Name of candidate:

Short Case 3 : Clinical studies and statistics

Ihr Patient ist vor einigen Jahren an einem follikulären Lymphom erkrankt und wurde im Rahmen der SAKK 35/03-Studie behandelt.

Der Patient hat aus der Zeitung vernommen, dass die Studie am Onkologenkongress 2015 in Chicago vorgestellt wurde. Er meldet sich deshalb bei Ihnen und möchte die Resultate und die möglichen Konsequenzen für seine Behandlung mit Ihnen diskutieren. Ihr Patient wurde damals in den kurzen Behandlungsarm randomisiert.

Auszug aus der Publikation in englischer Sprache beiliegend zur Vignette (Text und Statistik)

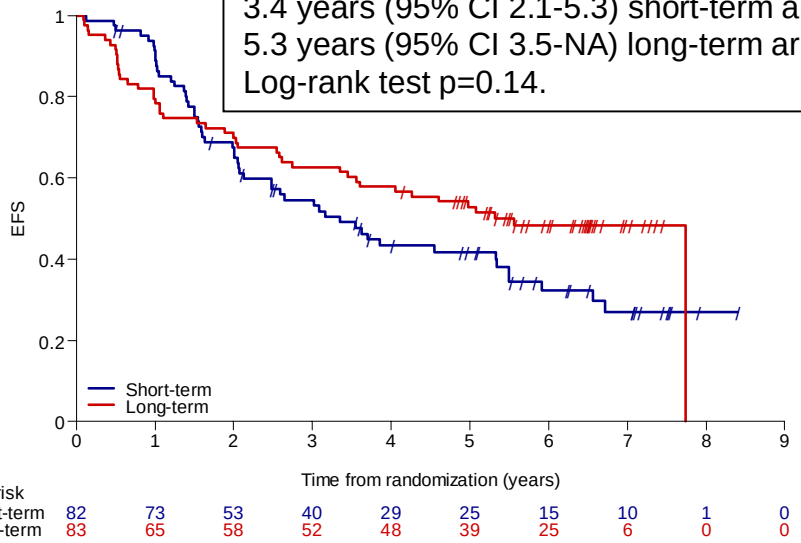
Study: Patients and Methods

Rituximab maintenance was shown to be effective in patients with follicular lymphoma. However, the optimal duration of maintenance treatment remains unknown

A total of 270 patients with either untreated, relapsed, stable or chemotherapy resistant follicular lymphoma were treated with 4 weekly doses of rituximab monotherapy (375 mg/m^2). Patients achieving at a least a partial response were randomized to receive maintenance with one infusion of rituximab every two months either on a short-term schedule (four administrations) or a long-term schedule (maximum of five years or until disease progression or unacceptable toxicity). The primary endpoint was event-free survival (EFS). Progression-free survival (PFS), overall survival (OS) and toxicity were secondary endpoints.

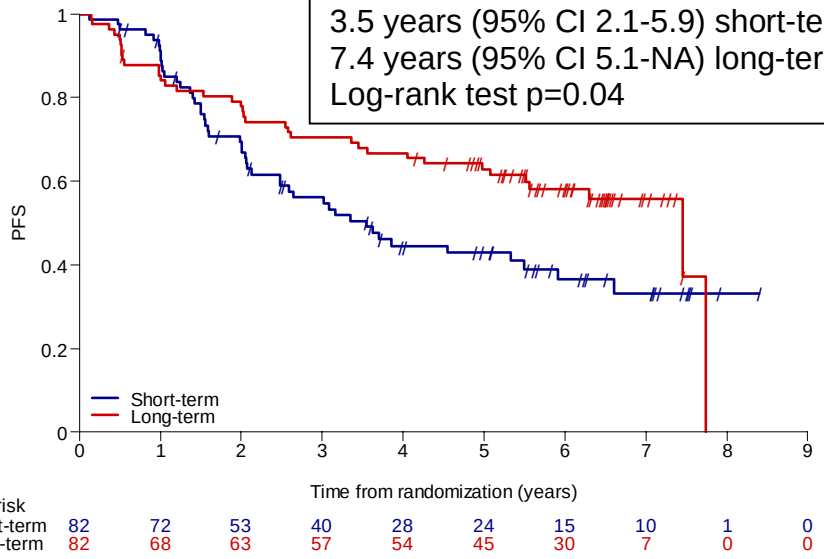
Name of candidate:

Median EFS
3.4 years (95% CI 2.1-5.3) short-term arm
5.3 years (95% CI 3.5-NA) long-term arm
Log-rank test p=0.14.



# at risk										
Short-term	82	73	53	40	29	25	15	10	1	0
Long-term	83	65	58	52	48	39	25	6	0	0

Median PFS
3.5 years (95% CI 2.1-5.9) short-term arm
7.4 years (95% CI 5.1-NA) long-term arm
Log-rank test p=0.04

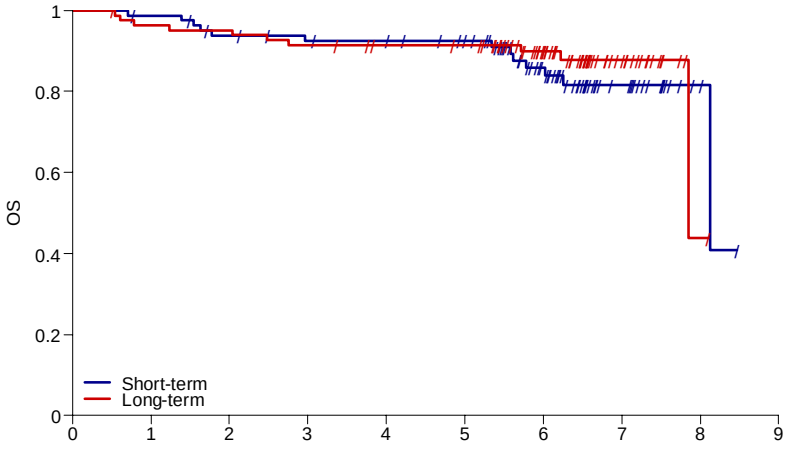


# at risk										
Short-term	82	72	53	40	28	24	15	10	1	0
Long-term	82	68	63	57	54	45	30	7	0	0

Statistical assumptions:

Based on a previous trial with short-term rituximab maintenance in follicular lymphoma.

Sample size calculation allowed detecting a median EFS increase with long-term maintenance from 2.5 to 4.5 years with 80% power and an overall two-sided type I error probability of 5%.



# at risk										
Short-term	82	80	74	71	70	66	45	18	3	0
Long-term	83	79	78	75	72	71	50	17	1	0

Name of candidate:

	Question / Task	Expected Answer	Answer given. One point for each correct answer.	Points reached
	Ask the candidate: - to summarize the study results - Is there a significant difference in the primary end point? - Significant difference in secondary end points?	- Randomized study - Primary endpoint: no significant difference - Secondary end points: significant difference for PFS but not for OS		……/3
	How do you explain EFS, PFS and OS to the patient?	PFS = Progression free survival is the time from randomization to relapse, progression or death from follicular lymphoma, whichever comes first. EFS = is a much broader term encompassing events such as distinct /particular toxicity of treatment, initiation of new treatments, death from any cause, secondary malignancies….. In the protocol of SAKK 35/03 EFS was defined as: Time from randomization to one of the following events: progressive disease or relapse, unacceptable toxicity, death from any cause, initiation of non-protocol anticancer treatment, secondary malignancy. OS = Overall survival is the time from randomization until death from any cause.		……/4

Name of candidate:

	Question / Task	Expected Answer	Answer given. One point for each correct answer.	Points reached
	Why was EFS chosen as the primary endpoint and not PFS?	Patients with FL have a long time to live. If treatment is not intended to improve survival but to prevent or delay distinct complications of the disease, all events related to the disease AND to the treatment have to be considered. e.g. infections due to treatment; cardiac dysfunction due to treatment. Such events could hamper the patient more than the slow growing FL.		……/4
	The separation of the curves in favor of the long-term treatment was expected. How could one explain the difference in the first year of treatment, when treatment in both arms was still identical?	More disease progression and relapse in long-term arm possibly due to imbalance of adverse prognostic factors in the long-term group.		……./2
	What is the null-hypothesis in this study	EFS in long-arm treatment does not increase above 4.5 years assuming EFS in short-arm will result in median EFS of 2.5 years.		……/1

Name of candidate:

	Question / Task	Expected Answer	Answer given. One point for each correct answer.	Points reached
	Explain the expression of "the study has a power of 80%" Explain "type I error"	A test's power is the probability of correctly rejecting the null hypothesis when it is false. 80% ability of a test to detect an effect, if the effect actually exists. In our setting: 80% probability that prolonged treatment with rituximab will increase median EFS from 2,5 to 4.5 (and more) years. 1- β-error (false negative rate) = power Type I error = α (false positive rate) Type II error = β (false negative rate)		……/2
	Assume EFS would have been significantly different in favor of the long-term treatment. On which statistical (and ethical) ground one could opt not to treat up to 5 years?	- No difference in OS. - Cost-effectiveness could be an issue.		…../1

Name of candidate:

	Question / Task	Expected Answer	Answer given. One point for each correct answer.	Points reached
	Topics of examiners choice	Questions:		……/3
Total points achieved				……/20

A minimum of 13 points (65% of 20 points) must be achieved to pass the exam.

Examiners: Name:…… Name:……