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Daratumumab + Bortezomib, Lenalidomide, and Dexamethasone vs Bortezomib, Lenalidomide, and Dexamethasone in Transplant-Ineligible/ Transplant-Deferred Newly Diagnosed Multiple Myeloma: Phase 3 CEPHEUS Trial Cytogenetic Subgroup Analysis

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Key Takeaway

The results of this cytogenetic subgroup analysis support use of DVRd for TIE or TD NDMM regardless of cytogenetic risk status

Conclusions

In CEPHEUS, DVRd consistently improved the key response outcomes of MRD negativity and PFS in patients with cytogenetic standard risk and revised cytogenetic standard risk

Consistent with associations between HRCAs and worse prognoses,[1] MRD and PFS outcomes trended lower in high- vs standard-risk groups in both treatment arms

In the protocol-defined high-risk group, despite comparable MRD-negative ≥CR rates with DVRd vs VRd, PFS trended toward improvement with DVRd, supporting use of DVRd for TIE or TD NDMM across cytogenetic risk groups

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Disclosures
NJB reports a consulting/advisory role for AbbVie, Amgen, BMS/Celgene, Genentech, GSK, Johnson & Johnson, Karyopharm, Kite (a Gilead company), Novartis, Pfizer, Roche, Sanofi, and Takeda; has received honoraria from AbbVie, Amgen, BMS/Celgene, Genentech, GSK, Johnson & Johnson, Karyopharm, Kite (a Gilead company), Novartis, Pfizer, Roche, Sanofi, and Takeda; and has received research funding from Johnson & Johnson and Pfizer.

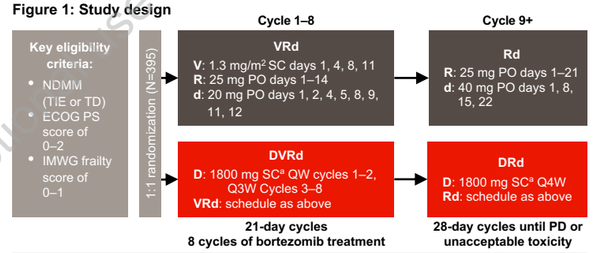
Introduction

- High-risk cytogenetic abnormalities (HRCAs) are associated with poor survival outcomes in patients with multiple myeloma[1]
- The phase 3 CEPHEUS trial in patients with transplant-ineligible (TIE) or transplant-deferred (TD) newly diagnosed multiple myeloma (NDMM) showed that the addition of daratumumab subcutaneous (SC) to bortezomib, lenalidomide, and dexamethasone (VRd)[2]:
  - Significantly improved rates of overall and sustained minimal residual disease (MRD) negativity with complete response (CR) or better in the intent-to-treat (ITT) population
  - Significantly improved progression-free survival (PFS) in the ITT population (hazard ratio [HR] 0.57; *P*=0.0005)
  - Had a safety profile consistent with each individual drug's profile
- Daratumumab previously showed benefit in patients with NDMM with HRCAs, including gain (3 copies) or amplification (amp; ≥4 copies) of chromosome 1q21 (1q)[3-5]
- In this post hoc analysis, we report outcomes in cytogenetic risk subgroups in CEPHEUS

Methods

- CEPHEUS is a randomized, open-label, multicenter, phase 3 trial (**Figure 1**)
- Bone marrow MRD was assessed by next-generation sequencing (clonoSEQ®; Adaptive Biotechnologies)
  - Overall MRD-negativity rate was defined as the proportion of patients who achieved both ≥CR and MRD-negative status; sustained MRD negativity was defined, in patients with ≥CR, as MRD negativity at 2 assessments without any MRD positivity in between
- Fluorescence in situ hybridization was used to detect the following HRCAs: del(17p), t(4;14), t(14;16), and gain(1q) or amp(1q)
- Protocol-defined HRCAs were del(17p), t(4;14), and t(14;16); revised HRCAs were del(17p), t(4;14), t(14;16), and gain/amp(1q)
  - Patients with cytogenetic standard risk, per protocol, were negative for all protocol-defined HRCAs; those with revised cytogenetic standard risk were negative for all revised HRCAs
  - Patients with cytogenetic high risk, per protocol, were positive for any protocol-defined HRCA; those with revised cytogenetic high risk were positive for any revised HRCA
- Additional cytogenetic risk subgroups assessed were those with gain(1q), amp(1q), 1 revised HRCA, ≥2 revised HRCAs, isolated gain(1q), isolated amp(1q), isolated gain/amp(1q), and gain/amp(1q) plus ≥1 HRCA

Figure 1: Study design



Primary endpoint: Overall MRD (≥CR) negativity
Key secondary endpoints: PFS; sustained MRD (≥CR) negativity (≥12 months)

[a]Daratumumab 1800 mg co-formulated with recombinant human hyaluronidase PH20 ([rHuPH20; 2000 U/mL; ENHANZE® drug delivery technology; Halozyme, Inc., San Diego, CA, USA). D, daratumumab; d, dexamethasone; DRd, daratumumab, lenalidomide, and dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; IMWG, International Myeloma Working Group; PD, disease progression; PO, orally; Q3W, every 3 weeks; Q4W, every 4 weeks; QW, weekly; R, lenalidomide; V, bortezomib.

Results

Study Population

- 395 patients were randomized 1:1 to receive DVRd (n=197) or VRd (n=198)
- HRCAs were generally balanced between treatment arms (**Table**)
  - Other baseline characteristics, which were previously described,[2] were also well balanced
- At median 58.7 months of follow-up, median treatment duration was 59.0 cycles with DVRd vs 37.0 cycles with VRd

Table: Baseline cytogenetic risk[a]

Characteristic, n (%)	DVRd (n=197)	VRd (n=198)
Protocol-defined standard risk	149 (75.6)	149 (75.3)
Protocol-defined high risk	25 (12.7)	27 (13.6)
Revised standard risk	94 (47.7)	90 (45.5)
Revised high risk	83 (42.1)	84 (42.4)
Gain(1q)	43 (21.8)	48 (24.2)
Amp(1q)	31 (15.7)	20 (10.1)
1 revised HRCA	66 (33.5)	72 (36.4)
≥2 revised HRCAs	17 (8.6)	12 (6.1)
Isolated gain(1q)	35 (17.8)	40 (20.2)
Isolated amp(1q)	23 (11.7)	17 (8.6)
Isolated gain/amp(1q)	58 (29.4)	57 (28.8)
Gain/amp(1q) plus ≥1 HRCA	16 (8.1)	11 (5.6)

[a]New cytogenetic risk criteria not available at time of analyses.

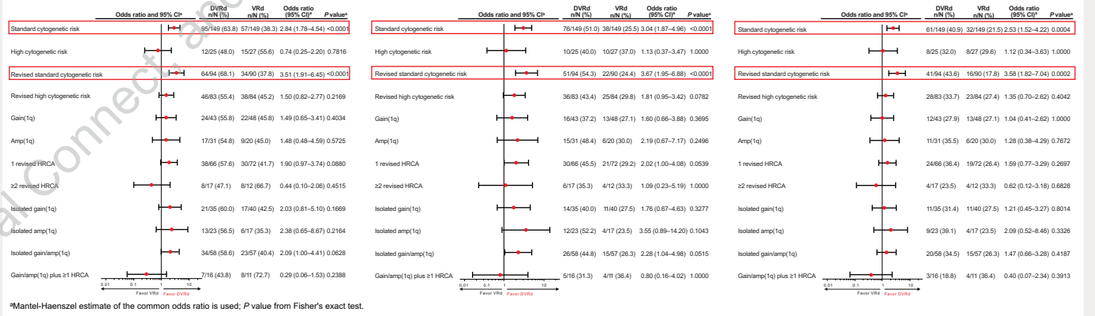
Overall and Sustained MRD-Negative ≥CR

- Overall and sustained (≥12- and ≥24-month) MRD-negative ≥CR rates at 10^{-5} were higher with DVRd vs VRd in cytogenetic standard-risk groups (**Figure 2**)
- In subgroups with HRCAs, at 10^{-5}, DVRd vs VRd led to generally favorable treatment effects for DVRd for overall MRD-negativity ≥CR rate (**Figure 2A**) and sustained (≥12- and ≥24-month) MRD-negative ≥CR rate (**Figure 2B**, **2C**), with some exceptions; in the protocol-defined high-risk group:
  - This, and an unexpectedly high overall MRD-negative ≥CR rate with VRd, was potentially due to small sample sizes (**Figure 2A**); furthermore, due to a shorter median treatment duration in the DVRd arm (27.0 vs 35.5 cycles, respectively), there was a higher rate of missing postbaseline samples (24.0% vs 14.8%); therefore, patients in the DVRd arm had fewer opportunities to achieve or be tested for MRD negativity
- Results at 10^{-6} were similar to those at 10^{-5} except (**Figure 3**):
  - Higher overall MRD-negative ≥CR rates with DVRd vs VRd in the 1 revised HRCA, isolated amp(1q), and isolated gain/amp(1q) groups (**Figure 3A**)
  - Higher ≥12-month sustained MRD-negative ≥CR rates at 10^{-6} with DVRd vs VRd in the isolated gain/amp(1q) group (**Figure 3B**)

PFS

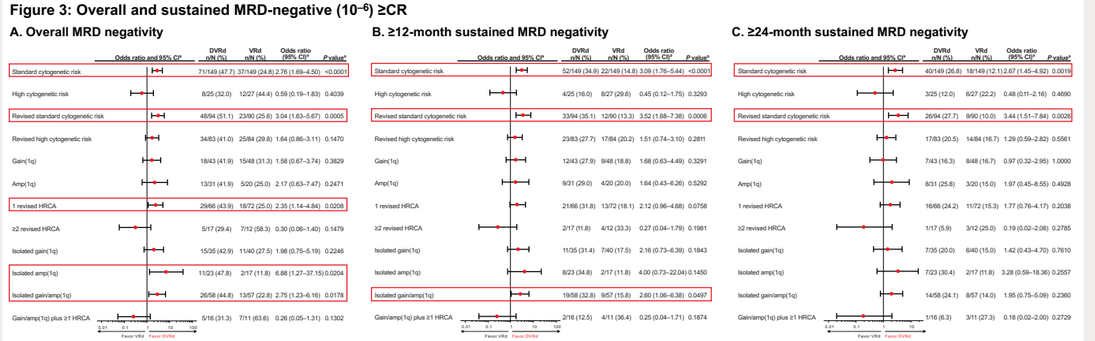
- In protocol-defined and revised standard-risk groups, DVRd reduced the risk of PD/death vs VRd by 39% and 46%, respectively; PFS trended to favor DVRd vs VRd in the protocol-defined and revised cytogenetic high-risk groups (**Figure 4A**, **4B**)
- Among MRD-negative (10^{-5}) ≥CR revised cytogenetic standard-risk subpopulations, DVRd reduced risk of PD/death vs VRd by 37% (HR, 0.63; 95% CI, 0.26–1.52; *P*=0.3003)
- There was a trend toward improved PFS with DVRd vs VRd in MRD-negative (10^{-5}) ≥CR patients with protocol-defined high-risk cytogenetics (**Figure 4C**) and a trend favoring DVRd vs VRd for PFS in MRD-negative (10^{-5}) ≥CR patients with revised high-risk cytogenetics (HR, 0.71; 95% CI, 0.32–1.58; *P*=0.3995)

Figure 2: Overall and sustained MRD-negative (10^{-5}) ≥CR



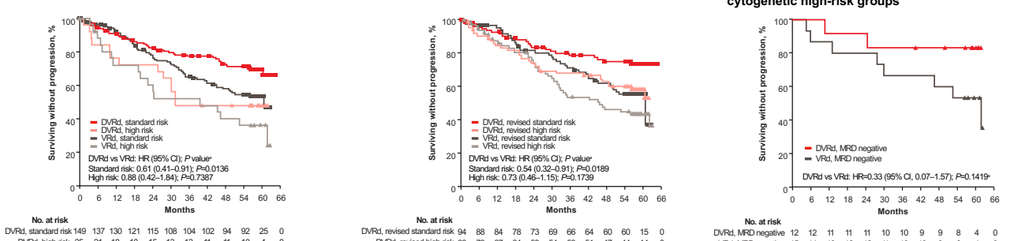
[a]Mantel-Haenszel estimate of the common odds ratio is used; *P* value from Fisher's exact test.

Figure 3: Overall and sustained MRD-negative (10^{-6}) ≥CR



[a]Mantel-Haenszel estimate of the common odds ratio is used; *P* value from Fisher's exact test.

Figure 4: PFS in cytogenetic risk subgroups



[a]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable; *P* value from the unstratified log-rank test.

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Multiple Myeloma

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