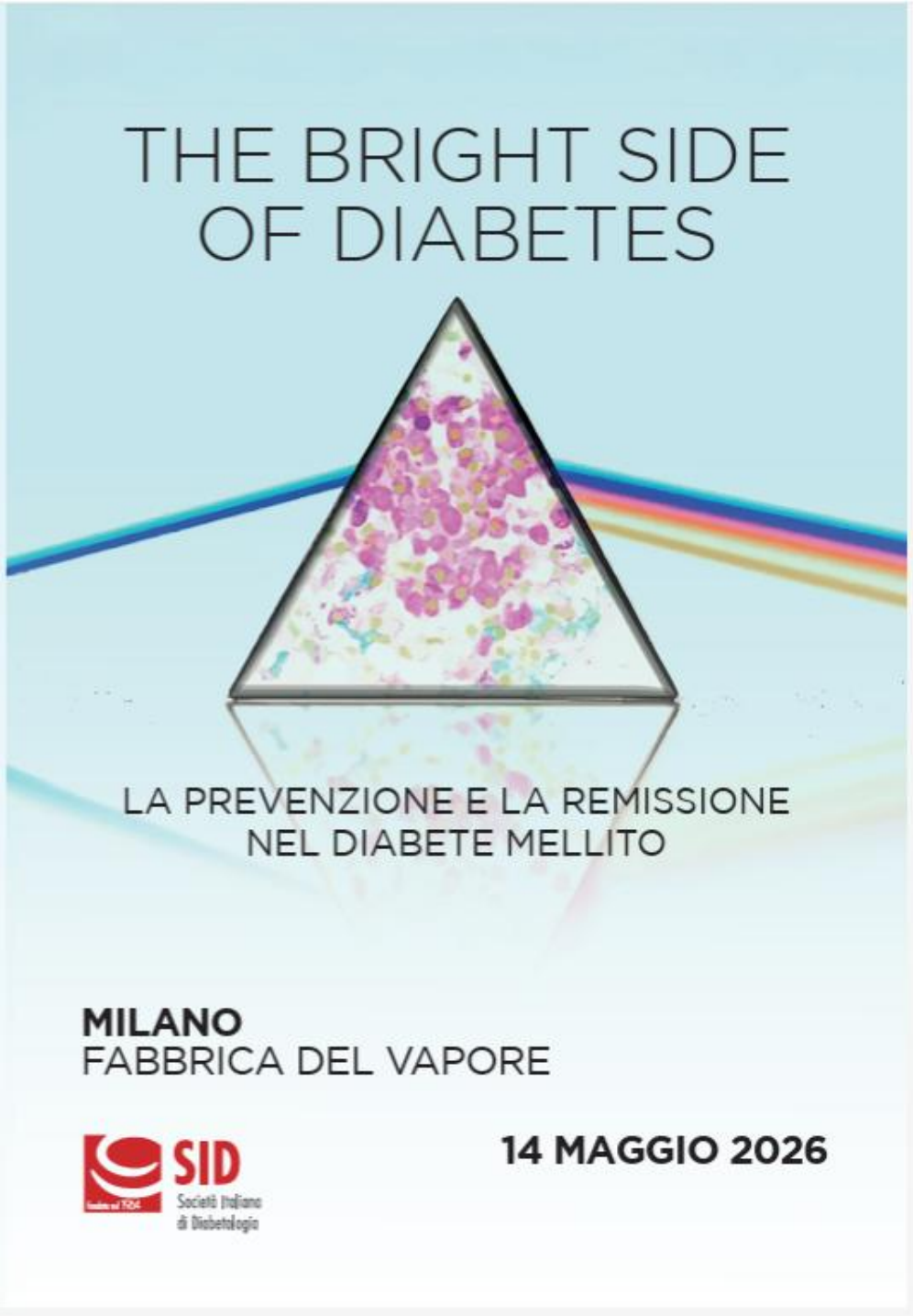


UNIVERSITÀ DEL PIEMONTE ORIENTALE

Pediatria Novara

Terapia immunofarmacologica nel Diabete Tipo 1

Valeria Castorani

Università Del Piemonte Orientale
SCDU Pediatria – Diabetologia pediatrica
AOU Maggiore Della Carità, Novara

La dott.ssa Valeria Castorani dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

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.).

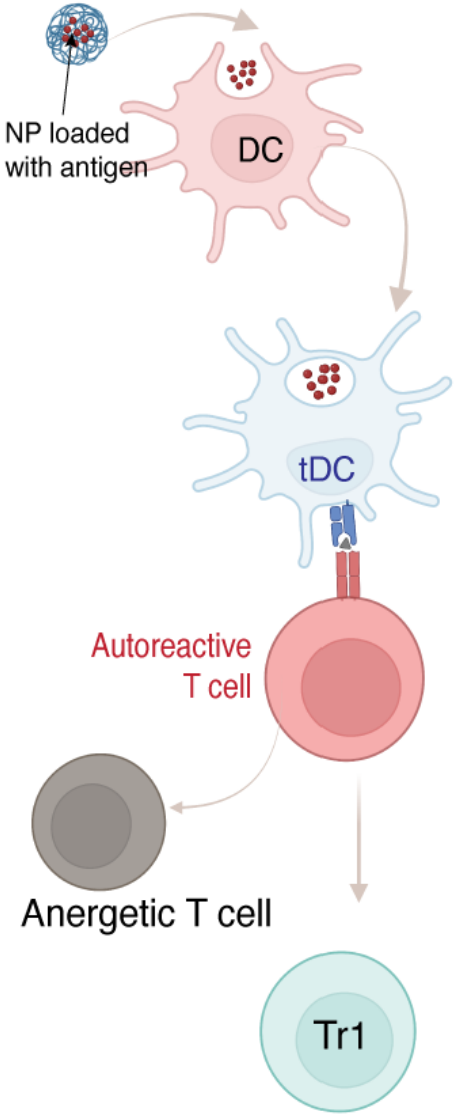
Type 1 Diabetes: Evolving Understanding

YESTERDAY

- Type 1 diabetes was considered to occur with the rapid onset of **symptomatic hyperglycemia**.
- It was also believed that nearly all insulin-producing beta-cells were destroyed by the time of clinical diagnosis.

NOW

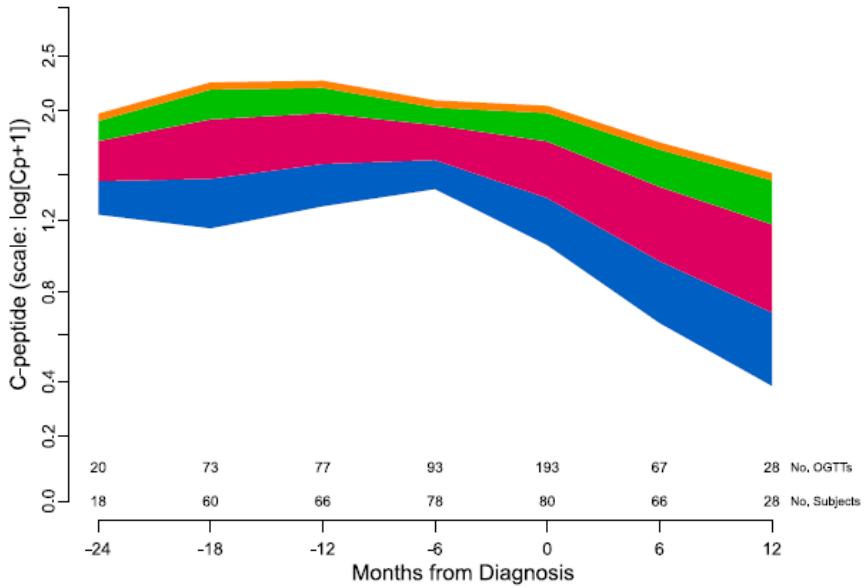
- Type 1 diabetes is a chronic, progressive disease, where beta-cell function deteriorates over time but is sufficient, during early, **presymptomatic phases** of disease, to circumvent overt signs and symptoms of hyperglycemia.
- For presymptomatic stages of T1D, there is an **opportunity window for immunotherapies.**



Laura M. Jacobsen et al. Diabetes Care. 2025

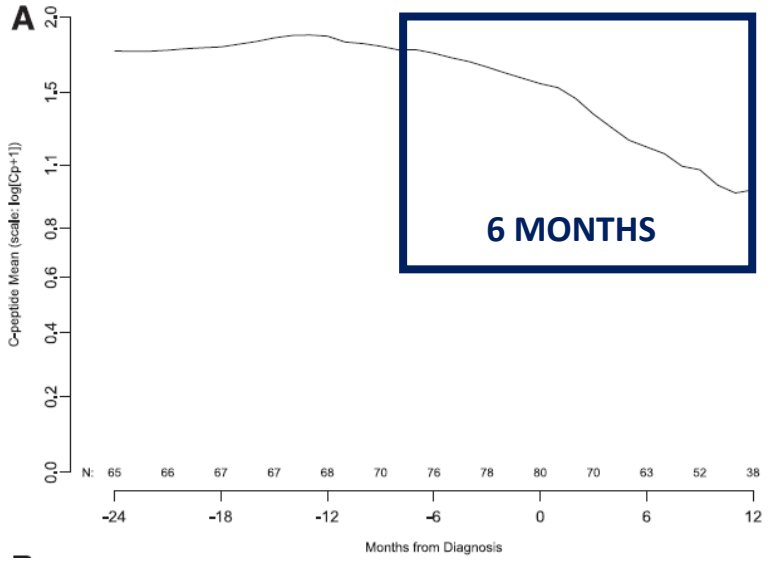
C-Peptide Levels in Subjects Followed Longitudinally Before and After Type 1 Diabetes Diagnosis in TrialNet

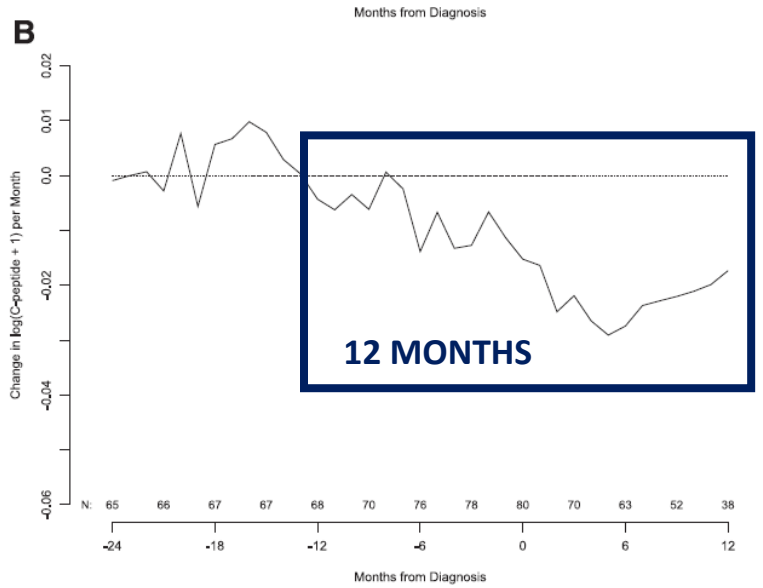
Diabetes Care 2020;43:1836–1842 | https://doi.org/10.2337/dc19-2288



- Older subjects had higher C-peptide levels throughout the time range, and age influenced the rate of decline.

- C-peptide did not change significantly **until 6 months before the clinical diagnosis of T1D** and continued to decline post-diagnosis.
- The rates of decline for the first 6 months post-diagnosis were **similar to the 6 months pre-diagnosis**.
- **Discordant timing** between accelerated b-cell dysfunction and the current glucose thresholds for clinical diagnosis.
- To preserve b-cell function, **disease-modifying therapy should start at or before** the acute decline in C-peptide.





Magdalena M. Bogun et al. Diabetes Care. 2020

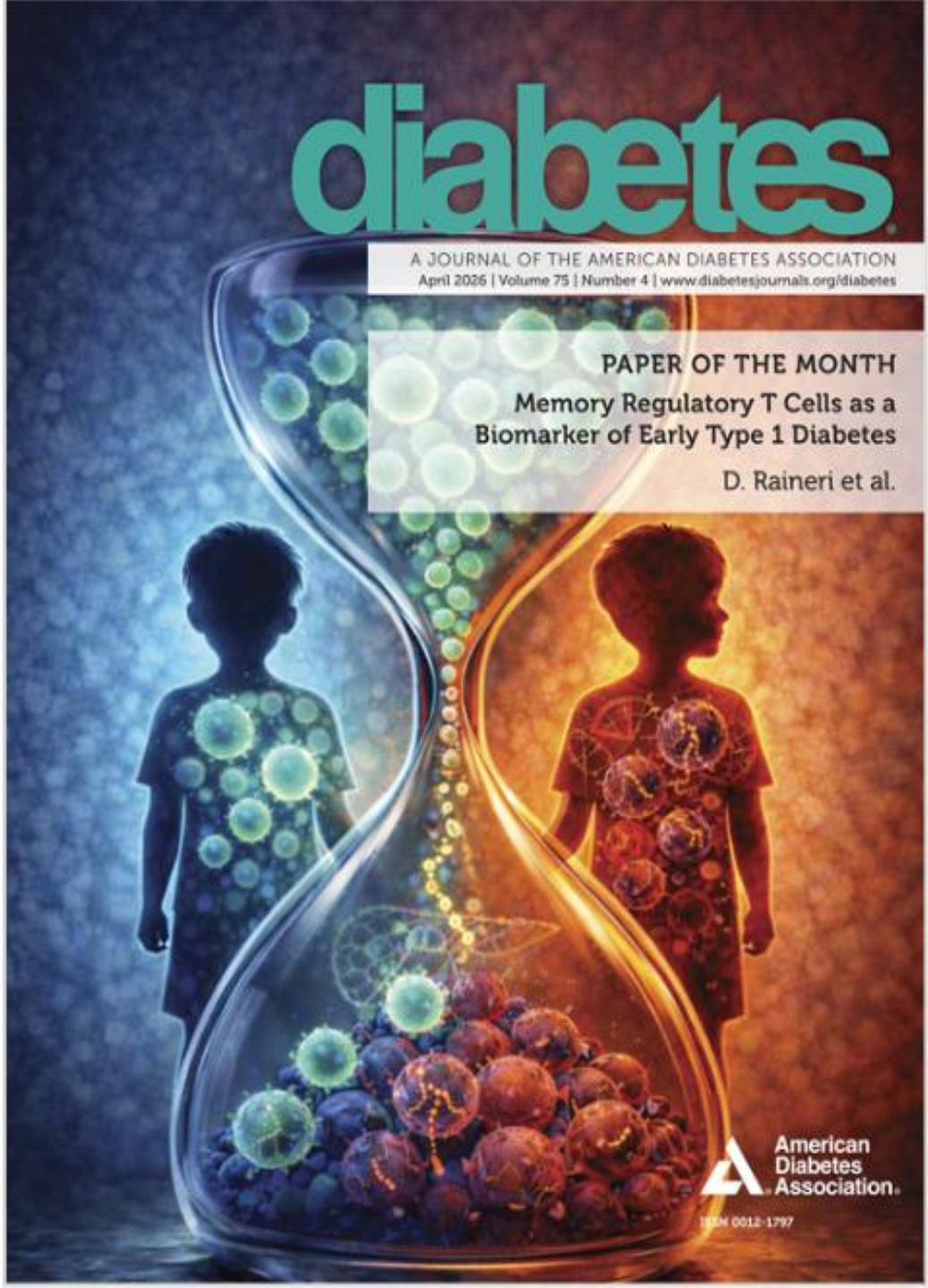
Memory Regulatory T Cells as a Biomarker of Early Type 1 Diabetes

Davide Raineri,[1,2] Silvia Savastio,[3] Simonetta Bellone,[1,3] Lorenza Scotti,[4] Camilla Barbero-Mazzucca,[1,2] Giuseppe Cappellano,[1,2] Flavia Prodam,[1,5] Erica Pozzi,[3] Ivana Rabbone,[1,3] and Annalisa Chiocchetti[1,2]

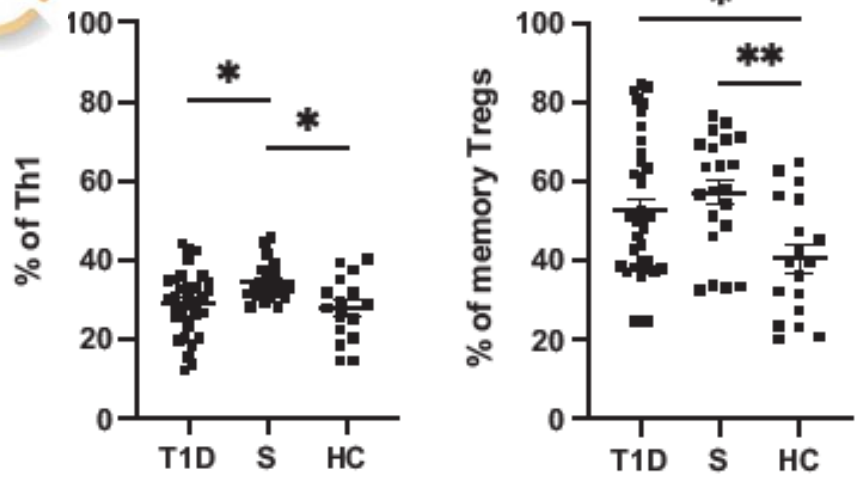
Diabetes 2026;75:676–682 | https://doi.org/10.2337/db25-0161

> T1D is a **multifactorial autoimmune disease** characterized by the progressive, immune-mediated destruction of insulin-producing pancreatic beta-cells; driven by a breakdown in self-tolerance and T cell-mediated immune attack of pancreatic beta-cells.

- Complex immune mechanisms, including cytotoxic autoreactive CD8+ T cells and sustained release of proinflammatory cytokines that contribute to beta-cell dysfunction and loss.
- Growing evidence points to the involvement of a broader network of both innate and adaptive immune cells.



01



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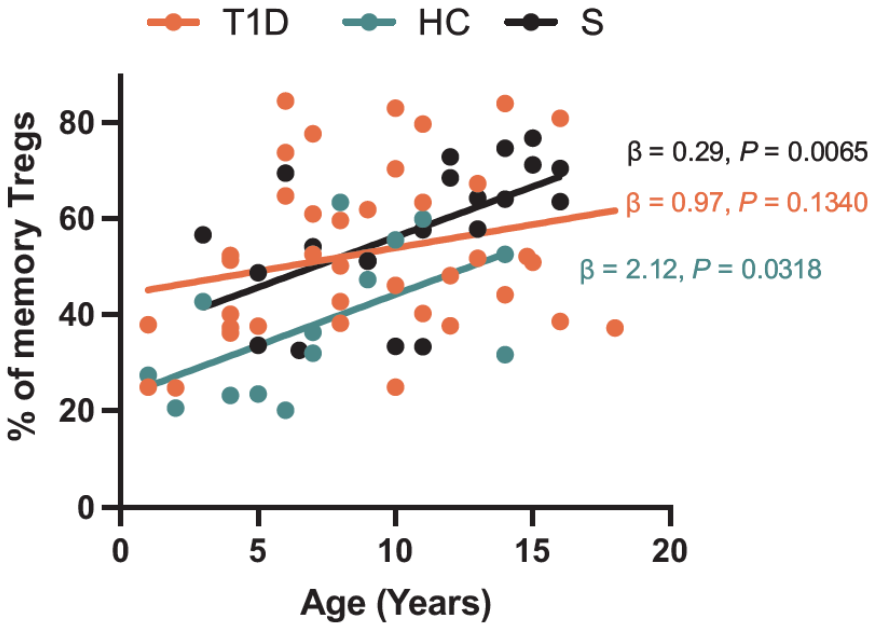


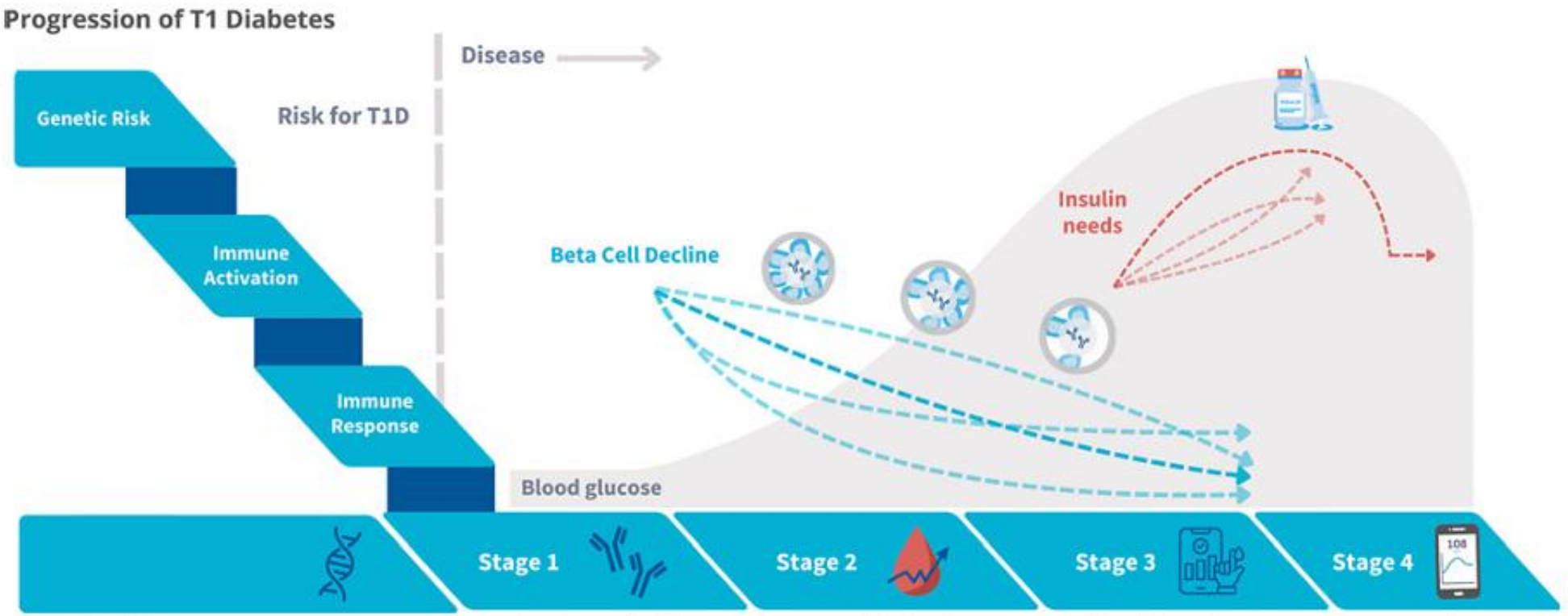
→ The results in individuals with T1D define a distinct immunological landscape characterized by an expansion of memory Tregs compared with HC participants.

→ A similar increase was also observed in their unaffected siblings, who nonetheless exhibited a **unique intermediate immune phenotype** marked by increased mDCs and CD8+ effector memory T cells, together with reduced intermediate monocytes and naïve Tregs. Siblings occupy a **transitional state between immune health and overt disease**.

The enrichment of T1D-associated risk polymorphisms in genes regulating Treg biology among siblings supports a genetically driven contribution to these immune alterations.

→ This finding aligns with previous reports describing increased yet functionally impaired memory Tregs in T1D.

ISPAD Guidelines



Genetic Risk
Individuals with a first degree relative with T1D are 15x increased risk of developing T1D

- Immune response (development of single autoantibody)
- Immune activation (beta cells attacked)

2+ Islet Autoantibodies Confirmed

- Normal blood glucose
- Pre-symptomatic

Start of T1D

Near 100% lifetime risk of progression to Stage 3

2+ Autoantibodies Plus Dysglycemia

- Abnormal glucose tolerance
- Usually pre-symptomatic
- More rapid progression of T1D

Stage 2a: Shows as early, mild dysglycemia
Stage 2b: Shows as late, robust dysglycemia without reaching threshold of Stage 3

- Tools available to predict rate of progression to Stage 3
- Progression quicker in younger people

Clinical diagnosis

- Blood glucose meets ADA diagnostic thresholds
- Multiple islet autoantibodies

Stage 3a: Asymptomatic, may not require insulin immediately
Stage 3b: Symptomatic, requires insulin

Long standing T1D

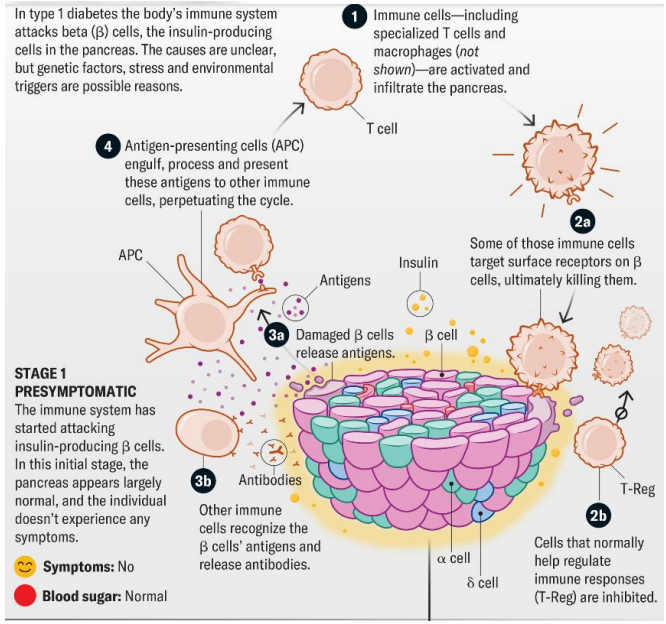
Dysglycemia:
IFG and/or IGT

- FPG 100-125 mg/dl
- 2-hour PG 140-199 mg/dl
- HbA1c 5.7%-6.4% or ≥10% from baseline

Hyperglycemia:

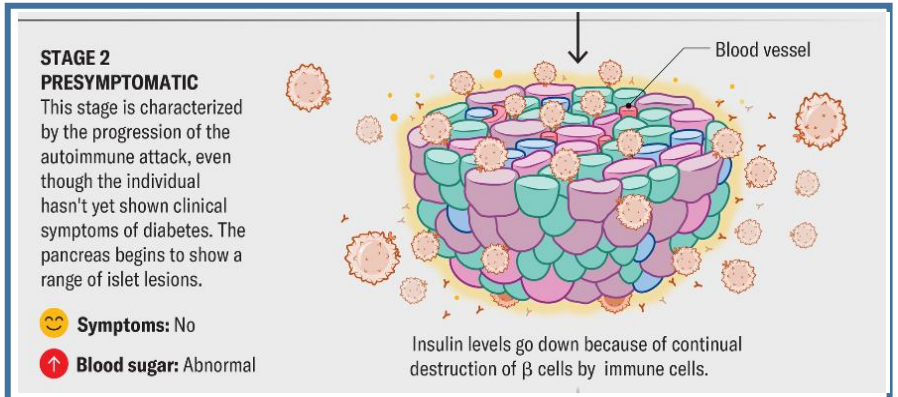
- FPG ≥126 mg/dl
- 2-hour PG or RPG ≥200 mg/dl
- HbA1c ≥6.5%

Michael J. Hallera et al. Horm Res Paediatr. 2024



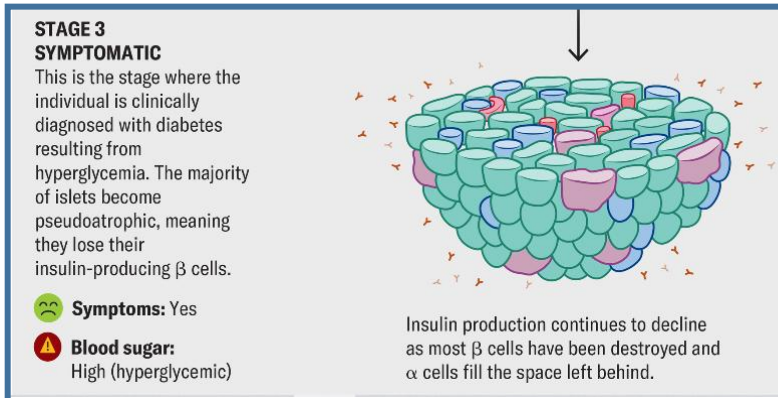
STAGE 1

- Among children living with **Stage 1 (normoglycemia),** 44% will progress to Stage 3 T1D in 5 years, and 80 to >90% will progress within 15 years.



STAGE 2

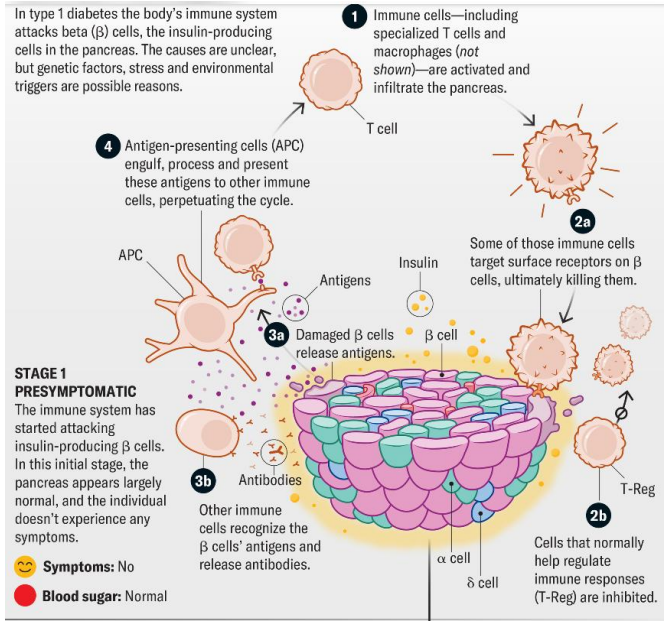
- In children living with **Stage 2 T1D (dysglycemia),** 75% will progress to Stage 3 T1D in 5 years and nearly 100% during their lifetime.

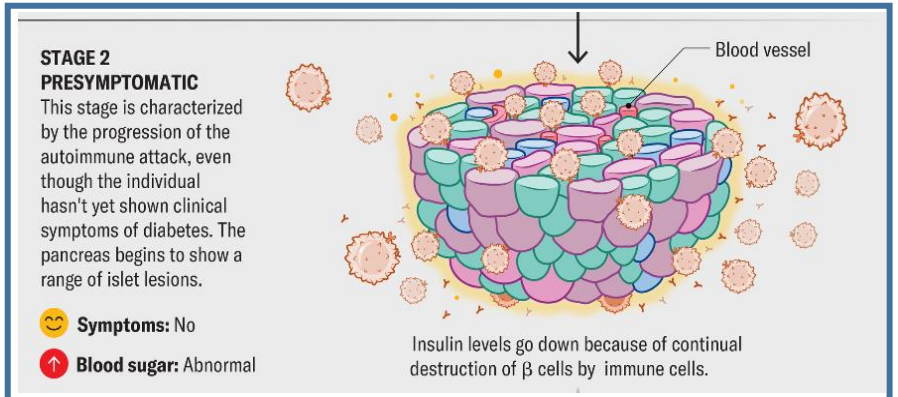


STAGE 3

- **Stage 3 T1D** is defined according to the ADA diagnostic criteria for clinical diabetes with or without symptoms of hyperglycemia.

Michael J. Hallera et al. Horm Res Paediatr. 2024





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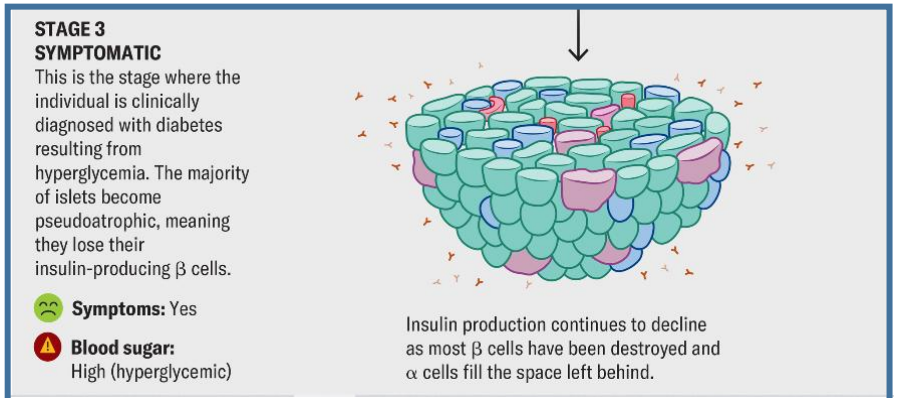
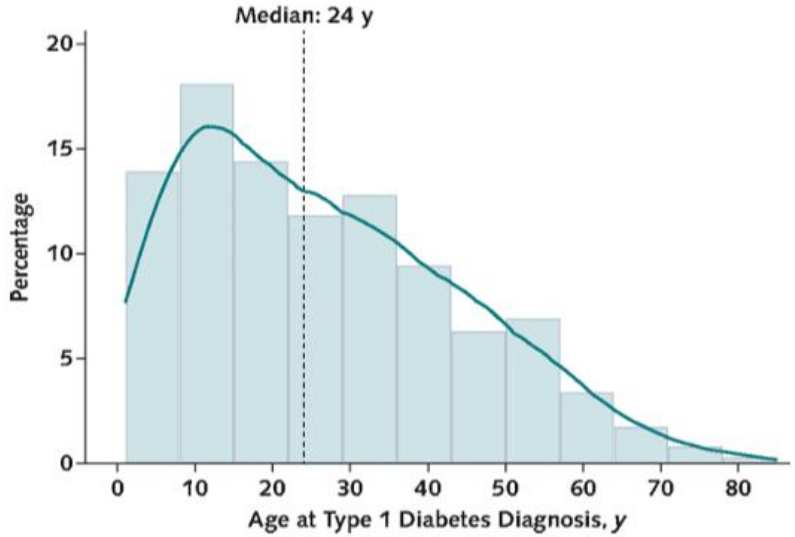


STAGE 3



- Global type 1 diabetes prevalence, incidence, and mortality estimates 2025: Results from the International diabetes Federation Atlas, 11th Edition, and the T1D Index Version 3.0

Graham D. Ogle [a,b,1,*], Fei Wang [c,1], Aveni Haynes [a], Gabriel A. Gregory [a], Thomas W. King [c], Kylie Deng [c], Dana Dabelea [d], Steven James [e], Alicia J. Jenkins [f], Xia Li [g,h,i], Ronald C.W. Ma [j,k,l], David M. Maahs [m], Richard A. Oram [n], Catherine Pihoker [o], Jannet Svensson [p,q], Zhiguang Zhou [g,h,i], Dianna J. Magliano [f,r], Jayanthi Maniam [a,s]

- ✓ Recent epidemiologic data clearly demonstrates a significant increase in the diagnosis of T1D in adults, challenging historical perceptions and underscoring the need for awareness and early detection in all age groups.

- ✓ An approximate 2-3% annual increase in childhood T1D incidence, and mounting evidence indicates that a substantial majority of new cases present in adulthood (≥18 years).

Diabetes Res Clin Pract. 2025

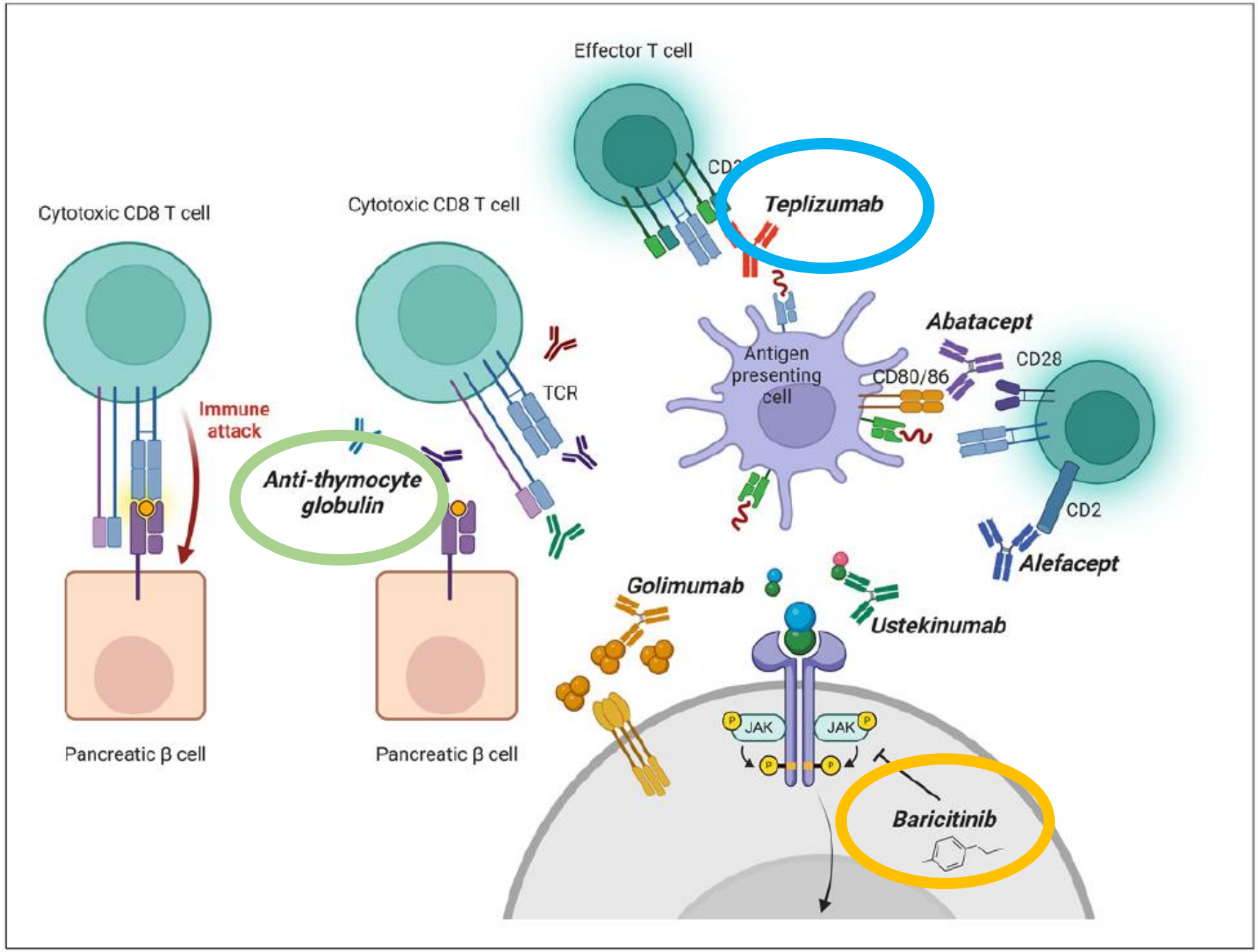
Immunoterapia: TIMING

Obiettivo delle immunoterapie	Stadio 2	Stadio 3
	Rallentare la progressione a stadio 3	**Preservare la funzione beta-cellule residua**
	Teplizumab (uso compassionevole) Baricitinib*	Teplizumab* Baricitinib* Frexalimab* SAB-142 Human ATG*

*** Farmaci disponibili nell'ambito di trial clinici sperimentali**

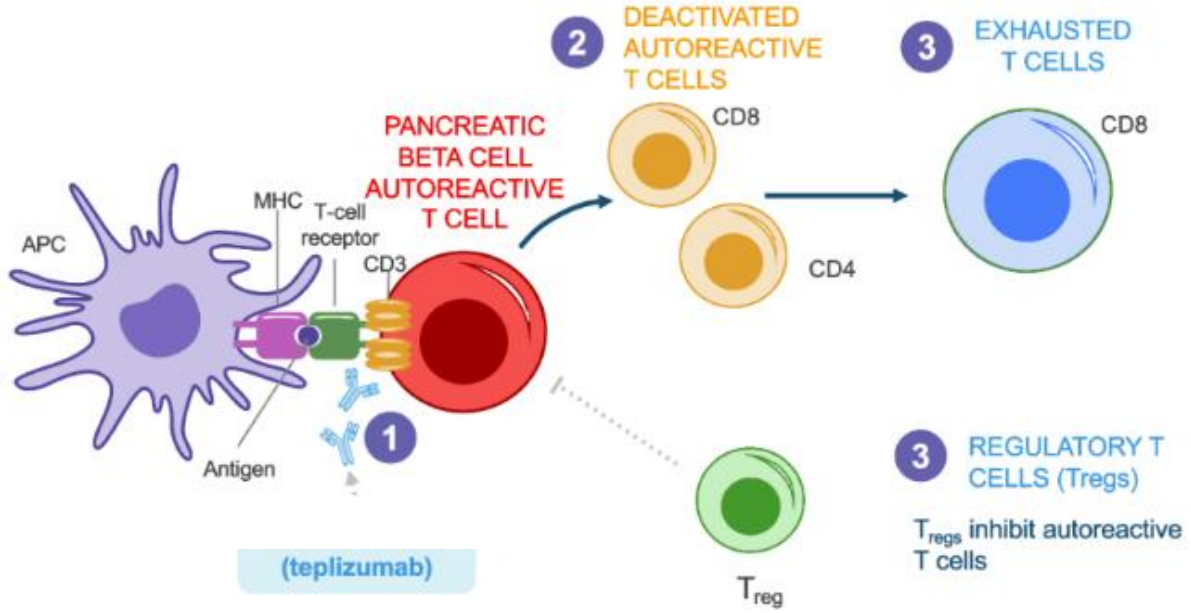
- Specifici criteri di inclusione/esclusione (peso oltre all'età!)
- Protocolli di somministrazione e sorveglianza rigidi
- Farmaco/placebo 2:1
- Tempo limitato di arroulamento

Immunoterapia: TARGET



Laura M. Jacobsen et al. Horm Res Paediatr. 2025

Teplizumab

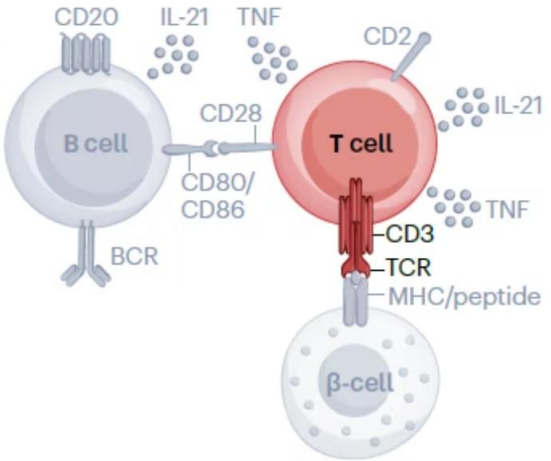


- **Ab monoclonale anti-CD3** che riconosce una parte di un complesso molecolare espresso sui linfociti T.

- L'interazione determina uno stato di **esaurimento funzionale dei Linfociti T**, con riduzione della secrezione di citochine e della proliferazione cellulare, contribuendo a **rallentare il processo autoimmune diretto contro le cellule β pancreatiche**

Teplizumab

Anti-CD3 mAb (see Fig. 5)
New-onset T1D; at-risk individuals, stage 2
New-onset T1D: improved C-peptide responses, reduced insulin needs and improved HbA1c levels depending on study
Stage 2: delay in T1D development



<u>Ciclo breve di somministrazione EV</u>

Eventi avversi lievi-moderati e transitori:

- linfopenia
- rash cutaneo

Long SA et al. Cell Immunol. 2017

Teplizumab

Teplizumab: study TN-10

TRIAL DESIGN — Phase 2, multicenter, randomized, double-blind, placebo-controlled trial of **76 children and adults with Stage 2 T1D**

76 people with early-stage T1D

- Non-diabetic relative of a person with T1D
- Age ≥8 years
- Stage 2 T1D defined as:
  - Two or more T1D-related autoantibodies
  - Evidence of dysglycemia during OGTT

14 daily IV infusions

Teplizumab* (n=44)

IV infusion administered over 14 days

Placebo (n=32)

Saline IV infusion administered over 14 days

Randomized 1:1

Primary outcome1

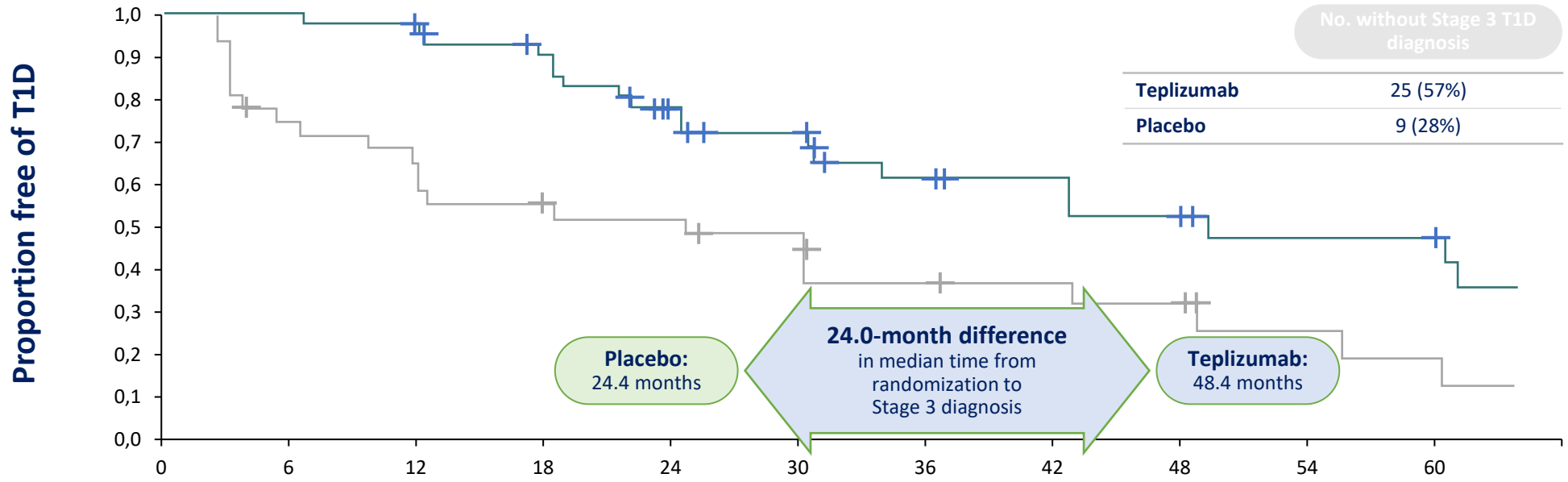
- Time to diagnosis of Stage 3 T1D
- **Measured by** OGTTs, performed at Month 3, 6, then every 6 months and random screening glucose levels at 3-month intervals
- **Median follow-up** of 745 days

Herold KC et al. N Engl J Med. 2019

Teplizumab

Teplizumab: study TN-10

Kaplan-Meier curve with number of individuals at risk



No. at risk

Teplizumab	44	44	40	36	27	21	15	14	10	9
Placebo	32	23	18	16	15	11	9	8	6	4

Herold KC et al. N Engl J Med. 2019

Teplizumab

The Journal of Clinical Investigation

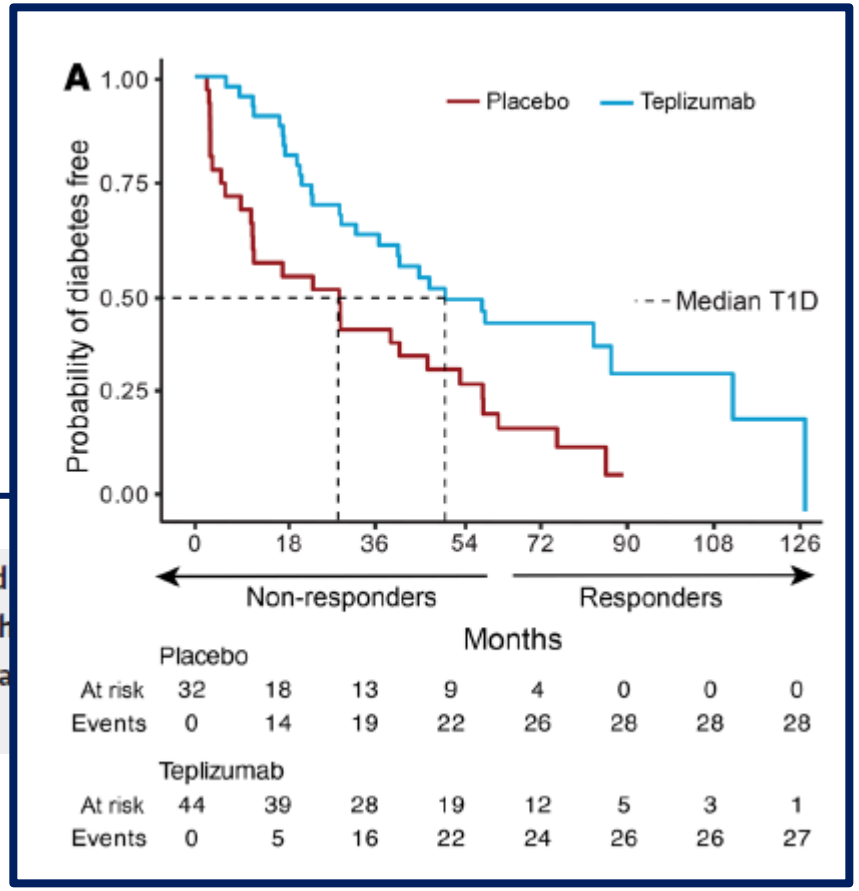
CLINICAL MEDICINE

Teplizumab induces persistent changes in the antigen-specific repertoire in individuals at risk for type 1 diabetes

Ana Lledó-Delgado,[1] Paula Preston-Hurlburt,[1] Sophia Currie,[1] Pamela Clark,[1] Peter S. Linsley,[2] S. Alice Long,[2] Can Liu,[3] Galina Koroleva,[4] Andrew J. Martins,[3] John S. Tsang,[3,4,5] and Kevan C. Herold[1]

[1]Departments of Immunobiology and Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, USA. [2]Benaroya Research Institute, Seattle, Washington, USA. [3]Center for Systems and Engineering Immunology and Department of Immunobiology, Yale University School of Medicine, New Haven, Connecticut, USA. [4]NIH Center for Human Immunology, National Institutes of Health, Bethesda, Maryland, USA. [5]Department of Biomedical Engineering, Yale University, New Haven, Connecticut, USA.

METHODS. With an extended analysis of study participants, we found that 36% were undiagnosed or remained diabetes after 5 years, suggesting operational tolerance. Using single-cell RNA sequencing, we compared the ph transcriptome, and repertoire of peripheral blood CD8⁺ T cells including autoreactive T cells from study participa after teplizumab and features of responders and non-responders.



- ✓ The median follow-up time was 80.46 months.
- ✓ The median time to diagnosis with clinical stage 3 T1D was **52.2 months in the teplizumab and 27.3 months in the placebo group.**
- ✓ Among the teplizumab-treated participants, 17/44 were classified as **responders** because they remained undiagnosed or were diagnosed with stage 3 after 60 months. The other 27/44 participants were classified as **non-responders**.

J Clin Invest. 2024

Teplizumab

The Journal of Clinical Investigation

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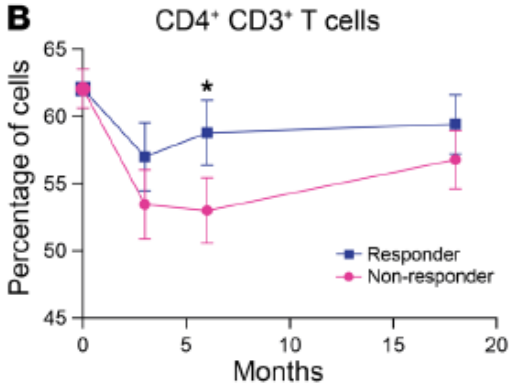
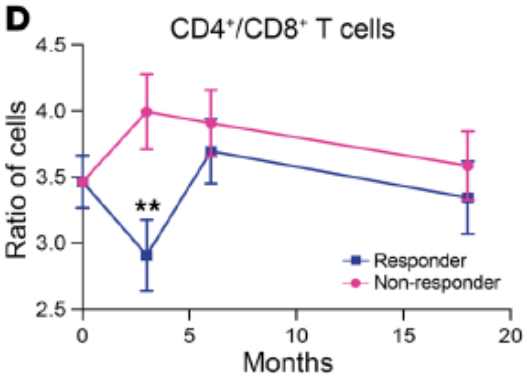
[1]Departments of Immunobiology and Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, USA. [2]Benaroya Research Institute, Seattle, Washington, USA. [3]Center for Systems and Engineering Immunology and Department of Immunobiology, Yale University School of Medicine, New Haven, Connecticut, USA. [4]NIH Center for Human Immunology, National Institutes of Health, Bethesda, Maryland, USA. [5]Department of Biomedical Engineering, Yale University, New Haven, Connecticut, USA.

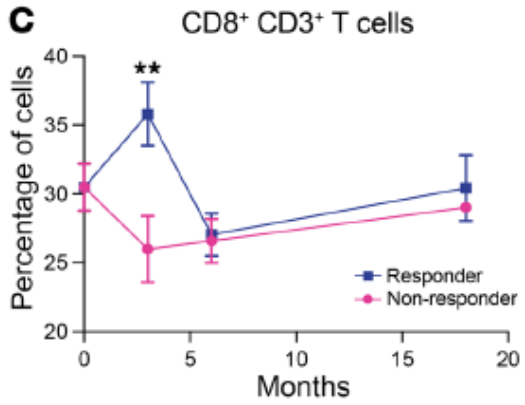
METHODS. With an extended analysis of study participants, we found that 36% were undiagnosed or remained free of clinical diabetes after 5 years, suggesting operational tolerance. Using single-cell RNA sequencing, we compared the phenotypes, transcriptome, and repertoire of peripheral blood CD8$^+$ T cells including autoreactive T cells from study participants before and after teplizumab and features of responders and non-responders.

RESULTS. At 3 months, there were transcriptional signatures of cell activation in CD4$^+$ and CD8$^+$ T cells including signaling that was reversed at 18 months. At that time, there was reduced expression of genes in T cell receptor and activation pathways in clinical responders. In CD8$^+$ T cells, we found increased expression of genes associated with exhaustion and immune regulation with teplizumab treatment. These transcriptional features were further confirmed in an independent cohort. Pseudotime analysis showed differentiation of CD8$^+$ exhausted and memory cells with teplizumab treatment. *IL7R* expression was reduced, and patients with lower expression of CD127 had longer diabetes-free intervals. In addition, the frequency of autoantigen-reactive CD8$^+$ T cells, which expanded in the placebo group over 18 months, did not increase in the teplizumab group.

CONCLUSION. These findings indicate that teplizumab promotes operational tolerance in T1D, involving activation followed by exhaustion and regulation, and prevents expansion of autoreactive T cells.







J Clin Invest. 2024

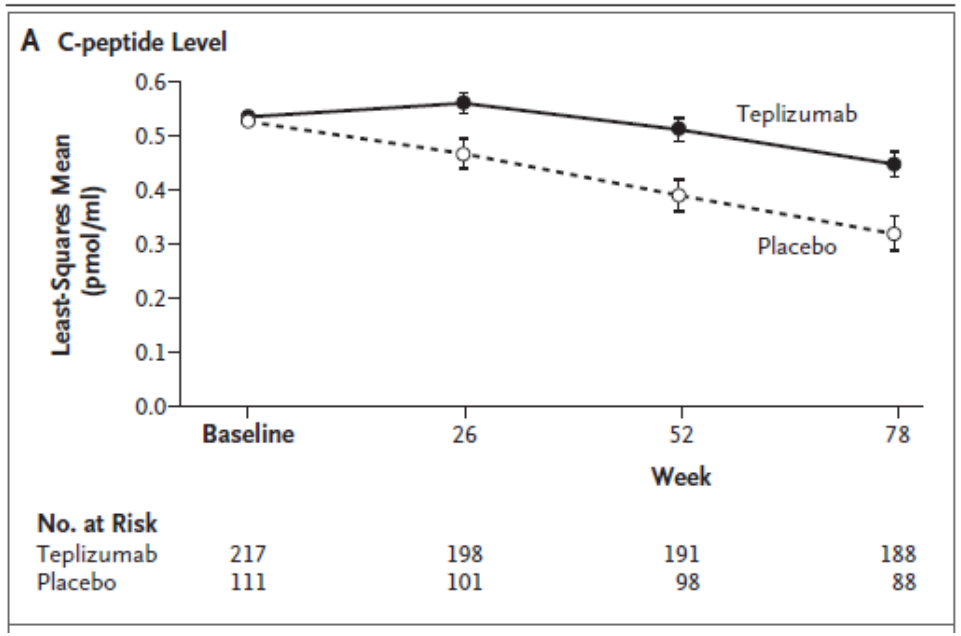
ORIGINAL ARTICLE

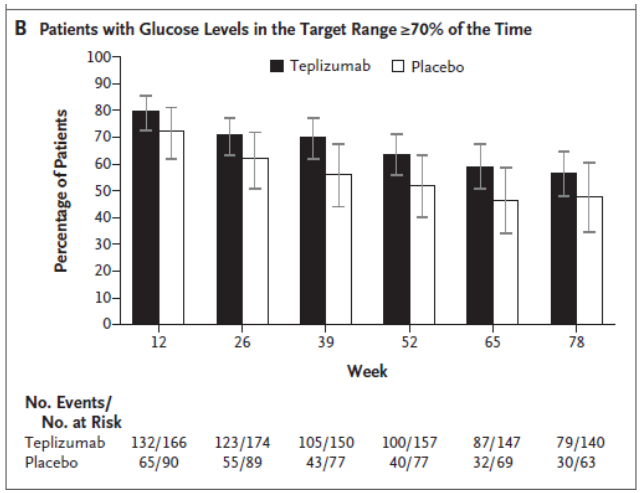
Teplizumab and β-Cell Function in Newly Diagnosed Type 1 Diabetes

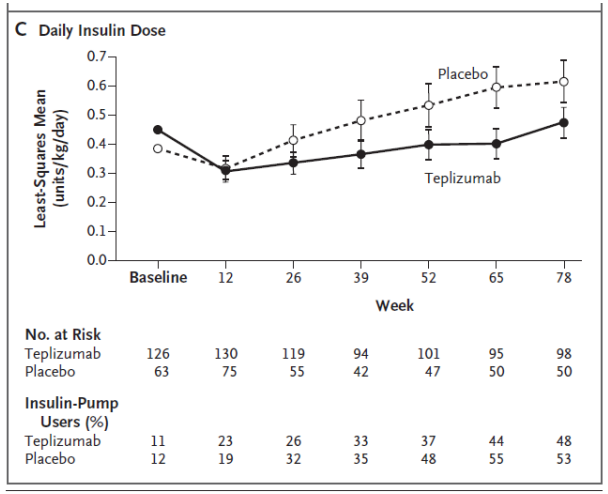
METHODS

In this phase 3, randomized, placebo-controlled trial, we assessed β-cell preservation, clinical end points, and safety in children and adolescents who were assigned to receive teplizumab or placebo for two 12-day courses. The primary end point was the change from baseline in β-cell function, as measured by stimulated C-peptide levels at week 78. The key secondary end points were the insulin doses that were required to meet glycemic goals, glycated hemoglobin levels, time in the target glucose range, and clinically important hypoglycemic events.

8-17 years







- There were no significant differences between the groups in the key secondary clinical end points – insulin dose, change in glycated hemoglobin, percent age of time in the target glucose range, and clinically important hypoglycemic events.
- The side effects of teplizumab observed in the present trial included headache, gastrointestinal symptoms, rash, lymphopenia, and mild cytokine release syndrome.
- These findings were consistent with previous experience and the events resolved spontaneously.

Ramos EL et al. N Engl J Med. 2023

- Il 17 Novembre 2022, Teplizumab è stato approvato da FDA (Food and Drug Administration) per ritardare l'esordio clinico del diabete di tipo 1
- Ad Aprile 2026 l'FDA ha esteso l'approvazione anche a bambini di età ≥ di 1 anno grazie ai risultati dello studio «Petite-T1D».
- In Italia in uso compassionevole da Ottobre 2024. Approvato dall'EMA a Gennaio 2026.
- Per persone che a seguito dello screening o di esami di routine sono state diagnosticate in stadio 2 del diabete di tipo 1.

I criteri di eleggibilità per il suo utilizzo includono:

- Età - Pazienti di età pari o superiore a 8 anni;
- Predisposizione al diabete di tipo 1 - Pazienti con due o più autoanticorpi associati al diabete di tipo 1;
- Condizione di disglicemia (OGTT o un appropriato test alternativo).

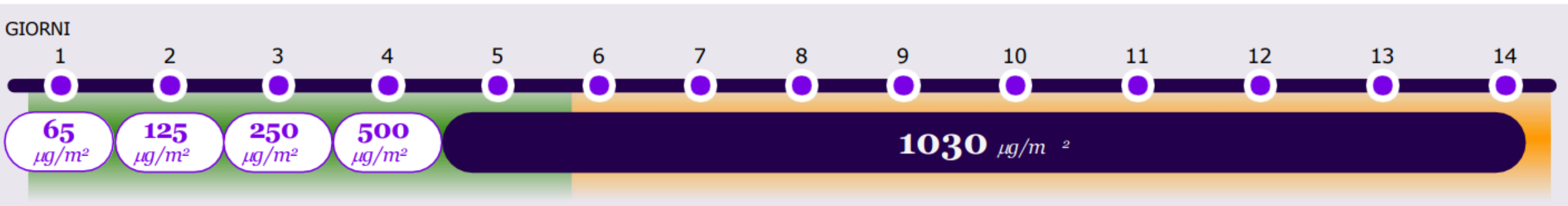
L'uso compassionevole in Italia

Condizioni da soddisfare per l'inclusione del paziente (Modulo di idoneità)

Disglicemia (ridotta tolleranza al glucosio o disglicemia con almeno 2 dei seguenti criteri o con un singolo criterio che presenta due valori alterati nell'arco di 12 mesi)

- FPG 100-125 mg/dL (5,6-6,9 mmol/L)
- 2 ore di PG 140-199 mg/dL (7,8-11,0 mmol/L)
- 30, 60 o 90 minuti PG ≥ 200 mg/dl (11,1 mmol/L)

HbA1c 5,7-6,4% (39-47 mmol/mol) o ≥10% di aumento dell'HbA1c



Treatment with Teplizumab in Children with Stage 2 Type 1 Diabetes: An Italian Case Series

ATTD Advanced Technologies & Treatments for Diabetes 11-14 MARCH 2026 BARCELONA, SPAIN

METHODS

This multicenter case series included eight pediatric patients (6 males, 2 females; median age 13.1 years) with stage 2 T1D treated with Teplizumab in 2025 across several Italian centers.

Eligibility criteria were: age ≥8 years, diagnosis of stage 2 T1D according to international guidelines, and absence of significant comorbidities.
Stage 2 T1D: presence of ≥2 β-cell autoantibodies and dysglycemia in the absence of clinical symptoms.

All patients underwent baseline clinical and laboratory assessments and then received a 14-day intravenous teplizumab regimen with dose escalation in inpatient or day-hospital settings.

RESULTS

All patients were diagnosed with stage 2 T1D, defined by at least two β-cell autoantibodies (ZnT8: 7 patients; GAD: 7; IA2: 7; IAA: 6) and dysglycemia (fasting glucose 100–125 mg/dL: 7 patients; HbA1c 5.7-6.4%: 6; 2-h glucose 140-199 mg/dL: 6).
Five were identified through family screening, one for occasional hyperglycemia, and two during evaluation for other autoimmune conditions.
Baseline laboratory tests (blood count, liver function, microbiological screening) were normal.
Eligibility and pre-treatment characteristics are illustrated in Tables 1 and 2.

Teplizumab was administered intravenously over 14 days with dose escalation in inpatient or day-hospital settings. All patients reached the target dose and completed treatment.
Premedication (antipyretic, antihistamine, antiemetic) was routinely given, especially in the first five days.

Adverse events, shown in Table 3, were mild and transient: fever (1 patient, 12.5%), nausea (1 patient, 12.5%), rash (5, 62.5%), and pruritus (1, 12.5%), all resolving with symptomatic treatment.
Transient lymphopenia occurred in all patients, reaching a nadir on days 4–5 (mean 418/mm³), with counts increasing by day 14 (mean 750/mm³).
The median lymphocyte trend during treatment is shown in Figure 1.
One developed mild transient thrombocytopenia. Liver enzymes remained normal.

Dati real-world italiani

18 pazienti pediatrici (età media 13.1 anni) con DT1 in stadio 2 trattati con Teplizumab in diversi centri in Italia nel 2025-2026

Piona C et al. ATTD 2026

Teplizumab

UTILIZZO PER LO STADIO 2 - programmi di individuali di uso compassionevole

- Primo farmaco approvato per modificare la progressione dell'autoimmunità nel diabete di tipo 1 cioè per ritardare l'insorgenza del DT1 di circa 2 anni ovvero la progressione dei soggetti **adulti e bambini di età ≥8 anni da stadio 2 a stadio 3 (Studio TN-10)**
- Approvato da FDA e EMA, prescrivibilità e rimborsabilità in Italia in discussione con AIFA, nel frattempo disponibile nell'ambito di **programmi di individuali di uso compassionevole**
- **Un solo ciclo di trattamento della durata di 2 settimane**

UTILIZZO PER LO STADIO 3 – Trial clinico sperimentale (BETA-PRESERVE)

- Studio randomizzato, in doppio cieco, di fase 3 volto a valutare l'efficacia e la sicurezza di teplizumab rispetto a placebo in soggetti di **età compresa tra 1 e 25 anni** con DT1 in stadio 3 di recente diagnosi
- **Durata totale dello studio:** 84 settimane (~1,5 anni)

  - Randomizzazione: entro 8 settimane (**56 giorni**) dalla diagnosi
  - Trattamento: **2 cicli di 12 giorni**, a distanza di **6 mesi**
  - Follow-up: **12 mesi**

UTILIZZO PER LO STADIO 3 – Trial clinico sperimentale (BETA-PRESERVE)

PRIMARY Objective: to demonstrate of Teplizumab versus (vs) placebo on glycemic control or prandial insulin indipendency over 52 weeks

PRIMARY Endpoints:
- Glycated hemoglobin (HbA1c) change from baseline to Week 52
- OR
- Total number of days **without** prandial insulin use from baseline to week 52

SECONDARY Objective: to evaluate efficacy of Teplizumab (vs) placebo on endogenous insulin secretion, glycemic control and reducing hypoglycemia

SECONDARY Endpoints:
- Change from baseline in mean 2 hours MMTT stimulated C-peptide concentration, calculated from AUC
- Proportion of participants with HbA1c ≤6.5% and requiring ≤0.25 IU/kg/day of insulin
- Change from basaline in TIR
- Number of level 2 and 3 hypoglycemic events per particpipant year

- Incidende of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs) and TEAEs leading to treatment discontinuation
- Teplizumab PK parameteres over time
- Antidrug antibody (ADA) assessment over time

Pediatric Endocrine Society Statement on Considerations for Use of Teplizumab ([redacted]) in Clinical Practice

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Ksenia N. Tonyushkina[k]

➢ Event schedules for BEFORE, DURING and AFTER infusions

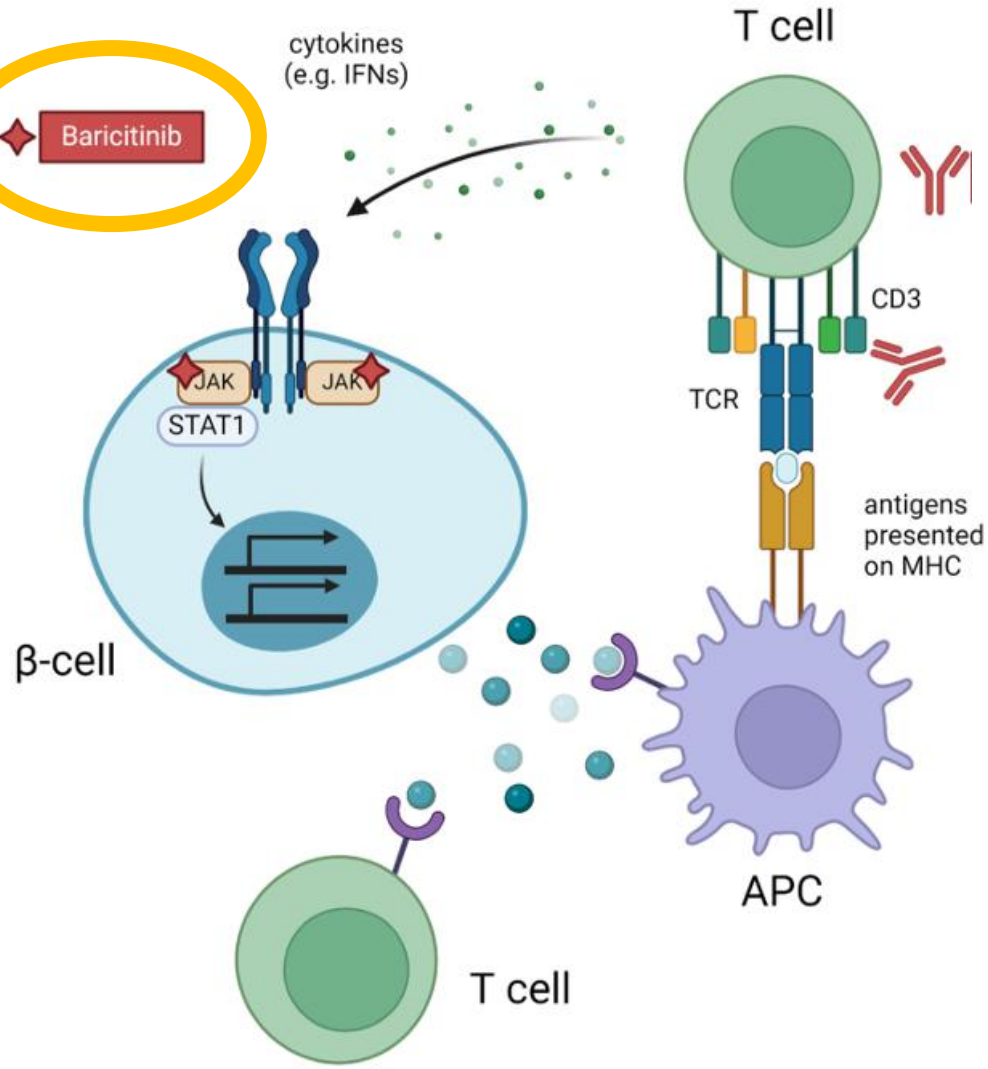
Pretreatment: need to have all of these to proceed	• No active serious infection or chronic active infection other than localized skin infections • Vaccines up to date • Hemoglobin >10 g/dL • Platelets> 150,000 platelets/μL • Lymphocyte count >1,000 lymphocytes/μL • Absolute neutrophil count >1,500 neutrophils/μL • ALT or AST <2 times the upper limit of normal (ULN) and bilirubin <1.5 times ULN • No laboratory or clinical evidence of acute infection with EBV or CMV • Negative rapid testing for COVID-19 • Negative pregnancy test for females of reproductive age
On infusion days	• Review any laboratories (see Table 4 for when to hold or permanently discontinue the infusion) • MD/APP evaluation of any new or worsening symptoms • Premedicate with an antipyretic and diphenhydramine at minimum on days 1–5 and PRN symptoms • Ensure home supply of ibuprofen, acetaminophen, diphenhydramine, and ondansetron • Observe for any immediate reactions
After the treatment course	• Follow laboratory tests 1–4 weeks posttreatment depending on severity of abnormalities at end of infusion and then periodically until abnormalities resolved • Educate the individual and their family on signs and symptoms of stage 3 T1D • Consider instituting a surveillance protocol trending OGTT or CGM results at least every 6 months using threshold values diagnostic for stage 3 T1D

➢ Selected AEs: frequencies from clinical trials and guidance

Adverse events (AEs)	Teplizumab, *N* = 791 (%)	Control, *N* = 245 (%)	Hold	Permanently discontinue
Cytokine release syndrome (CRS)[a]	46 (5.8)	3 (1.2)	Severe CRS[b] 1–2 days	Severe CRS >2 days
Hematologic abnormalities				
Leukopenia	501 (63.3)	41 (16.7)	see below for specific lymphocyte and ANC criteria	See below for specific lymphocyte and ANC criteria
Lymphopenia	632 (79.9)	41 (16.7)	N/A	ALC <500 cells/μL and no recovery trend by day 7 (based on prescribing information. This was not a discontinuation criterion in the PROTECT study [13])[c]
Neutropenia	313 (39.6)	53 (21.6)	ANC <500 cells/μL (based on PROTECT study [13], no recommendation in the prescribing information)	ANC <500 cells/μL and no recovery trend by day 7[d]
Anemia	228 (28.8)	55 (22.4)	Hgb <10 g/dL	Hgb <8.5 g/dL
Thrombocytopenia	172 (21.7)	24 (9.8)	Platelets <50,000/μL (based on PROTECT study [13], no recommendation in the prescribing information)	Platelets <50,000/μL and no recovery by day 7[d]
Transaminase elevations				
AST increased	222 (28.1)	50 (20.4)	2 × ULN	5 × ULN
ALT increased	210 (26.5)	28 (11.4)	2 × ULN	5 × ULN
Biochemical abnormalities				
Hyperbilirubinemia			1.5 × ULN	3 × ULN
Blood bicarbonate decreased	303 (38.3)	67 (27.3)	N/A	N/A
Rash	273 (34.5)	25 (10.2)	N/A	N/A
Hypersensitivity reaction				Angioedema, serum sickness, bronchospasm
Acute/chronic infections				
New EBV infection	18 (2.3%)	10 (4.1%)	Hold, call for infectious disease consult, check serology or viral load for EBV, CMV, likely stop infusions	
EBV reactivation	40 (5.1%)	6 (2.4%)		
EBV viremia	25 (3.2%)	3 (1.2%)		
New CMV infection	5 (0.6%)	2 (0.8%)		
CMV reactivation	4 (0.5%)	N/A		
COVID-19	N/A	N/A	No infusions	
Other infections: hepatitis, HIV, TB			No infusions	

Horm Res Paediatr. 2025

Baricitinb



- **Inibitore orale selettivo delle Janus chinasi (JAK) 1 e JAK2**

- Bloccando la via di segnalazione **JAK–STAT**, inibisce importanti pathway citochinici pro-infiammatori coinvolti nell'attivazione e nella persistenza delle cellule T autoreattive.

- Questa modulazione della risposta immunitaria **riduce l'infiammazione autoimmune** e **rallenta la distruzione immuno-mediata delle cellule β pancreatiche**, favorendo un ambiente immunologico più tollerante.

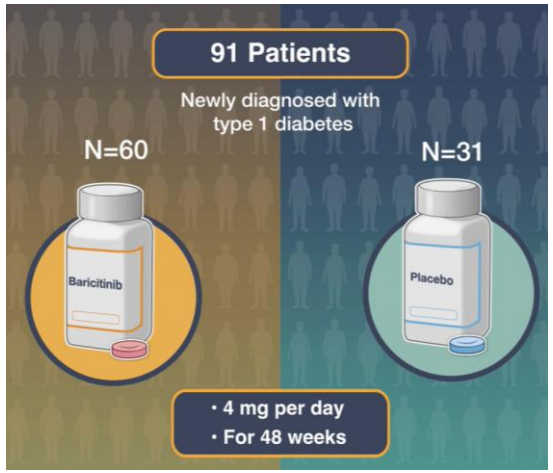
The NEW ENGLAND JOURNAL of MEDICINE

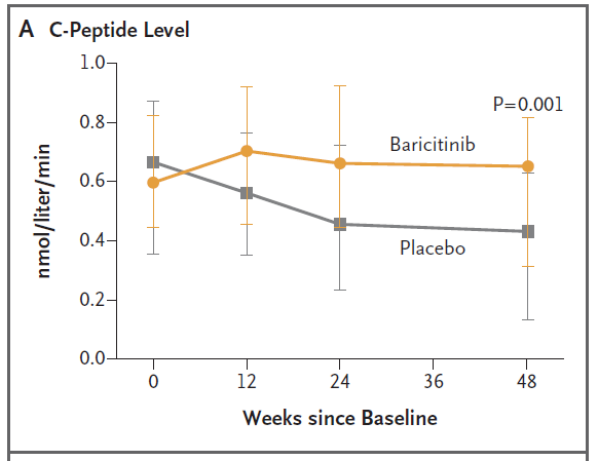
ORIGINAL ARTICLE

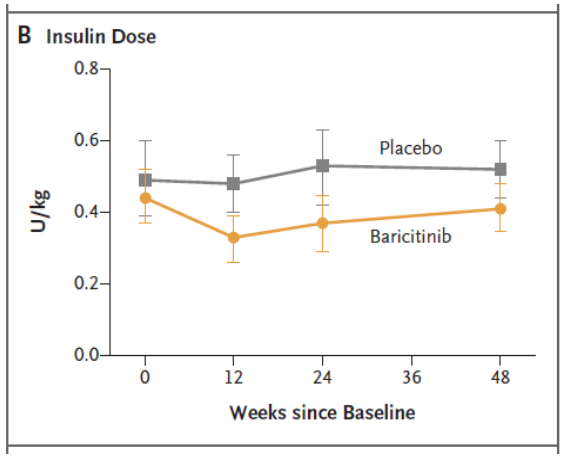
Baricitinib and β-Cell Function in Patients with New-Onset Type 1 Diabetes

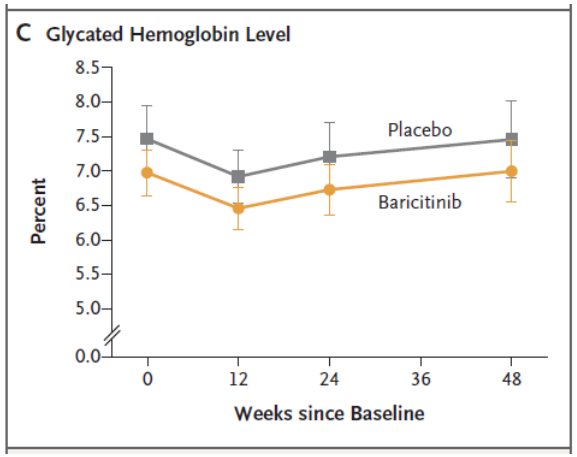
METHODS

In this phase 2, double-blind, randomized, placebo-controlled trial, we assigned patients with type 1 diabetes diagnosed during the previous 100 days to receive baricitinib (4 mg once per day) or matched placebo orally for 48 weeks. The primary outcome was the mean C-peptide level, determined from the area under the concentration–time curve, during a 2-hour mixed-meal tolerance test at week 48. Secondary outcomes included the change from baseline in the glycated hemoglobin level, the daily insulin dose, and measures of glycemic control assessed with the use of continuous glucose monitoring.









- Age between 10 and 30 years, a diagnosis of T1D within 100 days before starting baricitinib or placebo, the presence of at least one islet auto antibody, and either a random C-peptide level of more than 0.3 nmol per liter or a C-peptide level of more than 0.2 nmol per liter during a 2-hour MMTT.

- The median of the mixed-meal–stimulated mean C-peptide level at week 48 was **0.65 nmol per liter per minute** in the baricitinib group and **0.43 nmol per liter per minute** in the placebo group (P = 0.001).

- The frequency and severity of adverse events were similar in the two trial groups, and no serious adverse events were attributed to baricitinib or placebo.

N Engl J Med. 2023

Baricitinb

Two phase 3 trials to determine the impact of baricitinib on Stage 2 or 3 T1D

BARICADE-DELAY

Time-to-event study to delay or prevent the onset of Stage 3 T1D in those with Stage /2

BARICADE-PRESERVE

52-week study to preserve beta-cell function in new onset T1D (within 100d)

Objective: to demonstrate superiority of baricitinb versus placebo in **DELAY of Stage 3 type 1 diabetes** in persons at risk for T1D.

Objective: to demonstrate superiority of baricitinb versus placebo in **PRESERVE of beta-cell function** as measured by C-peptide in younger adult and pediatric parecipants with new-onset T1D after 52 weeks of treatment.

Baricitinb

BARICADE-DELAY

Time-to-event study to delay or prevent the onset of Stage 3 T1D in those with Stage 1b/2

→ 2:1 ratio of baricitinib or placebo

→ Age ≥2 to <36 years in EU; stage 2 T1D

Global time to event trial: diagnosis of Stage 3 T1D

Endpoints SECONDARY: change in C-peptide on MMTT at 52 weeks

BARICADE-PRESERVE

52-week study to preserve beta-cell function in new onset T1D (within 100d)

→ 2:1 ratio of baricitinb or placebo

→ Age 1-35 years; newly diagnosed Stage 3 T1D

Global trial: change in C-peptide on MMTT at 52 weeks

Endpoints SECONDARY: change from baseline to Week 52 in HbA1c, TIR and TITR, CGM-CV, change in number of insulin boluses, rate of clinucally significant hypoglycemic events throughout the treatment period

SAB-142 Human ATG

SAB-142
Anti-Thymocyte Globulin (Human)

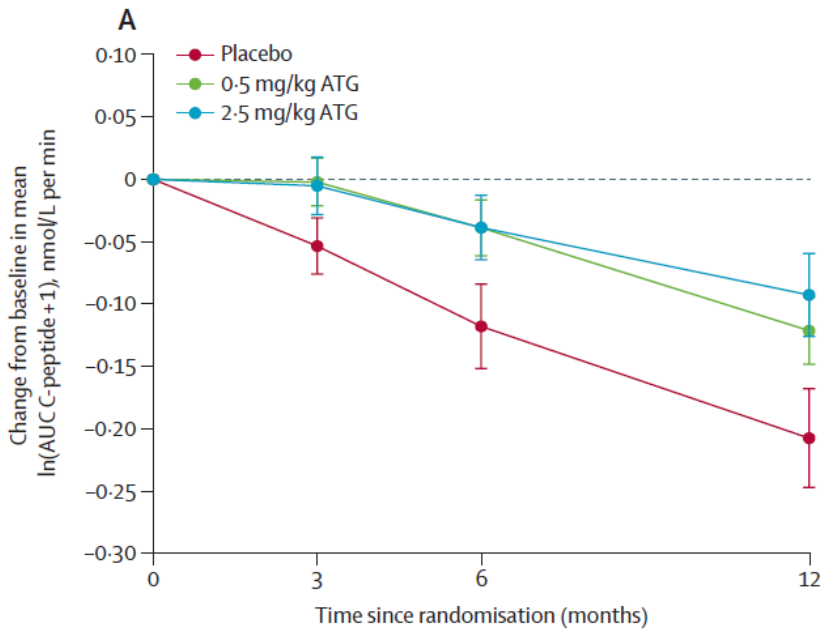
- **Anticorpo policlonale umano (IgG)** diretto contro antigeni multipli dei linfociti T (CD2, CD3, CD4, CD8)
- L'interazione induce una **immunomodulazione sostenuta** con sviluppo di uno stato di **"T-cell exhaustion"**, riducendo l'attivazione e la funzione effettrice dei linfociti T senza determinare una marcata immunosoppressione o linfodeplezione
- **Eventi avversi** generalmente **lievi-moderati e transitori**, con buon profilo di sicurezza

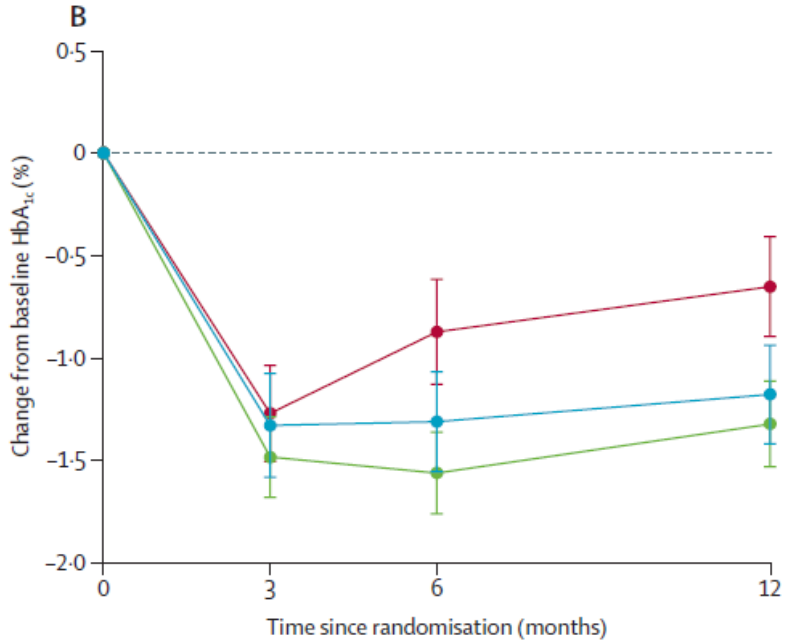
UTILIZZO PER LO STADIO 3

Trial clinico

Minimum effective low dose of antithymocyte globulin in people aged 5–25 years with recent-onset stage 3 type 1 diabetes (MELD-ATG): a phase 2, multicentre, double-blind, randomised, placebo-controlled, adaptive dose-ranging trial

THE LANCET



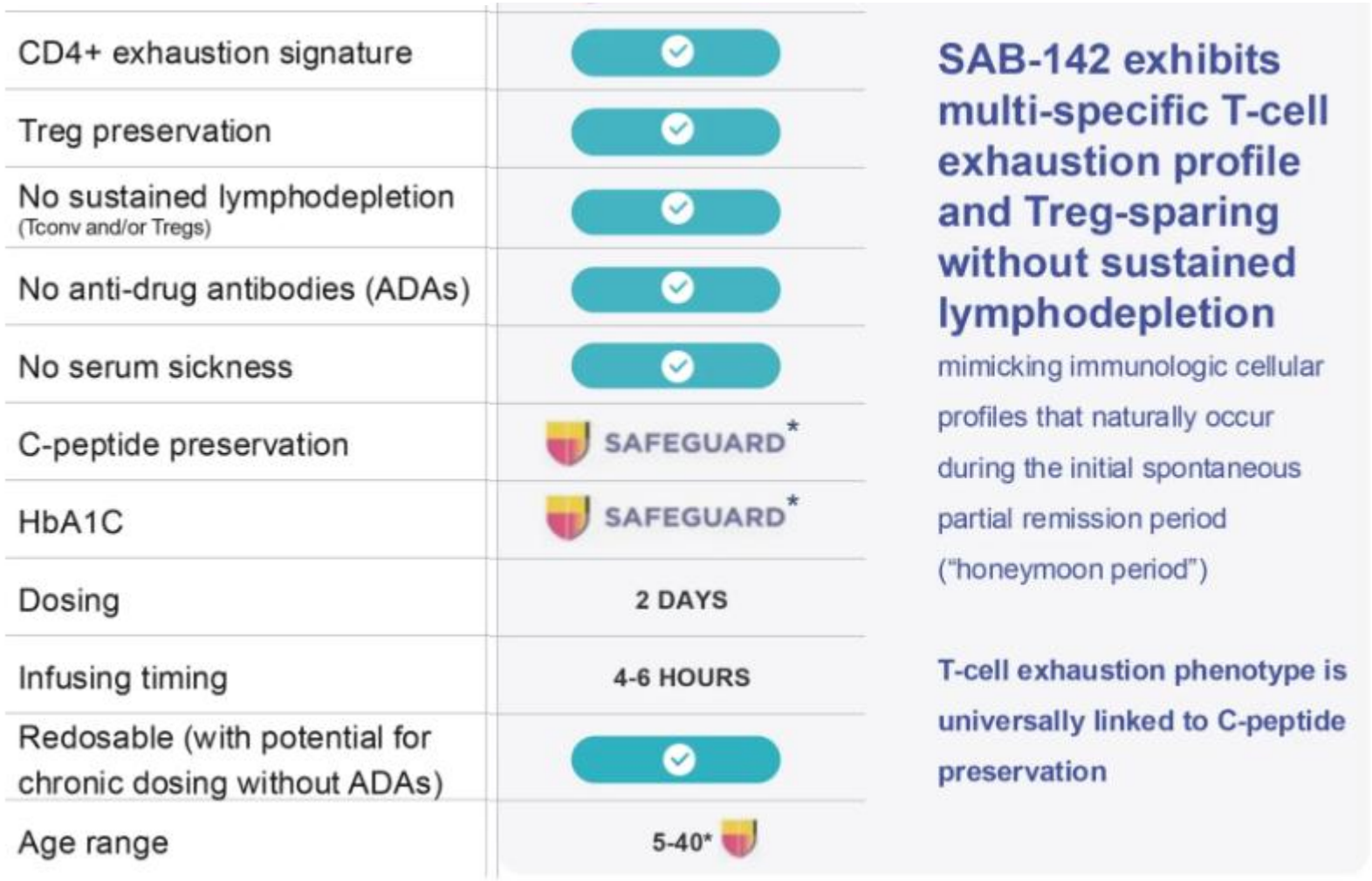


- Participants aged **5-25 years (117 subjects)**
- **Stage 3 T1D** 3-9 weeks before treatment day 1
- Randomly assigned by a web-based randomisation system into seven consecutive cohorts receiving **placebo, 2·5 mg/kg ATG, 0·5 mg/kg ATG**

➢ The adaptive trial design provided the power to identify a **minimum effective dose of ATG at 0·5 mg/kg**. This dose not only achieved the primary endpoint, reducing C-peptide decline compared with placebo at 12 months, but also resulted in lower HbA1c concentrations.

Mathieu C et al. Lancet. 2025

➢ ***A Randomised, Double-Blind, Placebo-Controlled, Parallel-Arm Dose Finding Study Evaluating the Efficacy and Safety of SAB-142 for Delaying the Progression of Type 1 Diabetes (T1D) in Patients with Stage 3 New Onset of Type 1 Diabetes.***



-**<u>Obiective PRIMARY</u>**: to determine whether SAB-142 slows the loss of beta-cell function over 12 months

-**<u>Obiective SECONDARY</u>**: to evaluate participant improvements in key clinical parameters management following administration of SAB-142

-**<u>PRIMARY End Points</u>**: area under the Curve (AUC) of C-PEPTIDE after 2 hours MMTT

-**<u>SECONDARY End Points</u>**: HbA1c, TIR, TITR

Other treatments...

Therapy	Mechanism of action	Intervention	Population & stage	Results
Teplizumab (69–72)	Anti-CD3 mAb; induces partial T-cell exhaustion and regulatory $CD8^+$ cells	Single 12–14-day IV course (in recent trials: two 12-day courses 6 months apart)	Stage 2 at-risk relatives; new-onset stage 3 T1D (mainly children/ adolescents)	In stage 2, delays clinical T1D by ≈2 years; in stage 3, consistently preserves stimulated C-peptide for ≥ 1–2 years with modest effects on insulin dose and HbA1c
Ustekinumab (78)	Anti-IL-12/23 p40 mAb; reduces Th1/Th17-mediated inflammation	Weight-based s.c. dosing at weeks 0 and 4, then every 12 weeks for ≈1 year	Adolescents with new-onset stage 3 T1D	Phase 2 trial: well tolerated and preserves stimulated C-peptide vs placebo with modest glycaemic benefit
Golimumab (79)	Anti-TNF-α mAb; blocks pro-inflammatory cytokine signalling	S.c. injections every 2 weeks for 52 weeks	Children and young adults with new-onset stage 3 T1D	Phase 2 trial: higher stimulated C-peptide AUC at 1 year vs placebo with lower insulin requirements and some improvement in glycaemic control
Baricitinib (80)	Oral JAK1/JAK2 inhibitor; blocks multiple cytokine pathways	4 mg orally once daily for 48 weeks	Adolescents and adults with new-onset stage 3 T1D	Phase 2 trial (BANDIT): met primary endpoint; −minimal decline in stimulated C-peptide vs substantial decline with placebo, with lower insulin dose and improved CGM metrics
Alefacept (81, 82)	LFA-3–Ig fusion protein; selectively depletes memory T cells ($CD2^+$)	Two 12-week courses of 15 mg i.m. weekly, separated by 12 weeks off-treatment	Adolescents and young adults with new-onset stage 3 T1D	Phase 2 T1DAL study: sustained preservation of stimulated C-peptide at 12–24 months vs placebo with reduced insulin dose and fewer major hypoglycaemic events
Abatacept (73, 74)	CTLA–4–Ig – blocks CD28 co–stimulation, reduces T–cell activation	10 mg/kg IV day 1, 14, 28 then every 4 weeks for 24 months	New–onset (<100 days since diagnosis, 6–45 years)	Stimulated C-peptide release significantly higher after 2 years
Rituximab (75, 76)	Anti–CD20 – depletes B cells that present β–cell antigen	Four weekly IV infusions 375 mg m^{-2}	New–onset (<3 months since diagnosis, 8–40 years)	Stimulated C-peptide release significantly higher, significantly lower HbA1c values and lower insulin requirement after one year, effects not maintained after 2 years
Low–dose ATG ± G–CSF (77, 87, 88)	Polyclonal T–cell depletion (spares T–regs); G–CSF promotes tolerance	2-day IV total 4.5 mg/kg with or without s.c. G-CSF; recent MELD-ATG trials with 0.5–2.5 mg/kg ATG alone	New-onset stage 3 T1D (children, adolescents and adults)	Preserves stimulated C-peptide and improves HbA1c vs placebo; MELD-ATG shows efficacy down to 0.5 mg/kg without clear added benefit of G-CSF
Anti–IL–21 + Liraglutide (89)	IL–21 blockade dampens TFH/ autoreactive B cells; GLP–1 RA gives metabolic rest	30 mg SC anti–IL–21 weekly + liraglutide 1.8 mg SC daily for 54 weeks	New–onset (<20 weeks since diagnosis, 18–45 years)	Stimulated C-peptide release significantly higher after 54 weeks, but only when both active ingredients are combined
Verapamil (83, 84)	L-type Ca^{2+}-channel blocker; reduces TXNIP, ER-stress and β-cell apoptosis	120–360 mg orally once daily for 12 months	Adults with new-onset stage 3 T1D; paediatric data from separate trials	Small adult trial showed higher stimulated C-peptide, lower insulin dose and fewer hypoglycaemic events; a larger multicentre phase 2 trial (Ver-A-T1D) is ongoing; first conference reports suggest trends towards β-cell preservation, but full peer-reviewed results are awaited
Imatinib (85)	c–Abl inhibition → reduced ER–stress & innate activation	400 mg orally daily for 26 weeks	New–onset (<100 days since diagnosis, 18–45 years)	Higher C–peptide at 12 months; no difference at 24 months

Wagner R et al. Diabetes Res Clin Pract. 2026

Other treatments…

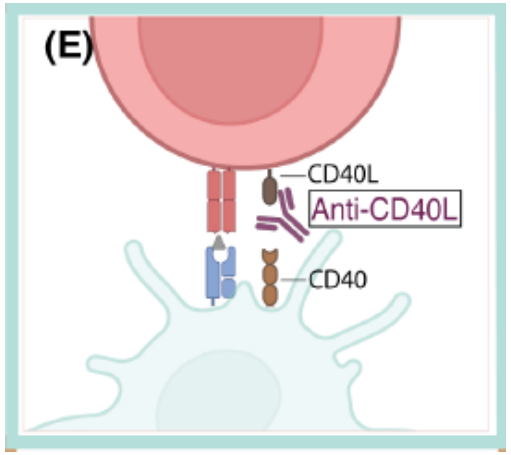
Therapy	Mechanism of action	Intervention	Population & stage	Results
Teplizumab (69–72)	Anti-CD3 mAb; induces partial T-cell exhaustion and regulatory $CD8^+$ cells	Single 12–14-day IV course (in recent trials: two 12-day courses 6 months apart)	Stage 2 at-risk relatives; new-onset stage 3 T1D (mainly children/	In stage 2, delays clinical T1D by ≈2 years; in stage 3, consistently preserves stimulated C-peptide for ≥ 1–2 years with modest effects on insulin dose and HbA1c

Frexalimab

- **Anticorpo monoclonale umanizzato (IgG1)** diretto contro **CD40L (CD154)**
- L'interazione blocca il segnale costimolatorio **CD40–CD40L**, determinando una **modulazione della risposta immunitaria adattativa**, con riduzione dell'attivazione dei linfociti T e B e della produzione di autoanticorpi
- **Somministrazione sottocutanea (SC)**, con schema di somministrazione periodico
- **Eventi avversi** generalmente **lievi–moderati**, con buon profilo di sicurezza:
  - reazioni nel sito di iniezione
  - infezioni lievi delle alte vie respiratorie
  - cefalea

UTILIZZO PER LO STADIO 3

Trial clinico



Vohidova D et al. Front Immunol 2026

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Wagner R et al. Diabetes Res Clin Pract. 2026

Take home messages

1. L’immunoterapia nel T1D sta spostando il paradigma terapeutico: da una gestione esclusivamente sostitutiva a un approccio disease-modifying.

2. L’intervento precoce è cruciale: preservare la funzione beta-cellulare significa migliorare controllo metabolico, variabilità glicemica e qualità di vita.

3. La sfida futura sarà identificare il paziente giusto, nel momento giusto, con strategie immunoterapiche sempre più personalizzate ed integrate.

University of Piemonte Orientale - Novara, Italy
(picture of the Diabetes team from out visit)

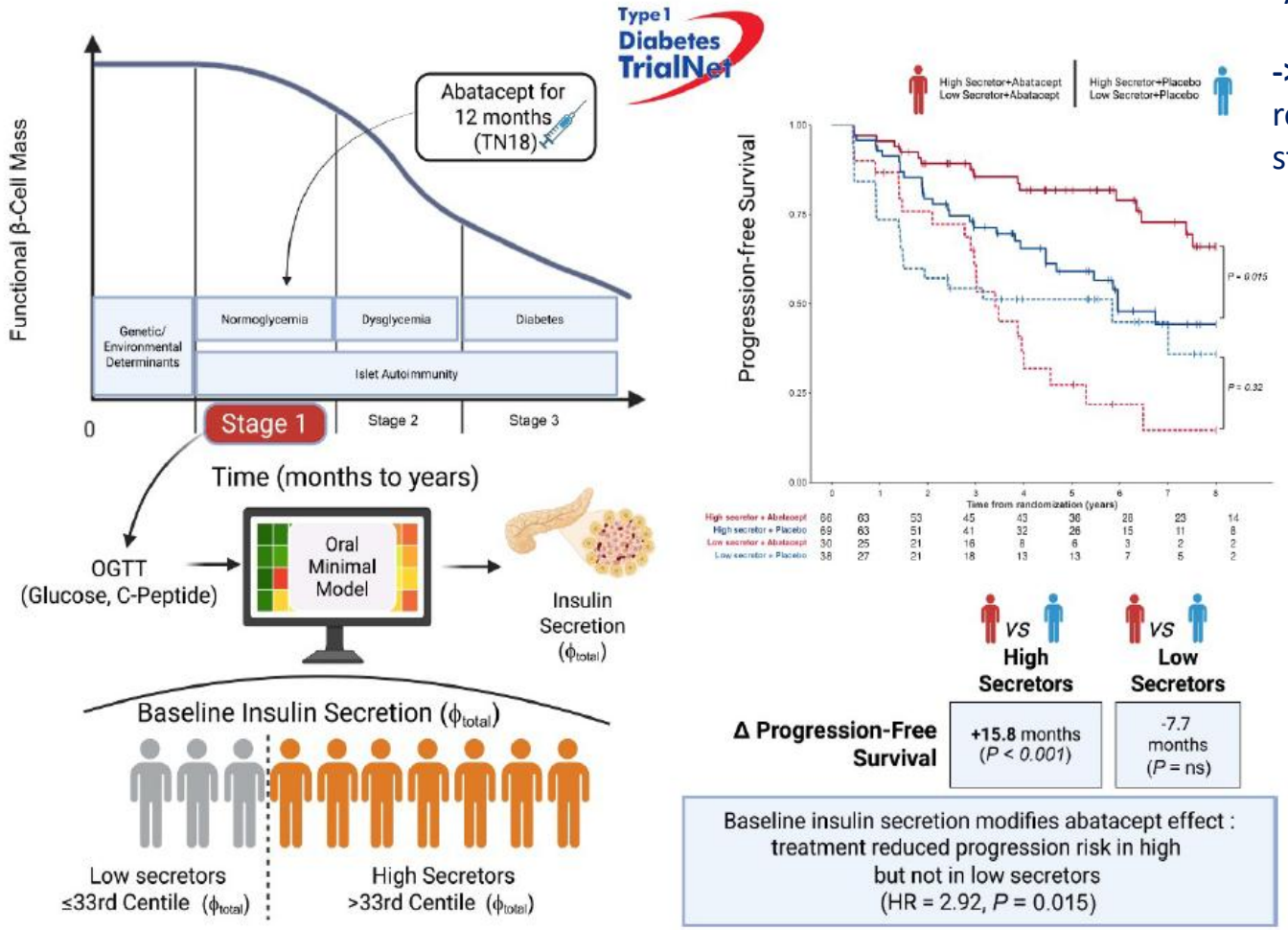
GRAZIE PER L'ATTENZIONE

UPO
UNIVERSITÀ DEL PIEMONTE ORIENTALE

Pediatria
Novara

Abatacept

Baseline Insulin Secretion Determines Response to Abatacept in Stage 1 Type 1 Diabetes



Δ Progression-Free Survival	vs High Secretors	vs Low Secretors
	+15.8 months ($P < 0.001$)	-7.7 months (P = ns)

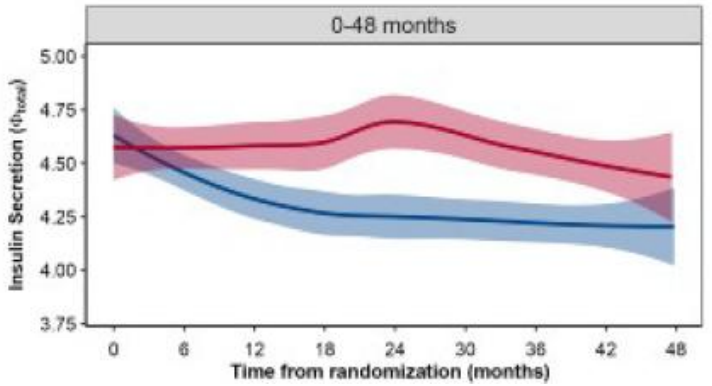
Baseline insulin secretion modifies abatacept effect : treatment reduced progression risk in high but not in low secretors (HR = 2.92, P = 0.015)

-> Abatacept is a CTLA4-Ig protein that blocks the costimulation of T lymphocytes, reducing the autoimmune attack against pancreatic β-cells.

-> Among 203 participants (abatacept *n* = 96; 107 placebo *n* = 107), 39% receiving abatacept and 47% receiving placebo experienced progression to stage 2 or 3 within 96 months.

-> **High secretors receiving abatacept gained 15.8 progression-free months and had a 54% lower hazard of progression versus those receiving placebo**.

-> The effect differed significantly by secretor status.



Galderisi A et al. Diabetes 2026

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Abatacept (73, 74)	CTLA–4–Ig – blocks CD28 co–stimulation, reduces T–cell activation	10 mg/kg IV day 1, 14, 28 then every 4 weeks for 24 months	New–onset (<100 days since diagnosis, 6–45 years)	Stimulated C-peptide release significantly higher after 2 years
Rituximab (75, 76)	Anti–CD20 – depletes B cells that present β–cell antigen	Four weekly IV infusions 375 mg m^{-2}	New–onset (<3 months since diagnosis, 8–40 years)	Stimulated C-peptide release significantly higher, significantly lower HbA1c values and lower insulin requirement after one year, effects not maintained after 2 years
Low–dose ATG ± G–CSF (77, 87, 88)	Polyclonal T–cell depletion (spares T–regs); G–CSF promotes tolerance	2-day IV total 4.5 mg/kg with or without s.c. G-CSF; recent MELD-ATG trials with 0.5–2.5 mg/kg ATG alone	New-onset stage 3 T1D (children, adolescents and adults)	Preserves stimulated C-peptide and improves HbA1c vs placebo; MELD-ATG shows efficacy down to 0.5 mg/kg without clear added benefit of G-CSF
Anti–IL–21 + Liraglutide (89)	IL–21 blockade dampens TFH/ autoreactive B cells; GLP–1 RA gives metabolic rest	30 mg SC anti–IL–21 weekly + liraglutide 1.8 mg SC daily for 54 weeks	New–onset (<20 weeks since diagnosis, 18–45 years)	Stimulated C-peptide release significantly higher after 54 weeks, but only when both active ingredients are combined
Verapamil (83, 84)	L-type Ca^{2+}-channel blocker; reduces TXNIP, ER-stress and β-cell apoptosis	120–360 mg orally once daily for 12 months	Adults with new-onset stage 3 T1D; paediatric data from separate trials	Small adult trial showed higher stimulated C-peptide, lower insulin dose and fewer hypoglycaemic events; a larger multicentre phase 2 trial (Ver-A-T1D) is ongoing; first conference reports suggest trends towards β-cell preservation, but full peer-reviewed results are awaited
Imatinib (85)	c–Abl inhibition → reduced ER–stress & innate activation	400 mg orally daily for 26 weeks	New–onset (<100 days since diagnosis, 18–45 years)	Higher C–peptide at 12 months; no difference at 24 months

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