15 novembre 2024

Prevenzione del diabete tipo 1 è possibile?

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CONGRESSO REGIONALE
SID-AMD
Calabria
2024

UMBERTO I
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Disclosures

La Prof.ssa Raffaella Buzzetti dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

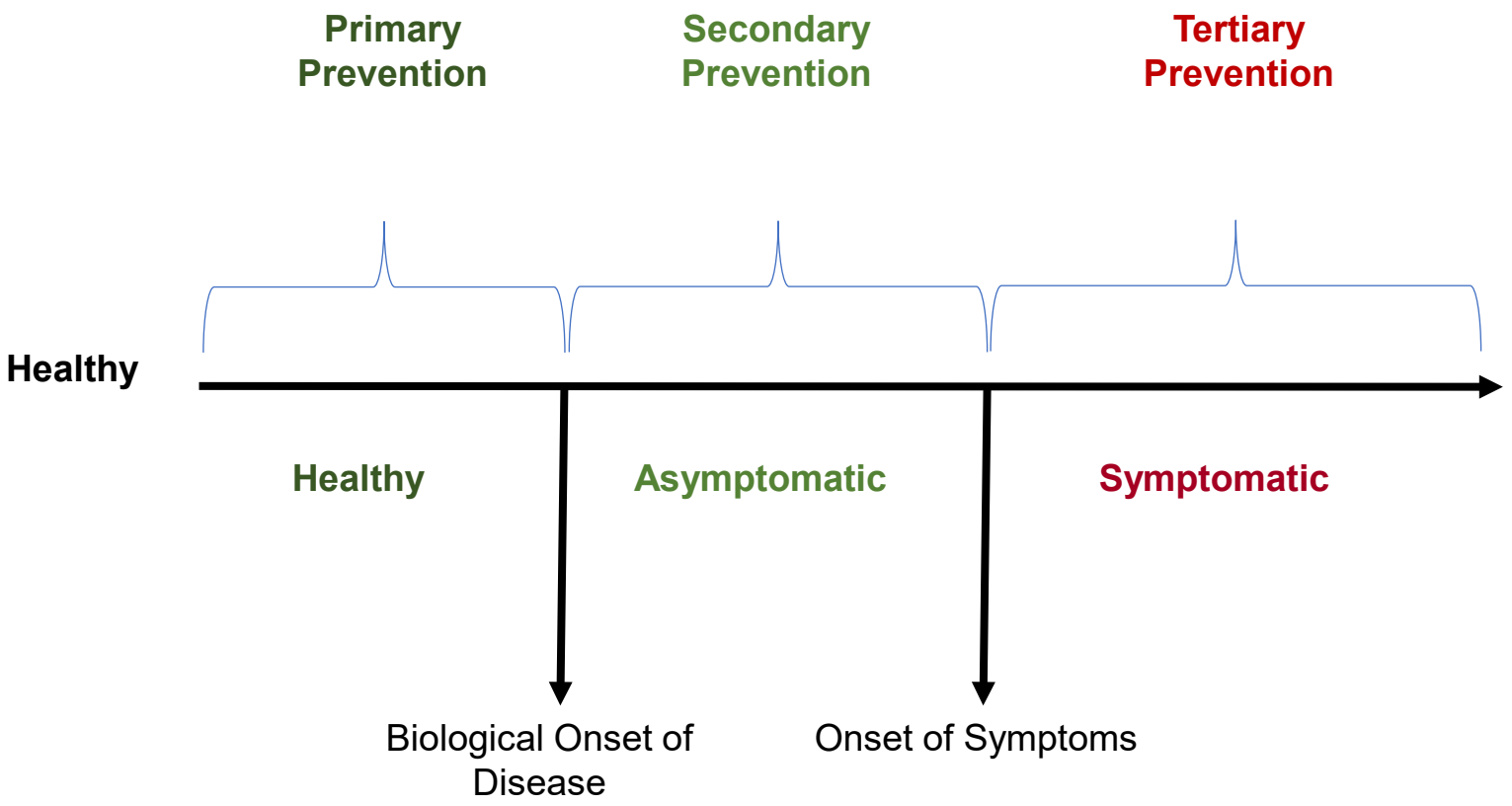
- Sanofi
- Novo Nordisk
- Eli Lilly
- Abbott
- Atrazeneca
- Vertex
- Guidotti

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Agenda

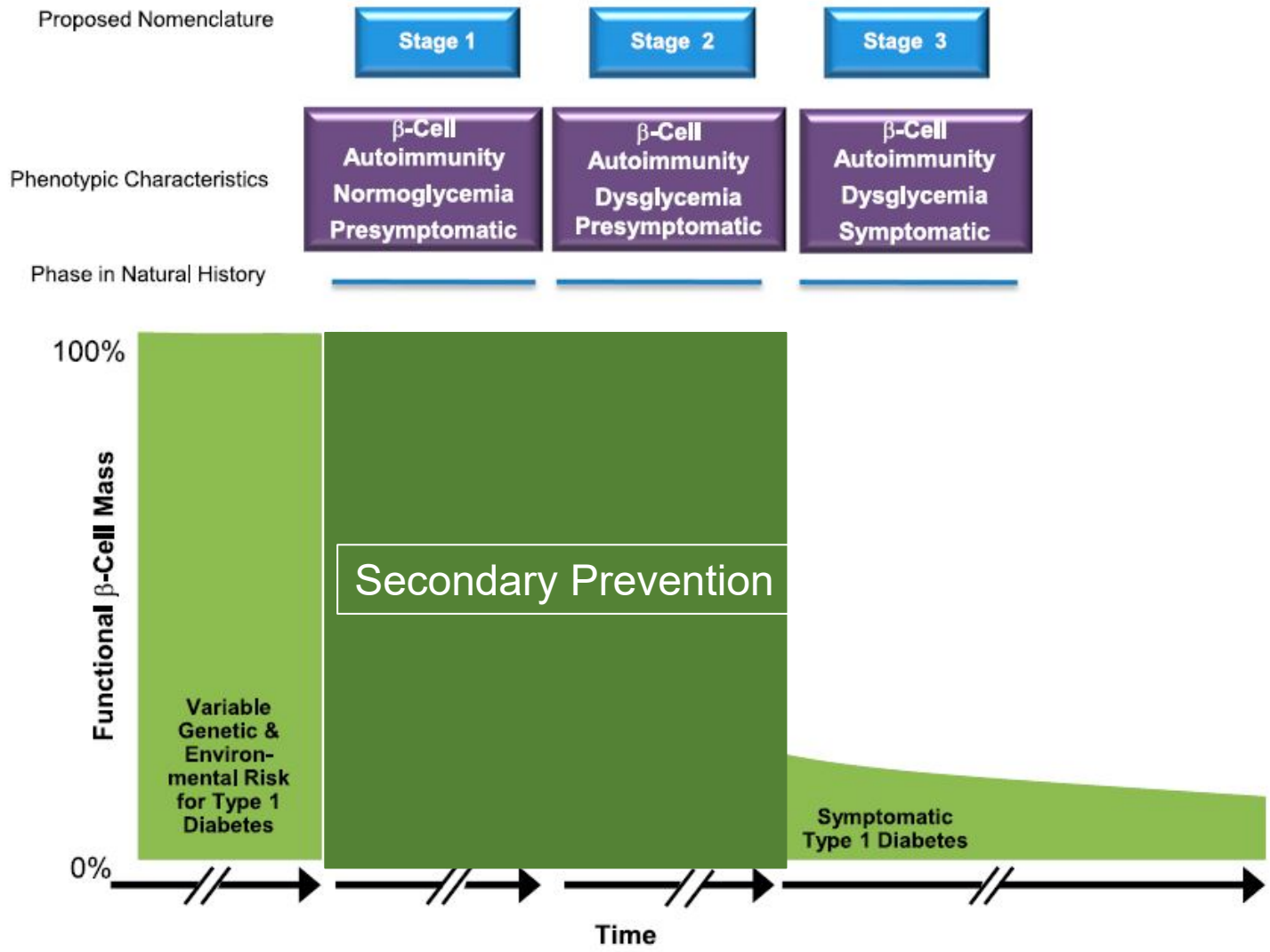
1. T1D prevention
2. Secondary prevention before anti-CD3 Mo-Ab use
3. The anti-CD3 Mo-Ab: teplizumab
4. What else?

T1D prevention



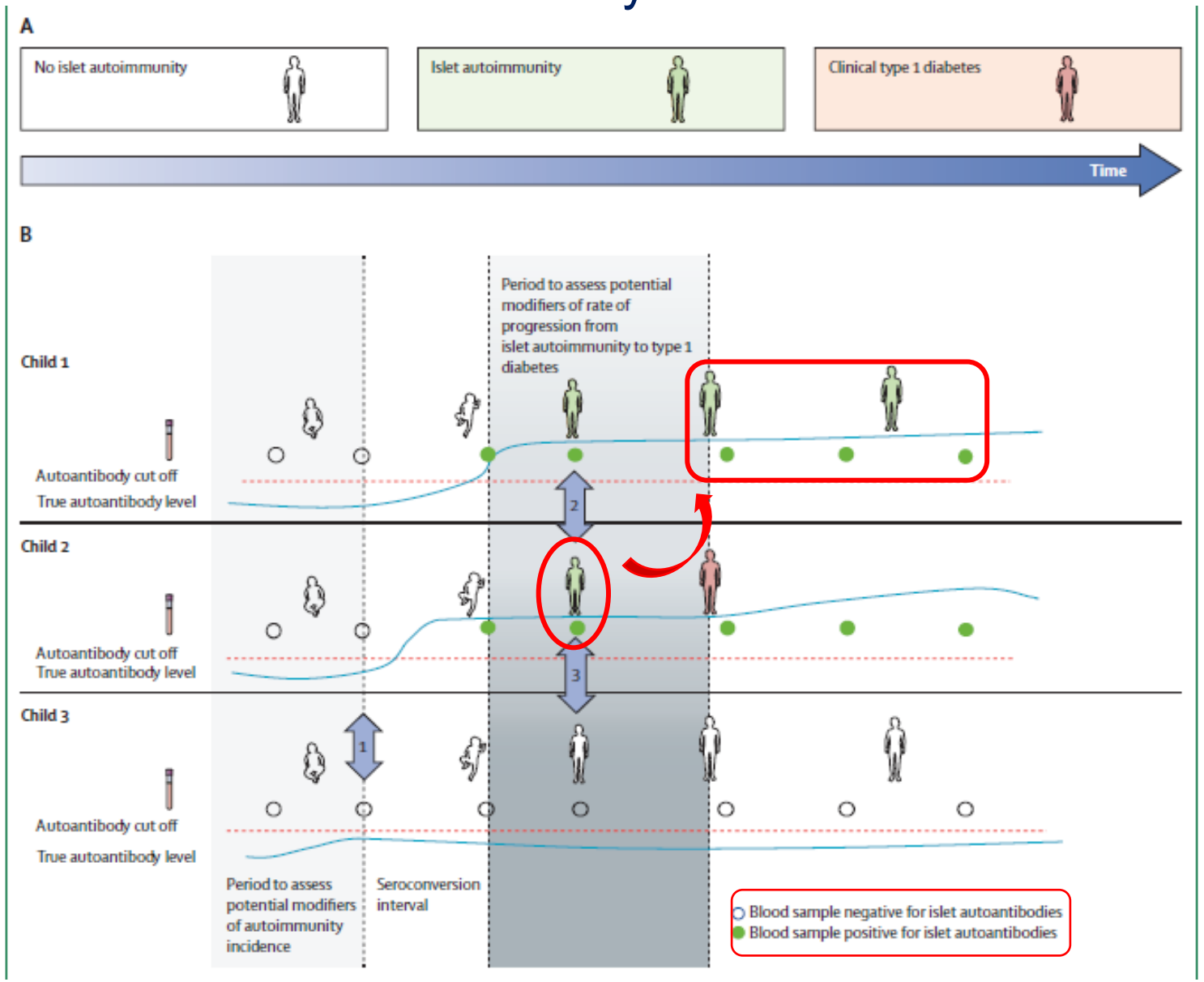
Secondary prevention applied to T1D natural history

Early stage of T1D



Insel RA et al. Diabetes Care 2015

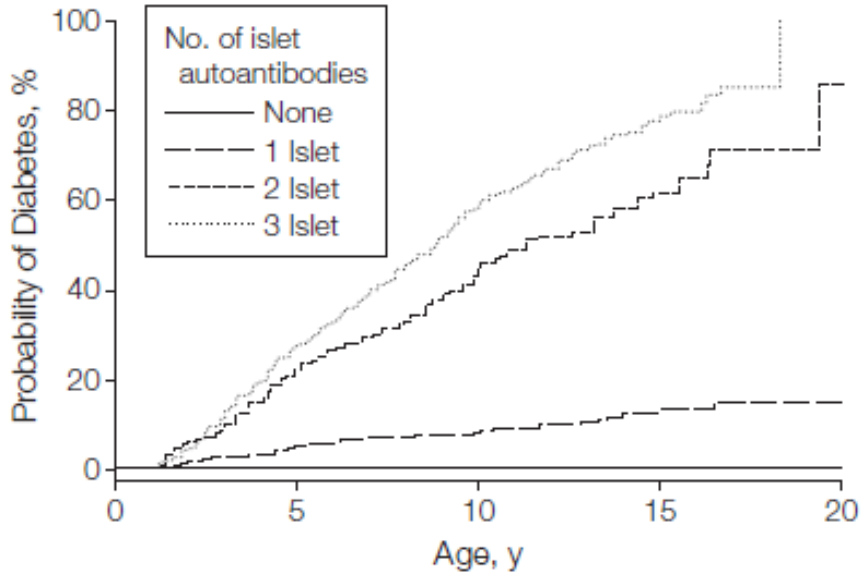
T1D: natural history



Norris JM et al. Lancet Diabetes Endocrinol. 2020

Increased incidence of type 1 diabetes is associated with increased number of autoantibodies

Figure 1. Development of Diabetes in Children Stratified for Islet Autoantibody Outcome



No. at risk Islet autoantibodies, No.					
3 Islet	358	250	112	20	
2 Islet	227	168	82	19	1
1 Islet	474	430	272	118	9
None	12318	8875	5253	1161	44

The numbers at risk represent the children receiving follow-up at age 0, 5, 10, 15, and 20 years.

Ziegler AG et al. JAMA. 2013;309(23):2473-2479

Secondary prevention before anti-CD3 Mo-Ab use

DPT-Parenteral Insulin **2002**

ENDIT **2004**

DPT-1 Oral Insulin **2005**

DIPP Birth Cohort **2009**

Study	Number		Therapy	1st Outcome	P. Value
ENDIT		3-	Nicotinam / Placeb	Diagnosis of 1 diabetes	NS
DPT-1 Parenteral Insulin			Insulin / ebo	Diagnosis of Ty etes	NS
DPT-1 Oral Insulin	372	3-45 years		Type 1 diabetes	NS

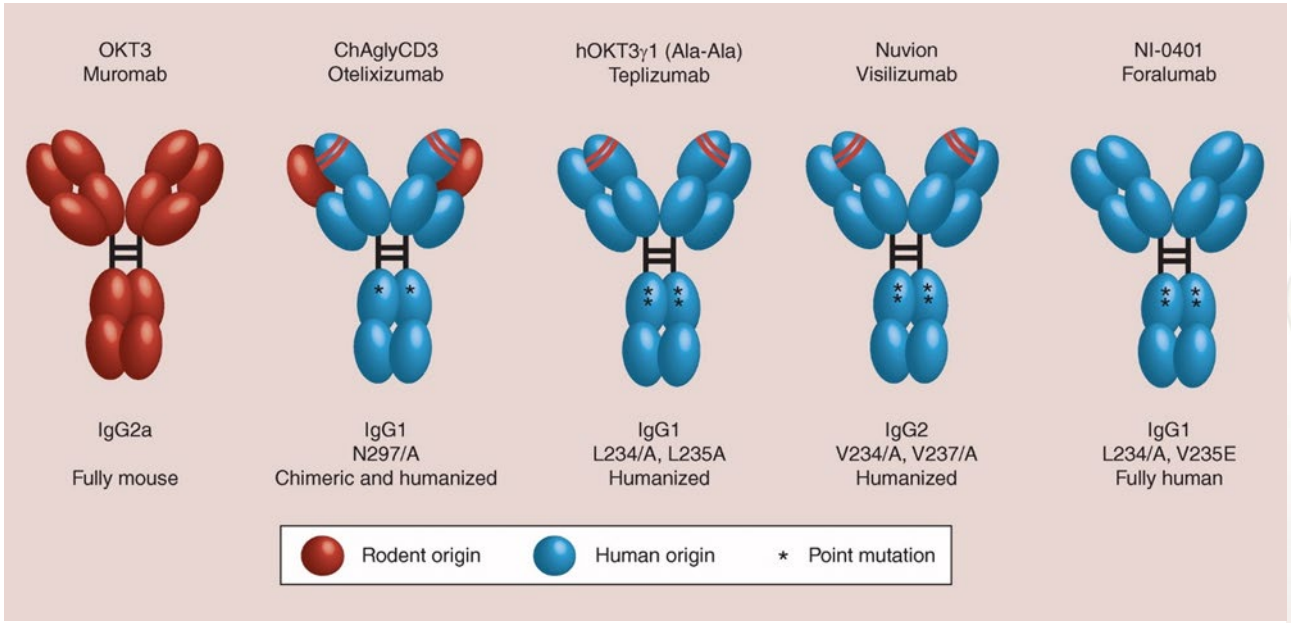
FAIL

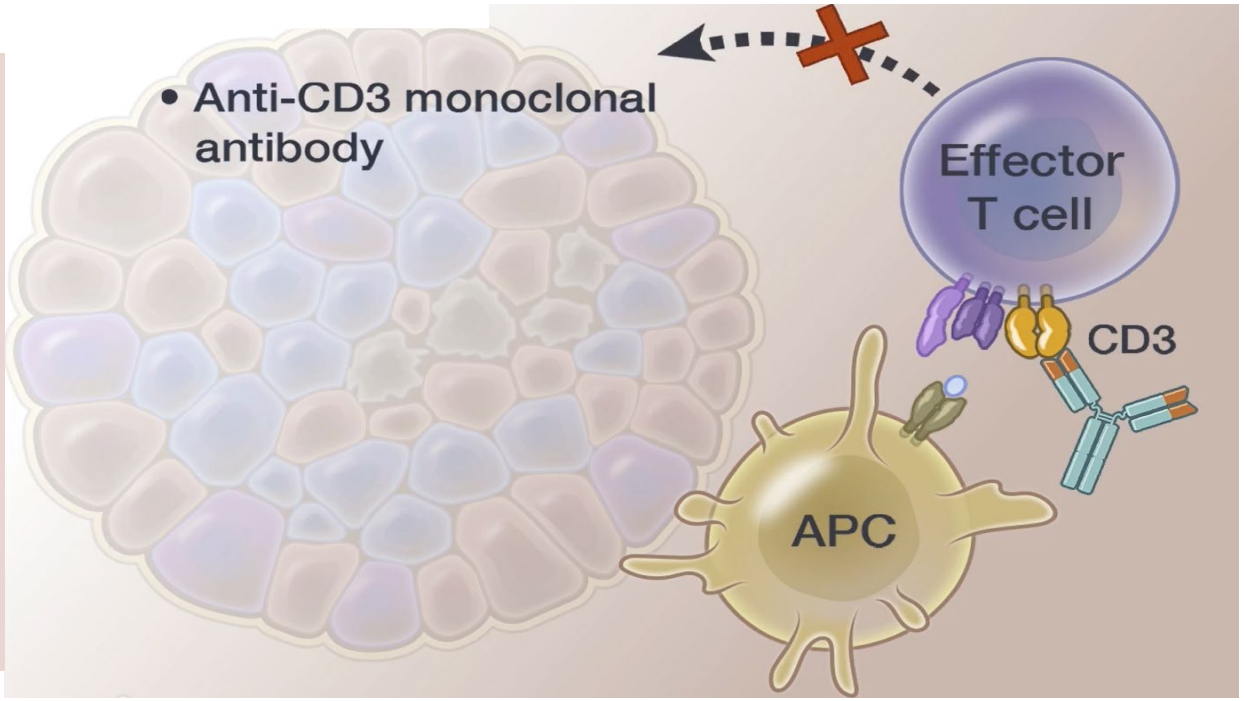
eral Insulin

Skyler JS. Diabet Med 2013

The anti-CD3 era

New generation of anti-human CD3 as
compared with the mouse anti-human CD3 mAb OKT3





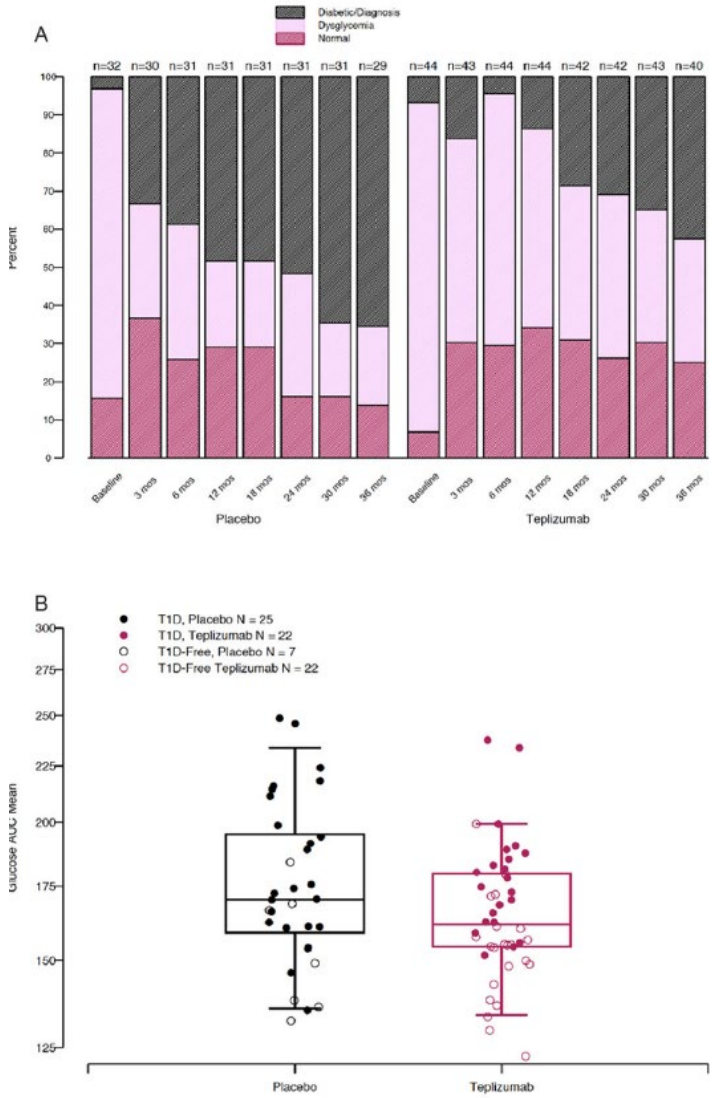
Kuhn C and Weiner HL. Immunotherapy, 2016

Herold KC et al. N Engl J Med. 2019 (from video file)

Anti CD3- Phase II Clinical Trials

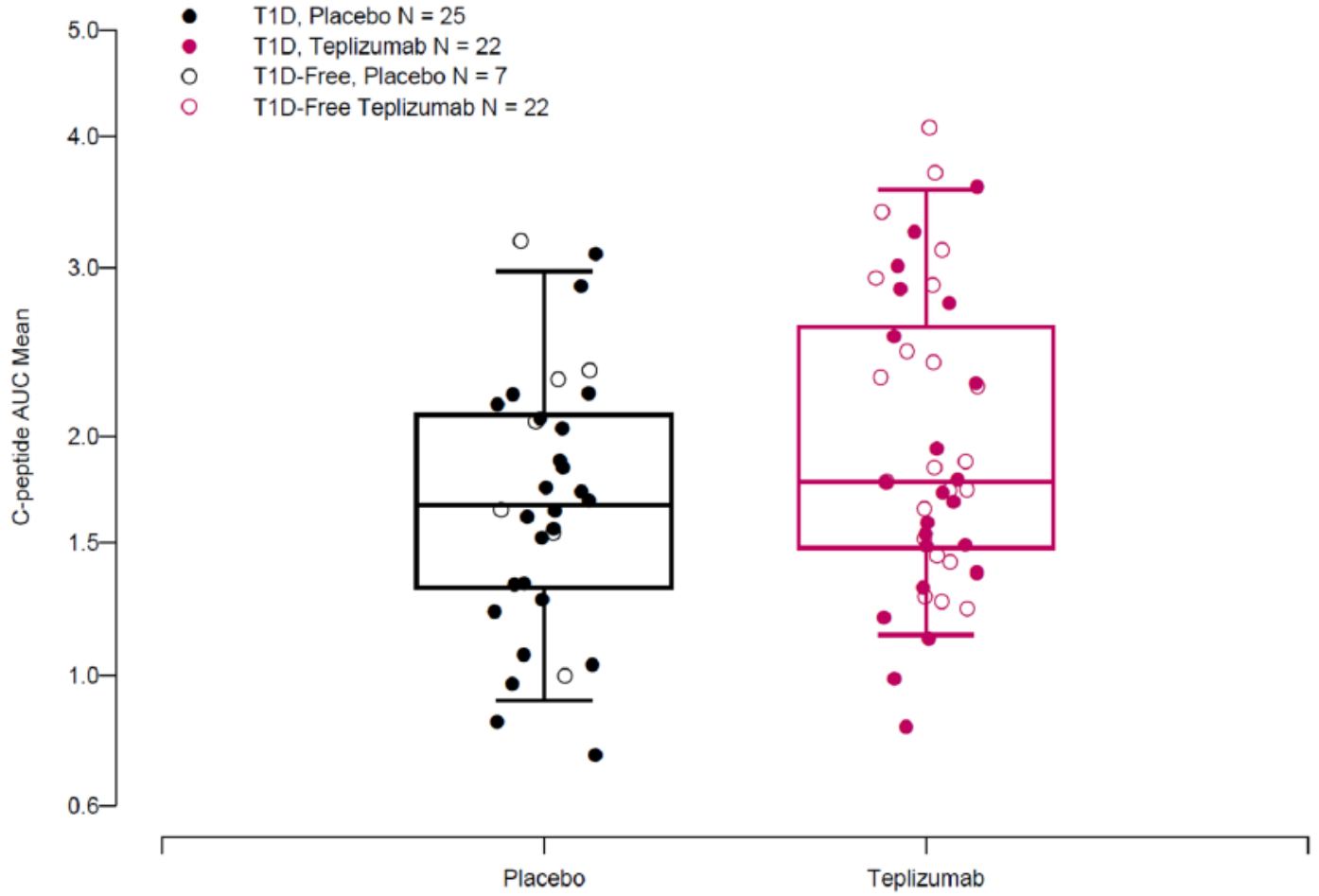
First autor	Study design	Intervention	Primary outcome	Relevant findings
Herold KC (2002)	Phase I–II trial, randomized, controlled N=24	14-day course i.v. Teplizumab at escalating "full" dose	C-peptide preservation one year after treatment	Treatment **maintained or improved insulin production after one year in the treatment group** (9/12 patients) (p = 0.01), **lowered HbA1c** (p = 0.08) **and insulin dose** (p = 0.03) in new onset T1D
Herold KC (2005)	Phase I–II trial, randomized, controlled, open-labeled N=42	12/14-day course i.v. Teplizumab at escalating "full" dose	C-peptide preservation two years after treatment	Treatment results in **improved C-peptide responses** both for 1 year (p < 0.01) and for at least 2 years (p < 0.02); the improved C-peptide responses were accompanied by **reduced HbA1c** (p = 0.004) **and insulin requirements** (p = 0.001)
Herold KC (2009)	24-month phase IIb, randomized, open labeled trial N=10	12-day course i.v. Teplizumab at higher dose than prior studies	C-peptide responses during MMTT, insulin use and hemoglobin A1c levels up to 5 years after treatment	**The trial was stopped because of increased AEs** without improved efficacy. **A trend for C-peptide preservation** over 2 yrs with drug treatment (p = 0.1) was observed, **and insulin use was lower** (p < 0.001)
Keymeulen B (2005)	Phase II, randomized, placebo-controlled trial; 18-month follow up N=80	6-day course i.v. Otelixizumab	The change in the residual beta- cell function from between baseline to six months later	A short-term treatment **preserves residual beta-cell function** for at least 18 months in patients with recent-onset T1D **and lowers the mean insulin dose** at 18 months (0.22 IU/kg/day vs. 0.61 IU/kgday) (p < 0.001)
Keymeulen B (2010)	Phase II randomized to placebo trial; 48 months of observation N=80	6-day course i.v. Otelixizumab	Change in insulin dose over 48 months	Treatment with otelixizumab **delayed the rise in insulin requirements** of patients with recent-onset diabetes over 48 months (+0.09 vs +0.32 U/kg/ day);

Improved glycemia in teplizumab treated participants is associated with maintenance of dysglycemic status



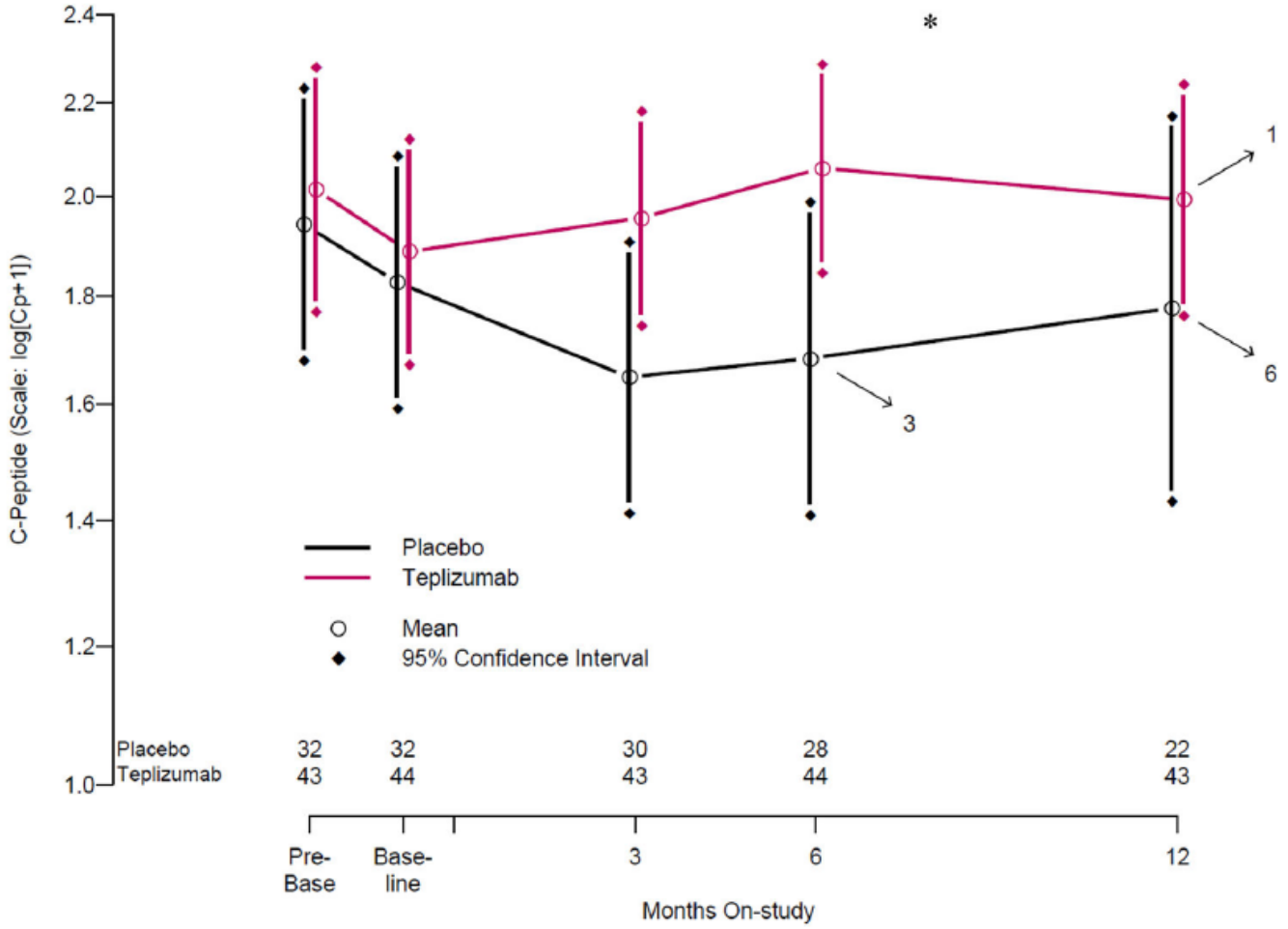
Sims E K et al, Sci Transl Med 2021

Teplizumab treatment was associated with increased average on-study C-peptide AUC



Sims E K et al, Sci Transl Med 2021

C-peptide over time in the two treatment arms over the first year



Sims E K et al, Sci Transl Med 2021

Results of Primary Prevention Trials for Type 1 Diabetes Published Through April 2024

STUDY (YEAR OF PUBLICATION) (REF.)	INTERVENTION	NUMBER RANDOMIZED	ACTIVE: PLACEBO	AGE RANGE*	PRIMARY OUTCOME	HAZARD RATIO (95% CI)	P-VALUE
Primary prevention studies—completed							
Finnish TRIGR pilot (2010) (62)	Casein hydrolysate formula	230	1:1	Birth	Autoantibodies	0.54 (0.29–0.95)	**0.005**
TRIGR (2014) (63)	Casein hydrolysate formula	2,159	1:1	Birth	Autoantibodies	1.21 (0.94–1.54)	0.14
TRIGR (2018) (68)	Casein hydrolysate formula	2,159	1:1	Birth	Diagnosis of T1D	1.1 (0.8–1.5)	0.46
FINDIA (2012) (64)	Insulin-free whey-based formula	1,104	1:1:1	Birth	Autoantibodies	0.39 (0.17–0.91)	**0.01**
BABYDIET (2011) (65,72)	Delayed gluten exposure	150	1:1	Birth	Autoantibodies	1.3 (0.6–3.0)	0.6
NIP pilot trial (2015) (66)	Docosahexaenoic acid	98	1:1	Birth	Cytokines	n/a	NS
Canadian Vitamin D pilot (2006) (67)	Supplemental vitamin D	9	1:1	Birth	25-OH-D level	n/a	n/a
Pre-POInT (2015) (69)	Oral insulin	25	1.5:1	2–7	Safety	No safety issues	n/a
Pre-POInT-EARLY (2021) (70)	Oral insulin	44	1:1	0.5–3	Immune response to insulin	n/a	0.54
Primary prevention studies—ongoing							
GPPAD-03 POInT (75)	Oral insulin	1,050	1:1	4–7 months	Autoantibodies and diagnosis of T1D	‡	‡
PINIT (76)	Nasal insulin	38	1:1	1–7	Immune response	‡	‡
GPPAD-04 SINT1A (77)	*Bifidobacterium longum* subsp. *infantis*	Target: 1,144	1:1		Autoantibodies	‡	‡

Jacobsen L M et al, Diabetes in America (Internet) 2024

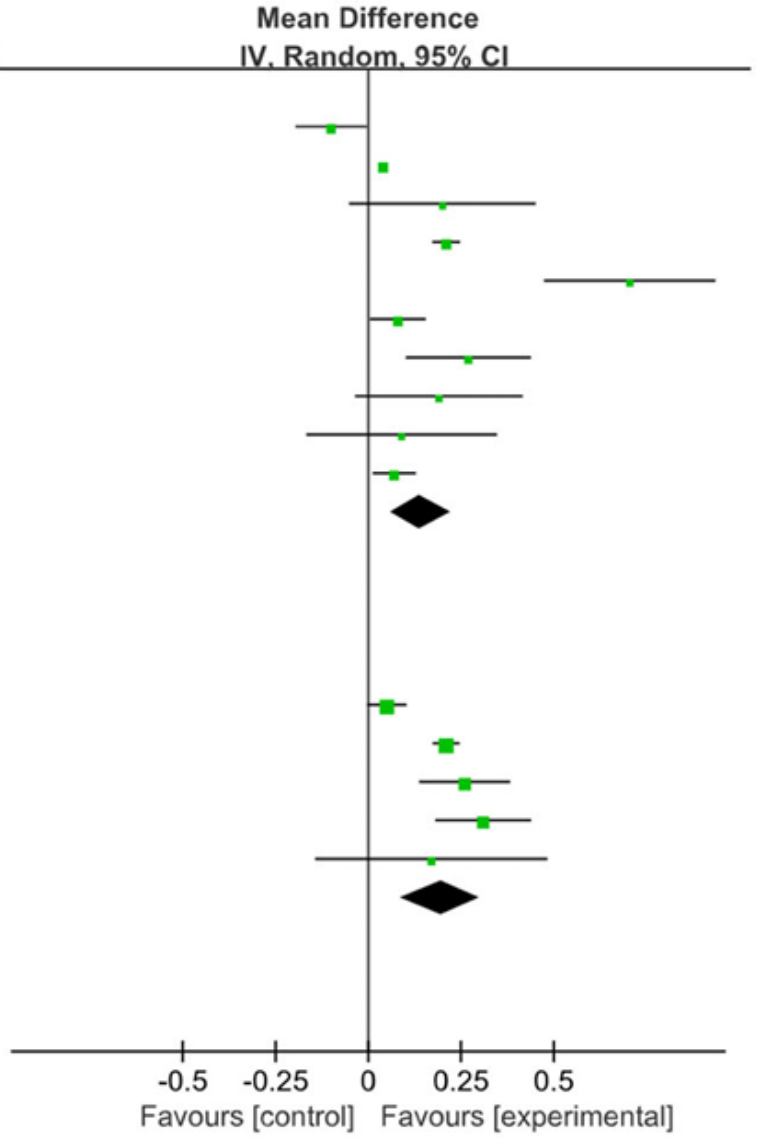
Results of Secondary Prevention Trials for Type 1 Diabetes Published Through April 2024

Secondary prevention studies—completed							
DENIS (1998) (80)	Nicotinamide	55	1:1	3–12	Diagnosis of T1D	0.79 (0.25–3.38)	0.97
ENDIT (2004) (81)	Nicotinamide	552	1:1	3–40	Diagnosis of T1D	1.07 (0.78–1.45)	0.69
DPT-1 Parenteral Insulin (2002) (82)	Injected insulin	339	1:1	4–45	Diagnosis of T1D	0.96 (0.69–1.34)	0.80
Belgian Parenteral Insulin (2009) (87)	Injected insulin	50	1:1	5–40	Diagnosis of T1D	n/a	0.97
EPPSCIT (2002) (218)	Injected insulin	29	1:1	3–18	Diagnosis of T1D	n/a	0.49
DPT-1 Oral Insulin† (2005) (83,84,85)	Oral insulin	372	1:1	3–45	Diagnosis of T1D	0.76 (0.51–1.14)	0.189
TrialNet Oral Insulin† (2017) (86)	Oral insulin	389	1:1	3–45	Diagnosis of T1D	0.87 (0–1.2)	0.21
TrialNet Oral Insulin Mechanistic (2020) (101)	Oral insulin	92	1:1 to 2 doses	3–45	Change in immune function	‡	‡
DIPP birth cohort (2008) (88)	Nasal insulin	224	1:1	1–5	Diagnosis of T1D	1.14 (0.73–1.77)	0.55
DIPP sibling cohort (2008) (88)	Nasal insulin	40	1:1	4–11	Diagnosis of T1D	1.93 (0.56–6.77)	0.30
INIT-1 pilot safety study (2004) (89)	Nasal insulin	38	Crossover	5–33	Safety	n/a	n/a
INIT-II (2020) (90)	Nasal insulin	110	1:1	4–30	Diagnosis of T1D	‡	‡
DIAPREV-IT (2018) (91)	GAD	50	1:1	4–18	Diagnosis of T1D	0.77	0.574
DIAPREV-IT2 (2020) (92)	GAD + vitamin D	Terminated	1:1	4–18	Diagnosis of T1D	Futility	NS
TrialNet hydroxychloroquine (2022) (93)	Hydroxychloroquine	Terminated	2:1	3–45	Diagnosis of T1D	Futility	n/a
TrialNet abatacept (2023) (94,95)	Abatacept	212	1:1	6–45	Stage 2 T1D	0.702	0.11
TrialNet teplizumab (2019) (96)	Anti-CD3 monoclonal antibody	76	1:1	8–45	Diagnosis of T1D	0.41 (0.22–0.78)	**0.006**
Secondary prevention studies—ongoing							
Fr1da Insulin Intervention (100)	Oral insulin	220	---	2–12	Immune response to insulin	‡	‡
TrialNet low-dose ATG (STOP-T1D) (102)	ATG	Target: 114	2:1	12–35	Stage 3 T1D	‡	‡
The CoRD study pilot (103)	Autologous cord blood	‡	n/a	1–12	Feasibility	‡	‡

Jacobsen L M et al, Diabetes in America (Internet) 2024

Meta-analyses of anti-CD3 mAbs vs. placebo for change in C-peptide AUC in recent-onset T1D

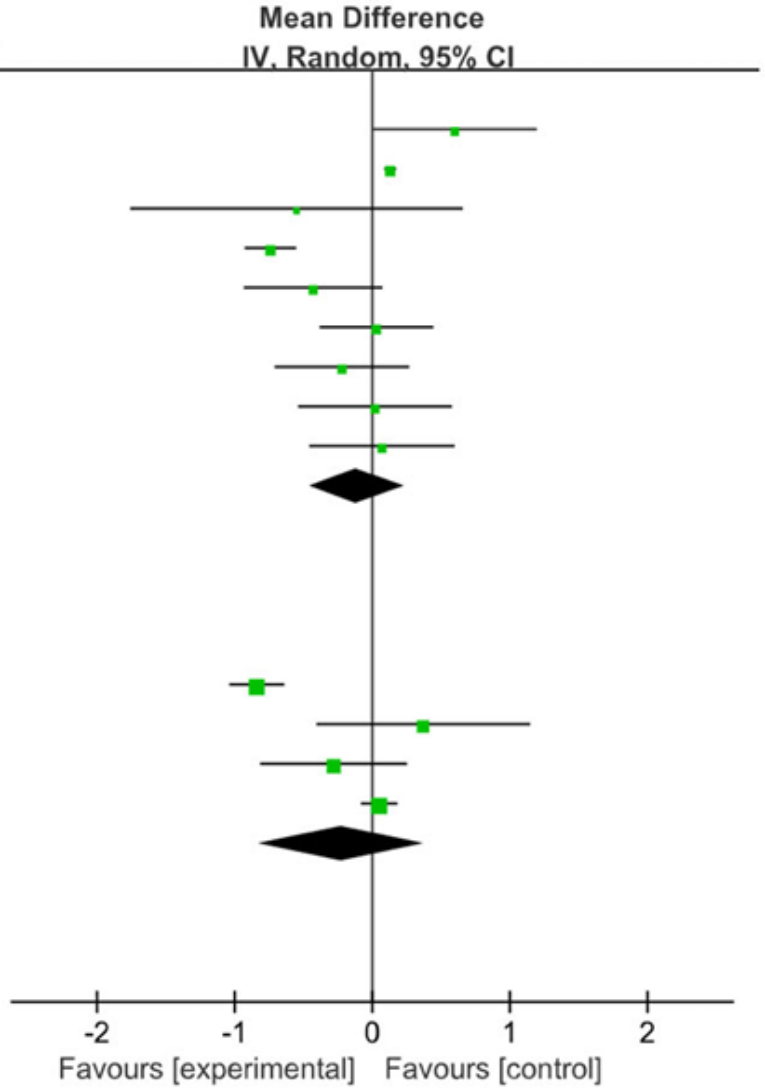
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Duration = 1 year								
Ambery 2014	-0.23	0.31	96	-0.13	0.24	45	11.9%	-0.10 [-0.19, -0.01]
Aronson 2014	0.54	0.03	181	0.5	0.04	91	14.2%	0.04 [0.03, 0.05]
Herold 2002	0.48	0.38	12	0.28	0.22	12	6.0%	0.20 [-0.05, 0.45]
Herold 2005	0.48	0.07	21	0.27	0.04	21	13.9%	0.21 [0.18, 0.24]
Herold 2009	0.894	0.245	6	0.189	0.119	4	6.6%	0.71 [0.48, 0.93]
Herold 2013(1)	0.45	0.15	31	0.37	0.13	27	12.8%	0.08 [0.01, 0.15]
Herold 2013(2)	0.61	0.38	52	0.34	0.33	25	8.8%	0.27 [0.10, 0.44]
Keymeulen 2005	0.89	0.41	40	0.7	0.59	40	6.7%	0.19 [-0.03, 0.41]
Keymeulen 2021	-0.06	0.28	24	-0.15	0.26	5	5.8%	0.09 [-0.16, 0.34]
sherry 2011	-0.07	0.29	415	-0.14	0.24	98	13.3%	0.07 [0.01, 0.13]
Subtotal (95% CI)			**878**			**368**	**100.0%**	**0.14 [0.06, 0.22]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 139.16$, df = 9 ($P < 0.00001$); $I^2 = 94\%$								
Test for overall effect: $Z = 3.51$ ($P = 0.0005$)								
Duration = 2 years								
Hagopian 2013	-0.14	0.16	131	-0.19	0.17	64	25.7%	0.05 [0.00, 0.10]
Herold 2005	0.35	0.06	21	0.14	0.05	21	26.6%	0.21 [0.18, 0.24]
Herold 2013(2)	0.44	0.32	52	0.18	0.21	25	20.1%	0.26 [0.14, 0.38]
Keymeulen 2010	0.87	0.15	21	0.56	0.2	13	19.5%	0.31 [0.18, 0.44]
Keymeulen 2021	-0.18	0.33	24	-0.35	0.32	5	8.0%	0.17 [-0.14, 0.48]
Subtotal (95% CI)			**249**			**128**	**100.0%**	**0.20 [0.09, 0.30]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 34.64$, df = 4 ($P < 0.00001$); $I^2 = 88\%$								
Test for overall effect: $Z = 3.66$ ($P = 0.0003$)								



Liu Y et al., Endocrine 2023

Meta-analyses of anti-CD3 mAbs vs. placebo for change in HbA1c in recent-onset T1D

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Duration = 1 year								
Ambery 2014	-0.3	1.8	97	-0.9	1.6	45	10.2%	0.60 [0.01, 1.19]
Aronson 2014	7.04	0.116	181	6.91	0.147	91	14.5%	0.13 [0.10, 0.16]
Herold 2002	6.98	1.7	12	7.53	1.27	12	5.3%	-0.55 [-1.75, 0.65]
Herold 2005	6.73	0.35	21	7.47	0.23	21	13.9%	-0.74 [-0.92, -0.56]
Herold 2009	6.78	0.48	6	7.21	0.32	4	11.2%	-0.43 [-0.93, 0.07]
Herold 2013(1)	7.11	0.81	31	7.08	0.76	27	12.1%	0.03 [-0.37, 0.43]
Herold 2013(2)	7.12	1	52	7.34	1.01	25	11.3%	-0.22 [-0.70, 0.26]
Keymeulen 2005	6.78	1.47	40	6.76	1	40	10.6%	0.02 [-0.53, 0.57]
sherry 2011	7.87	2.18	415	7.8	2.4	98	10.9%	0.07 [-0.45, 0.59]
Subtotal (95% CI)			**855**			**363**	**100.0%**	**-0.11 [-0.46, 0.23]**
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 97.48$, df = 8 ($P < 0.00001$); $I^2 = 92\%$								
Test for overall effect: Z = 0.63 (P = 0.53)								
Duration = 2 years								
Herold 2005	7.22	0.29	21	8.06	0.34	21	28.1%	-0.84 [-1.03, -0.65]
Herold 2009	8.42	0.76	6	8.05	0.48	4	19.6%	0.37 [-0.40, 1.14]
Herold 2013(2)	7.57	1.1	52	7.85	1.1	25	23.7%	-0.28 [-0.80, 0.24]
Keymeulen 2010	7.03	0.27	30	6.98	0.21	27	28.6%	0.05 [-0.07, 0.17]
Subtotal (95% CI)			**109**			**77**	**100.0%**	**-0.22 [-0.82, 0.38]**
Heterogeneity: $Tau^2 = 0.32$; $Chi^2 = 60.63$, df = 3 ($P < 0.00001$); $I^2 = 95\%$								
Test for overall effect: Z = 0.71 (P = 0.48)								



Liu Y et al., Endocrine 2023

EXPERT OPINION ON INVESTIGATIONAL DRUGS
https://doi.org/10.1080/13543784.2022.2022119

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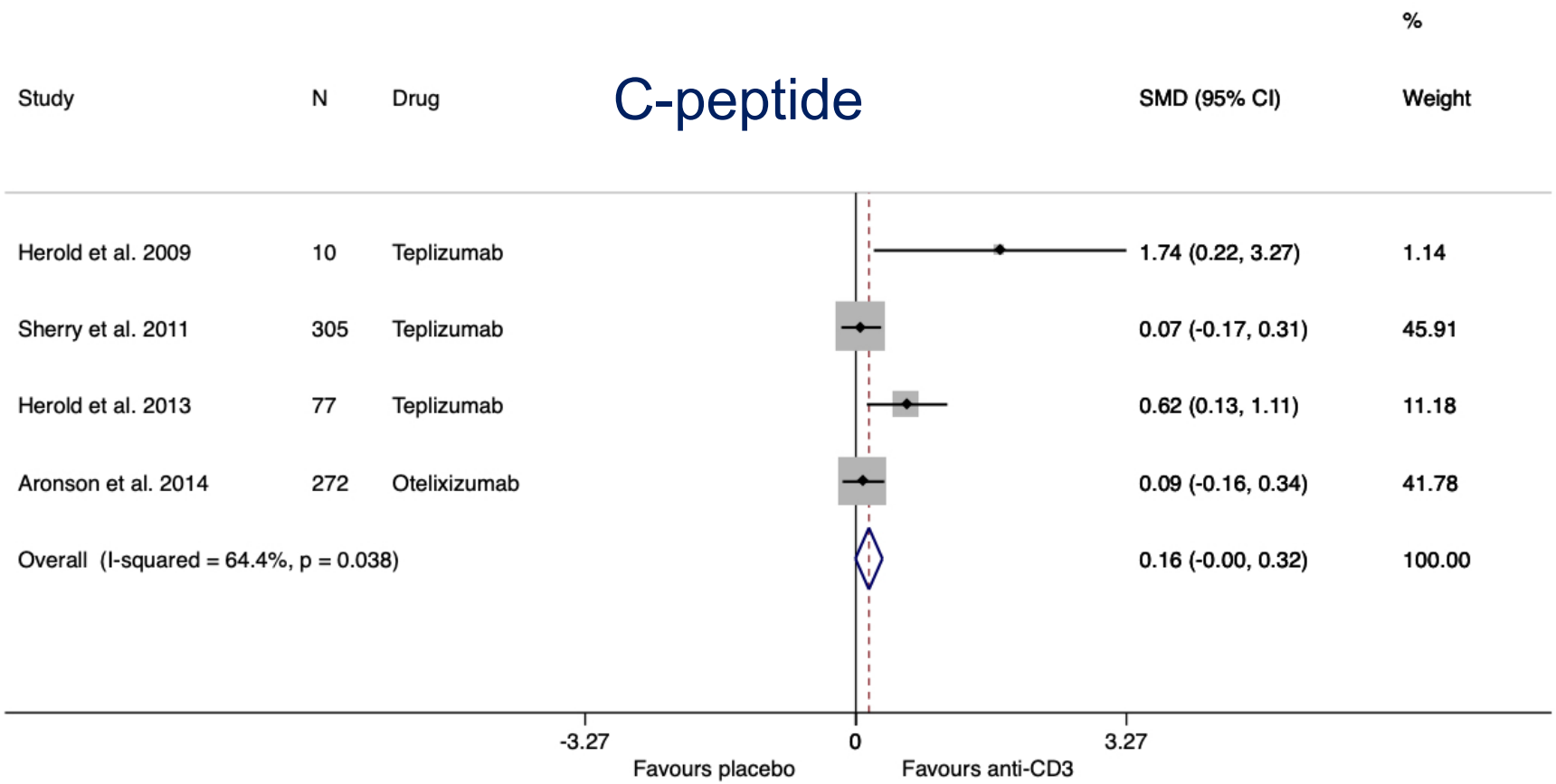
REVIEW

Investigational therapies targeting CD3 for prevention and treatment of type 1 diabetes

Carmen Mignogna, Ernesto Maddaloni, Luca D'Onofrio and Raffaella Buzzetti

C-peptide



Mignogna C et al. Expert Opin Investig Drugs 2021

An anti-CD3 Antibody, Teplizumab, In Relatives at Risk For Type 1 Diabetes

- Phase II
- Randomized (1:1) Double-blind

Population

- **Relatives of T1D patients** at high risk of developing clinical disease
- ≥2 autoantibodies + state of dysglycaemia (IFG,IGT or a postprandial glucose level at 30, 60, or 90 m >200 in 2 occasions.
- 76 randomized 1:1 (of which 55 ≤18 years)

Intervention

- Single 14-day Teplizumab cycle (n=44)
- 3 and then 6 months Follow-up with OGTT

Control

- Vs Placebo (n=32)

Outcome

- Disease onset

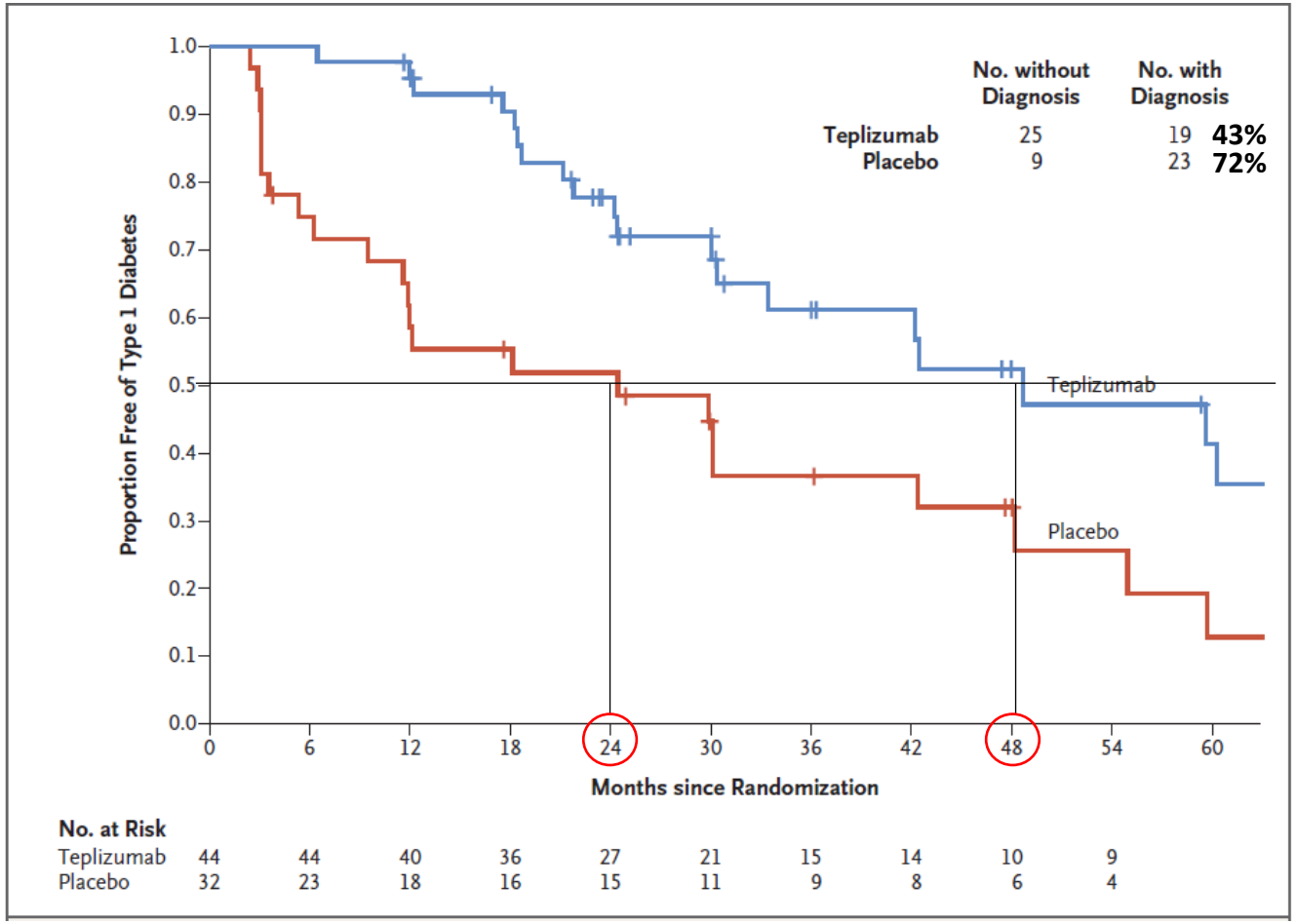
Herold KC et al. N Engl J Med. 2019

Baseline characteristics of participants

Characteristic	Teplizumab (N = 44)	Placebo (N = 32)
Age — yr		
Median (IQR)	14 (12–22)	13 (11–16)
Range	8.5–49.5	8.6–45.0
Age <18 yr — no. (%)	29 (66)	26 (81)
Male sex — %	57	53
Relationship to person with type 1 diabetes — no. (%)		
Sibling†	28 (64)	16 (50)
Offspring	6 (14)	6 (19)
Parent	6 (14)	3 (9)
Sibling and another first-degree relative	2 (5)	3 (9)
Second-degree relative	2 (5)	3 (9)
Third-degree relative or further removed	0	1 (3)
Autoantibodies — no. of participants positive (%)‡		
Anti-GAD65, harmonized	40 (91)	28 (88)
Micro insulin	20 (45)	11 (34)
Anti–IA-2, harmonized	27 (61)	24 (75)
ICA	29 (66)	28 (88)
Anti-ZnT8	32 (73)	24 (75)
Median glycated hemoglobin level (IQR) — %	5.2 (4.9–5.4)	5.3 (5.1–5.4)

Herold KC et al. N Engl J Med. 2019

TrialNet Study: results



P = 0.006 by adjusted Cox proportional-hazards model

Median time of T1D diagnosis:
Teplizumab: 48.4 months
Placebo: 24.4 months

The percentage of diabetes free-persons in the Teplizumab group (57%)was diuble that in the placebo group (28%)

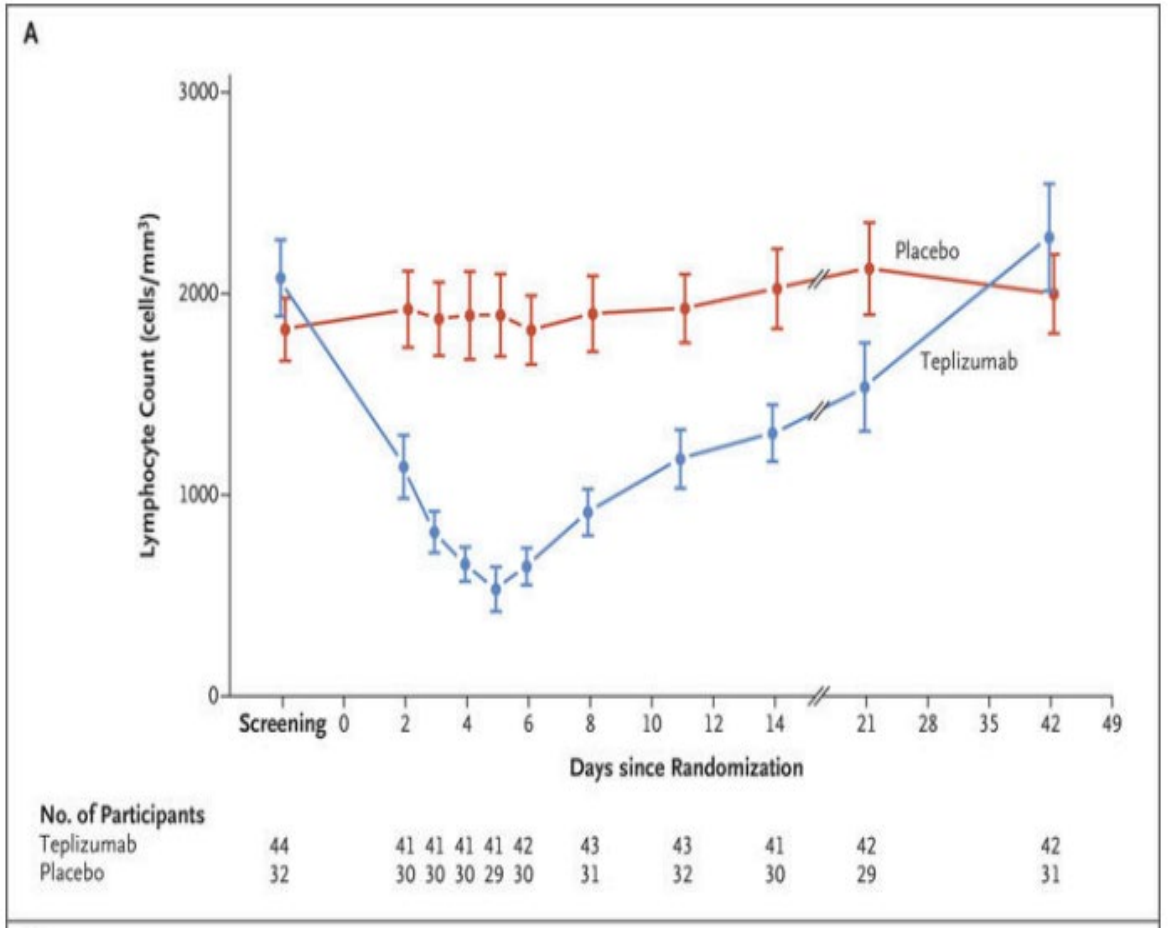
Herold KC et al. N Engl J Med. 2019

Teplizumab: side effects

Table 2. Adverse Events during Active Follow-up.*

Adverse Event Category	Teplizumab		Placebo	
	Events (N=112)	Participants (N=44)	Events (N=23)	Participants (N=32)
	no.	*no. (%)*	*no.*	*no. (%)*
Blood or bone marrow†	45	33 (75)	2	2 (6)
Dermatologic or skin†	17	16 (36)	1	1 (3)
Pain	11	5 (11)	5	3 (9)
Infection	8	5 (11)	5	3 (9)
Gastrointestinal	5	4 (9)	3	3 (9)
Metabolic or laboratory	7	4 (9)	2	2 (6)
Pulmonary or upper respiratory	6	4 (9)	0	0
Constitutional symptoms	3	2 (5)	0	0
Allergy or immunologic	2	2 (5)	0	0
Cardiac, general	1	1 (2)	1	1 (3)
Endocrine	0	0	2	2 (6)
Vascular	1	1 (2)	1	1 (3)
Neurologic	1	1 (2)	0	0
Ocular or visual	1	1 (2)	0	0
Musculoskeletal or soft tissue	2	1 (2)	0	0
Hepatobiliary or pancreatic	0	0	1	1 (3)
Syndrome	1	1 (2)	0	0
Hemorrhage or bleeding	1	1 (2)	0	0

* Events listed were attributed as possibly, probably, or definitely related to the trial agent by the trial-site investigator.
† The frequency of this type of event differed significantly between the two groups (P<0.001).



Herold KC et al. N Engl J Med. 2019

FDA approves teplizumab: a milestone in type 1 diabetes

Published: November 24, 2022

FDA Approves Tzield (Teplizumab) to Delay Type 1 Diabetes

Updated: 11/21/22 12:27 pm

Published: 11/17/22 3:12 pm

Patient Selection:

I. Select adult patients and pediatric patients 8 years of age and older for TZIELD treatment who have a diagnosis of Stage 2 type 1 diabetes.

II. Confirm Stage 2 type 1 diabetes by documenting:
   - At least two positive pancreatic islet cell autoantibodies
   - Dysglycemia without overt hyperglycemia using an oral glucose tolerance test (if an oral glucose tolerance test is not available, an alternative method for diagnosing dysglycemia without overt hyperglycemia may be appropriate)

III. - Ensure the clinical history of the patient does not suggest type 2 diabetes.

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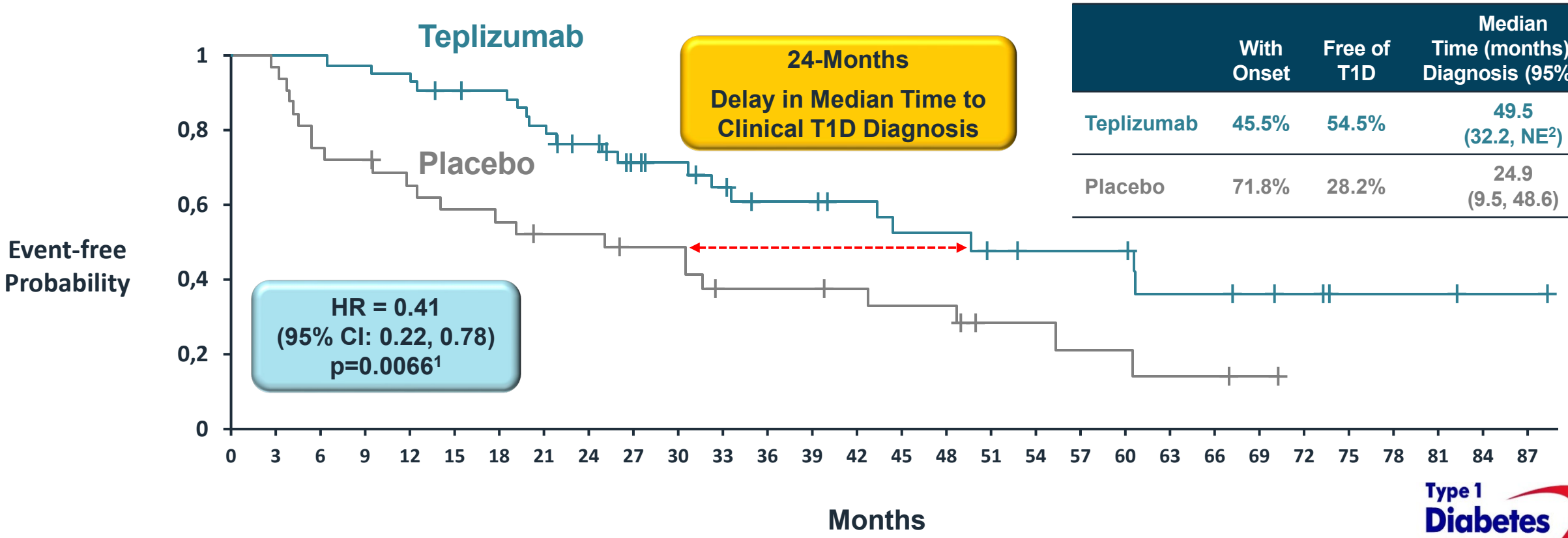
Sci Transl Med. 2021 March 03; 13(583): . doi:10.1126/scitranslmed.abc8980.

Teplizumab improves and stabilizes beta cell function in antibody positive high-risk individuals

Emily K. Sims[1], **Brian Bundy**[3], **Kenneth Stier**[4], **Elisavet Serti**[5], **Noha Lim**[5], **S Alice Long**[6], **Susan M Geyer**[7], **Antoinette Moran**[8], **Carla J Greenbaum**[6], **Carmella Evans-Molina**[2], **Kevan C. Herold**[4] **Type 1 Diabetes TrialNet Study Group**

Teplizumab Prevention Study
Significantly Delayed Onset of Stage 3 Clinical T1D vs Placebo



	With Onset	Free of T1D	Median Time (months) to Diagnosis (95% CI)
Teplizumab	45.5%	54.5%	49.5 (32.2, NE[2])
Placebo	71.8%	28.2%	24.9 (9.5, 48.6)

Number of Patients at Risk

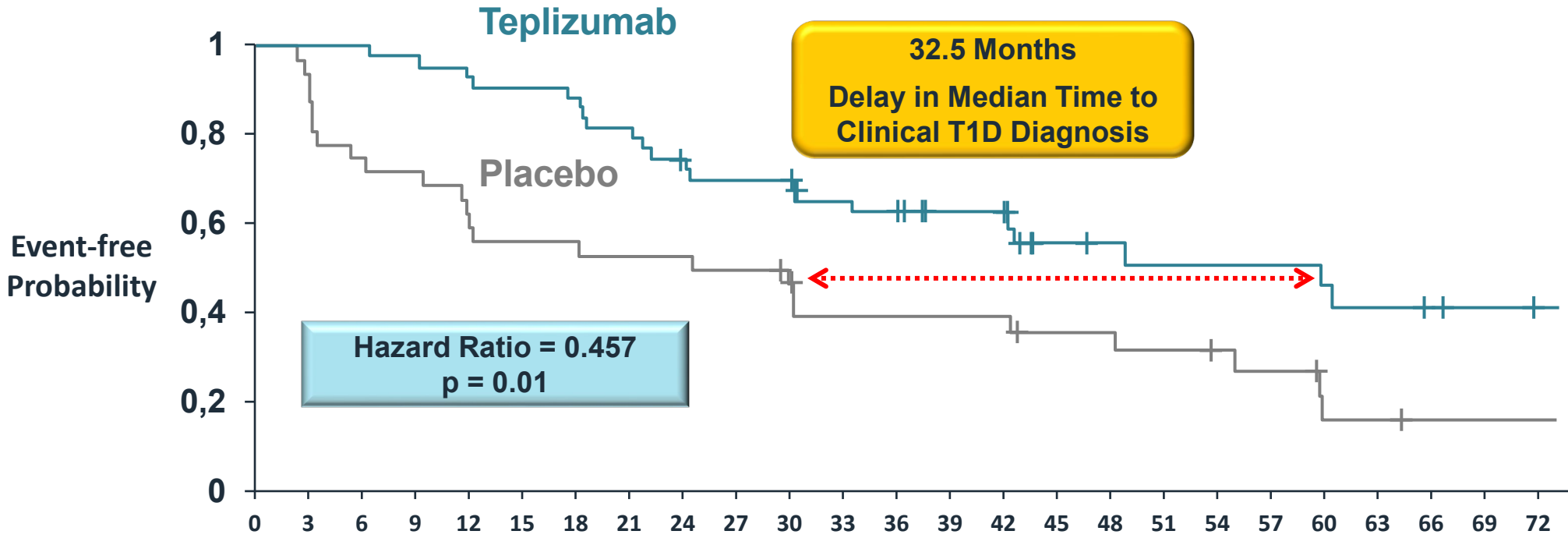
Teplizumab	44	44	44	43	41	39	38	34	30	24	22	19	16	16	14	12	12	10	9	9	9	6	6	5	4	2	2	2	1	1
Placebo	32	31	24	23	20	18	17	15	15	13	13	9	9	9	8	7	7	4	4	3	3	2	2	1	0					

Type 1 Diabetes TrialNet

1. Cox Proportional Hazards model; 2. Not Estimable

Herold et al. N Engl J Med 2019; 381:603-613

Teplizumab Prevention Study
Sustained Delay over Extended Follow-Up



	% With Onset	% Free of T1D	Median Time to Diagnosis
Teplizumab	50%	50%	59.6 months
Placebo	78%	22%	27.1 months

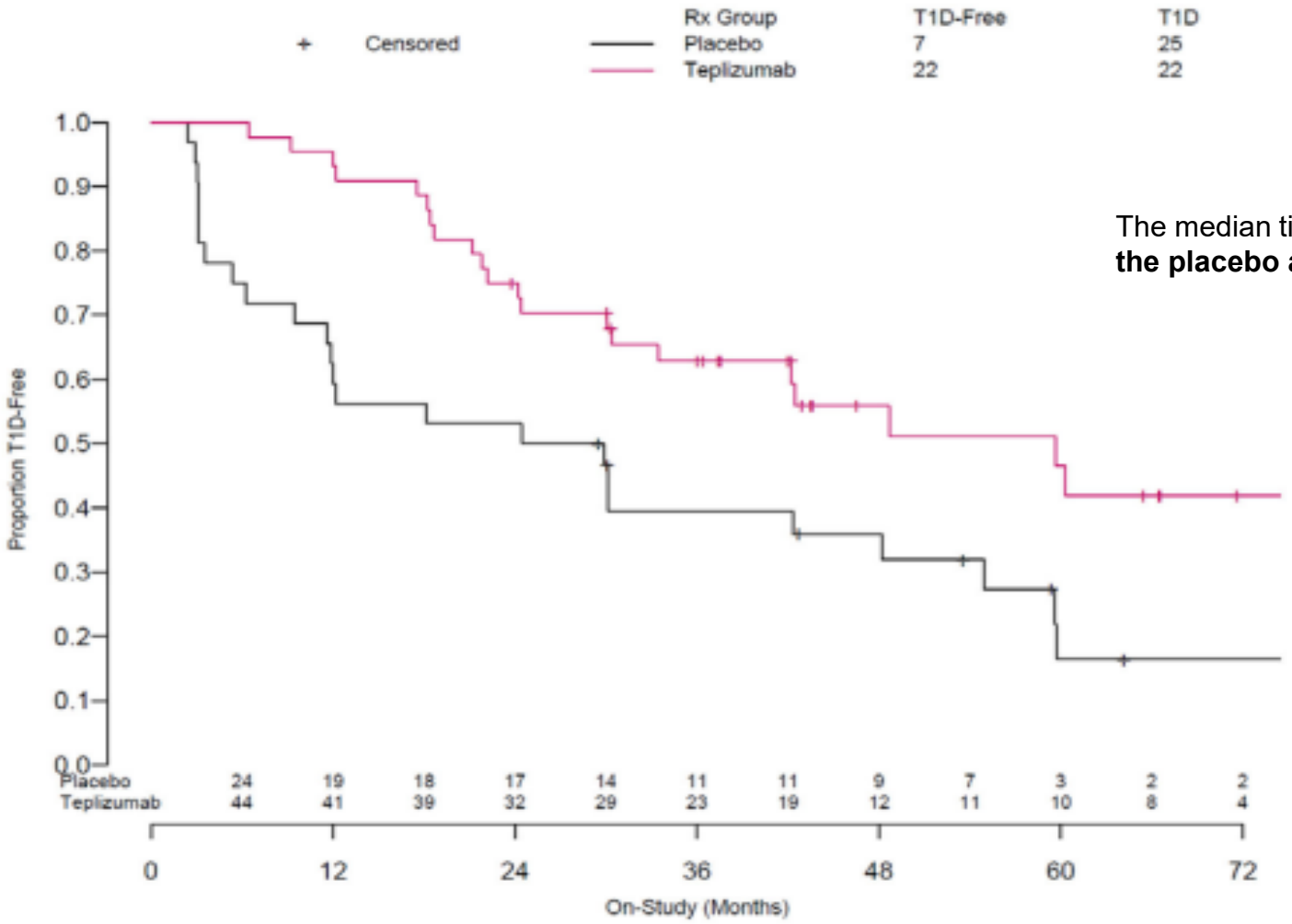
Number of Patients at Risk

Teplizumab	44	44	41	39	32	29	23	19	12	11	10	8	4
Placebo	32	24	19	18	17	14	11	11	9	7	3	2	2

Type 1 Diabetes TrialNet

Sims et al. Sci Trans Med 2021;13,eabc8980

Teplizumab Treatment is Associated with a Sustained Effect on Type 1 Diabetes



The median time to diabetes was **27.1 and 59.6 months in the placebo and teplizumab treatment groups** respectively

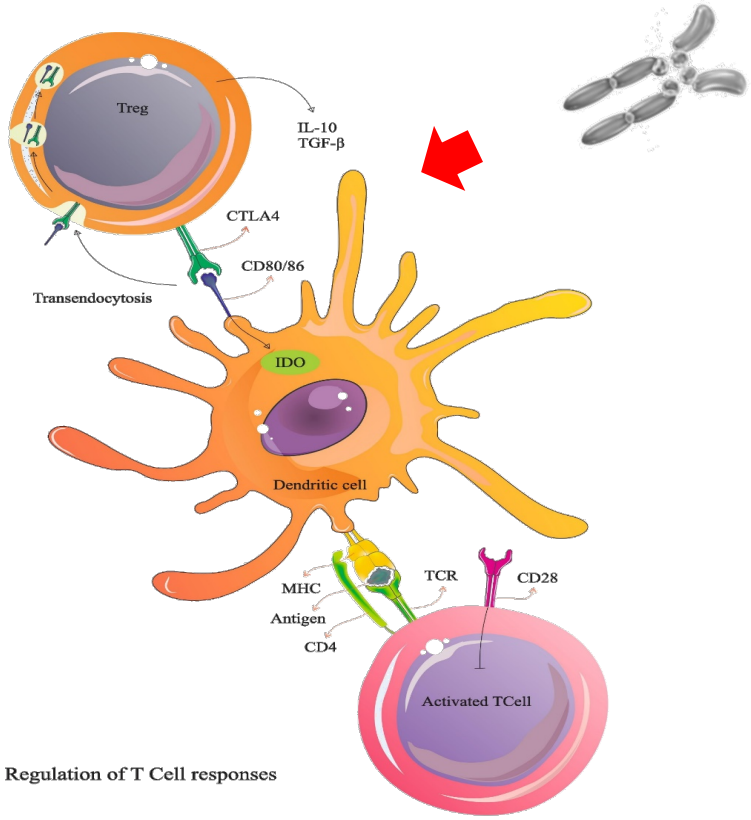
p=0.01

Anti-CTLA4: Abatacept

Human Molecular Genetics, 1996, Vol. 5, No. 7 1075–1080

The *CTLA-4* gene region of chromosome 2q33 is linked to, and associated with, type 1 diabetes

Lorenza Nisticò[1,2], Raffaella Buzzetti[1], Lynn E. Pritchard[3], Bart Van der Auwera[4], Claudio Giovannini[1], Emanuele Bosi[5], Maria Teresa Martinez Larrad[6], Manuel Serrano Rios[6], C. C. Chow[7], Clive S. Cockram[7], Karen Jacobs[8], Catherine Mijovic[8], Stephen C. Bain[8], Anthony H. Barnett[8], Christina L. Vandewalle[9], Frans Schuit[4], Frans K. Gorus[9], Belgian Diabetes Registry[10], Roberto Tosi[2], Paolo Pozzilli[1] and John A. Todd[3,*]



CTLA4Ig (abatacept) blocks costimulatory interaction with the CD28 on T lymphocytes by binding to **CD80 e CD86** on the APCs

Inhibits optimal T cell activation

Hosseini A et al. Int Immunopharmacol. 2020

Anti-CTLA4: Abatacept

- Phase II
- Randomized (1:1)
- Double-blind

Population

- **Stage 1** patients T1D:
  - ✓ ≥2 typical autoantibodies (exept IAA) + Euglycaemic status (NGT)

Intervention

- 14 infusions of Abatacept in 12 months (n=101)
- 47.6 months follow-up with OGTT (median)

Control

- Vs Placebo (n=111)

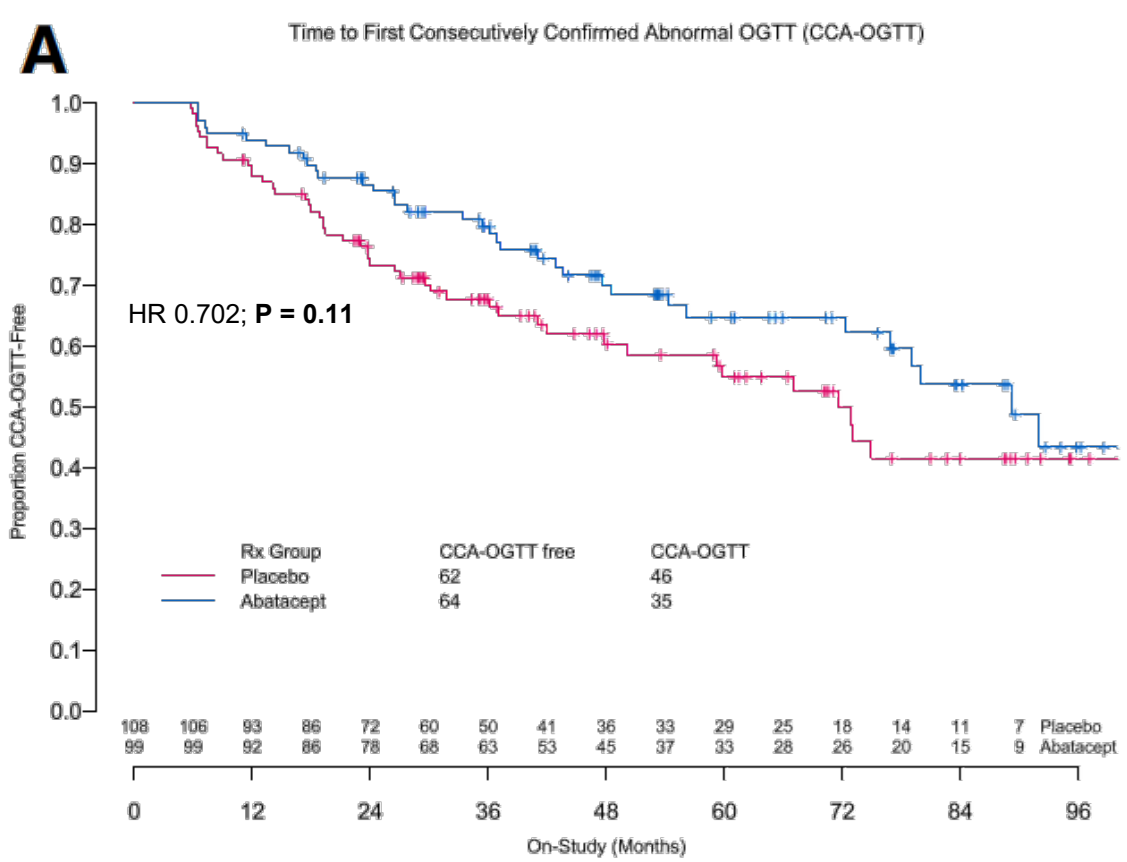
Outcome

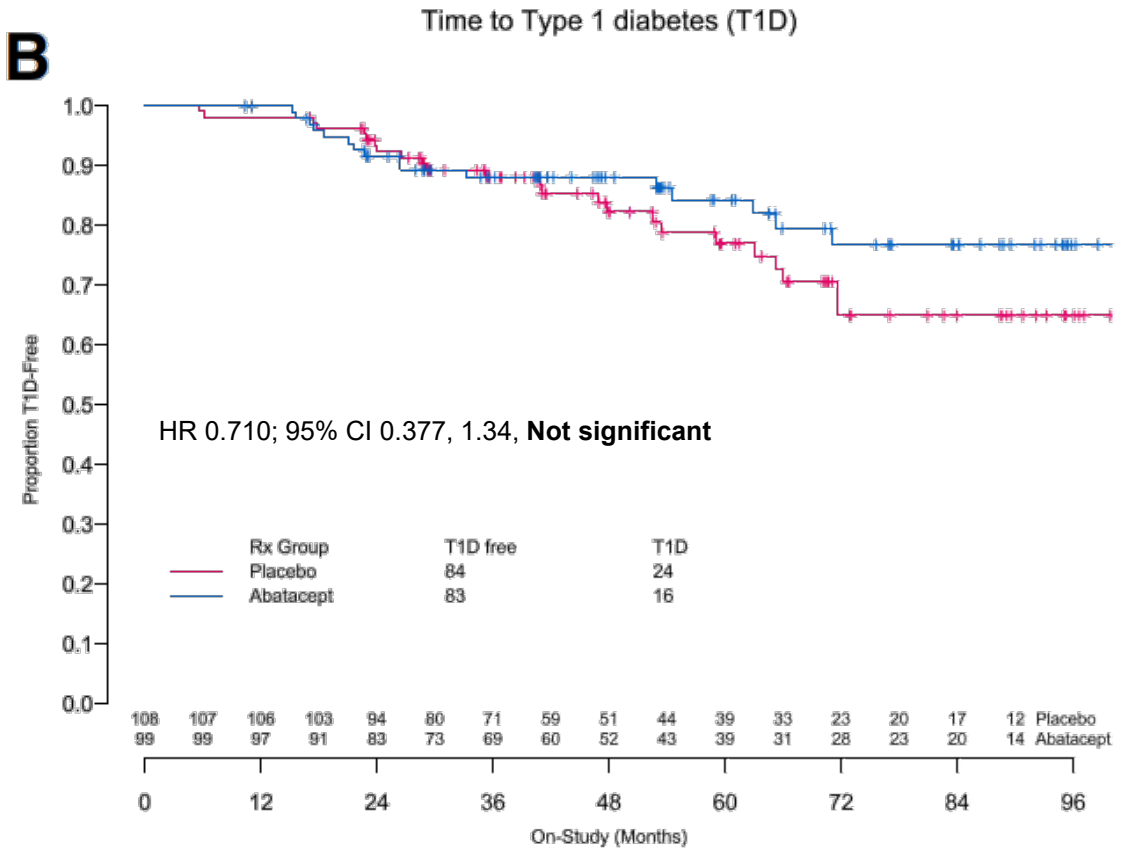
- Onset of the disease (or IFG/IGT) [= from stage 1 to stage 2 or 3]

Abatacept does not delay the IFG/IGT onset nor the onset of the disease

Russell WE et al. Diabetes Care 2023

Anti-CTLA4: Abatacept





Abatacept does not delay the IFG/IGT onset nor the onset of the disease

Low-Dose Anti-Thymocyte Globulin (ATG) Preserves β-Cell Function and Improves HbA_{1c} in New-Onset Type 1 Diabetes

Michael J. Haller; Desmond A. Schatz; Jay S. Skyler; Jeffrey P. Krischer; Brian N. Bundy; Jessica L. Miller; Mark A. Atkinson; Dorothy J. Becker; David Baidal; Linda A. DiMeglio; Stephen E. Gitelman; Robin Goland; Peter A. Gottlieb; Kevan C. Herold; Jennifer B. Marks; Antoinette Moran; Henry Rodriguez; William Russell; Darrell M. Wilson; Carla J. Greenbaum; Type 1 Diabetes TrialNet ATG-GCSF Study Group

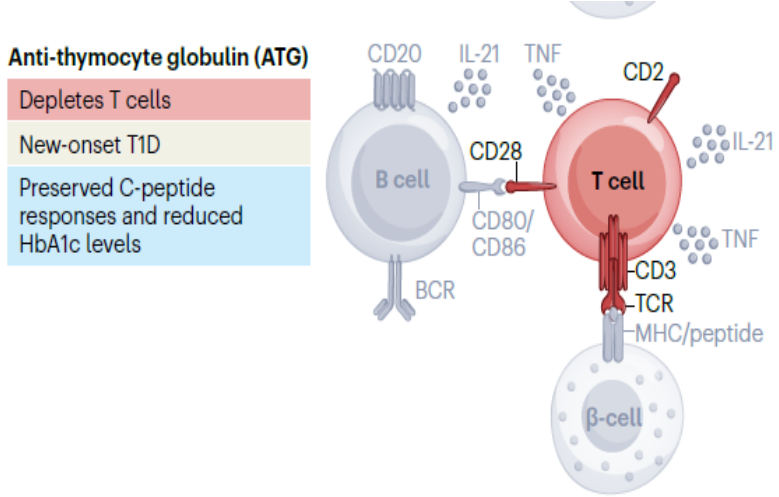
P Pazienti con DM1, 12-45 anni, diagnosi <100 giorni

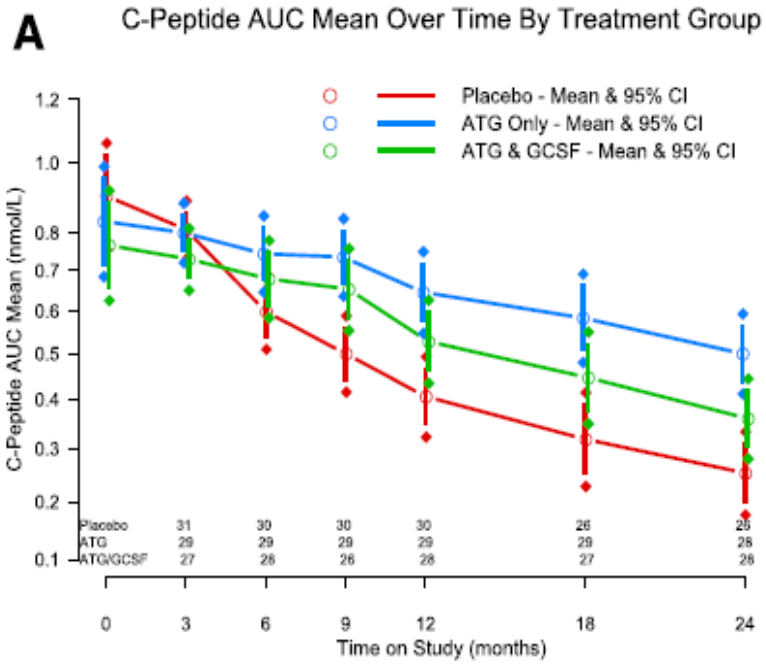
I ATG alla dose di 2,5 mg/kg

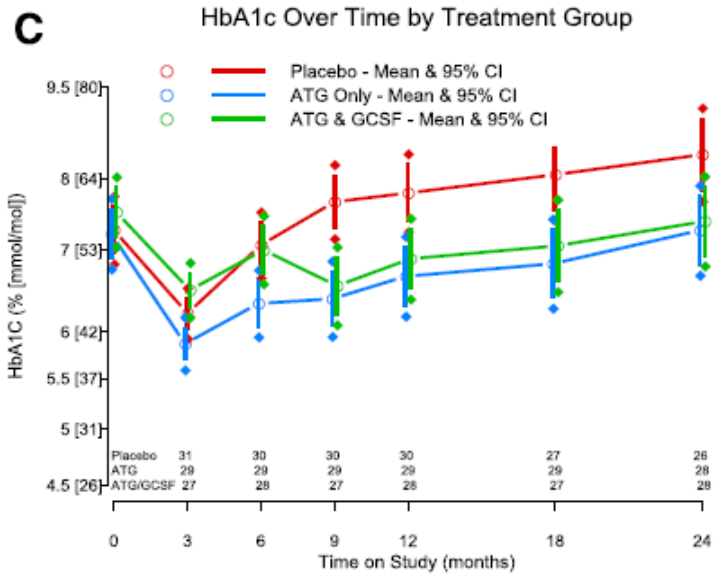
C Placebo; ATG + GCSF (ogni 2 settimane per max 6 dosi)

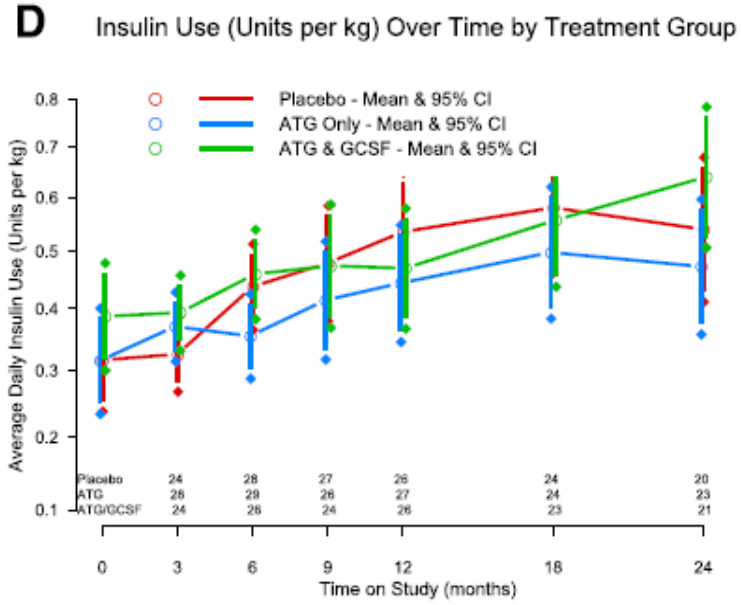
O C-peptide AUC post 2h-MMTT dopo 1 anno

GCSF: granuloccyte colony stimulating factor









Haller MJ, et al. Diabetes Care. 2018

Conclusions

The time for immunotherapy in T1D began in 1986 with cyclosporine. Since then, hundreds of trials have been carried out with a variety of compounds but without significant results.

Teplizumab was able to delay progression towards clinical T1D diabetes compared to placebo in 1° degree relatives of patiens with T1D and it **is the first disease modifyng therapy in type 1 diabetes**

Precision medicine for T1D should recognize that each individual has peculiar phenotypic and genotypic aspects possibly impacting the efficacy and safety of different treatments, therefore…..