5 Minute JournalClub

POST-ASH Issue 4, 2013

RAPID: IFRT versus No Further Treatment in Patients with Early-Stage Hodgkin Lymphoma and Negative PET Scan After 3 ABVD Cycles

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

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.

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FACULTY — 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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This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: March 2013
Expiration date: March 2014

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POST-ASH Issue 4, 2013

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

To go directly to slides and commentary for this issue, **click here**.

Vincent T DeVita Jr, MD
NCI Director 1980-88

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.

Neil Love, MD
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RAPID: IFRT versus No Further Treatment in Patients with Early-Stage Hodgkin Lymphoma and Negative PET Scan After 3 ABVD Cycles

Presentation discussed in this issue

Radford J et al. **Involved field radiotherapy versus no further treatment in patients with clinical Stages IA and IIA Hodgkin lymphoma and a 'negative' PET scan after 3 cycles ABVD. Results of the UK NCRI RAPID trial.** *Proc ASH* 2012;**Abstract 547**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Bruce D Cheson, MD (1/14/13)

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.

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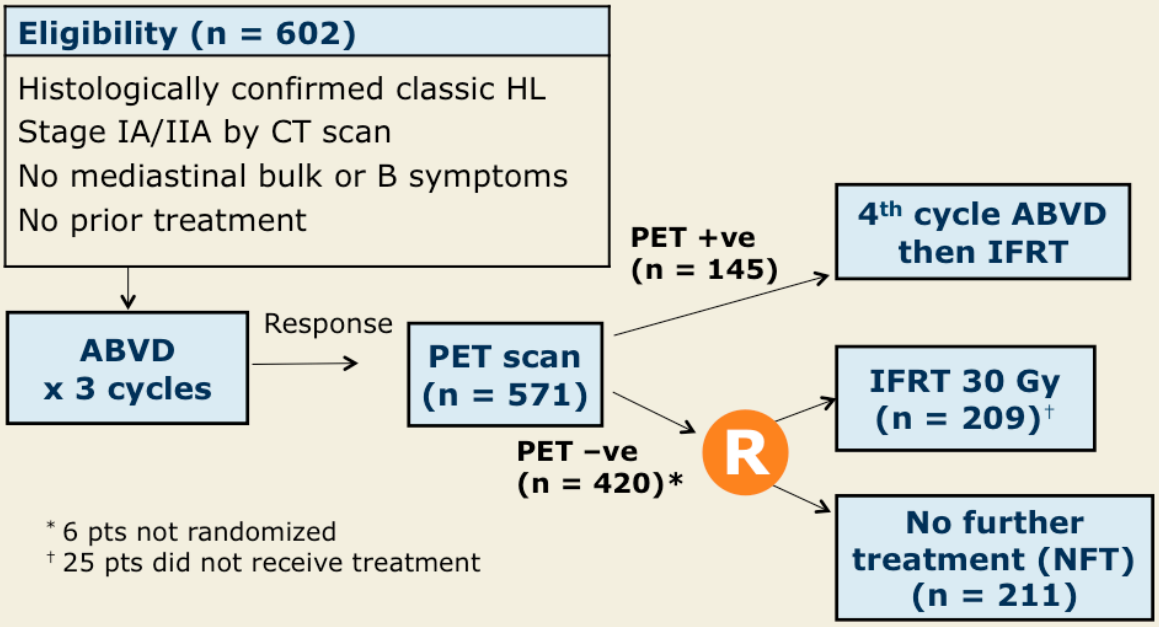
Phase III RAPID Study Design



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

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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.

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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.

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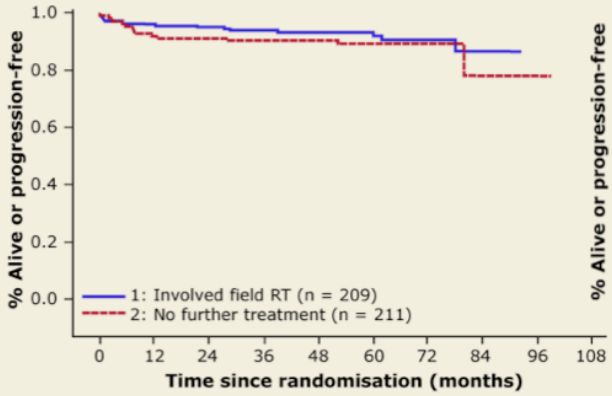
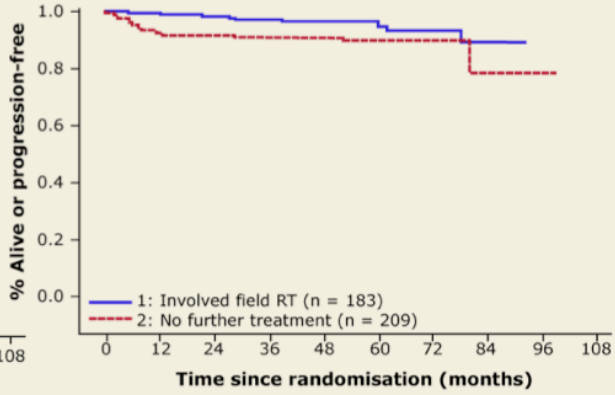
PFS in the PET-Negative Population

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.

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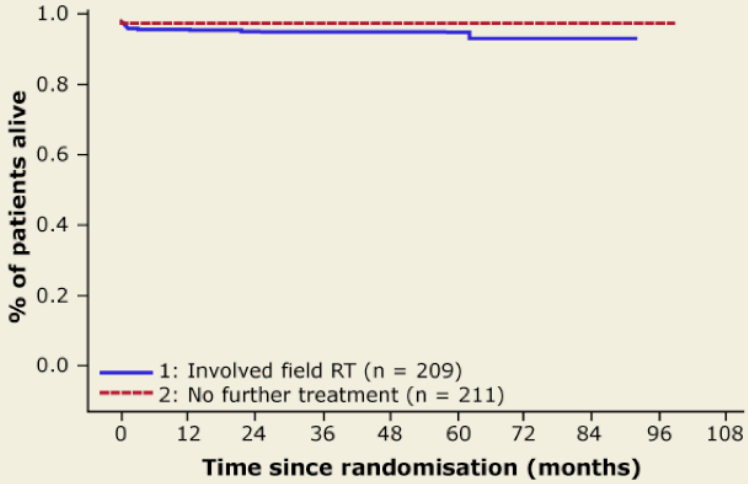
Overall Survival in the PET-Negative Population

ITT population (n = 420)



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.

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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.

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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