ELSEVIER

Blood 142 (2023) 4757–4758

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

GEN3014 (HexaBody ®-CD38) in Anti-CD38 Mab-Naive Patients with Relapsed/Refractory Multiple Myeloma: Preliminary Results from a Dose-Expansion Cohort of a Phase 1/2 Trial

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Background: The treatment landscape for relapsed/refractory multiple myeloma (RRMM) has changed dramatically with the approval of CD38-targeted antibodies such as daratumumab. Despite this advancement in therapy, some patients still experience progression following daratumumab regimens. Clinical outcomes may be improved by more potent CD38-targeted treatment options. GEN3014 (HexaBody ®-CD38) is a next-generation human IgG1 anti-CD38 monoclonal antibody (mAb) that contains a hexamerization-enhancing mutation, E430G, that facilitates highly efficient complement-dependent cytotoxicity (CDC). In preclinical studies, GEN3014 showed robust tumor-cell killing through highly potent CDC, with increased efficiency compared with daratumumab, as well as potent antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis (Hiemstra et al, *eBioMedicine* 2023). Preliminary dose-escalation data from the first-in-human phase 1/2 trial of GEN3014 in RRMM patients showed clinical activity and a tolerable safety profile, and the recommended phase 2 dose was 16 mg/kg (NCT04824794). Based on these findings, expansion was initiated. Herein we describe the preliminary results of an expansion cohort in anti-CD38 mAb-naive RRMM patients.
Methods: Adult RRMM patients were eligible if they had ≥3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory imide drug (IMiD), were double refractory to a PI and an IMiD, or had ≥2 prior lines of therapy with 1 combining a PI and an IMiD. Patients received GEN3014 16 mg/kg intravenously in 28-day cycles (QW, cycles 1-2; Q2W, cycles 3-6; Q4W, cycles ≥7). The primary objective was to assess the preliminary antitumor activity of GEN3014. Secondary objectives included assessment of safety, tolerability, and pharmacokinetics/pharmacodynamics.
Results: As of May 5, 2023, 11 anti-CD38 mAb-naive RRMM patients were treated in this expansion cohort (median age, 66 years; range, 56-75). With a median duration of exposure of 2.4 months (range, 0.2-8.3), 4 patients (36.4%) remained on treatment. Primary reasons for discontinuation included disease progression (n=3), AEs (n=3), and death (n=1). The most common treatment-emergent AEs (TEAEs) were neutropenia (36.4%), headache (27.3%), infusion-related reactions (IRRs; 27.3%), and thrombocytopenia (27.3%). IRRs were all grade 2 and did not lead to treatment discontinuation. There were 2 grade 5 TEAEs (respiratory tract infection, n=1; cardiac arrest, n=1). Of the 11 patients treated, 7 received ≥1 cycle of GEN3014, and among them, the best overall responses were 1 complete response, 2 very good partial responses, 2 partial responses, 1 minimal response, and 1 stable disease. GEN3014 treatment was associated with a transient reduction in either complement component C2 or total complement lytic activity in all patients, suggesting CDC activity. T cells transiently decreased after administration of the first dose in all patients, and T-cell expansion (≥50% increase from baseline for ≥2 visits) was observed in 2 of 4 evaluable patients who reached cycle 3 day 1 at the time of analysis. Updated data will be presented.

Conclusions: GEN3014 showed a manageable safety profile and clinical activity in anti-CD38 mAb-naive RRMM patients in this expansion cohort. The preliminary pharmacodynamic observations were in line with observations from the dose-escalation part of the study. The study is ongoing and open for enrollment.

Disclosures Plesner: *Genmab:* Consultancy, Research Funding, Speakers Bureau; *Celgene/BMS:* Consultancy. **Jurczak:** *BeiGene:* Consultancy; *AstraZeneca:* Consultancy; *AbbVie:* Consultancy; *Eli Lilly:* Consultancy; *Pfizer:* Consultancy; *Roche:* Consultancy; *SOBI:* Consultancy; *Takeda:* Consultancy; *AbbVie:* Research Funding; *AstraZeneca:* Research Funding; *Bayer:* Research Funding; *BeiGene:* Research Funding; *Celgene:* Research Funding; *Janssen:* Research Funding; *Eli Lilly:* Research Funding; *Merck:* Research Funding; *Pfizer:* Research Funding; *Roche:* Research Funding; *SOBI:* Research Funding; *Takeda:* Research Funding. **Radocha:** *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *GSK:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Malek:** *Karyopharm:* Speakers Bureau; *Medpacto Inc.:* Research Funding; *BMS:* Consultancy; *Sanofi:* Consultancy; *Amgen:* Speakers Bureau; *Cumberland Inc.:* Research Funding. **Hiemstra:** *Genmab:* Current Employment. **Brady:** *Genmab:* Current Employment, Current equity holder in publicly-traded company. **Chen:** *Genmab:* Current Employment. **Gong:** *Genmab:* Current Employment. **Hindsberger:** *Genmab:* Current Employment. **Spencer:** *Haemalogix:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Amgen:* Consultancy, Honoraria; *Sanofi:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *IDP Pharma:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Abbvie:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Roche:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Antengene:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau.

https://doi.org/10.1182/blood-2023-179504