Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Herold KC, Bundy BN, Long SA, et al. An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med 2019;381:603-13. DOI: 10.1056/NEJMoa1902226

Supplementary Appendix

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Yale University, New Haven, Connecticut: Kevan Herold, Laurie Feldman, Jennifer Sherr, Robert Sherwin, William Tamborlane, Stuart Weinzimer.

Supplementary methods:

Patient identification: Potential participants were identified in the TrialNet Pathway to Prevention (PTP) study. The PTP study enrolled first degree relatives of patients with T1D, ages 1-45, and up to age 20 in second- or third- degree relatives, evaluated diabetes autoantibodies to microinsulin (mIAA), glutamic acid decarboxylase-65 (GAD), and insulinoma-associated antigen-2 (IA-2, or ICA512). Islet cell (ICA) and zinc transporter 8 (ZnT8) autoantibodies were measured if at least 1 other antibody tested positive.

Drug Dosing: Those assigned to active study drug received teplizumab at a total dose of 9,034 μg/m^2 over 14 days as described in the Methods. Participants randomized to the placebo arm received a 14-day course of matching IV saline. Participants received ibuprofen and diphenhydramine prior to infusions on the first 5 days, and further dosing with ibuprofen, diphenhydramine and/or acetaminophen thereafter as needed for symptomatic relief. Protocol defined stopping criteria for study drug infusions were followed. During the entire study, all subjects had interim contact with study personnel for formal inquiry about adverse events and symptoms of diabetes.

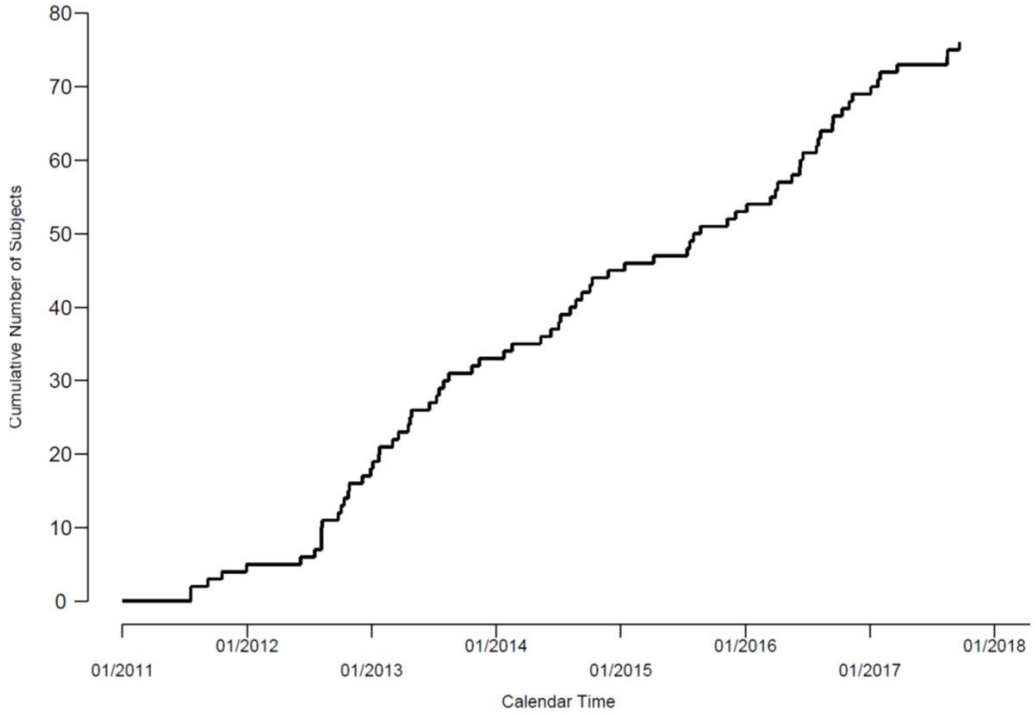
Laboratory Methods: mIAA, GAD-65Ab, ICA-512Ab, ZnT8A were measured using radio-immunobinding assays at the Barbara Davis Diabetes Center, Anschultz CO, and ICA using indirect immunofluorescence at the University of Florida at Gainesville. C-peptide, glucose and HbA1c were measured at the Northwest Research Laboratory, Seattle, WA. C-peptide was measured from frozen plasma by two-site immunoenzymometric assay (Tosoh Bioscience, South San Francisco, CA) at the HbA_{1c} was measured using ion-exchange high performance liquid chromatography (Variant II, Bio-Rad Diagnostics, Hercules, CA). Reliability coefficients for each assay were above 0.99 from split duplicate samples. EBV and CMV viral loads were measured in whole blood at the University of Colorado using previously described methods.[1] Positive viral loads were designated as > 500 copies of viral DNA.[2,3]

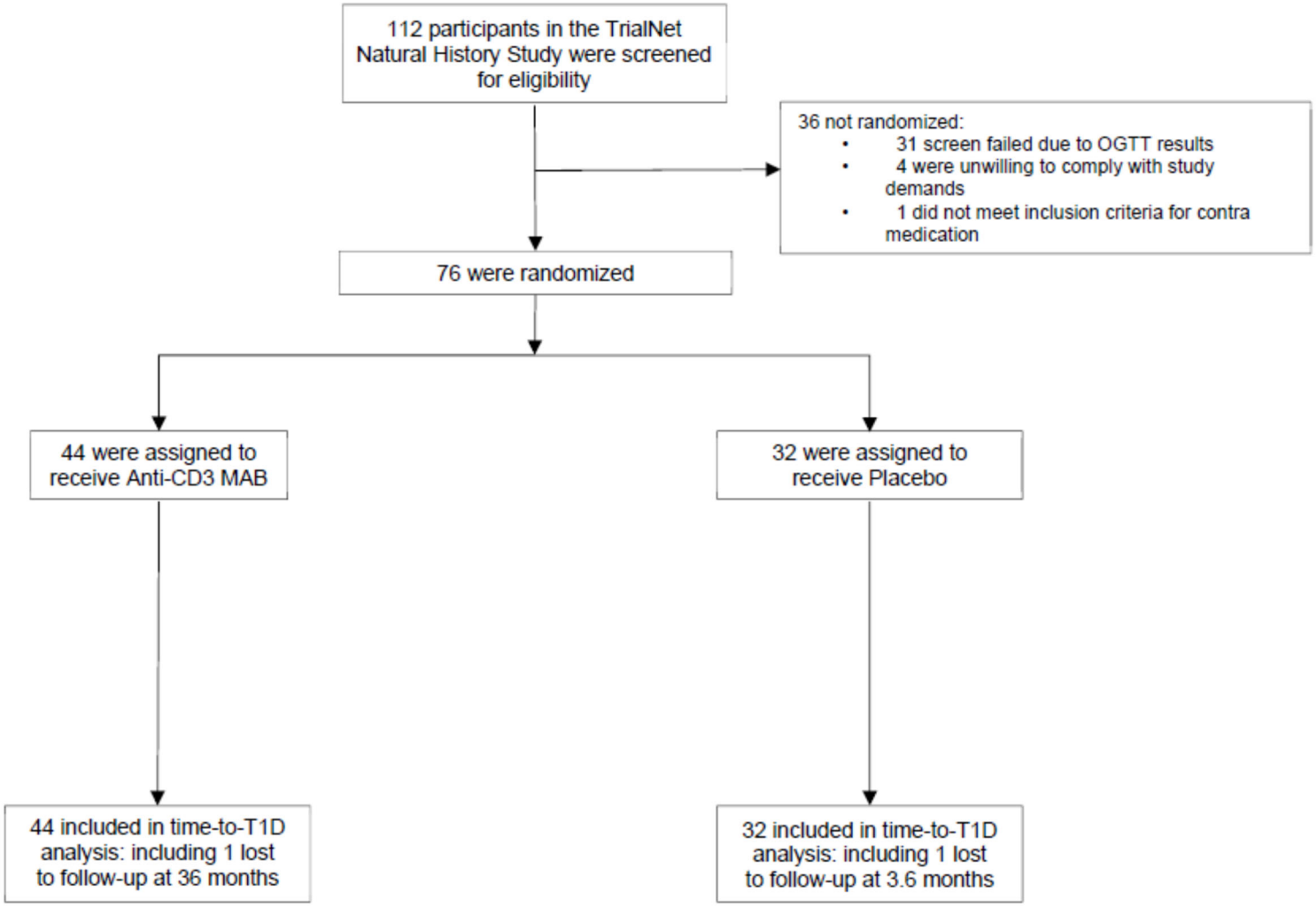
Flow cytometry: Peripheral blood mononuclear cells (PBMC) were processed and stored at the NIDDK repository. Frozen vials of PBMC were sent to Benaroya Research Institute for analysis by flow cytometry with antibody panels shown in Supplementary Table 1. T-cell phenotyping was performed on PBMC as previously described on an LSR-Fortessa (BD Biosciences) with FACS Diva software and analyzed with FlowJo software version 9.5 (Tree Star, Ashland, OR). The frequency of CD8+ T-cells that were TIGIT+KLRG+CD57-, TIGIT-KLRG1-CD57- , or $CD4+CD127^{lo}Foxp3+$ (CD4+Tregs) were determined as described previously.[4] The quadrants were placed based on staining controls.

Trial oversight: The results were shared with Provention Bio prior to publication. The statistical analysis plan is available at NEJM.org. The TrialNet Coordinating Center gathered, analyzed, and vouches for the data. The authors are fully responsible for the content and editorial decisions regarding the manuscript. The authors approved the final version for submission.

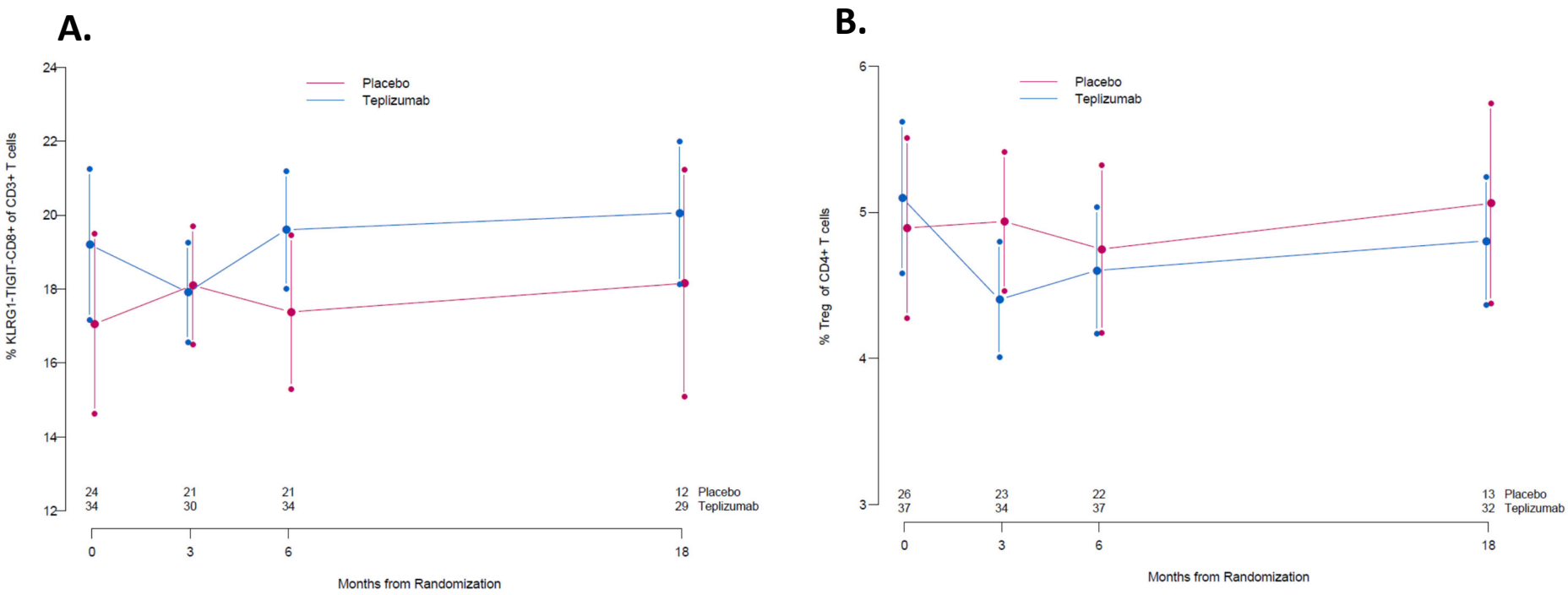
Participating sites: For screening, infusion, and follow up: Barbara Davis Center for Childhood Diabetes, Benaroya Research Institute, Indiana University - Riley Hospital for Children, Klinikum rechts der Isar, Technical University Munich, Germany, , The Children's Mercy Hospital, The Hospital for Sick Children, University of California - San Francisco, University of Florida, University of Iowa, Stead Family Children's Hospital, University of Miami, University of Minnesota, USF Diabetes Center, Vanderbilt Eskind Diabetes Clinic, Yale University School of Medicine; Follow up: Joslin Diabetes Center, University of Utah, University of Pittsburgh, GHS - Pediatric Endocrinology, Trustees of Dartmouth College, Endocrinology Specialist/Greenville Health System, Washington University, Columbia University, University of Texas Southwestern, UNC Chapel Hill, Stanford University, Children's Hospital of Los Angeles For screening: University of Chicago, University of Cambridge, Walter and Eliza Hall Institute. The TrialNet network of sites was used for screening into the Pathway to Prevention protocol.

Supplementary Appendix Figure S1: Enrollment in the Trial

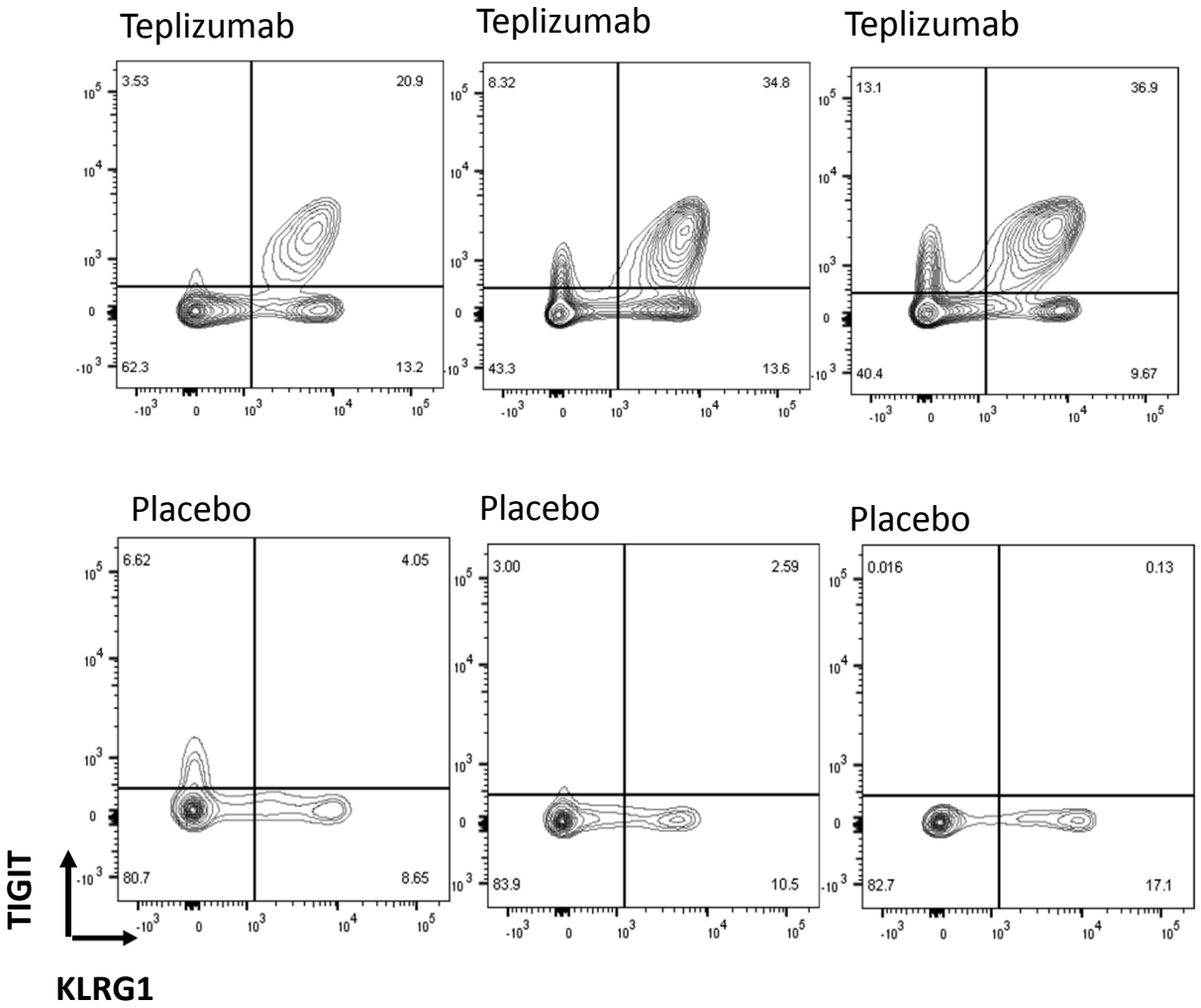




Supplementary Appendix Figure S2: Screening, enrollment and follow-up of the participants: A total of 112 participants from the TrialNet Natural History Study were screened for eligibility (see Appendix for a listing of study sites). Seventy-six of the participants were randomized to the drug or placebo arms. They were infused with study drug at one of 14 TrialNet sites and followed, as per study protocol at one of 33 sites. All randomized participants are included in the analysis.

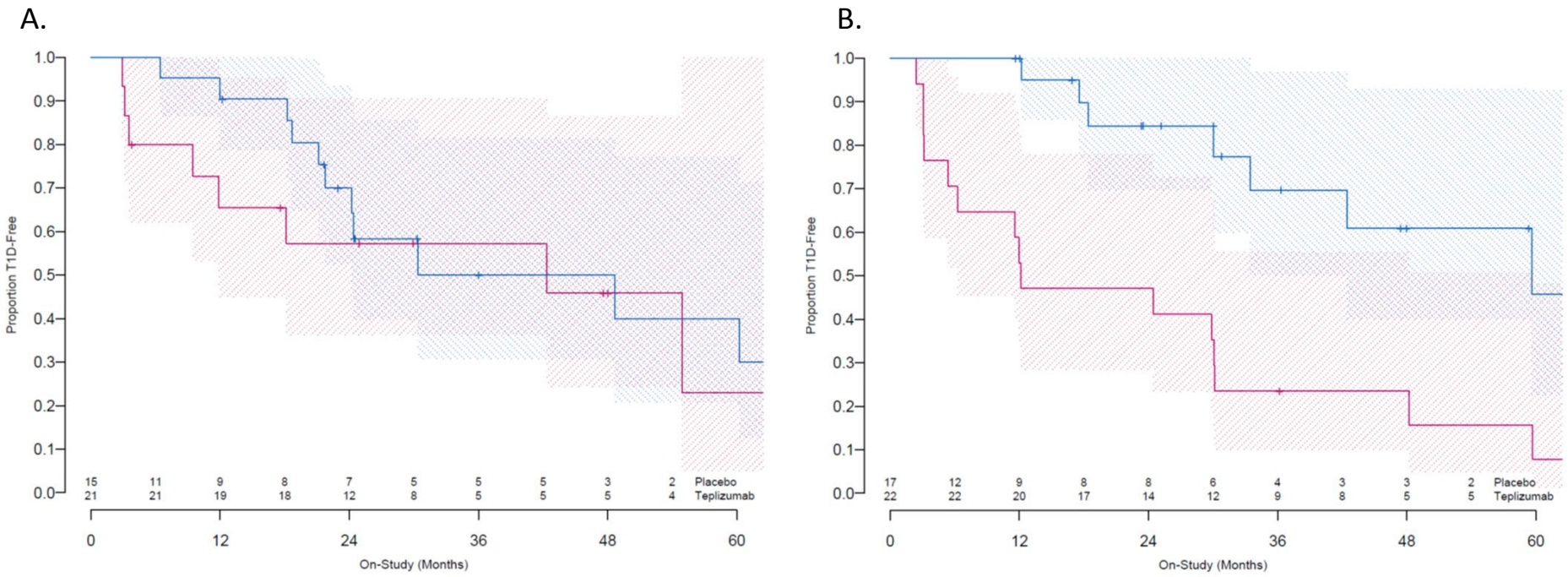


Supplementary Appendix Figure S3: The frequency of (A) KLRG1-TIGIT-CD8+ T cells (of total CD3+T cells) and (B) CD4+ Tregs ($CD4+CD25+CD127^{lo}$) in the teplizumab and placebo treated groups. The mean±95% CI are shown. The analysis was performed by ANCOVA and corrected for the baseline values. The numbers along the X axis indicate the number of samples analyzed.

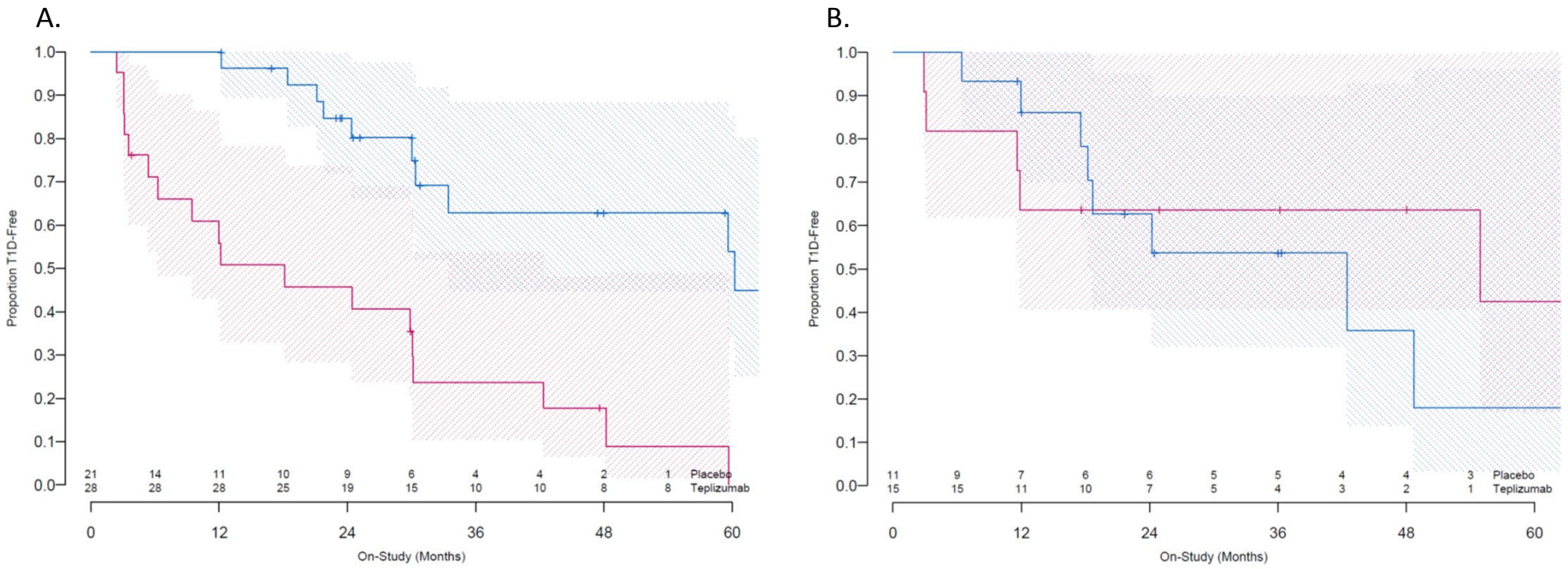


Supplementary Appendix Figure S4: FACS contour plots showing staining of TIGIT (Y axis) vs KLRG1 (X axis).

Electronic gates were placed on live CD8+CD57- T cells and the expression of KLRG1 and TIGIT are shown in peripheral blood cells from 3 subjects treated with teplizumab (top row) and 3 participants treated with placebo on samples that were acquired at month 3. The numbers refer to the proportion of the total gated cells in each quadrant. The quadrants were placed based on staining controls.

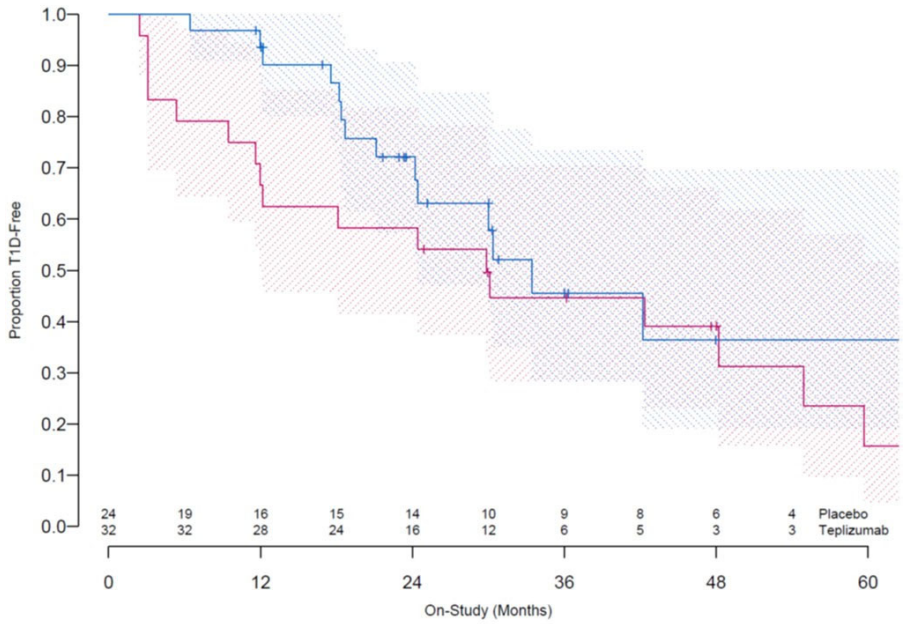


Supplementary Appendix Figure S5: The effects of teplizumab treatment in participants with (A) and without (B) HLA-DR3. The absence of HLA-DR3 (Hazard ratio:0.181 for negative, 0.907 for positive) was associated with response to teplizumab. (For each graph ----- = teplizumab, ----- = placebo, + = censored. The number of participants at risk are shown along the X axis. The shaded areas represent the 95% CIs.)



Supplementary Appendix Figure S6: The effects of teplizumab treatment in participants with (A) and without (B) HLA-DR4. The presence of HLA-DR4 (Hazard ratio: 1.47 for negative, 0.201 for positive) was associated with response to teplizumab. (For each graph ----- = teplizumab, ----- = placebo, + = censored. The number of participants at risk are shown along the X axis. The shaded areas represent the 95% CIs.)

A.



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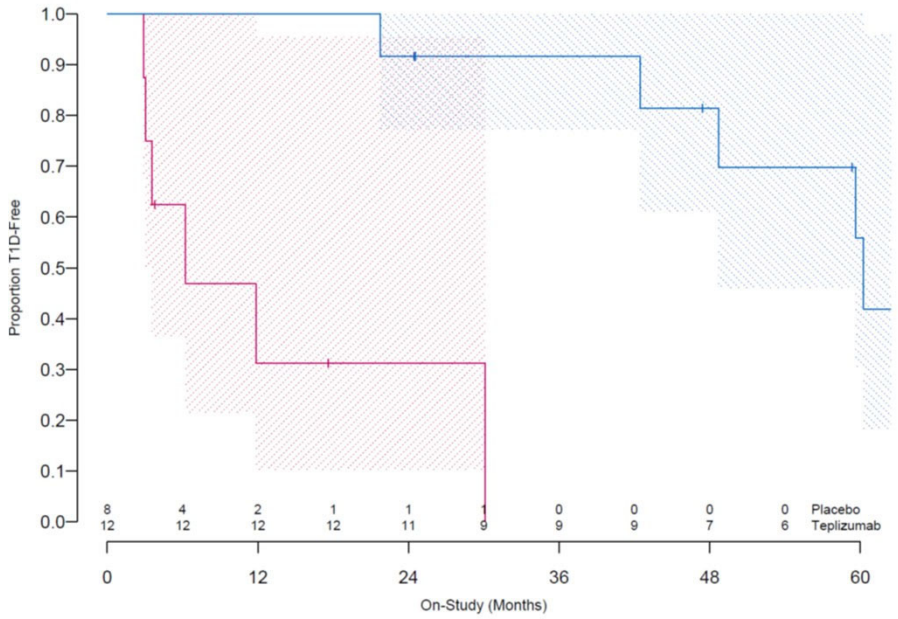
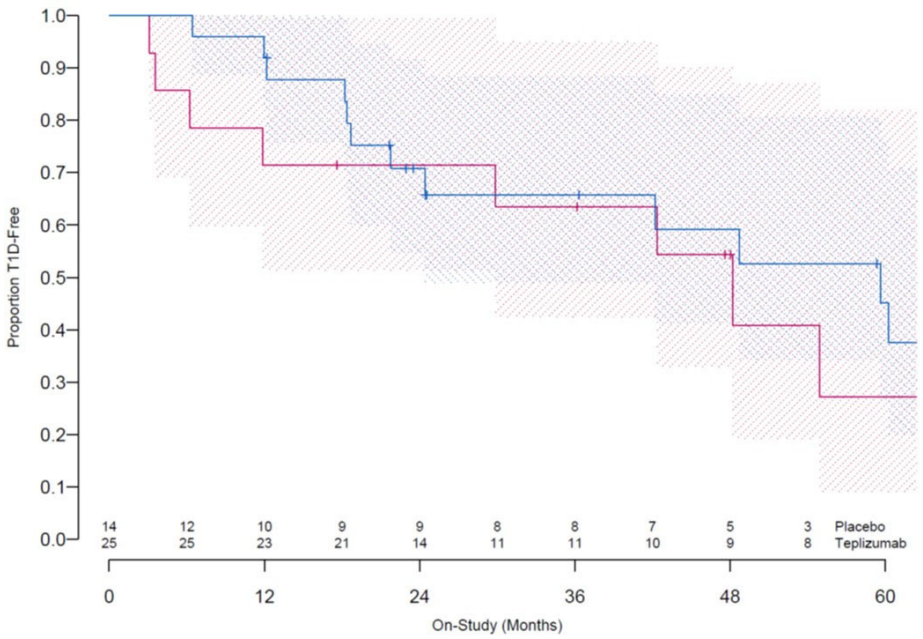


Supplementary Appendix Figure S7: The effects of teplizumab treatment in participants with (A) and without (B) anti-ZnT8 antibodies at randomization. The absence of anti-ZnT8 antibody (Hazard ratio: 0.064 for negative, 0.831 for positive) was associated with response to teplizumab. (For each graph ----- = teplizumab, ----- = placebo, + = censored. The number of participants at risk are shown along the X axis. The shaded areas represent the 95% CIs.)

A.



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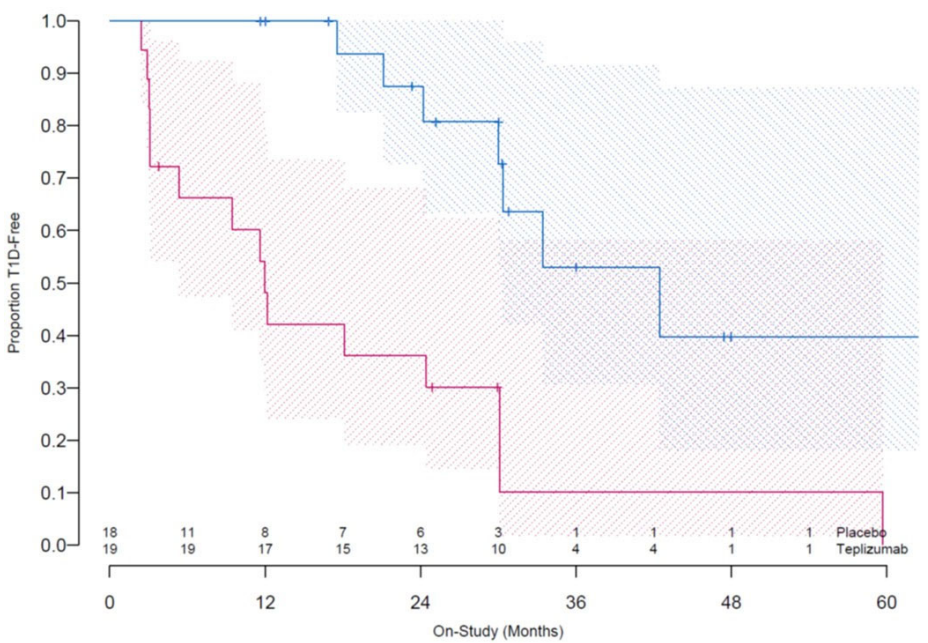

Supplemental Appendix, Figure S8: The effects of teplizumab treatment in participants whose C-peptide area under the curve during the oral glucose tolerance test at randomization was above (A) or below (B) the median (1.75 nmol/L). C-peptide responses below the median were associated with responses to teplizumab. (Hazard ratio=0.855 above (A) and 0.194 below (B) the median). (For each graph ----- = teplizumab, ----- = placebo, + = censored. The number of participants at risk are shown along the X axis. The shaded areas represent the 95% Cis.)

Supplementary Appendix Table S1: Monoclonal antibodies used for flow cytometry

Marker	Format	Clone	Vendor
CD56	BUV395	NCAM16.2	Becton Dickinson
CD45RA	BUV737	HI100	Becton Dickinson
Ki67	BV421	Ki-67	BioLegend
CCR7	BV510	G043H7	BioLegend
CD3	BV605	OKT3	BioLegend
PD1	BV650	EH12.2H7	BioLegend
CD127	BV711	A019D5	BioLegend
CD45R0	BV786	UCHL1	Becton Dickinson
CD4	BB515	RPA-T4	Becton Dickinson
Eomes	PE	WD1928	eBiosciences
FoxP3	PE-CF594	259D/C7	Becton Dickinson
KLRG1	PE-Vio770	REA261	Miltenyi
TIGIT	APC	MBSA43	eBiosiences
CD8	Ax700	SK1	BioLegend
CD57	APC-Vio770	REA769	Miltenyi
Live/dead	BUV496	NA	Becton Dickinson

Supplementary Appendix Table S2: Additional demographic data of participants

	Teplizumab, N=44	**Placebo N=32**
Male sex No. of subjects (%)	25 (56.8)	17 (53.1)
Body Mass Index (kg/m^2)-median* Z-score BMI-median*	19.6 (17.3 – 25.4) 0.259 (-0.754 - 1.19)	21.5 (18.2 – 24.7) 0.681 (0.339 – 1.11)
Race - No. of subjects (%)		
White African American Asian	44 (100.0) 0 (0.0) 0 (0.0)	30 (93.8) 0 (0.0) 2 (6.2)
Ethnicity - No. of subjects (%) Non-Hispanic	43 (97.7)	31 (96.9)
Autoantibodies titer – median*		
Anti-GAD65 (harmonized) Micro Insulin Anti-IA-2 (harmonized) ICA Zinc Transporter	240 (76.8 – 464) 0.0070 (0.0020 – 0.028) 52 (0 – 310) 20 (0 – 200) 0.157 (0.0133 – 0.496)	221 (42.3 – 520) 0.0040 (0.0020 – 0.0168) 187 (26 – 253) 80 (20 – 160) 0.096 (0.028 – 0.386)
No. of Autoantibodies Positive (% of total)^ 1 2 3 4 5	 1 (2.4) 11 (25.0) 12 (27.3) 11 (25.0) 9 (20.5)	 0 (0.0) 7 (21.9) 5 (15.6) 14 (43.8) 6 (18.8)
C-peptide AUC Mean, OGTT (nmol/L) Median*	1.76 (1.47 – 2.18)	1.73 (1.44 – 2.36)
HLA alleles present - no. of subjects (%)†		
Neither DR3 or DR4 DR3 only DR4 only	5 (11.6) 10 (23.3) 17 (39.5)	3 (9.4) 8 (25.0) 14 (43.8)

* Parenthetical value(s): The interquartile range is displayed with the median, and percent of subjects is displayed with the number of subjects.
^ at the time of randomization. All subjects had at least 2+ autoantibodies prior to randomization.
† Missing: HLA allele status missing for 1 teplizumab-treated subject

Year	No. of T1D*		Chi-square Test†	Hazard Ratio (95%CI)†	
	Teplizumab (%)	Placebo (%)		Cumulative	Interval
1	3 (6.8%)	14 (43.8%)	15.9	0.129 (0.0482, 0.343)	0.129 (0.0482, 0.343)
2	8 (18.2%)	2 (6.3%)	7.55	0.372 (0.169, 0.82)	1.8 (0.473, 6.88)
3	3 (6.8%)	3 (9.4%)	7.77	0.404 (0.198, 0.825)	0.58 (0.11, 3.05)
4	3 (6.8%)	2 (6.3%)	7.05	0.447 (0.23, 0.868)	0.864 (0.14, 5.33)
5	2 (4.5%)	2 (6.3%)	8.24	0.439 (0.233, 0.828)	0.359 (0.039, 3.32)

Supplementary Appendix, Table S3: Hazard ratios by yearly interval and cumulative. Frequency of clinical type I diabetes by treatment group and cumulative and interval hazard ratios (95% confidence Intervals) by year on-study. (* The number of participants developing T1D in each treatment arm during the year interval are shown. In addition, the cumulative HRs and the HR for each year interval were calculated. † Mantel- Haenszel method applied to time-to-event data, both chi- square test and hazard ratio estimate.[5] These hazard ratios are unadjusted for the enrollment/age strata. € Likelihood ratio test and hazard ratio estimate and 95% CI from the Cox model)

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1. Kroll J, Li S, Levi M, Weinberg A. Lytic and latent EBV gene expression in transplant recipients with and without post-transplant lymphoproliferative disorder. J Clin Virol 2011;52:231-5.
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