# 5 Minute JournalClub

## Key ASH Presentations

Issue 4, 2011

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# CME Information

**LEARNING OBJECTIVES**

- Describe the mechanism of action, activity and safety of brentuximab vedotin in the setting of relapsed or refractory Hodgkin lymphoma.
- Apply the results of the Phase III trial comparing ABVD to Stanford V to the initial management of Hodgkin lymphoma.
- Apply the results of new research to the evidence-based use of interim PET scans for patients with advanced-stage Hodgkin lymphoma.
- Recognize the limited role of consolidative radiation therapy for patients with Hodgkin lymphoma who have a negative post-treatment PET scan.

**CREDIT DESIGNATION STATEMENT**

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# CME Information (Continued)

**FACULTY DISCLOSURES**
The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

**Steven M Horwitz, MD**
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*Consulting Agreements:* Allos Therapeutics, Celgene Corporation, Millennium — The Takeda Oncology Company; *Paid Research:* Allos Therapeutics, Genzyme Corporation.

**Craig Moskowitz, MD**
Clinical Director, Division of Hematologic Oncology
Member, Lymphoma Service, Memorial Sloan-Kettering Cancer Center
New York, New York

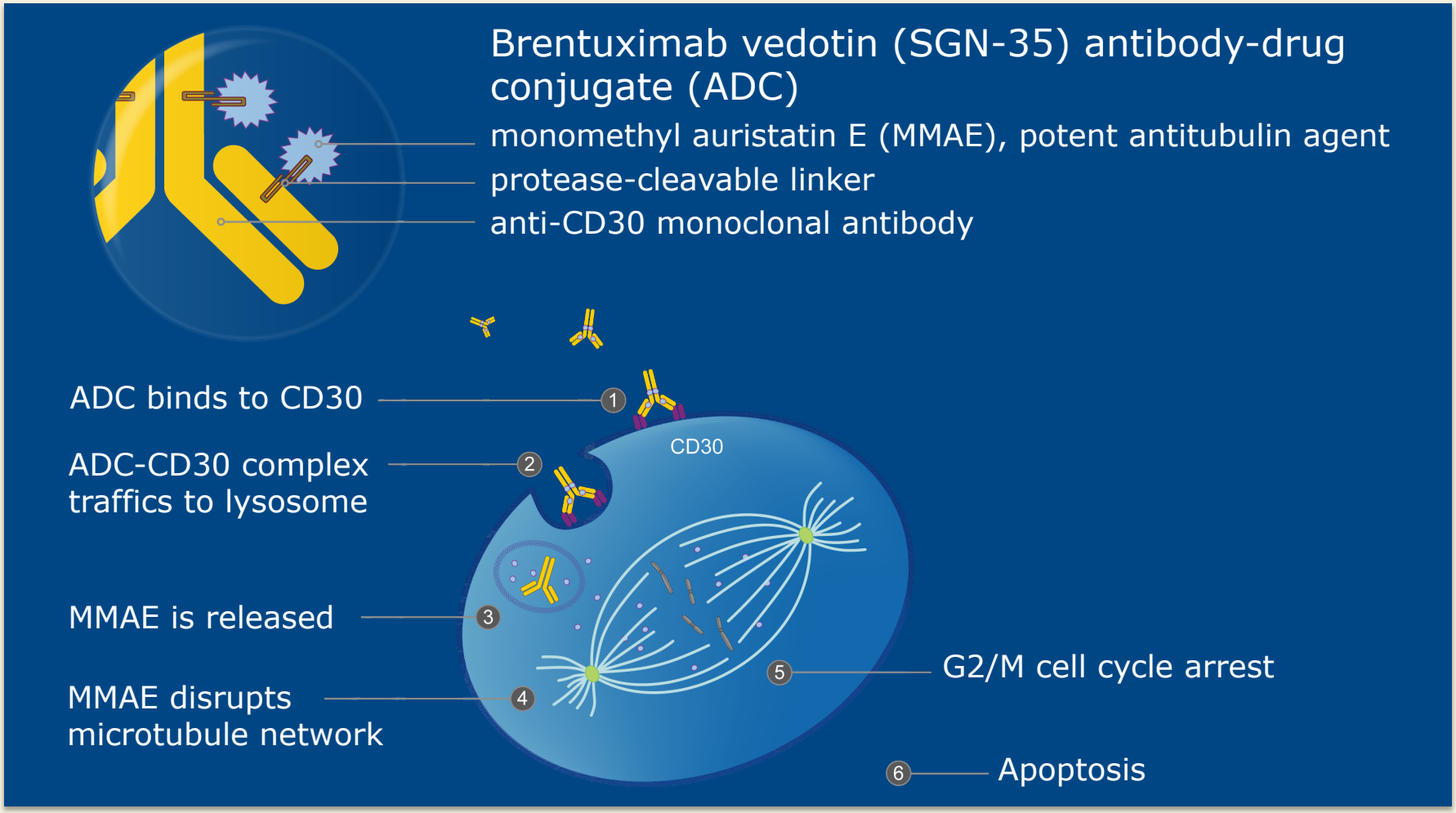
*Advisory Committee:* Cephalon Inc, Genentech BioOncology, Seattle Genetics; *Paid Research:* Cephalon Inc, Genentech BioOncology, Lilly USA LLC, Plexxikon Inc, Seattle Genetics.

# Results of a Pivotal Phase 2 Study of Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Hodgkin Lymphoma

**Chen R et al.**

*Proc ASH* 2010;Abstract 283.

# Brentuximab Vedotin Mechanism of Action




With permission from Chen R et al. *Proc ASH* 2010;Abstract 283.

# Study Schema

**Accrual** = 102 (Closed)

| Eligibility |
| --- |
| Relapsed or refractory CD30+ Hodgkin lymphoma (HL)<br>Post autologous stem cell transplant (ASCT) |

→ Brentuximab vedotin
1.8 mg/kg
IV over 30 minutes
q 3 weeks
x up to 16 cycles

**Primary Objective**

Overall objective response rate (CR + PR) by independent review facility (IRF)

**Secondary Objectives**

Assess duration of response and progression-free survival (PFS)
Assess overall survival
Assess safety and tolerability

Chen R et al. *Proc ASH* 2010;Abstract 283.

# Patient Characteristics

| Characteristic | |
|---|---|
| Age (median) | 31 years |
| Number of prior chemotherapy regimens (median) | 3.5 |
| Primary refractory disease* | 71% |
| Refractory to most recent salvage therapy (excluding transplant) | 42% |

* Failure to achieve a complete response or progression within 3 months of completing front-line therapy

Chen R et al. *Proc ASH* 2010;Abstract 283.

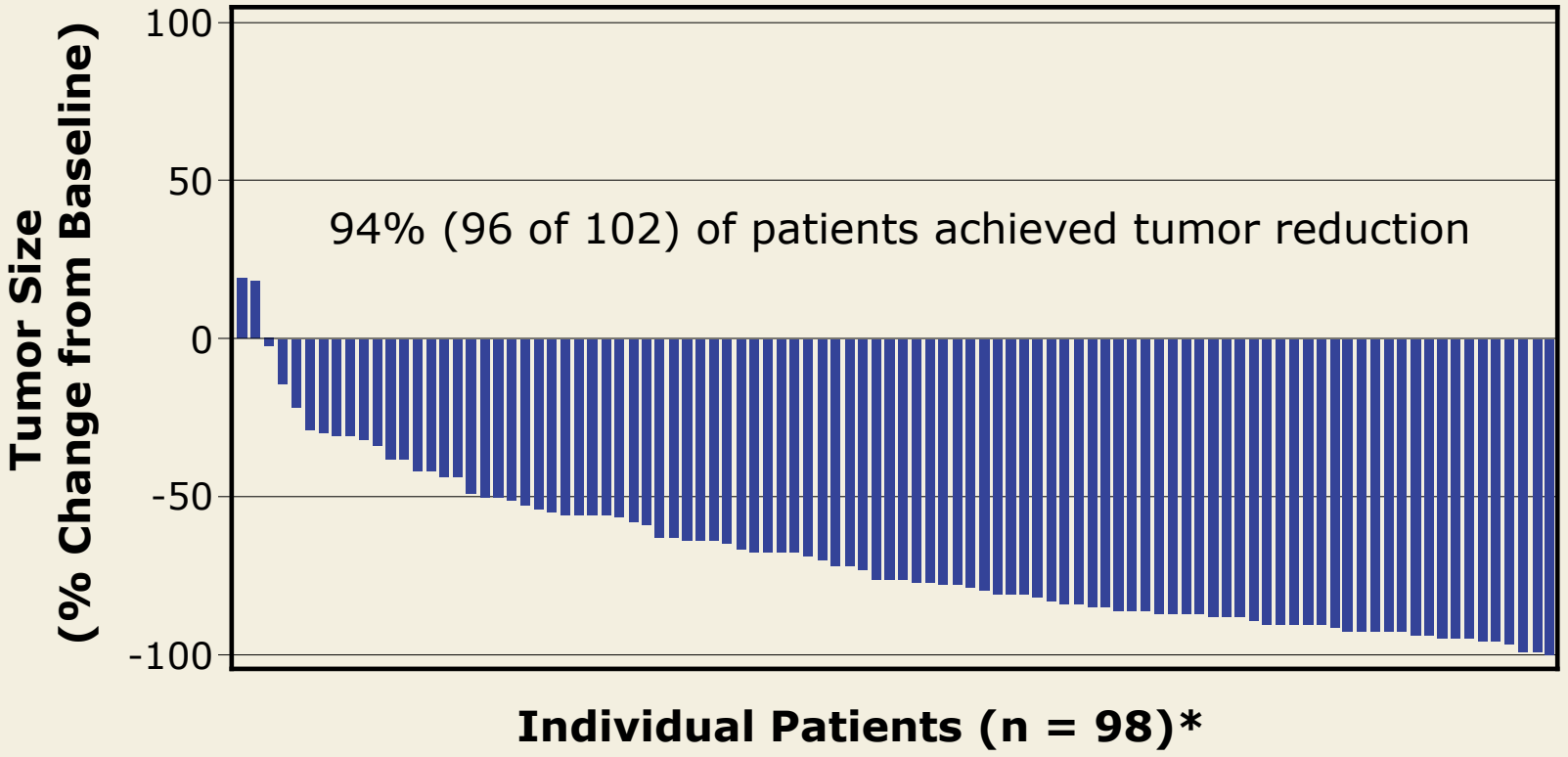
# Efficacy Outcomes (n = 102)

| Response | IRF | Investigator |
|---|---|---|
| Overall response rate (ORR) | 75% | 72% |
| Complete remission | 34% | 33% |
| Partial remission | 40% | 38% |

| Secondary endpoints | IRF | Investigator |
|---|---|---|
| Progression-free survival | 25.1 weeks | 39.1 weeks |
| Median duration of ORR | 29 weeks | 47 weeks |
| Median duration of CR | Not reached | Not reached |
| Overall survival (OS) | Not reached | Not reached |
| Estimated 12-month OS | 88% | |

Chen R et al. *Proc ASH* 2010;Abstract 283.

# Maximum Tumor Reduction per IRF




* 4 patients were not included in the analysis

- 3 patients had no measurable lesions per IRF
- 1 patient had no postbaseline scans

With permission from Chen R et al. *Proc ASH* 2010;Abstract 283.

# Select Safety Events

| Treatment-Related Adverse Events (AE) | All Grades* | Grade 3 or 4* |
|---|---|---|
| Peripheral sensory neuropathy | 47% | 8%† |
| Fatigue | 46% | Not reported |
| Nausea | 42% | Not reported |
| Diarrhea | 36% | Not reported |
| Neutropenia | 22% | 20% |

* All Grade AEs occurring in ≥20% of patients and Grade 3/4 AEs occurring in ≥5% of patients

† Grade 3 only

Chen R et al. *Proc ASH* 2010;Abstract 283.

# Author Conclusions

- Brentuximab vedotin is associated with encouraging activity in patients with heavily pretreated, relapsed/refractory HL.
  - ORR = 75% (median duration of response of 29 weeks by IRF)
  - CR = 34% (median duration not reached)
  - Patients achieving tumor reduction = 94%
  - Estimated 12-month OS = 88%
- Brentuximab vedotin treatment is associated with a manageable adverse-events profile.
  - Peripheral neuropathy largely reversible
- Brentuximab vedotin enables selective delivery of a potent cytotoxic agent to patients with relapsed/refractory HL.
- Ongoing Phase III AETHERA Trial is comparing brentuximab vedotin versus placebo in patients with residual Hodgkin lymphoma after ASCT (NCT01100502).

Chen R et al. *Proc ASH* 2010;Abstract 283; www.clinicaltrials.gov, January 2011.

## Investigator comment on brentuximab for patients with relapsed/refractory Hodgkin lymphoma

I believe in terms of the new drugs, brentuximab caused the most excitement at ASH because these are high response rates in a study that was well done. These data are compelling, and I believe there is a good chance that the drug will be approved for relapsed/refractory Hodgkin lymphoma. I also think there will be an expanded access or compassionate use program while approval is pending.

There is also interest in moving this drug into earlier lines or even up front for poor-risk Hodgkin lymphoma. The main issue with combining it with the current up-front regimens is neuropathy, as vinca alkaloids, which are universally used up front, are also neuropathic. Hematologic toxicity, I believe, is less likely to be a problem. There could be many ways to potentially add this drug and help people with Hodgkin lymphoma.

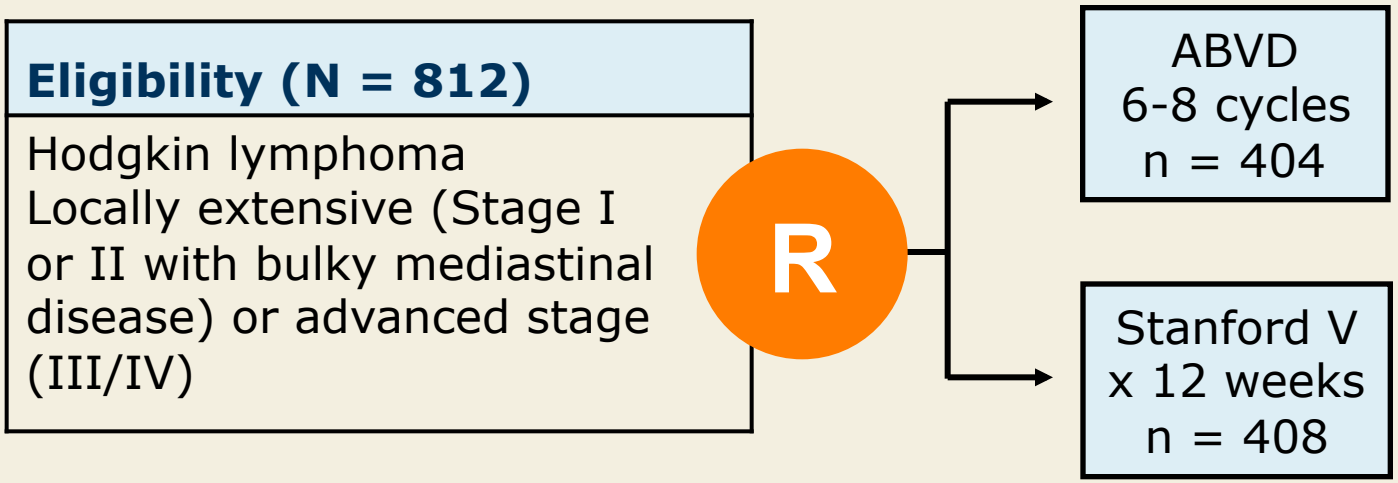
***Interview with Steven M Horwitz, MD, December 29, 2010***

# A Randomized Phase III Trial of ABVD vs Stanford V +/- Radiation Therapy in Locally Extensive and Advanced Stage Hodgkin's Lymphoma: An Intergroup Study Coordinated by the Eastern Cooperative Oncology Group (E2496)

**Gordon LI et al.**

*Proc ASH* 2010;Abstract 415.

# Study Schema




**Primary endpoint:**
Failure-free survival: 33% improvement with Stanford V

Radiation therapy (RT, modified IFRT 36 Gy) is administered to patients with bulky mediastinal disease in the ABVD arm.

In the Stanford V arm, RT (modified IFRT 36 Gy) is administered for sites >5 cm or for macroscopic splenic disease.

Gordon LI et al. *Proc ASH* 2010;Abstract 415.

# ABVD and Stanford V Chemotherapy Regimens

- **ABVD Regimen:**
  - Doxorubicin 25 mg/m$^2$ IV, d1 and d15
  - Bleomycin 10 u/m$^2$ IV, d1 and d15
  - Vinblastine 6 mg/m$^2$ IV, d1 and d15
  - Dacarbazine 375 mg/m$^2$ IV, d1 and d15

- **Stanford V Regimen:**
  - Doxorubicin 25 mg/m$^2$, q2wks
  - Vinblastine 6 mg/m$^2$, q2wks
  - Mustard 6 mg/m$^2$, q4wks
  - Etoposide 60 mg/m$^2$ x 2, q4wks beginning week 3
  - Vincristine 1.4 mg/m$^2$, q2wks beginning week 2
  - Bleomycin 5 u/m$^2$, q2wks beginning week 2
  - Prednisone daily, taper after week 9

Gordon LI et al. *Proc ASH* 2010;Abstract 415.

# Efficacy Outcome

| Efficacy Outcome | ABVD (n = 404) | Stanford V (n = 408) | Hazard Ratio | *p*-value |
|---|---|---|---|---|
| Complete remission (CR + CCR) | 72% | 69% | — | NS |
| 5-year failure-free survival | 73% | 71% | — | 0.29 |
| 5-year overall survival | 88% | 87% | 0.97 | 0.87 |

NS = not significant

Gordon LI et al. *Proc ASH* 2010;Abstract 415.

# Adverse Events

| Adverse Events | ABVD (n = 404) | Stanford V (n = 408) | *p*-value |
|---|---|---|---|
| Grade 3 or 4 neutropenia | 76% | 70% | — |
| Grade 3 lymphopenia | 42% | 78% | <0.0001 |
| Grade 3 or 4 sensory neuropathy | 3% | 10% | <0.001 |
| Second primary cancers, n | 12 | 14 | NS |

NS = not significant

Gordon LI et al. *Proc ASH* 2010;Abstract 415.

# Author Conclusions

- There is no significant difference in responses, failure-free survival or overall survival when ABVD (+ RT for bulky mediastinal disease) is compared to Stanford V (+ RT for nodal sites >5 cm and macroscopic splenic disease).
- There was more Grade 3 lymphopenia and more Grade 3 or 4 sensory neuropathy on Stanford V.
- ABVD (+ RT for bulky mediastinal disease) remains the standard treatment.
  - Stanford V did not meet the objective of 33% improvement in failure-free survival.

Gordon LI et al. *Proc ASH* 2010;Abstract 415.

# Investigator Commentary: ABVD versus Stanford V in the Initial Treatment of Hodgkin Lymphoma

Results of this large US randomized trial of Stanford V have been eagerly awaited. Stanford V is a seven-drug weekly chemotherapy regimen, developed at Stanford, with the advantage that it reduces the cumulative doses of doxorubicin and bleomycin. The disadvantage is that it is a combined-modality program in that in addition to chemotherapy almost everybody undergoes radiation therapy to original sites that are five centimeters or larger and contiguous areas.

The bottom line of the study is that ABVD with radiation therapy for bulky mediastinal disease remains the standard. No difference was recorded in response, failure-free survival and overall survival between Stanford V and ABVD. More sensory neuropathy and lymphopenia occurred with Stanford V. I believe there are certain patients to whom you might still administer Stanford V, if there is a particular concern about lung toxicity or cardiotoxicity from ABVD.

***Interview with Steven M Horwitz, MD, December 29, 2010***

# Early Interim $^{18}$f-FDG PET in Hodgkin's Lymphoma: Evaluation on 304 Patients (Italian study)[1]

# Assessment of Residual Bulky Tumor Using FDG-PET in Patients with Advanced-Stage Hodgkin Lymphoma After Completion of Chemotherapy: Final Report of the GHSG HD15 Trial (German study: slide 6)[2]


[1]**Zinzani PL et al.**
*Proc ASH* 2010;Abstract 3879.

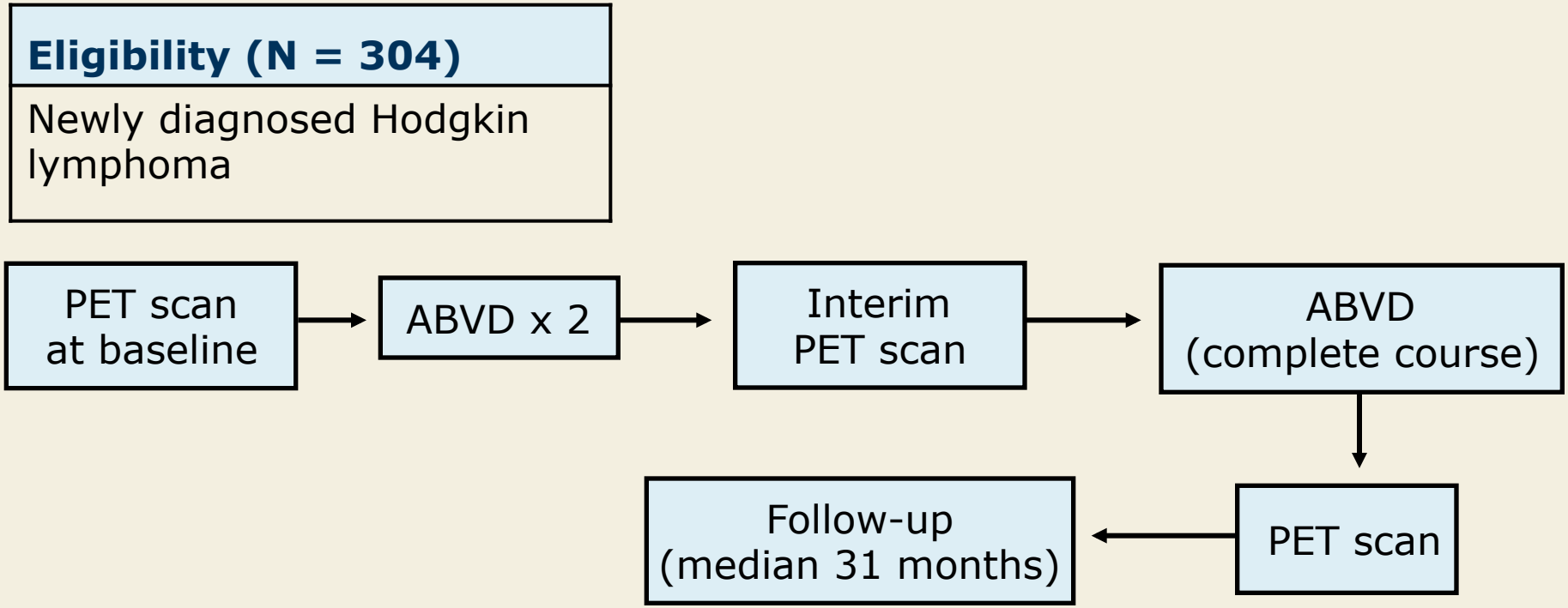
[2]**Engert A et al.**
*Proc ASH* 2010;Abstract 764.

# Early Interim $^{18}$f-FDG PET in Hodgkin's Lymphoma: Evaluation on 304 Patients

**Zinzani PL et al.**

*Proc ASH* 2010;Abstract 3879.

# Study Schema




Distribution of Patients
147 early stage
157 advanced stage

Zinzani P et al. *Proc ASH* 2010;Abstract 3879.

# Results (from Abstract)

| Efficacy Outcome | Positive Interim PET (n = 53) | Negative Interim PET (n = 251) |
|---|---|---|
| Complete Remission | 24.5% | 92.0% |
| Early Stage (n = 19, 128) | 21.0% | 97.6% |
| Advanced Stage (n = 34, 123) | 26.4% | 88.6% |

Comparison between interim PET-positive and interim PET-negative patients indicated a significant association between PET findings and 9-year PFS ($p$ = 0.0000) and 9-year overall survival ($p$ = 0.0000).

Zinzani P et al. *Proc ASH* 2010;Abstract 3879.

# Author Conclusions

- These results confirm the role of early PET as a significant step forward for the management of both early and advanced-stage Hodgkin lymphoma.
- Interim PET scans may offer the potential for an immediate switch to high-dose treatments, if required.

Zinzani P et al. *Proc ASH* 2010;Abstract 3879.

# Assessment of Residual Bulky Tumor Using FDG-PET in Patients with Advanced-Stage Hodgkin Lymphoma After Completion of Chemotherapy: Final Report of the GHSG HD15 Trial

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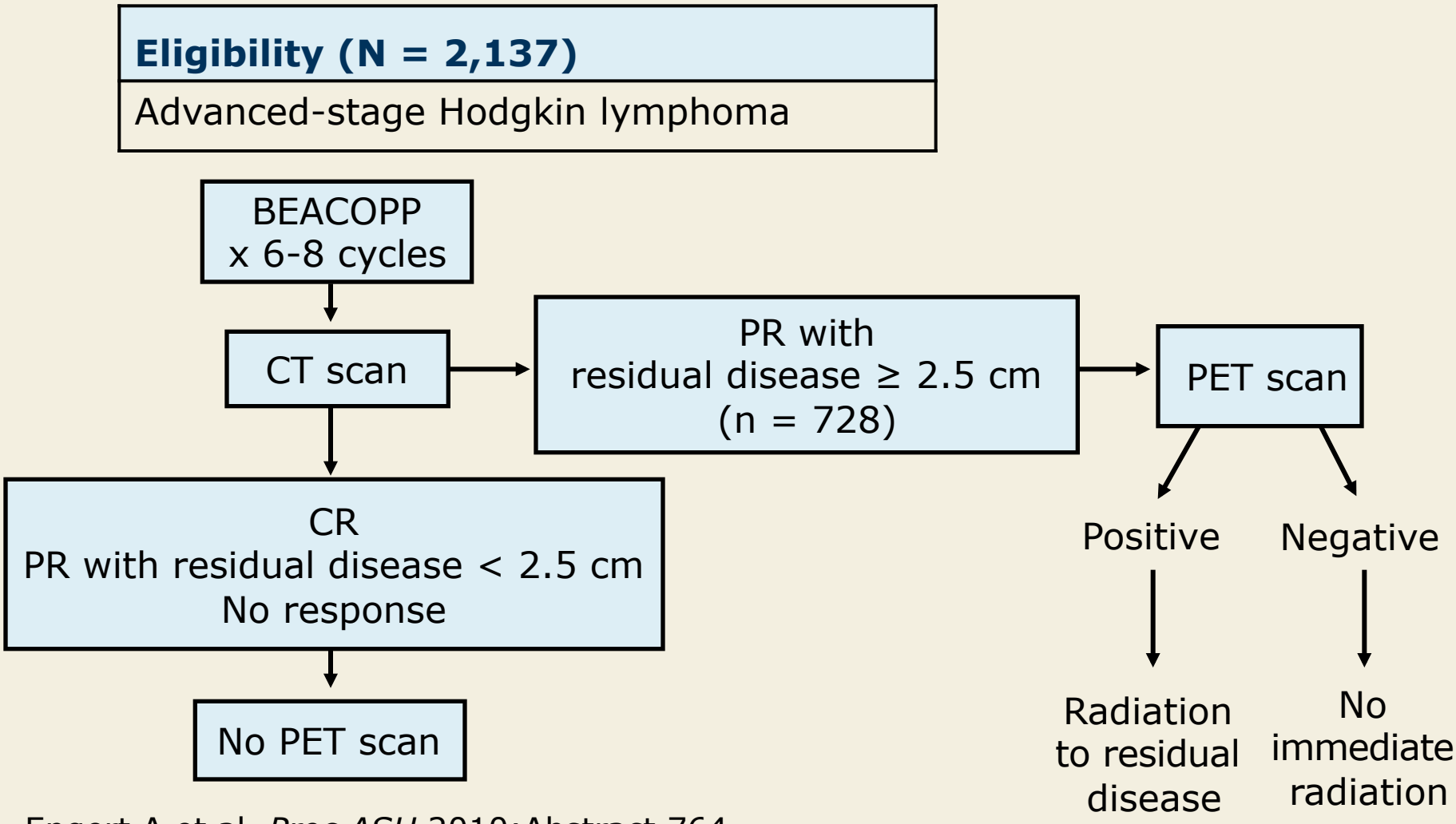


Engert A et al. *Proc ASH* 2010;Abstract 764.

# Results (from Abstract)

| Patients with PR and Residual Disease ≥ 2.5 cm (n = 728) | |
|---|---|
| PET Negative | 74.2% |
| PET Positive | 25.8% |

| | PET Negative | PET Positive[1] |
|---|---|---|
| Negative Prognostic Value | 94.6% | — |
| Lack of Progression Events[2] at 3 Years | 92.1% | 86.1% |

[1] Patients with PET-positive disease received immediate radiation.
[2] Radiation counted as a progression event in PET-negative patients.

Engert A et al. *Proc ASH* 2010;Abstract 764.

# Results (from Abstract)

| | Current Trial | Earlier Trials |
|---|---|---|
| Radiation after BEACOPP | 11% | 71% |

In addition, there was no difference in PFS or overall survival as compared to earlier trials in advanced-stage HL.

Engert A et al. *Proc ASH* 2010;Abstract 764.

# Author Conclusion

- Patients with a negative PET scan after BEACOPP do not need additional radiation therapy.
  - 94.6% negative prognostic value of negative PET

Engert A et al. *Proc ASH* 2010;Abstract 764.

## Investigator comment on role of PET scan in Hodgkin lymphoma

The study by Zinzani is important. The question in my mind is whether all patients with Hodgkin lymphoma (HL) need the interim PET scan. Approximately 90 percent of patients with early-stage HL are cured in the pre-PET era, and the corresponding proportion in advanced-stage HL is 75 percent. I believe that patients with advanced-stage HL and a positive PET after two cycles fare extremely poorly and should be referred to major academic centers for second-line therapy. For patients who have early-stage HL with positive interim PET, to me that is still a debatable issue.

The presentation by Engert is mainly applicable to patients receiving BEACOPP and to practices that have traditionally administered involved field radiation therapy to patients with residual disease of 2.5 cm or more. This might also be applicable to patients receiving ABVD, but I don't know that. For patients with advanced HL and a negative PET after BEACOPP, there is definitely no role for consolidative radiation therapy anymore.

***Interview with Craig Moskowitz, MD, January 3, 2011***