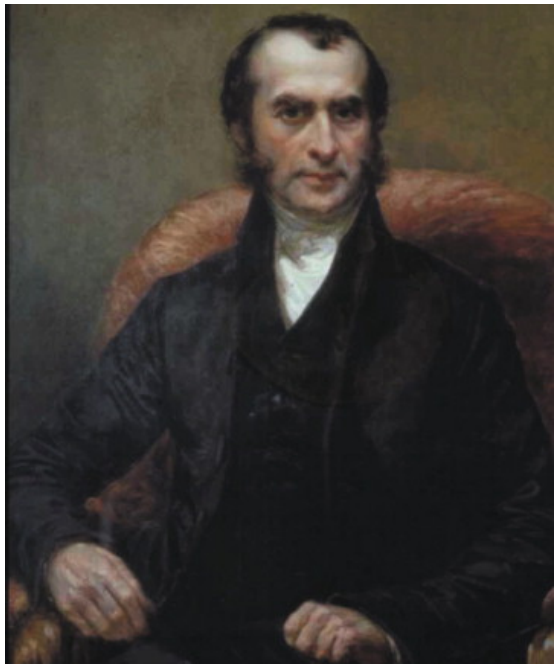
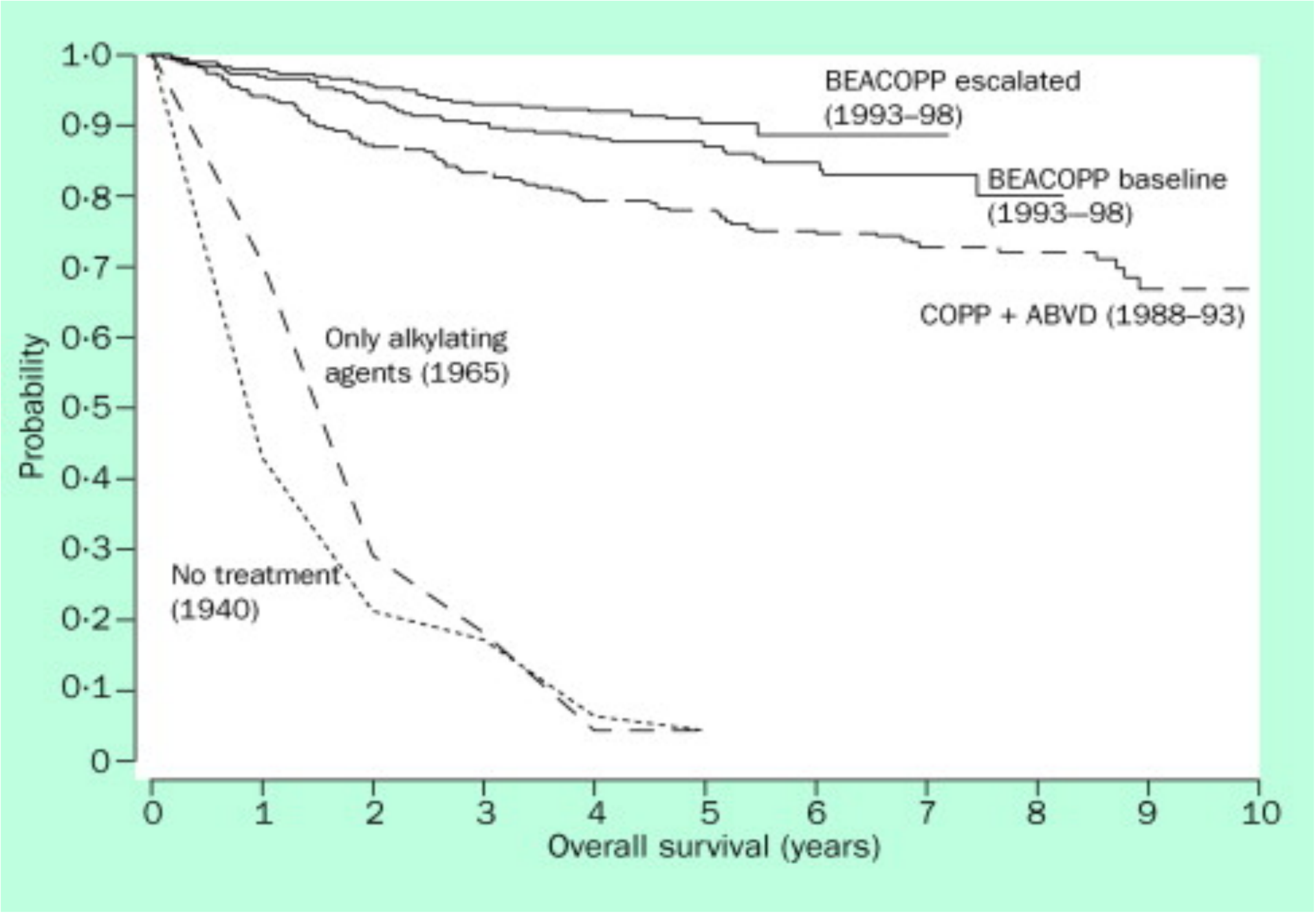


Thomas Hodgkin 1798-1866

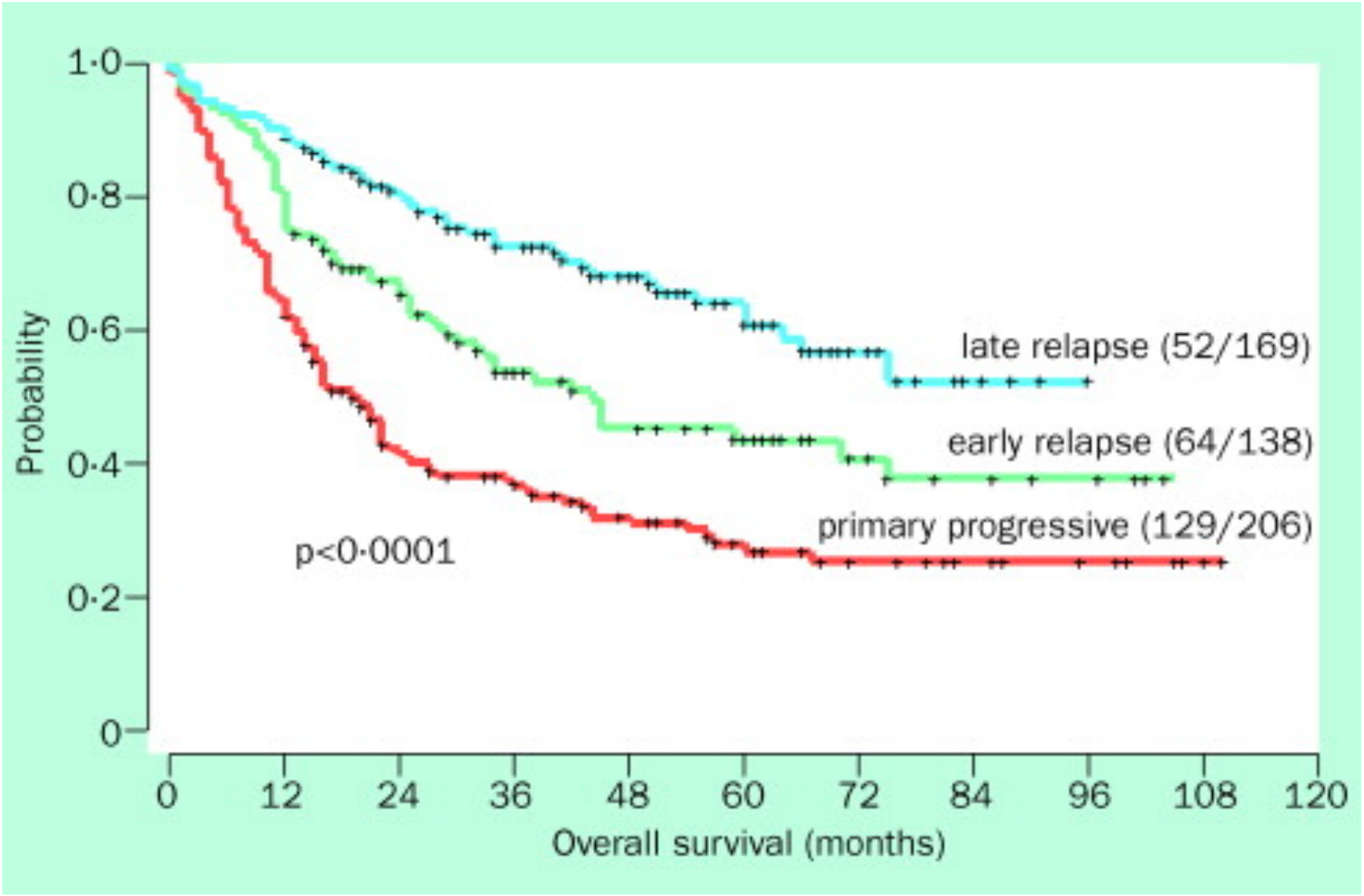
La gestione del linfoma di Hodgkin: il punto di vista dell'ematologo dell'adulto

Luigi Rigacci
U.O. Ematologia e Centro Trapianti Cellule Staminali
AO San Camillo Forlanini, Roma

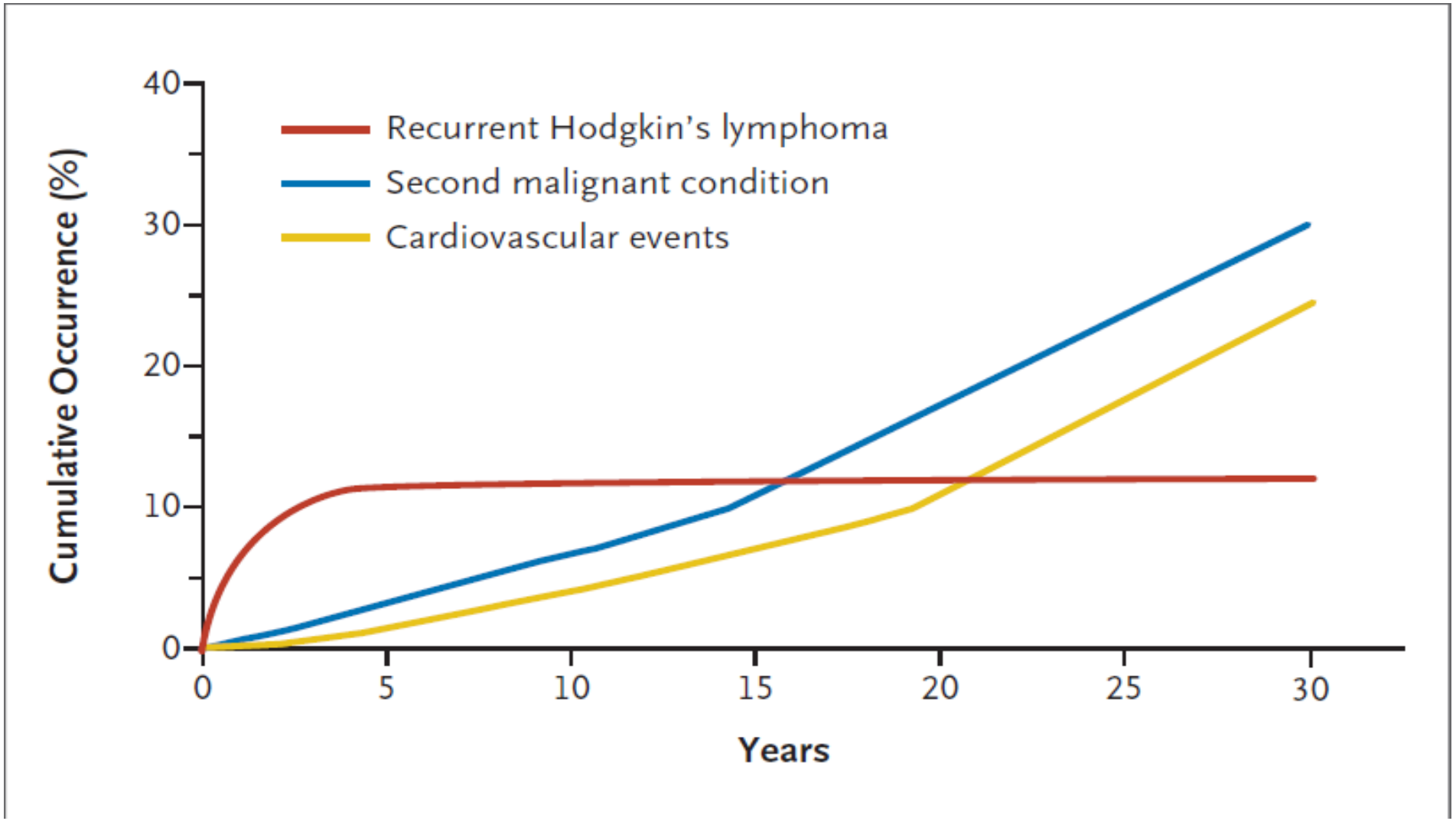
A success story

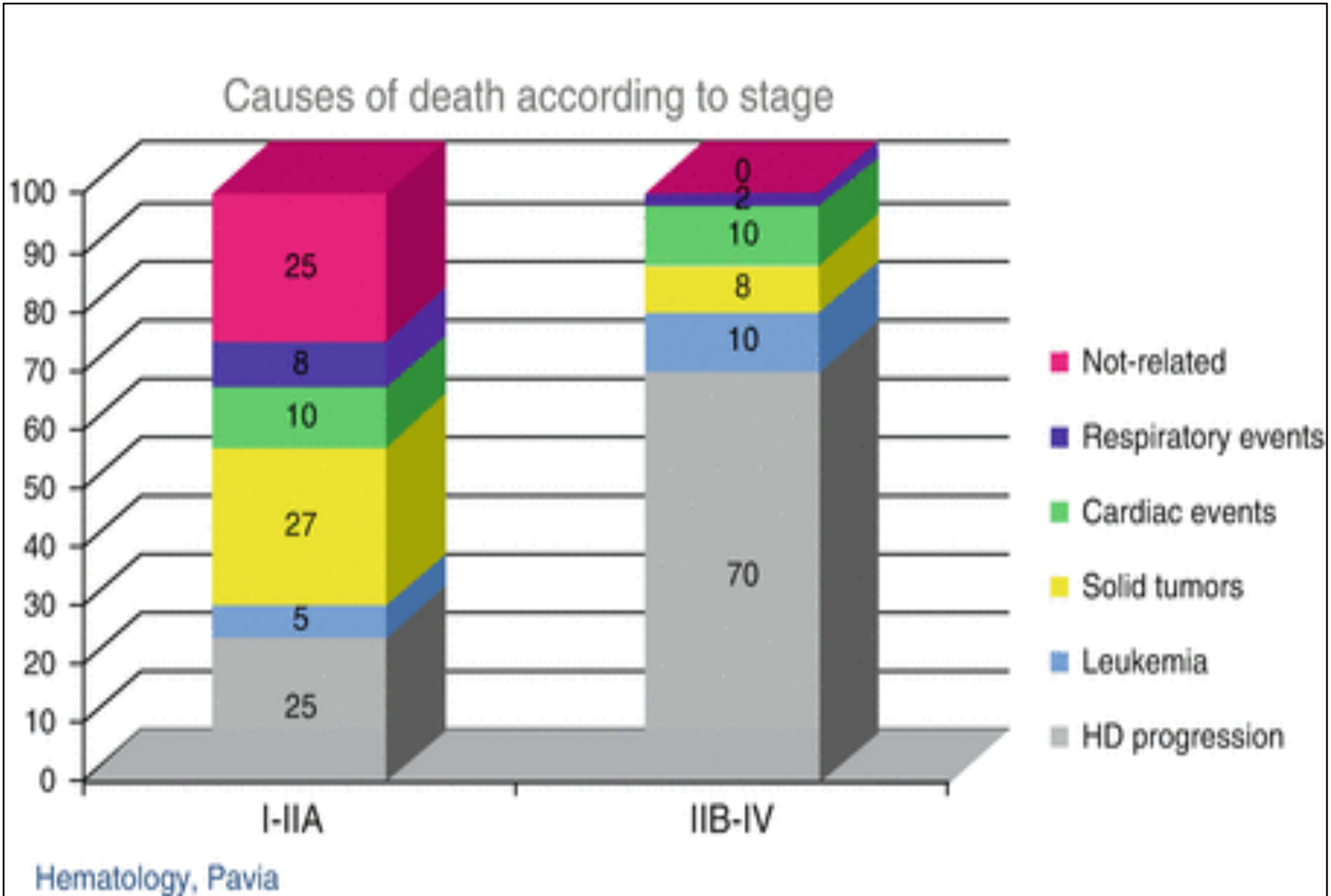


But, a fatal disease if……..



Causes of death




Causes of death according to stage
100
90
80
70
60
50
40
30
20
10
0
25
8
10
27
5
25
0
2
10
8
10
70
I-IIA
IIB-IV
Not-related
Respiratory events
Cardiac events
Solid tumors
Leukemia
HD progression
Hematology, Pavia

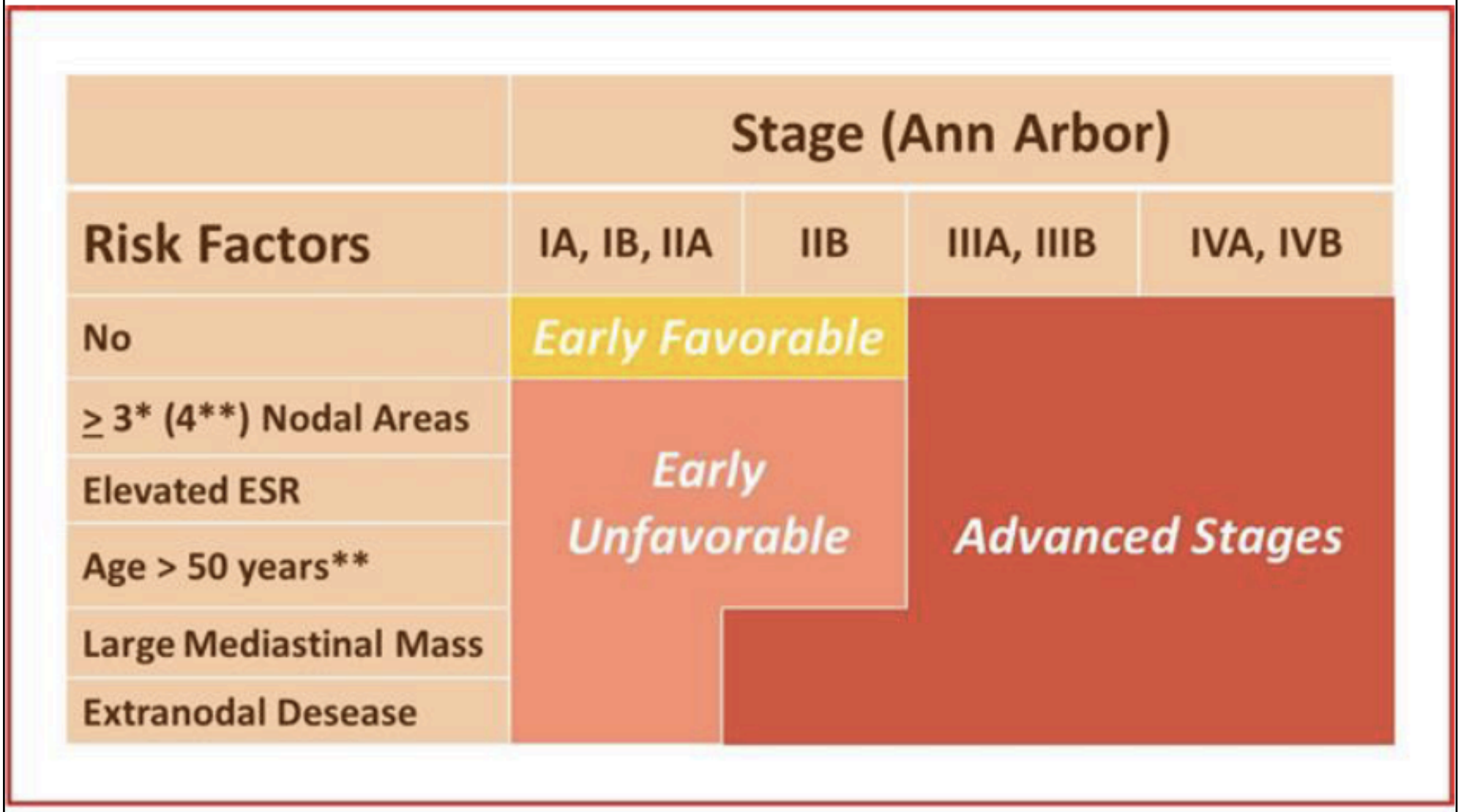
Topics

First line therapy:
- Localized favourable
- Localized unfavourable
- Advanced

Second line or salvage therapy:
- Relapsed disease
- Refractory disease

Toxicity reduction:
- Less radiotherapy (doses and fields)
- Less chemotherapy
- Early identification of chemoresisent patients

Stratification of HD according to stage and risk factors



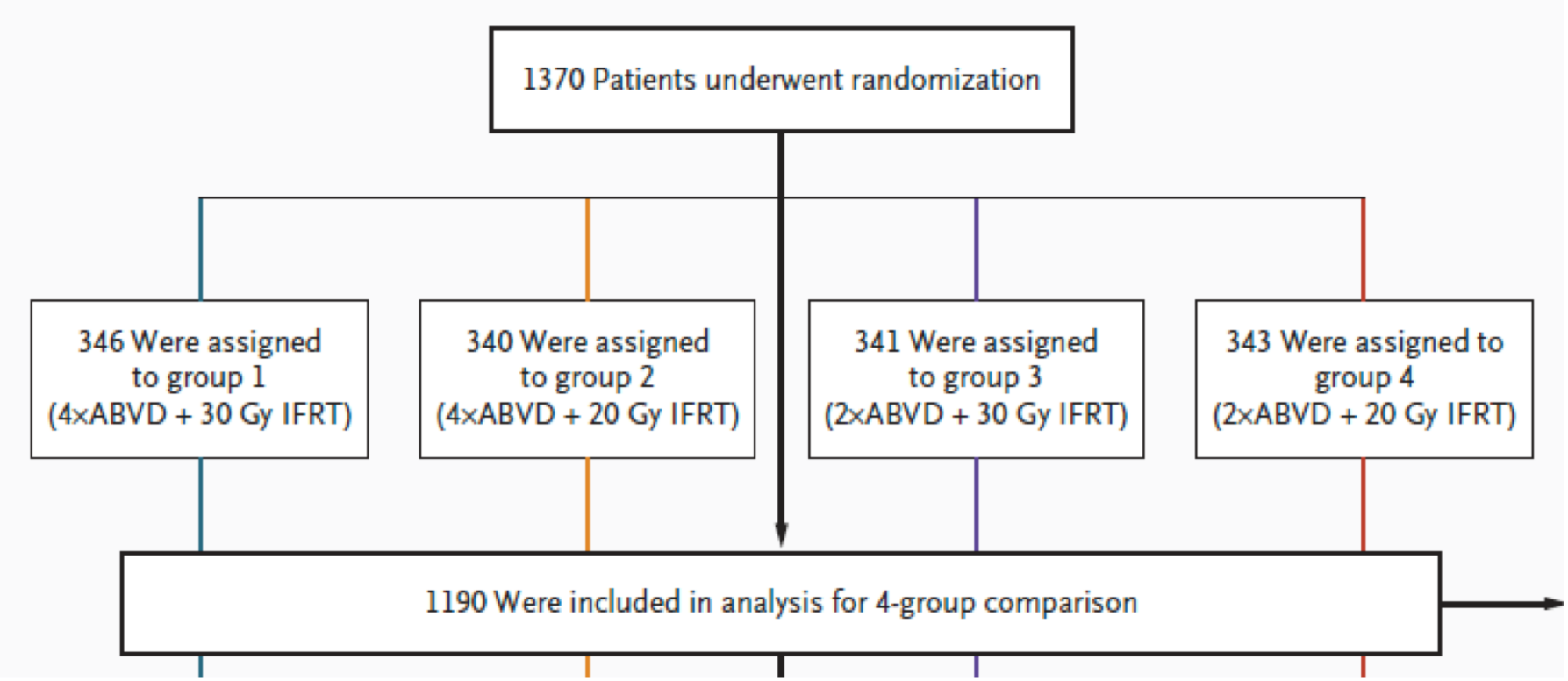
*GHSG ** EORTC

First line therapy

EARLY STAGE

Early stage favourable : GHSG HD10

Reduced Treatment Intensity in Patients with Early-Stage Hodgkin's Lymphoma



Engert et al, NEJM 363: 640; 2010

Early stage favourable : GHSG HD10

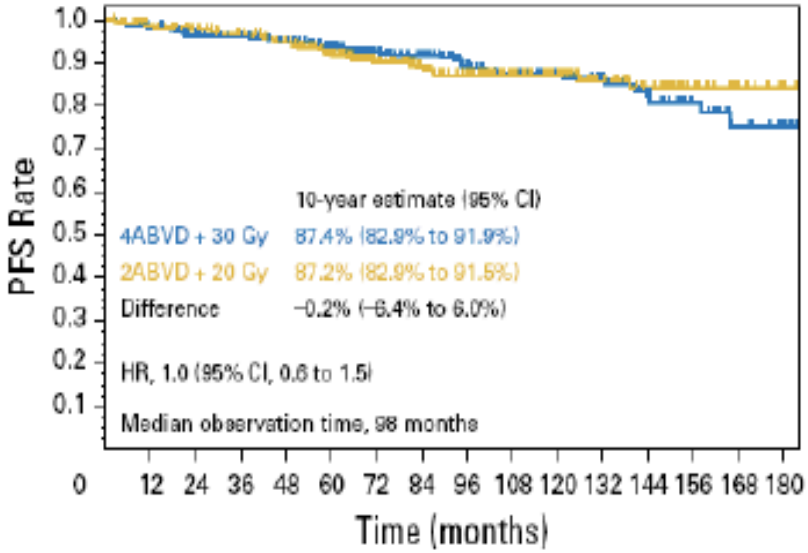
	CR %	5-yr PFS %	5-yr OS %
ABVD x 2	97	91.2	96.6
ABVD x 4	97	93.5	97.1
RT 20 Gy	97	93.2	97.5
RT 30 Gy	99	93.7	97.6

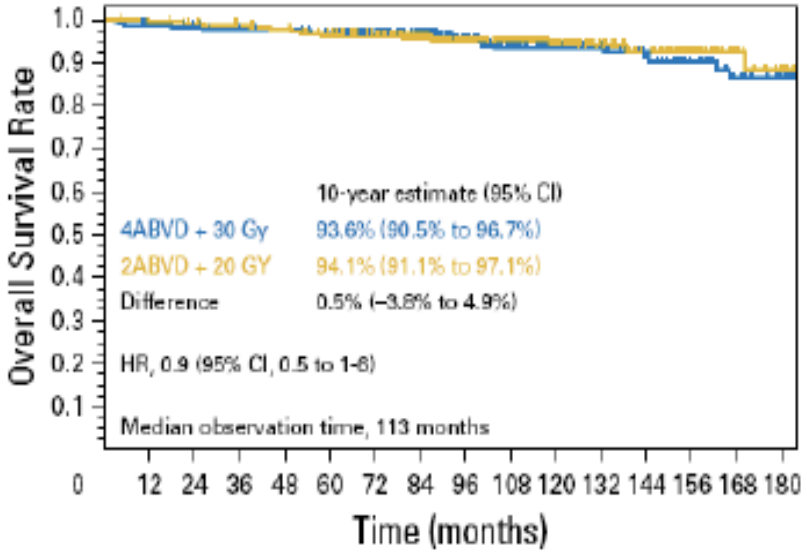
More adverse events for 4 ABVD vs 2 ABVD (52% vs 33%) and for 30 Gy vs 20 Gy RT (9% vs 3%)

2 ABVD + 20 Gy RT is the new standard

Engert et al, NEJM 363: 640; 2010

GHSG HD10 Update – 2017





ABVD x 4 c + IFRT 30 Gy vs. ABVD x 2 c + IFRT 20 Gy

At 10-years:

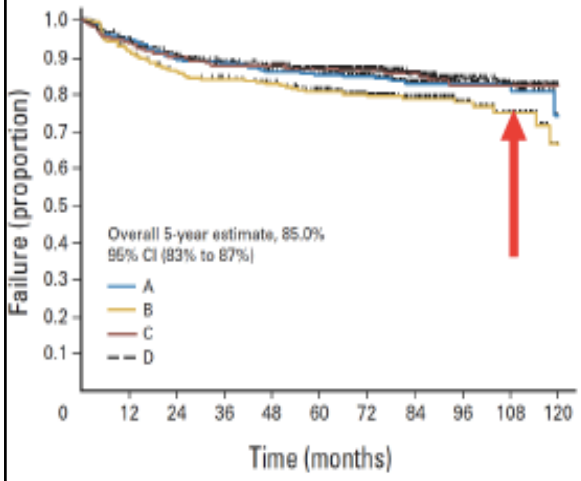
- PFS → 87.4% vs. 87.2% (NS)
- OS → 93.6% vs. 94.1% (NS)

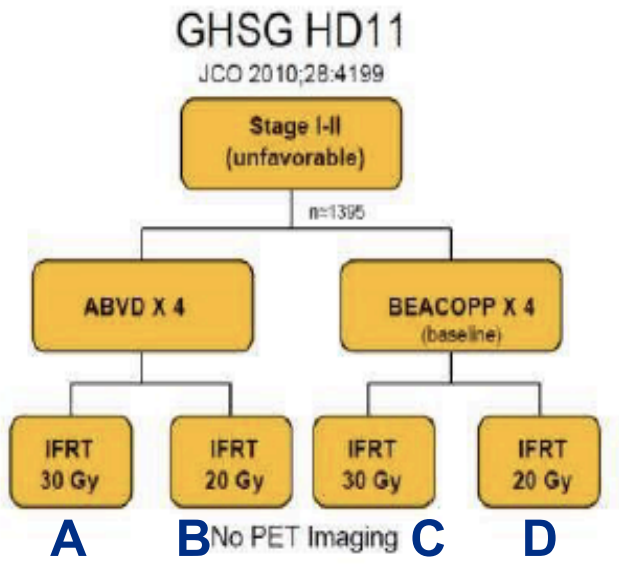
**Non-inferiority of 2c+20Gy regimen holds true*

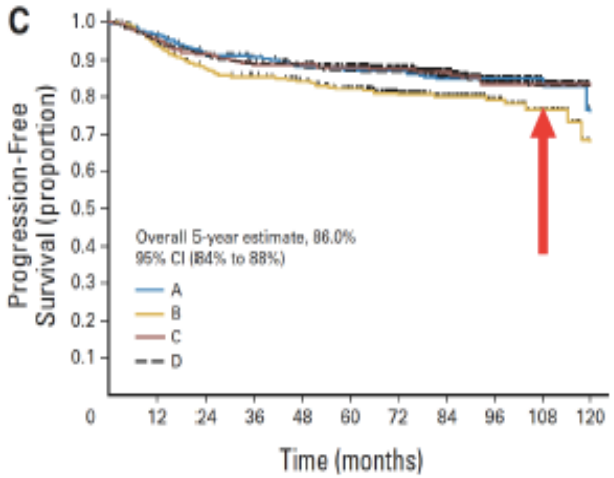
Sasse et al., JCO 2017

Early-stage cHL: Pre-PET Era Studies

Early Stage Unfavorable Disease: GHSG HD11





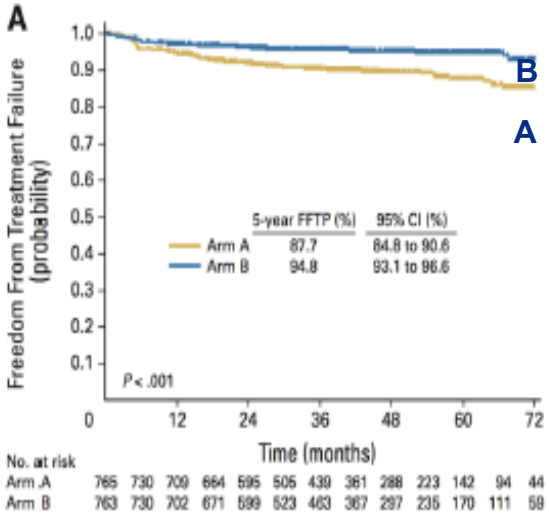


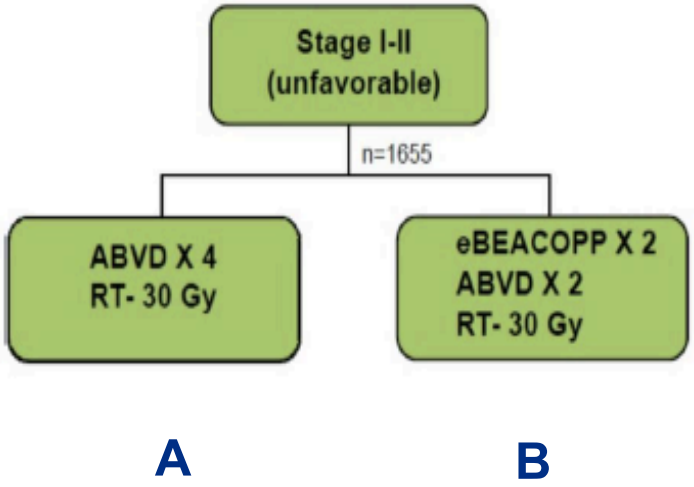
- Overall 5-yr FFTF 85% & OS 94.5%
- BEACOPP + 30 Gy did **not** improve FFTF over ABVD x 4 + 30 Gy
  - Concern for **inferior PFS/FFTF for ABVD x 4+ 20 Gy arm**
    - **Therefore, ABVD + 30Gy is standard of care**

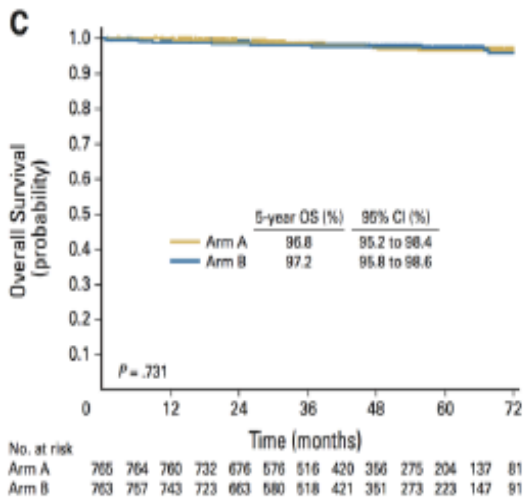
Eich HT, et al. J Clin Oncol. 2010;28(27):4199-4206.

Early-stage cHL: Pre-PET Era Studies

Early Stage Unfavorable Disease: GHSG HD14







N=1,655

Primary endpoint = FFTF

Improved PFS (by 7.2%), Similar OS

Increased hematologic toxicity with BEACOPP: 80% vs 24 %

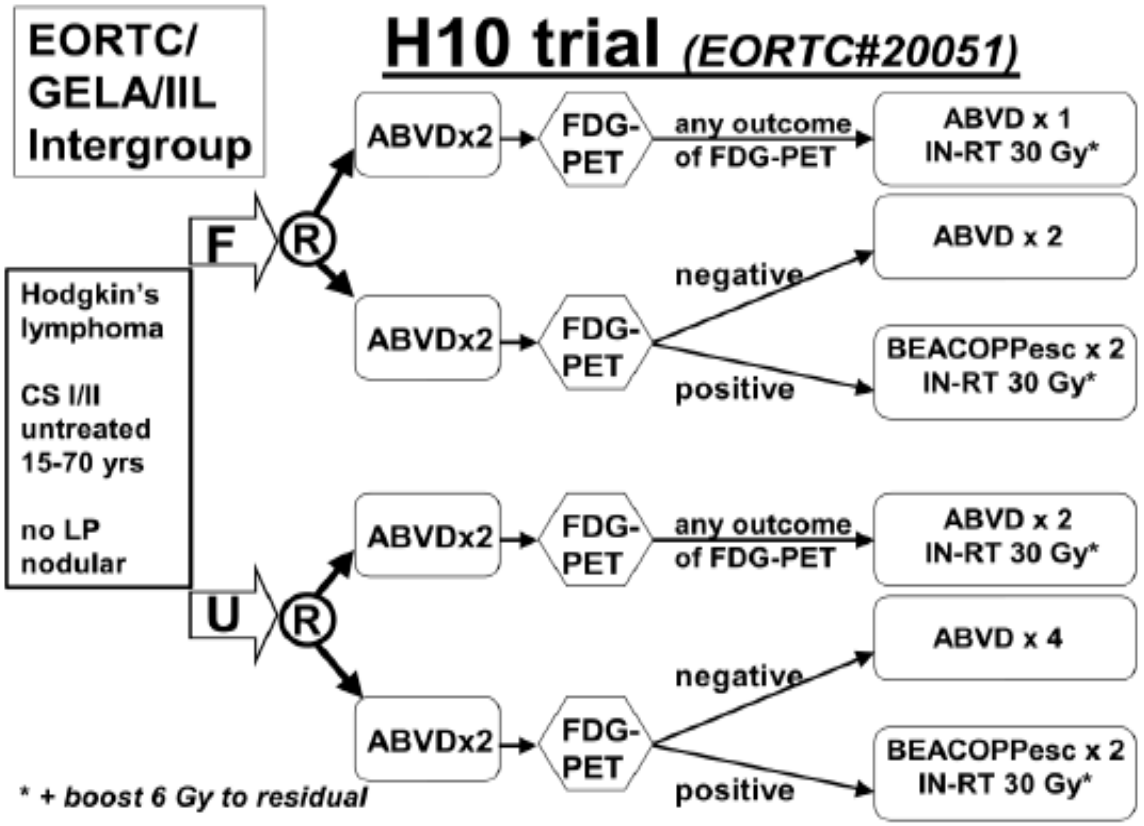
von Tresckow B, et al. J Clin Oncol. 2012;30(9):907-913

Early-stage cHL: Modern PET-Era Studies

EORTC H10

Can PET help identify patients in whom RT can be omitted?

- **1^0 endpoint=PFS, Non-inferiority (allow ≤10% diff)**
- Favorable disease per EORTC criteria:
  - Age <50
  - No bulky mediastinum
  - # nodal areas ≤3
  - ESR ≤ 50 if A or ESR ≤ 30 if B
- Note: 444 patients with favorable, early-stage HL (stage I/II)



Raemaekers et al., JCO 2014.

Early-stage cHL: Modern PET-Era Studies

EORTC H10

Raemaekers et al., JCO 2014

Planned Interim futility analysis after median follow-up of 1.1 years

Patients with early PET-negative disease (after 2 cycles of ABVD):

	# of pts	# of events	HR	1-yr PFS	P-value
ABVD x 3c + 30 Gy INRT	188	1	1.00	~100%	0.017
ABVD x 4 c	193	9	9.36	95%	

Events = progression of disease (no deaths)

- Could not demonstrate non-inferiority in the experimental arm

Interim analysis by the IDMC in June 2010:

-All investigators notified to stop all PET negative pts on the experimental "No RT" arm

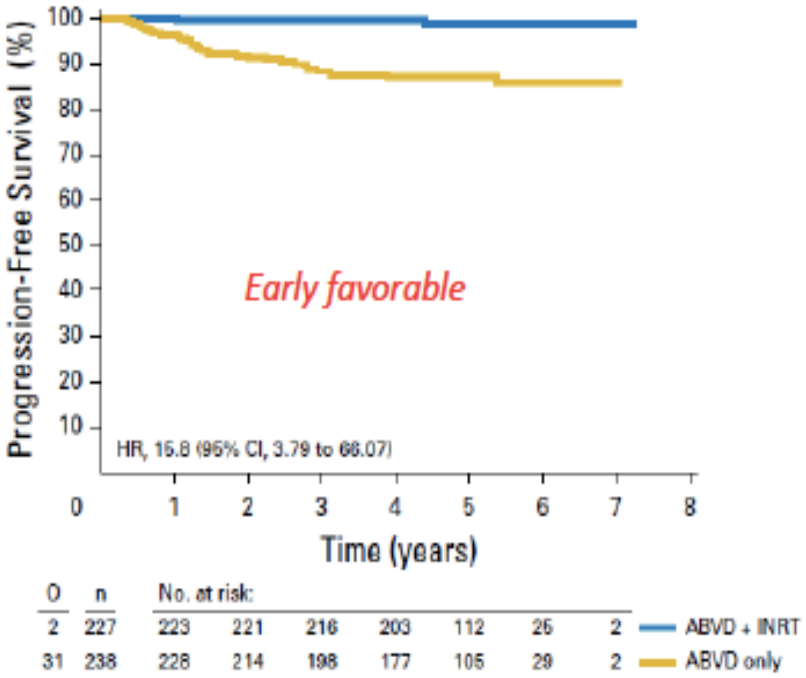
8th International Symposium on Hodgkin Lymphoma, 2010

- PET-negative experimental arm closed → patients in this arm converted if possible (within 6 weeks)

EORTC H10 update – 2017

Andre et al., JCO 2017

A

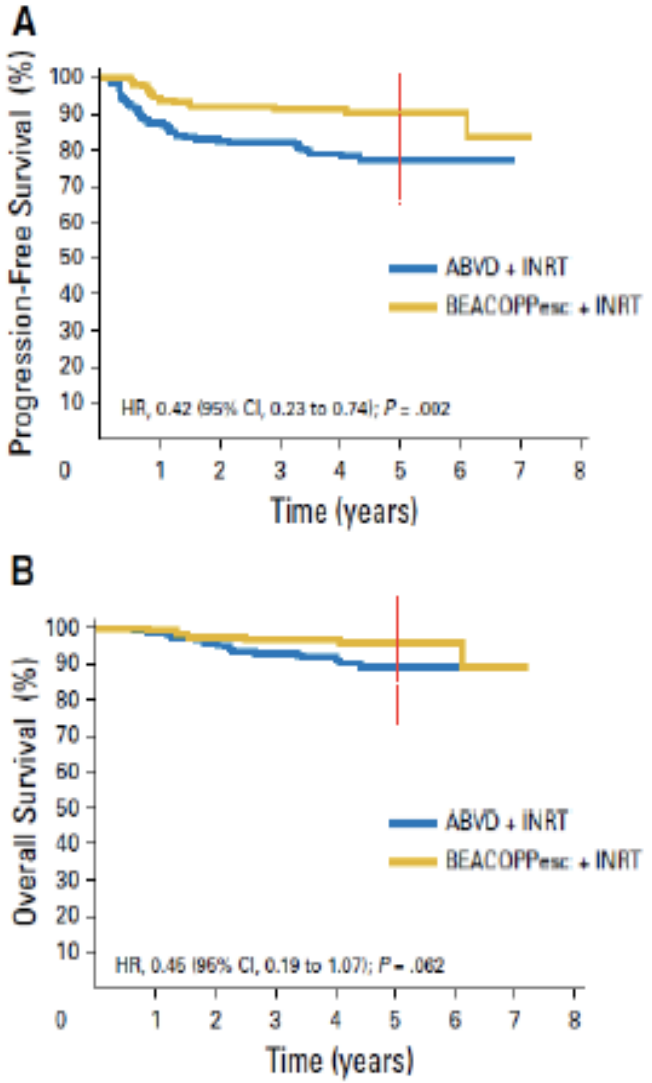


Update for Early PET-**negative** pts (favorable), med f/u 5 years:

	ABVD (n=238)	ABVD+INRT (n=227)
Events	30	2
Involved LN	22	0
Uninvolved LN	5	1
Both	3	1
5-yr PFS	87.1%	99.0%
5-yr OS	99.6%	100%

EORTC H10 update – 2017

Andre et al., JCO 2017



Early PET-**positive** patients (favorable + unfavorable <u>combined</u>):

	ABVD (n=192)	BEACOPP (n=169)	P-value
Events	41	16	
5-yr PFS	77.4%	90.6%	0.002
5-yr OS	89.3%	96.0%	0.062

<u>Control</u>: ABVD x 3 c → 30 Gy INRT

<u>Experimental</u>: ABVD x 2 c → BEACOPP x 2 c → 30 Gy INRT

EORTC H10 update – 2017

Andre et al., JCO 2017

Toxicity comparison		
Grade 3/4	**BEACOPPesc**	**ABVD**
Neutropenia	53.5%	30.3%
Anemia	4.9%	0.0%
Thrombocytopenia	19.7%	0.0%
Neutropenic fever	23.9%	1.1%
Infection	5.6%	1.1%

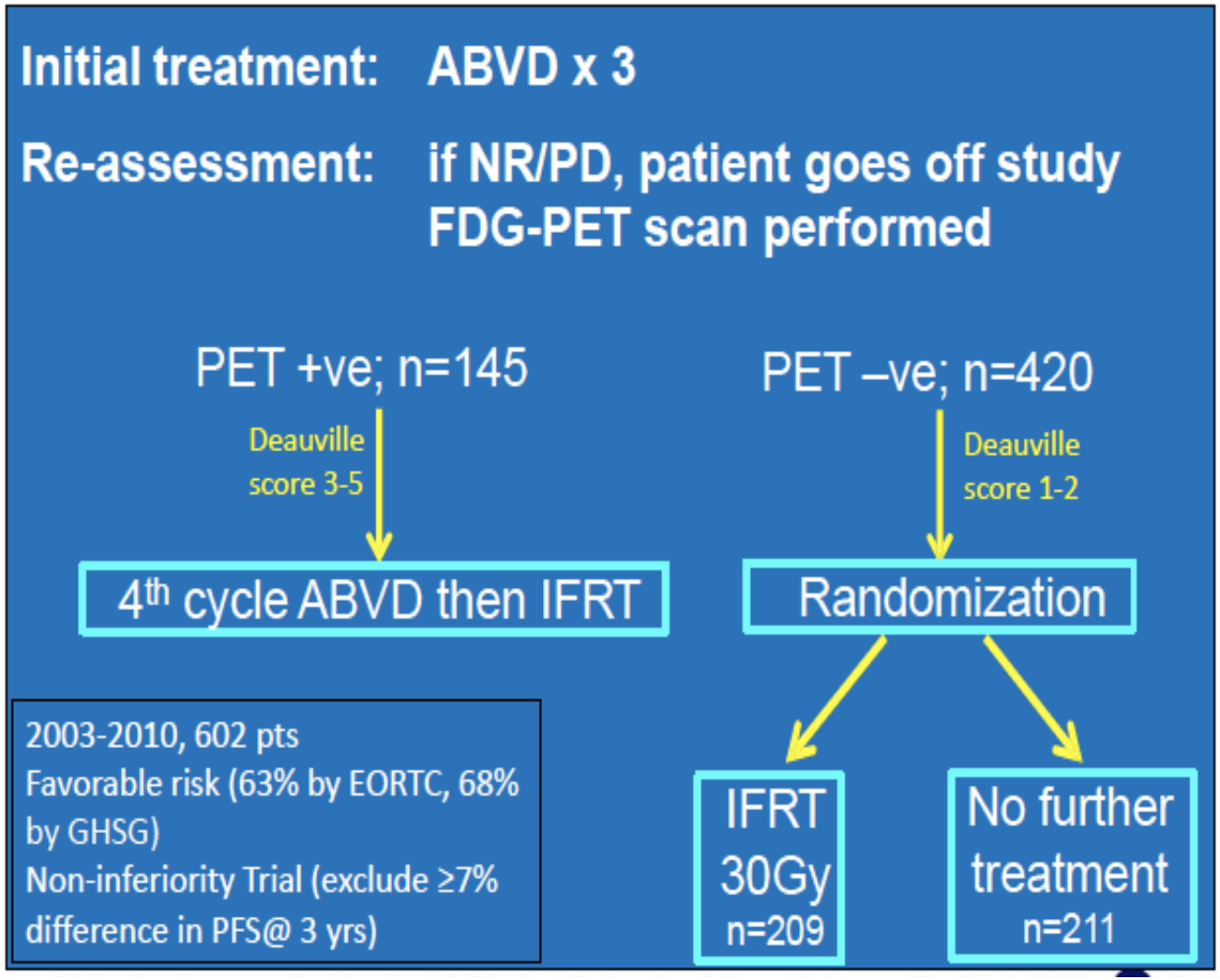
Control: ABVD x 3 c → 30 Gy INRT

Experimental: ABVD x 2 c → BEACOPP x 2 c → 30 Gy INRT

Chemo-escalation when PET2+ = increased toxicity…

Early-stage cHL, Modern PET-Era Trials: UK NCRI RAPID Trial

N = 602
- Stage IA/IIA cHL
- No bulky disease
- *# of nodal sites not an exclusion factor**



Radford et al. ASH Dec 2012

Radford et al. NEJM 2015

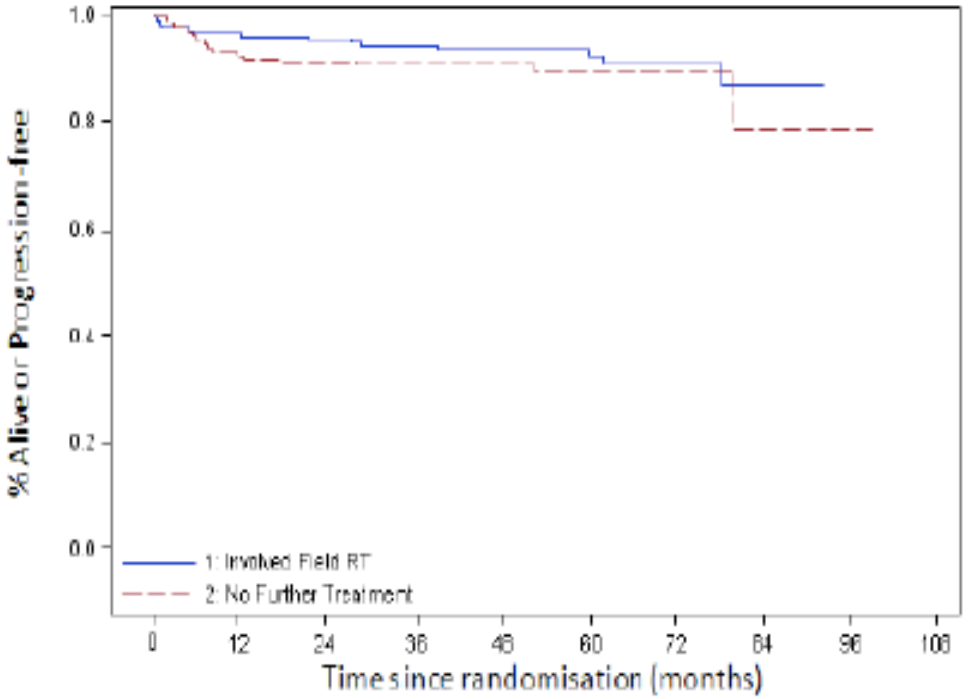
PET Scores after ABVD x 3c

- After 3 cycles ABVD - 571 pts had FDG PET CT scan :
- Deauville 5 point score *(centrally reviewed)*:
  - Score 1 : 301 (52.7%) **74.7% PET NEGATIVE**
  - Score 2 : 125 (22.0%)
  - Score 3 : 90 (15.7%) **25.3% PET POSTIVE**
  - Score 4 : 32 (5.6%)
  - Score 5 : 23 (4.0%)
- 420 of 426 PET–ve pts randomized to IFRT (209) or NFT (211)
  - 6 not randomized; pt choice 3, clinician choice 2, error 1
- **26 in the IFRT arm did not receive RT**
  - 19 patient or clinician choice
  - 5 died in IFRT arm (before IFRT)
  - 1 had pneumonia
  - 2 withdrew consent

Radford et al. ASH Dec 2012

Radford et al. NEJM 2015

PFS in the Randomized PET-ve Population (ITT, n=420, med f/u 48 mos)



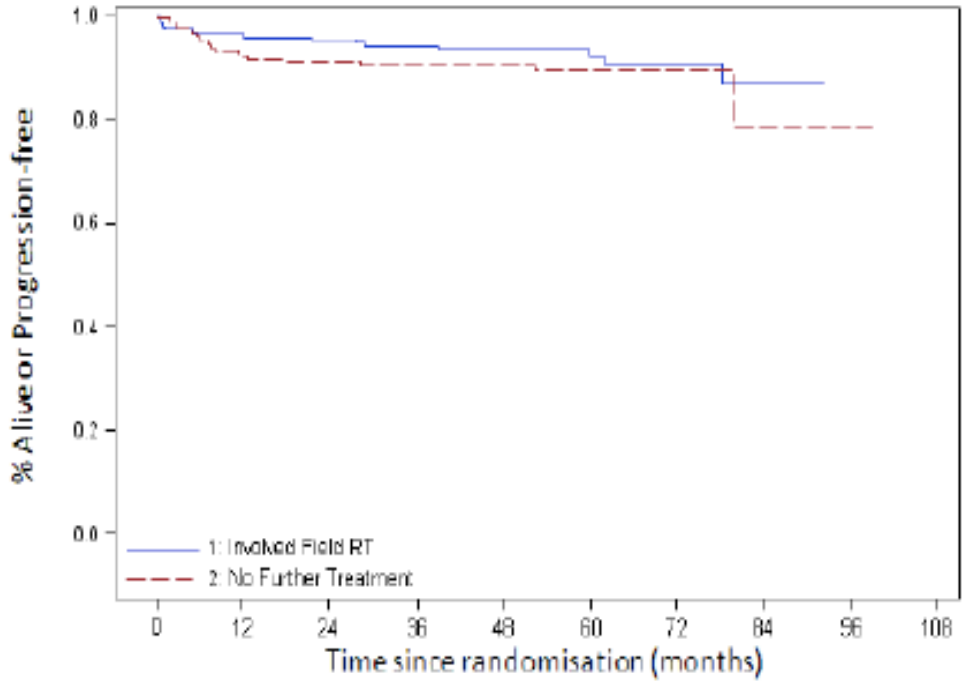
Number at risk:

IFRT	209	198	176	138	105	68	39	17	0	0
NFT	211	190	165	134	101	60	18	4	2	0

- 3 year PFS 94.5% IFRT vs 90.8% NFT (p=0.23) in favor of RT
- **BUT <7% difference in PFS @ 3 yrs**

Radford et al., NEJM 2015

PFS in the Randomized PET-ve Population ("As-treated" Analysis, n=392)



Number at risk:

IFRT	209	198	176	138	105	68	39	17	0	0
NFT	211	190	165	134	101	60	18	4	2	0

- 3 year PFS 97.0% IFRT vs 90.7% NFT (p=0.03) in favor of RT
- **Now ~7% difference in PFS @ 3 yrs**

Radford et al., NEJM 2015

Summary of UK NCRI RAPID Study

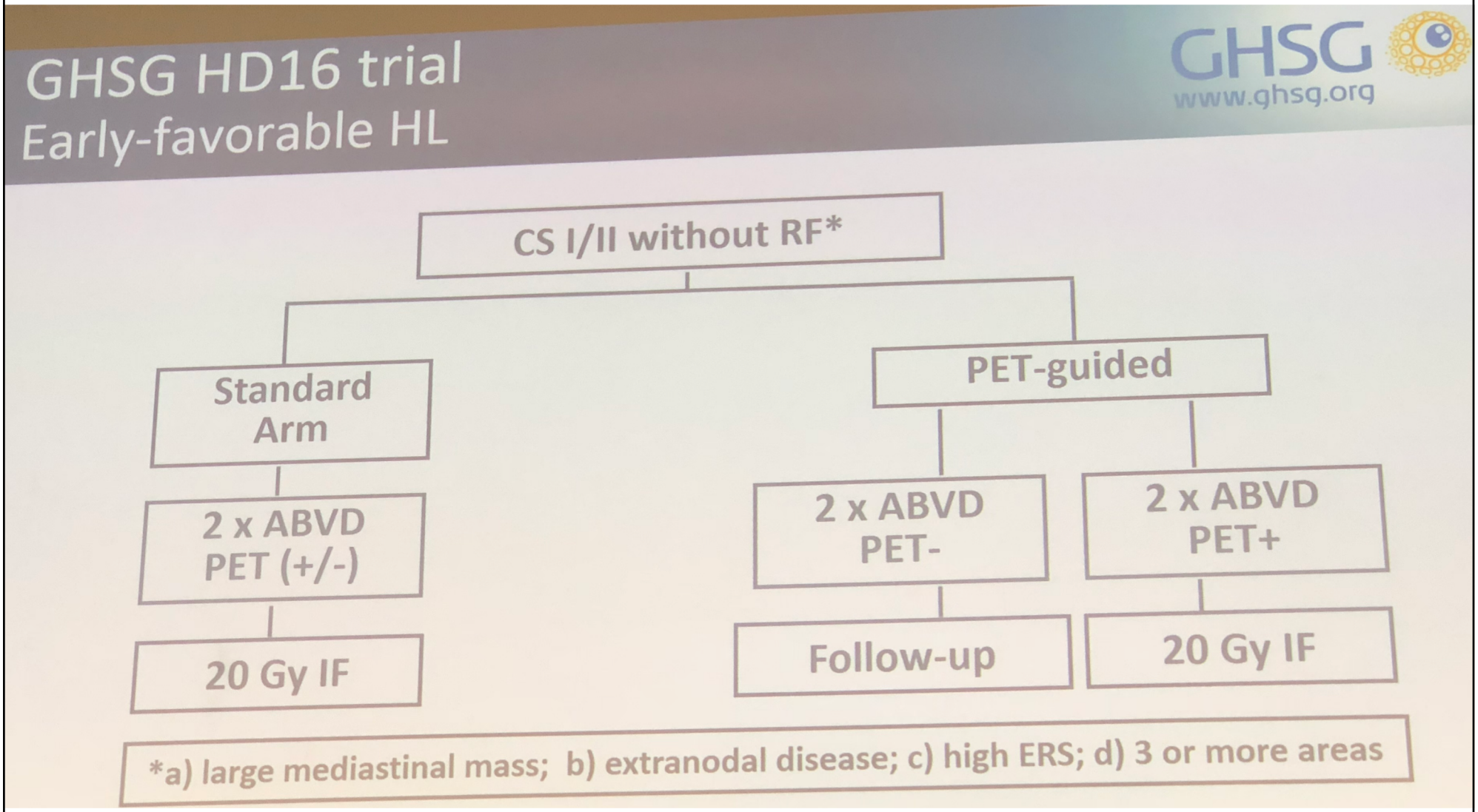
- Analysis presented at 48.6 months and following 36 events
- Conservative definition: 74.7% of patients PET –ve after ABVD x 3
  - Very conservative definition of PET results
  - Central review of PET images at the Core Lab
  - ***Rarely does this happen in routine clinical practice***
- *ITT Analysis* in 420 PET –ve patients 3 year PFS 94.5% IFRT vs 90.8% NFT (p=0.23)
- *Per protocol (as treated)* analysis in 392 PET – ve patients 3 year PFS 97.0% IFRT vs 90.7% NFT (p=0.03) *in favor of RT*
- PET-negative after chemo still benefits from RT to reduce risk of relapse

Radford et al. NEJM 2015

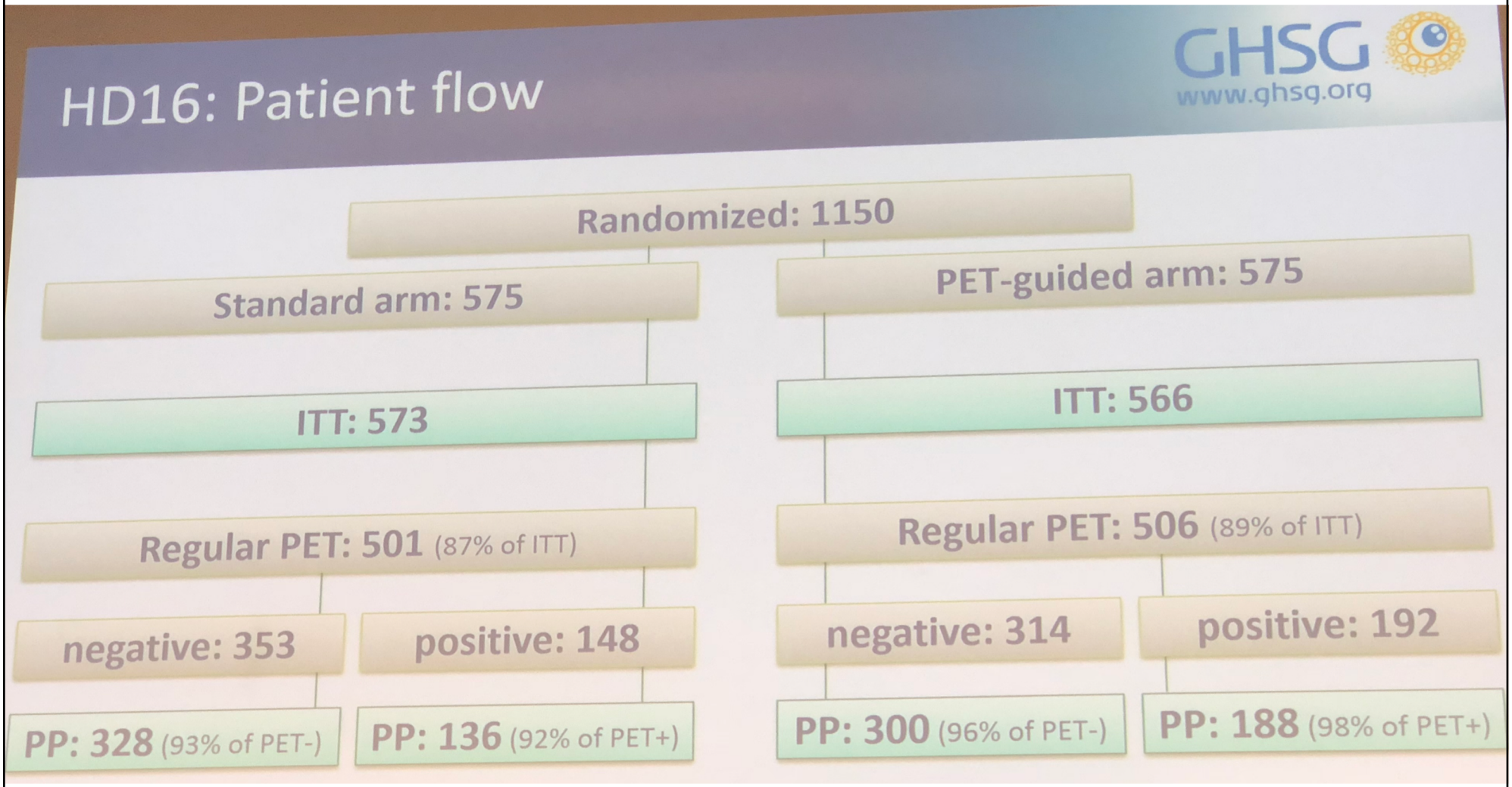
Conclusions for PET-era Studies:
EORTC H10/UK RAPID

- Using FDG PET, it may (*or may not*) be possible to identify patients with very favorable *interim* factors to omit consolidation RT
- PET-negative patients after chemo still benefit from IFRT/INRT (↑PFS but same OS)
- Evaluating PET response after chemo allows for treatment adaptation → identify those with less responsive disease to tailor optimal treatment regimen
- Field reduction from IFRT to INRT/ISRT is reasonable / validated
- BEACOPP more toxic → intensification with BEACOPP in less responsive disease improves PFS and trend to improve OS (if PET2+)
- Longer follow-up required to establish the impact of a PET negative approach

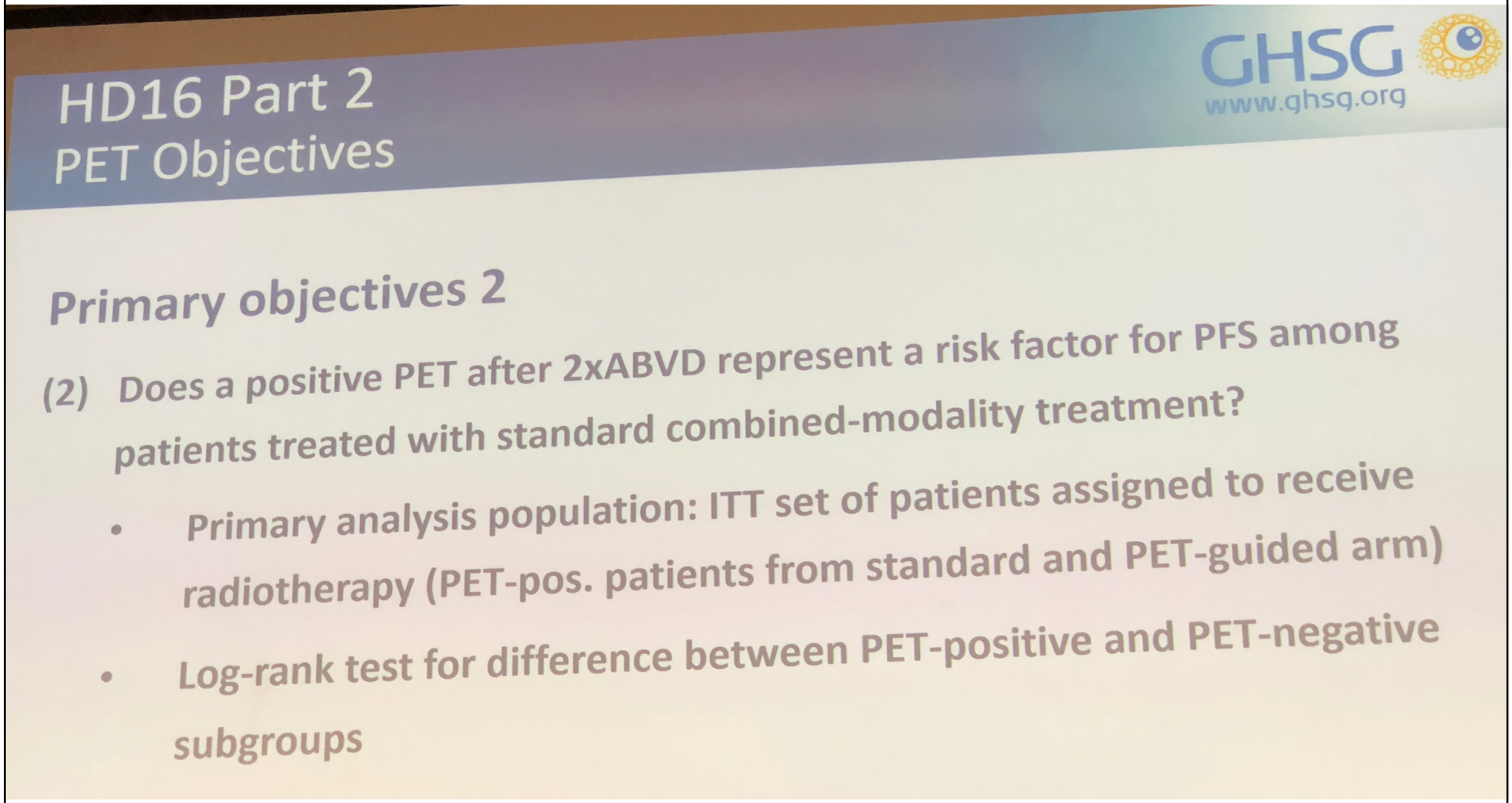
GHSG HD16


GHSG HD16 trial
Early-favorable HL
GHSG
www.ghsg.org
CS I/II without RF*
Standard Arm
PET-guided
2 x ABVD PET (+/-)
2 x ABVD PET-
2 x ABVD PET+
20 Gy IF
Follow-up
20 Gy IF
*a) large mediastinal mass; b) extranodal disease; c) high ERS; d) 3 or more areas

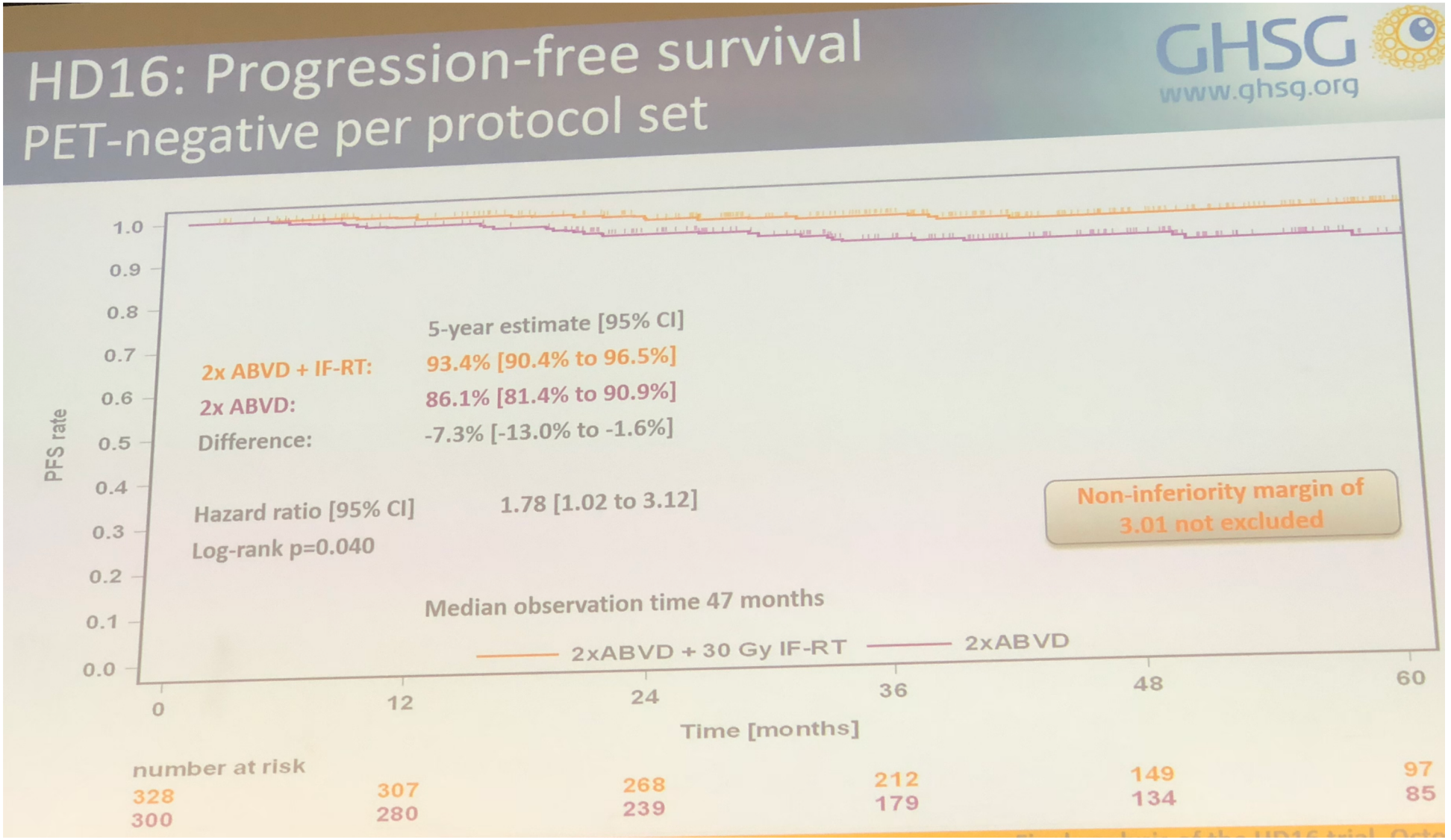
GHSG HD16


HD16: Patient flow
GHSG
www.ghsg.org
Randomized: 1150
Standard arm: 575
PET-guided arm: 575
ITT: 573
ITT: 566
Regular PET: 501 (87% of ITT)
Regular PET: 506 (89% of ITT)
negative: 353
positive: 148
negative: 314
positive: 192
PP: 328 (93% of PET-)
PP: 136 (92% of PET+)
PP: 300 (96% of PET-)
PP: 188 (98% of PET+)

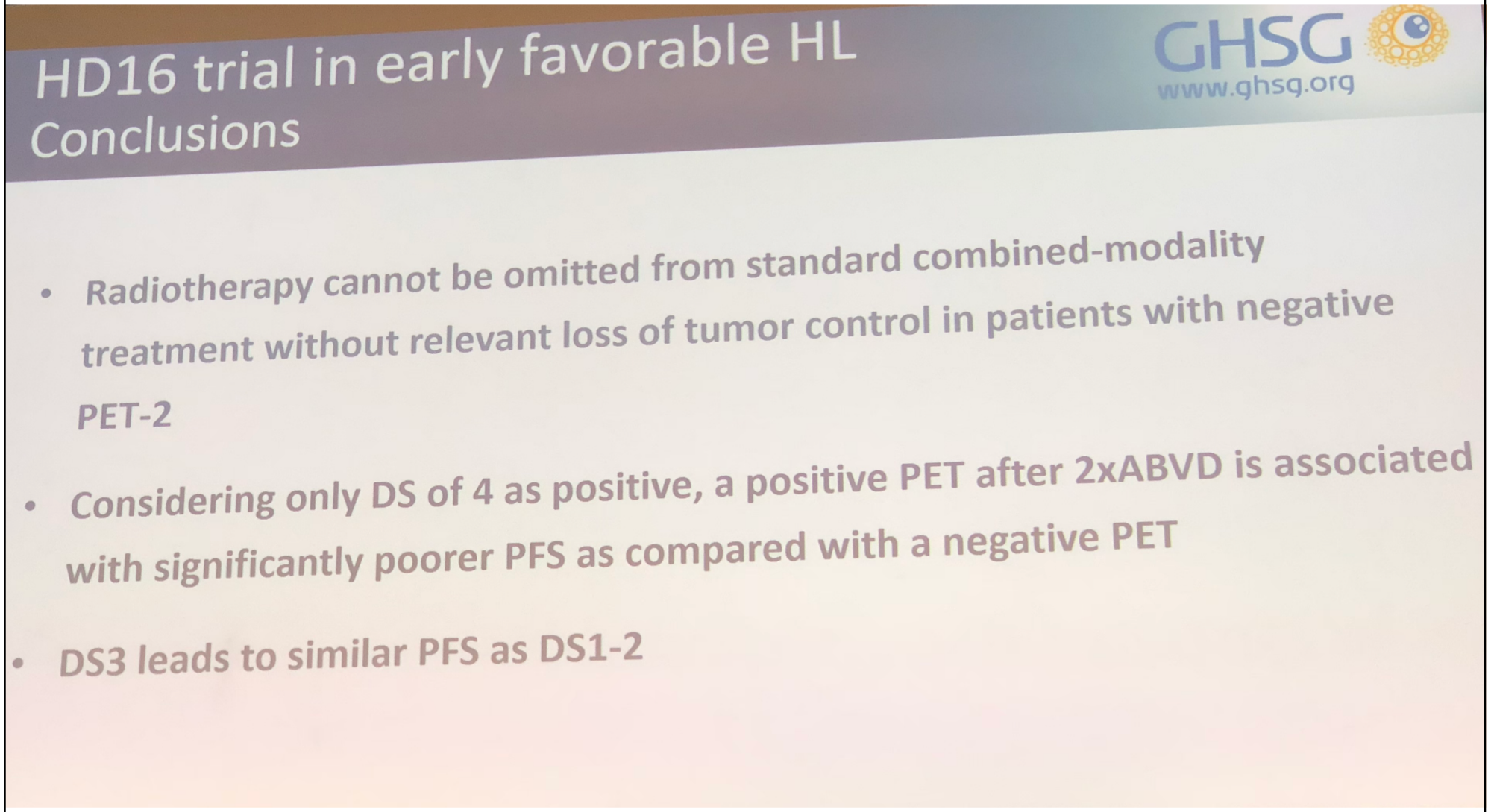
GHSG HD16


HD16 Part 2
PET Objectives
GHSG
www.ghsg.org
Primary objectives 2
(2) Does a positive PET after 2xABVD represent a risk factor for PFS among patients treated with standard combined-modality treatment?
• Primary analysis population: ITT set of patients assigned to receive radiotherapy (PET-pos. patients from standard and PET-guided arm)
• Log-rank test for difference between PET-positive and PET-negative subgroups

GHSG HD16


HD16: Progression-free survival
PET-negative per protocol set
GHSG
www.ghsg.org
PFS rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
5-year estimate [95% CI]
2x ABVD + IF-RT: 93.4% [90.4% to 96.5%]
2x ABVD: 86.1% [81.4% to 90.9%]
Difference: -7.3% [-13.0% to -1.6%]
Hazard ratio [95% CI] 1.78 [1.02 to 3.12]
Log-rank p=0.040
Non-inferiority margin of 3.01 not excluded
Median observation time 47 months
2xABVD + 30 Gy IF-RT
2xABVD
0
12
24
36
48
60
Time [months]
number at risk
328 307 268 212 149 97
300 280 239 179 134 85

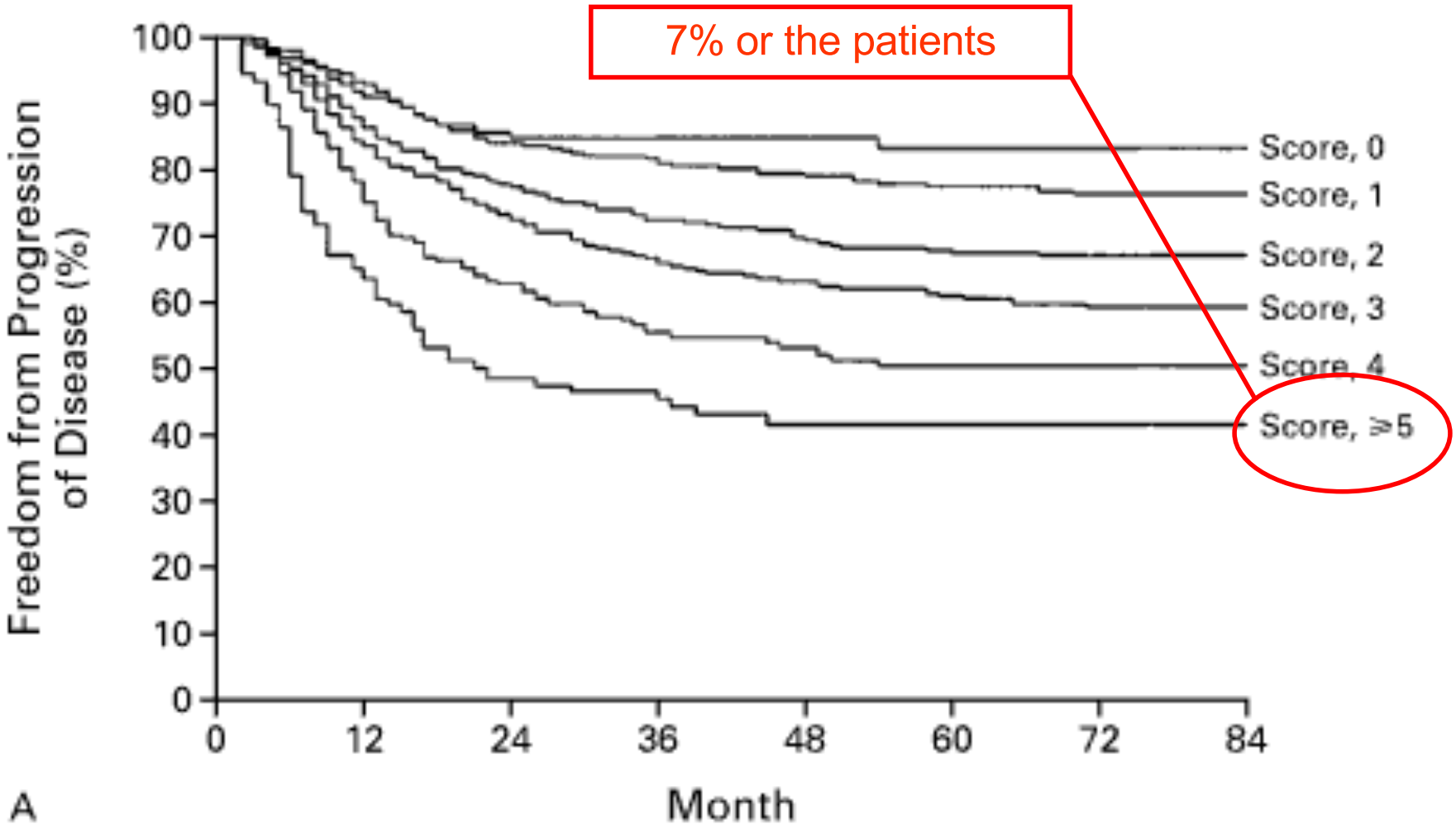
GHSG HD16


HD16 trial in early favorable HL
Conclusions
GHSG
www.ghsg.org
• Radiotherapy cannot be omitted from standard combined-modality treatment without relevant loss of tumor control in patients with negative PET-2
• Considering only DS of 4 as positive, a positive PET after 2xABVD is associated with significantly poorer PFS as compared with a negative PET
• DS3 leads to similar PFS as DS1-2

First line therapy

ADVANCED STAGE

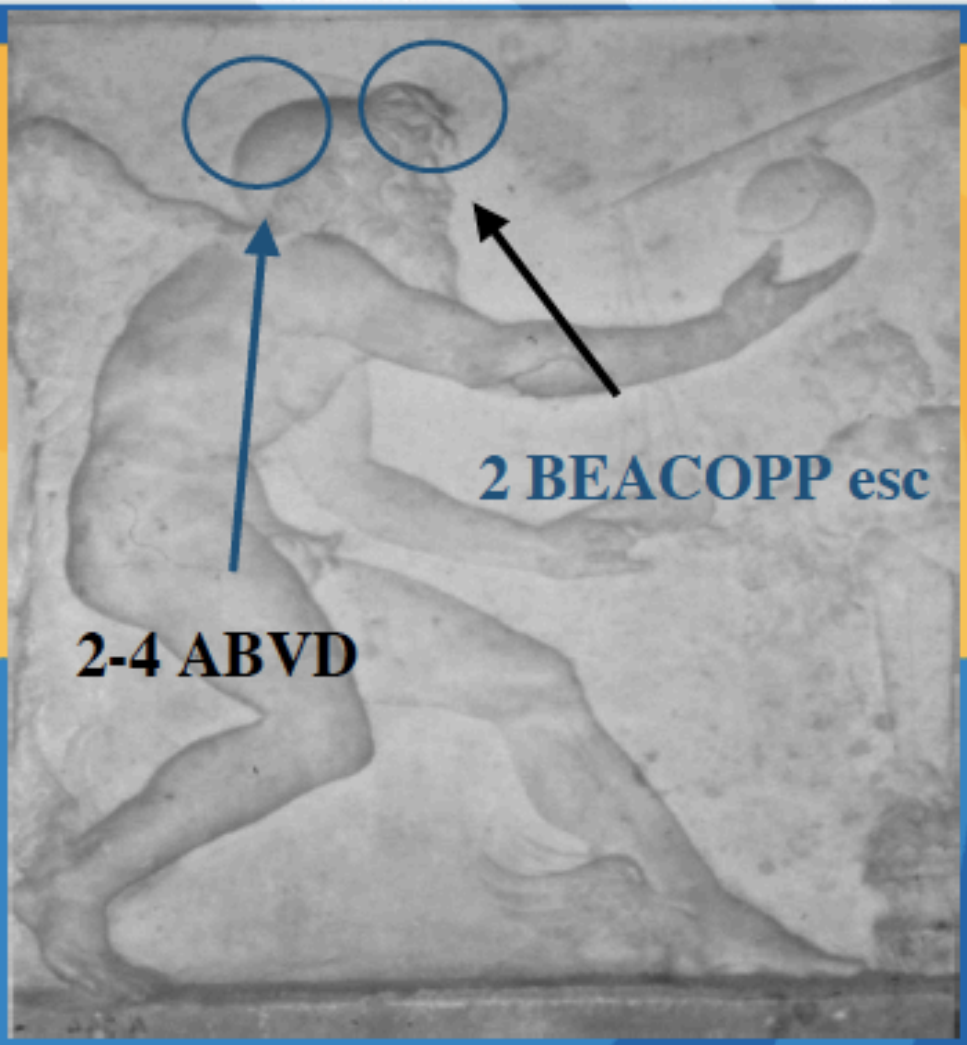
Advanced HL prognostic score: 7y-FFP & OS



Hasenclever D. NEJM 1988; 339:1506

„Catch the moment“...

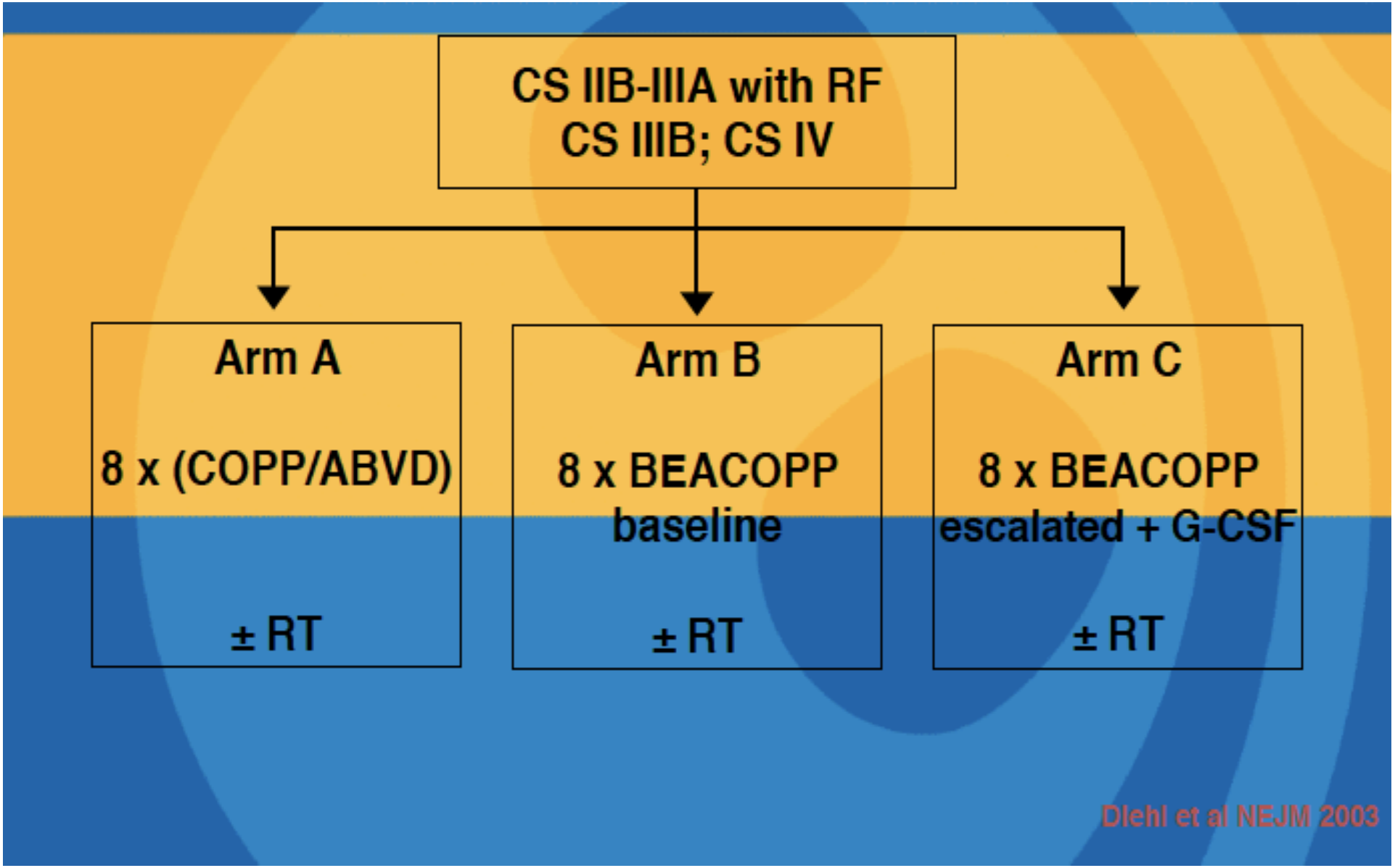
„Catch it with the first grip, otherwise you loose your chance!“



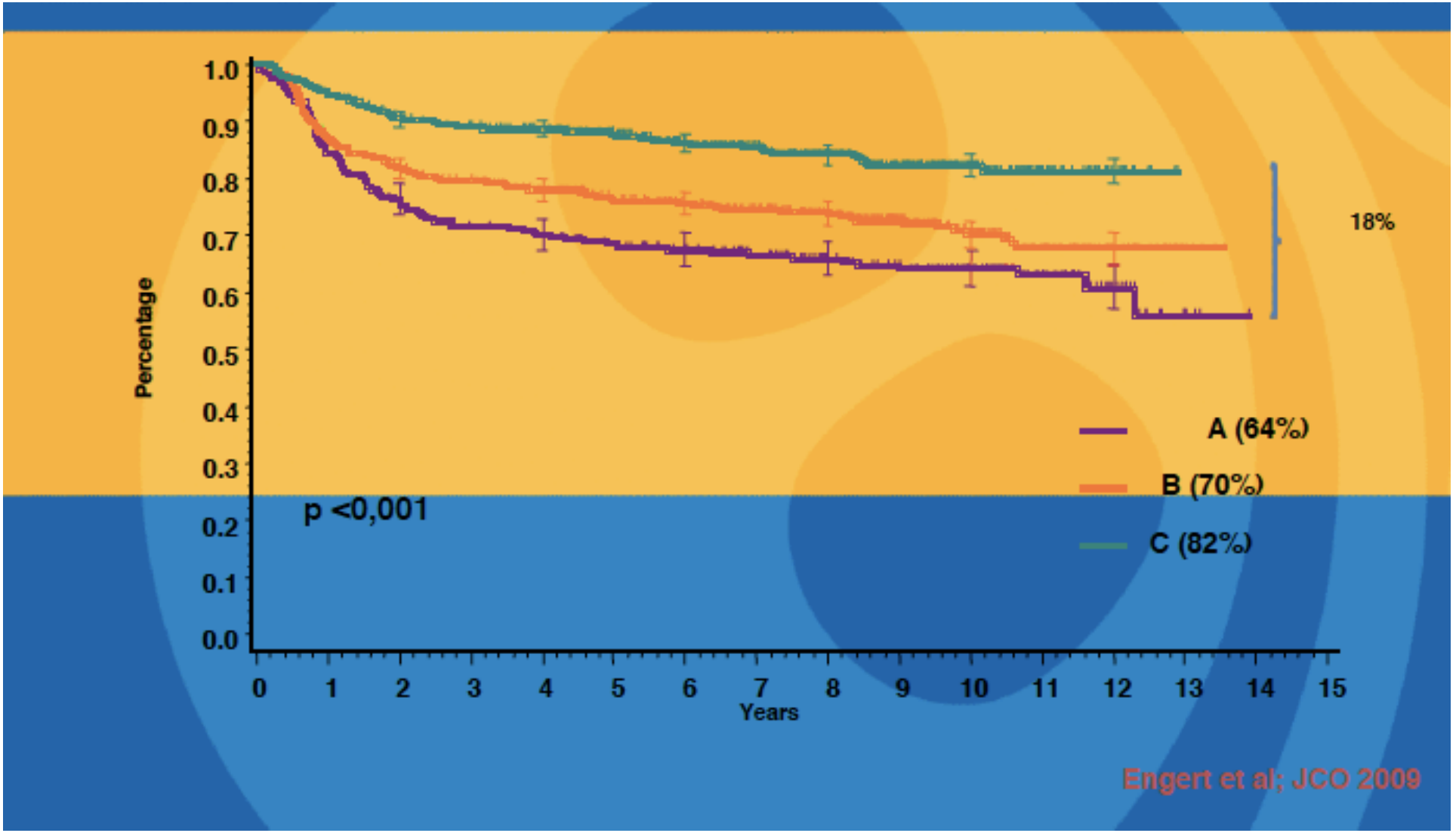
BEACOPP baseline and BEACOPP escalated

Drug	BEACOPP basic			BEACOPP escalated		
	Dose	Route	Day	Dose	Route	Day
Cyclophosphamide	650 mg/m²	i. v.	1	1250 mg/m²	i. v.	1
Doxorubicin	25 mg/m²	i. v.	1	35 mg/m²	i. v.	1
Etoposide	100 mg/m²	i. v.	1–3	200 mg/m²	i. v.	1–3
Procarbazine	100 mg/m²	p. o.	1–7	100 mg/m²	p. o	1–7
Prednisone	40 mg/m²	p. o.	1–14	40 mg/m²	p. o.	1–14
Vincristine	1.4 mg/m² (max. 2 mg)	i. v.	8	1.4 mg/m² (max. 2 mg)	i. v.	8
Bleomycin	10 mg/m²	i. v.	8	10 mg/m²	i. v.	8

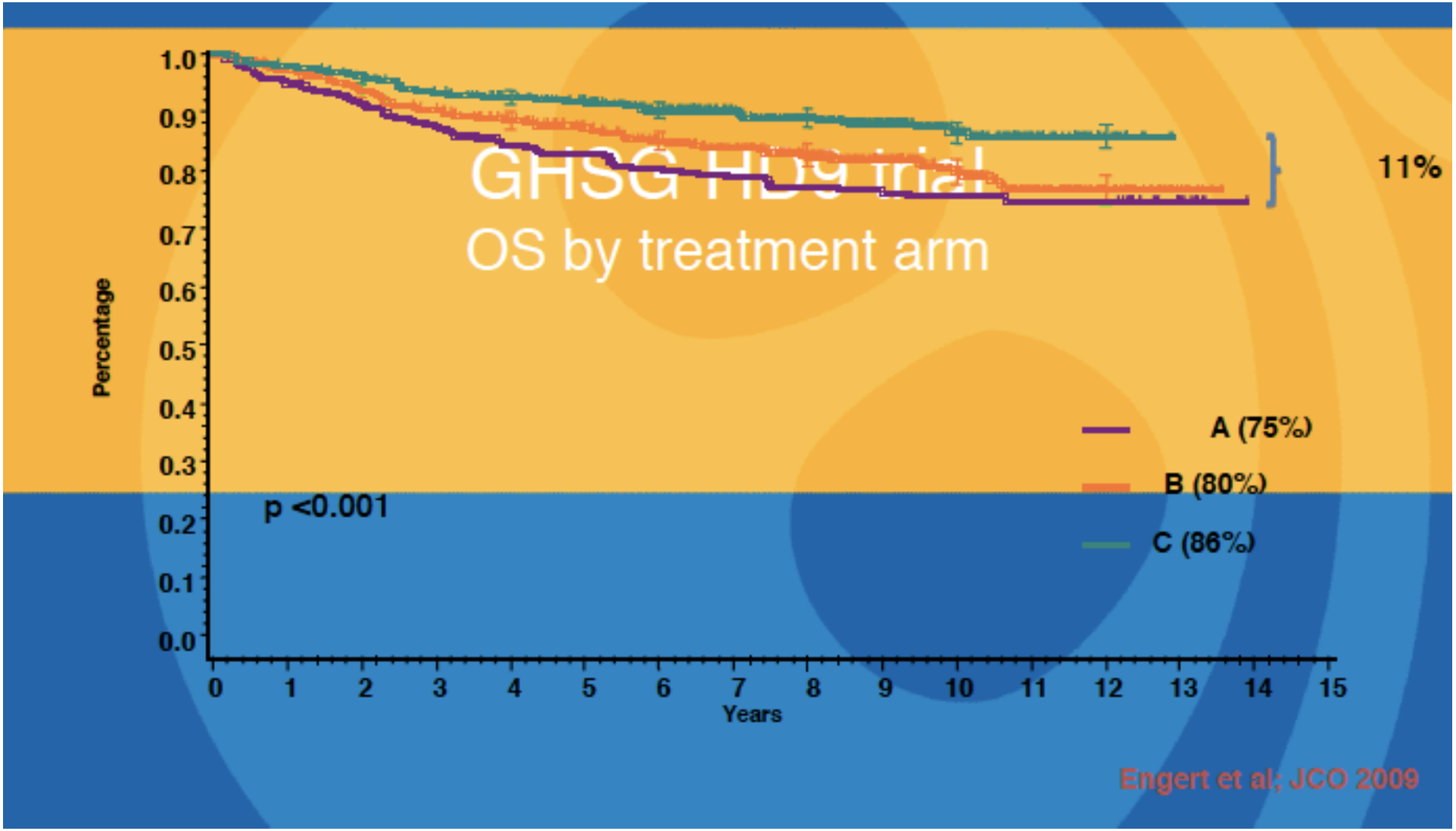
HD9 study GHSG: Advanced stage HD



HD9 study GHSG: Advanced stage HD Progression Free Survival



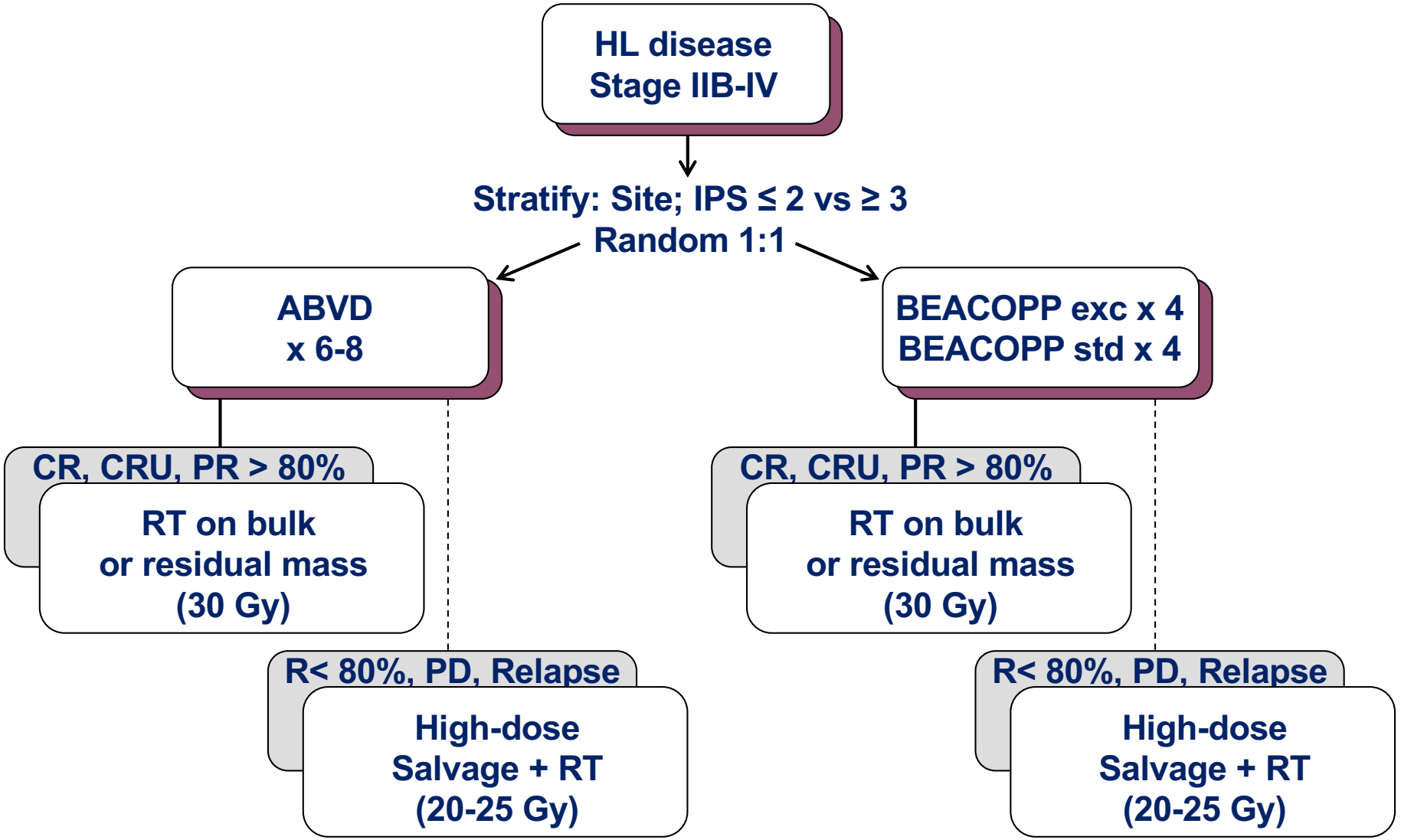
HD9 study GHSG: Advanced stage HD Overall Survival



Advanced stage: ABVD vs BEACOPP

Studio IIL-GITIL-Michelangelo

Study Outline

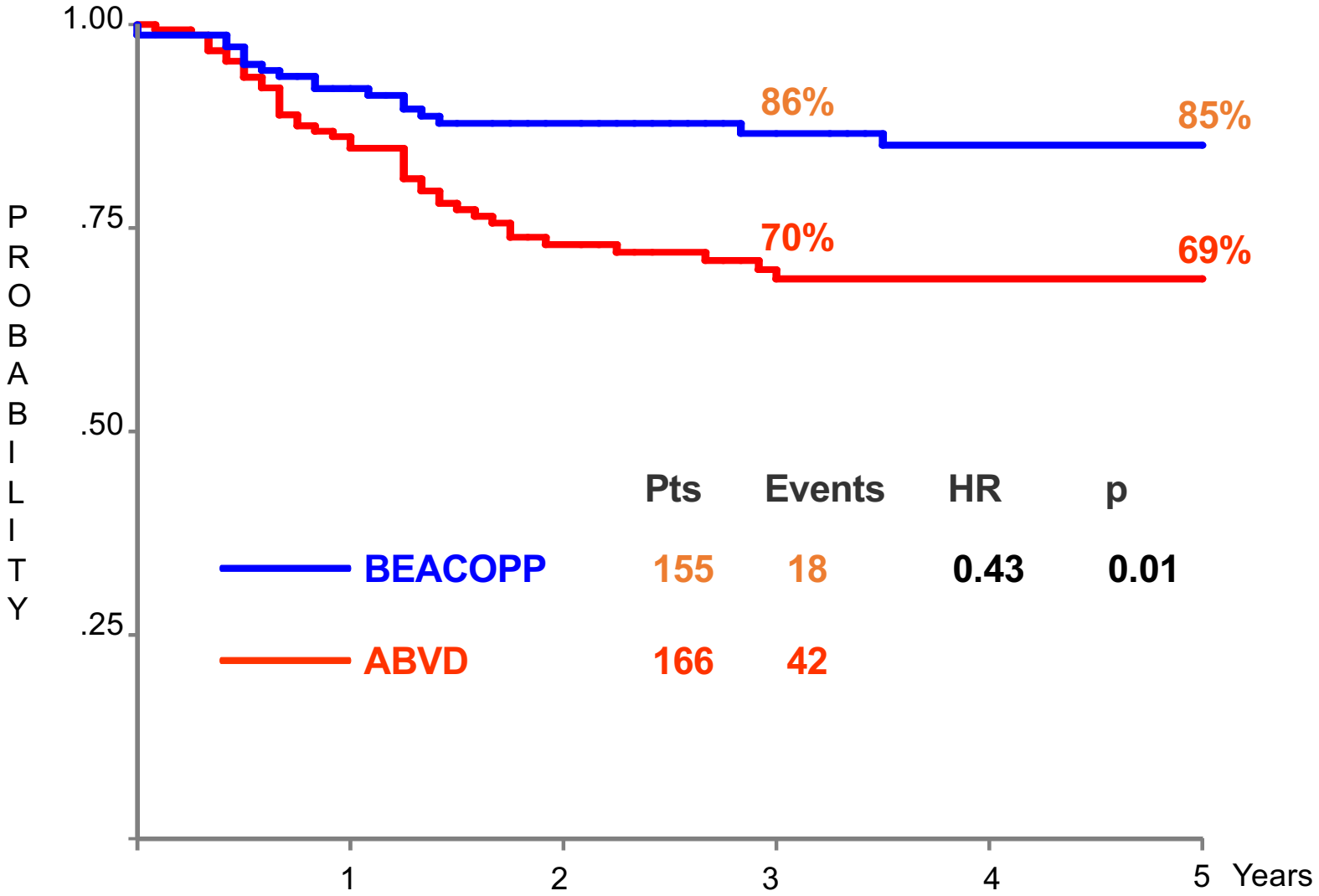


Response rate after first-line treatment

	ABVD (166 pts)	BEACOPP (155 pts)
CR after CT	65	73
CR after CT + RT	77	85
PR > 80%	8	4
No response	5	2
PD	10	4

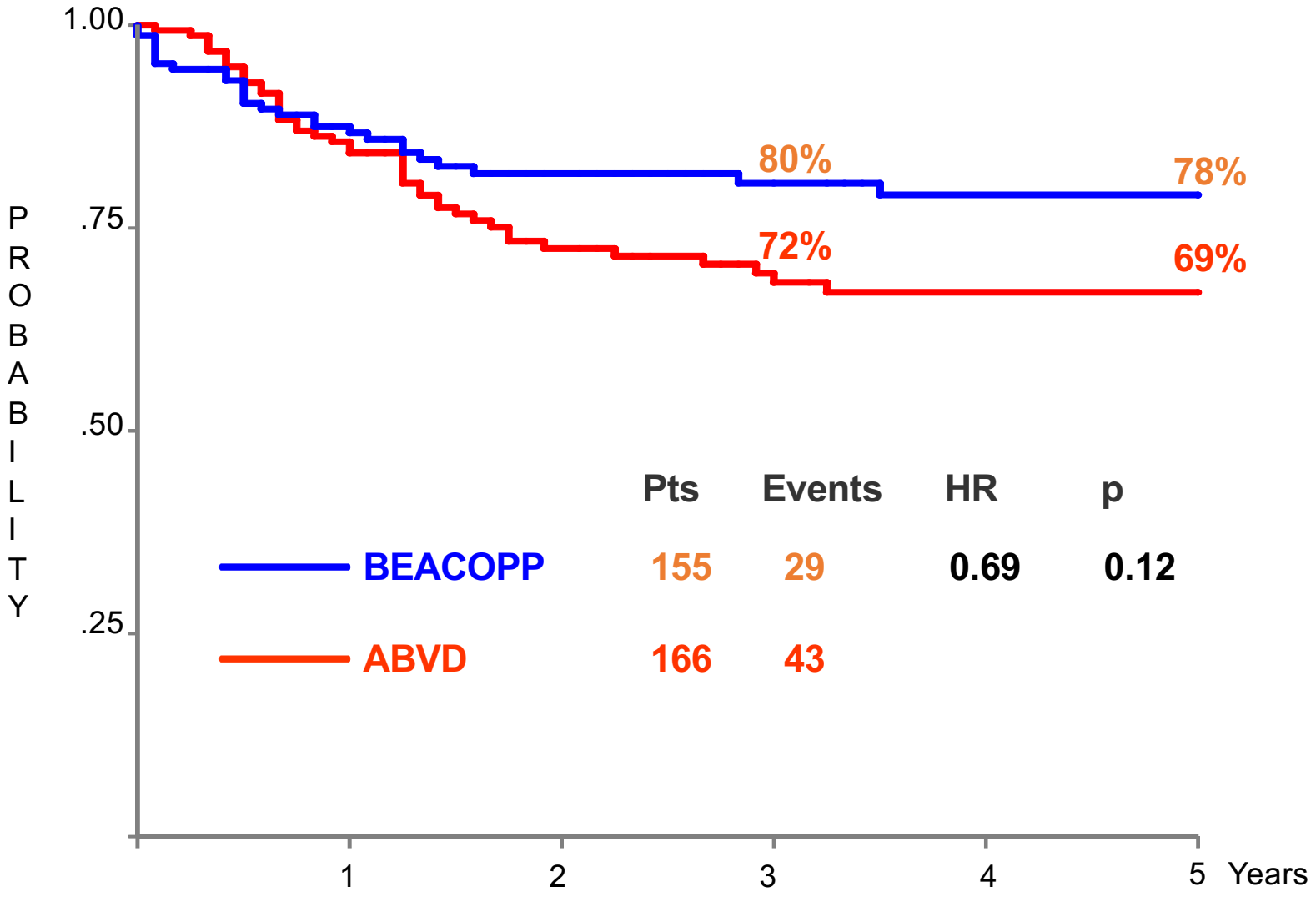
Viviani et al, NEJM 2011

Freedom from first progression



Viviani et al, NEJM 2011

Event-free survival



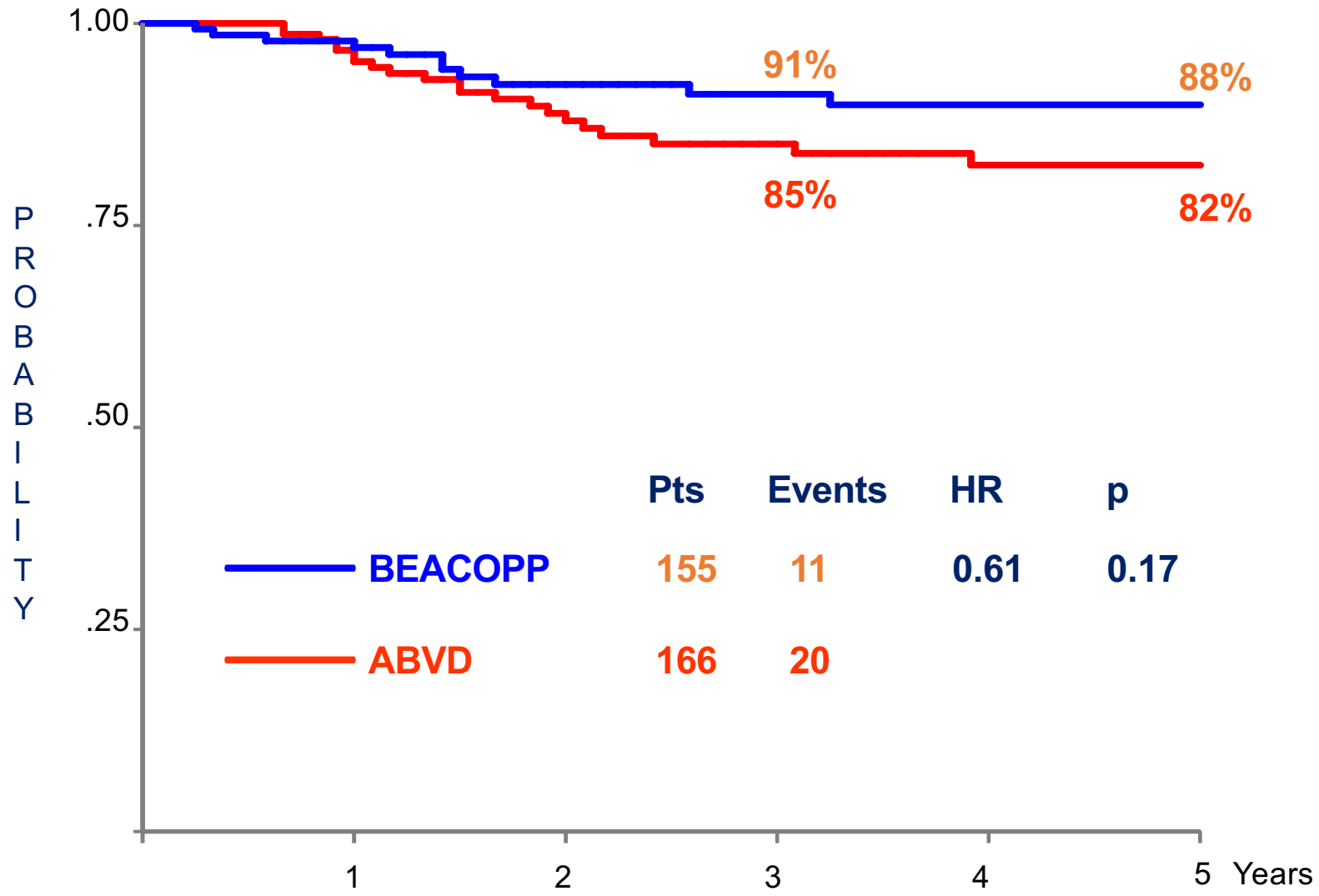
Viviani et al, NEJM 2011

Effects of salvage therapy

	ABVD	BEACOPP
Evaluable patients	37	16
Median time to further progression/death	17 mo (1-65)	6.5 mo (1-38)
CR	22 (59%)	6 (38%)
In continuous CR at cut-off date	17/37 (46%)	3/16 (18%)

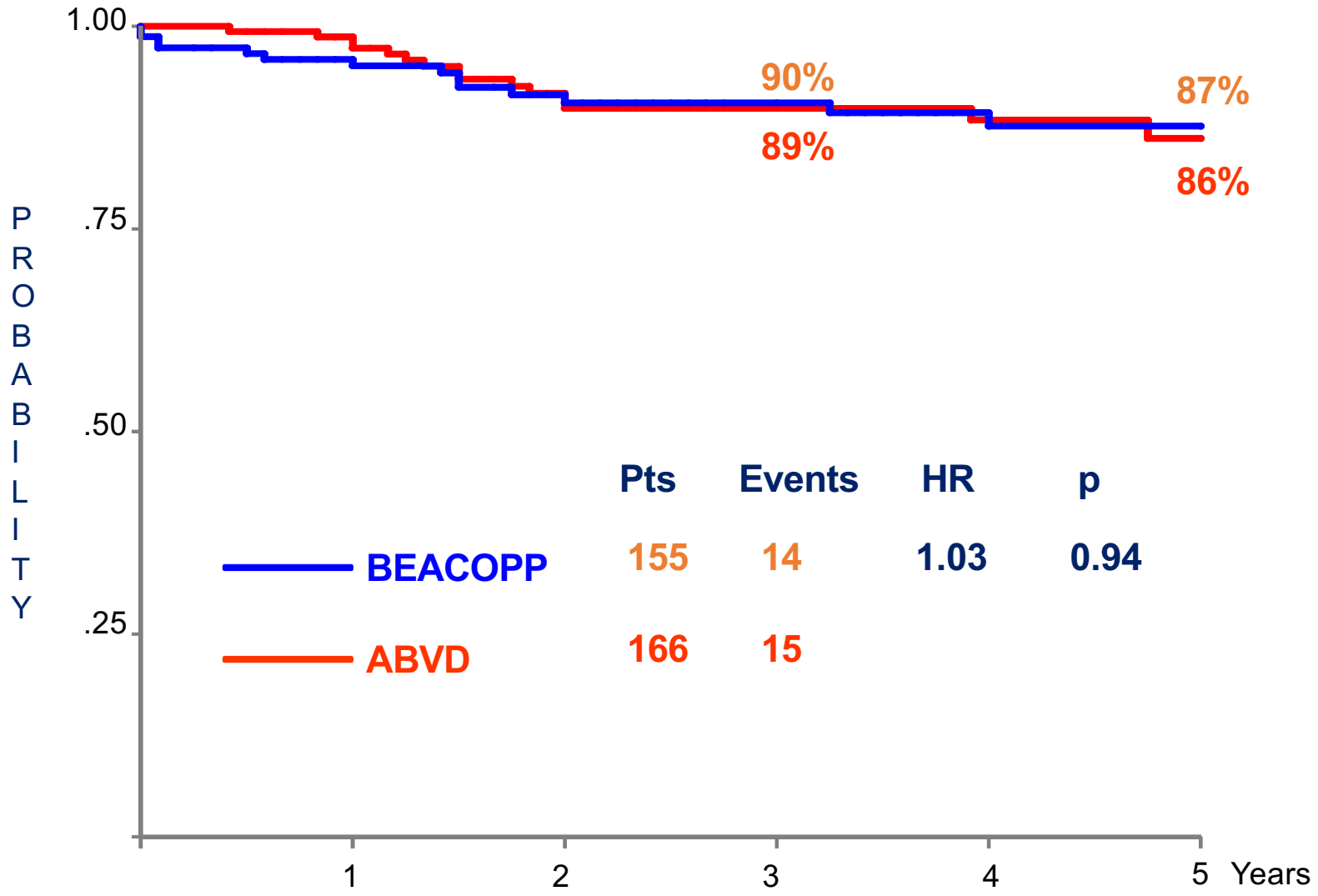
Viviani et al, NEJM 2011

Freedom from second progression

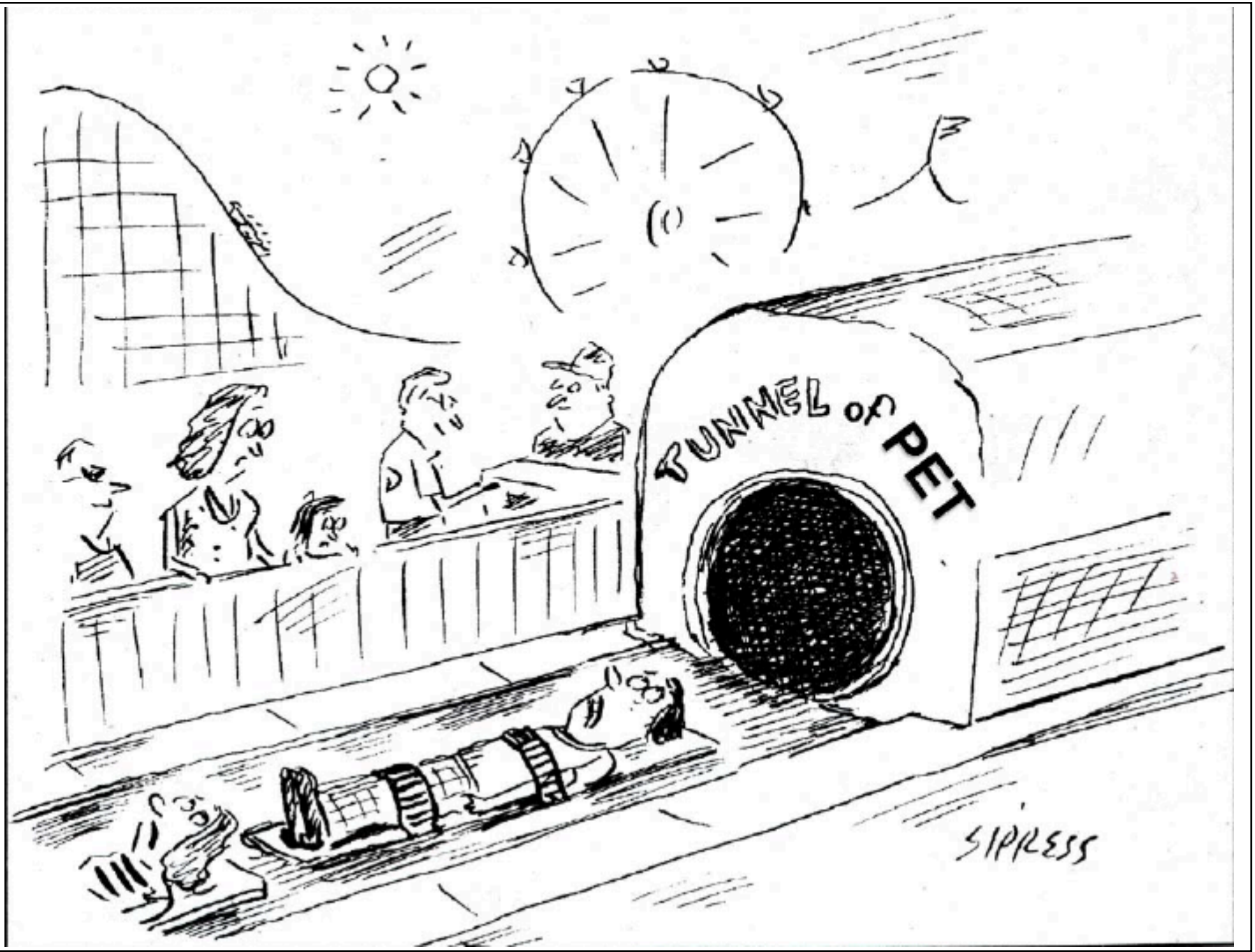


Viviani et al, NEJM 2011

Overall survival

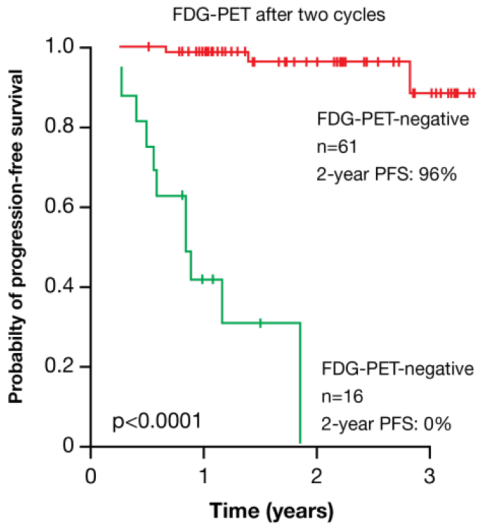


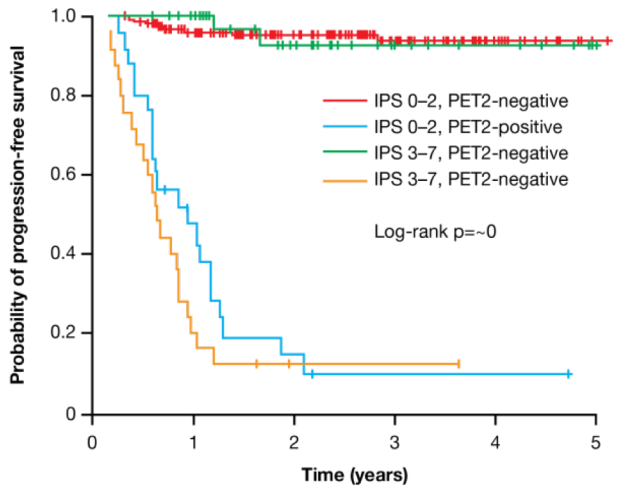
Viviani et al, NEJM 2011

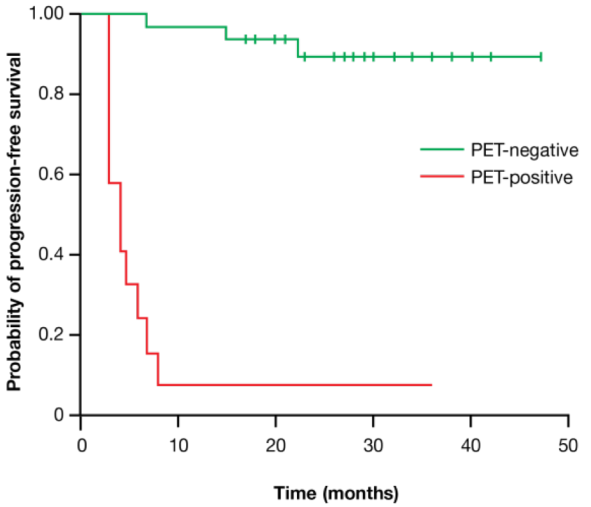

TUNNEL of PET
SIPRESS

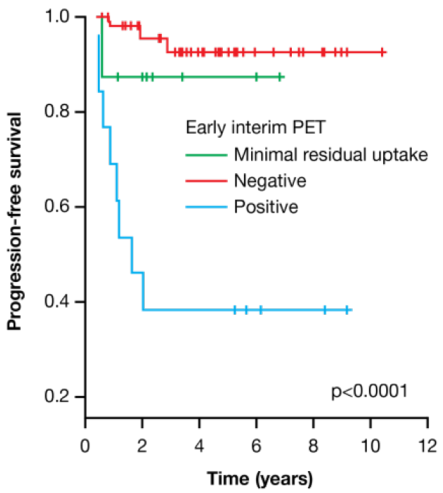
Early interim PET in lymphoma

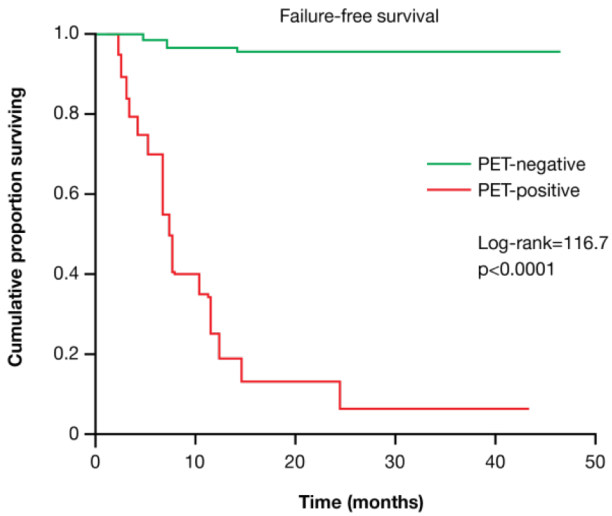
Many studies show excellent outcomes for FDG-PET-negative HL patients compared with those showing persistent FDG uptake[1–6]

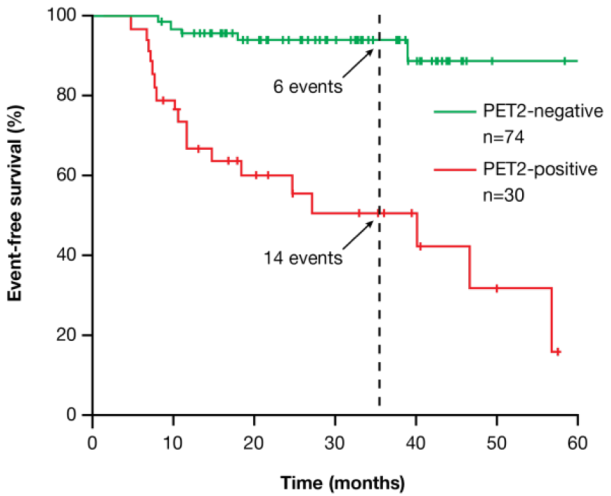












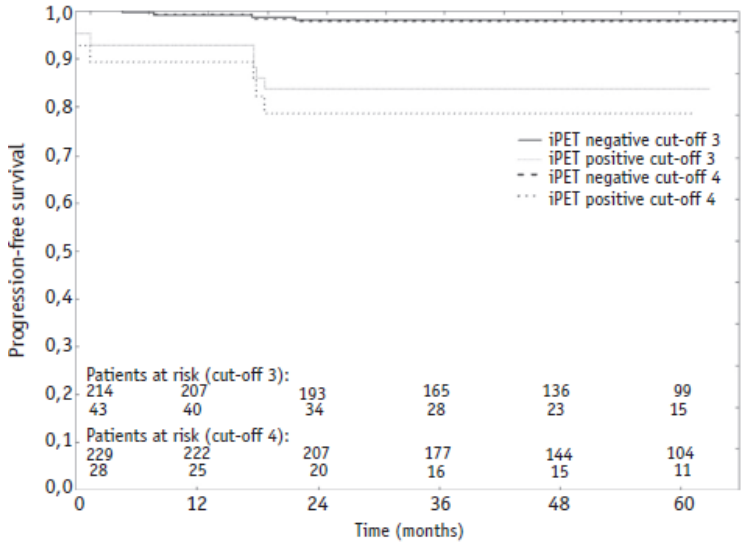
1. Hutchings M, *et al*. Blood 2006;107:52–9.
2. Hutchings M, *et al.* Ann Oncol 2005;16:1160–8.
3. Gallamini A, *et al*. J Clin Oncol 2007;25:3746–52.
4. Gallamini A, *et al.* Haematologica 2006;91:475–81.
5. Kostakoglu L, *et al*. Cancer 2006;107:2678–87.
6. Cerci JJ, *et al.* J Nucl Med 2010;51:1337–43.

Early interim PET in early stage HL

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

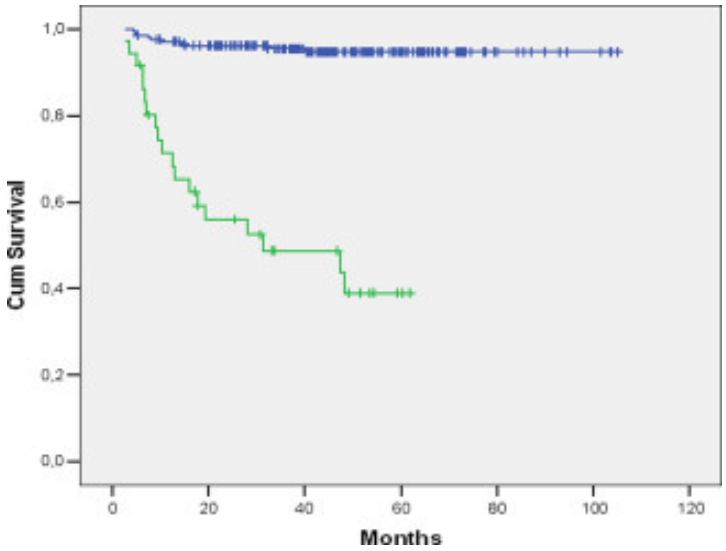
257 stage I-II (A+B) patients

Central, blinded PET review according to Deauville



246 stage IA-IIA patients

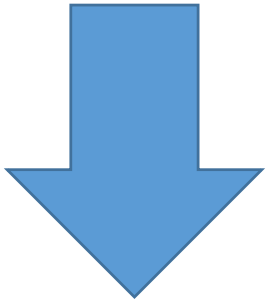
Central, blinded PET review according to Deauville



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.*

PET/CT for early treatment monitoring in HL

- PET-response to initial treatment is the most powerful prognostic indicator in lymphoma
- HL: NPV 90-95% PPV 60-80%



this has led to the development of PET oriented studies

The 5 points Deauville score: Specific

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

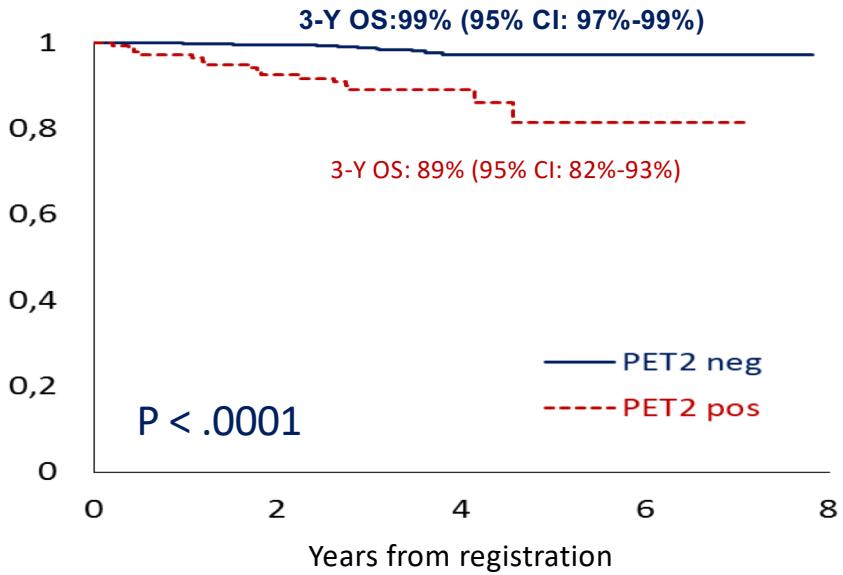
Early PET-response adapted therapy

PET response adapted treatment of advanced HL

Study	Patients	Main PET-driven intervention	Phase
GITIL HD0607 *(Completed)*	Stage IIB-IV + stage IIA with RF	Intensification to BEACOPPesc if PET-positive after 2xABVD	II
RATHL *(Completed)*	Stage IIB-IV	Intensification to BEACOPP if PET-positive after 2xABVD Randomisation between ABVD and AVD if PET-negative	III
Israel/Rambam (*Completed)*	Early stage + RF/bulk or advanced stage	PET after 2xBEACOPPbaseline or BEACOPPesc: Proceed to 4xBEACOPPesc If PET-positive or 4xBEACOPPbaseline if PET-negative	II
IIL HD0801 (*Completed)*	Stage IIB-IV	Salvage regimen if PET-positive after 2xABVD. Randomisation between radiotherapy and no further treatment after completion of 6xABVD if PET-negative after 2xABVD	III
GHSG HD18	Stage IIB-IV	4 vs. 6 x BEACOPPesc in experimental arm if PET-negative after 2 cycles. Standard arm: 6 x BEACOPPesc.	III
LYSA AHL2011	Early stage HL bulky	De-escalation from BEACOPPesc to ABVD in exper. arm in case of a negative PET after 2 and 4 cycles. Standard arm: 6 x BEACOPPesc.	III
SWOG S0816	Stage III-IV	Intensification to BEACOPPesc if PET-positive after 2xABVD	II

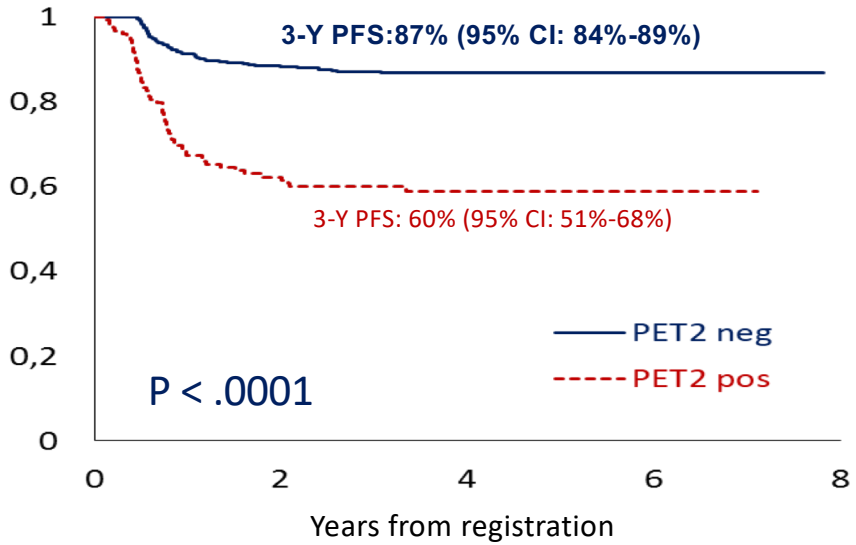
OS and PFS according to PET2 results GITIL HD06-07

Overall Survival



PET2 -	630	(3)	583	(9)	169	(0)	42	(0)	0
PET2 +	150	(10)	116	(4)	37	(2)	4	(0)	0

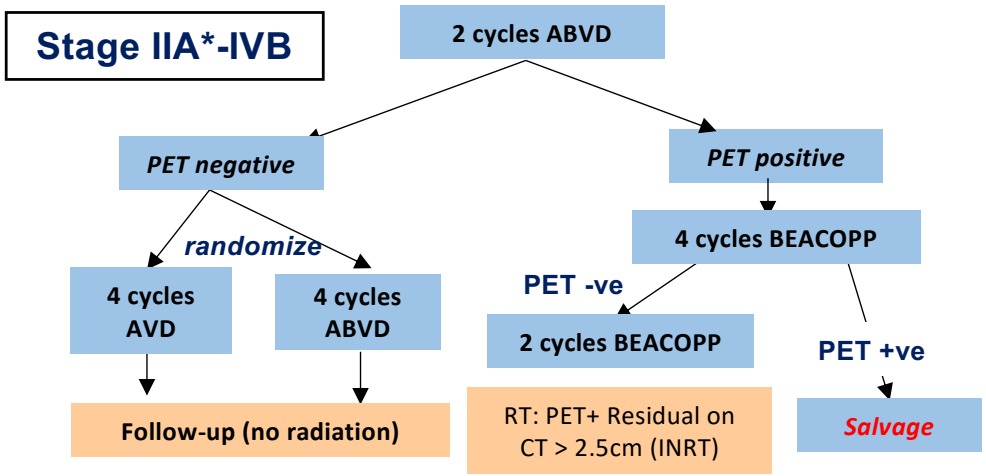
Progression free Survival

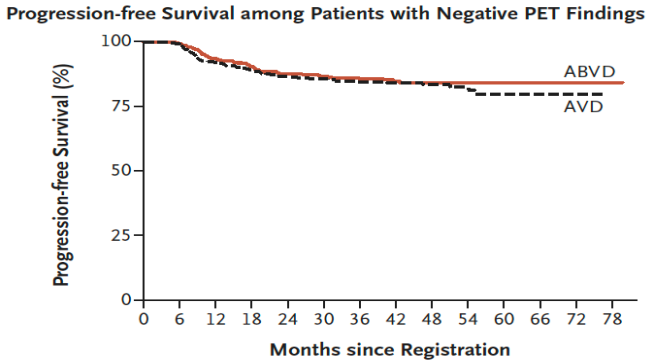


PET2 -	630	(73)	528	(8)	147	(0)	40	(0)	0
PET2 +	150	(53)	83	(4)	26	(0)	4	(0)	0

Gallamini A: J Clin Oncol. 2018; 10; 36(5): 454-462.

UK NCRI RATHL Study





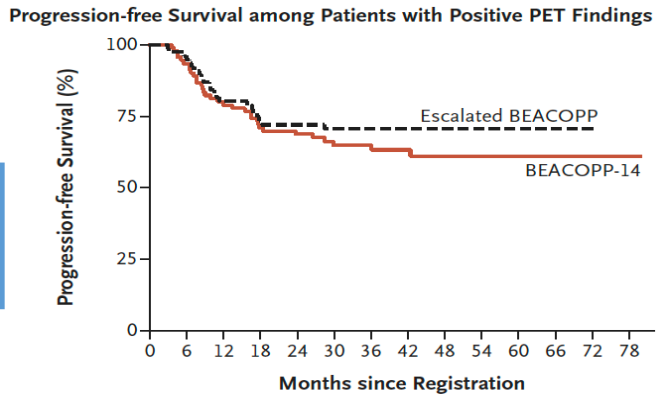
N= 1119. Median f-up: 41 months

- Omitting bleomycin
  - significantly reduced the rate of infections and pulmonary toxicity
  - had little impact on PFS and OS of early PET-negative patients

- 3-year PFS 85.7% in ABVD arm
- 3-year PFS 84.4% in AVD arm
- 3-year PFS 67.5% for both BEACOPP arm

*Stage II with risk factors: 41.6%

Stage II: 3-Y PFS: 90.0%
Stage III: 3-Y PFS: 83.1%
Stage IV: 3-Y PFS: 79.6%

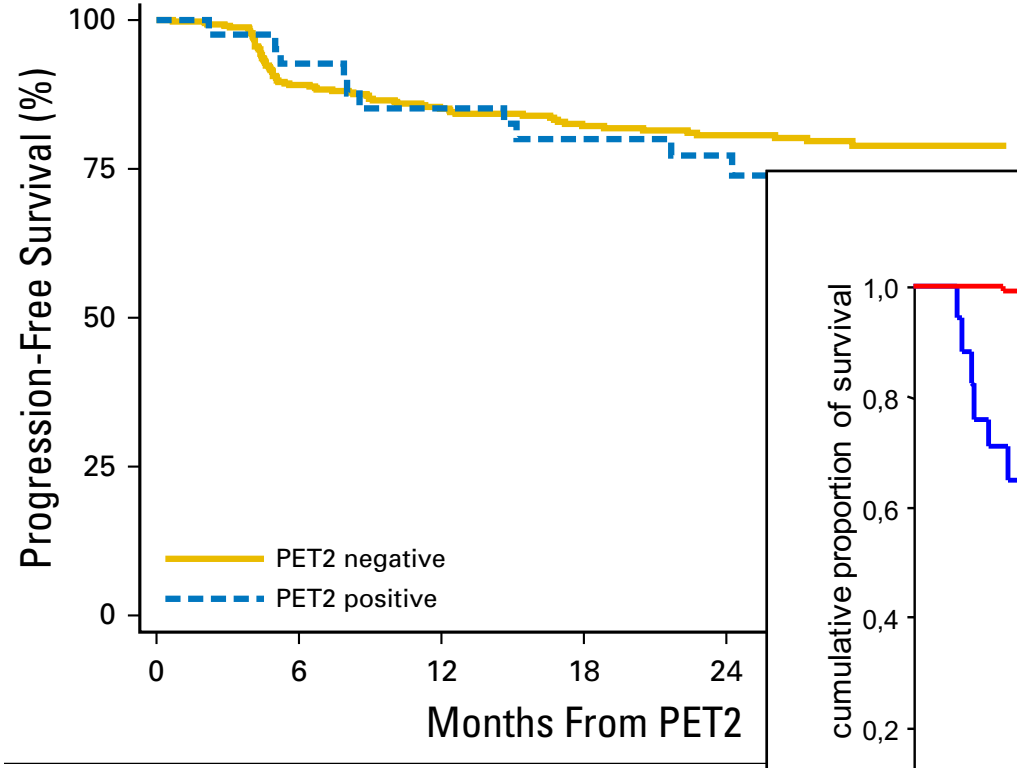


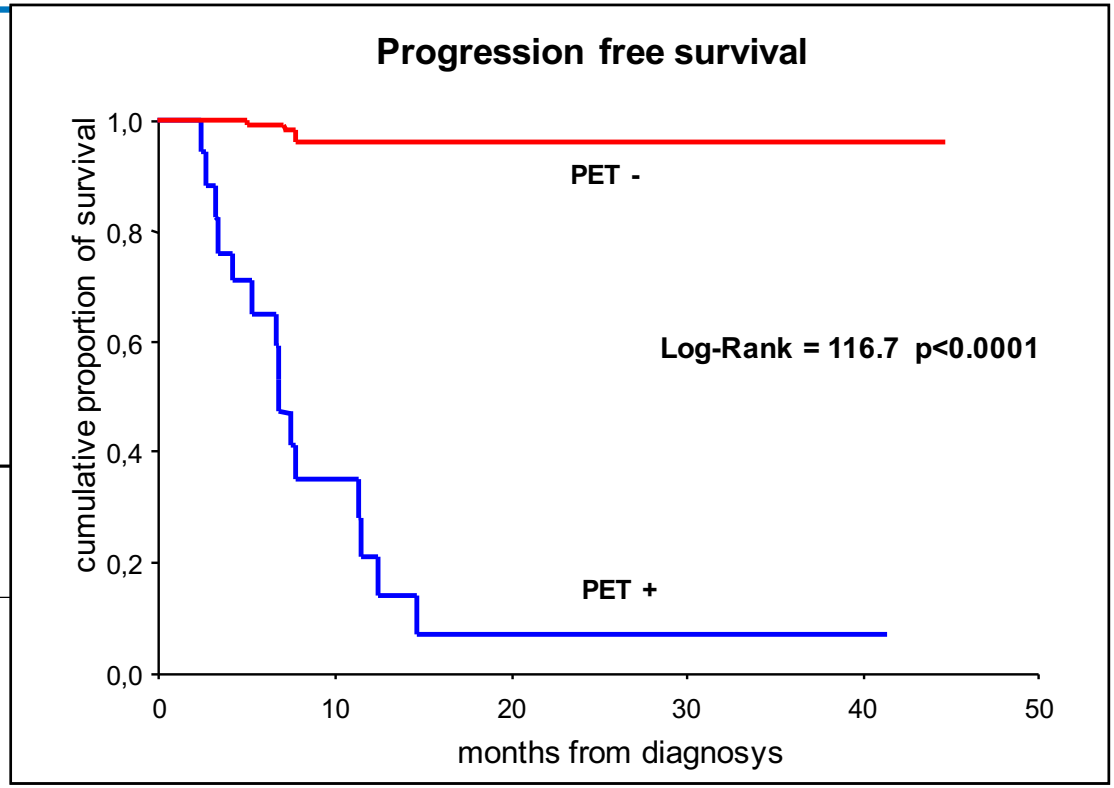
Johnson P.: N Engl. J Med. 2016; 374: 2419-29

HD0801 RESULTS:RELAPSED/REFRACTORY HODGKIN LYMPHOMA

Interim-PET

Progression Free Survival: Intention to treat analysis



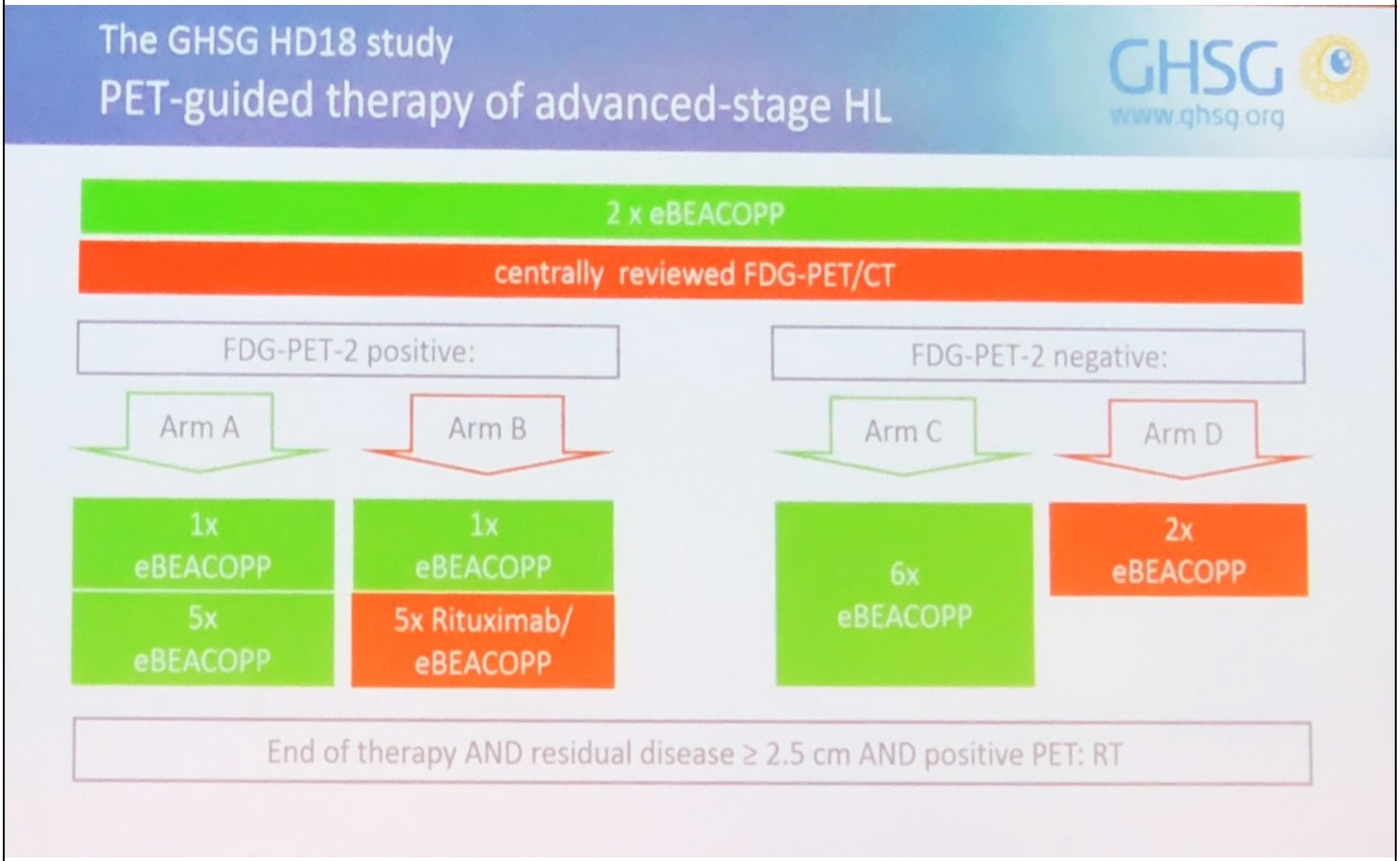


Haematologica 2006; 91:475-481

PET response adapted treatment of advanced HL

Trial	Stage	Number PET-positive	Initial therapy	% iPET positive (5PS PET score if used)	Post-PET therapy	Time to analysis	PFS %	OS %
CALGB 50604	I-II	14	2 ABVD	9	2 esc BEACOPP + IFRT	2.1 yrs	66%	N/A
EORTC H10	I-II	361	2 ABVD	19	2 ABVD + INRT 2 esc BEACOPP + INRT	5 yrs	77 91	89 96
RATHL	II with adverse features, III, IV	182	2 ABVD	16 (4-5)	4 esc BEACOPP or 6 BEACOPP-14	3 yrs	68	87
GITIL HD0607	II with adverse features, III, IV	98	2 ABVD	20 (4-5)	4 esc BEACOPP + 4 BEACOPP baseline +/- rituximab	2	66	N/A
SWOG S0816	III, IV	60	2 ABVD	18 (4-5)	6 esc BEACOPP	2	64	N/A
FIL HD0801	IIB-IV	103	2 ABVD	20 (3-5)	4 IGEV + BEAM	2	76	N/A

GHSG HD18: PET-guided therapy in advanced HL



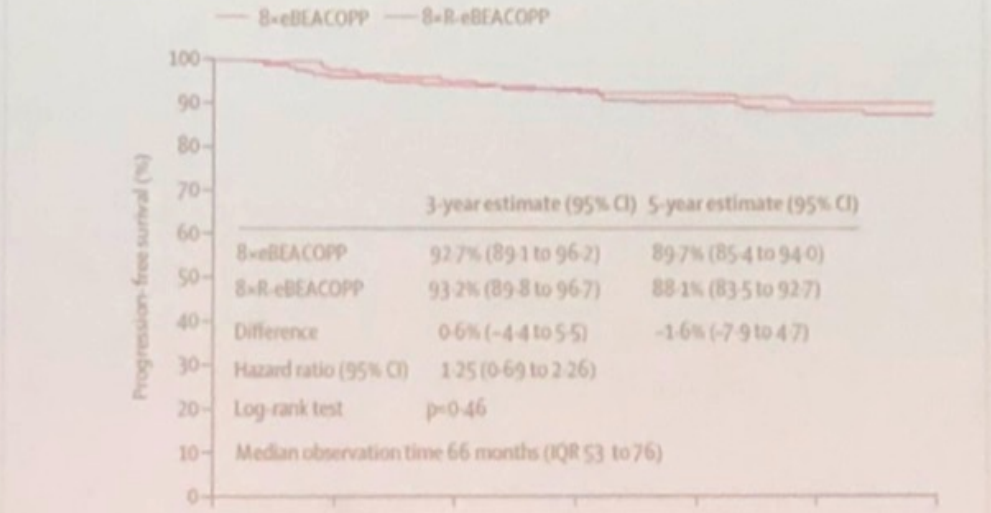
GHSG HD18

The GHSG HD18 study

PFS for PET2 negative and positive patients

GHSG
www.ghsg.org

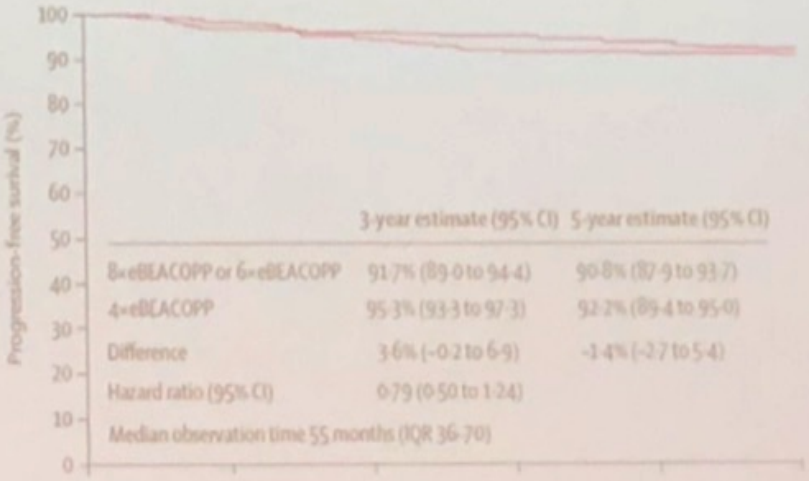
All PET-2 positive patients: 3y PFS: 93% [1]



	3-year estimate (95% CI)	5-year estimate (95% CI)
8×eBEACOPP	92·7% (89·1 to 96·2)	89·7% (85·4 to 94·0)
8×R-eBEACOPP	93·2% (89·8 to 96·7)	88·1% (83·5 to 92·7)
Difference	0·6% (−4·4 to 5·5)	−1·6% (−7·9 to 4·7)
Hazard ratio (95% CI)	1·25 (0·69 to 2·26)	
Log-rank test	p=0·46	
Median observation time 66 months (IQR 53 to 76)		

Number at risk (number censored)							
8×eBEACOPP	217 (0)	205 (7)	189 (17)	180 (22)	169 (32)	132 (65)	70 (127)
8×R-eBEACOPP	217 (0)	200 (8)	185 (20)	176 (27)	157 (40)	119 (75)	55 (138)

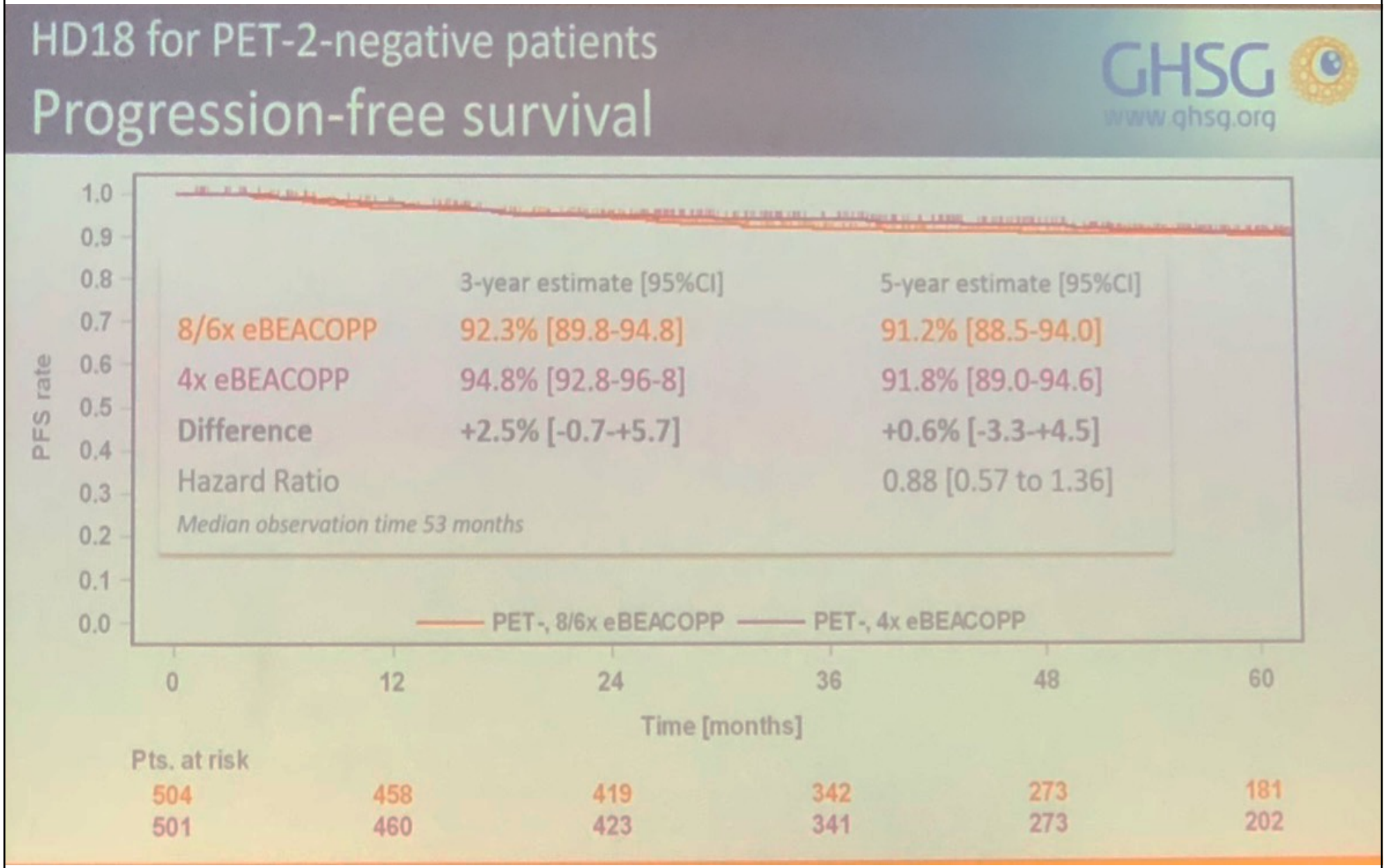
All PET-2 negative patients: 3y PFS: 93.5%[1]



	3-year estimate (95% CI)	5-year estimate (95% CI)
8×eBEACOPP or 6×eBEACOPP	91·7% (89·0 to 94·4)	90·8% (87·9 to 93·7)
4×eBEACOPP	95·3% (93·3 to 97·3)	92·2% (89·4 to 95·0)
Difference	3·6% (−0·2 to 6·9)	−1·4% (−2·7 to 5·4)
Hazard ratio (95% CI)	0·79 (0·50 to 1·24)	
Median observation time 55 months (IQR 36-70)		

Number at risk (number censored)						
8×eBEACOPP or 6×eBEACOPP	446 (0)	411 (21)	378 (45)	310 (102)	247 (164)	164 (246)
4×eBEACOPP	474 (0)	444 (22)	412 (43)	334 (119)	269 (180)	198 (246)

GHSG HD18


HD18 for PET-2-negative patients
Progression-free survival
GHSG
www.ghsg.org
PFS rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
3-year estimate [95%CI]
5-year estimate [95%CI]
8/6x eBEACOPP
92.3% [89.8-94.8]
91.2% [88.5-94.0]
4x eBEACOPP
94.8% [92.8-96-8]
91.8% [89.0-94.6]
Difference
+2.5% [-0.7-+5.7]
+0.6% [-3.3-+4.5]
Hazard Ratio
0.88 [0.57 to 1.36]
Median observation time 53 months
PET-, 8/6x eBEACOPP
PET-, 4x eBEACOPP
0
12
24
36
48
60
Time [months]
Pts. at risk
504
458
419
342
273
181
501
460
423
341
273
202

GHSG HD18

HD18 for PET-2-negative patients

Acute toxicities of chemotherapy

GHSG
www.ghsg.org

	8x eBEACOPP N=287		6x eBEACOPP N=215		4x eBEACOPP N=498	
	N	%	N	%	N	%
Organ toxicity of grade III/IV	62	22%	29	13%	38	8%
Anemia, thrombopenia or infection of grade IV	169	59%	115	53%	187	38%
Treatment-related morbidity*	189	66%	132	61%	204	41%
				P<0.001		
Onset of treatment-related morbidity						
Cycle 1-4	135	47%	100	47%	204	41%
Cycle 5-6	30	10%	32	15%		
Cycle 7-8	24	8%				

*documentation of toxicity missing in 5 of 1005 patients (<1%)

GHSG HD18

HD18 for PET-2-negative patients

Second neoplasia

GHSG
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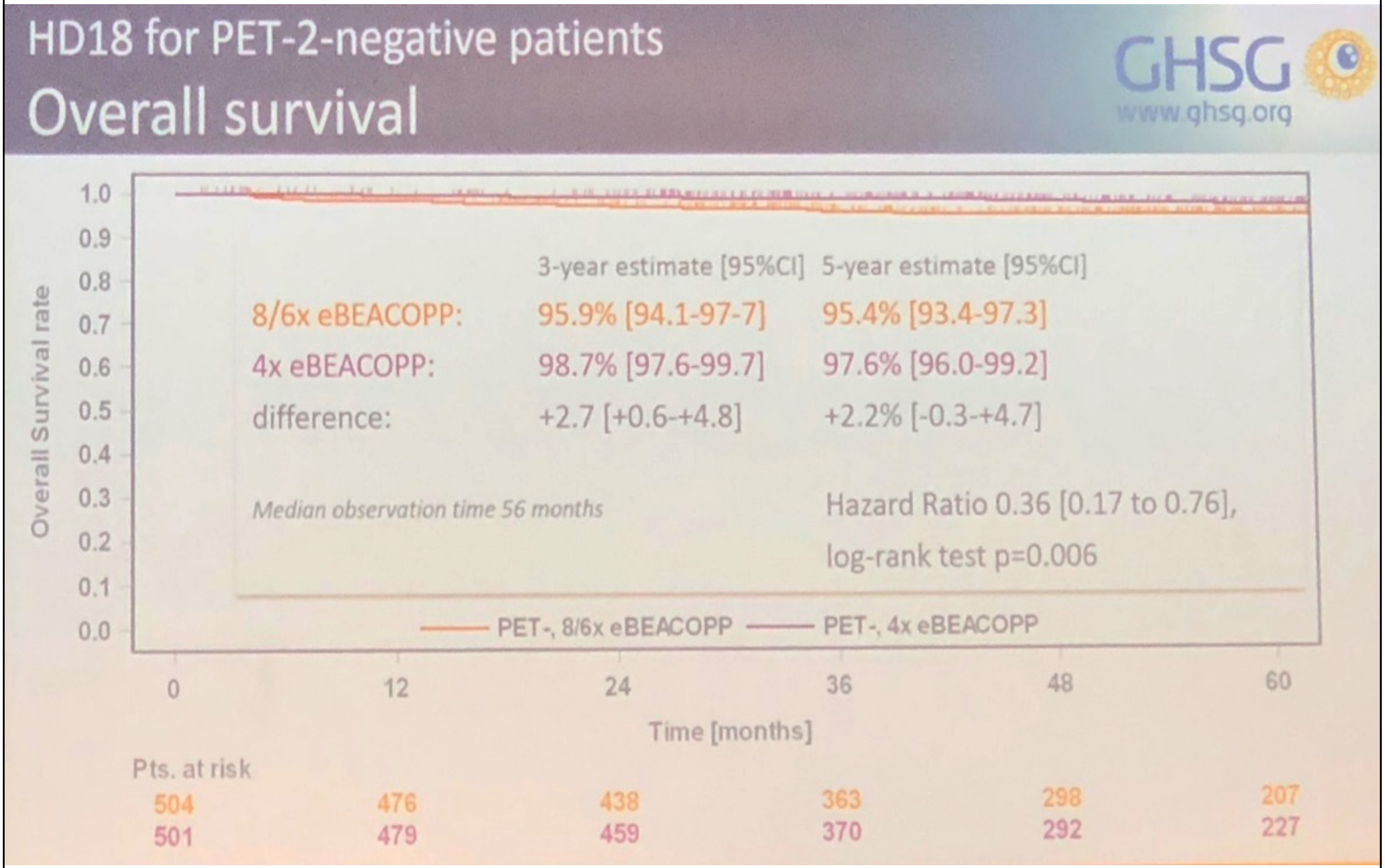
	6/8x eBEACOPP N=504		4x eBEACOPP N=501	
Median observation time	*53 months*		*54 months*	
	N	%	N	%
AML/MDS	**8**	**1.6%**	**2**	**0.4%**
NHL	5	1.0%	8	1.6%
Solid tumor	5	1.0%	3	0.6%
Any event	18	3.6%	13	2.6%

GHSG HD18


HD18 for PET-2-negative patients
Overall survival
GHSG
www.ghsg.org
Overall Survival rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
3-year estimate [95%CI]
5-year estimate [95%CI]
8/6x eBEACOPP:
95.9% [94.1-97-7]
95.4% [93.4-97.3]
4x eBEACOPP:
98.7% [97.6-99.7]
97.6% [96.0-99.2]
difference:
+2.7 [+0.6-+4.8]
+2.2% [-0.3-+4.7]
Median observation time 56 months
Hazard Ratio 0.36 [0.17 to 0.76],
log-rank test p=0.006
PET-, 8/6x eBEACOPP
PET-, 4x eBEACOPP
0
12
24
36
48
60
Time [months]
Pts. at risk
504
476
438
363
298
207
501
479
459
370
292
227

GHSG HD18

HD18 for PET-2-negative patients

Summary

GHSG
www.ghsg.org

- Non-inferior PFS for PET-2-negative patients after 4 cycles of eBEACOPP compared with 8/6 cycles (primary endpoint) at a very high level (95% at 3y, 92% at 5 y).
- Significant reduction of severe acute hematological and non-hematological toxicities.
- Relevant reduction of mortality for other reasons than HL.
- Elimination of HL as relevant cause of death (7/1005; i.e. 0.7%).
- **Significantly superior OS with 4 cycles of eBEACOPP (99% at 3 y, 98 % at 5 y) over 6/8 cycles.**

GHSG HD18

Early Interim PET in Patients with Advanced-Stage Hodgkin's Lymphoma Treated within the Phase 3 GHSG HD18 Study

Conclusions

GHSG
www.ghsg.org

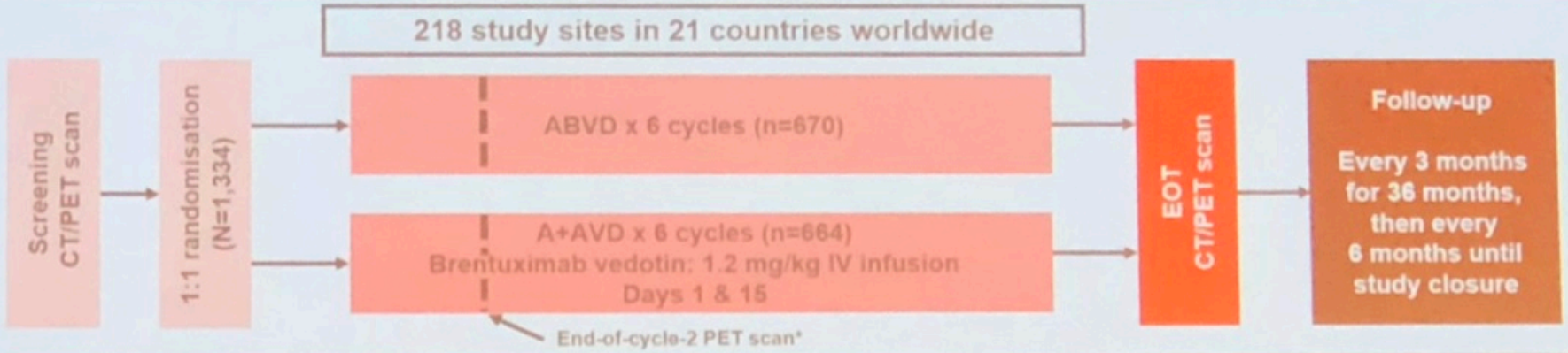
- PET-2 DS 4 allows to identify those patients, who really need an intensive treatment with 6 cycles of eBEACOPP and was thus defined as SOC in the GHSG.
- Excellent survival outcomes even for this patient cohort do not justify any treatment intensification beyond our standard of care.
- PET-2 DS 1-3 has a high negative predictive value and applies to 75 % of all eBEACOPP treated patients. They benefit from a very short, very safe, and very effective treatment.[1,2]
- **Overall, the balance of risks and benefits using eBEACOPP upfront in a personalized, PET-2-guided strategy makes it an attractive option for newly diagnosed, advanced stage HL patients.**

GERMAN HODGKIN LYMPHOMA STUDY GROUP

THEY TOO!!!

the German group also ‘converted’ to interim-PET

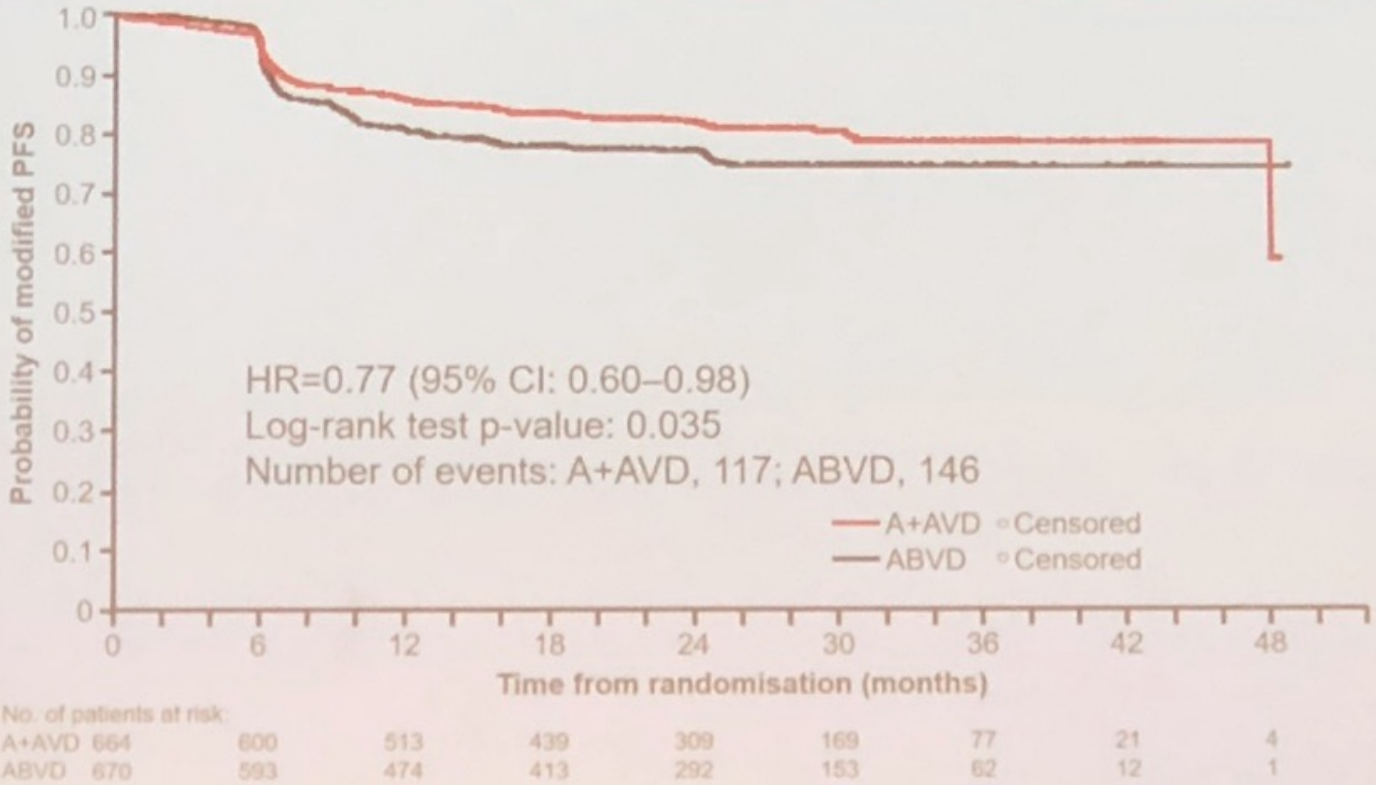
ECHELON-1: Open-label, global, randomised, phase 3 study of A+AVD versus ABVD in patients with newly diagnosed advanced cHL



- Inclusion criteria:
  - cHL stage III or IV
  - ECOG PS 0, 1 or 2
  - Age ≥18 years
  - Measurable disease
  - Adequate liver and renal function
- Primary endpoint: modified PFS per blinded IRF; a modified PFS event was defined as the first of:
  - Progression
  - Death from any cause
  - Non-CR (Deauville ≥3) after completion of frontline treatment and subsequent anticancer therapy

*Patients with Deauville 5 per IRF at PET2 were permitted to switch to an alternative frontline therapy at physician's discretion (this switch was not counted as a modified PFS event)
cHL, classic Hodgkin lymphoma; CT, computerised tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end-of-treatment; IRF, independent review facility; IV, intravenous; PET, positron emission tomography; PFS, progression-free survival

Modified PFS per IRF



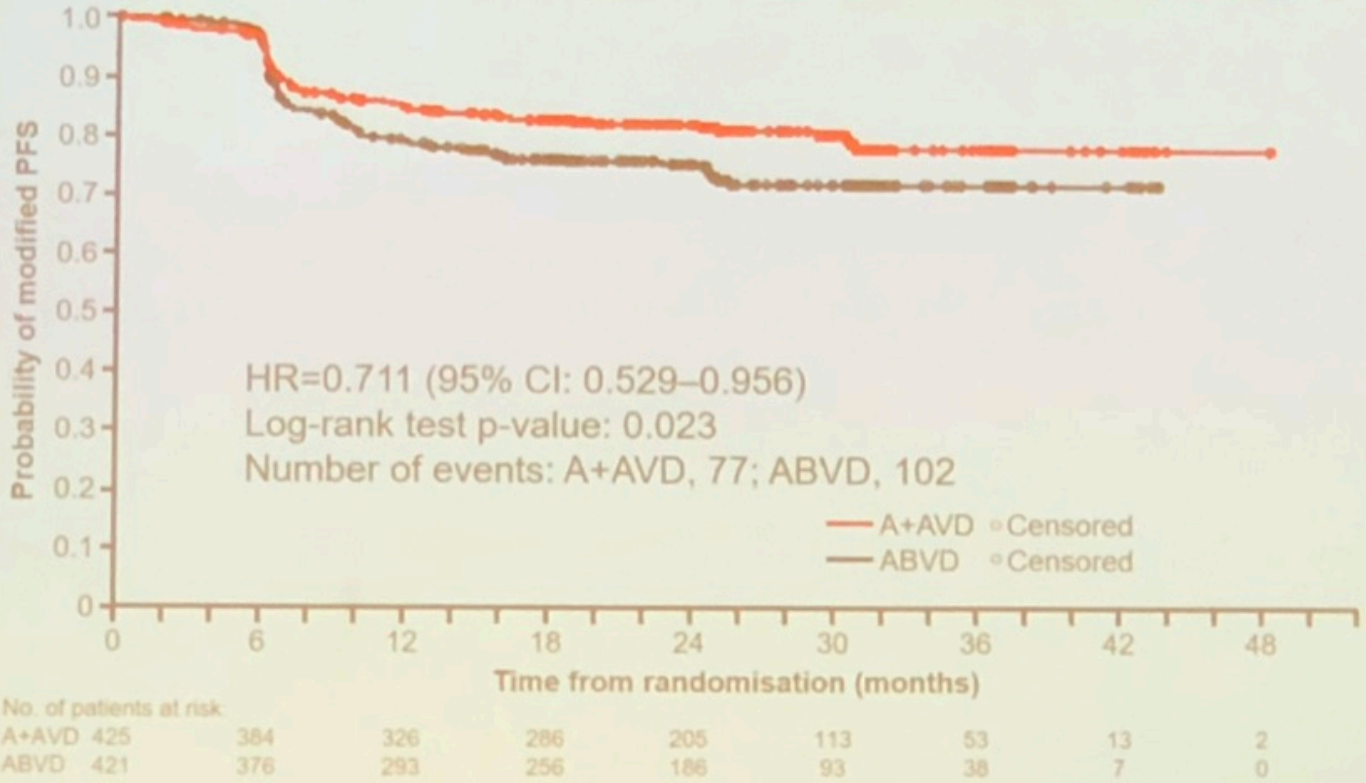
Number of events

Category	A+AVD n=117	ABVD n=146
Progression	90	102
Death	18	22
Modified progression	9	22
Chemotherapy	7	15
Radiotherapy	2	7

Median follow-up (range): 24.9 months (0.0–49.3)

CI, confidence interval; HR, hazard ratio; mPFS, modified PFS

Modified PFS per IRF in patients with stage IV disease[1]



No. of patients at risk

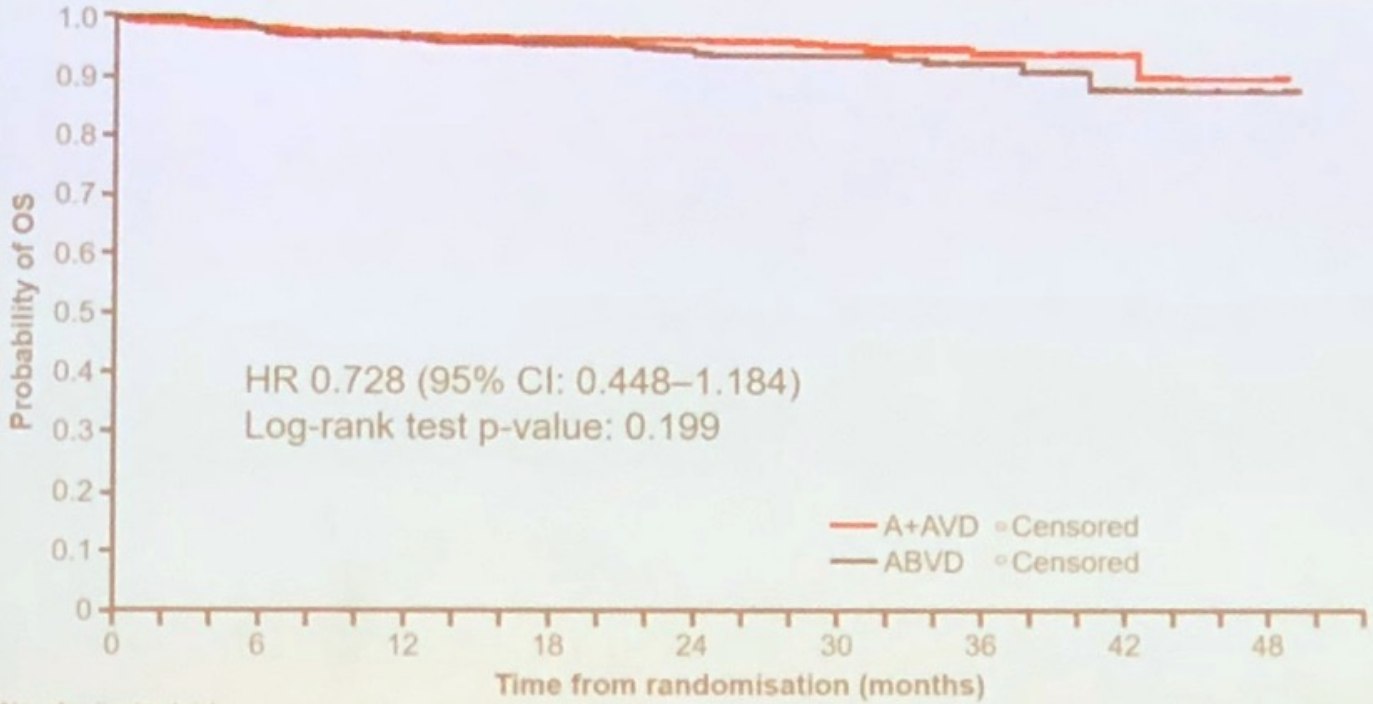
A+AVD	425	384	326	286	205	113	53	13	2
ABVD	421	376	293	256	186	93	38	7	0

Number of events

Category	A+AVD n=77	ABVD n=102
Progression	61	69
Death	9	14
Modified progression	7	19

1. Hutchings M. et al. Oral presentation at EHA 2018 (S112).

Interim overall survival*



Median follow-up (range):
24.6 months (0.0–49.0)

No. of patients at risk:

A+AVD	664	636	621	576	428	255	120	31	4
ABVD	670	631	610	571	414	246	113	19	3

*Interim OS analysis based on 67 deaths

Second line or salvage therapy

RELAPSED REFRACTORY DISEASE

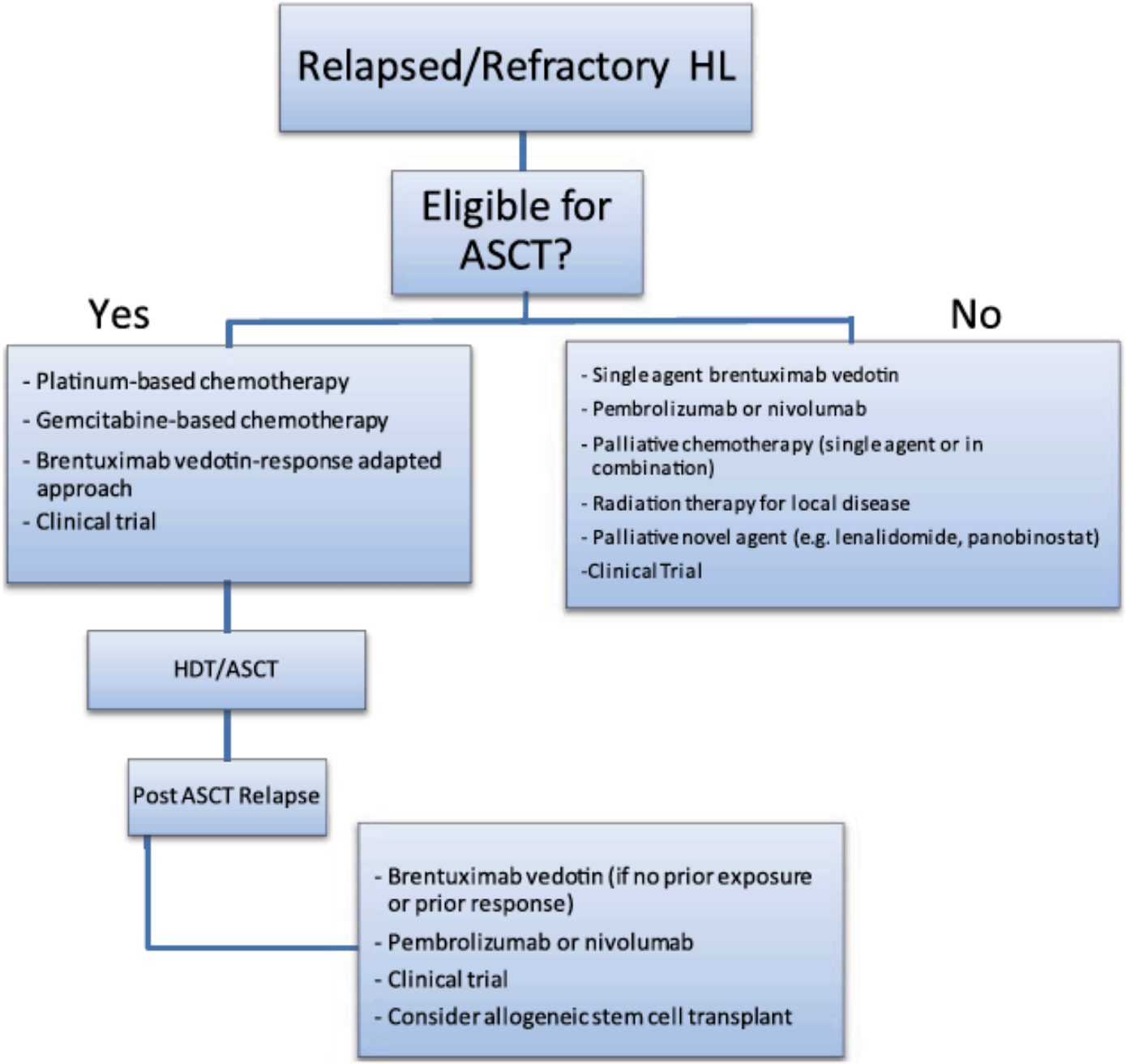
Background: Number and Facts

- 1.584 new cases/year in Italy
- 422 deaths/year in Italy
- 1° line of therapy: 15%-25% relapsed/refractory
- 2° line of therapy: 50% durable responses with autoSCT
- 3° line of therapy: 30-40% durable responses with alloSCT

RELAPSED/REFRACTORY HODGKIN LYMPHOMA

Today the definition of relapsed/refractory Hodgkin's lymphoma is extended to another entity:

Refractory or relapsed after first line therapy

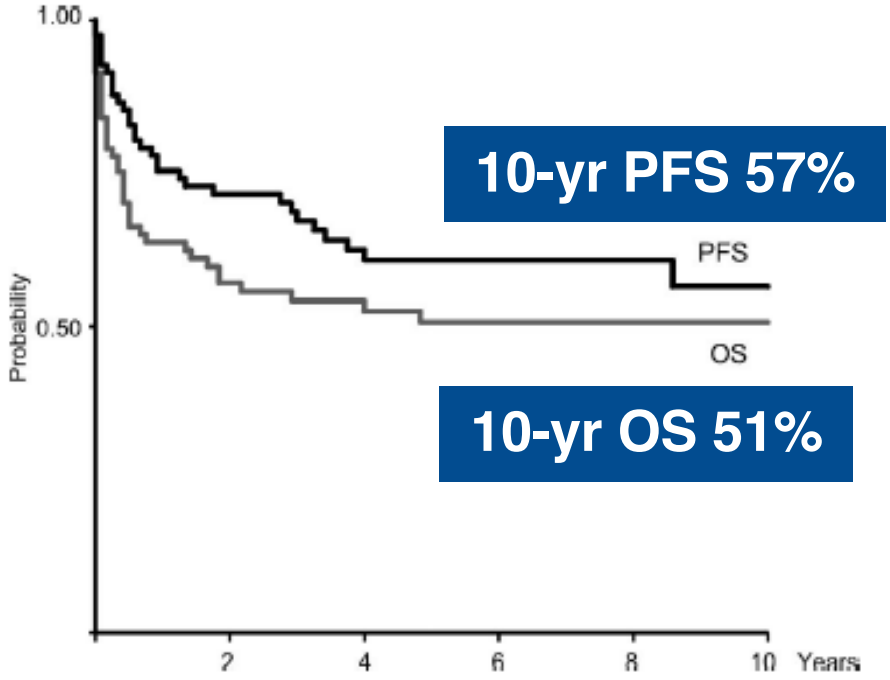


Refractory or relapsed after first line therapy

HIGH DOSE CHEMOTHERAPY AND PERIPHERAL STEM CELL REINFUSION

Survival in relapsed or refractory HL treated with Ifosfamide-based salvage regimens + ASCT: 10-year Results at INT

Background

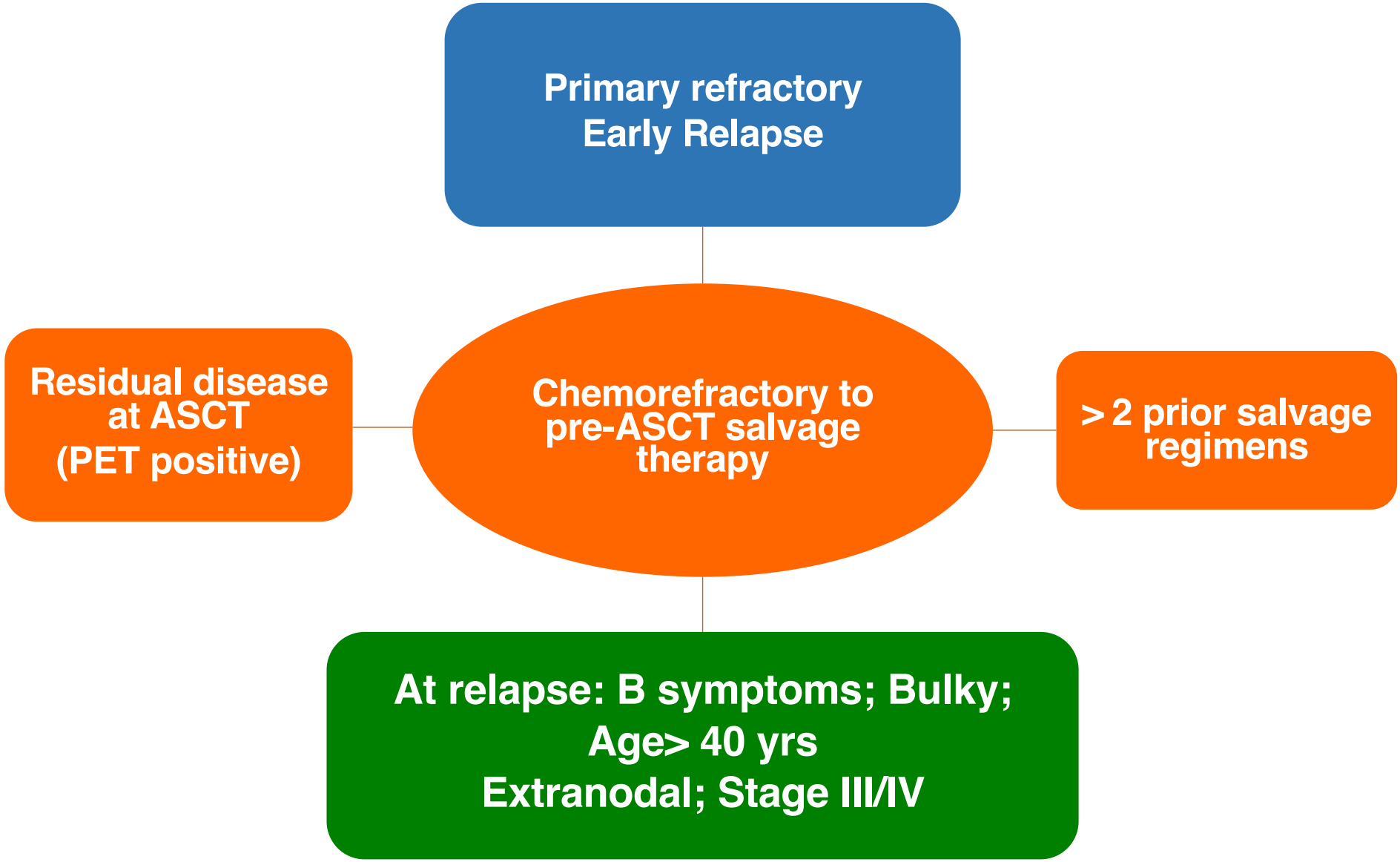


10-yr PFS 57%

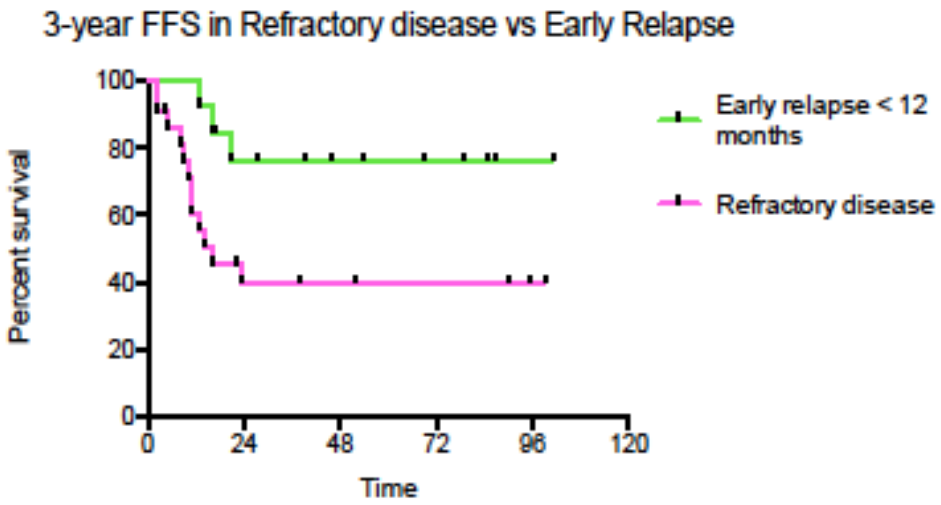
10-yr OS 51%

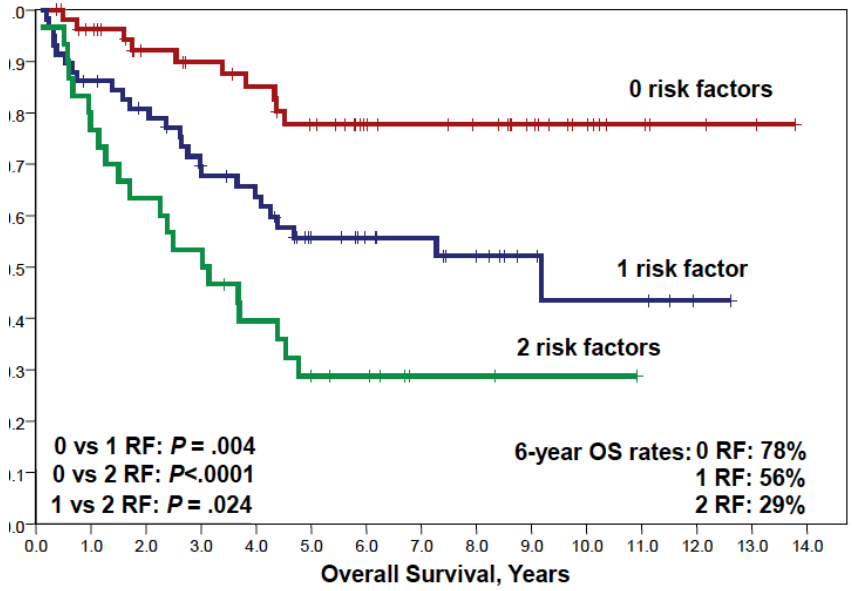
- ✓ ASCT in relapsed or refractory HL can achieve cure in 50% of pts
- ✓ Majority of patients will relapse in the first year after ASCT
- ✓ Over the past 20 years, no consistent Improvement in outcomes for ASCT

Risk factors for ASCT outcomes



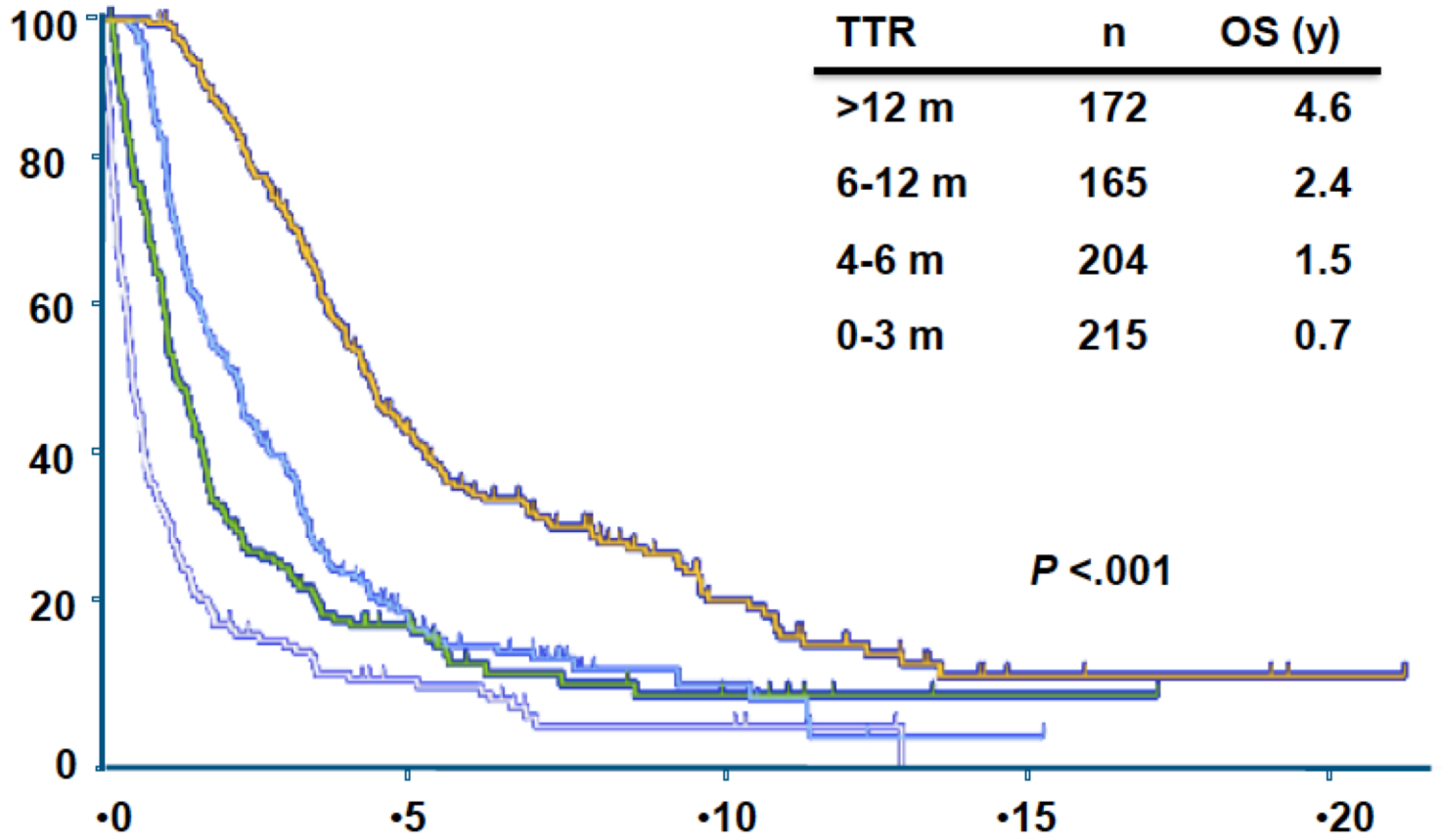
Risk factors for ASCT outcomes





Risk factors: extranodal diseas or bulky > 5 cm at relapse

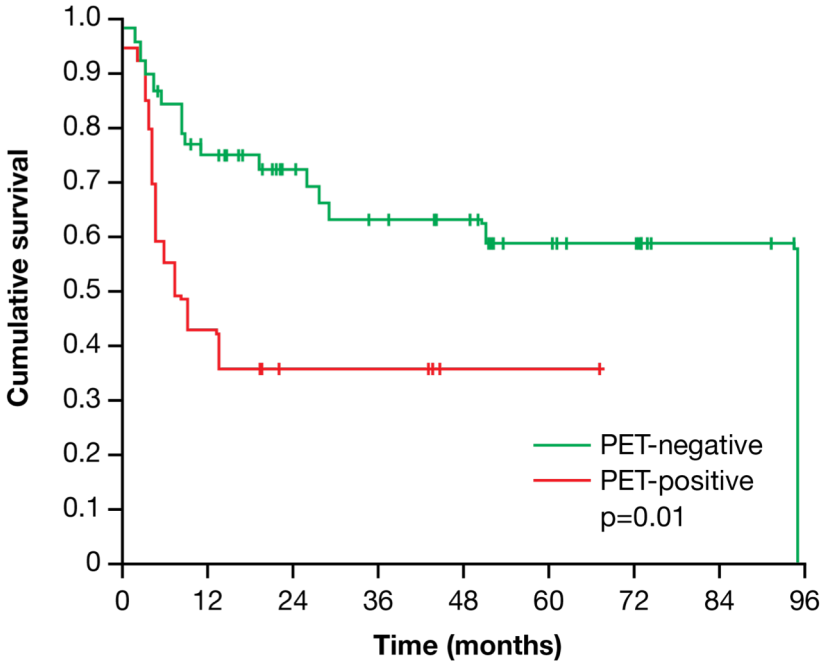
Survival in patients relapsing after ASCT



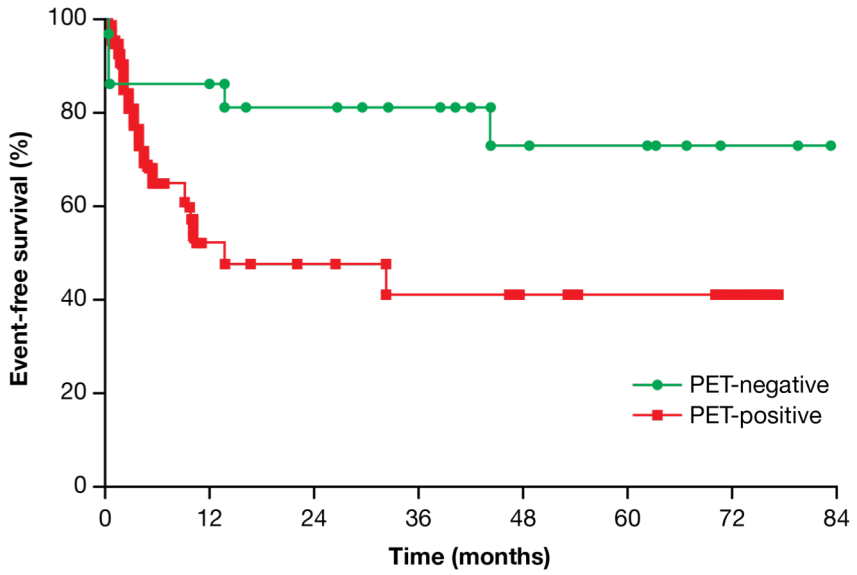
TTR, time to relapse; OS, overall survival

Post-induction PET/CT before HD+ASCT predicts outcome in relapsed HL patients

PFS/EFS for relapsed HL patients according to pre-transplant PET/CT



76 patients, 2-y PFS 73% vs. 36%[1]



46 patients, 3-y EFS 82% vs. 41%[2]

1. Mocikova H, *et al*. Leuk Lymphoma 2011;52:1668–74.
2. Smeltzer JP, *et al*. Biol Blood Marrow Transplant 2011;17:1646–52.

How to improve ASCT outcome

- First salvage therapy
- Post-ASCT maintenance therapy
- RT consolidation
- New drugs

Table 1. Salvage regimens for relapsed classical Hodgkin lymphoma.

Regimen	Number of patients	Median age (range) years	Number of prior lines of therapy	Number of patients with prior ASCT	ORR (%)	CR (%)
Chemotherapy-based regimens						
ICE	65	27 (12-59)	1-6	NA	88	26
ICE	6	52 (30-65)	1-2	NA	100	67
DHAP	102	34 (21-64)	1	NA	89	21
ESHAP	22	34 (18-66)	1	2	73	40
GVD	91	33 (19-83)	1	36	70	19
IGEV	91	30 (17-59)	1-4	NA	81	54
GDP	23	36 (19-57)	1	NA	70	17
GemOx	24	27 (14-76)	1-6	10	71	38
BeGEV	59	33 (18-68)	1	NA	83	73

Table 1. Salvage regimens for relapsed classical Hodgkin lymphoma.

Regimen	Number of patients	Median age (range) years	Number of prior lines of therapy	Number of patients with prior ASCT	ORR (%)	CR (%)
Novel agent-based therapy						
Sequential BV-chemo	37	34 (11-67)	1	NA	68	35
Sequential BV-chemo (ICE)	44	31 (13-65)	1	NA	NR	27 (BV alone) 76 (ove
BV-ESHAP	66	36 (18-66)	1	NA	96	70
BV-ICE	16	32 (23-60)	1	NA	94	69
BV-DHAP	12	30.5 (NR)	1	NA	100	100
BV-bendamustine	55	36 (19-79)	1	NA	93	74
BV-nivolumab	29	32 (18-69)	1	NA	90	62

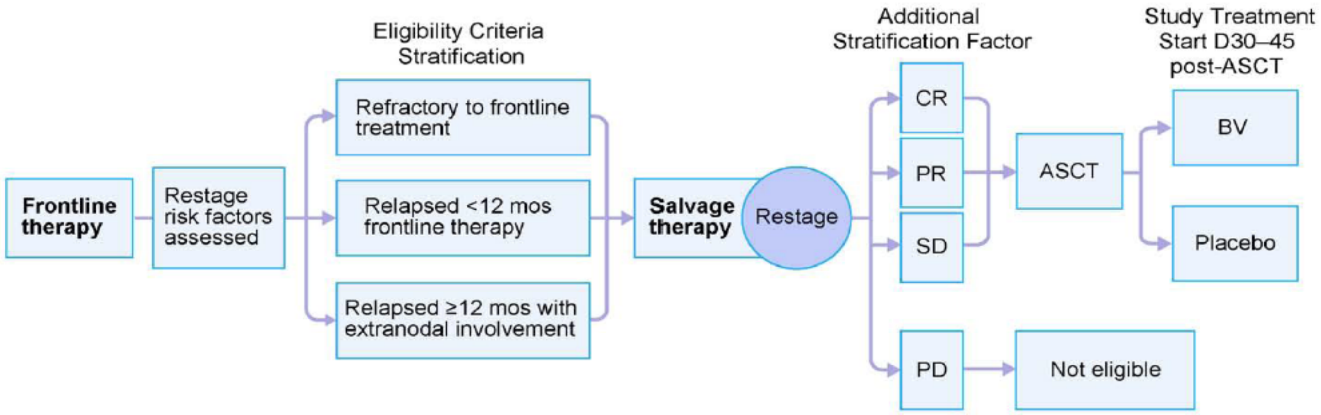
First Salvage Therapy: Conventional CT regimens

Goals:

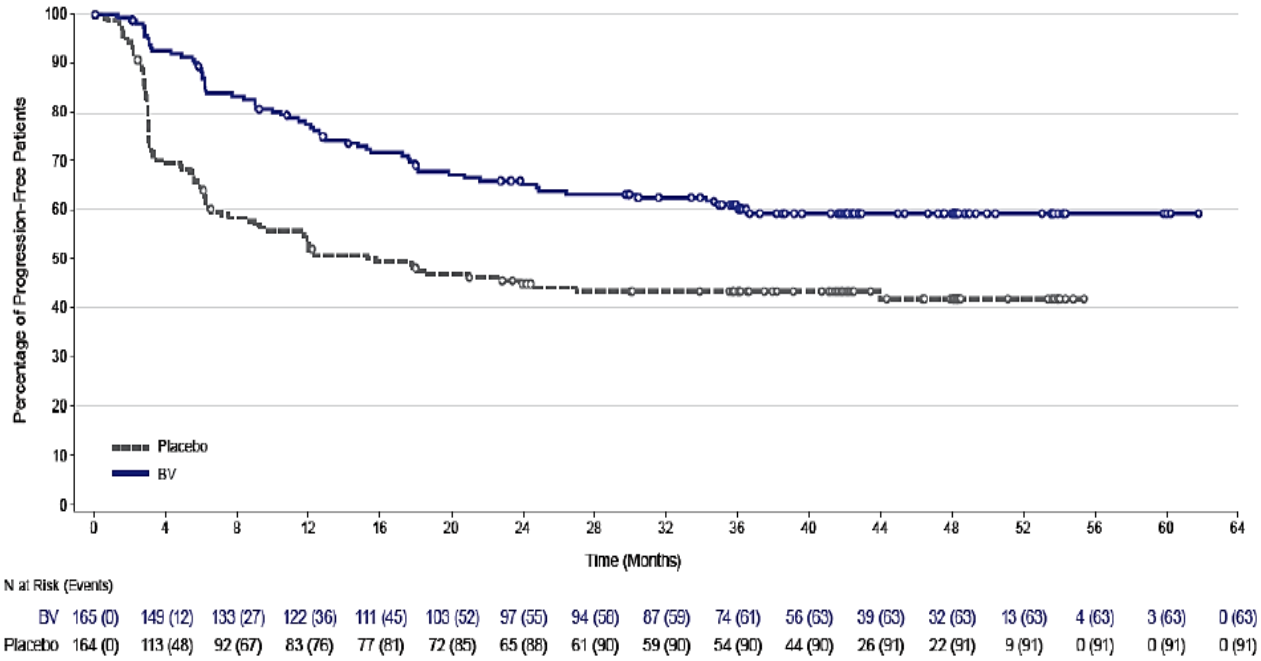
- Achieve CR = negative PET pre-ASCT
- Mobilize PBSC
- Minimize toxicity

Study Design and Key Eligibility Criteria

- 329 patients were randomized at 78 sites in North America and Europe



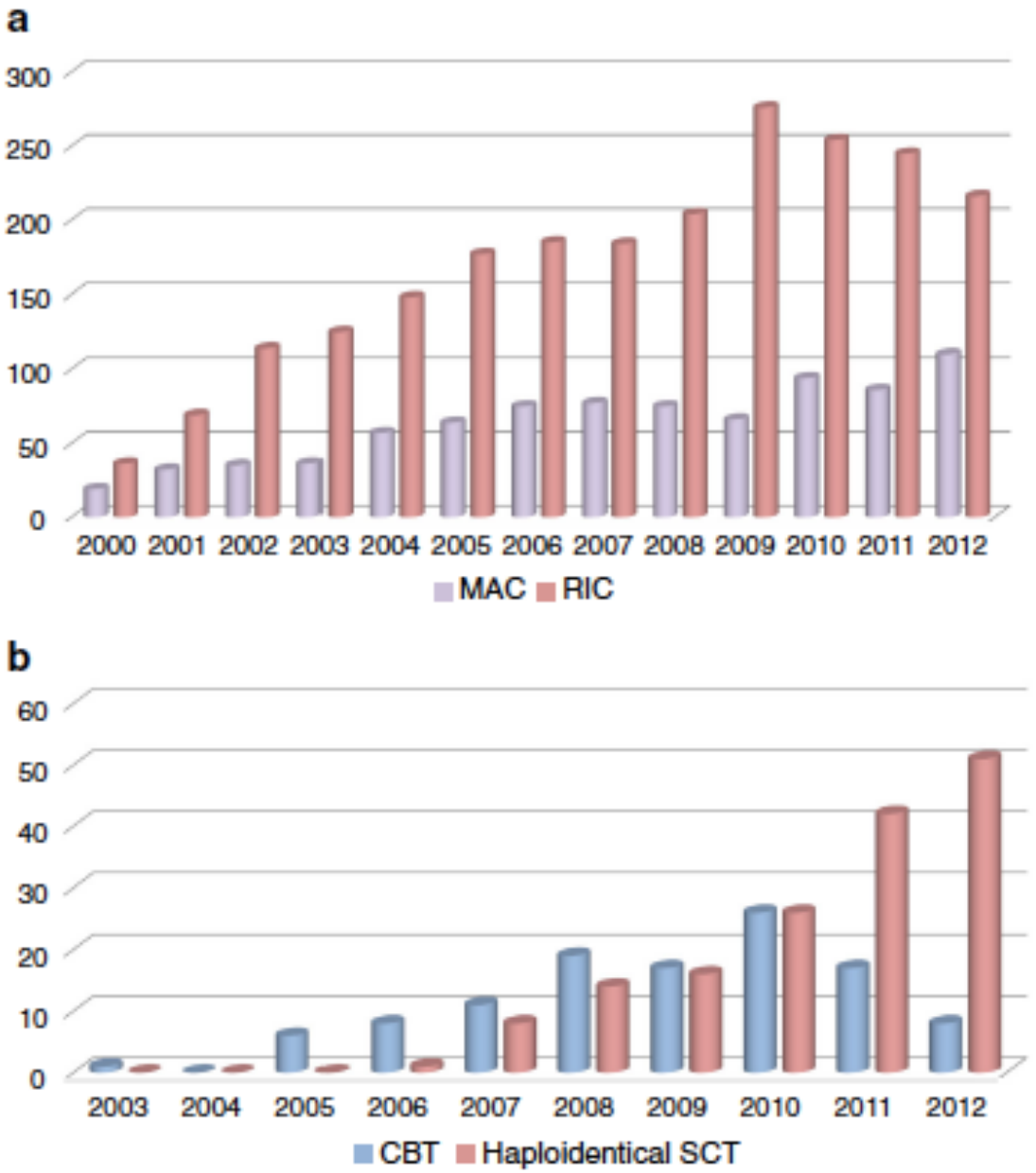
PFS* per Investigator – 3 Years Since Last Patient Randomized



RELAPSE AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION

Allogeneic transplant in Hodgkin's lymphoma.

EBMT data



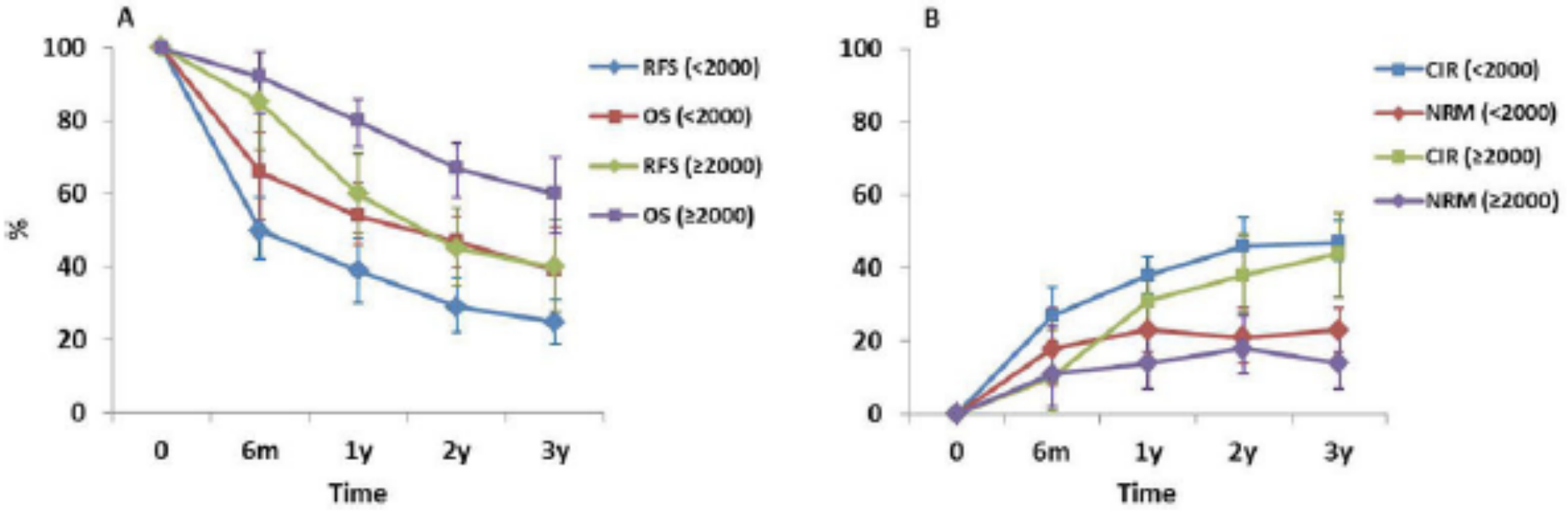
Bone Marrow Transplantation (2016) **51,** 521–528

www.nature.com/bmt

ORIGINAL ARTICLE

Allogeneic hematopoietic stem cell transplantation in Hodgkin lymphoma: a systematic review and meta-analysis

A Rashidi[1], M Ebadi[2] and AF Cashen[1]



NEW DRUGS

Antibody conjugated

BRENTUXIMAB VEDOTIN

BRENTUXIMAB VEDOTIN

SG035-0003: Phase 2 pivotal study of brentuximab vedotin in patients with rel/ref HL post ASCT: overview

Eligibility

- Relapsed or refractory CD30+ HL*
- Age ≥12 years
- Measurable disease ≥1.5 cm
- ECOG performance status of 0–1
- Prior ASCT

Treatment (N=102)

- Brentuximab vedotin 1.8 mg/kg IV Q3wk
- Administered outpatient over 30 min
- 8 to 16 cycles for SD or better
- Restage** at cycles 2, 4, 7, 10, 13 16

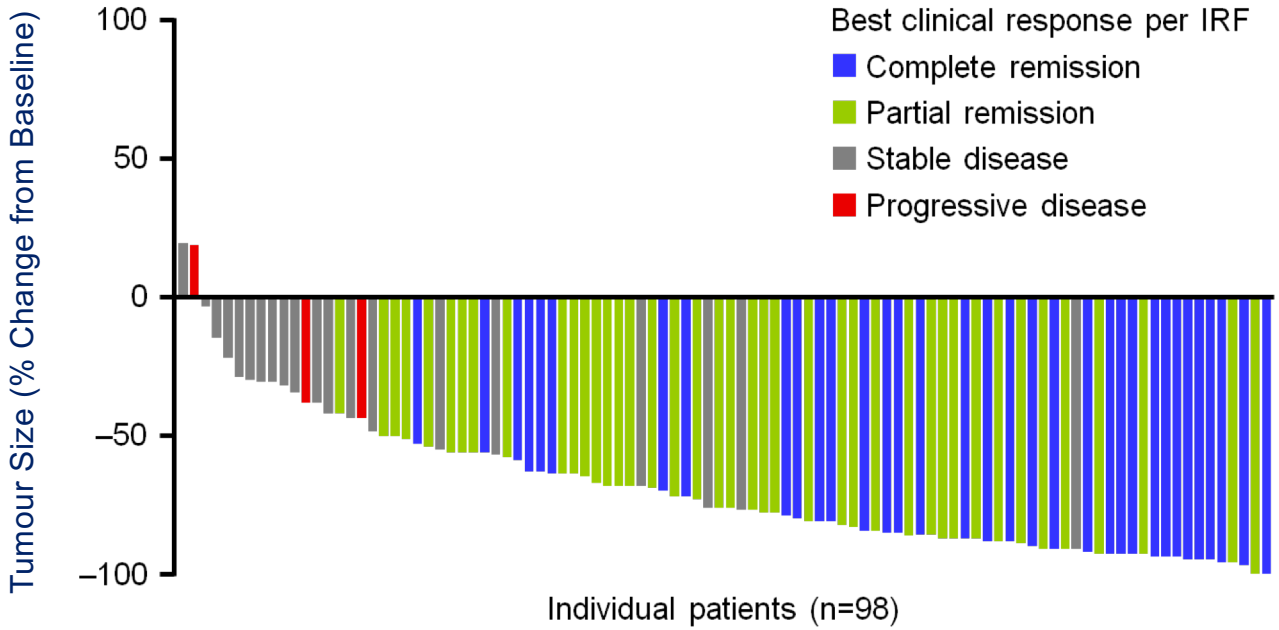
Every 12 weeks

Primary Endpoint: ORR by Independent Review Facility

* Histologically documented CD30-positive HL by central pathology review

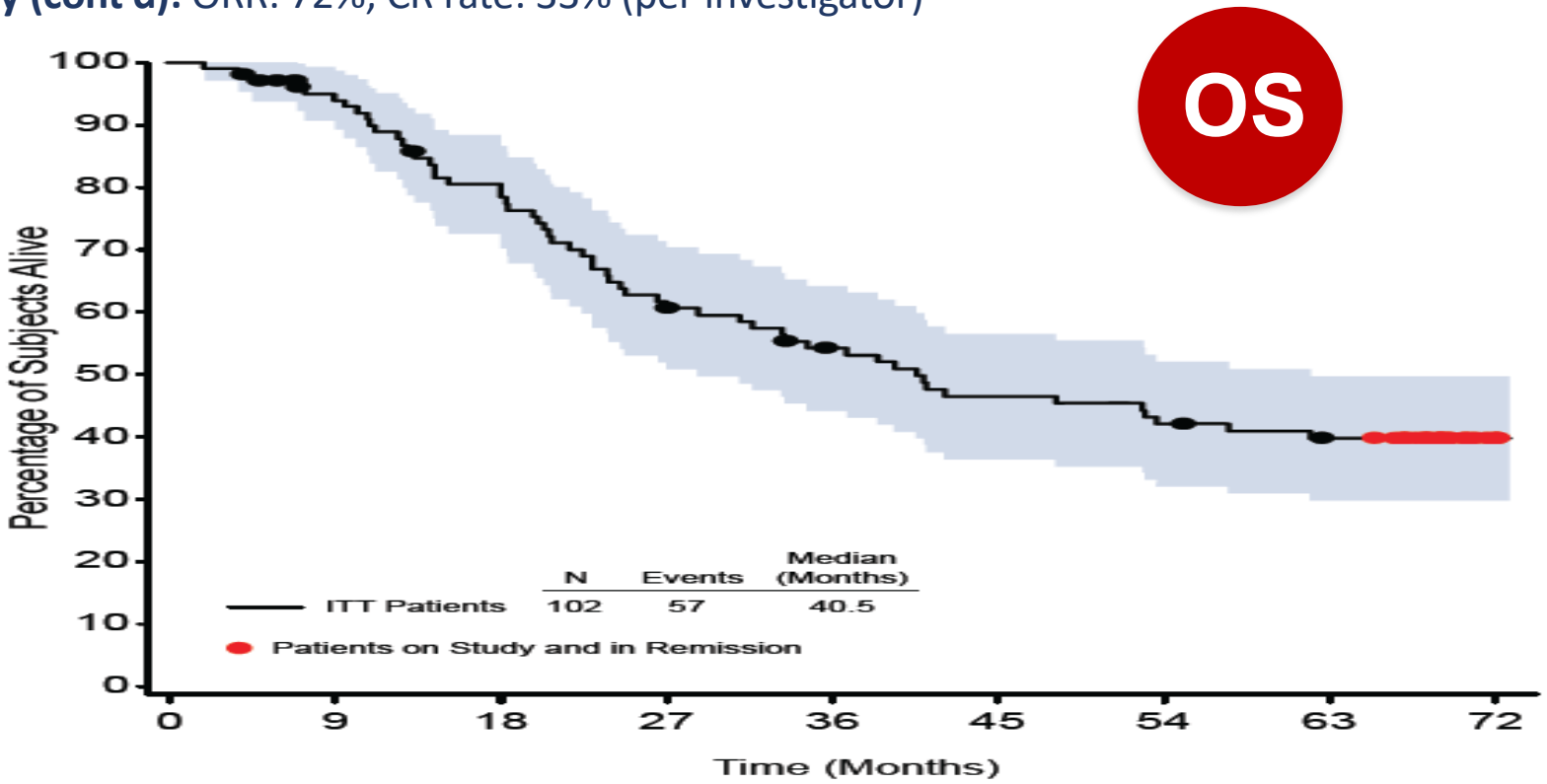
** Revised response criteria for malignant lymphoma (Cheson 2007)

% (95% CI)	IRF (N=102)
ORR	75 (65, 83)
CR	34 (25, 44)
PR	40
SD	22
PD	3
Not evaluable	1



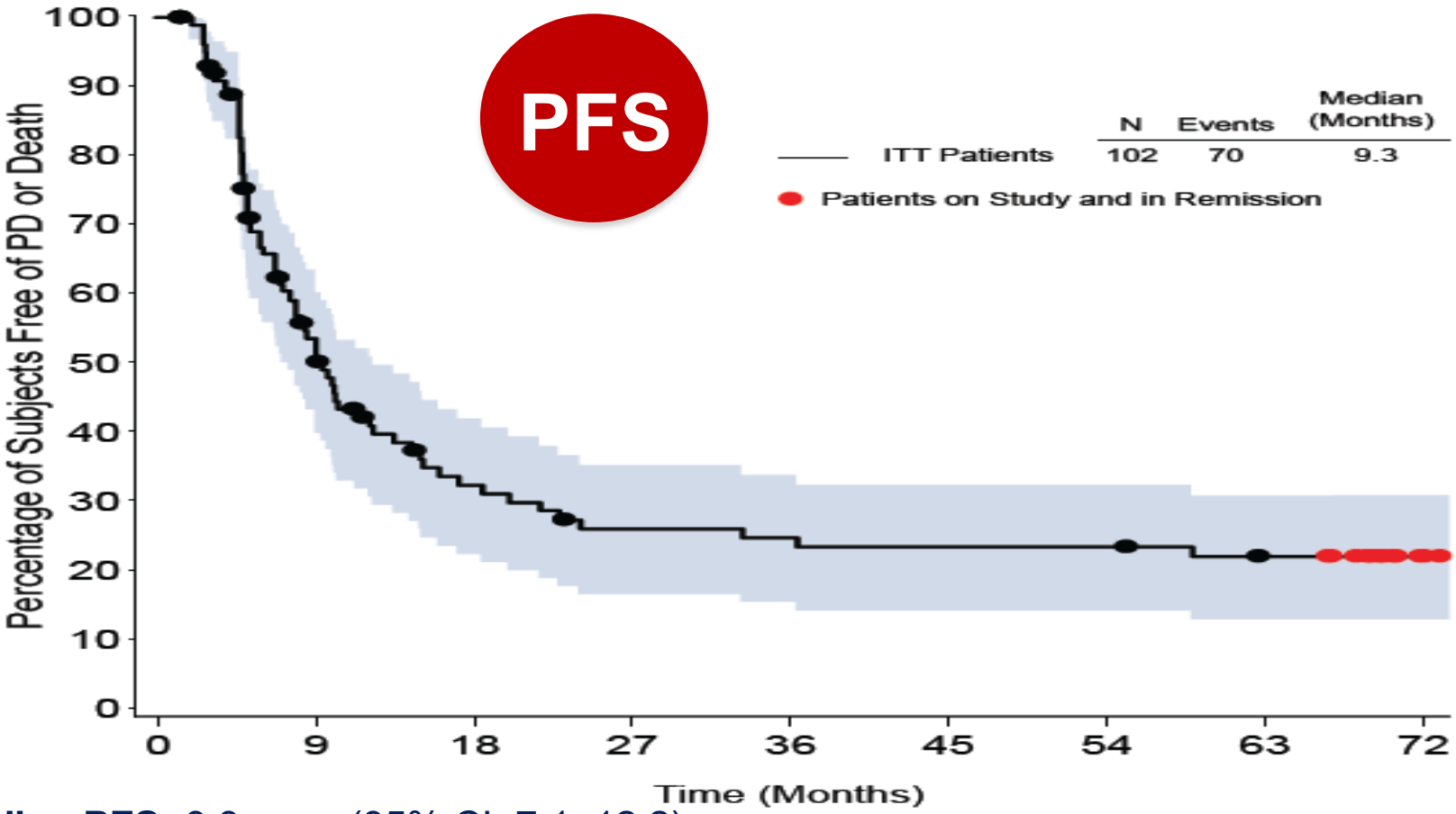
SGN35-003: 5-year follow-up from phase II study of brentuximab vedotin in R/R HL post-ASCT[1] – Update ASH 2015 (NCT00848926)

Efficacy (cont'd): ORR: 72%; CR rate: 33% (per investigator)



Median OS: 5-yr OS: 41% (95% CI: 31%, 51%)

SGN35-003: 5-year follow-up from phase II study of brentuximab vedotin in R/R HL post-ASCT[1] – Update ASH 2015 (NCT00848926)



Median PFS: 9.3 mos (95% CI: 7.1, 12.2)

Patients who Achieved CR Following Treatment with BV (N=34)

- **In the 34 pts who achieved CR with BV, the median response duration was not reached (95% CI: 20.5, –) and ranged from 2 to 71.6+ months.**

- ***13 of the 34 CR pts (38%) remained in remission at the time of study closure***

- **Of the 34 CR pts, 6 pts received allo-SCT as consolidation**
  - **Of these 6 pts, 4 pts (67%) remained in CR**
  - **Of the 28 pts who did not receive allo-SCT as consolidation, 9 pts (32%) remained in CR with no subsequent therapy**

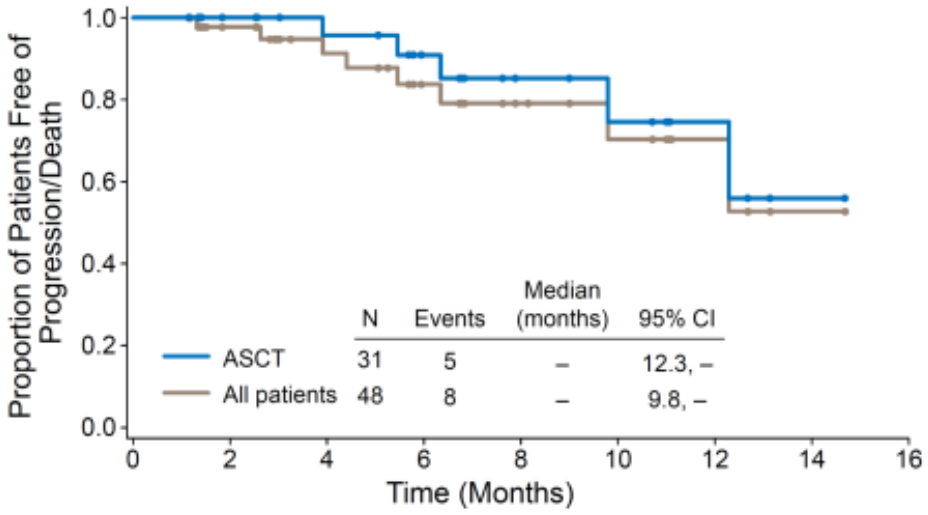
Brentuximab Vedotin in Combination With Bendamustine for Patients With Hodgkin Lymphoma Who Are Relapsed or Refractory After Frontline Therapy

LaCasce A, Bociek RG, Matous J, Sawas A, Caimi P, Ansell S, Islas-Cheung E, Agura E, Behler C, Crosswell H, Vose J, Josephson N

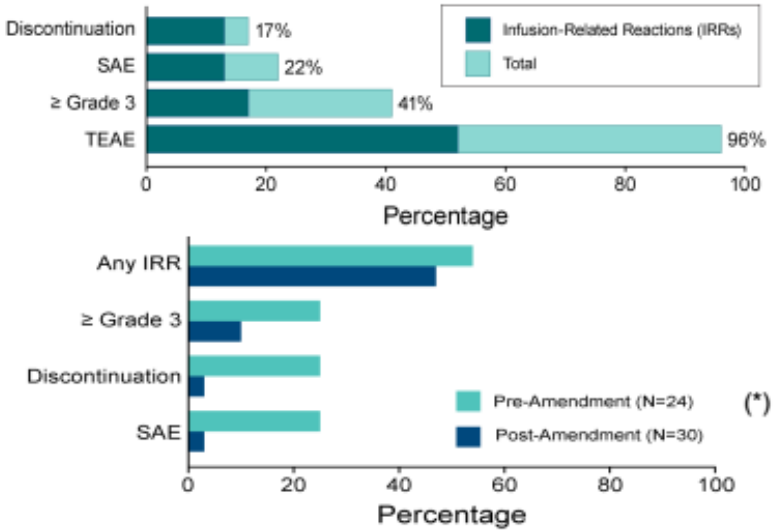
Data on 48 Evaluable Patients	N (%)	95% CI
Best clinical response (prior to ASCT)		
CR (*)	40 (83%)	69.8-92.5
PR	6 (13%)	
SD	1 (2%)	
PD	1 (2%)	
Overall response rate (CR + PR)	46 (96%)	85.8-99.5

(*) The majority of CR (34/40) achieved within cycle 2 reassessment

Progression-Free Survival



Toxicity



(*) Premedication with corticosteroids and antihistamines

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BRENTUXIMAB-VEDOTIN AND BENDAMUSTINE IS A FEASIBLE AND EFFECTIVE DRUG COMBINATION AS FIRST-LINE TREATMENT OF HODGKIN LYMPHOMA IN THE ELDERLY (HALO TRIAL)

A. Gallamini[1*] | F. Bijou[2] | J. Viotti[3] | A. Rossi[4] | A. Perrot[5] | C. Patti[6] | L. Gastaud[7] | R. Sorasio[8] | C. Debaigt[1] | E. Chamorey[3] | S. Viviani[9] | A. Thyss[7]

BeBV x 6 cicli

Response: 22 response evaluable pts thus far

	Evaluated treatment cycle				Follow-up			
	Cycle 2 (n=22)	Cycle 4* (n=8)	Cycle 6 (n=15)	End of TRT (n=18)	3 months (n=11)	6 months (n=6)	9 months (n= 3)	12 months (n=1)
CR	15 (68.2)	4 (50)	14 (93.3)	15 (83.3)	8 (72.7)	5 (83.3)	1 (33.3)	1 (100)
PR	5 (22.7)	2 (25)	0 (0)	0 (0)	1 (9.1)	1 (16.7)	0 (0)	0 (0)
NR or SD	2 (9.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PD	0 (0)	2 (25)	1 (6.7)	3 (16.7)	2 (18.2)	0 (0)	2 (66.7)	0 (0)
Not yet available	0	0	3	0	5	3	3	1

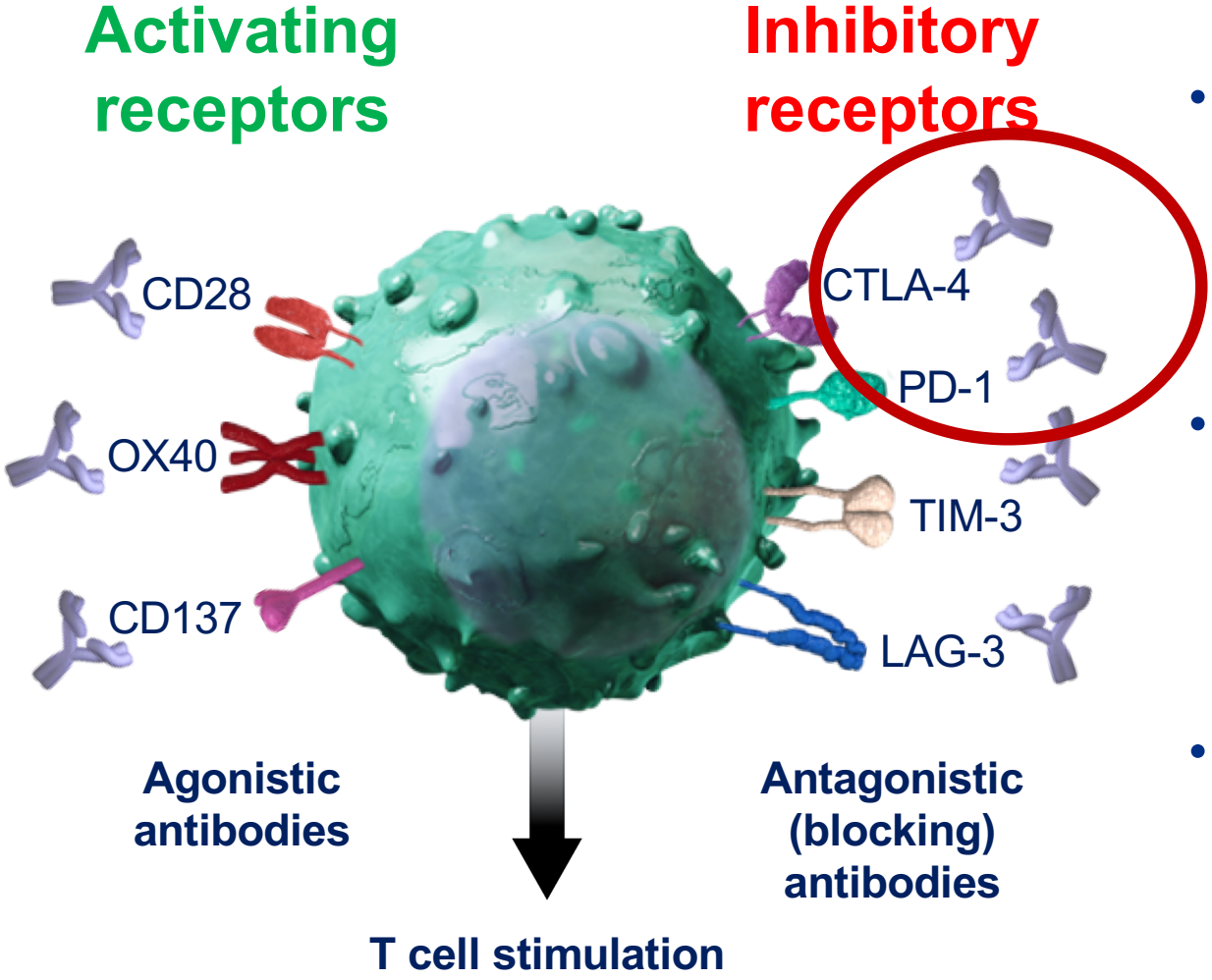
*Response was evaluated after C4 only on pts not in CR at C2
Response at C6 is the response assessed by PET-6 for pts who completed the entire planned treatment
Response at the end of treatment includes pts scanned at least with a PET-2 who failed to complete the 6 cycles of treatment

NEW DRUGS

Anti-check point inhibitors

NIVOLUMAB
PEMBROLIZUMAB
IPILIMUMAB

Regulating the T cell immune response

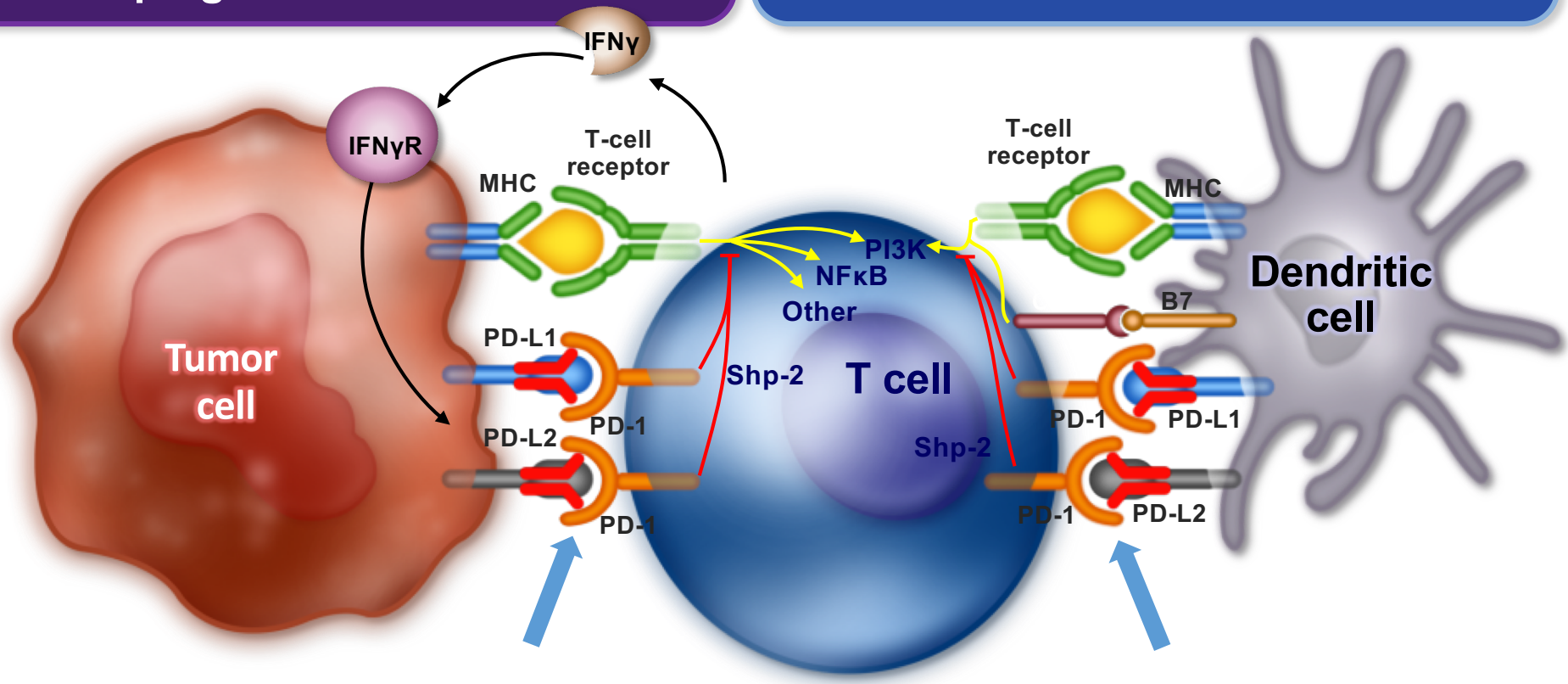


- T cell responses are regulated through a complex balance of inhibitory (checkpoint) and activating signals
- Tumors can dysregulate checkpoint and activating pathways, and consequently immune response
- Targeting these pathways is an evolving approach to cancer therapy, designed to promote an immune response

NIVOLUMAB mechanism of action

Recognition of tumor by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 upregulation on tumor

Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells



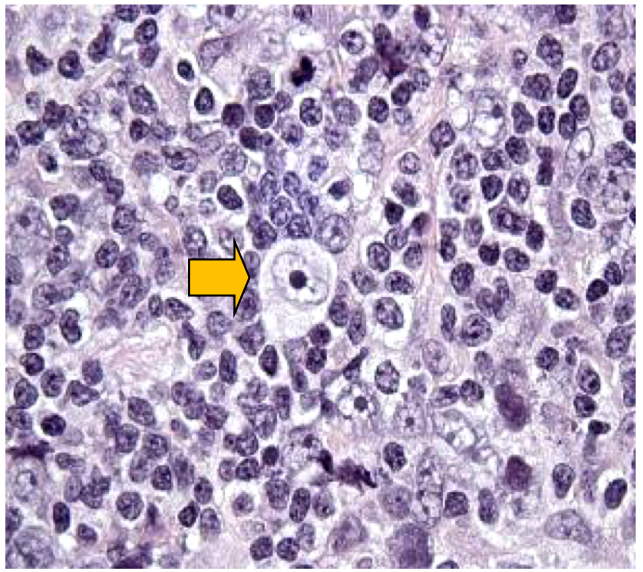
Nivolumab blocks the PD-1 receptor

CD28/B7, cluster of differentiation 28/B7; IFNγ, interferon-gamma; IFNγR, IFNγ receptor; MHC, major histocompatibility complex; NFκB, nuclear factor kappa B; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; PI3K, phosphoinositide-3 kinase; Shp-2, ubiquitously expressed tyrosine-specific protein phosphatase.

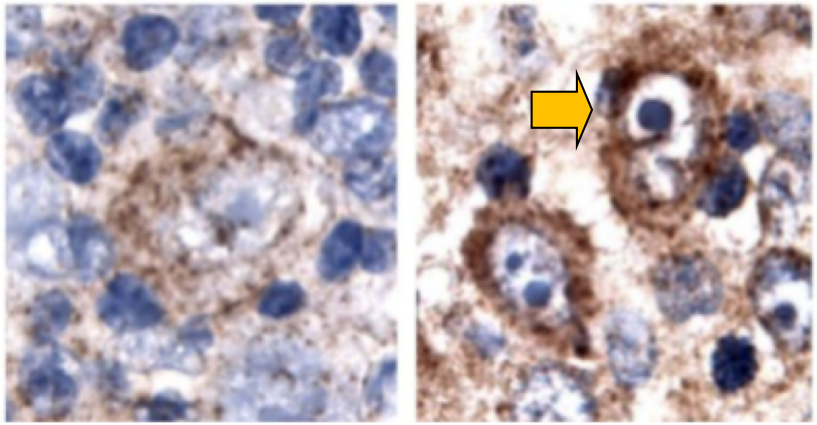
Pardoll DM. Nat Rev Cancer. 2012;12:252–264.

Rationale for PD-1 Blockade in cHL

- Pathology of cHL: rare malignant Reed-Sternberg (R-S) cells within an extensive inflammatory/immune cell infiltrate.

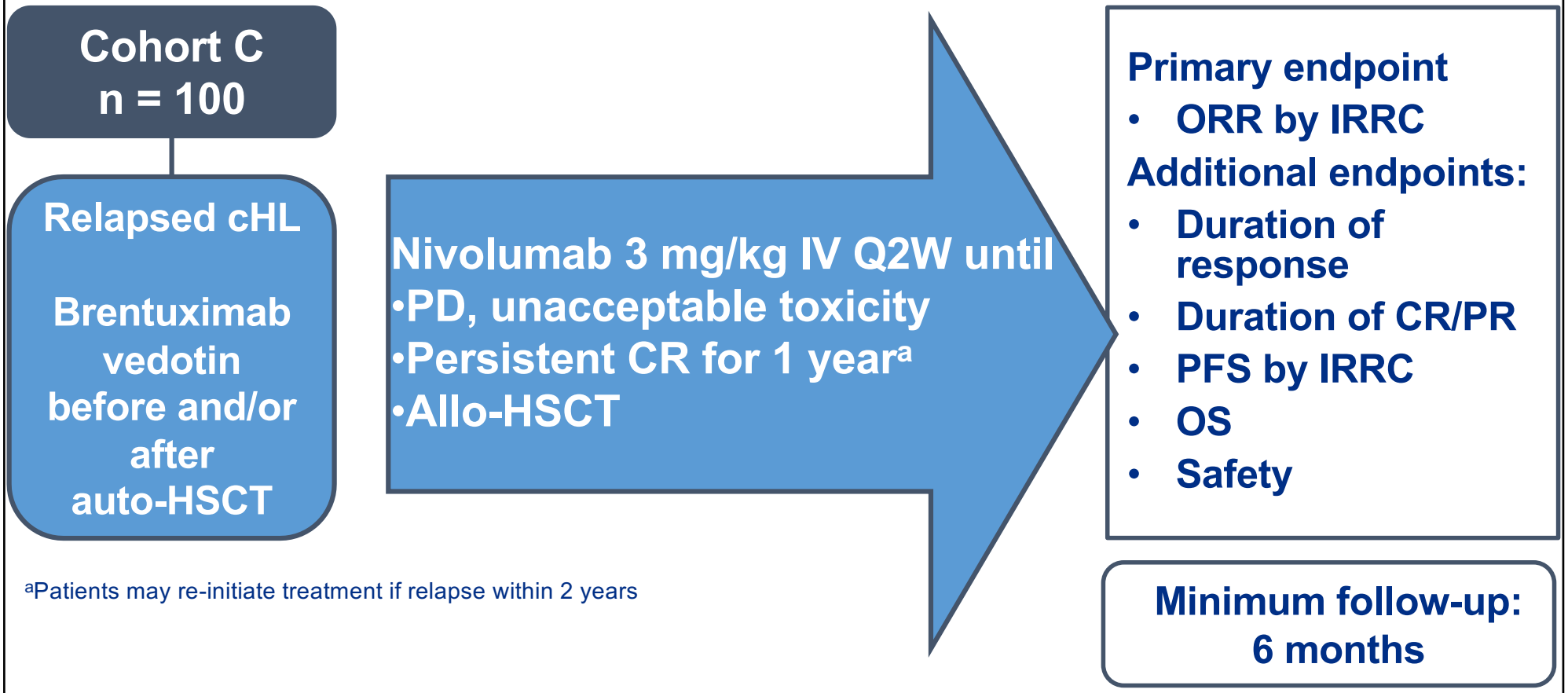


- Genetic analyses: frequent 9p24.1 amplification with upregulation of PD-1 ligands and JAK2.



- PD-L1 expression on R-S cells corresponds to 9p24.1 amplification

CheckMate 205: Study Design, Cohort C

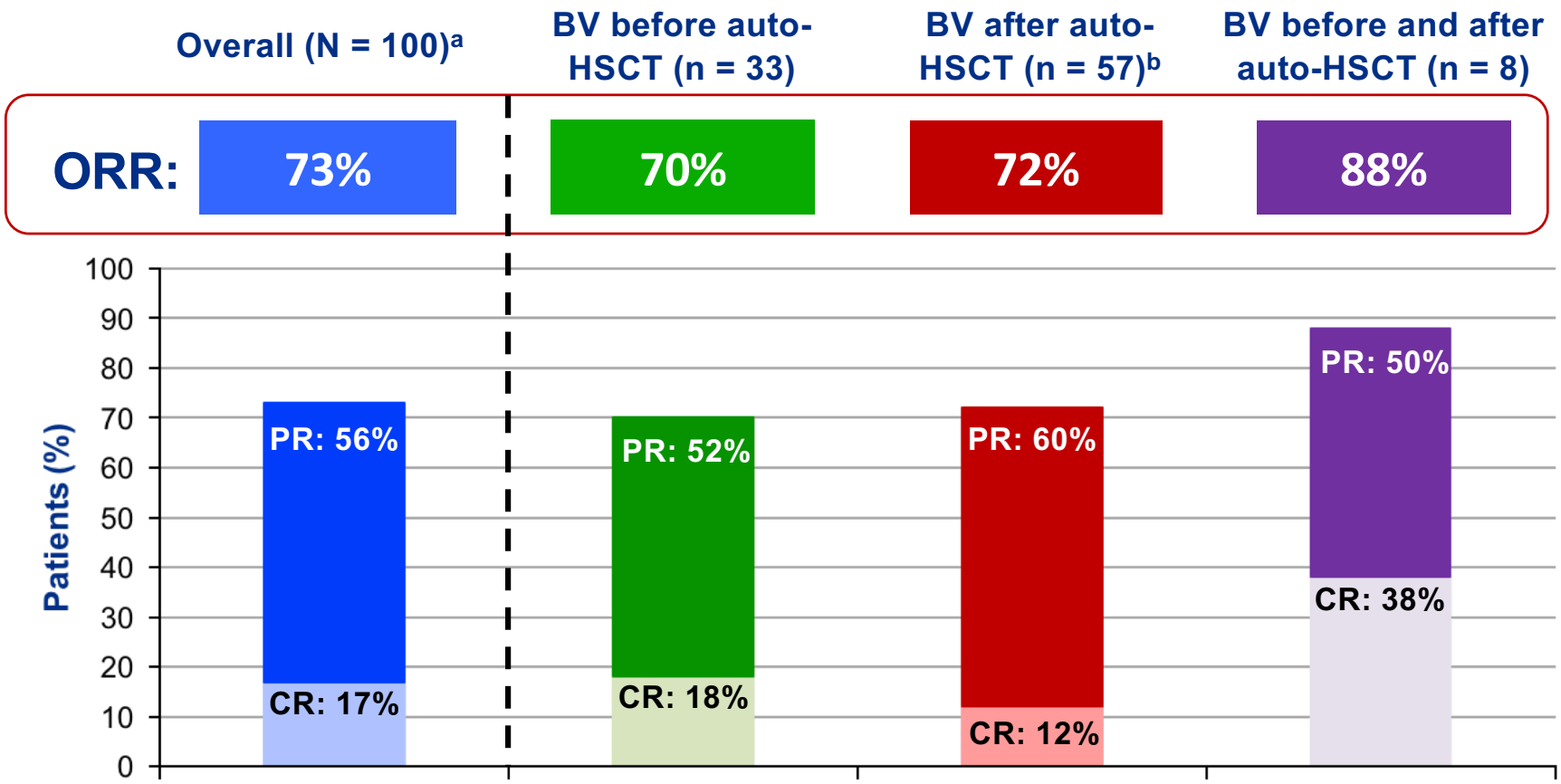


[a]Patients may re-initiate treatment if relapse within 2 years

CheckMate 205C – Baseline Characteristics

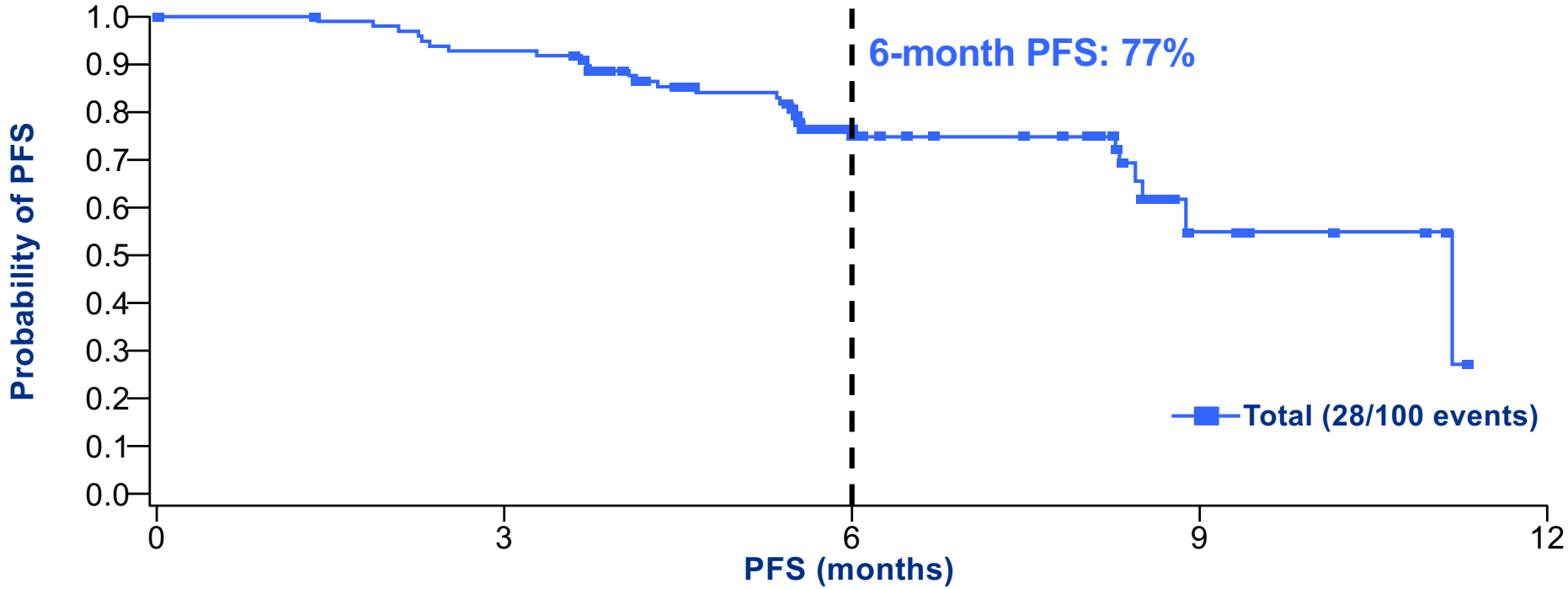
Characteristic	*Patients (N = 100)*
Age, median (range), years	32 (19-69)
Sex, %	
Male	56
Previous lines of therapy,[a] median (range)	4 (2-9)
≥5 lines of therapy, %	29
Previous radiation therapy, %	69
Previous autoSCT, %	
1	100
≥2	0
Time from transplant to first subsequent therapy, median (range), months	8 (0-201)
Time from transplant to first dose of nivolumab, median (range), months	21 (2-204)
BV history, %	
BV before autoSCT	33
BV after autoSCT	57
BV before and after autoSCT	8
Other[b]	2

CHECKMATE 205C – BEST RESPONSE (IRRC)



Stable disease	17 (17)	7 (21)	9 (16)	1 (13)
Progressive disease	6 (6)	3 (9)	3 (5)	0

Cohort C: Progression-Free Survival

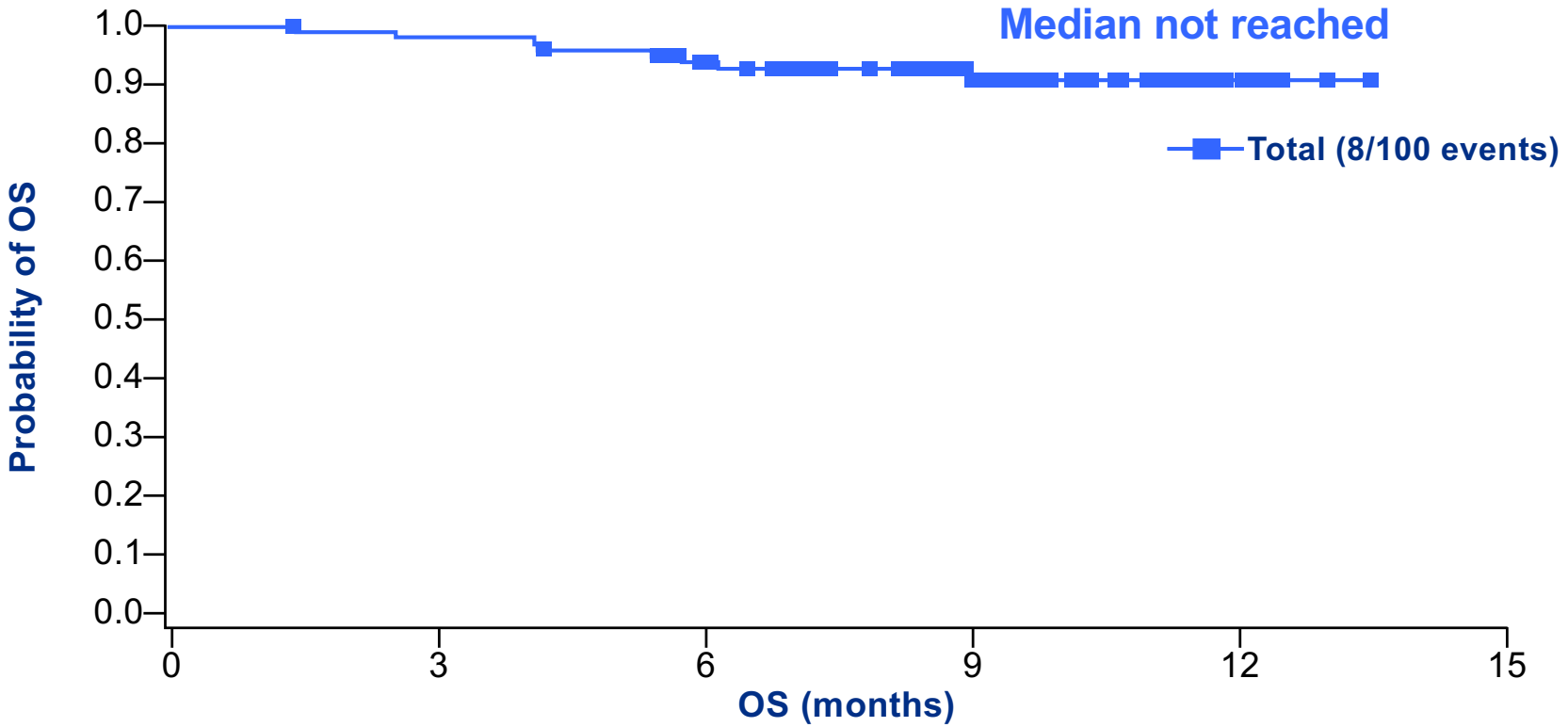


Number at risk: 100 91 44 7 0

	Total (N = 100)[a]	BV before auto-HSCT (n = 33)	BV after auto-HSCT (n = 57)	BV before and after auto-HSCT (n = 8)
PFS rate at 6 months, % (95% CI)	77 (66–84)	84 (65–93)	71 (57–82)	83 (27–98)
Median PFS, months (95% CI)	11 (9–NE)	11 (9–NE)	9 (8–NE)	NE (6–NE)

PFS per IRRC assessment. [a]Total includes 2 patients for whom order of BV relative to auto-HSCT could not be determined

Cohort C: Overall Survival



	Total (N = 100)[a]	BV before auto-HSCT (n = 33)	BV after auto-HSCT (n = 57)	BV before and after auto-HSCT (n = 8)
OS rate at 6 months, % (95% CI)	94 (87–97)	97 (80–100)	91 (80–96)	100 (100–100)

[a]Total includes 2 patients for whom order of BV relative to auto-HSCT could not be determined

New treatments:Pembrolizumab

Enrollment to date (n = 31)

- Nodular sclerosing or mixed cellularity HL
- Relapsed or refractory to brentuximab vedotin
- Failure of ASCT or transplant ineligible

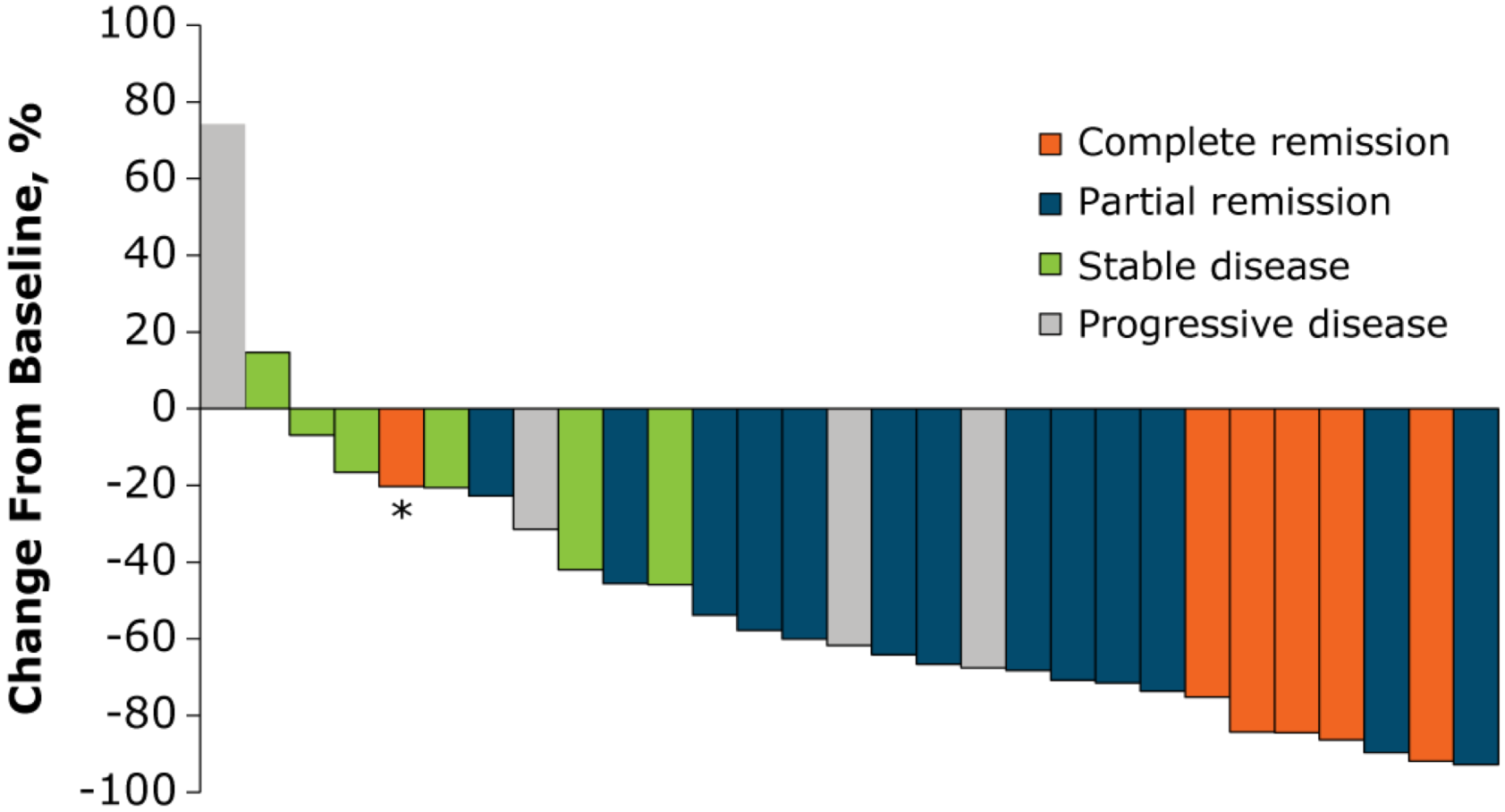
→ Pembrolizumab
10 mg/kg, IV, q2wk

Response	Transplant ineligible or refused* (n = 9)	Transplant failure (n = 9)	Total (n = 29)
Overall response rate	44%	75%	66%
Complete remission	22%	20%	21%
Partial remission	22%	55%	45%
Stable disease	33%	15%	21%
Clinical benefit rate	78%	90%	86%
Progressive disease	22%	10%	14%

- Median time to response: 12 weeks
- Duration of response:
  - Median: not reached (Range: 1+ to 185+ days)

Moskowitz CH et al. Proc ASH 2014;Abstract 290.

New treatments:Pembrolizumab



21% complete remission rate, 66% ORR, 86% clinical benefit rate

No Grade 4 treatment-related AEs, and no single Grade 3 treatment-related AE that occurred in >1 patient

Moskowitz CH et al. Proc ASH 2014;Abstract 290.

Toxicity reduction

Less radiotherapy

Less chemotherapy

Reducing RT fields: from IFRT to INRT

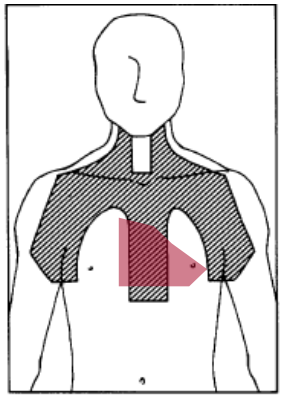
- INRT is expected to be as good as IFRT in terms of local control
- Significantly fewer late complications are expected because of limited irradiation of normal tissues

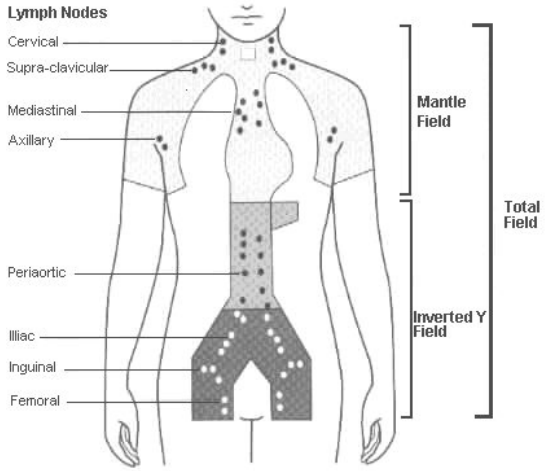
RT in HL has changed!

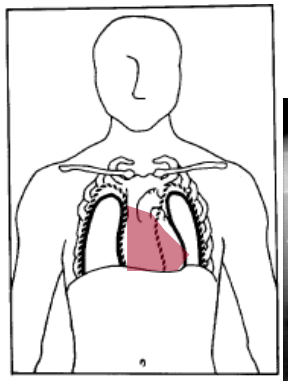
- **In Quantity:**
  - **Dose**
  - **Volume**

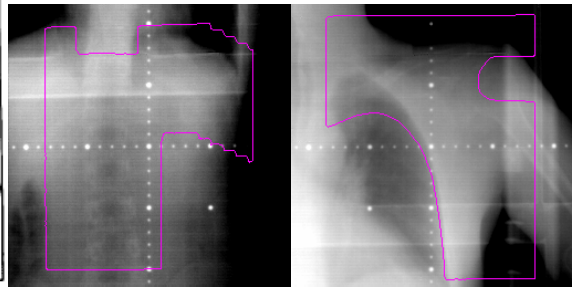
- **In Quality**

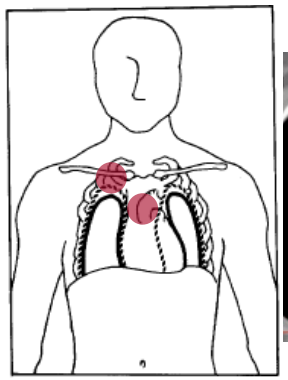
Timeline of major changes in RT in Hodgkin's Lymphoma

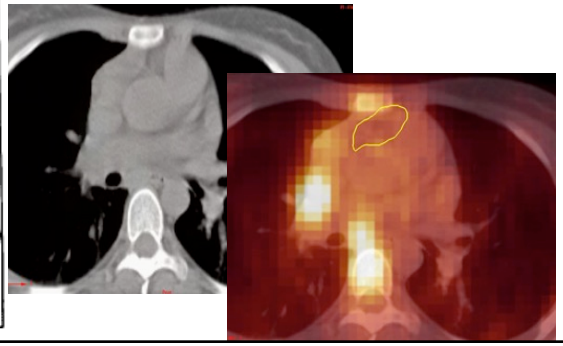












1960

Extended fields

DFT≈40 Gy

MOPP

Involved fields

DFT≈30 Gy

ABVD

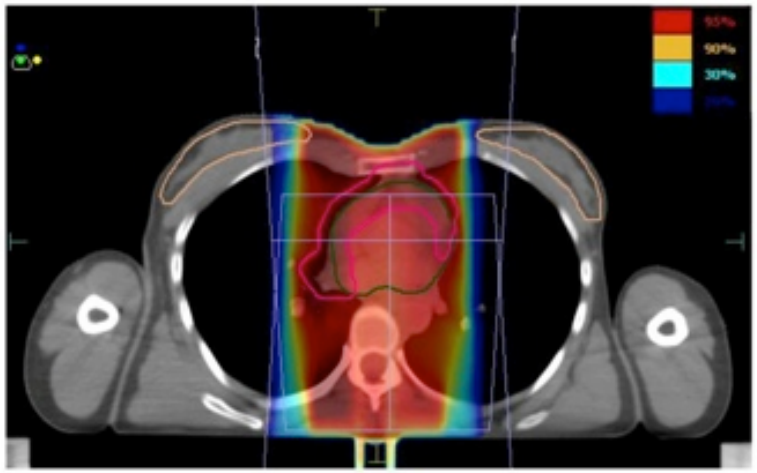
Involved node(s)

DFT≈20 Gy

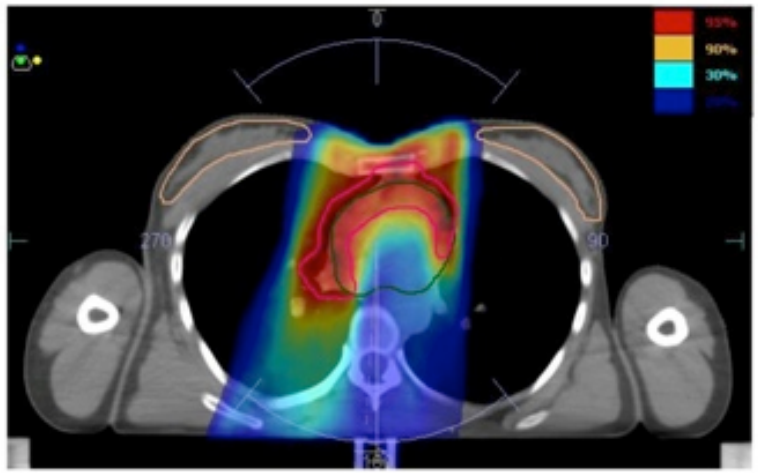
2011

Highly conformal RT

- Only the target volume is treated to the full dose
- Better sparing of normal tissues
- Low-dose bath to the surrounding normal tissues



3D-CRT



IMRT (VMAT)

Modern RT in lymphoma

Radiation therapy has changed dramatically over the last few decades in terms of both irradiated volumes and dose

Smaller treatment volumes, lower radiation dose and advanced conformal radiotherapy can certainly allow a safer radiation delivery, when/if needed (!!!)

”There is no doubt that radiation remains the most active single modality in the treatment of most types of lymphoma”

James O. Armitage

Toxicity reduction

Less radiotherapy

Less chemotherapy

GHSG HD18

HD18 for PET-2-negative patients

Summary

GHSG
www.ghsg.org

- Non-inferior PFS for PET-2-negative patients after 4 cycles of eBEACOPP compared with 8/6 cycles (primary endpoint) at a very high level (95% at 3y, 92% at 5 y).
- Significant reduction of severe acute hematological and non-hematological toxicities.
- Relevant reduction of mortality for other reasons than HL.
- Elimination of HL as relevant cause of death (7/1005; i.e. 0.7%).
- **Significantly superior OS with 4 cycles of eBEACOPP (99% at 3 y, 98 % at 5 y) over 6/8 cycles.**

I think that GHSG too come back to the future.

First ABVD and intensification only in patients with bad progostic factors:
Interim PET, cyrculating tumor DNA, Tumor Methabolic Volume, CD68 expression……

Il punto di vista dell'ematologo dell'adulto: CONCLUSIONI

- ✓ **La malattia di Hodgkin è la malattia che, senza dubbio, ci da le maggiori soddisfazioni con elevatissime percentuali di guarigione.**
- ✓ **Stiamo vivendo un'epoca veramente esaltante per la terapia dei linfomi**
- ✓ **Qualcuno dice che li "curiamo peggio" di prima andando alla ricerca in maniera spasmodica della remissione.**
  - ✓ **Ritengo che invece la disponibilità di molte terapie impone la ricerca di metodi per individuare precocemente i non responsivi (e non arrivare a definirli come facevamo un tempo dopo i 6-8 cicli di ABVD)**
  - ✓ **Allo stesso tempo imponga anche di raggiungere il salvataggio con trapianto nelle migliori condizioni possibili ovvero avendo ottenuto una RC**
- ✓ **In tutto questo non dobbiamo/possiamo dimenticarci di un'arma fondamentale nella cura di questo linfoma: la RADIOTERAPIA**

Il punto di vista dell'ematologo dell'adulto: CONCLUSIONI

Della TRADIZIONE a mio parere dobbiamo salvaguardare:

- ✓ **La radioterapia come arma ottimale per il controllo loco-regionale della malattia**
- ✓ **L'autotrapianto rimane la terapia di salvataggio per i R/R**
- ✓ **L'allogenico rimane la terapia di scelta per i recidivati da autologo**

Del NUOVO dobbiamo salvaguardare:

- **La PET, non sarà lo strumento perfetto ma è sicuramente il migliore a disposizione per definire la chemiosensbilità**
- **I nuovi farmaci che ci aiutano a curare pazienti fino a poco tempo fa non curabili (ci permettono di avviarli all'allogenico)**

Thank you!