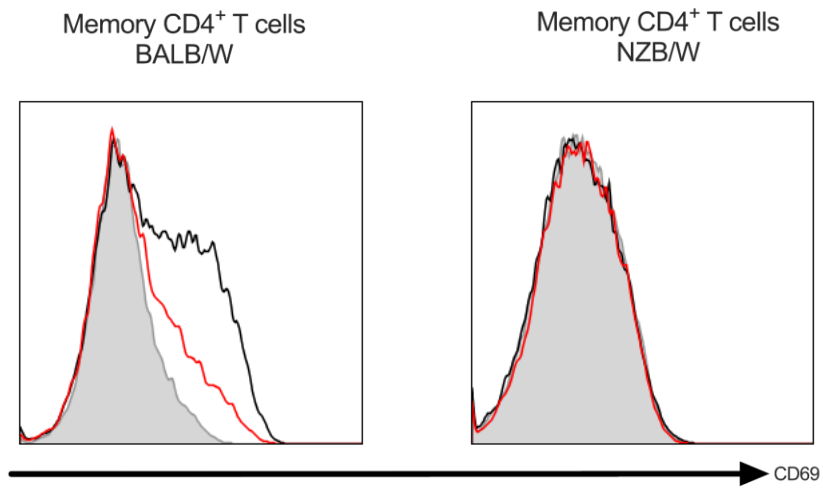
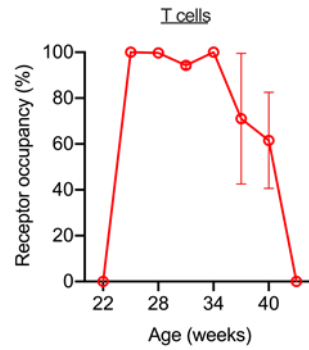
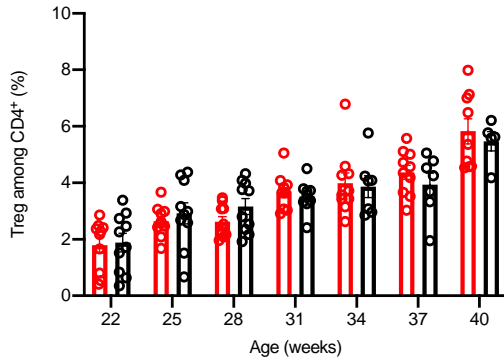
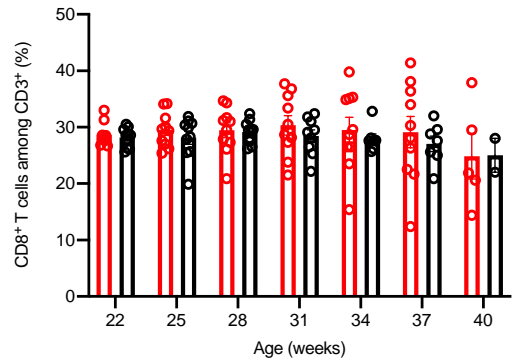
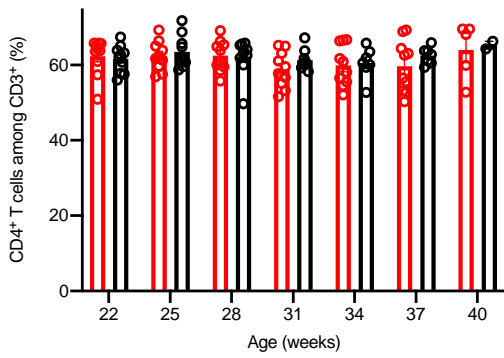


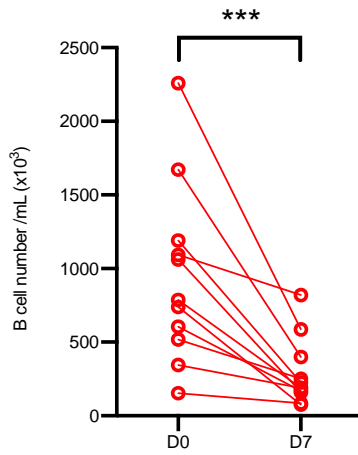
**Supplementary figure 1:** CD23<sup>+</sup>CD21<sup>-</sup> B cell frequency is enhanced in NZB/W mice. Frequencies of CD23<sup>+</sup>CD21<sup>-</sup> B cells in young BALB/W (10-12-week-old, n=13) or old BALB/W (>35-week-old, n=17) and young (10-12-week-old, n=16) or old NZB/W (>35-week-old, n=10) are represented. \*\*p<0.01; \*\*\*\*p<0.0001, Kruskal-Wallis with post hoc analysis (Dunn's test).



**Supplementary figure 2:** CD4<sup>+</sup> T cells from old NZB/W mice are refractory to *in vitro* activation. Purified memory CD4<sup>+</sup> T cells from old BALB/W and NZB/W mice were stimulated with anti-CD3/anti-CD28 antibody-coated beads in the presence of the anti-BTLA antibody (red line) or its isotype control (black line) and the expression of CD69 at 24h was analyzed by flow cytometry.



**Supplementary figure 3:** Anti-BTLA 6F7 antibody administrations do not modify peripheral T cell frequencies. Percentages of peripheral CD4<sup>+</sup> and CD8<sup>+</sup> T cells among CD3<sup>+</sup> T cells and of Tregs (CD25<sup>+</sup>FoxP3<sup>hi</sup>) among CD4<sup>+</sup> T cells were assessed by flow cytometry in the anti-BTLA-treated group (red) and the isotype-treated group (black) every 3 weeks. Blood T cells were stained with a PE-conjugated 6F7 antibody to evaluate receptor occupancy (RO) in 6F7-treated mice during the course of the treatment. RO for each timepoint was calculated as follow:  $1 - [\text{MFI } 6\text{F7}/\text{MFI } 6\text{F7 at day } 0] \times 100$ .



**Supplementary figure 4:** Anti-BTLA 6F7 antibody administration reduces peripheral B cell numbers. Comparison of B cell counts (day 0 and day 7) in mice (n=9) that had received 2 administrations (3mg/kg/administration on day 1 and day 4) of the anti-BTLA 6F7 antibody. \*\*\*p<0.001, Wilcoxon test.

BTLA expression (MFI±SEM x10 <sup>3</sup> )	Isotype-treated mice	6F7-treated mice	NZB/W#1 mouse
Total CD19 <sup>+</sup> B cells	9.5 ± 1.3	3 ± 0.5	13.3
FO B cells	12.6 ± 1.7	3.5 ± 0.6	20
MZ B cells	6.4 ± 1.2	2.5 ± 0.4	9.4
CD23 <sup>+</sup> CD21 <sup>-</sup> B cells	6 ± 0.9	2.3 ± 0.3	9

**Supplementary figure 5:** The mouse NZB/W#1 did not display any reduced BTLA expression following 6F7 administrations. Comparison of BTLA expression on B cell subsets in the spleen of isotype-treated mice, 6F7-treated mice and the NZB/W#1 mouse.

FO: follicular B cells, MZ: marginal zone B cells.