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Review Article

Bio-markers of immuno-oncology

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ABSTRACT

Since its inception until the rapid advancements, the immuno-oncology (I-O) landscape has undergone significant modifications. Thousands of possible I-O medicines and therapy combinations are being tested in clinical trials as part of the current drug development pipeline. Suppose these assets are to be developed effectively and successfully. In that case, it is necessary to invest in and use the proper techniques and technology to speed up the transition from preclinical evaluation to clinical development. These tools, which include suitable preclinical models, pharmacodynamics-related biomarkers, prediction and monitoring capabilities, and developing clinical trial designs, enable quick and effective evaluation during the development process.

The possibility of new findings and insights in each of these three areas to further address the clinical care needs of patients with cancer.

These tools include. 1. Appropriate preclinical models, 2. Biomarkers of pharmacodynamics, predictive and monitoring utility, and. 3. Evolving clinical trial designs allow rapid and efficient evaluation during the development process.

This article provides an overview of how novel discoveries and insights into each of these three areas have the potential further to address the clinical management needs of patients with cancer.

1. Introduction

The idea(s) behind immuno-(I-O) oncology's possible uses have existed for a while. The first attempts to use heat-inactivated Streptococcus pyogenes and Serratia marcescens to treat osteosarcoma were made more than a century ago, in 1891, by the early pioneer William Coley. This marked the beginning of research into using immune pathways to treat cancer.[1,2] The identification of programmed cell death protein 1 (PD-1) by Honjo and colleagues in the 2000s and cytotoxic T-lymphocyte antigen 4 (CTLA-4) by Allison and colleagues in the 1990s led to the development of a new class of anticancer medications known as immune checkpoint inhibitors (ICIs). ICIs are currently widely used to treat many kinds of cancer.[2]

The oncology community's attitude on I-O therapies has evolved over time as a result of multiple breakthroughs, challenges, and attempts to attain therapeutic success. The concept of tumor-infiltrating lymphocytes (TILs) and the development of effector T cells that express chimeric antigen receptors (CAR T) are two examples of advancement. Two instances of encouraging preclinical data that are occasionally followed by failures in subsequent clinical trials include the failures of I-O combination therapy in several tumor types. This intriguing therapeutic strategy has recently become a reliable clinical reality, which has caused the I-O field to quickly gather speed.[3,4]

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Biopharmaceutical companies have made large investments in the I-O region due to its rapid advances and practice-altering clinical victories for many difficult-to-treat tumors. Additionally, the area has inspired active research into new preclinical models and biomarkers to better our understanding.[5] To comprehend improved predictive preclinical models and translational methodologies are now more critical than ever. Furthermore, if current problems, disagreements, and constraints are resolved in the completed and ongoing clinical trials of ICIs, it will be feasible to continue giving patients new I-O medications.[6,7]

The three main elements that can improve the effectiveness of drug development are identifying the right biomarkers to select the right patient population, recommending the engagement of the relevant target, and carrying out the formal clinical planning procedure.[8]

2. Discussion

2.1. Immuno-oncology non-clinical research models

Preclinical oncology studies come in various forms, each with unique benefits and drawbacks, including tumor syngeneic mouse animal models in-vivo, genetically modified mouse models (GEMMs), patient-derived xenograft, mouse humanized models, and onco organoids/spheroids. Researchers must consider every model's characteristic in the content of this particular research queries when deciding which model is most appropriate.[9,10]

More than the years, the Immuno-Oncology configuration has been the most frequently utilized for synthetic mouse models. To create these models, existing cell lines belong to mouse or tumor engrafts are transplanted into immune-competent, strain-matched mouse hosts.[11] Commercially available syngeneic mouse models for hematological and solid tumors include ones engineered to consistently amplification of the luciferase gene to enable the utilization of in vivo animal imaging.[12,13]

These systems are simple to use logistically, can screen a huge number of drug candidates, and can be used to explore pharmacodynamics and the mechanism of action. Syngeneic models have limitations despite their widespread use and relevance to human tumors.[14,15] Since the tumor cells are originated from mice, for instance, not all characteristics of clinical disease in humans can be accurately predicted by the histocytes of mouse tumors. Additionally, these models' predictions of clinical outcomes for treatment responses can be subpar.[16] However, many of these drawbacks are outweighed by their use in understanding crucial elements of immunological response to therapy.[17,18]

Genetically altered, transgenic mouse models, also known as GEMMs, have been found to more closely monitor the affecting the supporting tissue biology of their human disease equivalents than syngeneic models, includes the tumor biology, which has a significant impact on tumor activity.[19,20] With the help of tissue-targeted factors and applicable mutations that are known to encourage tumor stimulation in the normal tissue or organ of specified, these animal models enable a more natural process of disease initiation. Historically, these models have been crucial for developing oncology drugs and offered insightful information regarding carcinogenesis.[21] For instance, Dow et al. have demonstrated the validation of therapeutics targeting the Wnt signaling pathway in colorectal cancer using a transgenic model.[22,23]

Although certain GEMMs and syngeneic mouse cell line models are helpful in developing I-O medicines, CDX models for human cancer must also be considered.[24] These also have the industries level for researching cell-based immunotherapies, even though they have been actively utilized for more traditional oncology techniques. With thousands of commercially accessible human cell lines, many of which stably express the firefly luciferase gene, CDX models are logistically simple to utilize, making them excellent for in vivo small animal imaging.[25–27] To explore the functions of the immune system in tumor formation and therapy response, these investigations must be carried out in immune-deficient mice strains.[28,29]

To address some of the drawbacks of conventional CDX animal models, PDX mouse animal models, depending on transplants and in-vivo repeated dissemination of modern human tumor biopsies in immune-deficient mice, has been created.[30] Even after recurrent passaging in mice, unlike CDX tumors, Patient Derived Xenograft tumors retain the genomic, chromosomal, and morphological changes seen in cancer patients, making them superior projections of clinical prognosis in human beings.[31,32] Additionally, Patient Derived Xenograft tumors are frequently defined, allowing for more detailed analyses of drug resistance and therapeutic uses. There are a few well-known problems with mentioned animal models, though. Although thousands of these cell-lines exist, some more tumor histology like prostate tumor and several hematology tumors—are much more challenges to identify.[33–35]

The main drawbacks of syngeneic and GEMMs are the absence of human targets and the innate immunologic variations between animals. As a result, a lot of work has gone toward humanizing the mouse immune system.[36] The immunoavatar animal model, which involves regenerating immune-deficient mice with human type of peripheral blood mononuclear cells (PBMCs), is one of the more popular methods for humanizing mouse models.[37–39] Even though complex purification methods are not required, substantial human xenograft-versus-host illness.[40,41]

As an alternative, it has been shown that immunocompromised-NOD SCID gamma (or NSG) mice results in the development of numerous lineages

of human hematopoietic and immunological cells.[42] The immune systems of these so-called HuNSG mice eventually become somewhat functional. It has become a busy area of research thanks to the expansion of humanized mice models, which have made it possible to define human cell function of CAR T in vivo and simplify the creation of new development of CAR therapeutics.[43] Mostly of this, each and every humanly optimized mouse method has particular benefits and drawbacks that should be examined before usage.[42,43]

Organoid technology has recently been used to produce a unique cell-based method for studying tumor immunobiology that is swiftly being adjusted to the I-O and environment. Organoids are three-dimensional in vitro cultures of healthy or malignant tissues that contain a variety of cell lineages, such as stem cells and differentiated cells, as well as tissue architecture. Organoids holds potential as a more clinically significant preclinical theoretical model for drug development and precision medicine than cell lines because of their closeness to the original malignancies and the capacity to culture organoids from each patient. Oncology and I-O medicines are being discovered and developed using various in vitro or ex vivo techniques.[44]

In conclusion, the proliferation of I-O clinical investigations has sparked new research into mice with functioning immune systems. As a result, the variety of tumor histotypes represented in syngeneic models is quickly increasing.[45] Syngeneic models with malignancies developed in orthotopic environments are also becoming more popular. This makes it possible to surgically insert tumor cells right into the organ, track and monitor their growth, and assess how well the treatment works. Using luciferase-expressing cell lines, transversal, non-invasive small animal bioluminescence imaging can be used in these situations, drastically reducing the number of mice used in the study and enabling semi-quantitative measurement of tumor burden.[45,46]

2.2. Synthetic mouse models can be used to find therapy response biomarkers

According to reports, synthetic mice models react variably to ICIs. This responsive is established for most of frequently employed model.[47,48] These models differ in the general elements of the tumor micro environment, in addition to changes in therapy response. Because of these variations, many of the models have been categorized where cold animal models tend to have a infiltration of both.[49]

To identify the most appropriate model for preclinical research, it is necessary to characterize the baseline tumor using the following metrics: (a) the infiltrating leukocyte population; (b) other molecular features of the models (RNASeq, whole exome sequencing, etc.); and (c) benchmark therapy efficacy; and to use these baseline treatment responses to study drug usages and identify phenotypic indicators of response.[50] For instance, in the 4T1-luciferase type of mouse mammary cancer, an immunologically "cold" tumor, the initial cancer is known to spread to the neck area, includes the lung and lymph nodes (axillary).[51]

Compared to anti-CTLA-4 or focused in this model, marginally shrinks the primary tumor size; however, it significantly delays the emergence of metastatic illness. Bioluminescence imaging techniques can be used to see, measure, and compare these therapy responses.[52] Furthermore, found and measured using flow cytometry and serial blood samples.[53]

Additionally, biomarkers can be utilized to choose the best models of researching a specific I-O agent or spot gene expression changing after treatment. For instance, microarray data demonstrate that successfully treated with immuno-modulatory agents, exhibit very different gene expression patterns, and this knowledge can be used to identify gene response.[54]

2.3. Clinical use of predictive biomarkers in immuno-oncology medication development

Biomarkers help evaluate many aspects of treatment response in preclinical models, as was previously indicated, but they are also increasingly used in the clinic for patient management. Biomarkers are "specified characteristics that are tested as indicators of normal biochemical functions, pathogenic processes, or reactions to an exposure or treatment, particularly treatment modalities," according to the US Food and Drug Administration (FDA).[55] Various biomarkers, including diagnostic, prognostic, and predictive biomarkers, are utilized to guide therapy decisions to maximize patients' reactions to different treatments. Predictive biomarkers are used to determine the likelihood of a clinical outcome, such as a disease recurrence or progression.[56] At the same time, diagnosing indicators are employed to identify or prove the presence of a disease or condition of interest.[57,58]

Clinical trials frequently use prognostic indicators to establish trial inclusion criteria to pinpoint highly-risk of the patients. The term "predictive biomarkers" refers to a changing in a biomarker this indicates whether a specific or group of particulars is more to experience a positive or negative reaction to exposure of specific medicinal agent; these biomarkers are particularly helpful in the planning and execution of clinical trial.[59] The classification of some diseases may change due to the development of diagnostic biomarkers.[60] Many predictive bio therapeutic agents are employed in diagnostic to maximize patients' reactions to different therapies, and others are used to advise therapy choices.[61,62]

Immunohistochemistry (IHC) staining is therefore advised prior to beginning a number of such therapies, such as pembrolizumab, which utilizes the PD-L1 SP142 IHC

assay established by studies have demonstrated that patients with high TMBs have longer projection-free survive and length of responsiveness to onco drugs than patients with lower mutational burdens.[63]

Research is now being done to establish the threshold values at the place of tumor cell mutation is deemed high, and to create practical diagnostic cellular assays and techniques of simplification. Predictive biomarkers are so crucial for guiding therapeutic agents that many tumor treatments are now available based on the main biomarkers linked with the tumor rather than where cancer started in the body. The immunosurveillance system's ability is improved due to TMB's promotion of the synthesis of neoantigens expressed on MHC.[64]

The fact that ICIs primed with chemotherapy are more effective against BRCA1-mutated TNBC cancers elevated TMB suggests that clinically determining BRCA1 status could act as a prognostic therapeutic agent. Interestingly, highest TMB (the overall mutants to the actual quantity of sequential mega base assessed using MSK-IMPACT (assay)) is associated with greater survival rates. This was discovered by studying the new genetic and medical evidence of 1662 advanced cancer patients treated with FDA-approved ICIs.[65] for the patient, this means that while deciding on a final course of treatment, it is crucial to concentrate efforts on malignant cells biochemical pathways that drive cancer growth and pinpoint the precise origin of their malignancies.[66]

Biomarkers primarily been investigated independently until recently. Still, current invention is focusing toward examining the variations of bioagents that address characteristics of the cancer, which include gene expression are tried to apply to clinical response and patient care. Such methods might increase the success of clinical trials for cutting-edge treatments or combinations.[67] To evaluate this crucial interaction, describe the patient response, and assist reverse translational techniques, is a helpful strategy. Tumor inflammation signatures, signatures associated with CD8-positive cells invading tumors, and signatures that combine the indicators are only a few of the gene expression signatures that have been established.[68]

Seven different types of biomarkers were detailed in the "Biomarkers, endpoints, and other Tools" framework, published on 2016 by the FDA. The monitoring, highly susceptible, safety, and pharmacodynamics biomarkers were also defined in this framework in add to clinical, predictive, and respective biomarkers covered.[69]

2.4. Paradigm for clinical trials is changing due to immuno-oncology

The general strategy for systemic anticancer therapy has changed during the past few decades. Chemicals used in cytotoxic chemotherapy were directed at any dividing cell. Then came targeted, which functioned only on cancer cells with particular molecular abnormalities. Recent advances in immunotherapy can be broadly divided into two categories: those that directly affect cancer cells (known as passive) and encourage immunological cells (known as active).[60,61]

The genomic characteristics of many tumors are becoming better understood as high-throughput techniques like next-generation sequencing become more widely available and less expensive. As a result, cancer patients are being divided into more manageable subpopulations, and populations with positive biomarkers are now enrolled in Immuno-Oncology trials based on the unique molecular level features of malignancies.[62,63]

A dramatic decrease in the time needed of clinical target of novel therapeutic anticancer medicines. For cytotoxicological agents, the new drug development procedures entailed a series of trials: from phase I to establish therapeutic dose and human safety, and phase II to fix the therapeutic dose, record unwanted effects, and prove the efficacy, phase III to ensure therapeutic effect and evaluate the new cancer treatment in comparison to the industry standard.[64] Regulatory approval was then given based on the positive outcomes of phase III. In the era of targeted medicines, encouraging phase II results occasionally sufficed to obtain accelerated approval, subject to the completion of subsequent confirmatory phase III studies. In the current era of immunotherapy, development frequently starts with a modest phase I study, with the gradual addition of various extensions cohorts for the same research, perhaps with randomized arms.[65,66]

One treatment may be used for several most diseases (a basket), many treatments may be applied to a single illness (an "umbrella study") with the use of "master" protocols.[67]

The Kaplan-Meier curves (I-O vs. standard chemotherapy) have an exciting tendency to separate later but eventually lead to a sustained separation (often evocatively referred to as "raising the tail of the curve"), signifying a durable advantage found in a percentage of patients. From a statistical perspective, this presents methodological difficulties. Therefore, in addition to progression-free survival, other more recent approaches, including landmark survival, landmark analysis, and confined mean survival rate, is additionally being researched in the I-O era.[68–70]

The oncology discipline has seen a substantial transition toward precision medicine concurrent with the emergence of I-O compounds. Precision medicine uses data on a person's cancer-related characteristics to identify and treat the specific disease.[70]

3. Conclusion

Increasing I-O therapy clinical trials have sparked new studies using immune system-competent mouse models. More thorough preclinical trials are required participation and identify biomarkers explored during further stages

of medication invention. A more concentrated effort is being made the correct volunteers, which is also causing significant changes in the methodology, design, and implementation of cancer clinical trials. Biomarkers are now a crucial component of the improvement to achieve this patient population.

Pembrolizumab illustrates a drug approval based on a phase I expansion study with patient-driven biomarkers. Populations refer to this novel approach to clinical development that requires fewer individuals and significantly reduces the time to approval. There is now the use of new technology, such as liquid biopsies.

This new technology will make it simpler for patients to continue taking part in further I-O studies because it has recently been approved as a diagnostic technique for NSCLC and breast cancer. Drug development cycles are getting shorter thanks to the trend towards smaller precision trials determined by biomarkers, which is also opening the door for more adaptable clinical trial models.

Indeed, the FDA's recent clearance of cancer indications based only on patient biomarkers offers hope for the future48, but newer, more adaptable models still need to be thoroughly tested. Even though preclinical models have contributed a significant amount of knowledge to aid in the clinical development of ICIs, further improvement of these models is encouraged to more accurately mimic human cancer.

Preclinical and clinical development needs to be more closely linked as treating various tumors with these treatments, becomes increasingly important. Linking non-clinical and clinical development requires using biotherapeutic agents that can aid in response prediction or provide insight into the nature of the treatment.

The prospective success rates of innovative therapeutics and immuno-oncology combo medicines will increase due to new drug inventions made possible by translation and reverse translational methodologies.

4. Source of Funding

None.

5. Conflict of Interest

None.

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