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Breakthroughs at Blueprint Medicines

In mid-March 2020, Blueprint Medicines CEO Jeff Albers and COO Kate Haviland (MBA 2005) were meeting to review company goals for the next quarter. Blueprint was a publicly-traded precision medicine company founded in 2011 in Cambridge, Massachusetts. In January 2020, the U.S. Food and Drug Administration (FDA) had approved the company's first drug, avapritinib,^a to treat patients with a genetically-defined form of gastrointestinal stromal tumor (GIST), a cancer affecting the digestive tract.

Drug development took an average of 12 years from discovery to final FDA approval, and only 11% of drug applications made it through the entire process (see **Exhibit 1** for the average timeline).¹ However, Blueprint had accelerated the timeline for avapritinib (known commercially as AYVAKIT) to around seven years. In addition, the company was nearly ready to file a New Drug Application (NDA) for its second drug candidate, pralsetinib, to treat a genetically-defined form of non-small cell lung cancer. An NDA was the last step in the FDA's review before a drug could be marketed to the public, and pralsetinib was on track for an even more condensed timeline than avapritinib, if approved (See **Exhibit 2** for Blueprint timeline).

Albers and Haviland felt that Blueprint was well on its way to becoming a fully integrated biopharmaceutical company that could move from drug discovery to development to marketing. But it was increasingly challenging to prioritize and manage programs, personnel, and partnerships. In the last few weeks, an unexpected complication appeared in the form of COVID-19, a highly contagious respiratory illness that started a global pandemic in December 2019. The pandemic complicated Blueprint's fast-moving efforts as stay-at-home orders were issued around the world and the company's leadership team made preparations for 400 employees to work from home, both to protect them and prevent the spread of the disease. Even so, Albers and Haviland felt confident that they could make progress on the company's strategic goals for 2020, which included marketing two commercial

^a Avapritinib was approved by the U.S. FDA for the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.

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launches in the U.S. and one in Europe, submitting multiple additional marketing applications to the FDA and its European equivalent, the European Medicines Agency (EMA) for their lead product candidates, and continuing to advance the company's clinical and research pipeline (see **Exhibit 3** for pipeline).²

Building Blueprint

In 2009, Boston-based biotechnology entrepreneur and venture capitalist Alexis Borisy was in the early stages of launching a precision diagnostics company that provided patient DNA sequencing to help identify the mutations that were driving a patient's cancer. Eventually Borisy hoped that this company, called Foundation Medicine, could provide a layout of mutations across all cancers. He knew what this would mean in the long term: "Within some period of time—a few years or a decade—we were going to have the roadmap of the genetic aberrations across all cancers. We could create THE precision medicine oncology company because if you know what is driving that cancer, you can create a super selective molecule for it."

Borisy realized this implied a different kind of business model for drug discovery since, if a drug could be made to precisely hit a specific target, the chances that the drug would be highly effective should substantially increase and fewer patients should be needed for clinical trials. Early in 2010, Borisy recruited two cofounders, oncologist Brian Druker and biochemist Nicholas Lydon, who led the team that created Gleevec, one of the first successful genomically-targeted drugs developed to treat chronic myeloid leukemia.³ As they incubated Blueprint, the cofounders decided to focus on a promising but understudied drug target—kinases. Kinases were enzymes that helped control the growth activities of a cell—such as signaling and division—and were associated with cancer. There were 518 kinases in the human genome, but only around 30 FDA-approved kinase medicines that targeted less than 5% of kinases.⁴ Gleevec was a kinase inhibitor,^b and Borisy felt there was an opportunity to create drugs like Gleevec that could block cancer-causing mutations in kinases.

A Different Kind of Library

Pharmaceutical companies typically amassed libraries with millions of compounds—combinations of chemical elements that were the building blocks of drug therapies—seeking to create as many drug options as possible. In 2011, Blueprint began to develop a library of compounds that might inhibit kinases. The team knew this would be challenging because outside of Gleevec, the biopharmaceutical industry had been largely unsuccessful in developing highly selective kinase inhibitors. As the leadership team investigated why this was, they realized that there were few compound libraries built specifically for kinases, and the ones that did target kinases focused largely on variants of just a few kinase inhibitors. This led to large libraries of similar compounds.

Blueprint took an agnostic approach to its compound library by casting a wide net, looking to create a diversity of compounds not directed at any particular kinase target, but seeking to cover the entire kinome^c tree (see **Exhibit 4** for the kinome tree and **Exhibit 5** for Blueprint's approach). Albers, who later joined Blueprint in 2014, described the creation of Blueprint's library:

The classic model is that you make all these molecules, you pick one, you find out where it's potent, and then you try to deconstruct what else is it doing. That's really hard

^b A kinase inhibitor blocked the activities of a kinase.

^c The kinome was the complete set of kinases encoded in the human genome.

to do. What Blueprint did was turn that on its head by making molecules even when we don't know what they do. It's like a 1,000-piece puzzle, and if you put 20 pieces in the right spot you still have no idea what it is. But as you get 500 pieces in, you start to see a couple of the shapes and you can tell that there's going to be a lake over here, or a little house over here, or it's blue sky and all your blue pieces should go over there.

This approach required a significant upfront investment. Blueprint raised \$40 million in its series A round in April 2011, led by Third Rock Ventures.⁵ Borisy said, "We were going to spend \$40 million and two years to build the library and would have no idea if it was any good until it was done."

Identifying a Winning Compound

In mid-2011, Blueprint recruited a handful of scientists with experience in kinases, and the team scoured the academic literature on kinases, looking for any information that could help direct their compound creation. The team slowly began to create molecules. By the end of 2011, they had a library of 1,700 compounds; by 2012 it grew to 7,000 compounds; ultimately, the library contained more than 20,000 compounds that reacted to different parts of the kinome tree. Blueprint scientists annotated the library with information based on testing each compound against almost every kinase.

Blueprint's approach paid off in November 2013, when researchers identified a compound that showed promise against diseases driven by mutations in the KIT and PDGFRA genes,^d in this case GIST. This compound would eventually become avapritinib. At the end of 2013, Blueprint had \$100,000 in the bank, but on the basis of its early compound, the company was able to raise a \$25 million B round, led by Nextech Invest in January 2014.⁶ By November 2014, when the company raised a \$50 million C round, Blueprint had synthesized the compound that became known as avapritinib.⁷

In April 2015, Blueprint went public, raising \$147 million, at a valuation of nearly \$400 million.⁸ Andy Boral, chief medical officer, said, "We raised a lot of money with our IPO, just on the basis of the promise of the platform and really interesting pre-clinical data." In mid-2015 that promise was realized when the company filed an Investigational New Drug (IND) application with the FDA to request approval to test avapritinib on human patients.

Blueprint's Approach to Drug Development

Blueprint's drug development strategy was twofold—it focused on creating a single drug compound for multiple disease indications, while at the same time developing drugs to track a disease through its progression. With the library as its engine, Blueprint's approach began with the identification of a single genetic driver of a disease that typically impacted a discrete patient population. Once scientists understood the basic driver, they could build on that knowledge to create therapies to treat broader patient populations with the same genetic driver but different disease indications. Blueprint could then repeat this process over and over again because, as Boral explained, once a drug had been proven effective against one disease, it was likely to be effective against others: "There's a lot of redundancy in biology and it is incredibly unlikely, I think, to find a target that's very active in some disease that is not relevant somewhere else."

^d KIT and PDGFRA were homologous tyrosine kinase receptors. In patients with GIST and certain other malignancies, a spectrum of clinically relevant mutations force the KIT or PDGFRA protein kinase into an increasingly active state, resulting in tumor formation and growth. Source: Blueprint Medicines, "Research Areas of Focus," <https://www.blueprintmedicines.com/science/research-areas-of-focus/>, accessed October 2019.

Blueprint then tracked the evolution of the disease to address mutations that created drug resistance. Many patients who responded well to initial treatments often developed resistance to the so-called first-line treatment as their cancer mutated. They then had to turn to another therapy, called a second-line treatment, and sometimes progressed to third and fourth-line treatment as their cancer became resistant to each subsequent therapy. Blueprint hoped to sidestep this problem by creating medicines that accounted for disease mutations. Jim Baker, Blueprint's vice president of corporate affairs said, "As patients begin to progress through treatment, we can evolve with the cancer and understand the mutation that drives its progression. Then we can develop new medicines that target the resistance mutations that evolve over time. Our vision is to follow patients along their treatment path and extend their lives." Eventually the company hoped its therapies might be used not to treat specific diseases, but to treat any disease caused by the disease driver (see **Exhibit 6** for an illustration of Blueprint's process).

Avapritinib

When Blueprint moved forward with clinical trials for avapritinib in July 2015, it was extremely selective about trial enrollment, meaning participating patients had to have genetic mutations in the KIT and PDGFRA genes targeted by the drug candidate. This meant that patients had to be genetically tested for the mutation before participating in the trial. Haviland explained, "The more precise you get, the fewer patients you need to enroll."

Some investors expressed concern that genetic testing created a hurdle for patients and smaller trials might mean slower results. PDGFRA-driven GIST accounted for only 5% to 6% of an already rare disease and finding patients for trials was a source of consternation for the team. Boral said, "We really had very little idea how we were going to find the PDGFRA-driven GIST patients. When we started out, we found a few patients, but there was a high level of anxiety. How would we get the 50 people we thought we needed?" Blueprint worked with patient groups, such as The Life Raft Group and GIST Support International, to raise awareness about the clinical trials and bolster patient recruitment.

The first patients were treated in October 2015. Two months later, the team received word that a patient was showing substantial tumor shrinkage. It was unusual to see a response to a new drug so soon because patients were treated with a very low dose of the drug at first. The purpose of a phase 1 study was to test the safety of the drug and discover the appropriate dosage while weighing any side effects. Many companies were not able to determine if their drug was effective until a phase 2 study (see **Exhibit 7** for the clinical trial process in the U.S.). A positive response in phase 1 enabled Blueprint to transition seamlessly into phase 2 by enrolling additional patients throughout 2016. With this response, Blueprint went from being worried about recruiting patients for its clinical trials to being almost overwhelmed by interest from patients and doctors in the GIST community. Albers said, "In essence, what we've done here is we've turned phase 1 safety studies into multi-registration broad-based trials. So, a study that started with 30 patients gets amended to go to 50 patients, and then gets amended to 100 patients and now we have studies that have 300 to 500 patients."

These early results led the FDA to grant Breakthrough Therapy Designation (BTD) status to avapritinib in June 2017 for a specific type of GIST. BTD gave the Blueprint team access to the FDA for faster feedback to expedite the development of avapritinib. Since the FDA created BTD in 2012, 37% of drug applications had received the designation⁹ (see **Exhibit 8** for BTD). As news of the BTD rippled out, it created additional buzz around avapritinib and it made a positive impression on the investor community. Boral wondered why this was, until he realized: "It's a credible and independent validation of our data and program. Until then, we had been telling the investor community what we

thought of avapritinib, and showing them the data, but this was the first indication that a completely independent entity had reviewed clinical data and agreed that it was good.”

Blueprint submitted the NDA for avapritinib in June 2019, and it was granted priority review by the FDA in August 2019. Priority review reduced the final approval process from a maximum of 12 months to eight months from the filing date. Blueprint received FDA approval of avapritinib for a form of GIST driven by specific mutations in January 2020.

Pralsetinib

As avapritinib moved into clinical trials in 2015, scientists at Blueprint were busy refining another compound that would eventually become pralsetinib, which targeted a mutation in the RET^e gene. This mutation was a known genetic driver of sub-sets of non-small cell lung and medullary thyroid cancers. The company created pralsetinib with the disease evolution in mind. Boral explained:

We made it so it would do three things: it hit the wild-type^f version of RET, it hit the mutant version with the driver mutation, but it also hit versions where we predicted resistant mutations would occur. Essentially it was a first and second generation inhibitor combined into one that was made to not only address where the tumor is, but where we thought the tumor was going to go next.

Similar to avapritinib, patients were only enrolled in the pralsetinib trial if they had the targeted mutation. The first patient was dosed in March 2017, and the first response came in June 2017 from an unexpected patient. Boral said, “We opened that clinical trial site with the goal of finding thyroid cancer patients, but actually the first response was in a lung cancer patient who one of the specialist’s colleagues sent to him because the patient had an RET-driven lung cancer.” This was an indication that Blueprint’s therapies were not limited by disease, but could be effective against any cancer with the targeted disease driver. Baker explained how Blueprint hoped to take this idea even further, “The broader concept is how do we develop, obtain approval, and market a selective inhibitor like pralsetinib not just for lung or thyroid cancer, but for any patient with RET-driven disease. Ultimately we believe cancer is better defined by the oncogenic driver than the location of the primary tumor, and we can help more patients if we change healthcare systems to think this way, too.” As a first step toward this vision, Blueprint hoped pralsetinib would be approved and available commercially in the fall of 2020 for patients with RET-driven lung cancer.

Commercialization

In October 2018, Blueprint hired Christy Rossi (MBA 2003) as chief commercial officer. By that point avapritinib and pralsetinib were well along the path towards NDA submission, and the company could plan its commercialization strategy around both drugs. Haviland said: “We could build the team and infrastructure in a way that considers the whole portfolio. If we had a big gap between commercialization of our first and second drug, we would only be able to justify investing in more modest infrastructure. But because we had pralsetinib and avapritinib potentially launching so close

^e Alterations in RET, a tyrosine kinase receptor, caused ligand-independent kinase activation, driving tumor formation and growth across a range of cancers, including non-small cell lung cancer, medullary thyroid cancer and papillary thyroid cancer, oncogenic. Source: Blueprint Medicines, “Research Areas of Focus,” <https://www.blueprintmedicines.com/science/research-areas-of-focus/>, accessed October 2019.

^f A wild-type gene was a non-mutated gene that occurred naturally in nature.

together with multiple indications to drive growth, we could build out a full commercial team to service the entire portfolio.”

When to put a field team in place was a balancing act. Rossi said, “If you wait until FDA approval you will delay initial launch uptake, but if you bring the field team on earlier you increase cash burn. In addition, if we had any regulatory surprises, we did not want to be in the position of having to lay people off.” Rossi knew that well-resourced drug companies generally staffed a sales team in the field three to six months before expected FDA approval for training purposes. She planned to extend offers to the full sales team in October 2019, three months before the FDA’s decision was expected on avapritinib. But in October, before offers were made, the company received news that the FDA planned to split its review of avapritinib into separate applications, one for PDGFRA-driven GIST and another for fourth-line GIST, which added an element of risk to the approval process. Rossi said, “We had to think about the right thing for the business. There were tradeoffs between investing in the team versus revenue. We decided to delay hiring until January even though we had identified people we wanted to hire and were ready to make offers in October.” Rossi believed keeping the company’s options open was the right decision, but acknowledged the downside, “By erring on the conservative side in our build out, we may put the launch trajectory at risk.”

As Rossi built up her team, she focused on the cultural fit of the new hires. She noted: “It was important to make sure we maintained cultural elements as we bridged into commercial. We made sure we identified Blueprint-type people in the field, people who were engaged in science, could sell clinically, and who bring a feeling of urgency and strong patient focus to everything they do.” Rossi even had Blueprint scientists interview some of the candidates for leadership roles on her team.

By March 2020, Blueprint had a sales force of 42 people across six U.S. sales regions. Each sales team was responsible for both avapritinib and pralsetinib. Two months after avapritinib was approved for marketing, company sales of the drug were already three times what Blueprint expected. Rossi predicted that going forward their commercial effort would start to shift to focus on pralsetinib to support its launch into RET-driven lung cancer which affected many more patients than those with PDGFRA-driven GIST.

Importantly, there was significant overlap in doctors who treated patients with GIST and lung cancer, allowing the Blueprint team to efficiently support both drugs. Blueprint focused sales first on major academic centers and large medical practice groups, however Haviland noted that community doctors treated 70% of cancer patients. She recognized the challenges of reaching community doctors: “It’s an overwhelmed group of people and they’re going to see a lot of breast cancer and colorectal cancer, but their opportunity to see PDGFRA-driven GIST is rare – maybe once every year, maybe once every couple of years. How do they stay on top of innovations like the ones that we are providing that target rare subsets of patients?”

To this end, Blueprint worked to raise awareness by collaborating with patient advocacy groups. Baker said, “We invest time and energy into building collaborative relationships with advocacy partners early in the drug development process even before we enter the clinic, so groups can understand the underlying science, we can understand the disease and care model, and clinical trials can be optimized to address patient needs. Over time, this collaboration has enabled our partners to be well informed and independently advocate for updates to clinical care guidelines including testing and innovative new therapies such as avapritinib, and empowering patients to advocate for themselves throughout the diagnosis and treatment journey.”

Partnerships

Blueprint was in a unique position as a small company to have built a broad and deep portfolio of innovative programs driven from its own drug discovery engine. Given a plethora of opportunities, the company had to be extremely careful in how it allocated resources so as to maintain flexibility to invest in research and development based on emerging data, as well as invest in commercial capabilities to enable the company to bring treatment innovations directly to patients. Albers and Haviland noted the company pursued a “one size too small” approach focused on operational discipline and efficiency to rapidly advance its most promising programs while maintaining financial sustainability. This meant that Blueprint sometimes looked for partners to maximize value from its library. Haviland said, “Although having capital to redeploy against other opportunities in the portfolio is helpful, we do not partner for capital alone. A partnership has to fit with our overall corporate strategy.” Albers added:

Some small companies do everything on their own from discovery to marketing and then get bought out. Others are good at the science in the early phases but will license out the rest of the development and commercial responsibilities. Blueprint has intentionally operated in the middle. Our view is that we need to understand where we are strong, but be humble and know that others can do certain things better. A partner can either accelerate the development timeline or expand the breadth of the development through geographic reach or areas of expertise.

Blueprint’s first partnership in March 2016 was with Swiss healthcare company, Roche, to discover and develop therapies targeting kinases important in cancer immunotherapy, a treatment that used a patient’s own immune system to fight disease. Baker commented, “We have the expertise to target kinases, but we don’t have expertise in immunotherapy. It’s a complex space and Roche is a leader so we paired their cancer immunotherapy expertise with our scientific platform to do work that we could not do on our own.” Their collaboration encompassed multiple targets including MAP4K1, a kinase believed to play a role in the regulation of T cells, which were important in the human immune system. The deal was worth around \$1 billion, including a \$45 million initial payment to Blueprint, with the rest contingent on meeting milestones.¹⁰ In March 2020, the program was in the research phase.

In June 2018, Blueprint signed a contract with Chinese company CStone Pharmaceuticals to develop and commercialize avapritinib, pralsetinib, and a third investigational therapy, fisogatinib, in Mainland China, Hong Kong, Macau, and Taiwan. Blueprint originally sought a partner to support development of fisogatinib, used to treat a genomically-defined subset of hepatocellular carcinoma (HCC), the most common type of liver cancer, of which more than half of all new cases worldwide occurred in China. At the same time China was also in the midst of important regulatory and economic reforms including more transparent and straightforward regulatory guidelines to enable innovative new drugs to be brought to market in China. Haviland said, “As we watched these reforms begin to take effect, it became clear to us there was a significant opportunity to expand our global development across Blueprint’s portfolio to patients in China sooner than we originally anticipated.” Haviland met with more than 30 potential Chinese partners spanning the traditional large domestic companies who had been commercializing drugs for decades, to the new generation of smaller China-focused biotechnology companies. Haviland said, “We focused on three key partner criteria, the first being the team and their global and regional expertise. The second was the opportunity to combine our portfolio with potentially complementary cancer therapeutics in a partner’s pipeline, and the third was alignment between the two companies’ strategic approach and values.”

As they worked on the deal with CStone, it made sense to license all three of Blueprint's late stage programs to them. Baker said, "From a strategic point of view, the partnership is more efficient and helps us be responsive to the tremendous needs of HCC patients and healthcare providers in China, while also defining a more rapid path to realizing the full value of our late stage programs in China than we could on our own." Blueprint received \$40 million upfront from the CStone partnership that could potentially result in a total payout of \$386 million.¹¹

In October 2019, Blueprint partnered with Ipsen subsidiary Clementia Pharmaceuticals, to develop and commercialize BLU-782 for the treatment of fibrodysplasia ossificans progressive (FOP), a very rare disorder in which a patient's muscle and connective tissue eventually turn into bone. Blueprint had a compound shown to be effective in pre-clinical models that targeted the genomic driver of FOP, but decided to pass it on to Ipsen to increase the program's probability of success and reduce the pull on Blueprint's internal resources, which were focused on avapritinib and pralsetinib. Albers said, "Ipsen had access to data that they had compiled over time that would make design of the clinical trials more effective and faster than anything we had or could build, ensuring that BLU-782 would get to patients as fast as possible." Blueprint was eligible to receive up to \$535 million from the deal, including \$45 million in upfront and near-term payments in the first year.¹²

On the other hand, Blueprint chose not to partner for the commercialization of avapritinib and pralsetinib in Europe. Haviland said, "Two years ago we looked for European partners for avapritinib. We had great partnering options but in the end it made more sense for us to do it ourselves. Avapritinib was the perfect way to build a European organization; we could start small and grow incrementally in a risk-gated way." The company had already submitted an application to market avapritinib and was on track for a decision from the EMA in the third quarter of 2020. It also planned to submit an application to market pralsetinib for RET-driven non-small cell lung cancer in Europe in the second quarter of 2020.

Balancing Thoughtfulness and Urgency

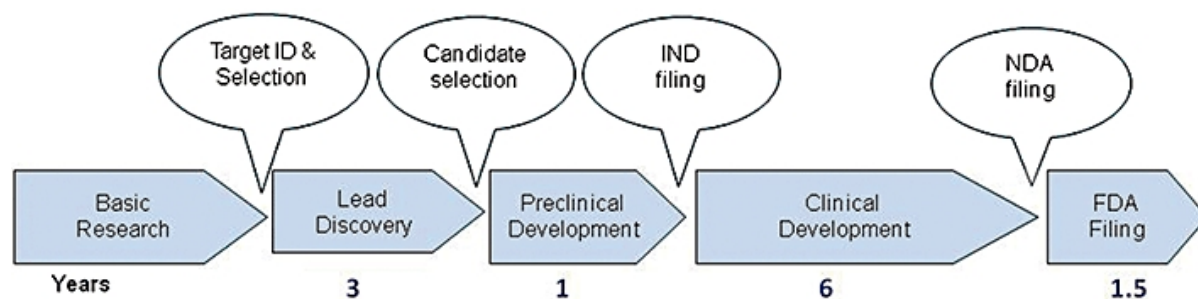
Blueprint had grown from 250 people in 2019, to 400 in early 2020, propelled by the build out of the commercial group. The leadership team wanted to maintain Blueprint's culture of thoughtfulness and urgency as it expanded into this new line of business and moved towards its goal of becoming a fully integrated biopharmaceutical company. Albers said, "I often urge employees to 'make haste slowly,' which means think about what you are doing, but move quickly. There are patients waiting at the end of every single one of these journeys." One way that Blueprint did that was through their philosophy on goal setting. Albers explained, "I ask people to aim high and miss rather than aim low and hit it every time. I have to reinforce that it's ok to miss." The leadership team also engaged in scenario planning, a tool that helped assess risk based on a multitude of possible outcomes so the team could pivot quickly when a particular plan did not go as intended.

Blueprint's expansion continued along multiple dimensions: expanding disease indications on existing therapies, developing therapies that followed the evolution of a disease, new research programs, and global expansion. Along these lines Albers and Haviland expected the rest of 2020 to be very productive. Besides continued marketing of avapritinib for PDGFRA-driven GIST, the company was preparing for NDA submission of avapritinib for a rare disease called systemic mastocytosis (SM), a blood disorder that could impair organ function and reduce life span.¹³ Avapritinib was designed to target the KIT D816V mutation that drove SM in nearly all cases. KIT D816V was genetically similar to the PDGFRA D842V mutation that drove GIST in a subset of patients. Similar to what had been seen in PDGFRA-driven GIST, robust clinical activity had been demonstrated in patients with the advanced form of SM when treated with avapritinib, a promising outcome in a disease with a median life

expectancy of about 3.5 years. The company also planned to submit an NDA to market pralsetinib for medullary thyroid cancer, which, like non-small cell lung cancer, was caused by a mutation in the RET gene (see **Exhibit 9** for anticipated milestones). In the meantime, its research programs continued to expand as its library drove discovery of new investigational therapies. But even success came with challenges. Haviland explained, “Because our science and scientific platform have been so successful, and our drugs have acted in the way we designed them enabling rapid development and filings for regulatory approval, our opportunities at times outpace our ability to capture them.”

Still, Albers and Haviland wanted to maintain Blueprint’s one size too small philosophy to sustain the efficiency and urgency that was the hallmark of their work thus far. But Albers acknowledged, “As you get bigger, you build a broader range of functional expertise requiring more thoughtful coordination across a larger number of people and functions which results in sacrificing some of that urgency. We have to think about how we maintain our drive so that the next new program from our drug discovery engine is moving the same way that avapritinib did four years ago.” Should Blueprint look for additional partnerships to maximize opportunities they might be unable to explore themselves? How should they decide to spend their limited resources without overextending their team?

As if this were not enough, now they had a pandemic to contend with. Albers mused, “There may be incremental delays but not wholesale delays to our strategy. Collectively our people are resilient and creative and will adapt to new ways of working. People at Blueprint are energized about the work we do and know that patients with advanced cancer and rare diseases do not have time on their side.”

Exhibit 1 Average Drug Development Timeline (2011)

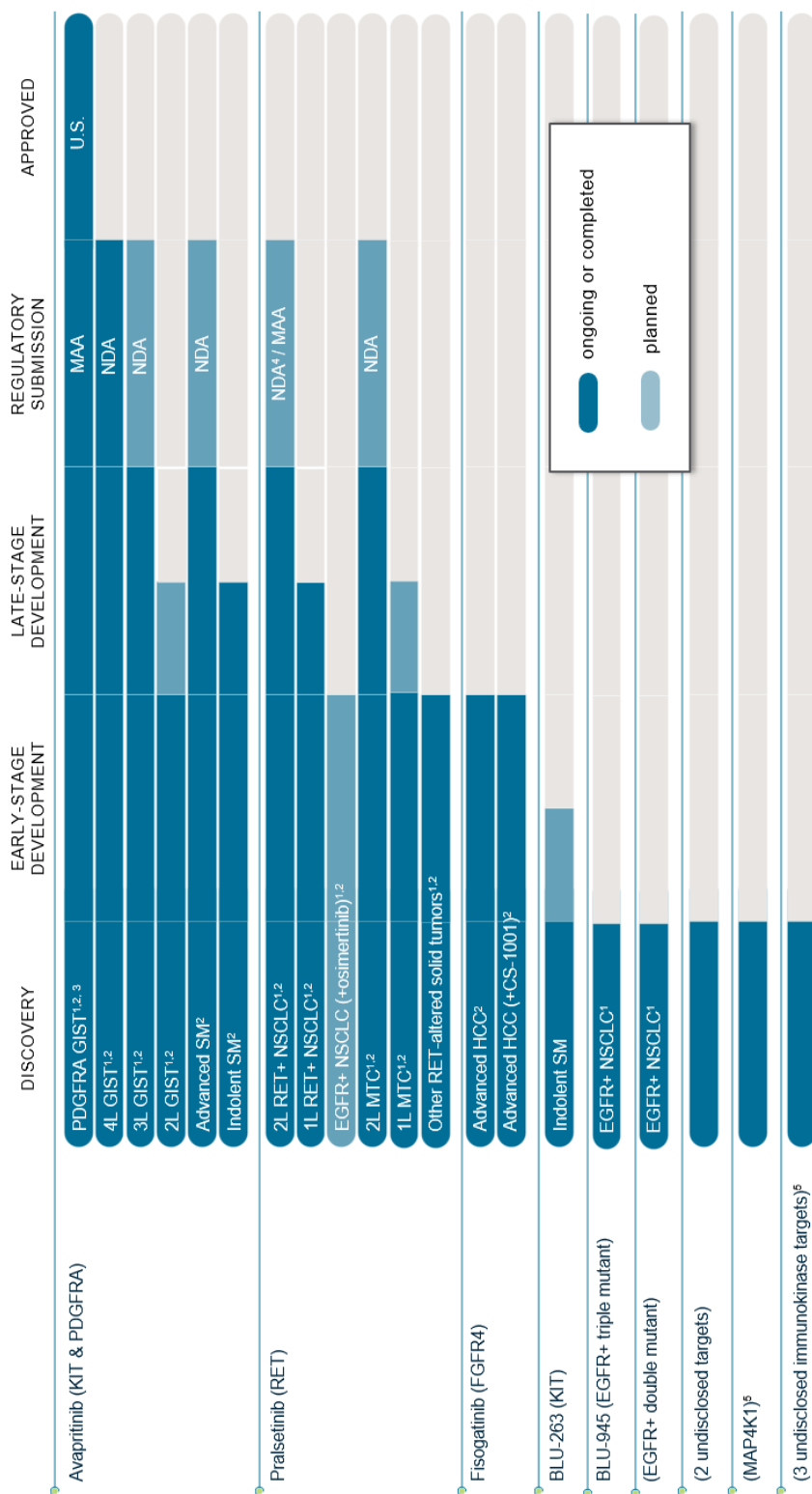
Source: JP Hughes, S Rees, SG Kalindjian, and KL Philpott, "Principles of Early Drug Discovery," *British Journal of Pharmacology*, March 2011, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3058157/>, accessed October 2019.

Exhibit 2 Blueprint Drug Development Timeline for Avapritinib and Pralsetinib (2013-2020)

November 2013	Lead compound that would become avapritinib synthesized
April 2014	Avapritinib becomes a development candidate
May 2015	Lead compound that would become pralsetinib synthesized
June 2015	Avapritinib IND submitted
October 2015	Avapritinib clinical trials begin
December 2015	Avapritinib first patient response
December 2015	Pralsetinib becomes a development candidate
November 2016	Pralsetinib IND submitted
March 2017	Pralsetinib clinical trials begin
June 2017	Pralsetinib first patient response
June 2017	Avapritinib Breakthrough Therapy Designation
February 2019	Pralsetinib Breakthrough Therapy Designation
June 2019	Avapritinib NDA submitted
January 2020	Avapritinib approved by FDA
March 2020	Pralsetinib NDA submitted

Source: Casewriter compiled from company interviews and documents.

Exhibit 3 Blueprint Pipeline (March 2020)

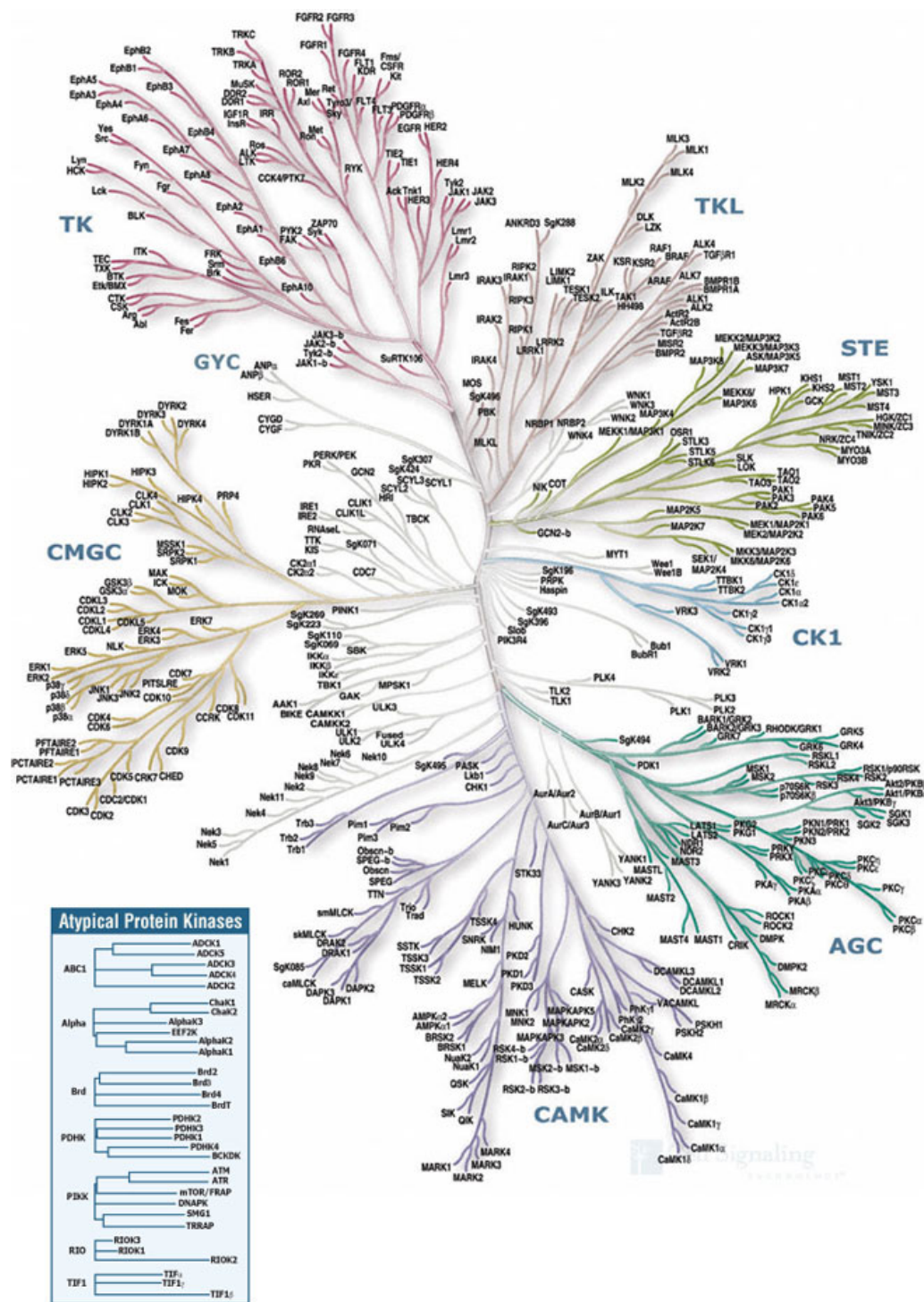


Source: Company documents.

Note:

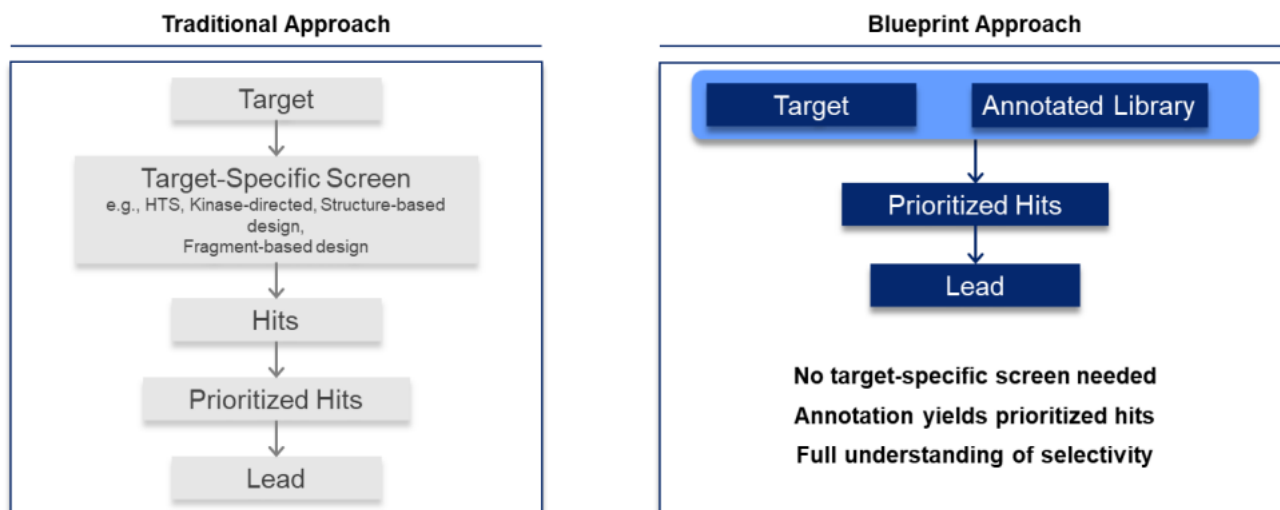
1. Unresectable or metastatic disease. 2. CStone Pharmaceuticals has exclusive rights to develop and commercialize avapritinib, pralsetinib and fisogatinib in Mainland China, Hong Kong, Macau and Taiwan. Blueprint Medicines retains all rights in the rest of the world. 3. Approved in the U.S. for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. The proposed MAA indication is unresectable or metastatic GIST harboring a PDGFRA D842V mutation. 4. Expect to complete rolling NDA in March 2020. 5. In collaboration with Roche. Blueprint Medicines has U.S. commercial rights for up to two programs. Roche has worldwide commercialization rights for up to two programs and ex-U.S. commercialization rights for up to two programs. 1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; MAA, marketing authorization application; MTC, medullary thyroid cancer; NDA, new drug application; NSCLC, non-small cell lung cancer.

Exhibit 4 Kinome Tree (2019)



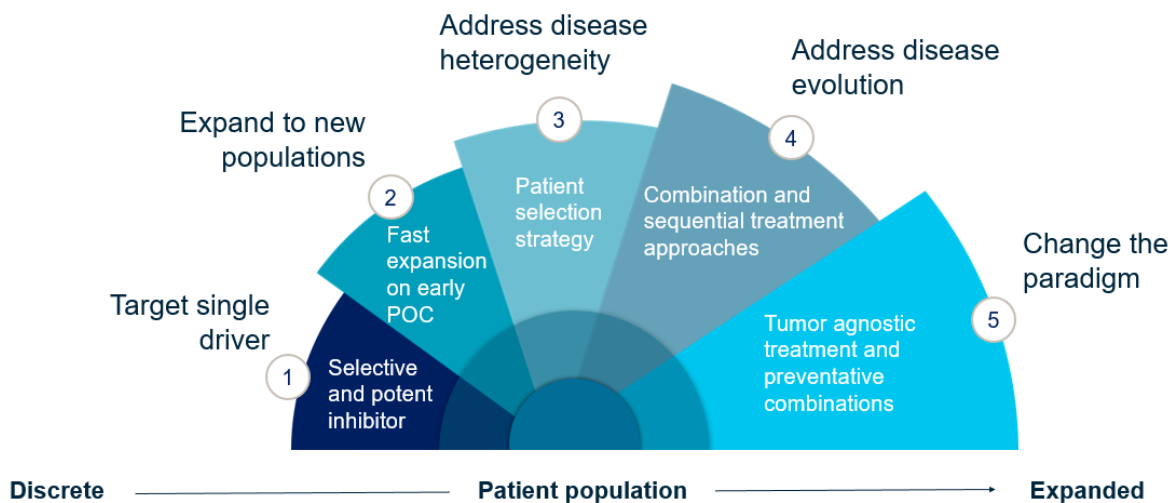
Source: “Protein Kinases: Human Protein Kinases Overview,” Cell Signaling Technology, <https://www.cellsignal.com/contents/science-protein-kinases/protein-kinases-human-protein-kinases-overview/kinases-human-protein>, Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com), accessed October 2019.

Exhibit 5 Comparison between Blueprint Medicines' Approach to Building its Library and a Traditional Approach

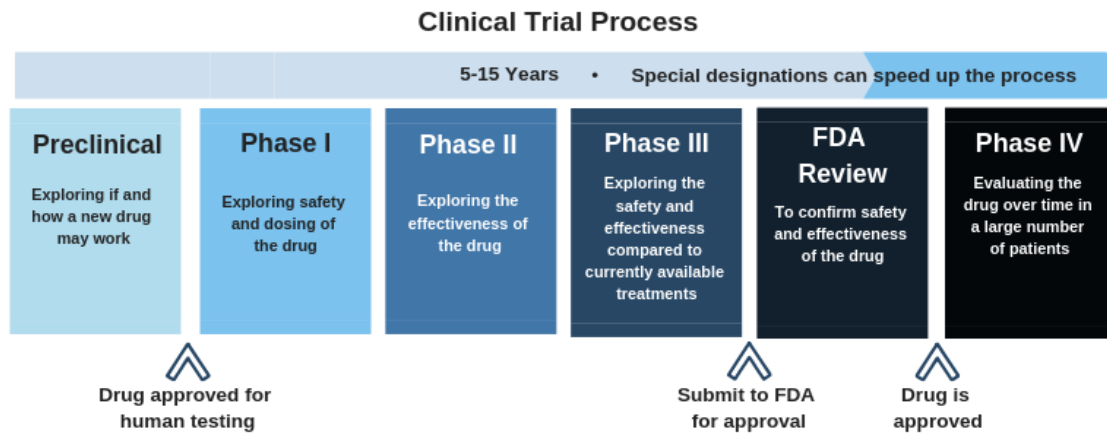


Source: Company documents.

Exhibit 6 Blueprint Medicines Expansion Fan



Source: Company documents.

Exhibit 7 Clinical Trial Process Based on FDA Requirements (2019)

Source: Hepatitis B Foundation, "Phase 3 Clinical Trials Opening for Hepatitis Delta Patients," March 21, 2019, <https://www.hepb.org/blog/phase-3-clinical-trials-opening-hepatitis-delta-patients/>, accessed October 2019.

Exhibit 8 FDA Description of Breakthrough Therapy Designation (BTD)

Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).

To determine whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the treatment effect, which could include duration of the effect, and the importance of the observed clinical outcome. In general, the preliminary clinical evidence should show a clear advantage over available therapy.

For purposes of Breakthrough Therapy designation, clinically significant endpoint generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. A clinically significant endpoint can also refer to findings that suggest an effect on IMM or serious symptoms, including:

- An effect on an established surrogate endpoint
- An effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
- An effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease
- A significantly improved safety profile compared to available therapy (e.g., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy

A drug that receives Breakthrough Therapy designation is eligible for the following:

- All Fast Track designation features
- Intensive guidance on an efficient drug development program, beginning as early as Phase 1
- Organizational commitment involving senior managers

Breakthrough Therapy designation is requested by the drug company. If a sponsor has not requested breakthrough therapy designation, FDA may suggest that the sponsor consider submitting a request if: (1) after reviewing submitted data and information (including preliminary clinical evidence), the Agency thinks the drug development program may meet the criteria for Breakthrough Therapy designation and (2) the remaining drug development program can benefit from the designation.

Ideally, a Breakthrough Therapy designation request should be received by FDA no later than the end-of-phase-2 meetings if any of the features of the designation are to be obtained. Because the primary intent of Breakthrough Therapy designation is to develop evidence needed to support approval as efficiently as possible, FDA does not anticipate that Breakthrough Therapy designation requests will be made after the submission of an original BLA or NDA or a supplement. FDA will respond to Breakthrough Therapy designation requests within sixty days of receipt of the request.

Source: "Breakthrough Therapy," U.S. Food and Drug Administration, <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy>, accessed October 2019.

Exhibit 9 Blueprint's Anticipated 2020 Milestones (January 2020)**Regulatory Approvals**

Avapritinib in fourth-line GIST in the U.S. in Q2 2020
Avapritinib in PDGFRA D842V GIST in the EU in Q3 2020
Pralsetinib in RET+ NSCLC in the U.S. by the end of 2020

Regulatory Submission

Pralsetinib NDA to FDA for RET+ NSCLC in Q1 2020
Pralsetinib NDA to FDA for 2L RET+ MTC in Q2 2020
Avapritinib sNDA to FDA for advSM in 2H 2020
Avapritinib sNDA to FDA for 3L GIST in 2H 2020

Top-Line Registration Data

Avapritinib VOYAGER trial in 3L GIST in Q2 2020

Medical Meeting Presentations

Avapritinib PIONEER trial Part 1 in ISM in Q1 2020
Pralsetinib ARROW trial in RET+ NSCLC in 2020
Pralsetinib ARROW trial in RET+ MTC in 2020
Avapritinib VOYAGER trial in 3L GIST in 2020
Avapritinib EXPLORER and PATHFINDER trials in advSM in 2H 2020
Complete Trial Enrollment
Avapritinib PIONEER trial Part 2 in ISM by the end of 2020

Trial Initiations

BLU-263 Phase 1 trial in healthy volunteers in 1H 2020
Pralsetinib Phase 3 trial in 1L MTC in 2H 2020

Research pipeline

Nominate up to 3 development candidates in 2020

Source: Company documents.

Endnotes

¹ Gail A. Van Norman, "Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs," JACC: Back to Translational Science, April 2016, <https://www.sciencedirect.com/science/article/pii/S2452302X1600036X>, accessed September 2019.

² "Blueprint Medicines Announces "2020 Blueprint" Global Business Strategy and Outlines Key Corporate Goals," press release, January 4, 2019, <http://ir.blueprintmedicines.com/news-releases/news-release-details/blueprint-medicines-announces-2020-blueprint-global-business#>, accessed June 2020.

³ Ben Fidler, "Blueprint Medicines Bags \$147M in Upsized IPO," Xconomy, April 29, 2015, <https://xconomy.com/boston/2015/04/29/blueprint-medicines-bags-147m-in-upsize-ipo/>, accessed September 2019.

⁴ Blueprint Medicines, "Selective Kinase Medicines," <https://www.blueprintmedicines.com/science/selective-kinase-medicines/>, accessed October 2019.

⁵ Gregory T. Huang, "Blueprint Medicines Brings In \$40M, Led by Third Rock, for Targeted Cancer Therapies," Xconomy, April 22, 2011, <https://xconomy.com/boston/2011/04/11/blueprint-medicines-brings-in-40m-led-by-third-rock-for-targeted-cancer-therapies/>, accessed September 2019.

⁶ "Blueprint Medicines Announces \$25 Million Series B Financing," press release, January 7, 2014, Business Wire, <https://www.businesswire.com/news/home/20140107006754/en/Blueprint-Medicines-Announces-25-Million-Series-B-Financing>, accessed September 2019.

⁷ "Blueprint Medicines Secures \$50 Million in Series C Financing," press release, November 12, 2014, PRNewswire, <https://www.prnewswire.com/news-releases/blueprint-medicines-secures-50-million-in-series-c-financing-282396331.html>, accessed September 2019.

⁸ BPMC, Crunchbase, <https://www.crunchbase.com/ipo/blueprint-medicines-ipo--328beb76>, accessed September 2019.

⁹ "Breakthrough Therapies," Friends of Cancer Research, <https://www.focr.org/breakthrough-therapies>, accessed September 2019.

¹⁰ "Blueprint Medicines Announces Worldwide Collaboration to Accelerate and Expand its Development of Novel Medicines in the Field of Cancer Immunotherapy," press release, May 15, 2016, <https://www.prnewswire.com/news-releases/blueprint-medicines-announces-worldwide-collaboration-to-accelerate-and-expand-its-development-of-novel-medicines-in-the-field-of-cancer-immunotherapy-300235920.html>, accessed June 2020.

¹¹ "Blueprint Medicines and CStone Pharmaceuticals Announce Exclusive Collaboration and License Agreement to Develop and Commercialize Avapritinib, BLU-554 and BLU-667 in Greater China," press release, June 4, 2018, <https://www.prnewswire.com/news-releases/blueprint-medicines-and-cstone-pharmaceuticals-announce-exclusive-collaboration-and-license-agreement-to-develop-and-commercialize-avapritinib-blu-554-and-blu-667-in-greater-china-300658810.html>, accessed June 2020.

¹² Blueprint Medicines Corporation, September 30, 2019, Form 10-Q, <https://www.sec.gov/ix?doc=/Archives/edgar/data/1597264/000155837019009888/bpmc-20190930x10q52dbde.htm>, accessed June 2020.

¹³ Genetics Home Reference, "Systemic Mastocytosis," <https://ghr.nlm.nih.gov/condition/systemic-mastocytosis>, accessed June 2020.