Tumor-derived exosomes (TEX) are present in body fluids of patients with cancer. By down-regulating functions of immune cells, TEX could promote tumor progression. To test this hypothesis, we isolated TEX from tumor cell supernatants or from plasma of patients with solid tumors or with acute myeloid leukemia (AML). The molecular profile of TEX was distinct from that of exosomes derived from normal cells. TEX were co-incubated with activated T cells, conventional CD+CD25neg T cells or CD56+CD16+ NK cells, respectively. TEX down-regulated CD3ζ and JAK3 expression in primary activated T cells and mediated Fas-FasL-driven apoptosis of CD8+ T cells. TEX promoted CD4+CD25neg T cell proliferation and their conversion into CD4+CD25hiFOXP3+ Treg which also expressed IL-10, TGF-β1, CTLA-4, GrB/perforin and effectively mediated suppression. Neutralizing antibodies specific for TGF-β1 and/or IL-10 inhibited TEX ability to expand Treg (p<0.01). TEX obtained at diagnosis from sera of AML patients sera were positive for blast-associated markers CD33, CD34, CD117 and for TGF-β1, and they decreased cytotoxic activity of NK cells isolated from NC (p<0.002), induced SMAD phosphorylation and down-regulated NKG2D receptor expression (p<0.004). Correlations between the TEX molecular profile or serum TEX protein levels and clinical data in patients with solid tumors or AML suggest that TEX-mediated effects on immune cells are prognostically important. In contrast to exosomes released by normal cells, TEX have immunosuppressive properties and are involved in regulating peripheral tolerance in patients with cancer.