This copy is for your personal, non-commercial use only. Distribution and use of this material are governed by our Subscriber Agreement and by copyright law. For non-personal use or to order multiple copies, please contact Dow Jones Reprints at 1-800-843-0008 or visit www.djreprints.com.

https://www.wsj.com/articles/merck-keeps-striking-out-on-expanding-its-cancer-drug-juggernaut-637c83d4

HEALTH

Merck Keeps Striking Out on Expanding Its Cancer-Drug Juggernaut

The company needs combinations to extend Keytruda sales after patent expires

By Jared S. Hopkins Follow

April 26, 2023 8:00 am ET

Merck says it has been doing deals and developing new drugs to reduce its dependence on Keytruda for sales. PHOTO: DAVID CROSLING/EPA-EFE/SHUTTERSTOCK

The gold rush from pioneering cancer immunotherapy Keytruda is about to run out for Merck & Co.

Keytruda, one of the world's top-selling drugs, powered its maker for the past decade. The therapy's annual sales neared $21 billion last year, about a third of Merck's revenue. Yet a drop in sales looms after Keytruda's main patent expires in 2028.

To extend sales further, Merck has been seeking to combine Keytruda with other drugs, which could get new patents if proven to work. Most haven't, however, intensifying pressure on the company to find other sources of revenue and contributing to a risky and costly deal-making spree.

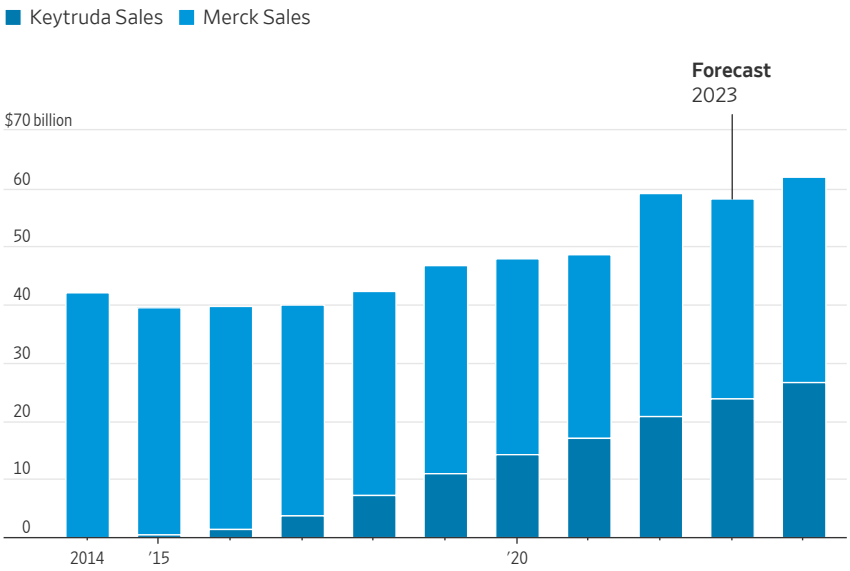
Keytruda has failed as a combination therapy in 21 late-stage studies spanning nine different partner drug technologies, according to SVB Securities LLC. Researchers also didn't advance at least 66 combination studies after early or midstage trials.

"The track record has been horrible," said Daina Graybosch, an SVB Securities pharmaceuticals analyst.

JHU 2078
Merck Sharp v. Johns Hopkins
IPR2024-00623

Counting on Keytruda

The cancer immunotherapy's sales are about one-third of Merck's revenue



Source: FactSet

Some Keytruda combinations have panned out. Doctors use the drug with chemotherapy for about a half-dozen cancers, and U.S. health regulators recently cleared a pairing with a targeted treatment for advanced bladder-cancer patients. This month, researchers found that Keytruda and a cancer vaccine from Moderna Inc. helped prevent relapses in high-risk melanoma patients in a midstage study.

Merck is also testing a tweaked version of Keytruda, which is currently infused intravenously, so it can be injected under the skin. And the company is studying the drug in new tumors and earlier stages of various cancers.

"We've learned a lot and certainly that gives us a leg up on our future development programs for our next generation of anticancer drugs, but it's still always going to be a game of chance," said Eliav Barr, Merck's chief medical officer. "Every cancer is different, and every setting within the cancer can be different."

The approved combinations don't promise to generate the revenue Merck needs to offset a roughly 40% drop in sales that the company could lose within two years if competitors launch their own off-brand versions of Keytruda, analysts said.

Merck has been making deals and developing new heart, immune-disease and other cancer drugs that will reduce the company's dependence on Keytruda and could add billions of dollars in sales, the company said.

Immunotherapies such as Keytruda belong to a class that lifts a natural brake on the immune system, allowing it to attack cancer cells. Bristol Myers Squibb Corp. secured the industry's first approval of the class in 2011.

Keytruda, which was cleared three years later to treat melanoma, became the go-to of the class in large part because it performed better than Bristol's rival in lung-cancer study subjects. The drug has earned 35 approvals across 16 types of cancer.

Merck says that failures are part of drug development. PHOTO: BRENDAN MCDERMID/REUTERS

Companies including Merck, academics and others are now conducting 1,935 clinical trials involving the drug, more than any other approved immunotherapy treatment, according to the Cancer Research Institute.

Merck scientists and other researchers have been especially interested in combining Keytruda with other agents because the drug alone doesn't help a sizable percentage of patients.

Combinations would also help extend sales because health insurers would agree to pay for Keytruda in addition to its partner drug. Merck could also package the combination under a new brand protected by new patents.

Yet researchers said Keytruda's early success might have encouraged Merck and its partners to move too quickly. After getting promising results in early studies in people, the companies sometimes skipped the next phase of studies, which could have helped sort out whether and how the pairings could work.

Some physicians and analysts also faulted certain study designs that, for instance, explored combinations in the wrong types of cancer patients or administered the pair of drugs in ways that hurt the response.

A patient receives an infusion of Keytruda. PHOTO: JAMES BORCHUCK/TAMPA BAY TIMES/ZUMA WIRE

"The field perhaps got overoptimistic and expected all of these combinations to work in people," said Gordon Freeman, a professor at Dana-Farber Cancer Institute in Boston who helped pioneer research of immunotherapy.

Merck said it balances the need for a midstage trial with the urgent needs of patients.

The most recent misfire involved Keytruda's combination with Eisai Co.'s Lenvima. The pair have been approved to treat forms of kidney and uterine cancers, but failed in pivotal studies against five other tumors.

A setback in liver cancer last year might have happened in part because Lenvima targets a receptor that plays a smaller role in liver cancer than kidney cancer, said Toni Choueiri, director of the Lank Center for Genitourinary Oncology at the Dana-Farber Cancer Institute, who was involved in the kidney-cancer trial.

Dr. Barr of Merck said it was unclear why study subjects responded to the combination, but not enough to generate a positive result. Eisai said the combination worked but not enough to demonstrate superiority statistically.

Merck and partner Amgen Inc. jumped to a late-stage study of a combination of Keytruda and an agent called Imlygic in advanced melanoma subjects, after a small, first-stage trial succeeded. In 2021, the larger trial failed.

Jason Chesney, director of UofL Health-Brown Cancer Center in Louisville, Ky., who was involved in the trial, said the companies took a gamble bypassing a midstage trial and might have been successful if they tested the cocktail in patients who previously failed Keytruda, rather than as a first-line treatment for patients.

The companies later started testing the combination in people who had previously failed immunotherapies such as Keytruda, and recently presented promising midstage study results. Amgen said that it jumped to a late-stage study based on other immunotherapy and Imlygic research. Merck said the program was based on solid science, and "not everything works in clinical trials."

In 2018, a combination of Keytruda and Incyte Corp.'s epacadostat failed to perform better than Keytruda alone in a later-stage trial in melanoma subjects.

Michael Atkins, an oncologist at the Georgetown Lombardi Comprehensive Cancer Center who has studied immunotherapy trial designs, said the companies could have learned the combination didn't provide a benefit and avoided the larger trial if they designed an earlier trial differently and tested the cocktail against Keytruda alone, rather than test only the combination.

He also said the companies should have tested Incyte's drug as a single agent against melanoma to verify that it worked by itself.

Steven Stein, Incyte's chief medical officer, said epacadostat didn't appear to block its targeted enzyme strongly enough. Merck said the companies only tested the combination during the midstage study to be efficient and failures are part of drug development. The company said it is doing more randomized midstage studies and limiting study of drugs that don't work alone.

Write to Jared S. Hopkins at jared.hopkins@wsj.com

Appeared in the April 27, 2023, print edition as 'Drug-Trial Failures Press Merck'.