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Review

Perspectives on the integration of Immuno-Oncology Biomarkers and drugs in a Health Care setting

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ABSTRACT

Immunotherapies, specifically checkpoint inhibitors, are becoming an important component in cancer care with the most application now in melanoma and lung cancer patients. Some drawbacks that converge with this new evolution are the rather low response rates to these drugs and their high cost with a significant economic impact on the health care system. These major challenges can likely be circumvented by implementing a "personalized immuno-oncology" approach to accomplish a selection of optimal responders based on biomarkers. In this paper we first discuss the legal framework for the development of valuable in vitro diagnostics. Based on a case study in lung cancer, the clinical validity and utility requirements of predictive immuno-oncology biomarkers is highlighted and an overview is given on the evolution towards multiplex or omics-based assays together with its challenges and pitfalls. Finally, some initiatives between the public and private sector are pinpointed to sustain the future access to innovative medicines in cancer therapy at a reasonable cost.

1. Introduction

At the moment immunotherapy relates to the clinical use of immune checkpoint inhibitors demonstrating impressive clinical benefit across several cancer types such as melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, Hodgkin lymphoma and bladder cancer [1–5]. They are not only resulting in a better outcome for the patients compared to the use of chemotherapy, they also provide a higher quality of life with fewer side effects. The first immune checkpoint drug that came on the market was the CTLA-4 blocker ipilumimab (Yervoy®) from Bristol-Meyers Squibb (BMS) and was followed by the PD-1 inhibitor pembrolizumab (Keytruda®) from Merck. Melanoma was the first cancer where these drugs proved their clinical benefit. Since then approvals were expanded to other tumor types like lung cancer and classical Hodgkin lymphoma as listed in Table 1. As many clinical trials are ongoing, it is foreseen that the use of immuno-oncology drugs will rapidly evolve for other cancers. The major challenge that converges with this new evolution is the high cost of these drugs and thus its major economic impact on the health care system (Table 1). A total of four doses ipilimumab given to the patient will have a price of around 90.000€. For PD-1 inhibitors the monthly cost is estimated to be between 8.000€ and 12.000€. These prices will continue to rise as combinations of checkpoint inhibitors will be used in clinical practice in the near future. For the combination of ipilimumab and nivolumab a cost of 95.200€ is estimated for the first four doses. Another major challenge is that not all patients respond as well to immunotherapy [2,6]. The high cost together with the variable responses observed with immuno-oncology drugs asks for a personalized approach that is defined by the EU as 'providing the right treatment to the right patient, at the right dose at the right time'. Identifying the patient population who will benefit from these expensive drugs will be crucial for patient care as well as for the economic sustainability of our health care system. Although immunotherapy has been associated with fewer side effects than chemotherapy, it is possible that patients treated with checkpoint inhibitors suffer from serious immune-related adverse events including skin toxicities, diarrhea, colitis, hepatotoxicity, pneumonitis, dysthyroidism [7]. A good selection could avoid unnecessary toxicities and also needless expenses. For this strategy immuno-oncology biomarkers would be essential as they predict treatment responses and most likely will also provide information on resistance mechanisms. Many efforts are made to identify and develop clinically relevant biomarkers, PD-L1 immunohistochemistry (IHC) being the most used today. A multitude of PD-L1 IHC assays are on the market and FDA has approved PD-L1 IHC as companion and complementary diagnostics in NSCLC for

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Table 1
An overview of approved immune-oncology drugs in oncology and its estimated price.

Drug	Target	Cancer type	Price (€/month)
Ipilumimab (Yervoy®)	CTLA-4	Advanced melanoma FDA, EMA	32.682€
Pembrolizumab (Keytruda®)	PD-1	Melanoma FDA, EMA Non-small cell lung cancer FDA, EMA Classical Hodgkin lymphoma FDA, EMA Urothelial carcinoma FDA, EMA MSI-H/dMMR solid tumors FDA Gastric/gastroeosophageal junction carcinoma FDA	9.897€
Nivolumab (Opdivo®)	PD-1	Melanoma[a] FDA, EMA Non-small cell lung cancer FDA, EMA Advanced renal cell carcinoma FDA, EMA Classical Hodgkin lymphoma FDA, EMA Head and neck squamous cell carcinoma FDA, EMA Urothelial carcinoma FDA, EMA MSI-H/dMMR colorectal cancer FDA	8160€
Atezolizumab (Tecentriq®)	PD-L1	Non-small cell lung cancer FDA, EMA Head and neck squamous cell carcinoma FDA Urothelial carcinoma FDA, EMA	11.428€
Avelumab (Bavencio®)	PD-L1	Urothelial carcinoma FDA Merkel Cell carcinoma FDA, EMA	ND
Durvalumab (Imfinzi®)	PD-L1	Urothelial carcinoma FDA	ND

Calculations were done based on the following dosing schemes.
Ipilimumab: 3 mg/kg, 3 weeks between each dose and 4 doses in total. Cost for 4 doses is 90.157€.
Pembrolizumab: 2 mg/kg (melanoma and lung cancer) or 200 mg (Hodgkin lymphoma), 3 weeks between each dose.
Nivolumab: 240 mg (melanoma, lung cancer, renal cell carcinoma, urothelial cancer) or 3 mg/kg (Hodgkin lymphoma, head and neck squamous cell carcinoma), 2 weeks between each dose.
Atezolizumab: 1200 mg, 3 weeks between each dose.
Cost is calculated on documented prices in Belgium and a weight of 80 kg. Price for atezolizumab was obtained from "BioWorld" website.
ND: not done.
[a] Nivolumab in combination with ipilimumab is FDA approved in advanced melanoma.

pembrolizumab, nivolumab and atezolizumab. The lower cost of PD-L1 testing compared to the more expensive checkpoint inhibitors is certainly of interest for its use to select patients for immunotherapy and thereby to economize on drug expenditures. At the moment, only PD-L1 IHC assays have proven its clinical utility and are used in the clinic. Since PD-L1 is not optimal to select patients responsive to checkpoint inhibition, biomarker evaluation studies are ongoing to improve this. The immune system is complex and dynamic and it is therefore hypothesized that a multiple biomarker approach would be more valid [8,9]. The new developments are mainly based on the concept that T-cell inflamed 'hot' tumors are more prone to immuno-oncology drugs than non-inflamed 'cold' tumors. In line with this is the assessment of tumor-infiltrating lymphocytes (TIL) by CD8 immunohistochemistry that can even be expanded to a multiplex IHC method to quantify different populations including cytotoxic T cells (CD8), tumor-associated macrophages (CD163), immune regulatory T cells (FOXP3/CD3) and B cells (CD20) in combination with PD-L1 expression or even other checkpoint molecules such as PD-L2, CTLA-4, LAG-3, TIM-3. In addition other high throughput technologies like next-generation sequencing (NGS) have boosted immuno-oncology biomarker research and have revealed mutational and neoantigen burden, T-cell receptor (TCR) clonality and immune gene signatures as emerging immuno-oncology biomarkers. A high mutational load, restricted TCR clonality and an IFNy induced gene signature could be valuable in selecting patients responding to checkpoint inhibition. Also, DNA mismatch repair deficiency or microsatellite instability (MSI) have been investigated as biomarkers to select responsive patients to checkpoint inhibitors and have recently been FDA approved for pembrolizumab in unresectable or metastatic solid cancers [10,11].

2. The legal framework for the development of valuable *in vitro* diagnostics: heaven or hell, or in between?

Simple PD-L1 IHC FDA approved assays are already available as companion and complementary diagnostics in NSCLC for respectively pembrolizumab and nivolumab. Although newer assays have shown promise, PD-L1 IHC assays are currently the only assays to have demonstrated clinical utility in prospective randomized control studies. Concerns have been raised though as to the clinical validation and regulatory requirements of the newer multi-dimensional diagnostic tests combining DNA, RNA, protein, and cellular markers. It is considered that co-development of biomarker test and drug or proper post marketing studies are needed to facilitate the implementation of biomarkers in clinical practice [12]. From a practical point of view, it has been proposed that a biomarker assay validation process can be organized in a tiered process approach and as stated by the Society for Immunotherapy of Cancer Immune Biomarker Task Force, is part of a continuum although usually performed by different research teams [13,14]. This is summarized in Fig. 1A. The analytical validation is the assessment of the basic assay performance. This is followed by evaluating the performance of the assay regarding its intended use and predefined specifications within a clinical trial (="fit-for-purpose" principle). The test is assessed for its clinical performance both in predicting the clinical outcome of interest (clinical validation) as well as in inducing better patient outcomes (clinical utility). The validation of clinical utility comprises the establishment of definitive acceptance criteria for clinical use. The Society for Immunotherapy of Cancer (SITC) Immune Biomarker Task Force has recently provided guidance on 1°) the pre-analytical and analytical validation of biomarkers in this context and 2°) the clinical validation process and regulatory consideration related to these late stages of biomarker development [13,15]. The clinical validation process of biomarkers is ideally by prospective clinical trials and in case of multiple biomarkers, not only