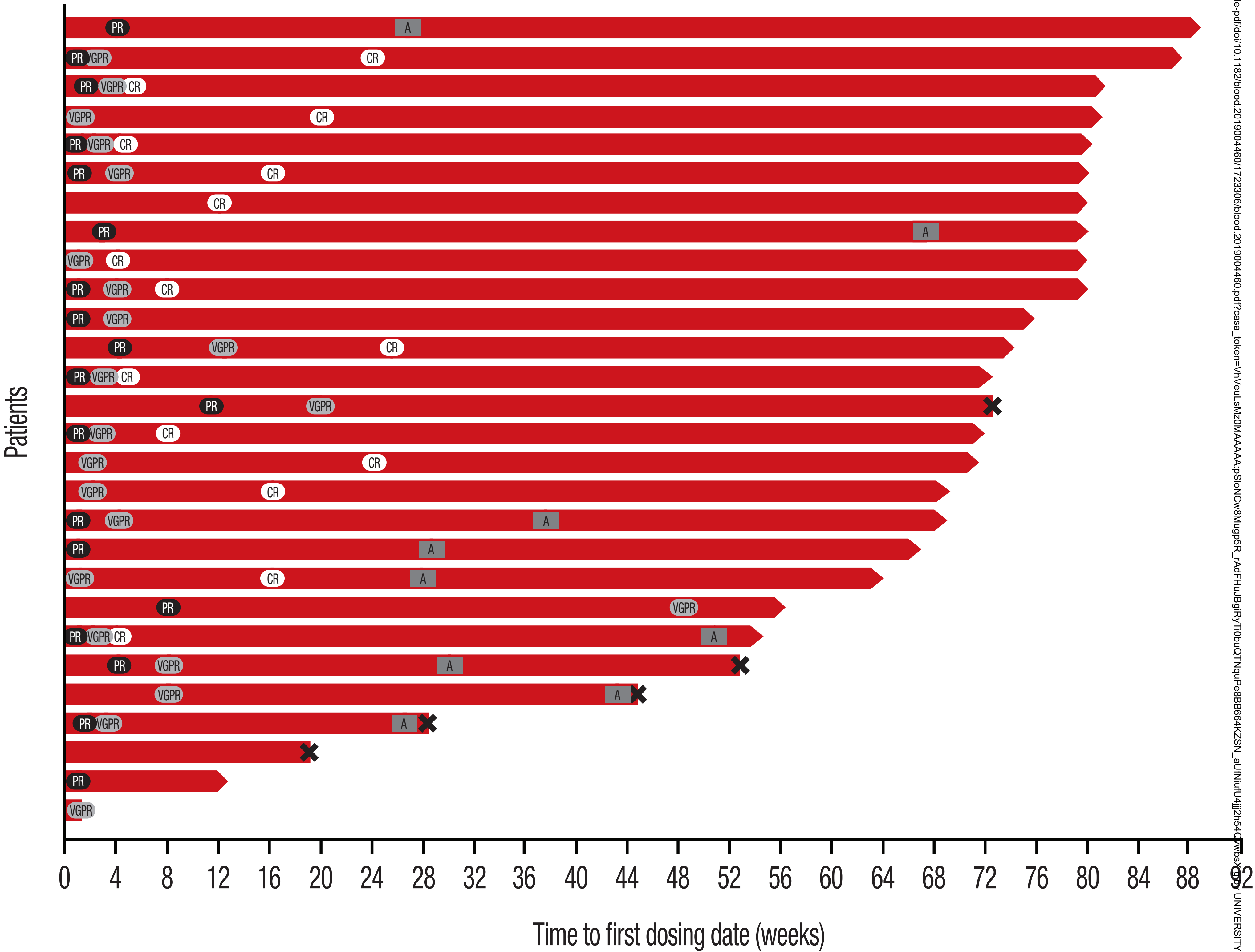
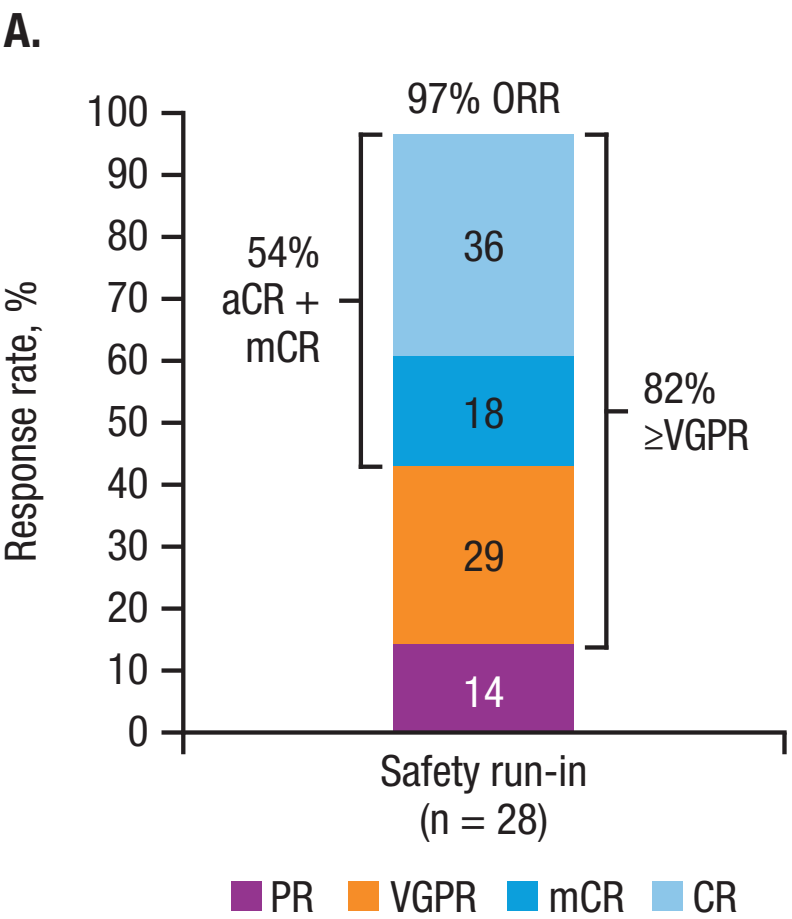


Figure 2



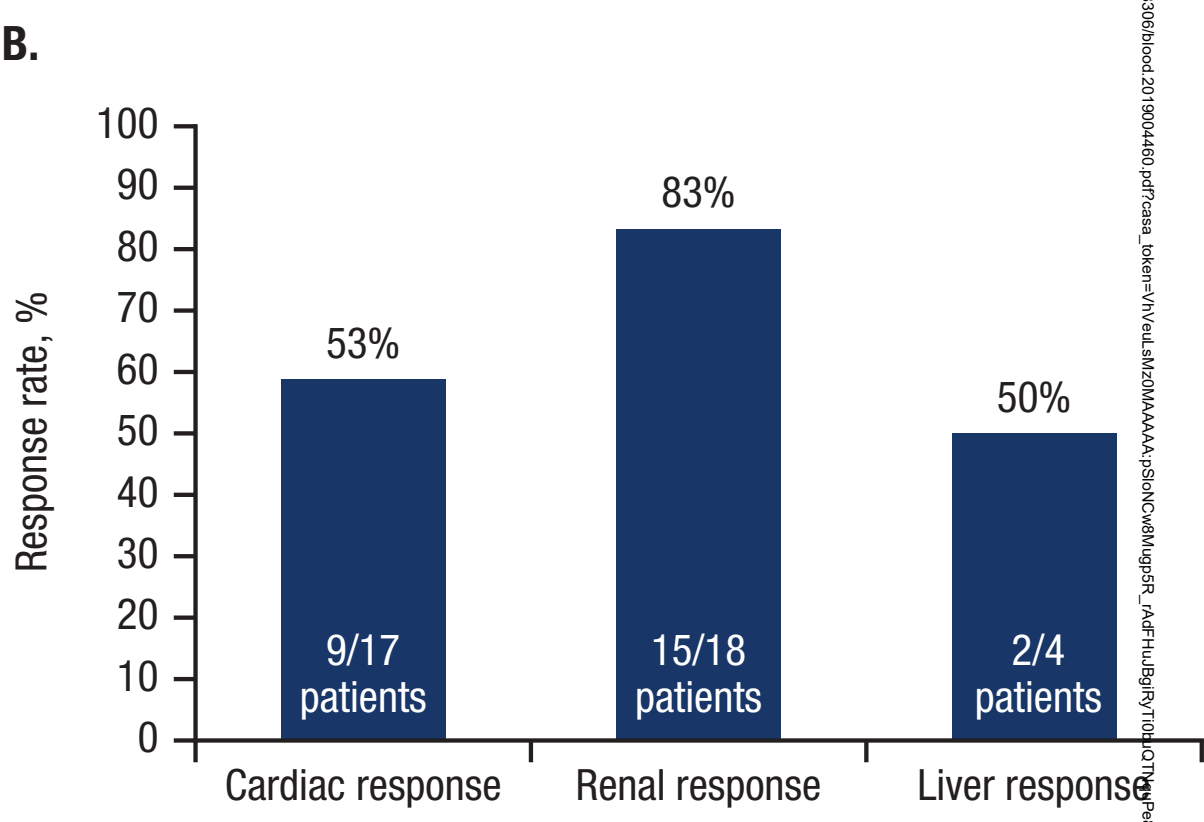


Figure 3