has experienced a marked revolution with the introduction of the antibody ipilimumab (Yervoy®) and the small molecule vemurafenib (Zelboraf®), which are directed against the mutated kinase bRaf V600E. The dual SRC and Abl kinase inhibitor bosutinib (Bosulif®) has improved the treatment of previously treated Philadelphia chromosome-positive chronic myeloid leukemia patients, and crizotinib (Xalkori®) is changing the management of ALK-positive lung cancers. The multikinase inhibitor regorafenib (Stivarga®) and the vascular endothelial growth factor-directed recombinant fusion protein aflibercept (Zaltrap®) are useful for metastatic colon cancer, and ruxolitinib (Jakafi®) and axitinib (Inlyta®) are used for myelofibrosis and for renal cell carcinoma, respectively. The advent of immunoconjugates in which antibodies are linked to toxins or radioisotopes has opened a new horizon for antibody-based targeted therapeutics. One example is the antibody–drug conjugate brentuximab vedotin (Adcetris®), which was approved in 2011 for the treatment of relapsed or refractory Hodgkin's lymphoma. Trastuzumab emtansine (T-DM1, Kadcyla®), approved in 2013, is another immunoconjugate for patients with metastatic breast cancer.

5 GENERAL COMMENTS ABOUT ANTICANCER DRUG DISCOVERY

Cancer therapy is based on local interventions such as surgery and radiotherapy, which are quite successful when viable, and on systemic chemotherapy. Approximately 50% of cancer patients are not cured by systemic chemotherapy and obtain only a prolonged survival.

Many cancer chemotherapeutic drugs currently in clinical use try to kill malignant tumor cells by inhibiting some of the mechanisms involved in cellular division. Accordingly, the antitumor compounds developed through this approach are cytostatic or cytotoxic to every dividing cell, including normal cells, and for this reason these drugs are nonspecific. However, the explosion in knowledge in tumor biology during the past decades has paved the way for specific, targeted anticancer drugs.[32] Success with the new molecularly targeted approach was demonstrated by the approval by the U.S. Food and Drug Administration (FDA) of a number of innovative drugs, both antibodies and small molecules, since the introduction of trastuzumab (Herceptin®) in 1998 as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of women with node-positive, HER-2-overexpressing breast cancer.[33] Trastuzumab is a humanized monoclonal antibody that targets the extracellular region of the HER-2 receptor, leading to its internalization and degradation. The introduction in 2001 of the tyrosine kinase inhibitor imatinib (Glivec®) as a highly effective drug for patients with Philadelphia chromosome-positive chronic myeloid leukemia and gastrointestinal stromal tumors[34] was proof of the concept of effective drug development based on the knowledge of tumor biology.[35] These anticancer drugs are signal transduction inhibitors that differ from compounds developed during the cytotoxic era because they target the precise molecular mechanisms responsible for the initiation and progression of cancer. Anti-oncogene drugs have had positive results and even cured some cancers, such as lung cancers with EGFR mutations, breast cancer with mutations in HER2, or, more recently, melanoma with b-RAF mutations. Unfortunately, currently known drugs cannot replace the function of tumor suppressor genes, whose mutations are more predominant that those that activate oncogenes.

Targeted therapies may use small molecule drugs or other macromolecular structures, such as monoclonal antibodies, to bind antigens that are preferentially or exclusively present on tumor cells. Other approaches try to develop compounds that interfere with gene expression in order to suppress the