

Promising Pipeline Pearls

Two industry analysts we interviewed believe immunoconjugates, multi-targeted kinase inhibitors, HSP90 inhibitors, and IGF-1 inhibitors may prove to be four of the most promising drug classes in the coming years for the treatment of cancer. Following is a sampling of the compounds they are keeping their eye on.

It seems that for every successful agent, there are hundreds for which the early embers of promise dim in late-stage trials. With a pessimistic economic overview looming, investors can be forgiven for remaining overly cautious when it comes to prognosticating which drugs might make it out of the lab and into a company's quarterly report. However, a careful assessment of recent data through the prism of their own experience has led two well-versed analysts—Richard Wagner, PhD, an oncology specialist at the MattsonJack Group, senior director of CancerMPact®, and Ziad Bakri, an analyst at the Cowen Company—to discuss the potential of four specific classes of oncology agents. According to the analysts, immunoconjugates, multi-targeted kinase inhibitors, HSP-90 inhibitors and insulin-like growth

factor receptor (IGF-1R) inhibitors have a high likelihood of eventual US Food and Drug Administration (FDA) approval.

Considering the Immunoconjugates

According to Wagner, a comprehensive oncology database that covers the United States, Western Europe, and Japan shows that immunoconjugates may have overcome some early limitations to realize their potential. He believes that the concept of combining targeted therapy and chemotherapy is a powerful one, while also acknowledging that historically, immunoconjugates have not been very successful. “Though many of these drugs were found to have exciting activity, they also had a lot of associative toxicity. Now, however, I think that companies like Genentech and



Richard Wagner, PhD,
MattsonJack Group

Seattle Genetics are showing that there is potential here,” he said.

After closely following developments in this class of agents and culling through many possible findings, Wagner and his colleagues at CancerMPact recently released their “Emerging Technologies Manual”, which forecasts the most promising late-stage oncology agents that will enter the marketplace in the next five years. Three immunoconjugates they believe that are especially poised to break away from the pack are: trastuzumab-DM1 (T-DM1), SGN-35, and CMC544.



on the Horizon

By Paul Watson

» Trastuzumab-DM1 (T-DM1)

“One way to think about promise, is to look at what’s tried and true,” said Wagner. “We know that drugs targeting the HER2 receptor, like Herceptin and Tykerb, have had a dramatic impact on treatment outcomes for metastatic breast cancer patients...but we know we can do better.”

T-DM1 is a first-in-class human epidermal growth factor receptor 2 (HER2) antibody-drug conjugate. It is comprised of Genentech’s antibody Herceptin® that is linked to ImmunoGen’s cell-killing agent DM1 (a maytansine derivative). T-DM1 is designed to deliver treatment directly to HER2-positive cancer cells and limit delivery to surrounding healthy tissue.

“We know the [HER2] target is a good target and we’ve seen that T-DM1 may be a more active drug because it has the added potency of chemotherapy,” said Wagner. “So it’s exciting, not only as a treatment for

breast cancer, but as a next step in the evolution for antibodies.”

Mark Sliwkowski, a senior research scientist at Genentech and Barbara Klencke, an associate group director in the Clinical Oncology Group, reported that T-DM1 combines two strategies: anti-HER2 activity and targeted intracellular delivery of the potent anti-microtubule agent, DM1. Both believe, based on clinical studies showing promising activity, that T-DM1 has the potential to become a viable therapy for patients with HER2-positive metastatic breast cancer.

Sliwkowski and Klencke also noted that it is the novel chemistry behind T-DM1 which separates it from immunoconjugates of the past, and is behind much of the excitement surrounding this agent. With T-DM1, Genentech has taken a more systematic approach focusing its efforts on the cytotoxic moiety (maytansine) and linker chemistry. Their researchers believe linker chemistry is a very



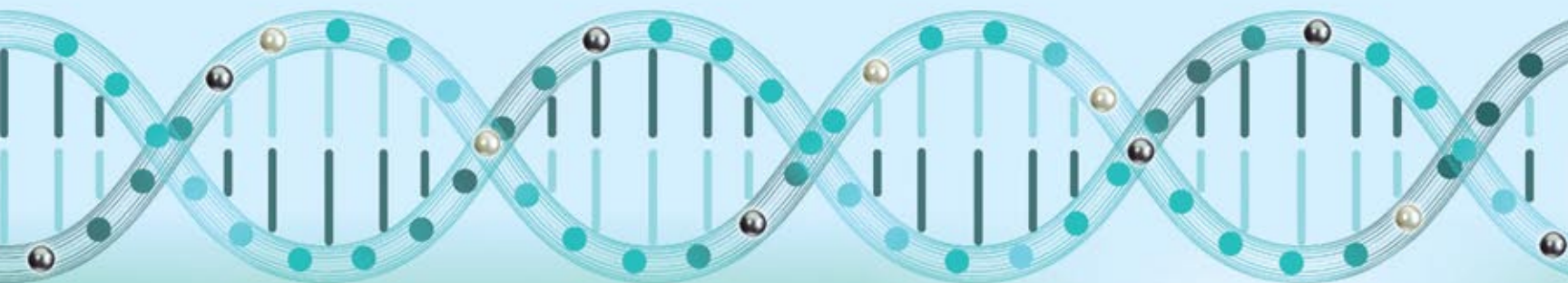
Ziad Bakri, Analyst,
Cowen Company, Inc.

important component in developing a safe and effective antibody drug conjugate.

According to Cowen Company analyst Ziad Bakri, successful testing of T-DM1 could prove to be an essential milestone for this class of agents as a whole. “If you can actually arm this antibody so that it gets directly to tumor cells, it would validate the whole platform for conjugate antibodies,” he said.

Interim data presented at the American Society of Clinical Oncology’s (ASCO) 2008 Annual Meeting and the San Antonio Breast Cancer Symposium 2008 seem to support the utility of this approach. In a single-agent Phase 2 study of T-DM1

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for previously-treated HER2-positive metastatic breast cancer patients, the objective response rate in 107 efficacy-evaluable patients was 39.3%. Genentech plans to initiate a Phase 3 trial evaluating T-DM1 as a second-line treatment for HER2-positive metastatic breast cancer in the first half of 2009.

Though he sees T-DM1 as holding considerable promise, Bakri thinks that other agents, such as monoclonal antibodies used in conjunction with chemotherapy, are even more exciting and much closer to market approval. He cited Erbitux® in combination with platinum-based chemotherapy in advanced non-small-cell lung cancer (NSCLC) as one such example. However, it is worth noting that in late January, ImClone Systems and Bristol-Myers Squibb withdrew their pending application for Erbitux to treat NSCLC after the FDA took issue with product differences between the United States and Europe.

» SGN-35

Seattle Genetics' SGN-35, an antibody-drug conjugate for Hodgkin's disease, is fast on its heels in the industry expectations race for approval. SGN-35 is an anti-CD30 monoclonal antibody that is attached to cytotoxic agents called auristatins. Like T-DM1, the linkage system in this area was found to be highly stable in plasma, meaning that it should have equally high specificity coupled with low toxicity.

"From the data that I've seen at the American Society of Hematology meeting, SGN-35 looks to be an active drug in Hodgkin's disease," said Wagner. "And researchers have found doses that seem to be tolerable when given to patients."

SGN-35 has an orphan drug designation from the FDA for Hodgkin's lymphoma, and early this year, Seattle Genetics announced that it had reached agreement with the FDA on a Special Protocol Assessment (SPA) for a pivotal trial of SGN-35 in patients with relapsed or refractory Hodgkin's lymphoma. The SPA agreement positions the Phase 2 trial to begin enrollment in the first quarter of 2009. According to Clay B. Siegall, PhD, president and chief executive officer of Seattle Genetics, the goal is to submit a New Drug Application in 2011 under the accelerated approval regulations. Seattle Genetics also plans to conduct a Phase 2 study of SGN-35 as a single-agent in relapsed or refractory systemic anaplastic large-cell lymphoma in the first quarter of 2009.

"The difference between T-DM1 and SGN-35 is that we know that Herceptin alone is an active drug," said Wagner. "Seattle Genetics has studied antibodies against CD30 in Hodgkin's disease and while they have found some activity, they haven't shown a lot. On the other hand, SGN-35 does seem to get a substantial boost when you combine the antibody against CD30 with a chemotherapeutic."

» CMC-544

Manufactured by Wyeth, CMC-544 (inotuzumab ozogamcin) is a CD22-targeted cytotoxic immunoconjugate currently being evaluated in Phase 3 clinical trials in patients with non-Hodgkin's B-cell lymphoma. Studies have demonstrated that CMC-544 has shown significant clinical activity in both follicular and diffuse large B-cell lymphoma patients who had failed multiple therapies.

Although anti-CD22 antibodies such as epratuzumab have previously shown some activity in non-Hodgkin's lymphoma, treatment in this area has been dominated by anti-CD20 drugs like Genentech's Rituxan®. Taking the if-you-can't-beat-them-join-them approach, Wyeth is studying CMC-544 in combination with Rituxan.

According to Wagner, the antibody by itself doesn't have a competitive position in the market. However, he indicates that CMC-544 could be a potent drug in relapsed, refractory patients when used with chemotherapy. "That's essentially Wyeth's approach and I think it's a promising one," he said.

Of the three antibody-drug conjugates, Wagner is most impressed by T-DM1, and also believes the other two agents could prove especially promising. "The strategy behind immunoconjugates is a good one, but none of these agents has reached the market and we need to remain cautious."

Angiogenesis and Multi-Targeted Kinase Inhibitors

As with immunoconjugates, angiogenesis and multi-targeted kinase inhibitors are considered promising because they address proven targets. For example Avastin® attacks vascular endothelial growth factor receptor (VEGFR), and Sutent® and Nexavar® attack tyrosine kinases. Three promising agents—zactima, pazopanib, and axitinib—are those that are expanding upon this proven commodity.

» Zactima

Zactima (vandetanib) is an orally administered tyrosine kinase inhibitor under development by AstraZeneca for the treatment of solid tumors and NSCLC. Zactima targets vascular endothelial growth factor receptor 2 (VEGFR-2), epidermal growth factor receptor (EGFR), and RET kinase.

“Zactima has a similar method of action as Tarceva, as well as an interesting data set,” said Bakri. “It can potentially be on the market in the next 18 months.”

According to AstraZeneca representatives, a Phase 3 study entitled ZODIAC demonstrated prolonged progression-free survival when Zactima was used in combination with docetaxel in NSCLC. However, a smaller Phase 3 study (ZEAL) of Zactima used in combination with pemetrexed and a monotherapy study (ZEST) comparing Zactima with Tarceva® did not demonstrate statistical significance in prolonging progression-free survival.

When aggregated together however, all three studies showed that Zactima shrank tumors and eased symptoms associated with lung cancer better than chemotherapy alone, which may be enough to gain FDA approval and compete with Tarceva.

Although Zactima failed to improve overall survival in all three studies, and did not offer improved progression-free survival in the ZEAL and ZEST trials, researchers believe its ability to shrink tumors and ease symptoms will make it competitive with Tarceva should it gain regulatory approval.

» Pazopanib

GlaxoSmithKline’s pazopanib is an oral angiogenesis inhibitor that targets VEGFR, platelet-derived growth factor receptor (PDGFR), and c-Kit. It is being evaluated as a monotherapy in combination with targeted therapies and in combination with cytotoxic chemotherapy. Phase 3 trials are currently underway in renal cell carcinoma and inflammatory breast cancer, as well as Phase 1/2 trials in ovarian cancer, soft tissue sarcoma, NSCLC, cervical cancer, and other solid tumors. “Pazopanib seems to have activity comparable to Sutent in renal cell cancer but with better tolerability,” said Wagner.

» Axitinib

Developed by Pfizer, axitinib is a multi-targeted tyrosine kinase inhibitor that targets VEGFR-1,-2, and -3, PDGFR, and c-Kit receptors, and has

shown particular promise in renal cell carcinoma (RCC). In a Phase 2 trial, axitinib had demonstrated a good response in combination with gemcitabine for advanced pancreatic cancer; however, in late January, Pfizer abruptly ended its Phase 3 trial after an independent board found no evidence of longer survival in patients treated with axitinib and gemcitabine, compared with gemcitabine alone.

Such results did not come as a surprise to either Bakri or Wagner. Despite positive data from Phase 2 trials, “most drugs typically fail in Phase 3 for pancreatic cancer,” said Bakri. He further added that even Tarceva, approved for use in combination with gemcitabine in advanced pancreatic cancer, “essentially only gives a two week improvement in median survival.”

“Axitinib is not the first drug to fail to improve survival when added to chemotherapy,” added Wagner. “Avastin—which we all consider to be a successful drug—also failed to improve survival when added to chemotherapy in pancreatic cancer. This is a difficult disease and it’s been very, very hard to improve outcomes.”

Despite this setback, Wagner believes axitinib has a much higher chance of success in RCC. “Axitinib is a good drug, but it’s looking for a home,” said Wagner. “Pfizer already has a drug, Sutent, with the same mechanism of action. Focusing on pancreatic cancer was a way for axitinib to complement but **cont. on pg 26 >>**

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not compete with Sutent.” Whether axitinib takes off in the marketplace will depend heavily on the results of the Phase 3 RCC trial, currently underway.

Hsp90 Inhibitors

Heat shock proteins (HSPs) are activated by stress in the cellular environment. When intracellular proteins come under attack from cytotoxic chemotherapy and begin to misfold, the HSPs quickly help repair them. Hsp90 is of particular interest to researchers because many of its client proteins (e.g., HER-2, Bcr-Abl, p53 mutations, Raf-1, ErbB2)—which are dependent on Hsp90 for their survival—are promising targets in cancer therapy. Hsp90 helps these proteins acquire and maintain the shape necessary to facilitate the spread of cancer. Researchers hope that by inhibiting Hsp90, the drug candidates will promote the proteasomal degradation of oncogenic signaling proteins and prevent cancers from evading molecularly targeted attacks.

» IPI-504

Infinity Pharmaceuticals’ IPI-504 (retaspimycin) is an intravenous Hsp90 inhibitor that recently began a Phase 3 trial in gastrointestinal stromal tumors (GIST) and soft tissue sarcomas. “This has a great chance for success as a third-line therapy for patients who are refractory to both Gleevec and Sutent,” said Wagner

In a paper he co-authored, Bakri referred to encouraging results from

a Phase 1/2 trial in GIST presented at ASCO 2008, in which retaspimycin achieved stable disease or partial response (as measured by RECIST criteria) in 25 of 36 patients. Although Hsp90 has always intrigued researchers, the success of targeting this protein was not immediately assured.

“The problem with Hsp90 inhibitors is that the chemical class has very poor pharmacologic properties,” said Wagner. “The early Hsp90 inhibitors had very poor solubility. So there were problems with delivering enough of the compound to patients in order to see any effect.”

According to Bakri, pharmacologically active concentrations of IPI-504 can be found 24 to 48 hours post administration, resulting in “preferential tumor targeting that should help limit systemic exposure and the potential for side effects, while allowing potent control of tumors.”

Infinity Pharmaceuticals hopes to have its Phase 3 study, entitled RING, completed by 2010. Additional Phase 1/2 trials are currently underway in NSCLC and solid tumors.

» KOS-953

Derived from the antibiotic geldanamycin, Bristol-Myers Squibb’s intravenous Hsp90 inhibitor KOS-953 (tanespimycin) is structurally related to retaspimycin and is currently being studied in a Phase 3 trial for multiple myeloma. Once tanespimycin becomes metabolized by enzymes in the body, it becomes the same chemical

as retaspimycin. As such, both IPI-504 and KOS-953 are closely related, though their modes of administration and mechanisms of action may differ somewhat.

“Tanespimycin seems to synergize with Velcade, and Velcade affects proteasome inhibition,” said Wagner. “Because folded proteins are degraded by the proteasome, it seems like there’s a natural synergy for this combined approach, which is why researchers are going forward in multiple myeloma.” A Phase 3 combination study, comparing KOS-953 plus Velcade® to Velcade alone in patients with multiple myeloma in first relapse, is currently recruiting patients. Tanespimycin is also in Phase 2 trials in breast, prostate, and thyroid cancer.

Insulin-like Growth Factor Receptor Inhibitors

Of the four agent classes, drugs that target IGF-1R inhibitors—CP-751,871 and MK-0646—are the most experimental. There is currently no published Phase 3 data available on these agents. Although IGF-1R inhibitors are an untested target, it is “one with a lot of potential,” said Wagner. Bakri echoes Wagner’s sentiment and agrees that IGF-1R inhibitors are a very hot target. He stated that a lot of these inhibitors are currently in development, and that they should be an interesting addition to the armamentarium. “But at the same time, it’s a crowded space and understanding

how early data translates is kind of haphazard. So it's difficult to handicap things," he said.

Perhaps Wagner's "tried and true" dictum can help explain the allure of IGF-1R inhibitors. He said that IGF-1R inhibitors may synergize with EGFR inhibitors as they both share a downstream signaling pathway that goes thru AKT. "And mTOR inhibitors, like Wyeth's Toricel and Novartis' everolimus, have helped validate the AKT signaling pathway."

» CP-751,871

A human monoclonal antibody directed against IGF-1R, Pfizer's investigational compound CP-751,871 (figitumumab) has shown promising results in NSCLC and Ewing's sarcoma—two disease states burdened with a substantial unmet medical need. Results from a Phase 2, randomized study presented at ASCO 2008 showed that 54% of patients with stage III/IV treatment-naive NSCLC receiving CP-751,871 in combination with carboplatin and paclitaxel experienced objective responses. Patients receiving only carboplatin and paclitaxel experienced a response rate of 41%.

Furthermore, a subset of squamous cell and adenocarcinoma patients receiving CP-751,871 plus carboplatin and paclitaxel experienced objective response rates of 78% and 57%, respectively, in comparison with 46% and 25% for patients receiving only carboplatin and paclitaxel. "Pfizer's

drug seemed to have its greatest activity in patients that don't receive Avastin," said Wagner. "That's one of the reasons that I'm excited about this drug. Non-squamous patients receive Avastin with their chemotherapy; squamous patients do not, so CP-751,871 is like an Avastin for the rest of us."

Based on the data presented at ASCO, Pfizer has initiated a large global Phase 3 clinical trial program for CP-751,871 in NSCLC.

» MK-0646

Another IGF-1R inhibitor that analysts will be watching closely in the coming months is Merck's MK-0646, a humanized monoclonal antibody currently being studied in a Phase 2/3 trial in metastatic colorectal cancer and a Phase 2 trial in NSCLC. When combined with chemotherapy in a certain subset of patients with a particular set of histologies, the data look promising.

MK-0646 is being combined with an EGFR inhibitor in both trials (either Erbitux in CRC or Tarceva in NSCLC), which Wagner believes is based on the perceived synergy between the two pathways—both signal through AKT downstream.

Other Noteworthy Agents

Not all oncology agents deemed promising fall within the parameters of the four aforementioned classes. Bakri was especially intrigued by the data surrounding Cougar

Pharmaceuticals' investigational prostate cancer compound, CB7630. "This could be on the market in the next 2 to 3 years," said Bakri. "And it's likely to be a very big drug in prostate cancer. Based on the Phase 2 data, CB7630 looks like it has very strong efficacy and a good safety profile."

» CB7630

Abiraterone acetate, or CB7630, is an orally administered inhibitor of the steroidal enzyme 17 α -hydroxylase/C17,20 lyase, a cytochrome p450 complex that is involved in testosterone production. Data from clinical studies has shown that CB7630 inhibits testosterone production in both the adrenals and the testes.

Bakri believes the mechanism of action of CB7630 is unique from other anti-androgen therapies, in that it appears to completely shut down testosterone synthesis. "The first-line treatment of prostate cancer is to give anti-androgens, but eventually the prostate cancer becomes hormone refractory," he said. "Researchers think that the main reason the tumor initially becomes refractory to anti-androgen therapy is because a residual amount of androgens are being produced by the adrenal glands. It's as though CB7630 essentially shuts off adrenal androgens."

Interim clinical trial data has shown that patients experienced confirmed declines in prostate specific antigen levels of up to 90+%, partial radiological responses **cont. on pg 28 >>**

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(as measured by the RECIST criteria), regressing bone disease, and improvement in pain. Cougar Pharmaceutical representatives believe that CB7630 has three potential therapeutic applications: as a second-line hormonal therapy for patients with hormone refractory prostate cancer; as a first-line hormonal therapy for patients with advanced prostate cancer; and as a second-line chemotherapy for patients with advanced prostate cancer who have failed docetaxel-based treatment.

Hedgehog Inhibitors

The Hedgehog signaling pathway, which is most active during embryogenesis, controls the differentiation, growth and proliferation of cells, and has been implicated in numerous cancers (e.g., pancreatic, prostate, lung, breast, and brain) as well basal cell carcinoma and medulloblastoma. As a result, researchers believe this pathway makes a promising target for novel cancer therapies.

» GDC-0499

Genentech's GDC-0499, an oral inhibitor of the hedgehog signaling pathway is currently being investigated in basal cell carcinoma (BCC), colorectal cancer, and ovarian cancer. "This drug had dramatic results in basal cell carcinoma patients," said Wagner. "It demonstrated extremely high activity. The kind of activity that reflects the promise—rarely achieved—of targeted therapies."

Data presented from a Phase 1 trial at the 2008 Annual Meeting of the American Association for Cancer Research (AACR) and reprised at ASCO 2008, showed that GDC-0449 provided promising activity in advanced BCC patients with minimal side effects.

"There was dramatic tumor reduction and extremely high activity," said Wagner. "So this drug may get to the market if the Phase 2 study confirms these spectacular results." He speculates that Genentech is using feedback from the FDA to carefully design its Phase 2 trial to achieve accelerated approval in basal cell carcinoma. Though extremely optimistic about the chances of GDC-0449 in this disease area, he is less enthusiastic about the Phase 2 trials currently underway in metastatic colorectal and ovarian cancer.

Measuring Success

How successful any of these inhibitors become depends, in part, on whether they are used primarily as monotherapy or in combination with chemotherapeutics. For example, Wagner cites the success of Avastin which is used with chemotherapy in lung, breast, and colorectal cancers. The question, he wonders, is can you use drugs like Sutent with chemotherapy as well. "These inhibitors are clearly active drugs, they shrink tumors, but multi-targeted kinase inhibitors and chemotherapy have lower expectations of success. That

is a key question that we'll know the answer to in the next two years, but my expectations that they will work are low."

Another factor that will determine the success of these pipeline agents is toxicity. Toxicity will likely be a key differentiator, and Wagner thinks that will be true with pazopanib.

With ASCO 2009 right around the corner, investors and industry analysts are sure to get a first-hand account of how these oncology agents are fast evolving. And, with the proven targets and powerful concepts driving the research behind these four promising drug classes, the chances that some of these agents will enter the marketplace in the next five years is a strong and exciting possibility.

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NICE, the agency that decides which treatments are made available in the U.K.'s publicly funded healthcare system, recently backed the use of Pfizer's Sutent® as a cost-effective, first-line treatment for advanced kidney cancer patients but the watchdog body has still rejected Roche AG's Avastin®, Bayer AG's Nexavar® and Wyeth's Torisel® as other first-line treatments for the disease. (Dow Jones Newswires, 2/3/09)