THE EMERGENCE OF IMMUNO-ONCOLOGY IN CLINICAL CANCER RESEARCH

Written by PAREXEL’s IMMUNO-ONCOLOGY STRATEGIC WORKING GROUP
Immuno-oncology has become one of the most promising and fastest growing areas of cancer research. Immuno-oncology clinical trials are emerging as an increasingly important activity within a rapidly expanding field of precision-oriented cancer drug development. Immuno-oncologic therapeutics offer the ability to harness and activate the patient’s immune system to attack and destroy tumor cells, potentially transforming the treatment landscape. Additional important advantages beyond enhanced efficacy include reduced toxicity and an increased tolerability, which can further improve the chances of therapeutic success across a broad range of potential cancer indications. Unlike specific targeted therapies directed against a driver mutation, immuno-therapy is not restricted by the expression of genomic abnormalities that are the targets of precision medicine. And as with many other successful approaches in cancer therapy, combinations of immuno-therapy and other targeted therapies may increase efficacy even further.

The cell-mediated immune system in cancer patients is suppressed for a number of cogent reasons. Cancer itself suppresses T-cell function as does prior anti-cancer therapy, especially chemotherapy and radiation therapy. Immune function decreases with age as the incidence of cancer increases with this demographic. Finally, upregulation and increased expression of specific immune checkpoints that suppress anti-cancer T-cell function and the increased suppressive activity of other cells and cytokines in the tumor microenvironment all conspire to blunt or put brakes on an effective immune-mediated anticancer response. Our expanded understanding of these suppressors and activators in the past decade and the application of this new knowledge has created a renaissance in cancer therapy.

Immunologically-based therapy has been part of the anticancer armamentarium since the late 1990’s with the approval of rituximab for the treatment of relapsed follicular lymphoma. Since then, other monoclonal antibodies have been synthesized to inhibit virtually every known receptor or growth factor that drives the oncogenic process in solid tumors and hematologic malignancies as well as benign hematologic disorders.

Today in laboratory and clinical cancer research, immuno-oncology is clearly the most rapidly advancing area as new pathways, combinations, and suppressors are being discovered, targeted, and investigated. Over the past three years, PAREXEL has managed over 600 clinical trials in oncology, of which nearly 20% are in the field of immuno-oncology (Figure 1).

PAREXEL has extensive experience with most of the different classes of immunotherapeutic anti-cancer drugs as shown in Figure 2. Monoclonal antibodies were evaluated in 72% of the studies we managed.

Immune checkpoint inhibitors (ICIs) are directed towards receptors and ligands that suppress the host’s immune system.
response against tumor antigens. These include monoclonal antibodies directed against CTLA-4, PD-1, and PD-L1 but other ICIs are under development and include small molecules directed against adenosine 2A receptors and monoclonals directed against LAG3, TIM3, OX40, and others.

Monoclonal antibodies include unarmed (e.g. rituximab, cetuximab, etc.) and antibody-drug conjugates or armed monoclonals (e.g. TDM-1), radiolabeled monoclonals (e.g. 90Yt-labelled anti-CD20), bispecific T-cell engagers (BiTE) so-called duo antibodies or full bispecific antibodies directed against antigens on B-cells and T-cells. (e.g. CD20xCD3), and chimeric antigen receptor T-cells or CART. Other monoclonal antibodies like bevacizumab are directed against the vascular endothelial growth factor (VEGF), which acts by blocking the binding of VEGF to its cognate receptor.

Immunomodulatory therapy agents like lenalidomide or pomalidomide were evaluated in 12%. Vaccines including autologous dendritic cell or combined autologous tumor cell/autologous dendritic cell immunotherapy and polypeptides were evaluated in 8%. We have also conducted studies with cytokines like interleukin-2 (IL-2) and interferons (IFN).

**EMERGING TRENDS**

The distribution of immuno-oncology studies by Phase is illustrated in Figure 3. The proportions of early phase studies (Phase I and II) and later phase studies (Phase III and IV) are nearly equal but the numbers of early phase studies in oncology is increasing rapidly. Studies classified as Phase I include Phase Ia, Phase Ib, and Phase Ib/Ii (when the Phase Ia stage was a dose expansion in a specific indication after the recommended Phase II dose was determined in Phase Ib).

A second rapidly emerging trend is the evaluation of combinations of immunotherapy (with two ICIs, an ICI and a small molecule targeted therapy, or an ICI with either chemotherapy, radiation therapy, or peptide vaccines). These combination studies are now being conducted as Phase I dose escalation again followed by dose expansion in enriched patient populations or those identified by specific indication (e.g. triple negative breast cancer) or by expression of a specific biomarker (e.g. T790M in NSCLC (NSCLC) or BRAF\textsuperscript{V600E} mutation in malignant melanoma.

However, unlike each of the above classes of immunotherapeutic agents all directed against specific targets on tumor cells, or endothelial cells supplying developing tumors with their required nutrition in the form of angiogenesis, ICIs target the immune system, including cytotoxic T-cells and dendritic or antigen presenting cells that are suppressed by the malignancy itself. Immune checkpoint inhibitors (ICI) activate cytotoxic T-cells by unleashing or unbraking their suppressed state. To date, monoclonal antibodies directed against CTLA4 (ipilimumab) and PD-1 (pembrolizumab, nivolumab) have been approved for the treatment of malignant melanoma, metastatic renal cell carcinoma, and NSCLC. PD-1 inhibitors are also extraordinarily active in patients not only with solid tumors, but also with refractory or recurrent hematologic malignancies including Hodgkin disease and non-Hodgkin lymphoma (NHL). More recently, combinations of ICIs (ipilimumab plus nivolumab) have been shown to be superior to monotherapy with one or the other in metastatic melanoma. The safety profile of this combination has been acceptable but a new and major adverse event, financial toxicity, is a realistic and impactful challenge that will stress the stability of even the most economically privileged health care systems and may obviate less-well-off countries from being able to afford these costly new agents.
Not unexpectedly, PAREXEL’s global footprint is clearly illustrated by the regional distribution of trials we have managed. The proportion of our immuno-oncology trials conducted in North America and Europe are nearly identical. Studies in the Asia/Pacific (APAC) region make up 20% but activity there is increasing rapidly. Latin America and the rest of the world make up the remaining 25% of our activities. These data are summarized in Figure 4.

Immunotherapy in cancer is rapidly expanding and has become the most exciting area in clinical research and translational medicine. Second and third generation monoclonal antibodies directed against growth factors (e.g. VEGF) or growth factor receptors (e.g. EGFR, VEGFR, IGFR), and in hematologic malignancies, and various clusters of differentiation or CDs (e.g. CD20 in B-cell malignancies) are demonstrating superiority in some cases when compared to their originator ancestors. (e.g. obinutuzumab vs. rituximab in chronic lymphocytic leukemia [CLL]). Arming monoclonal antibodies with cytotoxic agents is showing great potential.

PD-L1 is another target of this new class of immunostimulatory agents or ICI. A number of anti-PD-L1s (e.g. durvalumab or Medi4736, atezolizumab, avelumab) are in early and later phase development in an increasingly broadening group of malignancies. More and more of these studies are evaluating combinations of ICI, ICIs with small molecule tyrosine kinase inhibitors (e.g. inhibitors of Bruton tyrosine kinase, PARP inhibitors), anti-angiogenic agents [bevacizumab, cedirinib], other immunostimulant vaccines (e.g. gp100 oligopeptides and toll like receptor agonists), cytokines (e.g. interferon α), and even chemotherapeutic agents or hypofractionated radiation therapy. The PD-1 and PD-L1 inhibitors engage and interact with tumor cells, dendritic cells, T-cells, and other components of the microenvironment including Tregs, myeloid derived suppressor cells, macrophages, tumor infiltrating lymphocytes (TIL), and inflammatory cytokines.

**THE COMPETITIVE ENVIRONMENT**

The three approved immune checkpoint inhibitors are the two PD-1 inhibitors, nivolumab and pembrolizumab, and ipilimumab, an inhibitor of CTLA4. The 2015 market share of each is shown in Figure 5.

Reviewing the marketing success of approved and soon-to-be-approved immune checkpoint inhibitors since 2013 and projecting to 2020, Figure 6 illustrates major market sales estimates for the following major markets: [USA, UK, France, Germany, Italy, Spain, and Japan of inhibitors of CTLA-4, PD-1, and PD-L1 in cancer patients in millions of US$]. (Figure 6)

Despite the hype regarding response rates, durability of response, and an acceptable safety profile, most patients don’t respond to immune checkpoints and only 20-25% of patients reach the plateaued curve of survival three years or more after therapy has been completed. The huge cost of these compounds is also a negative that will undoubtedly limit their availability and affordability globally. Some strategies to improve the efficacy of immune checkpoint inhibitors will include 1) improving outcomes using innovative combinations; 2) identifying active agents to deal with patients who do not respond initially or progress after treatment with the available immune checkpoint inhibitors; 3) demonstrating that anti-PD-1 inhibitors are more efficacious than the available immune checkpoint inhibitors as monotherapy or in combination; 4) expanding the indications beyond the current tumors; and 5) furthering development of other ICIs with different mechanisms of action including...
• Priming and T-cell activation via anti-CTLA4
• T-cell activation via anti-OX, anti-GITR, anti-LAG3, anti-CD137 or urelumab)
• NK activation via anti-KIR or lirilumab or elastuzmab
• Inhibition of inhibitory components of the microenvironment including anti-CSF1R, IDO, anti-CD73, and adenosine receptor 2A. Some microenvironmental targets still awaiting a new inhibitor agent include myeloid-derived suppressor cells and Treg cells.

We recognize that PD-1, PD-L1, and CTLA-4 are important components of the microenvironment and immuno-suppression in cancer patients. More recently the complexity and heterogeneity of the tumor microenvironment has revealed its secrets. Somewhat analogous to driver mutations in other cancers, the differentiation of four types of the tumor...
microenvironment based on PD-L1 expression and the presence or absence of tumor infiltrating lymphocytes (TILs) will lead to much more specific immunotherapy (Table 1).

A more granular view of the cellular and humoral components of each subtype or node are shown in Figure 7.

Other components of activating the immune system and directing it against a malignancy for which targeted therapy is awaited include T-cell trafficking and infiltration, antigen release, and antigen presentation to dendritic cells. Interferon may have such a role as might agents like toll-like receptor agonists that stimulate interferon and IL12 production which in turn increase the response to anti-PD1 agents. Intratumor injection of these agents may increase both local and abscopal tumor responses. When using combinations of ICIs with other agents, the exact timing of administration may have a profound effect on efficacy and still require considerable investigation. The components of the immunostimulatory pathway that can be directed against cancer are shown in Figure 8 with approved therapies and those in clinical or preclinical development.

In 2016 regulatory approval of anti-PD1 ICIs in a number of additional indications and lines of therapy are shown in Table 2.

On May 16, 2016 US FDA approved Genentech’s anti-PD-L1 atezolizumab or Tactentriq for advanced urothelial cancer. The other major companies deeply involved in development of immune checkpoint inhibitors are BMS, Merck, Astra Zeneca/Medimmune. Without any attempt to commercialize the activities of one pharmaceutical company over another, the following tables are presented to provide an example of the immunotherapeutic program of one major player in this highly competitive field. Merck has a very ambitious development program for ICIs as shown in Figure 9.

Not to be surpassed by its competitors in New Jersey (BMS in Princeton, Merck in Kenilworth) Roche/Genentech (South San Francisco) has a large and growing developmental program for immunotherapy as shown in Figure 10. An increasing number of smaller

### Table 1.

<table>
<thead>
<tr>
<th>Subtype or Node of Tumor Microenvironment</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>I. (node 1): PD-L1 positive with TILs driving adaptive immune resistance</td>
<td>• Elimination of immune suppression</td>
</tr>
<tr>
<td>II (node 2): PD-L1 negative with no TILs indicating immune ignorance</td>
<td>• Immunogenic cancer cell death</td>
</tr>
<tr>
<td>III (node 3): PD0-L1 positive with no TILs indicating intrinsic induction</td>
<td>• Enhanced APC function/adjuvanticity</td>
</tr>
<tr>
<td>IV (node 4): PD-L1 negative with TILs indicating role of other suppressor pathways</td>
<td>• Enhance T/Macrophage Effector Activity</td>
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### Table 2. Approval of Anti PD-L1 ICIs in 2016

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Study Design</th>
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<tbody>
<tr>
<td>Hodgkin Lymphoma</td>
<td>CheckMate-205</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>CheckMate-141</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>CheckMate-139</td>
</tr>
<tr>
<td>Bladder</td>
<td>CheckMate-275</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>CheckMate-143</td>
</tr>
<tr>
<td>1L NSCLC</td>
<td>CheckMate-026</td>
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**Figure 7.**

A. Type 1. Elimination of Immune Suppression

B. Type 2. Immunogenic Cancer Cell Death

C. Type 3. Enhanced APC Function

D. Type 4. Enhance T/Macrophage Effector Activity


**Figure 8. Compartments of the Anti-Cancer Immune Response and Status of Immuno-Therapy**

but growing biotechnology companies, particularly in Asia, are in the earlier stages of developing ICIs as monotherapy and in combination for both solid tumors and hematologic malignancies.

Considering the ever-increasing number of immunotherapeutic agents, the broad array of indications from glioblastoma to acral melanoma of the hallux, the various lines of therapy, and finally the infinitesimal number of potential combinations with other ICIs, small molecule TKIs and other enzyme inhibitors, peptide vaccines, chemotherapy, cytokines, and radiation therapy, clinical research in the field of immuno-oncology is really just beginning to extend below the surface and should be a fruitful and productive and profitable area for the next decade.

**COMPANION DIAGNOSTICS AND PREDICTIVE/PROGNOSTIC BIOMARKERS**

Biomarkers and pharmacogenomics studies are increasingly used to identify patients most likely to benefit from an investigational drug in order to maximize potential benefits (increased response, prolonged progression-free and overall survival, and decreased toxicity). The expression of PD-L1 on tumor cells, as determined by immunohistochemistry, has been proposed as a prognostic biomarker of PFS and OS in patients with advanced NSCLC treated with the PD-1 inhibitor, pembrolizumab. As noted in Figure 11a, PD-L1 expression is a continuous variable. Three broad subgroups of expression (<1%, 1%-49%, and ≥50%) [Garon et al, NEJM 2015]. Expression of ≥50% was associated with a significant improvement in both PFS and OS [Figure 11b, c]. Of note is that PD-L1 expression was not prognostic in another study in NSCLC treated
with nivolumab but in this study, a different method and definition of PD-L1 positivity was used. The definitive final word on the value of PD-L1 expression is awaited because a number issues remain unresolved. These include the exact method used, the tissue evaluated (fresh, archival, initial diagnosis, recurrent disease), and the definition of negativity/positivity, to mention a few.

We anticipate the further refinements of companion diagnostics will be discovered, evaluated, and validated, becoming useful tools in evaluating candidates for therapy with ICI and serving as key predictive and prognostic biomarkers. Considering the large number of ICI and the need to identify companion diagnostics for them, this will be an ongoing area of research. PD-L1 expression as measured by immunohistochemistry is shown in Figure 11a.

**FUTURE PERSPECTIVES:**
WHERE ARE WE HEADED?

Huge advances have been made in the past five years. What can we expect in 2016? Figure 12 summarizes the major areas of activity and likely approval of immunotherapeutics in new or expanded indications and combinations.

PAREXEL’s Immuno-Oncology Strategic Working Group (I-O SWG) was created to keep pace with these extraordinary and exciting new advances. The Strategic Working Group is comprised of our leading experts in immuno-oncology across a number of functions, including medical oncology, immunology, medical imaging, biostatistics, regulatory affairs, translational research biomarkers, and business development. The
members of the SWG have participated in trials for many different classes of cancer therapeutic including extensive work in cytotoxics, biologics, targeted therapeutics, cancer vaccines, immunotherapy, and supportive-care products. The I-O SWG meets regularly to review recent advances in the field from the medical literature and recent scientific meetings, current immuno-oncology projects, recent RFP/RFIs, recent regulatory approvals/rejections, the competitive environment, and future perspectives. Considering the fact that immunotherapy is being utilized in other disease specific indications, the Immuno-Oncology SWG interacts with other disease-oriented SWGs, including:

- lung cancer
- breast cancer
- hematologic malignancies
- and Early Product Development. Members of the PAREXEL I-O SWG are the core team that will interface with our immuno-oncology counterparts and colleagues in pharmaceutical and biotechnology companies developing novel immunotherapeutic agents.

Figure 12. Perspectives for Immunotherapeutics in 2016

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Visit our website to learn more about our immuno-oncology and other therapeutic area experience.

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