Published OnlineFirst April 3, 2019; DOI: 10.1158/2159-8290.CD-ND2019-002

Targeting MCL1, Companies Aim to Unblock Apoptosis

Inhibitors of prosurvival protein in phase I testing for hematologic cancers

Venetoclax (Venclexta; AbbVie) has revolutionized the treatment of chronic lymphocytic leukemia (CLL), with the BCL2 inhibitor producing frequent, deep, and durable remissions. However, patients with other blood cancers don't typically respond as dramatically to BCL2 blockade, so drug companies are looking to target prosurvival proteins from the same family. Chief among them: MCL1.

Researchers began evaluating the first MCL1-targeted drug candidates for blood cancers, including multiple myeloma, acute myeloid leukemia (AML), and non-Hodgkin lymphoma, in 2016. Although data from these phase I studies won't be available until later this year at the earliest, preclinical evidence supporting MCL1 inhibition is mounting.

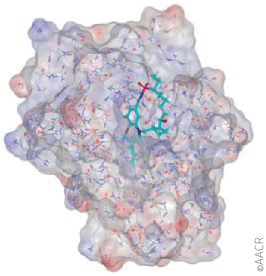
Reporting at the American Association for Cancer Research (AACR) Annual Meeting 2019 in Atlanta, GA, March 29–April 3, scientists described how potent MCL1 inhibitors developed by Amgen, AstraZeneca, and Novartis exhibited anticancer activity, especially when combined with other therapies, in hematologic tumor models (Proceedings of the 110th Annual Meeting of the AACR, 2019, abstracts 2180, 321, and 4482).

"There's a lot of excitement in the field about the MCL1 inhibitors," said Meike Vogler, PhD, of the Goethe-University Frankfurt in Germany. "We've been working on these molecules in the lab for so long, and now finally there are some specific drugs that are showing a lot of promise."

Most research on MCL1 inhibitors has centered on myeloma and AML. "They look like the two most sensitive diseases to MCL1 targeting," said Andrew Wei, MBBS, PhD, of Monash University's Alfred Hospital in Melbourne, Australia.

Just as CLL cells seem to be dependent on BCL2 for survival, myeloma cells display an addiction to MCL1, whereas AML cells show a need for both BCL2 and MCL1 to curb proapoptotic signals—which speaks to the promise of combining inhibitors of both molecules. Last year, for example, a team from Vanderbilt University in Nashville, TN, reported that an experimental MCL1 inhibitor reduced tumor burden in mouse models of AML, but it worked better when paired with venetoclax, in both venetoclax-resistant cells and patient-derived xenografts (Cancer Discov 2018;8:1566–81).

At the AACR meeting, scientists from Novartis and its development partner Servier described similar results in dozens of cell lines and rodent models of myeloma, diffuse large B-cell lymphoma, and AML treated with the clinical candidates MIK665 and BCL201, which target MCL1 and BCL2, respectively (Proceedings of the 110th Annual Meeting of the AACR, 2019, abstracts 257 and 4477). "In some cases, treated animals stayed tumor-free for several months after stopping the treatment, which was quite exciting for us," said Ensar Halilovic, PhD, of the Novartis Institutes for BioMedical Research in Cambridge, MA. "These could potentially be transformative agents." In the coming months, both Novartis and Amgen will begin recruiting participants for combination trials involving their experimental MCL1 inhibitors and venetoclax for hematologic cancers.



Here, MCL1 bound to AM-8621, a closely related analogue to the clinical candidate AMG 176. (Originally published in Caenepeel S, Brown SP, Belmontes B, Moody G, Keegan KS, Chui D, et al. Cancer Discov 2018;8:1582–97.)

Solid tumors may be amenable to the drug strategy as well. In small cell lung cancer, for example, Halilovic's collaborators from Massachusetts General Hospital in Boston, MA, presented data at the AACR meeting showing that combined treatment with BCL201 and a precursor to MIK665 induced regression in tumor models (Proceedings of the 110th Annual Meeting of the AACR, 2019, abstract 381). That dovetailed with work by Geoffrey Lindeman, MBBS, PhD, and his colleagues at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, showing synergistic effects between the same MIK665 forerunner—S63845—and breast cancer therapies (Sci Transl Med 2017;9:eaam7049). "There's a fairly compelling case now for extending the application to solid tumors," he said.

Still, MCL1 inhibition is not a panacea, and many researchers worry about on-target toxicities associated with blocking a prosurvival molecule that—unlike BCL2, a protein largely expressed only in blood cells—is found in all tissues. As knockout mouse models have shown, eliminating MCL1 leads to liver damage, heart failure, and other problems. As such, it's likely that MIK665, AZD5991, or any of the other candidate MCL1 inhibitors will prove less tolerable than venetoclax, said Martin Dyer, MA, DPhil, of the University of Leicester, UK.

Another problem: MCL1's shallow binding groove could make it hard for drugs to bind tightly to the target, especially with frequent mutational variants. In the CoMMpass cohort study of multiple myeloma, for example, 1% of participants had nonsynonymous coding mutations affecting baseline MCL1. Several of these mutations blocked the ability of AZD5991 or S63845 to displace MCL1's usual binding partner, a necessary step for the drugs to induce cell death (Blood 2018;132:951).

Darren Derksen, PhD, and Nizar Bahlis, MD, from the University of Calgary in Canada, hope to address the challenge with a proteolysis-targeting chimera drug that may only need to partially bind MCL1 to degrade, rather than inhibit the target. Their team sees a niche for this strategy if patients show resistance to any first-generation MCL1 inhibitors. "That's where our compound may have the advantage," Bahlis said.

Dyer is eager for clinical data to help inform how best to position MCL1 inhibitors alongside other drugs, and in which patients. "It's a long sought-after target, and if it works, it's going to open up all sorts of possibilities for our patients," he said. "That's very alluring." –*Elie Dolgin* ■

For more news on cancer research, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/CDNews.

AACR American Association for Cancer Research

CANCER DISCOVERY

Targeting MCL1, Companies Aim to Unblock Apoptosis

Cancer Discov 2019;9:572. Published OnlineFirst April 3, 2019.