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Strategies for clinical development of monoclonal antibodies beyond first-in-human trials: tested doses and rationale for dose selection

Marie Viala[1], Marie Vinches[1], Marie Alexandre[1], Caroline Mollevi[1], Anna Durigova[2], Nadia Hayaoui[1], Krisztian Homicsko[3], Alice Cuenant[1], Céline Gongora[4], Luca Gianni[5] and Diego Tosi*[,1,4]

[1]Institut du Cancer de Montpellier, Montpellier, France; [2]Geneva University Hospitals, Geneva, Switzerland; [3]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [4]Institut de Recherche en Cancérologie de Montpellier, Inserm U1194, Montpellier, France and [5]San Raffaele – Scientific Institute, Milan, Italy

Background: Our previous survey on first-in-human trials (FIHT) of monoclonal antibodies (mAbs) showed that, due to their limited toxicity, the recommended phase II dose (RP2D) was only tentatively defined.

Methods: We identified, by MEDLINE search, articles on single-agent trials of mAbs with an FIHT included in our previous survey. For each mAb, we examined tested dose(s) and dose selection rationale in non-FIHTs (NFIHTs). We also assessed the correlation between doses tested in the registration trials (RTs) of all FDA-approved mAbs and the corresponding FIHT results.

Results: In the 37 dose-escalation NFIHTs, the RP2D indication was still poorly defined. In phase II–III NFIHTs ($n = 103$ on 37 mAbs), the FIHT RP2D was the only dose tested for five mAbs. For 16 mAbs, only doses different from the FIHT RP2D or the maximum administered dose (MAD) were tested and the dose selection rationale infrequently indicated. In the 60 RTs on 27 FDA-approved mAbs with available FIHT, the FIHT RP2D was tested only for two mAbs, and RT doses were much lower than the FIHT MAD.

Conclusions: The rationale beyond dose selection in phase II and III trials of mAbs is often unclear in published articles and not based on FIHT data.

The main aim of first-in-human trials (FIHTs) is to explore the safety of multiple escalating doses of a drug in order to identify the highest dose associated with a tolerable toxicity. This is usually defined as the maximum-tolerated dose (MTD) (Eisenhauer *et al*, 2000; Le Tourneau *et al*, 2009) and is frequently selected for the subsequent drug development, on the basis of the assumption that a positive correlation exists between the drug dose and its effect. It is then indicated as the recommended phase II dose (RP2D) (Le Tourneau *et al*, 2009). Available data convincingly showed that FIHTs are the most important step in determining the dose of FDA-approved anticancer drugs, because for most molecules the RP2D is determined on the basis of the MTD, and the dose tested in registration trials (RTs) is within 20% on either side of the RP2D (Jardim *et al*, 2014). More uncertainty exists about dose selection for targeted agents, because in this case, the RP2D coincides less frequently with the MTD and predicts poorly the dose used in RTs (Jardim *et al*, 2014). Indeed, designing and interpreting FIHTs for targeted agents is difficult because of their limited acute toxicity

*Correspondence: Dr D Tosi; E-mail: diego.tosi@icm.unicancer.fr

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(the first-cycle toxicity is usually the endpoint for MTD selection), and because of the scarce correlation between pharmacokinetic (PK) or pharmacodynamic (PD) parameters and drug efficacy in this setting (Parulekar and Eisenhauer, 2004; Jardim *et al*, 2014; Janne *et al*, 2016; Sweis *et al*, 2016). The challenge is even greater in FIHTs of monoclonal antibodies (mAbs) due to the low risk of acute toxicity associated with these molecules as a consequence of their lack of off-target effects (Sachs *et al*, 2016), and also because conventional FIHTs cannot capture the medium- and long-term toxicity of tested drugs. We recently conducted a comprehensive analysis of the design, implementation and outcome of FIHTs on mAbs published between 2000 and 2013 (Tosi *et al*, 2015). We found that, for most of the tested molecules, early-occurring adverse events were rare and dose escalation could be continued up to the highest planned dose level in all trials. Consequently, the MTD could be identified only in a minority of trials. Conversely, the RP2D was indicated in an important proportion of FIHTs, mainly in the absence or independently of the MTD and on the basis of PK or PD considerations. The PK data used to justify the RP2D choice mostly relied on comparisons between the drug concentrations found to be effective in preclinical studies and the clinical PK findings. PD data often focused on receptor occupancy assessment. However, the correlation between PK or PD parameters in preclinical models and in patient samples is far from being clearly established, which makes RP2D recommendations based on these observations at least doubtful. Despite these uncertainties in RP2D selection, mAb clinical development achieved several important successes for the treatment of malignancies and immunologic disorders (Nelson *et al*, 2010); however, comprehensive reviews are not available on the strategies of mAb clinical testing following FIHTs.

The aim of this study was to evaluate the strategies of mAb clinical development by analysing single-agent non-FIHTs (NFIHTs) of mAbs the FIHT of which was included in our previous analysis (Tosi *et al*, 2015), as well as the RTs of all FDA-approved mAbs. After retrieving from MEDLINE all publications on these NFIHTs and RTs, we examined the trial design and results, with a particular focus on the relationship between FIHT data and doses tested in these trials.

MATERIALS AND METHODS

Article search. In June 2016 we performed a MEDLINE search to identify articles on single-agent trials of mAbs the FIHT of which was included in our previous analysis (Tosi *et al*, 2015). Separately, we identified mAbs approved as single agents by FDA up to 31 June 2016, and for each molecule we performed a MEDLINE search (using all the known names of each drug) to identify the FIHT and RTs. We excluded trials reporting on immunoconjugates, radioimmunoconjugates and non-systemic routes of administration (topical administration or *ex-vivo* treatment), trials on Asian patients performed to confirm previous results obtained in Western patients, phase III trials where the evaluated mAb was used as standard treatment, as well as articles not written in English language. The phase I and phase II parts of phase I/II studies were analysed separately when possible.

Data collection and analysis. From articles on the NFIHTs of mAbs with an FIHT included in our previous review (Tosi *et al*, 2015), we extracted treated disease, trial phase, rationale for dose(s) selection, administration route, dose calculation unit, schedule, presence of loading dose, tested dose(s), number of included patients, and availability of PK or PD data. From dose escalation trials, we also extracted the starting dose (SD), the maximum planned dose, the maximum administered dose (MAD), the MTD, the RP2D and the rationale for RP2D selection. For these trials, we calculated the ratio between FIHT MAD and NFIHT MAD, the ratio between NFIHT RP2D and FIHT MAD and the ratio between NFIHT RP2D and FIHT RP2D. For phase II and III trials, we calculated the ratio between the tested dose and FIHT MAD or FIHT RP2D. For the analysis of the RTs concerning mAbs approved by the FDA, we extracted treated disease, administration route, dose calculation unit, schedule, presence of loading dose, tested dose(s), number of included patients, and the three most frequent grade 3/4 toxicities. From the relevant FIHT, we recorded MAD, MTD, RP2D and the three most frequent grade 3/4 toxicities. We calculated the ratios between RT dose and FIHT MTD and MAD, respectively. When more than one trial was available for a given mAb in a data set, we used the mean of the ratios from all the trials of this mAb to calculate summary statistics on the dose ratios for the entire data set. We used descriptive statistics to report whether the top-three grade 3/4 toxicities in the RTs of each mAb were detected in the corresponding FIHT, and their grade in the FIHT. Statistical analyses were performed with the R software (version 3.3.2).

RESULTS

General results on NFIHTs. After reviewing the 139 articles retrieved with the MEDLINE search, we selected for analysis 144 NFIHTs of 42 mAbs (1–15 NFIHTs for each molecule). The study design and drug administration data of the selected NFIHTs are shown in Table 1. Specifically, 39 studies (27%) were phase I and 103 (72%) phase II or III trials. Most trials concerned patients with solid cancers or haematological malignancies ($n = 111$, 77%), while the others focused mainly on immunologic disorders. In 131 trials (91%), the mAb was administered only by intravenous route and a loading dose was used in 20 (14%). For most mAbs, the same dose calculation method was used in NFIHTs and the corresponding FIHT. However, in 16 NFIHTs, a flat dose was administered instead of the dose tested in the FIHT and calculated according to weight ($mg\,kg^{-1}$) or body surface ($mg\,m^{-2}$).

Analysis of dose escalation NFIHTs. In 37 of the 39 of phase I trials, a dose escalation procedure was implemented (for 21 mAbs). We found that the highest planned dose corresponded to the FIHT MAD for nine of the 19 (47%) mAbs tested in the NFIHTs that used the FIHT dose calculation method. Indeed, the range of ratios

Table 1. Characteristics of the 144 NFIHTs included in the study

Characteristic	Number of trials (%)	Number of mAbs
Trial phase		
I	39 (27)	24
II	82 (57)	39
III	21 (15)	9
Not applicable	2 (1)	2
Disease type		
Solid cancers	75 (52)	25
Haematological malignancies	36 (25)	13
Immunological/rheumatic diseases	32 (22)	13
Other diseases	1 (1)	1
Trials including a pharmacokinetic study	74 (51)	34
Trials including a pharmacodynamic study	81 (56)	36
Dose calculation		
$mg\,kg^{-1}$	87 (60)	28
$mg\,m^{-2}$	11 (8)	5
Flat dose	46 (32)	12

Abbreviations: NFIHT = non-first-in-human trial; mAb = monoclonal antibody.

between the highest NFIHT planned dose and FIHT MAD was quite wide (0.1 to 6); however, for 15 mAbs (71%) in 21 trials (65%) the highest planned dose level was lower or equal to the FIHT MAD, and for 15 mAb (71%) in 19 trials (59%) it was within 33% on either side of the FIHT MAD (Figure 1). Like in the FIHT, in all NFIHTs the mAb favourable safety profiles allowed dose escalation up to the highest planned dose level that, therefore, coincided with the MAD. An MTD was found for only seven of 21 mAbs (33%) tested in eighth (22%) dose escalation trials. An RP2D was indicated for 11 of the 21 mAbs (52%) tested in 15 of the 37 NFIHTs (40%), but it matched the FIHT RP2D for only three mAbs in four trials (Figure 1). The rationale for RP2D selection was described for only 11 mAbs (Table 2) and was based on considerations about safety ($n=6$), PK ($n=4$), and PD ($n=1$). The medians of the NFIHT RP2D/FIHT RP2D and NFIHT RP2D/FIHT MAD ratios were 2.2 (range: 1 to 6) and 0.65 (range: 0.3 to 1), respectively.

Analysis of phase II and III NFIHTs. We then analysed the doses tested in the 103 phase II and III trials (on 37 mAbs) with regard to the FIHT results to assess FIHT data relevance for the subsequent mAb development. First, we evaluated how the tested dose(s) was selected (Table 3). A rationale was indicated for 26 mAbs (70%) in 57 of the 103 trials (55%) and was based on the FIHT RP2D (19 trials), PK data (7 trials), efficacy (7 trials), FIHT MAD (4 trials), PD (2 trials), FIHT MTD (1 trial) or other considerations

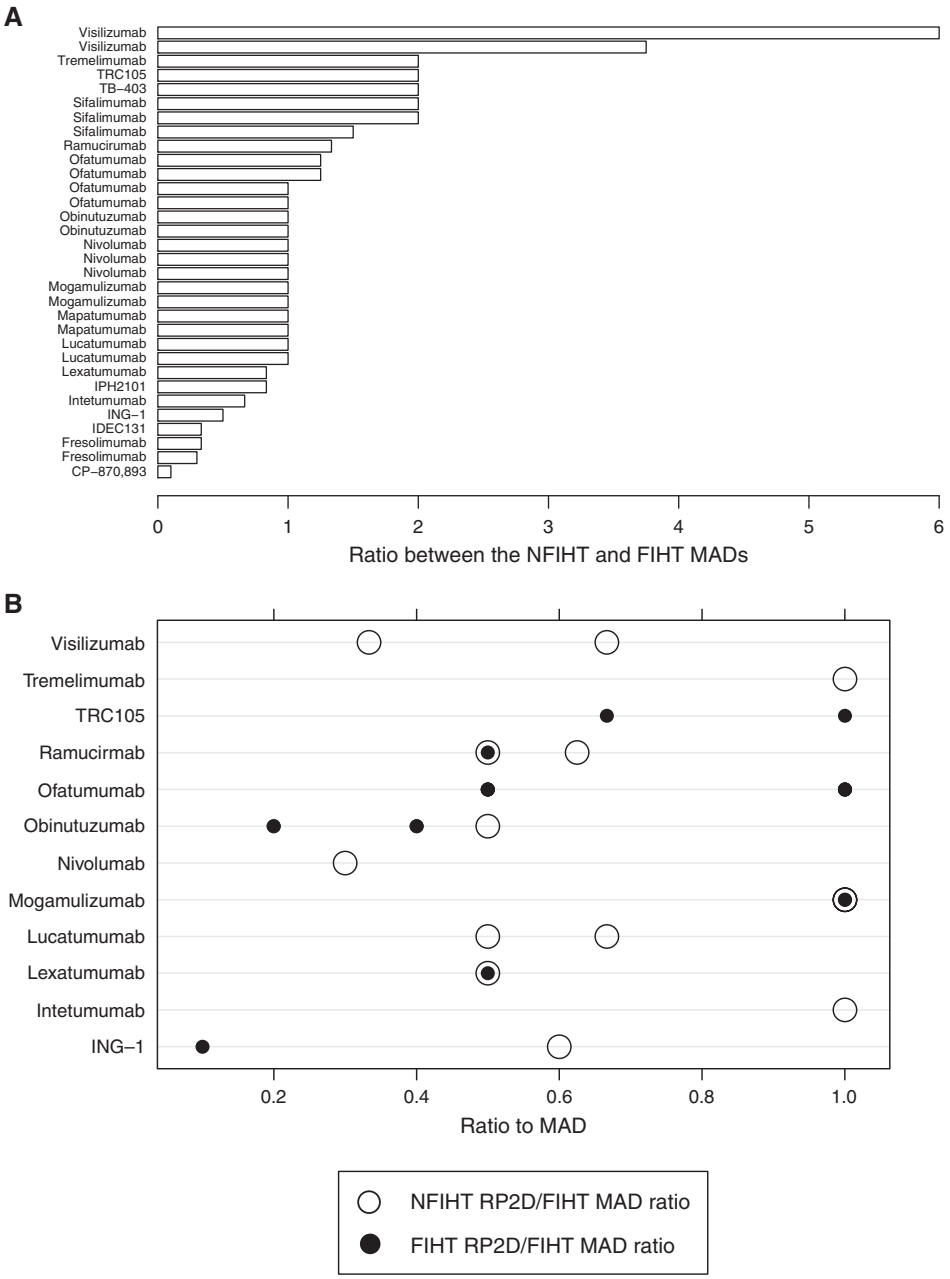

Figure 1. Relationship between NFIHT MAD, NFIHT RP2D and FIHT MAD for dose-escalating NFIHTs. (**A**) Ratio between the NFIHT MAD and the FIHT MAD for each NFIHT with dose escalation. Each bar represents the ratio between the highest planned dose of each NFIHT and the relevant FIHT. The names of tested mAb are indicated on the left. (**B**) Ratio between the NFIHT RP2D and the FIHT MAD for NFIHTs with dose escalation. Filled circles represent the ratio between NFIHT RP2D and FIHT MAD. Each circle refers to a dose tested in one or more NFIHTs. The names of tested mAb are indicated on the left. For comparison, hollow circles represent the ratio between RP2D and MAD in the corresponding FIHT. FIHT=first-in-human trial; MAD=maximum administered dose; NFIHT=non-first-in-human trial; RP2D=recommended phase II dose.

Table 2. Rationale for RP2D selection in trials with dose escalation

References		mAb name	Dose calculation	FIHT		NFIHT			
FIHT	*NFIHT*			*RP2D*	*MAD*	*MAD*	*MTD*	*RP2D*	*Rationale for RP2D selection*
Baselga *et al*, 2000	Tabernero *et al*, 2010	Cetuximab	$mg\,m^{-2}$		100 qw	700 q2w		500 q2w	These data indicate that the closest PK match to the weekly standard regimen will be provided by every-second-week administration of 500 or 600 $mg\,m^{-2}$, with 500 $mg\,m^{-2}$ being the dose of choice on this schedule in terms of convenience and feasibility.
De Bono *et al*, 2004	Goel *et al*, 2007	ING-1	$mg\,m^{-2}$	0.1 qw	1 q3w	2 qw	0.6 qw	0.6 qw	MTD
Mullamitha *et al*, 2007	O'Day *et al*, 2011	Intetumumab	$mg\,kg^{-1}$		10 d1, 29, 36, 43	20 q3w		10 q3w	The clinical activity of the two dose levels was very similar in this study with the exception of the duration of grade 1 uveitic reaction after the first dose (7–8 days in patients treated with 10 $mg\,kg^{-1}$ and 6–14 days in patients treated with 20 $mg\,kg^{-1}$). There was no sequela in any patient. Based on these results, it is recommended that future studies with intetumumab continue to include the 10 $mg\,kg^{-1}$ dose level.
Plummer *et al*, 2007	Wakelee *et al*, 2010	Lexatumumab	$mg\,kg^{-1}$	10 q3w	20 q3w	10 q2w		10 q2w	Based on the previously determined MTD of lexatumumab (10 $mg\,kg^{-1}$ every 21 days), escalation beyond 10 $mg\,kg^{-1}$ was not attempted.
Bensinger *et al*, 2012	Byrd *et al*, 2007	Lucatumumab	$mg\,kg^{-1}$		6 qw	6 qw	3 qw	3 qw	There was essentially 100% saturation of CD40 molecules at the end of each infusion for all dose groups, but this saturation was lost prior to the beginning of the next infusion in the 0.3 $mg\,kg^{-1}$ and 1.0 $mg\,kg^{-1}$ dose cohorts. In the remaining three dose cohorts ($\geqslant$3.0 $mg\,kg^{-1}$), bound lucatumumab remained on circulating chronic lymphocytic leukaemia cells between infusions.
Bensinger *et al*, 2012	Fanale *et al*, 2014	Lucatumumab	$mg\,kg^{-1}$		6 qw	6 qw	4 qw	4 qw	MTD
Yamamoto *et al*, 2010	Kurose *et al*, 2015	Mogamulizumab	$mg\,kg^{-1}$	1 qw	1 qw	1 qw × 8 then q1m		1 qw × 8 then q1m	Although we did not find any dose-limiting toxicity and did not detect Treg depletion at the tumour site, we did not perform dose escalation with concentrations >1 $mg\,kg^{-1}$ because we observed serious skin toxicities in patients with adult T-cell leukaemia during prolonged treatment for more than 1 year with 1 $mg\,kg^{-1}$, and because complete elimination of Tregs in PBMCs was easily obtained with 0.1 $mg\,kg^{-1}$.
Yamamoto *et al*, 2010	Duvic *et al*, 2015	Mogamulizumab	$mg\,kg^{-1}$	1 qw	1 qw	1 qw × 4		1 qw × 4	MAD
Brahmer *et al*, 2010	Ansell *et al*, 2015	Nivolumab	$mg\,kg^{-1}$		10 q2w	3 d1, 28 then q2w		3 d1, 28 then q2w	MAD
Salles *et al*, 2012	Sehn *et al*, 2015	Obinutuzumab	mg	1600/800 and 400/400 d1, 8, 21 then q3w	1200/2000 d1, 8, 21 then q3w	1200/2000 qw		1000/1000 qw	The observed plasma concentration data across the cohorts indicated substantially higher concentrations 14 days after completion of the induction phase at doses of 1000 mg and 1200/2000 mg, indicating target saturation. Consequently, a dose of 1000 mg was chosen for further clinical studies.

Table 2. (Continued)

References		mAb name	Dose calculation	FIHT		NFIHT			
FIHT	*NFIHT*			*RP2D*	*MAD*	*MAD*	*MTD*	*RP2D*	*Rationale for RP2D selection*
Spratlin *et al*, 2010	Chiorean *et al*, 2015	Ramucirumab	mg kg^{-1}	8 q2w	16 q2w	20		8 q2w or 10 q3w	Doses within this range yielded the minimum trough concentrations that exceeded the 20 μg ml^{-1} levels associated with growth inhibition in preclinical human tumour xenograft models and with preliminary evidence of efficacy. In addition, doses of $\geqslant$8 mg kg^{-1} Q2W were associated with relatively stable clearance profiles (as opposed to more dose-dependent patterns seen at lower doses), consistent with saturation of the target-mediated clearance pathway.
Ribas, 2005	Camacho *et al*, 2009	Tremelimumab	mg kg^{-1}		15 single dose	10 q4w		15 every 3 months	During the phase II study, 89 patients received 10 mg kg^{-1} tremelimumab once every month or 15 mg kg^{-1} every 3 months. The results of this study supported the choice of the 15 mg kg^{-1} every 3 months regimen for further clinical development. Within the limitations of this non-comparative phase II two-arm clinical trial, both regimens were associated with durable tumour responses, but 15 mg kg^{-1} every 3 months was more convenient to administer and was associated with fewer and less severe/serious adverse events.
Norman *et al*, 2000	Plevy *et al*, 2007	Visilizumab	μg kg^{-1}		15 once	15 d1, d2	10 d1, d2	10 d1, d2	MTD
Norman *et al*, 2000	Carpenter *et al*, 2002	Visilizumab	mg m^{-2}		15 μg kg^{-1} once	3 d1, d3, d5, d7, d9, d11, d13		3 d1, d3, d5, d7, d9, d11, d13	Our pharmacokinetic data suggest that the size of the first dose of visilizumab affects treatment outcome more than the total cumulative dose. The rates of complete response and survival were higher after a single dose of 3 mg m^{-2} compared with 7 doses of 0.25 or 1.0 mg m^{-2} where the cumulative dose administered was 1.75 mg m^{-2} or 7 mg m^{-2}.
Norman *et al*, 2000	Baumgart *et al*, 2010	Visilizumab	μg kg^{-1}		15 once	12.5 d1, d2		5 d1, d2	Chosen as the optimal clinical dose because of comparable efficacy and less toxicity than with higher doses.

Abbreviations: FIHT = first-in-human trial; mAb = monoclonal antibody; MAD = maximum administered dose; MTD = maximum tolerated dose; NFIHT = non-first-in-human trial; RP2D = recommended phase II dose; qw = one a week; q2w = every 2 weeks; q3w = every 3 weeks; q4w = every 4 weeks.

(17 trials). We then examined the relationship between FIHT RP2D and doses tested in NFIHTs (Figure 2). FIHT RP2Ds (one or more for each mAb) were available for 12 of the 37 mAbs and were tested for 11 mAbs, alone ($n = 5$ mAbs) or in association with other doses ($n = 6$ mAbs). The FIHT MAD was tested for eight mAbs (73%) in 17 trials (45%) of mAbs with available FIHT RP2D. The ratio between the doses tested in NFIHTs and the corresponding FIHT RP2Ds ranged from 0.1 to 5, and in 84% of cases the tested dose/FIHT RP2D ratio was not within 33% on either side of the FIHT RP2D (Figure 2). The FIHT MAD of 17 mAbs (46%) was tested alone or with other doses in 36 trials (35%). Only doses different from the FIHT RP2D or MAD were tested for 16 mAbs (43%) in 37 trials (36%). Finally, we verified that the tested doses were included in the range established as safe in the FIHT and compared them with the FIHT MAD (Figure 2). Only in nine trials on two mAbs, the tested dose was higher than the FIHT MAD. The median tested dose/FIHT MAD ratio was 0.71 (range: 0.25 to 2.5) in trials with comparable dose calculation methods.

Analysis of the correlation of doses and toxicities in RTs and the corresponding FIHT. We retrieved 27 FDA-approved mAbs with a FIHT and 60 RTs on these molecules (Supplementary Table S1). The mAb indication was cancer (solid tumours for eight mAbs, haematological cancers for three mAbs), immune system diseases (13 mAbs) and other diseases (four mAbs). The FIHT MTD was available for only one molecule, whereas the FIHT RP2D was indicated for seven mAbs (26%; five cancer trials and two other trials). We then evaluated the relevance of the FIHT results for the 17 mAbs with the same dose calculation method in FIHT and RTs. The RP2D was tested in RTs of five mAbs (but only in two with the same schedule), and the MAD in RTs of four mAbs (Figure 3). The median RT dose/FIHT MAD ratio was 0.78 (range: 0.1 to 2.5). When considering the nine mAbs for which an RP2D was not available, at least one RT dose was lower than 75% of the MAD for six of them (specifically, lower than 50% for four mAbs and lower than 25% for one). We determined whether the top-three grade 3/4 toxicities in the RTs of each mAb were reported in the corresponding FIHT, and their grade in the FIHT. For only seven

Table 3. Rationale for tested dose selection in NFIHT without dose escalation

References		mAb name	FIHT		NFIHT		
FIHT	NFIHT		MAD	RP2Ds	Dose	Rationale for dose selection	Rationale for dose selection, details
Oberneder *et al*, 2006	Schmidt *et al*, 2010	Adecatumumab	262 mg m^{-2} q2w	164 mg m^{-2} q2w, 262 mg m^{-2} q2w	2, 6 mg kg^{-1} q2w	See details	The dosage regimen and treatment duration selected for this study were based on PK modelling of the phase I clinical study results in patients with prostate cancer.
Oberneder *et al*, 2006	Marschner *et al*, 2010	Adecatumumab	262 mg m^{-2} q2w	164 mg m^{-2} q2w, 262 mg m^{-2} q2w	2, 6 mg kg^{-1} qw × 3 then q2w × 7	See details	A phase I trial in patients with hormone-refractory prostate cancer showed that adecatumumab is well tolerated with low immunogenicity at doses up to 262 mg m^{-2} (approximately 6.6 mg kg^{-1}) every other week.
Furie *et al*, 2008	Bishton *et al*, 2013	Belimumab	20 mg kg^{-1} q3w		10 mg kg^{-1} d1, 15 q28 then q28	See details	These belimumab levels are sufficient to neutralise the cytokine BLYS and are similar to those achieved in studies conducted in systemic lupus erythematous, in which an average peak concentration of 192.4 mg ml^{-1} was achieved at a 10 mg kg^{-1} dose level.
Furie *et al*, 2008	Wallace *et al*, 2009, De Vita *et al*, 2015	Belimumab	20 mg kg^{-1} q3w		10 mg kg^{-1} d1, 15 q28 then q28	NA	
Gordon *et al*, 2001	Ogita *et al*, 2012, Schuster *et al*, 2012	Bevacizumab	10 mg kg^{-1} d1, d28, d35, d42		10 mg kg^{-1} q2w	See details	The chosen dose was higher than the doses used in bevacizumab therapies for normalisation of tumour vasculature (5 mg kg^{-1} q14d) and in line with the dosing of bevacizumab monotherapy used in advanced renal cancer where a survival benefit was indicated (10 mg kg^{-1} q14d).
Baselga *et al*, 2000	Cunningham *et al*, 2004, Pessino *et al*, 2007, Neal *et al*, 2010, Tabernero *et al*, 2010, Maubec *et al*, 2011, Wierzbicki *et al*, 2011, Segelov *et al*, 2016	Cetuximab	100 mg m^{-2} qw		250 mg m^{-2} qw	NA	
Atzori *et al*, 2011	Reidy-Lagunes *et al*, 2012	Dalotuzumab	20 mg kg^{-1} qw	10 mg kg^{-1} qw, 20 mg kg^{-1} q2w, 30 mg kg^{-1} q3w	10 mg kg^{-1} qw	RP2D in FIHT	
Trachtman *et al*, 2011	Stevenson *et al*, 2013	Fresolimumab	4 mg kg^{-1} single dose		3 mg kg^{-1} q3w	See details	This dose was chosen based on non-human primate studies and data from the previous phase I trial in cancer, where an MTD up to 15 mg kg^{-1} was established, but clinical responses were observed in patients at doses of 1 mg kg^{-1} or lower.

Table 3. (Continued)

References		mAb name	FIHT		NFIHT		
FIHT	NFIHT		MAD	RP2Ds	Dose	Rationale for dose selection	Rationale for dose selection, details
Tolcher *et al*, 2009	Tap *et al*, 2012	Ganitumab	20 mg kg^{-1} q2w		12 mg kg^{-1} q2w	See details	In the FIHT, this regimen was tolerated, with a mean serum trough concentration (42 μg ml^{-1}) that exceeded the 90% inhibitory concentration (28 μg ml^{-1}) in a human MiaPaCa-2 cell xenograft model and provided 90% IGF1R receptor occupancy in a surrogate tissue assay.
Tolcher *et al*, 2009	Strosberg *et al*, 2013	Ganitumab	20 mg kg^{-1} q2w		18 mg kg^{-1} q3w	NA	
Scott *et al*, 2007	Krug *et al*, 2007	hu3S193	40 mg m^{-2} qw		10, 20 mg m^{-2} qw	NA	
Vey *et al*, 2012	Korde *et al*, 2014	IPH2101	3 mg kg^{-1} q4w		1 mg kg^{-1} q2m	NA	
Genovese *et al*, 2010	Leonardi *et al*, 2012	Ixekizumab	2 mg kg^{-1} q2w		10, 25, 75, 150 mg q2w 2 × then q4w × 3	NA	
Genovese *et al*, 2010	Gordon *et al*, 2014	Ixekizumab	2 mg kg^{-1} q2w		120 mg q1m	NA	
Genovese *et al*, 2010	Genovese *et al*, 2014	Ixekizumab	2 mg kg^{-1} q2w		80 mg q2w (12w) then q4w	NA	
Tolcher *et al*, 2009	Greco *et al*, 2008, Trarbach *et al*, 2010	Mapatumumab	10 mg kg^{-1} q14		10 mg kg^{-1} q3w	See details	The MTD was not identified at doses up to 20 mg kg^{-1} administered every 28 days. Stable disease was observed in a number of heavily pretreated patients at several dose levels. Therefore, 10 mg kg^{-1} was considered a safe and potentially effective dose for the treatment of non-small cell lung cancer.
Vanhoefer, 2003	Seiden *et al*, 2007	Matuzumab	2000 mg qw		800 mg qw	NA	
Yamamoto *et al*, 2010	Ishida *et al*, 2012		mogamulizumab	1 mg kg^{-1} qw	1 mg kg^{-1} qw	1 mg kg^{-1} qw	RP2D in FIHT
Brahmer *et al*, 2010	Gardiner *et al*, 2013, Borghaei *et al*, 2015, Brahmer *et al*, 2015, Hamanishi *et al*, 2015, Motzer *et al*, 2015a, 2015b, Rizvi *et al*, 2015, Robert *et al*, 2015, Weber *et al*, 2015	Nivolumab	10 mg kg^{-1} q2w		3 mg kg^{-1} q2w	NA	
Salles *et al*, 2012	Morschhauser *et al*, 2013, Salles *et al*, 2013	Obinutuzumab	1200/2000 mg d1, 8, 21, then q3w	400/400, 1600/800 mg d1, 8, 21, then q3w	400/400, 1600/800 mg d1, 8, 21, then q3w	RP2D in FIHT	We based the dose and schedule of nivolumab on safety and activity data from a phase 1 study that showed a similar proportion of objective responses in patients treated with 3 mg kg^{-1} or with 10 mg kg^{-1}; both doses achieved better responses than the 1 mg kg^{-1} dose. The safety profile was similar with each dose and for different tumour types in the phase 1 trial.

Table 3. (Continued)

References		mAb name	FIHT		NFIHT		
FIHT	NFIHT		MAD	RP2Ds	Dose	Rationale for dose selection	Rationale for dose selection, details
Salles *et al*, 2012	Cartron *et al*, 2014, Byrd *et al*, 2016	Obinutuzumab	1200/2000 mg d1, 8, 21, then q3w	400/400, 1600/800 mg d1, 8, 21, then q3w	1000 mg d1, 8, 15 then q3w	NA	
Forero-Torres *et al*, 2012	Ganjoo *et al*, 2015	Ocaratuzumab	375 mg m^{-2} qw		375 mg m^{-2} qw	See details	Phase 2 dose selection was based on safety and preliminary efficacy data and on modelling and simulation of PK data. The latter showed faster elimination of obinutuzumab in the first cycle than in later cycles, indicating the need for a more dose-dense regimen in the first cycle.
Genovese *et al*, 2008	Kappos *et al*, 2011	Ocrelizumab	750 mg m^{-2} q3w		300/600, 1000 mg d1, 15 then q24w	NA	The maximum ocaratuzumab dose of 375 mg m^{-2} was tested to support subsequent testing against rituximab at an equivalent dose.
Hagenbeek *et al*, 2008	Wierda *et al*, 2010	Ofatumumab	1000 mg qw	500 mg qw, 1000 mg qw	300/2000 mg qw × 8 then q4w × 4	NA	
Hagenbeek *et al*, 2008	Coiffier *et al*, 2013	Ofatumumab	1000 mg qw	500 mg qw, 1000 mg qw	300/1000 mg qw	RP2D in FIHT	
Hagenbeek *et al*, 2008	Czuczman *et al*, 2012	Ofatumumab	1000 mg qw	500 mg qw, 1000 mg qw	500, 1000 mg qw	RP2D in FIHT	
Hagenbeek *et al*, 2008	Furtado *et al*, 2014	Ofatumumab	1000 mg qw	500 mg qw, 1000 mg qw	1000 mg qw	RP2D in FIHT	
Hagenbeek *et al*, 2008	van Oers *et al*, 2015	Ofatumumab	1000 mg qw	500 mg qw, 1000 mg qw	1000 mg qw × 1 then q8w	NA	
Hagenbeek *et al*, 2008	Taylor *et al*, 2011	Ofatumumab	1000 mg qw	500 mg qw, 1000 mg qw	700 mg q2w × 2	NA	
Hagenbeek *et al*, 2008	Österborg *et al*, 2016	Ofatumumab	1000 mg qw	500 mg qw, 1000 mg qw	2000 mg qw × 8 then qm	NA	A phase I/II study of ofatumumab, administered as two intravenous infusions of 300, 700 or 1000 mg per 2 weeks apart, in patients with active rheumatoid arthritis and inadequate response to disease-modifying anti-rheumatic drugs demonstrated significant clinical benefit and reasonable tolerability at all doses investigated compared with placebo. The 700 mg dose was considered optimal.
Emu *et al*, 2012	Kennedy *et al*, 2014	Pateclizumab	3 mg q2w		360 mg q2w	See details	Based on safety and efficacy data from a phase I/II study in patients with chronic lymphocytic leukaemia.
Agus, 2005	Gordon *et al*, 2006, De Bono *et al*, 2007, Gianni *et al*, 2010	Pertuzumab	15 mg kg^{-1} q3w	420 mg q3w	840/420, 1050 mg q3w	MAD and RP2D in FIHT	This study regimen was selected based on the following considerations: (1) total exposure was, on average, 60% higher than with the 3 mg kg^{-1} biweekly subcutaneaously doses evaluated in the pateclizumab phase I study; (2) this regimen was expected to result in a maximal

Table 3. (Continued)

References		mAb name	FIHT		NFIHT		
FIHT	NFIHT		MAD	RP2Ds	Dose	Rationale for dose selection	Rationale for dose selection, details
							pharmacological effect as suggested by plateaued reductions in serum CXCL13 level in all dose groups at 1 mg kg^{-1} or higher doses; and (3) this regimen has 2.2- to 4.5-fold exposure safety coverage by the highest exposure level assessed in the phase I study.
Agus, 2005	Agus *et al*, 2007	Pertuzumab	15 mg kg^{-1} q3w	420 mg q3w	840/420 mg q3w	RP2D in FIHT	Pertuzumab infusions every 3 weeks at doses $\geqslant$5.0 mg kg^{-1} maintained serum concentrations in excess of 20 μg ml^{-1}. Dose–response studies of pertuzumab in non-clinical models showed that more than 80% suppression of tumour growth is achieved at steady-state trough concentrations of 5–25 μg ml^{-1}. The recommended regimen for phase II testing was therefore a fixed dose of 420 mg (equivalent to 6 mg kg^{-1} for a 70-kg patient) every 3 weeks. However, using this regimen, steady-state concentrations are only attained after about 90 days. A loading dose of 840 mg was therefore recommended. Simulated trough concentrations for pertuzumab predicted that with a fixed dose of 1050 mg (equivalent to a dose of 15 mg kg^{-1} for a 70-kg patient; the highest dose studied in phase I trials), 90% of patients would achieve steady-state trough concentrations $\geqslant$28.8 μg ml^{-1}. This dose was used because preclinical studies suggested a dose-dependent increase in efficacy.
Agus, 2005	Herbst *et al*, 2007	Pertuzumab	15 mg kg^{-1} q3w	420 mg q3w	840/420 mg q3w	RP2D in FIHT	
Berger *et al*, 2008	Armand *et al*, 2013	Pidilizumab	6 mg kg^{-1} single dose	1 mg kg^{-1} single dose	1.5 mg kg^{-1} q42	NA	
Díaz *et al*, 2003	Alfonso *et al*, 2007	Racotumomab	2 mg q2w		1 mg q2w × 5 then q4w	NA	
Díaz *et al*, 2003	Alfonso *et al*, 2014	Racotumumab	2 mg q2w		1 mg q2w × 5 then q4w × 10	NA	
Díaz *et al*, 2003	Neninger *et al*, 2007	Racotumumab	2 mg q2w		2 mg q2w × 5 then q4w 6 ×	NA	
Spratlin *et al*, 2010	Zhu *et al*, 2013, Fuchs *et al*, 2014, Garcia *et al*, 2014, Penson *et al*, 2014	Ramucirumab	16 mg kg^{-1} d1, 15 then q2w	8 mg kg^{-1} d1, 15 then q2w	8 mg kg^{-1} q2w	RP2D in FIHT	
Spratlin *et al*, 2010	Carvajal *et al*, 2014	Ramucirumab	16 mg kg^{-1} d1, 15 then q2w	8 mg kg^{-1} d1, 15 then q2w	10 mg kg^{-1} q3w	NA	A phase II dose of 8 mg kg^{-1} every 2 weeks was selected because it was associated with the minimum drug

Table 3. (Continued)

References		mAb name	FIHT		NFIHT		
FIHT	NFIHT		MAD	RP2Ds	Dose	Rationale for dose selection	Rationale for dose selection, details
							concentrations that exceeded the levels associated with tumour growth inhibition in preclinical models and with PK profiles suggesting receptor saturation, and because preliminary efficacy was observed across a range of phase I doses and schedules.
Paz-Ares *et al*, 2011	Delord *et al*, 2014	RGT160	1400 mg d1, d8 then q2w	1400 mg d1, d8 then q2w	1400 mg d1, d8 then q2w	RP2D	
Gordon *et al*, 2010	Schöffski *et al*, 2011, Wen *et al*, 2011	Rilotumumab	20 mg kg^{-1} d1, 29 then q2w	10 mg kg^{-1} q2w, 15 mg kg^{-1} q3w, 20 mg kg^{-1} q4w	10, 20 mg kg^{-1} q2w	MAD and RP2D in FIHT	
Bartlett *et al*, 2008	Forero-Torres *et al*, 2010	SGN-30	12 mg kg^{-1} qw	6 mg kg^{-1} qw	6, 12 mg kg^{-1} qw × 6 then 2 weeks off	MAD in FIHT, see details	
Bartlett *et al*, 2008	Duvic *et al*, 2009	SGN-30	12 mg kg^{-1} qw	6 mg kg^{-1} qw	4, 12 mg kg^{-1} q2w/q3w	See details	Based on the assessment of rilotumumab serum concentration in the FIHT and values of 90% inhibitory concentrations predicted in U-87 MG glioblastoma cell proliferation assays, 10 mg kg^{-1} was selected as the starting dose.
Scott *et al*, 2003	Hofheinz *et al*, 2003	Sibrotuzumab	50 mg m^{-2} qw		100 mg qw	NA	The first 40 patients enrolled in the study (15 in the Hodgkin lymphoma group and 25 in the anaplastic large cell lymphoma group) received SGN-30 at 6 mg kg^{-1} weekly. To increase the objective response rates and after an interim analysis of the safety data and review of the response data from the previous phase I study, SGN-30 dose was increased to 12 mg kg^{-1} weekly for the remaining patients.
Rosen *et al*, 2012	Duffy *et al*, 2015	TRC105	15 mg kg^{-1} qw	10 mg kg^{-1} qw or 15 mg kg^{-1} q2w	15 mg kg^{-1} q2w	RP2D	The first six patients enrolled received six doses (one course) of SGN-30 at 4 mg kg^{-1} administered as i.v. infusion every 2–3 weeks. If there was no response, the dose could be increased to 12 mg kg^{-1}. A protocol amendment increased the starting dose to 12 mg kg^{-1}, which was given to 17 patients.
Herbst *et al*, 2009	D' Angelo *et al*, 2015	Trebananib	30 mg kg^{-1} qw	30 mg kg^{-1} qw	30 mg kg^{-1} qw	RP2D in FIHT	
Herbst *et al*, 2009	Moore *et al*, 2015	Trebananib	30 mg kg^{-1} qw	30 mg kg^{-1} qw	15 mg kg^{-1} qw	NA	
Ribas, 2005	Chung *et al*, 2010, Kirkwood *et al*, 2010, Ralph *et al*, 2010, Sangro *et al*, 2013	Tremelimumab	15 mg kg^{-1} single dose		15 mg kg^{-1} q90	NA	
Norman *et al*, 2000	Carpenter *et al*, 2005	Visilizumab	0.015 mg kg^{-1} (once)		3 mg m^{-2} single dose	NA	

Table 3. (Continued)

References		mAb name	FIHT		NFIHT		
FIHT	NFIHT		MAD	RP2Ds	Dose	Rationale for dose selection	Rationale for dose selection, details
Norman *et al*, 2000	Sandborn *et al*, 2010	Visilizumab	0.015 mg kg^{-1} (once)		5 μg kg^{-1} d1, d2	See details	A phase I/II trial was conducted to evaluate the safety and efficacy of multi-dose tremelimumab regimens. In the phase II portion of the study, patients ($n=89$) received 15 mg kg^{-1} administered every 90 days or 10 mg kg^{-1} every month. The 15 mg kg^{-1} every 90 days regimen was selected for further development based on the incidence of grade 3/4 adverse events (13% with 15 mg kg^{-1} every 90 days *vs* and 27% with 10 mg kg^{-1} every month, respectively) and serious adverse events (9% and 25%).
Ricart *et al*, 2008	Bell-McGuinn *et al*, 2011	Volociximab	15 mg kg^{-1} d1, 15, 22, 29, 36 then qw		15 mg kg^{-1} qw	MAD in FIHT	In a phase I study, visilizumab was well tolerated in patients with steroid-resistant acute graft *vs* host disease, and improvement was documented in 10 of 11 patients who received a single dose (3 mg m^{-2}) of visilizumab.

Abbreviations: FIHT = first-in-human trial; mAb = monoclonal antibody; MAD = maximum administered dose; MTD = maximum tolerated dose; NFIHT = non-first-in-human trial; PK = pharmacokinetics; RP2D = recommended phase II dose; qw = one a week; q2w = every 2 weeks; q3w = every 3 weeks; q4w = every 4 weeks; qm = every month.

mAbs (25%) at least two of the top-three RT grade 3/4 toxicities were reported as grade 3/4 in FIHT. Conversely, for 16 (57%) none of the top-three grade 3/4 toxicities described in the RTs was reported as grade 3/4 in FIHT. In addition, for seven (25%) of mAbs none of the top-three grade 3/4 toxicities was reported in FIHT.

DISCUSSION

In our previous analysis concerning the FIHTs of mAbs published between 2000 and 2013, we showed that, for most of the tested molecules, acute toxicity events were rarely observed and did not allow the identification of an MTD. This frequently led to doubtful or questionable recommendations about the RP2D that was determined on the basis of surrogate endpoints (Tosi *et al*, 2015). Here, we analysed the NFIHTs of the same mAbs to evaluate how these trials used the FIHT-derived results, particularly the FIHT RP2D and MAD. We also investigated whether the FIHT results were relevant in the case of FDA-approved mAbs, relative to the tested doses and toxicities observed in RTs.

In the examined dose escalation NFIHTs, the dose level scheme was conservative relative to the FIHT, severe toxicities were infrequent, the MTD was rarely determined and the RP2D was indicated in a minority of trials. In addition, the rationale for RP2D selection was infrequently available and not always stringent, when present. These results indicate that even when a dose escalation trial for an mAb is performed in post-FIHT settings, a significant uncertainty persists over the RP2D indication. Moreover, we found that the FIHT RP2D had a limited influence on dose selection in phase II–III NFIHTs. This is in striking contrast with what generally occurs in anticancer drug development, where the final FDA-approved dose is within 20% on either side of the FIHT RP2D in 73% of cases (Jardim *et al*, 2014). In addition, the FIHT MAD was frequently tested in trials of mAb with available RP2D, suggesting a lack of confidence in the RP2D selection criteria. On the other hand, the FIHT MAD constituted a widely accepted upper limit for dose selection in phase II–III NFIHTs. Frequently, we could not retrieve a convincing justification for dose selection in NFIHTs of mAbs. In a significant percentage of trials, the dose tested in NFIHTs without dose escalation did not correspond to the RP2D or MAD and no rationale for dose selection was available, which did not allow evaluating whether the assumptions underlying the choice were appropriate. When the FIHT RP2D or MAD was not used to inform decisions about the dose to be tested in NFIHTs, preclinical data on the drug effective concentration and clinical PK data were frequently the parameters of choice, notably the serum concentrations attained in clinical trials. However, due to their size, mAb penetration in tissues occurs mainly by convective transport and is characterised by slow diffusion rates in tumour tissue (Tabrizi *et al*, 2010; Dostalek *et al*, 2013; Tibbitts *et al*, 2016). This poor tumour uptake is mostly explained by the scarce tumour vascularisation and the increased interstitial fluid pressure, secondary to vessel abnormalities, fibrosis and interstitial matrix contraction (Heldin *et al*, 2004). Consequently, it appears hazardous to simply infer the mAb tumour tissue concentration from their serum level.

The lack of association between the most frequent severe toxicities in FIHT and RTs suggests that the FIHT results are not useful to predict the actual mAb toxicity and that, consequently, an approach based on a toxicity-guided dose selection during the early clinical development of mAbs could be misguiding. Moreover, the

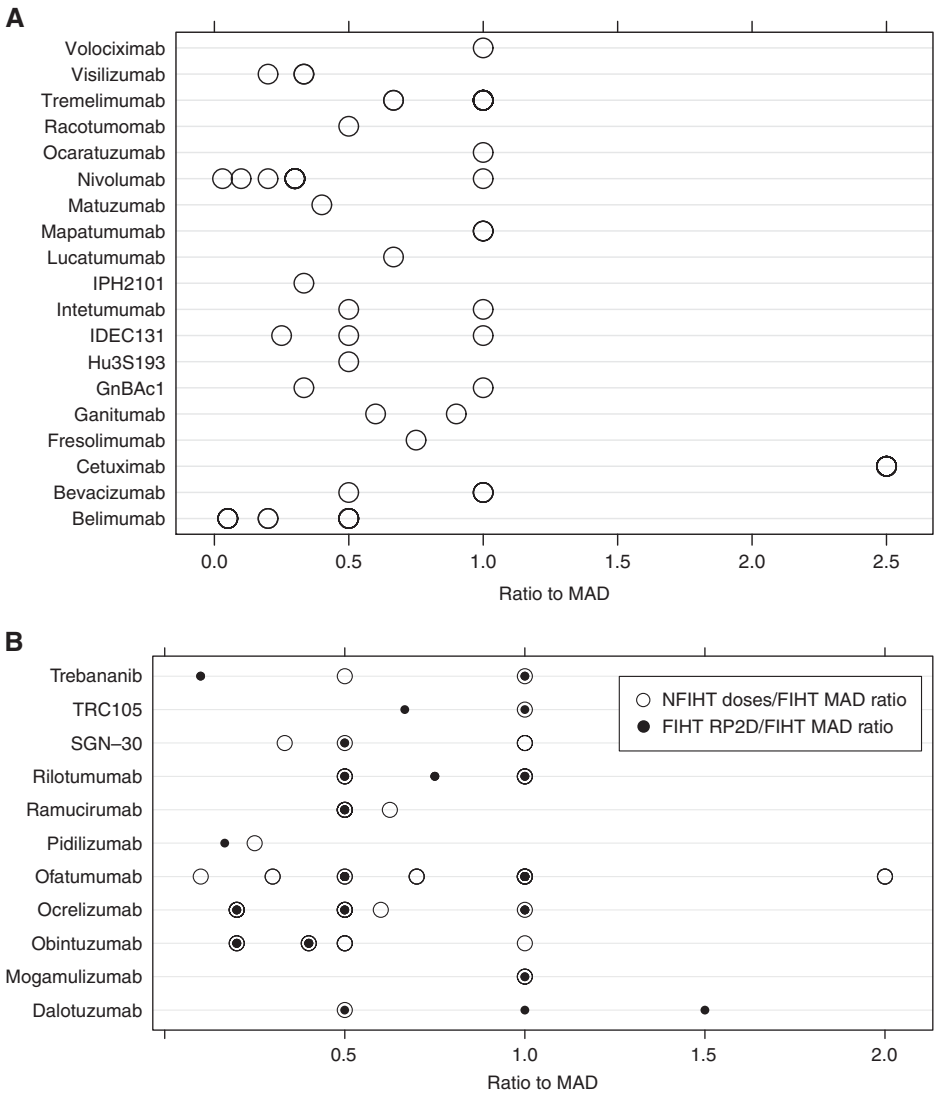

Figure 2. Ratio between the phase II/III NFIHT doses and the FIHT MAD. (**A**) Ratio between the dose tested in NFIHT and the FIHT MAD for each mAb without an FIHT RP2D. Circles represents the ratio between the tested dose of each mAb and the relevant FIHT MAD. Each circle refers to a dose tested in one or more NFIHTs. The names of tested mAb are indicated on the left. (**B**) Ratio between the dose tested in NFIHT and the FIHT MAD for each mAb with an FIHT RP2D. Hollow circles represent the ratio between the tested dose of each mAb and the relevant FIHT MAD. Each circle refers to a dose tested in one or more NFIHTs. Filled circles represent the ratio between the FIHT RP2D and the FIHT MAD. The names of tested mAb are indicated on the left. FIHT=first-in-human trial; MAD=maximum administered dose; NFIHT=non-first-in-human trial; RP2D=recommended phase II dose.

absence of significant toxicity in FIHTs could complicate the choice of the doses to be tested in later trials. Selecting an unnecessarily high mAb dose can be unsafe because rare dose-dependent toxicities could appear later during the drug development process. Inappropriately low doses also can affect efficacy and tolerability because, in the presence of an abundant target mass, the mAb PK could be altered due to target-mediated drug disposition (Cartron *et al*, 2016; Meulendijks *et al*, 2016), especially when the mAb target is also expressed in healthy tissues (Azzopardi *et al*, 2011).

Other approaches for optimal mAb dose selection could be suggested, such as correlating the mAb serum concentration with PD marker variations, or implementing PK/PD models. The choice and accessibility to the measured PD markers are crucial in this setting. Quantitative data on serum (soluble) mAb targets, receptor occupancy on circulating tumour cells, serum markers that indirectly reflect the mAb effect (Mayer *et al*, 2015), or clinical parameters directly linked to disease activity (Azzopardi *et al*, 2015) represent useful PD endpoints for clinical trials. However, for mAbs that alter intracellular signalling, PD marker assessment in tumour cells is an elusive endpoint due to the limited availability of repeated biopsies. Integrative evaluations, including gene expression and phosphokinome profiling in tumour samples and liquid biopsies, could represent suitable tools for dose-finding clinical trials when preclinical studies have established clear correlations between a molecular signature and drug efficacy.

In addition, we previously showed that in mAb FIHTs the safety data relevant for dose selection are collected during a short observation window, which frequently corresponds to the first cycle of treatment (Tosi *et al*, 2015). Indeed, mAb PK could be far from the steady state throughout this time, because of the long drug half-life and dosing schedules that are frequently at least weekly (Tosi *et al*, 2015). In addition, the effect of target-mediated drug disposition (Azzopardi *et al*, 2011), and the rare administration of loading doses (Tosi *et al*, 2015) could contribute to delay reaching the maximal serum concentrations. Consequently,

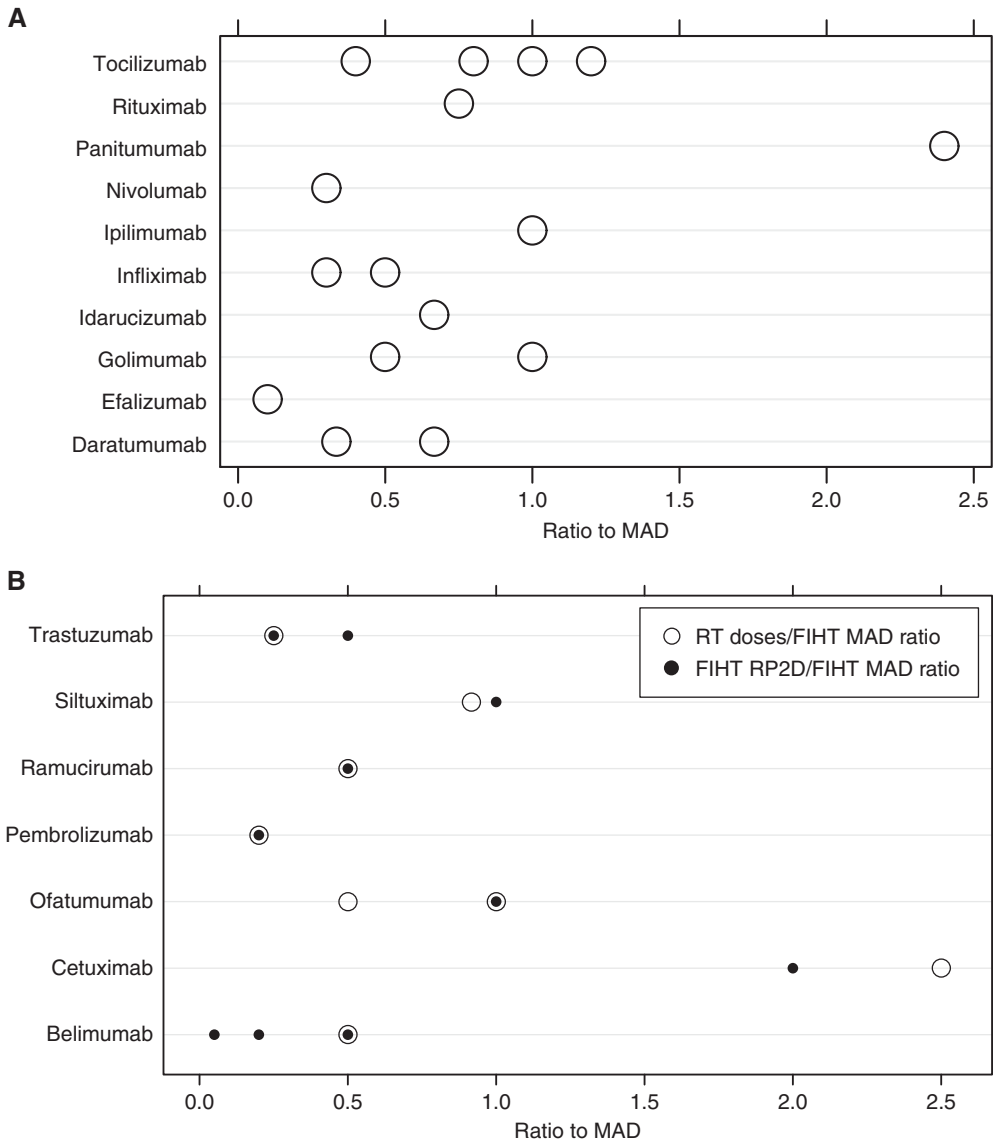

Figure 3. Ratio between RT doses and FIHT MAD. (**A**) Ratio between the dose tested in RT and the FIHT MAD for each mAb without an FIHT RP2D. Circles represent the ratio between the tested dose of each mAb and the relevant FIHT MAD. Each circle refers to a dose tested in one or more RTs. The names of tested mAb are indicated on the left. (**B**) Ratio between the dose tested in RT and the FIHT MAD for each mAb with an FIHT RP2D. Hollow circles represent the ratio between the tested dose of each mAb and the relevant FIHT MAD. Each circle refers to a dose tested in one or more RTs. Filled circles represent the ratio between the FIHT RP2D and the FIHT MAD. The names of tested mAb are indicated on the left. FIHT=first-in-human trial; MAD=maximum administered dose; NFIHT=non-first-in-human trial; RP2D=recommended phase II dose; RT=registration trial.

safety data or PK or PD evaluations obtained in this setting have limited value, suggesting that trial designs including a longer time frame for endpoint assessment at selected doses could be more appropriate.

CONCLUSIONS

We show that the results of FIHTs, particularly standard FIHT endpoints such as MAD, MTD and RP2D, are frequently not taken into account for the design of later clinical studies on mAbs. Moreover, while safety is the main endpoint of mAb FIHTs, other pharmacological aspects are often considered for dose choice in later clinical trials, although the relevance of these surrogate endpoints relative to the mAb clinical activity is questionable. New clinical development strategies are urgently needed for this class of molecules characterised by scarce toxicity, specific PK and high therapeutic potential. Particularly, these data strongly support shorter and more PD-focused phase I studies, as well as randomised phase II studies to compare different mAb doses.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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