

ESMO PRECEPTORSHIP
ON LYMPHOMA

27-28 NOVEMBER 2015
LUGANO, SWITZERLAND

Early stage Hodgkin lymphoma

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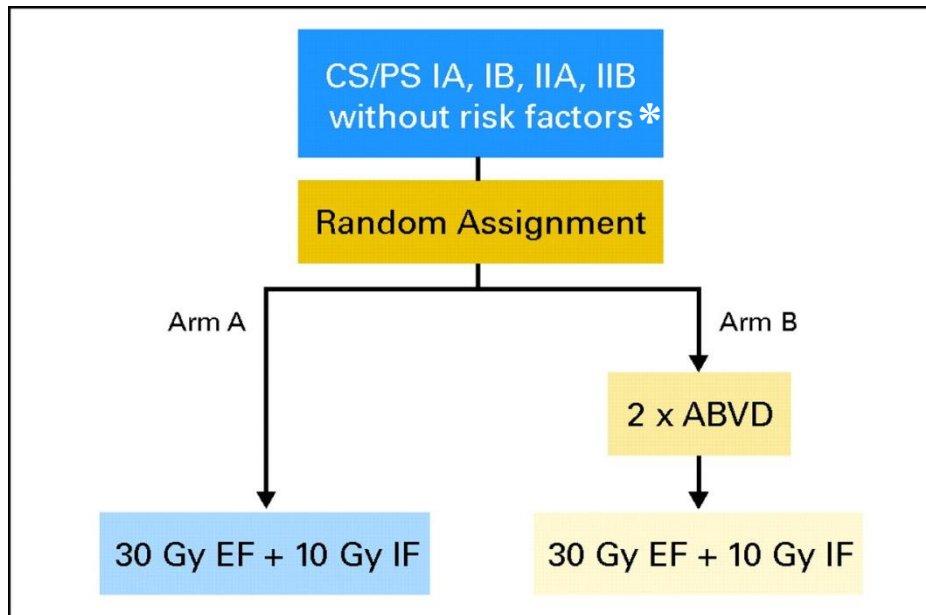


What are the challenges of early stage HL?

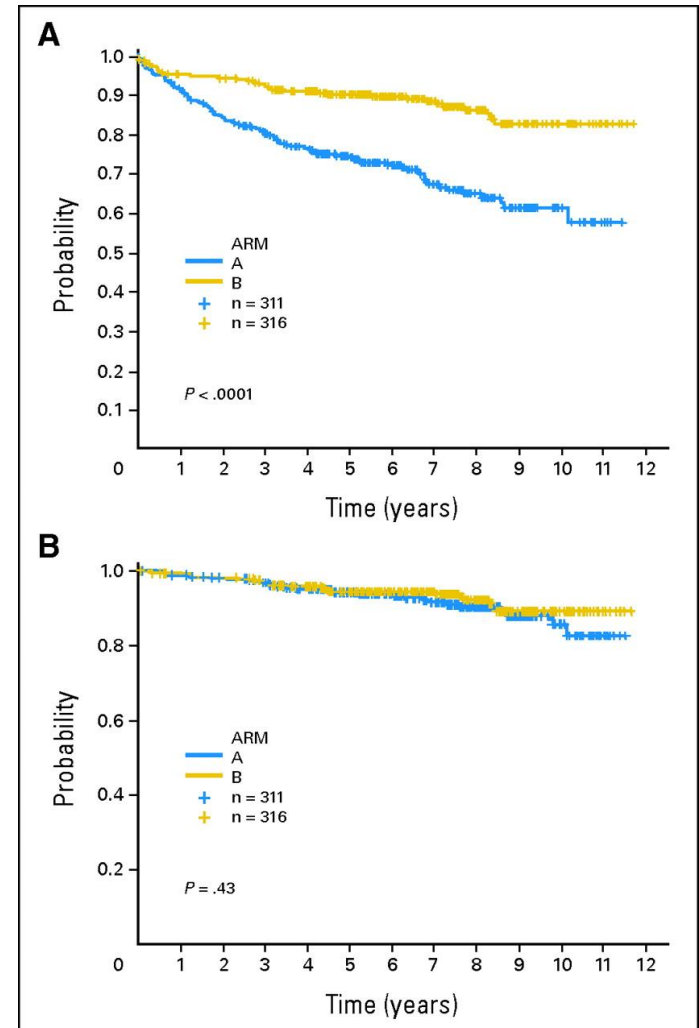
- ▶ The large majority of patients are cured although not 100%
- ▶ Late effects of treatment are a serious concern and include second cancers, cardiovascular disease, chronic fatigue, muscle weakness, psychosocial problems etc.
- ▶ Radiotherapy is probably the dominant cause of the late treatment-related morbidity and mortality seen today in survivors of HL treated 15-50 years ago
 - ▶ Since then, both radiotherapy doses and field sizes have been reduced dramatically along with fundamental improvements in radiotherapy techniques
- ▶ But chemotherapy also has late effects, serious and potentially fatal:
 - ▶ Cardiovascular disease, chronic muscle weakness and fatigue (dose-dependent effects of doxorubicin)
 - ▶ Pulmonary disease (bleomycin)



HD7 trial for early favorable HL (FFTF)

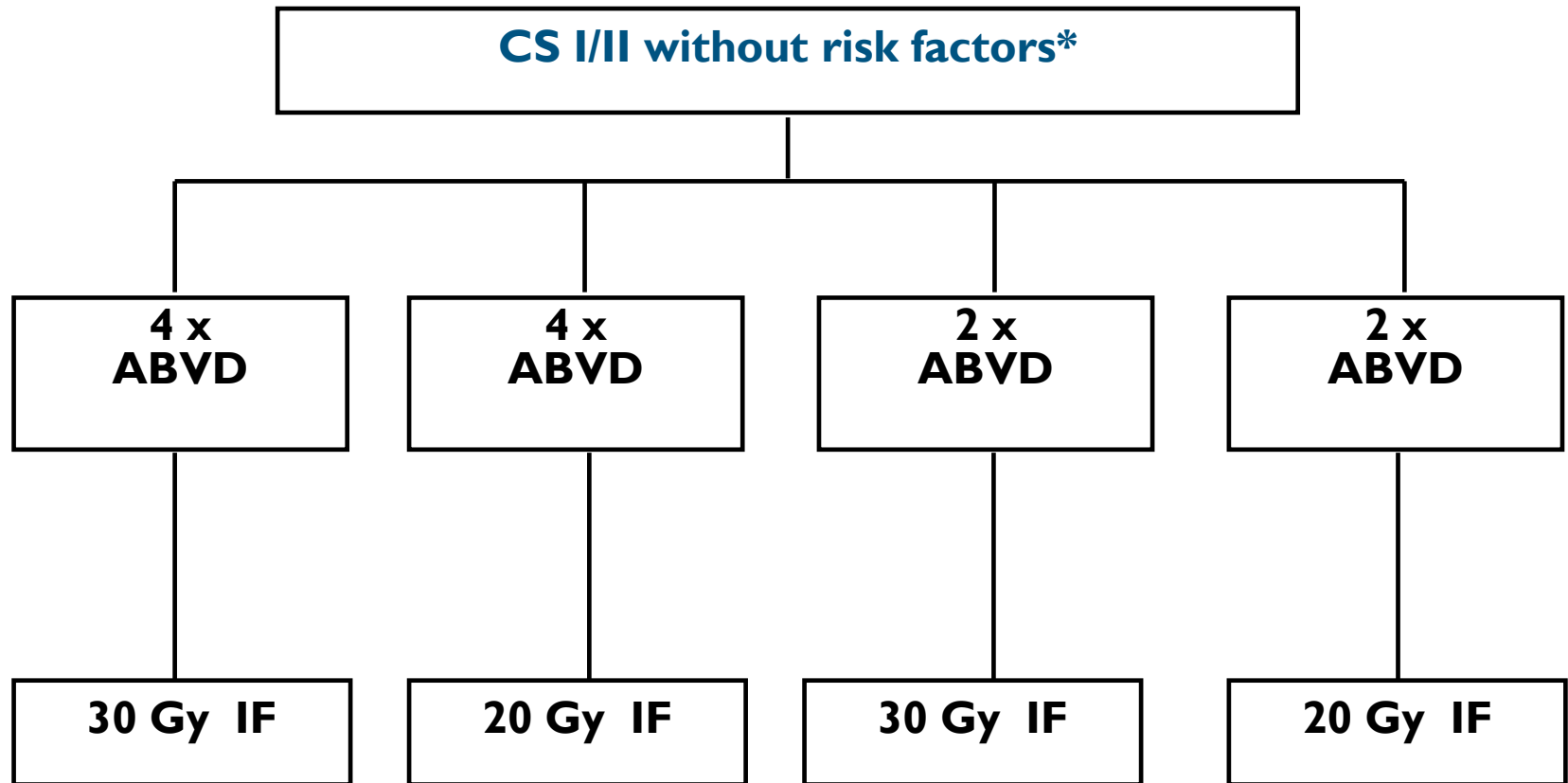


***Large mediastinal mass; extranodal disease; high ERS; 3 or more areas involved**



HD10 trial

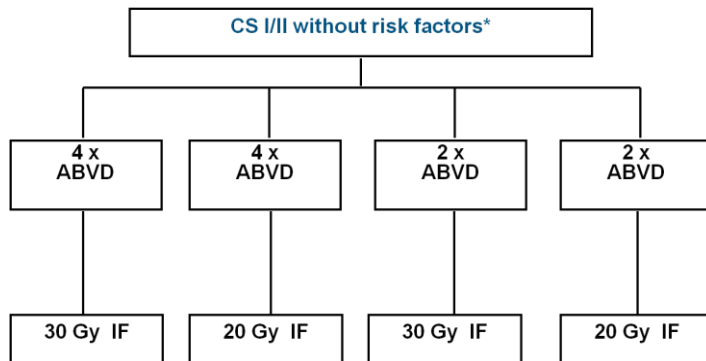
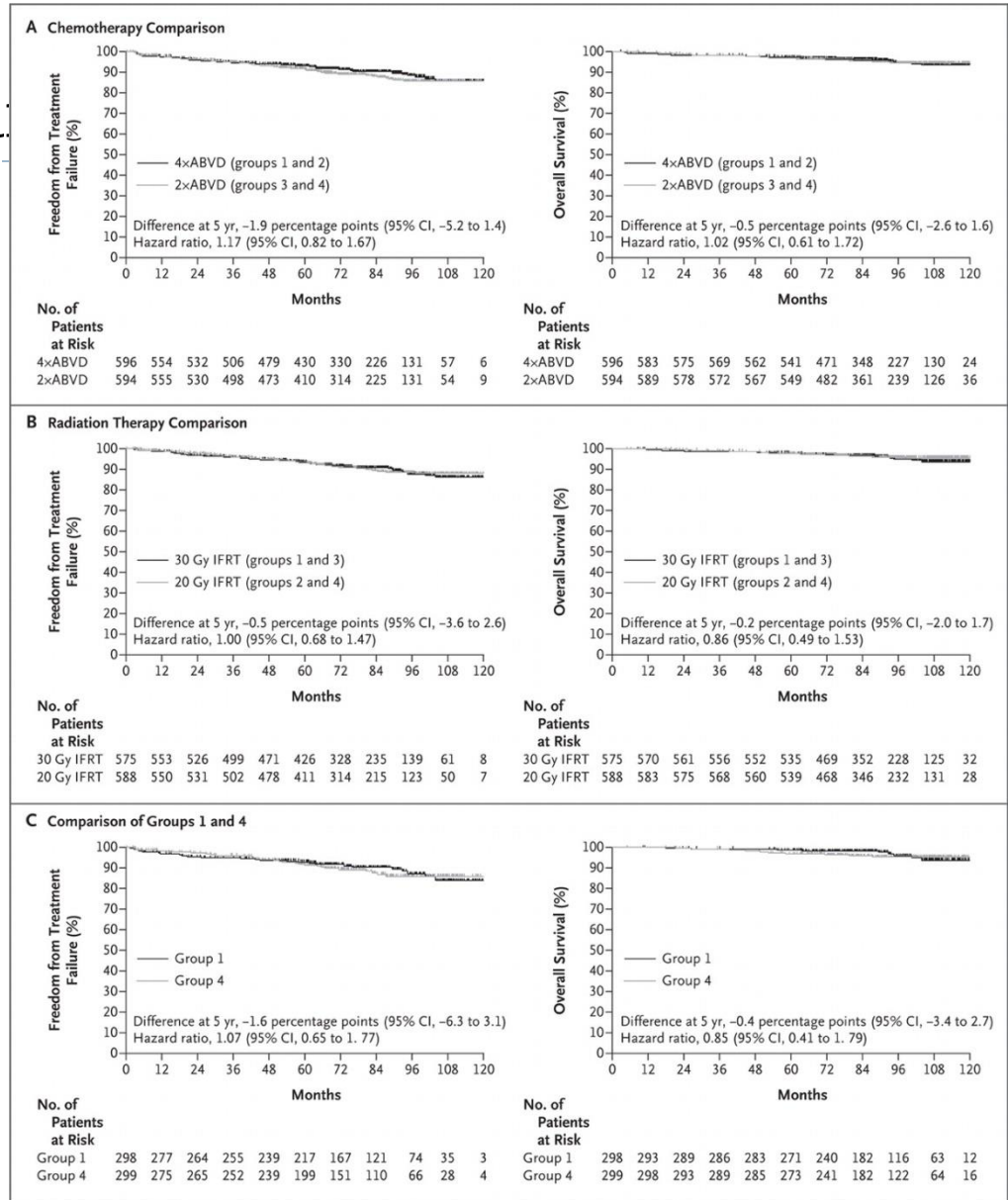
Comparison of CT and RT



***Large mediastinal mass; extranodal disease; high ERS; 3 or more areas involved**

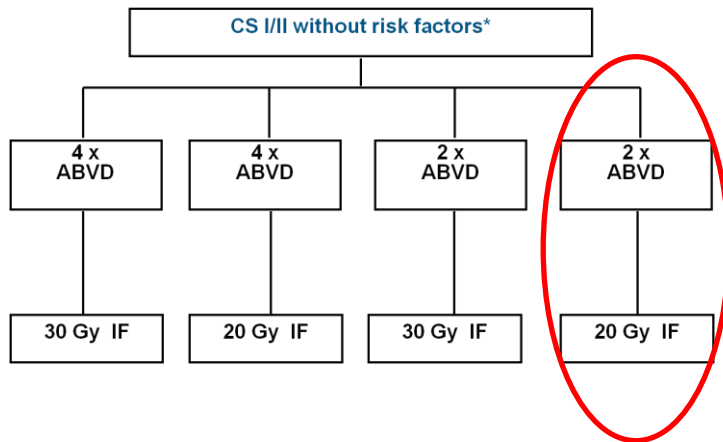
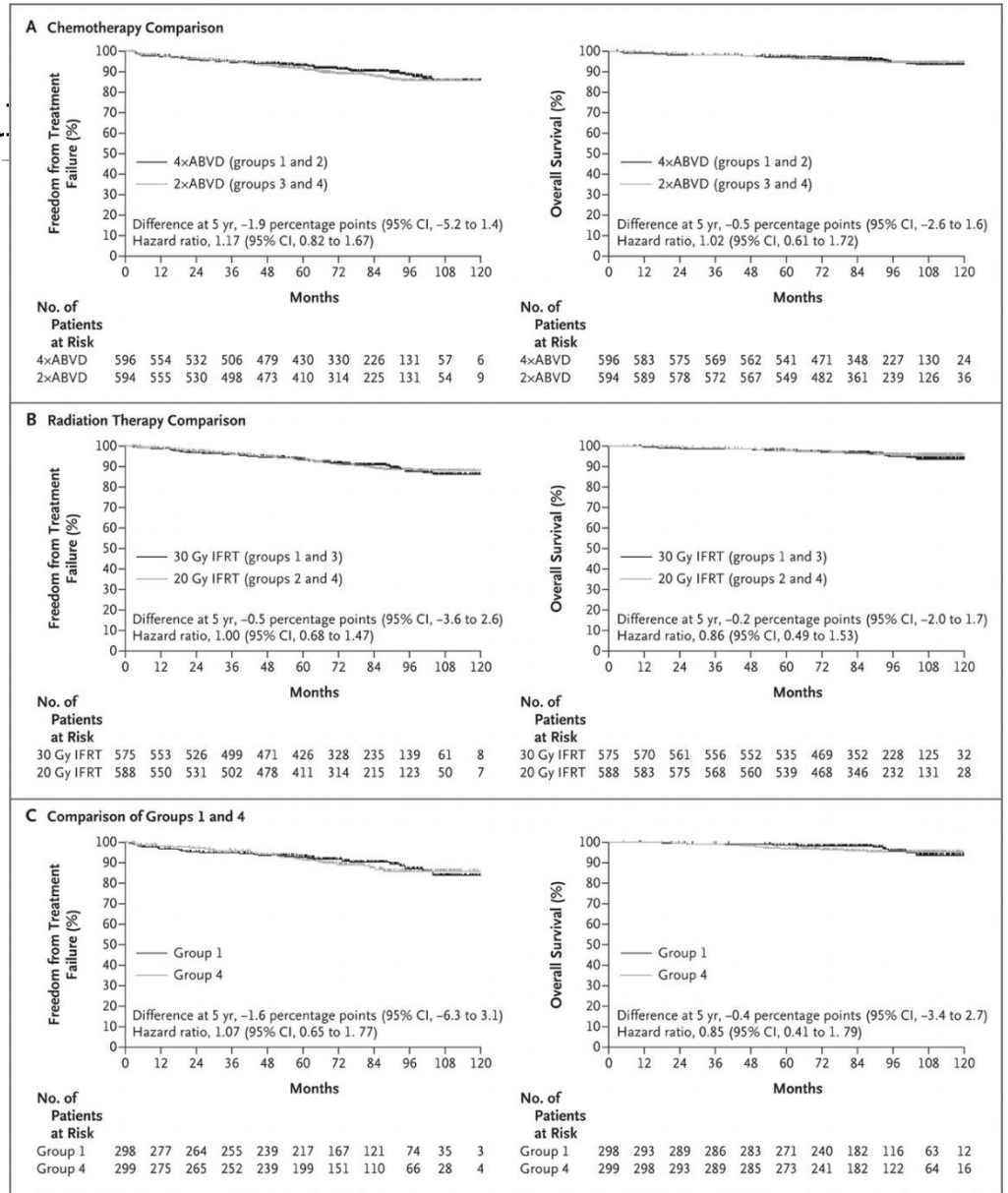
HD10 trial

Comparison of CT a

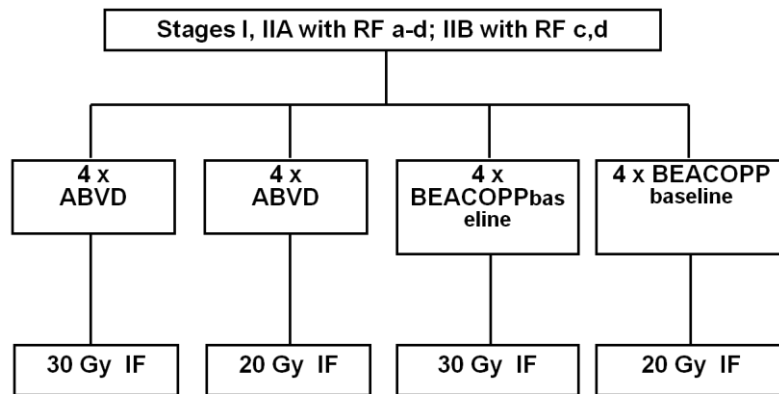


HD10 trial

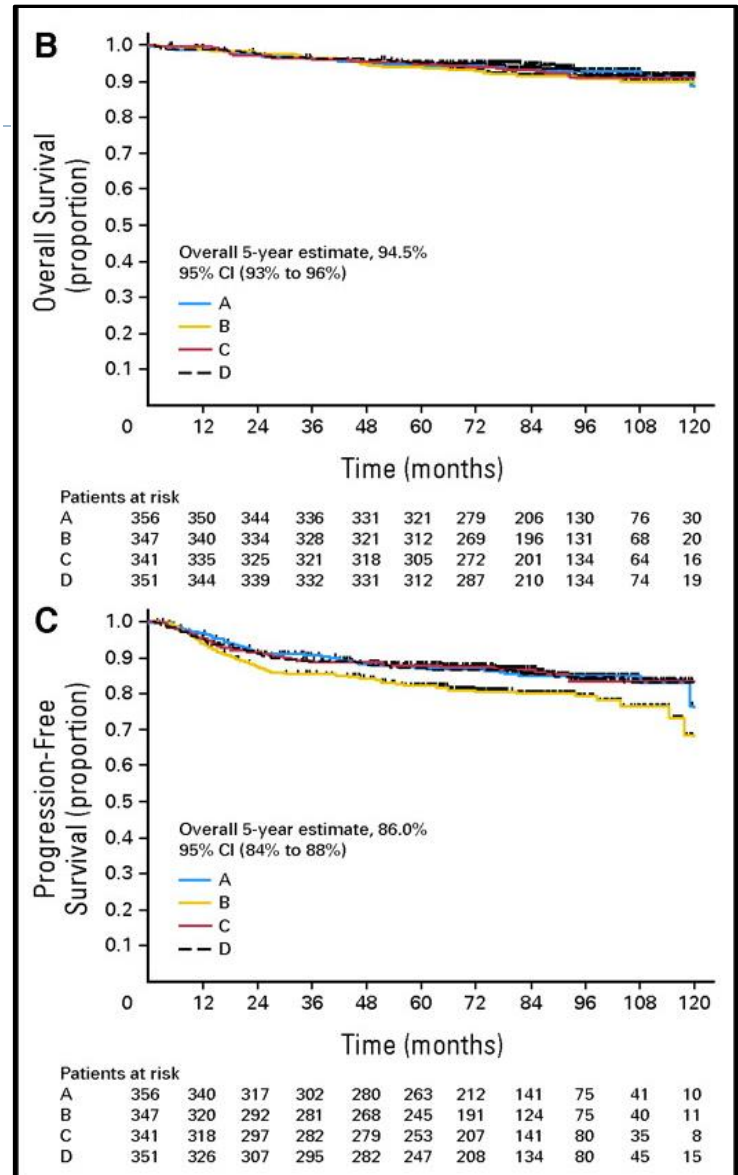
Comparison of CT a



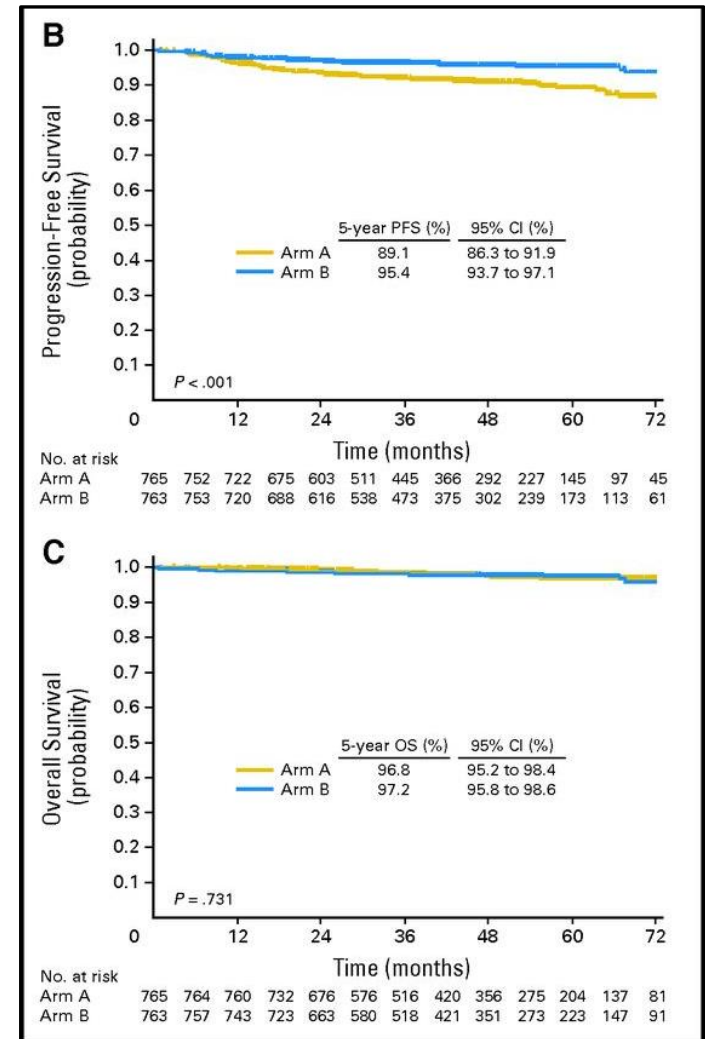
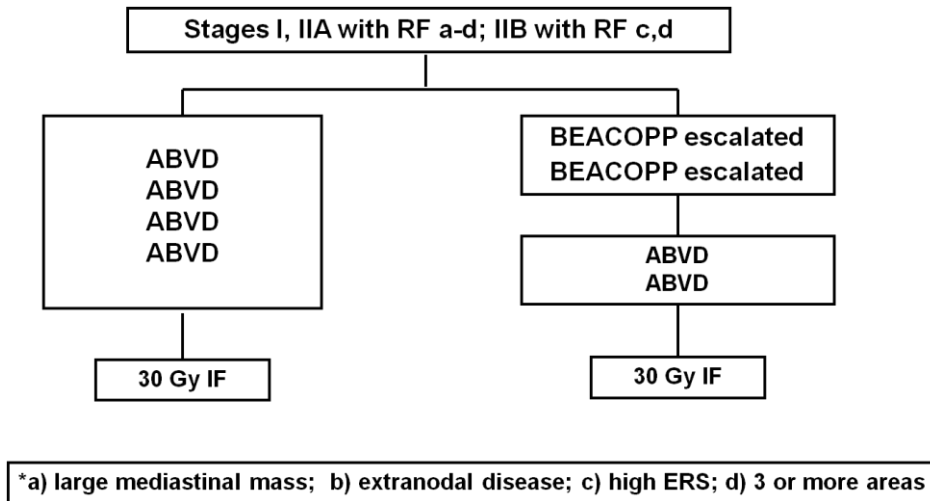
HD11 trial for early unfavorable HL



*a) large mediastinal mass; b) extranodal disease; c) high ERS; d) 3 or more areas



HD14 study for early unfavorable HL (PFS)



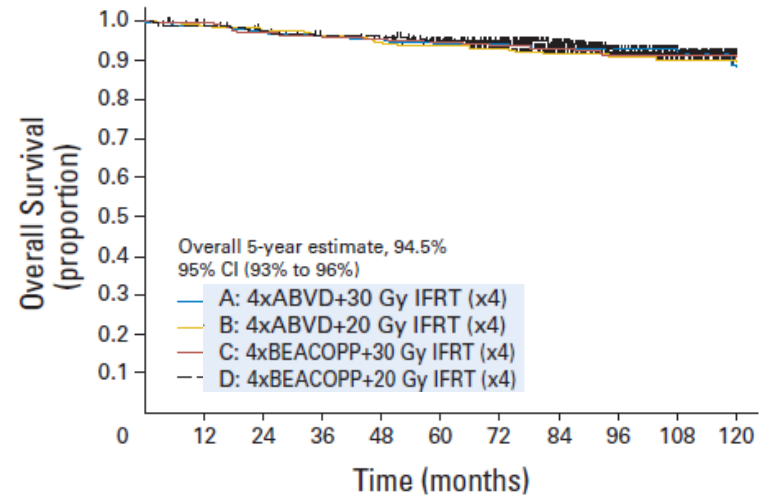
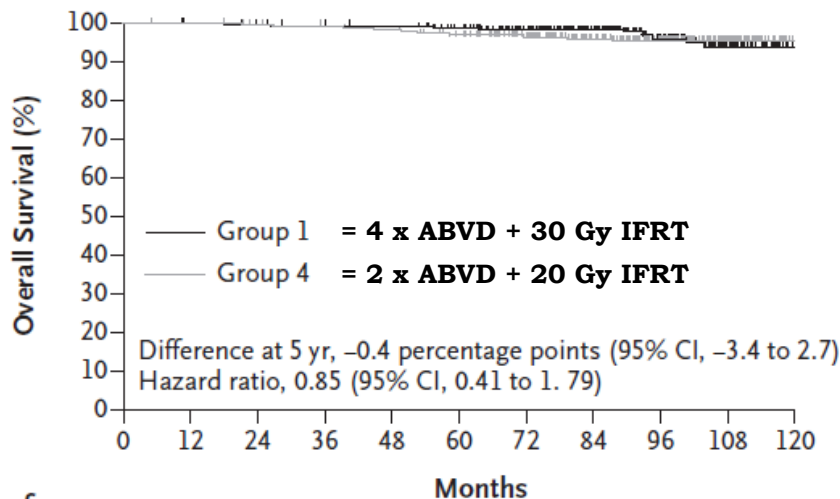
Current standard of care of early stage HL

Early favourable

- ▶ 2 x ABVD + 20 Gy ISRT (GHSB HD10)
 - ▶ 8-year FFTF 86%
 - ▶ 8-year OS 95%

Early unfavourable

- ▶ 4 x ABVD + 30 Gy ISRT (GHSB HD11 and HD14)
 - ▶ 5-year FFTF 85%
 - ▶ 5-year OS 94%



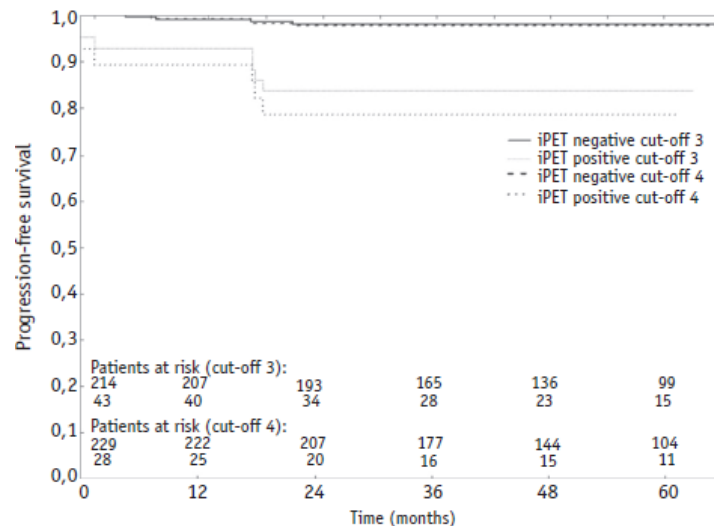
1. Engert A, et al. N Engl J Med 2010; 363:640-652.
2. Eich HT, et al. J Clin Oncol. 2010 Sep 20;28(27):4199-206

Early interim PET in early stage HL

- ▶ PET after 2xABVD is prognostic in early stage HL
 - ▶ when patients are given both chemotherapy and radiotherapy

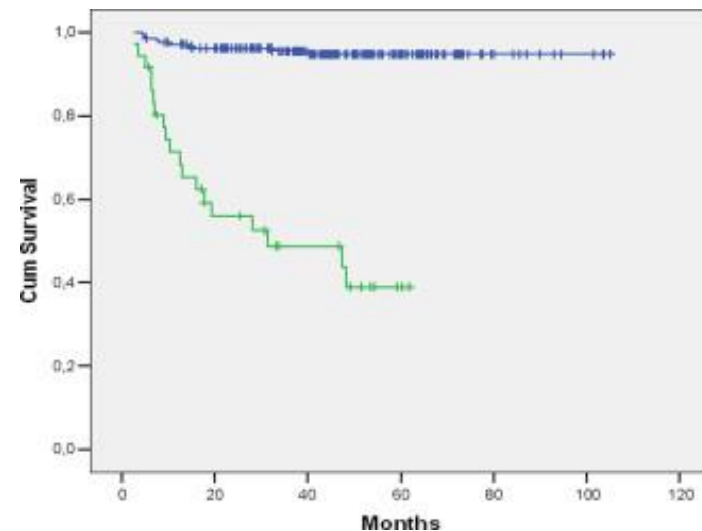
257 stage I-II (A+B) patients

Central, blinded PET review according to Deauville



246 stage IA-IIA patients

Central, blinded PET review according to Deauville



1. Simontacchi G, et al. Int J Radiat Oncol Biol Phys. 2015 Apr 17. (Epub ahead of print)
2. Rigacci L, et al. Am J Hematol. 2015 Jun;90(6):499-503.

Early interim PET in early stage HL

- ▶ PET after 2 cycles is also prognostic in early stage HL
 - ▶ when patients are given chemotherapy only

99 patients with stage I-II non-bulky HL

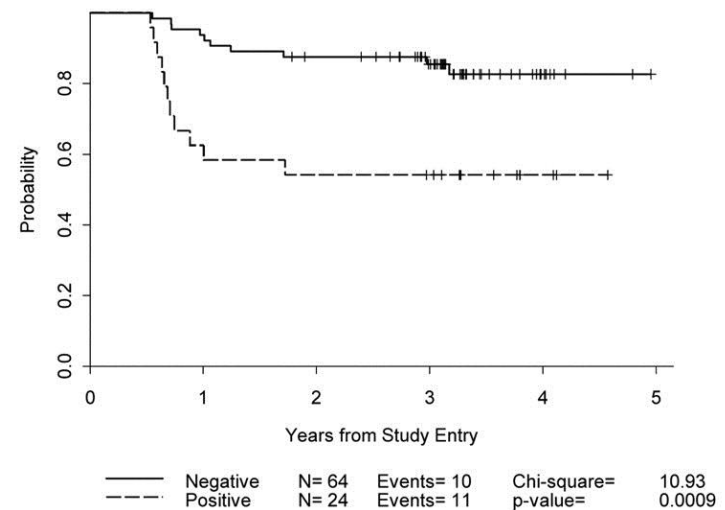
Treated with 6 cycles of AVG

PET after 2 cycles predictive of PFS

3-year PFS for all patients 77%

2-year PFS if PET2-neg = 88%

2-year PFS if PET2-pos = 54%



The focus of recent years:

- ▶ Q1: Should omission of radiotherapy be standard in early PET-negative patients?
- ▶ Q2: Should treatment be escalated in early PET-positive patients?



Q1: Should radiotherapy be omitted in early PET-negative patients?

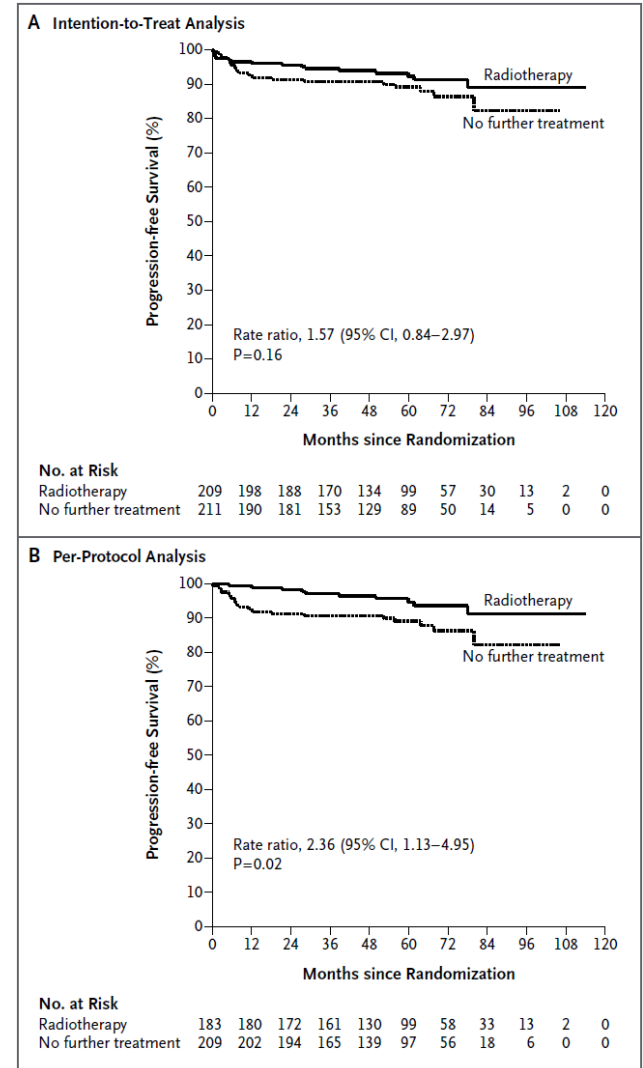
Prospective, randomised trials:

- | | |
|----------------------|------------------|
| ▶ UK/NCRI RAPID | Final analysis |
| ▶ EORTC/LYSA/FIL H10 | Interim analysis |
| ▶ GHSG HD16 | Still ongoing |



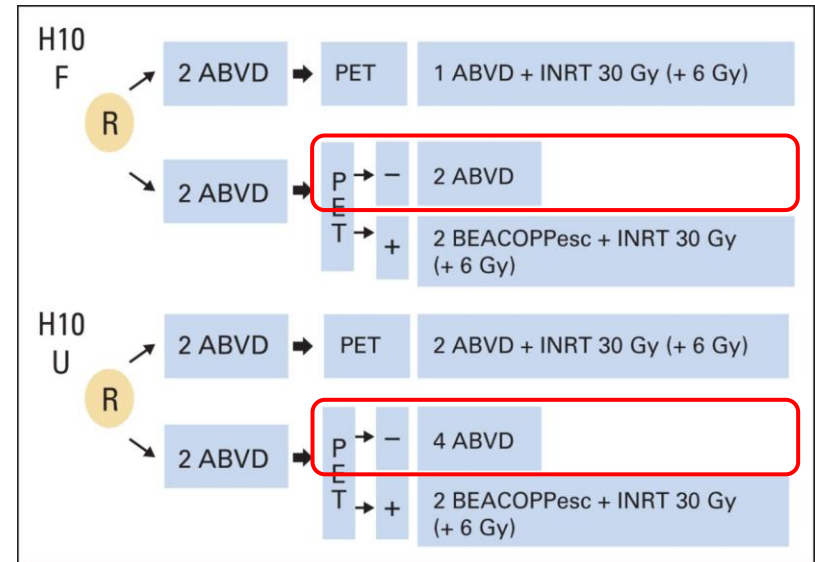
UK/NCRI RAPID final analysis

- ▶ 602 patients included
- ▶ 420 patients PET-negative after 3 x ABVD randomised to IFRT or NFT
- ▶ Non-inferiority margin = 7%
- ▶ Median follow-up 60 months
- ▶ 3-year PFS
 - ▶ 3 x ABVD + IFRT = 94.6%
 - ▶ 3 x ABVD + NFT = 90.8%
 - ▶ Difference = -3.8% (95% CI: -8.8 to 1.3%)
- ▶ 3-year OS
 - ▶ 97.1% vs 99.0% (NS)
- ▶ Conclusions:
 - ▶ **Study did not show non-inferiority**
 - ▶ **PET3 negative patients have a very good prognosis, regardless of consolidation radiotherapy**



EORTC/LYSA/FIL H10 interim analysis

- ▶ 1950 patients randomised
- ▶ 1137 patients available for interim analysis
- ▶ Non-inferiority margin 10%
- ▶ Median follow-up 13 months
- ▶ PET2 negative, favourable:
 - ▶ 1-y PFS 94.9% if no RT
 - ▶ 1-y PFS 100% if INRT
- ▶ PET2 negative, unfavourable:
 - ▶ 1-y PFS 94.7% if no RT
 - ▶ 1-y PFS 97.3% if INRT



IDMC conclusion: Unlikely to show non-inferiority; advised to stop randomisation of PET2 negative patients

Authors' conclusion: Cannot exclude non-inferiority of chemo only arm, but early outcome is excellent in both arms

Q1: Should omission of radiotherapy be standard in early PET-negative patients?

► NO, since

1. No prospective, randomised studies support this
2. Two large randomised studies investigating this very question have reached negative conclusions

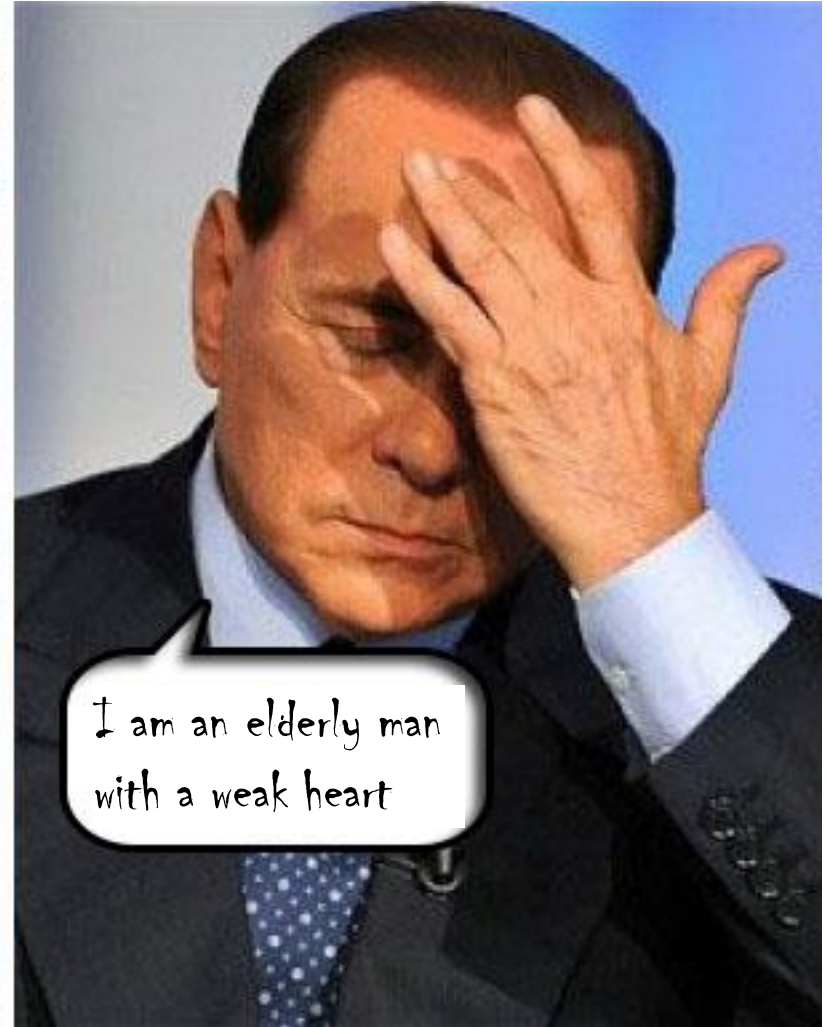
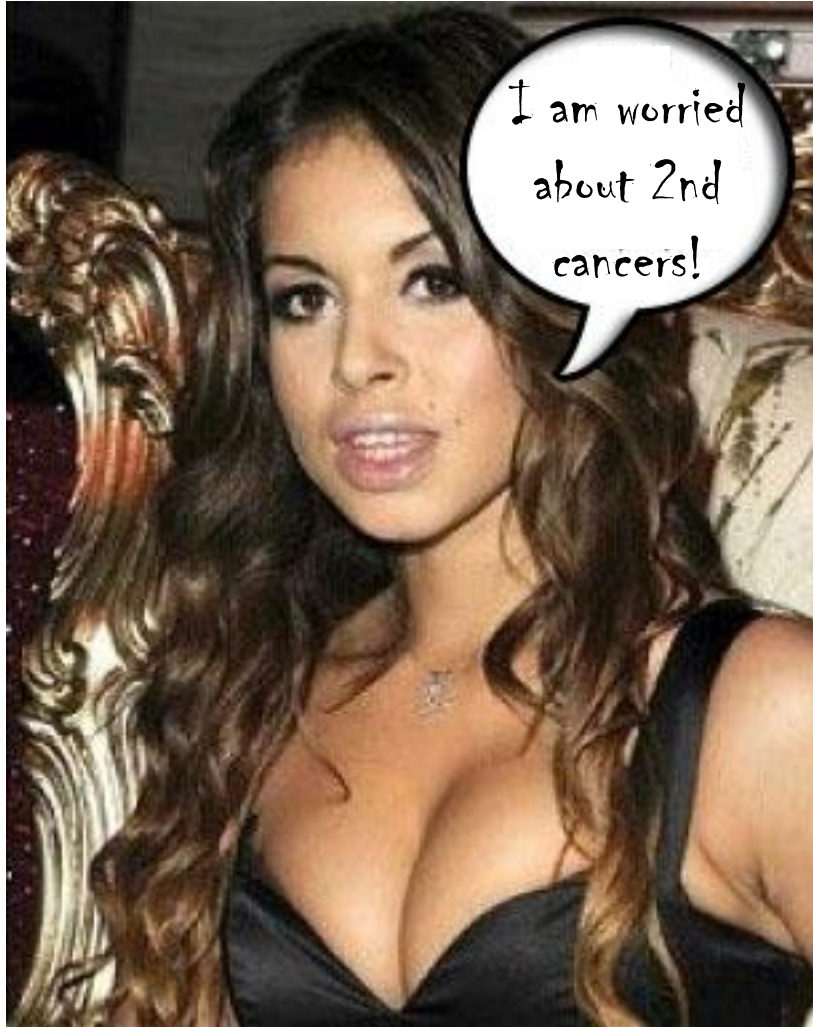


John Radford at ISHL Cologne 2007

How many babies of RFS is it throw
- What is the appropriate
acceptable to observe order
margin of non-inferiority
to save babies from the waste
for such a trial?
that really wait patients?



Is one answer to John's question true for all patients?



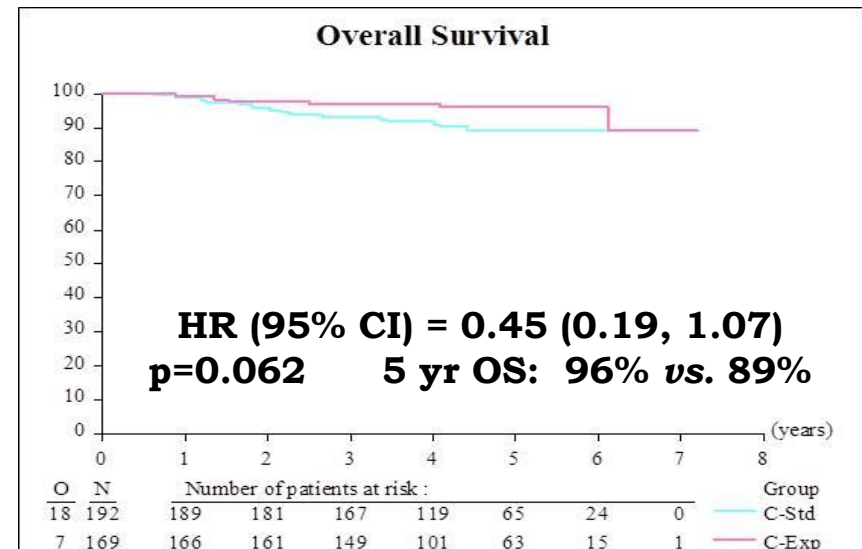
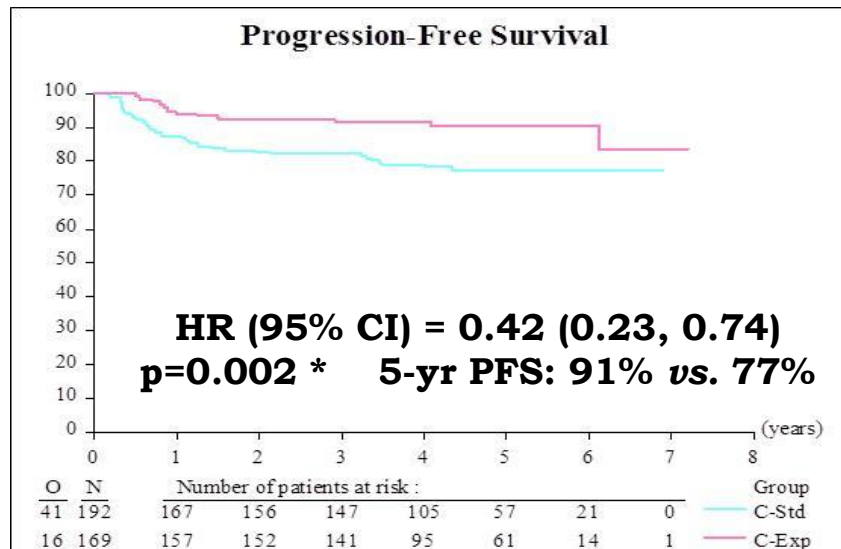
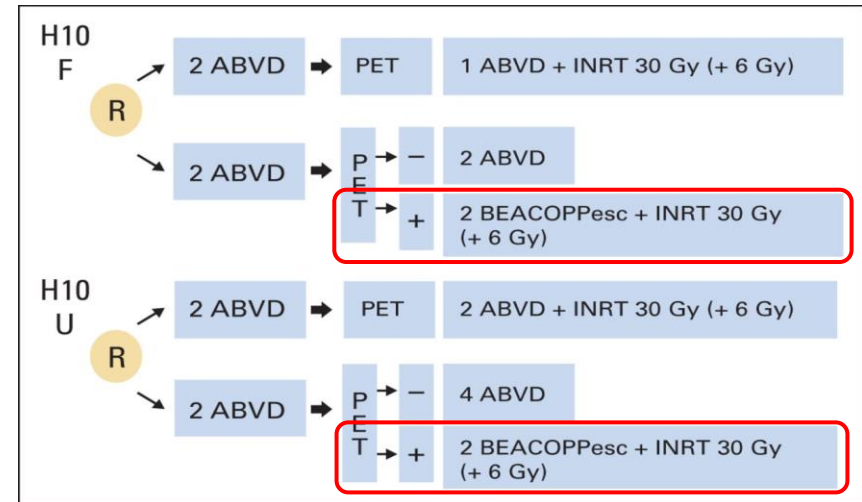
Negative trials can be useful

- ▶ RAPID and H10 data will probably reveal much useful information to help us tailor therapy to the individual patient with early stage HL, based on
 - ▶ Age
 - ▶ Sex
 - ▶ Disease location
 - ▶ Comorbidity
 - ▶ Early response (incl. PET)
 - ▶ Patient preference
 - ▶ Etc.



Q2: Should treatment be escalated in early PET-positive patients?

- ▶ 1950 patients randomised
 - ▶ 754 favourable
 - ▶ 1196 unfavourable
- ▶ Median follow-up 4.5 years
- ▶ PET2 positive:
 - ▶ F: 54 patients (14%)
 - ▶ U: 138 patients (23%)



-
- ▶ Q1: Should omission of radiotherapy be standard in early PET-negative patients?
 - ▶ No, but for some patients it may be appropriate
 - ▶ Q2: Should treatment be escalated in early PET-positive patients?
 - ▶ Yes, but for some patients it may be inappropriate
 - ▶ Q3: Should early sensitivity testing be part of future individualised therapy for early-stage HL?
 - ▶ Yes!
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Thank you!