5 Minute JournalClub

POST-ASH Issue 4, 2013

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CME Information

LEARNING OBJECTIVES

- Appraise recent clinical research findings on the use of PET scans after initial chemotherapy to identify patients with early-stage Hodgkin lymphoma who can avoid additional radiation therapy, and apply this information in the management of patients' disease.
- Recall emerging clinical research data with combined proteasome and histone deacetylase inhibition in patients with peripheral T-cell or NK/T-cell lymphoma.
- Evaluate the benefits and risks of novel therapeutic approaches under evaluation with brentuximab vedotin as front-line or later-line therapy in advanced and relapsed/refractory Hodgkin and T-cell lymphomas.
- Consider patient characteristics associated with long-term responses to single-agent romidepsin in the care of patients with relapsed/refractory peripheral T-cell lymphoma.

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)

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POST-ASH Issue 4, 2013

Will brentuximab vedotin increase the cure rate of advanced Hodgkin lymphoma?... and more

On a crisp autumn afternoon in 1990, I timidly entered the office of the Physician-in-Chief of Memorial Sloan-Kettering Cancer Center and former NCI Director Dr Vincent DeVita. My journey to the Big Apple was for our nascent breast cancer audio series (on cassette tapes!) and specifically focused on Dr DeVita's perspectives on the controversial "NCI Clinical Alert" he helped launch, defining the duration of adjuvant tamoxifen (discussed in our recent breast cancer email). Throughout the interview, Dr DeVita nibbled from a jar of chocolate-covered coffee beans, which seemed to further stimulate the conversation, and he became particularly animated when discussing his vision for combination chemotherapy exemplified by his prototypical MOPP regimen in Hodgkin lymphoma (HL) — or Hodgkin's disease, as it was known then. He then went on to describe for our listeners the principles of tumor cell kinetics and noncross-resistant combination regimens that spawned an entire generation of oncologic research.

A lot has happened since that fall day, and while tens of thousands of people

have been cured of HL and other cancers with chemotherapy, for most patients in the advanced setting treatment has been palliative in nature and marred by toxicities. In that regard, most investigators, including the one who now occupies Dr DeVita's august Memorial office and title (Dr José Baselga), have concentrated their efforts on developing novel targeted agents designed to make cytotoxics obsolete. Unfortunately, we are not there yet and chemotherapy remains a mainstay in our treatment armamentarium, and at ASH we saw this dynamic play out as both new agents and tried-and-true chemotherapy grabbed headlines in HL and T-cell lymphomas:

1. Chemotherapy without radiation therapy (RT) in early-stage HL

According to another Memorial maven, Dr Andy Zelenetz, the ASH presentation of the much-awaited UK RAPID trial may set a new standard in this disease — specifically for patients with Stage IA and IIA HL or mediastinal bulky disease who have a negative PET scan after 3 cycles of ABVD. In RAPID, at 4 years more than 90% of patients were progression free with or without involved-field RT and, based in part on these findings, investigators are continuing to carefully consider treatment without RT in early PET-negative cases, particularly for younger women at risk for delayed secondary breast cancers.

2. Brentuximab vedotin (BV) as part of up-front treatment of advanced HL

Dr DeVita must be pleasantly surprised at the advent of antibody-drug

conjugates (ADC) like BV and the just-approved (in metastatic breast cancer) T-DM1 (ado-trastuzumab emtansine) — agents that can deliver cytotoxics inside tumor cells with minimal normal cell kill. Although BV was approved only 18 months ago, ASH was a reminder that this ADC is here to stay for the long term. Phase II trials of BV in the relapsed/refractory (RR) HL setting revealed a 75% response rate (34% CR) and have helped foster attempts, including a randomized Phase II trial first reported at last year's ASH, to integrate this anti-CD30 ADC into up-front treatment of advanced HL. As part of last year's report, ABVD combined with BV yielded an unacceptable pulmonary toxicity rate. However, this was not seen with BV and AVD (ABVD without the bleomycin), and efficacy findings were encouraging enough to spawn a major ongoing multicenter Phase III trial comparing ABVD to BV + AVD. In this ASH update of the Phase II study, 24 of 26 patients had negative FDG-PET scans after 2 cycles of BV + AVD, which was well tolerated other than mostly reversible peripheral neuropathy.

3. BV as part of up-front treatment of systemic anaplastic large cell lymphoma (sALCL) and mature T- and NK-cell lymphomas

As with HL, encouraging findings in the RR setting (86% responses with 57% CR) have led to efforts to combine BV with up-front chemotherapy. At ASH we saw results from 2 arms of a Phase I study evaluating BV combined with CHP (the vincristine was omitted from CHOP to prevent neuropathy) in patients with sALCL or mature T- and NK-cell lymphomas. The regimen was well tolerated and response was observed in all 26 patients in the trial, including 23 CRs. These and

other encouraging data have led to an ongoing Phase III trial comparing BV-CHP to CHOP.

4. BV in RR mycosis fungoides (MF)/Sézary syndrome

A small Phase II study reported at ASH evaluated single-agent BV in patients with previously treated MF/Sézary syndrome, and responses occurred in 13 of 19 patients. Importantly, activity was observed with all levels of CD30 expression, although the authors point out significant limitations with conventional immunohistochemical staining compared to the multispectral image analysis used in this study. Based in part on these findings, a Phase III trial will compare BV to investigator's choice of bexarotene or methotrexate in these patients.

5. Histone deacetylase (HDAC) inhibition in T-cell lymphomas — bortezomib/panobinostat (BP) and romidepsin

Two reports unveiled in Atlanta further contribute to the growing database on the effectiveness of HDAC inhibitors in T-cell lymphoma. The first evaluated the novel BP combination in 11 patients with RR PTCL and NK-cell lymphoma. The results from this effort were encouraging, and the investigators are interested in studying longer-term maintenance with this regimen.

The second important HDAC paper was an update of the pivotal Phase II trial of romidepsin in 130 patients with RR PTCL. Previous data from that study demonstrated a 25% response rate (and led to the FDA approval of this agent in

this setting), and the ASH data set is noteworthy in that more follow-up reveals that responses are often durable, lasting on average more than a year, and up to 4 years, further solidifying the role of this agent in these patients.

The shift in research emphasis in HL, T-cell lymphomas and most other corners of oncology away from chemotherapy and toward novel agents clearly is in full swing, and it will be interesting to look back in a quarter of a century when we know whether this strategy delivers or if it repeats the limitations of chemotherapy that crushed the hopes of oncology leaders of the past generation.

Next…Another cancer for which biological treatment has yielded results never dreamed of in the cytotoxic era — multiple myeloma and a series of ASH papers evaluating two exciting novel proteasome inhibitors — the oral investigational compound ixazomib (formerly MLN9708) and the recently approved irreversible agent carfilzomib.

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Involved Field Radiotherapy versus No Further Treatment in Patients with Clinical Stages IA/IIA Hodgkin Lymphoma and a "Negative" PET Scan After 3 Cycles ABVD: Results of the UK NCRI RAPID Trial

Radford J et al.

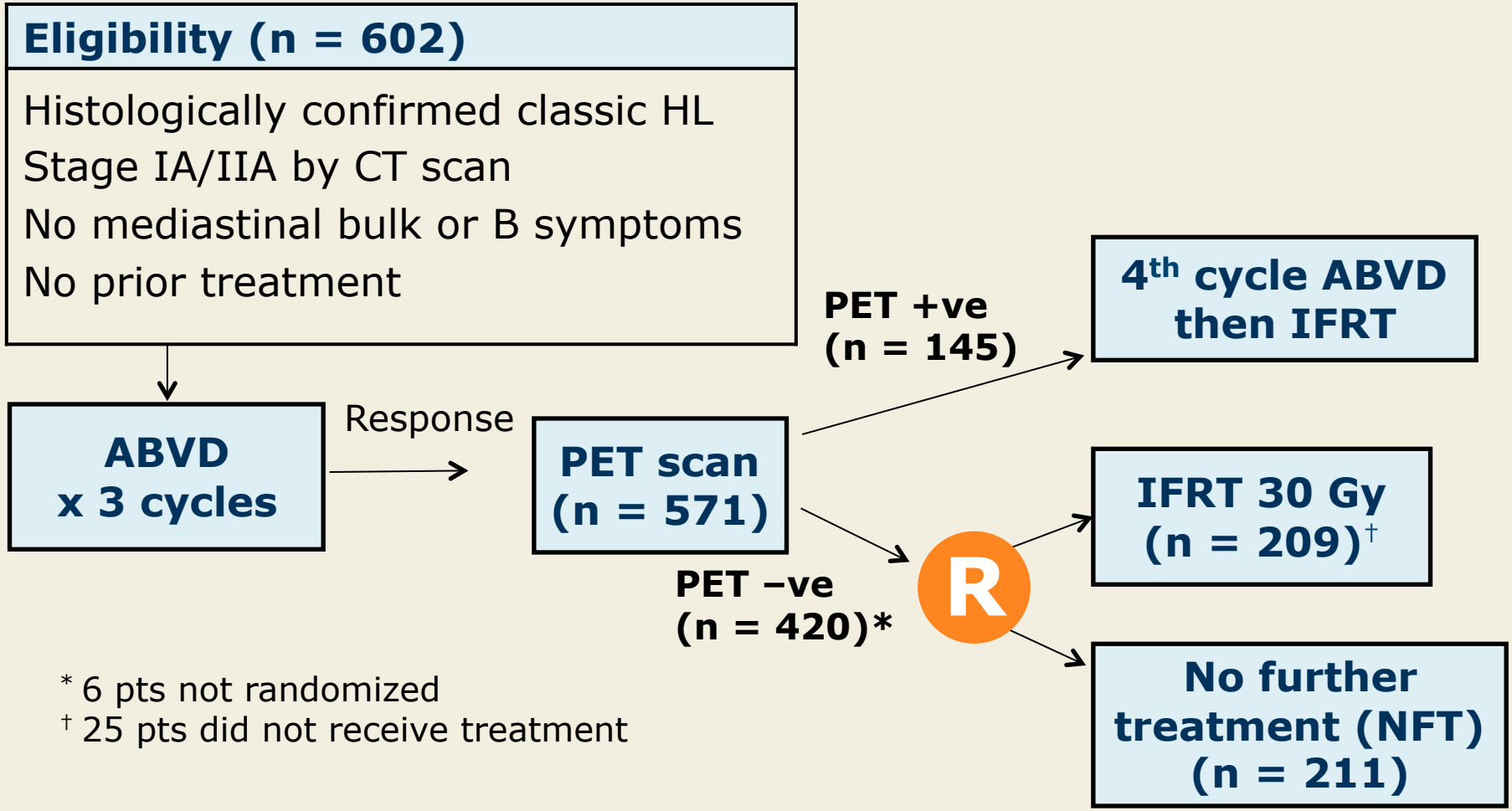
Proc ASH 2012;Abstract 547.

Background

- In early-stage Hodgkin lymphoma (HL), abbreviated chemotherapy (ACT) followed by involved field radiotherapy (IFRT) is the current standard of care, but some patients may be cured by ACT alone.
- PET imaging has the potential to identify patients with an excellent prognosis after ACT and thus provide the opportunity to avoid radiotherapy and reduce late treatment toxicity in these individuals.
- **Study objective:** To evaluate PET response-directed therapy for patients with previously untreated Stage IA or IIA HL.

Radford J et al. *Proc ASH* 2012;Abstract 547.

Phase III RAPID Study Design



* 6 pts not randomized
† 25 pts did not receive treatment

Radford J et al. *Proc ASH* 2012;Abstract 547.

RAPID Design (Continued)

- PET scanning: Quality-controlled PET images acquired and transmitted to a Core Lab
- PET score of 1 to 5 assigned at Core Lab review and is the sole determinant for randomization
  - Score of 1 or 2: PET-negative, score of 3, 4 or 5: PET-positive
- Statistics: Noninferiority design
  - Assumption that in IFRT arm, 3-y progression-free survival (PFS) would be 95%
  - With 400 pts with PET-negative HL randomly assigned and 46 events, RAPID was powered to exclude ≥7% difference in PFS (lowest acceptable: 3-y PFS of 88% in NFT arm)
- Analysis at median follow-up of 48.6 mo and following 36 of 46 events because results were considered significant by IDMC

Radford J et al. *Proc ASH* 2012;Abstract 547.

Events at a Median Follow-Up of 48.6 Months

	PET–, IFRT (n = 209)	PET–, NFT (n = 211)	PET+ (n = 145)
Alive without PD	194 (92.8%)	190 (90.0%)	125 (86.2%)
PD	8 (3.8%)	20 (9.5%)	12 (8.3%)
Deaths	7 (3.3%)	1 (0.5%)	8 (5.4%)

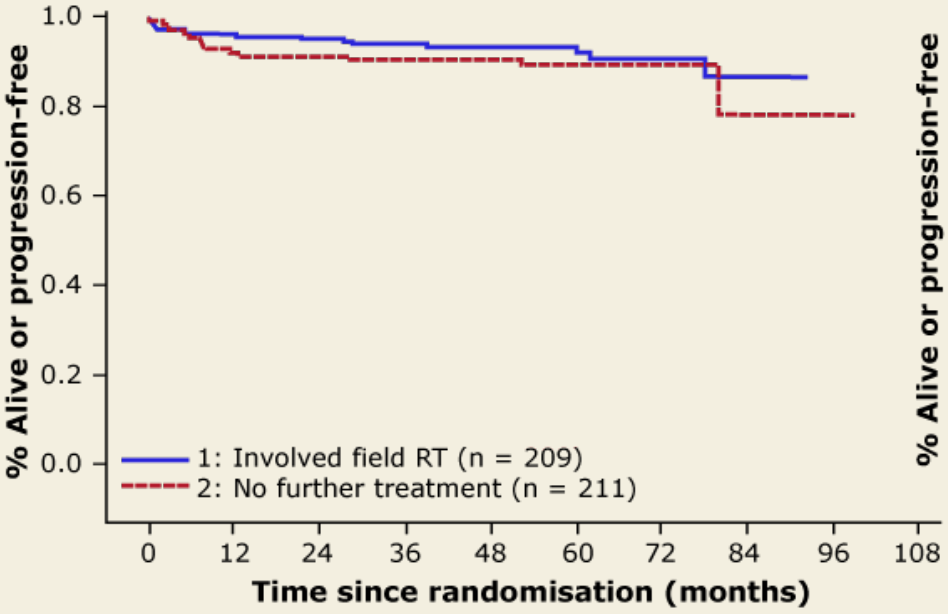
PD = progressive disease

- 74.6% pts PET-negative after 3 cycles of ABVD
- Deaths in IFRT arm (n = 7):
  - Pts who received RT (n = 2): Mycosis fungoides (n = 1), myocardial fibrosis and heart failure (n = 1)
  - Pts who did not receive RT (n = 5): AITL (n = 1), pneumonitis (n = 2), intracerebral hemorrhage and respiratory failure (n = 1), not determined (n = 1)

Radford J et al. *Proc ASH* 2012;Abstract 547.

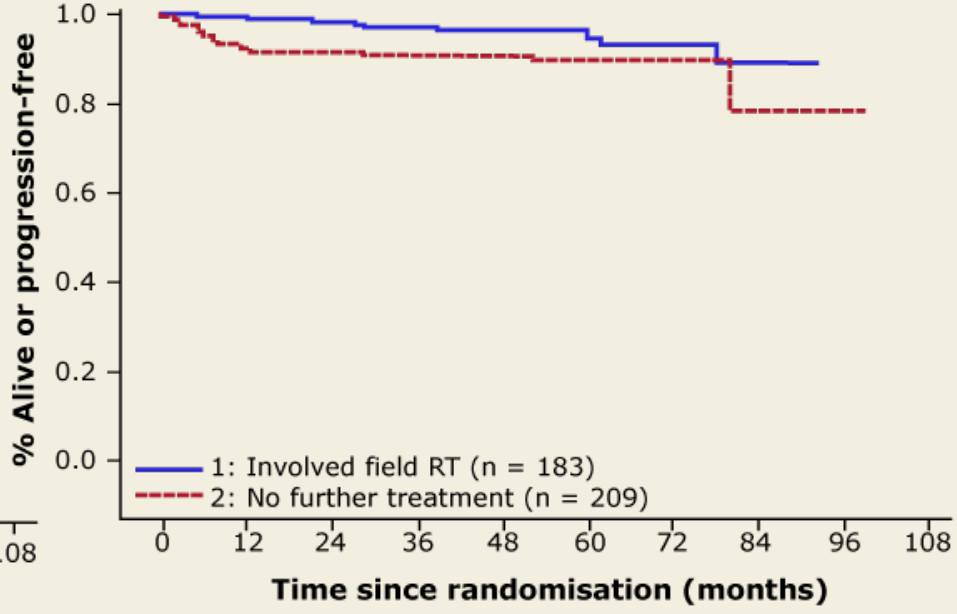
PFS in the PET-Negative Population

ITT population (n = 420)



3-year PFS: 94.5% vs 90.8%
HR 1.51 in favor of IFRT, $p = 0.23$

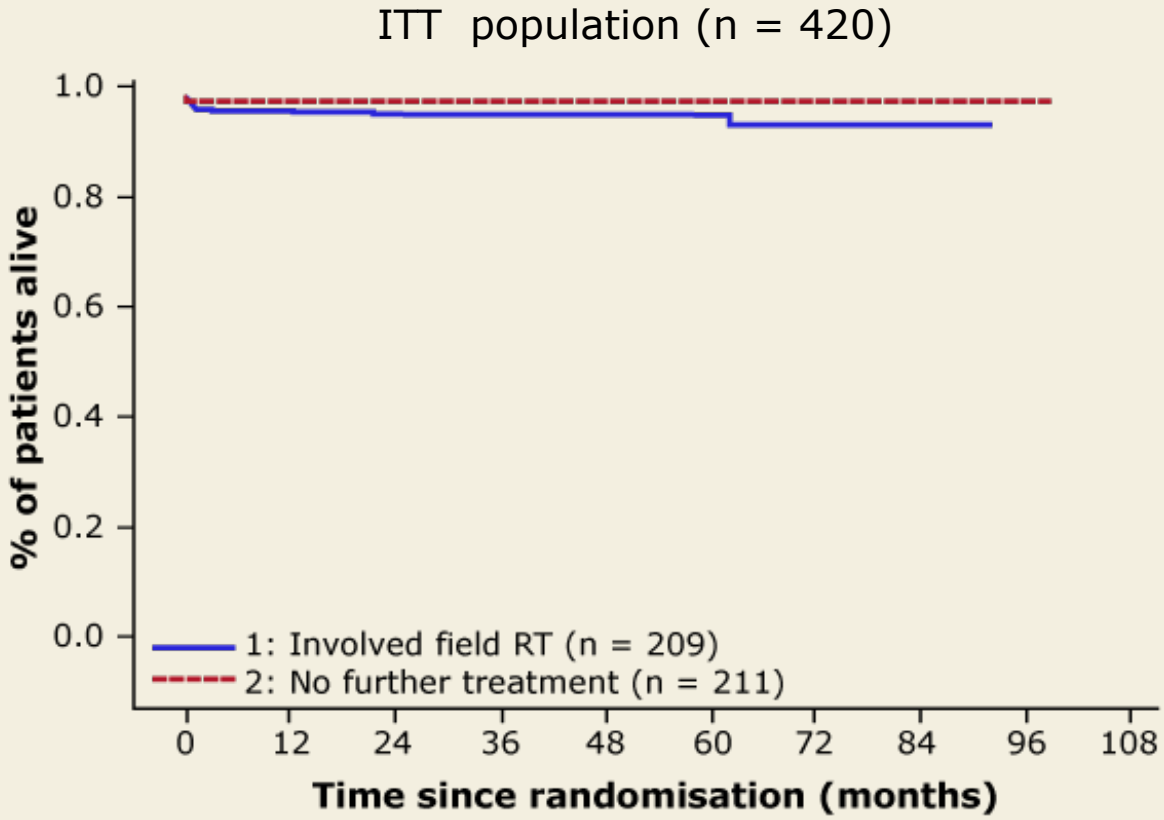
Per protocol analysis of patients who received allocated treatment (n = 392)



3-year PFS: 97% vs 90.7%
HR 2.39 in favor of IFRT, $p = 0.03$

With permission from Radford J et al. *Proc ASH* 2012;Abstract 547.

Overall Survival in the PET-Negative Population



3-year OS: 97.1% vs 99.5%
HR 0.15 in favor of NFT, $p = 0.07$

With permission from Radford J et al. *Proc ASH* 2012;Abstract 547.

Author Conclusions

- Using PET it is possible to identify a population of patients with Stages IA and IIA HL who have an excellent outcome after 3 cycles of ABVD.
- Crucially, these results have been obtained in the setting of:
  - Quality-controlled PET image acquisition
  - Central review of PET images at the Core Laboratory
  - A conservative definition of PET-negative
- Longer follow-up is required to establish the impact of a PET-directed approach on 10- and 20-year survival and cause of death.

Radford J et al. *Proc ASH* 2012;Abstract 547.

Investigator Commentary: RAPID — Involved Field Radiotherapy versus No Further Treatment for Patients with Stage IA or IIA HL and a "Negative" PET Scan After 3 Cycles of ABVD

Many patients with HL are being cured, so we are attempting to alter therapy for patients with high-risk disease and reduce the amount of therapy for patients with low-risk disease. In this large study, patients with early-stage HL received 3 cycles of ABVD, after which about 75% of patients had PET-negative disease. Those patients were randomly assigned to IFRT or NFT. After a follow-up of about 4 years, amazingly, more than 90% of the patients with PET-negative disease were free of disease progression. Comparison between the IFRT and NFT groups showed that the results were noninferior. So we can not only limit the amount of treatment to 3 cycles of ABVD but also safely eliminate radiation therapy for patients in this setting.

Community oncologists frequently refer patients for radiation therapy. Patients come to academic centers for a second opinion. I rarely recommend IFRT for any patient, particularly not for young women. I believe more and more academic physicians are recommending less radiation therapy.

Interview with Bruce D Cheson, MD, January 14, 2013

Frontline Therapy with Brentuximab Vedotin Combined with ABVD or AVD in Patients with Newly Diagnosed Advanced Stage Hodgkin Lymphoma

Ansell SM et al.

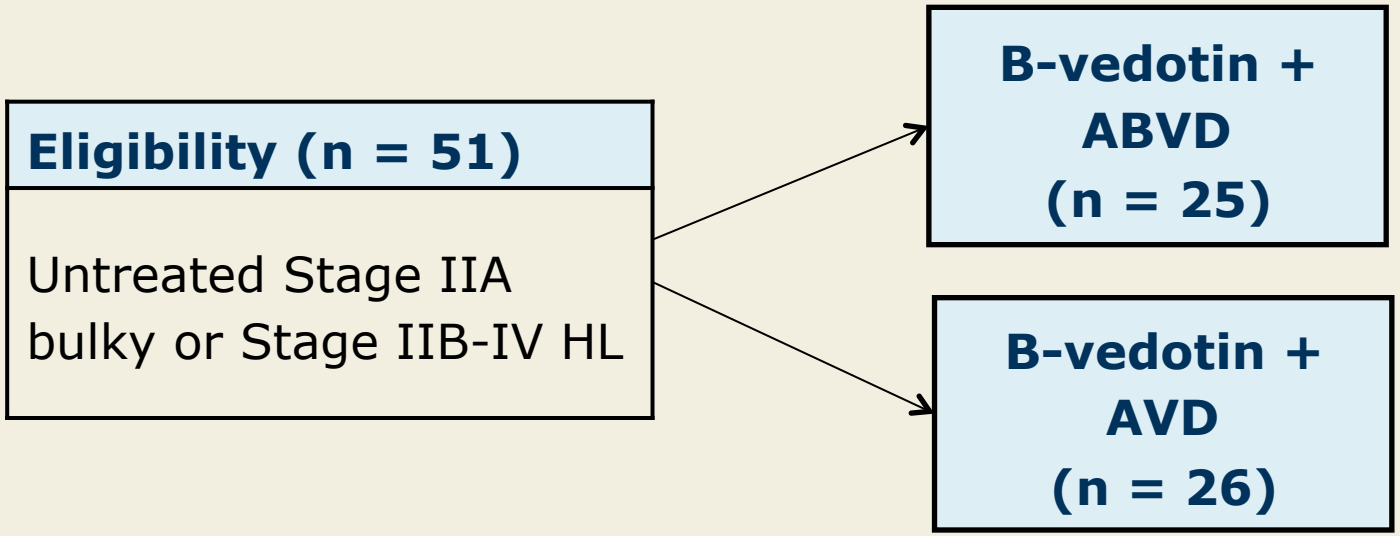
Proc ASH 2012;Abstract 798.

Background

- A Phase II trial of brentuximab vedotin (b-vedotin) in relapsed or refractory Hodgkin lymphoma (HL) showed an objective response rate of 75% (CR, 34%) after autologous stem cell transplant (*JCO* 2012;30:2183).
- Front-line therapy for HL with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) generally yields a 70% to 80% CR rate. However, bleomycin-induced pulmonary toxicity occurs in 10% to 25% of patients.
- **Study objective:** To evaluate the safety and efficacy of b-vedotin with ABVD or AVD (ABVD without bleomycin) in the front-line treatment of newly diagnosed, advanced HL.

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

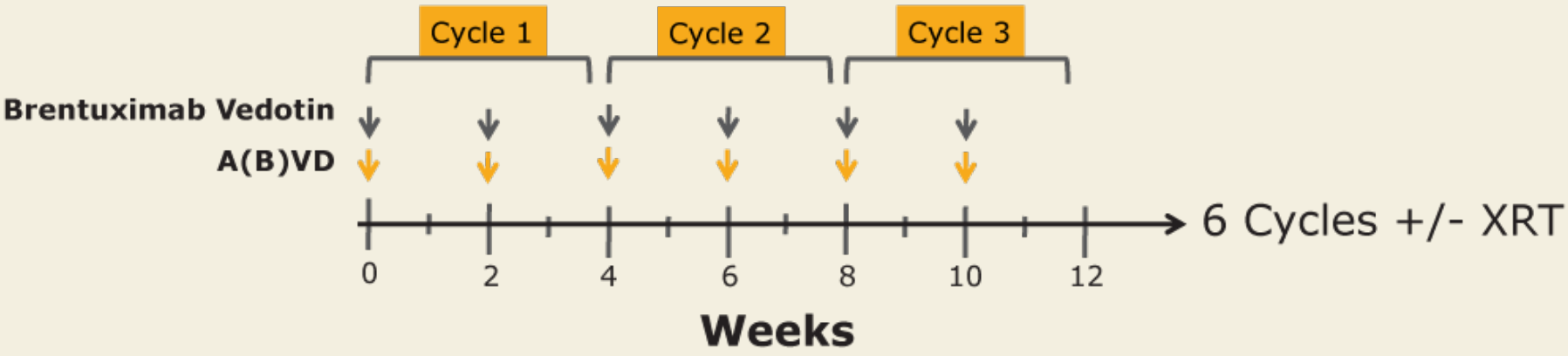
Phase I Dose-Escalation Study Design



- **Key objectives:**
  - Safety of b-vedotin in combination with ABVD or AVD
  - Maximum tolerated dose (MTD) of b-vedotin in combination with ABVD or AVD
  - Antitumor activity of b-vedotin in combination with ABVD or AVD

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Dose Schedule and Dose Cohorts



- 28-day cycles (up to 6 cycles) with dosing on days 1, 15
- Dose cohorts:
  - ABVD + b-vedotin (n = 25): Cohorts 1-3 (0.6-1.2 mg/kg)
  - AVD + b-vedotin (n = 26): Cohort 4 and an expansion cohort (both 1.2 mg/kg)

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Response

Response at end of front-line therapy	ABVD + b-vedotin (n = 22)	AVD + b-vedotin (n = 25)
Complete remission	95%	96%
Progressive disease	0%	4%
Not evaluable due to AEs*	5%	0%

* Patient had a Grade 5 pulmonary adverse event (AE) prior to end of front-line therapy

- Cycle 2 FDG-PET results evaluated by central review for 48 patients
  - ABVD cohorts: 100% (22/22) negative
  - AVD cohorts: 92% (24/26) negative
- Prognostic value of interim PET in these regimens not established

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Select Adverse Events

Grade ≥3 AEs*	ABVD + b-vedotin (n = 25)	AVD + b-vedotin (n = 26)
Neutropenia	80%	77%
Anemia	20%	12%
Febrile neutropenia	20%	8%
Pulmonary toxicity	24%	0%
Dyspnea	12%	4%
Pulmonary embolism	12%	0%
Leukopenia	4%	4%

* Occurring in >1 patient overall, regardless of relationship

- Peripheral neuropathy (PN), mostly Grade 1/2, occurred in 72% of pts in the ABVD + b-vedotin arm and 77% of pts in the AVD + b-vedotin arm and was managed with dose modifications.
- One pt had Grade 3 PN, but no Grade 4/5 events were reported.
- Overall 6/51 pts discontinued b-vedotin in treatment cycle 5 or 6, due to PN.

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Pulmonary Toxicity

	ABVD + b-vedotin (n = 25)	AVD + b-vedotin (n = 26)
Any event	44%	0%
Pulmonary toxicity	36%	0%
Interstitial lung disease	4%	0%
Pneumonitis	4%	0%

- Events generally occurred during cycles 3-4
- Events resolved in 9/11 (82%) of patients
- 8/11 patients with events discontinued bleomycin and were able to complete treatment with AVD + b-vedotin
- Deaths associated with pulmonary toxicity, n = 2

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Author Conclusions

- Concomitant administration of b-vedotin and bleomycin is contraindicated due to pulmonary toxicity.
- The recommended regimen is 1.2 mg/kg b-vedotin every 2 weeks combined with AVD.
- AVD combined with b-vedotin appears to be well tolerated with manageable AEs.
- A complete remission rate of 96% was observed at the end of front-line therapy with b-vedotin combined with AVD.
- A Phase III study to assess treatment with b-vedotin in combination with AVD as compared to ABVD alone in treatment-naïve patients is ongoing (NCT01712490).

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Investigator Commentary: Front-Line Therapy with Brentuximab Vedotin Combined with ABVD or AVD for Advanced HL

This study showed that the addition of b-vedotin to ABVD resulted in pulmonary toxicity, interstitial lung disease and pneumonitis in 44% of patients. However, this did not occur when b-vedotin was combined with AVD. A previous study by the CALGB had warned that the combination of GVD (gemcitabine, vinorelbine and doxorubicin) with SGN-30, the antibody backbone of b-vedotin, in patients with relapsed HL results in serious pulmonary toxicity (*Ann Oncol* 2010;21:2246).

Peripheral neuropathy was also observed in more than 70% of patients in both arms of this study. Although neuropathy can be a problem, it can be managed with dose modifications and is partially reversible in the majority of patients.

The current study showed spectacular response rates. It forms the basis for a pivotal Phase III trial for patients with untreated HL. This important trial has the potential to change how we care for these patients. I believe that b-vedotin-based regimens have a bright future, but the treatment will have to be fine-tuned and associated with less toxicity for it to make a major impact on HL in the front-line setting.

Interview with Bruce D Cheson, MD, January 14, 2013

Brentuximab Vedotin Administered Concurrently with Multi-Agent Chemotherapy as Frontline Treatment of ALCL and Other CD30-Positive Mature T-Cell and NK-Cell Lymphomas

Fanale M et al.

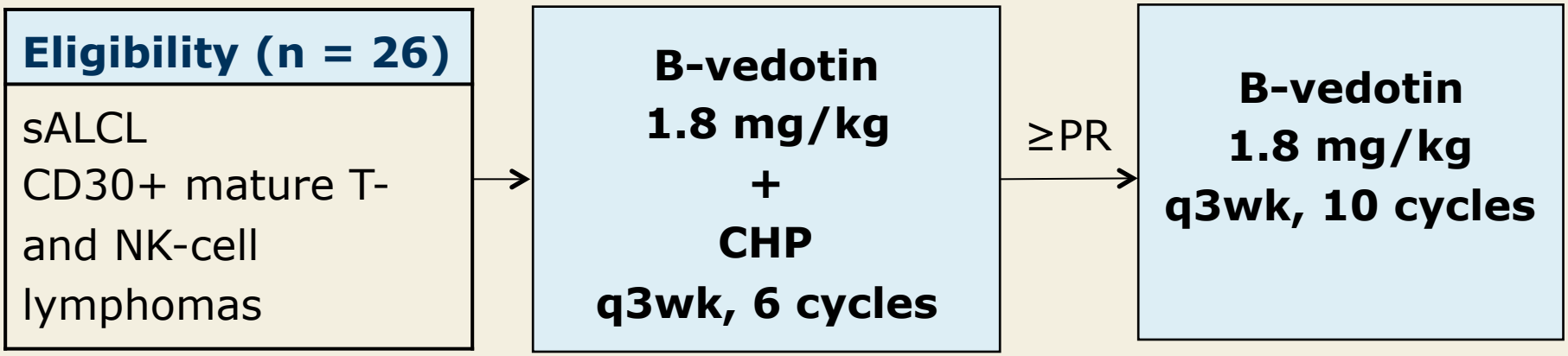
Proc ASH 2012;Abstract 60.

Background

- CD30 is expressed on systemic anaplastic large cell lymphoma (sALCL) and mature T- and NK-cell lymphomas.
- Front-line anthracycline-containing regimens achieve good response rates, but fewer than half of patients remain disease or progression free after 5 years (*JCO* 2008;26:4124).
- A Phase II pivotal trial of brentuximab vedotin (b-vedotin) in patients with relapsed or refractory sALCL showed an objective response rate of 86% (CR rate 57%) with manageable toxicity (*JCO* 2012;30:2190).
- **Objective:** Evaluate the safety and efficacy of b-vedotin with CHP (CHOP without vincristine) in the front-line treatment of CD30+ mature T-cell and NK-cell neoplasms, including sALCL.

Fanale M et al. *Proc ASH* 2012;Abstract 60.

Phase I Study Design: Arms 2 and 3



- Study had 3 arms:
  - Arm 1: B-vedotin (1.8 mg/kg, q3wk, 2 cycles) followed by CHOP (6 cycles), data previously presented (ESMO 2012)
  - Arm 2: Designed to determine recommended dose of b-vedotin in combination with CHP to be further evaluated in Arm 3
  - The maximum tolerated dose was not exceeded at 1.8 mg/kg q3wk
- **Primary endpoints:** Safety of b-vedotin + CHP and recommended dose of b-vedotin in combination with CHP
- **Secondary endpoint:** Antitumor activity of b-vedotin + CHP

Fanale M et al. *Proc ASH* 2012;Abstract 60.

Best Response by Disease Diagnosis

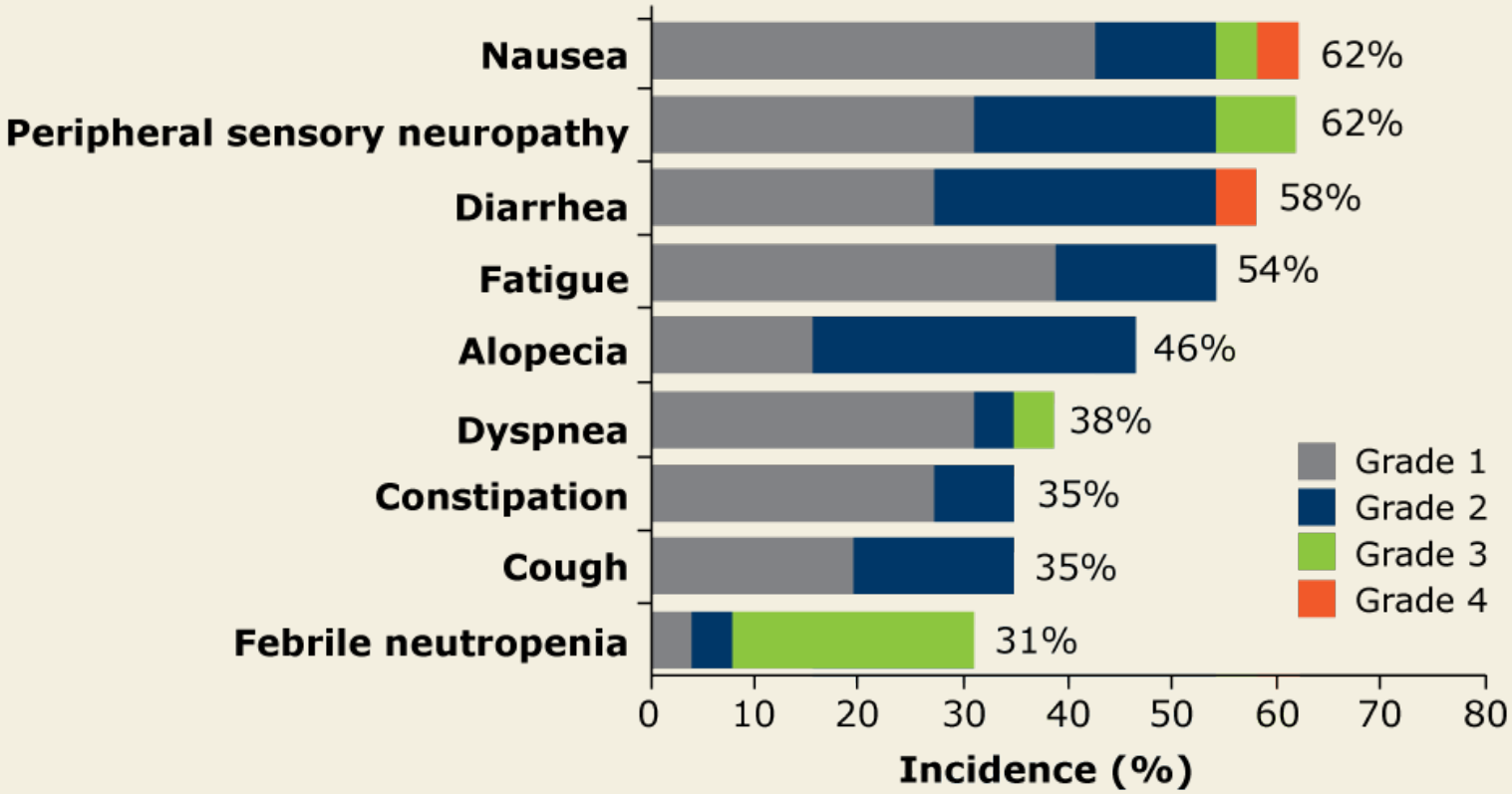
Response	sALCL (n = 19)	Other diagnoses (n = 7)	Total (n = 26)
ORR*	100%	100%	100%
CR	84%	100%	88%
PR	16%	—	12%
Median PFS	—	—	NR
Median OS	—	—	NR

* At end of cycle 6 or latest assessment for 3 pts who discontinued prior to cycle 6
NR = not reached, pts followed for a median of 9 mo

- 21/26 pts continue to receive single-agent b-vedotin after combination therapy
  - At end of cycle 12, ORR = 92%, CR = 85%
  - At end of cycle 16, ORR = 100%, CR =100%

Fanale M et al. *Proc ASH* 2012;Abstract 60.

Adverse Events (≥30% of Patients)



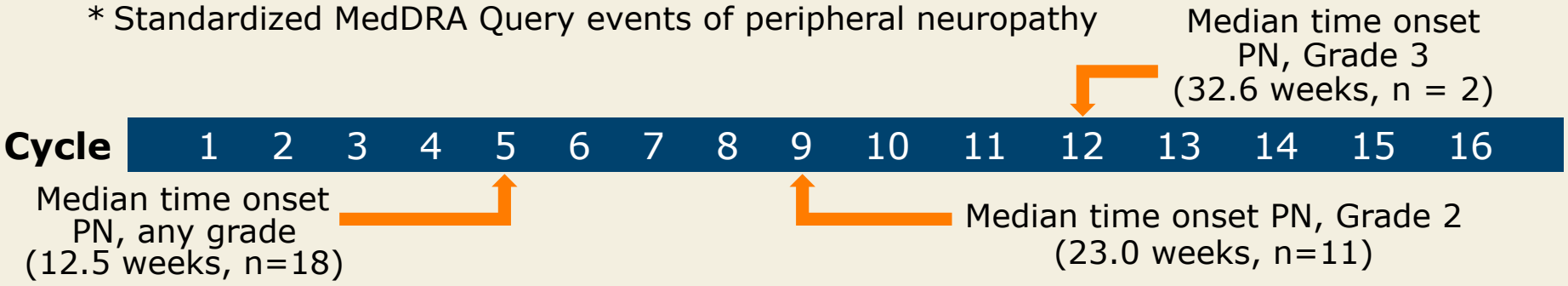
Additional Grade ≥3 adverse events occurring in >5% of patients were hyperglycemia, neutropenia, pulmonary embolism and respiratory failure (n = 2 each).

With permission from Fanale M et al. *Proc ASH* 2012;Abstract 60.

Peripheral Neuropathy (PN)

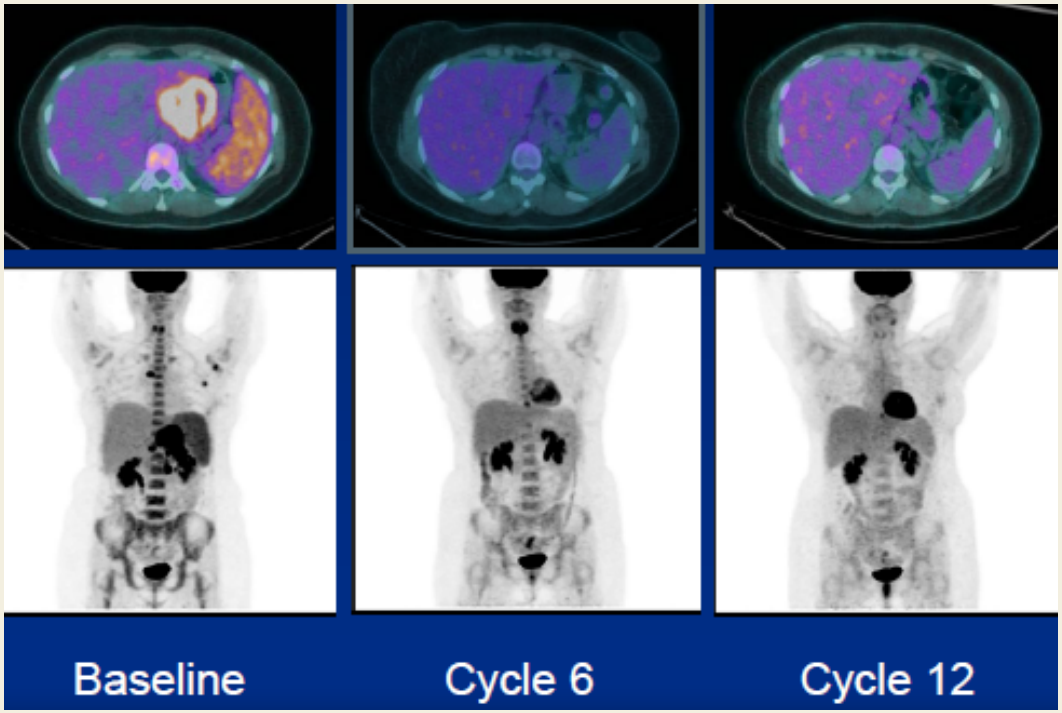
Preferred term*	Grade 1	Grade 2	Grade 3	Total N = 26
Any event, n (%)	7	9	2	18 (69)
Peripheral sensory neuropathy	8	6	2	16 (62)
Muscular weakness	2	1	—	3 (12)
Peripheral motor neuropathy	—	1	1	2 (8)
Burning sensation	1	—	—	1 (4)
Paresthesia	—	—	1	1 (4)
Peripheral sensorimotor neuropathy	—	1	—	1 (4)
Peroneal nerve palsy	1	—	—	1 (4)

* Standardized MedDRA Query events of peripheral neuropathy



Fanale M et al. *Proc ASH* 2012;Abstract 60.

Case Study



- 37-year-old pt, diagnosed with Stage IV PTCL-NOS
- CD30 expression positive by central review
- Received b-vedotin 1.8 mg/kg + CHP (6 cycles), then b-vedotin (9 cycles) alone
- At time of data cutoff, pt continued receiving single-agent b-vedotin

With permission from Fanale M et al. *Proc ASH* 2012;Abstract 60.

Author Conclusions

- B-vedotin with CHP every 3 weeks exhibited manageable toxicity at the recommended dose of 1.8 mg/kg in patients with CD30+ mature T- and NK-cell neoplasms.
- Combination therapy with b-vedotin demonstrated an objective response rate of 100% (CR rate 88%).
- Adverse events with an incidence greater than 30% included nausea, peripheral sensory neuropathy, diarrhea, fatigue, alopecia, dyspnea, constipation, cough and febrile neutropenia.
- A Phase III study comparing CHOP alone to b-vedotin with CHP in the front-line treatment of CD30+ mature T-cell lymphomas will begin in late 2012 or early 2013.

Fanale M et al. *Proc ASH* 2012;Abstract 60.

Investigator Commentary: B-Vedotin with Multiagent Chemotherapy as Front-Line Treatment of ALCL and Other CD30-Positive T-Cell and NK-Cell Lymphomas

This was a small Phase I study that evaluated the safety and efficacy of b-vedotin with CHP chemotherapy for patients with ALCL and CD30-positive T-cell lymphomas. B-vedotin is an antibody-drug conjugate that targets CD30 expressed on HL, ALCL and some T-cell lymphomas. It is not currently known how important the degree of CD30 expression is.

The results showed an overall response rate of 100% and a complete response rate of 88%. Though this is a small study, I think these results are incredibly impressive. T-cell lymphomas are a difficult group of cancers to treat. Prior studies with CHOP in T-cell lymphomas have shown overall response rates of around 80% and complete response rates of around 40%. So, even though this a small study, the results are highly encouraging.

A large, international, Phase III study has been initiated for patients with newly diagnosed ALCL or T-cell lymphomas that are CD30-positive. Patients will be randomly assigned to CHOP chemotherapy or CHP with b-vedotin. This trial represents an opportunity to move the field forward for that group of patients.

Interview with Brad S Kahl, MD, January 17, 2013

Brentuximab Vedotin Demonstrates Significant Clinical Activity in Relapsed or Refractory Mycosis Fungoides with Variable CD30 Expression

Krathen M et al.

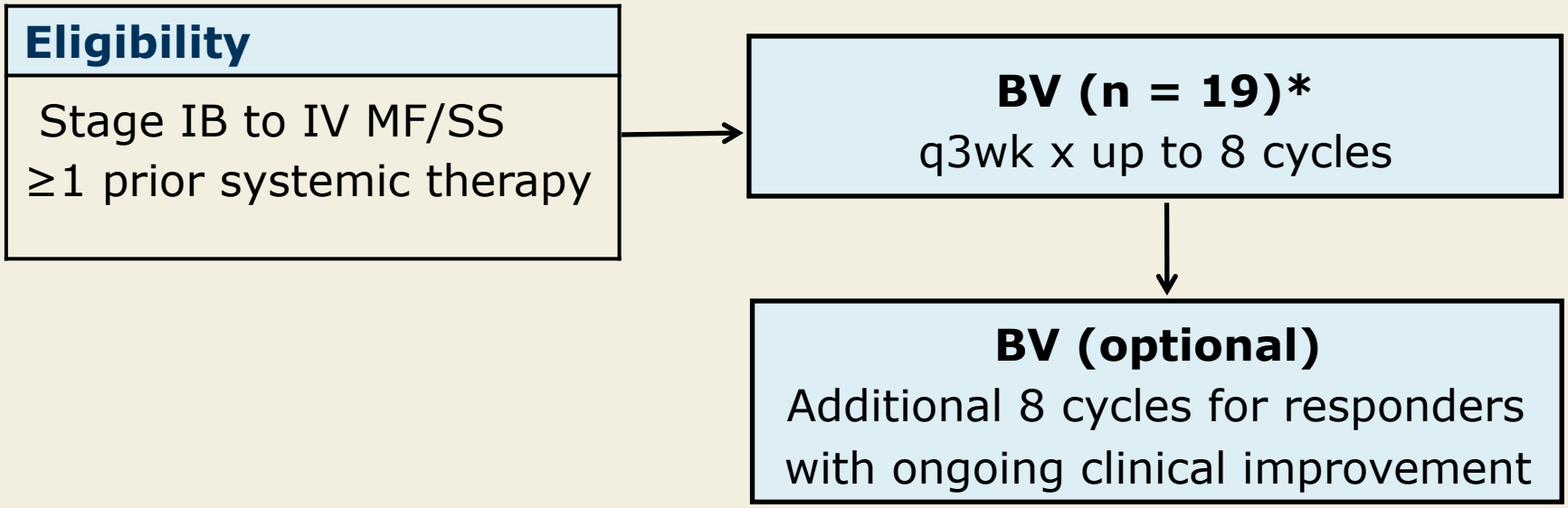
Proc ASH 2012;Abstract 797.

Background

- Malignant Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (ALCL) cells uniformly express the cell surface receptor CD30.
- CD30 expression is more variable, however, in mycosis fungoides/Sézary syndrome (MF/SS).
- Brentuximab vedotin (BV) is an anti-CD30 chimeric antibody approved for use for relapsed HL and ALCL.
- **Study objective:** To assess the efficacy of BV in patients with MF/SS and assess whether a correlation exists between CD30 expression and response.

Krathen M et al. *Proc ASH* 2012;Abstract 797.

Phase II Study Design



* Received at least one BV dose at 1.8 mg/kg

- CD30 expression in the skin (proportion of total lymphoid infiltrate) was evaluated by routine immunohistochemistry (IHC) and by quantitative imaging.
- Clinical response data and CD30 expression were confirmed by independent review.

Krathen M et al. *Proc ASH* 2012;Abstract 797.

Baseline Characteristics (Abstract Only)

Characteristic	
Median age, years (range)	59 (20-88)
Advanced disease (Stage IIB or greater)	17/19
Large cell transformation (LCT)	13/19
Folliculotropic MF (FMF)	8/19
Both LCT and FMF	3/19
Pretreatment CD30 expression*	
<10%	7/19
10-50%	10/19
>50%	2/19

* Percent positive of total lymphoid infiltrate

Krathen M et al. *Proc ASH* 2012;Abstract 797.

Clinical Response (Abstract Only)

Clinical response	n (%)
Overall patients	13/19 (68%)
Stage IB patients	
Partial response	2/2 (100%)
Stage IIB patients	
Partial response	10/11 (91%)
Stable disease	1/11 (9%)
Stage IVA/B patients	
Partial response	1/6 (17%)
Stable disease	1/6 (17%)

- Median time to response = 6 weeks
- At 25 weeks, 74% of responses were ongoing.

Krathen M et al. *Proc ASH* 2012;Abstract 797.

Survival Outcomes

	N = 19
Median event-free survival*	31 weeks
Median progression-free survival	Not reached
Proportion remaining progression free at 6 months	73%

* Event defined as progressive disease, early study termination or initiation of another significant treatment

Krathen M et al. *Proc ASH* 2012;Abstract 797.

CD30 Expression Summary (Abstract Only)

- Pretreatment CD30 quantitative image analysis staining data were available for 31 biopsy samples from 16 patients.
- CD30 staining of lymphoid cells was detected in all samples.
- Included as positive were 12 samples noted as negative by routine IHC.
- CD30 expression was detected on 3 tumors that developed during BV treatment.
- CD30 expression levels did not correlate with clinical response as assessed by routine IHC ($p = 0.17$) or by quantitative image analysis ($p = 0.74$).

Krathen M et al. *Proc ASH* 2012;Abstract 797.

Adverse Events Summary (Abstract Only)

- Grade 1/2 adverse events included:
  - Peripheral neuropathy (78%)
  - Fatigue (61%)
- Grade 3/4 adverse events included:
  - Rash (n = 3) and neutropenia (n = 2)
  - Single reports of peripheral neuropathy (PN), lymphocytosis, acute renal failure, leukopenia, thrombocytopenia, hyperglycemia, sepsis, pneumonia and pruritis
- Median time to development of PN: 14 weeks
- Median time to resolution/improvement in PN: 24 weeks
- One death was reported due to respiratory failure in the patient with pneumonia.

Krathen M et al. *Proc ASH* 2012;Abstract 797.

Author Conclusions

- BV demonstrates significant clinical activity with mostly Grade 1 and 2-related adverse events in heavily pretreated MF.
- Clinical responses were observed in those with all levels of CD30 expression.
- Responses in subjects with zero to low CD30 expression by routine IHC may be in part due to low sensitivity of standard IHC detection of the target.
- This study reports the successful utility of multispectral image analysis to demonstrate low levels of target expression.

Krathen M et al. *Proc ASH* 2012;Abstract 797.

Investigator Commentary: Clinical Activity of Brentuximab Vedotin in Patients with Relapsed/Refractory Mycosis Fungoides

This study accomplishes 2 important steps in terms of exploring the utility of brentuximab vedotin (BV) in diseases other than ALCL and HL. It establishes a principle of using BV for mycosis fungoides by showing a response rate of 68% and good tolerance. This study is too small to allow comparisons, but an ongoing Phase III study comparing BV to investigator's choice of bexarotene or methotrexate (NCT01578499) may establish a standard for BV in this disease.

Perhaps even more interesting is the complete lack of correlation between the level of CD30 expression and response to BV. Patients with less than 10% CD30 expression responded at the same rates as those with high expression. In a hypothesis-generating manner, this opens up the possibility that BV may have important activity beyond the universally high CD30-expressing tumors and may explain why CD30 expression by IHC has not correlated with response. Tumors classified as CD30-low or negative by routine IHC may actually express CD30 on most tumors cells that is detectable using quantitative multispectral image analysis as a more sensitive technique for detecting CD30 expression.

Interview with Steven M Horwitz, MD, March 14, 2013

Investigator Commentary: Clinical Activity of Brentuximab Vedotin in Patients with Relapsed/Refractory Mycosis Fungoides

Brentuximab vedotin is a game changer in oncology. This antibody-drug conjugate was approved for relapsed or refractory Hodgkin disease and ALCL, both CD30-positive disorders. A logical extension would be to study the drug in other CD30-positive disorders, including CTCL and diffuse large B-cell lymphomas that express this antigen.

This study is of great potential clinical importance for patients with advanced refractory CTCL, who have few effective treatment options. It showed a 68% response rate in a poor-prognosis population, many with advanced-stage, large cell transformation or folliculotropic histology, and a median event-free survival in excess of 6 months.

Importantly, the authors confirmed that use of the standard IHC assay for CD30 may result in an underestimation of the number of patients with that antigen and thus cause candidates for effective therapy to be overlooked. Future studies should evaluate this regimen earlier in the course of these disorders, when response rates and duration are likely to be even more impressive.

Interview with Bruce D Cheson, MD, January 14, 2013

Bortezomib (BTZ) and Panobinostat (PAN) Combination Is Effective in Patients with Relapsed/Refractory Peripheral T-Cell Lymphoma (PTCL) or NK/T-Cell Lymphoma (NKL) and Maintenance Treatment May Be Essential for Sustained Response

Tan D et al.

Proc ASH 2012;Abstract 3669.

Background

- Relapsed/refractory PTCL and NKL have a poor prognosis after conventional chemotherapy, and there is currently no effective treatment available.
- Panobinostat (PAN), a pan-deacetylase inhibitor, targets multiple oncogenic pathways, whereas bortezomib (BTZ) exerts pleotropic antitumor effects, leading to cell apoptosis.
- Inhibition of histone deacetylase (HDAC) 6 by PAN abrogates BTZ-induced protective aggresome formation and accentuates BTZ-induced endoplasmic reticulum stress, leading to further apoptosis.
- *In vitro* and *in vivo* studies have demonstrated potent synergistic cytotoxicity of the combination (*Leuk Res* 2012;36(6):e128).
- **Objective:** Evaluate the efficacy and safety of BTZ and PAN in relapsed/refractory PTCL or NKL.

Tan D et al. *Proc ASH* 2012;Abstract 3669.

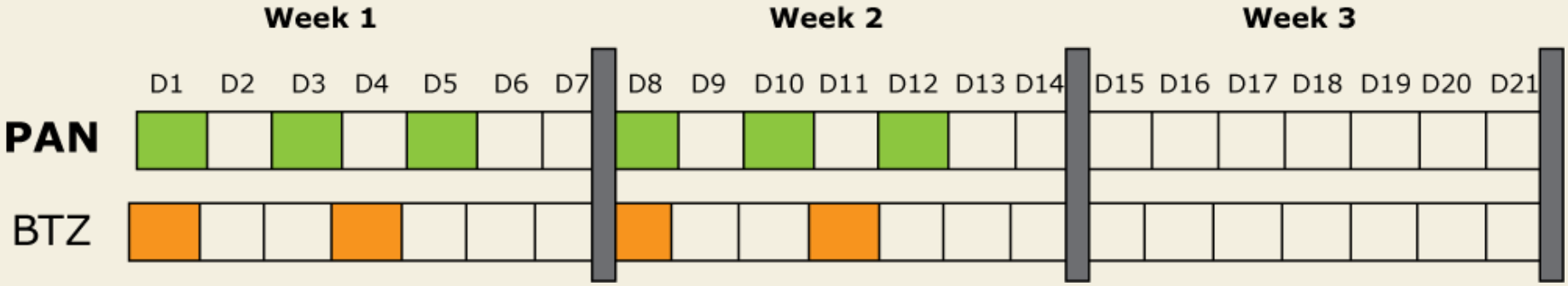
Phase II Study Eligibility and Endpoints

- Eligibility (n = 20 patients enrolled)
  - Histologically confirmed PTCL-NOS, angioimmunoblastic T-cell lymphoma (AITL), extranodal NK/T-cell lymphoma nasal type, enteropathy-type T-cell lymphoma, hepatosplenic T-cell lymphoma, ALCL (ALK-1 negative), or patients with ALK 1-expressing ALCL who have relapsed after ASCT or are ineligible to undergo an ASCT
  - Progressive disease following at least one systemic therapy or refractory to at least one prior systemic therapy
  - ANC ≥1,000 x 10^9 cells/L
- **Primary endpoint:** Objective response rate
- **Secondary endpoints:** Include time to response, PFS, OS, safety, tolerability

Tan D et al. *Proc ASH* 2012;Abstract 3669.

Phase II Study Design

- **<u>Dosing schedule</u>**
  PAN (20 mg, PO), thrice weekly + BTZ (IV 1.3 mg/m^2) twice weekly, both for 2 of 3 weeks, up to 6 cycles or until unacceptable toxicity or disease progression.



- **<u>Statistics:</u>** Gehan's 2-stage optimum design: Aiming for a response rate of ≥25%, 11 patients recruited in stage 1 and 14 in stage 2 if ≥1 responses are observed at stage 1.
- Assessment of response and progression evaluated after every 2 cycles of treatment.

Tan D et al. *Proc ASH* 2012;Abstract 3669.

Response to Combination of BTZ and PAN in Stage 1

Response, n (%)	(n = 11)
ORR	6 (54%)
CR	2 (18%)
PR	4 (36%)
Stable disease	2 (18%)
Progressive disease	3 (27%)

- Among patients who responded or had stable disease, the median PFS was 6 months and disease progression occurred at a median of 2.5 months after stopping therapy.
- Three patients successfully underwent subsequent allogeneic SCT.
- Six patients demonstrated a decrease in tumor size of >50% from baseline.

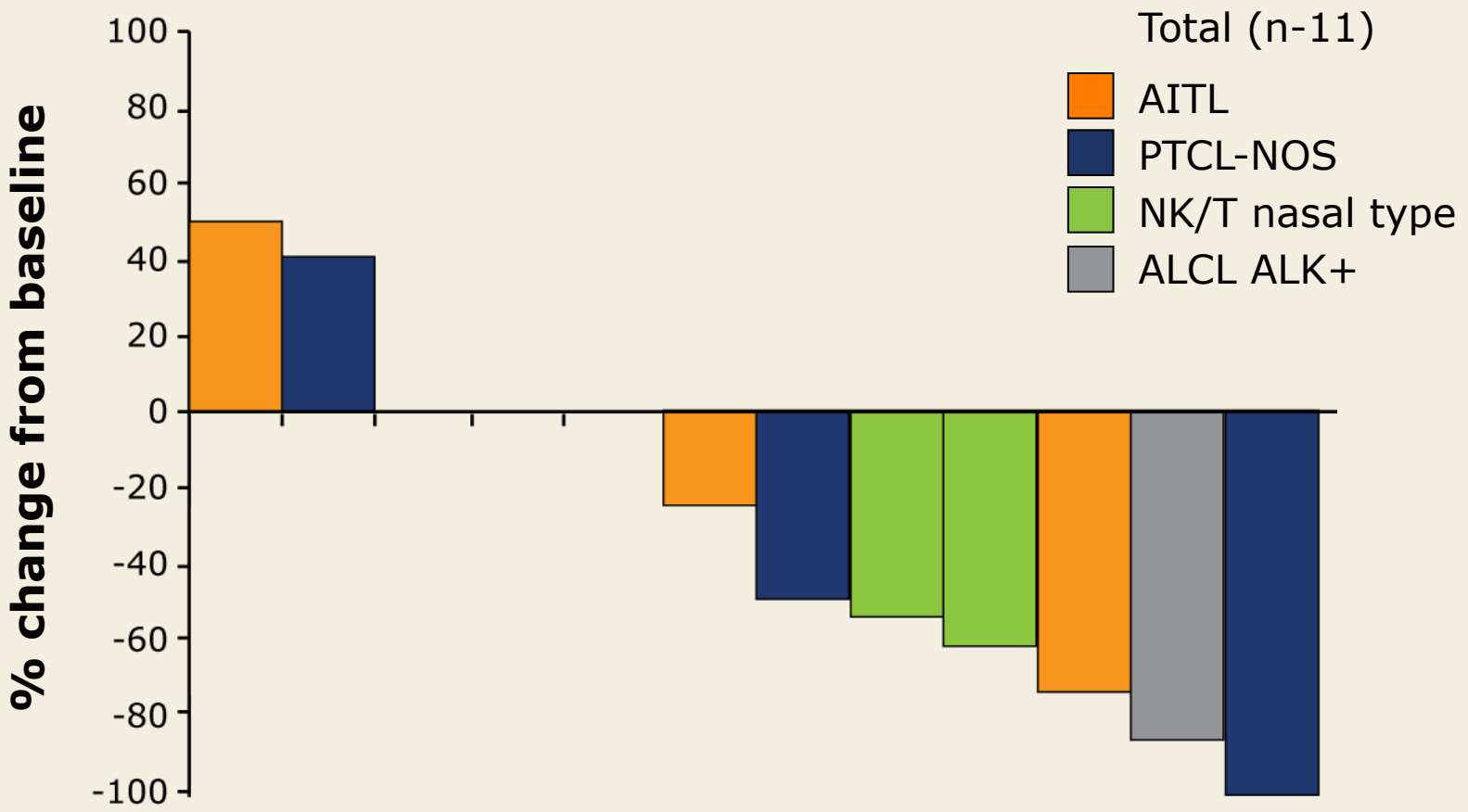
Tan D et al. *Proc ASH* 2012;Abstract 3669.

Select Treatment-Emergent Adverse Events

Adverse event	All grades	Grade 3/4
Hematologic		
Thrombocytopenia	64%	55%
Neutropenia	45%	36%
Nonhematologic		
Diarrhea	45%	18%
Vomiting	36%	9%
Rash	27%	0
Fever	64%	27%
Peripheral neuropathy	45%	18%

Tan D et al. *Proc ASH* 2012;Abstract 3669.

Maximal Tumor Change from Baseline



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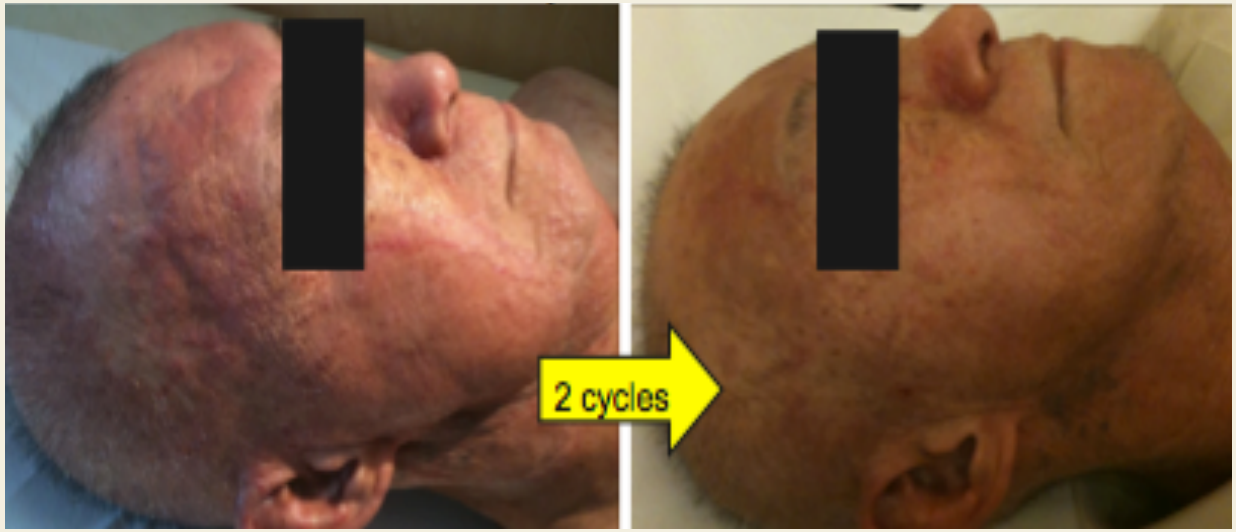
Patient with PTCL-NOS Refractory to CHOP



Anecdotal case of response to 2 cycles of BTZ+PAN in a patient with PTCL-NOS refractory to CHOP.

With permission from Tan D et al. *Proc ASH* 2012;Abstract 3669.

Author Conclusions

- The study regimen shows activity across T/NK-cell lymphoma subtypes.
- ORR of 54% greatly exceeds the predefined threshold of 25%, allowing, together with early tolerability data, continuation of study enrollment into stage 2.
- The early progression of the disease after stopping therapy suggests that the novel combination provides a tonic suppression of tumor proliferation and that continual treatment will be beneficial for patients without the option of sequential treatment like stem cell transplantation.
- An extension phase for maintenance treatment will be incorporated into stage 2 of the study to allow patients to optimally benefit from the combination.
- Ongoing correlative studies are designed to determine if the study regimen is more active in diseases with upregulation of NF-kappa B or transcription factors/coregulators known to be modified by acetylation.

Tan D et al. *Proc ASH* 2012;Abstract 3669.

Investigator Commentary: BTZ and PAN Are Effective for Relapsed/Refractory PTCL or NKL, and Maintenance Treatment May Be Essential for Sustained Response.

This study investigated the efficacy of a combination of BTZ and PAN in patients with relapsed/refractory peripheral T-cell lymphoma or NK T-cell lymphoma. Many preclinical data suggest that proteasome inhibition with HDAC inhibition is a good combination in vitro and would be a good combination in patients.

This was a small study with only 11 patients. The overall response rate was impressive at 54%. However, the responses tended to be relatively brief. On average, within 2.5 months of stopping the treatment, patients experienced recurrence. The authors speculated that perhaps a long-term maintenance strategy might be important to help keep these patients in remission once they have responded.

Interview with Brad S Kahl, MD, January 17, 2013

Romidepsin Induces Durable Responses in Patients with Peripheral T-Cell Lymphoma: GPI-06-0002 Study Update

Coiffier B et al.

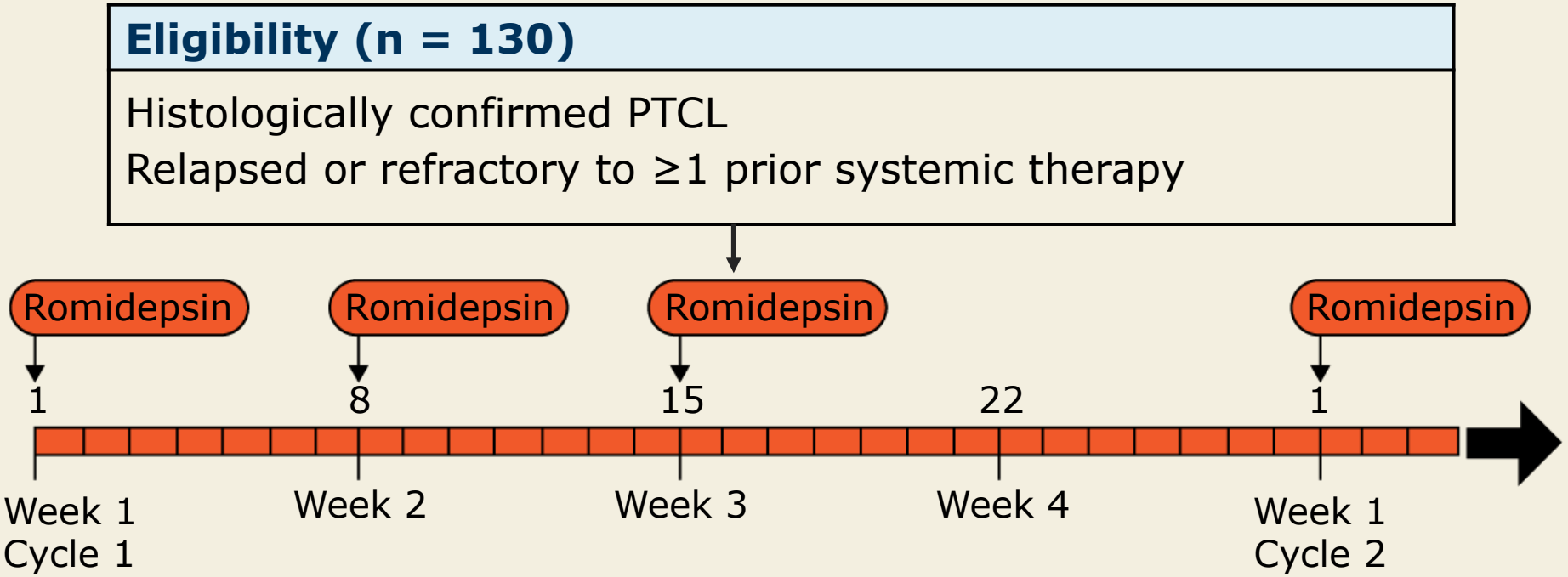
Proc ASH 2012;Abstract 3641.

Background

- Romidepsin is a histone deacetylase (HDAC) inhibitor that is FDA approved for the treatment of peripheral T-cell lymphoma (PTCL) after failure of 1 or more prior therapy.
- Preliminary analysis of the single-arm Phase II GPI-06-0002 study demonstrated clinical benefit and tolerability of romidepsin in patients with relapsed or refractory PTCL (*Blood* 2010;116:114).
- **Study objective:** To present updated efficacy analysis of romidepsin from the GPI-06-0002 study and characterize patients who achieved long-term responses of 12 months or longer after a median follow-up of 22.3 months.

Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

Phase II GPI-06-0002 Trial Design



- Romidepsin: 14 mg/m^2 (IV) for 4 h on days 1, 8 and 15 of a 28-day cycle x 6 cycles; treatment could be extended for responding patients
- **Primary endpoint:** Confirmed/unconfirmed complete response (CR/CRu) by independent review committee (IRC)

Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

Demographics and Baseline Characteristics

Characteristic	n = 130
Median number of prior systemic therapies (range)	2 (1-8)
Patients with PTCL refractory to last line of therapy	38%
Patients with Stage III or IV PTCL	70%
Patients with bone marrow involvement	28%
PTCL subtype (%)	
PTCL-NOS*	53%
Angioimmunoblastic T-cell lymphoma*	21%
ALK-1-negative anaplastic large cell lymphoma*	16%

* Most common PTCL subtypes

Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

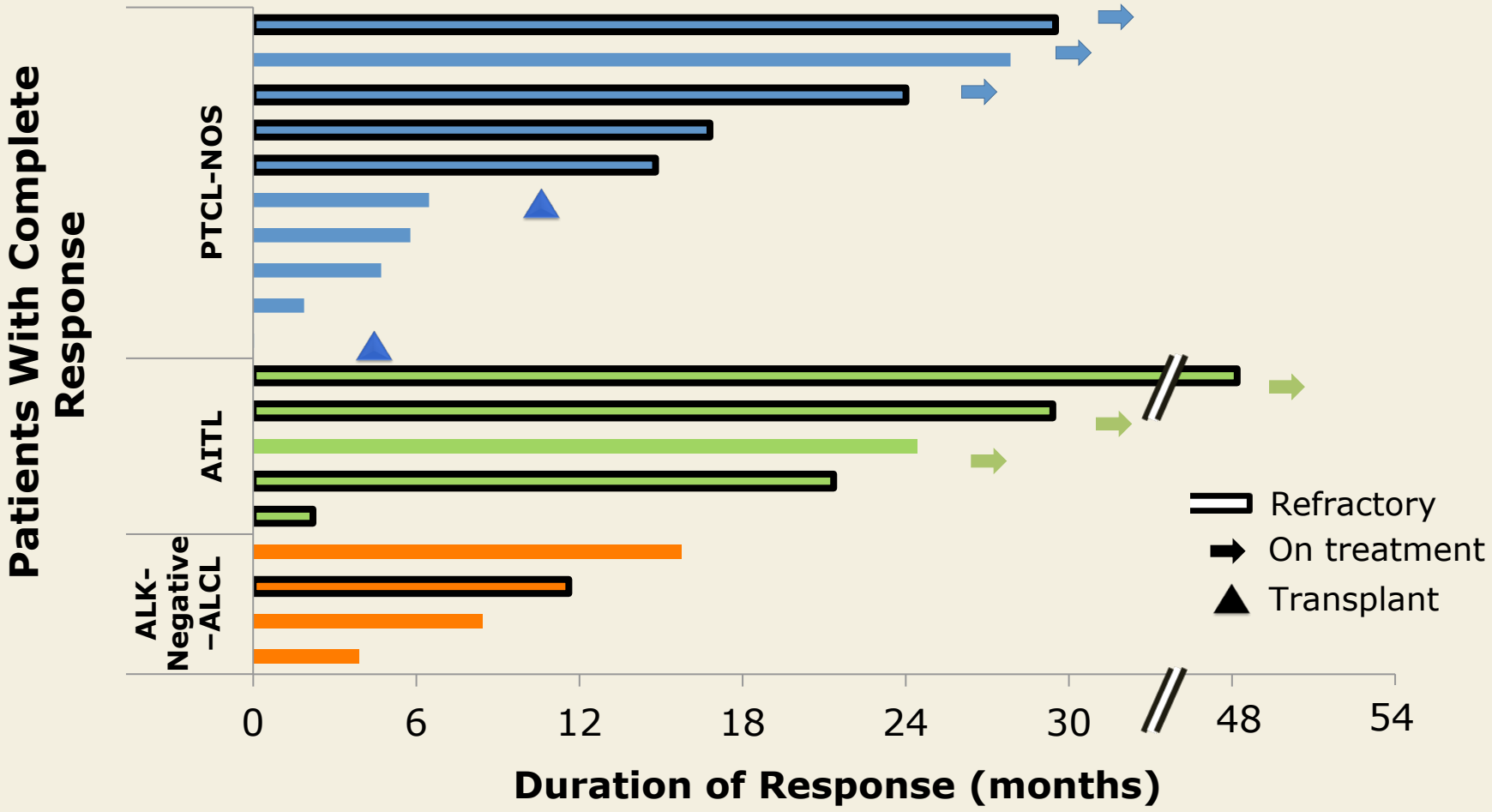
Best Response

Response, n (%)	n = 130
Overall response rate (ORR)	33 (25%)
CR/CRu	19 (15%)
CR	14 (11%)
CRu	5 (4%)
Partial response (PR)	14 (11%)
Stable disease (SD)	33 (25%)
Progressive disease/not evaluable	64 (49%)

- Median time to response was 1.8 months.
- Median duration of response (DoR) was 28 months.
- Median duration of CR/CRu has not been reached (range, <1-48+ months).
  - Patient with DoR <1 month discontinued to receive stem cell transplant.

Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

DoR for Patients with CR/CRu



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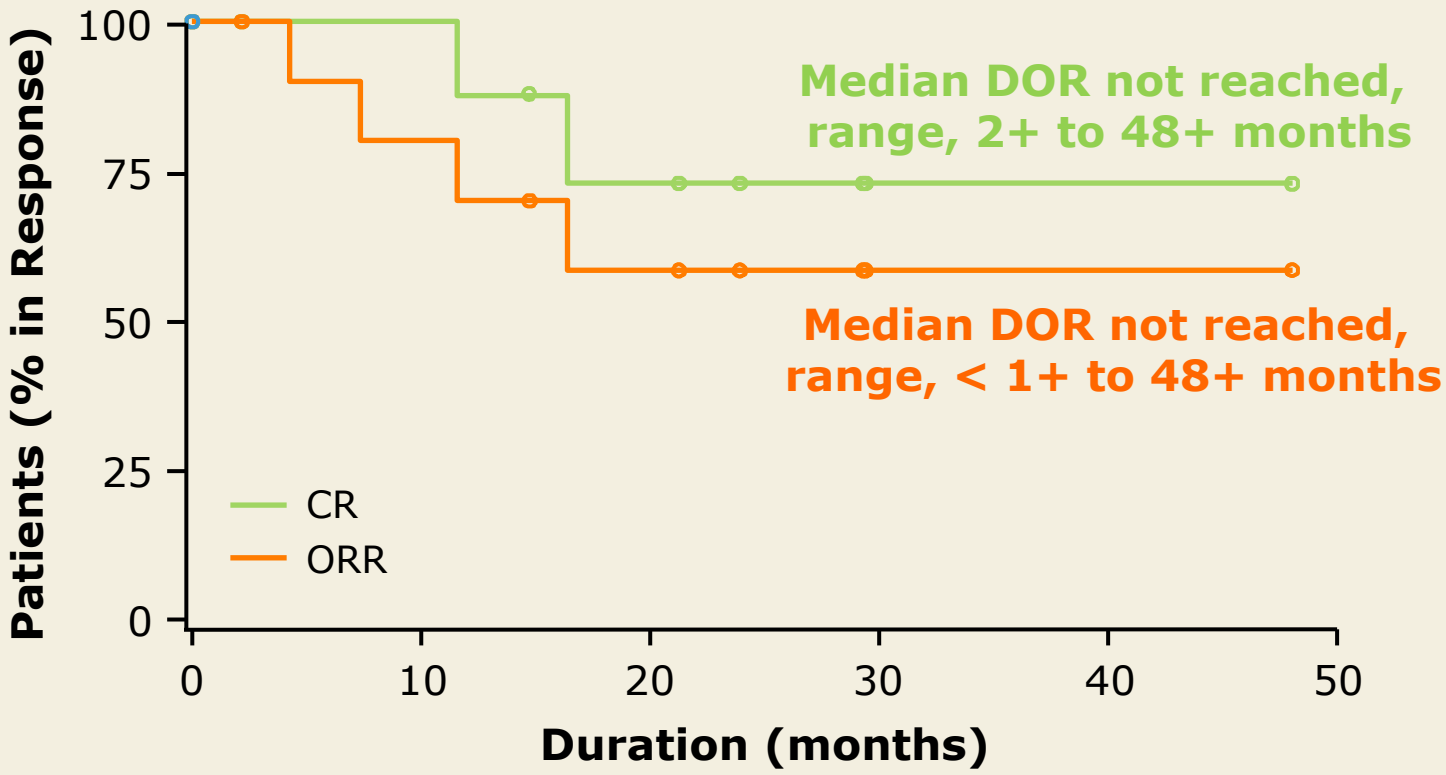
Characteristics of Patients Who Achieved CR/CRu with Romidepsin

Of the 19 patients who achieved CR/CRu,

- Thirteen (68%) had not experienced disease progression by IRC at a median follow-up of 25.8 months.
- Two patients who achieved CR/CRu discontinued treatment to receive stem cell transplant.
- Ten patients were long-time responders (≥12 months).
- Six patients with responses of 2 years or more continued to receive romidepsin therapy.

Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

DoR for Patients with PTCL Refractory to Last Prior Therapy (n = 49)



- Median DoR has not been reached for all patients who achieved a response
  - Patients who achieved response (n = 14)
  - Patients who achieved CR/CRu (n = 9)

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Author Conclusions

- Single-agent romidepsin induced durable responses in patients with heavily pretreated relapsed or refractory PTCL:
  - Median time to objective response was 1.8 mo.
  - Median DoR was 28 mo, with responses ongoing at 48 mo.
  - Median DoR for patients with CR/CRu has not been reached.
  - Long-lasting responses were observed in the 3 major PTCL subtypes and in patients with PTCL refractory to the last prior therapy.
- More than 50% of patients who achieved CR/CRu experienced long-term responses (≥12 months) to romidepsin.
  - CR was achieved in patients with typically poor prognoses.
  - None of the examined patient and disease characteristics predicted failure to achieve long-term remission.
  - CR/CRu was associated with prolonged survival.
- Extended dosing of romidepsin can be tolerated.

Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

Investigator Commentary: GPI-06-0002 — Romidepsin Induces Durable Responses in Patients with PTCL

This presentation is an update of the registration or pivotal trial of romidepsin that led to its approval for PTCL. With a longer follow-up period, the overall response rate remains about the same with 25% of patients responding. A significant proportion of the responders (a minority of the entire group of patients who received treatment) experienced durable or maintained responses to therapy. The median duration of response for all responders was 28 months, and that curve is largely upheld by the complete responders (19/33 responders), for whom the median duration of response was not reached.

This presentation highlights the point that of the minority of patients who respond, many can achieve disease control beyond 1 year. In this data set a handful of patients are now at 2 to 3 years and up to 4 years with maintained responses on therapy. We know from participation in the trial that some of the patients with particularly long-term responses had their schedule reduced after a time and received less frequent dosing than 3 out of every 4 weeks.

Interview with Steven M Horwitz, MD, March 20, 2013