Paper DH09

Closing the Gap: Identifying Missing Tumor Assessments in Oncology Studies

Zhiheng Chen, Boehringer Ingelheim, Shanghai, China
Ke Xiao, Boehringer Ingelheim, Ridgefield, United States

ABSTRACT

The definition and identification of "missing two or more consecutive tumor assessments" (Missing2TAs) is a key consideration for censoring in progression-free survival (PFS) analysis in oncology clinical trials. However, operationalizing this concept can be challenging, especially in the presence of unscheduled assessments and protocol deviations. This paper introduces and compares three methods for identifying Missing2TAs: a visit-based method that utilizes mapping to protocol defined scheduled visits, a date-based method that relies solely on assessment intervals, and a hybrid method that combines visit mapping with assessment dates. Each approach is described in detail, with practical examples illustrating their applications. The paper aims to provide a clear framework for statistical programmers and clinical teams to select and implement the most appropriate method that fits their study context.

INTRODUCTION

Progression-free survival (PFS), defined as the time from randomization until objective tumor progression or death, whichever occurs first (FDA, 2018), is a widely used endpoint in oncology clinical trials. Accurate estimation depends on appropriate handling of censoring events, including the occurrence of two or more consecutive missing tumor assessments (Missing2TAs) immediately prior to a PFS event. The operational definition and programming implementation of Missing2TAs can have significant impact on the interpretation of trial results and regulatory acceptability.

METHODS

Several methods have been observed in practice to identify Missing2TAs. Each has its own justifications and operational characteristics. This paper introduces and compares three approaches: a visit-based method, a date-based method, and a hybrid approach of considering both visit mapping and assessment date. The purpose of this paper is to provide a comprehensive overview of these methods so as to facilitate informed decision-making in clinical trial analysis.

VISIT-BASED METHOD

In the framework of visit-based method, tumor assessments are mapped to protocol scheduled visits, typically defined by specific time window documented in statistical analysis plan (SAP) (e.g. Table 1). Based on this method, Missing2TAs is identified if two or more consecutive scheduled visits immediately prior to the PFS event lack evaluable tumor assessments. This approach aligns closely with the protocol-defined assessment schedule.

Key features:

- Scheduled visit windows serve as the primary reference.
- Assessments are mapped to the nearest scheduled visits according to the pre-defined mapping algorithm.
- Flagged as Missing2TAs if two or more consecutive scheduled visits without evaluable assessments occur immediately before a PFS event.

Table 1: Nominal time points and windows for imaging

Nominal time point [Weeks from Cycle 1 Day 1]	Due Date of Scans [Days from Cycle 1 Day 1]	Windows [Days]
Week 0	1	≤1 day
Week 6	43	2 to ≤ 64 days
Week 12	85	65 to ≤ 106 days
Week 18	127	107 to ≤ 148 days
Week 24	169	149 to ≤ 190 days
Week 30	211	191 to ≤ 232 days
Week 36	253	233 to ≤ 274 days
From week 36 onwards, 12-week interval	etc.	etc.

DATE-BASED METHOD

Unlike visit-based method, the date-based method is completely dependent upon the actual tumor assessment dates, independent of visit mapping. The interval between the last evaluable tumor assessment date before the PFS event and the PFS event date is calculated. If the timespan exceeds the duration of two scheduled assessments (including any protocol-defined buffer time), the criteria for Missing2TAs is met.

A simplified algorithm for pre-defined interval between assessments is described as below. In practice, the interval should be subjected to team's decision depending on various assessment schedules as well as adjusting for exceptional circumstances.

Assuming there are evaluable post-baseline assessments available, tumor response is assessed every 6 weeks for the first 36 weeks, and every 12 weeks afterwards according to RECIST v 1.1. As an illustration, one week buffer time is considered to calculate pre-defined interval.

- If the last evaluable assessment immediately prior to the event onsets **before week 29** (days since randomization <= *203*), Missing2TA is identified if the interval exceeds *91* days [6 weeks + 6 weeks + *1* week buffer time].

- If the last evaluable assessment immediately before the event is **after week 29** (days since randomization >= 204) but **before week 35** (days since randomization <= 245), Missing2TAs is identified if the interval goes beyond 133 days [6 weeks + 12 weeks + 1 week buffer time].

- If the last evaluable assessment immediately before the event is **after week 35** (days since randomization >= 246), then *175* days [12 weeks + 12 weeks + 1 week buffer time] will be considered as the pre-defined interval.

Key features:

- Utilize actual assessment dates and pre-defined intervals between assessments.
- No need to map to scheduled visits.
- More robust in presence of multiple unscheduled visits and protocol deviations.
- Flagged as Missing2TAs if the duration between assessments exceeds pre-specified intervals.

HYBRID OF VISIT AND DATE METHOD

The hybrid method incorporates elements from both visit scheduling and assessment dates. To start with, the last evaluable tumor assessment before the PFS event is mapped to its scheduled visit. Following a pre-specified algorithm (e.g. Table 2), a scheduled date of the second assessment after the last evaluable assessment is calculated. Actual PFS event date is then compared with the calculated date. If the actual event occurs after the calculated second scheduled assessment date, Missing2TAs is identified.

Table 2: Scheduled visit days

Visit	Scheduled day	2nd Visit Day after scheduled date *(+ 1 week buffer time*)
Week 0	1	91
Week 6	43	133
Week 12	85	175
Week 18	127	217
Week 24	169	259
Week 30	211	343
Week 36	253	427
From week 36 onwards, 12-week interval	etc.	etc.

Key features:

- Like visit-based approach but incorporate both visit mapping and actual assessment timing.
- Map the last evaluable assessment immediately prior to the PFS event to a scheduled visit.
- Use the calculated scheduled date of the second subsequent assessment as the anchor point for comparison.
- Flagged as Missing2TAs if the actual event date onsets beyond the calculated date of the second assessment date.

CASE STUDIES

In a hypothetical setting, tumor response is assessed every 6 weeks for the first 36 weeks, and every 12 weeks afterwards according to RECIST v 1.1. In addition, +/- 1 week visit window is also considered. For all the case studies presented in this paper, for demonstration purposes, Missing2TAs is the only intercurrent event (ICE) under discussion, i.e. assuming no other ICEs, e.g. no subsequent anti-cancer therapies etc. Visit mapping window and target scheduled days follow table 1 and 2 respectively. The simplified interval algorithm specified in previous session will be applied for date-based method.

CASE STUDY 1

One patient was randomized on 02JAN2025. The response assessments together with other relevant information are as shown in the table below.

Table 3: Case study 1

Actual Visit	Actual tumor assessment date [Response]	Days since Randomization	Mapped to scheduled visit	Interval	2nd scheduled assessment date
Cycle 3 Day 1	13FEB2025 [SD]	43	Week 6		
Cycle 5 Day 1	27MAR2025[SD]	85	Week 12		
Cycle 7 Day 1	*08MAY2025**[NE]***	*127*	*Week 18*		
Cycle 9 Day 1	19JUN2025[PD]	169	Week 24	*85*	*26JUN2025*

If using visit-based method, instead of two or more consecutive missing visits and/or not evaluable assessments, the patient has only one “NE” at week 18. In addition, the interval between the last evaluable assessment [Stable disease on 27MAR2025] and objective progression [19JUN2025] is 85 days, which is less than the pre-specified interval 91 days. Lastly, referring to the hybrid approach, the date for the scheduled second visit after the last evaluable assessment [27MAR2025] is 26JUN2025. The actual progression date is 19JUN2025, which happens before the projected scheduled date. Therefore, none of these three methods detect Missing2TAs in case study 1.

CASE STUDY 2

Similar as in case study 1, the patient was randomized on 02JAN2025. However, unlike in the previous case, the patient has a few unscheduled visits. The response assessments together with other relevant information are as shown in table 4 below.

Table 4: Case study 2

Actual Visit	Actual tumor assessment date [Response]	Days since Randomization	Mapped to scheduled visit
Cycle 3 Day 1	03MAR2025 [SD]	61	Week 6
UNSCHED 1	16MAY2025[SD]	135	Week 18
UNSCHED 2	25AUG2025 [PD]	236	Week 36

In visit-based method: after mapping to the scheduled visit according to SAP (Table 1), there are indeed two consecutive missing tumor assessments (week 24 and week 30) before disease progression (Table 5). Therefore, this case needs to be censored back at the last evaluable assessment on 16MAY2025.

Table 5: Case study 2 - visit based

Assessment date [Response]	Days since randomization	Weeks	Window	Visit based method
03MAR2025 [SD]	61	Week 6	2 to ≤ 64 days	
-	-	*Week 12*		
16MAY2025[SD]	135	Week 18	107 to ≤ 148 days	
-	-	*Week 24*		
-	-	*Week 30*		
25AUG2025 [PD]	***236***	***Week 36***	***233 to ≤ 274 days***	***Miss 2 TAs***

If implementing date-based method, as pre-defined in the SAP, since the last evaluable assessment date is before week 29 (day 203), the duration between the last evaluable tumor assessment before progression [16MAY2025] and the PFS event date [25AUG2025] does exceed pre-specified 91 days. Missing2TAs will then be flagged.

Table 5 : Case study 2 - date based

Assessment date [Response]	Days since randomization	Interval between two assessments [Days]	Date based
03MAR2025 [SD]	61		
16MAY2025[SD]	135		
25AUG2025 [PD]	***236***	***102 [> 91]***	***Miss 2 TAs***

Lastly, if considering the hybrid method, last evaluable assessment performed at unscheduled visit 1 is mapped to protocol defined scheduled visit at week 18. The calculated second assessment date is 07AUG2025 based on the algorithm in table 2. The actual event date is 25AUG2025, which is after the calculated second assessment date. Therefore, Missing2TAs criteria are met, and this case is censored back on 16MAY2025.

Table 6: Case study 2 - hybrid

Actual Visit	Actual tumor assessment date [Response]	Mapped to scheduled visit [2nd Visit Day after scheduled date]	Projected assessments after 2nd visit	Hybrid approach
Cycle 3 Day 1	03MAR2025 [SD]			
UNSCHED 1	16MAY2025[SD]	Week 18 [217]		
UNSCHED 2	***25AUG2025 [PD]***		***07AUG2025***	***Miss 2 TAs***

CASE STUDY 3

In the third example, the patient was also randomized on 02JAN2025. Instead of having objective disease progression assessed by RECIST v1.1, the patient deceased on 20JUN2025. Response assessments together with other relevant information are as below.

Table 8: Case study 3

Actual Visit	Actual tumor assessment date [Response]	Days since Randomization	Mapped to scheduled visit
Cycle 3 Day 1	13FEB2025 [SD]	43	Week 6
Cycle 5 Day 1	17MAR2025[SD]	75	Week 12
Death	20JUN2025	170	Week 24

If using visit-based method: after mapping death event to protocol scheduled visit, no Miss2TAs are identified (Table 9). There is only one missing assessment at week 18. As a result, this is an event and the event date is the death date on 20JUN2025.

Table 9: Case study 3 - visit based

Assessment date [Response]	Days since randomization	Weeks	Window	Visit based method
13FEB2025 [SD]	43	Week 6	2 to ≤ 64 days	
17MAR2025[SD]	75	Week 12	65 to ≤ 106 days	
-	-	*Week 18*	-	
20JUN2025 [Death]	170	Week 24	149 to ≤ 190 days	Not Miss 2 TAs

When applying the date-based logic, the last evaluable assessment prior to death onsets before week 29 (day 203), and the interval in between is 96, which exceeds the pre-specified interval 91 days. Therefore, Missing2TAs is detected, and this case will be censored back on 17MAR2025.

Table 10: Case study 3 - date based

Assessment date [Response]	Days since randomization	Interval between two assessments [Days]	Date based
13FEB2025 [SD]	43		
17MAR2025[SD]	75		
20JUN2025 [Death]	***170***	***96 [>91]***	***Miss 2 TAs***

When it comes to the hybrid approach, the last evaluable assessment date [17MAR2025] before death is mapped to the scheduled visit at week 12. The corresponding targeted second assessment date will be projected to 26JUN2025. Death event happened on 20JUN2025, which is within the prespecified time window. Consequently, this case does not qualify for Missing2TAs and will be an event with death date [20JUN2025] as the event date.

Table 11: Case study 3 - hybrid

Actual Visit	Actual tumor assessment date [Response]	Mapped to scheduled visit [2nd Visit Day after scheduled date]	Projected assessments after 2nd visit	Hybrid approach
Cycle 3 Day 1	13FEB2025 [SD]			
Cycle 5 Day 1	17MAR2025[SD]	Week 12 [175]		
	20JUN2025 [Death]		26JUN2025	Not Miss 2 TAs

CASE STUDY 3.1

This example is very similar to previous case study 3 but with a subtle variation, which, however, results in quite different outcomes. The patient was randomized on 02JAN2025. Instead of having objective disease progression assessed by RECIST v1.1, the patient deceased on 12JUL2025. Response assessments together with other relevant information are as below.

Table 12: Case study 3.1

Actual Visit	Actual tumor assessment date [Response]	Days since Randomization	Mapped to scheduled visit
Cycle 3 Day 1	13FEB2025 [SD]	43	Week 6
Cycle 5 Day 1	16APR2025[SD]	105	Week 12
Death	12JUL2025	192	Week 30

If using visit-based method: after mapping death event to protocol scheduled visit at week 30, two missing assessments at week18 and 24 are observed, which meets the criteria of Missing2TAs. Therefore, this case is censored on 16APR2025.

Table 13: Case study 3.1 - visit based

Assessment date [Response]	Days since randomization	Weeks	Window	Visit based method
13FEB2025 [SD]	43	Week 6	2 to ≤ 64 days	
16APR2025[SD]	105	Week 12	65 to ≤ 106 days	
-	-	*Week 18*	-	
-	-	*Week 24*	-	
12JUL2025 [Death]	***192***	***Week 30***	***191 to ≤ 232 days***	***Miss 2 TAs***

For date-based logic, the last evaluable assessment prior to death happens before week 29 (day 203), and the interval in between is 88, which does not exceed the pre-specified interval 91 days. Therefore, Missing2TAs is not detected, and this case is an event with death date 12JUL2025 as the event date.

Table 14: Case study 3.1 - date based

Assessment date [Response]	Days since randomization	Interval between two assessments [Days]	Date based
13FEB2025 [SD]	43		

Assessment date [Response]	Days since randomization	Interval between two assessments [Days]	Date based
16APR2025 [SD]	105		
12JUL2025[Death]	192	88 [<91]	Not Miss 2 TAs

Lastly, if we consider the hybrid approach, the last evaluable assessment date [16APR2025] before death is mapped to the scheduled visit at week 12. The corresponding targeted second assessment date will be projected to 26JUN2025. Death event happened on 12JUL2025, which is outside the prespecified time window. Consequently, this case does qualify for Missing2TAs and will be censored back on last evaluable assessment date on 16APR2025.

Table 15: Case study 3.1 - hybrid

Actual Visit	Actual tumor assessment date [Response]	Mapped to scheduled visit [2nd Visit Day after scheduled date]	Projected assessments after 2nd visit	Hybrid approach
Cycle 3 Day 1	13FEB2025 [SD]			
Cycle 5 Day 1	16APR2025[SD]	Week 12 [175]		
	12JUL2025 [Death]		***26JUN2025***	***Miss 2 TAs***

CASE STUDY 4

Finally, in the last example, as in previous cases, the patient was randomized on 02JAN2025. Without objective disease progression, the patient deceased on 15DEC2025. Response assessments together with other relevant information are as below.

Table 16: Case study 4

Actual Visit	Actual tumor assessment date [Response]	Days since Randomization	Mapped to scheduled visit
Cycle 3 Day 1	13FEB2025 [SD]	43	Week 6
Cycle 5 Day 1	27MAR2025[SD]	85	Week 12
Cycle 7 Day 1	08MAY2025[SD]	127	Week 18
Cycle 9 Day 1	19JUN2025[SD]	169	Week 24
Cycle 11 Day 1	31JUL2025[SD]	211	Week 30
Death	15DEC2025	348	Week 48

If the logic from visit-base method is applied, this patient does not have Missing2TAs with only one missing assessment at week 36. Event date is the death date on 15DEC2025.

Table 17: Case study 4 - visit based

Assessment date [Response]	Days since randomization	Weeks	Window	Visit based method
13FEB2025 [SD]	43	Week 6	2 to ≤ 64 days	
27MAR2025[SD]	85	Week 12	65 to ≤ 106 days	
08MAY2025[SD]	127	Week 18	107 to ≤ 148 days	
19JUN2025[SD]	169	Week 24	149 to ≤ 190 days	
31JUL2025[SD]	211	Week 30	191 to ≤ 232 days	
		Week 36		
Death 15DEC2025	348	Week 48	275 to <=358 days	Not Miss 2 TAs

On the other hand, if date-based method is considered, in this case, the last evaluable assessment prior to death (stable disease on 31JUL2025) is after week 29 (day 203) but before week 35 (day 245), the pre-defined interval to detect Missing2TAs is 133 days [6 weeks + 12 weeks + 1 week buffer time]. The actual interval between death and the last evaluable disease assessment is 138 days, which goes beyond the pre-specified duration and therefore makes it a censor case. The censor date is the last evaluable assessment date on 31JUL2025.

Table 18: Case study 4 - date based

Assessment date [Response]	Days since randomization	Interval between two assessments [Days]	Date based
13FEB2025 [SD]	43		
27MAR2025[SD]	85		
08MAY2025[SD]	127		

Assessment date [Response]	Days since randomization	Interval between two assessments [Days]	Date based
19JUN2025[SD]	169		
31JUL2025[SD]	211		
Death 15DEC2025	***348***	***138[> 133]***	***Miss 2 TAs***

In the hybrid approach, the last evaluable disease assessment before death is 31JUL2025, the calculated second planned assessment date is projected to 11DEC2025. Actual death date is 15DEC2025, which is after the projected assessment date. As a result, Missing2TAs will be flagged, and this case is censored on 31JUL2025.

Table 19: Case study 4 - hybrid

Actual Visit	Actual tumor assessment date [Response]	Mapped to scheduled visit [2nd Visit Day after scheduled date]	Projected assessments after 2nd visit	Hybrid approach
Cycle 3 Day 1	13FEB2025 [SD]			
Cycle 5 Day 1	27MAR2025[SD]			
Cycle 7 Day 1	08MAY2025[SD]			
Cycle 9 Day 1	19JUN2025[SD]			
Cycle 11 Day 1	31JUL2025[SD]	Week 30		
Death	***15DEC2025***		***11DEC2025***	***Miss 2 TAs***

DISCUSSION AND CONSIDERATION

In general, for most cases, there would be no significant differences detected from applying these three methods. However, under certain extreme circumstances, as demonstrated in previous case studies, implementing different approaches could indeed lead to different outcomes, since each method handles identification of Missing2TAs from different perspectives. Visit-based approach closely follows protocol defined assessment schedules and is straightforward when visit adherence is high. However, visit-based methods could be biased and may not fully account for unscheduled assessments and/or protocol deviations. On the other hand, date-based method provides a relatively flexible, dynamic, schedule-independent approach that would be particularly useful and efficient in studies with frequent unscheduled assessments and/or protocol deviations. Furthermore, the logic behind date-based method is also straightforward and relatively easier to implement from programming's perspective. Last but not the least, the hybrid approach, a variant of visit-based approach, taking both visit and date into consideration, well balances protocol adherence with real-world deviations and consider both scheduled visits and actual assessment dates.

This paper does not intend to identify the "best" method. Instead, we acknowledge that every approach has its own unique characteristics and can fit for different use cases. The selection and consideration of handling approach should be guided by the study design, the frequency of unscheduled assessments, adherence to protocol and the intended regulatory or clinical interpretation, etc.

In practice, it is critical to engage clinical, statistical and/or regulatory stakeholders into the discussion regarding method selection and documentation at an early stage during planning. When it comes to the implementation phase, SAP should explicitly specify the selected method for handling Missing2TAs, since clear documentation and justification are essential for traceability, transparency, replicability and reproducibility. Furthermore, detailed algorithms and mapping rules on handling unscheduled assessments should be well delineated in the SAP as programming guidance. Finally, if deemed necessary, sensitivity and/or supplementary analysis should also be planned and conducted in order to evaluate the impact resulting from implementing different methods.

CONCLUSION

The identification of Missing2TAs is a nuanced process with significant implications for PFS analysis in oncology studies. This paper introduces and compares three methods—visit-based, date-based and the hybrid approach of both visit and dates. Instead of seeking to determine the "best" approach, this paper aims to provide a framework for selecting and implementing the most appropriate and optimum approach that can fit into different study contexts.

REFERENCES

Cheng, X. (2022), Identification Rule for Missing2TAs. PharmaSUG China 2022 - Paper CC-137

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R.,... & Verweij, J. (2009). New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, 45(2), 228-47. https://doi.org/10.1016/j.ejca.2008.10.026.

Food and Drug Administration, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, December 2018 URL: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics | FDA

CONTACT INFORMATION

Zhiheng Chen
Boehringer Ingelheim (China) Investment Co., Ltd
zhiheng.chen@boehringer-ingelheim.com

Ke Xiao
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road | Ridgefield CT 06877
ke.xiao@boehringer-ingelheim.com