Hodgkin Lymphoma: Latest Concepts

THE MAIN INTENT: LESS TOXICITY

At least 85% of Hodgkin patients can anticipate a cure: how to cure with the least impact on the patient?

What role does PET Scans play in this effort?

Can interim PET/CAT scans be of value or should scans be used only at the end of treatment?

FDG-PET: After one (two treatments) versus two cycles (four treatments) of therapy

Early determination of treatment sensitivity in Hodgkin lymphoma: FDG-PET/CT after one cycle of therapy has a higher negative predictive value than after two cycles of therapy

Hutchings, M., Kostakoglu,L., Coleman, M., et al. Submitted for publication

Participating Nations

Denmark

United States

Italy

Poland

Patient Population:126 Pts.

- Stage I 8%
- Stage 2 46%
- Stage 3 19%
- Stage4 27%
- B Sxs 56%
- Bulky 37%

Comparison of the prognostic value of PET 1 and PET 2: Progression Free Survival at 2 Years

	PET 1	PET2
• Negative predictive value	98%	91%
• Positive predictive value	63%	85%
• Sensitivity	95%	61%
• Specificity	86%	97%
• Concordance	>90%	

The RAPID Trial in Patients With Clinical Stages IA/IIA Hodgkin Lymphoma and a "Negative" PET Scan After 3 Cycles ABVD

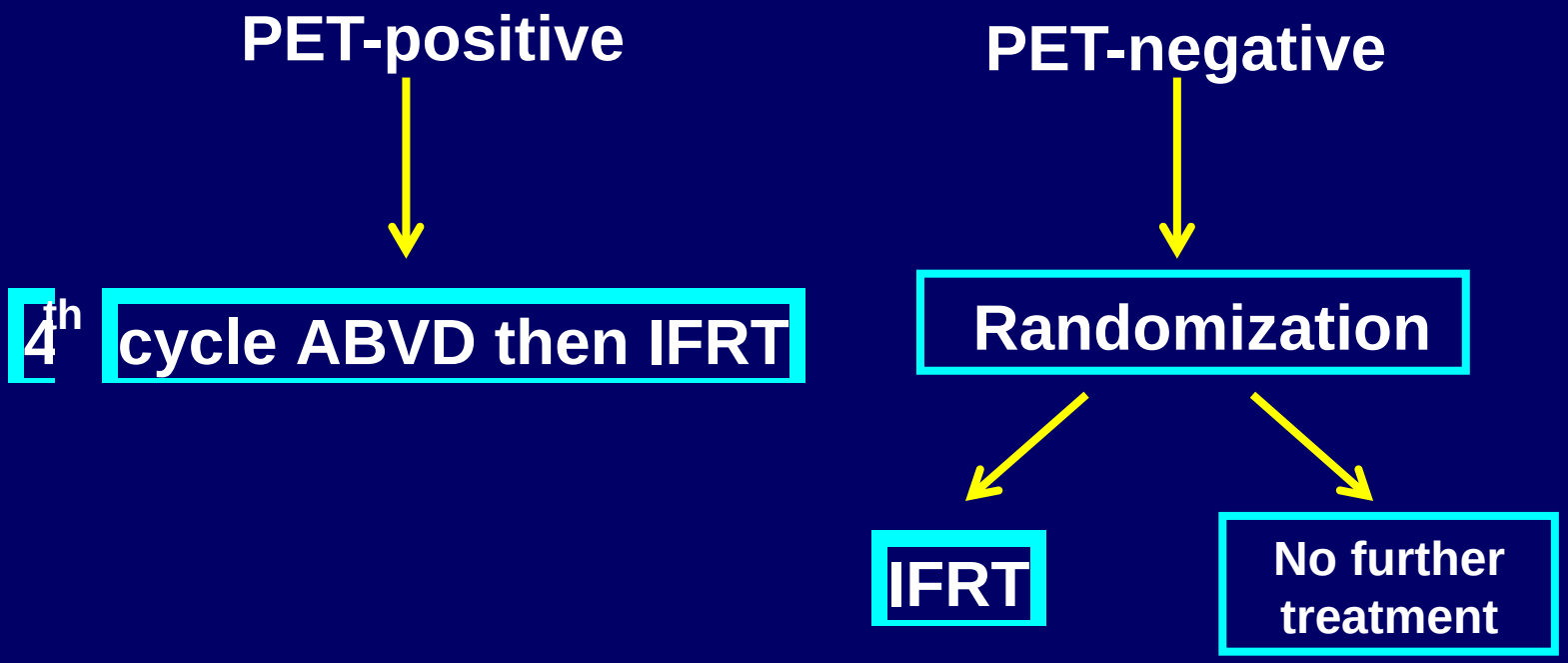
Abstract 547

Radford J, Barrington S, Counsell N, Pettengell R, Johnson P, Wimperis J, Coltart S, Culligan D, Lister A, Bessell E, Kruger A, Popova B, Hancock B, Hoskin P, Illidge T, O'Doherty M

RAPID Trial Design

Initial treatment: ABVD x 3

Reassessment: if NR/PD, patient goes off study
if CR/PR, FDG-PET scan performed



Outcomes After Median Follow-Up of 45.7 Months

	PET negative; randomized to IFRT (n = 209)	PET negative; randomized to NFT (n = 211)	PET positive; 4th cycle ABVD/IFRT (n = 145)
Progressions	9	20	11
Deaths	6	1	8
PFS at 3 years	93.8%	90.7%	85.9%
OS at 3 years	97.0%	99.5%	93.9%

Progressions and Deaths in the Randomized PET-Negative Population (n = 420)

- IFRT arm; progressions 9, deaths 6
  - Pneumonitis, n = 2
  - HL, n = 1
  - Cardiovascular disease, n = 1
  - Intracerebral hemorrhage, n = 1
  - AITL, n = 1
- NFT arm; progressions 20, deaths 1
  - Bronchopneumonia, n = 1

Summary

- 602 pts registered between 2003 and 2010
- 75% PET-negative at central review after ABVD x 3
- In the randomized PET-negative population, 3 yr PFS is 93.8% IFRT and 90.7% NFT
- Risk difference -3% is within the maximum allowable difference of -7%

Conclusion

Patients having low stage disease with a negative PET scan after 3 cycles of ABVD have an excellent prognosis without further treatment, and for these patients RT can be avoided

Commentary

An Individual Patient-Data Comparison of German Hodgkin Study Group HD10 and HD11 Combined Modality Therapy and NCIC Clinical Trials Group HD.6 ABVD Alone

Abstract 549

Hay AE, Klimm B, Chen BE, Goergen H, Shepherd LE, Fuchs M, Gospodarowicz M, Borchmann P, Connors JM, Markova J, Crump

M, Lohri A, Winter JN, Borchert B, Pearcey RG, Volker D, Horning SJ, Eich HT, Engert A, Meyer RM

GHSG Early-Stage HL Risk Factors

Favorable: CS IA,IB, IIA, IIB without risk factors

Unfavorable: CS IA, IB, with at least one of the risk factors a-d given below or CS IIB with risk factor c, d, or both given below: and IIA

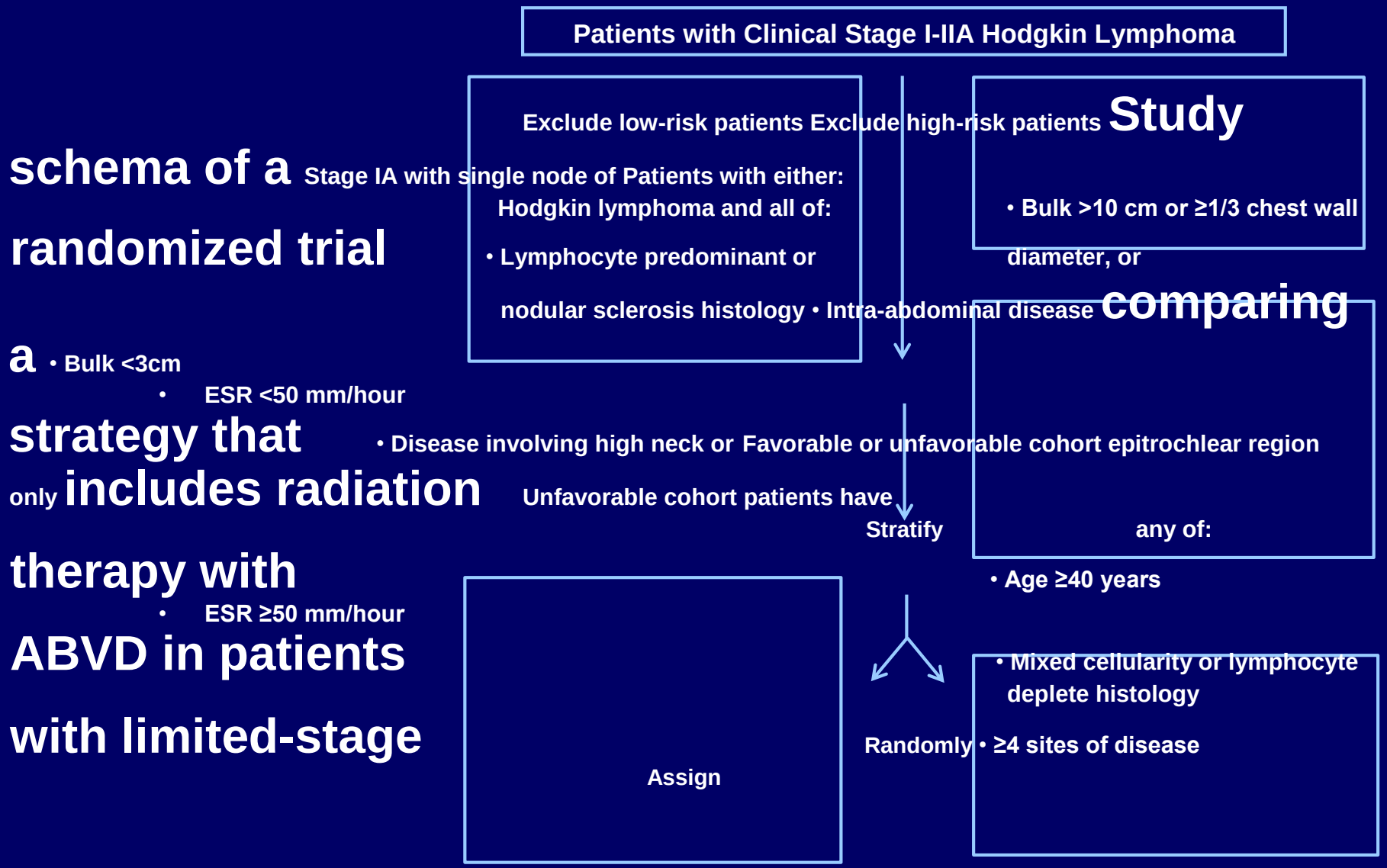
a) Large mediastinal mass (≥1/3 of maximum transverse thorax diameter) b) Extranodal involvement

c) High erythrocyte sedimentation rate (≥50 mm/h in patients without B-symptoms, ≥30 mm/h in patients with Bsymptoms)

d) 3 or more involved lymph node areas

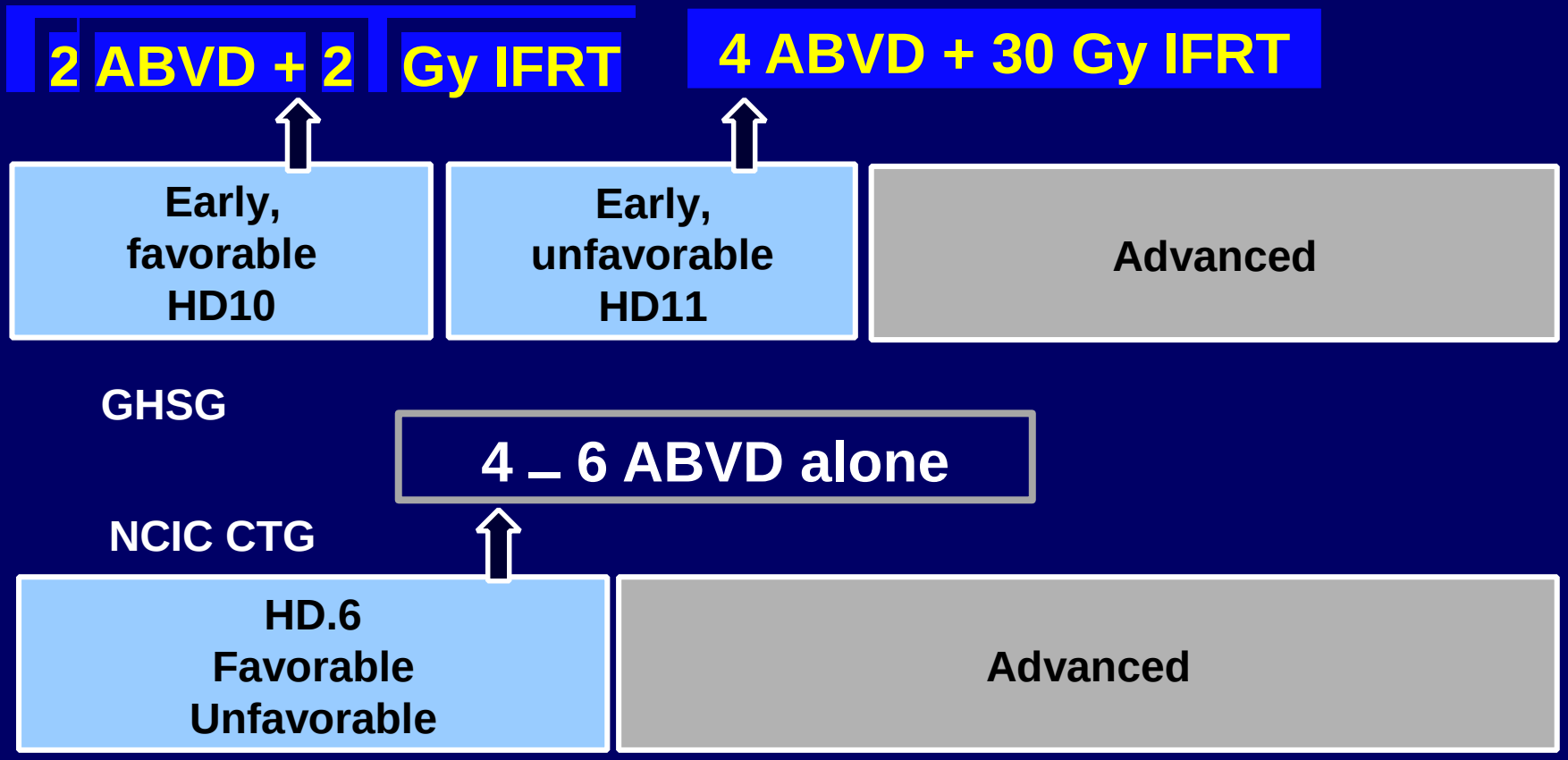
Eich HT, et al. *J Clin Oncol.* 2011;28:4199-4206.

HD.6 Trial



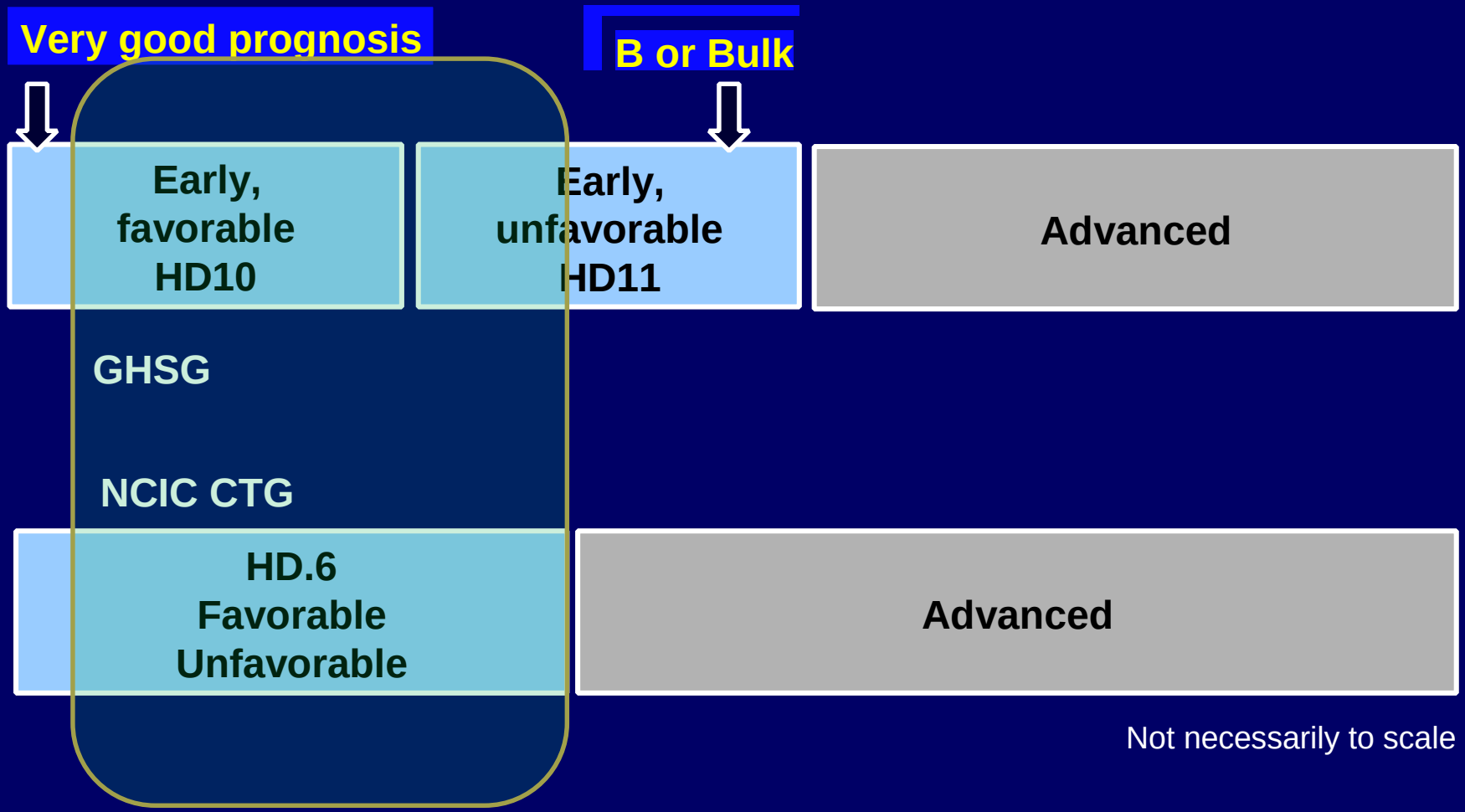
schema of a randomized trial comparing a strategy that only includes radiation therapy with ABVD in patients with limited-stage

Comparison of NCIC CTG HD.6 and GHSG HD10 and HD11 Staging, Eligibility and Preferred Arms



Not necessarily to scale

Comparison of NCIC CTG HD.6 and GHSG HD10 and HD11 Staging, Eligibility and Preferred Arms



Attribution of Death: All Patients

Cause of Death	GHSG HD10/11	NCIG CTG HD.6
Number	406	182
Med. F/U	7.6 Years	11.2 Years
Hodgkin lymphoma	5	4
Immediate toxicity	2	1
Second cancer	2	3
Cardiac	4	2
Other	6*	0
Total	19	10

*Other deaths were: 1 suicide, 1 respiratory failure, 1 cerebral hemorrhage, 1 progression of NHL, 2 unknown

Outcomes: All Patients

Endpoint ***Number*** ***Med. F/U***	**GHSG HD10/11** ***406*** ***7.6 Years***	**NCIG CTG HD.6** ***182*** ***11.2 Years***	**HR** (95% CI)	**GHSG PD/OS**	**NCIC CTG PD/OS**
8-yr TTP	**93%**	**87%**	**0.44** (0.24, 0.78)	**25/0**	**23/0**
8-yr PFS	**89%**	**86%**	**0.71** (0.42, 1.18)	**25/13**	**23/4**
8-yr OS	**95%**	**95%**	**1.09** (0.49, 2.40)	**19**	**10**

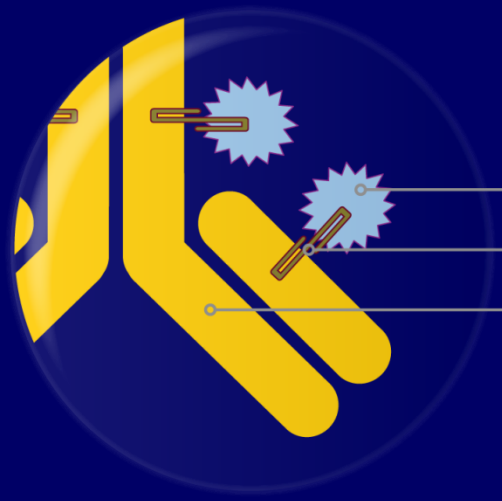
Overall Summary

- Combined modality therapy (CMT) improves disease control by 4%-7%
- Superior long-term overall survival with CMT is highly unlikely
- In selecting patients at lowest risk of disease recurrence if treated with ABVD alone:
  - Non-PET CR/CRu criteria may be most rigid
  - A portion of CT-based non-CR/CRu pts will be PET negative and will have an excellent outcome
- The relatively long term outcomes associated with IFRT remain to be clarified

What's new for refractory/relalpsing disease?

Evolving Data on Brentuximab Vedotin

Brentuximab Vedotin Mechanism of Action



Brentuximab vedotin (SGN-35) ADC

monomethyl auristatin E (MMAE), potent antitubulin agent

protease-cleavable linker

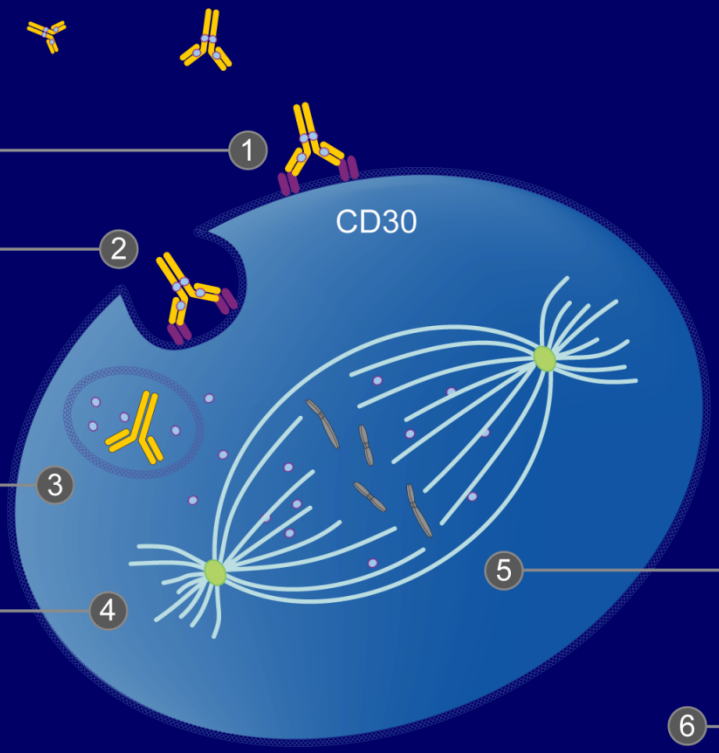
anti-CD30 monoclonal antibody

ADC binds to CD30

ADC-CD30 complex traffics to lysosome

MMAE is released

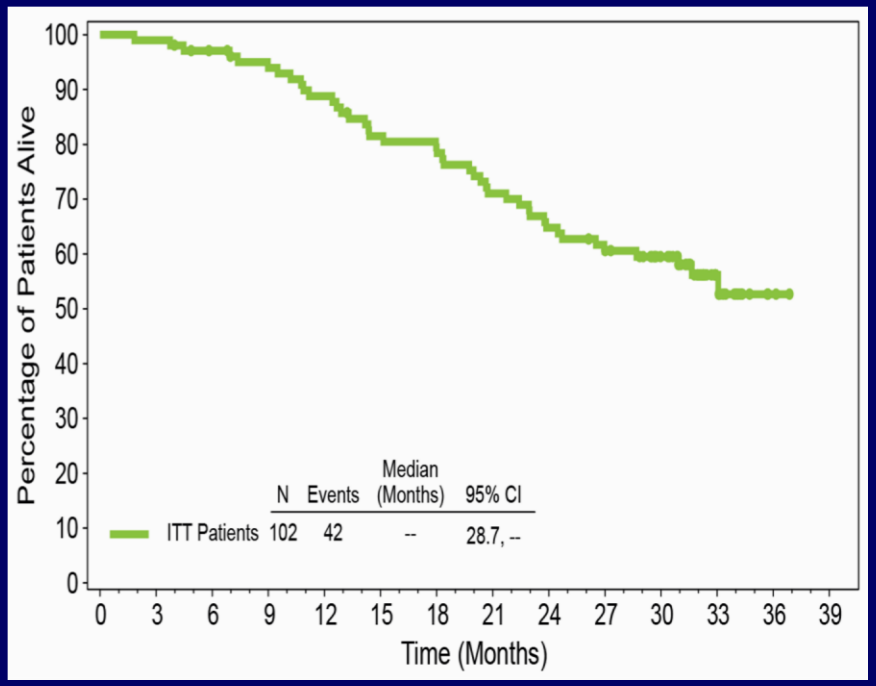
MMAE disrupts microtubule network



G2/M cell cycle arrest

Apoptosis

Overall survival after treatment with Brentuximab vedotin



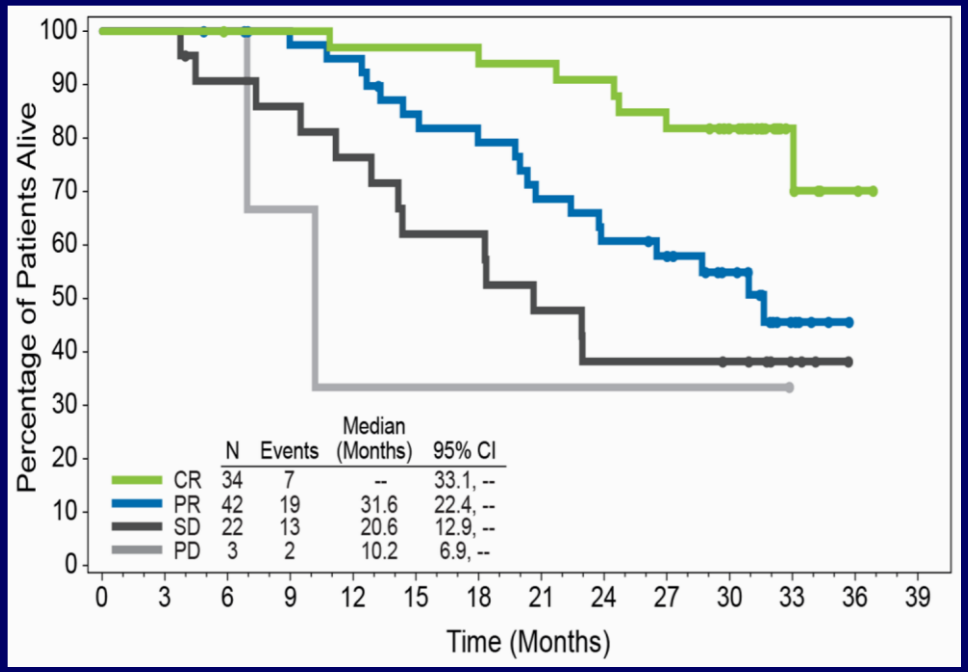
- Median observation time from 1st dose:
  - All patients = 29.5 months (range, 1.8 to 36.9)
  - CR patients = 29.1 months (range, 2.6 to 34.3)
- 60/102 patients (59%) remain alive; median OS has not been reached (95% CI: 28.7, NE)
- Estimated 24-month survival rate* = 65% (95% CI: 55, 74)

Long-Term Survival Analyses of an Ongoing Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory Hodgkin Lymphoma

Abstract 3689

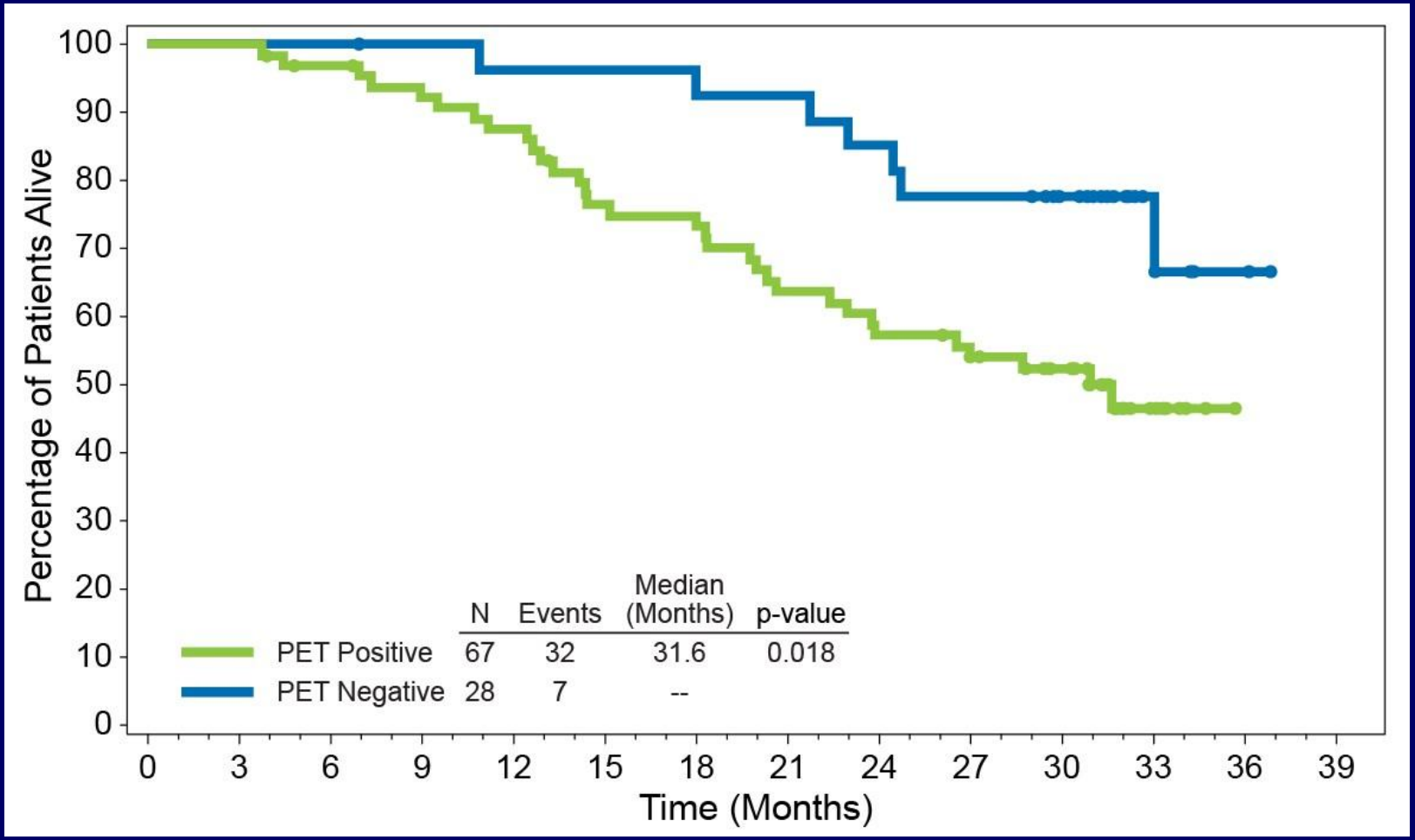
R Chen, AK Gopal, SE Smith, SM Ansell, JD Rosenblatt, KJ Savage, JM Connors, A Engert, EK Larsen, EL Sievers, A Younes

Overall Survival by Best Clinical Response



- Estimated 24-month survival rate* by best response:
  - CR: 91% (95% CI: 81, 100)
  - PR: 61% (95% CI: 45, 76)
  - SD: 38% (95% CI: 17, 59)
  - PD: 33% (95% CI: 0, 87)

Overall Survival by Cycle 4 PET Status



Conclusions

- After a median observation time of ~2.5 years from first brentuximab vedotin dose, 60 of 102 patients (59%) remain alive at last follow up
- Median OS has not yet been reached; the estimated 24-mo survival rate was 65%
  - Improved OS strongly correlated with both:
    - Achievement of CR
    - Negative PET scan at Cycle 4
  - Prolonged OS was observed in patients with both long and short progression-free intervals after auto-SCT

Overall Survival Benefit for Patients With Relapsed Hodgkin Lymphoma Treated With Brentuximab Vedotin After Autologous Stem Cell Transplant

Abstract 3701

Karuturi MS, Arai S, Chen RW, Gopal AK, Feng L, Yuan Y, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, Ramchandren R, Bartlet NL, Cheson BD, Forero-Torres A, Moskowitz CH, Connors JM, Fanale MA, de Vos S, Engert A, Illidge T, Borchmann P, Morschhauser F, Horning SJ, Younes A

Overall Survival Benefit for Patients Treated With Brentuximab Vedotin After Autologous Stem Cell Transplant

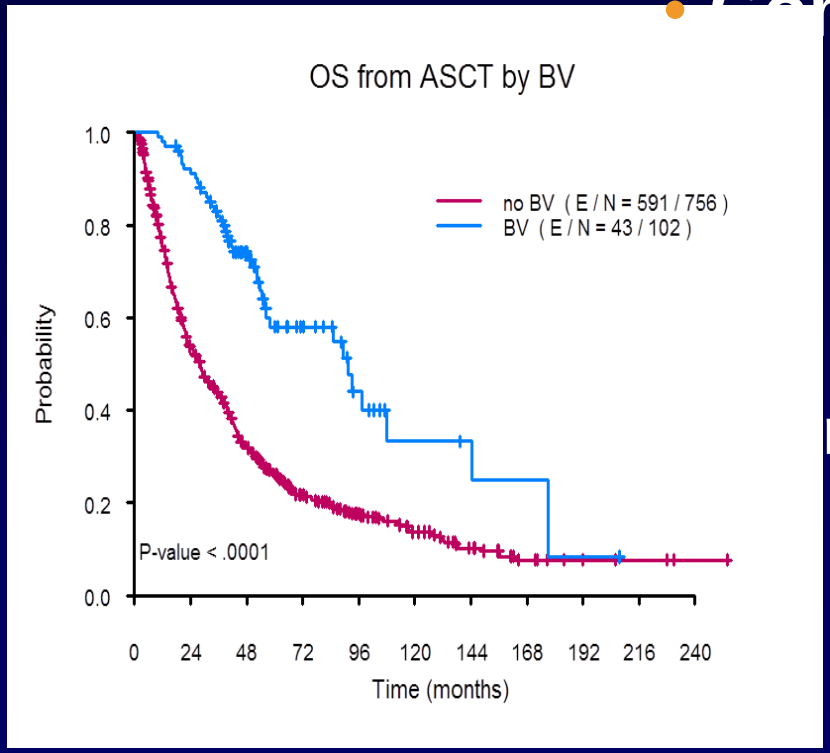
Objective

1) Compare OS in patients with relapsed Hodgkin lymphoma (HL) after receiving ASCT in a cohort of 102 HL pts treated with brentuximab vedotin (BV), with 756 pts from 6 international centers before the introduction of BV

2) Evaluate predictors of durable complete remission (CR) in patients treated with BV

Karuturi MS, et al. *Blood.* 2012;120: Abstract 3701.

Overall Survival Benefit for Patients Treated With Brentuximab Vedotin After Autologous Stem Cell Transplant



- Comparison
  - Significant difference in median OS (*P*<.0001) between BV and no BV (91.49 mos vs 27.99 mos)
  - Improvement in OS irrespective of time to relapse from ASCT

What are we doing new for Advanced-Stage HL

How can we improve the cure rate and reduce the toxicity for advanced stage disease?

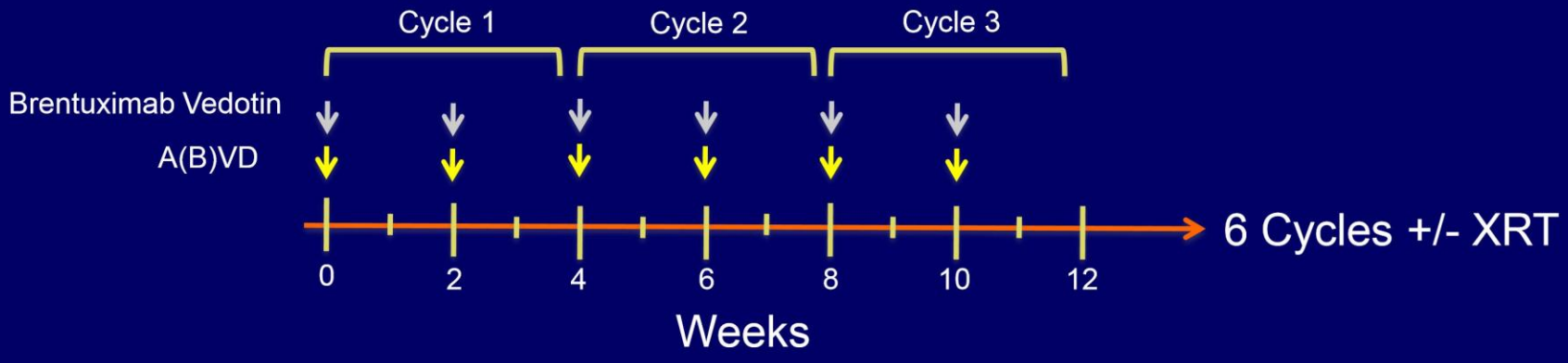
Frontline Therapy With Brentuximab Vedotin Combined with ABVD or AVD in Patients with Newly Diagnosed Advanced-Stage Hodgkin Lymphoma

Abstract 798

Ansell SM, Connors JM, Park SI, O'Meara M, Younes A

Study Design

- Phase I, multicenter, dose-escalation study
- Major eligibility criteria
  - Treatment-naïve HL patients
  - Age ≥18 to ≤60 years
  - Stage IIA bulky disease or Stage IIB-IV disease
- Treatment design
  - 28-day cycles (up to 6 cycles) with dosing on Days 1 and 15
  - Dose escalation cohorts – I-6, II-13, III-6, IV-6, expansion-20



Cycle 2 FDG-PET Response Results

FDG-PET Interpretation[a]	ABVD with brentuximab vedotin N = 22[b]	AVD with brentuximab vedotin N = 26
PET negative, n (%)	22 (100)	24 (92)
PET positive, n (%)	0	2 (8)

a FDG-PET interpretation for Cycle 2 performed by a central review per Deauville criteria with uptake above liver background considered positive

b Three patients did not have results for Cycle 2 and are not included in the summary

- Cycle 2 FDG-PET results were performed and evaluated by central review for 48 patients
  - ABVD cohorts: 22 of 22 negative
  - AVD cohorts: 24 of 26 negative
- Prognostic value of interim PET in these regimens not established

Response Results at End of Front-Line Therapy

Response per Investigator[a]	ABVD with brentuximab vedotin N = 22	AVD with brentuximab vedotin N = 25
Response at end of front-line therapy, n (%)		
Complete remission	21 (95)	24 (96)
Progressive disease	0	1 (4)
Not evaluable due to AEs	1[b] (5)	0

a Assessed using Cheson 2007 b Patient had a Grade 5 event of pulmonary toxicity prior to the end of front-line therapy

- Response results at end of front-line therapy:
  - ABVD cohorts: 21 of 22 CR (95%)
  - AVD cohorts: 24 of 25 CR (96%)
- In addition, 1 patient withdrew consent and 3 patients were lost to follow-up prior to completion of front-line therapy and were not evaluable for response

Conclusions

- Recommended regimen is 1.2 mg/kg brentuximab vedotin every 2 weeks combined with AVD
- AVD combined with brentuximab vedotin appears to be well tolerated with manageable AEs
- Concomitant administration of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity
- CR rate of 96% observed at the end of front-line therapy with brentuximab vedotin combined with AVD

BEACOPP (escalated x4 + baseline x4 cycles) *vs.* ABVD (x8 cycles) in stage III & IV Hodgkin Lymphoma high-risk (IPS ≥3)

Intergroup study 20012
led by the EORTC Lymphoma Group

Patrice Carde, Mathias Karrasch, Catherine Fortpied, Pauline Brice, H. Khaled, D. Caillot, I. Gaillard, S. Bologna, C. Fermé, P. Lugtenburg, F. Morschhauser, I. Aurer, B. Coiffier, R. Meyer, M. Seftel, M. Wolf, B. Glimelius, A. Sureda, Nicolas Mounier

Lysa
THE LYMPHOMA STUDY ASSOCIATION

National Cancer Institute of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe des essais cliniques

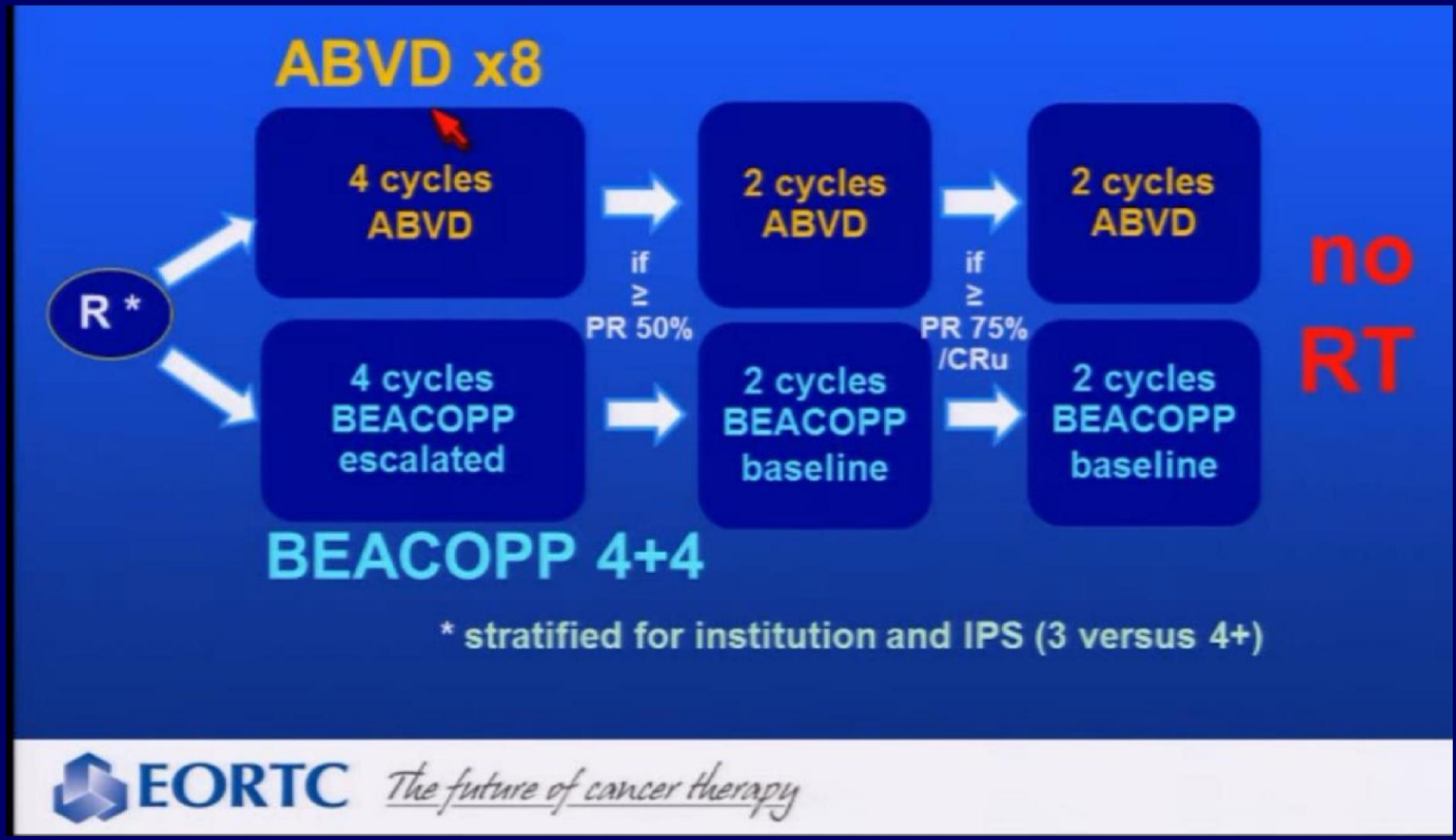
ALLG
LEUKAEMIA & LYMPHOMA

Nordic Lymphoma Group

gelcab

Carde et al. J Clin Oncol 30, 2012 (suppl; abs 8002)

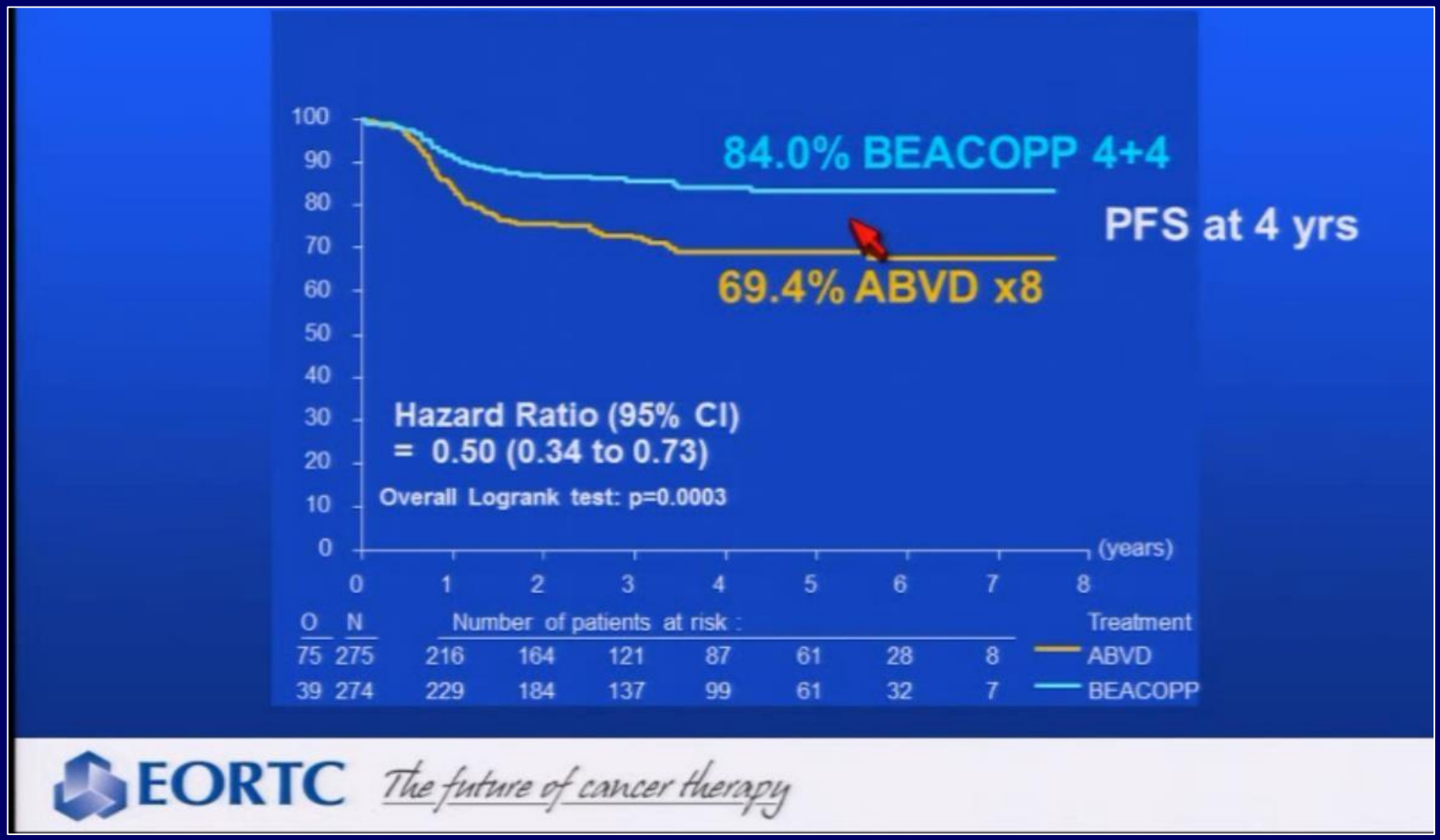
Study Design HL Stages III-IV IPS ≥ 3 Randomized Phase III Trial



Carde et al. J Clin Oncol 30, 2012 (suppl; abs 8002)

Progression-Free Survival

(Not a predefined study endpoint)



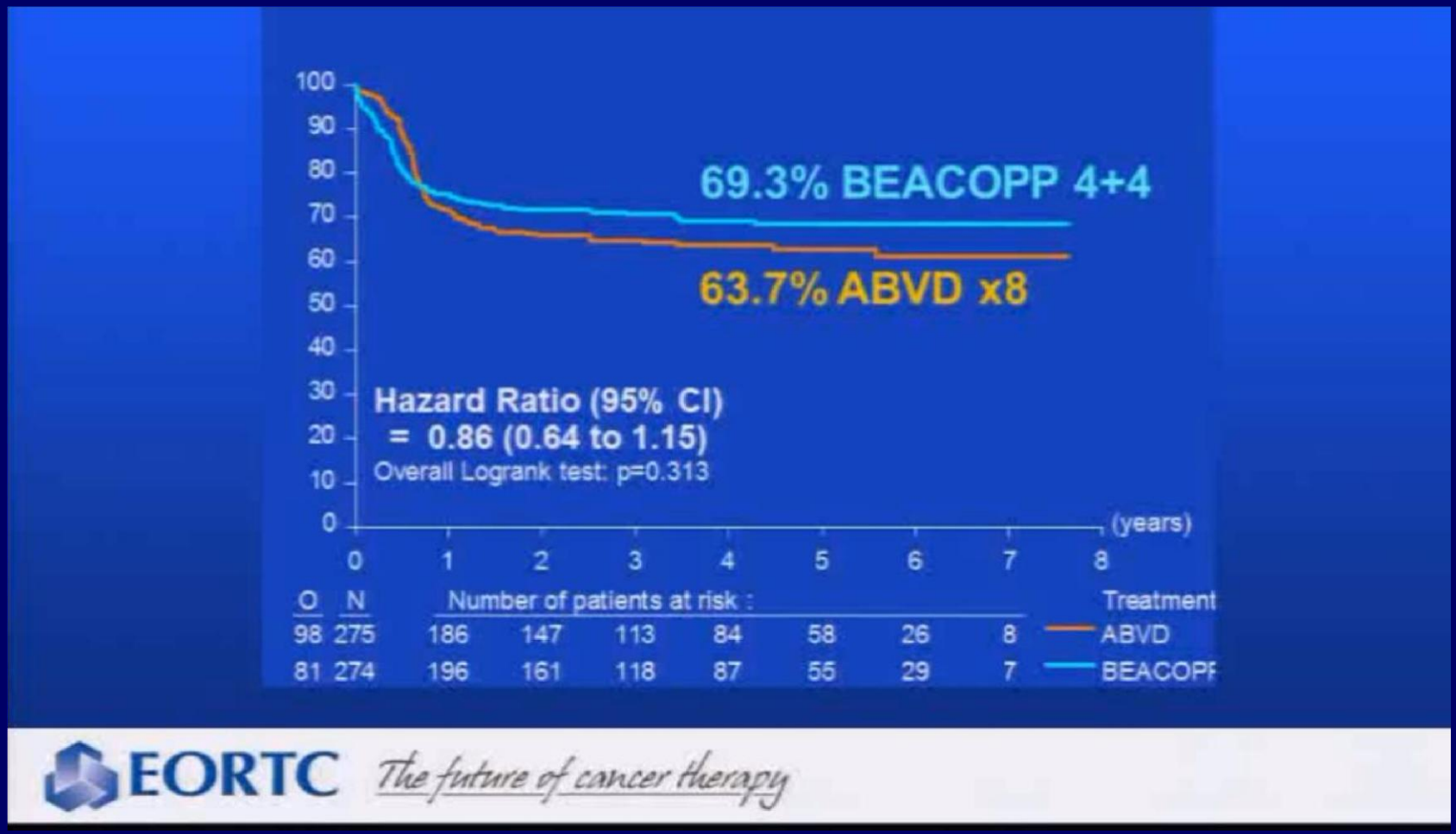
Carde et al. J Clin Oncol 30, 2012 (suppl; abs 8002)

Treatment Discontinuations for Toxicity

	ABVD n = 272	BEACOPP n = 269
Toxicity	**10**	**28**
Respiratory related (not including infections)	**7**	**5**
Hematological		**4**
Infection / meningitis / septicemia		**10**
Septic / toxic shock	**1**	**4**
Hepatic	**2**	**2**
Cardiac		**1**
Neurological		**1**
Allergy to etoposide		**1**

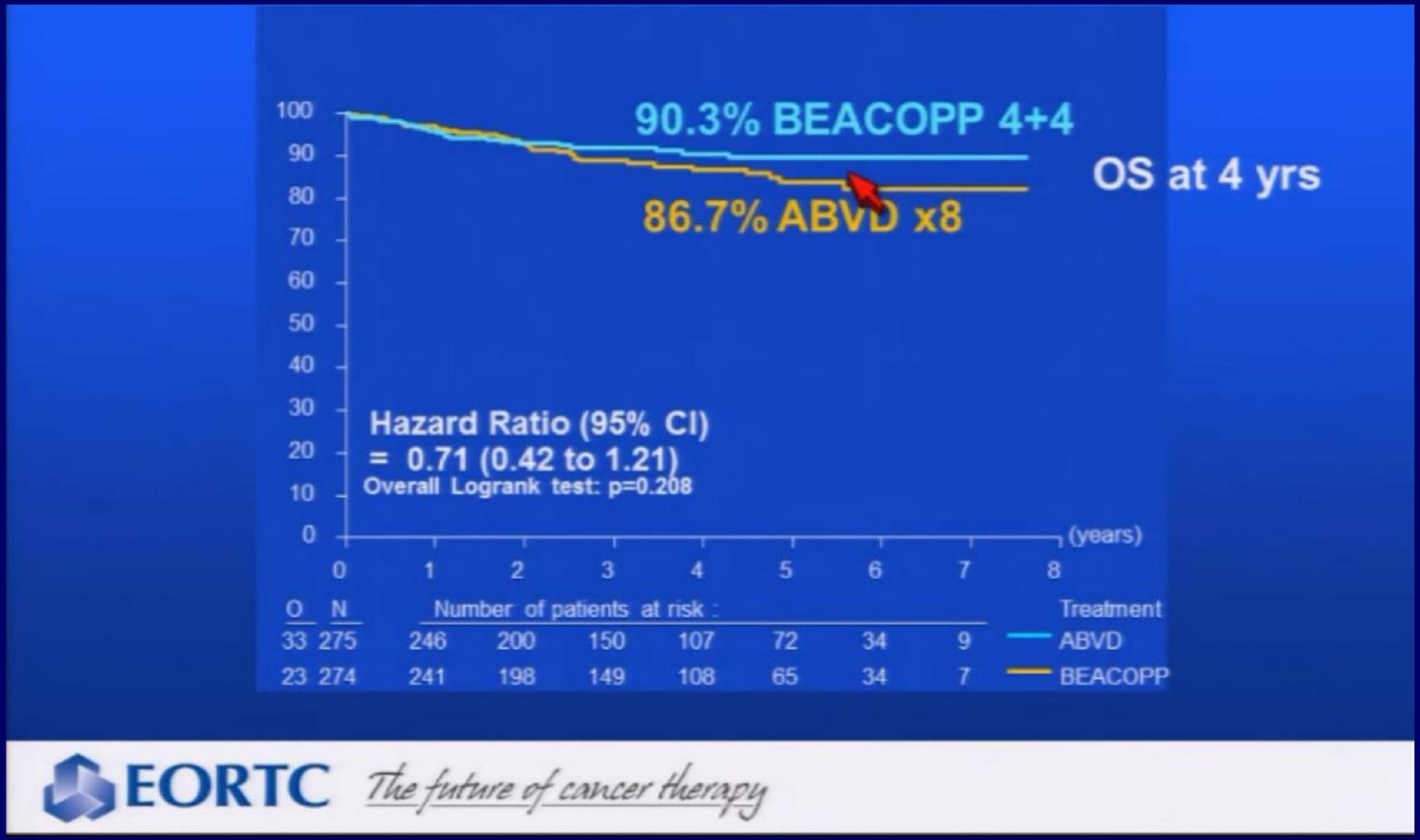
Carde et al. J Clin Oncol 30, 2012 (suppl; abs 8002)

Event-Free Survival



Carde et al. J Clin Oncol 30, 2012 (suppl; abs 8002)

Overall Survival



Carde et al. J Clin Oncol 30, 2012 (suppl; abs 8002)

Conclusions

- EFS (primary endpoint) is similar between treatment arms. However, more progressions / relapses were observed with ABVD while early discontinuations were more frequent with BEACOPP
- In this high-risk group, conventional dose escalation with BEACOPP 4+4 provides a better PFS compared to ABVD, yet not good enough to improve OS
- Additional considerations (treatment burden & cost, fertility issues, risk of relapse, risk of salvage, immediate & late morbidities) may guide physician / patient decisions toward ABVD or BEACOPP, which currently may share the claim for “current standard

Carde et al. J Clin Oncol **of care”**30, 2012 (suppl; abs 8002)

BOTTOM LINE

- **3 cycles of ABVD without IFRT has an excellent outcome for favorable stage IA/IIA patients who are at the conclusion of treatment.**
- **Disease control may be slightly better for CMT as compared with CT (3%-7%), although a survival difference is unlikely (long-term effects of IF RT unknown).**
- **In retrospective analysis, survival of HL patients relapsed after autologous SCT superior with BV compared with treatments prior to BV availability. Role of BV in autologous SCT is under investigation.**
- **BV + AVD results in PET CR after 2 cycles and at completion of treatment comparable to ABVD for patients with stage III/IV HL.**

Phase III comparison has opened (C25003).

BOTTOM LINE

A GENERAL SURVEY OF STUDIES COMPARING BEACOPP TO ABVD ALMOST ALL CONSISTENTLY SHOW A SUPERIOR PROGRESSION FREE SURVIVAL FOR BEACOPP BUT LONG TERM SURVIVAL SEEMS TO BE COMPARABLE DUE TO THE TOXICITY OF BEACOPP.

AS WITH LIMITED STAGE DISEASE, CAN INTERIM PET SCANS BE USED TO SELECT OUT THOSE PATIENTS NOTNEEDING MORE AGGRESSIVE THERAPY AND THEREBY AVOID ALL THE UNNECESSARY TOXICITY OF BEACOPP? IS GENETIC INSTABILITY ADVANCED BY DR DIEHL TRULY OPERATIVE EVEN AS EARLY AS (A PET

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Hodgkin Lymphoma: Latest Concepts

MANY THANKS TO DR. DAVID STRAUSS FOR ALLOWING US TO DISPLAY MANY OF HIS SLIDES.