

*[Editor's note:
Dr. Even's video
transcript has been
edited to improve
readability]*

Differential Treatment Strategies in Newly Diagnosed Patients with Early- vs Advanced-Stage Disease

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Tufts Medical Center
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Welcome to
*Managing Hodgkin
Lymphoma*. My
name is Andy Evens,
and I am Professor of
Medicine and Chief
in the Division of
Hematology/
Oncology and
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Tufts Cancer Center
at Tufts Medical
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Massachusetts, USA.
I am going to talk to

you today about the management of Hodgkin lymphoma in 2016.

In this activity, I will touch on early-stage and advanced-stage Hodgkin lymphoma, and then address response-adapted therapy. I will discuss our current standards in the treatment of elderly or older patients with Hodgkin lymphoma, and will finish with our current progress in targeted therapy for Hodgkin lymphoma, including the latest research in biomarkers.

Outline

- Early-stage disease
 - Advanced-stage disease
 - Elderly Hodgkin lymphoma
 - Integration of new/targeted agents and biomarkers
- } **Response
Adapted Rx**

The Changes in the Management of HL Since 1980...

- No lap-splenectomy
- No maintenance therapy
- No MOPP → ABVD → ? BEACOPP
- Less or no RT: reduction in dose-field
- “Special” Rx for elderly patients
- Moving towards targeted/individualized therapy

Let's begin with changes in the management of Hodgkin lymphoma that have occurred since 1980. In terms of staging, we no longer perform lap-splenectomies, and are using functional imaging, PET scan and CT scans instead. I think most of us will still do bone marrow biopsies, although emerging data with certain criteria suggests that we might not do a

bone marrow biopsy. We don't use maintenance therapy. We have progressed from MOPP, where the standard in most cases is ABVD, although there is consideration for BEACOPP in certain situations. There is less radiotherapy. There are special or modified treatment regimens for older patients, and we are very hopeful, as we move toward paradigms that integrate targeted and novel therapeutics.

In terms of early-stage disease for Hodgkin lymphoma, in most instances, and certainly in large randomized studies in Europe, results have been divided between early-stage favorable and unfavorable, which is also called intermediate. As you can see here, there is a line between intermediate and advanced-stage disease, which is a line mainly for

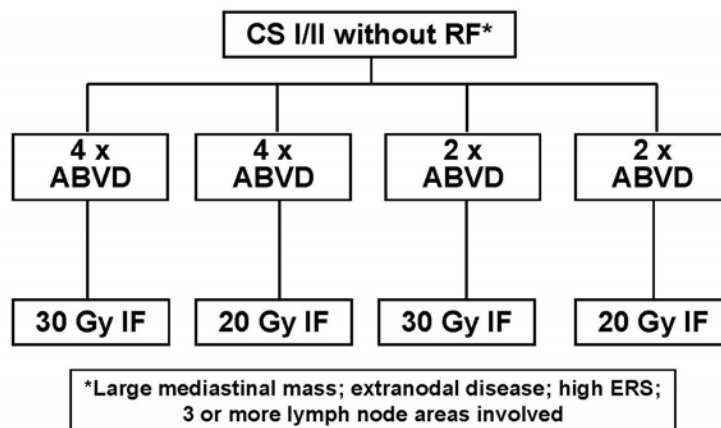
Hodgkin's Disease: Early-Stage Treatment Groups

- Early-stage: favorable I, II (with 0 RF)
- Early-stage: unfavorable (Intermediate) I, II with RF
- Advanced stages III, IV (IIB with bulk >10 cm)
- Stage I/II risk factors
 - a) Large mediastinal mass (LMM)
 - b) Extranodal involvement
 - c) Elevated ESR
 - d) ≥3 involved lymph node areas

****EORTC definition of risk factors differs from GHSG****

clinical trials. Some clinical trials have launched both groups of early stage together. If you are going to split the early stage groups, this is the German Hodgkin Study Group criteria. Using these criteria, if you have one or more of these risk factors, you would fall into the unfavorable or intermediate early stage. Risk factors include large bulky mediastinal mass, extranodal involvement, elevated erythrocyte sedimentation rates (ESR) over 50 in the absence, or over 30 in the presence, of B symptoms, and three or more lymph node regions. A subtle line here is that lymph node regions have varied by study group.

HD-10 Trial for Patients with Early-favorable HD: German Hodgkin Study Group (GHSG)



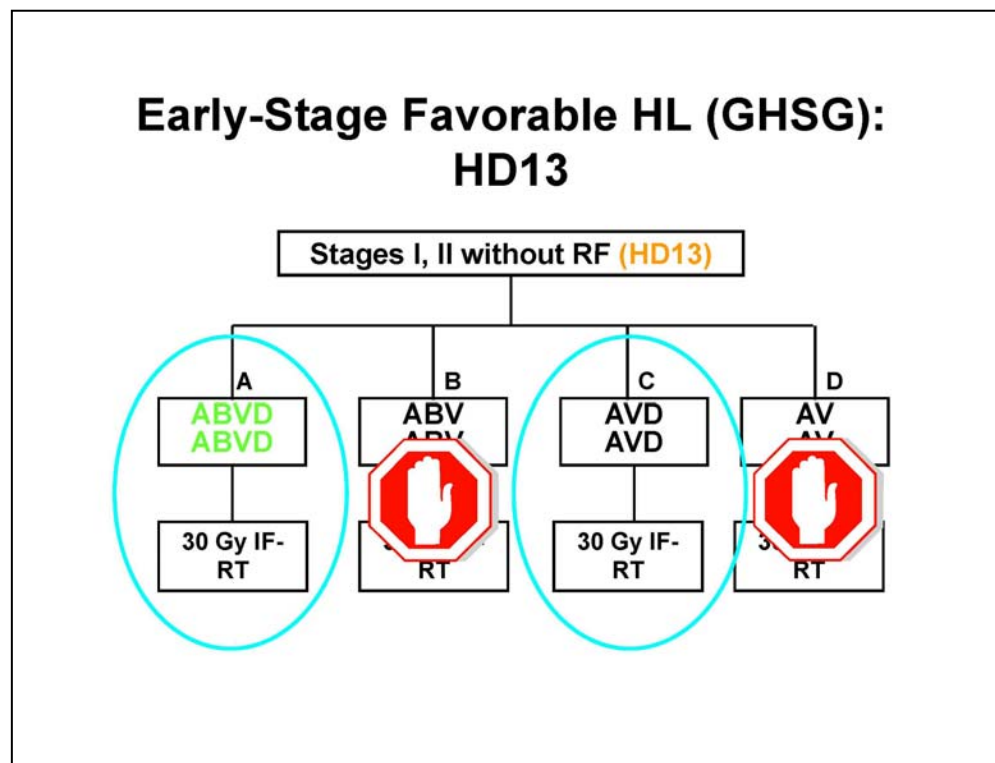
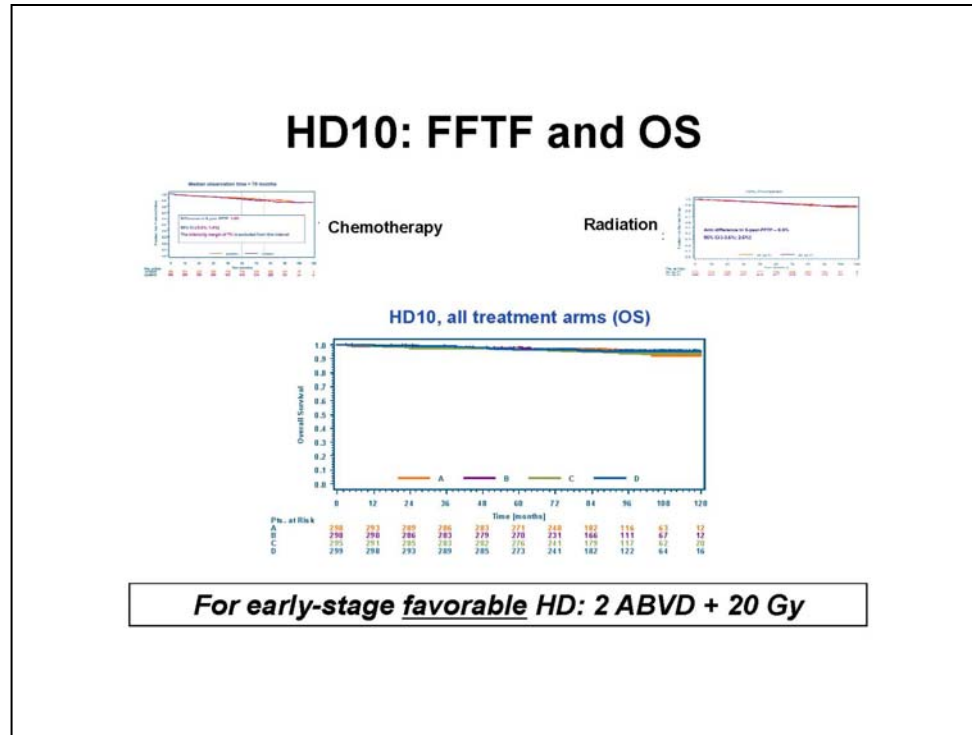
Engert A, Diehl V. *N Engl J Med*. 2010;363:640.

So, what about the top early-stage favorable? The HD-10 study was published in the *New England Journal* by the German Hodgkin Study Group (GHSG). It was a 2 x 2 factorial design, with the standard at the time of the study being 4 cycles of ABVD followed by 30 Gy of involved-field radiotherapy. And you can see here different modulations, in terms of the

chemotherapy, as well as decreasing radiation.

And, long story short, in essence, all four groups were overlapping in terms of freedom from treatment failure (FFTF) and overall survival (OS). As you can see, the chemotherapy lines overlapped, and, in terms of the radiation question, there was no difference between 20 Gy versus 30 Gy. The bottom graph shows all four arms in terms of overall survival. I would submit that this is

one option—not the only option, but an option for patients with early-stage favorable Hodgkin lymphoma: 2 cycles of ABVD and 20 Gy of involved-field radiotherapy.



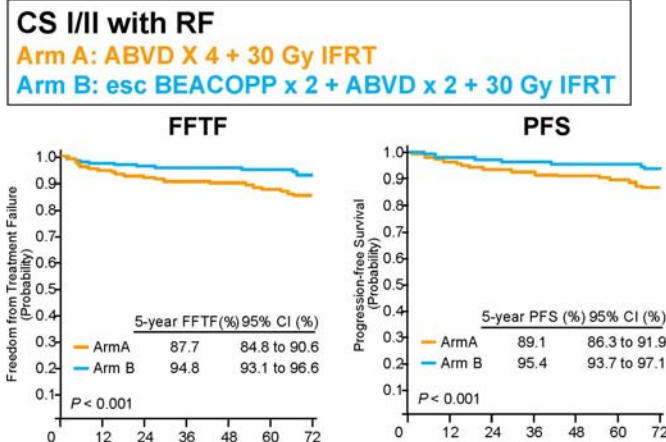
The successor to HD10 was the HD13 study. This study had four arms, similar to HD10; however, the goal of the HD13 study was to attempt to delete or drop chemotherapy from the regimen. Early in the study, there was an unexpected increase in the relapse rate for the arms that did not have dacarbazine in them. So, these arms closed early and the study continued on between ABVD and

AVD. This has since been presented, and we have seen that there still is a decline in patients who did not

receive bleomycin. There is no difference in overall survival, but, according to preset criteria, there was a statistically significant difference in freedom from treatment failure.

What about the HD14 trial, which was for early-stage unfavorable patients? This trial looked at the standard regimen of ABVD x4 cycles followed by 30 Gy of involved-field radiotherapy (IFRT) to all sites versus 2 cycles of escalated BEACOPP followed by 2 cycles of ABVD and 30 Gy involved-field radiotherapy.

Early-Stage Unfavorable Disease: GHSG HD 14 Trial



von Tresckow B, et al. *J Clin Oncol*. 2012;30(9):907-913.

As you can see, there was a difference in freedom from treatment failure without a difference in overall survival. The difference was approximately 7 percentage points in terms of progression-free survival (PFS). This was viewed as a positive study and is a standard treatment in Germany: 2 cycles of escalated BEACOPP and two of ABVD. This is not necessarily the standard in the U.S. and in other parts of the world. There are still many who would advocate including just ABVD as a chemotherapy, and others who would include 4 to 6 cycles of chemotherapy without involved-field radiotherapy.

Chemotherapy vs. Chemotherapy + RT: Previous Studies

- 2002-2005: Four randomized early-stage studies
 - Chemotherapy/RT (CMT): improved acute disease control (FFP and EFS)
- Absolute FFP/EFS improvements **3% to 8%**
- Overall survival similar (or better: *New Engl J Med* 2012) with chemotherapy alone
- Analysis of HD10/11 vs. NCIC/ECOG: 8-year TTP improved 6% with CMT (PFS 3%)

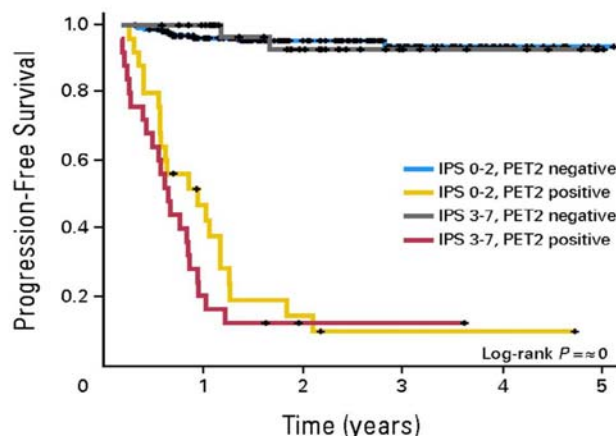
Meyer RM, et al. *N Engl J Med*. 2012;366(5):399-408.; Nachman JB, et al. *J Clin Oncol*. 2002; 20(18):3765-3771.; Straus DJ, et al. *Blood*. 2004;104(12):3483-3489.; Laskar S, et al. *J Clin Oncol*. 2004;22(1):62-68.; Meyer RM, et al. *J Clin Oncol*. 2005;23(21):4634-4642.; Hay AE, et al. *Ann Oncol*. 2013;24(12):3065-3069.

The question of inclusion of radiotherapy after chemotherapy has been hotly debated over the last few decades, and it continues to be so. Before I talk about response-adapted studies using early interim PET scan, I did want to set the baseline, in terms of what those studies have shown. Since 2000, there have been four randomized early-stage studies

looking at chemotherapy alone versus chemotherapy plus radiation, otherwise known as combined modality therapy. In all four of those studies, there was an improvement in acute disease control, whether measured by event-free survival or freedom from progression. If you look at the absolute numbers across those studies, that range is between 3% and 8%. In one study with longer follow-up, albeit with older radiation techniques, there was improved survival with chemotherapy alone, although most studies have shown similar overall survival. There was a combined meta-analysis done between the NCIC/ECOG study and the German Hodgkin Study Group HD10 and HD11 that put it right in the middle, with a time to treatment progression (TTP) improvement of 6% with combined modality therapy or PFS of 3%. So, those numbers are important as we look at response-adapted therapy right between 3% and 8%.

This study set off a wave of response-adapted therapy studies across the world, when it was published looking at interim early PET scan after the second cycle of ABVD. It showed that, irrespective of Hasenclever international prognostic score, the early PET scan results, whether positive or negative, predicted progression-free survival.

Early PET-2 in HL: 2-year PFS According to IPS



Gallamini A, et al. *J Clin Oncol*. 2007;25(24):3746-3752.

5-Point Scale for Interim-PET Interpretation Deauville Score: Early-Stage

1. No uptake
2. Uptake \leq mediastinum
3. Uptake $>$ mediastinum but \leq liver
4. Moderately increased uptake compared to liver
5. Markedly increased uptake compared to liver or new areas of FDG uptake

Negative
scan

Positive
scan

Barrington SW, et al. *Eur J Nuc Med Molec Imag*. 2010;37:1824-1833.; Meignan M, et al. *Leuk Lymph*. 2009;50:1257-1260.

An important factor when interpreting any response-adapted study, or when managing patients, is how you score the scan. Thankfully, in the lymphoma world, we had harmonization several years ago using what is now called the Deauville criteria. With this criteria, the score ranges from 1 to 5, where 1 is no uptake; 2 is

uptake equal to, or less than the mediastinum; 3 is uptake greater than the mediastinum, but less than the liver; and 4 and 5 are greater than the liver. Most early-stage studies have drawn the line between 2 and 3. In other words, if you have uptake greater than a mediastinal blood pool, it is positive. It either has to be equal or less to be considered negative, and this was to enrich the negative predictive value, because as you move the line, it changes your negative and positive predictive value.

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JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Omitting Radiotherapy in Early Positron Emission Tomography–Negative Stage I/II Hodgkin Lymphoma Is Associated With an Increased Risk of Early Relapse: Clinical Results of the Preplanned Interim Analysis of the Randomized EORTC/LYSA/FIL H10 Trial

John M.M. Raemaekers, Marc P.E. André, Massimo Federico, Theodore Girinsky, Renan Oumedaly, Ercole Brusamolino,† Pauline Brice, Christophe Ferné, Richard van der Maazen, Manuel Gotti, Reda Bouabdallah, Catherine J. Sebban, Yolande Lievens, Alessandro Re, Aspasia Stamatoullas, Frank Morschhauser, Pieterella J. Lugtenburg, Elisabetta Abruozese, Pierre Olivier, Rene-Olivier Casanovas, Gustaaf van Imhoff, Tiana Raveloarivaly, Monica Bellei, Thierry van der Borgh, Stéphane Bardet, Annibale Versari, Martin Hutchings, Michel Meignan, and Catherine Fortpied

Eligibility: Patients age 15-70 years with untreated stage I/II HL (*Favorable and Unfavorable: a) large mediastinal mass; b) age >40 years; c) high ESR; d) 4 or more areas*)

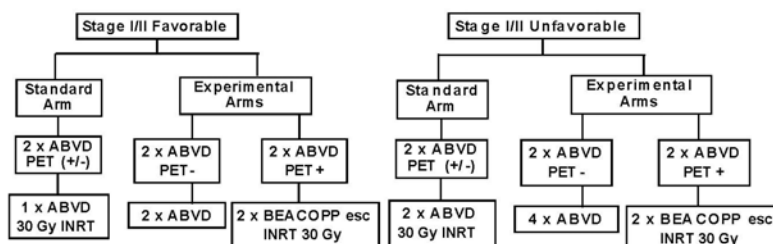
Randomized: 1,137 total patients (F: 444; U: 693)

Two studies have been published to date. The first was the EORTC trial by Raemaekers et al. This trial included patients between the ages of 15 and 70, and, using the EORTC criteria of favorable and unfavorable, over one thousand patients were randomized with the

different numbers of favorable and unfavorable.

The Favorable study looked at a randomization to two different treatment strategies. One was a non-response-adapted strategy, on the far left for favorable, and the experimental strategy used response-adapted strategy. So, if the PET scan was negative after 2 cycles, you gave two more ABVD and no radiation, whereas if it was

EORTC/LYSA/FIL H10F + H10U Studies



- Statistics: allow 10% decrease in PFS (from 95% F and 90% U)
- Enrollment: ~190 each arm (F) and ~260 each arm (U)
- PET-2 negative rates: 86% (F) and 75% (U)
- F: 1 vs. 9 events (RT vs. no RT), $P=.017$; U: 7 vs. 16 events, $P=.026$
- Null hypotheses of inferiority not rejected (futility)

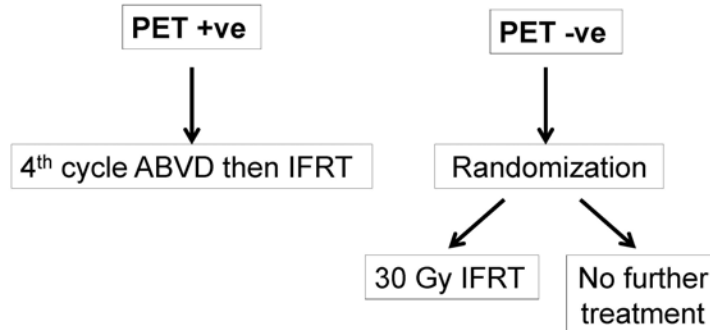
Raemaekers JM, et al. *J Clin Oncol*. 2014;32(12):1188-1194.

positive, you escalated therapy to BEACOPP followed by involved nodal radiotherapy. The Unfavorable study, was similar to the Favorable, except it had more chemotherapy in the standard arm for ABVD and radiation. In the experimental arm, it provided 6 cycles of ABVD for PET negative versus the same in terms of increasing therapy to two escalated BEACOPP for PET positive. These predetermined statistics are important, as they would allow for a 10% decrease in PFS. The enrollment for the Favorable study was about 190 for each arm, and about 260 for each arm of the Unfavorable. The early PET to negative rates were 86% for Favorable, 75% for Unfavorable with added pre-planned interim analysis. There were increased relapse rates seen in both arms in the Unfavorable and the Favorable. This was not absolute over 10%, but it predicted statistically that it would greatly exceed that. Thus, the null hypothesis of inferiority was rejected, or in other words, there was futility that it was not non-inferior. As a result, the study was then modified for all patients to receive radiation.

RAPID - Trial Design

Initial treatment: ABVD x 3

Re-assessment: If response, PET scan performed



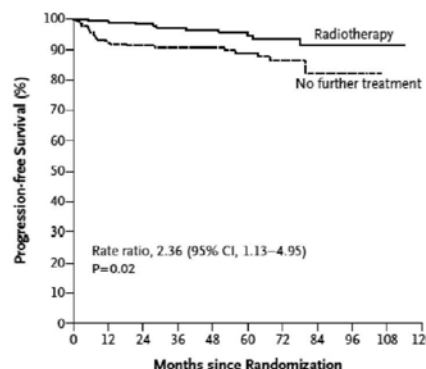
Radford J, et al. *N Engl J Med.* 2015;372(17):1598-1607.

The RAPID trial was a similar study, although with a slightly different design, in that these were mostly more favorable patients: approximately three quarters fell into a favorable category. As a result, patients could not have B symptoms to enroll in the RAPID study. It was a slightly cleaner study in that, even though

it lumped early and unfavorable, and most of the patients enrolled were early favorable, all patients received 3 cycles of ABVD and then, based on PET scan, were randomized to either radiation or no radiation.

What did the result show? This was also a noninferiority study, and it is important to always look at the protocol analysis when doing a noninferiority study, which is converse to looking at intent-to-treat on superiority. What was shown is that the 3-year progression-free survival was 7% better for

PFS in the Per Protocol Population



3-year absolute risk difference: 95% CI -8.8-1.3 (exceeds pre-specified non-inferiority boundary)

3-year PFS 97.1% (94.7%-99.6%) vs 90.8% (86.8%-94.7%)

Rate Ratio 2.36 in favor of IFRT, P = 0.02

Radford J, et al. *N Engl J Med.* 2015;372(17):1598-1607.

patients who still receive radiotherapy. There is no difference in overall survival, but despite this negative PET scan, this acute disease control rate was still increased. When looking at the intent-to-treat, it was 4%, but as you can see, it still exceeded the noninferiority, so, officially by statistics, this was not noninferior, similar to the EORTC study.

EORTC and RAPID: My Conclusions

- Current data: interim negative FDG-PET-2 in early-stage HL has *not* proven to be predictive thus far
 - For the question asked (ie, PET-2 – PFS difference <7-10% without RT)
- Need longer follow-up, especially towards late effects and OS
- Data re: *intensification* of therapy

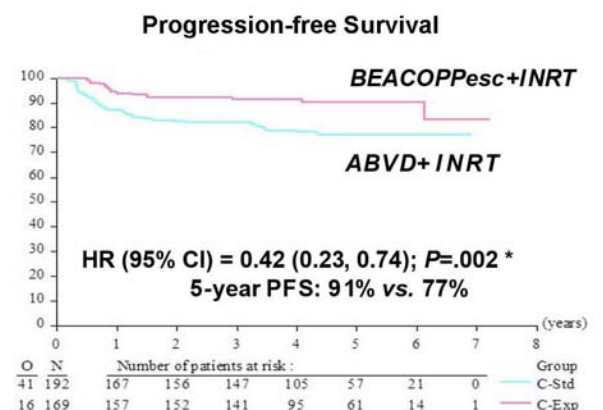
Adapted from Evens AM, Kostakoglu L. *Blood*. 2014;124(23):3356-3364.

Overall, what are my conclusions to these two studies? That interim negative PET has not been proven to be predictive. By “predictive”, we mean you have a result and you know, based on randomized study, that you can make a change, at least for the question asked. And here, the question asked was whether we can see a difference

less than 7-10% in progression-free survival without radiation. Of course we need longer follow-up, especially toward late effects and overall survival, but again, remember that on the earlier studies, the difference was already between 3% and 8%. So, this result still falls within that percentage range. Now, this does not mean that all patients should receive radiotherapy. It absolutely still remains an individual choice. Now, what about intensification of therapy?

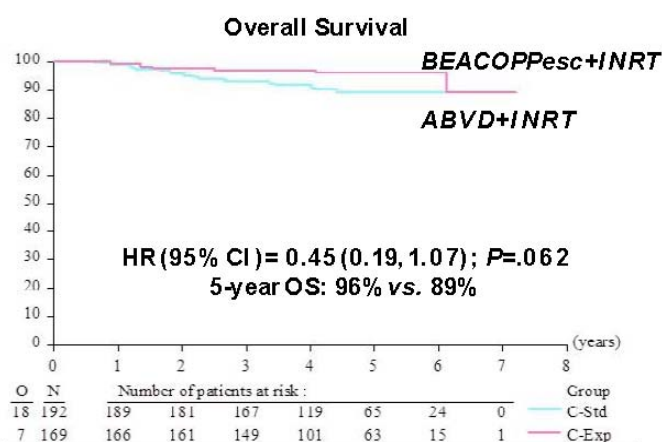
This data has not been published yet, but was presented at the 2015 Lugano, Switzerland (ICML) meeting. This study looked at patients from the EORTC study who had a positive PET scan who went to escalated BEACOPP. At the time of the presentation, progression-free survival in these patients was increased by 14 percentage points.

PET+ Group: BEACOPPesc vs. ABVD Progression-free Survival (PFS)



*Alpha=0.037 is the significant level to be used at the final analysis as alpha=0.018 has already been spent at the IA
HR=hazard ratio BEACOPPesc vs. ABVD
Raemaekers J, et al. Lugano ICML 2015.

PET+ Group: BEACOPPesc vs. ABVD Overall Survival (OS)



HR=hazard ratio BEACOPPesc vs. ABVD
Raemaekers J, et al. Lugano ICML 2015.

What was also interesting, while not significant at 0.06, was that these patients had overall survival at 5 years that was increased by 7 percentage points. This is fairly thought-provoking data. We certainly await the published and final data set, but it is intriguing data nonetheless.

How do I treat early-stage Hodgkin's? My treatment strategy remains individualized; it is not a one-size-fits-all. For younger females, less than age 35, or anybody with other significant risk factors, such as strong family history of arterial disease who have favorable early stage Hodgkin's, I will use 3 to 4 cycles of ABVD without radiation. For all

others, including slightly older patients, not central chest disease, but with only one site in the neck or one site in the neck and submandibular area, at this time, I will use 2 cycles of ABVD and 20 Gy radiotherapy involved field, as we saw in HD10. I still treat unfavorable, non-bulky disease similar to the NCIC study, with 4 to 6 cycles of ABVD, acknowledging that, even in early PET negative patients, it is still likely that a slight increase in acute relapse rate will occur, by anywhere from 4% to 6%. What about end-of-treatment positive PETs or even interim-positive PETs? I believe, for these patients, we still do not know what to do. It will be very intriguing to see the EORTC data published, as changing or escalating therapy to escalated BEACOPP and radiation represents a treatment option, as well. For bulky disease, I think the worldwide standard is still chemotherapy followed by involved-field radiotherapy, although some studies have looked at PET scan. There is interesting data from the British Columbia Group presented at the recent American Society of Hematology Annual Meeting (ASH), suggesting that we may be able to avoid radiation. In older patients, I would recommend similar paradigms with the a priori exclusion of bleomycin. I feel that the risks in particular, bleomycin lung toxicity, do not outweigh the benefits of this therapy.

How I Treat Early-Stage HL

Favorable*	<ul style="list-style-type: none"> • Younger women (ie, ages <35 years) with chest disease and/or other risk factors (e.g, arterial disease): 3-4 cycles ABVD • All others: 2 x ABVD followed by 20 Gy IFRT
Unfavorable (non-bulky)	<ul style="list-style-type: none"> • 4-6 x ABVD End of Tx PET+ (? BEACOPP)
Bulky	<ul style="list-style-type: none"> • 6 x ABVD followed by 30 Gy IFRT
Older patients (>65 years)	<ul style="list-style-type: none"> • Similar as above except with <i>a priori</i> exclusion of bleomycin (ie, AVD)

*As determined by German Hodgkin Study Group criteria (ie, none of the following):
a) large mediastinal mass; b) extranodal disease; c) high ESR; d) 3 or more areas

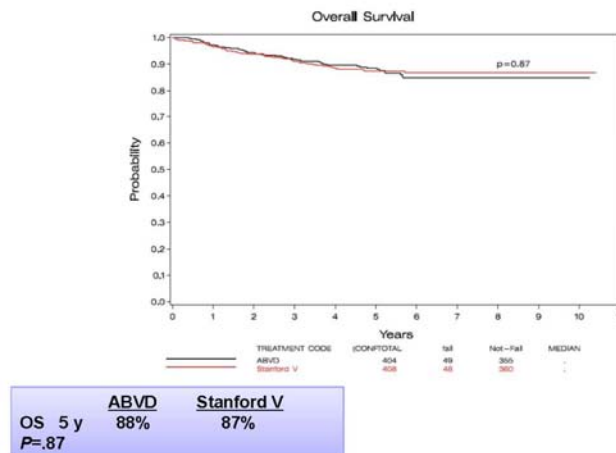
Advanced Stage HD

- Stage III and IV (IIBX)
- MOPP not acceptable; MOPP/ABV early closure for “toxicity”
- ABVD has been a “standard”
- Stanford V inferior to ABVD in Italian trial and equivalent in US trial
- German data with ‘intensive’ regimen BEACOPP (escalated, 4+4, -14)

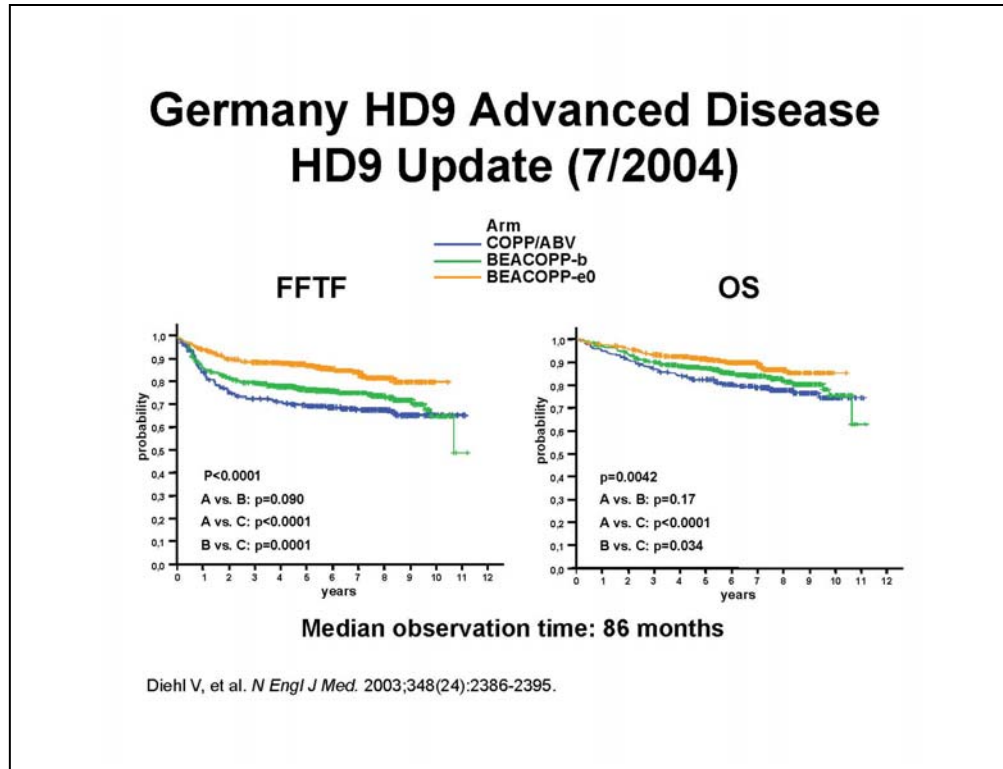
What about advanced stage?
I would say that treatments are a little bit cleaner. For at least the last decade or so, the standard has been six cycles of ABVD. An Italian study found that Stanford V was inferior to ABVD, and we know there was good German data looking at intensifying treatment with BEACOPP.

This graph summarizes the Stanford V overall survival data versus ABVD in the ECOG United States study by Leo Gordon et al. You can see the 5-year overall survival of ABVD at 88% and Standard V at 87%. This analysis did include patients over age 60; if you remove patients over 60, the overall survival is actually 93% to 94%.

Intergroup Trial E2496: Overall Survival Stanford V vs. ABVD



Gordon LI, et al. *J Clin Oncol*. 2013;31(6):684-691.



This is the *New England Journal* data published by Volker Diehl, showing the improved overall survival for escalated BEACOPP versus COP ABV. This is the study that shifted the paradigm in Germany towards BEACOPP.

There are some caveats of BEACOPP that we need to consider. There has been an increased risk, albeit not a huge one, but an increased risk nevertheless, of second malignancies seen with BEACOPP; in particular, leukemia, questions of infertility, avascular necrosis, infections, etc. But we also have

“Issues” with BEACOPP

- Second malignancies (leukemia)
- Other concerns
 - Infertility, AVN, infections, etc.
- Dose intensity
 - HD12 median treatment duration: COPP-ABVD 33.4 weeks (original report 46.3 weeks) versus 24.4 and 24.7 weeks for BEACOPP-base + escalated (COPP-ABVD 36% longer)

to really consider the dose intensity of that initial study, in which the dose intensity of COP ABV therapy was much longer than BEACOPP, which could have explained some of the differences seen. Today, most

people want to give ABVD at its full-dose intensity, with no delays, irrespective of the neutrophil counts, at least for patients less than age 60 and 65. So, we give ABVD in a much different fashion nowadays.

5-Point Scale for Interim-PET Interpretation Deauville Score: Advanced-Stage

1. No uptake
2. Uptake \leq mediastinum
3. Uptake $>$ mediastinum but \leq liver
4. Moderately increased uptake compared to liver
5. Markedly increased uptake compared to liver or new areas of FDG uptake

Negative
scan

Positive
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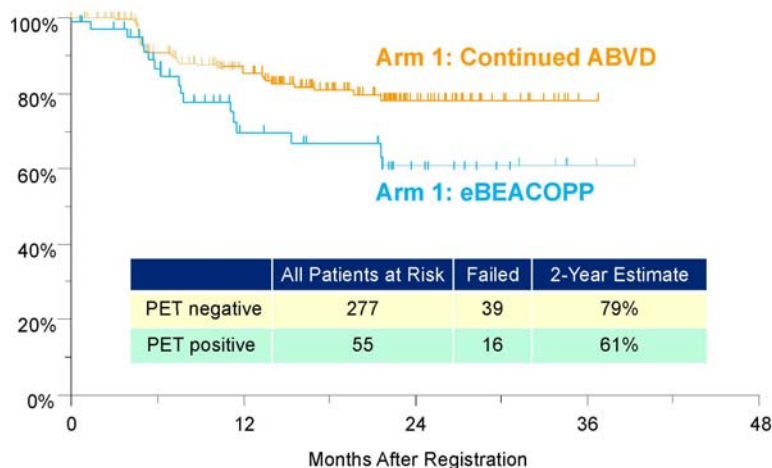
Barrington SW, et al. *Eur J Nuc Med Molec Imag.* 2010;37:1824-1833.; Meignan M, et al. *Leuk Lymph.* 2009;50:1257-1260.

What about response-adapted therapy for advanced-stage disease? There have been several studies that should be published soon, with data that has been presented several times previously. Most of these studies have drawn the line lower, between 3 and 4, with 4 representing positive. In other words, the

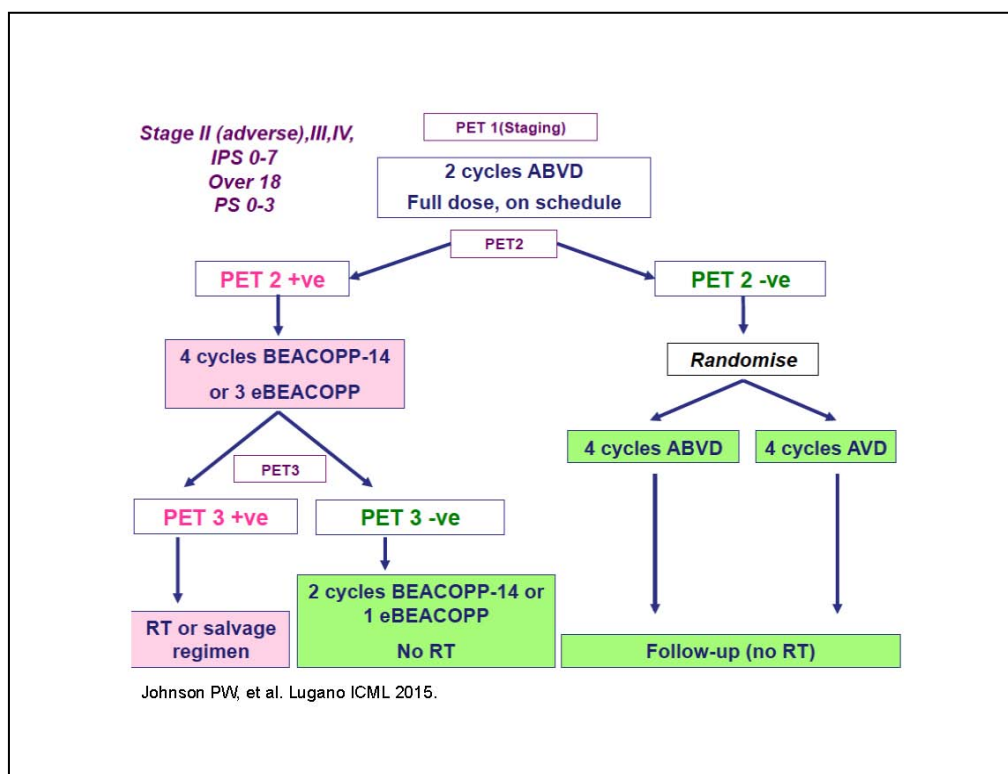
uptake of visual interpretation had to be greater than the liver to be considered positive. This increases your positive predictive value.

This data should be published very soon in a high-impact journal. It summarizes the US phase 2 prospective study in which patients who had a positive PET scan after 2 cycles had therapy escalated to BEACOPP. The study was not randomized, but you can see that, at least compared to historical controls, 2-year survival rates were over 60%.

S0816 PFS by PET2 Result



Should this be accepted as the standard of care, I am using this approach in patients. We do not have randomized data supporting it, but this is the best available data. The other caveat is that we always need to look at the PET scan and understand that this is truly a Deauville 4 or 5 before escalating.



What about randomized data in the advanced-stage space? This data from Peter Johnson, was presented at Lugano (ICML). It has not been published yet, but they evaluated diminishing therapy for an early PET negative scan after the second cycle of ABVD. As you can see on the right, there was a

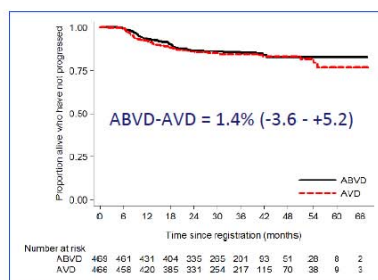
randomized continuing of ABVD versus deleting or dropping the bleomycin. All patients with a positive PET scan had therapy escalated.

The primary endpoint was PFS for the PET negative, and, as you can see here, there was really no difference, either on intent-to-treat or per protocol analysis. So, while I think some would say this is a minor change, I would say this is a paradigm shift, and a change in standard of care that, at least for negative PET, advanced-stage patients, we would remove or delete bleomycin from future treatments.

Primary Endpoint: PFS for PET-negative Randomized, Eligible Patients

(Median follow up 36.3 months)

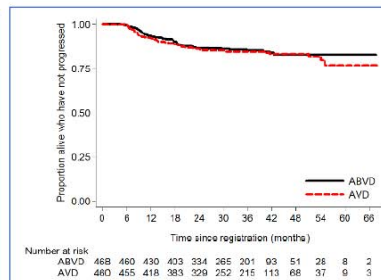
Intention to treat analysis:



HR: 1.11 (0.79 - 1.54), $p = 0.53$
3 Year PFS, ABVD: 85.4% (95% CI: 81.6 - 88.5)
3 Year PFS, AVD: 84.4% (95% CI: 80.7 - 87.6)

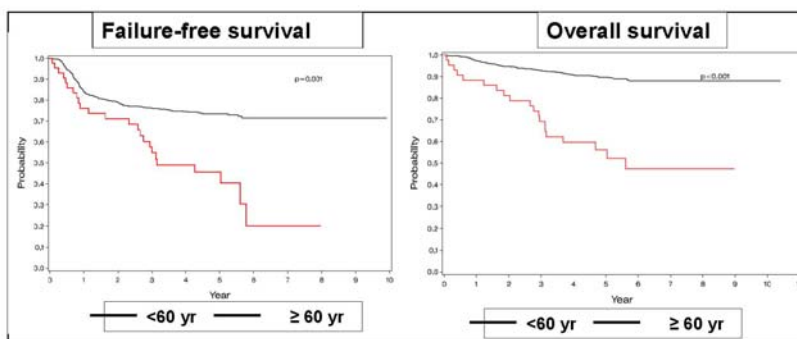
Johnson PW, et al. Lugano ICML 2015.

Per protocol analysis:



HR: 1.09 (0.78 - 1.53), $p = 0.59$
3 Year PFS, ABVD: 85.3% (95% CI: 81.6 - 88.4)
3 Year PFS, AVD: 84.6% (95% CI: 80.8 - 87.7)

Survival: Older vs. Younger HD



		< 60 years	≥ 60 years	P
FFS	3-year	76%	56%	0.002
	5-year	74%	48%	
OS	3-year	93%	70%	<0.0001
	5-year	90%	58%	

I had mentioned that we would discuss the treatment of older patients, who have historically been defined in Hodgkin disease as over age 60. This has been an issue for over 30 years. We looked at this data recently from the aforementioned ECOG2496 advanced-stage study and a significant

discrepancy still remains in both failure-free survival and overall survival. As you can see from the tables at the bottom of the graphic that, while the situation may not be not as bad today as it was in the 20th century, there still remains a significant drop off, even with 21st century ABVD therapy. Why is that? Is it tolerability? That's probably part of it. Is it a different disease? You do see more mixed cellularity. It's probably a little bit of both.

Older HD Summary

- Outcomes suboptimal with conventional therapy
- Toxicity and TRM (caution re: bleomycin-lung toxicity)
- Recent retrospective prognostic/outcomes
- Recent phase II studies: VEPEMB and PVAG
- Off study: AVD (or CHOP)
- Need more prospective studies and improved therapeutic options
 - Examine functional tools in elderly (ie, PET)
 - Incorporate comorbidity and ADL assessments

So, we know outcomes are suboptimal with conventional therapy because of toxicity and treatment-related mortality (TRM). TRM of older patients was almost 10% in this ECOG study, and not just because of bleomycin-lung toxicity, also through sepsis, etc. There have been some phase 2 studies conducted in Europe that have

looked at unique regimens, including a publication using CHOP. Off study, I will typically use AVD without bleomycin, but we certainly need more prospective studies in this patient population, including studies that address comorbidities, ADL assessments, etc.

Novel (Targeted) Therapies

Mechanism	Agent(s)
Antibody-drug conjugate	Brentuximab vedotin, anti-CD79a
PD-1/PDL-1 blockade	Nivolumab, pembrolizumab
Antibody/receptor therapy	CD30, CD20, IL-13, TRAIL, Bi-specific Ab
Radioimmunotherapy-based	anti-CD25 and anti-CD30
Anti-apoptotic molecules	Proteasome pathway inhibition, XIAP, darinaparsin (organic arsenic)
Transcriptional pathways	HDAC inhib, PIK3 inhib, mTOR inhib, anti-HSP-90, galectin-1, nutlin-3A
EBV-directed therapy	EBV-cytotoxic T-cells, LMP-2A inhibition

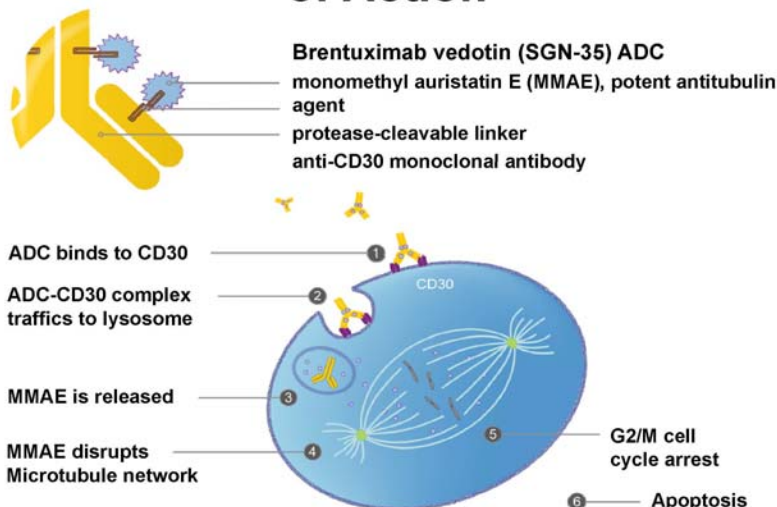
What about novel-targeted therapies? Thankfully, there are a number of targeted therapies that are being actively integrated into treatment paradigms in Hodgkin lymphoma. The leader of the pack is brentuximab vedotin, which is an antibody-drug conjugate. This is quickly followed by checkpoint inhibitors, in particular PD1 inhibitors, as well as others, as you

can see here listed in this table.

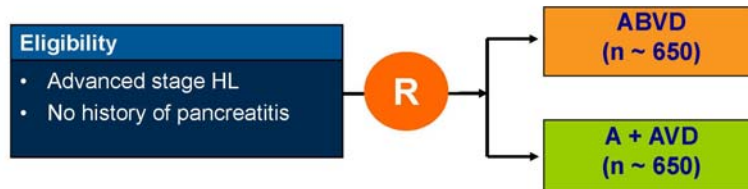
Brentuximab vedotin is an antibody-drug conjugate. It is an anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E (MMAE). When it is internalized, in an acidic environment, it cleaves the protease and releases the chemotherapy. This is now FDA-

approved for relapsed/refractory Hodgkin lymphoma, as well as maintenance therapy after autologous transplant for high-risk Hodgkin lymphoma.

Brentuximab Vedotin Mechanism of Action



Phase III ECHELON-1 Study



- Accrual completed 10/27/15
- Febrile neutropenia 15-20% on A-AVD arm (GCSF mandated)
- Results 2017

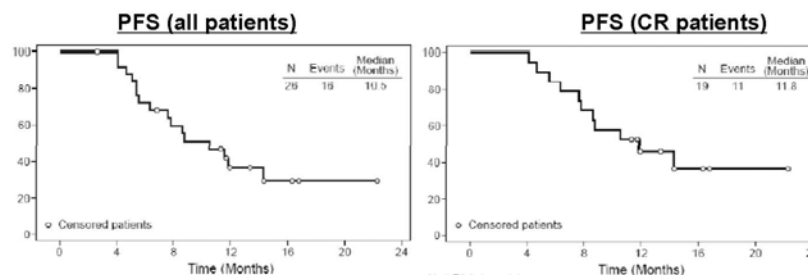
This image summarizes the phase 3 ECHELON-1 study, in which accrual has completed. We are anxiously awaiting the data from this front-line randomized study of ABVD versus brentuximab vedotin and AVD. Importantly, brentuximab vedotin should never be utilized in conjunction with bleomycin, as there are

untoward pulmonary side effects.

What about the elderly? This is a recently published single-arm open-label phase 2 study using brentuximab vedotin. You can see an older patient population with a median age of 78 years, and a decent response rate. There was neurotoxicity which is important to understand, and you can see the PFS rate may be as good as what we saw in E2496. Interestingly, though, even in CR patients, it was not super-robust in

Brentuximab Vedotin in Elderly HD

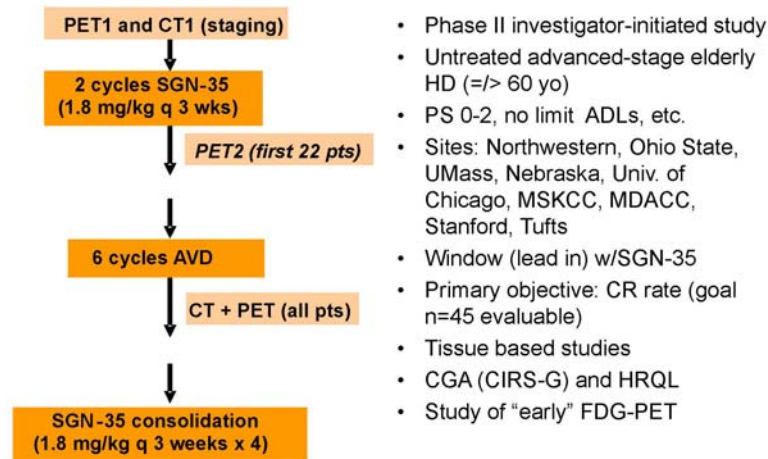
- Single-agent brentuximab vedotin 1.8 mg/kg q 3 weeks in 27 elderly HD patients
 - Median age 78 years, 63% stage III/IV
- ORR 92% (73% CR)
- 30% patients grade 3 neuropathy



terms of single-agent therapy. So, I know this study has been amended, and they are now adding chemotherapy, such as dacarbazine and adriamycin, to see how much we need to treat these patients.

We have almost completed a study here in Boston and at several sites across the US. This study is evaluating sequential brentuximab vedotin, starting with that targeted therapy and followed by what we considered standard chemotherapy. We then finish with maintenance or consolidation therapy with additional brentuximab vedotin.

Incorporation of Brentuximab Vedotin (BV) into Frontline Therapy



BV/AVD: Outcomes

- BV x 2: ORR 85% (CR 30%); and after BV/AVD: ORR 95% (CR 95%)
- Median follow-up 14 months: 92% all patients alive
- Of evaluable patients, 95% free of disease
- Safety
 - G3 AEs: 46%; patients G4 AEs: 31% (4% grade 3 peripheral neuropathy)

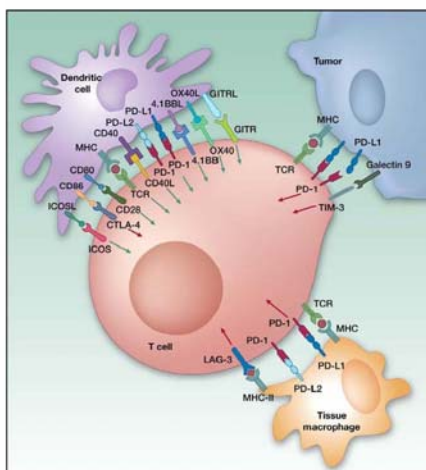
Evens AM, et al. Lugano ICML 2015.

This is very preliminary data that was presented at Lugano, but after brentuximab vedotin, you can see the response rates from 2 cycles, and then after chemotherapy, there was quite a rate of both high remission and CR. We need longer follow-up, but, of evaluable patients, you can see that 95%

were free of disease. Still, there was some neuropathy that needs to be followed, but this was definitely a manageable adverse event.

What about checkpoint blockers? Checkpoint inhibitors are quite exciting therapies. This cartoon summarizes the action of the PD1 receptor on T cells, and of PDL1 on tumor cells. And we know that it is important that tumors co-opt this and cause, in part, T cell exhaustion. Thankfully now, we have medications that can block this receptor.

Immune Checkpoint Blockade Strategies: PD-1 and PD-L1 Inhibition



Ott PA, et al. *Clin Cancer Res*. 2013;19(19):5300-5309

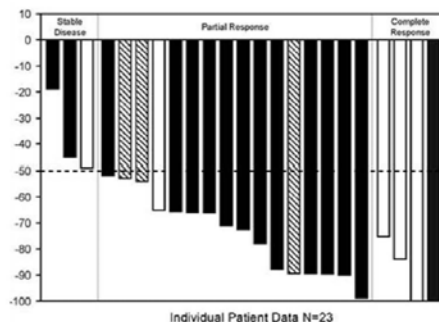
- PD-1 cell surface marker on T- and immune cells
- Interacts with its ligands (PD-L1 and PD-L2) initiating inhibitor signaling network (T-cell exhaustion)
- Tumor cell co-opt this pathway

Nivolumab for Rel/Ref cHL

- Human anti-PD1 blocking IgG4
- n=23 (78% prior BV/ASCT)
- IV 3 mg/kg Q2 wk
- AE: GI, fatigue, pruritus, rash (22% G3/4)
- Median f/u 101 weeks (median PFS NR)

Ansell S, et al. *N Engl J Med*. 2015; 372:311-319.

- ORR: 87%, CR: 17%



This data was published by Steve Ansell in the *New England Journal*. This study looked at 23 patients, 78% of whom had prior BV and stem cell transplants. When these patients were treated with nivolumab, a human anti-PD1 antibody blocking IgG4, they had a remarkable response rate of

87%, which was quite high. The CR rate may be not as robust at 17%, but this is really very exciting data nonetheless.

This image summarizes data from the KEYNOTE-13 trial, looking at pembrolizumab. This study showed very similar data, as you can see where the transplant ineligible or failure had high overall response rates, with more modest CR rates. The other point with both this study and the prior one, is that the median

Pembrolizumab (KEYNOTE-013): Efficacy

	Total N = 31	Transplant Ineligible/Refused N = 9	Transplant Failure N = 22
Overall Response Rate	20 (65%)	4 (44%)	16 (73%)
Complete Remission	5 (16%)	2 (22%)	3 (14%)
Partial Remission	15 (48%)	2 (22%)	13 (59%)
Stable Disease	7 (23%)	3 (33%)	4 (18%)
Progressive Disease	4 (13%)	2 (22%)	2 (9%)

Armand P, et al. ASH 2015.

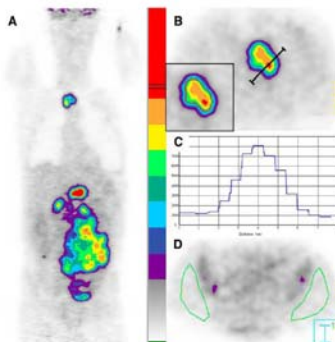
progression-free survival rates in both have been very impressive; a median of over 100 weeks has still not been reached with the NEVO study. So, we need longer follow-up with more numbers, but this is very exciting data, and these results are quickly being integrated into frontline therapy.

In the last two slides, I will talk about biomarkers. We are still hoping that the early functional image PET scan is going to be the answer, but there might be some niches where we use it. I think we're looking at more and newer technology.

Metabolic Tumor Burden

- Definition (quantitative)
 - EG: Δ SUV-max and MTV (volume in mL) of tumor tissue demonstrating FDG uptake (segmentation technique/3D software); and tumor heterogeneity
 - Total lesion glycolysis (TLG): integrates tumor volume and glycolytic activity (TLG = MTV x SUV-mean)

Lin C, et al. *J Nucl Med*. 2007;48(10):1626-1632.;
Wahl RL, et al. *J Nucl Med*. 2009;50 Suppl 1:122S-50S.; Casasnovas RO, et al. *Blood*. 2011;118(1):37-43.; Kostakoglu L, et al. *Leuk Lymphoma*. 2012;53(11):2143-2150.



One that I think is interesting, but is still research and not standard of care by any means, is metabolic tumor burden. In other words, we're looking at a more quantitative test, and not just a qualitative scan, which is what a PET scan is, in today's world.

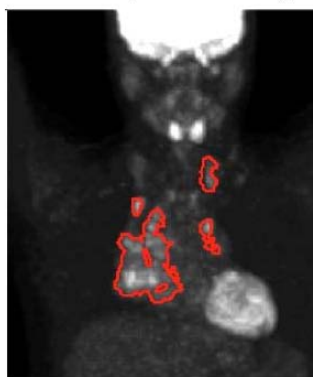
Can we quantitate the tumor burden? As you can see, we can quantitate not just by the volume of tumor, but by the intensity as this image shows.

This is the Δ SUV-max and metabolic tumor burden can be measured, as well as total lesion glycolysis, and you can map this out. There was a Hodgkin lymphoma study published by colleagues at Stanford that showed that this type of analysis was highly predictive, with

Metabolic Tumor Burden

- Definition (quantitative)
 - EG: Δ SUV-max and MTV (volume in mL) of tumor tissue demonstrating FDG uptake (segmentation technique/3D software); and tumor heterogeneity
 - Total lesion glycolysis (TLG): integrates tumor volume and glycolytic activity (TLG = MTV x SUV-mean)
- 30 HL patients (47% stage I/II)
 - MTV = 94 mL, SUVmax = 8.9, SUVmean = 3.4, and TLG = 319.8
 - MTV(int/pre), SUV-max(int/pre), and TLG all predicted PFS + OS

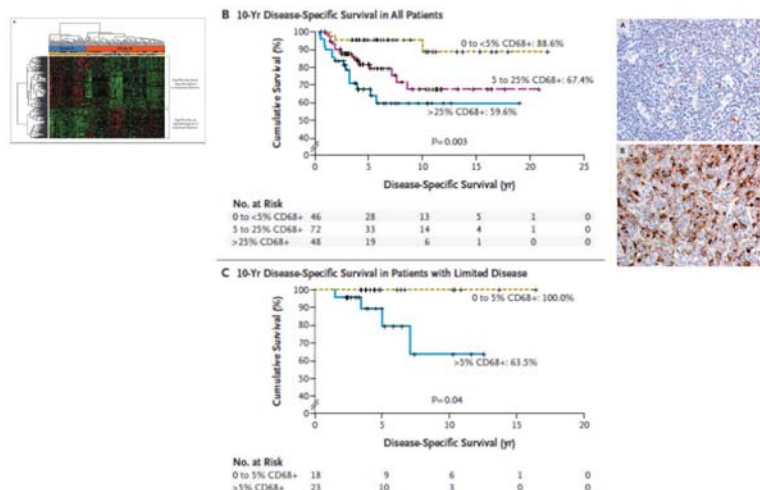
Tseng D, et al. *Radiat Oncol*. 2012;7:5.



the metabolic tumor burden as well as SUVmax all predicting both progression-free survival and overall survival. So, this will be interesting as we go along.

What has also been important is looking at gene expression profiling of baseline tumor tissue in Hodgkin lymphoma. The British Columbia Cancer Agency has done outstanding work to this end. In this image, you can see gene expression profiling, as well as immuno-histochemistry panels [top] of patients with low amounts of

Tumor-associated Macrophages



Steidl C, et al. *N Engl J Med*. 2010;362(10):875-885.

macrophage on the IHC and patients with high levels of macrophages in their biopsy specimen. What does this translate to? It was prognostic, showing that low-macrophage patients had a good outcome and patients who had high macrophages had a poorer outcome. We would say this is definitely prognostic. We do not know if, like PET scans, this is predictive, but hopefully studies will address this in the near future. In other words, now based on this, can you possibly increase therapy for patients with high macrophage, or, alternatively, decrease therapy with low macrophage? Those studies will be interesting to design and we await those.

Overall Summary

- Early-stage HD: 90-95% cured
 - Individualized therapy
 - Continued study of response-adapted Rx
- Advanced-stage HD
 - ABVD; response adapted and await BV phase III data
- Elderly HD: modified therapy
- Current/future: integration of novel therapeutics and identification of predictive biomarkers

As an overall summary for managing Hodgkin lymphoma in 2016, we know that, for patients with early-stage Hodgkin lymphoma who are treated with chemotherapy or chemotherapy plus radiation, a majority of these patients are cured. I think it still is an individualized choice whether you administer combined

modality therapy with radiation or chemotherapy alone. I think it is still evolving, in terms of response-adapted therapy. We await more data looking at positive, as well as negative, response-adapted therapy and early stage as well as advanced stage. In my practice, the majority of patients for advanced stage will receive 6 cycles of ABVD. I will dose-escalate to BEACOPP for an interim-positive PET after 2 cycles, but we also anxiously await the brentuximab vedotin randomized data, as well. Older patients certainly need modified therapy, and different regimens are being evaluated, including incorporation of novel agents. In closing, I think that is the most exciting part. I think we are poised over the next decade to find a cytotoxic-free regimen for patients, whether it is a combination of different novel targeted therapeutics. It definitely is an exciting time, and we need to continue to leverage the science in identifying truly predictive biomarkers, but, whether it is imaging, tissue-based, or a matrix of all of these, this is definitely an exciting time in Hodgkin lymphoma.

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