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Project Optimus: An Overview of the Principles and Challenges

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ABSTRACT

Phase 1 trial designs to establish the appropriate dose for cytotoxic agents are based on the assumption that both clinical benefit & toxicity increase with dose. These studies seek to establish the maximum tolerated dose (MTD) for future development, for targeted non-cytotoxic therapies maximum efficacy may be achieved at doses below the MTD. The FDA has set up Project Optimus (PO) to reform the dose optimisation and dose selection paradigm for cancer drug development. PO is a bid for balance: maintaining treatment efficacy at a therapeutic dose that does not generate toxicities that could otherwise be avoided with a different dose. PO guidance includes that dose escalation decisions in Phase I trials should consider preclinical data (ideally using models that predict human efficacy, toxicity, and receptor engagement), toxicity (including early and delayed, low-grade toxicities, and patient-reported outcomes), pharmacokinetic (PK) data, efficacy data and pharmacodynamic (PD) data. Phase I studies should identify a dose range within which efficacy has been observed rather than a single dose for further development. Adherence to PO principles will have a large impact on early oncology development. This presentation summarises the key PO guidance and the challenges that ensue.

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Background

The assumption underpinning dose selection for cytotoxic chemotherapy in oncology is that both clinical benefit & toxicity increase with dose. Initial studies seek to establish the MTD, which can be used in subsequent studies, and ultimately in the clinic. Traditionally, the MTD has been established using a 3+3 design, which was originally introduced in the 1940s [1]. Simply put, in these studies three participants receive the initial dose. If 0/3 patient has Dose Limiting Toxicity (DLT), escalate the dose. If 1 of the 3 participants has a DLT treat 3 more patients at the same dose, if 2 of the 3 participants have DLTs then dose needs to be de-escalated. Once 6 participants have received a dose; if 0/6 or 1/6 patients have DLT, escalate the dose and if 2/6 patients have DLT, de-escalate the dose, or select the next lower dose as the MTD if 6 patients have been treated at that dose (see Figure 1). Some key definitions & standard parameters for this study design are included in Table 1 [2].

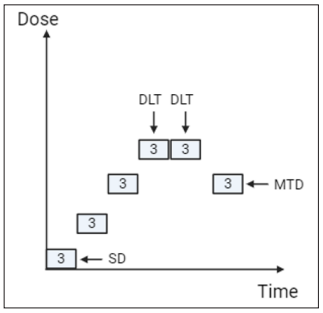

Figure 1: Traditional 3+3 Design (Created with BioRender.com)

Table 1: Terminology for Classical 3+3 Dose Escalation Studies

Dose-limiting toxicities (DLTs)	Predefined toxicities (generally clinically relevant grade 3 or higher toxicities using severity criteria defined in CTCAE) that emerge during the DLT period
DLT period	The period during which participants are observed for DLTs, generally within 1 cycle or 3 to 4 weeks from the first exposure to the investigational agent.
Maximum tolerated dose (MTD)	The highest dose at which fewer than 1/3 of the participants experience DLTs. This dose is typically evaluated in later studies for chemotherapy.
Maximum administered dose (MAD)	The pre-agreed maximum dose is administered in a study if the MTD is not identified.
Recommended Phase two-dose (RP2D)	The dose is recommended for further development following a dose escalation study. This may be the MTD or a lower dose, depending on the findings.
Study population	Typically includes individuals who have exhausted all therapeutic options for their disease. Different tumour types are commonly included.
Starting dose (SD)	The initial dose administered to the first cohort in the study. This is generally a dose anticipated to provide an exposure that caused no toxicities in animals during preclinical safety studies (i.e. a fraction of the no-observed-adverse-effect level in animals). For agents where animal data may not predict human toxicity (e.g. immuno-oncology agents), the starting dose may be based on an exposure level at which the first signs of biological activity were observed in preclinical models.

Dose escalation increments	The magnitude of dose escalation for each new cohort may be predetermined (e.g. using a modified Fibonacci sequence with smaller increases for each new cohort). Alternatively, the magnitude of escalation may be agreed upon by the safety review committee based on emerging safety data. Bayesian statistics may also be used to support these decisions

To protect participants' well-being, the starting dose is set well below the anticipated efficacious dose (see Table 1). In addition, for a first-in-class investigational agent, it is recommended that only one individual receives the trial therapy and is monitored for a predefined period before recruitment is opened for the rest of the cohort. This approach is known as sentinel dosing.

One criticism of the 3+3 approach is that it can result in a high proportion of patients receiving sub-therapeutic doses. Alternative designs, such as Accelerated Titration Designs (ATD), have been developed to limit the number of patients (using cohorts of 1 or 2) receiving doses where little or no biological effect is expected. In an ATD, once low-grade adverse events (AEs) are reported, or a predefined exposure threshold is reached, the design can switch to the classic 3+3 approach (see Figure 2) [3].

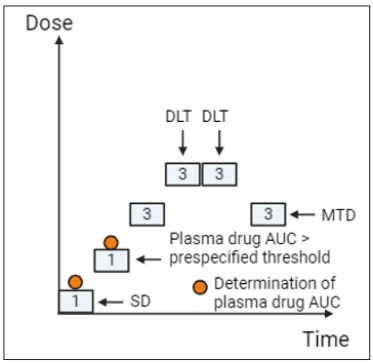

Figure 2: Accelerated Titration Design Example (Created with Biorender.Com)

Dose decision-making based solely on predefined Dose-Limiting Toxicities (DLTs) within the predefined DLT period—usually 21 or 28 days—means that toxicities that develop in later periods or lower-level but distressing toxicities (e.g., Grade 2 diarrhoea) may not be taken into consideration. Additionally, establishing a maximum tolerated dose (MTD) may not always be appropriate, especially if there is clear efficacy in the absence of DLTs. Trial designs using Bayesian statistical methods can incorporate tolerability information in addition to DLTs to support dose escalation decisions and provide alternative approaches to predict toxicity [3].

As a rule, evidence of therapeutic efficacy and/or biological efficacy are sought using radiological investigations & liquid (blood/plasma) or tumour biopsies. The concept of biologically effective doses is well established, and a recommended phase two dose (RP2D) can be identified using this information in addition to toxicity data and is regularly reported from dose escalation studies, many of which utilise Bayesian statistical approaches [4].

What Data is Needed to Characterise Doses for Further Development?

For cytotoxic chemotherapy agents with a narrow Therapeutic Index (TI) (see Figure 3), it is generally appropriate to develop these agents at the maximum tolerated dose (MTD). However, over the past few decades, a deeper understanding of tumour biology and the interactions between tumours and the immune system has led to unprecedented growth in novel classes of agents for cancer treatment. These include molecularly targeted small molecules such as tyrosine kinase inhibitors, immune-oncology therapies like immune checkpoint inhibitors (ICIs), and more recently, cell-based approaches such as CAR-T therapies [5]. For new targeted agents in oncology with wider therapeutic windows, the maximal clinical enefit may be observed at doses lower than the MTD. New molecularly targeted agents, biologics, and immunotherapies often saturate their targets at doses below the MTD, indicating that lower doses may provide comparable efficacy while reducing the toxicity burden [6].

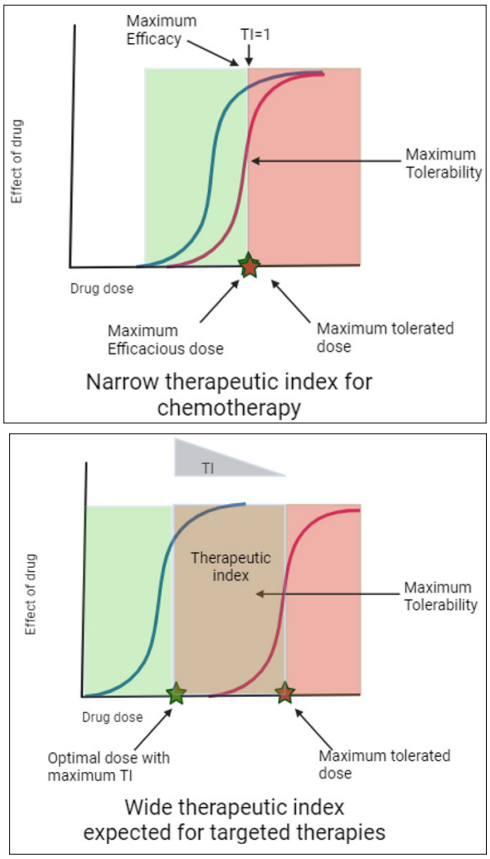

Figure 3: Illustration of Potential Difference in Therapeutic Indices (Tis) for Chemotherapy & Mta (Molecular Targeted Agents) In Oncology (Created with Biorender.Com)

One of the clinical challenges associated with immunotherapy is the emergence of a new spectrum of immune-related adverse events (irAEs), which differ significantly from classical chemotherapy-related toxicities. Due to the increasing use of immune checkpoint inhibitors (ICIs) in oncology, clinicians are likely to encounter irAEs affecting various organs, such as colitis, pneumonitis, endocrinopathy, liver toxicity, and nephritis. These toxicities can manifest many months into treatment, may be life-threatening, and often require a multidisciplinary approach for effective management [7].

These newer agents are administered until the patient's disease progresses, whereas many chemotherapies have limited courses. With the long-term benefit being experienced, late toxicities and persistent low-grade toxicities are becoming increasingly significant issues causing dose interruptions and therapy discontinuations [8].

Doses and schedules for several oncology therapies have required modification post-approval to address safety or tolerability concerns. Notable examples include ceritinib, dasatinib, niraparib, and gemtuzumab ozogamicin [8].

The FDA has expressed concern that the approaches used to identify appropriate doses for new agents are often suboptimal. It has stated, "Too often, the current paradigm for dose selection—based on cytotoxic chemotherapeutics—results in doses and schedules for molecularly targeted therapies that are inadequately characterised before initiating registration trials." In response, Project Optimus has been established by the FDA to advance a "dose-finding and optimization paradigm in oncology, emphasising the selection of doses that maximise not only the efficacy of a drug but also its safety and tolerability"[7] The FDA has collaborated with other regulatory agencies, academia, the pharmaceutical industry, and patients to develop guiding principles and guidelines for dose and schedule optimization in oncology drug development. An example of such a multidisciplinary group is the Methodology for the Development of Innovative Cancer Therapies Taskforce (MDICT), which has published guidelines on this topic [8]. This article outlines some of the key recommendations and discusses their implications.

Key Aspects from Project Optimus Recommendations

Preclinical data should inform trial design by predicting efficacious dose ranges, assessing the impact of dose and schedule on target engagement, efficacy, and toxicity, understanding how tumor biology affects efficacy, and identifying pharmacodynamic (PD) markers to determine treatment effects [9-12]. While it is already standard practice to consider these factors in drug development, the FDA aims to make these considerations explicit. During the study design phase, the study sponsor should align with regulators on how PD modeling based on preclinical findings will influence dose decisions.

Early dose escalation studies should identify a recommended dose range (RDR) for future development. Project Optimus emphasises the importance of understanding how varying doses affect efficacy and toxicity, rather than focusing solely on a maximum tolerated dose (MTD) or a single RP2D. The recommended dose (RD) may differ by disease, tumour site (as certain sanctuary sites may require higher doses), or molecular alterations (e.g., the dose of imatinib varies by indication). Establishing an MTD, if feasible, can provide valuable data for managing overdose situations or drug-drug interactions (DDIs) that increase exposure Dose escalation decisions should consider all aspects of safety and tolerability data, as well as pharmacokinetics (PK), efficacy, and biological data.

- In addition to reviewing dose-limiting toxicities (DLTs), it is important to consider adverse events (AEs) reported beyond the DLT period (late toxicities), lower-grade toxicities, and any necessary dose interruptions or reductions at any time.
- It is recommended that patient-reported outcomes (PRO) data be collected where possible. There are validated quality of life (QOL) questionnaires, some of which are general, while others are designed to collect detailed information on specific aspects (e.g., pain, fatigue, diarrhoea).
- All available efficacy and pharmacodynamic data should be reviewed. Classical tumour shrinkage (RECIST 1.1) using radiological imaging remains the gold standard. Additional imaging approaches, such as radiomics and PET CT, can provide valuable insights.
- Pharmacodynamic (PD) biomarkers may indicate biological effects specifically developed for that agent in preclinical models (e.g., evidence of pathway disruption in tumour biopsies or surrogate tissue) or may reflect a general impact on the tumour (e.g., changes in circulating tumour DNA [ctDNA]).
- Real-time PK data for all participants should be available for each dose escalation decision. Relationships between dose/exposure and efficacy, as well as dose/exposure and toxicity, should be reviewed.

It is recommended that at least two dose levels be compared by randomizing participants to the two different arms to properly assess efficacy, tolerability, and safety. The upper dose may include the maximum tolerated dose (MTD), and there should be evidence of clinical activity at the selected lower dose(s). The PK overlap between the dose levels should also be minimized. The trial does not need to be powered to demonstrate superiority or non-inferiority but should be sized to allow for sufficient assessment of safety and anti-tumour activity at each dose level. This comparison may be conducted within the dose escalation study (through the addition of backfill cohorts) or, ideally, in a separate Phase II study. It is recognized that such randomized studies may not be feasible (e.g., very rare diseases) or may not be necessary (for agents with a known narrow therapeutic index, such as chemotherapies) or where there is clear efficacy in a homogeneous population with oncogene-addicted tumours. There are two option to collect dose ranging data as represented in Figure 4 & 5.

The parameters observed in Project Optimus are represented in Table 2.

Table 2: Definition and Terminology Utilised in Project Optimus

Parameter	Explanation
Treatment Limiting toxicity (TLT)	Includes chronic low-grade toxicity, late-emerging toxicities, and non-dose-dependent toxicity that may limit the duration of therapy.
Recommended dose range (RDR)	The range of doses identified in the dose escalation study to be tested in a randomized setting
Recommended dose (RD)	The dose recommended for later-phase trials is identified through dose-ranging or dose-confirmation studies.
Minimal reproducible active dosage (MRAD)	Lowest dose where there is evidence of clinical activity

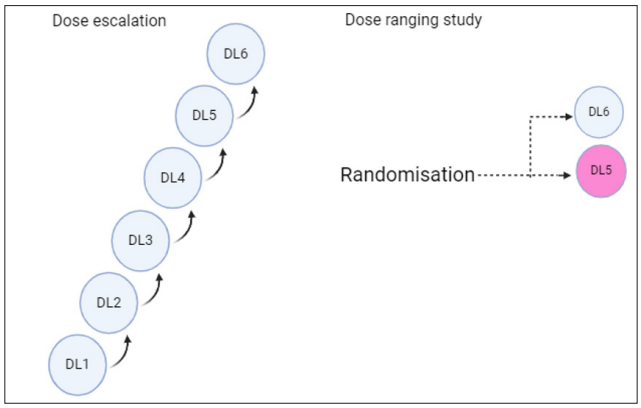

Figure 4: Dose Finding Using Separate Dose Escalation & Dose Ranging Studies (Created with BioRender.com)

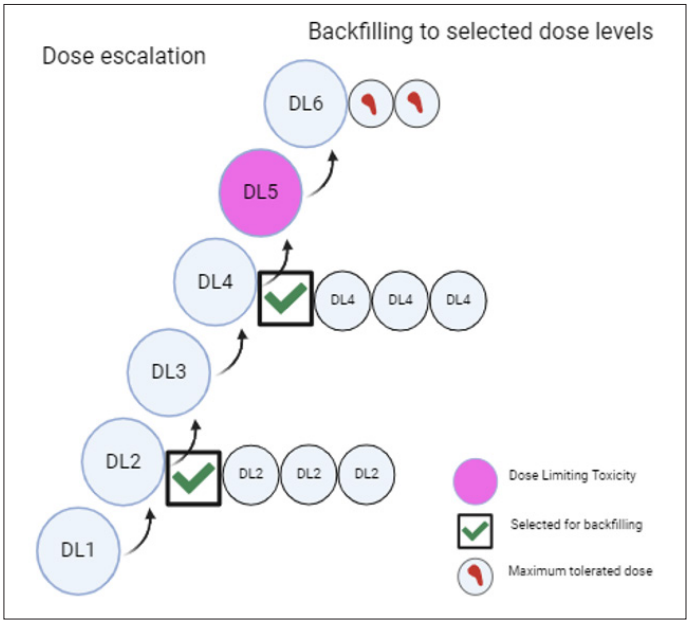

Figure 5: Dose Finding through Backfilling to Cohorts in the Dose Escalation Study(Created With Biorender.Com)

Implications for the Project Optimus Recommendations

When considering some of the individual elements within the guidelines, it is likely to be very challenging to demonstrate differences in efficacy between doses with small patient numbers. Response rates (i.e. tumour shrinkage demonstrated radiologically using RECIST 1.1) is an efficacy endpoint, often from single arm studies, that is used to support approval for a minority of oncology agents. Cancer drugs are generally approved based on comparisons with standard of care therapy in Phase III randomized studies. Overall survival (OS, the gold standard) or progression free survival (PFS) are the usual primary regulatory endpoints. Demonstration of improvement in OS &/or PFS that is statistically significant & clinically meaningful requires large studies. There may be a disconnect between response rates and PFS & OS outcomes . As an example the Phase III Confirm study evaluated 2 dose levels of fulvestrant (250mg and 500mg IM monthly) in metastatic HR+ breast cancer. In this study with over 700 patients the objective response rate was 9.1% at the 500mg dose level and 10.2% at the 250mg dose level, but the progression free survival (PFS) favoured the 500mg dose level (Hazard Ration (HR) 0.80 (0.68-0.94)) [13]. In this case the response rate difference did not reflect the more clinically relevant difference in PFS.

Will higher, and possibly more effective doses, be discarded early in development because of lack of difference in surrogate outcomes such as overall response rate or duration of responses or PD biomarker changes?

To address this issue the clinical community is seeking to validate alternative endpoints based on novel imaging approaches to define efficacy other than those included in RECIST 1.1, including using radiomics and PET scans to define responses [14]. In parallel there is an initiative to standardize approaches to ctDNA measurements, and to define responses based on ctDNA changes [15]. Data from ongoing and upcoming early studies will contribute to the validation processes for novel efficacy endpoints, and it need to be recognized that it will take time to demonstrate if changes in these dynamic markers predict for better long-term clinical outcomes and become new standard endpoints.

PD biomarkers used to demonstrate biological effect need to be validated and discussed with the FDA prior to starting the study.

Many of the approaches to evaluating patient reported outcome (PRO) data are in very early development will need to be considered carefully as to how they are integrated into dose escalation studies effectively. In general dose escalation studies include participants who have exhausted all standard of care therapies, and include very heterogenous populations. The sites of metastases, the disease burden the extent and number and type of prior therapies can vary considerably. These factors may have a significant impact on the patient's symptoms, co-morbidities, and quality of life, which may independent of the effect of the investigational agent, and may make the interpretation of the overall data difficult, especially if the cohorts have small patient numbers. Additionally, appropriate health-related quality of life (HQOL) instruments need to be validated for early clinical development, bearing in mind the time taken for patients, with a limited life-span, to participate in a clinical study.

Project Optimus imposes additional design complexities to the conduct of early clinical trials for the development of oncology drugs, impacting both the pace of drug development and the initial cost of drug development. Smaller companies will feel the effect most because of constrained resources, especially funding, where there is pressure from investors to see clinical results being delivered as quickly as possible.

On the positive side, many of the concepts contained in the PO guidelines have been included in early clinical drug design for many years, e.g., the use of preclinical data modelling, Bayesian model-based designs and simulations, more complex dose escalation decisions based on longer-term safety/tolerability data and PK-PD relationships. PO is imposing a more formalized and explicit approach to the dose escalation decision-making processes, normally conducted by the Safety or Cohort Review Committee (SRC/CRC).

Finally, PO is not just a set of guidelines to be implemented in early study designs. It is a fundamental change in the philosophy of how to identify appropriate doses throughout all phases of oncology drug development, and ultimately paves the way for a more collaborative approaches between the drug developers and the regulatory authorities. Dose optimisation plans require early interaction and engagement with the regulatory authorities as part of the clinical study design discussion and may be revisited at milestone meetings. The FDA has stated that discussions regarding dose finding strategies need not be tied to the milestone meetings, and separate meetings may be warranted as new clinical data becomes available. It is hoped that this collaborative approach will identify the best optimal dose and schedule for patients based on the emerging risk/benefit based on the explored doses and schedules prior to the study drug entering it's Phase III study and ultimately into the clinics for cancer patients.

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