Hodgkin

The PET World

King's College London & Guy's and St Thomas' PET Centre

Sally Barrington

2nd POSTGRADUATE Lymphoma Conference

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PET-CT Staging in HL

PET-CT changes stage 15-30%

RATHL - Advanced HL 1171 pts

Stage by PET-CT compared with ceCT and BMB

20% stage change; upstaging 14%

Most upstaging due to EN disease PET

118 patients - BM lung liver pleura multiple sites

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Rigacci L et al *Annals of hematology.*2007;86(12):897-903.
Hutchings M et al *Haematologica.* Apr 2006;91(4):482-489.
Barrington SF et al Blood 2016 in press

Impact PET-CT for staging

- Fewer patients under/over staged

Probably leads better treatment selection

More treatment failures

stage I/II on CT + III/IV PET vs. stage I/II on CT +PET

PET for staging using GHSG stage of

early v intermed v advanced predicts PFS & OS

Higher risk of progression with PET BM lesions

- RT planning – more selective
- No need for bone marrow biopsy
- Baseline for response assessment

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Munker R et al Annals Oncol 2004; 15:1699-1704
El-Galaly T et al *Leuk Lymphoma.* 2014;55(10):2349-2355.
Illidge T et al Int J Radiat Oncol Biol Phys. 2014; 89:49-58

Response Assessment
Deauville criteria

1. no uptake
2. uptake ≤ mediastinum
3. uptake > mediastinum but ≤ liver
4. moderately increased uptake compared to liver
5. markedly increased uptake compared to liver and/or new lesions

** markedly increased uptake is taken to be uptake > 2-3 times the SUV max in normal liver

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Meignan, et al. Leuk Lymphoma, 2009; 50(8): 1257-60
Barrington, et al. JCO 2014; 32: 3048-58

De-escalation Escalation

Score 1 no uptake

Score 2 uptake ≤ mediastinum

Score 3 uptake > mediastinum but ≤ liver

Score 4: uptake > liver at any site

Score 5 uptake > liver and new sites of disease

***Score X**:*

new areas of uptake unlikely to be related to lymphoma

Negative scan

Positive scan

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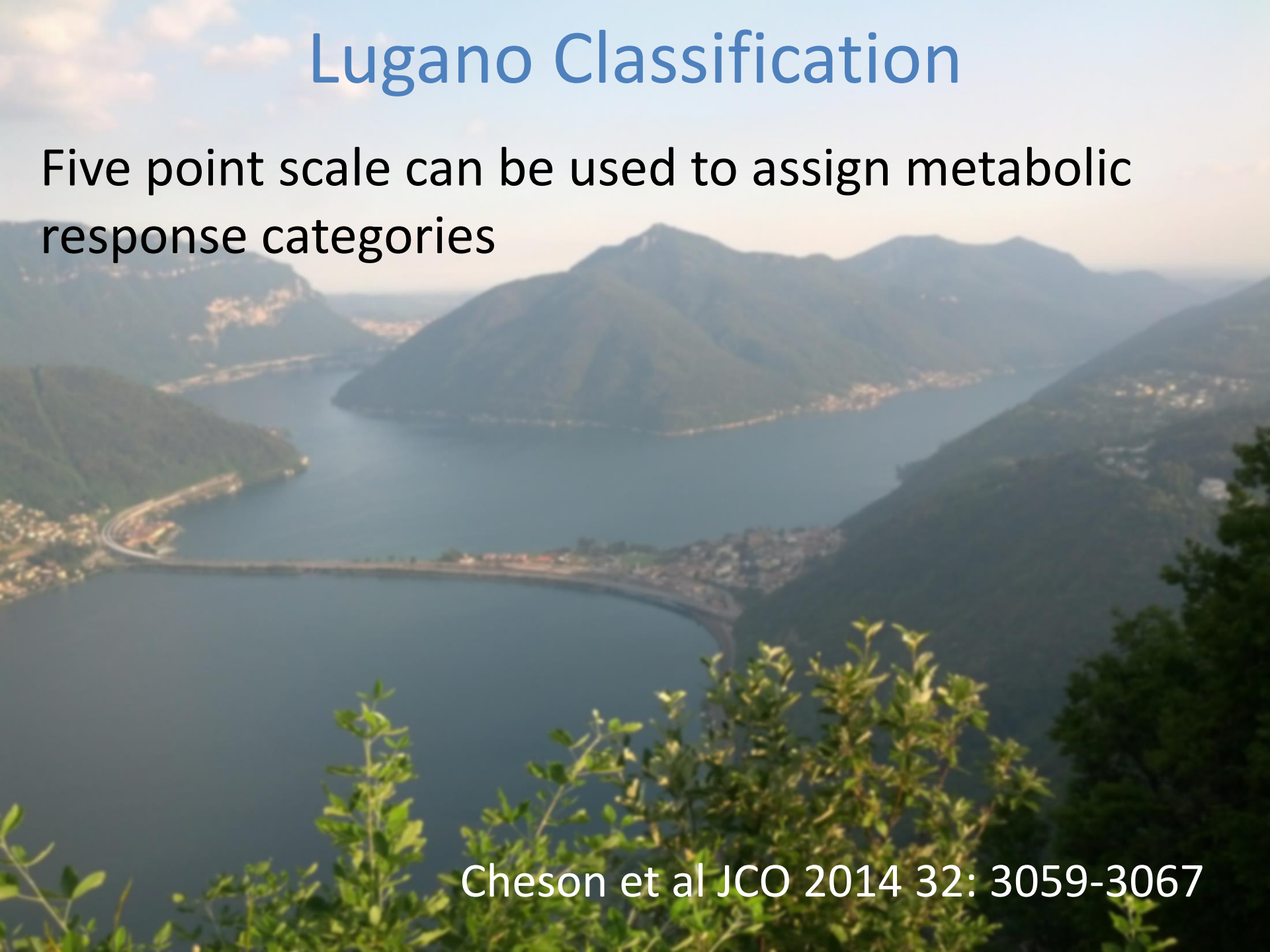
Lugano Classification

Five point scale can be used to assign metabolic response categories



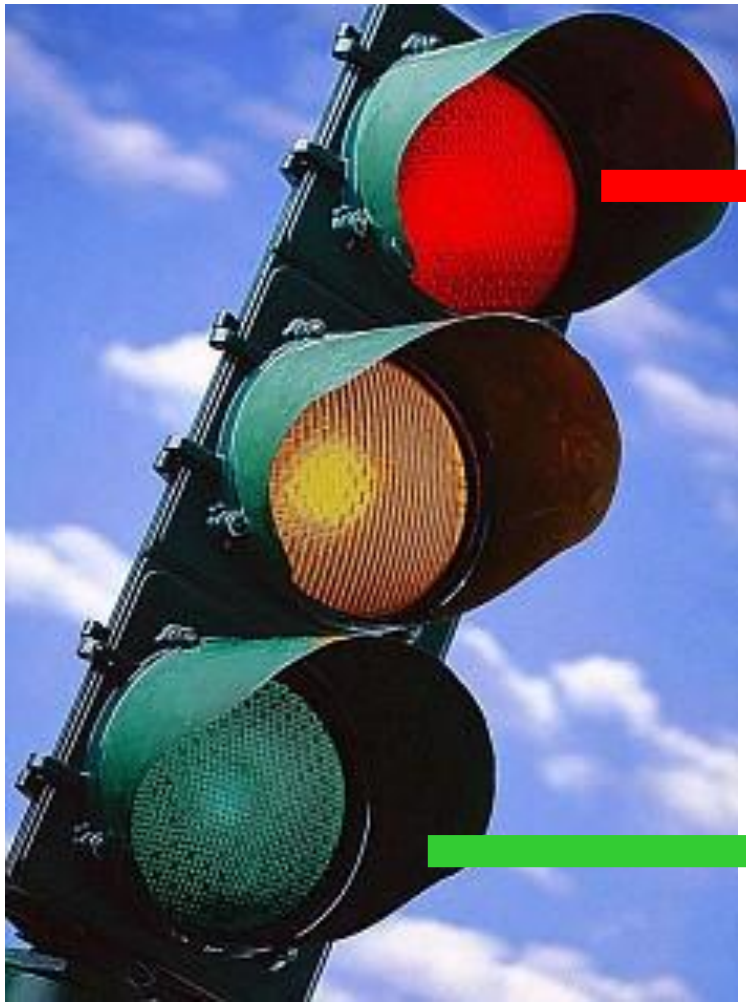
Cheson et al JCO 2014 32: 3059-3067

CATEGORY	PET – CT based metabolic response
CMR	Score 1,2,3* in nodal or extranodal sites with or without a residual mass using 5-PS
PMR	Score 4 or 5, with reduced uptake compared with baseline and residual mass(es) of any size. *At interim* , these findings suggest responding disease *At end of treatment* these findings indicate residual disease Bone marrow: Residual marrow uptake > normal marrow but reduced compared with baseline (diffuse changes from chemotherapy allowed). If there are persistent focal changes in marrow with a nodal response, consideration should be given to MRI, biopsy or interval scan.
NMR	Score 4 or 5 with no significant change in uptake from baseline *At interim or end of treatment*
PMD	Score 4 or 5 with an increase in uptake from baseline and /or New FDG-avid foci consistent with lymphoma *At interim or end of treatment*

* **Score 3 in many patients indicates a good prognosis with standard treatment. However in trials involving PET where de-escalation is investigated, it may be preferable to consider score 3 as inadequate response to avoid under-treatment**

Cheson et al JCO 2014 on line

PET Guided Therapy



PET positive

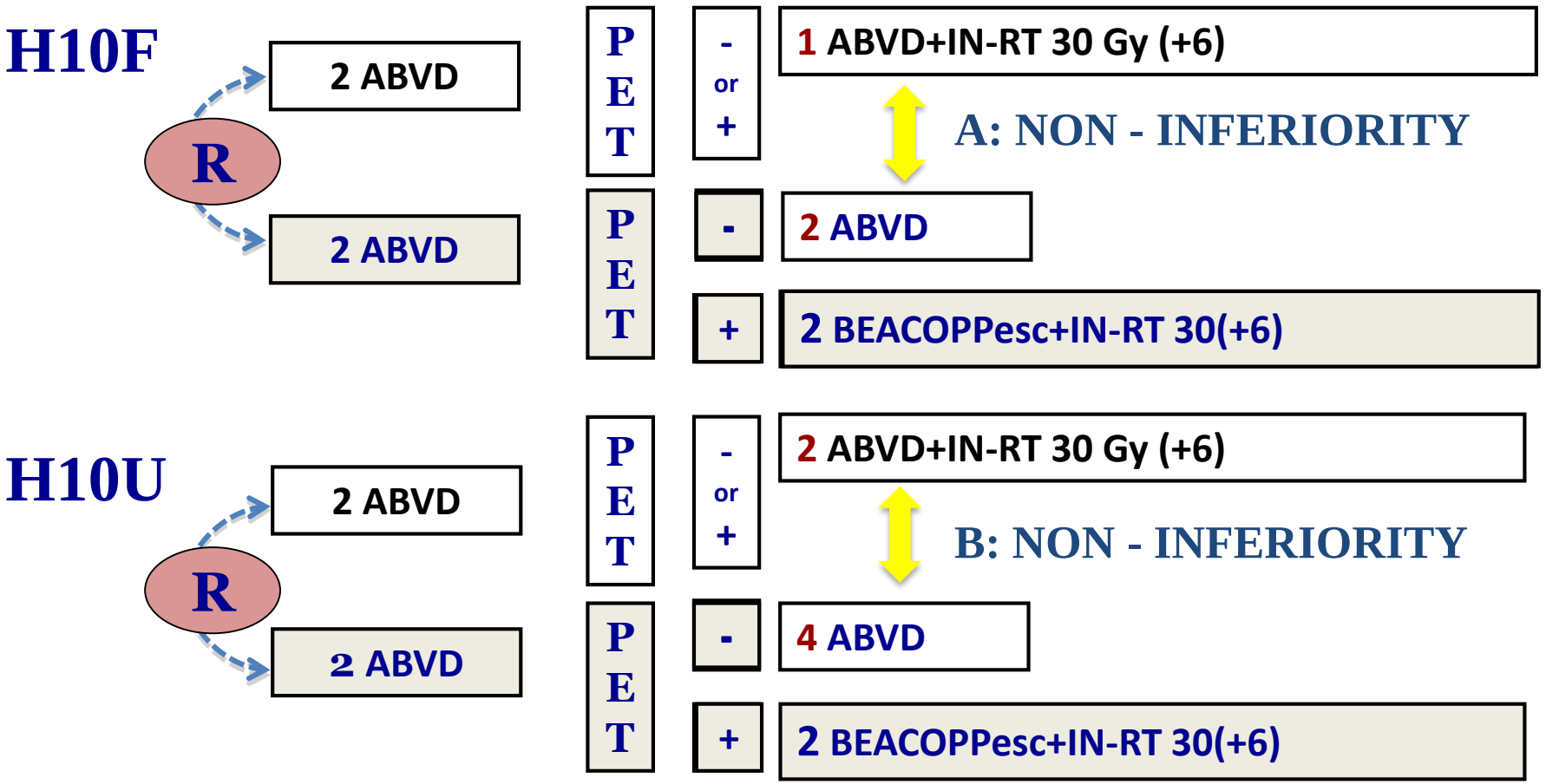
ESCALATION

PET negative

DESCALATION

Published studies

EORTC/LYSA/FIL H10:
Study design and primary objectives



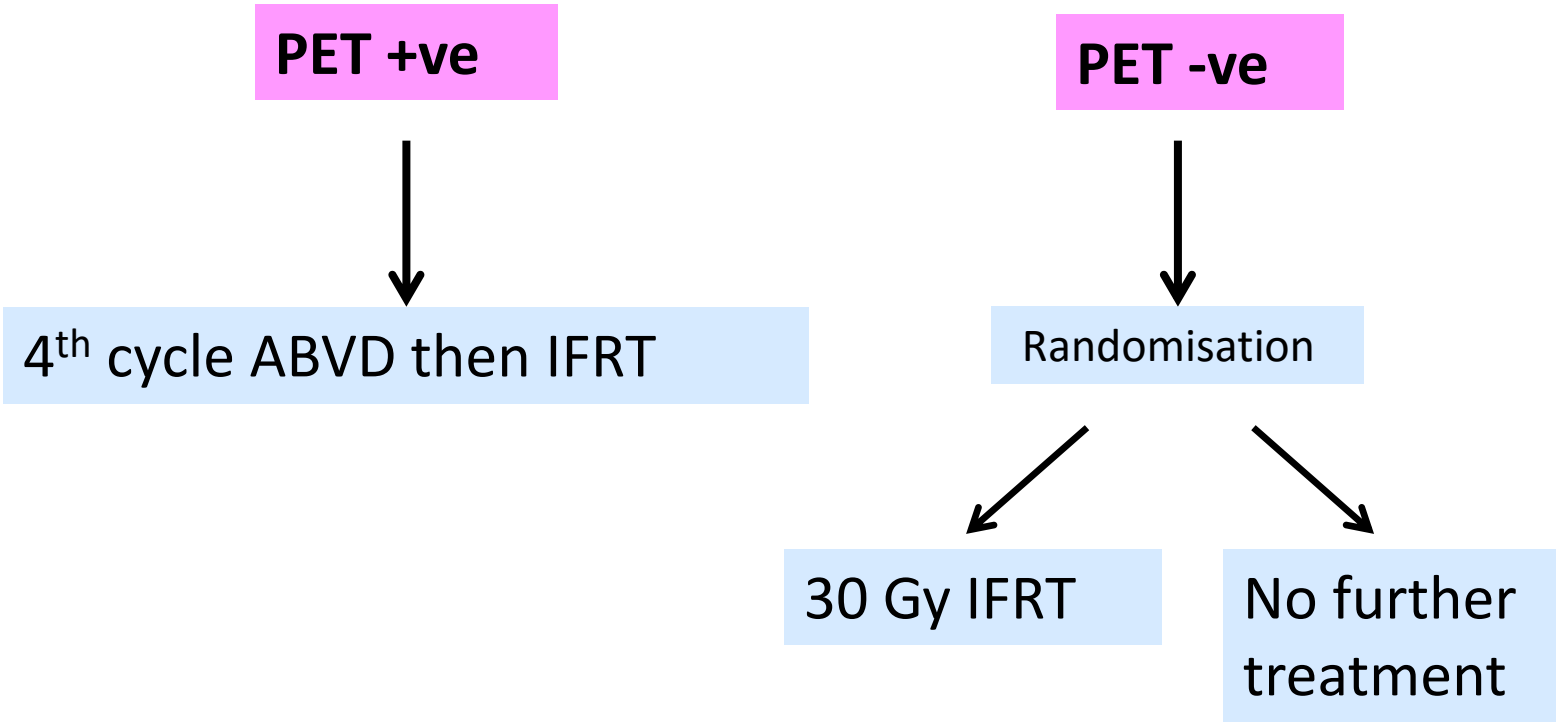
Primary endpoint : Progression-free survival

Raemaekers J et al JCO 2014;32: 1188-94

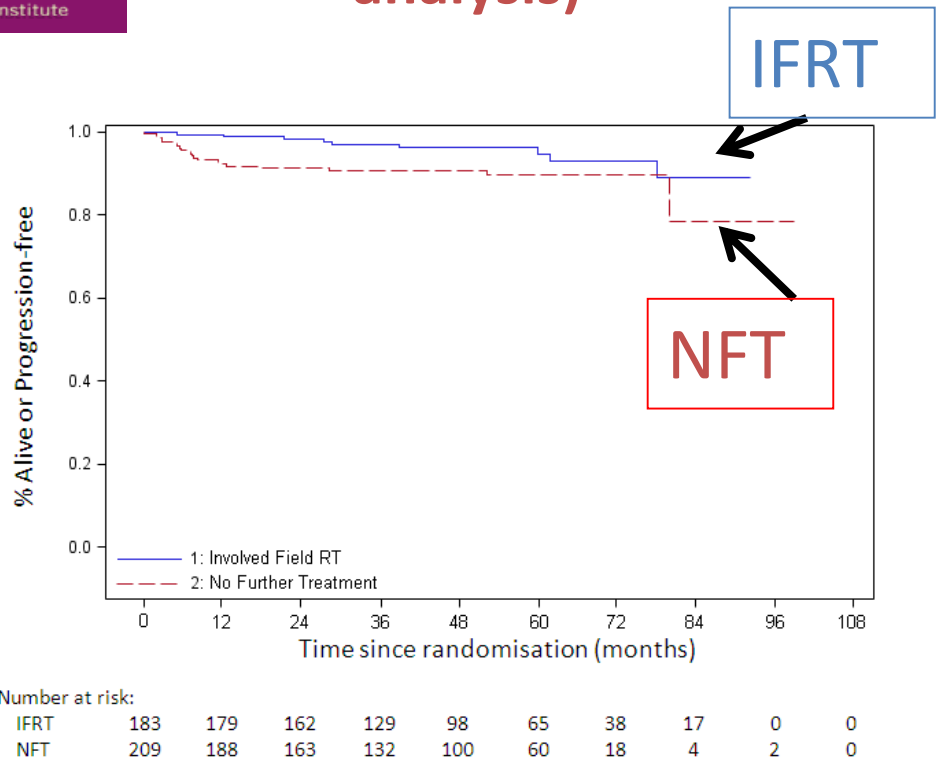
UK NCRI RAPID - trial design

Initial treatment: ABVD x 3

Re-assessment: if response, PET scan performed



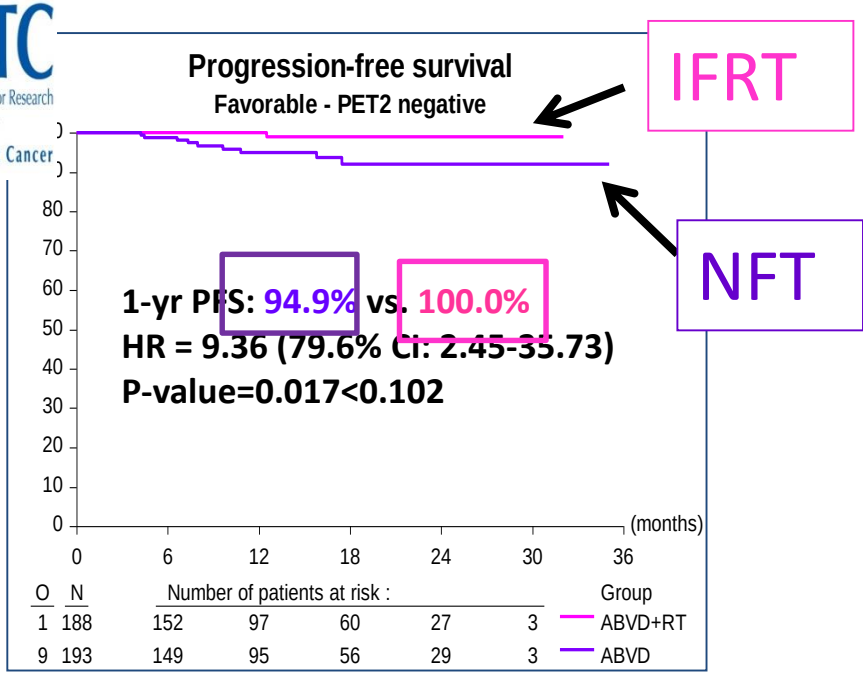
RAPID : PFS in PET -ve population (per protocol analysis)

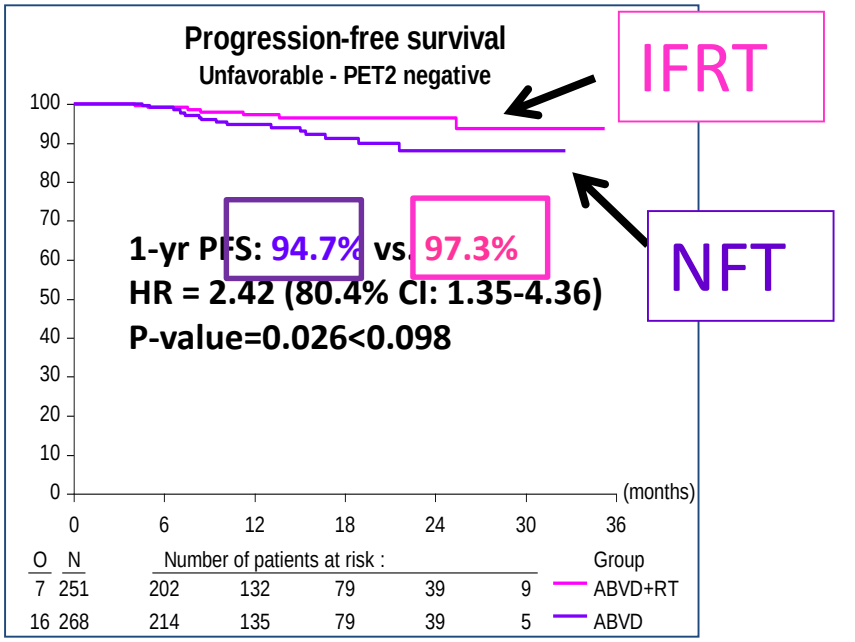


3 year PFS 97% vs 90.7%

HR 2.39 in favour of IFRT, p=0.03

Radford et al, NEJM 2015; 372:1598-607





Raemaekers J et al JCO 2014;32: 1188-94

What does this tell us about early HL ?

- 90% patients with – ve PET (DS 1,2) cured with short course chemo

RT improves PFS by 3 - 6%

But at the expense of irradiating all patients most of whom are already cured

Decision making: individual patient will depend on age, prognosis, fitness and disease distribution

Longer FU needed to know if not treating ALL patients with RT will ↑ survival with ↓ second ca and cardiovascular disease.

RAPID and H10 offers patients choices

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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.63.0699

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

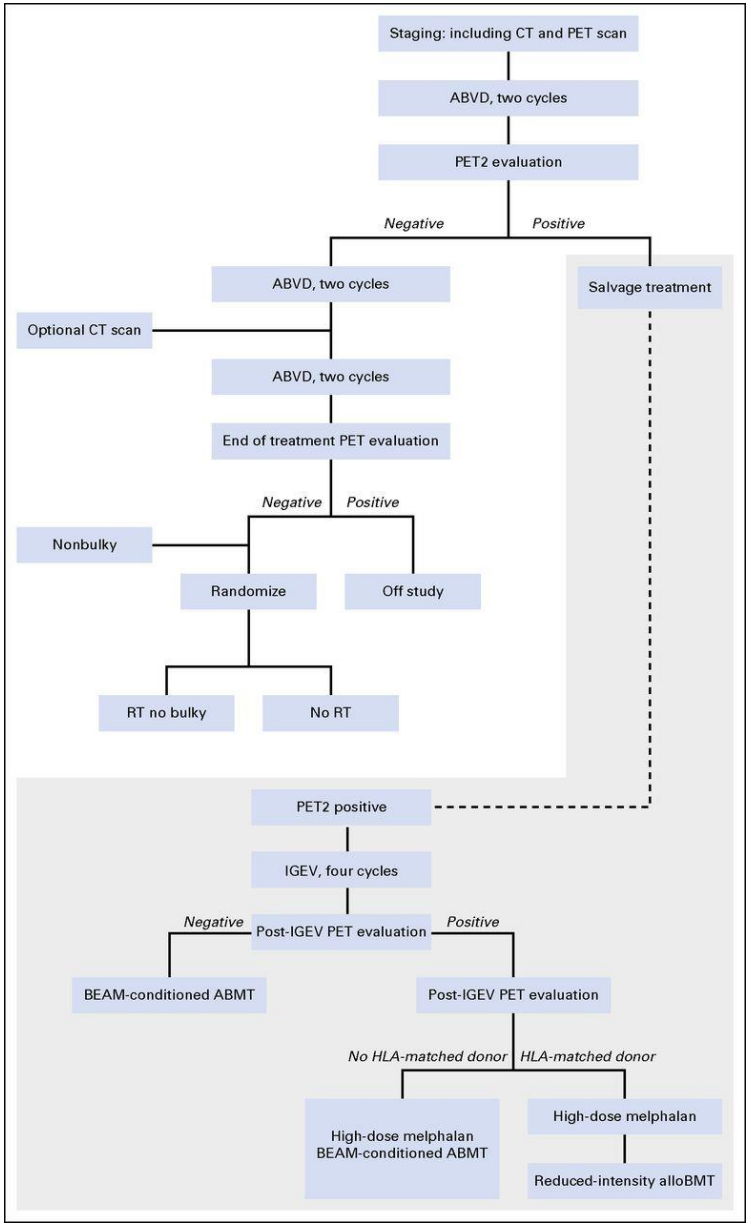
Interim Positron Emission Tomography Response–Adapted Therapy in Advanced-Stage Hodgkin Lymphoma: Final Results of the Phase II Part of the HD0801 Study

Pier Luigi Zinzani, Alessandro Broccoli, Daniela Maria Gioia, Antonio Castagnoli, Giovannino Ciccone, Andrea Evangelista, Armando Santoro, Umberto Ricardi, Maurizio Bonfichi, Ercole Brusamolino,† Giuseppe Rossi, Antonella Anastasia, Francesco Zaja, Umberto Vitolo, Vincenzo Pavone, Alessandro Pulsoni, Luigi Rigacci, Gianluca Gaidano, Caterina Stelitano, Flavia Salvi, Chiara Rusconi, Monica Tani, Roberto Freilone, Patrizia Pregno, Eugenio Borsatti, Gian Mauro Sacchetti, Lisa Argnani, and Alessandro Levis

N =512

IHP criteria

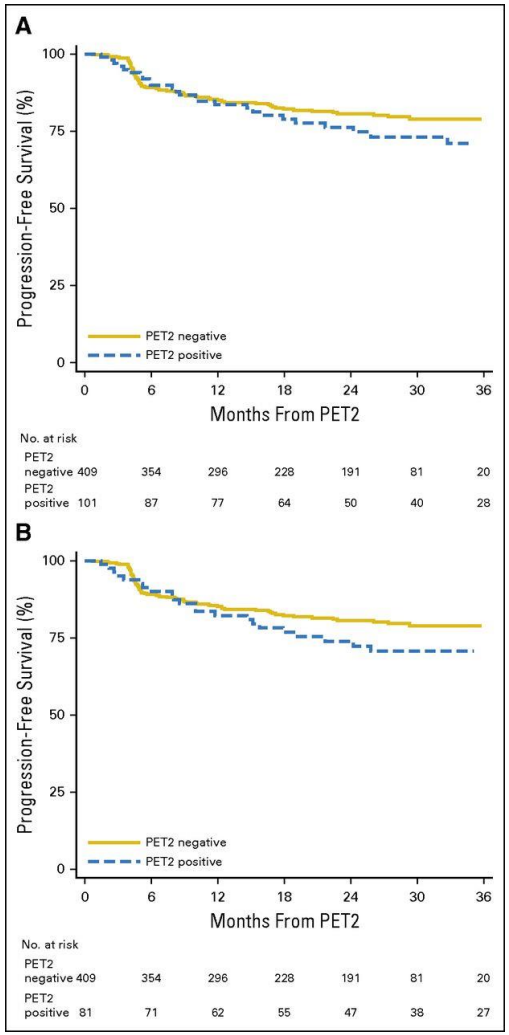
Post hoc DC



Pier Luigi Zinzani et al. JCO doi:10.1200/JCO.2015.63.0699

(A) Progression-free survival on an intention-to-treat basis for PET 2-positive (dashed line; n = 101) and PET2-negative (solid line; n = 409) patients who received either IGEV chemotherapy and transplantation or an alternative salvage treatment (including ...

ITT analysis



2y PFS 81%
2y PFS 76%

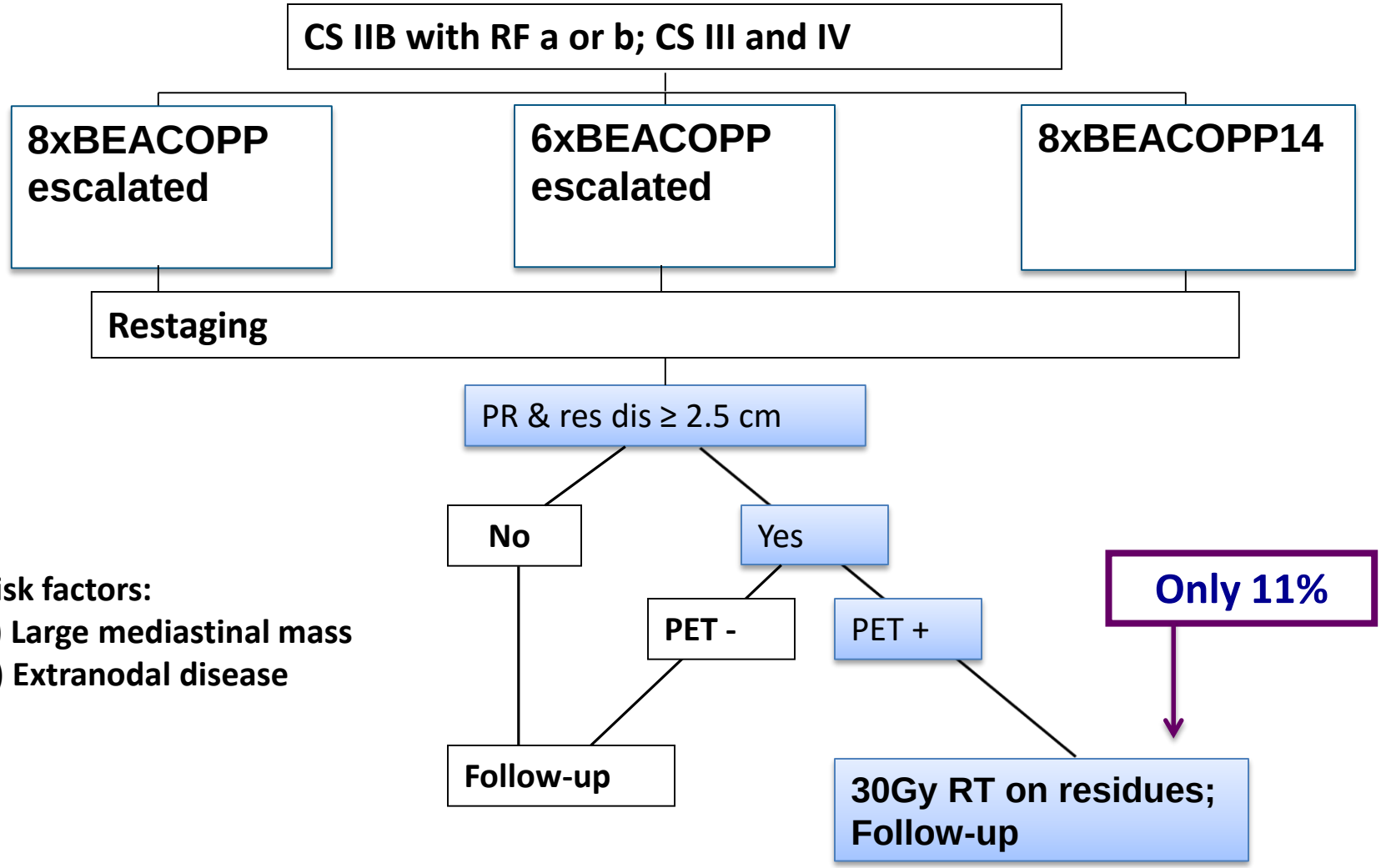
Per protocol analysis

2y PFS 81%
2y PFS 74%

Pier Luigi Zinzani et al. JCO doi:10.1200/JCO.2015.63.0699

JOURNAL OF CLINICAL ONCOLOGY ASCO

GHSG HD15 trial for advanced-stage HL



Risk factors:
a) Large mediastinal mass
b) Extranodal disease

HD15 HL advanced stage

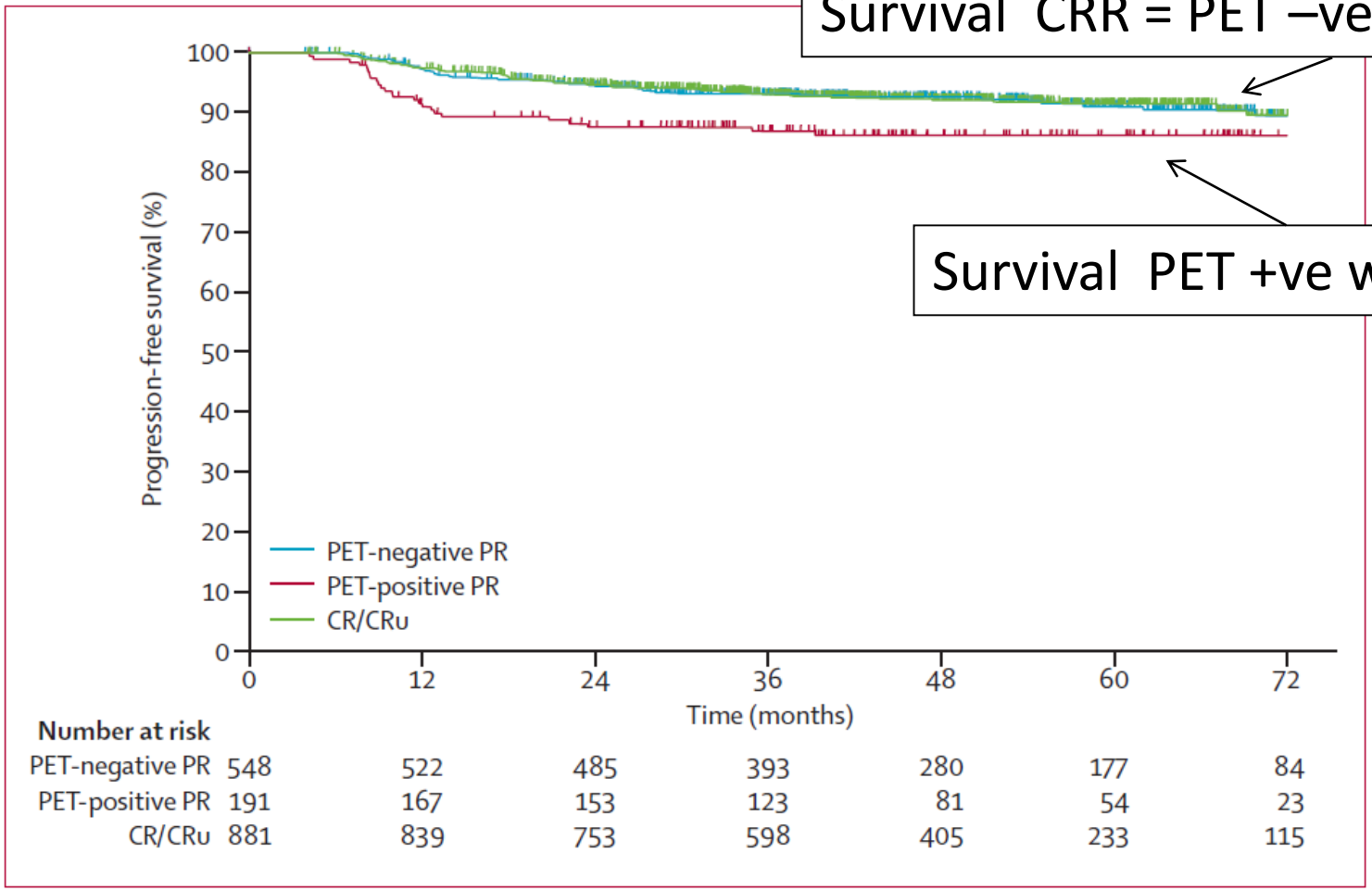


***Figure 3*: Progression free survival for PET study objective**
PR=partial remission at the end of chemotherapy. CR/Cru=complete remission without or with residual abnormalities at the end of chemotherapy.

Engert A et al Lancet 2012 379(9828): 1791-9

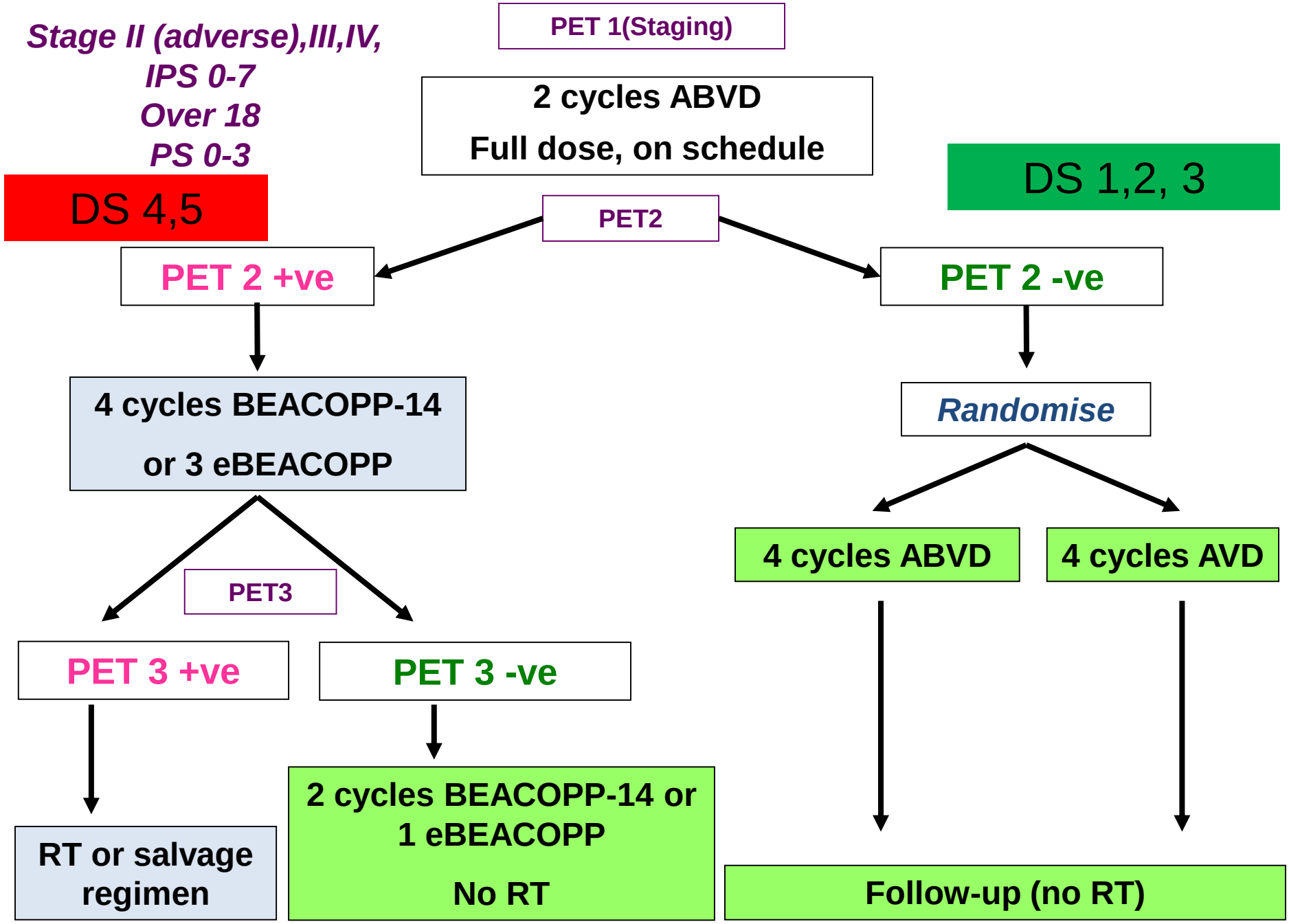
(Some) presented studies

Conclusions Intergroup H10 trial

- First trial that incorporates Involved Node Radiotherapy in combined modality setting
- Patients with early PET +ve scan (two cycles of ABVD) significantly* benefit from intensification of ABVD to BEACOPPesc followed by INRT
  - 5 yr PFS increase from 77% to 91%*
    - *5 yr OS increase from 89% to 96%*

- Despite increased toxicity, intensifying chemotherapy in early PET positive patients should be seriously considered in stage I/II HL in the combined modality treatment setting

c/o Dr John Raemaekers


Stage II (adverse),III,IV,
IPS 0-7
Over 18
PS 0-3
DS 4,5
PET 1(Staging)
2 cycles ABVD
Full dose, on schedule
DS 1,2, 3
PET2
PET 2 +ve
PET 2 -ve
4 cycles BEACOPP-14
or 3 eBEACOPP
Randomise
4 cycles ABVD
4 cycles AVD
PET3
PET 3 +ve
PET 3 -ve
RT or salvage regimen
2 cycles BEACOPP-14 or
1 eBEACOPP
No RT
Follow-up (no RT)

Toxicity of therapy: ABVD vs AVD

% of patients experiencing grade 3-4 events

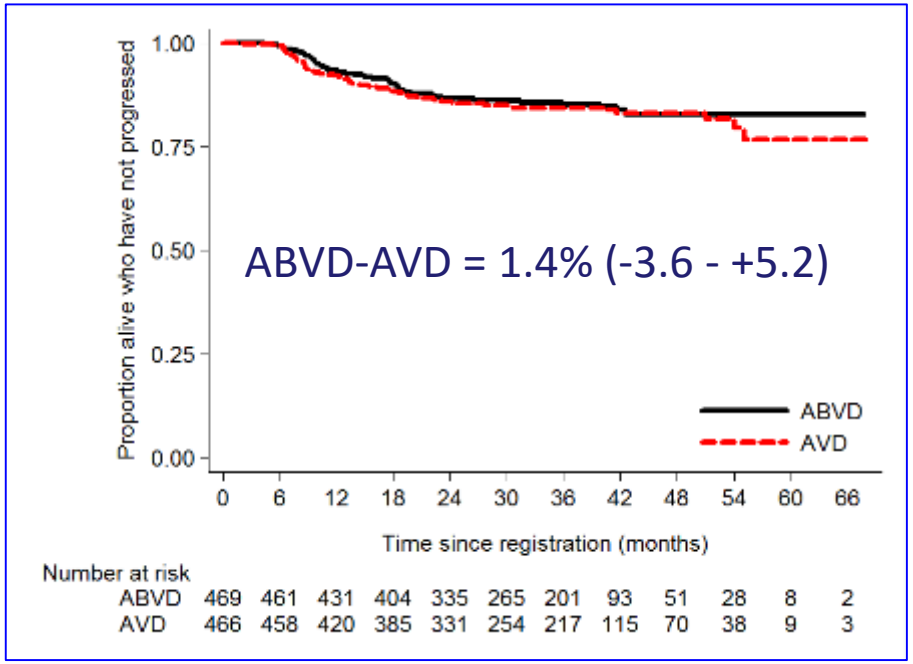
	ABVD cycles 1-2	ABVD cycles 3-6	AVD cycles 3-6	P-value
Neutropenia	57.3	58.4	57.5	0.78
Thrombocytopenia	1.3	1.3	3.2	0.045
Neutropenic fever	2.1	4.7	2.2	0.032
Infection	6.3	14.5	10.1	0.040
Thrombo-embolism	1.4	4.9	2.6	0.061
Respiratory AEs	0.7	3.6	0.6	0.002
Any non-haematological toxicity	16	31	21	<0.001

Johnson P et al Hematol Oncol, 2015;33(Suppl S1)100–180, abstract 8.

Primary Endpoint: PFS for PET-negative randomized, eligible patients

(Median follow up 36.3 months)

Intention to treat analysis:

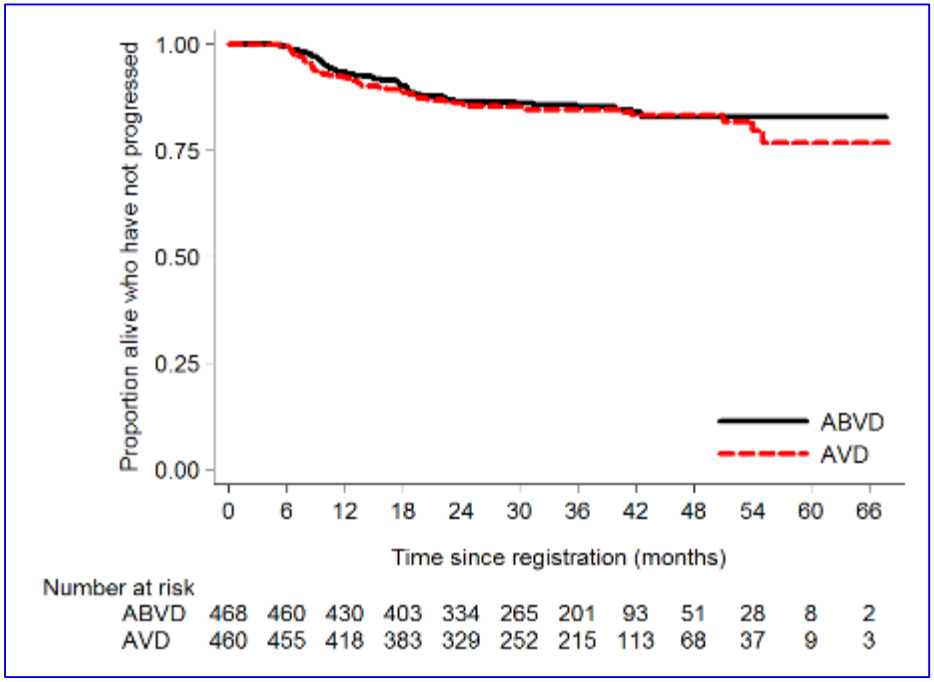


HR: 1.11 (0.79 – 1.54), p = 0.53

3 Year PFS, ABVD: **85.4% (95% CI: 81.6 – 88.5)**

3 Year PFS, AVD: **84.4% (95% CI: 80.7 - 87.6)**

Per protocol analysis:



HR: 1.09 (0.78 – 1.53), p = 0.59

3 Year PFS, ABVD: **85.3% (95% CI: 81.6 – 88.4)**

3 Year PFS, AVD: **84.6% (95% CI: 80.8 - 87.7)**

Association between baseline factors and PFS following negative PET-2

		Hazard ratio (95% CI)	p	3 year PFS %
Stage	II III IV	1.00 1.64 (1.09-2.47) 1.85 (1.23-2.81)	0.008	88.8 84.0 80.0
IPS	0-2 ≥3	1.00 1.41 (1.01-1.97)	0.043	86.7 81.6
Bulk	- +	1.00 0.80 (0.55-1.18)	0.263	87.8 83.8
PET-2 score	1 2 3	1.00 1.09 (0.62-1.90) 1.28 (0.72-2.27)	0.555	87.9 85.4 83.4

Results for patients with positive PET-2

3 year PFS %

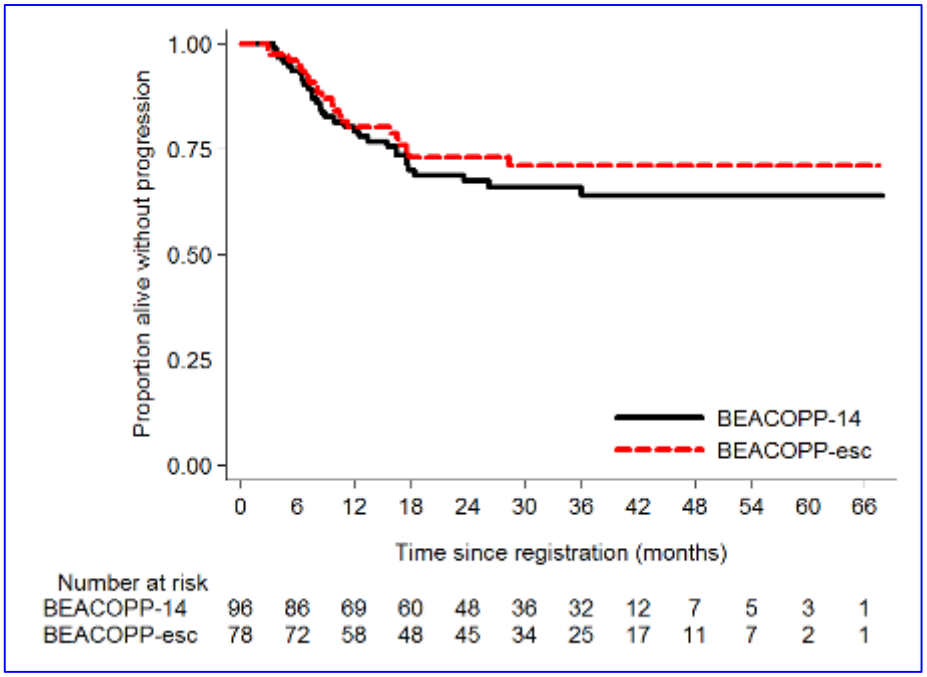
BEACOPP-14: 66.0 (55.0 – 74.9)

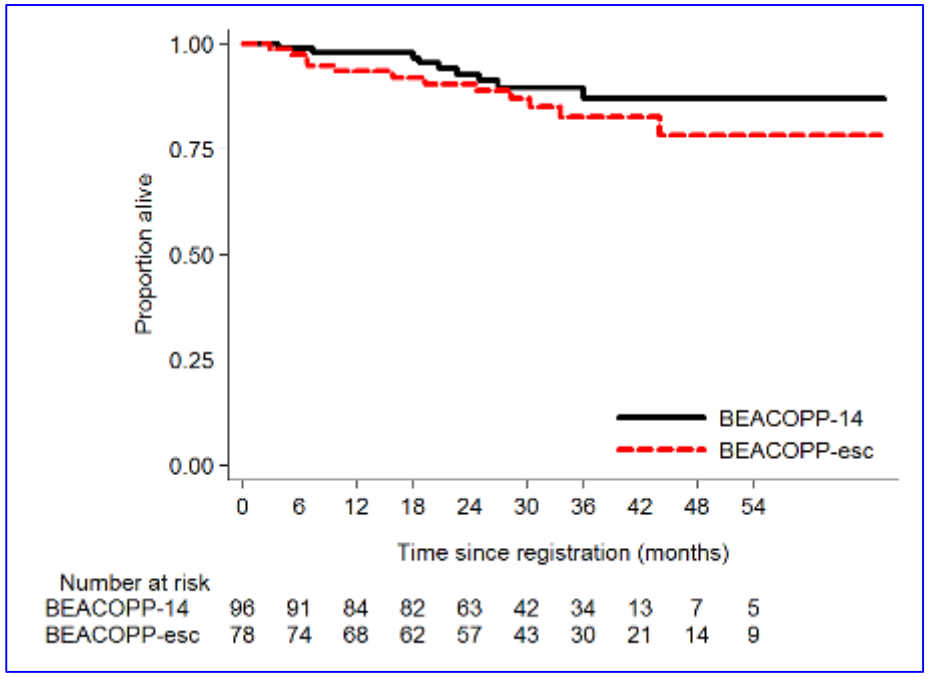
eBEACOPP 71.1 (59.0 – 80.2)

3 year OS %

BEACOPP-14: 89.6 (80.0 – 94.7)

eBEACOPP: 82.8 (70.5 – 90.2)





Johnson P et al Hematol Oncol, 2015;33(Suppl S1)100–180, abstract 8.

PET Interpretation

Themes:

- DS 1,2 has been used for de-escalation RAPID/H10/H15

- DS 1,2,3 used in RATHL, HD 0607

PET score no influence on PFS if PET –ve RATHL
post hoc HD0801 outcomes DS ≥ 4 favourable

DS 1-3 is likely CMR with standard treatment
Prudent to continue to use DS2 if omitting RT

- DS 5 worse prognosis RAPID/H0607/RATHL

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HL PET Prediction pre ASCT

		PET CMR	No CMR	
Devillier 2012 N = 111	5y PFS 5y OS	79 90	23 55	P < 0.001 P = 0.001
Gentzler 2014 N = 54	5y PFS 5y OS	85 100	52 48	P = 0.09 P = 0.007
Mocikova 2011 N = 76	2y PFS 2y OS	73 90	36 61	P = 0.01 P = 0.009
Moskowitz 2012 N = 97	EFS Median FU 51m	80	29	P < 0.001
Smeltzer N = 46	3y EFS 3y OS	82 91	41 64	P = 0.02 P = 0.08 NS

Pitfalls

- Thymic hyperplasia
- Infection and inflammation
- Treatment effects

eg xanthomatous granuloma

New agents ?

Summary

In the PET World, PET is now used in HL for
Staging in place of ceCT and BMB
At interim and EOT using DC

- For prognosis
- Response adapted treatment

Clinicians need to be aware of nuances of using DC and pitfalls of PET

- PET role in new agents needs to be explored
- No role for surveillance imaging (of any kind)

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Patients and their families