MSR26

Exploring the Validity of Non-Responders As a Surrogate for Treatment Comparator Survival Outcomes in the Context of Histology Independent Therapies

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Key Findings

- **Pembrolizumab non-responders are a poor surrogate for comparator survival outcomes in previously treated MSI-H/dMMR solid tumors**
- **Despite not achieving objective response, data suggests patients treated with pembrolizumab still experience long-term survival benefits versus existing standard of care therapies**
- **Importantly, the results of this study are limited by differences in trial populations, sample size, and class of therapy. These factors vary by individual histological site**

Background

- Clinical evaluation of histology independent therapies is commonly conducted using open-label, uncontrolled basket trials, including multiple tumor types with a specific biomarker
- In the absence of an internal control arm or published comparative data, literature recommends that patients treated with the intervention therapy who do not achieve a complete or partial response may be used as a surrogate (proxy) for comparator outcomes[1]
- This study compared pembrolizumab (Keytruda®) non-responder overall survival (OS) data from the KEYNOTE-164 study and KEYNOTE-158 basket trial with published comparator data identified in a systematic literature review[2, 3]
- OS data for five previously treated MSI-H/dMMR tumors were explored (see Table 1) consistent with the approved EMA label

Objective

The objective of this study was to explore the validity of using non-responders as a surrogate for treatment comparator survival outcomes

Methods

Systematic literature review

- In each tumor site, relevant comparators were determined by treatment guidelines and validated by clinical experts at the time of study initiation[4]
- A systematic literature review was conducted to identify relevant published evidence to July 2022. A total of 33 studies were identified, representing 16 unique trials; however, the majority of published data were unselected for the MSI-H/dMMR patient population. Where multiple studies were available for individual comparators, survival data were pooled
- Chosen to maximize relevant data for CRC, a pooled group of three regimens was included as a comparator. Treatments included FOLFIRI, FOLFOX4 and FOLFOX6. This grouping was permitted where there was sufficient clinical rationale for a class effect, confirmed by clinical experts[4]

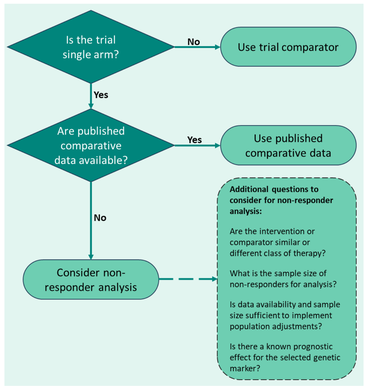
Non-responder analysis

- Non-responders were defined as patients who did not achieve a complete or partial response. Participants with unknown or missing response information were treated as non-responders[21, 22]

Naïve visual Kaplan–Meier comparison

- For each of the five tumor sites, non-responder OS was considered a “reasonable proxy” if the Kaplan–Meier curve appeared similar to the comparator OS curve, based on the following visual inspection criteria:
  - Curve shape, scale, and adjacency
  - Event observation similarities
  - Identification of survival plateaus, where relevant

Figure 1: Decision process



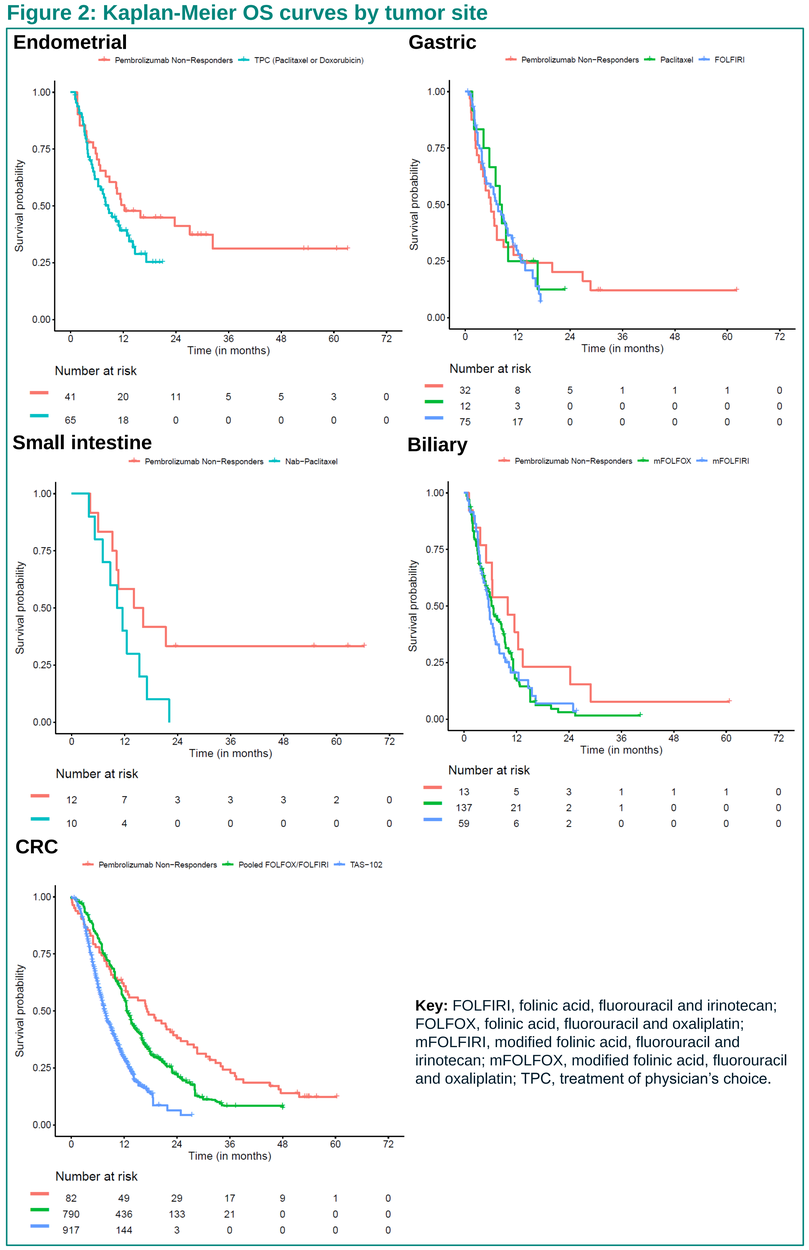
Results

Table 1: Comparators by tumor site

Endometrial	Gastric	Small intestine	Biliary	Colorectal
Paclitaxel*[5]	Paclitaxel[6]	Nab-paclitaxel[7]	mFOLFOX[8-10]	TAS-102[11-13]
Doxorubicin*[5]	FOLFIRI[14, 15]	-	mFOLFIRI[8]	Pooled FOLFOX/FOLFIRI[16-20]

Key: FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; mFOLFIRI, modified FOLFIRI; mFOLFOX, modified FOLFOX.
Note:* Paclitaxel and doxorubicin were assumed to be identical

Figure 2: Kaplan-Meier OS curves by tumor site



Key: FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; mFOLFIRI, modified folinic acid, fluorouracil and irinotecan; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin; TPC, treatment of physician’s choice.

Results by tumor site

Endometrial	• Pembrolizumab non-responder OS overlaps comparator OS curves until approximately 3 months, after which pembrolizumab non-responder lies above doxorubicin/paclitaxel and has a plateau after 36 months
Gastric	• After approximately 18 months, pembrolizumab non-responders and paclitaxel demonstrate a plateau • The survival plateau for non-responders is more sustained than paclitaxel; however, this could be due to the shorter comparator follow-up time
Small intestine	• Non-responder and nab-paclitaxel Kaplan–Meier curves experience a continuous decline until the non-responder Kaplan–Meier plateaus before 2 years
Biliary	• The pembrolizumab non-responder OS shape is similar to the comparator OS • Pembrolizumab non-responder OS is consistently above the comparator OS after approximately 3 months
CRC	• The non-responder Kaplan–Meier curve remains below the TAS-102 and pooled FOLFOX/FOLFIRI Kaplan–Meier's to 3 months and 7 months, respectively • OS for the non-responder cohort continues to be greater than OS for the comparators after approximately 7 months • Comparing against the non-responder curve, a large degree of separation begins to be observed shortly before 1 year for TAS-102, and shortly after 1 year for pooled FOLFOX/FOLFIRI

Discussion

The key strength of a non-responder analysis is that data informing comparator survival outcomes are collected from the same patient population as the intervention arm. However, there are various limitations and mitigating factors to consider:

- Sample size: small patient numbers and high response rates demonstrated by pembrolizumab resulted in limited non-responder patients
- Trial population differences: differences between pembrolizumab and comparator trial populations could impact results. While population adjustment methods could enhance analyses, they were not viable due to data constraints. Additionally, comparing responders and non-responders in a non-randomized analysis could result in further imbalances. These may or may not require further adjustment
- Class of therapy: the validity of the surrogacy assumption may vary depending on the class of the therapy constituting standard of care
- All things being equal, the value of a non-responder analysis may be greater where the hypothesized prognostic effect of the selected biomarker is large

Additional research is warranted to corroborate these findings, including a formal comparison between matching-adjusted indirect comparison results and non-responder analyses

Conclusion

- The non-responder surrogate approach requires the strong assumption that non-responders derive benefit similar to that of the current standard of care
- In this case study, previously treated MSI-H/dMMR patients receiving pembrolizumab who do not respond to therapy obtained additional clinical benefit compared with existing treatment options, and therefore may not be a suitable surrogate for comparator OS
- There are many limitations of using non-responders as a surrogate for comparator OS. Where available, published data for comparator OS outcomes appears to provide more reliable estimates than a non-responder analysis

References

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