



Towards new methods for the determination of dose limiting toxicities and the assessment of the recommended dose for further studies of molecularly targeted agents – Dose-Limiting Toxicity and Toxicity Assessment Recommendation Group for Early Trials of Targeted therapies, an European Organisation for Research and Treatment of Cancer-led study

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KEYWORDS

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Abstract Introduction: Traditional dose-limiting toxicity (DLT) definition, which uses grade (G) 3–4 toxicity data from cycle 1 (C1) only, may not be appropriate for molecularly targeted agents (MTAs) of prolonged administration, for which late or lower grade toxicities also deserve attention.

Patients and methods: In collaboration with pharmaceutical companies and academia, an European Organisation for Research and Treatment of Cancer (EORTC)-led initiative, Dose-Limiting Toxicity and Toxicity Assessment Recommendation Group for Early Trials of Targeted therapies (DLT-TARGETT), collected data from completed phase 1 trials evaluating MTAs as monotherapy. All toxicities at least possibly related to the study drugs that occurred during C1–6, their type, grade (CTCAEv3.0), and duration as well as patients' relative dose-intensity (RDI), were recorded.

Results: The 54 eligible trials enrolled 2084 evaluable adult patients with solid tumours between 1999 and 2013, and evaluated small molecules (40), antibodies (seven), recombinant peptides (five) and antisense oligodeoxynucleotides (two). A maximum tolerated dose was set in 43 trials. Fifteen percent of the patients received <75% of the intended RDI in C1, but only 9.1% of them presented protocol-defined DLTs. After C1, 16–19% of patients received <75% of the intended RDI. A similar proportion of G $\geq$ 3 toxicities was recorded in C1 and after C1 (936 and 1087 toxicities, respectively), with the first G $\geq$ 3 toxicity occurring after C1 in 18.6% of patients.

Conclusion: Although protocol-defined DLT period is traditionally limited to C1, almost 20% of patients present significant reductions in RDI at any time in phase 1 trials of MTAs. Recommended phase 2 dose assessment should incorporate all available information from any cycle (notably lower grade toxicities leading to such RDI decrease), and be based on achieving >75% RDI.

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1. Introduction

Phase 1 trials represent a crucial and critical step in oncology drug development, as their key objective is to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of novel investigational agents [1]. Most importantly, the recommended dose is almost never re-evaluated at later stages of drug development, while its thorough establishment is a cornerstone of successful drug development [2].

In the era of molecularly targeted agents (MTAs), the traditional phase 1 design faces several challenges, which has been established for conventional cytotoxic chemotherapies (CCC) more than 40 years ago and remained almost unchanged since then. First, these designs have been established to mainly detect acute and severe toxicities only [3–9]. However, contrary to CCC, MTAs are likely to be administered in a chronic fashion and therefore, late severe toxicities, or persistent low grade disabling toxicities also deserve attention and need to be taken into account in the dose limiting toxicity (DLT) definition. The concept of adding 'chronic DLT', besides the classical 'acute DLT' (based on toxicities observed in cycle 1 only and driving the dose-escalation process), to enhance the dose recommendation process for MTAs has recently been proposed [3]. In addition, DLT definitions used in phase 1 trials of MTAs are surprisingly

variable in terms of grade and type, highlighting the absence of consensus for drug development of such agents as well as the need to customise such definitions, notably based on the hypothesised safety profile of the agents under study [10–12]. Finally, recent publications have reported the poorer ability of phase 1 trials of MTAs (compared to CCC) to prognosticate future approved doses of agents as well as their safety profiles [11,13,14].

The purpose of this European Organisation for Research and Treatment of Cancer (EORTC)-led initiative, therefore, was to provide a comprehensive description of all drug-related toxicities reported in phase 1 trials of MTAs (in terms of type, grade, cycle of occurrence) and to investigate their impact on reductions in relative dose intensity (RDI) received by the patient, to ultimately propose recommendations for DLT definition and phase 2 dose recommendation process, customised for phase 1 trials of novel MTAs.

2. Patients and methods

2.1. Partners' contact and studies collection

Between June 2010 and July 2013, a total of 16 academic institutions and pharmaceutical companies were contacted by EORTC headquarters. After establishment

of contracts, four academic institutions (Cancer Research UK (United Kingdom), EORTC, National Cancer Institute-Canada and National Cancer Institute (NCI)) and three pharmaceutical companies (Pfizer, Roche and Sanofi) accepted to provide full toxicity data of completed phase 1 studies evaluating MTAs (Fig. 1).

2.2. Patient and trial characteristics

This retrospective study included clinical trials in which the MTA (defined as any agent with an extra- or intra-cellular target different from those associated with conventional chemotherapy) was given as single agent to adult patients with solid tumours, and for which the relative dose intensity could be calculated. All patients who received at least one cycle of treatment were included in the data set.

2.3. Toxicity data

All grade 1 or above severity adverse events (AEs) reported as at least ‘possibly drug-related’, which were not present at baseline and occurred between cycle 1 and cycle 6 – based on previous data showing that the quasi-totality of AEs occurred during the first 6 cycles, were recorded [3]. To ensure comparability of the AEs over trials that used different grading systems, the grade

of all reported toxicities was harmonised to the National Cancer Institute Common Terminology Criteria of Adverse Events, version 3.0 and regrouped for description according to Medical Dictionary for Regulatory Activities (MedDRA) 15. DLTs were recorded as reported in the original case report form (CRF).

2.4. Statistical analysis

A treatment cycle as defined per protocol was used as time unit, irrespective of the duration in days. Relative dose intensity (expressed as a percentage) was defined for each cycle as the ratio between ‘actual dose/actual duration’ over ‘intended dose/intended duration’. If the same AE was reported at different severity grades during a given cycle, only the worst toxicity grade was taken into account in the statistical analysis. Statistical analyses were performed using the SAS[®] version 9.4 (SAS Institute, Cary, NC) software.

3. Results

3.1. Trial characteristics

A total of 54 phase 1 trials carried out between February 1999 and May 2013 were included in this study (Fig. 1). They included a total of 2084 patients

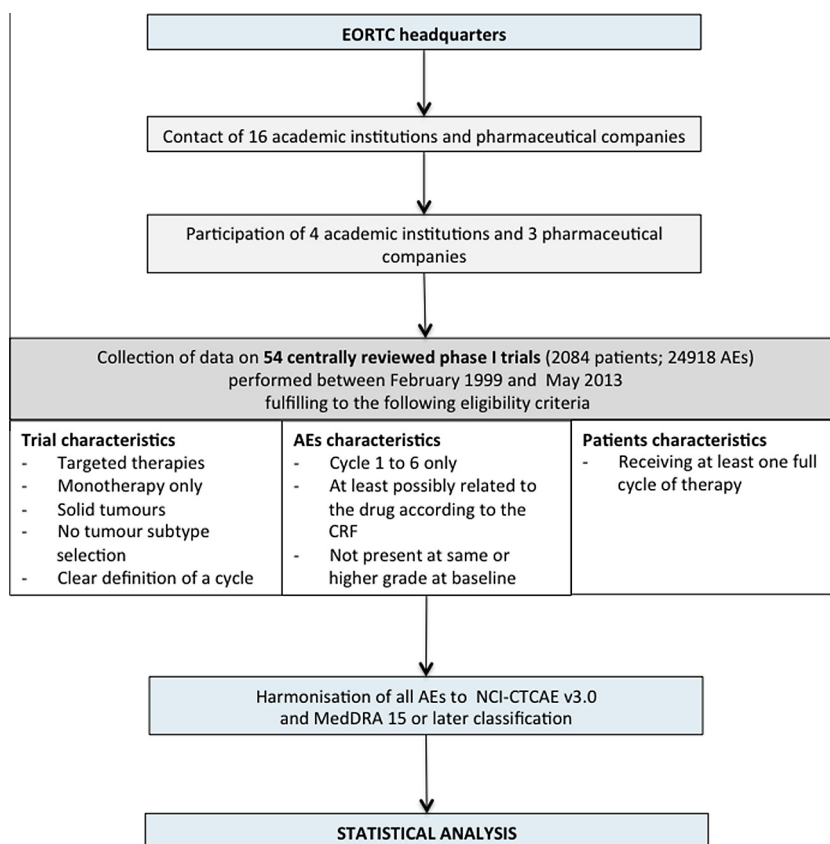


Fig. 1. Flowchart of the study. Overview of the study design and trial selection. Abbreviations: AE, Adverse Event; CRF, Case Report Form; NCI-CTCAE, NCI Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.

Table 1
Trial characteristics.

	Number of trials (N = 54) N (%)
Type of agent	
Antibody	7 (13)
Small molecule	40 (74)
Antisense oligodeoxynucleotide	2 (4)
Recombinant peptide	4 (7)
Recombinant IgG immunotoxin	1 (2)
Target category	
Signal transduction inhibitor	11 (20)
Angiogenesis/VDA	15 (28)
Intracytoplasmic/metabolism	12 (22)
Epigenetic modulation	5 (9)
DNA repair/cell cycle	9 (17)
Others	2 (4)
Administration route	
Intravenous	37 (68)
Multiple	25 (46)
Single	10 (18)
Both	2 (4)
Oral	15 (28)
Other (SC, IP)	2 (4)
MTD reached	
Yes	43 (80)
No	11 (20)
RP2D defined	
Yes	40 (74)
No	14 (26)

Abbreviations: VDA, vascular disrupting agent; SC, subcutaneous; IP, intraperitoneal; MTD, maximum tolerated dose; RP2D, recommended phase II dose.

and evaluated 35 different agents directed against a variety of targets (Table 1); 48 trials used the 3 + 3 design (including 9 trials that used the ‘accelerated 3 + 3 design’). The MTD was reached in 43 (80%) trials, and a RP2D was defined in 40 (74%) of them.

3.2. Overall toxicities

The 2084 patients received a total of 5708 cycles of treatment (the number of cycles taken into account per patient being capped at 6 based on previous results [3]), with a median number of 2 cycles per patient. They presented 24 918 AEs (16463 G1, 6532 G2, 1736 G3, 187 G45) of all types (Supplementary Tables A and B). Overall, 8812 toxicities (5580 G1, 2396 G2, 745 G3, 191 G4–5) were recorded in cycle 1, and 16106 toxicities (10883 G1, 4136 G2, 991 G3, 96 G4–5) were recorded after cycle 1.

3.3. Toxicities over time

Out of the 599 patients with $G \geq 3$ AEs, approximately half (49.7%) presented their first episode of $G \geq 3$ toxicity after the first cycle, a proportion that was similar to that for $G \geq 2$ toxicities (Fig. 2A).

Overall, 301 (14.4%) patients presented their first $G \geq 3$ AE in C1, and 298 (18.6%) after cycle 1. For the first episode of $G \geq 2$ AE, the proportion was 659 (31.6%) patients in C1 and 583 (36.3%) after cycle 1, respectively (Fig. 2B and C). The probability of presenting a G2, G3, or $G \geq 4$ toxicity as worst grade toxicity was relatively constant across the first six cycles ($p = 0.0762$), and ranged between 29–39%, 28–32% and 16–20% of patients for G1, G2, G3 or more toxicities, respectively (Fig. 2D).

The classification of AEs of any severity grade by cycle of occurrence (C1, C2 or C3–6) revealed different profiles according to the type of toxicity considered. While some AEs presented a constant incidence – including anaemia, headache, fever or constipation – the incidence of some disabling AEs – such as fatigue, diarrhoea, or anorexia – varied significantly over time. Importantly, for this latter group of AEs, the proportion of patients experiencing the toxicity in cycle 1 was not representative of the proportion observed later on trial (Fig. 3A). Similarly, when considering only G3 AEs, most of them presented a constant frequency in cycles 1, 2 and 3–6, but this was not the case for AEs such as diarrhoea and neutropenia (Fig. 3B). For G2 AEs such as fatigue, diarrhoea and neutropenia, the highest frequency was not always observed in cycle 1, but rather in cycles 3–6 (Fig. 3C). These observations suggest that toxicities observed in cycle 1 are not representative of toxicities observed later on trial.

3.4. Dose-limiting toxicities

One hundred and eighty-nine (9.1%) patients experienced a total of 300 protocol-defined DLTs (5 G1, 28 G2, 225 G3, and 42 $G \geq 4$); 270 (90.0%) DLTs were recorded at cycle 1. The most frequent clinical DLTs included fatigue, nausea, vomiting, gastro-intestinal disorders and hypertension (Table 2A, Supplementary Tables C and D), and were mostly observed in trials evaluating small molecules (Supplementary Table E). Of note, some AEs of Grade < 3 were marked as DLTs, such as fatigue, increased transaminases, nausea, vomiting and mucositis (Table 2B).

3.5. Reduction in relative-dose intensity

At cycle 1, 15% and 23% of patients received less than 75% or 90% of the intended RDI, respectively; after cycle 1, these proportions were 16–19% and 23–29% of patients, respectively. This suggests that significant reductions in RDI were not only driven by severe toxicities observed in cycle 1 or protocol-defined DLTs (Fig. 4A; Supplementary Table F). Also, no correlation could be detected between the proportion of patients presenting with reduction in RDI and the administration route ($p = 0.20$) (Supplementary Table G).

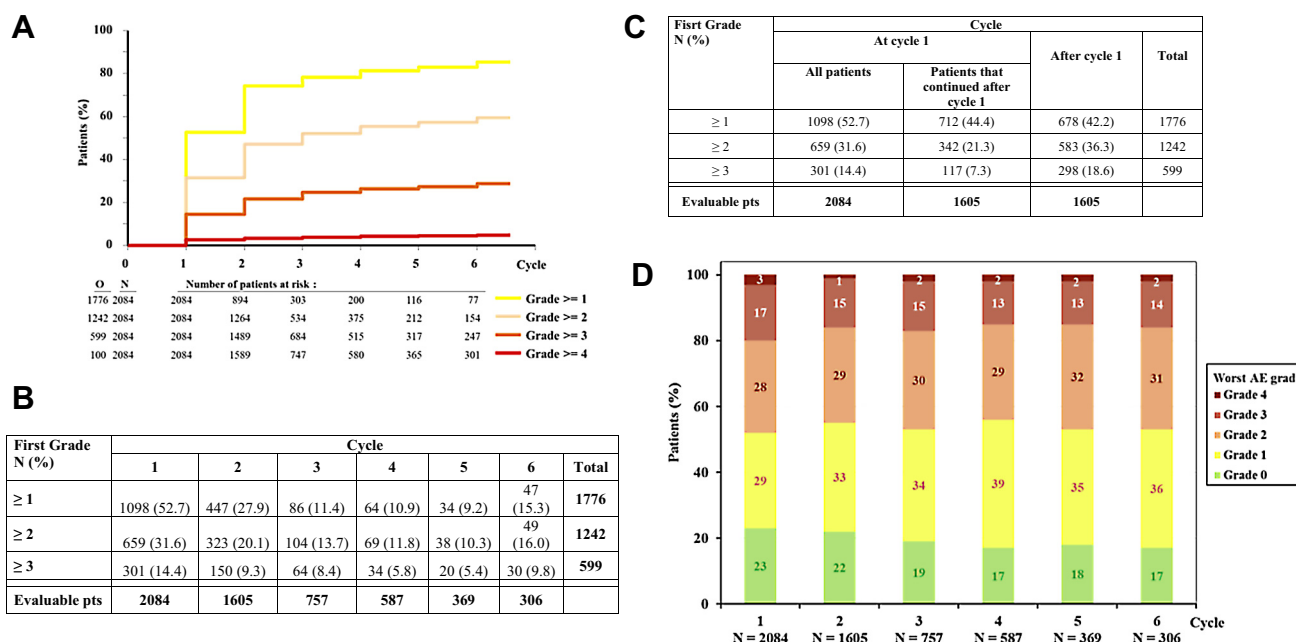


Fig. 2. Incidence of adverse events (AEs) over time. (A) Time to first AE, classified by Grade (G); (B) number of patients presenting their first G1, 2, or 3–5 AE by cycle; (C) number of patients presenting their first G1, 2, or 3–5 AE at cycle 1 (traditional dose-limiting toxicity (DLT) period) or after cycle 1; for cycle 1, patients that continued after cycle 1 are represented separately; (D) percentage of patients presenting their worst grade AE over time.

Importantly, DLTs were not reported in 72.9% and 89.3% of the patients receiving <75% and 75–90% of the theoretical dose-intensity in C1, respectively, suggesting that the majority of patients did experience reductions in RDI despite not being reported as presenting a DLT (Fig. 4B). Notably, some G1 and G2 toxicities were associated with >25% reduction in RDI in C1 in 43 and 92 patients who did not present DLTs, respectively, and included fatigue, nausea, diarrhoea, vomiting and anorexia (Supplementary Table H). Finally, reductions in RDI occurred frequently also after C1 in patients presenting selected G < 3 life-disabling toxicities, such as fatigue, nausea or vomiting.

4. Discussion

It is now clear that molecularly targeted agents (MTAs) often display a different toxicity profile from conventional chemotherapy, present a broader therapeutic window and are likely to be administered in a chronic fashion. For these reasons there is an increasing debate around the need to adapt the design of phase 1 trials to the characteristics of these agents [3,8,9], and there is now a consensus among experts and a call for a change. Notably, recent retrospective studies and literature reviews suggest that current definitions of dose-limiting toxicities (DLTs) and recommended phase 2 dose (RP2D) may not be relevant for trials evaluating MTAs and that optimisation is necessary [12,13].

Although retrospective studies have obvious limitations, our comprehensive analysis of 24918 adverse

events (AEs) from 2084 patients included in 54 completed phase 1 trials is, to our knowledge, the first and largest toxicity dataset of phase 1 trials evaluating MTAs sponsored by academia or industry. As such, it represents an unbiased dataset, which does not suffer from deficiencies in data reporting inherent to retrospective analysis based on published data or selected clinical data from incomplete phase 1 datasets. Moreover, the access to raw data, irrespective of stage or outcome of development for individual drugs, as well as the selection process of eligible trials, based only on the willingness of academic and industrial partners to participate – and not on publicly available data, efficacy of the drugs, or later approval of the agents by regulatory authorities – ensure that results are representative of all-comers MTAs entering into phase 1.

The observation that more than half of the patients with G3–5 toxicities present their first severe AE after the 1st cycle is consistent with the previous results from a retrospective study that focused on skin, GI and renal toxicities only [3]. This confirms that a significant proportion of severe toxicities occur after the end of the protocol-defined DLT observation period and are currently not taken into account in the dose-recommendation process. Although the type of these late toxicities is usually described in phase 1 publications, their cycle of occurrence is usually not reported. Phase 2 trials traditionally provide a better report of such toxicities, but the recommended phase 2 dose is almost never re-evaluated [13]. Interestingly, previous studies as well as a recent retrospective analysis from Fontes-Jardim et al.

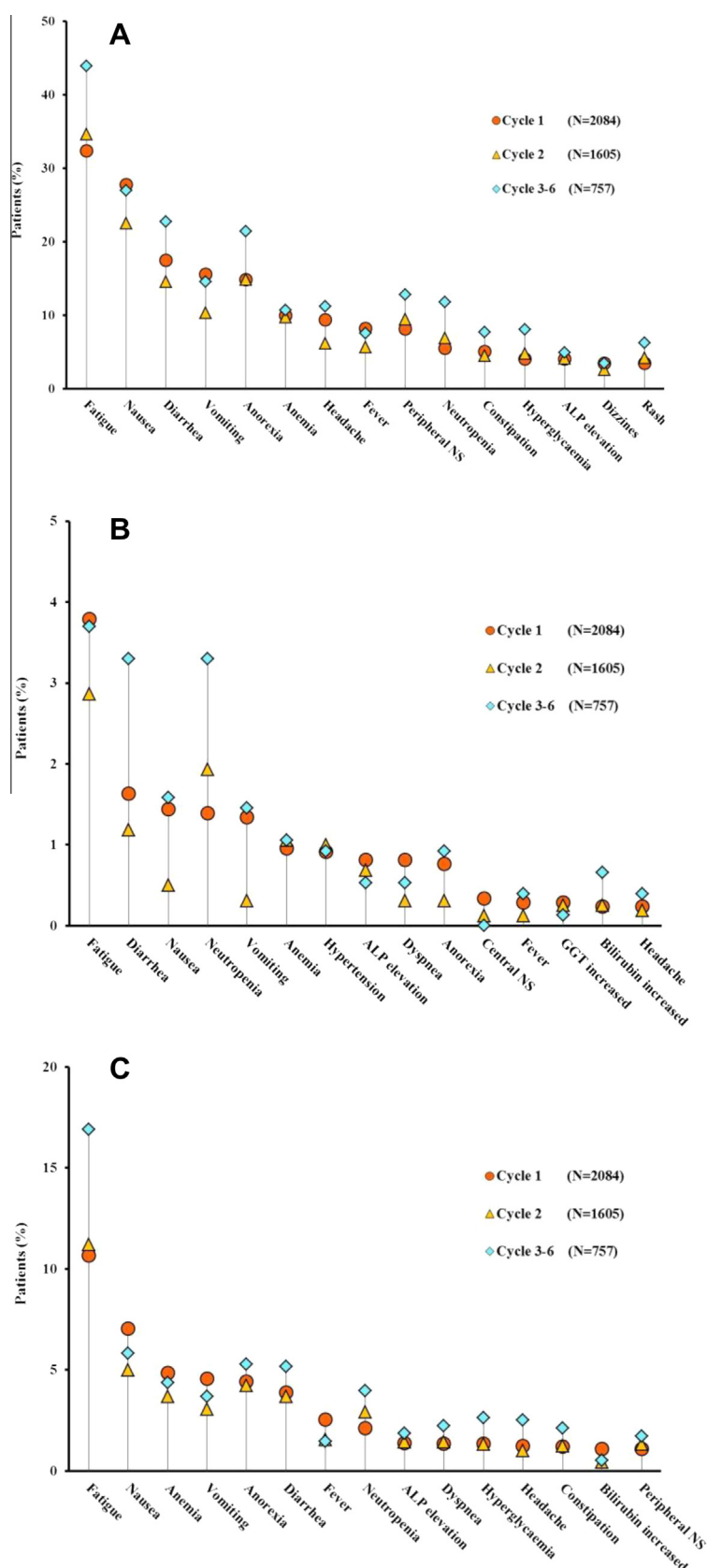


Fig. 3. Frequency of the most common adverse events (AEs) over time (cycle 1, cycle 2 and cycles 3–6). (A) Frequency of AEs of any Grade (G); (B) frequency of G3 AEs; (C) frequency of G2 AEs.

Table 2

Dose-limiting toxicities (DLTs). (A) Cycle of occurrence and incidence of the DLTs; (B) adverse events scoring as DLTs but of Grade <3 (i.e. non-severe toxicities).

(A)			
Cycle	N DLT (%)	N patients (%)	
1	270 (90.0)	168 (88.8)	
2	18 (6.0)	12 (6.3)	
3	6 (2.0)	5 (2.6)	
4	0	0	
0	2 (0.7)	2 (1.1)	
6	4 (1.3)	2 (1.1)	
Total	300 (100)	189 (100)	
(B)			
DLTs	G1	G2	Total
Fatigue	0	3	3
Transaminases increase	2	1	3
Nausea	0	2	2
Vomiting	0	2	2
Dehydration	0	2	2
Mucositis	0	2	2
Creatinine abnormality	0	2	2
Troponin I elevation	0	2	2
Blood pressure disorders and shock	1	1	2
Cardiac arrhythmias	1	1	2
GI disorders nec	0	1	1
Diarrhoea	0	1	1
Central NS	0	1	1
Proteinuria	0	1	1
Anaemia	0	1	1
Cardiac disorder signs and symptoms	0	1	1
Fever	0	1	1
Coronary artery disorders	0	1	1
Platelet disorders	1	0	1
Total	5	28	33

reported that, for cytotoxic agents, DLTs detected in phase 1 trials were more predictive of frequently occurring high-grade toxicities during later stages of development compared to MTAs [11,13,14], suggesting that the current DLT definitions may need to be customised for these new agents. Therefore, we recommend that all severe toxicities should be thoroughly reported in phase 1 trial publications together with their specific cycle of occurrence, even if taking place after the end of the protocol-defined DLT period.

Our analysis showed that 15–20% of patients received less than 75% of the theoretical RDI at any time on trial, and that some selected $G < 3$ toxicities led to significant reductions in RDI after cycle 1. Although it would have been desirable to integrate PK and PD data, which are other determinants of the RP2D process, these were not available. Nevertheless, the question still arises of whether a DLT should be defined as ‘any drug-related toxicity leading to the delivery of less than a given threshold (e.g. 75%) of the intended dose during the DLT observation period’, or whether a given threshold of RDI should be achieved at the RP2D. Experts in drug development have a consensus that a threshold of >75%

of the intended RDI is an acceptable RDI. Indeed, the inability to achieve a certain threshold of RDI reflects the intolerability of the investigated agent at the studied dose-level, even if this dose-level is not associated with protocol-defined DLTs. Such a broad DLT definition would present multiple advantages: (i) it would reduce the high site-to-site variability of toxicity reporting, which is known to be physician-, experience-, culture-dependent and increasing with the number of participating centres due to unfamiliarity with the drug [15]; (ii) it would help in making the distinction between on-target toxicities (that, unless intolerable, should theoretically not lead to dose-reductions, i.e. reductions in RDI, as often associated with activity of the molecule) and off-target toxicities (that should be avoided and would as such lead to RDI dose-reductions). The recent approval of axitinib (Inlyta®, Pfizer) at an adaptable dosage allowing intra-patient dose-escalation illustrates the relevance of such ‘on-target’/‘off-targets’ AE distinction; (iii) it would allow integrating indirectly the impact of ‘subjective toxicities’, prolonged or life-disabling G2 toxicities, and patient-reported toxicities into the DLT definition. If introducing such RDI-based criteria may be challenging to implement in the DLT definition (mainly because of practical reasons, such as its high sensitivity to inter-patient variability and the requirement of not delaying the dose-escalation process), we suggest that RP2D assessment should take into account any toxicity leading to a significant decrease in RDI (e.g. <75%) and that correlation with PK/PD data should also be taken into account. Further, the causality assessment of any RDI is crucial and should be exhaustively documented in the CRF as well as Phase 1 reports. Indeed, AEs should not by default be labelled ‘treatment-related’ without using all available information, including the effects of drug-holidays or dose-reductions, as well as correlation between disease and symptoms evolution.

Importantly, although our study identifies the need to take into account lower grade and delayed toxicities into the dose-recommendation process, phase 1 trials should remain time- and cost-effective, in order to (i) allow bringing rapidly effective molecules to the largest number of patients in later stage trials, (ii) limit the number of patients exposed to too low – potentially ineffective – doses and (iii) to keep the drug development cost sustainable for sponsoring industry or academic institutions. Therefore, the timing of the dose-escalation in phase 1 trials should not be delayed and still be based on data from cycle 1 only. However, dose-increment recommendation should take into account all available information, notably toxicities leading to significant reductions in RDI after cycle 1 observed at prior dose levels.

Several limitations to our study should be acknowledged. First, only trials of targeted agents were included

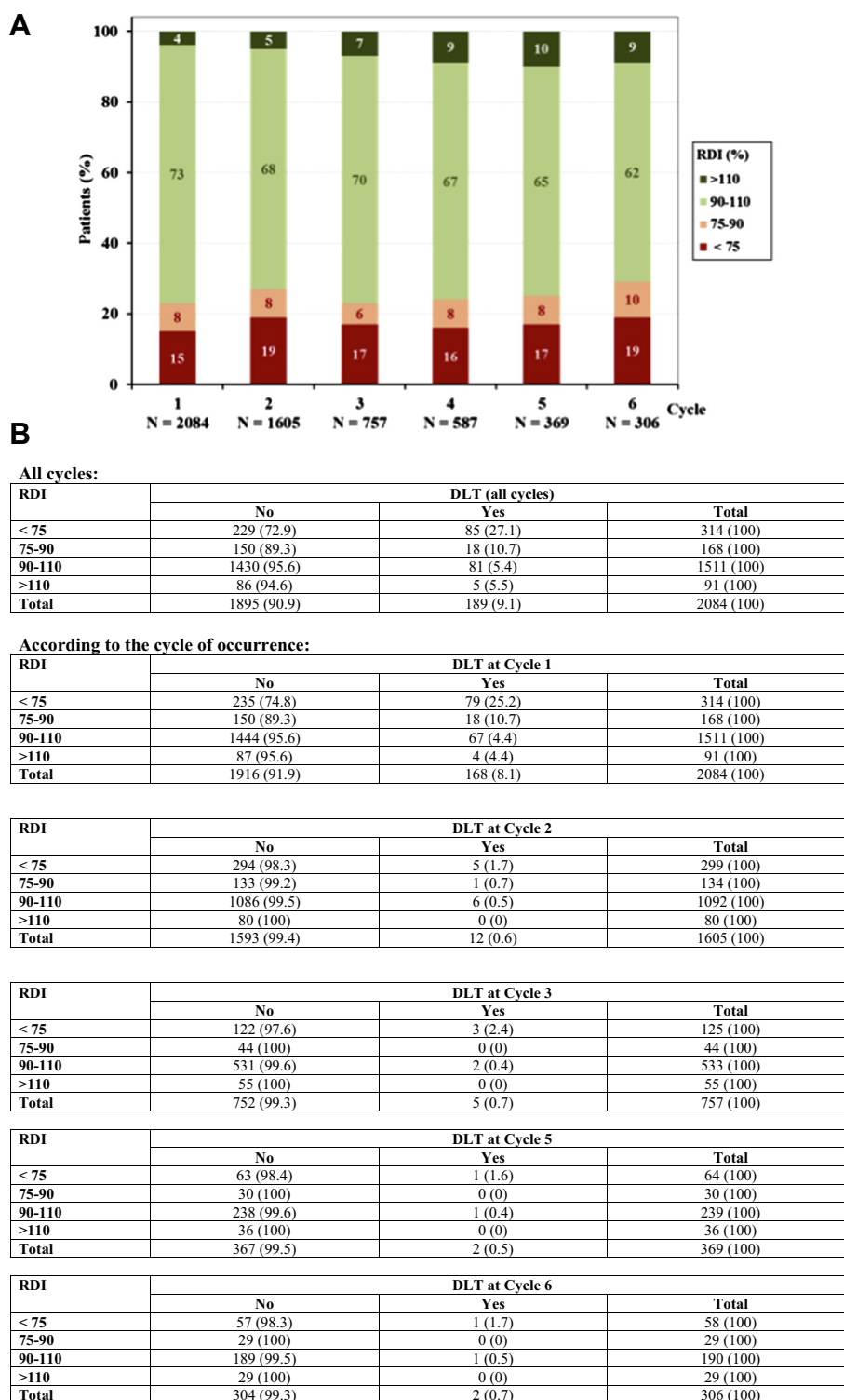


Fig. 4. Reductions in relative dose-intensity (RDI). (A) Percentage of patients experiencing reductions in RDI over time on trial; (B) Number of patients presenting adverse events associated with significant reductions in RDI that were (or were not) recorded as DLTs.

in this work and no ‘control arm’, constituted – for example – of data from trials evaluating traditional cytotoxic agents, is available. Such comparison would have been of interest, notably with regard to the frequency of reductions in RDI over cycles. Second, although a strength of our study is to be representative

of all-coming drugs in phase 1 trials, the small number of molecules that were eventually licenced included in our sample renders this work less translatable to future ‘winner’ molecules that will be developed in later phase trials and eventually licenced. Third, the absence of data on individual patient characteristics currently precludes

the identification of predictive factors of late toxicities, and further data collection and analysis on this topic is warranted and this should be the purpose of future work. Similarly, the low number of immune therapies included in our database unfortunately prevents us from performing specific analysis for these agents, which undoubtedly require some very specific and dedicated drug development rules and designs, as illustrated by the recurrent difficulties in establishing a MTD and RP2D for a number of them [16–18]. Fourth, since most trials included in this analysis used the 3 + 3 traditional phase I design, our findings cannot be extrapolated to other adaptive or model-based designs, which make a better use of all toxicity data. Finally, we did not manage, using statistical approaches, to correlate the occurrence of RDIs to specific toxicities observed at the same or in the previous cycle. Similarly, an accurate list of prolonged or disabling clinical G2 toxicities leading to reductions in RDI could not be defined. Although this may be because most reductions in RDI are multifactorial – which may be solved by the expansion of the database that should allow more accurate correlations, this highlights the key role of trial investigators in smart and thorough causality assessment.

To conclude, our comprehensive retrospective analysis of complete data of phase 1 trials evaluating MTAs identified several inadequacies of the current DLT definition, RP2D process and drug development model for such agents. Based on the available results of our analysis, the following recommendations should be made for future relevant drug development of MTA:

1. Dose-escalation and DLT definition
 - 1.1. Timing of the dose escalation should still be based on data from C1 only and should not be delayed.
 - 1.2. Dose-increment recommendation needs to take into account all available information, notably DLTs observed beyond cycle 1 in prior (and current, if feasible) dose levels.
 - 1.3. Any toxicity – whatever the grade – leading to a significant decrease in RDI should deserve particular attention.
2. Toxicity reporting
 - 2.1. All toxicities should be comprehensively reported, together with their cycle of occurrence, even if not occurring during the DLT observation period.
 - 2.2. Thorough assessment of the causality of AEs is key, and should be done by using all available information, notably effects of drug holidays or dose-reductions and correlation between disease evolution and symptom evolution.

3. RP2D determination

- 3.1. Dose expansion cohorts in phase 1 studies should focus on fine-tuning the dose-defining process, if needed through evaluating two dose levels or schedules.
- 3.2. The recommended dose for further studies should incorporate all available information – notably toxicities observed after C1 and intolerable clinical G2 toxicities – and be based on achieving >75% RDI.

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Conflict of interest statement

Authors declare no financial disclosures.

CF is an employee of Pfizer; PM is an employee of Sanofi; BL is an employee of Roche.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ejca.2014.04.031>.

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