

CONGRESSO **SID-AMD** *Umbria*

UMBRIA DIABETE 2024

Ritorno al futuro

PERUGIA

22-23 NOVEMBRE 2024

Sangallo Palace Hotel

22 novembre 2024

È possibile ritardare l'insorgenza del diabete di tipo 1? Se sì, di quanto?

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UMBERTO I
POLICLINICO DI ROMA



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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:

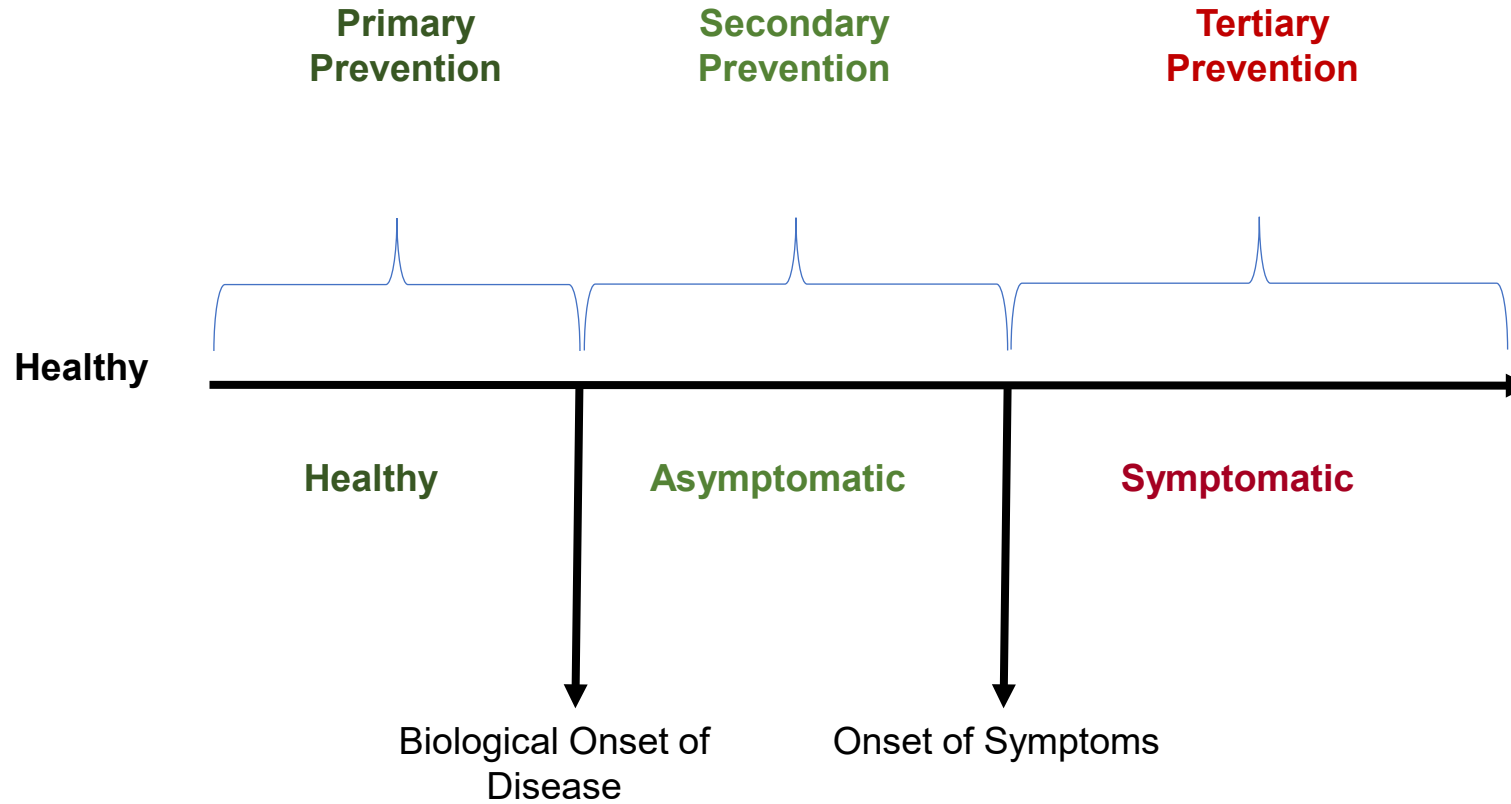
- Sanofi
- Novo Nordisk
- Eli Lilly
- Abbott
- Atrazeneca
- Vertex
- Guidotti

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.).

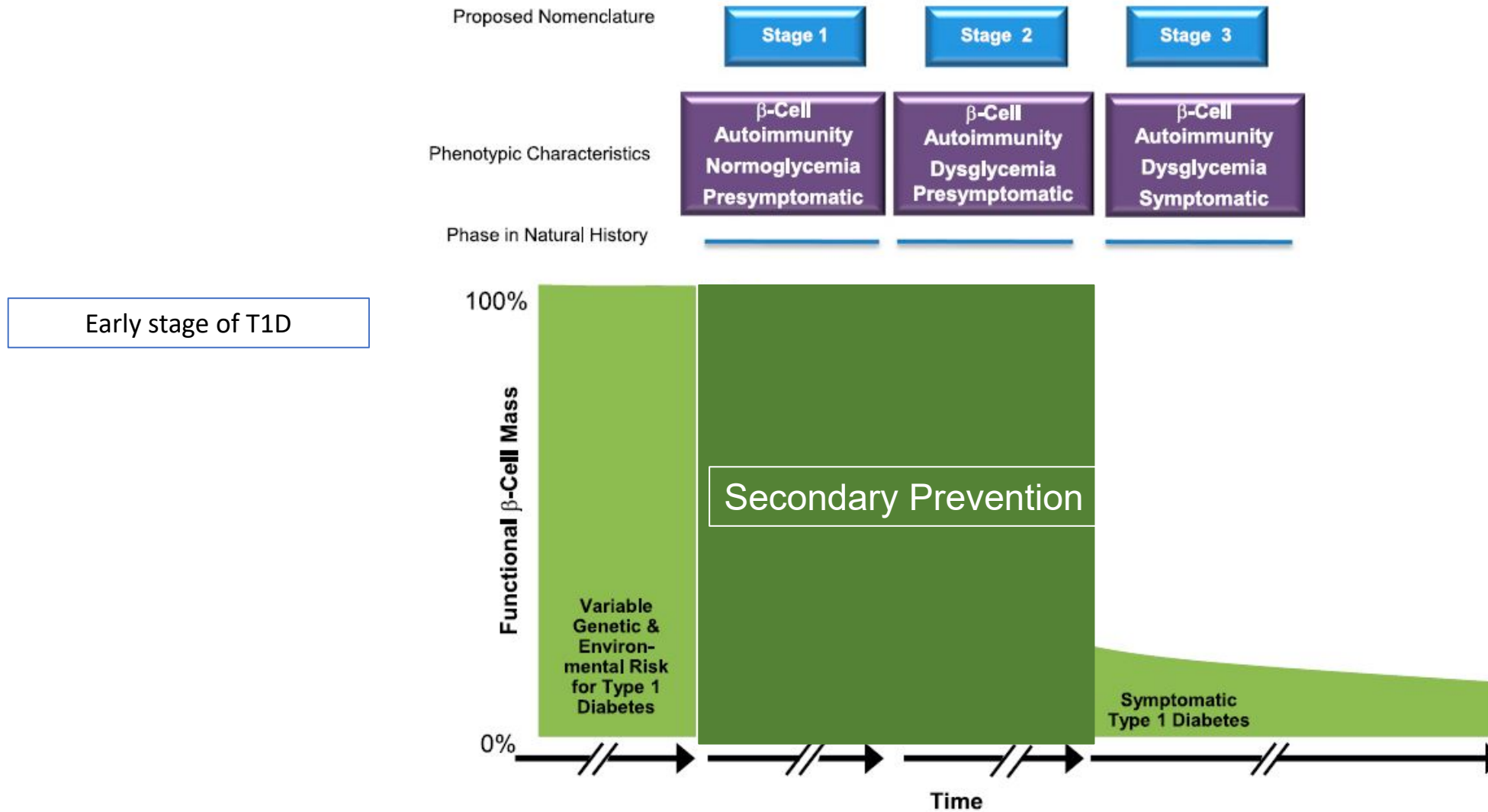
Agenda

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

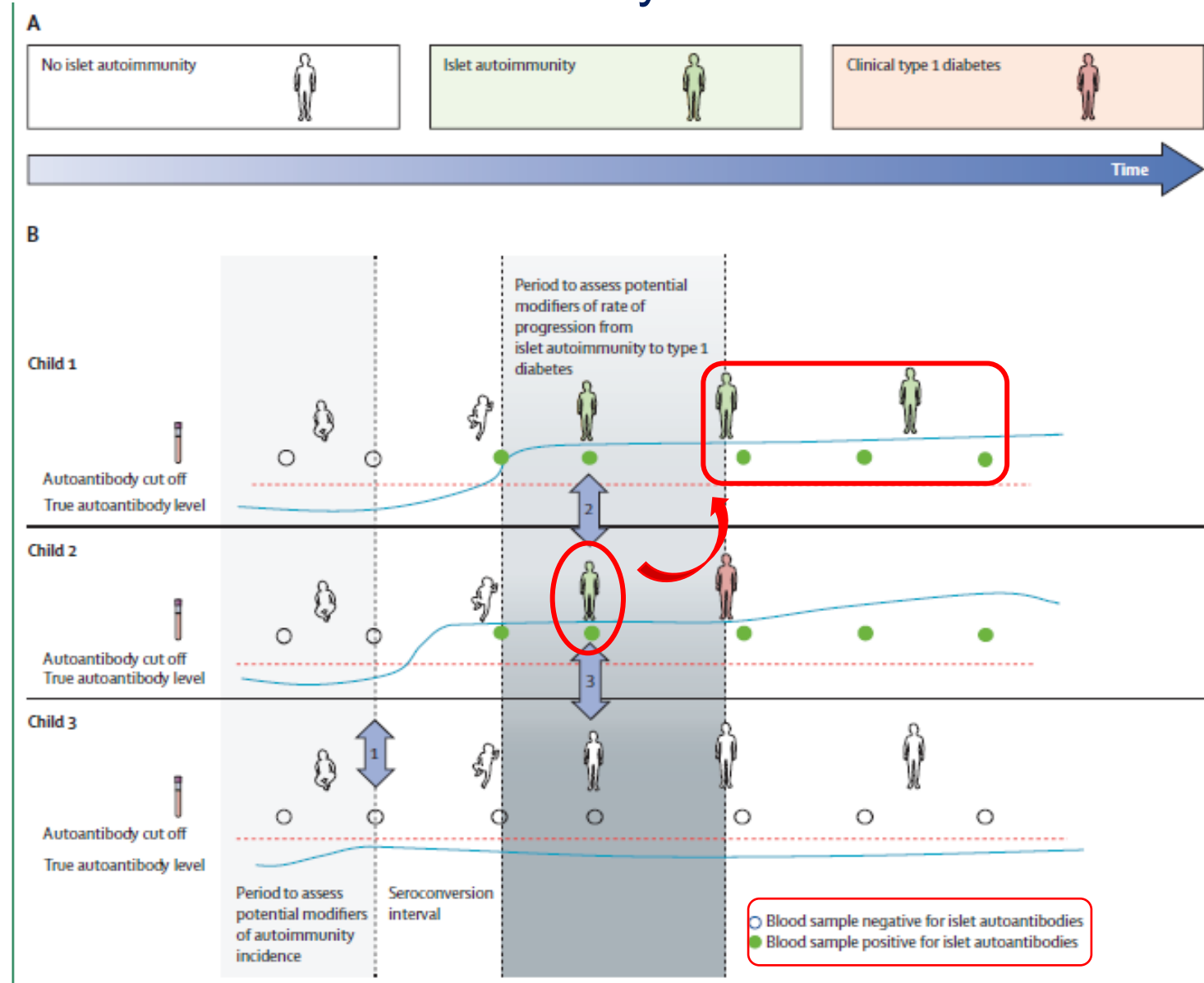
T1D prevention



Secondary prevention applied to T1D natural history

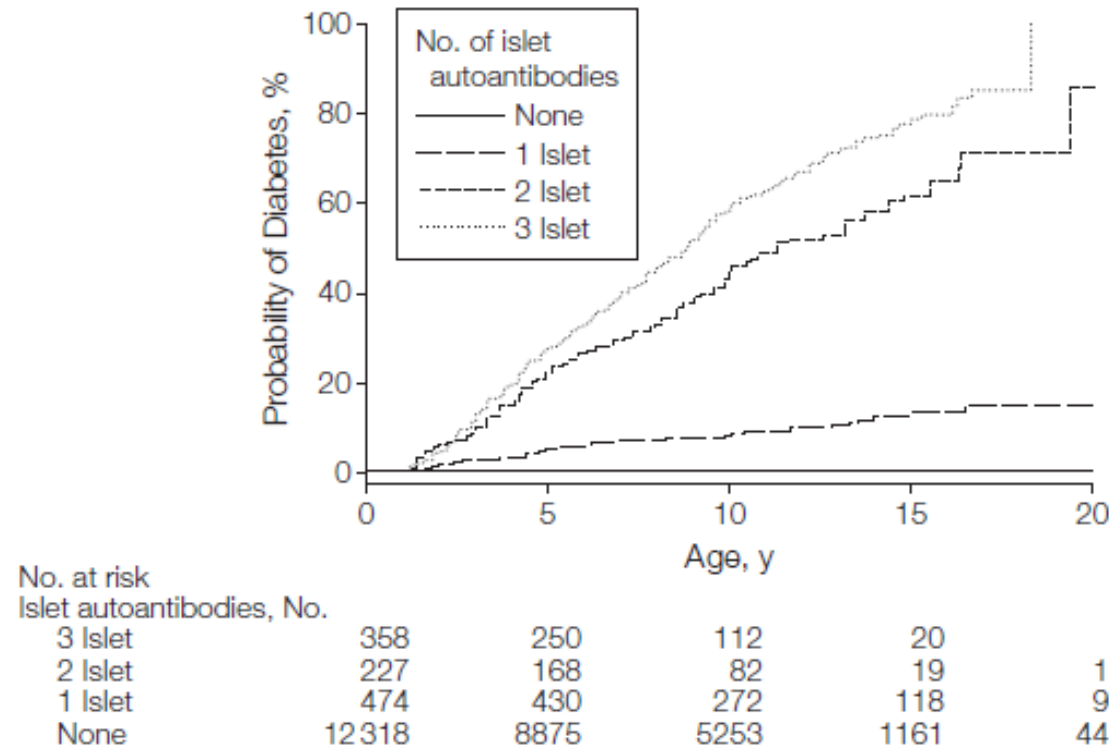


T1D: natural history



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



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

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-	Nicotinamide Placebo	Diagnosis of Type 1 diabetes	NS
DPT-1 Parenteral Insulin		Insulin Placebo	Diagnosis of Type 1 diabetes	NS
DPT-1 Oral Insulin	372	3-45 years	Diagnosis of Type 1 diabetes	NS

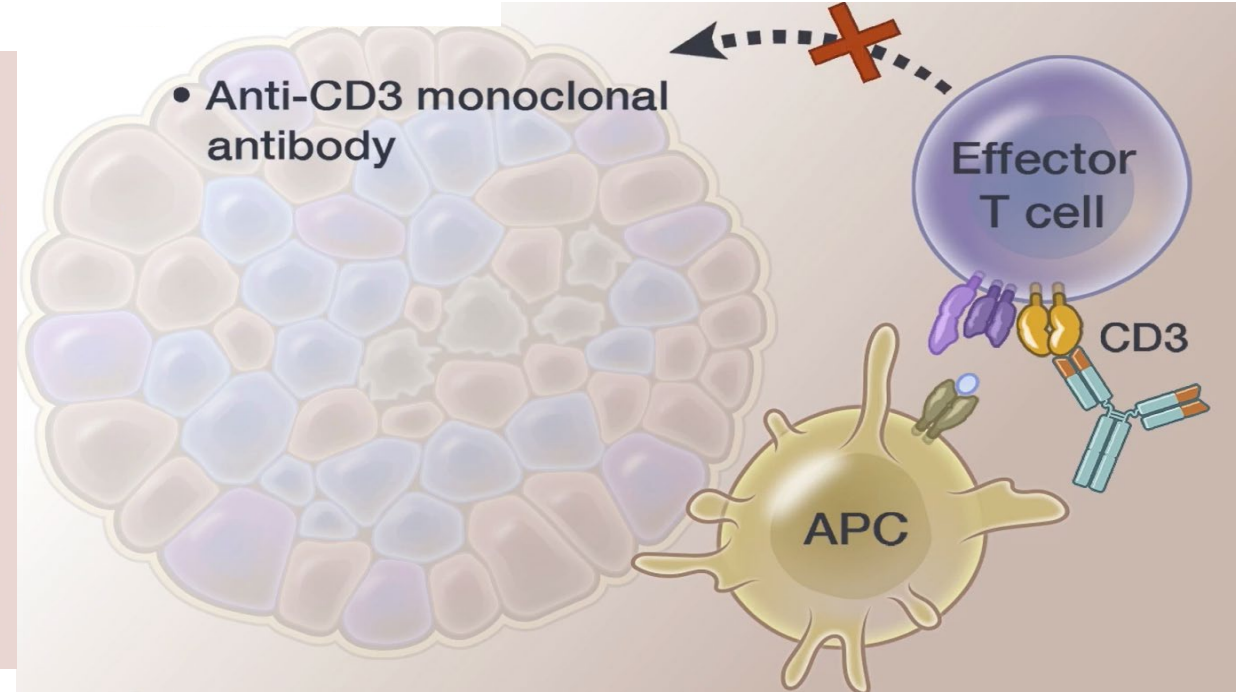
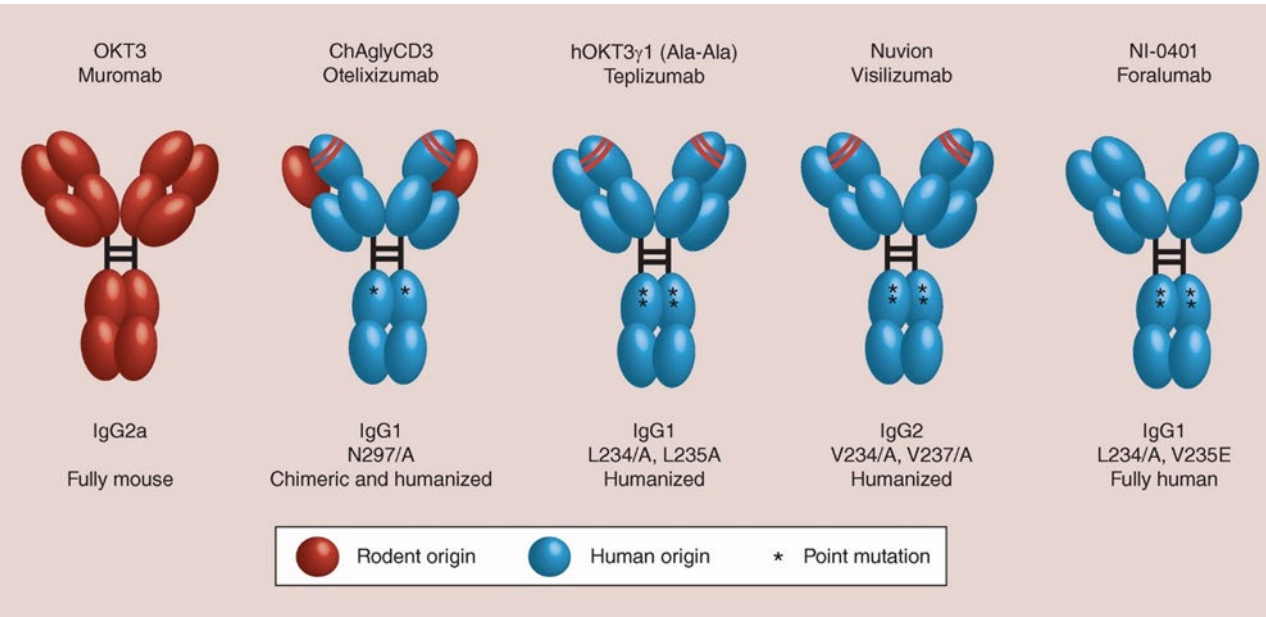
FAIL



Parental Insulin

The anti-CD3 era

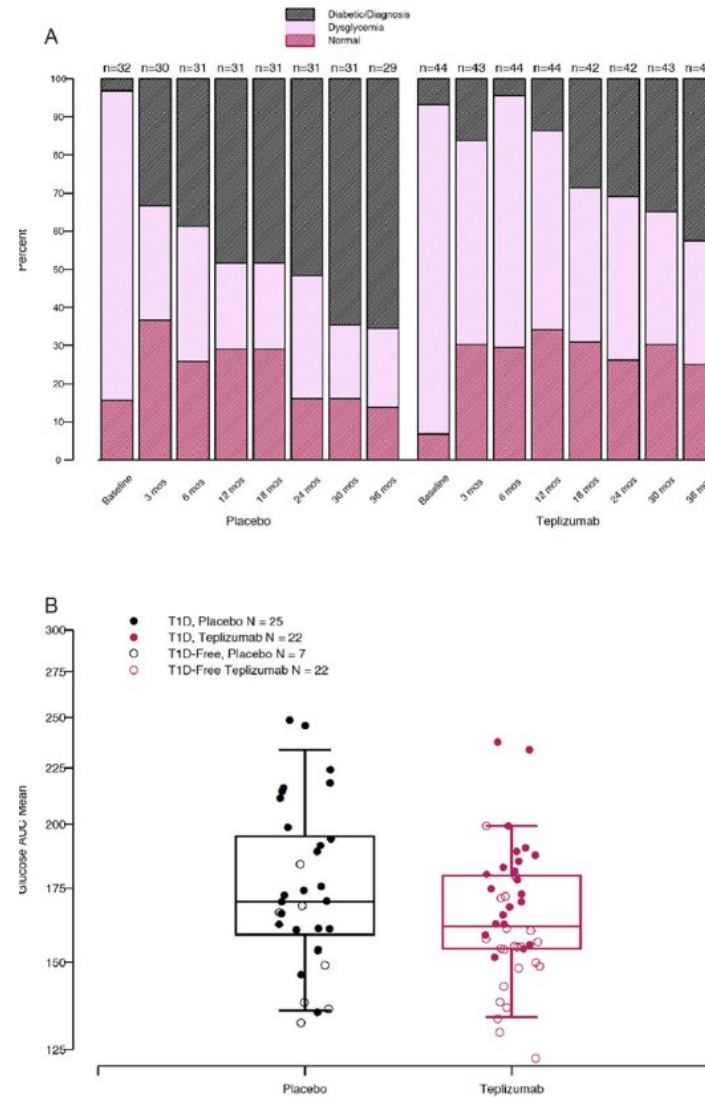
New generation of anti-human CD3 as compared with the mouse anti-human CD3 mAb OKT3



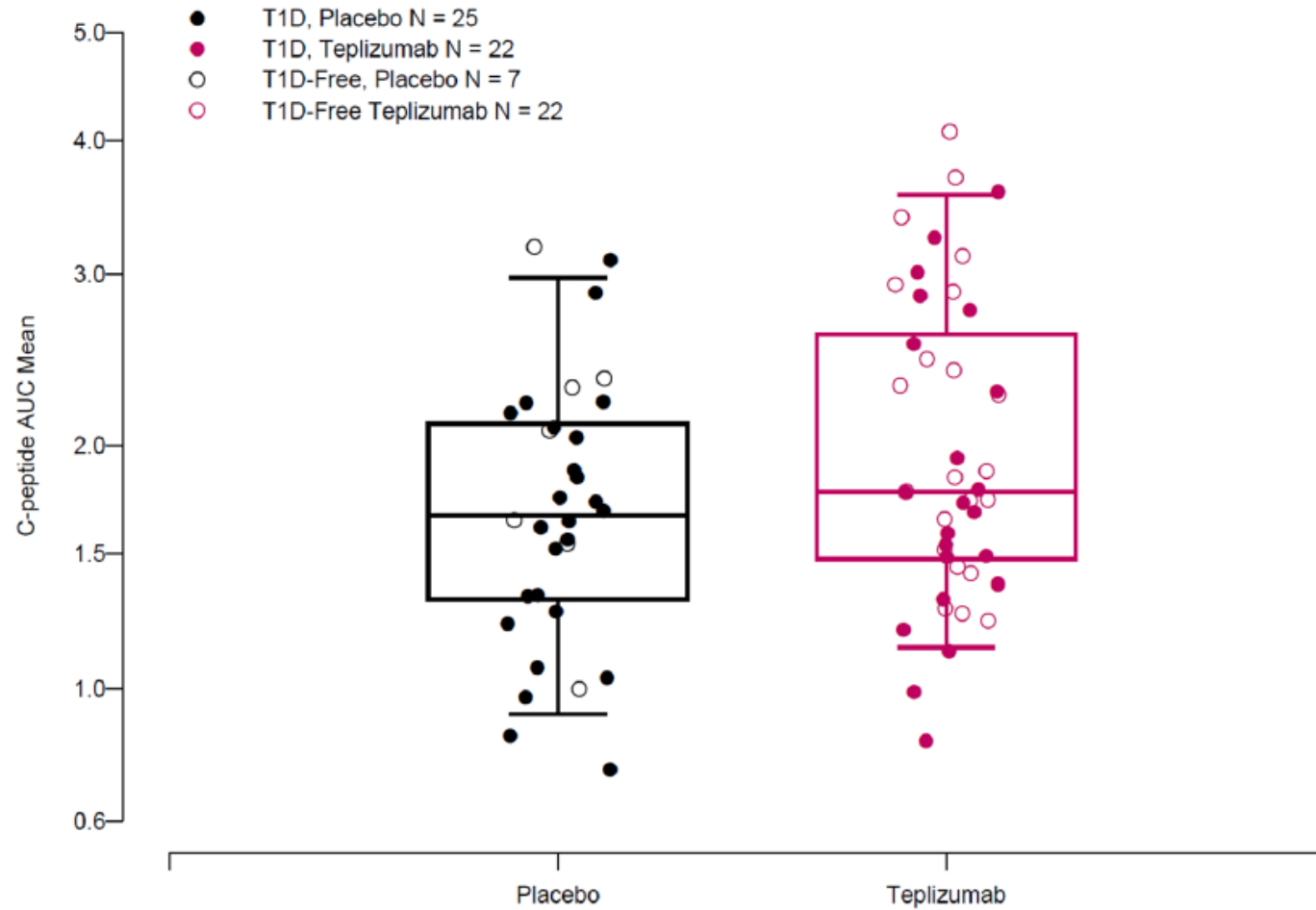
Anti CD3- Phase II Clinical Trials

First autor	Study design	Intervention	Primary outcome	Relevant findings
<i>Herold KC (2002)</i>	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/kg/day) (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);

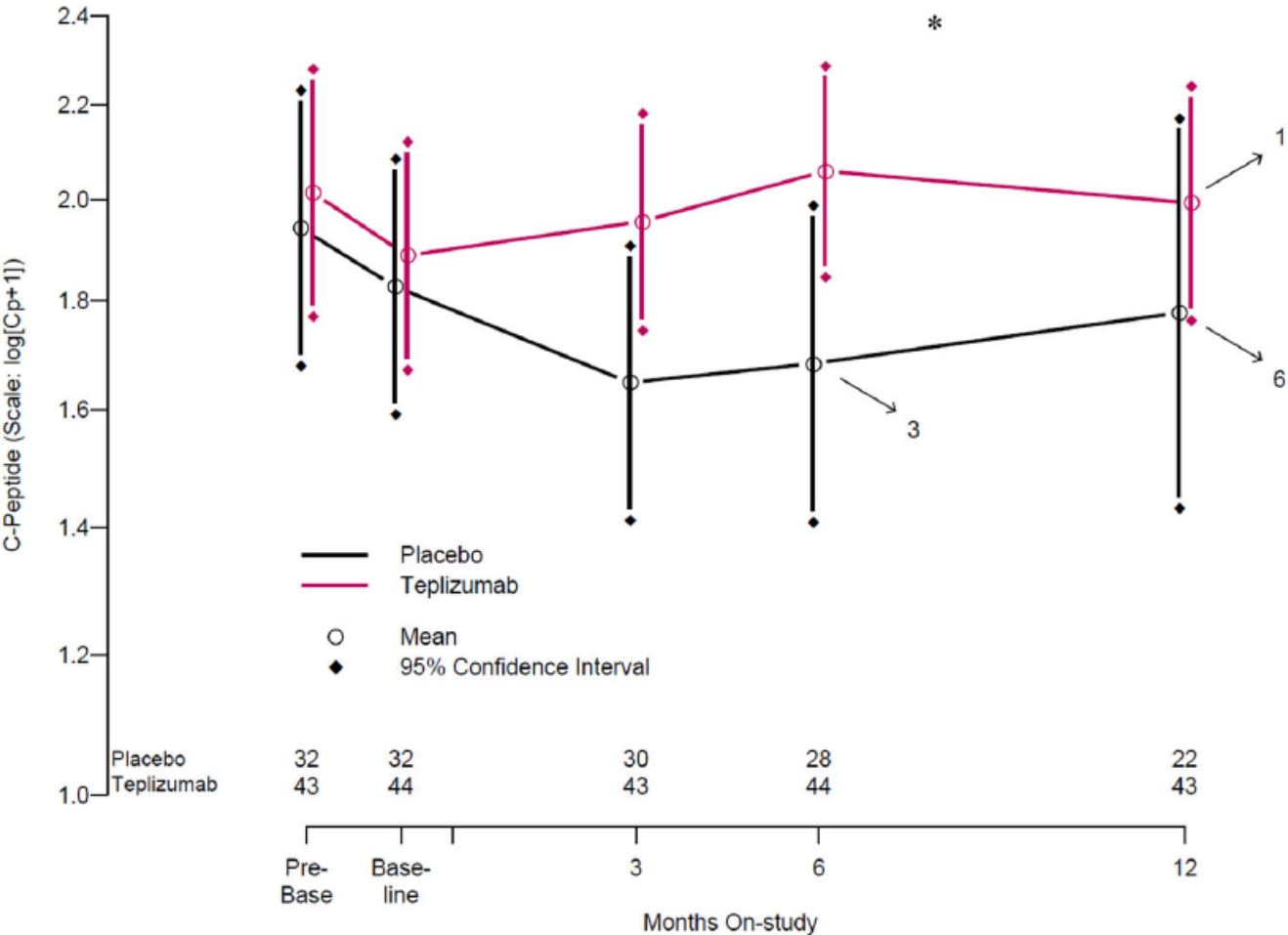
Improved glycemia in teplizumab treated participants is associated with maintenance of dysglycemic status



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



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



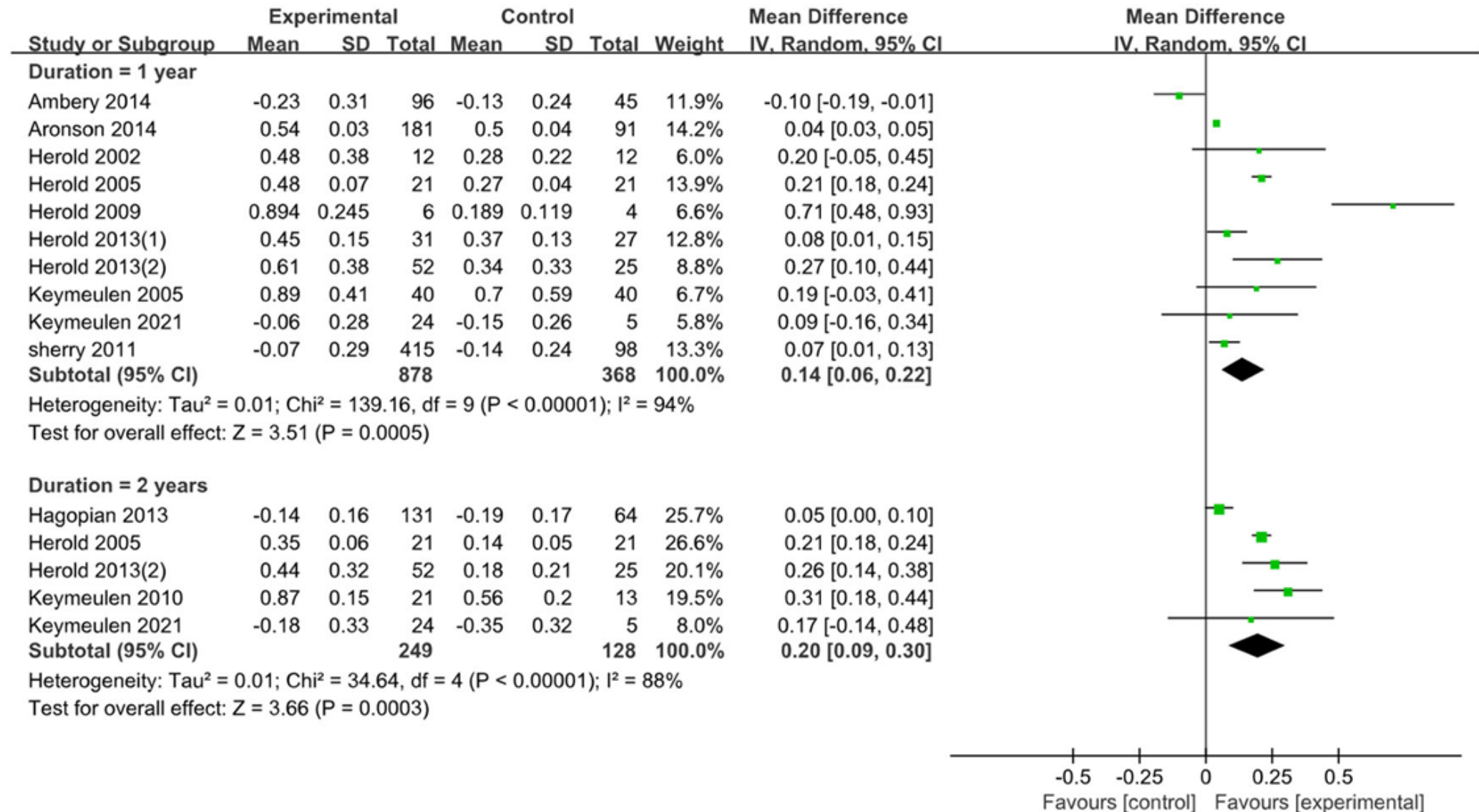
Results of Primary Prevention Trials for Type 1 Diabetes Published Through April 2024

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)	<i>Bifidobacterium longum</i> subsp. <i>infantis</i>	Target: 1,144	1:1		Autoantibodies	‡	‡

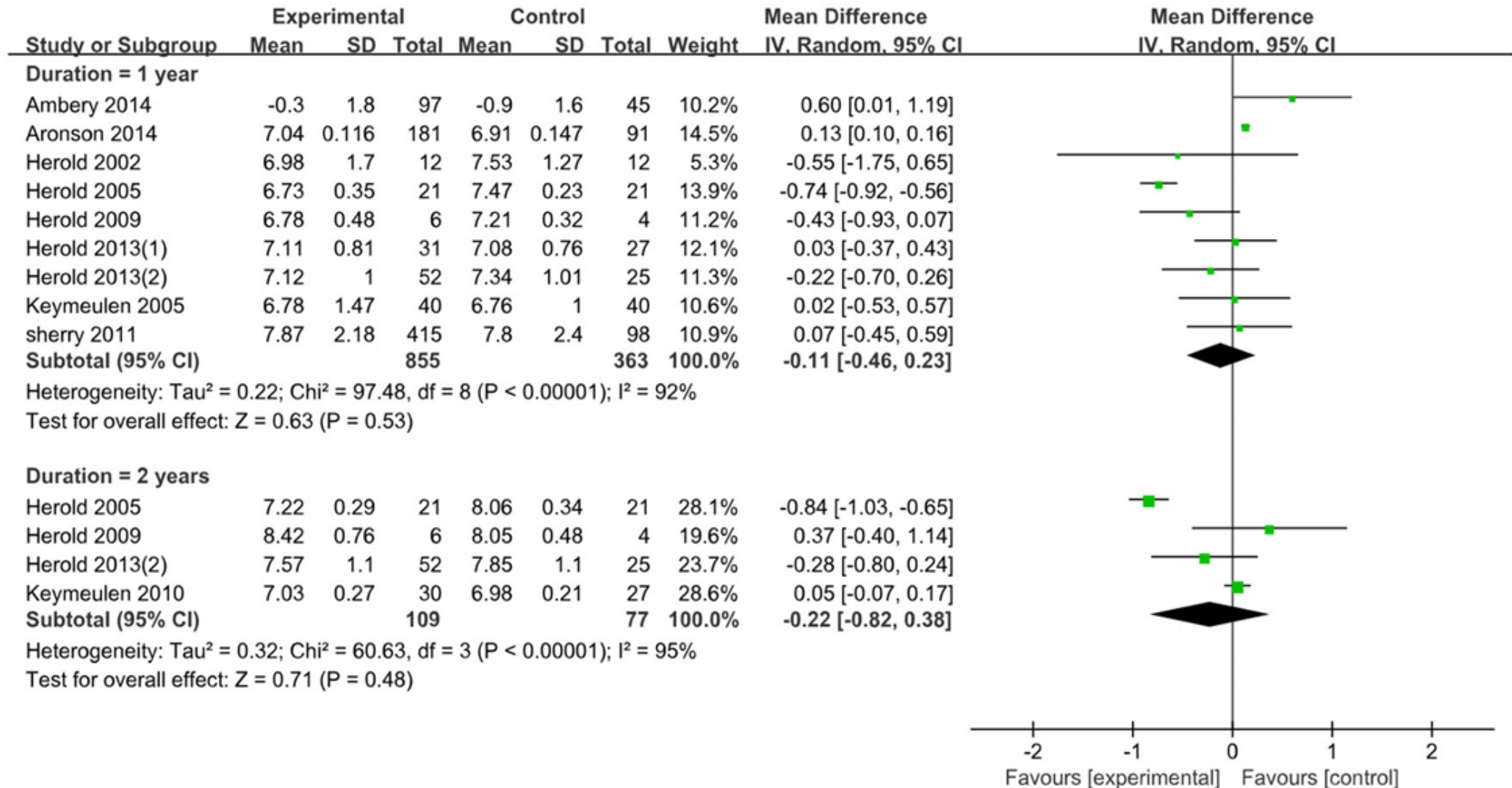
Results of Secondary Prevention Trials for Type 1 Diabetes Published Through April 2024

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	‡	‡

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



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



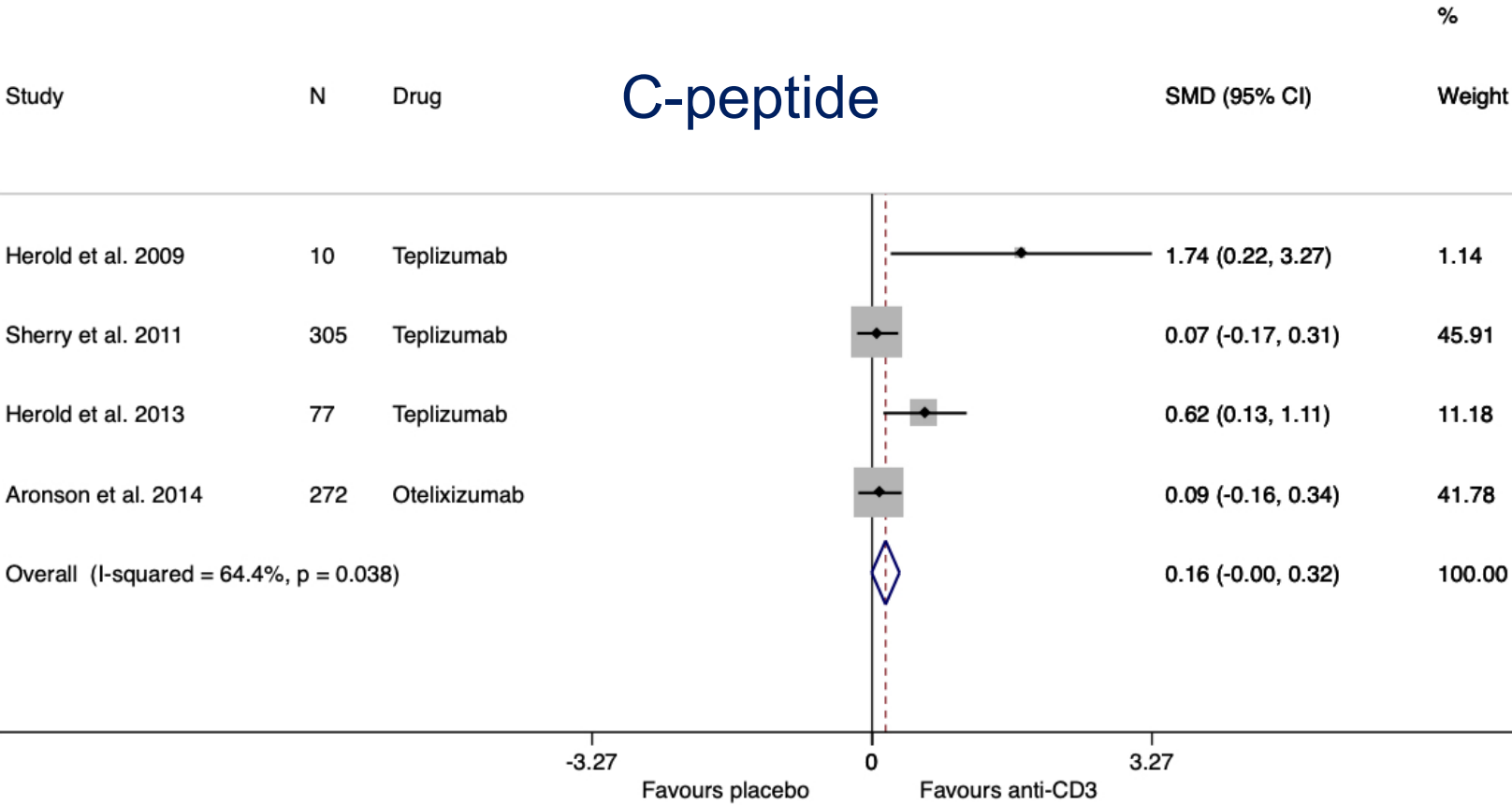
REVIEW

 Check for updates

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

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

C-peptide



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 min > 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)

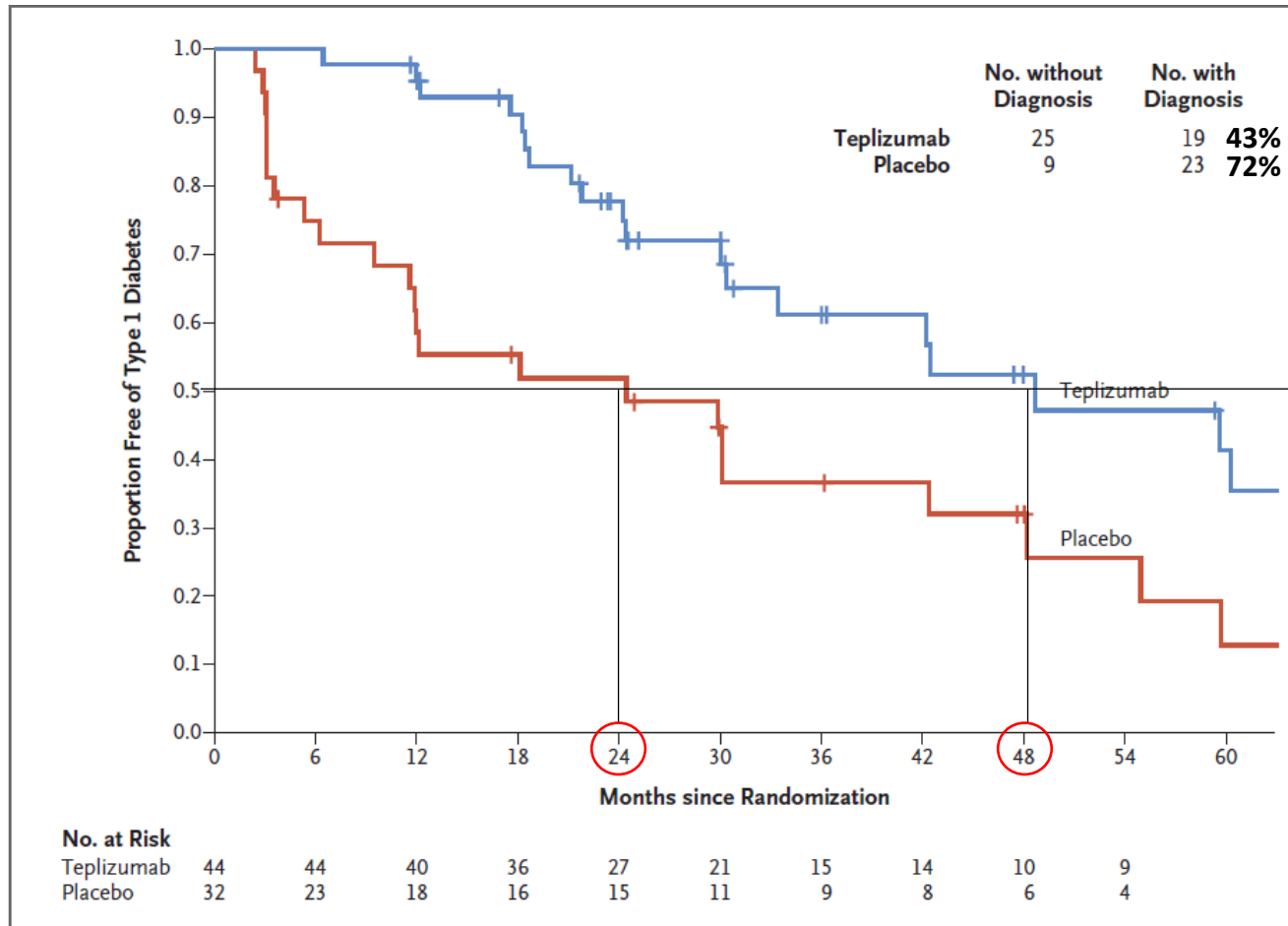
Outcome

- Disease onset

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)

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 double that in the
placebo group (28%)

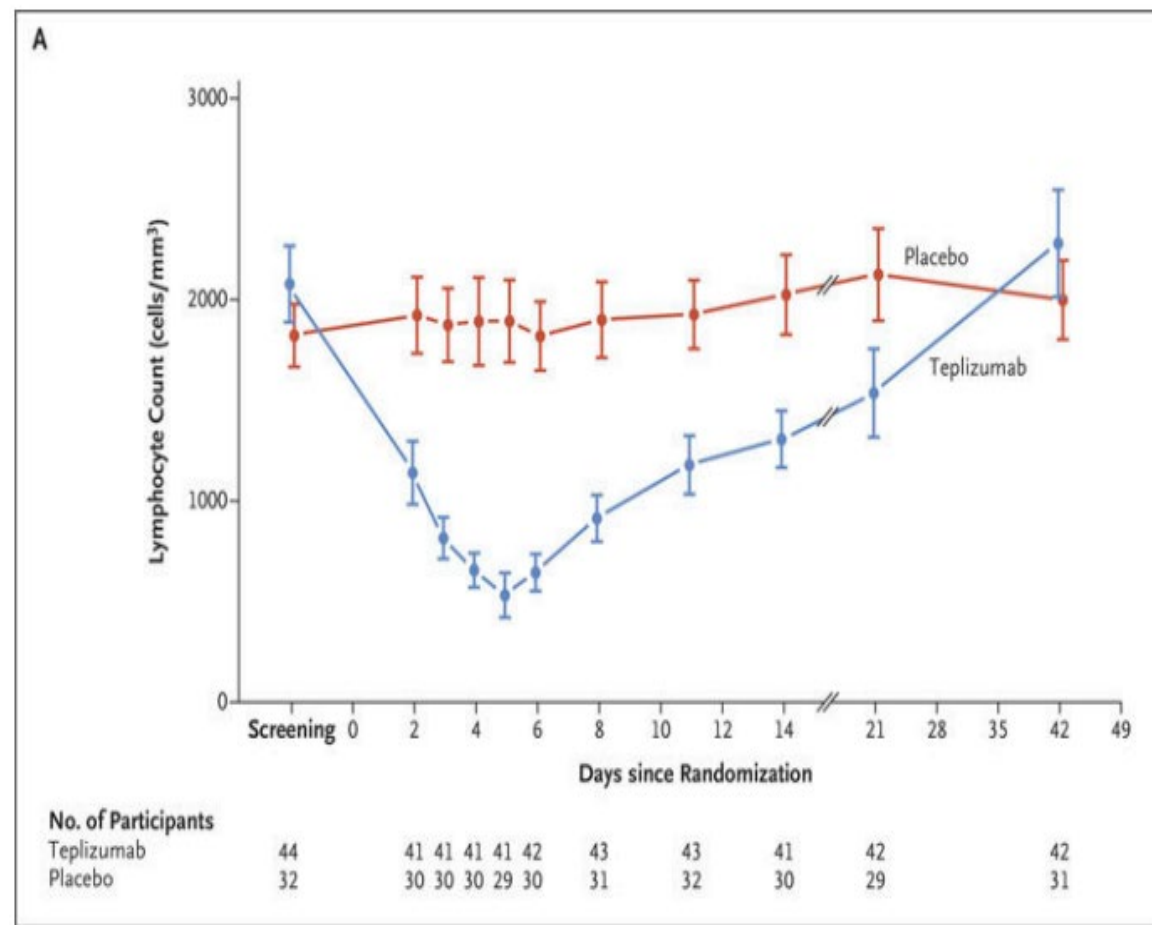
Teplizumab: side effects

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 ($P<0.001$).





HHS Public Access

Author manuscript

Sci Transl Med. Author manuscript; available in PMC 2021 November 23.

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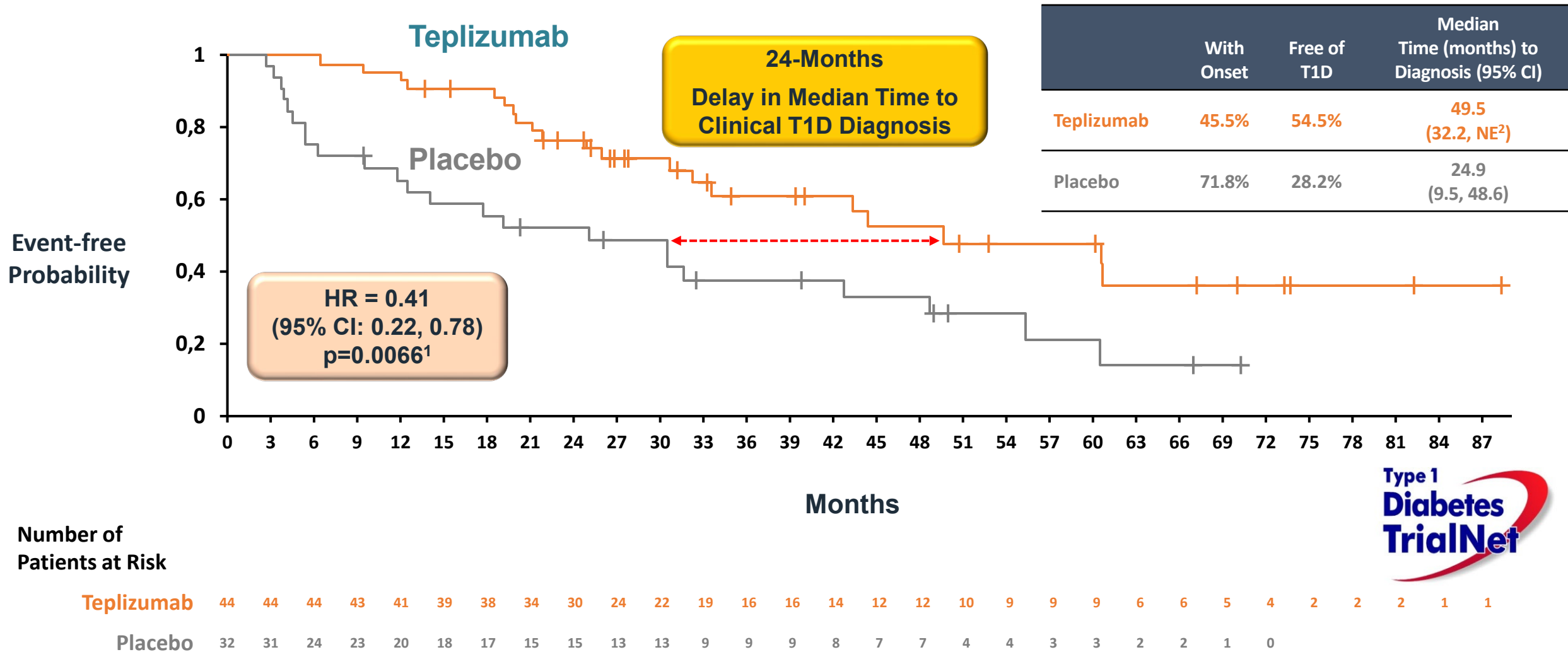
Sci Transl Med. 2021 March 03; 13(583): . doi:10.1126/scitranslmed.abc8980.

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

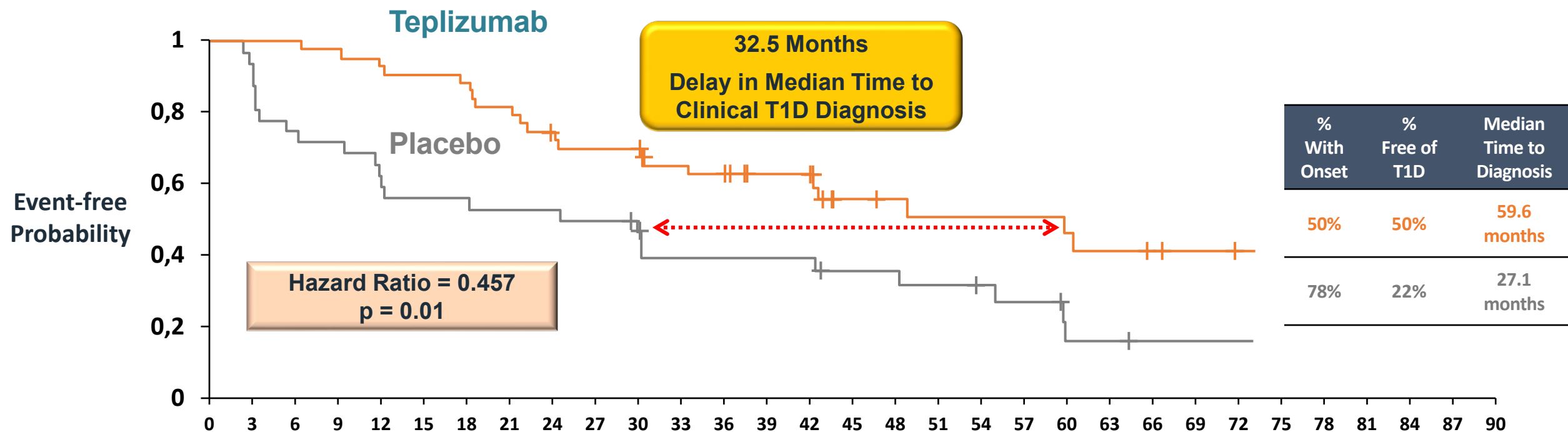
Emily K. Sims¹, Brian Bundy³, Kenneth Stier⁴, Elisavet Serti⁵, Noha Lim⁵, S Alice Long⁶, Susan M Geyer⁷, Antoinette Moran⁸, Carla J Greenbaum⁶, Carmella Evans-Molina², Kevan C. Herold⁴ Type 1 Diabetes TrialNet Study Group

Teplizumab Prevention Study

Significantly Delayed Onset of Stage 3 Clinical T1D vs Placebo



Teplizumab Prevention Study Sustained Delay over Extended Follow-Up

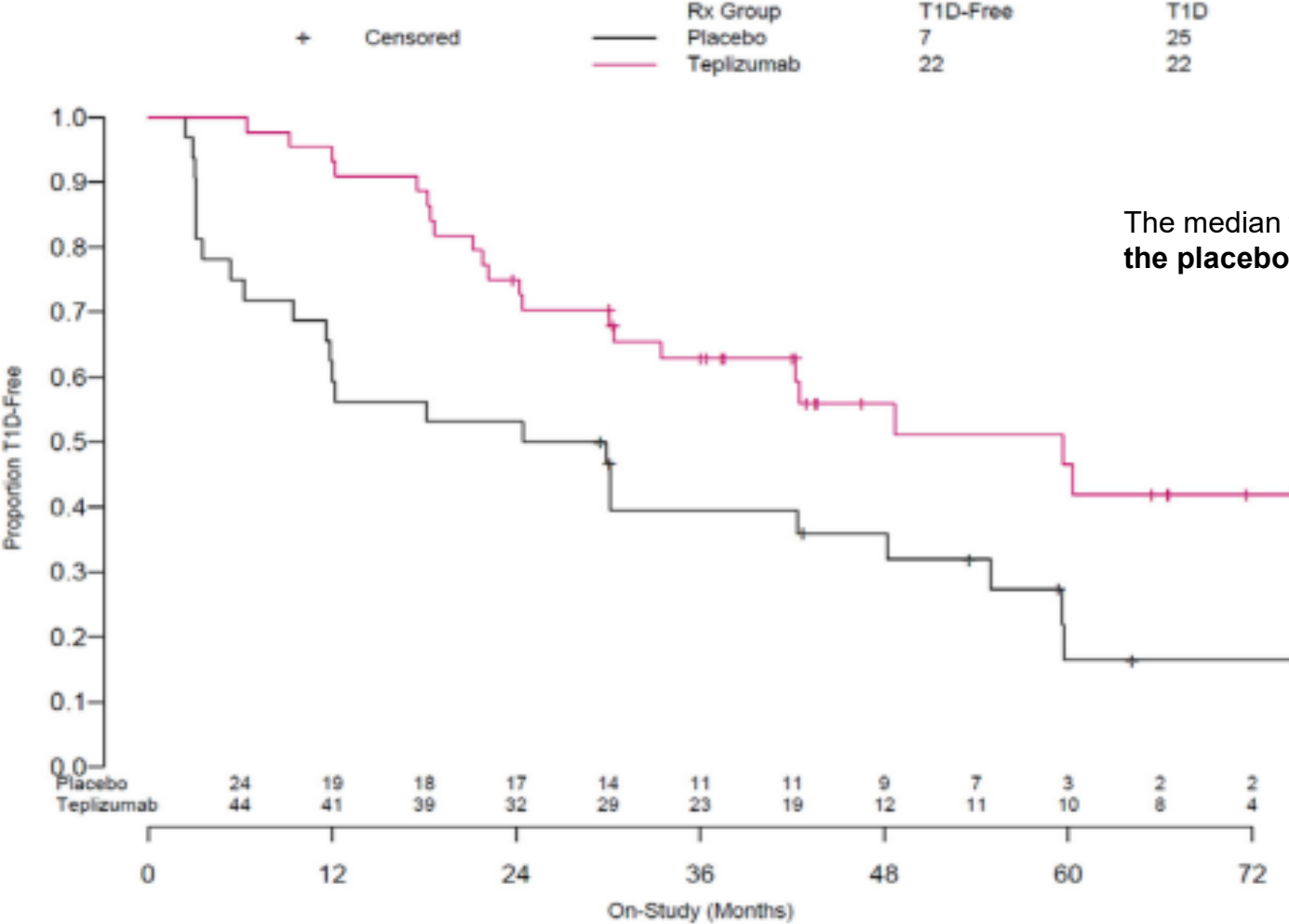


Number of Patients at Risk

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



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



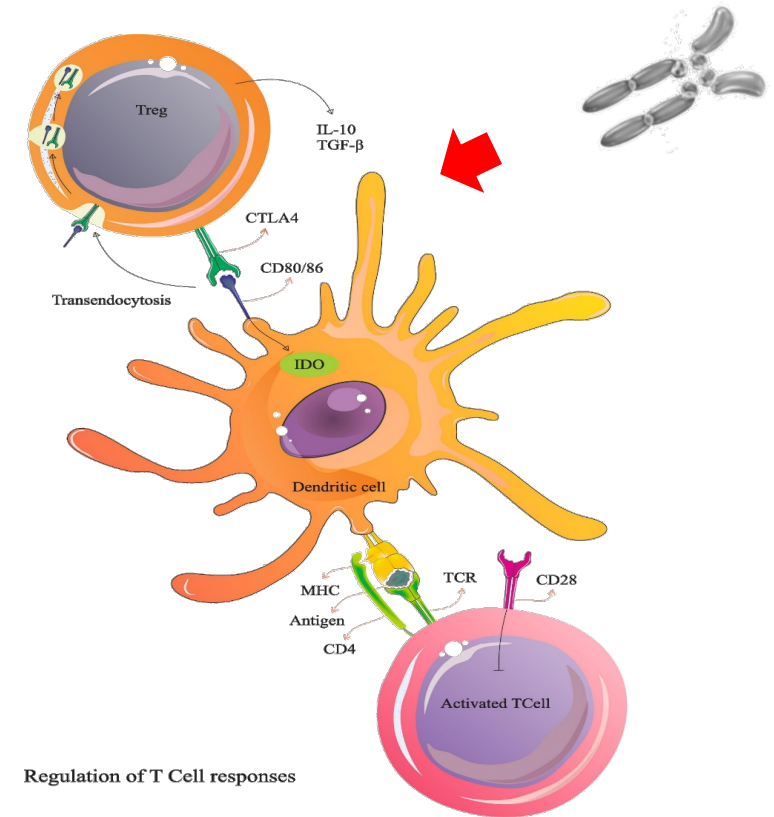
Anti-CTLA4: Abatacept

© 1996 Oxford University Press

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 Buzzetti¹, Lynn E. Pritchard³, Bart Van der Auwera⁴, Claudio Giovannini¹, Emanuele Bosi⁵, Maria Teresa Martinez Larrad⁶, Manuel Serrano Rios⁶, C. C. Chow⁷, Clive S. Cockram⁷, Karen Jacobs⁸, Catherine Mijovic⁸, Stephen C. Bain⁸, Anthony H. Barnett⁸, Christina L. Vandewalle⁹, Frans Schuit⁴, Frans K. Gorus⁹, Belgian Diabetes Registry¹⁰, Roberto Tosi², Paolo Pozzilli¹ 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

Anti-CTLA4: Abatacept

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

Population

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

Intervention

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

Control

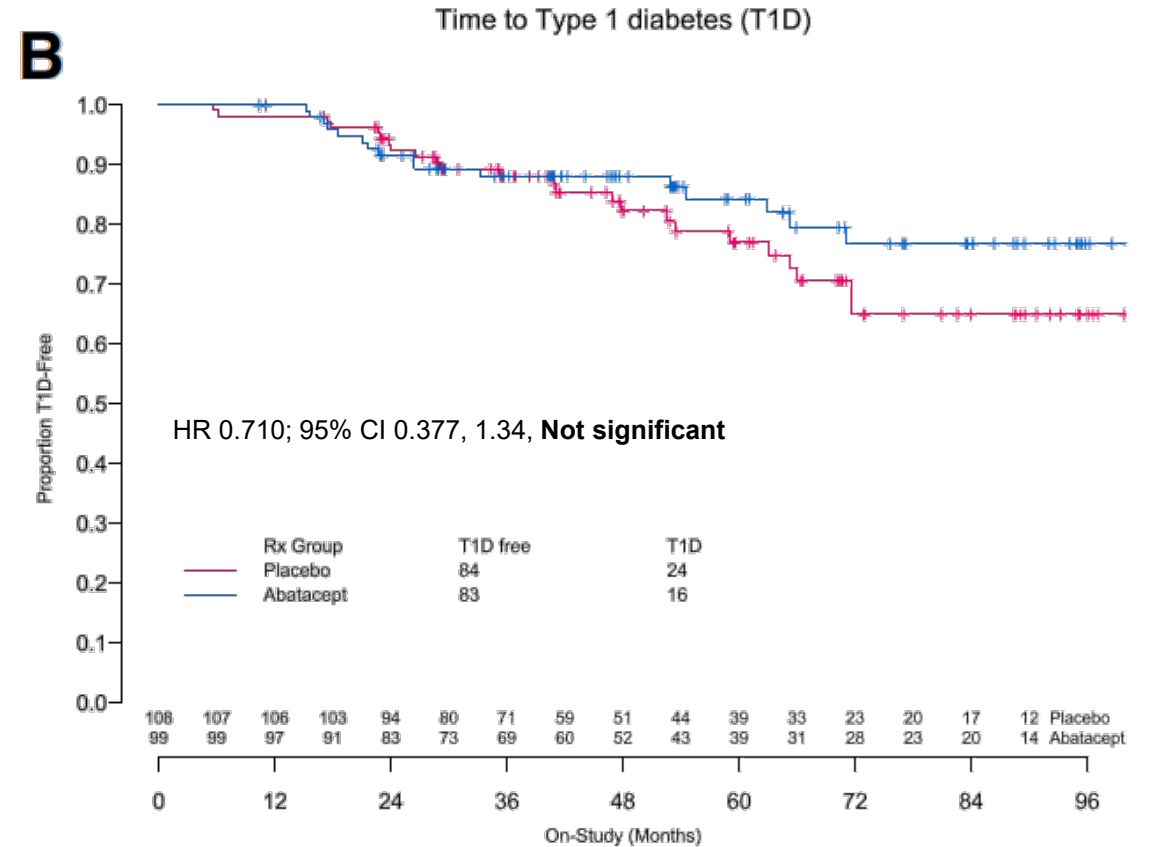
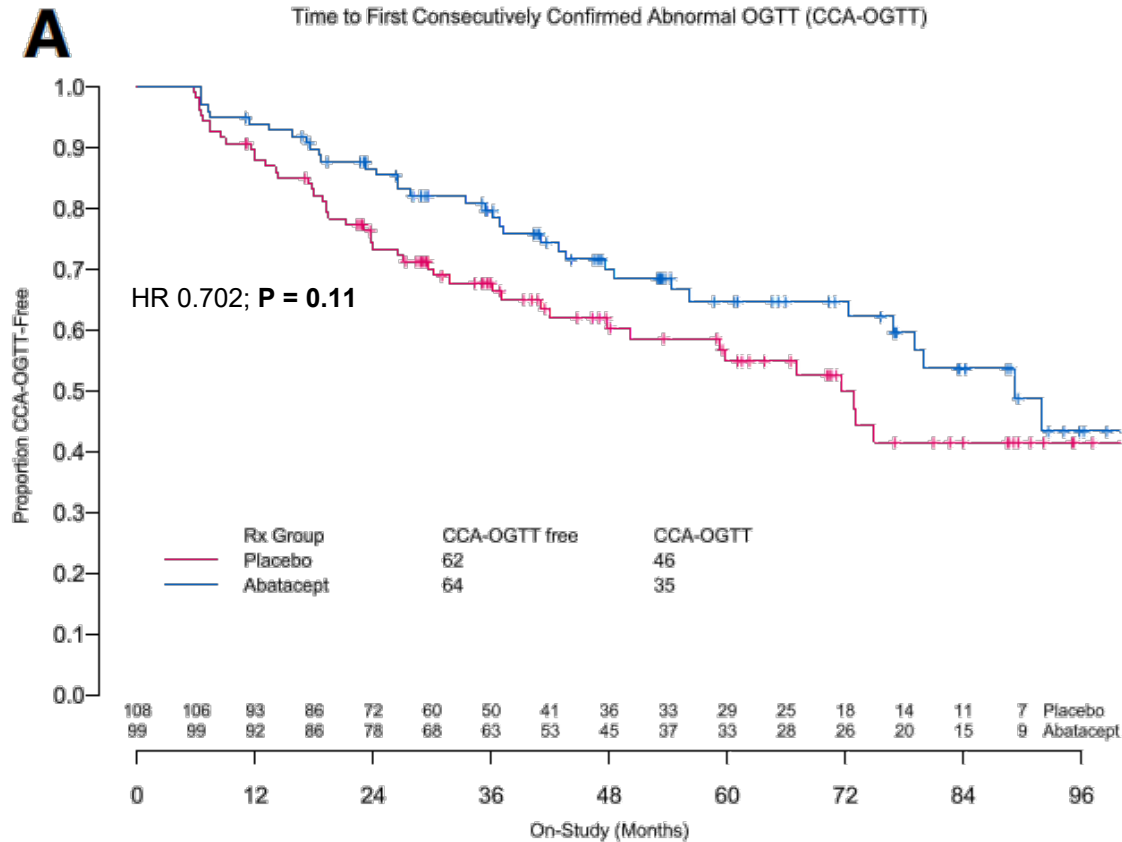
- Vs Placebo (n=111)

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

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

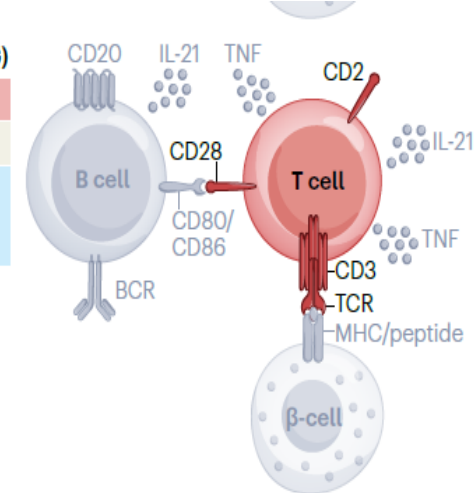
GCSF: granulocyte colony stimulating factor

Anti-thymocyte globulin (ATG)

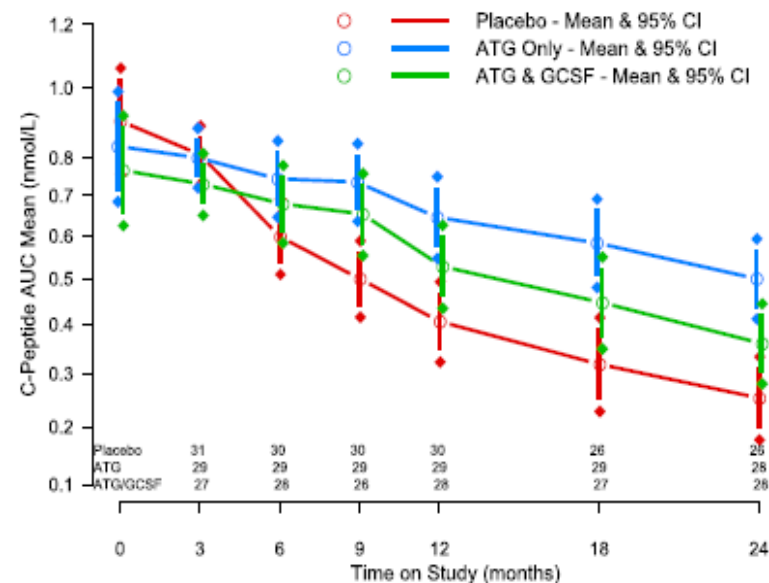
Depletes T cells

New-onset T1D

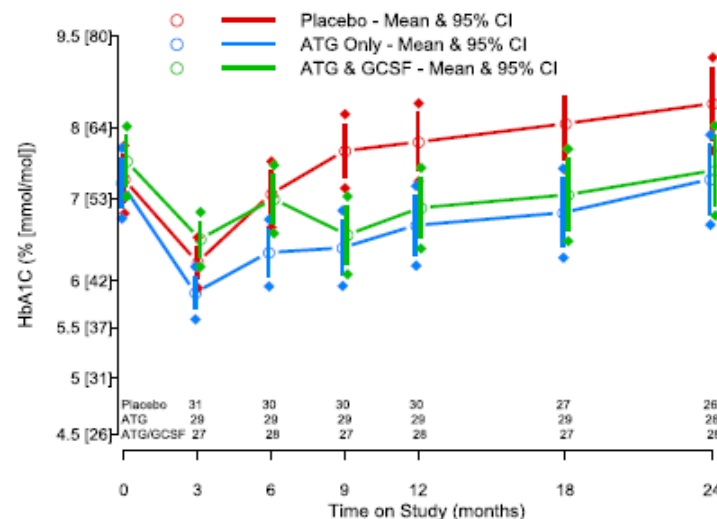
Preserved C-peptide responses and reduced HbA_{1c} levels



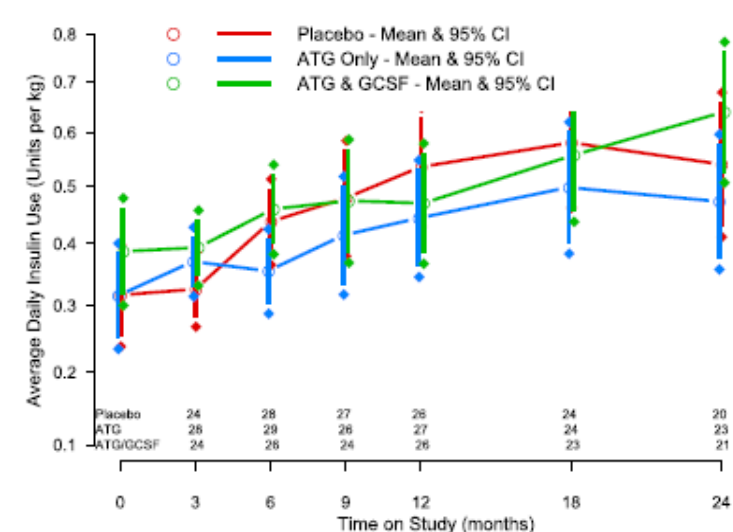
A C-Peptide AUC Mean Over Time By Treatment Group



C HbA_{1c} Over Time by Treatment Group



D Insulin Use (Units per kg) Over Time by Treatment Group



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 patients with T1D and it **is the first disease modifying 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.....