Acknowledging infection risk in bispecific antibody trials in the treatment of multiple myeloma

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Bispecific antibodies (BsAbs) create an immunologic synapse between T-cells and malignant cells, via T-cell surface marker CD3 and a tumor cell surface marker, activating T-cells to achieve tumor cell killing. B-cell maturation antigen (BCMA)×CD3-directed BsAbs show promising activity against multiple myeloma (Table 1).[1] Teclistamab is the first BCMA-BsAb approved by the European Medicines Agency in relapsed/refractory myeloma (RRMM), and is currently under review by the FDA.[2]

D'Souza et al report preliminary results of a first-in-human phase I study of ABBV-383, a BCMA×CD3-directed BsAb: 57% of evaluable patients demonstrated an objective response and 43% achieved at least a very good partial response.[3] Median duration of response was not reached after 10.8 months follow-up. These responses are unquestionably impressive, especially in heavily pre-treated patients, and compared to other drugs' single-agent response rates. Daratumumab, an anti-CD38 antibody, and pomalidomide, a second-generation immunomodulatory drug, achieved single-agent response rates of ~31-36% and 17% respectively, in similarly heavily pre-treated patients.[4,5]

Response rates are pivotal to ascertain a treatment's activity in early phase studies, and thus inform which therapies warrant further study. However, early stage trials are often single-arm and a therapy's optimal usage should be delineated through randomized controlled trials, which can better quantify effect sizes and attribute toxicities. There are instances when improved efficacy, manifesting as improved response rate and progression-free survival, may be outweighed by toxicity, resulting in inferior overall survival. Examples include Pi3K inhibitors for lymphoma, which were withdrawn after being approved based on

their promise in early-stage studies, and inferior overall survival in cytogenetically-unselected RRMM patients receiving venetoclax.[6,7]

Early phase clinical trials can provide important insights into drugs' safety. We thus write with concern over the emerging data on infection rates in some trials evaluating BCMA-targeted BsAbs (Table 1). In the ABBV-383 trial, Treatment-Emergent Adverse Events (AEs) of infection occurred in 41% of patients, with >20% grade ≥3 (pneumonia, sepsis, COVID-19 [6% each], urinary tract infections [5%]). Surprisingly, seven deaths from COVID-19 and one death from sepsis were considered by the investigators to be unrelated to ABBV-383. Similarly, in a recent study investigating teclistamab, ≥19 patients (11%) died from infection and only three were attributed by investigators to teclistamab.[2]

Patients with RRMM are often heavily pretreated and immunosuppressed; the relative contribution of disease- and treatment-factors to infection can be challenging to distinguish. In the ABBV-383 trial, 14% of patients developed hypogammaglobulinemia and 23% received intravenous gammaglobulins. In patients receiving BCMA-targeted therapy, antibody responses to COVID-19 vaccines are particularly poor.[8] Given that BCMA-targeted therapies often cause profound B-cell aplasia, severe infections in patients receiving BCMA-targeted therapy should be considered at least possibly related to therapy. Thus, it is important to understand the details underlying how the ABBV-383 trial investigators concluded no association exists between specific treatments and infection.

Improved reporting of AEs in hematology, particularly infections that are often poorly reported, is crucial to guiding supportive care of patients currently receiving new therapies.[9]

Rather than attributing AEs in early-phase studies to the investigational drug (or not), more details on infections should be routinely reported to assist clinicians who will need to manage and prevent infections associated with therapies after they are FDA-approved. Core components of infectious adverse events such as category (e.g. microbiologically-diagnosed, clinically-diagnosed), site, severity and outcomes should be reported instead of imprecise and potentially overlapping clinical syndromes such as 'pneumonia' and 'respiratory tract infection'. Line-reporting of infection data, or reporting only infections affecting subgroups, risks the inability to identify emerging signals.

Such information could also help compare infection risks across drug classes. In the original pre-pandemic studies of daratumumab in heavily pre-treated disease, only three (2%) infection-related AE deaths were recorded with much lower frequency of markers of immunesuppression such as neutropenia in contrast with ABBV-383.[5]

It is not only fair but also important for the design of future trials – including treatment duration, combination therapies, and highlighting 'adverse events of interest' – to accurately characterize and attribute infection risk. Fixed-duration treatment or treatment-free intervals may not only potentially reduce toxicity and infection risk, but may also reduce T-cell exhaustion.[10] Additionally, accurate knowledge of AEs may help with risk-stratification and supportive measures (e.g. growth-factor, immunoglobulins or antimicrobials), especially as survival of myeloma patients continues to improve.

Randomized trials with contemporary control arms (e.g. MajesTEC-3, NCT05083169) will quantify the optimal use of BsAbs, helping us to integrate these drugs into therapy. In the interim, as we use these drugs clinically, reporting AEs – Including infections – In detail can help inform clinicians' communication with patients and help prevent and optimize future treatment of such toxicities.

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Table 1. Rates of infection in bispecific antibody trials for relapsed/refractory multiple myeloma

Drug/s	Target	Pts in trial	ORR	≥VGPRR	Incidence of infections (grade ≥3)	Deaths from infection	Neutropenia (grade ≥3)	Hypogamma-globulinemia
ABBV-383[3]	BCMA	124	57%	43%	41% (≥20%)	8 (6.5%)	37% (34%)	14%*
Teclistamab[2]	BCMA	165	63%	59%	76% (45%)	≥19 (11%)	71% (64%)	75%
Teclistamab + daratumumab[11]	BCMA CD38	33	78%	43%	52% (24%)	1 (3%)	36% (36%)	NR
Elranatamab[12]	BCMA	94	61	NR	47% (18%)	1 (2%)	37% (35%)	NR
Linvoseltamab REGN5458[13]	BCMA	73	51%$	43%	NR	5 (7%)	23% (22%)	NR
Pavurutamab (AMG 701)[14]	BCMA	85	26%@	17%	17%@	2 (2%)	25% (NR)	NR
Alnuctamab (CC-93269)[15]	BCMA	30	43%	30%	57% (30%)	1 (3%)	47% (43%)	NR
Talquetamab[16]	GPRC5D	74	66%	54%	39% (8%)	-	48% (35%)	NR
Talquetamab + daratumumab[17]	GPRC5D CD38	46	77%	65%	50% (13%)	-	NR	NR
Cevostamab[18]	FcRH5	160	45%^	NR	43% (19%)	-	38% (36%)	NR

BCMA – B-cell maturation antigen, GPRC5D - G Protein-Coupled Receptor Family C Group 5 Member D, ORR – objective response rate, ≥VGPRR – rate of very good partial responses or better, NR – Not reported, Pts – patients

*in this trial, although only 14% were documented to be hypogammaglobulinemic, 23% received immunoglobulin

^ORR 55% among the higher (160mg) dose level cohort

$More recent reports at higher doses (200-800mg) suggest an ORR of 75%

@This is overall ORR; higher response rates were observed with higher dose cohorts. Rate of "serious" infections.