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Rethinking cancer drug dosing: How Project Optimus is redefining oncology drug dose optimisation

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The Food and Drug Administration (FDA) launched Project Optimus, an initiative to establish a dose-optimisation paradigm for cancer therapies. The goal is to collaborate with medicine developers, academia and patients to develop oncology therapies with dosing regimens that improve safety while maintaining efficacy.

Put simply, Project Optimus aims to *'reform the dosing paradigm in oncology drug development.'* [1]

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Why does the dosing paradigm for oncology medicines need to change?

Historically, dose-finding trials for oncology medicines have followed a paradigm of determining the maximum tolerated dose (MTD) to be used in later-phase clinical trials.

The MTD paradigm often takes the form of a 3+3 trial design in which three patients are given a selected dose of a therapeutic agent, and if there are no dose-limiting toxicities (DLTs), an escalated dose is given to a further three patients. This continues until two out of three patients get DLTs and the MTD is identified. This dose selection paradigm typically involves a limited number of patients over a short observation period.[2-4]

However, this dose-finding programme was originally designed for cytotoxic chemotherapies, which followed a steepdose-response relationship, with an inherent lack of target specificity. Furthermore, patients may have been more willing to accept toxicity due to a lack of treatment options.[2-4] All of these considerations have been significant in driving an MTD paradigm. However, the treatment landscape has changed significantly. Modern oncology therapies include molecularly targeted agents (MTAs), biologics and immunotherapies (as single agents or in combination),[2] all of which act on specific molecular pathways that are critical to cancer cell proliferation. The reason this is important in the context of dose selection and dose escalation is that these targeted therapies have an inherently different dose-response relationship compared with cytotoxic chemotherapies. In addition, the MTD dosing paradigm has a short observation period, which is better suited to limited/defined-treatment-duration cytotoxic chemotherapy; consequently, this paradigm does not adequately evaluate dosing during the longer-term treat-to-progression posology of contemporary targeted therapies.[2] Utilising the historical MTD dosing paradigm doesn't sufficiently consider pharmacokinetics (PK), pharmacodynamics (PD), and dose- and exposure-response relationships, to select a dosage(s) for later-stage trials.[2,4] As a result, novel therapies may show a similar efficacy to the MTD, but at lower doses.

Project Optimus recognises that insufficient dose evaluation may lead to increased chronic low-grade toxicity, which may jeopardise long-term maintenance on an effective therapy.[3] Additionally, severe toxicities can lead to dose reductions, premature discontinuation in clinical trials and irreversible toxicities that reduce a patient's options to benefit from future therapies with overlapping toxicity. Both low-grade chronic and acute severe toxicity may narrow the treatment landscape, potentially impacting the overall survival (OS) of cancer patients.[3] From a medicine developer's regulatory perspective, the consequences of not optimising dosage can include the medicine not being approved, being withdrawn from the market, or requiring additional time-consuming and costly dosing exploration in phase 3 or post-marketing studies.

Even with the evolution of targeted therapies to treat cancers, many advanced and metastatic cancers remain incurable, and patients are still waiting for safe, tolerable and efficacious therapeutic options, making the rapid access to such medicines critical.

Practical examples of the oncology dose-selection conundrum

To put the need for better dosing paradigms in a practical perspective, a review of sixty European Public Assessment Reports from oncology medicines approved between 2015 and 2020 was conducted to determine if the optimal dose was selected in the novel anti-cancer agents that were approved. The review highlighted that:[5]

- A dose-response relationship was identified in five dossiers (8%)
- The MTD was the selected dose for 15 anti-cancer agents (25%)
- The MTD was not determined in 27 out of 60 cases (59%)

Additionally, when the MTD was determined but not selected as the final dose, the dose selection criteria included toxicity, exposure response, PK data and PD data in 7 out of 18 cases.[5] For protein kinase inhibitors and monoclonal antibodies (mAbs), tolerability was analysed separately as it was determined that the dosing interval and mitigation of adverse events (AEs) differ for these types of therapies.[5]

Regarding the median discontinuation, dose reduction and dose interruption rates due to AEs of protein kinase inhibitors were 10%, 26% and 45% for monotherapy and 13%, 47% and 55% for combination therapy, respectively.[5] The median discontinuation rates due to AEs for mAbs were 8% for monotherapy and 26% for combination therapy.[5]

The review concluded that the dose-response relationship had not been established for the majority of oncology medicines approved during this time period and that these medicines were not well tolerated, as reflected in the high discontinuation and dose reduction rates. The review also highlighted that, as there was inadequate dose-response data, it is unknown if the optimal dose was selected for the medicines that were approved. It is worth noting that these medicines were approved before the FDA introduced Project Optimus and before the European Medicines Agency's (EMA's) guideline on the clinical evaluation of anti-cancer medicinal products.[5]

So, to compare, a more recent review of anti-cancer drugs with initial EMA and FDA approval between 1 January, 2020 and 30 June, 2023 was conducted by Op 't Hoog et al., 2024 (Project Optimus was created in 2021).[6] A total of 31 anti-cancer drugs were included, in which 20 out of the 31 anti-cancer drugs were considered to be potential candidates for dose optimisation.[6] Specifically, the review deemed that the safety of 10 of the 31 drugs could be improved by reducing the dose without compromising efficacy, and a further 10 drugs could have the dosage regimen modified to improve patient convenience with less frequent dosing or reducing pill burden. *Overall, the review considered 9 out of the 31 drugs had an optimum dose selection.*[6]

Additionally, the review found that the traditional 3+3 trial design was the most frequently used dosing paradigm in phase 1 trials to select the recommended phase 2 dose (RP2D; 25 out of 31 drugs).[6] Similar to the review by Maliepaard et al., 2021,[5] the MTD was not determined in 19 of the 31 drugs in phase 1 trials, and this was determined to be due to no DLTs observed within the investigated dosing range.[6]

Among these 19 drugs where MTD was not determined, the highest administered dose within the investigated dosing range was used as the RP2D in five drugs; for the remaining 14 drugs, a lower dose was selected as the RP2D due to multiple reasons (e.g. target saturation or efficacy data).[6] For 12 of 31 drugs, the MTD was determined, and in four of these 12 drugs, the MTD was selected as the RP2D. For the remaining eight drugs in which the MTD was determined, a lower dose than the MTD was selected as the RP2D. *For only 3 out of 31 drugs, two or more dose levels were studied in phase 2.*[6]

Both of the reviews highlight that the traditional 3+3 dose-finding design was widely used, with the MTD being either used as the RP2D or not being determined at all. Despite the development of targeted agents in oncology to enable precision medicine, the traditional 3+3 design does not necessarily lead to the selection of the most favourable dose, and the tolerability of these agents often remains poor. It is worth noting that although these reviews were conducted on anti-cancer drugs that were approved during Project Optimus' inception, the phase 1 trials were most certainly conducted years before the FDA rolled out this initiative. Nevertheless, they confirm the shortcomings of the traditional dose-selection approach.

Practical examples of toxicities in novel anti-cancer therapies using traditional dose-finding paradigms

Regorafenib

Regorafenib (STIRVAGA®) is an oral multikinase inhibitor approved for colorectal cancer, gastrointestinal stromal tumour and hepatocellular carcinoma at a recommended dose of 160mg. A meta-analysis investigated the scheduled treatment modifications of regorafenib associated with AEs across seven randomised controlled clinical trials involving 2,099 patients.[7] The meta-analysis observed that regorafenib was associated with higher incidences of permanent discontinuation, dose interruptions and dose reductions in patients receiving regorafenib, which were 9.7%, 57.2% and 47%, respectively, compared with 3.3%, 16.7% and 7.7% in the placebo group at the recommended 160mg dose.[7]The meta-analysis also highlighted that in real-world practice and retrospective studies of regorafenib dosing, initial doses of 80-120mg resulted in lower Grade 3-4 AEs but with similar efficacy to the recommended 160mg dose.[7] Similarly, using a dose-escalation strategy starting at 80mg and increasing to 160mg via 40mg increases over 3 weeks also showed a safe and effective alternative dosing strategy to the initial 160 mg recommended dose.[7]

Sotorasib– the poster child for Project Optimus

Sotorasib (LUMAKRAS®) is known as the poster child for the limitations associated with the MTD dosing paradigm, coinciding with the initiation of Project Optimus. Approved in 2021 for metastatic non-small cell lung cancers (NSCLCs) harbouring the KRAS p.G12C mutation, sotorasib was a promising therapy to treat KRAS(Kirsten rat sarcoma proto-oncogene) mutations.[8] It was approved by the FDA based on data from the phase 2 CodeBreaK100 trial.[8] However, insufficient dose finding pre-approval led the FDA to require post-marketing trials to evaluate safety and efficacy at lower doses than the dose approved, specifically, 960 mg (approved dose) vs 240 mg and a phase 3 confirmatory trial comparing sotorasib with docetaxel.[9] This decision was made based on data suggesting that PK drug exposure, target saturation, and tumour response rates were similar at the approved (960mg) dose and at lower doses.[8,9]

The original sotorasib approval

The original 2021 FDA approval of LUMAKRAS was based on the efficacy demonstrated in a single-arm, open-label, multicentre trial (CodeBreaK100 trial) in patients with an advanced, KRAS G12C-mutated NSCLC. All enrolled patients had received at least one prior systemic therapy (an immune checkpoint inhibitor and/or platinum-based chemotherapy).[8-10]

A total of 124 patients had at least one measurable lesion at baseline and were treated with LUMAKRAS 960 mg once daily (QD) until disease progression or unacceptable toxicity (primary efficacy analysis population). The major efficacy outcome measures were objective response rate (ORR), and duration of response (DOR).[10]

The ORR of the primary efficacy population, as determined by Blinded Independent Central Review was 36% (95% confidence interval [CI]: 28, 45). The median DOR was 10.0 months (range:1.3+, 11.1) with 58% of responders experiencing a DOR ≥6 months.[10]

Safety of sotorasib

NSCLC subset safety analysis

In the subset of patients with KRAS G12C-mutated locally advanced or metastatic NSCLC in CodeBreaK 100 treated with 960 mg (n=204), serious adverse reactions occurred in 50% of patients. Serious adverse reactions in ≥2% of patients were pneumonia (8%), hepatotoxicity (3.4%) and diarrhoea (2%).[10]

Fatal adverse reactions occurred in 3.4% of patients who received LUMAKRAS due to respiratory failure (0.8%), pneumonitis (0.4%), cardiac arrest (0.4%), cardiac failure (0.4%), gastric ulcer (0.4%) and pneumonia (0.4%).[10]

Permanent discontinuation of LUMAKRAS due to an adverse reaction occurred in 9% of patients. Adverse reactions resulting in permanent discontinuation of LUMAKRAS in ≥2% of patients included hepatotoxicity (4.9%).[10]

Dosage interruptions of LUMAKRAS due to an adverse reaction occurred in 34% of patients. Adverse reactions which required dosage interruption in ≥2% of patients were hepatotoxicity (11%), diarrhoea (8%), musculoskeletal pain (3.9%), nausea (2.9%) and pneumonia (2.5%).[10]

Dose reductions of LUMAKRAS due to an adverse reaction occurred in 5% of patients. Adverse reactions which required dose reductions in ≥2% of patients included increased ALT (2.9%) and increased AST (2.5%).[10]

The most common adverse reactions (≥20%) were diarrhoea, musculoskeletal pain, nausea, fatigue, hepatotoxicity and cough. The most common laboratory abnormalities (≥25%) were decreased lymphocytes, decreased haemoglobin, increased AST, increased ALT, decreased calcium, increased alkaline phosphatase, increased urine protein and decreased sodium.[10]

Specific FDA post-marketing requirements for sotorasib

As part of the accelerated approval, the FDA issued a post-marketing requirement (PMR) to investigate the safety and efficacy of a lower sotorasib daily dose as compared with the 960 mg dose. This was because sotorasib demonstrated saturable absorption with steady-state exposures (C_{max} and $AUC_{0\text{-}24h}$) comparable among 180 mg to 960 mg QD dose levels. The observed dose–ORR relationship for efficacy suggested that a lower dose could provide acceptable effectiveness for the proposed indication.[10] The FDA also ordered the sponsor (Amgen) to conduct a multicentre, randomised clinical trial and submit the final progression-free survival (PFS) results that verified the clinical benefit of sotorasib in patients with locally advanced or metastatic NSCLC. The rationale for this was that the FDA's accelerated approval of sotorasib was based on single-arm study information with a primary endpoint of ORR. PFS results from clinical trials were required to obtain additional efficacy data to confirm the clinical benefit of sotorasib.[10]

Results of sotorasib's post-marketing requirements

In the open-label, phase 2, post-marketing study, adults with KRAS G12C advanced NSCLC were randomised 1:1 to sotorasib 960 mg or 240 mg QD. The primary endpoint in the trial was ORR. Secondary endpoints included disease control rate (DCR), PFS, OS and PK.[11]

The results showed ORR/DCR were 32.7%/86.5% for 960 mg vs 24.8%/81.9% for 240 mg. The median PFS was 5.4 months for 960 mg vs 5.6 months for 240 mg (hazard ratio [HR] for 960 mg/240 mg: 0.95 [95% CI: 0.67, 1.35]). With a median follow-up of 17.5 months, median OS was 13.0 months at 960 mg vs 11.7 months at 240 mg (HR 0.75 [95% CI: 0.53, 1.07]). Geometric mean C_{max} was 22% lower at 240 mg vs 960 mg.[11]

Regarding safety, the most common treatment-related adverse events (TRAEs; 960 mg vs 240 mg) were diarrhoea (35.6% vs 21.2%), nausea (15.4% vs 13.5%), elevated ALT (11.5% vs 13.5%) and elevated AST (10.6% vs 11.5%). The sponsor concluded that sotorasib 960 mg, as compared with 240 mg, had a higher ORR/DCR and an improved OS, with a higher rate of Grade 3 TRAEs. AEs were generally manageable at both doses with label-directed dose modifications.[11]

The sponsor (Amgen) also conducted a randomised, open-label phase 3 trial in which 345 patients were randomly assigned (1:1) to oral (PO) sotorasib (960 mg QD) or intravenous [IV] docetaxel (75 mg/m^{2}once every 3 weeks).[12] The primary endpoint was PFS. Amgen reported a significant increase in the PFS for sotorasib, compared with docetaxel (median PFS 5·6 months [95% CI: 4·3, 7·8]vs 4·5 months [3·0, 5·7]; HR 0·66 [0·51, 0·86]; p=0·0017).[12]

Regarding safety, the most common TRAEs of Grade 3 or worse were diarrhoea (n=20 [12%]), ALT increase (n=13 [8%]) and AST increase (n=9 [5%]). For docetaxel, the most common TRAEs of Grade 3 or worse were neutropenia (n=13 [9%]), fatigue (n=9 [6%]) and febrile neutropenia (n=8 [5%]).[12]

Continued contention with sotorasib's approved dose

To date, the approved 960mg dose remains the appropriate and FDA-recommended dose for the NSCLC indication.[11] However, contention remains as doctors Strohbehn, Lichter, and Ratain wrote a summary in the ASCO Post detailing that in the phase 3 trial investigating the effect of sotorasib vs docetaxel, the FDA noted there was asymmetric early dropout among participants in the study, with greater dropout seen among those in the docetaxel arm, raising concerns that investigators' assessments of progressive disease had biased the study in favour of the sotorasib arm.[9] This potential bias resulted in the FDA convening the Oncology Drug Advisory Committee (ODAC), an independent third-party comprising oncologists, statisticians and patient advocates. After hearing nearly 8 hours of sponsor and FDA arguments, ODAC ultimately concluded, in a vote of 10 to 2, that these conduct issues had irreparably biased the study results, rendering it "uninterpretable."

The ongoing contention also has a financial aspect to it. Sotorasib at the approved 960mg dose was reported to have a list price of $21,000 per month,[9] and the authors note that reducing the dose to 240mg would drastically reduce the revenue sotorasib could generate for the sponsor.[9]

Alongside sotorasib's contentious dosing paradigm and approved dose, Shah et al. (2021)[8] highlighted several other oncology therapies whose doses or dosing schedules were modified for safety and tolerability after approval (see Table 1 for details).[8]

Table 1: Oncology therapies with modified dosing

Medicinal product	Initial approval indication	Dosing information
Ceritinib (Zykadia®)	The treatment of adults with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.	Initially dosed at 750 mg PO QD fasted (Ascend-1 trial). The modified dose was 450 mg PO QD with food to reduce gastrointestinal toxic effects.[8]
Dasatinib (Sprycel®)	The treatment of adults with chronic, accelerated or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.	Initially dosed at 70 mg PO twice daily. The modified dose was 100 mg PO QD to reduce haematological toxic effects and fluid retention.[8]
Niraparib (Zejula®)	The maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to 1st line platinum-based chemotherapy. The maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to 1st line platinum-based chemotherapy.	Initially dosed at 300mg PO QD. The modified dose was 200 mg PO QD to reduce thrombocytopenia in patients with a lower platelet count or lower body weight.[8]
Gemtuzumabozogamicin (Mylotarg®)	The treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults. The treatment of relapsed or refractory CD33-positive AML in adults and pediatric patients 2 years and older.	Initially dosed at 9 mg/m^2 IV on Days 1 and 15. The modified dose was 3 mg/m^2 IV on Days 1, 4 and 7 to reduce veno-occlusive disease and treatment-related mortality.[8]

What does Project Optimus propose?

The FDA's dosage optimisation recommendations emphasise a shift toward a data-driven, patient-centric approach to drug development. The overarching goal is to identify an optimised dosage that maximises the benefit–risk profile by providing the desired therapeutic effect while minimising toxicity, rather than simply finding the MTD.[3] The FDA also outlines that review through an expedited programme, i.e. breakthrough therapy designation, does not justify avoiding the need to conduct dosage optimisation before or at the same time as establishing a drug's safety and efficacy.[3] Taking advantage of early FDA engagement is recommended, as oncology development programmes can vary tremendously.

Core principles of the dosing strategy

PK and PD data:[3]

- Include a PK sampling and analysis plan in every protocol to characterise the PK such as linearity, absorption, distribution and elimination.
- Initiate population PK and dose-response/exposure-response analyses early and update them as data becomes available.
- Evaluate the effects of food and potential drug interactions early in development to support the dosage selected for pivotal trials.

Intrinsic factors and subpopulations:[3]

- Evaluate the impact of factors like genetic variation and organ impairment early; if alternative dosages are identified for specific subpopulations, incorporate them into pivotal trials when feasible.

Trial design for dose comparison:[3]

- Compare multiple dosages in trials designed to assess anti-tumour activity, safety and tolerability.
- Use randomised, parallel dose-response trials to minimise bias and improve the comparability of patients.
- Consider adaptive designs to stop enrolment in inferior dosage arms based on interim assessments.
- Evaluate adding more patients to existing cohorts (backfilling) to gather more data before initiating randomised comparisons.

Safety and tolerability assessments:[3]

- Compare dosages based on long-term tolerability metrics, including the proportion of patients requiring dose interruptions, reductions or discontinuations.
- Carefully assess persistent low-grade (Grade 1-2) symptomatic toxicities, as these can significantly impact a patient's ability to remain on treatment.
- Incorporate patient-reported outcomes (PROs) to systematically quantify symptomatic side effects and their impact on patient function.
- Pre-specify trial stopping rules for excessive toxicity in protocols.

Drug formulation:[3]

Plan for various dose strengths to facilitate the evaluation of multiple dosages; difficulty in manufacturing is not considered a sufficient reason to avoid comparing doses.

Subsequent indications:[3]

Tailor dosages for different disease settings or combinations, as different populations may require different doses based on tumour biology or concurrent therapies.

Dosing recommendations by development phase

1. Early development: Focus on characterising PK and identifying PD endpoints for both safety and activity. Sponsors should consider backfilling cohorts during initial dose escalation to gather more robust data early on and evaluate preliminary dose-response relationships.[1]

2. Dosage optimisation phase: This phase should involve randomised trials evaluating multiple dosages in patients, targeting specific diseases. The goal is to further characterise dose- and exposure-response relationships to select the best dosage for registration.[1]

3. Registrational trial: Using the selected optimised dosage, this trial focuses on developing a comprehensive assessment of the drug's efficacy, safety and tolerability to support a marketing application.[1]

Additionally, the FDA recommends using the totality of data at each step of development. Dosage selection should be based on an integrated assessment of all available information, including non-clinical data, PK, PD, safety, tolerability, dosage convenience, clinical activity, and established dose- and exposure-response relationships.[1]

Global regulatory guidance for dose selection in oncology medicines

Although Project Optimus is a standalone initiative by the FDA, the EMA is also taking strides to ensure dose selection and dose optimisation in oncology therapies are developed in line with the evolution of MTAs, immunomodulating drugs and other non-cytotoxic agents.[13]

European Medicines Agency's guidance

Non-cytotoxic compounds

Unlike traditional chemotherapy, non-cytotoxic compounds (e.g. signal transduction or cell cycle inhibitors) are typically administered continuously, and toxicity may not be the most appropriate endpoint for dose-finding trials.[13]

In cases where MTD is not adequate to establish the recommended dose, dose escalation can be based on PD and safety data in relevant animal models, and on human PK/PD data from initial and later dose cohorts, as well as using mechanism-based PK/PD modelling.[13]

Dose-finding for MTAs should extend beyond a purely safety-focused approach to identifying the optimal biologically active dose, defined as the dose at the start of the dose-response plateau, where higher doses provide no additional benefit.[13]

Because these therapies are often administered continuously for long periods, traditional DLT and MTD definitions must be broadened beyond Cycle 1 to capture late-occurring severe toxicities and persistent low-grade toxicities that impact long-term tolerability. Consequently, the RP2D should be determined through an integrated assessment of safety and activity across the entire treatment course to ensure the selected dose is tolerable for long-term use.[13]

mAbs and immune-modulators

mAbs:
In vitro non-clinical studies should be used to understand the main activity of mAbs and may include assays on target binding, potential "unwanted" targets, and both Fab- and Fc-associated functions.[13] Continued evaluation of PK during clinical development involving different tumour types and disease stages is encouraged to characterise the often-seen non-dose-proportional PK behaviourof mAbs.[13]

Immune-modulating compounds/vaccines:
Non-clinical in vitro and in vivo proof-of-concept studies are necessary to justify the planned starting dose and schedule in phase 1 studies. On a case-by-case basis, the rationale for the starting dose may be supported by using the 'Minimal Anticipated Biological Effect Level' approach and by non-clinical and clinical data from related compounds. [13]

Early clinical trials aim to determine the safety and the dose and schedule that induce a desired immune response. Dose-finding studies are generally required to establish the RP2D. Monitoring the immune response, i.e. the induction of antigen-specific T cells or the presence of a humoral response, can determine the appropriate dose and schedule. Therefore, multiple monitoring assays may be necessary and should be explored.[13]

The design of clinical studies using clearly experimental therapies in patients with limited and measurable disease, not heavily pretreated with cytotoxic regimens, has to be justified. As for other agents, evidence of anti-tumour activity is essential prior to starting confirmatory studies.[13]

Combination therapy studies

Irrespective of the class of medicinal product and if there are no informative PD endpoints suitable for dose optimisation, dose finding relies on toxicity and tolerability.[13]

The dose-finding study design depends on the class of drug, including the need for prolonged treatment and DLT/safety observation time to identify dose-limiting but late adverse reactions of many non-cytotoxic agents.[13]

The optimal dose intensity of the individual compounds in the regimen is rarely identifiable in terms of both safety and efficacy. For combinations where co-enhancement of pharmacology activities and worsening of the safety profile of the combination compared with single partner are anticipated, particular attention should be paid to the need for a dose-finding combination study before conducting phase 2 studies.[13]

Comprehensive PK/PD assessment for potential interactions and characterisation of on- and off-target toxicities are particularly important in combination studies. Apart from identifying a regimen that is tolerable, sponsors should aim to identify the product(s) causing the observed adverse reactions in order to guide dose reductions in relation to observed toxicity. The toxicity profile of the drugs used as monotherapy provides some guidance, but class experience, mode of action, etc. should also be considered.[13]

Potential limitations of Project Optimus

As with any new initiative proposing significant changes, questions are circulating regarding how this will impact drug development. Subbiah (2024)[14] and Murphy et al. (2023)[2] outlined the potential challenges medicine developers may perceive when implementing Project Optimus' dose-optimisation initiatives.

1) Longer development timelines

Aiming for more comprehensive dose finding could lengthen clinical development timelines, particularly if this calls for additional phase 2 trials. Increasing the development timeline inevitably delays bringing new medicines to market. However, this must be balanced against the potential for increased discontinuation rates due to toxicity in patients receiving unnecessarily high doses and reduced PMRs to evaluate lower doses.[14]

2) Increased trial complexity

The proposed shift from trial designs such as the 3+3 MTD early phase dose finding trials may significantly increase clinical trial complexity. For instance, it may be necessary to increase intervals between dose cohorts to capture PD and longer-term effects and integrate data on broad tolerability into dose-finding models, alongside PD and activity measures.[2] Project Optimus proposes several dose-selection strategies at different stages of development, which require implementing sophisticated and adaptive trial designs.

3) Increased resources

Dose selection under Project Optimus may also be resource-intensive. The guidance recommends robust PK sampling and detailed analysis plans, which may strain sponsor resources and increase the operational burden of early-phase trials. There is also the concern of increased cost of clinical development, which may pose a greater challenge to smaller biotechnology companies and academic institutions.[14]

4) Manufacturing

Manufacturing considerations represent another potential hurdle. Project Optimus emphasises evaluating multiple dose strengths during development, which may pose challenges for companies that must produce and supply several dosing options simultaneously. For some sponsors, the perceived difficulty of manufacturing multiple strengths could affect the feasibility of conducting dose comparisons in early-stage clinical trials.[14]

5) Paediatric and rare cancers

Sponsors may be hesitant to invest in paediatric and rare cancers in part due to financial return, and also due to small enrolment numbers as a function of these types of cancers. Subbiah (2024)[14] outlined industry's potential concerns that hesitancy to develop medicines for paediatric cancers under the Project Optimus initiative could lead to delays or discontinuation in paediatric cancer development altogether. Critics argue the initiative, designed primarily for adults, may not suit paediatric needs, and highlight the importance of flexibility and collaboration with the FDA to tailor policies for rare and paediatric populations.[14]

6) The effect on small biotechnology companies

Smaller biotechnology companies have expressed concerns about unexpected regulatory expectations associated with Project Optimus. Some sponsors report that expanded phase 1 trials and additional dose-optimisation cohorts may require more funding than originally anticipated. This can create financial pressure, particularly when additional trial arms or extended studies are needed.[14]

7) Heterogeneity and endpoints

For MTAs, the minimal biological dose may not be consistent across different patient populations, tumour types, disease stage and specific mutations.[2] Additionally, comparing doses may be more difficult in situations where response rates are lower or combination products are used. Although PD endpoints can provide further evidence, PD data may depend on the mode of action and could result in increased tumour biopsies, which increases patient burden.[2]

Is the FDA waiving dose optimisation for orphan drugs?

Alongside implementation concerns from the industry, the FDA's consistency in practising its new dose optimisation guidance through Project Optimus has also been called into question, particularly in the case of orphan drugs for rare diseases.

A 2023 paper used the FDA approval of pirtobrutinib (JAYPIRCA®) as a case study to highlight potential inconsistencies in regulatory oversight.[15]

Pirtobrutinib was approved in 2023 for mantle cell lymphoma at 200 mg QD. However, the authors argue this is not clearly the "optimal" dose because only 5% of patients in the clinical trial received lower doses, leaving minimal evidence to support 200 mg over lower, potentially safer levels.[15]

Additionally, serious adverse reactions occurred in 38% of patients at the approved dose, often leading to treatment interruptions or discontinuations.[15] The authors suggest that PK in these patients might be confounded by cachexia and high protein binding.[15]

While some argue that dose optimisation is difficult in rare diseases due to small patient populations, the authors point to drugs like mitapivat, pacritinib, and mavacamten as proof that preapproval dose-finding is feasible for orphan indications.[15]

Much like the sotorasib dosing contention, the authors also point to a significant pharmacoeconomic burden associated with higher doses. They reported that pirtobrutinib costs approximately $25,200 per month at the 200 mg dose, whereas the minimally effective dose of 50 mg dose would cost $8,400.[15] Optimising to a lower effective dose could drastically reduce "financial toxic effects" for patients and payers but reflects a lower reimbursement effect for the sponsor.[15]

Concern was expressed that ongoing phase 3 trials for pirtobrutinib in chronic lymphocytic leukaemia are using only a single dose level, which contradicts the central teachings of Project Optimus. They urge the FDA to mandate dose-ranging studies to ensure that patients with rare cancers are not receiving unnecessarily toxic or expensive treatments.[15]

Examples of dose-finding done right with Project Optimus

Shah et al., 2021[8] highlighted the development of programmed death 1 (PD-1)–blocking antibody therapies, such as pembrolizumab (Keytruda®) and nivolumab (Opdivo®), whose clinical development programme included extensive clinical pharmacological analysis and examined multiple doses.[8]

This led to "*an understanding of receptor occupancy and the relationship between exposure and response in terms of efficacy and safety.*" [8] Shah et al., 2021 concluded that "*dose- and exposure-response data from these trials and modelling led sponsors to select doses lower than the highest dose studied, while preserving efficacy.*" [8]

Another great example of dosing optimisation that aligns with the Project Optimus initiative comes in the form of the accelerated approval of fam-trastuzumab deruxtecan-nxki (T-DXd;ENHERTU®) in 2022, to treat adult patients with unresectable or metastatic NSCLC whose tumours have activating human epidermal growth factor receptor 2 (HER2) mutations and who had previously received systemic therapy.[16] The applicant (Daiichi Sankyo) received guidance from the FDA Oncology Center of Excellence's Project Optimus to conduct a randomised, dose-optimisation study (DESTINY-Lung02), which was one of the first trials to be reported based on advice from Project Optimus.[16]

The approval of T-DXd was based on the results of DESTINY-Lung01 and DESTINY-Lung02. DESTINY-Lung01 treated patients with 6.4 mg/kg every 3 weeks and the primary efficacy endpoints were ORR and DOR.[16] Emerging results from DESTINY-Lung02 were submitted during review of the marketing application. Patients were randomised 2:1 to receive either T-DXd 5.4 mg/kg every 3 weeks or T-DXd 6.4 mg/kg every 3 weeks.[16] The primary endpoint was ORR. The totality of population PK data, safety and efficacy data, and exposure-response analyses from the DESTINY-Lung02 trial supported a more favourable benefit–risk assessment at the 5.4 mg/kg every 3 weeks dosage versus the 6.4 mg/kg every 3 weeks dosage.[16]

Given the dose-optimisation results, clinical trial data from patients enrolled on DESTINY-Lung02 and treated with T-DXd 5.4 mg/kg every 3 weeks were used to derive the primary efficacy results.[16]

At the approved dose of 5.4 mg/kg given IV every 3 weeks, the ORR was 58% (95% CI: 43, 71) and the median DOR was 8.7 months (95% CI: 7.1, not estimable).[16] These results were consistent with response rates observed at the 6.4 mg/kg dose level. The most common (≥20%) adverse reactions were nausea, constipation, decreased appetite, vomiting, fatigue and alopecia.[16] The rate of ILD or pneumonitis, previously identified as an important risk of treatment with T-DXd, was 6% at the 5.4 mg/kg dose level and 14% at the 6.4 mg/kg dose level. Additionally, compared with the 6.4 mg/kg every 3 weeks dosage, patients treated with the 5.4 mg/kg every 3 weeks dosage experienced fewer Grades 3-4 treatment-emergent adverse events, including neutropenia, and fewer dosage interruptions, dose reductions, and drug discontinuations.[16]

Therefore, ENHERTU, the first targeted therapy for HER2-mutated NSCLC, is a good example of an approved product with dosage optimised for safety and efficacy.

Conclusion

Overall, Project Optimus reflects a necessary shift in oncology drug development away from the historical MTD paradigm and toward a more data-driven, patient-centred approach to dose optimisation that better reflects the realities of modern targeted therapies, biologics and immunotherapies.

The evidence reviewed suggests that traditional dose-selection methods have often failed to establish clear dose-response relationships and have contributed to high rates of dose interruptions, reductions and discontinuations, while practical examples such as sotorasib illustrate the consequences of insufficient pre-approval dose optimisation. In response, the FDA has set out a framework that emphasises PK and PD analysis, comparative dose evaluation, long-term tolerability, PROs and the totality of evidence, with parallel movement seen in EMA guidance.

While the implementation of Project Optimus may create potential challenges relating to timelines, trial complexity, resource requirements, manufacturing feasibility and investment in rare and paediatric cancers, it also offers the opportunity to improve the safety, efficacy and overall benefit–risk profile of oncology medicines before approval.

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