Imaging in Lymphoma from 1999 to Lugano: What is Next?

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Washington, D.C., USA
Disclosure
Bruce D. Cheson, M.D.
Menton PET Workshop 2016

I have a PET (Annie)
No PETs have been harmed during the preparation of this presentation
The History of Imaging

- Lymphangiogram
- IV pyelogram
- Ultrasound
- Liver/spleen scan
- CT
- Gallium scan
- MRI
International Working Group (IWG) 
Response Criteria for NHL: 1999 
Cheson et al, J Clin Oncol 17:1244, 1999

- Complete remission (CR)
- Complete remission/unconfirmed (CRu)
- Partial remission (PR)
- Stable disease (SD)
- Relapsed disease (RD)
- Progressive disease (PD)
Limitations of IWG Response Criteria

- Unclear/misinterpretations (e.g. CRu)
- Dependent on inadequate methods
  - Physical examination
  - CXR, CT scan, MRI
  - SPECT gallium
  - Visual bone marrow evaluation
PET/CT SCANNING

Concept originated in 1974 by Hoffman and Phelps
Invented by Dr David Townsend and Dr Ron Nutt
First applied to lymphoma in 1990
Medical Invention of the year, TIME magazine 2000
Concordance of Response Classifications Between IWG and IWG/PET in DLBCL

<table>
<thead>
<tr>
<th>IWG</th>
<th>CR</th>
<th>CRu</th>
<th>PR</th>
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<tr>
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Juweid et al, JCO 23:4652, 2005
Concordance of Response Classifications Between IWG and IWG/PET in DLBCL

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Jeweid et al, JCO 23:4652, 2005
Progression-free survival by the International Workshop Criteria and IWC plus PET

Juweid M E et al. JCO 2005;23:4652-4661
Revised Response Criteria for Malignant Lymphoma


ABSTRACT

Purpose
Standardized response criteria are needed to interpret and compare clinical trials and for approval of new therapeutic agents by regulatory agencies.

Methods
The International Working Group response criteria (Cheson et al, J Clin Oncol 17:1244, 1999) were widely adopted, but required reassessment because of identified limitations and the increased use of $[^{18}\text{F}]$fluorodeoxyglucose-positron emission tomography (PET), immunohistochemistry (IHC), and flow cytometry. The International Harmonization Project was convened to provide updated recommendations.

Results
New guidelines are presented incorporating PET, IHC, and flow cytometry for definitions of response in non-Hodgkin’s and Hodgkin’s lymphoma. Standardized definitions of end points are provided.

Conclusion
We hope that these guidelines will be adopted widely by study groups, pharmaceutical and biotechnology companies, and regulatory agencies to facilitate the development of new and more effective therapies to improve the outcome of patients with lymphoma.
Revised Response Criteria 2007

- **FDG-PET**
  - Primarily for DLBCL and Hodgkin
  - Recommended before treatment (not staging)
  - Standard for response assessment
  - Visual assessment
  - Mediastinal blood pool for background
- **IHC and flow cytometry included for BM**
Revised Response Criteria 2007

- CR – no FDG-avid disease in DLBCL or HL
  - Includes persistent mass
- CRu eliminated
- CT criteria used for other histologies
Closed Workshop:
Lymphoma pretreatment assessment and response criteria in the New Millennium: Beyond Ann Arbor

Tuesday, June 14, 2011 – USI Auditorium, Lugano University

Steering Committee: B.D. Cheson, R.I. Fisher, T.A. Lister, E. Zucca
Session Co-Chair – Sally Barrington
Overarching Goals of the Lugano Classification

- Improve lymphoma patient evaluation
- Eliminate ambiguity
- Universally applicable
- Facilitate the comparison of patients and results amongst studies
- Simplify the evaluation of new therapies by regulatory agencies.
Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group

Sally J. Berrington, Ng George Mühlbacher, Luke Kekula, Michel Melgosa, Martin Hoolings, Stefan P. Müller, Laurent H. Schwartz, Emmanuelle Zucca, Richard I. Fohren, Judith Trummel, Otto J. Heubner, Radley J. Hanks, Michael J. O'Dwyer, Roland Hofer, Alberto Riggio, and Bruce D. Cheson

See accompanying article doi: 10.1200/JCO.2013.54.8800

ABSTRACT

Purpose

Recent advances in imaging, use of prognostic indices, and molecular profiling techniques have the potential to improve disease characterization and outcomes in lymphoma. International trials are under way to test image-based response-adapted treatment guided by early interim position emission tomography (PET)–computed tomography (CT) Progress in imaging is influencing trial design and affecting clinical practice. In particular, a five-point scale to grade responses using PET-CT, which can be adapted to suit requirements for early- and late-response assessment with good interobserver agreement, is becoming widely used both in practice and response-adapted trials. A workshop held at the 11th International Conference on Malignant Lymphomas (ICML) in 2011 concluded that revision to current staging and response criteria was timely.

Methods

An imaging working group composed of representatives from major international cooperative groups was asked to review the literature, share knowledge about research in progress, and identify key areas for research pertaining to imaging and lymphoma.

Results

A working paper was circulated for comment and presented at the Fourth International Workshop on PET/CT Lymphoma in Midtown, France, and the 12th ICML in Lugano, Switzerland, to update the International Harmonisation Project guidelines regarding PET. Recommendations were made to optimize the use of PET/CT in staging and response assessment of lymphomas, including quantitative and quantitative measurements.

Conclusion

This article comprises the consensus reached to update guidance on the use of PET/CT for staging and response assessment for FL, diffuse large B-cell lymphoma, and mantle cell lymphoma. Lesions are detected on PET CT when they are ≥1 cm, and PET/CT is now considered to be the standard of care for lymphomas.

J Clin Oncol 32. © 2014 by American Society of Clinical Oncology

Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard I. Fohren, Sally J. Berrington, Frances Cavalli, Laurent H. Schwartz, Emmanuelle Zucca, and T. Andrew Lin

See accompanying article doi: 10.1200/JCO.2013.53.9229

ABSTRACT

The purpose of this work was to develop recommendations for evaluation, staging, and response assessment of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). A workshop was held at the 11th International Conference on Malignant Lymphomas in Lugano, Switzerland, in June 2011, that included leading hematologists, oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine physicians, representing major international lymphoma clinical trials groups and cancer centers. Clinical and imaging subcommittees presented their conclusions at a subsequent workshop at the 12th International Conference on Malignant Lymphomas, leading to revised criteria for staging and of the International Working Group Guidelines of 2007 for response. As a result, fluorodeoxyglucose (FDG) positron emission tomography (PET-CT)–computed tomography (CT) was formally incorporated into standard staging for FDG-avid lymphomas. A modification of the Ann Arbor descriptor terminology will be used for anatomic distribution of disease extent, but the suffixes A or B for symptoms will only be included for HL. A zone marrow biopsy is no longer indicated for the routine staging of HL and most diffuse large B-cell lymphomas. However, regardless of stage, general practice is to treat patients based on limited (stages I and II) or advanced (stages III and IV) disease, with stage II bulky disease considered as limited or advanced disease based on histology and a number of prognostic factors. PET-CT will be used to assess response in FDG-avid histologies using the 5-point scale. The product of the perpendicular diameters of a single node can be used to identify prognostic disease. Routine surveillance scans are discouraged. These recommendations should improve evaluation and care for patients with lymphoma and enhance the ability to compare outcomes of clinical trials.

J Clin Oncol 32. © 2014 by American Society of Clinical Oncology
Postinduction response assessment with PET-CT: limitations to these studies...

**PRIMA** 122 patients 2004-2010  
- Hypothesis generating.  
- Retrospective analysis of local PET interpretation within a prospective study with independent CT assessment.  
- Results confirmed by independent scan review of 61 patients.  
  Trotman J, JCO 2011  
  Tychyj-Pinel C, EJNMMI 2014

**FOLL05** 202 patients 2005-2010  
- Retrospective analysis of local PET reports within a prospective study with local CT assessment.  
  Luminari S, Ann Oncol 2013

**PET Folliculaire** 106 patients 2007-2009  
- Prospective standardised PET acquisition / assessment in accordance to the 5 Point Scale (5PS), with local CT assessment.  
- Shorter follow-up  
  Dupuis J, JCO 2012
PFS according to CT response

SD/PD vs.
- PR, HR 4.2
- CRu, HR 5.6
- CR, HR 7.8, p<.0001

PR vs.
- CR/CRu, HR 1.7 (1.1-2.5)
  p=0.02

CRu/PR vs.
- CR, HR 1.6 (1.1-2.4), p=0.02

Trotman et al, Lancet Haematol, 2014
Both PET cut-offs predictive of PFS

Score ≥3

Score ≥4

HR 3.9 (95% CI 2.5-5.9, p<.0001)
Median PFS:
16.9 (10.8-31.4) vs. 74.0 mo (54.7-NR)

Trotman et al, Lancet Haematol, 2014
Postinduction PET status (cut-off ≥4) and Overall Survival

97% vs. 87%

HR 6.7, 95% CI 2.4-18.5, p=0.0002
Median OS: 79 months vs. NR

Trotman et al, Lancet Haematol, 2014
Hodgkin Lymphoma: Protecting the Victims of Our Success

Bruce D. Cheson, Georgetown University Hospital, Lombardi Comprehensive Cancer Center, Washington, DC

See accompanying article on page 4508

The only saving grace of the present is that it’s too damned stupid to question the past very closely.
—H.P. Lovecraft

In few instances in oncology has progress been so methodical. Total nodal irradiation became subtotal, then extended field, and then involved field. Randomized trials demonstrated that regimens such as doxorubicin, bleomycin, vinblastine, and dacarbazine were more...
Routine Bone Marrow Biopsy in Hodgkin Lymphoma

- 454 newly diagnosed pts
- Bone marrow involvement
  - 18% focal lesions by PET
  - 8% involvement by trephine
- No pt with BM+ had CS I-II by PET
- Pts with BM+ had other evidence of stage IV
- BM Bx upstaged 5 pts from III-IV
- No treatment decisions changed by BM Bx

PET-CT For Staging and Early Response in HL (n=1214)

- RATHL (ceCT) and PET-CT staging compared
- Concordance in 80%
  - PET-CT upstaged 14% (BM 92, lung 11, multiple 12)
  - Downstaged 6%
  - ceCT identified 7 PET-CT-neg lesions (bowel, Liver, spleen)
  - BMBx – positive 0.4% where PET was negative

BMBx and PET-CT in DLBCL

- 130 pts; 35 (27%) with BM involvement: 33 by PET, 14 by BMBx
- PET identified all positive BMs
- BX did not upstage any patients
- Sensitivity/specificity
  - PET-CT – 94%, 100%
  - BMBx – 40%, 100%
- Prognosis of PET+/Bx- similar to stage IV w/o BM involvement
- Pts with BM+ had other evidence of stage IV

Khan et al, Blood 122:61, 2013
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>BMB+PET+</th>
<th>BMB+PET-</th>
<th>BMB-PET+</th>
<th>BMB-PET-</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
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<td>FL at diagnosis</td>
<td>57</td>
<td>16</td>
<td>8</td>
<td>5</td>
<td>28</td>
<td>.67</td>
<td>.85</td>
<td>.77</td>
</tr>
<tr>
<td>FL at relapse</td>
<td>30</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>17</td>
<td>.73</td>
<td>.89</td>
<td>.83</td>
</tr>
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</table>

Ujjani et al, Br J Haem e-pub, 2016

PET vs BMBx in Follicular Lymphoma
BM Bx in the Staging of Lymphomas

- If PET-CT is performed, BM biopsy is no longer indicated for HL, and only for DLBCL if PET is negative and identifying discordant histology is important for patient management

- BM remains part of staging for other histologies
Staging of Lymphomas: The Lugano Classification

- PET-CT is the standard for FDG-avid lymphomas; CT is indicated for non-avid histologies (CLL/SLL, MZL, LPL, MF)
- A modified Ann Arbor staging system is recommended for disease localization; however, patients are treated according to prognostic and risk factors
- Suffixes A and B are only required for HL
- “X” for bulky disease is no longer necessary, but record the largest tumor diameter
Summary: What is New in the Lugano *Staging* Criteria?

- Splenomegaly: >13 cm
- No routine CXR
- No BMBx in HL or most DLBCL
Summary: What is New in Lugano

*Response* Criteria

- PET-CT for all FDG-avid histologies
- CR includes persistent nodes that are PET-negative in FDG-avid histologies
- CT-PR retains SPD 6 nodes/extranodal lesions
- Single lesion adequate for PD
- Deauville 5-PS now the standard
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 and/or new lesions

**markedly** increased uptake is taken to be uptake $> 2$-$3$ times the SUV max in normal liver
### CMR/CR

<table>
<thead>
<tr>
<th></th>
<th>PET-CT-based response</th>
<th>CT-based response</th>
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<tbody>
<tr>
<td></td>
<td>Complete Metabolic Response (CMR)</td>
<td>Complete Radiologic Response (ALL of the following)</td>
</tr>
<tr>
<td><strong>Target Nodal/Extranodal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Target</td>
<td>Score 1, 2, or 3* by 5-PS with or without a residual mass</td>
<td>Nodal Disease: ≤ 1.5 cm in LDi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extranodal Disease: Absent</td>
</tr>
<tr>
<td>Spleen</td>
<td></td>
<td>Regress to normal</td>
</tr>
<tr>
<td>New lesions</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>No evidence of FDG-avid disease in marrow</td>
<td>Normal by morphology; if indeterminate, IHC negative</td>
</tr>
</tbody>
</table>

*Score of 3*
- Good prognosis with standard treatment (interim scan) for some
- De-escalation is investigated→ may consider a score of 3 as inadequate response (to avoid undertreatment).

Cheson et al, JCO 32:3059, 2014
<table>
<thead>
<tr>
<th>PMR/PR</th>
<th>PET-CT-based response</th>
<th>CT-based response</th>
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<tr>
<td></td>
<td><strong>Partial Metabolic Response (PMR)</strong></td>
<td><strong>Partial Remission (PR) (ALL of the following)</strong></td>
</tr>
<tr>
<td>Target</td>
<td>Score 4,5 with reduced uptake compared with baseline and residual mass(es) of any</td>
<td>≥ 50% decrease from baseline in SPD of all Target lesions</td>
</tr>
<tr>
<td>Nodal/</td>
<td>size. • <strong>Interim</strong>: suggest responding disease</td>
<td>No Increase</td>
</tr>
<tr>
<td>Extranodal</td>
<td></td>
<td><strong>Spleen</strong>: ≥ 50% decrease from baseline in enlarged portion (value over 13cm)</td>
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<tr>
<td>Non-Target</td>
<td></td>
<td><strong>Liver</strong>: no progression</td>
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<tr>
<td>Spleen</td>
<td></td>
<td>None</td>
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<tr>
<td>New lesions</td>
<td></td>
<td>Not applicable</td>
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<tr>
<td>Bone</td>
<td>Residual uptake higher than uptake in normal marrow but reduced compared with baseline</td>
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<tr>
<td>marrow</td>
<td>Persistent focal changes in the marrow with nodal response, • Further evaluation</td>
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<td></td>
<td>with MRI or biopsy, or an interval scan</td>
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<tr>
<td>NMR/SD</td>
<td>PET-CT-based response</td>
<td>CT-based response</td>
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<tr>
<td>No Metabolic Response (NMR)</td>
<td></td>
<td>Stable disease</td>
</tr>
<tr>
<td>Target Nodal/Extranodal</td>
<td>Score 4 or 5 with no significant change in FDG uptake from baseline, at interim or EoT.</td>
<td>• &lt; 50% decrease from baseline in SPD of all Target lesions</td>
</tr>
<tr>
<td>Non-Target</td>
<td></td>
<td>• No criteria for PD are met</td>
</tr>
<tr>
<td>Spleen</td>
<td></td>
<td>No progression</td>
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<tr>
<td>New lesions</td>
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<td>No progression</td>
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<td>Bone marrow</td>
<td>No change from baseline</td>
<td>Not applicable</td>
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<td>PMD/PD</td>
<td>PET-CT-based response</td>
<td>CT-based response</td>
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<tr>
<td>Target Nodal/Extranodal</td>
<td>• Score 4, 5 with increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or EoT</td>
<td>PPD Progression: An individual node/lesion must be abnormal with: • LDi &gt; 1.5 cm AND • Increase by ≥ 50% from PPD nadir AND An increase in LDi or SDi from nadir • &gt; 0.5 cm for lesions &lt; 2 cm • ≥ 1.0 cm for lesions &gt; 2 cm</td>
</tr>
<tr>
<td>Non-Target</td>
<td></td>
<td>Unequivocal Progression</td>
</tr>
<tr>
<td>Spleen/Liver</td>
<td></td>
<td>Unequivocal Progression: • Progression of existing Splenomegaly • New or Recurrent Splenomegaly • New or Recurrent liver involvement</td>
</tr>
<tr>
<td>New lesions</td>
<td>• Consider biopsy or interval scan if etiology of new lesions uncertain</td>
<td>• Regrowth of previously resolved lesions • New node &gt; 1.5 cm in any axis • New extranodal site &gt; 1.0 cm in any axis • New extranodal site &lt;1.0 cm in any axis • Unequivocal/attributable to lymphoma. • Any size assessable disease unequivocal/attributable to lymphoma</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>New/recurrent FDG avid foci</td>
<td>New/recurrent involvement</td>
</tr>
</tbody>
</table>
RAPID - trial design

Initial treatment: ABVD x 3

Re-assessment: if NR/PD, patient goes off study
if CR/PR, FDG-PET scan performed

PET +ve

4th cycle ABVD then IFRT

PET -ve

Randomisation

IFRT

No further treatment

RAPID Trial: Progression-free Survival.

A Intention-to-Treat Analysis

Progression-free Survival (%)

Rate ratio, 1.57 (95% CI, 0.84–2.97)
P=0.16

Months since Randomization

No. at Risk
Radiotherapy
No further treatment

209
211
198
190
188
181
170
153
134
129
99
89
57
50
13
14
30
5
2
13
2
0
0
0
0
RAPID Trial: Overall Survival.

Rate ratio, 0.51 (95% CI, 0.15–1.68)
P = 0.27

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>36</td>
<td>100</td>
</tr>
<tr>
<td>48</td>
<td>100</td>
</tr>
<tr>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>72</td>
<td>100</td>
</tr>
<tr>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>108</td>
<td>100</td>
</tr>
<tr>
<td>120</td>
<td>100</td>
</tr>
</tbody>
</table>

No. at Risk
- Radiotherapy: 209, 200, 191, 175, 139, 103, 60, 34, 13, 2, 0
- No further treatment: 211, 204, 196, 167, 140, 97, 56, 18, 6, 0, 0

GHSG study for advanced-stage HL (HD15; 2003-08)

CS IIB with RF a, b
CS III and IV

8x BEACOPP escalated
EPO/Placebo

6x BEACOPP escalated
EPO/Placebo

8x BEACOPP 14
EPO/Placebo

Restaging

PR & res dis >2.5 cm

No
PET -
Follow-up

Yes
Pet +
30 Gy RT on residues

Risk factors:
a) Large mediastinal mass
b) Extranodal disease

Additional RT after chemo in advanced stages
GHSG studies HD9, HD12 and HD15 (% of all pts)

Comparison of GHSG trials HD9, HD12, HD15 for advanced-stage HL (PFS)

RATHL: Schema

Stage II (adverse), III, IV, IPS 0-7, Over 18, PS 0-3

PET 1 (Staging)

2 cycles ABVD
Full dose, on schedule

PET 2 +ve

4 cycles BEACOPP-14
or 3 eBEACOPP

PET 3 +ve

RT or salvage regimen

PET 3 -ve

2 cycles BEACOPP-14 or 1 eBEACOPP
No RT

PET 2 -ve

Randomise

4 cycles ABVD
4 cycles AVD

Follow-up (no RT)

Johnson et al, NEJM 374:2419, 2016
Progression-free and Overall Survival.

A Progression-free Survival among Patients with Negative PET Findings

B Overall Survival among Patients with Negative PET Findings

C Progression-free Survival among Patients with Positive PET Findings

D Overall Survival among Patients with Positive PET Findings

Toxicity of therapy: ABVD vs AVD

% of patients experiencing grade 3-4 events

<table>
<thead>
<tr>
<th></th>
<th>ABVD cycles 1-2</th>
<th>ABVD cycles 3-6</th>
<th>AVD cycles 3-6</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>57.3</td>
<td>58.4</td>
<td>57.5</td>
<td>0.78</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.3</td>
<td>1.3</td>
<td>3.2</td>
<td>0.045</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>2.1</td>
<td>4.7</td>
<td>2.2</td>
<td>0.032</td>
</tr>
<tr>
<td>Infection</td>
<td>6.3</td>
<td>14.5</td>
<td>10.1</td>
<td>0.040</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>1.4</td>
<td>4.9</td>
<td>2.6</td>
<td>0.061</td>
</tr>
<tr>
<td>Respiratory AEs</td>
<td>0.7</td>
<td>3.6</td>
<td>0.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Any non-haematological toxicity</td>
<td>16</td>
<td>31</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Johnson et al NEJM 374:2419, 2016
Interim PET in HL Using the Deauville 5-PS

## Risk-Adapted Studies of Increased Treatment in PET-2 Positive Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage</th>
<th>Number PET-positive</th>
<th>Initial therapy</th>
<th>% iPET positive (5PS PET score if used)</th>
<th>Post-PET therapy</th>
<th>Time to analysis</th>
<th>PFS %</th>
<th>OS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 50604</td>
<td>I-II</td>
<td>14</td>
<td>2 ABVD</td>
<td>9</td>
<td>2 esc BEACOPP + IFRT</td>
<td>2.1 yrs</td>
<td>66%</td>
<td>N/A</td>
</tr>
<tr>
<td>EORTC H10</td>
<td>I-II</td>
<td>361</td>
<td>2 ABVD</td>
<td>19</td>
<td>2 ABVD + INRT 2 esc BEACOPP + INRT</td>
<td>5 yrs</td>
<td>77</td>
<td>91</td>
</tr>
<tr>
<td>RATHL</td>
<td>II with adverse features, III, IV</td>
<td>182</td>
<td>2 ABVD</td>
<td>16 (4-5)</td>
<td>4 esc BEACOPP or 6 BEACOPP-14</td>
<td>3 yrs</td>
<td>68</td>
<td>87</td>
</tr>
<tr>
<td>GITIL HD0607</td>
<td>II with adverse features, III, IV</td>
<td>98</td>
<td>2 ABVD</td>
<td>20 (4-5)</td>
<td>4 esc BEACOPP + 4 BEACOPP baseline +/- rituximab</td>
<td>2</td>
<td>66</td>
<td>N/A</td>
</tr>
<tr>
<td>SWOG S0816</td>
<td>III, IV</td>
<td>60</td>
<td>2 ABVD</td>
<td>18 (4-5)</td>
<td>6 esc BEACOPP</td>
<td>2</td>
<td>64</td>
<td>N/A</td>
</tr>
<tr>
<td>FIL HD0801</td>
<td>IIB-IV</td>
<td>103</td>
<td>2 ABVD</td>
<td>20 (3-5)</td>
<td>4 IGEV + BEAM</td>
<td>2</td>
<td>76</td>
<td>N/A</td>
</tr>
</tbody>
</table>
A New Problem

• ~15% of solid tumor pts have a flare response on immunomodulatory agents (CPIs)
• Confused with PD
• Result in premature termination
• Agents induce flare reactions in lymphoma:
  – Lenalidomide
  – Rituximab
  – Brentuximab vedotin
  – Ibrutinib
  – Check point inhibitors
Immune Response Criteria (IRC)*

- Not applicable to lymphoma:
  - Rely on RECIST rather than Lugano
  - Timing of response assessment differs
  - Confirmatory studies not required with lymphoma
  - Definition of PD differs
  - Do not include PET-CT
  - Tumors are always abnormal; lymphomas involve nodes which are normally present
    - Normal size despite involvement
    - Enlarged despite non-involvement

Discordance Between IRC and Lugano

• Lymphomas often have non-measurable disease, imperceptible on CT
  – Bone marrow
  – Soft tissue involvement
• Cannot be integrated into tumor burden
Discrepancy Between Lugano and Immune Response Criteria

Restaging FDG-PET/CT 1

12 weeks

Restaging FDG-PET/CT 2

20 weeks
Discordance Between IRC and Lugano

- Restaging PET-CT shows resolution of lesions
- If persistent CT lesions would be considered a PR by IRC
- Considered CR by Lugano if no longer FDG avid
Dicrepancy Between Lugano and IRC

Baseline PET/CT and Contrast-enhanced CT

Restaging PET/CT and Contrast-enhanced CT
Response Criteria in Lymphoma Patients Treated with Immunomodulatory Agents Including Immune Checkpoint Inhibitors

Overview: The Response Criteria in Lymphoma Patients Treated with Immunomodulatory Agents Workshop (the workshop) will allow leading clinicians and pharmaceutical researchers to share their experience with immune regulating agents which may induce an immune flare reaction in lymphoma. Lymphoma is one of the major cancer types for which new immune-based cancer treatments are currently in development.

Objective: The objective of the workshop is to address the unique patient response to this class of drugs and recommend appropriate adaptations of current lymphoma response criteria

Logistics: One-day program on November 20; the workshop will be held in Washington, DC.
Immune Response Workshop

- Included presentations from investigators and industry representatives on experience with check point inhibitors
- Discussed the relevance of solid tumor IRC to lymphoma
- Determined lymphoma-specific criteria were needed
- Developed Lymphoma Response to Immunomodulatory Therapy Criteria (LyRIC)
Refinement of the Lugano classification response criteria for lymphoma in the era of immunomodulatory therapy


Blood 2016 :blood-2016-05-718528; doi:10.1182/blood-2016-05-718528
Indeterminate Response (IR)

- Provisional term
- To identify lesions that may be flare vs PD
- Does not make direct reference to underlying mechanism
- Allows appropriate patients to remain on treatment
  - until reassessment to confirm or refute PD
  - or biopsy proven disease
Definitions of Types of IR

IR1: Increase in overall tumor burden (by SPD) of ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration

Cheson et al, Blood, e-pub online, Sept 2016
Definitions of Types of IR

IR2: Appearance of new lesions; or growth of one or more existing lesion(s) \( \geq 50\% \); at any time during treatment; occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, by SPD of up to 6 lesions at any time during the treatment.
Definitions of Types of IR

**IR3**: Increase in FDG uptake of one or more lesion(s) without a concomitant increase in lesion size or number.
IR(3) an increase in FDG uptake of one or more lesions suggestive of lymphoma without a concomitant increase in size of those lesions meeting PD

July 2, 2014

Sept 3, 2014
Follow-up of IR

- Repeat scan in 12 wks (earlier if indicated)
- PD if:
  - IR1 – further increase in SPD
  - IR2 – new lesion added to SPD (unless benign) and, if ≥50% increase – PD
  - IR3 – PD if increase in size or new lesions
Future Directions

• Quantitative assessment of response
  – $\Delta$ SUV
  – Total tumor glycolysis
  – Metabolic tumor volume
• Combined modality approaches
• Understand contribution of the microenvironment
• Stratify patients pre-treatment
Visual vs SUV analysis
Early response assessment (2 cycles), n=92

Visual Analysis
(positive or negative)

SUV Analysis
(ΔSUV\text{max} PET0/PET2)

- Decreases the number of false positive studies
- 14/17 "false positive" patients reclassified with ΔSUV\text{max}
- 2 cycles: ΔSUV better than visual assessment

Interim PET and SUVmax Reduction in DLBCL

Interim PET vs SUVmax in HL

DS 5PS

A

PFS probability (%)

PET2-

PET2+

P < 0.002

Time (mo)

B

TTP probability (%)

PET2-

PET2+

P < 0.006

Time (mo)

ΔSUVmax

A

PFS probability (%)

ΔSUVmaxPET0-2 > 71

ΔSUVmaxPET0-2 ≤ 71

P < 0.0001

Time (mo)

B

TTP probability (%)

ΔSUVmaxPET0-2 > 71

ΔSUVmaxPET0-2 ≤ 71

P < 0.0001

Time (mo)

Combining PET with MRD in FL

- Subset analysis of FOLLO5 study
- MRD by BM aspirate for \( BCL2/IGH \) fusion gene at diagnosis and, if possible, EOT
- Positive scan – DS \( \geq 4 \)
- 41 patients had both PET and MRD data EOT
- PET/MRD concordance 76%
(A) PFS by PET. (B) PFS by MRD.
PFS in FOLLO5 according to combination of PET and MRD results.
Detection of ctDNA During Treatment of DLBCL (Cycle 3, Day 1) Predicts Relapse

PPV 62.5%
NPV 79.8%
Sensitivity 46.9%
Specificity 88.2%

Survival analysis based on macrophage content

Tan et al. Blood 2012;120:3280-3287
Biomarkers and the Microenvironment in HL

- PET-2 strong predictor of outcome.
- NPV suboptimal: ~12% still relapse.
- Retrospective test in 208 pts with cHL treated with ABVD, validated in 102 pts.
- Assessed biomarkers on neoplastic cells.
- Evaluated biomarkers in microenvironmental cells from TMAs.
- Classification and Regression Tree (CART)

Agostinelli et al, Lancet Haem e-pub online
PET and Outcome in cHL

Agostinelli et al, Lancet Haematol e-pub on line
FOXP3 and Outcome in cHL

Agostinelli et al, Lancet Haematol e-pub on line
PD1 and Outcome in cHL

Agostinelli et al, Lancet Haematol e-pub on line
Classification tree for relapse/progression, learning set: 208 patients

High risk biologic profile:
- CD68KP1 ≥25%
- PD1 diff
- PD1 rosettes
- STAT1 -

Low risk biologic profile:
- CD68KP1 <25%
- PD1 scattered
- PD1 scatt
- STAT1 +

Agostinelli et al Lancet Haematol e-pub online
PFS By Biomarkers

Agostinelli et al, Lancet Haematol e-pub on line
TMTV in Hodgkin Lymphoma

SUV$_{\text{max}}$, MTV and TLG in PMBCL in IELSG-26 Trial

- Prospective study of 103 pts with PMBCL
- All treated with R-doxorubicin; 90% with RT
- Median follow-up – 36 months
- Overall PFS/OS – 87%/94%
- Outcome correlated with functional imaging at diagnosis

Ceriani et al, Blood, e-pub online 2015
MTV and TLG in PMBCL

Ceriani et al, Blood 126:950, 2015
Kaplan–Meier estimates of PFS and OS according to baseline TMTV in DLBCL

Baseline TMTV and Outcome in Patients with Untreated FL

- Pooled analysis from 3 R-chemo trials
- N = 185
- Median age 55 yrs
- 92% advanced disease; 37% FLIPI 3-5
- Median f/u 64 mos
- Used cut off of 510 cm³

Meignan et al, JCO, in press
Pre-Treatment TMTV in FL

Meignan et al, JCO, in press
Issues With TMTV

- Retrospective nature of the studies
- Various cut-offs in different studies
- Various therapies
- Variable equipment
- Variable time to imaging
- Threshold may vary with primary tumor SUV or location
- Need to merge with more biological indicators
PFS of FL according to the level of pre-tx circulating tumor DNA (Clonoseq)

Clémentine Sarkozy et al. Blood 2015;126:2675
Conclusions

• PET-CT has revolutionized the staging and response assessment in lymphoma
  – Fewer patients overtreated
  – Fewer patients undertreated
  – Fewer patients trephined
• Response adapted approaches decrease toxicity and improve efficacy in HL
• PET-CT may be useful in pretreatment stratification
• Combined modality approaches should be explored
• Continued study will improve patient outcome
1999 NCI-Working Group NHL (HL) response guidelines

2007 Revised Response Criteria for Malignant Lymphoma - IWG 2007 response guidelines

Workshop June 2011:
11th International Conference on Malignant Lymphoma in Lugano, Switzerland

Subsequent workshop: 12th ICML
→ Revised criteria for staging and of the IWG 2007 response guidelines

2014 – Lugano Classification

2016 LYRIC

1999......TO LUGANO AND……….