

The Kaplan-Meier Plot

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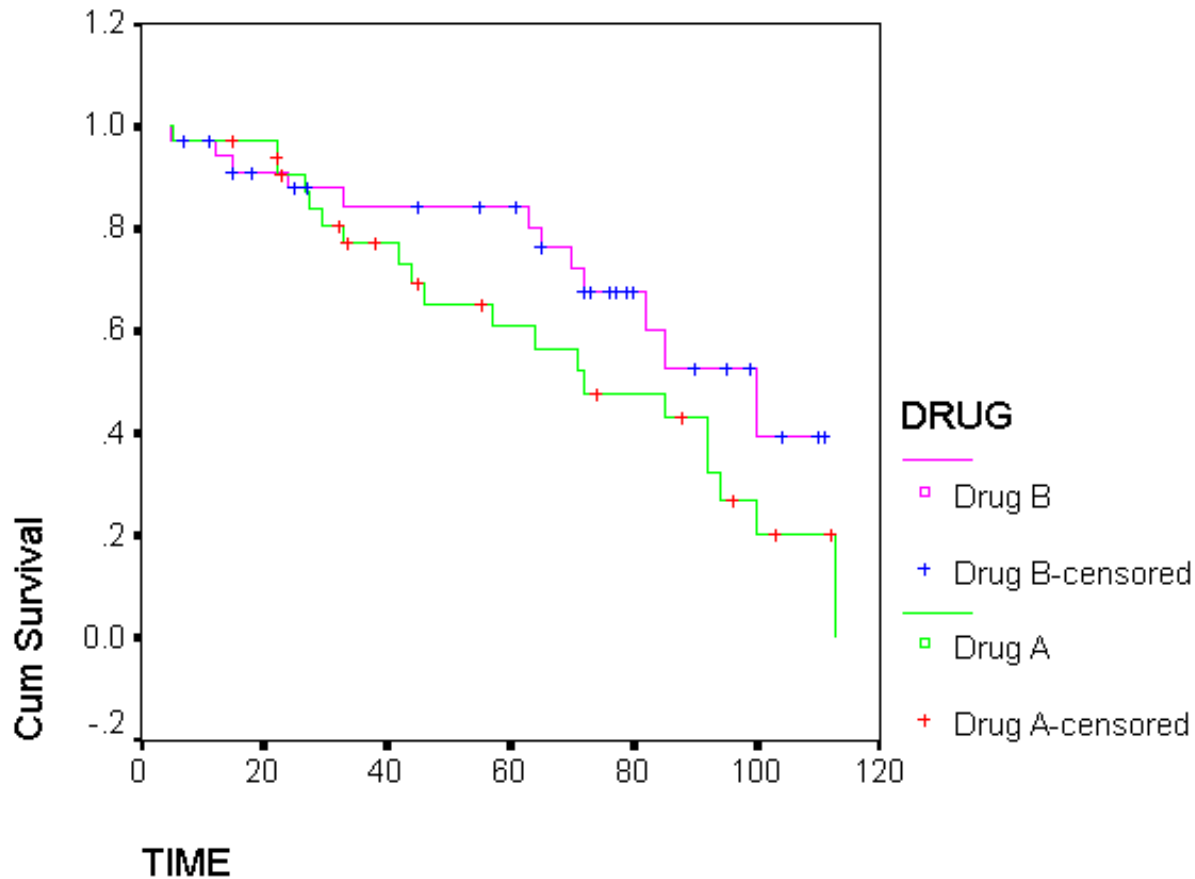
(product limit estimator)

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1 Introduction



- typical Kaplan-Meier curve, comparing survival outcome for two different drugs (A/B)

1 Introduction

- The Kaplan-Meier curve is a graphicalization of information collected from medical trials
- Data is estimated using different analytical tests (log-rank test, cox-regression)
- y-axis: probability of defined study objective (overall survival, progression free survival, etc.)
- x-axis: time of observation
- each drop in the graph displays an event e.g. death, relapse, therapeutic effect
- A vertical tick on the curve displays a censored patient

1 Introduction

- **Censoring:** patients dropping out of the study, dying of other cause, etc.
 - are taken out of the “group at risk” -> do not display an event during study time
 - overall patient number reduction but no risk reduction
 - still have to be taken into analysis, using complex strategies like the Kaplan-Meier estimate
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- **Oncology:** differentiation between tumor-related death and death of other origin
 - sometimes non-tumor related deaths are taken out of trial (censoring)
 - more complex study models allow for them to be taken into analysis as well

2 The Kaplan-Meier-Estimator (product limit estimator)

- Estimator to calculate the mostly progressional reduction of survival probability
- using the following formula:

$$S(t) = \prod_{t(i) \leq t} \frac{n(i) - d(i)}{n(i)}$$

$S(t)$ -> survival at time t

$n(i)$ -> objects at risk/objects under observation at time t

$d(i)$ -> objects with event/deaths at time t

2 The Kaplan-Meier-Estimator (product limit estimator)

- This leads to establishment of a table like the following:
- ($n = 300$)

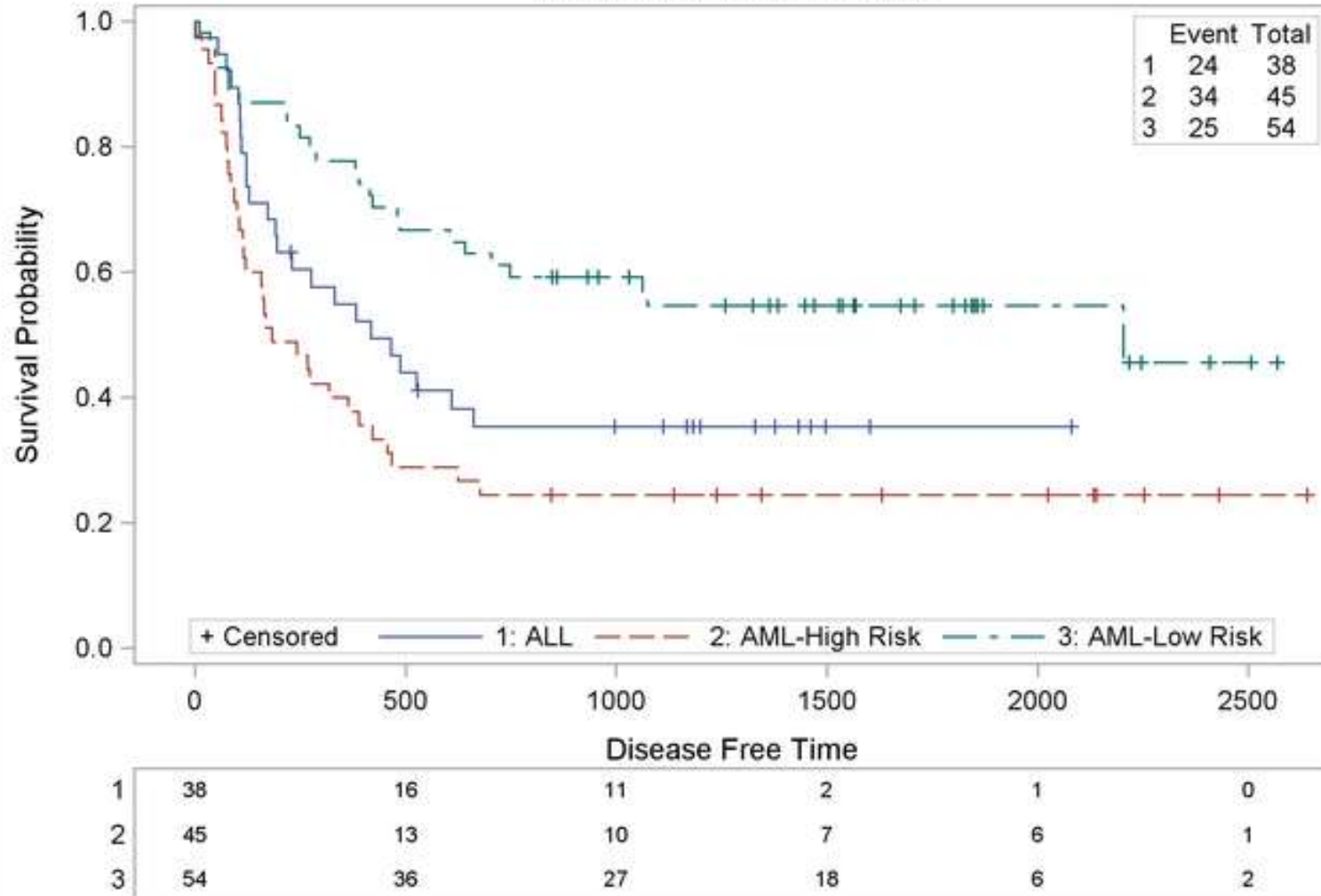
Object No.	Time (t) (months)	1= event 0= censored patient	$n(t)$	$S(t)$
1	3	1	300	0.996
2	5	0	299	-
3 ; 4	9	1 ; 1	298	0,993
5	10	0	296	-
...

2 The Kaplan-Meier-Estimator (product limit estimator)

- The table is then used to establish a Kaplan-Meier curve
- Important: censored patients are taken into analysis, for they reduce object at risk but not overall risk
- typical failures:
 - Exclusion of censored patients -> misinterpretation of survival, as for example there might be different patient numbers in 2 different (therapy) groups -> impression that one therapy is of greater benefit
 - Censored patients are taken into analysis as an event.

3 The Kaplan-Meier Curve

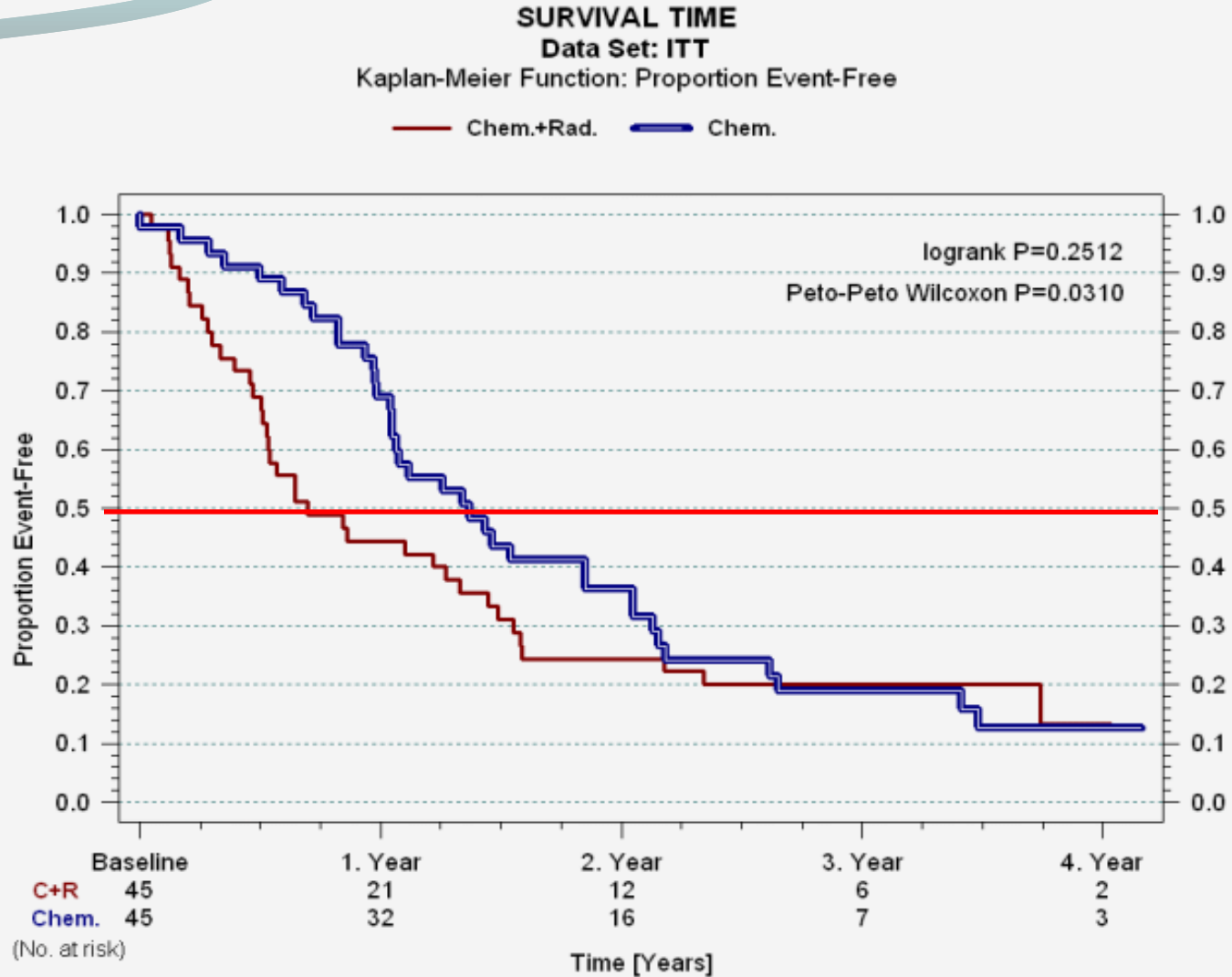
Kaplan-Meier Plot
With Number of Subjects at Risk



3 The Kaplan-Meier Curve

- y-axis: probability of defined study objective (page before: survival probability)
- x-axis: time of observation (page before: disease free time)
- each drop in the graph displays an event e.g. death, relapse, therapeutic effect
- A vertical tick on the curve displays a censored patient
- usually the number of patients under observation is shown beneath the curve
- comparison of different outcome groups, combined into one plot

3 The Kaplan-Meier Curve



3 The Kaplan-Meier Curve

- **Median survival** can be read from the plot -> red line indicates 50% mark of cumulative percentage with event at the time of 8 months for chemo- + radiotherapy and of 16.5 months for chemotherapy
- If the curve does not cross the 50% mark during observation, one cannot make a statement
- Using this, one can give an estimate for the 25% and 75% and other survival rates
- One can also give an estimate for survival percentage in years

3 The Kaplan-Meier Curve

- **Variance or standard deviation:** describes the dispersion rate of values -> how far are our measured values spread?

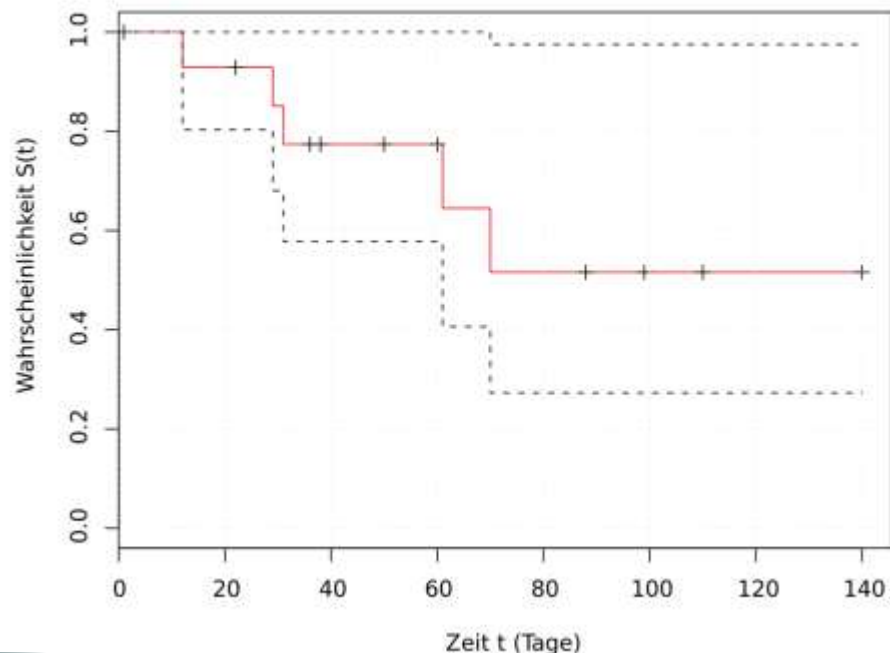
$$\text{var}\{\hat{S}(t)\} \approx [\hat{S}(t)]^2 \left\{ \sum_{i=1}^k \frac{d_i}{n_i(n_i - d_i)} \right\}$$

- The confidence interval is calculated from the variance

3 The Kaplan-Meier Curve

- **Confidence interval:** predicted interval, in which most of the measured data (points) fall, if the test is repeated often enough
- usually 95%, sometimes 99% (larger group) or 90% (smaller group)
- in the Kaplan-Meier plot the confidence interval can be displayed as dotted lines

Beispiel Kaplan-Meier-Schätzer



- 95% confidence interval means: with a probability of 95% our measured values lie within our predicted/precalculated interval. (interval: $a < x < b$)

$$s.e.\{\hat{S}(t)\} \approx [\hat{S}(t)] \left\{ \sum_{i=1}^k \frac{d_i}{n_i(n_i - d_i)} \right\}^{\frac{1}{2}}$$

3 The Kaplan-Meier Curve

- **Log-rank test:** test used to compare survival times for two or more patient groups, using hazard ratios of the groups at the observed time. Censored data is taken into equation. Hazards have to be “proportional” -> curves do not cross (-> Wilcoxon test)
- **Hazard:** risk to have an event at time (t) -> $h(t)$
- **Hazard ratio:** comparison of two groups hazards at time (t)

$$H(t) = \frac{h_2(t)}{h_1(t)}$$

$h_1(t)$ -> reference group: $HR > 1$ -> Risk group 2 > Risk group 1; $HR < 1$ -> Risk group 1 > Risk group 2

3 The Kaplan-Meier Curve

- **Cox-Regression (proportional Hazards model)**: comparison of models with 2 or more variables -> age, gender, therapy, resection grade, metastasis grade, etc measures the time that passes until an event takes place dependent on the variables, using Hazard-ratios

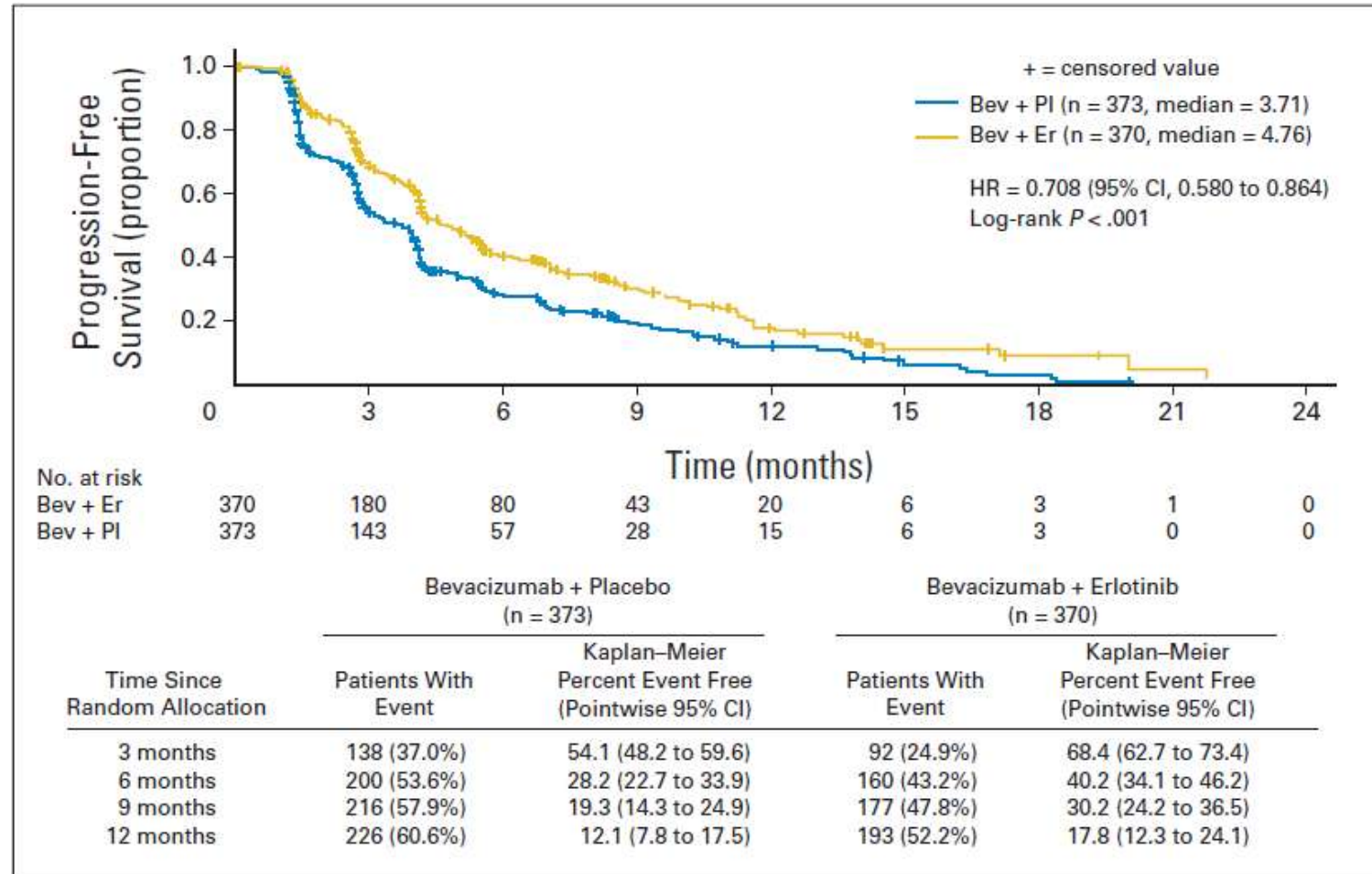
4 From planning to establishment of the Kaplan- Meier Curve. An Example

- Using the **ATLAS Trial** by Johnson et al, 2013 (Johnson et al., 2013)
- Avastin Tarceva Lung Adenocarcinoma study (ATLAS) -> phase III, multicenter, randomized, placebo-controlled trial
- conducted at 187 institutions worldwide from Jan. 10th 2006 to June 29th 2009
- 1145 Patients with confirmed NSCLC received 4 cycles with chemotherapy plus bevacicumab
- 745 Patients were randomly assigned to bevacicumab + erlotinib or bevacicumab + placebo group

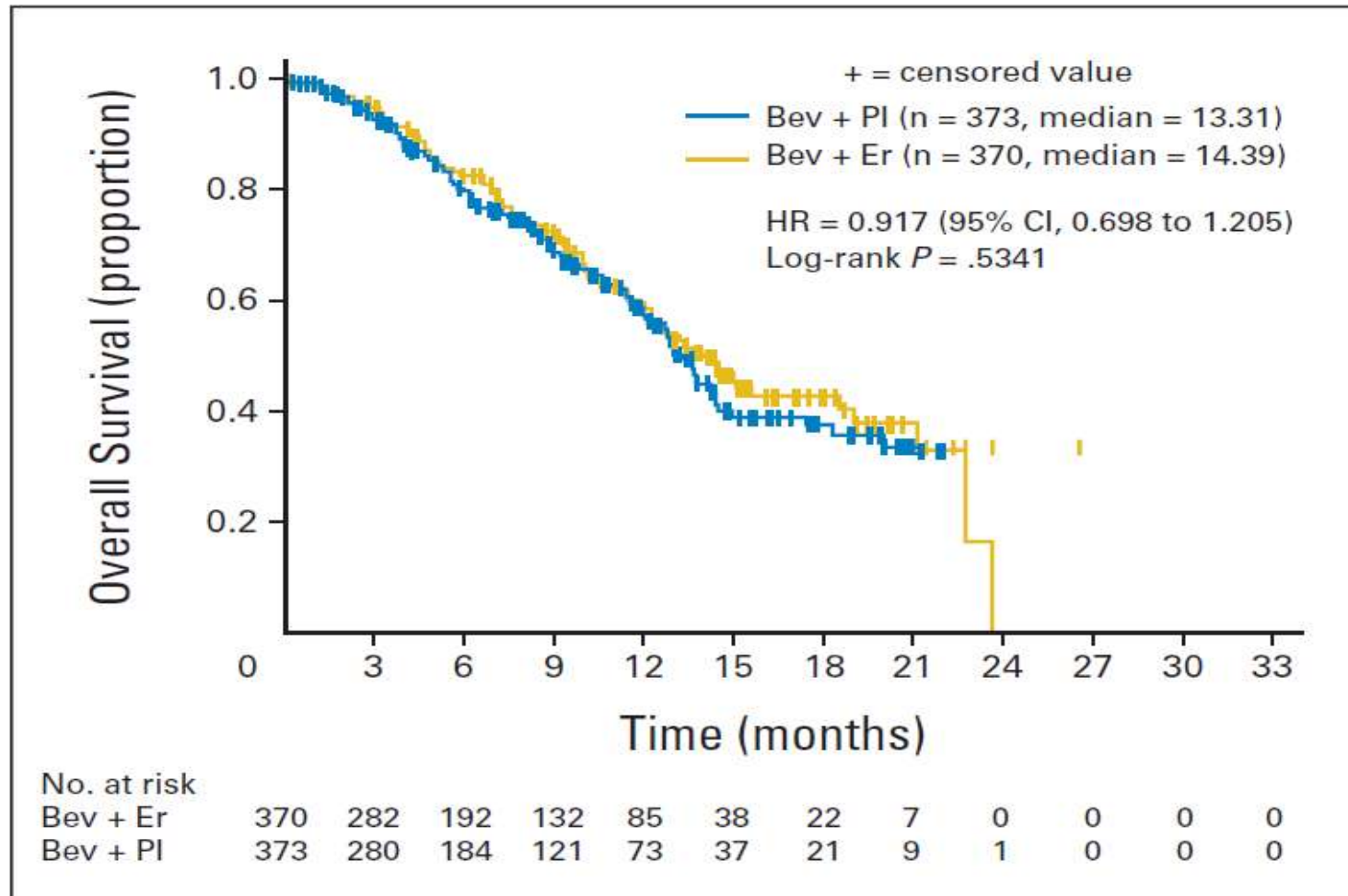
4 From planning to establishment of the Kaplan- Meier Curve. An Example

- Primary objective was the evaluation of Progression free survival (PFS)
- secondary objectives were overall survival (OS -> time from random assignment to death) and safety
- markers for progression (PFS) -> Tumor measurements from assessment before random assignment
- PFS and OS were tested using a Log-rank test
- Median PFS and OS were established using the Kaplan-Meier method, the HR was estimated using a stratified Cox-regression model.

4 From planning to establishment of the Kaplan-Meier Curve. An Example



4 From planning to establishment of the Kaplan-Meier Curve. An Example



- Dr. Christel Weiß: Basiswissen Medizinische Statistik, 4. Überarbeitete Auflage, Springer Medizin Verlag 2008
- Harald Heinze, Georg Heinzl: Medical Biostatistics 1 – Lecture Notes, Version 2009-10
- http://en.wikipedia.org/wiki/Proportional_hazards_model
- http://en.wikipedia.org/wiki/Confidence_interval
- <http://de.wikipedia.org/wiki/Kaplan-Meier-Sch%C3%A4tzer>

1. ZWIENER, I., BLETTNER, M. & HOMMEL, G. 2011. Survival analysis: part 15 of a series on evaluation of scientific publications. *Dtsch Arztebl Int*, 108, 163-9.
2. Johnson BE, Kabbinavar F, Fehrenbacher L, Hainsworth J, Kasubhai S, Kressel B, Lin CY, Marsland T, Patel T, Polikoff J *et al*: **ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer.** *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013, **31**(31):3926-3934.

Bildquellen:

http://www.ganfyd.org/images/c/cd/Kaplan-Meier_example.png (08.01.14; 14:13h)

<http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/images/lftdone.png>

(08.01.14; 15:57h)

<http://www.idvgauting.com/cms/uploads/pics/kaplan1.png> (08.01.14; 16:16h)

<http://upload.wikimedia.org/wikipedia/commons/thumb/f/f9/Kaplan-Meier-sample-plot.svg/2000px-Kaplan-Meier-sample-plot.svg.png> (08.01.14; 16:57h)