Fortrea

Bridging the translation gap in immuno-oncology

A pragmatic approach to nonclinical testing

Introduction

Navigating the translation gap between identifying a promising new drug candidate and seeing that promise replicated in humans has always been a problem for drug developers. The path from preclinical to clinical success can be difficult even for single-target, small-molecule drugs, but making the leap from concept to clinic for immuno-oncology (IO) treatments presents unique hurdles.

IO treatments are transforming cancer care, achieving remissions in previously intractable diseases and, as recent data show, achieving sustained anti-tumor immunity that can last up to 10 years after treatment. As an umbrella term, IO covers a diverse range of treatment modalities from simple monoclonal antibodies (mAbs) to cell-based treatments and cancer vaccines. Therefore, no one-size-fits-all approach or guidance applies across the field. Another challenge is the complexity of the human immune system and being able to effectively model it with *in vitro* and *in vivo* tools in a relevant, robust and cost-effective way.

Because of the inherent risk in developing drugs that target such a complicated and powerful human biological system, drug developers have tended to carry out as many preclinical tests as possible. Yet, from our experience working across a great spectrum of IO products in this industry, it pays to start with the end product in mind and conduct fewer, more focused tests. In this article, we share some of the most common mistakes we see and argue for a more pragmatic, pared-back approach.

KEY TAKEAWAYS

The transformational benefit of immuno-oncology (IO) drugs has led to a new accepted product profile of highly personalized biological therapies with a short shelf-life administered to patients only once

With the rapid emergence of a diverse range of novel IO agents, conducting nonclinical research that robustly predicts the safety and efficacy of IO drugs is increasingly difficult

What's needed is a continuous thread from nonclinical to first-in-human trials, which starts with a solid, scientific evaluation of your novel IO drug in preclinical models. Yet, faced with so many possible factors to test and limited robust models in which to do so, choosing the optimal nonclinical package is a challenge. Moreover, too many tests can generate noncritical or nontranslatable information that delays progression and is expensive

In this article, we share Fortrea's experience of taking novel IO products across the entire development pathway as our experts discuss the importance of taking a pragmatic approach to nonclinical IO development

Common mistakes in nonclinical IO development

When you have a completely novel IO agent, such as a gene or cell therapy, where no one has forged a path for you, making decisions on what type of nonclinical development package you require can be a major challenge. There is often no prescribed path to follow, and regulatory guidance therefore needs to be adapted on a case-by-case basis.

In this scenario, many organizations will opt for a "belt and braces" philosophy: running multiple tests in different models with the aim of providing reassurance to stakeholders that the agent is a safe bet. In fact, doing too many noninformative tests is one of the common mistakes we see organizations making when it comes to nonclinical IO development.

This includes carrying out multiple *in vitro* and/or *in vivo* pharmacology studies with a form of candidate drug that is not representative of the clinical end product or conducting pharmacology and/or toxicity studies in animal models that are not relevant (perhaps because they do not share similar target antigen properties to the target population).

It can also be tempting to carry out additional tests even when they are not strictly necessary—for example, carrying out tumor penetration studies, immune memory or tumor rechallenge studies even though your mechanism of action (MOA) does not depend on these factors.

Too many tests can generate noncritical or nontranslatable information that delays progression and is expensive. We would argue that it's more cost-effective and efficient to choose a few judiciously selected tests that provide a solid understanding of your agent's biology rather than jumping into a large battery of tests that may not be reliable indicators of safety or efficacy in humans.

For this pragmatic approach to IO nonclinical development, you need to find the "sweet spot" between too few and too many tests. That means reflecting on what you and your stakeholders really need to learn from this stage of development.

What goals and motivations are shaping your nonclinical development?

When considering the optimal nonclinical package for your IO candidate, it's best to start with the end in mind. Do this by taking a step back to consider the proposed clinical end use of your product. The easiest way is to start with a target product profile (TPP). This document highlights the desired properties of your end product and can be used to guide your translational work as you progress development. Some companies go further in presenting the development pathway in a clinical development plan.

With the TPP in hand, you can then consider your organization's motivations or objectives for this stage of development. It might sound obvious, but reflecting on this can help to rationalize exactly which questions you need to address in nonclinical studies and the data you need to provide to different stakeholders, either to choose your optimal IO candidate or progress your chosen IO candidate further. A well-drafted TPP will help you make hard decisions to change, delay or cancel product development when the emerging data require them.

The motivations or objectives for your organization are likely to include some, if not all, of the following:

- Convincing investors that your agent is worth developing further
- Gaining a deep understanding of your agent's MOA
- Demonstrating to regulatory agencies that your agent has acceptable safety to be evaluated in trial participants and the selected first-in-human dose is "reasonably safe"
- Demonstrating why your IO agent supplements or improves on existing treatments and will be beneficial for patients and healthcare providers

Using the TPP and being clear on the objectives of your nonclinical development will mean you are in a better position to evaluate and choose the most appropriate package of tests for nonclinical evaluation.

Determining the optimal nonclinical development package for your IO agent

The nonclinical testing model for new small-molecule chemical entities is well-established and supported by regulatory guidelines that stipulate testing in two species, rodent and non-rodent, including one that is pharmacologically relevant. But for novel IO agents, this picture is much more complex.

IO is an umbrella term for a diverse range of modalities—including small-molecule immune checkpoint inhibitors, mAbs, anticancer vaccines, bispecific engagers and chimeric antigen receptor T-cell therapies. Each modality poses distinct challenges when it comes to nonclinical development, and each requires a bespoke approach.

A further challenge is recreating the complexity of the human immune system in a preclinical model. Experience from developing existing IO therapies and using them in the clinic shows that many of our conventional nonclinical development models are not optimal for predicting the main adverse events seen with IO. This situation can necessitate using alternatives to traditional *in vitro* cytotoxicity testing or tumor xenograft models.

Thankfully, there is an increasing range of *in vitro* models that can help bridge the gap between the limitations of animal studies and predicting safety and reasonable dosing in the clinic.

Let's take two different IO modalities that illustrate how these might be used:

Bispecific T cell engagers are designed to bind to a target tumor-associated antigen (TAA) and to the invariant CD3 chain component of the T-cell receptor complex. This results in an agent that can induce targeted T-cell-mediated killing of tumor cells bearing the target antigen.

Bispecific immune checkpoint inhibitors are antibodies that bind immune checkpoint molecules on T-cells or tumor cells such as PD-L1/PD-1/CTLA-4. They may also bind to a TAA making the checkpoint inhibition localized to tumor cells.

At first sight, these agents look almost identical and both require a functional immune system to determine preclinical pharmacology. But when you consider testing needs, they could not be more different.

For bispecific T-cell engagers, if *in vitro* evaluation shows that the T-cell-engaging arm only binds in humans, toxicity studies in healthy animals will not be informative. In this scenario, you may consider conducting a range of *in vitro* tests:

- Tissue cross-reactivity studies to assess target distribution and understand on-target, off-tumor toxicity risk. These can be carried out both *in vivo* and *in vitro*, but it is especially important if you are only using *in vitro* methods
- *In vitro* cell-based potency assays and flow cytometry immunophenotyping using cells from multiple human donors
- Specificity studies—e.g., on-target killing of a cell line expressing TAA and off-target killing of a cell line lacking TAA expression
- Preclinical pharmacokinetics (PK) plus *in silico* PK/pharmacodynamics (PD) modeling that could inform PK/PD relationship in the clinic
- Depending on format of the construct (e.g., whether it has an Fc region), *in vitro* assessment of cytotoxicity potential—for example, potential for binding Fc receptors on innate immune effector cells

For a bispecific immune checkpoint inhibitor where both arms bind only in humans and primates, it is possible to integrate *in vitro* proof-of-concept testing with more conventional pharmacology, PK and toxicology assessments, with some adaptations:

- A mouse surrogate bispecific antibody or a transgenic model can be used for establishing *in vivo* pharmacology/PD
- Profiling inhibition of the target pathway *in vitro* (human and primate cell lines) and *in vivo* (e.g., in a mouse syngeneic tumor model) allows proof of concept that inhibition of the target will provide tumor killing
- PK in primates establishes kinetic performance and if target-mediated clearance is an issue for predicting exposure
- Toxicity testing in the primate reflects the proposed clinical plan with consideration of inclusion of immunogenicity endpoints. Use of immunophenotyping by multiparameter flow cytometry in the primate allows examination of the potential for proliferation or ablation of immune components

These examples highlight the unique complexity of emerging IO modalities. There is no one-size- fits-all approach to nonclinical development. The priority given to a particular data set and focus of similar techniques (e.g., immunophenotyping) may shift between the use of preclinical and human samples as required by the target.

A further challenge to nonclinical IO development is the opportunity to use IO treatments in combination. Such combinations may result in synergistic or additive anti-tumor responses, but they also increase the complexity of predicting adverse events. You may wish to combine your candidate drug with the standard of care treatment for a certain cancer with an agent that is clinically well-understood or you may be producing a novel combination. This raises issues such as dose- and schedule-dependent effects on the tumor and immune system, predicting and balancing immunotoxicity and trying to show IO treatment efficacy in immunocompromised patients.

The way in which you approach the development of these scenarios will differ, and organizations will need to decide if and when to include this treatment aspect into a nonclinical development plan. Ultimately, with so many possible factors to test and limited robust models in which to do so, the best nonclinical path to take will be one based on a sound understanding of your agent's biology and MOA, and an evaluation of which *in vitro* and *in vivo* models can reliably inform you about the different aspects of this biology.

The below decision tree summarizes some of the key questions and considerations any organization developing IO treatments will need to consider.

- Initial testing of any IO drug candidate starts with *in vitro*/MOA studies before moving into *in vivo* work, if a relevant model exists:
  - There should be a carefully considered rationale for any additional tests you add on top of this. Too many tests can generate noncritical or nontranslatable insights that result in delays and additional costs
- To consider which additional tests you might need, look for intel:
  - What have others done for similar IO treatments?
  - Are there relevant regulatory guidelines for your type of IO or a similar product?
  - Use evidence such as website-published European Public Assessment Reports or Food and Drug Administration (FDA) drug pharmacology/toxicology reviews
- Understand regulators' expectations:
  - Engage with regulators early to ascertain their requirements, especially for novel IOs
  - The FDA and European Medicines Agency now have dedicated teams to support development of some novel modalities, such as cell- based therapies
  - Consider that for novel IOs you may be able to present your unique case and challenge the regulators on their requirements
- Find expert support:
  - Fortrea works across the entire development pipeline and has experience in taking different types of IO modalities through nonclinical testing to first-in-human trials and beyond
  - We have been presented with many of the challenges highlighted above and have worked with clients to develop nonclinical packages that provide the insights and data regulators and potential commercial partners want to see
  - Our range of reliable models and approaches for evaluating products with innovative and unique MOAs, and we can help provide rationale/justification for choosing particular nonclinical evaluations

In the next article in this series, we will look further into some of the tests commonly used in place of conventional preclinical models for IO.

Conclusion

With no universal standard nonclinical testing paradigm in IO, a pragmatic approach to nonclinical development is needed. It's important to question the value of every test you add into your development package to avoid spending time and money on tests that are at best redundant and at worst don't give you the answers you need. Too many tests can provide insights that are noncritical or nontranslatable to the clinic and can delay development timelines and incur unnecessary costs. Take each product on a case-by-case basis and use intel and your relationship with regulators to give your nonclinical package the best chance of getting your agent successfully into clinical trials.

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