

Paper #AS18

From Data Cutoffs to Decision-Making: Programming Futility Analysis in Oncology Clinical Trials



INVENTING
FOR LIFE

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Mani Mudumba

Author Details

- Mani Mudumba
 - Associate Principal Scientist, Stat programming at Merck & Co., Inc., Rahway, NJ, USA
 - 15+ Years of experience in SAS programming
 - TA: Oncology

Agenda

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Introduction

- Interim analyses are increasingly incorporated into oncology clinical trials to support faster decision-making and improve overall drug development efficiency.
- When studies include predefined futility rules, sponsors can stop a trial early if the experimental treatment is unlikely to show meaningful clinical benefit.
- Early stopping conserves patient participation, reduces operational workload, and enables reallocation of development efforts to more promising therapies.
- This paper highlights SAS programming for futility analysis in a Phase 3 oncology trial with a Run-In portion, followed by a Phase 3 treatment portion and planned interim analysis.
- Key objectives include:
 - Managing interim data cutoffs
 - Defining populations for safety and efficacy
 - Generating PFS-based efficacy outputs
 - Supporting timely IDMC review

Study Design Overview

Two-part oncology trial:

- The run-in portion is conducted to evaluate safety, tolerability, and early efficacy of the study drug.
- Data from the run-in are generally not included in the primary Phase 3 efficacy analysis.
- Phase 3 evaluates clinical benefit with adequate statistical power.
- Interim futility analysis at a predefined timepoint checks if continuing the trial remains appropriate.



Why a Run-In Portion?

ADVANTAGES

- Satisfies regulatory requirements
- Enables earlier assessment of safety, tolerability, and efficacy prior to the Phase 3 data readout

CHALLENGES

- Additional operational complexity
- Separate population determination logic
- Additional datasets, flags, and derivations

From a programming perspective, the Run-In portion introduces population transitions, which must be carefully tracked to define who qualifies for randomized analysis.

Futility Analysis Concept

➤ Stopping early when:

- Experimental treatment shows insufficient benefit
- Low probability of later success

➤ Benefits:

- Protects patient
- Reduces unnecessary operational burden
- Allows strategic reallocation

Event Monitoring & Data Cutoff

- Monitor ongoing event accrual to estimate when the required number of events will occur.
- Generate forecasts using current follow-up and observed events to predict future event rates.
- Use forecasts to identify the operational cutoff date for the interim analysis.
- Account for enrollment patterns, varying follow-up, and changing risk; update estimates routinely.
- Futility decision is based on PFS at the cutoff, ensuring all relevant data are available for dataset lock.

Populations Flags

Flag	Label	Derivation	Purpose
RANDFL	Randomized Population Flag	If Date of Randomization is not missing, then RANDFL="Y", otherwise RANDFL="N"	Identifies subjects who were randomized
SAFFL	Safety Population Flag	If Date of First Exposure to Treatment is not missing, then SAFFL="Y", otherwise SAFFL="N".	Identifies subjects included in safety analyses
FUTANAFL	Futility Analysis Population Flag	FUTANAFL = "Y" for randomized subjects included in the prespecified futility analysis population, defined in the SAP as the first N randomized subjects (where N ensures adequate minimum follow-up for post-baseline assessments).	Identifies subjects eligible for the futility analysis at the interim cutoff

Primary Endpoint: PFS

- Time from randomization → progression or death
- If no event by cutoff → censored
- Key variables for PFS calculations: PDDT, DTHDT, TUMASDT, RANDDT, DCUTDT

Date	Label	Purpose
PDDT	Date of tumor progression	Used for the event indicator and PFS Duration
DTHDT	Date of Death	Used for event indicator if death occurs before progression
TUMASDT	Last Adequate Tumor Assessment Date	Used for censoring
RANDDT	Date of Randomization	Used for Time zero
DCUTDT	Data Cutoff Date	Used for data cutoff

PFS Derivation Logic

➤ Event if:

- PD before cutoff
- OR death before progression and cutoff

➤ Else:

- Censored at last adequate tumor assessment before cutoff

```
/* Derive PFS time and event flag */
if (pddt <= dcutdt and pddt ne .) or
   (dthdt <= dcutdt and dthdt ne .) then do;
  /* Subjects with PD or death before cutoff */
  aval = (min(pddt, dthdt) - randdt + 1) / 30.4375;
  cnsr = 0;
end;
else do;
  /* Censored at last adequate tumor assessment before cutoff */
  aval = (min(tumasdt, dcutdt) - randdt + 1) / 30.4375;
  cnsr = 1;
end;
```

Statistical Methods

- Hazard ratio via Cox PH model (PROC PHREG)
- KM curves via PROC LIFETEST
- Confidence intervals & p-values summarized
- HR vs futility boundary guides decision

Futility Boundary:

The actual rule depends on the trial design but for the interpretation purpose we are using the HR Futility Boundary as 1. Futility conclusion based on observed HR is shown below:

Observed HR	Conclusion
HR < 1.0 (Futility Boundary) favoring Experimental Treatment	Positive trend → continue
HR ≥ Futility boundary	Insufficient benefit, Consider early stop

PFS Summary Table (Scenario 1: Continue Study)

Key observations:

- Table 1 shows $HR < 1.0$, favoring the experimental treatment.
- Experimental arm has fewer events (46.9% vs. 70.9%) and longer median PFS (10.5 vs. 6.7 months).
- Hazard ratio 0.527 (95% CI: 0.42–0.65) with $p = 0.001$ indicates 47% reduced risk of progression or death.
- Results support continuation of the study.

Stats	Experimental	Control
N	283	282
Events (%)	133 (46.9)	200 (70.9)
Median PFS (Months)	10.5	6.7
Hazard Ratio	0.527 (0.42, 0.65)	
p-value	0.0010	

Table 1: PFS Summary Table ($HR < 1.0$, Continue Study)

PFS Summary Table (Scenario 2: Consider Early Stop)

Key observations:

- Table 2 shows $HR > 1.0$, indicating insufficient benefit of the experimental treatment.
- Experimental arm has more events (60.3% vs. 55.5%) and shorter median PFS (5.79 vs. 6.58 months).
- Hazard ratio 1.127 (95% CI: 0.90–1.40) with $p = 0.2805$ indicates not statistically significant.
- Results suggest weak efficacy, supporting consideration of early study termination for futility.

Stats	Experimental	Control
N	280	281
Events (%)	169 (60.3)	156 (55.5)
Median PFS (Months)	5.79	6.58
Hazard Ratio	1.127 (0.90, 1.40)	
p-value	0.2805	

Table 2: PFS Summary Table ($HR > 1.0$, Consider Early Stop)

KM Plot (Scenario 1: Continue Study)

Key observations:

- KM plots illustrate PFS for experimental and control arms under favorable scenario.
- Experimental arm curve consistently above control throughout study period.
- Clear separation of curves demonstrates strong and consistent treatment benefit.
- Supports continuation of the study by IDMC.
- Highlights efficacy signal and validates interim decision-making process.

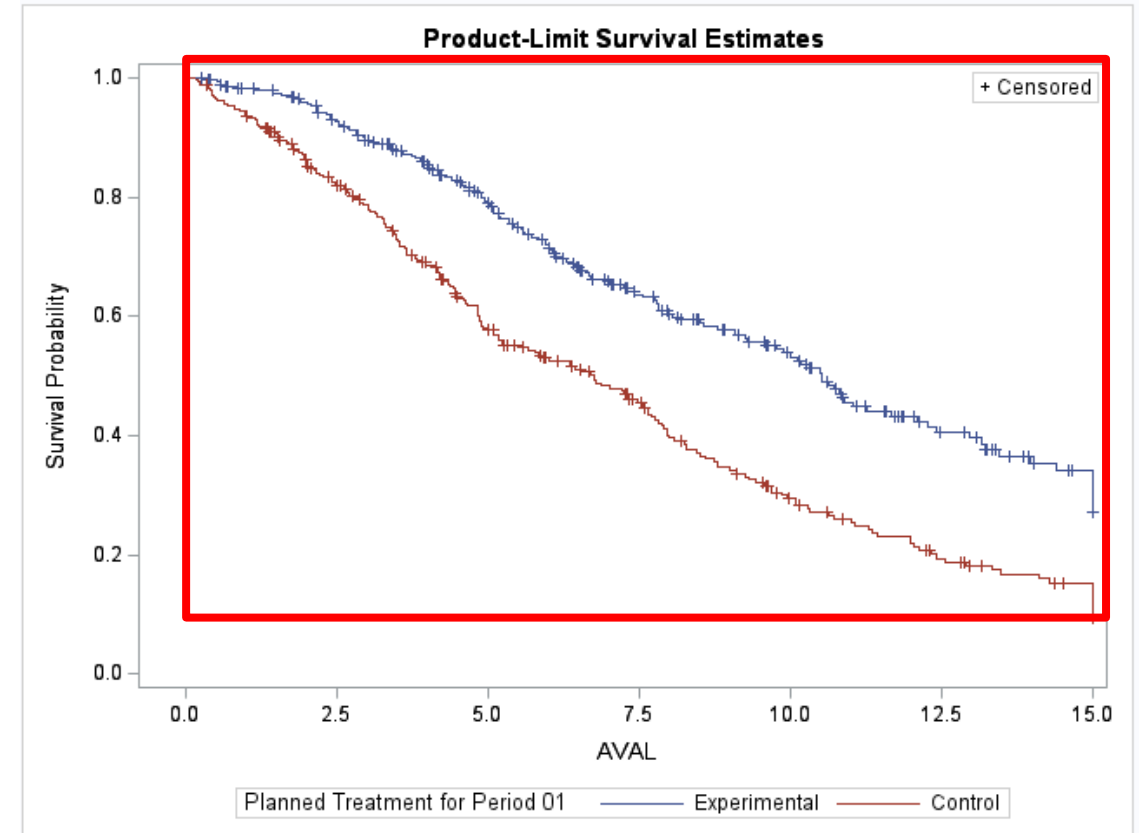


Figure 1: Kaplan–Meier Analysis of PFS (Experimental Treatment Favorable - Study to Continue)

KM Plot (Scenario 2: Consider Early Stop)

Key observations:

- KM curves for experimental and control arms are close and overlap at multiple time points.
- Control arm occasionally above experimental arm, indicating inconsistent benefit.
- Overlapping/crossing curves suggest weak efficacy of experimental treatment.
- Supports consideration of early termination for futility.
- Demonstrates how KM plots inform IDMC decisions on continuation vs. stop.

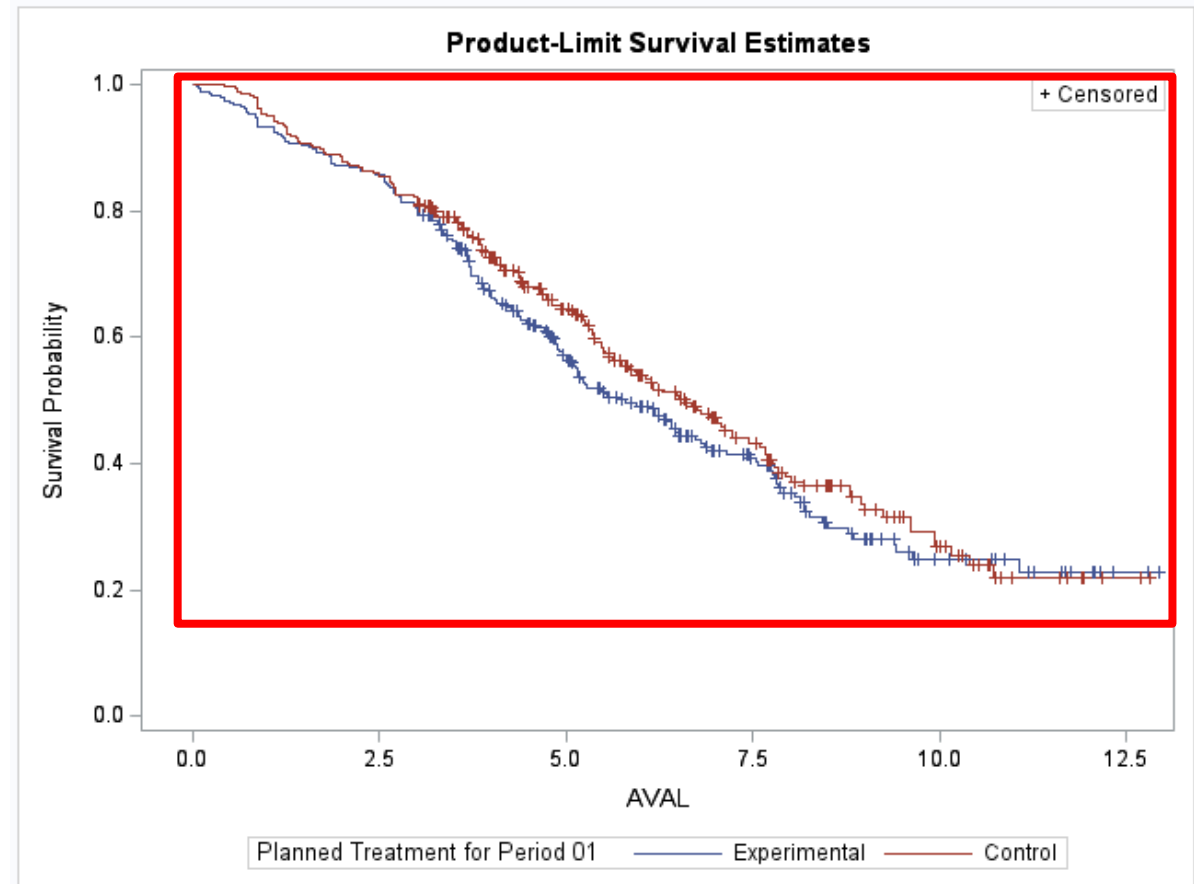


Figure 2: Kaplan–Meier Analysis of (Experimental Treatment Not Favorable - Consider Early Stop)

Key Takeaways – PFS Tables and KM Plots

- HR and median PFS guide interim decisions on study continuation or early stop.
- Clear separation in KM curves + $HR < 1.0 \rightarrow$ strong efficacy, study continues.
- Overlapping/crossing KM curves + $HR \geq 1.0 \rightarrow$ weak efficacy, consider early termination.
- Combining PFS tables and KM plots provides robust evidence for IDMC decision-making.
- Ensures timely assessment while minimizing patient exposure to ineffective treatment.

Safety Outputs (Brief)

- Simulated safety datasets included to demonstrate standard interim analysis workflow.
- Adverse events were balanced between experimental and control arms.
- No major safety concerns expected to influence interim decisions.
- Detailed safety results not shown; focus is on PFS-based futility analysis.
- Illustrates how safety is typically summarized alongside efficacy for IDMC review.

Independent data monitoring committee (IDMC) Interpretation

- PFS tables and KM plots guide IDMC decisions on interim futility.
- Clear separation of curves → strong efficacy → study continuation recommended.
- Overlapping or crossing curves → weak efficacy → consider early termination.
- Decisions consider both effect magnitude and consistency.
- Balances patient safety with efficient trial conduct.

Conclusion



- Correct population flags are critical—misclassification can distort hazard ratios and IDMC decisions.
- Strict data cutoff handling prevents bias and ensures a clean futility analysis dataset.
- Accurate PFS derivations rely on proper censoring and event date rules.
- Tables and KM plots help IDMC interpret treatment benefit—clear separation favors continuation; overlap may trigger early stop.
- **Overall:** Strong programming discipline plus clear visual outputs enable reliable, data-driven interim decisions.

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Contact Information

Your comments and questions are valued and encouraged. Contact the authors at:

Mani Mudumba

Merck & Co., Inc., Rahway, NJ, USA

Email: mani.mudumba@merck.com

A vibrant watercolor splash in shades of blue, yellow, orange, red, and pink, with small dark red and yellow dots scattered around it, set against a light yellow background.

Thank
you

QUESTIONS