ANTIBODY THERAPEUTICS IN THE PIPELINE

JANICE M. REICHERT, PH.D., Executive Director, **The Antibody Society**
& Editor-in-Chief, **mAbs**

The Antibody Society, an international, non-profit association representing individuals and organizations involved in antibody-related research and development, collects information about targeted therapeutics developed by commercial firms from publicly available sources (e.g., press releases, company websites, meeting abstracts, published literature, clinicaltrials.gov, regulatory agency websites). Our data are cross-checked against databases generously provided by our corporate partners, including Hanson Wade's Beacon Targeted Therapies and the Therapeutic Antibody Database. We report trends and metrics for antibody therapeutics development via the Society's website, presentations and publications. Please visit our website (www.antibodysociety.org) for more information.

ANTIBODY SOCIETY.

As part of our mission to inform and educate, The Antibody Society (www.antibodysociety.org) tracks the commercial clinical pipeline of antibody therapeutics and reports on trends in their development and approval. Antibodies are already a critical part of treatment regimens for many diseases. The number of new antibody therapeutics granted approvals each year in the United States or European Union has increased recently, and ~ 70 such products are now marketed in these regions. There remains, however, substantial need for new drugs, especially for cancer. The biopharmaceutical industry has responded to this need by expanding the clinical pipeline to include more highly innovative antibodies designed to have enhanced functionality compared to the currently marketed products. Here, we present a brief overview of the clinical pipeline, with a focus on the antibodies for cancer, which can offer insight into which approaches may result in new drugs for patients in the future.

The commercial clinical pipeline includes nearly 600 antibody therapeutics in development for cancer, as well as immune-mediated disorders, cardiovascular diseases, and other pathologies. Canonical antibodies comprise the majority, but the clinical pipeline also includes a growing number of antibodies that function via innovative mechanisms of action, including antibody-drug conjugates (ADCs), bispecific antibodies, and antibodies that modulate the responses of the immune system.

Composed of an antibody, a small molecule drug and a linker, ADCs are designed to deliver cytotoxic agents inside targeted cells, where the cytotoxin acts to kill the cells. To date, 4 ADCs have been granted marketing approvals, 3 for hematological malignancies and 1 for breast cancers that over express the human epidermal growth factor receptor 2 (HER2). Over 70 ADCs are currently in the clinical pipeline, and nearly all of these are being evaluated as treatments for cancer. While most of these ADCs are in early-phase clinical studies, 10 are in pivotal Phase 2 or Phase 3 studies. These ADCs include several undergoing evaluation in cancer patients for whom there are limited treatment options, such as those with HER2-positive gastric or gastroesophageal junction adenocarcinoma, small-cell lung cancer, triple-negative breast cancer and glioblastoma. Positive results from the late-stage clinical studies may enable the submission of marketing applications for these ADCs in the near future.

As the name suggests, bispecific antibodies are designed to bind two different targets. The clinical pipeline includes ~ 70 bispecific antibodies, nearly three-quarters of which are being evaluated as treatments for cancer. T-cell redirection is an innovative mechanism of action employed by over 30 bispecific antibodies in clinical development. These molecules bind a T cell-specific antigen such as CD3 and a disease-specific antigen, typically on a tumor cell, thereby enabling the T cell to kill the targeted cell. This approach is exemplified by blinatumomab (Blincyto®), a tandem single-chain variable fragment targeting CD19 and CD3 approved to treat relapsed or refractory B-cell precursor acute lymphoblastic leukemia. The T-cell dependent bispecific antibodies in the pipeline are in early-phase studies of patients with numerous types of hematological cancers or solid tumors.

Antibody immune checkpoint modulators can be used to treat many types of cancer, which makes them highly attractive for biopharmaceutical development. For example, the approved antibody immune checkpoint modulators, which target only 3 of the many proteins involved in either stimulating or inhibiting the responses of the human immune system, are treatments for melanoma, non-small-cell lung cancer, head and neck cancer, Hodgkin's lymphoma, bladder cancer, gastric/gastroesophageal junction adenocarcinoma, renal cell cancer, hepatocellular cancer, Merkel cell carcinoma and colorectal cancer. More than 80 antibody immune checkpoint modulators sponsored by commercial firms are in clinical development. Most are in early development, with 50 and 28 antibody immune checkpoint modulators undergoing evaluation in Phase 1 and Phase 2 clinical studies, respectively. Seven are undergoing evaluation in late-stage studies. If approved, availability of these antibody therapeutics would provide physicians with additional options for cancer patients.

While the antibodies for cancer garner substantial attention, the commercial pipeline includes ~240 antibodies for non-cancer indications. Of these, most are in early-stage clinical studies, but over 20 are in Phase 3 studies. This late-stage pipeline includes antibodies undergoing evaluation for prevalent diseases such as rheumatoid arthritis, but also for less common disorders, including thyroid eye disease, sickle cell disease, primary systemic amyloidosis, and primary hemophagocytic lymphohistiocytosis. As with the antibodies for cancer, those for non-cancer indications represent opportunities for new drugs for patients in need.