Mirati Therapeutics Using NGS to Identify Best Responders to Multiple Oncology Drugs

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NEW YORK (GenomeWeb) – Mirati Therapeutics is studying a number of personalized medicine cancer drugs, for which it is planning to use next-generation sequencing platforms to interrogate complex genetic markers associated with patient response. Ultimately, if these programs are successful, the company hopes to launch the drugs alongside NGS-based companion diagnostics, according to company executives.

Most recently Mirati announced that it is seeking orphan drug designation from the US Food and Drug Administration for its HDAC inhibitor mocetinostat as a treatment for bladder cancer patients who have specific genetic alterations. "We have a hypothesis related to two genes that are mutated in bladder cancer that we would like to [use to] enrich the study," James Christensen, Mirati's chief scientific officer, told *PGx Reporter* last week. In particular, Mirati will study bladder cancer patients that have defects in histone acetylation – a process that's important for regulation of chromatin structure – due to mutations in CREBBP or EP300 genes.

Studies have shown that these loss-of-function mutations show up in 30 percent of bladder cancer and diffuse large B-cell lymphoma (DLBCL) patients. Mirata has already received orphan designation for mocetinostat in DLBCL, as well as for the drug in combination with another therapy, Vidaza, for intermediate- and high-risk myelodysplastic syndrome. The company is in Phase II studies for mocetinostat in bladder cancer and DLBCL, and is enrolling only patients with the mutations in the two genes. The third indication in MDS is not for a molecular targeted population.

The FDA grants orphan designation to drugs that are intended to treat diseases impacting fewer than 200,000 people in the US. With a designation of orphan status the drug garners seven years of market exclusivity, during which time the FDA cannot approve a generic version of the treatment. For a new molecular entity, the FDA grants five years of exclusivity.

Mocetinostat selectively inhibits a number of HDAC enzymes that are critical for regulating gene expression. Certain HDAC isoforms are known to drive cancer, and mocetinostat targets these isoforms. Mirati CEO Charles Baum recently highlighted in a statement that pre-clinical tumor studies have suggested that DLBCL and bladder cancer patients with CREBBP or EP300 mutations are likely to respond well to mocetinostat.

Mirati is working with a diagnostic company that markets an NGS panel to initially profile bladder cancer patients with these mutations in early phase studies. Mirati hasn't made public its partner for this project, during which the firm's researchers will also be looking for other molecularly defined subpopulations responsive to mocetinostat.

"If the [bladder cancer] trial is successful, we would move down the companion diagnostic path," Christensen said.

Mirati is also developing two kinase inhibitors: MGCD265 and MGCD516. The first, MGCD265, is an inhibitor of Met, Axl, and VEGFR that Mirati is developing in non-small cell lung cancer and squamous cell carcinoma of the head and neck. The company will investigate this agent in patients who have alterations in MET and AXL genes.

In addition to studying the drug as a single agent, Mirati is combining it with VEGF and EGFR inhibitors and testing it in cancer patients who have become resistant to these classes of drugs. The company is currently wrapping up dose-escalation studies for MGCD265, and is about to start enrolling patients with alterations in MET and AXL, also with the help of an NGS test.

MGCD516, meanwhile, inhibits Trk, RET, and DDR, as well as Met, Axl and VEGFRs. Mirati is studying this agent in patients with NSCLC and other tumor types, and those with genetic alterations in Trk, RET, and DDR.

The drug is currently in Phase I trials, and Mirati hopes to establish a maximum tolerated dose by year end. After that, the company will start enrolling patients in trials with specific gene variations.

For these kinase inhibitors, Mirati is working with ResearchDx to advance a next-generation sequencing profiling assay with a "small panel of genes," looking at gene fusions, mutations, and copy number changes. "Again, if this is successful, we would look to partner with ResearchDx and perhaps another provider to commercialize … a [companion] diagnostic," Christensen said.

An NGS platform is particularly necessary in the context of these drug programs because Mirati is interested in studying how patients with different types of variations in MET, AXL, TRK, and other genes respond to the drug. For example, within MET, Mirati is looking at gene amplifications and mutations, while in AXL, researchers are interested in translocations.

"Also, we can add capabilities to that [NGS assay], since our second kinase inhibitor is focused on different targets, such as TRK and RET translocations, and another locus called DDR," Baum said.

"There are certain pathways that are more complex than a one-marker, one-diagnostic [strategy]," Christensen added. "For example, for our mocetinostat drug in bladder cancer, there are two markers that are mutually exclusively mutated in that disease that both may be determinants [of response].

These markers are closely related but it wouldn't be efficient to look at one marker and then the other."

At other times, the regulation of a particular molecular pathway may be so complex that it takes more than one marker to understand whether it's activated. "For example, with our drug MGCD265, in certain settings there is the receptor and its mutations, the receptor and how it's expressed, and then there is a way that the receptor is activated by the ligand," Christensen said. "It may be important to get an understanding of all of that together and it would take a multiplex approach … to get that answer."

Increasingly drugmakers are using NGS in later phases of drug development, whereas in the past pharmas generally thought of the technology as a discovery tool. For example, Illumina announcedearlier this month it was working with AstraZeneca, Sanofi, and Janssen Biotech to develop and bring to market a universal, next-generation sequencing-based companion diagnostic for drugs being developed by these pharma companies. Similarly, Amgen, Clovis Oncology, BioMarin, and PharmaMar, have made public their intention to develop companion tests for their drugs on NGS platforms.

Baum and Christensen were previously at Pfizer and were closely involved in the development of NSCLC ALK inhibitor Xalkori (crizotinib), which is indicated for patients with ALK rearrangements and was co-approved with a FISH assay that identifies best responders. Having that previous experience, they understand the evolving regulatory environment for advanced molecular diagnostics

The FDA to date has reviewed and cleared Illumina's NGS MiSeqDx platform, but never an NGS-based companion test. And now with FDA's forthcoming guidance on lab-developed tests (LDTs), the regulatory front has gotten a bit more complex, Christensen observed. "Our initial strategy is to get a demonstration of both technical validity for the next-generation sequencing assay, as well as some clinical utility, showing some degree of benefit in the selected patient population," he said. "There may be a suggestion now to go even earlier to the agency to talk about the assay."

The FDA gave notice to the US Congress over the summer that it would release guidance outlining a regulatory framework for LDTs, which have traditionally been overseen by the Centers for Medicare & Medicaid Services. The FDA has also previously told *PGx Reporter* it plans to issue separate guidance on NGS-based panel tests for oncology drugs.

Mirati was established in May 2013 when the board of MethylGene approved a change in the company's legal jurisdiction from Canada to Delaware. Under the arrangement, Mirati became the holding corporation and the parent company for MethylGene and subsidiaries.

Although Mirata's drugs are in early phases of development, the firm has started the process to have discussions with the agency about these programs. "Even in Phase I, we know it's important to make FDA aware so we don't have any delays later," Baum said.