SHOULD THERAPY FOR HD BE MODIFIED BY THE RESULTS OF THE EARLY PET?

YES

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Barcelona, September 7 2012
What is Interim PET/CT?

An interim PET/CT is a scan done during the midst of induction therapy (after 1, 2, 3 or 4 cycles of therapy)?

Why Do It?

Interim PET/CT might identify patients who are highly likely to be cured with induction therapy.

Interim PET/CT might identify patients who are highly likely to relapse following induction therapy.

Interim PET/CT might guide changes in therapy (de-escalation or escalation of therapy intensity) that might improve patient outcomes.
Deauville Five Point Scale

1. No uptake
2. Uptake • mediastinum
3. Uptake > mediastinum but • liver
4. Uptake moderately increased above liver at any site
5. Markedly increased uptake at any site including new sites of disease
Proportion of interim-PET cases interpreted as positive by reader, according to ECOG and London criteria

Reviewers agreement – 68%
Reviewers vs Central review – 68%
Agreement using London criteria – 71%

Horning, Blood 2010; 115:775
# Interim PET in HL

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts</th>
<th>Cycles of Tx</th>
<th>PET- (%)</th>
<th>PRS/EFS (%)</th>
<th>PET+ (%)</th>
<th>PFS/EFS (%)</th>
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<tbody>
<tr>
<td>Zinzani 1999</td>
<td>40</td>
<td>2</td>
<td>80</td>
<td>97</td>
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<td>Kostakoglu 2006</td>
<td>23</td>
<td>1</td>
<td>74</td>
<td>100</td>
<td>26</td>
<td>12.5</td>
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<td>Hutchings 2005</td>
<td>85</td>
<td>2-3</td>
<td>72</td>
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<td>Gallamini 2007</td>
<td>260</td>
<td>2</td>
<td>81</td>
<td>95</td>
<td>19</td>
<td>14</td>
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</tbody>
</table>
Sensitivity & Specificity of Interim FDG-PET for HL

Terasawa, JCO 27:1906, 2009
Early PET in Advanced HL
Combined Gallamini + Hutchings Data
PFS by PET2 and IPS

For interim PET interpretation in HL, the visual assessment, as recommended by the experts, is currently preferred over the semiquantitative evaluation using standardized uptake values (SUV). Quantitative evaluation using SUV measurements may be more suitable for aggressive B-cell lymphomas where the residual FDG uptake results from a balanced combination between cell kill and tumour regrowth.
International Validation Study of the Prognostic Role of Interim-PET Scan in ABVD-treated, Advanced Stage Hodgkin Lymphoma.
I vs endpoints

**Primary endpoint**
Overall accuracy and Predictive Value of interim-PET scan in terms of 3-year failure-free survival

**Secondary endpoints**
- Propose easy reproducible international rules for early PET interpretation during ABVD chemotherapy for Hodgkin lymphoma.
- Evaluate the Concordance rate of reviewers among the members of Central review panel.
Inclusion criteria

- Advanced-stage (IIIB-IVB) or poor-prognosis stage IIA* HL.
- Therapy: ABVD x 6 cycles plus or minus consolidation radiotherapy.
- Staging at baseline and after 2 ABVD with PET-CT (PET-0 and PET-2)
- No treatment change depending on interim-PET results.
- Patients treated with 2nd line chemotherapy for progressive/resistant lymphoma during ABVD chemotherapy were eligible only with **clinical** and/or radiological evidence of disease progression.
- PET-0 and PET-2 performed in the same PET center
- Minimum follow-up of one year after treatment completion

* One of the following: ≥ 3 nodal sites involved, subdiaphragmatic presentation, bulky disease, and ESR > 40 mm.
Patient selection

400 patients enrolled

336 patients with PET/CT scans uploaded & quality controlled

261 patients with PET/CT scans approved & sent to review

Reason for PET scan exclusion
- Absence of CT images: 22
- Absence of baseline PET: 25
- Absence of interim PET: 1
- CT slices missing: 3
- PET slices missing: 10
- Poor quality scans: 6
- Miscellaneous: 8

REVIEWERS
- Sally Barrington - London - UK
- Alberto Biggi - Cuneo - I
- Michele Gregianin - Padova - I
- Martin Hutchings - Copenhagen - DK
- Lale Kostakoglu - New York - USA
- Michel Meignan - Paris - F

Review results acquired and statistical analysed
1st line treatment outcome according to PET-2 and IPS

IPS 0-2

260

195

PET-2 +

25

CR 4
PRO 15
REL 6

CR 162
PRO 6
REL 2

PET-2 -

170

PET-2 +

25

CR 3
PRO 21
REL 1

CR 38
PRO 1
REL 1

IPS 3-7

65

PET-2 -

40

IPS 0-2

261

190

PET-2 +

24

CR 9
PRO 12
REL 3

CR 159
PRO 6
REL 1

PET-2 -

166

PET-2 +

22

CR 7
PRO 14
REL 1

CR 45
PRO 3
REL 1

IPS 3-7

71

PET-2 -

49

JCO 2007

IVS 2011
FFS for patients with PET acquisition time < 90’ (N=226)

Failure Free Survival

- PET2 negative: 5-y FFS = 95%
- PET2 positive: 5-y FFS = 26%

Time [months]
FFS according to PET-2 and IPS (N= 261)

Failure Free Survival

- IPS 0-2, PET2 negative
- IPS 0-2, PET2 positive
- IPS 3-7, PET2 negative
- IPS 3-7, PET2 positive

Time [months]
PET-2 response adapted treatment strategy for advanced-stage HL patients (Retrospective study N = 160)

# INTERIM PET-DIRECTED ONGOING STUDIES IN EARLY STAGE HL

<table>
<thead>
<tr>
<th>Phase</th>
<th>Sample</th>
<th>Stage</th>
<th>End-point</th>
<th>Pre-iPET CHT</th>
<th>iPET- Arm/s</th>
<th>iPET+ Arm</th>
<th>Group/ Title/NCT #</th>
<th>End year</th>
</tr>
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<tbody>
<tr>
<td>II</td>
<td>660</td>
<td>IA- IIAf</td>
<td>5 yr EFS</td>
<td>ABVD x 2, ABVD x 2</td>
<td>INRT, ABVDx2+INRT</td>
<td>ABVDx2 +/- INRT, ABVDx2 +/- ABVDx2+INRT</td>
<td>RHC/na 00392314</td>
<td>2016</td>
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<tr>
<td>III</td>
<td>1797</td>
<td>IA-IIIBf</td>
<td>PFS</td>
<td>ABVD x 2, ABVD x 2</td>
<td>ABVD x 1, escBEACOPPx2</td>
<td>escBEACOPPx 2</td>
<td>EORTC- GELA/H10 00433433</td>
<td>2011</td>
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<tr>
<td>II</td>
<td>123</td>
<td>IA-IIIB blk</td>
<td>3 yr PFS</td>
<td>ABVD x 2</td>
<td>ABVD x 4</td>
<td>escBEACOPPx 4 + IFRT</td>
<td>CALGB/50801 01118026</td>
<td>2015</td>
</tr>
<tr>
<td>II</td>
<td>200</td>
<td>IA-IIIB blk</td>
<td>3 yr PFS</td>
<td>ABVD x 2</td>
<td>ABVD x 4+INRT</td>
<td>escBEACOPPx 4+ INRT</td>
<td>ECOG/2410 01390584</td>
<td>2016</td>
</tr>
<tr>
<td>II</td>
<td>149</td>
<td>IA-IIIN-blk</td>
<td>3 yr PFS</td>
<td>ABVD x 2</td>
<td>ABVD x 2 +IFRT</td>
<td>escBEACOPPx 2</td>
<td>CALGB/50604 01132807</td>
<td>2013</td>
</tr>
<tr>
<td>III</td>
<td>575</td>
<td>IA-IIAn-blk</td>
<td>PFS</td>
<td>ABVD x 3</td>
<td>IFRT or no therapy</td>
<td>ABVD x 1 + IFRT</td>
<td>NHSFT/RAPID 00943423</td>
<td>2012</td>
</tr>
<tr>
<td>III</td>
<td>1100</td>
<td>I-IIAf</td>
<td>5 yr PFS</td>
<td>ABVD x 2</td>
<td>no therapy</td>
<td>ABVD x 2 + IFRT</td>
<td>GHSG/HD16 00736320</td>
<td>2013</td>
</tr>
<tr>
<td>III</td>
<td>1100</td>
<td>I-IIIf</td>
<td>3 yr PFS</td>
<td>escBEACOPPx2 + ABVDx2 + IFRT</td>
<td>no therapy</td>
<td>escBEACOPPx 2 + ABVD x 2</td>
<td>GHSG/HD17 01356680</td>
<td>2013</td>
</tr>
</tbody>
</table>

INTERIM RESPONSE ASSESSMENT: EARLY STAGE HL

The first interim analysis of EORTC/GELA H10 study of early stage supra-diaphragmatic HL inclusive of favourable and unfavourable risk categories reported on 894 of 1097 recruited patients.

Using IHP criteria, interim PET was positive in 14% and 24% in the favourable and unfavourable categories, respectively. FDG-PET treatment adaptation was, thus, proven feasible in an intergroup randomized trial. There were 12 and 22 events in favorable and unfavorable groups, respectively, during a median follow-up of 1.1 years. Upon conclusion that chemotherapy alone would be unlikely to be non-inferior to combined modality treatment in interim-PET negative patients, chemotherapy alone arm was discontinued.
## INTERIM PET-DIRECTED ONGOING STUDIES IN ADVANCED STAGE HL

<table>
<thead>
<tr>
<th>Phase</th>
<th>Sample</th>
<th>Stage</th>
<th>End-point</th>
<th>Pre-iPET CHT</th>
<th>iPET- Arm/s</th>
<th>iPET+ Arm</th>
<th>Group/ Title/NCT #</th>
<th>End year</th>
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<tbody>
<tr>
<td>II</td>
<td>450</td>
<td>IIb-IV</td>
<td>3 yr PFS</td>
<td>ABVD x 2</td>
<td>ABVD x 4</td>
<td>escBEACOPP x 4, stdBEACOPP x 4</td>
<td>GITL/HDO0607 00795613</td>
<td>2012</td>
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<tr>
<td>II</td>
<td>230</td>
<td>III-IV</td>
<td>2 yr PFS</td>
<td>ABVD x 2</td>
<td>ABVD x 2</td>
<td>escBEACOPP x 6</td>
<td>SWOG/S0816 00822120</td>
<td>2012</td>
</tr>
<tr>
<td>III</td>
<td>798</td>
<td>III-IV or IIb&lt;sup&gt;®&lt;/sup&gt;</td>
<td>5 yr PFS</td>
<td>escBEACOPP x2</td>
<td>ABVD x 4 (exp. Arm), escBEACOPP x4 (std arm)**</td>
<td>escBEACOPP x 4 (std and experimental arms)**</td>
<td>GELA/AHL 2011 01358747</td>
<td>2016</td>
</tr>
<tr>
<td>III</td>
<td>1200</td>
<td>II&lt;sup&gt;®&lt;/sup&gt;-IV</td>
<td>3 yr PFS</td>
<td>ABVD x 2</td>
<td>ABVD x 4 or AVD x 4</td>
<td>escBEACOPP x 4</td>
<td>CR-UK/RATHL 00678327</td>
<td>2012</td>
</tr>
<tr>
<td>III</td>
<td>1500</td>
<td>IIb-IV</td>
<td>5 yr PFS</td>
<td>escBEACOPP x2</td>
<td>escBEACOPP x 6 or escBEACOPP x 2</td>
<td>escBEACOPP x 6 or escBEACOPP x 6 + ritux</td>
<td>GHSG/HDO18 00515554</td>
<td>2012</td>
</tr>
<tr>
<td>III</td>
<td>300</td>
<td>IIb-IV</td>
<td>2 yr PFS</td>
<td>ABVD x 2</td>
<td>ABVD x 4&lt;sup&gt;®&lt;/sup&gt;</td>
<td>IGEV x 4 + ASCT</td>
<td>FI/HDO0801 00784537</td>
<td>2014</td>
</tr>
<tr>
<td>II</td>
<td>660&lt;sup&gt;®&lt;/sup&gt;</td>
<td>III-IV&lt;sup&gt;®&lt;/sup&gt;</td>
<td>5 yr EFS</td>
<td>ABVD x 2, escBEACOPP x2</td>
<td>ABVD x 4</td>
<td>escBEACOPP x 2 + escBEACOPP x 2 + INRT&lt;sup&gt;PET&lt;sub&gt;4&lt;/sub&gt;&lt;/sup&gt;, escBEACOPP x 2 + escBEACOPP x 2 + INRT&lt;sup&gt;PET&lt;sub&gt;4&lt;/sub&gt;&lt;/sup&gt;</td>
<td>RHC/na 00392314</td>
<td>2016</td>
</tr>
</tbody>
</table>

INTERIM RESPONSE ASSESSMENT: ADVANCED STAGE HL

There are at least 5 studies designed to test the survival equality with de-escalation of standard therapy in those patients with an interim PET negative result. These studies include the HD18 trial by the GHSG, investigating 6 cycles vs. 4 cycles BEACOPP, the RATHL study comparing ABVD to AVD, the GELA AHL study comparing BEACOPP to standard ABVD, the HD 0607 and HD0801 trials by the FIL (Fondazione Italiana Linfomi) investigating RT versus no RT after 6 cycles of ABVD in patients with interim and final PET negative results.
Multicentre clinical study with early treatment intensification in advanced-stage, high-risk Hodgkin lymphoma, defined as FDG-PET scan positive after two conventional ABVD courses (HD 0607 study: NIH registration code: NCT00795613)
HD 0607 interim analysis (24.04.11) on 318 patients who completed the therapy

Mean follow-up 406 days (120-1220)

- 318
  - ABVD x 2
    - PET-2
      - 54
        - BEACOPP / R-BEACOPP
          - CR + PR
            - 42*
          - PD/RE
            - 10
          - Death
            - 2
      - 8 data missing
      - 256
        - ABVD x 4 +/- Rx therapy
          - CR + PR
            - 239*
          - PD/RE
            - 13
          - Death
            - 4

* Most PR reverted to CR
Progression-Free Survival according to Pet 2 Results

Log-Rank test: $p = 0.0003$

Negative 17/300 (5.7%)
Positive 12/69 (17.4%)

Pts (Events)
Negative 300 (0) 290 (0) 282 (3) 254 (8) 189 (4) 156 (2) 137
Positive 69 (1) 64 (0) 58 (2) 49 (3) 39 (5) 28 (1) 24
In the first interim analysis, 13 of 17 PET-2 positive patients (76 %) became PET-negative at the end of treatment and continued to have a durable CR.
RATHL study

2 cycles ABVD

PET 1

PET -ve (good prognosis)

Pet de-escalation; randomise

4 cycles AVD

4 cycles ABVD

PET 2

PET +ve (poor prognosis)

Tx escalation; BEACOPP

PET 3

Q: Can PET defined good prognosis guide de-escalation of treatment?

Q: Can PET defined poor prognosis be overcome by escalation of treatment?
Interim analysis of April 26°, 2012

HL IIB-IV B. IPS 0-7

ABVD x 2

CT-PET

+ -

ABVD x 4

GITIL HD0607 Protocol

R

BEACOPP-esc. x 4

R-BEACOPP-esc. x 4

PET-2+:

17.4%

Score 1 no uptake
Score 2 uptake ≤ mediastinum
Score 3 uptake > mediastinum but ≤ liver

Score 4: moderately ↑ uptake > liver
Score 5 markedly ↑ uptake > liver and/or new sites of disease

negative

positive
2 cycles ABVD

PET-2+:
17.4%

RATHL

PET positive

PET negative

CT2 + PET2

CT1 + PET 1(Staging)

IPS 0-7

IVS

PET positive

PET negative

CT2 + PET2

CT1 + PET 1(Staging)

IPS 0-7

PET-2+:
17.3%
INTERIM PET TO GUIDE POST-CHEMOTHERAPY CONSOLIDATION RADIOTHERAPY
30Gy RT on residues;

Follow-up PR & res dis \(\geq 2.5\) cm

No

CS IIB with RF a or b; CS III and IV

Restaging

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

Yes

GHSG HD15 trial for advanced-stage HL

Engert et al, Lancet 2012

2182 patients

6 x BEACOPP escalated

8 x BEACOPP escalated

8 x BEACOPP14

PET

PR & res dis \(\geq 2.5\) cm

Follow-up

PET +

30Gy RT on residues; Follow-up

PET −
HD15-PET trial
(pts with residual mass: N = 728/2182)

NPV@12m: 94% (95% CI: 92% to 96%)

PET-negative: 540 (74%)
PET-positive: 188 (26%)

Engert et al, Lancet 2012
The 4-year PFS of irradiated and non-irradiated patients were 86.2% and 92.6%, respectively (p=0.022). These data suggest that radiotherapy can be safely omitted in advanced stage HL patients who are PET-negative after BEACOPPescalated treatment. It should be emphasized, however, that the negative predictive value of end-therapy PET depends on the effectiveness of chemotherapy administered.
The obvious question of whether or not the results of the HD15 trial also applies to patients treated with ABVD and to those with initial bulky disease was addressed by the British Columbia Cancer Agency in a retrospective analysis. In 163 advanced-stage HL patients with a residual mass of ≥ 2 cm following ABVD therapy, those patients who had a FDG-avid mass were treated with consolidation RT and the others were observed.

Savage et al, JCO29:2011 (suppl; abstract 8034)
Patients with a PET-negative scan (n=130, 80%) had a far superior 3-year time to progression compared to those with a PET-positive scan (89% vs 55%, p= .00001) with no difference between those with bulky vs non-bulky disease. These results strongly support the omission of RT in advanced stage HL patients who achieve a PET-negative remission after six cycles of chemotherapy.

Savage et al, JCO29:2011 (suppl; abstract 8034)
# CURRENT STATUS OF INTERIM PET-DIRECTED ONGOING TRIALS IN HL

<table>
<thead>
<tr>
<th>GROUP/STUDY</th>
<th>Stage</th>
<th>Recruited / Target</th>
<th>iPET+</th>
<th>iPET-</th>
<th>Interpretation Rules</th>
</tr>
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<tbody>
<tr>
<td>GITIL/HD0607</td>
<td>Advanced</td>
<td>389 / 450</td>
<td>77 (20%)</td>
<td>312 (80%)</td>
<td>5PS</td>
</tr>
<tr>
<td>SWOG/ S0816</td>
<td>Advanced</td>
<td>248 / 300</td>
<td>45 (20%)</td>
<td>176 (80%)</td>
<td>5PS</td>
</tr>
<tr>
<td>GELA/AHL 2011</td>
<td>Advanced</td>
<td>100 / 798</td>
<td>--</td>
<td>--</td>
<td>5PS</td>
</tr>
<tr>
<td>CR-UK/RATHL</td>
<td>Advanced</td>
<td>680 / 1200</td>
<td>106 (16%)</td>
<td>574 (84%)</td>
<td>5PS</td>
</tr>
<tr>
<td><strong>GHSG/HD18</strong></td>
<td>Advanced</td>
<td><strong>1146 / 1500</strong></td>
<td><strong>535 (47%)</strong></td>
<td><strong>611 (53%)</strong></td>
<td>Modified 5PS</td>
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<tr>
<td><strong>FIL/ HD0801</strong></td>
<td>Advanced</td>
<td><strong>291 / 300</strong></td>
<td><strong>70 (24%)</strong></td>
<td><strong>221 (76%)</strong></td>
<td>IHP</td>
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<tr>
<td>RHC/na</td>
<td>Early + Advanced</td>
<td>226 / 660</td>
<td>29 (13%)</td>
<td>197 (87%)</td>
<td>Dynamic</td>
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<tr>
<td>EORTC-GELA/H10</td>
<td>Early</td>
<td>124 / 1797</td>
<td>24 (19%)</td>
<td>100 (81%)</td>
<td>Modified IHP</td>
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<tr>
<td>CALGB/50801</td>
<td>Bulky Early</td>
<td>17 / 123</td>
<td>4 (31%)</td>
<td>9 (69%)</td>
<td>5PS</td>
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<tr>
<td>ECOG/2410</td>
<td>Bulky Early</td>
<td>-- / 200</td>
<td>--</td>
<td>--</td>
<td>5PS</td>
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<tr>
<td>CALGB/50604</td>
<td>n-bulky Early</td>
<td>75 / 149</td>
<td>5 (9%)</td>
<td>51 (91%)</td>
<td>5PS</td>
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<tr>
<td>NHS-FM/RAPIID</td>
<td>n-bulky Early</td>
<td>571 / 575</td>
<td>145 (25%)</td>
<td>426 (75%)</td>
<td>5PS</td>
</tr>
<tr>
<td>GHSG/HD16</td>
<td>f-Early</td>
<td>-- / 1100</td>
<td>--</td>
<td>--</td>
<td>Modified 5PS</td>
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<td>GHSG/HD17</td>
<td>Early rf</td>
<td>-- / 1100</td>
<td>--</td>
<td>--</td>
<td>Modified 5PS</td>
</tr>
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</table>
INTERIM PET FOR HL

CONCLUSIONS

• The above PET-adapted treatments could, in future, reduce the morbidity of the current chemoradiation-based therapeutic approach in early stage HL, at least, in favorable-prognosis patient subgroup

• At this time, there are some preliminary evidences, in retrospective and preliminary data of prospective studies, in which the alterations/modifications of therapy based on interim PET scan improve patient outcomes

• A multitude of trials are currently underway to test the accuracy of PET as a marker of tumor chemosensitivity. However, whether a PET-adapted individualized treatment strategy leads to a long-term survival benefit compared to standard chemotherapy remains unknown for the HL population.

• In clinical practice, HL therapy should be individualized based on established clinical factors but not on interim PET until the ongoing trials provide more definitive guidance about the impact of interim PET-tailored approach.