Efficacy analysis and graphical representation in Oncology trials - A case study

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Agenda

- Oncology endpoints
- A Case Study
  - Analysis
  - Graphical Representation
- Take away points

Oncology endpoints

- Early phase – maximum tolerated dose/ recommended phase 2 dose, biological drug activity
- Late phase – Clinical benefit
- Endpoint choice depends on – indication, line of therapy, available treatment options, etc.

Oncology endpoints

Time to Event (Survival) Endpoints

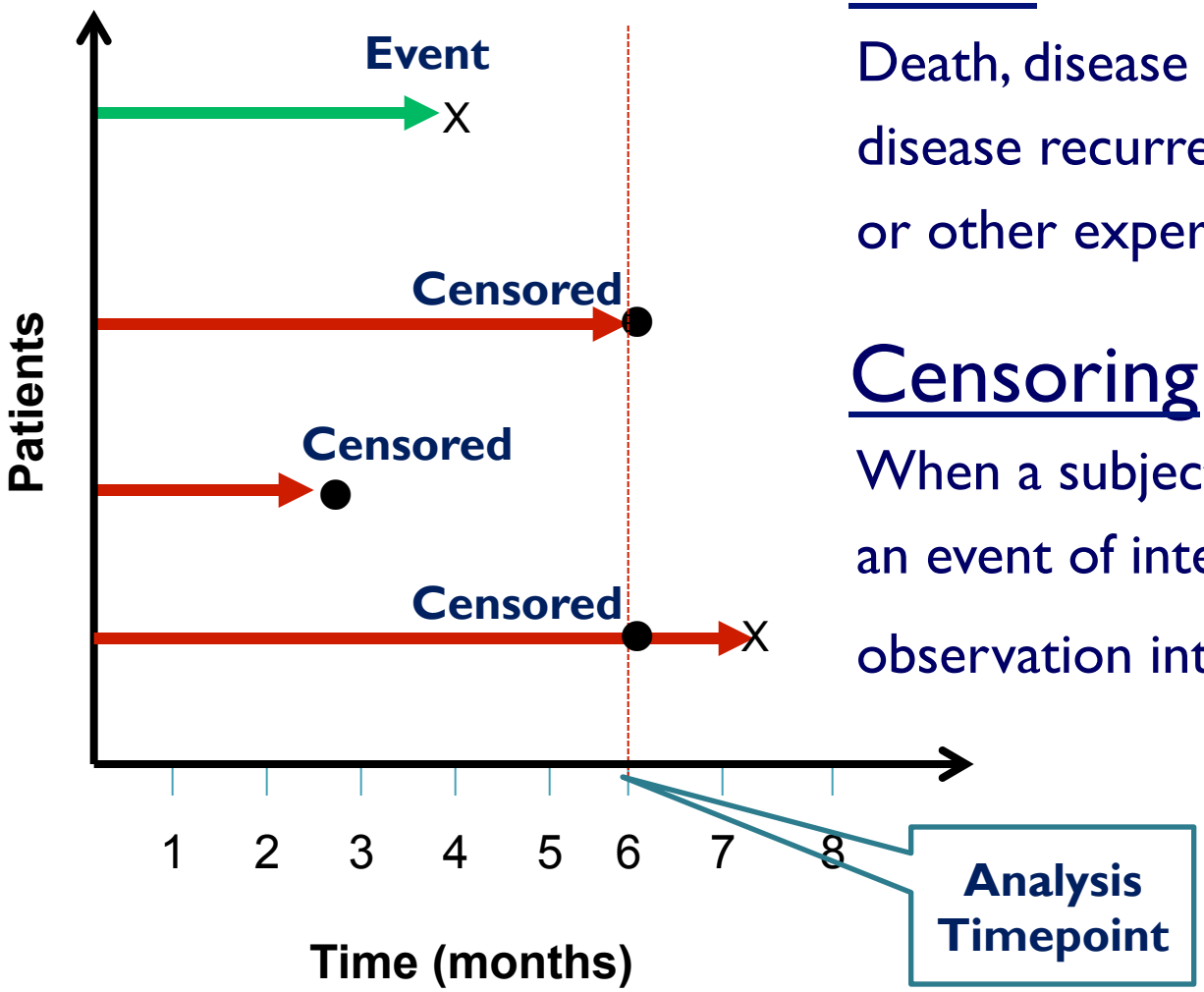
Endpoint	Definition	Advantages	Disadvantages
Overall Survival (OS)	Randomization until death	Precise and easy to measure – most reliable	May involve larger studies
Progression Free Survival (PFS)	Randomization until progression/ death	Smaller sample size	Not precisely measured

Oncology endpoints

Response and Symptom Endpoints

Endpoint	Definition	Advantages	Disadvantages
Objective Response Rate (ORR)	Proportion of responders (Complete or Partial)	Assessed earlier and in smaller studies	Not a direct measure of benefit
Symptom Endpoints	Patient's quality of life (QOL)	Patient perspective of direct clinical benefit	Data are frequently missing or incomplete

Time to Event data: Concepts



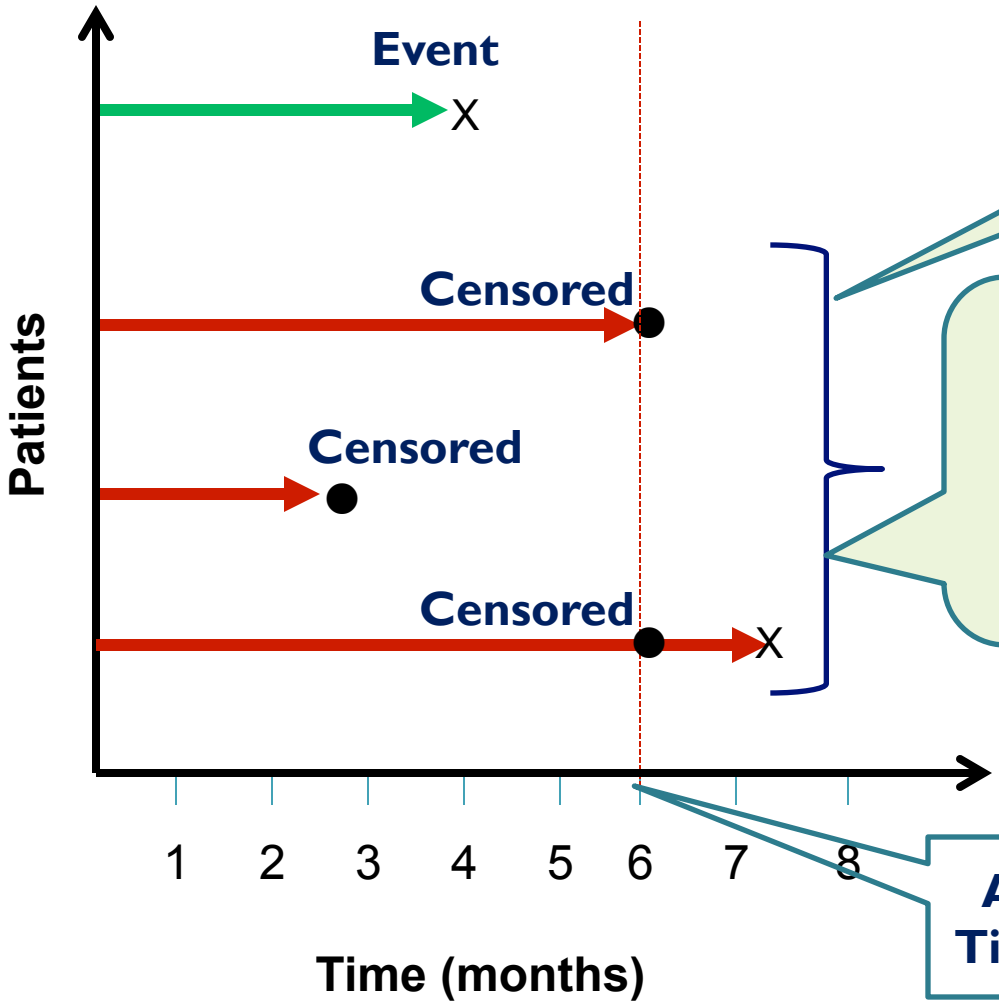
Event

Death, disease occurrence, disease recurrence, recovery, or other experience of interest

Censoring

When a subject does not have an event of interest during the observation interval

Time to Event data: Concepts



Prevent Loss of information

Retain original sample size – as decided in the hypothesis in Protocol

Case Study – Efficacy Analysis

- Protocol
- Analysis Dataset
  - Derivation
- Graphical Analysis
  - Primary and secondary endpoints

Protocol

Title

- A Phase III randomized lung cancer study, two arms

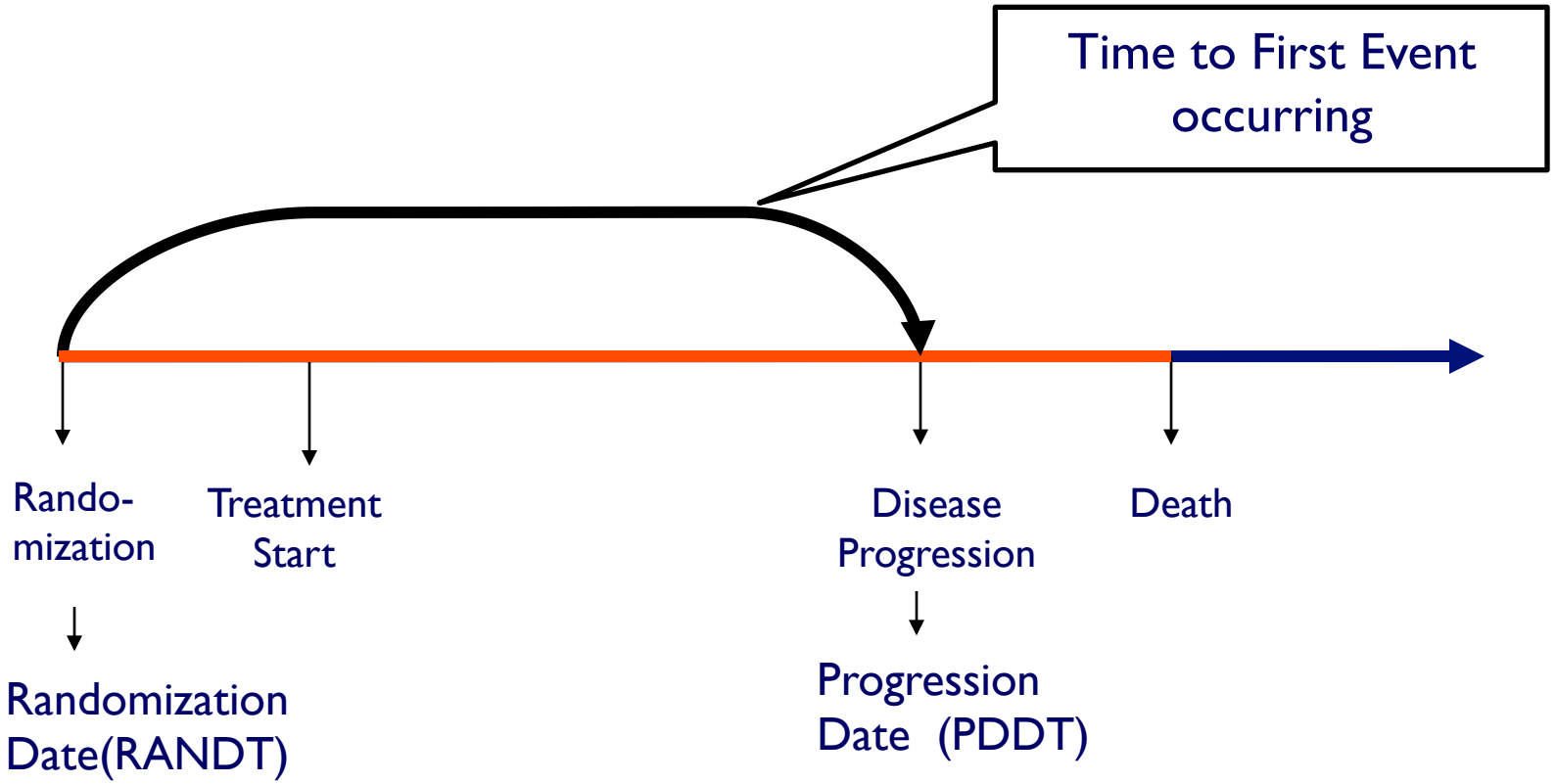
Primary Endpoint

- Progression Free Survival (PFS)

Secondary Endpoint

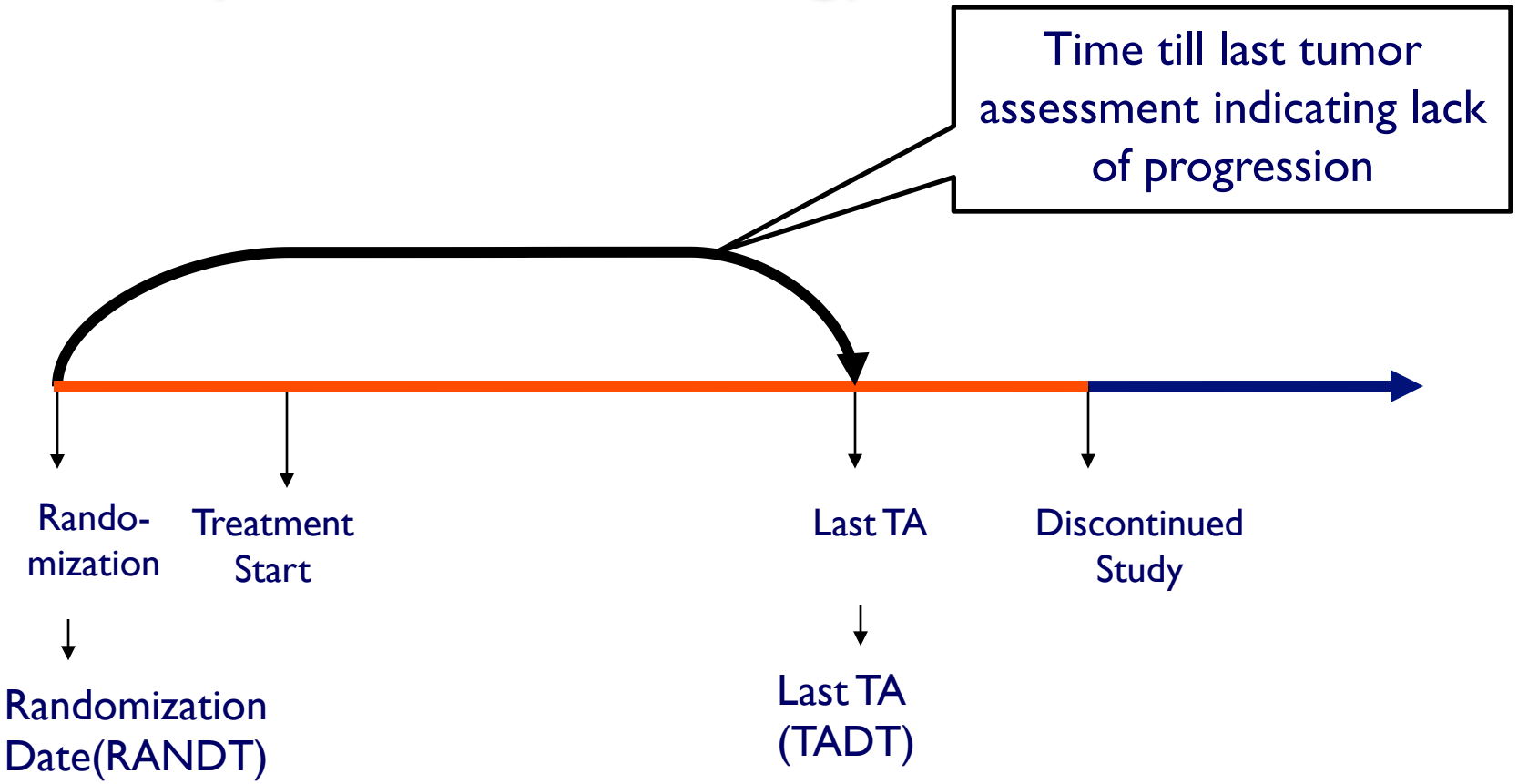
- Objective response rate(ORR)

PFS (with event)



PFS (in days) = (PDDT - RANDT + 1)
Censor = 0

PFS (with censoring)



PFS (in days) = (TADT - RANDT + 1)
Censor = 1

Analysis dataset (ADPFS)

Unique Subject Identifier

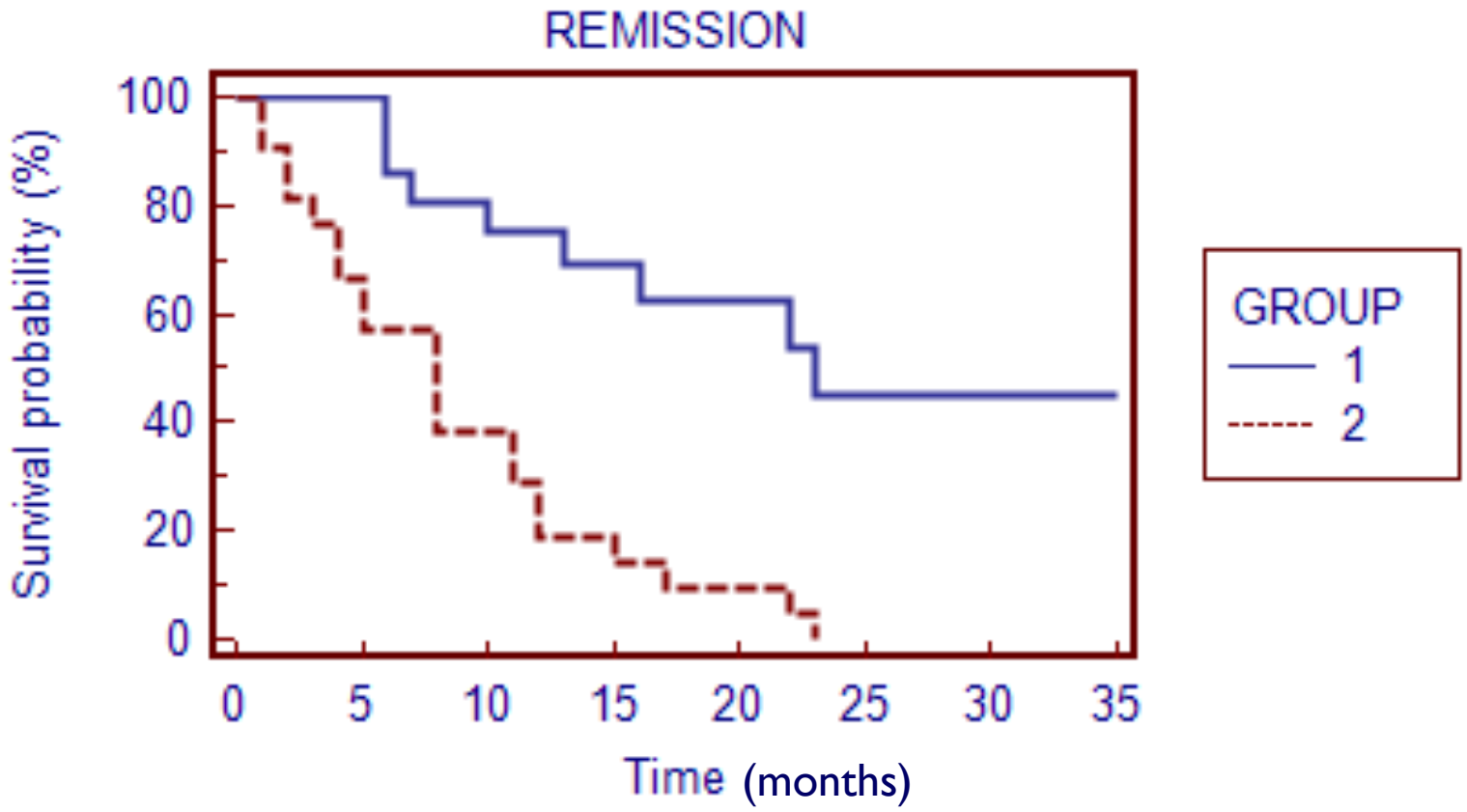
Disposition/ Response/ Tumor Assessment

nsoring Flag

USUBJID	TRT	PFSDATE	PFSTIME	CENSOR
CYTEL_01_01	A	21-Jun-2002	4.7	0
CYTEL_01_02	B	1-Aug-2003	11.2	0
CYTEL_01_03	B	21-Oct-2007	33.9	1
CYTEL_01_04	B	21-Feb-2008	34.5	1
CYTEL_01_05	A	11-Jan-2005	15.5	0
CYTEL_01_06	B	21-Jun-2003	5.5	0
CYTEL_01_07	B	1-Aug-2007	30.0	0
CYTEL_01_08	A	21-Oct-2002	1.0	0
CYTEL_01_09	B	1-Dec-2002	1.4	0
CYTEL_01_10	A	21-Oct-2004	9.1	1
CYTEL_01_11	A	21-Feb-2004	3.1	0
CYTEL_01_12	A	1-Aug-2004	4.4	0
CYTEL_01_13	B	11-May-2008	26.6	1
CYTEL_01_14	B	1-Apr-2008	25.8	1
CYTEL_01_15	A	1-Apr-2004	1.3	0
CYTEL_01_16	B	1-Aug-2004	2.8	0
CYTEL_01_17	A	11-Sep-2004	1.8	0
CYTEL_01_18	A	21-Feb-2006	8.6	0
CYTEL_01_19	B	1-Apr-2005	3.2	1

Graphical Representation

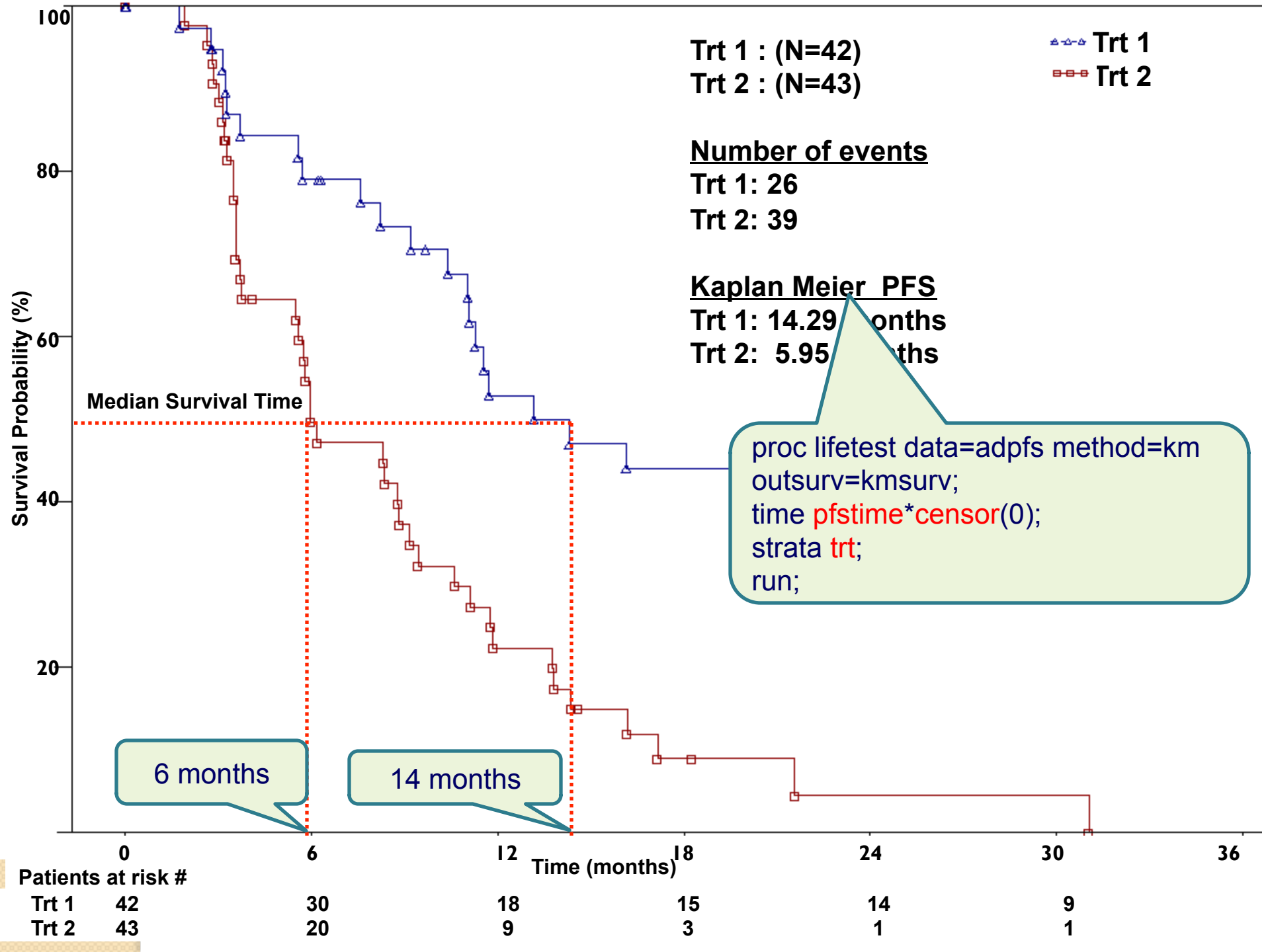
Kaplan-Meier Survival Analysis Method:

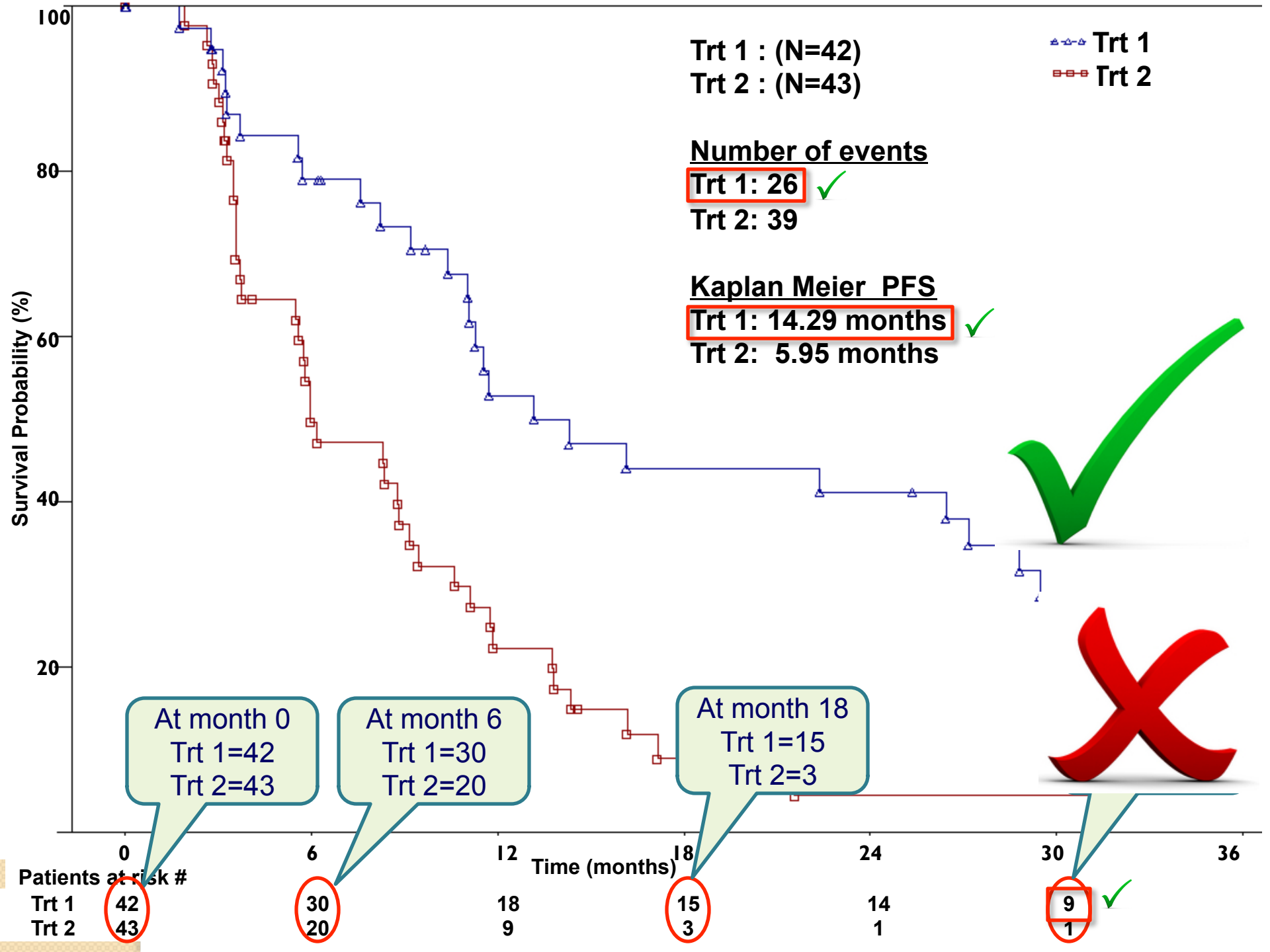


Primary Endpoint

Kaplan-Meier Survival Analysis Method:

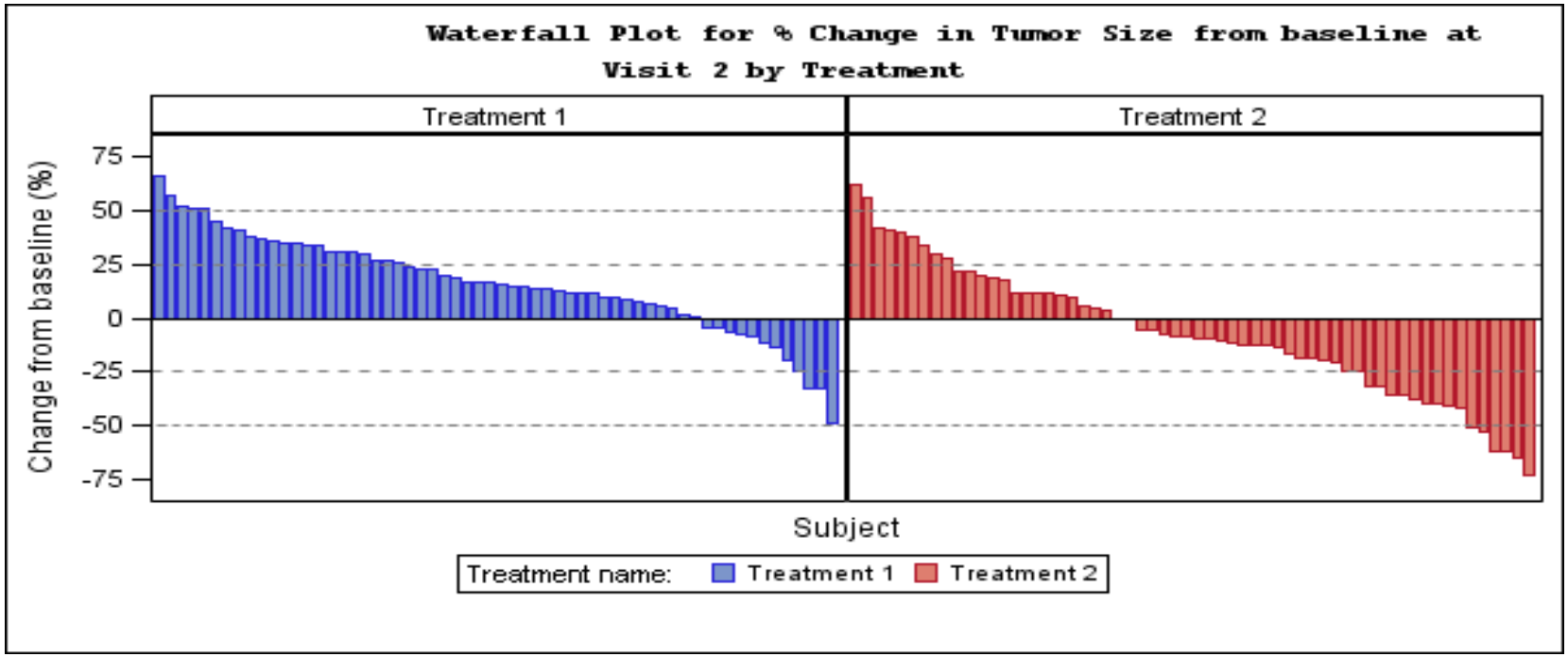
- Estimates the probability of survival to a given time using the proportion of patients who have survived to that time
- Accounts for censoring


Trt 1 : (N=42)
Trt 2 : (N=43)
Trt 1
Trt 2
Number of events
Trt 1: 26
Trt 2: 39
Kaplan Meier PFS
Trt 1: 14.29 onths
Trt 2: 5.95 ths
Median Survival Time
proc lifetest data=adpfs method=km
outsurv=kmsurv;
time pfstime*censor(0);
strata trt;
run;
6 months
14 months
Survival Probability (%)
100
80
60
40
20
0
6
12
18
24
30
36
Time (months)
Patients at risk #
Trt 1 42 30 18 15 14 9
Trt 2 43 20 9 3 1 1


Trt 1 : (N=42)
Trt 2 : (N=43)
Trt 1
Trt 2
Number of events
Trt 1: 26
Trt 2: 39
Kaplan Meier PFS
Trt 1: 14.29 months
Trt 2: 5.95 months
Survival Probability (%)
100
80
60
40
20
At month 0
Trt 1=42
Trt 2=43
At month 6
Trt 1=30
Trt 2=20
At month 18
Trt 1=15
Trt 2=3
0
6
12
18
24
30
36
Time (months)
Patients at risk #
Trt 1 42 30 18 15 14 9
Trt 2 43 20 9 3 1 1

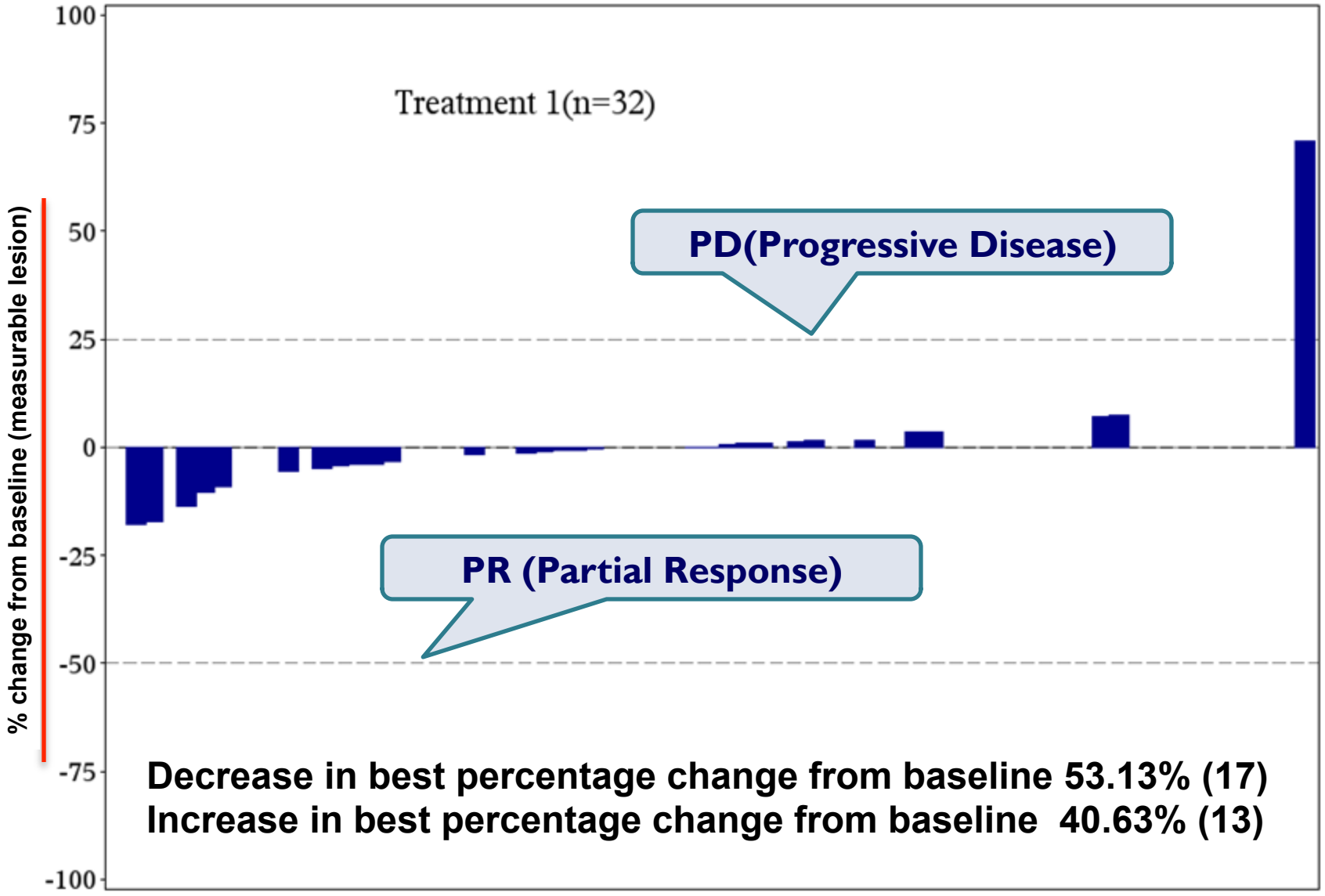
Secondary endpoints:

- Objective Response Rate can be analyzed using a Waterfall plot



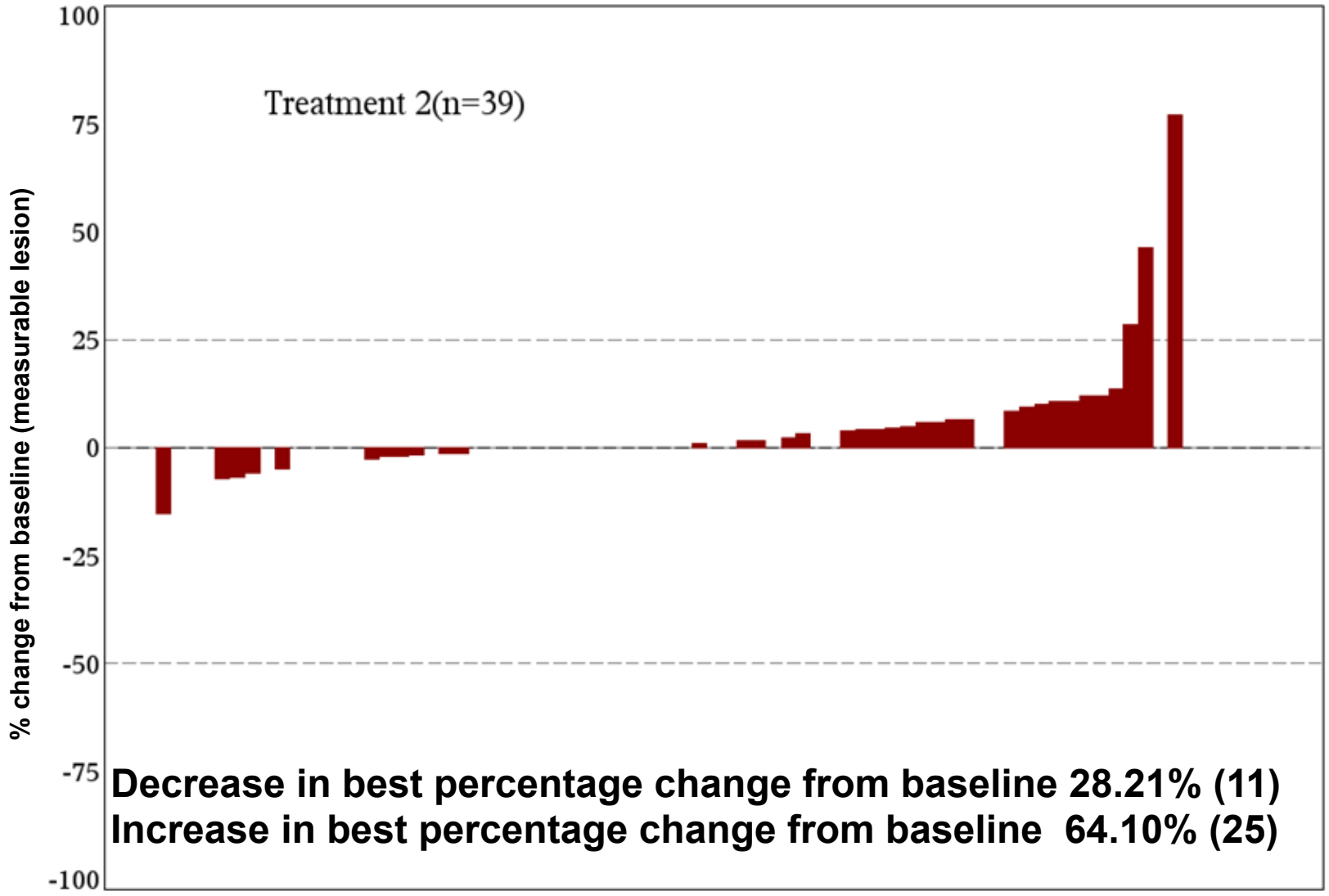
- Depicts increase or decrease in rate for a parameter of interest.

Waterfall Plot

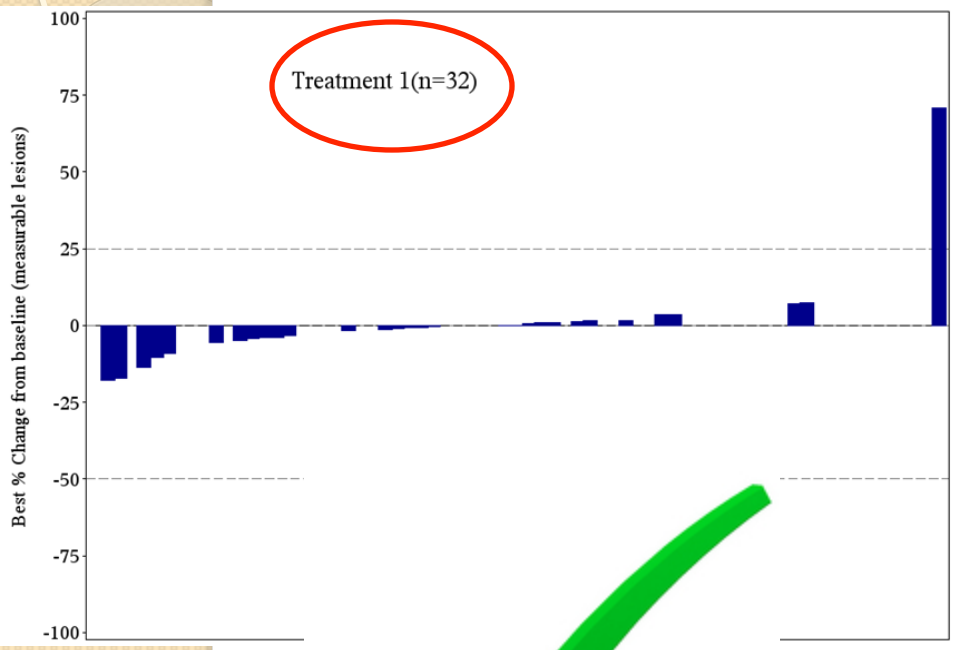


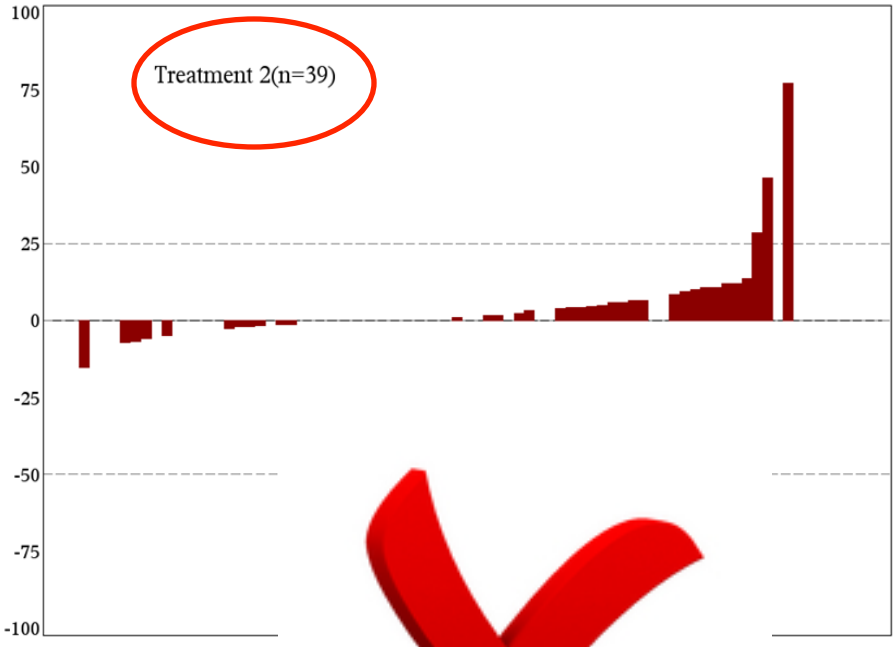
Decrease in best percentage change from baseline 53.13% (17)
Increase in best percentage change from baseline 40.63% (13)

Waterfall Plot



Waterfall Plot





Decrease in best percentage change from baseline	53.13%(17)	28.21%(11)
Increase in best percentage change from baseline	40.63%(13)	64.10%(25)

Take away points

- Understand data and SAP

Tumor response data listing

Patient	Cycle	Eval Date	Type	Les Numb	Resp	Best Resp	Prog/ Cens Date	Prog 1=Yes 0=No
CYT-202-901	0	05/22/2012	TARGET	1	PR	PR	07/30/2012	0
CYT-202-901	0	05/22/2012	TARGET	2	PR	PR	07/30/2012	0
CYT-202-901	0	05/22/2012	NON-TARGET	1	PR	PR	07/30/2012	0
CYT-202-901	2	07/30/2012	TARGET	1	PR	PR	07/30/2012	0
CYT-202-901	2	07/30/2012	TARGET	2	PR	PR	07/30/2012	0
CYT-202-901	2	07/30/2012	NON-TARGET	1	PR	PR	07/30/2012	0
CYT-205-901	0	09/14/2012	TARGET	1			09/14/2012	0
CYT-205-901	0	09/14/2012	TARGET	2			09/14/2012	0
CYT-205-901	0	09/14/2012	TARGET	3			09/14/2012	0
CYT-205-901	0	09/14/2012	NON-TARGET	1			09/14/2012	0
CYT-205-901	0	09/14/2012	NON-TARGET	2			09/14/2012	0
CYT-205-901	0	09/14/2012	NON-TARGET	3			09/14/2012	0

Take away points

- Annotate Tables, Listings and Figures

Table 14.2-1.10 Analysis of progression free survival (Full Analysis Set) **FAS = 1**

Source = ADPFS

CENSOR = 0	**Event / N (%)**	**Median time (95%CI) (a) (months)** **PFSTIME**
All Patients (FAS)		
Treatment 1 **TRT**	xxx/xxxx (xx.x)	xx.x (x.xx,x.xx)
Treatment 2 **TRT**	xxx/xxxx (xx.x)	xx.x (x.xx,x.xx)
Functionally active tumor **FUNC = 1**		
Treatment 1	xxx/xxxx (xx.x)	xx.x (x.xx,x.xx)
Treatment 2	xxx/xxxx (xx.x)	xx.x (x.xx,x.xx)
Functionally non-active tumor **FUNC = 0**		
Treatment 1	xxx/xxxx (xx.x)	xx.x (x.xx,x.xx)
Treatment 2	xxx/xxxx (xx.x)	xx.x (x.xx,x.xx)

Take away points

- Censoring algorithm
  - Latest tumor evaluation
  - Last contact date
  - Randomization date
- Data checks – raise flag
  - Missing data (e. g. missing PFS)
  - Cross check across Tables, Listings and graphs
  - Heavy censoring

References

- *Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*
- *FDA's Richard Pazdur: Drug Approval Entails Evaluation of Clinical Benefit, Not Just Endpoints*
- *Oncology Clinical Trials Successful Design, Conduct and Analysis – W.M. Kevin Kelly, Susan Halabi*
- *Thomas R. Fleming, Mark D. Rothmann, and Hong Laura Lu - Journal Of Clinical Oncology - Issues in Using Progression-Free Survival When Evaluating Oncology Products - J Clin Oncol 27:2874-2880, 2009*

Thank You!

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