2.3 BISPECIFIC ANTIBODIES

Many mAb shortcomings could be overcome by creating bispecific antibodies (bsAbs)[29]—which are able to simultaneous bind to two different targets—because such molecules would have the possibility to target a large variety of payloads to cancer cells.

Catumaxomab (Removab®) is a trifunctional antibody that binds to EpCAM and to CD3 antigens and also to Fc receptors on APCs. It was approved in the European Union in 2009 for the intraperitoneal treatment of patients with malignant ascites, a condition that occurs in patients with metastasizing cancer,[30] and then by the FDA in 2011. It is also being studied for the treatment of peritoneal carcinomatosis in patients with gastric adenocarcinomas. Another bispecific antibody under clinical evaluation for breast or ovarian cancer that overexpresses the proto-oncogene HER-2 is MDX-210, which binds to HER-2 and CD64.[31]

Bispecific T-cell engagers (BiTEs®) are another class of bispecific antibodies, which are aimed at inducing the immune system to act against cancer cells by simultaneously binding to a cancer cell and T lymphocytes (Figure 12.5).

Ertumaxomab (Rexomun®) has two antigen-recognition sites, one for CD3 (an antigen expressed on mature T cells) and one for HER-2. In early clinical trials of patients with malignant ascites due to peritoneal carcinomatosis, administration of rather low doses of ertumaxomab led to the complete elimination of tumor cells and the disappearance of ascites accumulation in all patients.[32] Ertumaxomab has entered phase II trials for the treatment of metastatic breast cancer.

Blinatumomab (AMG103, Blincyto®) has an antigen-recognition site for the CD3 complex, a group of T-cell surface glycoproteins that bind to the TCR, and another for CD19, a tumor-associated antigen (TAA) overexpressed on the surface of B cells. Thus, blinatumomab allows T cells in the cancer patient to recognize malignant B cells. It was approved by the FDA in late 2014 for acute lymphoblastic leukemia.

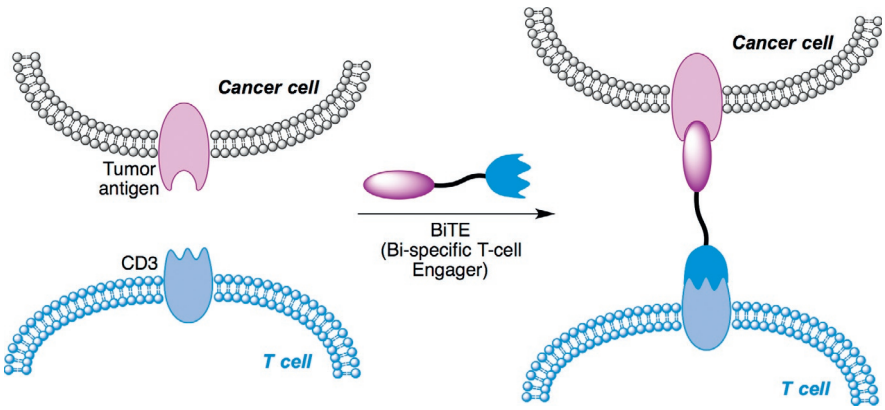

FIGURE 12.5

Mechanism of action of bispecific T-cell engagers (BiTEs®).