Regulatory Toxicology and Pharmacology xxx (2017) 1–8

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Commentary

Non-clinical efficacy-related studies for human medicines: An overview and retrospective analysis of data for a group of approved medicines

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ARTICLE INFO

Article history:
Received 20 March 2017
Received in revised form
29 September 2017
Accepted 2 October 2017
Available online xxx

Keywords:
Efficacy
Drug development
Cancer
Animal studies
In vitro studies
Monoclonal antibodies
Anticancer medicines
Clinical development
Preclinical studies

ABSTRACT

The lack of efficacy is a major cause of medicine's development failure at the clinical phase, which may lead to question, among other aspects, the translation of the non-clinical data into humans. The objectives of the work here presented were (i) to get an overview (based on public assessment reports) of the nature of the non-clinical efficacy-related studies presented to the regulatory authorities at the marketing authorization application's stage for a group of approved anticancer human medicines (15 in total) and (ii) to conduct a retrospective analysis of such studies in terms of any identified insufficiencies and consistency with the current regulatory non-clinical guidelines. Each medicine has been tested in a number of *in vitro* assays and animal studies, which, all together, are judged to be capable of providing information on the activity of the active substance and demonstrating an anti-tumour effect, as well as to be generally consistent with the available, although limited detailed, guidance. In spite of this, some aspects were identified which could have a potential impact on the translation on non-clinical data into humans, namely, apparent insufficiencies in terms of animal model/human bridging data/knowledge and *in vivo* data on pharmacokinetics/pharmacodynamics relationships.

1. Introduction

The lack of efficacy constitutes a major cause of failure from Phase II of clinical development up to the submission stage of human medicines (Arrowsmith, 2011a, 2011b; Arrowsmith and Miller, 2013). This is the conclusion drawn from the analyses of the reasons for failure of medicines development across all therapeutic areas, conducted by Thomson Reuters Life Science Consulting. In fact, as based on these studies, at Phase II of clinical development, 51 and 59% of the failures in 2008–2010 and 2011–2012, respectively, were due to lack of efficacy; at Phase III and submission stages, these values were 66 and 52%, in 2007–2010 and 2011–2012, respectively.

Moreover, it is apparent that lack of efficacy may not be uniformly the major cause of failure for every therapeutic class and that anticancer medicines may be amongst the most affected. The analyses conducted by Thomson Reuters Life Science Consulting (Arrowsmith, 2011a, 2011b; Arrowsmith and Miller, 2013) also revealed that some therapeutic classes, which included anticancer medicines, were overrepresented among those that failed during clinical development. Other analyses such as the one reported by Waring and co-workers (Waring et al., 2015), showed lower percentages of failure during drug development due to unproven efficacy. Although remaining as a main reason for failure, according with these authors, only 34% of oral small molecules have failed at Phase II of clinical development due to a lack of efficacy. A review of the nature of the major clinical issues which have been raised by the European Medicines Agency (EMA) during the assessment of marketing authorization applications for medicines intended to be used in central nervous system disorders has revealed concerns over efficacy for more than one-third of the applications, while more than half were related to safety concerns (Butlen-Ducuing et al., 2016).

There may be different explanations for the failures in demonstrating efficacy during clinical development, namely, progression into Phase III clinical trials in spite of only marginal statistically significant efficacy at the Phase II stage (Arrowsmith, 2011a).

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https://doi.org/10.1016/j.yrtph.2017.10.003
0273-2300/

However, issues related to the quality of animal data and/or translation of animal data into humans have also been considered (Breyer, 2014; Zeiss, 2015; van der Worp et al., 2010).

In terms of regulatory guidance, it is noted that there are no guidelines published at the European Medicines Agency (EMA)'s website (EMA, a) solely addressing non-clinical efficacy-related studies. Nevertheless, anticancer medicines are among the medicines for which there is a dedicated non-clinical guideline that also includes guidance on the investigation of potential efficacy. This is the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use's guideline S9 (ICH S9) on nonclinical evaluation for anticancer pharmaceuticals (EMA, 2010a), a guideline adopted in 2009 for which a questions & answers document (EMA, 2016a) is under preparation.

The objectives of the work here presented were (i) to get an overview (based on public assessment reports) of the nature of the non-clinical efficacy-related studies which have been presented to the regulatory authorities at the time of the marketing authorization application for a group of anticancer medicines, and (ii) to conduct a retrospective analysis of such non-clinical set of studies in terms of any identified insufficiencies and consistency with the current regulatory non-clinical guidelines. With few exceptions, the results from the studies were not addressed.

There is a large number of approved anticancer medicines, and potential difficulties related to the level of detail of the public assessment reports and/or, for instance, inter-species differences in terms of metabolite profiles (EMA, 2013a). It was, therefore, decided to focus on a group of medicines consisting of currently authorized innovative anticancer human medicines containing unconjugated and monospecific monoclonal antibodies as active substances and which have been authorized up to October 2016 through the centralized procedure, as established in the European Regulation (EC) No 726/2004 (European Commission, 2004). By innovative it is meant that the medicine contained a new active substance and the respective marketing authorization application was submitted in accordance to Article 8 (3) of the Directive 2001/83/EC (European Commission, 2001).

2. Material and methods

The medicines with the intended characteristics have been identified through a combined search of the full set of European public assessment reports (EPARs) for currently authorized human medicines (EMA, b), and internal databases from the National Authority of Medicines and Health Products, I.P. (Infarmed, Portugal).

The information on the non-clinical efficacy-related studies (i.e., non-clinical primary pharmacodynamics studies) conducted for the selected medicines was extracted from the respective EPARs (EMA, b) and, when available, the corresponding reviews prepared by the US Food and Drug Administration (FDA) (FDA).

3. Results

3.1. Overview of the selected group of medicines

The combined search of the EPARs for human medicines (EMA, b) and Infarmed's internal databases has revealed a total number of 15 medicines with the intended characteristics. The European trade names of these medicines, together with their year of marketing authorization in Europe, name of the active substance and respective molecular target, as based on the respective medicine EPAR's authorization details and product information, are listed in Table 1.

As based on information in the respective medicines' approved product information and also, in the case of bevacizumab, the EPAR's initial scientific discussion (EMA, 2006a), all monoclonal antibodies that are the active substances of the selected group of medicines belong to the IgG1 subclass, except for panitumumab, which is an IgG2 antibody, and pembrolizumab and nivolumab, which are IgG4 antibodies. Except for bevacizumab, ramucirumab, ipilimumab, pembrolizumab and nivolumab, all the other antibodies are directed against targets expressed on the surface of tumour cells.

According to the respective medicines' approved product information, the anti-tumour effects of the antibodies directed against targets expressed on the surface of tumour cells result from two main modes of action: antibody's Fc region-dependent immune-mediated cell killing and receptor's antagonism. Antibodies with anti-tumour effects mediated by the first mechanism include rituximab, ofatumumab, obinutuzumab, daratumumab and elotuzumab. Moreover, it is of note that, in the case of elotuzumab, the target (SLAMF7) is also expressed on natural killer (NK) cells. This allows for activation of the natural killer cells through both the SLAMF7 pathway and the Fc receptors. Antibodies with anti-tumour effects mediated by receptor's antagonism include trastuzumab, pertuzumab, cetuximab, panitumumab and necitumumab.

Table 1
Currently authorized innovative anticancer human medicines, approved through the European centralized procedure up to October 2016, which contain as active substances unconjugated and monospecific monoclonal antibodies.

Year of MA in EU	Name of the active substance (trade name in EU)	Molecular target	References
1998	Rituximab (MabThera)	CD20	EMA, c
2000	Trastuzumab (Herceptin)	HER2	EMA, d
2004	Cetuximab (Erbitux)	EGFR	EMA, e
2005	Bevacizumab (Avastin)	VEGF	EMA, f
2007	Panitumumab (Vectibix)	EGFR	EMA, g
2010	Ofatumumab (Arzerra)	CD20	EMA, h
2011	Ipilimumab (Yervoy)	CTLA-4	EMA, i
2013	Pertuzumab (Perjeta)	HER2	EMA, j
2014	Ramucirumab (Cyramza)	VEGFR2	EMA, k
2014	Obinutuzumab (Gazyvaro)	CD20	EMA, l
2015	Pembrolizumab (Keytruda)	PD-1	EMA, m
2015	Nivolumab (Opdivo)	PD-1	EMA, n
2016	Daratumumab (Darzalex)	CD38	EMA, o
2016	Elotuzumab (Empliciti)	SLAMF7	EMA, p
2016	Necitumumab (Portrazza)	EGFR	EMA, q

MA = marketing authorization; EU = European Union; HER2 = human epidermal growth factor receptor 2; EGFR = epidermal growth factor receptor; VEGF = vascular endothelial growth factor; CTLA-4 = cytotoxic T lymphocyte antigen-4; VEGFR2 = vascular endothelial growth factor receptor 2; PD-1 = programmed cell death-1; SLAMF7 = signalling lymphocyte activation molecule family member 7.

Please cite this article in press as: Figueiredo, A.C., Non-clinical efficacy-related studies for human medicines: An overview and retrospective analysis of data for a group of approved medicines, Regulatory Toxicology and Pharmacology (2017), https://doi.org/10.1016/j.yrtph.2017.10.003