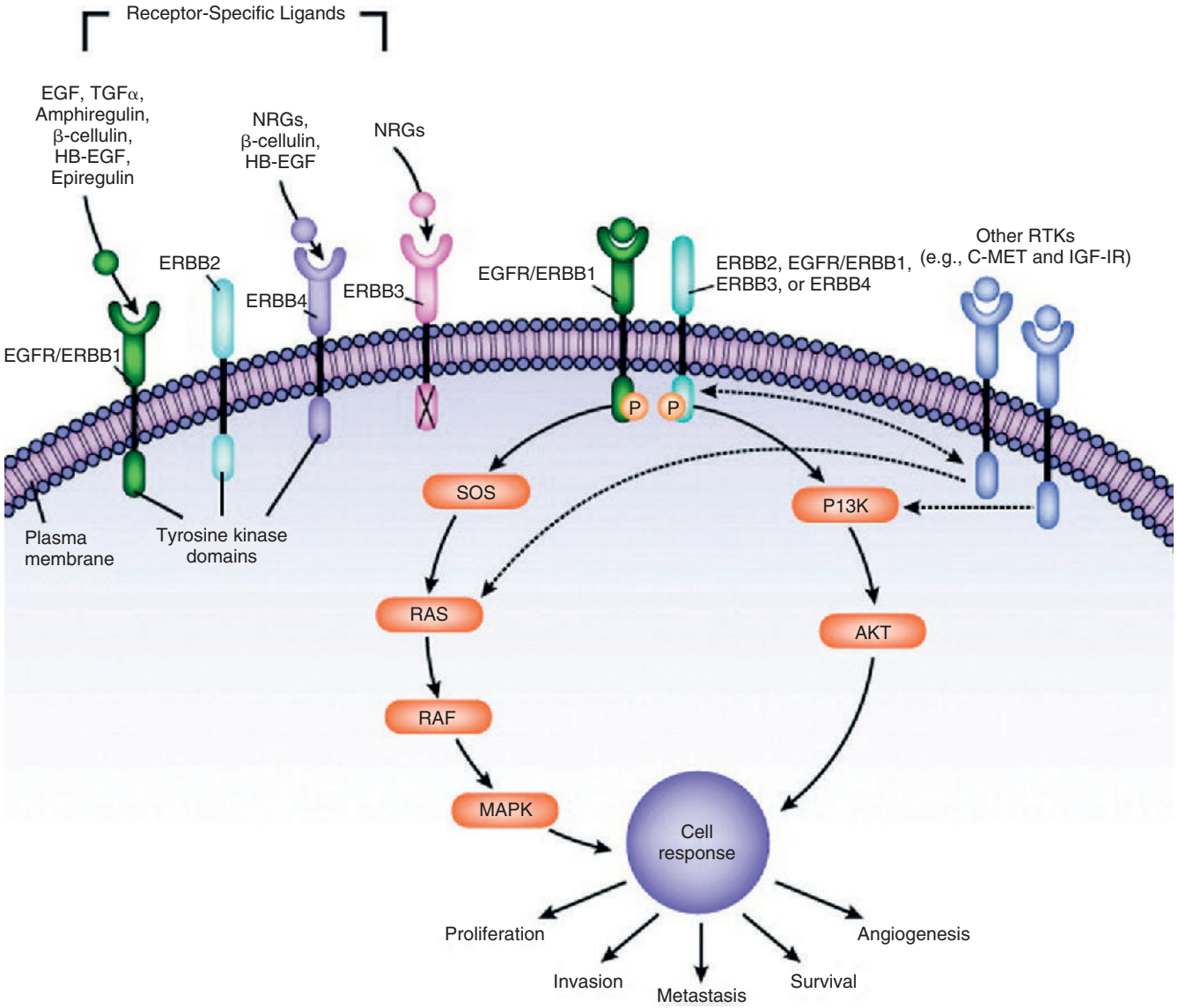

FIGURE 55-1 The epidermal growth factor receptor (EGFR) pathway and related therapeutic targets. This figure depicts the transmembrane receptors of the EGFR family and the molecules involved in downstream signal transduction that ultimately lead to control of key proteins affecting cell survival, growth, and proliferation. Approved therapeutic agents targeting these molecules include cetuximab and panitumumab (EGFR); erlotinib and gefitinib (EGFR tyrosine kinases); trastuzumab, pertuzumab, and lapatinib (ERBB2); and sorafenib and vemurafenib (RAF). Several other agents are currently in clinical development, including those targeting PI3K, AKT, MAPK, and ERBB3. HB-EBF, Heparin-binding EGF-like growth factor; IGF-IR, insulin-like growth factor-I receptor; NRGs, neuregulins; P, elemental phosphorus; RTKs, receptor tyrosine kinases; TNF-α, tumor necrosis factor-α. (Modified from Doebele RC, Oton AB, Peled N, et al: New strategies to overcome limitations of reversible EGFR tyrosine kinase inhibitor therapy in non-small cell lung cancer. Lung Cancer 69:1–12, 2010.)

arising from the Philadelphia chromosome of CML, and KIT (c-kit, CD117), which is overexpressed in gastrointestinal stromal tumors (GIST). The daily oral administration of imatinib results in complete hematologic responses in more than 90% of patients in chronic-phase CML and partial responses in more than 50% of patients with metastatic GIST. Although imatinib is a major advance, it is not considered curative in most patients. Cancer cells rapidly evolve to escape cell kill from targeted therapies by employing new mutations and redundant intracellular pathways. Multiple parallel clones evolve within a given tumor, and some are resistant to the targeted therapy. Drug resistance to imatinib occurs in the form of a mutation in the kinase domain of *ABL* that leads to poor binding of the drug.

The success of imatinib as a single agent is unlikely to be replicated in many other malignancies, in which multiple redundant signaling pathways are dysregulated. Increasingly, tyrosine kinase inhibitors with multiple (as opposed to specific) targets are being studied. Sorafenib and sunitinib are two examples of such agents that inhibit various pathways, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and KIT. Studies have shown these drugs to be effective in renal and liver cancers.

Targeted therapy drugs can increase the efficacy of chemotherapy through various mechanisms. For instance, bevacizumab, an anti-angiogenic agent directed against the pro-angiogenic VEGF, increases both response and survival rates when