Hodgkin Lymphoma

Which Group of Patients

benefits

from the use of

BEACOPP

Volker Diehl

for the

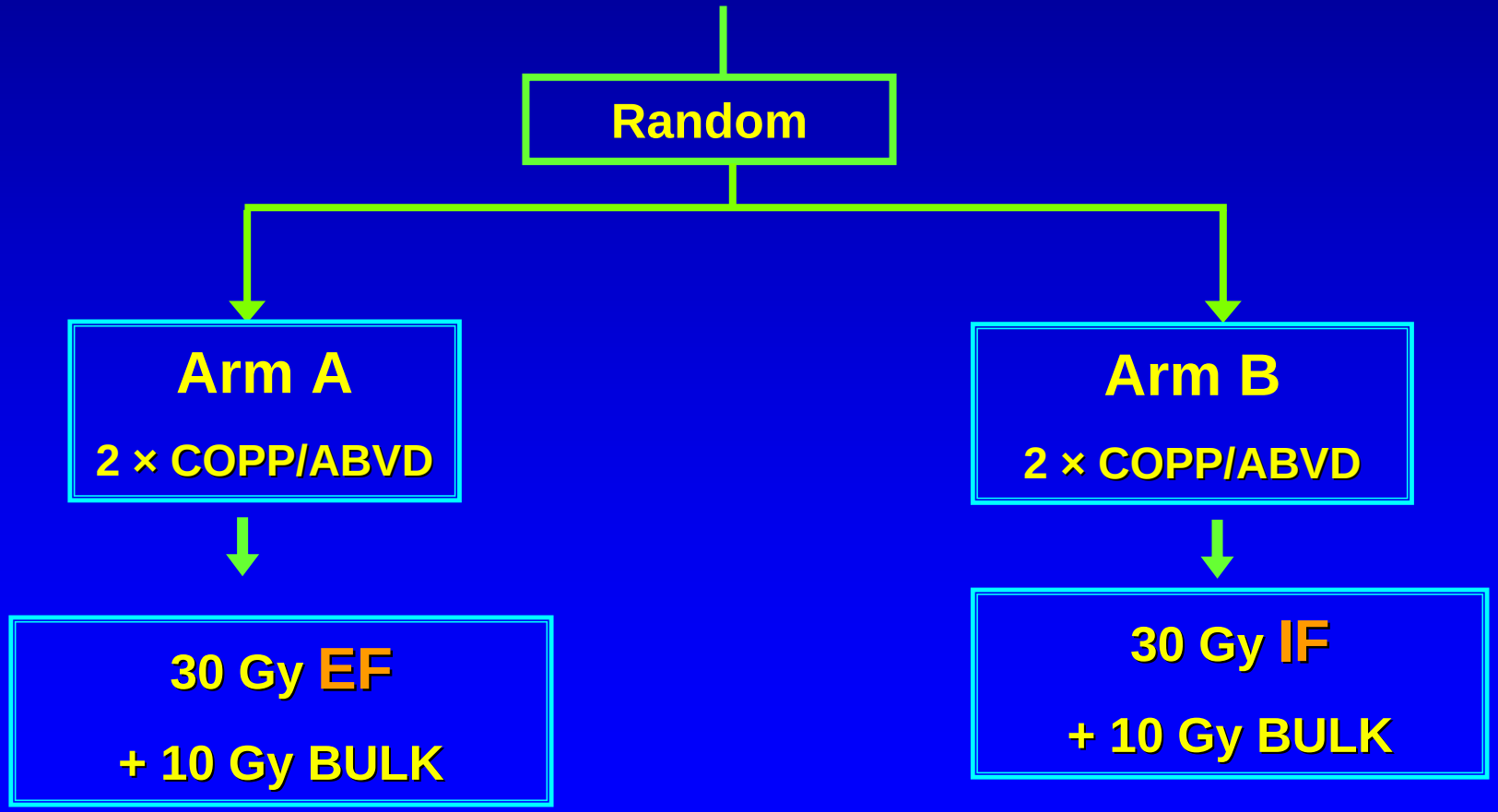
German Hodgkin Study Group

Moscow

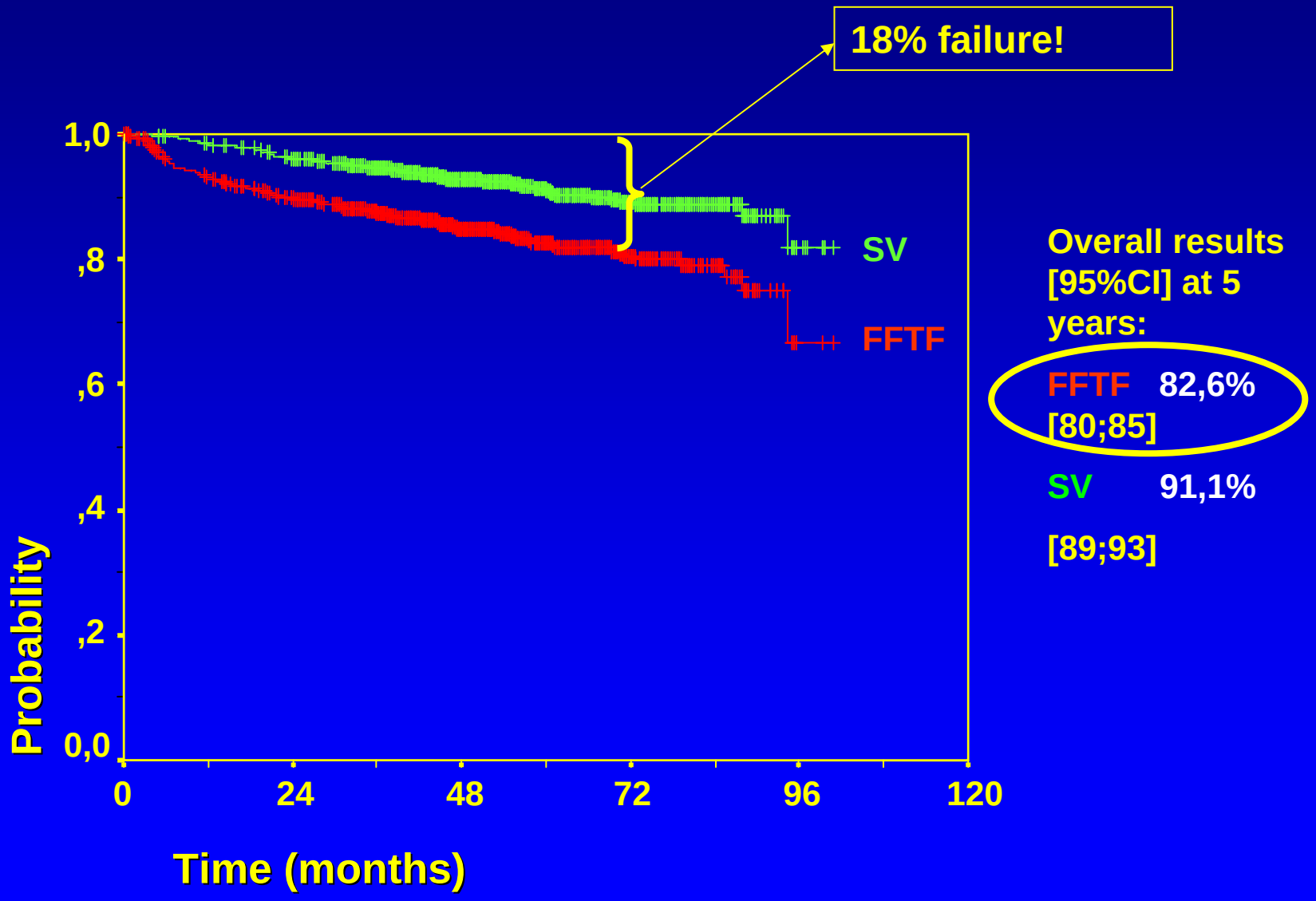
25.October 2007

HD8 trial design

CS IA, IB, IIA,B with risk factors



Overall results (all evaluable patients)



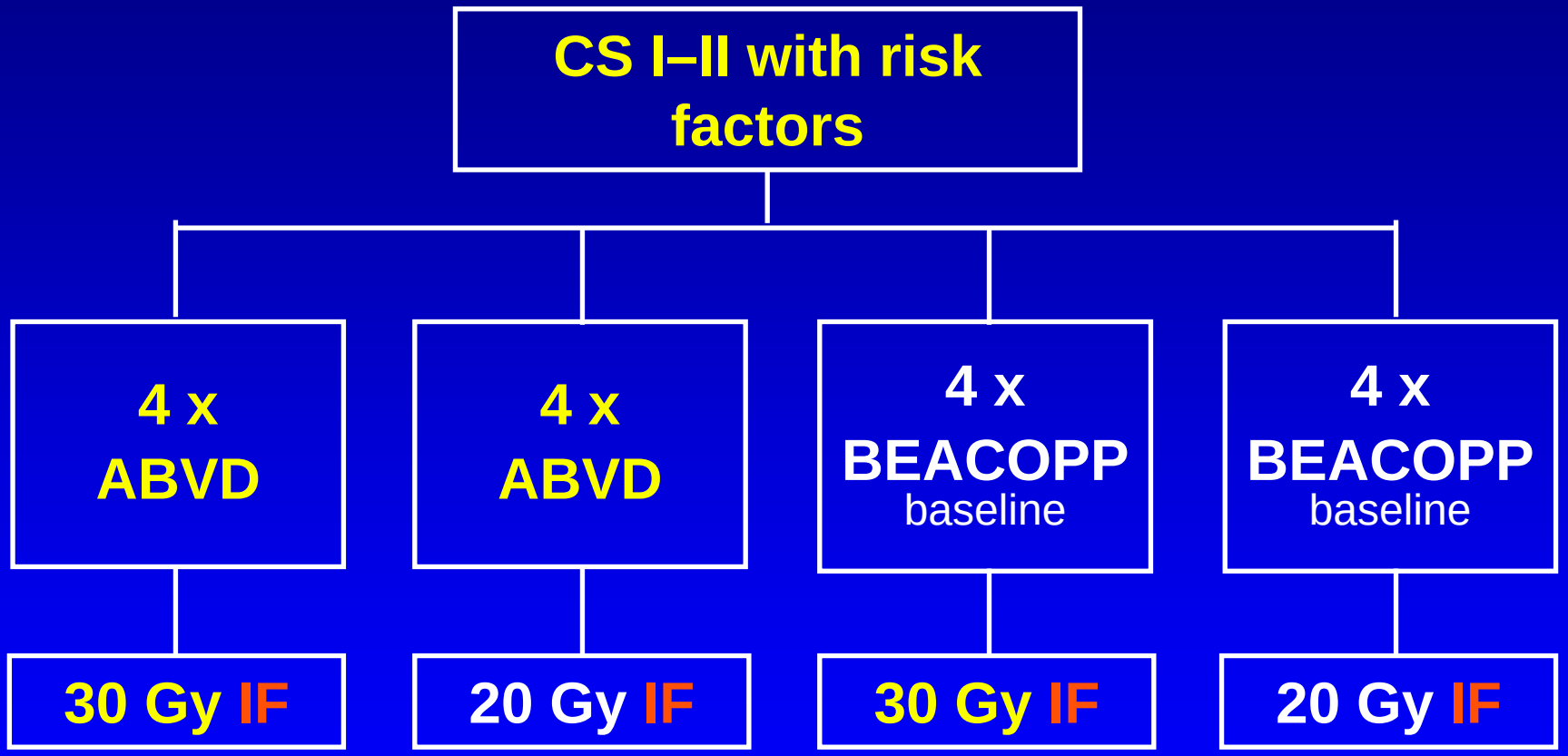
Overall results [95%CI] at 5 years:

FFTF 82,6% [80;85]

SV 91,1% [89;93]

Intermediate Group

(GHSG) HD11- Trial

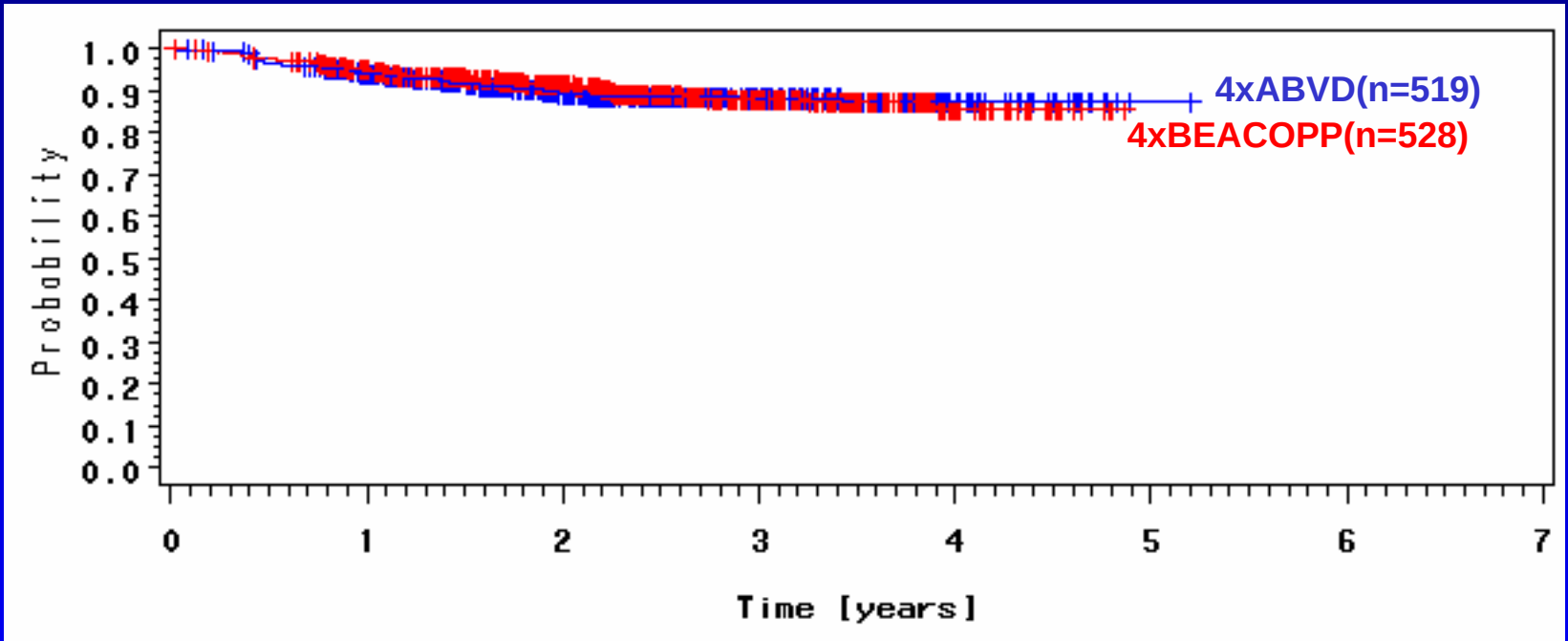


2003: 1456 patients recruited.
Trial closed in 1/2003.

Which group of HL patients benefits from BEACOPP

1. Intermediate Stages (HD-8,-11,-14)
2. Failures after 2- 4 ABVD+/-RT
3. All advanced stage HL patients
4. Late relapsing pats after ABVD

FFTF by CT-arm



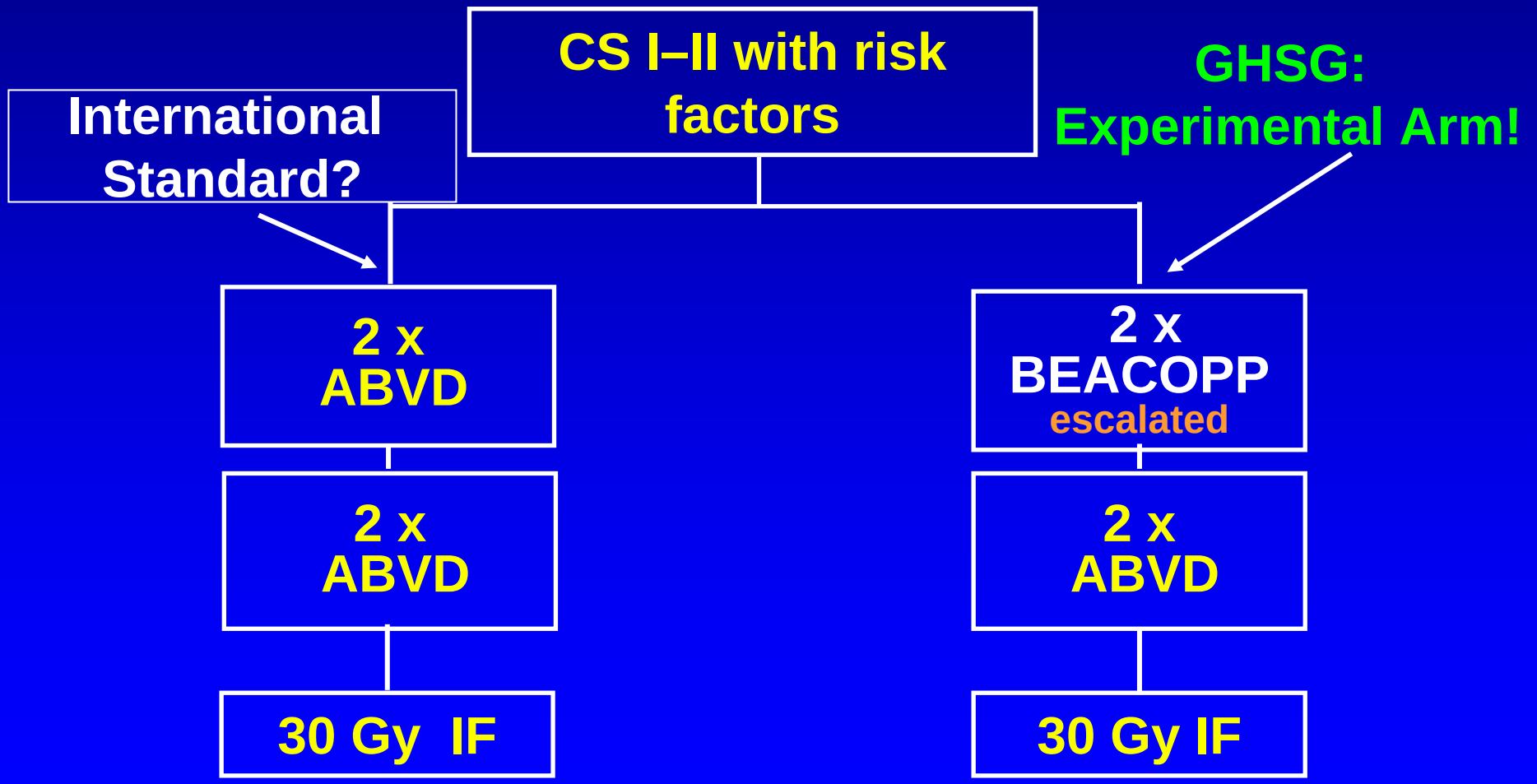
at 2 years, **4xABVD : 89,3 %** 95% KI: [86,4 ; 92,2]

4xBEACOPP : 91,2 % 95% KI: [88,7 ; 93,8]

Intermediate Group
HD14-trial

Start 1/2003

(1250 patients recruited)

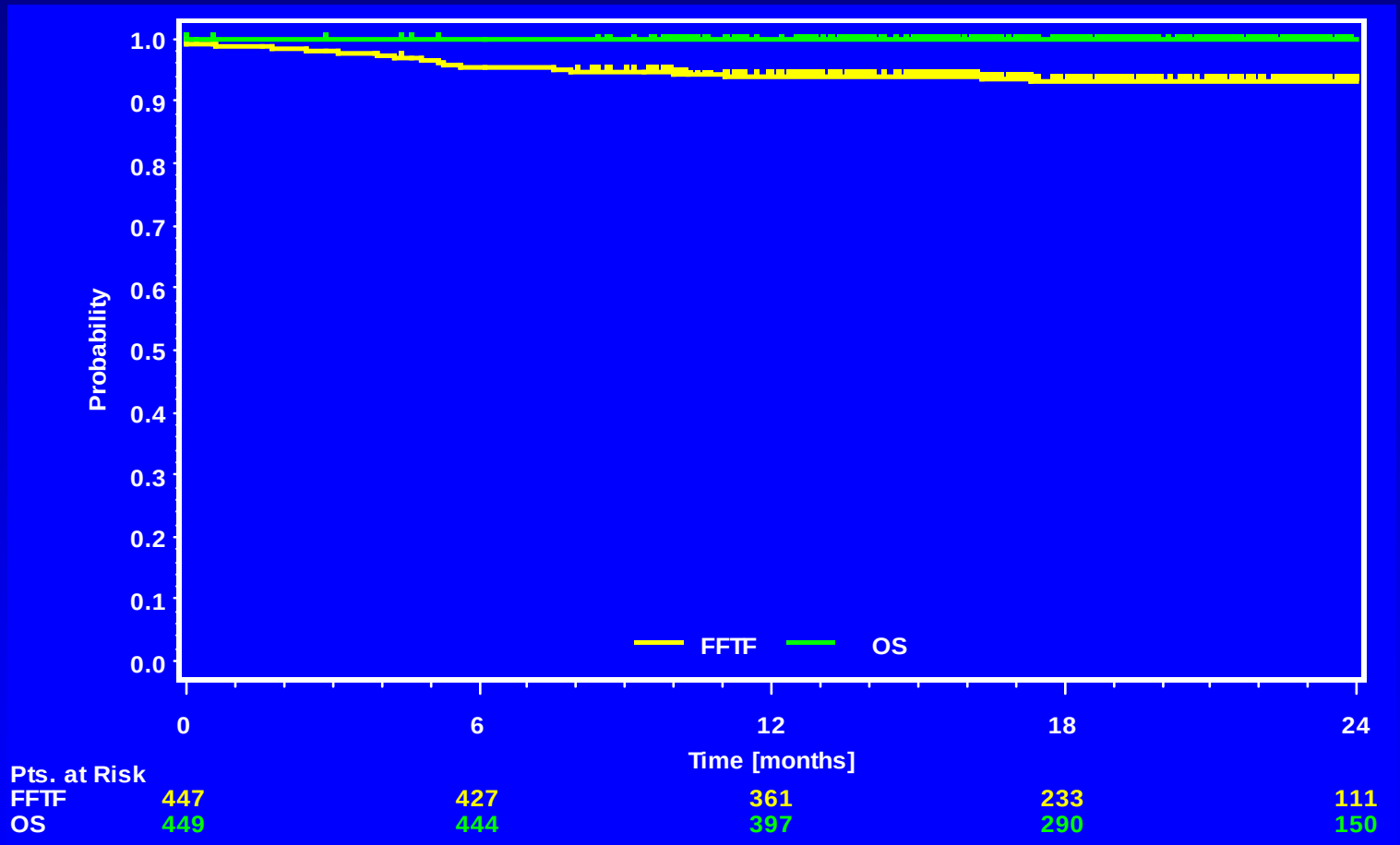


IIB with Large Mediast. Mass, → Advanced disease.

Overall results

(all evaluable patients)

Median follow up : 20 months



At 20 months **FFTF : 93 %** 95% CI: [90 ; 96]

OS : 100 % 95% CI: [99 ; 100]

Intermediate Stage Hodgkin Lymphoma

- Increased PFS from HD8→ HD14:

		PFS	OS at 2 years
HD 8:	4x C/ABVD	83%	91%
HD 11:	4x ABVD	90%	91%
HD 11:	4 BEACOPP	91%	93%
HD 14:	2 BEA esc+ 2 ABVD	93%	100%
HD 17:	4 EACOPP-14	??	??

Conclusion
For Early and Intermediate HL

- BEACOPP baseline not better than ABVD!!
- BEACOPP escalated achieves better tumor control
- Toxicity not increased compared to HD-11 trial
- Female gonadal toxicity very low (a few babies)
- Male gon.tox.under investigation!
- Future trial using PET to eliminate RT?
- „EACOPP“ = BEACOPP?? (HD-17)

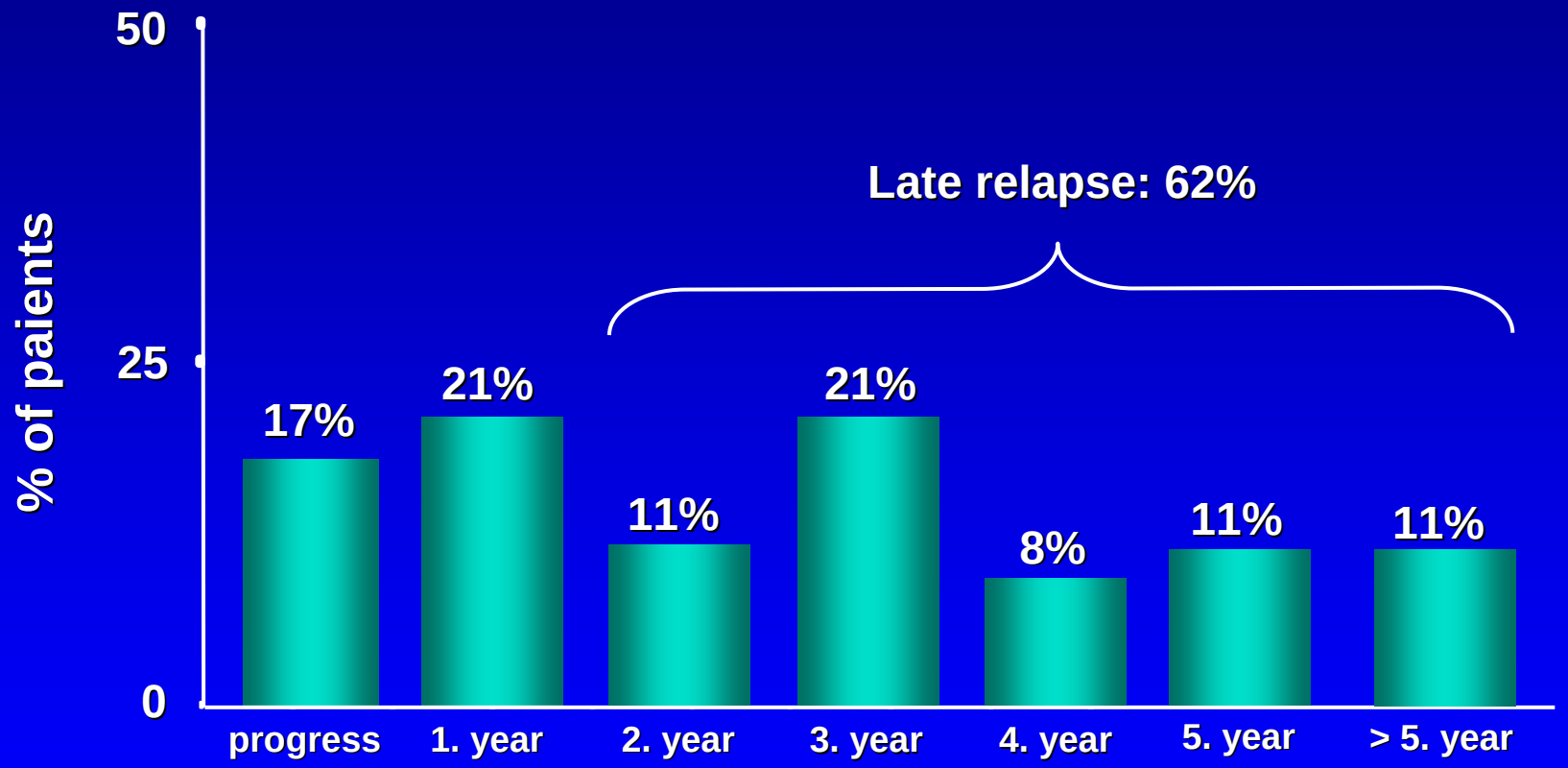
Outcome of patients progressing or relapsing after primary treatment with 2-4 cycles of ABVD and radiotherapy for early / intermediate stage Hodgkin lymphoma

The GHSG experience

Patient selection: Early stage Hodgkin`s disease with no risk factors (GHSG)

Trial	Years	Treatment protocol	Total No.	Pts. with progress or relapse after 2 x CT	
HD7	94-98	EF RT 30 Gy + 10 Gy IF	311		
		vs.			
		2 x ABVD + 30 Gy EF RT	316	11	(3.5%)
HD10	98-02	4 x ABVD + 30 Gy IF RT	303		
		vs.			
		4 x ABVD + 20 Gy IF RT	302		
		vs.			
		2 x ABVD + 30 Gy IF RT	297	14	(4.7%)
		vs.			
		2 x ABVD + 20 Gy IF RT	302	10	(3.3%)
Total pats: 2 ABVD +/- RT			**915**	**35**	**(3,8%)**

Time of relapse after the end of therapy (n = 35)



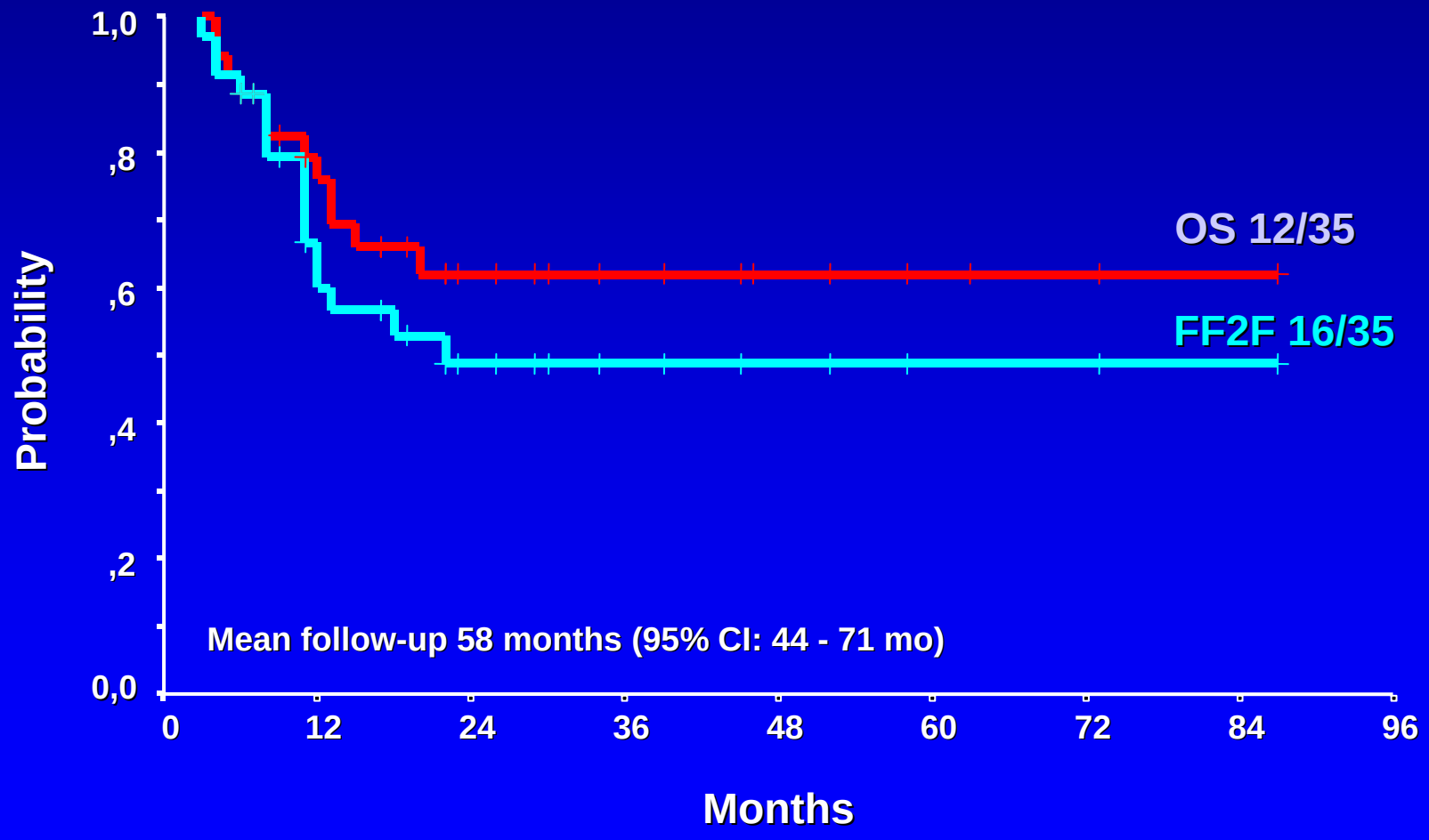
Salvage therapy after primary treatment with 2 x ABVD plus radiotherapy

Regimen	No	%
BEACOPP escalated	10	29
HDCT + ASCT	10	29
BEACOPP baseline	5	14
COPP/ABVD	5	14
ABVD	2	6
Radiotherapy	3	8
Comined modality	4	11

Response after salvage therapy

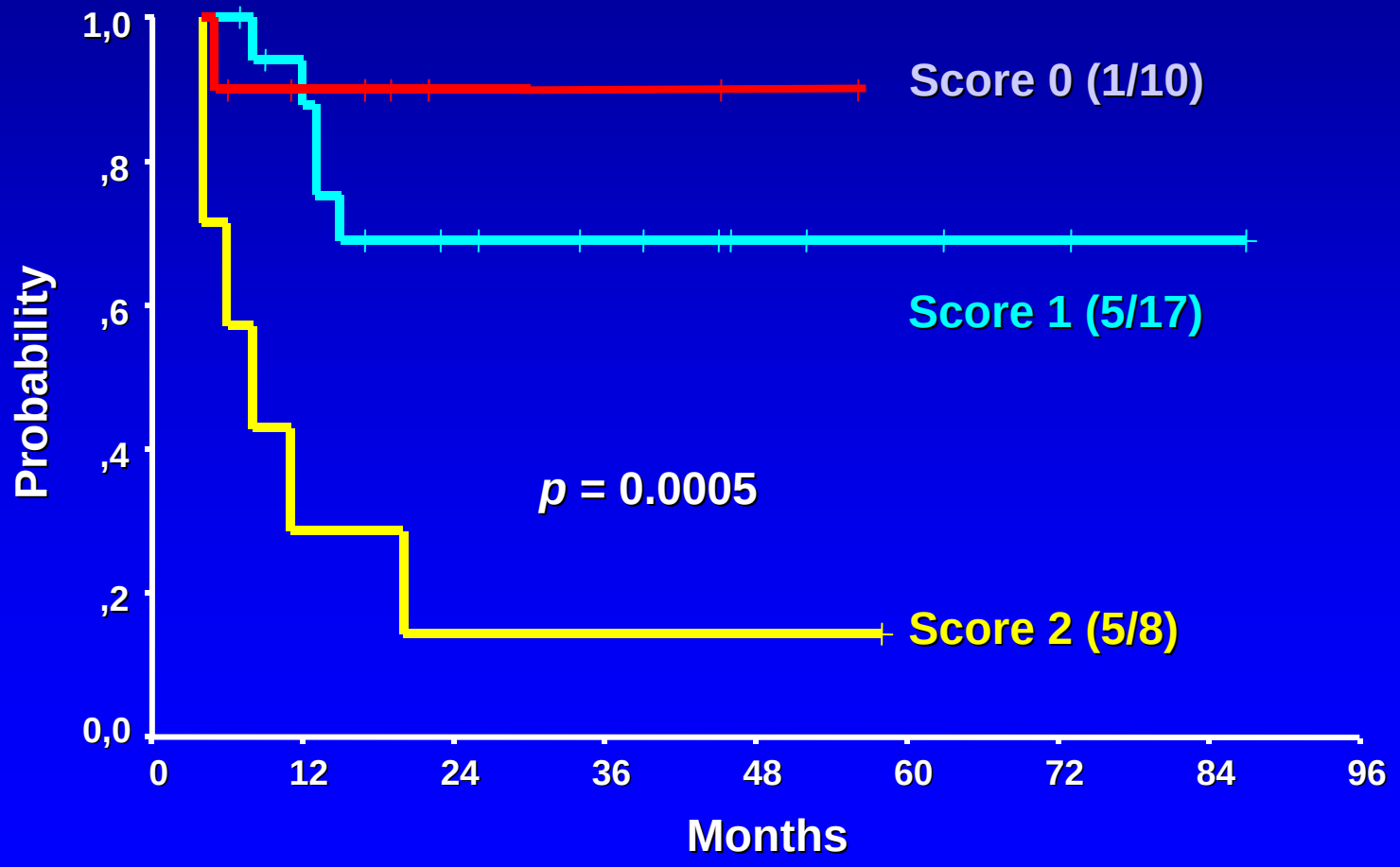
	BEACOPP esc. (n=10)	HDCT/ ASCT (n=10)	BEACOPP base. (n=5)	C/A-like (n=7)	Radio-therapy (n=3)
CR (%)	80	50	80	57	67
PR (%)	-	30	-	-	33
Failure (%)	20	20	20	43	-

FF2F and OS for all patients

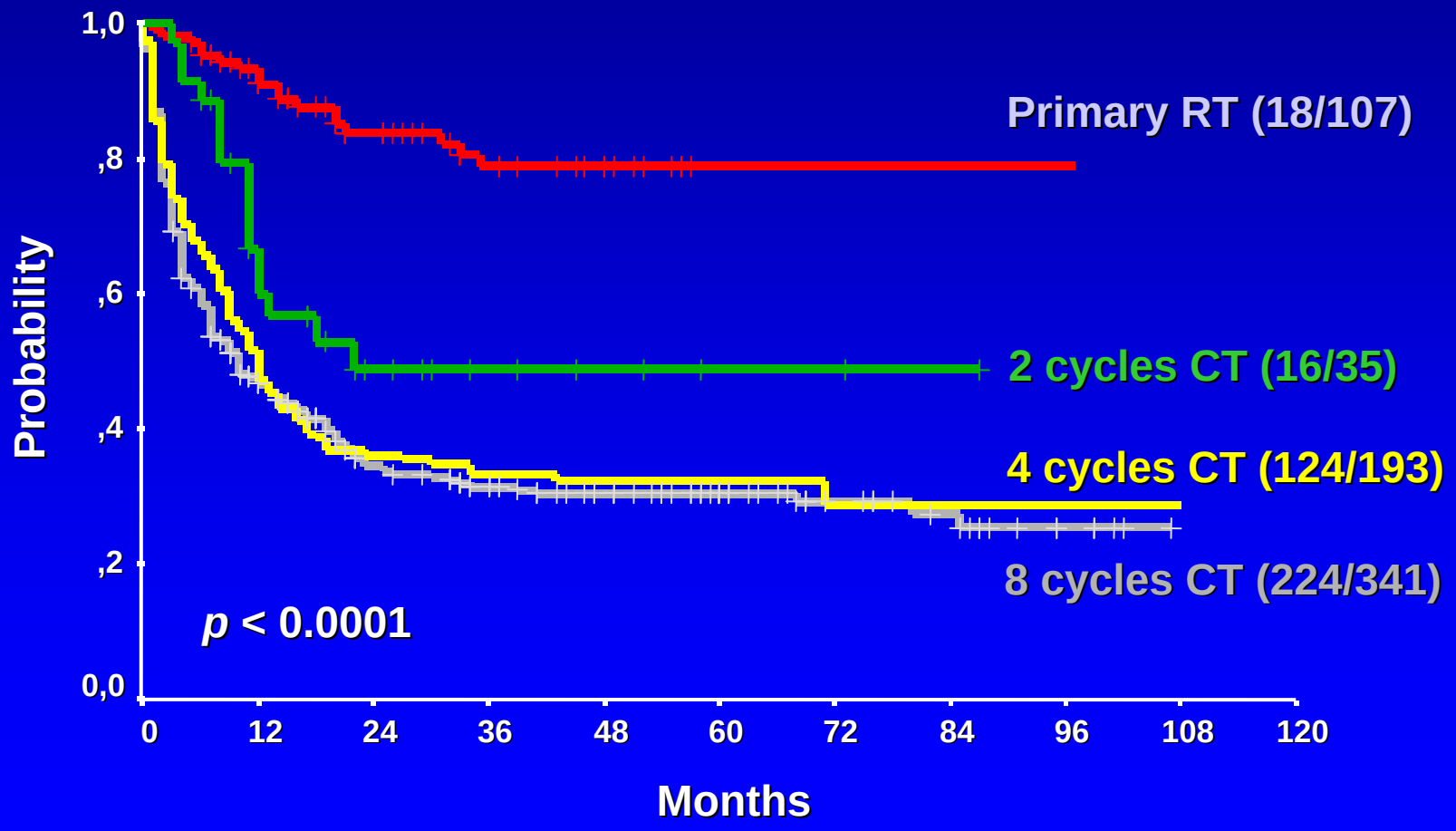


OS according to the prognostic score

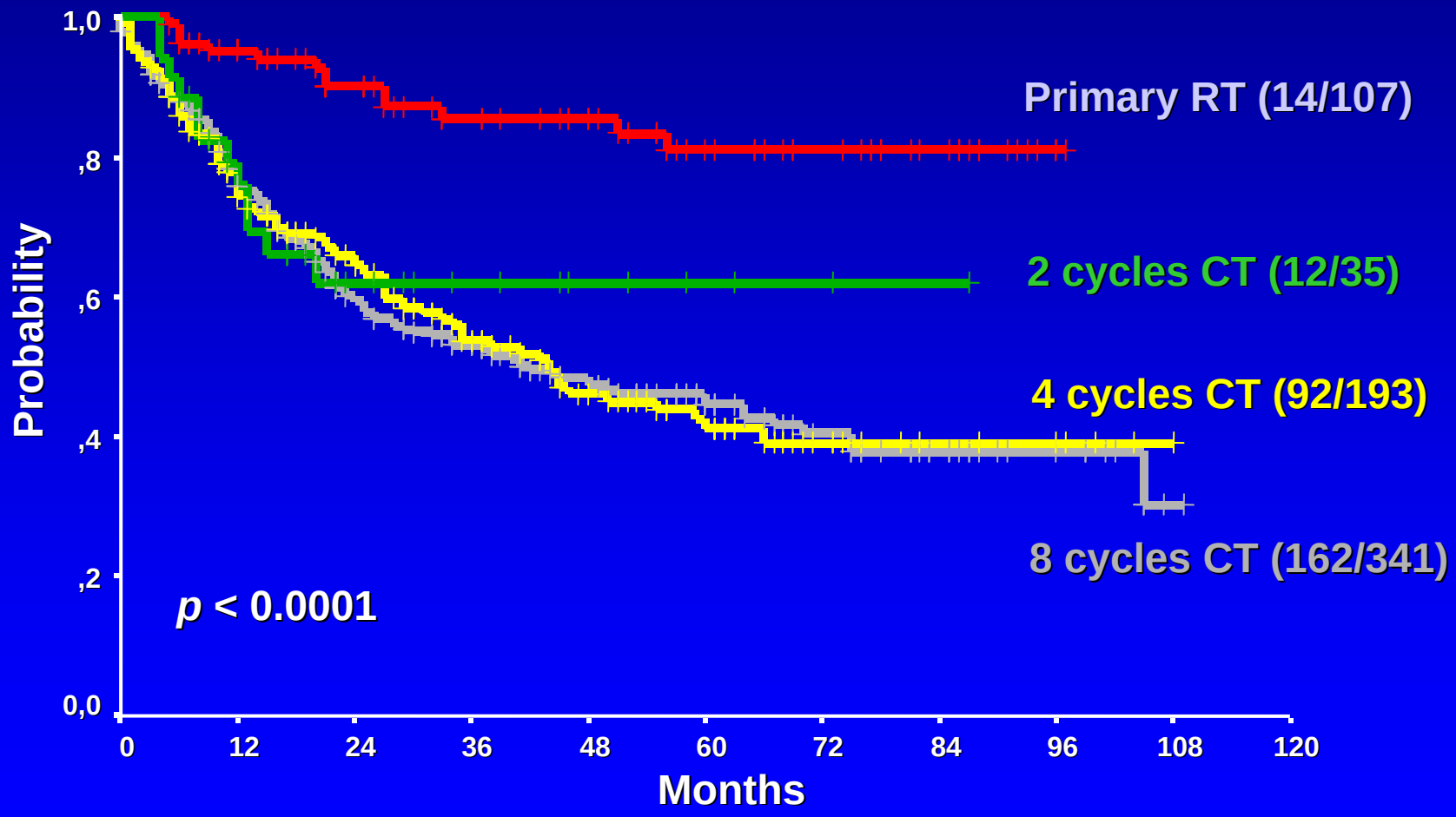
(remission status, anemia, stage at relapse)



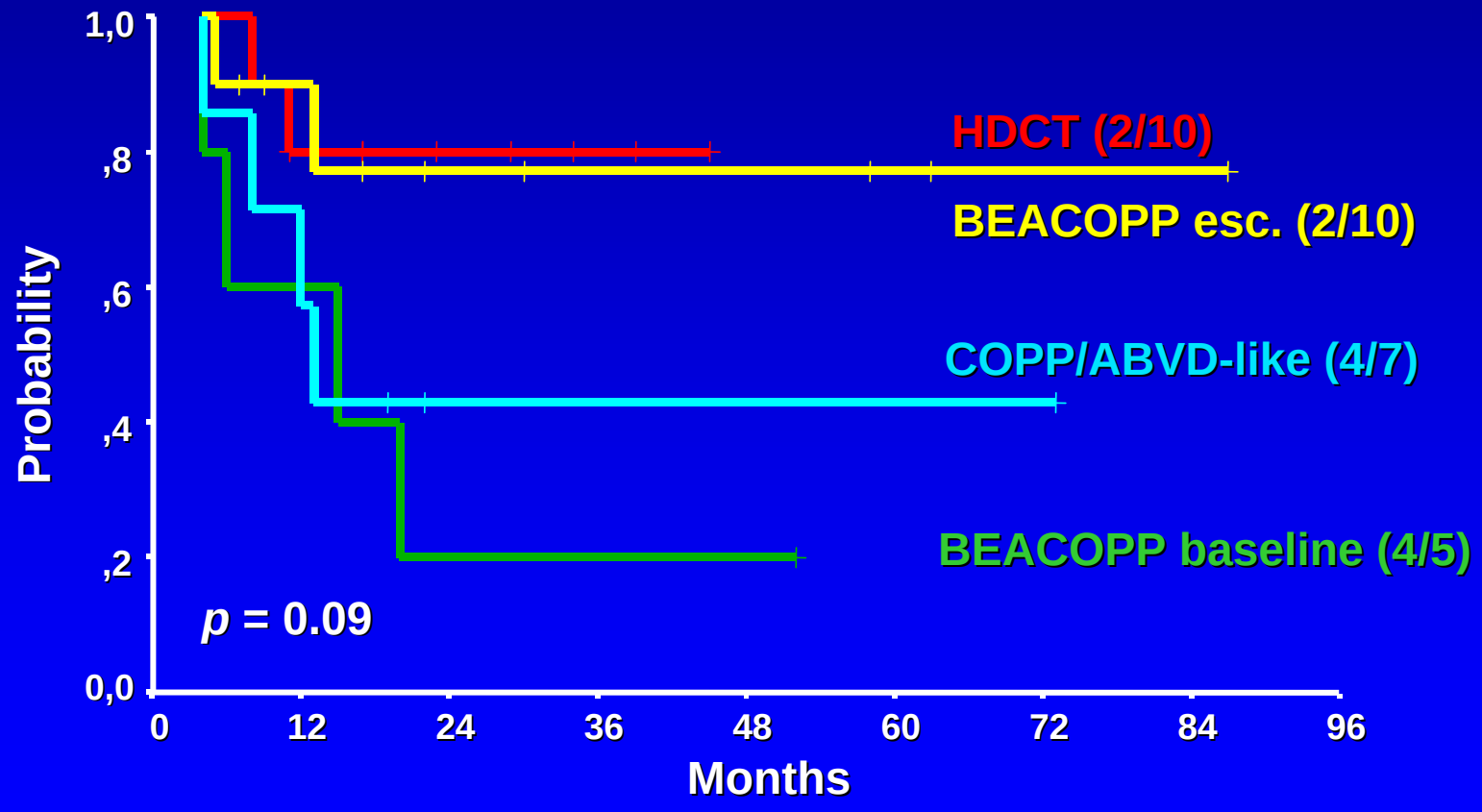
FF2F according to primary treatment



OS according to primary treatment



OS according to the type of salvage chemotherapy



Hodgkin Lymphoma:

A resolved Problem!?

(YES)

for Early and Intermediate Stages:

Early: 2 ABVD + 20 Gy IF-RT

Intermediate: 4 ABVD + 20- 30 Gy IF-RT

Open Question: ABVD alone??

→ 90-95% Cure

Hodgkin Lymphoma:

A Resolved Problem?

For

Advanced Stages:

No!

Open Questions

1. Which initial chemotherapy?
2. Definition of Risk Groups ?
3. Is PET a reliable prognosticator?
4. Overrules PET the IPS?
5. When to intensify therapy: when PET pos after 1 or 2 ABVD ?
6. Which intensified regimen? BEACOPPesc or BEA- 14 or HDCT? Others?

.

New Strategies for the management of Advanced Hodgkin lymphoma

and

Ten-year results of the HD9 Trial of the German Hodgkin Study Group

Outcome in different treatment groups: Europe and North- America

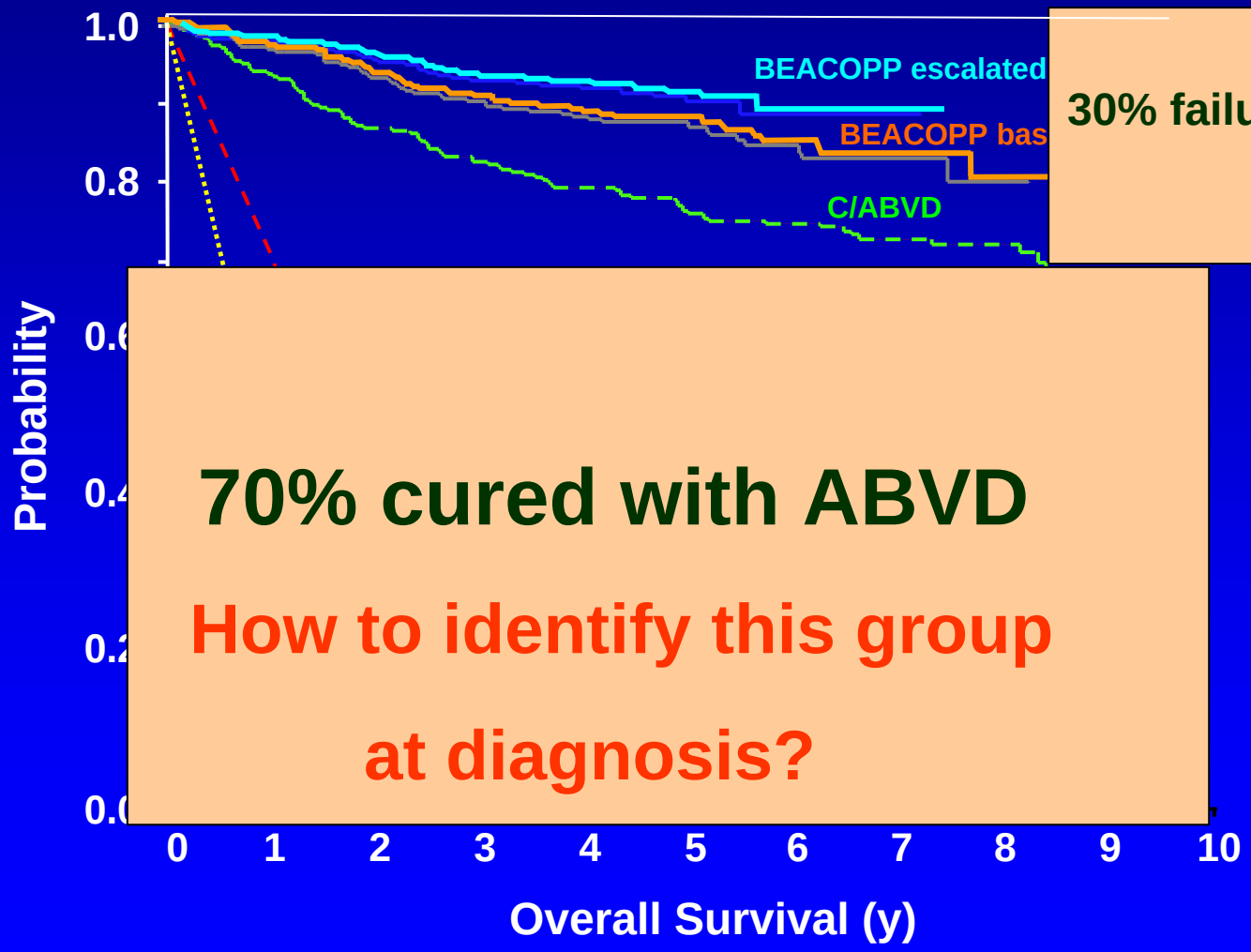
Europe (GSHG and EORTC)	Stage	Cure Rates
Early favorable Stage	CS I,IIA,B no risk factors	98%
Early unfavorable Stage (intermediate)	CS I,IIA,B with risk factors	93%
Advanced Stage HL	CS III – IV, Selected CS IIB	
	with ABVD	65-80%
	with BEACOPP escalated	90- 92%

The Potential of ABVD

in trials of advanced stage HL

Source	Chemotherapy	5 y failure-free survival	5 y overall survival
Canellos 1992	6-8 ABVD	61 %	73%
	6 (MOPP+ABVD)	65 %	75 %
Duggan 2003	8-10 ABVD	63%	82%
	8-10 MOPP/ABV	66%	81%
GHSG HD9	4 (COPP+ABVD)	68%	83%
	8 BEACOPP esc.	88%	92%

Hodgkin Lymphoma Advanced Stages
How to Identify the Good & Bad Risk Groups?



30% failures with ABVD

70% cured with ABVD

How to identify this group at diagnosis?

New Instruments as Early Predictors of Prognosis

1. International Prognostic Risk-Score =

   Risk- Adaptation

2. FDG- PET/CT =

   Response Adaptation

IPS

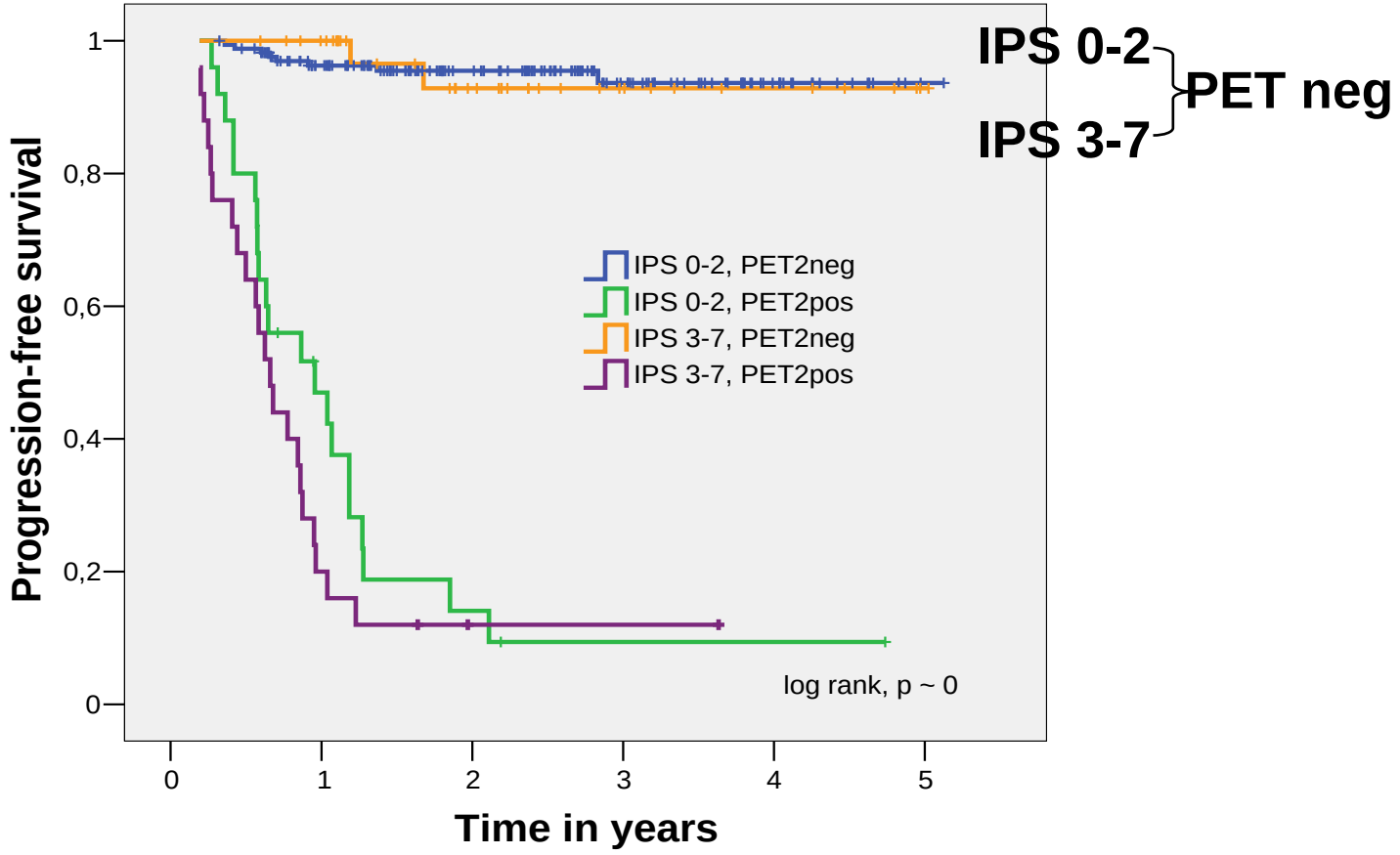
Survival rates according to IPS at 10 ys

GHSG HD9 Data

Freqency %	FFTF OS (%, 10 y)	C/ABVD n=261	BEA$_{base}$ n=469	BEA$_{esc}$ n=466	log-rank p (A vs. C)
28	IPS 0-1 *n=307*	78 88	79 85	91 94	0.015 0.27
40	IPS 2-3 *n=464*	59 73	71 84	83 87	<0.0001 0.0027
15	IPS 4-7 *n=170*	54 61	56 63	71 70	0.020 0.16

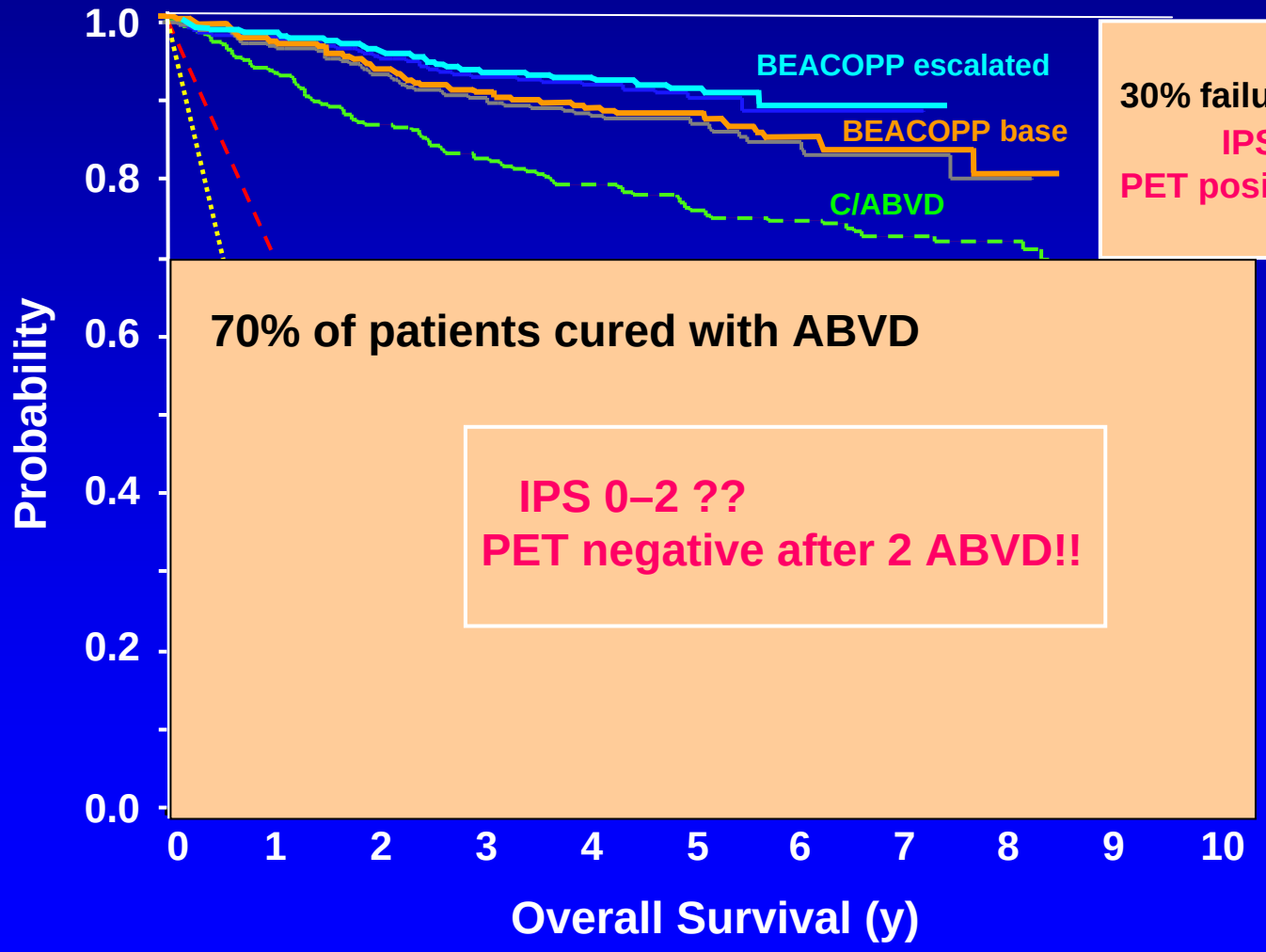
Early PET in HL: *Independent* of IPS??

- PET after 2 cycles ABVD, followed by 4 more ABVD



Courtesy of Gallamini + Hutchings JCO 2007

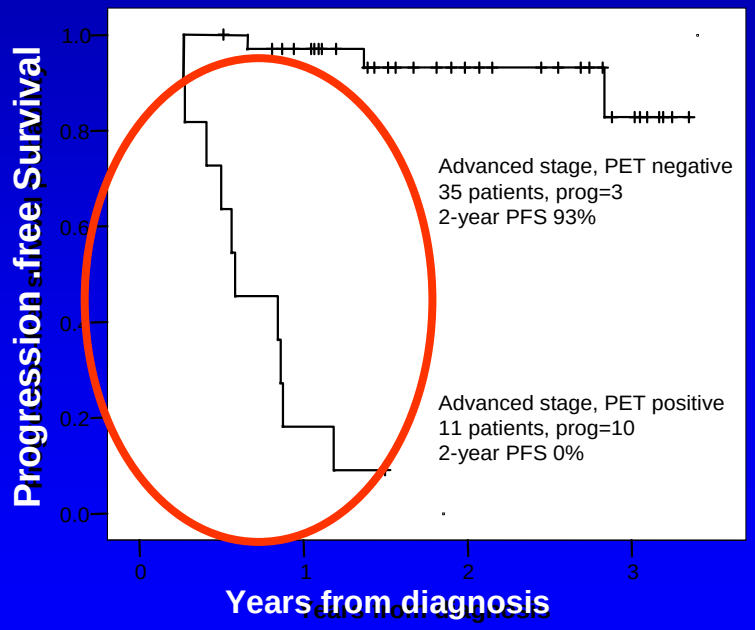
Hodgkin Lymphoma Advanced Stages
How to Identify the Good & Bad Risk Groups?



PET as indicator of response / prognosis?

Prospective Danish study, 46 advanced stage patients:

2 ABVD→ PET +/- continue with 4-6 ABVD +IF-RT



35 PET-negative patients: (75%) with 2 ABVD

32 patients entered satisfactory remission.

1 patient progressed early after initial PR.

2 patients relapsed later during follow-up.

11 PET-positive patients: (25%) with 2 ABVD

1 patient entered satisfactory remission.

4 patients had primary refractory disease.

4 patient progressed early after initial PR.

2 patients relapsed later during follow-up.

Courtesy of Martin Hutchings

Hutchings M, Loft A, Hansen MT, Pedersen LM, Buhl T, Jurlander J, Buus S, Keiding S, D'Amore F, Boesen AM, Berthelsen AK, Specht L. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin Lymphoma. Blood 2006;107(1):52-9.

2-year progression-free survival after 2 ABVD + 4-6 ABVD/RT

	PET-negative	PET-positive
Copenhagen study 46 pts, prospective	93%	0%
London study 40 pts, retrospective	88%	0%
IIL study 88 pts, prospective	96%	6%

European-UK Study

Chair: Peter Johnson

CT1 (Staging)

2 cycles ABVD

IPS 0-7

N= ? 650 pts

CT2 + PET1

PET positive

PET negative

randomize

4 -6 cycles BEACOPP-14

4 cycles ABVD

4 cycles AVD

CT3 + PET2

CT3

CT3

RT: PET+ Residual on CT >2.5cm (involved node)

Follow-up (no radiation)

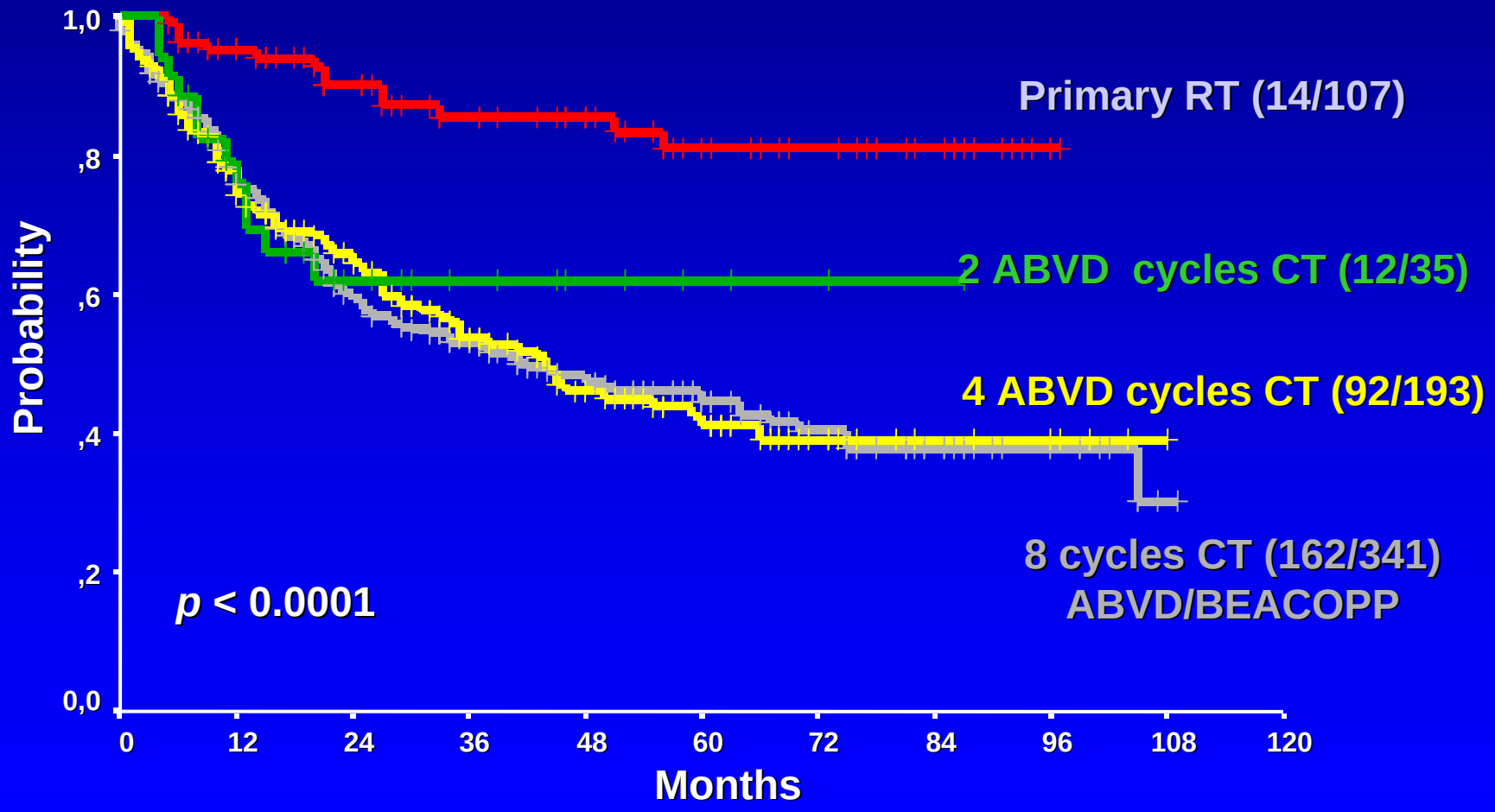
A

B

C

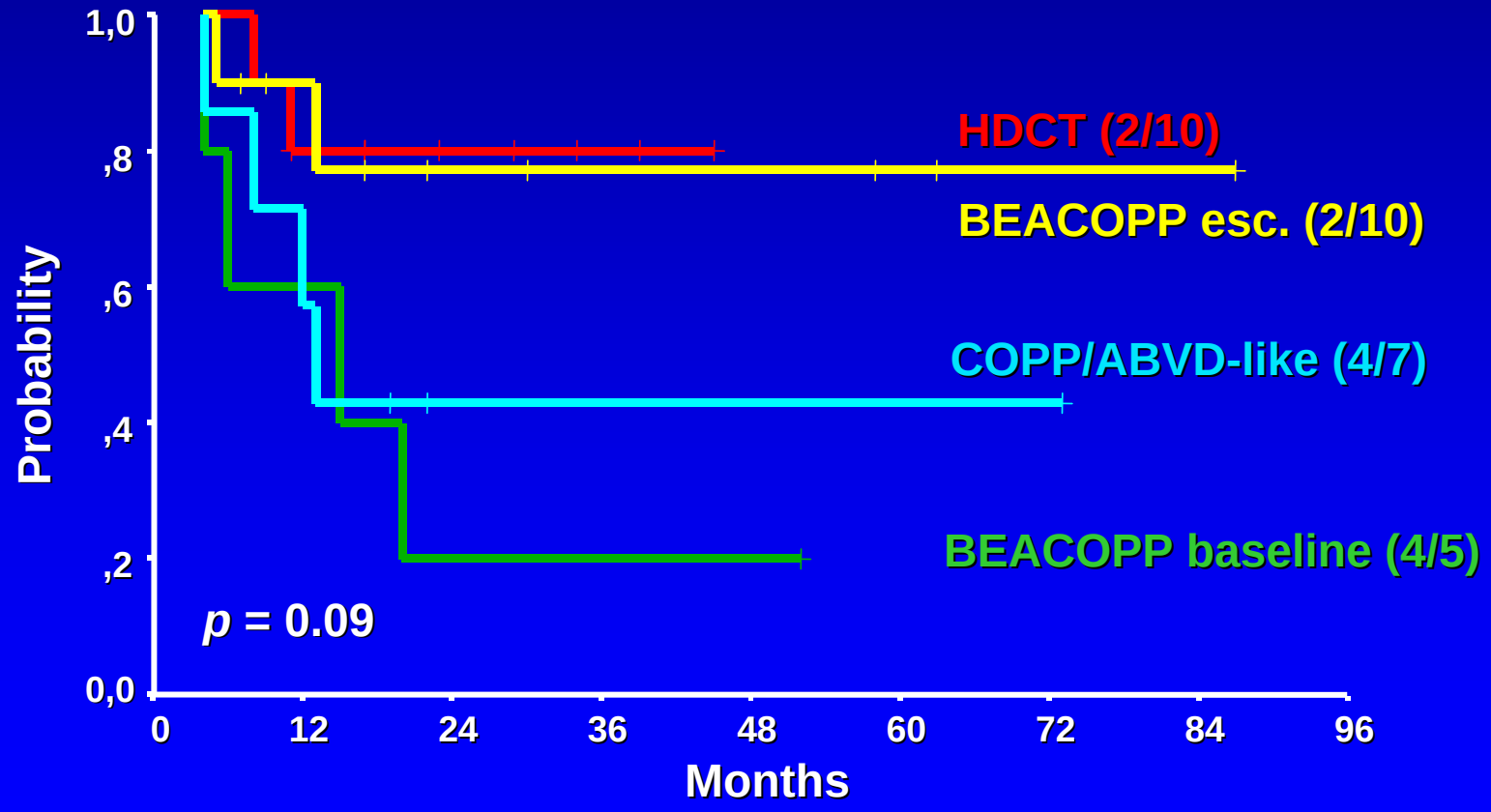
Salvagebility of failures according to primary treatment:

RT, 2 or 4 or 8 ABVD



OS
salvagebility after 2 ABVD
Early Stages

Caveat: BEACOPP14 not tested !!

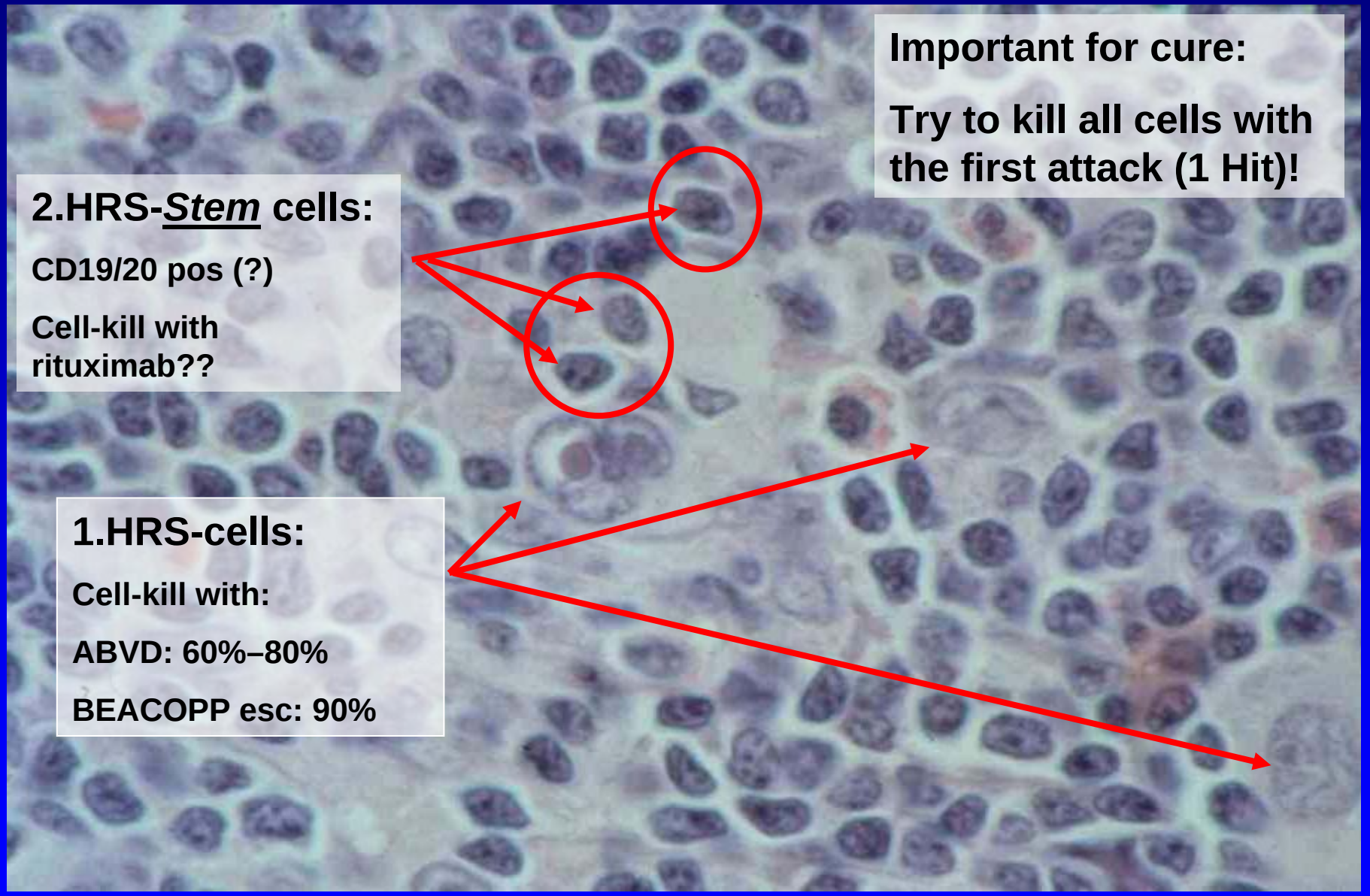


What can we do better....?

Overcome the biological problems:

- the HRS- tumor- stem cells
- the genetic instability (Early intensification!)

Hodgkin- Reed- Sternberg- " Stem" Cell - Hypothesis



The Stem Cell Concept
Hodgkin Stem Cells

- Genetically very unstable (in vitro data)
- Develop rapid, early resistance (in vitro data)
- Detected by molecular/cytogenetic techniques (FISH, in situ data)
- Carry the identical IG-gene rearrangements of the HD-RS-cells (in situ data)
- CD30; CD15: negative (in situ data)
- Do they disseminate already in early stages? (R. Ambinder)
- CD19, CD20: positive (in vitro data, Ambinder et al.)

Future GHSG Study: HD18

Start December 2007

Advanced HL

IPS 0 -7

2x BEACOPP esc.

PET positive

PET negative

2BEA esc-4 base
0 Rituximab

2 BEA esc-4 base
+ Rituximab

2 BEA esc.-4 base

2x BEACOPP esc.

RT PET+ Rests >2,5cm
(‚involved node'-technique)

No RT

No RT

A

B

C

The Contrasting Philosophies for Advanced Hodgkin Lymphoma.....
The necessity for Early Intensification

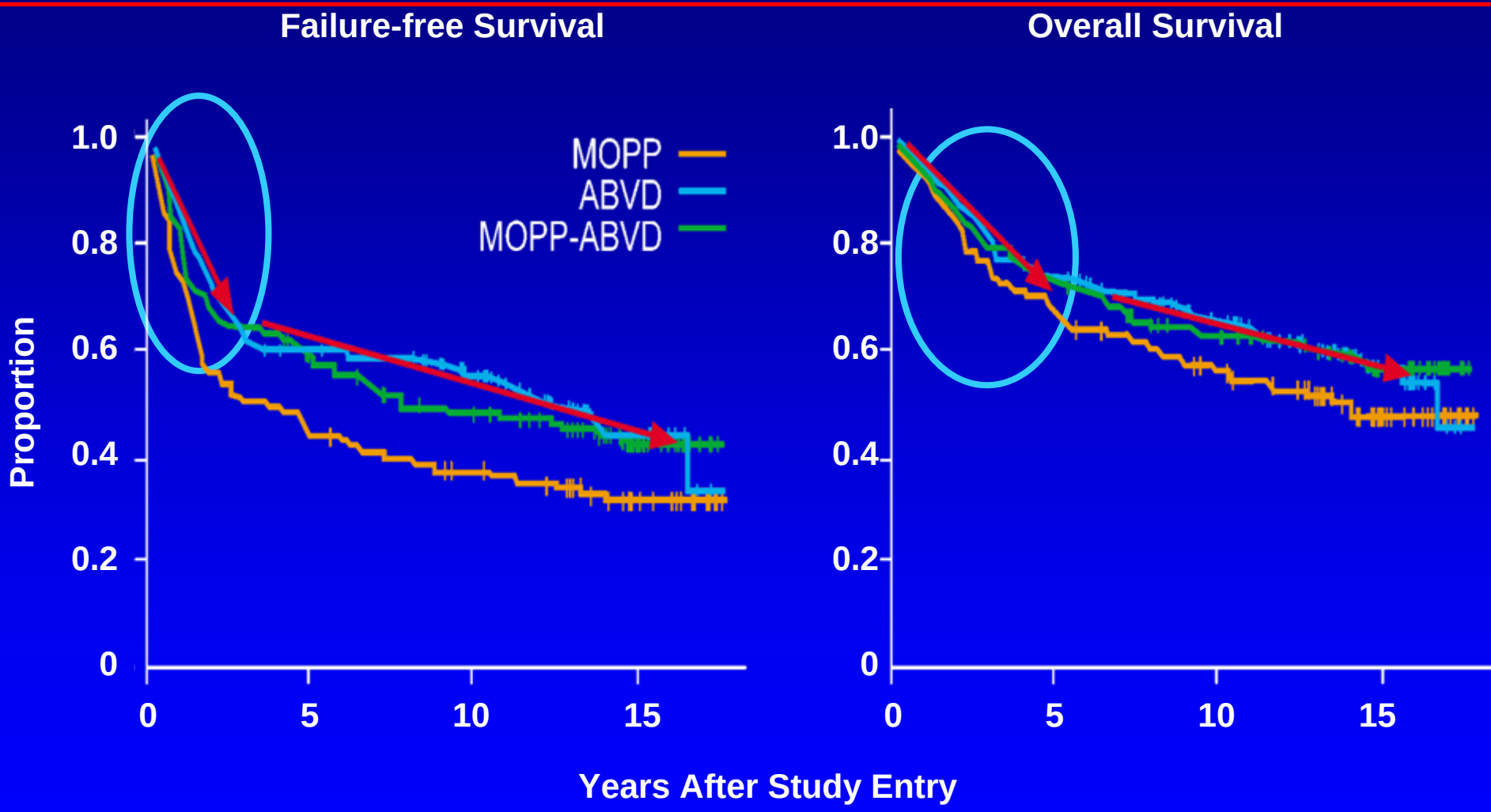
...some people think you have two shots to cure Advanced Stage Hodgkin Lymphoma!

- I think it is better to kill the HD-RS/-"stem" cells with the first attack!
- Arguments:
  - Genetic Instability
  - Early Resistance
  - Gain of multiple genetic hits during insufficient therapy
  - Germline genetic predisposition for secondary tumors (ST)
  - STs increase with multiple therapies

AML/MDS Post Auto-Transplant For Lymphoma

Institution	Patients	Actuarial Incidence
St. Barts	230	14% (5 yr)
Toronto	156	9% (10 yr)
Minnesota	138	14% (5 yr)

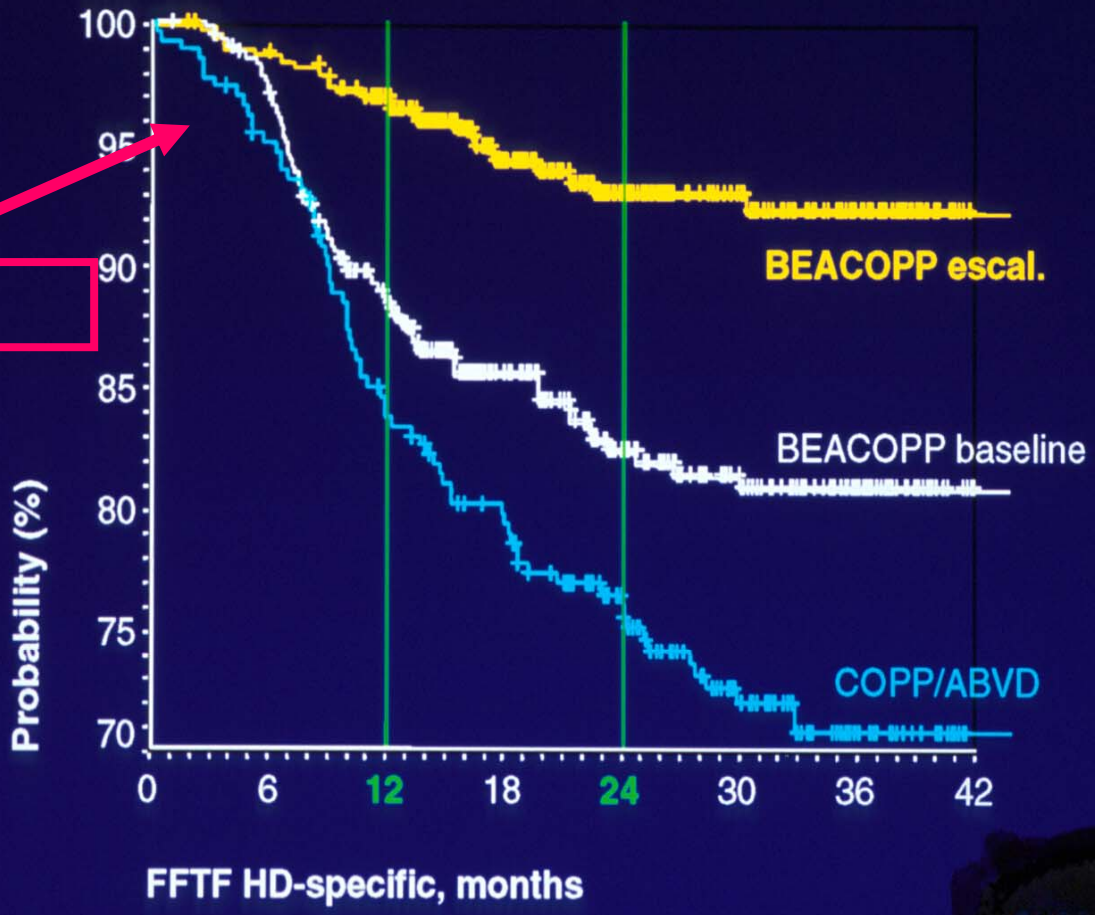
Long-term Follow-up



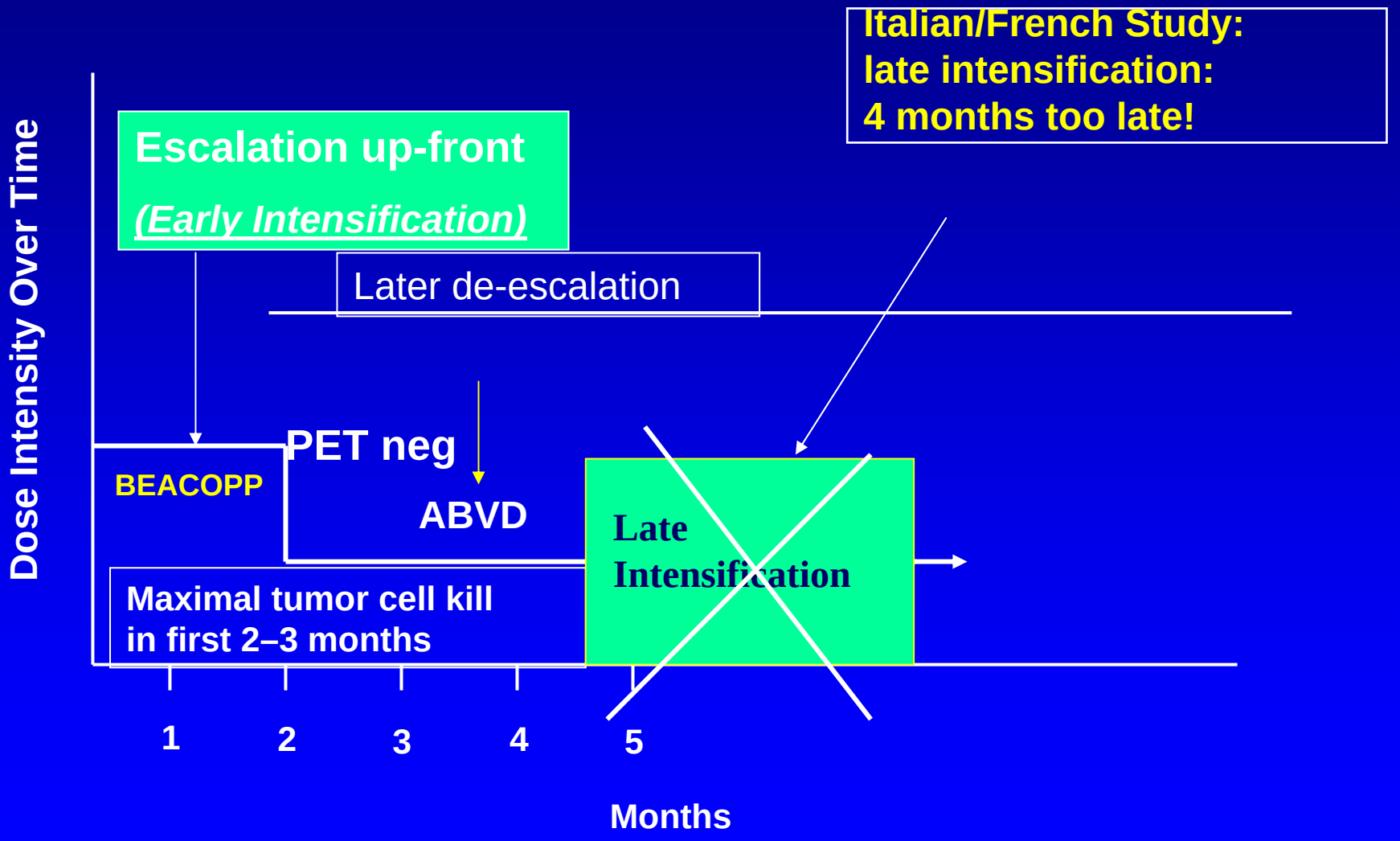
Canellos GP, Niedzwiecki D. *N Engl J Med*. 2002;346(18):1417-1418.

HD9: primary progression / early relapse

Intensify early!!

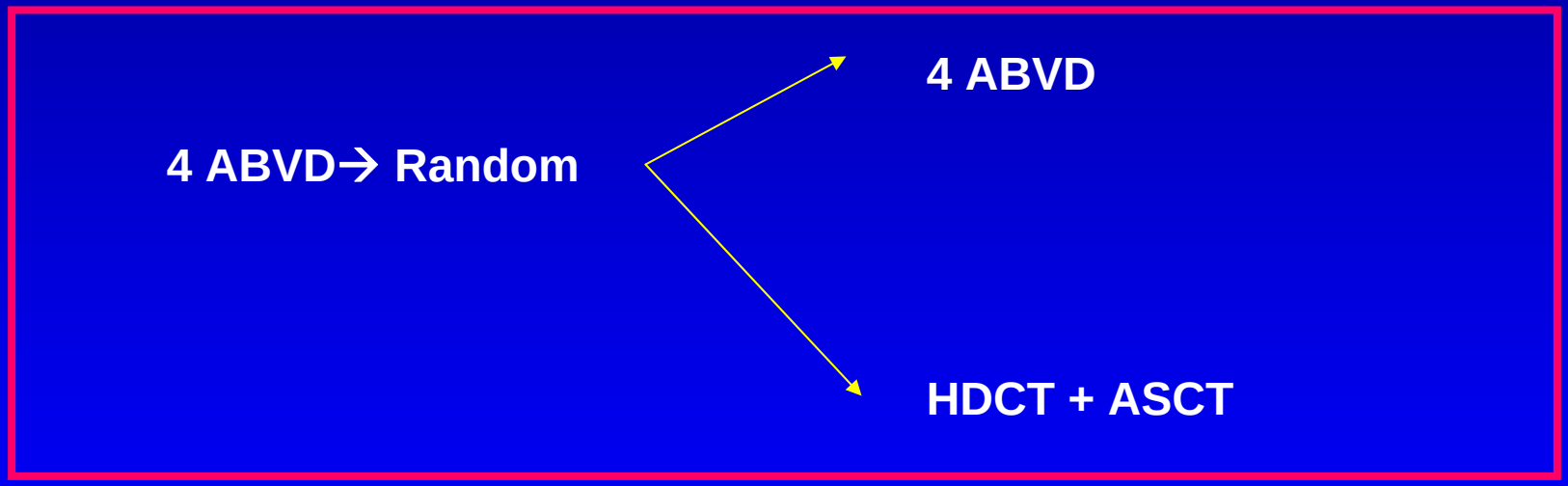


Possible Future Strategy... For Advanced HL



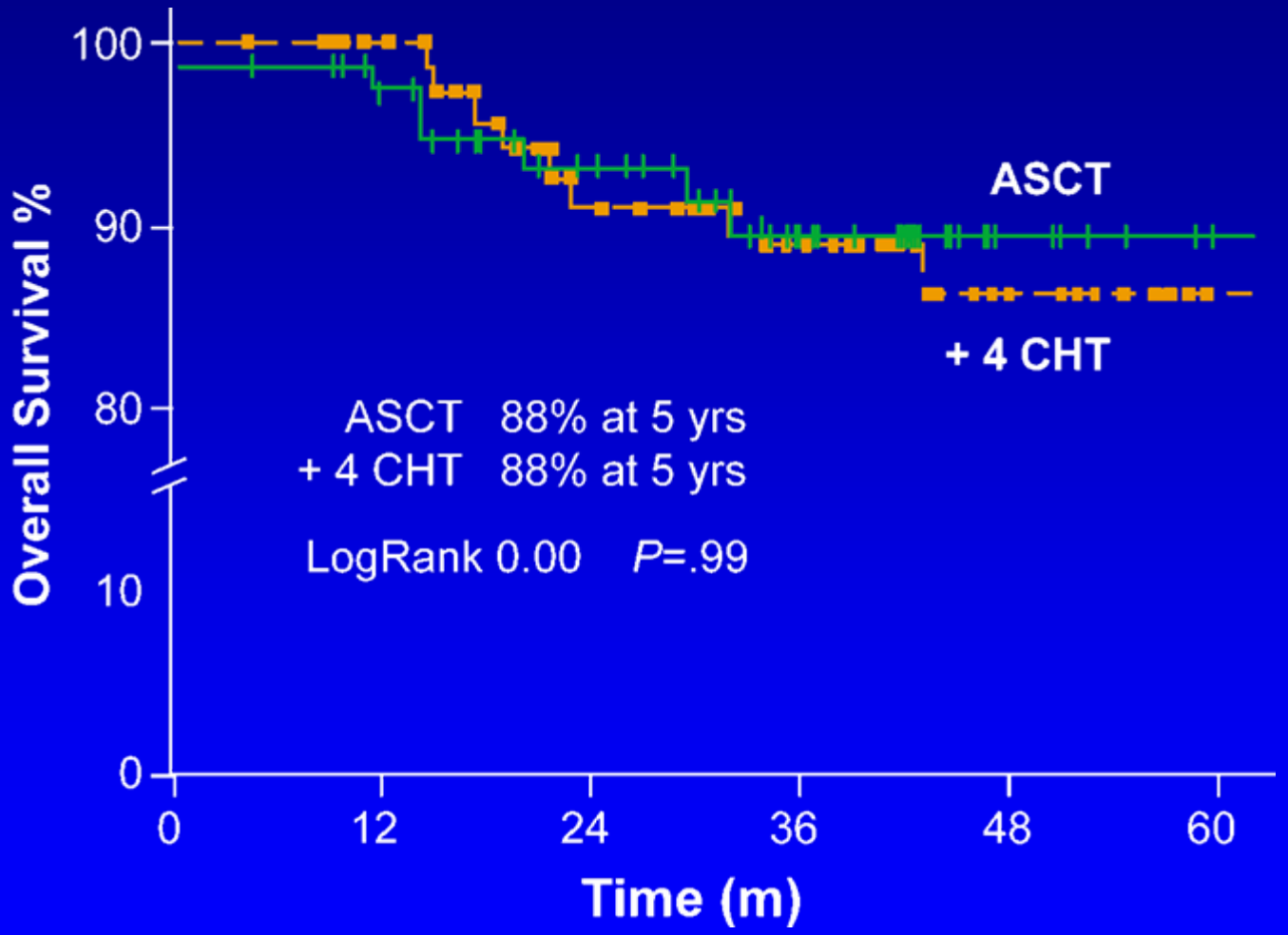
Another proof for "Early Intensification"

Italian/French Study



Result: No difference!!
Because escalation is 4 months too late!!
(>20% failures)

Overall Survival

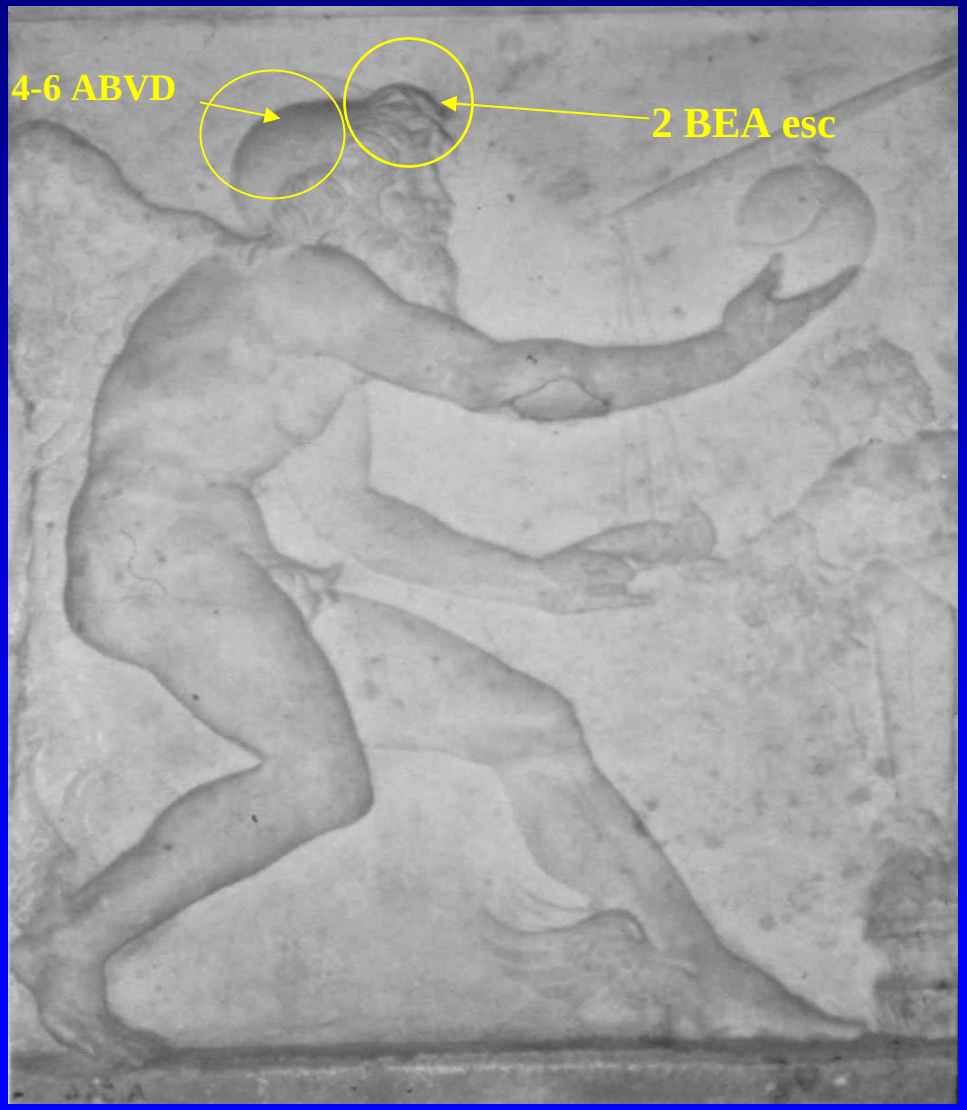


EBMT/ANZLG/SFGM/GELA.
Federico M, et al. *J Clin Oncol.* 2003;21(12):2320-2325.

Remember: „Kairos“ -Principal of the Greeks:

„Catch the moment“...

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



HD9 Trial Design

10 Year Results

CS IIB-IIIA with risk factors

CS IIIB-IV

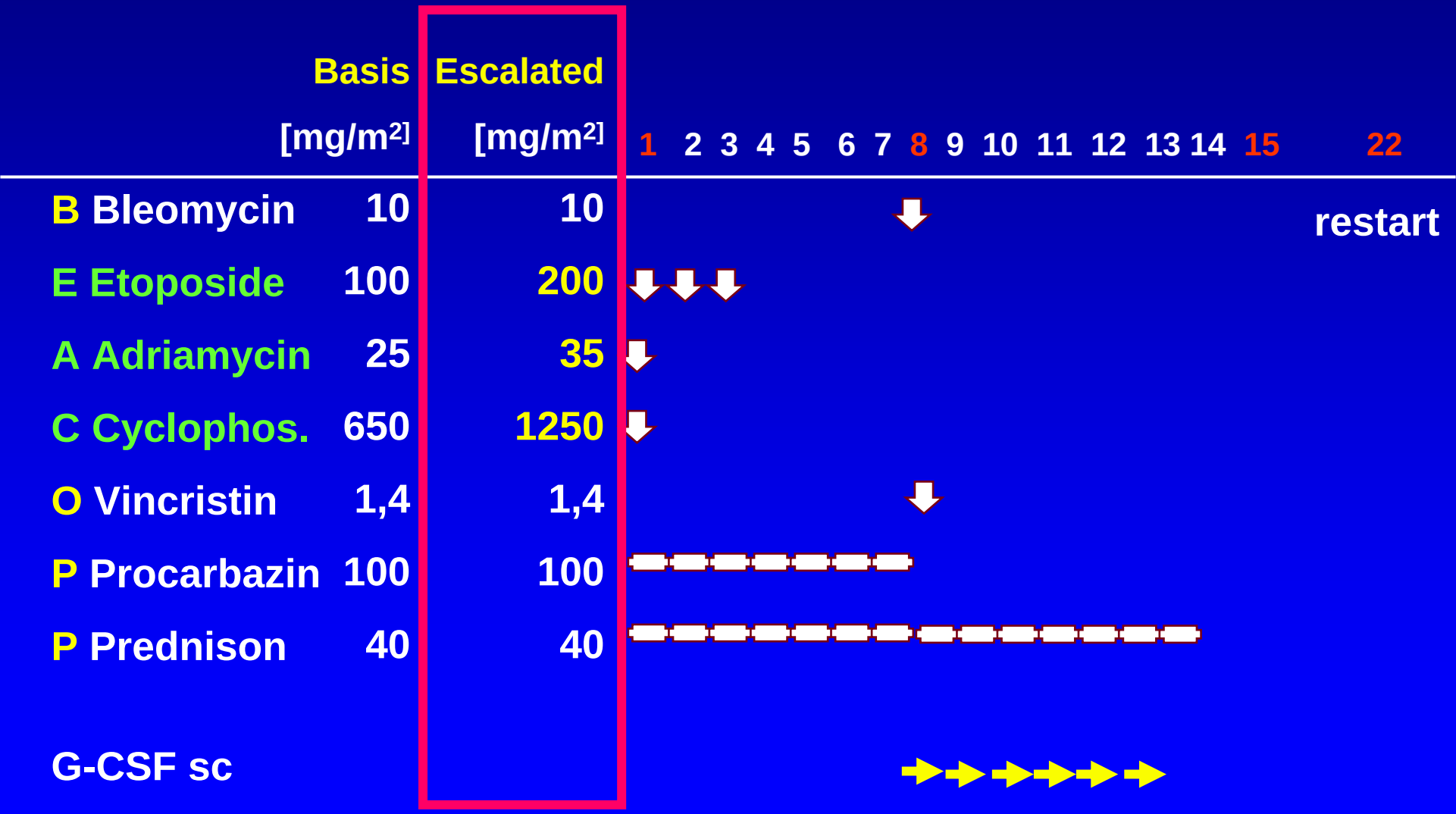
Arm A	Arm B	Arm C
4 × COPP+ABVD	8 × BEACOPP baseline	8 × BEACOPP escalated*
± RT (63%)	± RT (71%)	± RT (70%)

* with G-CSF

RT to initial bulk and residual tumor

GHSG 2007 HD9

The BEACOPP-21 - Schedule



Recruitment and Analysis
10 year follow up

- randomised in HD9 n = 1282
- qualified for HD9 n = 1201
- evaluable n = 1196*

→ 99.6% of patients were evaluable

per arm: A n = 261* B n = 469 C n = 466

* One additional arm A pt. became evaluable since the previous analysis (2004)

Acute Hematological Toxicity

% of pts.	WHO grade	C/ABVD n=261	BEA base n=469	BEA esc n=466
Leukopenia	III	52 %	36 %	8 %
	IV	**19 %**	**37 %**	**90 %**
Thrombocytopenia	III	4 %	6 %	23 %
	IV	**2 %**	**3 %**	**47 %**
Anemia	III	4 %	16 %	51 %
	IV	**1 %**	**1 %**	**15 %**
Infection	III	2 %	13 %	14 %
	IV	**1 %**	**3 %**	**8 %**

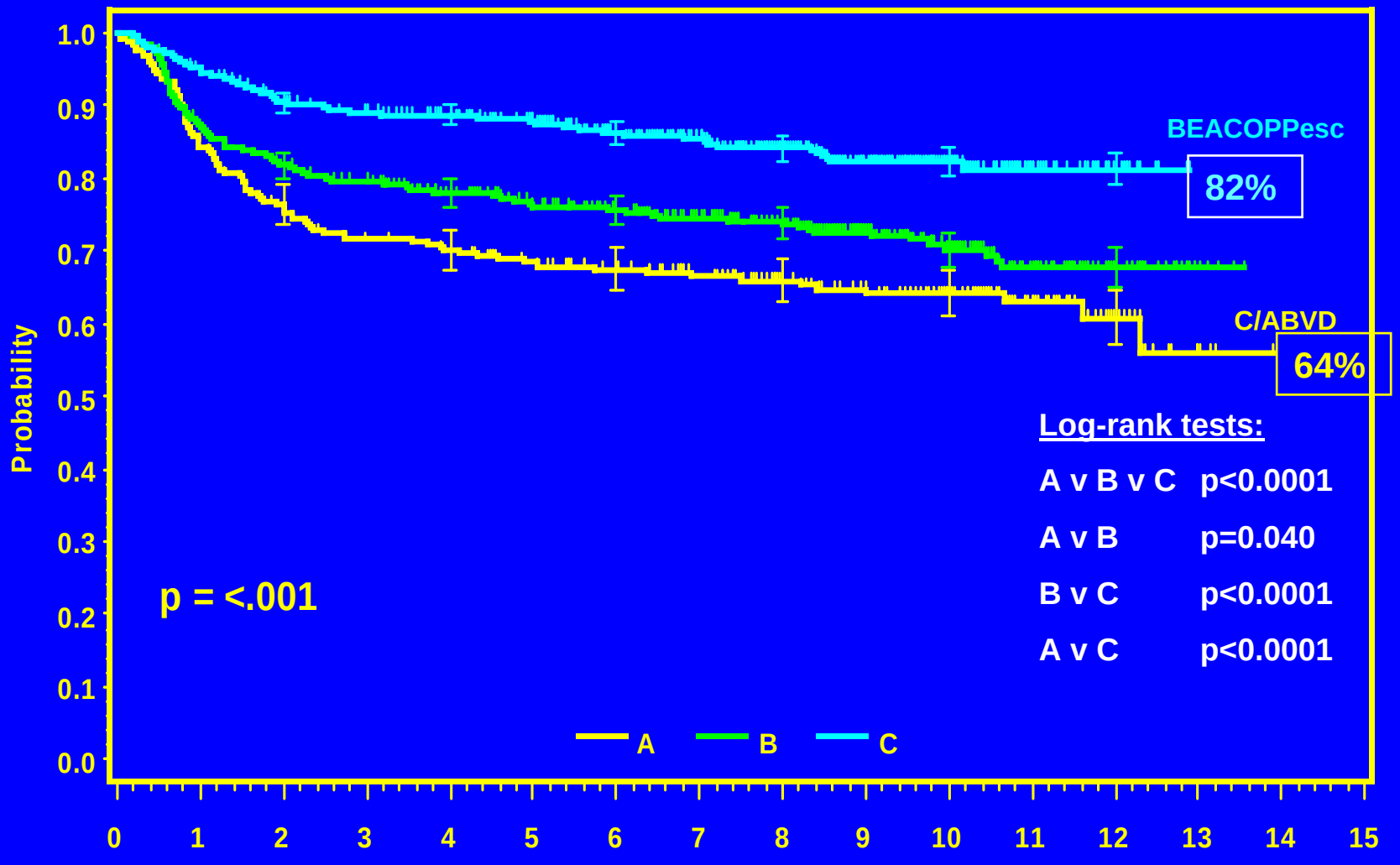
GHSG 2007 HD9

Causes of Death

10 year results

% of all pts.	C/ABVD n=261	BEA base n=469	BEAesc n=466
HL	11.5	8.1	2.8
acute tox. (first-line)	1.9	1.5	1.7
acute tox. (salvage)	1.9	1.5	0.6
second malignancy	3.1	3.6	3.2
cardio-respiratory	1.2	0.9	0.9
pulmonary	0.4	0.4	0.2
other/unknown	3.8	3.0	2.1
all deaths	24	19	12

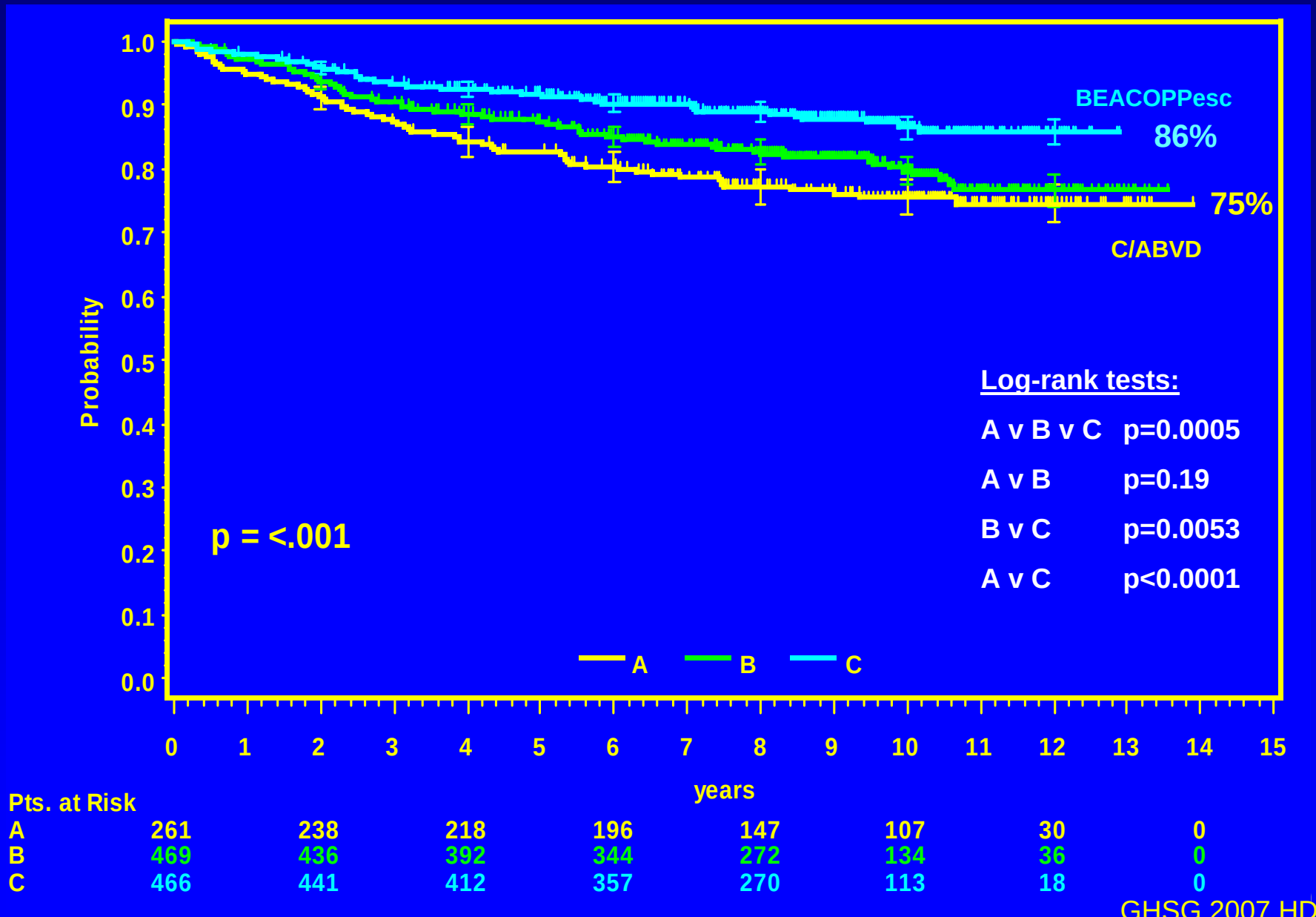
FFTF by treatment arm



Pts. at Risk								
A	261	194	173	146	110	75	19	0
B	469	378	332	282	222	106	26	0
C	466	412	384	321	234	92	14	0

GHSG 2007 HD9

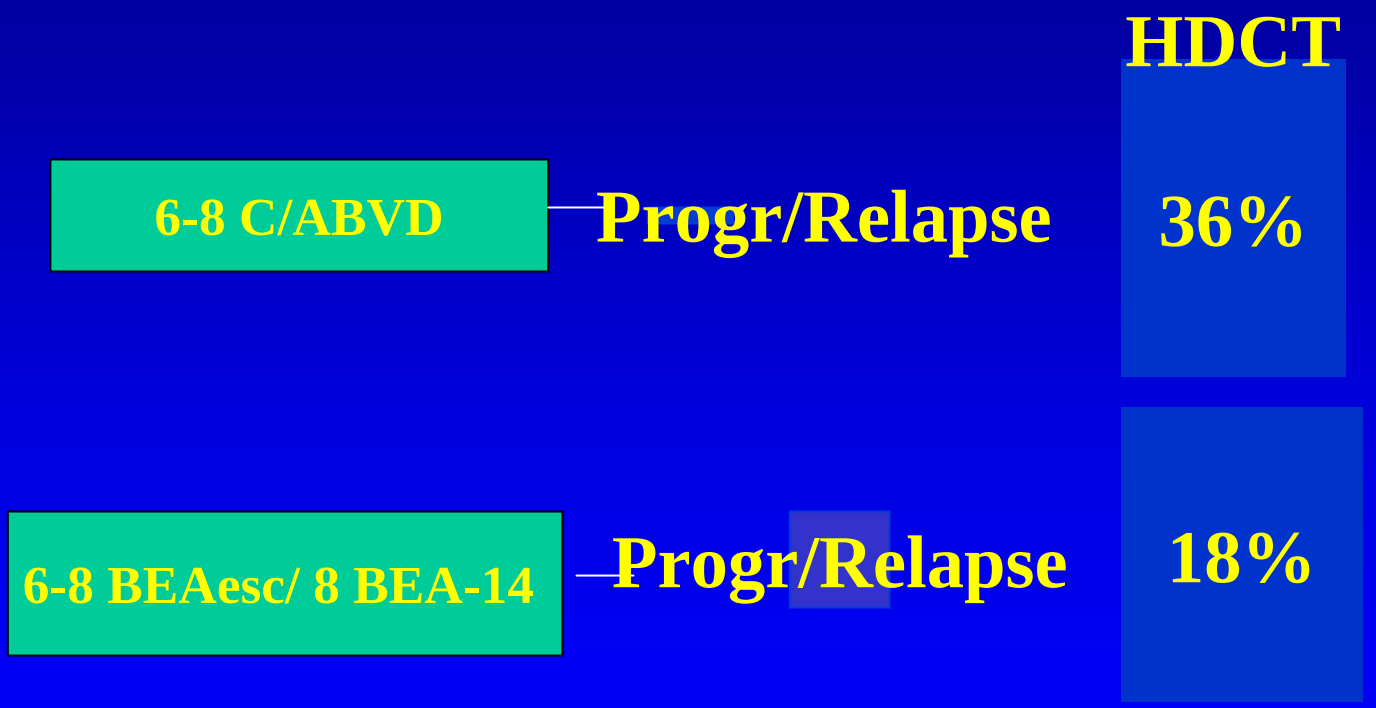
OS by treatment arm



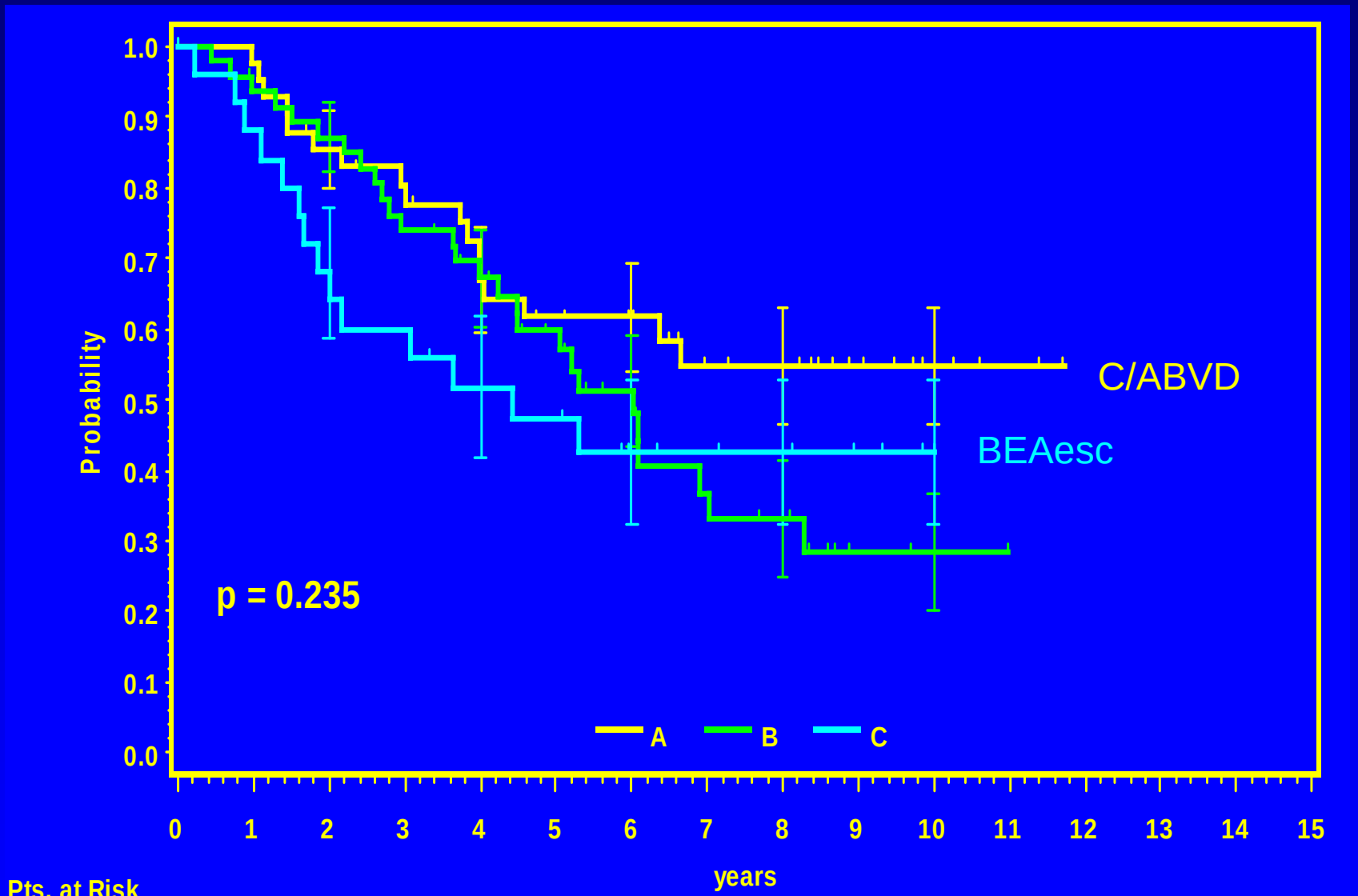
Survival rates according to IPS at 10 ys

	FFTF OS (%, 10 y)	Arm A n=261	Arm B n=469	Arm C n=466	log-rank p (A vs. C)
28%	IPS 0-1 *n=307*	78 88	79 85	91 94	0.015 0.27
40%	IPS 2-3 *n=464*	59 73	71 84	83 87	<0.0001 0.0027
15%	IPS 4-7 *n=170*	54 61	56 63	71 70	0.020 0.16

Advaned HD: Different Strategies



Survival after Relapse at 10 ys



Pts. at Risk							
A	42	34	25	20	13	4	0
B	47	40	29	15	8	1	0
C	25	17	12	7	5	1	0

GHSG 2007 HD9

Secondary Malignancies

number of cases and 10-year cumulative incidences (CI)*

n C I (10 y)	Arm A n=261	Arm B n=469	Arm C n=466
AML/MDS	1 0.4 %	7 2.2 %	14 3.2 %
NHL	7	8	5
solid tumors	7	16	9
total	15 6.0 %	31 7.9 %	28 6.5 %

* allowing for competing risks (deaths from other causes)

Summary

HD9- Trial: 10 year m.o.t. follow up

1. Superiority of escalated BEACOPP confirmed
2. BEAesc > C/A (or ABVD):
   FFTF: 18%!!
   OS: 11%
3. BEA base not superior to ABVD or C/A!
4. BEA esc superiority inspite of higher number of AML/MDS
5. Death due to HD: C/A : 11.5%
   BEAesc: 2,8%
6. Survival after salvage:
   no significant difference between A,B,C

What comes next…..
The GHSG-
Current/Future Trials

HD-12 **1998-2002**

HD-15 **2003-2007**

HD-18 **2008-2012**

Three Trial Generations of the GHSG
HD9, HD12, HD15 (1992–2007)

	Chemotherapy		Radiotherapy	Patients (%)	End
HD9:	*8* BEACOPP esc		+ IF-RT	(70)	1997
HD12:	*4* BEACOPP esc + 4 BEA baseline		+ IF-RT	(35)	2002
HD15:	6 BEACOPP esc	PET+	+ IF-RT	(<15)	2007
	8 BEACOPP-14 baseline	PET+	+ IF-RT	(<15)	

HD18: *2* BEA esc →PET neg 2 BEA esc no RT Start 12/2007

→PET pos 2 BEA esc + 4 BEA base +/- RT

+/- Rituximab

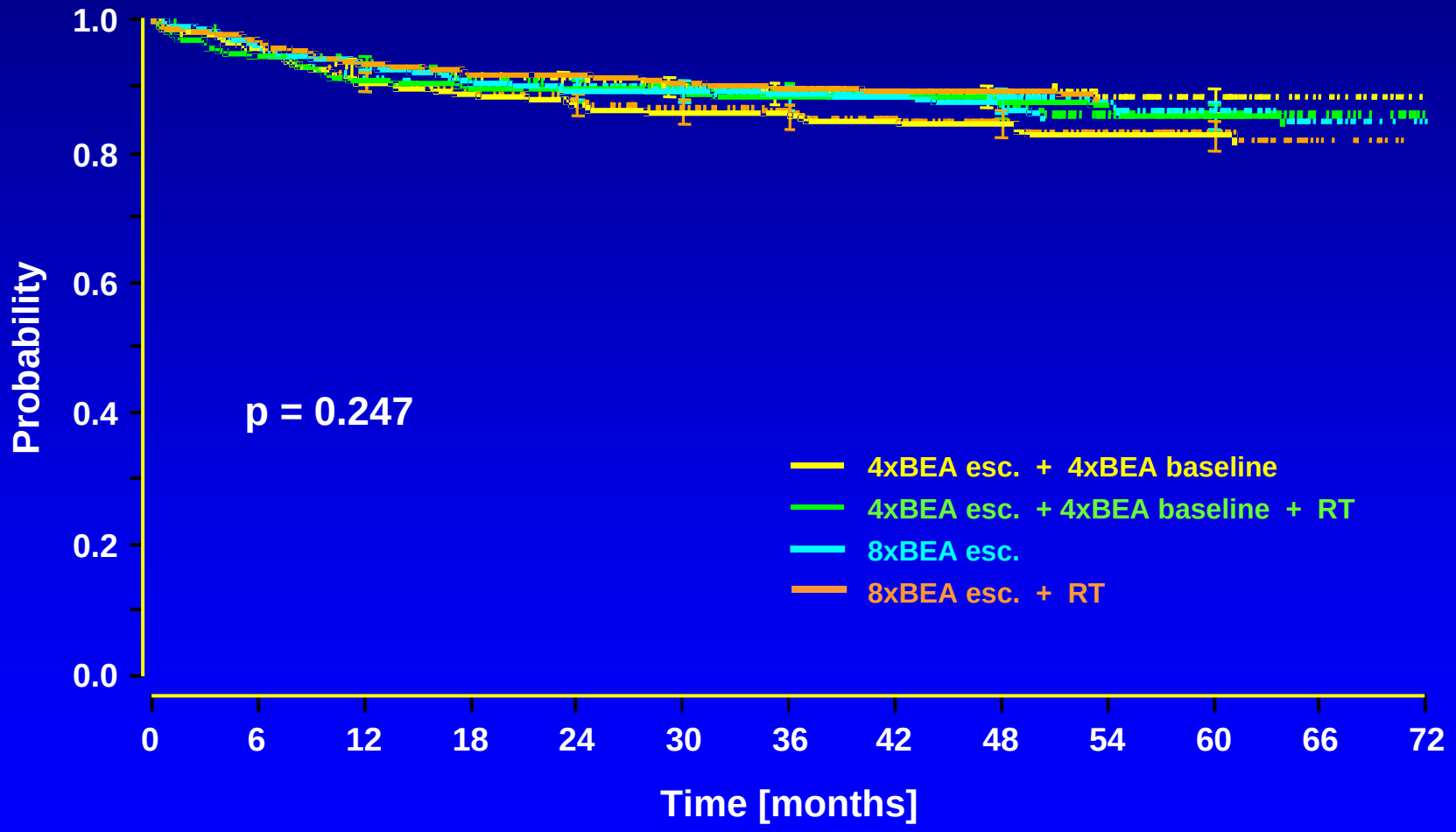
De-escalation of BEACOPP in HD12 and HD15 trials

HD12: (1520 pts, closed 2002)

- 8 BEACOPP escalated vs. 4 BEACOPP-esc + 4 BEACOPP-base
- RT vs. no RT

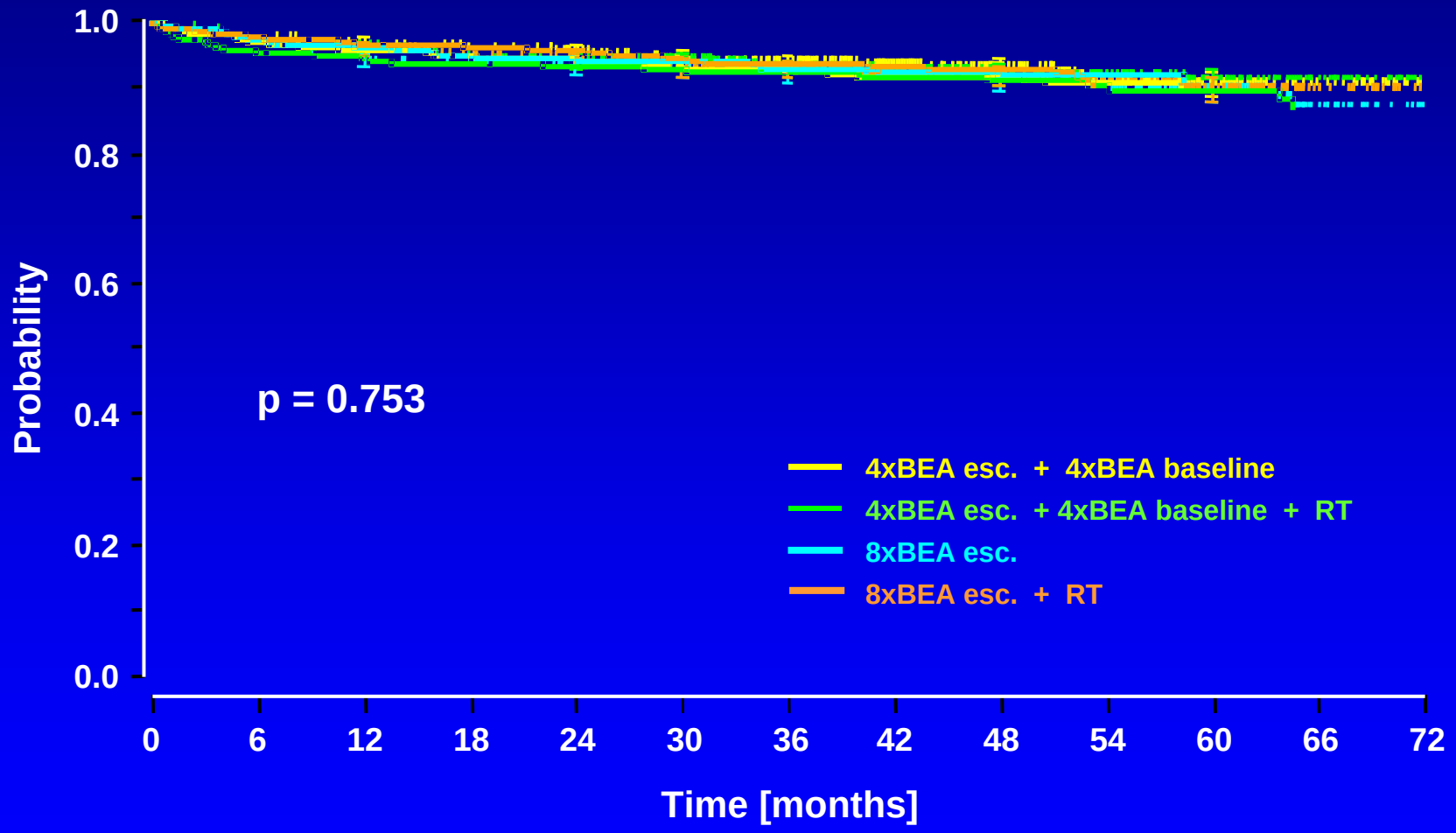
HD12 (5/2006): FFTF

All 4 Arms at 4 Years Med. Obs. Time

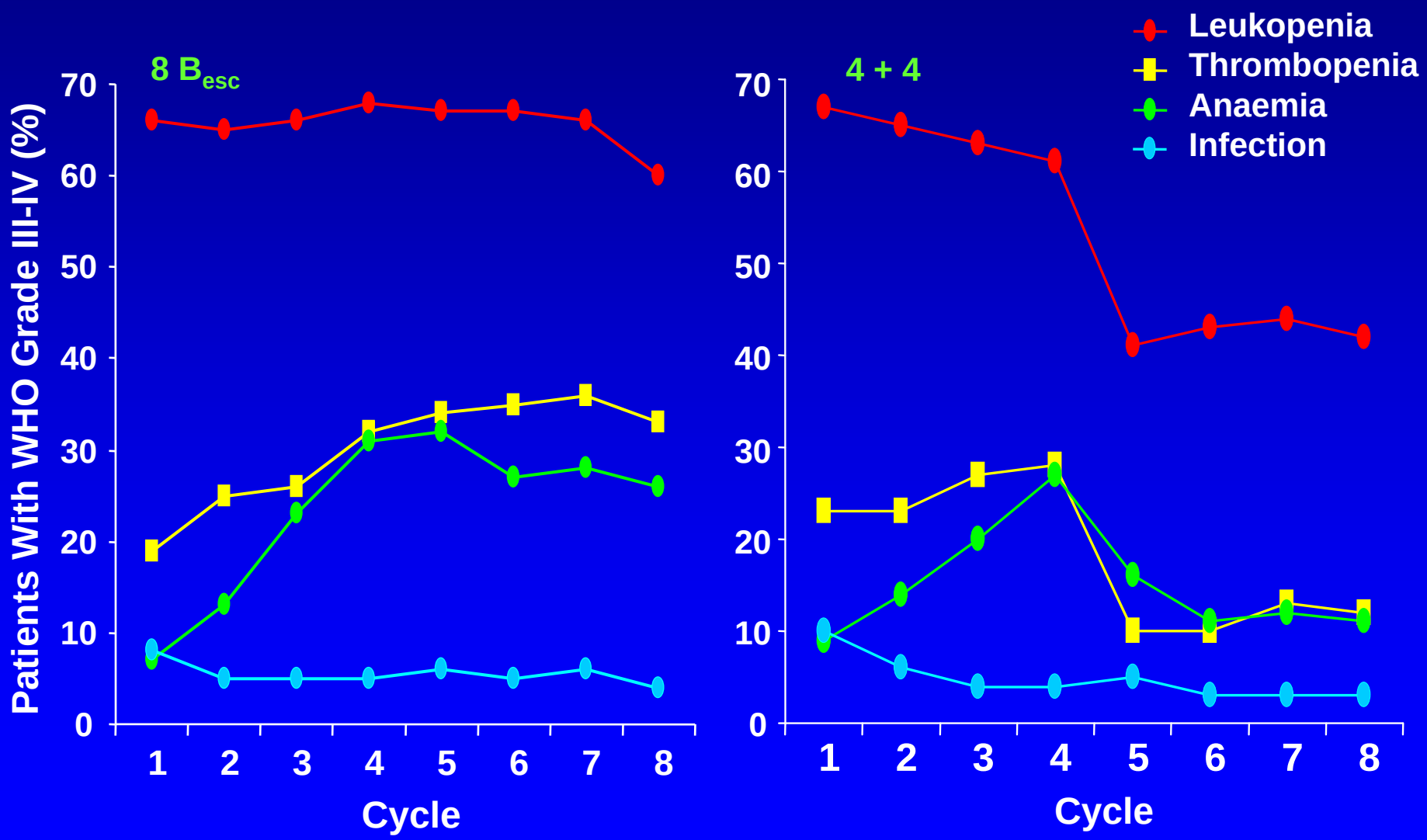


HD12 (5/2006): OS

All 4 Arms at 4 Years Med. Obs. Time



HD12 (5/2006): Acute Hematological Toxicity Per Chemotherapy Cycle Per Arm



HD12 (7/2004): Secondary neoplasia (CT)

4 year follow up data (1498 pats)

	N= 748	N= 750	
	$8B_{esc}$	4+4	n
AML / MDS	6 0.8%	5 0.7%	11 0.8%
NHL	8	1	9
Solid tumors/ others	3	6	9
Total	17 2.5%	12 1.7%	29 2.1%

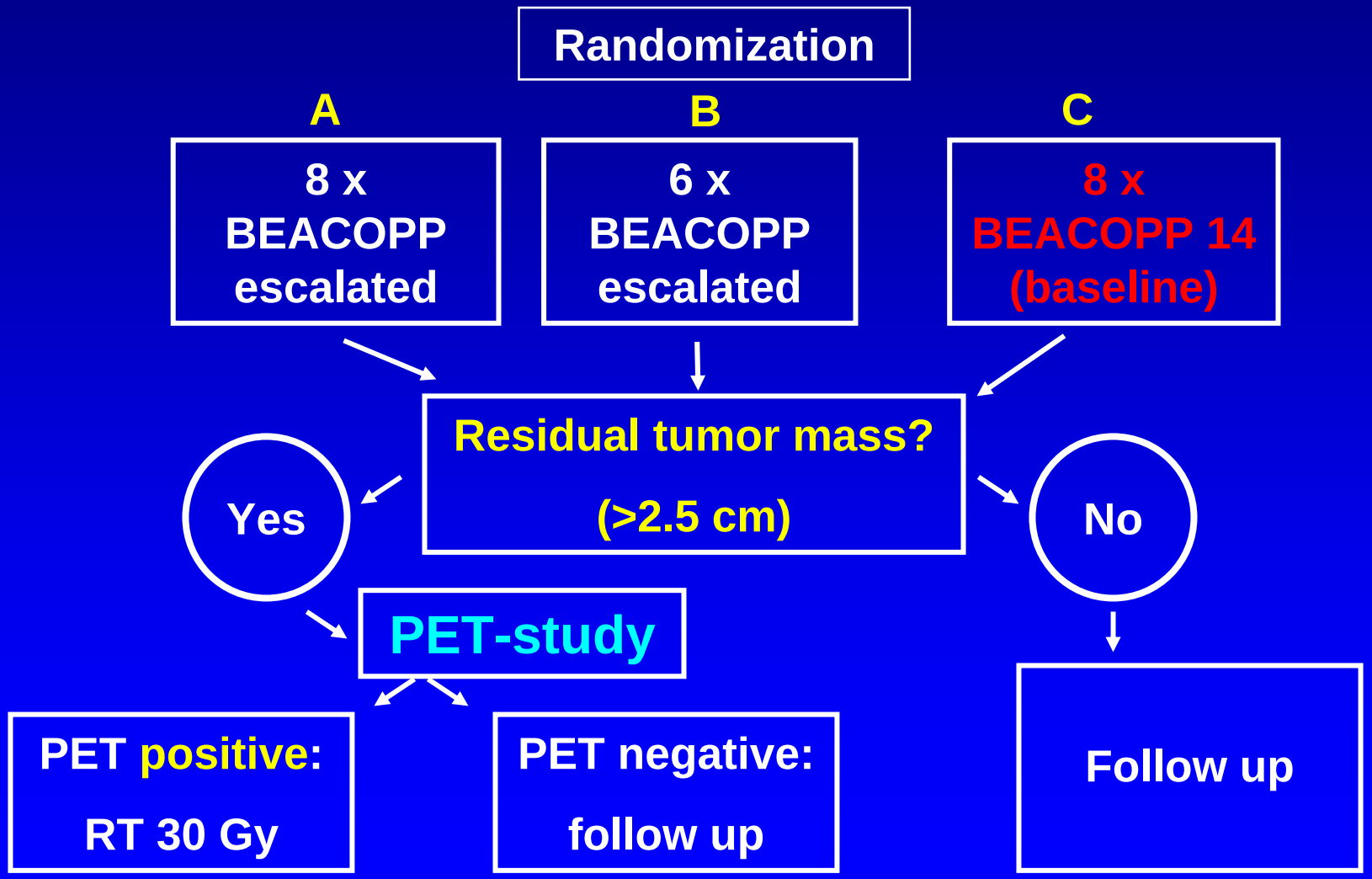
Role of PET at the end of chemotherapy

HD-15 Trial

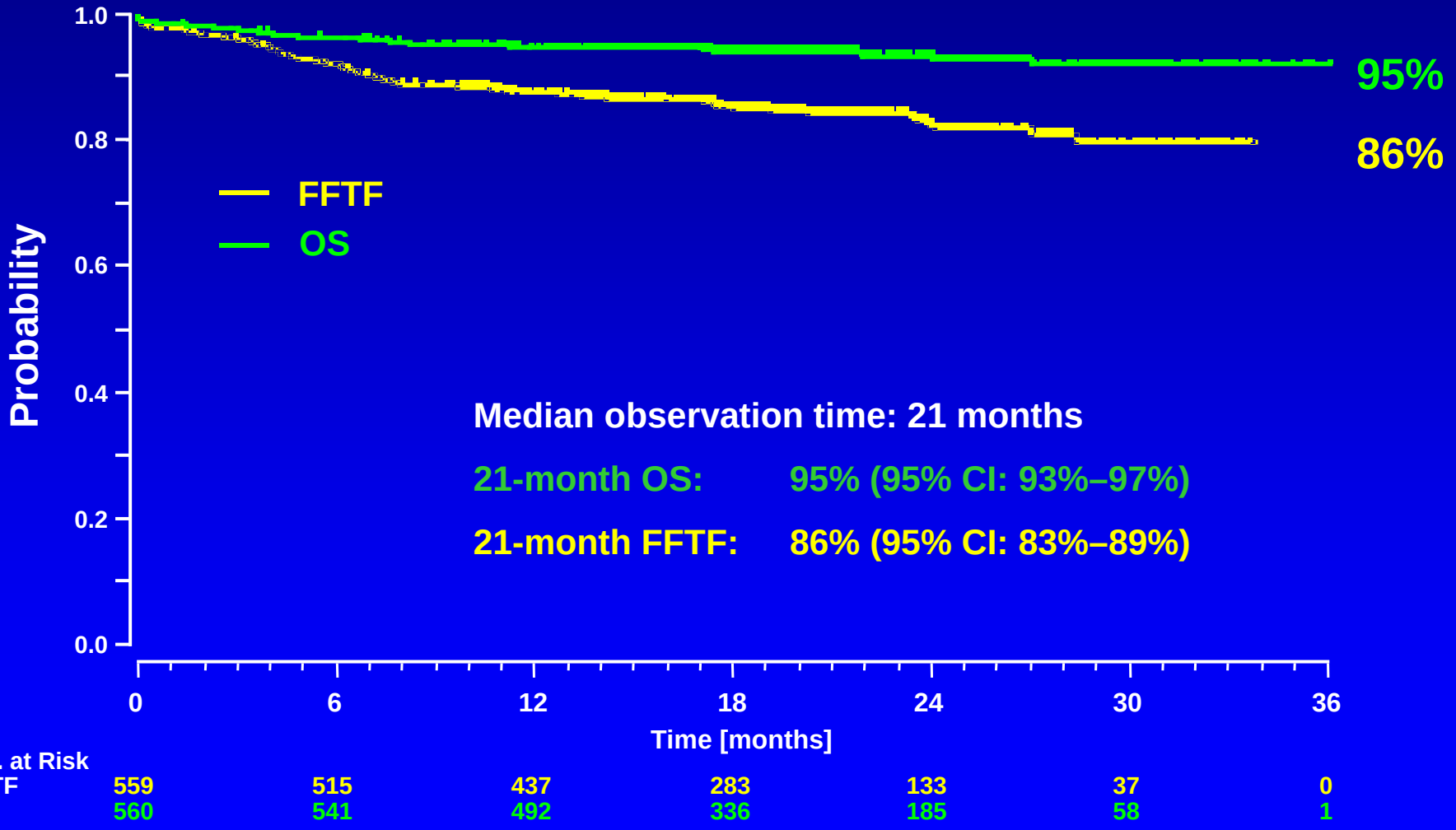
Questions:

1. In PET neg patients: do we need RT?
2. Will RT suffice in PET pos pats after chemo?

HD15 Study (started 1/2003)
1889 patients recruited (10/2007)

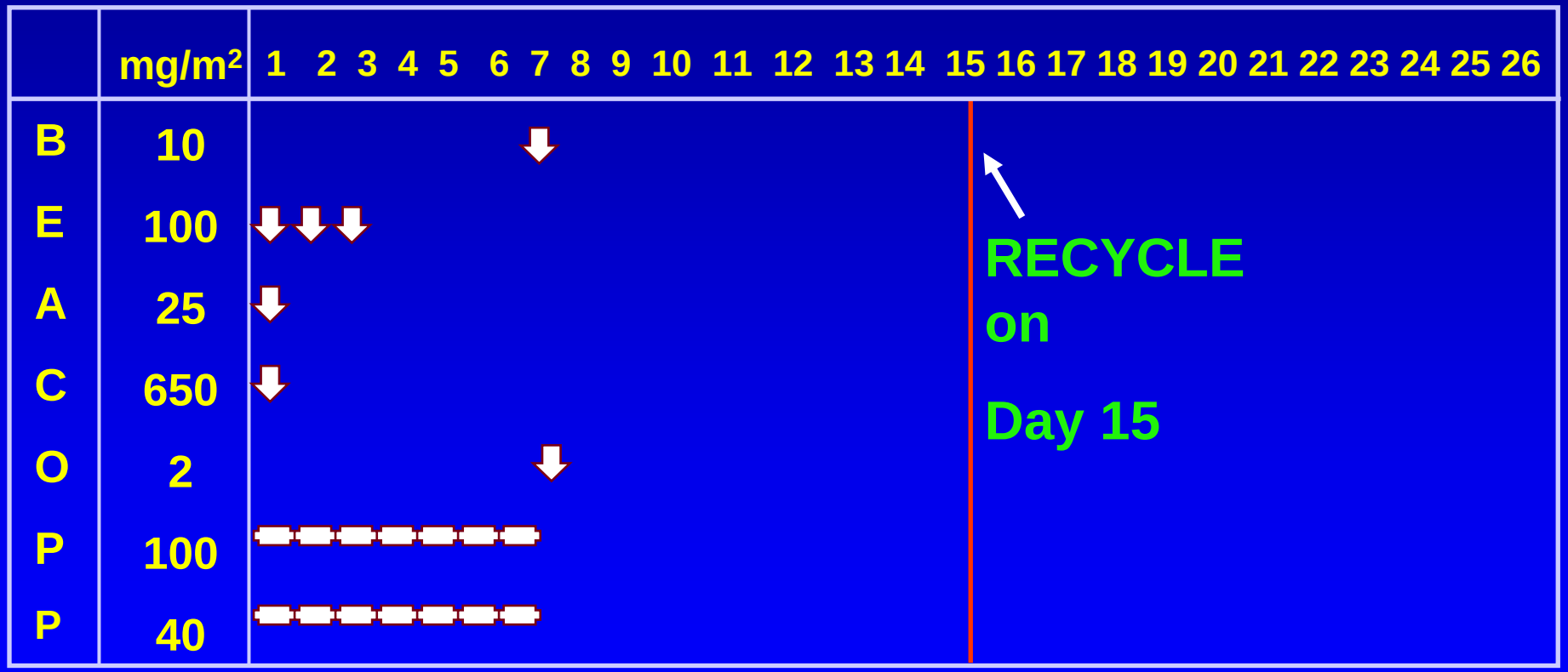


HD15: Second Interim Analysis
FFTF and Overall Survival

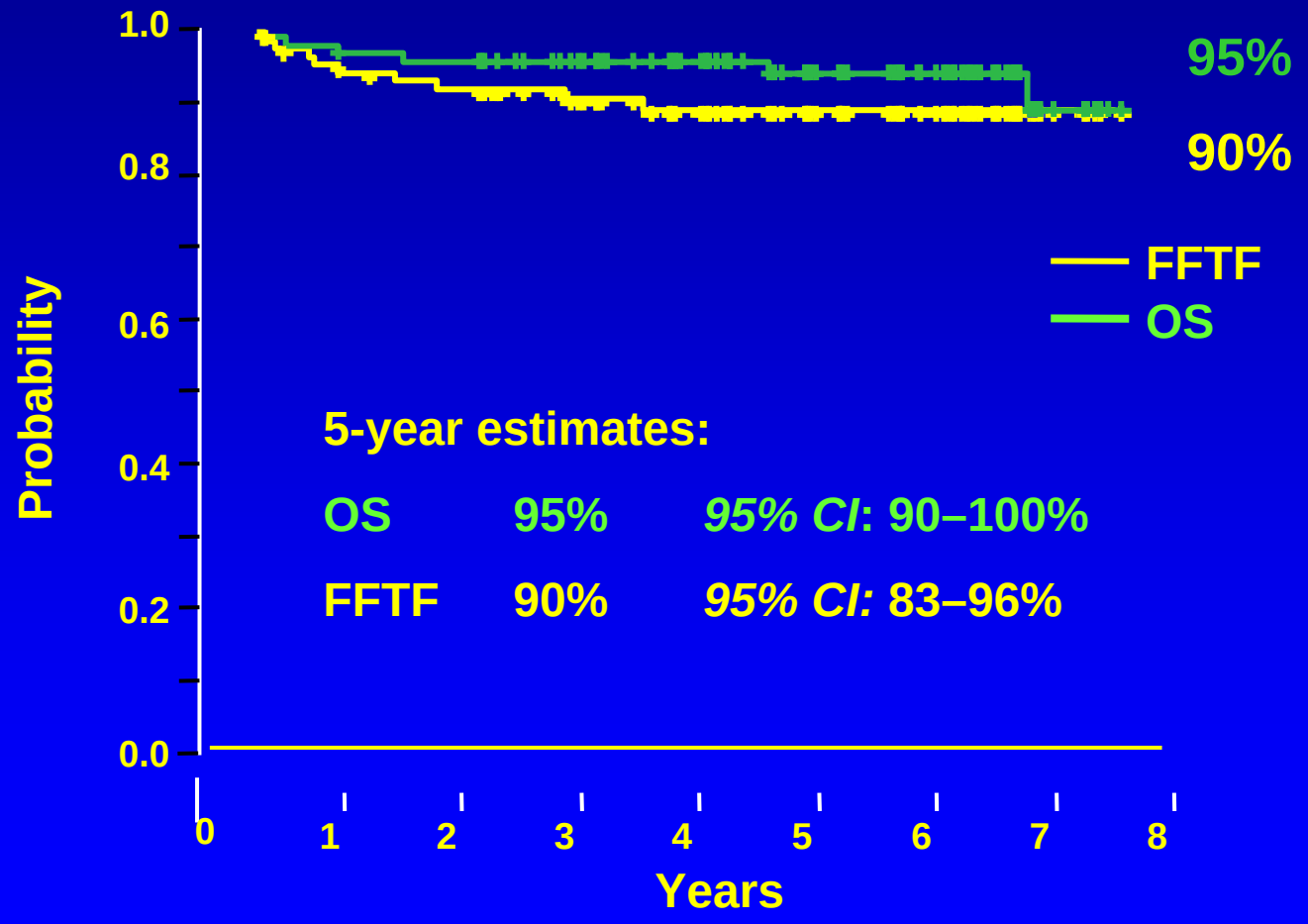


Reduction of Toxicity Advanced Stages

BEACOPP 14-DAY REGIMEN (baseline)



BEACOPP-14: Overall Survival and FFTF (4/2005)



HD15 trial:
1. Interim Analysis

Tumor progression in PET neg and PET pos pts after 6-8 BEACOPP esc/14

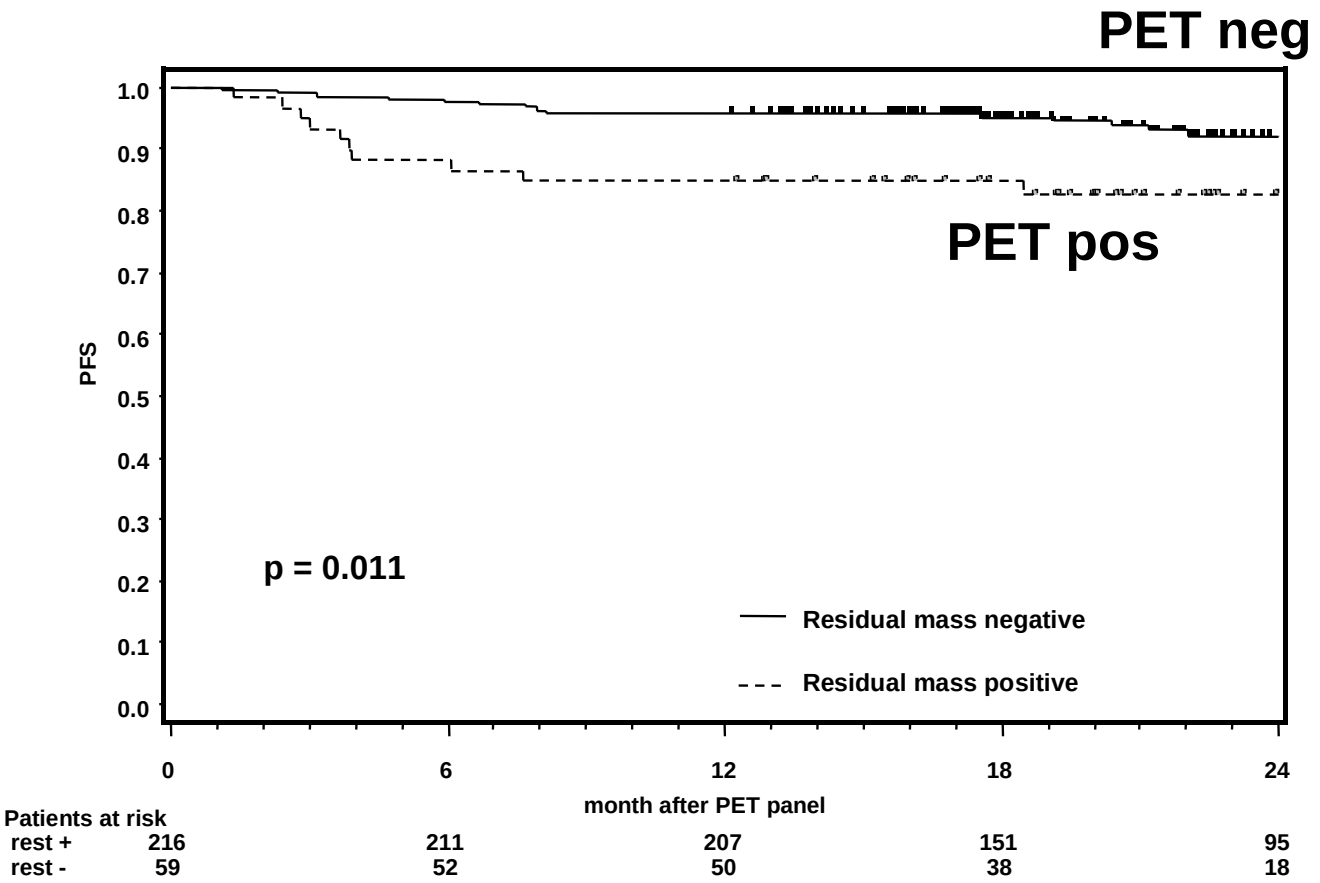
PET result	Progression/Relapse within 1 year:	
• PET neg (80%):	9 / 257 (= 3,5%)	
• PET pos (20%):	10 / 65 (= 15,3%)	p< 0,0053

RT given:

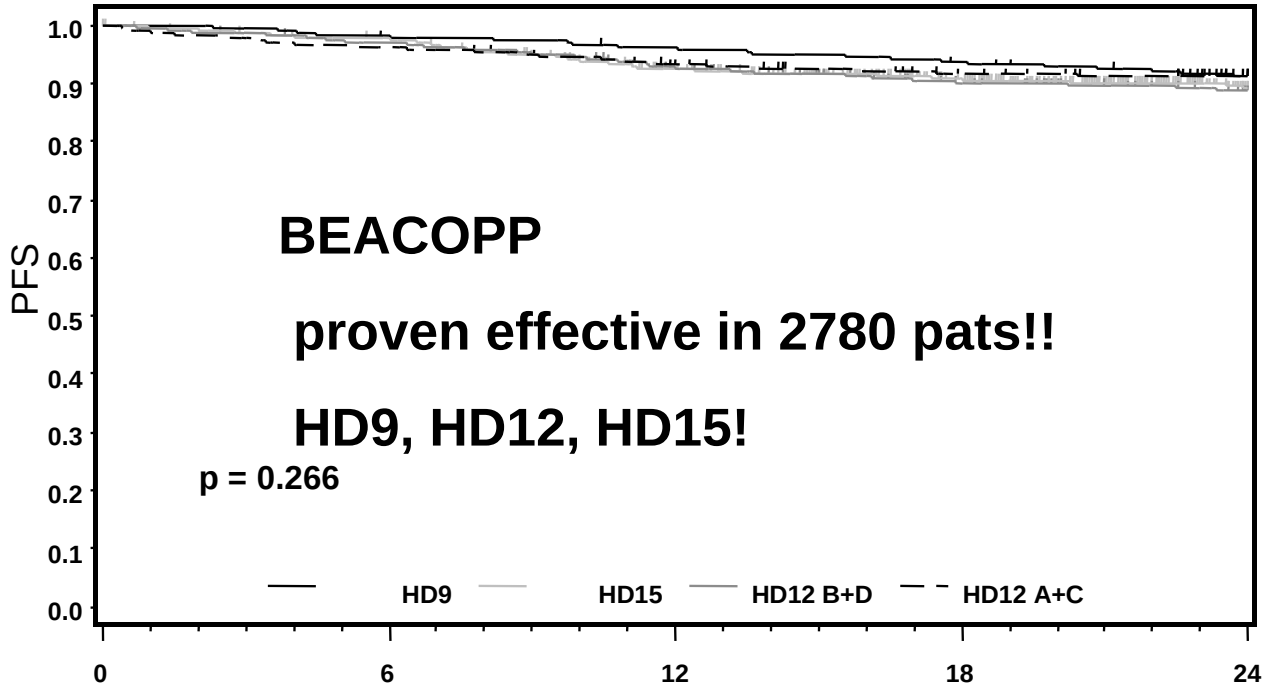
PET neg: 1/257

PET pos: 62/65

Progression free survival (PFS) for patients with positve and negative residual mass

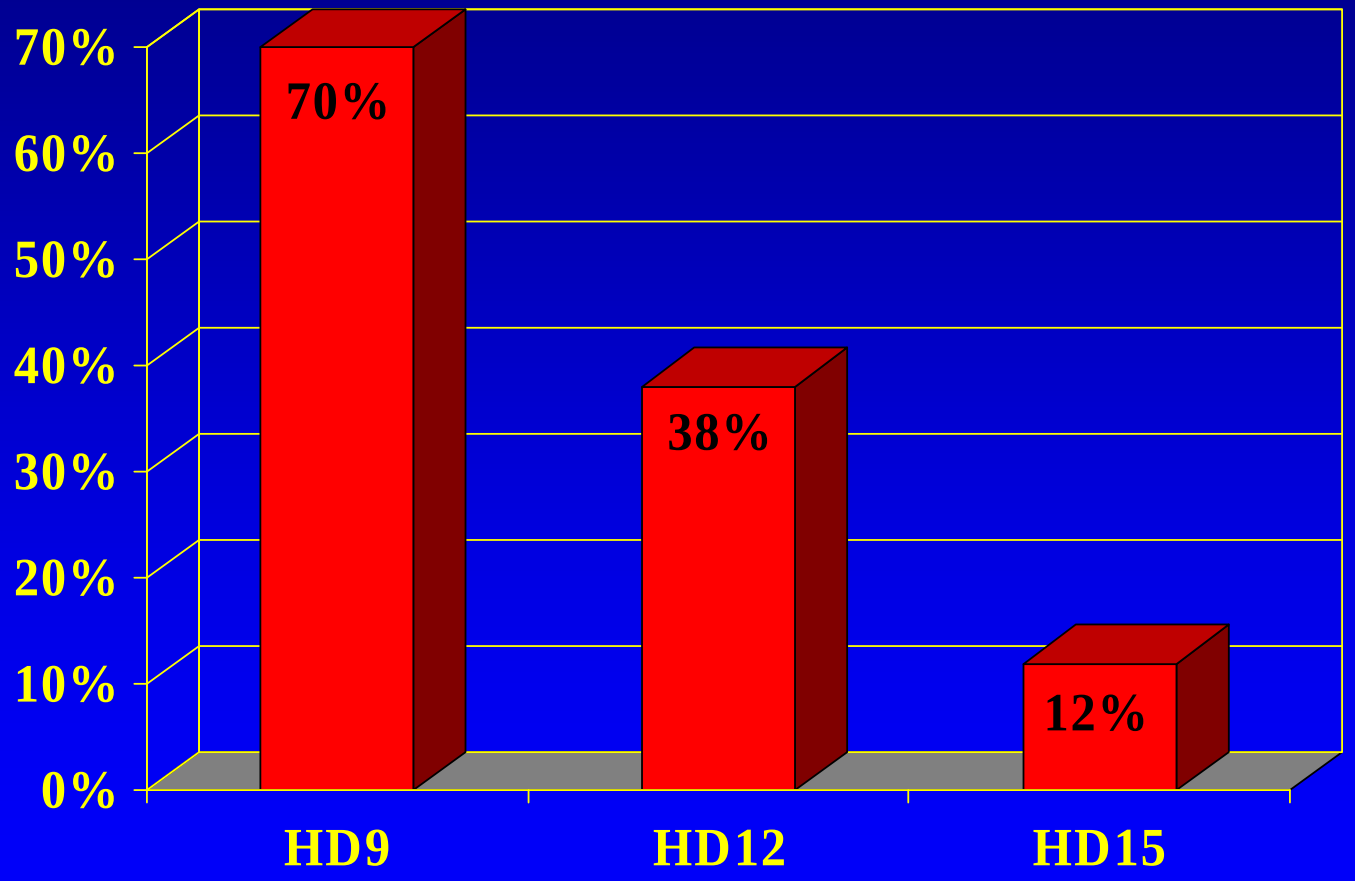


Comparison of PFS in HD9, HD12, HD15



Patients at risk					
HD12 A+C	748	720	690	666	0
HD12 B+D	750	725	689	653	0
HD15	816	792	719	643	0
HD9	466	457	446	434	0

Comparison of patients with RT in HD9, HD12, HD15



BEACOPP esc/ BEA-14

- Proof of Principle
  in 3 Randomized Prospective Trials
  in > 500 centers including
  220 private oncologists all over Europe
- > 2500 patients treated:
  - Results:
    - CR: >90% (RT: <15%)
    - FFTF: 82-88%, 4-10 yr follow up
    - **OS: 86-90%, 4-10 yr follow up**
    - **MDS/AML: 0.9%!!!**

Italian Trial (2000-2007)
(307 patients recruited!)

ABVD vs **MOPP-EBV-CAD (MEC)** vs **BEACOPP esc/base**

+ RT

Results:
3 years follow up for 270 pts:

Overall Survival: difference: not significant yet

Progression Free Survival

4+4 BEA esc/base **90%**

MEC **80%**

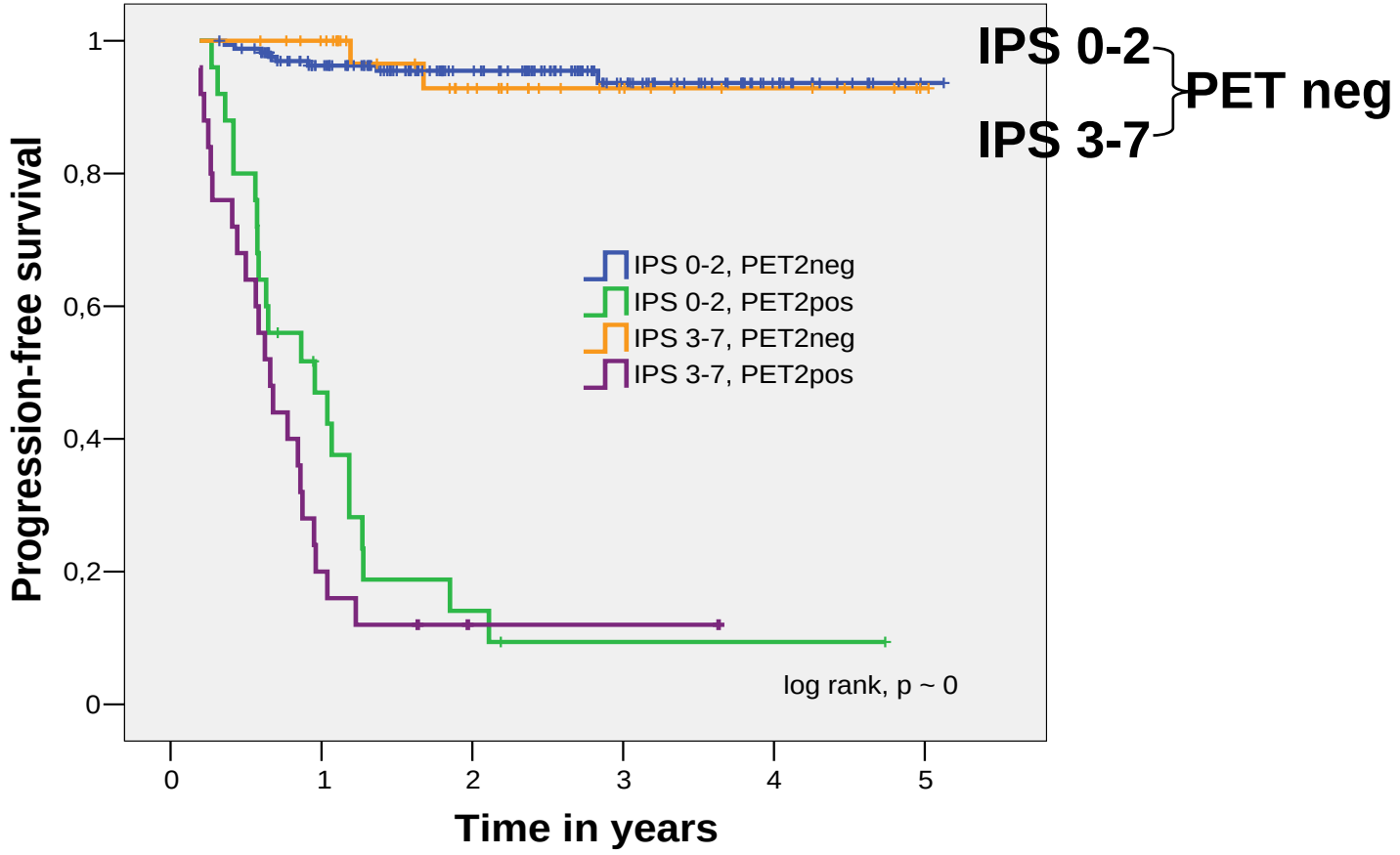
ABVD **72%**

P< 0,024

M.Federico, personal communication

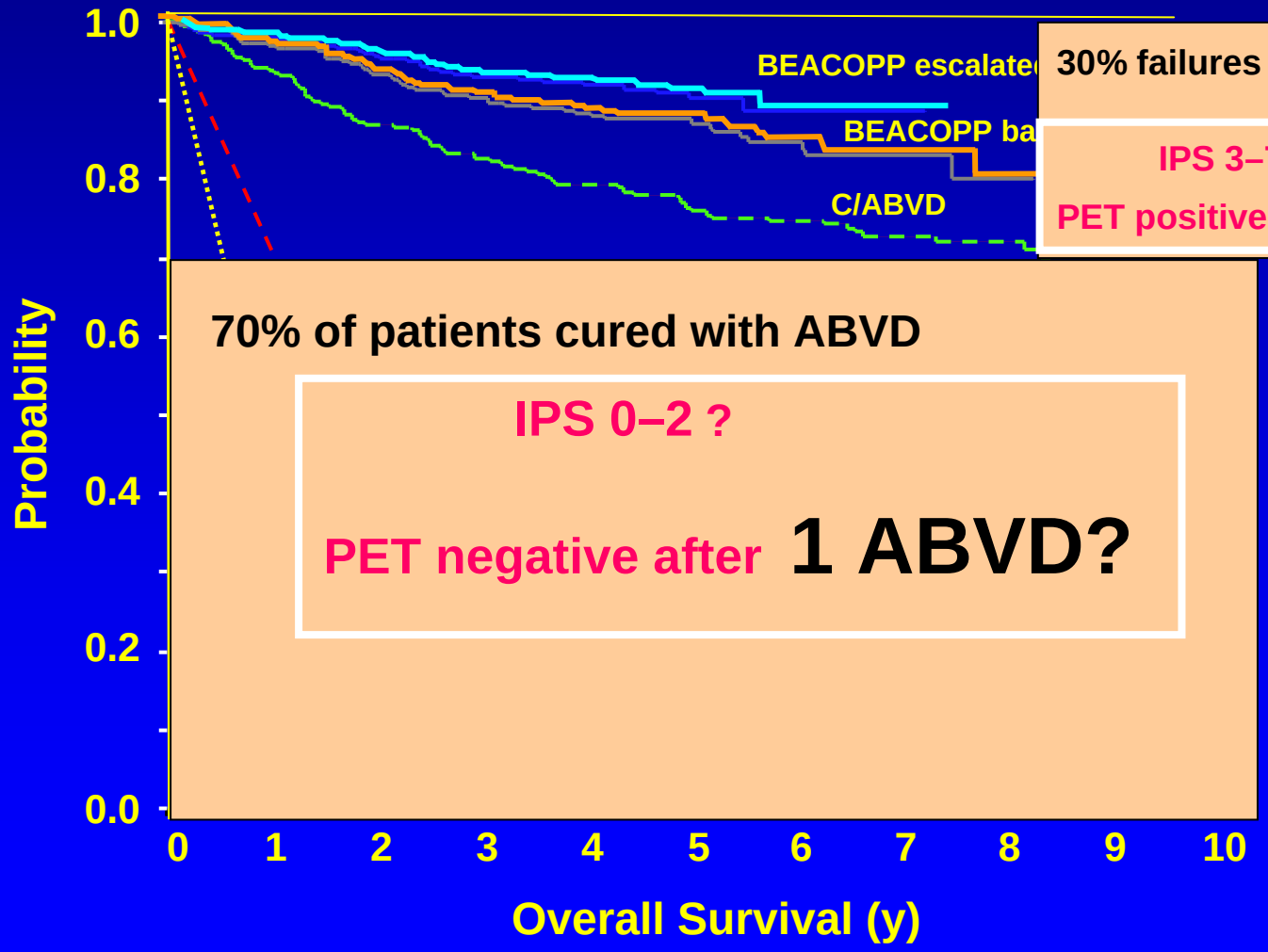
Early PET in HL: *Independent* of IPS

- PET after 2 cycles ABVD, followed by 4 more ABVD



Courtesy of Gallamini + Hutchings JCO 2007

Hodgkin Lymphoma Advanced Stages
How to Identify the Good & Bad Risk Groups?



30% failures with ABVD

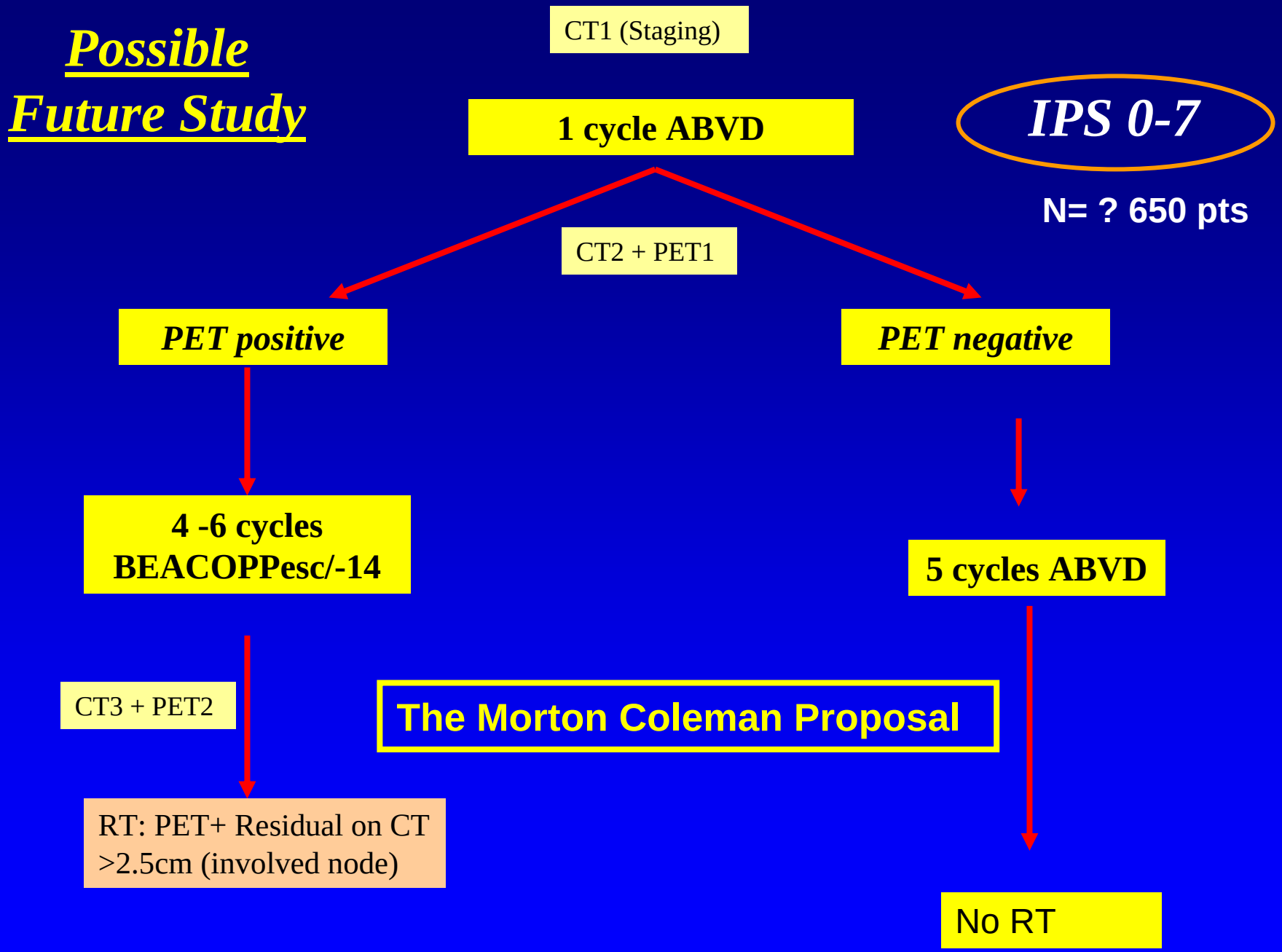
IPS 3–7 ?

PET positive after **1 ABVD?**

70% of patients cured with ABVD

IPS 0–2 ?

PET negative after **1 ABVD?**


Possible
Future Study
CT1 (Staging)
1 cycle ABVD
IPS 0-7
N= ? 650 pts
CT2 + PET1
PET positive
PET negative
4 -6 cycles
BEACOPPesc/-14
5 cycles ABVD
CT3 + PET2
The Morton Coleman Proposal
RT: PET+ Residual on CT
>2.5cm (involved node)
No RT

Future Strategies for Advanced Hodgkin Lymphoma

1. Use IPS for risk stratification
2. Use **very early** PET as indicator of response/prognosis?
3. Tailor intensity of therapy according to PET result

Open Questions and a Caveat!:

1. BEACOPP-14 strong enough???
2. How reliable is PET??

   90% Negative Predictability = 10 % false negatives!!

   65% Positive Predictability!

The argument of Infertility:
What does the (male-) patient prefer???

- Infertility does not mean sexual dysfunction!!
- 70% of males with advanced HL have dys-or a-zoospermia before treatment
- < 10% of male patients have asked for their frozen sperms for i.v fertilization

  (> 3000 sperm samples frozen away!! GHSG experience)
- What is more important for the patient:

  - to be infertile but be cured by primary induction therapy

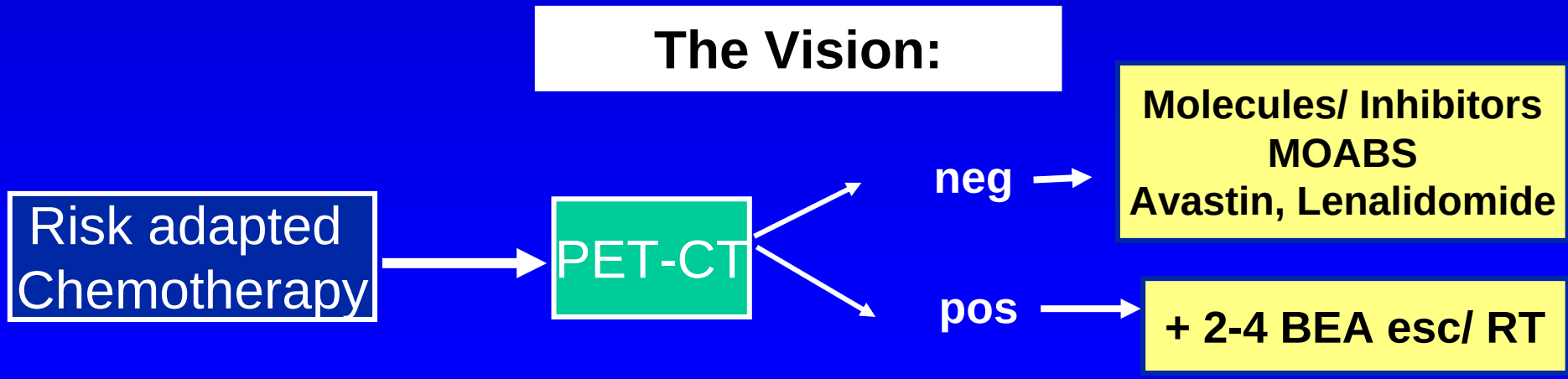
    (18% more PFS with BEAesc than with C/ABVD after 10 ys)

  - to be fertile but have a relapse/progression- and then become infertile anyway under salvage therapy!

The Post- BEACOPP Era

Molecular therapy for HL:

Immuntherapy and small molecules/ inhibitors are most promising strategies for future treatment in HL



Thanks to

- the GHSG-team -the participating doctors/nurses
- the thousands of patients
- the „Deutsche Krebshilfe" for support
- you for your attention


International Symposium
7th on Hodgkin Lymphoma
Cologne, Germany
German Hodgkin Study Group
www.hodgkin2007.de
November 4–7, 2007
Gürzenich, Cologne