Paper AS03

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

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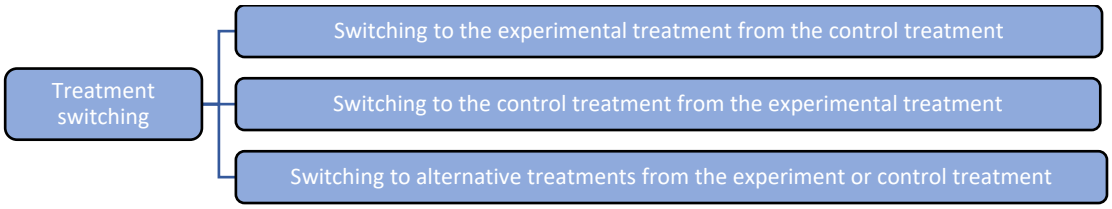
ABSTRACT

Overall survival (OS) is an ideal primary end point for the majority of Phase III clinical studies in oncology. Treatment switching happens frequently in oncology randomized controlled trials. Some control participants switch from the control treatment to the experimental treatment or new anti-cancer therapy after progression of disease (PD), which causes a bias in analyses for endpoints measured after treatment switch. In that instance, the treatment effect of the investigational drug may be underestimated The two-stage method is one of the methods generally used for estimating the treatment effect taking treatment switching in to consideration. The development of statistical programming deliverables, which include analysis dataset and outputs, along with our learnings using the "two-stage method" proposed by Latimer et al., will be explained in this paper.

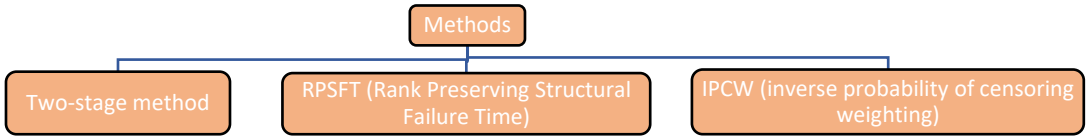
INTRODUCTION

Treatment switching happens frequently in oncology trials. The most common types of treatment switching include:



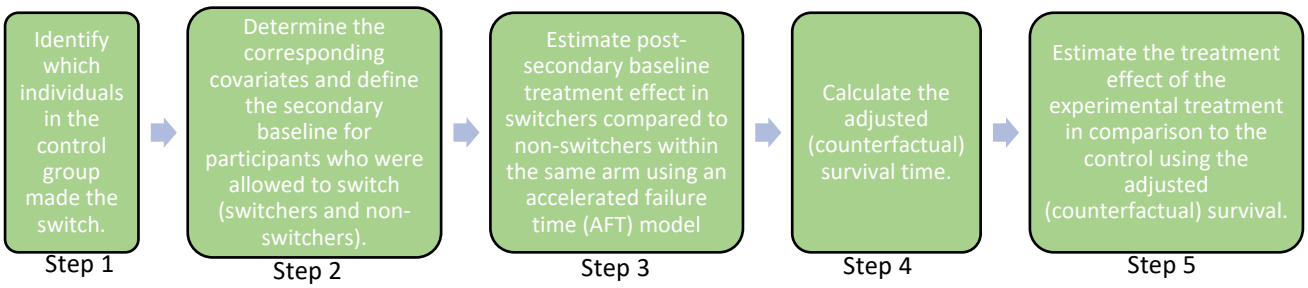
The bias in analyses for endpoints measured in the control treatment may partially represent the effect of the experimental treatment because of the treatment switch outcome in the control treatment. In that case, the actual treatment effect can be underestimated by the observed OS difference.

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 first estimating the effect associated with switching treatments and then using this estimated effect to derive counterfactual survival times for switchers. The method involves the following steps:



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.

This paper explains the development of statistical programming deliverables, which include an analysis dataset and outputs, as well as our lessons learned for switching to the experimental treatment from the control treatment using the "two-stage method." An illustrative scenario based on a SAS dummy ADTTE (Time to Event) dataset will be used throughout the paper to help with understanding the concept. The snippet of the dummy ADTTE is shown below:

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 (ANALYSIS DATASET OF 2-STAGE OS) DATASET

The ADOS2STG dataset is derived using the ADTTE dataset with overall survival data as an input (the appendix contains a dummy ADTTE). Below, we explained the dataset derivation and provided the specification.

Please refer to the specifications and the dataset derivation together for ease of understanding:

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

Variable Name	Variable Label	Type	Length/ Format	Define Derivation
USUBJID	Unique Subject Identifier	Char	16	ADSL.USUBJID
RACE	Race	Char	5	ADSL.RACE
ETHNIC	Ethnicity	Char	7	ADSL.ETHNIC
TRT01P	Planned Treatment for Period 01	Char	12	ADSL.TRT01P
TRT01PN	Planned Treatment for Period 01 (N)	Integer	1	ADSL.TRT01PN
ECOGPD	ECOG Performance Status at Progression	Integer	1	ECOG Performance Status at Progression
NEWPD1DT	Start Date of Subsequent Trt	Integer	Date9.	Start Date of Subsequent Treatment date
PDSTARDT	Tm to Evnt Crossover Origin Dt for Subj	Integer	Date9.	Date of Progression
TTPROG	Time to Progression (Days)	Integer	8	PDSTARDT-RANDDT+1
CRODT	Crossover Date	Integer	Date9.	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'; 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' 2 = 'No Crossover'
ELIGFL	Eligibility Flag for Indirect Switch	Char	1	ELIGFL='Y' for Control subjects with disease progression.
ACFA	Acceleration Factor (Overall)	float	8	Obtaining ACFA: Fit a parametric survival model based on Log-normal distribution for modelling time-to-event data (from disease progression to ADTTE.ADT where ADTTE.PARAMCD='OS' for subjects with ELIFGL='Y' in Control arm), with Race, Ethnicity, ECOG Performance Status, and time to progression. Take exponential of ESTIMATE from the ODS PARAMETERESTIMATES.
PARAM	Parameter	Char	110	"Overall Survival - Observed " "Overall Survival - Adjusted for Switching Treatments (Secondary Baseline: Time of Progression)"
PARAMCD	Parameter Code	Char	8	"OS" = "Overall Survival - Observed" "OS2STG" = "Overall Survival - Adjusted for Switching Treatments (Secondary Baseline: Time of Progression)"
PARAMN	Parameter (N)	Integer	8	1 = "Overall Survival - Observed" 2 = "Overall Survival - Adjusted for Switching Treatments (Secondary Baseline: Time of Progression)"
AVAL	Analysis Value	Integer	8	If PARAMCD= "OS" then AVAL=ADTTE.AVAL; If PARAMCD="OS2STG" then derive as follows: For subjects in the Experimental arm and in Control arm without switching treatment, AVAL= (ADT-STARTDT+1); For subjects in Control arm switching treatment (i.e., CRODT not equal to Missing and TRT01PN equals to 2), AVAL= (ADT – CRODT) × (1/ACFA) + (CRODT - STARTDT+1);
STARTDT	Time-to-Event Origin Date for Subject	Integer	Date9.	ADTTE.RANDDT
ADT	Analysis Date	Integer	Date9.	ADTTE.ADT
CNSR	Censor	Integer	1	ADTTE.CNSR

All randomized subjects with available measurements were included in the ADOS2STG dataset.
ADOS2STG is an ADaM basic data structure class dataset with one record per subject per parameter.

The derivation of the key variables is explained in the paper, and the full ADaM program is provided in the appendix.

Step 1: Identify which individuals in the control group made the switch:

CRODT:

CRODT is the cross-over date for subjects who started subsequent treatment in the Control arm only, i.e., CRODT = NEWPD1DT.

CROTRT and CROTRTN:

CROTRT is derived to know if there is a crossover from Control arm to subsequent therapy.

```
if crodt ne . and pdstardt ne . and crodt >=pdstardt then do;
        CROTRT = "Crossover Experimental drug or other Subsequent Therapies";
        CROTRTN =1;
end;
else do;
        CROTRT = "No Crossover";
        CROTRTN=2;
end;
```

ELIGFL:

Eligibility Flag is derived as 'Y' for Control subjects with disease progression.

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.

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 ACFA to adjust the OS for participants who switched from the control to the experimental treatment.

We can determine the ACFA for our dataset by fitting a parametric acceleration failure time in lognormal distribution model to the post progression survival and controlling for covariates at baseline and secondary baseline.
For illustration purpose the parametric lognormal distribution model is fitted using the PROC LIFEREG method.

```
%let class_vars =race ethnic ecogpd;
%let model_vars = race ethnic ecogpd ttprog;
ods output parameterestimates=parests(where=(parameter eq "CROTRT" and upcase(level1) ne "NO
CROSSOVER") keep=parameter level1 estimate lowercl uppercl)
convergencestatus=converge(where=(status eq 0) keep=status);

/*Run lifereg*/
proc lifereg data=acfadata order=internal;
   where eligfl="Y";
   class crotrt &class_vars.;
   model aval_pd * cnsr(1) = crotrt &model_vars. /distribution=lognormal;
run;

ods output close;
ods listing;

data acfactor(drop=estimate lowercl uppercl);
  merge parests(drop=parameter level1 in=a) converge(in=b);
  acfa=exp(estimate);
  mgvar='OSSEN';
```

Based on dummy ADTTE, the acceleration factor is **1.14**.

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.

Below is a snippet of the ADOS2STG dataset, which also highlights changes in AVAL for crossover subjects:

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

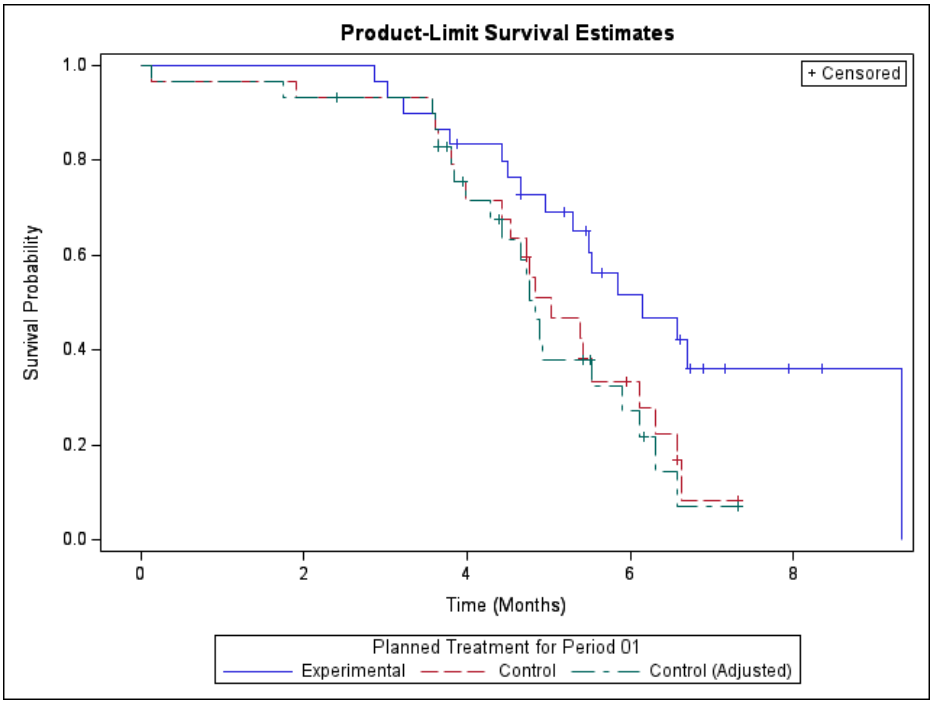
The ADOS2STG dataset, as derived in the previous section, is used as input to generate the table and figure outputs.

The Kaplan-Meier plot (Figure 1) below, which we created using the PROC LIFETEST procedure, indicates that the survival probability of the control arm is higher than that of the control (adjusted) arm. This is because, 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.

```
/*Kmplot, OS Rate at Month 6 in a (95% CI)*/
proc lifetest  data= result method=KM alpha=0.05 timelist=6 outsurv=stat reduceout;
        time aval_m*CNSR(1);
        strata trt01pn/order=internal;
        format trt01pn trtfmt.;
        label trt01pn=Planned Treatment for Period 01;
run;
```

code 1: To output the Kaplan-Meier plot (figure 1)

Figure 1: Kaplan-Meier Analysis of Overall Survival



To gain a deeper understanding of the analysis results, we generated the table below (Table 1). From this table, we observe that the overall survival rate at 6 months, with a 95% Confidence Interval (CI) is, 33.49% (15.98, 52.07) for the control arm, whereas 27.11% (10.94, 46.30) for the control (adjusted) arm. Similarly, the event rate for control arm is 15.16 per 100 person-months, whereas the control (adjusted) arm has the event rate of 15.57 per 100 person - months.

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/ 100 Person-Months (%)	10.25	15.16	15.57
OS Rate at Month 6 in % (95% CI)	51.65 (31.05, 68.88)	33.49 (15.98, 52.07)	27.11 (10.94, 46.30)

We used PROC PHREG to fit the Cox proportional hazards model and obtained the corresponding hazard ratio and Cox p-value, as shown in Table 2 below. The table displays the treatment effect of the experimental arm versus the control arm and control (adjusted) arm. The hazard ratio of 0.507 (experimental vs control) 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 (experimental vs control (adjusted)) 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 of 0.0441 and 0.0212 in the two comparisons, demonstrate the effect of adjusting the overall survival time for treatment switchers.

```
/*Experimental vs Control*/
proc phreg data = result alpha=0.05;
    where trt01pn in (1,2);
    class trt01pn(ref='2');
    model aval_m*CNSR(1) = trt01pn/ rl  TIES=EFRON;
    ods output ParameterEstimates=stat1;
run;

/*Experimental vs Control (Adjusted)*/
proc phreg data = result alpha=0.05;
    where trt01pn in (1,3);
    class trt01pn(ref='3');
    model aval m*CNSR(1) = trt01pn/ rl  TIES=EFRON;
    ods output ParameterEstimates=stat2;
run;
```

code 2: To output the Table 2 to show Treatment Effect

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 paper 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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REFERENCES

1. Latimer, N. R., Abrams, K. R., & Lambert, P. C. (2016). Treatment switching: Statistical and decision-making challenges and approaches. *International Journal of Technology Assessment in Health Care, 32*(3), 160–166. https://doi.org/10.1017/S026646231600026X
2. Latimer, N. R., Abrams, K. R., Lambert, P. C., & Wailoo, A. J. (2020). Improved two-stage estimation to adjust for treatment switching in randomized trials: G-estimation to address time-dependent confounding. *Statistical Methods in Medical Research, 29(12), 3551–3570.* https://doi.org/10.1177/0962280220912524

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APPENDIX:

```
%*-------------------------------------------------------------------------*;
%*                          Dummy ADTTE dataset                            *;
%*-------------------------------------------------------------------------*;

data adtte;
  length USUBJID $16 TRT01P $12 RACE $5 ETHNIC $7 PARAM $16 PARAMCD $2 RANDDT $9 PDSTARDT $9
NEWPD1DT $9 STARTDT $9 ADT $9;
  input USUBJID $ TRT01P $ TRT01PN RACE $ ETHNIC $ RANDDT $ PDSTARDT $ NEWPD1DT $ ECOGPD PARAM $
PARAMCD $ PARAMN STARTDT $ ADT $ AVAL CNSR;
  label
              USUBJID='Unique Subject Identifier'
              TRT01P='Planned Treatment for Period 01'
              TRT01PN='Planned Treatment for Period 01 (N)'
              RACE='Race'
              ETHNIC='Ethnicity'
              RANDDT='Date of Randomization'
              PDSTARDT='Date of Progression'
              NEWPD1DT= 'Start Date of Subsequent Trt'
              ECOGPD='ECOG Performance Status at Progression'
              PARAM='Parameter'
              PARAMCD='Parameter Code'
              PARAMN='Parameter (N)'
              STARTDT='Time-to-Event Origin Date for Subject'
              ADT='Analysis Date'
              AVAL='Analysis Value'
              CNSR='Censor';
  datalines;
Study_100000001        Control        2       Race1   Ethnic1 29NOV2020       12DEC2020       .
        0       Overall_Survival       OS      1       29NOV2020       25APR2021       147     0
Study_100000002        Experimental   1       Race1   Ethnic1 14OCT2020       .               .
        .       Overall_Survival       OS      1       14OCT2020       21MAR2021       158     1
Study_100000003        Control        2       Race1   Ethnic1 16JUL2020       30JUL2020       .
        1       Overall_Survival       OS      1       16JUL2020       27SEP2020       73      1
Study_100000004        Experimental   1       Race2   Ethnic2 11MAY2020       .               .
        .       Overall_Survival       OS      1       11MAY2020       05NOV2020       178     0
Study_100000005        Control        2       Race2   Ethnic2 12APR2020       .               .
        .       Overall_Survival       OS      1       12APR2020       07AUG2020       117     0
Study_100000006        Experimental   1       Race2   Ethnic2 29NOV2020       06JAN2021       .
        0       Overall_Survival       OS      1       29NOV2020       05JUL2021       218     1
Study_100000007        Control        2       Race2   Ethnic2 28OCT2020       09JAN2021       .
        0       Overall_Survival       OS      1       28OCT2020       08MAY2021       192     0
Study 100000008        Experimental   1       Race2   Ethnic2 23MAY2020       26JUL2020       .
        0       Overall_Survival       OS      1       23MAY2020       10DEC2020       201     1
Study_100000009        Control        2       Race1   Ethnic1 08FEB2020       02APR2020       .
        1       Overall_Survival       OS      1       08FEB2020       18SEP2020       223     1
Study_100000010        Experimental   1       Race1   Ethnic1 11JUN2020       .               .
        .       Overall_Survival       OS      1       11JUN2020       11SEP2020       92      0
Study_100000011        Control        2       Race1   Ethnic1 18JUN2020       23JUN2020       .
        0       Overall_Survival       OS      1       18JUN2020       03DEC2020       168     0
Study_100000012        Experimental   1       Race1   Ethnic1 25DEC2020       .               .
        .       Overall_Survival       OS      1       25DEC2020       11JUN2021       168     0
Study_100000013        Control        2       Race2   Ethnic2 07SEP2020       15OCT2020       .
        0       Overall_Survival       OS      1       07SEP2020       26DEC2020       110     0
Study_100000014        Experimental   1       Race2   Ethnic2 30AUG2020       .               .
        .       Overall_Survival       OS      1       30AUG2020       19JAN2021       142     0
Study_100000015        Control        2       Race2   Ethnic2 07MAY2020       18JUN2020       .
        0       Overall_Survival       OS      1       07MAY2020       26AUG2020       111     1
Study_100000016        Experimental   1       Race2   Ethnic2 11OCT2020       .               .
        .       Overall_Survival       OS      1       11OCT2020       17JAN2021       98      0
Study_100000017        Control        2       Race2   Ethnic2 07MAR2020       21MAR2020
        11APR2020       0       Overall_Survival       OS      1       07MAR2020       18AUG2020
        164     0
Study_100000018        Experimental   1       Race1   Ethnic1 14DEC2020       .               .
        .       Overall_Survival       OS      1       14DEC2020       02JUL2021       200     0
Study_100000019        Control        2       Race1   Ethnic1 16OCT2020       03DEC2020       .
        1       Overall Survival       OS      1       16OCT2020       30MAR2021       165     1
Study_100000020        Experimental   1       Race1   Ethnic1 07JAN2021       .               .
        .       Overall_Survival       OS      1       07JAN2021       27APR2021       110     0
```

```
Study_100000021        Control        2       Race1   Ethnic1 02DEC2020       31DEC2020
        09FEB2021       0       Overall_Survival        OS      1       02DEC2020       19APR2021
        138     0
Study_100000022        Experimental   1       Race2   Ethnic2 13JUL2020       .               .
        .       Overall_Survival        OS      1       13JUL2020       08FEB2021       210     1
Study_100000023        Control        2       Race2   Ethnic2 17FEB2020       22FEB2020
        01MAR2020       0       Overall_Survival        OS      1       17FEB2020       06SEP2020
        202     0
Study_100000024        Experimental   1       Race2   Ethnic2 19DEC2020       05FEB2021       .
        0       Overall_Survival        OS      1       19DEC2020       10MAY2021       142     1
Study_100000025        Control        2       Race2   Ethnic2 16AUG2020       .               .
        .       Overall_Survival        OS      1       16AUG2020       08JAN2021       145     0
Study_100000026        Experimental   1       Race2   Ethnic2 15APR2020       .               .
        .       Overall_Survival        OS      1       15APR2020       05NOV2020       204     0
Study_100000027        Control        2       Race1   Ethnic1 29JAN2021       .               .
        .       Overall_Survival        OS      1       29JAN2021       03AUG2021       186     0
Study_100000028        Experimental   1       Race1   Ethnic1 03DEC2020       .               .
        .       Overall_Survival        OS      1       03DEC2020       19APR2021       137     0
Study_100000029        Control        2       Race1   Ethnic1 10APR2020       .               .
        .       Overall_Survival        OS      1       10APR2020       09AUG2020       121     0
Study_100000030        Experimental   1       Race1   Ethnic1 16NOV2020       20DEC2020       .
        0       Overall_Survival        OS      1       16NOV2020       16APR2021       151     0
Study_100000031        Control        2       Race2   Ethnic2 04JAN2021       08FEB2021
        10MAR2021       0       Overall_Survival        OS      1       04JAN2021       04JUL2021
        181     1
Study_100000032        Experimental   1       Race2   Ethnic2 22JUN2020       .               .
        .       Overall_Survival        OS      1       22JUN2020       26DEC2020       187     0
Study_100000033        Control        2       Race2   Ethnic2 07NOV2020       22NOV2020       .
        0       Overall_Survival        OS      1       07NOV2020       26MAY2021       200     0
Study_100000034        Experimental   1       Race2   Ethnic2 20NOV2020       12MAR2021       .
        0       Overall_Survival        OS      1       20NOV2020       20JUL2021       242     1
Study_100000035        Control        2       Race2   Ethnic2 12FEB2020       22MAR2020       .
        0       Overall_Survival        OS      1       12FEB2020       11JUN2020       120     1
Study_100000036        Experimental   1       Race1   Ethnic1 18MAR2020       27APR2020       .
        0       Overall_Survival        OS      1       18MAR2020       27DEC2020       284     0
Study_100000037        Control        2       Race1   Ethnic1 04JUN2020       10JUN2020       .
        0       Overall_Survival        OS      1       04JUN2020       23SEP2020       111     0
Study_100000038        Experimental   1       Race1   Ethnic1 10OCT2020       .               .
        .       Overall_Survival        OS      1       10OCT2020       05JAN2021       87      0
Study_100000039        Control        2       Race1   Ethnic1 09MAY2020       08JUN2020       .
        1       Overall_Survival        OS      1       09MAY2020       31AUG2020       114     1
Study_100000040        Experimental   1       Race2   Ethnic2 24JUL2020       01OCT2020       .
        0       Overall_Survival        OS      1       24JUL2020       04APR2021       254     1
Study_100000041        Control        2       Race2   Ethnic2 03JUL2020       14AUG2020       .
        0       Overall_Survival        OS      1       03JUL2020       15NOV2020       135     0
Study_100000042        Experimental   1       Race2   Ethnic2 15NOV2020       18DEC2020       .
        0       Overall_Survival        OS      1       15NOV2020       06MAY2021       172     1
Study_100000043        Control        2       Race2   Ethnic2 02JUL2020       20JUL2020
        22AUG2020       0       Overall_Survival        OS      1       02JUL2020       23NOV2020
        144     1
Study_100000044        Experimental   1       Race2   Ethnic2 12JUN2020       16JUL2020       .
        0       Overall_Survival        OS      1       12JUN2020       08OCT2020       118     1
Study_100000045        Control        2       Race1   Ethnic1 23MAY2020       .               .
        .       Overall_Survival        OS      1       23MAY2020       16SEP2020       116     0
Study_100000046        Experimental   1       Race1   Ethnic1 21APR2020       .               .
        .       Overall_Survival        OS      1       21APR2020       04OCT2020       166     1
Study_100000047        Control        2       Race1   Ethnic1 11JUL2020       23AUG2020
        13OCT2020       1       Overall_Survival        OS      1       11JUL2020       27JAN2021
        200     1
Study_100000048        Experimental   1       Race1   Ethnic1 05OCT2020       24NOV2020       .
        0       Overall_Survival        OS      1       05OCT2020       21MAR2021       167     0
Study_100000049        Control        2       Race2   Ethnic2 12SEP2020       24OCT2020       .
        0       Overall_Survival        OS      1       12SEP2020       03FEB2021       144     0
Study_100000050        Experimental   1       Race2   Ethnic2 11MAY2020       25MAY2020       .
        0       Overall_Survival        OS      1       11MAY2020       23SEP2020       135     0
Study_100000051        Control        2       Race2   Ethnic2 02FEB2020       03FEB2020
        13FEB2020       0       Overall_Survival        OS      1       02FEB2020       31MAR2020
        58      0
Study_100000052        Experimental   1       Race2   Ethnic2 15AUG2020       .               .
        .       Overall_Survival        OS      1       15AUG2020       08MAR2021       205     1
```

```
Study_100000053        Control        2       Race2   Ethnic2 22APR2020       02MAY2020
        26MAY2020       0       Overall_Survival        OS      1       22APR2020       04OCT2020
        165     0
Study_100000054        Experimental   1       Race1   Ethnic1 04JUL2020       26JUL2020       .
        0       Overall_Survival        OS      1       04JUL2020       27OCT2020       115     0
Study_100000055        Control        2       Race1   Ethnic1 12DEC2020       .               .
        .       Overall_Survival        OS      1       12DEC2020       16DEC2020       4       0
Study_100000056        Experimental   1       Race1   Ethnic1 25SEP2020       27OCT2020       .
        1       Overall_Survival        OS      1       25SEP2020       14FEB2021       142     1
Study_100000057        Control        2       Race1   Ethnic1 01MAR2020       06APR2020
        25APR2020       0       Overall_Survival        OS      1       01MAR2020       01AUG2020
        153     0
Study_100000058        Experimental   1       Race2   Ethnic2 01JAN2021       22FEB2021       .
        0       Overall_Survival        OS      1       01JAN2021       11JUN2021       161     0
Study_100000059        Control        2       Race2   Ethnic2 22JAN2021       16FEB2021       .
        0       Overall_Survival        OS      1       22JAN2021       11MAY2021       109     0
Study_100000060        Experimental   1       Race2   Ethnic2 18SEP2020       23SEP2020       .
        0       Overall_Survival        OS      1       18SEP2020       07APR2021       201     1
;
run;

data adtte;
  set adtte;
  /*Convert Dates from Charecter to Numeric*/
        RANDDT1=input(RANDDT,date9.);
        PDSTARDT1=input(PDSTARDT,date9.);
        NEWPD1DT1=input(NEWPD1DT,date9.);
        STARTDT1=input(STARTDT,date9.);
        ADT1=input(ADT,date9.); ;
        format RANDDT1 PDSTARDT1 NEWPD1DT1 STARTDT1 ADT1 date9.;
        drop RANDDT PDSTARDT NEWPD1DT STARTDT ADT;
        rename RANDDT1=RANDDT PDSTARDT1=PDSTARDT NEWPD1DT1=NEWPD1DT STARTDT1=STARTDT ADT1=ADT;
run;

%*-------------------------------------------------------------------------*;
%*                                          OS Stage 2 dataset             *;
%*-------------------------------------------------------------------------*;

/*Read adtte data to derive flags, add new derived variables*/
data adosap1;
        set adtte;

/*CRODT*/
        if trt01pn eq 2 and newpd1dt ne . then crodt = newpd1dt;
        format crodt yymmdd10.;

/*CROTRT, CROTRTN*/
        if crodt ne . and pdstardt ne . and crodt >=pdstardt then do;
                CROTRT = "Crossover Experimental drug or other Subsequent Therapies";
                crotrtn =1;
        end;
        else do;
                CROTRT = "No Crossover";
                crotrtn=2;
        end;

/*TTPROG*/
        if pdstardt ne . and randdt ne . then ttprog = pdstardt - randdt  + 1;

/*ELIGFL*/
         if not ((not missing(crodt) and not missing(pdstardt) and crodt < pdstardt) or trt01pn =
1 or pdstardt = .) then do;
        eligfl = "Y";
   end;

        mgvar='OSSEN';
run;

proc sort; by mgvar; run;
```

```
/*Calculate Acceleration factors*/
data acfadata;
  set adosap1;
  if n(adt, pdstardt)=2 then aval_pd = adt - pdstardt + 1;
run;


%let class_vars =race ethnic ecogpd;
%let model_vars = race ethnic ecogpd ttprog;
ods output parameterestimates=parests(where=(parameter eq "CROTRT" and upcase(level1) ne "NO
CROSSOVER") keep=parameter level1 estimate lowercl uppercl)
convergencestatus=converge(where=(status eq 0) keep=status);

/*Run lifereg*/
proc lifereg data=acfadata order=internal;
   where eligfl="Y";
   class crotrt &class_vars.;
   model aval_pd * cnsr(1) = crotrt &model_vars. /distribution=lognormal;
run;

ods output close;
ods listing;

data acfactor(drop=estimate lowercl uppercl);
  merge parests(drop=parameter level1 in=a) converge(in=b);
  acfa=exp(estimate);
  mgvar='OSSEN';

proc sort; by mgvar; run;

/*Merge adosap1 and acfactor*/
data final;
       merge adosap1 acfactor;
       by mgvar;
run;

/*OS Observed dataset */
data final_os;
       length param $200. paramcd $8.;
       set final;
       param = "Overall Survival - Observed";
       paramcd = "OS";
       paramn = 1;
run;

/*OS Adjusted dataset */
data final_os2stg;
       length param $200. paramcd $8.;
    set final;
       param = "Overall Survival - Adjusted for Switching Treatments (Secondary Baseline: Time
of Progression)";
       paramcd = "OS2STG";
       paramn =2;

/*For subjects in Control arm switching treatment*/

        if crodt ne . and trt01pn eq 2 then aval = (adt-crodt)*(1/acfa) + (crodt-startdt+1);
run;

/*ados2stg Dataset*/
data ados2stg;
       RETAIN USUBJID TRT01P TRT01PN RACE ETHNIC ECOGPD NEWPD1DT PDSTARDT TTPROG CRODT CROTRT
CROTRTN ELIGFL ACFA PARAM PARAMCD PARAMN AVAL STARTDT ADT CNSR;
       set final_os final_os2stg;
       keep usubjid trt01p trt01pn race ethnic ecogpd newpd1dt pdstardt ttprog crodt crotrt
crotrtn eligfl acfa param paramcd paramn aval startdt adt cnsr;
run;

proc sort data=ados2stg; by usubjid paramn; run;
```

```
%*-------------------------------------------------------------------------*;
%*                                    Results                              *;
%*-------------------------------------------------------------------------*;

/*Adjust dataset to include 3 results */
data result;
  length trt01p $20;
  set ados2stg;
  if paramcd in ("OS", "OS2STG");
  if paramcd ="OS2STG" and trt01pn=1 then delete; /*Remove experimental arm*/
  if paramcd ="OS2STG" and trt01pn=2 then do; /*Rename control arm to adjusted contrtol arm*/
               trt01pn=3; trt01p="Control (Adjusted)";
  end;
  aval_m=aval/30.4367; /*aval converted to month*/
  label aval_m="Time (Months)";
run;

/*Format*/
proc format;
       value trtfmt
                    1 = "Experimental"
                    2 = "Control"
                    3 = "Control (Adjusted)";
run;

/*N*/
proc freq data=result noprint;
       tables trt01pn/out=N_count(drop=percent);
       format trt01pn trtfmt.;
run;

/*Number of Events (%)*/
proc freq data=result noprint;
       tables trt01pn /out=event_count(drop=percent);
       where CNSR EQ 0;
       format trt01pn trtfmt.;
run;

/*Kmplot, OS Rate at Month 6 in %a (95% CI)*/
proc lifetest  data= result method=KM alpha=0.05 timelist=6 outsurv=stat reduceout;
       time aval_m*CNSR(1);
       strata trt01pn/order=internal;
       format trt01pn trtfmt.;
       label trt01pn=Planned Treatment for Period 01;
run;

/*Person-Months*/
proc means data=result sum nway;
   var aval_m;
   class trt01pn;
   output out=des_stats sum=sum;
run;

/*Event Rate / 100 person time = number of events / person-time * 100*/
data rate;
  merge des_stats event_count;
  by trt01pn;
  rate=(count/sum)*100;
  keep trt01pn rate;
run;

/*HR and P Value from Cox regression Model*/

/*Experimental vs Control*/
proc phreg data = result alpha=0.05;
    where trt01pn in (1,2);
    class trt01pn(ref='2');
    model aval_m*CNSR(1) = trt01pn/ rl  TIES=EFRON;
    ods output ParameterEstimates=stat1;
run;
```

```
/*Experimental vs Control (Adjusted)*/
proc phreg data = result alpha=0.05;
    where trt01pn in (1,3);
    class trt01pn(ref='3');
    model aval_m*CNSR(1) = trt01pn/ rl  TIES=EFRON;
    ods output ParameterEstimates=stat2;
run;


%*-------------------------------------------------------------------------*;
%*                                    Program END                          *;
%*-------------------------------------------------------------------------*;
```