Year in Review

Year in Review

A CME monograph summarizing the year's most important meeting presentations and journal articles

Non-Hodgkin's Lymphomas: 2009-2010

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Monograph

Non-Hodgkin's Lymphomas: 2009-2010

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Year in Review — Non-Hodgkin's Lymphomas: 2009-2010 Continuing Medical Education (CME) Information

OVERVIEW OF ACTIVITY

Given the prevalent nature of the disease, extensive resources are allocated to hematologic cancer research and education. The current utility of cytotoxic chemotherapies, autologous and/or allogeneic hematopoietic stem cell transplant and biologic or molecular-targeted therapies has been the focus of treatment algorithms designed to assist clinicians in the care of patients with non-Hodgkin's lymphomas (NHL). The variety of recognized practical management scenarios for NHL may cause clinician confusion and controversy. Educational opportunities relevant to the clinical management of NHL are essential to general oncologists' delivery of comprehensive cancer care. To bridge the gap between research and patient care, this CME activity uses the input of cancer experts and community physicians to frame a relevant discussion of recent research advances in hematologic cancer that can be applied to routine clinical practice. This information will help medical oncologists, hematologists and hematology-oncology fellows formulate up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Appraise recent data on therapeutic advances and changing practice standards in NHL, including chronic lymphocytic leukemia (CLL), and apply this information to clinical practice.
- Use prognostic and predictive clinical and molecular markers to aid in treatment decision-making for NHL.
- Individualize the use of maintenance and/or consolidation therapy in the management of newly diagnosed and relapsed follicular lymphoma.
- Recall the emerging data for novel agents and combinations in the treatment of mantle-cell lymphoma.
- Develop an algorithm for the risk-stratified induction treatment of diffuse large B-cell lymphoma.
- Apply the results of emerging clinical research to the selection of optimal systemic therapy for patients with newly diagnosed or relapsed/refractory CLL.
- Communicate the benefits and risks of evidence-based systemic treatments to patients with advanced cutaneous or peripheral T-cell lymphoma.
- Identify patients with NHL who may experience quantitative and qualitative benefit from salvage therapy regimens with stem cell transplantation.

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COMMERCIAL SUPPORT

This program is supported by educational grants from Celgene Corporation and Genentech BioOncology/Biogen Idec.

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This educational activity includes discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Fisher** — **Consulting Agreements:** Millennium Pharmaceuticals Inc, Pfizer Inc, Roche Laboratories Inc. **Dr Foss** — **Advisory Committee:** Allos Therapeutics; **Speakers Bureau:** Allos Therapeutics, Celgene Corporation, Eisai Inc. **Dr Vose** — **Paid Research:** Allos Therapeutics, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Celgene Corporation, Exelixis Inc, Genentech BioOncology, Genzyme Corporation, GlaxoSmithKline, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Pharmacyclics Inc, US Biotest Inc.

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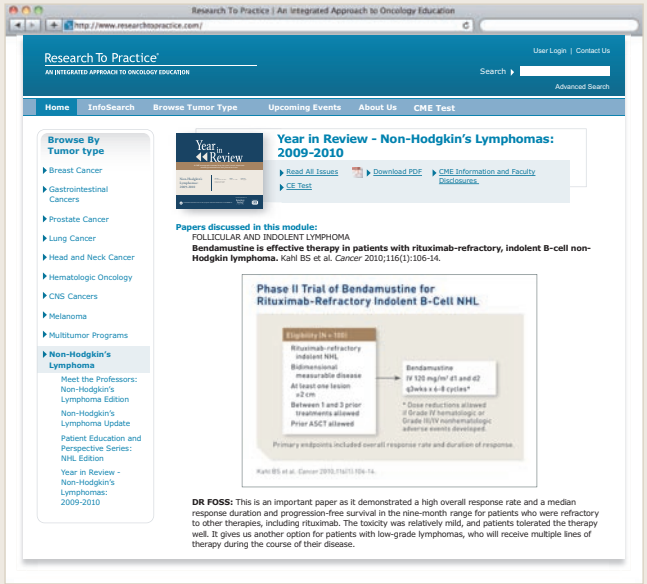

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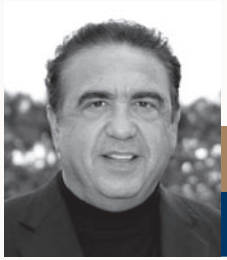
The online version of *Year in Review — Non-Hodgkin's Lymphoma* 2009-2010 includes:

- Interactive slide modules with faculty commentary reviewing the 21 "Priority 1" papers and presentations featured in the monograph
- An annotated bibliography listing all "Priority 2" papers and presentations
- References with active web links for all papers and presentations taking users to actual abstracts and full-text publications
- Downloadable PowerPoint slides for each of the Priority 1 publications
- A convenient, downloadable PDF-based version of the monograph



NEIL LOVE, MD

TWELVE MONTHS OF ACTION, BUT COULD WE MOVE EVEN FASTER?

Every December the American Society of Hematology Annual Meeting features an explosion of clinical research presentations unveiling important new data sets across all hematologic cancers. Even as the months pass and other meetings such as ASCO take place, discussions focused on the management of patients with these unique diseases inevitably return to "what happened at ASH" and how these themes are being incorporated into practice and/or further elucidated in more recent peer-reviewed publications.

For the enclosed distillation of data in one corner of this busy field — NHL and CLL, which is not an inconsequential proportion of patient cases (Figure 1) — we once again asked clinical investigators and oncologists in community-based practice to sift through a mountain of information (including a hefty dose of ASH abstracts) and pick out the pearls most relevant to daily patient care (see Figure 2). The 21 papers selected as "Priority 1" publications are considered by our reviewers to be required reading for any physician providing care for patients with NHL or CLL. Twelve additional "Priority 2" papers are also highlighted and annotated.

These reports are tangible representations of the substantial progress that has been made in the field, but it is also worth considering that we still are not moving forward optimally. Although many (most) patients with NHL and CLL are not cured, very few are being managed as part of a clinical trial (Figure 3). Even fewer are having their tissue, sera and marrow banked for use as part of translational research. Yes, all physicians caring for people with these cancers must fully understand evolving data and standards of care, but they must also help voice the need to find a way to fund a more comprehensive research platform that might solve these critical problems more quickly.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
December 8, 2010

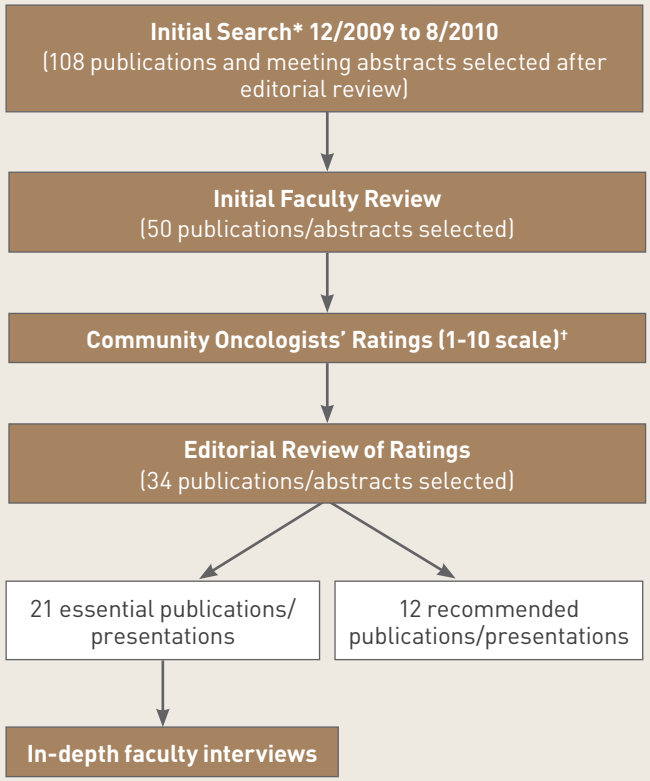
1. Management of Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia

Approximately how many new patients do you see per year with the following diseases?

	Median
Chronic lymphocytic leukemia (CLL)	15
Diffuse large B-cell lymphoma (DLBCL)	15
Follicular lymphoma (FL)	14
Mantle-cell lymphoma (MCL)	2
T-cell lymphoma (TCL)	2

Survey of 100 Practicing Medical Oncologists.
Research To Practice, 2010.

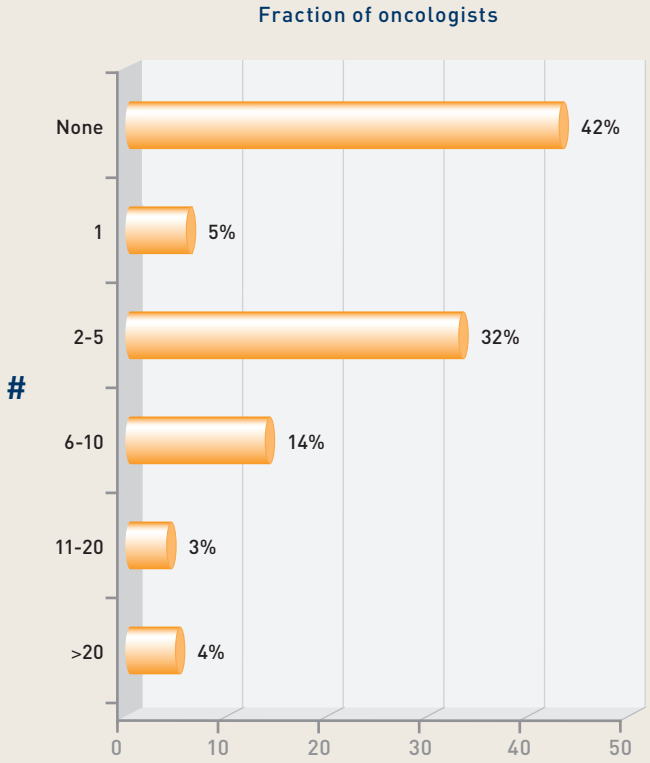
2. Process for Identifying Key Recent Reports on the Management of Non-Hodgkin's Lymphomas



*PubMed. January 1, 2010 to August 20, 2010, English language, clinical trials, randomized clinical trials, practice guidelines, meta-analysis, key core clinical journals. Search of meeting abstracts from 2009 ASH and 2010 ASCO annual meetings.
†Importance for medical oncologists in community-based practice, 1 = least important, 10 = very important

3. Management of Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia

In the past year, how many of your patients with NHL/CLL have been enrolled on a clinical trial, either directly or through a referral?



Survey of 100 Practicing Medical Oncologists. Research To Practice, 2010.

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FOLLICULAR AND INDOLENT LYMPHOMA

6 Kahl BS et al. **Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: Results from a multicenter study.** *Cancer* 2010;116(1):106-14.

8 Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized Phase III study of the StiL (Study group indolent Lymphomas, Germany).** *Proc ASH* 2009;Abstract 405.

10 Salles GA et al. **Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy.** *Proc ASCO* 2010;Abstract 8004.

12 Van Oers MH et al. **Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: Long-term outcome of the EORTC 20981 phase III randomized intergroup study.** *J Clin Oncol* 2010;28(17):2853-8.

14 Fowler N et al. **Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: Encouraging activity in the Phase 2 VERTICAL study.** *Proc ASH* 2009;Abstract 933.

16 Kaminski MS et al. **Tositumomab and iodine I-131 tositumomab for previously untreated, advanced-stage, follicular lymphoma: Median 10 year follow-up results.** *Proc ASH* 2009;Abstract 3759.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)/SMALL LYMPHOCYTIC LYMPHOMA (SLL)

18 Hallek M et al. **Addition of rituximab to fludarabine and cyclophosphamide in patients with CLL: A randomized, open-label, Phase 3 trial.** *Lancet* 2010;376(9747):1164-74.

20 Fischer K et al. **Bendamustine combined with rituximab (BR) in first-line therapy of advanced CLL: A multicenter Phase II trial of the German CLL Study Group (GCLLSG).** *Proc ASH* 2009;Abstract 205.

22 Wierda WG et al. **Ofatumumab combined with fludarabine and cyclophosphamide (O-FC) shows high activity in patients with previously untreated chronic lymphocytic leukemia (CLL): Results from a randomized, multicenter, international, two-dose, parallel group, Phase II trial.** *Proc ASH* 2009;Abstract 207.

24 Badoux X et al. **A phase II study of lenalidomide as initial treatment of elderly patients with chronic lymphocytic leukemia.** *Proc ASCO* 2010;Abstract 6508.

26 Ferrajoli A et al. **Combination therapy with lenalidomide and rituximab in patients with relapsed chronic lymphocytic leukemia (CLL).** *Proc ASH* 2009;Abstract 206.

DIFFUSE LARGE B-CELL LYMPHOMA

28 Reeder CB et al. **Lenalidomide (LEN) in patients with transformed lymphoma: Results from a large international phase II study (NHL-003).** *Proc ASCO* 2010;Abstract 8037.

30 Coiffier B et al. **Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: A study by the Groupe d'Etudes des Lymphomes de l'Adulte.** *Blood* 2010;116(12):2040-5.

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

34 Larouche JF et al. **Lymphoma recurrence 5 years or later following diffuse large B-cell lymphoma: Clinical characteristics and outcome.** *J Clin Oncol* 2010;28(12):2094-100.

36 Gisselbrecht C et al. **Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era.** *J Clin Oncol* 2010;28(27):4184-90.

T-CELL LYMPHOMA

38 Whittaker SJ et al. **Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma.** *J Clin Oncol* 2010;28(29):4485-91.

40 Horwitz SM et al. **Pralatrexate is active in cutaneous T-cell lymphoma (CTCL): Results of a multicenter, dose-finding trial.** *Proc ASH* 2009;Abstract 919.

MANTLE-CELL LYMPHOMA

42 Friedberg JW et al. **Bendamustine, bortezomib and rituximab in patients (pts) with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma (NHL): A multicenter Phase II clinical trial.** *Proc ASH* 2009;Abstract 924.

44 Morrison VA et al. **A phase II trial of bortezomib plus lenalidomide for relapsed/refractory mantle cell lymphoma (MCL) (CALGB 50501): Results of a planned interim analysis.** *Proc ASCO* 2010;Abstract 8106.

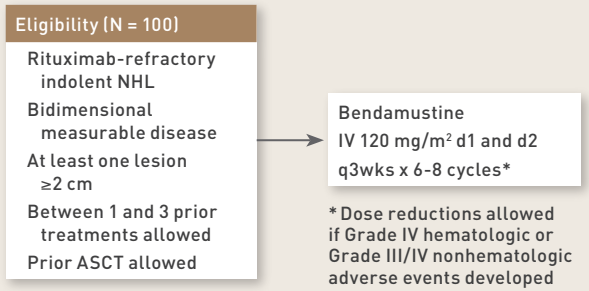
POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)

46 Trappe R et al. **Sequential treatment with rituximab and CHOP chemotherapy in B-cell PTLD — Moving forward to a first standard of care: Results from a prospective international multicenter trial.** *Proc ASH* 2009;Abstract 100.

Bendamustine is Effective Therapy in Patients with Rituximab-Refractory, Indolent B-Cell Non-Hodgkin Lymphoma

Kahl BS et al.
Cancer 2010;116(1):106-14.

Phase II Trial of Bendamustine for Rituximab-Refractory Indolent B-Cell NHL



Primary endpoints included overall response rate and duration of response.

Kahl BS et al. *Cancer* 2010;116(1):106-14.

Introduction

- Bendamustine is a novel alkylating agent with a benzimidazole ring that inhibits tumor cell growth by inducing mitotic failure and apoptosis.
- In March 2008, bendamustine was approved for the treatment of chronic lymphocytic leukemia in the United States.
- A previously published Phase II study demonstrated that single-agent bendamustine produced durable objective responses in patients with recurrent, rituximab-refractory, indolent B-cell lymphoma (*JCO* 2008;26:204).
- Current study objective:
  - Assess the safety and efficacy of single-agent bendamustine in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma (NHL).

Kahl BS et al. *Cancer* 2010;116(1):106-14.

Patient Characteristics — Previous Therapies

Variable	No. of Patients (%)
Median number of previous chemotherapy regimens [range]	**2 [0-6]**
Type of previous therapy	
Single-agent rituximab	1 (1%)*
CHOP-like chemo rituximab	37 (37%)
CVP ± rituximab	38 (38%)
Purine analog-based ± rituximab	44 (44%)
Radioimmunotherapy	24 (24%)
External beam radiation therapy	20 (20%)

* Patient in protocol violation but included in primary analysis according to prespecified analysis conditions

Kahl BS et al. *Cancer* 2010;116(1):106-14.

Overall Response Rate (ORR) and Median Duration of Response (DoR)

Patient Subgroup	ORR*
Total (n = 100)	75%
Chemosensitive (n = 51)	88%
Chemorefractory (n = 36)	64%
Patient Subgroup	**DoR (95% CI)**
Overall (n = 75)	9.2 mos (7.1-10.8)
Chemosensitive (n = 45)	10.0 mos (8.4-11.7)
Chemorefractory (n = 23)	6.3 mos (4.9-NA)

NA = not available
* ORR was assessed by independent review committee. ORR was defined as proportion of patients with best response ≥ partial response.

Kahl BS et al. *Cancer* 2010;116(1):106-14.

Conclusions

> Single-agent bendamustine produced a high rate of response in patients with recurrent, indolent NHL.
  – ORR: 75% for overall patient group
  – DoR: 9.2 mos for overall patient group
  – Median progression-free survival: 9.3 mos for overall patient group (data not shown)
> The toxicity profile of bendamustine was acceptable.
  – Major toxicities associated with treatment were reversible myelosuppression, gastrointestinal toxicity and infection.
> These data support the clinical benefit of bendamustine in patients with indolent B-cell NHL that is refractory to rituximab.

Kahl BS et al. *Cancer* 2010;116(1):106-14.

Adverse Events* (N = 100)

Hematologic Adverse Events	Grade 3	Grade 4
Anemia	7%	3%
Thrombocytopenia	19%	6%
Neutropenia	38%	23%
Febrile neutropenia	5%	1%
Nonhematologic Adverse Events		
Infection	15%	6%
Fatigue	12%	2%
Diarrhea	5%	0%

* Six possible treatment-related deaths occurred on study.

Kahl BS et al. *Cancer* 2010;116(1):106-14.

Faculty Comments

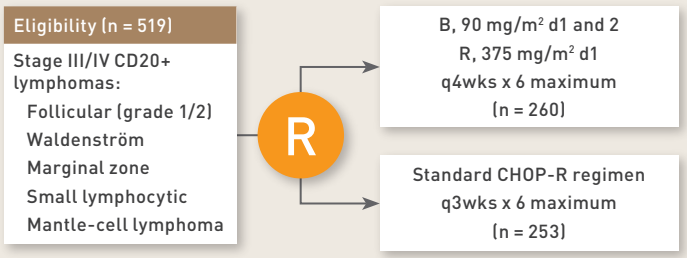
DR FOSS: This is an important paper as it demonstrated a high overall response rate and a median response duration and progression-free survival of approximately nine months for patients with disease that was refractory to other therapies, including rituximab. The toxicity was relatively mild, and patients tolerated the therapy well. It gives us another option for patients with low-grade lymphomas who will receive multiple lines of therapy during the course of their disease.

DR VOSE: The study used a bendamustine dose of 120 mg/m^2 on days 1 and 2 every three weeks. I would say that most people nowadays use the 90-mg/m^2 days 1 and 2 dose to start with, and that is better tolerated.

StiL NHL 1-2003: Bendamustine Plus Rituximab versus CHOP Plus Rituximab in the First-Line Treatment of Patients with Indolent and Mantle Cell Lymphoma

Rummel MJ et al.
Proc ASH 2009;Abstract 405.

StiL NHL 1-2003 Phase III Trial Design



Rummel MJ et al. *Proc ASH* 2009;Abstract 405.

Introduction

> Bendamustine is approved as a single-agent treatment for relapsed/refractory indolent non-Hodgkin's lymphoma (NHL).
> A Phase II trial of bendamustine and rituximab (BR) showed high activity in relapsed indolent lymphomas that was accompanied by low toxicity (*JCO* 2005;23:3383).
  – Overall response rate (ORR): 90%
  – Complete remission rate: 60%
> Current study objective:
  – Compare BR to CHOP-R as a first-line treatment for indolent and mantle-cell lymphomas.

Rummel MJ et al. *Proc ASH* 2009;Abstract 405.

Efficacy Results

Clinical Parameter	BR (n = 260)	CHOP-R (n = 253)	*p*-value
ORR	92.7%	91.3%	—
Complete response (CR)	39.6%	30.0%	0.0262
Progression-free survival (PFS)	54.9 mos	34.8 mos	0.00012
Follicular lymphoma patients (n = 277)	Not reached	46.7 mos	0.0281

Rummel MJ et al. *Proc ASH* 2009;Abstract 405.

Grade 3/4 Adverse Events - Hematologic

Adverse Event	BR (n = 1,450) % of cycles	CHOP-R (n = 1,408) % of cycles	*p*-value
Leukocytopenia	12.1	38.2	< 0.0001
Neutropenia	10.7	46.5	< 0.0001
G-CSF administered	4.0	20.0	< 0.0001
Thrombocytopenia	0.7	1.2	—
Anemia	1.4	1.9	—

Rummel MJ et al. *Proc ASH* 2009;Abstract 405.

Summary and Conclusions

> BR significantly improved CR and PFS compared to CHOP-R in patients with indolent and mantle-cell lymphoma.
  – CR: 39.6% vs 30.0%
  – PFS: 54.9 mos vs 34.8 mos
> Overall survival did not differ between the two study arms (data not shown).
> The tolerability profile with BR was better compared to CHOP-R.
  – No alopecia
  – Less hematotoxicity, less G-CSF used and fewer infections and neuropathy
> BR has the potential to become a standard treatment option for select patients with indolent and mantle-cell lymphoma.

Rummel MJ et al. *Proc ASH* 2009;Abstract 405.

Adverse Events - All CTC Grades

Adverse Event	BR (n = 260) # of patients	CHOP-R (n = 253) # of patients	*p*-value
Alopecia	—	+++	< 0.0001
Paresthesias	18	73	< 0.0001
Stomatitis	16	47	< 0.0001
Erythema	42	23	0.0122
Allergic reaction (skin)	40	15	0.0003
Infectious complications	96	127	0.0025

Rummel MJ et al. *Proc ASH* 2009;Abstract 405.

Faculty Comments

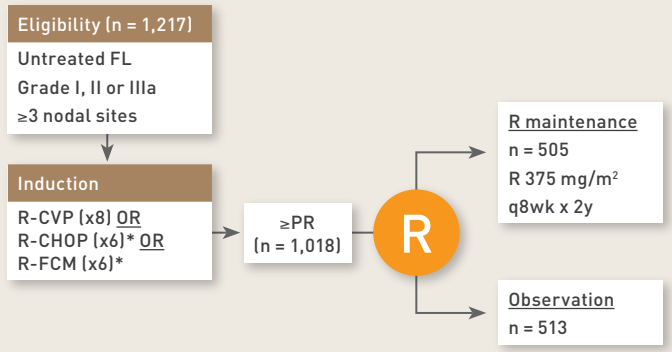
DR FISHER: This paper was impressive in its results, and it evaluated BR compared to R-CHOP in all kinds of indolent lymphomas, particularly follicular lymphoma (FL) and mantle-cell lymphoma (MCL). Though we have not seen publication yet, BR produced a better PFS and CR rate with less toxicity. BR also appears to work better preferentially in FL and MCL. When the toxicity of CHOP is prohibitive, BR is a reasonable option, and with additional analysis it may emerge as a treatment with value to all patients.

DR FOSS: This is a key study for the initial management of low-grade lymphomas, and based on the efficacy and tolerability data, BR is an option for first-line therapy for patients with low-grade lymphomas who require cytotoxic chemotherapy.

Rituximab Maintenance for 2 Years in Patients with Untreated High Tumor Burden Follicular Lymphoma After Response to Immunochemotherapy

Salles GA et al.
Proc ASCO 2010;Abstract 8004.

PRIMA: Phase III Study Design



Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

Introduction

> Rituximab (R) maintenance has shown clinical benefit for patients with follicular lymphoma (FL):
  – In the relapsed setting after induction with chemotherapy plus R (*JCO* 2010;28:2853).
  – In the first-line setting after induction chemotherapy alone[1] or R alone[2] ([1]*JCO* 2009;27:1607, [2]*Blood* 2004;103:4416).
> The role of R maintenance in FL after first-line R-chemotherapy induction has not been defined.
> Current study objective:
  – Assess the benefit of two years of R maintenance for patients (pts) with FL responding to first-line R-chemotherapy induction.

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

Primary Endpoint: Progression-Free Survival

Progression-Free Survival	Observation (n = 513)	R maintenance (n = 505)
2-year progression-free survival (PFS)	66%	82%
Hazard ratio (95% CI)	0.50 (0.39-0.64)	
p-value	<0.0001	

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

Response Status at the End of Maintenance or Observation

Clinical response after maintenance	Observation (n = 398)	R (n = 389)
Complete response (CR/CRu)	190 (47.7%)	260 (66.8%)
Partial response (PR)	29 (7.3%)	28 (7.2%)
Progressive disease (PD)	162 (40.7%)	79 (20.3%)

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

Conclusions

> R maintenance therapy for two years significantly improved PFS for pts with previously untreated FL who responded to induction with R-chemotherapy.

> Benefits of R maintenance were seen in all major subgroups (data not shown).

> These data provide evidence of an incremental benefit with R maintenance following initial R-chemotherapy for patients with FL.

> Data from the ongoing ECOG-E4402 (RESORT) trial will address how R maintenance compares to re-treatment with R at disease progression.

Salles GA et al. *Proc ASCO* 2010;Abstract 8004; Fisher RI. Discussant. *Proc ASCO* 2010. No abstract available

Safety: Rituximab Maintenance

	Observation (n = 508)	Rituximab (n = 501)
Any adverse event	35%	52%
Grade ≥2 infections	22%	37%
Grade 3/4 adverse events	16%	22%
Grade 3/4 neutropenia	<1%	4%
Grade 3/4 infections	<1%	4%

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.

Faculty Comments

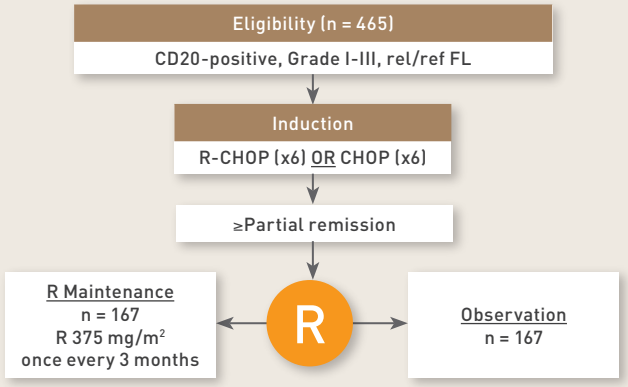
DR FISHER: This is a landmark study and confirms the role of maintenance rituximab in patients with FL treated with rituximab/chemotherapy as initial therapy. The study shows convincingly that two years of rituximab maintenance adds to failure-free-survival, progression-free-survival and time to treatment failure. The benefit was in all patient subgroups, and in my view it is indicated for all of these patients and should be used in a uniform fashion. Most people agree with me, though some believe that we should wait for a survival benefit.

DR FOSS: This is a long-awaited paper and is quite important as it demonstrates the benefit of rituximab maintenance even after receiving a rituximab-based induction regimen.

Rituximab Maintenance Treatment of Relapsed/Resistant Follicular Non-Hodgkin's Lymphoma: Long-Term Outcome of the EORTC-20981 Phase III Study

van Oers MH et al.
J Clin Oncol 2010;28(17):2853-8.

EORTC-20981: Phase III Study Design



van Oers MH et al. *J Clin Oncol* 2010;28(17):2853-8.

Introduction

> In previously untreated and relapsed/refractory (rel/ref) FL, R maintenance has a clinical benefit after induction with R-chemotherapy, chemotherapy alone or R alone (*Haematologica* 2007;92:826; *Proc ASCO* 2010;Abstract 8004).
> Initial reports of R-CHOP induction for patients with rel/ref FL resulted in increased complete and overall response rates, and R maintenance (at median 33 months follow-up) strongly improved median progression-free survival (PFS) — both after induction with CHOP and R-CHOP — and overall survival (OS) when compared to observation (*Blood* 2006;108:3295).
> Current study objective:
  – To evaluate the long-term outcome of R maintenance treatment, with a median follow-up of 6 years.

van Oers MH et al. *J Clin Oncol* 2010;28(17):2853-8.

Overall Efficacy and Safety

	Maintenance rituximab (n = 167)	Observation (n = 167)	Hazard ratio (HR)	*p*-value
Median PFS	3.7 years	1.3 years	0.55	<0.0001
5-year OS	74%	64%	0.70	0.07
Grade 3/4 infection	9.7%	2.4%	–	0.01

Median follow-up = 6 years

van Oers MH et al. *J Clin Oncol* 2010;28(17):2853-8.

Effect of R Maintenance on PFS After CHOP or R-CHOP Induction

	Maintenance rituximab	Observation	Hazard ratio (HR)	*p*-value
Median PFS after R-CHOP induction (n = 98, 91)	4.4 years	1.9 years	0.69	0.043
Median PFS after CHOP induction (n = 69, 76)	3.1 years	1.0 year	0.37	<0.001

Median follow-up = 6 years

van Oers MH et al. *J Clin Oncol* 2010;28(17):2853-8.

Faculty Comments

DR FOSS: R maintenance in the setting of relapsed/refractory FL was shown to have improved clinical outcome compared to observation. These long-term data reconfirm the benefit on PFS with R maintenance in this setting. The study is important in providing insight on how to care for patients with low-grade lymphoma who achieve remission in the relapsed setting.

DR FISHER: This study asked the question of clinical benefit with R maintenance for relapsed/refractory FL. The benefit is clear in terms of PFS, for which — even in the relapsed/refractory setting — R maintenance is valuable and works effectively, and the difference in five-year survival is reported as 74 percent with R maintenance and 64 percent with observation, although it is not statistically superior with a *p*-value of 0.07.

van Oers MH et al. *J Clin Oncol* 2010;28(17):2853-8.

Conclusions

- Rituximab maintenance significantly improved PFS compared to observation.
  - Median - 3.7 years vs 1.3 years (HR 0.55; $p < 0.001$)
  - After CHOP induction (HR 0.37; $p < 0.001$)
  - After R-CHOP induction (HR 0.69; $p = 0.043$)
- The 5-year OS was 74% in the rituximab maintenance arm and 64% in the observation arm ($p = 0.07$).
  - Lack of statistical significance possibly due to unbalanced use of rituximab in post-protocol salvage treatment.
- Rituximab maintenance was associated with a significant increase in Grade 3/4 infections: 9.7% vs 2.4% ($p = 0.01$).
- With long-term follow-up, the superior PFS with rituximab maintenance in rel/ref FL is confirmed.

van Oers MH et al. *J Clin Oncol* 2010;28(17):2853-8.

Bortezomib, Bendamustine, and Rituximab in Patients with Relapsed or Refractory Follicular Lymphoma: Encouraging Activity in the Phase 2 VERTICAL Study

Fowler N et al.
Proc ASH 2009;Abstract 933.

VERTICAL: Phase II Study Design

Eligibility (N = 63)

- Rel/Ref FL
- ≥4 prior doses of R
- No prior tx with V or B
- ≥1 measurable tumor mass
- No active CNS lymphoma
- No Grade ≥2 peripheral neuropathy

→ V 1.6 mg/m² (d1, 8, 15, 22)
B 90 mg/m² (d1, 2)
R 375 mg/m² (cycle 1: d1, 8, 15, 22; cycles 2-5: d1)
q35 days x 5

When given on the same day, the order of administration was V, B, R.

Fowler N et al. *Proc ASH* 2009;Abstract 933.

Introduction

> The introduction of rituximab (R) has led to improved survival for patients with follicular lymphoma (FL).
> Despite improved survival with R, relapse is inevitable and new treatment algorithms are needed.
> The addition of R to bortezomib (V) or to bendamustine (B) has demonstrated activity in relapsed or refractory (rel/ref) FL.
  – Overall response rate (ORR) V + R: 49% (*JCO* 2009;27:5023)
  – ORR B + R: 92% (*JCO* 2008;26:4473)
> Current study objective:
  – Determine the safety and efficacy of bortezomib and rituximab plus bendamustine (VBR) in patients with rel/ref FL.

Fowler N et al. *Proc ASH* 2009;Abstract 933.

Best Response Status

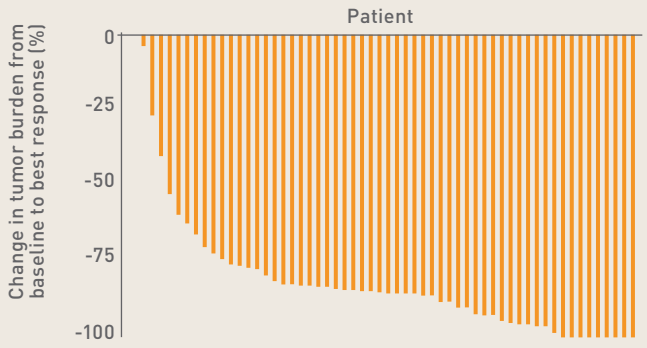
Status	Last Prior Regimen n = 62*	VBR n = 59
Overall response rate Complete response Partial response	37 (59%) 20 (32%) 17 (27%)	51 (86%) 31 (53%) 20 (34%)
Stable disease	18 (29%)	5 (8%)
Progressive disease	7 (11%)	3 (5%)

*Data are missing for one patient.

- Time since last regimen (range): 9 mos (0-76)
- Median follow-up was 177 days (11 patients remained on treatment)
- **Improved VBR response rates compared to last prior regimen**

Fowler N et al. *Proc ASH* 2009;Abstract 933.

Percent Change in Tumor Burden with VBR



With permission from Fowler N et al. *Proc ASH* 2009;Abstract 933.

Conclusions

> VBR was generally well tolerated in this patient population, which included patients with heavily pretreated (46% ≥3 prior lines of therapy) and high-risk FL (data not shown).

> The response rates were improved in patients treated with VBR when compared to their last prior regimens.

> Additional follow-up is required to assess long-term outcomes, including progression-free survival and overall survival.

Fowler N et al. *Proc ASH* 2009;Abstract 933.

Adverse Events (N = 63)

Adverse Event (AE)	%
Any adverse event	100
Grade 3/4 AEs	
Anemia	3
Neutropenia	27
Thrombocytopenia	6
Peripheral neuropathy (PN)	10*

*** Of the 6 patients with PN, 3 (50%) had neuropathy symptoms at baseline.**

Fowler N et al. *Proc ASH* 2009;Abstract 933.

Faculty Comments

DR VOSE: This is a single-arm, Phase II study, which combined weekly bortezomib with standard doses of bendamustine and rituximab. The patient characteristics were fairly typical of relapsed/refractory follicular lymphoma.

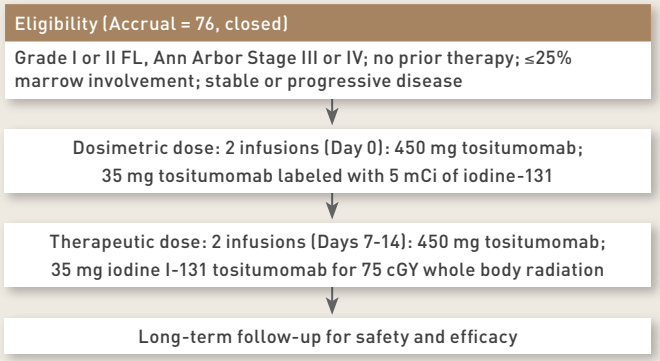
The waterfall plot shows that the majority of patients had an excellent response, with most having a more than 50 percent reduction in the tumors. Among the safety endpoints, the major adverse events were hematologic, and neuropathy was also reported in some patients. Overall, the regimen was fairly well tolerated by most patients.

I believe this is an active combination that will have to be evaluated with a randomized trial to determine whether it is better than the current standard regimens.

Tositumomab and Iodine I-131 Tositumomab for Previously Untreated, Advanced-Stage, Follicular Lymphoma: Median 10-Year Follow-Up Results

Kaminski MS et al.
Proc ASH 2009;Abstract 3759.

Phase II, Open-Label, Single-Center Study of Tositumomab and Iodine I-131 Tositumomab



Kaminski MS et al. *Proc ASH* 2009;Abstract 3759.

Introduction

> Patients with relapsed follicular lymphoma (FL) or FL refractory to chemotherapy or to rituximab respond to tositumomab and iodine I-131 tositumomab treatment (*JCO* 2000;18:1316, *Blood* 2000;96:1259, *JCO* 2001;19:3918).
  – ORR = 47-68%; CR = 20-38%
> Phase II trial of this regimen for previously untreated, advanced-stage FL also demonstrated clinical activity (*NEJM* 2005;352:441).
  – ORR = 95%; CR = 75%
> Current study objective:
  – Provide 10-year median follow-up of the Phase II trial of a single one-week course of tositumomab and iodine I-131 tositumomab in patients with untreated Stage III and IV FL.

Kaminski MS et al. *Proc ASH* 2009;Abstract 3759.

Patient Characteristics (n = 76)

Median age (range), years ≤60 years >60 years	49 (23-69) 91% 9%
Female	46%
FL stage at study entry III IV	 30% 70%
Grade I FL, Grade II FL, mantle-cell lymphoma	70%, 29%, 1%
Bone marrow involvement of 1-25%, none	64%, 36%
FLIPI risk: low, intermediate, high	15%, 50%, 35%

Kaminski MS et al. *Proc ASH* 2009;Abstract 3759.

Efficacy: Median 10-Year Follow-Up

Patient Subgroup (total n = 76)	Outcome
Objective response (CR, CCR, PR), n (%) Median PFS Median duration of response	74 (97%) 6.2 years 6.0 years
Complete response (CR), n (%) Median PFS	56 (74%) 10.9 years
Complete and clinical complete response (CR, CCR), n (%) Median PFS	59 (78%) 9.2 years
Partial response, n (%) Median PFS	15 (20%) 0.8 years

Kaminski MS et al. *Proc ASH* 2009;Abstract 3759.

Conclusions

> Long-term follow-up of a one-week course of front-line treatment with tositumomab and iodine I-131 tositumomab therapy demonstrated:
  – Median PFS: 6.2 years
  – 10-yr PFS rate: 38% (data not shown)
  – 10-yr OS rate: 83% (data not shown)
> One case of MDS occurred 8 years after initial therapy, but any causal relationship with the tositumomab-based regimen is unclear (data not shown).
> These data suggest clinical benefit of tositumomab and iodine I-131 tositumomab at front-line therapy, and further studies including combination treatments are warranted.

Kaminski MS et al. *Proc ASH* 2009;Abstract 3759.

Adverse Events (n = 76)

Grade 3/4 Acute Toxicity	Incidence
Neutropenia	5% (Grade IV)
Arthralgia and myalgia	13%
Headache	5%
Long-Term Toxicity	**Incidence**
Elevated TSH or began thyroid medication before therapy	12%
Elevated TSH or began thyroid medication after therapy	25%
Deaths from lymphoma progression	8%

Kaminski MS et al. *Proc ASH* 2009;Abstract 3759.

Faculty Comments

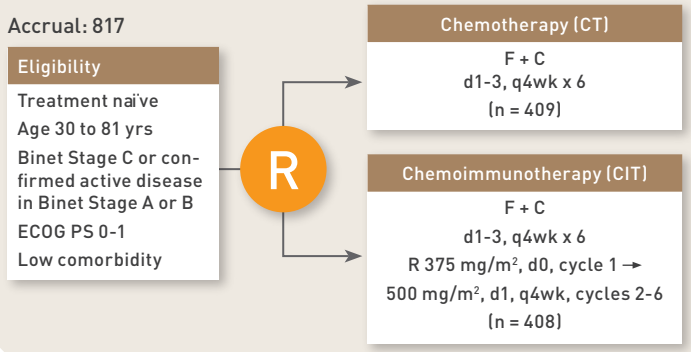
DR VOSE: This is a 10-year follow-up of the previously published study of tositumomab as initial treatment for untreated, advanced FL. With a long follow-up, the good data continue to hold. The median duration of response was six years, and about 40 percent of patients remained progression free at 10 years.

The short-term hematological toxicity is minimal, with Grade 4 only toxicity occurring in only five percent of patients. The long-term toxicities are also few with some cases of hypothyroidism and a small number of cases of secondary cancer, including one case of MDS diagnosed eight years after initial treatment. For a single agent, this is a high response rate with excellent survival data and minimal short- and long-term toxicities.

Addition of Rituximab to Fludarabine and Cyclophosphamide in Patients with CLL: A Randomized, Open-Label, Phase III Trial

Hallek M et al.
Lancet 2010;376:1164-74.

German CLL Study Group Phase III Open-Label Trial



Hallek M et al. *Lancet* 2010;376:1164-74.

Introduction

> In patients with CLL, the low expression of CD20 antigen on the leukemic cells (*Blood* 2001;98:3383) and poor response rates have raised concern regarding the clinical benefits of R in this particular setting (*Blood* 2001;98:1326).
> The use of higher doses of R has improved response rates in CLL (*JCO* 2001;19:2165), and Phase II trial data suggest that the combined use of R with chemotherapy may provide additive or synergistic effects (*Blood* 2002;100:3115; *JCO* 2005;23:4079).
> Current study objective:
  – Evaluate the safety and efficacy of combined fludarabine (F), cyclophosphamide (C) and R as first-line therapy for advanced, symptomatic CLL.

Hallek M et al. *Lancet* 2010;376:1164-74.

Three-Year Progression-Free Survival (PFS) for All Patients and Subgroups

Subgroups	CIT	CT	*p*-value
All (n = 817)	65%	45%	<0.0001
Del(17p) (n = 51)	18%	0%	0.019
Del(11q) (n = 142)	64%	32%	<0.0001
Trisomy 12 (n = 61)	83%	48%	0.01
Del(13q) (n = 224)	76%	52%	0.0002
IgVH mutated (n = 229)	80%	55%	0.0002
IgVH unmutated (n = 390)	55%	35%	0.0003

Median PFS: 51.8 mo (CIT) vs 32.8 mo (CT)

Hallek M et al. *Lancet* 2010;376:1164-74.

Response in All Patients and Subgroups

Subgroups	CR, CIT	CR, CT	*p*-value CR
All (n = 817)	44%	22%	<0.0001
Del(17p) (n = 51)	5%	0%	0.43
Del(11q) (n = 142)	51%	15%	<0.0001
Trisomy 12 (n = 61)	71%	19%	0.0001
Del(13q) (n = 224)	48%	23%	0.0001
IgVH mutated (n = 229)	50%	21%	<0.0001
IgVH unmutated (n = 390)	40%	19%	<0.0001

CR = complete remission

Hallek M et al. *Lancet* 2010;376:1164-74.

Conclusions

> The addition of fludarabine and cyclophosphamide to rituximab was associated with substantial increases in complete remission and progression-free survival at 3 years.
  – CR, 44% (CIT) vs 22% (CT); P<0.0001
  – 3-year PFS, 65% (CIT) vs 45% (CT); P<0.0001
> CIT also improved the 3-year overall survival (data not shown).
  – OS, 87% (CIT) vs 83% (CT); P=0.012
> The incidence of Grade 3/4 adverse events was similar in both groups, with the exception of neutropenia and leukocytopenia (higher with CIT).
> These data may help establish a new treatment model for first-line treatment of CLL in physically fit patients.

Hallek M et al. *Lancet* 2010;376:1164-74.

Grade 3/4 Hematologic Adverse Events (AEs)

Events	CIT N = 404	CT N = 396	*p*-value
Total hematologic	56%	40%	<0.0001
Neutropenia	34%	21%	<0.0001
Leukocytopenia	24%	12%	<0.0001
Thrombocytopenia	7%	11%	0.07
Anemia	5%	7%	0.42
Autoimmune hemolytic anemia	<1%	1%	0.69

Hallek M et al. *Lancet* 2010;376:1164-74.

Faculty Comments

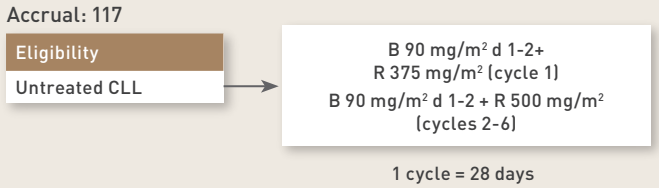
DR FOSS: This is the long-term follow-up of the randomized study evaluating the FCR chemotherapy regimen. The FCR arm remained superior, with higher overall response rates and more complete remissions. The median PFS was 51.8 months for the FCR arm versus 32.8 months for the FC arm.

Most importantly, the OS rates are also clinically and statistically superior with the FCR regimen. More hematological AEs occurred in the FCR arm. This is the first CLL trial that has clearly demonstrated a survival improvement with up-front therapy.

Bendamustine Combined with Rituximab (BR) in First-Line Therapy of Advanced CLL: A Multicenter Phase II Trial of the German CLL Study Group (GCLLSG)

Fischer K et al.
Proc ASH 2009;Abstract 205.

CLL2M: Phase II Study Design



Fischer K et al. *Proc ASH* 2009;Abstract 205.

Introduction

> Bendamustine is an alkylating agent that causes cell-cycle inhibition, ultimately resulting in apoptosis (*Am J Health Syst Pharm* 2010;67(9):713).
> Bendamustine monotherapy has shown significant activity in patients with untreated chronic lymphocytic leukemia and is FDA approved in this setting (*JCO* 2009;27:4378).
> In vitro studies have demonstrated a synergistic effect with bendamustine and rituximab (BR) combination therapy (*Proc ASCO* 2005;Abstract 6565).
> Current study objective:
  – Assess the efficacy and toxicity of BR in previously untreated CLL.

Fischer K et al. *Proc ASH* 2009;Abstract 205.

Efficacy Data (median follow-up 15.4 months)

Clinical Response (n = 110)	N (%)
Overall response rate (ORR) Complete response Nodular partial response Partial response	100 (90.9) 36 (32.7) 3 (2.7) 61 (55.5)
Stable disease	10 (9.1)
Median progression-free survival	Not reached

After 18 months, 75.8% of the patients were still in remission.

Fischer K et al. *Proc ASH* 2009;Abstract 205.

Responses According to Cytogenetics

Characteristic	N	ORR n (%)
FISH Del 17p	7	3 (42.9%)
FISH Del 11q	21	19 (90.5%)
IgVH (unmutated)	63	56 (88.9%)

Fischer K et al. *Proc ASH* 2009;Abstract 205.

Conclusions

> Bendamustine and rituximab combination therapy is tolerable and effective as first-line treatment for patients with CLL:
  – ORR: 90.9%
  – Median PFS: Not reached
> The major side effects, myelosuppression and infections, were not frequent.
> A Phase III study evaluating bendamustine and rituximab combination therapy in comparison to fludarabine-based immunochemotherapy (FCR) for first-line treatment of CLL is currently under way (NCT00769522).

Fischer K et al. *Proc ASH* 2009;Abstract 205; www.clinicaltrials.gov.

Grade 3/4 Adverse Events (n = 114)

Adverse Event*	% of cycles
Leukopenia	14.6
Neutropenia	6.5
Thrombocytopenia	6.1
Anemia	4.9

*Treatment-related mortality occurred in 2.6% of the patients.

Fischer K et al. *Proc ASH* 2009;Abstract 205.

Faculty Comments

DR FOSS: This study investigated up-front bendamustine and rituximab in untreated CLL. The regimen shows good activity with an overall response rate of more than 90 percent, and 75 percent of patients are still in remission at 18 months of follow-up. Among the high-risk genetic subgroups, patients with 11q-minus subtype had a high remission rate, with an ORR of more than 90 percent. These data support up-front bendamustine/rituximab as a reasonable regimen in the setting of untreated CLL.

DR VOSE: The results show bendamustine/rituximab to be an effective and safe first-line treatment for CLL. A randomized trial comparing this regimen to fludarabine-based chemoimmunotherapy is under way.

Ofatumumab Combined with Fludarabine and Cyclophosphamide (O-FC) Shows High Activity in Patients with Previously Untreated CLL

Wierda WG et al.
Proc ASH 2009;Abstract 207.

Introduction

- Chemoimmunotherapy regimens have become standard therapy for patients with chronic lymphocytic leukemia (CLL).
- Ofatumumab, a human monoclonal antibody that targets a unique small loop epitope on CD20 cells, elicits complement-dependent cytotoxicity and antibody cellular-dependent cytotoxicity in vitro.
- Recent studies of single-agent ofatumumab have shown high overall response rates in patients with refractory CLL, and it is FDA approved in this setting (*Blood* 2008;111:1094; *J Clin Oncol* 2010;116:1831).
- Current study objective:
  - Evaluate the efficacy and tolerability of two different doses of O-FC in untreated CLL.

Wierda WG et al. *Proc ASH* 2009;Abstract 207.

Multicenter Phase II Study of O-FC in Previously Untreated CLL

Eligibility (N = 61)

- ≥18 years with previously untreated CLL, $CD5^+/20^+/23^+$
- Active disease (1996 NCI-WG criteria)
- Lymphocyte count >5 x 10^9/L
- ECOG PS≤2
- No CLL transformation
- No CNS involvement
- No HIV positivity

R

- 500 mg O-FC q4wk x 6
- 1,000 mg O-FC q4wk x 6

Follow-up at mo 1, mo 3 and q3 mos thereafter

Cycle 1: Ofatumumab 300 mg, d1; fludarabine 25 mg/m^2, d2-4; cyclophosphamide 250 mg/m^2, d2-4; Cycles 2-6: Ofatumumab 500 or 1,000 mg, d1; fludarabine 25 mg/m^2, d1-3; cyclophosphamide 250 mg/m^2, d1-3

Wierda WG et al. *Proc ASH* 2009;Abstract 207.

Efficacy Results*

Clinical Parameter	OF-C 500 mg n = 31	OF-C 1,000 mg n = 30
Complete response (CR)	32%	50%
Nodular partial response	3%	3%
Partial response	42%	20%
Overall response rate (ORR)	**77%**	**73%**

*1996 NCI-WG criteria used

Wierda WG et al. *Proc ASH* 2009;Abstract 207.

Efficacy by Cytogenetic Characteristics and Treatment Received

Patient Characteristic		n	CR	ORR
All patients		61	41%	75%
IgVH genes	Mutated	28	46%	75%
	Unmutated	25	36%	84%
FISH hierarchy	Del13q	25	32%	80%
	Negative	7	71%	100%
	Trisomy 12	9	56%	56%
	Del 11q	10	40%	70%
	Del 17p	8	13%	63%

Wierda WG et al. *Proc ASH* 2009;Abstract 207.

Conclusions

> O-FC was highly active at both doses in patients with previously untreated CLL.
  – ORR: 73% (1,000 mg); 77% (500 mg)
  – CR: 32% (500 mg); 50% (1,000 mg)
> Myelosuppression is the most common toxicity.
> Time-to-event endpoint analyses are ongoing.
> Adverse events were manageable with no unexpected toxicities.
> Other studies are under way to evaluate ofatumumab 1,000 mg in combination with chemotherapy in patients with CLL (NCT01125787, NCT01131247).

Wierda WG et al. *Proc ASH* 2009;Abstract 207; www.clinicaltrials.gov.

Adverse Events

Grade 3/4 Adverse Events	O-FC 500 mg n = 31	O-FC 1,000 mg n = 30
Neutropenia	35%	60%
Thrombocytopenia	6%	23%
Anemia	6%	20%
Infections	13%	23%
Febrile neutropenia	3%	3%
Sepsis	0%	2%
Herpes virus infection	1%	0%
Respiratory infection	0%	1%
Unspecified infection	0%	1%

Wierda WG et al. *Proc ASH* 2009;Abstract 207.

Faculty Comments

DR FOSS: This Phase II study shows that ofatumumab combined with fludarabine and cyclophosphamide is significantly active in the up-front treatment of CLL. However, the therapy has not been compared to FCR, which is considered the standard treatment for these patients.

DR VOSE: The toxicities were easily managed, with hematological toxicity being the major one. It was believed that the 1,000-mg dose of ofatumumab is perhaps a bit better based on this small study, and that dose is currently going forward in larger trials.

A Phase II Study of Lenalidomide as Initial Treatment of Elderly Patients with Chronic Lymphocytic Leukemia

Badoux X et al.
Proc ASCO 2010;Abstract 6508.

Introduction

- The majority of patients with chronic lymphocytic leukemia (CLL) are older than age 70.
- No standard treatment has been established for elderly patients with CLL.
- Elderly patients with CLL are under-represented in clinical trials and experience increased toxicity from chemoimmunotherapy.
- Lenalidomide is an immunomodulatory drug that is administered orally and is active in patients with relapsed CLL (*JCO* 2006;24:5343, *Blood* 2008;111:5291).
- Current study objective:
  - To evaluate the activity of single-agent lenalidomide as front-line therapy for elderly patients with CLL.

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Phase II Study of Lenalidomide in Elderly Patients with CLL

Eligibility (N = 60)

Untreated and symptomatic CLL PS 0-2
Age ≥ 65 years

↓

Lenalidomide 5 mg/day x 2 cycles (56 days)
Increase by 5 mg/cycle (28 days) if well tolerated to maximum 25 mg/day
Treatment continued until disease progression
Allopurinol 300 mg PO QD days 1-14 (cycle 1)

No mandated antibiotic, antiviral, DVT or tumor flare prophylaxis
Response assessed at the end of cycle 3 and then every 6 cycles

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Efficacy Results

Clinical Response	N = 60	
Overall response rate (ORR)	62%	
Complete response (CR)/CRi	10%/5%	
Nodular partial response (nPR)/PR	5%/42%	
Response by Baseline Characteristic	**CR/CRi/nPR**	**ORR**
Age, ≥75 years (n = 17)	6%	35%*
IgVH genes, mutated (n = 22)	5%*	50%
FISH hierarchy, deletion 17p (n = 6)	0%	0%

* $p < 0.05$. CRi = CR with incomplete blood count recovery

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Progression-Free and Overall Survival Data

2-Year Survival	Lenalidomide N = 60
Progression-free survival (PFS)	60%
Overall survival (OS)	90%

Median follow-up = 23 months

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Conclusions

> Lenalidomide as a single agent induces clinical responses in the front-line treatment of elderly patients with CLL.
  - ORR: 62%
  - CR/CRi: 15%
  - 2-year OS: 90%
  - 2-year PFS: 60%
> The most common Grade 3/4 toxicity was myelosuppression.
> No severe tumor flare or tumor lysis syndrome was observed.

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Grade 3/4 Adverse Events (N = 60)

Toxicity, % of cycles	Grade 3	Grade 4
Neutropenia	26%	12%
Thrombocytopenia	13%	<1%
Anemia	0%	0%
Tumor flare*	0%	0%
Infections	**Grade ≥3, n (%)**	
All (sepsis, pneumonia/bronchitis, upper respiratory, fever, other)	9 (15%)	

*50% of patients experienced Grade I/II tumor flare.

Badoux X et al. *Proc ASCO* 2010;Abstract 6508.

Faculty Comments

DR VOSE: The study evaluated lenalidomide as initial therapy for older patients with CLL. The overall response rate was approximately 62 percent, with 10 percent complete remissions.

The therapy was fairly well tolerated, and the major complication was hematological toxicity. Authors believed single-agent lenalidomide to be a fairly good potential treatment for older patients with CLL.

Combination Therapy with Lenalidomide and Rituximab in Patients with Relapsed Chronic Lymphocytic Leukemia (CLL)

Ferrajoli A et al.
Proc ASH 2009;Abstract 206.

Phase II Study Design

Accrual: 60

Eligibility
Active CLL
Prior treatment with purine analog-based therapy

→

LEN + R:
LEN: 10 mg/d day 9 (cycle 1) → daily x 28 d (cycles 2-12)
R: 375 mg/m^2 weekly (cycle 1) → q4wk (cycles 3-12)

Median number of prior treatments: 2
All patients received prior treatments of R.

Ferrajoli A et al. *Proc ASH* 2009;Abstract 206.

Introduction

- Lenalidomide (LEN) with rituximab (R) combination therapy has shown clinical responses in a small number of patients with CLL who experienced disease progression while receiving LEN monotherapy (*JCO* 2006;24:5343).
- R monotherapy has modest activity but significantly synergizes with chemotherapy agents when administered to patients with CLL (*JCO* 2010;28:1756, *Lancet* 2010;376:1166).
- Current study objective:
  - Evaluate the safety and efficacy of LEN with R combination therapy in patients with relapsed CLL.

Ferrajoli A et al. *Proc ASH* 2009;Abstract 206.

Efficacy Data

Efficacy After 6 Cycles of Treatment (n = 37)	LEN + R N (%)
Overall response rate Nodular partial response Partial response	25 (68%) 6 (16%) 19 (51%)
Stable disease	6 (16%)
Failure to respond*	6 (16%)

*One patient died on day 34 from infectious complications.

Ferrajoli A et al. *Proc ASH* 2009;Abstract 206.

Responses According to CLL Stage and Cytogenetics

Characteristic	N	% nPR	% PR	% ORR
All patients	**37**	**16**	**51**	**68**
Rai Stage III/IV	15	7	53	60
FISH Del 17p	9	33	33	67
FISH Del 11q	10	10	60	70
IgVH (unmutated)	26	23	46	69

PR = partial response; nPR = nodular PR; ORR = overall response rate

Ferrajoli A et al. *Proc ASH* 2009;Abstract 206.

Conclusions

> When compared to historical data with single-agent LEN, R in combination with LEN may have superior activity in relapsed CLL.

> LEN-associated tumor flare reaction was both less frequent and less severe than has been reported with single-agent LEN.

> When compared to baseline, there were significant differences in the distribution of circulating B, T and NK cell populations after three cycles of therapy (data not shown):
- **B cells:** decreased percentage of $CD19^{+}CD20^{+}$
- **T cells:** increased percentage of $CD4^{+}$, $CD8^{+}$, $CD4^{+}CD25^{hi}CD127^{-}$
- **NK cells:** increased percentage of $CD3^{-}CD16^{+}CD56^{+}$

> Research is ongoing to determine the clinical relevance of these immune cell changes.

Ferrajoli A et al. *Proc ASH* 2009;Abstract 206.

Common Grade 3/4 Adverse Events

Adverse Event	N (%)
Neutropenia	16 (43)
Fatigue	6 (16)
Thrombocytopenia	4 (11)
Tumor lysis syndrome (Grade 3)	1 (3)
Joint pain (Grade 3)	1 (3)

Grade 1 (22%) and Grade 2 (3%) LEN-associated tumor flare reaction was observed.

Ferrajoli A et al. *Proc ASH* 2009;Abstract 206.

Faculty Comments

DR VOSE: This study was designed on the basis of preclinical data indicating that lenalidomide and rituximab have potentially synergistic activity. The patients included in the study had heavily pretreated disease and had received rituximab in prior regimens.

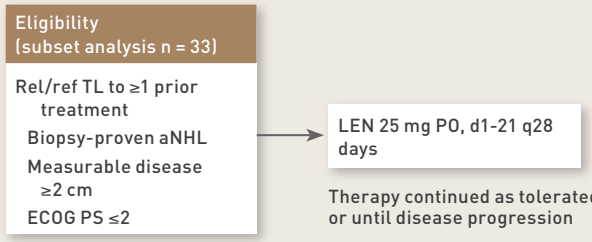
The overall response was 68 percent, with 51 percent PR and 16 percent nodular PR. None of the patients were reported to have achieved CR. The regimen was fairly well tolerated with major toxicities being hematological.

A correlative part of the study examines proportions of different immune cells to see if they might correlate with outcome. That research is still ongoing.

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.

NHL-003 Phase II Study Design



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.

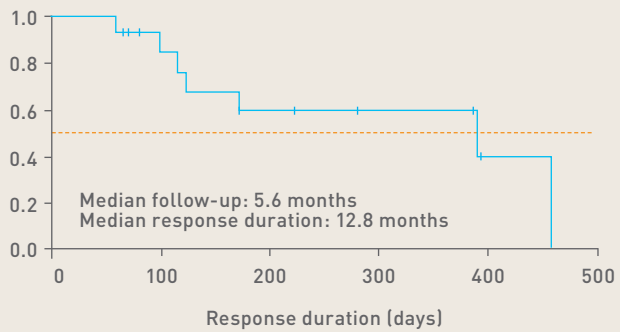
Efficacy Data

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.

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.

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.

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

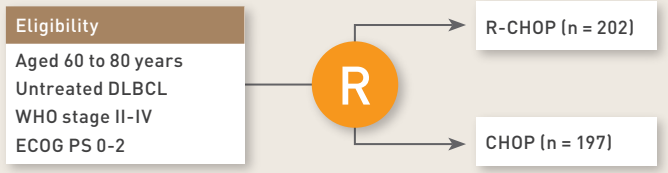
Coiffier B et al.
Blood 2010;116(12):2040-5.

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 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.

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.

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.

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.

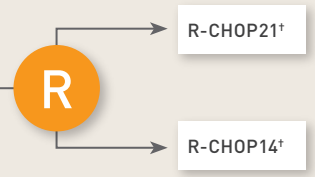
R-CHOP14 Compared to R-CHOP21 in Elderly Patients with Diffuse Large B-Cell Lymphoma: Results of the Interim Analysis of the LNH03-6B GELA Study

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

Trial Schema

Accrual: 602 (Closed)*

Eligibility
Age 60 to 80 y
Untreated DLBCL
Ann Arbor Stage II-IV
ECOG PS 0-2
Age-adjusted IPI, 1-3



* 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.

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.

Patient Characteristics and Treatment (N = 202)

Characteristic	R-CHOP21 (n = 99)	R-CHOP14 (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	75%	67%	NS
Partial response (PR)	9%	14%	
Overall response rate (ORR)	84%	81%	
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.

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.

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.

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 Characteristics	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 Characteristics	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.

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.

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%
	Histological Subtype at Relapse		
Survival	DLBCL	Indolent	*p*-value
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.

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.

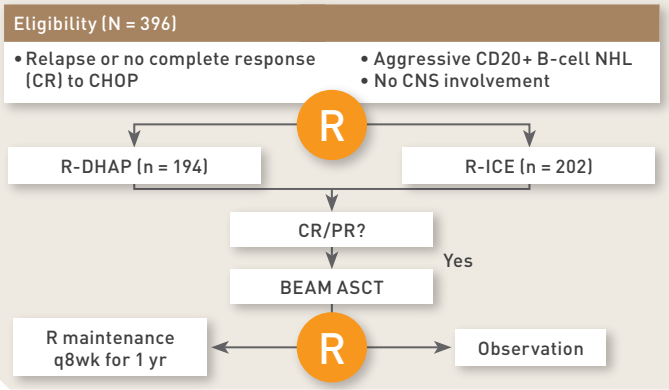
Overall, only 54 patients out of approximately 1,500 experienced late relapses, and most of these patients initially with low-stage or low IPI disease often had extranodal involvement of germinal center B-cell type.

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.

CORAL: A Phase III Multicenter, Randomized Trial



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.

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.

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.

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.

Faculty Comments

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

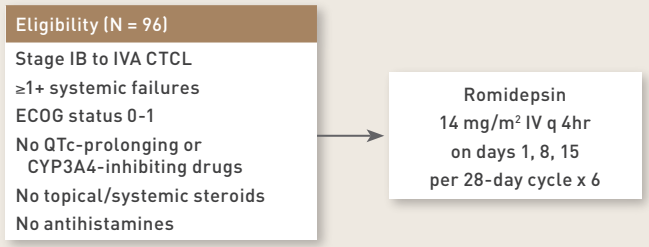
The study did not demonstrate any significant difference between the two regimens, suggesting once again that the different salvage regimens have similar efficacy.

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.

Final Results from a Multicenter, International, Pivotal Study of Romidepsin in Refractory Cutaneous T-Cell Lymphoma

Whittaker SJ et al.
J Clin Oncol 2010;28(29):4485-91.

Phase II Study Design



Whittaker SJ et al. *J Clin Oncol* 2010;28(29):4485-91.

Introduction

> Primary cutaneous T-cell lymphoma (CTCL) is a rare class of non-Hodgkin's lymphoma that originates in the skin.
> Single-agent romidepsin induces apoptotic events in cancer cells by inhibiting histone deactylase (HDAC) enzymes.
> A Phase II trial of romidepsin monotherapy has shown clinical benefit in patients (pts) with CTCL (*JCO* 2009;27:5410).
> Current study objective:
  – Confirm the safety and efficacy of romidepsin in pts with pretreated CTCL in support of the US Food and Drug Administration approval of this agent in this patient population.

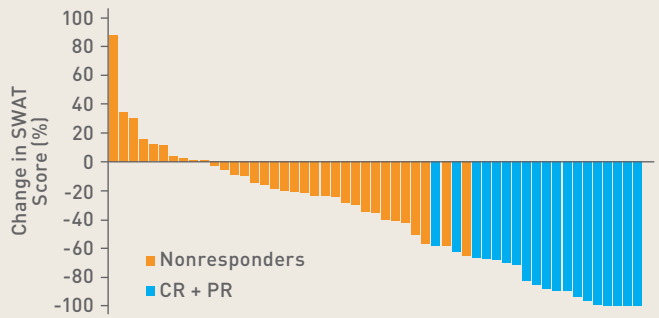
Whittaker SJ et al. *J Clin Oncol* 2010;28(29):4485-91.

Efficacy Data

Clinical Response Status	Romidepsin n (%)	95% CI
Overall response rate (ORR) (N = 96) Complete response (CR) Partial response (PR)	33 (34) 6 (6) 27 (28)	25 - 45 2 - 13 19 - 38
Median duration of response (n = 33)	15.0 mo	—
Median time to response (n = 33)	2.0 mo	—
Median time to progression (n = 33)	8.0 mo	—
Disease Status		
Stable disease	45 (47)	37 - 57
Progressive disease	10 (10)	5 - 18

Whittaker SJ et al. *J Clin Oncol* 2010;28(29):4485-91.

Severity-Weighted Assessment Tool (SWAT)



All pts with a clinical response had a > 50% improvement in SWAT scores

With permission from Whittaker SJ et al. *J Clin Oncol* 2010;28(29):4485-91.

Conclusions

> Single-agent romidepsin is effective for the treatment of previously treated CTCL, including advanced disease (≥Stage IIB):
  – ORR: 34% and 38%, respectively
  – CR: 6% and 7%, respectively
> Assessment of the disease sites indicate that romidepsin has clinical benefit (RECIST and flow cytometry data are not shown).
> The results of this Phase II trial are consistent with the Phase II NCI-sponsored trial.
  – Subsequently, both of these studies have led to the FDA approval in the US on November 2009 for the use of romidepsin in patients with CTCL.

Whittaker SJ et al. *J Clin Oncol* 2010;28(29):4485-91.

Select Grade 3/4 Adverse Events

Adverse Event N = 96	Romidepsin n (%)
Nausea	2 (2)
Asthenic conditions*	6 (6)
Vomiting	1 (1)
Diarrhea	1 (1)
Anemia	2 (2)
Tumor lysis syndrome	2 (2)

*Includes asthenia, fatigue, lethargy and malaise

Whittaker SJ et al. *J Clin Oncol* 2010;28(29):4485-91.

Faculty Comments

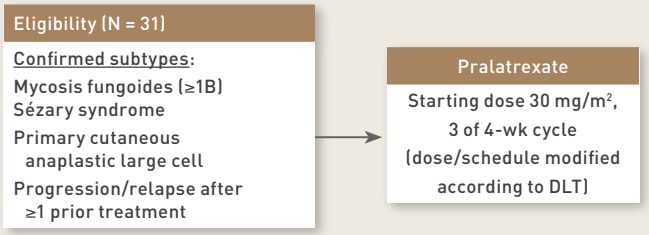
DR FOSS: Romidepsin has now been approved for CTCL and may also be approved soon for PTCL. The most common adverse events include fatigue and thrombocytopenia, shown as transient with a quick recovery. No direct or long-term effects on bone marrow stem cells are apparent.

DR VOSE: Romidepsin is a potent HDAC inhibitor and has been studied in CTCL and PTCL. It resulted in an ORR of approximately 35 percent. The potential for QTc prolongation has been observed with all HDAC inhibitors, but at this time no serious cause for concern about this issue is apparent. The investigators also evaluated hematological toxicities and found a quick reversibility of and recovery from thrombocytopenia.

Pralatrexate is Active in Cutaneous T-Cell Lymphoma (CTCL): Results of a Multicenter, Dose-Finding Trial

Horwitz SM et al.
Proc ASH 2009;Abstract 919.

PDX-010: Study Design



- Protocol-defined dose-limiting toxicities (DLT) leading to dose reduction: ≥Grade 3 neutropenia, ≥Grade 2 thrombocytopenia (or any grade with clinically significant bleeding), febrile neutropenia, ≥Grade 2 stomatitis, any toxicity leading to dose reduction or omission in cycle 1
- All patients received vitamin B_{12} 1 mg IM q 8-10 wk and folic acid 1 mg po qd.

Horwitz SM et al. *Proc ASH* 2009;Abstract 919.

Introduction

> CTCL is an indolent, clinically heterogeneous group of non-Hodgkin's lymphomas that develop in the skin.
> The most common subtypes are mycosis fungoides and Sézary syndrome and are most often managed with maintenance treatment.
> Pralatrexate is an antifolate recently approved for PTCL and acts by selectively entering cancer cells that express the reduced folate carrier type-1 protein.
> Current study objectives:
  – Assess the effective, well-tolerated dose and schedule of pralatrexate in patients with relapsed or refractory CTCL.
  – Evaluate the safety and efficacy of pralatrexate at the optimal dose for additional patients with relapsed or refractory CTCL.

Horwitz SM et al. *Proc ASH* 2009;Abstract 919.

Dose-Limiting Toxicities by Dose Cohort

Cohort	Pralatrexate (mg/m²), Schedule (wk/wk cycle)	N	DLTs N (toxicity/grade)
1	30 mg/m², 3/4 weeks	2	2 (Anorexia/2, Weakness/3)
2	20 mg/m², 3/4 weeks	3	2 (Stomatitis/2)
3	20 mg/m², 2/3 weeks	7	3 (Stomatitis/2-3, LFT/3)
4	15 mg/m², 3/4 weeks	6	3 (Stomatitis/2, Fatigue/2)
5	15 mg/m², 2/3 weeks	3	2 (Stomatitis/2, Dehydration/2)
6	10 mg/m², 3/4 weeks	10	3 (Thrombocytopenia + Neutropenia/3, Skin Lesion/3, Zoster/3)

Horwitz SM et al. *Proc ASH* 2009;Abstract 919.

Response Status

Cohort	Response Rate	Response Type	
#	N (%)	Partial Response	Complete Response
1	2 (100)	2	0
2	2 (67)	2	0
3	4 (57)	3	1
4	3 (50)	3	0
5	0	0	0
6	1 (10)	0	1

Overall response rate: 61% for doses ≥15 mg/m^2 weekly for 3/4 wk

Horwitz SM et al. *Proc ASH* 2009;Abstract 919.

Conclusions

> Pralatrexate shows impressive clinical activity in patients with relapsed or refractory CTCL at a lower dose intensity than in studies for PTCL.

> The optimal tolerable starting dose and schedule for pralatrexate in patients with CTCL is 15 mg/m^2 qwk for 3/4 wk:
- Overall response rate: 61% for doses ≥15 mg/m^2
- Dose escalation was allowed in patients with stable disease or who showed a progressive response.
- Expansion cohort is enrolling 20 additional patients at this dose and schedule (NCT00554827).

Horwitz SM et al. *Proc ASH* 2009;Abstract 919; www.clinicaltrials.gov.

Select Adverse Events

Adverse Event (All Grades)	All Cohorts (n = 31)	Pralatrexate 15 mg/m^2 qwk 3/4 wk (n = 6)
Stomatitis	18 (58%)	4 (67%)
Nausea	16 (52%)	4 (67%)
Fatigue	15 (48%)	4 (67%)
Pyrexia	9 (29%)	3 (50%)
Vomiting	8 (26%)	3 (50%)
Neutropenia	1 (3%)	0
Thrombocytopenia	1 (3%)	0

Horwitz SM et al. *Proc ASH* 2009;Abstract 919.

Faculty Comments

DR VOSE: Pralatrexate is a folate inhibitor that has been mostly studied in PTCL. This study examined the activity of pralatrexate in refractory CTCL and showed activity without unexpected toxicity. This is a potential agent in CTCL also and is continuing to be studied in combinations as well.

DR FOSS: This was a dose and schedule determination study of pralatrexate in patients with refractory CTCL. The study demonstrates good activity in these patients, with an overall response rate of 61 percent for doses greater than or equal to 15 mg/m^2 for three of four weeks. The toxicity profile is similar to what has been seen in patients with PTCL. The dose and schedule moving forward in Phase II is 15 mg/m^2 weekly for three out of four weeks.

Bendamustine, Bortezomib and Rituximab in Patients with Relapsed/Refractory Indolent and Mantle-Cell Non-Hodgkin Lymphoma

Friedberg JW et al.
Proc ASH 2009;Abstract 924.

Phase II Trial Schema

Friedberg JW et al. *Proc ASH* 2009;Abstract 924.

Introduction

- Bendamustine (B) is approved for the treatment of relapsed/refractory indolent non-Hodgkin's lymphoma.
- Phase II trials of bendamustine and rituximab (R) demonstrated tolerability and high response rates in indolent and mantle-cell lymphomas (*JCO* 2008;26:4473, *JCO* 2005;23:3383).
- Bortezomib (V) has significant single-agent activity in indolent and mantle-cell lymphoma (MCL) (*Clin Cancer Res* 2010;16(2):719; *J Clin Oncol* 2005;23(4):676).
- Current study objective:
  - Evaluate the activity and tolerability of combined bendamustine/rituximab and bortezomib in patients with relapsed/refractory indolent B-cell or mantle-cell lymphomas.

Friedberg JW et al. *Proc ASH* 2009;Abstract 924.

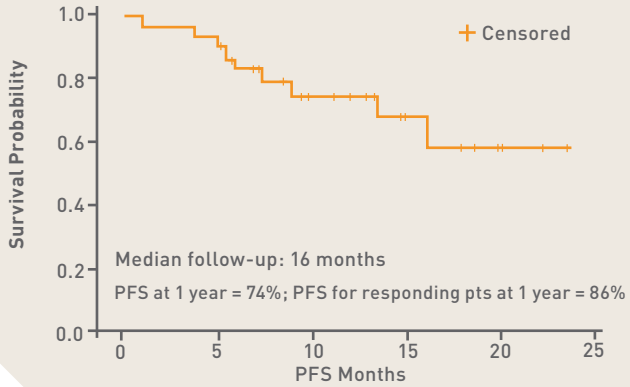
Best Response

Response Rate	N = 29*
Overall response rate (ORR)	79%
Complete response	51%
Partial response	28%
Stable disease	10%
Response by Histology	
Follicular NHL (n = 16)	85%
Mantle cell (n = 7)	71%

* One patient was not evaluable for response; one patient was not eligible.

Friedberg JW et al. *Proc ASH* 2009;Abstract 924.

Progression-Free Survival (PFS)



With permission from Friedberg JW et al. *Proc ASH* 2009;Abstract 924.

Conclusions

> VBR is highly active (ORR = 79%) and more toxic than BR.
  – Prophylaxis against varicella zoster reactivation is indicated with this regimen.
> There is no association between prior R sensitivity and response to VBR (data not shown).
> Ongoing correlative studies are being conducted to determine predictors of toxicity and response.

Friedberg JW et al. *Proc ASH* 2009;Abstract 924.

Adverse Events (n = 30)

Select Adverse Events	Grade 3 (%)	Grade 4 (%)
Neutropenia	12	3
Thrombocytopenia	15	—
Varicella-zoster virus reactivation	6	—
Peripheral neuropathy	14	3
Fatigue	7	—
Nausea	3	—
Diarrhea	3	—

Grade 5 adverse events: One patient died of sepsis. Alopecia was not observed.

Friedberg JW et al. *Proc ASH* 2009;Abstract 924.

Faculty Comments

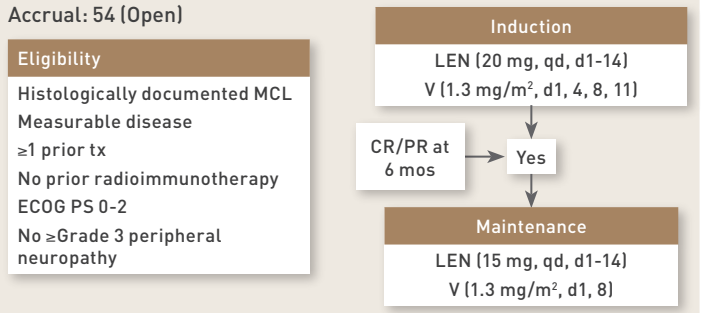
DR FOSS: VBR in this setting is an interesting combination, but a randomized trial comparing it to BR is necessary before one can conclude that VBR is superior. The usefulness of this regimen to the practicing physician is for relapsed MCL, for which the goal is to achieve a CR to salvage therapy so that a patient can then receive an autotransplant. The study also demonstrated a good response rate with reasonable toxicity.

DR FISHER: This Phase II study demonstrated that VBR is tolerable with a good ORR. Interestingly, responses were higher in the follicular histology and toxicity was manageable. Thus, it will be explored in untreated FL as an alternative to established regimens. Evaluation will continue for patients with MCL, with some variation in schedule and dosing.

Phase II Trial of Bortezomib/ Lenalidomide for Relapsed/ Refractory MCL (CALGB 50501): Results of a Planned Interim Analysis

Morrison VA et al.
Proc ASCO 2010;Abstract 8106.

Methods



Sept 2009 protocol dose-reduction schedules for V and LEN with neuropathy and myelosuppression, respectively; CR = complete response; PR = partial response

Morrison VA et al. *Proc ASCO* 2010;Abstract 8106.

Introduction

- Patients with mantle-cell lymphoma (MCL) typically experience relapse despite high response rates to initial treatment.
- Treatments (tx) such as stem cell transplant (SCT) are not curative and many patients are not eligible for SCT because of age or comorbid conditions.
- As single-agent therapies, thalidomide (an immunomodulatory agent in the same therapeutic class as lenalidomide) and bortezomib are both active against MCL.
- Current study objective:
  - The purpose of the CALGB-50501 study was to evaluate the use of bortezomib (V) and lenalidomide (LEN) in patients with relapsed or refractory MCL.

Morrison VA et al. *Proc ASCO* 2010;Abstract 8106.

Methods

- Primary endpoint
  - Overall response rate
- Secondary endpoints
  - Time to disease progression
  - Disease-free/overall survival
  - Correlating changes in activated NK/T-cells and plasma cytokines with response
- Study began in November 2007
- Interim analysis planned after 19 patients
- 10 or more responses required to reopen study (achieved)
- As of December 2, 2009, 38 patients were accrued
- Interim toxicity available for 31 patients

Morrison VA et al. *Proc ASCO* 2010;Abstract 8106.

Grade 3/4 Adverse Events

Toxicity	N = 31
Anemia	3%
Leukopenia	3%
Thrombocytopenia	32%
Fatigue/aesthenia	19%
Dyspnea	16%

Morrison VA et al. *Proc ASCO* 2010;Abstract 8106.

Conclusions

> Therapy was fairly well tolerated.

> Most common Grade 3/4 toxicities:
- Thrombocytopenia (32%)
- Fatigue/aesthenia (19%)
- Dyspnea (16%)

> Interim data suggest that the combination of lenalidomide and bortezomib has an acceptable toxicity profile in patients with MCL.

Morrison VA et al. *Proc ASCO* 2010;Abstract 8106.

Grade 3/4 Adverse Events (continued)

Toxicity	N = 31
Infection	6%
Motor neuropathy	13%
Sensory neuropathy	3%
Hypotension	13%

Morrison VA et al. *Proc ASCO* 2010;Abstract 8106.

Faculty Comments

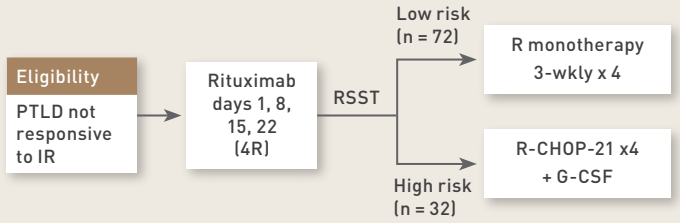
DR VOSE: The study is evaluating the combination of bortezomib and lenalidomide in relapsed/refractory mantle-cell lymphoma.

The planned interim analysis showed acceptable efficacy to continue further enrollment. The regimen was fairly well tolerated with minimal toxicity.

Sequential Treatment with Rituximab and CHOP Chemotherapy in B-Cell PTLD: Results from a Multicenter Phase II Trial

Trappe R et al.
Proc ASH 2009;Abstract 100.

Modified Phase II Study Design Including Risk Stratification*



- Low Risk = Complete remission
- High Risk = Partial response, stable disease or progressive disease

* Initially, treatment was sequential (ST): 4R → CHOP-21 x 4. The protocol was amended in 2007 to introduce risk stratification (RSST) after interim analysis showed response to R predicted overall survival (OS).

Trappe R et al. *Proc ASH* 2009;Abstract 100.

Introduction

> Post-transplant lymphoproliferative disorder (PTLD) is associated with the use of immunosuppressive drugs following transplantation (*Transplant Proc* 1969;1:106)
> Immunosuppression reduction (IR) is the initial therapy for PTLD (*Transplantation* 2008;86:215).
> A Phase II trial was initiated in January 2003 to assess sequential treatment with rituximab (R) and CHOP-21 in patients with PTLD unresponsive to IR (*Proc ASH* 2007;Abstract 390).
> Current study objective:
  – Report on the interim analysis of safety and efficacy from a study of sequential treatment (ST) with R and CHOP-21 with G-CSF in patients (pts) with PTLD unresponsive to IR.
  – Protocol amended to evaluate therapy based on risk stratification.

Trappe R et al. *Proc ASH* 2009;Abstract 100.

Patient Characteristics

Characteristic	ST	RSST
Median age, years	53	60
Advanced stage (Ann Arbor III/IV), %	59	58
Monomorphic or (Polymorphic) PTLD, n	61 (3)	35 (5)
Transplant recipients		
Kidney/Kidney + Pancreas	27/3	23/0
Liver	15	8
Heart	13	6
Lung OR Heart + Lung	6	3
Epstein-Barr virus positive, %	49	47
Late PTLD (>1 year post-transplant), %	75	75

ST = sequential treatment; RSST = risk-stratified sequential treatment

Trappe R et al. *Proc ASH* 2009;Abstract 100.

Interim Analysis: Efficacy

Response to 4R	ST and RSST (n = 104)*	
Overall response (ORR) Complete response (CR)	54% 32%	
Efficacy Parameter	**ST (n = 64)**	**RSST (n = 40)**
Final ORR (%), CR (%)	89, 69	90, 73
No disease progression at years 1, 2, 3 (%)	86, 75, 75	90, —, —
Disease-free survival at years 1, 2, 3 (%)	87, 78, 70	—

*Median follow-up, ST = 34 months; RSST = 9.1 months

Trappe R et al. *Proc ASH* 2009;Abstract 100.

Conclusions

> Sequential treatment with R and CHOP-21 + G-CSF is well tolerated and highly effective and may improve overall survival in patients with PTLD.
  – Treatment-related mortality: <10%; ORR up to 90%
> Compared to historic series of R monotherapy, more patients achieve complete remission and prolonged TTP with ST.
> Compared to historic series of CHOP chemotherapy, ST is better tolerated. This may be due to lower tumor burden and better patient fitness at the time of chemotherapy.
> Use of RSST according to response to 4 courses of R might improve overall response, tolerability and overall survival:
  – Chemotherapy limited to patients at high risk.
  – R monotherapy extended for patients at low risk.

Trappe R et al. *Proc ASH* 2009;Abstract 100.

Treatment-Related Deaths

ST (n = 64)	Patients (n)
Cytomegalovirus colitis	1
Pneumocystis pneumonia	1
Fulminant hepatitis/sepsis	1/3
Refractory PTLD	2
Hemorrhage during treatment	2
RSST (n = 40)	**Patients (n)**
Sepsis (due to intestinal perforation)	1

No difference in toxicity was observed between CHOP and R-CHOP in ST/RSST.

Trappe R et al. *Proc ASH* 2009;Abstract 100.

Faculty Comments

DR VOSE: This is the largest prospective study of a common type of treatment used for PTLD. The population studied had several mixed patient populations including both monomorphic and polymorphic PTLD and patients having different types of solid organ transplants. Median age at diagnosis was 53 years, and most patients had advanced-stage disease. Approximately half the patients were EBV-positive, and about 75 percent of patients had late PTLD. The overall response to four initial courses of rituximab was 54 percent, and the rate went up with CHOP or R-CHOP to 89 percent with a 69 percent CR rate. These rates compare favorably to historical information using other types of agents. Although this is already a sort of standard treatment used by physicians, this study outlines well the approach to PTLD, and the results are compelling.

PRIORITY 2 PUBLICATIONS/PRESENTATIONS (RECOMMENDED)

FOLLICULAR AND INDOLENT LYMPHOMA

1 Tarella C et al. **A recent update of three consecutive prospective trials with high-dose therapy and autograft, without or with rituximab, as primary treatment for advanced-stage follicular lymphoma (FL) shows a sizeable group of patients surviving in continuous complete remission up to 16 years after the end of treatment: Should we still consider FL an incurable disease?** *Proc ASH* 2009;Abstract 882.

An update of three trials of high-dose sequential chemotherapy (HDS) and autograft as first-line therapy for high-risk FL with a median of 10 years of follow-up revealed a 70.2 percent survival rate with 48 percent of patients in first continuous complete remission, most of which are molecular remission.

2 Hagenbeek A et al. **Evaluation of ofatumumab, a novel human CD20 monoclonal antibody, as single agent therapy in rituximab-refractory follicular lymphoma.** *Proc ASH* 2009;Abstract 935.

Patients (N = 116) with Grade I or II CD20-positive and rituximab (with chemotherapy)-refractory FL received eight cycles of ofatumumab. The ORR was 22 percent among patients with disease refractory to prior rituximab and nine percent in patients with disease refractory to maintenance rituximab or rituximab/chemotherapy.

MANTLE-CELL LYMPHOMA

3 LaCasce A et al. **R-CHOP, followed by high dose therapy and autologous stem cell rescue (HDT/ASCR), and R-hyperCVAD have equivalent progression-free survival and are superior to R-CHOP alone in younger patients with mantle cell lymphoma: A comparative effectiveness analysis from the National Comprehensive Cancer Network (NCCN) non-Hodgkin's lymphoma outcomes database project.** *Proc ASH* 2009;Abstract 403.

In this indirect comparison series, first-line R-CHOP was inferior to both R-hyper-CVAD and R-CHOP with HDT/ASCR, which had equivalent PFS and OS, in 229 patients younger than age 65 with newly diagnosed MCL treated at NCCN institutions.

DIFFUSE LARGE B-CELL LYMPHOMA

4 Ziepert M et al. **Standard international prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era.** *J Clin Oncol* 2010;28(14):2373-80.

Efficacy of rituximab is superimposed on the efficacy of CHOP without an interaction between chemotherapy and rituximab and with a significant improvement in outcome within each of the standard IPI groups. These results confirm the validity of standard IPI in the rituximab era.

5 Hernandez-Ilizaliturri FJ et al. **Response of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) with nongerminal center B-cell phenotype to lenalidomide (L) alone or in combination with rituximab (R).** *Proc ASCO* 2010;Abstract 8038.

Relapsed-refractory DLBCL treated with lenalidomide, either alone or in combination with rituximab, was retrospectively analyzed by the germinal center (GCB) versus the nongerminal center (non-GCB) subtype. Results show an overall response of 77 percent in non-GCB versus 11 percent in the GCB group with single-agent lenalidomide, with a median PFS and OS of 336 days and more than 420 days in the non-GCB subtype and corresponding durations of 72 and 73 days for GCB subtype.

6 Sparano JA et al; AIDS Malignancy Consortium. **Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma.** *Blood* 2010;115(15):3008-16.

Patients with HIV-associated B-cell NHL were treated with sequential EPOCH and rituximab or concurrent rituximab-EPOCH. Patients who received concurrent rituximab/EPOCH had a CR rate of 73 percent, showing high efficacy of the concurrent regimen.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) / SMALL LYMPHOCYTIC LYMPHOMA (SLL)

7 Dreger P et al. **Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: Long-term clinical and MRD results of the GCLLSG CLL3X trial.** *Blood* 2010;116(14):2438-47.

Allogeneic stem cell transplantation is studied in this prospective Phase II study in poor-risk CLL (n = 90) and shows a durable benefit with a four-year event free-survival and OS of 42 percent and 65 percent, respectively.

8 Elter T et al. **Chemoimmunotherapy with fludarabine, cyclophosphamide and alemtuzumab (FC-Cam) in patients with relapsed or genetic high-risk CLL: Final analysis of the CLL2L trial of the German CLL Study Group.** *Proc ASH* 2009;Abstract 209.

Chemoimmunotherapy with fludarabine, cyclophosphamide and alemtuzumab (FCCam) is an effective approach in relapsed CLL and shows OR and CR rates of 68 percent and 22 percent, respectively.

9 Sutton L et al. **Autologous stem cell transplantation (ASCT) in CLL. Results of a Phase III randomized multicenter trial.** *Proc ASH* 2009;Abstract 878.

Autologous stem cell transplant (ASCT) among patients attaining CR with initial chemotherapy improves event-free survival from 26.2 months to "not-reached" with a median follow-up of 40.2 months. For patients not in CR with initial chemotherapy, ASCT or consolidation chemotherapy achieve similar results.

T-CELL LYMPHOMA

10 Prince HM et al. **Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma.** *J Clin Oncol* 2010;28(11):1870-7.

Denileukin diftitox (DD) has shown increased efficacy in this Phase III trial, with an improvement in response rates to 44 percent OR and 10 percent CR in the patients with DD-treated disease from 15.9 percent OR and two percent CR in the patients who received placebo. ORR was higher in the 18-μg/Kg/d group versus the 9-μg/Kg/d group (49.1 percent versus 37.8 percent, respectively), and both doses were significantly superior to placebo.

11 Pohlman B et al. **Final results of a Phase II trial of belinostat (PXD101) in patients with recurrent or refractory peripheral or cutaneous T-cell lymphoma.** *Proc ASH* 2009;Abstract 920.

Belinostat has activity in relapsed/refractory T-cell lymphomas with an overall response of 25% in relapsed-refractory PTCL (n = 20) and 13.7% in relapsed-refractory CTCL (n = 29).

12 Dueck G et al. **Interim report of a phase 2 clinical trial of lenalidomide for T-cell non Hodgkin's lymphoma.** *Cancer* 2010;116(19):4541-8.

Lenalidomide 25 mg on days 1-21 of 28-day cycles has clinical activity in relapsed and refractory T-cell lymphomas with on ORR of 30 percent (n = 23).

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the study by Badoux and colleagues, significant (Grade ≥3) tumor flare was not associated with the use of first-line lenalidomide in elderly patients with chronic lymphocytic leukemia (CLL).**
   a. True
   b. False
2. **Interim data from the GELA study LNH03-6B suggested that _____ was the more favorable treatment for elderly patients with diffuse large B-cell lymphoma (DLBCL), although no significant differences in efficacy were yet identified.**
   a. R-CHOP-21
   b. R-CHOP-14
   c. CHOP-21
   d. CHOP-14
3. **In the Phase II VERTICAL study of patients with relapsed or refractory follicular lymphoma (FL), the majority of patients who received the triplet regimen of bortezomib, bendamustine and rituximab (VBR) experienced a more than 50 percent reduction in tumor burden.**
   a. True
   b. False
4. **In a multicenter Phase II trial by Friedberg and colleagues, the dose of bendamustine used in combination with rituximab and bortezomib for relapsed or refractory indolent or mantle-cell lymphoma (MCL) was _____ days 1 and 4 on an every 28-day schedule.**
   a. 90 mg/m^2
   b. 100 mg/m^2
   c. 120 mg/m^2
5. **In the Phase II trial by Kahl and colleagues that evaluated single-agent bendamustine for relapsed indolent B-cell NHL, all patients had disease that was refractory to rituximab at the time of study enrollment.**
   a. True
   b. False
6. **In a dose-finding study, what was the optimal starting dose and schedule of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma?**
   a. 30 mg/m^2 weekly for three of four weeks
   b. 15 mg/m^2 weekly for three of four weeks
7. **Which of the following are characteristics of patients with DLBCL who experience relapse five years after treatment?**
   a. Initial localized disease
   b. Extranodal involvement
   c. Low or low-intermediate IPI score
   d. All of the above
8. **Which of the following was true about lenalidomide monotherapy in transformed lymphoma in the Phase II NHL-003 study?**
   a. Lenalidomide was not active in this poor-risk population
   b. The activity of lenalidomide depended on the original histology
   c. Lenalidomide resulted in excessively high rates of Grade 4 thrombocytopenia
9. **Based on the results of two Phase II studies, romidepsin has received FDA approval for the treatment of refractory cutaneous T-cell lymphoma.**
   a. True
   b. False
10. **In the Phase III StiL NHL 1-2003 study comparing BR to R-CHOP in the up-front treatment of FL, indolent lymphomas and MCL, which of the following was improved with BR?**
    a. Progression-free survival
    b. Complete response rate
    c. Both a and b
11. **BR was associated with a greater level of alopecia than R-CHOP in the StiL NHL 1-2003 study for patients receiving up-front treatment for FL, indolent lymphomas or MCL.**
    a. True
    b. False

Post-test answer key: 1a, 2a, 3a, 4a, 5a, 6b, 7d, 8b, 9a, 10c, 11b

QUESTIONS (PLEASE CIRCLE ANSWER):

12. The PRIMA trial demonstrated a significant improvement in progression-free survival with the use of maintenance rituximab for two years for patients with untreated FL after response to immunochemotherapy.

a. True
b. False

13. In a multicenter Phase II study, sequential treatment with rituximab and CHOP chemotherapy for B-cell post-transplant lymphoproliferative disorder was highly effective in patients who were _____.

a. Responsive to immunosuppression reduction (IR)
b. Unresponsive to IR

14. In the Phase II German CLL Study Group (GCLLSG) trial , first-line bendamustine/rituximab resulted in an ORR in excess of 90 percent.

a. True
b. False

15. The open-label, Phase III study from the German CLL Study Group of fludarabine and cyclophosphamide with or without rituximab in patients with CLL found that chemoimmunotherapy was associated with significant increases in _____ compared to chemotherapy alone.

a. ORR
b. Complete response
c. Overall survival at three years
d. All of the above

16. The Phase II study by Ferrajoli and colleagues that evaluated the combination of lenalidomide and rituximab for patients with relapsed CLL showed *inferiority* when compared to historical data with single-agent lenalidomide.

a. True
b. False

17. Long-term follow-up of the EORTC-20981 trial, which evaluated maintenance rituximab versus observation after induction with CHOP or R-CHOP for relapsed/refractory follicular lymphoma, demonstrated that maintenance rituximab improves _____.

a. Progression-free survival
b. Overall survival
c. Both a and b

18. In the study by Gisselbrecht and colleagues, predictors of response to second-line treatment with R-ICE or R-DHAP for patients with relapsed or refractory DLBCL included _____.

a. No prior use of rituximab
b. ECOG PS
c. Gender
d. All of the above

19. Elderly patients with DLBCL who received R-CHOP in the study by Coiffier and colleagues experienced significantly greater _____ over 10 years than those who received CHOP alone.

a. Overall survival
b. Progression-free survival
c. Both a and b
d. None of the above

20. Long-term follow-up (median, 10 years) of a Phase II study of tositumomab and iodine I-131 tositumomab for untreated Stage III and Stage IV FL revealed a median progression-free survival of _____.

a. Two years
b. Six years
c. 10 years

Post-test answer key: 12a, 13b, 14a, 15d, 16b, 17a, 18a, 19c, 20b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential. **Please tell us about your experience with this educational activity.**

How would you characterize your level of knowledge on the following topics? 4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	Before	After
Overall response rate with BR versus R-CHOP therapy for patients with indolent lymphomas	4 3 2 1	4 3 2 1
PRIMA: A Phase III study of maintenance rituximab for patients with untreated FL	4 3 2 1	4 3 2 1
Long-term survival rates for patients with DLBCL treated with R-CHOP versus standard CHOP chemotherapy	4 3 2 1	4 3 2 1
Hematologic toxicities associated with single-agent lenalidomide therapy for patients with CLL	4 3 2 1	4 3 2 1
Best response rates with bortezomib/bendamustine/rituximab among patients with follicular NHL or MCL	4 3 2 1	4 3 2 1
Incidence of tumor lysis syndrome associated with romidepsin among patients with cutaneous T-cell lymphoma	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No If no, please explain: .....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable If no, please explain: .....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No If no, please explain: .....

Please respond to the following learning objectives (LOs) by circling the appropriate selection: 4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Appraise recent data on therapeutic advances and changing practice standards in NHL, including chronic lymphocytic leukemia (CLL), and apply this information to clinical practice..... 4 3 2 1 N/M N/A
- Use prognostic and predictive clinical and molecular markers to aid in treatment decision-making for NHL..... 4 3 2 1 N/M N/A
- Individualize the use of maintenance and/or consolidation therapy in the management of newly diagnosed and relapsed follicular lymphoma..... 4 3 2 1 N/M N/A
- Recall the emerging data for novel agents and combinations in the treatment of mantle-cell lymphoma..... 4 3 2 1 N/M N/A
- Develop an algorithm for the risk-stratified induction treatment of diffuse large B-cell lymphoma..... 4 3 2 1 N/M N/A
- Apply the results of emerging clinical research to the selection of optimal systemic therapy for patients with newly diagnosed or relapsed/refractory CLL..... 4 3 2 1 N/M N/A
- Communicate the benefits and risks of evidence-based systemic treatments to patients with advanced cutaneous or peripheral T-cell lymphoma..... 4 3 2 1 N/M N/A
- Identify patients with NHL who may experience quantitative and qualitative benefit from salvage therapy regimens with stem cell transplantation..... 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity? .....

What additional information or training do you need on the activity topics or other oncology-related topics? .....

Additional comments about this activity: .....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey. ☐ Yes, I am willing to participate in a follow-up survey. ☐ No, I am not willing to participate in a follow-up survey.

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YIRNHL10

Year in Review

Non-Hodgkin's Lymphomas: 2009-2010

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Hematologic Oncology™
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