Inducible co-stimulator (ICOS) interaction with its ligand (ICOSL) is involved in several T cell effector functions. While blockade of ICOS:ICOSL interaction in chronic graft versus host disease (GVHD) seems beneficial, results for acute GVHD remain controversial. To further elucidate its role in acute GVHD, C57BL/6 mice were reconstituted with allogeneic spleen cells in the absence or presence of ICOSL-blocking mAb. Mice reconstituted with allogeneic spleen cells experienced severe GVHD and died untreated within 6-9 days after transplantation. Mice treated with an anti-ICOSL mAb starting from day 3 after transplantation gained weight again and survived for at least additional 12 days, although the treatment was already stopped at day 11 after transplantation. In contrast, the anti-ICOSL treatment starting from day 0 did not prevent GVHD. The difference between therapeutic (day 3) and prophylactic (day 0) anti-ICOSL treatment was independent of CD25+CD4+ regulatory T cells since their depletion did not abrogate the therapeutic effect of ICOSL blockade. Microarray analysis revealed IFN-gamma and chemokine up-regulation in spleen cells of prophylactically treated mice, emphasizing kinetic dependence of acute GVHD modulation via blockade of ICOS:ICOSL interaction.