Lenalidomide (LEN) in Patients with Transformed Lymphoma: Results From a Large International Phase II Study (NHL-003)

Reeder CB et al.

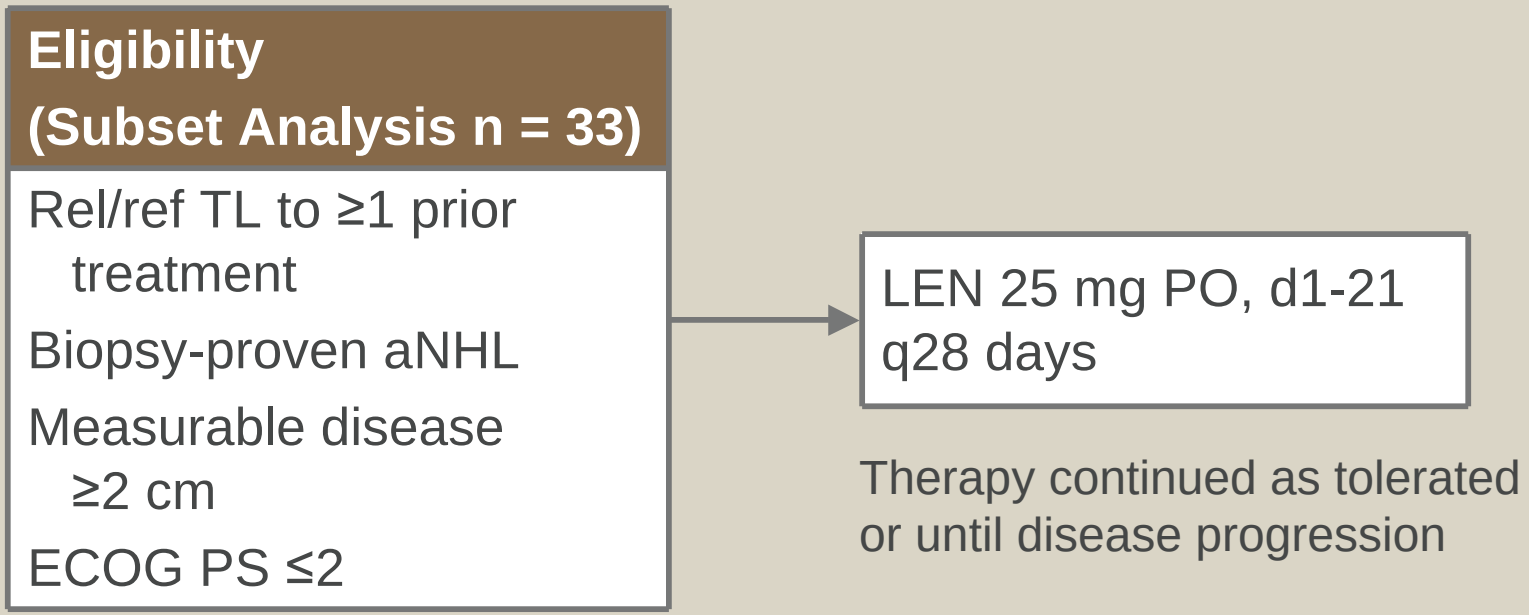
Proc ASCO 2010;Abstract 8037.

Introduction

- Patients (pts) with low-grade lymphoma have a 10-year 30 percent risk of transformation to aggressive non-Hodgkin's lymphoma associated with poor outcomes and few effective therapies (*Hematology Am Soc Hematol Educ Program* 2009;532).
- Lenalidomide (LEN) has shown clinical activity in Phase II studies of pts with relapsed or refractory (rel/ref) indolent or aggressive non-Hodgkin's lymphoma (aNHL) (*JCO* 2008;26:4952; JCO 2009;27:5404).
- Current study objective:
  - Evaluate the safety and efficacy of LEN monotherapy in pts with transformed lymphoma (TL) in the NHL-003 trial.

Reeder CB et al. *Proc ASCO* 2010;Abstract 8037.

NHL-003 Phase II Study Design



Reeder CB et al. *Proc ASCO* 2010;Abstract 8037.

Efficacy Data

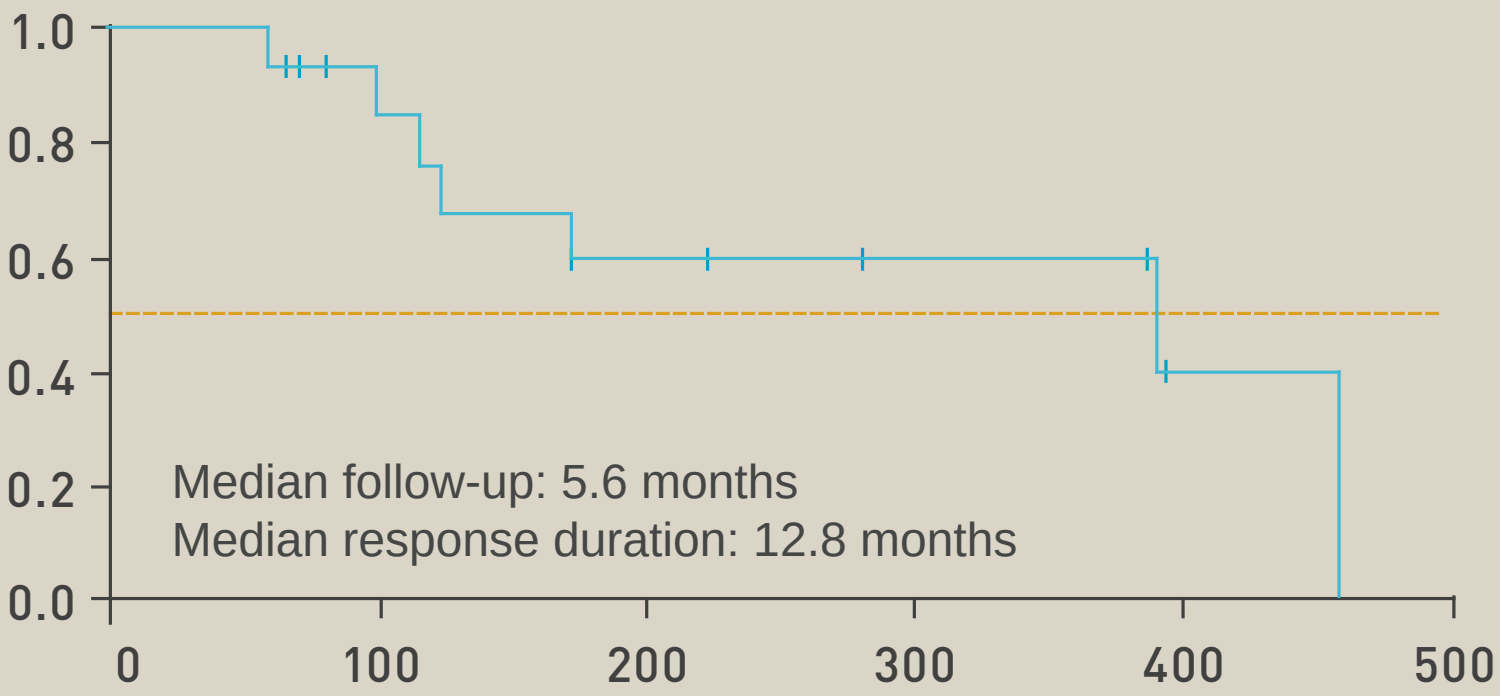
Patient Subgroups (n)	ORR %	CR/CRu %	Median PFS (Months)
All patients (n = 33)	45.5	21.2	5.4
According to histology*			
Transformed FL (n = 23)	57.0	36.1	7.7
Transformed CLL/SLL (n = 7)	0	0	1.9

CR = complete response; CRu = unconfirmed CR; FL = follicular lymphoma; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma

* There were three patients who transformed from histologies other than FL or CLL/SLL, of whom two achieved responses to LEN monotherapy (ORR 67%).

Reeder CB et al. *Proc ASCO* 2010;Abstract 8037.

Response Duration



With permission from Reeder CB et al. *Proc ASCO* 2010;Abstract 8037.

Grade 3/4 Adverse Events (n = 33)

Adverse Events	Grade 3 n (%)	Grade 4 n (%)
Neutropenia	11 (33.3)	5 (15.2)
Thrombocytopenia	4 (12.1)	1 (3)
Pneumonia	3 (9.1)	0
Abdominal pain	2 (6.1)	0
Anemia	2 (6.1)	0
Back pain	2 (6.1)	0
Leukopenia	2 (6.1)	0

Reeder CB et al. *Proc ASCO* 2010;Abstract 8037.

Conclusions

- LEN monotherapy shows promising clinical activity and achieves durable responses in patients with TL.
  - ORR = 45.5%; CR/CRu = 21.2%
  - Median response duration = 12.8 months
- Responses appear to be dependent on original histology:
  - Transformed FL: 57%
  - Transformed CLL/SLL: 0%
  - Other histologies: 67%
- The tolerability profile is consistent with other studies of LEN in hematological disease.
- Further study of LEN is warranted in this poor-risk population and the original histology should be taken into consideration.

Reeder CB et al. *Proc ASCO* 2010;Abstract 8037.

Faculty Comments

DR VOSE: The study evaluated single-agent lenalidomide in the subset of transformed lymphomas. Out of a total of 217 patients with lymphoma who received treatment, 15 percent were found to have transformed lymphomas.

All of these patients received multiple prior treatments, and the efficacy analysis showed approximately a 45 percent response rate and a 21 percent CR rate in this subset.

These are good data in a “very difficult to treat” patient population. However, most responses were among patients in whom FL had transformed, and it appears that patients with transformed CLL did not yield much benefit.

Long-Term Outcome of Patients in the LNH-98.5 Trial, the First Randomized Study Comparing R-CHOP to Standard CHOP Chemotherapy in DLBCL Patients

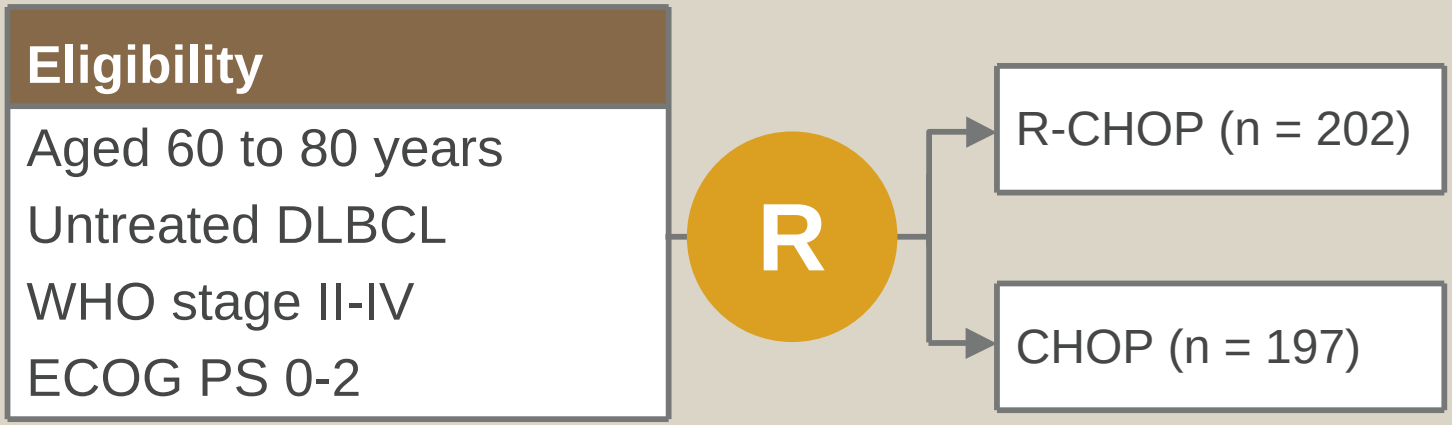
Coiffier B et al.
Blood 2010;116(12):2040-5.

Introduction

- LNH-98.5 was the first randomized trial to compare CHOP plus rituximab (R-CHOP) to CHOP alone in patients with diffuse large B-cell lymphoma (DLBCL), age 60 to 80.
- Significant improvements in the proportion of complete response (CR) and longer event-free survival (EFS) and overall survival (OS) were observed with R-CHOP at the 2- and 5-year follow-up points.
- The major benefits of R-CHOP treatment (tx) include decreases in the numbers of patients (pts) with refractory or relapsing (rel) disease.
- Current study objective:
  - Evaluate the data from the LNH-98.5 study at median 10-year follow-up.

Coiffier B et al. *Blood* 2010;116(12):2040-5.

Methods



R-CHOP = 375 mg/m^2 rituximab, 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, 1.4 to 2 mg/m^2 vincristine, d1; 40 mg/m^2 per day prednisone, d1-5

CHOP = 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, 1.4 to 2 mg/m^2 vincristine, d1; 40 mg/m^2 per day prednisone, d1-5

G-CSF was administered as supportive therapy if a patient developed Grade IV neutropenia or febrile neutropenia after a cycle of CHOP or R-CHOP.

Coiffier B et al. *Blood* 2010;116(12):2040-5.

Events Observed After 10-Year Follow-Up

Event	CHOP	R-CHOP
Progressive disease (PD) during tx	22.3%	8.1%
New unplanned tx	4.6%	5.4%
Progression after stable disease	0.5%	0.5%
PD after partial response	2.5%	3.0%
Rel for CR pts	36.0%	24.3%
Death without PD during tx	6.1%	5.9%
Death without PD after tx	8.1%	16.3%

Coiffier B et al. *Blood* 2010;116(12):2040-5.

Survival Outcomes

Event	CHOP	R-CHOP	*p*-value
10-y progression-free survival	20.1%	36.5%	<0.0001
10-y overall survival	27.6%	43.5%	<0.0001
10-y disease-free survival*	42.6%	64.3%	<0.0001
5-y survival after progression	14.6%	25.0%	NS
10-y survival after progression	10.5%	8.6%	NS

* CR or undocumented CR
NS = not significant

Coiffier B et al. *Blood* 2010;116(12):2040-5.

Survival in Patients with Progressive Disease

	Median survival (y)	2-y (%)	3-y (%)	5-y (%)
PD within first 3 y				
CHOP	0.6	25.9	19.6	14.3
R-CHOP	0.6	18.2	18.2	16.7
PD between y 4 and 5				
CHOP	3.0	83.3	50.0	16.7
R-CHOP	Not reached	83.3	66.7	66.7
PD after 5 y				
CHOP	0.9	22.2	22.2	22.2
R-CHOP	Not reached	87.5	87.5	58.3

Coiffier B et al. *Blood* 2010;116(12):2040-5.

Conclusions

- The benefits of R-CHOP compared to CHOP alone are maintained during a 10-year period.
  - Progression-free survival, 36.5% versus 20.1%
  - Overall survival, 43.5% versus 27.6%
  - Disease-free survival, 64.3% versus 42.6%
- Risk of death due to other diseases or secondary cancer is not higher in the R-CHOP group compared to CHOP alone.
  - Deaths, 55.4% versus 71.1%
  - Secondary cancer, R-CHOP (n = 21), CHOP (n = 22)
    - Deaths, R-CHOP (n = 10); CHOP (n = 12)
- These findings underscore the need to treat elderly patients with DLBCL with curative chemotherapy and confirm the benefits of treatment during a long follow-up period.

Coiffier B et al. *Blood* 2010;116(12):2040-5.

Faculty Comments

DR FOSS: These are long-term outcome data from the pivotal randomized study comparing R-CHOP to CHOP alone in DLBCL. The risk of long-term complications was similar between the two arms, and these results definitely underscore the benefit of R-CHOP.

What this paper is adding to the current knowledge is the long-term outcome data with respect not only to PFS or OS but also to the risks of secondary cancer and other treatment-related morbidities when rituximab is added to up-front therapy.

DR FISHER: This is the landmark practice-changing study that changed the world of large-cell lymphoma. The trial has been presented multiple times, has been consistent in its results and shows clinically and statistically significant results for 10 years.

R-CHOP14 Compared to R-CHOP21 in Elderly Patients with Diffuse Large B-Cell Lymphoma: Results of the Interim Analysis of the LNH03-6B GELA Study

Delarue R et al.

Proc ASH 2009;Abstract 406.

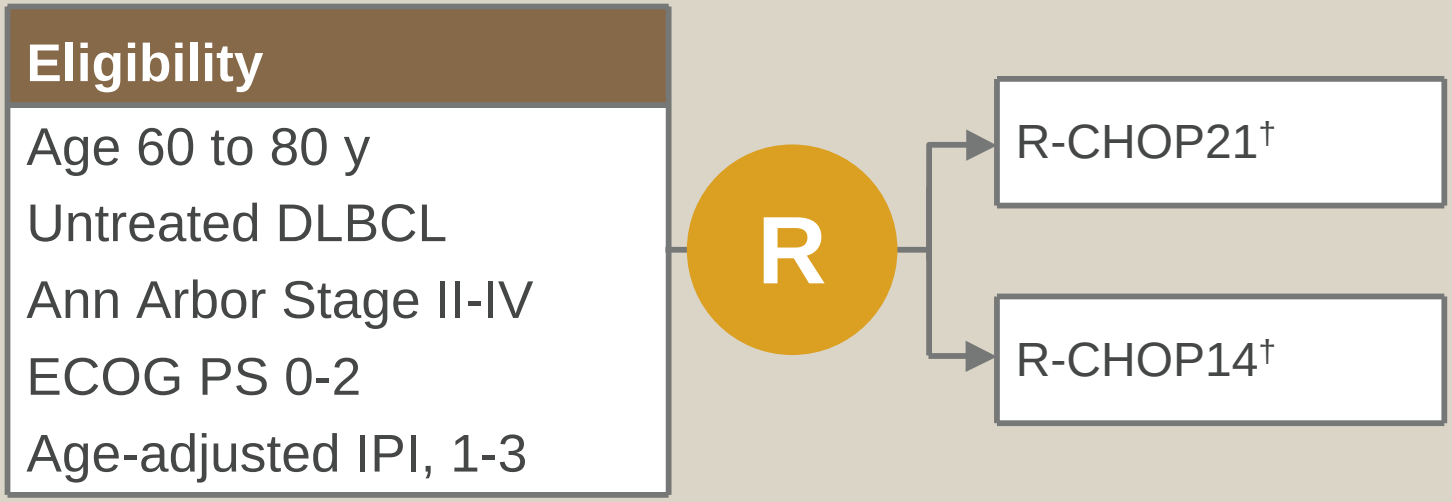
Introduction

- GELA demonstrated that survival is improved in elderly patients (pts) with DLBCL with the addition of rituximab (R) to standard CHOP21.
- Shortening the interval between the doses of R-CHOP (q2wk [R-CHOP14] vs q3wk [R-CHOP21]) may improve outcomes in pts with diffuse large B-cell lymphoma (DLBCL).
- Consecutive studies by the GELA group have found survival advantages associated with CHOP14 compared to CHOP21 and then with R-CHOP14 compared to CHOP14.
- Current study objective:
  - Compare the efficacy at 24 months median follow-up of R-CHOP14 to R-CHOP21 in elderly pts with DLBCL.

Delarue R et al. *Proc ASH* 2009;Abstract 406.

Trial Schema

Accrual: 602 (Closed)*



* N = 202 patients evaluable at the time of the interim analysis
† Subsequent randomization between prophylactic darbepoetin alfa and conventional treatment of anemia

Delarue R et al. *Proc ASH* 2009;Abstract 406.

Patient Characteristics and Treatment (N = 202)

Characteristic	CHOP (n = 99)	R-CHOP (n = 103)
Median age, y	72	71
aaIPI, 2-3	59%	67%
B symptoms	43%	37%
Treatment	**R-CHOP21**	**R-CHOP14**
Interval between cycles, median time	21 days	15 days
Completed 8 cycles without progression	76%	71%
Received G-CSF	68%	90%

Delarue R et al. *Proc ASH* 2009;Abstract 406.

Response and Survival

Event	R-CHOP21 n = 98	R-CHOP14 n = 103	*p*-value
Response CR + uCR Partial response (PR) Overall response rate (ORR)	 75% 9% 84%	 67% 14% 81%	NS
2-y event free-survival (EFS)	61%	48%	0.1112
2-y overall survival (OS)	70%	67%	0.3664

NS = not significant

Delarue R et al. *Proc ASH* 2009;Abstract 406.

Adverse Events (AEs)

Selected AEs* (%)	R-CHOP21	R-CHOP14
Grade 3/4 hemoglobin	22%	26%
Grade 3/4 leukocytes	73%	83%
Grade 3/4 neutrophils	69%	83%
RBC transfusion	36%	50%
Platelet transfusion	11%	15%
Hospitalization (median no. of nights)	8.5	13
Deaths due to treatment toxicity, n	4	9

* Grade 3/4 nonhematologic AEs were similar between groups.

Delarue R et al. *Proc ASH* 2009;Abstract 406.

Conclusions

- The results of this interim analysis (N = 202) did not confirm clinical benefit of R-CHOP14 compared to R-CHOP21 and favor treatment with R-CHOP21 in elderly patients with DLBCL.
  - CR/uCR, 75% vs 67%
  - EFS, 61% vs 48%
  - OS, 70% vs 67%
- Hematologic adverse events and febrile neutropenia leading to increased hospitalizations were more common in the R-CHOP14 group compared to the R-CHOP21 group.
- The final findings from all patients (N = 602) are planned to be presented in 2010 and will provide more information.

Delarue R et al. *Proc ASH* 2009;Abstract 406.

Faculty Comments

DR FOSS: The study compared R-CHOP21 to dose-dense R-CHOP14 in elderly patients and showed that the toxicity was higher in the dose-dense group. Among the efficacy endpoints, it is hard to say if one was better but certainly they were equal. The ORRs appeared similar and the EFS was superior with R-CHOP21. In view of higher toxicity with the dose-dense R-CHOP14 regimen, R-CHOP21 remains the standard.

DR FISHER: This study investigated whether R-CHOP14 is superior to R-CHOP21. Although CR rates are not statistically different, they appear numerically superior on the R-CHOP21 arm. This, combined with an early report of the British national study, suggests to me that there is no indication for R-CHOP14 in routine treatment for these patients.

Lymphoma Recurrence 5 Years or Later Following Diffuse Large B-Cell Lymphoma: Clinical Characteristics and Outcome

Larouche JF et al.
J Clin Oncol 2010;28(12):2094-100.

Introduction

- Patients with diffuse large B-cell lymphoma (DLBCL) who relapse usually do so within 2 to 3 years following treatment, although late recurrences after 5 years have been described and are considered rare (*Blood* 1992;79:1024-8).
- Patients who experience late relapse are thought to comprise a distinct subgroup with disease behavior that is different from those with early relapse.
- The clinical characteristics at diagnosis of patients who relapse are not well defined.
- Current study objective:
  - This study was designed to better understand the clinical characteristics and prognosis of patients with DLBCL who develop late relapse.

Larouche JF et al. *J Clin Oncol* 2010;28(12):2094-100.

Methods

- Retrospective analysis of patients from two centers in France.
- Inclusion criteria:
  - Diagnosis of DLBCL between 1985 and 2003
  - Biopsy-confirmed relapse ≥5 years after DLBCL diagnosis
  - Complete response or unconfirmed complete response to initial treatment
  - No primary CNS lymphoma at diagnosis
  - Non-Hodgkin's lymphoma histology at relapse included
  - No history of indolent lymphoma or transformation
- All pathology reports at diagnosis and relapse were reviewed by expert hematopathologists.
- All available pathology specimens were recovered to revise diagnosis and complete missing immunohistochemistry data.

Larouche JF et al. *J Clin Oncol* 2010;28(12):2094-100.

Patient Characteristics at Diagnosis*

Clinical Character-istics	DLBCL Relapse† n = 45	Indolent Relapse n = 9	Pathologic‡	DLBCL Relapse† n = 45	Indolent Relapse n = 9
Median age	57 yrs	58 yrs	CD20†	37/37	9/9
Stage I-II	67%	44%	Bcl-6†	6/14	3/4
Extranodal	62%	78%	CD10†	8/31	2/5
IPI score, 0-2	84%	71%	MUM1†	11/20	0/3
Indolent DLBCL	18%	56%	Bcl-2†	15/25	4/4

*Histology at relapse; † DLBCL subgroup includes indolent DLBCL;
‡ Positive data for the number of patients analyzed

Larouche JF et al. *J Clin Oncol* 2010;28(12):2094-100.

Patient Characteristics at Relapse*

Clinical Character-istics	DLBCL Relapse† n = 45	Indolent Relapse n = 9	Pathologic‡	DLBCL Relapse† n = 45	Indolent Relapse n = 9
Median age	66 yrs	66 yrs	CD20†	41/41	7/7
Stage I-II	49%	44%	Bcl-6†	18/24	2/3
Extranodal	73%	44%	CD10†	13/37	3/7
Median time to relapse	7.5 yrs	6.7 yrs	MUM1†	17/27	1/3
Indolent DLBCL	18%	56%	Bcl-2†	27/32	4/5

* Histology at relapse; † DLBCL subgroup includes indolent DLBCL;
‡ Positive data for the number of patients analyzed

Larouche JF et al. *J Clin Oncol* 2010;28(12):2094-100.

Patient Characteristics at Relapse: Response to Treatment and Survival

Response to Treatment	All Patients n = 54	DLBCL n = 45	Indolent n = 9
Complete response	65%	61%	88%
Partial response	25%	29%	0%
No response	10%	10%	12%
Survival	**Histological Subtype at Relapse**		***p*-value**
	DLBCL	**Indolent**	
Event-free survival (5 y)	17%	61%	0.027
Overall survival (5 y)	27%	75%	0.029

Larouche JF et al. *J Clin Oncol* 2010;28(12):2094-100.

Conclusions

- Relapse after 5 years was rare and occurred in 3.6% of patients with DLBCL. This was in accordance with the incidence reported by others (Ko AH, Yuen AR. *Leuk Lymphoma* 2002;43:1789-93).
- Patients with late relapse seemed to present with distinct clinical features at diagnosis including initial early stage disease, extranodal involvement and favorable IPI.
  - 63% had initial localized disease
  - 82% had low or low-intermediate IPI score
  - 65% had extranodal involvement and 50% had primary extranodal involvement
- Aggressive treatment with induction multiagent chemotherapy with rituximab and ASCT should be pursued at relapse whenever possible.

Larouche JF et al. *J Clin Oncol* 2010;28(12):2094-100.

Faculty Comments

DR VOSE: This is a review of a subset of patients from a large patient population initially diagnosed with DLBCL who experienced disease recurrence five or more years after their initial therapy.

Overall, only 54 patients out of approximately 1,500 experienced late relapses, and most of these patients initially with low-stage or low IPI disease often had extranodal involvement of germinal center B-cell type.

Most patients achieving the five-year mark without relapse will remain relapse free. However, late relapses are difficult to treat and those patients don’t have many options other than autologous stem cell transplant.

Salvage Regimens with Autologous Transplantion for Relapsed Large B-Cell Lymphoma in the Rituximab Era

Gisselbrecht C et al.

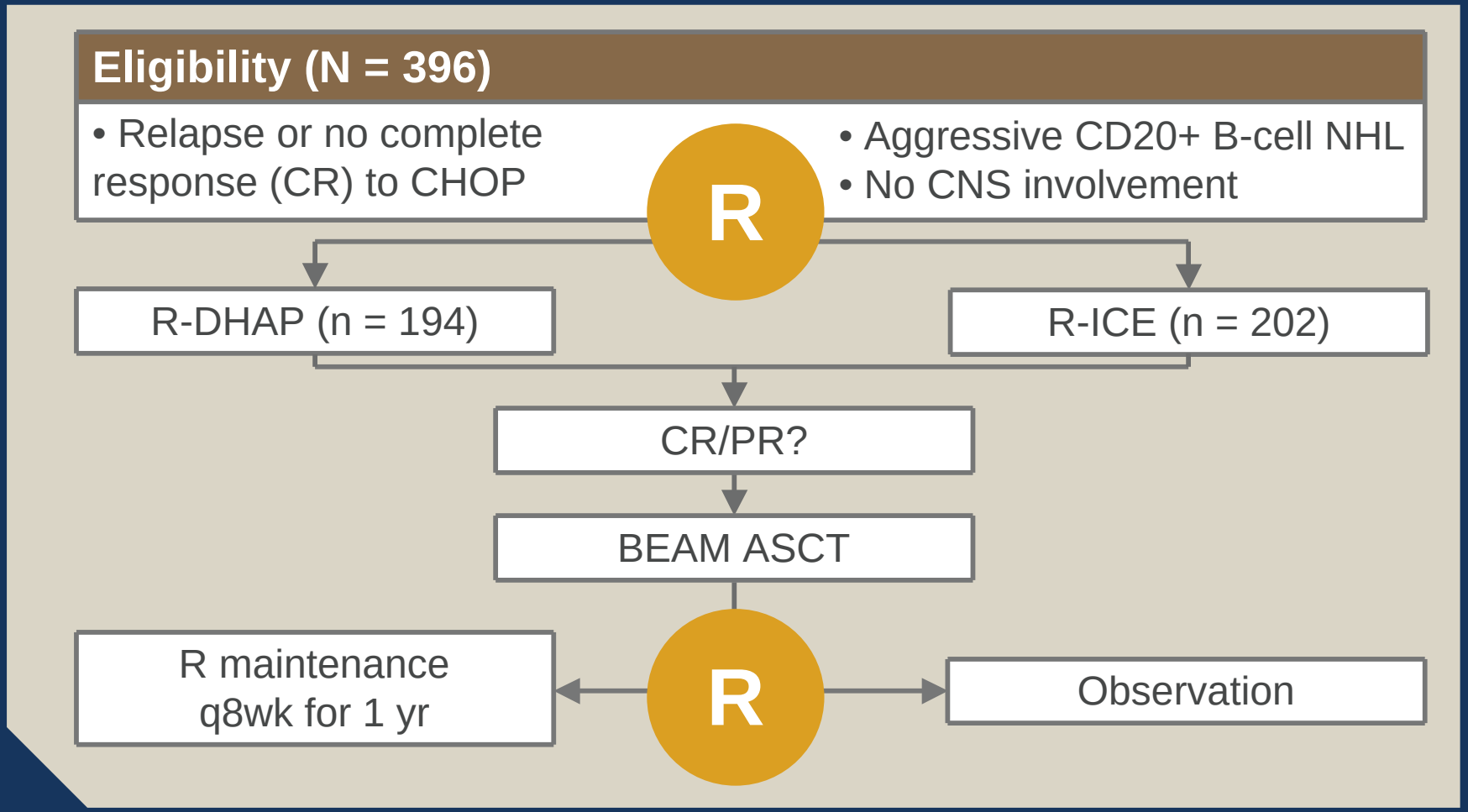
J Clin Oncol 2010;28(27):4184-90.

Introduction

- In the second-line setting, rituximab (R) and chemotherapy followed by autologous stem cell transplantation (ASCT) significantly improves survival in patients with non-Hodgkin's lymphoma (NHL) who are R naïve (*Blood* 2008;111:537).
- Comparative studies have not evaluated the efficacy of salvage regimens in patients with B-cell NHL who experience relapse.
- Current study objectives:
  - Compare the efficacy of two established salvage regimens — R, dexamethasone (D), high-dose cytarabine (HA) and cisplatin (P) versus R, ifosfamide (I), carboplatin (C) and etoposide (E) — followed by ASCT.
  - Identify factors influencing treatment outcomes, including the prior use of R.

Gisselbrecht C et al. *J Clin Oncol* 2010;28(27):4184-90.

CORAL: A Phase III Multicenter, Randomized Trial



Gisselbrecht C et al. *J Clin Oncol* 2010;28(27):4184-90.

Response After Salvage Treatment and Before ASCT

Clinical Response	R-ICE (n = 197)	R-DHAP (n = 191)
Overall response rate (ORR)	64%	63%
Complete response (CR)/ unconfirmed CR (uCR)	24%/12%	28%/12%
Partial response (PR)	27%	24%
Stable disease (SD)	12%	12%
Progressive disease (PD)	19%	18%
Death	3%	5%

Gisselbrecht C et al. *J Clin Oncol* 2010;28(27):4184-90.

Response and Survival According to Prognostic Factors

Prognostic Factor	CR/uCR/PR	3-yr EFS	3-yr OS
All patients (N = 398)	63%	31%	50%
CR/uCR	38%	51%	70%
Prior R no/yes (n = 147,244)	83%*/51%	47%*/21%	66%*/40%
Relapse, >12 mo (n = 160)	88%*	45%*	64%
Refractory, <12 mo (n = 228)	46%	20%	39%*

EFS = event-free survival; OS = overall survival; R = rituximab;
* $p < 0.001$

Gisselbrecht C et al. *J Clin Oncol* 2010;28(27):4184-90.

3-Year Survival

Survival	R-ICE	R-DHAP	*p*-value
Event-free survival	26%	35%	0.6
Progression-free survival (PFS)	31%	42%	0.4
Overall survival	47%	51%	0.4

Gisselbrecht C et al. *J Clin Oncol* 2010;28(27):4184-90.

Conclusions

- The response rates before ASCT in the R-ICE and R-DHAP groups were similar.
  - ORR: 64% vs 63%
  - CR or uCR: 36% vs 40%
- Similar survival rates between the R-ICE and R-DHAP arms were observed.
  - EFS: 26% vs 35%
  - PFS: 31% vs 42%
  - OS: 47% vs 51%
- Early relapse (<12 mo) and prior rituximab-containing first-line therapy defined a population of patients with a poor response to the standard salvage treatment.

Gisselbrecht C et al. *J Clin Oncol* 2010;28(27):4184-90.

Faculty Comments

DR FISHER: The CORAL study evaluated R-ICE versus R-DHAP as salvage chemotherapy prior to high-dose chemotherapy with autologous transplant.

The study did not demonstrate any significant difference between the two regimens, suggesting once again that the different salvage regimens have similar efficacy.

An important finding of the study is that with up-front rituximab-containing regimens in the initial treatment of DLBCL, the salvage rate is decreased and transplant cures a smaller proportion of patients than when rituximab was not part of up-front therapy. It means that transplant will fail in a significant number of patients who will need different forms of treatment.