Roadmap for European Hematology Research and Hodgkin Lymphoma

Andreas Engert, MD

Chairman, German Hodgkin Study Group
University Hospital of Cologne
Roadmap for Hematology and Hodgkin Lymphoma: Overview

- **Background**
- The Research Roadmap
- Hodgkin Lymphoma 1\textsuperscript{st} line
- Relapsed HL
- Summary
• Total of 28 member states

• Variety of rules and regulations

• Different handling of EU directives between countries

• Fragmented clinical and preclinical research
# Directive 2001/20 EG
SUSAR-reporting, duties of the sponsor

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</table>
Roadmap for Hematology and Hodgkin Lymphoma: Overview

• Background

• The Research Roadmap

• Hodgkin Lymphoma 1st line

• Relapsed HL

• Summary
EHA Research Roadmap for Hematology in Europe

- A consensus document covering both, basic and clinical research in European hematology
- Describes state of the art in European hematology
- Major goal is to identify future research needs for hematological disorders in Europe
- Should be used for EU grant applications
<table>
<thead>
<tr>
<th>Topic</th>
<th>Authors</th>
</tr>
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<tbody>
<tr>
<td>1. Normal haematopoiesis</td>
<td>T. Jaffredo, J. Schuringa</td>
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<tr>
<td>2. Malignant lymphoid diseases</td>
<td>G. Salles, B. Coiffier</td>
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<tr>
<td>3. Malignant myeloid diseases</td>
<td>H. Döhner</td>
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<tr>
<td>4. Anemias and related diseases</td>
<td>A. Iolascon</td>
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<td>5. Platelet disorders</td>
<td>C. Balduini</td>
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<tr>
<td>6. Coagulation &amp; hemostatic disorders</td>
<td>S. Eichinger</td>
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<tr>
<td>7. Transfusion medicine</td>
<td>A. Brand</td>
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<tr>
<td>8. Infections in hematology</td>
<td>C. Cordonnier</td>
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<tr>
<td>9. Hem. SCT &amp; cell-based therapy</td>
<td>W. Fibbe</td>
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</tbody>
</table>
Total of 9 sections (disease groups)

11 section editors

Sections divided into 60 subsections (diseases)

275 subsection editors and authors
Composition of authors

Must: Clinician, basic researcher
Desirable: Pediatrician, patient representative
Optional: Radiation oncologist
Possible: Representative from industry
Hematologic diseases cost the economies of the European countries approx €23 billion in 2012

Of the total cost:

- 68% spent on healthcare
- 7% informal care costs
- 11% due to early mortality
- 14% due to absence from work or early retirement

Costs in Germany (€4bn), Italy (€3bn), the UK (€3bn), and France (€3bn) represented nearly 60% of total costs

Luengo-Fernandez, Burns, Leal. HERC, University of Oxford, UK
Cost of Blood disorders
Costs per Capita - Healthcare

Disorders of the blood healthcare costs per 10 in the population

Luengo-Fernandez, Burns, Leal. HERC, University of Oxford, UK
Cost of Blood disorders
Malignant – Non malignant

Blood Cancers (C81-C96; D47) €12 Billion/year

Diseases of the Blood and Blood Forming Organs (D50-D89) €11 Billion/year
## Cost comparison

### Different Cancers in Europe

<table>
<thead>
<tr>
<th>Types of Cancer</th>
<th>% of total cancer healthcare costs</th>
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<tbody>
<tr>
<td>Breast Cancer</td>
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<tr>
<td>Malignant hematologic disorders</td>
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<tr>
<td>Colorectal Cancer</td>
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<tr>
<td>Prostate Cancer</td>
<td>11</td>
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<tr>
<td>Lung Cancer</td>
<td>8</td>
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Luengo-Fernandez, Burns, Leal. HERC, University of Oxford, UK
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Hodgkin Lymphoma
Cumulative relative Survival (Sweden)

Sjöberg et al, Blood 2012
Hodgkin Lymphoma
Late side effects after treatment

- 2nd NPL
  - AML
  - NHL
  - NHL Solid tumours

- Organ damage
  - Lung
  - Heart
  - Thyroid

- Others
  - Fertility
  - OPSI
  - Fatigue
  - Psycho-social

NPL, neoplasias; AML, acute myeloid leukemia; NHL, non-Hodgkin lymphoma; OPSI, overwhelming post-splenectomy infection
Hodgkin Lymphoma
Evolution of Radiotherapy

Mantle field

Involved Field

Involved Node

Courtesy R v.d. Maazen
### GHSG Risk Allocation for HL

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>IA, IB, IIA</th>
<th>IIB</th>
<th>IIIA, IIIB</th>
<th>IVA, IVB</th>
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<tr>
<td>None</td>
<td>Early favorable</td>
<td></td>
<td></td>
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<tr>
<td>≥ 3 LK- Areas</td>
<td>Early unfavorable</td>
<td></td>
<td>Advanced</td>
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<tr>
<td>Elevated ESR</td>
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<tr>
<td>Large Med Mass</td>
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<tr>
<td>Extranodal disease</td>
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Stage IA NLPHL in GHSG trials
FFTTF according to treatment

- **EF-RT (n=45):** 72 months (89%)
- **CMT (n=41):** 70 months (93%)
- **IF-RT (n=45):** 19 months (96%)

Log-Rank: p=0.7048

Nogova et al, A Oncol 2006
GHSG HD7 trial
For early favorable HL (FFTF)

Arm A, EFRT 65.8% [59.5% - 72.0%]
Arm B, ABVD+EFRT 86.2% [81.7% - 90.7%]
Arm difference 20.4% [12.7% - 28.1%]

Engert et al, JCO 2007
CS I/II without risk factors*

- 4 x ABVD
  - 30 Gy IF
- 4 x ABVD
  - 20 Gy IF
- 2 x ABVD
  - 30 Gy IF
- 2 x ABVD
  - 20 Gy IF

*Large mediastinal mass; extranodal disease; high ERS; 3 or more areas involved
Engert A et al, NEJM 2010

GHSG HD10 Trial
Weakest vs strongest arm (FFTF)

At 5 years:
4xABVD + 30Gy IFRT: 92.8%
2xABVD + 20Gy IFRT: 91.2%
Difference -1.6%; 95% CI [-6.3%; 3.1%]
GHSG HD11 Trial (early unfavorable)

FFT.F – all four arms

Arm B (4xABVD+20 Gy)

p = 0.052

Eich et al, JCO 2010
HD14 Trial (GHSG)
Early unfavorable HL (PFS)

N=1528 pts

von Tresckow et al, JCO 2012
UK NCRI RAPID Trial
Early and intermediate stage HL patients

B Per-Protocol Analysis

Progression-free Survival (%)

Rate ratio, 2.36 (95% CI, 1.13–4.95)
P = 0.02

Months since Randomization

No. at Risk
Radiotherapy 183 180 172 161 130 99 58 33 13 2 0
No further treatment 209 202 194 165 139 97 56 18 6 0 0

Overall Survival (%)

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

Months since Randomization

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

Radford J et al, NEJM 2015
GHSG HD15 trial
Advanced stage HL

CS IIB with RF a or 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
Follow-up

Yes

PET -

PET +

30 Gy RX on res. disease; Follow-up

Risk factors:
a) Large mediastinal mass
b) Extranodal disease
HD15-PET
Impact on Response and PET Status (TTP)

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

Engert A et al, Lancet 2012
GHSG HD18 trial for advanced stages

2 x BEACOPP escalated (esc)

PET +
- 6xBEACOPPesc
- 6xR-BEACOPPesc

PET -
- 6xBEACOPPesc
- 2xBEACOPPesc

After chemo: PET; RX to PET+ res nodes >2.5 cm
PET-: Follow up
HD18: PET-2 negative HL patients
Overall Survival

Overall Survival rate

3-year estimate 5-year estimate
8/6x eBEACOPP: 95.9% [94.1-97.7] 95.4% [93.4-97.3]
4x eBEACOPP: 98.7% [97.6-99.7] 97.6% [96.0-99.2]
Difference: +2.7 [+0.6-+4.8] +2.2% [-0.3+4.7]

Hazard Ratio 0.36 [0.17 to 0.76], log-rank test p=0.006
Median observation time 56 months

Pts. at risk

504 476 438 363 298 207
501 479 459 370 292 227

Borchmann et al, Lancet 2017
HD18 for advanced stage HL
Deauville Score: 3-Jahres PFS (%)

Pts. at risk
216
270
236
196
240
203
169
206
180
113
133
107
60
84
63

Deauville 1-2
Deauville 3
Deauville 4

Time [months]
HD21: GHSG Perspective
BV in advanced stage HL

2 x BEACOPP esc

2 x BrECADD

Centrally reviewed PET

4x BEACOPP esc

4x BrECADD

End of therapy and residual nodes > 2.5 cm:

PET positive: Rx
PET negative: Follow up

HL, Hodgkin Lymphoma; GHSG, German Hodgkin Study Group; BV, brentuximab vedotin; BEACOPPesc, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BrECADD, brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; PET, positron emission tomography; RX, radiotherapy
ECHELON-1: Randomized phase 3 A+AVD vs ABVD in newly diagnosed advanced cHL

- Inclusion criteria
  - cHL stage III or IV
  - ECOG PS 0, 1 or 2
  - Age ≥ 18 years
  - Measurable disease
  - Adequate liver and renal function

- Screening CT/PET scan
- 1:1 randomization (N=1334)
- ABVD x 6 cycles (n=670)
- A+AVD x 6 cycles (n=664)
  - Brentuximab vedotin: 1.2 mg/kg IV infusion
  - Days 1 & 15
- EOT CT/PET scan
- Follow-up
  - Every 3 months for 36 months, then every 6 months until study closure

End-of-Cycle-2 PET scan
- Deauville 5; could receive alternate therapy per physician’s choice (not a modified PFS event)

218 study sites in 21 countries worldwide

cHL, classic Hodgkin lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end-of-treatment; PFS, progression-free survival
ECHELON-1: Phase III Trial
BV + AVD vs. ABVD in Frontline Advanced cHL

Log-rank test p-value: 0.035
Hazard ratio (95% CI): 0.770 (0.603, 0.982)
Number of events: A+AVD, 117; ABVD, 146

Number of patients at risk:
A+AVD 664 640 623 606 544 530 516 496 474 447 350 334 311 200 187 174 99 85 77 27 24 21 6 4 4 0 0
ABVD 670 644 626 613 522 496 476 459 439 415 328 308 294 179 168 153 78 68 62 16 13 12 1 1 1 0 0
### Side Effects

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<th>Side Effects</th>
<th>A+AVD (%)</th>
<th>ABVD (%)</th>
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<tr>
<td>Neutropenia (%)</td>
<td>58</td>
<td>45</td>
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<td>Infections Grade ≥3 (%)</td>
<td>18</td>
<td>10</td>
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<tr>
<td>Peripheral Neuropathy (PN: all) (%)</td>
<td>67</td>
<td>43</td>
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<td>Peripheral Neuropathy (PN), Grade ≥3 (%)</td>
<td>11</td>
<td>2</td>
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<td>Lungtoxicity, Grade ≥3</td>
<td>&lt;1</td>
<td>3</td>
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<td>Neutropenia associated deaths (no G-CSF Prophylaxis)</td>
<td>7</td>
<td>9</td>
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<tr>
<td>Lungtoxicity associated deaths</td>
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HDR2 Study for relapsed HL
PFS by treatment arm (final analysis)

Time, months

Probability

Standard (at 3y: 72%)

Intensified (at 3y: 67%)

$P = 0.505$

HL, Hodgkin lymphoma; PFS, progression free survival

Relapse After Auto-TX
OS by time to relapse after TX (n=756)

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<th>TTR</th>
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<td>&gt;12 m</td>
<td>172</td>
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<td>6-12 m</td>
<td>165</td>
<td>2.4</td>
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<tr>
<td>4-6 m</td>
<td>204</td>
<td>1.5</td>
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<tr>
<td>0-3 m</td>
<td>215</td>
<td>0.7</td>
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p <0.001

auto-TX, autologous stem cell transplant; OS, overall survival; TTR, time to relapse

Arai et al, Leuk & Lymphoma 2013:54:2531-33
• Genomic profiling and target identification
  – Antibodies and ADCs in malignant lymphoma
  – Anti-complement moabs in PNH
  – TKIs in CML and others

• Cellular therapy
  - Stem cells, NK cells, T-cells
  - Chimeric antigen receptors (CARs)
  - Bispecific antibodies (BITE)
  - Immune checkpoint inhibitors
Immunohistology of cHL
CD30 staining

Courtesy Harald Stein
**Mechanism of action**

**Brentuximab vedotin (SGN-35) ADC**

1. **ADC binds to CD30**
2. **ADC-CD30 complex traffics to lysosome**
3. **MMAE is released**
4. **MMAE disrupts Microtubule network**
5. **G2/M cell cycle arrest**
6. **Apoptosis**

**Brentuximab vedotin** (SGN-35) is an ADC that binds to CD30, traffic to lysosome, release MMAE (monomethyl auristatin E, a potent antitubulin agent), and disrupts microtubule network, leading to G2/M cell cycle arrest and apoptosis.
Phase II Pivotal Study of BV
Patients with R/R HL post ASCT

Maximum tumor reduction per IRF

Tumour Size (% Change from Baseline)

0
-50
-100

100
50

Tumour size (% change from baseline)

Best clinical response per IRF

- CR
- PR
- SD
- PD

Individual patients (n=98)

Reused with permission. ©2012 Journal of Clinical Oncology. American Society of Clinical Oncology. All rights reserved.
PD1 Inhibition in classical HL
Mechanism of action

- Patients with cHL show high frequency of 9p24.1 alterations and overexpression of PD-L1 and PD-L2\(^1\)

- Nivolumab is a fully human immunoglobulin G4 monoclonal antibody targeting the programmed death-1 (PD-1) receptor immune checkpoint pathway

---

**Nivolumab blocks signaling through the PD-1 receptor**

\(cHL = \text{classical Hodgkin lymphoma}; \ MHC = \text{major histocompatibility complex}; \ \text{NFkB} = \text{nuclear factor kappa B}; \ PD-L1/2 = \text{programmed death ligand 1/2}; \ \text{PI3K} = \text{phosphoinositide-3–kinase}; \ \text{Shp-2} = \text{Src homology region 2-containing protein tyrosine phosphatase 2}. \)

95% of evaluable patients showed a reduction in tumor burden. The best reduction from baseline in target lesion (%) for different cohorts is shown in the graph. Asterisks (*) denote responders.

Best reduction from baseline in target lesion (%)

- BV naïve (Cohort A)
- BV after auto-HSCT (Cohort B)
- BV before and/or after auto-HSCT (Cohort C)

Engert et al, EHA 2017
Phase 2 CheckMate 205
PFS by Best Overall Response

Median (95% CI) PFS for overall patients (N = 243) was 15 (11, 19) months

Engert et al, EHA 2017
Patient M.M.; 39y
Diagnosed 2011 (5 prior therapies)
Randomized GHSG Phase II Pilot
PD1 Inhibition in 1st-line early unfavorable HL (ongoing)

Arm A:
- AVD Cycle 1
  - AVD D1
  - PD1 D1
- AVD Cycle 2
  - AVD D1
  - PD1 D1
- AVD Cycle 3
  - AVD D1
  - PD1 D1
- AVD Cycle 4
  - AVD D1
  - PD1 D1

Restaging 1
- PD: biopsy + off-study

Restaging 2
- 30Gy IS-RT

Arm B:
- PD1: biopsy + off-study

AVD: Adriamycin, Vinblastin, Dacarbazine
PD1: Nivolumab (anti-PD1 moab)
# Immunomodifiers in Lymphoma Selection

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<tr>
<th>Antibody</th>
<th>Target</th>
<th>Company</th>
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<tr>
<td>Nivolumab</td>
<td>PD1</td>
<td>BMS</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD1</td>
<td>MSD</td>
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<tr>
<td>REGN2810</td>
<td>PD1</td>
<td>Regeneron</td>
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<td>Durvalumab</td>
<td>PD-L1</td>
<td>Celgene</td>
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<td>Avelumab</td>
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<td>Pfizer</td>
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<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>BMS</td>
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EHA Research Roadmap for hematology in Europe describes state of the art of blood disorders and identifies research gaps.

Involved 300 authors and many other contributors.

HL is one of the best curable cancers; CMT in early stages: 2xABVD +20Gy; „2+2“ or 4xABVD+30Gy.

Advanced stages: HD18 showed that only 4 cycles of B.esc needed in PET- pts (3y FFTF 94.8%; OS 98.7%).

ECHELON-1: 2-year modified PFS 82.1% for BV+AVD vs. 77.2% for ABVD (HR 0.77, p-value 0.035).

HDCT and ASCT in r/r HL.

Future trials including BV and anti-PD1 Moabs will increasingly replace chemo- and radiotherapy in HL.
GHSG
Countries participating in current trials
German Hodgkin Study Group
Coordination Center and Boards

Chairman:
A. Engert

Co-Chairman:
P. Borchmann

Honorary Chairman:
V. Diehl

Pathology:
M.L. Hansmann, P. Möller

Radiotherapy:
S. Marnitz-Schulze, H.T. Eich

Nuclear Medicine:
M. Dietlein, C. Kobe

Physicians:

Head Trial Coordination Center:
M. Fuchs

Trial physicians:
S. Borchmann, R. Scheuvens

Data Management:
D. Armbrust, B. Koch, H. Ossadnik, B. van den Hoonaard

Project /Quality Management:
S. Kebekus, D. Redweik, D. Siury

Database / IT:
D. Böhmer, T. Schober, P. Zerhusen

Statistics:
H. Görgen, H. Müller, A. Plütschow

Assistant /Secretary:
K. Rust, M. Schumacher, K. Tittmann
ISHL 11
October 27–29, 2018
www.hodgkinsymposium.org
PD1 Inhibition, klinische Studien
Hohe Effektivität beim Hodgkin Lymphom

East of England Cancer Network: A 10-Year Analysis of Patients Treated with ABVD or BEACOPPesc