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An FDA oncology analysis of CD3 bispecific constructs and first-in-human dose selection

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ABSTRACT

We retrospectively examined the nonclinical studies conducted with 17 CD3 bispecific constructs in support of first-in-human (FIH) trials in oncology. We also collected information on the design of dose-finding clinical trials. Sponsors have used different MABEL approaches for FIH dose selection. To better assess acceptable approaches, FIH doses were computed from nonclinical studies and compared to the maximum tolerated doses (MTDs) in patients, to the highest human doses (HHDs) when an MTD was not identified, or to the recommended human dose (RHD) for blinatumomab. We concluded that approaches based on receptor occupancy, highest non-severely toxic dose, or no-observed adverse effect level are not acceptable for selecting the FIH dose as they resulted in doses close to or above the MTDs, HHDs, or the RHD. A FIH dose corresponding to 10%–30% pharmacologic activity (PA) was an acceptable approach. A FIH dose corresponding to 50% PA was acceptable for all except one construct, potentially due to its biological or structural properties. The most common toxicities in animals and patients were those related to cytokine release. Doses were better tolerated when intra-animal or intra-patient dose escalation was used. Exposing naïve patients to an MTD achieved with intra-patient dose escalation design may be unsafe.

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1. Background

Advances in science and a better understanding of mechanisms of tumor progression have led to innovative medicines for the treatment of cancer. Pharmaceuticals that activate the immune system to recognize and kill tumor cells, e.g., by activating T-lymphocytes and antigen-presenting cells (immune oncology [IO] pharmaceuticals) are among these innovative products (Couzin-Frankel, 2013; Mellman et al., 2011). Examples of IO pharmaceuticals include but are not limited to conventional antibodies activating the immune system (e.g., immune checkpoint inhibitors and stimulators), and CD3 bispecific constructs. Bispecific constructs contain two or more binding domains for simultaneous binding to two different antigens or two different epitopes on the same antigen. CD3 bispecific constructs bind to CD3 on T cells and a surface antigen on tumor cells resulting in T-cell activation and lysis of tumor cells (Bargou et al., 2008; van Spriel et al., 2000). While the concept of bispecific antibodies was introduced by Nisonoff and Rivers (1961) and refined by various research groups in the 1980s and 90s (Raso and Griffin, 1981; Glennie et al., 1988; and George et al., 1994), in the last decade interest in bispecific products has increased mainly due to advances in technology, a better understanding of targets, and renewed interest by the pharmaceutical industry since EU and US approvals of two CD3 bispecific constructs.

In 2009, Removab (catumaxomab; CD3-EpCam) was the first CD3 bispecific construct approved in Europe, for the treatment of malignant ascites. In 2014, Blincyto (blinatumomab; CD3-CD19) was the first CD3 bispecific construct approved in the U.S., for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia. Currently, a

Abbreviations: FIH, first-in-human; CRA, cytokine release assay; CRS, cytokine release syndrome; GLP, good laboratory practice; HHD, highest human dose; HNSTD, highest non-severely toxic dose; IB, Investigator's Brochure; ICH, International Council on Harmonization; IND, investigational new drug application; IO, Immune oncology; IRR, infusion-related reactions; MABEL, minimally-anticipated biological effect level; MTD, maximum tolerated dose; OBD, optimal biologic dose; NHP, non-human primate; NOAEL, no-observed adverse effect level; OHOP, Office of Hematology and Oncology Products; PA, pharmacologic activity; RHD, recommended human dose; RO, receptor occupancy.

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variety of formats for CD3 bispecific constructs are being tested in clinical trials (Kontermann and Brinkmann, 2015; Spiess et al., 2015). The availability of different bispecific formats widens the potential therapeutic applications of these molecules. For example, low molecular weight constructs may have better access to antigens; however, these products may have to be dosed more frequently (or continuously) than traditional therapeutic antibodies. Blinatumomab (54 kDa) is dosed by continuous intravenous (civ) infusion for 28 days followed by 14-day treatment-free period (Amgen, 2017). CD3 bispecifics with an Fc domain have long half-lives and are dosed weekly or less frequently, making them more convenient for patients. Some of these challenges and advantages associated with different formats are discussed by Garber (2014) and Ha et al. (2016). An additional challenge is the complexity associated with selecting a safe first-in-human (FIH) dose for a heterogeneous group of products. Other challenges with CD3 bispecific constructs include difficulties in conducting toxicology studies in support of FIH trials as both antigen binding regions should recognize their respective antigens for meaningful study results, but many constructs bind poorly to the non-human targets or the target antigen may be absent (or expressed at very low levels) in healthy animals. In an attempt to better understand the safety profile of CD3 bispecific constructs and identify acceptable approaches for selecting a safe FIH dose, we examined investigational new drug applications (INDs) for this class of products.

The approach to FIH dose selection for biological products in oncology is discussed in ICH S9 (ICH, 2010), including an approach based on minimally-anticipated biological effect level (MABEL) for biopharmaceuticals with immune agonistic properties. Previously, we reported acceptable approaches for FIH dose selection for first generation antibody-drug conjugates (Saber and Leighton, 2015) and immune activating antibodies (Saber et al., 2016). For immune activating antibodies that included immune checkpoint inhibitors and stimulators (Saber et al., 2016), we concluded that selection of the FIH dose based on animal toxicology studies using 1/6th the HNSTD or 1/10th the NOAEL using body surface area (BSA) or body weight (BW) for animal-to-human dose conversion resulted in human doses that were unsafe for several antibodies examined. For these antibodies, FIH doses based on 20%–80% receptor occupancy (RO) or pharmacologic activity (PA) resulted in human doses with acceptable/manageable toxicities. We define PA as pharmacologic activity at a specific drug concentration using the Hill Equation. While the approaches of computing the FIH dose at 20% pharmacologic activity (PA) or receptor occupancy (RO), obtained from in vitro studies with human cells, were safe for the antibodies examined, they resulted in doses that were substantially lower than the human maximum tolerated dose (MTD), optimal biological dose (OBD), or recommended human dose (RHD), suggesting that further optimization of approaches to setting the FIH dose or FIH trial design may be needed. At that time, there was insufficient information to evaluate CD3 bispecific products and draw definitive conclusions. We are now reporting a similar retrospective analysis based on an extended database with CD3 bispecific constructs. We have reviewed the development programs submitted to support 17 separate INDs. Our review included an evaluation of pharmacology and animal toxicity studies and initial dose-finding clinical trial designs with an emphasis on FIH dose selection. One CD3 bispecific product is FDA-approved.

2. Methods

The FDA archival database was searched for keywords “CD3” and “bispecific” for INDs in the Office of Hematology and Oncology Products (OHOP). All CD3 bispecific constructs included were for treatment of patients with cancer. The INDs were included in the dataset if an MTD in humans was identified. The INDs were also included in our dataset if an MTD was not identified but there were sufficient clinical safety data; e.g., clear drug-related toxicities in patients. If an MTD was not identified by the sponsor but due to toxicities the protocol was amended to reduce the frequency of administration, increase the duration of infusion, or to include a step dose, and no fatality occurred at doses tested, we called the highest dose prior to the amendment an “HHD” (highest human dose). If a clinical study under the initial protocol was ongoing (no amendments) and an MTD was not identified, we called the highest dose administered at the cut-off date of May 15, 2017 the HHD. Only 1 of the 17 INDs fell under this latter case. Seventeen INDs were identified; 16 were with intravenous (iv) route of administration and 1 was with both iv and intraperitoneal (ip) route of administration in patients. Due to dosing errors for one bispecific construct, the HHD for this product is an estimation of the doses patients received based on the re-analysis of the dosing formulation.

2.1. Data collected

The following information was collected for each IND from FDA/OHOP reviews and relevant modules of the IND electronic database:

Product characteristics: structure and molecular weight, target antigens, presence or absence of an Fc domain, IgG subtype when an Fc domain was present and modifications to the Fc domain for altered effector function. Hereafter, “second antigen” refers to the antigen other than CD3.

In vitro data: activity studies conducted and corresponding EC_{50}s when provided by the sponsors; binding data and corresponding dissociation constants (K_Ds).

Animal data: good laboratory practice (GLP)-compliant toxicology studies in non-human primates (NHPs) in support of FIH trials. Occasionally, pilot toxicology studies were examined if findings in the GLP toxicology studies were unclear.

Clinical data: the sponsors’ approach for FIH dose selection; the MTDs or HHDs; dose-finding clinical trial design (single patient versus 3 + 3 design; intra-patient versus inter-patient dose escalation); monitoring and treatment for infusion-related reactions (IRRs)/cytokine release syndrome (CRS). We refer to infusion reactions and antigen binding-associated cytokine release in patients as IRR/CRS as symptoms overlap (Brennan et al., 2010; Doessegger and Banholzer, 2015) and the terms were at times used interchangeably in INDs.

2.2. FIH dose computation

We used the principles of the Hill equation for FIH dose calculation (Goutelle et al., 2008; Saber et al., 2016). This also allowed comparing the results obtained in this manuscript to those presented in our previous publication using the same method. Our method does not take into consideration the number of receptors, receptor turnover, pharmacokinetic data, or duration of pharmacological effects. The Hill coefficient is dependent on the shape and slope of the concentration-effect curve. A Hill coefficient of one ($\alpha = 1$) was used in our previous project for conventional antibodies, as all doses below 50% RO or PA were safe independent of alpha and for doses above 50% RO or PA, increasing alpha-as expected-resulted in a lower FIH dose. Therefore, examining alpha greater than one was not necessary. For bispecific constructs, we used a Hill coefficient of 1–3 ($\alpha = 1–3$) as an estimation of cooperative binding and projected shape of the concentration-effect curve. Very steep response curves are not expected and Hill coefficient greater than 3 was not examined. Below 50% RO or PA, increasing the coefficient will result in increasing FIH doses, and if

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