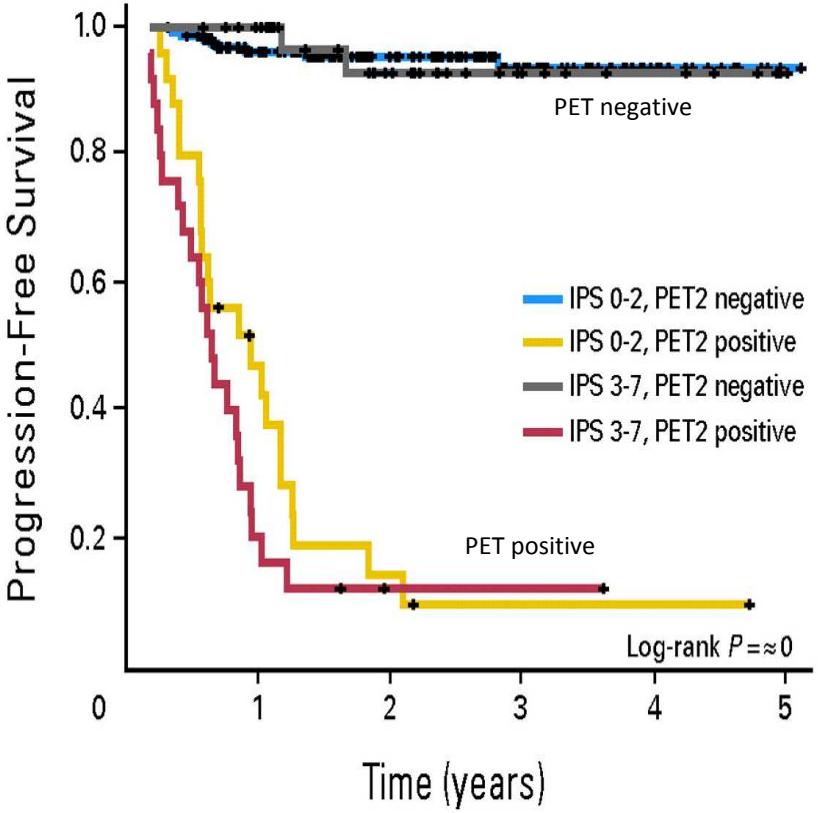
What did we learn from the H10 trial?

M. André

The H10 EORTC/LYSA/FIL randomized Intergroup trial on early FDG-PET scan guided treatment adaptation versus standard combined modality treatment in patients with supradiaphragmatic stage I/II Hodgkin's lymphoma.



Gallamini, A. et al. J Clin Oncol, 2007

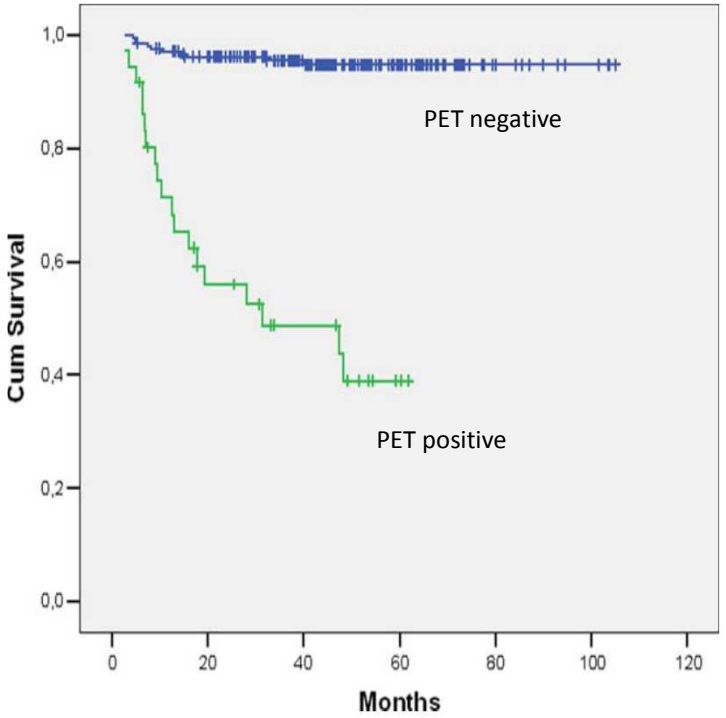
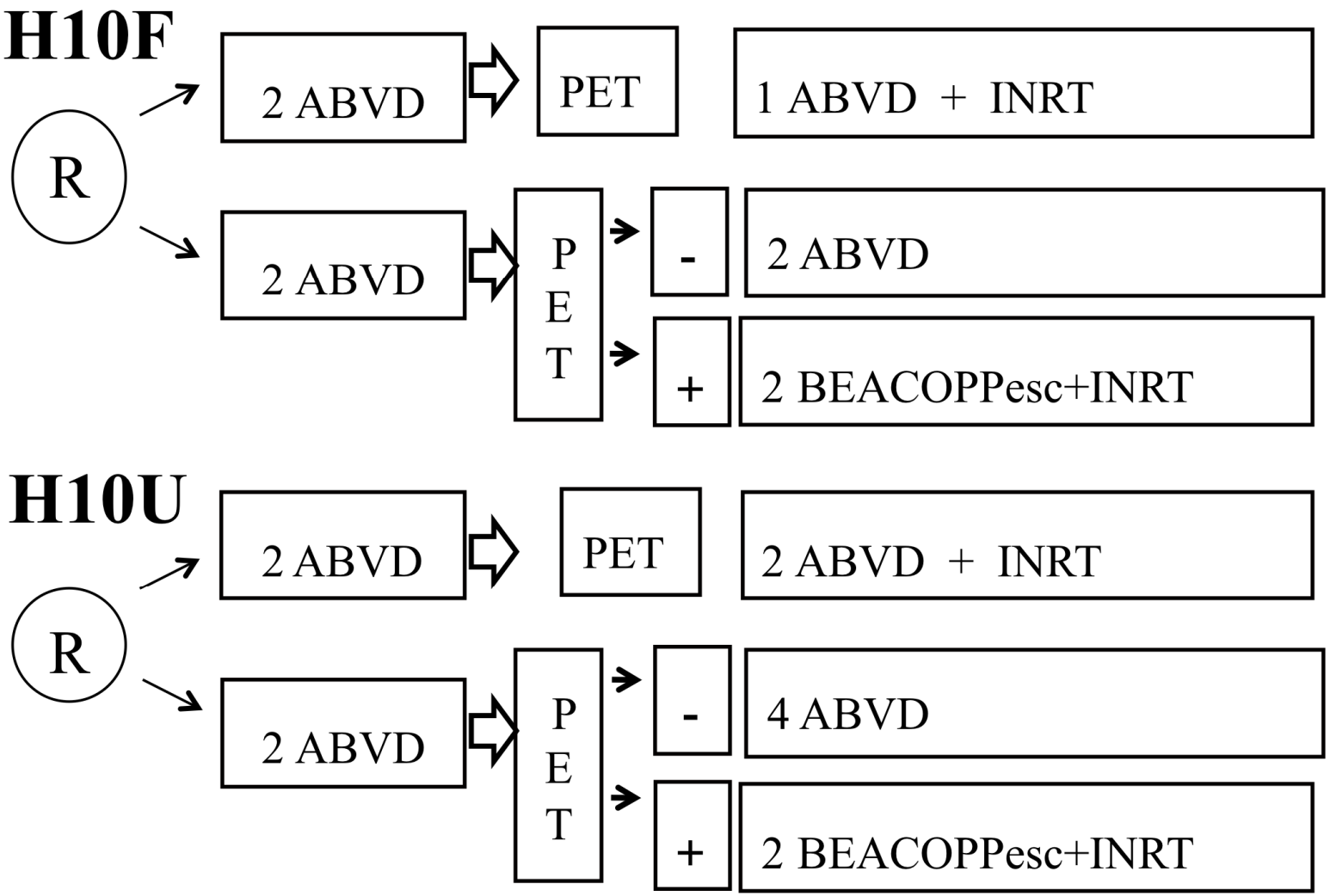


Figure 2. Progression-free survival according to interim-PET results using IHP criteria. Upper line negative interim-PET, lower line positive interim-PET. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Rigacci L. et al. Am. J. Hematol, 2015


H10F
R
2 ABVD
PET
1 ABVD + INRT
2 ABVD
P
E
T
-
2 ABVD
+
2 BEACOPPesc+INRT
H10U
R
2 ABVD
PET
2 ABVD + INRT
2 ABVD
P
E
T
-
4 ABVD
+
2 BEACOPPesc+INRT

Total randomized n=1950 (including n=30 not eligible)		
	Standard	Experimental
Favorable	375	379
Unfavorable	597	599

EARLY PET SCAN

- *25 patients did not start or complete the first 2 cycles ABVD or did not perform early PET scan*
- *505 early PET negative patients randomized after the safety amendment of 2010 were treated according to the standard arm irrespective of the randomized arm (not reported in the present presentation)*

Early PET negative		
	Standard (ABVD+INRT)	Experimental (ABVD only)
Favorable	227	238
Unfavorable	292	302

Early PET positive	
Standard (ABVD+INRT)	Experimental (BEACOPPesc +INRT)
192	169

Main messages H10

- Early FDG-PET helps to define risk groups
- Early PET positive: treatment adaptation (BEACOPPesc) improves disease control
- Early PET negative patients: non-inferiority of no radiotherapy could not be demonstrated
- PET adapted strategy is warranted

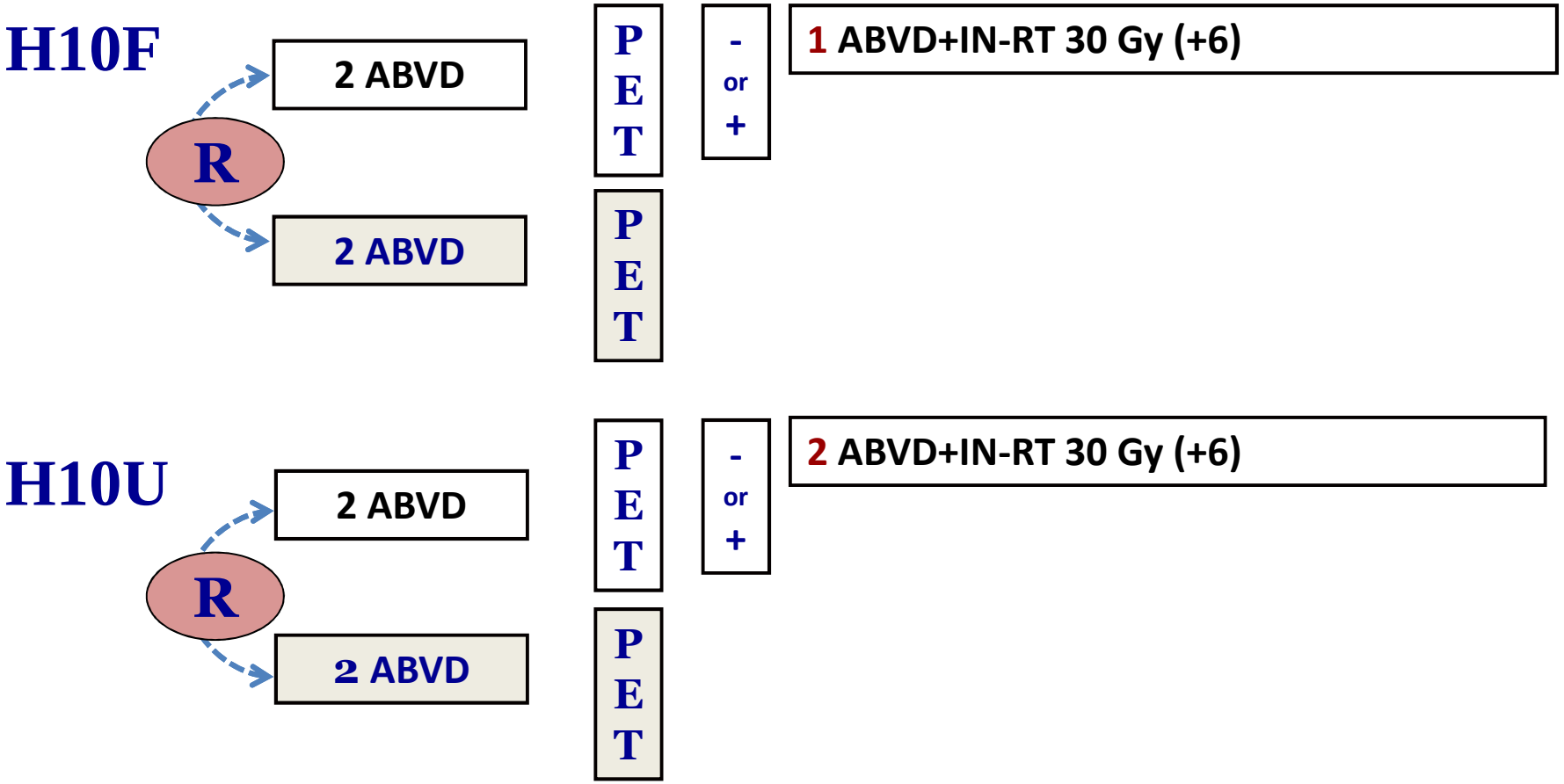
Preview

- FDG-PET
- PET positive
- PET negative

PET in H10

- 96% had a baseline PET
- IHP criteria
- Central review of 75% of patients
- 93% concordance with local assesment
- Cohen's kappa=0.78, 95%CI=0.74 to 0.82
- Early PET positivity was reported in 18.8%
  - 13.0% in F
  - 22.4% in U

H10 Study design

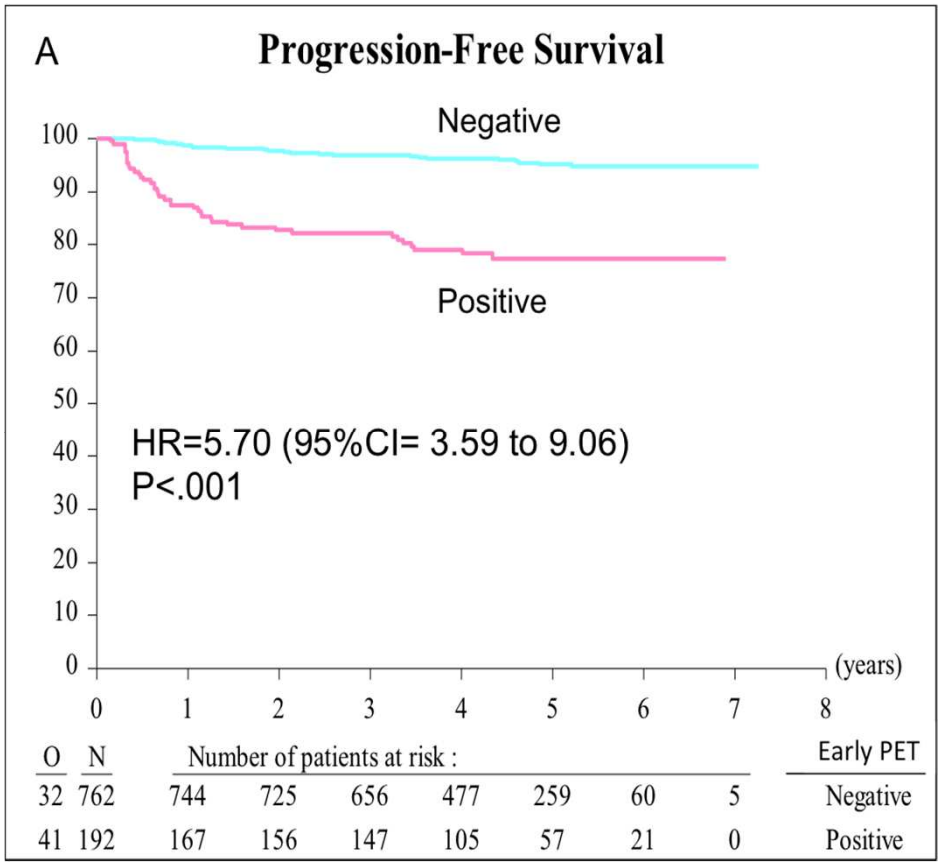


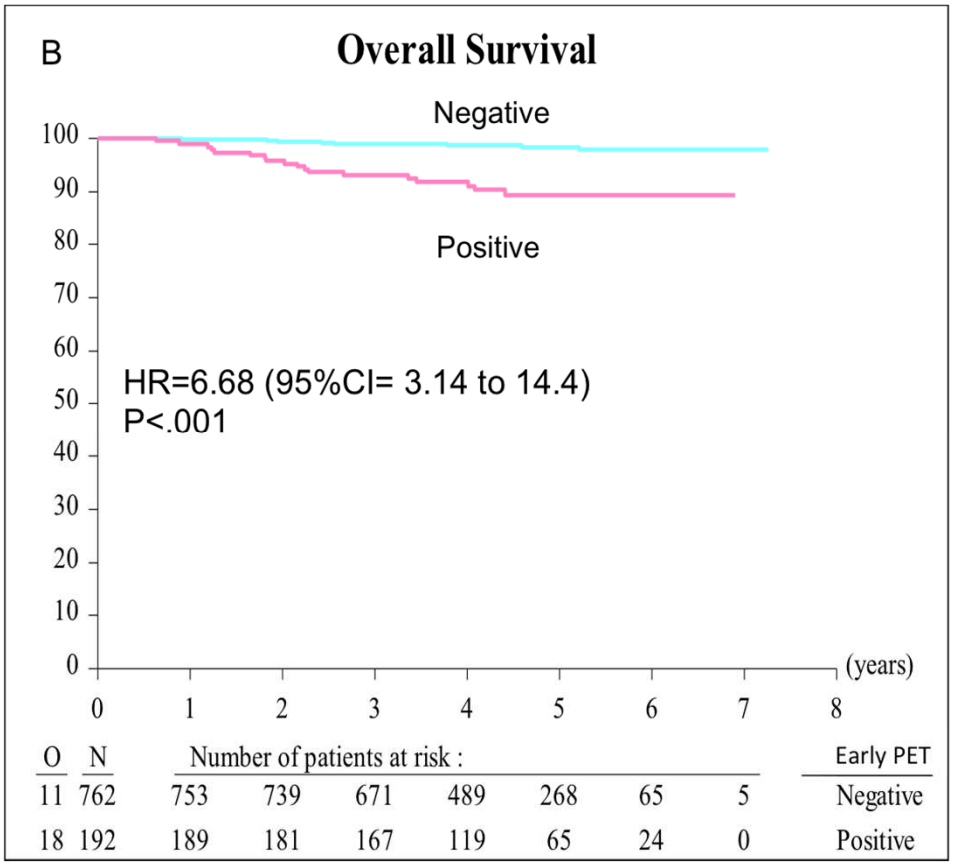
EORTC The future of cancer therapy

Lysa THE LYMPHOMA STUDY ASSOCIATION

FONDAZIONE FIL ITALIANA LINFOMI

H10 : 954 randomised to ABVD + Radiotherapy,
Early PET after 2 ABVD
no treatment modification according to early PET

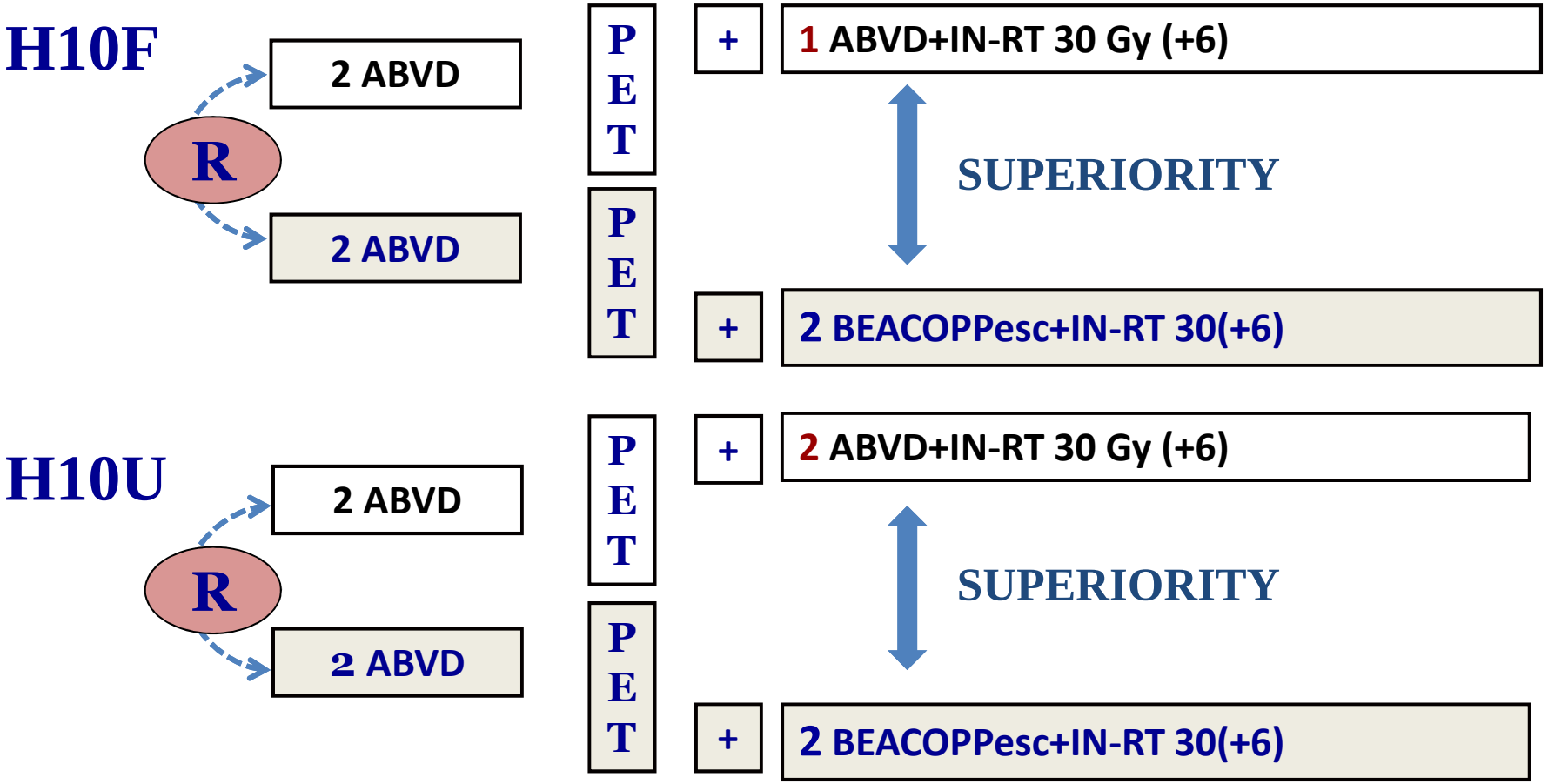




Preview

- FDG-PET
- PET positive
- PET negative

H10 Study design



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Early PET positive	
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192	169

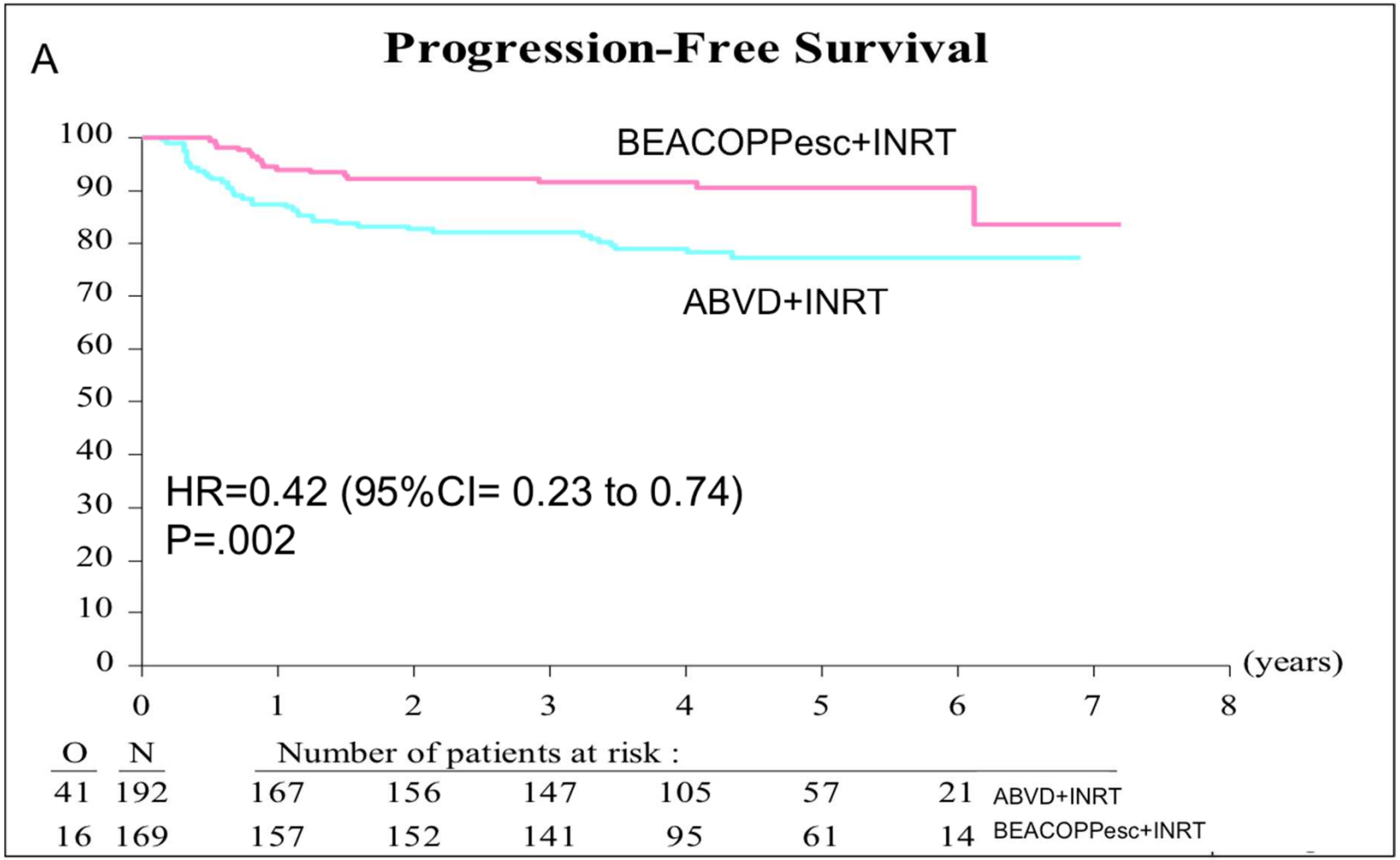
clinical characteristics N=361

	Std ABVD+RT N=192 N (%)	Exp BEACOPPesc+RT N=169 N (%)
Sex		
Male:Female ratio	51 : 49	56 : 44
Age years		
Median (range)	30.0 (15-66)	30.0 (15-70)
Age >60	9 (4.7)	11(6.5)
Treatment group		
Unfavorable	138 (71.9)	126 (74.5)
B-symptoms	67 (34.9)	63 (37.3)
Ann Arbor		
Stage II	144 (75.0)	136 (80.5)
Number of nodal areas		
Median (range)	2.0 (1-5)	2.0 (1-5)
Bulky mediastinum MT ratio>=0.35	71 (37.0)	69 (40.8)

PET+ group: ABVD *vs.* BEACOPPesc
Progression-free survival (intention-to-treat)

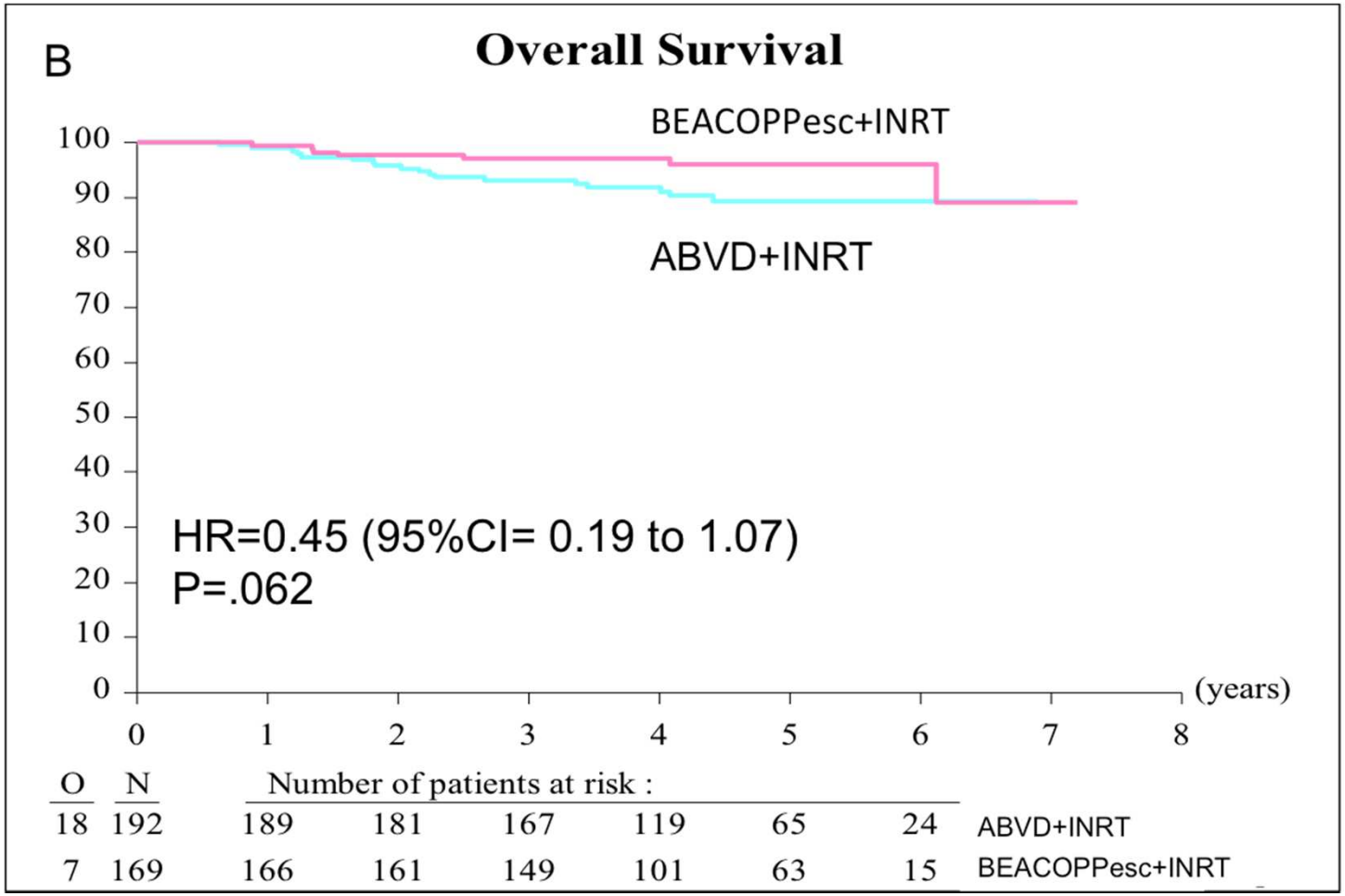
	Std. ABVD+RT N=192	Exp. BEACOPPesc+RT N=169
	N (%)	N (%)
Progression/relapse	36 (18.8)	13 (7.7)
Death	5 (2.6)	3 (1.8)
PD/relapse or death, whichever first	41 (21.4)	16 (9.5)

H10: PET positive



HR: Hazard Ratio BEACOPPesc *vs.* ABVD

H10: PET positive

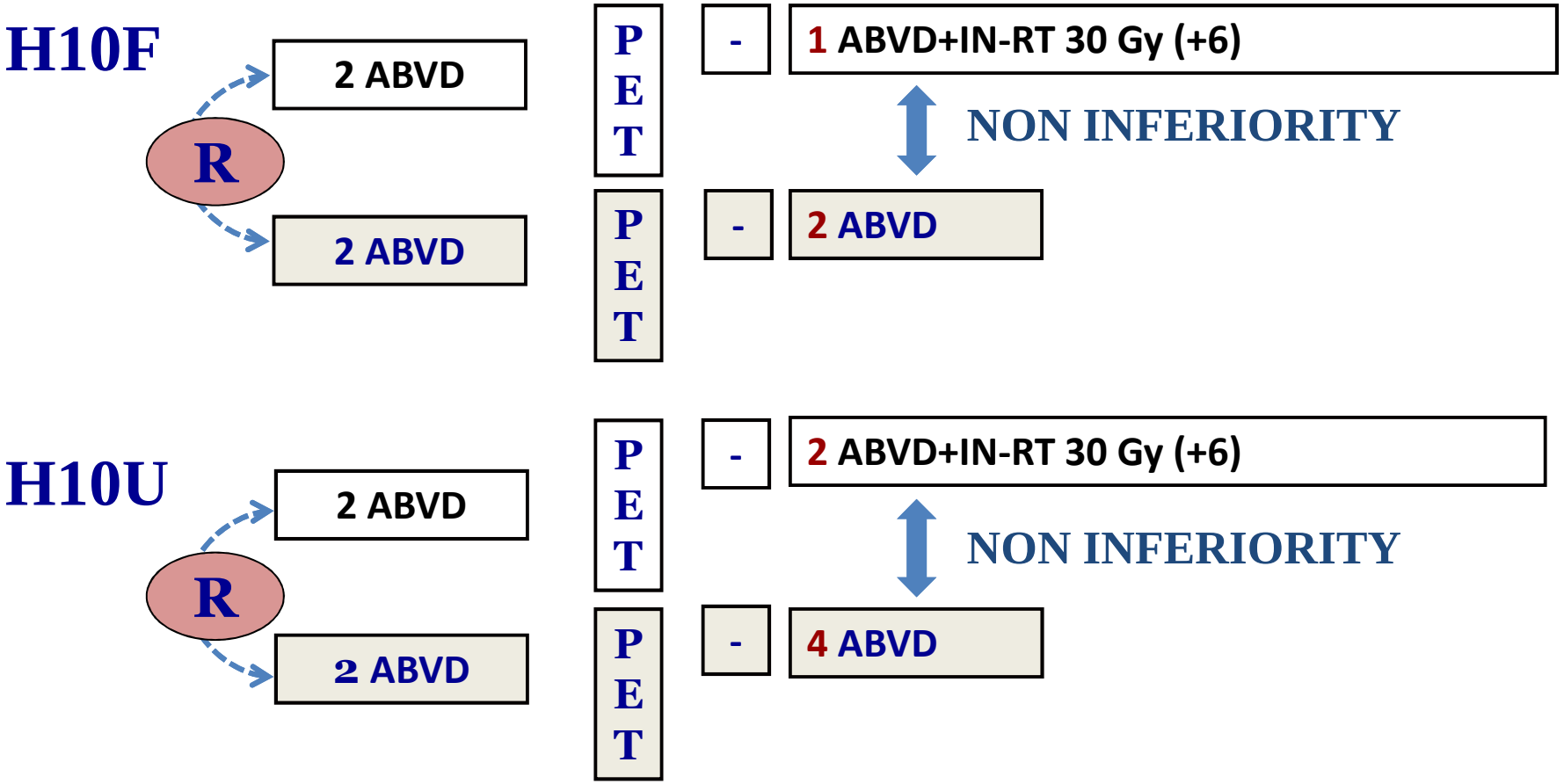


HR: Hazard Ratio BEACOPPesc *vs.* ABVD

Preview

- FDG-PET
- PET positive
- PET negative

H10 Study design



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Interim Analysis & IDMC conclusions (2010)

Based on the IA results, it is ***unlikely*** that the primary objective of the trial will be met, so:

- *Unlikely that we could show the non-inferiority of the experimental arm*

PET2 negative: futility analysis

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

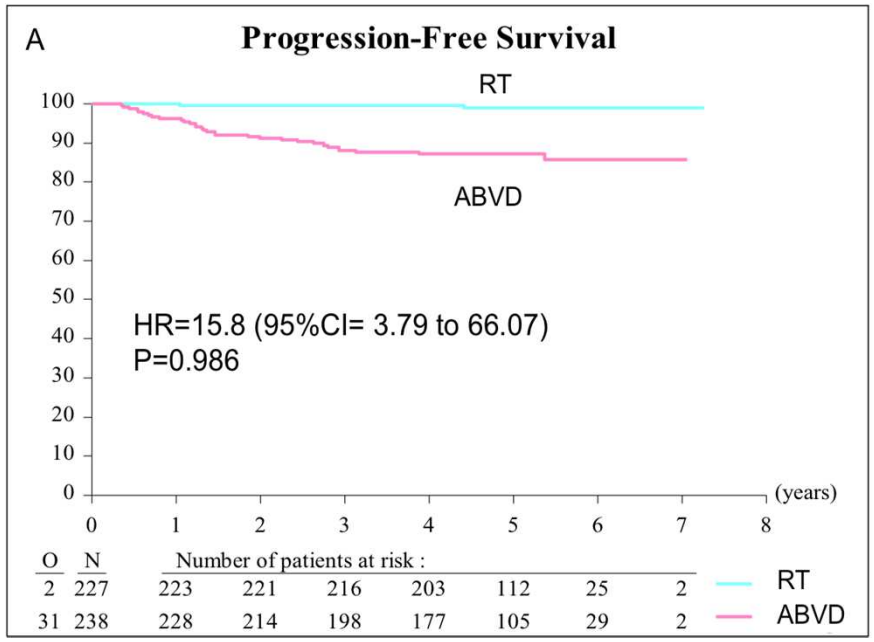
Omitting Radiotherapy in Early Positron Emission Tomography–Negative Stage I/II Hodgkin Lymphoma Is Associated With an Increased Risk of Early Relapse: Clinical Results of the Preplanned Interim Analysis of the Randomized EORTC/LYSA/FIL H10 Trial

John M.M. Raemaekers, Marc P.E. André, Massimo Federico, Theodore Girinsky, Reman Oumedaly,

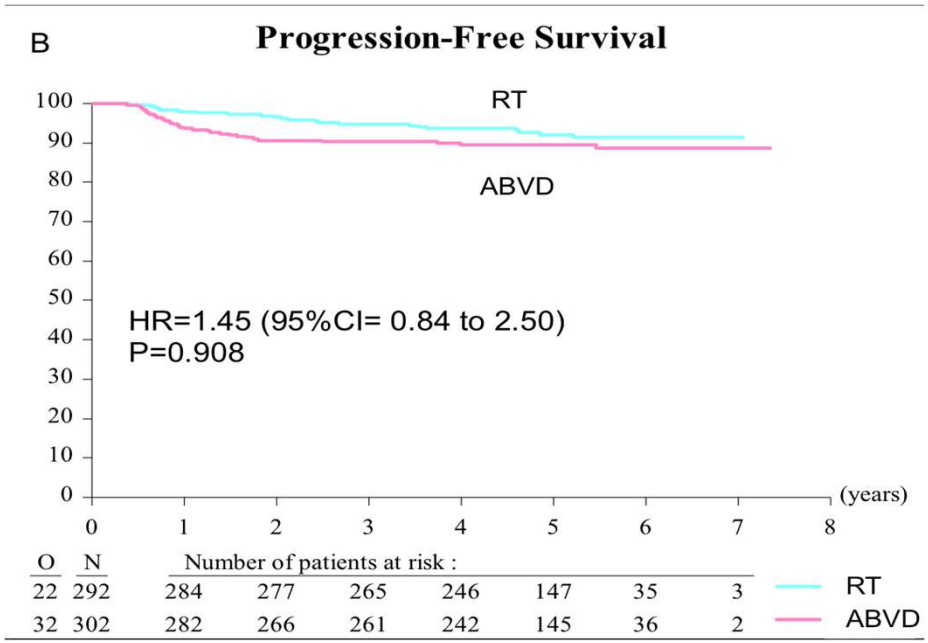
PET- group: ABVD+RT vs ABVD only
Progression-free survival (intention-to-treat)

	F ABVD+RT N=227	F ABVD only N=238	U ABVD+RT N=292	U ABVD only N=302
	N (%)	N (%)	N (%)	N (%)
Progression/relapse	2 (0.9)	30 (12.6)	16 (5.5)	30 (9.9)
Death	0 (0.0)	1 (0.4)	6 (2.1)	2 (0.7)
PD/relapse or death,	2 (0.9)	31 (13.0)	22 (7.5)	32(10.6)

favorable group



unfavorable group

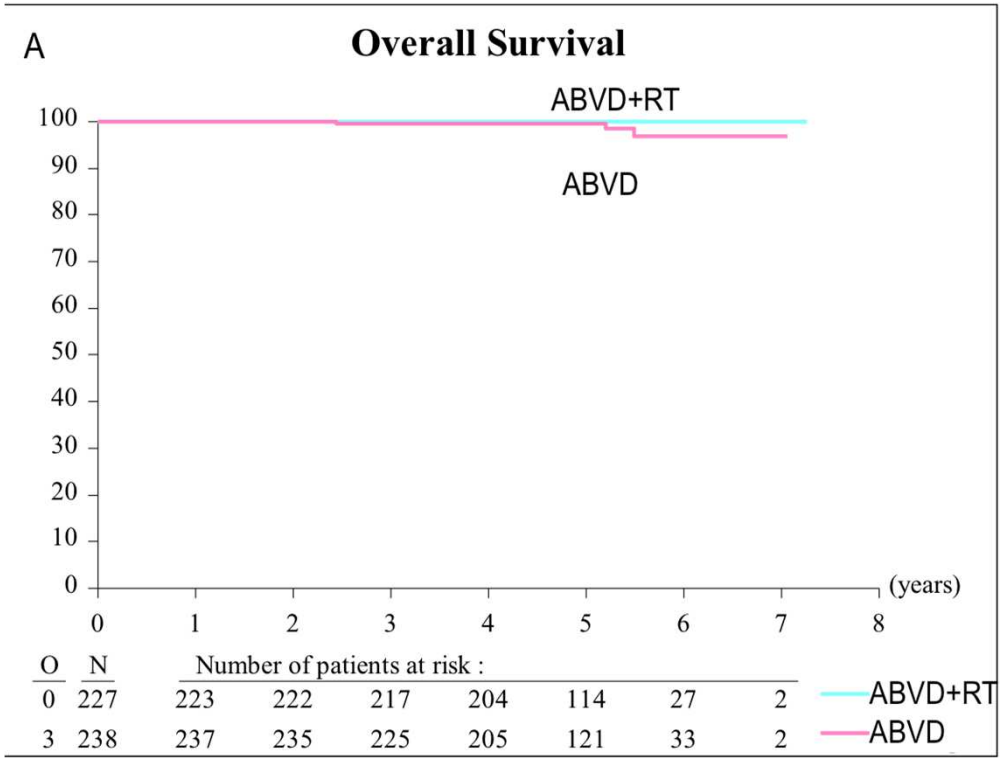


The final result of H10 confirmed the published results of the interim analysis:
Non inferiority could not be demonstrated.

Non-inferiority is concluded if the upper bound of the 95% confidence interval for the estimated hazard ratio does not exceed the non-inferiority margin.

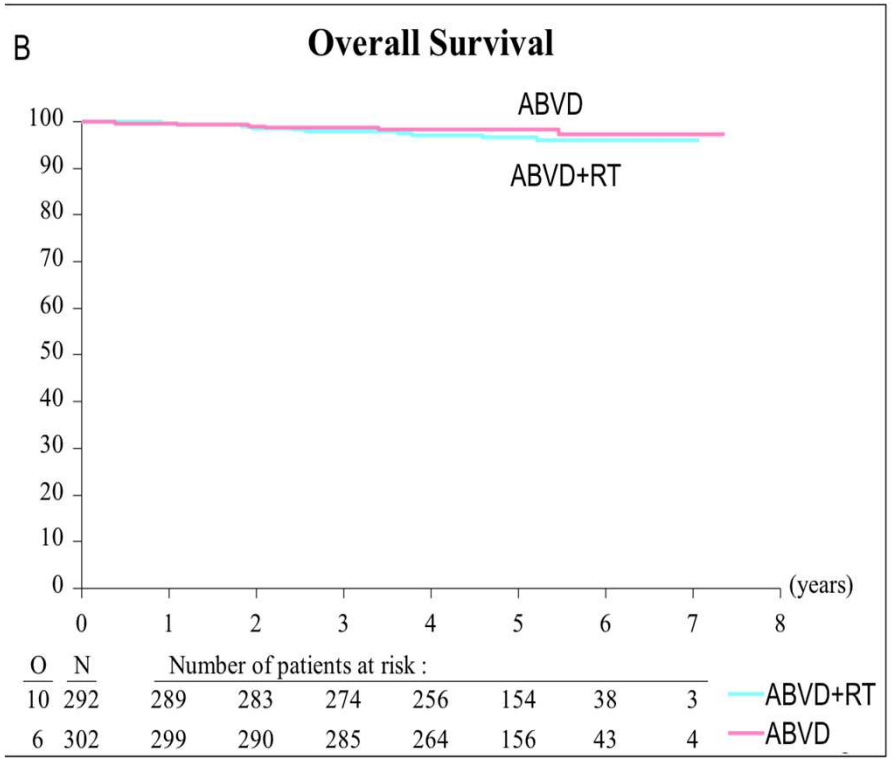
F group: HR < 3.2
U group: HR < 2.1 (upper bound is 2.5)

Favorable



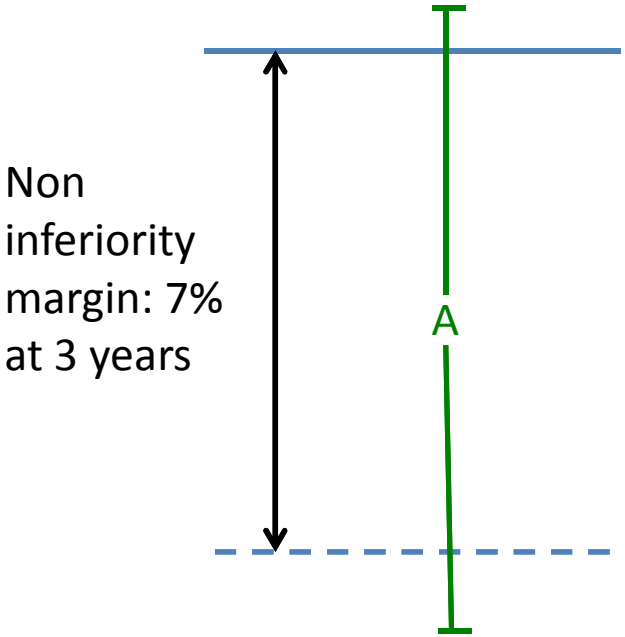
OS rates at 5 years were similar; 100.0% vs 99.6% in the ABVD+RT and ABVD arm

Unfavorable



OS rates at 5 years were similar; 96.2% vs 98.1 % in the ABVD +RT and ABVD arm

RAPID

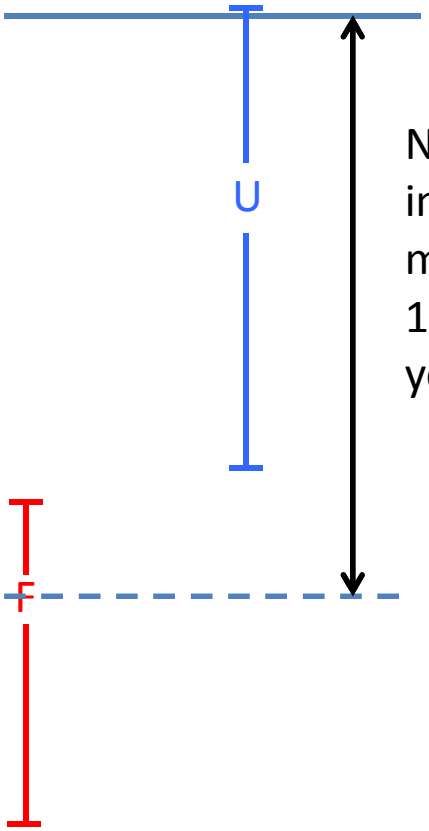


PFS standard arm

PFS experimental arm

A = -3.8 (95% CI:-8.8 to 1.3)

H10



F = -11.9 (95% CI:-16.9 to -8.2)

U = -2.5 (95% CI:-6.6 to 0.5)

	PET NEGATIVE N=1059				PET POSITIVE N=361	
	Favorable N=465		Unfavorable N=594		Favorable and Unfavorable	
	ABVD +INRT N=227	ABVD only N=238	ABVD +INRT N=292	ABVD only N=302	ABVD +INRT N=192	BEACOPPesc +INRT N=169
	N	N	N	N	N	N
Second malignancies	3	7	10	10	5	4
Deaths	0	3	10	6	18	7
Progression/relapse	0	0	3	3	11	3
Toxicity of protocol treatment	0	0	0	1	0	1
Toxicity of second line treatment	0	1	1	0	3	0
Cardio-vascular event	0	0	2	0	0	0
Second malignancy	0	2	2	1	2	1
Other/unknown	0	0	2	1	2	2

Median Fup: PET negative: 5 years, PET positive: 4.5 years.

Review

- Early PET defines 2 risk populations in stage I-II

- Early PET positive:
  - BEACOPP improves PFS
  - OS is of borderline significance

- Early PET negative:
  - H10 failed to demonstrate non inferiority of PFS in no RT arm
  - In U group: the benefit of CMT appears less clinically relevant and challenges the use of radiotherapy.
  - Outcome (OS) w/wo RT is excellent
  - Impact on late toxicities is unknown

Conclusions

- Early FDG-PET is a tool to define a risk adapted strategy and should become SOC
- Early PET positive: early intensification (BEACOPPesc) should be considered as the best treatment option.
- Early PET negative patients: no radiotherapy is an option at the price of some reduction of disease control (U group)
- PET adapted strategy is warranted for early stage HL

Study coordination team

Study coordinators	
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M. André, O. Reman	**LYSA**
M. Federico, E. Brusamolino†	**FIL**
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M. Meignan	**LYSA**
A. Versari	**FIL**
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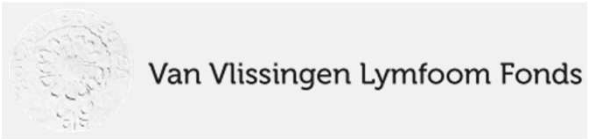
C. Fortpied	**EORTC**
Clinical Research Physician	
S. Marréaud, V. Fiaccadori	**EORTC**
Central data management	
T. Raveloarivahy	**EORTC**
A. Zarour	**LYSA**
M. Bellei, S. Badiali, A. Dondi	**FIL**

Acknowledgements



- Back-up slide

The preset non-inferiority margins were defined in terms of hazard ratios (HRs), according to standard statistical methodology for time-to-event endpoints. They were calculated from the clinically accepted decrease of 10% in PFS rate at 5 years, assuming exponentially distributed survival times. However, one may question whether the proportional hazard assumption is valid in this particular setting and therefore whether the hazard ratio is an adequate measure to compare two treatments. Violation of the proportional hazard assumption explains why we obtained an apparently paradoxical result in the U group, as non-inferiority could not be concluded while the observed difference in PFS rate at 5 years was not clinically relevant (2.5%).