



Closing the Gap: Identifying Missing Tumor Assessments in Oncology Studies

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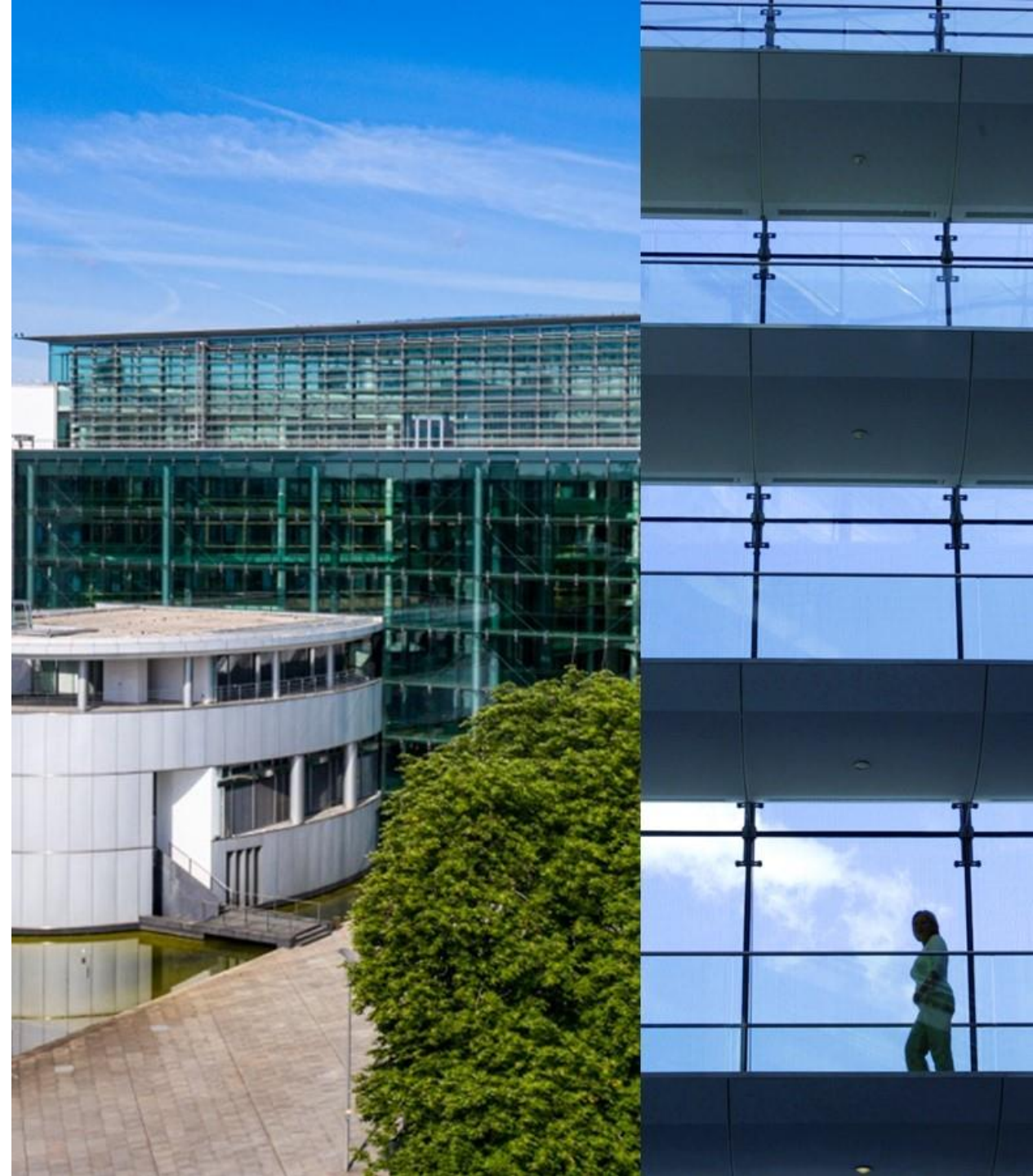
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- This presentation is for the purpose of technical discussion only.
- The views and opinions expressed are solely those of the presenters and do not necessarily reflect the official policy or position of Boehringer Ingelheim.



Introduction



Outline

- ❖ Introduction
- ❖ Methods
- ❖ Case studies
- ❖ Discussion and Consideration



Motivation

Censoring complication: Missing2TAs prior to a PFS Event

- PFS is a widely used end point in oncology studies.
- Accurate estimation depends on appropriate handling of censoring events.
- **A critical challenge** : occurrence of two or more consecutive missing tumor assessments (Missing2TAs) immediately prior to a PFS event.

Progression free survival [PFS]

“...time from randomization until objective tumor progression or death, whichever comes first.”
(FDA, 2018)



METHODS



Visit Based Method

Key features:

- Scheduled visit windows serve as the primary reference.
- Assessments are mapped to the nearest scheduled visit 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

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.

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.

Hybrid of Visit and Date Method

Key features:

- Incorporate both visit mapping and actual assessment timing.
- Map the last evaluable assessment 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.

Table 2: Scheduled visit days

Visit	Scheduled day	2 nd 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.

CASE STUDIES



Case studies

- Tumor response is assessed every 6 weeks for the first 36 weeks, and every 12 weeks afterwards according to RECIST v 1.1. +/- 1 week visit window is considered.
- Missing2TAs is the only intercurrent event (ICE) under discussion for all the cases presented, 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.
- For illustration purpose, assume there are evaluable post baseline assessment available in all cases.



Actual Visit	Actual tumor assessment date [Response]	Days since Randomization	Mapped to scheduled visit	Interval	2 nd 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

Patient was randomized on 02JAN2025

Method	Missing2TAs?
Visit based	No, since there is only one NE assessment.
Date based	No, the interval is 85 days, less than pre-defined interval [91 days].
Hybrid	No, event date was onset before the 2 nd scheduled assessment date.

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

Patient was randomized on 02JAN2025.

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

Case study 2 – cont'd

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

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

Method	Missing2TAs?
Visit based	Yes , two consecutive missing assessments prior to PD
Date based	Yes , the interval between two assessments exceeds pre-defined interval [91 days].
Hybrid	Yes , event date occurred targeted assessment dates after the 2 nd visit.

Case study 3

Patient was randomized on 02JAN2025, deceased on 20JUN2025.

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

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

Case study 3 - cont'd

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

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

Method	Missing2TAs?
Visit based	No, there is only one missing assessment prior to PD.
Date based	Yes , the interval between two assessments exceeds pre-defined interval [91 days].
Hybrid	No, patient deceased before the projected assessment dates.

Case study 3 - cont'd

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

Actual Visit	Actual tumor assessment date [Response]	Mapped to scheduled visit [2 nd Visit Day after scheduled date]	Projected assessments after 2 nd visit	Hybrid method
Cycle 3 Day 1	13FEB2025 [SD]			
Cycle 5 Day 1	17MAR2025[SD]	Week 12 [175]		
	20JUN2025 [Death]		26JUN2025	No 2

Method	Missing2TAs?
Visit based	No, there is only one missing assessment prior to PD.
Date based	Yes, the interval between two assessments exceeds pre-defined interval [91 days].
Hybrid	No, patient died before the projected assessment dates.

Case study 4

Patient was randomized on 02JAN2025, deceased on 15DEC2025.

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

Assessment date [Response]	Days since randomization	Weeks	Window	Visit based
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



Case study 4 – cont'd

Assessment date [Response]	Days since randomization	Interval between two assessments [Days]	Date based
13FEB2025 [SD]	43		
27MAR2025[SD]	85		
08MAY2025[SD]	127		
19JUN2025[SD]	169		
31JUL2025[SD]	211		
Death 15DEC2025	348	138 [> 133]	Miss 2 TAs

Actual Visit	Actual tumor assessment date [Response]	Mapped to scheduled visit [2 nd Visit Day after scheduled date]	Projected assessments after 2 nd 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	31JUL 2025[SD]	Week 30		
Death	15DEC2025		11DEC2025	Miss 2 TAs

Method	Missing2TAs?
Visit based	No, there is only one missing assessment prior to PD.
Date based	Yes, the interval between two assessments exceeds pre-defined interval [133 days].
Hybrid	Yes, patient deceased after the projected assessment dates.

Case study 4 – cont'd

Assessment date [Response]	Days since randomization	Interval between two assessments [Days]	Date based
13FEB2025 [SD]	43		
27MAR2025[SD]	85		
08MAY2025[SD]	127		
19JUN2025[SD]	169		
31JUL2025[SD]	211		
Death 15DEC2025	348	138 [> 133]	Miss 2 TAs

Actual Visit	Actual tumor assessment date [Response]	Mapped to scheduled visit [2 nd Visit Date]	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

Method	Missing2TAs?
Visit based	No, there is only one missing assessment prior to PD.
Date based	Yes, the interval between two assessments exceeds pre-defined interval [133 days].
Hybrid	Yes, patient deceased after the projected assessment dates.

Discussion and Consideration



Discussion

Three methods have their own unique perspectives to handle Missing2TAs:

Visit-based

- ❖ Closely follows protocol defined assessment schedules and is straightforward when visit adherence is high.
- ❖ Could be biased and may not fully account for unscheduled assessments and/or protocol deviations.

Date-based

- ❖ Provides a relatively flexible, dynamic, schedule-independent approach.
- ❖ Particularly useful and efficient in studies with frequent unscheduled assessments and/or protocol deviations.
- ❖ Robust yet simplified logic; easier to implement from programming's perspective

Hybrid of Visit and Date

- ❖ A variation of visit-based method and considers both visit and date.
- ❖ Well balances protocol adherence with real-world deviations.

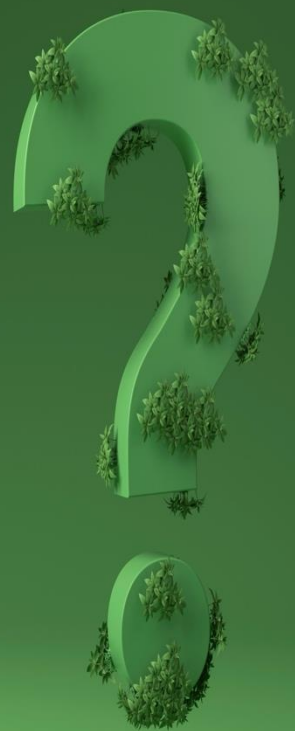


Consideration

- ❖ Acknowledge each approach has its own unique characteristics and can fit for different use cases.
- ❖ **Engage clinical, statistical and/or regulatory stakeholders** early in planning.
- ❖ Select methods based on **study design, frequency of unscheduled assessments, protocol adherence, and intended regulatory or clinical interpretation.**
- ❖ Clear documentation as programming guidance.
- ❖ Consider **sensitivity and/or supplementary analysis** as appropriate.



Thank you!



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