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Review

Dose optimization in cancer drug development: Review and outcome of a multi-stakeholder workshop

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ABSTRACT

Poor dose optimization of oncology therapies may result in reduced efficacy, greater toxicity, worse adherence, and reduced clinical benefit. The traditional approach to dose-finding for cytotoxic cancer drugs – based on determining the maximum tolerated dose in the first course of treatment – is no longer appropriate for modern targeted therapies and immunotherapies. Dose finding is instead moving towards defining an optimal biological dose, and regulatory authorities have begun to adopt applicable recommendations. Based on the findings of a multi-stakeholder workshop held by the Cancer Drug Development Forum, we recommend that dose optimization should commence in the pre-clinical development phase with particular consideration for preclinical models and the specific therapeutic target, and with appropriate modelling based on preclinical testing. Clinical trials should characterize the dose–response curve and identify a range of possible doses early in development. Ideally, selected doses should be assessed in a subsequent dose-selection study (or sub-study), preferably in a randomized fashion if more than one dose is being considered. Dose selection should be informed and justified by all available and relevant clinical and nonclinical evidence. Successful adoption of a new dose-finding paradigm will require multi-stakeholder engagement and exchange but will bring benefits to patients, sponsors, and healthcare providers.

1. Introduction

Determining an optimal dose and schedule is a critical part of the development cycle for oncology therapies, and poor dose optimization may result in patients experiencing reduced efficacy and greater incidence of toxicities [1,2]. Inadequate dose optimization early in therapy development is challenging to fix later, as dose optimization in the post-approval phase is time-consuming and costly, and does not allow avoidance of potential harm to patients.

Traditional dose-finding for cancer drugs involves identifying the maximum tolerated dose (MTD), i.e. the highest dose that does not cause significant toxicity [3]. However, this model is an increasingly poor fit for modern targeted cancer therapies and immunotherapies, where increased doses may mean increased toxicities but not necessarily greater efficacy [4]. Of course, dose optimization is not the only goal of early-phase trials in modern drug development, with other primary endpoints including determining toxicity and tolerability, target patient populations, biomarkers, patient-reported outcomes (PROs), and efficacy, and other modalities such as radiotherapy, radioligand therapy, and radiological imaging have their own dose optimization challenges [5,6]. Nevertheless, regulators have recognized the need to reform the existing dose optimization and dose selection methodology for oncology drugs, and have adopted initiatives accordingly, with the FDA's Project Optimus being a high-profile example [7,8]. Regulators are also more

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likely to require manufacturers to re-evaluate approved doses via post-marketing requirements: The FDA recently required the manufacturer of the non-small cell lung cancer drug sotorasib to compare the approved 960 mg dose with a 240 mg dose as part of their post-marketing requirements [4]. The question of how dose selection needs to be revised continues to be the subject of debate.

2. Dose-finding in the era of traditional cytotoxic drugs

Traditional cytotoxic drugs are characterized by having steep dose–response relationships for both efficacy and safety, with narrow therapeutic indexes (Fig. 1A) [9]. A higher dose of a cytotoxic drug is expected to produce a higher degree of antitumor activity, but also a higher degree of toxicity due to its non-specific cytotoxic mechanism of action. Cytotoxic drugs are also usually intended to be taken for a fixed, short duration, and most toxicities are predictable and occur early in treatment. Traditional dose-finding for cancer drugs is therefore typically based on the notion that 'more is better', and dose-finding usually involves the identification of the MTD, i.e. the highest dose that does not cause significant dose-limiting toxicities (DLTs; generally defined as clinically relevant adverse events of grade 3 or higher that occur in the first cycle of treatment) [3,10].

In practice, dose-finding is usually carried out in a phase 1 dose escalation study, in which the dose of a study drug is increased in successive groups of patients until the highest dose with acceptable toxicity is identified [11]. In brief, if a predefined number and type of DLTs are reported during the DLT period (usually 21 or 28 days after first administration of study drug, with DLTs most commonly being hematologic in nature), the dose is usually reduced and this lower dose declared the MTD; the MTD is frequently used as the recommended phase 2 dose (RP2D) [3,9]. The MTD and RP2D are therefore usually determined by toxicities occurring in the first cycle of treatment; toxicities in later cycles are not regularly taken into account [12].

3. Dose-finding for molecular targeted therapies and immunotherapies

Advances in our understanding of cancer biology have led to the development and adoption of a new generation of molecularly targeted therapies and immunotherapies, including small molecules, monoclonal antibodies, cell therapies, and antibody–drug conjugates [13,14]. More than 90 % of the new anti-cancer therapeutics approved by the FDA between 2000 and 2022 were either targeted agents (small molecule drugs, 277/573 approvals) or biologics (246/573); 8.7 % of approvals were cytotoxic drugs (50/573) [15].

Modern cancer therapies are often designed to interact with specific molecular targets; their dose–response profiles differ significantly from traditional chemotherapeutic agents, and the optimal response to targeted therapies and immunotherapies can be reached at doses far below the MTD (Fig. 1B and C). Increasing the dose of a targeted drug or immunotherapy beyond a certain level therefore does not necessarily lead to enhanced anti-tumor activity (e.g. if the molecular target is saturated at relatively low doses) [16]. No clear dose–response relationship is seen with checkpoint inhibitors such as pembrolizumab for example, and receptor saturation does not appear to meaningfully increase with higher doses [17].

The toxicity profiles of modern oncology therapies also differ from those of cytotoxic agents. As cancer is increasingly treated as a chronic disease, newer therapies are to be taken continuously and for longer periods than cytotoxic drugs, with few (if any) off-treatment periods. Certain adverse events may only occur after the first cycle of treatment, [18] and less severe but more persistent toxicities (such as grade 1–2 diarrhea or fatigue) can have a negative effect on patients over longer treatment durations [19]. This can mean that the approved recommended dose identified under the MTD paradigm (where the focus is on toxicities in the first treatment cycle) is poorly tolerated when given over longer periods, leading to reduced patient adherence and lower clinical benefit. Lower doses of modern therapies may therefore have comparable efficacy but fewer toxicities than the traditional MTD [16,20].

The 'more is better' paradigm that has developed in the context of traditional cytotoxic drugs thus does not apply to modern targeted therapies and immunotherapies [11,16]. Nevertheless, the paradigm has persisted and is still used as the basis for dose selection for modern therapies [16,21]. Perhaps as a result, dose–response data from clinical trials may not be reflected in the doses that are eventually approved. In a phase 2 study of nivolumab for patients with metastatic renal cell carcinoma, no dose–response relationship was observed for progression-free survival between the three doses tested (0.3 mg/kg, 2 mg/kg, and 10 mg/kg, all administered once every 3 weeks) [22]. Despite this, the initial approved dose was 3 mg/kg every 2 weeks, fifteen times higher than the lowest dose tested. Similarly, patients in a phase 1 study of sotorasib for the treatment of non-small-cell lung cancer received daily doses of 180, 360, 720, and 960 mg; although the study found no evidence of a dose–response relationship, the 960 mg dose was selected for the phase 2 registration trial and as the FDA-approved dose [4,23,24]. The FDA later instructed the sotorasib study sponsor to compare the approved 960 mg dose with a 240 mg dose as part of their post-marketing requirements [4] and no difference in efficacy between the two doses, apart from much worse toxicity with the higher dose, was demonstrated [25]. Inadequate dose optimization can also result in avoidable treatment interruptions due to toxicity and thus reduced efficacy. In a phase 3 trial of ibrutinib for patients with chronic

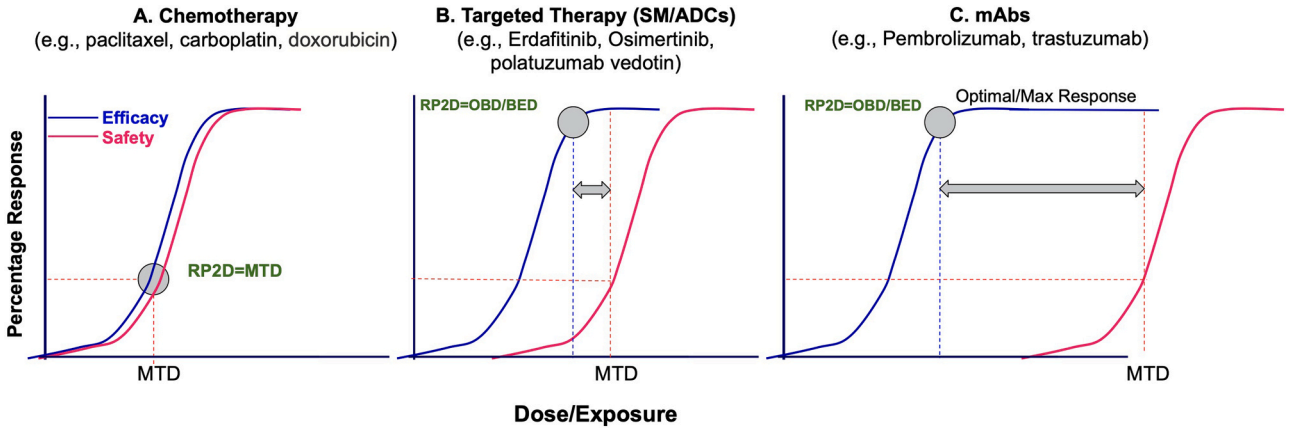

Fig. 1. Dose/exposure–response and therapeutic index for traditional cytotoxic chemotherapy (A), targeted therapy (B), and monoclonal antibodies (C). ADC, antibody–drug conjugate; BED, biologically effective dose; mAbs, monoclonal antibodies; MTD, maximum tolerated dose; OBD, optimal biological dose; RP2D, recommended phase 2 dose; SM, small molecule.

lymphocytic lymphoma/small lymphocytic lymphoma, 40 % of patients experienced dose holds due to adverse events [26]. The FDA had already determined that the recommended ibrutinib dose of 420 mg for patients with chronic lymphocytic lymphoma was 2.4-fold higher than the lowest dose that resulted in maximum clinical response and recommended the study sponsor consider exploring lower doses in the future [27].

Concerns about the continued use of the MTD paradigm have understandably led to calls for other options [18,21,28,29]. We suggest the use of the optimal biological dose (OBD) which can be defined as the lowest dose that provides the highest rate of efficacy while also being tolerable [30]. Whereas selection of the MTD is driven by toxicity, the OBD accounts for both efficacy and toxicity. Encouragingly, data suggest that 83 % of final approved doses are consistent with the OBD when the OBD is selected as the RP2D, compared with 58 % for MTDs [20]. However, there is as yet no consensus on how the OBD should be determined, including which efficacy endpoints should be used or what the most appropriate dose escalation strategy would be in studies to find the OBD [30]. Similarly, there is no consensus on how tolerability and toxicity should be assessed, with most trials appearing to use a binary toxicity endpoint based on the proportion of patients who experienced a DLT, or else relying on a descriptive analysis of adverse events [30]. Furthermore, the OBD is not always assessed in clinical trials, and it may not be possible to identify the OBD for all therapies e.g. due to a lack of validated biomarkers [20].

Regardless, a new dose-finding paradigm is needed which considers the perspectives of the various stakeholders involved, including patients, regulators, academic researchers, and industry sponsors.

4. Regulatory perspectives

The FDA and EMA have noted limitations in the MTD paradigm that mean alternative strategies may be required for non-cytotoxic cancer drugs [31,32]. Evidence appears to back this up: A review of 60 European Public Assessment Reports (EPARs) for anticancer agents evaluated between 2015 and 2020 found that the MTD was the approved dose for just 25 % of drugs, and the MTD was not determined for 59 % [33]. However, the dose–response relationship was determined for only 8 % of approved anticancer drugs, making it difficult or impossible to determine whether the optimal dose had been selected. Reports by the FDA also suggest that it is not uncommon for cancer therapy dosing and dose scheduling to require modification after approval on the grounds of safety or tolerability [16]. For example, 8 of 31 kinase inhibitors approved by the FDA between 2001 and 2015 had post-marketing requirements or post-marketing commitments to study alternate dosing, suggesting that further studies were required to identify the optimal dose [29,34]. Subsequent studies have also led regulators to approve lower doses of a treatment despite an earlier approval at a higher dose; in 2017, the FDA approved a lower dose of cabazitaxel (20 mg/mm^2 every 3 weeks) in combination with prednisone for patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment after a randomized open-label trial involving 1200 patients demonstrated noninferiority in overall survival versus the previously approved dose of 25 mg/m^2 every 3 weeks [35,36].

This is not just a recent concern, however, as dose-finding has been a topic of discussion among regulators for at least three decades. In 1994, the International Council on Harmonisation (ICH) E4 guideline outlined key principles for establishing a safe and effective dose for new therapies, including the recommendation that "dose–response assessment should be an integral part of drug development" [2,37]. The authors of ICH E4 cautioned against selecting higher doses of oncology therapies that were associated with worse toxicities on the grounds that patients will not be able to experience clinical benefit if they cannot tolerate the dose. Key principles of ICH E4 included the need to base the recommended starting dose for a drug on dose–response relationship data gained from well-controlled clinical trials, the need for dose-ranging or concentration-response studies to be carried out early in development, and the recommendation that at least two doses (in addition to placebo) should be studied.

Since 2005, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) guideline on the evaluation of anticancer medical products has been continually revised to reflect the growing use of non-cytotoxic agents for the treatment of cancers [32,38]. The 2017 revision of the guideline distinguished between cytotoxic and non-cytotoxic compounds, stating that non-cytotoxic therapies may require alternative dose-optimization strategies as they are typically administered continuously, with DLTs potentially only occurring after multiple treatment cycles. The guideline also noted that dose-finding for targeted therapies should not be limited to safety but rather should aim to determine an "optimal biologically active dose", defined as the dose "at which optimal biological response according to a predefined effect marker is achieved" and at which "giving a higher dose does not further improve outcomes." In contrast to identifying the highest dose that patients can tolerate – the MTD – the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency recommended escalating the dose until the maximum pharmacodynamic effect is observed (for example, when the targeted pathway is optimally altered or the biological target becomes saturated), and then identifying the minimal dose required to achieve this maximum pharmacodynamic effect. Along with noting the importance of identifying a target population and demonstrating overall survival benefits, the CHMP guideline emphasized that assessment of benefit–risk should involve all relevant efficacy, safety, and biomarker data (including to identify appropriate target populations and for pharmacokinetic and pharmacodynamic (PK/PD) efficacy and safety analysis). An update to the guideline noted that the traditional reporting of cumulative incidences of adverse events was by itself insufficient to characterize toxicity [32].

Recognizing the need for a new approach to dose-finding in the era of targeted therapies and immunotherapies, in 2021 the FDA initiated Project Optimus, an initiative to reform the existing dose optimization and dose selection paradigm for oncology drugs [7,8]. Project Optimus emphasized the need for dose optimization prior to approval and the use of both clinical and non-clinical data.

In August 2024, the FDA published guidance for industry on optimizing the dosage of oncology therapies [7,31,39]. The FDA guidance recommended that sponsors identify an optimal dose prior to the marketing application while considering novel approaches to dose selection (rather than a 'one-size-fits-all' strategy). The guidance also recommended that doses selected for use in clinical trials should be adequately supported by relevant non-clinical and clinical data, as well as dose-response and exposure-response relationships for efficacy and safety, and that identification of an optimal dose or doses should occur before or at the same time as establishing the drug's safety and efficacy. The FDA guidance also recommended that trials should be designed to compare multiple doses to decrease uncertainty in identifying an optimal dose, and that the dose optimization plan should also consider the use of randomized comparisons, to support identification of the optimal dose. The FDA has also issued guidance for specific therapy types. Antibody–drug conjugates combine targeted antibodies with potent cytotoxic drugs, but systemic toxicities often limit their effectiveness and narrow their therapeutic index. While there are methods to predict the initial dose for antibody–drug conjugates based on effectiveness, predicting toxicities that determine the MTD remains a challenge. To standardise and encourage dose optimisation of antibody–drug conjugates, the US FDA issued a guidance detailing clinical pharmacology considerations for antibody–drug conjugate development, highlighting the importance of bioanalytical methods, dosing strategies, and exposure–response analyses [40]. These efforts stress the importance of integrated PK/PD modelling and exposure–response analysis for dose selection, underlining the push toward more granular and scientifically robust dose optimisation strategies.

5. Industry perspectives

Data from a survey of pharmaceutical companies suggest that dose optimization strategies at most companies have been influenced by Project Optimus, with most already adapting early clinical development based on its recommendations [41]. Also, companies recognize a need for a good understanding of the exposure–response relationship (including the long-term safety and tolerability), the pharmacokinetics and pharmacodynamics of target engagement, for a case-by-case approach to dose optimization (with randomized dose finding having value if tailored to suit the specific indication, mechanism of action, etc.), and for close communication with relevant health authorities.

Pharmaceutical companies have highlighted challenges related to dose optimization, including a lack of meaningful or accessible biomarkers [41]. The use of biomarkers and models are also important to enhance the efficiency and rigor of dose optimization. The pharmacodynamic effects of targeted therapeutics are driven by their interaction with the therapeutic target; this can be assessed by measuring target engagement and receptor occupancy in the case of soluble protein targets and cell-surface receptors, respectively. Although target engagement and receptor occupancy do not necessarily equate to efficacy, they are quantifiable parameters that can be used to support optimal doses related to downstream pharmacodynamic effects and provide a mechanism to extrapolate treatment effects from preclinical species to humans and from healthy to patient populations [42]. Mechanism-based PK/PD modelling or quantitative systems pharmacology allows for integrated analysis of multiple factors that affect drug efficacy, while differentiating system-specific effects (e.g. target cell abundance or tumor growth rate) from compound-specific effects (e.g. affinity to a target receptor) [43]. By modifying disease-specific parameters, it is possible to use these models to extrapolate data between different patient subpopulations [44]. Mechanistic pharmacokinetics and pharmacodynamics could provide evidence for dose–response relationship, especially when the clinical dose–response relationship is highly confounded by patient heterogeneity.

Pharmaceutical companies may also face particular challenges with combination therapies. Combination drug development in oncology is inherently complex and often involves either “novel–approved” combinations (an investigational agent with an approved drug) or “novel–novel” combinations (two investigational agents). In the case of novel–approved combinations, the label dose of the approved drug is often used in the combination unless there are safety or tolerability concerns. Zhou et al. summarized five dose-finding trial designs for oncology combinations involving novel–approved agents [45]. They highlighted that selecting an appropriate design should consider expected differences in dose/exposure–response relationships between monotherapy and combination therapy, potential pharmacokinetic and pharmacodynamic interactions, and the overall benefit–risk to patients. For novel–novel combinations, similar principles apply; however, if neither agent has an optimized dose or schedule, a two-dimensional dose-escalation approach may be warranted (e.g., escalating one agent while holding the other constant, and then reversing roles) [46]. If one agent has a well-characterized exposure–response profile and can serve as the backbone, the trial design can be simplified to resemble a novel–approved strategy. Given the complexity of combination dose-finding, a case-by-case approach is essential — integrating mechanistic insights, nonclinical and clinical pharmacology, PK/PD data, safety and efficacy findings, as well as translational and model-informed analyses for both the combination and corresponding monotherapies.

Effective dose optimization also requires the definition of an appropriate and homogeneous patient population (with appropriate definitions of factors such as cancer type and tumor molecular profile) early in the development cycle. Pharmaceutical companies can experience significant difficulties with enrolling a suitably homogeneous patient enrollment, for example, if the indication of interest is associated with a small patient population [41].

Changes to the way in which the recommended phase 2 dose is selected, or the use of OBD, also necessitate the adoption of new statistical approaches. There is a need for new statistical models that incorporate DLTs beyond cycle 1. Existing dose optimization methods that incorporate late-onset toxicities include the time-to-event continuous reassessment method (Tite-CRM) and time-to-event Bayesian optimal interval (Tite–Boin) models [47], which include prolonged periods for assessing DLTs while allowing early escalation. Step-up dosing may require the use of statistical models such as the recurrent event survival model, which accounts for multiple doses and multiple events per patient. Tumor growth modelling could serve as an early indicator of antitumor activity and thus aid in dose selection [48,49].

Pharmaceutical companies may also experience challenges with internal alignment, where there are disagreements regarding the value of dose optimization [41]. Interdisciplinary collaboration and multidimensional iterative optimization will be necessary to evaluate a totality of clinical and nonclinical evidence, including patient-reported outcomes and longitudinal efficacy and safety data [50].

In addition to the ethical motivation, there are also strong commercial incentives to define the optimal dose as early as possible in the drug development path. If the selected dose is too high patients are more likely to terminate treatment early and not realize the potential clinical benefit; this may in turn reduce the probability of success in phase 3 [51] or, post-approval, impact treatment duration. Reduction of the recommended dose post-approval often occurs late, after additional clinical trials, and likely cannot be compensated in pricing in many markets.

6. Academic perspectives

Drug delivery to tumor cells remains challenging due to factors such as high tumor hydrostatic pressure, poor blood flow, and dense stromal barriers [52–55]. Identifying an optimal dose is also complicated by the fact that the “optimal” dose may vary from patient to patient and from site to site in the same patient. Patient and tumor heterogeneity complicate dose finding, with different patient populations potentially requiring different dosages.

The example of antibody–drug conjugates is illustrative of the complexities of dose optimization. Currently approved antibody–drug conjugates utilise 6 unique types of cytotoxic payloads, and this diversity significantly complicates the characterisation of their efficacy and safety profiles. Pharmacokinetic analytical approaches in the clinical development of antibody–drug conjugates has varied considerably, from analysis of both the payload and antibody–drug conjugate or total antibody exposure levels for exposure–response analyses up to solely on antibody–drug conjugate or total antibody levels, often excluding payload due to detection challenges. Notably, among antibody–drug conjugates incorporating payload levels in their exposure–response analyses, none demonstrated a positive correlation between payload exposure and therapeutic response. Conversely, positive correlations have been shown between antibody–drug conjugate exposure and response. Overall, simultaneously analysing total antibody, antibody–drug conjugate, and payload analytes can inform a comprehensive mechanistic understanding of both the disposition of an antibody–drug conjugate and its exposure–response relationships [56]. However, antibody–drug conjugate analysis alone may often suffice to support late-stage clinical pharmacology strategies. In addition, whether total antibody exposure can be used as a surrogate for antibody–drug conjugates in an exposure–response analysis remains to be validated due to the lack of case studies showing a direct comparison [57]. Published experiences underscore the importance of using dosing strategies such as dosing fractionation, supported by robust dose-finding data including PK modelling and simulation. For example, Liao et al. reported dosing optimization strategies employed by several approved antibody–drug conjugates, including body weight-capped dosing, treatment duration capping, dose schedule modifications, and randomized dose-finding studies [58]; modifying the dose frequency has been widely used to

improve efficacy and safety, while simultaneously improving patient convenience.

Academic clinical trials provide an opportunity to explore novel designs, biomarkers, and patient populations and can differ from industry-led trials in terms of patient characteristics, dosing strategies, or toxicity–benefit considerations. Academic trials also allow for exploration of questions such as whether target engagement, target sensitivity, or biology differ between patient populations or cancer types. Other developments include developing and assessing new approaches to how data from dose-finding studies are evaluated [59,60].

In 2023, the Methodology for the Development of Innovative Cancer Therapies (MDICT) published guidelines for phase 1 oncology trial design and conduct [58]. These guidelines include recommendations that trial design should be informed by robust non-clinical data, that endpoints should include evaluation of all longitudinal toxicities, and that phase 1 trials should define a recommended dose range rather than a single recommended phase 2 dose [61].

7. Patient perspectives

As modern therapies are often used for prolonged periods of time, there must be a stronger emphasis on long-term tolerability, particularly as DLTs that occur after the first treatment cycle (particularly non-hematologic DLTs that may take longer to emerge) may not be factored into the dose-finding process. Furthermore, the definition of 'tolerability' should include the patient perspective, with a direct measurement from the patient on how they feel and function while on treatment. This is particularly important as patients' and physicians' perception of the tolerability of adverse events can differ considerably, with clinicians often underestimating the severity of patient symptoms [62]. In a survey of 52 patients with cancer, enrolled in 27 phase 1 trials, the most-feared grade 1–2 adverse events among patients were those that directly impacted their quality of life (gastrointestinal toxicities, neurological toxicities, and personality change), whereas the most feared adverse events among physicians were eye disorders, confusion, and blurred vision [63].

A complete understanding of a drug's tolerability necessarily requires direct measurement from the patient on how they are feeling and functioning during treatment. In 2018, Friends of Cancer Research worked with various stakeholders to define 'tolerability', to include PROs such as patient-reported symptomatic adverse events, the patient-reported overall burden of adverse events, and patient-reported physical functioning [64]. PROs can be of great value for assessing the tolerability profile of an agent as primary, secondary and exploratory endpoints in phase 1 or 2 studies during dose finding. Importantly, validated, multilingual libraries are available (such as the PRO version of the Common Terminology Criteria for Adverse Events, or PRO-CTCAE; https://healthcaredelivery.cancer.gov/pro-ctcae) and facilitate the use of PROs in early drug development even when information on toxicity is still limited. PROs like the PRO-CTCAE [65,66] could be incorporated into dosing studies; a broad range of PROs sign and symptom items could be collected in early phases and used to inform targeted use of PROs in later phases. PROs should be collected during the whole duration of a patient exposed to study drug, potentially factoring in dose modifications or interruptions by statistical methods, to obtain the most of safety/tolerability information reported by patients.

The PRO-CTCAE is fully validated and very flexible; a subset of items from the library can be selected for use in a particular study reducing the burden on the patient. Furthermore, items can be administered on paper or electronically to accommodate the requirements of individual data collection settings. PRO-CTCAE data complement existing safety assessments reported by clinicians using the CTCAE, and both systems provide unique, non-overlapping information relevant to understanding a product's tolerability profile. The selection of specific PRO-CTCAE items and timing of assessment are critical design decisions, but fortunately methods and consensus recommendations are available to support this [66]. We recommend that trial designers consider weekly assessments during key periods in the trial, including crucial timepoints based on knowledge of the anticipated toxicity profile. Individual PRO symptom items can ideally be analyzed separately and descriptively, as combining item scores may mask trends in individual symptoms. Other PRO measures, like those developed by FACT/FACIT (www.facit.org), the European Organisation for Research and Treatment of Cancer (EORTC), and the MD Anderson Cancer Center, can be considered in addition to the PRO-CTCAE.

A recent roundtable of experts from regulatory agencies, patient advocacy groups, clinical trialists, and PRO methodological experts recommended the integration of patient reported outcomes for tolerability assessment and dose optimization in early phase clinical trials [67]. The consensus supported the adoption of the FDA core PRO concepts (overall adverse event impact and symptomatic adverse events for phase 1 and phase 2, plus physical function, role function, and disease symptoms for phase 2) as outcomes measures [67].

8. Redefining the dose optimization paradigm

We recommend that early phase clinical trials aim to determine several candidate dosages (or a range of doses) for further evaluation, while also identifying potential pharmacodynamic biomarkers [2]. Early phase trials may use basket, umbrella, or platform study designs to examine a single therapeutic agent in various specific patient populations or tumor types, or multiple agents or combination therapies, or both, while also including multiple dose-level cohorts, backfill cohorts, or randomization between dose levels to help better define optimal dosing and dose–response effects [68].

The endpoints in early phase clinical trials should also not be limited to identifying DLTs, the MTD, and pharmacokinetics (although these remain important), but should include novel endpoints such as PROs or assessment of cell-free DNA [68]. Similarly, the EMA recommends that the dose-finding strategy for oncology therapies should focus not only on safety endpoints, but also determine the OBD, i.e. the dose at which optimal biological response according to a predefined effect marker is achieved and at which giving a higher dose does not further improve outcomes [32]. The FDA recommends that selected doses should be supported and justified by non-clinical and clinical data, including dose–response and exposure–response data for efficacy and safety [31]. These recommendations will require innovative and adaptive study designs that allow collection of robust data to characterize dose–response and exposure–response relationships. This could involve 'backfilling' dose cohorts (in which additional patients are assigned to doses considered safe, in contrast to the traditional '3 +3' design) or the use of multiple dose expansion cohorts [12,61,69].

It will also be necessary to collect and evaluate a wide spectrum of data to support dose selection, including preclinical and translational data, pharmacodynamic biomarker data, and patient-reported outcomes. These data can be used to support predictive modelling to provide quantitative data to support dose selection.

The FDA's recommended trial design for dose comparison is a randomized, parallel dose–response trial, in which multiple doses are compared and assessed for activity, safety, and tolerability [31].

We propose that dose-finding should involve a dose-ranging study (Fig. 2), in which the key objective is to characterize the dose-response curve and identify a range of possible doses (rather than identify a single MTD). The range might include the dose at which the maximum pharmacodynamic effect is observed (e.g. measured by drug target saturation). Biomarker data, especially relating to biomarkers that correlate with target engagement or response, should be incorporated into dose-ranging trials to inform and justify dose selections [18].

The selected doses could be further evaluated in a dose selection study or cohorts, ideally in randomized fashion, with a key objective to determine whether a lower or higher dose has similar efficacy to the dose with maximum pharmacodynamic effect while having better or

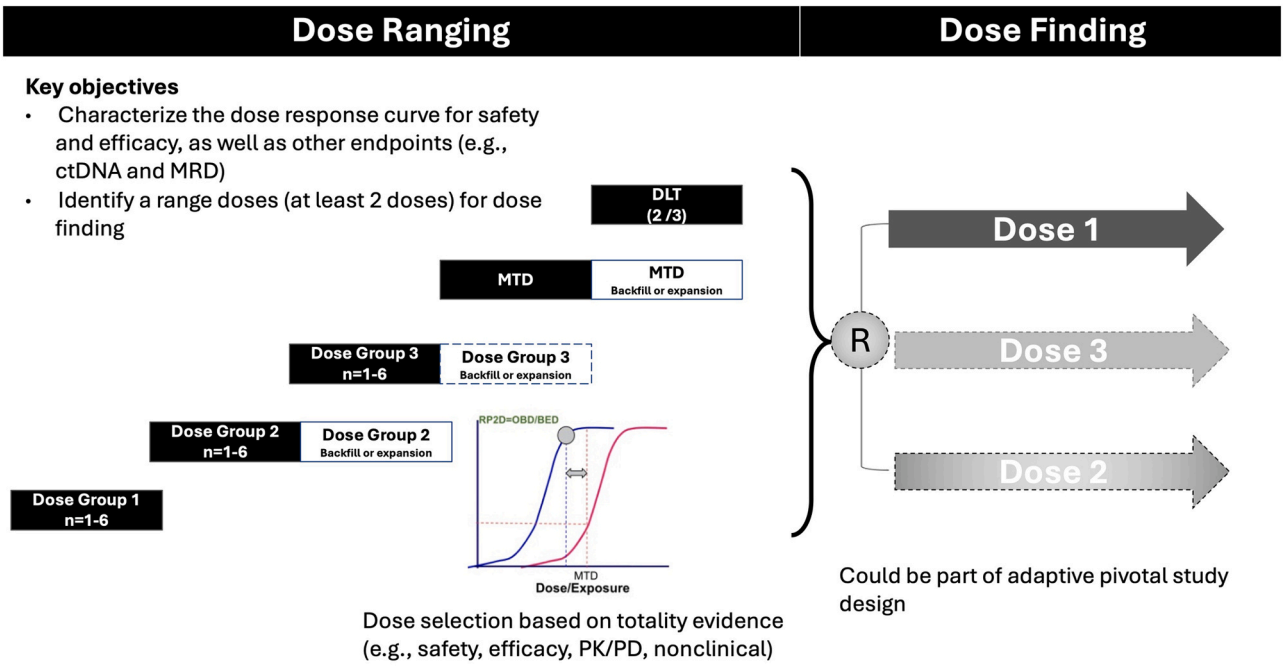

Fig. 2. Proposed clinical dose-finding trial design. BED, biologically effective dose; ctDNA, circulating tumor DNA; MRD, minimal residual disease; MTD, maximum tolerated dose; OBD, optimal biological dose; PK/PD, pharmacokinetics/pharmacodynamics; R, randomization; RP2D, recommended phase 2 dose.

worse tolerability.

Long-term tolerability and safety data need to be included into dosing decisions. The MTD model, in which DLTs occurring in the first cycle of treatment are used to determine the recommended dose, does not reflect the tolerability profile of modern targeted oncology therapies, and is likely to lead to the selection of doses that are poorly tolerated in the long run. More than half of patients with solid tumors experiencing grade 3–5 toxicities in phase 1 trials of molecularly targeted agents had their first severe adverse event after the end of the protocol-defined DLT observation period, and a significant proportion of patients required dose reduction for selected grade ≤ 2 toxicities as early as cycle 1 [70]. We recommend that all toxicities should be reported comprehensively, even if they do not occur during the DLT period, and the recommended dose should incorporate all available information, notably toxicities observed after cycle 1.

It will also be important to continue to evaluate dosing throughout the development of a drug, and to investigate whether different doses are needed in different disease settings. Finally, patients should also be kept informed of any changes to how doses are selected, perhaps at the informed consent stage, as there may be a concern among patients that a lower dose might be associated with reduced efficacy.

9. Potential benefits and challenges

The use of doses below the MTD may lead to a reduction in the frequency and severity of adverse events, which can in turn improve efficacy through the reduced occurrence of treatment interruption due to adverse events and thus lead to better patient adherence. Although it is possible that the increased cost of drug development will affect long-term affordability and access to therapy, this may be offset by the fact that lower doses may lead to a reduction in the indirect costs associated with adverse events, as well as the need for fewer challenging post-approval trials to support changes to dosing. It is likely to be more efficient to evaluate multiple doses early in development, as doing so can lead to an earlier understanding of dose–response and exposure–response relationships, thereby allowing for more rapid and efficient extrapolation of therapies, including combination regimens, subsequent indications, new dosing regimens, and new formulations. Conversely, there is likely to be a risk of long-term financial burden on healthcare systems if dose optimization is not taken seriously.

There are a number of examples of fast-moving clinical development programs in areas of unmet medical need which incorporated randomized dose trials for dose optimization [2]. To support the clinical development of pembrolizumab for advanced melanoma, KEYNOTE-001, a phase I clinical trial, included a randomly assigned expansion cohort with two different dosages. The two dosages were 2 or 10 mg/kg administered intravenously every 3 weeks, and ultimately the 2 mg/kg dosage was selected for further development and approval. Another example is belantamab mafodotin for multiple myeloma, which was evaluated in the DREAMM-2 trial, a two-dose trial in which patients were randomly assigned to receive either 2.5 or 3.4 mg/kg IV every 3 weeks. The DREAMM-2 trial enrolled 196 patients over 6 months, although only 130 patients were planned per protocol.

However, open questions and potential challenges remain. An "optimal" characterization of the dose–response and exposure–response may require exposing some patients to doses that are likely to be suboptimal in a randomized dose-comparison trial. The need for robust data to support dose selection will likely necessitate greater patient enrollment in phase 1 trials, which could be challenging for rare diseases. There is also a need to identify new relevant and accessible biomarkers and preclinical models. New methodologies (such as new statistical and model-based methods) will also need to be adopted, which will require time and education. New study designs will also add to the complexity of drug development, as intervals between dose cohorts need to be longer to capture pharmacodynamic and longer-term toxicity data, for example. There may also be a need to re-evaluate the typical study end points used in clinical trials if response rates are lower and overall response rate and duration of response are therefore no longer suitable. Pharmacodynamic endpoints could provide alternative data but will also require an increased number of tumor biopsies. However, it may be possible to leverage advances in radiographic, circulating tumor DNA, and measurable residual disease biomarkers to provide data at multiple timepoints with less variability and greater accessibility when compared with biopsies. Validation of biomarkers will also need to be performed earlier and more extensively than in the past to enable optimal patient selection and PK/PD decision-marking. While the overall speed and

duration of drug development may be negatively impacted by the need for increasingly rigorous dose characterization, this effect could be counterbalanced by the possibility of better optimized dosing for registration studies.

A key requirement for future trials based on the 2024 FDA guidelines will be the enrollment of a sufficiently broad population of patients early in the drug development cycle to assess the impact of covariates on pharmacokinetics, safety, and efficacy. Differences in patient disease characteristics may mean that the OBD differs across different patient subpopulations (e.g. due to differences in tumor type and the presence of mutations that affect drug affinity or inhibitory activity). This leaves the question of how to meet the need for a broader patient population without undermining the identification of the OBD.

10. Conclusions and proposed future directions

A paradigm shift is underway in how doses are selected for oncology therapies. Dose optimization is moving away from the historic ('more is better') MTD paradigm, reflecting the shift from cytotoxic drugs to targeted therapies. Regulatory authorities have already begun to adopt recommendations for randomized evaluation of optimal dosing, in addition to the traditional single-arm dose-expansion methods. However, how this randomized evaluation should work remains something of an open question. Preclinical research and the use of biomarkers, such as target engagement and receptor occupancy, should be incorporated into the dose-selection process when possible.

We recommend that dose-finding should involve a dose-ranging study to characterize the dose-response curve and identify a range of possible doses early in the drug development cycle. The selected doses can then be evaluated in a subsequent randomized dose-selection study. Dose selection should be informed and justified by all available and relevant clinical and nonclinical evidence, including biomarker data, PK/PD data, and PROs. Multi-stakeholder engagement and exchange is required to overcome the challenges involved in the successful adoption of a new dose-finding paradigm.

A summary of practical recommendations for dose optimization is available in the Online Appendix.

Author contributions

This paper was written based on discussions at the CDDF hybrid workshop on Dose Optimization in Early Oncology Drug Development. The manuscript was drafted by AG, CL, HW, and KR. All authors contributed to workshop discussions, made suggestions on the manuscript, and approved the final version. Writing and editorial support was provided by James O'Reilly, PhD.

Declaration

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CRediT authorship contribution statement

Harald Weber: Writing – review & editing, Writing – original draft, Conceptualization. **Axel Glasmacher:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization. **Katrin Rupalla:** Writing – review & editing, Writing – original draft, Conceptualization. **Chunze Li:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Elena Garralda:** Writing – review & editing, Writing – original draft, Conceptualization. **Chad Gwaltney:** Writing – review & editing, Writing – original draft.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: AG is a member of the board directors of the Cancer Drug Development Forum asbl, a non-profit organization in Belgium, and a member of the supervisory boards of Ryvu Therapeutics SA and Active Biotech AB. He has received consultancy fees from Oncopeptides AB. CG reports no competing interests. CL are employed by Genentech, Inc. and hold company stocks. EGC received research support from Novartis, Roche, Thermo Fisher, AstraZeneca, Taiho, BeiGene, Janssen, and Anaveon; is a consultant/advisor for Roche, Ellipses Pharma, Boehringer Ingelheim, Janssen Global Services, Seattle Genetics, Skypta, Sotio, Sanofi, Anaveon, Abbvie, Astex Therapeutics, Alentis Therapeutics, Marengo Therapeutics, Hengrui, Incyte, Medpace, Medscape, Pfizer, Amgen, GenMab, GreyWolf, Gilead, and Daiichi Sankyo; is a member of the Speakers Bureau for MSD, Roche, Novartis, SeaGen, PPD, Aran, TRRF, ESMO, Fundación SEOM, CDDF, Springer Nature, Karger, Doctaforum, Tactics, AEFI, Fundación ECO, MeetingPharma, AstraZeneca, Alcura, Horizon CME, and ESO; is employed by NEXT Oncology; and holds stocks in 1TRIALSP. HW is employed by Pfizer AG, and holds company stocks of Pfizer and Roche. KR is employed by Johnson & Johnson and holds Johnson & Johnson company stocks.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115593.

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