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Roche Pushes The Boundaries Of Cancer Immunotherapy

by Bridget Silverman

Roche is betting that its tumor immunophenotype research can guide combination therapy that will alter the tumor microenvironment, making tumor types than have been resistant to PD-1/L1 inhibitors sensitive to immunotherapy.

Roche's long-term focus on the biology of the cancer immune cycle may ultimately help the cancer specialist gain an edge in the immuno-oncology field, by allowing the company to move cancer immunotherapy (CIT) into previously unresponsive tumor types.

Although Roche has long held the top spot in the oncology field, it was slower off the blocks than some rivals with CIT, as the early lead went to competitors *Bristol-Myers Squibb Co.* and *Merck & Co. Inc.* in immuno-oncology.

Roche's lead CIT product, the immune checkpoint inhibitor *Tecentriq* (atezolizumab), was the third PD-1/L1 inhibitor to reach the US market. But the firm's extensive clinical trial program has also fed massive amounts of biomarker and outcomes data back into its research engine, allowing Roche and its subsidiary *Genentech Inc.* to investigate why CIT works in some tumors, like melanoma, lung and bladder cancers, but has not been effective in others, like colorectal cancer.

In the past, the company has played up its early research into immuno-oncology – Roche's Global Head of Cancer Immunotherapy Dan Chen and Genentech VP-Cancer Immunotherapy Ira Mellman authored some of the pivotal research on the cancer immunity cycle – and how it is leveraging its diagnostics capabilities to amass and exploit a massive amount of data.

Roche's Oncology Strategy: The Long Game Comes Into Focus

By Bridget Silverman

Roche has used this information about immune response, biomarkers and outcomes to refine its tumor immunophenotype model. "This type of categorization then helps us to design our clinical trials," Roche Chief Medical Officer Sandra Horning told a June 5 analyst meeting held in conjunction with the American Society of Clinical Oncology annual meeting. "It helps us with prioritization and rational immunotherapy combinations."

15 Jun 2015
Roche may be behind Merck and Bristol in the PD-L1/PD-1 immune checkpoint inhibitor race, but its patient plans for atezolizumab are starting to demonstrate the power of the company's strategy of combining "comprehensive diagnostics" and a broad pipeline to establish a dominant position in immuno-oncology.

Read the full article here

Combinations are where Roche has been planning to shine, taking full advantage of its oncology pipeline to test IO in combination with other IO mechanisms, targeted therapy and chemotherapy. (Also see "*For Roche Immuno-Oncology, It's Steady As She Goes*" - Scrip, 24 Jun, 2016.)

It is the increasing understanding of the immune response that is bearing out the idea that combinations to turn "cold" tumors that wouldn't respond to IO into "hot" tumors that are primed to respond, and that is playing out across the industry. It also may be the area where Roche is best positioned to differentiate itself in the increasingly competitive sector.

PD-1/L1 inhibitors are often described as "releasing the brakes" on the immune system, but Roche has found that anti-tumor immune response can only be accelerated if the tumor already shows some level of immune response. The company is now striving to use combination regimens and new approaches to activate sluggish or potential immune response and to generate de novo immune response.

Roche's ability to design rational combinations that could expand the use of immunotherapy to patients who would not respond to first-generation CIT agents comes from the company's long-term, science-driven strategy. It bet that increasing knowledge about the cancer immune cycle ultimately would be more valuable than being first to market or achieving early market dominance, a strategy that is starting to play out.

Follow The Immunophenotypes

The refinement of Roche's immunophenotype model has been rapid, in turn spurring rapid pipeline expansion. As recently as the 2014 ASCO meeting, Mellman described the idea that "tumors defend themselves against T-cell attack by creating an environment that is inherently immunosuppressive" as a "dramatic" and "very, very recent" conceptual advance. (Also see "*Roche Sees Biomarker-Guided Discovery As Key To Unlocking Tumor Microenvironment*" - Pink Sheet, 18

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Jun, 2014.)

The company came to the June 2017 meeting, just three years later, with 12 novel cancer immunotherapies in the clinic and one on the market. *(See sidebar.)*

Roche quickly homed in on the role of inflammation in the cancer immune cycle, initially characterizing tumors as either inflamed or uninflamed based on the activity of CD8 T-cells. (Also see "*Beyond PD-1: Roche Maps Further Checkpoints On Cancer Immune Cycle*" - Pink Sheet, 15 Jun, 2015.) Now, however, "the work that we've done to-date with biomarkers has really led us to think that there are three basic types of immune profile or immune phenotype that exist in tumors," Mellman explained, known as the immune-inflamed, immune-excluded, and immune-desert phenotypes. (*See graphic below.*)

A Quick Primer On Roche's Immuno-Oncology Assets

By Bridget Silverman

08 Jun 2017

Roche's broad cancer immunotherapy pipeline features a dozen novel agents, including the first candidates from new therapeutic platforms for bispecific antibodies and personalized cancer vaccines.

Read the full article here

Tumors with the inflamed phenotype show infiltration by CD8+ T-cells and "some level of objective immunity," so the goal of immunotherapy is to accelerate or "remove the brakes" on T-cell response, he explained. "Most of the responses that we see to Tecentriq and to similar agents in fact fall within this group," Mellman noted. Melanoma and lung cancers are notably inflamed tumors.

Patients in the immune-excluded group "seem to have T-cell responses, but those T-cells have difficulty actually in entering the tumor and often can be shown to be sequestered in the stroma that often surrounds the tumor," Mellman continued. The goal of therapy for immune-excluded tumors, which include triple-negative breast cancer, is to bring T-cells in contact with cancer cells.

"Finally, there is the immune desert, where one finds patients that are generally devoid of any evidence whatsoever of T-cell immunity coursing into their tumors," Mellman said. "And as a consequence, these are individuals for whom we may have to generate immunity de novo," for instance by increasing the number of antigen-specific T-cells or by increasing antigen presentation.

"The excluded and the desert areas do represent, I think, great opportunities, and also great areas

for unmet need," Mellman stated. Such areas include the major market of colorectal cancer, as well as gastric and ovarian cancer.

"The cancer types that have not yet responded well to what I would call the checkpoint inhibitors or first-generation cancer immunotherapies are very large," Roche Pharmaceuticals CEO Daniel O'Day said. "We're talking about more than 70% of the potential out there. You can see colorectal at about 150,000 [patients,] pancreas 57,000, gastric 59,000."

Roche is hardly alone in seeing the market opportunity in patients who fail first-wave immunotherapy, but it may be the company with the most systematic and disciplined campaign. Bristol also has a broad pipeline looking at many of the same new mechanisms to activate immune response in patients who failed or relapsed after existing CIT, but Bristol Head of Early Oncology Development Tim Reilly used words like "daunting" and "haphazard" to describe it in an interview with *Scrip* during ASCO. (Also see "*BMS's Early Oncology Head On Novel IO Approaches & Disruptions*" - Scrip, 4 Jun, 2017.)

Bristol's New Chief Scientific Officer Lists Oncology Priorities, But Little New

By Lucie Ellis-Taitt

06 Jun 2017
At ASCO, Bristol-Myers-Squibb's new Chief Scientific Officer Thomas Lynch highlighted key R&D priorities for advancing the company's cancer pipeline and staying ahead of its competitors.

Read the full article here

Roche is also the most active oncology trial sponsor. A Trialtrove analysis of clinical trials completed in 2016 found that Roche was the sponsor of more oncology trials than any other company by a sizable margin. (Also see "*Clinical Trial Snapshot 2016: Novartis Leads On Volume, But Novo Nordisk Posts Highest Success Rate*" - Scrip, 30 May, 2017.)

Changing The Immune Context

Roche's Cancer Immunotherapy Pipeline

Roche's Tecentriq combination strategy goes beyond the traditional combination chemotherapy method of bringing different methods of killing cancer together in an anti-tumor package – instead it is trying to use non-CIT drugs to alter the tumor microenvironment so that Tecentriq can work. *AstraZeneca PLC* is similarly testing whether its DNA damage response inhibitors, like the PARP inhibitor *Lynparza*, can prime tumors for treatment with immunotherapy.

Roche's strategy benefits from its vast oncology pipeline, which provides a wealth of combination options even before deal-making brings in external candidates. As Mellman said,

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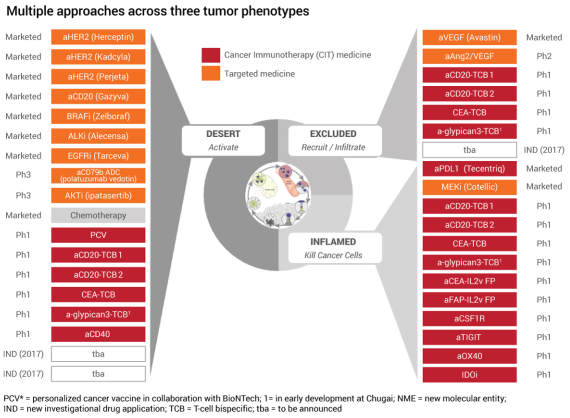
Roche is "very committed" to understanding "how we can leverage our targeted agent pipeline in conjunction with immunotherapies."

One of the most advanced examples of the targeted therapy/immunotherapy approach is Roche's combination of its MEK inhibitor *Cotellic* (cobimetinib) with Tecentriq, a pairing that is currently being studied in Phase III for first-line metastatic melanoma and third-line treatment of advanced colorectal cancer.



Source: Source: Roche presentation to analysts June 5, 2017, during the American Society for Clinical Oncology annual meeting in Chicago

Mellman called Cotellic an "unexpected combo partner" for Tecentriq. "MEK [inhibition] shouldn't have worked, because we all know the T-cells, in order to become primed to recognize their targets, require MAP kinase signaling," he said; in "immune-excluded" and "immune-desert" cancers, which include most CRC patients, single-agent Cotellic has not shown activity.

Nor, as Chen pointed out at last year's ASCO meeting, have anti-PD-1/L1 immunotherapies like Tecentriq. "We think that some of the reasons why colon cancer may not respond [to single-agent immunotherapy] is that you get things like down-regulation of MHC class 1 in colon cancer, the molecule that's required to show there's something foreign. If a cancer cell down-regulates that protein, it can become invisible to T cells." (Also see "*Q&A: Roche's Dan Chen Talks Immuno-Oncology Combinations*" - Pink Sheet, 20 Jun, 2016.)

"What was really surprising," Mellman said, and "what we've been now leveraging in the clinic is the fact that MEK also blocks the process of T-cell exhaustion, or at least inhibits it, without really affecting any aspect of other ... T-cell biology." The MEK inhibitor Cotellic's direct effects on T-cells and the tumor microenvironment, including reversing the down-regulation of MHC class 1, thus "may help to unlock the full anti-tumor potential of PD-L1 inhibition."

Roche followed up last year's presentation of early-phase Tecentriq/Cotellic data in CRC with data from two Phase Ib studies of the drugs in melanoma. The melanoma studies provided "encouraging" data, including a mean progression-free survival of 15.7 months for the two-agent combo compared with 5.5 months for Tecentriq alone in first-line treatment of metastatic melanoma. Early data from another Phase Ib study that added the BRAF inhibitor *Zelboraf* (vemurafenib) to Tecentriq and Cotellic in first-line BRAF mutation-positive melanoma found an 82% overall response rate.

The Phase Ib studies helped move Tecentriq/Cotellic into a "large" Phase III program in metastatic melanoma, Mellman indicated. The IMspire150 study of the triple regimen with Zelboraf is ongoing in first-line BRAF v600 mutation-positive patients, and the company is planning the IMspire170 trial in first-line BRAF wild-type metastatic melanoma.

Comprehensive Oncology Strategy

Roche's clinical program was designed to generate massive amounts of data on biomarkers and cancer biology, thanks to trial-design measures like routine, repeated biopsies as well as investment in diagnostic and analytic technology, from assays to the ISIS digital pathology system. As Roche's Chen said in an interview at ASCO 2016, "we believe because we have so much biologic data collected from those studies, it will help us start to understand human immune biology so we can pick the right targets and can pick the right combinations." (Also see "*Q&A: Roche's Dan Chen Talks Immuno-Oncology Combinations*" - Pink Sheet, 20 Jun, 2016.)

Roche spent less time discussing its diagnostic and data platforms at this year's ASCO analyst meeting than at some years past, thanks to a mature and active targeted therapy program. The company highlighted the ALK inhibitor *Alecensa* (alectinib) and the anti-HER combination of *Perjeta* (pertuzumab) and *Herceptin* (trastuzumab) following presentation of Phase III results from the ALEX and APHINITY trials, respectively, at the oncology conference. (Also see "*APHINITY Combo Details Contain No Surprise, Puma's Nerlynx May Benefit*" - Scrip, 5 Jun, 2017.) and (Also see "*Roche "Disappointed" By ASCO Focus, Progressing CEA-CD3 Bispecific*" - Scrip, 7 Jun, 2017.)

> ***INTERVIEW: Roche's Dan Chen Talks Immuno-Oncology Combinations***
>
> By Mary Jo Laffler
>
> 24 Jun 2016
> The head of Roche/Genentech's immuno-oncology programs discussed the firm's combination strategy at the recent American Society of Clinical Oncology annual meeting in Chicago.
>
> *Read the full article here*

Nonetheless, O'Day emphasized that "we're clearly being more and more enabled every day by the high-quality availability of data outside of our walls and inside of our walls as it relates to real-world data and better analysis on our randomized clinical trial data and we're growing our expertise on analytics, deep learning that we think is really fundamental."

NGS In Practice

Roche's presentation of data from the Phase II LOTUS trial of one of its targeted therapy candidates, the AKT inhibitor ipatasertib, provided a look at how the company incorporates diagnostics from both its *Ventana Medical Systems Inc.* diagnostics business, which markets immunohistochemistry (IHC) assays, and its stake in *Foundation Medicine Inc.*'s next-generation

sequencing (NGS) platform. NGS can run more tests on a small tissue sample than traditional IHC assays – Roche says the *FoundationOne* NGS platform is designed to detect alterations in more than 300 oncogenes – and O'Day said FoundationOne is "key to identifying relevant patient subpopulations." FoundationOne is under review at FDA.

The Phase II LOTUS trial of ipatasertib plus paclitaxel for first-line therapy of metastatic triple-negative breast cancer (TNBC) had two primary endpoints: progression-free survival (PFS) in all patients and PFS in patients with low levels of phosphate and tensin homology (PTEN). PTEN-low or PTEN-high status was determined by Ventana's IHC assay. As a secondary endpoint, Roche also used FoundationOne NGS to look for another biomarker profile based on PI3K/Akt pathway status – altered PI3KCA/AKT1/PTEN.

The Ventana PTEN assay showed "no projective ability" over the regular intent-to-treat analysis of all patients, Horning said. Roche did, however, see "an improved progression-free survival hazard ratio in those patients that were identified by the FoundationOne NGS assay," she reported. "I think this is a demonstration of our partnership and collaboration that shows that we can streamline the assay in our development program."

"For triple-negative breast cancer, this is a particularly important diagnostic because of the complex biology, which can include both alterations of the PI3 kinase and AKT, as well as PTEN," Horning said. The FoundationOne NGS data "gives us confidence to move forward with ipatasertib in this [triple-negative breast cancer] setting." Ipatasertib is also being tested with paclitaxel in a Phase II trial in neoadjuvant early-stage TNBC, according to clinicaltrials.gov, and is in Phase III for castration-resistant prostate cancer.

O'Day also highlighted the performance of the NGS assay in the ipatasertib LOTUS trial. "This is again a reason why the comprehensive diagnostic and comprehensive immunodiagnostic paradigm that we're entering into is really going to become more and more important in the years to come," he said.

While NGS is still emerging commercially, uptake is expected to swift, especially as less-invasive "liquid biopsy" technology advances. (Also see "*Companion Diagnostics: The Expanding Reach Of Personalized Medicine*" - In Vivo, 14 Mar, 2017.) Roche has made sure it will be well-positioned to take advantage.