Comprehensive analysis of the clinical immuno-oncology landscape

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Advances from immuno-oncology (IO) are changing the standard of care of many types of cancer, and the paradigm of cancer treatments and drug development is being rewritten on a regular basis. Moreover, an unprecedented number of new investigational agents and companies are entering the field of IO. As such, it has become challenging for oncology physicians conducting clinical trials, industry veterans developing IO drugs, and even regulators reviewing novel IO agents to keep track of the rapidly evolving landscape. To help the key stakeholders in the field understand the latest IO landscape, we sought to present an unbiased, neutral, scientifically curated, and timely updated analysis of all the current IO agents in clinical development and the clinical trials testing these agents. We based our analyses on information collected from numerous trusted and publicly available sources. We have developed two databases. One database tracks 2004 IO agents (940 in clinical stage and 1064 in preclinical stage) against 303 targets, from 864 companies; the other tracks 3042 active clinical trials of these agents with a target enrollment of 577 076 patients. This report provides key analyses of these data. Furthermore, we will discuss a number of important and actionable trends in the current IO landscape: a large number of companies developing agents against the same IO targets; a rapid increase in the number of anti-PD-1/L1 combination studies, many of which are testing the same combinations and following inefficient patterns; and a significant increase in the number of small, investigator-initiated studies. For each of the findings, we speculate the causes and discuss a few initiatives that aim to address some of these challenges. Finally, by making these landscape analyses available, we aspire to inform the cancer community as they seek to strive for efficiencies and innovation while avoiding duplication.

Key words: immuno-oncology, cancer immunotherapy, landscape analysis, clinical trials, tumor immunology

Introduction

Advances in immuno-oncology (IO) are revolutionizing the standard of care for many types of cancer. As of our data cut-off date (September 2017), 26 immunotherapies have been approved, and 17 types of cancer have at least one approved immunotherapy as a treatment option. The first approval of modern cancer immunotherapy was interferon-α in 1986 for hairy cell leukemia, and later for chronic myelogenous leukemia, follicular non-Hodgkin lymphoma, melanoma, and AIDS-related Kaposi’s sarcoma [1]. Several other agents have been approved since then, but a transformation in the landscape of IO started with the approval of ipilimumab—a checkpoint inhibitor targeting CTLA-4—for advanced melanoma in 2011 [2, 3]. In the past 3 years alone, five new checkpoint inhibitors (targeting PD-1 or PD-L1), two new cell therapies (targeting CD19), and one new CD3-targeted bispecific antibody (also targeting CD19) have been approved [4–7]. These novel immunotherapies, in most cases, are designed to treat advanced, refractory, or relapsed cancers that did not respond to standard-of-care cancer treatments (Table 1).

Since the approval of ipilimumab, the pipeline of IO agents in clinical and preclinical development has become very crowded [8]. As of September 2017, there were 940 IO agents in clinical development, with another 1064 in preclinical phase. We also found that 3042 interventional active clinical trials are evaluating these clinical-stage immunotherapies with a target of enrolling 577 076 patients (supplementary Table S1, available at Annals of Oncology online). These IO trials cover all common cancer types and the majority of the less common ones, and promising results are being reported on a daily basis in major conferences and clinical
The large numbers of promising experimental therapies, active clinical trials, and planned patient enrollment suggest that we are entering a new era that could change the standard-of-care in even more cancer types. However, the fast-expanding and ever-changing IO field could overwhelm even the most experienced clinical investigators as they seek treatment options for their patients. To help the cancer community stay informed of the current IO landscape, the Anna-Maria Kellen Clinical Accelerator of the Cancer Research Institute (CRI), the clinical research program of CRI, provides herein an unbiased, neutral, comprehensive, and scientifically curated landscape analysis that aims to inform the physician-scientists, drug developers, regulators, and other stakeholders of the latest trends in IO clinical development.

The landscape of clinical immuno-oncology

A large number of IO drugs in clinical development with significant duplication

Overview of the Clinical Accelerator IO database. Our database included 2004 IO agents as of September 2017, 940 of which are in clinical development. On the basis of different mechanisms of actions, we classified these agents into six categories: (i) T-cell-targeted immunomodulators that act on inhibitory or activating molecules expressed by T cells (e.g. agents targeting CTLA-4, PD-1, CD40, and GITR); (ii) other immunomodulators that act on other immune cells or the tumor immune microenvironment to unleash antitumor immunity (e.g. agents modulating IFNAR, CSF1R, IDO1, A2AR, and KIR); (iii) cancer vaccines that induce antigen-specific antitumor immunity (e.g. sipuleucel-T); (iv) cell therapies that engineer immune cells such as T cells to directly attack cancer cells (e.g. anti-CD19 CAR-T); (v) oncolytic viruses that rely on both direct tumor killing and activation of antitumor immunity (e.g. T-VEC); and (vi) CD3-targeted bispecific antibodies that bring T cell to the targeted tumor cells for direct killing (e.g. blinatumomab) (Figure 1).

Concentration of agents on a few targets. The 940 clinical-stage IO agents are owned by 462 different companies or academic institutes (supplementary Table S2, available at Annals of Oncology online), and these agents modulate 271 different targets. Interestingly, a closer investigation of the 940 agents revealed that almost half of them modulate only 40 targets (Figure 2). For example, we found 164 agents targeting PD-1 or PD-L1 (PD-1/L1), with 34 of which are monoclonal antibodies (Figure 3). This confirms our assumption of significant duplication, despite the fact that five anti-PD-1/L1 monoclonal antibodies have already been approved [9]. Although it is still unclear if targeting the PD-1 receptor or its ligand PD-L1 will result in any differences in efficacy and safety, none of the agents or studies in our database show any head-to-head evaluation in patients. In another example, agents targeting...
unspecified tumor-associated antigens (unspecified TAA) represent the largest number of clinical IO agents. There are now 114 agents in the clinic, 98 of which are cancer vaccines. Of the 114 unspecific TAA-targeted IO agents, only sipuleucel-T (an autologous dendritic cell vaccine) has been approved for prostate cancer [10]. This number of agents raises questions on efficiencies of resources and, importantly, the patients who enroll into clinical trials. The concentration of IO development and patient resources on a few targets, some with already approved drugs, could potentially be stalling future innovation. Rather, investing these precious resources more efficiently could help accelerate needed progress in finding cures to this deadly disease.

Rapid proliferation of CAR-T-cell therapy, especially in China. CAR-T-cell therapy has delivered unprecedented results, with two recent approvals of CD19-targeted CAR-T-cell therapies [11, 12]. CD19 is also the most common CAR-T target, with 56 clinical-stage therapies against it (supplementary Table S3, available at Annals of Oncology online). Surprisingly, by interrogating our IO drug database, we found 291 different CAR-T therapies, with 162 of them being tested clinically. These agents are being developed by 136 different companies and academic centers. Interestingly, companies and academic centers from China seem to lead the total number of clinical-stage CAR-T therapies, with 98 clinical-stage agents owned by 46 companies from China.
compared with 51 clinical agents owned by 22 companies from the United States, with a much smaller number in other countries combined (Figure 4 and supplementary Table S4, available at Annals of Oncology online).

The landscape of anti-PD-1/L1 combination trials

Trends in the landscape of 1105 PD-1/L1 combo therapy trials. Despite the approval of five anti-PD-1/L1 antibody agents, our database shows that there are numerous clinical trial programs that are ongoing and actively recruiting patients. The clinical-stage PD-1/PD-L1 agents are evaluating clinical questions across 1502 different studies. Of these, 1105 are combination trials that combine anti-PD-1/L1 agents with other IO therapies, targeted therapies, chemotherapies, radiotherapies, or chemoradiotherapies. It is worth noting that 49 of the combination trials are testing agents that have not been approved, whereas the majority of combination trials focus on the five approved agents (Figure 5).

Fragmentation and lack of coordination in PD-1/L1 combination trial landscape. A deeper analysis of the 1105 trials reveals some interesting observations. First, there has been a rapid increase in new combination studies in the past 5 years. Analysis of our database shows that in 2017 alone, 469 new studies were started, with a target enrollment of 52,539 patients (Figure 6). Second, agents against 165 different targets are being combined with anti-PD-1/L1 agents (supplementary Table S5, available at Annals of Oncology online).
Many of these studies we observed have significant overlap and duplication of the combination partner targets. For instance, anti-CTLA-4 agents and chemotherapies are the two most prevalent classes of therapies being combined with anti-PD-1/L1 agents, with 251 and 170 studies, respectively (Figure 7). This could possibly be driven by the evidence of preclinical synergy of the combination [13], or the recent approvals of anti-PD-1/anti-CTLA-4 combination for advanced melanoma and anti-PD-1/chemotherapy combination as the first-line treatment of advanced non-small-cell lung cancer (NSCLC) [14, 15]. However, it should be questioned if 251 and 170 studies are needed to answer clinically relevant questions. Other prevalent combination partners are anti-VEGFA agents (predominantly with bevacizumab) and radiochemotherapy, with some having already shown clinical benefits [16]. This wide coverage of distinct targets, in our opinion, reflects a fragmented and uncoordinated approach to drug development across the anti-PD-1/L1 combination trial landscape.

New trial designs should be considered for IO development

Breakthrough treatments sooner. The early activity observed with anti-PD-1/L1 agents across multiple tumor types has accelerated the use of novel trial designs, several of which have led to regulatory approvals. There are several examples of novel study designs where drugs have leaped through the drug development phases: from first-in-human, dose selection, safety, efficacy, biomarker selection, all the way to regulatory approval, in one single study. Particularly, the proliferation of agents has resulted in a competitive drug development landscape with a need to answer clinical questions faster within a shorter timeframe by using these novel trial designs. One example is KEYNOTE-001, a phase I trial that led to two FDA approvals, one in melanoma and the other in advanced NSCLC [17]. Moreover, the PD-L1 biomarker was evaluated and confirmed all within the same study. KEYNOTE-001 is arguably the largest phase I trial, which finally recruited...
1245 patients. Its adaptive design allowed the trial to seamlessly transition from generating safety data to producing regulatory submission-quality efficacy data rather than starting separate studies for each clinical question [17]. Speed of development was also demonstrated in this innovative trial design. In <4 years, KEYNOTE-001 went from IND filing to the approval of pembrolizumab for ipilimumab-resistant metastatic melanoma [18]. One year after the first approval, results from this same trial led to the second approval in advanced NSCLC [19].

Another example of novel study design involves biomarker-based, histology-agnostic basket trial design. It was known that tumors with high level of microsatellite instability (MSI-H) or deficiency in mismatch DNA repair (dMMR) have very high level of nonsynonymous mutations and high immunogenicity, which associates with a high response rate to anti-PD-1 therapy [20, 21]. In KEYNOTE-059, a phase II basket trial, patients with solid tumors tested positive with MSI-H or dMMR were enrolled, regardless of their cancer types. Indeed, 149 enrolled patients with MSI-H or dMMR tumors demonstrated a 39.6% objective response rate, which led to the first histology-agnostic approval of a cancer treatment in the United States [22].

A notable shift in study sponsorship from companies to investigators. Rapid increase of investigator-initiated trials in the early development cycle. Traditionally, companies conduct most early- and mid-stage development of a compound themselves—through multicenter, industry-sponsored trials. Once the agent is closer to regulatory approval, the companies would allow more ‘investigator-initiated’ exploratory studies to be conducted. However, for IO agents, our analysis shows that this traditional development paradigm is no longer followed. First, we found that of the 1105 anti-PD-1/L1 combo trials, 60% (655 out of 1105) are sponsored by non-industry sources, such as individual academic centers, government agencies, collaborative groups, or nonprofit entities (Figure 8). Investigator-initiated studies are deemed more exploratory and have an enrollment target of 76 patients per trial on average, compared with 257 patients per industry-sponsored trial (Figure 9). Furthermore, as most of the investigator-initiated trials are being conducted at single centers, it is unrealistic that these 655 non-industry trials will ever achieve the overall target enrollment of ~50 000 patients (Figure 8). This enormous recruitment target, in our opinion, is also a challenging hurdle with many duplicate questions being addressed and limited patient resources.

Summary and discussion

In summary, the current clinical landscape of IO presents enormous enthusiasm from academia and industry, which is exemplified by 940 clinical-stage IO agents, 3042 immunotherapy trials, and 1 105 anti-PD-1/L1 combination trials. The field is very promising and has the potential to deliver many breakthroughs to change the standard of care of many cancer types. However, it is also very crowded, fragmented, and uncoordinated with approvals (FDA sub-part H), which require confirmatory trials to validate the results [23, 24]. These novel trial designs, coupled with highly flexible and cooperative attitudes from regulators globally have significantly accelerated the delivery of innovative and clinically beneficial immunotherapies to patients with cancer.
significant duplication. Our research has identified and confirmed several opportunities and challenges: many IO agents concentrate on a few targets such as PD-1; anti-PD-1/L1 combination trial space is very fragmented and uncoordinated; traditional trial designs are not suited for the fast-changing landscape of clinical IO development; and a significant proportion of the increase in studies can be attributed to investigator initiated IO trials—small, single-center trials that may fail to recruit enough patients and produce high-quality results. We now discuss several ongoing trends that could address these challenges.

There are clear limitations to traditional trial designs, namely single-center studies and the pursuit of the same biological targets by multiple companies. From our research of the IO landscape, there is an urgent need to enhance efficiencies. In a recent publication led by the FDA, the authors provided an eloquent summary and examples of collaborative and novel trial designs, which could allow more questions to be answered more efficiently in a single multicenter trial [25]. These umbrella, basket, or platform designs create a unique opportunity to drive collaboration, coordination, and accelerated innovation.

Although many biopharmaceutical companies are adopting such study designs, they still tend to include drugs only from their own portfolio. The nonprofit and public sectors can play an important role in facilitating and conducting these innovative trials across multiple companies and research centers. There are now several examples of nonprofit organizations leading these novel study designs that have made significant contributions to the field. Notably the I-SPY program for breast cancer [26] is a unique nonprofit-led collaborative that has recruited over 1000 patients and has graduated multiple agents into pivotal developmental.

In another program, the LUNG-MAP for lung cancer [27] was a multi-party collaboration between Friends of Cancer Research, Foundation for NIH, National Cancer Institute, the Southwest Oncology group, and multiple biopharmaceutical and diagnostic companies. Despite a slow start and operational complexities, the study is now open with multiple arms at hundreds of sites. There is an opportunity to learn from these experiences and apply them to future collaborative opportunities to help avoid further fragmentation and duplication.

Public IO-focused information hubs would help coordinate efforts, optimize research resources, and identify rising opportunities in the field. In basic research, the online cancer-immunity cycle (https://cancer-immunity.nature.com/pages/map), which evolved from a recent landmark review paper, serves as a centralized information hub for new IO targets and factors that affect tumor immunology [28]. In clinical development, we realized the urgent need of an updated, scientifically curated landscape for the clinical IO community. Along with this publication, we will make all related resources available on CRI’s website (www.cancerresearch.org/IO-landscape). These analyses will be updated on a quarterly basis. Working with the IO community, we aim to build an unbiased, neutral, comprehensive information hub for clinical IO.

Conclusion

It is probably the best time for progress in oncology in the past decades. The historic opportunity would be maximally capitalized if people from academia, industry, regulatory agencies, and nonprofit organizations work together. This cross-sector collaboration, deep commitment to following the science, and adopting novel study design would be the best ways to bring the true promise of cancer immunotherapies to patients, sooner than later.