used to treat colorectal cancer. HER1 is human epidermal growth factor-1 (40). The MOA of ADCC is made more interesting by the fact that activating CD137 of the NK cell can increase the NK cell's ability to kill its target. CD137, also known as 4-1BB, is a membrane-bound protein of the NK cell. Triggering CD137 by artificial means using an anti-CD137 antibody (41), or by natural means by way of the CD137 ligand that is expressed by one type of T cell (gammadelta T cells) (42), enhances the ability of the T cell to kill its target.

### c. Regulatory T Cells

Anticancer drugs also include drugs that block normally occurring mechanisms that set upper limits to immune response. Upper limits to immune response are imposed by a class of T cells called T-regulatory cells (Tregs). If Tregs did not exist, it is likely that every human being would suffer from various autoimmune disorders, and would die from massive inflammation (43). In fact, a component of the MOA of some autoimmune diseases is naturally occurring mutations that impair function of the Tregs (44). Consistent with this mechanism in autoimmune diseases is the fact that an antibody that inhibits Treg activity (anti-CD25 antibody; daclizumab), may be effective in treating cancer (45,46). In short, the fact that Treg activity can protect tumors from being attacked by $CD8^+$ T cells, serves as the rationale for impairing Treg activity, in the treatment of cancer.

Various types of Treg exist, but the most physiologically relevant type of Treg is $CD4^+CD25^+$ T cells. These Tregs are distinguished by their expression of the transcription factor, Foxp3 (47). The gene and the protein are called Foxp3, while the encoded protein is sometimes called "scurfin." Foxp3 means, "forkhead box protein-3." The $CD4^+CD25^+$ Tregs account for about 10% of all the $CD4^+$ T cells in the body.

Tregs guard against autoimmunity, but in the context of a cancer patient, what is desirable is to inhibit Tregs (48). Cancer patients may have increased levels of Tregs and, in particular, an increase in Tregs infiltrating their

[40]Assenat E, Azria D, Mollevi C, et al. Dual targeting of HER1/EGFR and HER2 with cetuximab and trastuzumab in patients with metastatic pancreatic cancer after gemcitabine failure: results of the "THERAPY" phase 1-2 trial. Oncotarget 2015;6:12796–808.

[41]Kohrt HE, Colevas AD, Houot R, et al. Targeting CD137 enhances efficacy of cetuximab. J. Clin. Invest. 2014;124:2668–82.

[42]Maniar A, et al. Human gammadelta T lymphocytes induce robust NK cell-mediated antitumor cytotoxicity through CD137 engagement. Blood 2010;116:1726–33.

[43]Kim JM, et al. Regulatory T cells prevent catastrophic autoimmunity throughout the lifespan of mice. Nat. Immunol. 2006;8:191–7.

[44]Barbi J, et al. Treg functional stability and its responsiveness to the microenvironment. Immunol. Rev. 2014;259:115–39.

[45]Tse BW, et al. Antibody-based immunotherapy for ovarian cancer? Ann. Oncol. 2014;25:322–31.

[46]Barbi J, et al. Treg functional stability and its responsiveness to the microenvironment. Immunol. Rev. 2014;259:115–39.

[47]Barbi J, et al. Treg functional stability and its responsiveness to the microenvironment. Immunol. Rev. 2014;259:115–39.

[48]Siddiqui SA, Frigola X, Bonne-Annee S, et al. Tumor-infiltrating Foxp3-CD4 + CD25 + T cells predict poor survival in renal cell carcinoma. Clin. Cancer Res. 2007;13:2075–81.