MEETING HIGHLIGHTS

Inhibiting the Akt Pathway in Cancer Treatment
Three Leading Candidates

Walter Alexander

INTRODUCTION
Targeted therapies have brought the treatment of many cancers to a level of success surpassing that witnessed with traditional chemotherapeutic and immunosuppressive agents. Prominent among these targeted drugs have been imatinib (Gleevec, Novartis) for chronic myeloid leukemia, trastuzumab (Herceptin, Genentech) for breast cancers overexpressing human epidermal growth factor receptor 2 (HER-2), the angiogenesis inhibitors sunitinib (Sutent, Pfizer) and sorafenib ( Nexavar, Bayer/Onyx), and other therapies for metastatic renal cell carcinoma.

The search for therapeutic strategies to go beyond, replace, or complement these targeted agents has advanced to include serine–threonine protein kinase B (Akt), a mediator of multiple signaling cascades, leading ultimately to cell growth and proliferation. Among an extensive list of Akt pathway inhibitors in development, three are the farthest along and show the most promise in early clinical research: perifosine (KRX-0401, Aeterna Zentaris/Keryx), MK-2206 (Merck), and GSK-2141795 (GlaxoSmithKline). The three drug candidates were discussed at the American Society of Hematology (ASH) meeting (December 4–7, 2010) and at a Research & Development (R&D) review, sponsored by Aeterna Zentaris, on December 14.

PERIFOSINE
Perifosine, a novel oral inhibitor of Akt activation in the phosphoinositide 3-kinase (PI3K) pathway, is considerably farther along in testing than the rest of the field of investigational Akt inhibitors and is moving into phase 3 clinical trials. In presentations at the recent ASH meeting and at a subsequent presentation by perifosine’s developer, Aeterna Zentaris, experts underscored that high levels of activated phosphorylated Akt (pAkt) are often seen in many types of cancer that have become resistant to cancer therapies working through other mechanisms. High pAkt levels are correlated with a poor prognosis.

In addition to inhibiting Akt, perifosine affects other key signal transduction pathways, such as c-Jun N-terminal kinase (JNK) and nuclear transcription factor–κB (NF-κB), which are associated with apoptosis, cell growth, differentiation, and survival.

Perifosine in Colorectal Cancer
• Johanna Bendell, MD, Director of Gastrointestinal Oncology Research, Sarah Cannon Research Institute, Nashville, Tenn.

The combination of perifosine plus capecitabine (Xeloda, Roche) was investigated in an exploratory phase 1 study in heavily pretreated multiple tumor types. Results showed activity with no dose-limiting toxicities, Dr. Bendell stated at the Aeterna Zentaris R&D meeting. She noted that perifosine and 5-fluorouracil (5-FU), an active metabolite of capecitabine (CAP), have shown profound synergistic cytotoxicity, ostensibly through inducing distinct types of cell cycle arrest in colon cancer cell lines. She added that 20% to 40% of colorectal cancers have P13K/Akt pathway mutations.

Although single-agent perifosine did not demonstrate activity in metastatic colorectal cancer, Dr. Bendell suggested that limited single-agent activity with greater activity in combination with chemotherapy is likely to occur with targeted agents, particularly in cancers of the lung, colon, and breast. That pattern was indeed revealed in a randomized phase 2 trial of second-line or third-line treatment of metastatic colorectal cancer. On days 1 to 14, patients received twice-daily CAP 825 mg/m² plus perifosine 50 mg once daily (P-CAP) (n = 20) or placebo (n = 18).

The primary endpoint was time to disease progression.

Table 1 Capecitabine (Xeloda) With and Without Perifosine in Pretreated Metastatic Colorectal Cancer

<table>
<thead>
<tr>
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<th>Capecitabine</th>
<th>Perifosine Plus Capecitabine (5-FU Refractory Disease)</th>
<th>Capecitabine (5-FU Refractory Disease)</th>
<th>Perifosine Plus Capecitabine (5-FU Refractory Disease)</th>
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<tbody>
<tr>
<td>Median time to disease progression</td>
<td>11 weeks</td>
<td>28 weeks ($P = 0.0012$, HR = 0.284)</td>
<td>10 weeks ($P = 0.0004$, HR = 0.186)</td>
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<tr>
<td>Median overall survival</td>
<td>10.9 months</td>
<td>17.7 months ($P = 0.016$, HR = 0.410)</td>
<td>6.6 months ($P = 0.011$, HR = 0.313)</td>
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5-FU = 5-fluorouracil; HR = hazard ratio; $P =$ significance.
MEETING HIGHLIGHTS: Inhibiting the Akt Pathway in Cancer Treatment

(TTP). An analysis showed one complete response (CR) with a duration of 34 months for the P-CAP group and three partial responses (PRs) with durations of 21, 19, and 11 months, respectively. Only one PR lasting seven months was noted in the CAP group.

“Average survival in metastatic colorectal cancer is about two years, so this is going way past that,” Dr. Bendell commented.

Among 25 patients with 5-FU refractory disease (Table 1, page 225), there was one P-CAP response of 19 months and no CAP responses. The median TTP was 28 weeks for P-CAP and 11 weeks for CAP (P = 0.0012), with a hazard ratio (HR) of 0.284. Among patients with disease refractory to 5-FU, the median TTP was 18 weeks and 10 weeks, respectively (P = 0.0004; HR = 0.186).

Similarly, in terms of overall survival, median TTP was 17.7 months and 10.9 months for P-CAP and CAP, respectively (P = 0.016; HR = 0.410). Among 5-FU refractory patients, the median TTP was 15.1 and 6.6 months, respectively (P = 0.011; HR = 0.313).

“These are very impressive hazard ratios,” Dr. Bendell said.

Again, no dose-limiting toxicities were reported. These encouraging phase 2 results have led to the ongoing phase 3 X-PLECT Trial (Xeloda + Perifosine Evaluation in Colorectal Cancer Treatment), which is comparing P-CAP and CAP in refractory metastatic colorectal cancer. Approximately 215 patients will be enrolled in each arm.

Perifosine in Multiple Myeloma

- Paul G. Richardson, MD, Clinical Director, Jerome Lipper Center for Multiple Myeloma, Dana Farber Cancer Institute, Boston, Mass.

Strategic advances over the last decade have lengthened median survival for multiple myeloma (MM) from two to three years to five to seven years, said Dr. Richardson at the Aeterna Zentaris R&D review.

However, he added: “The disease remains incurable. In the relapsed/refractory arena, once bortezomib [Velcade, Millennium] has failed and once the immunomodulatory drugs have failed, data show that time to progression and survival remain dismally short.”

MM remains the second most common hematological cancer in the U.S., with 20,000 new cases each year and 11,000 deaths. In Dr. Richardson’s view, that incidence is increasing.

Initial interest in perifosine for MM was high because of its ability to inhibit up-regulation of Akt and NF-xB and to enhance the activity of bortezomib. In phase 1 research presented at the 2010 ASH meeting by Jakubowiak,4 minimal responses (MRs) or better, which correlate with clinical benefit, were reported in 73% of patients receiving a combination of perifosine, lenalidomide (Revlimid, Celgene), and dexamethasone. All patients had relapsed disease and were heavily pretreated, with half having relapsed and refractory MM. Dr. Richardson characterized the median survival of 30.6 months as “really quite encouraging in this population.”

Further promising findings from Dr. Richardson’s phase 1/2 study of perifosine plus bortezomib revealed a median overall survival of 23 months in patients with more advanced and relapsed bortezomib-refractory MM. All 73 evaluable patients had received prior bortezomib therapy.5

“This is a group of patients in whom you simply would not expect this degree or magnitude of clinical benefit,” he said.

Clinical benefit, defined as stable disease or better, was reported in 82% of the patients, and the overall response rate (MR + PR + near-CR) was 41%.

“These results bode well for perifosine in the future as a combination agent in this setting,” Dr. Richardson concluded.

Consistent signs of activity and benefit with tolerability have been shown for perifosine in other hematological cancers, including in relapsed/refractory chronic lymphocytic leukemia6 and in relapsed/refractory lymphomas with the multikinase inhibitor sorafenib (Nexavar, Bayer/Onyx).7 A potential benefit has also been documented for perifosine in Waldenström’s macroglobulinemia.8

MK-2206

- Clifford Hudis, MD, Chief, Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, N.Y.

The notion that Akt shortens patient survival by allowing cancer cells to escape the cytotoxic effects of various drugs has been around for a long time, Dr. Hudis said in an interview. His own research, as well as that of others, has demonstrated specifically that in response to targeted therapies thought to inhibit HER-2 and other signaling, there may be up-regulation of signal transduction pathway components, including Akt, that enables cancer cells to be spared the effects of chemotherapy. Dr. Hudis explained:

Like many other biological systems, we have here multiple parallel pathways to accomplish vital functions. So if you knock one down, you may get a compensatory rise in another. That’s what we think is happening when you inhibit HER-2 with a very targeted agent like trastuzumab. You get a compensatory increase in downstream and parallel signal transduction pathway components, and Akt is a node in that system. That leads to the hypothesis that multitargeting the pathway with selective inhibitors would be useful, and inhibiting Akt directly will restore sensitivity to trastuzumab.

He added that his laboratory collaborators felt that among the candidate agents they had worked with, Merck’s MK-2206 was the most effective.

Preclinically, MK-2206, an allosteric inhibitor of Akt, demonstrated synergistic activity when combined with other targeted therapies, such as erlotinib (Tarceva, OSI/Genentech), in non–small-cell lung cancer (NSCLC) cell lines, and lapatinib (Tykerb, GlaxoSmithKline), in breast cancer cell lines. In phase 1 research in patients with advanced solid tumors, MK-2206 caused central tumor necrosis, a reduction in index lesions, and improvements in ascites and peripheral edema.1

Dr. Hudis is the lead investigator for an ongoing phase 1 study that is evaluating the addition of MK-2206 to trastuzumab in patients with solid tumors that produce HER-2. Results are expected later in 2011. Another phase 1 study is being conducted to evaluate MK-2206 in combination with trastuzumab and lapatinib for the treatment of HER-2-positive, advanced solid tumors.
The importance of the Akt pathway is clear from both the previously reported responses to its inhibitors in a variety of solid tumors, stated Dr. Kurkjian, and from the fact that it seems to play a significant role in the resistance of tumors to a variety of therapies. She noted that early experience with GlaxoSmithKline’s GSK-21417195, an oral Akt inhibitor, demonstrated promising signals with archival gynecological, head and neck, prostate, and colon cancer tumors.

“What’s not yet determined is whether a mutation in the pathway is a requirement for responses to the pathway’s inhibitors and whether some of the emerging toxicities, including skin reactions and diarrhea, are indicative of a treatment effect or are merely inherent properties of the drug,” she said in an interview.

A phase 1, dose-escalation study of GSK-2141795 in solid tumors or lymphomas is ongoing. It is anticipated that 70 subjects will be enrolled.

THE BIOMARKER Hurdle

Sumanta Kumar Pal, MD, Assistant Professor of Medical Oncology, and Co-Director, Kidney Cancer Program, City of Hope, Duarte, Calif.

In a review of the investigational Akt inhibitors, Dr. Pal urged researchers to focus on those disease subtypes in which other small molecules have been shown to have the largest effects.1 Identifying the most effective combinations, however, means conducting comparative-effectiveness research in phase 3 trials that, by necessity, would be large and extremely costly.

“It’s not that we have a shortage of active drugs,” Dr. Pal said in an interview. “It’s that we have a shortage of the understanding of how to use them optimally.”

Finding the agents most likely to elicit the best response in a population calls for identification and validation of biomarkers, which must go through the same testing stages that investigational drugs go through. Some Akt inhibitors decrease phosphorylated Akt (pAkt) in whole blood and decrease Akt messenger RNA levels. It remains to be determined whether these or other related mediators can predict Akt pathway inhibitor efficacy, Dr. Pal said.

His estimate was that using pAkt as a biomarker for Akt inhibitor response in a comparison with a standard cytotoxic agent like docetaxel (Taxotere, Sanofi-Aventis) in second-line NSCLC treatment would require more than 2,200 patients per arm to produce sufficient statistical power. In view of the resources needed to validate a putative biomarker, investigators need to be somewhat certain about its value, he said. After a biomarker is validated, it can then be used as a surrogate to find the drug that is most appropriate for a given patient population and to achieve the goal of individualizing cancer therapy.

REFERENCES