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Time-Based vs. Cycle-Based Approaches To Account For Patient-Reported Outcome Assessments In Oncology Trials

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Introduction

- In oncology trials, dose delays can uncouple dosing from nominal visits, which may impact longitudinal analyses of patient-reported outcome (PRO) data
- This study evaluated two approaches to windowing PRO assessments when performing analyses of oncology trial data[1]
  - Time-based: Matching the date of the PRO assessment to nominal visit windows
  - Cycle-based: Matching the date of the PRO assessment to the date of each dosing cycle
- Each approach assesses different questions of interest
- CheckMate 141 (a phase 3 trial of nivolumab for recurrent or metastatic squamous cell carcinoma of the head and neck, NCT02105636)[2] was selected for analysis, as 133 (38%) of 347 patients had dose delays in CheckMate 141
  - Dose delay is defined as delay exceeding three days from scheduled dosing date
- The PRO results from CheckMate 141 have been previously published[3]

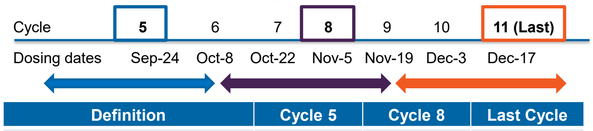
Objectives

- To compare time-based and cycle-based approaches to windowing by evaluation of the proportion of matches and mismatches for patients' PRO assessments over time

Methods

- Patients in CheckMate 141 were randomized 2:1 to nivolumab (n=236) versus the investigator's choice of chemotherapy (IC, n=111 [docetaxal, n=52; methotrexate, n=46; cetuximab, n=13])
- EQ-5D-3L visual analogue scale (VAS) was selected as PRO measure of interest
- PRO assessments were taken before dosing
  - Nivolumab dosing was every 2 weeks; IC was weekly (both until disease progression)
  - PRO assessments were taken at Baseline and every 6 weeks (3 nivolumab / 6 IC cycles) from Week 9 (Cycle 5 for nivolumab) onwards
- Off-treatment and follow-up visits were not of interest and excluded
- Time-based approach used contiguous visit windowing where every on-treatment PRO assessment was assigned to the nearest nominal treatment visit (Figure 1)
- Cycle-based approach assigned assessments to the nearest treatment cycle using a window of +0/-3 days:
  - PRO assessment is assigned to treatment cycle if PRO assessment date is either the treatment date for cycle or up to three days before the treatment date for cycle (Figure 1)
- Only patients with more than one PRO assessment (i.e., baseline plus at least one subsequent timepoint) were included in the analysis presented
- Similarities and differences in the two approaches were explored:
  - Visual exploration
  - Summarised at visit level (not presented) and at patient level
  - Considering treatment and if patients experienced dose delays

Figure 1. Illustration of time-based and cycle-based approaches in CM141 study (nivolumab dosing)



Definition	Cycle 5	Cycle 8	Last Cycle
Time-based window Contiguous approach (assumes 1st dose on Jul-31)	Aug-1 to Oct-14	Oct-15 to Nov-25	Nov-26 to Jan-6
Cycle-based window Includes day of dosing and three days before dosing only	Sep-21 to Sep-24	Nov-2 to Nov-5	Dec-14 to Dec-17

Results

Figure 2. Patients with all visits assigned the same using time-based and cycle-based approaches (nivolumab treatment)

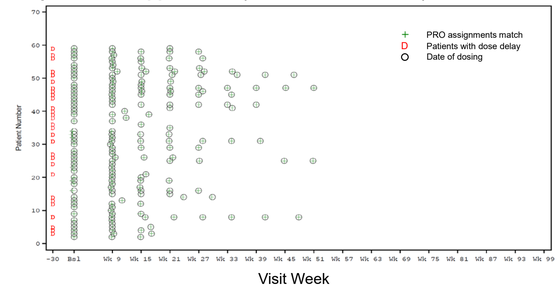
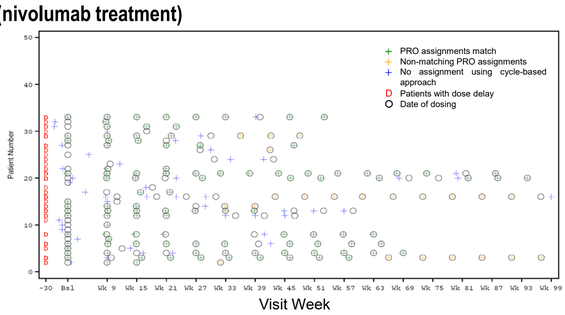


Figure 3. Patients with at least one assessment not assigned with cycle-based approach, and showing some mismatched assessments (nivolumab treatment)



Patients and PRO Data

- Dose delays: Within the all randomized population, 77 (33%) of 236 patients on nivolumab and 56 (50%) of 111 patients on IC had a dose delay
- 137 patients had >1 EQ-5D-3L assessment and were included in this analysis
  - 102 patients on nivolumab and 35 patients on IC (~40% out of 347 randomized)
- 537 PRO assessments were completed by these 137 patients
  - In the 102 patients on nivolumab there were 444 PRO assessments and in the 35 patients on IC there were 93 PRO assessments

Results (continued)

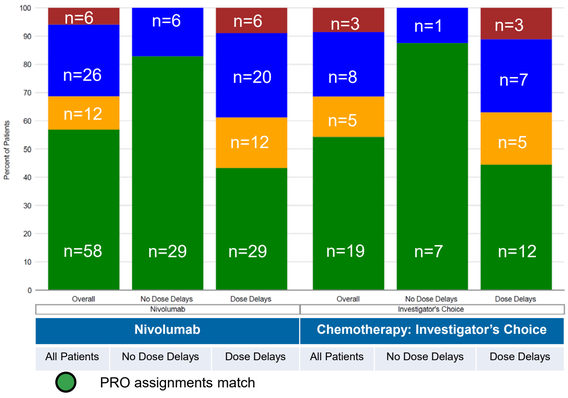
Visual Exploration

- Plots were used to view each patient and the timing of their PRO assessments over time (each patient viewed as a horizontal "line")
- The alignment of the PRO assessments with time-based approach and cycle-based approach for each of the patients in each treatment arm over time was color coded to indicate agreement, mis-matches, and assessments not assigned
  - Figure 2 shows nivolumab patients where the PRO assessments were assigned to the same visit with both approaches
  - Figure 3 shows nivolumab patients where some of the PRO assessments were not assigned by cycle-based approach

Patient-Level Summary

- Of the 137 patients, 77 patients (56%) (58 nivolumab and 19 IC) had all PRO assessments assigned to the same visit using time-based and cycle-based approaches (Figure 4)
  - In these patients, dosing adhered to the prescribed schedule so that the windowing approach did not impact analysis
- For 60 patients (44%) (44 nivolumab and 16 IC), cycles were dissociated from nominal visits
- Among these 60 patients:
  - 17 (28%) (12 nivolumab, 5 IC) had ≥1 PRO assessments for which the cycle-based approach excluded the nominal visit at which treatment was to be administered
  - 34 (57%) (26 nivolumab, 8 IC) had ≥1 assessments not included in any cycle-based window
  - 9 (15%) (6 nivolumab, 3 IC) had ≥1 assessments meeting both of these criteria
- Considering dose delays:
  - All patients with one assessment assigned to a different visit had a dose delay
- ~50% of patients with all assessments assigned to the same visit had a dose delay

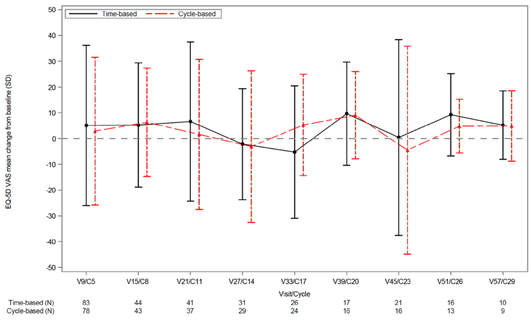
Figure 4. Using time-based or cycle-based approaches for assigning PRO assessments to visits, overall, over 50% of patients had all assignments at the same visit; patients with assessments assigned to different visit, all had a dose delay; similar for nivolumab and IC



Impact on PRO Interpretation

- Summarising EQ-5D-3L VAS scores over time resulted in very similar mean scores for both time-based and cycle-based approaches (Figure 5)

Figure 5. EQ-5D-3L VAS mean changes from baseline using time-based and cycle-based approaches were similar (nivolumab treatment)



Conclusions

- Although time-based and cycle-based windowing approaches entail different assumptions and limitations, the choice between them appears to have minimal impact on analyses of PRO data
- A more important consideration is how the selected approach frames the hypotheses that can be tested
- Choice of windowing approach in assignment of PRO data made no difference in 56% of patients
- All patients where the windowing approach differed had experienced a dose delay
- Findings were generally similar for nivolumab and IC arms
- Whilst the choice of windowing approach impacted analytic results for 44% of patients, mean differences in summarising EQ-5D-3L VAS scores were seldom large

References

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