4671 A Phase II Study of Isatuximab, Once Weekly Carfilzomib, Lenalidomide, Dexamethasone, in Newly Diagnosed, Transplant-Eligible Multiple Myeloma (The SKylaRk Trial)

Program: Oral and Poster Abstracts
Session: 651. Multiple Myeloma and Plasma Cell Dyscrasias: Basic and Translational: Poster III
Hematology Disease Topics & Pathways:
Research, clinical trials, Clinical Research, Plasma Cell Disorders, Combination therapy, Diseases, Therapies, Lymphoid Malignancies
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Background:
Clinical data support the combination of a CD38 monoclonal antibody, an immunomodulatory drug, a proteasome inhibitor, and a glucocorticoid for the treatment of newly diagnosed multiple myeloma (NDMM). Isatuximab (Isa) is approved in combination with carfilzomib and dexamethasone (dex) for relapsed, refractory MM based on the results of the IKEMA study, as well as with pomalidomide and dex based upon ICARIA and is now being explored in novel combinations in the newly diagnosed setting. Our study evaluated the addition of isa to weekly carfilzomib (K), lenalidomide (len), and dex in all-risk, transplant-eligible patients with NDMM and stratifies maintenance based on cytogenetic risk.

Study Design and Methods:
Phase II study of isa-KRd in 50 transplant-eligible NDMM patients (NCT04430894). All patients received 4 cycles of isa-KRd followed by stem cell collection with option of upfront versus deferred stem cell transplant (SCT). Upfront SCT patients received 2 additional cycles then maintenance. Deferred SCT patients received 4 additional cycles then maintenance. Each 28-

day cycle consisted of isa 10 mg/kg iv weekly cycles 1-2, Q2 weeks cycles 3-6, then Q4 weeks; K (20 mg/m2 cycle 1, day 1 only) 56 mg/m2 iv days 1, 8, 15; len 25 mg po days 1-21; and dex 20 mg po days 1, 2, 8, 9, 15, and 16 (and days 22, 23 cycles 1-2).

For maintenance, standard-risk received len 10 mg po days 1-21 and high-risk (del 17p, gain 1q, t(4:14), t(14;16), t(14;20)) isa 10 mg/kg iv day 1; K 56 mg/m2 iv days 1, 15; len 10 mg po days 1-21.

Main Outcomes and Measures:
Primary end point was complete response (CR + stringent CR) rate after 4 cycles by the IMWG response criteria. Secondary endpoints included safety and tolerability; minimal residual disease (MRD), progression-free survival (PFS), and overall survival (OS) rates, quality of life, body composition, and T cell repertoire.

Results:
Fifty patients enrolled between August 2020 and February 2022. Median age was 59 years (range 39-70) and 54% were male. Forty-six percent of patients had high-risk cytogenetics. Median follow-up is 26 months. Of 45 patients evaluable for response after 4 cycles, ORR was 100% and 89% (39/45) achieved a very good partial response (VGPR) or better and 36% (16/45) a CR. Of those, 43% (12/28) were MRD negative at 10-5. After the completion of C6/C8, ORR was 100% and 64% (29/45) achieved a CR and 96% (43/45) achieved a VGPR or better. After C6/C8, 41 patients, 66% (27/41) were MRD negative at 10-5. The 24-month PFS was 91.3% (95% CI 83.4% -99.8%) and OS was 95.8% (95% CI 90.2%-100%). SCT was deferred in most patients (40/45, 89%). Grade 3 or 4 side effects (≥2 patients) included neutropenia (24%), elevated alanine aminotransferase (10%), acute kidney injury (6%), and thrombocytopenia (6%). Grade 1-2 infusion-related reactions in 20%, no grade 3. Hypertension in 49% grade 1-2 and one grade 3; one grade 3 myocardial infarction. There was one death assessed as unrelated. Two patients withdrew for acute kidney injury. Two patients were not evaluable at C4 and C6/C8 because measurable disease could only be assessed by PET CT. There were statistically significant within-patient improvements in global health status ($p<.01$), physical ($p<.01$), role ($p<.01$), emotional ($p=.01$), and social functioning ($p<.01$), body image ($p<.01$), future perspective ($p<.01$), fatigue ($p<.01$), pain ($p<.01$), loss of appetite ($p<.01$), and symptoms ($p<.01$). There were no statistically significant changes in body composition measurements between baseline and the completion of 4 cycles or consolidation/induction. There was a significant improvement in total lean mass ($p=0.01$) between baseline and end of induction adjusted for SCT status. In terms of correlatives to-date, there were no significant differences in total T cells, total templates, total productive templates; total and productive rearrangements; or clonality, maximum productive frequency and T cell fraction between those patients achieving MRD negativity and those not and no significant differences between clonality at baseline and post-induction/consolidation.

Conclusions:

Isa-KRd induces deep and durable responses, with an ORR of 100% (including 96% VGPR or better, 66% MRD negative) as well as improved quality of life in transplant-eligible patients with NDMM, with or without SCT. The overall safety profile was favorable and consistent with similar regimens in this setting, with toxicities proving generally manageable.

Disclosures: O'Donnell: *Sanofi:* Honoraria; *BMS:* Honoraria; *Takeda:* Consultancy; *Janssen:* Honoraria. **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. **Yee:** *AbbVie:* Consultancy; *Adaptive:* Consultancy; *Amgen:* Research Funding; *BMS:* Consultancy, Research Funding; *GSK:* Consultancy; *Janssen:* Consultancy, Research Funding; *Karyopharm:* Consultancy; *Regeneron:* Consultancy; *Sanofi:* Consultancy; *Takeda:* Research Funding. **Nadeem:** *GSK:* Membership on an entity's Board of Directors or advisory committees; *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; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding. **Branagan:** *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *BeiGene:* Membership on an entity's Board of Directors or advisory committees; *CSL Behring:* Membership on an entity's Board of Directors or advisory committees; *Genzyme:* Membership on an entity's Board of Directors or advisory committees; *Karyopharm:* Membership on an entity's Board of Directors or advisory committees; *Pharmacyclics:* Membership on an entity's Board of Directors or advisory committees; *Adaptive:* Membership on an entity's Board of Directors or advisory committees. **Rosenblatt:** *Bristol Myers Squibb:* Research Funding; *Bioclinica:* Consultancy; *Karyopharm:* Membership on an entity's Board of Directors or advisory committees, Other: Karyopharm; *Sanofi:* Research Funding; *Advare:* Consultancy; *Parexel:* Consultancy. **Richardson:** *Takeda:* Research Funding; *GSK:* Consultancy; *Bristol Myers Squibb:* Consultancy, Other: Contracted research, Research Funding; *AstraZeneca Pharmaceuticals LP, Bristol-Myers, Squibb Company, Celgene Corporation, GlaxoSmithKline, Janssen Biotech Inc, Karyopharm Therapeutics, Oncopeptides, Sanofi, Secura Bio, Takeda Pharmaceuticals USA Inc;:* Consultancy; *Karyopharm:* Consultancy, Research Funding; *Oncopeptides:* Consultancy, Research Funding; *Sanofi:* Consultancy. **Raje:** *bluebird bio:* Other: Contracted Research; *Amgen Inc, Roche Laboratories Inc.:* Other: Steering Committee; *bluebird bio, Bristol-Myers Squibb Company, Caribou Biosciences Inc, Celgene Corporation, Immuneel Therapeutics, Janssen Biotech Inc, Merck, Novartis, Onyx Pharmaceuticals, an Amgen subsidiary, Takeda Pharmaceuticals USA Inc:* Other: Advisory Committee.