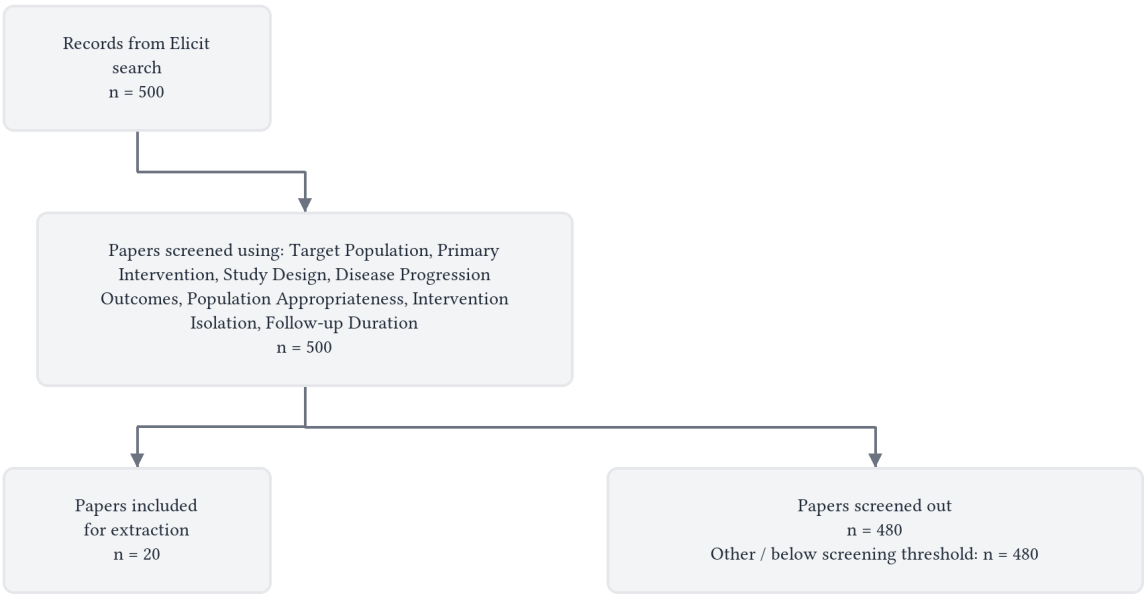
In non-diabetic individuals with Stage 2 type 1 diabetes, what is the median delay in months to the clinical onset of Stage 3 disease following a single 14-day course of teplizumab compared to placebo?

In the sole completed randomized trial (TN10, n = 76), a single 14-day course of teplizumab delayed the median onset of stage 3 type 1 diabetes by approximately 24 months compared to placebo (48.4 vs. 24.4 months; HR 0.41), an effect that remained durable over nearly 7 years of follow-up.

Abstract

All available evidence derives from a single pivotal trial — the TrialNet Anti-CD3 Prevention Trial (TN10) — a phase II, double-blind, placebo-controlled RCT of 76 participants with stage 2 type 1 diabetes (≥2 autoantibodies with dysglycemia) randomized to a single 14-day intravenous course of teplizumab (n = 44) or placebo (n = 32) [1, 2]. In the primary analysis, median time to stage 3 diagnosis was 48.4 months with teplizumab versus 24.4 months with placebo (HR 0.41; 95% CI 0.22–0.78; p = 0.006), corresponding to an approximately 24-month delay [1]. Extended follow-up confirmed durability: at a median of 80.46 months, 36% of teplizumab-treated participants remained free of clinical diabetes compared with 12.5% on placebo [3, 4]. The treatment effect was accompanied by reversal of pre-enrollment C-peptide decline and induction of partially exhausted CD8+ T cells [2, 3], and was substantially modulated by HLA genotype [5], genetic risk score (HR 0.263 for GRS2 ≥13 vs. 0.898 for GRS2 <13) [6], and baseline proinsulin:C-peptide ratio [7]. Common adverse effects included lymphopenia (73%) and rash (36%) [5]. Notably, the trial was small, enrolled exclusively White participants with a family history of T1D [3, 4], and whether the observed delay translates into reduced long-term complications or improved quality of life remains unestablished [4].

Flow Diagram



Paper search

We performed a semantic search across over 138 million academic papers from the Elicit search engine, which includes all of Semantic Scholar and OpenAlex.

We ran this query: "In non-diabetic individuals with Stage 2 type 1 diabetes, what is the median delay in months to the clinical onset of Stage 3 disease following a single 14-day course of teplizumab compared to placebo?"

The search returned 500 total results from Elicit.

We retrieved 500 papers most relevant to the query for screening.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Target Population**: Does the study focus on participants with Stage 2 type 1 diabetes (presymptomatic diabetes with dysglycemia) who have not yet progressed to clinical diabetes requiring insulin therapy?
- **Primary Intervention**: Does the study evaluate teplizumab as the primary intervention?
- **Study Design**: Is this a randomized controlled trial with a placebo or control group?
- **Disease Progression Outcomes**: Does the study report time-to-event data on progression to Stage 3 type 1 diabetes with sufficient detail to extract or calculate median time to progression?
- **Population Appropriateness**: Are participants free from established Stage 3 type 1 diabetes, type 2 diabetes, and other forms of diabetes?

- **Intervention Isolation**: Is teplizumab studied as a single intervention (not in combination with other experimental treatments that could confound results)?
- **Follow-up Duration**: Does the study have adequate follow-up duration to capture disease progression events?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

At abstract screening, the number of papers excluded for each primary reason was:

- **Other / below screening threshold**: n = 480

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Population**:

  Extract details confirming this study included non-diabetic individuals with Stage 2 type 1 diabetes, including:

- Explicit statement that participants had Stage 2 T1D (not Stage 1 or 3)
- Confirmation participants were non-diabetic at enrollment
- Autoantibody status (multiple positive antibodies expected for Stage 2)
- Glucose tolerance status at baseline (normal or impaired, but not diabetic)
- Any risk stratification criteria used
- Exclusion of participants with existing diabetes diagnosis

- **Teplizumab Regimen**:

  Extract complete details about the teplizumab intervention to verify it matches the research question criteria of a single 14-day course, including:

- Exact duration of treatment (should be 14 days)
- Number of treatment courses (should be single course)
- Dosage and administration schedule
- Route of administration
- Any dose modifications or interruptions
- Time between enrollment and treatment initiation

- **Control Group**:

  Extract details about the control/comparison group to confirm placebo comparison:

- Type of control (placebo vs. no treatment vs. standard care)
- Placebo administration details if applicable
- Any co-interventions provided to both groups
- Blinding procedures

- **Stage 3 Diagnosis**:

  Extract the definition and criteria used to diagnose Stage 3 type 1 diabetes (clinical diabetes onset), including:

- Specific diagnostic criteria (ADA, WHO, or other guidelines)
- Required glucose thresholds (fasting, OGTT, random, HbA1c)
- Number of abnormal tests required for diagnosis

- Whether diabetes symptoms were considered
- Who made the diagnosis and how it was confirmed

- **Time-to-Stage 3 Data**:

  Extract all time-to-event data for progression to Stage 3 diabetes, including:

- Median time to Stage 3 diagnosis in teplizumab group (in months)
- Median time to Stage 3 diagnosis in placebo group (in months)
- Hazard ratio with 95% confidence intervals
- P-values for time-to-event comparisons
- Kaplan-Meier survival estimates at key time points
- Percentage of participants remaining diabetes-free at study end
- Any competing risks or censoring details

- **Follow-up Duration**:

  Extract follow-up and monitoring details:

- Total study follow-up period (median and range)
- Frequency of assessments for diabetes progression
- Lost to follow-up rates in each group
- Date of study completion or data cut-off
- Any extended follow-up beyond the primary study period

- **Sample Characteristics**:

  Extract baseline sample characteristics relevant to Stage 2 T1D progression, including:

- Total sample size per group
- Age distribution (mean/median, range)
- Sex distribution
- Family history of type 1 diabetes
- Baseline C-peptide levels
- Baseline glucose tolerance status
- Time since autoantibody detection
- Any baseline predictors of progression risk

- **Study Design**:

  Extract study design elements affecting the quality and interpretability of time-to-event results:

- Study design type (RCT, observational cohort, etc.)
- Randomization method and concealment
- Blinding of participants, investigators, and outcome assessors
- Multicenter vs. single center
- Industry sponsorship or funding source
- Registration details (ClinicalTrials.gov number, protocol publication)

Results

Characteristics of Included Studies

All 20 sources pertain to or reference a single pivotal clinical trial: the TrialNet Anti-CD3 Prevention Trial (TN10, NCT01030861), a phase II, randomized, double-blind, placebo-controlled trial that enrolled 76 participants with stage 2 type 1 diabetes (T1D) [1, 2]. The sources include the primary trial publication, extended follow-up analyses, post hoc biomarker and genetic substudies, regulatory assessments, clinical guidelines, and narrative reviews or commentaries. No additional independent trial of a single 14-day teplizumab course in stage 2 T1D was identified.

Source	Full text retrieved?	Type	Focus
P. Beninger, 2023	No [8]	Drug capsule / summary	FDA approval summary for teplizumab [8]
Nuha A. ElSayed et al., 2023	Yes [5]	Clinical guideline addendum	ADA Standards of Care update incorporating teplizumab recommendation [5]
E. Sims et al., 2020	No [9]	Conference abstract (primary study substudy)	C-peptide and beta cell function analysis from TN10 [9]
I. Idris, 2023	No [10]	Commentary	Summary of FDA approval and TN10 trial results [10]
Alfonso Galderisi et al., 2024	Yes [11]	Post hoc analysis of TN10	Oral minimal model-derived metabolic indices in stage 2 T1D [11]
Dominika A. Michalek et al., 2024	No [12]	Conference abstract (genetic substudy)	Genome-wide analysis of genetic modifiers of teplizumab response [12]
Herold Kc et al., 2019	No [1]	Primary RCT publication	TN10 primary efficacy and safety results [1]
E. Sims et al., 2021	Yes [2]	Extended follow-up of TN10	Extended time-to-event and beta cell function analysis [2]
Ana Lledó-Delgado et al., 2024	Yes [3]	Extended immunological analysis of TN10	Single-cell RNA sequencing of CD8+ T cells and autoreactive repertoire [3]
E. Sims et al., 2023	Yes [7]	Post hoc biomarker analysis of TN10	Proinsulin:C-peptide ratio as predictor of progression and treatment response [7]
Z. Bloomgarden, 2024	Yes [13]	Narrative review	Overview of T1D prevention and reversal strategies including teplizumab [13]

Source	Full text retrieved?	Type	Focus
M. Redondo et al., 2024	No [6]	Conference abstract (genetic substudy)	T1D genetic risk score influence on teplizumab response [6]
I. Idris, 2020	No [14]	Commentary	Summary of updated TN10 follow-up data presented at ADA 2020 [14]
Q. Xie et al., 2023	No [15]	Biomarker study using TN10 sera	Anticommensal antibodies as predictors of T1D progression and teplizumab response [15]
CDA-AMC, 2026	Yes [4]	Health technology assessment	Canadian regulatory reimbursement review of teplizumab [4]
Howard D Larkin, 2023	No [16]	News summary	Brief report on FDA approval of teplizumab [16]
Immunotherapy delays type 1 di, 2019	No [17]	News summary	Brief report on TN10 phase II results [17]
E. Bonifacio & Gita Gemulla, 2022	No [18]	Commentary (German language)	Discussion of teplizumab for delaying T1D manifestation [18]
Ana Maria Lledo Delgado et al., 2024	No [19]	Conference abstract (immunological substudy)	T cell phenotype and repertoire changes after teplizumab [19]
Emily K. Sims et al., 2025	No [20]	Conference abstract (methodological)	Novel binary metabolic endpoint for T1D prevention trials [20]

Full texts were available for 7 of the 20 sources; the remaining 13 were available as abstracts only. Critically, all sources derive from or reference the single TN10 trial. The primary publication reported initial results [1], while subsequent sources represent progressively longer follow-up or secondary analyses of the same cohort.

Study Population and Design

The TN10 trial enrolled 76 participants — 44 randomized to teplizumab and 32 to placebo [1, 8]. All participants had stage 2 T1D, defined by the presence of two or more islet autoantibodies with dysglycemia but without clinical diabetes [3, 7]. Eligibility required a family history of T1D (i.e., a relative with stage 3 disease) [2, 4], confirmed positivity for at least two islet autoantibodies [4, 7], and dysglycemia on oral glucose tolerance testing (OGTT) with fasting glucose 110–125 mg/dL or 2-hour glucose 140–199 mg/dL [2, 13]. The majority of participants were pediatric: 72% were aged 18 years or younger [1], with a median age of approximately 13–14 years [2, 4]. Before enrollment, 75% of participants were positive for three or more autoantibodies [4].

Teplizumab was administered as a single 14-day course of intravenous infusion [1, 8, 10], with body surface area–

based dosing escalating from 51 μg/m² on day 0 to 826 μg/m² on days 4–13 [2]. The placebo group received saline infusion over the same 14-day period [2, 7]. The trial was double-blind [1, 2, 4, 8], placebo-controlled, event-driven, and multicenter [2, 3], registered under ClinicalTrials.gov NCT01030861 [1, 11]. Funding was primarily from the National Institutes of Health and the Juvenile Diabetes Research Foundation, with MacroGenics donating study agents [3, 11]. Stage 3 T1D diagnosis required confirmation by ADA criteria, including two consecutive diabetic OGTTs [2, 3]. Follow-up OGTTs were performed at approximately 6-month intervals [1, 2, 7].

Effects: Median Delay in Progression to Stage 3 T1D

Because all sources reference the same trial but at different follow-up time points or with different analytic subsets, the reported median times to stage 3 diagnosis vary. The table below summarizes the time-to-event estimates across all sources that provided quantitative data.

Source	Median follow-up	Median time to Stage 3: Teplizumab	Median time to Stage 3: Placebo	Difference (months)	Hazard ratio (95% CI)	p-value	Diabetes-free at end of follow-up: Teplizumab	Diabetes-free at end of follow-up: Placebo
Herold Kc et al., 2019	Not reported [1]	48.4 months [1]	24.4 months [1]	~24 months	0.41 (0.22–0.78) [1]	0.006 [1]	57% [1]	28% [1]
E. Sims et al., 2020	912 days (~30 months) [9]	Not reported [9]	Not reported [9]	~24 months (stated as median delay) [9]	Not reported [9]	Not reported [9]	Not reported [9]	Not reported [9]
I. Idris, 2020	Not reported [14]	Not reported [14]	Not reported [14]	Up to 3 years [14]	Not reported [14]	Not reported [14]	53% [14]	28% [14]
E. Sims et al., 2021	923 days (~31 months) [2]	59.6 months [2]	27.1 months [2]	~32.5 months	0.457 [2]	0.01 [2]	50% [2]	22% [2]
P. Beninger, 2023	51 months [8]	50 months [8]	25 months [8]	25 months	Not reported [8]	Not reported [8]	55% (inferred) [8]	28% (inferred) [8]
Nuha A. ElSayed et al., 2023	51 months [5]	50 months [5]	25 months [5]	25 months	Not reported [5]	Not reported [5]	Not reported [5]	Not reported [5]
I. Idris, 2023	51 months [10]	50 months (mean) [10]	25 months (mean) [10]	25 months	Not reported [10]	Not reported [10]	55% [10]	28% [10]

Source	Median follow-up	Median time to Stage 3: Teplizumab	Median time to Stage 3: Placebo	Difference (months)	Hazard ratio (95% CI)	p-value	Diabetes-free at end of follow-up: Teplizumab	Diabetes-free at end of follow-up: Placebo
E. Sims et al., 2023	72 months [7]	59.7 months [7]	35.4 months [7]	~24.3 months	Not reported for overall [7]	0.037 [7]	Not reported [7]	Not reported [7]
Alfonso Galderisi et al., 2024	Not explicitly reported [11]	46.7 months [11]	27.3 months [11]	~19.4 months	Not reported for overall [11]	0.014 [11]	Not reported [11]	Not reported [11]
Ana Lledó-Delgado et al., 2024	80.46 months [3]	52.2 months (95% CI: 30.5–86.7) [3]	27.3 months (95% CI: 9.5–48.4) [3]	~24.9 months	Not reported [3]	0.0026 [3]	36% [3]	12.5% [3]
Z. Bloom-garden, 2024	Not reported [13]	50 months [13]	25 months [13]	25 months	Not reported [13]	Not reported [13]	55% [13]	27% [13]
CDA-AMC, 2026	80.46 months [4]	49.5 months [4]	24.9 months [4]	~24.6 months	0.41 (0.22–0.78) [4]	0.0066 [4]	36% [4]	12.5% [4]
Howard D Larkin, 2023	Not reported [16]	Not reported [16]	Not reported [16]	~24 months (stated as ”about 2 years”) [16]	Not reported [16]	Not reported [16]	Not reported [16]	Not reported [16]
E. Bonifacio & Gita Gemulla, 2022	Not reported [18]	Not reported [18]	Not reported [18]	~3 years (stated as ”fast 3 Jahre”) [18]	Not reported [18]	Not reported [18]	Not reported [18]	Not reported [18]

Six sources (Dominika A. Michalek et al., 2024; M. Redondo et al., 2024; Q. Xie et al., 2023; Immunotherapy delays type 1 di, 2019; Ana Maria Lledo Delgado et al., 2024; Emily K. Sims et al., 2025) did not report specific median time-to-event estimates [6, 12, 15, 17, 19, 20].

The primary publication by Herold et al. (2019) reported a median time to stage 3 diagnosis of 48.4 months in the teplizumab group versus 24.4 months in the placebo group (HR 0.41; 95% CI 0.22–0.78; p = 0.006), corresponding to an approximate 24-month delay [1]. The annualized diagnosis rate was 14.9% per year for teplizumab versus 35.9%

per year for placebo [1]. With extended follow-up to a median of 923 days, Sims et al. (2021) found median times of 59.6 versus 27.1 months (HR 0.457; p = 0.01), with 50% of teplizumab-treated participants remaining diabetes-free compared with 22% on placebo [2]. The longest reported follow-up, at a median of 80.46 months, showed that 36% of the teplizumab group and 12.5% of the placebo group remained free of stage 3 T1D [3, 4], with median times to diagnosis of approximately 49.5–52.2 months versus 24.9–27.3 months [3, 4].

The variation in reported medians (teplizumab group ranging from 46.7 to 59.7 months; placebo group from 24.4 to 35.4 months) reflects differences in follow-up duration, analytic subsets used in post hoc analyses, and whether all 76 or a subset of participants were included. The post hoc analysis by Sims et al. (2023) included only 63 of 76 participants for whom proinsulin samples were available, yielding a placebo median of 35.4 months—higher than in the full cohort [7, 7]. Similarly, Galderisi et al. (2024) analyzed 67 of 76 participants with evaluable metabolic data and reported a teplizumab median of 46.7 months [11, 11]. Across all reports using the full cohort, the median delay attributable to teplizumab converges on approximately 24–25 months, with the hazard ratio consistently estimated at 0.41 [1, 4].

Effects: Beta Cell Function

Multiple analyses of TN10 demonstrated that the delay in clinical progression was accompanied by measurable improvements in beta cell function. Prior to enrollment, C-peptide area under the curve (AUC) was declining at similar rates in both groups [9]. In the 6 months following treatment, teplizumab reversed this decline, with C-peptide AUC increasing significantly compared to continued decline in the placebo group (p = 0.003) [9]. Average on-study C-peptide AUC was 1.94 pmol/mL in the teplizumab group versus 1.72 pmol/mL in the placebo group (p = 0.006) [2]. Oral minimal model analyses further showed that insulin secretion rose in teplizumab-treated participants over 12 months while declining in those receiving placebo [11]. Notably, slow-progressors in both treatment arms showed decreased insulin clearance relative to rapid-progressors, and this metric predicted longer progression-free survival independently of treatment assignment [11].

Effects: Adverse Events

The most common adverse reactions were lymphopenia (73%) and rash (36%) [5]. Additional reported adverse effects included headache, leukopenia, anemia, low IgM, thrombocytopenia, and liver function abnormalities [13]. Serious infection developed in 9% of teplizumab-treated participants compared with none in the placebo group, and one case of cytokine release syndrome was reported [13]. The CDA-AMC assessment noted that while short-term safety data documented these side effects, no long-term safety data or quality-of-life data were available [4].

Effects: Predictors of Response

Several substudies identified baseline characteristics that modulated the magnitude of teplizumab's effect.

- **HLA genotype**: Among participants who were HLA-DR3−negative or HLA-DR4−positive, the treatment effect was more pronounced (HR 0.20; 95% CI 0.09–0.45 and HR 0.18; 95% CI 0.07–0.45, respectively) [1, 5].
- **Genetic risk score**: A T1D genetic risk score (GRS2) dichotomized at 13 showed a significant interaction with treatment. For GRS2 ≥13, the hazard ratio for teplizumab versus placebo was 0.263 (95% CI 0.123–0.562), while for GRS2 <13, it was 0.898 (95% CI 0.295–2.74; interaction p = 0.03) [6]. This suggests that individuals with higher genetic burden of T1D risk derived substantially greater benefit from teplizumab.
- **Proinsulin:C-peptide ratio**: Elevated baseline PI:C ratios were associated with more rapid progression in both arms, but teplizumab abrogated the impact of high PI:C on progression (treatment × PI:C interaction p = 0.017)

[7]. This positions PI:C as a potential biomarker to identify optimal candidates for treatment.

- **Anticommensal antibodies**: IgG2 responses against three gut bacterial species were associated with both time to diagnosis and treatment response, suggesting that intestinal immune tone may influence teplizumab efficacy [15].
- **Genome-wide variants**: SNP–drug interaction analyses identified known T1D loci (CCR9, SH2B3, UBASH3A, INS) that differentially influenced progression in the teplizumab versus placebo arm [12]. Polygenic score traits with similar genetic architecture to teplizumab response included vitamin B12 and vitamin D [12].

Effects: Immunological Mechanism

The clinical benefit of teplizumab was paralleled by characteristic changes in CD8+ T cell populations. Treatment was associated with increased frequencies of partially exhausted KLRG1+TIGIT+ CD8+ T cells, which showed reduced secretion of IFNγ and TNFα [1, 2]. Increases in C-peptide AUC correlated with increases in these exhausted effector cells ($r = 0.44$; $p = 0.014$) [2]. Single-cell RNA sequencing at 3 months post-treatment revealed transcriptional signatures of T cell activation that were subsequently reversed at 18 months, giving way to increased expression of exhaustion- and immune regulation–associated genes [3]. Pseudotime analysis demonstrated differentiation of CD8+ T cells into exhausted and memory phenotypes after teplizumab [3]. Critically, autoantigen-reactive CD8+ T cells expanded in the placebo group over 18 months but did not expand in the teplizumab group, consistent with the induction of operational tolerance [3, 19]. Reduced IL7R/CD127 expression was associated with longer diabetes-free intervals [3], and persistent EOMES expression predicted time to clinical diagnosis [19].

Synthesis

The apparent variation in reported median delay — ranging from approximately 19 to 33 months — does not reflect genuine heterogeneity in treatment effects but rather stems from methodological differences across analyses of the same trial. Three factors account for the observed variation.

First, the analytic subset matters. Post hoc analyses that excluded participants without available biomarker samples (e.g., 63 of 76 in Sims et al. 2023 [7]; 67 of 76 in Galderisi et al. 2024 [11]) produced different median estimates because the excluded individuals may have had systematically different progression rates. The full-cohort analyses consistently yield a median delay of approximately 24–25 months [1, 4].

Second, longer follow-up reveals evolving survival curves. At the initial report (median follow-up ~51 months), the teplizumab group median was 48.4 months [1]. At extended follow-up (~923 days median), the median increased to 59.6 months [2], reflecting additional time needed for remaining participants to reach the event. By the longest follow-up (median 80.46 months), 36% of the teplizumab group remained diabetes-free versus 12.5% in the placebo group [3, 4], indicating that a substantial minority experienced durable delay from a single treatment course. However, the difference in median times remained in the range of 24–25 months across these analyses.

Third, the sources that report round figures of "50 versus 25 months" or "approximately 2 years" [5, 8, 13, 16] are summarizing or rounding from the primary data rather than presenting independent estimates.

Several important caveats limit the generalizability of these findings. The trial enrolled only 76 participants, a small sample size for a time-to-event study, and imbalances existed in baseline characteristics (e.g., proportion of first-degree relatives, specific autoantibody profiles) [4]. All participants had a family history of T1D [4], whereas most individuals who develop T1D do not [8], raising questions about applicability to a general screening-identified population. The trial enrolled exclusively White participants [3], limiting racial and ethnic generalizability. The CDA-

AMC assessment concluded that although the approximately 2-year delay in progression was demonstrated, the evidence does not establish whether this delay translates into reduced long-term macrovascular or microvascular complications, improved quality of life, or reduced insulin burden [4]. No long-term safety data beyond the trial period were available [4]. The cost of the 14-day regimen is approximately $193,900 [8], which the CDA-AMC considered in recommending against public reimbursement [4].

The response to teplizumab is not uniform. Genetic risk scores [6], HLA genotype [5], baseline metabolic status (PI:C ratio) [7], and even anticommensal antibody profiles [15] all modulate the magnitude of benefit. Participants with higher genetic risk (GRS2 ≥13) showed a hazard ratio of 0.263 for teplizumab versus placebo, whereas those with lower genetic risk showed essentially no benefit (HR 0.898) [6]. This heterogeneity suggests that precision biomarkers may be essential for identifying individuals most likely to benefit from treatment and that population-level estimates of a 24-month median delay may understate the benefit in high-risk subgroups while overstating it in others.

In summary, across all available analyses of the TN10 trial — the sole completed randomized trial of a single 14-day course of teplizumab in stage 2 T1D — the median delay in progression to stage 3 disease is approximately 24 to 25 months relative to placebo (HR 0.41; 95% CI 0.22–0.78; $p \approx 0.006$) [1, 4]. A durable effect is evident, with over one-third of treated participants remaining free of clinical diabetes at nearly 7 years of follow-up [3, 4], though the proportion continues to decline with time.

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