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Insights and Perspectives Series

August 2014

Immuno-Oncology: Breakthrough but Not Unbounded

- The development of immuno-oncology therapies is among the industry's most important achievements.
- The commercial performance for these products is likely to dominate the oncology category over the next decade.
- The commercial experiences of the first immuno-oncology products in the market, Provenge® and Yervoy®, offer important lessons for the next generation of entrants.
- Going forward, developments within seven areas should be watched closely because they will define the commercial opportunity for immuno-oncology.

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Introduction

Researchers have long known that the immune system regularly identifies and removes cancer cells from the body. Tumor growth becomes uncontrolled only when the cancer either overwhelms or evades these defenses. It's not surprising, then, that finding a means of providing advantages to the immune system has been a priority for drug developers.

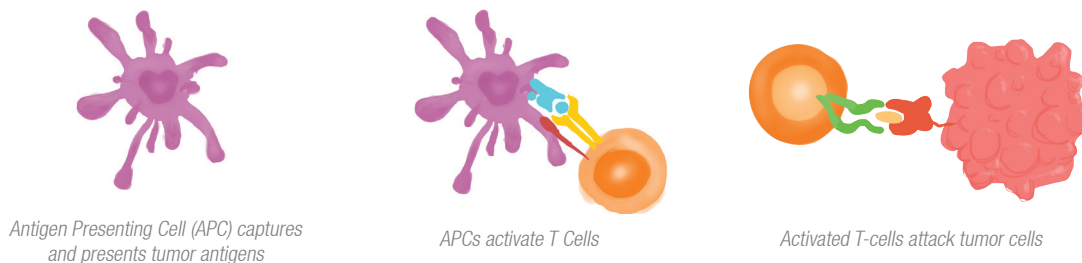
It appears successful immuno-oncology strategies are now at hand. The clinical and commercial implications of such a success are profound. For some patients, clinicians will overcome their experience-weary caution in using the term

“cure.” For investors, anticipation is already driving many analysts to project product sales in the tens of billions of dollars. Fully cognizant of the many remaining uncertainties, we believe the emergence of immuno-oncology therapies will fundamentally alter the cancer treatment landscape. As this occurs, successful innovators will be the recipients of huge swings in economic value. However, the commercial rewards will not be unbounded. Leaders cannot assume that immuno-oncology therapies will be absorbed by a static healthcare environment. In fact, the emergence of such a transformative technology will likely accelerate change to the commercial system in which that technology will be applied.

Box 1: Immuno-Oncology Mechanisms

Cancer cells have unique proteins that are carried on their surface. These proteins can act as targets for immune system attack. When the cancer is being effectively controlled, antigen presenting cells will capture tumor antigens and use them to activate T-cells. Those activated T-cells will then attack and remove tumor cells.

Key Steps of Immune System Attack on Tumor Cells



Tumor growth is aided by factors that diminish the number of activated T-cells or interrupt the ability of activated T-cells to attack cancer cells. In debilitating tumors, on-going mutations are thought to drive multiple mechanisms for evading the immune system.

The emerging wave of immuno-oncology treatments are designed to leverage the body's natural means of removing cancerous invaders. Some use ex-vivo processes to expand the number of antigen presenting cells, and thus increase the number of activated T-cells. Others, representing one class of checkpoint inhibitors, target proteins that slow the rate of T-cell activation by antigen presenting cells. Yervoy®, for example, targets a protein called CTLA4. CTLA4's role is to slow the immune system by inhibiting T-cell activation. With apologies for the circular nature of the description, ipilimumab works by inhibiting the immune system-inhibiting actions of CTLA4. The term “check-point” has emerged to describe the action of molecules like CTLA4. The protein acts as a check-point on the immune system. In turn, products like ipilimumab are described as check-point inhibitors.

Currently, new therapies that focus on mechanisms by which activated T-cells attack tumor cells are receiving the greatest level of attention. Notably, PD-1 has been identified as a check-point in the ability of T-cells to remove cancer cells. Strategies to either inhibit PD-1 or its ligand, PD-1L are expected to amplify the immune system's attack on the tumor. BMS' lead product nivolumab and Merck's MK3475 (also called pembrolizumab) pursue the first approach and Roche's MPDL3280A (also called RG7446) applies the latter.

Figure 1

Factors That Will Define the Commercial Opportunity

- Demonstration of Attractive Tolerability Profile
- Level of Price Sensitivity and Impact of Cost Sharing
- Patient Inclusion/Exclusion Based on Biomarkers
- Entry of Competing Targeted Therapies
- Evidence of Superiority from Combination Products
- Commercial Positioning in Light of Intensifying Competition
- Industry's Ability and Willingness to Invest

There are seven factors that should be watched closely by leaders responsible for setting immuno-oncology strategies (Figure 1). This paper is designed to provide the background and context for interpreting new information related to these factors as it becomes available. We start by reviewing the emerging approaches for immuno-oncology therapies (Box 1). We then describe factors that could justify the extraordinary commercial expectations. Finally, we identify the seven forces that have the potential to put boundaries on the market.

Lessons From the Pioneers

In April of 2010, Dendreon signaled the beginning of the immuno-oncology era with the approval of Provenge®. This product requires collection of the patient's antigen presenting cells and incubating them ex-vivo in the presence of prostate acid phosphatase (PAP), an antigen that is present in most prostate tumors. The expanded antigen presenting cells are then returned to the body yielding an increased number of T-cells that are activated against the tumor. In the pivotal IMPACT study, men with metastatic hormone resistant prostate cancer who were treated with Provenge had a median survival of 25.8 months while those treated with a placebo had a median survival of 21.7 months.

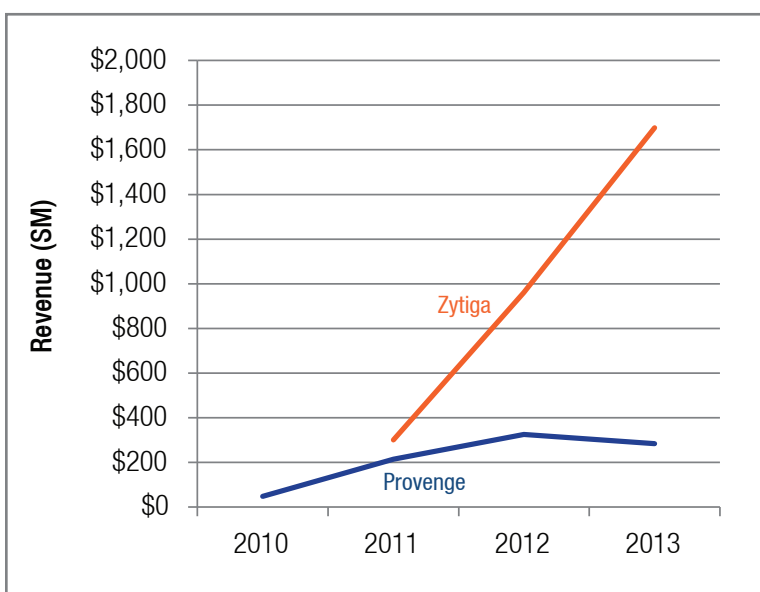
The technology is elegant, but Provenge has struggled commercially and Dendreon has implemented a series of restructuring efforts. Multiple factors have contributed. Notably, at 4.1 months, the increase in median survival is modest. While others have certainly built successful oncology franchises on similar benefits, the healthcare system has been generally unresponsive to pursuing such performance in the face of a steep \$93,000 per patient launch price and a treatment process requiring steps that did not fit neatly within existing systems. Dendreon also did not have the benefit of addressing these challenges within a closed system. In April of 2011, one year after the approval of Provenge, J&J received approval for Zytiga® (abiraterone acetate). Zytiga had been the key asset driving the one billion dollar acquisition of Cougar Biotech by J&J. Clinical studies suggested a similar benefit of approximately four months increased overall survival in the same patient group being targeted for Provenge. Zytiga is administered orally and was priced at launch at approximately \$40,000 for a course of treatment. Figure 2 reveals the market's

preference for the lower priced, more easily administered option.

As the first product pursuing an entirely new treatment approach, Provenge suffers the fate of many innovations. It tantalizes with exciting potential, but it also presents negative trade-offs that cannot be justified in light of progress of more traditional approaches. The second immuno-oncology product to be launched presented a more attractive overall profile.

BMS received US approval for Yervoy® (ipilimumab) in March of 2011. Based on data from the pivotal ipilimumab study, the overall survival for pre-treated metastatic melanoma patients receiving Yervoy was approximately three and a half months longer than

Figure 2: Revenue Performance Provenge and Zytiga

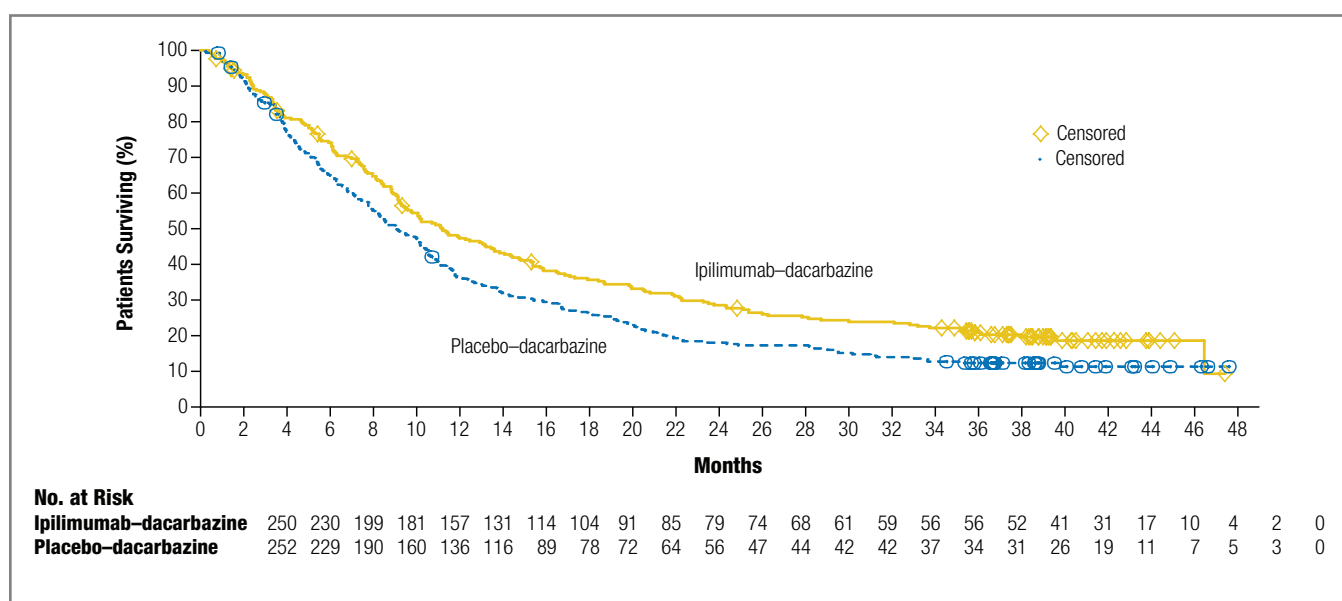


the median survival for patients treated with an active control. Because there was a lack of effective treatments for metastatic melanoma this performance justified quick regulatory approval. The truly remarkable study result was seen in the durability of response for some patients. As seen in Figure 3, the study results for patients treated with Yervoy reveal an asymptotic survival curve – more than 20% of the treated patients were still living at 24 months¹. Later reviews suggest this benefit can still be

observed at ten years.

BMS quickly launched Yervoy and by 2013, US sales reached almost \$600M. The commercial performance of Yervoy suggests several important lessons that may be applied to future immuno-oncology entrants. The most important of these are discussed in the next section.

Figure 3: Ipilimumab Clinical Performance



Source: Robert, C, et al. (2011) Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma, New England Journal of Medicine, 364: 2517-26

Commercial Observations

1) Broad Epidemiology is Irrelevant:

The commercial opportunity for melanoma treatments can be deceptive. The disease is the fifth highest incidence cancer in the US, following only breast, prostate, lung, and colorectal cancer. For the vast majority of patients, melanoma is identified in its early stages—as a single lesion or a group of lesions restricted to the skin with no migration to the lymph nodes. For this comparatively, fortunate group – estimated at over 80% of the incident population—treatment involves surgical removal of the tumor and ten year survival far exceeds ninety percent.

The remaining patients, those for whom the cancer has spread to the lymph nodes or other organs, represent the primary targets for pharmaceutical treatment approaches. In the United States, the incident melanoma patient population is over 75,000. Those who are identified when the cancer is past stage 1 (local disease) number only approximately 10,500. Sadly, some of these patients are beyond the point where pharmaceutical treatment is advised. In 2012, Roche released the company's estimate for metastatic melanoma patients receiving first line pharmaceutical treatment at 8,900².

¹ Robert, C, et al. "Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma", New England Journal of Medicine, 2011 364: 2517-26

² The Future of Medicine is Personalised, Roche Investor Day 2012, Appendix: Target Population Data

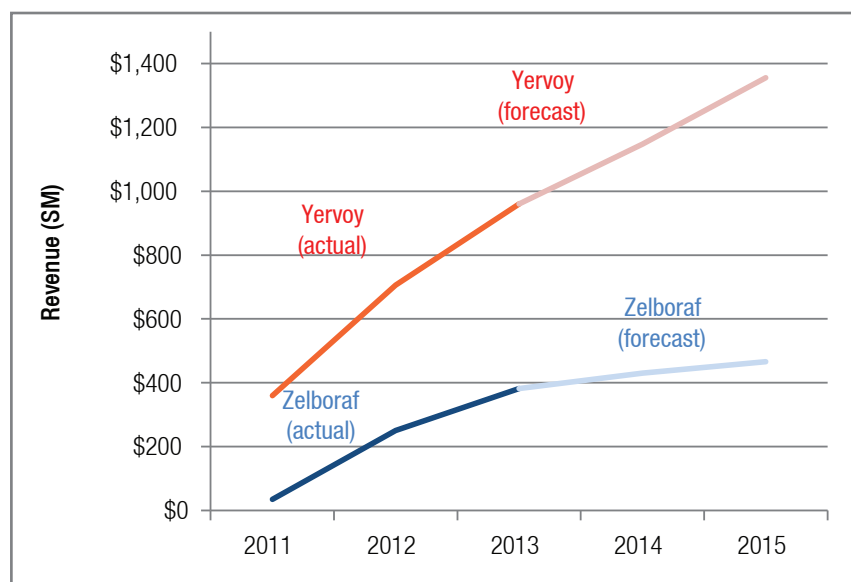
2) Pricing is Scaled to Patient Benefit:

In the last few years, even the largest pharmaceutical companies have become comfortable pursuing small patient populations when the substantial benefits of their therapies can be rewarded with high product pricing. Nevertheless, it was still remarkable to observe BMS launch Yervoy at a cost of \$120,000 per patient. At that price, the 2013 US revenue of \$577M suggests approximately 4,800 patients received the product.

3) Adoption Can be Rapid:

Figure 4 shows the first three years of revenue for Yervoy. In the US, the product quickly achieved over a half billion dollars in sales. It might be surprising to see a tailing off of growth in year three relative to year two. Rather than suggesting a deficiency in the product's further penetration of the market, this pattern is characteristic for the launch of highly innovative and broadly anticipated oncology therapies. The market is concentrated with approximately 13,000 oncologists (including hematologists) in the US, and physicians had been tracking Yervoy's development progress. Once it was available, many were poised for rapid adoption. Similar behaviors are anticipated as other immuno-oncology products receive approval.

Figure 4: Revenue Performance Comparison Yervoy and Zelboraf



Source: EvaluatePharma

4) The Market is Not Static:

In a pattern with notable similarities to Dendreon's experience with Provenge, BMS quickly faced competition from another large pharma that had completed a headline grabbing transaction that was completed with an eye toward entering a highly under-served group of cancer patients. In August of 2011, Roche received FDA approval for Zelboraf® (vemurafenib) for patients with metastatic melanoma with the BRAF V600E mutation³.

The pivotal Zelboraf study demonstrated an improvement in overall survival at six months in the vemurafenib treated patients compared to those treated with dacarbazine (84% vs. 64%) and improvement in progression free survival (5.3 vs. 1.6 months).

Estimates place the share of metastatic melanoma patients with the BRAF V600E mutation at approximately 50%. The treatment decision for these patients presents a trade-off between the high-confidence of delayed disease progression offered by Zelboraf vs. the lower odds of a durable response achieved by the 20% or so of patients who receive Yervoy. The NCCN guidelines for metastatic melanoma do not specify a uniform approach for these patients, but commercial performance suggests that many

BRAF positive patients receive Zelboraf as first line therapy. Upon disease progression, these patients often receive Yervoy.

As with Provenge, competition with an effective, well tolerated oral therapy has reduced the potential commercial performance of Yervoy. For Yervoy, however, the effect is moderated because the oral therapy is only applicable for approximately half of the relevant patients, and many of those patients go on to receive the immuno-oncology treatment in second line. Until there is an increased share of patients achieving durable response, many treatment decision makers are likely to be inclined to select therapies that can be demonstrated to have been developed specifically for patients with a pre-identified set of genetic characteristics.

³ Roche had gained access to Zelboraf from Plexxikon in a 2006 licensing deal. As the time of the product's approval approached, Daiichi Sankyo purchased Plexxikon for an initial \$805 million plus \$130 million in contingent value rights.

Immuno-Oncology Takes Off

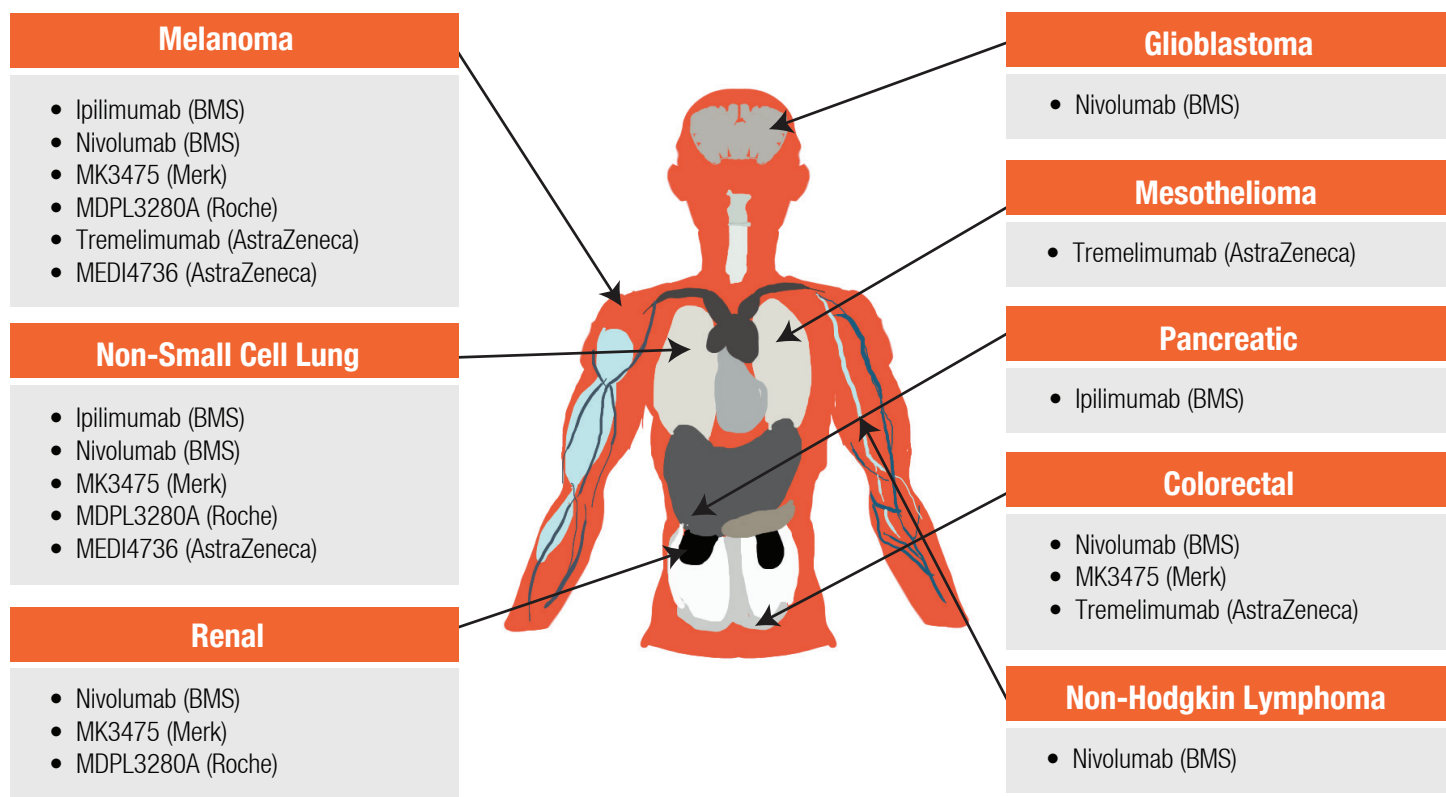
Limited to products like Provenge and Yervoy, the immuno-oncology market would develop as an important but isolated category of treatments relevant to a small set of patients. As researchers have identified additional checkpoint targets, expectations have leaped forward. Most important among these is PD-1 and its ligand PD-1L. PD-1 acts as a checkpoint on the interaction between activated T-cells and their targets. Researchers have demonstrated that one of cancer's insidious mechanisms involves stalling an immune system attack by facilitating the action of PD-1 and other checkpoint proteins. Suppression of PD-1 or blocking of the ligand returns the T-cells' efficacy in removing tumors. BMS with nivolumab, Merck with MK-3475, and Roche with MPDL3280A have taken the lead in developing products to inhibit the PD-1 checkpoint.

Early results for these products have been remarkable. Further, encouraging performance has been observed across a wide variety of tumors (Figure 5). Following early success in metastatic melanoma, unprecedented efficacy has been announced in lung

cancer, renal cell carcinoma, and several other tumor types. As the clinical performance has been extended into areas with comparatively high levels of incidence, commercial analysts' expectations for the product class have soared. As of May of 2014, the sum of EvaluatePharma's estimate for the four leading PD-1 checkpoint inhibitors was \$14 billion for 2020. This is for a class of products with no current revenue. In June 2013, Andrew Baum from Citi announced an estimate for the immuno-oncology class at \$35B by 2023.

A review of commercial drivers provides substantial support for these heady expectations, but there are, of course countervailing factors that could place boundaries on the performance of immuno-oncology therapies. In the following section, we will provide a build-up of the potential market for these products and then, in the final section of this white paper, we will identify several factors that will influence whether (and how quickly) these results will be achieved.

Figure 5: Phase 2 and Phase 3 Immuno-Oncology Studies (April 2014)



The Potential Revenue Story

Introduction:

Estimating the revenue potential for oncology products can be challenging. Studies are conducted and indications may be received based on the site of the initial tumor, histology, genetic characteristics, the stage of disease (degree of metastasis), the line of therapy, and the overall health of the patient. Because studies may apply different patient inclusion and exclusion criteria, competing therapies may address some, but not all of a target group of patients. Even with the guidance offered by regulatory approvals and compendia listings, physicians and payers may expand or narrow the group of patients receiving a treatment. For all of these reasons, forecasting in oncology starts with a detailed review of the patient characteristics, epidemiology, and current treatment approaches.

In the next few pages, we outline available information for the number of patients that could receive immuno-oncology therapies and for the potential pricing of these therapies.

Identifying Relevant Patient Groups:

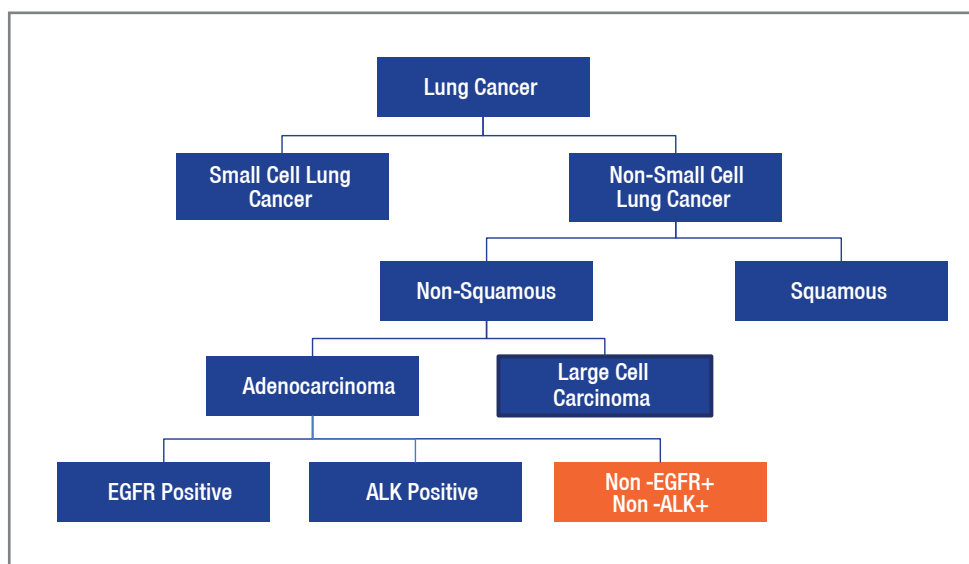
Early studies in immuno-oncology are covering a large number of tumor types. For this review, we will look at the three that are receiving the most attention: metastatic melanoma, lung cancer, and renal cell carcinoma. In particular, the largest near-term market for immuno-oncology products is likely to be lung cancer.

As shown in Figure 6, lung cancer is classified first as small cell or non-small cell. Within non-small cell lung cancer, tumors are segmented based on histology as either squamous or non-squamous, and then according to whether the tumor type is adenocarcinoma or large cell carcinoma. Finally, within the adenocarcinoma portion of non-squamous, non-small cell lung cancer, patients are stratified based on whether the tumor is genetically identified as ALK-positive or EGFR-positive. If diagnostically identified, patients with tumors that are ALK-positive are likely to receive a targeted therapy such as Xalkori® or the recently approved Zykadia™. Those with EGFR-

positive tumors may receive Tarceva®, Iressa®, or Gilotrif®. The largest group, those who are negative for both genetic markers typically receive a combination regimen that includes a platinum therapy, paclitaxel, and Avastin®.

With the epidemiology in hand, we need to next develop an estimate of the number of patients who will receive an immuno-oncology therapy. A review of Avastin's performance in this market offers some guidance on the share of patients that may receive a highly innovative but costly therapy. In a 2012 Investor's Day presentation, leaders at Roche estimated the number of patients with non-squamous, non-small cell lung cancer at 51,000 in the US and 56,000 in Europe⁴. One can roughly estimate Avastin's penetration of this market by pairing an assumption that approximately 40% of the product's US revenue (\$1.2B of the \$3.2B total) is derived from the treatment of patients with lung cancer with an estimate of \$65,000 for the annual cost of treatment for these patients. This suggests approximately 19,000 patients, or 37%.

Figure 6: Patient Segmentation in Lung Cancer



All of the leading companies with immuno-oncology products are conducting trials in non-small cell lung cancer (Figure 7). For the most part, these studies are testing the efficacy of single products as a second line approach to non-small cell, non-squamous patients who have failed a prior therapy. Notably, BMS is already conducting a substantial

⁴The Future of Medicine is Personalised, Roche Investor Day 2012, Appendix: Target Population Data

Figure 7: Immuno-Oncology Studies in Lung Cancer

Product	Study	Comparator	Sub-Group	Line	Patients
Nivolumab	CHECKMATE-153		Non-Squamous	2 nd	780
Nivolumab	CHECKMATE-057	Docetaxel	Non-Squamous	2 nd	574
Nivolumab	CHECKMATE-017	Docetaxel	Squamous	2 nd	264
Nivolumab	CHECKMATE-063		Squamous	3 rd	100
Nivolumab	CHECKMATE-026	Investigator Choice	Non-Squamous	1 st	495
MK-3475	KEYNOTE-010	Docetaxel	Non-Squamous	2 nd	920
MK-3475	KEYNOTE-021	Multiple	Non-Squamous		320
MPDL3280A	OAK	Docetaxel	Non-Squamous	2 nd	850
MEDI14736			Non-Squamous		210

phase 3 study using nivolumab as a first line treatment. If the early results of these trials confirm the promising early analyses, it is reasonable to assume half or more of all patients could receive an immuno-oncology therapy as a first or second line treatment. Some may even receive one immuno-oncology product in first line and another in second line.

In Figure 8, we have prepared a first pass estimate of patient populations for the three tumor types where immuno-oncology studies are most advanced. We have included populations for the US and the five largest European countries. Obviously including only these tumor types and only these countries underestimates a product's potential. For mature products, the US and Europe typically contribute approximately 80% of revenue⁵.

Inclusion of additional tumor types could be even more important to the final commercial estimate. Notably, BMS has not limited its investigation of nivolumab to patients with non-squamous, non-small cell lung cancer. In May of 2014, the company announced a rolling regulatory submission for the second line treatment of squamous cell lung

cancer. At the same time, Merck has highlighted the extensive range of studies for MK-3475. Using phrases that were once attributed to J&J's development of Remicade®, analysts have highlighted Merck's approach to MK-3475 as "a portfolio in a product."⁶ Inclusion of areas such as colorectal and head and neck cancer would dramatically increase the number of patients who may be treated with immuno-oncology therapies.

Pricing:

There are many benchmarks to consider when anticipating pricing for immuno-oncology products. Yervoy is a natural place to start. The benefits of Yervoy are clearly evident for those patients who receive a durable response. However, as noted earlier, for every patient that does achieve a durable response, approximately three others will have limited benefit. Marking pricing at the cost per patient suggests \$125,000 – but the cost per durable response is more like \$500,000. As remarkable as this price level may seem, it still falls below the current long term costs for treating many types of cancer. For example, for patients

Figure 8: Estimated Patients

Segment Name	Region	Total Population (2020)	Share of Population	Share Receiving Product	Treated Patients (2020)
Metastatic Melanoma	United States	350 M	.00267%	75%	7,100
Non-Small Cell Lung Cancer (non-squamous)			.01529%	50%	26,200
Renal Cell Carcinoma			.00462%	50%	8,000
Metastatic Melanoma	EU5	343 M	.00274%	75%	6,900
Non-Small Cell Lung Cancer (non-squamous)			.01669%	50%	29,200
Renal Cell Carcinoma			.00513%	50%	8,700

⁵ A rule of thumb places 80% of European revenue in the five largest countries. The Japanese market is the next important area for consideration, but approval for oncology therapies can lag the US and European markets by five to seven years. Other markets including Canada, Australia, Turkey, and Brazil may represent 10% of the overall potential.

⁶ Carroll, J., AstraZeneca Rushes Immuno-Oncology Star Into Phase III Lung Cancer Study, "FireceBiotech, May 8, 2014

with chronic myelogenous leukemia, the availability of products such as Gleevec®, Sprycel®, Tasigna®, or Bosulif® transformed a fatal diagnosis into a chronic disease. The treatments, however, come at a price of over \$100,000 per year. With ten year survival now the norm, overall, the long term cost of therapy for individual patients exceeds \$1 million.

On the other hand, the emergence of \$10,000 per month oncology treatments is a relatively new phenomenon. In the mid-2000s, the multi-tumor type breakthrough treatments of the day such as Taxotere® (docetaxel) or Alimta® (pemetrexed) were priced at \$1,500 to \$3,000 per cycle—and even then, there were calls from oncologists and payers about the fear of rising oncology treatment costs.

While recognizing that there is a very large range in potential pricing, for purposes of discussion, we will use the price per patient for Yervoy in our first pass model. It is the most similar currently marketed product. We will, however, also assume that pricing is allowed to increase by 5% per year in the US and by 2% per year in Europe.

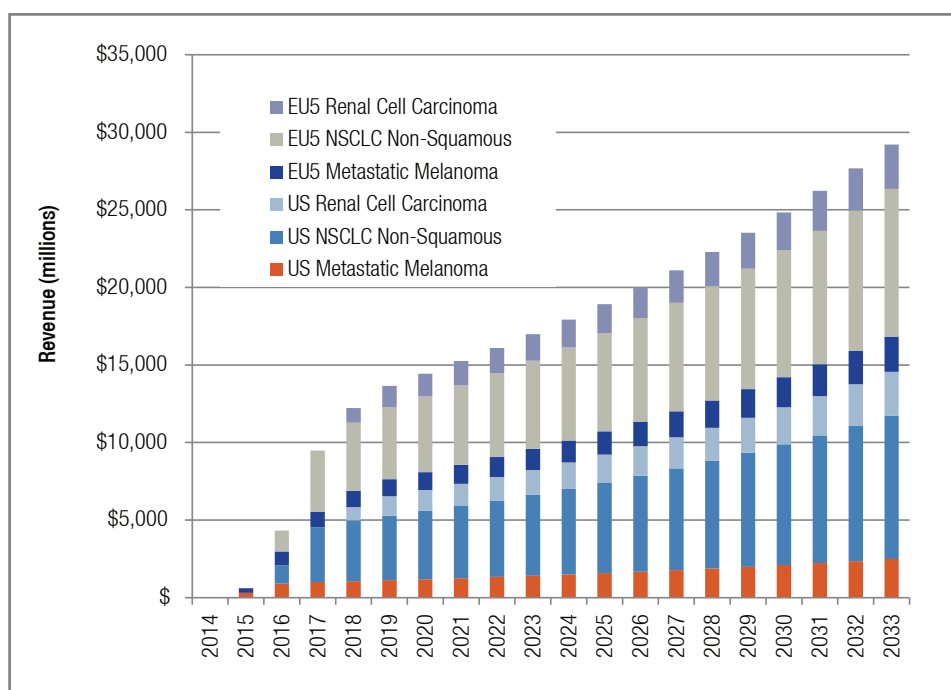
Consolidating Observations for Initial Commercial Estimate:

Along with patient numbers and pricing, the launch timing for immuno-oncology products remains uncertain. Bullish analysts, pinning hopes on the FDA's breakthrough therapy pathway, are hoping for initial launches in metastatic melanoma as early as mid-2015. Subsequent indications in non-small cell lung cancer and renal cell carcinoma may follow within the next two years. The initial model assumes promotion in lung cancer occurs in mid-2016 and in renal cell carcinoma in early 2017.

Joining these observations explains why there are extraordinary expectations for the immuno-oncology class of therapies. With only the first three indications, and accounting for only the US and top five European markets, revenue for the class could rapidly exceed \$20 billion (Figure 9). Pricing scaled to higher share of patients achieving a durable response and inclusion of only one additional high incidence tumor type could quickly double that level. Putting this in perspective of other comparators, in a matter of a few years, this class of therapies could have revenue that exceeds all spending on multiple sclerosis therapies or the total spending on immune-modulators used to treat rheumatoid arthritis, Crohn's disease, and psoriasis (the TNFα class).

Even using highly conservative alternatives to the inputs that we have used in this model, the immuno-oncology market will become an important segment of the biopharma industry. In the remaining section of this paper, we will discuss seven factors that will govern its eventual size and pace of growth.

Figure 9: Revenue Potential in Immuno-Oncology



Checks on the Checkpoint

Toxicity and Tolerability:

Anyone familiar with products like Pfizer's torcetrapib or BMS' Vanlev® knows that even products with tremendous clinical and commercial promise can be brought down by unacceptable adverse events. The success of immuno-oncology depends

on the products' ability to reinvigorate the immune system at the site of the tumor without putting it in overdrive throughout the body. Researchers are vigilantly monitoring toxicities including enterocolitis, hepatitis, dermatitis, neuropathy, and endocrinopathy.

To date, there is a high level of confidence among researchers that an acceptable balance will be identified for each of the leading programs. However, as companies pursue ever higher efficacy, adverse event potential also rises. Even if a suitable balance is identified for each product, competitive commercial battles will surely be fought on nuanced differences in tolerability and practitioners' skill in addressing the appearance of toxicities through supportive care intervention.

Even a Breakthrough May Face Price Sensitivity:

When Paraplatin® (carboplatin) was launched in 1991, the monthly cost in the US was \$860. Taxol® (tamoxifen) launched in 1994 at what was then seen as a very high monthly price of \$2,600. Today, launch prices for oncology therapies regularly are set above \$10,000 per month, and then annual price increases of 5 to 7% are the norm.

Payers' incentives to push back on increased pricing are easy to understand. Recently, however, it is physicians that have voiced concerns regarding the value that is received at these costs. Dr. Peter Bach at Memorial Sloan Kettering Cancer Center has tracked and published a graph that compares cancer drug prices going back to 1960⁷. His charts (whether displayed in nominal or current dollars) confirm a substantial trend upward. Information like this, along with practical clinical experience, has led physicians to use journals (for example a 2013 article in *Blood* regarding the cost of CML treatments⁸) and associations (including ASCO⁹) to voice awareness and concern about pricing of therapeutics.

Manufacturers of immuno-oncology treatments will undoubtedly face increased use by payers of tools to limit access and reimbursement. Notably, many of these treatments will trigger co-insurance payments from patients. At the anticipated prices, a single co-insurance payment may represent the entire annual out-of-pocket limit for an individual patient. Those in health plans where such limits are very high may begin making personal cost-benefit analyses. If those patients do not understand or do not appreciate the statistically complex nature of the benefits, their choices could introduce a previously unheard of elasticity to the oncology pricing model.

Boundaries on pricing tolerance also play a role in each of the following potential market limiting factors.

Personalized Therapies Could Limit the Number of Patients:

The pharmaceutical industry has experienced a steady march toward personalized medicines. There are multiple factors that can define personalization, but most frequently it involves identification of genetic characteristics of the patient and linking those qualities to the suitability of a particular therapy. The linkage with genetics is established during clinical trials where only patients with particular characteristics are included or cohorts of patients are prospectively segmented to demonstrate the relevance of the marker. Because the mechanisms of immuno-oncology therapies are very well characterized, it is logical to assume there could be a means of identifying those patients for whom efficacy of the treatment is most likely.

Roche has emphasized the role of patient selection in the development of MPDL3280A. During ASCO 2013, the company released a segment analysis for patients with lung cancer showing substantially greater efficacy in PD-L1 positive patients. At ASCO 2014, study results were shared showing encouraging performance for PD-L1 positive advanced urothelial bladder cancer patients. Merck has also been providing information on the stratification of patients based on PD-L1 status. Again at ASCO 2014, information showing substantially greater efficacy for PD-L1 positive melanoma patients treated with MK-3475 was highlighted.

BMS has run fewer studies with rigorous genetic inclusion criteria. However, one nivolumab study (CHECKMATE – 026) has included only patients who are positive for a PD-L1 marker.

Biomarkers will pose many questions for the commercial development of immuno-oncology. Currently, each company has its own test and its own threshold for defining whether or not a patient is "positive." Further, while some of the early results are strongly directional, there are no studies suggesting that the presence of the biomarker is definitive. With even a diminished expectation for a response, many patients who test negative for the biomarker are likely to lobby aggressively for treatment.

If pre-identification of patients proves critical to isolating relevant patients, the overall number of treated patients will be smaller. Industry leaders have not, however, viewed personalized

⁷Bach, P., Memorial Sloan-Kettering Cancer Center, available at <http://www.mskcc.org/research/health-policy-outcomes/cost-drugs> (accessed June 2014)

⁸Kantarjian, H, et.al, "The Price of Drugs for Chronic Myeloid Leukemia (CML); A Reflection of the Unsustainable Prices of Cancer Drugs: From the Perspective of a Large Group of CML Experts", *Blood*, April 2013

⁹ASCO in Action Brief: Value in Cancer Care, posted January 21, 2014, available at <http://www.asco.org/advocacy/asco-action-brief-value-cancer-care>

medicine as a threat. They respond that it effectively overcomes unwarranted medication of inappropriate patients. The challenge, however, is to assure that the manufacturer's per patient compensation can be increased as quickly as the patient pool is reduced.

Targeted Therapies May Drive Sharing of Patients or of Per Patient Revenues:

The competition between Zelboraf and Yervoy in metastatic melanoma, and that between Zytiga and Provenge in prostate cancer, reveals that immuno-oncology products will not launch into static markets. The same segments targeted by immuno-oncology are priorities for targeted therapies. The on-going movement to personalized treatment in lung cancer was recently highlighted by the approvals of Zykadia for patients who are ALK+ and by the announcement by Cancer Research UK, AstraZeneca, and Pfizer of a program for isolating treatment approaches for narrow groups of patients based on genetic characteristics. Similarly, renal cell carcinoma has been among the most dynamic settings for adoption of targeted therapies.

To reach the highest commercial performance, immuno-oncology therapies will need to demonstrate superior efficacy to targeted and personalized therapies. In the near term, the trade-offs are likely to echo the experience in metastatic melanoma where targeted therapies offer higher odds of overall survival benefit, but less potential for a durable response. This trade-off could place immuno-oncology products in a second line of treatment.

Combination Approaches May Be Required:

Even before the imminent wave of immuno-oncology products achieve approval, a wide range of combination approaches are being pursued in early stage trials. The combination of immuno-oncology and targeted therapies is easy to explain. As seen in Figure 10, developers are already combining checkpoint inhibitors with other checkpoint inhibitors, with immune stimulators, with growth inhibitors, and with anti-angiogenesis therapies.

Interestingly, with products like Zelboraf, Tarceva, and Avastin, Roche has the ability to dip into the company's own portfolio for attractive combination candidates. Similarly, AstraZeneca is exploring

a combination with the company's own targeted therapy, Iressa. Lacking such an arsenal of relevant options, BMS and Merck have announced a series of partnering programs designed to combine targeted and immuno-oncology therapies.

Attacking multiple mechanisms of tumor progression is, of course, a foundational aspect of cancer treatment. The combination dosing represents a balance between the desired increased efficacy and the miserable side effects that result from multi-agent toxicities.

Unfortunately, the balance could not be found in one of the first attempts at combining targeted and immuno-oncology therapies. That trial, combining Yervoy and Zelboraf, was halted because of hepatotoxicity when seven of ten patients experienced severe side effects. In the future, the negative trade-offs may be mitigated in combinations that pair the remarkably clean side-effect profiles of targeted treatments with immuno-oncology approaches where undesirable treatment effects are managed through dosing and supportive care interventions.

If these approaches prove superior, the major challenge could be reimbursement. The very high expectations for immuno-oncology are built on pricing that fully compensates for patient's clinical benefits. If those benefits are only achieved through combination with other high priced therapies, the compensation will need to be shared. This could reduce the appropriate pricing for the immuno-oncology component.

Competition Will Intensify:

BMS, Merck, Roche, and AstraZeneca are the acknowledged leaders in the race to immuno-oncology. However, the industry is full of examples where later entrants leap-frogged the class innovators (think of Lipitor® among the statins or Humira® among TNFα inhibitors). At a minimum, the later entrants chip away at

Figure 10: Compounds Being Used in Combination with PD-1 and PD-1L Products

	Merck	BMS	AstraZeneca	Roche
Nivolumab	Yervoy (BMS) INCB 24360 (Incyte)	Yervoy (BMS) INCB 24360 (Incyte)	Tremelimumab (AZ) INCB 24360 (Incyte)	
Nivolumab	PF-2566 (Pfizer) Talmogene laherparepvec (Amgen)	Varlilumab (CellDex)		
Nivolumab	Inlyta (Pfizer)	Sutent (Pfizer) Votrient (GSK)	Iressa (AZ)	Zelboraf (Roche) Tarceva (Roche)
Nivolumab				Avastin (Roche/Genentech)

the potential market for the leaders.

Given the industry's remarkable efficiency at developing therapies once a target has proven accessible, we can expect a steady introduction of PD-1 and CTLA4 inhibitors. We can also expect a financially renewed biotech industry to pursue additional checkpoints. A 2012 review article in *Nature* suggested twelve additional targets for restoring the immune system's ability to successfully attack tumors¹⁰. Surely, competition will be as robust in this class as in other parts of the industry. Developments in other means of leveraging the immune system are also expected. Notably, chimeric antigen receptor T-cell (CART) therapies are being developed and showing exceptional levels of complete responses. To date, those therapies have been directed at hematology while the approaches discussed in this paper have pursued solid tumors. Cross-over for each treatment approach is anticipated.

Amid emerging competition, manufacturers and investors should remain cognizant of pricing pressures. If durable response levels are comparable and there are no means of differentiating which patients are best served by which therapies, price competition facilitated by payers could emerge. Similar conditions will

exist soon in the market for treating patients with HCV as new competitors emerge for Gilead's Sovaldi®. If payers are successful in guiding patients to lower cost alternatives in that market, they will strive to apply similar tools in immuno-oncology.

The Investment will Be Substantial:

Developing a therapy for multiple oncology indications is an expensive endeavor. As of April 2014, more than 1,600 studies of Avastin could be found in clinicaltrials.gov. In 327 of these trials—evaluating performance in almost 40,000 patients—Genentech was either the sole or a contributing investor.

Early studies suggest immuno-oncology candidates may have utility in even more areas than Avastin. Such investment can strain even the largest research budgets.

Surprisingly then, because the approach may have applicability in so many classes of tumors, one of the governors on immuno-oncology may be the pace at which the industry can invest. Commitments to development in one area may expose flanks where smaller companies with different treatment approaches may enter.

Closing

The excitement about immuno-oncology is well-founded. Never before has a new therapeutic approach with such rich benefits for so many patients been positioned to enter a market where there is a concentrated group of prescribers who's high level of awareness is expected to yield rapid adoption.

Despite the enormous potential, one thing remains certain. Forecasts made today – either for the class or at the product level – will need to be adjusted as new information becomes available. Some areas of uncertainty will be resolved and new information about the commercial environment will become available. Leaders must remain aware of the key factors that

will influence immuno-oncology's ultimate commercial success. There will be no point in time where any of these issues have come to a static resolution. Instead, decision makers will need to constantly monitor developments and incorporate the changes in the landscape into their expectations. In the meantime, the best approach is to build as deep an understanding as possible of the current environment—and honestly identify what is not known. Applying an open mind and creativity to anticipate how the areas of uncertainty may play out, leaders can approach this incredible opportunity with an appropriate level of adjustment to the uncertainty and risks that remain.

About Triangle Insights Group

Headquartered in Research Triangle Park, Triangle Insights Group, LLC is a strategy consulting firm providing guidance on the most critical business issues to leaders in life sciences organizations. The firm's approach combines deep knowledge of the industry across therapeutic areas and functional groups, with a dedication to creativity and disciplined critical thinking. Recommendations from Triangle Insights Group are original, relevant to the industry

environment, and supported by rigorous analytics. Clients of Triangle Insights Group include large pharmaceutical companies, emerging biotechnology firms, diagnostics manufacturers, medical device companies, and private equity investors.

For more information about Triangle Insights Group, visit www.triangleinsights.com or call (919) 813-6079.

¹⁰ Pardoll, D. "The Blockade of Immune Checkpoints in Cancer Immunotherapy," *Nature*, April 2012



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Ben is a member of the Life Sciences Executive Committee of the Licensing Executive Society. He has also been a member of the program committee for the BIO International Convention. Prior to the founding of Triangle Insights Group, Ben was the leader of the Business Development Practice at Campbell Alliance and a partner in the Strategy practice at Oliver Wyman (formerly Mercer Management Consulting/Strategic Planning Associates). Ben earned an M.B.A. from the Stanford Graduate School of Business and a B.S. from Duke University.



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Gautam has provided strategic advice to a wide range of clients, spanning Top-5 pharmaceutical manufacturers, emerging biotechnology manufacturers, bio-pharmaceutical investors, and service providers to bio-pharmaceutical companies. He has spoken at several industry conferences (LES, CED, EBD, BIO-Windhover, CHLA, Banff Venture Forum) and has published a peer-reviewed article on deal timing.

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