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An FDA oncology analysis of immune activating products and first-in-human dose selection

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ABSTRACT

As sub-therapeutic doses are not medically justifiable in patients with cancer, we retrospectively analyzed data on immune activating products, to assess approaches used in first-in-human (FIH) dose selection, the utility of animal toxicology studies in dose selection, and the length of time to complete FIH trials. The information collected included pharmacology and toxicology data, FIH dose and rationale, and dose-finding trial design. We used the principles of the Hill equation to estimate the FIH doses for antibodies and compared them to the doses administered to patients with acceptable toxicities. For approximately half the antibodies (44%) examined, the FIH doses were at least a hundred-fold lower than the doses safely administered to patients, indicating optimization of FIH dose selection and/or optimization of dose-finding trial design is needed to minimize patient exposure to sub-therapeutic doses. However, selection of the FIH dose for antibodies based on animal toxicology studies using 1/6th the HNSTD or 1/10th the NOAEL resulted in human doses that were unsafe for several antibodies examined. We also concluded that antibodies with Fc-modifications for increased effector function may be less tolerated, resulting in toxicities at lower doses than those without such modifications. There was insufficient information to evaluate CD3 bispecific products.

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1. Introduction

Advances in science and a better understanding of mechanisms of tumor progression have led to innovative medicines for the treatment of cancer. Immune oncology (IO) pharmaceuticals are among these innovative products and activate the body's immune system against tumor cells, e.g. by activating T-lymphocytes and antigen-presenting cells (Couzin-Frankel, 2013; Mellman et al., 2011). The field of IO pharmaceuticals has been growing rapidly, with interest spurred by the recent approvals of the PD-1 inhibitors Keytruda and Opdivo, and the CD3 bispecific construct Blincyto. While the science is advancing rapidly, there are regulatory areas to be addressed, specifically regarding the safety assessment of IO pharmaceuticals prior to initiation of clinical studies and first-in-human (FIH) dose selection (Muller and Brennan, 2009; Vatsan et al., 2013).

In 2006, administration of the anti-CD28 monoclonal antibody (mAb) TGN1412 to healthy volunteers resulted in multi-organ dysfunction in six subjects due to cytokine storm; its adverse effects occurred within 90 min of a single infusion (Suntharalingam et al., 2006). Subsequent to the TGN1412 tragedy, cautionary approaches to FIH dose selection have been proposed for products that may activate the immune system (EMA, 2007; EMA, 2013; ICH S9, 2010). As a result, a conservative method to select the FIH start dose was proposed for agonists based on the minimally-anticipated biological effect level (MABEL) that results in no more than 10% receptor occupancy (RO).

Various approaches for estimating RO or selecting a dose based on a desired RO have been described (Goutelle et al., 2008; Lowe et al., 2007; Muller and Brennan, 2009); one approach is based

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CRA, cytokine release assay; CRS, cytokine release syndrome; DLT, dose limiting toxicity; EMA, European Medicines Agency; FIH, first-in-human; HHD, highest human dose; ICH, International Council on Harmonization; IND, investigational new drug application; IO, immune oncology; IRR, infusion-related reactions; mAb, monoclonal antibody; MABEL, minimally-anticipated biological effect level; MTD, maximum tolerated dose; NHP, non-human primate; NOAEL, no-observed adverse effect level; OBD, optimal biologic dose; OHOP, Office of Hematology and Oncology Products; PA, pharmacologic activity; PAD, pharmacologically active dose; RHD, recommended human dose; RO, receptor occupancy; RP2D, recommended Phase 2 dose.

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on the Hill equation (Goutelle et al., 2008), which we used in our analysis for FIH dose estimation. The Hill equation assumes that the concentration of the drug is much greater than the concentration of the receptor. Other approaches that take into account the number of receptors, clearance, or the receptor turnover rate may be used when such data are available; the FIH dose obtained using these factors is anticipated to be higher than by using solely the equations below. These factors were not available for sufficient number of products for cross-IND comparison. The following Hill- and Michaelis-Menten- based equations were used for FIH dose estimation, based on in vitro activity data (A) or binding constants (B):

$$PA = \frac{[C]}{EC_{50} + [C]} \quad (A)$$

$$RO = \frac{[C]}{K_D + [C]} \quad (B)$$

C is the human plasma concentration of the biopharmaceutical, PA is the pharmacologic activity, RO is the receptor occupancy, EC50 refers to human values obtained from in vitro activity (i.e. not binding) data and K_D is the human antigen dissociation constant. For the purpose of our analysis, we used a Hill coefficient of 1 (Goutelle et al., 2008) due to lack of data to estimate the coefficient. A coefficient of 1 will result in a more conservative FIH dose compared to doses obtained when the coefficient is > 1.

One objective of nonclinical studies is to identify a safe FIH dose that is sufficiently high to minimize exposure to sub-therapeutic doses in serious and life-threatening diseases, such as metastatic cancer, and to allow rapid attainment of the recommended Phase 2 dose (RP2D). The FIH dose selection for small molecules (1/10th STD_{10} or 1/6th HNSTD) is well established and discussed in ICH S9. Recently we also examined acceptable approaches to dose selection for the first generation antibody-drug conjugates (Saber and Leighton, 2015). The approach to FIH dose selection for biological products in oncology is also discussed in ICH S9, including the MABEL approach for biopharmaceuticals with immune agonistic properties.

We have conducted a retrospective analysis of nonclinical development programs for immune checkpoint inhibitors and stimulators and other antibodies with the potential to activate the immune system, and CD3 bispecific constructs. We reviewed the nonclinical development programs submitted to support 32 separate investigational new drug applications (INDs), including pharmacology and animal toxicity studies, and initial dose-finding trial designs with an emphasis on FIH dose selection. Some of the products examined are now FDA-approved.

2. Methods

The FDA archival database was searched for the keyword "MABEL" to identify anticancer products that used a MABEL approach for setting the FIH dose; this search identified over 100 potential INDs. This search also identified some INDs in which the MABEL approach was discussed but not used to set the FIH dose, e.g., when a side-by-side comparison of the investigational IO product and an IO product in clinical trials was conducted to allow a higher FIH dose than supported by nonclinical data. The INDs were then screened for antibodies and bispecific antibody constructs for which a sufficient number of patients received the drug to identify a maximum tolerated dose (MTD), an optimal biologic dose (OBD), or a recommended human dose for further investigation, and for those still dose escalating, to have dose-limiting toxicities (DLTs), have multiple cohorts completed in the absence of DLTs, or to have reached receptor saturation. Thirty-two INDs were identified and included in our analysis.

2.1. Data collected

When available, the following information was collected for each IND: date of IND submission; product characteristics (molecular weight, target antigen, IgG subtype, modifications to the mAb for modified effector function); in vitro activity studies conducted and corresponding EC50s; in vitro antigen binding data and corresponding dissociation constant (K_D); non-human primate (NHP) toxicology data; the sponsor's approach to setting the FIH dose; highest human doses (HHDs) with acceptable safety profile (based on Investigator's Brochure, annual reports, or safety reports at the cut-off date of July 15, 2016); human MTD, OBD, or the recommended human dose (label dose for approved drugs); dose-finding clinical trial design (single patient versus 3 + 3 design; intra-patient versus inter-patient dose escalation, dose increments); monitoring and treatment for infusion-related reactions (IRRs)/cytokine release syndrome (CRS). In this article we refer to infusion reactions and antigen binding-associated cytokine release 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. Product characteristics

In this analysis, we only included products with the potential to activate the immune system, directly or indirectly. During screening, products were selected based on common knowledge of target involvement in immune activation (e.g. checkpoint inhibitors and stimulators), or based on data presented in the IND or a literature search suggesting the potential involvement of the target in immune activation.

Of the 32 INDs in our database, five were CD3 bispecific constructs, one was an IgG4 trimeric antibody, and 26 were monoclonal antibodies of IgG1 (18 products), IgG2 (3 products) or IgG4 (5 products) isotype. The targets of antibodies in our dataset include, but are not limited to: PD1, PD-L1, CD40, GITR, OX40, OX40L, CD33, CD38, CD19, CD137 (4-1BB), c-fms, B7 family member antigen, and CTLA-4. Products targeting other antigens were also included in this analysis but are not specifically identified in this article.

2.3. FIH dose computation

Due to low number of CD3 bispecific constructs, structural heterogeneity, and schedule differences in administration, these products have been excluded from FIH dose computation.

We utilized the principles of Hill equation as described in the Introduction, with a plasma volume of 2.8 L, and data from in vitro assays, to calculate a FIH dose that would result in 20%–80% RO or 20%–80% PA. We chose 20%–80% range for the RO and PA because 20% is currently the most common occupancy and activity level used for FIH dose selection (by sponsors and by FDA/OHOP), and 80% is below the RO that resulted in cytokine storm with TGN1412 (TGN1412 was at 90% RO at the FIH dose).

In our analysis, only K_D was used for FIH dose computation at the pre-defined RO of 20%–80% (equation B); binding EC50s were not used since cell-based assays are associated with variability (e.g. based on the cell line used and the expression level of antigen). Multiple approaches could be used to estimate the FIH dose based on RO and PA; however, the decision to use the Hill equation was based on the fact that it is commonly used by sponsors and reviewers of INDs and binding and activity data were available for most INDs. This allowed for estimation of the dose and for cross IND examination. Moreover, as binding data is available for TGN1412,