P1808 Survival Analysis

Logistics

- Instructor:
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- TAs
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  - Ruiyang Li: rl3034@cumc.columbia.edu
- Office hours
  - Instructor:
    - Wednesday 6:00-8:00 pm EST
  - TAs
- Text books:
  - Klein, J.P. and Moeschberger, M.L. "Survial Analysis – Techniques for Censored and Truncated Data", Springer 2003, ISBN #0-387-95399-x.
  - Collett, D. *Modeling Survival Data in Medical Research* , London: Chapman & Hall 1994.
  - Cox DR and Oakes D. *Analysis of Survival Data*. London: Chapman & Hall, 1984.
  - Kalbfleisch JD and Prentice RL. *The Statistical Analysis of Failure Time Data.* New York: Wiley, 2003
  - Lawless, JF. *Statistical Models and Methods for Lifetime Data.* New York: Wiley, 1980.
- Softwares:
  - SAS
    - proc lifetest,
    - proc phreg
  - R
    - Package: survival and biostat3

Syllabus

1. Introduction
   - Survival data
   - Censoring mechanism
   - Application in medical field
2. Concepts and definitions
   - Survival function
   - Hazard function
3. Non-parametric approach
   - Life table
   - Kaplan-Meier survival estimate
   - Hazard function
   - Median and percentile survival time
4. Hypothesis testing - nonparametric
   - Overview – hypothesis, test statistics, p-values
   - Log-rank
   - Wilcoxin
   - Gehan test, etc
5. Study design and sample size estimation
   - Overview
   - Survival sample size estimation
   - Accrual time and Study duration
6. Semiparametric model – proportional hazard model
   - Partial likelihood
   - Inference
   - Time varying covariates
   - Stratification
7. Model checking in the PH model
   - Model checking
   - Residuals
8. Parametric model
   - Parametric proportional hazard model
   - Accelerate failure model
9. Other topics
   - Competing risk
   - Recurrent events
   - Non-proportional hazard ratio
   - Interval censoring

Course Evaluation

- Homework: 20%
  - Due in next lecture
  - Not accept late homework
    - Unless there are legitimate reasons
  - Writing in report format
    - 3 Cs: clean, concise, clear
- Attendance: 5%
- Mid-term exam: 20%
  - October 31st
- Final exam: 20%
  - December 19th
- Project: 35%
  - Proposal, 10%, October 3rd
  - In class presentation, 10%, November 21st
  - Final report, 15%, December 19th

- Project
  - Possible Topics in survival analysis
    - Choose a design project
    - Analysis project
    - Literature review
  - Projects cover
    - Propose
    - Rationale
    - Background
    - Assumptions (design)
    - Sample size calculation for survival endpoints (design)
    - Analysis methods (analysis)
    - Analysis results (analysis)
    - Interpretation (analysis)
    - Conclusion/discussion
  - Presentation
    - PowerPoint
    - 10 minutes per group
  - ~ 5 students per group
    - Select a team lead
    - Divide and conquer
    - Final report – 10-15 pages

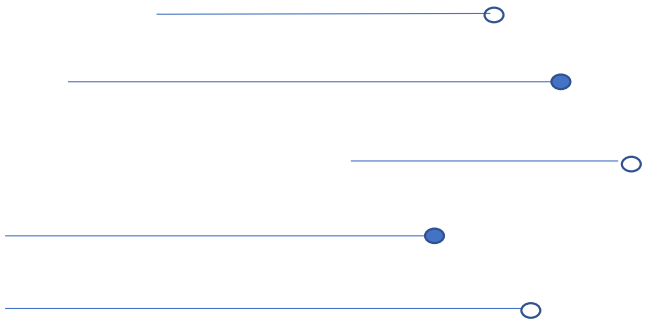
Introduction Topics

- Survival data
- Censoring mechanism
- Application in medical field

Survival Data

- Survival data, also known as
  - Lifetime data
  - Failure time data

- Examples
  - Time from randomization to death
  - Time from beginning treatment to disease progression
  - Mileage from the initial use to first out-of-order

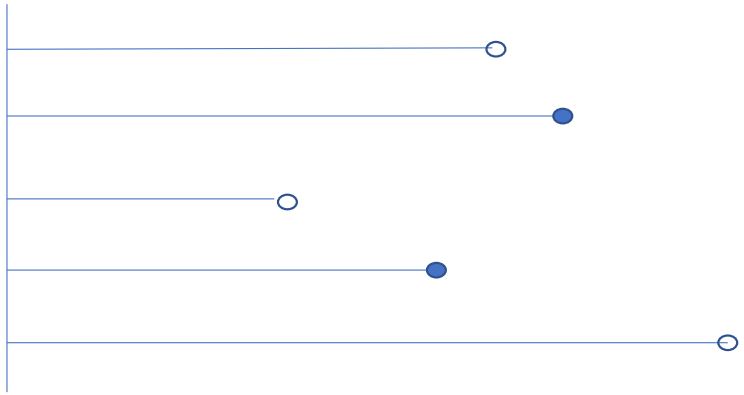


Survival Data Can Be

- Combination of
  - Complete data
    - Time
      - Continuous random variable
      - Discrete time variable – survival data can only take values over a discrete grid
    - Event
      - Categorical variable
      - Event has been observed
  - Incomplete data - censoring
    - Partially observed data
    - No event has been observed by T

Survival Data Can Be

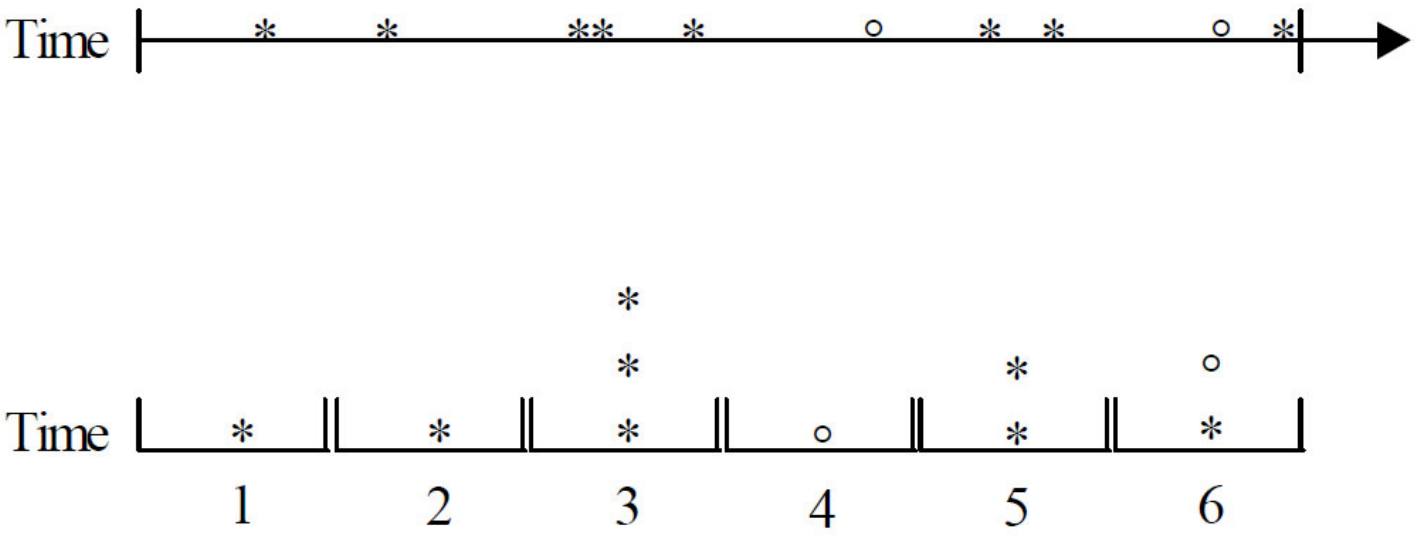
- More about time (T_L, T_R)
  - T_L - Starting point
  - T_R - Ending point
  - Relative time T
    - $T_L = 0,\ T_R = T$
  - Time scale
    - year, month, hours, etc
    - milage
- More on the incomplete data
  - Events can occur before T_L or after T_R
- More about event
  - Need clear definition
  - In clinical trials
    - May also need event adjudication committees to confirm the events



Distributions of Survival Data

- Survival time
  - Discrete
  - Continuous
    - Exponential
    - Piecewise exponential
    - Weibull
    - Gamma
    - Log-logistic
    - Lognormal

Continuous vs Discrete Survival Data



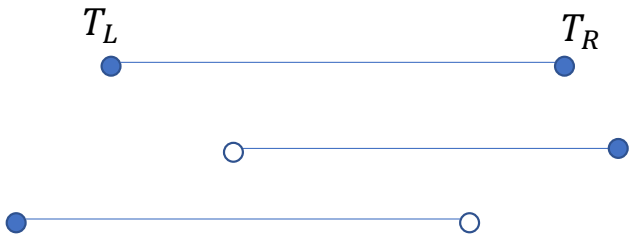
Discrete Survival Time

- Survival are truly discrete
  - The event can only happen at discrete value of time
- Survival time can only be observed by intervals
  - Event may happen in continuous time
  - It can be considered as “Interval censoring”

- Example: An experiment to test the life-time of a device:
  - The device status can only be tested when switches are flipped
  - The switch can only be flipped every “Monday”
- Example: The event of disease progression in oncology studies
  - Subjects can only be evaluated every three months due to feasibility concerns
  - The assessment might be invasive
  - Inconvenient to patients

Censoring

- Survival time $\{T_L, T_R\}$ contains missing parts
  - Either T_L or T_R is not observed
  - Relative time $T \geq 0$ can be unknown
    - $T_L = 0$, $T_R = T$



- Right censoring
  - Type I
  - Type II
  - Random censoring
  - Independent censoring vs Informative censoring
- Left censoring
- Interval censoring

Right Censoring

- Type I censoring
  - Fixed censoring at time c
  - X_i - event time
  - T_i - observed time
  - c – fixed censoring time
  - Δ_i - I($X_i \leq c$) – event indicator
  - $i = 1,2, \ldots, n$ – subjects

$$T_i = \min(X_i, c) = \begin{cases} X_i \; if \; X_i \leq c \\ c \;\; if \; X_i > c \end{cases}$$

- Survival data
  - (T_i, Δ_i)

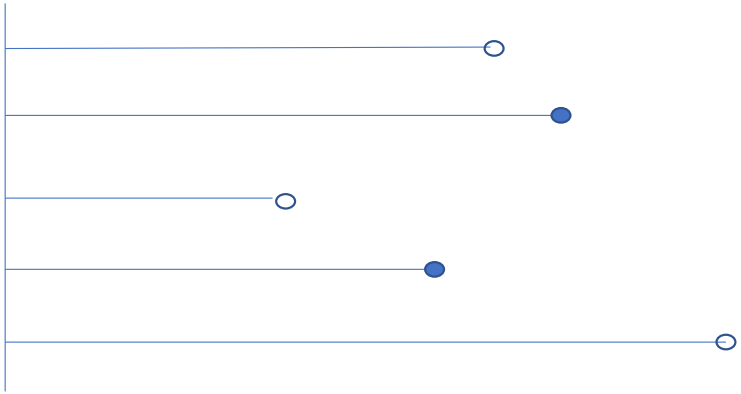
- Examples
  - Product life-span
    - Test device operating time
    - Study terminated after a period
  - Pre-clinical studies
    - Carcinogenicity study
    - Animals are scarified after 24 months
  - Clinical trials
    - Each subject is followed up the same length of time
    - Controlled Adverse Environment
      - Time to develop allergic reaction
      - No more than 2-hour stay

Right Censoring

- Type II censoring
  - Stop observation after r/n events are observed
  - X_i - event time
    - $X_{(i)}$ are ordered statistics of X_i
    - $X_{(1)}, X_{(2)}, \dots, X_{(r)}$
  - T_i - observed time
  - $i = 1,2, \dots, n$

$$T_{(i)} = \begin{cases} X_{(i)} \; if \;\; i \leq r \\ C_i \; if \; X_i > c \end{cases}$$

- Examples
  - Oncology clinical trial
    - Trial will be stopped after a pre-determined number of events are observed – administrative censoring
  - Engineering
    - Study terminated 50% product failed



Right Censoring

- Random censoring
  - Censor may follow certain distribution
  - $C \sim G(c, \eta)$
- The data $\{T_i, \Delta_i\}$
  - $T_i = \min(X_i, C_i)$
  - $\Delta_i = \mathrm{I}(X_i < C_i)$

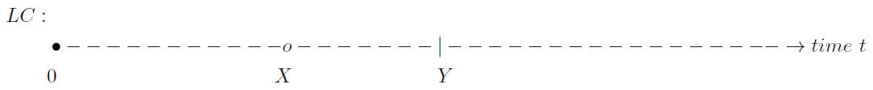
- Examples
  - Subjects enter the study randomly over a period $(0, t_a)$
  - The study is terminated after 5-year follow-up for the last enrolled subject
  - Loss to follow-up
  - Drop out due to adverse events
  - Dropout due to lack of efficacy
  - Dropout due to inconvenient treatment schedule and assessment burden

Right Censoring

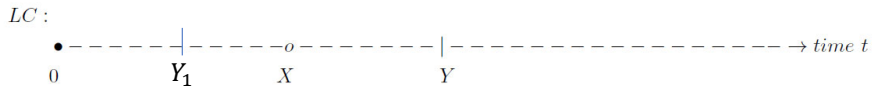
- Independent censoring
  - X $\sim F(x, \theta), C \sim G(c, \eta)$
  - X $\perp C$
- Noninformative censoring
  - Censoring mechanism does not contain any information about the outcomes of the study
  - X $\perp C$
  - (θ, η) does not contain each other's information
- Dependent censoring
  - Accrual distribution
    - $A \sim Unif(0,1) \ if \ T \leq t_c$
    - $A \sim Unif(0, 1/2) \ if \ T > t_c$
    - Subjects who live longer tend to be enrolled early
- Informative censoring
  - Competing risk
  - Dropout due to

Other Censoring Type

- Left censoring
  - Events occurred before the assessment time
  - Sometimes called left truncation

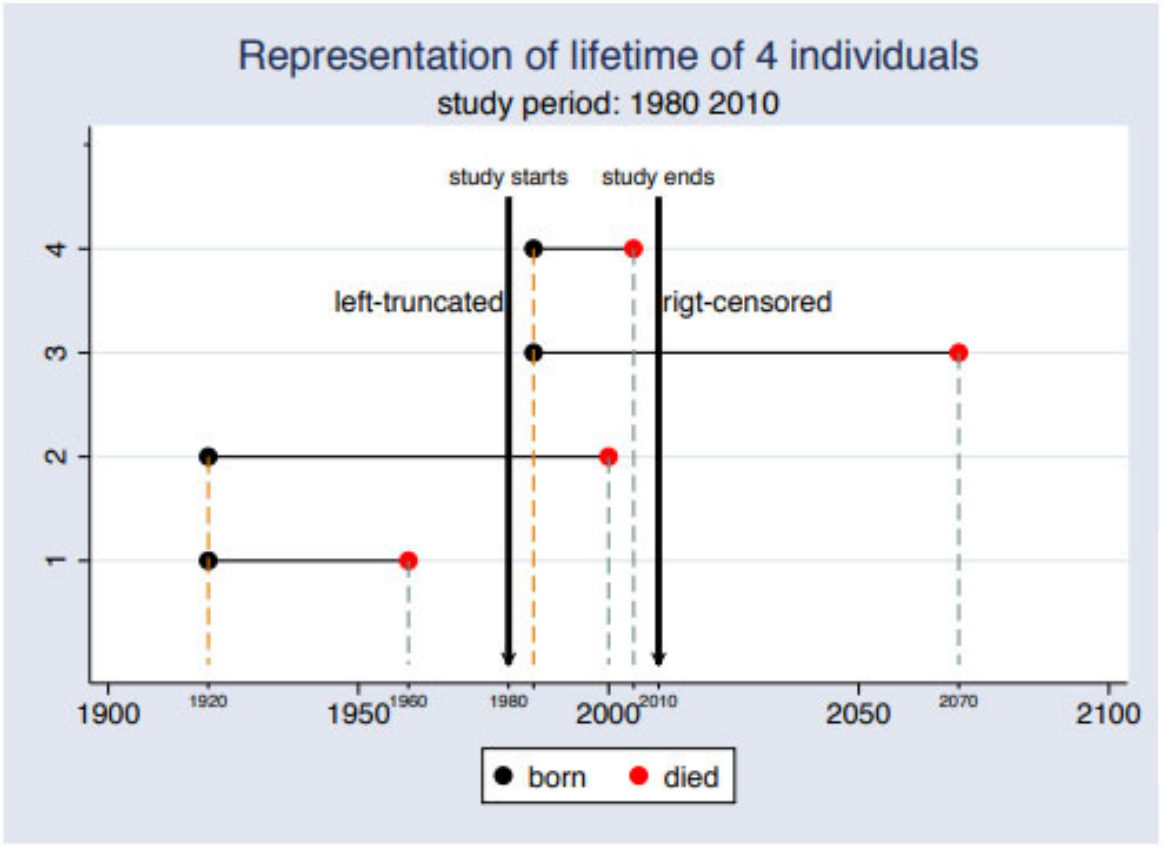


- Interval censoring
  - Events occurred before the current assessment time (left censoring) and after the previous assessment, or not observed yet (right censoring)



- Examples
  - Tumor recurrence is assessed by every 3 months

Also Known as Truncated Data



	id	born	study_starts	enter	last_time_observed	died
1.	4	1985	1980	1985	2005	1
2.	3	1985	1980	1985	2010	0
3.	2	1920	1980	1980	2000	1

Curtsey of Canette (sats Corp)

Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Tel: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
Tel: 800-835-4709 or 240-402-7800; Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2015

Clinical Trial Basics

- Studies to evaluate therapeutic efficacy and safety
  - Randomized
  - Controlled
  - Blinded

  To minimize bias
- Select a well-defined patient population
- Defined endpoints
  - Efficacy
  - Safety
- Powered with adequate sample size
- Treatment
  - Dose levels
  - Treatment schedules
  - Treatment duration and follow-up time
- Data collection
  - Endpoint assessments
  - Establish database
  - Standardized datasets
- Statistical analyses to evaluate the treatment effect in
  - Efficacy
  - Safety

FDA Recommendation – Survival Endpoints for NSCLC

- Overall survival

  We consider OS to be the standard clinical benefit endpoint that should be used to establish efficacy of a treatment in patients with locally advanced or metastatic NSCLC. However, other endpoints can be considered for regulatory decision-making based on the population and riskbenefit profile of a drug. We also recognize that it may not always be feasible to conduct separate trials in patients with locally advanced and metastatic NSCLC.

- Progression-free-survival – composite endpoint

  PFS may be appropriate as the primary endpoint to establish efficacy for drug approval if the trial is designed to demonstrate a large magnitude for the treatment effect as measured by both the hazard ratio and absolute difference in median PFS and an acceptable risk-benefit profile of the drug is demonstrated. Sponsors should justify use of PFS as the primary efficacy endpoint and the magnitude of PFS effect considered likely to predict OS or to represent clinical benefit versus the risk of the drug in the context of the lung cancer stage and results of treatment with alternative therapy. Because of the subjectivity in the measurement of PFS assessments and the fact that the assessments depend on frequency, accuracy, reproducibility, and completeness, the observed magnitude of effect should be substantial and statistically robust….

Considerations for PFS Analysis

APPENDIX B: ISSUES TO CONSIDER IN PFS ANALYSIS

The protocol and statistical analysis plan (SAP) should detail the primary analysis of PFS. This analysis should include a detailed description of the endpoint, appropriate modalities for evaluating tumors, and procedures for minimizing bias. One or two secondary analyses should be specified to evaluate anticipated problems in trial conduct and to assess whether results are robust. The following important factors should be considered.

APPENDIX C: EXAMPLE TABLES FOR PRIMARY PFS ANALYSIS

Examples of prespecified censoring scheme that can be used are provided in the following tables.

Table C1. Example 1 for censoring scheme for PFS

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for toxicity or other reason	Date of last progression with no documented progression	*Censored*
New anticancer treatment started	Date of last progression assessment with documented nonprogression before start of new treatment	*Censored*
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last progression assessment with documented nonprogression	*Censored*

Table C2. Example 2 for censoring scheme for PFS

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for toxicity or other reason	Date of documented progression with protocol specified continued follow-up in all treatment arms	*Progressed*
New anticancer treatment started	Date of documented progression with protocol specified continued follow-up in all treatment arms	*Progressed*
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of documented progression	*Progressed*

Case Studies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

Robert S. Bresalier, M.D., Robert S. Sandler, M.D., Hui Quan, Ph.D., James A. Bolognese, M.Stat., Bettina Oxenius, M.D., Kevin Horgan, M.D., Christopher Lines, Ph.D., Robert Riddell, M.D., Dion Morton, M.D., Angel Lanas, M.D., Marvin A. Konstam, M.D., and John A. Baron, M.D., for the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators*

BACKGROUND

Selective inhibition of cyclooxygenase-2 (COX-2) may be associated with an increased risk of thrombotic events, but only limited long-term data have been available for analysis. We report on the cardiovascular outcomes associated with the use of the selective COX-2 inhibitor rofecoxib in a long-term, multicenter, randomized, placebo-controlled, double-blind trial designed to determine the effect of three years of treatment with rofecoxib on the risk of recurrent neoplastic polyps of the large bowel in patients with a history of colorectal adenomas.

METHODS

A total of 2586 patients with a history of colorectal adenomas underwent randomization: 1287 were assigned to receive 25 mg of rofecoxib daily, and 1299 to receive placebo. All investigator-reported serious adverse events that represented potential thrombotic cardiovascular events were adjudicated in a blinded fashion by an external committee.

RESULTS

A total of 46 patients in the rofecoxib group had a confirmed thrombotic event during 3059 patient-years of follow-up (1.50 events per 100 patient-years), as compared with 26 patients in the placebo group during 3327 patient-years of follow-up (0.78 event per 100 patient-years); the corresponding relative risk was 1.92 (95 percent confidence interval, 1.19 to 3.11; P=0.008). The increased relative risk became apparent after 18 months of treatment; during the first 18 months, the event rates were similar in the two groups. The results primarily reflect a greater number of myocardial infarctions and ischemic cerebrovascular events in the rofecoxib group. There was earlier separation (at approximately five months) between groups in the incidence of nonadjudicated investigator-reported congestive heart failure, pulmonary edema, or cardiac failure (hazard ratio for the comparison of the rofecoxib group with the placebo group, 4.61; 95 percent confidence interval, 1.50 to 18.83). Overall and cardiovascular mortality was similar in the two groups.

CONCLUSIONS

Among patients with a history of colorectal adenomas, the use of rofecoxib was associated with an increased cardiovascular risk.

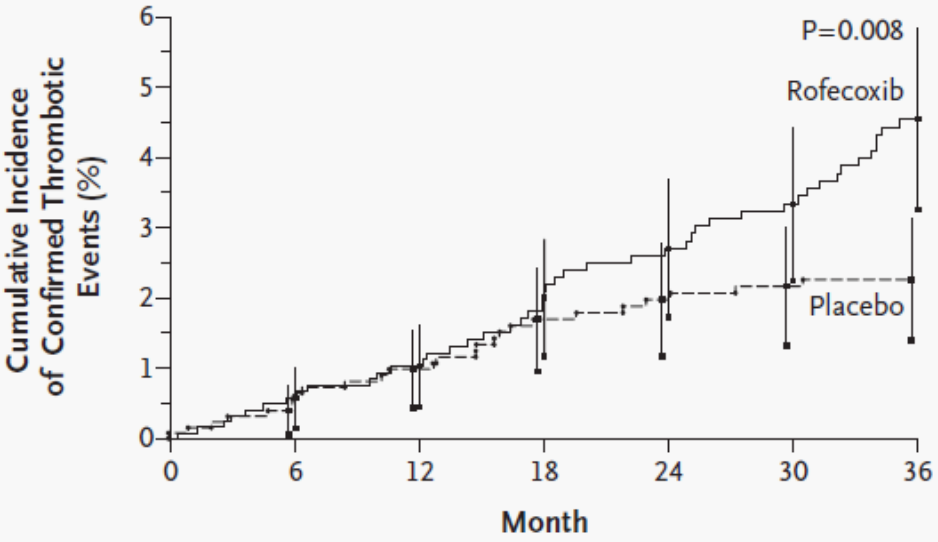
Table 1. Baseline Characteristics of the Patients.

Characteristic	Rofecoxib (N=1287)	Placebo (N=1299)
Age (yr)		
Mean	59	59
Range	40–96	40–86
Height (cm)		
Mean	170	170
Range	137–198	133–199
Weight (kg)		
Mean	81	81
Range	38–160	34–159
Male sex (%)	62	62
White race (%)*	84	84
Use of low-dose aspirin (%)†	17	16
Use of antihypertensive medication (%)	30	29
High cardiovascular risk (%)‡	30	26
History of symptomatic atherosclerotic cardiovascular disease (%)	9	8
History of hypertension (%)	36	34
History of hypercholesterolemia (%)	29	26
History of diabetes (%)	9	9
Current cigarette use (%)	22	22

Table 2. Incidence of Adjudicated Thrombotic Adverse Events.*

Adverse Event	Rofecoxib Group (N=1287)		Placebo Group (N=1299)		Hazard Ratio (95% CI)
	No. of Patients (%)	Rate/100 Patient-yr	No. of Patients (%)	Rate/100 Patient-yr	
Total	46 (3.6)	1.50	26 (2.0)	0.78	1.92 (1.19–3.11)
Cardiac events	31 (2.4)	1.01	12 (0.9)	0.36	2.80 (1.44–5.45)
Myocardial infarction	21		9		
Fatal myocardial infarction	2		3		
Sudden death from cardiac causes	3		1		
Unstable angina pectoris	7		4		
Cerebrovascular events	15 (1.2)	0.49	7 (0.5)	0.21	2.32 (0.89–6.74)
Fatal ischemic stroke	1		0		
Ischemic stroke	11		6		
Transient ischemic attack	5		2		
Peripheral vascular events	3 (0.2)	0.10	7 (0.5)	0.21	0.46 (0.08–2.03)
Peripheral arterial thrombosis	1		1		
Peripheral venous thrombosis	2		4		
Pulmonary embolism	0		2		

* The total duration of follow-up was 3059 patient-years in the rofecoxib group and 3327 patient-years in the placebo group. Although a patient may have had two or more clinical adverse events, the patient was counted once within a category. The same patient may appear in different categories. CI denotes confidence interval.



No. at Risk							
Rofecoxib	1287	1129	1057	989	938	896	727
Placebo	1299	1195	1156	1079	1042	1001	835

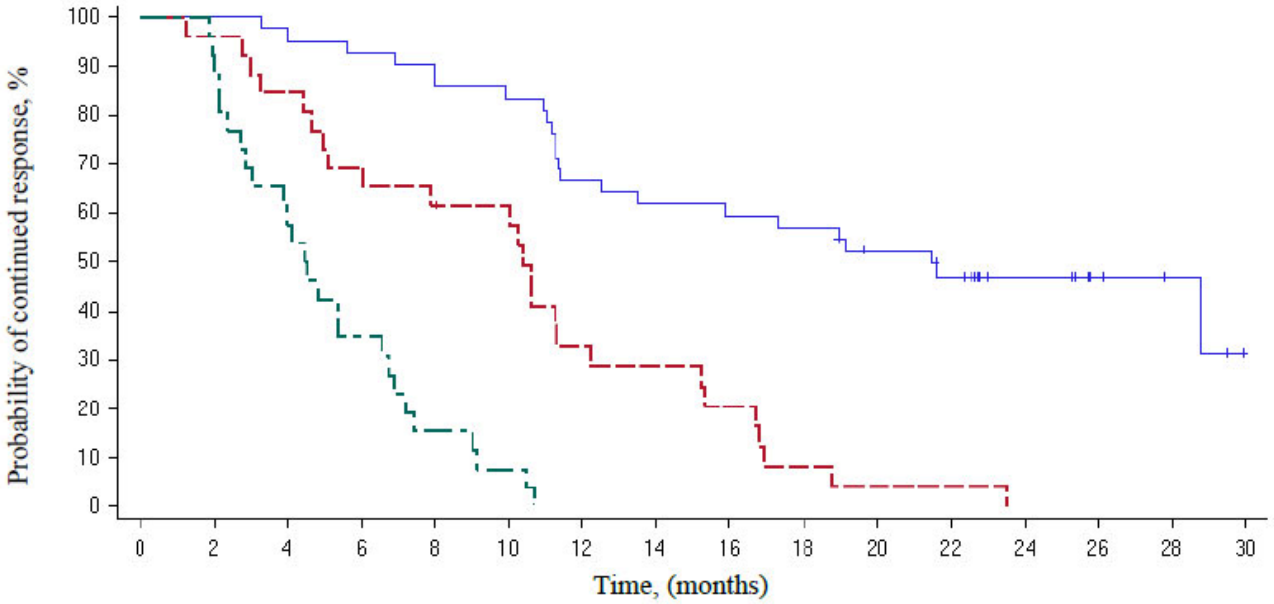
Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Confirmed Serious Thrombotic Events.

Vertical lines indicate 95 percent confidence intervals.

Case 2 – Summary of Product Characteristics

- Abecma – autologous CAR-T therapy for multiple myeloma

Figure 1. **Kaplan-Meier curve of duration of response based on independent response committee review according to IMWG criteria – by best overall response (Abecma-treated population)**



CR or better	42	42	40	39	36	35	28	26	25	24	20	17	10	6	3	0
VGPR	26	25	22	18	16	15	8	7	5	2	1	1	0	0	0	
PR	26	23	15	9	4	2	0	0	0	0	0	0	0	0	0	

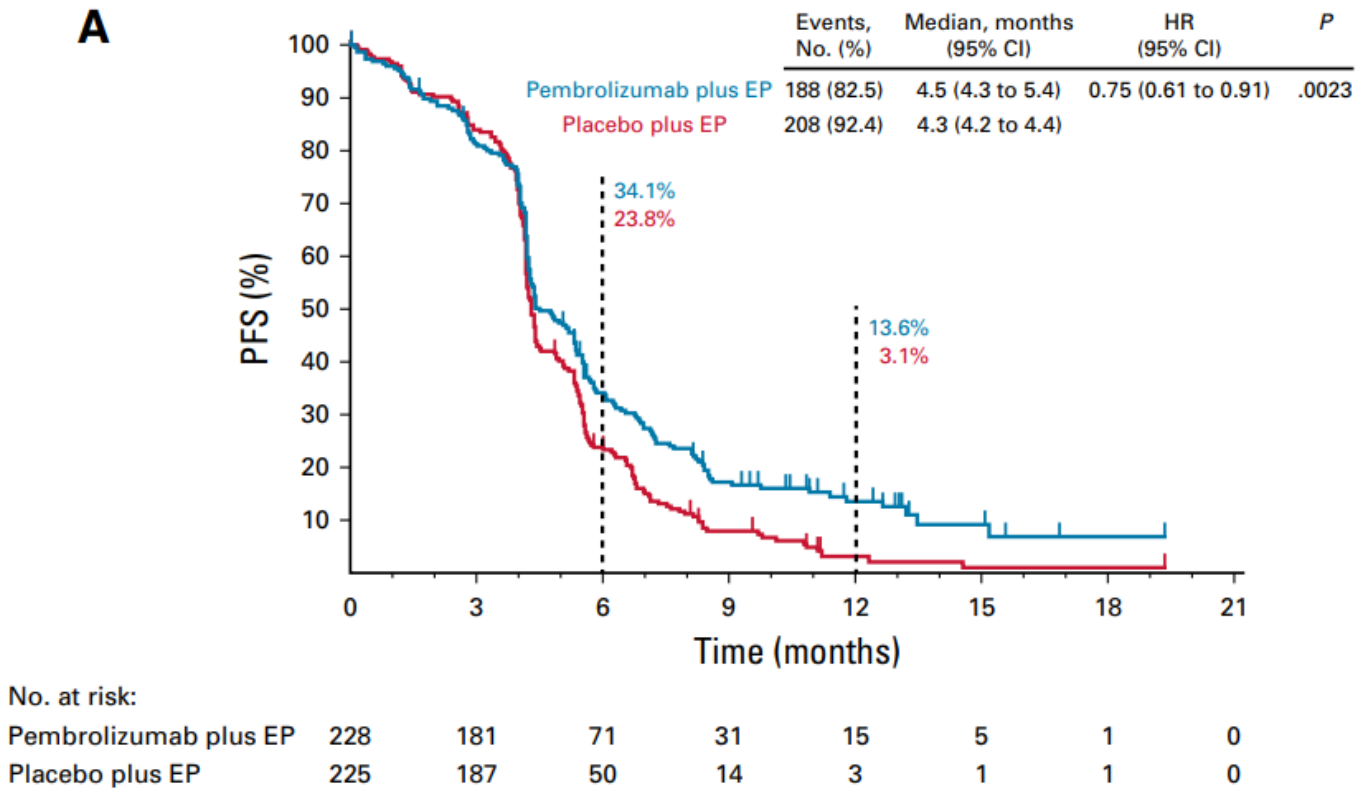
CR or better: Subjects: 42; Events: 23; Median: 21.45 (95% CI: 12.52, NE)
VGPR: Subjects: 26; Events: 25; Median: 10.38 (95% CI: 5.09, 12.22)
PR: Subjects: 26; Events: 26; Median: 4.50 (95% CI: 2.86, 6.54)

CI= confidence interval; IMWG = International Myeloma Working Group; NE = not estimable. Two patients with 150 x 10^6 CAR-positive T cell dose, which is not part of the approved dose range, are included in Figure 1.

Case 3

Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study

Charles M. Rudin, MD, PhD[1]; Mark M. Awad, MD, PhD[2]; Alejandro Navarro, MD[3]; Maya Gottfried, MD[4]; Solange Peters, MD, PhD[5]; Tibor Csöszi, MD[6]; Parneet K. Cheema, MD[7]; Delvys Rodriguez-Abreu, MD[8]; Mirjana Wollner, MD[9]; James Chih-Hsin Yang, MD, PhD[10]; Julien Mazieres, MD, PhD[11]; Francisco J. Orlandi, MD[12]; Alexander Luft, PhD, MD[13]; Mahmut Gümüş, MD[14]; Terufumi Kato, MD[15]; Gregory P. Kalemkerian, MD[16]; Yiwen Luo, PhD[17]; Victoria Ebiana, MD[17]; M. Catherine Pietanza, MD[17]; and Hye Ryun Kim, MD[18] on behalf of the KEYNOTE-604 Investigators


A
Events, No. (%)
Median, months (95% CI)
HR (95% CI)
P
Pembrolizumab plus EP 188 (82.5) 4.5 (4.3 to 5.4) 0.75 (0.61 to 0.91) .0023
Placebo plus EP 208 (92.4) 4.3 (4.2 to 4.4)
34.1%
23.8%
13.6%
3.1%
PFS (%)
100
90
80
70
60
50
40
30
20
10
0
3
6
9
12
15
18
21
Time (months)
No. at risk:
Pembrolizumab plus EP 228 181 71 31 15 5 1 0
Placebo plus EP 225 187 50 14 3 1 1 0

R Packages

- install.packages(“biostat3”)
- Install.packages("survival")

CRAN Task View: Survival Analysis

- https://cran.r-project.org/web/views/Survival.html

CRAN Task View: Survival Analysis

Maintainer:	Arthur Allignol, Aurelien Latouche
Contact:	arthur.allignol at gmail.com
Version:	2022-03-07
URL:	https://CRAN.R-project.org/view=Survival
Source:	https://github.com/cran-task-views/Survival/
Contributions:	Suggestions and improvements for this task view are very welcome and can be made through issues or pull requests on GitHub or via e-mail to the maintainer address. For further details see the Contributing guide.
Citation:	Arthur Allignol, Aurelien Latouche (2022). CRAN Task View: Survival Analysis. Version 2022-03-07. URL https://CRAN.R-project.org/view=Survival.
Installation:	The packages from this task view can be installed automatically using the ctv package. For example, `ctv::install.views("Survival", coreOnly = TRUE)` installs all the core packages or `ctv::update.views("Survival")` installs all packages that are not yet installed and up-to-date. See the CRAN Task View Initiative for more details.

Statistical Inference

- Estimation
  - Questions
    - How long subjects can live?
    - At time t, what is the survival rate?
    - What is the event rates?
    - What is the time point at which subjects have 50% chance to be event-free?
  - Statistical tools
    - Point estimate
      - 1-sample: Mean, median, quantiles
      - 2-samples: difference, ratio, odds ratio
    - Variance, standard error
    - Confidence intervals, confidence band
- Testing
  - Questions
    - Is the treatment prolonging life?
    - Which treatment has better survival function?
  - Statistical tools
    - 1-sample or 2-samples
    - Hypotheses
      - Superiority
      - Non-inferiority
    - Significance level and power -> sample size
    - Test statistics
    - P-values

Survival Analysis

- Also known as
  - Event history analysis in social science
  - Reliability analysis in engineering

- Models for statistical analyses
  - Parametric
    - The cumulative distribution function of data is known $F(t, \theta), \theta \in \Theta$, parameter space
  - Nonparametric
    - No parameter to describe $F(t)$
  - Semiparametric
    - $T = \alpha + \beta X + \epsilon$, ϵ can not be characterized by parameters

Discrete Survival Function

- Events occur at discrete time values $t_1 < t_2 < \cdots$

$$f(t_i) = P(T = t_i) \;\; i = 1,2, \ldots$$

- Cumulative distribution function

$$P(T \leq t_k) = \sum_{i=1}^{k} f(t_i)$$

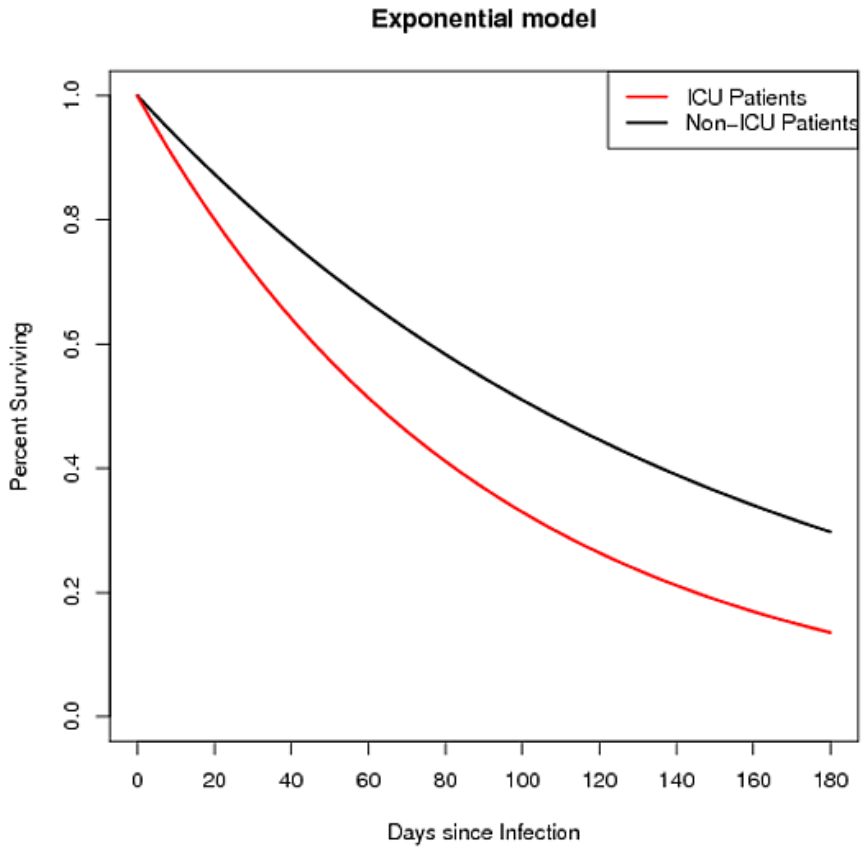
- The Survival function

$$S(t) = P(T > t_k) = 1 - P(T \leq t_k) = \sum_{j \backslash t_j > t_k} f(t_j)$$

Continuous Survival Time

- $S(t) = P(T > t) = 1 - P(T \leq t) = \int_t^{\infty} f(x)dx$

- $P(T \leq t)$ cumulative distribution function



Homework Due Sept 19

1. Identify a real survival data set from literature or R packages such survival, Biostat3.
   - Describe the background of the data set
   - Identify the type of censoring
   - Summarize the data
     - Number of subjects
     - Number of events
     - Number of censoring

2. Identify a study in medical journals that uses survival analysis
   - Summarize the study
     - The study design
     - Analysis method
     - Study results