Oncology Revolution: The Rise of Immunotherapy

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Contributors:

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With the arrival of immunotherapy, oncology treatment is undergoing a paradigm shift that is dramatically changing the investment and innovation patterns around cancer-fighting drugs.

The new landscape:

• In 2016, immunotherapy treatments captured 33% of spending on oncology drugs, despite accounting for just 9% of FDA-approved oncology drugs.

• All of the large oncology drug companies are building robust immunotherapy pipelines, driving increased M&A and investor interest.

• Underscoring investor confidence, between 2014 and September 2017 immunotherapy companies on average were acquired at an earlier stage and with less invested capital, generating a higher multiple than other oncology companies. The pipeline of late-stage immunotherapy drugs is large and varied, and is likely to support continued growth for groundbreaking treatments.

Note: Immunotherapy refers to the cancer treatment designed to boost the body's immune system to fight the cancer. Non-immuno targeted therapy refers to the cancer treatment targeting specific genes or proteins that are found in cancer cells or in cells related to cancer growth, other than immune cells. Radiotherapy includes imaging agents.

Sources: BiomedTracker, Pitchbook
Key Points

**Newcomer immunotherapies capture outsize dollar sales.**
- In 2016, immunotherapies achieved dollar volume market share (33%) disproportionate to their share of FDA-approved oncology drugs (9%)

**Immunotherapies have rapidly become a required component of any leading oncology portfolio.**
- But there is wide variation in how the market leaders have positioned themselves for future growth

**Immunotherapy dominates oncology M&A.**
- Immunotherapy M&A deals have risen from 31% of total oncology deals in 2014 to 70% in the first half of 2017

**Immunotherapy companies exit earlier in drug development, with less invested capital and at a higher return on invested capital than other oncology companies.**
- Immunotherapy companies were acquired at a median of nine times invested capital as compared to seven times for non-immuno targeted oncology drugs since 2014

**PD-1/PD-L1 combination trials underpin the rise of immunotherapy.**
- By 2015, combo trials with PD-1/PD-L1 therapies accounted for a third of all combo trials in oncology

**Robust late-stage immunotherapies pipeline predicts continued growth.**
- With over 10 phase III immunotherapies in development, their market share will only continue to grow, but interclass cannibalization is also expected
Immunotherapy Drug Sales Take Off

Immunotherapy drugs captured one-third of U.S. oncology drug sales in 2016

Immunotherapy treatments accounted for 33% of oncology drug sales in 2016 but made up just 9% of FDA-approved oncology drugs.

Increased use of immunotherapy and non-immuno targeted therapies in combination has expanded treatment options for patients and spurred an increase in overall dollars spent on drugs.

Sources: BiomedTracker, Corporate Reports. As of 12/31/2016.
Oncology Leaders Vary Immunotherapy Strategies

Oncology strategy to stay on top: Build, buy or partner

Strong pipelines from market leaders indicate a dynamic future for immunotherapy drugs.

Celgene and Novartis are establishing strong market share with a single approved immunotherapy drug targeting multiple indications.

Roche and Bristol-Myers Squibb are launching treatments aimed at a variety of indications.

Note: As of 6/30/2017.
Sources: BiomedTracker, ClinicalTrials.gov, Press Releases, Company Website.
Immunotherapies Now Dominate Oncology M&A

Immunotherapy Accounts for 70% of Oncology M&A through Q3 2017

Responding to competition, biopharma’s appetite for acquiring immunotherapy companies is growing. Immunotherapy M&A deals rose from 31% of oncology deals in 2014 to 70% in 2017 (through Q3).

Sources: BiomedTracker, Corporate Reports. As of 12/31/2016. *Includes Q1 through Q3 2017.
Investors Reap Healthy Returns from Immunotherapy M&A

Immunotherapy companies exit earlier in drug development, with less invested capital and higher return multiples than other oncology companies.

Return on invested capital (2014 to Q3 2017)

Stage at Acquisition:  
- Clinical
- Preclinical

- Immunotherapies
  - Median Invested Capital: $32M
  - Median Deal Size: $277M
  - Return on invested capital: 9x
  - 38% Clinical, 62% Preclinical

- Non-immuno targeted therapies
  - Median Invested Capital: $100M
  - Median Deal Size: $485M
  - Return on invested capital: 7x
  - 67% Clinical, 33% Preclinical

The median multiple from immunotherapy activity between 2014 and 1H 2017 was nine times compared to seven times for other oncology investments.

Highlighting the competition to get in early, more than 60% of immunotherapy companies acquired were preclinical.

Note: Includes 79 strategic acquisition deals in the oncology therapeutics market between 1/1/2014 to 9/30/2017 and 37 deals with disclosed financing history and deal value. Oncology diagnostics, medical devices, research tools and services are excluded. Sources: Company Websites, Pitchbook, Press Releases.
Combo Strategy Bolsters Immunotherapy Pipeline

Combining immunotherapy/non-immuno targeted therapies has spurred higher overall oncology drug sales and shows little sign of slowing down.

Number of new combination therapy oncology trials with PD-1/PD-L1 inhibitors

<table>
<thead>
<tr>
<th>Year</th>
<th>% of all new combination oncology trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>3%</td>
</tr>
<tr>
<td>2014</td>
<td>13%</td>
</tr>
<tr>
<td>2015</td>
<td>31%</td>
</tr>
<tr>
<td>2016</td>
<td>37%</td>
</tr>
<tr>
<td>1H 2017</td>
<td>37%</td>
</tr>
</tbody>
</table>

Sources: BiomedTracker, ClinicalTrials.gov, Press Releases.

PD-1/PD-L1 inhibitors are effective as monotherapies in about a third of patients, which is fueling rapid growth in combination trials based on PD-1/PD-L1 drugs.

The first PD-1/PD-L1 inhibitor was FDA-approved in 2014. Since 2015, PD-1/PD-L1 combo trials have comprised about a third of all new oncology clinical trials.
# Diversified Late-Stage Drug Pipeline Derisks Immunotherapy Market

A large and diverse number of late-stage therapies in development mean more new treatments for patients, but competition and phase III failures make it anyone’s game.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Current Phase</th>
<th>Modality</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTL019</td>
<td>Novartis</td>
<td>Approved</td>
<td>Cell therapy</td>
<td>CAR-T/CD19</td>
<td>Acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>Axicabtagene Ciloleucel</td>
<td>Gilead (Kite)</td>
<td>BLA</td>
<td>Cell therapy</td>
<td>CAR-T/CD19</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Vigil EATC</td>
<td>Gradalis</td>
<td>III</td>
<td>Vaccine</td>
<td>Furin/GM-CSF</td>
<td>Ovarian cancer, breast cancer</td>
</tr>
<tr>
<td>Axalimogene Filolisbac</td>
<td>Advaxis</td>
<td>III</td>
<td>Vaccine</td>
<td>HPV</td>
<td>Cervical cancer</td>
</tr>
<tr>
<td>Epacadostat</td>
<td>Incyte</td>
<td>III</td>
<td>Small molecule</td>
<td>IDO1</td>
<td>Melanoma</td>
</tr>
<tr>
<td>AM0010</td>
<td>ARMO Biosciences</td>
<td>III</td>
<td>Small molecule</td>
<td>IL-10/IL-10R</td>
<td>Pancreatic cancer</td>
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<tr>
<td>SHR-1210</td>
<td>Incyte</td>
<td>III</td>
<td>Antibody</td>
<td>PD-1</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>PDR001</td>
<td>Novartis</td>
<td>III</td>
<td>Antibody</td>
<td>PD-1</td>
<td>Melanoma</td>
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<tr>
<td>REGN2810</td>
<td>Regeneron</td>
<td>III</td>
<td>Antibody</td>
<td>PD-1</td>
<td>Non-small cell lung cancer</td>
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<tr>
<td>Prostvac(1)</td>
<td>Bavarian Nordic</td>
<td>III</td>
<td>Vaccine</td>
<td>PSA</td>
<td>Prostate cancer</td>
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<tr>
<td>Seviprotimut-L</td>
<td>Polynoma</td>
<td>III</td>
<td>Vaccine</td>
<td>Immune system</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Tedopi</td>
<td>OSE Immunotherapeutics</td>
<td>III</td>
<td>Vaccine</td>
<td>Immune system</td>
<td>Non-small cell lung cancer</td>
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<td>DCVax</td>
<td>Northwest Biotherapeutics</td>
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<td>Vaccine</td>
<td>Immune system</td>
<td>Brain cancer</td>
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<td>TT10 EB-VST</td>
<td>Tessa Therapeutics</td>
<td>III</td>
<td>Cell therapy</td>
<td>EBV</td>
<td>Head and neck cancer</td>
</tr>
</tbody>
</table>

More than 10 phase III immunotherapy drugs targeting a wide variety of indications are currently in development.

There have been some phase III clinical trial failures that could lead to slower growth.

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(1) Announced negative phase III results on 9/25/17.

Note: As of 6/30/2017.

Sources: BiomedTracker, ClinicalTrials.gov, Press Releases.
Andrew Olson, Ph.D. is a Life Sciences Manager at SVB in San Francisco, where he performs strategic advisory services with a focus on biotech mergers and acquisitions. Combining his extensive training as a chemist with his passion for the commercial side of innovation, Andrew is a valuable partner to both early-stage and larger biotech companies.

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Xiaoqi Liu, formerly of SVB, contributed greatly to this report while he was an associate at the firm.
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