Project Optimus:
What you need to know

We asked Parexel regulatory experts to share their insights about FDA's Project Optimus.

1. It is clear that small molecules will fall under Project Optimus. Likewise, large molecules (nivolumab) and cytotoxics (capecitabine) have been used as 'poster children.' Do you believe that vaccines and cell-based therapies, etc., will also be included?

Generally, the type of drug does not exempt from assessing a proper dose-(R)response analysis. D-R or E(xposure)-R analyses applies to all drugs and uses both non-clinical and clinical data.

2. Under Project Optimus, should a sponsor plan to request meeting requests with US FDA at least twice? The first one to discuss dose optimization study design, and the second one to get FDA agreement on the "optimized dose" for the pivotal study?

Discussing the selected dose for a pivotal study with the FDA would be beneficial. You could discuss your initial plan during the pre-IND meeting and then plan at least one more additional meeting to discuss pivotal study design, including the dose selection.

3. Do you think the US FDA will also apply this standard to TIL and TCR therapies which have a one-time administration?

Overall, the tools/approaches discussed are not typically used for individually optimized treatments and precision dosing. However, we are seeing increasing importance of assessing clinical pharmacology aspects for CAR-T cells (e.g., https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1111/cts.13349) and the principles of quantitative clinical pharmacology are also applied to understand these drugs. Dose exposure can be explored for these products, assessment of covariates, etc.

4. You state that Bayesian Optimal Interval (BOIN) designs are better than 3+3. However, it is not great for dose escalation (due to the low sample size). 3+3 is typically only used during dose escalation, so how do you justify recommending BOIN instead of 3+3 when BOIN is not ideal during a dose escalation? It seems not to make much sense.

The BOIN design is also algorithm-based but has better-operating characteristics than the 3+3 design. It allows for more flexibility, e.g., setting the DLT rate and the cohort size. It allows for decision-making at any time during the trial by comparing the observed DLT rate at the current dose with the escalation and de-escalation boundaries. It can also be combined easily and seamlessly with an accelerated titration design for faster dose escalation at lower dose levels.

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5. RECIST ORR is a very blunt endpoint. What about the use of biomarkers, e.g., ctDNA?

We agree that ORR is a blunt measure of efficacy. Dynamic endpoints such as ctDNA, tumor kinetics, and other biomarkers should be considered during the exposure-response analysis to identify the efficacy gains with increasing doses. It would be beneficial to discuss all planned dynamic endpoints with the FDA. The most appropriate biomarkers are blood-based or imaging biomarkers rather than biopsies to estimate dose response.

6. How early would you recommend implementing PRO-CTCAE- dose escalation? And dose expansion?

PRO-CTCAE should be implemented at least in dose expansion.

7. Please elaborate on randomization in dose-finding studies: why (what to randomize for), how (small N), when (Ph1 expansion or Ph2/3), and why not to randomize/alternate strategies.

The population should be randomly assigned to treatments to avoid bias in selecting patients, which can falsify the results by a biased pre-selection. There can be seamless designs with study sub-parts as a continuum from Phase 1 to Phase 2.

8. The reason most companies go up to MTD/MAD might be due to hesitancy in leaving efficacy on the table, considering that tumor microenvironment availability of the drug is based on assumptions. Is that correct?

With targeted therapy, you may not reach MTD. If D-R or E-R response relationship is flat, a lower dose may work as well. Safety as a response needs to be factored in and appropriate analyses provided to the agency. It may still be that the MTD is the most appropriate dose to carry forward.

9. Should you be looking for a sub-optimal dose in the randomized phase 2 with multiple doses?

It would be best if you did not look for a sub-optimal dose. The goal is to find the optimal dose that does not compromise efficacy or safety.

10. While not typically done - in light of Project Optimus, do you see any role of initial dose finding in healthy volunteers in Oncology, such as for molecularly targeted agents? Is there a stepping stone to obtaining data in patients in a more targeted range of doses?

Healthy volunteer studies typically are not performed with oncology therapies because of the potential short- and long-term adverse reactions associated with such therapies. Some therapies may have a toxicology profile that lends itself to healthy volunteer studies, but these are rare.

11. For oncology studies that have already started, what are the options? E.g., what should we do regarding looking back at your expansion cohorts and opening up additional dose cohorts to support dose justification?

Many sponsors will find themselves in late-stage drug development using the MTD approach to identify the RP2D. We would suggest reviewing all the data and material to assess the quality of the dose justification arguments. Modeling and simulations may play a role in supporting a registrational dose; however, this will be highly dependent upon the study designs and data collected. Without a defendable dose justification argument, additional studies may be requested.

12. What mechanisms are available for early and often FDA interactions?

There are pre-IND meetings that FDA highly encourages to use. Afterward, sponsors may engage with the appropriate FDA division during type B or C meetings when more data are available to be discussed.

13. Are there mechanisms (besides a pre-IND meeting) to discuss dosing considerations with the Project Optimus team?

Sponsors may engage with the appropriate FDA division during a type B or C meeting when more data is available to be discussed.

14. How would you build ctDNA into your strategy for dose optimization?

Dynamic endpoints and biomarkers such as ctDNA have the potential to add to the traditional efficacy endpoints and the E-R analyses and support dose justification arguments. Graphical review of dynamic endpoints and biomarkers over time has the potential to allow for differentiation between efficacy at different dose levels during Phase 1/2, which may not be captured with traditional blunt endpoints such as ORR. Discussing all dynamic endpoints with the FDA before conducting the studies is recommended.

15. What would you see as a "perfect" Ph 1 trial design, and why?

A phase I study in which adequate patients are dosed to explore a therapy's safety and activity profile such that the biologically effective and safe dose (based on scientific principles) is selected for further development. There is no perfect design, as it depends on the target patient population, mechanism of action, and PK profile of the therapy.

16. Is the dose of PD-1 pembrolizumab and Nivo too high? Occupancy studies indicate that 5-10 fold lower doses would be equally efficacious.

It is clearly seen that across the 10 mg/kg to 2 mg/kg dose range, the efficacy results are comparable for pembrolizumab. It is possible that a lower dose would be equally as efficacious based on occupancy studies; however, it will be unknown until tested in the clinic.

17. Does this webinar information also apply to antibody-drug conjugates (ADC)?

In general, the information provided in the webinar is applicable to ADCs too. The mTPI is not a required design; however, even for ADCs, MTD does not always equate to optimal dose (note the number of ADC with PMRs/PMCs for dose optimization). mTPI or another more innovative design can provide advantages for an ADC too, and is potentially a better option than a 3+3.

18. What's the "average" number of subjects needed to settle on a final dose, if evaluating two dose levels? 10, 20, 30 patients?

This is highly dependent on the characteristics of the therapy on which you are working, including the variability in PK and response, as well as the slope of the exposure-response relationships for safety and activity.

19. Pivotal clinical trials are on hold due to Project Optimus. Do you have specific examples?

As IND communications between FDA and sponsors are confidential, we are unable to provide specific examples.

20. What are some of the Patient Reported Outcomes (PORs) you recommend for an FIH oncology study in an all comers study?

FDA recommends the use of the NCI's PRO-CTCAE as an instrument to capture the patient's grading and experience of adverse events. The statistics for this data would be descriptive.

21. It might be hard to quantify, but what is the estimated additional effort (time and $) needed to meet these new requirements?

There is a time and cost implication as additional studies or cohorts need to be conducted. However, over the last years, the FDA has asked sponsors to provide additional data as PMR/PMC, but this is shifting to pre-approval.

22. Does dose optimization need to occur in more than one tumor type for oncology, or can it be done in one tumor type (expansion cohort) and applied to all?

Ideally, it should be done for each tumor type. However, you may be able to provide justification to conduct in a single tumor type and extrapolate to others.

23. Where does EMA stand on the dose optimization issue?

Project Optimus is an initiative of the US FDA. In our experience, however, EMA has historically been equally as critical of application with poor dose justification, i.e., RP2D using MTD has shown to be poorly tolerated.

24. Can you please link the discussion on moving away from 3+3 to BOIN and the discussion on moving two doses forward using randomization? Do you start with BOIN and introduce various doses using BOIN and then pick two doses to expand further using randomization?

BOIN can be used during the dose escalation phase and provides an algorithm to escalate or de-escalate dose levels. Dose expansion is usually done to gain additional data on promising dose levels, as data is scarce during dose escalation. When applying the BOIN approach, dose levels may be "expanded" by employing the method, and no additional expansion cohort may be needed. For targeted therapies, dose-finding should be done in a randomized fashion to avoid introducing bias in the selection of the population and unintentionally skewing the results.

25.Under Project Optimus, does the sponsor need to have found MTD?

The MTD may not be reached nor needed for a targeted molecular therapy or a monoclonal antibody. The maximum administered dose (MAD) would define the upper range of doses, and the goal is to find a biologically effective dose with an appropriate balance of activity and safety.

26. Given only a 10% success rate from FIH to approval in oncology, how appropriate is it to conduct dose optimization early in development (from an optimal allocation of resources point of view for small biotechs)? As most of the optimization issues appear related to small molecules, should this only be limited to small molecules?

No, the type of drug generally does not exempt from assessing a proper dose-(R)response analysis. D-R or E(xposure)-R analyses applies to all drugs and uses both non-clinical and clinical data. You will probably be unable to find the optimal dose in your FIH study; however, if the study is well designed, you can collect enough data to support optimal design for further studies. Collecting sufficient PK, PD, and clinical information in the early studies, foreseeing in the protocol the possibility to backfill cohorts, etc., is something to think about when designing the initial study to save time and money later.

27. Are there examples of PROs being used earlier to inform dose optimization? What is the guidance on PROs since sample size won't be available at such early stages? Essentially, how do we incorporate PROs earlier to ensure it is money well spent?

It would be best if you considered PRO-CTCAE as an instrument. FDA recommends using the PRO-TCAE as another safety assessment with descriptive statistics to enrich the safety data collected and better inform the exposure-response analyses for safety with these additional data. Unlike the use of a PRO as an endpoint in a pivotal study, these data do not have to come from a randomized study.

28. In modeling to inform RP2D, what is the shift? Is it adding more PKPD analyses in the modeling?

Historically RP2D has been selected based on the MTD approach. Most of the data collected to support registration is at one dose level with E-R modeling often used to add to the dose justification arguments as opposed to selecting the RP2D. The shift needs to occur where E-R modeling and simulation can be used to support the Phase II doses selected.

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