TRANSFORMING PROMISING IDEAS INTO COMMERCIAL REALITY

Time to Event Analyses – Fear Not:

What Every Programmer and Statistician Wants & Should Know

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Overview

- Prevalence
- Key components
- Examples
  - OS: Overall Survival
  - PFS: Progression Free Survival
    - Multiple definitions
- Sensitivity analyses
- ADaM dataset structure
- SAS code
- Quality review

Time to Event Analysis Prevalence

- Eight leading medical journals
  - Of the 58 breast cancer trials that were reviewed, 64% of the primary endpoints were time to event endpoints of which overall survival was only the primary 2% of the time (Saad, 2010)
- Prevalence of the analysis indicates the need for all statisticians and programmers to understand time to event analysis
  - At some point, you will have to conduct a time to event analysis

Time to Event Key Components

- ***Event:*** The change or transition in state of interest. Needs to be clearly defined up front.

- ***Time:*** Measures the time for the occurrence of an event to occur. Measuring when the change or transition has occurred. The start of the time interval as well as the event are clearly defined.

- ***Censor:*** From the start time after multiple measures, no event has been reported. In this case, the time is censored at the pre-specified time.

Time to Event Example

Progression Free Survival(PFS)

Event: progressive disease (PD) or death, whichever occurred first

Start of interval: date of enrollment or randomization

End of interval: date of death/PD (not censored). If PD/death is not reported, time is usually censored at the last “evaluable” tumor assessment.

Time to Event Endpoint Problems

- **Problem with PFS**
  - What if they missed scan(s) before PD?
    - When did the progression really occur?
- What if they died before a scan was possible?
  - Did the subject die with or without PD?
- What if they started new treatment before PD?
  - New treatment could be more effective
  - New treatment could be more toxic
  - More subjects on one arm starting new treatment

Common Sensitivity Analyses for PFS

- Try and control possible bias due to:
- New treatment
  - PFS2
- Missed visits
  - PFS3/PFS4
- Not following scheduled visits
  - PFS4
- Symptomatic progression versus radiographic progression
  - PFS2-PFS4
  - PFS5: events PD, death, symptomatic progression [not presented]

Example Patients

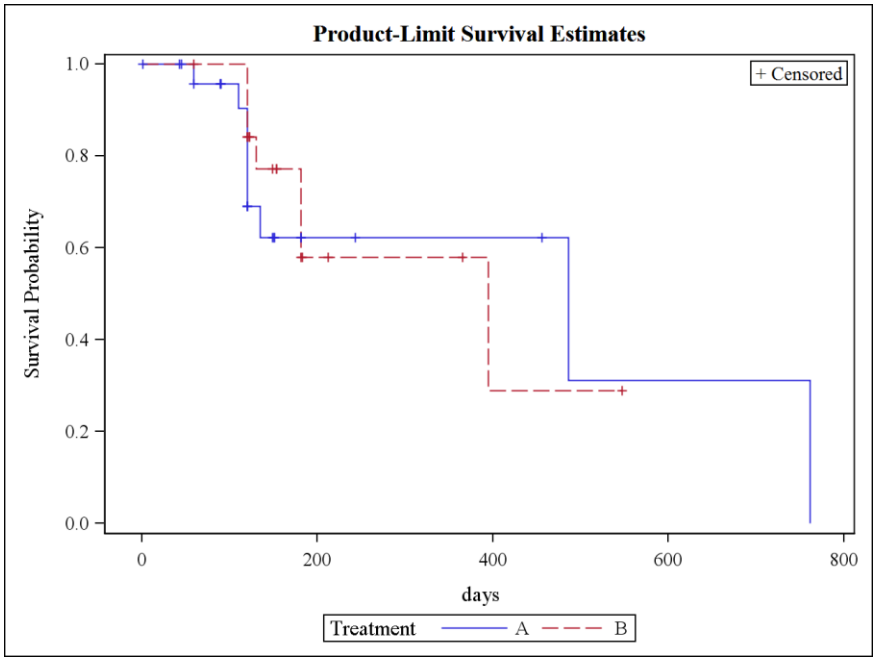
Pt ID	Rand Date	Resp Date	Resp	Prev Sched Visit	New Anti Cancer Tx	Death Date
1	01JAN2001	03FEB2001	SD	01FEB2001		
1		05MAR2001	SD	01MAR2001		
1		09JUN2001	PD	01JUN2001	15MAR2001	17JUL2001
2	01JAN2001	03FEB2001	SD	01FEB2001		
2		05MAR2001	SD	01MAR2001		
2		09JUN2001	PD	01JUN2001		17JUL2001

Tumor scans for this study are planned every 4 weeks per protocol.

SD= Stable Disease
PD= Progressive Disease

Ex 0: Overall Survival

- Time from randomization to death
  - Number of events: 16 (100%)
  - HR (95% CI): 1.18 (0.43, 3.29)
  - Log Rank p-value: 0.7356



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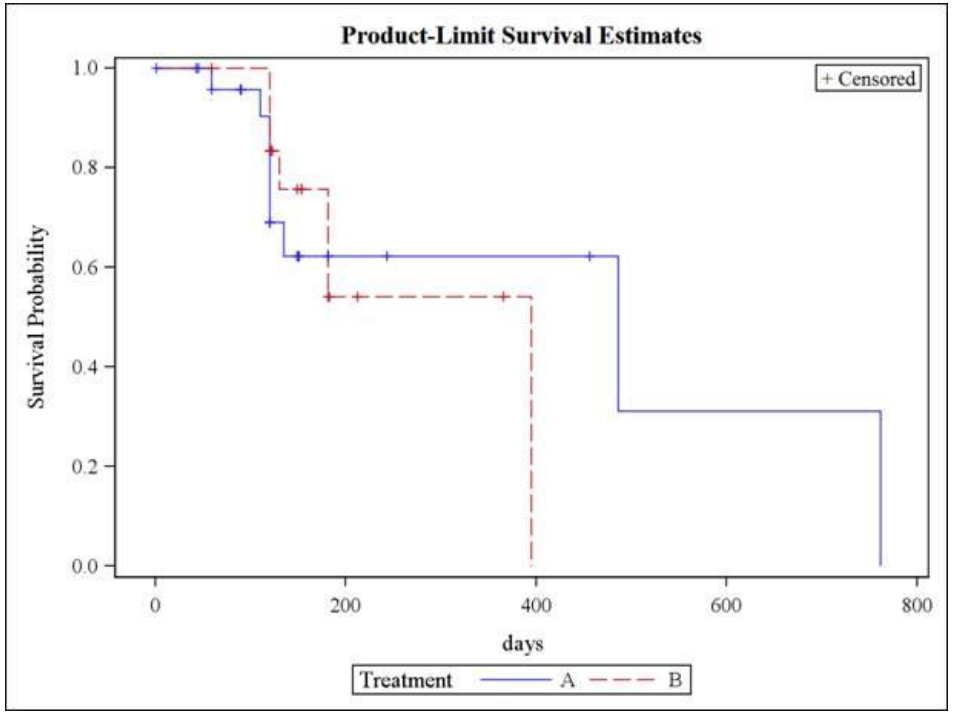

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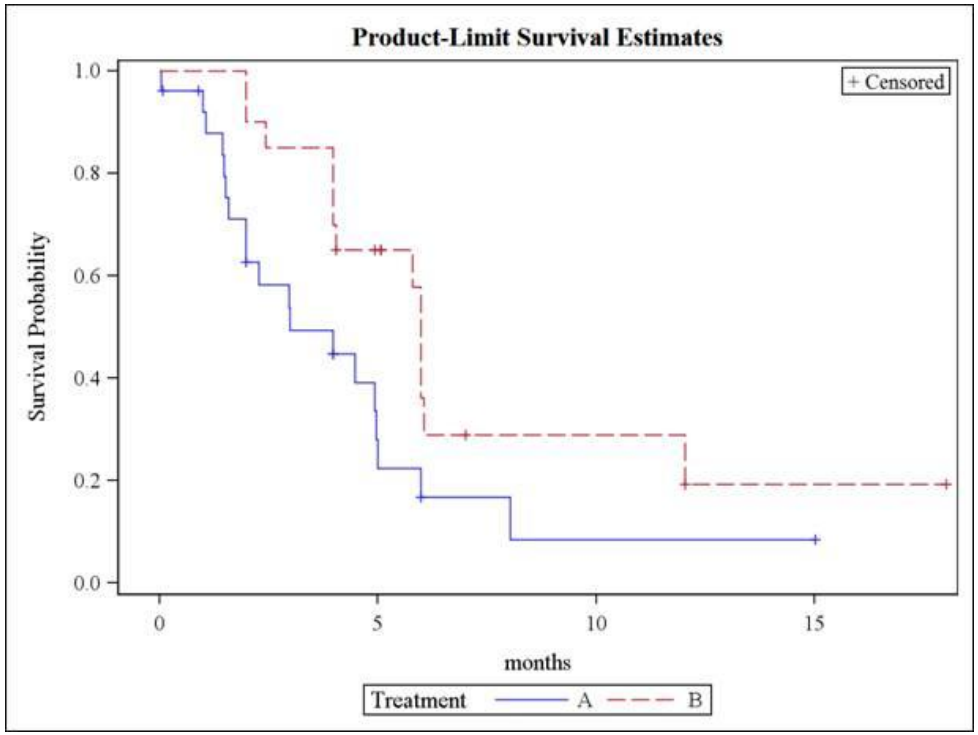
1		05MAR2001	SD			
1		09JUN2001	PD	15MAR2001	17JUL2001	0 - Death

Ex 1: Progression Free Survival 1

- Time from randomization to progression or death, whichever occurs first
  - Number of events: 32 (100%)
  - HR (95% CI): 2.15 (1.05, 4.40)
  - Log Rank p-value: 0.02660



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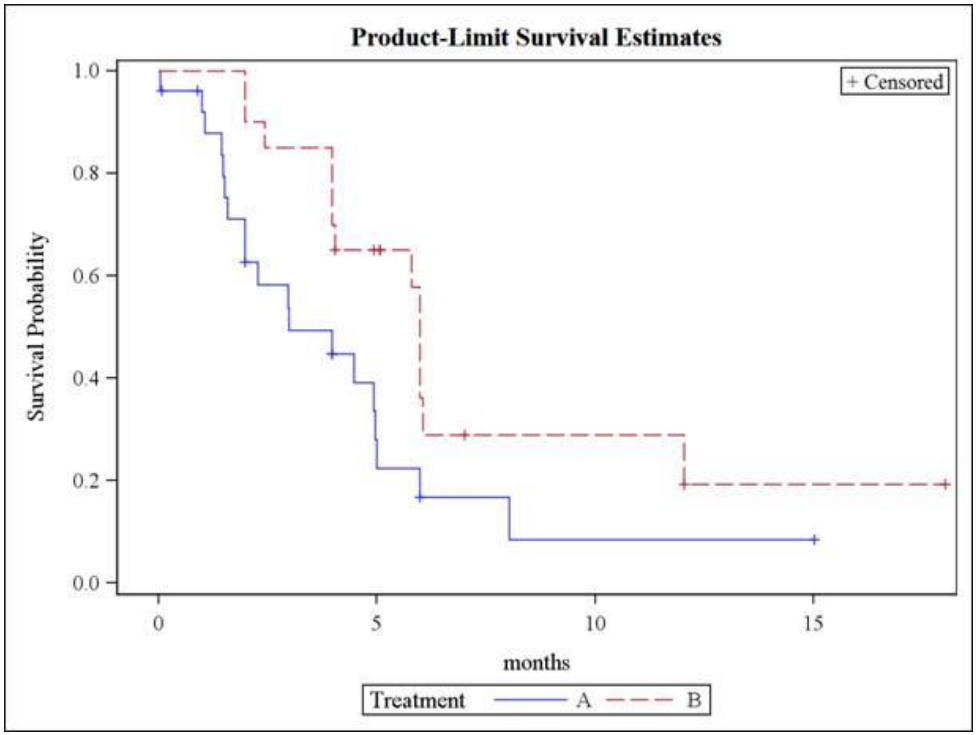

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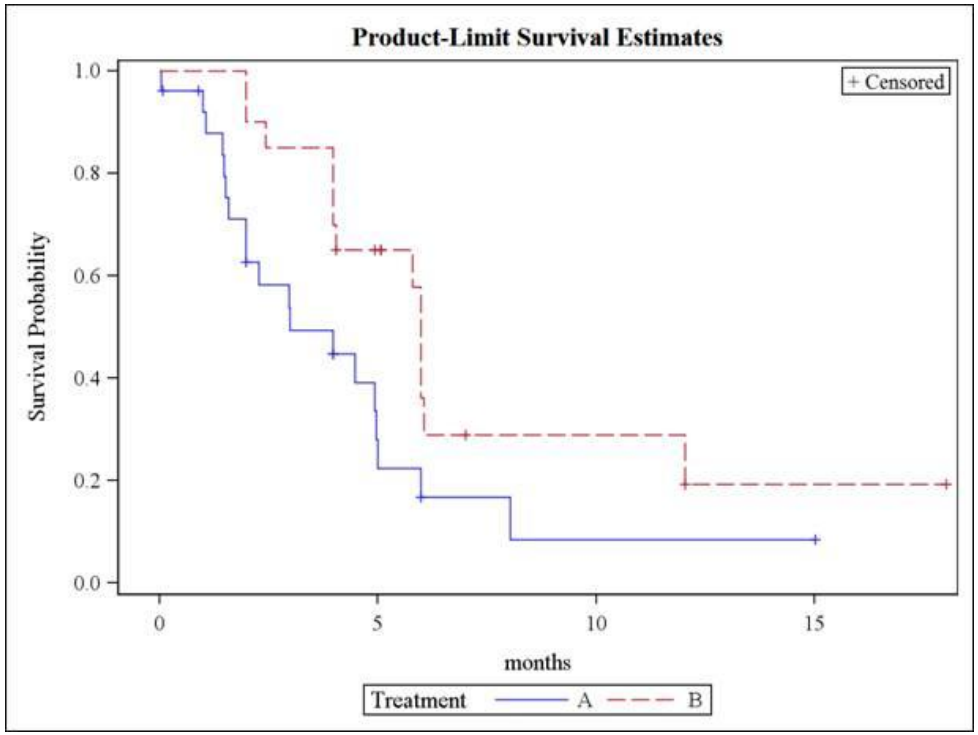
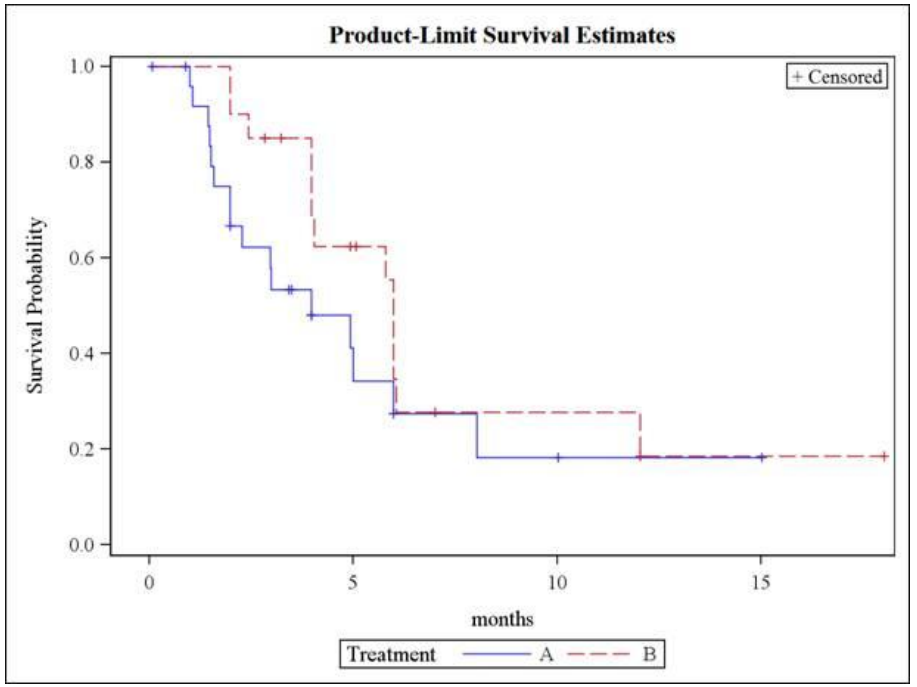


Pt ID	Rand Date	Resp Date	Resp	New Anti Cancer Tx	Death Date	Cens-Desc
1	01JAN2001	03FEB2001	SD			
1		05MAR2001	SD			
1		09JUN2001	PD	15MAR2001	17JUL2001	0-Prog

Ex 2: Progression Free Survival 2

- Time from randomization to progression or death, whichever occurs first. Time is censored if new treatment is started before an event.
  - Number of events: 29 (91%)
  - HR (95% CI): 1.626 (0.78, 3.40)
  - Log Rank p-value: 0.1790



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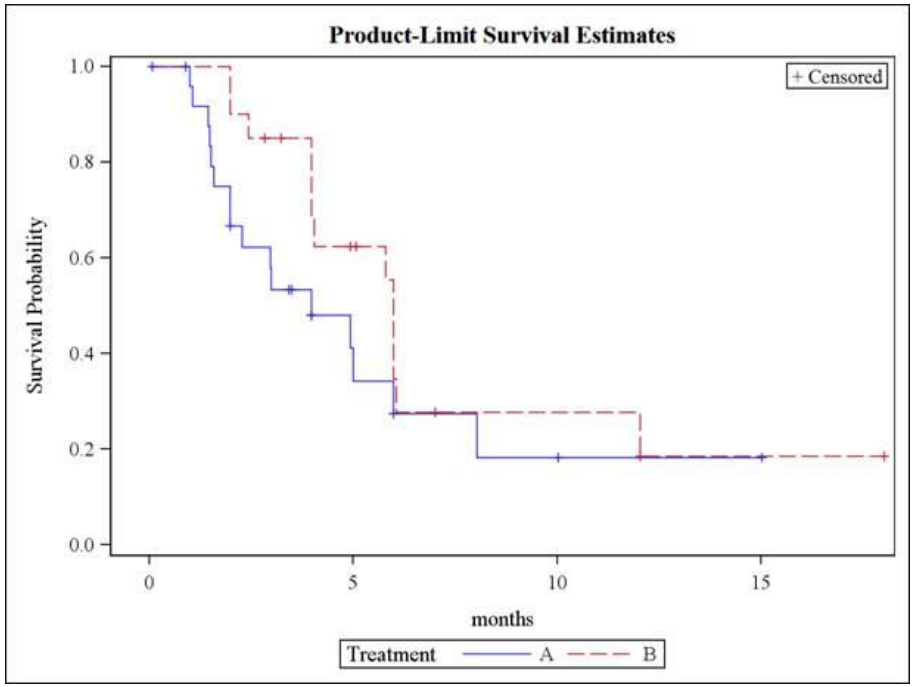

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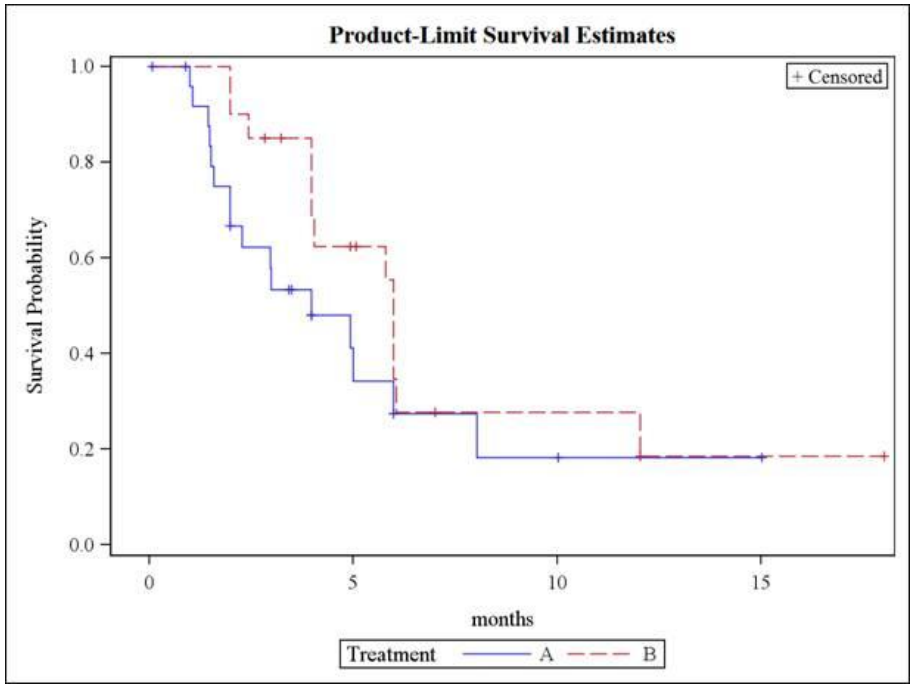

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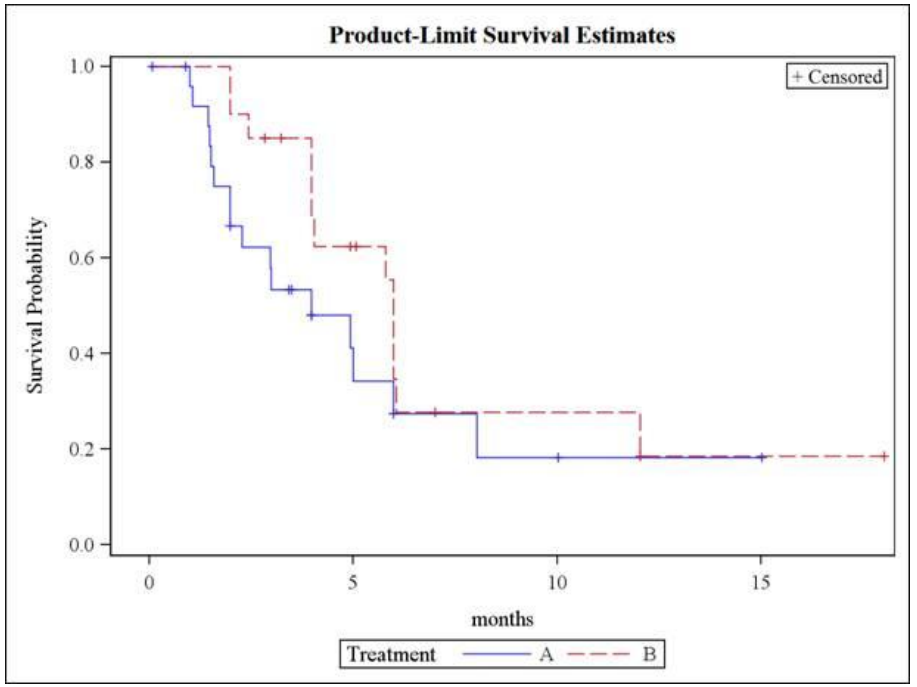

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* Usually censored at previous tumor assessment.

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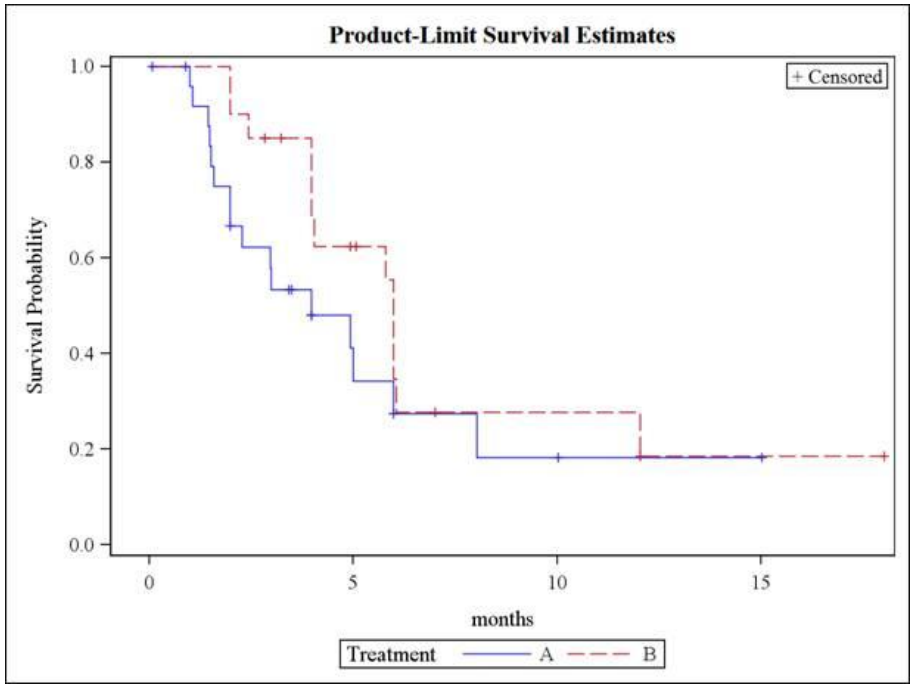
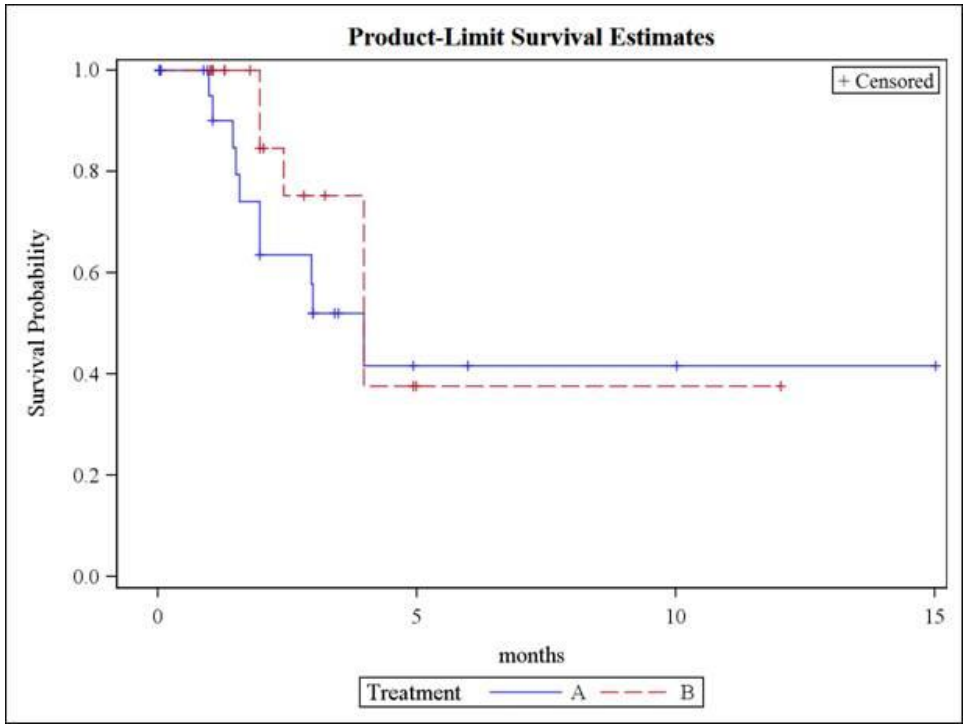


Pt ID	Rand Date	Resp Date	Resp	New Anti Cancer Tx	Death Date	Cens/Desc
1	01JAN2001	03FEB2001	SD			
1		05MAR2001	SD			1-New Tx
1		09JUN2001	PD	15MAR2001	17JUL2001	

* Usually censored at previous tumor assessment.

Ex 3: Progression Free Survival 3

- Time from randomization to progression or death, whichever occurs first. Time is censored* if there are missed visits before an event or new treatment is started before an event
  - Number of events: 16 (50%)
  - HR (95% CI): 1.575 (0.57, 4.35)
  - Log Rank p-value: 0.3505



Vis	Pt ID	Rand Date	Resp Date	Resp	New Anti Cancer Tx	Death Date
1	2	01JAN2001	03FEB2001	SD		
2	2		05MAR2001	SD		
3	2		09JUN2001	PD		17JUL2001

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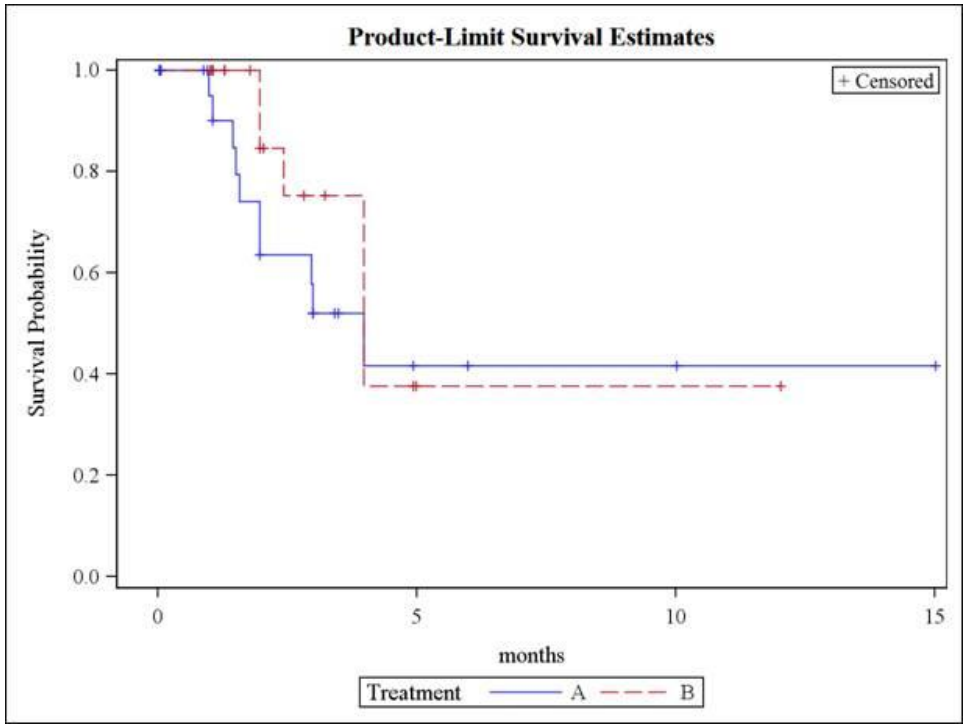

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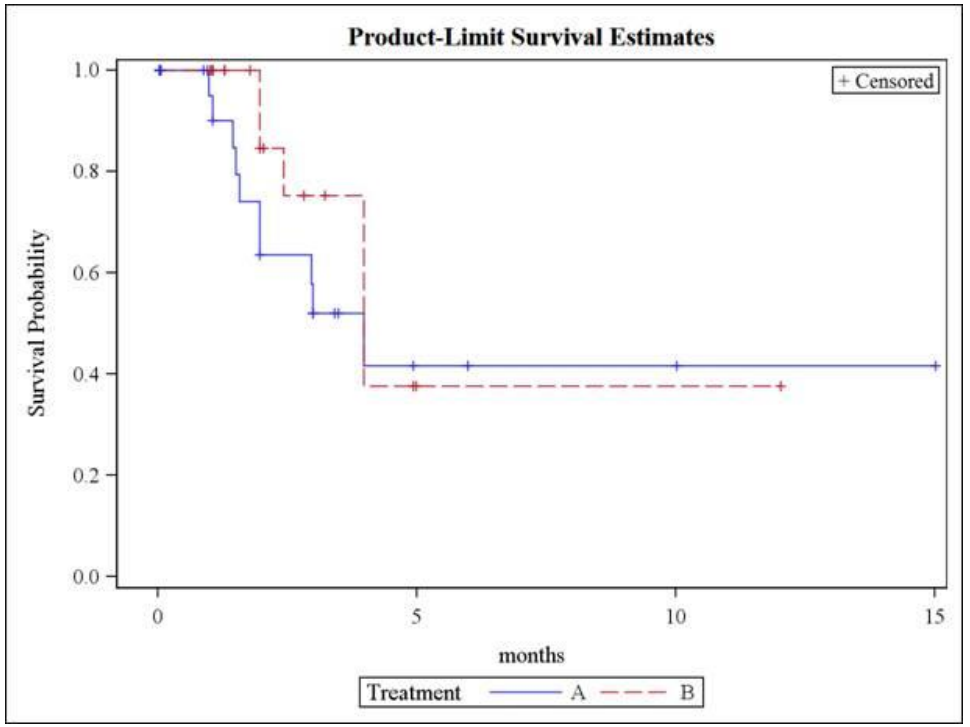
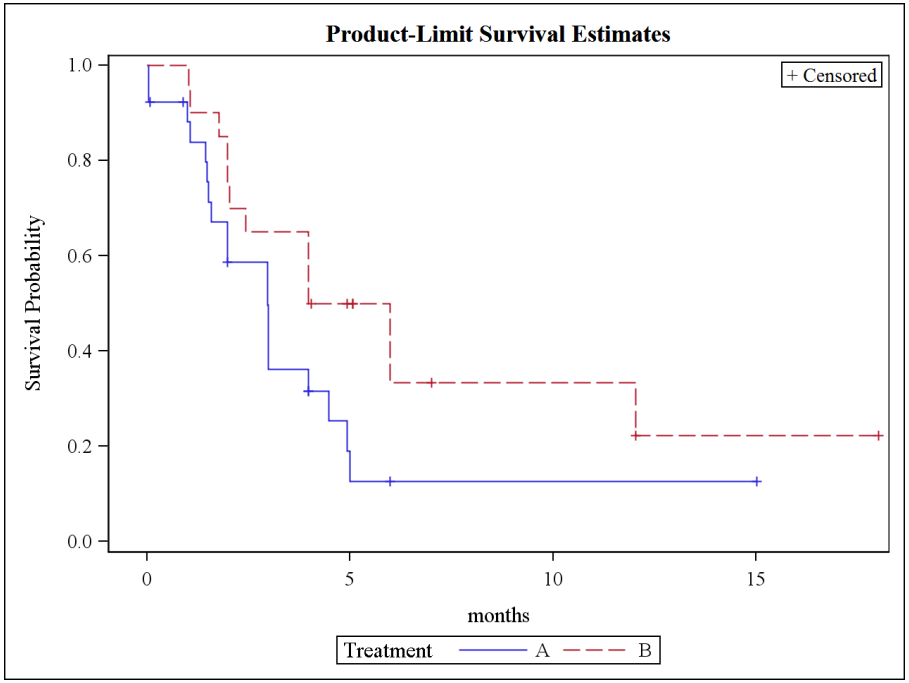


Vis	Pt ID	Rand Date	Resp Date	Resp	New Anti Cancer Tx	Death Date	Cens/Desc
1	2	01JAN2001	03FEB2001	SD			
2	2		05MAR2001	SD			1- Miss Vis
3	2		09JUN2001	PD		17JUL2001	

Ex 4: Progression Free Survival 4

- Time from randomization to progression or death, whichever occurs first. Missed visit prior to an event but move event (PD or death) earlier ie to previous scheduled or between last and next scheduled.
  - Number of events: 32 (100%)
  - HR (95% CI): 1.878 (0.92, 3.86)
  - Log Rank p-value: 0.0733



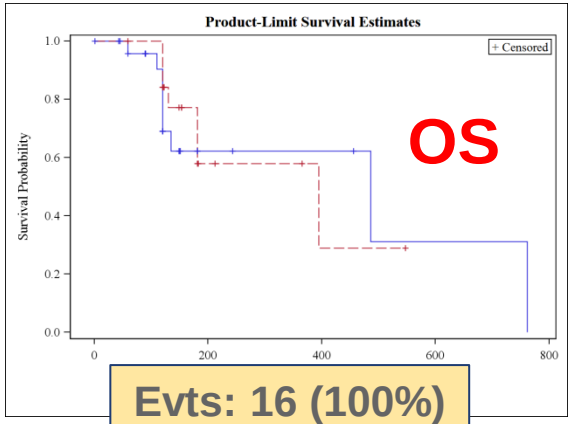
Pt ID	Rand Date	Resp Date	Prev Sched Visit	Resp	New Anti Cancer Tx	Death Date	Cens/ Desc
2	01JAN2001	03FEB2001	01FEB2001	SD			
2		05MAR2001	01MAR2001	SD			
2		09JUN2001	01JUN2001	PD		17JUL2001	0-PD

ADaM Time to Event: ADTTE

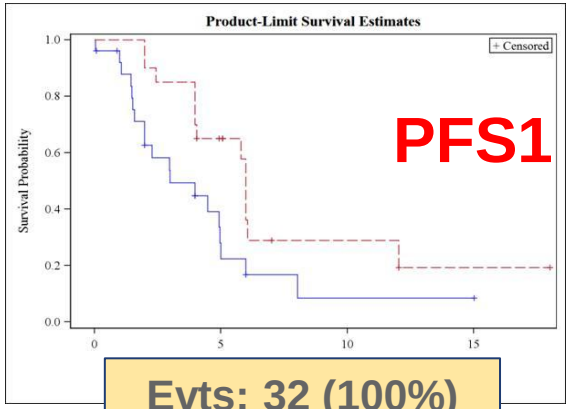
usubjid	Paramcd	startdt	adt	Aval	cnsr	evntdesc
1	**OS**	**01JAN2001**	**17JUL2001**	**198**	**0**	**Death**
1	**PFS1**	**01JAN2001**	**09JUN2001**	**160**	**0**	**PD**
1	**PFS2**	**01JAN2001**	**05MAR2001**	**64**	**1**	**New tx**
1	PFS3	01JAN2001	05MAR2001	64	1	New tx*
1	PFS4	01JAN2001	01JUN2001	152	0	PD
2	OS	01JAN2001	17JUL2001	198	0	Death
2	PFS1	01JAN2001	09JUN2001	160	0	PD
2	PFS2	01JAN2001	09JUN2001	160	0	PD
2	**PFS3**	**01JAN2001**	**05MAR2001**	**64**	**1**	**Missed vis**
2	**PFS4**	**01JAN2001**	**01JUN2001**	**152**	**0**	**PD**

0- event 1- censored * could be missed tx too however New tx came first.
You also would want to look at ADaM dataset ADEVENT, but we will not discuss

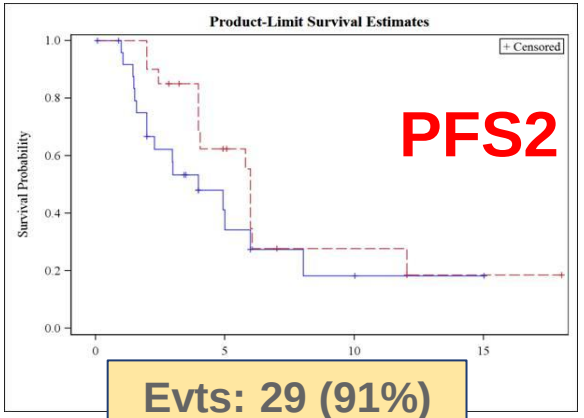
Comparison of All Endpoints



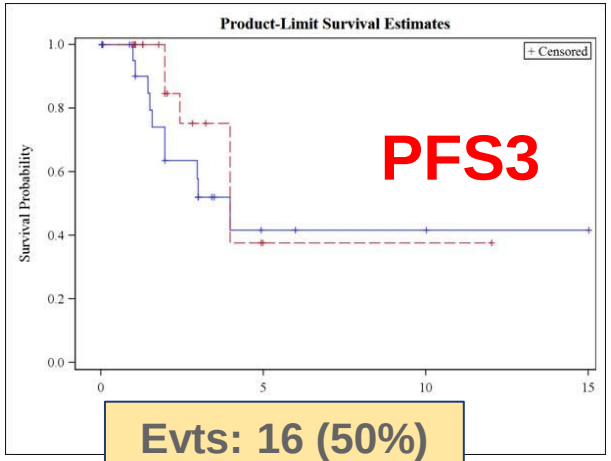
Evts: 16 (100%)
HR=1.18
P-value: 0.7356



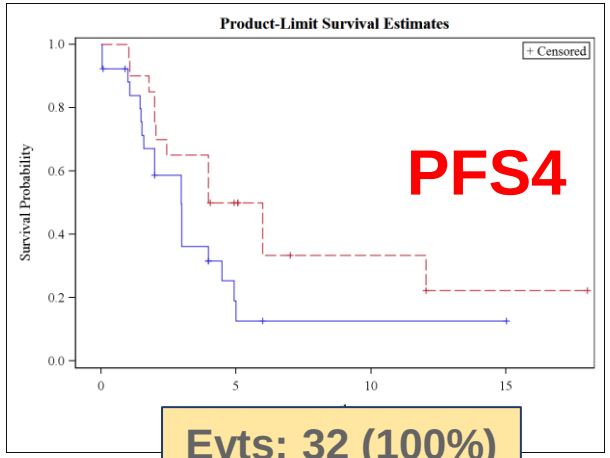
Evts: 32 (100%)
HR=2.15
P-value: 0.02660



Evts: 29 (91%)
HR=1.63
P-value: 0.1790



Evts: 16 (50%)
HR=1.58
P-value: 0.3505



Evts: 32 (100%)
HR=1.88
P-value: 0.0733

SAS Code: Lifetest & PHReg

```
*** survival plots, log-rank pvalue, number of events;
PROC LIFETEST  DATA=WORK.[indat] PLOTS=SURVIVAL;
     TIME months*censor(0); **** 0=censoring value;
      STRATA treatment;
RUN;
*** hazard ratio from proportional hazard model;
PROC PHREG DATA=WORK.[indat];
     CLASS treatment;
     MODEL months*censor(0)=treatment / RISKLIMITS;
RUN;
```

Quality Review Checks

- One record per patient per endpoint in ADTTE
  - Traceability in ADEVENT
- Time cannot be negative
- Time cannot be missing
  - For the population
  - If missing, means some endpoint criteria has not been programmed
- Censoring variable is 0 or 1
  - Make sure you understand which one is an event, and which one is not.
  - Cannot be missing
- Correct bucket for censoring reason or event
- Look at raw data in comparison to TTE dataset
- OS is always ≥ PFS

Conclusions

- A lot to understand
  - What data do you need?
    - What data do you NOT need
  - Break the endpoint up into the necessary parts
  - Ask questions
  - But not too difficult
  - Take your time to understand the endpoint
  - Take your time to review and re-review the Protocol/SAP through study duration
    - Prevent knowledge slide
    - A lot to remember
  - Ask questions

Contact me

- Supplemental document
  - Includes additional time to event information
  - Includes time to event SAS programs
    - Additional SAS code - covariates
  - Simulated dataset
  - References
- Any questions?

- **donna.levy@inventivhealth.com**

Questions

Extra Slides

Objectives

- The objective of this presentation is to help programmers and statisticians alike become familiar and be able to create, understand and analyze time to event data.

- Starting with a straightforward example of overall survival (OS), we will proceed to more involved definitions of progression free survival (PFS).

Time to Event Endpoint Problems

- PFS is not as “clean” an analysis as Overall Survival (OS)
  - Though the “cleanness” of OS can also be debated
- No endpoint is perfect
  - Bias can be introduced
- Thus the reason for multiple sensitivity analyses

Time to Event Key Components con't

Example: Overall survival

Event: death

Start of interval: date of enrollment or randomization

End of interval: date of death (not censored). If death is not reported, time is usually censored at the last reported date alive.

Possible Issues, Solutions & Quality Review Checks

- Incomplete data (ie no lesion assessment, only PD, 1st visit date used).
- Unclear definition of censoring rules and events. As we have seen, there are many ways to define an endpoint.
- As a programmer, if you are not sure you should ask.
- As a statistician, you may define multiple endpoints that measure similar things. Each endpoint may measure something slightly different. Ideally one hopes that each sensitivity analysis will correspond with the primary analysis. However if they do not, you can compare the endpoint definitions and try and determine the reason for the difference.
-

Possible Issues, Solutions and Quality Review Checks con't

- In the final dataset, the start date, end date or censoring variable is missing.
- Negative time not possible.
- Incorrect bucket for censoring reason or event
- Informative censoring. First we should talk about non-informative censoring --- underlying assumption. Censoring should be random and non informative. Include example of informative censoring.
- Not enough follow up time for events. Needs to be considered in design and events should be followed and estimated for full information.
- Missing time.

Key Dataset [ADAM] Components

- Patient Identifier
- Clear start date
- Clear endpoint: How the endpoint is derived.
- Events and censoring clearly defined
- Text for reason of censoring
- Identifier for endpoint: short and long version ie. OS and Overall Survival. When there are multiple sensitivity analyses for an endpoint, but sure that each endpoint is identified clearly.
- Character and numeric version of the censoring variable. So clear in dataset what value indicates an event and what value indicates censoring.

Key Components con't

- Clear censoring rules. As we have seen, there are many ways to define an endpoint. Need to be very specific in definition.

- Final dataset: 1 record per subject per endpoint. No key fields should be missing.

Key Components con't

- It is helpful in the dataset to include the reason for censoring. This is now a ADAM requirement. Can read more here. Reference. (Clinical Data Interchange Standards Consortium, Inc, 2011). http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam_adtte_v1.0.pdf