Regulatory Matters

Immuno-oncology adaptive design studies

Background for immuno-oncology studies

Accumulated research of more than a century has led to our current expansive understanding of the vertebrate immune system as a complex, multi-functional, evolutionary unit: a diverse, powerful, and adaptable network of cells and pathways that provides constant monitoring of the body to provide host defence against infection and inflammation.

Although an appreciation of the role of the immune system to prevent the development and/or progression of cancer is perceived to be more recent, the beginnings of cancer immunotherapy under different names may be traced back as far as antiquity. And several discoveries over the past 50 years in the field of immunology, such as, in 1967, the discovery of the existence of T cells and their crucial role in immunity, have brought the clinical world to the current state of research involving cancer immunotherapy that we know today.

Currently, research oncologists have come to recognise that avoidance of immune destruction or suppression of natural anti-tumour immune responses are two of the escape mechanisms that allow cancer cells to grow, and both are widely accepted as emerging hallmarks of tumour resistance to anti-cancer treatment. Turning on the body's own immune system with biologic agents, including monoclonal antibodies and receptor agonists/antagonists, to combat cancer whilst dismantling key immune escape mechanisms (both part of so-called immuno-oncology therapy) represents a transformational approach to cancer care with a potential for long-term sustained efficacy.

Adaptive design for immuno-oncology studies

Emerging clinical evidence supporting the development of new agents with diverse mechanisms of action has also raised the possibility that combination therapies could potentially lead to both greater depth of response and prolonged survival. Such combinations could also aid in combating the avoidance/suppression "strategies" employed by various neoplasms. Proof of principle has been established with the combination of anti-PD-1 and anti-CTLA4 in patients with advanced melanoma.[1] At the same time, the large number of potential therapeutic combinations has created an issue of practicality for industry, health authorities, and clinical investigators who all share the same goal of understanding which agents bring the greatest value to patients. Thus, there is a need for a clinical trial framework that facilitates a robust assessment of novel combinations across a broad range of patient populations within any given tumour type, and which

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allows for the evaluation of combinations relative to one another.

One strategy for such efficient, expeditious, and rigorous evaluation of combination therapies has been the implementation of a complex clinical trial design, which has the defining feature of separate parts that could, in effect, be perceived as individual clinical trials, but are in fact elements of a single protocol. This approach is characterised by extensive adaptations, such as planned additions of new investigational medicinal products or new target populations. One such specific design is the master/sub-protocol clinical trial concept.[2] Master protocols, which apply to all combination treatments selected for evaluation under a tumour-specific study, define:

- The overall study plan
- The background and rationale
- The study design and duration
- Inclusion and exclusion criteria
- Time and events, including all procedures, labs, pharmacokinetics (PK), and pharmacodynamics (PD) that are not treatment specific
- The statistical plan

Additional treatment combinations can then be introduced into the study via sub-protocols that are appended to the master protocol for that study and include information appropriate to the specific treatment combinations and/or contemporaneous controls being added.

An important regulatory component of this design, and one that sponsor global regulatory functions may consider carefully, is that each study (including both master and sub-protocols) can be identified by single EudraCT and IND numbers, with all elements being linked by a single research hypothesis. Each sub-protocol is then submitted as a substantial amendment for separate regulatory and ethics committee review prior to implementation. The sub-protocols detail the specific study treatments and contain:

- Background – scientific rationale to support evaluation of additional combinations based on preclinical and clinical data
- Preclinical toxicology on single agents
- Clinical safety package for new agents
  - Monotherapy safety information
  - Combination safety data on at least six participants to support the protocol-specified dose; although safety data may be from a different patient population and/or tumour type
- Drug dose and administration
- Adverse events and dosing modifications
- Treatments and evaluations that include treatment-specific procedures, including PK (not found in the master protocol)

Reporting challenges for adaptive design studies

For health authorities across the world, data transparency and safety are considered hallmarks of modern ethical clinical research. For EU/EEA and US FDA, consistent with these goals, the summary clinical study reports for Phase II-IV and paediatric Phase I trials are provided not only to competent authorities, but are also published on the public EU and FDA Clinical Trials Register within one year of the end of the trial (last-patient-last-visit [LPLV]), and even earlier for paediatric clinical trials (6 months).[3,4]

Complex clinical trials are most often early exploratory trials in relatively few participants and, therefore, the limited availability of safety data make transparency even more of a regulatory/clinical obligation. One challenge and potential obstacle in regard to data transparency for studies with a master/sub-protocol design may be that, when all sub-protocols within the master protocol design are registered with the same EudraCT and IND numbers as the master, information from each completed sub-protocol will become available only after the end of the entire trial. This circumstance limits the technical obligation for regulatory reporting of multiple treatment arms (sub-protocols) to one year post LPLV, thus reducing the documentation burden, but increases the need to find robust and ethical reporting strategies.

For complex clinical designs registered as one trial, for timely and transparent reporting of key information, sponsors are strongly advised to engage health authorities to propose periodic safety/status reports that provide a summary of the current study status, including:

- How many participants have been enrolled, randomised, and treated
- Which arms have been closed or newly opened
- Proposed plans for the next periodic interval, including known amendments or upcoming sub-protocol initiations
- Presentation of overall safety parameters (adverse events, serious adverse events, discontinuations, deaths, etc.)
- An assessment of the overall benefit/risk of the trial should be provided for each amendment of a new sub-protocol addressing how all the risks will be mitigated

Sponsors are also strongly advised to include data from closed sub-protocols in the appropriate investigator's brochure.

The pharmaceutical industry has firmly embraced the current era of combinatorial clinical trial design, with the intention of quickly, accurately, and safely conducting investigations to increase the options for patients with cancer. This new era offers great promise for additional progress in the battle against neoplastic diseases in their many forms. Communication within sponsor regulatory and clinical organisations, in addition to robust interactions between such organisations and the relevant health authorities, are critical to ensure the realisation of such potential.

References

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