5 Minute JournalClub

POST-ASH Issue 7, 2015

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CME Information

LEARNING OBJECTIVES

- Evaluate the efficacy and safety of rituximab and bortezomib as maintenance therapies for patients with MCL.
- Assess the results of recent Phase II studies evaluating the immunotherapeutic agents brentuximab vedotin and blinatumomab for the treatment of DLBCL.
- Appraise emerging clinical data from early-phase studies evaluating novel chemobiologic combination regimens for the treatment of TCL.
- Compare and contrast the benefits and risks of the novel up-front treatment approaches of rituximab combined with lenalidomide and obinutuzumab alone or in combination with CHOP for patients with FL.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

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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:

Stephen M Ansell, MD, PhD
Professor of Medicine
Division of Hematology
Mayo Clinic
Rochester, Minnesota

Research Funding: Bristol-Myers Squibb Company, Celldex Therapeutics.

CME Information (Continued)

Jonathan W Friedberg, MD, MMSc
Samuel Durand Professor of Medicine
Director, Wilmot Cancer Center
University of Rochester
Rochester, New York

Advisory Committee and Other Uncompensated Activities: Genentech BioOncology.

Craig Moskowitz, MD
Clinical Director, Division of Hematologic Oncology
Attending Physician, Lymphoma and Adult BMT Services
Member, Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University
New York, New York

Advisory Committee: Genentech BioOncology, Seattle Genetics; *Contracted Research:* Genentech BioOncology, GlaxoSmithKline, Merck, Seattle Genetics.

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Jeff Sharman, MD

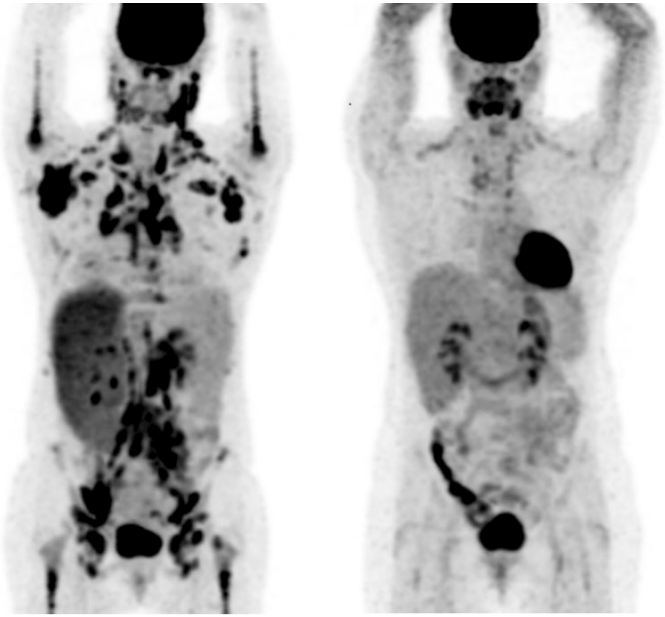
To begin a recent interview for our *Hematologic Oncology Update* audio series, Dr Jeff Sharman presented from his practice the fascinating and highly instructive case of a 57-year-old yoga instructor and motivational speaker with follicular lymphoma (FL). He started by noting that after migrating from Stanford to his current location in Eugene, Oregon, he quickly learned that a lot of people in the Pacific Northwest don't much like chemotherapy. I have heard this comment from others who practice in the area, and as a fan of the TV show Portlandia — where the characters regularly inquire about the detailed life histories of the chicken they are about to eat in a restaurant and the like — it really resonated. More importantly, however, this case relates to a critical issue in contemporary oncology: When is it acceptable to reach for an investigational therapy with encouraging Phase II data?

This patient — described as charismatic and dynamic — presented with bulky inguinal and cervical adenopathy and increased abdominal girth. She had previously consulted her naturopath, who palpated an enlarged spleen, and this led to a “second opinion” from Jeff.

Massive splenomegaly, hepatomegaly and extensive bulky adenopathy were observed on CT, and excisional biopsy of an inguinal node revealed Grade 3a FL. Flow cytometry confirmed peripheral blood involvement with mild anemia and thrombocytopenia. Because of the high tumor burden by GELF criteria and the possibility of occult transformation, Dr Sharman recommended R-CHOP (rituximab [R]/cyclophosphamide/ doxorubicin/vincristine/ prednisone). However, the patient absolutely refused chemotherapy, stating, in essence, “There’s no way you’re going to do that to me. I would rather die of my disease than go through what you’re talking about.”

Taking a deep breath, Jeff brought up the possibility of treatment without chemotherapy and the patient listened with rapt attention. R monotherapy seemed suboptimal given the extent of the disease, and he reluctantly raised the possibility of a regimen that is currently being studied by many research entities, the so-called “R squared” (R^2) combination of the immunomodulatory agent lenalidomide (len) with R.

The patient was more than interested, and Dr Sharman initiated 4 weekly doses of R followed by 4 more doses every 2 months as per the SAKK regimen along with len at 25 mg PO daily for 21 out of 28 days. In Jeff’s words, here is what happened: “She did develop some cytopenias, had a little bit of fatigue, but the disease simply melted away. It was really a quite



Before and after treatment with lenalidomide/rituximab

stunning response. Her adenopathy resolved within the first 8 weeks of therapy, and when we repeated the PET scan, she'd actually had a PET-negative complete response (CR). We even redid her marrow, which had cleared as well. Len was discontinued about the same time she completed R, and currently she's still in a CR and feeling great more than 4 years later."

As part of last week's email focused on multiple myeloma, we discussed the immune effects of len creating synergy with elotuzumab, and Dr Sharman suggests that a similar dynamic may be in play with R. He notes the suboptimal function of T cells in patients with B-cell cancers and emerging data suggesting that malignant cells are able to induce T-cell anergy/apathy.

Because the activity of R is in part through antibody-dependent cellular cytotoxicity, the effect may be blunted with a poorly functional T-cell component. For this reason, Jeff describes the R^2 combination as planning a road trip with a map (R) and a highly synergistic pot of coffee (len) — an analogy perhaps prompted by the beautiful outdoor scenes nearby. This combination is now being studied in the Intergroup Phase III RELEVANCE trial with the challenging randomization comparing R^2 to R-chemotherapy. The study is not restricted to patients with low tumor burden, and Dr Sharman hopes the result will be a new paradigm in this disease.

At a more macro level, this case illustrates the continuing dilemma that occurs every day in oncology practice — whether to recommend an intervention that involves the use of approved therapies but is the subject of ongoing investigation. In terms of Dr Sharman's yoga teacher, it could be that the same benefit would have accrued had only R been used, and it is also possible that in the long run she would have been better off embarking initially on an

R-chemotherapy regimen, although that seems unlikely given what happened. It is also true that patients ideally should receive new therapies as part of clinical trials, but that is not always feasible, and in the end, the clinician evaluating the patient hopefully makes the optimal recommendation for that individual. Any way you look at it, though, Dr Sharman's case is compelling, thought provoking and may be a sign of what is to come in the near future.

With that said, on this final ASH review we profile new data with R2 as well as a number of other intriguing papers focused on the management of FL, mantle-cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL) and T-cell lymphoma (TCL).

FL

- **More on R^2**

Whether trials like RELEVANCE will establish equal or greater efficacy of R^2 versus R-chemotherapy, it seems clear that len adds substantially to the benefit of R monotherapy. At ASH the randomized **Phase II SAKK 35/10 study** comparing R to R^2 as up-front therapy in 154 patients with FL mirrored the results of previous trials demonstrating a substantial improvement in overall response rate (45% versus 75% at week 10), although the impact on progression-free survival (PFS) and overall survival has not been established.

- **Obinutuzumab (O) with CHOP or bendamustine (benda) in untreated FL**

Not many people expected another anti-CD20 antibody to outperform R in any disease, but the encouraging results and FDA approval of O in chronic lymphocytic leukemia (CLL) led to the hope that similar benefits will be observed

with other B-cell cancers. As such, the Phase 1b GAUDI study **Phase 1b GAUDI study** investigated O-CHOP and O-benda with 2 years of O maintenance in 81 patients with FL. Although much of the emphasis of this effort was on safety, perhaps the most interesting finding was that the CR rate increased substantially during the 2 years of O maintenance (O-benda: 37% to 61%; O-CHOP: 35% to 70%).

Phase III research is ongoing to define not only the efficacy but also the tolerability of these regimens compared to R-based approaches — particularly with the prolonged B-cell depletion during maintenance O. In a related manner, next week at ASCO we will see the results from the Phase III GADOLIN study evaluating O-benda versus benda alone in patients with R-refractory indolent non-Hodgkin lymphoma. A press release has already hinted that the data will be positive, but what that means for clinical practice remains unknown.

Over the past year there has been a great deal of understandable excitement about the rapid changes that have occurred in the management of CLL, but it seems that a similar upheaval will soon take place in FL, for which O and len may join the recently approved PI3 kinase delta inhibitor idelalisib (Id) in the clinical algorithm. Interestingly, it is Dr Sharman's impression that many clinicians mistakenly believe that ibrutinib has good activity in FL despite the documented modest benefit and fail to realize that Id — the first agent in 6 years approved in FL — on the other hand is for real and has sparked a number of combination trials up front.

In this vein, although **one ASH paper** reported durable responses with BR-Id, another data set is a **cautionary tale** of the potential dangers of empiric attempts to combine agents outside a trial setting, specifically Phase I research

evaluating Id with R2 that had to be discontinued for unacceptable toxicity after 4 of the first 8 patients developed rash, fevers and hypotension suggestive of a cytokine release syndrome.

MCL

- **R maintenance after autologous stem cell transplant (ASCT)**

Previous work had demonstrated the benefit of R maintenance in older patients receiving induction therapy. However, the role of this approach in younger individuals undergoing ASCT was poorly understood, and at ASH we saw data from the **Phase III LYMA trial** evaluating 3 years of R maintenance in 257 patients who received 4 cycles of R-DHAP followed by ASCT. At 2 years, R maintenance increased the event-free survival from 81.5% to 93.2%, but no overall survival benefit has yet been observed, although the influx of new and effective therapies for relapsed/refractory (R/R) MCL will complicate the evaluation of this important endpoint. However, from a clinical perspective these findings are likely to be practice changing as many investigators view the delay in disease progression as enough benefit to justify the use of this strategy for many/most patients with MCL.

- **SWOG trial of R-CHOP/bortezomib (bor) with bor maintenance**

At ASH we saw the results of a **Phase II trial** in 65 evaluable patients exploring the role of the proteasome inhibitor bor (which now has a limited approval as up-front therapy in the disease) as maintenance treatment. The activity of this approach was viewed as encouraging (PFS: 2 years 62%; 5 years 28%) with acceptable tolerability, but how this will fit into the increasingly crowded MCL “space” remains to be determined.

DLBCL

- **Brentuximab vedotin (BV) with R-CHOP**

BV has demonstrated compelling activity as a single agent in R/R DLBCL even in patients with low CD30 expression, and this has led to interest in its use up front. A Phase II trial reported at ASH evaluated the **addition of BV to R-CHOP** in 33 patients with newly diagnosed DLBCL and reported excellent activity (overall response rate: 92%; CR: 58%) with an acceptable tolerability profile. Peripheral neuropathy (PN) was about what is typically observed with BV alone and only 5 patients required dose reductions as a result. Further research will define the future role of BV up front (as is being studied in Hodgkin lymphoma), probably without the concurrent use of vincristine, and how CD30 expression relates to treatment benefit.

- **Blinatumomab**

A recent issue of this series focusing on acute leukemias discussed the profound clinical activity with this bispecific T-cell engager antibody in acute lymphoblastic leukemia. However, the benefits of this novel agent — which engages CD3-positive cytotoxic cells leading to T-cell expansion and lysis of CD19-positive B cells — appears not to be confined solely to that disease, as objective responses have been previously reported in a number of patients with DLBCL. At ASH we saw **more evidence to substantiate** that claim as a Phase II study of 21 patients with R/R DLBCL demonstrated responses in 43%. More to come.

TCL

- **BV in mycosis fungoides (MF) and Sézary syndrome (SS)**

Although much has been previously made of the activity of BV in peripheral TCL (PTCL) — most relevantly anaplastic large cell lymphoma — it appears that this agent may also have utility in cutaneous TCL. Notably, we saw data from a **Phase II trial** of 30 evaluable patients, the majority of whom had advanced-stage MF or SS, that demonstrated a 70% response rate (mostly partial responses) with acceptable toxicity (mainly PN). While there was a suggested correlation of activity with CD30 levels and it remains to be seen whether an antitumor effect occurs without CD30 expression, these results will likely lead to the use of BV in these patients.

- **Romidepsin/CHOP in PTCL**

For quite some time investigators have been struggling to develop more impactful long-term treatment strategies for patients with PTCL, who generally face a bleak prognosis even with postinduction ASCT. In this regard there has been significant interest in moving novel agents with activity in the R/R setting into up-front regimens. This dynamic was on full display at ASH as we saw final results from a **Phase Ib/II report** of 35 evaluable patients who received romidepsin-CHOP as up-front therapy with a CR rate of 51% and 17% partial responses. These data are far from definitive but suggest the combination is safe, providing additional support for ongoing Phase III studies.

This concludes our ASH series, and as we saddle up and head out to the Windy City we encourage you to stay tuned this summer for virtual replays of the 4

evening satellite symposia focused on **lung cancer**, **GI cancers**, **myeloma/ lymphoma** and **breast cancer** we will be hosting at the annual ASCO extravaganza.

Neil Love, MD
Research To Practice
Miami, Florida

Rituximab plus Lenalidomide Improves the Complete Remission Rate in Comparison with Rituximab Monotherapy in Untreated Follicular Lymphoma Patients in Need of Therapy. Primary Endpoint Analysis of the Randomized Phase-2 Trial SAKK 35/10

Kimby E et al.

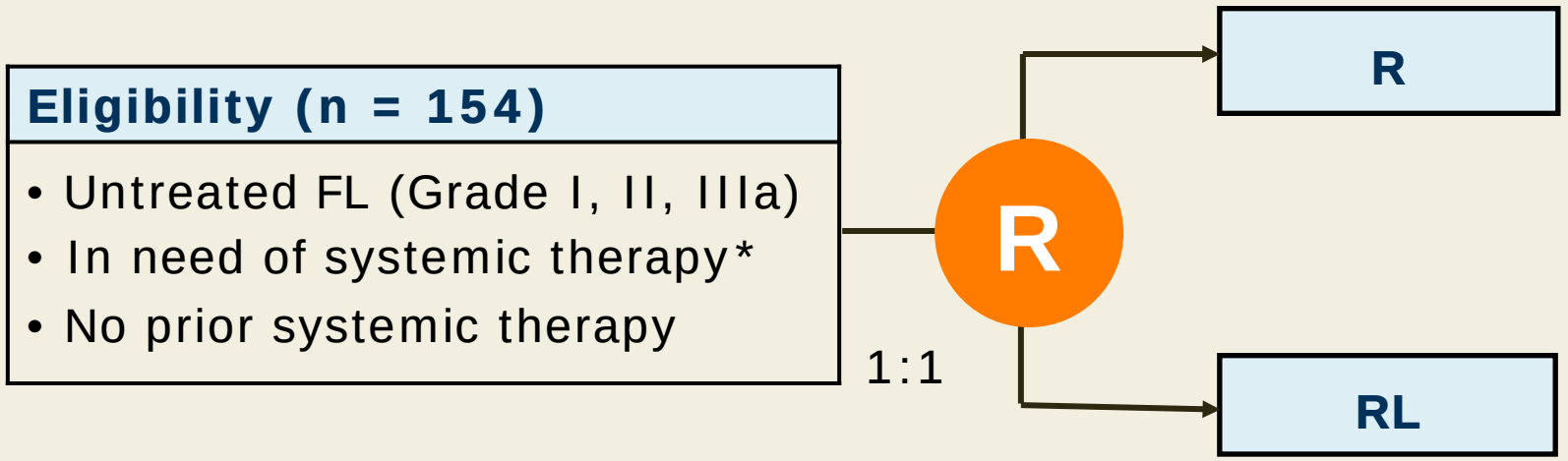
Proc ASH 2014;Abstract 799.

Background

- Previous studies showed that therapy with single-agent rituximab (R) can produce long-term remissions in a sizeable subset of patients with follicular lymphoma (FL).
- Overall survival with R was not inferior to chemo-immunotherapy.
- Promising results have also been reported with the combination of R and lenalidomide (L) for patients with untreated FL:
  - Complete response (CR) rate 87%, overall response rate (ORR) 98% (*Lancet Oncol* 2014;15:1311)
  - CR rate 72%, ORR 93% (*Proc ASCO* 2014;Abstract 8521)
- **Study objective**: To compare the activity of RL to that of single-agent R in the first-line treatment of FL.

Kimby E et al. *Proc ASH* 2014;Abstract 799.

Phase II SAKK 35/10 Design



R: 375 mg/m^2, IV, d1, wk 1, 2, 3, 4, 12, 13, 14 and 15

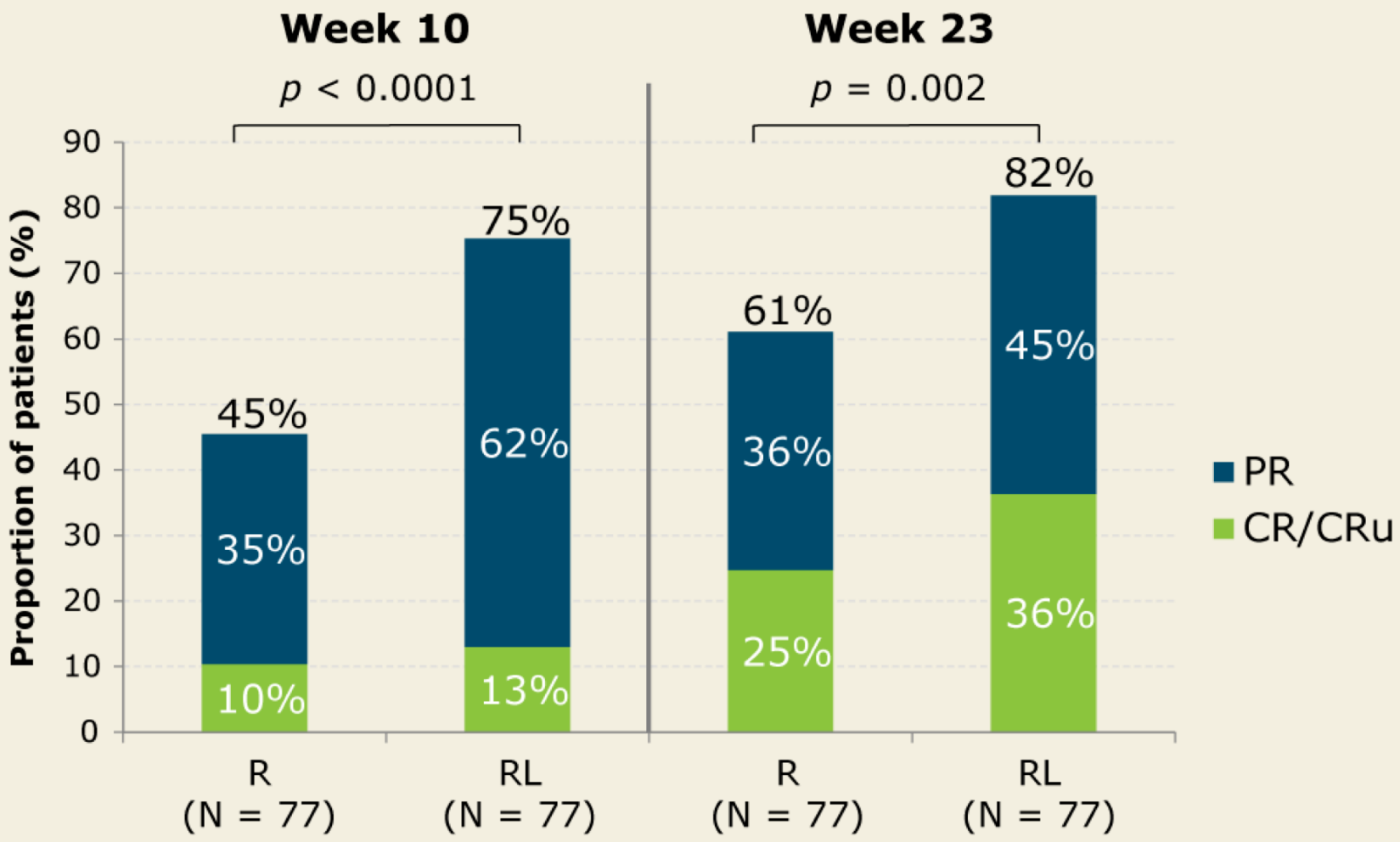
L: 15 mg, PO, 14 d before first R dose, continuously until 14 d after last R dose

- **Primary endpoint:** Complete response rate (CR/unconfirmed CR) at week 23

* At least 1 of the following: symptomatic enlarged lymph node, spleen or other FL manifestations, clinically significant progression over ≥6 mo, bulky disease ≥6 cm in long diameter, clinically significant progressive anemia/thrombocytopenia due to FL, B symptoms

Kimby E et al. *Proc ASH* 2014;Abstract 799.

Response at Weeks 10 and 23 (ITT)



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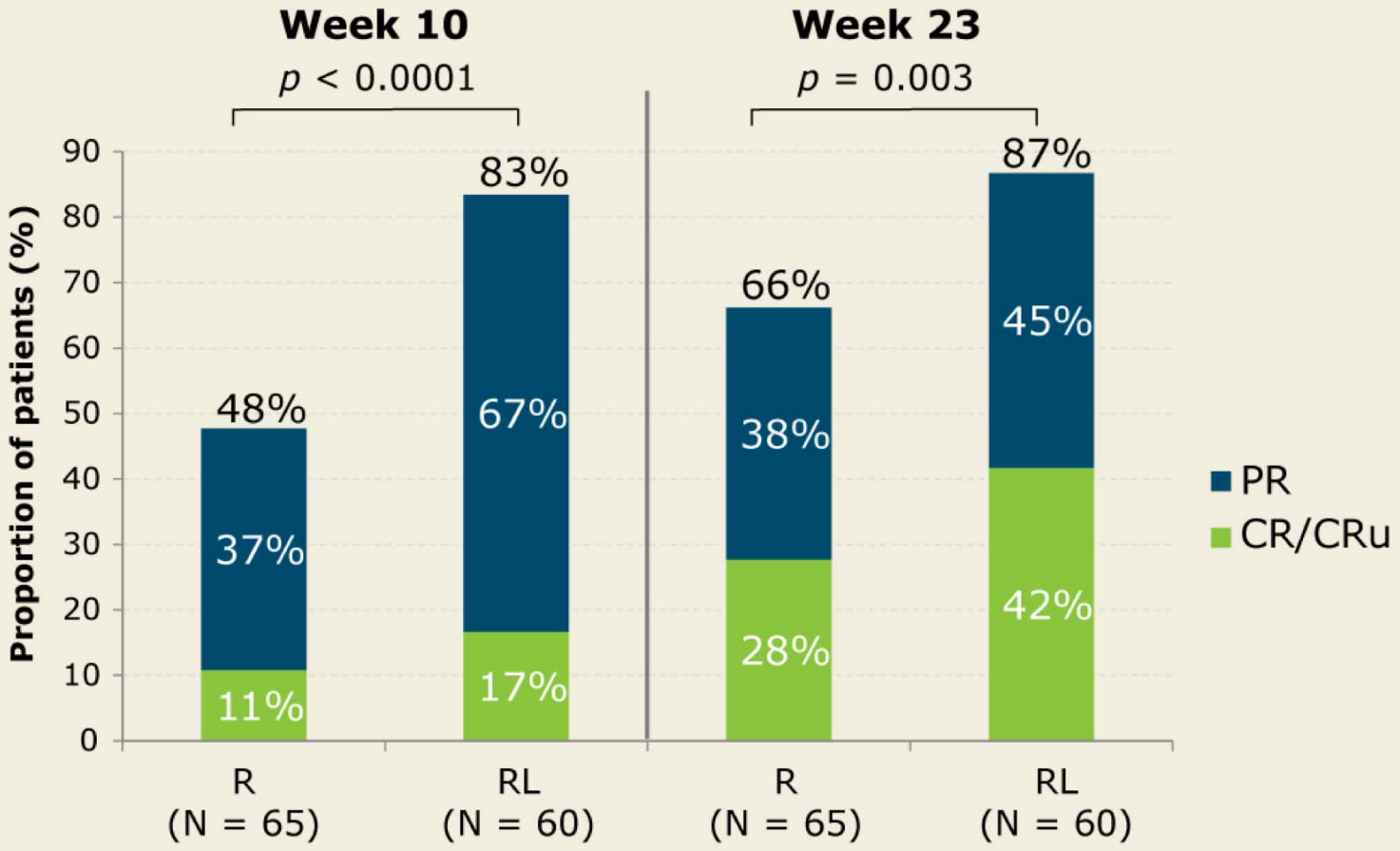
Response at Weeks 10 and 23 (PP population*)



* Fulfilled major inclusion criteria, received effective Tx, adequate tumor assessment at 1st or 2nd restaging or at failure

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Adverse Events

Select adverse events (Grade 3 or 4)	R (n = 76)	RL (n = 77)
Fatigue	1.3%	2.6%
Allergic reaction	0%	2.6%
Neutropenia	1.3%	19.5%
Thrombocytopenia	0%	3.9%
Rash maculopapular	0%	5.2%
Hypertension	3.9%	9.1%

One death due to progression: Review of initial biopsy showed FL Grade IIIb

Kimby E et al. *Proc ASH* 2014;Abstract 799.

Author Conclusions

- Addition of L to R resulted in a significantly better CR/ unconfirmed CR rate
  - Comparison to previous single-arm studies was difficult because of different treatment schedule and patient characteristics
  - L toxicity may be related to the continuous dosing
- Further follow-up will ascertain whether the response improvement will lead to a better time to next treatment, progression-free survival and overall survival

Kimby E et al. *Proc ASH* 2014;Abstract 799.

Investigator Commentary: Phase II SAKK 35/10 — RL in Untreated FL

This is a Phase II study from a European group that randomly assigned 154 patients with untreated FL to RL (R^2) versus R alone. Previous Phase II studies conducted in the United States by the Alliance and at MD Anderson had shown high response rates with the R^2 combination regimen.

The results of this study not surprisingly demonstrated an improved CR rate for patients with the combination compared to R alone. What was unexpected was that the CR rate with the R^2 regimen was relatively low compared to what had been reported in the US studies. It is difficult to understand the reason for that. It may be the way that CR was determined. These patients are being followed further.

The results are sobering and speak to why we need Phase III data before this regimen can be routinely used up front. An ongoing Phase III trial is randomly assigning patients with untreated FL to either the R^2 regimen or R with chemotherapy (NCT01476787). The results of that study will ultimately define how this regimen is used.

Interview with Jonathan W Friedberg, MD, MMSc, January 8, 2015

Obinutuzumab (GA101) in Combination with CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) or Bendamustine for the First-Line Treatment of Follicular Non-Hodgkin Lymphoma: Final Results from the Maintenance Phase of the Phase Ib GAUDI Study

Dyer MJS et al.

Proc ASH 2014;Abstract 1743.

Background

- Previously, the Phase Ib GAUDI trial showed that obinutuzumab (GA101), an anti-CD20 monoclonal antibody, has activity when used in combination with chemotherapy in relapsed/refractory follicular lymphoma (FL) (*Blood* 2013;122(7):1137).
- The open-label, randomized GAUDI trial also investigated the safety and efficacy of obinutuzumab with CHOP (O-CHOP) or with bendamustine (O-B) as induction therapy followed by obinutuzumab maintenance therapy for patients with previously untreated FL (*Proc ASH* 2012;Abstract 3686):
  - Data from the induction phase showed an overall response rate >92% in both arms.
  - The safety profile was consistent with that reported in the subset of patients with relapsed/refractory FL.

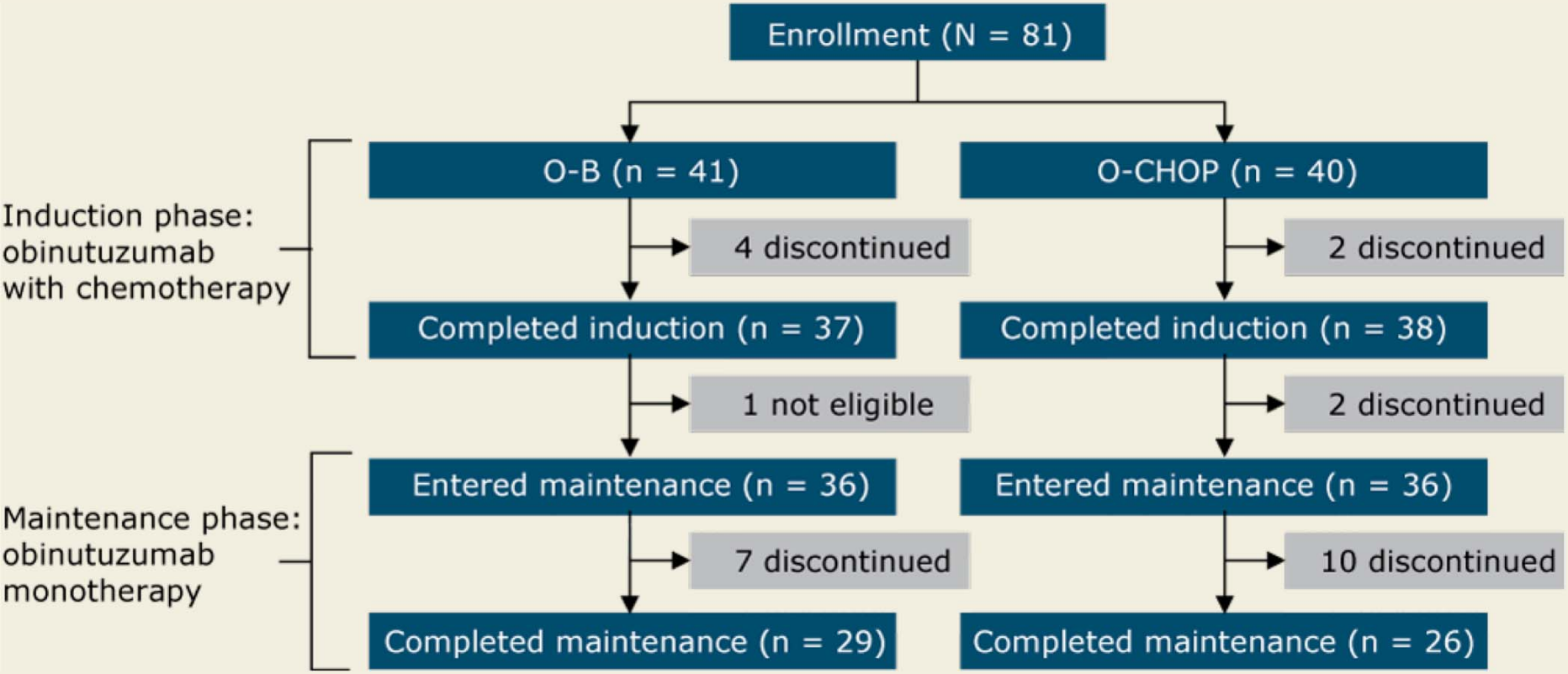
Dyer MJS et al. *Proc ASH* 2014;Abstract 1743.

Background (continued)

- **Study objective:** To report data from the maintenance phase of the GAUDI trial for patients with previously untreated FL who received maintenance obinutuzumab after responding to obinutuzumab-based induction chemotherapy.

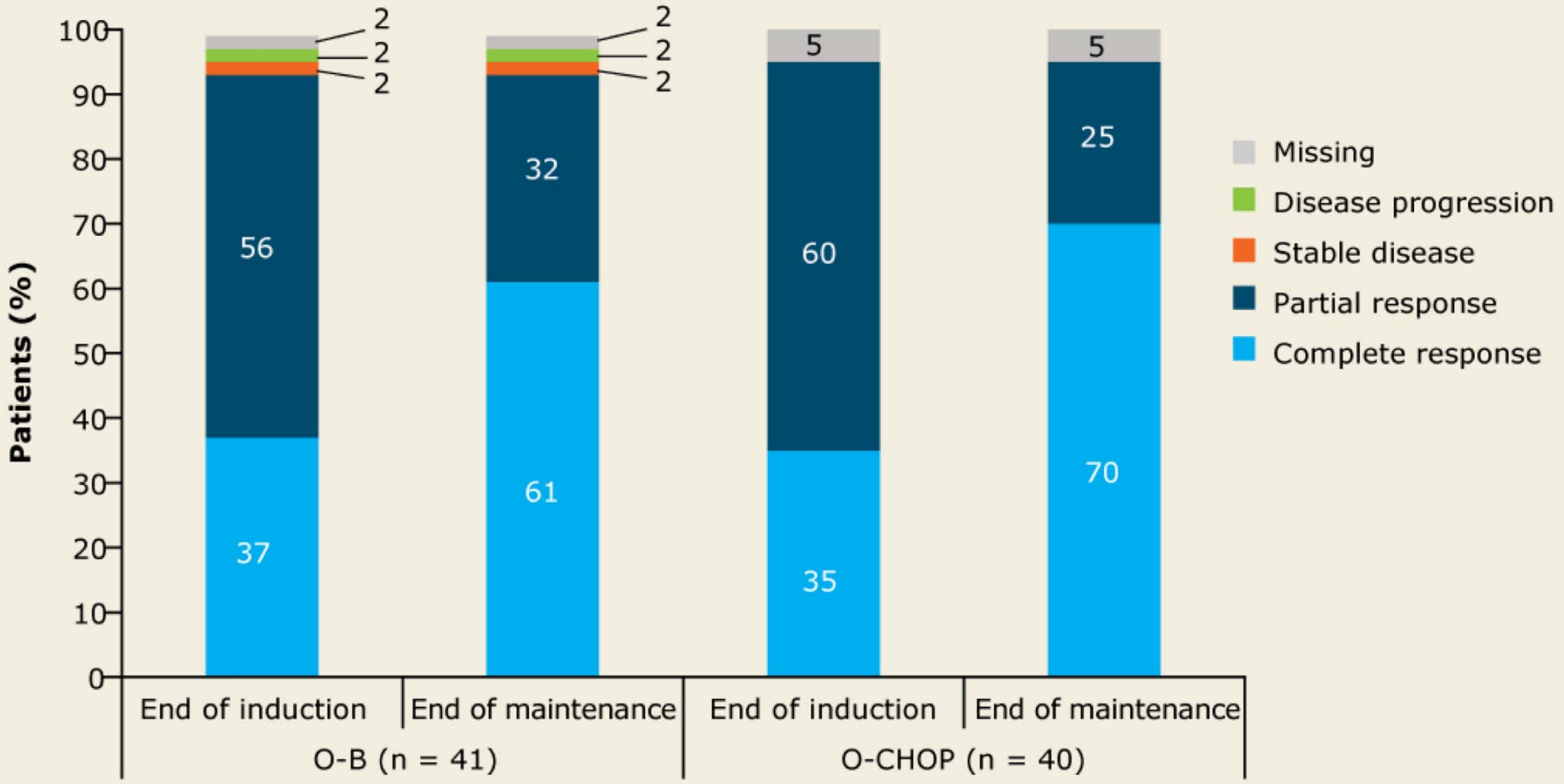
Dyer MJS et al. *Proc ASH* 2014;Abstract 1743.

Phase Ib GAUDI Trial: Patient Disposition



Dyer MJS et al. *Proc ASH* 2014;Abstract 1743.

Responses at the End of the Induction and Maintenance Periods by Induction Arm



With permission from Dyer MJS et al. *Proc ASH* 2014;Abstract 1743.

Efficacy Summary

- In the overall safety population, the complete response (CR) rate increased from the end of induction to the end of maintenance.
  - O-B: 37% to 61%
  - O-CHOP: 35% to 70%
- In the overall safety population at a median follow-up time of 32 months, 92% of patients on the O-B arm and 84% of patients on the O-CHOP arm were progression free.
  - Median progression-free survival from the start of induction was not reached
  - 10 patients experienced progressive disease:
    - O-B, n = 4
    - O-CHOP, n = 6, including 1 transformation to diffuse large B-cell lymphoma

Dyer MJS et al. *Proc ASH* 2014;Abstract 1743.

B-Cell Depletion After End of Treatment (EOT) by Induction Arm

Percent B-cell depletion	O-B	O-CHOP
At EOT (n = 41, 39)	100%	100%
EOT to 6 mo follow-up after EOT (n = 31, 30)	100%	100%
6-9 mo follow-up after EOT (n = 10, 12)	100%	100%
9-12 mo follow-up after EOT (n = 7, 5)	86%	80%
12-18 mo follow-up after EOT (n = 5, 4)	100%	50%
18-24 mo follow-up after EOT (n = 2, 2)	50%	50%

Dyer MJS et al. *Proc ASH* 2014;Abstract 1743.

Adverse Events (AEs) During Maintenance by Induction Arm

Event (all grades)	O-B (n = 36)	O-CHOP (n = 36)
Infections and infestations	72%	56%
Upper respiratory tract infection	11%	14%
Urinary tract infection	11%	8%
Gastrointestinal disorders	31%	25%
Diarrhea	11%	8%
Respiratory, thoracic and mediastinal disorders	33%	19%
Cough	17%	11%

- Grade ≥3 AEs:
  - Infections and infestations: 17% (O-B) versus 14% (O-CHOP)
  - Neutropenia 14% (O-B) versus 0% (O-CHOP)

Dyer MJS et al. *Proc ASH* 2014;Abstract 1743.

Treatment-Related AEs During Maintenance by Induction Arm

Event (all grades)	O-B (n = 36)	O-CHOP (n = 36)
Infections and infestations	22%	39%
Lower respiratory tract infection	3%	11%
Urinary tract infection	6%	8%
Respiratory tract infection	3%	8%
Gastrointestinal disorders	14%	11%
Nausea	6%	6%
Respiratory, thoracic and mediastinal disorders	6%	17%

Dyer MJS et al. *Proc ASH* 2014;Abstract 1743.

Author Conclusions

- Maintenance treatment with obinutuzumab monotherapy after obinutuzumab/chemotherapy induction was generally well tolerated.
  - No new safety signals emerged during maintenance treatment with obinutuzumab.
  - Infections (Grade ≥3) occurred in 17% (O-B) and 14% (O-CHOP) of patients.
  - Clinically relevant neutropenia occurred in 14% of patients who received O-B induction but was not observed in patients who received O-CHOP induction.
  - Median IgG, IgA and IgM levels remained within the normal range during maintenance therapy (data not shown).

Dyer MJS et al. *Proc ASH* 2014;Abstract 1743.

Author Conclusions (continued)

- CR rates at the end of maintenance were high (60% for O-B vs 70% for O-CHOP) and most patients were progression free at 32 months (92% with O-B vs 84% with O-CHOP).
  - In the Phase III PRIMA study for patients with untreated FL who received induction rituximab/chemotherapy followed by rituximab maintenance, 72% achieved CR at the end of maintenance and 75% were progression free at 36 months (Salles G et al. *Lancet* 2011;377(9759):42).
- The Phase III GALLIUM trial (NCT01332968) is now investigating obinutuzumab- versus rituximab-based induction chemotherapy followed by immunotherapy maintenance for patients with untreated indolent non-Hodgkin lymphoma.

Dyer MJS et al. *Proc ASH* 2014;Abstract 1743.

Investigator Commentary: GAUDI — Final Results from the Maintenance Phase of a Phase Ib Trial of O-B versus O-CHOP as First-Line Therapy for FL

The hope was that this study would demonstrate benefit with an obinutuzumab-based chemotherapy combination in comparison to published data with rituximab-based chemotherapy for patients with untreated FL (*Lancet* 2011;377:42). Of a total of 81 patients on the study, 41 received O-B and 40 received O-CHOP. The main focus of this analysis was safety, and there did not seem to be a whole lot of difference in toxicity to what you might expect with rituximab combinations.

The investigators followed these patients for a prolonged period of time and demonstrated prolonged B-cell depletion. Whether this will have implications in the long term for some of the sinopulmonary infections and other side effects we sometimes observe with rituximab maintenance remains to be seen. But this study does lay the groundwork for the ongoing Phase III GALLIUM study, which is appropriately evaluating induction chemoimmunotherapy with either rituximab or obinutuzumab followed by immunotherapy maintenance for up to 2 years.

Interview with Jonathan W Friedberg, MD, MMSc, January 8, 2015

Rituximab Maintenance versus Wait and Watch After Four Courses of R-DHAP Followed by Autologous Stem Cell Transplantation in Previously Untreated Young Patients with Mantle Cell Lymphoma: First Interim Analysis of the Phase III Prospective LYMA Trial, a LYSA Study

Le Gouill S et al.

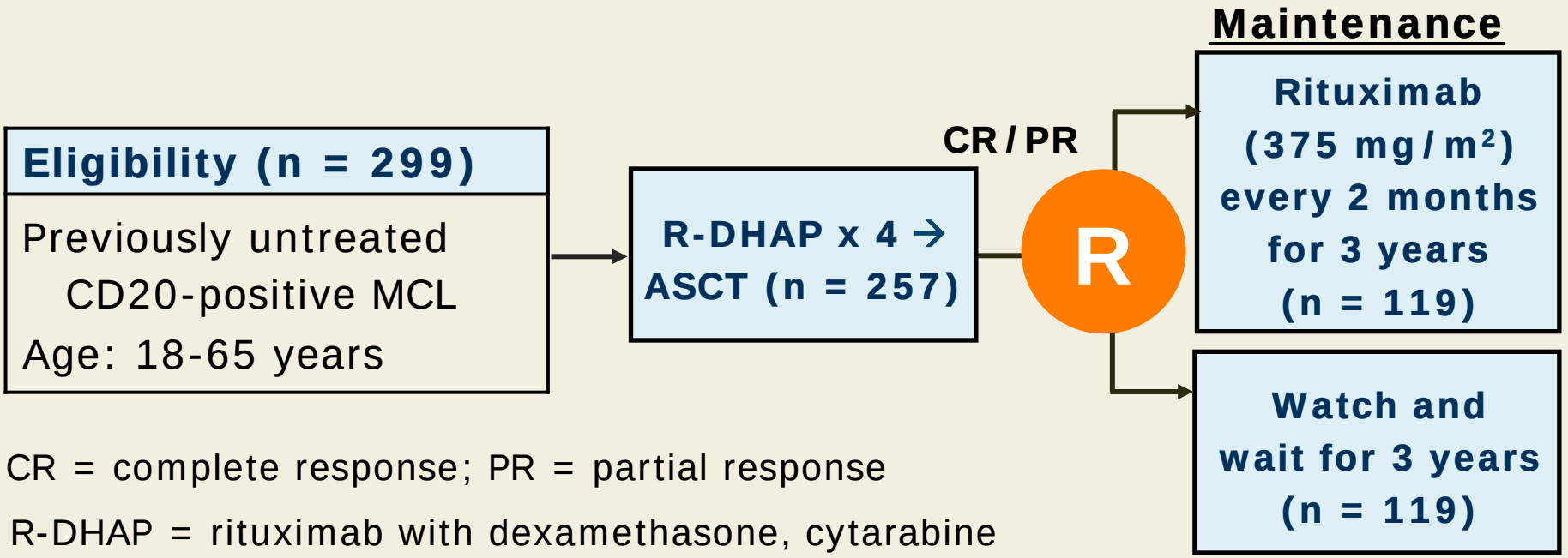
Proc ASH 2014;Abstract 146.

Background

- Standard therapy for patients with mantle-cell lymphoma (MCL) consists of CHOP chemotherapy combined with rituximab, though only a minority of patients experience a complete remission.
- Although autologous stem cell transplantation (ASCT) can provide a high response rate for young patients with MCL, it may not be sufficient to cure MCL even after up-front ASCT (*Ann Hematol* 2014;93:233).
- Previously, it was shown that rituximab maintenance after induction therapy is effective for older patients with MCL (*NEJM* 2012;367:520).
- **Study objective:** To report the first planned interim analysis of the efficacy of rituximab maintenance therapy in younger patients with MCL after first-line ASCT.

Le Gouill S et al. *Proc ASH* 2014;Abstract 146.

Phase III LYMA Trial Design (NCT00921414)



CR = complete response; PR = partial response

R-DHAP = rituximab with dexamethasone, cytarabine and cisplatin

- Patients who did not achieve ≥PR after DHAP could receive 4 additional courses of R-CHOP
- **Primary endpoint:** Event-free survival (EFS) at 4 years after randomization

Le Gouill S et al. *Proc ASH* 2014;Abstract 146.

Baseline Characteristics

Characteristic	n = 299
Median age (range)	57 years (27-65)
Male	236 (78.9%)
Low MIPI score	159 (53.2%)
Intermediate MIPI score	82 (27.4%)
High MIPI score	58 (19.4%)

Le Gouill S et al. *Proc ASH* 2014;Abstract 146 (Abstract only).

Treatment Outcomes from Study Entry (Median Follow-Up 35.8 Months)

Response rate	
CR/CRu rate before ASCT (n = 299)	81.4%
CR/CRu rate after ASCT (n = 257)	92%
Survival	
Median progression-free survival (PFS)	Not reached
Estimated 3-year PFS	73.7%
Median overall survival (OS)	Not reached
Estimated 3-year OS	82.6%

CRu = unconfirmed CR

Le Gouill S et al. *Proc ASH* 2014;Abstract 146 (Abstract only).

Survival Outcomes from Randomization (Median Follow-Up 29.7 Months)

Survival	Rituximab (n = 119)	Watch and Wait (n = 119)	Hazard ratio	*p*-value
Two-year EFS	93.2%	81.5%	2.1	0.015
Two-year OS	93.4%	93.9%	NR	NS

NR = not reported; NS = not significant

- PFS was statistically different between the 2 study arms ($p = 0.015$).

Le Gouill S et al. *Proc ASH* 2014;Abstract 146 (Abstract only).

Author Conclusions

- This planned interim analysis of the LYMA trial showed that 3 years of rituximab maintenance therapy after receiving R-DHAP followed by ASCT as first-line treatment for young patients with MCL significantly improves both EFS and PFS.
- Therefore, as reported for elderly patients with MCL, the LYMA trial demonstrates that rituximab should be used as maintenance therapy after ASCT, and it provides the rationale for a new standard therapy in MCL.

Le Gouill S et al. *Proc ASH* 2014;Abstract 146 (Abstract only).

Investigator Commentary: First Planned Interim Analysis of the Results from the Phase III LYMA Trial of R-DHAP Followed by ASCT for Patients with Previously Untreated MCL

In many respects, this study is based on already existing data from elderly patients with MCL, for whom an R-CHOP-like approach followed by rituximab maintenance is thought to be a standard therapy (Kluin-Nelemans HC et al. *NEJM* 2012;367(6):520-31). Because patients tend to experience relapsed disease, these investigators administered 4 cycles of R-DHAP followed by ASCT and then assessed the benefits of administering 3 years of rituximab maintenance for these younger patients. The data presented were analyzed close to the end of maintenance.

The 2-year EFS was better with rituximab than with the watch and wait approach, at 93.2% versus 81.5%. This is not entirely surprising in that you're continuously treating one group versus completing treatment and now observing the second group. The investigators concluded that, similar to what has been reported for elderly patients with MCL, the use of rituximab as a maintenance strategy after ASCT provides a rationale for a new standard therapy for younger patients with MCL.

Interview with Stephen M Ansell, MD, PhD, January 20, 2015

continued

Investigator Commentary: First Planned Interim Analysis of the Results from the Phase III LYMA Trial of R-DHAP Followed by ASCT for Patients with Previously Untreated MCL (continued)

Typically in my practice we would observe patients after the completion of therapy and ASCT. However, the results of this study make a strong case for one further therapeutic option, which is to continue to treat with maintenance rituximab. Because patients with MCL are destined, in many respects, to develop progressive disease, everything one can do to keep the disease in remission for as long as possible is reasonable. Certainly the addition of maintenance approaches such as a maintenance rituximab is worth considering, particularly for younger patients, for whom, obviously, keeping the disease in remission is a good thing.

Interview with Stephen M Ansell, MD, PhD, January 20, 2015

Phase II Trial of R-CHOP plus Bortezomib Induction Therapy Followed by Bortezomib Maintenance for Previously Untreated Mantle Cell Lymphoma: SWOG 0601

Till BG et al.

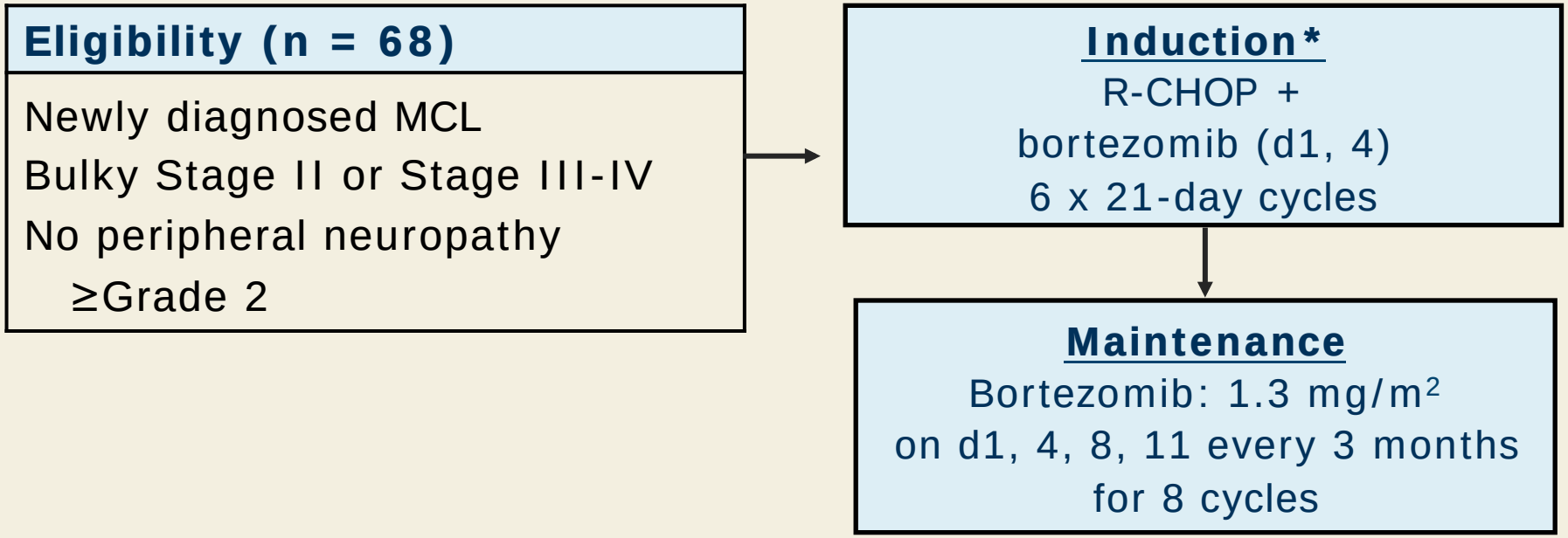
Proc ASH 2014;Abstract 149.

Background

- Mantle-cell lymphoma (MCL) is incurable with current standard therapies, and there is no consensus for the optimal induction regimen.
- Bortezomib, a 26S proteasome inhibitor, is active as a single agent in MCL, and preclinical data suggest that its combination with chemotherapy may be synergistic.
- A recent randomized trial found that maintenance rituximab (R) after R-CHOP led to a survival benefit, suggesting that maintenance strategies are worth investigating in MCL (*NEJM* 2012;367:520).
- **Study objective:** To evaluate the safety and efficacy of combining bortezomib with R-CHOP as induction therapy followed by bortezomib maintenance for 2 years.

Till BG et al. *Proc ASH* 2014;Abstract 149.

Phase II SWOG-S0601 Trial Design



* R: 375 mg/m^2 + CHOP: 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, 1.4 mg/m^2 vincristine, 100 mg prednisone daily for 5 days and 1.3 mg/m^2 bortezomib

- Patients achieving at least stable disease after induction were eligible for bortezomib maintenance therapy.
- **Primary endpoint:** 2-year progression-free survival (PFS)
- The study was designed to estimate the 2-year PFS rate within 13% (95% CI).

Till BG et al. *Proc ASH* 2014;Abstract 149.

Baseline Characteristics

Characteristic	n = 68
Median age	61 years (36-85)
Male	80%
Bulky disease	15%
Stage III-IV disease	98%
Elevated lactate dehydrogenase	37%
MIPI score: Low risk	45%
Intermediate risk	43%
High risk	12%

Till BG et al. *Proc ASH* 2014;Abstract 149 (Abstract only).

Survival Outcomes

Survival	n = 65*
2-year PFS	62%
5-year PFS	28%
2-year overall survival (OS)	85%
5-year OS	66%

* Of the 68 patients enrolled on the study, 65 were evaluable.

- With a median follow-up time of 5.9 years, 52 patients have experienced disease progression or died.
- Based on prior studies, the historical 2-year PFS rate for R-CHOP alone in this setting is 30%.

Till BG et al. *Proc ASH* 2014;Abstract 149 (Abstract only).

Correlative Studies

- MIPI scores were significantly associated with outcome.
  - 2-year PFS was:
    - Low risk: 72%
    - Intermediate risk: 61%
    - High risk: 25%
- However, in a regression analysis to identify prognostic factors associated with a ≥5-year PFS, the only significant factor found was the absence of splenic involvement.
- Additional correlative studies are planned to identify predictive biological markers associated with long-term remissions.

Till BG et al. *Proc ASH* 2014;Abstract 149 (Abstract only).

Adverse Events (AEs)

- In general, the study treatment was well tolerated.
  - During induction therapy:
    - Grade 4 hematologic AEs: 48%
    - Grade 3 nonhematologic AEs: 38.5%
      - Peripheral neuropathy: 8%
    - Grade 4 nonhematologic AEs: 6%
  - During maintenance therapy:
    - Grade 3 nonhematologic AEs: 13%
      - Peripheral neuropathy: 2%
- There was no Grade 4 peripheral neuropathy.
- Deaths due to AEs possibly related to therapy (n = 1):
  - Complete heart block in the setting of pneumonia and acute respiratory distress syndrome

Till BG et al. *Proc ASH* 2014;Abstract 149 (Abstract only).

Author Conclusions

- The combination of R-CHOP with bortezomib followed by maintenance bortezomib appears to improve outcomes compared to historical data with R-CHOP alone.
  - The historical 2-year PFS rate was doubled, with nearly one third of patients achieving a PFS of ≥5 years.
- These results suggest that the addition of bortezomib to induction chemotherapy and/or maintenance is promising and warrants further exploration.

Till BG et al. *Proc ASH* 2014;Abstract 149 (Abstract only).

Investigator Commentary: The Phase II SWOG-S0601 Trial of R-CHOP and Bortezomib Induction Followed by Bortezomib Maintenance in Previously Untreated MCL

In this study, patients received R-CHOP/bortezomib followed by maintenance bortezomib. Maintenance therapy included about 2 weeks of treatment every 3 months for approximately 2 years. Being a Phase II trial, it's not randomized, but it includes a fairly sizable cohort of patients. The results are encouraging, with an estimated 2-year PFS rate of 62% and a 2-year OS rate of 85%. Almost a third of the patients had a PFS of 5 years or longer. The study made the case that this regimen can be safely administered and is reasonably well tolerated, and the results look promising. Before this becomes something that we would standardly practice in the clinic, it would require a randomized trial.

A variety of different agents are vying for a position in the management of MCL. However, one would need to see pretty significant and dramatic benefits for an agent to become the standard therapy. Although there may be a modest benefit with some agents and a significantly greater benefit with others, the agent that shows a dramatic improvement, particularly in terms of OS benefit, would clearly end up being the winner.

Interview with Stephen M Ansell, MD, PhD, January 20, 2015

Brentuximab Vedotin in Combination with RCHOP as Front-Line Therapy in Patients with DLBCL: Interim Results from a Phase 2 Study

Yasenchak CA et al.

Proc ASH 2014;Abstract 1745.

Background

- Treatment outcomes for patients with diffuse large B-cell lymphoma (DLBCL) have improved in the past decade with the addition of rituximab to CHOP or CHOP-like chemotherapy regimens.
- However, patients with high-intermediate- or high-risk DLBCL have relatively poor outcomes with the standard R-CHOP regimen (*JCO* 2010;28:2373; *Proc ASCO* 2011;Abstract 8016).
- Brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate, has demonstrated compelling activity as a single agent in patients with relapsed or refractory DLBCL, even those with low CD30 expression (*Blood* 2015;125:1394).
- **Study objective:** To evaluate the preliminary activity and safety results of BV in combination with R-CHOP as front-line therapy for patients with high-intermediate/high-risk DLBCL.

Yasenchak CA et al. *Proc ASH* 2014;Abstract 1745.

Ongoing Phase II Trial Design — Part I (NCT01925612)

Eligibility

Treatment-naïve DLBCL or Grade IIIb follicular lymphoma

IPI score ≥3 (>60 y) or age-adjusted IPI (aaIPI) score of 2 or 3 (≤60 y)

No history of indolent lymphoma

R

BV 1.2 mg/kg IV + R-CHOP

BV 1.8 mg/kg IV + R-CHOP

BV was administered on d1, q3wk for up to 6 cycles.

- **Primary endpoint:** Complete response (CR) rate at the end of treatment (EOT) and the type, incidence and severity of adverse events.
- **Secondary endpoints** include objective response rate (ORR), progression-free survival and overall survival.

Yasenchak CA et al. *Proc ASH* 2014;Abstract 1745; www.clinicaltrials.gov.

Baseline Characteristics

Characteristic	All patients (n = 33)*
Median age (range)	66 years (21-81)
High-intermediate risk (IPI 3, aaIPI 2)	64%
High risk (IPI 4-5, aaIPI 3)	36%
Stage IV disease	73%
ECOG PS 2	33%

* At the time of the planned interim analysis, 33 patients were enrolled.

- BV at 1.2 mg/kg + R-CHOP (n = 17)
- BV at 1.8 mg/kg + R-CHOP (n = 16)

Yasenchak CA et al. *Proc ASH* 2014;Abstract 1745 (Abstract only).

Preliminary Efficacy Results

Response	All patients (n = 12)*
ORR	11 (92%)
CR	7 (58%)
Partial response (PR)	4 (33%)
Progressive disease (PD)	1 (8.3%)

* At the time of interim analysis, a total of 12 patients (6 patients on each arm) had completed EOT.

- The patient with PD subsequently died.
- Patients with PR had a median reduction of baseline tumor size of 84% (range, 92% to 83%).
- The only patient with follow-up after EOT converted from PR to CR without subsequent therapy.

Yasenchak CA et al. *Proc ASH* 2014;Abstract 1745 (Abstract only).

Adverse Events

- Treatment-emergent events occurring in ≥30% of patients (26/33) were:
  - Nausea
  - Diarrhea
  - Peripheral sensory neuropathy
  - Fatigue
  - Decreased appetite
- Grade ≥3 events occurring in more than 2 patients were febrile neutropenia and neutropenia.
- Three patients (12%) had dose reductions due to febrile neutropenia.
- One patient who received 1.2 mg/kg BV + R-CHOP discontinued the study drug due to thrombocytopenia.

Yasenchak CA et al. *Proc ASH* 2014;Abstract 1745 (Abstract only).

Peripheral Neuropathy Events

- Events of peripheral neuropathy (PN) occurred equally per arm (46%) and were generally Grade 1 or 2 (15% and 23%, respectively); events were of similar grade across dose levels.
- The median time to onset of any grade of PN was 6 weeks (range, 2 to 10 weeks).
- Five patients (19%) had dose reductions due to PN.

Yasenchak CA et al. *Proc ASH* 2014;Abstract 1745 (Abstract only).

Author Conclusions

- BV doses of 1.2 or 1.8 mg/kg in combination with R-CHOP demonstrated manageable toxicity in patients with newly diagnosed DLBCL.
  - The incidence of PN was similar to that with single-agent administration of BV (*JCO* 2012;30:2183) and R-CHOP alone (*Lancet* 2013;381:1203; *Blood* 2014;123:2944).
- In 12 patients with response-assessable, high-intermediate- and high-risk DLBCL, BV + R-CHOP showed encouraging antitumor activity:
  - ORR = 92%
  - CR rate = 58%

Yasenchak CA et al. *Proc ASH* 2014;Abstract 1745 (Abstract only).

Investigator Commentary: Interim Results of the Phase II Trial of Front-Line BV and R-CHOP for Patients with DLBCL

Previous studies of BV alone in relapsed DLBCL showed promising response rates for patients with CD30 expression and, interestingly, even for those lacking CD30 expression as detected by immunohistochemistry. So the sense was that it may be beneficial to add BV to R-CHOP in a Phase II trial to determine whether this significantly benefits patients. Specifically, patients with high-risk or high-intermediate-risk disease were randomly assigned to receive either 1.2 or 1.8 mg/kg of BV in combination with R-CHOP.

Overall, therapy was well tolerated. Although increased PN was of concern, it was manageable. The ORR was encouraging at 92% across both treatment arms, with a CR rate of 58%. This seemed to be a lot better than what one would expect from standard R-CHOP chemotherapy alone. Certainly the addition of BV to R-CHOP looks promising. The study is being expanded to include the use of BV without vincristine (R-CHP). It will be important to know if the addition of BV can replace the beneficial effects of vincristine.

Interview with Stephen M Ansell, MD, PhD, January 20, 2015

Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma with the Bispecific T-Cell Engager (BiTE®) Antibody Construct Blinatumomab: Primary Analysis Results from an Open-Label, Phase 2 Study

Viardot A et al.

Proc ASH 2014;Abstract 4460.

Background

- Treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) is challenging, with little progress in recent years.
- Blinatumomab, a bispecific T-cell engager (BiTE®) antibody construct, engages CD3-positive cytotoxic T cells, resulting in T-cell expansion and lysis of CD19-positive B cells.
- In a prior Phase I study, blinatumomab treatment resulted in an overall response rate (ORR) of 55% in a subset of patients with DLBCL (*Proc ASH* 2011;Abstract 1637).
- **Study objective:** To compare stepwise versus flat dosing of blinatumomab and evaluate its efficacy in patients with relapsed/refractory DLBCL.

Viardot A et al. *Proc ASH* 2014;Abstract 4460.

Ongoing Phase II Study Design (NCT01741792)

Eligibility (n = 25)

DLBCL refractory to first or later therapy or relapsed after auto-HSCT or relapsed and ineligible for auto-HSCT

→ **Blinatumomab, IV**

Auto-HSCT = autologous hematopoietic stem cell transplant

- Nine, 2 and 14 patients enrolled in cohorts I, II and III, respectively.
- Stage 1: Stepwise dosing (cohort I: 9, 28 and 112 µg/d) compared to constant dosing of 112 µg/d (cohort II).
- Based on the benefit/risk assessment from stage 1, stepwise dosing was chosen for cohort III in stage 2.
- Patients achieving response after 8 weeks could receive a 4-week consolidation cycle after a 4-week treatment-free period.
- All patients received prophylactic dexamethasone.
- **Primary endpoint:** ORR

Viardot A et al. *Proc ASH* 2014;Abstract 4460; www.clinicaltrials.gov.

Patient Characteristics

Characteristic	N = 25
Median age (range)	66 years (34-85)
Men	56%
Patients who had received prior auto-HSCT	7 (28%)
Median duration of exposure for stepwise dosing*	46.8 days

* Cohorts I and III

- Blinatumomab was received as a fourth-line systemic therapy after a median (range) of 3 (1-7) prior treatments.

Viardot A et al. *Proc ASH* 2014;Abstract 4460 (Abstract only).

Response to Blinatumomab

Response	n = 21*
ORR	43%
Complete response	4 (19%)
Partial response	5 (24%)

* Evaluable patients (cohort I, n = 7; cohort II, n = 1; cohort III, n = 13)

- Four patients were not evaluable for ORR due to early treatment discontinuation (<1 week on target dose in the absence of disease progression): 1 due to investigator's decision and 3 due to adverse events.
- All patients who responded did so within the first 8-week cycle.
- Among responders (n = 9), the median duration of response was 11.6 months.

Viardot A et al. *Proc ASH* 2014;Abstract 4460 (Abstract only).

Adverse Events

- All patients (n = 25) experienced ≥1 adverse event (AE).
- The most common AEs were tremor (52%), pyrexia (44%), diarrhea (24%), fatigue (24%), edema (24%) and pneumonia (24%).
- Grade 3 and 4 AEs occurred in 96% and 20% of patients, respectively.
- Serious AEs occurred in 92% of patients.
  - Most common: pneumonia (24%), device-related infection (16%) and pyrexia (16%)
- Seven patients (cohort I, n = 3; cohort II, n = 2; cohort III, n = 2) had Grade 3 neurologic AEs.
  - Grade 3 AEs occurring in >1 patient were disorientation, encephalopathy, aphasia and epilepsy (n = 2 each).

Viardot A et al. *Proc ASH* 2014;Abstract 4460 (Abstract only).

Adverse Events (continued)

- No Grade 4 or 5 neurologic events were reported.
- Fourteen patients have died (cohort I, n = 5; cohort II, n = 1; cohort II, n = 8):
  - 11 due to disease progression, 1 due to cardiogenic shock, 1 due to organ failure after transplantation; no cause of death was reported for 1 patient

Viardot A et al. *Proc ASH* 2014;Abstract 4460 (Abstract only).

Author Conclusions

- In this Phase II study, a stepwise dosing regimen (9, 28 and 112 µg/day) was established as the preferred dosing for blinatumomab in DLBCL.
- Treatment with blinatumomab showed an acceptable safety profile and resulted in objective and durable responses in heavily pretreated relapsed/refractory DLBCL.

Viardot A et al. *Proc ASH* 2014;Abstract 4460 (Abstract only).

Investigator Commentary: Primary Analysis of a Phase II Study of Blinatumomab for Relapsed/Refractory DLBCL

Blinatumomab is a bispecific antibody that binds to CD19 on B cells and CD3 on T cells. It brings these cells into close proximity and promotes their activation. In patients with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL), the results have been promising, leading to approval of blinatumomab in that setting.

In this study, the investigators assessed the efficacy of blinatumomab in patients with disease progression on standard approaches, including auto-HSCT. One of the goals was to determine the optimal dose of blinatumomab. Twenty-five patients were enrolled, with a number of cohorts and dose levels. In the 21 patients who were evaluable for responses, an ORR of 43% was reported with 4 complete responses and 5 partial responses. So in patients who haven't responded to available therapies for DLBCL, a high response rate, particularly 4 complete responses, I believe is promising and encouraging.

There are some toxicities, however. Common side effects included immune-related adverse events like fever, diarrhea, fatigue and infections. However, based on experience with other diseases like ALL, I believe this agent has real promise for relapsed/refractory DLBCL.

Interview with Stephen M Ansell, MD, PhD, January 20, 2015

Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides or Sezary Syndrome: Final Results Show Significant Clinical Activity and Suggest Correlation with CD30 Expression

Kim YH et al.

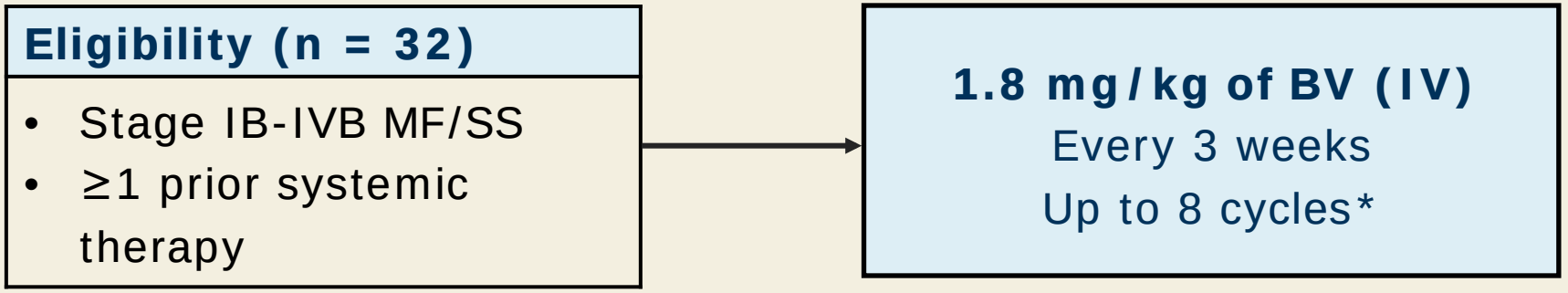
Proc ASH 2014;Abstract 804.

Background

- While CD30 expression on malignant cells in Hodgkin lymphoma and anaplastic large cell lymphoma is uniform, in mycosis fungoides/Sézary syndrome (MF/SS), the CD30 expression is more variable.
- Previously, we reported that brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate, has clinical activity in MF/SS across all CD30 expression levels (*Proc ASH* 2012;Abstract 797).
- **Study objective:** To report the updated clinical data and present new biomarker and correlative tissue analyses from the study of BV in MF/SS.

Kim YH et al. *Proc ASH* 2014;Abstract 804.

Phase II Trial Design



* Optional extension of up to 2 cycles if complete response or 8 cycles if partial response and ongoing clinical improvement

- **Primary endpoint:** Overall response rate
- **Secondary endpoints include:** Time to response, duration of response, progression-free survival (PFS) and safety
- CD30 expression and clinical response were confirmed by independent review.
- Tumor microenvironment was assessed using immunohistochemical (IHC) staining for CD8, CD20, CD163, FoxP3 and PD-1.
- Multispectral image analysis was used to evaluate CD30 antigen coexpression.

Kim YH et al. *Proc ASH* 2014;Abstract 804.

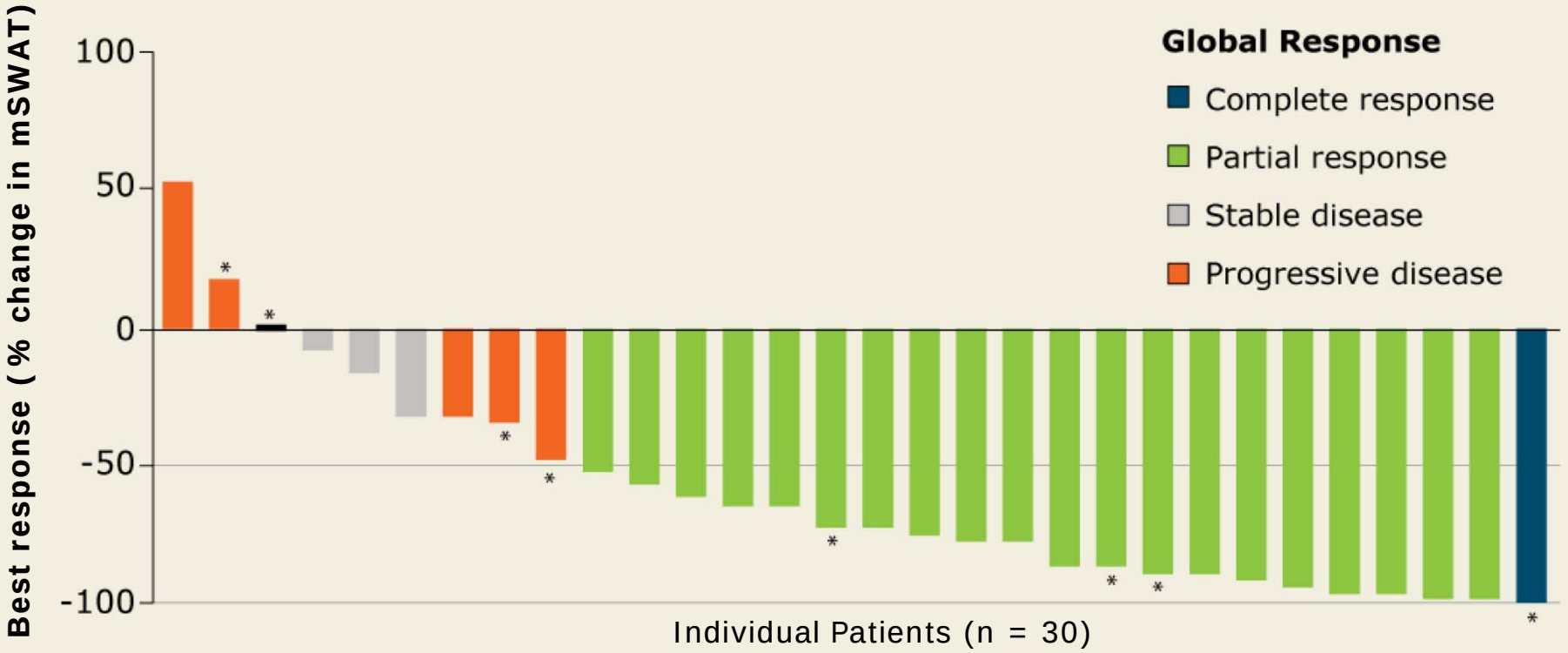
Response Rates by Category

Category (n)	ORR	CR	PR	SD	PD
All patients (30)	70%	3.3%	66.7%	13.3%	16.7%
Stage IB (4)	75%	0%	75%	25%	0%
Stage IIB (18)	78%	0%	77.8%	11.1%	11.1%
IV/SS (8)	50%	12.5%	37.5%	12.5%	37.5%

ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

Kim YH et al. *Proc ASH* 2014;Abstract 804.

Percent Change in Skin mSWAT Score at Best Skin Response



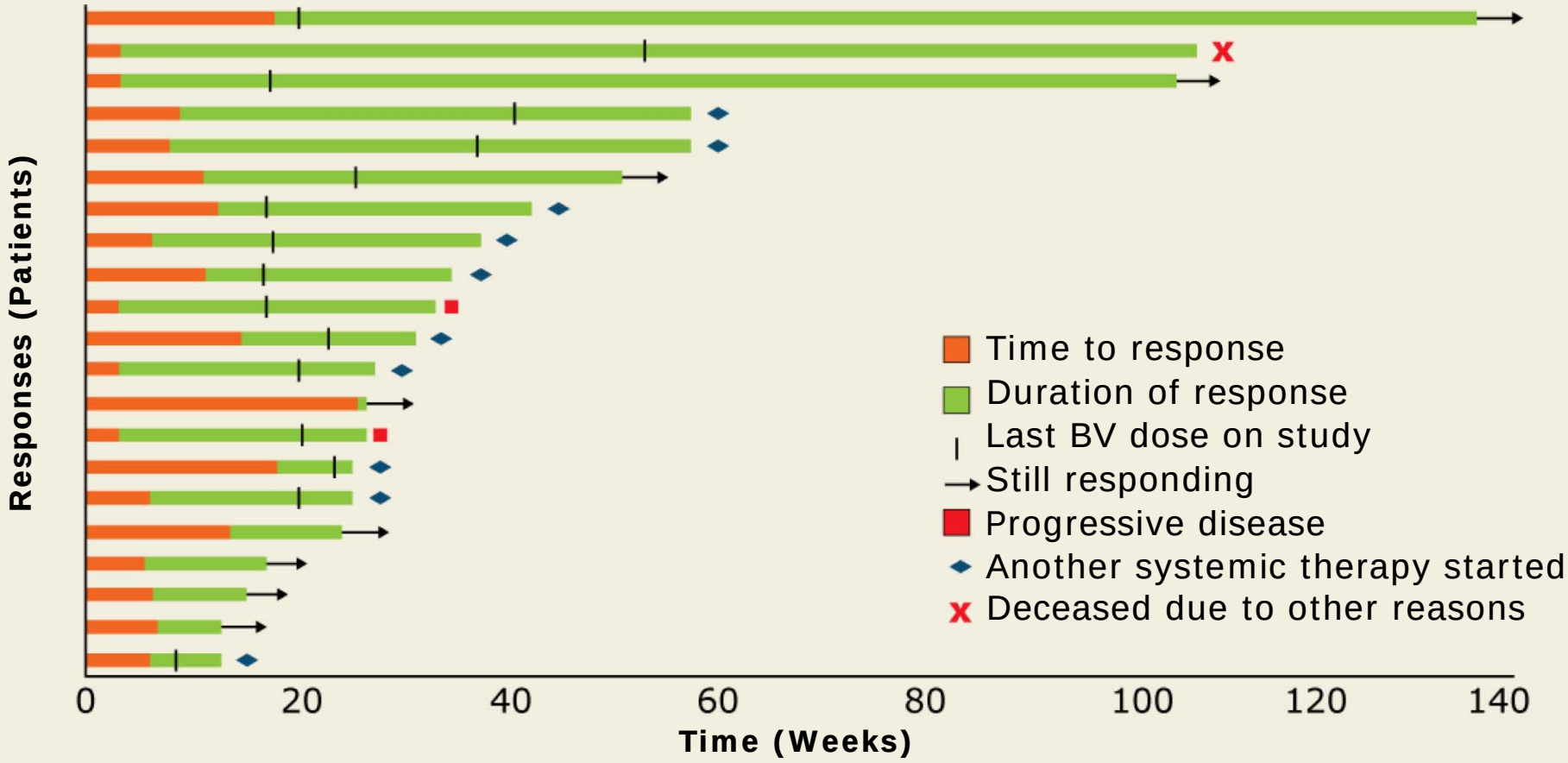
* Stage IV

mSWAT = modified severity weighted assessment tool

- Medium best mSWAT reduction: 73% (100% to -54%)
- Patients with mSWAT reduction >90%: 8

With permission from Kim YH et al. *Proc ASH* 2014;Abstract 804.

Time Course for Patients with Objective/Global Clinical Response (N = 21)

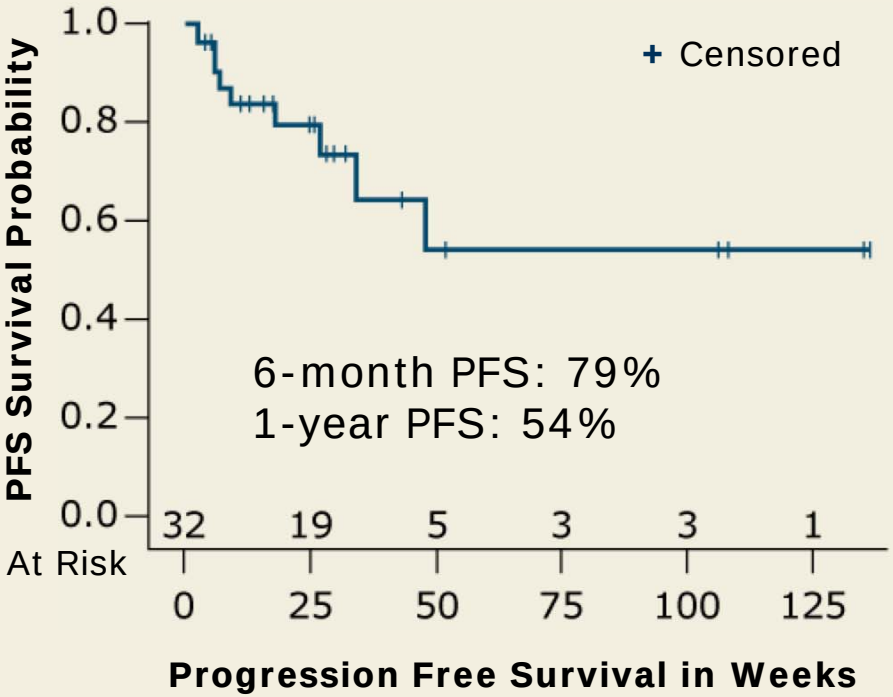


- Medium time to response: 6.6 wk
- Patients with continued response at 6 and 12 mo: 90% and 79%, respectively

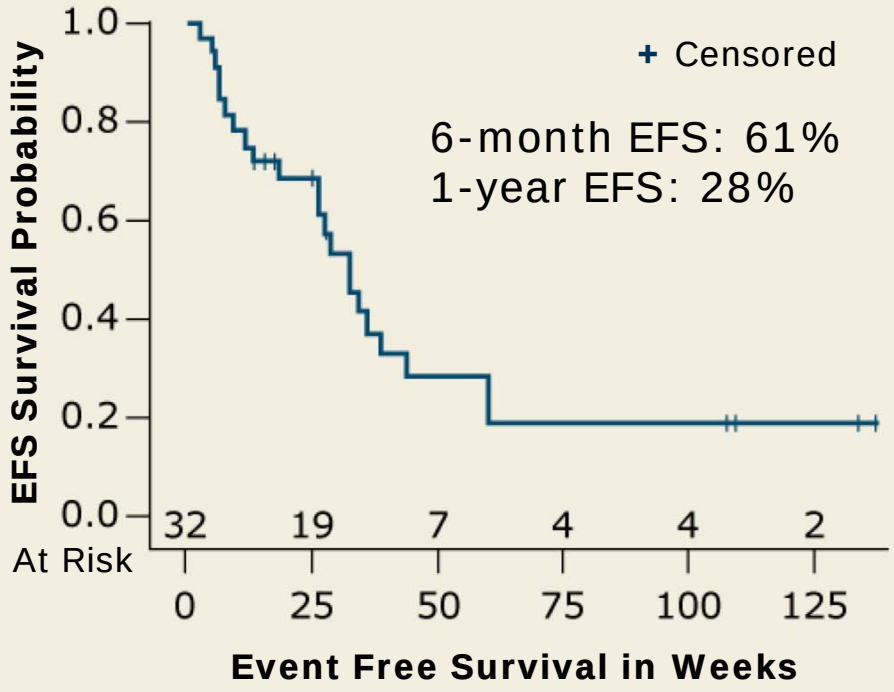
With permission from Kim YH et al. *Proc ASH* 2014;Abstract 804.

Survival Outcomes

PFS



Event-free survival (EFS)



- Event-free survival event: PD, early termination, death or initiation of other significant treatment

With permission from Kim YH et al. *Proc ASH* 2014;Abstract 804.

CD30 Expression and Treatment Outcomes

Outcome	Value
Median maximum CD30 expression level in all patients (range)	13% (0%-100%)
Median maximum CD30 expression level in responders (CR/PR) vs nonresponders (SD/PD)	15% vs 3%
p-value	0.037

- The correlation with CD30 level was greatest in the IIB/skin tumor subset ($p = 0.0072$).
- Patients with CD30 level <5% had a lower likelihood of clinical response (17% vs 83%; $p = 0.0046$).

Kim YH et al. *Proc ASH* 2014;Abstract 804.

Assessment of the Tumor Microenvironment

- No correlation of pretreatment tissue-infiltrating CD8-positive, Foxp3-positive or PD-1-positive T cells with clinical response
- No correlation of soluble CD30 between responders and nonresponders (p = 0.92)
- No correlation of pretreatment tissue-infiltrating CD20-positive B cells or CD163-positive macrophages with clinical response
- Tumor-associated CD163-positive macrophages were the most abundant.
  - Median of total infiltrate: 40% (range 5-80%)

Kim YH et al. *Proc ASH* 2014;Abstract 804.

Select Adverse Events

N = 32	All grades	Grade 3/4
Peripheral neuropathy (PN)	66%	3%
Fatigue	47%	0%
Nausea	28%	0%
Alopecia	22%	0%
Neutropenia	19%	13%
Anorexia	19%	0%
Skin eruption	13%	9%
Dyspepsia	13%	0%
Diarrhea	9%	0%

- Medium time to any PN = 13 weeks
- Median time to improvement/resolution of PN = 49 weeks

Kim YH et al. *Proc ASH* 2014;Abstract 804.

Author Conclusions

- BV showed significant clinical activity in patients with refractory or advanced MF/SS, most of whom had transformed or folliculotropic MF.
- Not all BV-associated PN is reversible.
- Clinical responses were observed in all CD30 groups, but reliability or depth of response correlates with $CD30_{max}$ expression.
- No significant correlation was observed between pretreatment tissue microenvironment factors and clinical response.
- The abundance of tumor-associated macrophages with significant coexpression of CD30 may contribute to an additional mode of action for BV.
- Further studies of biomarkers and effects on the microenvironment are warranted and may help optimize management strategies with BV.

Kim YH et al. *Proc ASH* 2014;Abstract 804.

Investigator Commentary: Final Analysis of a Phase II Study of BV in MF/SS

One of the interesting aspects of this study is the availability of multiple biopsy samples, which allowed the quantification of CD30 expression levels. In tumors with at least 5% CD30 expression, there was no correlation with response to BV. The overall response rate for all patients was 70%, and some of these patients have been receiving therapy for up to 1 year.

A debate is ongoing on whether BV has activity in tumors that are CD30-negative. In this study, there was no evidence of response to BV in CD30-negative MF/SS. In my institution, we would never be able to get approval to study the efficacy of BV in a CD30-negative patient population due to issues with the testing assays.

There is absolutely no doubt in my mind that BV will become a standard treatment for patients with CD30-positive cutaneous lymphomas based on the results of this study.

Interview with Craig Moskowitz, MD, January 6, 2015

Romidepsin in Association with CHOP in Patients with Peripheral T-Cell Lymphoma: Final Results of the Phase Ib/II Ro-CHOP Study

Dupuis J et al.

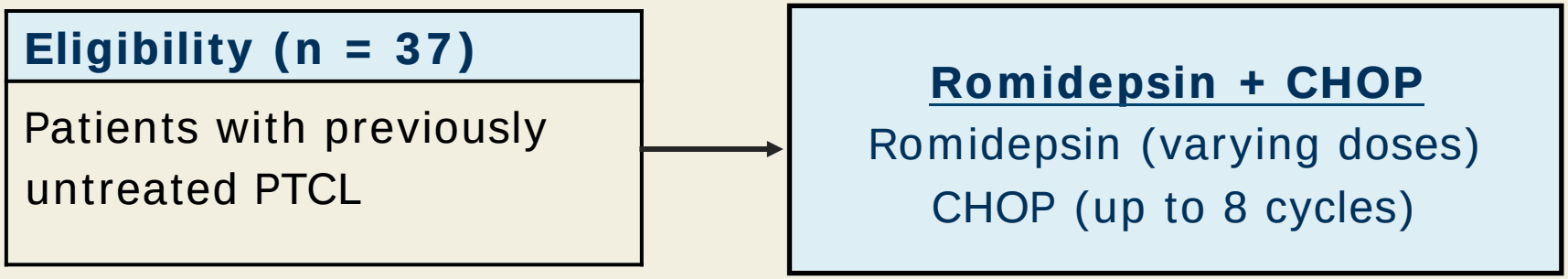
Proc ASH 2014;Abstract 504.

Background

- Romidepsin is a histone deacetylase inhibitor approved by the Food and Drug Administration for the treatment of cutaneous T-cell lymphoma and peripheral T-cell lymphoma (PTCL) who have received at least 1 prior therapy.
- In recurrent or refractory PTCL, it has been evaluated as a single agent in 2 Phase II studies:
  - Overall response rate: 25%-38% (*Blood* 2011;117(22): 5827 and *J Clin Oncol* 2012;30(6):631).
- Toxicity of romidepsin is mainly hematologic and gastrointestinal.
- **Study objective:** To report the final analysis of a Phase Ib/II trial evaluating the safety, tolerability and efficacy of romidepsin in combination with CHOP for patients with previously untreated PTCL.

Dupuis J et al. *Proc ASH* 2014;Abstract 504.

Phase Ib/II Trial Design



- Based on pharmacokinetic data and previous Phase II studies, the starting dose of romidepsin was 10 mg/m^2 days 1, 8.
- CHOP: Cyclophosphamide 750 mg/m^2 day 1, doxorubicin 50 mg/m^2 day 1, vincristine 1.4 mg/m^2 day 1, prednisone 40 mg/m^2 days 1-5.
- The dose-variation scheme followed a traditional “3 + 3” study design.
- Dose-limiting toxicities (DLTs) were assessed during the first 2 cycles.
- DLT was initially defined as nonhematologic toxicity Grade 3/4 or hematological toxicity Grade 3 lasting for >7 days or Grade 4 lasting for >3 days.
- The protocol was subsequently amended to tolerate events lasting for <10 days (Grade 3) or 7 days (Grade 4).

Dupuis J et al. *Proc ASH* 2014;Abstract 504.

3 + 3 Dose-Escalation Scheme

Level	Days	Romidepsin dose	n
-2	D1	8 mg/m^2	3-6
-1	D1, 8	8 mg/m^2	3-6
1	D1, 8	10 mg/m^2	3-6
2	D1, 8	12 mg/m^2	3-6
3	D1, 8	14 mg/m^2	3-6
Expansion cohort	D1, 8	RP2D	25

RP2D = recommended Phase II dose

Dose-Escalation Phase

- Cohort 1 (n = 3): 10 mg/m^2
- Cohort 2 (n = 3): 10 mg/m^2
- Cohort 3 (n = 3): 8 mg/m^2
- Cohort 4 (n = 3): 10 mg/m^2
- Cohort 5 (n = 3): 12 mg/m^2
- Cohort 6 (n = 3): 12 mg/m^2

Dupuis J et al. *Proc ASH* 2014;Abstract 504.

Treatment and Outcomes

- Phase II recommended dose of romidepsin: 12 mg/m^2
- Patients who received treatment in the Phase II part of the study: n = 19
- Significant albeit tolerable hematological toxicity was observed in the first 2 cohorts of patients
  - Hence, the definition of DLT was modified during the course of the study.
- Patients who completed 8 planned cycles: 26/37 (70%)

Dupuis J et al. *Proc ASH* 2014;Abstract 504.

Responses After 8 Cycles

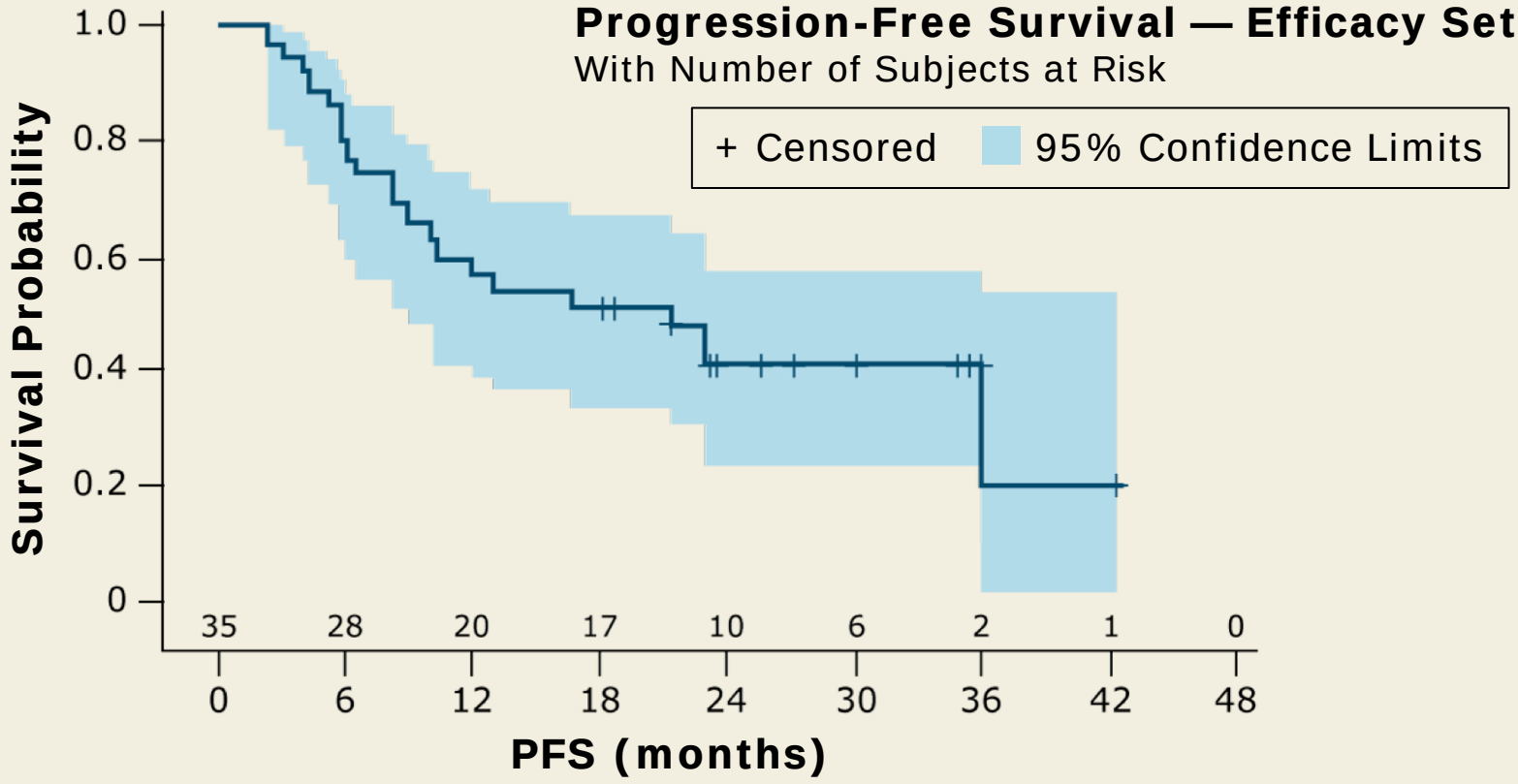
Response	N = 35*
Complete response	51%
Partial response	17%
Progressive disease (PD)	26%

* Evaluable patients

- Two patients experienced early cardiac events (myocardial infarction) and were excluded from the efficacy analysis.

Dupuis J et al. *Proc ASH* 2014;Abstract 504.

Progression-Free Survival (PFS)

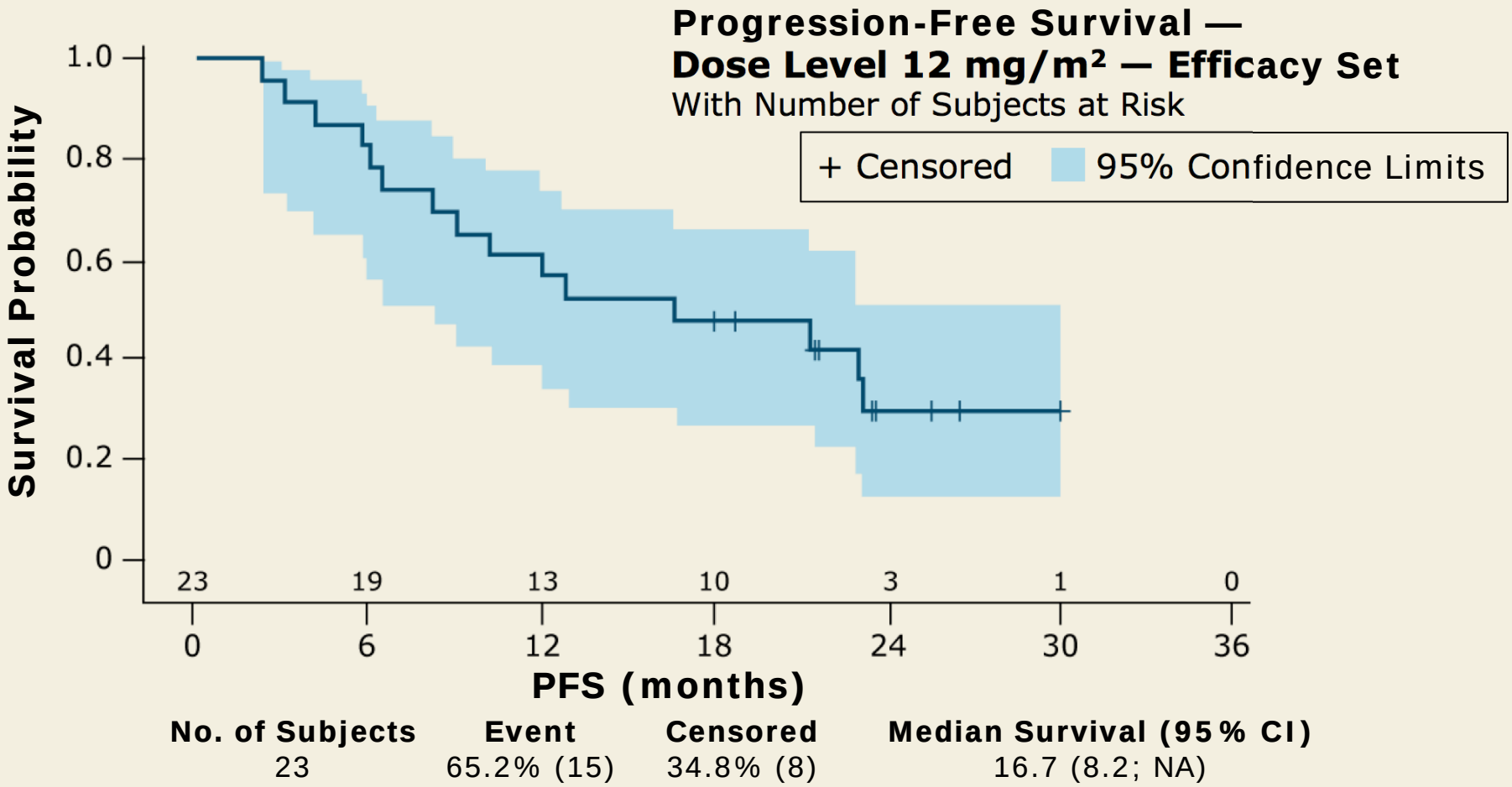


No. of Subjects	Event	Censored	Median Survival (95% CI)
35	60% (21)	40% (14)	21.3 (9; NA)

- 1-year estimated PFS = 57%
- Median follow-up = 30 months

With permission from Dupuis J et al. *Proc ASH* 2014;Abstract 504.

PFS at 12 mg/m² of Romidepsin



- 1-year estimated PFS = 56.5%

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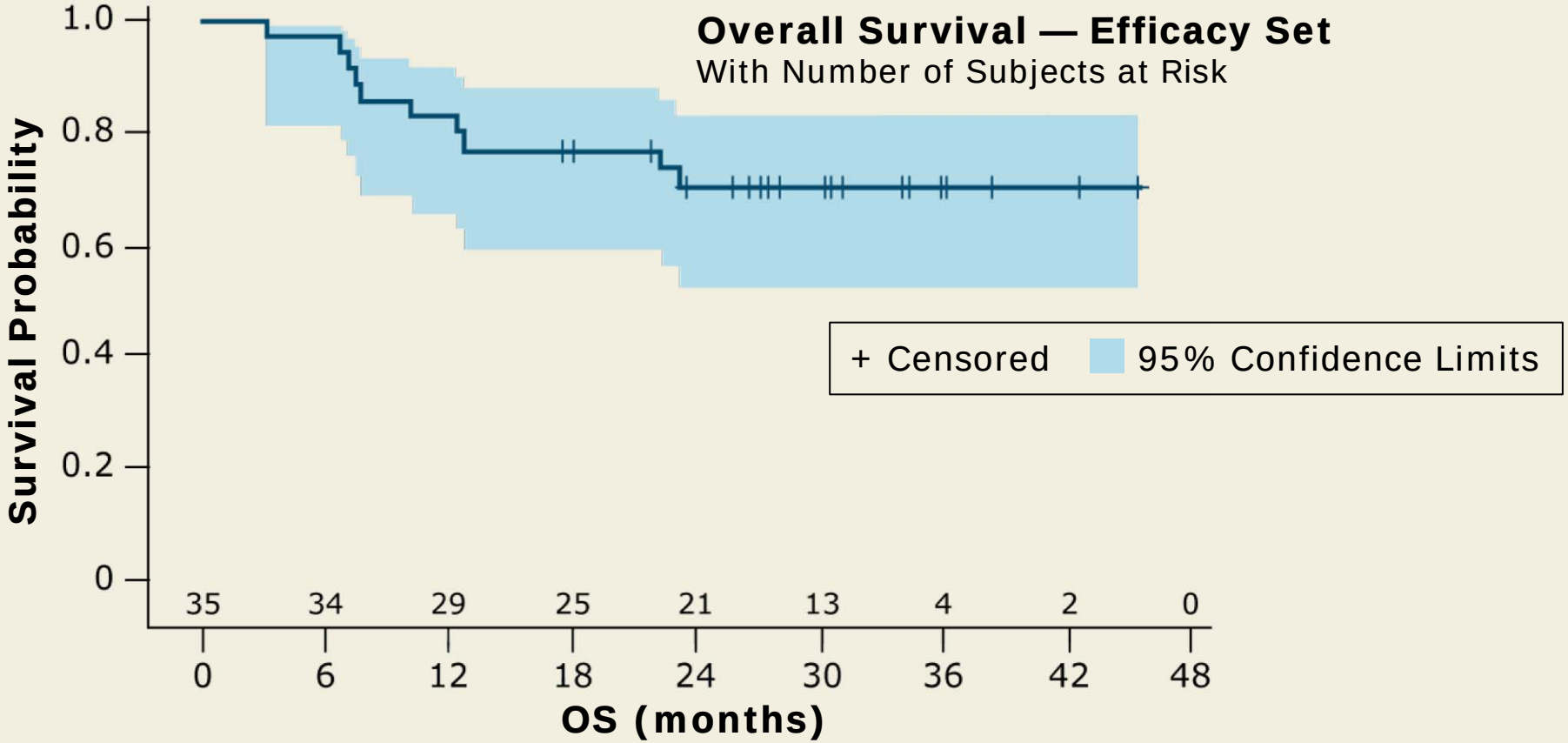
Overall Survival (OS)



No. of Subjects	Event	Censored	Median Survival (95% CI)
35	28.6% (10)	71.4% (25)	NA (NA; NA)

- 1-year estimated OS = 82%
- Median follow-up = 30 months

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Adverse Events (AEs)

- Patients who experienced at least 1 AE: 100%
- Median number of AEs per patient: 49
- Proportion of AEs that occurred during cycle 1 or 2: 38%
- AEs of Grade 1-2: 84%
- No AE-related deaths were reported
- Some severe toxicities were observed during the expansion phase:
  - Sensory peripheral neuropathy leading to treatment discontinuation (n = 1)
  - Nonfatal acute cardiac toxicity after first cycle (n = 3)
- Severity of thrombocytopenia led to discontinuation of romidepsin in 5 patients
- Reasons for romidepsin discontinuation:
  - PD (n = 5); toxicity (n = 6)

Dupuis J et al. *Proc ASH* 2014;Abstract 504.

AEs Occurring in ≥10% of Patients

Event (n = 37)	All grades	Grade 3-4
Neutropenia	100%	85%
Thrombocytopenia	94%	35%
Anemia	89%	8%
Fatigue	80%	5%
Hypocalcemia	62%	3%
Nausea/vomiting	59.5%	10%
Mucositis	27%	5%
Diarrhea	24%	0%
QT prolongation	24%	0%
Hypophosphatemia	22%	8%
Febrile neutropenia	19%	19%

Dupuis J et al. *Proc ASH* 2014;Abstract 504.

Author Conclusions

- Romidepsin can be combined with CHOP at the price of foreseeable hematological toxicity.
- Some cardiovascular events have been observed, but the relationship with romidepsin is questionable.
- The PFS rates seem promising.
- The ongoing Phase III Ro-CHOP trial is evaluating romidepsin and CHOP versus CHOP alone for patients with previously untreated PTCL (NCT01796002):
  - Estimated enrollment: 420
  - Primary endpoint: PFS

Dupuis J et al. *Proc ASH* 2014;Abstract 504.

Investigator Commentary: Final Results of the Phase Ib/II Trial of Romidepsin in Combination with CHOP in Previously Untreated PTCL

This is the final analysis of a small Phase Ib/II study of romidepsin and CHOP in patients with previously untreated PTCL. The results are interesting. The 1-year PFS for the overall population was 57%. In the elderly patient population this rate is reasonable and supports the need for a randomized study of romidepsin/CHOP.

The cardiac toxicity associated with this treatment combination does not appear to be negligible. Two early cardiac events (myocardial infarction) occurred, and an additional patient experienced acute cardiac failure. There's no doubt that romidepsin in combination with CHOP also causes more thrombocytopenia than CHOP alone.

In my practice I administer CHOP with etoposide (CHOEP) for younger patients with PTCL before transplantation. We perform autotransplantation at first remission. For patients with CD30-positive PTCL, we administer CHOP/brentuximab vedotin up front.

Interview with Craig Moskowitz, MD, January 6, 2015