

Paper #AS03

# SAS Programming approach for adjustment of treatment switching using Two-Stage Method



**INVENTING**  
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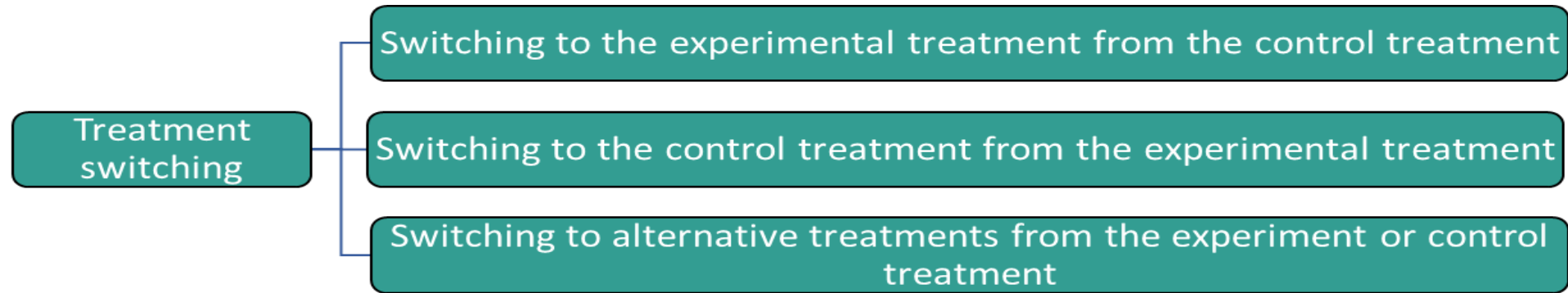
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# Introduction

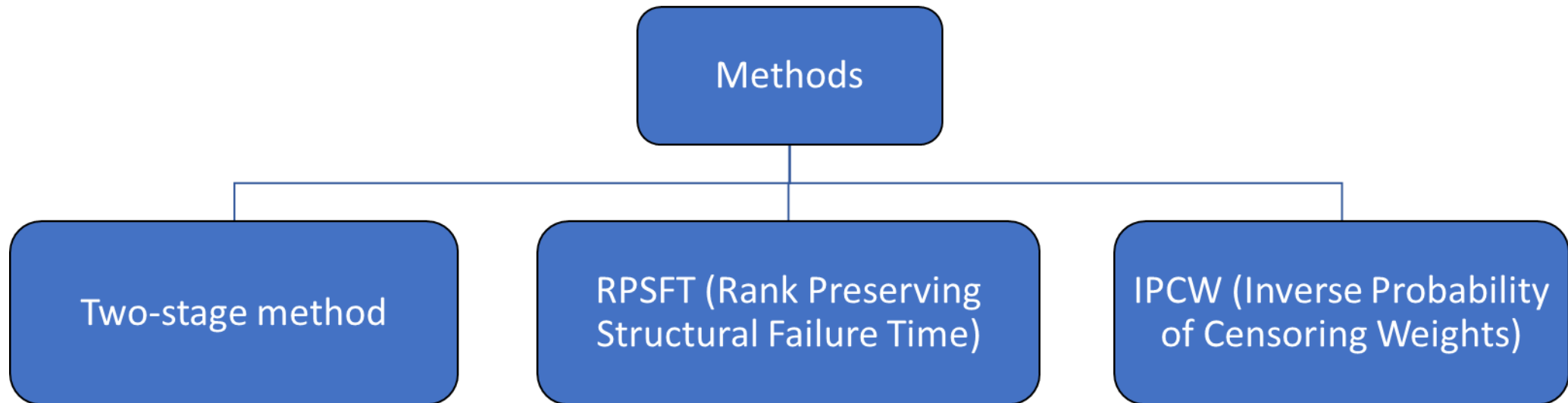
- Treatment switching happens frequently in oncology trials.



- The bias in analyses for endpoints measured in the control treatment may partially represent the effect of the experimental treatment because of the treatment switch outcome in the control treatment. In that case, the actual treatment effect can be underestimated by the observed OS difference.

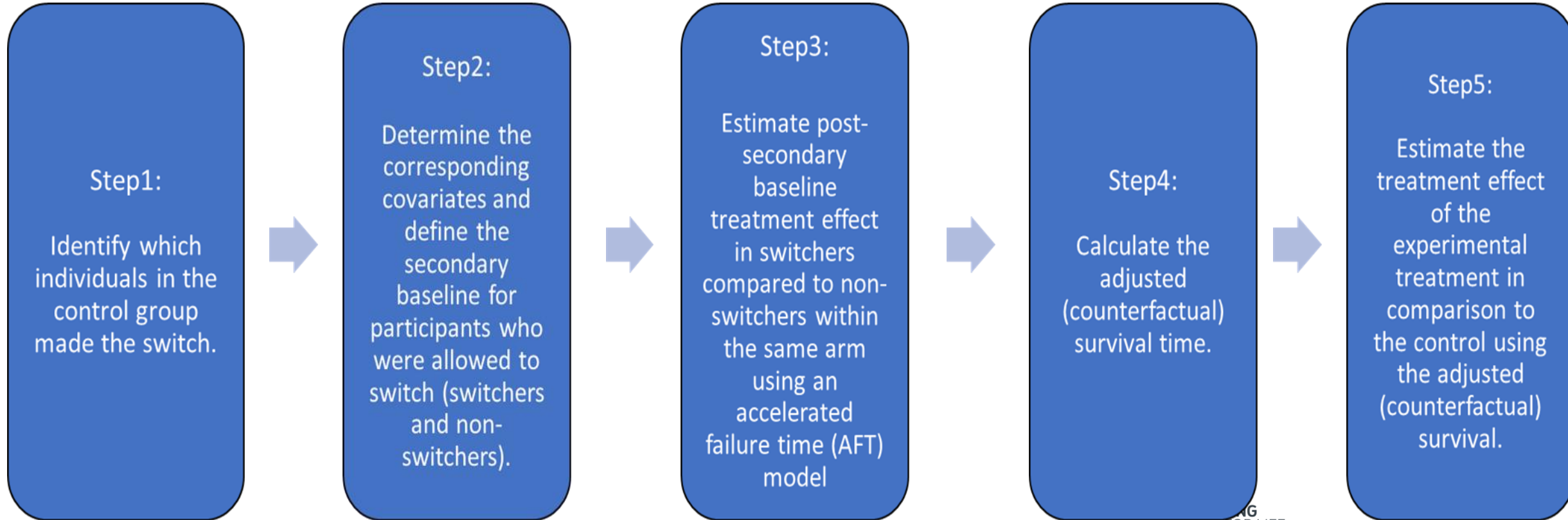
# Introduction (Continued..)

- Across the industry, the following methods are used for estimating the treatment effect after adjustment for the switch:



# Two-stage method

The two-stage method is used in oncology trials where treatment switching occurs among participants only after disease progression. The method involves the following steps:



# Two-stage method (Continued..)

## ASSUMPTIONS:

The following are the primary assumptions for using the two-stage method:

1. No confounders that are unmeasured.
2. OS data follow a parametric distribution, as need to fit a parametric accelerated failure time (AFT) model.
3. It is expected that switching will occur quickly after the PD.

# ADOS2STG (Analysis dataset of 2-stage OS) dataset

The ADOS2STG dataset is derived using the ADTTE (Time to Event) dataset with overall survival data as an input (the appendix contains a dummy ADTTE).

## Dummy ADTTE:

| USUBJID         | TRT01P       | TRT01PN | RACE  | ETHNIC  | PARAM            | PARAMCD | PARAMN | STARTDT   | ADT       | AVAL | CNSR | ECOGPD | PDSTARDT  | NEWPD1DT  |
|-----------------|--------------|---------|-------|---------|------------------|---------|--------|-----------|-----------|------|------|--------|-----------|-----------|
| Study_100000013 | Control      | 2       | Race2 | Ethnic2 | Overall_Survival | OS      | 1      | 07SEP2020 | 26DEC2020 | 110  | 0    | 0      | 15OCT2020 | .         |
| Study_100000014 | Experimental | 1       | Race2 | Ethnic2 | Overall_Survival | OS      | 1      | 30AUG2020 | 19JAN2021 | 142  | 0    | .      | .         | .         |
| Study_100000015 | Control      | 2       | Race2 | Ethnic2 | Overall_Survival | OS      | 1      | 07MAY2020 | 26AUG2020 | 111  | 1    | 0      | 18JUN2020 | .         |
| Study_100000016 | Experimental | 1       | Race2 | Ethnic2 | Overall_Survival | OS      | 1      | 11OCT2020 | 17JAN2021 | 98   | 0    | .      | .         | .         |
| Study_100000017 | Control      | 2       | Race2 | Ethnic2 | Overall_Survival | OS      | 1      | 07MAR2020 | 18AUG2020 | 164  | 0    | 0      | 21MAR2020 | 11APR2020 |
| Study_100000018 | Experimental | 1       | Race1 | Ethnic1 | Overall_Survival | OS      | 1      | 14DEC2020 | 02JUL2021 | 200  | 0    | .      | .         | .         |
| Study_100000019 | Control      | 2       | Race1 | Ethnic1 | Overall_Survival | OS      | 1      | 16OCT2020 | 30MAR2021 | 165  | 1    | 1      | 03DEC2020 | .         |
| Study_100000020 | Experimental | 1       | Race1 | Ethnic1 | Overall_Survival | OS      | 1      | 07JAN2021 | 27APR2021 | 110  | 0    | .      | .         | .         |
| Study_100000021 | Control      | 2       | Race1 | Ethnic1 | Overall_Survival | OS      | 1      | 02DEC2020 | 19APR2021 | 138  | 0    | 0      | 31DEC2020 | 09FEB2021 |
| Study_100000022 | Experimental | 1       | Race2 | Ethnic2 | Overall_Survival | OS      | 1      | 13JUL2020 | 08FEB2021 | 210  | 1    | .      | .         | .         |
| Study_100000023 | Control      | 2       | Race2 | Ethnic2 | Overall_Survival | OS      | 1      | 17FEB2020 | 06SEP2020 | 202  | 0    | 0      | 22FEB2020 | 01MAR2020 |

# ADOS2STG (Continued..)

## ADOS2STG Structure:

| Dataset  | Description                    | Class                | Structure                            | Keys             | Documentation                                        | Location     |
|----------|--------------------------------|----------------------|--------------------------------------|------------------|------------------------------------------------------|--------------|
| ADOS2STG | Analysis Dataset of 2-Stage OS | BASIC DATA STRUCTURE | One record per subject per parameter | USUBJID, PARAMCD | All randomized subjects with available measurements. | ados2stg.xpt |

The derivation of the dataset needs the key variables including the PD Start dates and ECOG at PD:

|          |                                         |         |   |           |                                         |
|----------|-----------------------------------------|---------|---|-----------|-----------------------------------------|
| ECOGPD   | ECOG Performance Status at Progression  | Integer | 1 |           | ECOG Performance Status at Progression  |
| NEWPD1DT | Start Date of Subsequent Trt            | integer | 8 | yymmdd10. | Start Date of Subsequent Treatment date |
| PDSTARDT | Tm to Evnt Crossover Origin Dt for Subj | Integer | 8 | yymmdd10. | Date of Progression                     |

# ADOS2STG (Continued..)

## Step1: Identify which individuals in the control group made the switch:

|         |                                      |         |    |           |                                                                                                                                                                                                                                    |
|---------|--------------------------------------|---------|----|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CRODT   | Crossover Date                       | Integer | 8  | yymmdd10. | For subjects in Control arm only, CRODT= NEWPD1DT                                                                                                                                                                                  |
| CROTRT  | Crossover Trt Grp                    | Char    | 70 |           | If CRODT and PDSTARDT are valued and CRODT greater than or equals to PDSTARDT then CROTRT equals to 'Crossover Experimental drug or other Subsequent Therapies';<br>else if CRODT is missing, then CROTRT equals to 'No Crossover' |
| CROTRTN | Crossover Trt Grp (N)                | Integer | 8  |           | 1 = 'Crossover Experimental drug or other Subsequent Therapies'<br>2 = 'No Crossover'                                                                                                                                              |
| ELIGFL  | Eligibility Flag for Indirect Switch | Char    | 1  |           | ELIGFL='Y' for Control subjects with disease progression.                                                                                                                                                                          |

# ADOS2STG (Continued..)

**Step 2: Determine the corresponding covariates and define the secondary baseline for participants who were allowed to switch (switchers and non-switchers).**

Covariates can be identified based on the protocol needs. For the analysis purpose of this paper, we are using below as the baseline and secondary baseline covariates:

1. Baseline covariates: **Race (RACE), Ethnicity (ETHNIC).**
2. Secondary baseline covariates: **ECOG Performance Status (ECOGPD) and Time to Progression (TTPROG).**

## **TTPROG:**

Time to Progression is derived as  $PDSTARDT - RANDDT + 1$ .

# ADOS2STG (Continued..)

**Step 3: Estimate post-secondary baseline treatment effect in switchers compared to non-switchers within the same arm using an accelerated failure time (AFT) model:**

## **Acceleration Factor (ACFA):**

In overall survival (OS) analysis, the acceleration factor quantifies the effect of a covariate (i.e., treatment) on the rate at which time to an event occurs, such as death.

- $< 1$ : The event is accelerated, so the individual is expected to experience the event sooner.
- $> 1$ : The event is decelerated, so the individual is expected to experience the event later.
- $= 1$ : No effect; the survival time is unaffected by the covariate.

We apply Acceleration Factor (ACFA) to adjust the OS for participants who switched from the control to the experimental treatment by fitting a parametric acceleration failure time model to the post progression survival and controlling for covariates at baseline and secondary baseline.

For eligible participants (ELIFGL='Y'), the parametric model is fitted using the **PROC LIFEREG method**.

Based on dummy ADTTE, the acceleration factor is **1.14 ( $> 1$ : The event is decelerated)**.

# ADOS2STG (Continued..)

## Step 4: Calculate the adjusted (counterfactual) survival time:

### AVAL:

For the participants who switched, the ACFA is applied inversely to calculate the adjusted survival time (AVAL).

1. For subjects in Control arm who switched treatment,

AVAL= (ADT – CRODT) × (1/ACFA) + (CRODT - STARTDT+1) in days.

2. For subjects who did not switch, the treatment AVAL is same as ADTTE.AVAL.

### Final ADOS2STG Dataset:

| USUBJID         | TRT01P       | TRT01PN | RACE  | ETHNIC  | ECOGPD | NEWPD1DT  | PDSTARDT  | TTPROG | CRODT      | CROTRT                                                    | CROTRTN | ELIGFL | ACFA        | PARAM                                                                                          | PARAMCD | PARAMN | AVAL  | STARTDT   | ADT       | CNSR |
|-----------------|--------------|---------|-------|---------|--------|-----------|-----------|--------|------------|-----------------------------------------------------------|---------|--------|-------------|------------------------------------------------------------------------------------------------|---------|--------|-------|-----------|-----------|------|
| Study_100000015 | Control      | 2       | Race2 | Ethnic2 | 0      | .         | 18JUN2020 | 43     | .          | No Crossover                                              | 2       | Y      | 1.142596654 | Overall Survival - Observed                                                                    | OS      | 1      | 111   | 07MAY2020 | 26AUG2020 | 1    |
| Study_100000015 | Control      | 2       | Race2 | Ethnic2 | 0      | .         | 18JUN2020 | 43     | .          | No Crossover                                              | 2       | Y      | 1.142596654 | Overall Survival - Adjusted for Switching Treatments (Secondary Baseline: Time of Progression) | OS2STG  | 2      | 111   | 07MAY2020 | 26AUG2020 | 1    |
| Study_100000016 | Experimental | 1       | Race2 | Ethnic2 | .      | .         | .         | .      | .          | No Crossover                                              | 2       |        | 1.142596654 | Overall Survival - Observed                                                                    | OS      | 1      | 98    | 11OCT2020 | 17JAN2021 | 0    |
| Study_100000016 | Experimental | 1       | Race2 | Ethnic2 | .      | .         | .         | .      | .          | No Crossover                                              | 2       |        | 1.142596654 | Overall Survival - Adjusted for Switching Treatments (Secondary Baseline: Time of Progression) | OS2STG  | 2      | 98    | 11OCT2020 | 17JAN2021 | 0    |
| Study_100000017 | Control      | 2       | Race2 | Ethnic2 | 0      | 11APR2020 | 21MAR2020 | 15     | 2020-04-11 | Crossover Experimental drug or other Subsequent Therapies | 1       | Y      | 1.142596654 | Overall Survival - Observed                                                                    | OS      | 1      | 164   | 07MAR2020 | 18AUG2020 | 0    |
| Study_100000017 | Control      | 2       | Race2 | Ethnic2 | 0      | 11APR2020 | 21MAR2020 | 15     | 2020-04-11 | Crossover Experimental drug or other Subsequent Therapies | 1       | Y      | 1.142596654 | Overall Survival - Adjusted for Switching Treatments (Secondary Baseline: Time of Progression) | OS2STG  | 2      | 148.9 | 07MAR2020 | 18AUG2020 | 0    |

# Analysis Results

**Step 5: Estimate the treatment effect of the experimental treatment in comparison to the control using the adjusted (counterfactual) survival:**

- The ADOS2STG dataset, as derived in the previous section, is used as input to generate the table and figure outputs.
- PROC LIFETEST procedure was used to generate Kaplan-Meier plot (Next slide).

# Analysis Results (Continued..)

- The plot indicates that the survival probability of the control arm is higher than that of the control (adjusted) arm.
- In the control arm, the overall survival is overestimated due to treatment switching by eligible participants.
- To mitigate and demonstrate this bias, we plotted the control (adjusted) arm, where the overall survival of the treatment switchers is adjusted by applying the acceleration factor inversely to the treatment switchers.

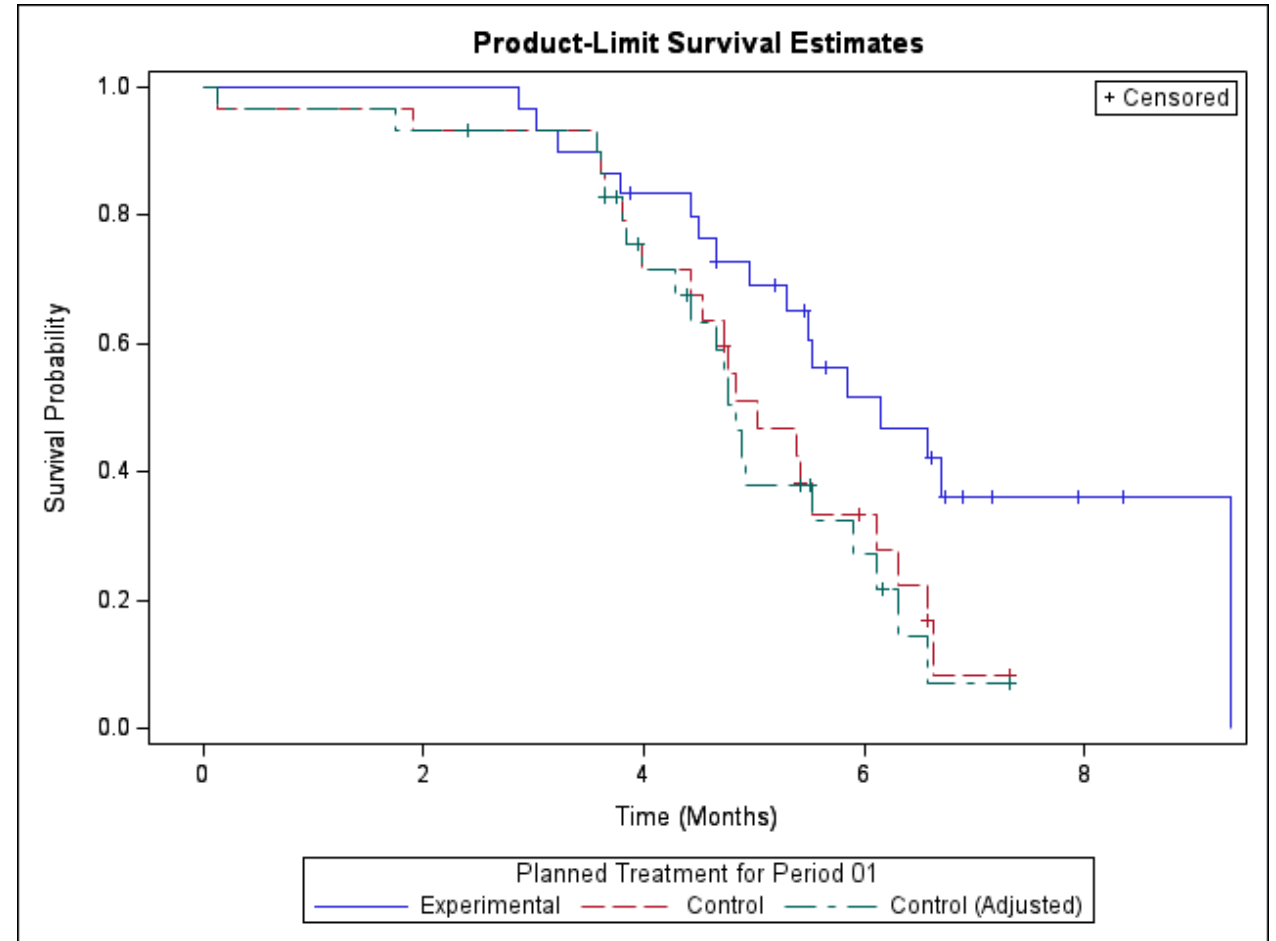


Figure 1: Kaplan-Meier Analysis of Overall Survival

# Analysis Results (Continued..)

- For a better understanding of the analysis results, we generated the table (Table 1).
- These results demonstrate that the OS rate for the control arm is overestimated if the overall survival (OS) time is not adjusted.
- A more accurate estimate of the OS rate and event rate can be obtained by adjusting the overall survival time for treatment switchers, as demonstrated in the control (adjusted) arm.

**Table 1: Analysis of Overall Survival showing Survival Statistics  
(Experimental vs Control vs Control (Adjusted))**

| Stats                                    | Experimental         | Control              | Control (Adjusted)   |
|------------------------------------------|----------------------|----------------------|----------------------|
| N                                        | 30                   | 30                   | 30                   |
| Events (%)                               | 17 (56.7)            | 21 (70)              | 21 (70)              |
| Person-Months                            | 165.7                | 138.5                | 134.8                |
| Event Rate/<br>100 Person-<br>Months (%) | 10.25                | 15.16                | 15.57                |
| OS Rate at<br>Month 6 in %<br>(95% CI)   | 51.65 (31.05, 68.88) | 33.49 (15.98, 52.07) | 27.11 (10.94, 46.30) |

# Analysis Results (Continued..)

- PROC PHREG was used to fit the Cox proportional hazards model.
- The hazard ratio of 0.507 implies that the experimental arm has a 49.3% lower risk of an event occurring compared to the control arm.
- Similarly, the hazard ratio of 0.456 implies that the experimental arm has a 54.4% lower risk of an event occurring compared to the control (adjusted) arm.
- The Cox p-values in the two comparisons, demonstrate the effect of adjusting the overall survival time for treatment switchers.

Table 2: Analysis of Overall Survival showing Treatment Effect (Experimental vs Control vs Control (Adjusted))

| Stats                 | Experimental vs. Control | Experimental vs. Control (Adjusted) |
|-----------------------|--------------------------|-------------------------------------|
| Hazard Ratio (95% CI) | 0.507 (0.26, 0.98)       | 0.456 (0.23, 0.89)                  |
| Cox p-Value           | 0.0441                   | 0.0212                              |

# Conclusion



- Treatment switching is common in oncology trials, and the two-stage method, implemented through the ADOS2STG dataset with ADTTE as input, provides an effective solution to mitigate bias in treatment effect estimation.
- By identifying eligible treatment switchers, defining a secondary baseline, and selecting appropriate covariates, the acceleration factor is derived and applied inversely to accurately estimate the overall survival of the control (adjusted) arm.
- This presentation outlines the development of the ADOS2STG dataset, provides a clear implementation framework, and dataset specifications to support regulatory submissions in ADaM format.
- To conclude, we emphasize the importance of meeting assumptions and selecting appropriate covariates. As demonstrated in the results section, the derived acceleration factor is applied inversely to treatment switchers, ensuring an accurate estimation of overall survival for the control (adjusted) arm.

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## Contact Information

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

Thank  
you

# QUESTIONS

