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POSTER ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

Updated Safety and Efficacy Results of Abbv-383, a BCMA x CD3 Bispecific T-Cell Redirecting Antibody, in a First-in-Human Phase 1 Study in Patients with Relapsed/Refractory Multiple Myeloma

Ravi Vij, MD MBA[1], Shaji Kunnathu Kumar, MD[2], Anita D'Souza, MD MS[3], John T Mckay, MD[4], Peter M. Voorhees, MD[5], Alfred Chung, MD[6], Sascha Alexander Tuchman, MD MHS[7], Neha Korde, MD[8], Katja Weisel, MD[9], Raphael Teipel, MD[10], Orlando Bueno, MD PhD[11], Zhongling Feng, MD PhD[12], Tanya S Rosenberg, MD[11], Rajvineeth Kumar Pothacamury, MD[13], Akshanth R Polepally, PhD[11], Shane Lee, MS[14], Ziyi Jin, MS[13], Jeremy A Ross, PhD[11], Aarif Ahsan[15], Chetasi Talati, MD[16], Cesar Rodriguez, MD[17]

[1] Division of Oncology, Washington University School of Medicine, Saint Louis, MO
[2] Division of Hematology, Mayo Clinic, Rochester, MN
[3] The Medical College of Wisconsin Inc, Milwaukee, WI
[4] Wake Forest School of Medicine, Winston-Salem, NC
[5] Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Atrium Health Wake Forest University School of Medicine, Charlotte, NC
[6] Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA
[7] Division of Hematology, University of North Carolina School of Medicine, Chapel Hill, NC
[8] Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[9] University Medical Center of Hamburg-Eppendorf, Hamburg, Germany
[10] Department of Internal Medicine I, University Hospital Dresden, Dresden, Germany
[11] AbbVie Inc., North Chicago, IL
[12] AbbVie Inc., Cambridge, MA
[13] AbbVie, North Chicago
[14] AbbVie Inc., North Chicago
[15] AbbVie, Inc., North Chicago, IL
[16] AbbVie, Inc., Collierville, TN
[17] Department of Medicine, Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York

Background
ABBV-383 is an off-the-shelf, fully human B-cell maturation antigen (BMCA) X CD3 bispecific antibody with bivalent BCMA domain and low CD3 affinity that targets both BCMA-expressing multiple myeloma (MM) cells and CD3-expressing T cells. ABBV-383 has shown promising activity in an ongoing phase 1 study in patients (pts) with relapsed/refractory (RR) MM (*Voorhees et al. ASH 2022; Weisel et al. EHA 2023*). Here, we report the safety and efficacy results from the ABBV-383 IV Q3W at 20 mg, 40 mg and 60 mg dose levels.
Methods
The phase 1 dose escalation (ESC) and expansion (EXP) study (NCT03933735) of ABBV-383 enrolled pts with RRMM with ≥3 prior lines of therapy (LOT), including a PI, IMiD, and an anti-CD38 mAb with no prior BCMA exposure. After exploring 14 dose levels in dose ESC, 3 dose levels were further explored in dose EXP including ABBV-383 Q3W IV 20 mg, 40 mg, and 60 mg, until disease progression/unacceptable toxicity. The primary objectives were to determine safety/tolerability, PK/PD, and RP2D. The secondary objective was to evaluate clinical activity. Responses were investigator assessed per IMWG 2016 criteria and adverse events (AEs) by CTCAE v5.0.
Results
As of 17May2023, 220 pts were treated with ABBV-383, 73 pts in the dose ESC and 147 in the dose EXP with 32 pts at 20 mg, 55 pts at 40 mg, and 61 pts at 60 mg Q3W. Median duration of follow up was 7.1 (0.8-36.9), 12.2 (1.3-34.4) and 24.2 (0.6-33.4) months (mo) in the 20 mg, 40 mg and 60 mg dose levels with 25%, 36% and 21% pts continuing treatment (tx), respectively.

Median age for all pts was 68 yrs (range, 35-92 yrs), Median prior LOT was 5 (range, 3-23), and 80% were triple-class refractory. Baseline characteristics are summarized in **Table 1** by dose level.

Treatment-emergent (TE) AEs were reported in 97% (78% ≥G3) of pts at 20 mg, 100% (84% ≥G3) of pts at 40 mg, and 100% (82% ≥G3) of pts at 60 mg. CRS, the most common TEAE, occurred in 50% (34% G1/13% G2/3% G3) of pts at 20 mg, 71%(45% G1/25% G2/0% ≥G3) of pts at 40 mg, and 70%(51% G1/18% G2/2% G3) of pts at 60mg. At the 3 dose levels, CRS occurring after the first dose had median time to onset of 1 day (range, 1-2) and median duration was 2 days (range, 1-10). ICANS occurred in 3% (3% G1/0% ≥G2) of pts at 20 mg, 5% (2 % G1/4% G2/0% ≥G3) of pts at 40 mg, and 5% (3% G2/2% G3) of pts at 60 mg. No G4/5 CRS or ICANS occurred. Infections occurred in 56% (25% ≥G3) of pts at 20 mg, 71% (26% ≥G3) of pts at 40 mg, and 57% (34% ≥G3) of pts at 60 mg; most frequently (≥10%) reported were upper respiratory tract infections (15%, G3/4 1%), pneumonia (14%, G3/4 12%), urinary tract infections (12%, G3/4 3%), and COVID-19 (11%, G3/4 1%). At 20 mg, 40 mg, and 60 mg, the incidence of neutropenia was 41% (25% ≥G3), 42% (31% ≥G3), and 43% (34% ≥G3); anemia 50% (25% ≥G3), 55% (31% ≥G3), and 38% (13% ≥G3); thrombocytopenia 44% (28% ≥G3), 36% (16% ≥G3) and 26% (13% ≥G3), respectively. The tx discontinuation due to AEs was 6%, 11%, 10% in 20 mg, 40 mg and 60 mg, respectively, with no single PT reported in >2 pts.

Clinical responses are shown in **Figure 1**. The median time to ≥VGPR was 0.7mo (0.7-5.8) at 20 mg, 1.0mo (0.7-10.4) at 40 mg, and 1.4 mo (0.7-7.8) at 60 mg. The median DOR was 9.7 mo (3.5-not reached (NR)) at 20 mg, and NR at 40 mg and 60 mg. The Kaplan-Meier (KM) estimates for DOR at 12 mo was 42% at 20 mg, 70% at 40 mg, 66% at 60 mg. The mPFS was 3.8 mo (2.4-7.9) at 20mg, 13.7mo (5.0-NR) at 40 mg, and 11.2 mo (4.8-NR) at 60 mg. The KM estimates for PFS at 12 mo was 19% at 20 mg, 51% at 40 mg, 49% at 60 mg. The median OS was 21.6 mo (7.9-NR) at 20 mg, and NR at 40 mg and 60 mg.

ABBV-383 at 20 mg, 40 mg, and 60 mg led to rapid and transient production of key proinflammatory cytokines (IL-6, IL8, IFN-γ, and TNF-α), and reduction of soluble BCMA levels over time that were associated with disease response. ABBV-383 also promoted T-cell activation and proliferation with upregulation of CD69 and KI67 markers on peripheral CD4 and CD8 T cells in evaluable pts.

Conclusions

ABBV-383 showed a manageable safety profile at dosages of 20 mg, 40 mg, and 60 mg IV Q3W, with low incidence of TEAEs leading to discontinuation. Also, extended Q3W dosing interval with no step-up dosing schedule of ABBV-383 may provide enhanced convenience. However, 20 mg yielded numerically lower responses when compared to 40 mg and 60 mg. At 40 mg and 60 mg, ABBV-383 monotherapy yielded deep and durable responses with mPFS of 13.7 mo and 11.2 mo, and 12-month DOR of 70% and 66% (mDOR NR in pts with ≥CR), respectively. These results in heavily pretreated RRMM pts support further clinical evaluation.

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Table 1: Demographics and Baseline Characteristics

Characteristic	20 mg Q3W	40 mg Q3W	60 mg Q3W
	N=32, n(%)	N=55, n (%)	N=61, n (%)
Age (yrs), median (range)	68 (36-89)	69 (42-84)	68 (35-92)
Gender			
Male	16 (50)	36 (65)	32 (52)
Female	16 (50)	19 (35)	29 (48)
Race			
White	25 (78)	40 (73)	47 (77)
Black or African American	6 (19)	11 (20)	10 (16)
Asian	1 (3)	1 (2)	1 (2)
Other	0 (0)	3 (5)	3 (5)
Disease Characteristics			
R-ISS Disease Stage (At Screening)			
I	12 (41)	11 (20)	15 (25)
II	9 (28)	29 (53)	28 (46)
III	10 (31)	14 (25)	17 (28)
Extramedullary Plasmacytoma			
Presence	7 (22)	15 (27)	15 (25)
Absence	25 (78)	39 (71)	29 (48)
Prior Lines of Therapy, median (range)	5 (3-10)	4 (3-11)	4 (3-12)
Prior Cancer Therapy			
Triple-class exposed	32 (100)	55 (100)	61 (100)
Triple-class refractory[a]	24 (75)	42 (76)	50 (82)
Penta-drug exposed	27 (84)	48 (87)	56 (92)
Penta-drug refractory[b]	8 (25)	18 (33)	25 (41)

[a] Refractory to at least one PI, IMiD, and anti-CD38 mAb (Daratumumab or Isatuximab)
[b] Refractory to at least two PIs, two IMiDs, and one anti-CD38 mAb (Daratumumab or Isatuximab)

Figure 1: Overall Response Rates of ABBV-383 Monotherapy in Patients with RRMM with at least 3 Prior Lines of Therapies.

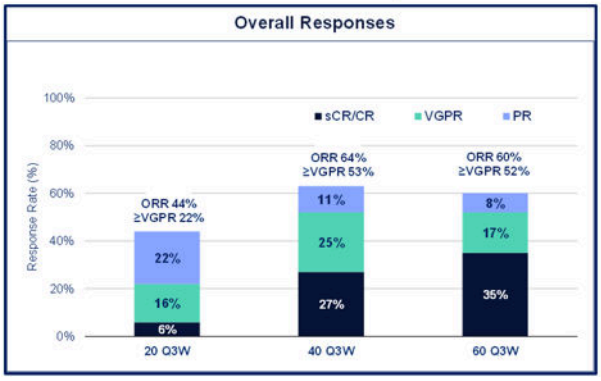

Figure 1

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