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Fighting cancer with the immune system: Hope or hype?

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The United States is spending more than $125 billion on cancer care each year, but our expensive modern medicine has plenty of room for improvement as only 66% of cancer patients live longer than five years, according to the National Institutes of Health (NIH). Investors are beginning to take notice, however, as scientists and drug companies are chasing a new approach, called immuno-oncology, which unleashes the body's immune system to target and kill cancer.

Should investors try to gain exposure to companies working on this new class of cancer drugs? Or do valuations already include the anticipation of a flood of new sales? Our analysis suggests a middle ground, in which investors consider companies with moderate exposure to these new cancer drugs. In contrast, LMIC is more cautious on companies where investors already expect immuno-oncology drug sales to drive meaningful growth, despite limited evidence of safety or efficacy.

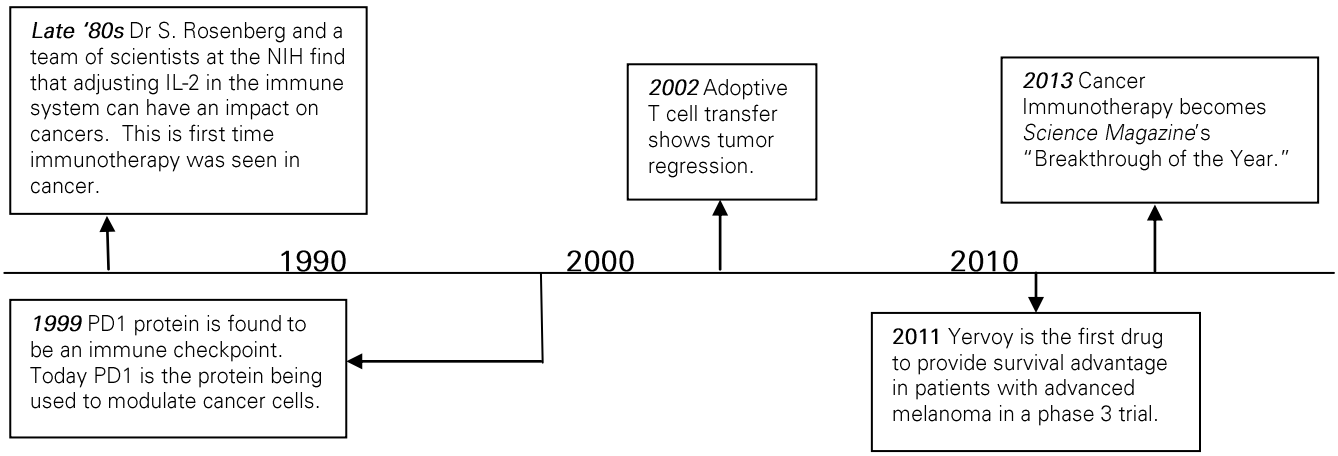
This White Paper explores the scientific rationale for immuno-oncology and looks at some of the upside drivers and downside risks which could impact investors. Our work suggests that investors can benefit from the hope of immuno-oncology while avoiding companies with valuations that seem overly hyped.

What is immuno-oncology?

Immuno-oncology is a branch of treatment dubbed "immuno-therapies," in which drugs are designed to facilitate a reaction from one's own immune system to fight off a disease. Looking at cancer specifically, researchers are using new drugs to induce a reaction from the body's immune system so that naturally occurring T cells can attack the cancerous cells.

The timeline below shows that in the 1980s, scientists began early research on using the immune system to fight cancer. However, research accelerated in the late 1990s and has become more widespread since the 2011 approval of Yervoy, a skin cancer drug using the immune system, which now generates more than $1 billion in annualized sales.

Timeline: How did we get here?



Source: Cancer Research Institute

How does it work?

When a cell is cancerous, it will camouflage itself to copy the image and structure of a healthy cell. Attached to both a cancerous and healthy cell are a number of protein pathways that allow T cells to bind to cancerous cells. Scientists found that a certain protein pathway (PD1 / PDL1) can be blocked, unveiling the true identity of the cancerous cell to the immune system. Using an analogy, PD1 acts like a blindfold that keeps the immune system from seeing a tumor cell. Drugs that remove the blindfold (PDI pathway) can allow the immune system to find and kill the cancer cell.

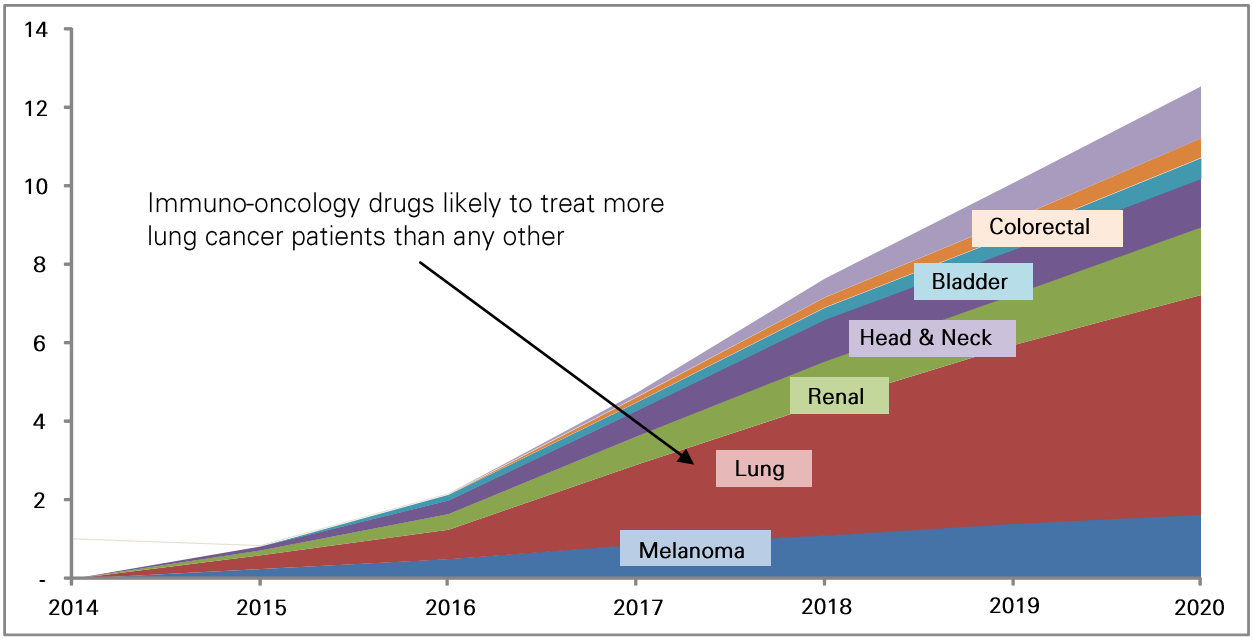
Going after hard-to-treat cancers

Drug companies are using the immune system to target cancers that have proven difficult to treat, resulting in high mortality. For example, the five-year survival rate for lung cancer is a mere 17% (US) compared to 65% for colorectal cancer patients and 89% for people with breast cancer, according to the NIH. With these ranges in mind, scientists are using immuno-oncology drugs to target cancers where existing drugs fail to offer adequate long-term survival, including lung cancer, advanced melanoma (skin cancer), and renal cell carcinoma (RCC).

What happens next?

Two new immuno-oncology drugs using the anti-PD1/PDL1 pathway to treat melanoma are beginning to penetrate the global market. One drug, called Opdivo, won approval in Japan in July 2014 and another, called Keytruda, won approval in the U.S. in September. However, LMIC expects sales for melanoma treatment to be a fairly small market, especially in Japan, and compared to other cancers (lung, renal, head & neck, etc.). The chart below shows that we expect immuno-oncology lung cancer sales to dominate this drug class, starting in 2016-17.

Figure 1. LMIC projections for immuno-oncology sales by disease, 2014-2020 ($ billions)



Source: LMIC estimates

LMIC expects immuno-oncology sales to reach nearly $13 billion by 2020, excluding sales of Yervoy, which won approval in 2011. We start with approximately1.5 million new diagnoses per year for the cancer types in the chart above, and then remove patients with cancers that might be poor candidates for immuno-oncology drugs. We then apply a $100,000 annual price in the U.S. and a $60,000 price in other countries.

Upside Drivers

Scientific data for the new immuno-oncology drugs suggest they will effectively treat cancer patients, while avoiding major side effects. However, we view our 2020 $13 billion sales estimate as generally conservative because the drug class has yet to win approvals in the U.S. or Europe. Despite this conservative approach, we identify at least four upside drivers that could boost 2020 sales above $20 billion:

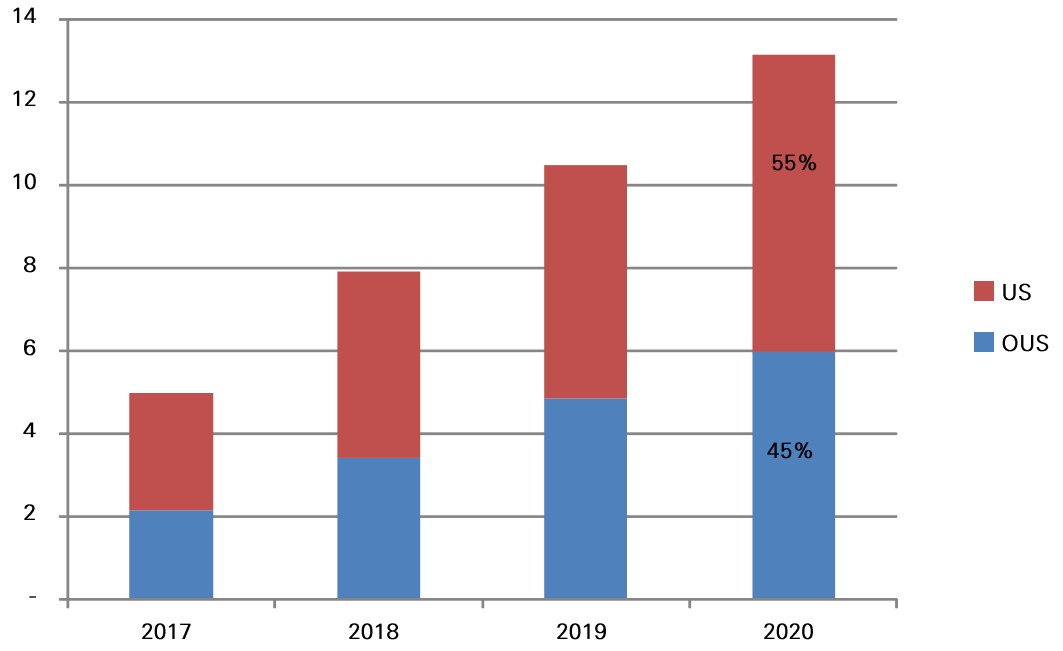
- Combinations: Our model anticipates that patients take only one immuno-oncology drug at a time. However, some doctors believe that a large majority of cancer patients will need to combine more than one immuno-oncology drug to improve survival. In theory, drug combinations could double or triple our sales estimates, although payors may require price discounts if patients combine the new cancer drugs.

- Pricing: Specialty drug pricing is in the headlines this year following the launch of a new hepatitis-C drug, Sovaldi, with an $84,000 price tag. In light of this Sovaldi debate, LMIC anticipates annual pricing of $100,000 for the new immuno-oncology drugs, a slight discount to the ~$120,000 Yervoy price tag. Still, new drug companies could raise the price at or above $120,000 or even higher for combinations. What's more, early pricing indications for Opdivo in Japan and Keytruda in the U.S. suggest immuno-oncology drugs may price at $150,000 per year or more. A 25% increase in pricing above our $100,000 per year estimate drives a $3B increase in our 2020 industry sales estimate.

- Blood cancers: LMIC's current modeling focuses on solid tumors in lung, skin, liver, etc. However, early-stage research in liquid tumors, such as leukemia and lymphoma suggest potential upside to our estimates.

- International vs. United States: Figure 2 below shows that by 2020, LMIC assumes that 55% of anti-PD1/PDL1 sales will be in the U.S. However, LMIC believes that if the anti-PD1/PDL1 market evolves like other cancer markets, the split could approach one-third U.S., two-thirds international, suggesting an additional $9 billion in 2020 sales.

Figure 2. LMIC projections for immuno-oncology sales by geography, 2017-2020 ($ billions)



Source: LMIC estimates

Obstacles Remain

Investors are already anticipating billions of dollars in sales for immuno-oncology drugs and we generally agree that regulators, doctors, patients, and payors will favor the new drug class. However, investors should keep in mind that many of the new immuno-oncology drugs have yet to demonstrate efficacy in large phase 3 trials. What's more, the new drugs could show unexpected side effects as prescription volumes increase after approval. Finally, initial sales could disappoint investors if the immuno-oncology drugs win approval only for smaller indications, such as second or third line therapy.

Conclusion

Harnessing the immune system could provide doctors and patients with a new tool for fighting hard-to-treat cancers. Early data seems to validate the science behind immuno-oncology and our conversations with experts suggest the new drug class has a reasonable chance of succeeding. LMIC expects these drugs to generate at least $13 billion in 2020 sales, and possibly more than $20 billion, if the new cancer drugs overcome key regulatory and commercial challenges. These downside risks could be considerable for companies expecting immuno-oncology drugs to fuel the majority of growth over the next 5-10 years. In contrast, LMIC prefers companies with reasonable valuations and multiple new growth drivers, including potential sales from new immuno-oncology drugs.

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Mike is a Principal at Legg Mason Investment Counsel. His primary responsibility is as an Equity Research Analyst covering the healthcare and insurance industries. Mike is part of a working group including members of equity research and our Socially Responsive Investing (SRI) group focusing on environment, social, and governance (ESG) issues.

Mike earned a B.A. in International Studies from Emory University, an M.A. with Distinction in International Economics and Japan Studies from Johns Hopkins University, and an M.B.A. from Johns Hopkins University. Mike was also Co-President of the Stern Pharmaceutical & Healthcare Association while attending NYU's graduate program at the Stern School of Business. He is a CFA charterholder and participates in the Baltimore CFA Society Mentoring Program.

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