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ORAL ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

Immuno-PRISM: A Randomized Phase II Platform Study of Bispecific Antibodies in High-Risk Smoldering Myeloma

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Background: B-cell Maturation antigen-directed immunotherapies have demonstrated significant efficacy in relapsed and refractory multiple myeloma (RRMM), with recent approval of the bispecific antibody teclistamab (TEC) . However, the use of immunotherapy in high-risk smoldering myeloma (HR-SMM) has not been examined to date. We hypothesized that bispecific antibody therapy would have greater benefit in HR-SMM due to this population having a more intact immune system, lower disease burden and may therefore have a higher efficacy and less toxicity compared to RRMM. Based on previous studies of lenalidomide and dexamethasone demonstrating benefit in HR-SMM, the Immuno-PRISM trial is studying various bispecific antibodies against a control arm of lenalidomide and dexamethasone. Herein, we report our first results of TEC in HR-SMM.
Methods: This is a multiple arm, randomized, phase II, platform study evaluating TEC vs lenalidomide and dexamethasone in HR-SMM. Eligibility criteria included HR-SMM per Mayo 2018 "20-2-20" model, total IMWG risk score of 9 or greater, and other previously established high-risk criteria including PETHEMA criteria, evolving-type SMM, and high-risk FISH abnormalities.
This study has an initial, safety run-in cohort of 6 patients treated with TEC. All patients receive 2 step-up doses of subcutaneous TEC. In the safety run-in, patients receive a dose lower than the recommended phase 2 dose (RP2D) of TEC. If no dose limiting toxicities (DLTs) are observed, the next cohort receives the RP2D of TEC. Once safety run-in is complete, the randomized trial begins with 2:1 randomization to TEC (30 patients) vs control arm of lenalidomide and dexamethasone (15 patients). Treatment duration is for 24 cycles. All eligible patients undergo stem cell collection after 4 cycles of therapy.
The primary objective is complete response rate. Secondary objectives include PFS, ORR, MRD negativity rates, safety, pharmacokinetics of TEC, and safety. Exploratory objectives include mass spectrometry quantification of M protein, molecular evolution of tumor cells, and immune biomarkers of response.
Results: At the time of data cut off, 19 patients have been enrolled to study with median follow up of 6 months. The median age is 59 years old (range 35-73) with 9 females (47%) and 10 males (53%). Sixty-four percent of patients that had evaluable FISH results had high-risk abnormalities as follows: 1q gain (7 pts), t(4;14) 1 patient.
No DLTs were observed in the safety run-in cohort and patients are now enrolling into the randomized portion of trial. In the TEC-cohort (12 patients), grade 3 or greater hematologic toxicities were neutropenia (4 patients, resolved) and thrombocytopenia (1 patient, resolved). Grade 3 or greater non-hematologic toxicities were ALT increased in 3 patients (grade 3, resolved) and pancreatitis in 1 patient (grade 3, resolved). Infections occurred in 9 patients but only 1 patient had grade 3 infection (sinusitis). Remainder of the infections were low grade and were mostly upper respiratory infections (6 patients). One patient had grade 2 uveitis. CRS occurred in 75% of patients (all grade 1 except 2 patients with grade 2 CRS requiring tocilizumab, all resolved). No patients experienced ICANS with no delayed neurotoxicity observed. All patients treated with TEC are receiving IVIG with mean IgG level at start of IVIG treatment of 418 mg/dL, with 64% of patients achieving normalization of IgG values within two IVIG doses.
In the TEC- treated cohorts (12 patients), the ORR is 100% with 42% achieving a CR, 25% VGPR, 33% PR. Four patients with high risk FISH receiving TEC have achieved a CR within 5 cycles.In control arm of lenalidomide and dexamethasone (3 patients), the ORR is 66% without any complete responses to date. Of the 8 evaluable patients treated with TEC, the MRD negative rate at 10^{-6} is 100%, including 2 patients with VGPR-MRD negative disease. Average time to MRD negativity observed among

evaluable patients was 4.25 cycles. No patients have progressed on treatment. Stem cell collection was successful in all eligible patients with an average stem cell yield of 9.06 x 10 ^{6}CD34+ cells/kg.
Conclusions: TEC in HR-SMM demonstrates significant activity with 100% ORR with MRD-negative disease in 100% of evaluable patients to date, and overall significantly improved safety profile compared to RRMM.

Disclosures Nadeem: *BMS:* Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *GSK:* 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; *GPCR Therapeutics:* 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. **Midha:** *Abbvie:* Current equity holder in publicly-traded company; *Pfizer:* Consultancy. **O'Donnell:** *Janssen:* Honoraria; *Takeda:* Consultancy; *BMS:* Honoraria; *Sanofi:* Honoraria. **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. **Sperling:** *Roche:* Consultancy; *Novartis:* Consultancy. **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. **Richardson:** *Bristol Myers Squibb:* Consultancy, Other: Contracted research, Research Funding; *Sanofi:* Consultancy; *Takeda:* Research Funding; *Karyopharm:* Consultancy, Research Funding; *Oncopeptides:* Consultancy, 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. **Anderson:** *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; *Oncopep:* Current equity holder in private company, Current holder of *stock options* in a privately-held company; *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; *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. **Ghobrial:** *AbbVie:* Consultancy, Honoraria; *10x Genomics:* Honoraria; *Janssen:* Consultancy, Honoraria; *Oncopeptides:* Consultancy; *Amgen:* Consultancy; *Janssen:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria, Research Funding; *GlaxoSmithKline:* Consultancy, Honoraria; *The Binding Site:* Consultancy; *Window Therapeutics:* Consultancy; *Pfizer:* Consultancy, Honoraria; *Regeneron:* Consultancy, Honoraria; *Menarini Silicon Biosystems:* Consultancy, Honoraria; *Sanofi:* Consultancy, Honoraria; *Huron Consulting:* Consultancy; *Takeda:* Consultancy, Honoraria; *Vor Biopharma:* Ended employment in the past 24 months, Honoraria, Speakers Bureau; *Adaptive:* Honoraria; *Aptitude Health:* Consultancy; *Disc Medicine:* Other: Spouse is Chief Medical Officer and holds equity in the company; *Bristol-Myers Squibb:* Consultancy, Honoraria.

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