TABLE 103e-5 MOLECULARLY TARGETED AGENTS (*CONTINUED*)

Drug	Target	Adverse Events	Notes
Everolimus	Renal cell carcinoma, advanced; subependymal giant-cell astrocytoma; breast cancer, hormone receptor positive, resistant to antiestrogen; pancreatic neuroendocrine	Stomatitis Fatigue	
Miscellaneous			
Arsenic trioxide	APL	↑ QTc	APL differentiation syndrome (see under tretinoin)
Vismodegib	Metastatic basal cell carcinoma	GI Hair loss Fatigue Muscle spasm Dysgeusia	Target smoothened receptor in hedgehog pathway

Abbreviations: APL, acute promyelocytic leukemia; ALL, acute lymphocytic leukemia; CHF, congestive heart failure; CML, chronic myeloid leukemia; EGFR, epidermal growth factor receptor; GI, gastrointestinal; mTOR, mammalian target of rapamycin kinase; NSCLC, non-small-cell lung cancer; PDGFR, platelet-derived growth factor receptor; Pgp, P-glycoprotein; VEGFR, vascular endothelial growth factor receptor.

trials in NSCLC; an overall survival advantage was demonstrated in subsets of patients who were treated after demonstrating progression of disease and who also had not been preselected for the presence of activating mutations. Thus, although even patients with wild-type EGF receptors may benefit from erlotinib treatment, the presence of EGF receptor tyrosine kinase mutations has recently been shown to be a basis for recommending erlotinib and afatinib for first-line treatment of advanced NSCLC. Likewise, crizotinib targeting the *alk* protooncogene fusion protein has value in the initial treatment of *alk*-positive NSCLC. Lapatinib is a tyrosine kinase inhibitor with both EGF receptor and HER2/neu antagonist activity, which is important in the treatment of breast cancers expressing the HER2/neu oncoprotein.

In addition to the $p210^{bcr\text{-}abl}$ kinase, imatinib also has activity against the c-kit tyrosine kinase (the receptor for the *steel* growth factor, also called stem cell factor) and the platelet-derived growth factor receptor (PDGFR), both of which can be expressed in gastrointestinal stromal sarcoma (GIST). Imatinib has found clinical utility in GIST, a tumor previously notable for its refractoriness to chemotherapeutic approaches. Imatinib's degree of activity varies with the specific mutational variant of kit or PDGFR present in a particular patient's tumor.

The *BRAF* V600E mutation has been detected in a notable fraction of melanomas, thyroid tumors, and hairy cell leukemia, and preclinical models supported the concept that *BRAF* V600E drives oncogenic signaling in these tumors. Vemurafenib and dabrafenib, with selective capacity to inhibit the *BRAF* V600E serine kinase activity, were each shown to cause noteworthy responses in patients with *BRAF* V600E–mutated melanomas, although early relapse occurred in many patients treated with the drugs as single agents. Trametinib, acting downstream of *BRAF* V600E by directly inhibiting the MEK serine kinase by a non-ATP binding site mechanism, also displayed noteworthy responses in *BRAF* V600E–mutated melanomas, and the combination of trametinib and dabrafenib is even more active, by targeting the *BRAF* V600E–driven pathway at two points in the pathway leading to gene activation.

ONCOGENICALLY ACTIVATED PATHWAYS This group of agents also targets specific regulatory molecules in promoting the viability of tumor cells, but they do not require the diagnostically verified presence of a particular target or target variant at this time.

"Multitargeted" kinase antagonists are small-molecule ATP site-directed antagonists that inhibit more than one protein kinase and have value in the treatment of several solid tumors. Drugs of this type with prominent activity against the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase have activity in renal cell carcinoma. Sorafenib is a VEGFR antagonist with activity against the *raf* serine-threonine protein kinase, and regorafenib is a closely related drug with value in relapsed advanced colon cancer. Pazopanib also prominently targets VEGFR and has activity in renal carcinoma and soft tissue sarcomas. Sunitinib has anti-VEGFR, anti-PDGFR, and anti-c-kit activity. It causes prominent responses and stabilization of disease in renal cell cancers and GISTs. Side effects for agents with anti-VEGFR activity prominently include hypertension, proteinuria, and, more rarely, bleeding and clotting disorders and perforation of scarred gastrointestinal lesions. Also encountered are fatigue, diarrhea, and the hand-foot syndrome, with erythema and desquamation of the distal extremities, in some cases requiring dose modification, particularly with sorafenib.

Temsirolimus and everolimus are mammalian target of rapamycin (mTOR) inhibitors with activity in renal cancers. They produce stomatitis, fatigue, and some hyperlipidemia (10%), myelosuppression (10%), and rare lung toxicity. Everolimus is also useful in patients with hormone receptor–positive breast cancers displaying resistance to hormonal inhibition and in certain neuroendocrine and brain tumors, the latter arising in patients with sporadic or inherited mutations in the pathway activating mTOR.

In hematologic neoplasms, bortezomib is an inhibitor of the proteasome, the multisubunit assembly of protease activities responsible for the selective degradation of proteins important in regulating activation of transcription factors, including nuclear factor-κB (NF-κB) and proteins regulating cell cycle progression. It has activity in multiple myeloma and certain lymphomas. Adverse effects include neuropathy, orthostatic hypotension with or without hyponatremia, and reversible thrombocytopenia. Carfilzomib is a proteasome inhibitor chemically unrelated to bortezomib without prominent neuropathy, but with evidence of a cytokine release syndrome, which can be a cardiopulmonary stress. Other agents active in multiple myeloma and certain other hematologic neoplasms include the immunomodulatory agents related to thalidomide, including lenalidomide and pomalidomide. All these agents collectively inhibit aberrant angiogenesis in the bone marrow microenvironment, as well as influence stromal cell immune functions to alter the cytokine milieu supporting the growth of myeloma cells. Thalidomide, although clinically active, has prominent cytopenic, neuropathic, procoagulant, and CNS toxicities that have been somewhat attenuated in the other drugs of the class, although use of these agents frequently entails concomitant anticoagulant prophylaxis.

Ibrutinib is representative a novel class of inhibitors directed at Bruton's tyrosine kinase, which is important in the function of B cells. Initially approved for use in mantle cell lymphoma, it is potentially applicable to a number of B cell neoplasms that depend on signals through the B cell antigen receptor. Janus kinases likewise function downstream of a variety of cytokine receptors to amplify cytokine signals, and Janus kinase inhibitors including ruxolitinib have approved activity in myelofibrosis to ameliorate splenomegaly and systemic symptoms.

Vorinostat is an inhibitor of histone deacetylases, which are responsible for maintaining the proper orientation of histones on DNA, with resulting capacity for transcriptional readiness. Acetylated histones allow access of transcription factors to target genes and therefore