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Lymphomas

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Advancing the possibilities…

Disclosures

Consultant: Genentech (unpaid), Millennium (unpaid), Celgene, Allos, Spectrum, Seattle Genetics

Research Funding: Millennium, Spectrum, Novartis

NonHodgkin Lymphomas

Diffuse Large B-Cell Lymphoma
Is there anything beyond R-CHOP?

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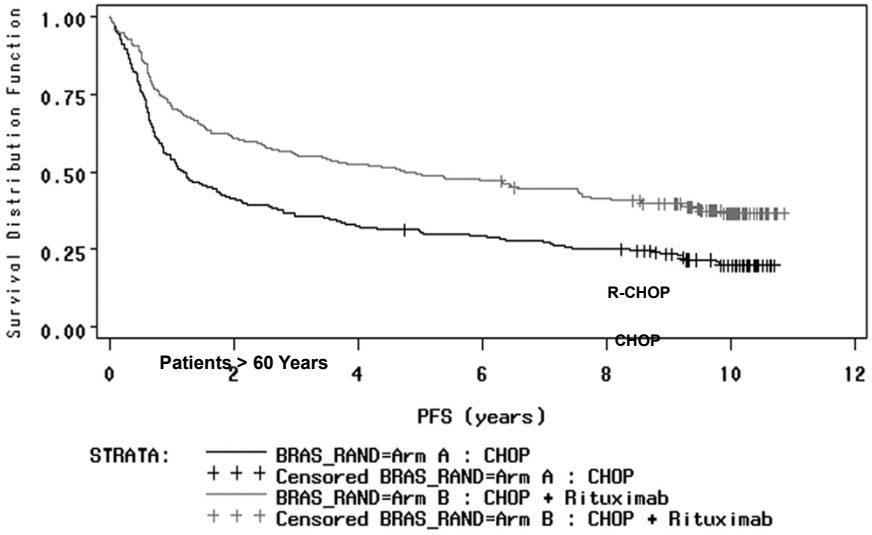
Outcome of Standard Treatment in DLBCL

Phase III Randomized Study of R-CHOP vs. CHOP



Coiffier, B. et al. Blood 2010;116:2040-2045

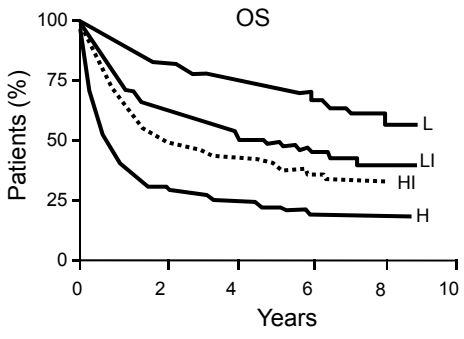
International Prognostic Index Stratifies Risk by Clinical Factors in Aggressive NHL

Prognostic factors (APLES)

- Age >60 years
- Performance status >1
- LDH >1× normal
- Extranodal sites >1
- Stage III or IV

OR

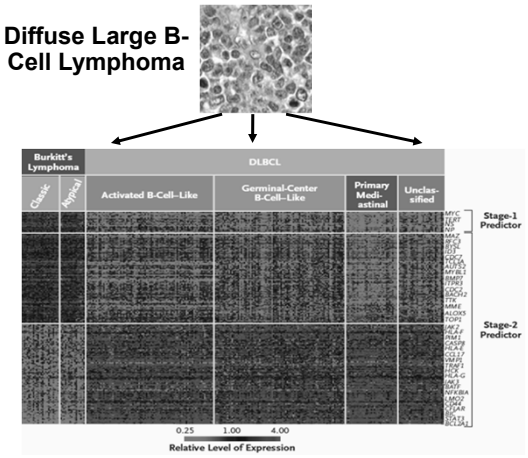
Risk Category	Factors
Low (L)	0 or 1
Low intermediate (LI)	2
High intermediate (HI)	3
High (H)	4 or 5



International NHL Prognostic Factors Project. *N Engl J Med.* 1993;329:987.

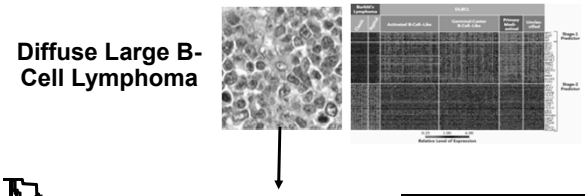
Armitage. *CA Cancer J Clin.* 2005;55:368.

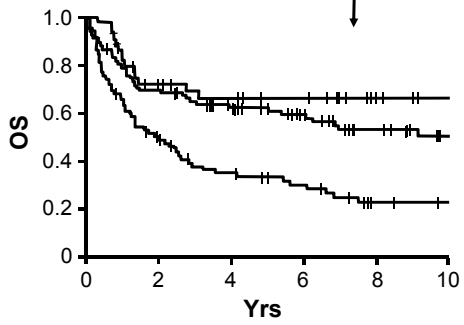
Gene Expression Defines Molecularly and Clinically Distinct Subgroups in DLBCL



Dave SS, et al. N Engl J Med 2006;354:2431-2442.

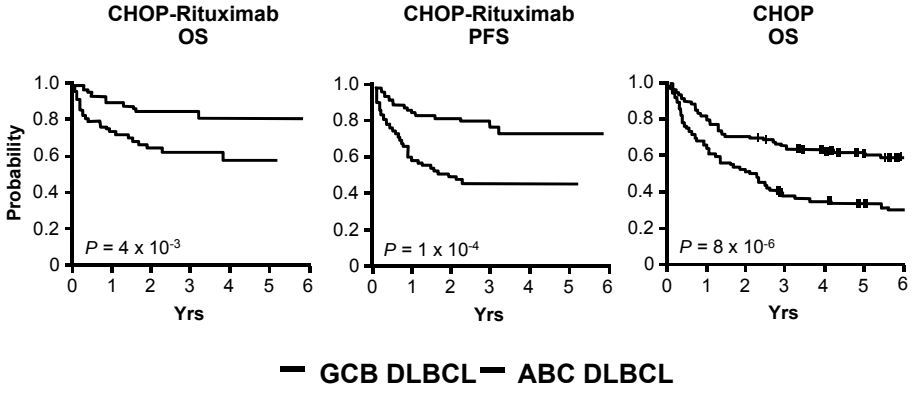
Gene Expression Defines Molecularly and Clinically Distinct Subgroups in DLBCL





DLBCL Subgroup	5-Yr OS, %
PMBL	64
GCB DLBCL	59
ABC DLBCL	30

DLBCL Subtype Retains Prognostic Value With CHOP-R Therapy



Lenz G, et al. N Engl J Med. 2008;359:2313-2323.

Diffuse Large B-Cell Lymphoma
Is there anything beyond R-CHOP?

CHOP-21 → GELA / ECOG / MInT → RCHOP-21

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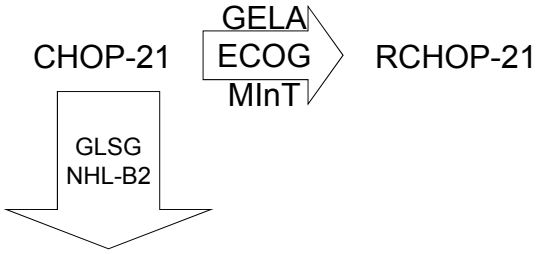
Diffuse Large B-Cell Lymphoma
Is there anything beyond R-CHOP?



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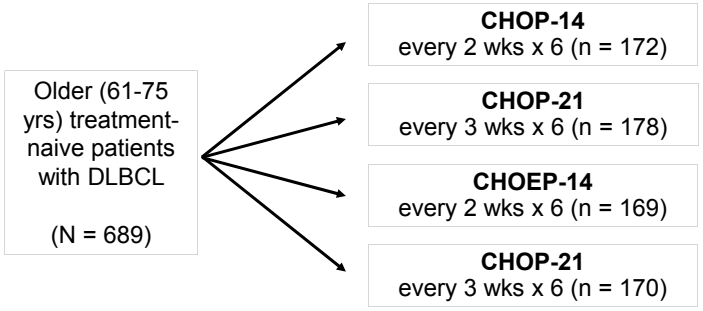
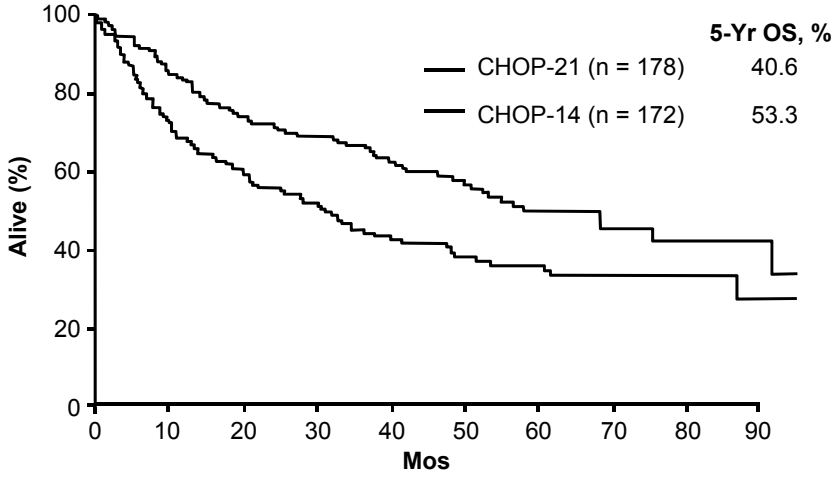
Chemotherapy in Older Patients With DLBCL (NHL-B2 Study)



Pfreundschuh M, et al. Blood. 2004;104:634-641.

CHOP Chemotherapy in Older Patients With DLBCL (NHL-B2 Study): OS



Pfreundschuh M, et al. Blood. 2004;104:634-641.

Diffuse Large B-Cell Lymphoma
Is there anything beyond R-CHOP?

CHOP-21 → GELA / ECOG / MInT → RCHOP-21

CHOP-21 → GLSG NHL-B2 → CHOP-14 → RICOVER 60

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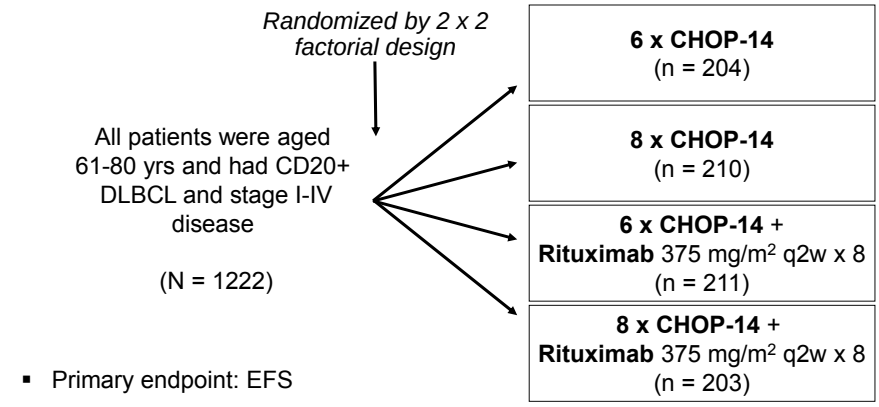
CHOP-14 vs R-CHOP-14 RICOVER-60 Trial: Patients Aged 61-80 Yrs

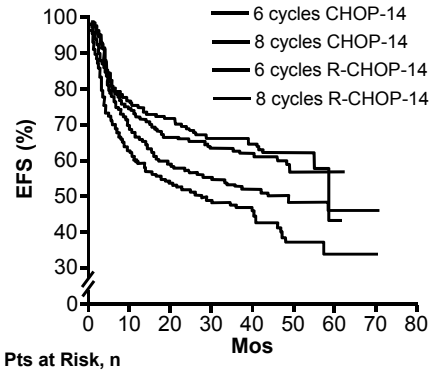


- Primary endpoint: EFS

*Radiotherapy (36 Gy) was planned for patients with initial bulky disease or extranodal involvement.

Pfreundschuh M, et al. Lancet Oncol. 2008;9:105-116.

CHOP-14 ± Rituximab in Elderly Patients With DLBCL (RICOVER-60 Trial): EFS



Pts at Risk, n

1:	183	139	88	51	21	11	0
2:	201	146	103	56	27	18	1
3:	223	188	119	79	28	1	0
4:	218	170	114	82	27	3	0

- EFS was significantly superior with R-CHOP-14 vs CHOP-14
  - *P* < .0001 for both 6 cycles and 8 cycles
- 8 cycles of R-CHOP-14 not superior to 6 cycles
  - 6 cycles R-CHOP-14 is preferred treatment for elderly patients

Pfreundschuh M, et al. Lancet Oncol. 2008;9:105-116.

Diffuse Large B-Cell Lymphoma
Is there anything beyond R-CHOP?

CHOP-21 → GELA / ECOG / MInT → RCHOP-21

CHOP-21 → GLSG NHL-B2 → CHOP-14 → RICOVER 60 → RCHOP-14 x6

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Diffuse Large B-Cell Lymphoma
Is there anything beyond R-CHOP?

CHOP-21 → GELA / ECOG / MInT → RCHOP-21

CHOP-21 → GLSG NHL-B2 → CHOP-14 → RICOVER 60 → RCHOP-14 x6

Randomize → **GELA LNH 03-6B** (ASH 2009), **UK NCRI** (ASCO 2011)

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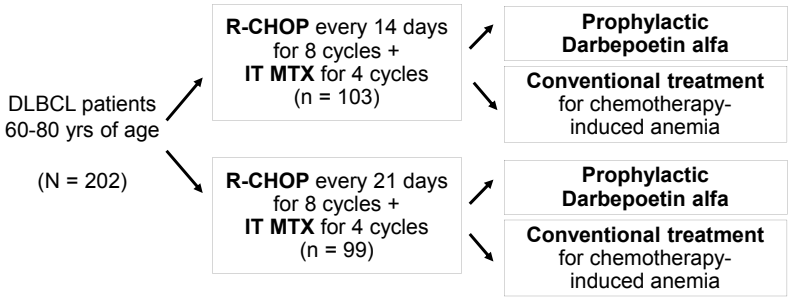
LNH03-6B GELA: R-CHOP-14 vs R-CHOP-21 in Elderly DLBCL Patients

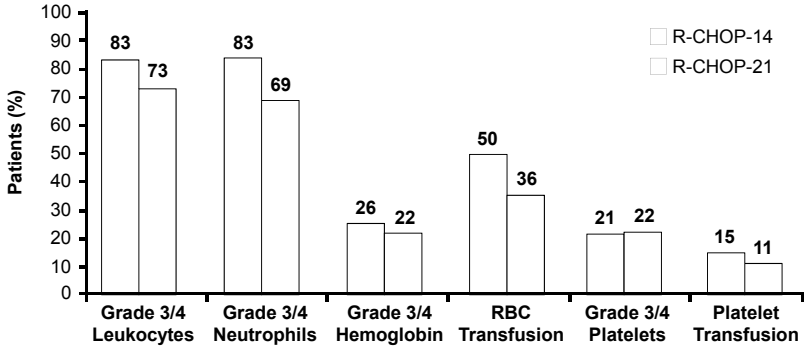


- Primary endpoint: EFS
- Secondary endpoints: CR or CRu , ORR, PFS , DFS, OS, dose intensity, toxicity

Delarue R, et al. ASH 2009. Abstract 406.

LNH03-6B GELA Trial: Toxicities

- Hematologic toxicities greater for R-CHOP-14



- Patients on R-CHOP-14 had higher rates of febrile neutropenia, hospitalization, and death due to toxicity

Delarue R, et al. ASH 2009. Abstract 406.

LNH03-6B GELA Trial: Results

Outcome	R-CHOP-21 (n = 99)	R-CHOP-14 (n = 103)	*P* Value
End of treatment response rates			
▪ CR/CRu	75	67	NS
▪ PR	9	14	NS
▪ ORR	84	81	NS
2-yr EFS, %	61	48	.11
2-yr PFS, %	63	49	.12
2-yr DFS, %	70	57	.40
2-yr OS, %	70	67	.37
Median EFS, mos	Not reached	22	--
Median PFS, mos	Not reached	23	--

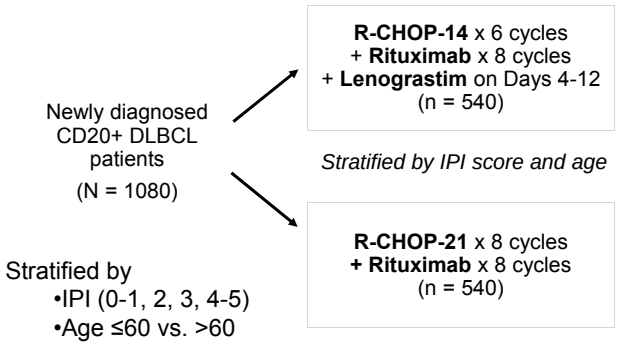
Delarue R, et al. ASH 2009. Abstract 406.

A phase III trial comparing R-CHOP 14 and R-CHOP 21 for the treatment of newly diagnosed diffuse large B cell lymphoma

Abstract 8000

D. Cunningham, P. Smith, P. Mouncey,
W. Qian, C. Pocock, K. M. Ardeshna,
J. Radford, J. Davies, A. McMillan, D. Linch
on behalf of the NCRI trial collaborators

R-CHOP-14 vs R-CHOP-21 in Newly Diagnosed DLBCL (Phase III study)



Stratified by
- •IPI (0-1, 2, 3, 4-5)
- •Age ≤60 vs. >60
- •Treatment center

Primary endpoint: overall survival

Secondary endpoint: FFS, toxicity, response rates

Cunningham D, et al. ASCO 2011 Abstract 8000 Cunningham D, et al. ASCO 2009 Abstract 8506.

Patient characteristics

		R-CHOP21 (n=540) %	R-CHOP14 (n=540) %
Age	≤ 60 yrs	47	48
	median	61yrs (19-88)	61yrs (19-85)
Gender	male	54	54
WHO PS	0-1	87	87
	2	13	13
B symptoms	yes	44	47
Stage	I-II	37	38
	III-IV	63	62
Bulky disease	yes	51	48
IPI score	0-1	27	27
	2-3	54	56
	4-5	19	16

Treatment administration

	R-CHOP21 n=540 n (%)	R-CHOP14 n=540 n (%)
Total no. of cycles received		
0-4	36 (6)	35 (6)
5-6	69 (13)	26 (5)
7-8	435 (81)	479 (89)*
Total number stopped early	n=107	n=58
Reasons for stopping early		
Toxicity	35	20
PD/death	23	12
Patient choice	14	4
Other medical condition	7	5
Other	33	16

* R CHOP 14- Cycle 7 & 8- Rituximab only

Patients without Treatment delays

	R-CHOP21		R-CHOP14*
Cycle	# treated without delay / # receiving cycle	# patients receiving G-CSF	# treated without delay / # receiving cycle
1		16 %	
2	80 %	28 %	86 %
3	85 %	36 %	91 %
4	85 %	40 %	91 %
5	83 %	45 %	87 %
6	83 %	48 %	81 %
7	85 %	51 %	90 % (R alone)
8	86 %	44 %	95 % (R alone)

*R-CHOP14: all receive G-CSF cycles 1-6

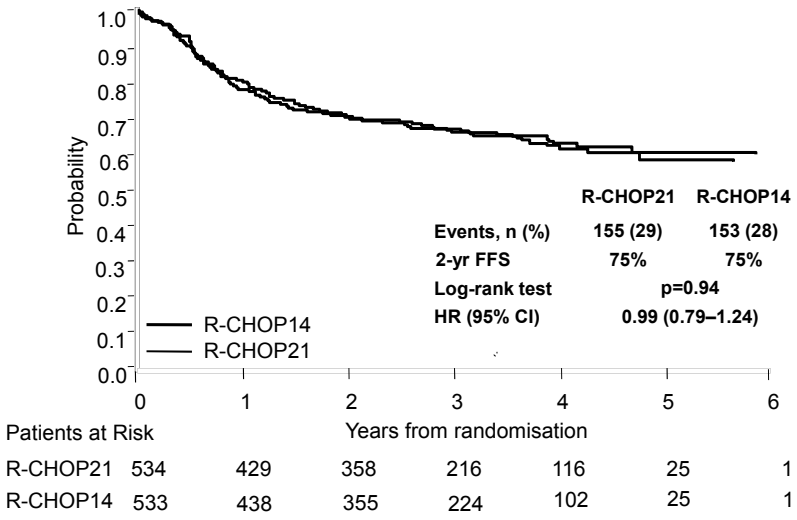
Cunningham D, et al. ASCO 2011 Abstract 8000 Cunningham D, et al. ASCO 2009 Abstract 8506.

Overall response rates

Based on end of treatment scan	R-CHOP21 %	R-CHOP14 %
CR	49	41
CRu	14	17
PR	25	32
SD	6	5
PD/relapse	6	4
CR/CRu, p=0.15	**63**	**58**
CR/CRu/PR, p= 0.11	**88**	**90**

Cunningham D, et al. ASCO 2011 Abstract 8000 Cunningham D, et al. ASCO 2009 Abstract 8506.

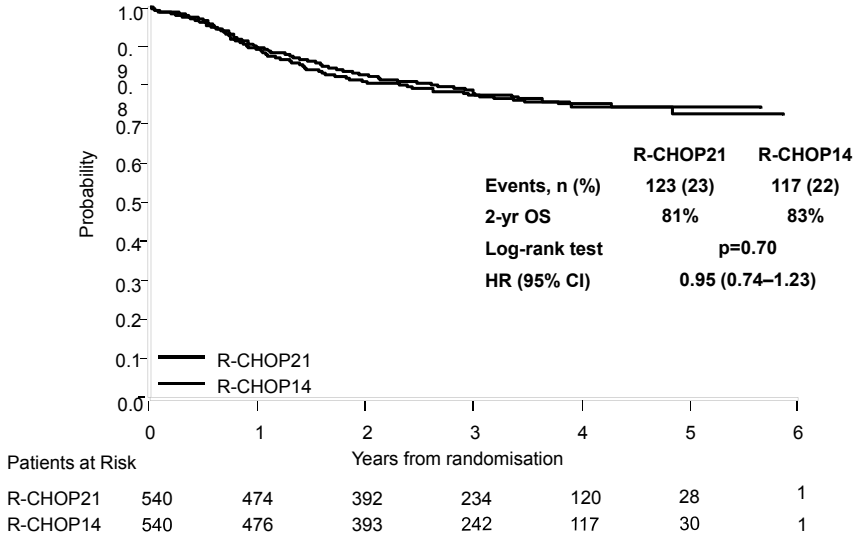
Failure-free survival



Patients at Risk

R-CHOP21	534	429	358	216	116	25	1
R-CHOP14	533	438	355	224	102	25	1

Overall survival



	R-CHOP21	R-CHOP14
Events, n (%)	123 (23)	117 (22)
2-yr OS	81%	83%
Log-rank test	p=0.70	
HR (95% CI)	0.95 (0.74–1.23)	

Patients at Risk

R-CHOP21	540	474	392	234	120	28	1
R-CHOP14	540	476	393	242	117	30	1

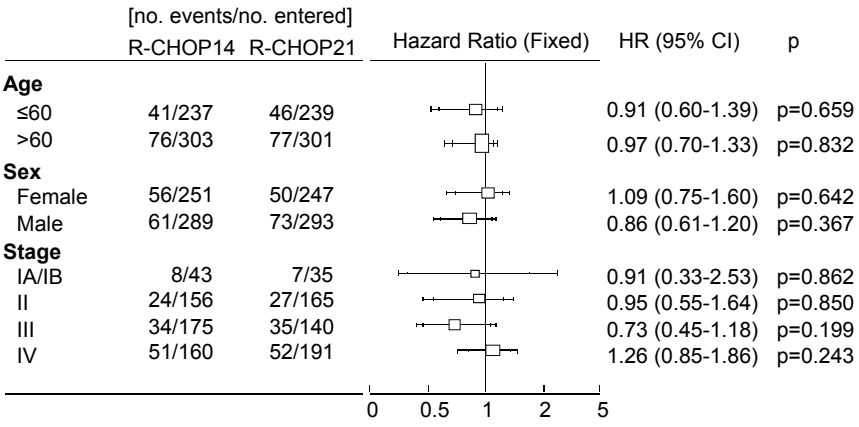
Cause of death

	R-CHOP21 n= 540 n (%)	R-CHOP14 n= 540 n (%)
Total Deaths	**123 (23)**	**117 (22)**
Disease	79 (15)	76 (14)
Treatment related toxicity	3 (0.5)	8 (1)
Cardiac*	7 (1)	5 (0.9)
Secondary malignancy	7 (1)	6 (1)
Other	22 (4)	17 (3)
Unknown	5 (0.9)	4 (0.7)

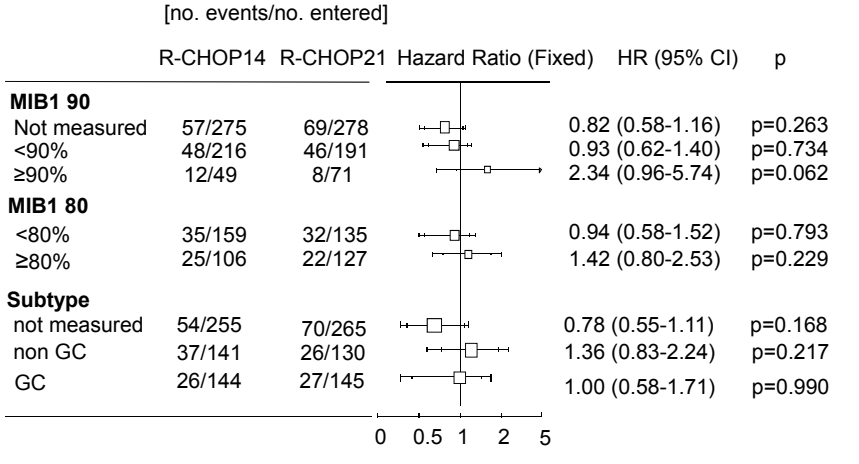
*All cardiac deaths occurred 3-15 months after completing Rx

Cunningham D, et al. ASCO 2011 Abstract 8000 Cunningham D, et al. ASCO 2009 Abstract 8506.

Subgroup analysis of OS



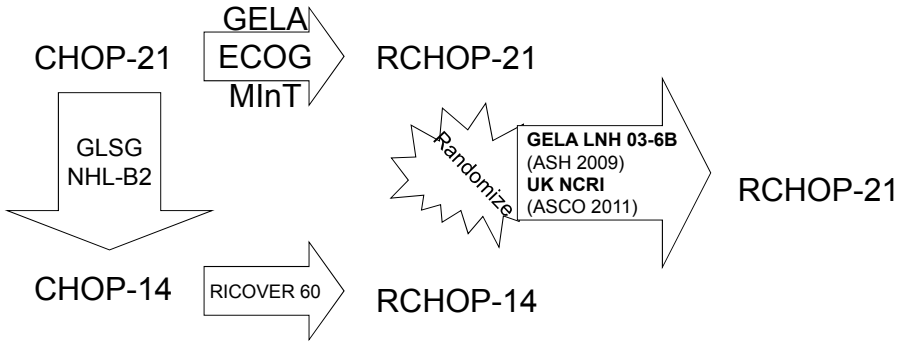
Subgroup analysis of OS



Conclusions

- In patients receiving Rituximab, CHOP14 for 6 cycles is not superior to CHOP21 for 8 cycles
- No obvious sub group appears to derive a greater benefit from R-CHOP14, including age > 60, high IPI, high MIB1 or non-GC phenotype
- As expected a higher frequency of neutropenia was observed in R-CHOP21 which reflects the primary prophylaxis with G-CSF in R-CHOP14

Diffuse Large B-Cell Lymphoma
Is there anything beyond R-CHOP?



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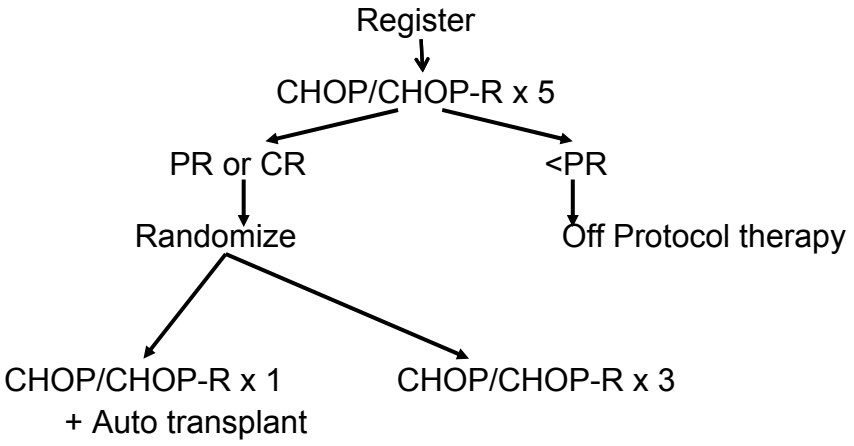
Randomized phase III US / Canadian Intergroup trial (SWOG S9704) comparing CHOP±R x 8 vs CHOP±R x 6 followed by high dose therapy and auto transplant for patients with diffuse aggressive non-Hodgkin's lymphoma (NHL) in high-intermediate (H-Int) or high IPI risk groups.

Abstract 8001

P.J. Stiff[1], J.M. Unger[2] J.R. Cook[3], L.S. Constine[4], S. Couban[5], T.C. Shea[6], J.N. Winter[7], T.P. Miller[8], R.R. Tubbs[3], D.C. Marcellus[9], J. Friedberg[4], K. Barton[1], G. Mills[10], M. LeBlanc[2], L. Rimsza[8], S.J. Forman[11], R.I. Fisher[4]

[1]Loyola University Medical Center, Maywood, IL; [2]SWOG Statistical Center, Seattle, WA; [3]Cleveland Clinic Foundation, Cleveland, OH; [4]University of Rochester, Rochester, NY; [5]Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, CAN; [6]University of North Carolina at Chapel Hill, Chapel Hill, NC; [7]Northwestern University, Chicago, IL; [8]University of Arizona, Tucson, AZ; [9]Margaret and Charles Juravinski Cancer Centre, Hamilton, Ontario, CAN; [10]Louisiana State University Medical Center, Shreveport, LA; [11]City of Hope Medical Center, Duarte, CA

Schema



Patients were permitted to have 1 cycle of CHOP(R) prior to protocol registration

Transplant regimens: SWOG TBI (12 Gy/8 Fx) or BCNU (150 mg/m^2 x 3d) + VP16 (60 mg/kg) + Cyclophosphamide (100 mg/kg)

Patient Characteristics: CHOP-(R) x 5 (N=370)

International Index High – Int High	 68% 32%
Treated with CHOP: B-Cell T-Cell B-Cell Treated with CHOP-R	52% 40% 12% 48%
# of treatment centers	40

Stiff O, et al. ASCO 2011 Abstract 8001

Characteristics of Randomized Patients

	CHOP(R) x 1 + ASCT (N =125)	CHOP x 3 (N=128)
Age - years Median % ≥ 60 yrs	49.6 20%	51.3 18%
Sex – Male	61%	56%
B Cell Histology Diffuse Large Cell T Cell Histology Peripheral T, NOS	88% 81% 12% 5%	90% 75% 10% 4%
Immunophenotyping B cell CHOP-R B cell CHOP	60% 28%	59% 31%
Stage Bulky II III / IV	3% 36% / 61%	7% 32% / 61%
Performance Status ≥ 2	34%	38%
Elevated LDH	85%	81%
B Symptoms	60%	61%
International Index: High	34%	35%
Extra nodal Sites ≥ 2	25%	23%
Bone marrow involvement –Yes	15%	24%

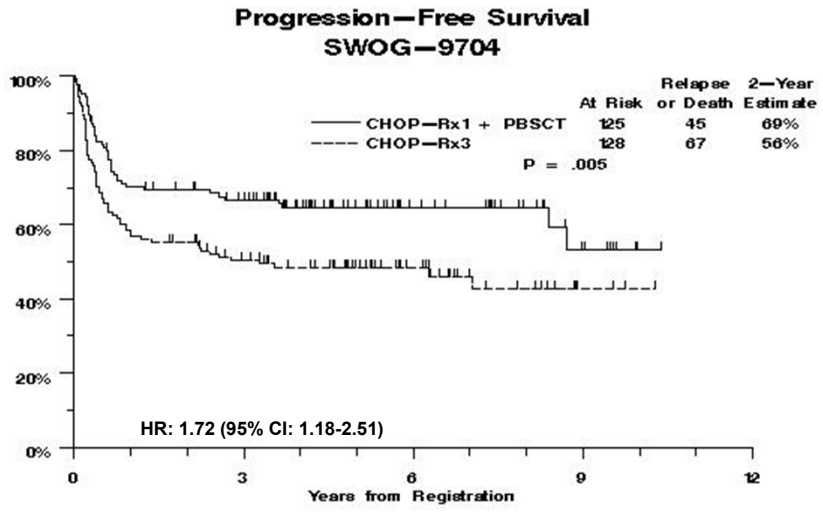
Stiff O, et al. ASCO 2011 Abstract 8001

Results: Grade III –IV Toxicities of Randomized Patients

Toxicities	CHOP (R) x 1 + ASCT (%)	CHOP (R) x 3 (%)
Infection	50	13
GI	26	5
Metabolic	13	1
Lung	11	2
CV	10	4
Neurologic	7	2
Dyspnea	7	2
Hyperglycemia	6	0
Hypoxia	4	0
Hepatic	3	0

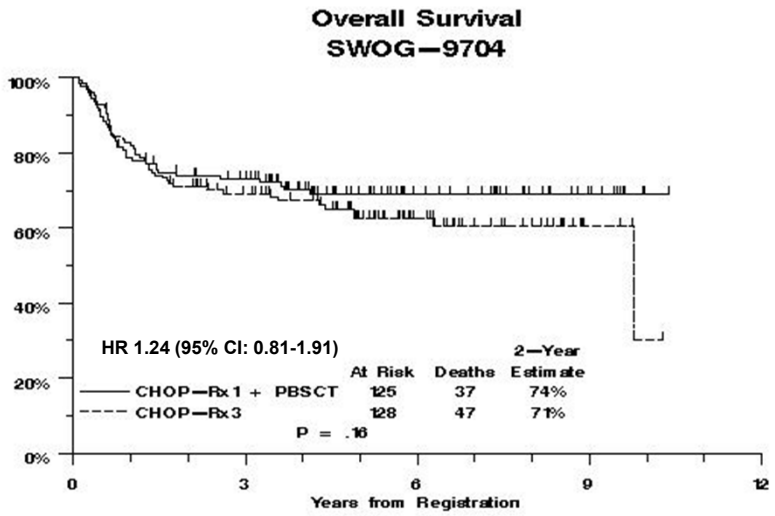
Stiff O, et al. ASCO 2011 Abstract 8001

Overall Outcome : PFS



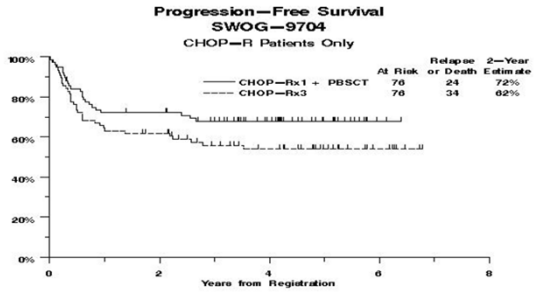
Stiff O, et al. ASCO 2011 Abstract 8001

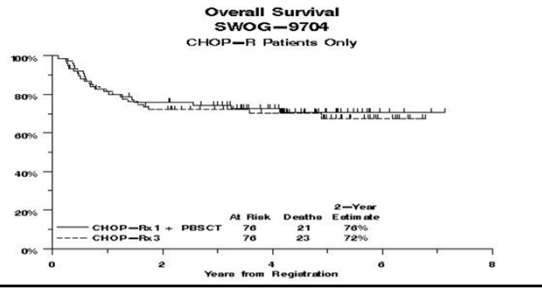
Overall Outcome: Survival



Stiff O, et al. ASCO 2011 Abstract 8001

Outcome of Randomized Patients with B Cell Disease Treated with R-CHOP Only





Conclusions

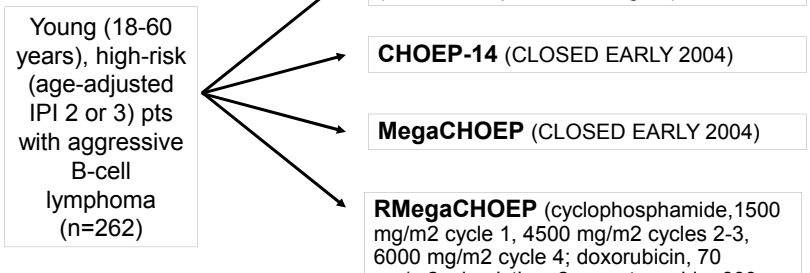
- **Patients with High Risk diffuse aggressive NHL have a superior 2 year PFS with ASCT in first PR/CR**
- **This improvement has not yet led to a survival advantage, as 18% of those who relapsed on the standard arm have had a long term PFS after a salvage ASCT.**
- **Exploratory analyses indicated that the majority of the ASCT benefit occurred in the High IPI group for which transplant had both a PFS and OS advantage.**

Conventional chemoimmunotherapy (R-CHOEP-14) or high-dose therapy (R-Mega-CHOEP) for young, high-risk patients with aggressive B-cell lymphoma: Final results of the randomized Mega-CHOEP trial of the German High-Grade Non-Hodgkin Lymphona Study Group (DSHNHL).

Abstract 8002

N. Schmitz, M. Nickelsen, M. Ziepert, M. Haenel, P. Borchmann, C. Schmidt, A. Viardot, M. Bentz, N. Peter, G. Ehninger, G. Doelken, L. H. Truemper, M. Loeffler, M. Pfreundschuh, B. Glass

R-CHOEP14 vs R-MegaCHOEP and auto-SCT in high-risk young DLBCL



Schmitz, et al. ASCO 2011 Abstract 8002

R-CHOEP14 vs R-MegaCHOEP and auto-SCT in high-risk young DLBCL

	R-CHOEP14	R-MegaCHOEP	*P*
CR / CRu	79%	71%	NS
3-year EFS	69.5%	61.4%	0.140
3-year PFS	74%	70%	
3-year OS	85%	77%	0.081

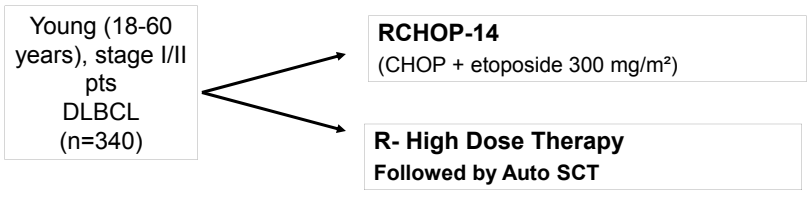
Smitz, et al. ASCO 2011 Abstract 8002

First-line rituximab (R) high-dose therapy (R-HDT) versus R-CHOP14 for young adults with diffuse large B-cell lymphoma: Preliminary results of the GOELAMS 075 prospective multicenter randomized trial.

Abstract 8003

S. Le Gouill, N. J. Milpied, T. Lamy, V. Delwail, R. Gressin, D. Guyotat, G. L. Damaj, C. Foussard, G. Cartron, H. Maisonneuve, E. Deconinck, F. Dreyfus, E. Gyan, L. Sutton, N. Morineau, M. Alexis, F. Perry, M. Sauvezie

R-HDT vs R-CHOP14 in newly diagnosed high or intermediate-risk DLBCL



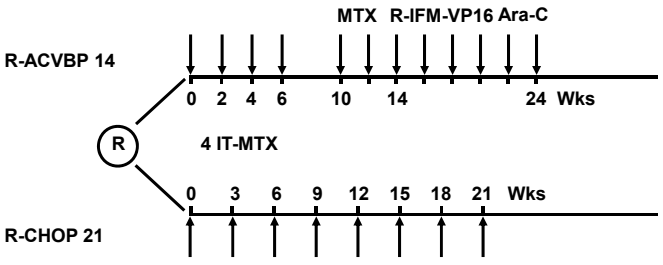
Le Gouill, et al. ASCO 2011 Abstract 8003

R-HDT vs R-CHOP14 in newly diagnosed high or intermediate-risk DLBCL

	R-CHOP14 N = 156	R-HDT N = 156	*P*
CR	71%	72%	NR
CR / CRu / PR	88%	88%	NR
3-year EFS	56%	41%	0.03
3-year PFS	81%	79%	0.90
3-year OS	85%	82%	NS

Le Gouill, et al. ASCO 2011 Abstract 8003

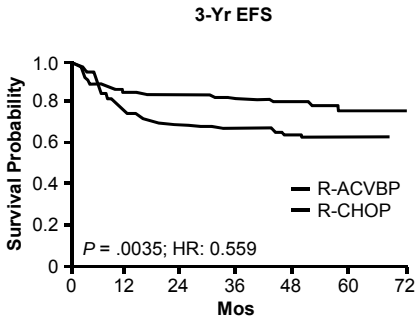
LNH 03-2B: R-ACVBP vs R-CHOP in Treatment-Naive Pts With CD20+ DLBCL

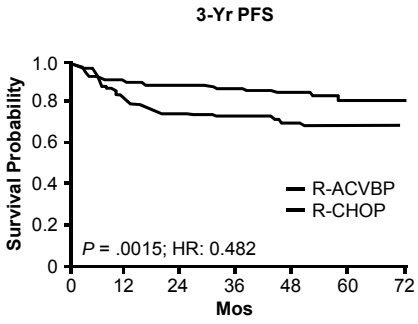


- Patients aged 18-59 yrs
- No radiotherapy in either treatment arm
- Primary endpoint: EFS
- Secondary endpoints: response rate at end of therapy, PFS, FDS (CR/CRu patients only), OS, CNS relapse rate, toxicity

Récher C, et al. ASH 2010. Abstract 109.

LNH 03-2B Study: Results



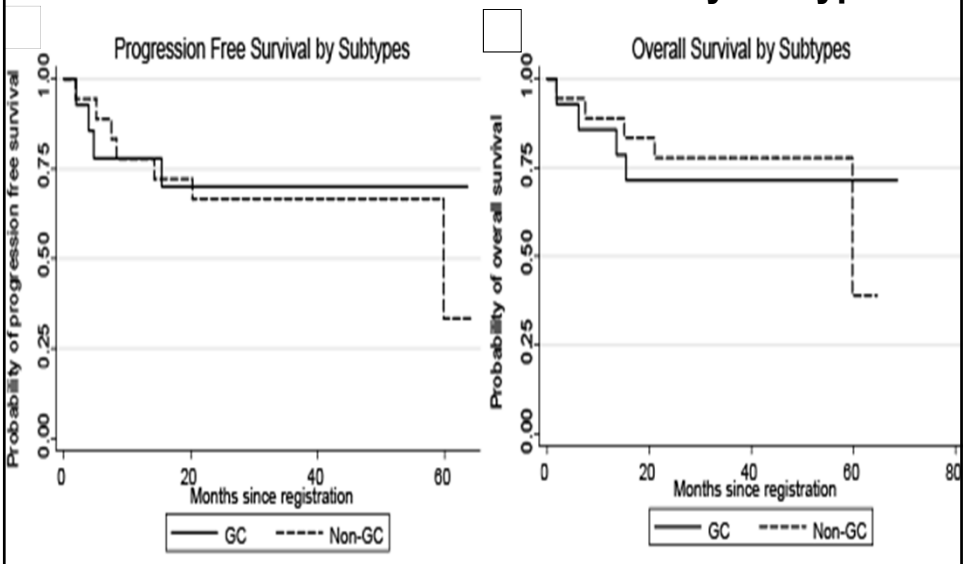


	No. of Subjects	Event	Censored	Median Survival (95% CI)
R-ACVBP	196	20% (40)	80% (156)	NA (NA)
R-CHOP	183	34% (63)	66% (120)	NA (NA)

	No. of Subjects	Event	Censored	Median Survival (95% CI)
R-ACVBP	196	14% (28)	86% (168)	NA (NA)
R-CHOP	183	28% (51)	72% (132)	NA (NA)

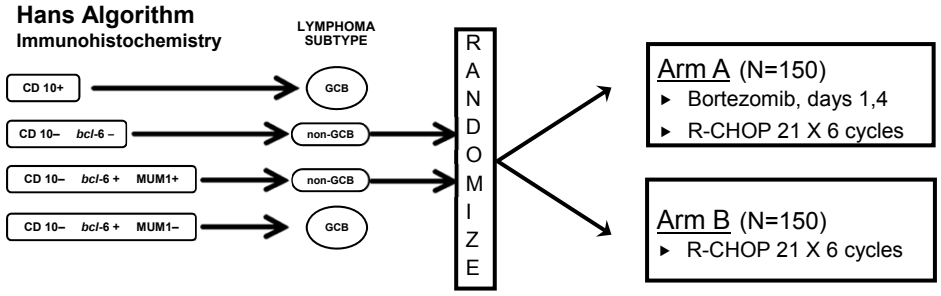
Récher C, et al. ASH 2010. Abstract 109.

R-CHOP-Bortezomib – PFS and OS by subtype



Ruan et al, J Clin Oncol. 2011

Randomized Phase II of BR-CHOP vs. R-CHOP in non-GCB DLBCL



- Patients: 300, non-GCB (by IHC) DLBCL
- Primary Endpoint: PFS at 1 year; 80% power to detect an increase from 67% to 78%

Hodgkin Lymphoma

Date of origin: 1999
Last review date: 2011

American College of Radiology
ACR Appropriateness Criteria®

HODGKIN'S LYMPHOMA — FAVORABLE PROGNOSIS STAGE I AND II

Expert Panel on Radiation Oncology — Hodgkin's Lymphoma: Prajnan Das, MD, MPH[1]; Andrea Ng, MD[2]; Louis S. Constine, MD[3]; Ranjana Advani, MD[4]; Christopher Flowers, MD, MS[5]; Jonathan W. Friedberg, MD[6]; David C. Hodgson, MD[7]; Cindy L. Schwartz, MD[8]; Richard B. Wilder, MD[9]; Lynn D. Wilson, MD, MPH[10]; Michael J. Yunes MD.[11]

Summary of Literature Review

This topic addresses the treatment of newly diagnosed stage I and II favorable-prognosis Hodgkin's lymphoma. For most cases of favorable-prognosis stage I and II Hodgkin's lymphoma, combined-modality therapy (chemotherapy followed by involved-field radiotherapy [IFRT]) constitutes the current standard of care. Increasing information about the late effects of treatment has led to attempts to decrease toxicity by using less chemotherapy (decreased duration, intensity, agents) or less radiotherapy (RT) (reduced volume, dose).

adenopathy (one-third of the maximum thoracic diameter), an erythrocyte sedimentation rate (ESR) of less than 50 and no "B" symptoms or an ESR of <30 with "B" symptoms, no extranodal disease and one to two sites of nodal involvement. In contrast, the European Organisation for Research and Treatment of Cancer (EORTC) criteria for favorable prognostic features include age 50 or younger, no large mediastinal adenopathy, an ESR of <50 and no "B" symptoms or an ESR of <30 with "B" symptoms, and lymphoma limited to one to three regions of involvement [1-2]. In interpreting trial results, it is important to pay attention to the risk group definition, as the results are applicable only to patients who fit the specific inclusion criteria.

Long-term Outcome of Treatment for Early-stage Hodgkin's Lymphoma

Much of the long-term follow-up data (15 years or longer) for early-stage Hodgkin's lymphoma is derived from

Date of origin: 1999
Last review date: 2010

American College of Radiology
ACR Appropriateness Criteria®

HODGKIN'S LYMPHOMA — UNFAVORABLE CLINICAL STAGE I AND II

Expert Panel on Radiation Oncology–Hodgkin's Lymphoma: Prajnan Das, MD, MPH[1]; Andrea Ng, MD[2]; Louis S. Constine, MD[3]; Ranjana Advani, MD[4]; Christopher Flowers, MD, MS[5]; Jonathan Friedberg, MD[6]; David C. Hodgson, MD[7]; Cindy L. Schwartz, MD[8]; Richard B. Wilder, MD[9]; Lynn D. Wilson, MD, MPH[10]; Michael J. Yunes MD.[11]

Summary of Literature Review

Numerous studies have evaluated the impact of

the maximum width of the mediastinal mass on standing posteroanterior (PA) chest radiograph, compared with the maximum intrathoracic diameter. A ratio >1/3 is defined as "bulky." Other reports have used a ratio with the intrathoracic width at T5–6 as the denominator [8], while still others use absolute measurements [9], surface area calculations, or volume measurements. Bulky disease in nonmediastinal sites has similarly been classified with varying definitions. Some protocols define bulky as ≥10 cm, while others use ≥5 cm or ≥6 cm.

Date of origin: 1999
Last review date: 2010

American College of Radiology
ACR Appropriateness Criteria®

HODGKIN'S LYMPHOMA — STAGE III AND IV

Expert Panel on Radiation Oncology–Hodgkin's Lymphoma: Richard B. Wilder, MD[1]; Andrea Ng, MD[2]; Louis S. Constine, MD[3]; Ranjana Advani, MD[4]; Prajnan Das, MD, MPH[5]; Christopher Flowers, MD, MS[6]; Jonathan W. Friedberg, MD[7]; David C. Hodgson, MD[8]; Cindy L. Schwartz, MD[9]; Lynn D. Wilson, MD, MPH[10]; Michael J. Yunes MD.[11]

Summary of Literature Review

This review for Hodgkin's lymphoma addresses the treatment of patients who are newly diagnosed with clinical stage (CS) III or IV Hodgkin's lymphoma. Since

suggest, however, that there may be a role for radiation therapy in patients with initially bulky disease or in patients with a partial response (PR) to chemotherapy. Given the strong prognostic value of early positron emission tomography (PET) findings showing the disease's response to chemotherapy in patients with advanced-stage Hodgkin's lymphoma, investigators are exploring response-adapted therapy, including changing the chemotherapy regimen or omitting radiation therapy based on early PET-detected response.

Diagnosis of Advanced-Stage Hodgkin's Lymphoma

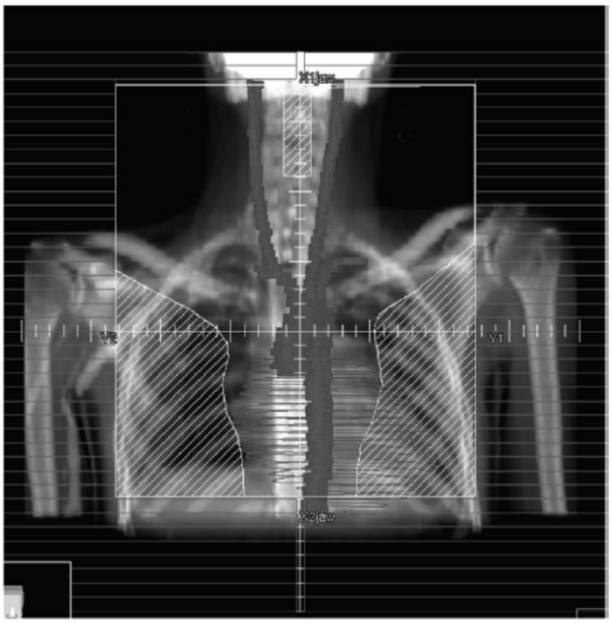


Figure 2. Schematic representation of the area covered by radiotherapy of the mediastinum and neck, including heart, aorta, and carotid arter-

Long-term survivors of HL are at increased risk for a number of radiation-related late complications

- Cardiovascular disease
- Hypothyroidism
- Second malignancies
- Other risks: dental carries, dry mouth, dysgeusia, transverse myelitis, hypothyroidism, sterility

The use of FDG-PET to guide consolidative radiotherapy in patients with advanced-stage Hodgkin lymphoma with residual abnormalities on CT scan following ABVD chemotherapy

Abstract 8034

K. J. Savage, J. M. Connors, R. J. Klasa, P. Hoskins, T. N. Shenkier, R. D. Gascoyne, S. Bhimji, T. Pickles, F. Benard, D. Wilson, L. H. Sehn

Use of FDG-PET to guide consolidative XRT in pts with advanced-stage HL

- Advanced stage HL pts with age > 16 yrs underwent FDG-PET imaging if residual abnormalities > 2 cm were found on post-chemotherapy scan
  - If the PET scan was negative, pts were observed, regardless of initial disease bulk.
  - If the PET scan was positive, RT was administered.

Patient Characteristics

- Median age: 31 (range 17-76 yrs)
- Stage II: 52%
- Bulky disease: 50%
- International Prognostic score > 3: 15%

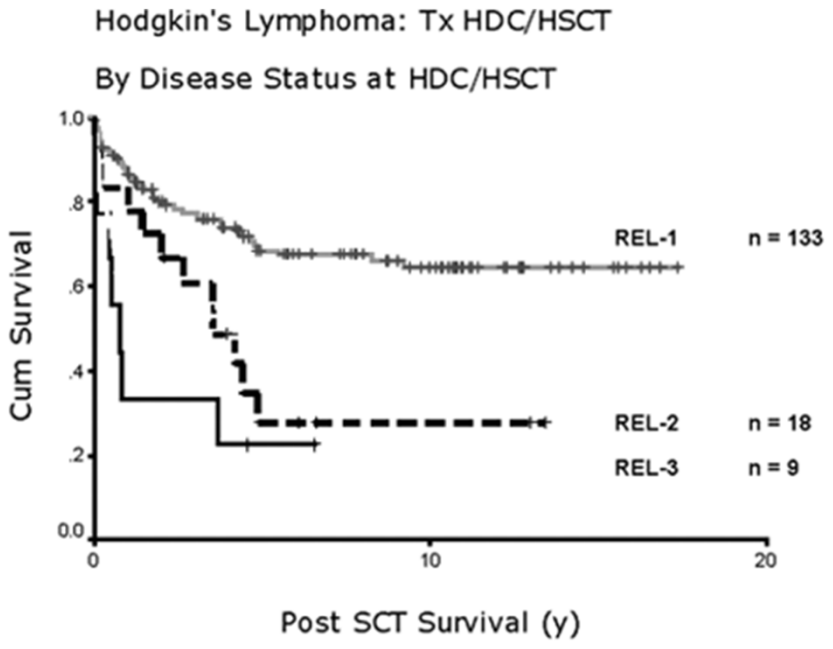
Savage, et al. ASCO 2011 Abstract 8034

Use of FDG-PET to guide consolidative XRT in pts with advanced-stage HL

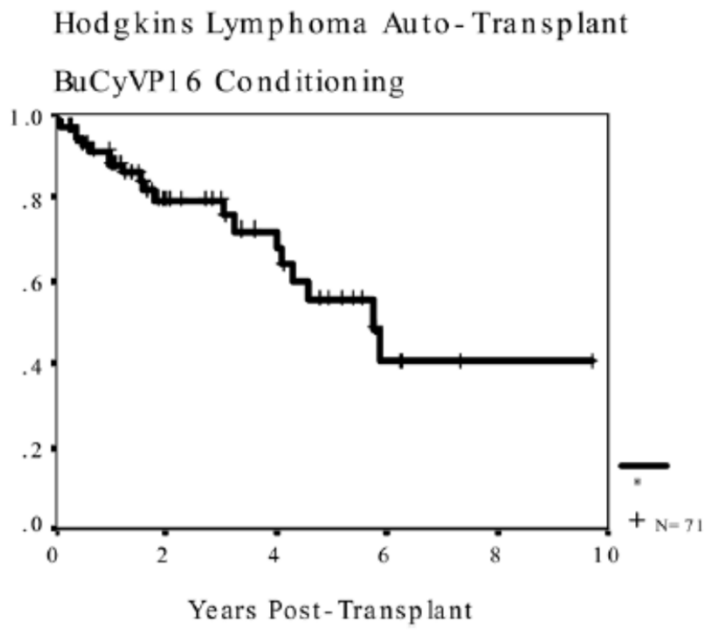
(n=163)	**PET Negative**	**PET Positive**	***P***
	80%	19%	
XRT	0	85%	
Relapse p XRT (n=25)	---	40%	
3-year TTP	89%	55%	<0.0001
3-year TTP bulky / nonbulky	86% / 91%		0.71

Savage, et al. ASCO 2011 Abstract 8034

Relapsed Hodgkin Lymphoma



Diehl et al. ASH Education Program Book 2003



Santos et al. Biol Blood Marrow Transplant 2007

Results from a pivotal phase II study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma (HL)
Abstract 8031

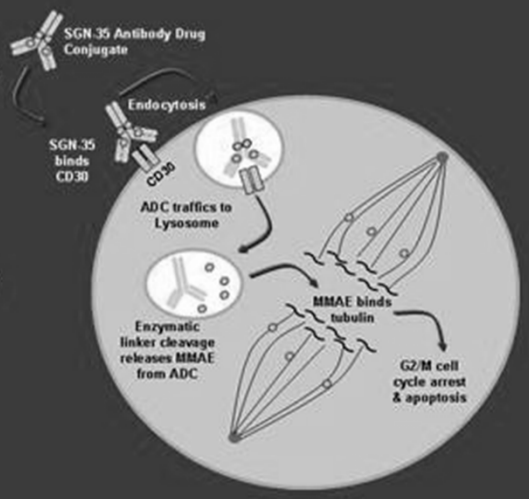
Robert Chen, Ajay K. Gopal, Scott E. Smith, Stephen M. Ansell, Joseph D. Rosenblatt, Richard Klasa, Joseph M. Connors, Andreas Engert, Emily K. Larsen, Dana A. Kennedy, Eric L. Sievers, and Anas Younes

- Phase 1 study q 3 week, 11/12 patients treated at MTD 1.8 mg/kg had tumor reductions and 6/12 patients CR/PR
- 102 patients with relapsed or refractory HL were treated at 26 study centers

- Grade 4 AEs: neutropenia (4%), and thrombocytopenia, abdominal pain, and pulmonary embolism (1% each)
- Any grade AEs peripheral sensory neuropathy (43%), fatigue (40%), nausea (35%), neutropenia (19%), diarrhea (18%), fever (16%)
- Tumor shrinkage observed in 95% of patients
- B symptom resolution rate was 83%.

SGN-35 Mechanism of Action

- SGN-35 consists of a CD30-targeted antibody (cAC10) conjugated to an auristatin E derivative (MMAE)
- MMAE is a potent anti-tubulin agent selectively delivered to CD30-positive cells via antibody-drug conjugate technology



Brentuximab Vedotin (SGN-35) in Relapsed/ Refractory Hodgkin's Lymphoma

- Brentuximab vedotin anti-CD30 monoclonal antibody

Patients with relapsed/ refractory CD30+ disease, 12 yrs of age or older, measurable disease ≥ 1.5 cm, ECOG PS 0-1, previous ASCT

(N = 102)

→ **Brentuximab vedotin 1.8 mg/kg** Administered every 21 days on outpatient basis over 30 min for a max of 16 cycles until at least SD achieved; patients restaged at cycles 2, 4, 7, 10, 13, 16 →

Follow-up every 12 wks

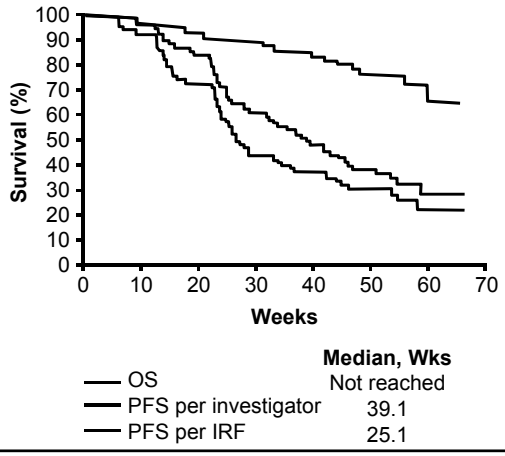
- Primary endpoint: overall objective response rate (CR + PR) by independent review facility
- Secondary endpoints: OS and PFS

Chen, et al. ASCO 2011 Abstract 8031 Chen et al. ASH 2010. Abstract 283.

Brentuximab Vedotin (SGN-35) in Relapsed/Refractory HL: Results

- 94% achieved tumor reduction
- Median treatment cycles: 9 (range: 1-16)

Response	IR (%)	PFS (mos)	DOR (mos)
ORR	75		6.7
CR	34	21.7	20.5
PR	40	5.1	
SD	22	3.5	
PD	3	1.2	
Not evaluable	1		



Chen, et al. ASCO 2011 Abstract 8031
Chen, et al. ASH 2010. Abstract 283.

Brentuximab Vedotin (SGN-35) in Relapsed/Refractory HL: Adverse Events

- Peripheral neuropathy: 47% of pts
  - 9% Grade 3
  - Dose reduction or delay resulted in resolution for 50%
- Other common AEs: nausea, fatigue, neutropenia, and diarrhea
- ≥Grade 3 AEs occurring in ≥ 5% of pts:
  - neutropenia, PN, thrombocytopenia, and anemia.

Chen, et al. ASCO 2011 Abstract 8031 Chen et al. ASH 2010. Abstract 283.

Multiple Myeloma: ASCO 2011 Update

Jonathan L. Kaufman, MD

Assistant Professor of Hematology and Medical Oncology

Winship Cancer Institute of

Emory University

Melphalan, Prednisone, Lenalidomide (MPR) Versus High Dose Melphalan and Autologous Transplantation (MEL200) in Newly Diagnosed Multiple Myeloma (MM) Patients: A Phase III Trial

Abstract 8020

Boccadoro M, Cavallo F, Nagler A, Ben Yehuda D, Omedè P, Cavalli M, Levi A, Crippa C, Siniscalchi A, Brasca P, Carella AM, Zanetti BA, Patriarca F, Pezzati S, Montefusco V, Stanevsky A, Lupo B, Caravita T, Di Raimondo F, Palumbo AP

Boccadoro M, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8020.

Elotuzumab With Lenalidomide and Low-Dose Dexamethasone in Patients With Relapsed Multiple Myeloma: A Randomized Phase 1/2 Study

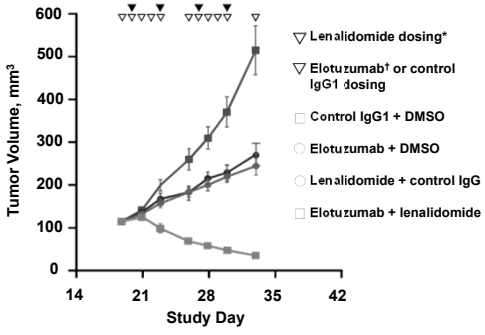
Abstract 8014

Richardson PG, Moreau P, Jakubowiak AJ, Facon T, Jagannath S, Vij R, Reece DE, White D, Zonder J, Raab MS, Benboubker L, Rossi JF, Tsao C, Parli T, Berman D, Singhal AK, Lonial S

Richardson PG, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8014.

Elotuzumab: Background

- Elotuzumab is a humanized IgG1 mAb targeting human CS1, a cell surface glycoprotein[1,2]
- CS1 is highly expressed on >95% of MM cells[1-3]
  - Lower expression on NK cells
  - Little to no expression on normal tissues
- MoA of elotuzumab is primarily through NK cell-mediated ADCC against myeloma cells[1,2]
- In a MM xenograft mouse model, antitumor activity of elotuzumab was enhanced by the addition of lenalidomide[4]

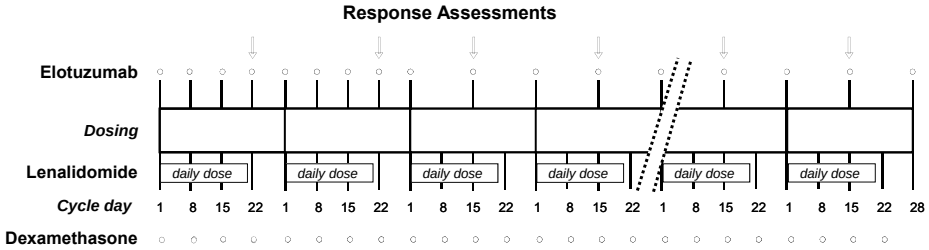


*Lenalidomide dosed at 50 mg/kg.
†Elotuzumab dosed at 1 mg/kg (below MED of 10 mg/kg).

ADCC, antibody-dependant cellular cytotoxicity; DMSO, dimethyl sulfoxide; mAb, monoclonal antibody; MED, maximum efficacious dose; MM, multiple myeloma; MoA, mechanism of action; NK, natural killer.

1. Hsi ED, et al. *Clin Cancer Res*. 2008;14(9):2775-2784. 2. Tai YT, et al. *Blood*. 2008;112:1329-1337. 3. van Rhee F, et al. *Mol Cancer Ther*. 2009;8(9):2616-2624. 4. Lonial S, et al. *Blood*. 2009;114: Abstract 432.

Phase I/II Study Design



- **Phase 1***
  - **Dose escalation study of elotuzumab 5, 10, and 20 mg/kg IV in combination with:**
    - **Lenalidomide 25 mg PO**
    - **Low-dose dexamethasone 40 mg PO**
- **Phase 2**
  - **Pts randomized to elotuzumab 10 or 20 mg/kg IV as above**
  - **Treatment continued until disease progression or unacceptable toxicity**

***First 5 pts limited to 6 cycles of therapy; remaining 23 pts treated until disease progression or unacceptable toxicity.**
Richardson PG, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8014.

Efficacy

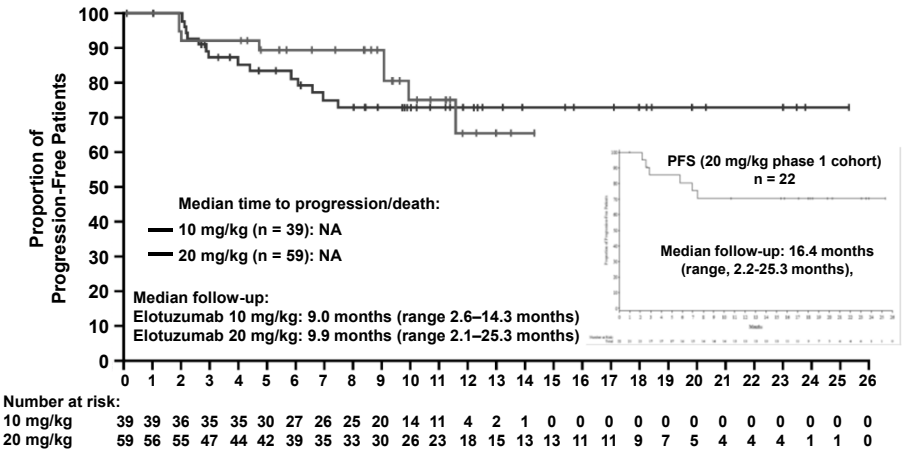
Best Confirmed Response (IMWG Criteria)

	Elotuzumab 10 mg/kg	Elotuzumab 20 mg/kg	Total
Pts, n	39	59	98
ORR (≥PR), n (%)	36 (92)	44 (75)	80 (82)
Stringent CR/CR, n (%)	5 (13)	4 (7)	9 (9)
VGPR, n (%)	10 (26)	22 (37)	32 (33)
PR, n (%)	21 (54)	18 (31)	39 (40)
SD, n (%)	3 (8)	11 (19)	14 (14)
PD, n (%)	0	2 (3)	2 (2)
IMWG nonevaluable, n (%)	0	2 (3)	2 (2)

CR, complete response; IMWG, International Myeloma Working Group; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Richardson PG, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8014.

Progression-Free Survival



Richardson PG, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8014.

Infusion Reactions*

Infusion Reaction AE	Patients without Premedication			Patients with Premedication		
	Elotuzumab		Total†	Elotuzumab		Total†
	10 mg/kg n = 3	20 mg/kg n = 8	n = 11	10 mg/kg n = 36	20 mg/kg n = 37	n = 73
All Grades, n (%)	3 (100)	8 (100)	11 (100)	20 (56)	21 (57)	41 (56)
Grade 3/4‡, n (%)	0	2 (25)	2 (18)	1 (3)	0	1 (1)

†The 14 patients in phase I who received suboptimal IV corticosteroid-containing premedication were not included.

AEs (≥5% of total patients)

- **Nausea, headache, pyrexia, dizziness, dyspnea, cough (≥10%)**
- **Rash, chills, erythema, vomiting, hyperhidrosis (5% to 9.9%)**

*Infusion reaction was predefined by the sponsor as the occurrence, regardless of causality, of one or more of ≈110 adverse events deemed potential manifestations, that occurred on the day of or the day after elotuzumab infusion; ‡There were no Grade 5 infusion reaction AEs.

Richardson PG, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8014.

Conclusions

- **10 mg/kg elotuzumab is the recommended phase III dose**
  - **High ORR (92%)**
  - **Similar safety profile for 10 and 20 mg/kg doses**
  - **Both doses saturate target CS1**
- **ORR of 90% in patients who had received only 1 prior therapy provides rationale for investigating this combination earlier in the disease course**

Interim Results from PX-171-006, a Phase (Ph) 2 Multicenter Dose Expansion Study of Carfilzomib (CFZ), Lenalidomide (LEN), and Low-Dose Dexamethasone (loDex) in Relapsed and/or Refractory Multiple Myeloma (R/R MM)

Abstract 8025

Wang M, Bensinger W, Martin T, Alsina M, Siegel D, Gabrail N, Hari P, Singhal S, Vescio R, Assouline S, Kunkel L, Vallone M, Wong A, Niesvizky R

Wang M, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8025.

Best Response to CRd Therapy

Response (n = 51)		n (%)	
≥VGPR		21 (41)	ORR= 78%
CR/nCR	12 (24)		
VGPR	9 (18)		
PR		19 (37)	
MR		1 (2)	
SD		3 (6)	
PD		4 (8)	
NE		3 (6)	

Wang M, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8025.

Safety

- No dose-limiting toxicities were reported with full doses of each agent, in this CRd combination regimen
- As of Oct 2010, the most common AEs were fatigue (50%) and diarrhea (42%) and the most common grade 3/4 AEs were neutropenia, anemia, and hypophosphatemia
- Of 52 patients, 5 (9.6%) reported drug-related serious adverse events (SAEs)

Wang M, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8025.

Does Zoledronic Acid (ZOL) Reduce Skeletal-Related Events (SREs) and Improve Progression-Free Survival (PFS) in Patients With Multiple Myeloma (MM) With or Without Bone Disease?

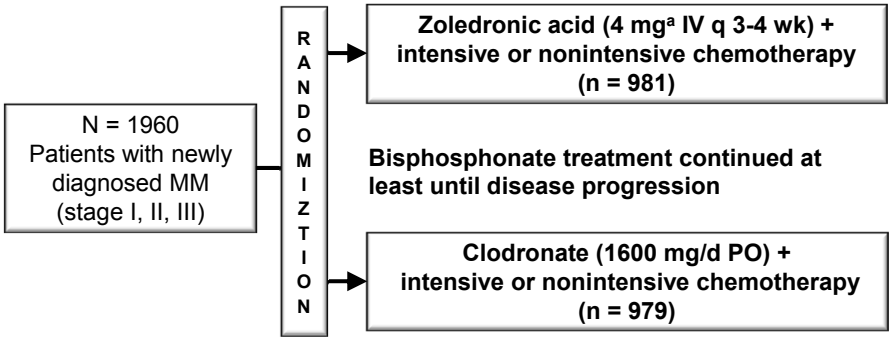
MRC Myeloma IX Study Results

Abstract 8010

Boyd K, Morgan G, Davies F, Wu P, Gregory W, Bell SE, Szubert A, Navarro Coy N, Drayson M, Owen RG, Feyler S, Ashcroft F, Ross F, Byrne J, Roddie H, Rudin C, Cook G, Jackson GH, Child JA

Boyd K, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8010.

MRC Myeloma IX—Analysis Schematic for ZOL vs CLO



Endpoints (ZOL vs CLO)

Primary: PFS, OS, and Response

Secondary: SREs (time to first SRE, SRE incidence) and Safety

SREs were defined as vertebral fractures, other fractures, spinal cord compression, and the requirement for radiation or surgery to bone lesions, or the appearance of new osteolytic bone lesions.

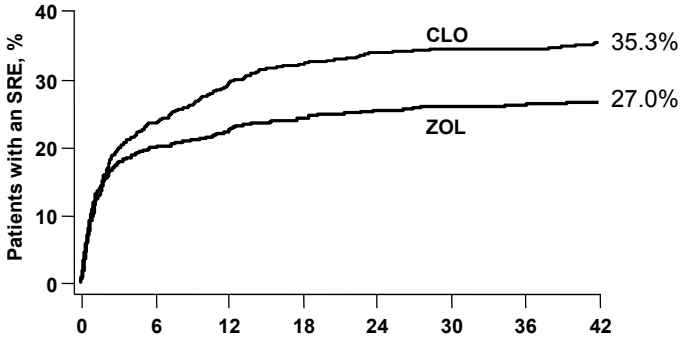
CLO, clodronate; IV, intravenous; MM, multiple myeloma; OS, overall survival, PFS, progression-free survival; PO, oral; SRE, skeletal-related event; ZOL, zoledronic acid.

[a] Dose-adjusted for patients with impaired renal function, per the prescribing information.

Boyd K, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8010.

MRC Myeloma IX—ZOL Significantly ⬇ SREs vs CLO in the Overall Population

- ZOL reduced the risk of SREs by 26% vs CLO (HR = 0.74; *P* = .0004)

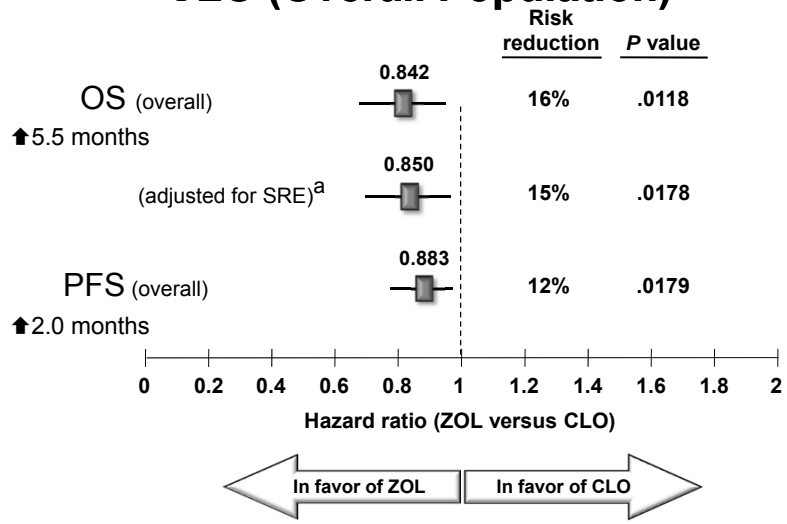


Patients at risk, n								
ZOL	981	663	506	390	284	201	138	97
CLO	979	629	465	337	256	173	112	74

HR, hazard ratio

Boyd K, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8010.

MRC Myeloma IX—ZOL ⬆ OS and PFS vs CLO (Overall Population)



[a]Time to first SRE was included as a time-dependent covariate in an exploratory Cox model examining OS.

Data from Morgan GJ, et al. *Lancet*. 2010;376(9757):1989-1999.

Boyd K, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8010.

MRC Myeloma Conclusions

- **Patients initiating therapy for MM are at a substantial risk for SREs**
  - **Prior SREs and osteolytic bone lesions place patients at ⬆ risk**
  - **Hypercalcaemia and MP are also associated with ⬆ risk**
- **ZOL significantly ⬇ SRE risk vs CLO**
  - **Regardless of bone disease status at presentation**
  - **Regardless of treatment pathway or regimen**
- **ZOL SRE benefits were seen within the first year**
  - **Supports early initiation of ZOL**

Davies F, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 8011.

GASCO's Best of ASCO® Lymphomas **Summary**

- **DLBCL**
  - **Intensification of induction or HDT consolidation does not improve outcomes**
- **HL**
  - **PET may aid in selecting pts with advanced HL who can avoid XRT following ABVD**
  - **Brentuximab vedotin provide an option for HL pts who fail auto**

Questions?