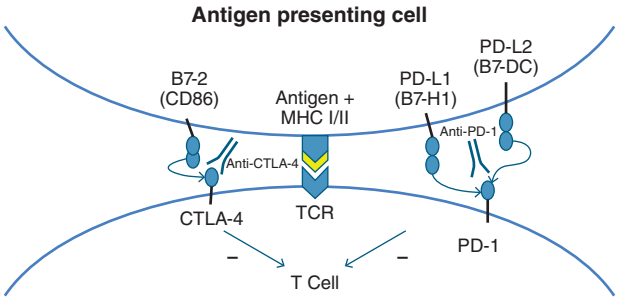

FIGURE 105-3 Inhibitory regulatory pathways that influence T cell function, memory, and lifespan after engagement of the T cell receptor by antigen presented by antigen-presenting cells in the context of MHC I/II. CTLA-4 and PD-1 are part of the CD28 family and have inhibitory effects that can be mitigated by antagonistic antibodies to the receptors or ligand, resulting in enhanced T cell function and antitumor effects. CTLA-4, cytotoxic T lymphocyte antigen-4; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; TCR, T cell receptor.

In addition to its antitumor effects, ipilimumab's interference with normal regulatory mechanisms produced a novel spectrum of side effects that resembled autoimmunity. The most common immune-related adverse events were skin rash and diarrhea (sometimes severe, life-threatening colitis), but toxicity could involve most any organ (e.g., hypophysitis, hepatitis, nephritis, pneumonitis, myocarditis, neuritis). Vigilance and early treatment with steroids that do not appear to interfere with the antitumor effects are required to manage these patients safely. Widespread use of ipilimumab has not been completely embraced by the oncology community because of the low objective response rate, significant toxicity (including death), and high cost (drug cost alone for a course of therapy is approximately $120,000 in 2013). Despite these reservations, ipilimumab's overall survival benefit (17% of patients alive at 7 years) indicates that treatment should be strongly considered for all eligible patients.

Chronic T cell activation also leads to induction of PD-1 on the surface of T cells. Expression of one of its ligands, PD-L1, on tumor cells can protect them from immune destruction (Fig. 105-3). Early trials attempting to block the PD-1:PD-L1 axis by IV administration of anti-PD-1 or anti-PD-L1 have shown substantial clinical activity in patients with advanced melanoma (and lung cancer) with significantly less toxicity than ipilimumab. Anti-PD-1 therapy looks promising, but is not currently available except by participation in clinical trials. Intriguingly, preliminary results from a clinical trial indicate that blocking both inhibitory pathways with ipilimumab and anti-PD-1 leads to superior antitumor activity than treatment with either agent alone. The main benefit to patients from immune-based therapy (IL-2, ipilimumab, and anti-PD-1) is the durability of the responses achieved. Although the percentage of patients whose tumors regress following immunotherapy is lower than the response rate after targeted therapy (see below), the durability of immunotherapy-induced responses (>10 years in some cases) appears to be superior to responses after targeted therapy and suggests that many of these patients have been cured.

TARGETED THERAPY

RAF and MEK inhibitors of the MAP kinase pathway are a new and exciting approach for patients whose melanomas harbor a *BRAF* mutation. The high frequency of oncogenic mutations in the RAS-RAF-MEK-ERK pathway, which delivers proliferation and survival signals from the cell surface to the cytoplasm and nucleus, has led to the development of inhibitors to BRAF and MEK. Two BRAF inhibitors, vemurafenib and dabrafenib, have been approved for the treatment of stage IV patients whose melanomas harbor a mutation at position 600 in the gene for *BRAF*. The oral BRAF inhibitors cause tumor regression in approximately 50% of patients, and overall survival is improved compared to treatment with chemotherapy. Treatment is accompanied by manageable side effects that differ from those following immunotherapy or chemotherapy. A class-specific complication of BRAF inhibition is the development of numerous skin lesions, some of which are well-differentiated squamous cell skin cancers (seen in up to a quarter of patients). Patients should be co-managed with a dermatologist as these skin cancers will need excision. Metastases have not been reported, and treatment can be continued safely following simple excision. Long-term results following treatment with BRAF inhibitors are not yet available, but the current concern is that over time the vast majority of patients will relapse and eventually die from drug-resistant disease. There are a number of mechanisms by which resistance develops, usually via maintenance of MAP kinase signaling; however, mutations in the *BRAF* gene that affect binding of the inhibitor are not among them. The MEK inhibitor trametinib has activity as a single agent, but appears to be less effective than either of the BRAF inhibitors. Combined therapy with the BRAF inhibitor and MEK inhibitor showed improved progression-free survival compared to BRAF inhibitor therapy alone; and, interestingly, the neoplastic skin lesions that were so troubling with BRAF inhibition alone did not occur. Although the durability of responses following combined therapy remains to be determined, its use in metastatic melanoma is FDA approved. Activating mutations in the c-kit receptor tyrosine kinase are found in a minority of cutaneous melanomas with chronic sun damage, but more commonly in mucosal and acral lentiginous subtypes. Overall, the number of patients with *c-kit* mutations is exceedingly small, but when present, they are largely identical to mutations found in gastrointestinal stromal tumors (GISTs); melanomas with activating *c-kit* mutations can have clinically meaningful responses to imatinib.

CHEMOTHERAPY

No chemotherapy regimen has ever been shown to improve survival in metastatic melanoma, and the advances in immunotherapy and targeted therapy have relegated chemotherapy to the palliation of symptoms. Drugs with antitumor activity include dacarbazine (DTIC) or its orally administered analog temozolomide (TMZ), cisplatin and carboplatin, the taxanes (paclitaxel alone or albumin-bound and docetaxel), and carmustine (BCNU), which have reported response rates of 12–20%.

INITIAL APPROACH TO PATIENT WITH METASTATIC DISEASE

Upon diagnosis of stage IV disease, whether by biopsy or diagnostic imaging, a sample of the patient's tumor needs to undergo molecular testing to determine whether a druggable mutation (e.g., *BRAF*) is present. Analysis of a metastatic lesion is preferred, but any biopsy will suffice because there is little discordance between primary and metastatic lesions. Treatment algorithms start with the tumor's *BRAF* status. For *BRAF* "wild-type" tumors, immunotherapy is recommended. For patients whose tumors harbor a *BRAF* mutation, initial therapy with either a BRAF inhibitor or immunotherapy is acceptable. Molecular testing may also include *N-RAS* and *c-kit* in appropriate tumors.

The majority of patients still die from their melanoma, despite improvements in therapy. Therefore, enrollment in a clinical trial is always an important consideration, even for previously untreated patients. Most patients with stage IV disease will eventually progress despite advances in therapy, and many, because of disease burden, poor performance status, or concomitant illness, will be unsuitable for therapy. Therefore, a major focus of care should be the timely integration of palliative care and hospice.

FOLLOW-UP

Skin examination and surveillance at least once a year are recommended for all patients with melanoma. The National Comprehensive Cancer Network (NCCN) guidelines for patients with stage IA–IIA