Censoring and choice of Tau in Quality Adjusted Time Without Symptoms of Toxicity (QTWiST)

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Q-TWiST: What (Definition)

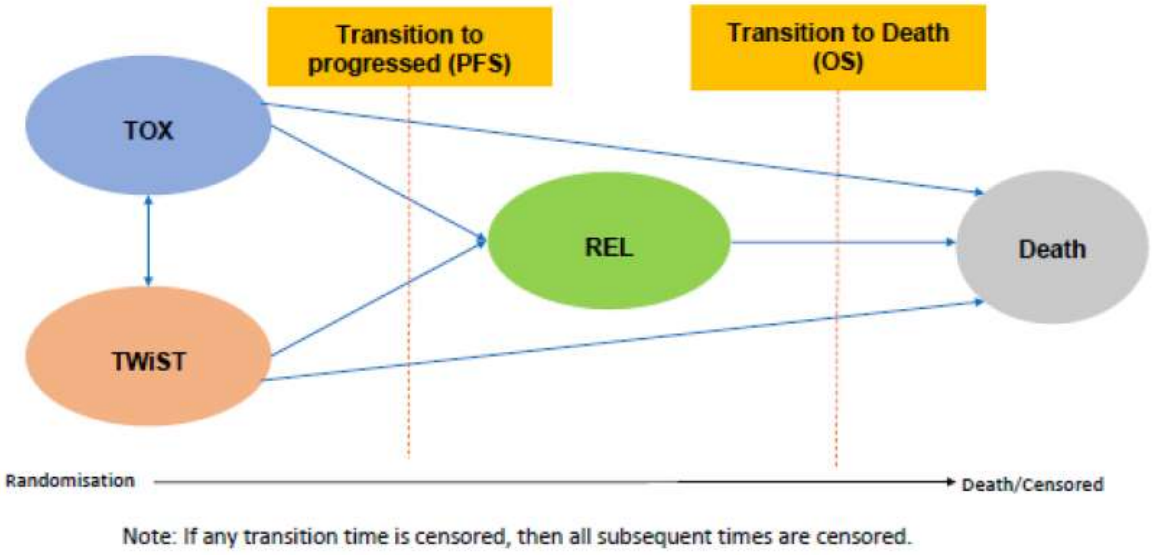

Fig 1: Q-TWiST: Transitions between the states during follow-ups

Q-TWiST: Quality-adjusted Time Without Symptoms of disease progression or Toxicity of treatment

The overall survival (OS) time (death from any cause) are partitioned into time spent in clinically important health states and estimates the time spent in each health state for patients (Gelber 1996, Goldhirsh 1989).

Toxicity (TOX) - time spent with toxic effects of cancer treatment or symptoms of disease

TWiST - time without symptoms of disease progression or treatment toxicity

Relapse (REL) - time from disease progression to death

Q-TWiST: Why (Rationale)

In general, treatments are compared by a head-to-head analysis of each endpoint separately. This approach is ideal if there are **important trade-offs** between endpoints such as increased survival time with side effects of treatment but longer time to progression comparatively in one arm. Q-TWiST allows integration of both the quality and quantity of survival time.

Regulatory Agencies (e.g. FDA), and American Society of Clinical Oncology (ASCO) Value Framework proposed **metrics that combine** clinical benefits, side effects, and improvement in patient symptoms or QoL (Schnipper 2016).

QTWiST can be applied to understand the benefits and risks of therapy when survival data is immature or not significantly improved but differences in disease-free survival/progression-free survival and toxicities exist (Gelber 1995).

Useful when new treatment does not show significant prolongation of life but may have advantage of improving/maintaining quality of life of the patient (Gelber 1995).

Q-TWiST: Overview of Methods

The mean Q-TWiST represents QoL-adjusted mean OS. Sum of the product of the restricted mean survival **time spent** in three mutually exclusive health states: TOX, TWiST and REL and their respective **Utility weights**

Q − TWiST = (*U*tox× TOX) + (*U*twist × TWiST) + (*U*rel× 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.

95% CI for each health state is calculated with percentiles estimated from 1000+ replications of samples.

The duration in **each state** is weighted by a utility score for that state and summed to give the Q-TWiST for the time that the person is alive or until the end of the follow-up period.

QoL measures like EQ-5D-5L is the most common measure used for calculating the weights. Linear Mixed Model are used for repeated QoL measure.

If patient level QoL measures are not available, threshold measure of utility weights are also used for these three states over the follow ups. [Gelber D. etal 1995]

RMST: Calculation of states

TOX= time spent in the AEs;

TWiST = PFS − TOX;

REL = OS−PFS.

- If **AE start date** is missing and **AE end date** is after Randomisation, then **Rand date** set as **AE Start date**
- If **AE start date** is before **Rand date** and **AE end date** after **Rand date** or missing, then **Rand date** is set as **AE Start date**.
- If **AE end date** is missing or AE has not been resolved by progression date, then **AE end date** is set as progression date. ***Explore the cases like these.***

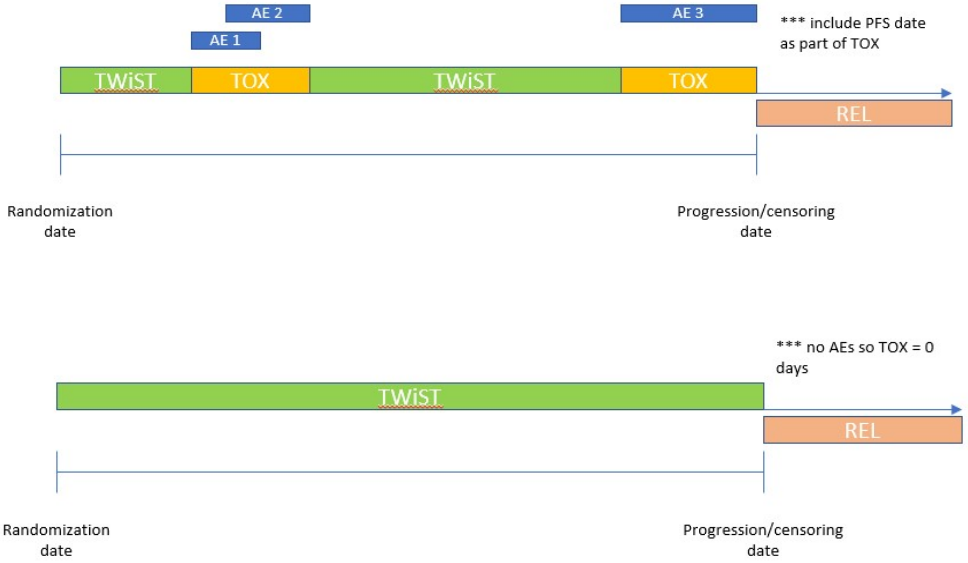

Fig 2: Q-TWiST: Calculation of the three states

Q-TWiST: States under the KM Curve

TOX is the area under the KM for time unit (e.g. months) due to the AE by the defined grade (e.g. grade 2, 3 etc), i.e. months with symptom of toxicity

TWiST is the area under the KM curve for months to progression event minus area under the KM curve for months with toxicity, i.e., months without the symptoms of toxicity prior to disease progression.

REL is the area to OS event minus the area to progression event from randomization, i.e., time from disease progression to death.

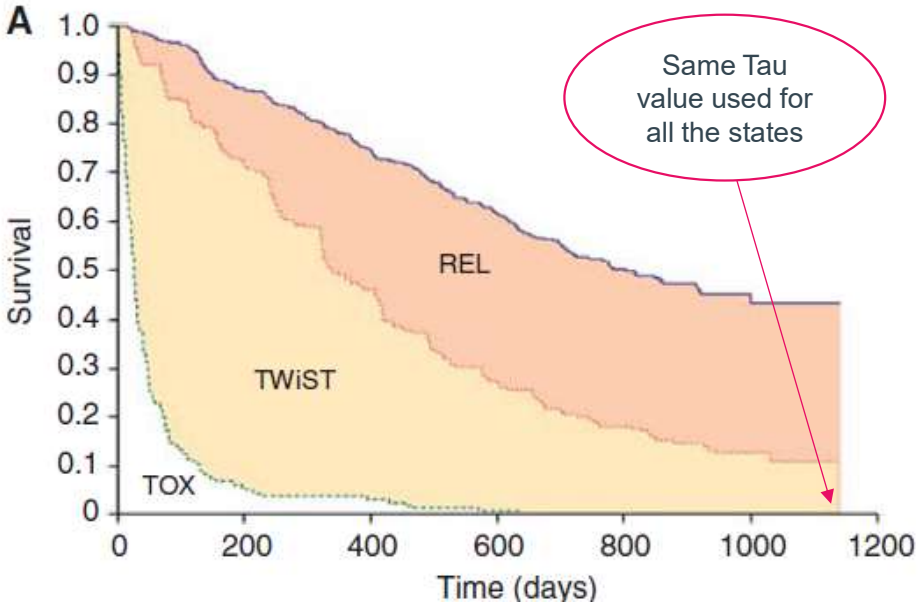

Fig: Kaplan-Meier Curve for OS, PFS and TOX for the intervention group (Patel et.al. BJC 2012)

Censoring in Q-TWiST

- In general, in RMST, patients with censored progression (pfs censored) will also have their tox time censored.
- However, if for any patients where the AE is resolved, tox time will not be considered as censored.

- The study team should consider discussing cases with the clinicians if there is a lot of AE events for which AE is not resolved by the progression date.
- Other wise we may end up quite large open ended (non progressed) TOX curves, which is advised to be avoided as much possible.

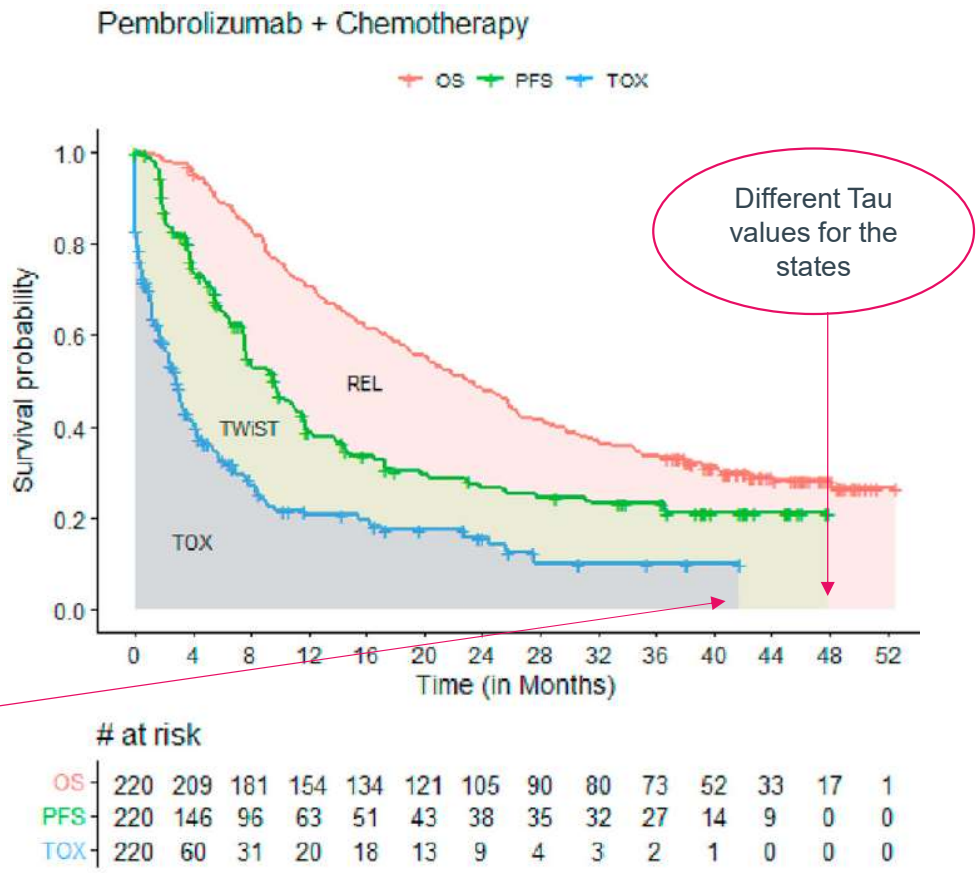

Fig: Partitioned survival plots between pembrolizumab plus chemotherapy (Haung et.al., EJC 2022)

RMST: Choice of Tau

- RMST, a novel alternative measure to survival analysis
- Can be interpreted as the mean event free-survival time up to a pre-specified clinically important point
- Useful during the lack of proportionality assumptions and low event rate

Defined as “the minimum of the maximum observed from two groups”… a data driven approach….

Need to be based on clinical relevance

Not be too small to lose a bigger chunk of the follow-ups. RMST tends to lose power if there is many events after τ

Generally, as large as possible since everything later than τ is ignored

Problematic with large censored values

Consideration of the data distribution

RMST: Considerations in Choice of Tau

- The RMST difference measures the gain or loss in the event free survival time for the treatment vs control during the follow up time
- Researchers must formulate an appropriate rationale for selecting a particular time point (tau) before the analysis because the significance of the results depends on the chosen time point.

Data Exploration:

- Explore the data, follow ups for progression and possible generic τ
- Know the distribution of the follow-ups and censoring
- Check the AE dates

In SAP:

- Describe the choice of τ
- Literature review of the median follow-ups for similar subgroups

Most importantly:

- Consider the clinical significance of the choice of τ and discuss with the therapeutic expert clinicians
- In QTWiST, unique tau value for all the states is important for better reporting and comparability of the results.

Conclusion

Q-TWiST as an analytical method has potentiality in serving the treatment comparisons, especially due to lack of proportionality in the hazards.

The practice of performing the analysis with states-specific data driven approach is quite prominent and unfortunately misleading.

Standardization of the choice of Tau and censoring rule for the states needs to described in the SAP. This should further complement the clinical relevance behind this choice and exploration of AE data for each study.

References

- Gelber, R.D., Cole, B.F., Gelber, S. and Goldhirsch, A., 1995. Comparing treatments using quality-adjusted survival: the Q-TWiST method. *The American Statistician*, *49*(2), pp.161-169.
- Huang, M., O'Shaughnessy, J., Haiderali, A., Pan, W., Hu, P., Chaudhuri, M., De Tilleghem, C.L.B., Cappoen, N. and Fasching, P.A., 2022. Q-TWiST analysis of pembrolizumab combined with chemotherapy as first-line treatment of metastatic triple-negative breast cancer that expresses PD-L1. *European Journal of Cancer*, *177*, pp.45-52.
- Huang, M., Pietanza, M.C., Samkari, A., Pellissier, J., Burke, T., Chandwani, S., Kong, F. and Pickard, A.S., 2019. Q-TwiST analysis to assess benefit–risk of pembrolizumab in patients with PD-L1–positive advanced or metastatic non-small cell lung cancer. *Pharmacoeconomics*, *37*, pp.105-116.
- Patil, S., Figlin, R.A., Hutson, T.E., Michaelson, M.D., Negrier, S., Kim, S.T., Huang, X. and Motzer, R.J., 2012. Q-TWiST analysis to estimate overall benefit for patients with metastatic renal cell carcinoma treated in a phase III trial of sunitinib vs interferon-α. *British journal of cancer*, *106*(10), pp.1587-1590.
- Han, K. and Jung, I., 2022. Restricted mean survival time for survival analysis: a quick guide for clinical researchers. *Korean Journal of Radiology*, *23*(5), p.495.
- Hasegawa, T., Misawa, S., Nakagawa, S., Tanaka, S., Tanase, T., Ugai, H., Wakana, A., Yodo, Y., Tsuchiya, S., Suganami, H. and JPMA Task Force Members, 2020. Restricted mean survival time as a summary measure of time-to-event outcome. Pharmaceutical statistics, 19(4), pp.436-453.
- Revicki, D.A., Feeny, D., Hunt, T.L. and Cole, B.F., 2006. Analyzing oncology clinical trial data using the Q-TWiST method: clinical importance and sources for health state preference data. Quality of life research, 15, pp.411-423.

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