JUL 26, 2017 @ 02:15 AM EDITOR'S PICK

The Startling History Behind Merck's New Cancer Blockbuster



David Shaywitz, CONTRIBUTOR

I write about entrepreneurial innovation in medicine. FULL BIO

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No area is hotter or attracting more dollars in pharma than immuno-oncology–the idea of harnessing the immune system to fight cancer. My fellow Forbes contributor Bruce Booth has recently characterized the intensifying interest in this space as the "exploding supernova" of cancer research.



The former Oss, Netherlands, headquarters of the pharmaceutical company Organon, where the project leading to Merck's blockbuster pembrolizumab (Keytruda) was originally conceived. Photo Credit: VINCENT JANNINK/AFP/Getty Images [-]

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Few programs capture this enthusiasm better than Merck's pembrolizumab, or pembro (brand name: Keytruda), a humanized monoclonal antibody blocking the T-cell "off" switch, PD1. Pembro, according to a Merck presentation at the American Society of Clinical Oncology (ASCO) conference in June 2017, is currently under evaluation in more than 500 clinical trials, including more than 300 combination trials. It's been approved for ten indications, and is aiming for many more.

The success of pembro is likely to define the legacy of Merck research chief Roger Perlmutter, the immunologist who assumed leadership of Merck Research Labs in 2013 after being passed over for that role 13years earlier, when 42-year-old Peter Kim of MIT's Whitehead Institute was selected to run the organization, and Perlmutter and a number of colleagues decamped to Amgen.

Yet the success of pembro was anything but inevitable. It was discovered accidentally, by biotech scientists looking for drugs that would tamp down the immune response in patients with autoimmune disease, and would stimulate, not block, PD1. Even after a potent PD1 inhibitor was identified and recognized as a potential cancer drug, the research program had to fight for funding through two mergers and acquisitions. After the program finally wound up at Merck, in 2009, it was considered such a low priority that it was shut down and placed on the out-license list. A term sheet (valuing the program at next to nothing) was reportedly in place, but pulled at the last minute, as promising results from competitor Bristol-Myers Squibb (BMS) motivated a reconsideration of the mechanism.

A remarkably rapid drug development program ensued, initiated under Peter Kim and in close partnership with the FDA, ultimately under the brand-new breakthrough designation program. Merck–in effort to close what it perceived as a four- or five-year gap with BMS–opted to pursue a companion diagnostic program for the use of pembro in lung cancer patients, a decision intensely questioned not only by investors, but also by the new Merck research leadership when they joined in 2013. In the end, the companion diagnostic program was retained, and while critiqued by the *Wall Street Journal* as recently as March 2016, it ultimately proved to be vital, catapulting Merck ahead of BMS when the BMS drug failed in first-line therapy for lung cancer among less stringently selected patients, while Merck succeeded brilliantly by focusing on the 30% of patients deemed most likely to respond.

While drug development is often viewed as a simple linear exercise of progressing science from laboratory to clinic, the reality is generally far more circuitous, involving more uncertainty and luck than is typically appreciated. But it's not just luck; as pembro demonstrates, success is ultimately dependent upon people--in

particular the internal champions who urge a program forward and the senior executives who are willing to get fully behind a program, own the difficult decisions and stake their careers on the molecule's success.

Happy Accidents

When Greg Carven was a chemistry graduate student at MIT in the late 1990s, his first project was to crystallize a cell surface structure involved in immune recognition –the class II MHC molecule HLA-DR1. After several years of intensive work, however, he found himself abruptly scooped by a lab in Slovenia. It had elegantly solved the structure, and Carven was left to cast about for a new project. Ultimately, he decided to focus his dissertation on the examination of HLA-DR1 using exquisitely specific antibodies as elegant probes, enabling him to detect subtle differences in the molecule's conformation.

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After graduation, Carven started working at an oncology startup in Waltham, Massachusetts–but the company "failed miserably" according to Carven, and after a year, he was out looking for another job.

He found one at a biotech company in Cambridge called Organon, a 20-person outpost of a larger, 20,000-person Dutch pharmaceutical company headquartered in Oss, Netherlands. Organon itself was the health products division of a much larger, Amsterdam-based conglomerate, Akzo Nobel, that was focused primarily on paints.

Organon sold products related to women's health, neurology and anesthesia; their R&D operations were led by David Nicholson (now chief R&D officer at Allergan), who told me the Cambridge operation represented an effort to leverage the company's expertise in antibodies–previously used by the company for target validation–to develop novel therapeutics.

When Carven joined the company, he focused on raising antibodies against the cell surface protein PD1, hoping to find agonists–molecules that activate the receptor and thus turn T-cells off, suppressing overly exuberant responses in patients with autoimmune disease.

This project was originally initiated in Oss in the lab of Andrea van Elsas, who explained to me:

> "Organon's PD1 antibody program was conceived in 2003 as part of an antibody portfolio we were setting up to support Organon's core objectives which included autoimmune disease (rheumatoid arthritis and other) but not oncology.

> The antibody portfolio was initiated in the Netherlands in my group in preparation of moving to Cambridge, MA (mid-2005). The PD1 program ultimately yielded no good agonists but exceptional antagonists.

When Carven and team recognized they had identified promising PD1 antagonists, they were not immediately sure what to do. There was much skepticism in the world around immuno-oncology, yet also strong protagonists, including the legendary researcher Jim Allison, an immunologist who believed strongly in targeting immune molecules such as CTLA4, the target of ipilimumab (Yervoy), which was developed initially by Medarex (later acquired by BMS) and ultimately approved in 2011 for the treatment of refractory melanoma. While the response rates were fairly low, the responses that were seen were often unusually durable.

But these encouraging data were still several years in the future, and the Organon team considered a range of potential uses for the PD1 antagonist, including as an antiviral agent and as a vaccine enhancer. Ultimately, however, the team coalesced around the oncology indication and persuaded Organon management to go along–presumably an easy sell, since according to Nicholson, Organon leadership was interested in using antibodies as cancer therapeutics. As van Elsas (who was just appointed Chief Scientific Officer of Aduro Biotech) put it:

> “ With my academic history in anti-CTLA4 (even though, clinically, cancer immunotherapy was still highly controversial at the time), and with a growing appreciation for the portfolio's potential in oncology, we had enough reasons to pivot to oncology.

A **Series Of Acquisitions**

The team set to work on a validation package for the most promising asset in this program, a humanized version of a highly potent and selective antibody, which would come to be known as pembro, in anticipation of new drug filing (known as an investigation new drug, or IND, application). Unfortunately, as work was continuing, Organon was acquired by Schering Plough in 2007, reportedly to plug a gap in Schering’s phase 2 pipeline.

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While "no one had given much thought to the preclinical programs in either company," as one researcher put it, the acquisition inevitably led to an integration process associated with a re-prioritization of all the combined assets. The PD1 program reportedly emerged with a very low ranking among all the oncology activities–"low if not dead last" one scientist said, "because nothing in tumor immunology ever worked." Nevertheless, the program retained its champions–most prominently, van Elsas–and was permitted to continue and prove its value to skeptical but convincible Schering executives. As encouraging results began to come in, the team collaborated with the oncology group at Schering to again work on the IND application, the prerequisite for clinical studies.

Just when it seemed like the team was starting to gain momentum, Schering itself was acquired by Merck in 2009, initiating, of course, a new reprioritization process for the integrated companies. This time, the PD1 program was less fortunate, and the team was told to stop work. Yet, they persisted–in skunkworks fashion, variously pitching their work as an oncology

project, an antiviral project and a vaccine enhancement project. Eventually, however, management caught on and formally shut down their work. The molecule was placed on the out-license list, and ultimately a term sheet was drafted setting the terms for a specific interested party to obtain rights to the molecule at what was said to be a negligible cost.

Everything changed, however, by the middle of 2010. First, BMS published in the *New England Journal of Medicine* (*NEJM*) a successful Phase III study in refractory metastatic melanoma involving ipilimumab (Yervoy), a drug targeting the different but related T-cell inhibitor molecule CTLA4, pointing to the potential efficacy of the so-called "checkpoint inhibitor" approach. Second, word began to filter through to Merck that nivolumab, or nivo (brand name: Opdivo), an earlier-stage molecule targeting PD1 that BMS also acquired though its recent acquisition of Medarex, was showing signs of promise.

From what was literally a standing stop, Merck urgently reactivated IND development in mid-2010, targeting a filing by the end of the year and achieving it in December. Enrollment in the first study began in early 2011. Eric Rubin–who, in an interesting twist of fate, did his oncology training at Dana Farber with Thomas Lynch, who now leads R&D at BMS–was the head of clinical oncology at the time and would eventually become the clinical lead for the program.

Development of pembro was unlike any program in Merck's history. For starters, the team realized they were years behind BMS; one researcher told me they calculated that BMS must have filed their IND for nivo in 2006. But Merck had an aggressive plan, and benefited from unusually good timing.

"I Could Not Go To Sleep If Trial Closed"

The pembro phase 1 program began like any other; the first-in-human study was a simple dose escalation, designed primarily to understand the safety and tolerability of the new medicine in patients with a range of advanced cancers. Efficacy was also examined in a preliminary fashion, typical for phase 1 studies. When early results suggested some melanoma patients–already suspected to be good fit for PD1 mechanism–seemed to be responding to the drug, an expansion cohort, focused entirely on advanced melanoma patients, was added.

The results from the melanoma cohort were striking. According to UCLA's Antoni Ribas, a key investigator in this advanced melanoma study:

> Among the first 7 patients we enrolled, 6 patients had objective responses. I realized I was probably lucky and this high rate of responses would not hold up forever, but also realized that [pembro] was different from all the other cancer immunotherapy we had tested to date, all of which had response rates in the 10-15% range.

Ribas then started sending before and after scans to the Merck team running the study, urging them to share with upper management. He worried Merck was "going too slow in recognizing how important this was."

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Merck scientists involved in the program tell me they needed little prodding from Ribas, saying they were acutely aware of the both the potential clinical utility of their drug and the commercial need to close the gap with a competitor who seemed to be years ahead.

Ribas emphasizes his "main concern was that the study as designed had very few additional patients to enter, and I could not go to sleep if the trial closed and I would have suitable patients who could respond like the others and no slots for them." His pleading apparently dovetailed with the strategy on which Merck had embarked. As Ribas notes, the study "eventually grew to include 655 patients with metastatic melanoma and a similar number of patients with lung cancer, becoming the largest phase 1 trial ever done in oncology." (Note: This extraordinary Phase 1 study was recently summarized by Eric Rubin and colleagues in the *Annals of Oncology*.)

Merck's decision to focus on melanoma seems to reflect both scientific and commercial considerations. Melanomas had already demonstrated responsiveness to ipilimumab (Yervoy)–recall that this targets CTLA4, a different but related T cell off switch–so there was reason to believe pembro would work in this cancer as well. Commercially, Merck was terribly concerned by how far they were behind BMS' nivo, and thought–from the time it filed its original IND in 2010–that its best chance to get to market rapidly was by focusing on refractory melanoma patients; in particular, it thought that if it could demonstrate its drug was effective in patients failed by all known treatments–including ipilimumab–it might be able to develop the drug in a single-arm trial–without a comparator arm. While normally drugs need to demonstrate superiority to placebo or to standard of care, patients who have been failed by all existing options by definition have no viable

alternative. A new medicine that demonstrates compelling success in such a population might garner rapid approval.

Regulatory Breakthrough (Designation)

Merck had another ace up its sleeve as well. At a safety conference in Japan in 2012, the head of non-clinical safety, Joseph DeGeorge–who earlier in his career had spent 13 years at the FDA–learned from FDA colleagues how they intended to apply and implement a pathway called breakthrough designation (BTD), designed to accelerate and rationalize the approval of new drugs for unmet needs. While BTD does not mandate any specific schedule acceleration for molecules accepted into this category, it fundamentally changes the relationship between the FDA and the company developing the drug. Meetings can occur with greater frequency, and–most significantly–the FDA works in much closer partnership with the company to identify the most efficient path to approval (while not changing the specific approval standards).

With its promising early results in advanced melanoma, Merck applied for and, in January 2013, received BTD status for Keytruda in this indication–a fact it did not immediately publicize, as it didn't want to alert potentially drowsy competitors to the possibility of using this novel regulatory mechanism.

In speaking with a number of Merck scientists, it appears one of the key benefits of BTD status was to backstop the pembro-inspired shakeup of Merck's historically conservative and linear drug development mindset and assure Merck that its new approach–involving doing more work at risk, and with far greater agility–was regarded favorably by regulators and represented a move in the right direction.

As the melanoma work was proceeding, the Merck team–motivated by promising results nivo was reporting–considered the potential benefit of the drug in non-small cell lung cancer (NSCLC) and added cohorts to the phase 1 study to explore this possibility, specifically the use of pembro as second-line therapy.

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The expansion of the pembro program at Merck created a logistical challenge for the company. At the time, Merck was hardly an oncology powerhouse, and it just didn't have enough people in its clinical development organization to throw at the growing need. On the other hand, the intrinsic excitement of the program motivated some to step up. The lung program, for example, would be led by a seasoned veteran, Martin Huber, who had led oncology programs in lung cancer more than decade earlier, and had worked his way to a senior role, director of pharmacovigilance at Merck. In this role, he was also on a review committee for compounds in clinical development and quickly recognized both the promise of the drug and the need for his involvement. He stepped out of his management role and into the arena, leading the pembro NSCLC program.

Saved By The Biomarker

When Merck started the lung cancer program, they viewed themselves as years behind BMS and thought their only chance for rapid approval would be to demonstrate unusually high response rates in second-line therapy. The challenge was how to achieve this–and they turned to a biomarker.

Merck's instinct to utilize a biomarker in clinical development is hardly surprising; a hallmark of Peter Kim's tenure at Merck was a strong emphasis on biomarkers–molecular signposts that can be used to segment patient populations, either to identify those most (or least) likely to respond or to get an early indication that a new drug is behaving as expected.

(A quick aside: I had a front row seat to Merck's embrace of biomarkers during the Kim years; I worked in Merck's newly-formed Department of

Experimental Medicine from 2006-2008 and developed a firsthand appreciation for both the possibility and the limitations of biomarkers in clinical development.)

In this case, Merck turned to a molecule called PDL1, which is expressed on the surface of a number of cells, including some tumor cells, and is the natural ligand of PD1. The hope was that by selecting patients with tumors that expressed high levels of PDL1, they could achieve increased efficacy. (This was based on empiric observations, including those reported by nivo researchers, as well as the thought that if a tumor doesn't express PDL1, it's less likely that the PD1 pathway has been upregulated.) It was never exactly clear why PDL1 expression should predict efficacy–a relationship that to this day remains unclear and the subject of intensive discussion.

The decision to utilize a biomarker for clinical development is often fraught, and was particularly so here, for a combination of commercial, scientific and humanistic reasons.

In general, commercial teams tend not to favor biomarkers and seek to avoid them wherever possible. They would rather target an entire population than a subpopulation, and also recognize the inconvenience of requiring a patient to get tested prior to using a drug. All things being equal, a doctor would prefer to prescribe a drug immediately, without waiting for a test to be ordered and the results received and interpreted.

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But all things are rarely equal; the ability to define a population that responds well to a drug can result in clinical trials that yield far more impressive results –and require far fewer patients to demonstrate that the drug is effective. In this case, the Merck team felt they were years behind BMS in lung cancer and thought their only way to stay relevant was to use an effective biomarker to identify a subgroup of patients that would respond in a such a compelling fashion that regulators would be impressed and would want to ensure the drug was available as soon as possible to serve this defined group of patients.

Scientifically, the challenge is that biomarkers are rarely perfect, and the PDL1 biomarker assay was perhaps a bit messier than most–yet Merck believed that it had developed a reliable assay that could support clinical development and incorporated this in yet another arm of its ever-expanding phase 1 study.

Humanistically, the challenge is that by requiring the use of a companion diagnostic, or biomarker, patients who test negative generally cannot receive the drug. This makes sense if the biomarker works perfectly, but if not, it means you are effectively denying the drug to patients who might benefit. As Alise Reicin, a Merck executive who oversaw much of the early pembo program (and is now SVP and head of global clinical development at EMD Sorono) recalls, “We heard from physicians that late-line lung cancer patients had no options, so even if they had only a 7-8% chance of responding" because the tumors did not express high levels of PDL1, the doctors still "wanted the option to use the drug.”

At the time the pembro team was engaging in these internal debates, Roger Perlmutter replaced Peter Kim as head of Merck Research Labs; many of Perlmutter’s former Amgen colleagues soon joined him, and one of their first

tasks was reviewing the pembro development program. According to a number of scientists, the new leadership team was very concerned about the biomarker approach that had been adopted. Some speculated that perhaps the new leadership team felt it had been burned by previous challenging experiences with biomarkers at Amgen, possibly during the development and commercialization of Amgen's Vectibix.

But many were convinced the main worry about the use of the PDL1 assay was scientific–which was how Perlmutter himself explained his concerns. "Decisions in early research are based on scientific, not commercial, considerations," Perlmutter told me, adding that from the outset, he embraced the idea of a biomarker for the lung program, but wanted to be sure it worked.

As Perlmutter explained, while PDL1 is the natural ligand of PD1, the biology is not so straightforward. Drugs that block PD1 may be especially effective in tumors with high levels of PDL1 because PDL1 itself may be a surrogate marker for local inflammation–it's upregulated in the presence of inflammatory cytokine interferon gamma, Perlmutter points out.

After considerable review and often-anguished debate, Perlmutter and colleagues backed the continued use of the biomarker in the NSCLC second-line program (the first studies had already kicked off by the time Perlmutter joined in April, 2013)–as well as in another, extremely important (and hugely valuable) set of studies evaluating the use of Keytruda as first-line therapy for NSCLC.

Even after this decision was made, it wasn't clear it was the right choice; BMS, for example, had elected to develop its PD1 agonist for lung without a biomarker–a decision that as recently as March 2016 was seen as yielding better results; consider this lede from the *Wall Street Journal*: "Bristol-Myers Squibb has sprinted to an early lead in the race to sell a new class of cancer treatment by bucking the trend toward precision medicine." The authors go on to observe that "Bristol has outflanked Merck partly by sticking to the old, mass-marketing approach."

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However, these results were for second-line therapy; when the results for pembro and nivo for first-line NSCLC were reported in 2016, there was a shock: Merck's study was strongly positive, while the BMS study–which used a biomarker, but with a far lower threshold–failed, a result that stunned many observers but seemingly vindicated Merck's approach.

The Merck team also used PDL1 levels to prioritize which tumors to target next; a preliminary study of the top four–head and neck, bladder, triple negative breast cancer and gastric cancer–led to promising results and dedicated studies in each of these indications (although the phase 3 program in advanced head and neck cancers reported negative results this week). An even more expansive program–evaluating pembro in a number of other advanced tumors, selected based on measured PDL1 level, soon followed.

"There Is No Line"

While the pembro clinical development program began under Kim, and was even placed on accelerated or "gold track" status internally, the key impact Perlmutter had on the program was recognizing it as an exceptional asset and redirecting virtually all work at Merck towards this program. According to Perlmutter, "I told everyone in research: stop what you're doing now. We've got to do this."

The organization got the message, and stories of Permultter's emphasis on Keytruda abound. According to one scientist, Perlmutter reportedly said, "I don't want to wake up in five years and wish I blew another $1 billion on this drug." Former Merck executive Reicin recalls presenting Perlmutter with a prioritized list of potential Keytruda clinical studies and asking him, based on

resources, where to draw the line. “There is no line,” Perlmutter reportedly responded. “Do them all.”

I asked Perlmutter about this, and he told me that given the melanoma results, you “didn’t need to be a genius” to figure out “there was something special here,” and to realize pembro had significant promise.

But what Perlmutter did that was distinctive was take this logic one step further. When he stepped back from the details of the program and considered the big picture, he recognized that pembro wasn’t just a promising product in Merck’s portfolio–it was more valuable than the entire rest of the portfolio put together. His resourcing of pembro work, to the exclusion of most other activities, reflected this conviction. “When you realize the potential of something like this,” he explained to me, “you need to bet your career on it.”

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Good Luck Coming In Over The Transom

It was Pasteur who famously observed that fortune favors the prepared mind –and Merck was the beneficiary of just this sort of good fortune when pembro leaders received a call from legendary Johns Hopkins cancer researcher Bert Vogelstein, saying, "We need to talk."

One of Vogelstein's colleagues at Hopkins, Suzanne Topalian, had just completed a clinical study of the BMS PD1 inhibitor nivo and was struck by a couple of observations. First, melanoma and NSCLC patients seemed to respond better than other tumor types. Second, while few patients with colorectal cancer (CRC) responded, the one CRC response that was observed was unusually durable. Vogelstein explains that he and his genetically oriented colleagues immediately had an idea: both melanomas and NSCLC –associated as there are with mutagens like sunlight and cigarette smoke, respectively–typically have many more mutations than other cancers. Cancers with high "mutational burdens" are more likely to have recognizable novel antigens–called mutation-associated neoantigens, or MANAs–to which T-cells can respond.

Perhaps, Vogelstein and his fellow geneticists suggested, the patient with CRC suffered from a relatively rare form of the cancer associated with a defect in mismatch repair, resulting in a similarly high mutational burden. *If you test the patient with CRC who responded to the PD1 drug*, Vogelstein predicted, *I bet he'll have the molecular signature of mismatch repair*–a finding known as "MSI-High." Sure enough, the patient was tested and found to have this marker.

Vogelstein told me that he and his colleagues promptly drafted a letter to a "prominent medical journal," articulating their theory–and almost immediately it was rejected as mere conjecture. So Vogelstein picked up the phone and proposed a study to Merck; Hopkins would both conduct and pay for the study, he said. All Merck needed to do was provide the drug–which at this point had not yet been approved for any indication. Merck agreed, and the results–as Gina Kolata eloquently describes in a recent *New York Times* article–confirmed the investigators' hypothesis, leading ultimately, in May 2017, to an unprecedented type of FDA approval for pembro–authorizing its use in a wide range of cancers, based on the presence of the MSI-high signature–"the FDA's first tissue/site-agnostic approval," according to the agency.

Lessons Learned

1. *Vast Distance Between Discovery and Commercialization*. It can be really hard to know in advance what discovery projects will succeed. When pembro was initiated, it began as a search for autoimmune therapeutics, looking for PD1 agonists. Even once an attractive PD1 antagonist was identified and recognized as potential oncology drug, it's potential wasn't obvious to either Schering Plough, when it acquired Organon, or to Merck, when it acquired Schering. Again, this is hardly unusual: When Millennium acquired Leukosite in 1999, for example, it was primarily for alemtuzumab (Campath); no one at either company likely appreciated at the time that Millennium also acquired a future blockbuster, bortezomib (Velcade).

2. *History Linearized Over Time*. The often circuitous history of drug development inevitably gets polished and more linear over time; lucky breaks and even fortunate missteps get cast as more intentional than they really were. The story told by the researchers in the trenches is generally much grittier than the version to which senior executives often cleave.

3. *People Matter*. Drugs neither discover nor develop themselves; the ultimate success of pembro is unquestionably attributable to a series of champions who believed in the possibility of the molecule and strove to enable it to demonstrate its potential. Every person with whom I spoke seemed to go out of their way to highlight several "unsung heroes"–frequently citing distinct sets of names.

4. *Circumstances Matter*. I'm especially struck by the role of Roger Perlmutter in the story of pembro–not because he was involved in the

discovery or early development of the molecule, but because of his decision to bet both his career and Merck's enterprise on this program. Every person to whom I spoke–which included a mixture of fans and critics–spoke of the singular impact of this decision. Less obvious, however, is how best to contextualize this choice. Perhaps any new leader who saw the early compelling data would make a similar decision. Conversely, maybe the program's success is directly attributable to his intrinsically good judgment and instinctive boldness –and this is the sort of decision he would have made any time in his career. Or maybe it reflects decades of experience in drug development –he had the perspective to recognize something truly special when he saw it. Or perhaps you are more likely to bet your career on a decision when you're in what's likely the last (and also the most coveted) role of your career, and realize you have a limited amount of time to make your name; perhaps under these circumstances, you are more likely to place a big bet–and also more likely (as some have observed) to prioritize a white-hot present-day program rather than invest your time and resources in discovery-stage research that's unlikely to bear fruit during your tenure, if at all. With so many possibilities, it feels like a bit like "choose your own narrative–pharma executive edition."

5. *Relationships With Regulators Matter*. Merck researchers involved with the early pembo clinical program were struck by the impact of working closely in partnership with regulators, rather than the more typical relationship, which tends to be more adversarial. As DeGeorge put it, "Regulators really want to get important new drugs to patients quickly," a sentiment shared by many members of the pembro team. As the researchers describe it, the FDA didn't relax its criteria but helped the development team understand what the agency was looking for, and what approaches might best get them there. It's a shame most drug development isn't this synergistic–but it's also a shame most drugs aren't this impactful. (Some critics worry such collegial drug development may not be in the best interests of patients; FDA oncology leaders discuss the issue thoughtfully in this 2016 *NEJM* commentary.)

6. *Agility Matters*. Pembro's rapid route to market and to patients reflects a commitment by Merck to develop this drug in what many pembro team members described as a conspicuously un-Merck-like fashion, foreshadowing a more general trend in the industry where, as FDA oncology leaders observed in *NEJM*, "the three distinct sequential phases of [cancer] drug development have…become increasingly blurred." One example cited by former Merck executive Reicin: going into a confirmatory phase 3 study for advanced melanoma (and before

pembro received accelerated [contingent] approval for this indication), the team wasn't sure about the exact dose (2mg/kg vs 10 mg/kg, each every third week) or the regimen (10mg/kg every two weeks or every three weeks), as the cohorts looking at this in early phase studies hadn't yet read out. Rather than test all three possibilities in each of two phase 3 studies–a more traditional approach–Reicin notes that Merck tested the two doses in one phase 3 study and the two regimens in the second, with the permission of the FDA. It then examined the combined data set to make the final determination (it turned out the two doses and two regimens all worked about the same). Without a willingness to contemplate such trial designs–and without the willingness of the FDA to consider them–the trial would unquestionably have taken far longer, and involved many more patients.

7. *Ars Longa*. The story of PD1 antognists, and of immunoloncology, has just begun, and no one knows how it will ultimately play out. The role of PDL1 as a biomarker remains the subject of much discussion. Merck researchers tend to attribute the use of this biomarker to their high response rates in both second- and first-line NSCLC, yet at least some data from BMS suggests the same biomarker–measured by a different assay–is less determinative (even when the same cutpoint is used as a criterion in an exploratory evaluation–see this recent *NEJM* paper). Vogelstein, for his part, shares Perlmutter's original sense that the PD1 story is about more than PDL1 levels, telling me "there's something about the whole process that's yet to be discovered." Keytruda's recently reported and unexpected failure in patients with advanced head and neck cancer speaks to the degree of uncertainty that remains.

8. *Translational Impact*. Ultimately, the goal of most academic and industry cancer researchers alike is to translate their insight into patient impact. Vogelstein provided a poignant example, describing a graduate student with Lynch Syndrome (an inherited disorder of DNA repair leading to a high mutation rate and often gastrointenstinal tumors) who had developed CRC in his 20s and metastatic disease by his 30s. Available therapies no longer worked, and he was scheduled to be admitted to hospice on Friday. On Wednesday, however, the patient got word that his tumor tested positive for MSI-high, meaning that he was now a good candidate for pembro. He responded incredibly well to the medicine, Vogelstein said, and in the last four years, has gotten married and moved away to start his life anew. Stories like this may remain the exception, but also highlight the transformative potential of biomedical innovation.