5 Minute JournalClub

Key ASH Presentations

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CME Information

LEARNING OBJECTIVES

- Consider the inclusion of single-agent romidepsin in the treatment algorithm for relapsed or refractory peripheral T-cell lymphoma.
- Integrate new and existing therapeutic strategies into the best-practice management of diffuse large B-cell lymphoma.
- Apply the results of emerging clinical research to the selection of optimal systemic therapy for patients with relapsed/refractory mantle-cell lymphoma.
- Recall new data with investigational agents demonstrating promising activity in non-Hodgkin lymphomas.

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CME Information (Continued)

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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:

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CME Information (Continued)

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Phase II Trial of Lenalidomide-Rituximab +/- Dexamethasone in Relapsed or Refractory Indolent B-Cell or Mantle Cell Lymphomas Resistant to Rituximab

Ahmadi T et al.

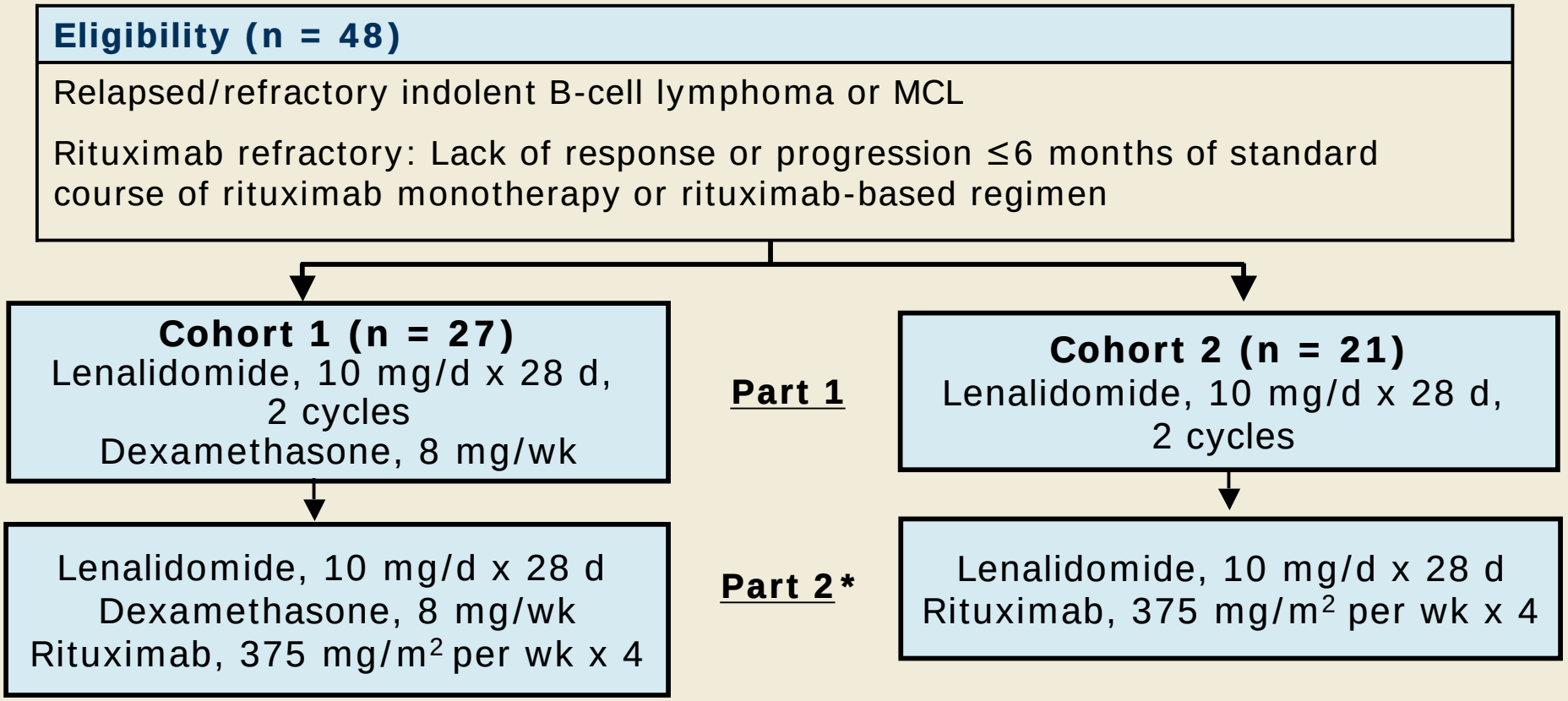
Proc ASH 2011;Abstract 266.

Background

- Single-agent rituximab has demonstrated activity in patients with relapsed low-grade or follicular lymphoma (*JCO* 1998;16:2825).
- However, approximately 50% of patients may not respond to initial rituximab treatment and most will become resistant to rituximab.
- Preclinical studies suggest that lenalidomide may act synergistically with rituximab to overcome clinical resistance to rituximab.
- **Objective:**
  - Test the efficacy of lenalidomide combined with rituximab in patients with relapsed or refractory indolent B-cell or mantle-cell lymphoma (MCL).

Ahmadi T et al. *Proc ASH* 2011;Abstract 266.

Trial Design



* Only patients with stable or responsive disease after Part 2 continued with treatment of lenalidomide +/- dexamethasone until disease progression.

- Response assessments were performed after Part 1 and after Part 2.

Ahmadi T et al. *Proc ASH* 2011;Abstract 266.

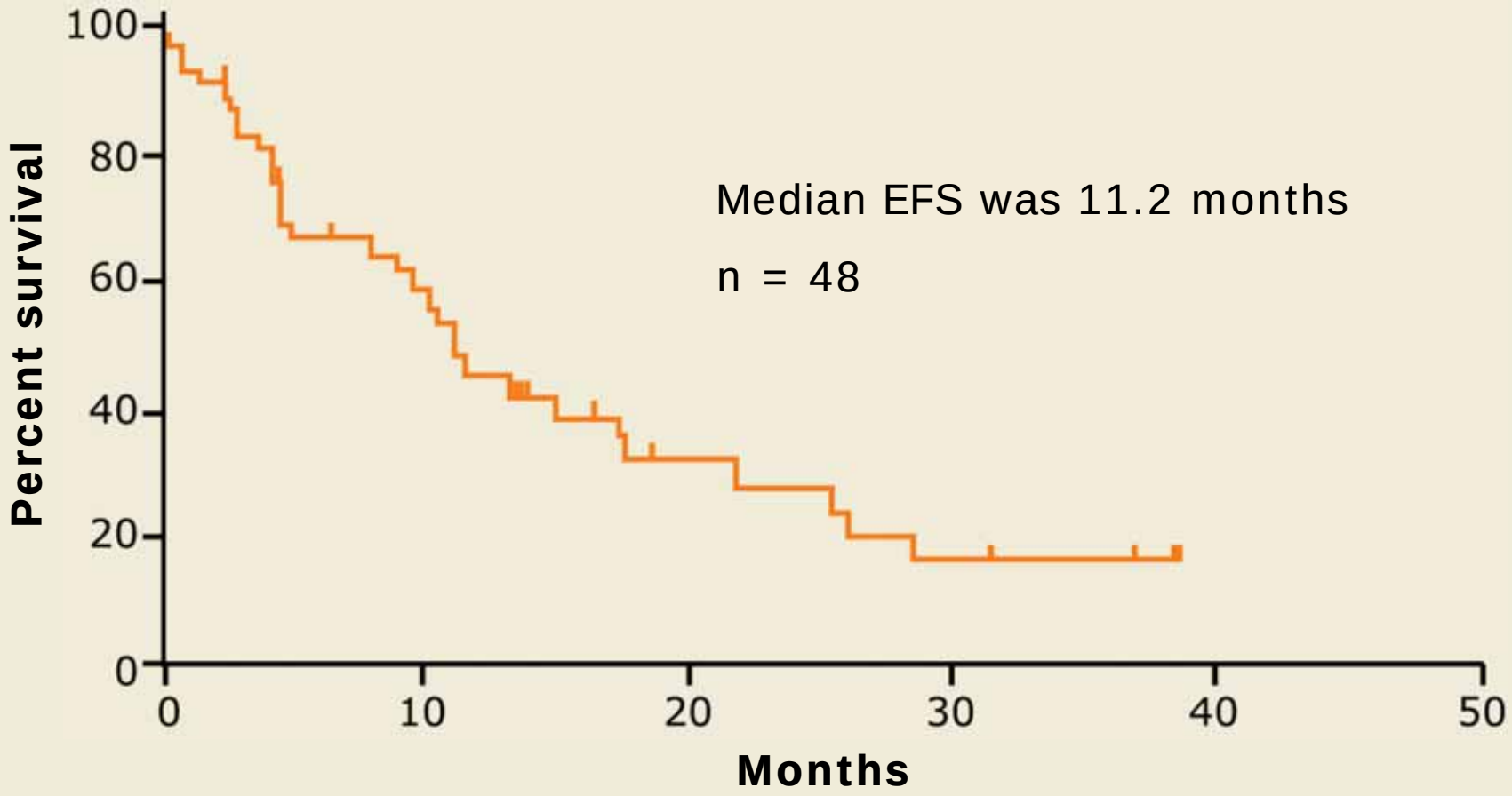
Response Rates (Evaluable Patients, n = 40)

Response	Cohort 1 (n = 24)		Cohort 2 (n = 16)	
	Part 1	Part 2	Part 1	Part 2
Complete response (CR)	17%	33%	19%	50%
Partial response (PR)	13%	25%	19%	25%
Stable disease (SD)	63%	33%	44%	19%
Progressive disease (PD)	8%	8%	19%	6%
Overall response rate (ORR)	29%	58%	37%	75%

- For all evaluable patients (n = 40), ORR was 33% (Part 1) and 65% (Part 2).
- ORR by histology (after completion of Part 2): 67% (FL, n = 24); 60% (MCL, n = 10); 75% (SLL, n = 4); 50% (MZL, n = 50).

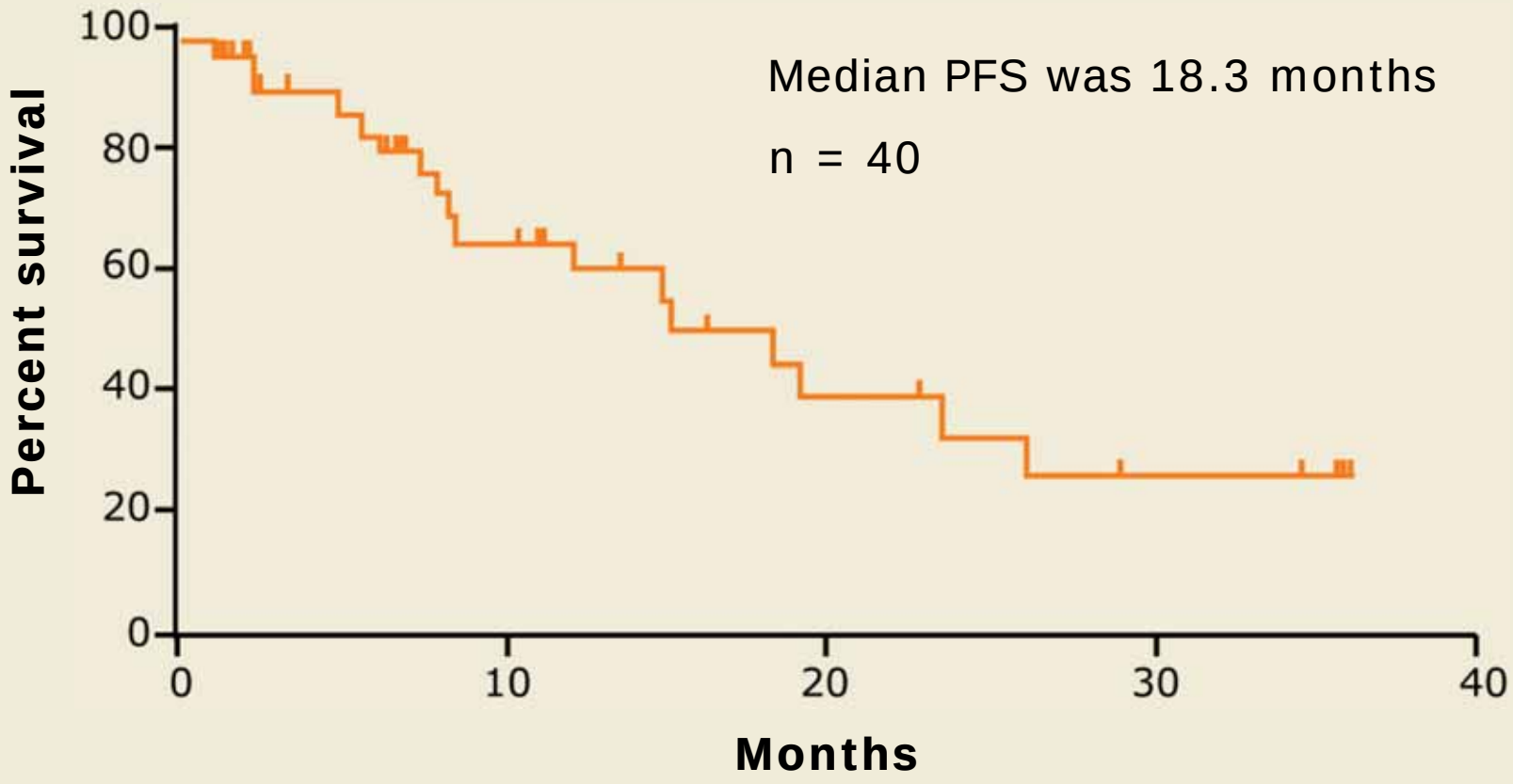
Ahmadi T et al. *Proc ASH* 2011;Abstract 266.

Event-Free Survival (EFS) Intent to Treat



With permission from Ahmadi T et al. *Proc ASH* 2011;Abstract 266.

Progression-Free Survival (PFS) from Last Dose of Rituximab



With permission from Ahmadi T et al. *Proc ASH* 2011;Abstract 266.

Selected Adverse Events

Event, n	Cohort 1 (n = 27)	Cohort 2 (n = 18)
Fatigue	10	3
GI complaint	8	6
Tumor flare	5	6
Rash	4	6
Neutropenia	4	2
Neuropathy	3	3
Anemia	2	—
Leukopenia	2	—
Weight loss	2	—
Periorbital edema	—	2

Patients with dose interruptions: 14.8% (cohort 1); 50% (cohort 2), $p = 0.02$.

Ahmadi T et al. *Proc ASH* 2011;Abstract 266.

Author Conclusions

- The combination of lenalidomide with low-dose dexamethasone and a 4-week course of rituximab produced a high ORR with durable responses (data not shown) in patients with rituximab-resistant small B-cell lymphoma.
- The response rate appears to improve following the addition of rituximab to lenalidomide-dexamethasone, although a delayed response to lenalidomide-dexamethasone is possible for some patients.
- It is possible that the “immunomodulatory” effects of lenalidomide may overcome resistance to rituximab in some patients.

Ahmadi T et al. *Proc ASH* 2011;Abstract 266.

Investigator Commentary: Phase II Trial of Lenalidomide-Rituximab with or without Dexamethasone in B-Cell Lymphoma or MCL

Lenalidomide has emerged as a promising drug for different types of non-Hodgkin lymphoma, including follicular lymphoma and MCL, especially in combination with rituximab. A registration-directed study is evaluating the potential approval of lenalidomide for patients with MCL.

This study uses an interesting regimen. Presently, I use lenalidomide for patients, including a fair number of elderly patients, with relapsed or refractory MCL. Some have been receiving lenalidomide (10 mg/d, without breaks) for 1 to 2 or more years, and the drug is well tolerated. When administered at 25 mg/d for shorter periods, we find that lenalidomide is not as well tolerated in many of the elderly patients with MCL. Therefore, combinations such as lenalidomide with rituximab and dexamethasone may be particularly good for elderly patients with MCL who may not be great candidates for other combination therapies, let alone autologous stem cell transplant.

Interview with Owen A O'Connor, MD, PhD, February 3, 2012

The Bruton's Tyrosine Kinase Inhibitor PCI-32765 is Highly Active as Single-Agent Therapy in Previously-Treated Mantle Cell Lymphoma (MCL): Preliminary Results of a Phase II Trial[1]

The Addition of Rituximab to Fludarabine and Cyclophosphamide (FC) Improves Overall Survival in Newly Diagnosed Mantle Cell Lymphoma (MCL): Results of the Randomised UK National Cancer Research Institute (NCRI) Trial[2]

[1] **Wang L et al.**

Proc ASH 2011;Abstract 442.

[2] **Rule L et al.**

Proc ASH 2011;Abstract 440.

The Bruton's Tyrosine Kinase Inhibitor PCI-32765 Is Highly Active as Single-Agent Therapy in Previously-Treated Mantle Cell Lymphoma (MCL): Preliminary Results of a Phase II Trial

Wang L et al.

Proc ASH 2011;Abstract 442.

Background

- Bruton's tyrosine kinase (Btk) is a central mediator of B-cell receptor signaling, essential for normal B-cell development.
- PCI-32765 is an irreversible inhibitor of Btk that induces apoptosis and blocks cellular migration and adhesion in malignant B cells.
- A Phase I trial showed that treatment with PCI-32765 resulted in objective responses in patients with relapsed B-cell or MCL (*ASH* 2010;Abstract 964).
- **Objective:**
  - Report the preliminary efficacy and safety results of an ongoing Phase II trial of single-agent PCI-32765 in patients with previously treated MCL (PCYC-1104 trial).

Wang L et al. *Proc ASH* 2011;Abstract 442.

PCYC-1104 Study Method

- PCYC-1104 is a Phase II trial of single-agent PCI-32765 (560 mg PO daily x 28-day continuous cycles) in patients with relapsed or refractory MCL who were either bortezomib naïve or bortezomib exposed.
- Bortezomib-naïve and bortezomib-exposed cohorts were analyzed separately and tumor response was evaluated every 2 cycles by 2007 NHL IWG criteria.
- Safety analysis includes patients (n = 39) who have initiated treatment and have reported 1 adverse event (AE).
- Efficacy analysis includes patients (n = 24) who have undergone at least 1 tumor follow-up assessment.

Wang L et al. *Proc ASH* 2011;Abstract 442.

Efficacy Results (Abstract Only)

Response	Bortezomib naïve (n = 12)	Bortezomib exposed (n = 12)
Objective response rate (ORR)	58%	75%
ORR (all patients, n = 39)	67%	

- 35 out of 39 patients (90%) remain on PCI-32765
- Four patients have discontinued PCI-32765
  - Progressive disease (n = 3)
  - Investigator decision (n = 1)

Wang L et al. *Proc ASH* 2011;Abstract 442.

AEs (Abstract Only)

Event	Patients (n = 39)
Grade >3 AEs potentially related to PCI-32765	11%
Serious AEs (SAEs)	21%
SAEs potentially related to PCI-32765 Rash Febrile neutropenia	 3% 3%
Death*	3%

* Patient (n = 1) did not receive PCI-32765 due to rapid disease progression.

- No patient has discontinued treatment due to AEs.
- Grade 1 or 2 diarrhea, fatigue and nausea have been the most frequently reported AEs.

Wang L et al. *Proc ASH* 2011;Abstract 442.

Author Conclusions (Abstract Only)

- Preliminary data from the PCYC-1104 Phase II trial suggest that PCI-32765 induces a high response rate in patients with relapsed or refractory MCL.
- PCI-32765 is well tolerated.
- Phase III trials of PCI-32765 in patients with MCL are planned.

Wang L et al. *Proc ASH* 2011;Abstract 442.

Investigator Commentary: The Btk Inhibitor PCI-32765 Is Highly Active as Single-Agent Therapy in Pretreated Patients with MCL: Preliminary Results

Without question, targeting unique biological features of large B-cell lymphoma such as Btk has become attractive. One of the first such drugs targeting the downstream components of the B-cell receptor inhibited the Syk kinase. The Btk inhibitor is actually downstream of the Syk kinase and has proved to be a target that has produced significant benefits in several large B-cell lymphomas.

In patients with MCL who had received prior bortezomib therapy, ORR was a little higher compared to bortezomib-naïve patients. The difference is, however, too small to make major dogmatic comments regarding the impact of prior bortezomib on the response rate. Achieving a response rate of 67% is significant in this patient population that has been exposed to prior chemotherapies, especially considering the observation that none of the patients discontinued treatment because of secondary AEs. It will be interesting to see duration data on how long these beneficial responses last.

Interview with Owen A O'Connor, MD, PhD, February 3, 2012

The Addition of Rituximab to Fludarabine and Cyclophosphamide (FC) Improves Overall Survival in Newly Diagnosed Mantle Cell Lymphoma (MCL): Results of the Randomised UK National Cancer Research Institute (NCRI) Trial

Rule S et al.

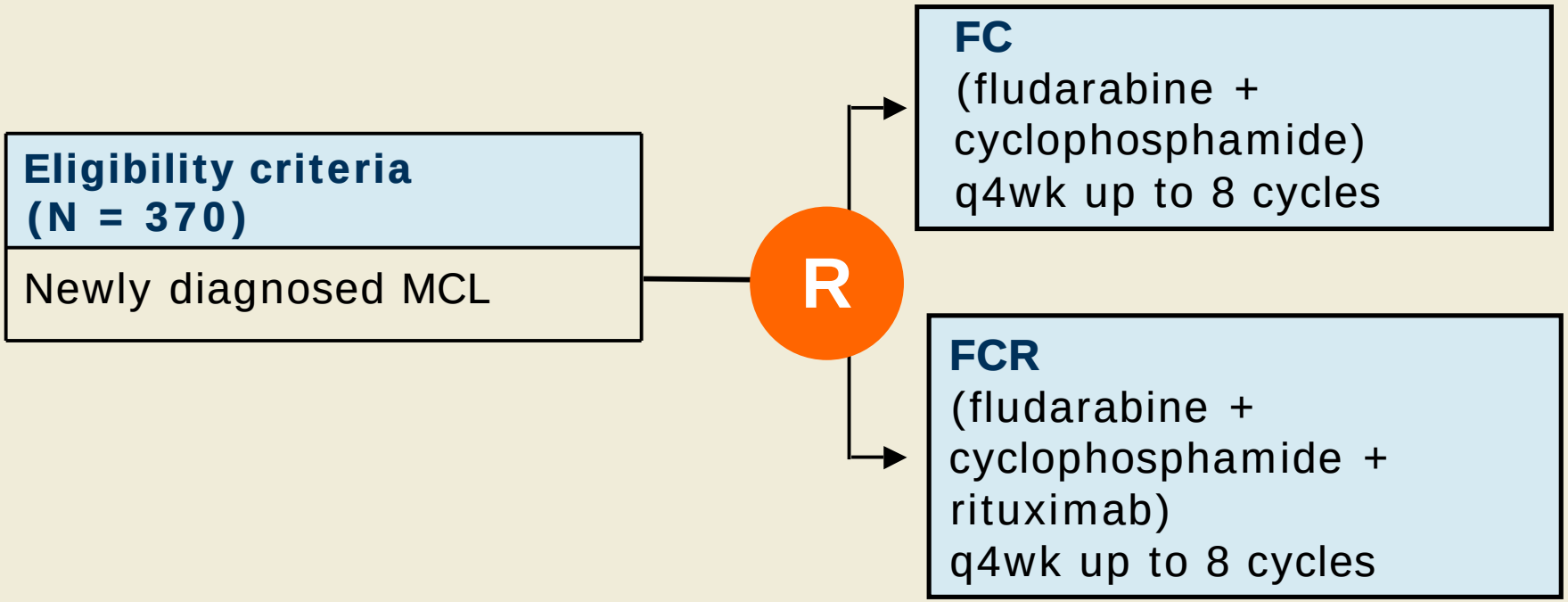
Proc ASH 2011;Abstract 440.

Background

- The role of rituximab in the treatment of mantle-cell lymphoma (MCL) is unclear.
- Prior studies showed improved response rates to chemotherapy in combination with rituximab.
- The survival benefit of rituximab is less reliable due to heterogeneity among the trials (*Cochrane Database Syst Rev* 2007;4:CD003805; *Blood* 2011;118:4808).
- **Current study objective**: Assess the efficacy and safety of fludarabine and cyclophosphamide with or without rituximab in the treatment of MCL.

Rule S et al. *Proc ASH* 2011;Abstract 440.

Study Design



Rule S et al. *Proc ASH* 2011;Abstract 440.

Efficacy of FCR versus FC (Abstract Only)

Outcome	FCR	FC	HR	*p*-value
Overall response rate CR + CRu	90.6% 64.7%	79.8% 46.9%	NR	0.01 0.002
Progressive disease	5.8%	11.9%	NR	NR
Median progression-free survival	30.6 mo	16.1 mo	0.56	<0.001
Median overall survival	45.7 mo	37 mo	0.72	0.03

HR = hazard ratio; CR = complete response; CRu = unconfirmed complete response

Median follow-up 38.8 months

Rule S et al. *Proc ASH* 2011;Abstract 440.

Grade 3/4 Adverse Events and Causes of Death (Abstract Only)

Adverse event (N = 370)	Incidence
Neutropenia	51.4%
Leucopenia	45.8%
Thrombocytopenia	23.3%
Anemia	12.9%
Infections	11.8%

- One patient had Grade 3 renal toxicity.
- Significantly more patients in the FCR arm had Grade 3/4 leukopenia, thrombocytopenia.
- Most common cause of death: Lymphoma.
- Death due to other causes: FCR 29%, FC 24%.
  - Almost half were infection related.
- Eleven patients died of secondary cancer, 4 due to AML.
- Death without disease progression: FCR 14%, FC 10%.

Rule S et al. *Proc ASH* 2011;Abstract 440.

Author Conclusions

- The addition of rituximab to FC chemotherapy leads to a significant improvement in both progression-free survival and overall survival with an acceptable level of additional toxicity.
- A significant number of patients who received FC-based chemotherapy died of nonlymphoma-related causes while in remission.

Rule S et al. *Proc ASH* 2011;Abstract 440.

Investigator Commentary: The Addition of Rituximab to FC Improves Overall Survival in Newly Diagnosed MCL: Results of the UK NCRI Trial

This study was performed in a fairly representative group of patients with MCL and showed major clinical benefits with the addition of rituximab to FC. This is important because previous studies in MCL had raised questions about the value of adding rituximab to the chemotherapy regimen. This trial should help to put uncertainties about the addition of rituximab to chemotherapy to rest. The observation that both treatment arms had significant rates of infections, with some leading to death, is notable. Despite the fact that the efficacy of the FCR regimen was reasonably good, a high rate of infection-related toxicity is associated with fludarabine-based therapy in older patients with MCL.

Although these data demonstrated the value of adding rituximab to FC, the toxicity profile leads me to believe that FC is not the appropriate chemotherapy backbone for older patients with MCL.

The Kluin-Nelemans study showed unequivocally that R-CHOP is a better induction choice than FCR. Hence, rituximab should be added to either CHOP or bendamustine when treating MCL in older patients.

Interview with Brad S Kahl, MD, March 9, 2012

Dose-Adjusted EPOCH plus Rituximab in Untreated Patients with Poor Prognosis Large B-Cell Lymphoma, with Analysis of Germinal Center and Activated B-Cell Biomarkers

Purroy N et al.

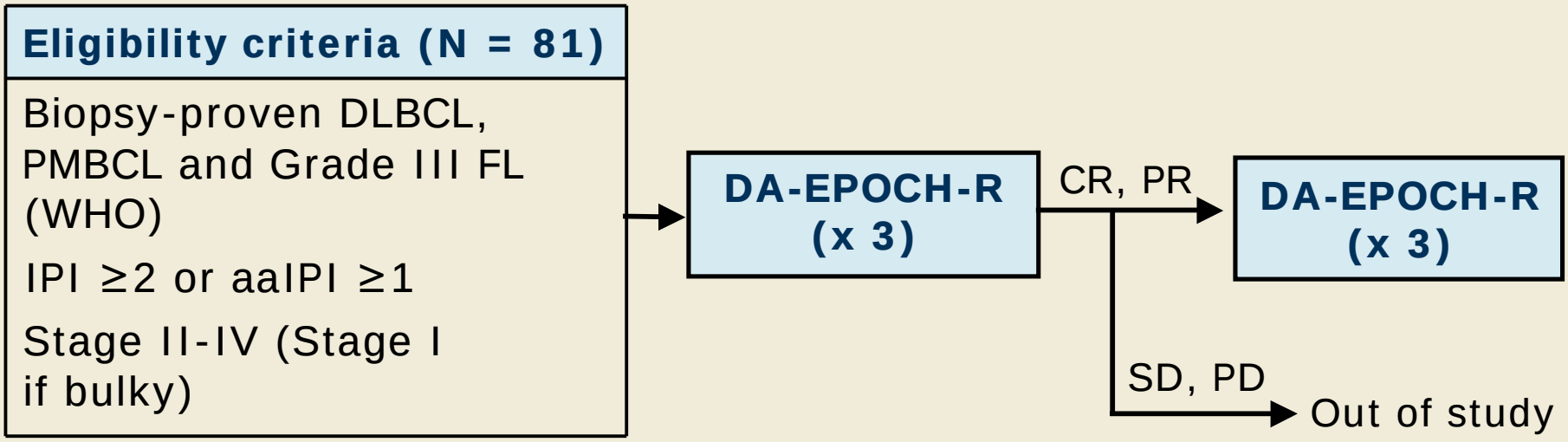
Proc ASH 2011;Abstract 593.

Background

- Patients with large B-cell lymphomas treated with front-line, dose-adjusted EPOCH (DA-EPOCH) have a complete response (CR) rate of 92% and 5-year progression-free survival (PFS) of 70% (*Blood* 2002;99:2685).
- Combination of rituximab (R) with DA-EPOCH (DA-EPOCH-R) showed promising results in patients with untreated diffuse large B-cell lymphomas (DLBCL) (*J Clin Oncol* 2008;26:2717; *Br J Haematol* 2007;136:276).
- **Current study objective**: Assess the efficacy and safety of DA-EPOCH-R in patients with untreated large B-cell lymphomas with poor prognosis in a Phase IV study.

Purroy N et al. *Proc ASH* 2011;Abstract 593.

Phase IV Study Design



- Tumor samples analyzed by IHC for biomarkers of proliferation (Ki-67) and markers of cellular differentiation.
- IHC to determine the histological origin of patients according to the Choi and Hans algorithms was performed retrospectively.
- Follow-up: Evaluation every 3 mo for 2 y, then every 6 mo for 3 y

Primary endpoint: PFS

Purroy N et al. *Proc ASH* 2011;Abstract 593.

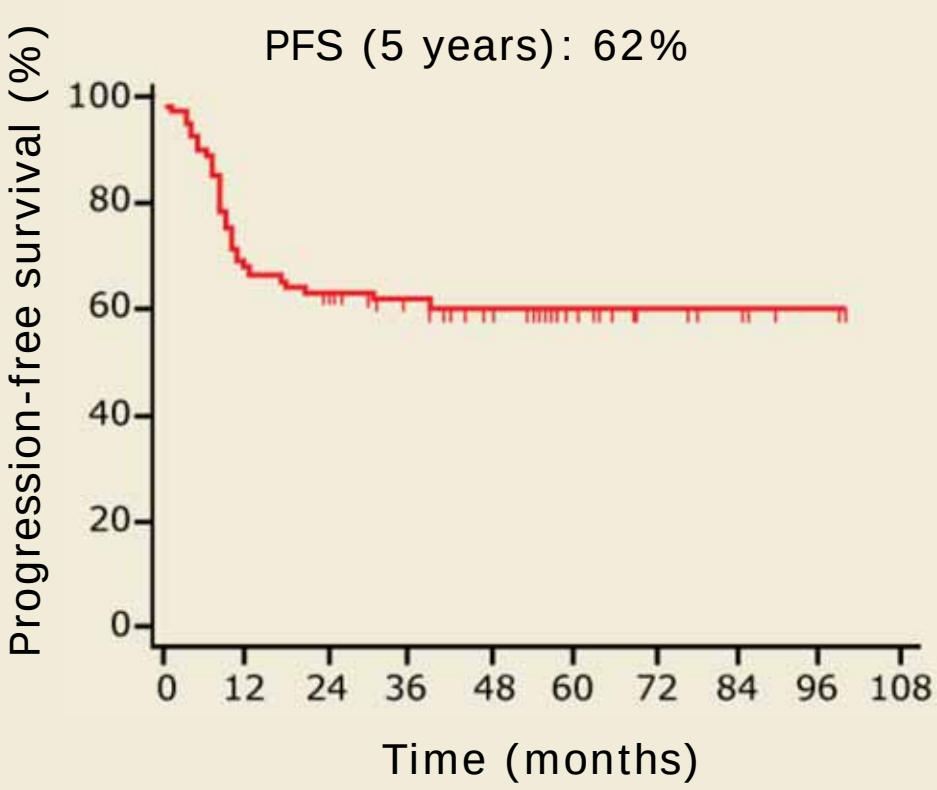
DA-EPOCH-R Dosing Schedule

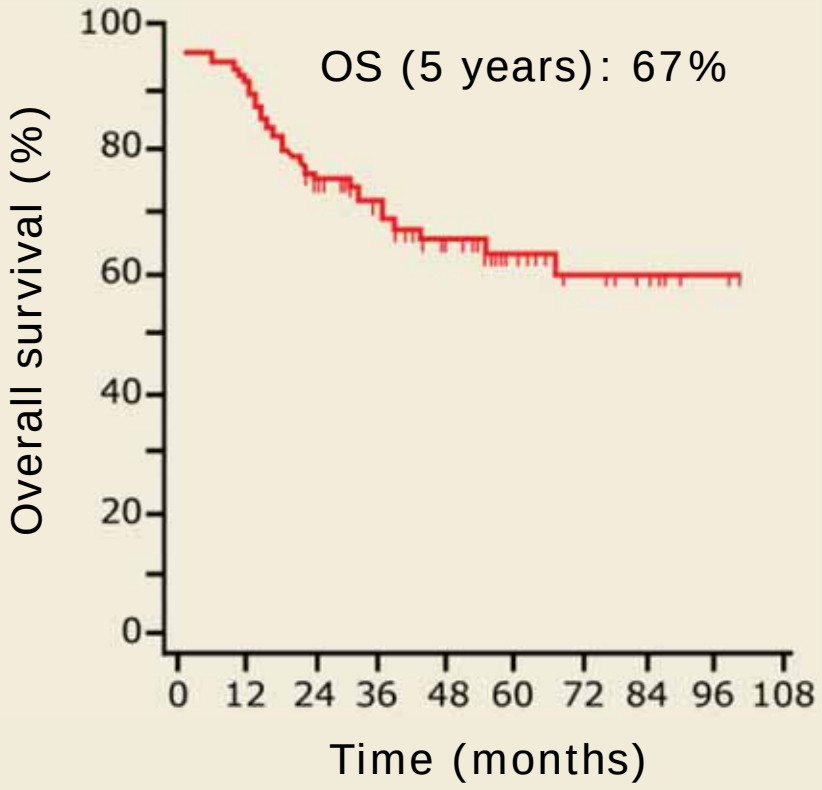
Drug	Dose	Treatment days
Etoposide (CIV)	50 mg/m^2/day	1,2,3,4
Doxorubicin (CIV)	10 mg/m^2/day	1,2,3,4
Vincristine (CIV)	0.4 mg/m^2/day	1,2,3,4
Rituximab (IV)	375 mg/m^2/day	1
Cyclophosphamide (IV)	750 mg/m^2/day	5
Prednisone (PO)	60 mg/m^2/day	1,2,3,4,5

- Radiation therapy (30 Gy): For bulky/residual disease
- Cycles administered q3wk if ANC ≥1 x 10^9/L and platelet ≥100 x 10^9/L
- After every cycle, doses were adjusted according to known hematological parameters
- For neutropenic fever, dose reduced 20% below the last cycle

Purroy N et al. *Proc ASH* 2011;Abstract 593.

PFS and OS





Median follow-up: 55 months

With permission from Purroy N et al. *Proc ASH* 2011;Abstract 593.

Complete Response Rates in Patient Subgroups

Characteristic	CR rate	*p*-value
IPI		
0-2 (n = 13)	100%	0.06
3-5 (n = 68)	75%	
Choi algorithm		
GCB (n = 22)	86.3%	1.0
ABC (n = 17)	88.2%	
Hans algorithm		
GCB (n = 16)	81.2%	0.631
Non-GCB (n = 23)	91.3%	
Ki-67		
<80% (n = 29)	82.7%	1.0
≥80% (n = 29)	86.7%	

GCB = germinal center B cell; ABC = activated B cell

Overall (N = 81) CR/uCR: 80.2%, PR: 9.9%, failure rate: 9.9%

Purroy N et al. *Proc ASH* 2011;Abstract 593.

Adverse Events

Adverse event (N = 81)	Incidence (%)
Anemia (Grade 3/4)	84.0%
Thrombocytopenia (Grade 3/4)	71.6%
Neutropenic fever	45.7%
Mucositis (Grade 3/4)	11.1%
Neurotoxicity (Grade 3/4)	2.5%

Discontinuation: 6 patients, 2 due to disease progression

Deaths: 4 (pneumonia: 2, septic shock: 2)

Purroy N et al. *Proc ASH* 2011;Abstract 593.

Author Conclusions

- Patients with DLBCL who had adverse prognostic features showed a high response rate to DA-EPOCH-R.
- PFS was 62% at 5 years and was comparable to dose-dense or other high-dose regimens.
- DA-EPOCH-R seems to diminish the impact of adverse clinical variables and the value of histological origin and tumor proliferation (data not shown).
- Randomized studies comparing R-CHOP to DA-EPOCH-R in patients with high-risk DLBCL are warranted.

Purroy N et al. *Proc ASH* 2011;Abstract 593.

Investigator Commentary: Dose-Adjusted EPOCH with Rituximab in Patients with Untreated Poor-Prognosis Large B-Cell Lymphoma

This is an interesting, large, single-arm study evaluating dose-adjusted EPOCH in a patient population with an age-adjusted IPI of 1 or higher. They reported an overall response rate of about 90%, with 80% of patients having a CR and an overall survival of 67%. In the absence of a randomized trial it is hard to determine whether this regimen is better than R-CHOP-21. When the Intergroup study comparing R-CHOP to EPOCH-R is completed, we should have good evidence indicating whether we can improve on the standard R-CHOP regimen.

Interview with Owen A O'Connor, MD, PhD, February 3, 2012

In comparison to these data, the study by Pfreundschuh and colleagues (*Proc ASH* 2011;Abstract 592) showed better efficacy. Because the dose of EPOCH-R is adjusted based on blood counts, it requires a costly double-lumen catheter procedure in which patients are admitted for 5 days every 3 weeks. Hence, for the EPOCH-R regimen to be used, especially in the United States, it will have to be superior to R-CHOP-21 in an Intergroup study.

Interview with Craig Moskowitz, MD, January 11, 2012

BMT CTN Protocol 0401: Results of a Phase III Randomized Multicenter Trial of Rituximab/BEAM vs 131-Iodine Tositumomab/BEAM Conditioning Regimen for Relapsed Diffuse Large B-Cell Lymphoma

Vose JM et al.

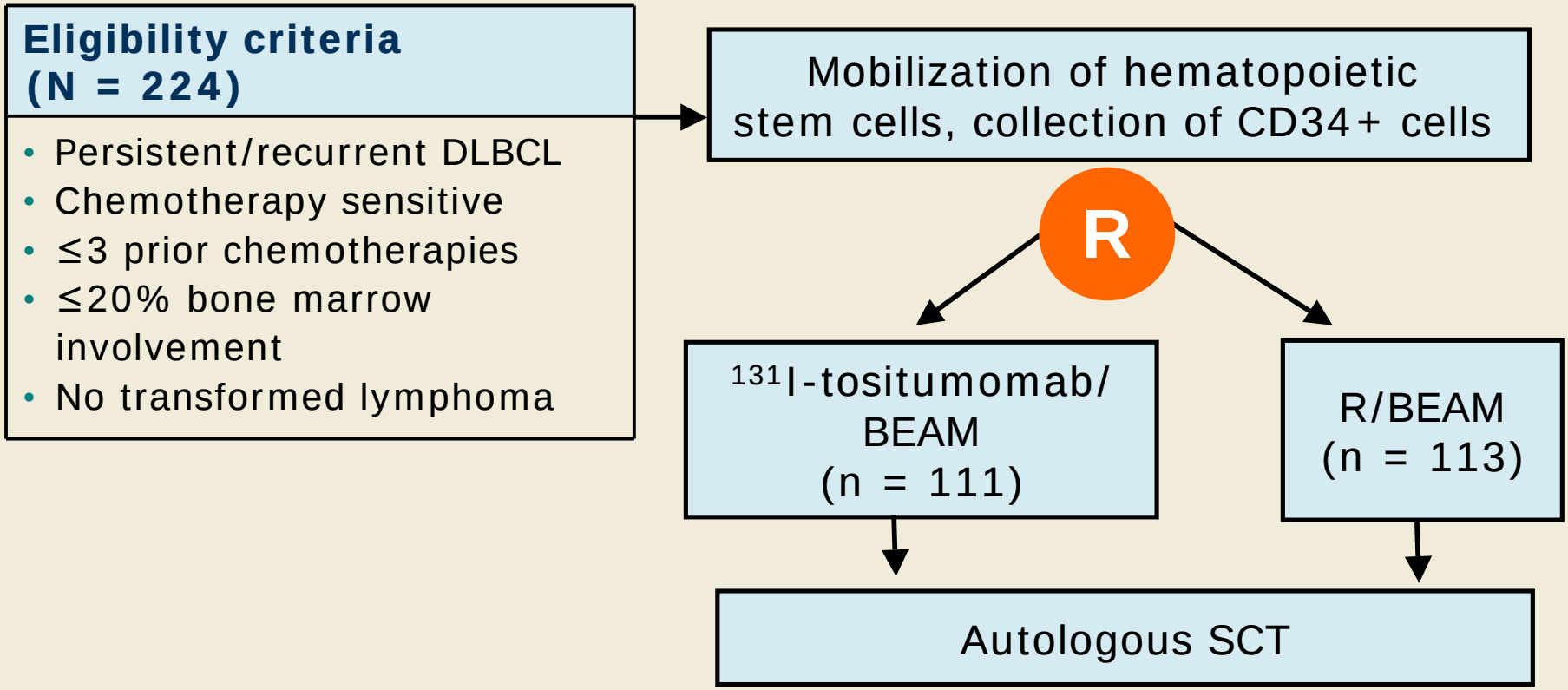
Proc ASH 2011;Abstract 661.

Background

- High-dose chemotherapy and autologous stem cell transplant (SCT) are the standard of care for patients with relapsed DLBCL.
- Patients who have received prior rituximab (R) therapy have a 2-year PFS rate of 40%.
- A Phase II trial of ^{131}I-tositumomab with BEAM (carmustine/etoposide/cytarabine/melphalan) chemotherapy prior to autologous SCT showed a 3-year PFS rate of 70% for patients with relapsed and high-risk DLBCL (*Proc ASCO* 2007, Abstract 8013).
- **Current study objective**: Compare R/BEAM to ^{131}I-tositumomab/BEAM prior to SCT in patients with relapsed DLBCL.

Vose JM et al. *Proc ASH* 2011;Abstract 661.

Phase III Study Schema



Vose JM et al. *Proc ASH* 2011;Abstract 661.

Survival Rates

Outcome	^{131}I-tositumomab/ BEAM	R/BEAM	*p*-value
Two-year progression-free survival (PFS) rate			
All patients (n = 111, 113)	48.6%	49.0%	0.65
Patients in CR (n = 55, 52)	52.7%	61.9%	0.32
Patients not in CR (n = 56, 61)	44.6%	38.0%	0.88
Two-year overall survival (OS) rate			
All patients (n = 111, 113)	60.1%	66.3%	0.29
Second CR*	76.9%	79.9%	0.61

* Patients in CR after salvage chemotherapy

Multivariate analysis for PFS and OS rates:

- PFS: CR patients, HR = 1; Non-CR patients, HR = 1.63 (p = 0.008)
- OS: CR patients, HR = 1; Non-CR patients, HR = 2.42 (p = 0.0005)

Vose JM et al. *Proc ASH* 2011;Abstract 661.

Causes of Death

Cause of death	^{131}I-tositumomab/BEAM (n = 103)	R/BEAM (n = 107)
Relapse/progression	83.8%	83.3%
Graft rejection/failure	2.7%	0
Organ failure	5.4%	5.4%
Secondary AML	0	2.8%
Acute respiratory distress syndrome	8.1%	0
Lung cancer	0	2.8%
Thromboembolic	0	2.8%

Vose JM et al. *Proc ASH* 2011;Abstract 661.

Author Conclusions

- No difference in PFS, OS or relapse/progression was seen when tositumomab/BEAM was compared to R/BEAM.
- Disease state at transplant (ie, complete remission after salvage chemotherapy) was the most predictive of outcome.
- Mucositis was significantly increased in patients receiving tositumomab/BEAM conditioning compared to R/BEAM, and the hematologic recovery and other toxicities were similar between the 2 treatment arms (data not shown).

Vose JM et al. *Proc ASH* 2011;Abstract 661.

Investigator Commentary: Rituximab/BEAM vs ^{131}I-Tositumomab/BEAM for Relapsed DLBCL

The role of radioimmunotherapy is an area of significant debate, with many single-arm studies evaluating both tositumomab and ibritumomab tiuxetan integrated into BEAM-based chemotherapy regimens. I'm not sure that this particular trial puts to rest the issue of RIT for patients with DLBCL. Many follow-up studies will investigate higher doses of ibritumomab tiuxetan integrated into BEAM. These studies should shed additional light on the value of integrating radioimmunotherapy into the autologous stem cell transplant arena.

Interview with Owen A O'Connor, MD, PhD, February 3, 2012

This was the most disappointing study at the ASH meeting. It was a high-priority lymphoma study and "make or break" for radioimmunotherapy for transplant patients. If it was positive, it would have been great for patients with lymphoma and would have put tositumomab on the map. The Phase II results were phenomenal, but this study was completely negative with superimposable survival curves. This is sad for lymphoma patients and by far the most disappointing news of the meeting.

Interview with Craig Moskowitz, MD, January 11, 2012

Results from a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma After Prior Systemic Therapy[1]

Final Results of Phase II Trial of Pegylated Liposomal Doxorubicin (PLD) Followed by Bexarotene (Bex) in Advanced Cutaneous T-Cell Lymphoma (CTCL)[2]

[1]Coiffier B et al.
J Clin Oncol 2012;30(6):631-6.
Proc ASH 2011;Abstract 591.

[2]Straus DJ et al.
Proc ASH 2011;Abstract 882.

Results from a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma after Prior Systemic Therapy

Coiffier B et al.

J Clin Oncol 2012;30(6):631-6.

Proc ASH 2011;Abstract 591.

Background

- Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of rare disorders resulting from clonal proliferation of mature post-thymic lymphocytes (*Ann Oncol* 1998;9:849).
- Currently, no agents are approved for use as first-line treatment of PTCL.
- Romidepsin is a structurally unique, selective inhibitor of histone deactylase (HDAC) approved for the treatment of patients with cutaneous T-cell lymphoma following ≥1 prior systemic therapies.
- Prior Phase I and II trials showed clinical activity of romidepsin in PTCL (*Blood* 2011;117:5827; *Blood* 2001;98:2865).
- **Objective:**
  - Confirm the efficacy of romidepsin in patients with relapsed or refractory PTCL.

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

Trial Design

Eligibility (n = 130)

Histologically confirmed PTCL by central review for PTCL subtypes

Relapsed disease or refractory to ≥1 systemic therapies

No use of any investigational therapy within 4-6 weeks of study entry

→ **Romidepsin**
14 mg/m² IV d1, 8, 15
q4wk x 6 cycles*

* Patients with stable disease (SD), partial response (PR) or complete response/unconfirmed complete response (CR/CRu) could elect to extend therapy until progressive disease or another withdrawal criterion was met.

Primary endpoint:

- Rate of CR/CRu as determined by an independent review committee (IRC)

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

Response Rates: Overall IRC and Investigators' Assessments (INA)

Best response rate	IRC (n = 130)	INA (n = 130)
ORR (CR/CRu + PR)*	25%	29%
CR/CRu†	15%	16%
CR	10%	15%
CRu	5%	2%
PR	11%	13%
SD	25%	17%
PD or N/E	49%	54%

ORR, objective response rate; PD, progressive disease; N/E, not evaluable

* Median time to response was 1.8 mo; duration of response was 16.6 mo by IRC.
† Median time to response was 3.7 mo; duration of response was 16.6 mo by IRC.

- Baseline disease characteristics, prior therapeutic regimen or number of prior therapies had no impact on the ability of patients to respond to romidepsin.

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

Response Rates by Overall IRC Assessments in Patient Subgroups

Subgroup (n = 130)	CR/CRu rate		ORR	
	%	*p*-value	%	*p*-value
PTCL subtype		0.83*		0.92*
PTCL NOS (n = 69)	14		29	
AITL (n = 27)	19		30	
ALK-1-neg ALCL (n = 21)	19		24	
Others (n = 13)	0		0	

PTCL NOS, PTCL not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ALK-1-neg-ALCL, ALK-1-negative anaplastic large-cell lymphoma

* Based on PTCL NOS, AITL and ALK-1-negative ALCL (n = 117)

- No meaningful differences were seen in ORR or CR/CRu rates based on sex, age, baseline disease characteristics, prior therapeutic regimen or number of prior therapies.

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

Progression-Free Survival (PFS)

Median PFS	IRC
Overall (n = 130)	4 months
Achieved CR/CRu (n = 19)	18 months
With PR (n = 14)	7 months
With SD (n = 33)	6 months
With PD or N/E (n = 64)	<2 months

- Patients who had achieved CR/CRu had substantially longer PFS than those in all other response categories.

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

Selected Drug-Related Adverse Events (AEs)

Event (n = 131)*	All grades	Grade ≥3
Nausea	54%	2%
Infections SOC†	18%	6%
Asthenia/fatigue	52%	5%
Thrombocytopenia	40%	23%
Vomiting	34%	4%
Diarrhea	23%	2%
Pyrexia	17%	4%
Neutropenia	29%	18%
Anemia	21%	5%

* Inclusive of 1 patient with a diagnosis of diffuse large B-cell lymphoma

† System organ class according to the Medical Dictionary for Regulatory Activities

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

Author Conclusions

- Romidepsin, as a single-agent, induced complete and durable responses in patients with relapsed or refractory PTCL.
- Romidepsin improved outcomes across all major PTCL subgroups, regardless of the number or type of prior therapies.
- These data demonstrated that romidepsin produced manageable toxicity in patients with relapsed or refractory PTCL.
- Based on the results from this Phase II study, romidepsin was approved by the US Food and Drug Administration for the treatment of patients with relapsed or refractory PTCL.

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

Investigator Commentary: Results from a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory PTCL

Romidepsin is one of 3 drugs that were approved for the treatment of T-cell lymphoma in the past 1 or 2 years. The original presentation of the investigators that led to the approval of romidepsin was based on 130 patients with relapsed or refractory PTCL. By IRC assessments, the ORR was 25% and 10% of the patients had CR.

However, the response rates presented in the abstracts at the recent ASH meeting were a lot higher than what was observed in the original presentation. This is because the meeting abstract presents a subset ORR analysis of the larger registration-directed study in the 3 most common PTCL subtypes (n = 117): PTCL NOS (29%), AITL (30%) and ALK-1-negative ALCL (24%). In the total patient population analysis (n = 130), the ORR is slightly lower. Overall, the data suggest that romidepsin may have more activity in the more common PTCL subtypes than what one may be led to believe by the larger data set of 130 patients.

Interview with Owen A O'Connor, MD, PhD, February 3, 2012

Final Results of Phase II Trial of Pegylated Liposomal Doxorubicin (PLD) Followed by Bexarotene (Bex) in Advanced Cutaneous T-Cell Lymphoma (CTCL)

Straus DJ et al.

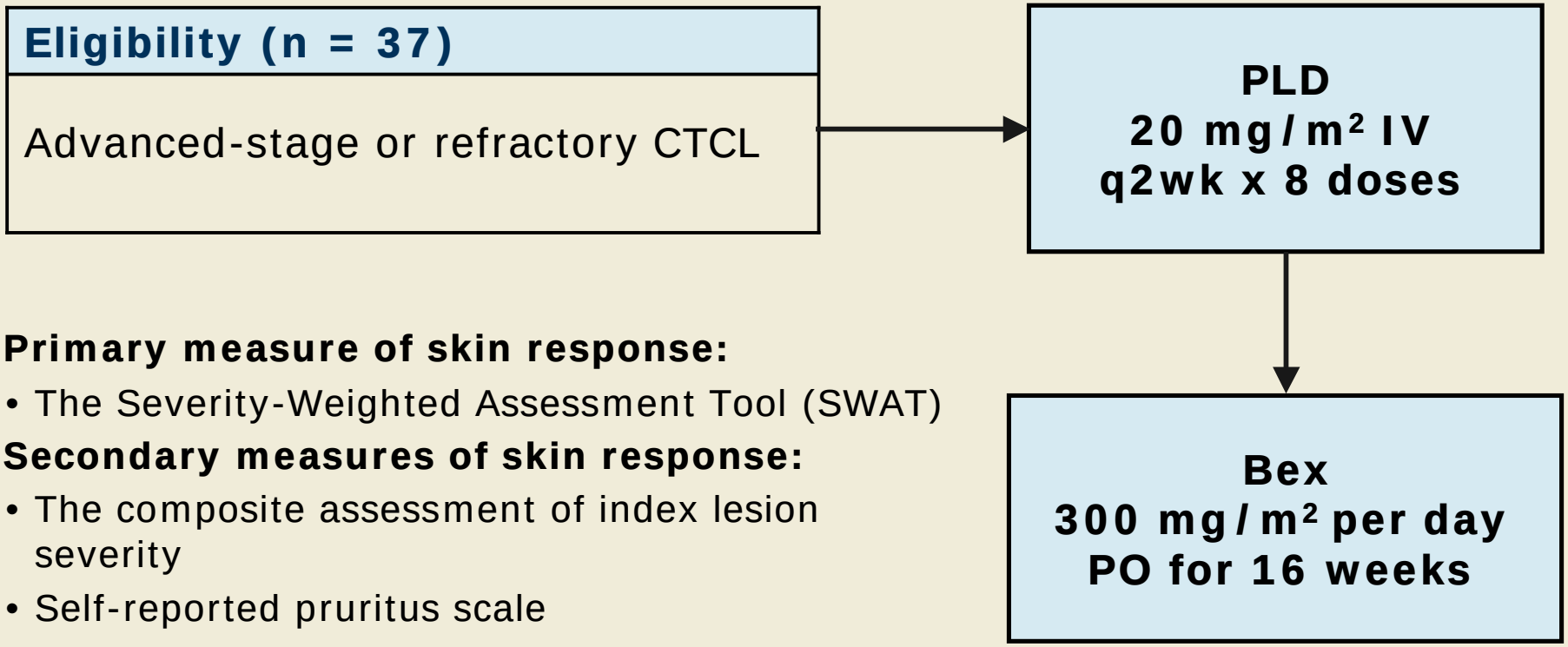
Proc ASH 2011;Abstract 882.

Background

- Pegylated liposomal doxorubicin (PLD) is approved for the treatment of Kaposi's sarcoma and concentrates highly in the skin.
- Previous studies have demonstrated the effectiveness of PLD in patients with advanced cutaneous T-cell lymphoma (CTCL) but without a strictly defined response criteria (*Arch Dermatol* 2008;144:727; *Cancer* 2003;98:993).
- Bexarotene (Bex) is a synthetic retinoid that has been reported to have an objective response rate (ORR) of about 50% in patients with relapsed or refractory CTCL (*JCO* 2001;19:2456; *Arch Dermatol* 2001;137:581).
- **Objective:**
  - Determine the true ORR for PLD and assess if the ORR and remission durations can be improved by sequential Bex following PLD in advanced or refractory CTCL.

Straus DJ et al. *Proc ASH* 2011;Abstract 882.

Trial Design



Primary measure of skin response:

- The Severity-Weighted Assessment Tool (SWAT)

Secondary measures of skin response:

- The composite assessment of index lesion severity
- Self-reported pruritus scale

Response assessments were performed after 8 weeks (PLD) and 16 weeks (Bex).

Straus DJ et al. *Proc ASH* 2011;Abstract 882.

Efficacy Results (Abstract Only)

Clinical parameter	n = 34
ORR*	41%
Clinical complete response (CCR)	6%
Partial response (PR)	35%
Median PFS	4.82 months

CCR: Complete disappearance of skin lesions on examination

* Maximum responses were all seen after 16 weeks of PLD.

Straus DJ et al. *Proc ASH* 2011;Abstract 882.

Adverse Events (AEs) and Deaths (Abstract Only)

Event, n	
Grade 3/4 serious AEs	9
Tumor pain	4
Grade 3 hand-foot syndrome	2
Infection — unknown ANC-skin (cellulitis)	1
Infection — normal ANC-skin (cellulitis)	1
Neutropenia	1
Deaths	19
Progressive disease	18
Congestive heart failure*	1

* Patient (n = 1) was pretreated for LVEF of 60%

Straus DJ et al. *Proc ASH* 2011;Abstract 882.

Author Conclusions

- With strict criteria, ORR for PLD is one of the highest reported for single agents in CTCL.
- However, the ORR for PLD determined in this study is lower than previously reported.
- The study population contained a high proportion of patients with advanced disease (data not shown) as reflected in the poor survival outcomes.
- Sequentially administering Bex did not increase the response rate or duration (data not shown).

Straus DJ et al. *Proc ASH* 2011;Abstract 882.

Investigator Commentary: Final Results of a Phase II Trial of PLD followed by Bex in Advanced CTCL

This study, of which I was a part, was designed to determine whether clinical responses can be induced with a relatively safe chemotherapy and then maintained with a milder agent like Bex. The results showed a reasonable response rate of about 40% with liposomal doxorubicin, although others in the literature report a rate of about 80%.

This study did not demonstrate a benefit in terms of durability of response with Bex, although we have seen a couple of patients who have had long-term remissions after follow-up with maintenance therapy. I believe the study was rationally designed but it inadvertently selected for a highly aggressive, somewhat atypical patient population. This is because a patient with mycosis fungoides suitable for chemotherapy but never having received Bex is unusual. Such a patient tends to start off with an early aggressive disease. This may explain why the durability of responses to Bex was so short.

Overall, these data demonstrate that PLD is an active drug but it is uncertain whether maintenance therapy with Bex improves response.

Interview with Steven M Horwitz, MD, March 9, 2012