5 Minute JournalClub

POST-ASH Issue 3, 2014

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CME Information

LEARNING OBJECTIVES

- Compare the efficacy of consolidation therapy with a single dose of ^{90}Y-ibritumomab tiuxetan to that of rituximab maintenance for patients with newly diagnosed follicular lymphoma (FL).
- Examine the utility of early disease progression within 2 years of R-CHOP therapy as a way to identify a subset of patients with FL who are at high risk of death.
- Assess the efficacy and safety of short-term versus long-term rituximab maintenance in FL.
- Evaluate the benefits and risks of brentuximab vedotin for newly diagnosed cutaneous T-cell lymphoma or relapsed or refractory B-cell lymphomas and the effect of CD30 expression on response to this agent.
- Appraise recent clinical findings on the use of front-line lenalidomide with rituximab in mantle-cell lymphoma and of single-agent crizotinib in advanced, chemoresistant ALK-positive non-Hodgkin lymphoma.

CME Information (Continued)

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FACULTY DISCLOSURES
The following faculty (and his spouse/partner) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

CME Information (Continued)

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5 MinuteJournalClub

POST-ASH Issue 3, 2014

Andrew M Evens, DO, MSc

The rapid integration of novel systemic agents into the management of B- and T-cell lymphomas has the rapt attention of all medical oncologists who see these patients in their practices every day. In the *next* issue of this series we focus on chronic lymphocytic leukemia (CLL), as Dr Brad Kahl reviews the newly approved type II anti-CD20 monoclonal antibody obinutuzumab and 3 new and exciting small molecules, the Bruton tyrosine kinase inhibitor ibrutinib (now FDA endorsed for mantle-cell lymphoma [MCL] and CLL), the PI3 kinase delta inhibitor idelalisib and ABT-199, an anti-BCL2 pro-apoptotic agent.

Similarly, a future edition of the series will delve into ASH papers on Hodgkin lymphoma, where brentuximab vedotin (BV) continues to shake up traditional paradigms. But for this program we turned our full attention to non-Hodgkin lymphoma (NHL) and asked Dr Andrew Evens, principal investigator of one of the few ongoing major randomized US Cooperative Group NHL trials — ECOG-E2408, a 3-arm Phase II study evaluating bendamustine and rituximab (R) with or without bortezomib followed by R with or without lenalidomide — to provide his perspectives on a number of ASH data sets and what these mean to current practice and future research.

R^2 (rituximab/lenalidomide) up front in MCL

As has been observed in follicular lymphoma (FL), useful objective responses to this well-tolerated nonchemotherapy regimen are common, and perhaps not surprisingly, in **this Phase II study** 87% of patients with treatment-naïve MCL derived benefit from therapy. A major Phase III trial (RELEVANCE) compares R^2 to R-chemotherapy followed by R in previously untreated FL, and a number of studies, including Dr Evens', are evaluating the equally interesting concept of R^2 maintenance. However, the sudden and very welcome appearance of ibrutinib in MCL and the obvious logic of evaluating it up front has complicated current discussions regarding new trial designs. While R^2 involves 2 approved agents and is tempting to consider for older patients and those for whom chemotherapy may be problematic, most investigators, including Dr Evens, are currently conservative about attempting to use the regimen up front in patients with lymphoma, although it is a consideration with refractory disease.

Crizotinib in ALK-positive lymphomas, mainly anaplastic large cell lymphoma (ALCL)

ALK expression is present in more than 50% of patients with ALCL, and an intriguing 2011 *New England Journal* report revealed the impressive short-term therapeutic activity of crizotinib in 2 individuals with ALK-positive lymphoma. At ASH 2013 we saw **a small but stunning new series** in which all 9 patients with ALK-positive, refractory ALCL experienced complete responses (CRs) on crizotinib. In addition, 1 partial response was observed among 2 patients with ALK-positive diffuse large B-cell lymphoma (DLBCL) treated with the drug. This

important development has Dr Evens and others scratching their heads about how to integrate crizotinib into current lymphoma practice and where it will fit in with the other fairly new kid on the block, BV, as part of new research initiatives.

Maintenance treatment for FL

A fascinating report from the Swiss group comparing R monotherapy followed by short-course (4 doses) or extended (5 years) R maintenance revealed that although the primary endpoint of event-free survival was not statistically different, an impressive prolongation of progression-free survival (PFS) was observed with longer treatment (3.5 years for patients on short maintenance versus 7.4 years with the long-term approach). These intriguing findings seem out of place given that the previously reported results of the ECOG RESORT trial were somewhat unimpressive, and because of this Dr Evens' personal standard for low-risk disease remains watchful waiting or at most 4 weeks of R with no maintenance. At ASH we also saw more follow-up from the classic PRIMA trial evaluating 2 years of R maintenance after R-chemotherapy in indolent lymphoma, and the 73-month follow-up continues to demonstrate a significant delay in disease progression.

A somewhat surprising Phase II report compared radioimmunotherapy (RIT) consolidation with ^{90}Y-ibritumomab tiuxetan to 2 years of R maintenance in patients with newly diagnosed FL responding to R-CHOP. At 3 years, a clear PFS advantage (77% versus 63%; $p = 0.044$) in favor of R maintenance was observed. Based in part on these data, Dr Evens believes that 2 years of R maintenance remains the standard, but he will still consider RIT consolidation in

highly select situations in which a patient's life plans don't meld well with regular infusions.

Finally, **another report** from the now well-publicized National LymphoCare Study in FL provides some solid evidence to back up the collective impression that the approximately 20% of patients who experience relapse in the first 2 years after R-chemotherapy have a poor prognosis. In this analysis of 122 such patients who received R-CHOP up front with a median follow-up of 7 years, the 5-year overall survival rate was approximately 50%. When this is compared to the almost 100% survival rate for those who did not relapse within 2 years, it seems clear that these individuals should be considered for clinical trials designed to find ways to reverse the rapid downhill trajectory in this situation.

BV in cutaneous lymphomas and NHL

Two fascinating papers at ASH reported on Phase II studies evaluating this always-exciting antibody-drug conjugate in several unique lymphoma subsets. **In cutaneous disease** (primarily mycosis fungoides) 34 of 48 patients obtained objective responses (71%), of which half (35%) were CRs, and in **the NHL study** 21 of 50 patients with DLBCL (42%) responded, including 16% CRs. What was intriguing and a bit confusing was that activity was observed across a broad range of CD30 expression, including in patients with low or undetectable CD30 expression by standard immunohistochemical staining. Dr Evens believes that while it is possible that BV has off-target antitumor effects, the more likely explanation is that current assays for CD30 are not detecting lower but clinically

significant levels of antigen. While this is sorted out, oncologists in practice must consider that useful clinical responses have been seen with BV in patients with a variety of heavily pretreated lymphomas and that perhaps referral for trial participation should be explored for interested individuals regardless of CD30 positivity.

As stated previously, next we check in with Dr Brad Kahl about perhaps the most exciting area of new drug development in oncology — chronic lymphocytic leukemia.

Neil Love, MD
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Combination Biologic Therapy without Chemotherapy as Initial Treatment for Mantle Cell Lymphoma: Multi-Center Phase II Study of Lenalidomide plus Rituximab

Ruan J et al.

Proc ASH 2013;Abstract 247.

Background

- Initial treatment for mantle-cell lymphoma (MCL) is not standardized.
- Current conventional up-front chemoimmunotherapies are generally not curative and can be deferred in some patients (*J Clin Oncol* 2009;27:1209).
- Lenalidomide, an immunomodulatory agent that targets both the tumor cells and the tumor microenvironment, has shown clinical efficacy alone or in combination with rituximab in relapsed MCL.
  - Single-agent lenalidomide: overall response rate 28%, complete remission 7.5% (*J Clin Oncol* 2013;31:3688)
  - Lenalidomide with rituximab: overall response rate 57%, complete remission 36% (*Lancet Oncol* 2012;13:716)
- **Study objective:** To evaluate the efficacy and safety of lenalidomide with rituximab as initial therapy for MCL.

Ruan J et al. *Proc ASH* 2013;Abstract 247.

Phase II Study Eligibility and Endpoints

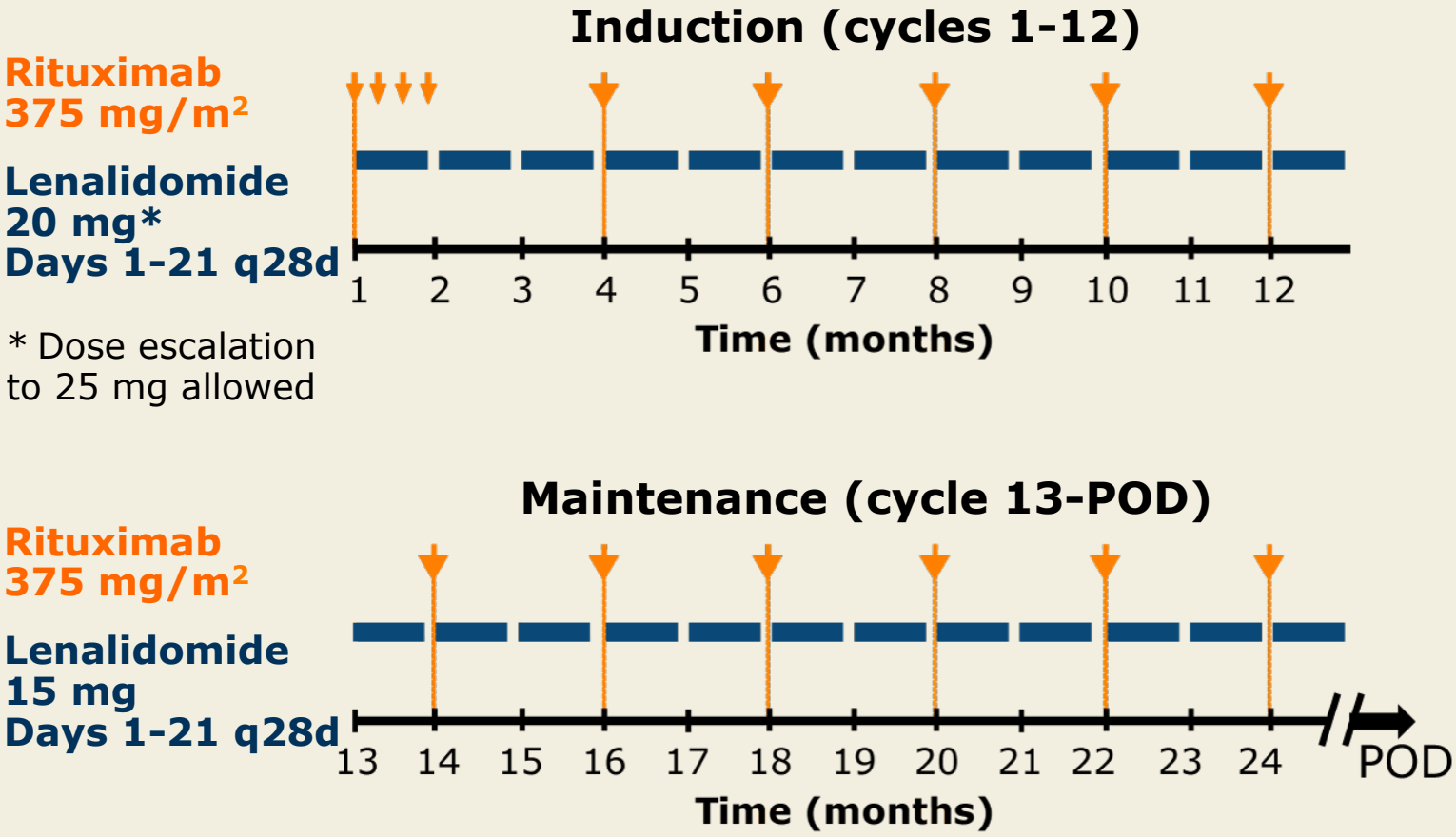
Eligibility (n = 32)
Untreated MCL
Low-intermediate-risk MIPI
High-risk MIPI if patients refused or were ineligible for chemotherapy
Tumor mass ≥1.5 cm

Primary endpoint: Overall response rate

Secondary endpoints: Progression-free survival (PFS), overall survival, safety, quality of life assessment

Ruan J et al. *Proc ASH* 2013;Abstract 247.

Phase II Study Design



POD = progression of disease

Aspirin administered for deep vein thrombosis (DVT) prophylaxis

Ruan J et al. *Proc ASH* 2013;Abstract 247.

Overall Response Rate

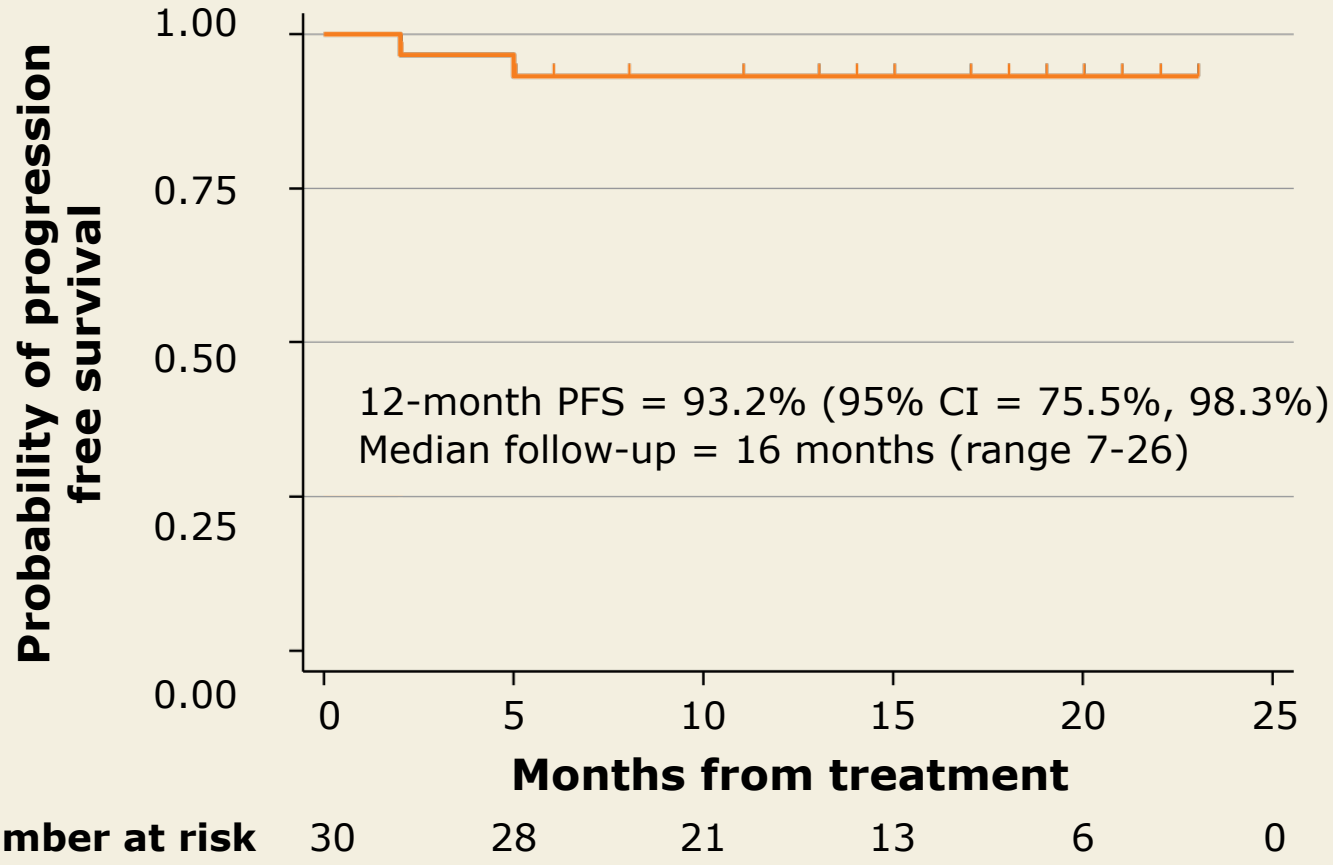
Response	ITT (n = 32)	Evaluable (n = 30)*
Overall response rate	81%	87%
Complete remission	53%	57%
Partial remission	28%	30%
Stable disease	6%	7%
Progressive disease	6%	7%

* Treatment discontinued in 2 patients due to tumor flare without disease progression before response evaluation

- Median follow-up = 16 mo
- Median time to partial remission = 3 mo
- Median time to complete remission = 11 mo

Ruan J et al. *Proc ASH* 2013;Abstract 247.

Progression-Free Survival



Overall survival: All subjects remain alive at last follow-up

With permission from Ruan J et al. *Proc ASH* 2013;Abstract 247.

Select Adverse Events

Event (n = 32)	Any grade	Grade ≥3
Hematologic		
Neutropenia	75%	47%
Anemia	50%	6%
Thrombocytopenia	34%	16%
Nonhematologic		
Fatigue	78%	9%
Rash	59%	22%
Tumor flare	34%	9%
Infusion reactions	41%	6%
Pneumonia	9%	3%
DVT/pulmonary embolism	6%	3%

No cases of febrile neutropenia or second malignancy were reported.

Ruan J et al. *Proc ASH* 2013;Abstract 247.

Author Conclusions

- The combination of lenalidomide and rituximab appears to be safe and active as initial therapy for MCL.
- At a median follow-up of 16 months, the overall response rate was 87% with 57% complete remissions in evaluable patients.
  - Response quality appears to improve over time on therapy.
- The 12-month progression-free survival was 93.2% and overall survival was 100%.
- A high proportion of patients with MCL could achieve an objective response with significant durability using a chemotherapy-free approach as initial therapy.
- These findings justify further evaluation of the lenalidomide/rituximab regimen both alone and in combination with other novel agents in MCL therapy both in the up-front and relapsed settings.

Ruan J et al. *Proc ASH* 2013;Abstract 247.

Investigator Commentary: Phase II Study of Lenalidomide and Rituximab as Initial Treatment for MCL

This study produced high response rates with lenalidomide/rituximab for previously untreated MCL. The results are not surprising because lenalidomide has shown promising activity in MCL and was recently approved in the relapsed/refractory setting. In this trial, it was administered at a dose of 20 mg during induction and 15 mg during the maintenance phase. It will be important to determine whether the responses are durable.

Response rates with the lenalidomide/rituximab combination may not be as high as those with rituximab/chemotherapy. Most of the patients in the study were at low to intermediate risk, and for those patients it may not be necessary to consider chemotherapy up front.

This study was performed before ibrutinib, which is a game changer in MCL and the most active nonchemotherapeutic agent. It has remarkable activity in relapsed/recurrent MCL and was recently approved in that setting. We will have to wait for the studies of ibrutinib in the front-line setting.

Interview with Andrew M Evens, DO, MSc, February 12, 2014

High Response Rates to Crizotinib in Advanced, Chemoresistant ALK+ Lymphoma Patients[1]

Crizotinib in Advanced, Chemoresistant Anaplastic Lymphoma Kinase-Positive Lymphoma Patients[2]

[1]**Redaelli S et al.**

Proc ASH 2013;Abstract 368.

[2]**Gambacorti Passerini C et al.**

J Natl Cancer Inst 2014;106(2):djt378.

Background

- Anaplastic large cell lymphomas (ALCL) represent an aggressive group of lymphomas with a tendency to invade known nodal sites, such as mucosa and skin.
- Anaplastic lymphoma kinase (ALK) expression is present in more than 50% of patients with ALCL.
- Patients with ALK-positive ALCL respond well to cytotoxic treatment, but relapses are possible and typically bear a poor prognosis (*Crit Rev Oncol Hematol* 2012;83:293).
- Crizotinib is an orally bioavailable small-molecule ALK and c-MET inhibitor active in ALK-positive lung cancer (*N Engl J Med* 2010;363:1693).
- Impressive short-term therapeutic activity has been reported in 2 patients with ALK-positive lymphoma (*N Engl J Med* 2011;364:775), but no long-term data are available.
- **Study objective:** To report the long-term follow-up results for patients with advanced, resistant, ALK-positive lymphomas treated with crizotinib.

Gambacorti Passerini C et al. *J Natl Cancer Inst* 2014;106(2):djt378.

Study Methods

- Patients were diagnosed with ALK-positive non-Hodgkin lymphoma by IHC and FISH using an ALK break-apart probe (n = 11).
  - ALCL histology (n = 9)
  - Diffuse large B-cell lymphoma histology (n = 2)
- Patients had relapsed/refractory disease after at least 1 prior chemotherapy regimen (typically CHOP) and measurable disease.
  - Resistant to 1 to 4 lines of treatment (median = 3), including:
    - Autologous bone marrow transplant (BMT) (n = 3)
    - Allogeneic BMT (n = 2)
- Patients received 250 mg of crizotinib twice daily as monotherapy until disease progression.
- Response to therapy was assessed according to the RECIST criteria.

Gambacorti Passerini C et al. *J Natl Cancer Inst* 2014;106(2):djt378.

Response Rate

n (%)	n = 11
Overall response rate	10 (90.9%)
Complete response (CR)	9 (81.8%)*
Partial remission	1 (9.1%)†

* All 9 patients were diagnosed with ALCL; † This patient was diagnosed with diffuse large B-cell lymphoma.

- Median follow-up for all patients = 8 months (range 1–40)
- Median follow-up for patients still on crizotinib = 32.5 months (range 21–40)

Gambacorti Passerini C et al. *J Natl Cancer Inst* 2014;106(2):djt378.

Disease Status as of Last Follow-Up (October 2013)

- Patients in CR under continuous crizotinib administration (n = 4):
  - At months >21, >30, >35, >40
- Patients experiencing disease progression (n = 4):
  - At months 1, 2, 2, 2
- Patients who obtained CR on crizotinib received an allogeneic BMT and remain in CR (n = 1).
- Two patients (treated before and/or after allogeneic BMT) obtained and are still in CR but have stopped crizotinib.

Gambacorti Passerini C et al. *J Natl Cancer Inst* 2014;106(2):djt378.

Survival

	n = 11
2-year overall survival	72.7%
2-year progression-free survival	63.7%

Gambacorti Passerini C et al. *J Natl Cancer Inst* 2014;106(2):djt378.

Grade 1/2 Adverse Events

	n = 11
Ocular flashes	91%
Peripheral edema	27%
Skin rash	9%
Erectile dysfunction	9%
Neutropenia	18%
Thrombocytosis	9%
Liver function test elevation	9%

- All toxicities were of Grade 1 or 2.
- Crizotinib-related toxicities observed were mild.
- No patient died from a cause related to treatment.
- No treatment-related event led to treatment discontinuation.

Gambacorti Passerini C et al. *J Natl Cancer Inst* 2014;106(2):djt378.

Author Conclusions

- These positive results extend our initial observation on 2 patients and provide long-term follow-up data (*New Engl J Med* 2011;364:775).
- Crizotinib was well tolerated, with objective responses observed within 30 days after starting treatment in 10 of 11 patients.
  - Nine patients obtained CR.
- These data indicate that patients with heavily pretreated ALK-positive lymphoma have a high chance of responding to crizotinib.
  - Approximately half of the patients on the study did not experience relapse within the first months and attained long-lasting responses.
  - However, no available pretreatment parameter is able to predict durable CRs.
- These data will be useful for the management of this aggressive disease.

Gambacorti Passerini C et al. *J Natl Cancer Inst* 2014;106(2):djt378.

Investigator Commentary: Crizotinib in Advanced, Chemoresistant ALK-Positive Lymphomas

The authors of this study reported impressive activity with crizotinib in ALK-positive lymphomas. Most of the patients had ALCL, but 2 had diffuse large B-cell lymphoma. The overall response rate was approximately 90% (10 of 11 responders), and the complete response rate was approximately 82%.

If these data held true, that would mean crizotinib would be even more active than brentuximab vedotin (B-vedotin) for CD30-positive lymphomas. I emailed the author, Dr Gambacorti-Passerini, to ask him whether any of the patients on this study had received prior B-vedotin, and he replied that none of the patients in this study had.

But he and his colleagues are now running a trial in which at least 2 patients with ALCL for whom B-vedotin has failed are responding to crizotinib. B-vedotin had its "foot in the door" first, so it will be difficult to replace, but these data are exciting and make you wonder whether crizotinib could replace B-vedotin. It also raises the question of whether the combination of these agents could bear fruit in this setting.

Interview with Andrew M Evens, DO, MSc, February 12, 2014

Rituximab Maintenance Treatment for a Maximum of 5 Years in Follicular Lymphoma: Results of the Randomized Phase III Trial SAKK 35/03

Taverna C et al.

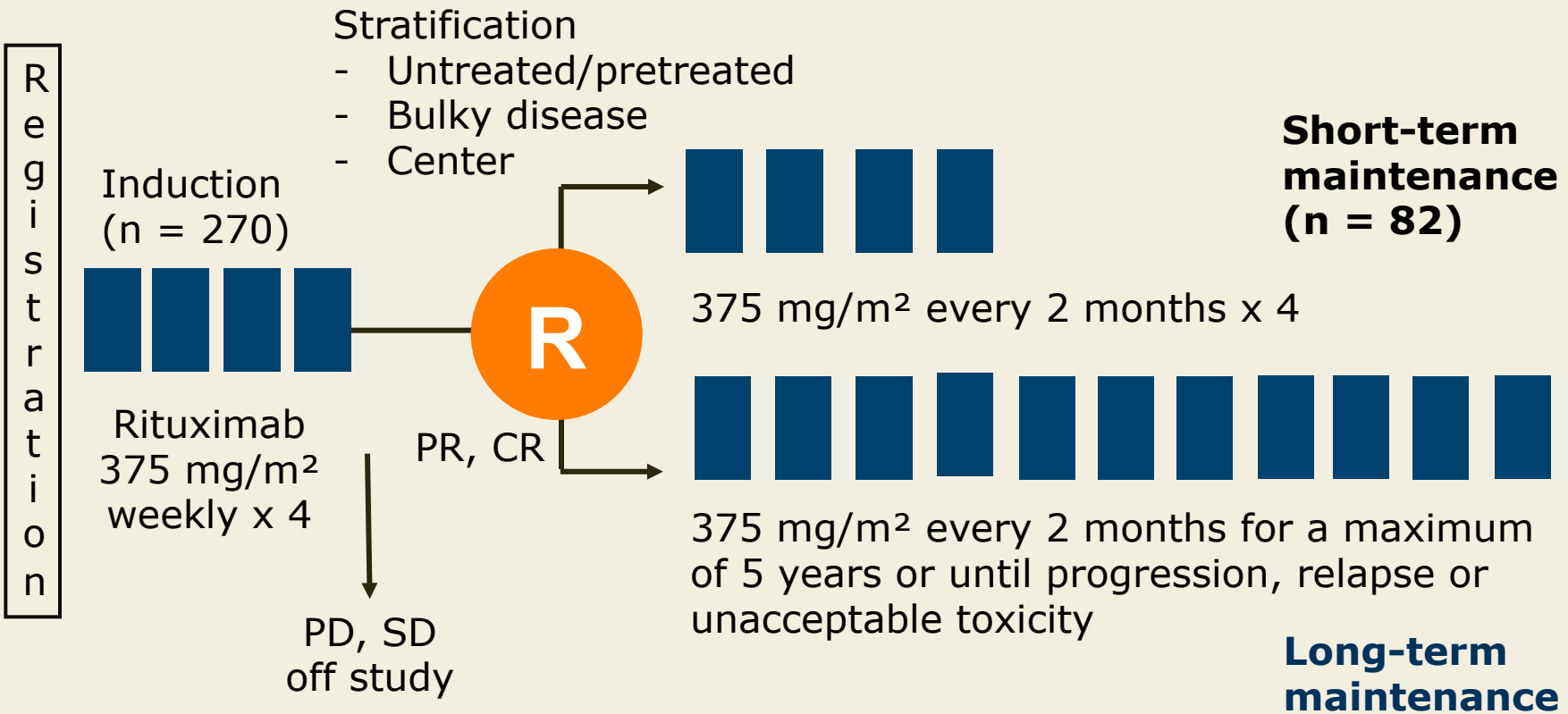
Proc ASH 2013;Abstract 508.

Background

- Observation continues to be adequate for patients with asymptomatic follicular lymphoma (FL) (ie, low-bulk disease and no cytopenias) (*Am J Hematol* 2012;87(10):988).
  - Most patients requiring therapy receive chemotherapy and rituximab.
- Rituximab maintenance has been shown to be an effective therapy for patients with newly diagnosed and relapsed/ refractory FL (*Lancet* 2011;377(9759):42; *J Clin Oncol* 2010; 28(17):2853).
- The optimal duration of maintenance therapy remains unknown.
- **Study objective:** To investigate whether rituximab maintenance every 2 months for 5 years or until relapse/ progression, unacceptable toxicity or death is superior to rituximab maintenance every 2 months x 4 for patients with FL.

Taverna C et al. *Proc ASH* 2013;Abstract 508.

SAKK 35/03: Phase III Trial Design



Primary endpoint: Event-free survival (EFS)

Secondary endpoints: Progression-free survival (PFS), overall survival, objective response, adverse events during and after maintenance

Taverna C et al. *Proc ASH* 2013;Abstract 508.

Response at Restaging

	(n = 261)
Overall response rate	62.8%
Complete response (CR)	13.4%
CR unconfirmed	3.4%
Partial response	46.0%
Stable disease	29.9%
Progressive disease	7.3%

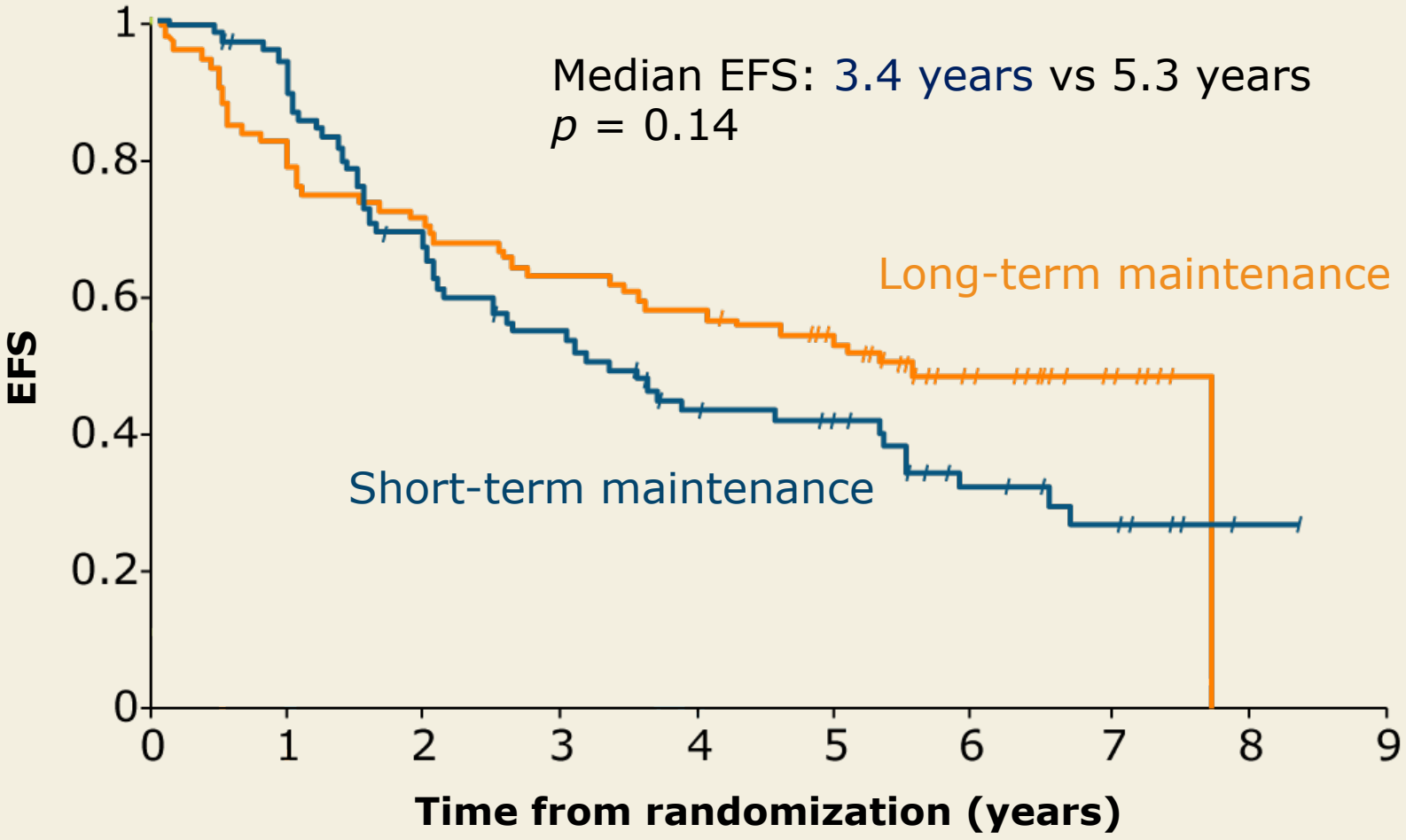
Taverna C et al. *Proc ASH* 2013;Abstract 508.

Patient Characteristics

	Short-term maintenance (n = 82)	Long-term maintenance (n = 83)
Sex Female Male	 55% 45%	 69% 31%
Median age (range)	55 (34-81)	57 (25-81)
Disease status Untreated Relapsed/progressed Stable	 67% 33% 0%	 70% 29% 1%
Previous chemotherapy	24%	25%
Previous anti-CD20 therapy	11%	8%
Previous radiotherapy	9%	6%

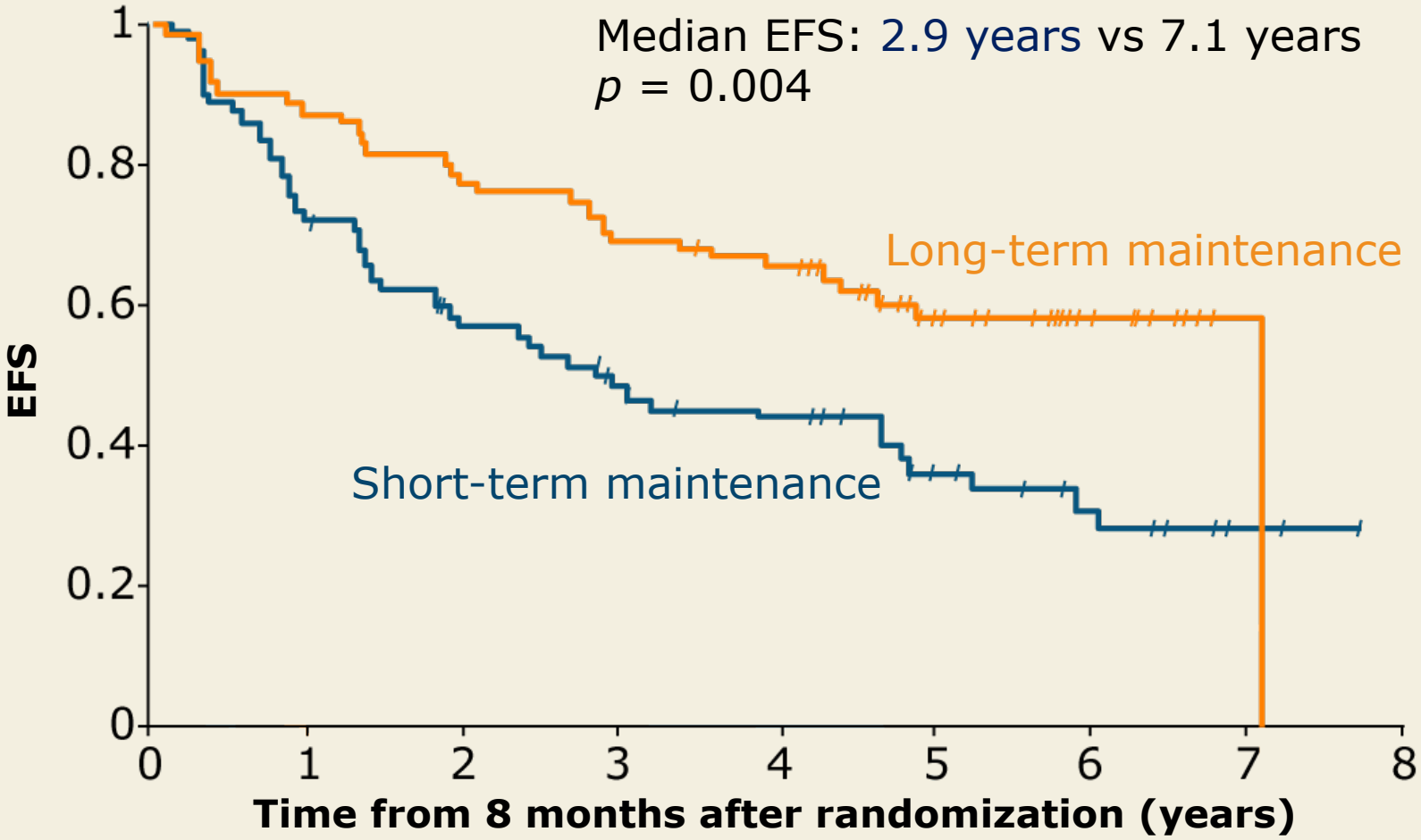
Taverna C et al. *Proc ASH* 2013;Abstract 508.

EFS



With permission from Taverna C et al. *Proc ASH* 2013;Abstract 508.

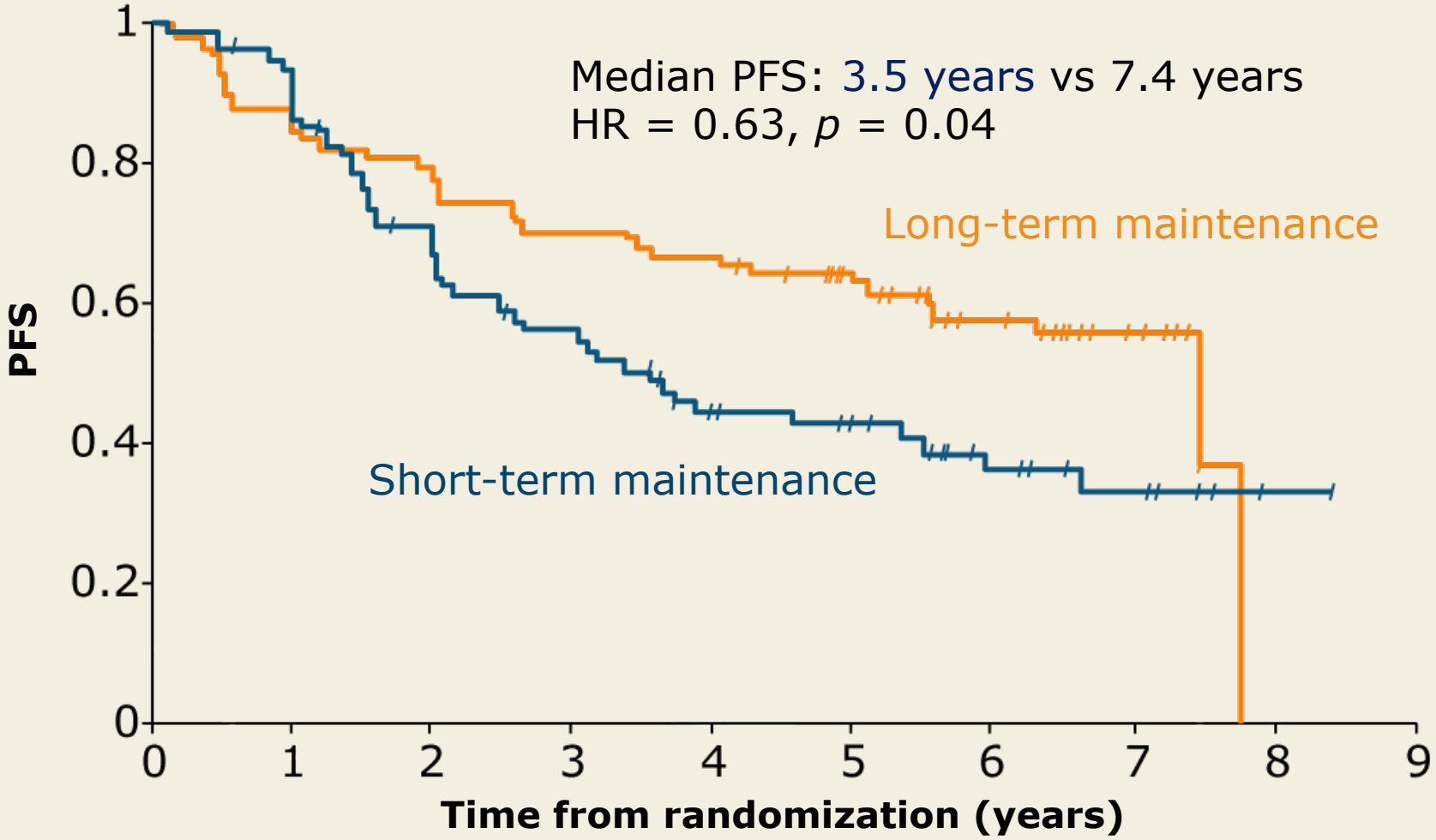
EFS*
(Retrospectively Defined Analysis)



* Only patients at risk 8 months after randomization

With permission from Taverna C et al. *Proc ASH* 2013;Abstract 508.

PFS



With permission from Taverna C et al. *Proc ASH* 2013;Abstract 508.

Adverse Events

	Short-term maintenance (n = 82)	Long-term maintenance (n = 83)
At least 1 adverse event	50%	76%
Highest grade		
Grade 1	30%	22%
Grade 2	18%	37%
Grade 3	1%	14%
Grade 4	0%	2%
Grade ≥3 infection	1%	6%
Secondary malignancy	7%	10%

Taverna C et al. *Proc ASH* 2013;Abstract 508.

Author Conclusions

- The primary endpoint of the Phase III SAKK 35/03 trial was not met (median EFS: 3.4 y vs 5.3 y; $p = 0.14$) due mainly to the early separation of the curves favoring short-term maintenance at a time when the treatment in both arms was the same.
- A retrospectively defined analysis considering only EFS events from the time when treatment was different in the 2 arms shows a statistically significant increase in EFS with long-term maintenance (median EFS: 2.9 y vs 7.1 y; $p = 0.004$).
- Long-term rituximab maintenance doubles the median PFS without leading to increased undue toxicity.

Taverna C et al. *Proc ASH* 2013;Abstract 508.

Investigator Commentary: Results of SAKK 35/03 — A Phase III Trial of Rituximab (R) Maintenance Treatment for a Maximum of 5 Years in FL

These data are interesting, but they conflict with the RESORT data (*Proc ASH* 2011;Abstract LBA-6) to a certain extent. The endpoint of the RESORT study wasn't exactly the same, and among patients with at least low-risk FL no difference in the primary endpoint, time to treatment failure, was evident between R maintenance and R re-treatment at disease progression. The SAKK 35/03 study administered R maintenance for up to 5 years, and based on the curves presented at ASH, results for the primary endpoint of EFS were not significant. Results for the secondary endpoint of PFS were significant, as was an unplanned retrospective analysis of EFS. I am a bit of a statistical purist and find those types of analyses to contain biases. Obviously we'll have to wait for the formal publication.

I would say the bottom line is that the standard for patients with high-risk FL remains R/chemotherapy followed by 2 years of R maintenance. But in the low-risk setting, including patients on the RESORT study — in other words, for disease you don't have a reason to treat — my personal standard is still watchful waiting. At most I would administer 4 weeks of R and then wait with no maintenance therapy.

Interview with Andrew M Evens, DO, MSc, February 12, 2014

A Randomized Phase II Study Comparing Consolidation with a Single Dose of ^{90}Y Ibritumomab Tiuxetan (Zevalin®) (Z) vs Maintenance with Rituximab (R) for Two Years in Patients with Newly Diagnosed Follicular Lymphoma (FL) Responding To R-CHOP. Preliminary Results at 36 Months from Randomization

López-Guillermo A et al.

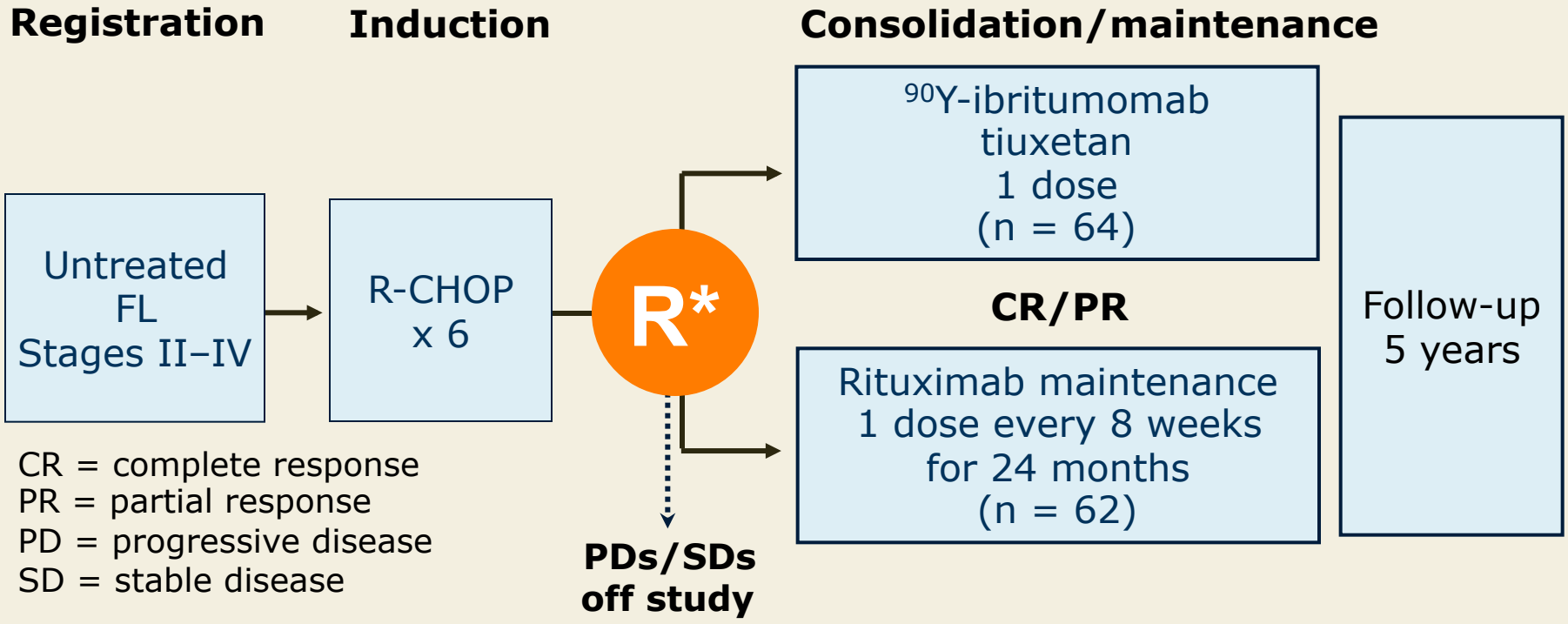
Proc ASH 2013;Abstract 369.

Background

- Patients with follicular lymphoma (FL) can survive for a long time, but disease progression typically occurs 3 to 5 years after treatment.
- Consolidation with ^{90}Y-ibritumomab tiuxetan after initial therapy, mainly in the prerituximab era, significantly improved progression-free survival (PFS) and time to next treatment (TTNT) (*J Clin Oncol* 2013;31:1977).
- Rituximab maintenance has also demonstrated a substantial benefit in terms of PFS and TTNT in patients who initially received immunochemotherapy (*Lancet* 2011;377:42).
  - This approach can be considered a standard for patients with FL.
- **Study objective:** To compare ^{90}Y-ibritumomab tiuxetan consolidation to rituximab maintenance for patients with FL responding to the R-CHOP regimen.

López-Guillermo A et al. *Proc ASH* 2013;Abstract 369.

Phase II ZAR2007 Trial Design



* Stratification by response (CR/PR)

Primary endpoint: PFS

Secondary endpoints: Complete response rate at end of maintenance period, event-free survival, time to re-treatment, overall survival (OS), safety and toxicity profile, quality of life

López-Guillermo A et al. *Proc ASH* 2013;Abstract 369.

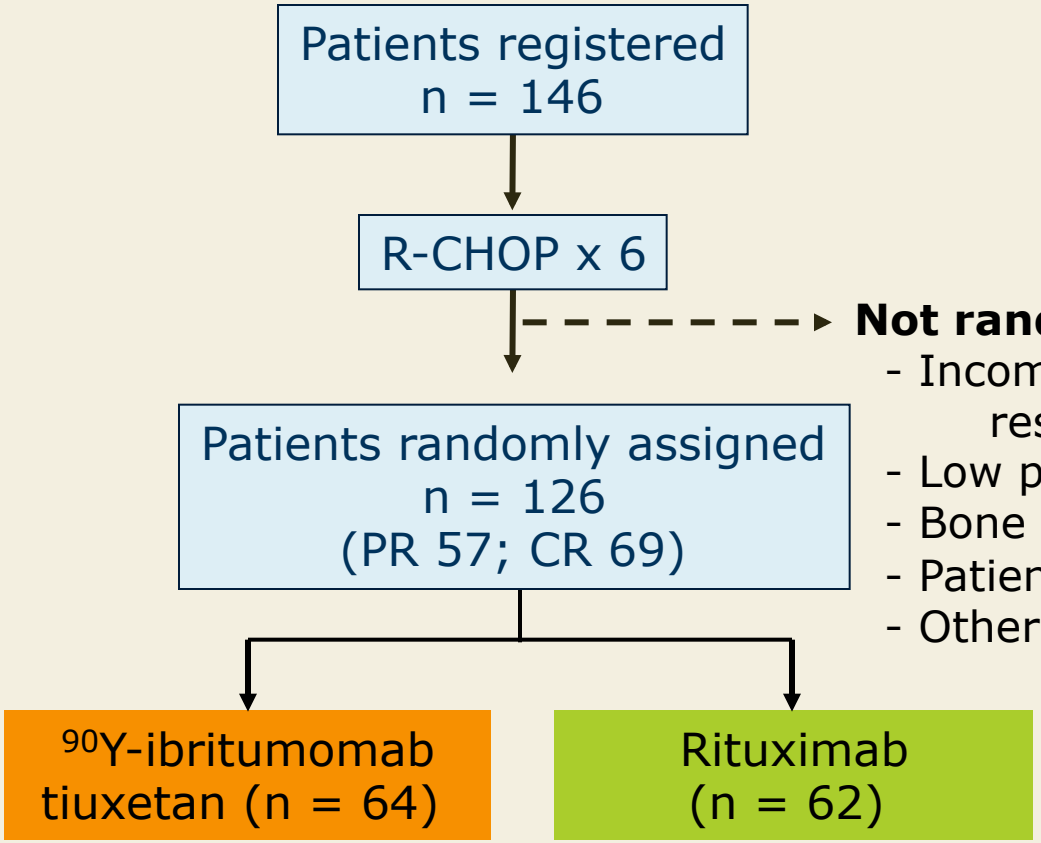
ZAR2007 Trial Design (continued)

- **CONSOLIDATION:** ^{90}Y-ibritumomab tiuxetan
  - 0.4 mCi/kg IV (total dose capped at 32 mCi)
  - Rituximab 250 mg/m^2 days -8 and 0
  - Between 60 and 90 days after last dose of rituximab (induction period)

- **MAINTENANCE:** Rituximab
  - 375 mg/m^2 administered by IV infusion every 8 weeks x 12 doses (24 months)
  - Starting 60 to 90 days after last dose of rituximab (induction period)
  - No dose adjustment

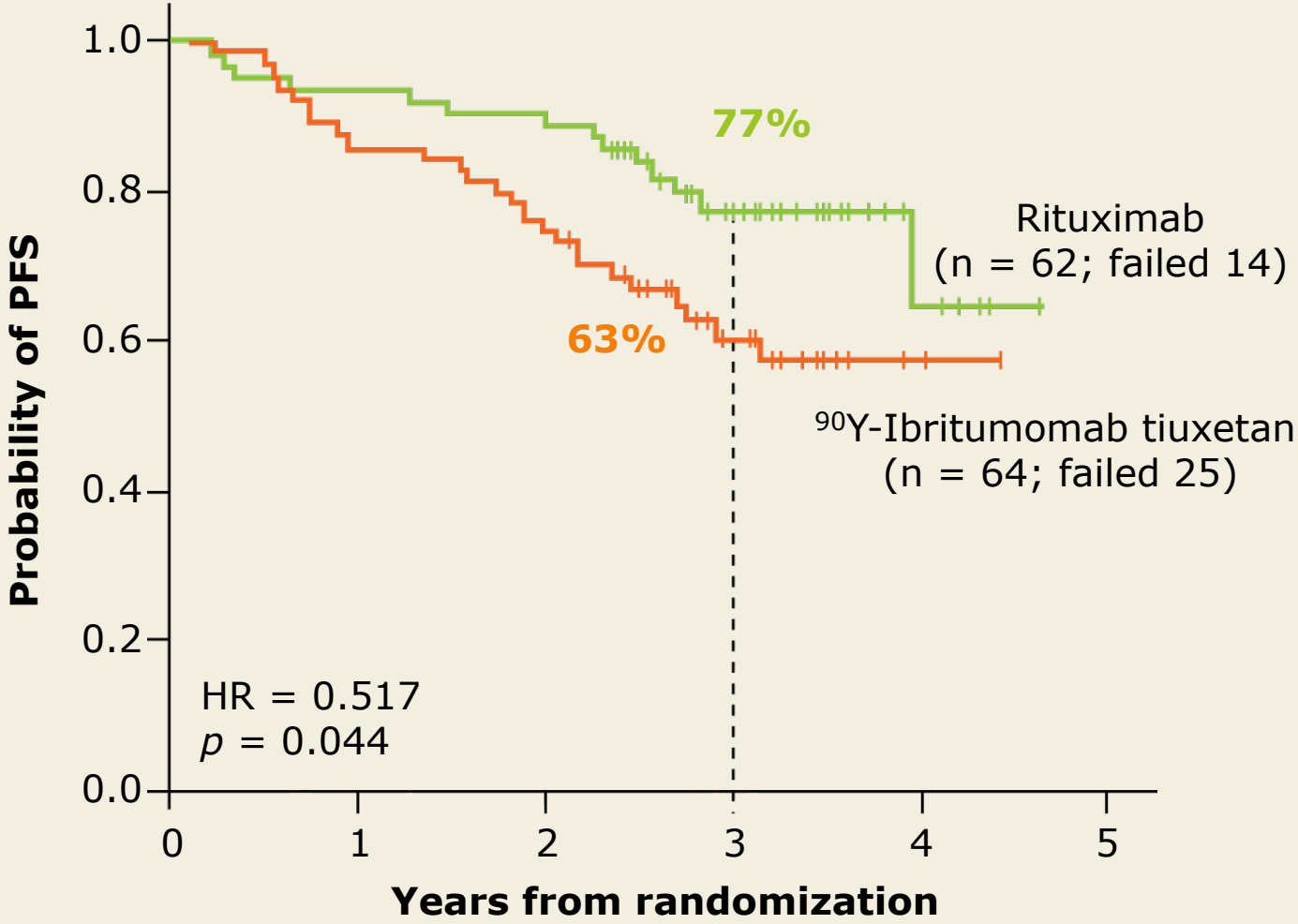
López-Guillermo A et al. *Proc ASH* 2013;Abstract 369.

Patient Disposition



López-Guillermo A et al. *Proc ASH* 2013;Abstract 369.

PFS



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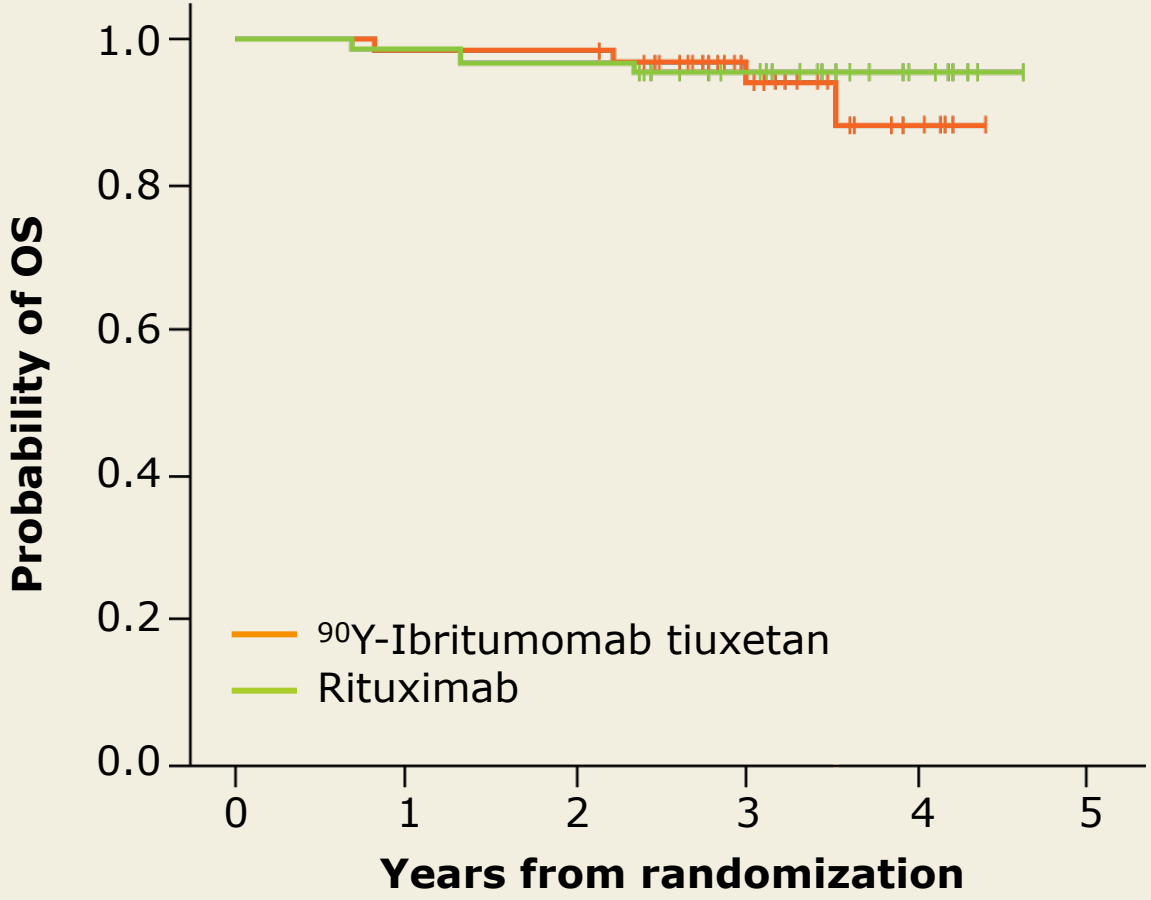
OS



Causes of death: Progression (n = 6), graft-versus-host disease (n = 1)

With permission from López-Guillermo A et al. *Proc ASH* 2013;Abstract 369.

Author Conclusions

- In patients with FL requiring therapy and responding to R-CHOP, rituximab maintenance was superior to consolidation with ^{90}Y-ibritumomab tiuxetan in terms of PFS.
  - 3-year PFS: 77% vs 63% (HR = 0.517, p = 0.044)
- However, no significant differences were observed regarding the TTNT (data not shown) or OS.
- The safety profile was reasonable, with no unexpected toxicities observed in either arm (data not shown).

López-Guillermo A et al. *Proc ASH* 2013;Abstract 369.

Investigator Commentary: ZAR2007 — Preliminary Results of a Phase II Trial Comparing Consolidation with a Single Dose of ^{90}Y-Ibritumomab Tiuxetan to Rituximab Maintenance for 2 Years in Patients with Newly Diagnosed FL Responding to R-CHOP

This randomized Phase II trial evaluated either 2 years of rituximab maintenance or 1 dose of consolidation ^{90}Y-ibritumomab tiuxetan for patients with FL responding to R-CHOP. I was a little surprised by the results. I thought any differences would be insignificant at the end of the day. But the PFS analysis, at least, favored the rituximab arm. These data are not yet mature, and we need to follow the results as they emerge.

I'm not sure these data will change practice per se. I believe the standard is still 2 years of rituximab maintenance, but I might consider administering ^{90}Y-ibritumomab tiuxetan consolidation in certain situations, eg, for a patient who is planning to be out of town for a significant period — on an 18-month cruise or a year-long trip to Alaska, et cetera. In these circumstances, consolidation with a single dose of ^{90}Y-ibritumomab tiuxetan may be of benefit for as long as 2 years.

Interview with Andrew M Evens, DO, MSc, February 12, 2014

Early Relapse of Follicular Lymphoma After R-CHOP Uniquely Defines Patients at High Risk for Death: An Analysis from the National Lymphocare Study

Casulo C et al.

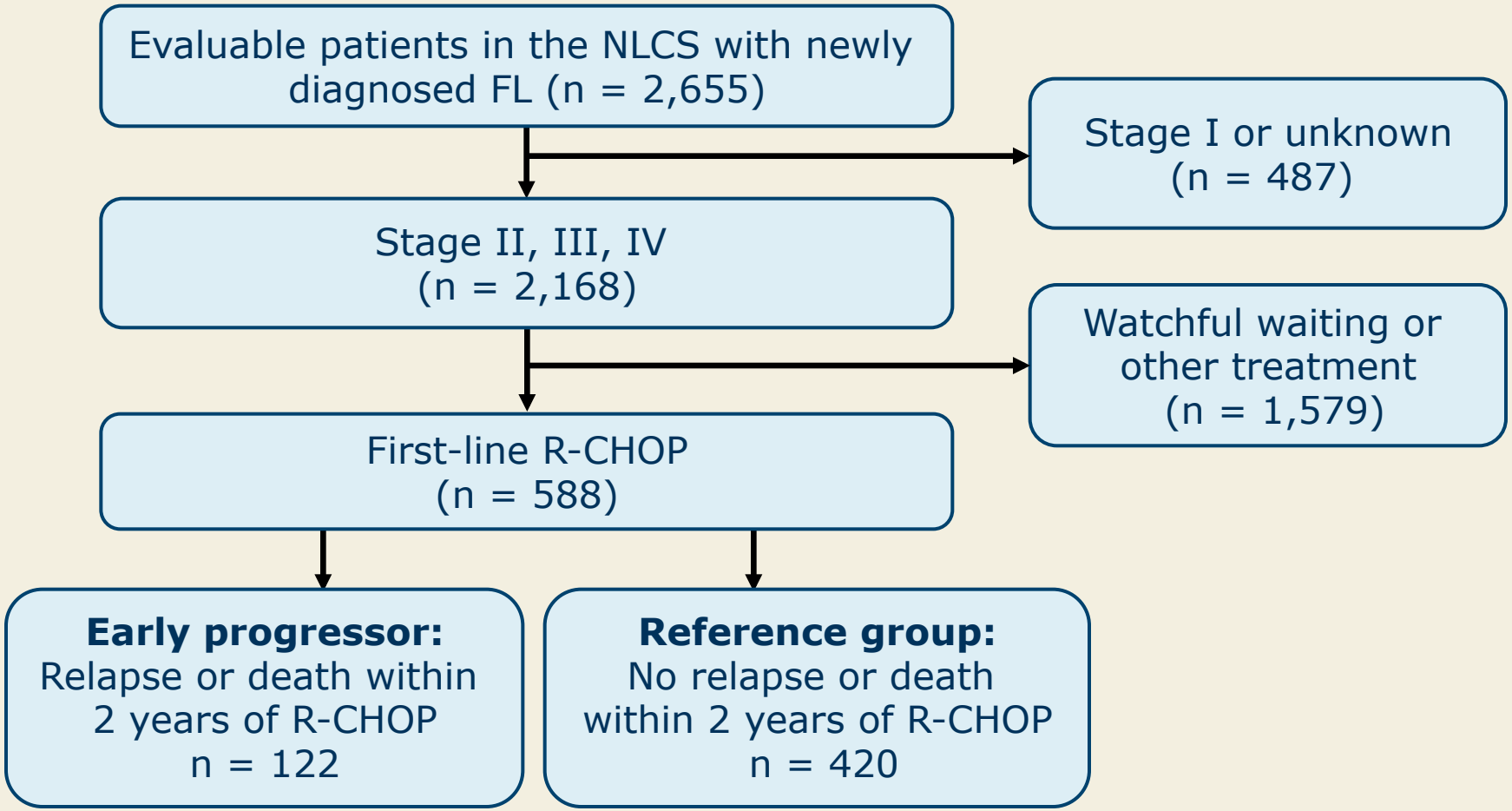
Proc ASH 2013;Abstract 510.

Background

- Despite gains in survival outcomes in follicular lymphoma (FL) with aggressive treatment strategies and maintenance rituximab, a subset of patients with FL demonstrates a consistent pattern of early relapse after treatment.
  - Approximately 20% of patients with FL will experience disease progression (PD) within 24 months of receiving chemoimmunotherapy (*JCO* 2013;31:314; *Lancet* 2013;381:1203).
  - This suggests that a group of patients at high risk will experience early relapse.
- **Study objective:** To determine whether PD within 2 years of R-CHOP therapy would define a subset of patients with FL who are at high risk of death.

Casulo C et al. *Proc ASH* 2013;Abstract 510.

Observational National LymphoCare Study (NLCS) Design



- Patients were diagnosed from 2004 to 2007 at 265 sites in the US (n = 2,727)

Casulo C et al. *Proc ASH* 2013;Abstract 510.

NLCS: Baseline Characteristics by Group

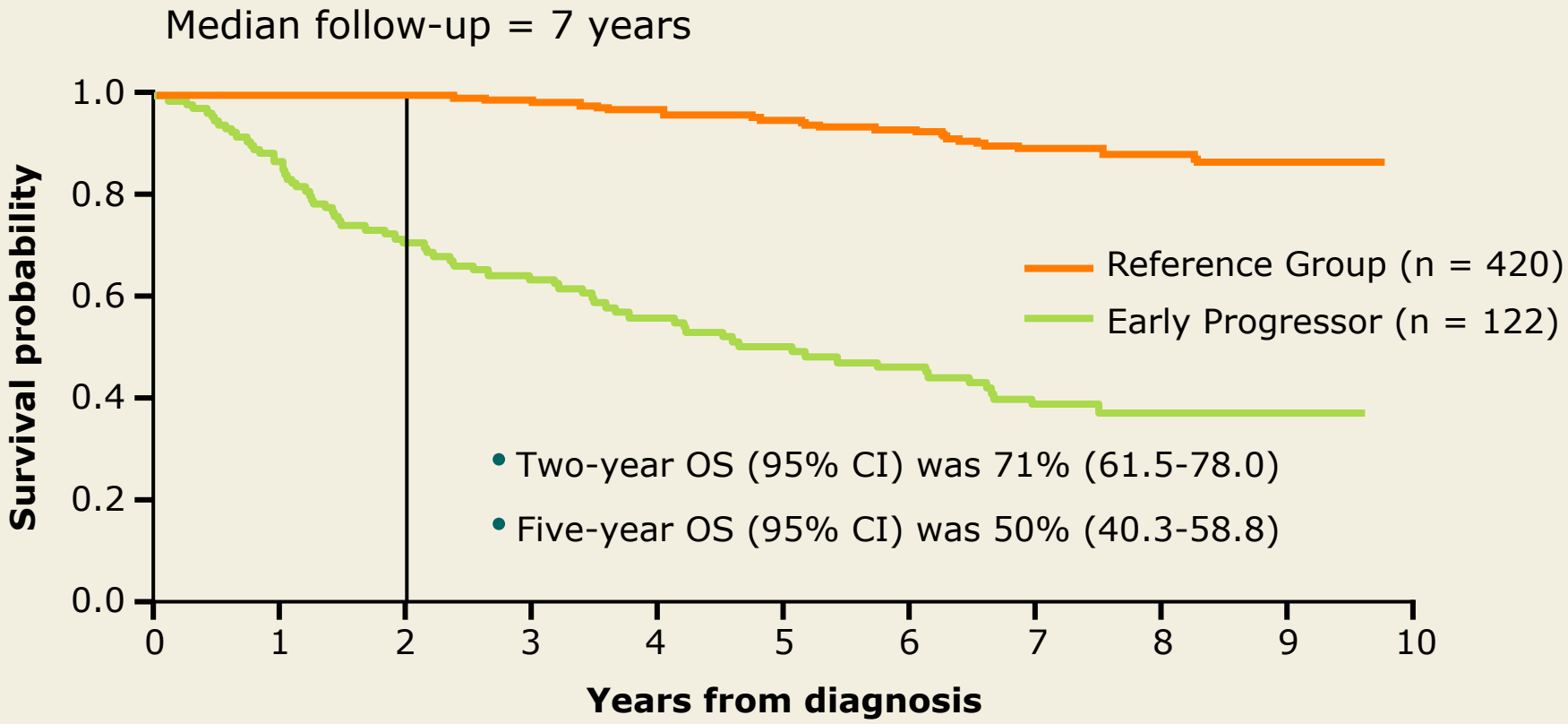
Characteristic	Early progressors (n = 122)	Reference group (n = 420)	*p*-value*
Grade 3 FL	34%	40%	0.5
High-risk FLIPI	57%	40%	0.01
Elevated LDH	43%	28%	0.01
Low hemoglobin	35%	22%	0.01
≥2 nodal sites	40%	25%	0.01
Poor ECOG PS	16%	4%	<0.01

* X^2

FLIPI = Follicular Lymphoma International Prognostic Index; LDH = lactate dehydrogenase; ECOG PS = Eastern Cooperative Oncology Group performance status

Casulo C et al. *Proc ASH* 2013;Abstract 510.

NLCS: Overall Survival (OS) in Relapsed FL within 2 Years of R-CHOP



- 122 patients were classified as early progressors
  - PD (n = 110) and non-PD death within 2 years (n = 12)

With permission from Casulo C et al. *Proc ASH* 2013;Abstract 510.

NLCS: Outcomes

- After a median follow-up of 7 years:
  - Patients classified as early progressors: 21%
  - Patients in the reference group: 71%
  - Patients lost to follow-up: 8%
- After adjusting for baseline characteristics, early PD was dramatically associated with poor OS.
  - Hazard ratio (HR) = 13.3 (95% CI: 7.94-22.4)
- After adjusting for FLIPI score, early PD was associated with an increased risk of death.
  - HR = 15.4 (95% CI: 9.6-24.7)
- Logistic regression model analysis showed that high LDH, poor ECOG status, B symptoms and bone marrow involvement were significantly associated with early PD ($p < 0.05$).

Casulo C et al. *Proc ASH* 2013;Abstract 510.

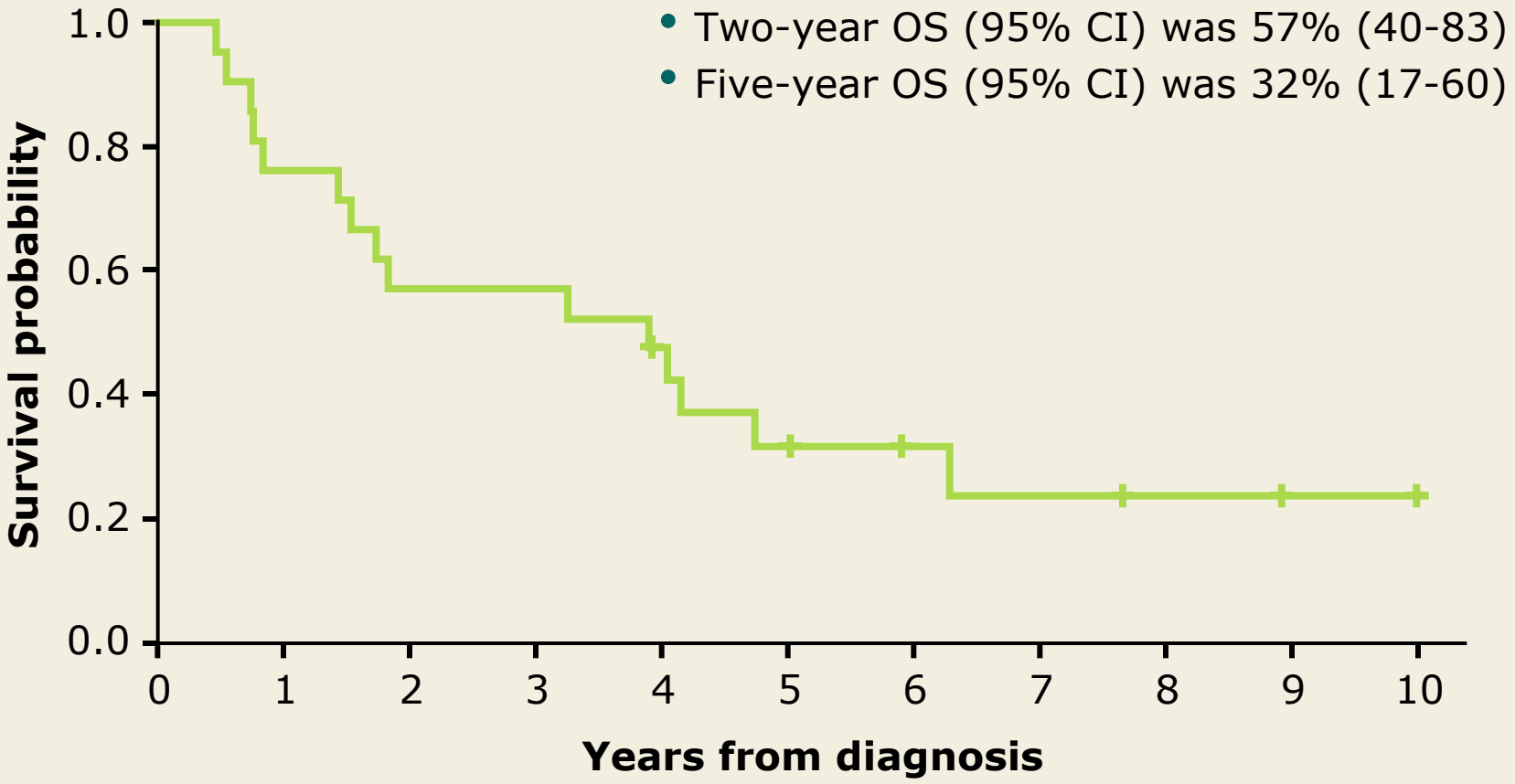
Replication/Validation Study

- The NLCS was replicated at the University of Iowa (UI)/ Mayo Clinic to validate the NLCS results.
  - UI/Mayo cohort of patients with FL (n = 103)
- All patients received first-line R-CHOP.
- Baseline characteristics of patients were well balanced across all groups except that more patients had Grade 3 FL in the UI/Mayo cohort compared to the NLCS (62% versus 38%, $p < 0.01$).

Casulo C et al. *Proc ASH* 2013;Abstract 510.

UI/Mayo: OS in Relapsed FL within 2 Years of R-CHOP

Median follow-up = 6 years



With permission from Casulo C et al. *Proc ASH* 2013;Abstract 510.

UI/Mayo Validation Study Outcomes

- At a median follow-up of 6 years, a total of 21 patients (20%) had experienced early PD or death.
- Cox model analysis confirmed that patients with early PD after R-CHOP have an increased risk of death.
  - Unadjusted HR = 24.2 (95% CI: 8.6-67.8)
  - FLIPI adjusted HR = 22.6 (95% CI: 7.9-64.3)

Casulo C et al. *Proc ASH* 2013;Abstract 510.

NLCS: Second-Line Treatments

Treatment	PD ≤2 years (n = 110)
None	12%
Rituximab monotherapy	26%
Chemotherapy +/- rituximab	38%
Investigational therapy	5%
Radiotherapy-containing regimens	6%
Radioimmunotherapy-containing regimens	6%
Other noninvestigational therapy	1%
Hematopoietic transplant-containing regimen	8%

Casulo C et al. *Proc ASH* 2013;Abstract 510.

Author Conclusions

- PD within 2 years of R-CHOP uniquely defines a group of patients at a substantially greater risk of death.
  - The NLCS data set confirms that early PD occurs in 20% of patients with FL.
  - In this cohort of 588 patients with a median follow-up of 7 years, 61% (69/113) of deaths occurred in the group of patients classified as early progressors.
- This newly defined group of patients at high risk may represent a distinct population warranting further exploration in studies directed at understanding the biology and treatment of FL.

Casulo C et al. *Proc ASH* 2013;Abstract 510.

Investigator Commentary: NLCS — A Study to Evaluate Early Disease Progression within 2 Years of R-CHOP in Patients with FL

The NLCS analysis was interesting, but the findings were not surprising. Patients who experience disease progression earlier than usual or earlier than what is expected have worse clinical outcomes. In today's world, the median PFS for patients with high-risk FL who receive R-CHOP and no maintenance therapy is 3 to 4 years. We see patients who experience disease progression within a year or two, and we think of such patients as having "bad follicular lymphoma." While this study demonstrated that FL does worsen, it also showed that the OS for these patients was significantly worse because half of the patients were dead in 5 years.

The situation is probably worse than expected. We assume that we can salvage all patients with FL and that everyone ends up with about the same survival rate. But clearly this group of patients, if they experienced disease progression within 2 years, had a significantly inferior survival. Intuitively we consider more aggressive therapy for these patients — they quickly start heading down the transplant avenue. At this point we need the next therapeutic step, and it is unclear whether we can change the natural history by treating more aggressively.

Interview with Andrew M Evens, DO, MSc, February 12, 2014

Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphomas and Lymphoproliferative Disorders

Duvic M et al.

Proc ASH 2013;Abstract 367.

Background

- Brentuximab vedotin (BV), an antibody-drug conjugate containing an anti-CD30 monoclonal antibody (cAC10), is FDA approved for 2 indications (*JCO* 2012;30:2183; *JCO* 2012;30:2190):
  - Treatment of Hodgkin lymphoma after failure of autologous stem cell transplantation (ASCT) or failure of ≥2 prior chemotherapy regimens in ASCT-ineligible patients (overall response rate [ORR]: 75%)
  - Treatment of systemic anaplastic large cell lymphoma (ALCL) after failure of ≥1 prior chemotherapy regimen (ORR: 86%)
- The naked cAC10 antibody was active in CD30+ skin lymphomas (ORR: 70%) (*Clin Cancer Res* 2009;15:6217).
- **Study objective:** To determine the efficacy and safety of BV in primary cutaneous (pc) CD30+ lymphoproliferative disorders.

Duvic M et al. *Proc ASH* 2013;Abstract 367.

Phase II Open-Label Trial Design

Eligibility (n = 48)

pc CD30+ lymphoproliferative disorders*

Skin lesion expression of CD30

>10 LyP lesions

≥1 tumor

Need for systemic therapy

→

BV

1.8 mg/kg (IV)

Every 21 days

Patients who achieved a complete response (CR) received 2 more doses, and those with partial responses (PR) after 8 cycles could receive up to 16 doses.

LyP = lymphomatoid papulosis

* Including LyP and pc-ALCL or CD30+ mycosis fungoides (MF)

- Patients with CD30+ MF had Stage IB disease or higher and had received ≥1 prior topical or systemic therapies.
- Response criteria were a 50% decrease in lesions for LyP, 50% tumor reduction for pc-ALCL and a 50% decrease in modified skin weighted assessment tool (mSWAT) for MF.
- CD30 pretreatment skin biopsies and serum sCD30 were correlated with response.

Duvic M et al. *Proc ASH* 2013;Abstract 367.

Response by Clinical Diagnosis

Primary diagnosis, n (%)	ORR	CR	PR
All patients (n = 48)	34 (71%)	17 (35%)	17 (35%)
MF only* (n = 28)	14 (50%)	2 (7%)	12 (43%)
LyP only (n = 9)	9 (100%)	5 (56%)	4 (44%)
pc-ALCL only (n = 2)	2 (100%)	2 (100%)	0 (0%)
LyP with MF (n = 7)	7 (100%)	6 (86%)	1 (14%)
LyP with pc-ALCL (n = 2)	2 (100%)	2 (100%)	0 (0%)

* Regardless of whether the lesions had low, medium or high CD30 levels at baseline

- In the intent-to-treat population, patients received at least 1 dose (n = 56)
  - ORR = 61%

Duvic M et al. *Proc ASH* 2013;Abstract 367 (abstract only).

Time to Response (TTR), Duration of Response (DoR) and Relapse Rate by Clinical Diagnosis

Primary diagnosis	TTR (range)	DoR (range)
MF only (n = 28)	10.5 weeks (3-39)	13.5 weeks (3-56)
LyP only (n = 9)	3 weeks (3-6)	23 weeks (6-44)
pc-ALCL only (n = 2)	3 weeks (3)	18 weeks (NR)
LyP with MF (n = 7)	3 weeks (3-9)	18 weeks (18-44)
LyP with pc-ALCL (n = 2)	NR	NR

NR = not reported

- Relapse rate in all patients with LyP and pc-ALCL (n = 20): 40%
  - TTR: 25 weeks (range: 6-41)
- Relapse rate in responders with MF (n = 14): 36%

Duvic M et al. *Proc ASH* 2013;Abstract 367 (abstract only).

Clinical Outcomes

- Median progression-free survival:
  - From diagnosis: 9.7 years
  - From first dose: 1.68 years
- Soluble CD30 levels from baseline to end of study differed significantly among the patients who achieved a CR compared to those with a PR or stable disease.
  - $p = 0.036$

Duvic M et al. *Proc ASH* 2013;Abstract 367 (abstract only).

Author Conclusions

- This Phase II trial demonstrated that BV is active in patients with MF with an ORR of 50%, irrespective of the level of CD30-positive expression.
- For patients with CD30-positive pc-ALCL, the ORR was 100%.
- In all evaluable patients with LyP, BV elicited activity.
  - ORR: 71%
  - CR: 36%

Duvic M et al. *Proc ASH* 2013;Abstract 367 (abstract only).

Investigator Commentary: Results from a Phase II Trial of BV in CD30-Positive Cutaneous T-Cell Lymphomas and Lymphoproliferative Diseases

A conclusion of this Phase II study is that BV is active irrespective of the intensity of CD30 levels. Whether the patient has a 1% or 90% level of CD30 expression, BV elicits activity. This probably has a lot to do with the sensitivity of the currently commercially available antibodies used for IHC stains. From a clinical point of view, the troubling aspect is that if you use the available antibodies or assays, you will have patients with disease recorded as CD30-negative — not even with 1% expression — that will respond to this agent.

Because of this, ongoing studies are investigating BV in patients with CD30-negative disease. This is necessary because CD30 positivity is not emerging as an important marker for response. That being said, my bet is that BV will result in a lower response rate in CD30-negative versus positive disease.

Interview with Andrew M Evens, DO, MSc, February 12, 2014

A Phase 2 Study of Brentuximab Vedotin in Patients with Relapsed or Refractory CD30-Positive Non-Hodgkin Lymphomas: Interim Results in Patients with DLBCL and Other B-Cell Lymphomas

Bartlett NL et al.

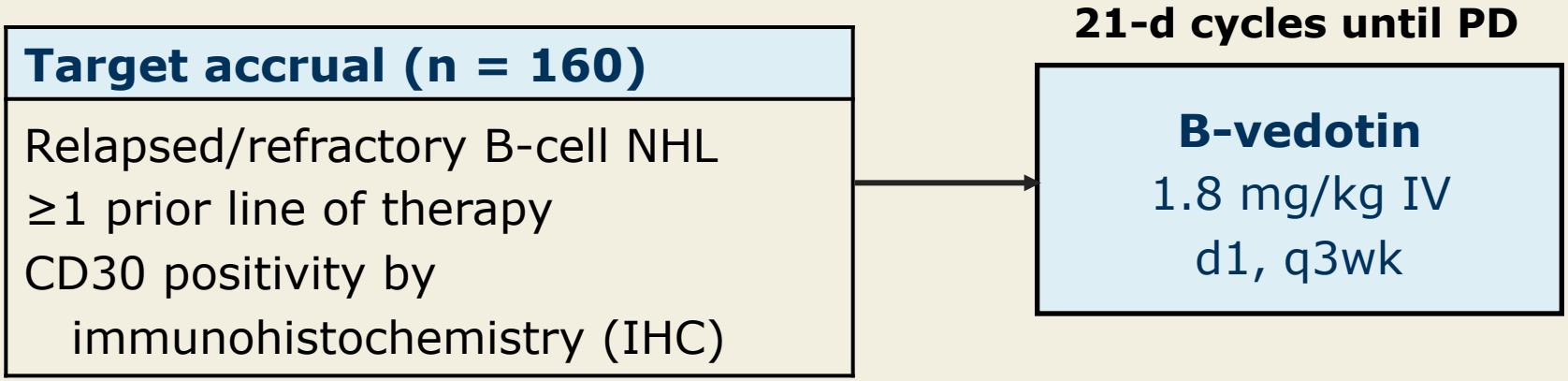
Proc ASH 2013;Abstract 848.

Background

- Brentuximab vedotin (B-vedotin), a CD30-directed antibody-drug conjugate, has demonstrated durable responses and manageable safety in relapsed/refractory Hodgkin lymphoma and anaplastic large cell lymphoma (*J Clin Oncol* 2012;30:2183; *J Clin Oncol* 2012;30:2190).
- Variable CD30 expression has been demonstrated in several B-cell non-Hodgkin lymphoma (NHL) subtypes, such as diffuse large B-cell lymphoma (DLBCL).
- Patients with relapsed/refractory DLBCL have a poor outcome, and there is no standard treatment for transplant-ineligible patients.
- **Study objective:** To evaluate the efficacy and safety of B-vedotin in relapsed/refractory CD30-positive B-cell NHL.

Bartlett NL et al. *Proc ASH* 2013;Abstract 848.

Ongoing Phase II Study Design (NCT01421667)



Study start date: August 2011
Estimated completion date: January 2017

Primary endpoint: Overall response rate

Key secondary endpoint: Correlation of CD30 expression with response

Bartlett NL et al. *Proc ASH* 2013;Abstract 848.

Pathological Diagnoses

Diagnosis	(n = 68)
DLBCL	74%
DLBCL-NOS	63%
EBV+ DLBCL of the elderly	7%
Plasmablastic lymphoma	1%
T cell-rich B-cell lymphoma	1%
Other B-cell lymphomas	26%
Grey zone lymphomas	9%
Primary mediastinal B-cell lymphoma	9%
Follicular lymphoma	4%
Post-transplant lymphoproliferative disorder	4%

Bartlett NL et al. *Proc ASH* 2013;Abstract 848.

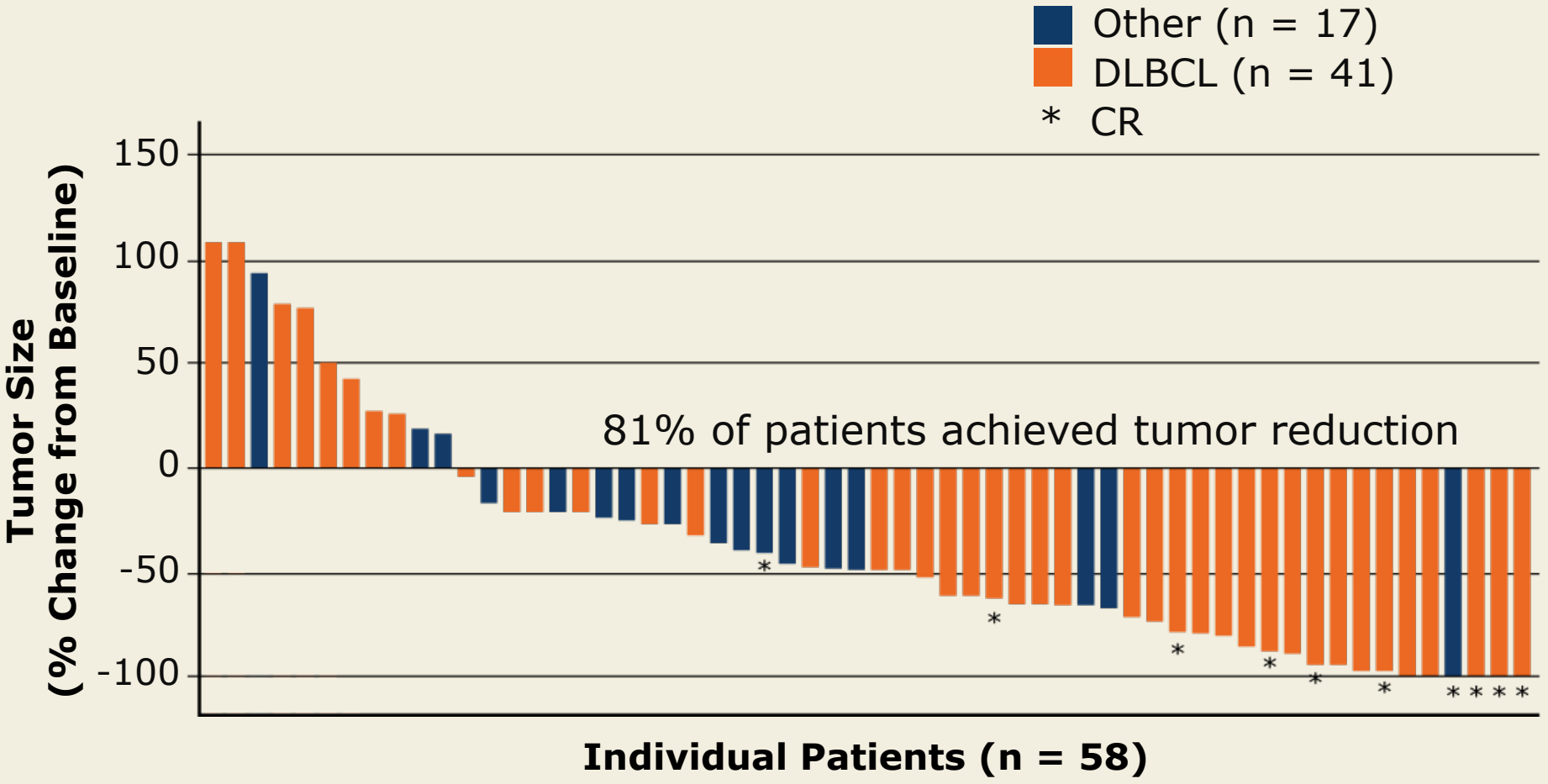
Best Response by Diagnosis

Response	DLBCL (n = 50)	Other B-cell (n = 18)
Overall response rate Complete remission (CR) Partial remission (PR)	42% 16% 26%	22% 11% 11%
Stable disease (SD)	20%	50%
Progressive disease (PD)	36%	28%
Median duration of objective response	5.8 mo	5.0 mo
Median progression-free survival	4.0 mo	2.9 mo

- Median no. of cycles = 4 (range: 1-19); 8 patients remain on treatment
- Median duration of CR:
  - DLBCL, 11.5 mo
  - Other B-cell, not reached

Bartlett NL et al. *Proc ASH* 2013;Abstract 848.

Maximum Tumor Reduction



10 patients not included in analysis due to incomplete data (5/10 had clinical progression)

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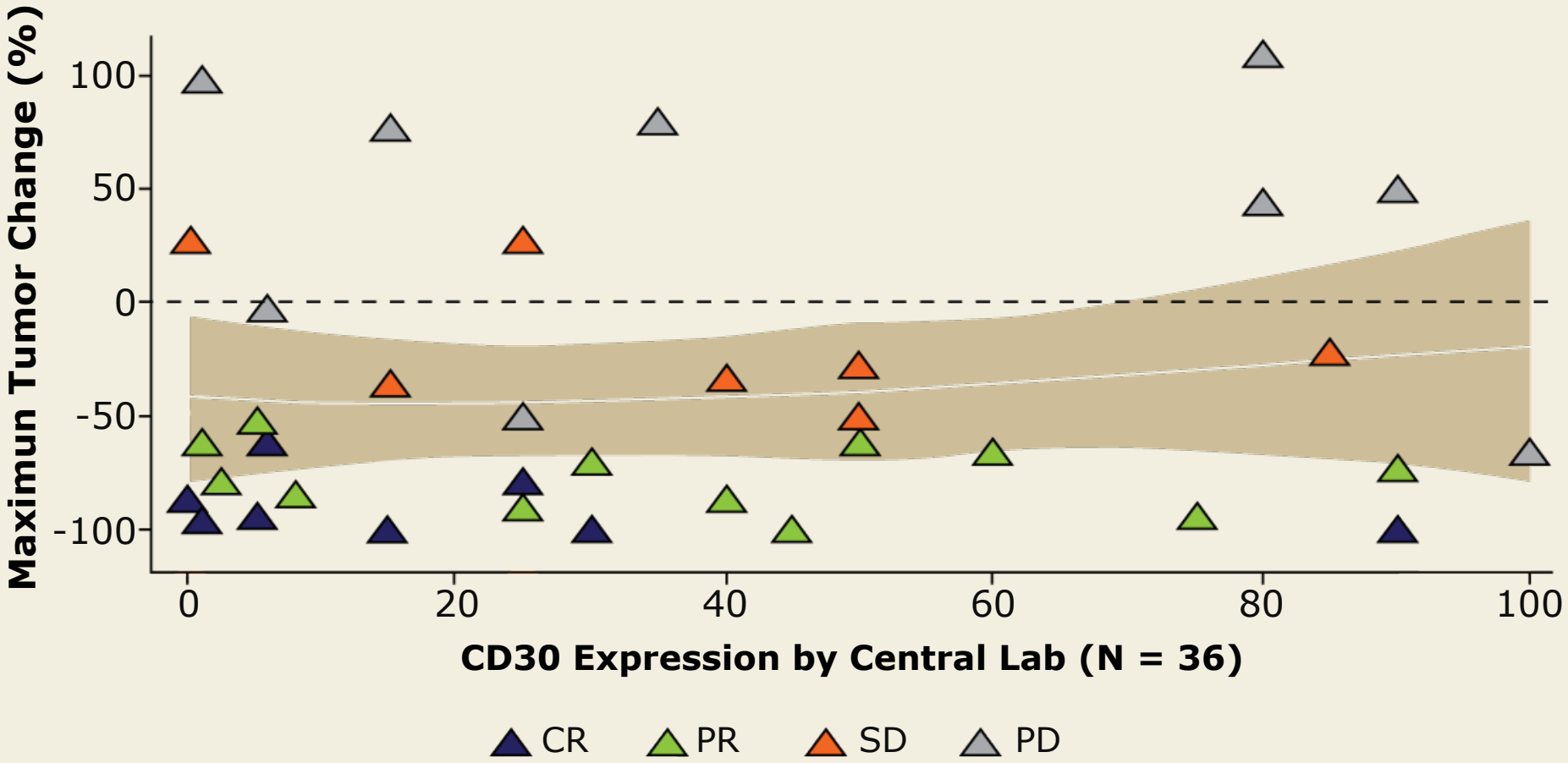
Maximum Tumor Reduction in Patients with DLBCL by CD30 Expression



Remissions observed in patients with undetectable and up to 90% CD30 expression

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DLBCL: CD30 Expression versus Response

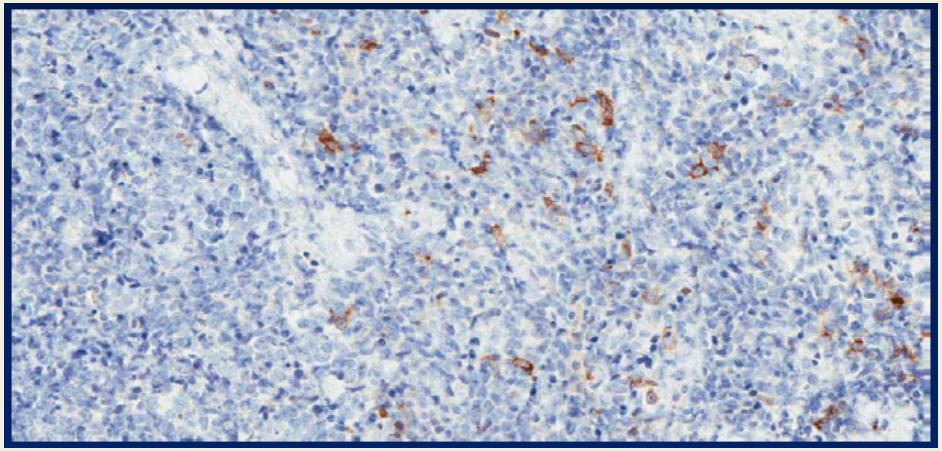
Response	CD30 expression		
	0%-9% (n = 14)	10%-100% (n = 30)	Not available (n = 6)
Overall response rate	57%	40%	17%
CR	29%	13%	—
PR	29%	27%	17%
SD	7%	20%	50%
PD	36%	37%	33%

Activity was observed across all levels of CD30 expression.

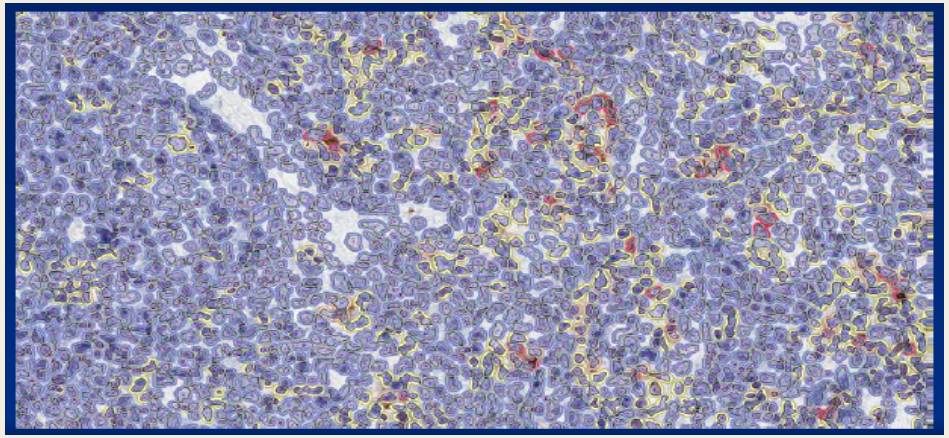
Bartlett NL et al. *Proc ASH* 2013;Abstract 848.

76-Year-Old Male — Refractory DLBCL

Standard IHC using BerH2 antibody, central lab
- 1% CD30+ malignant cells



Computer-assisted IHC using quantitative digital pathology image analysis
- 34% CD30+ malignant cells



Patient achieved CR after 2 cycles of treatment with B-vedotin

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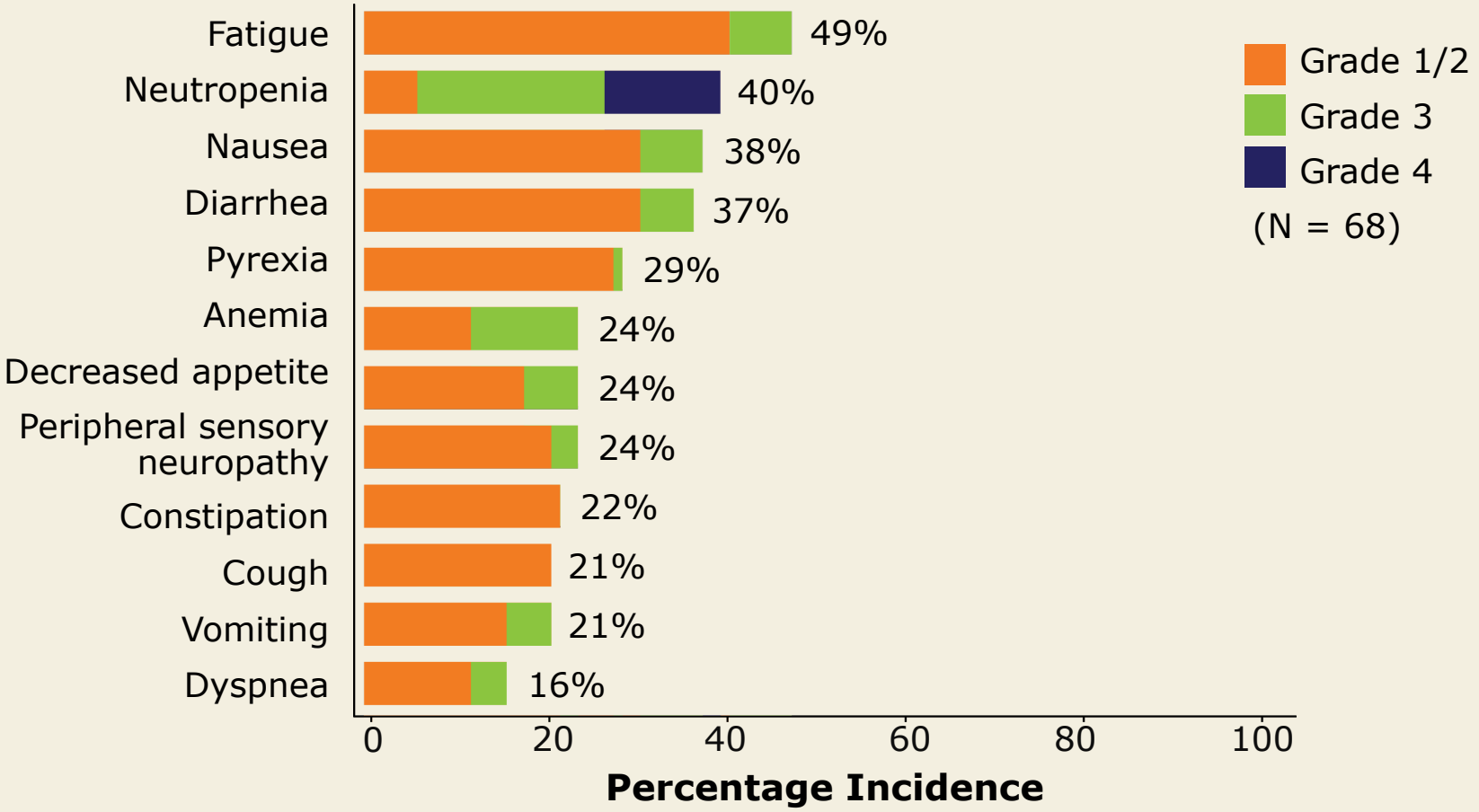
Adverse Events (>15% of Patients)



Related serious adverse events (>1 patient): Pneumonia (n = 3); anemia, febrile neutropenia, neutropenia, thrombocytopenia (n = 2 each)

With permission from Bartlett NL et al. *Proc ASH* 2013;Abstract 848.

Author Conclusions

- Promising antitumor activity was observed in relapsed/ refractory DLBCL with an overall response rate of 42% (8 CR, 13 PR) and a median remission duration of 11.5 months in patients who achieved a CR.
- Responses were observed across a broad range of CD30 expression, including low or undetectable CD30 expression by standard IHC.
- The safety profile in DLBCL is consistent with labeled indications.
- An additional cohort of patients with DLBCL with undetectable CD30 expression by standard IHC is currently enrolling.
- A front-line study of B-vedotin with R-CHOP in high-risk DLBCL is currently enrolling (NCT01925612).

Bartlett NL et al. *Proc ASH* 2013;Abstract 848.

Investigator Commentary: Phase II Study of Brentuximab Vedotin in Relapsed/Refractory CD30-Positive B-Cell NHL

This study demonstrated a good response rate with single-agent B-vedotin for patients with relapsed/refractory DLBCL, a notably difficult-to-treat population. Response to B-vedotin was irrespective of the intensity of CD30 levels obtained by a high-resolution IHC staining method, a theme that is also emerging with other B-vedotin studies. This could be due in part to off-target effects.

The lack of correlation of response with CD30 expression could also be due to the fact that currently available staining techniques may not be highly sensitive and CD30 expression is probably higher than we can detect. In one interesting case, malignant cells were 1% CD30-positive by standard IHC but 30% to 40% CD30-positive with computer-assisted IHC using quantitative digital pathology image analysis.

We would not want to exclude patients from therapy because our technology cannot detect a certain marker. Hence, ongoing studies are evaluating the efficacy of B-vedotin in patients with CD30-negative disease.

Interview with Andrew M Evens, DO, MSc, February 12, 2014