Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRD) Induction, Autologous Transplantation and MRD Response-Adapted Consolidation in Newly Diagnosed Multiple Myeloma

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INTRODUCTION

The CD38-targeting MoAb daratumumab when added to PI, IMiD or PI+ IMiD combinations increases the depth and duration of responses in NDMM, including patients treated with AHCT.

Carfilzomib, a second generation, irreversible PI, is superior to bortezomib in RRMM and, when combined with Rd, leads to high rates of ≥VGPR in NDMM.

While responses are heterogeneous, treatment combinations have traditionally been developed with fixed number of cycles, not accounting for kinetics or depth of response

Response-adapted therapy for achievement of MRD (-) status has not been formally tested.

Natural history of patients with confirmed MRD (-) responses managed without maintenance has not been described

OBJECTIVE

To test the safety and activity of Dara-KRd in patients with NDMM and the feasibility of measurable residual disease (MRD)-guided post autologous transplantation (AHCT) consolidation and treatment-free observation with MRD-surveillance (TREFOMS) upon achievement of confirmed MRD negative status.

METHODS

Key eligibility:NDMM with measurable disease; Untreated (up to 1 cycle of VCD allowed); No age limit; ECOG 0-2; CrCl ≥ 40 ml/min; No significant cardiopulmonary disease, concomitant or recent malignancy

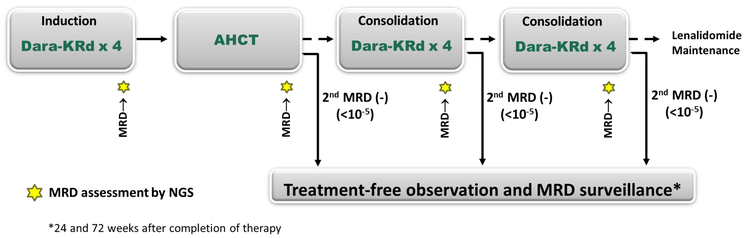
Primary Endpoint

- Rate of MRD(-) responses (<10^{-5}) utilizing NGS (clonoSEQ®)in patients treated with Dara-KRd induction, AHCT, and MRD-based response-adapted Dara-KRd consolidation.

Key Secondary/Exploratory endpoints

- Toxicity of Dara-KRd
- Frequency of imaging plus MRD (-) CR
- MRD (-) rates by NGS with threshold of 10^{-6}
- Outcomes of observation without maintenance upon confirmed MRD (-)

Dara-KRd: Daratumumab 16 mg/m^2 days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6); Carfilzomib (20) 56 mg/m^2 Days 1,8,15; Lenalidomide 25 mg Days 1-21; Dexamethasone 40mg PO Days 1,8,15,22



*24 and 72 weeks after completion of therapy

RESULTS

101 patients recruited, 82 completed induction, 63 completed post AHCT assessment (data cut Feb 2020)

Patient characteristics

- Median age: 61 years (range 35-79) years,
- 19% ISS 3,
- 29% have high-risk chromosomal abnormalities [del17p, t(4;14) or t(14;16)].
- 96% have MRD trackable by clonoSEQ®.

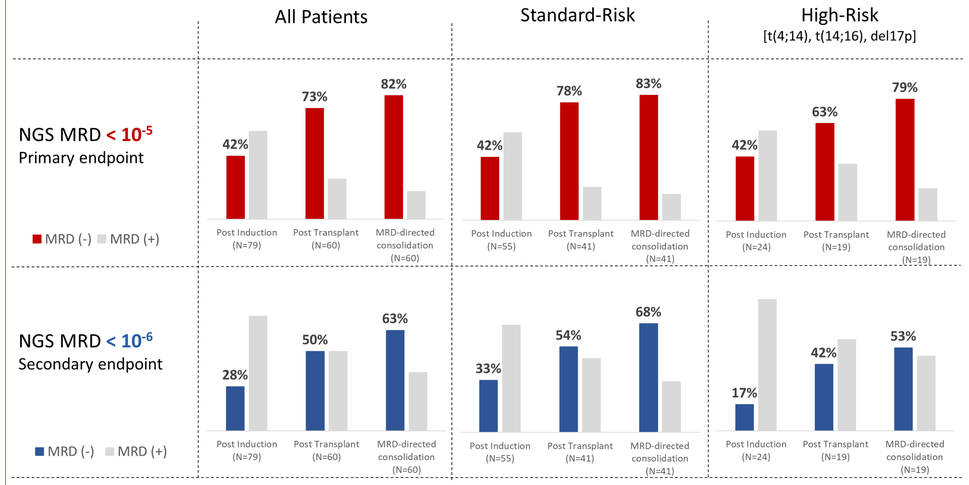
Most common grade 3 and 4 AEs were neutropenia (25%), lymphopenia (23%), infection (12%) and anemia (11%).

There were two deaths without progression (metapneumovirus pneumonia and sudden death, both after AHCT and before consolidation) and 1 progression.

IMWG traditional response

- 91% ≥VGPR after induction
- 92% ≥CR post AHCT and MRD-guided consolidation

None of the 40 patients who have so far achieved confirmed MRD negative status and entered TREFOMS had progression or resurgence of MRD (follow up 0.7-15.3 months).



CONCLUSIONS

- Dara-KRd is a safe regimen with rapid responses and unprecedented rates of MRD negative responses in NDMM.
- NGS MRD-based, response adapted therapy is feasible in ~96% of patients in multi center setting.
- Intense, quadruplet therapy and achievement of confirmed MRD (-) CR may enable safe transition to observation/MRD surveillance and reduce the physical and financial burden of continuous therapy.
- Accrual is continuing and will reach 123 patients to further inform outcomes by cytogenetic subsets

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