Italian Stata Users Group Meeting

November 12, 2015

Assessment of proportional hazards assumption: restricted mean difference as a potential alternative to the hazard ratio for the analysis of time-to-event endpoint on aggregate data

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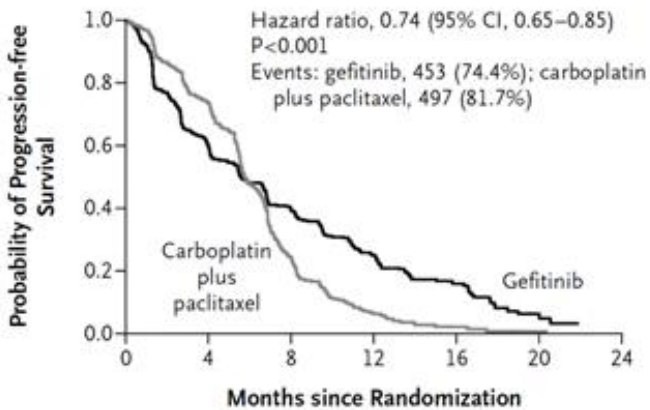
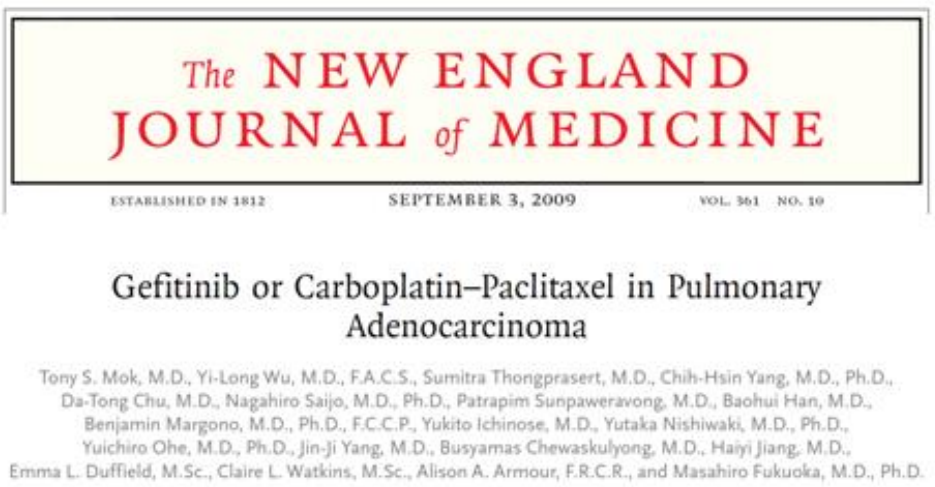
Background

- Survival improvement is an appropriate measure of clinical benefit
- Time-to-event endpoint is the outcome of interest in many oncological clinical studies
- Log-rank and proportional hazards (PH) Cox model are the most common techniques used for analyzing survival time data

Rationale

- The hazards need to be proportional but rarely PH assumption is assessed
- Survival curve convergences and crossings are common in medical research




The NEW ENGLAND JOURNAL of MEDICINE

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Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D., Da-Tong Chu, M.D., Nagahiro Saijo, M.D., Ph.D., Patrapim Sunpaweravong, M.D., Baohui Han, M.D., Benjamin Margono, M.D., Ph.D., F.C.C.P., Yukito Ichinose, M.D., Yutaka Nishiwaki, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Jin-Ji Yang, M.D., Busyamas Chewaskulyong, M.D., Haiyi Jiang, M.D., Emma L. Duffield, M.Sc., Claire L. Watkins, M.Sc., Alison A. Armour, F.R.C.R., and Masahiro Fukuoka, M.D., Ph.D.

Objectives

Conduct a **systematic review** to quantify the phenomenon of survival curve convergences and crossings

Propose the use of **meta-regression** as a method to test the **PH assumption** when only **aggregate data** are available

Propose the use of **restricted mean difference** as a potential alternative to the HR in case of non-PH

Systematic review

- Inclusion criteria for the **review**
  - Phase II/III RCTs
  - Advanced non-small-cell lung cancer (NSCLC)
  - Antitumor therapies
  - Time-to-event primary endpoint

Data extraction:

Study design, patient and treatment characteristics, metodological and statistical features

Systematic review

- Inclusion criteria for the **analysis**
  - Number of patients at risk reported at each time-point p
  - At least 3 time-points available

Data extraction:

Survival probabilities from the KM curves at p time-points, number of patients at risk

Estimates of log(HR) and its variance

- Life-table approach
- Censoring uniform within each time interval

$$s^*_{j,i} = s^*_{j,i-1} \cdot \left[1 - \frac{d^*_{j,i}}{n_{j,i-1} - (c^*_{j,i}/2)}\right] \quad (1)$$

$$n_{j,i} = n_{j,i-1} - d^*_{j,i} - c^*_{j,i} \quad (2)$$

Rearranging (1) e (2) gives the number of events $d^*_{j,i}$, the number censored $c^*_{j,i}$ and the number at risk $n^*_{j,i}$ during the interval $[t_{i-1}, t_i)$

more

Williamson, P.R. *Statistics in medicine*, 2002

Estimates of log(HR) and its variance

Logarithm of the Hazard Ratio whitin the i^{th} time interval

$$log(HR)_i = \frac{(d^*_{2,i} - e^*_{2,i})}{v_i}$$

Variance of the log(HR) whitin the i^{th} time interval

$$var(log(HR)_i) = \frac{1}{v_i}$$

more

Assessing the PH assumption

- GRAPHICAL APPROACH
  - **log(-log S)** plot against time

```
twoway (scatter ln_ln1 ln_t, connect(l)) ///
(scatter ln_ln2 ln_t, connect(l))
```

  - **Forest plot** within each study to visualize the relation between the HR and the time of follow-up

```
metan ln_hr se_hr, fixedi eform label(namevar=t)
```

Assessing the PH assumption

- ANALYTICAL APPROACH
  - **Meta-regression** to test for a linear trend with time
    - Outcome: log(HR) at each time-point
    - Explanatory variable: follow-up time
    - Inverse-variance weighting

```
statsby _b e(chi2) e(df_m),by(id):  vwls ln_hr t1,sd(se_hr)

rename _eq2_stat_1 chi2
rename _eq2_stat_2 df_m
gen pvalue=chi2tail(df_m, chi2)
gen z=sqrt(chi2)
list if pvalue<0.1
```

Association between non-PH and study characteristics

- Type of treatment comparison
  - different mechanism of action
  - same mechanism of action

conventional therapy, biologics, tyrosine-kinase inhibitor (TKI), non-conventional target

- Type of endpoint
  - Overall Survival (OS)
  - Progression Free Survival (PFS)

Restricted Mean Survival Time (RMST)

- Select a time-point t^*, up to which we wish to compute the RMST
- For a random time-to-event variable T, we estimate:

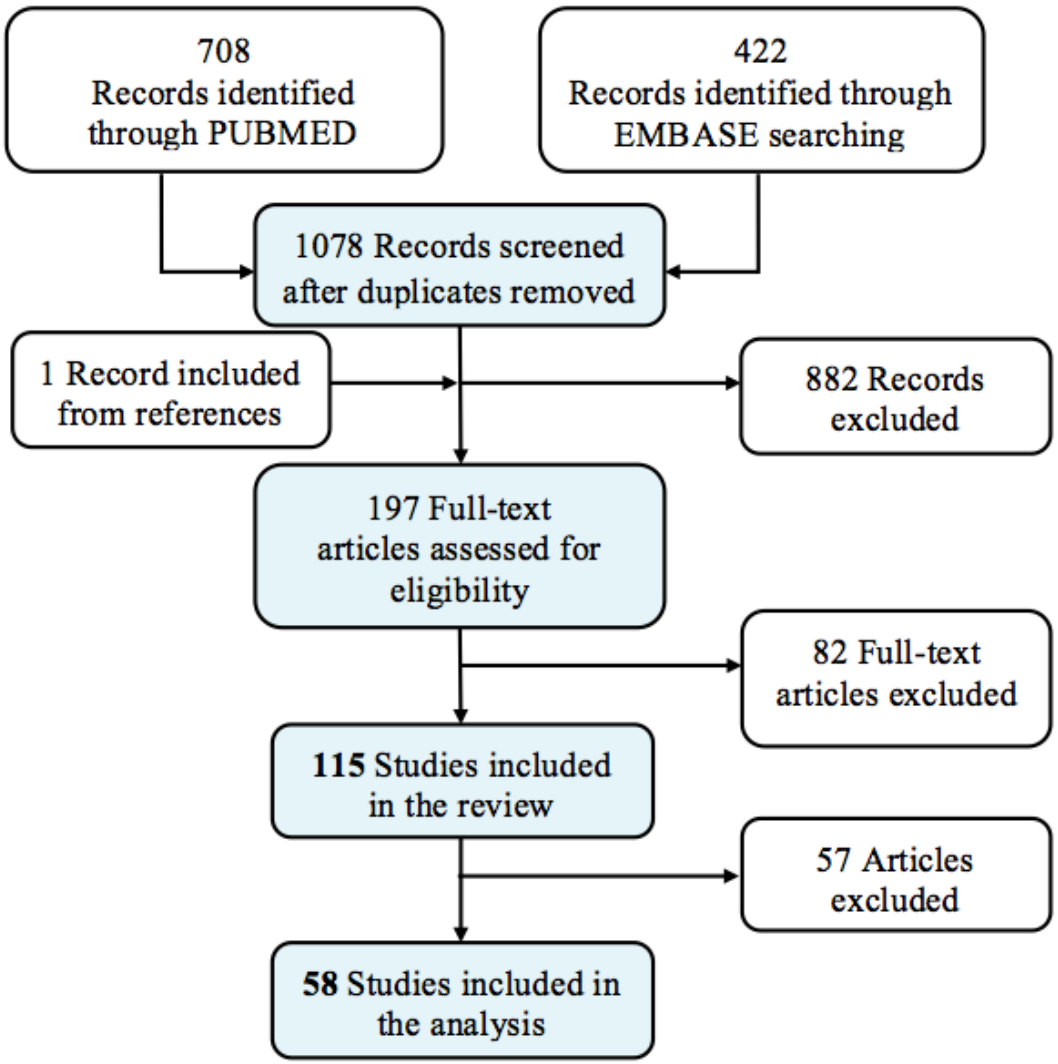
$$\mu(t^*) = E[min(T, t^*)] = \int_0^{t^*} S(t)dt \qquad (3)$$

- Area under the survival curve up to t^*
- Can think of it as the *'t^*-year life expectancy'*
- Difference in RMST between arms could be used as an alternative to the HR

more

Royston, P. and Parmar, M.K. *Statistics in medicine*, 2011

Flow-chart


708
Records identified through PUBMED
422
Records identified through EMBASE searching
1078 Records screened after duplicates removed
1 Record included from references
882 Records excluded
197 Full-text articles assessed for eligibility
82 Full-text articles excluded
115 Studies included in the review
57 Articles excluded
58 Studies included in the analysis

Characteristics of the studies included in the review

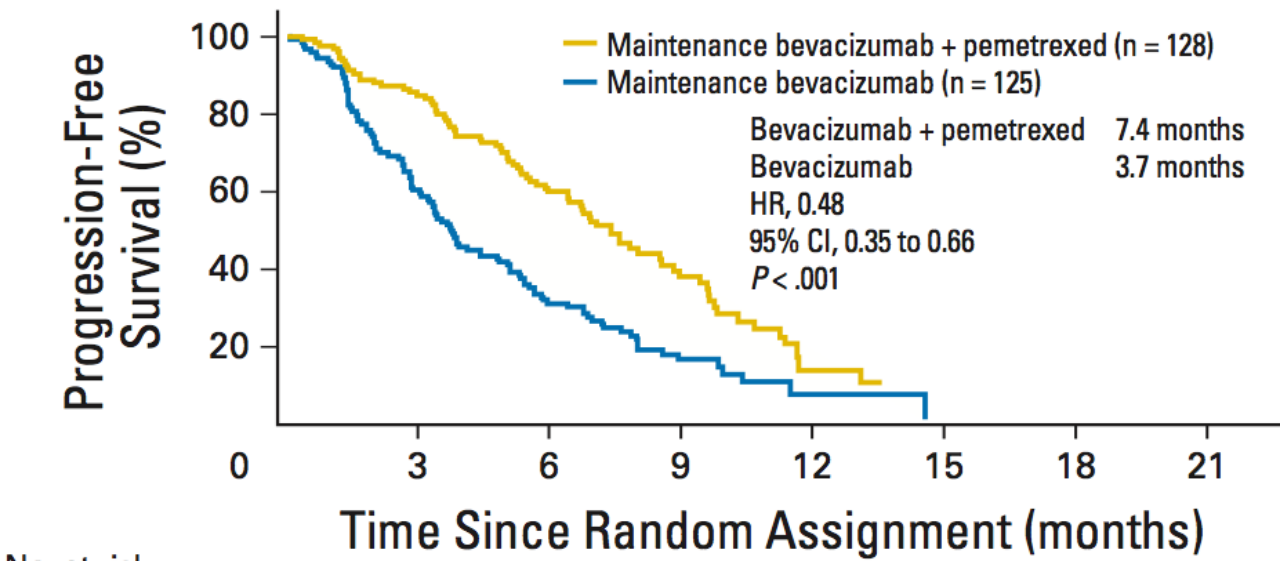
- **Phase:** 33% were phase II studies, 67% were phase III
- **Primary endpoint:** 49% OS, 51% PFS
- **Treatment comparisons:** 41% same mechanism of action, 59% different mechanism
- **Partecipants:** The median number randomized was 332
- **Statistical analysis:** Log-rank test, Cox model

Only 4 (3%) out of 115 studies reported whether PH assumption was satisfied or not

PH assumption assessment

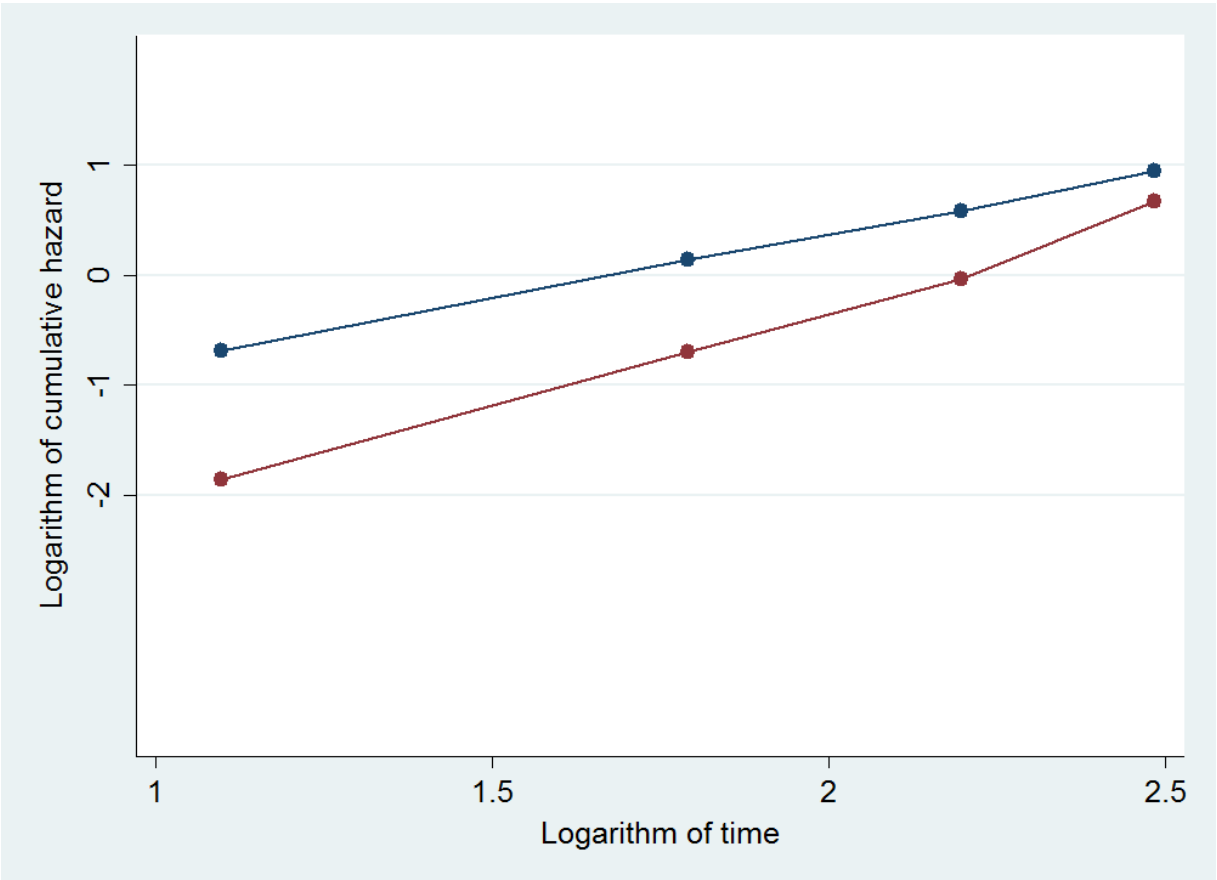
For 12 (19%) out of 62 treatment comparisons non-PH was detected

- Two studies in which PH assumption is violated:



Barlesi, F. *Journal of clinical oncology*, 2013

PH assumption assessment



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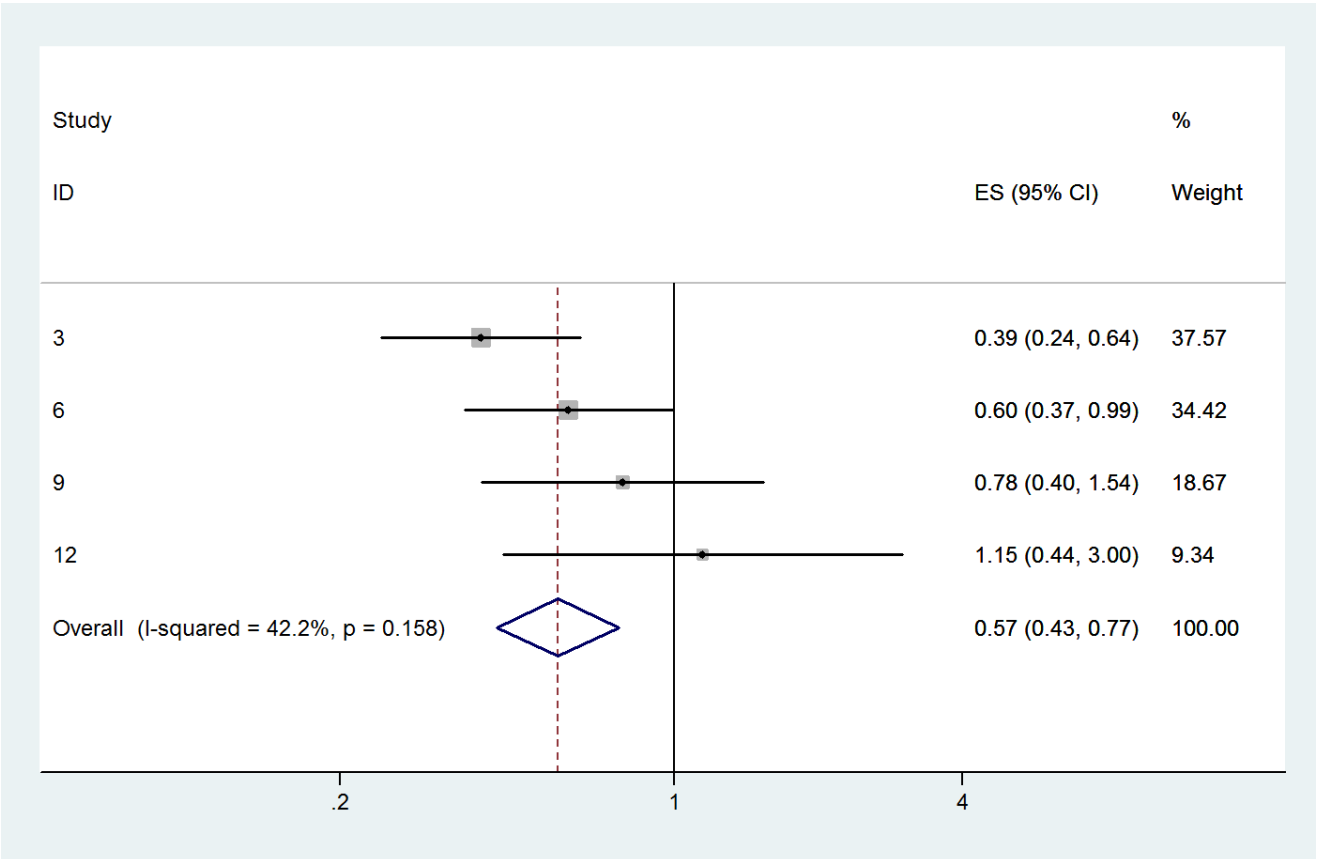

Barlesi, F. *Journal of clinical oncology*, 2013

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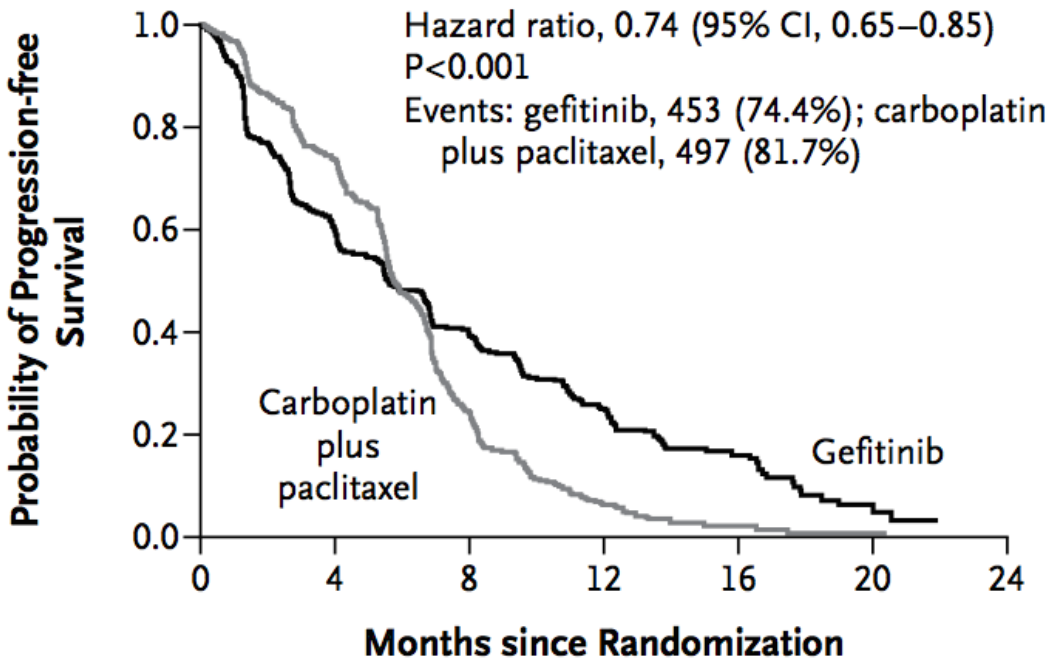
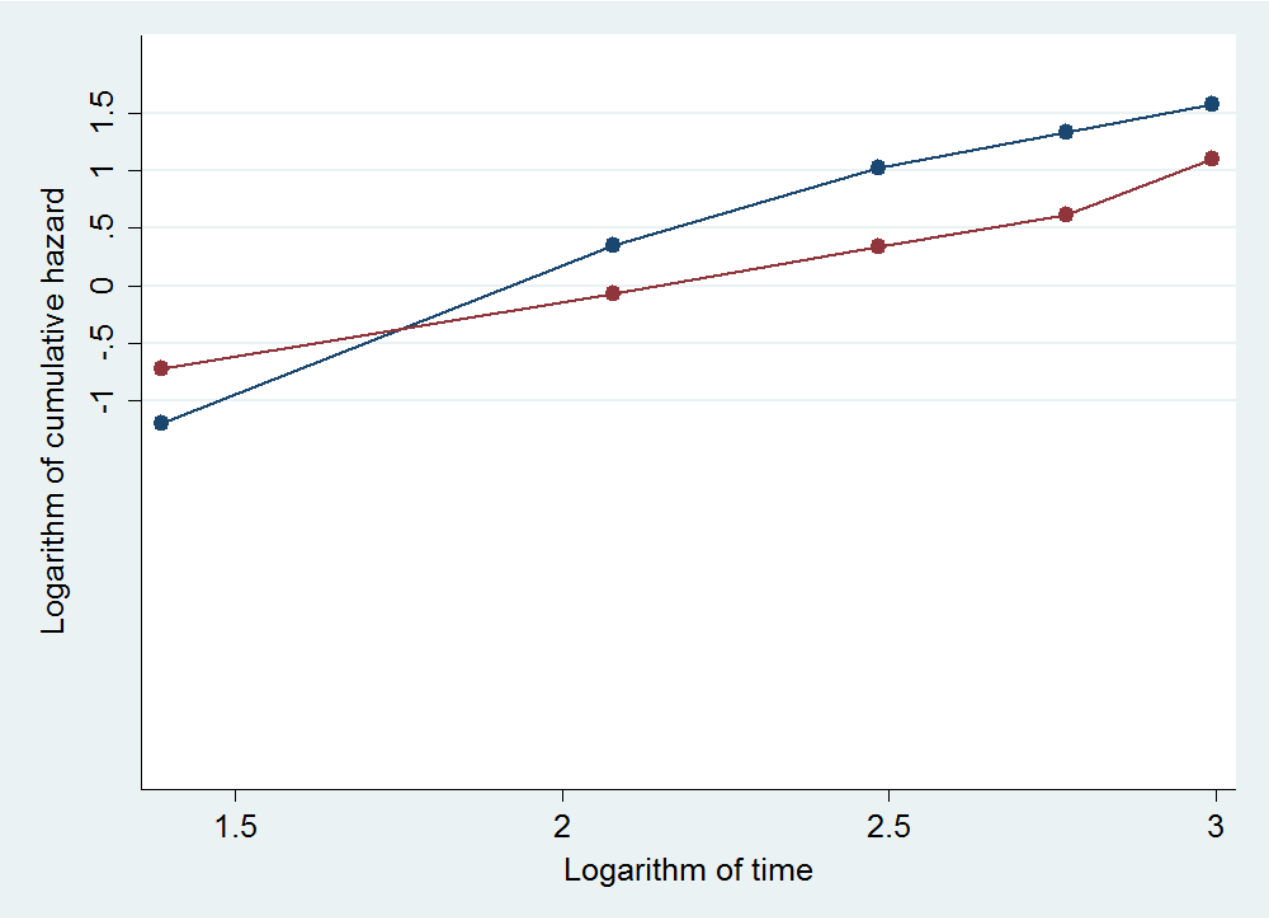


No. at Risk

Gefitinib	609	363	212	76	24	5	0
Carboplatin plus paclitaxel	608	412	118	22	3	1	0

Mok, T.S. *New England Journal of Medicine*, 2009

PH assumption assessment



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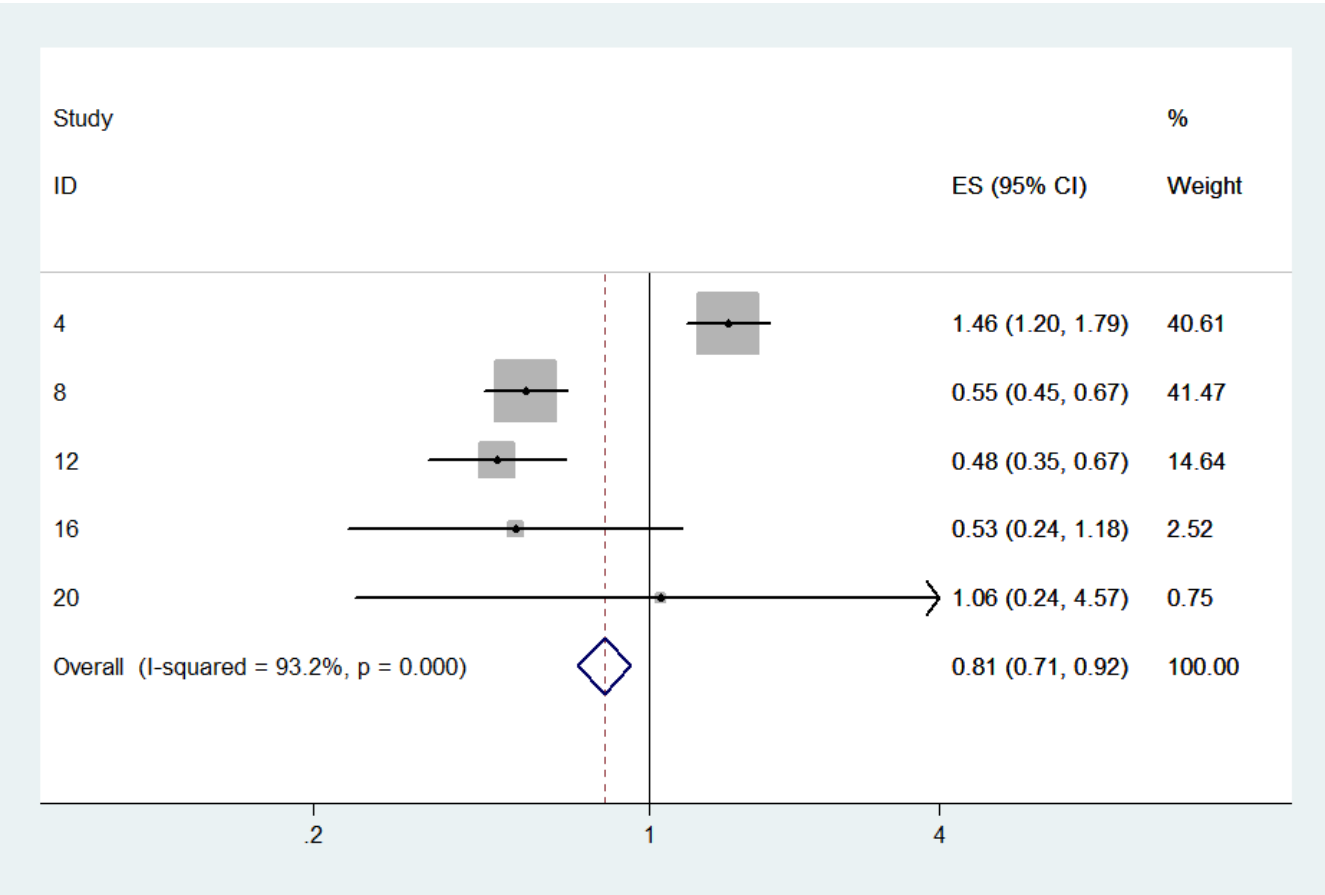

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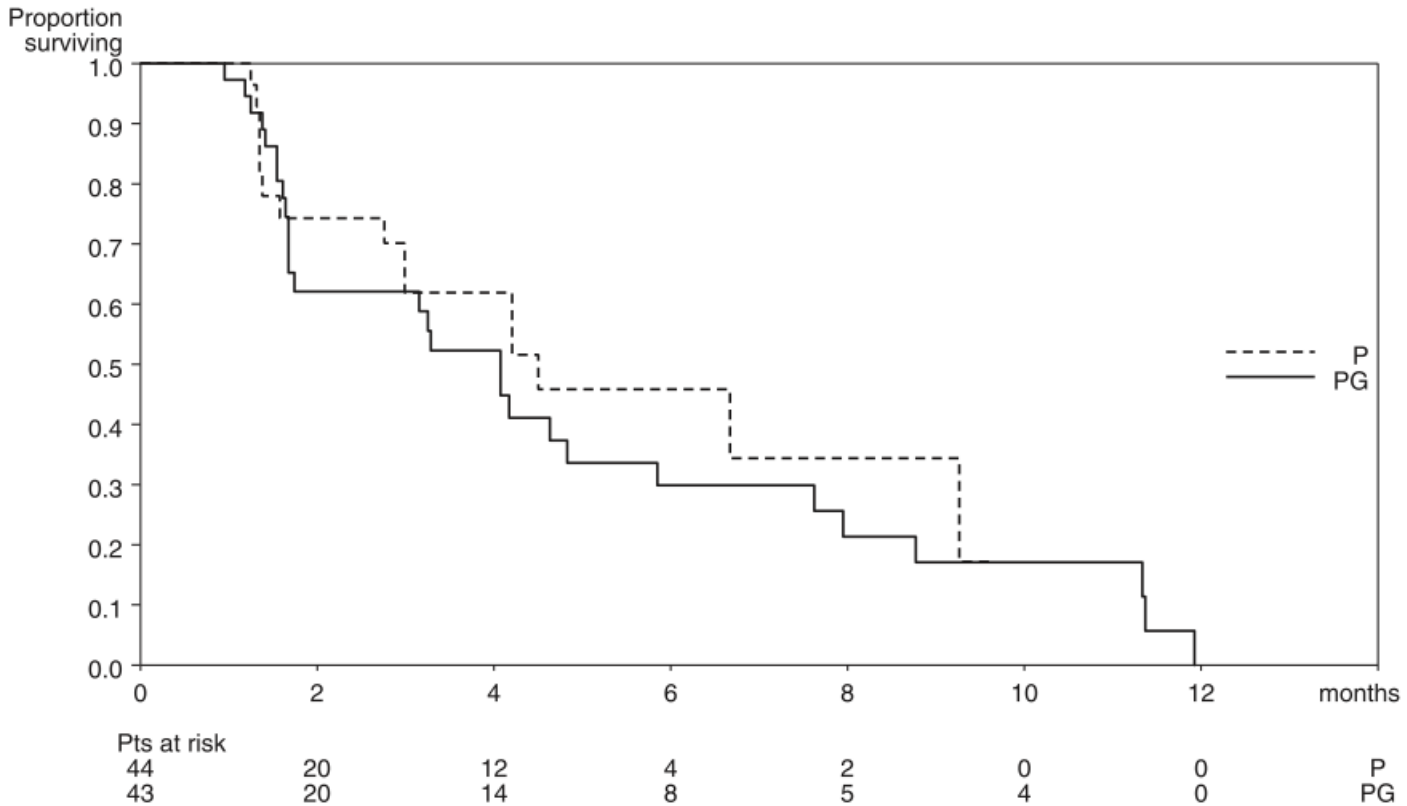
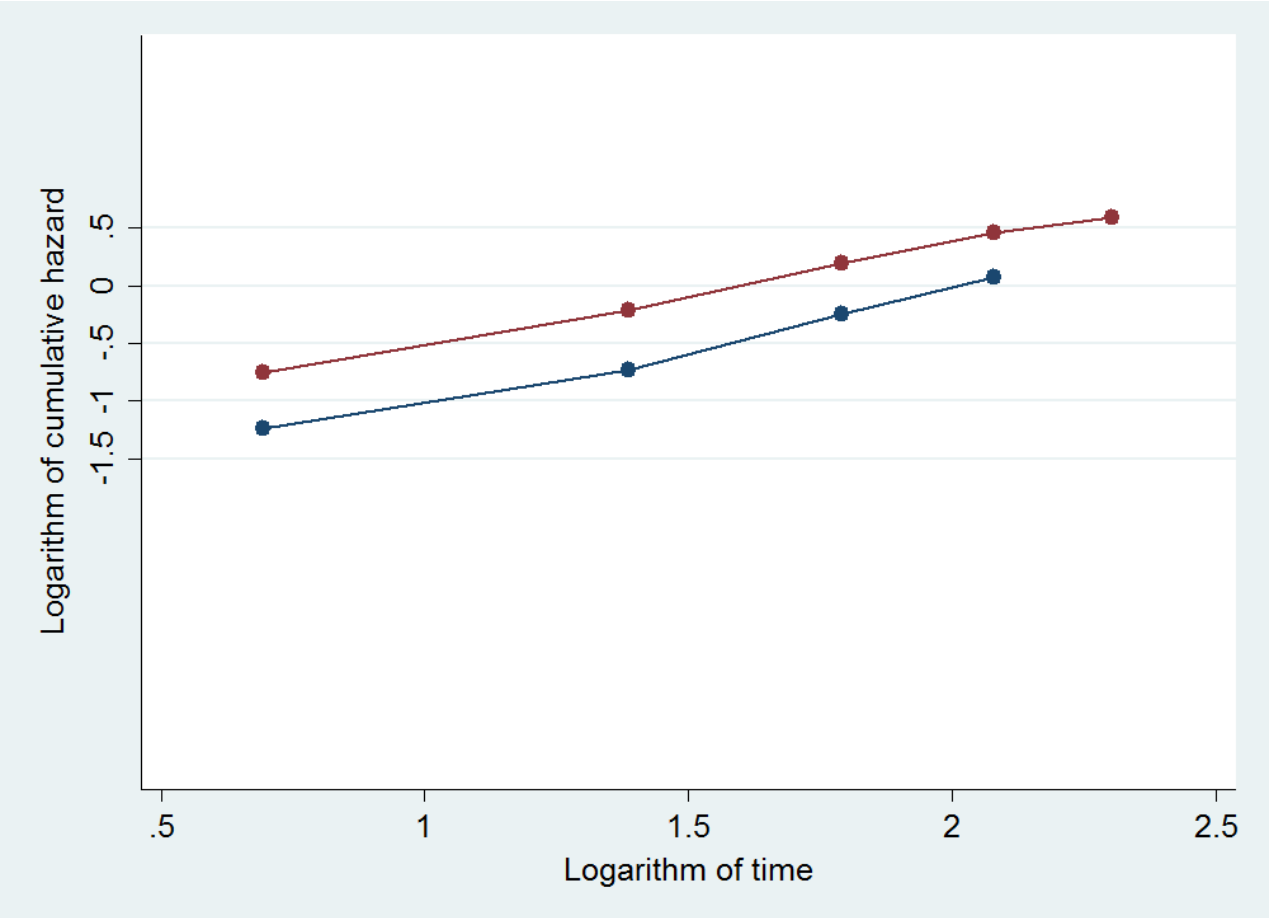


Gridelli, C. *Journal of thoracic oncology*, 2007

PH assumption assessment



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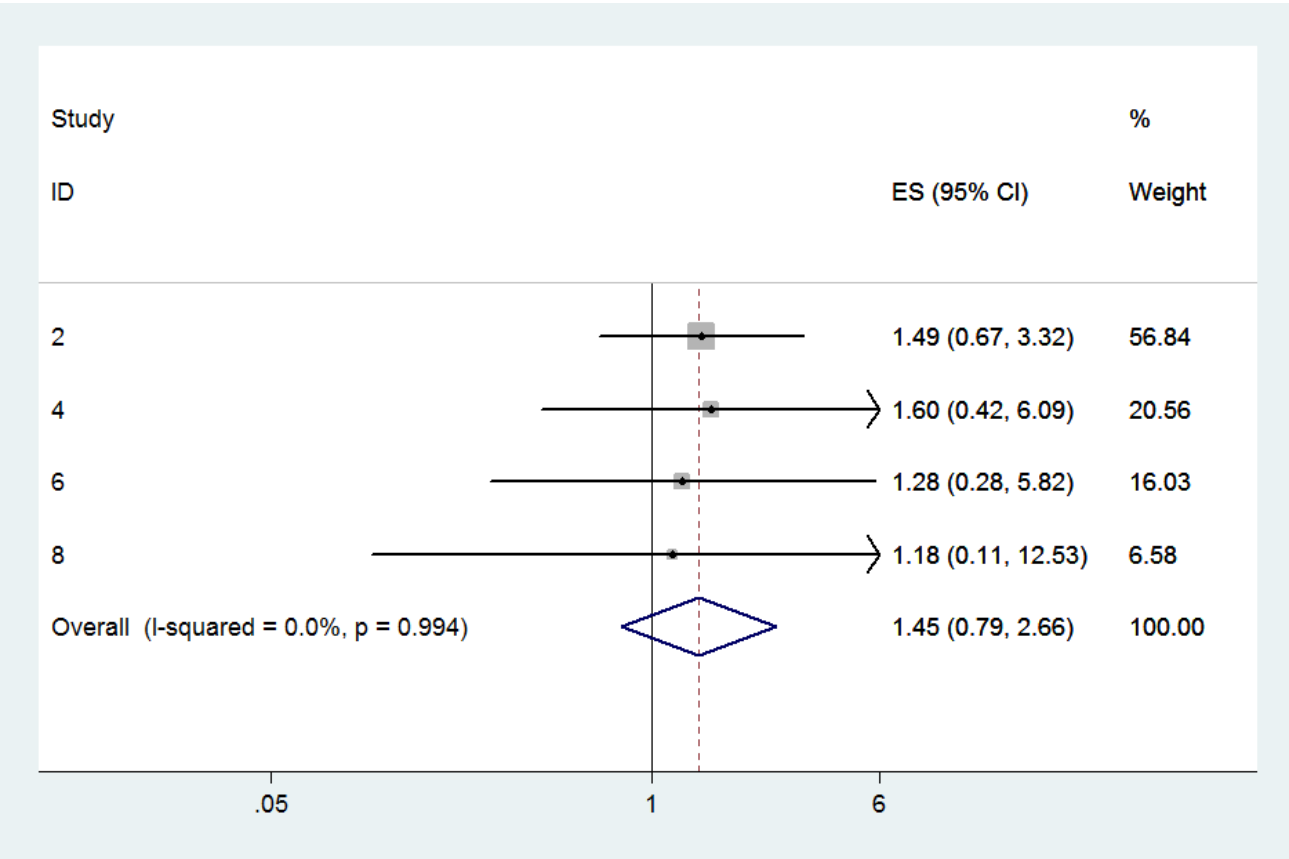

Gridelli, C. *Journal of thoracic oncology*, 2007

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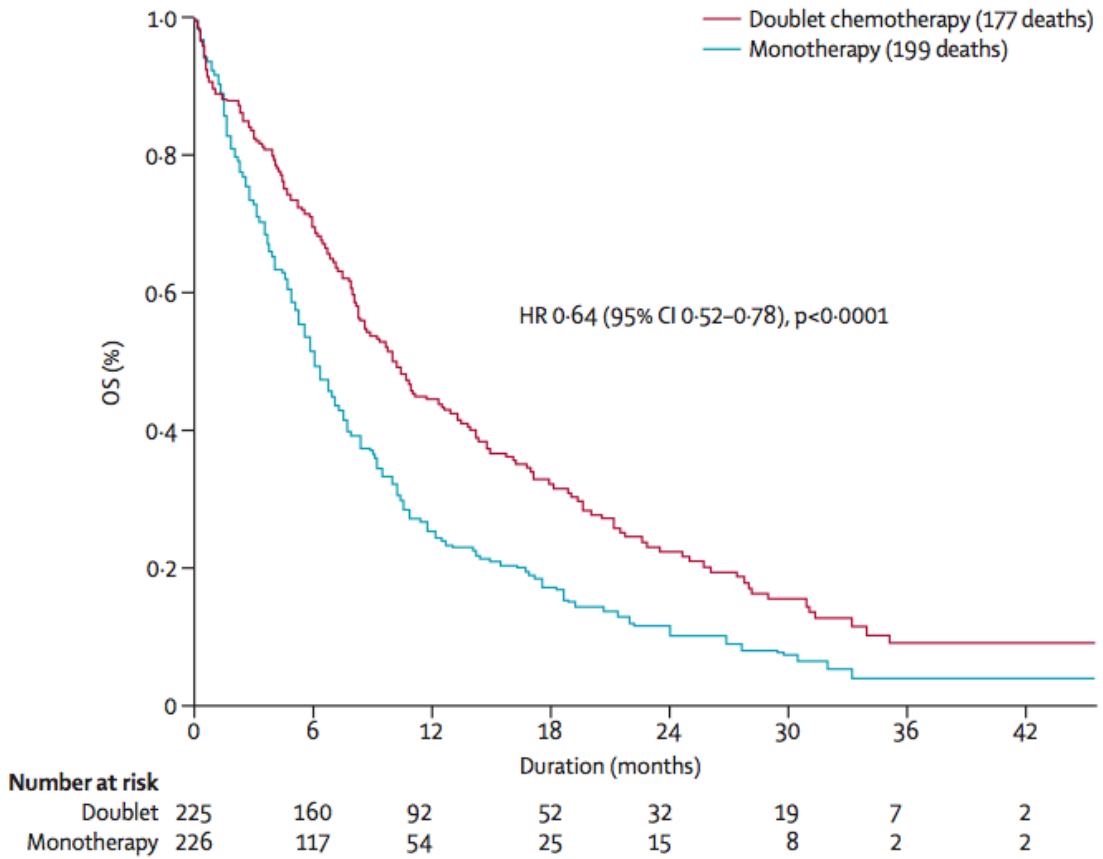
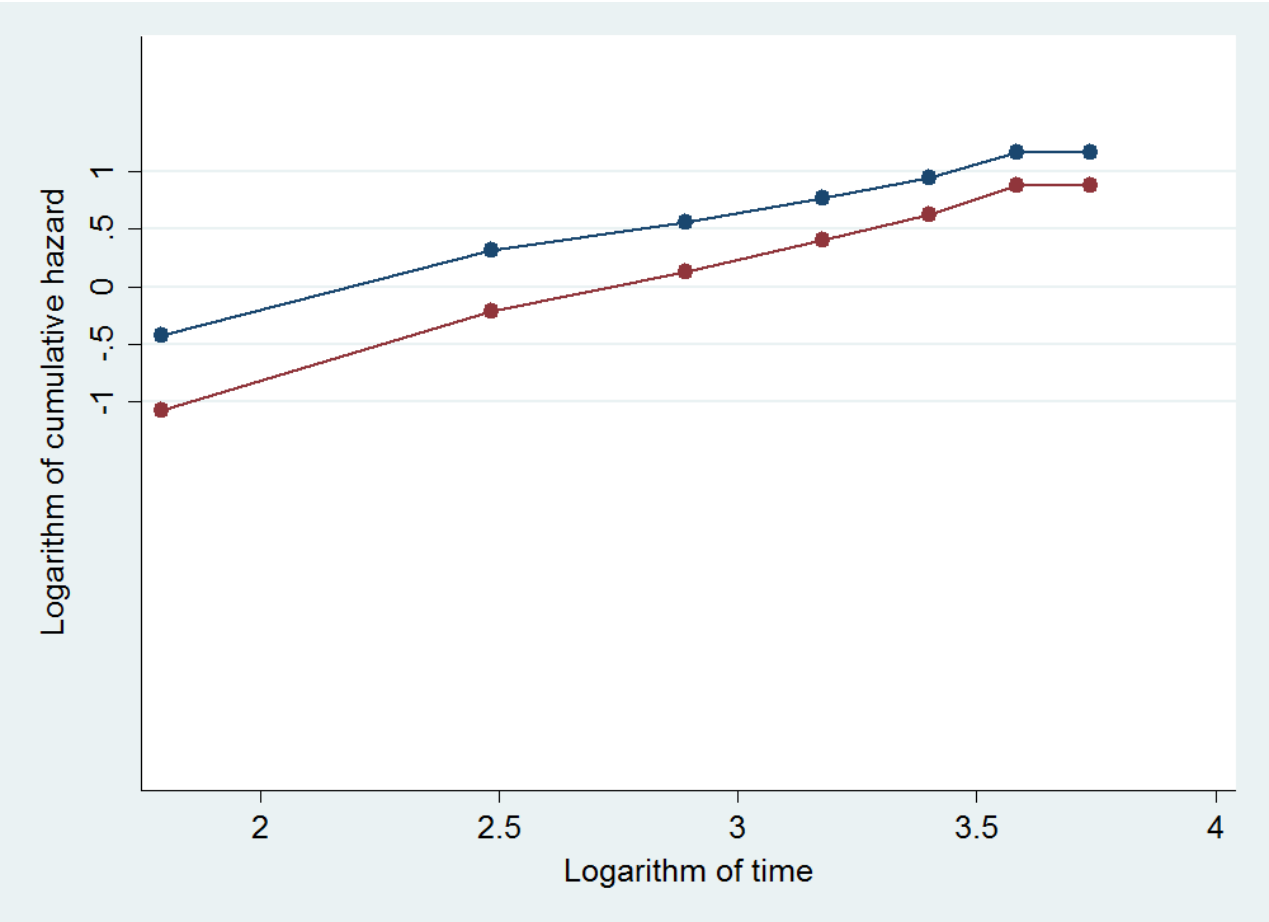


Quoix, E. *The Lancet*, 2011

PH assumption assessment



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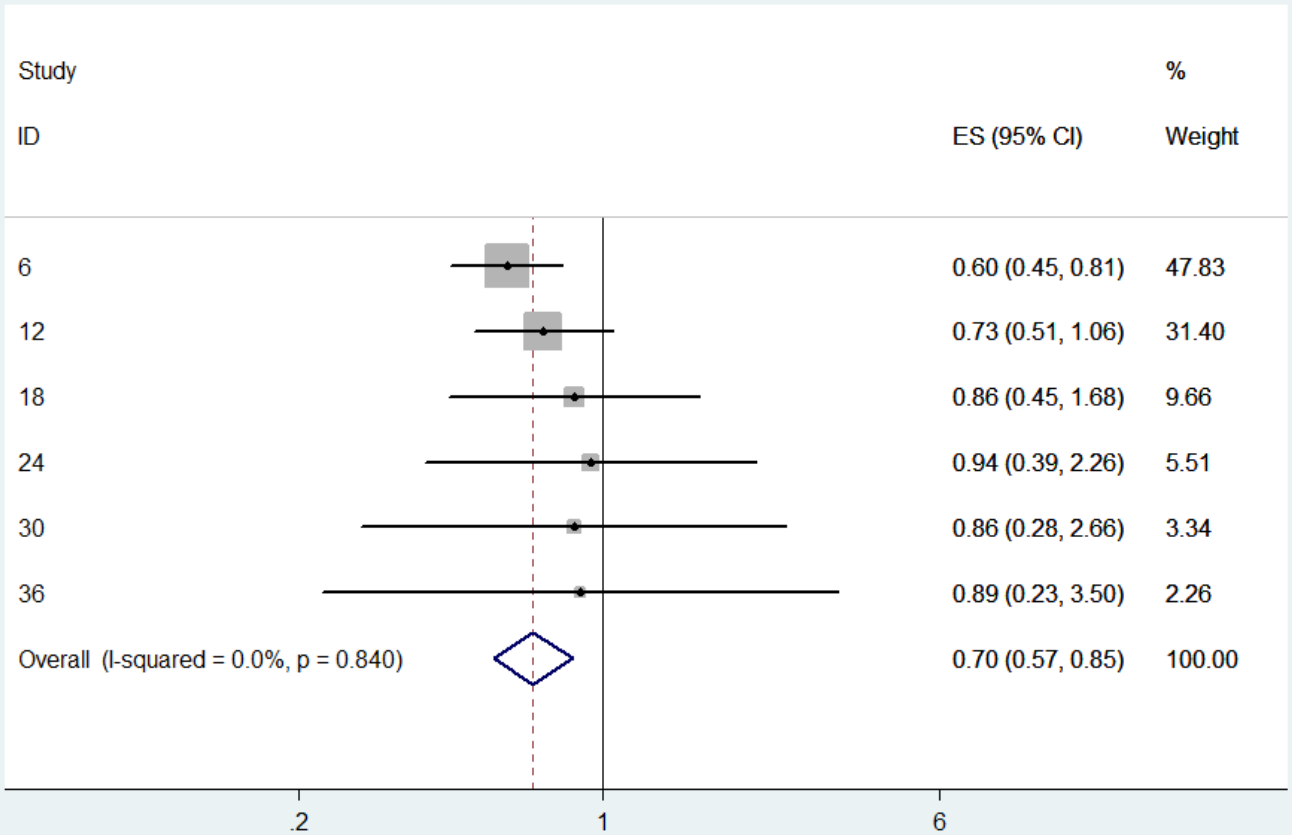

Quoix, E. *The Lancet*, 2011

PH assumption results

Table: Association between non-PH and study characteristics

	PH assumption violated		**Fisher's**
	No	Yes	**exact test**
Treatments			
Same treatment comparison	20 (100%)	0 (0%)	
Different treatment comparison	30 (71%)	12 (29%)	0.006
Primary endpoint			
OS	23 (92%)	2 (8%)	
PFS	27 (73%)	10 (27%)	0.101

Table: Comparison between the RMST results and the results reported by authors

Study	RMST results		Median Results			HR Results	
	RMST diff [a]	p-value test Z	Median (control)	Diff (HR)[b]	Diff (KM)[c]	HR	p-value
Wu	6.66	< 0.001	5.6	14.4	8.1	0.28	< 0.001
Solomon	6.13	< 0.001	7.0	8.56	3.9	0.45	< 0.001
Seto	5.13	< 0.001	9.7	8.26	6.3	0.54	0.002
Shaw	3.33	0.004	3.0	3.12	4.7	0.49	< 0.001
Barlesi	2.37	< 0.001	3.7	4.01	3.7	0.48	< 0.001
Lee	1.23	0.15	3.4	1.26	-0.1	0.73	0.04[§]
Jänne	0.82	0.61	5.2	1.30	4.2	0.80	0.21[§]
Reck	0.76	0.018	2.7	0.72	0.8	0.79	0.002
Belani	0.65	0.73	7.1	0.88	0.9	0.89	0.36

[a] Restricted Mean Survival Time difference (months)
[b] Median difference derived from HR (months)
[c] Median difference derived from KM curve (months)
[§] one-sided

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[§] one-sided

Pros and Cons

- **New!** Assess the PH assumption using aggregate data
- Conclusions are in line with the log-log plots and with the results reported by authors

- Data constrained by the quality of figures
- Assumption about the mechanism of censoring
- Only studies with patients at risk reported

Future research

- Compare the conclusions obtained with individual patient data (IPD) and with aggregate data
- Investigate how many time-points are needed

Thank you for your attention!

Joined work with:

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Eliana Rulli [2]

Valter Torri [2]

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2 Mario Negri Institute for Pharmacological Research

Appendix

Numbers at risk during a time interval are:

$$n^*_{j,i} = \frac{(n_{j,i-1} + n_{j,i}) \cdot s^*_{j,i-1}}{(s^*_{j,i-1} + s^*_{j,i})} \tag{4}$$

Number of events during a time interval is:

$$d^*_{j,i} = \frac{(n_{j,i-1} + n_{j,i}) \cdot (s^*_{j,i-1} - s^*_{j,i})}{(s^*_{j,i-1} + s^*_{j,i})} \tag{5}$$

Numbers censored during a time interval are:

$$c^*_{j,i} = \frac{2 \cdot (n_{j,i-1} \cdot s^*_{j,i} - n_{j,i} \cdot s^*_{j,i-1})}{(s^*_{j,i-1} + s^*_{j,i})} \tag{6}$$

Back to 7.

Appendix

$$log(HR)_i = \frac{(d^*_{2,i} - e^*_{2,i})}{v_i} \tag{7}$$

$$var(log(HR)_i) = \frac{1}{v_i} \tag{8}$$

where

$$e^*_{2,i} = (d^*_{2,i} + d^*_{1,i}) \cdot \frac{(n^*_{2,i})}{(n^*_{2,i} + n^*_{1,i})} \tag{9}$$

$$v_i = (d^*_{2,i} + d^*_{1,i}) \cdot \frac{n^*_{2,i} \cdot n^*_{1,i}}{(n^*_{2,i} + n^*_{1,i})^2} \tag{10}$$

Back to 8.

Appendix

The area under the curve for group j was estimated by:

$$\mu_j = \sum_{i=1}^{p} \mu_{j,i} = \sum_{i=1}^{p} \frac{(s^*_{j,i-1} + s^*_{j,i}) \cdot (t_i - t_{i-1})}{2} \qquad (11)$$

To estimate the variability of this quantity the formula reported by Klein was used:

$$V(\mu_j) = \sum_{i=1}^{p} \left[\int_{t_i}^{t^*} S(t)dt \right]^2 \cdot \frac{d_i}{n_i \cdot (n_i - d_i)} \qquad (12)$$

Back to 12.