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02 Jun 2016 |

Immuno-Oncology's Next Wave: Key Targets And Emerging Players

by Mandy Jackson

Doesn't every biopharma company have an immuno-oncology strategy these days? It certainly seems that way, considering the number of drug developers that are labeling their therapeutic candidates as immunotherapies regardless of whether the description truly fits their asset.

While there are plenty of drug makers that aren't developing cancer treatments, there's no denying that immuno-oncology (IO) is the hottest ticket in biopharma today based on the ever-increasing number of novel IO targets, the growing pipeline of immunotherapies in development, and the volume of dealmaking in the space.

The companies who've been first to market with programmed cell death-1 (PD-1) and PD ligand-1 (PD-L1) checkpoint inhibitors are leading the way forward in immuno-oncology: *Bristol-Myers Squibb Co.* with *Opdivo* (nivolumab), *Merck & Co. Inc.* with *Keytruda* (pembrolizumab) and, just recently, *Roche*'s *Genentech Inc.* subsidiary with *Tecentriq* (atezolizumab). Following close on their heels with Phase III compounds are *AstraZeneca PLC* with durvalumab and avelumab from partners *Pfizer Inc.* and *Merck KGAA*. (Also see "*Early Tecentriq OK Gives Roche/Genentech Jump On PD-L1 Bladder Cancer Market*" - Scrip, 18 May, 2016.)

Bristol-Myers is likely to maintain its commercial lead, and possibly it's lead in the clinic, since Merck's Keytruda revenue lags Opdivo, which got the early lead in the lucrative lung cancer market. And, unlike Keytruda, Opdivo's label doesn't require lung cancer patients' tumor samples to be screened for PD-L1 expression levels. (Also see "*Bristol Getting Eagerly Awaited First-Line Opdivo Lung Data Earlier Than Expected*" - Scrip, 28 Apr, 2016.) Bristol's immuno-oncology edge in sales and clinical programs is boosted by the firm's first approved checkpoint inhibitor, the cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor *Yervoy* (ipilimumab), for patients with unresectable or metastatic melanoma. Bristol then nabbed the first combination approval, for Opdivo and Yervoy in melanoma, and is leveraging both as the base for IO combinations.

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Ten Key Targets, Most Drugs Preclinical

But PD-1/PD-L1 and CTLA-4 are just the beginning for immuno-oncology as the field expands to other mechanisms and from single-agent therapies to therapeutic combinations that not only take the brakes off of the immune system, but also shift it into overdrive for an even more aggressive attack against tumor cells.

Scrip looked at 10 different immuno-oncology targets for the purposes of this report and spoke with some companies that are focused on novel immunotherapies based on these other targets. The field is so new, however, that most programs still are in early stages of development.

Of 10 targets with 99 different immunotherapies in development, only five have been approved, 39 are in the clinic and 55 are preclinical, according to Pharma Intelligence's Biomedtracker database. Those 10 targets are: PD-1/PD-L1, CTLA-4, granulocyte-macrophage CSF or its receptor (GM-CSF/GM-CSFR), lymphocyte-activation gene 3 (LAG3), T-cell immunoglobulin and mucin domain 3 (TIM3), toll-like receptor (TLR) family, indoleamine 2,3-dioxygenase (IDO), cluster of differentiation 47 (CD47), CD40 and OX40 (CD134). (Also see "*Scrip's Rough Guide to Immuno-Oncology*" - Scrip, 1 Jun, 2015.)

These targets generally are addressed by monoclonal antibodies, small molecule drugs and therapeutic vaccines, but cell therapies also are an important modality for the immuno-oncology field. Two out of the top 10 therapies to watch in *Scrip*'s preview of the American Society of Clinical Oncology (ASCO) annual meeting from June 3 to 7 in Chicago are chimeric antigen receptor T-cell (CAR-T) therapies from *Juno Therapeutics Inc.* and *Novartis AG*. (Also see "*Ten Programs To Watch Out For At ASCO*" - Scrip, 20 May, 2016.)

However, there are no approved CAR-T therapies. The five FDA-approved immuno-oncology agents include four monoclonal antibodies and one oncolytic viral therapy – *Amgen Inc.*'s *Imlygic* (talimogene laherparepvec), which produces the immuno-stimulatory protein GM-CSF and is indicated for local treatment of unresectable melanoma lesions that recur after surgery. (Also see "*Amgen's Imlygic 1st FDA-Approved Oncolytic Virus Therapy*" - Scrip, 28 Oct, 2015.)

The PD-1/PD-L1 inhibitors, Yervoy, Imlygic and the forthcoming CAR-T therapies were preceded by *Dendreon Corp.*'s *Provenge* (sipuleucel-T), an autologous cellular immunotherapy. However, the prostate cancer treatment generally has been a commercial failure with Dendreon filing for bankruptcy to pay its debts and selling Provenge and related assets to *Valeant Pharmaceuticals International Inc.* in 2015. (Also see "*Valeant ups bid for Dendreon's Provenge to $400m*" - Scrip, 6 Feb, 2015.)

Early-Stage Doesn't Reduce Excitement

Among the 10 targets *Scrip* reviewed recently, only 40% of the therapeutic candidates in the pipeline are being studied in humans and only four therapies are in Phase III clinical trials.

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Another five are in Phase II, seven are in Phase I/II and 23 are in Phase I trials. Yet the early stage of development in these targets hasn't reduced the interest in them.

In fact, Genentech probably wouldn't present its Phase I data for the OX40 inhibitor RG7888 (MOXR0916) at ASCO, given the monoclonal antibody's early development stage. But there is so much interest in immuno-oncology, especially in relation to new targets, that the company decided to share its OX40 data at the annual cancer treatment meeting, Genentech VP-BioOncology and Exploratory Clinical Development Stuart Lutzker told *Scrip*. The company also wanted to share noteworthy efficacy that's been observed even in early dose escalation results.

In a June 4 presentation at ASCO, data will show objective response rates among 44 patients treated with RG7888 plus the company's newly approved PD-L1 inhibitor Tecentriq in seven different dose cohorts (n=25) and a serial biopsy cohort (n=19) during the Phase I dose escalation portion of an ongoing clinical trial. The abstract indicates that the combination was well tolerated with no treatment-related adverse events leading to study discontinuation. Efficacy data will be presented at the meeting.

Genentech Vice President Stuart Lutzker

Source: Genentech Inc.

Lutzker noted that patients with sarcoma – a group that hasn't been well-served by anti-PD-1 monotherapy – and renal cell carcinoma were among the Phase I study's participants, which included five people previously treated with a PD-1 inhibitor. Some of the renal cell carcinoma patients had confirmed partial responses and some patients experienced tumor shrinkage.

"We think that mechanistically [RG7888] will work best in a combination," Lutzker said. "Atezolizumab as a single agent provides benefit to patients, but we think the benefit could be enhanced by an agonist antibody that increases the pool of effector immune cells where atezolizumab takes the brakes off the immune system. We think that's a very exciting combination."

Biomedtracker analysts were optimistic about RG7888 in a mid-May report issued after ASCO released abstracts for its annual meeting. "The observation of objective responses here is promising, particularly if the five patients who had previously received PD-1/PD-L1 antibody therapy showed enhanced responses," the report notes.

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Combinations To Follow In PD-1 Footsteps

Regeneron Pharmaceuticals Inc. also has a PD-1 inhibitor in the clinic – the mid-stage biologic REGN2810 – that it's developing as a backbone for immunotherapy combinations that contain the company's other immune system-boosting therapeutic candidates.

Regeneron Chief Scientific Officer and President of Regeneron Laboratories George Yancopoulos told *Scrip* in an interview during the J.P. Morgan Healthcare Conference in January that combinations can improve the impressive efficacy seen with PD-1 inhibitor monotherapy and the right combinations will do so with manageable side effects. (Also see "*IPM Parting Shots: Immuno-Oncology Plans For Regeneron, Incyte, Molecular Partners*" - Scrip, 16 Feb, 2016.)

"There are few companies that have made a long-term, deep commitment in this area, years ago, to come up with a lot of different potential agents to bring to bear on this problem," Yancopoulos said.

Preclinical programs in Regeneron's immuno-oncology portfolio include therapies that target LAG3 and glucocorticoid-induced tumor-necrosis-factor-receptor-related protein (GITR). The company also has a Phase I bispecific antibody called REGN1979 that targets CD20 on B cells and CD3 receptors on T-cells.

Regeneron Pharmaceuticals Inc. CSO George Yancopoulos

Regeneron Pharmaceuticals Inc.

Regeneron and *Sanofi* agreed to expand their long-term relationship in July with a new collaboration worth more than $2bn to Regeneron, including a $640m upfront fee, to co-develop immuno-oncology therapies. The deal included REGN2810, which is in Phase II for the treatment of advanced cutaneous squamous cell carcinoma – a study that could support US FDA approval. (Also see "*Sanofi plays catch-up in immuno-oncology with new Regeneron deal*" - Scrip, 28 Jul, 2015.)

In Phase I data for REGN8210 that will be presented at ASCO on June 5, the disease control rate was 62.8% in patients with solid tumors, including 27 out of 43 clinical trial participants who achieved complete responses, confirmed and unconfirmed partial responses, or stable disease.

Less Competition, But A Lot Of Interest

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Incyte Corp. has one of the hottest properties in immuno-oncology, an IDO inhibitor called epacadostat that is or will be tested in combination with all three of the approved PD-1/PD-L1 inhibitors as well as AstraZeneca's PD-L1 inhibitor durvalumab. There are just eight IDO-targeting therapies in the development pipeline with only three in the clinic, although two of the clinical drug candidates are in Phase II, including epacadostat.

Scrip also interviewed Incyte Chairman, President and CEO Herve Hoppenot about his company's immuno-oncology pipeline during the J.P. Morgan Conference in January, and Hoppenot claimed that Wilmington, Delaware-based Incyte began developing its IDO inhibitor before anyone else was interested in the target. Now, the company has clinical collaborations with multiple big pharma players to test its drug in combination with their PD-1/PD-L1 inhibitors. (Also see "*Merck, AZ, Roche, BMS work off grid for mix-and-match immuno-oncology*" - Scrip, 12 Jun, 2015.)

Incyte and Merck announced a pivotal Phase III clinical trial in October to test Keytruda plus epacadostat as a first-line treatment for advanced metastatic melanoma. Other epacadostat trials include a Phase I/II study with Keytruda and another in combination with Opdivo in certain advanced solid tumors and lymphomas; a Phase I study with Tecentriq for previously treated metastatic non-small cell lung cancer (NSCLC); and a Phase I/II study in combination with durvalumab for certain advanced solid tumors. (Also see "*Incyte and Merck Push I/O Drug Forward*" - Scrip, 13 Oct, 2015.)

And like Regeneron, Incyte also is developing its own PD-1 inhibitor – an asset licensed from *Jiangsu Hengrui Medicine Co. Ltd.* in September – which it will market in combination with its other immuno-oncology drugs. The Hengrui deal was about "adding optionality to our portfolio for the long term," Hoppenot said. (Also see "*Incyte, Hengrui In 'Biggest Ever' China Pharma Out-Licensing Deal*" - Scrip, 4 Sep, 2015.)

"We have to prove that a PD-1 inhibitor plus an IDO drug is better than PD-1 plus CLTA-4," he said.

Forget Boosting Anti-PD-1 Therapies; Can A PD-1 Inhibitor Boost Novel Agents?

PD-1 inhibition may be just the savior that Berkeley, California-based *Aduro Biotech Inc.* needs to rescue its lead development program. Aduro had a setback recently with two of its lead therapeutic candidates in the Phase IIb ECLIPSE clinical trial testing its immunotherapies CRS-207 and GVAX Pancreas in patients with advanced pancreatic cancer.

Median overall survival for patients with metastatic pancreatic cancer, who failed at least two prior therapeutic regimens and were treated with the company's combination of CRS-207 and GVAX Pancreas, was 3.8 months – significantly lower than the 5.4 months of survival achieved by patients treated with CRS-207 alone and 4.6 months for individuals who received chemotherapy. (Also see "*Stockwatch: Fireworks Or Ballistic Missiles In Biotechnology?*" - Scrip, 23

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May, 2016.)

CRS-207 is a product of Aduro's live, attenuated, double-deleted Listeria monocytogenes (LADD) technology. It uses the listeria virus to deliver mesothelin to provoke an immune system attack against tumor cells expressing that antigen. GVAX Pancreas is a cell-based cancer vaccine that is designed to induce an immune response against multiple pathogens, including GM-CSF.

Aduro Chairman, President and CEO Stephen Isaacs noted during a conference call after the ECLIPSE results were revealed on May 16 that late-stage, metastatic pancreatic cancer is very difficult to treat, but he said the company still was "surprised" that the Phase IIb results diverged from Phase IIa data for Aduro's combination regimen. (Also see "*Aduro shows survival benefit with pancreatic cancer vaccine duo* " - Scrip, 16 Jan, 2014.)

While the company will no longer pursue CRS-207 plus GVAX for heavily pre-treated pancreatic cancer patients, Aduro remains hopeful for success in the ongoing Phase II STELLAR trial, which is testing CRS-207 and GVAX in combination with Opdivo versus CRS-207 and GVAX alone in metastatic pancreatic cancer patients who've gone through one prior round of chemotherapy.

Aduro Biotech Inc. CEO Stephen Isaacs

Aduro Biotech Inc.

William Blair analyst John Sonnier said in a May 16 research note that Aduro's LADD platform is likely to perform well when used in combination with other immunotherapies, because it "has continually shown the ability to stimulate an immune response to the target antigen while also exhibiting a favorable safety profile."

There are higher hopes for the STELLAR trial. Prior to the ECLIPSE failure, Isaacs told *Scrip* in an interview that "We all hope the ECLIPSE trial is positive, and we think it will be, but we think STELLAR will be even better."

Sonnier noted that overall survival for advanced pancreatic cancer patients treated with standard-of-care chemotherapy combinations is six to eight months, so STELLAR will have to exceed that to prove the value of CRS-207 and GVAX in combination with Opdivo.

In addition to STELLAR, Aduro is testing CRS-207 plus Incyte's epacadostat in a Phase I/II

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clinical trial called SEASCAPE, which began in March to evaluate the combination in up to 126 women with platinum-resistant ovarian, fallopian or peritoneal cancers. Aduro is funding the trial, but Incyte is supplying its drug for the study; neither firm has any rights to the other company's asset.

Beyond The 10 Key Targets, But Still Combined With PD-1

Armo BioSciences Inc. has a fresh perspective on immuno-oncology outside of key targets like PD-1 and IDO. The company is developing pegylated formulations of recombinant human interleukins, starting with lead program AM0010, a pegylated Interleukin 10 (IL-10) that's being studied in a Phase I/Ib clinical trial. ARMO's $50m Series C venture capital round, which closed in February, will fund a Phase II/III trial and support clinical development of pegylated versions of additional cytokines – IL-12 and IL-15. (Also see "*ARMO Rides Immuno-Oncology Wave With $50m For Its PD-1 Booster*" - Scrip, 17 Feb, 2016.)

The drug candidates are designed to boost the activity of PD-1 inhibitors and other first-generation immuno-oncology therapies. A cytokine, such as a pegylated interleukin, should cause the immune system to produce more T-cells, so that the immune system is more fully activated upon administration of an anti-PD-1 therapy or chemotherapy.

The combination could make PD-1 inhibitors viable treatments for cancers in which they are not particularly effective as a monotherapy, such as pancreatic, triple-negative breast and colorectal cancers. ARMO is testing AM0010 with approved PD-1 inhibitors, but the company is developing its own anti-PD-1 therapy that it plans to study in combination with its pegylated IL-15 in a Phase I trial that could kick off in 2017.

Data from 24 patients with advanced pancreatic cancer who were treated with AM0010 alone or with chemotherapy and 16 patients with colorectal cancer who received AM0010 monotherapy will be presented in a poster session during ASCO on June 5. Four patients achieved greater than six months of progression-free survival. The median overall survival among 20 pancreatic cancer patients was 5.1 months, while median overall survival was 15.4 months for 13 colorectal cancer patients.

Data also will be presented on June 5 at ASCO in a poster for AM0010 in combination with a PD-1 inhibitor, including objective responses observed in four out of eight renal cell carcinoma, two out of five NSCLC patients, and two out of six melanoma patients.

ARMO and its IL-10-targeting therapy could be a surprise hit at the ASCO meeting, although as a private company it has no stock price to indicate what investors think of the data. Even so, stock analysts are watching ARMO's early results to see whether the IL-10 data live up to early expectations.

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Leerink analyst Seamus Fernandez described the ARMO data as the "most interesting" combination immunotherapy results that will be presented during the ASCO meeting.

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