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Bristol/Medarex: A Transformational Acquisition Rooted In Collaboration

by Joseph Haas

Bristol's \$2.4 billion buyout of Medarex in 2009 yielded value equivalent or greater to that realized in larger M&A transactions signed that year, such as Pfizer/Wyeth, Merck/Schering-Plough and Roche/Genentech. The deal made BMS a leader in immuno-oncology and by most accounts is the highlight of the pharma's "string of pearls" strategy.

- Bristol-Myers Squibb's 19-year relationship with Medarex epitomizes the pharma's deal-making strategy of using alliances and acquisitions to access new technologies in core therapeutic areas.
- Through the deal, which brought Opdivo and Yervoy in-house, BMS became an early leader in immuno-oncology.
- So what? This collaboration-turned-acquisition shows the importance of taking the time to nurture long-term business relationships. The value of the deal was not only in the assets, but what the partners, working together, made of them.

From an early-stage platform technology collaboration to a multi-year co-development pact in cancer to an outright acquisition of the smaller company by the larger, [Bristol-Myers Squibb Co.](#)'s nearly two-decade relationship with [Medarex Inc.](#) has proven one of the most fruitful big pharma/biotech deals – and the key to that success may be in the slow, gradual buildup of familiarity and shared priorities.

Now, 19 years after Bristol first partnered with the California biotech and eight years after purchasing its cancer R&D partner for about \$2.4 billion, it's fair to ask whether the Medarex buyout ended up delivering the most value among the big pharma mergers signed in the hyperactive deal-making year of 2009.

"What Bristol paid for Medarex, versus what they got out of it, is pretty remarkable," Sanford C.

Bernstein analyst Tim Anderson tells *In Vivo*.

Making bigger headlines that year – not to mention generating larger fees for investment banks – also were [Pfizer Inc.](#)'s acquisition of [Wyeth Pharmaceuticals](#) (price tag \$66.7 billion; [\[See Deal\]](#)), [Merck & Co. Inc.](#)'s purchase of [Schering-Plough Corp.](#) (price tag \$42.1 billion; [\[See Deal\]](#)) and [Roche](#), like Bristol, acquiring a longtime biotech R&D partner, [Genentech Inc.](#) (Roche acquired the roughly 44.1% of Genentech it didn't already own for \$43.7 billion in February 2009.) [\[See Deal\]](#)

"It's hard to say for sure, but I can pretty confidently say the percent return on that Medarex acquisition is probably much higher than those very large acquisitions," says Damien Conover, Morningstar's director of health care equity research.

Further linking those transactions is the coincidence that three of them played direct roles in establishing the early leaders in the booming field of immuno-oncology. From Medarex, Bristol obtained, developed and launched the anti-CTLA-4 drug *Yervoy* (ipilimumab) and the anti-PD-1 therapy *Opdivo* (nivolumab). Likewise, Merck got and eventually launched its anti-PD-1 product *Keytruda* (pembrolizumab) via its merger with Schering-Plough, while the genesis of Roche's immuno-oncology success stemmed from early research at Genentech that ultimately yielded anti-PD-L1 drug *Tecentriq* (atezolizumab) as well as the cancer immunotherapy *Gazyva* (obinutuzumab), a CD20 antibody. (Also see "[Keytruda And The Surprising Fruits Of M&A](#)" - Scrip, 18 Sep, 2015.)

Firms Created Value Opportunity In Partnership

Beyond evaluating the "bang for the buck" Bristol derived from acquiring Medarex, with many M&A transactions at that time being driven partially or even largely by a desire for cost synergies, it be might worth asking if Bristol got such value from Medarex precisely because of the way the relationship between the two companies developed gradually over more than a decade. (While the buyout was much pricier, it is undeniable that Roche obtained significant value from its even-longer relationship with Genentech, in which the Swiss pharma became majority shareholder in 1990.)

"Bristol and Medarex's relationship, and then later Bristol's acquisition of Medarex, has been arguably one of the smartest biotech collaborations to date (alongside Gilead's acquisition of Pharmasset [[Gilead Sciences Inc.](#) and [Pharmasset Inc.](#)]," *Datamonitor Healthcare* senior analyst Amanda Micklus says. "From this relationship, Bristol has built the most commercially successful franchise in immuno-oncology, and I think Bristol really was a forward thinker in this area, getting involved in immuno-oncology so early on when big pharma wasn't yet paying attention."

The Bristol/Medarex pairing got its start in June 1998, when the New York pharma licensed rights to Medarex's *HuMab* technology platform – a transgenic mouse developed by Nils Lonberg, PhD, at Medarex predecessor [Genpharm Inc.](#) that offered the ability to create fully human, high-affinity

antibodies in a few months – to develop antibody therapy candidates for cancer. [\[See Deal\]](#) Bristol also got a commercialization option on any products resulting from the collaboration, with the potential for \$20 million in licensing fees, milestones and royalties to Medarex.

In an interview, Lonberg tells *In Vivo* that it was clear the two companies' interests were aligned from early on in the partnership.

"We were looking for a partnership with a drug company where we would make them a drug and then we were looking for milestones and royalties associated with that," he says. "In 1998, couple of months after we started that effort, we formed a partnership with Bristol. The drug that we made for Bristol targeted a molecule called CD-137, and the idea was to actually enhance immune response in cancer."

Lonberg, who is now SVP of Biologics Discovery and head of Oncology Discovery at Bristol, thinks Medarex ultimately brought forth significant innovation in what would come to be known as immuno-oncology by not being afraid to fail. "Part of [our] success was to go from one failure to another with no loss of enthusiasm," he says. "At Medarex, we certainly failed a lot but we did not lose enthusiasm."



Nils Lonberg, PhD

Early Prostate Cancer Data Led To Ipilimumab Partnership

Medarex first presented ipilimumab to Bristol in 2001, overviewing early data in prostate cancer, and by 2003 the biotech had determined it wanted to find a partner to help develop the antibody. At the American Society of Clinical Oncology meeting that year, Medarex presented data from a trial of ipilimumab in melanoma conducted by the [National Cancer Institute](#) that showed durable complete response. The logical partner to take ipilimumab further was Bristol, and in November 2004, the companies signed a co-development deal for the asset, then known as MDX-010. [\[See Deal\]](#)

Medarex got \$50 million up front in that agreement – but a key characteristic of the deal was that \$25 million was cash, whereas the other half was an equity investment by Bristol. The pharma got 2.9 million shares in Medarex at an 11.3% premium and committed to pay up to \$205 million in milestones, pledged to cover 65% of US and European development costs, and gave Medarex an option to co-promote ipilimumab in the US.

"It really wasn't a challenging exercise to explain the science to Bristol. All the scientists at Bristol were steeped in this field." –Nils Lonberg, PhD

By early 2009, Bristol owned 2.4% of Medarex, an investment of roughly \$16 million.

Then an R&D executive at the pharma, but now its business development chief, Paul Biondi recalls that around 2006, CEO James Cornelius placed Bristol on a transformational path toward becoming a "next-generation biopharma." Out of this goal arose Bristol's "string of pearls" business development strategy – an effort to do targeted deal-making around licensing, partnerships and small-scale acquisitions, as opposed to the mega-mergers being pursued by some of its industry peers. "There was a discussion at the time principally around the importance of biologics and, obviously, Nils and his team had a preeminent platform there," he tells *In Vivo*. "The other piece was obviously there was an interest in expanding our capabilities within oncology and recognizing that there was a strong immunology bent to the company as well."

Bristol's interest in ipilimumab specifically stemmed from the company already possessing deep familiarity with CTLA-4 – it was developing autoimmune drugs intended to down-regulate the pathway, resulting in the rheumatoid arthritis drug *Orencia* (abatacept) and the kidney transplant drug *Nulojix* (belatacept). Medarex's work intrigued Bristol with the cancer-fighting potential of stimulating this immune response, Biondi explains.

This overlapping interest deepened the partnership between Bristol and Medarex, leading to the 2004 collaboration around ipilimumab, which also included rights to MDX-1379, a Phase III peptide vaccine for melanoma, and an antibody-drug conjugate program Medarex had initiated. "It really wasn't a challenging exercise to explain the science to Bristol," Lonberg notes. "All the scientists at Bristol were steeped in this field."



Paul Biondi

As often is the case with multi-asset or multi-target collaborations, not everything included in

the 2004 deal came to fruition. MDX-1379 was never really intended to become a drug, but was licensed from NCI to serve as a placebo in clinical studies of ipilimumab, Lonberg explains, while the ADC program was explored further and then shelved. The latter decision largely reflects a strategy to focus on the opportunity in immuno-oncology instead, he says.

Bristol Leaped Before Seeing Phase III Data

By 2009, Phase III data for ipilimumab in metastatic melanoma were expected in about a year. Bristol decided to roll the dice and buy out its partner, paying a 92% premium of \$16 per share in Medarex, before seeing the pivotal data. (Also see "[Bristol-Myers Squibb Buys Medarex: Adds Eighth 'Pearl' To String](#)" - Pink Sheet, 27 Jul, 2009.) Of course, as co-development partner, the pharma probably had a pretty good idea of how the trial was progressing.

"Initially, we had a collaboration around an early target, and we got to know Nils and his team and build up a lot of rapport scientifically and then partner on the asset," Biondi explains. "I think due to the familiarity at the time, the thinking was that we had a lot of comfort with both the benefit and the risk, but if we went in before and were willing to take the risk recognizing that we had some confidence in how this would play out we would realize the most value to the company, because if we had waited until post-data, obviously the [Medarex] management at that time would have had a very different view of the acquisition value."

From its \$2.4 billion investment, Bristol obtained two of its three top-growing sales products today (along with anticoagulant *Eliquis*).[\[See Deal\]](#) On July 27, during its second-quarter earnings presentation, the pharma reported that Opdivo yielded sales of \$2.3 billion over the first six months of 2017, up 50% from one year earlier, while Yervoy brought in \$652 million for the half-year, up 29% from 2016. (Also see "[Post-MYSTIC, Bristol Renews CTLA-4 Vows, But Is 'Not Wedded' In Lung Cancer](#)" - Scrip, 27 Jul, 2017.)

Morningstar analyst Conover says the Medarex acquisition has proven to be both transformative for Bristol and the highlight of the string of pearls. "When we think about that string of pearls strategy that Bristol had at that time, they were doing a lot of important deals, but out of the

BMS-Medarex Time Line

1998: BMS licenses Medarex's HuMab technology platform to develop antibody therapy candidates for cancer.

2001: Medarex first presented ipilimumab (now Yervoy) to Bristol, overviewing early data in prostate cancer.

2003: Medarex decides to seek a partner to help develop the antibody.

2004: BMS and Medarex sign a co-development deal to develop ipilimumab as well as nivolumab (Opdivo).

deals that they did then, this one stands out as probably being the most transformative for the company," he notes.

The transaction succeeded for two reasons, he adds – it gave Bristol multiple chances for success and it stemmed from an already fruitful partnership of some duration. (Also see "[*With The Launch Of Yervoy, Early Signs Of R&D Success For Bristol*](#)" - In Vivo, 1 May, 2011.)

"When a company does these sort of bolt-on acquisitions – whether it's an outright acquisition or a staged approach – it's important to think about multiple shots on goal and diversifying the portfolio of acquisition targets," Conover points out. "By doing that, you'll likely get hits but you occasionally might get a home run. Obviously, you're going to strike out as well, but by having that series of opportunities, that can line you up well."

As far as the staging and the strategy, I do think that is a successful way to start a relationship – to get closer and closer to the technology and understand it well, and then you ultimately make the acquisition," he continues. "I think that is probably one of the more successful ways that an acquisition can happen, in the sense that you de-risk it to some extent by starting with a lower investment and then increasing the investment as you learn more about the technology."

Seeing the full extent of Medarex's science encouraged Bristol to want to buy the biotech, Biondi says. "This played into our thoughts around acquisition, which was if we could be successful in this space, the depth and breadth of what Nils and his team had provided in terms of all the various targets they had been looking at in this space would allow for the ability to move forward if Yervoy was successful," he says. "Obviously, nobody could have predicted what has happened since but that kind of optionality, the possibility that that could [occur] was part of the thought process at the time."

The Medarex technology continues to deliver for Bristol, as well. Currently, in its clinical pipeline are Medarex-derived candidates BMS-986016, an anti-lymphocyte activation gene 3 (LAG-3) candidate being studied in tandem with Opdivo in advanced melanoma patients who are refractory to or relapsed following anti-PD-1/PD-L1 therapy, and a pair of Phase I candidates – anti-CXCR-4 ulocuplumab and an anti-fucosylated anti-CTLA-4 candidate.

In addition, Bristol is working with [*CytomX Therapeutics Inc.*](#) on a *Probody* next-generation anti-

2009: BMS buys Medarex before ipilimumab data are released.

2011: Yervoy receives first FDA approval.

2014: Opdivo receives first FDA approval.

Fast forward to 2017: Opdivo yielded sales of \$2.3 billion over the first six months of 2017, up 50% from one year earlier, while Yervoy brought in \$652 million for the half-year.

CTLA-4 drug that it thinks could offer enhanced tumor targeting and less binding to healthy tissue than earlier CTLA-4 antibodies. [\[See Deal\]](#) Currently preclinical, that program may move into Phase I later this year or early in 2018, a Bristol spokesperson says.

Meanwhile, despite some recent clinical trial disappointments, Bristol thinks it has only begun to scratch the surface of Opdivo and Yervoy's potential, as solo agents, in combination with each other and in combination with other companies' drugs or drug candidates. Bristol has more than 300 ongoing trials involving one or both of those drugs in more than 50 types of cancer, including more than 120 combination therapy trials. Opdivo alone has yielded roughly 250 approvals worldwide to date, according to the company.

Bristol's Ongoing Deal-Making Strategy Impacted

Biondi says its success with Medarex has continued to inform Bristol's deal-making strategy, calling it "the kind of deal we like to do." R&D has been and remains a "major driver" of Bristol's deal-making approach, he adds. (Also see ["Bristol Looking For Deals, Immuno-Oncology And Otherwise"](#) - Pink Sheet, 24 Jul, 2014.)

"If you look at most of the deals that we do, whether licensings or acquisitions, they tend to be at an earlier stage in time, because we do this type of process where we like to partner and get some comfort on both sides, but also in the belief that collaboration and working together is where we can create the most value," Biondi says. "Not to say we wouldn't do different arrangements – we have done deals for later-stage assets and we might in the future – but that is why the relationship and the series of transactions that we did with Medarex provide a really good example of the strategy that we try to employ to this day."

Both executives say a factor in the ongoing success of the acquisition was the decision to fully integrate Medarex into Bristol, a process Lonberg says he and his colleagues embraced. Through its three R&D sites in California, Medarex has grown from about 40 people at the time of the sale to a headcount of roughly 300 today. It is Bristol's largest oncology discovery arm.

"What was important to us was not trying to keep Medarex separate, not trying to establish sort of a team B that would not be able to become part of Bristol, but in fact to fully integrate," Lonberg notes. "So we came up with an identity which was biologics discovery California, which we really tried to completely integrate within Bristol. We tried to use all of the resources that were available already at Bristol in our drug discovery efforts. I think it worked a lot better than an attempt to maintain a separate identity that would never be fully embraced by the acquirer."

Today, that process has resulted in a "lack of walls," the exec says, which benefits discovery and R&D productivity.

"We don't have walls between the immunology therapeutic areas where the main focus is on

inflammatory diseases and the oncology therapeutic area, where there is discovery," Lonberg says. "So the teams are integrated in a number of ways, not just intellectually but also operationally in how we do drug discovery. And that I think has given us a real head start in a lot of important mechanisms in immunotherapy."