Management of Diffuse Large B-cell Lymphoma: 10 Questions….. and Some Answers

Professor Mark Hertzberg
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## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
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<tr>
<td>Employee</td>
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<tr>
<td>Research Support/P.I.</td>
<td>ALLG funding NHL21 (Amgen, Roche, Bayer)</td>
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<td>Major Stockholder</td>
<td>Nil</td>
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<td>Takeda, Roche, BMS</td>
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<tr>
<td>Scientific Advisory Board</td>
<td>Amgen, Roche, Takeda, Janssen, Gilead, Celgene</td>
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</table>
1. Which prognostic score should we use for risk stratification of DLBCL in the Rituximab era?

Is the IPI relevant?
## DLBCL: Prognostic Factors

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Risk Factors</th>
<th>CR, %</th>
<th>5-Yr OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients all ages = IPI</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low</td>
<td>0-1</td>
<td>87</td>
<td>73</td>
</tr>
<tr>
<td>Low intermediate</td>
<td>2</td>
<td>67</td>
<td>51</td>
</tr>
<tr>
<td>High intermediate</td>
<td>3</td>
<td>55</td>
<td>43</td>
</tr>
<tr>
<td>High</td>
<td>4-5</td>
<td>44</td>
<td>26</td>
</tr>
<tr>
<td>Patients ≤ 60 yrs = age adjusted IPI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0</td>
<td>92</td>
<td>83</td>
</tr>
<tr>
<td>Low intermediate</td>
<td>1</td>
<td>78</td>
<td>69</td>
</tr>
<tr>
<td>High intermediate</td>
<td>2</td>
<td>57</td>
<td>46</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>46</td>
<td>32</td>
</tr>
</tbody>
</table>

- Adverse risk factors correlated with response to chemotherapy and survival
  - Older than 60 yrs of age
  - LDH > normal
  - ECOG PS ≥ 2
  - Ann Arbor stage III/IV
  - Extranodal > 1 site*

*Prognostic for patients older than 60 yrs of age only.

RICOVER-60 Trial
61-80 years, CD20+ B-cell, with Rituximab (n=610)
by IPI score

EFS

PFS

OS

IPI 1: 184 (30%); IPI 2: 172 (28%); IPI 3: 155 (26%); IPI 4, 5: 99 (16%)

Ziepert et al., J Clin Oncol 2010
Risk-adapted Approaches for Aggressive Lymphomas

Germany et al.

France (GELA)

USA (SWOG)

USA (CALBG)

UK (NCRI)

Japan (JCOG)
2. Young Good-Prognosis Patients ≤ 60 yrs IPI=0, non-bulky

Can we give less than 6 cycles of R-CHOP-21?
**MInT** Trial Design

**CD20⁺ DLBCL**
- 18–60 years
- IPI 0,1
- Stages II-IV, I with bulk

**Random.**

- 6 x CHOP-like + 30–40 Gy (Bulk, E)
- 6 x CHOP-like + rituximab + 30–40 Gy (Bulk, E)

**IPI≥0; No bulk**
- Bulk and/or
- IPI =1
MlnT

Progression-free Survival

- **R-CHEMO (n=413)**
  - 79.9% at 72 months
  - 63.8% at 72 months

- **CHEMO (n=410)**
  - 79.9% at 72 months
  - 63.8% at 72 months

\[ p < 0.0001 \]

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Favourable Subgroup (IPI=0 / no Bulk): 6 x R-CHOP-21

Event-free Survival

Overall Survival

91.3%

100%

Difficult to improve upon 100% OS

Pfreundschuh et al. Lancet Oncol 2011

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FLYER (6-6/6-4) STUDY DESIGN

Stage I/II, aalPl=0, no Bulk, 18-60 years

Interim Analysis (200 pts): 4 events = 1 death (swine flu), 3 other events (?arm 2); Worst case scenario:
4 x R-CHOP +2R: EFS = 97%, OS = 100%; study safe → 600 patients needed.
FLYER (6-6/6-4): 2nd PLANNED INTERIM ANALYSIS (07/13)
FLYER (6-6/6-4): 2nd PLANNED INTERIM ANALYSIS

406 Patients:

⇒ excellent outcome overall

⇒ study safe

⇒ 600 patients planned

⇒ R-CHOP x 4 + R x 2 may be sufficient in young patients ≤ 60 yrs with IPI=0, no bulk
3. Young Good Prognosis Patients $\leq 60$ yrs, Bulky disease and/or IPI = 1

Can we improve upon 6 cycles of R-CHOP-21?
Prognostic Groups in the Rituximab Era:
Favourable vs. Unfavourable

**EFS**
- Favourable: IPI=0 / Ø bulk
- Probability after 72 months: 84.2%
- Probability after 120 months: 70.7%
- p = 0.004

**PFS**
- Favourable: IPI=0 / Ø bulk
- Probability after 72 months: 89.5%
- Probability after 120 months: 76.7%
- p = 0.002

**OS**
- Unfavourable: IPI=1 and/or bulk
- Probability after 72 months: 94.8%
- Probability after 84 months: 88.1%
- p = 0.017
Patients aged 18-59 yrs; aAIPI = 1 (LDH, or stage III/IV, or ECOGPS)
No radiotherapy in either treatment arm
Primary endpoint: EFS
Secondary endpoints: response rate at end of therapy, PFS, FDS (CR/CRu patients only), OS, CNS relapse rate, toxicity

LNH 03-2B vs. MlnT$_{aalPl=1}$

3-Year Results

- **EFS:**
  - GELA: R-CHOP-21 (n=183) 67%
  - GELA: R-ACVBP (n=196) 81%
  - MlnT: R-CHOP-21 (n=118) 86%
  - MlnT: R-CHEMO (n=203) 92%

- **PFS:**
  - GELA: R-CHOP-21 (n=183) 73%
  - GELA: R-ACVBP (n=196) 87%
  - MlnT: R-CHOP-21 (n=118) 83%
  - MlnT: R-CHEMO (n=203) 90%

- **OS:**
  - GELA: R-CHOP-21 (n=183) 84%
  - GELA: R-ACVBP (n=196) 91%
  - MlnT: R-CHOP-21 (n=118) 90%
  - MlnT: R-CHEMO (n=203) 91%
R-ACVBP vs R-CHOP

Group < 60 yrs: Bulk and/or IPI=1

8 x R-CHOP-21_{GELA}^{*} < 6 x R-CHOP-21_{MlnT}^{**}

R-ACVBP_{GELA}^{*} = 6 x R-CHOP-21_{MlnT}^{**}

* No Radiotherapy  ** Radiotherapy to bulky disease

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### UNFOLDER (21/14) STUDY DESIGN

<table>
<thead>
<tr>
<th>HP21</th>
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### Radiation

- + / - Radiation
- Bulk / E

### IPI = 1

- and/or Bulk

### Doses

- d 1
- d 75
- d 105
UNFOLDER Study

Patients 18-60 years, B-cell (CD20+), aalPl=0 with bulk or aalPl=1, ITT (n=443)

EFS – Patients randomised to 4 arms (n=285)

- R-CHOP 21/14 + IF-RT
  - Proportion: 81%
  - p=0.004

- R-CHOP 21/14 + No IF-RT
  - Proportion: 65%

Months

Courtesy of Michael Pfreundschuh, 2012
UNFOLDER (21/14) STUDY DESIGN

+/- Radiatio to Bulky Disease

IPI = 1 and/or Bulk

+/- Radiatio to Bulky Disease

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UNFOLDER (21/14) STUDY DESIGN

IPI = 1 and/or Bulk

Radiation to bulky Disease

Radiation to bulky Disease

CHOP 21

CHOP 21

CHOP 21

CHOP 21

CHOP 21

CHOP 21

CHOP 14

CHOP 14

CHOP 14

CHOP 14

CHOP 14

CHOP 14

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UNFOLDER study
Patients 18-60 years, B-cell (CD20+), aalPl=0 with bulk or aalPl=1, ITT (n=443)

PFS – Patients randomised to 4 arms with RX (n=285)

- **R-CHOP-14**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>2-Years Rate</th>
<th>3-Years Rate</th>
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</thead>
<tbody>
<tr>
<td>R-CHOP 21 (n=72)</td>
<td>77%</td>
<td>74%</td>
</tr>
<tr>
<td>R-CHOP 14 (n=74)</td>
<td>84%</td>
<td>84%</td>
</tr>
</tbody>
</table>

**Months**

Proportion
Conclusions:

- Radiotherapy to bulky disease is indicated (possibly not with R-CHOP14)
- UNFOLDER to be continued as planned
  - to answer R-CHOP-14 vs R-CHOP-21
to consolidate treatment effects (PFS, OS)
(is CHOP-14 as good as ACVBP ?)
Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma

Kieron Dunleavy, M.D., Stefania Pittaluga, M.D., Ph.D., Lauren S. Maeda, M.D., Ranjana Advani, M.D., Clara C. Chen, M.D., Julie Hessler, R.N., Seth M. Steinberg, Ph.D., Cliona Grant, M.D., George Wright, Ph.D., Gaurav Varma, M.S.P.H., Louis M. Staudt, M.D., Ph.D., Elaine S. Jaffe, M.D., and Wyndham H. Wilson, M.D., Ph.D.

A  Event-free Survival (NCI Patients)  B  Overall Survival (NCI Patients)

- Only 51 patients from one centre
- 12 yrs to accrue
- Too early: wait 24 m for all patients
- Need randomised *multicentre* study!
UNFOLDER Study

OS – Patients randomised to 4 arms with reference pathology, according to pathology (n=269)

- PMBCL n=69

- PMBCL, CHOP14/21 +/- Radiotherapy (n=69)

- all other with existing pathology, CHOP14 (n=200)

_months_
PMBCL in Young Patients: „Unfolder“

- N = 69 patients
  Overall survival to date = 100%

- To date, no differentiation between those who did and did not get RT

- To date, no differentiation between those receiving 14 vs 21 day R-CHOP
2. PMBCL: IELSG Study: Can IFRT be withheld in PET-negative?

Hence:
1. ≤60 yrs with bulk and/or IPI=1
   → R-CHOP-21/14 x 6 + IF-RT to bulk
2. PMBCL, possibly no RT esp if PET-neg
4. Young Poor-Prognosis Patients ≤ 60 yrs (aa IPI = 2, 3)

What is the optimal therapy in the Rituximab era?
At least 11 prospective trials and 3 meta-analyses have failed to confirm HDCT & ASCT as part of first-line Rx in aggressive DLBCL in pre-Rituximab era.
DSHNHL 2002-1 ("Mega-CHOEP"):
TRIAL DESIGN (≤ 60 Yrs, AGE-ADJUSTED IPI ≥ 2)

n=230

PBS C

mCHOEP I
CYC 1500
ADR 70
VCR 2
ETO 600
PRD 500

mCHOEP II
CYC 4500
ADR 70
VCR 2
ETO 960
PRD 500

mCHOEP III
CYC 4500
ADR 70
VCR 2
ETO 960
PRD 500

mCHOEP IV
CYC 6000
ADR 70
VCR 2
ETO 1480
PRD 500

1 22 43 64 77 98 days

CHOEP-14
CHOEP-14
CHOEP-14
CHOEP-14
CHOEP-14
CHOEP-14
CHOEP-14
CHOEP-14
CHOEP-14

n=230

★ = Rituximab

CHOEP-14: CYC 750  VCR 2
ADR 50  PRED 500
ETO 300  G-CSF

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R-MegaCHOEP Study

PFS ACCORDING TO TREATMENT ARM

73.7% R-CHOEP-14 vs 69.8% R-MegaCHOEP

3-yr PFS
R-MegaCHOEP Study

OS ACCORDING TO TREATMENT ARM

R-CHOEP-14 = 84.6%
R-MegaCHOEP = 77.0%

3-yr OS

Months

Proportion

R-CHOEP-14 (n=130)
R-MegaCHOEP (n=132)
p=0.081
Prognostic factors in DLBCL

Young Poor-Prognosis DLBCL (Mega-CHOEP Trial): Overall-Survival with 8 x R-CHOEP-14

What about other recent studies of up-front autologous SCT in DLBCL?

Schmitz et al., Lancet Oncology 2012
SWOG 9704: R-CHOP x 5 → If PR/CR then randomised to SCT or 3 x R-CHOP

- 253/370, ie, 2/3rd of eligible were randomised
- 60% of randomised B-NHL received Rituximab
- 21% (78/370) early PD/death/toxicity=no randomisation

2-yr PFS

(R)-CHOP21 x 5 → ASCT
(R)-CHOP21 x 8
(R)-CHOP21 by itt

P = 0.005
SWOG 9704: R-CHOP x 5 → If PR/C paternalised to SCT or 3 x R-CHOP

• For the R-CHOP patients, the 2-yr PFS = 63% vs 73% in the transplant gp (HR, 1.56; 95% CI, 0.92 to 2.63; P=0.10)

→ this 10% difference in PFS is not statistically significant, since the study was highly underpowered to allow a meaningful comparison (Schmitz N et al. NEJM)

→ R-CHOP-21 = inadequate therapy in this high risk group

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3-year OS:

A. R-HDC+ASCT vs R-dose dense
- 81% (95% CI: 74-86)
- 79% (95% CI: 72-84)
- P = 0.8008

B. R-CHOP14 vs R-MegaCHOP14
- 80% (95% CI: 74-85)
- 80% (95% CI: 73-85)
- P = 0.6842
# Young Poor-Prognosis DLBCL: Upfront ASCT in Rituximab Era

<table>
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<tr>
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<th>Conventional Therapy</th>
<th>Transplant</th>
<th>p</th>
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<tr>
<td><strong>SWOG (a) R=253/397</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-yr PFS</td>
<td>56%</td>
<td>69%</td>
<td>0.005</td>
</tr>
<tr>
<td>2-yr OS</td>
<td>71%</td>
<td>74%</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>DSHNHL (b)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-yr PFS</td>
<td>74%</td>
<td>70%</td>
<td>0.4</td>
</tr>
<tr>
<td>3-yr OS</td>
<td>85%</td>
<td>77%</td>
<td>0.008</td>
</tr>
</tbody>
</table>

- AutoSCT provides no advantage in treatment of young poor prognosis patients in Rituximab era

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<tr>
<td><strong>FIL(d)</strong></td>
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<tr>
<td>3-yr PFS</td>
<td>59%</td>
<td>71%</td>
<td>0.008</td>
</tr>
<tr>
<td>3-yr OS</td>
<td>79%</td>
<td>81%</td>
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Comparison of R-CHOP14 and R-CHOEP14 as First Line Treatment in Young Patients with High-Risk (aaIPI 2-3) diffuse Large B-Cell Lymphoma (DLBCL): A Joint Analysis of Two Prospective Phase III Randomized Trials Conducted by the Fondazione Italiana Linfomi (FIL)

Is German R-CHOEP-14 better than Italian R-CHOP-14?

GERMAN HIGH-GRADE NHL STUDY GROUP (DSHNHL)
www.lymphome.de/en/Groups/DSHNHL
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>R-CHOEP14 130 pts</th>
<th>R-CHOP14 100 pts</th>
<th>P-value</th>
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<tbody>
<tr>
<td>males</td>
<td>82 (63%)</td>
<td>45 (45%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Age median yrs</td>
<td>50</td>
<td>48.5</td>
<td>0.992</td>
</tr>
<tr>
<td>LDH level</td>
<td>127 (98%)</td>
<td>87 (87%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Stage (III-IV)</td>
<td>126 (97%)</td>
<td>94 (94%)</td>
<td>0.281</td>
</tr>
<tr>
<td>ECOG 0-1</td>
<td>88 (68%)</td>
<td>55 (55%)</td>
<td>0.049</td>
</tr>
<tr>
<td>IPI= 2</td>
<td>95 (73%)</td>
<td>75 (75%)</td>
<td>0.742</td>
</tr>
<tr>
<td>IPI= 3</td>
<td>35 (27%)</td>
<td>25 (25%)</td>
<td></td>
</tr>
<tr>
<td>N. extran.&gt;1</td>
<td>56 (43%)</td>
<td>38 (38%)</td>
<td>0.437</td>
</tr>
<tr>
<td>Bulky</td>
<td>77 (59%)</td>
<td>37 (37%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BM involvement</td>
<td>16 (12%)</td>
<td>21 (21%)</td>
<td>0.075</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>63 (43%)</td>
<td>18 (18%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Radiotherapy on Bulky</td>
<td>57/77 (74%)</td>
<td>6/37 (16%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

More high risk patients in R-CHOEP-14 group.
1. Germany vs Italy; 3-yr PFS
R-CHOEP-14 (n=130) vs R-CHOP-14 (n=100)

Log-rank test $p=0.1776$
2. Danish: R-CHOEP-14 vs R-CHOP-14 in Young High Risk DLBCL (n=159)

4-yr PFS = 70% vs 58% (p=0.02)
HR = 0.49
3. Swedish Registry DLBCL ≤ 70 yrs: R-CHOEP-14 vs R-CHOP-14/21

- Of 1745 patients, 1331 had either R-CHOP-21 (n=302), R-CHOP-14 (n=872) or R-CHOEP-14 (n=157)
- In multivariate analysis:
  \[ \text{R-CHOEP-14 = significantly superior to R-CHOP-21 (HR 0.53, CI:0.3-0.9, } P=0.026) \text{ and R-CHOP-14 (HR: 0.63, CI: 0.4-1.0, } P=0.048) \]

  \[ \text{R-CHOP-14 = R-CHOP-21 (HR: 0.84, CI: 0.6-1.2, p=0.3), consistent with findings from randomised trials} \]
Conclusions: Young Poor-Prognosis Patients ≤ 60 yrs (aAIPI = 2, 3)

- 6-8 cycles R-CHOP-21 is inferior in this group
- To date, best results with R-CHOEP-14 × 8
  - aAIPI=2 → 3-yr OS = 90%: difficult to improve;
  - aAIPI=3 → 3-yr OS = 70%: need to improve
- ? Do we need 8 cycles; probably 6.
5. For Elderly Patients

> 60 years

Which R-CHOP?
## Elderly DLBCL: Randomised trials CHOP ± Rituximab

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Outcome</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coiffier(^1)</td>
<td>R-CHOP-21 x 8</td>
<td>5-yr PFS 54% ((↑24)%)</td>
<td>5-yr 58%</td>
</tr>
<tr>
<td>Habermann(^2)</td>
<td>R-CHOP-21</td>
<td>3-yr PFS 52% ((↑13)% )</td>
<td>3-yr 67%</td>
</tr>
<tr>
<td>Pfreibuschuh(^3)</td>
<td>R-CHOP-14 x 6</td>
<td>3-yr EFS 66% ((↑19)% )</td>
<td></td>
</tr>
<tr>
<td>Lugtenburg(^4)</td>
<td>R-CHOP-14</td>
<td>5-yr FFS 50% ((↑13)% )</td>
<td>5-yr 53%</td>
</tr>
</tbody>
</table>

LNH03-6B GELA: R-CHOP-14 vs R-CHOP-21 in Elderly DLBCL

DLBCL patients 60-80 yrs of age
(N = 602)

R-CHOP every 14 days for 8 cycles + IT MTX for 4 cycles (n = 304)

R-CHOP every 21 days for 8 cycles + IT MTX for 4 cycles (n = 296)

Prophylactic Darbepoetin alfa
Conventional treatment for chemotherapy-induced anemia

Prophylactic Darbepoetin alfa
Conventional treatment for chemotherapy-induced anemia

G-CSF administered at physician discretion in both arms

- Primary endpoint: EFS
- Secondary endpoints: CR or CRu, ORR, PFS, DFS, OS, dose intensity, toxicity

GELA LNH03-6B: The French CHOP-14 Over Time

OS Pts. #1-200

- 2-year OS: 67% (R-CHOP14) vs 70% (R-CHOP21)
- $p=0.3664$

OS Pts. #1-600

- 3y-OS: 70% vs 73%
- HR: 0.98 (95%CI: 0.74-1.30); $p=0.89$

Delarue et al., ASH 2009 / Lancet Oncology 2013
LNH 03-6B: R-CHOP14 vs R-CHOP21 in Elderly DLBCL (n=602)

**RFS**

Progression-free survival (%)

Log rank p=0.8982

Time since randomisation (months)

229 190 139 95 49 22 0

226 194 144 99 44 23 0

**OS**

Overall survival (%)

Log rank p=0.7486

Time since randomisation (months)

251 230 163 115 64 31 2 0

253 229 168 119 53 29 3 0

LNH-03 6B
The French Learning Curve (I) ...
Toxic Deaths with R-CHOP-14

Delarue et al., ASH 2009 / Lancet Oncoloy 2013
LNH 03-6B: R-CHOP14 vs R-CHOP-21 in Elderly DLBCL

BUT problems with R-CHOP-14 in this GELA study:

1. G-CSF not mandated → 90% got G-CSF, mostly after treatment delays, BUT, only 73% G-CSF in cycle#1

2. No pre-phase prednisone to improve ECOGPS etc

3. Relative dose intensity (RDI) = 83% → but cumulative doses not known from all cycles vs RICOVER-60 RDI = 96%

4. “Learning phase” since therapy-associated deaths = 9% in first 200 patients, but only 2.5% in the last 200 versus RICOVER-60 = 6% total [or 2% last 500 patients] with use of pre-phase + G-CSF

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Aggressive Lymphomas in the Elderly

Prephase treatment:

- (Vincristine 1 mg IV day −7)
- Prednisone 100 mg PO days −7 to −1

Effects:

- Improvement of performance state
- Prevention of tumor lysis syndrome
- Amelioration of 1st-cycle effect
Therapy-associated Deaths before and after Introduction of Prephase Therapy*

* DSHNHL NHL-B2 Trial

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Reduction In Therapy-Related Deaths with R-CHOP-14

- Pre-phase prednisone
- Addition of Aciclovir for CMV reactivation
- Bactrim for PJP prophylaxis
- G-CSF from cycle#1
UK NCRI: R-CHOP-14 vs R-CHOP-21 in 1st line DLBCL (Phase III study)

- Newly diagnosed CD20+ DLBCL patients (N = 1080)
- CHOP-14 x 6 cycles + Rituximab x 8 cycles + Lenograstim on Days 4-12 (n = 540)
- CHOP-21 x 8 cycles + Rituximab x 8 cycles (n = 540)

Stratified by IPI score, treatment center, and age

- Primary endpoint: OS
- Secondary endpoint: FFS, toxicity, response rates

UK NCRI: R-CHOP-14 vs R-CHOP-21 in 1st line DLBCL (Phase III study)

**PFS**

![Survival Graph](image)

Hazard ratio = 0.94, 95% CI = 0.76-1.17, p = 0.5907

**OS**

![Survival Graph](image)

Hazard ratio = 0.90, 95% CI = 0.70-1.15, p = 0.3763

*Cunningham et al. Lancet Oncol 2013*
NCRI CRUKE/03/019: R-CHOP-21 vs. R-CHOP-14: Grade 3&4 Toxicity

Cunningham et al., ASCO 2009; Abstract # 8506
ESMO GUIDELINES 2012

Recommendations for Elderly DLBCL:

• 6 cycles R-CHOP-14 + R x 2

OR

• 8 cycles R-CHOP-21
RITUXIMAB PHARMACOKINETICS: Trough Serum Levels

Reiser et al., ASH 2006, Abs # 778
PK model based on median PK parameter values [KELM, V1 (1/kgLBMc), K12 and K21] of 20 patients treated with R-CHOP-14 according to a 2-compartment model. Model calculated for 21-day interval.
Rituximab Schedules for DLBCL

SMARTe-R-CHOP-14
(8 x R)

RICOVER-60 R-CHOP-14
(8 x R)

 Supported by Mark Hertzberg 2016
SMARTE-R-CHOP-14

All Patients PFS and OS

PFS

75% vs 73%

OS

88% vs 86%

Mark Hertzberg 2016
SMARTE-R-CHOP-14 IPI=3-5 PFS and OS

PFS

71% vs 59%

OS

80% vs 67%
Conclusions (I)

- Pharmacokinetics of 8 x R-14: adequate for elderly patients with good-prognosis (IPI=1,2) / low tumor burden DLBCL, but not for higher tumor loads.

- Compared to 8 x R-14, 8 x pharmacokinetically-based SMARTE-R gives significantly better outcomes among elderly DLBCL patients with IPI > 2.

- SMARTE-R-CHOP-14: best results for elderly poor-prognosis DLBCL reported to date.
RICOVER-60 Trial (n=1222)
PFS according to Sex and Rituximab

**MALES**
- Males w Rituximab (n=325)
- Males wo Rituximab (n=325)
- Proportion: 49% (p=0.003)

**FEMALES**
- Females w Rituximab (n=285)
- Females wo Rituximab (n=287)
- Proportion: 72% (p<0.001)

Mark Hertzberg 2019
### RICOVER-60 Trial (n=1222)
#### Multivariate Analysis PFS

<table>
<thead>
<tr>
<th>Without Rituximab</th>
<th>With Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>RR</td>
</tr>
<tr>
<td>p</td>
<td>p</td>
</tr>
<tr>
<td>LDH</td>
<td>2.210</td>
</tr>
<tr>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECOG</td>
<td>1.743</td>
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<tr>
<td>0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Stage</td>
<td>1.450</td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>0.045</td>
</tr>
<tr>
<td>Ex&gt;1</td>
<td>1.075</td>
</tr>
<tr>
<td>0.001</td>
<td>0.724</td>
</tr>
<tr>
<td>Male vs. Female</td>
<td>1.127</td>
</tr>
<tr>
<td>0.348</td>
<td>1.592</td>
</tr>
<tr>
<td>Female</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Pfreundschuh et al., ASH 2009*
RICOVER-60 Trial:
Rituximab Serum Elimination Half Life

Müller et al., Blood 2012
Rituximab Clearance in DLBCL Subpopulations

- Elderly female patients: 8.5 ± 2.5 ml/hr
- Elderly male patients: 13.0 ± 3.0 ml/hr
- Young female patients: 11.5 ± 2.0 ml/hr
- Young male patients: 14.0 ± 3.5 ml/hr

Significant differences:
- Elderly vs. young female patients: p=0.015
- Elderly vs. young male patients: p=0.004
- Elderly female vs. elderly male patients: p=0.005

Mark Hertzberg 2016
SEXIE-R-CHOP-14

Study Design

- **Rituximab 375 mg/m²**
  - 0, 2, 4, 6, 8, 10, 12, 14 weeks

- **Rituximab 500 mg/m²**
  - 0, 2, 4, 6, 8, 10, 12, 14 weeks

**CD20⁺ DLBCL**
- Stages I-IV
- 61 to 80 years
SEXIER-CHOP-14 and RICOVER-60: PFS According to SEX

RICOVER-60

SEXIER-CHOP-14

- Females (n=285)
- Males (n=325)

- Females (n=120)
- Males (n=148)
SEXIER-CHOP-14 and RICOVER-60: OS According to SEX

**RICOVER-60**

- **Males**

**SEXIER-CHOP-14**

- **Females (n=285)**
- **Males (n=325)**

- **Females (n=120)**
- **Males (n=148)**
Conclusions:

- Rituximab 500 mg/m² instead of 375 mg/m² eliminates the increased risk of elderly males compared to females.

- Since both young male and female patients have unfavourable rituximab pharmacokinetics compared to elderly females increasing the dose in these populations should also result in a better outcome.

- Whether 375 mg/m² for elderly females is optimal, is unclear.

- Suboptimally-dosed rituximab can easily be beaten by other CD20 Abs that are higher dosed and/or given more often.
6. For Older Patients

> 60 yrs

If and when should we use radiation therapy in DLBCL?
1. SWOG 0014: R-CHOP + RT in Localized DLBCL (stage I/II + 1 risk factor)

- Patients (n = 60) aggressive NHL,
  - DLBCL (n = 56); Burkitt-like (n = 3); High grade B (n = 1); 73% > 60 yrs
- Treatment: Rituximab x 4: Days -7, 1, 22, and 43
  - CHOP-21 x 3: Days 3, 24, 45
  - 40-46 Gy IFRT

- CHOP x 3 + R x 4 + RT
  - Still ongoing relapses
  - Insufficient R-chemo
  - adding Rx4 = minimal gain

2. Phase III 02-03 Trial: R-CHOP ± RT in Non-bulky Limited-Stage DLBCL (n=356)

- Prospective registry data in limited stage I/II non-bulky (< 10 cm)
- N=299 given R-CHOP x 6-8 vs N= 58 with R-CHOP x 3-4 + IF-RT

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP x 6-8</th>
<th>R-CHOP x 3-4 + RT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS</td>
<td>91.7%</td>
<td>81.8%</td>
<td>0.0028</td>
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<tr>
<td>OS</td>
<td>96.1%</td>
<td>89.9%</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Park JH et al ASH 2014, abstract 4421
3. Survival of patients with **bulky** disease **receiving** RT or not according to RiCOVER-60 protocol

- Limited R-chemo before RT is insufficient!
- Following R-CHOP, RT benefits those with bulk
- BUT, the role of IF-RT is not yet defined for those with initial bulk and PET-negative after R-CHOP?
7. For All Patients

Should CNS prophylaxis be given to patients and if so in whom and how?
CNS events in the RICOVER-60 trial
"high-risk" patients with/without i.th. MTX and with/without Rituximab

- Incidence of CNS relapse is low = 3.6%
- Most of CNS events [36/58 (62%)] were in patients in PR or PD at first restaging (Only 34% in CR !)
- Alone, it MTX provided no benefit
- Parenchymal relapses > 2/3 (n=38) of CNS relapses !
- Similar to the 1.48% rate seen in the NCRI UK R-CHOP 14 vs 21 study (Gleeson M et al ASH 2014 1723a)
CNS Disease in Younger Patients With Aggressive DLBCL: Results

- CNS disease was reduced in patients with IPI 0 or 1 receiving rituximab: incidence of 0% or 0.5%

Suggests CNS prophylaxis should not be used in good risk but may be appropriate in high risk

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th></th>
<th>A</th>
<th>B</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>754</td>
<td>1.0</td>
<td>166</td>
<td>0</td>
<td>920</td>
<td>0.8</td>
<td></td>
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<tr>
<td>1</td>
<td>615</td>
<td>2.6</td>
<td>243</td>
<td>0.5</td>
<td>858</td>
<td>2.0</td>
<td></td>
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<tr>
<td>2</td>
<td>156</td>
<td>4.6</td>
<td>157</td>
<td>4.2</td>
<td>313</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>13.2</td>
<td>53</td>
<td>9.7</td>
<td>104</td>
<td>11.4</td>
<td></td>
</tr>
</tbody>
</table>

DSHNHL Prognostic Model to Assess the Risk of CNS Disease in Aggressive B-Cell Lymphoma

- Predict the risk of 2° CNS disease: DSHNHL examined 7 trials (2,164 patients) → a new prognostic model
  = the 5 IPI factors
  age > 60 yrs, LDH > N, stage 3/4, ECOGPS > 1, EN sites > 1
  + kidney/adrenal involvement

<table>
<thead>
<tr>
<th>3 risk groups (6 factors)</th>
<th>2-yr CNS relapse risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low 0-1 factors</td>
<td>0.6%</td>
<td>0-1.2%</td>
</tr>
<tr>
<td>Intermediate 2-3 factors</td>
<td>3.4%</td>
<td>2.2-4.6%</td>
</tr>
<tr>
<td>High 4-6 factors</td>
<td>10.2%</td>
<td>6.3-14.1%</td>
</tr>
</tbody>
</table>

Schmitz et al. Hematol. Oncol. 2013: 31, 047a
What represents a high risk of CNS relapse?
= high risk score of 4 to 6 (5 IPI factors + adrenal/kidney)
Or extranodal sites > 2

≤2 extranodal sites vs. >2 extranodal sites

**DHSNHL risk model**

- ≤2 extranodal sites, n=1,310 (90%)
- >2 extranodal sites, n=140 (10%)

- DHSNHL low risk, n=484 (34%)
- DHSNHL intermediate risk, n=676 (47%)
- DHSNHL high risk, n=277 (19%)
CNS Directed Prophylaxis in DLBCL: IV High dose Methotrexate
CNS Directed Prophylaxis in DLBCL

- No IT MTX since it does not work
  BUT, need systemic therapy:
- eg IV MTX 1.5 g/m² x 2 (?3)
  = before cycle #1 R-CHO(E)P such as between d-7 to d-4, AND at the end of R-chemo (DSHNHL)

since:

1. CNS recurrence is early and among those with PD or PR
2. Before R-chemo means early CNS penetration when BBB is already potentially disrupted
3. Minimises mucositis duration, and, won’t interrupt scheduling and relative dose intensity R-chemo (vs during R-chemo cycles)
8. Are there prognostic factors other than the IPI?

Should we use DLBCL subtype analysis to tailor therapy?
Prognostic factors in DLBCL

Prognosis of GCB and ABC after R-CHOP

Progression-free Survival

Overall Survival

Molecular Outcome Prediction: Surrogate Markers in the RICOVER Trial

Ott et al., Blood 2010
BCCA: Molecular Outcome Prediction: 21-gene Lymph2Cx Nanostring FFPE Validation

Scott et al., Blood 2014
BCCA: Molecular Outcome Prediction: 21-gene Lymph2Cx Nanostring FFPE Validation

PFS

OS

Lympth2Cx Nanostring

Gold standard Gene Expression

Scott et al., Blood 2014

ABC

P < 0.001  RR = 3.6 (1.6-8.4)

P = 0.01  RR = 2.6 (1.1-6.3)

P = 0.01  RR = 2.8 (1.1-7.3)

P = 0.04  RR = 2.3 (0.8-6.3)
Prognostic factors in DLBCL

**ABC- vs. GC-DLBCL:**

- Immunohistochemical algorithms debated
- Strong prognosticator by digital gene expression on FFPE by Nanostring
- Offers a molecular basis for drug development
- Differential drug effects suggested (bortezomib*, lenalidomide**, ibrutinib*** for ABC-DLBCL)

** Novakovwsky et al. JCO 2015; 33: 251-7; Vitolu U et al. Lancet Oncology 2014; 730-7
*** Wilson W et al., ASH 2012; Younes A et al Lancet Oncology 2014; 1019-1026
C-MYC & Double-Hit (DH) DLBCL

- Defined as a MYC-rearrangement + other chromosomal rearrangement = mostly BCL-2 &/or BCL-6 in 30%
- In ≤ 5% of DLBCL
- Use of FISH vs Immunohistochemistry; IHC difficult assignment with varying cut-off values for % positivity
- Studies also show the adverse impact of single hit C-MYC
- Studies mostly retrospective
- Most studies in patients > 60 yrs (difficult to intensify Rx)
- Intensified regimens disappointing (GMALL B-ALL, CODOX-M / IVAC, hyperCVAD)
MYC BREAK in DLBCL

Survival *without* Rituximab*:

- No MYC break (n=186)
- MYC break (n=17)

Survival *with* Rituximab*:

- No MYC break (n=185)
- MYC break (n=19)

*p=0.001
*p=0.072

* RICOVER-60 Trial
3. Unresolved Issue in DLBCL

„Double-hit“ DLBCL: Intergroup efforts

100 pats being treated in 4 groups for comparison:

- DSHNHL (German): R-CHOEP-14
- LYSA (French): R-ACVBP
- Stanford (USA): DA-EPOCH-R
- NCRI (UK): R-CODOX-M / IVAC
9. For All Patients

Can we incorporate interim PET scans for therapeutic monitoring?
Interim PET

Predictive value in aggressive non-Hodgkin’s lymphomas
DLBCL:  
L-I to H risk, LR + bulk (≥ 7.5cm)  
Age ≤ 70 yrs; fit for HDT  

R-CHOP-14 x 4  

iPET/CT*  

iPET-pos  

R-ICE x 3  

Zevalin-BEAM HDT  

iPET-neg  

R-CHOP-14 x 2 + R x 2  

Observation  

*Delay C5 chemotherapy by 7 days: PET d17-d20  
Assessed centrally, IHP criteria using MBP
### Patient Characteristics (n=151)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age yrs</td>
<td>57 (21-69)</td>
</tr>
<tr>
<td>Age &gt; 60 yrs</td>
<td>61 (40%)</td>
</tr>
<tr>
<td>Age ≤ 60 yrs</td>
<td>90 (60%)</td>
</tr>
<tr>
<td>Males</td>
<td>94 (62%)</td>
</tr>
<tr>
<td>Stages 3 or 4</td>
<td>119 (79%)</td>
</tr>
<tr>
<td>ECOG PS &gt; 1</td>
<td>20 (13%)</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>118 (78%)</td>
</tr>
<tr>
<td>B symptoms</td>
<td>76 (50%)</td>
</tr>
<tr>
<td>BM involvement</td>
<td>25 (17%)</td>
</tr>
<tr>
<td>Extranodal sites &gt; 1</td>
<td>72 (48%)</td>
</tr>
<tr>
<td>Bulky dis. ≥ 7.5 cm</td>
<td>81 (54%)</td>
</tr>
<tr>
<td>IPI 0,1</td>
<td>30 (20%)</td>
</tr>
<tr>
<td>IPI 2</td>
<td>40 (27%)</td>
</tr>
<tr>
<td>IPI 3</td>
<td>47 (31%)</td>
</tr>
<tr>
<td>IPI 4,5</td>
<td>34 (23%)</td>
</tr>
<tr>
<td>aalPI 2-3</td>
<td>83 (55%)</td>
</tr>
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</table>
PFS is equivalent: iPET- vs. iPET+

Median follow up: 35 m

Number at risk

<table>
<thead>
<tr>
<th>Status</th>
<th>PET +ve</th>
<th>PET -ve</th>
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<tbody>
<tr>
<td>PETstatus =</td>
<td>42</td>
<td>101</td>
</tr>
<tr>
<td>Number at risk</td>
<td>27</td>
<td>73</td>
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<tr>
<td></td>
<td>11</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

$P = 0.32$
OS is equivalent: iPET- vs. iPET+

Median follow up: 35 m

\[ P = 0.11 \]
10. What about Relapsed / refractory DLBCL?
ESMO Guidelines:

Standard for younger patients:
2 to 3 cycles R-DHAP/R-ICE followed by ASCT

Elderly patients:
Remission induction with Gemcitabine / Oxaliplatin only palliative in most cases

Tilly et al., Annals of Oncology 21 (Supplement 5): v172–v174
## Salvage Therapy in the Rituximab Era

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response to frontline</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>EFS</th>
<th>OS</th>
<th>HSCT</th>
<th>Mob failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORAL R-ICE (n=202)</td>
<td></td>
<td>64</td>
<td>36</td>
<td>3yr 26%</td>
<td>3 yr 47%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-DHAP (n=194)</td>
<td></td>
<td>63</td>
<td>40</td>
<td>3 yr 35%</td>
<td>3 yr 51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-ICE or R-DHAP</td>
<td>Prior rituximab</td>
<td>51</td>
<td></td>
<td>3yr 21%</td>
<td>3yr 40%</td>
<td>53%</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>CR &lt;12m (regardless of rituximab)</td>
<td>46</td>
<td></td>
<td>3yr 20%</td>
<td>3yr 39%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCIC LY.12 R-GDP (n=303)</td>
<td>CR≤12m 42% &lt;CR 30%</td>
<td>45</td>
<td>14</td>
<td>4yr-43%</td>
<td>4yr-62%</td>
<td>52.1</td>
<td>12</td>
</tr>
<tr>
<td>R-DHAP (n=302)</td>
<td></td>
<td>46</td>
<td>14</td>
<td>4yr-48%</td>
<td>4yr-63%</td>
<td>49.3</td>
<td>18</td>
</tr>
<tr>
<td>ORCHARRD R-DHAP (n=225)</td>
<td>≤12m 12% PR 37% SD 8% PD 15%</td>
<td>42</td>
<td>22</td>
<td>2yr -17%</td>
<td>2yr-41%</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>O-DHAP (n=222)</td>
<td></td>
<td>38</td>
<td>15</td>
<td>2yr-14%</td>
<td>2yr-46%</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>
CORAL-Study
Failure from diagnosis < 12 months

Prior Rituximab + Failure < 12 m from diagnosis

Guglielmi et al., Blood, 1999, 94 Suppl1:599a
10 + 1. For All Patients

Can we add new Agents?
New targets, new drugs

<table>
<thead>
<tr>
<th>Microenvironment</th>
<th>Pathways</th>
<th>Cell surface markers</th>
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<tbody>
<tr>
<td><strong>Lenalidomide (consolid\textsuperscript{n})</strong></td>
<td>BCR (Syk) Fostamatinib</td>
<td>CD20 Ofatumomab</td>
</tr>
<tr>
<td>Bortezomib (ABC type)</td>
<td>mTOR Temsirolimus</td>
<td>GA101 (vs Ritux)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>NF-κβ Bortezomib</td>
<td>Y\textsuperscript{90} Zevalin (consolid\textsuperscript{n})</td>
</tr>
<tr>
<td></td>
<td>BCL-2 Obatoclax</td>
<td>CD22 Epratuzumab</td>
</tr>
<tr>
<td></td>
<td>ABT-199</td>
<td>+ Calicheamicin</td>
</tr>
<tr>
<td>HDAC</td>
<td>Vorinostat</td>
<td>+ Y\textsuperscript{90}</td>
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<tr>
<td></td>
<td>Panabinostat</td>
<td>CD40 Dacetuzumab</td>
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<tr>
<td>Romidepsin</td>
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<td>CD79b + MMAE</td>
</tr>
<tr>
<td>Btk</td>
<td>Ibrutinib (+R-CHOP)</td>
<td>CD22 + MMAE</td>
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<tr>
<td>PI3K</td>
<td>Idelalisib</td>
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</tbody>
</table>
• THE END
Prognostic Value of FDG-PET after Salvage and Prior to SCT in DLBCL (n=129)

A. Progression free survival
- deauville 1-3
- deauville 4

B. Overall survival
- deauville 1-3
- deauville 4

P<0.001

Sauter CS et al. Blood 2015; 126:257982
Univariate analysis of MYC-IG for OS. (A) The global population, (B) SH, and (C) DH subgroups of DLBCL patients compared with MYC-non-IG and MYC-negative DLBCL patients.
Univariate analysis of MYC-R for OS. (A) The global population, (B) SH, and (C) DH subgroups of DLBCL patients.

Christiane Copie-Bergman et al. Blood 2015;126:2466-2474
OS & PFS after R-CHOP in DLBCL patients carrying gene breaks in MYC, BCL2, or both

Green T M et al. JCO 2012;30:3460-3467
OS & PFS after R-CHOP in DLBCL patients carrying gene breaks in MYC, BCL2, or both

A. Overall Survival (proportion)
   - MYC n=21
   - MYC-break positive
   - MYC-break negative
   - Time (months)
   - $P = .009$

B. Overall Survival (proportion)
   - BCL2 n=47
   - BCL2-break positive
   - BCL2-break negative
   - Time (months)
   - $P = .159$

C. Overall Survival (proportion)
   - DH n=11
   - DHL
   - Non-DHL
   - Time (months)
   - $P = .002$

D. Progression-Free Survival (proportion)
   - DH n=11
   - DHL
   - Non-DHL
   - Time (months)
   - $P = .012$

Green TM et al. JCO 2012;30:3460-3467
Outcomes in DLBCL patients treated with R-CHOP a/c to groups defined by *IHC* for *MYC* (≥ 40%) and *BCL2* (≥ 50%)

What interventions may overcome the adverse effects of *MYC* or *BCL2*?

David W. Scott et al. JCO 2015; 33:
DA-EPOCH-R in MYC-Rearranged Aggressive B-Cell Lymphoma: PFS and OS

1. Too early: wait 24 m for all patients
2. Single centre! → Need multicentre study!

Median follow-up: 14 mos

Prognostic value of $MYC, BCL2, BCL6$ by FISH & IHC in DLBCL ≤ 60 aalPI 2-3 in Mega-CHOEP study

- German DSHNHL: $n=112 \leq 60$ yrs aalPI =2,3 treated with either R-CHOEP14 or MegaCHOEP on study
- FISH and IHC* for $BCL2, BCL6, MYC$ and IHC for COO
- *Concurrent $MYC \geq 30\% + BCL2 > 60\%$ (= IHC DH)

Horn H et al Leukemia 2015
Mark Hertzberg 2016
Prognostic value of MYC, BCL2, BCL6 by FISH & IHC in DLBCL ≤ 60 aalPI 2-3 in Mega-CHOEP study

BCL2 FISH

B

EFS

PFS

OS

Proportion

BCL2 break negative (n=88) p=0.003

BCL2 break positive (n=23)

BCL2 break negative (n=88) p=0.008

BCL2 break positive (n=23)

BCL2 break negative (n=88) p=0.005

BCL2 break positive (n=23)

MYC FISH

C

EFS

PFS

OS

Proportion

MYC break negative (n=89) p=0.955

MYC break positive (n=14)

MYC break negative (n=89) p=0.589

MYC break positive (n=14)

MYC break negative (n=89) p=0.082

MYC break positive (n=14)
Cox Regression adjusted for aalPI & treatment

<table>
<thead>
<tr>
<th>Single parameter*</th>
<th>EFS HR (95% CI)</th>
<th>PFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCL2 break +</td>
<td>3.0 (1.5-6.0)</td>
<td>3.2 (1.5-6.9)</td>
<td>4.7 (1.8-12.2)</td>
</tr>
<tr>
<td></td>
<td>0.002</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
<td>MYC break +</td>
<td>0.9 (0.3-2.7)</td>
<td>1.3 (0.4-3.8)</td>
<td>2.4 (0.8-7.5)</td>
</tr>
<tr>
<td></td>
<td>0.922</td>
<td>0.634</td>
<td>0.119</td>
</tr>
<tr>
<td>BCL2 IHC (60-100%)</td>
<td>2.2 (0.9-5.5)</td>
<td>2.8 (1.0-8.2)</td>
<td>1.3 (0.4-4.0)</td>
</tr>
<tr>
<td></td>
<td>0.075</td>
<td>0.060</td>
<td>0.690</td>
</tr>
<tr>
<td>MYC IHC (30-100%)</td>
<td>1.5 (0.8-3.0)</td>
<td>1.9 (0.9-4.1)</td>
<td>2.4 (0.9-6.5)</td>
</tr>
<tr>
<td></td>
<td>0.215</td>
<td>0.091</td>
<td>0.086</td>
</tr>
<tr>
<td>CD10 IHC (1-100%)</td>
<td>1.5 (0.8-2.9)</td>
<td>2.0 (1.0-4.2)</td>
<td>2.8 (1.1-7.3)</td>
</tr>
<tr>
<td></td>
<td>0.231</td>
<td>0.065</td>
<td>0.034</td>
</tr>
<tr>
<td>LMO2 IHC (30-100%)</td>
<td>0.4 (0.2-0.8)</td>
<td>0.5 (0.2-1.0)</td>
<td>0.7 (0.2-1.9)</td>
</tr>
<tr>
<td></td>
<td>0.010</td>
<td>0.063</td>
<td>0.449</td>
</tr>
<tr>
<td>Morphology**</td>
<td>1.5 (0.8-2.9)</td>
<td>2.4 (1.2-5.1)</td>
<td>1.6 (0.7-3.6)</td>
</tr>
<tr>
<td></td>
<td>0.209</td>
<td>0.017</td>
<td>0.275</td>
</tr>
</tbody>
</table>

Multivariate model (n=80)*

| BCL2 break +      | 2.5 (1.1-5.9)  | 3.0 (1.2-7.4)  | 4.5 (1.6-12.9) |
|                   | 0.030          | 0.018          | 0.005          |
| Morphology**      | 1.7 (0.8-3.7)  | 3.7 (1.4-10.1) | 2.8 (0.9-8.8)  |
|                   | 0.194          | 0.011          | 0.078          |

*Horn H et al Leukemig 2015
Prognostic value of *MYC, BCL2, BCL6* by FISH & IHC in DLBCL ≤ 60 aalPI 2-3 in Mega-CHOEP study

- Unlike in older patients, *BCL-2* rearrangement is a novel prognostic marker in young high risk DLBCL
- All COO classifiers by IHC failed to predict survival time
- The negative impact of *MYC* rearrangement was confirmed
- In contrast to other studies, mostly involving older patients, single or combined *MYC* and *BCL2* expression patterns showed much weaker association with clinical risk
- Some more intensive regimens (R-CHOEP-14) may abrogate the impact of combined over-expression of *MYC* and *BCL-2*
Validation of a Prognostic Model to Assess the Risk of CNS Disease in Patients with Aggressive B-Cell Lymphoma (BCCA)

- N=1597 patients with DLBCL and received at least 1 cycle of R-CHOP. The median follow-up for living patients = 4.2 years.

- Using the 6 factor model, identified very similar risk groups:
  - 2 yr CNS relapse risk:
    - Low (0-1 factors) = 0.8% (95% CI 0.0-1.6%)
    - Intermediate (2-3 factors) = 3.9% (95% CI 2.3-5.5%)
    - High (4-6 factors) = 12% (95% CI 7.9-16.1%)

- Median time to CNS relapse = 6.7 m from diagnosis (vs 7.2 mo in the DSHNHL) ie typically occurs early in the disease course.
Validation of a Prognostic Model to Assess the Risk of CNS Disease in Patients with Aggressive B-Cell Lymphoma (BCCA)

IT MTX: Overall survival is equivalent for those +/- it MTX

→ and no difference in CNS relapse risk for those with BM, testicular or craniofacial involvement

Figure 1

Savage K et al. ASH 2014 394A
Interim PET
Problem 1: Method of PET evaluation

Visual assessment at cycle#2

SUV-based assessment

92 DLBCL patients
PET after cycle 2

At optimal cut-off of $65.7\%$ SUV_{BW,max}
reduction from baseline to mid-Rx -->
↑accuracy of PET with reduction of
14/17 false positives

Deauville 5-point scale

- 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

Meignan M. Leukemia & Lymphoma. 2009; 50(8): 1257-1260
**PETAL Trial Design**

- **Baseline PET**
- **2 x R-CHOP**

**Key inclusion criteria**
- Aggressive B- or T-NHL (except cerebral, Burkitt and lymphoblastic lymphomas)
- Age 18 – 80 years
- ECOG 0 – 3
- Baseline PET positive

**Interim PET**

- Reduction of SUVmax by at least two thirds

**Part A**
- **A1**
  - 4 x R-CHOP

**Part B**
- **B1**
  - 6 x R-CHOP
- **B2**
  - 6 x Burkitt Protocol

**Part A**
- **A2**
  - 4 x R-CHOP + 2 x R

Mark Hertzberg 2016
PETAL Trial

Favorable (part A) versus unfavorable interim PET (part B)

Time to Treatment Failure

- iPET Favorable
- iPET Unfavorable

Overall Survival

- iPET Favorable
- iPET Unfavorable

- n=853; iPET was favorable in 746 (87%) and unfavorable in 107 (13%)
- iPET highly predictive: 2-yr TTF 79% v 47%; HR=3.4, CI 2.6–4.6 p<0.0001
- On multivariate: iPET response, IPI, and B vs. T cell predicted TTF
- Interim PET was also predictive of OS (HR 3.9, CI 2.7 – 5.7, p<0.00001)
“PETAL” Study of Interim PET

- Although treatment related deaths (3 vs. 2 pts.) were comparable in both treatment arms, the Burkitt protocol was associated with more grade 3/4 leukopenia (84 % vs. 67 %, p=0.043), thrombocytopenia (63 % vs. 35 %, p=0.007) and mucositis (41 % vs. 12 %, p=0.002).

HENCE:

- iPET proved highly predictive of outcome in pts. with aggressive lymphomas in a large multicenter trial
- Because switching to a more aggressive protocol failed to improve outcome, there is no support as yet to change cytotoxic regimens in poor iPET responders

Duehrsen U et al ASH 2014 391a
DLBCL and Interim PET/CT

- FDG-PET/CT performed after 2-4 cycles of R-chemotherapy is predictive of DLBCL outcome.
- However, methodological variation had led to wide variations in negative and positive predictive values.
- Interim PET after cycle 4 of R-chemotherapy has a higher positive predictive value than after 2-cycles.
- A high PPV is desirable for selection of patients for treatment intensification.
NHL21 Consort Diagram

Enrolled = 162

Excluded = 11
did not fulfill I/E criteria

Eligible = 151

Failed to reach iPET = 8
- PD = 1
- Toxicity n=7
  - bowel perforation=2,
  - hepatic failure =1,
  - cardiac=2,
  - dose-delay=2

iPET status = 143

PET-neg = 101

Completed R-CHOP = 96
- PD = 3; Toxicity = 1; rituximab omitted=1

PET-pos = 42

Completed R-ICE/HDT = 32
- PD = 6; 2nd cancer = 1; Consent withdrawn = 3

<table>
<thead>
<tr>
<th>IFRT</th>
<th>iPET-</th>
<th>iPET+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5/101 (5%)</td>
<td>10/42 (24%)</td>
</tr>
</tbody>
</table>
### Adverse Events

<table>
<thead>
<tr>
<th>≥ Gd 3 AEs: R-CHOP/R-ICE</th>
<th>iPET- (n=101)</th>
<th>iPET+ (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>30%</td>
<td>45%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>11%</td>
<td>48%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7%</td>
<td>50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Zevalin-BEAM (n=32)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to ANC &gt; 1.0 x 10^9/L</td>
<td>y days (a-b)</td>
</tr>
<tr>
<td>Days to platelets &gt; 50 x 10^9/L</td>
<td>x days (c-d)</td>
</tr>
<tr>
<td>Death</td>
<td>2.4%*</td>
</tr>
</tbody>
</table>

*One patient died d+33 ASCT from hypoxic respiratory failure + viral pneumonitis*
IPI 3-5: PFS and OS are equivalent

**PFS:**

iPET- vs iPET+

**OS:**

iPET- vs iPET+

\[ P = 0.79 \]

\[ P = 0.98 \]
iPET-
MTV-0 < 550 cm³ vs MTV-0 ≥ 550 cm³

PFS
MTV < 550 cm³
MTV ≥ 550 cm³

OS
MTV < 550 cm³
MTV ≥ 550 cm³

Number at risk n = 98
MTV-0 < 550  49
MTV-0 ≥ 550  49

log-rank p < 0.001
log-rank p = 0.002
iPET+
Score 4 vs. 5 on 5-PS
R-MegaCHOEP Study: aaIPI=2

OS ACCORDING TO TREATMENT ARM

3-yo OS

- R-CHOEP-14 = 91.0%
- R-MegaCHOEP = 77.1%

p=0.013
R-MegaCHOEP Study: aaIPI=3

OS ACCORDING TO TREATMENT ARM

3-yr OS

R-CHOEP-14 = 68.1%

R-CHOEP-14 (n=35)
R-MegaCHOEP (n=35)

p=0.753
3. **Bulky disease (≥ 7.5 cm)** in RICOVER-60 (n=117) (6 vs 8 CHOP-14 ± R) and RICOVER-no RT (n=47)

- **EFS**
- **PFS**
- **OS**

*Held G et al. JCO 2014;32:1112-1118*
1. Germany vs Italy: 3-yr OS
R-CHOEP-14 vs R-CHOP-14

Log-rank test p=0.4228

At risk:
R-CHOEP 130
R-CHOP 100
R-CHOP: Reduction of LVEF

![Box plot showing ejection fraction (%) before and after CHOP therapy.](image)

- 6xCHOP pre
- 6xCHOP post
- 8xCHOP pre
- 8xCHOP post

*p < 0.01

Courtesy of Michael Pfreundschuh 2012