White Paper

Clinical value is top priority in cancer drug trials, CDE says.

By Chang Jianqing
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Tigermed Group

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While Chinese regulators have been receiving more IND filings for oncology drugs, treatment targets and indications have been jammed into a few choices, such as PD-1/L1 and VEGFR. Regulators are now trying to turn things around with a top-down approach.

From the perspective of patients' need, to help drugmakers to develop better cancer treatments by implementing the clinical value-oriented and patient-centric R&D concept, the CDE published the guidelines for clinical value-oriented clinical trials of oncology drug on Nov. 19 and enacted immediately. The guidelines are the CDE's attempt to summarize how regulators d review and approve oncology drugs based on their clinical value since China's State Council pledged to reform the country's drug approval process initiated in 2015.

China's biopharma industry has seemingly welcomed the guidelines, as the finalized version is largely the same as the draft published in July for soliciting comments. Looking forward, drugmakers are expected to develop better quality oncology drugs in accordance with the guidelines to meet patients' needs.

Basic Research for **More Precise Medicines**

As there are still no treatments available for most cancers, the CDE noted that there is a lot of room for basic research and mechanism of action studies due to the complex pathogenesis of malignant tumors.

Naturally, the very first thing the CDE wants is to strengthen basic research on tumor occurrence and development mechanisms. It will help optimize drug design to develop new treatment options with an innovative approach.

The CDE also calls on drugmakers to make their products more precise to match patients with the most effective drugs, as precision medicine is now an integral part of cancer treatment and diagnosis.

Drugmakers are advised to explore various combination regimens to improve treatment efficacy. They are also encouraged to improve the safety profile, dosage and route of administration of their drugs to make treatment more convenient for patients, which the CDE also sees as a form of innovation.

The CDE also highlighted the needs of pediatric and elderly patients, two groups that are often overlooked.

For children's indications extension, drug makers are encouraged to actively conduct clinical trials in children, explore the dosage and administration of children, and obtain the evidence of the safety and efficacy of the product in children or adopt real-world study.

For the elderly, it is necessary to consider the impact of declining liver and kidney function on the drugs' pharmacokinetic profile to develop safer drugs.

Understanding **Patients' Needs**

To enable patient-centered care, the CDE encourages trial sponsors to communicate more with the patients to understand how the disease affects their lives, what they prefer, expect and need, and how treatments have become a help.

To do so, the guidelines suggest trial sponsors to carry out surveys and initiate conversations with patients at the beginning of drug development. They should ask about patients' expectations for the treatment, the impacts of symptoms and signs of disease on patients' body function and daily life, the adverse reactions and burdens of current treatments, the potential impacts of disease or treatment, and patient's evaluation on the benefits and risks they may receive.

While doing so, trial sponsors should pay attention to whether the interviewees represent the patient group and match the patient population that the future drug product targets. They should also protect the patients' privacy when conducting surveys.

Testing Drugs **Against Best Standard of Care**

As many Chinese drugmakers are developing me-too drugs, the CDE is advocating using the best standard of care as a control in clinical trials to demonstrate a new drug's clinical value.

Placebo and best supportive care may also be considered as a control when there is no standard treatment for this indication in clinical practice, and best supportive care is preferred over placebo as a control.

The guidelines also define the best control as a drug whose safety and efficacy have been fully validated in the clinic after marketing to win recognition as best standard of care.

Using **Single-arm Trials**

In the guidelines, the CDE explained when single-arm trials should be used.

The single-arm trial is an important method to develop oncology drugs, but it also shows uncertainties. Once the early data has demonstrated outstanding efficacy of a drug candidate, it is hoped that all trial subjects could be treated with the drug candidate. In this case, single-arm trials can be adopted with historical data as a control.

In principle, single-arm trials are suitable for testing drugs for refractory diseases that are severely life-threatening and lack effective standard treatments, such as refractory/relapsed advanced malignancies and rare diseases, and for monotherapy that has shown outstanding efficacy early on. The CDE is expected to elaborate on the applicability of single-arm trials in another guideline next year.

Planning for **Patient-reported Outcome Measures** Early On

Clinical outcome is essential for evaluating the benefits and risks of a new drug. Patient-reported outcome (PRO) indicators have been mostly used as secondary or exploratory endpoints in registrational trials.

PRO Tools

The guidelines encourage drugmakers to use PRO tools, such as quality of life assessment and symptom assessment, and to design and develop PRO tools early on. This will help them better use PRO tools in the later stage of drug development.

Common methods to evaluate PRO include self-rating scales or patient questionnaires, face-to-face qualitative interviews, and telephone interviews. Drugmakers are encouraged to use or develop different evaluation methods, including electronic patient-reported outcome measures to make the process easier for patients.

Communicating More With Regulators

While the guidelines cover a lot of areas in clinical trials of oncology drugs, the CDE still encourages drugmakers to get in touch with regulators as much as possible early on to ensure clinical trials can fully reflect the clinical value of an investigational drug.

One important dialogue is on the trial design to make early and pivotal trials more efficient. Drugmakers are also advised to read through the CDE's guidelines on single-arm trials to reach a consensus with regulators on the key indicators and other requirements of these trials to support product registration.

As for PRO, drugmakers are encouraged to talk to the regulators to develop and verify PRO assessment endpoints and discuss the feasibility of these endpoints to support regulatory decision-making.

Key Messages to Takeaway

To discourage me-too drugs, China's CDE is now calling for more efforts in conducting basic research, improving treatment regimens, and understanding what patients really need. It made clear that patients' needs, now a top priority, are the basis for making the decision on R&D project, launching clinical trials and granting marketing approvals.

For the clinical trial design in the early and pivotal studies, it is encouraged to apply model-guided research tools , the design to improve trial efficiency, to preset R&D decision thresholds and to make necessary interim analysis to reduce trial subjects' invalid exposure and protect the rights and interests of subjects, while improving the efficiency of research and development.

In order to best satisfy the medical needs of different types of patients population in clinical practice, attention should also be paid to the representativeness of the patients population and the development of drugs for special populations.

The patient-centric drug research and development should run through the entire drug research and development process.

About the **Author**:

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