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Product Discovery & Development

Rigosertib's arresting story

By Aaron Bouchie
Senior Writer

Onconova Therapeutics Inc. believes the dual mechanism of its rigosertib against PLK1 and PI3K will give it an advantage over compounds that inhibit either mitosis or PI3K alone. The company also believes rigosertib will be safer than other mitotic inhibitors, including other PLK1 inhibitors in development.

Japanese in-licenser **SymBio Pharmaceuticals Ltd.** thinks the concept fits into its fast-moving specialty pharma model, and this month obtained rights to late-stage compound for Japan and Korea in exchange for undisclosed upfront payments, milestones and royalties.

Rigosertib is in the U.S. and European Phase III ONTIME trial for myelodysplastic syndrome (MDS), the Phase II/III ONTRAC trial in combination with gemcitabine to treat pancreatic cancer, and Phase I/II and Phase II trials in various hematologic cancers and solid tumors.

The compound inhibits tumor growth by blocking phosphoinositide 3-kinase (PI3K), whose signaling promotes a range of cellular functions, including cell growth, proliferation, survival and metabolism.

It also blocks polo-like kinase 1 (PLK1; STPK13), thus arresting cancer cells in the M phase and triggering apoptosis.

Onconova CEO Ramesh Kumar noted that all cancer cells have defects in the G1 regulatory mechanisms. These defects make them go past this checkpoint and become arrested in the M phase, which triggers apoptosis.

However, unlike other mitotic inhibitors such as taxanes and vinca alkaloids, which kill any rapidly dividing cells, rigosertib maintains healthy cells in the G1 phase, which does not trigger apoptosis.

As a result, "rigosertib kills cancer cells but doesn't cause things like cytopenia, leukopenia, neutropenia and anemia that other mitotic inhibitors cause," Kumar said.

First-generation PLK1 inhibitors, like BI 2536 from **Boehringer Ingelheim GmbH**, caused side effects similar to those seen with other mitotic inhibitors, like neutropenia, leukopenia and gastrointestinal events. The pharma company attributes these side effects to the compound arresting both cancer and rapidly dividing healthy cells in the M phase and triggering apoptosis.

> ***"We can have the synergism of inhibiting two essential pathways without the cumulative toxicity from two drugs."***
>
> **Ramesh Kumar, Onconova Therapeutics**

There are at least two other PLK1 inhibitors in clinical trials. BI's volasertib (BI 6727) is in Phase II testing for non-small cell lung cancer (NSCLC), ovarian cancer and urothelial cancer and in Phase I/II testing for acute myelogenous leukemia (AML).

TKM-PLK1 from **Tekmira Pharmaceuticals Corp.** is in a Phase I trial in patients with solid tumors or lymphomas with interim data expected by year end.

Boehringer spokesperson Julia Meyer-Kleinmann said both volasertib and BI 2536 showed reversible, dose-dependent hematotoxicity. The company decided to prioritize volasertib for clinical development "based on pharmacokinetic characteristics indicative of high and sustained exposure in tumor tissue," she said.

There are at least 13 PI3K inhibitors in clinical development.

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Kumar said rigosertib's dual mechanism enables development for cancers such as relapsed/refractory MDS that could not be treated with a PI3K inhibitor or mitotic inhibitor alone.

"By using a single drug that targets two non-overlapping pathways we can have the synergism of inhibiting two essential pathways without the cumulative toxicity from two drugs," he said.

The company is leading with second-line MDS, where existing treatments leave room for improvement and there are no approved drugs for patients with relapsed/refractory disease.

There are three drugs approved for MDS in the U.S. Two are the hypomethylating agents Vidaza azacitidine from **Celgene Corp.** and **Nippon Shinyaku Co. Ltd.** and Dacogen decitabine from **SuperGen Inc.**, **Johnson & Johnson** and **Eisai Co. Ltd.** The third, Celgene's thalidomide analog, Revlimid lenalidomide, is approved for a subgroup of patients who are missing part of chromosome 5 (del 5q).

Vidaza is approved in Europe, and Vidaza and Revlimid are approved in Japan.

"The main MDS drugs are the two hypomethylating agents, and neither has a really high rate of success. And even those patients who do respond have a high rate of resistance," Kumar said. "The Phase I and II data we have suggest we have very good activity in these relapsed/refractory patients, and we are helping these patients live longer."

A meta-analysis of 48 MDS or AML patients refractory to hypomethylating agents enrolled in four Phase I, I/II or II trials showed 19 (40%) had an initial bone marrow response by weeks 4 to 8 or a complete bone marrow response.

These responses were significantly associated with an increase in overall survival compared with patients who did not have a bone marrow response (p=0.0001), including in MDS patients alone (p=0.008). The underlying OS data were not reported.

Data were presented at the **American Society of Hematology** (ASH) meeting last year in Orlando.

SymBio CFO Hiroki Maekawa said the company had been looking for another hematological cancer product to go with bendamustine, which it in-licensed from **Astellas Pharma Inc.** in December 2005.

SymBio has since received approval of bendamustine for non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma (MCL) in Japan; NHL and chronic lymphocytic leukemia (CLL) in China and Singapore; and CLL and multiple myeloma (MM) in Korea.

Cephalon Inc. markets bendamustine as Treanda in the U.S., while **Mundipharma International Ltd.**, which has European rights, markets it in Germany as Ribomustin.

"We were very impressed that in less than five years they in-licensed a product, conducted clinical trials and launched in Japan, Singapore and Hong Kong," Kumar said.

SymBio has not disclosed details of its rigosertib program, but Maekawa said the company plans to start clinical trials in Japan "soon."

While SymBio partnered out the marketing of bendamustine because it could not afford a sales force at that time, Maekawa said the company plans to market rigosertib itself with a sales force of 30-40 reps at launch.

Onconova also is looking to partner out the commercialization of rigosertib in most, if not all, other parts of the world.

"We are a discovery and development company right now. Realistically, there is no way we can commercialize rigosertib in many territories," Kumar said.

Onconova hopes to receive approval of the compound for MDS in the U.S. in 2013. Rigosertib has Orphan Drug designation for MDS in the U.S., where it is called Estybon.

Onconova has completed Phase I tolerability trials with an oral formulation of rigosertib in MDS and solid tumor patients, but has not yet decided how to pursue it. The company could submit an sNDA for second-line MDS after the injectable formulation is approved or conduct additional trials as a first-line therapy.

COMPANIES AND INSTITUTIONS MENTIONED

American Society of Hematology (ASH), Washington, D.C.
Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan
Boehringer Ingelheim GmbH, Ingelheim, Germany
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Cephalon Inc. (NASDAQ:CEPH), Frazer, Pa.
Eisai Co. Ltd. (Tokyo:4523; Osaka:4523), Tokyo, Japan
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Mundipharma International Ltd., Cambridge, U.K.
Nippon Shinyaku Co. Ltd. (Tokyo:4516; Osaka:4516), Kyoto, Japan
Onconova Therapeutics Inc., Newton, Pa.
SuperGen Inc. (NASDAQ:SUPG), Dublin, Calif.
SymBio Pharmaceuticals Ltd., Tokyo, Japan
Tekmira Pharmaceuticals Corp. (TSX:TKM; NASDAQ:TKMR), Burnaby, B.C.