Which statement regarding 1st line treatment of early stage HL is correct?

1. The differentiation between early favourable and unfavourable stage HL does not reflect different prognostic subgroups any longer

2. PET guided omission of RT in early favourable HL results in a significant loss of tumor control as determined by PFS

3. Early interim PET+ guided escalation of ABVD to BEACOPPesc does not improve the outcome (PFS/OS) in early unfavourable HL

4. Consolidating radiotherapy puts the majority of female patients at high risk for second breast cancer
### GHSG staging and treatment concepts

<table>
<thead>
<tr>
<th>Risk factor</th>
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<tr>
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"State of the art" early favourable stage HL: The GHSG HD10 study

CS I/II, no RF

4 x ABVD
30 Gy IF

4 x ABVD
20 Gy IF

2 x ABVD
30 Gy IF

2 x ABVD
20 Gy IF

objective: to show non-inferiority (6%)
HD10: Strongest (A, 4xABVD + 30Gy) vs weakest (D, 2xABVD + 20Gy) group

\[
p = 0.59 \\
\text{Arm difference in 5y-PFS} = -2.2\% \\
\text{95\% CI } [-6.7\%; 2.3\%]
\]

5-year PFS: 91.6 \%, 5-year OS: 96.6\%
Do we need further studies at all?
Long term risk of Rx: Cumulative breast cancer incidence in women

(1,122 female 5-year survivors treated for HL <51 years between 1965 and 1995)
Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. The UK NCRI RAPID non-inferiority trial (lower margin 7%).
1. Radiotherapy *improves* the PFS significantly in PET-negative (!) patients

2. This is the same result as in the EORTC10 trial (Raemaekers et al., JCO): evidence for this observation is good.

3. Nonetheless, omission of Rx for PET negative patients has been recommended (Longo, NEJM). SOC?
Should we expose ~ 85% of our patients to an increased risk for relapse, though they do not have a risk for developing second breast cancer at all?
## GHSG staging and treatment concepts

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- 2x ABVD plus 20Gy IF-RT (HD10) still is a reasonable SOC
### GHSG staging and treatment concepts

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Different stages, same treatment: the GHSG experience

HD10
Early favourable stages
- 2*ABVD
- 30/20 Gy IF-RT
- Arms C/D

HD 11
Early unfavourable stages
- 4*ABVD
- 30/20 Gy IF-RT

Arms A/B

Engert A; NEJM 2010

Eich HT, JCO 2011
In the era of non-inferiority studies, the differentiation between early favourable and unfavourable stages becomes very important.
Escalating from ABVD to BEACOPP ("2+2") in early unfavourable HL: PFS difference after 7y FU in the GHSG HD14 trial

- PFS difference after 7y FU in the GHSG HD14 trial
- "2+2" vs ABVD:
  - ABVD: 85.6% (82.5%-88.6%)
  - "2+2": 93.7% (91.7%-95.8%)

von Tresckow et al., J Clin Oncol. 2012 Mar, 0:30(9):907-13
“2+2” for patients at high risk for failure with ABVD only: The EORTC H10 study

Early unfavourable PET2+ patients (after 2x ABVD) were randomized to receive either 2x ABVD or 2x eBEACOPP

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients at risk</th>
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<tr>
<td>ABVD+INRT</td>
<td>41 192</td>
</tr>
<tr>
<td>BEACOPPesc+INRT</td>
<td>167 156 147 105 57 21 0</td>
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</tbody>
</table>

5-yr PFS: 91% vs. 77%
HR (95% CI) = 0.42 (0.23, 0.74)
p = 0.002

Raemaekers et al., 13th ICML, late breaking abstracts, 2015
## GHSG staging and treatment concepts

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<tr>
<td>Extranodal disease</td>
<td>Early unfavourable</td>
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</table>

4x “chemo” (ABVD, 2+2 upfront, 2+2 PET adapted), plus IF-RT ad 30 Gy
### GHSG staging and treatment concepts

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Question No 2:

Which statement regarding 1st line treatment of advanced stage HL is correct?

1. PET2 guided escalation of ABVD to BEACOPPesc equals the outcome (PFS) to early interim PET- patients treated with ABVD alone in advanced stage HL

2. PET2 negative after 2x ABVD patients have a PFS of around 95 % at 3y confirming the high negative predictive value of PET2.

3. PET2 positive patients after 2x eBEACOPP have a dismal prognosis

4. PET2 has a different positive predictive value depending on the treatment strategy (e.g. ABVD, BEACOPP, cons. Rx)
Current international standards and approaches in advanced stage HL

ABVD (E2496)\(^1\)

- PFS (stage III/IV) @3 y: 71% (29% failure rate)
- OS @5 y 88%

- Escalation (PFS)

RATHL

Brentuximab

6x BEACOPPPesc (HD15)\(^2\)

- PFS (stage III/IV) @3 y: 91% (9% failure rate)
- OS @5 y 95%

- De-escalation (tox)

HD18

Brentuximab

If we cannot predict the individual prognosis before treatment, maybe we can do better taking into account the *early response*?

Early interim PET overcomes the international prognostic score (IPS)
RATHL: study-design

2 cycles ABVD, full dose, on schedule

+ PET2 -

Randomise

4 cycles ABVD

4 cycles AVD

Follow-up (no RT)

RT or salvage regimen

2 cycles BEACOPP-14 or 1 eBEACOPP (no RT)

4 cycles BEACOPP-14 or 3 eBEACOPP

Johnson et al., Hematol Oncol 2015; 33: 100–180 abs 008.
ABVD versus AVD in PET2 negative patients (Median FU 36.3 months)

HR: 1.11 (0.79 – 1.54), p = 0.53
3 Year PFS, ABVD: 85.3% (95% CI: 81.6 – 88.4)
3 Year PFS, AVD: 84.6% (95% CI: 80.8 - 87.7)

Assumption for NPP of PET2: PFS 95% at 3 years. Observed PFS at 3 years: 85%. NPP of PET?

Johnson et al., Hematol Oncol 2015; 33: 100–180 abs 008.
PFS for PET2 positive patients

3 year PFS [%]
BEACOPP-14: 66.0 (55.0 – 74.9)
eBEACOPP 71.1 (59.0 – 80.2)

1. 2x ABVD, PET+, BEACOPP, PFS at 3 y: 68 %
2. Positive predictive value of PET might be overcome by intensification to BEACOPP?

Johnson et al., Hematol Oncol 2015; 33: 100–180 abs 008.
3y PFS of PET2 positive patients in the GHSG HD18 study (8x eBEACOPP +/- R)

1. There is no (!) positive predictive value of PET in HD18 at all
2. 3y PFS in HD18 91% vs 68% in RATHL: are the first two cycles decisive?

**Graphical Data:***

- **PFS** vs **Time [months]**
- **8x BEACOPP, PET+**
- **8x R-BEACOPP, PET+**
- **Difference**

**3-year PFS [95% CI]**
- **8x BEACOPP, PET+** 91.4% [87.0%, 95.7%]
- **8x R-BEACOPP, PET+** 93.0% [89.4%, 96.6%]
- **Difference** 1.6% [-4.0%, 7.3%]

**Additional Information:**
- Borchmann et al., ASH, 2014, abs 500
Current international standards and approaches

**ABVD (E2496)**
- PFS (stage III/IV) @3 y: 71% (29% failure rate)
- OS @5 y 88%
- Escalation (PFS)
- PET guided

**6x BEACOPPesc (HD15)**
- PFS (stage III/IV) @3 y: 91% (9% failure rate)
- OS @5 y 95%
- De-escalation (tox)
- PET guided

Phase III study of A-AVD versus ABVD in advanced stage HL (NCT01712490)

Primary endpoint: improvement of PFS from 75% to 82.5% at 3 y (?)
### targeted BEACOPPP: Phase II

<table>
<thead>
<tr>
<th>Drug</th>
<th>day</th>
<th>BEACOPP</th>
<th>BrECAPP</th>
<th>BrECADD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>8</td>
<td>10</td>
<td>200</td>
<td>150</td>
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<tr>
<td>Etoposide</td>
<td>1-3</td>
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<td>Doxorubicin</td>
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<td>Cyclophosphamide</td>
<td>1</td>
<td>1250</td>
<td>1250</td>
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<tr>
<td>Vincristine</td>
<td>8</td>
<td>1.4</td>
<td>1.8</td>
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<tr>
<td>Procarbazine</td>
<td>1-7</td>
<td>100</td>
<td>100</td>
<td>250</td>
</tr>
<tr>
<td>Prednisone</td>
<td>1-14</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

**Results for BrECADD (compared to HD18, current results)**

- Primary endpoint CR after Ctx reached (BrECADD 88%, HD18: 88%)
- Hematological toxicity grade 3/4: 80 % versus 93 %
- Non-Hem toxicity grade 3/4: 2 % versus 14,7 %
The GHSG HD21 study

randomization

- 2 x BEACOPP esc
- 2 x BrECADD

PET/CT Staging

First GHSG NI-study with a co-primary endpoint:
1. Non-inferiority for PFS
2. Superiority for treatment related morbidity

- 4x BEACOPP esc
- 4x BrECADD

End of therapy AND residual nodes > 2.5 cm:
- PET positiv: Rx
- PET negative: Follow up
1. Early favourable HL:
   - The negative predictive value of PET does not allow omission of radiotherapy without significant loss of tumor control (RAPID, EORTC H10)
   - A loss of tumor control might be acceptable, but the degree needs to be defined upfront (RAPID, EORTC H10) and should be regarded afterwards. However, the determination of an acceptable loss of efficacy is challenging!

2. Early unfavourable HL:
   - The positive predictive value of PET2 after 2x ABVD does allow restriction of eBEACOPP to high risk patients (EORTC H10), if followed by Rx, with superior PFS and OS compared to 4x ABVD in this subgroup of patients.

3. Advanced stage HL:
   - The negative and positive predictive value of PET2 might change over time (Gallamini 2007, RATHL), and might be dependent on the treatment itself (RATHL, HD18)
   - The potential benefit of Brentuximab vedotin will depend on the comparator. For example, the target PFS of 82.5% at 3y (ECHELON I) would be a negative result in any GHSG study (3y PFS 91% in HD15 already).
Thank you very much for your attention!

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