Impact of Censoring Rules on Q-TWiST Analysis and Challenges in Oncology Research: A Simulation Study

MSR106

Digital poster

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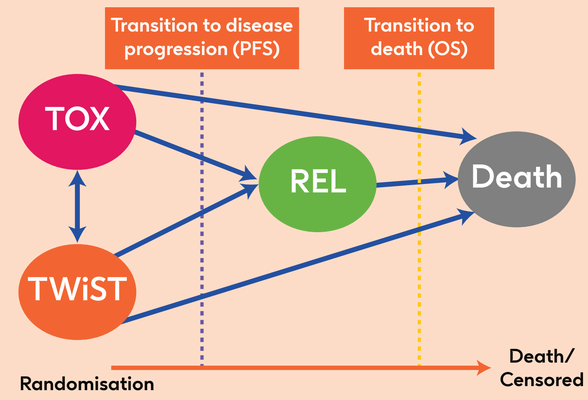
Background

- Quality-adjusted Time Without Symptoms of disease progression or Toxicity of treatment (Q-TWiST) allows for the integration of both quality of life (QoL) and survival time, and enhances the ability of health technology assessment (HTA) bodies to evaluate treatment effects
- In Q-TWiST analysis, the overall survival (OS) time (death from any cause) is partitioned into three clinically important health states[1]: TOX: the time spent experiencing adverse events, TWiST: the time spent progression free and without adverse events (time without significant toxicity), and REL: the time spent alive following progression. The duration in each state is weighted by a utility score reflective of the QoL for that state and summed to give the Q-TWiST value for the time that the patient is alive or until the end of the follow-up period (**Figure 1**)
- This approach is useful if there are important trade-offs between endpoints such as increased survival time with treatment side effects and QoL but longer time to progression comparatively in one arm
- Q-TWiST analyses are therefore useful to help differentiate the potential value of a treatment based on QoL and time spent in different health states. This analysis helps regulatory and HTA bodies with policy decisions, economic evaluation and reimbursement decisions

Figure 1. Q-TWiST: Transitions between the states during follow-ups



Note: If any transition time is censored, then all subsequent times are censored.
PFS, progression-free survival.

Conclusions

- Impact of censoring is negligible when a higher proportion of AEs ends up in progression
- The censoring rule for TOX could have an impact in the resultant Q-TWiST if a lower proportion of patients has progression
- Q-TWiST analysis is a valuable tool for health authorities to support cancer treatment evaluation
- Sufficient follow-up and the maturity of data are crucial considerations when conducting Q-TWiST analysis

Objectives

- To consider two TOX censoring rules and study the impact on Q-TWiST in 36 scenarios using simulated data
- To evaluate the methodology and challenges in performing Q-TWiST analysis with different types of data

Methodology

- Three health states, TOX, TWiST and REL, were calculated using the area under the Kaplan–Meier (KM) curves. See example in **Figure 2**

Figure 2. KM curve for OS, PFS and TOX for the intervention group[2]

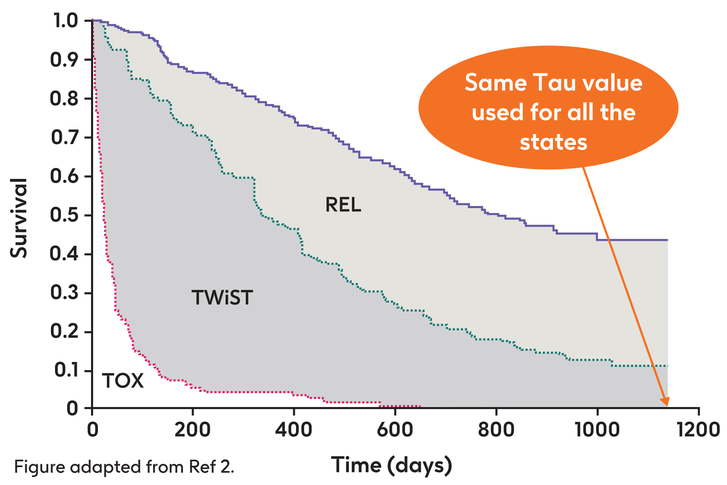


Figure adapted from Ref 2.

- TOX is the area under the KM curve for time (e.g. months) due to adverse events (AEs) of the defined grade (e.g. Grade 2, 3) (TOX=time spent in the AEs)
- TWiST is the area under the KM curve for time to progression event minus area under the KM curve for time with toxicity (TWiST=PFS-TOX)
- REL is the area to OS event minus the area to progression event from randomisation (REL=OS-PFS)
- The mean Q-TWiST represents QoL-adjusted mean OS. Q-TWiST is the sum of the product of the restricted mean survival time spent in three mutually exclusive health states and their respective utility weights

$$\text{Q-TWiST} = (U_{TOX} \times \text{TOX}) + (U_{TWiST} \times \text{TWiST}) + (U_{REL} \times \text{REL})$$

where TOX, TWiST and REL represent the mean health state durations, and U_{TOX}, U_{TWiST} and U_{REL} denote the average utility weight for each health state

- The corresponding 95% confidence interval (CI) is calculated using bootstrapped samples
- QoL measures like EuroQoL-5 dimensions-5 levels (EQ-5D-5L) are one of the most common measures used for calculating utility weights. Generalised Estimating Equations (GEE)/Linear Mixed Model may be used for analysing the repeated QoL measures
- If patient-level QoL measures are not available, threshold measures of utility weights are also used for the three states over the follow-up times

Use of simulated data to identify Q-TWiST variations

Two censoring rules for TOX time were considered (Table 1)

- **No censoring[1]:** All TOX values considered as events
- **PFS censoring[3]:** Patients with censored PFS had TOX time censored

Simulation set-up (Table 1 and Table 2)

- Parametric simulations employed parameters which were based on an immuno-oncology trial
- In this analysis, considering two censoring rules, a total of 36 scenarios were explored, and the trends in Q-TWiST were studied using 1000 simulations for each scenario, with a sample size of 200 patients

Table 1. Stratification and distribution of measures

Measure	Stratification	Distribution
TOX: duration of grade 3+ AE before disease progression (or progression censoring date if no progression)	PFS status	Log-normal
PFS: time from randomisation to disease progression/death or last known follow-up date if no progression and alive	PFS censoring	Weibull
OS: time from randomisation to death or last known follow-up date if alive	OS censoring	Weibull

Table 2. Variables used in simulation

Proportion with AE	Proportion with progression in patients with AE	Multiplier of mean AE duration
20%	40%	1
40%	60%	2
60%	80%	0.5
80%	-	-

AE refers to grade 3+ AE

Results

Table 3. Simulation results

Proportion of patients with AE	Patients with AE and progression	Multiplier of mean AE duration	TOX curve – No censoring			TOX curve – PFS censoring			Q-TWiST ratio†
			TOX	TWIST	Q-TWiST*	TOX	TWIST	Q-TWiST*	(Ref PFS censoring)
20%	40%	1	0.472	23.899	29.120	3.537	20.833	27.587	1.06
20%	60%	1	0.425	22.391	28.366	2.261	20.556	27.448	1.03
20%	80%	1	0.374	20.959	27.650	1.412	19.921	27.131	1.02
40%	40%	1	0.946	24.475	29.408	5.188	20.234	27.287	1.08
40%	60%	1	0.858	21.506	27.924	3.069	19.296	26.818	1.04
40%	80%	1	0.755	18.730	26.535	1.791	17.694	26.017	1.02
60%	40%	1	1.419	25.080	29.711	6.720	19.779	27.060	1.10
60%	60%	1	1.281	20.552	27.447	3.749	18.084	26.213	1.05
60%	80%	1	1.131	16.550	25.446	2.116	15.565	24.953	1.02
80%	40%	1	1.894	25.698	30.020	8.216	19.376	26.859	1.12
80%	60%	1	1.714	19.674	27.008	4.486	16.902	25.622	1.05
80%	80%	1	1.512	14.523	24.432	2.469	13.566	23.954	1.02

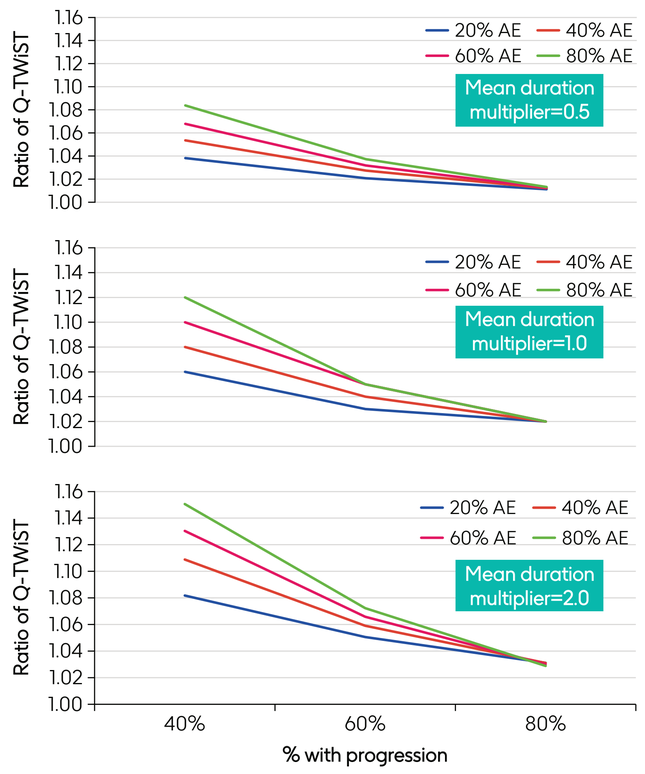
*Q-TWiST = 0.5 x TOX + 1 x TWiST + 0.5 x REL. †Q-TWiST ratio was defined as Q-TWiST without censoring divided by Q-TWiST with PFS censoring.

- No censoring, compared with PFS censoring, resulted in a smaller TOX value and, hence, a larger TWiST and Q-TWiST (**Table 3**)
- For any given AE proportion, the Q-TWiST ratio decreased (impact of censoring rules diminished) as the proportion of patients with progression increased (**Table 3**)

Impact on Q-TWiST (Figure 3)

- The Q-TWiST ratio increased as the AE proportion increased
- The Q-TWiST ratio also increased as the mean duration of AEs increased
- Conversely, as the proportion of patients with progression increased, the Q-TWiST ratio decreased

Figure 3. Q-TWiST ratio vs proportion of patients with progression



Abbreviations

AE, adverse event; CI, confidence interval; EQ-5D-5L, EuroQoL-5 dimensions-5 levels; GEE, Generalised Estimating Equations; HTA, health technology assessment; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; QoL, quality of life; Q-TWiST, Quality-adjusted TWiST; REL, relapse; TOX, toxicity; TWiST, Time Without Symptoms of disease progression or Toxicity of treatment

International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe 2024 | 17–20 November 2024 | Barcelona, Spain

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Acknowledgements

Medical writing and coordination support was provided by Dr. Alap P. Chavda, an employee of GSK.

Disclosures

Funding: GSK. All authors are employed by GSK and declare no other financial or non-financial interests, relationships and activities.

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