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REVIEW

Early-drug development in the era of immuno-oncology: are we ready to face the challenges?

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The classical development of drugs has progressively faded away, and we are currently in an era of seamless drug-development, where first-in-human trials include unusually big expansion cohorts in the search for early signs of activity and rapid regulatory approval. The fierce competition between different pharmaceutical companies and the hype for immune combinations obliges us to question the current way in which we are evaluating these drugs. In this review, we discuss critical issues and caveats in immunotherapy development. A particular emphasis is put on the limitations of pre-clinical toxicology studies, where both murine models and cynomolgus monkeys have underpredicted toxicity in humans. Moreover, relevant issues surrounding dose determination during phase I trials, such as dose–escalation methods or flat versus body-weight dosing, are discussed. A proposal of how to face these different challenges is offered, in order to achieve maximum efficacy with minimum toxicity for our patients.

Key words: immunotherapy, early-drug development, toxicology studies, dose determination

Introduction

During the past few years we have faced an unprecedented evolution in the design of immunotherapy phase I (Ph1) trials. This change is mainly due to the desire to facilitate patient's access to drugs with promising activity from early stages of development, and also a consequence of pharmaceutical companies striving to obtain rapid regulatory approval of their drugs. These facts, added to the strong collaboration of the regulatory agencies, approving drugs based on data obtained from Ph1 trials, has made the number of early-immunotherapy trials increase notably.

The traditional trial design has progressively faded away, and in early-drug development (EDD) units we are currently facing rapid Ph1 dose escalation trials followed by strikingly large expansion cohorts. This is well illustrated with the development of pembrolizumab, an antiprogrammed cell death protein 1 (PD-1) monoclonal antibody (mAb). The initial Ph1 trial started in 2011, and in 2014 pembrolizumab obtained U.S. Food and Drug Administration (FDA) approval for metastatic melanoma patients [1]. A 3-year period represents an exceptional time-line in comparison to the more than 10 years that it traditionally took old drugs to be approved [2], establishing a trend in EDD in immuno-oncology (IO) and being an example followed by many others.

The number of checkpoint inhibitors approved during the last years is unprecedented. Only during 2017, the FDA approved ten indications for immunotherapies [3]. The number of trials registered at ClinicalTrials.gov under 'immunotherapy' and 'oncology' retrieves 1431 registered trials as of April 2018, numbers which are progressively growing.

The fierce competition between pharmaceutical companies and the hype for immune combinations obliges us to question the current way in which we are evaluating these drugs. In this review, we discuss critical issues and caveats in immunotherapy development (ITD), with a particular emphasis on the limitations of pre-clinical toxicology studies (TS) and relevant issues surrounding dose determination during Ph1 trials, and how these

could be improved in order to achieve maximum efficacy with minimum toxicity.

The challenges depicted throughout the article are applicable to immunotherapy drug development (DD) either in monotherapy or in combination. We acknowledge that trial designs of combinations have their own particular challenges added to those discussed here, but these are beyond of the scope of this article. Although immunotherapy comprises a wide range of treatment types with different mechanisms of action, for the purpose of this review we will limit to Immune Checkpoint Targeted Monoclonal Antibodies (ICT mAbs), since they are currently the principal branch of IO clinical research and the most frequently approved therapy so far [4].

Methods

PubMed database was searched under the terms 'murine models', 'mouse models', 'IO' and 'immunotherapy' for the retrieval of murine models' data. Moreover, preclinical and toxicology data from approved ICB mAbs were reviewed. ICB mAbs still under clinical research are only mentioned if data from preclinical and TS were available. Phase I trials of approved ICB mAbs were also reviewed and their characteristics were compared.

Preclinical toxicology challenges

In vitro and *in silico* TS

In order to reduce the risk of toxicity in first-in-human (FIH) trials, it is important to perform nonclinical immunopharmacology and immunotoxicology assays. There are a wide range of *in vitro* [5] and *in silico* [6, 7] assays which try to characterize the immunotoxicity and immunopharmacology of mAbs, in an intent to identify candidate drugs with high efficacy and low adverse toxicity potential. Although the *in silico* techniques are more widely used for small molecule DD, their full potential has been less used for biological DD, and therefore further efforts are needed in this field in order to apply them to ITD [6].

These assays are important for the identification of ICT mAbs with higher risk of producing toxicity, hence helping to detect molecules with an optimum balance between safety and efficacy.

Preclinical models

An ideal pre-clinical model should be able to characterize toxicity, safety and preliminary antitumor activity, but currently there is no optimal model able to mimic human conditions for IO research. A major hurdle is the well-known difference between the human and mice immune system (IS), and that the absence of human targets in mice limits the research with immunotherapies [8]. Since descriptions of each mouse model have been previously done elsewhere [9–12], we will only discuss the main models for IO pre-clinical research. A summary of their advantages and disadvantages is shown in Table 1.

Mice models. Syngeneic mouse models (SMM): This model is based on the inoculation of murine cancer cell lines into immunocompetent mice. Despite this model's limitations, such as arising in an artificial way from genetically homogeneous cancer cells, or the rapid tumor growth they present and thus not managing to mimic completely the human tumor microenvironment (TME), these models continue to be the most commonly used in IO. This lies on the fact that—due to its intact IS—this model allows the evaluation of mechanisms of action and the study of IO drug activity [9]. A major contribution of SMM to ITD was its use in the identification of the first actionable immune checkpoints, such as PD-1, programmed cell death-ligand 1 (PDL-1) and cytotoxic T-lymphocyte-associated protein 4 [13, 14].

Patient derived xenografts (*PDX*): The most frequently used animal models in non-IO cancer research are PDX, where freshly resected pieces of human solid tumors are implanted into immunodeficient mice [15–17]. Although PDX have the advantage of preserving the tumor's original histological and molecular complexity very faithfully [18, 19], the original TME is not well represented as mice are immunodeficient [20]. This fact makes this model not feasible for the research of immunomodulatory effects of antineoplastic drugs [21]. Despite this, it can be used for IO research when exogenous immunity is introduced (e.g. certain cell therapies or passive immunization) [9].

Genetically engineered mouse models (*GEMM*): GEMM consist of genetically engineered mice with germline transgenic expression of oncogenes or with the inactivation of tumor suppressor genes. Tumors spontaneously arise, providing a physiologically relevant TME [17, 22]. Therefore, tumors grow in a full immunocompetent environment, thus being a good model to evaluate therapeutic responses to checkpoints and for biomarker analyses. However, since all the cells in this model have an altered genome, different tumors can develop synchronically. This fact can overwhelm the IS due to the multiplicity of the events [23], therefore hampering data interpretation. For this reason, GEMMs have not been widely used for IO research [9].

Humanized mouse models (*HMM*): Given the fact that the aforementioned models may not accurately reflect human immunity nor the interaction between the IS and the tumor cells, the development of models of human tumors in mice with competent human immunity has become a priority. For the humanization of mice, human immune cells have to graft into immunodeficient mice. This is usually accomplished by two means (i) engraftment of human peripheral blood mononuclear cells (PBMC) [24, 25] or (ii) engraftment of stem cells of human fetal liver or umbilical cord blood [8, 26]. Despite the fact that there are several challenges to be addressed with humanized mice, such as graft-versus-host disease (GvHD) [27], they seem the optimal model to study the interrelation between human tumor and human immune cells, and thus are the most promising models for future IO research and evaluation of agents that target checkpoint blockade pathways [9, 11]. For this reason, most efforts are currently focusing on improving this model. Nevertheless, immune-mediated toxicity is an important issue, since it can be indistinguishable from GvHD, making this model not reliable for predicting toxicity in humans.

Toxicology studies. In order to conduct a Ph1 clinical trial, nonclinical TS have to be carried out in appropriate species, and the relevance of the selected animal model has to be justified [28, 29].

Table 1. Characteristics of the main four mouse models used in IO

Mouse model	Advantages	Disadvantages
Syngeneic tumor models	• Intact murine immune-system • Useful for identification of actionable immune-checkpoints • Allows to study mechanisms of action and efficacy	• Tumor arises in an artificial form from genetically homogeneous cancer cells (mouse tumor cell lines) • Rapid tumor growth not similar to human TME • Can only test molecules targeting the mice IS • Availability of few cancer types; limited response to IO drugs
Patient derived xenograft	• Original histological and molecular complexity remains very similar and faithful to the original tumor • Allows the study of certain cell therapies • The remaining partial immunity in the mice can be studied/used as therapies	• Defective murine immune-system • Lacks the tumor-immune surveillance and the immune-mediated editing
GEMM	• Presence of physiologically relevant TME • Useful for evaluation of therapeutic responses to checkpoints and biomarker analyses	• Synchronic tumors may overwhelm the IS due to the multiplicity of the events • Can only test molecules targeting the mice IS
Humanized mice	• Human tumors with competent human immunity • Allows study of the interrelation between human tumor and human immune cells • Useful for pre-clinical testing regarding study of mechanisms of action, toxicity (detection of human off-target effects) and efficacy • Most promising models for future IO research and evaluation of agents that target checkpoint blockade pathways	• GvHD • Uncertainty whether functional human immunity resembles real human immunity for IO research • Bad predictor of toxicity in humans since immune-mediated toxicity and GvHD can be indistinguishable

GEMM, Genetically engineered mouse models; GvHD, graft-versus-host disease; IO, immuno-Oncology; IS, immune system; TME, tumor microenvironment.

Because of similarities in the expression of target molecules, cynomolgus monkeys are the most frequent species used for testing in the repeated dose TS [30]. Despite all the efforts done in pre-clinical studies, there is always a degree of uncertainty with medicinal products with high human-specificity. Thus, a cautious approach in conduction of FIH trials is always needed [31]. An unfortunate example of under-prediction of toxicity was observed with CD28 superagonist mAb TGN1412 [32]: in this case, the failure to predict a cytokine storm in humans was probably due to the lack of CD28 expression on the CD4+ effector memory T cells of the species which was used for pre-clinical safety testing of the mAb [33]. In fact, most of the human side-effects of ICT mAbs where not described in nonhuman primates during TS, as illustrated in Table 2. Therefore, the limitation in predicting toxicity when performing TS of ICT mAbs in nonhuman primates is a frequent and relevant situation in ITD.

Summarizing this data, it is clear that there is currently no ideal model for ITD. *In vitro* and *in silico* TS must be improved for precise prediction of toxicities, adapting them for ICT mAbs. Moreover, in order to prioritize which new agents should be further pursued, we face the dilemma that the mouse models that could better evaluate activity are not useful to determine toxicity. Currently, the most frequently used models for IO research are SMM, but to obtain a whole picture of activity and toxicity, an approach could be to test new ITs on more than one of the models mentioned before, trying to cover the multiple hurdles that have been depicted. The HMM might represent better the interaction between human tumor and human IS, and is, in our opinion, the most promising model for the study of antitumoral activity. For toxicity studies, SMM seem to be the ones which better represent the interaction between host cells and a competitive IS, assuming the differences between a human IS and a mouse IS. There are evident time and money issues in using multiple models for each drug, but an important effort is needed for the overall improvement of preclinical IO research. Regarding animal TS and learning from the superagonist mAb TGN1412 incident, special care has to be taken when selecting the species for animal TS, with particular attention to the characterization of the target's expression.

Stakeholders involved in the development of immunotherapies need to be fully aware of these limitations when developing FIH protocols in IO. There can be an underestimation of toxicity and this should affect the study design to minimize the risk (for example staggering the inclusion of patients, prolonging observation period after infusions or even requiring mandatory hospitalization for the first 24 h). Importantly, these studies should be carried out cautiously in EDD Units with expertise in managing immune-mediated side-effects and with access to intensive care units.

Dose determination challenges

Traditional DD lies under the paradigm that the higher the dose, the higher the effect and the higher the toxicity. While this might be true for chemotherapy, it does not seem to be applicable to ICB mAbs, since no dose-limiting toxicities (DLTs) were found in the vast majority of the six regulatory approved ICT mAbs Ph1 trials (Table 3). Moreover, the maximum tolerated dose (MTD)

Table 2. Preclinical toxicities observed across different immune-checkpoint antibodies, compared with known human toxicities

		Pre-clinical				Clinical		
Antibody	**Company**	**Species**	**Dose**	**Toxicities**	**Ref.**	**Dose**	**Toxicities**	**Ref.**
Atezolizumab (anti-PDL-1)	Genentech	Mouse C57BL/6, CD-1	0–50 mg/kg	Asymptomatic neuropathy of the sciatic nerve. Anatomic pathology: minimal axonal degeneration with lymphocytic infiltration (not in CD-1 mice)	[71]	1200 mg i.v./ 21 days	**AEs overall incidence** (50%–70%) **IrAEs overall incidence** • Any grade: 16%–17% • Grade 3–4: 5%–6% **By type:** Cutaneous (rash, pruritus) 15%–20% (G3–4: <2%) Altralgia 7% (G3–4: 0%) Diarrhea 8% (G3–4: colitis 1%) LFTs increase 3% (G3–4: 1%) Neumonitis 2% (G3–4: 1%) Nephritis/Kidney failure 2% (G3, 4 1%) **General AEs** Fatigue 30 % (G3–4: 2%) Nausea 14% (G3–4: 0%) Anorexia 12% (G3–4: 1%) Pyrexia 9%	[72–76]
		cynomolgus monkey	0–5 0 mg/kg	Asymptomatic inflammation of several organs (heart, liver, kidney, stomach, epididymis, periaortic connective tissue, tongue, pancreas, cecum, rectum, reproductive tract). Anatomic pathology: mixed inflammation around and involving blood vessels.				
Ipilimumab (anti-CTLA-4)	BMS	Cynomolgus monkey	10 mg/kg	No side-effects, no histological changes	[77]	3 or 10 mg/kg every 21 days	**AEs overall incidence** (50%-90%) **IrAEs overall incidence** • Any grade: 50%–75% • Grade 3–4: 10%–25% **By type:** Cutaneous (rash, pruritus) 40%–70% (G3–4: 0%–4%) Endocrine (hypophysitis) 4%–6% (G3–4: 1%–5%) Gastrointestinal (Diarrhea-Colitis) 29%–46% (G3–4: colitis 5%–23%) Hepatitis 3%–9% (G3–4: 3%–7%) Pancreatitis <1.5% Uveitis/episcleritis <1% Neuropathies <1%	[42, 78–81]
Nivolumab (anti-PD-1)	BMS	Cynomolgus monkey	Up to 50 mg/kg	No side-effects	[82]	3 mg/kg every 15 days	**AEs overall incidence** (50%–60%) **IrAEs overall incidence**: Any grade: 45%–50% Grade 3–4: 8%–9% **IrAEs by type:** Cutaneous (rash, pruritus) 15%–20% (G3–4: <2%) Altralgia 7% (G3–4: 0%) Gastrointestinal (diarrhea-Colitis) 8% (G3–4: 1%)	[76, 80, 83]

Continued

Table 2. *Continued*

		Pre-clinical				Clinical		
Antibody	**Company**	**Species**	**Dose**	**Toxicities**	**Ref.**	**Dose**	**Toxicities**	**Ref.**
							Pancreatitis 1% all grades. Hepatitis 4%–5% (G3–4: <3%) Pneumonitis 3% (G3–4: 1%) Nephritis/kidney failure 2% (G3–4: 1%)	
Pembrolizumab (anti-PD-1)	MSD	Cynomolgus monkey	Up to 200 mg/kg	Increased incidence of inguinal swelling, increase in spleen weight, focal mononuclear cellular infiltration of certain tissues	[84]	200 mg/21 days	**AEs overall incidence** (62%–64%) **AEs by type:** Fatigue 15%–18% (G3–4: 1%–2%) Hypothyrodism 6%–9% (G3–4: 0%) Pruritus 14% (G3–4: 0%) Diarrhea 7% (G3–4: 1%) Nausea 6%–7% (G3–4: <1%) AST increase 3%–6% (G3–4: 1%–2%) Asthenia 4% (G3–4: 1%)	[85, 86]
Ipilimumab +nivolumab	BMS	Cynomolgus monkey	Nivo 10 mg/kg+Ipi 3 mg/kg	20% recurrent diarrhea. Anatomic pathology: spleen changes[a] (33%), lymphnode changes[b] (NA%), gastrointestinal tract inflammation (33%).	[87]	Nivolumab 1 mg/kg+ipilimumab 3 mg/kg followed by nivolumab 3 mg/kg	**AEs overall incidence:** 90%–95% **IrAEs overall incidence:** 85%–90% • Any grade: 80%–90% • Grade 3–4: 40% **IrAEs by type** Cutaneous (rash, pruritus) 60%–70% (G3–4: 7%–8%) Gastrointestinal (diarrhea-Colitis) 40%–50% (G3–4: 10%–20%) Hepatitis 25%–30% (G3–4: 15%–20%) Pancreatitis 10% all grades (lipase elevation) Pneumonitis 6%–8% (G3–4: <2%) Nephritis/kidney failure <5% (G3–4: <2%) **General AEs** Fatigue 30%–40% (G3–4: 4%–5%) Pyrexia 15%–20% (G3–4: <2%) Arthralgia 10%–15% (G3–4: <1%) Nausea 20%–30% (G3–4: <2%)	[76, 80, 88, 89]
			Nivo 50 mg/kg+Ipi 10 mg/kg	40% recurrent diarrhea; 20% decreased food consumption. A single male monkey in the high-dose group was found dead on day 23 (the animal's early death was attributed to acute gastric dilatation (bloat). Anatomic pathology: spleen changes[a] (80%), lymphnode changes[b] (NA%), gastrointestinal tract inflammation (60%)				
Anti-LAG3 (BMS-986016)	BMS	Nonhuman Primates	NA	No side-effects	[90]	20–800 mg	**Overall incidence** Any grade: 50% Grade 3/4: 9% **AE by type** Fatigue 27% (G3–4: 0%) Decreased appetite 14% (G3–4: 0%) Myalgia 9% (G3–4: 0%) Nausea 9% (G3–4: 0%) Lipase increased 5% (G3–4: 5%)	[91]

Continued

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Table 2. *Continued*

		Pre-clinical				Clinical		
Antibody	**Company**	**Species**	**Dose**	**Toxicities**	**Ref.**	**Dose**	**Toxicities**	**Ref.**
							Rash maculopapular 9% (G3–4: 5%)	
anti-LAG3 +nivolumab	BMS	Nonhuman primates	NA	Lymphoid infiltration of choroid plexus (NA%)	[90]	Anti-LAG3 80 mg+nivolumab 240 mg i.v./15 days	**AEs overall incidence** 46% Any grade: 46% Grade 3–4: 9% **AE by type** Fatigue 9% (G3–4: 0%) Diarrhea 6% (G3–4: 0.5%) Pruritus 6% (G3–4: 0%) AST increased 4% (G3–4: 1.4%) Colitis 6% (G3–4: 3.3%) Arthritis 0.5% (G3–4: 0%)	[92]
Urelumab (CD137 agonist)	BMS	Nonhuman primates	NA	No side-effects	[90]	0.1–15 mg/kg	Fatigue 14%–24% Nausea 5%–13% Anorexia 3.6%–12.2% Rash/pruritus 5%–20% Hepatitis 30%–60% Pyrexia 2%–6% Neutropenia 14%–28%	[93, 94]
Urelumab +nivolumab	BMS	Nonhuman primates	NA	NA	[90]	Urelumab 8 mg/28 days+nivolumab 240 mg/15 days	**Overall incidence**: 63% Grade 3–4: 17% **AE by type** Fatigue 31% ALT increased 11% Anemia 10% AST increased 9%	[94, 95]
GITR agonist (BMS-986156)	BMS	Nonhuman primates	NA	No side-effects	[90]	BMS-986156 10–800 mg i.v./15 days	**Overall AEs incidence:** 59% No grade 3–4 **AE by type** Fatigue 10% Nausea 17% Pyrexia 30% Anorexia 3% Diarrhea 6% Arthralgia 10%	[96]

N, nivolumab; I, ipilimumab; NA, not available.

[a]Spleen changes: lymphoid follicle hypertrophy and/or marginal zone expansion.

[b]Lymphnode changes: decreased germinal centers and/or hypocellularity.

Table 3. Phase I trials of currently approved checkpoint inhibitors

Antibody	Type of escalation	Range of doses (mg/kg)	Schedule	DLT period	RP2D	DLT	MTD	RP2D determination	Registered dose (s)	
Ipilimumab	No standard escalation, multiple phase I/II monotherapy or combination trials	0.1–20	Single dose, Q3W, Q8W	NA	3 mg/kg Q3W and 10 mg/kg Q3W	No	ND	NA	Unresectable or metastatic melanoma: 3 mg/kg. Adjuvant melanoma stage III: 10 mg/kg	[97–102]
Nivolumab	3+3 design	0.1–10	Q2W	56 days	Initially 3 mg/kg Q2W; later some indications changed to flat dose 240 mg Q2W based on dose–/exposure–response and safety analysis [71]	No	ND	Based on an integrated analysis of safety and efficacy, dose–response/exposure–response relationships of efficacy, safety, and pharmacodynamic biomarkers	Unresectable or metastatic melanoma, metastatic NSCLC, advanced renal cell carcinoma: 240 mg. In combination with ipilimumab: 1 mg/kg	[103, 104]
Pembrolizumab	3+3 design	0.005–10	Q2W, Q3W, Q4W	28 days	2 mg/kg Q3W to 10 mg/kg Q2W, being 2 mg/kg Q3W chosen for pivotal trials; later new dosing introduced: 200 mg flat dose Q3W [72]	No	ND	Translational modeling and simulation [58]	200 mg	[52]
Atezolizumab	3+3 design	0.01–20	Q3W	21 days	1200 mg flat dose Q3W	No	ND	Preclinical and clinical data, population PK analysis	1200 mg	[105]
Avelumab	3+3 design	1–20	Q2W	21 days	10 mg/kg Q2W	Yes	ND	Pharmacokinetics, target occupancy, immunological analysis	10 mg/kg	[106]
Durvalumab	3+3 design	0.1–10, 15	Q2W, Q3W	28 days (Q2W) or 42 days (Q3W)	10 mg/kg Q2W	No	ND	Pharmacokinetics, pharmacodynamics, clinical safety data	10 mg/kg	[107–110]

MTD, maximum tolerated dose; ND, not defined; Q2W, every 2 weeks; Q3W, every 3 weeks.

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Table 4. Representative trials showing dose–response relationship

IO Abs	Tumor	Doses	ORR	PFS	OS	Ref.
Nivolumab	metastatic renal cell carcinoma	0.3 mg/kg 2 mg/kg 10 mg/kg Difference	20% 22% 20% Stratified odds ratio: 2 versus 0.3 mg/kg: HR 1.2 (80% CI 0.6–2.4) 10 versus 0.3 mg/kg: HR 0.9 (80% CI 0.4–1.8) 10 versus 2 mg/kg: HR 0.9 (80% CI 0.4–1.8)	2.7 m (80% CI, 1.9–3.0 m) 4.0 m (80% CI, 2.8–4.2 m) 4.2 m (80% CI 2.8–5.5 m) 2 versus 0.3 mg/kg: HR 1.0 (80% CI 0.7–1.3) 10 versus 0.3 mg/kg: HR 1.0 (80% CI 0.8–1.3) 10 versus 2 mg/kg: HR 1.0 (80% CI 0.8–1.3)	18.2 m (80% CI, 16.2–24.0 m) 25.5 m (80% CI, 19.8–28.8 m) 24.7 months (80% CI 15.3–26.0 months 2 versus 0.3 mg/kg: HR 0.8 (80% CI, 0.6–1.1) 10 mg/kg versus 0.3 mg/kg: HR 0.9 (80% CI, 0.6–1.2)	[48]
Pembrolizumab	Metastatic melanoma	2 mg/kg 10 mg/kg Difference	26% 26% Difference 0%, 95% CI, 14–13; *P*=0.96	22 w (95% CI 12–36) 14 w (12–24) HR 0.84, 95% CI 0.57–1.23	58% (95% CI 47–68)[a] 63% (51–72)[a] HR 1.09 (95% CI 0.68–1.75)	[49]
Pembrolizumab	Metastatic NSCLC	2 mg/kg 10 mg/kg Difference	30% 29% HR NC	3.9 m (95% CI 3.1–4, 1) 4.0 m (2.7–4.3) HR 1.01 (95% CI 0.75–1.36)	10.4 m (95% CI 9.4–11.9) 12.7 m (10.0–17.3) HR 1.12 (95% CI 0.77–1.62)	[50]
Ipilimumab	Unresectable stage III or IV melanoma	3 mg/kg 10 mg/kg Difference	12% 15% HR NC	2.8 m (2.8–2.8) 2.8 m (95% CI 2.8–3.0) HR NC	11.5 m (9.9–13.3) 15.7 m (95% CI 1., 6–17.8) HR 0.84 (95% CI 0.70–0.99; *P*=0.04)	[51]

On the one hand, one trial with nivolumab [61] and two trials with pembrolizumab [53, 62] show no dose–response relationship. On the other hand, a trial with ipilimumab [63] in metastatic melanoma patients showed higher OS at higher ipilimumab doses.

[a]Kaplan–Meier estimated overall survival at 1 year (proportion of patients alive at 1 year).

ORR, overall response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; NC, not calculated; m, months; w, weeks.

was not reached in any of these studies, and the recommended Ph2 dose (RP2D) was determined based on different parameters, such as clinical response plateau, pharmacokinetic (PK) data or PK modeling. The diversity on the methods to determine the RP2D and the fact that two drugs (namely nivolumab and pembrolizumab) changed their dosing regimen actually shows the difficulties when designing IO Ph1 trials. Main pitfalls in the design of these Ph1 trials are summarized in Figure 1.

Dose escalation methods

The starting dose for an FIH Ph1 trial is determined based on the aforementioned TS and the subsequent human-equivalent dose [29, 31, 34]. There is currently no consensus regarding the best escalation method in ITD. Rule-based designs, such as the '3 + 3' design [35] are the most frequently used until recently [36]. This type of design escalates or de-escalates doses according to prespecified rules and based on the presence of DLTs in previous cohorts [37]. Model-based designs (MBD) [38] are a second way of escalating (e.g. escalation with overdose control [39], time-to-event continual reassessment method [40]). MBD use statistical models to estimate the probability of DLTs when increasing doses, taking into account toxicity data from all treated patients; a precise dose–toxicity curve is computed and a confidence interval for the RP2D is provided at the end of the trial [37]. Important advantages of MBD are that they are more flexible, have a higher accuracy at estimating the MTD and require a smaller sample size [41]. A recent review of published trials between 2008 and 2014 shows that 93% of the trials used rule-based designs for dose–escalation, where only 5% used an MBD [36]. This is currently changing, and our personal experience in a large Ph1 Unit is that MBD are progressively being more frequently used for ITD. In our unit, during 2017, 65% of IO Ph1 trials used a 3 + 3 design, and 35% used an MBD. These numbers show that although the implementation of novel-based designs is slow, it is definitively making its way in ITD.

DLT definition and DLT period

As seen across the different Ph1 trials of approved ICT mAbs, DLT periods varied widely, with the shortest being 21 days and the longest 56 days (Table 3). DLT periods commonly correspond to one treatment cycle, but the definition of DLT period of ITs remains unclear since immune-related adverse events have characteristically a late onset [42]. All this raises the question of how severe toxicities beyond the DLT period should influence dose escalation decisions.

A possible approach for handling these late onset toxicities could be to consider them for the definite RP2D determination [43]. For this, severe toxicities occurring outside the predetermined DLT period should be considered separately before defining the RP2D. Data to be carefully analyzed should include

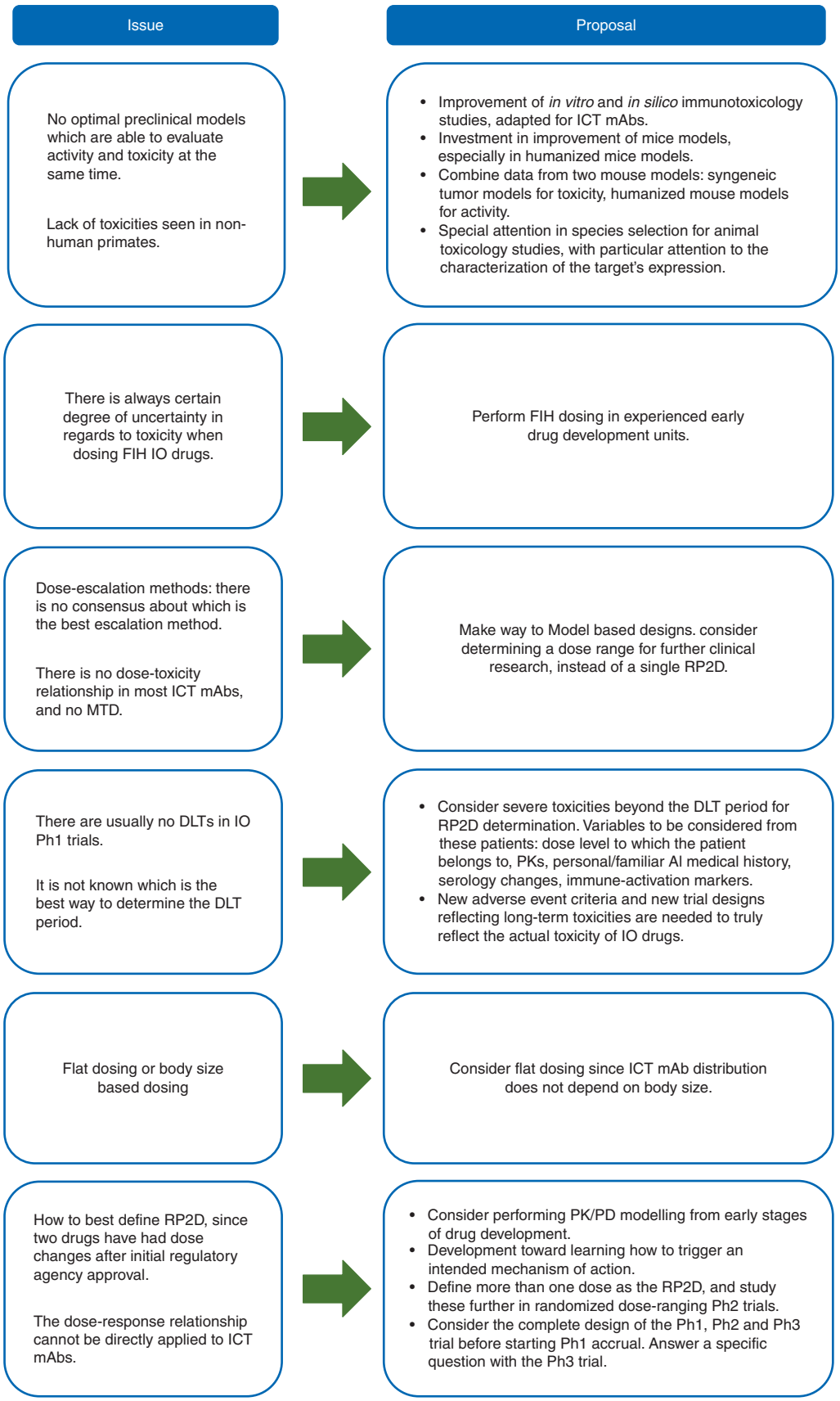

Figure 1. Summary of issues and proposals. FIH, first-in-human; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; MBD, model-based design; RP2D, recommended phase II dose; AI, autoimmune.

personal and familiar autoimmune medical history, baseline and after-treatment serologies, markers of immune activation and [44] and patient's PKs. All these could be considered to decide if a certain severe toxicity occurring outside the DLT period should be taken into account for RP2D determination. Moreover, there is a need for new adverse event criteria and new trial designs reflecting these long-term toxicities in order to truly reflect the actual toxicity of ITs [45].

On top of that, until now in DD the establishment of predictive biomarkers of toxicity has not been a priority, but this is currently becoming of increased importance, and clinical trials should include baseline biomarkers in order to detect patients who are at a higher risk of developing toxicity, a strategy which is currently being implemented in adoptive cell therapy [46, 47].

How to define RP2D

Since the classical DD assumes a direct dose–response curve, the MTD has been used as the principal parameter for determining the RP2D. However, this linear relationship is not directly applicable to IT as is reflected in the clinical data from ICT mAbs (Table 4), where nivolumab [48] and pembrolizumab [49, 50] show no dose–response relationship, in contrast to ipilimumab [51], where higher doses show an increase in overall survival (OS). Although these results could seem contradictory, their different mechanisms of action could partially explain these differences. In any case, the heterogeneity in defining the RP2Ds for the approved ICT mAbs should make us question our current dosing methods. In fact, as it is depicted in Table 3, for the six approved drugs, PK, pharmacodynamic (PD) and safety data were considered for determining the RP2D.

Pembrolizumab's dose determination strategy merits a separate mention. Promising preliminary results from the Ph1b multicohort trial [52] led to seek fast-track development for regulatory submission at a time when little dose ranging had been conducted in the program [49, 53]. Therefore, to determine the dose of pembrolizumab, PK/PD modeling and simulation was carried out, applying mathematical and statistical models to describe disease progression, PK and PD and eventually predicting the relationship between exposure and response and enabling the DD program move forward much faster [54–56].

Indeed, as many ICT mAbs do not have a linear dose–response relationship and given the fact that the MTD is usually not reached, a mathematical model can be of use for the determination of RP2D in these studies [43, 45, 57, 58]. PK modeling arises therefore as a helpful strategy to guide the determination of a suitable RP2D. We acknowledge that establishing a reliable PK/PD model could be challenging in the preclinical setting given the lack of a validated efficacy model and the lack of relevant toxicology species, but an effort in implementing this strategy from early stages of DD could help determine RP2Ds in a more efficient manner.

A further step towards determining an optimal dose during Ph1 trials would be to establish more than one dose as the RP2D, in order to perform posterior dose-range studies. In this manner, a Ph1 trial would actually determine various RP2Ds, which would be further studied in randomized dose-ranging Ph2 trials to define an optimal experimental arm for a phase III (Ph3) trial. Consequently, as recently proposed, Ph1 IO trials would focus on defining a range of Ph2 doses rather than a single RP2D, determining both an upper limit (MTD) and lower limit (minimally effective dose), which may be hypothetical and based on plasma concentrations and/or serum biomarkers [59, 60]. By defining more than one dose for Ph2 trials, a wider range of doses could be studied in a higher number of patients before moving forward to a Ph3 trial. Consequently, more objective data could be gathered, rather than just collecting data from a single RP2D.

In our opinion, given the particularities of IO drugs, with the possibility of long lasting results and not so easy to predict toxicity, Ph1 trials should not only be seen as a way to determine the RP2D, but also as an opportunity to learn how to trigger a certain mechanism of action which makes a patient have a response, and learn which triggered mechanisms produce toxicity. Despite this is currently theoretical, a lot of effort is being done in biomarker development. Therefore, although traditional dose escalating methods are still being used, we have to consider it may not be the best way to do it, since tumor response or toxicities are not always dose related.

Despite all the research in biomarker development there is still not a definitive predictive biomarker of response. Given the multi faced relationship and heterogeneity between the IS and the tumor, combination of biomarker assays will most certainly be required, since a single biomarker will not be able to cover the TME complexity [61, 62]. We clearly need predictive biomarkers to address which patients will likely derive most benefit from any given approach. For this means, thorough research of the TME status and the tumor-immunity interaction has to be carried out, and therefore tumor biopsies and circulating biomarkers are of uttermost importance. This is reflected in the current strategy already implemented in most clinical trials in IO, where baseline and on-treatment biopsies are mandatory.

Another important topic to discuss, given the rapid increase of IO trials in recent years, and seeing that very similar ICT mAbs have achieved the same approved indications [3], is to consider changing strategy for ITD altogether. As proposed recently, before designing an IO trial, an unmet medical need should be detected or an answer to a specific question should be sought. Once any of these are identified, the trials should be subsequently designed, starting by the Ph3 trial, and ending with the design of the Ph1 trial. Only after this is completed, should the accrual for the Ph1 trial actually start [60]. If the DD program does not respond to a specific question, it should be considered to not move forward to the Ph1 trial. This strategy is opposed to the currently used ITD strategy, with a clear competitive setting between pharmaceutical companies, where rapid escalations are carried out, followed by strikingly big expansion cohorts, in an aim to be first to obtain accelerated approval by regulatory agencies. With the currently used DD strategy in IO, we are running the risk—in a near future—of having too many drugs in the market with similar or identical indications, covering the same medical needs. We should therefore question our current strategy, since it is very time- and money-consuming, and we should consider if the patients' benefits driven from this strategy will be proportional to all efforts and resources invested in an ITD program.

Flat dosing versus body-weight dosing

mAb dosing is usually based on body size, with the objective of correcting inter-patient variability in drug distribution and

elimination [63]. However, immunoglobulins tend to distribute to the blood plasma and extracellular fluids, having thus a typically low and constant distribution volume independent on body weight, making dose adjustments based on body size questionable [63, 64]. Moreover, fixed dosing has certain advantages, such as elimination of wastage, increased convenience, reduction in dosing errors and improved compliance [65, 66].

Initially, both nivolumab and pembrolizumab were dosed by body weight, but were later changed to flat dosing. These changes were based on population PK modeling, where both types of dosing demonstrated to be comparable from a PK, safety and efficacy point of view [67–69]. In the case of pembrolizumab, the population PK modeling carried out was later verified in real patients [28, 68].

Discussion

Conclusions

Important clinical benefit is currently seen with immunotherapy, and for the first time we can actually start considering the possibility of cure in the metastatic setting [70]. IO has grown very fast, translating into a significant economical expense and implicating a not insignificant amount of resources. In this context, we have to be critical with our own work and question ourselves if we are actually applying all these efforts in an optimal and rational manner.

As we have seen, preclinical models currently used for IO DD lack the characteristics of ideal models for predicting toxicity and activity in humans, and therefore prioritization of research with humanized mouse models could help this field move forward. When performing TS in animals, the best species for the desired target should be carefully chosen. Despite all these efforts, special caution will always have to be taken when dosing FIH ICT mAbs, as a degree of uncertainty will never be excluded.

IO drugs are being developed basically under the same premises of cytotoxic and targeted agents. Despite this, there are higher uncertainties regarding the dose escalation methods and safety monitoring. Moreover, the possibilities of long term benefit or even cure increase the pressure when evaluating the risk/benefit ratio.

Implementing the use of PK/PD modeling since early stages in DD could have a substantial impact on the development of these agents, mainly to help determine an RP2D or a range of RP2Ds for further clinical development. All nonclinical information available should be also integrated in the decision-making process in order to reduce uncertainties. Moreover, long-term toxicities should be also considered when determining the RP2Ds.

We need novel study designs that help us understand the real mechanisms of action behind ICT mAbs in order to establish predictive biomarkers of response and also predictive biomarkers of toxicity. As we evolve from determining the MTD to the optimal biological dose, the need for validated biomarkers will be of uttermost importance. New response and efficacy assessments will also be needed to optimize and expedite the development of these drugs.

Despite all the limitations in Ph1 IO trials (Figure 1), general safety safeguards, such as a staggered inclusion of patients, exposing few patients to a dose until deemed safe, clear stopping rules and performing these trials in specialized Ph1 units, are helpful to ensure an adequate risk/benefit balance to the patients.

All the stakeholders involved in IO DD—patients, investigators, pharmaceutical industry and regulatory agents—will need to collaborate and think out of the box to ensure an optimization in the development of these agents, obtaining the maximum benefit for our patients in a sustainable way.

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CORRIGENDUM

Early-drug development in the era of immuno-oncology: are we ready to face the challenges?

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