Article

Precision Medicine in Oncology and Immuno-Oncology: Where We Stand and Where We're Headed

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Keywords

Biomarkers · Immuno-oncology · Precision medicine

Abstract

Background/Aims: Precision medicine has only been a clinical reality only since the start of the 21st century, spurred on by the coevolution of science and technologies, as well as the increasing medical needs of aging societies of industrialized countries. Its overarching objective, from the perspective of the pharmaceutical and diagnostic industry, is to develop innovative therapeutic "concepts" with increased value for patients in a global health economy context. This article analyzes the recent advances and remaining challenges from a research, medical, and regulatory perspective in the development and introduction of precision medicine in oncology, more precisely in immuno-oncology. ***Methods:*** Analysis of the most recent scientific publications and clinical evidence. ***Results and Conclusion:*** Stakeholders need to combine efforts in order to turn scientific insights, such as those related to predictive biomarkers, into superior and affordable therapeutic concepts. Policymakers should also help to bring this about by ensuring that a suitable regulatory framework and incentive system are in place in order to encourage groundbreaking innovation, and hence the availability of new treatment options for patients.

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Introduction

Precision medicine has only been a clinical reality only since the start of the 21st century, spurred on by the coevolution of science and technologies, as well as the increasing medical needs of aging societies of industrialized countries. Its overarching objective, from the perspective of the pharmaceutical and diagnostic industry, is to develop innovative therapeutic "concepts" with increased value for patients in a global health economy context. This

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approach still requires concrete improvements, for instance to develop rational-based combination strategies, optimized monitoring systems, and treatment regimens, as well as biomarker-based patient selection.

All attempts to further improve precision medicine need to consider three main pillars:
- Patient information
- Human biosample information
- Biomarker information

Without a doubt, precision medicine has been fostered and elevated to the next level by the most recent successes in immuno-oncology. Thanks to our deeper understanding of cancer and its interaction with the immune system, industry is currently moving away from an over-simplistic single hypothesis approach towards a drug development strategy based on a hybrid hypothesis-free and hypothesis-based model.

Multi-omics data from longitudinal patient profiles appear to be the ideal starting point for transforming clinically actionable insights into superior therapeutic concepts. However, this process is not without difficulties, and many hurdles complicate the efficient and effective execution of this concept, notably:
- High costs and complex diagnostic partnership models
- Different degree of maturity of the various diagnostic platforms
- Health technology assessment (HTA) bodies require a standard of care reference, although updates of treatment guidelines are often lagging behind

On the more positive side, emerging clinical evidence shows that indication-agnostic biomarkers such as MSI-H (microsatellite instability-high) or ALK (anaplastic lymphoma kinase) status are paving the way for fewer barriers between various clinical disciplines. In addition, scientific publications including "Hallmarks of Cancer – The Next Generation" [1] and "Oncology Meets Immunology: The Cancer-Immunity Cycle" [2, 3] as well as "Cancer Immunology. The 'Cancer Immunogram'" [4] help to illustrate how individualized therapeutic concepts may be designed.

Immuno-Oncology

Immunotherapies Target the Interaction of the Immune System and Cancer
According to Chen and Mellman [3], anticancer immunity in humans can be segregated into three main phenotypes: the immune-desert phenotype, the immune-excluded phenotype, and the inflamed phenotype. Each phenotype is associated with specific underlying biological mechanisms that may prevent the host's immune response from eradicating the cancer.

Before continuing, it should be emphasized that these three phenotypes have been defined based on our current understanding of the disease biology. Future studies may suggest a number of intermittent phenotypes, which would require different individualized therapeutic concepts.

Actual immunotherapies like PD-L1/PD-1, IDO, TIGIT, and TIM-3 inhibition have been designed to target specific biological mechanism within these cancer phenotypes. While high response rates have been observed for PD-1/PD-L1 inhibitors in melanoma, only relatively low objective response rates of approximately 20% have been observed in a number of other indications.

Patient enrichment strategies based on PD-L1 expression so far have been only successful to a limited extent. Patient selection, based on PD-L1 expression in tumor tissue was considered to be essential for the benefit versus risk ratio only in lung cancer. As a result, non-small-cell-lung cancer (NSCLC) is the only patient population with a companion diagnostics in the label (pembrolizumab, MSD).

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Cross-industry efforts to better understand the technical comparability of the five major in vitro diagnostics (IVD) to assess PD-L1 expression have been recently summarized in the International Association for the Study of Lung Cancer (IASLC) atlas of PD-L1 immunohisto-chemistry testing in Lung Cancer [5].

The authors who have approached this topic with a "wider lens," looking at the changing landscape of laboratory testing in general, conclude that PD-L1 is a challenging biomarker. While approved companion diagnostics and complementary diagnostics are on the market, PD-L1 is the subject of several controversial discussions which have been triggered because of tissue specific relevance, time-dependent/dynamic regulation, and other potential confounding factors.

Beyond PD-L1, a number of other biomarkers have been associated with higher objective response rates and prolonged progression free survival.

An approach, which combines a set of specific biomarkers with a selection of potential therapeutic options, is referred to as personalized cancer immunotherapy [4].

Tumor Foreignness

Cancers with high "mutational burden" are more likely to have recognizable "foreign" antigens called mutation-associated neoantigens, to which T cells can respond.

The induction of T-cell responses is dependent on the presentation of an altered repertoire of major histocompatibility complex associated peptides. The outcome of a T-cell antigen encounter is modulated by T-cell checkpoints such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1).

Clinical evidence suggests that the foreignness of human cancers may in large part be determined by their expression of neoantigens. In this context, a correlation between mutational load – a surrogate marker for tumor neoantigen load – and outcome upon the blockage of T-cell checkpoint inhibitors has been observed in NSCLC [6] and other indications. In the meantime, an extensive investigation described the distribution of tumor mutational burden across a diverse cohort of 100,000 cancer cases and tested for association between somatic alterations and tumor mutational burden in over 100 tumor types [7].

Despite emerging clinical evidence, mutational load represents a challenging biomarker for tumor foreignness because it does not consider a possible contribution of self-antigen recognition to tumor control. Further, the formation of neoantigens from individual mutations is a probabilistic process. In conclusion, although tumor foreignness can likely be assessed for tumors with very high mutational loads, the assessment of tumor foreignness is limited for tumors with an intermediate or low mutational load. Additional methods to assess tumor mutational burden need to be taken into account.

General Immune Status

Given the mode of action of immuno-oncology therapies, it can be assumed that the general immune status will be relevant in many clinical settings. A number of clinical observations support this assumption:

- A decrease in lymphocyte counts has been associated with poor outcome upon CTLA-4 blockade in melanoma patient cohorts [8]
- A high neutrophil/lymphocyte ratio correlated with poor patient outcome after immunotherapy whereas elevated eosinophil counts may be associated with improved outcome in melanoma patients treated with anti-CTLA-4 antibody [9]
- Myeloid-derived suppressor cell counts in circulating blood seem to be a negative predictor of immunotherapy outcome [10]

Immune Cell Infiltration/Cancer Immune Phenotype

The presence of activated T cells in the tumor parenchyma is considered to be essential for response. Conversely, the absence of such T-cell infiltration into a tumor (immune excluded/immune desert phenotype) may be the result of:

- A defect at the level of T-cell priming
- A mechanical barrier by cancer-associated fibrosis
- Impermeable tumor-associated vasculature, or the absence of T-cell-attracting chemokines

A more comprehensive description of biomarkers defining the "immune phenotype" can be found in Chen and Mellman [3].

Absence of Checkpoints

Tumor cells escape eradication by the immune system via inhibiting the recognition of cancer-specific antigens by T cells. Checkpoints like PD-1 are expressed on regulatory T cells.

So far, most attention has been paid to PD-L1, which is thought to reflect the activity of effector T cells because it can be adaptively expressed by most cell types following exposure to IFN-γ [11, 12]. However, PD-L1 expression on tumor cells can also occur in an interferon-independent fashion.

An efficient elimination of cancer is further complicated by the upregulation of co-inhibitory receptors on effector T cells. These inhibitory receptors include the lymphocyte activation gene 3 protein, T-cell immunoglobulin- and mucin-containing molecule-3 (Tim-3), CTLA-4, and many other inhibitory receptors [12].

The complex biology suggests that the predictive value of a single biomarker will be of limited value. Thus, companies active in the checkpoint inhibitor field tend to consider combinations of various different markers such as PD-L1 expression and IFN-γ expression for their predictive biomarker strategy or for rational-based combination strategies.

Absence of Soluble Inhibitors

Soluble factors are associated with tumor inflammation and can promote tumor progression. Tumor inflammation is characterized by the presence of subtypes of neutrophils, γδ cells, and macrophages that secrete proinflammatory factors, such as vascular endothelial growth factor A, colony-stimulating factors, interleukins, and chemokines. A correlation of high serum concentrations of proinflammatory TNFα, IL-6, or IL-1 has been observed for advanced malignancies, and has been associated with reduced survival [13]. Such soluble factors could be used to define a predictive biomarker strategies based on longitudinal assessments or for rational development of anticytokine therapies in the context of cancer treatment.

Absence of Inhibitory Tumor Metabolism

In healthy cells, glycolysis generally results in entry of pyruvate into the Krebs cycle in the mitochondria. Under hypoxic conditions, pyruvate is converted to lactate by lactate dehydrogenase and pumped out of the cell. In cancer cells, the conversion of pyruvate into lactate takes place even in the presence of sufficient oxygen. High serum lactate dehydrogenase concentrations correlate strongly with poor outcome upon CTLA-4 and PD-1 blockade, and phase 3 clinical trial data have confirmed these results prospectively [4].

Advanced metabolomics approaches may foster the discovery of further potential biomarkers in this category.

In summary, innovative therapeutic concepts need to consider the dynamic interplay of the various different factors reflected in a "cancer patient immunogram" (Fig. 1). It has been realized that inflammation represents a link between intrinsic (oncogenes, tumor suppressors, and genome stability genes) and extrinsic (immune and stromal components) factors
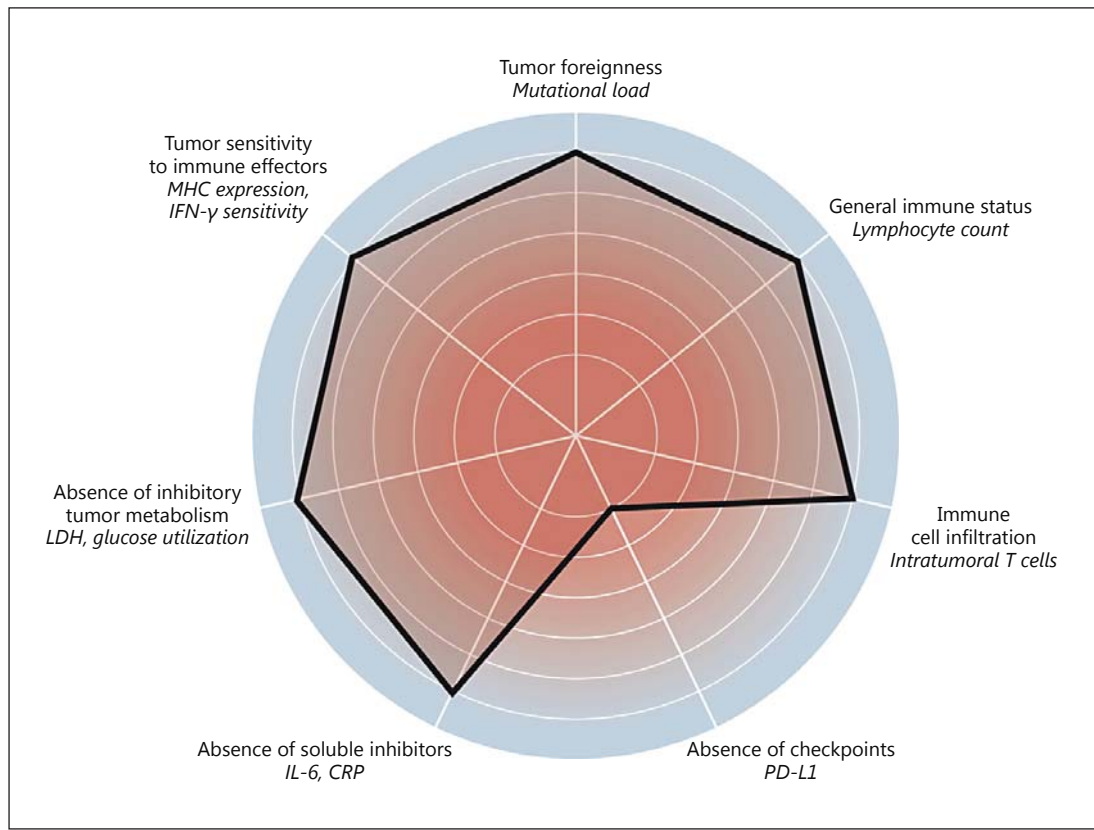
Fig. 1. Cancer immunogram of a hypothetical patient [4]. The radar plot displays seven parameters that characterize aspects of cancer-immune interactions for which biomarkers have been identified or are scientifically plausible. Potential biomarkers for the different parameters are shown in italics. Desirable states are located in blue; progressively undesirable states are shown in the red gradient. The black line connecting the data values for each parameter represents a plot for a single hypothetical patient. In the case shown, it may be argued that single-agent PD-1 blockade, rather than combined PD-1 and CTLA-4 blockade, could be a first treatment of choice.

contributing to tumor development. This knowledge offers not only new and novel candidate targets for therapeutic intervention in combination with more conventional therapeutic approaches [14], but also more sophisticated patient selection strategies.

An Important Consequence of Personalized Cancer Immunotherapy: Several New Biomarkers Compete for Limited Amounts of Biomarker Samples

This competition means that improved sample processing and alternative testing strategies will be required. In this context, the addition of new biomarkers for testing has the greatest effect on small-biopsy specimens, due to the limited amount of tissue material per specimen and to the unavoidable loss of tissue during repeated re-cutting of the paraffin blocks [15].

This issue first became apparent within the field of lung cancer where biopsy material is very limited due to the existing paradigm. Clear guidelines on preservation of biopsy tissue for predictive biomarker testing have thus been outlined in a collaborative effort by the IASLC, the American Thoracic Society, and the European Respiratory Society, as well as by the World Health Organization [16, 17].

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In parallel, many diagnostic companies together with pharmaceutical partners are currently undertaking remarkable efforts in order to overcome the "hierarchical sequential testing approach" which creates a disadvantage for less prevalent markers, which are tested later than, for example, ROS1 versus EGFR in NSCLC.

In this context, in June 2017 the FDA approved Thermo Fisher Scientific's Oncomine™ Dx Target Test as the first next-generation sequencing-based companion diagnostic that screens tumor samples against panels of biomarkers to identify patients who may respond to one of three different treatments for NSCLC. The test exploits high-throughput, parallel-sequencing technology to screen tumor samples for 23 NSCLC genes to identify patients who may be eligible for therapy using dabrafenib/trametinib for tumors with BRAF V600E mutations, treatment with crizotinib for ROS1 fusions, or therapy using gefitinib for EGFR L858R mutation and exon 19 deletions.

Combination Strategy

Cancer immunotherapy has become a key element of clinical development strategies. Due to the multifactorial nature of cancer-immune interactions, combinations of biomarker assays will – by definition – be required.

Approximately 800 studies involving combinations with PD-1 or PD-L1 inhibitors as immuno-oncology "backbones" have been listed on Clinicaltrials.gov as of June 2017. A high number of these studies involve chemotherapy combinations and to a lower extent targeted therapies.

The large number of chemo-based strategies to increase the benefit of immuno-oncology combos may turn out to dominate safety and tolerability aspects. This observation may be due to the fact that immuno-oncology is currently considered as a "substitution market" from a pharma perspective.

Advanced Biomarker Technologies

Digital Pathology as a Novel Tool in Precision Medicine to Help Drive Drug Development

First of all, a significantly improved, more comprehensive understanding of the mode of action is a key objective of any new biomarker technology. Digital pathology empowers biomarker intense assessments in standardized fashion at short turn-around times, as requested by immunotherapy and combination strategy. It is on its way to become standard.

Liquid biopsy-based biomarker assessments are of course more convenient. In addition, they have the potential of fostering longitudinal generation of clinically actionable insights, which makes a lot of sense from a systems pharmacology perspective.

Liquid biopsy-based and tissue-based biomarker assessments are expected to differ. Molecular alterations in the tumor or circulating tumor cells, exosomes, circulating tumor DNA, and systemically assessed cancer-immune phenotypes may be of different relevance than tissue-based results. Both need to be interpreted in context.

Regulatory Framework and Health Technology Assessment

In contrast to the situation in the US, the approval procedures covering the marketing of medicinal products and IVD medical devices are not consistently linked across the EU.

In conjunction with the publication of the new European Union In Vitro Diagnostics Regulation, it is becoming more urgent to develop a precision medicine enabling EMA (European Medicines Agency) guidance, relating to the interface between medicinal products and predictive biomarker assays, including companion diagnostics. In order to mitigate the risk that the harmonization of IVD regulation may slow down the approval of new technology

platforms, a dedicated accelerated path needs to be formally installed for "breakthrough diagnostics."

This is becoming an increasingly pressing issue since more complex companion diagnostics (next-generation sequencing-based, multiplex, indication agnostic) and indication agnostic approaches (i.e., MSI-H, tumor mutational burden) need to be assessed.

Furthermore, harmonization of HTA frameworks needs to be accelerated in the EU. Heterogeneous or inadequate requirements for study end points and comparator definition represent significant risks for precision medicine-based therapeutic concepts. HTA represents a hurdle for many reasons, but in particular because it refers to clinical guidelines which are not consistently updated on a regular basis. Better synergy will be needed between regulatory, clinical guidelines, and HTA.

In the light of limited health care budgets and multiple emerging new therapies, which address multiple unmet medical needs, outcome-based or value-based pricing will become very important. Pharma companies will have to convert their existing business model into a service model offering "therapeutic concepts." On the other hand, the national and supranational health care systems have to apply a higher rigor to the accuracy of outcome measurements. Centralized testing will help to introduce a robust and efficient cost management.

Conclusion and Further Perspective

Despite recently published positive clinical data concerning the effect of pembrolizumab in a PD-L1-enriched 1L NSCLC patient population, the impact of predictive biomarker identification in cancer immunotherapies in clinical practice remains relatively low (ESMO 2016, Copenhagen, Denmark; ASCO 2017, Chicago, IL, USA). Although emerging scientific data suggest multiple promising predictive biomarker candidates in a number of cancer indications, robust clinical evidence is still lagging somewhat behind. In addition, a subsequent change of the testing landscape appears to be challenging [5].

The complex and highly diverse reimbursement situation around companion diagnostics further complicates an efficient introduction of precision medicine in global health care systems. On a general level, stakeholders within the global health care system thus need to combine efforts in order to turn scientific insights about predictive biomarkers into superior and affordable therapeutic concepts. European policymakers more specifically should help to bring this about by ensuring that a suitable regulatory framework and incentive system are in place in order to encourage groundbreaking innovation, and hence the availability of new treatment options for patients.

Disclosure Statement

The author declares no conflicts of interest.

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