Developments in the Use of Antibody-Drug Conjugates

Howard A. Burris III, MD

OVERVIEW

With the recent approvals of brentuximab for the treatment of refractory Hodgkin lymphoma and ado-trastuzumab emtansine for relapsed metastatic HER2+ breast cancer, the hope for delivering targeted chemotherapy in the form of an antibody-drug conjugate (ADC) against many cancers is rapidly growing. The strategy of delivering a potent cytotoxic via a monoclonal antibody to a tumor has been made feasible by marked advances in the technology of formulating and manufacturing these ADCs. The development of stable linkers together with the identification of relevant biomarkers has been a key to the success of this class of agent. The possibilities for deploying this technology in the treatment of a wide range of solid cancers are limited only by the discovery of suitable targets, those which are highly expressed on cancer cells and not, or minimally, on normal tissues. That said, with the improved linker engineering, the ADC affords the best opportunity at shrinking tumors while minimizing side effects. A variety of ADCs are in clinical trials studying a number of different tumor types as diverse as small cell lung and renal cell cancer. A future of potent anticancer therapy with minimal toxicity appears closer to reality for our patients.

Discoveries of prevalent antigens on these cancers, coupled with the promise of the better linker strategies, have made these advances possible.

ADCs IN DEVELOPMENT

IMGN388 consists of a maytansinoid, DM4, attached to an alpha-v integrin targeting antibody. The agent’s integrin target is expressed on a wide variety of solid tumors as well as endothelial cells involved in angiogenesis. In phase I studies, patients treated at the upper doses of 80–130 mg/m² IV q 3 weeks benefited, including shrinkage of non–small cell lung, prostate, breast, neuroendocrine, and uterine cancer. The high expression of alpha-v integrins on specific cancers, while minimally expressed on normal tissues, makes it an attractive target.

IMGN901 (lorvotuzumab mertansine), is a CD56 targeted ADC with effectiveness against small cell lung cancer (SCLC) as well as multiple myeloma, ovarian, and Merkel cell carcinoma. The cytotoxic is a proprietary maytansinoid and the linker is engineered by Immunogen. The initial studies in SCLC have been conducted in combination with carboplatin plus etoposide and include patients that have already been previously treated with these agents. The high expression of alpha-v integrins on specific cancers, while minimally expressed on normal tissues, makes it an attractive target.

Various ADCs have now entered the clinic in trials against a variety of solid tumors in addition to breast cancer, including lung, both nonsmall cell and small cell, ovarian, renal cell, mesothelioma, melanoma, and prostate cancer. From the Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN. Author's disclosures of potential conflicts of interest are found at the end of this article.

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progression. The first stage results of 40 patients met the pre-specified parameters to allow the full accrual of 120 patients to be completed.

Clinical trials with IMGN901 in combination with lenalidomide plus dexamethasone against multiple myeloma are showing positive results. In a phase I study of weekly dosing plus chronic oral lenalidomide plus dexamethasone, including patients of which more than 50% had been previously treated with thalidomide or lenalidomide, eight of 13 had an objective response, including five very good partial responses and three partial responses. A dose of 75 mg/m² weekly x 3 q 4 weeks will be used in the follow-up phase II studies with standard dose lenalidomide plus dexamethasone. Phase I studies have shown tumor shrinkage in patients with the rare but often aggressive Merkel cell cancer, as well as ovarian cancer. A full development strategy is underway.

CDX-011 (glembatumumab vedotin) is an ADC that links CR011, a human IgG2 monoclonal antibody with high affinity for the extracellular domain of glycoprotein NMB (GPNMB) to the dolastatin-like tubulin inhibitor monomethyl-auristatin E (MMAE). The linker is the technology of Seattle Genetics. GPNMB is thought to be highly expressed in 40% of breast cancers. Activity has been documented against breast cancer, with encouraging results seen in triple negative subtypes, especially those over expressing GPNMB by immunohistochemical. The EMERGE study randomly assigned 122 patients in a 2:1 fashion to CDX-011 or investigator's choice in patients whose breast cancers over expressed by at least 5%. The overall results showed only 19% compared with 14% response rates in the two groups. In the much smaller group of patients with triple negative, high GPNMB-expressing disease, four of 11 (36%) responded, and additional trials are now underway in this subset.

GPNMB is highly expressed in more than 80% of melanomas. A phase I study of CDX-011 established a dose of 1.88 mg/kg q 3 weeks and a phase II trial of heavily treated patients yielded a progression-free survival of 4 months and some tumor shrinkage in 56% of patients. Interestingly, in the melanoma phase II trial, development of a rash (44 patients) compared with no rash (13 patients) resulted in an overall partial response rate difference of 23% compared with 0%, and a progression-free survival difference of 4.8 months compared with 1.2 months (p < 0.001). High GPNMB expression correlated with both rash and activity. Further studies are in progress in relapsed melanoma.

SGN-75 is an ADC utilizing their own proprietary linker coupling an anti-CD70 monoclonal antibody with monomethyl auristatin F (MMAF). CD70 is often highly expressed on renal cell cancers (RCC) as well as non-Hodgkin lymphomas (NHL). Among the first 16 patients in the phase I trial,

### KEY POINTS
- The components of an antibody-drug conjugate are a monoclonal antibody, a stable linker, and a cytotoxic agent.
- Delivery of chemotherapy via an antibody drug conjugate improves the benefit-to-risk profile.
- The approval of antibody-drug conjugates for the treatment of metastatic HER2+ breast cancer and relapsed Hodgkin’s lymphoma has created great enthusiasm for the technology as proven paradigm for treating cancer.
- Antibody drug conjugates are in development for a number of solid tumors, including breast, melanoma, lung, prostate, ovarian, and other cancers.
- The possibilities for developing and utilizing these agents are limited only by the discovery of suitable targets, highly expressed on and relatively specific to cancer cells.

### TABLE 1. Selected Antibody-Drug Conjugates in Development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Biomarker</th>
<th>Tumor</th>
<th>Phase of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentuximab vedotin</td>
<td>Seattle Genetics</td>
<td>CD30</td>
<td>Hodgkin lymphoma, Anaplastic large cell lymphoma</td>
<td>Approved</td>
</tr>
<tr>
<td>Ado-trastuzumab emtansine</td>
<td>Genentech</td>
<td>HER-2</td>
<td>Breast</td>
<td>Approved</td>
</tr>
<tr>
<td>IMGN388</td>
<td>Immunogen</td>
<td>alpha-v integrin</td>
<td>Lung, Breast, Prostate</td>
<td>I</td>
</tr>
<tr>
<td>IMGN901 (lorvotuzumab mertansine)</td>
<td>Immunogen</td>
<td>CD56</td>
<td>SCLC, MM, Ovarian, MCC</td>
<td>I, II</td>
</tr>
<tr>
<td>CDX-011 (glembatumumab vedotin)</td>
<td>Cellidex</td>
<td>Glycoprotein NMB (GPNMB)</td>
<td>Breast, Melanoma</td>
<td>I, II</td>
</tr>
<tr>
<td>SGN-75</td>
<td>Seattle Genetics</td>
<td>CD70</td>
<td>RCC, NHL</td>
<td>I</td>
</tr>
<tr>
<td>BAY 94-9343</td>
<td>Bayer</td>
<td>Mesothelin</td>
<td>Mesothelioma, Ovarian, Gastric, Pancreatic, Lung</td>
<td>I</td>
</tr>
<tr>
<td>5E9 ADC</td>
<td>Roche/Genentech</td>
<td>EDNRB</td>
<td>Melanoma</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Anti-NaPi3b-vc-E</td>
<td>Roche/Genentech</td>
<td>NaPi3b</td>
<td>Lung, Ovarian</td>
<td>Preclinical</td>
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</tbody>
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one complete remission in a patient with heavily pretreated NHL and one partial remission in a relapsed RCC were observed. Based on this single agent activity noted against RCC and promising preclinical surgery, a phase 1b trial has begun in combination with everolimus.

BAY 94–9343 is a novel ADC targeted against the cancer antigen mesothelin. The cytotoxic is DM4, a maytansinoid, and the antibody is a fully human IgG1, BAY 86–1903. Mesothelin is a membrane associated antigen found on the normal cells of the pleura and peritoneum. It is often over expressed in mesotheliomas as well as ovarian, gastric, pancreas, and lung adenocarcinoma. Mesothelin has also been reported to exist on squamous cell cancers of the esophagus, lung, and cervix. Studies are now being conducted to determine the dose, schedule, and toxicities of this very unique ADC.

The endothelin B receptor (EDNRB) has been found to be highly expressed across a variety of melanomas. A monoclonal antibody, 5E9 reactive with the N-terminal tail of EDNRB internalizes rapidly into melanoma cells. When linked with monomethyl auristatin E (MMAE), the resulting ADC demonstrates remarkable efficacy against human cell lines.

NaPi3b (SLC34A2) is a multitransmembrane, sodium-dependent phosphate transporter expressed in nonsquamous lung and ovarian cancers.

**CONCLUSION**

The possibilities for deploying this technology in the treatment of solid tumors is limited only by the discovery of suitable targets, which are highly expressed on cancer cells and not, or minimally, on normal tissues. Resistance will still eventually develop within the cancer cells to the various cytotoxics through normal channels, as it will to the antibodies through mechanisms such as truncation or internalization of receptors. That said, with the improved linker engineering, the ADC affords the best opportunity at maximizing cancer cell kill while minimizing side effects.

Described in this brief overview are just some of the many agents being studied against a wide variety of solid tumors, with pathology as different as clear cell carcinoma of the kidney to small cell lung cancer and melanoma. Many patients will benefit over the next few years from these clinical studies, and many more will have improved outcomes as these ADCs are first approved and then moved into the adjuvant and first-line settings.

**References**


