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Blood 142 (2023) 3382–3383

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

Phase II Trial of Daratumumab, Bortezomib, Lenalidomide and Dexamethasone in High-Risk Smoldering Multiple Myeloma

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Background: Daratumumab, bortezomib, lenalidomide and dexamethasone (D-RVD) has shown high rates of minimal residual disease (MRD) negativity in newly-diagnosed multiple myeloma (MM) and is now a standard regimen in transplant-eligible patients. Lenalidomide has shown to delay progression in patients with high-risk smoldering multiple myeloma (HR-SMM) and curative intent trials with carfilzomib-based therapy and stem cell transplantation have been recently reported in HR-SMM leading to deep responses but with concern for treatment-related toxicities. Thus, we proposed to examine the activity and safety of fixed duration D-RVD in patients with HR-SMM, with MRD-adaptive duration of therapy.

Methods: This is a phase II, open-label study evaluating D-RVD in HR-SMM. Eligibility criteria includes HR-SMM per Mayo 2018 "20-2-20" model and other previously established criteria including Mayo 2008 criteria, PETHEMA criteria, evolving type of SMM, and high-risk FISH.

Treatment with D-RVD is 2 years (24 cycles) with daratumumab subcutaneous (SQ) per standard dose and schedule, bortezomib 1.3mg/m2 SQ on days 1, 8, 15 for cycles 1-6 then biweekly until completion of cycle 24, lenalidomide 25mg on days 1-21 for cycles 1-6 followed by 15mg d1-21 from cycles 7-24 with weekly low dose dexamethasone. All eligible patients undergo stem cell collection after 6 cycles of therapy. The primary objective is rate of MRD-negativity at 2 years. Secondary objectives include PFS, ORR, and safety.

In part 2 of the study, patients that are MRD-positive after 2 years of treatment will be randomized to observation vs continued therapy with daratumumab and lenalidomide for an additional 24 months. The primary objective of part 2 is rate of MRD conversion from positive to negative.

Results: At the time of data cut off in May 2023, 38 patients have been enrolled to part 1 with a median follow up of 18 months. The median age is 62 years old (range 36-77) with 23 females (61%) and 15 males (39%). The median plasmacytosis of enrolled patients was 20%, with median M-protein of 2.17 g/dL and median FLC ratio of 8.1. Twenty-four patients (62%) had at least one high-risk FISH abnormality (fifteen with 1q gain, four with t(4;14), one with t(14;16) and one with del 17p). Eight patients (21%) had more than one high-risk FISH abnormality.

Most common grade 3 toxicities included neutropenia (13%), ALT increased (8%), and diarrhea (8%). Upper respiratory infections occurred in 61% of patients but were mostly low-grade (COVID-19 infection in 11 patients, 1 with grade 3). No patients discontinued therapy due to toxicity.

Of the 35 patients that completed at least 2 cycles of therapy, the ORR is 100% with 43% CR, 34% VGPR and 17% PR with responses deepening over time. Seventy-seven percent of patients achieved VGPR or greater. MRD was evaluable in 22 patients at 6 months with MRD negativity rate of 59% and 14% at thresholds of 10^{-5} and 10^{-6}, respectively. At 12 months, 20 patients were MRD-evaluable with 65% and 20% achieving MRD negativity at $10^{-5}$and 10^{-6}, respectively. Of the 10 MRD-evaluable patients at 24 months, 60% were MRD negative at 10^{-5} and 40% at 10^{-6}. No patients have progressed on treatment. Stem cell collection was successful in all eligible patients with average stem cell yield of 5.53×10^{6} CD34+ cells/kg.

Conclusions: D-RVD in HR-SMM demonstrates significant activity, including a 100% ORR and high rates of MRD-negative disease, preventing progression to overt myeloma.

Disclosures Nadeem: *GPCR Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *GSK:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Mo:** *AbbVie, BioLine, GSK, Janssen, Karyopharm, Pfizer, Pharmacyclics, Sanofi, Spectrum, Takeda:* Consultancy; *AbbVie, Janssen:* Membership on an entity's Board of Directors or advisory committees. **O'Donnell:** *Janssen:* Honoraria; *Takeda:* Consultancy; *BMS:* Honoraria; *Sanofi:* Honoraria. **Sperling:** *Novartis:* Consultancy; *Roche:* Consultancy. **Hartley-Brown:** *Pfizer:* Consultancy, Honoraria; *Bristol Myers Squibb/Celgene:* Consultancy, Honoraria; *GlaskoSmith Kline:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria; *Sanofi:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *Karyopharm:* Consultancy, Honoraria. **Midha:** *Abbvie:* Current equity holder in publicly-traded company; *Pfizer:* Consultancy. **Anderson:** *Dynamic Cell Therapies:* Current equity holder in private company, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees; *Window, Starton:* Current equity holder in private company, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees; *NextRNA:* Current equity holder in private company; *Pfizer, Janssen, Astrazeneca, Daewoong, Amgen, Starton, OncoPep, Precision Biosciences, Window Therapeutics, Mana Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Oncopep:* Current equity holder in private company, Current holder of *stock options* in a privately-held company; *C4 Therapeutics, Raqia, NextRNA,Dynamic Cell Therapy:* Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees. **Richardson:** *Takeda:* Research Funding; *GSK:* Consultancy; *AstraZeneca Pharmaceuticals LP, Bristol-Myers, Squibb Company, Celgene Corporation, GlaxoSmithKline, Janssen Biotech Inc, Karyopharm Therapeutics, Oncopeptides, Sanofi, Secura Bio, Takeda Pharmaceuticals USA Inc;:* Consultancy; *Sanofi:* Consultancy; *Bristol Myers Squibb:* Consultancy, Other: Contracted research, Research Funding; *Karyopharm:* Consultancy, Research Funding; *Oncopeptides:* Consultancy, Research Funding. **Ghobrial:** *Amgen:* Consultancy; *Sanofi:* Consultancy, Honoraria; *Vor Biopharma:* Ended employment in the past 24 months, Honoraria, Speakers Bureau; *Oncopeptides:* Consultancy; *Janssen:* Consultancy, Honoraria; *GlaxoSmithKline:* Consultancy, Honoraria; *Disc Medicine:* Other: Spouse is Chief Medical Officer and holds equity in the company; *Takeda:* Consultancy, Honoraria; *Window Therapeutics:* Consultancy; *Janssen:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria; *Huron Consulting:* Consultancy; *Regeneron:* Consultancy, Honoraria; *Bristol-Myers Squibb:* Consultancy, Honoraria; *Adaptive:* Honoraria; *10x Genomics:* Honoraria; *Pfizer:* Consultancy, Honoraria; *Menarini Silicon Biosystems:* Consultancy, Honoraria; *Aptitude Health:* Consultancy; *The Binding Site:* Consultancy.

https://doi.org/10.1182/blood-2023-177947