Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST) Analysis of Nirogacestat in Patients With Desmoid Tumors

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INTRODUCTION

- Desmoid tumors (DT) are rare, locally aggressive, soft-tissue tumors that infiltrate surrounding structures, can be life-threatening when vital organs are impacted, and can cause debilitating symptom burden[1,2]
- Nirogacestat, an oral, targeted gamma secretase inhibitor, is the only US FDA- and European Commission-approved treatment for adults with progressing DT who require systemic treatment[3-5]
- In the phase 3 DeFi trial, nirogacestat demonstrated significant improvement in progression-free survival (PFS), objective response, and patient-reported outcomes compared with placebo; 95% of all adverse events (AEs) were grade ≤2[6]

OBJECTIVE

- To investigate the benefit of nirogacestat in terms of survival, disease progression, and treatment toxicity versus placebo in patients with progressing DT via the comparative quality-adjusted survival, a Quality-adjusted Time Without Symptoms of disease progression or Toxicity (Q-TWiST) analysis

METHODS

Q-TWiST methodology

- The Q-TWiST analysis partitioned survival into 3 health states
  - (i) **TOX**, the time spent with treatment-related toxicity prior to disease progression
  - (ii) **TWiST**, the time without progression or toxicity
  - (iii) **REL**, the time from disease progression until death or end of follow-up
- Each health state was weighted with fixed utility values (U_{TWiST}=1.0, U_{TOX}=0.5, U_{REL}=0.5), consistent with prior Q-TWiST literature, to evaluate trade-off between treatment-related toxicity and survival outcomes[7-9]

Time point for restricted means estimation

- The analysis utilized the double-blind phase of the DeFi trial to maintain randomization and minimize confounding[10]
- Outcomes were assessed over 20.6 months, which corresponds to the median treatment duration for nirogacestat[7]

Long-term extrapolations of TOX, PFS, and overall survival

PFS

- An unanchored indirect treatment comparison (ITC) was conducted to model the PFS curves for nirogacestat versus active surveillance over a longer time horizon (base case, 20.6 mo; scenarios, 2–5 y). The resulting hazard ratio for nirogacestat was applied to the active surveillance PFS curve, which was then extrapolated using parametric distributions and log-normal distribution for best fit
- The model provided the option to use a piece-wise approach (base case) or parametric approach to extrapolate PFS over a longer time horizon

Overall survival

- The model provided the option to include background mortality that was adjusted for the disease using a standardized mortality ratio of 3.70. The ratio was applied to the general population mortality sourced from the US Centers for Disease Control and Prevention (2022)
- This ratio was estimated using the number of expected and observed deaths between the general population and patient population with a mean age of 34 years, over a 5-year period (based on the DeFi trial). The estimated 5-year overall survival (OS) for patients is 96%[11]

TOX

- The tail ends of TOX survival curves were conservatively extrapolated using a simple exponential distribution

Model specification

- The base case analysis included only treatment-related grade ≥3 AEs by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, with the assumption that such events are more likely to have a meaningful impact on quality of life
  - Sensitivity analysis only pertains to base case scenario
- Scenario analyses for grade ≥3 AEs across multiple time frames (2–5 y) and serious treatment-emergent AEs were conducted
- AEs were regrouped according to the US prescribing information for nirogacestat[3]

Sensitivity analyses

- Sensitivity analyses were conducted to ascertain the impact of uncertainty on the utility values of TOX and REL health states and the time in each state
  - Threshold utility analysis computes the average Q-TWiST gained between the two groups, where the utility values for TOX and REL health states are varied between 0 and 1 while keeping the utility value for the TWiST health state constant at 1
  - Q-TWiST gain function assesses how average Q-TWiST gain (days) group effect unfolds over longer patient follow-up times, where UTOX and UREL are varied between 0 and 1 while keeping U_{TWiST} constant at 1

Assumptions

- Analyses excluded observations with missing AE grade or end date
- Regardless of severity, U_{TOX} was fixed at 0.5, consistent with published Q-TWiST conventions
- AEs were assigned a start and end date, defined as resolution, disease progression, death, or last follow-up, whichever occurred first
- Days with multiple AEs were counted once, and all days with AEs prior to progression were aggregated to calculate TOX duration

Practical interpretation

- The Q-TWiST framework provides an integrated measure of net clinical benefit by balancing survival gains with treatment-related toxicity
- The relative gain in Q-TWiST for nirogacestat compared with placebo was calculated as the difference in Q-TWiST divided by the OS of the placebo arm
- Positive value indicates more time in good health
- A relative gain ≥10% is considered clinically important[7]

Limitations

- This analysis did not include patient-reported utility data, preventing insight into real-world quality of life
- The same utility value was applied to AEs, regardless of the type of AE

RESULTS

Base case

- Nirogacestat treatment is associated with significantly longer mean restricted TWiST (+137.57 days; *P*<.001), significantly longer TOX (+11.41 days; *P*<.001), and significantly shorter REL (-143.33 days; *P*<.001) versus placebo (**Table 1**)
  - With nirogacestat treatment, the majority of AEs occurred early and were grade ≤2
- Patients treated with nirogacestat had statistically significant and superior Q-TWiST gain of 71.60 days (*P*<.001) and a clinically important relative gain of 11.52% versus placebo

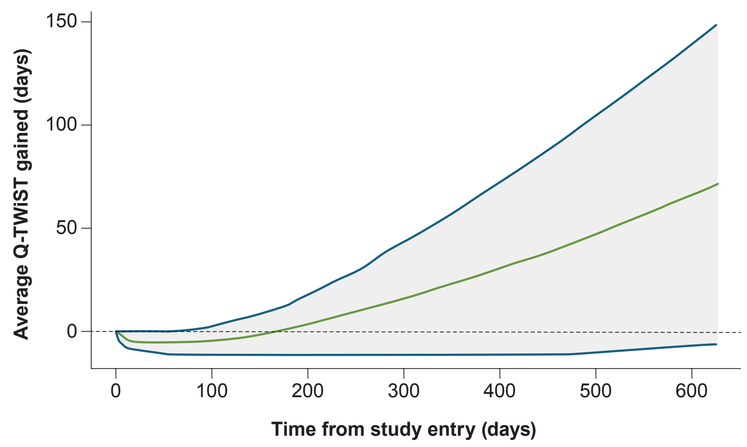
Table 1. Restricted mean duration of health states

	Nirogacestat	Placebo	Difference	*P*-value
Health state, days				
TWiST	543.65	406.09	137.57	<.001
TOX	11.41	0.00	11.41	<.001
REL	71.94	215.27	-143.33	<.001
PFS, days	555.07	406.09	148.98	<.001
OS, days	627	621.36	5.64	0.306

OS, overall survival; PFS, progression-free survival, TWiST, time without progression or toxicity.

- In the threshold utility analysis of the base case, the between-group difference in Q-TWiST ranged from -6.84 days to +149.35 days (relative gain ranges from -1.1% to 24.1%) when comparing nirogacestat with placebo, and a majority exceeding the threshold for minimal importance as previously defined[7]
  - Q-TWiST gain decreased for higher REL and lower TOX utility weights
  - There was no combination where placebo was significantly better than nirogacestat
- In the Q-TWiST gain function, the average Q-TWiST gain dips below 0 days and steadily increases over 200 days from study entry (**Figure 1**); Q-TWiST gain function was primarily driven by longer PFS time with nirogacestat versus placebo
  - There were greater gains for nirogacestat versus placebo with longer follow-up time

Figure 1. Q-TWiST gain function: base case



Q-TWiST, Quality-adjusted Time Without Symptoms of disease or Toxicity.
Green line represents the time gained for Q-TWiST evaluated with U_{TOX}=0.5, U_{REL}=0.5, and U_{TWiST} held constant at 1.0. Shading represents the time gained for Q-TWiST as the coefficient values for TOX and REL range between 0 and 1. Upper line represents U_{TOX}=1 and U_{REL}=0; the lower line represents U_{TOX}=0 and U_{REL}=1.

Scenarios

- When analyzed over a longer time horizon, greater Q-TWiST gains for nirogacestat were observed that were primarily driven by lower relapse durations and limited toxicity duration (**Table 2**)
- When TOX was defined to include serious treatment-emergent AEs only, the Q-TWiST and sensitivity analyses were similar to those of the base case (**Table 2**)

Table 2. Scenario analyses

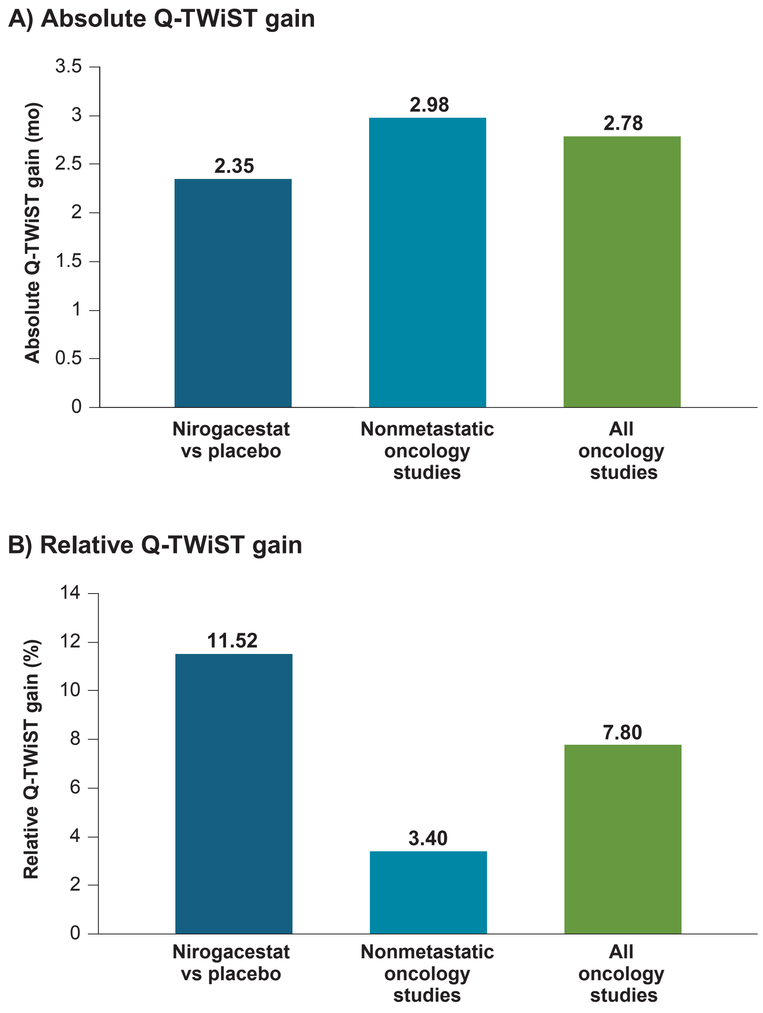
Scenario	Q-TWiST difference (days)	Relative Q-TWiST gain (%)
Base case grade ≥3 AEs at 20.6 mo	71.60	11.52%
Serious treatment-emergent AEs at 20.6 mo	73.48	11.83%
Grade ≥3 AEs at		
2 y	92.71	12.90%
3 y	176.66	16.58%
4 y	268.21	19.09%
5 y	364.22	20.96%

AE, adverse events; Q-TWiST, Quality-adjusted Time Without Symptoms of disease or Toxicity.

Discussion

- At the analysis point of 20.6 months, Q-TWiST analysis demonstrated that nirogacestat provided a clinically important improvement in quality-adjusted survival, superior to placebo
  - Gains were primarily driven by sustained increases in TWiST beginning at 6 months, with longer follow-up further amplifying the Q-TWiST advantage of nirogacestat
- In a systematic literature review, the observed absolute Q-TWiST gain for nirogacestat versus placebo of 2.35 months is consistent with gains reported in nonmetastatic oncology studies and across all oncology studies (**Figure 2A**)[8]
- The relative Q-TWiST gain of 11.52% with nirogacestat was greater than the average reported in both nonmetastatic studies and all oncology studies (**Figure 2B**)[8]
- Only 18.2% of nonmetastatic studies and 40% of oncology studies achieved relative Q-TWiST gains ≥10%[8]

Figure 2. Comparative Q-TWiST gains between nirogacestat and reported oncology studies



Q-TWiST, Quality-adjusted Time Without Symptoms of disease or Toxicity.

CONCLUSIONS

- Based on DeFi trial data, nirogacestat resulted in a statistically significant and clinically important (≥10%) longer quality-adjusted survival, superior to placebo, which increased over the longer time horizon
- Q-TWiST gains were primarily driven by time in "good" health (ie, TWiST), which largely resulted from the long-term PFS benefits and lower differences in adverse events observed for nirogacestat versus placebo
- This analysis highlights the overall positive net benefit of nirogacestat versus placebo

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