Is Oncology Back At GSK? Did It Ever Leave?

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Axel Hoos, M.D., Ph.D., is probably one of the biggest names in cancer drug development. After all, his scientific leadership not only led to a new paradigm for how to create cancer immunotherapies, but his development of ipilimumab while at Bristol-Myers Squibb (BMS) helped launch the entire immuno-oncology (IO) field! That being said, when the Wall Street Journal ran the April 22, 2014, headline, “Glaxo Exits Cancer Drugs,” one has to wonder if Hoos (who joined the company in 2012 and is the SVP, therapeutic area head for oncology R&D and head of immuno-oncology) suddenly regretted his most recent career move. If GSK was truly exiting oncology drug
development, would they still need him? While Hoos attests, “Oncology is back at GSK,” the truth of the matter is that it actually never left. Though the mammoth deal included GSK shedding its marketed oncology portfolio and related R&D activities for $16 billion to Novartis, it also included a contractual obligation called a right of first negotiation (ROFN). This basically means that if GSK files an oncology R&D program for regulatory approval, it needs to first be shown to Novartis. In other words, despite various media outlets arguing to the contrary, GSK isn’t walking away from one of biopharmaceutical’s biggest and fastest-growing markets (i.e., cancer drugs), but, instead, transforming its oncology R&D engine.

OUT WITH THE OLD — TO FOCUS ON THAT WHICH IS NEW

Sometimes it is tough to let things go, especially when it means getting rid of revenue-generating oncology assets. But if you want to be able to focus on oncology’s R&D future, a divestiture can add more than just billions of dollars to your books. “You are not only shedding products that are on the market. You are removing some commercial and development infrastructure,” Hoos explains. One of the benefits of the GSK oncology divestiture to Novartis is it provides focus. “GSK is not going to reenter research areas that were just divested (i.e., targeted therapy discovery and development),” he states. This is good, because in the field of oncology there are constantly new mechanisms being explored, with the biggest and fastest-growing being IO. “This is where GSK wants to place its bets,” Hoos affirms.

In addition to IO and epigenetics, GSK also plans to focus on cell and gene therapy (CGT). But because CGT is highly complex, it requires a different business approach. “Technically, CGT is immunotherapy,” he clarifies. “However, from an infrastructure perspective, it is very unique, because to make it work, it requires many diverse resources.” This is why GSK opted not to have cell and gene therapy R&D initiatives subsumed under immunotherapy or immuno-oncology, but established its own parallel unit within the Oncology Therapeutic Area.

Another benefit Hoos sees from divesting the marketed oncology medicines is that it gives GSK the room to come up with new waves of innovation, as those former medicines are no longer taking up the resources. “When you think about how much money goes into product lifecycle management (PLM) [i.e., marketing, label expansion] relative to discovery and development [i.e., R&D], it can be a significant portion of your overall budget,” he says. Hoos notes that the divestiture also eliminated internal R&D competition. “When I arrived at GSK, new oncology discovery performance units (DPUs) [which are discussed in detail later in this article] were competing for resources
with other, more-established parts of the business (e.g., small molecules for tyrosine-kinase inhibition and BRAF and MEK inhibitors),” he states.

When Hoos landed at GSK, throughout the biopharmaceutical industry, “generation two” of immuno-oncology R&D was well under way. As his previous work at BMS (i.e., ipilimumab) represented “generation one,” if he wanted to build something from scratch, GSK would basically have to skip working on a generation of IO drug development. “There were at least 15 PD-1s being developed,” he shares. “As all the PD-1 and PD-L1-blocking agents represented IO generation two, we knew that everyone else was pretty much already there.” Rather than try to play generation two catch-up, GSK instead opted to focus on generation three via its DPU approach.

**HOW GSK CREATES SMALL BIOTECHS WITHIN A BIG PHARMA**

Although the transaction was complex (as well as expensive), because GSK sold its marketed-oncology products for a premium (i.e., 10 times their annual sales), the company is able to reinvest some of those funds and basically “rebuild” its oncology business, which it is doing using DPUs. “The DPU model is actually one of the things that attracted me to GSK, because it enables you to be more entrepreneurial with a focus on one area of science,” Hoos states. At GSK, a DPU is treated like a small biotech company within the structure of a large pharma.

The process of creating a DPU — which GSK/Hoos did for immuno-oncology — involves developing a business plan that is presented to governance for review and, if approved, funded for a three-year cycle. “While a DPU may have some touchpoints to assess if it’s working or not, like a small biotech, you are in charge of your own budget and deliverables, and the structure allows you to work beyond just doing in-house discovery,” he states.

For example, if building in an area of science where there exists a technology that would benefit the DPU’s vision, the DPU can make an acquisition, develop an in-licensing deal, or create a partnership that enables it to build a portfolio. “We do a lot of option deals with milestones, and, if achieved, we can opt to buy the technology,” he attests. This is why Hoos views the DPU approach as an excellent means of de-risking R&D. “It allows you to work closely with other companies that have specific expertise, rather than spending a lot of money up front to acquire it, thereby diversifying what you are able to do.”
A DPU head — functioning like a CEO of a biotech — can build their own team, recruiting either internally or from GSK or outside the company. For example, the immuno-oncology DPU began with 15 GSK employees, most of whom came to the unit without having previous IO experience. “This is because the generation three IO area we were trying to build did not yet exist,” Hoos says. Today, the IO DPU consists of 85 employees, not all of whom came from within GSK. The other two areas of GSK oncology science (i.e., epigenetics and cell and gene therapy) are also set up as DPUs with their own heads. However, after the closing of the Novartis transaction, GSK is now rebuilding the Oncology Therapeutic Area with these three DPUs as building blocks. While GSK’s structure results in DPUs being treated like stand-alone, small biotechs, unlike a small biotech, these DPUs have the resources that only a Big Pharma can provide.

THE FOUR PILLARS OF GSK’S DIVERSIFIED ONCOLOGY R&D PIPELINE

There is no question that Hoos is interested in creating at GSK the same kind of transformational drug he worked on at BMS. “Right now, I’m focused on building something that is different and diversified,” he says. The first part — or “pillar” — of the plan to create the immuno-oncology R&D pipeline was to establish a set of checkpoint modulating antibodies of the third generation. Two of these are already in the clinic — an agonistic antibody against OX40 [CD134] and an agonistic antibody against the inducible co-stimulator (ICOS).

The second pipeline pillar is bispecific antibodies (i.e., putting two targets into one molecule). “Instead of having the antibody bind to one thing, you can have an antibody bind two things, and with that you end up having a combination therapy in one molecule,” he reiterates. While this is still in the discovery science phase, Hoos attests to GSK working on three different platforms of bispecific antibodies.

The third pillar involves small molecules. “We are leveraging our small molecule expertise and focusing it on immunotherapy targets, which is basically an unused area,” he says. Last year Hoos and three of his colleagues (Jerry Adams, James Smothers, and Roopa Srinivasan) wrote an article (Big Opportunities for Small Molecules in Immuno-oncology) published in Nature Reviews (July 2015) about how to use small molecules in immunooncology. He says the article was well-received and sets a framework under which small molecules can be used to make medicines in immuno-oncology. To that end, GSK has developed a set of new small molecule
immunooncology targets and anticipates these moving into the clinic within the next 18 months.

“The fourth pillar is actually the most challenging, as well as the most exciting — cell therapy,” he says. While cell therapy is currently being attempted by many players using different approaches, at GSK it is viewed as an immuno-oncology component that needs its own infrastructure. “When I started at GSK, we built a group within the IO DPU that did cell therapy,” he shares. “But now that this area is reaching critical mass, it really needs to be its own DPU if it is going to be successful, and that’s what we are just starting to do.” To create next-generation cellular medicines, GSK Oncology is using a modular approach with multiple technologies integrated on a central platform. This approach includes different cell carriers, targeting receptors (CARs, T-cell receptors), signaling cascades, immune checkpoint or cytokine genes, supply chain technologies, and other components. Academic and industry partners also contribute key knowledge and technologies to the central R&D effort at GSK.

After the Novartis transaction was announced, many people thought GSK had just exited the hottest therapeutic category — oncology. Hoos doesn’t see it that way, though. He believes GSK seized this opportunity to transform its oncology R&D engine. “Immuno-oncology is clearly transformational, as are the checkpoint modulating antibodies currently being marketed,” he avows. For GSK to transform oncology, it meant striving to be a leader in the next generation of immuno-oncology products. “It has taken us almost four years to build the current pipeline of more than 15 immuno-oncology assets, and we just put the first drugs into the clinic,” he concludes. Targets and modalities were chosen to create synergies and enable novel combination therapies that may deliver transformational effects for patients. The focus remained on generation-three assets (OX40, ICOS, TCR-Ts) and not duplicating generation-two assets (PD-1, PD-L1, IDO, CD-19 CAR-T).