5 Minute JournalClub

Key ASH Presentations

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CME Information

LEARNING OBJECTIVES

- Counsel younger patients with newly diagnosed mantle-cell lymphoma about the benefits and risks of aggressive induction therapy, including the contribution of high-dose Ara-C.
- Summarize the response rates and tolerability of salvage treatment with combination lenalidomide/dexamethasone in adult patients with relapsed or refractory MCL.
- Recall survival and toxicity results with R-CHOP followed by iodine-131 tositumomab consolidation as initial management of DLBCL.
- Recognize the rationale for avoidance of local radiation therapy in PMBCL, and summarize outcomes achieved with induction R-CHOP followed by ICE consolidation alone.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES
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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Alternating Courses of CHOP and DHAP Plus Rituximab (R) Followed by a High-Dose Cytarabine Regimen and ASCT is Superior to Six Courses of CHOP Plus R Followed by Myeloablative Radiochemotherapy and ASCT in Mantle Cell Lymphoma

Hermine O et al.

Proc ASH 2010;Abstract 110.

Background

- Although the outcomes of patients with MCL have improved over the last decades, the disease has been characterized by poor long-term prognosis.
- A Phase II trial of myeloablative consolidation followed by ASCT demonstrated significant prolonged progression-free survival in advanced stage MCL (*Blood* 2005;105:2677).
- Sequential R-CHOP/R-DHAP followed by ASCT demonstrated an overall response rate of 95% and a 75% survival rate at five years in a Phase II study of patients with MCL (*Proc ASH* 2008;Abstract 581).

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Study Schema

Accrual: 497 (Closed)

Eligibility

Untreated mantle-cell lymphoma (MCL)

Stage II to IV

Age ≤ 65 years

R

Control arm:
R-CHOP x 6 → myeloablative radiochemotherapy[1] and ASCT

Experimental arm:
Alternating CHOP x 3 and DHAP x 3 + R → high-dose ARA-C containing myeloablative radiochemotherapy[2] and ASCT

Primary endpoint: Time to treatment failure (TTF), monitored continuously.

[1] 12 Gray total body irradiation (TBI), cyclophosphamide 60 mg/kg x 2; [2] 10 Gray TBI, ARA-C 1.5 g/m^2 x 4, melphalan 140 mg/m^2

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Patient Characteristics

	Control arm	Experimental arm
Age, median	55 years	56 years
Male gender	78%	79%
Stage IV	85%	79%
B symptoms	43%	33%
ECOG >2	5%	5%
Elevated LDH	37%	38%
MIPI risk level (low/ intermediate/high)	61%/25%/14%	62%/23%/15%

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Efficacy Results (from Abstract)

	Control arm	Experimental arm	*p*-value
Time to treatment failure	49 months	Not reached	0.0384*
3-year overall survival	79%	80%	0.74

*Mainly due to a lower number of relapses in the experimental arm after complete or partial response (control arm, 20%; experimental arm, 10%) as the rate of ASCT-related deaths during remission was similar in both arms (control arm, 3%; experimental arm, 4%).

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Efficacy Results (from Abstract)

	Control arm	Experimental arm	*p*-value
Response following induction			
Overall response	90%	94%	0.19
Complete response (CR)	26%	39%	0.012
CR/unconfirmed CR	41%	60%	0.0003

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Efficacy Results (from Abstract)

	Control arm	Experimental arm	*p*-value
Patients transplanted	72%	73%	—
Response following transplant			
Overall response	97%	97%	Not reported
Complete response (CR)	63%	65%	Not reported
Remission duration (All patients)	48 months	Not reached	0.047
Remission duration (Patients achieving CR)	51 months	Not reached	0.077

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Grade 3 or 4 Adverse Events (from Abstract)

	Control arm	Experimental arm
Induction regimen		
Anemia	8%	28%
Leucopenia	48%	75%
Thrombocytopenia	9%	74%
Renal toxicity	0%	2%
Conditioning regimen		
Mucositis	43%	61%

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Author Conclusions

- The use of high-dose ARA-C in addition to R-CHOP and ASCT significantly increases complete response rates and TTF compared to standard therapy.
  - CR: 26% vs 39% (p = 0.012)
  - CR/CRu: 41% vs 60% (p = 0.0003)
  - TTF: 49 months vs not reached (p = 0.0384; HR, 0.68)
- High-dose ARA-C plus R-CHOP followed by ASCT does not cause clinically relevant increases in toxicity.
- Based on these data, the new standard regimen for patients up to 65 years of age with MCL should contain high-dose ARA-C followed by ASCT.

Hermine O et al. *Proc ASH* 2010;Abstract 110.

Investigator comment on alternating courses of 3x CHOP and 3x DHAP and rituximab followed by a high-dose Ara-C-containing myeloablative regimen as part of ASCT

Though the pretransplant OR rates are equal, the CR is significantly higher in the experimental arm with R-CHOP/R-DHAP induction. It is also interesting that even though both arms were equal in terms of OR and CR rates after transplantation, the time to treatment failure was improved in the arm with a high-dose Ara-C-containing myeloablative regimen. It tells us that all complete responses are not created equal.

I believe this trial provides additional information that a more aggressive therapy that includes high-dose Ara-C, in a younger patient, will get to the goal of a longer disease-free survival. Until we learn more about how to treat mantle-cell lymphoma with a curative intent, I believe this is an appropriate mode of approaching younger patients with MCL.

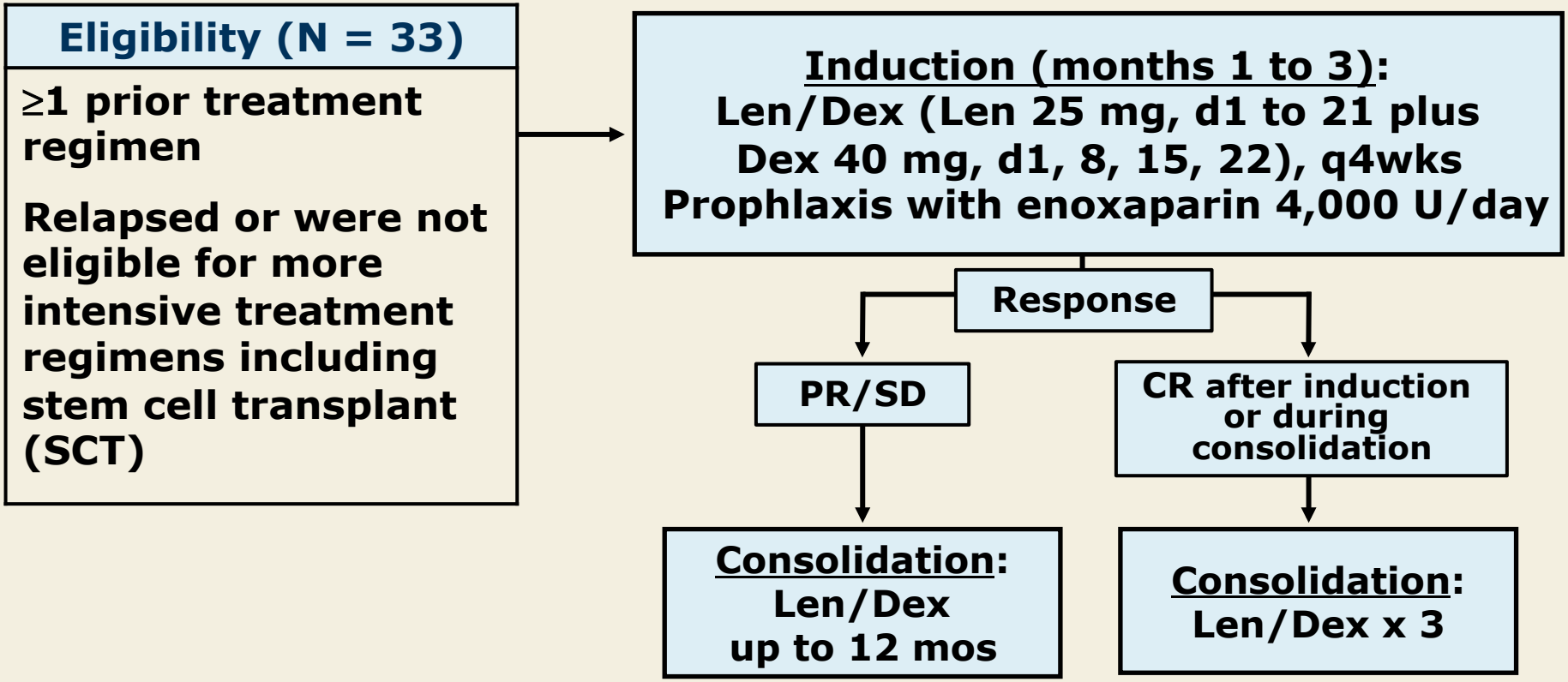
Interview with Lauren C Pinter-Brown, MD, January 7, 2011

Salvage Treatment with Lenalidomide and Dexamethasone in Patients with Relapsed Refractory Mantle Cell Lymphoma (MCL): Clinical Results and Modifications of Angiogenic Biomarkers

Zaja F et al.

Proc ASH 2010;Abstract 966.

Phase II Study Schema



The objectives were to evaluate the safety and efficacy (overall response and complete response rates) of combination lenalidomide/dexamethasone (Len/Dex) in adult patients with MCL

Zaja F et al. *Proc ASH* 2010;Abstract 966.

Patient Characteristics

	Len/Dex N = 33
Age, median	68 years (range 51-80)
Histology	
Classic	30
Blastoid	3
Prior treatments, median	3 (1-7)
Autologous SCT	12
Prior therapy with bortezomib	8

Zaja F et al. *Proc ASH* 2010;Abstract 966.

Efficacy Results

Response following induction	Len/Dex N = 33
Overall response (OR)*	67%
Stable disease	3%
Complete response	15%
No response or progressive disease	30%

* 50% OR in patients previously treated with autologous SCT or bortezomib

Zaja F et al. *Proc ASH* 2010;Abstract 966.

Efficacy Results

Final response status	Len/Dex N = 33
Overall response	52%
Complete response	24%
No response or progressive disease	45%
Median duration of response*	18 months
Survival	
Median overall survival	20 months
Median progression-free survival	12 months

After a median follow-up of 6 months from the end of therapy, none of the patients with CRs had subsequent progression whereas 2 patients with partial response had progression 7 to 10 months after therapy was completed.
* Median follow-up = 30 months

Zaja F et al. *Proc ASH* 2010;Abstract 966.

Efficacy Results

- Angiogenic plasma biomarkers (ie, bFGF, VEGF, HGF) showed a trend to decrease after the first 3 months of therapy.
- Macrophage counts significantly increased after the first 3 months of therapy, in parallel with significant increases in microvessel counts.
  - Bone marrow counts ($P<0.01$)
  - Microvessel counts ($P<0.05$)
  - Both counts were always significantly correlated ($P<0.001$)

Zaja F et al. *Proc ASH* 2010;Abstract 966.

Grade 3/4 Adverse Events

	Len/Dex N = 33
Neutropenia	52%
Thrombocytopenia	18%
Neutropenic fever	12%
Bacterial pneumonia	9%
Dyspnea	9%
Anemia	6%
Hypotension	3%

Zaja F et al. *Proc ASH* 2010;Abstract 966.

Author Conclusions

- These data confirm the efficacy of Len/Dex in patients with relapsed or refractory MCL.
  - Final OR, 52%; CR, 24% (6-month follow-up)
- The safety profile of the Len/Dex combination was favorable.
- The significant infiltration of macrophages into the bone marrow may be due to an immunomodulatory effect of lenalidomide.
- The increased microvessel counts may be induced by activated macrophages, although angiogenic plasma biomarker concentrations suggest only a limited effect of lenalidomide on neovascularization.

Zaja F et al. *Proc ASH* 2010;Abstract 966.

Investigator comment on lenalidomide/dexamethasone for relapsed or refractory mantle-cell lymphoma

Lenalidomide is interesting in mantle-cell lymphoma and has been associated with response rates of approximately 50 percent among patients with relapsed or refractory disease. The current study sought to improve on that by adding dexamethasone to the lenalidomide in a relatively small number of patients. An overall response rate of 67 percent was observed after induction, with 15 percent being complete remissions. Many of these responses also appear to be durable. Whether the addition of dexamethasone adds to the efficacy of lenalidomide would require a randomized trial.

Interview with Bruce D Cheson, MD, December 23, 2010

R-CHOP with Iodine-131 Tositumomab Consolidation for Advanced Stage Diffuse Large B-Cell Lymphoma (DLBCL): Southwest Oncology Group Protocol S0433

Friedberg JW et al.

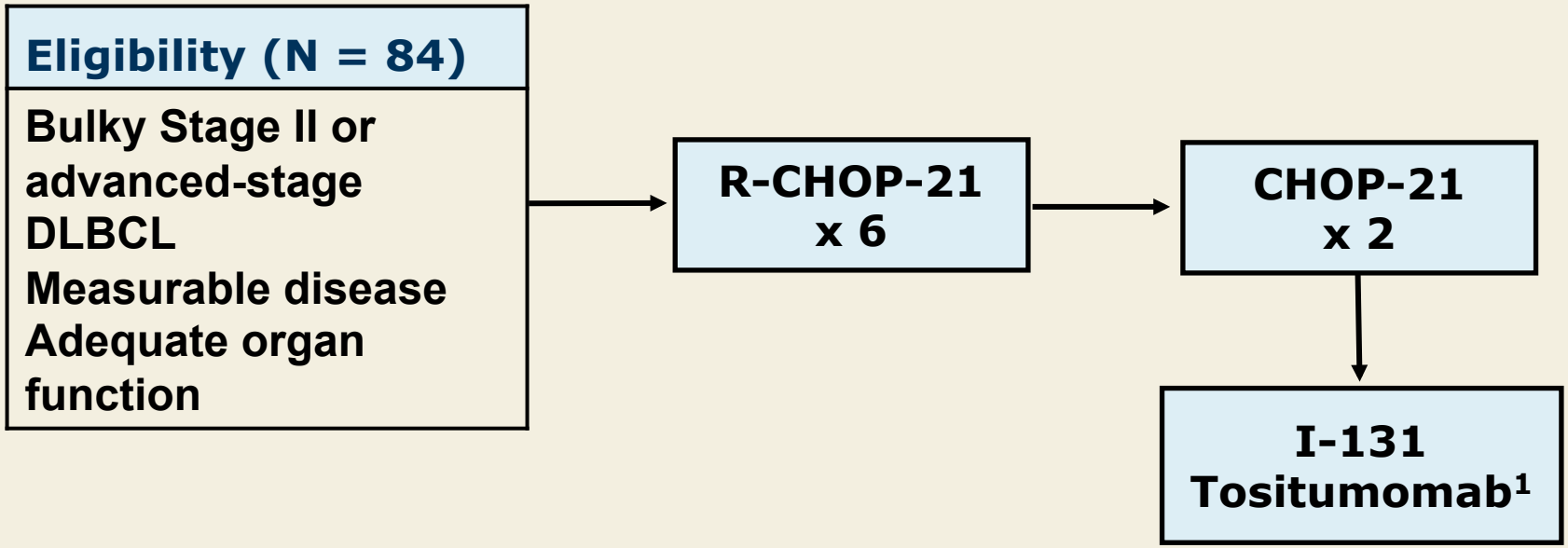
Proc ASH 2010;Abstract 590.

Background

- A substantial proportion of patients with advanced DLBCL and other clinical risk factors are not cured by R-CHOP chemotherapy.
- Therapeutic options with low toxicity are needed for the majority of DLBCL patients who are over age 60.
- Radioimmunotherapy (RIT) is a low toxicity treatment option that has been shown to
  - Have activity in relapsed DLBCL (*Blood* 2007;110:54)
  - Improve progression-free survival when used as consolidation therapy in advanced follicular lymphoma (*JCO* 2008;26:5156)

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

S0433: Phase II Trial of Consolidative RIT in DLBCL



[1] I-131 tositumomab 65 cGy was administered if platelet count between 100,000 and 150,000/mm^3 or 75 cGy if normal platelet count. I-131 tositumomab was administered 30 to 60 days after last dose of CHOP.

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

Patient Characteristics

Characteristic	N = 86
Median Age, Years (Range)	64 (29-85)
International Prognostic Index	
Low Risk	24%
Low-Intermediate Risk	32%
High-Intermediate Risk	32%
High Risk	12%

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

I-131 Tositumomab Administration

- Twenty-three patients (27%) did not receive I-131 tositumomab:
  - Early progression: 3 patients
  - Adverse event or death: 9 patients
  - Refusal: 6 patients
  - Other reasons: 5 patients
- Patients who did not receive I-131 tositumomab were more likely to have high-intermediate/high IPI-risk disease compared to those who received therapy.
  - 60% versus 35% (p = 0.004)

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

Efficacy Outcomes (Median Follow-Up 1.2 Years)

Outcome	N = 84
One-Year Overall Survival Estimate (95% CI)	85% (77-93%)
One-Year Progression-Free Survival Estimate (95% CI)	75% (65-85%)

Prior experience from population-based registry used to estimate survival rates for patient population of this study based on IPI score distribution:

- Estimated, adjusted one-year overall survival rate: 86%
- Estimated, adjusted one-year progression-free survival rate: 80%

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

Common Serious Adverse Events (N = 84)

Adverse Event	Grade 3	Grade 4
Hematologic	19%	54%
Infection	15%	1%
Flu-like symptoms	12%	1%
Neuropathy	11%	—

- Five treatment-related Grade 5 adverse events occurred:
  - Cardiac ischemia = 2
  - Acute myelogenous leukemia = 1
  - Renal failure = 1
  - Febrile neutropenia = 1

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

Author Conclusions

- A consolidation strategy utilizing iodine-131 tositumomab after 8 cycles of CHOP chemotherapy (6 with rituximab) for advanced-stage DLBCL does not appear to be promising.
  - Early progressions, deaths and declining performance status during CHOP chemotherapy limit the number of patients who ultimately can benefit from a planned consolidation approach
  - Relapse events occurred in the group who received consolidation despite more favorable prognostic features
- Incorporation of novel agents earlier in therapy may have more impact in DLBCL than consolidation or maintenance approaches.

Friedberg JW et al. *Proc ASH* 2010;Abstract 590.

Investigator Comment on R-CHOP with Iodine-131 Tositumomab Consolidation for Advanced-Stage Diffuse Large B-Cell Lymphoma (DLBCL)

The results from this Phase II study from SWOG are in contrast to a study at Memorial Sloan-Kettering, where we administered R-CHOP followed by yttrium-90 ibritumomab and showed excellent results in a similar patient population.

The issue I see with this presentation is that the data are only analyzed for the intent-to-treat (ITT) population. A number of patients experienced disease progression prior to receiving radioimmunotherapy, and if the data were analyzed by therapy received — meaning in patients who received R-CHOP followed by I-131 tositumomab consolidation — I suspect the results would have appeared much better. We suggested this to the presenter, and I suspect they will review the data and analyze them based upon therapy received, in addition to the ITT population.

Interview with Craig Moskowitz, MD, January 3, 2011

Sequential Dose-Dense R-CHOP Followed by ICE Consolidation (MSKCC Protocol 01-142) without Radiotherapy for Patients with Primary Mediastinal Large B Cell Lymphoma

Moskowitz C et al.

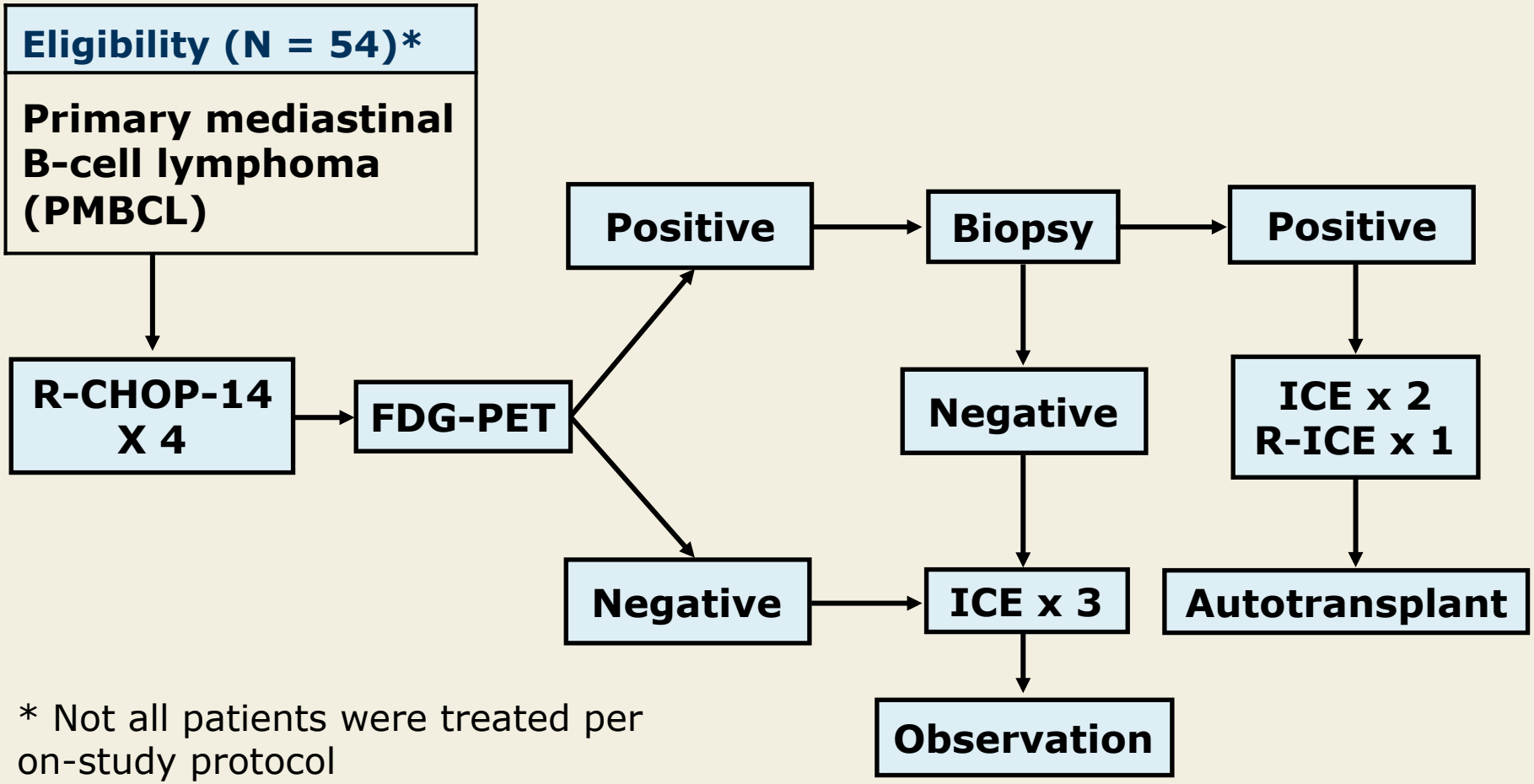
Proc ASH 2010;Abstract 420.

Background

- Primary mediastinal large B cell lymphoma (PMBCL) is a distinct subtype of diffuse large B cell lymphoma (DLBCL) that is more closely related to Hodgkin lymphoma.
  - More common in women
  - Median age ~ 30 years
  - Represents a high percentage of aggressive lymphomas in patients under 40 years of age
  - Bulky mediastinal disease is common
- Combined chemotherapy and radiation therapy have been the mainstay of treatment.
- Radiation therapy is associated with a risk of secondary breast cancer and coronary artery disease.
- Protocols that do not use radiation therapy are therefore desirable, provided they maintain efficacy outcomes.

Moskowitz C et al. *Proc ASH* 2010;Abstract 420.

MSKCC 01-142 Study Schema: Primary Mediastinal B-Cell Lymphoma Subgroup



* Not all patients were treated per on-study protocol

Moskowitz C et al. *Proc ASH* 2010;Abstract 420.
Moskowitz C et al. *J Clin Oncol* 2010;28:1896-903.

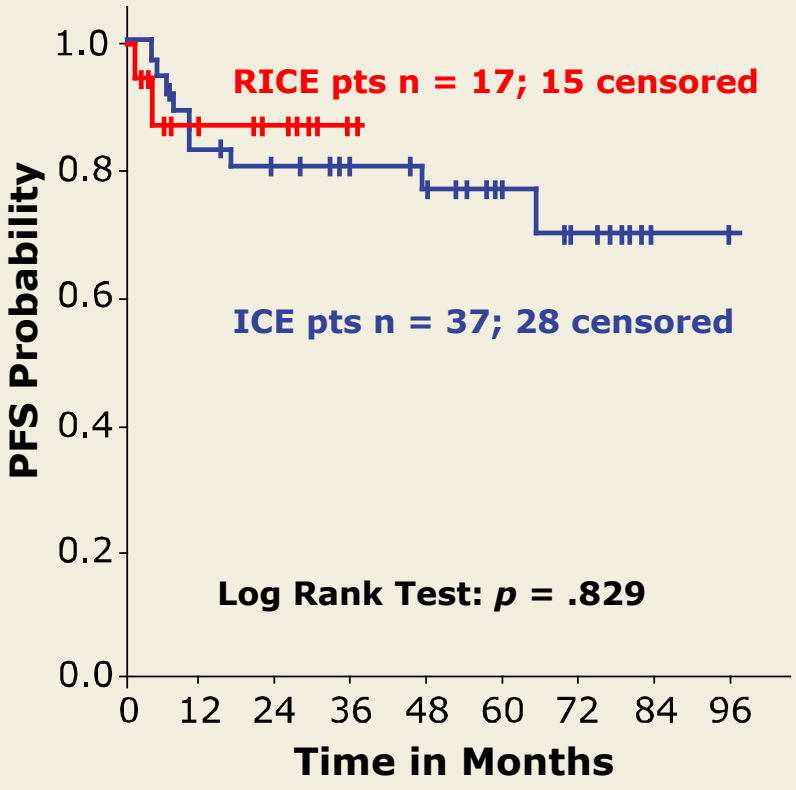
Patient Characteristics

Characteristic	N = 54
Median Age	33
Female	56%
Elevated LDH	87%
Karnofsky Performance Status < 80%	24%
Stage IV Disease	57%
Extranodal Disease	74%
Bulky Mediastinal Disease ≥ 10cm	67%

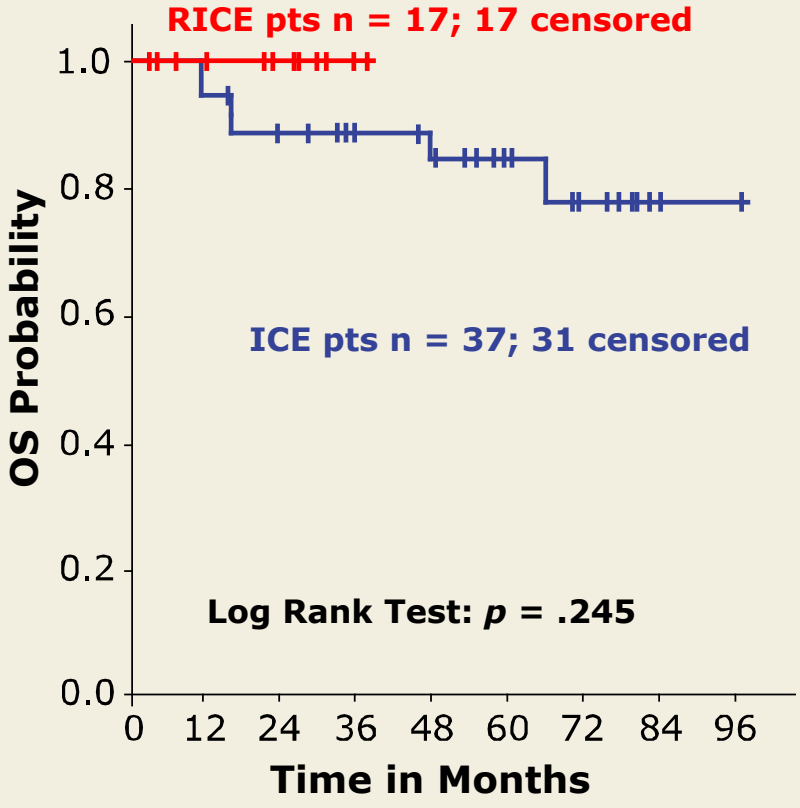
Moskowitz C et al. *Proc ASH* 2010;Abstract 420.

Survival: RICE versus ICE Consolidation

Progression Free Survival: RICE vs ICE



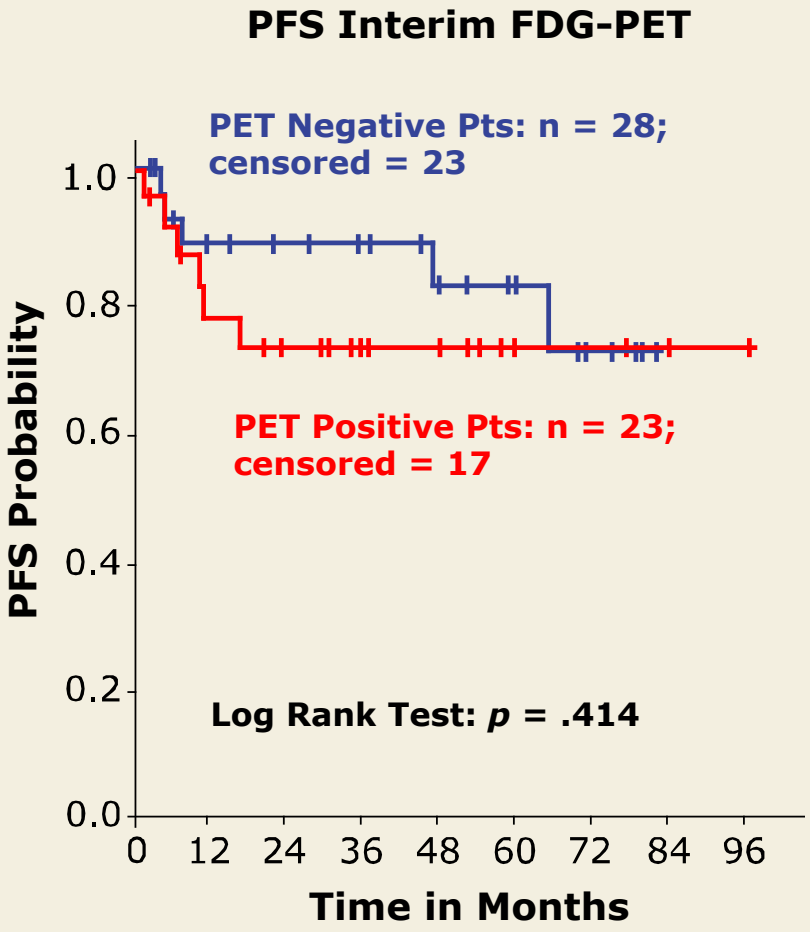
Overall Survival: RICE vs ICE



With permission from Moskowitz C et al. *Proc ASH* 2010;Abstract 420.

Interim FDG-PET

- 51/54 patients had an FDG-PET interim scan
- 23 patients had a +FDG-PET (SUV > 3.0)
  - All + scans had uptake > mediastinal blood pool
- 14 patients had a biopsy due to +FDG-PET
  - 11/14 had a negative biopsy
- Change in SUV between initial and interim scan (cutoff of >66% as being favorable) also did not predict outcome (p = 0.216)



With permission from Moskowitz C et al. *Proc ASH* 2010;Abstract 420.

Outcome of Patients with Events

- Eleven patients had an event after treatment
  - One patient died from AML (6 years post-treatment)
  - One patient was lost to follow-up — died of unknown causes (4 years post-treatment)
  - Nine patients have relapsed
    - Six patients received HDT/ASCT
      - Five patients are progression free after salvage therapy and autotransplant, which included pretransplant radiation to the mediastinum
      - One patient did not respond to ASCT and died of disease progression
    - Three patients died from PMBCL secondary to primary refractory disease

Moskowitz C et al. *Proc ASH* 2010;Abstract 420.

Author Conclusions

- The MSKCC dose-dense R-CHOP/ICE program is highly effective in PMBCL.
- Importantly, 50% of patients with progression can be salvaged with a radiation-based transplant.
- Based on these results, an interim FDG-PET scan is not warranted as it provides no useful information in this subset of patients with DLBCL.

Moskowitz C et al. *Proc ASH* 2010;Abstract 420.

Investigator Comment on Sequential Dose-Dense R-CHOP Followed by ICE Consolidation without Radiation Therapy for Patients with Primary Mediastinal Large B-Cell Lymphoma

This is a follow-up to the study that we published in the *JCO,* in which we treated advanced-stage diffuse large B-cell lymphoma in 98 patients and had an overall survival rate of 79 percent at a median of 44 months follow-up. This presentation is from patients with primary mediastinal large B-cell lymphoma (PMBCL) and is the largest study reported in this entity without consolidative radiation therapy.

Currently, most patients with PMBCL treated in the community receive R-CHOP followed by radiation therapy. Most physicians would prefer not to administer mediastinal radiation therapy, particularly to a young woman. This study shows that radiation therapy is not necessary and it could be reserved for patients who experience relapse. Treated this way, without initial consolidative radiation therapy, the issues of secondary breast cancer and long-term coronary artery disease could be prevented.

Interview with Craig Moskowitz, MD, January 3, 2011