Combinaciones Quimioterápicas en Hemopatías Malignas. Linfoma de Hodgkin

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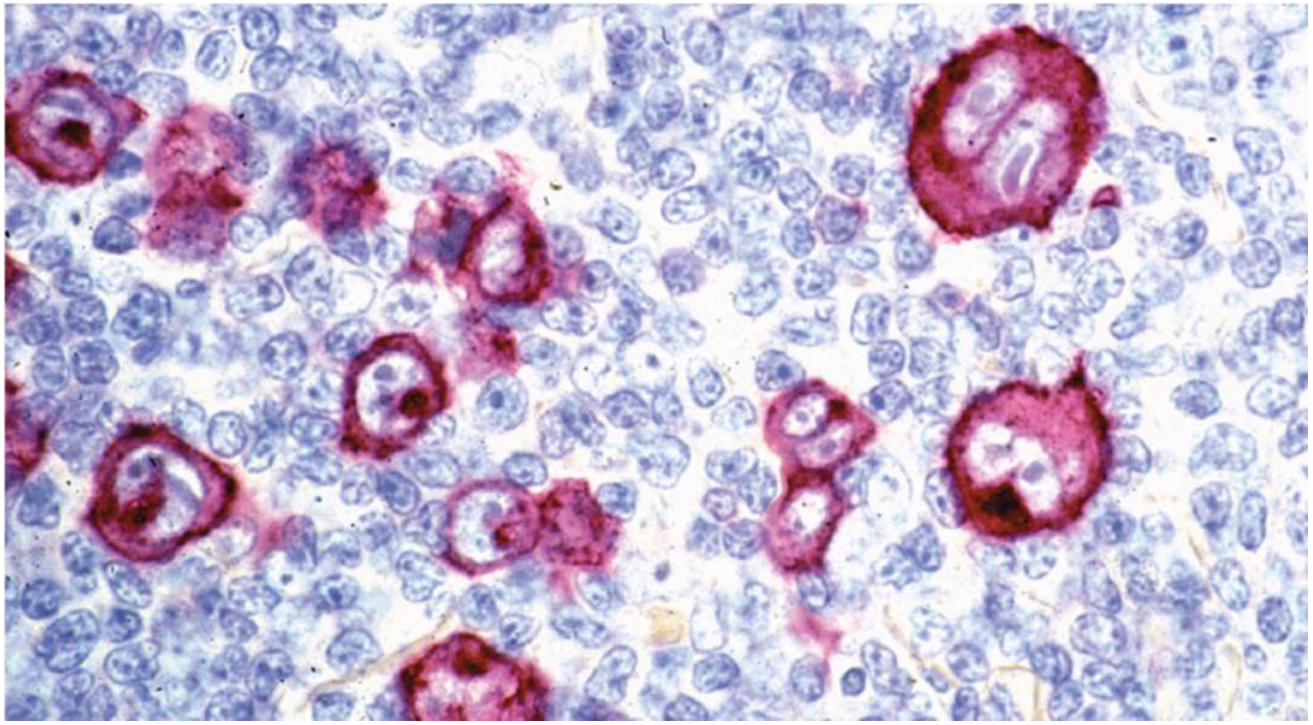
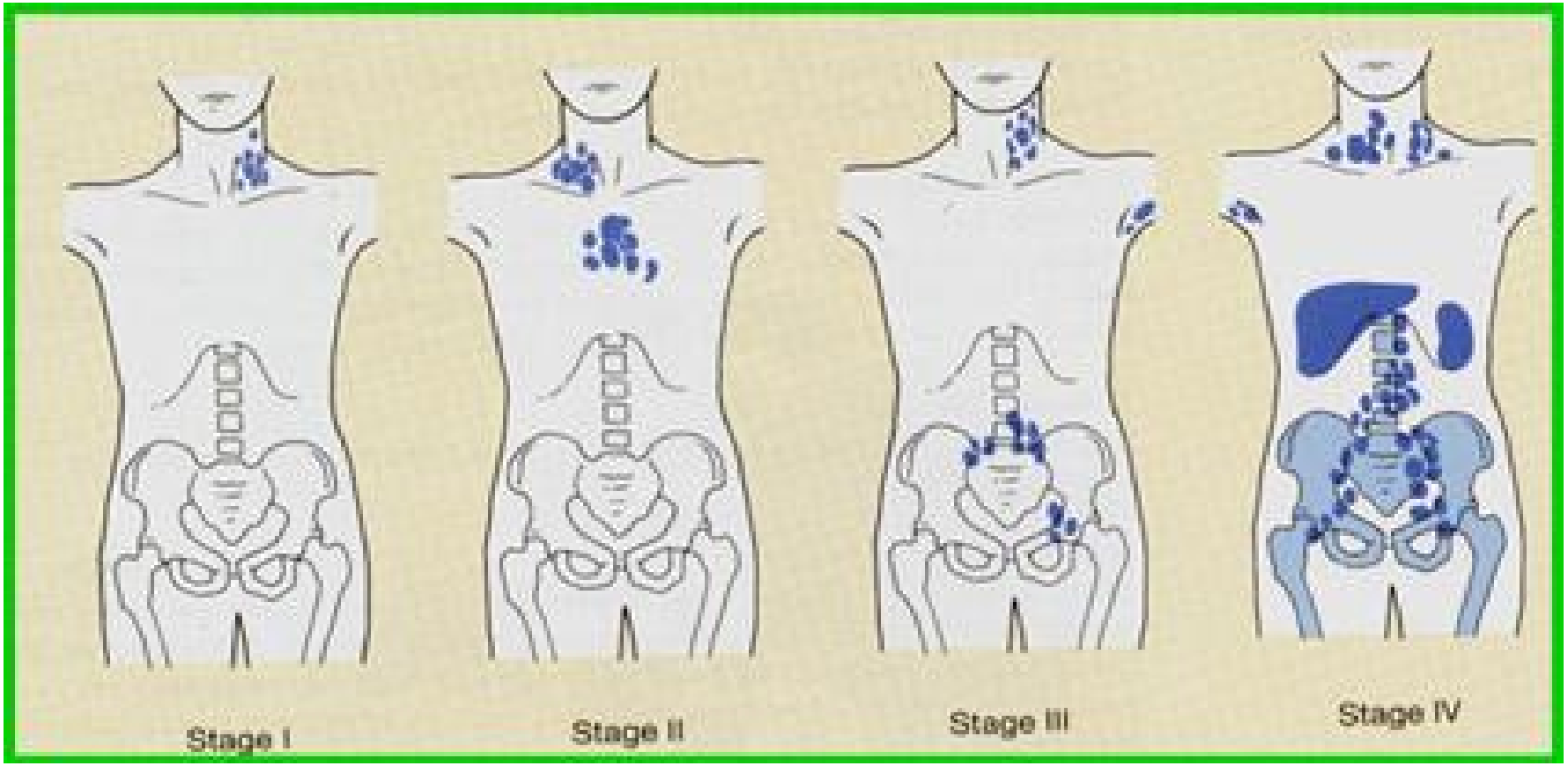
Tratamiento Antineoplásico en Hematología: Mucho que Aprender, Mucho que Recordar

Madrid, Octubre 2014

Hodgkin's Lymphoma. CD30 Expression



Ann Arbor Classification



Early Stages

Advanced Stages

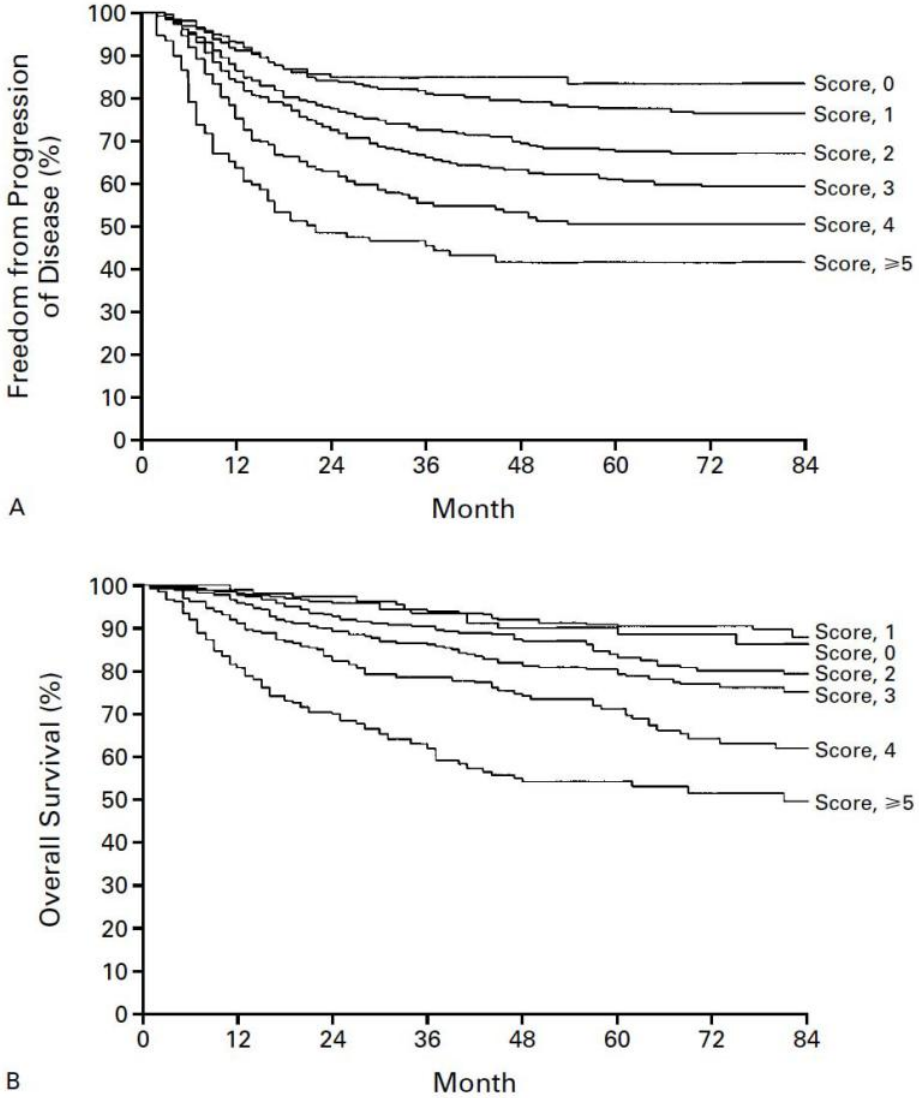
Early Stages. Risk Factors

	EORTC	GHSG
Risk Factors	a) Large mediastinal mass b) Age ≥ 50 years c) ESR ≥ 50 without B-symptoms or ≥ 30 with B-symptoms	a) Large mediastinal mass b) Extranodal disease c) ESR ≥ 50 without B-symptoms or ≥ 30 with B-symptoms d) ≥ 3 nodal areas
Favorable	CS I-II (supradiaphragmatic) without risk factors	CS I-II without risk factors
Unfavorable	CS I-II (supradiaphragmatic) with ≥ 1 risk factors	CS I or CS IIA with ≥ 1 risk factors CS IIB with c) or d) without a) and b)

Advanced Stages. Hasenclever Index

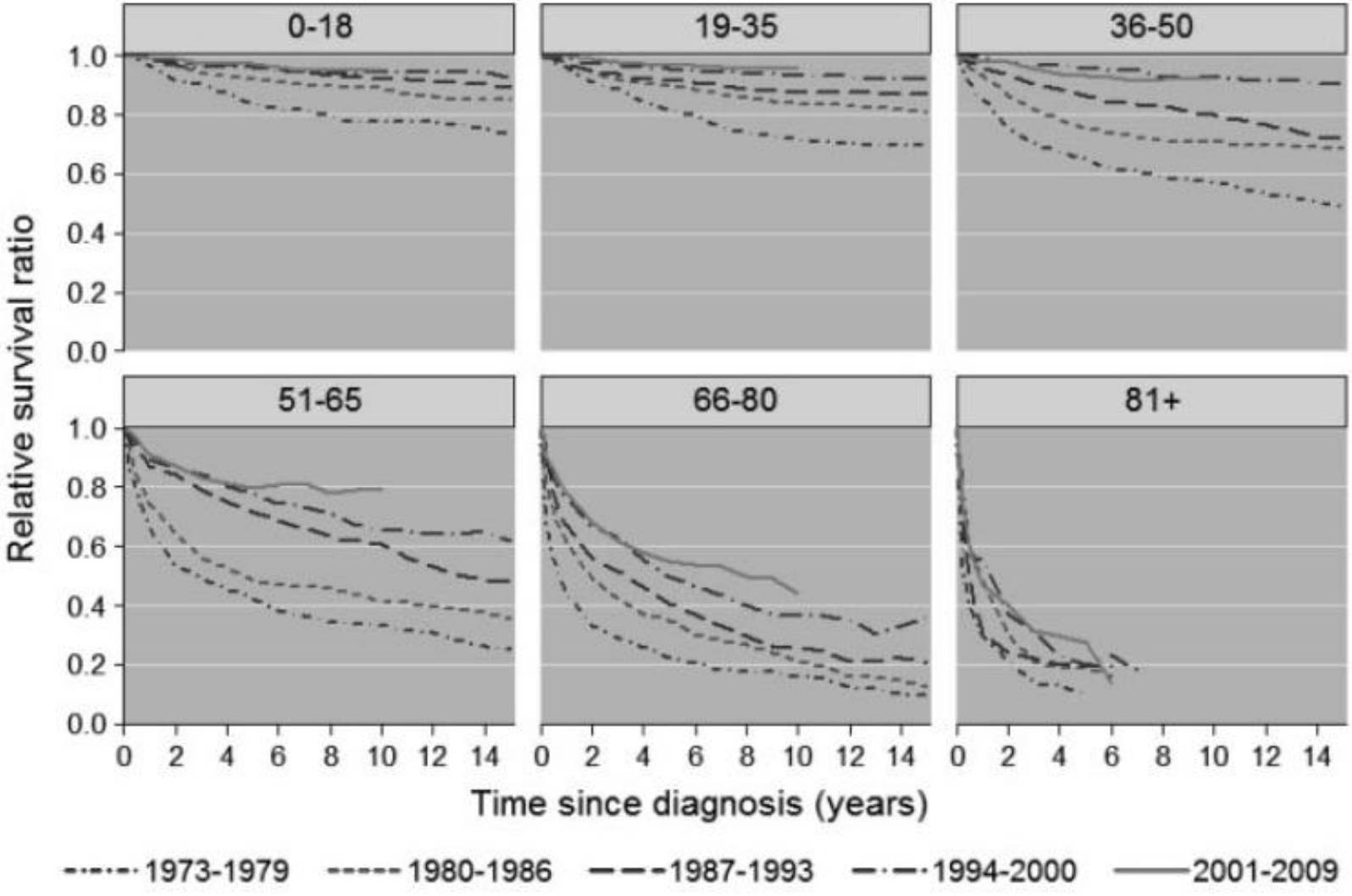
TABLE 2. THE FINAL COX REGRESSION MODEL.*

FACTOR	LOG HAZARD RATIO	P VALUE	RELATIVE RISK
Serum albumin, <4 g/dl	0.40±0.10	<0.001	1.49
Hemoglobin, <10.5 g/dl	0.30±0.11	0.006	1.35
Male sex	0.30±0.09	0.001	1.35
Stage IV disease	0.23±0.09	0.011	1.26
Age, ⩾45 yr	0.33±0.10	0.001	1.39
White-cell count, ⩾15,000/mm³	0.34±0.11	0.001	1.41
Lymphocyte count, <600/mm³ or <8% of white-cell count	0.31±0.10	0.002	1.38



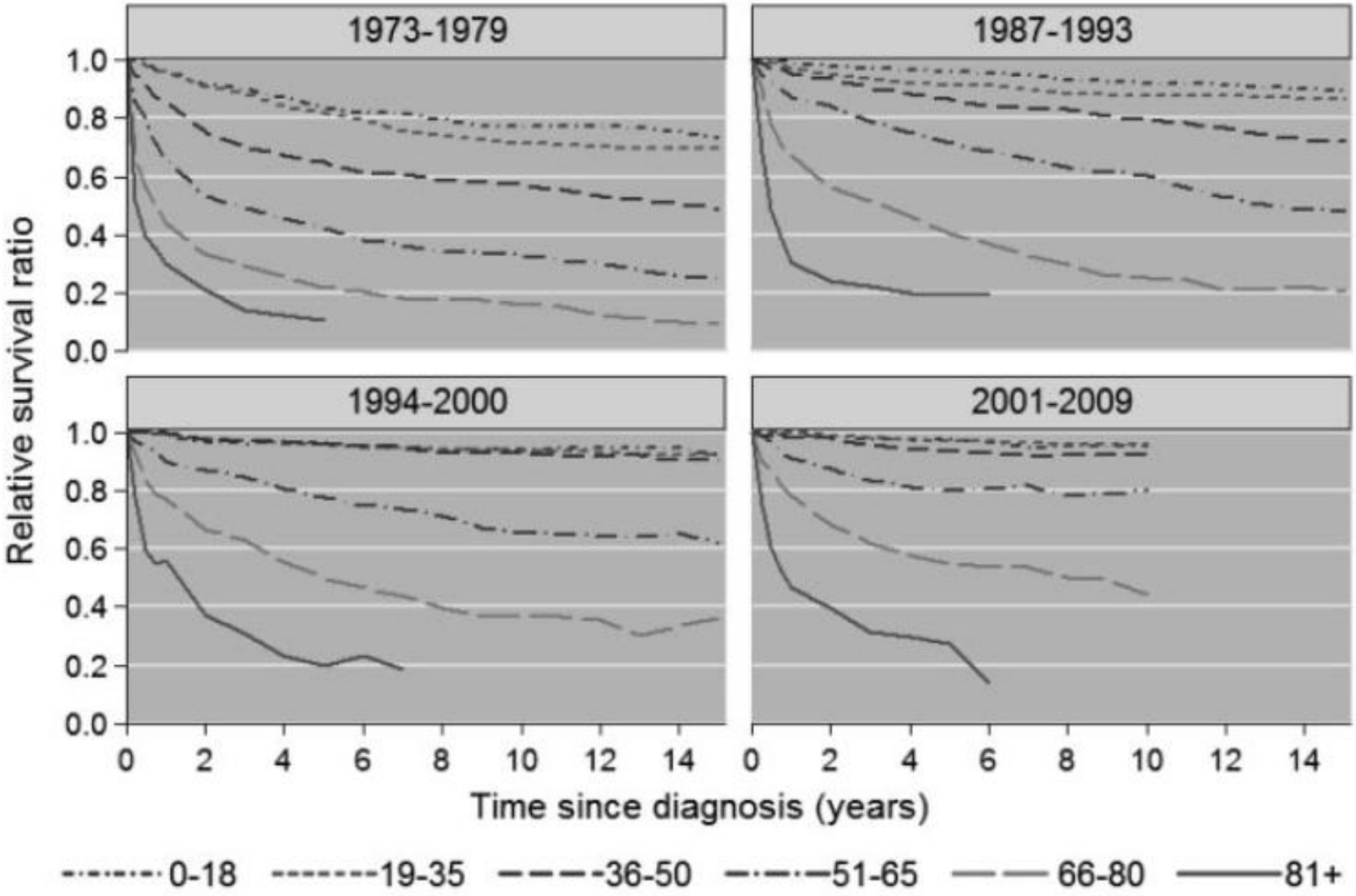
Hasenclever and Diehl, NEJM 1998

Outcome of Patients with HL has Improved Over Time



Sjöberg et al, Blood, 2012

Outcome of Patients with HL has Improved Over Time



Sjöberg et al, Blood, 2012

Quimioterapia MOPP

- Mostaza nitrogenada 6 mg/m^2 ev (días 1 y 8) (se sustituye por ciclofosfamida 650 mg/m^2 ev, días 1 y 8 en el esquema COPP)
- Vincristina 1,4 mg/m^2 ev (días 1 y 8)
- Procarbacina 100 mg/m^2 po (días 1-14)
- Prednisona 40 mg/m^2 po (días 1-14)

Cada 28 días

De Vita et al. Ann Intern Med 1970

Quimioterapia ABVD

- Adriamicina 25 mg/m^2 ev (días 1 y 15)
- Bleomicina 10 mg/m^2 ev (días 1 y 15)
- Vinblastina 6 mg/m^2 ev (días 1 y 15)
- Dacarbacina 375 mg/m^2 ev (días 1 y 15)

Cada 28 días

ABVD significativamente superior a MOPP en SLP (80,8% vs 62,8%, p = 0,002), SLR (87,7% vs 77,2%, p = 0,06) y SG (77,4% vs 67,9%, p = 0,03)

Santoro et al, J Clin Oncol, 1987

CHEMOTHERAPY OF ADVANCED HODGKIN'S DISEASE WITH MOPP, ABVD, OR MOPP ALTERNATING WITH ABVD

George P. Canellos, M.D., James R. Anderson, Ph.D., Kathleen J. Propert, Sc.D., Nis Nissen, M.D., M. Robert Cooper, M.D., Edward S. Henderson, M.D., Mark R. Green, M.D., Arlan Gottlieb, M.D.,* and Bruce A. Peterson, M.D.

Abstract *Background and Methods.* MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) has been the standard treatment for Hodgkin's disease for almost 20 years. In a randomized, multicenter trial, we compared three regimens of primary systemic therapy for newly diagnosed advanced Hodgkin's disease in Stages $IIIA_2$, IIIB, and IVA or IVB: (1) MOPP alone given for 6 to 8 cycles, (2) MOPP alternating with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) for 12 cycles, and (3) ABVD alone for 6 to 8 cycles. Patients in a first relapse after radiation therapy were eligible. No additional radiation therapy was given. Patients who did not have a complete response or who had a relapse with either MOPP alone or ABVD alone were switched to the opposite regimen.

Results. Of 361 eligible patients, 123 received MOPP, 123 received MOPP alternating with ABVD, and 115 received ABVD alone. The patients were stratified according to age, stage, previous radiation, histologic features, and performance status. The overall response rate was 93 percent, with complete responses in 77 percent: 67 percent in the MOPP group, 82 percent in the ABVD group, and 83 percent in the MOPP–ABVD group ($P = 0.006$ for the comparison of MOPP with the other two regimens, both of which contained doxorubicin). The rates of failure-free survival at five years were 50 percent for MOPP, 61 percent for ABVD, and 65 percent for MOPP–ABVD. Age, stage (III vs. IV), and regimen influenced failure-free survival significantly. Overall survival at five years was 66 percent for MOPP, 73 percent for ABVD, and 75 percent for MOPP–ABVD ($P = 0.28$ for the comparison of MOPP with the doxorubicin regimens). MOPP had more severe toxic effects on bone marrow than ABVD and was associated with greater reductions in the prescribed dose.

Conclusions. In this trial, ABVD therapy for 6 to 8 months was as effective as 12 months of MOPP alternating with ABVD, and both were superior to MOPP alone in the treatment of advanced Hodgkin's disease. ABVD was less myelotoxic than MOPP or ABVD alternating with MOPP. (N Engl J Med 1992;327:1478-84.)

MOPP *vs* ABVD *vs* MOPP-ABVD

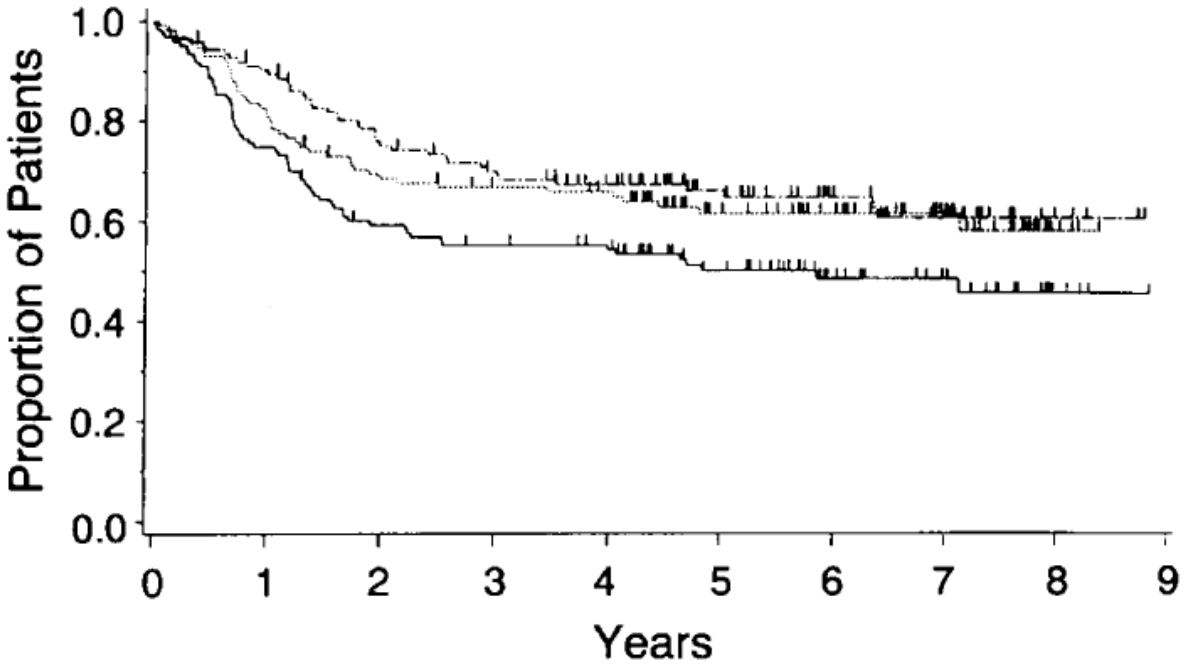
Table 3. Response to Treatment of Patients with Advanced Hodgkin's Disease, According to Regimen.

Type of Response	MOPP	ABVD	MOPP–ABVD
No. of patients	123	115	123
		no. (% of group)	
Complete response	83 (67)*	94 (82)*	102 (83)*
Partial response	29 (24)	15 (13)	12 (10)
Improvement	4 (3)	3 (3)	7 (6)
No response or progression	5 (4)	2 (2)	0 (0)
No evaluation	2 (2)	1 (1)	2 (2)

*P = 0.006 for MOPP as compared with ABVD and MOPP–ABVD.

Canellos et al, NEJM 1992

MOPP *vs* ABVD *vs* MOPP-ABVD



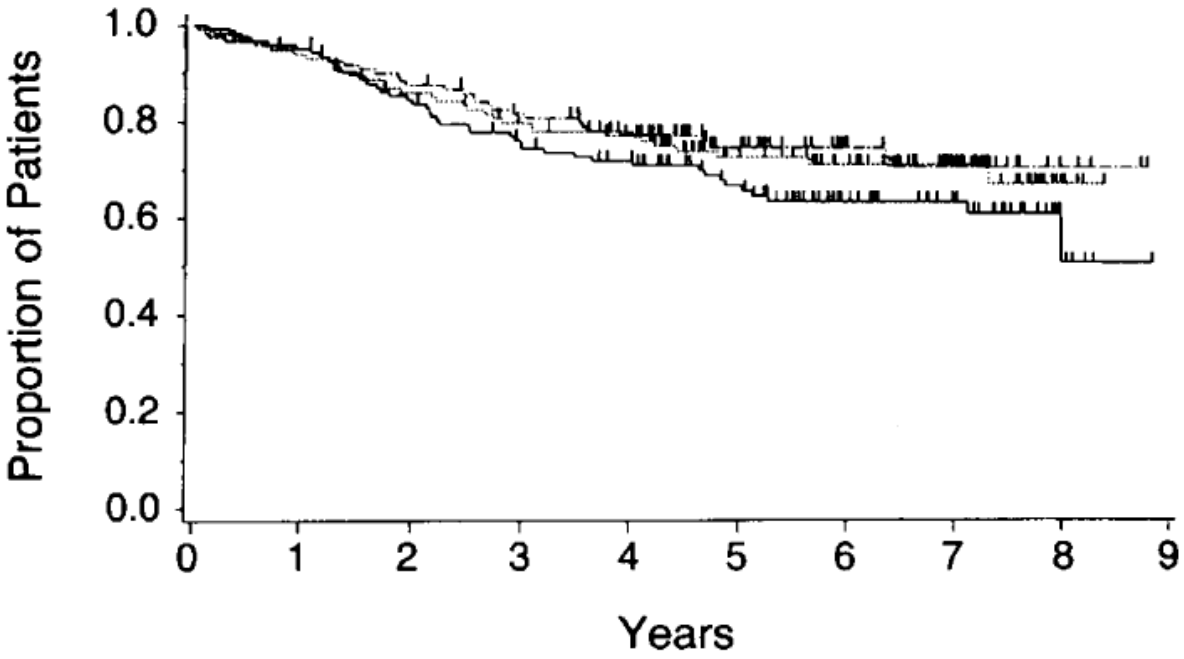
Regimen	No. of Patients	No. (%) of Treatment Failures	Median Survival
—— MOPP	123	62 (50)	4.84
····· ABVD	115	44 (38)	None
-·-·- MOPP–ABVD	123	43 (35)	None
All	361	149 (41)	—

Figure 1. Failure-free Survival According to Primary Chemotherapeutic Regimen.

P = 0.02 for the difference between MOPP, ABVD, and MOPP–ABVD. In the column for median years of survival, none indicates that the median survival has not yet been reached.

Canellos et al, NEJM 1992

MOPP *vs* ABVD *vs* MOPP-ABVD



	Regimen	No. of Patients	No. (%) of Treatment Failures	Median Survival
——	MOPP	123	44 (36)	None
·····	ABVD	115	32 (28)	None
-·-·-	MOPP–ABVD	123	31 (25)	None
	All	361	107 (30)	—

Figure 2. Overall Survival According to Primary Chemotherapeutic Regimen.

No significant differences between the three regimens were noted (P = 0.28). In the column for median years of survival, none indicates that the median survival has not yet been reached.

Canellos et al, NEJM 1992

MOPP *vs* ABVD *vs* MOPP-ABVD

Table 4. Toxicity of Induction Therapy.

Type of Toxicity	MOPP	ABVD	MOPP–ABVD	P Value
	*percent of patients**			
Neutropenia	47, 21, 1	18, 3, 0	53, 28, 0	<0.001
Thrombocytopenia	36, 15, 1	2, 3, 0	28, 13, 0	<0.001
Anemia	31, 12, 0	5, 0, 0	25, 8, 0	<0.001
Infection	11, 1, 1	2, 0, 0	12, 2, 1	<0.001
Peripheral neuropathy	8, 0, 0	1, 0, 0	2, 0, 0	<0.001
Alopecia	5, 0, 0	24, 0, 0	14, 0, 0	<0.001
Nausea/vomiting	28, 0, 0	33, 0, 0	39, 0, 0	0.09
Pulmonary	3, 1, 0	4, 0, 3	3, 0, 1	0.34

*The first number in each entry denotes the percentage with severe toxicity, the second the percentage with life-threatening toxicity, and the third the percentage with fatal toxicity. Severe toxicity was defined as a granulocyte count ranging from 0.5 to 1.0×10^3 per cubic millimeter and a platelet count ranging from 25 to 50×10^3 per cubic millimeter. Any counts below these were considered to constitute life-threatening toxicity.

Canellos et al, NEJM 1992

Advanced Stages. Hasenclever Index

TABLE 2. THE FINAL COX REGRESSION MODEL.*

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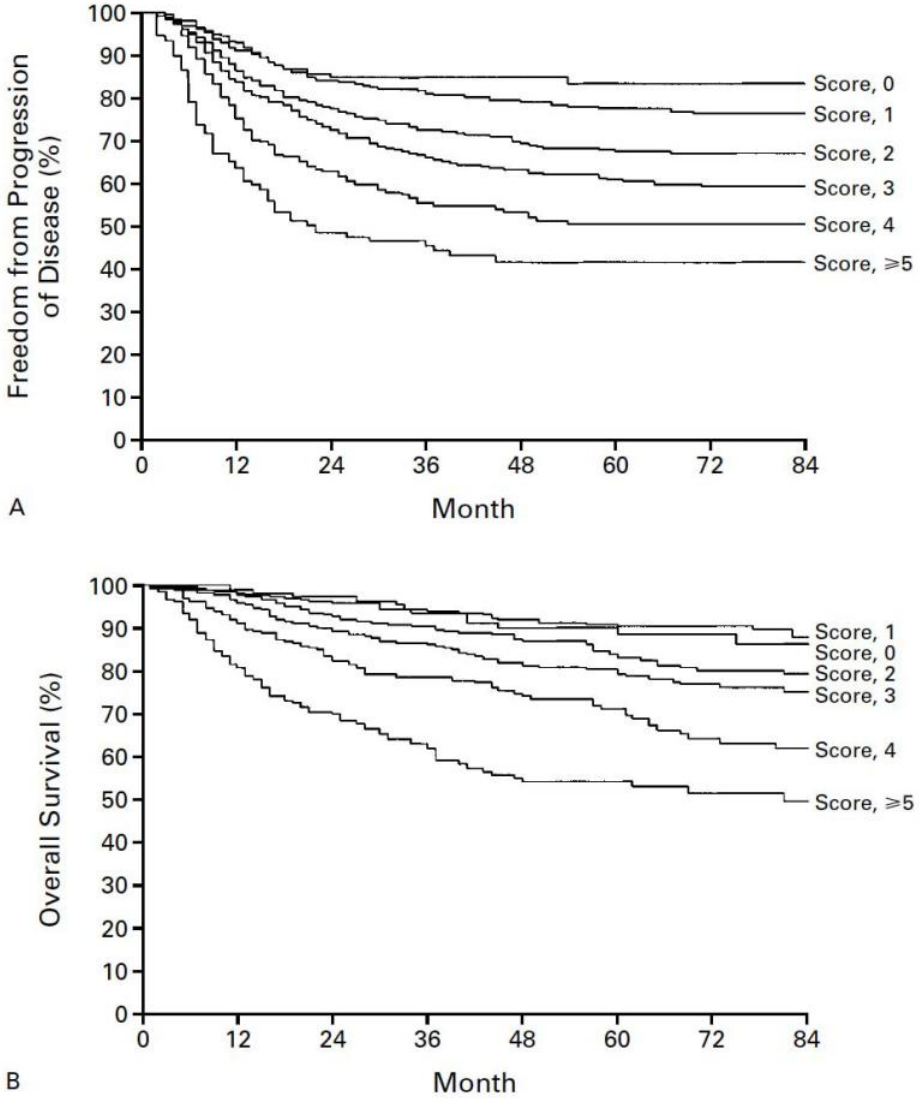


Hasenclever and Diehl, NEJM 1998

El Esquema BEACOPP

Table 1. Planned Regimens of Cyclophosphamide, Vincristine, Procarbazine, Prednisone, Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine (COPP-ABVD) and Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone (BEACOPP).

Drug	COPP-ABVD		Standard BEACOPP		Increased-Dose BEACOPP	
	Single Dose	Days Given*	Single Dose	Days Given†	Single Dose	Days Given†
	mg/m²		*mg/m²*		*mg/m²*	
Bleomycin	10	29, 43	10	8	10	8
Etoposide	—	—	100	1–3	200	1–3
Doxorubicin	25	29, 43	25	1	35	1
Cyclophosphamide	650	1, 8	650	1	1200	1
Vincristine	1.4‡	1, 8	1.4‡	8	1.4‡	8
Procarbazine	100	1–14	100	1–7	100	1–7
Prednisone	40	1–14	40	1–14	40	1–14
Vinblastine	6	29, 43	—	—	—	—
Dacarbazine	375	29, 43	—	—	—	—

* The days were counted from the beginning of the double cycle of COPP-ABVD. The regimen was repeated on day 57.
† The regimen was repeated on day 22.
‡ The absolute dose of vincristine was limited to 2.0 mg.

Diehl et al, NEJM 2003

El Esquema BEACOPP

Table 3. Acute Adverse Effects of Chemotherapy.*

Adverse Effect	COPP-ABVD	Standard BEACOPP	Increased-Dose BEACOPP
		percent	
Leukopenia			
Grade 3	52	36	8
Grade 4	19	37	90
Thrombocytopenia			
Grade 3	4	6	23
Grade 4	2	3	47
Anemia			
Grade 3	4	16	51
Grade 4	1	1	15
Infection			
Grade 3	2	13	14
Grade 4	1	3	8
Mucositis of grade 3 or 4	1	2	8
Respiratory tract effects of grade 3 or 4	2	5	4
Nausea of grade 3 or 4	20	12	20
Digestive tract effects of grade 3 or 4	3	2	4
Neurologic effects of grade 3 or 4	4	5	4
Skin effects of grade 3 or 4	1	1	3
Pain of grade 3 or 4	2	3	9
Hair loss of grade 3 or 4	36	75	79

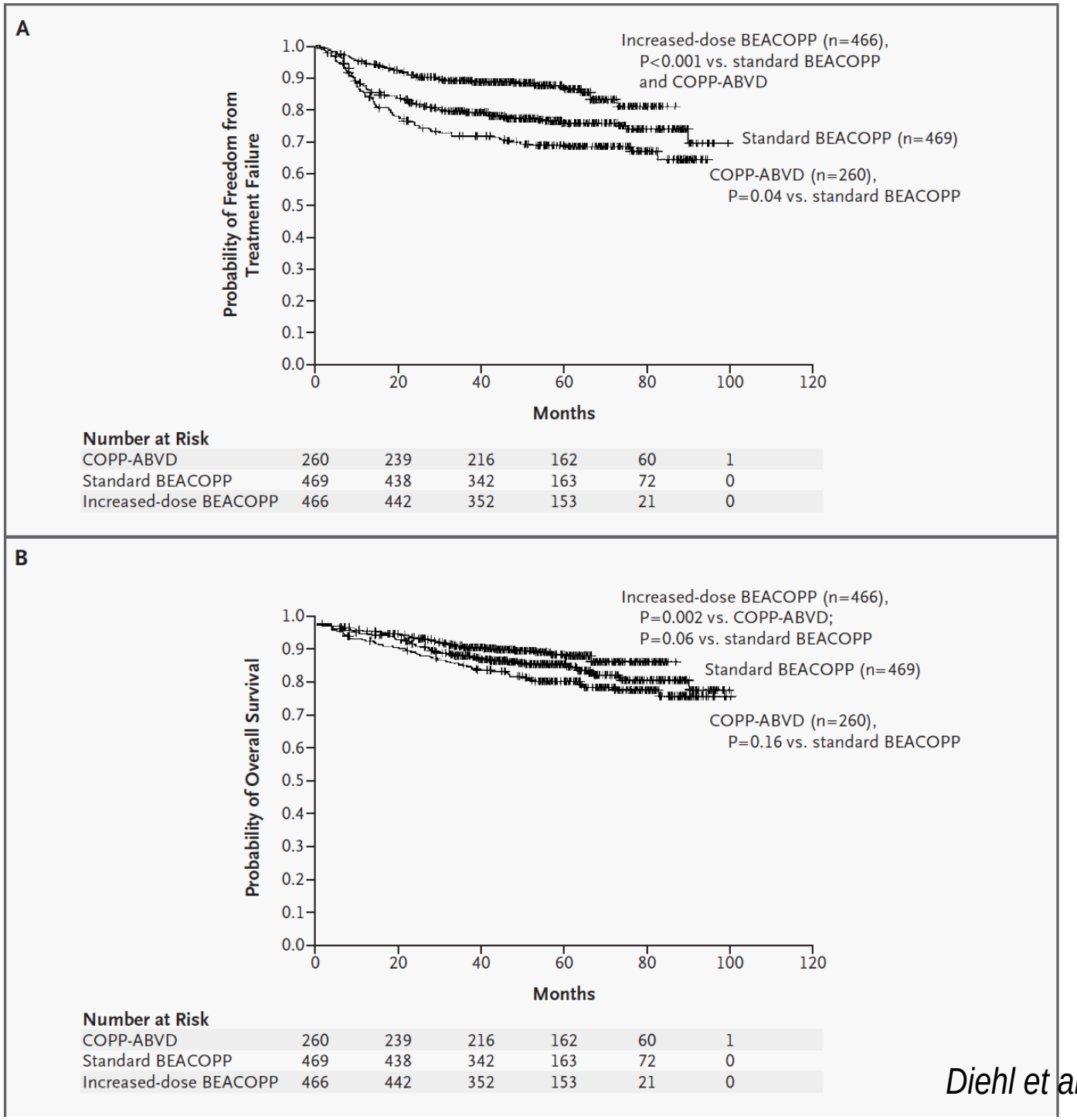
Diehl et al, NEJM 2003

El Esquema BEACOPP

Table 4. Outcome of Treatment and Five-Year Survival Rates.*

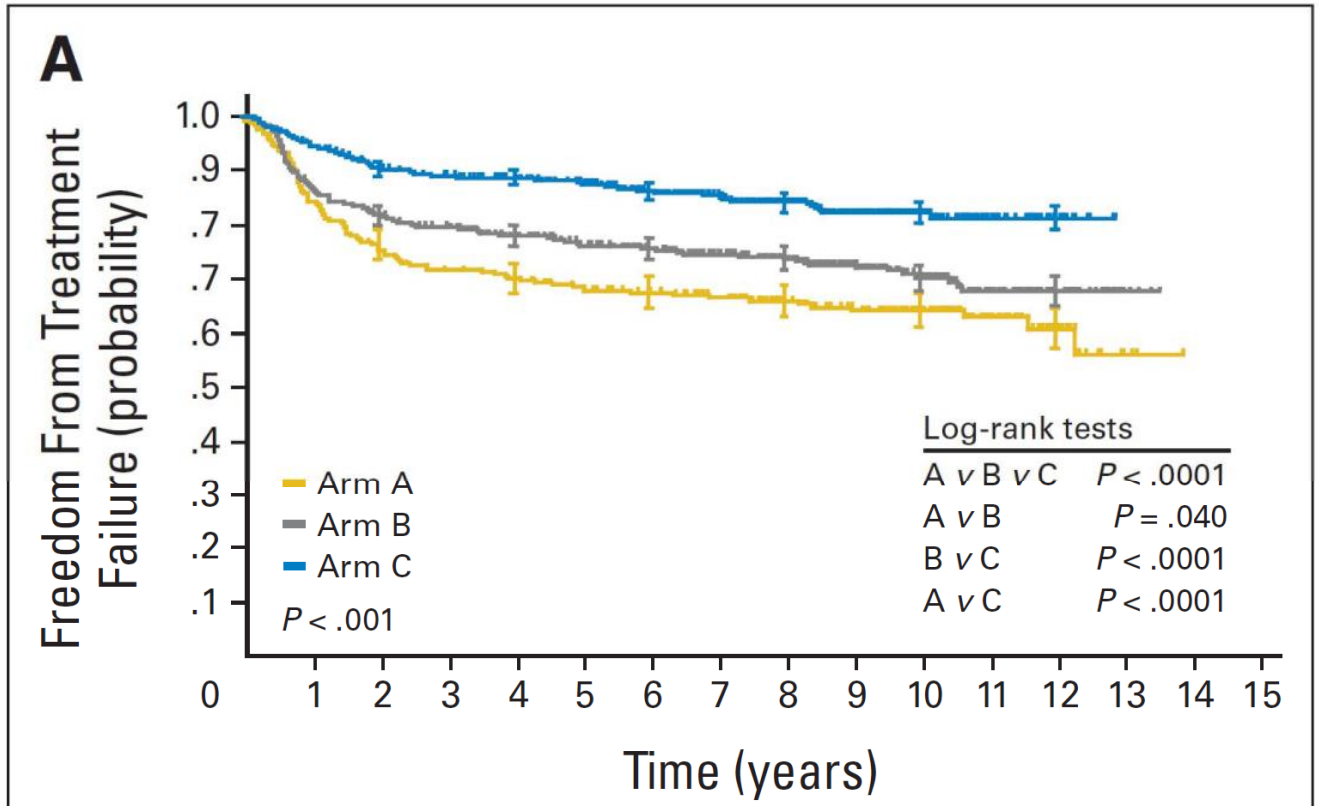
Variable	COPP-ABVD (N=260)	Standard BEACOPP (N=469)	Increased-Dose BEACOPP (N=466)
		percent (95% CI)	
Complete remission	85 (80–89)	88 (85–91)	96 (93–97)
Early progression	10 (7–15)	8 (5–10)	2 (1–4)†‡
Freedom from treatment failure at 5 yr	69 (63–75)	76 (72–80)§	87 (83–91)†‡
Overall survival at 5 yr	83 (78–87)	88 (85–91)	91 (88–94)¶‖

Diehl et al, NEJM 2003



Diehl et al, NEJM 2003

COPP-ABVD vs BEACOPP Escalado vs BEACOPP Basal. Seguimiento a largo plazo del Protocolo HD9

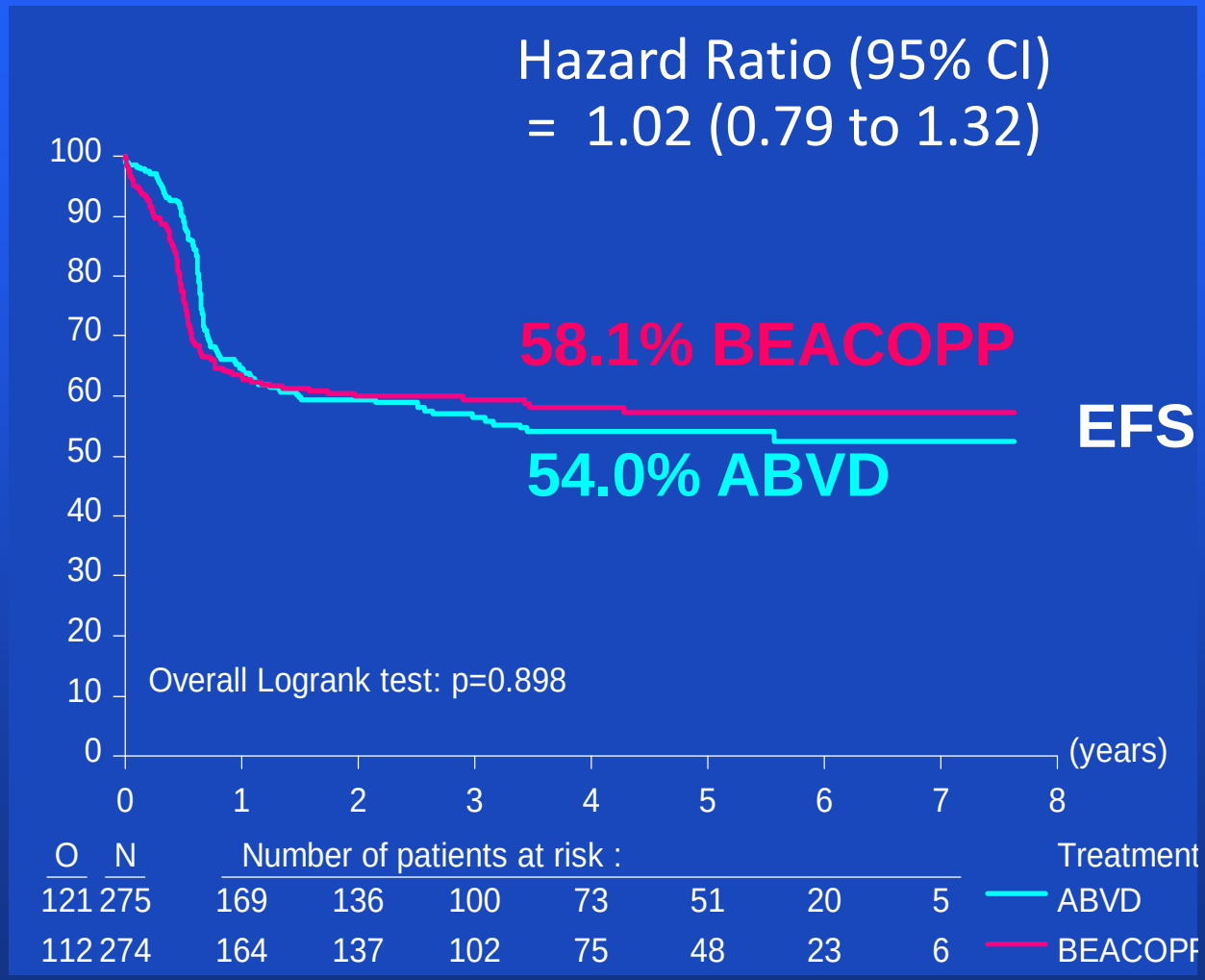


No. of patients at risk

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

Engert el al, JCO, 2009

primary endpoint – Event-Free Survival

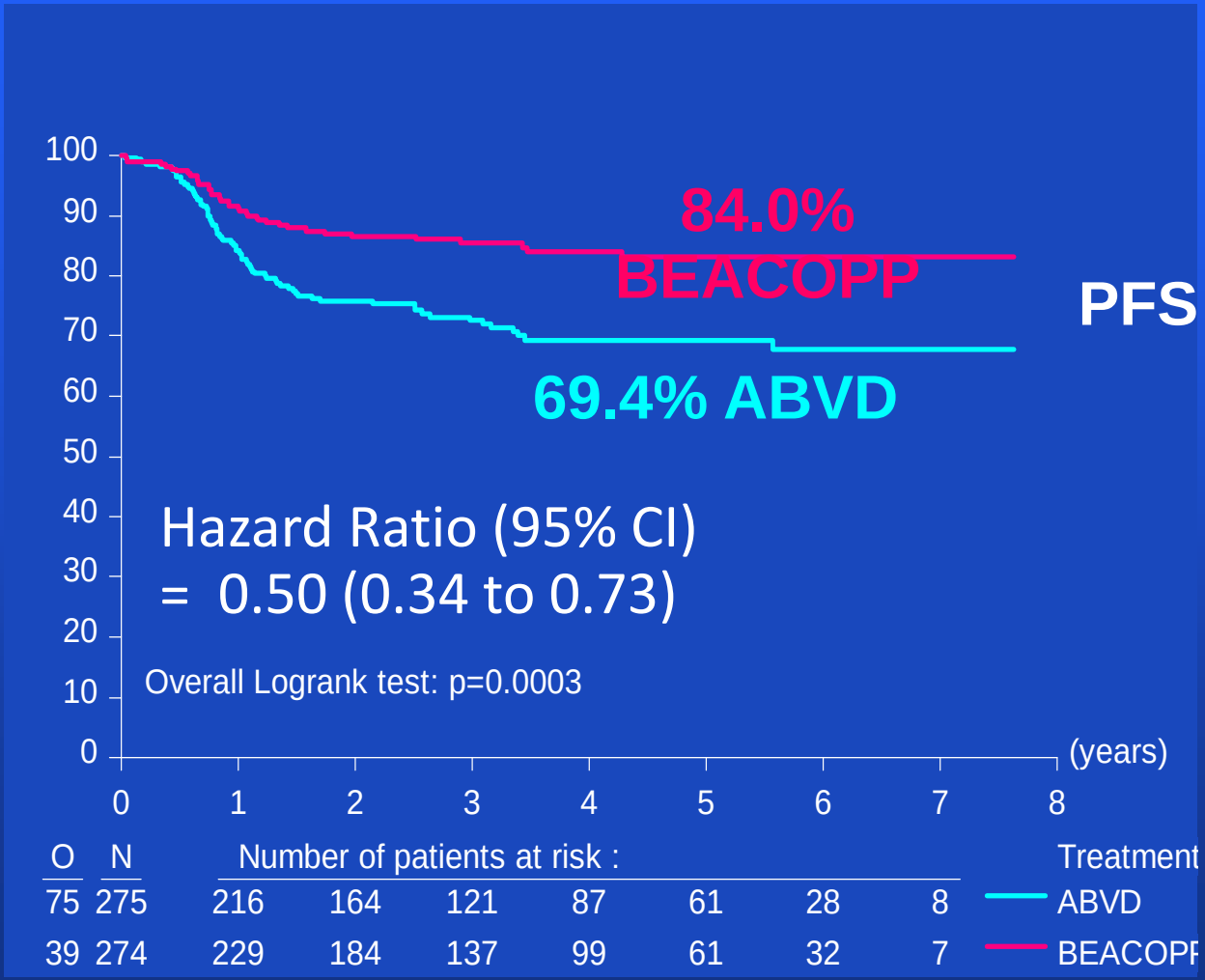


EFS at 4 yrs

EORTC *The future of cancer therapy*

Progression Free Survival*

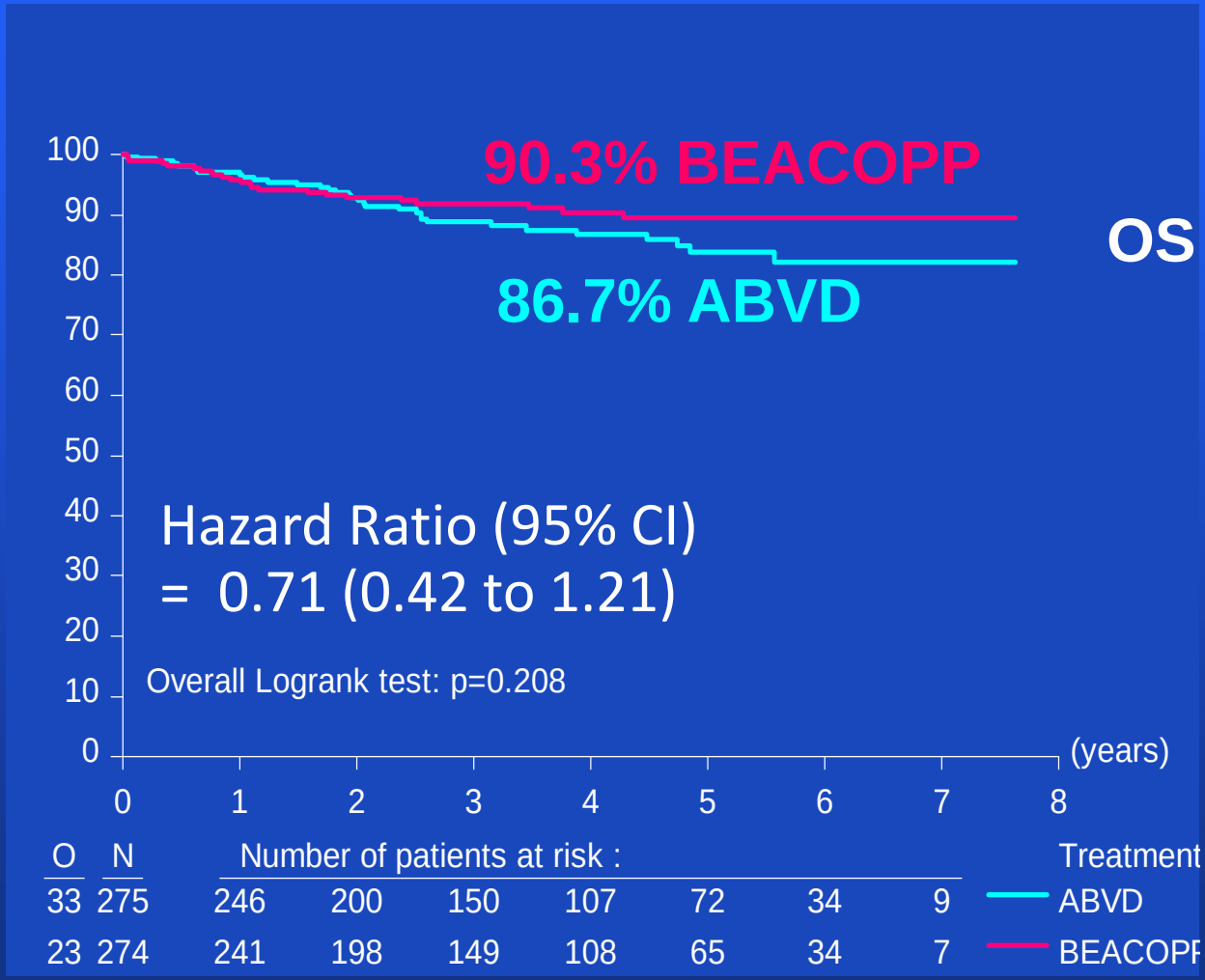
*** not defined explicitly as an endpoint of the study**



PFS at 4 yrs

EORTC *The future of cancer therapy*

Overall Survival



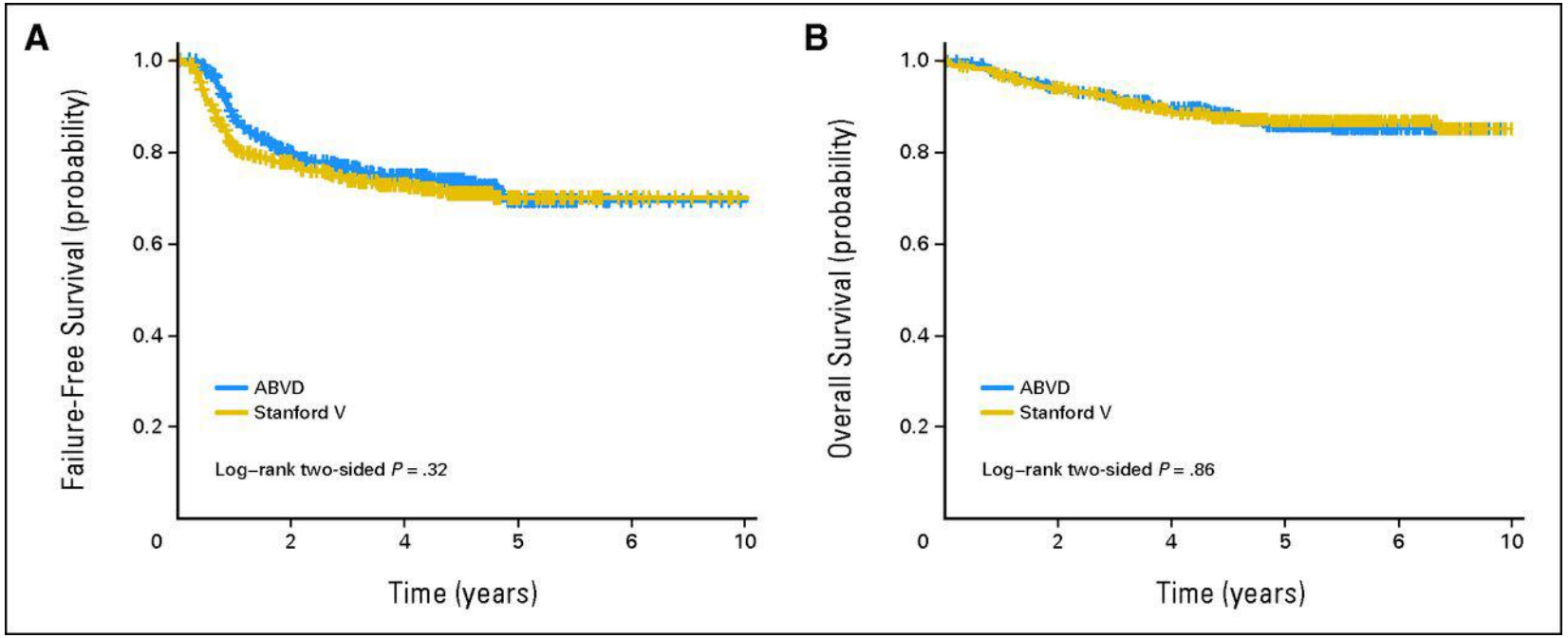
OS at 4 yrs

Quimioterapia Stanford V

- Doxorrubicina 25 mg/m^2 ev (días 1, 15, 29, 43, 57, 71)
- Vinblastina 6 mg/m^2 ev (días 1, 15, 29, 43, 57, 71)
- Mostaza nitrogenada 6 mg/m^2 ev (días 1, 29, 57)
- Vincristina 1,4 mg/m^2 ev (días 8, 22, 36, 50, 64, 78)
- Bleomicina 5 mg/m^2 ev (días 8, 22, 36, 50, 64, 78)
- Etopósido 60 mg/m^2 ev (días 15, 43, 71)
- Prednisona 40 mg/m^2 po (alternos durante 12 semanas)

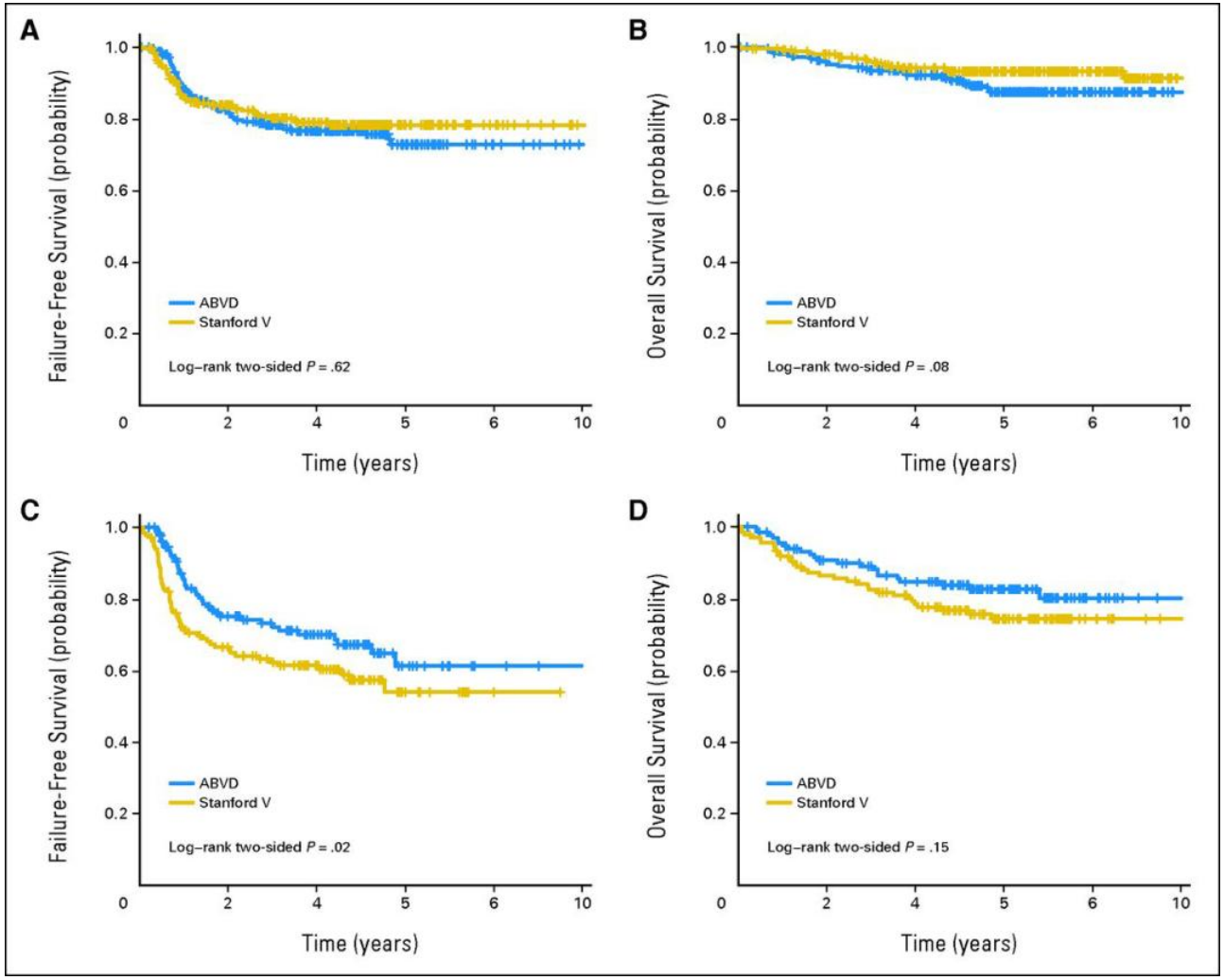
Horning et al. JCO 2002

(A) Failure-free (P = .32) and (B) overall survival (P = .86) are shown for all patients, showing no difference between the two arms.



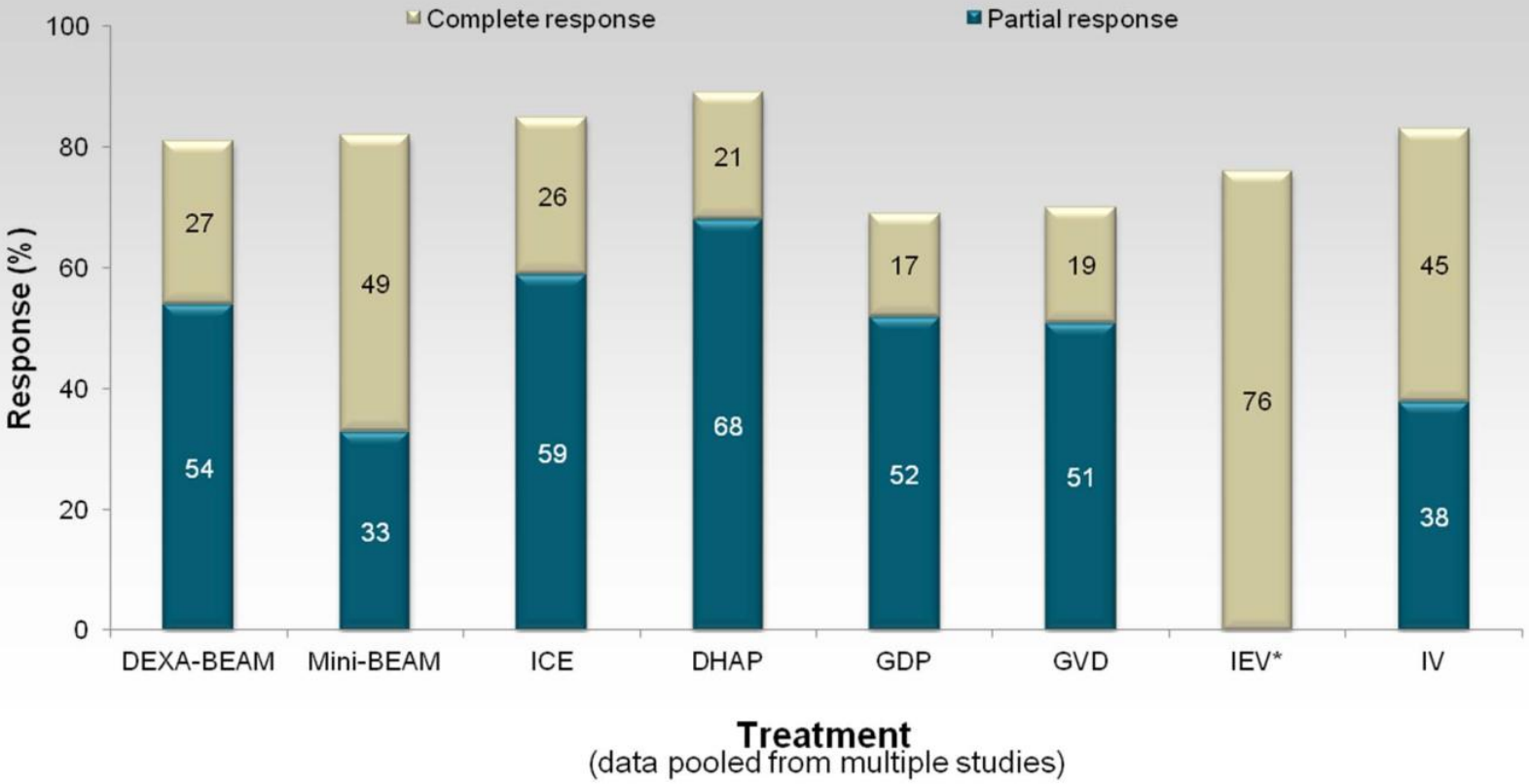
Gordon L I et al. JCO 2013;31:684-691

JOURNAL OF CLINICAL ONCOLOGY ASCO



Gordon L I et al. JCO 2013;31:684-691

SALVAGE CHEMOTHERAPY REGIMENS IN R/R HL



*Partial response data not reported.
R/R – relapsed / refractory; HL – Hodgkin lymphoma; BEAM - carmustine, etoposide, cytarabine, melphalan; DEXA - dexamethasone; DHAP - dexamethasone, ara-C, cisplatin; GDP - gemcitabine, dexamethasone, cisplatin; GVD, gemcitabine, vinorelbine, doxil (liposomal doxorubicin); ICE - ifosfamide, carboplatin, etoposide; IEV - ifosfamide, etoposide, vinorelbine; IV - fosfamide, vinorelbine.

Kuruvilla J et al. Blood 2011;117:4208–17

Date of Prep 09/10/13 EUCAN/ADC/2013-10029l

- Resultados excelentes de la quimioterapia de primera línea
- ABVD, tratamiento estandard:
  - Estadios iniciales, pronóstico favorable: ABVD (x2) + RT
  - Estadios iniciales, pronóstico desfavorable: ABVD (x4) + RT
  - Estadios avanzados: ABVD (x 6 – 8) +/- RT
- Objetivos de la quimioterapia de primera línea en el momento actual:
  - Reducir toxicidad a largo plazo
  - Identificar aquellos pacientes en los que se pueda reducir la intensidad de dosis