PS1318

Subcutaneous Daratumumab (DARA SC) + Cyclophosphamide, Bortezomib, and Dexamethasone (CyBorD) in Patients With Newly Diagnosed Amyloid Light Chain (AL) Amyloidosis: Safety Run-in Results of ANDROMEDA

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INTRODUCTION

- Systemic amyloid light chain (AL) amyloidosis is characterized by deposition of insoluble amyloid fibrils, which are derived from immunoglobulin (Ig) light chains produced by clonal CD38$^+$ plasma cells, into tissues and organs[1,2]
- AL amyloidosis is a rare disease, with approximately 4,000 new cases each year in the United States[3]
- Untreated patients have a median survival of 13 months from diagnosis[4]; while early diagnosis and treatment have recently decreased the rate of early mortality in the United States,[5] there remains an urgent need for development of more effective therapies
- Daratumumab is a human IgG1κ monoclonal antibody targeting CD38 with direct on-tumor mechanisms of action, including complement-dependent cytotoxicity,[6] antibody-dependent cellular cytotoxicity,[6] antibody-dependent cellular phagocytosis,[7] apoptosis,[8] and direct enzymatic inhibition[9] (**Figure 1**)
- Daratumumab also demonstrates an immunomodulatory mechanism of action and can induce lysis of myeloid-derived suppressor cells, regulatory B cells, and a subpopulation of regulatory T cells (CD4$^+$CD25$^+$CD127^{dim}) to promote T-cell activity[10] (**Figure 1**)
- Daratumumab (16 mg/kg intravenously [IV]) is approved as monotherapy and in combination with standard of care regimens for the treatment of patients with relapsed/refractory multiple myeloma (MM)[11-13]
- Recently, daratumumab 16 mg/kg IV in combination with bortezomib, melphalan, and prednisone was approved for the treatment of patients with newly diagnosed MM who are ineligible for autologous stem cell transplant[11]
- Daratumumab monotherapy demonstrated a tolerable safety profile and encouraging hematologic responses in patients with heavily treated AL amyloidosis,[14-16] providing rationale for further examination of daratumumab in AL amyloidosis
- We report the safety run-in findings of daratumumab plus cyclophosphamide, bortezomib, and dexamethasone (CyBorD) in patients with newly diagnosed AL amyloidosis in ANDROMEDA (ClinicalTrials.gov Identifier: NCT03201965)

CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis.
1. DARZALEX® (daratumumab) injection, for intravenous use [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2018. 2. Liszewski MK, et al. *Adv Immunol*. 1996;61:201-283. 3. Debets JM, et al. *J Immunol*. 1988;141(4):1197-1201. 4. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321. 5. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219. 6. Plesner T, et al. Presented at: ASH; December 8-11, 2012; Atlanta, GA. Abstract 73. 7. Krejcik J, et al. *Blood*. 2016;128(3):384-394. 8. Adams H, et al. Presented at: ASH; December 3-6, 2016; San Diego, CA. Abstract 4521. 9. Chiu C, et al. Presented at: ASH; December 3-6, 2016; San Diego, CA. Abstract 4531.

Figure 1. Daratumumab mechanism of action in multiple myeloma.

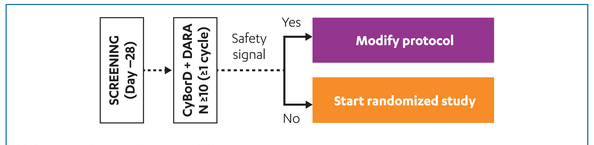
METHODS

Patients

- Eligible patients were ≥18 years of age with a histopathologic diagnosis of amyloidosis and measurable disease of AL amyloidosis (serum monoclonal protein ≥0.5 g/dL or serum free light chain ≥5.0 mg/dL with an abnormal kappa:lambda ratio or the difference between involved and uninvolved free light chains ≥5 mg/dL)
- Patients were required to have ≥1 organ impacted and an Eastern Cooperative Oncology Group performance status of 0 to 2
- Patients were excluded for the following:
  - Prior therapy for AL amyloidosis or MM, including medications that target CD38
  - Previous or current diagnosis of symptomatic MM
  - Grade 2 sensory or grade 1 painful peripheral neuropathy
  - New York Heart Association classification IIIB or IV heart failure

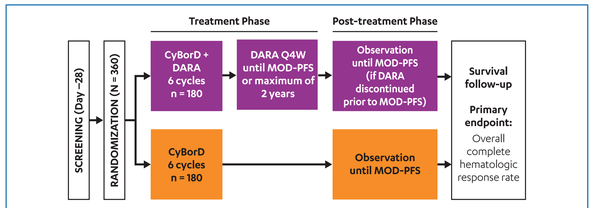
Study Design and Treatment

- ANDROMEDA (AMY3001) is a randomized, open-label, active-controlled, multicenter, phase 3 study with a safety run-in phase
- ≥10 patients were to be enrolled in the safety run-in cohort to determine the safety and tolerability of daratumumab in combination with CyBorD (**Figure 2**)
  - Daratumumab 1,800 mg and recombinant human hyaluronidase enzyme PH20 (rHuPH20 [30,000 U]; ENHANZE® drug delivery technology, Halozyme, Inc.) administered subcutaneously (SC) in a single, pre-mixed vial (15 mL) in combination with CyBorD (D 40 mg IV or orally [PO], followed by Cy 300 mg/m^2 IV or PO, followed by Bor 1.3 mg/m^2 SC)
- If no safety signal is observed after ≥1 cycle of treatment, particularly in regard to volume overload, approximately 360 patients are planned to be randomized 1:1 to receive CyBorD with or without daratumumab (**Figure 3**)



CyBorD, cyclophosphamide/bortezomib/dexamethasone; DARA, daratumumab.

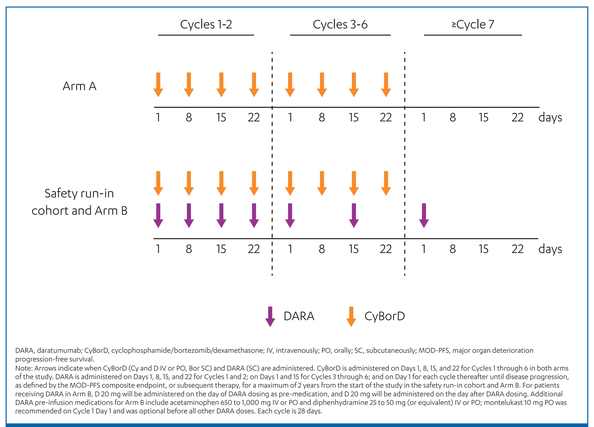
Figure 2. ANDROMEDA study design: safety run-in cohort.



CyBorD, cyclophosphamide/bortezomib/dexamethasone; DARA, daratumumab; Q4W, every 4 weeks; MOD-PFS, major organ deterioration progression-free survival.

Figure 3. ANDROMEDA study design: randomized study.

- The dosing schedule is summarized in **Figure 4** (28-day cycles)
  - Arm A: CyBorD alone weekly for Cycles 1 through 6
  - Arm B: CyBorD weekly for Cycles 1 through 6 plus daratumumab weekly for Cycles 1 and 2, every 2 weeks for Cycles 3 through 6, and then every 4 weeks until disease progression or subsequent therapy for a maximum of 2 years from the start of the study



DARA, daratumumab; CyBorD, cyclophosphamide/bortezomib/dexamethasone; IV, intravenously; PO, orally; SC, subcutaneously; MOD-PFS, major organ deterioration progression-free survival.
Note: Arrows indicate when CyBorD (Cy and D IV or PO, Bor SC) and DARA (SC) are administered. CyBorD is administered on Days 1, 8, 15, and 22 for Cycles 1 through 6 in both arms of the study. DARA is administered on Days 1, 8, 15, and 22 for Cycles 1 and 2; on Days 1 and 15 for Cycles 3 through 6; and on Day 1 for each cycle thereafter until disease progression, as defined by the MOD-PFS composite endpoint, or subsequent therapy, for a maximum of 2 years from the start of the study in the safety run-in cohort and Arm B. For patients receiving DARA in Arm B, D 20 mg will be administered on the day of DARA dosing as pre-medication, and D 20 mg will be administered on the day after DARA dosing. Additional DARA pre-infusion medications for Arm B include acetaminophen 650 to 1,000 mg IV or PO and diphenhydramine 25 to 50 mg (or equivalent) IV or PO; montelukast 10 mg PO was recommended on Cycle 1 Day 1 and was optional before all other DARA doses. Each cycle is 28 days.

Figure 4. ANDROMEDA dosing schedule.

Assessments

- In the safety run-in phase, safety was assessed after ≥10 patients received ≥1 treatment cycle
- Dosing will be staggered ≥48 hours between patients to assess infusion-related reactions (IRRs)
- Preliminary efficacy (overall best hematologic response based on International Amyloidosis Consensus Criteria [IACC] guidelines) was assessed

RESULTS

Patients and Treatments

- A total of 25 patients received treatment; demographics and baseline characteristics are shown in **Table 1**
- Patients received a median (range) of 4 (1-7) treatment cycles with a median (range) treatment duration of 3.1 (0.2-5.8) months
  - The median (range) dose intensity of daratumumab was 5,400 (3,600-7,200) mg/cycle
  - The median (range) cumulative bortezomib and daratumumab dose was 33.0 (5.8-64.4) mg/m^2 and 19,800 (3,600-28,800) mg, respectively

Safety

- The most common (≥20%) treatment-emergent adverse events (TEAEs) are shown in **Table 2**
- Dyspnea and peripheral edema were reported in 3 (12%) patients and 9 (36%) patients, respectively
- 11 (44%) patients experienced grade 3/4 TEAEs and 5 (20%) patients experienced serious TEAEs
  - Most common (>1 patient) grade 3/4 TEAEs and all serious TEAEs are listed in **Table 3**
- IRRs occurred in 1 (4%) patient (all grade 1; **Table 4**); most IRRs occurred during Cycle 1 Day 1

Table 1. Demographics and Baseline Characteristics in the Safety Run-in Cohort

Characteristic	Patients (N = 25)
Age	
Median (range), years	68 (35-83)
<65, n (%)	10 (40)
≥65, n (%)	15 (60)
Male, n (%)	15 (60)
Race, n (%)	
White	24 (96)
Black/African American	1 (4)
ECOG performance status, n (%)	
≤1	22 (88)
2	3 (12)
Time from diagnosis	
Median (range), days	61 (16-157)
Involved organs	
Number, median (range)	2 (1-3)
≥2 organs, n (%)	15 (60)
Kidney, n (%)	15 (60)
Heart, n (%)	12 (48)
Mayo Clinic cardiac stage, n (%)	
I	6 (24)
II	14 (56)
IIIa	4 (16)
IIIb	1 (4)
Baseline creatinine clearance, n (%)	
N	24
≥60 mL/minute	17 (68)
<60 mL/minute	7 (28)

ECOG, Eastern Cooperative Oncology Group.

Table 2. Most Common (≥20%) All-grade TEAEs in the Safety Run-in Cohort

TEAEs, n (%)	Patients (N = 25)
Diarrhea	12 (48)
Peripheral edema	9 (36)
Nausea	8 (32)
Anemia	8 (32)
Lymphopenia	7 (28)
Fatigue	7 (28)
Constipation	7 (28)
Cough	6 (24)
Upper respiratory tract infection	6 (24)
Injection-site erythema	5 (20)
Hyperglycemia	5 (20)
Hypokalemia	5 (20)

TEAE, treatment-emergent adverse event.

Table 3. Most Common (>1 Patient) Grade 3/4 and All Serious TEAEs in the Safety Run-in Cohort

Grade 3/4 TEAEs, n (%)	Patients (N = 25)
Hypertension	2 (8)
Diarrhea	2 (8)
Anemia	2 (8)
Serious TEAEs, n (%)	
Anemia	1 (4)
Peripheral swelling	1 (4)
Cellulitis	1 (4)
Myopathy	1 (4)
Acute kidney injury	1 (4)

TEAE, treatment-emergent adverse event.

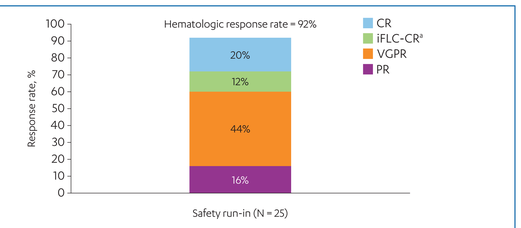
Table 4. IRRs in the Safety Run-in Cohort

IRRs, n (%)	Patients (N = 25)
Patients with IRRs[a]	1 (4)
Hypotension	1 (4)
Chest discomfort[b]	1 (4)
Cough[b]	1 (4)
Oropharyngeal pain[b]	1 (4)
Sneezing[b]	1 (4)

IRR, infusion-related reaction.
[a]One patient reported a grade 1 injection-site bruising that was considered to be an injection-site reaction.
[b]Occurred during Cycle 1 Day 1.

Preliminary Efficacy

- Except for 2 patients, all remaining patients demonstrated hematologic responses based on IACC Guidelines (**Figure 5**)



IACC, International Amyloidosis Consensus Criteria; CR, complete response; LLN, lower limit of normal; iFLC, involved free light chain; VGPR, very good partial response; PR, partial response.
[a]Patients with negative serum and urine immunofixation and normalization of involved FLC level; if uninvolved FLC level is below LLN and FLC ratio is abnormal or normal, patient will be assigned to iFLC-CR (involved FLC CR) response category.

Figure 5. Summary of overall best hematologic response based on IACC.

CONCLUSIONS

- **Daratumumab in combination with CyBorD is tolerable in patients with AL amyloidosis, with a low IRR rate and no new safety signals**
- **Preliminary efficacy demonstrated high rates of deep responses**
- **Based on the tolerability of daratumumab plus CyBorD in the safety run-in cohort, randomization into ANDROMEDA has begun**

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