5 Minute JournalClub

Hematologic Oncology

Issue 3, 2013

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CME Information

LEARNING OBJECTIVES

- Evaluate emerging efficacy and safety data with the anti-CD30 agent brentuximab vedotin and the novel histone deacetylase inhibitor belinostat as therapy for patients with relapsed or refractory T-cell lymphoma.
- Demonstrate knowledge of currently recruiting trials of the targeted agents brentuximab vedotin, belinostat and romidepsin as single agents or in combination with chemotherapy, and counsel appropriate patients with T-cell lymphoma for participation in these ongoing trials.

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:

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CME Information (Continued)

Advisory Committee: Allos Therapeutics, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Onyx Pharmaceuticals Inc, Spectrum Pharmaceuticals Inc; *Consulting Agreements:* Bristol-Myers Squibb Company, Celgene Corporation, Millennium: The Takeda Oncology Company.

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One of the best examples of the recent transformation of clinical and translational science in the many variants of T-cell lymphoma (TCL) was a case presented by Dr Andrew Evens during a lymphoma think tank we hosted this summer in our Miami recording studio.

This 61-year-old man was diagnosed 2 years ago with Stage IV ALK-negative anaplastic large-cell lymphoma (ALCL) and received CHOEP — a common up-front choice among investigators — which resulted in a complete response (CR). Like many patients with peripheral T-cell lymphoma (PTCL) who hear the pros and cons of various forms of transplant, the patient balked at taking that difficult step and was followed expectantly for a year, when an obvious and significant recurrence was detected. Until recently this man's treatment options would have been confined to intensive salvage chemotherapy regimens, like ICE, DHAP and ESHAP, and other less intense options, including romidepsin, pralatrexate and other agents, but in 2013 we know that ALCL is uniformly CD30-positive and, as with about 60% of individuals with this disease who receive the antibody-drug conjugate (ADC) brentuximab vedotin (BV), this patient experienced a rapid CR and no significant toxicity. He then reconsidered his decision and elected to receive an autologous stem cell transplant and remains in CR 6 months later.

Unlike many other corners of oncology, including B-cell lymphomas, for which novel agents and strategies abound, TCL has until recently been devoid of these hopeful entities and the unfortunate result is painfully evident in a recent JCO paper. This retrospective study of 153 patients in British Columbia who underwent treatment for PTCL (mostly PTCL NOS, angioimmunoblastic TCL [AITL] or ALCL) from 1976 to 2010 demonstrated a dismal median time from diagnosis to first relapse of 6.7 months and an even worse 5.5 months from first relapse to death. However, as seen with Dr Evens' patient, critical inroads have now been made, and equally as important, an effective clinical research infrastructure has emerged that is generating well-designed and executed studies. The ASCO and Lugano TCL papers summarized on this issue of *5-Minute Journal Club* typify recent steps forward and shine a light on where we might be in a few years.

1. Belinostat: The BELIEF Phase II trial

The big T-cell story out of ASCO was this report of significant single-agent activity with a 26% response rate with this novel pan-histone deacetylase inhibitor (HDACi) in patients with relapsed/refractory (R/R) PTCL. Although on the surface some might review the data and think this is just another HDACi, during a recent interview for our audio series BELIEF principal investigator Dr Owen O'Connor discussed the potential game-changing difference of this drug. Specifically, unlike other agents with significant activity in PTCL, including romidepsin, the rate of myelosuppression is relatively low with belinostat and as such it can be administered to patients with platelet counts above 50,000.

From a clinical perspective this unique attribute may prove invaluable in the R/R setting, in which many patients have poor marrow reserve because of prior chemotherapy and in some cases transplant. Similarly, in terms of clinical research belinostat may be safer and easier to combine with chemotherapy, potentially allowing for more effective drug delivery — a strategy now being tested in up-front trials. The news did not stop at ASCO, as in Lugano Dr Steven Horwitz presented further data from BELIEF demonstrating that patients with AITL were particularly likely to benefit from the drug (46% response rate). These data have led many to become “believers” that belinostat may have real value and perhaps a role soon in clinical practice.

2. CD30 and BV

We’ve talked a lot about this fascinating ADC in past programs, but the database continues to build and at Lugano we saw an interesting report from a Phase II US trial of 29 patients with mature T-/NK-cell lymphomas. Importantly, of 17 patients with postbaseline assessments, all but 3 experienced tumor size decreases and CRs were observed in 4 of 10 patients with AITL and 2 of 12 patients with PTCL NOS. These and prior data sets suggest that clinicians might want to consider CD30 testing for all patients with PTCL and maybe some B-cell cancers like diffuse large B-cell lymphoma along with cutaneous TCL, in which an ongoing Phase III trial is evaluating the efficacy of BV and anecdotal benefit has been observed. Interestingly, the correlation between CD30 status and response to BV is not as clear as one might think, and this paper like others before it reports durable responses in patients with low or undetectable CD30 expression.

Last week in the Big Apple during the first of our 4 daylong regional Year in Review (YIR) symposia, Dr Bruce Cheson commented on the challenge of using this marker and cited the example of Hodgkin lymphoma, in which most cells in the tumor mass are stroma and are CD30-negative but virtually all Reed-Sternberg cells have the antigen, thus explaining the impressive clinical activity in these patients. Another YIR faculty member, Dr Lauren Pinter-Brown, commented on 2 other factors confounding current CD30 evaluation, namely tumor heterogeneity and the evolution of newer, more sensitive assays, including quantitative image analysis, that may be able to identify many more patients than the estimated 30% with PTCL currently considered to have CD30-positive tumors. Where this leads in the future is uncertain, but it's possible that BV and other ADCs will eventually be utilized in most patients with TCL.

3. The next generation of TCL clinical trials

Despite the many advances in TCL treatment, continued research is of course needed, and at ASCO Dr O'Connor presented a Trials in Progress poster (TPS) featuring the newly launched and much anticipated Phase III ECHELON-2 study. This critical effort compares up-front CHOP to CHBVP, in which BV replaces vincristine in the front-line treatment of patients with CD30-positive mature TCLs, and should be widely embraced by clinicians who otherwise must turn to suboptimal standard options. In a similar manner, another relevant ASCO TPS focused on the Phase III RoCHOP trial, which adds the HDACi romidepsin to CHOP in patients with previously untreated PTCL. In terms of new agents, Dr Anas Younes, the new Chief of the Memorial Sloan-Kettering Lymphoma

Service, in a brilliant ASCO review of many exciting ADCs in development said it's "prime time" for these agents in lymphoid cancers. He then underscored the immense value of this therapeutic concept by noting the important example of ALCL, where the unconjugated anti-CD30 antibody produced a 17% response rate that increased to 86% when the same naked antibody was conjugated to monomethyl auristatin E (MMAE).

Many other novel agents and strategies are being actively investigated in TCL, and Dr Pinter-Brown told our highly attentive and knowledgeable New York audience that TCL needs a "rituximab." In that regard, she is intrigued by mogamulizumab, a defucosylated humanized monoclonal antibody targeting C-C chemokine receptor 4 (CCR4) that is approved in Japan for R/R adult T-cell leukemia/lymphoma and is currently working its way through trials in North America, where the face of this disease is considerably different.

Next, for our final issue of this series on summer heme-onc data sets we flip back to the "B" side and check out papers on follicular, mantle-cell and diffuse large B-cell lymphoma.

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Belinostat, a Novel Pan-Histone Deactylase Inhibitor (HDACi), in Relapsed or Refractory Peripheral T-Cell Lymphoma: Results from the BELIEF Trial[1]

Belinostat in Angioimmunoblastic T-Cell Lymphoma: Results from the Pivotal BELIEF Trial[2]

[1] **O'Connor OA et al.**
Proc ASCO 2013;Abstract 8507.

[2] **Horwitz S et al.**
Proc ICML 2013;Abstract 153.

Belinostat, a Novel Pan-Histone Deactylase Inhibitor (HDACi), in Relapsed or Refractory Peripheral T-Cell Lymphoma: Results from the BELIEF Trial

O'Connor OA et al.

Proc ASCO 2013;Abstract 8507.

Background

- Currently approved therapies for relapsed or refractory PTCL have overall response rates of 25% to 29% (*JCO* 2011;29(9):1182-9; *JCO* 2012;30(6):631-6).
- Previously, a Phase II CLN-6 trial demonstrated that belinostat monotherapy yielded an overall response rate of 25% in relapsed/refractory PTCL (*Proc ASH* 2009;Abstract 920).
  - Belinostat was well tolerated, with the most common toxicities being Grade 1/2 gastrointestinal and constitutional side effects.
- **Study objective:** To assess the safety and efficacy of single-agent belinostat for patients with relapsed or refractory PTCL.

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

Phase II BELIEF Trial Design

Eligibility (n = 129)

Relapsed or refractory PTCL*
≥1 prior systemic therapy
Platelet counts ≥50,000/uL
No prior HDACi therapy
No relapse within 100 days of autologous or allogeneic bone marrow transplant

→

Belinostat
1,000 mg/m^2 (IV), d1-5 q3wk

* Confirmed by central pathology review (CPRG)

- **Primary endpoint:** Objective response rate (ORR)
- Secondary endpoints include: Safety, time to response, progression-free and overall survival and duration of response
- Exploratory analyses were conducted to determine response by PTCL subtypes

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

Response by Central Review

Response rate	n = 120
ORR	26%
Complete response (CR)	11%
Partial response (PR)	15%
Stable disease	15%
Progressive disease	40%
Not evaluable*	19%

* Prior to first radiologic assessment due to death (n = 7); clinical progression (n = 10); patient withdrawal (n = 5); lost to follow-up (n = 1)

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

Response Rates According to Disease Characteristics

Characteristic	Response rate
Bone marrow involvement (n = 120)	
No (n = 65)	31%
Yes (n = 35)	23%
Indeterminate (n = 8)	25%
Not assessed (n = 12)	8%
Platelet counts (n = 120)	
≥100,000/uL (n = 100)	28%
<100,000/uL (n = 20)	15%

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

Response Rates by CPRG Lymphoma Diagnosis

Diagnosis	ORR
PTCL-NOS (n = 77)	23%
AITL (n = 22)	46%
ALCL, ALK-negative (n = 13)	15%
ALCL, ALK-positive (n = 2)	0%
Enteropathy-associated TCL (n = 2)	0%
Extranodal NK/TCL, nasal type (n = 2)	50%
Hepatosplenic TCL (n = 2)	0%

PTCL-NOS = PTCL-not otherwise specified; ALCL = angioimmunoblastic T-cell lymphoma; TCL = T-cell lymphoma

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

Clinical Outcomes

Outcome	All patients (n = 120)	Baseline platelet counts	
		≥100,000/uL (n = 100)	<100,000/uL (n = 20)
ORR by CPRG	25.8%	28.0%	15.0%
Median DoR	13.6 months	13.6 months	4.1 months
Median PFS	1.6 months	1.8 months	1.3 months
Median OS	7.9 months	9.2 months	4.3 months
Median TTR	5.6 weeks	5.6 weeks	6.4 weeks

DoR = duration of response; PFS = progression-free survival; OS = overall survival; TTR = time to response

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

Select Grade ≥3 Adverse Events

Event	All patients (n = 129)	Baseline platelet counts	
		≥100,000/uL (n = 105)	<100,000/uL (n = 24)
Thrombocytopenia	15%	6%	54%
Neutropenia	13%	10%	25%
Leukopenia	13%	9%	29%
Anemia	12%	8%	29%
Dyspnea	6%	Not reported	
Pneumonia	6%	Not reported	
Febrile neutropenia	5%	Not reported	
Fatigue	5%	Not reported	
Hypokalemia	4%	Not reported	

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

Author Conclusions

- Belinostat demonstrated activity in patients with relapsed/refractory PTCL.
  - All patients (n = 120), ORR: 26%
  - Baseline platelet counts ≥100,000/uL, ORR: 28%
  - Baseline platelet counts <100,000/uL, ORR: 15%
- Belinostat was well tolerated with a favorable safety profile.
  - This included patients who had previously undergone autologous or allogeneic stem cell transplantation.
- Patients with poor marrow reserve and low platelet counts tolerated and benefited from belinostat treatment.
- Further investigation of belinostat in combination with other therapies is warranted to develop new treatment paradigms for PTCL.

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

Discussant Conclusions

- Belinostat demonstrated a 26% to 28% ORR and was well tolerated with a favorable safety profile in patients with relapsed/refractory PTCL, including patients with a previous stem cell transplant.
- Patients with poor marrow reserve and low platelet counts due to marrow involvement and those who had undergone stem cell transplantation tolerated belinostat therapy.
  - This included 3 patients with baseline platelet counts of ≤25,000/uL.
- The low incidence of myelosuppresion observed warrants further investigation of belinostat combination therapy to develop new treatment paradigms for relapsed or refractory PTCL.

Gisselbrecht C et al. *Proc ASCO* 2013;Discussant.

Investigator Commentary: Phase II BELIEF Trial of Belinostat in Relapsed/Refractory PTCL

Many of the data from the BELIEF study are similar to what we've seen with other HDAC inhibitors. One of the most interesting observations of the BELIEF study was the activity of belinostat in patients with low platelet counts. Patients had a platelet count cutoff of 50,000/uL, with most having counts of >100,000/uL. Many of these patients get "beat up" and have counts of <100,000/uL and technically would not be eligible for the drug if it gets approved for those with a platelet count of ≥100,000/uL. For many of the patients with platelet counts between 50,000/uL and 100,000/uL and even a few with counts <50,000/uL, the response rate was respectable. More importantly, belinostat was well tolerated irrespective of the pretreatment platelet count.

In this study, about 20 patients had platelet counts <100,000/uL. However, in clinical practice most patients with PTCL have platelet counts <100,000/uL. That's probably because they've gone through multiple lines of chemotherapy. Many would have received CHOP, oxaliplatin or gemcitabine and possibly autologous stem cell transplants. So the patients in the clinical trial are selected to meet certain eligibility criteria.

Interview with Owen A O'Connor, MD, PhD, August 20, 2013

Belinostat in Angioimmunoblastic T-Cell Lymphoma: Results from the Pivotal BELIEF Trial

Horwitz S et al.

Proc ICML 2013;Abstract 153.

Background

- Peripheral T-cell lymphoma (PTCL) is a heterogeneous, aggressive disease that is associated with poor prognosis.
  - 5-year overall survival rate: 32% (*JCO* 2013;31:240)
- Angioimmunoblastic T-cell lymphoma (AITL) is a subcategory of PTCL representing 15% to 20% of patients with PTCL (*JCO* 2008;26:4124).
- The current treatment for AITL is similar to that for other subtypes of PTCL.
- In a Phase II CLN-6 trial, single-agent belinostat, a novel hydroxamic-based HDACi, was well tolerated and yielded response rates of 25% in relapsed/refractory PTCL (*Proc ASH* 2009;Abstract 920).
- **Study objective:** To evaluate the efficacy of single-agent belinostat for patients with relapsed or refractory PTCL, with specific analysis of patients with the AITL subtype.

Horwitz S et al. *Proc ICML* 2013;Abstract 153.

Efficacy Summary

All patients*	**n = 120**
Overall response rate	26%
Median progression-free survival	1.6 months
Patients with AITL*	
Overall response rate	46%
Median progression-free survival (n = 22)	4.2 months

* By central review

Horwitz S et al. *Proc ICML* 2013;Abstract 153.

Select Grade ≥3 Adverse Events

Hematologic	All patients (n = 129)	AITL (n = 22)
Thrombocytopenia	15%	23%
Neutropenia	13%	9%
Leukopenia	13%	9%
Anemia	12%	27%
Nonhematologic	**n = 120**	**n = 22**
Dyspnea	6%	Not reported
Pneumonia	6%	Not reported
Febrile neutropenia	5%	Not reported
Fatigue	5%	Not reported
Hypokalemia	4%	Not reported

Horwitz S et al. *Proc ICML* 2013;Abstract 153.

Author Conclusions

- Belinostat was well tolerated with a favorable safety profile.
- Patients with poor marrow reserve and low platelet counts tolerated and benefited from belinostat therapy.
  - This included patients who had previously undergone stem cell transplantation.
- Belinostat demonstrated activity in:
  - Patients with relapsed or refractory PTCL (ORR: 26%)
  - Patients with relapsed or refractory AITL (ORR: 46%)
- This study demonstrates the need to collect tissue samples on future prospective trials.
- Future up-front trials in PTCL should:
  - Study uncommon diseases that are often lumped together
  - Maximize treatment effect to find differences

Horwitz S et al. *Proc ICML* 2013;Abstract 153.

Investigator Commentary: Pivotal Phase II BELIEF Trial of Belinostat in AITL

The BELIEF study evaluated a new hydroxamic acid analog, belinostat, in relapsed or refractory PTCL and reported an ORR of 26%. Belinostat is probably a little more potent than vorinostat but is probably not nearly as potent as romidepsin in terms of IC50 values that one might look at in in vitro assays. Interestingly, in the initial agreement with the FDA, the primary objective of the study was to have a response rate in excess of 20% in this patient population. This provides some insight into how low our expectations are for responses in this population.

BELIEF reaffirms that HDAC inhibitors have a unique single-agent class effect in PTCL. This is yet another example in which an ORR in the range of 25% to 30% is seen, similar to vorinostat, romidepsin or panobinostat. An important observation is that the ORR in AITL was markedly higher than in the overall study population and than that reported in the PROPEL study with pralatrexate. That was taken as a signal that belinostat may be targeting some interesting biology in AITL that's not being targeted by other HDAC inhibitors. This is a provocative finding, but I wouldn't make too much of it yet because we need more data. This is a relatively small study of about 120 patients. When you consider the individual number of patients, it's still between 10 and 20 with this particular PTCL subtype.

Interview with Owen A O'Connor, MD, PhD, August 20, 2013

ECHELON-2: Phase 3 Trial of Brentuximab Vedotin and CHP versus CHOP in the Frontline Treatment of Patients (Pts) with CD30+ Mature T-Cell Lymphomas (MTCL)[1]

Safety and Efficacy of Brentuximab Vedotin for Treatment of Relapsed or Refractory Mature T-/NK-Cell Lymphomas[2]

Phase 3 Study of Brentuximab Vedotin versus Physician's Choice of Methotrexate or Bexarotene in Patients (Pts) with CD30-Positive (CD30+) Cutaneous T-Cell Lymphoma. The ALCANZA Study[3]

[1]O'Connor OA et al.
Proc ICML 2013;Abstract 138;
Proc ASCO 2013;Abstract TPS8611.

[2]Oki Y et al.
Proc ICML 2013;Abstract 152.

[3]Kim YH et al.
Proc ICML 2013;Abstract 572.

ECHELON-2: Phase 3 Trial of Brentuximab Vedotin and CHP versus CHOP in the Frontline Treatment of Patients (Pts) with CD30+ Mature T-Cell Lymphomas (MTCL)

O'Connor OA et al.

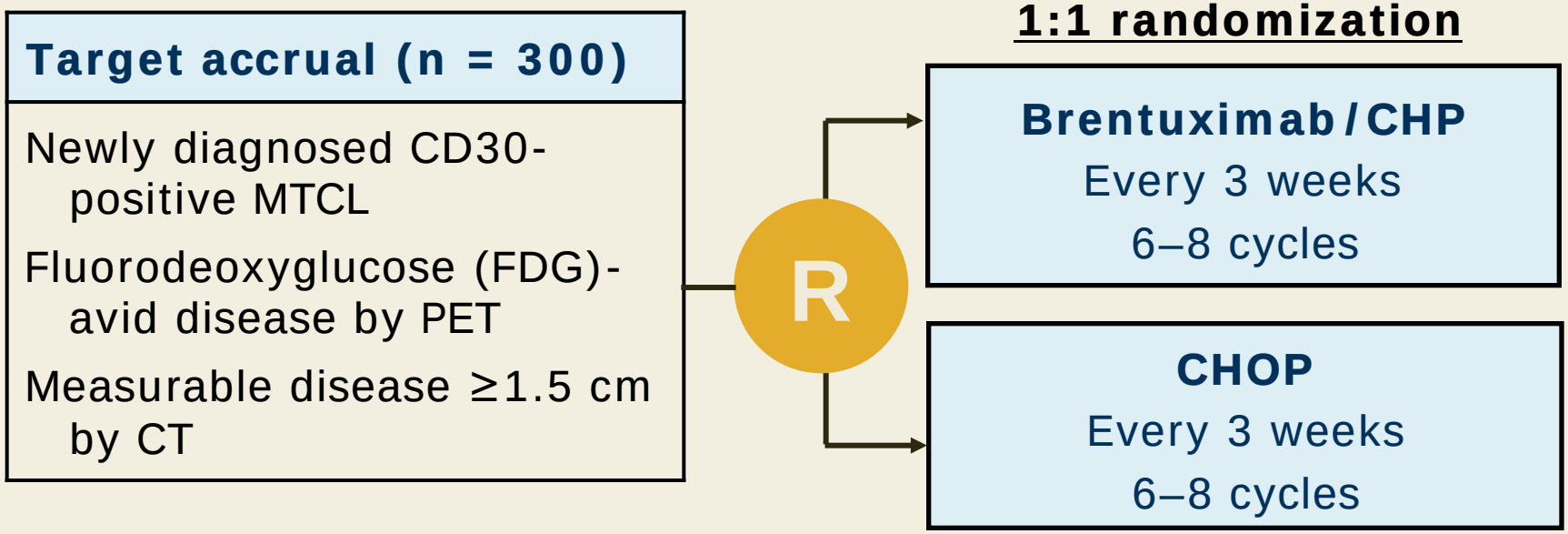
Proc ICML 2013;Abstract 138;
Proc ASCO 2013;Abstract TPS8611.

Background

- MTCLs, including systemic anaplastic large cell lymphoma (sALCL), are aggressive neoplasms.
- Anthracycline-based multiagent chemotherapy regimens have demonstrated response rates ranging from 76% to 88% (*JCO* 2012;30(25):3093-9).
- Brentuximab vedotin is an anti-CD30 monoclonal antibody conjugate that has demonstrated activity in a pivotal Phase II study as a single agent in relapsed/refractory sALCL (*JCO* 2012;30(18):2190-6).
- In a Phase I study, it showed evidence of clinical activity when used in combination with CHP as front-line therapy for sALCL (*Proc ASH* 2012;Abstract 60).
- **Study objective:** To evaluate the safety and efficacy of brentuximab vedotin with CHP versus CHOP as front-line therapy for patients with CD30-positive MTCL.

O'Connor OA et al. *Proc ICML* 2013;Abstract 138; *Proc ASCO* 2013;Abstract TPS8611.

Ongoing Phase III ECHELON-2 Trial Design (NCT01777152)



Study start date: January 2013

Estimated study completion date: December 2019

Brentuximab vedotin dose: 1.8 mg/kg (IV)

- **Primary endpoint:** Progression-free survival (PFS) by independent review
- **Secondary endpoints include:** PFS in sALCL by independent review, complete remission rate, overall survival, objective response rate, safety

O'Connor OA et al. *Proc ICML* 2013;Abstract 138; *Proc ASCO* 2013;Abstract TPS8611.

Study Methods

- Patients will be stratified prior to randomization by:
  - ALK-positive sALCL versus other histologic subtypes
  - International prognostic index score (0-1, 2-3 or 4-5)
- The target proportion of patients with a diagnosis of sALCL will be 75%.
- After completion of treatment, all patients will be followed for disease progression, medical resource utilization, quality of life and survival.
- Post-treatment stem cell transplant is allowed.

O'Connor OA et al. *Proc ICML* 2013;Abstract 138; *Proc ASCO* 2013;Abstract TPS8611.

Efficacy and Safety Assessments

- Efficacy assessments will use the Revised Response Criteria for Malignant Lymphoma (*JCO* 2007;25(5):579).
- CT and PET scans will be performed:
  - At baseline
  - After Cycle 4
  - After completion of treatment
- CT scans will also be performed at regular intervals during follow-up until disease progression, death or analysis of primary endpoint.
- An independent data monitoring committee will review safety data on an ongoing basis.
- Safety assessments will occur throughout the study until 30 days after last dose of study treatment.

O'Connor OA et al. *Proc ICML* 2013;Abstract 138; *Proc ASCO* 2013;Abstract TPS8611.

Assessment of Peripheral Neuropathy and Patient-Reported Outcomes

- Peripheral neuropathy will be graded according to Common Terminology Criteria for Adverse Events and all dose modifications will be based on these grades.
- In addition, Total Neuropathy Score — nurse (TNSn) will be used to assess the onset and resolution of peripheral neuropathy:
  - TNSn is designed to be used by trained medical professionals, not restricted to neurologists or physicians.
  - TNSn includes the measure of sensory, autonomic and motor symptoms; pin sensibility; and vibration sensibility.
- Patient-reported outcomes will include questionnaires completed prior to the administration of treatment on study days:
  - Patient reports may be collected by phone upon disease progression and during survival follow-up.

O'Connor OA et al. *Proc ASCO* 2013;Abstract TPS8611.

Investigator Commentary: Ongoing ECHELON-2 Trial of Front-Line Brentuximab Vedotin/CHP versus CHOP in CD30-Positive MTCL

The ECHELON-2 trial is a registration-directed study. I believe that the study is important because of the addition of brentuximab to CHP. Since it is only for CD30-positive MTCL, it will account for about a third of patients with T-cell lymphoma. At the moment, accrual is relatively slow as people get their arms around considering CD30 as part of their up-front diagnostic workup for patients with these diseases, but this trial could have a significant impact on the natural history of T-cell lymphoma. The early signals in patients with CD30-positive T-cell lymphoma and diffuse large B-cell lymphoma suggest that this agent is highly active in those patients. I believe that it may represent one of our first big advances to a CHP backbone by adding something new that could advance the up-front induction care of these patients. At the planning stage of the trial, the treatment schedule was a big discussion. The FDA judged that a fair comparison should include 6 to 8 cycles of CHOP chemotherapy versus 6 to 8 cycles of brentuximab vedotin/CHP. The trial includes no provision to administer an extended brentuximab vedotin regimen to patients who are randomly assigned to that treatment arm.

Interview with Owen A O'Connor, MD, PhD, August 20, 2013

Safety and Efficacy of Brentuximab Vedotin for Treatment of Relapsed or Refractory Mature T-/NK-Cell Lymphomas

Oki Y et al.

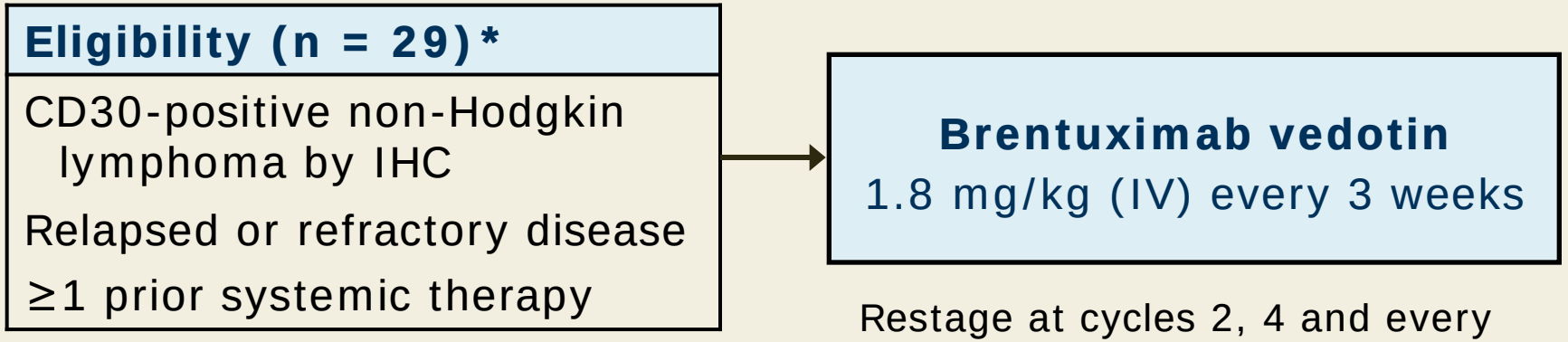
Proc ICML 2013;Abstract 152.

Background

- The MTCL subtypes angioimmunoblastic T-cell lymphoma (AITL) and PTCL not otherwise specified (PTCL-NOS) generally respond poorly to chemotherapy and often relapse (*JCO* 2013;31(16):1970).
- Few effective treatment options are available and there is no standard therapy for relapsed/refractory MTCL.
- CD30 is a target antigen variably expressed on several non-Hodgkin lymphoma cells, including B-cell lymphomas and MTCLs.
- Brentuximab vedotin is an anti-CD30 monoclonal antibody conjugate.
- **Study objective:** To assess the safety and efficacy of brentuximab vedotin in relapsed or refractory CD30-positive MTCL.

Oki Y et al. *Proc ICML* 2013;Abstract 152.

Phase II Trial Design



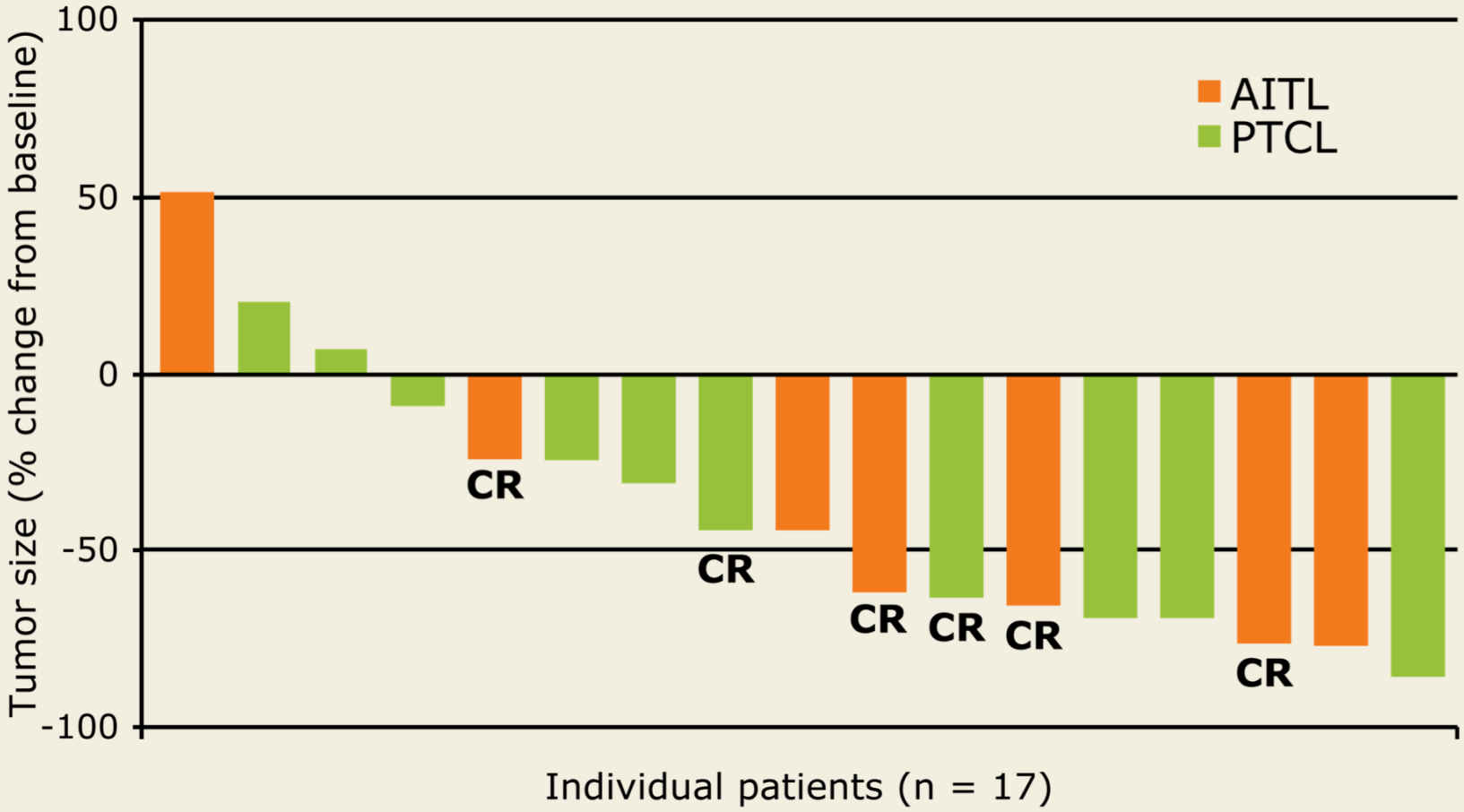
* Enrollment to date

- Diagnosis excludes anaplastic large-cell lymphoma (ALCL), Sézary syndrome and mycosis fungoides (MF) but includes:
  - AITL: n = 11
  - PTCL-NOS: n = 18

- **Primary endpoint:** Objective response rate (ORR)
- **Secondary endpoints include:** Correlation of CD30 expression with response, progression-free survival and safety

Oki Y et al. *Proc ICML* 2013;Abstract 152.

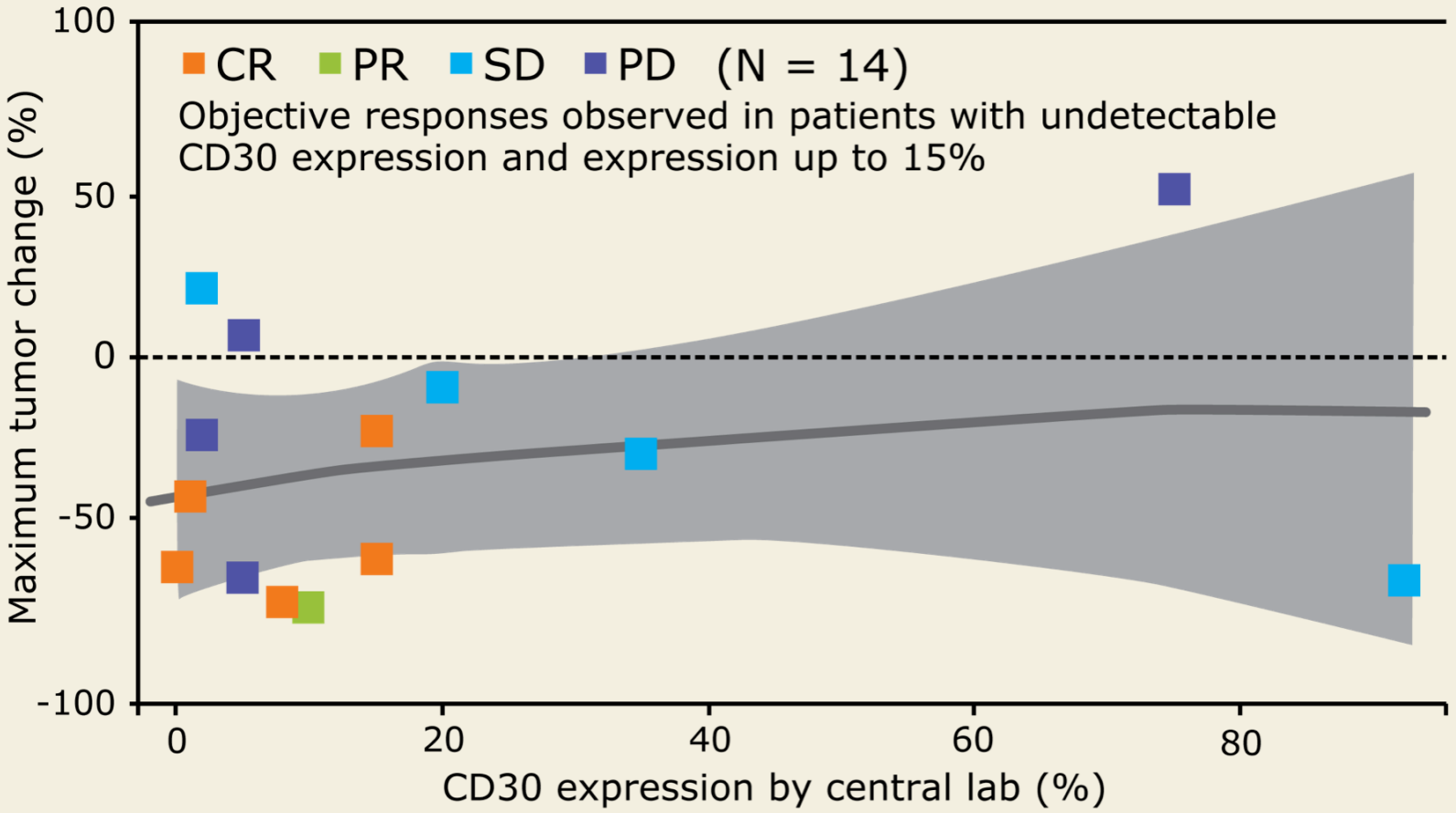
Maximal Tumor Volume Reduction



17 of 18 patients with postbaseline CT assessments

With permission from Oki Y et al. *Proc ICML* 2013;Abstract 152.

Maximal Tumor Volume Reduction by Frequency of CD30+ Cells



Includes patients with both postbaseline radiographic response assessments and CD30 expression data

With permission from Oki Y et al. *Proc ICML* 2013;Abstract 152.

Best Clinical Response

Response rate	All patients (n = 22)	AITL (n = 10)	PTCL-NOS (n = 12)
ORR	36%	50%	25%
Complete response	27%	40%	17%
Partial response	9%	10%	8%
Stable disease	27%	20%	33%
Progressive disease	36%	30%	42%

Median duration of response: Not yet reached

Oki Y et al. *Proc ICML* 2013;Abstract 152.

Adverse Events (AEs) Occurring in >10% of Patients

AEs (n = 29)	All grades	Grade 3
Any AE	72%	28%
Fatigue	24%	0%
Pyrexia	17%	0%
Chills	14%	3%
Decreased appetite	14%	3%
Peripheral sensory neuropathy	14%	0%
Rash	14%	3%

- Grade 3 neutropenia (n = 3)
- Grade 4 AEs to date include: Pulmonary edema, increased lipase and confused state (n = 1 each)

Oki Y et al. *Proc ICML* 2013;Abstract 152.

Author Conclusions

- In this interim analysis, brentuximab vedotin demonstrated antitumor activity in patients with AITL
  - Objective response rate: 50% (CR = 40%; PR = 10%)
  - Median duration of response: not reached
- Durable responses were observed in patients across a broad range of CD30 expression, including those with low or undetectable CD30 expression.
- Brentuximab vedotin demonstrated antitumor activity in patients with relapsed/refractory MTCL and a safety profile consistent with labeled indications.

Oki Y et al. *Proc ICML* 2013;Abstract 152.

Investigator Commentary: Safety and Efficacy of Brentuximab Vedotin in Relapsed or Refractory Mature T-/NK-Cell Lymphomas

This is a Phase II trial evaluating brentuximab vedotin for relapsed and refractory CD30-positive T-/NK-cell lymphomas that do not include ALCL. This setting is technically not an indication for brentuximab vedotin at the moment, but interest has arisen in evaluating this drug in different patient populations. Data were presented with a small number of patients from the trial so far, about 29 patients, and the authors specifically evaluated PTCL-NOS and angioimmunoblastic T-cell lymphoma (AITL). In the overall patient population the response rate was fairly high. It was about 36% for these patients. Among patients with AITL, about 50% of the patients responded, including 4 complete responses. Apparently this represents an interesting signal with which to move forward particularly in the population of patients with AITL.

Interview with Julie M Vose, MD, MBA, July 19, 2013

Phase 3 Study of Brentuximab Vedotin versus Physician's Choice of Methotrexate or Bexarotene in Patients (Pts) with CD30-Positive (CD30+) Cutaneous T-Cell Lymphoma (CTCL). The ALCANZA Study

Kim YH et al.

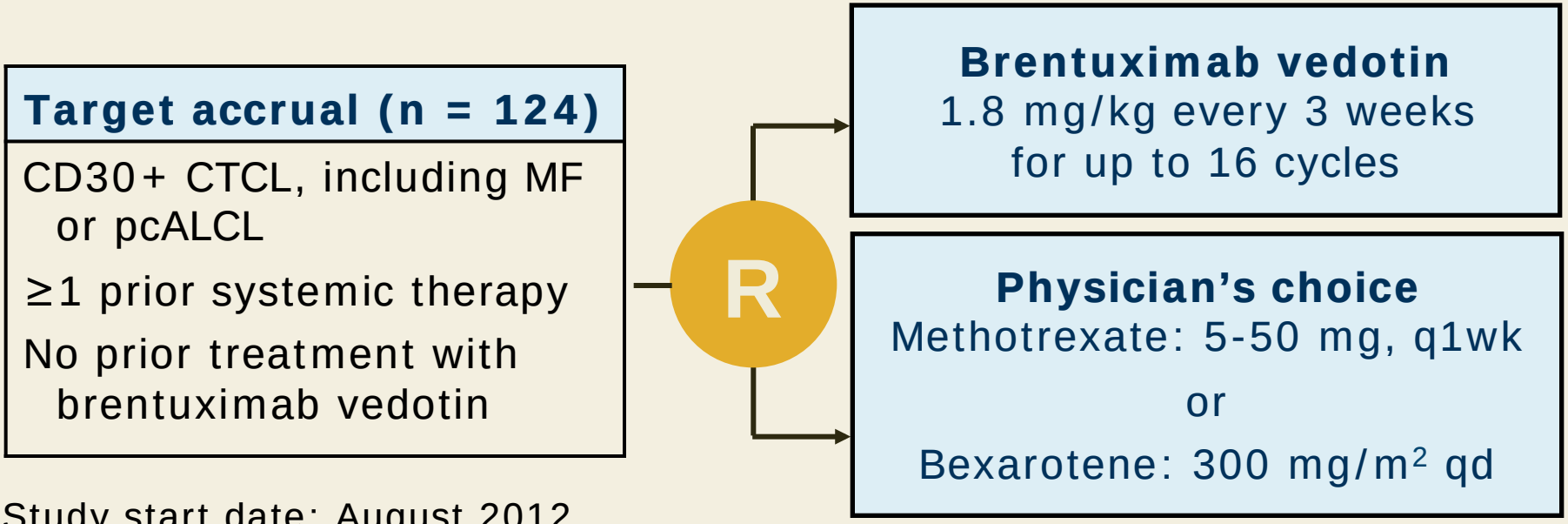
Proc ICML 2013;Abstract 572.

Background

- A Phase II trial demonstrated clinical activity and a manageable safety profile with brentuximab vedotin in relapsed/refractory CD30+ mycosis fungoides (*Proc ASH* 2012;Abstract 797).
  - Overall response rate (ORR): 13/19 (68%)
- Another Phase II trial demonstrated that brentuximab vedotin is an effective and safe targeted therapy for CD30+ CTCL and cutaneous lymphoproliferative disorders (*Proc ASH* 2012;Abstract 3688).
  - ORR: 63% (24/38)
- The most common adverse events associated with brentuximab vedotin include peripheral neuropathy and fatigue.
- **Study objective:** To evaluate the efficacy and safety of brentuximab vedotin versus physician's choice in CD30+ CTCL.

Kim YH et al. *Proc ICML* 2013;Abstract 572.

Ongoing Phase III ALCANZA Trial Design (NCT01578499)



Study start date: August 2012

Estimated study completion date: June 2015

MF = mycosis fungoides; pcALCL = primary cutaneous anaplastic large-cell lymphoma

- **Primary endpoint:** ORR lasting ≥4 months
- **Secondary endpoints include:** Complete response, progression-free survival and changes in burden of symptom domain per Skindex-29 questionnaire

Kim YH et al. *Proc ICML* 2013;Abstract 572.

Study Treatments

- Patients will be stratified by diagnosis and randomly assigned to receive brentuximab vedotin or physician's choice of methotrexate or bexarotene.
- Patients who achieve a complete or partial response at cycle 3 may continue the study drug for up to 48 weeks.
- Patients with stable disease and evidence of benefit may continue for a further 3 cycles.
- Patients with increasing skin score (modified severity weighted assessment tool; mSWAT) prior to cycle 3 may continue until cycle 3 if it is due to tumor flare.

Kim YH et al. *Proc ICML* 2013;Abstract 572.

Efficacy and Safety Assessments

- Response assessments will include:
  - Skin (mSWAT)
  - Nodal and visceral radiographic assessments
  - Detection of circulating Sézary cells (MF only)
- ORR will be evaluated until disease progression or study closure.
- Safety assessments will include:
  - Incidence and severity of adverse events
  - Changes to physical and laboratory tests
- Enrollment into the ALCANZA trial is ongoing.

Kim YH et al. *Proc ICML* 2013;Abstract 572.

Investigator Commentary: The Phase III ALCANZA Trial of Brentuximab Vedotin versus Physician's Choice in CD30+ CTCL

This ongoing Phase III trial is comparing brentuximab to physician's choice of either methotrexate or bexarotene for patients with CD30-positive cutaneous T-cell lymphoma. Most of these patients would be patients with mycosis fungoides, although other types of CTCL are represented. Prior to this trial studies have evaluated brentuximab vedotin for patients with CTCL, and data from a Phase II study were interesting. Anecdotally, I have used brentuximab for some patients with CTCL and they have had good responses, and I believe this will likely be an important setting to continue to investigate.

Interview with Julie M Vose, MD, MBA, July 19, 2013

RoCHOP Study: A Phase III Randomized Study of CHOP Compared to Romidepsin-CHOP in Untreated Peripheral T-Cell Lymphoma

Delarue R et al.

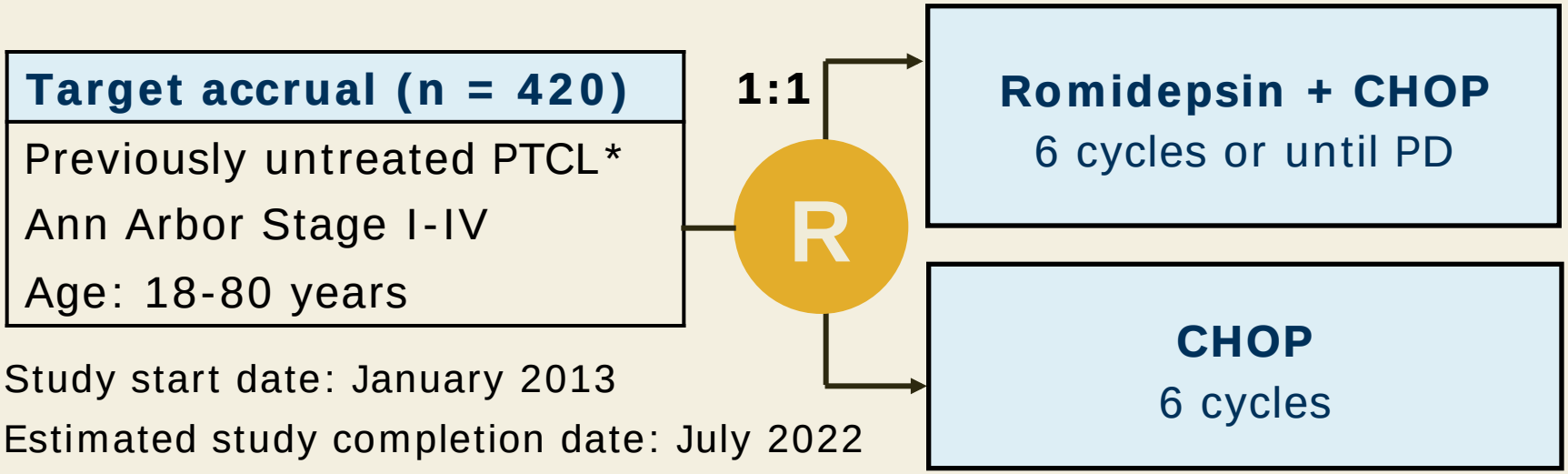
Proc ASCO 2013;Abstract TPS8616;
Proc ICML 2013;Abstract 564.

Background

- Peripheral T-cell lymphoma (PTCL) is an aggressive disease that accounts for about 15% of non-Hodgkin lymphoma and is associated with poor prognosis even with up-front CHOP therapy.
- A pivotal Phase II trial of romidepsin, a histone deacetylase inhibitor, showed a response rate of 25% among patients with heavily pretreated PTCL (*JCO* 2012;30:631).
  - Patients (15%) achieved a CR/Cru.
  - Of those who achieved CR/CRu, 89% were without disease progression at a median follow-up of 13.4 months.
- In the Phase Ib part of the Ro-CHOP study, the recommended dose for romidepsin was 12 mg/m^2 on days 1 and 8 of each cycle (*Proc ASH* 2012;Abstract 1617).
- **Study objective:** To compare the efficacy and safety of romidepsin/CHOP versus CHOP in previously untreated PTCL.

Delarue R et al. *Proc ASCO* 2013;Abstract TPS8616; *Proc ICML* 2013;Abstract 564.

Ongoing Phase III Ro-CHOP Trial Design (NCT01796002)



Study start date: January 2013

Estimated study completion date: July 2022

* Includes PTCL not otherwise specified (PTCL-NOS); angioimmunoblastic T-cell lymphoma; ALK-negative anaplastic large cell lymphoma (ALCL); enteropathy-associated T-cell lymphoma; hepato-splenic T-cell lymphoma; subcutaneous panniculitis-like T-cell lymphoma

- **Primary endpoint:** Progression-free survival (PFS) by independent review
- **Secondary endpoints include:** Overall survival, response rate, duration of response, safety and quality of life

Delarue R et al. *Proc ASCO* 2013;Abstract TPS8616; *Proc ICML* 2013;Abstract 564.

Study Methods

- Patients will be stratified prior to randomization by:
  - International Prognostic Index (IPI) score (<2 vs ≥2)
  - Age (≤60 vs >60 years)
  - Investigator-assessed histology (nodal vs extranodal)
- A recruitment of 10.5 patients per month is anticipated, with a total duration of the study of 60 months.
- Romidepsin (IV) will be administered before CHOP on days 1 and 8 of each 3-week cycle:
  - Starting dose: 12 mg/m^2
  - Dose adaptations (2 levels: 10 and 8 mg/m^2) according to toxicities (neutropenia, thrombocytopenia, cardiac toxicity)
- CHOP will be administered in 3-week cycles.

Delarue R et al. *Proc ASCO* 2013;Abstract TPS8616; *Proc ICML* 2013;Abstract 564.

Concomitant Treatments

- Concomitant treatments allowed on the study include:
  - Prophylaxis for tumor lysis syndrome prior to cycle 1 or for *Pneumocystis jirovecii* infection
  - Primary prophylaxis with G-CSF — mandatory
  - Antiemetics prior to CHOP or romidepsin administration
  - Serum potassium or magnesium before each dose of romidepsin; low levels must be corrected, orally or by IV, prior to romidepsin administration
- Prohibited concomitant treatments include:
  - Steroids other than those specified in the study protocol
  - Use of drugs that cause prolongation of QTc
  - Use of strong CYP3A4 inhibitors or potent inducers
  - Use of therapeutic warfarin

Delarue R et al. *Proc ASCO* 2013;Abstract TPS8616.

Measurement of Endpoints

- All responses will be assessed by central review.
- CT scans will occur at study entry, after cycle 3, at the end of treatment, every 3 months during the first 2 years and then every 6 months.
- Central review will occur in real time of all suspected progression during the treatment and follow-up study phases.
- ^{18}FDG-PET scan (not mandatory) may be performed at study entry and at the end of treatment.
- There will be a central review of all pathological samples at disease diagnosis and relapse.
- Quality of life will be assessed using the EORTC QLQC-30 questionnaire.

Delarue R et al. *Proc ASCO* 2013;Abstract TPS8616.

Exploratory Objectives

- Evaluation of response rate by FDG-PET scan assessment
- Concordance between investigator-assessed and centrally reviewed efficacy data
- Association between biological profile in tumor sample and the efficacy of romidepsin

Delarue R et al. *Proc ASCO* 2013;Abstract TPS8616.

Investigator Commentary: The Phase III Ro-CHOP Trial of Romidepsin/CHOP versus CHOP in Previously Untreated PTCL

This is a follow-up Phase III study to a Phase II study that was presented at the 2013 12th International Conference on Malignant Lymphoma in Lugano that combined romidepsin with CHOP. The results of the Phase II study were somewhat disappointing in that the response rates did not appear to be much higher than what would be expected with CHOP alone, and the toxicity was substantial. I'm unsure as to what the results of the Phase III trial will be, but I believe the toxicity issue will be apparent in this trial also. I would like to see us get away from using CHOP, but I don't know that we have the data yet to say that we can.

Interview with Julie M Vose, MD, MBA, July 19, 2013