

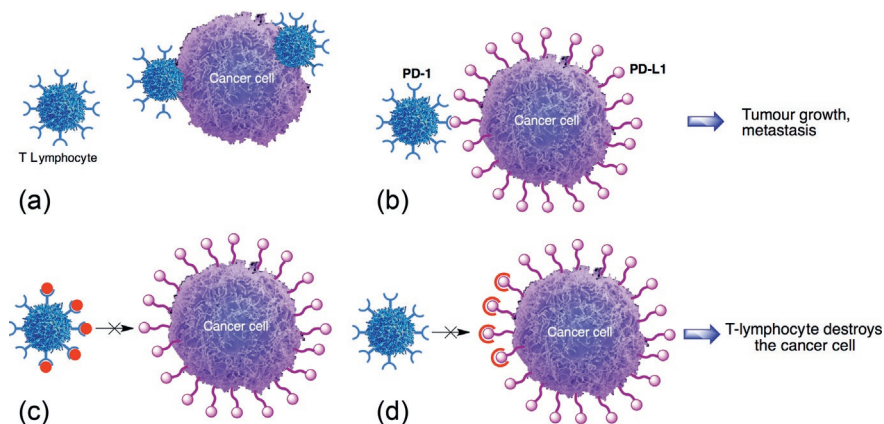
adaptive immune resistance and unprecedented rates of durable clinical responses in patients with various cancer types.<sup>22</sup>

The PD-1/PD-L1 axis was validated as a therapeutic target in two phase I clinical trials with the anti-PD-1 antibody nivolumab (Opdivo<sup>®</sup>, formerly known as BMS936558) and the anti-PD-L1 antibody BMS936559.<sup>23</sup> The FDA assigned a priority review designation to nivolumab as a treatment for pretreated patients with advanced melanoma, and it assigned a breakthrough designation for patients with Hodgkin's lymphoma. The EMA also granted an accelerated assessment to nivolumab.

Pembrolizumab (lambrolizumab, MK-3475, Keytruda<sup>®</sup>), which is a highly selective mAb against PD-1 receptor expressed by T cells, is being developed for potential use in metastatic melanoma (Figure 12.4).<sup>24</sup> It was approved by the FDA in 2014 for use following treatment with ipilimumab or after treatment with ipilimumab and a b-Raf inhibitor in patients who carry a b-Raf mutation.

MPDL3280A is an engineered anti-PD-L1 antibody designed to target PD-L1 expressed on tumor cells and tumor-infiltrating immune cells and also to prevent binding to PD-1 and B7.1 on the surface of T cells. This process, as well as the blocking of PD-1 receptors, may enable the activation of T cells as well as recruit other T cells to attack the tumor, thus empowering the body's own immune system to fight multiple types of cancer.<sup>25</sup> Phase I data for MPDL3280A in monotherapy or combination regimens are encouraging.<sup>26</sup>

Other monoclonal antibodies, including edrecolomab (Panorex<sup>®</sup>) and adecatumumab (MT201), target the Wnt receptor EpCAM (epithelial cell adhesion molecule) that is highly expressed on human carcinomas and is recognized as a target for immunotherapy of cancer. Both antibodies have shown interesting results in colorectal carcinoma,<sup>27</sup> but a phase III trial with edrecolomab in combination with 5-fluorouracil showed no statistically significant effect on overall survival.<sup>28</sup>



**FIGURE 12.4**

Mechanism of action of pembrolizumab. (a) T lymphocytes are able to destroy normal cancer cells. (b) Some cancer cells have in their membrane a protein (PD-L1) that protects them by recognizing a complementary protein at the surface of the T lymphocytes (PD-1). (c and d) Drugs able to block either PD-1 or PD-L1 restore the ability of T lymphocytes to recognize the cancer cells as a target for immune response. In this particular case, pembrolizumab acts by binding to PD-1 (mechanism C).