PA-373

Subcutaneous Daratumumab + Bortezomib, Cyclophosphamide, and Dexamethasone in Asian Patients with Newly Diagnosed Light-chain (AL) Amyloidosis: Subgroup Final Analysis of the Phase 3 ANDROMEDA Study

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Key Takeaway

The ANDROMEDA study was designed to investigate the efficacy and safety of D-VCd in newly diagnosed patients with AL amyloidosis. Robust hematologic and organ responses as well as favorable survival outcomes in the Asian patients were observed, consistent with the overall population in the ANDROMEDA study, which further supports the use of D-VCd in Asian patients with newly diagnosed AL amyloidosis.

Conclusions

- The D-VCd elicited deeper and more rapid hematologic response compared with VCd in the Asian patients, consistent with the ANDROMEDA overall population.
- Higher cardiac and renal response rates were observed compared with VCd, consistent with the overall population in the ANDROMEDA study.
- Improved survival outcomes including MOD-PFS and OS were also observed, consistent with those in ANDROMEDA overall population.
- D-VCd demonstrated an acceptable safety profile with no new significant safety concerns in Asian patients that was generally consistent with the overall safety population from ANDROMEDA.

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Acknowledgments

The authors would like to acknowledge the patients participating in this study and their families, the staff members at the study sites, the data and safety monitoring committees, and the staff members who were involved in data collection and analyses. Medical writing support for the development of this poster, under the direction of the authors, was provided by Li Wang, of MIMS SHANGHAI LIMITED, funded by Johnson&Johnson, and complied with the Good Publication Practice 2022. Design and typeset support for the development of this poster, under the direction of the authors, was provided by MIMS SHANGHAI LIMITED, funded by Johnson&Johnson, and complied with the Good Publication Practice 2022. This study (ClinicalTrials.gov Identifier: NCT03201965) was sponsored by Johnson&Johnson.

Disclosures

Johnson&Johnson generative AI tool Evidence CoPilot was used to draft this abstract, authors reviewed, edited, and take full take responsibility for the content.

Introduction

- Systemic immunoglobulin light chain (AL) amyloidosis is a rare plasma cell disorder caused by clonal expansion of CD38+ plasma cells that produces immunoglobulin light chains which misfold and aggregate into insoluble amyloid fibrils and leads to organ dysfunction[1].
- In patients with newly diagnosed AL amyloidosis, the phase 3 ANDROMEDA study (NCT03201965) evaluated the efficacy and safety of subcutaneous DARA (DARA SC) plus bortezomib, cyclophosphamide, and dexamethasone (D-VCd)[2-3].
- To determine whether the efficacy and safety results of D-VCd in Asian patients with newly diagnosed AL amyloidosis are similar to the overall population, we performed the subgroup analysis of Asian patients from ANDROMEDA study.

Methods

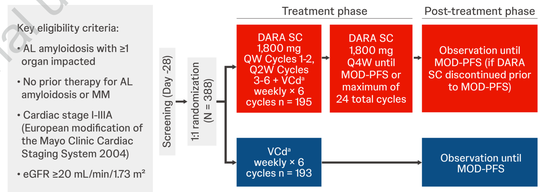
Study design and patients

- The study design of ANDROMEDA was illustrated in Figure 1.

Endpoints

- The primary endpoint was overall hematologic complete response (CR) rate. Key secondary endpoints included major organ deterioration progression free survival (MOD-PFS), major organ deterioration event free survival (MOD-EFS), organ response rate, organ response rate at 6 months, overall survival (OS), hematologic CR at 6 months, hematologic very good partial response (VGPR) or better rate, time to and duration of hematologic CR, and safety.

Figure 1: Study design of ANDROMEDA study



AL, light chain; MM, multiple myeloma; eGFR, estimated glomerular filtration rate; DARA, daratumumab; SC, subcutaneous; QW, weekly; Q2W, every 2 weeks; VCd, bortezomib/cyclophosphamide/dexamethasone; Q4W, every 4 weeks; MOD-PFS, major organ deterioration progression-free survival.
* Dexamethasone 40 mg IV or PO, followed by cyclophosphamide 300 mg/m² IV or PO, followed by bortezomib 1.3 mg/m² subcutaneous on Days 1, 8, 15, and 22 in every 28-day cycle for a maximum of 8 cycles.

Results

Baseline characteristics

- As of the cutoff date (14 February 2020), a total of 60 patients with AL amyloidosis were included in the Asian cohort.
- Baseline characteristics between two arms were well balanced in the Asian cohort and consistent with overall population. **(Table 1)**

Table 1: Baseline characteristics[a]

Characteristic	D-VCd N=29	VCd N=31
Age		
Median (range), y	62 (42-82)	68 (46-79)
Category, n (%)		
<65 years	17 (58.6)	10 (32.3)
≥65 years	12 (41.4)	21 (67.7)
Sex, Male, n (%)	17 (58.6)	21 (67.7)
ECOG PS, n (%)		
0	18 (62.1)	15 (48.4)
1	10 (34.5)	14 (45.2)
2	1 (3.4)	2 (6.5)
AL isotype, n (%)		
Lambda	22 (75.9)	26 (83.9)
Kappa	7 (24.2)	5 (16.1)
Time from diagnosis, Median (ranges), days	49 (11-236)	43 (11-304)
Involved organs		
Median (ranges)	2 (1-3)	2 (1-5)
Heart, n (%)	19 (65.5)	23 (74.2)
Renal, n (%)	18 (62.1)	17 (54.8)
Liver, n (%)	2 (6.9)	3 (9.7)
Other, n (%)	12 (41.4)	17 (54.8)
Cardiac stage, n (%)		
I	12 (41.4)	5 (16.1)
II	5 (17.2)	12 (38.7)
IIIA	12 (41.4)	12 (38.7)
IIIB	0	2 (6.5)
Renal stage, n (%)		
I	16 (55.2)	16 (51.6)
II	11 (37.9)	10 (32.3)
III	2 (6.9)	5 (16.1)
Creatinine clearance, n (%)		
<60 mL/min	14 (48.3)	10 (32.3)
≥60 mL/min	15 (51.7)	21 (67.7)

D-VCd, subcutaneous daratumumab/bortezomib/cyclophosphamide/dexamethasone; VCd, bortezomib/cyclophosphamide/dexamethasone; y, year; ECOG PS, Eastern Cooperative Oncology Group performance status; AL, light chain.
[a]Data from intent-to-treat population, defined as all randomized patients.

Patients disposition and exposure

- In the Asian cohort, the median time of follow-up time was 59.1 months. As of the cutoff date, a total of 16 patients had died, with 3 (10.3%) patients in D-VCd arm and 13 (41.9%) patients in VCd arm.
- The median duration of treatment was 21.32 (range: 0.99, 26.71) months with D-VCd and 5.29 (range: 0.03, 6.08) months with VCd. The median number of cycles received was 24 (range: 2.0, 24.0) with D-VCd and 5.29 (range: 1.0, 6.0) with VCd.

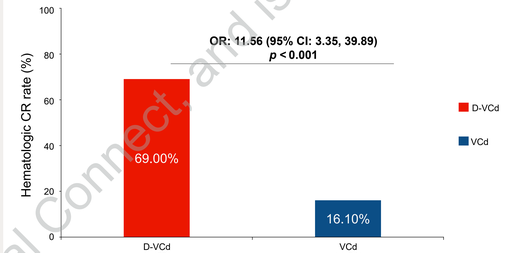
Hematologic CR rate

- The overall hematologic CR rate was substantially higher with D-VCd vs. VCd (69% vs. 16.1%, OR=11.56 [95% CI: 3.35, 39.89], p <0.0001). Similarly, a remarkably higher hematologic CR rate at 6 months was observed in the D-VCd arm compared with the VCd arm (58.6% vs. 9.7%, OR=13.22 [95% CI: 3.26, 53.69]; p <0.0001). Among patients who achieved hematologic CR, the median time to hematologic CR was 74.5 days with D-VCd and 113 days with VCd. **(Figure 2)**

Organ response rate

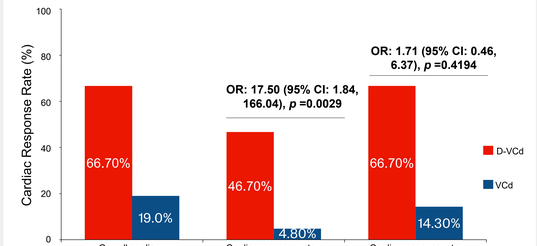
- The overall cardiac response rate in the D-VCd arm was 66.7% vs. 19.0% in the VCd arm. The cardiac response rate at 6 months was substantially higher with D-VCd vs. VCd (46.7% vs. 4.8%, OR=17.50 [95% CI: 1.84, 166.04], p =0.0029). Similar results of the cardiac response rate at 12 months was observed (66.7% vs. 14.3%, OR=12.0 [95% CI: 2.36, 61.05], p =0.0013). The median time to cardiac response was reached earlier in the D-VCd arm compared with the VCd arm (3.78 months vs. 6.03 months). **(Figure 3)**

Figure 2: Overall hematologic CR rate in the Asian cohort[a]



CR, complete response; OR, odds ratio; CI, confidence interval; D-VCd, subcutaneous daratumumab/bortezomib/cyclophosphamide/dexamethasone; VCd, bortezomib/cyclophosphamide/dexamethasone.
[a]Data from intent-to-treat population, defined as all randomized patients.

Figure 3: Cardiac response rate in the Asian cohort[a]



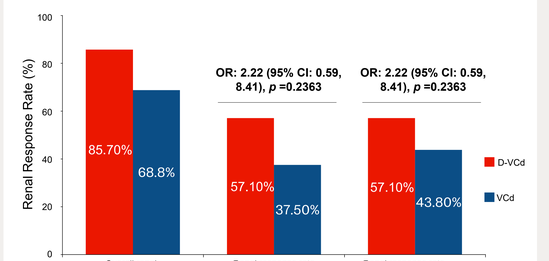
OR, odds ratio; CI, confidence interval; D-VCd, subcutaneous daratumumab/bortezomib/cyclophosphamide/dexamethasone; VCd, bortezomib/cyclophosphamide/dexamethasone.
[a]Data from intent-to-treat population, defined as all randomized patients. *During the study.

- The overall renal response rate in the D-VCd arm was 85.7% vs. 68.8% in the VCd arm. The renal response rate at 6 months was higher with D-VCd vs. VCd (57.10% vs. 37.5%, OR=2.22 [95% CI: 0.59, 8.41], p =0.2363). Similar results of the renal response rate at 12 months was observed (57.1% vs. 43.8%, OR=1.71 [95% CI: 0.46, 6.37], p =0.4194). The median time to renal response in the D-VCd arm was 1.97 months vs. 2.83 months in the VCd arm. **(Figure 4)**

Survival outcomes

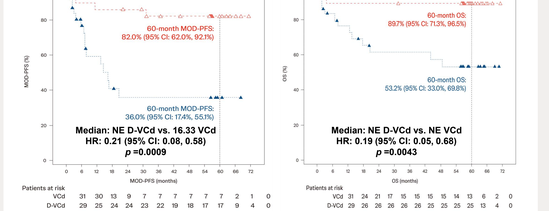
- The median MOD-PFS time in the D-VCd arm was not estimable (NE) vs. 16.33 months (HR=0.21 [95% CI: 0.08, 0.58], p =0.0009) in the VCd arm. A higher 60-month MOD-PFS rate was observed with D-VCd vs. VCd (82.0% [95% CI: 62.0%, 92.1%] vs. 36.0% [95% CI: 17.4%, 55.1%]). **(Figure 5)**
- The median OS time was NE in either arm (NE vs. NE, HR=0.19 [95% CI: 0.05, 0.68], p =0.0043). A higher 60-month survival rate was observed with D-VCd vs. VCd (89.7% [95% CI: 71.3%, 96.5%] vs. 53.2% [95% CI: 33.0%, 69.8%]). **(Figure 5)**

Figure 4: Renal response rate in the Asian cohort[a]



OR, odds ratio; CI, confidence interval; D-VCd, subcutaneous daratumumab/bortezomib/cyclophosphamide/dexamethasone; VCd, bortezomib/cyclophosphamide/dexamethasone.
[a]Data from intent-to-treat population, defined as all randomized patients. *During the study.

Figure 5: Kaplan-Meier plot for MOD-PFS A) and OS B) in the Asian cohort[a]



MOD-PFS, major organ deterioration progression free survival; OS, overall survival; D-VCd, subcutaneous daratumumab/bortezomib/cyclophosphamide/dexamethasone; VCd, bortezomib/cyclophosphamide/dexamethasone; NE, not estimable; HR, hazard ratio; CI, confidence interval.
[a]Data from intent-to-treat population, defined as all randomized patients.

Safety

- The safety profile of D-VCd and VCd in Asian patients was generally consistent with the overall safety population.
- The most common (≥10%) grade 3/4 treatment-emergent adverse events (TEAEs) of interest were lymphopenia, neutropenia and diarrhoea. The incidence of grade 3/4 infections and infestations was 12.9% with D-VCd vs. 27.6% with VCd.
- Serious AEs occurred in 37.9% of patients with D-VCd vs. 45.2% with VCd. The most common serious AE was cardiac failure (D-VCd,10.3% vs. VCd, 12.9%).
- TEAEs leading to treatment discontinuation occurred in 1 patient in each arm. TEAEs leading to death occurred in 3 (10.3%) patients with D-VCd vs. 5 (16.1%) patients with VCd.
- No patients experienced local injection injection-site reactions.

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1. Merlini G, et al. Nat Rev Dis Primers. 2018;4(1):38. 2. Palladini G, et al. Blood. 2020;136(1):71-80. 3. Kastritis E, et al. N Engl J Med. 2021;385(1):46-58.

Systemic AL Amyloidosis

Presented by Prof. Jin Lu at 22nd International Myeloma Society (IMS) Annual Meeting; September 17-20, 2025; Toronto, Canada