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Nearly One Year Post-Celgene: BMS CMO On Pipeline Progress, Clinical Trial Diversity

by Mandy Jackson

Chief medical officer Samit Hirawat outlines R&D successes – though there have been some setbacks since it bought Celgene for $74bn last year – and the company's commitment to clinical trial diversity.

As the one-year anniversary of *Bristol-Myers Squibb Company*'s $74bn acquisition of *Celgene Corporation* approaches, *Scrip* spoke with chief medical officer Samit Hirawat about the big pharma's achievements during a challenging period in which the COVID-19 pandemic threatened to derail clinical trials and a national spotlight on racial inequality shined a light on the industry's lack of diversity.

Key products, such as the PD-1 inhibitor Opdivo (nivolumab), delivered positive results in important studies and won new approvals since the BMS-Celgene merger closed in November. However, Bristol promised Celgene shareholders an additional payout if three key product candidates were approved by certain dates and the company has struggled to meet those deadlines – though approvals for the final two therapies may come through just in time. (Also see "*With Celgene Acquisition Closed, Bristol Faces Major Milestones*" - Scrip, 21 Nov, 2019.)

Approval Of BMS/Bluebird's Ide-Cel May Come Just In Time

By Mandy Jackson

22 Sep 2020
In last year's acquisition, Bristol Myers Squibb agreed to pay Celgene investors another $9 per share based on three approvals, including idecabtagene vicleucel (bb2121) by 30 March 2021.

Read the full article here

Nevertheless, Hirawat describes the BMS research and development team's achievements over the past 10 months as remarkable given the challenge of keeping programs on schedule during a global pandemic. COVID-19 forced employees to work from home, but clinical trials largely

continued.

At the same time, biopharmaceutical companies have been compelled to address concerns in the US and globally about racial inequality. (Also see "*Leading A Diverse Company: Biopharma Executives Offer Ways Forward*" - Scrip, 12 Jun, 2020.) BMS responded with a $300m commitment that includes training clinical trial investigators from diverse backgrounds and increasing the diversity of participants in the company's trials – two efforts that go hand in hand, Hirawat noted in a recent interview.

The CMO joined Bristol from *Novartis AG*, where he was head of oncology development, as BMS assembled a new R&D leadership team in preparation for the integration of Celgene's pipeline programs into the company. Hirawat oversees drug development from its earliest stages through commercialization and works with Rupert Vessey, who oversaw early R&D at Celgene and now has a similar role at BMS. (Also see "*Bristol Unveils Post-Celgene Leadership Team, With Big R&D Changes* " - Scrip, 5 Jun, 2019.)

Aiming For Transformative Science

"Our vision is to transform patients' lives through science," Hirawat said, "which is something we've continued to focus on since the closing of the transaction last year."

He noted six clinical trials with positive results in areas of large unmet medical need:

- The Phase III CheckMate-9LA study of Opdivo, the CTLA-4 inhibitor Yervoy (ipilimumab) and low-dose chemotherapy versus high-dose chemotherapy in first-line metastatic non-small cell lung cancer (NSCLC);
- The Phase III CheckMate-9ER study of Opdivo and *Exelixis, Inc.*'s Cabometyx (cabozantinib) in previously untreated advanced renal cell carcinoma (RCC); (Also see "*Bristol/Exelixis Detail Survival Benefit For Opdivo/Cabometyx In Renal Cancer*" - Scrip, 19 Sep, 2020.)
- The Phase III CheckMate-743 study of Opdivo and Yervoy versus chemotherapy in first-line unresectable pleural mesothelioma; (Also see "*Pipeline Watch: Phase III Readouts In Mesothelioma, Insomnia, Pruritus*" - Scrip, 28 Apr, 2020.)

Bristol Wins First Of Two Important Opdivo/Yervoy First-Line NSCLC Approvals

By Mandy Jackson

17 May 2020
Data from CheckMate-9LA and -227 that will be presented at the ASCO virtual meeting support a low-dose chemo combo with the two drugs and the newly US FDA-approved chemo-free indication.

Read the full article here

- The Phase III True North study of the S1P receptor modulator Zeposia (ozanimod) in ulcerative colitis; (Also see "*BMS's Zeposia Shines in Ulcerative Colitis Phase III Study*" - Scrip, 3 Jun, 2020.)

- The Phase III placebo-controlled CheckMate-577 study of Opdivo in the adjuvant setting for patients with resected esophageal cancer; and

- The CheckMate-649 study of Opdivo and Yervoy or Opdivo and chemotherapy versus chemotherapy alone in previously untreated advanced or metastatic gastric cancer. (Also see "*Pipeline Watch: Phase III Readouts For SER-109, Etrolizumab, Nivolumab*" - Scrip, 14 Aug, 2020.)

“These are absolutely remarkable stretches of positive outcomes for patients despite the challenges and unexpected setbacks,” Hirawat said. “We never imagined that there would be a pandemic that we will have to live through as we go through our first year as a combined company. But despite that, if you think about the success rate, we got 17 approvals in the last six months.”

In the US, those include Opdivo plus Yervoy in first-line NSCLC, Zeposia for relapsing multiple sclerosis, Reblozyl for myelodysplastic syndromes and, most recently, Onureg (CC-486) – an oral formulation of the legacy Celgene drug Vidaza (azacitidine) – for acute myeloid leukemia. (Also see "*Keeping Track: Gavreto, Sogroya Bring Annual CDER Novel Approvals To 40; New Analgesic Products Make It Past US FDA*" - Pink Sheet, 13 Sep, 2020.)

Zeposia’s approval for multiple sclerosis in March came well ahead of a 31 December deadline under BMS’s agreement to buy Celgene, which included a $9 per share contingent value right (CVR) payable to Celgene shareholders if three drug candidates win US Food and Drug Administration approval by certain dates. (Also see "*Bristol Values Celgene's Hematology, Immunology Portfolio At $74bn, But Does It Price In Risk?*" - Scrip, 3 Jan, 2019.)

The FDA action dates for the other two – the CD19-targeting chimeric antigen receptor T-cell (CAR-T) therapy lisocabtagene maraleucel (liso-cel) for relapsed or refractory large B-cell lymphoma and the BCMA-targeting CAR-T therapy idecabtagene vicleucel (ide-cel, formerly bb2121) in fourth-line-plus multiple myeloma – are 19 November and 27 March, respectively. (Also see "*Bristol’s CAR-T Strategy Comes Into Focus With Two Near-Term Filings*" - Scrip, 10 Dec, 2019.)

The user fee dates for both CAR-T therapies cut close to the 31 December deadline for liso-cel and 31 March deadline for ide-cel under the CVR terms. Both products were in danger of being approved late after the FDA requested more information about the biologic license application (BLA) for liso-cel and responded to the initial BLA filing for ide-cel with a refuse-to-file letter.

(Also see "*A BCMA Setback For Bristol And Bluebird With FDA Refuse-To-File Letter*" - Scrip, 13 May, 2020.)

Delivering Despite Pandemic Constraints

Hirawat noted that, at this time, the liso-cel and ide-cel programs are on track to meet their approval goals and said that in general the BMS R&D team has locked clinical trial databases and delivered results on time despite the fact that development teams are working from home during the pandemic.

"Like most companies, we did experience a slight slowdown in the beginning of the pandemic in our clinical trial enrollments but we have seen a nice recovery that has started in the third quarter of this year as many of the countries – especially on the European side and the Asian side – as they started to recover," he said.

CEO Giovanni Caforio noted during Bristol's second quarter earnings call last month that clinical trial enrollment is beginning to resume in regions where studies were on hold and scientists are returning to the company's labs, but remote working continues for many employees. (Also see "*Bristol's Opdivo Continues Slide, But First-Line Lung Offers Optimism*" - Scrip, 6 Aug, 2020.)

> ***BMS Outlines Clinical Trial Disruptions, Reassures Supply Chain Secure***
>
> By Jessica Merrill
>
> 25 Mar 2020
> The company is the latest big pharma to announce clinical trial delays due to the COVID-19 pandemic and has postponed an R&D day, but it also delivered the message that supply and commercial operations appear on track.
>
> *Read the full article here*

"We took a proactive action of putting our cell therapy trials on hold in the early part of the pandemic because we knew that the health care system was inundated with a high rate of COVID infections and we knew that ICUs and emergency rooms have the infrastructure that was being were overwhelmed," he added. "Because of that, we took a short hiatus, but then we reopened the trials as the pandemic was evolving and we learned where the sites could be reopened."

New Opdivo data in early cancer treatment settings are among key upcoming milestones for Bristol's R&D group, including results early next year from a Phase II/III clinical trial testing the PD-1 inhibitor in combination with the anti-LAG3 antibody relatlimab in first-line treatment of melanoma. The company reported preclinical results in 2017 showing the potential for a LAG3-targeting therapy to boost Opdivo's efficacy. (Also see "*Bristol's Strong SITC: IDO, 1L Kidney Cancer And New Mechanism Data Bode Well*" - Scrip, 13 Nov, 2017.)

Also, the first Phase III data in psoriasis for the TYK2 inhibitor BMS-986165 are expected in the fourth quarter of 2020 and first quarter of 2021 – a highly anticipated readout following the oral drug's positive Phase II results in 2018. (Also see "*Bristol Engineers An Oral TYK2 Inhibitor With Biologic-Like Efficacy That Rivals JAK Safety*" - Scrip, 12 Sep, 2018.)

In hematology, BMS has multiple programs in protein homeostasis and protein degradation with clinical trials ongoing for the cereblon modulators iberdomide (CC-220) and CC-92480 that are being tested in multiple myeloma – programs the company gained through its acquisition of Celgene. (Also see "*BMS/Celgene Post-Merger Early R&D Strategy: Partnerships Are Still Key, Vessey Says*" - Scrip, 6 Feb, 2020.) Bristol is also gearing up for additional data from its T-cell engagers, including CC-93269 for multiple myeloma. (Also see "*Bispecifics Could Be A Threat To CAR-Ts, But Efficacy May Trump Convenience*" - Scrip, 19 Dec, 2019.)

In gastroenterology, BMS is planning to start the Phase III program for its interleukin-13 (IL-13)-targeting antibody cendakimab in eosinophilic esophagitis.

And in cardiovascular diseases, the company is building on its experience with the *Pfizer Inc.*-partnered coagulation factor Xa inhibitor Eliquis (apixaban). The factor XIa inhibitor BMS-986177 is in Phase II development under a collaboration with *Janssen Pharmaceutical Cos.* for a next-generation anticoagulant.

Ensuring More Diverse Trials

With so many programs in the clinic, BMS has dozens of opportunities to pursue its plans to make its clinical trials more inclusive of all the different patients it serves. The company and its Bristol Myers Squibb Foundation said in August that they would commit $300m to address health disparities, increase clinical trial diversity, increase spending with diverse suppliers and continue to increase African-American and Hispanic representation at all levels of the company.

"While our company has had a long history of addressing health disparities as part of the overall mission to serve the patients, we recognize the urgent need now to do more to address these serious gaps, which have become even more apparent as this pandemic struck," Hirawat said.

As part of the company's recent financial commitment to diversity and inclusion initiatives, "we are extending the reach of our clinical trials into underserved patient communities in the urban and rural US geographies. In addition, the foundation will – working in concert with organizations outside as well as academic centers – be developing a curriculum to train 250 new racially and ethnically diverse clinical investigators who will have mentorship and training opportunities."

Ultimately, the goal is for these newly trained clinical trial investigators to enroll patients from their communities into clinical trials.

“We cannot let where people live dictate whether they have access to clinical trials or not, so we have to do more and we are committed to that,” Hirawat said.

BMS and other biopharma companies must become more involved in ensuring that there’s education and trust-building within diverse patient communities while training the next generation of clinical trial investigators from racially and ethnically diverse communities to help with those efforts, he noted.

“It is not something that only one company or only one segment of the industry can do,” Hirawat said. “It has to be a collaborative effort at every level and from all segments – from regulatory to academic to researchers as well as the companies – we all have to work together.”