10th Edition Lymphoma WP Educational Event - Treatment of Malignant Lymphoma

Diffuse large B cell lymphoma.

Lessons to be learned from molecular analysis

Christian Gisselbrecht MD Paris Saint Louis

16 - 17 October 2014, Nicosia, Cyprus
Heterogeneity in DLBCL

• Detection of oncogenic pathways-related biomarkers by immunohistochemistry on FFPE

• Cell of origin - prognostic groups using gene expression in FFPE (NanoString)

• GEP selection of groups for NGS technology
  Recognition of specific oncogenic pathways

• Cell of origin – prognostic groups by immunohistochemistry

• Cell of origin - prognostic groups application of GEP to human lymphomas

• Characterization by immunohistochemistry on FFPE of MUM1 in normal and malignant lymphoid cells

• Cloning of MUM1/IRF4gene

• Characterization by immunohistochemistry on FFPE of BCL6 in normal and malignant lymphoid cells

• Cloning of BCL6 gene

• Modern histologic classifications

Antonino Carbone & Annunziata Gloghini & Yok-Lam Kwong & Anas Younes
DIFFUSE LARGE B-CELL LYMPHOMA: SUBGROUPS AND SUBTYPE/ENTITIES
WHO classification 2008

- Diffuse large B-cell lymphoma, not otherwise specified (NOS)
  - Common morphologic variants
    - Centroblastic
    - Immunoblastic
    - Anaplastic
  - Rare morphologic variants
  - Molecular subgroups
    - Germinal centre B-cell-like (GCB)
    - Activated B-cell-like (ABC)
  - Immunohistochemical subgroups
    - CD5-positive DLBCL
    - GCB
    - Non germinal centre B-cell-like (non-GCB)
- Diffuse large-B-cell-lymphoma subtypes
  - T-cell/histiocyte-rich large B-cell lymphoma
  - Primary DLBCL of the CNS
  - Primary cutaneous DLBCL, leg type
  - EBV positive DLBCL of the elderly

- Other lymphomas of large B cells
  - Primary mediastinal (thymic) large B-cell lymphoma
  - Intravascular large B-cell lymphoma
  - DLBCL associated with chronic inflammation
  - Lymphomatoid granulomatosis
  - ALK-positive LBCL
  - Plasmablastic lymphoma
  - Large B-cell lymphoma arising in HHV8-associated multicentric Castelman disease
  - Primary effusion lymphoma

- Bordeline cases
  - B-cell lymphoma, unclassifiable, intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
  - B-cell lymphoma, unclassifiable, intermediate between diffuse large B-cell lymphoma and classical Hodgkin’s lymphoma

Should we use the same treatment?
Diagnosis and outcome of DLBCL subtypes by GEP. (A) Heat map showing differential expression of genes in GCB, ABC, and PMBL DLBCL subtypes.

Wilson W H Hematology 2013;2013:584-590
Gene-Expression Predictors of Survival among Patients with Diffuse Large-B-Cell Lymphoma Treated with R-CHOP

Independent from IPI

The Hans Classifier
A surrogate for GEP?

Hans et al., Blood 2003
The Hans algorythm: controversies in the CHOP and R-CHOP era

Immunohistochemical Prognostic Markers in Diffuse Large B-Cell Lymphoma: Validation of Tissue Microarray As a Prerequisite for Broad Clinical Applications—A Study From the Lunenburg Lymphoma Biomarker Consortium

Daphne de Jong, Andreas Rosenwald, Mukesh Chhanabhai, Philippe Gaulard, Wolfram Klapper, Abigail Lee, Birgitta Sander, Christoph Thorns, Elias Campo, Thea Kullas, Sandra Horning, Andrew Lister, John Raemaekers, Peter Witzig, Takeshi Shipp, and The Lymphoma Study Group

Conclusion
This study shows that semiquantitative immunohistochemical scoring is feasible and reproducible, but exhibits varying reproducibility. These findings may explain the wide variation of biomarker prognostic impact reported in the literature. Harmonization of techniques and centralized consensus review appears mandatory when using immunohistochemical biomarkers for treatment stratification.


A challenge for the pathologist

New technologies are coming on Formalin fixed paraffin embedded (FFPE) material: improvement in reproductibility

<table>
<thead>
<tr>
<th></th>
<th>NanoString GEP assay – NCI</th>
<th>Hans algorithm</th>
<th>Tally algorithm</th>
<th>Choi algorithm</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>GCB</td>
<td>U</td>
<td>ABC</td>
<td>GCB</td>
</tr>
<tr>
<td>Frozen GEP</td>
<td>GCB</td>
<td>28</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>U</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>ABC</td>
<td>1</td>
<td>3</td>
<td>25</td>
</tr>
</tbody>
</table>

119 well-characterized DLBCL cases from the LLMPP, previously subtyped by our published disease-defining algorithm using frozen-GEP, were used to develop a highly accurate and robust NanoString 20 gene assay, applicable to RNA from FFPET that is routinely obtained for diagnosis. This new assay shows excellent performance in archival FFPET, and the rapid turn-around time (<36 hours from FFPET block to result) will allow prospective implementation in future therapeutic trials and, ultimately, clinical practice.
Abstract 84 Accurate Classification Of GCB/ABC and MYC/BCL2 Diffuse Large B-Cell Lymphoma With a 14 Genes Expression Signature and a Simple and Robust RT-MLPA Assay:

Philippe Ruminy, PhD, Herve Tilly, and Fabrice Jardin, MD, PhD et al
Centre Henri Becquerel, Rouen, France

10 genes expression signature incorporated into Reverse Transcriptase Mutiplex Ligation-dependent Probe Amplification assay RT-MLPA
50 cases: 46 classified as expected, 3 unclassified. Validation on 185 DLBCL.RNA extraction from FFPE
Rapid method: 40 samples in parallel less than 24h
Cheap 5 dollars each can be achieved with FFPE.
Do we have a different treatment effect on a subtype?

<table>
<thead>
<tr>
<th>Author</th>
<th>Therapy</th>
<th>Better than R-CHOP?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham</td>
<td>R-CHOP-14</td>
<td>No</td>
</tr>
<tr>
<td>ASCO 2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delarue</td>
<td>R-CHOP-14</td>
<td>No</td>
</tr>
<tr>
<td>Lugano 2011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfreundshuh</td>
<td>R-CHOEP</td>
<td>No</td>
</tr>
<tr>
<td>Lancet Oncology 2011</td>
<td></td>
<td>Subgroup young good risk</td>
</tr>
<tr>
<td>Gang</td>
<td>R-CHOEP</td>
<td>Yes</td>
</tr>
<tr>
<td>Ann Oncol 2011</td>
<td></td>
<td>Retrospective young high risk</td>
</tr>
<tr>
<td>Recher</td>
<td>R-ACVBP</td>
<td>Yes</td>
</tr>
<tr>
<td>Lancet 2011</td>
<td></td>
<td>Age &lt;60 y, IPI 1</td>
</tr>
<tr>
<td>Wilson</td>
<td>DA-EPOCH-R</td>
<td>?</td>
</tr>
<tr>
<td>J Clin Oncol 2008</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The 3-year PFS was 87% in the R-ACVB/P arm compared with 73% in the R-CHOP arm.

The 3-year OS was 92% in the R-ACVB/P arm compared with 84% in the R-CHOP arm.

Differential efficacy of treatment within molecular subtypes of DLBCL (LNH03-2B)

Hans score=GC

Hans score=n-GC

Molina et al ASH 2012
Background

Differential efficacy of treatment within molecular subtypes of DLBCL

First line treatment

R-CHOP

Relapse treatment

DA-EPOCH-B


D. Lenz et al. NEJM 2008
Bio CORAL Trial: RICE vs RDHAP
Strong interaction between RDHAP and GCB profile

Distribution of GCB profile (n=115, 49.5%)
and non GCB (n=117, 50.5%) with Hans algorithm:

## Major recurring genetic alterations in DLBCL

<table>
<thead>
<tr>
<th>Gene</th>
<th>frequency</th>
<th>Location</th>
<th>Mechanism of deregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCL6</td>
<td>35-40%</td>
<td>3q27</td>
<td>t(3;…. ) and SHM</td>
</tr>
<tr>
<td>BCL2</td>
<td>15% [t(14;18)]</td>
<td>18q21</td>
<td>t(14,18), amplification</td>
</tr>
<tr>
<td></td>
<td>25% (amplification)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cMYC</td>
<td>6-15%</td>
<td>8q24</td>
<td>t(8;14) or variants, SHM</td>
</tr>
<tr>
<td>P53</td>
<td>15-20%</td>
<td>17p</td>
<td>mutation, deletion</td>
</tr>
<tr>
<td>FAS</td>
<td>20%</td>
<td>10q24</td>
<td>mutations (DD), ?SHM</td>
</tr>
<tr>
<td>SHM</td>
<td>40-50%</td>
<td>IgV, Bcl6, FAS</td>
<td>SHM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bcl6, cMyc, Pax5,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RhoH/TTF, PIM1,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>?FAS</td>
<td></td>
</tr>
<tr>
<td>CARD11</td>
<td>&lt;10% (ABC)</td>
<td></td>
<td>mutation</td>
</tr>
</tbody>
</table>

Adapted from Abramson et al. Blood 2005
# Reported Molecular Prognostic Markers in DLBCL Patients Treated with R-CHOP

<table>
<thead>
<tr>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMO2</td>
<td>MYC</td>
</tr>
<tr>
<td>HIF-1α</td>
<td>CD5</td>
</tr>
<tr>
<td>P21</td>
<td>BCL2 (?)</td>
</tr>
<tr>
<td>CD30 (?)</td>
<td>Dim CD20</td>
</tr>
<tr>
<td>CD40</td>
<td>Mutated p53</td>
</tr>
<tr>
<td>Caspase 3a</td>
<td>STAT3</td>
</tr>
<tr>
<td>Beclin 1</td>
<td>Skp2</td>
</tr>
<tr>
<td>SOCS1 major (# 419)</td>
<td>High microvessel density</td>
</tr>
<tr>
<td></td>
<td>Indoleamine 2,3-dioxygenase</td>
</tr>
<tr>
<td></td>
<td>RCOR1 del (# 295)</td>
</tr>
<tr>
<td></td>
<td>CDKN2A/2B del (# 415)</td>
</tr>
<tr>
<td></td>
<td>SOCS1 minor (# 419)</td>
</tr>
</tbody>
</table>
Clinical IPI remains an independent factor when challenges with most biomarker

Limitations of Biomarker Studies

- Discrepant results
- Small retrospective patient cohorts
- Patient selection and treatment variability
- Lack of uniformity in methodology
- Failure to control for other biologic processes that may confound outcome
- Have not been validated in independent population treated with standard of care
## Significance of BCL2 Expression in DLBCL

<table>
<thead>
<tr>
<th>Author</th>
<th>Cut Off (%)</th>
<th>BCL2 Pos (%)</th>
<th>Prognostic Impact on OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrans</td>
<td>50</td>
<td>88</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood 2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colomo</td>
<td>25</td>
<td>59</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood 2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hans</td>
<td>30</td>
<td>50</td>
<td>No</td>
</tr>
<tr>
<td>Blood 2004</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>de Paepe</td>
<td>30</td>
<td>77</td>
<td>No</td>
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<tr>
<td>J Clin Oncol 2005</td>
<td></td>
<td></td>
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<tr>
<td>Imhoff</td>
<td>30</td>
<td>53</td>
<td>Yes</td>
</tr>
<tr>
<td>J Clin Oncol 2006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mounier</td>
<td>50</td>
<td>66</td>
<td>Yes (CHOP) No (R-CHOP)</td>
</tr>
<tr>
<td>Blood 2003</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BCL2 Expression and DLBCL Subtype

BCL2 expression associated with t(14;18):
- Not prognostic
- Prognostic

BCL2 expression associated with amplification and NFκB:
- CHOP
- Prognostic
- R-CHOP
- Not prognostic
Oncogenic mechanisms of MYC in aggressive mature B-cell lymphomas.

### Table 1. Aggressive lymphomas with MYC genetic and protein alterations

<table>
<thead>
<tr>
<th>MYC genetic alterations</th>
<th>MYC protein overexpression without evidence of genetic aberrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>BLBCL, BCLU, PBL</td>
</tr>
<tr>
<td>DLBCL</td>
<td>Transformed lymphoma (rare)</td>
</tr>
<tr>
<td>ALK-positive LBCL</td>
<td></td>
</tr>
</tbody>
</table>

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Ott G et al. Hematology 2013;2013:575-583
Impact of MYC and BCL2 Protein Expression in DLBCL treated with R-CHOP

- Recently available MYC antibody measures MYC protein expression by IHC
- MYC translocation seen in 11%, but MYC overexpression in 33%
- MYC translocation and MYC expression only prognostic if BCL2 overexpressed
Overall Survival of Patients with DLBCL According to MYC and BCL2 Translocation or MYC and BCL2 Protein Expression

5% double hit

20% “dual expressors”
Overall Survival According to Double-Hit Score and Cell of Origin and IPI Status

GCB

Non-GCB

Low IPI

High IPI

MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program

HU et al (Blood. 2013;121(20):4021-4031)
Prognostic impact of MYC/BCL2 coexpression in DLBCL is independent of MYC/BCL2 corearrangement and TP53 mutation status.

HU et al (Blood. 2013;121(20):4021-4031)
Comparison of long-term, progression-free, and overall survival.

Are we moving towards cell-of origin as a guide to therapy?

**Non GC-B type**
- NF-kB activated
- BCR signalling
- TLR/IRAK signalling
- Bortezomib
- Ibrutinib
- Fostamatinib
- Lenalidomide

**GC type**
- Epigenetic regulation mutant/lost
- EZH2,CREBBP
- ? EPOCH,DHAP
- GSK 126
- EPZ6438
Signaling pathways in malignant lymphoma.

Reeder C B, Ansell S M Blood 2011;117:1453-1462
Therapeutic Agents that may Selectively Benefit Molecular Subtypes

<table>
<thead>
<tr>
<th>Target</th>
<th>Example Agent</th>
<th>GCB</th>
<th>ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF-κB</td>
<td>bortezomib</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>PI3 Kinase</td>
<td>CAL-101</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>PKCβ</td>
<td>enzastaurin</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>BTK</td>
<td>ibrutinib</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Syk</td>
<td>fostamatinib</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Multi-target/angiogenesis</td>
<td>lenalidomide</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>EZH2</td>
<td>EZH2 inhibitor</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Bcl-2 family</td>
<td>ABT-263</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Headlines news! How to make a choice or to combine new treatments?

Cell signaling pathway small molecule inhibitors
- PI3K/AKT/mTOR inhibitors: GS-1101, perifosine, temsirolimus, everolimus
- BTK inhibitors: ibrutinib
- Syk inhibitors: Fostamatinib disodium

Inducers of apoptosis
- Bcl-2 family inhibitors: Oblimersen, novatisclax

Monoclonal antibodies
- Anti-CD20: ocrelizumab, ofatumumab, veltuzumab
- Non anti-CD20: epratuzumab, galiximab, mogamulizumab
- Bispecific abs: Blinatumomab

HDAC inhibitors
- Romidepsin
- Volutostat

Antibody-drug conjugates
- Brentuximab vedotin
- Inotuzumab ozogamicin

Novel chemotherapies
- Bortezomib
- Lenalidomide
- Pixantrone

Radioimmunotherapy
- ^131I-lositumomab
- ^90Y-ibritumomab
Issues/questions for targeted therapy (DLBCL)

• What is on the market now or will be soon in (low grade) lymphoma? restrict my talk to

• Exploratory studies:
  • Several phase 2 completed with new agents: alone or in combination sign of limited activity, hypothesis generating and enthusiasm.

• Confirmatory studies:
  • Several phase 3 completed with new targeted agents: none positive. Time consuming and depressing
NFkB signalling pathway is constitutively activated in ABC DLBCL

- ABC DLBCL are **less curable**
- More than 50% ABC DLBCL carry mutations in positive or negative regulators of NFkB (*Compagno et al. Nature 2009*)
- anti-apoptotic effect and can inhibit chemotherapy

- A20 (TNFAIP3): 24%
- CARD11: 11%
- RANK: 8%
- TRAF5: 5%
- TRAF2: 3%
- MAP3K7 (TAK1): 5%

*Adapted from Küppers et al. 2009*
Survival curves in diffuse large B-cell lymphoma. (A) Progression-free survival (PFS) curve and PFS stratification based on International Prognostic Index (IPI; C) and subtype (E). (B) Overall survival (OS) curve and OS stratification based on IPI (D) and subtype (F).

Bortezomib Plus CHOP-Rituximab for Previously Untreated Diffuse Large B-Cell Lymphoma and Mantle Cell Lymphoma

DLBCL: 35 pts
ORR 100%
PYRAMID study design

DLBCL diagnosis & subtyping

Non-GCB

Hans method

GCB

Not enrolled

R

Vc-R-CHOP
- Bortezomib 1.3 mg/m², d 1, 4
- Rituximab 375 mg/m², d 1
- Cyclophosphamide 750 mg/m², d 1
- Doxorubicin 50 mg/m², d 1
- Vincristine 1.4 mg/m², d 1
- Prednisone 100 mg/d, d 1–5
- Six treatment cycles q21 days

R-CHOP
- Rituximab 375 mg/m², d 1
- Cyclophosphamide 750 mg/m², d 1
- Doxorubicin 50 mg/m², d 1
- Vincristine 1.4 mg/m², d 1
- Prednisone 100 mg/d, d 1–5
- Six treatment cycles q21 days

Follow up every 3 months for 2 yrs
Microenvironment & DLBCL: expression of lymph node signature predicts outcome in R-CHOP DLBCL patients

Extracellular Matrix, histiocytes

Angiogenesis - Vessel density

Antiangiogenic agents?

Lenz et al, NEJM 2008
Kaplan-Meier analysis of (A) PFS and (B) OS by treatment arm.
MAIN study: avastin in combination with R-CHOP

787 pts enrolled
R-CHOP = RA-CHOP
But RA-CHOP more toxic: increased cardiac events

Kaplan-Meier curves of progression-free survival in patients stratified by (A) International Prognostic Index risk and (B) cell-of-origin profiles GCB=germinal centre B-cell-like..

(U. Vitolo et al., Lancet Oncology, 15:730-737, 2014)

- LRCHOP21 in elderly untreated DLBCL
- lenalidomide 15 mg from day 1 to day 14
- 49 patients: At a median follow-up of 28 months,
  - 2-year PFS was 71% (95% CI: 40-88) in GCB-group
  - 2-years PFS was 81% (95% CI: 51-93) in non-GCB-group
Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-cell lymphoma: A phase II study

(Nowakowski, GS. et al, JCO 2014, in press)
Senior

**DLBCL**
- ≥ 80 years old
- ECOG: 0-2
- LVEF > 50%
- Creatinin clearance (MDRD) ≥ 40 ml/min

**DLBCL Evaluation - Randomization**
- Stratification on:
  - CD10 expression: Positive/Negative
  - age: <80 to ≥80 years old

**6-RminiCHOP (3 weeks cycles):**
- Pre-phase: D-7 to D-4
- R-miniCHOP (IV) R-miniCHOP (SC) R-miniCHOP (SC) R-miniCHOP (SC) R-miniCHOP (SC) R-miniCHOP (SC)

**Follow-up phase:**
- every 3 months the first two years then every 6 months

**6-R2miniCHOP (3 weeks cycles):**
- Pre-phase: D-7 to D-4
- Lenalidomide 10 mg
- Aspirin 100 mg or LWMH

**Evaluation → Follow-up phase**
- 65% ABC 21% non-ABC
- 35% 79%
REMARC study design

**Induction**

- At diagnosis
- R-CHOP x 8/6
- SD, PD study withdrawal

**Maintenance**

- CR/PR
- Until 3 months after D1 of last R-CHOP

**Randomization**

- ARM 1: Lenalidomide 25mg/day (cl creat 30-60=10) 3 weeks every 4 weeks over 24 months
- ARM 2: Placebo Daily for 3 weeks every 4 weeks over 24 months

**Registration**
BCR and MYD88 signaling pathways and potential targets.

Wilson W H Hematology 2013;2013:584-590
Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naive patients with CD20-positive B-cell non-Hodgkin lymphoma: a non-randomised, phase 1b study.

The combination of ibrutinib and R-CHOP has an acceptable safety profile in treatment-naïve patients with NHL, with no new toxicities noted.

The expanded 560 mg ibrutinib + R-CHOP cohort is ongoing to further explore safety and efficacy of the combination in patients with newly diagnosed DLBCL.

Randomized phase III trial of R-CHOP +/- ibrutinib in de novo non GCB DLBCL: PHOENIX NCRN 607
Maintenance treatment: PRELUDE

Michael Crump, et al  ASH 2013 Abst.371

IPI 3-5 ≥18y. N=758

(enzastaurin, n=504)

(placebo, n=254)

High risk DLBCL patients in remission after R-CHOP

Arm A
Oral Enzastaurin
500 mg/ day
(1125-mg loading dose/Day 1)

Arm B
Placebo
daily, oral dose
/loading dose/day)

Treatment continued for 3 years or until disease progression

Primary Endpoint: Disease-free survival
Secondary Endpoints: Overall survival, Safety, pharmacokinetic & Biomarker assessment

- DFS at 24 and 48 months were 79% and 70% for the enzastaurin arm, and 75% and 71% for placebo, respectively.
conclusion

Several new agents have already been eliminated in randomized studies. Need for significant activity as single agent? >30% ORR or Role of « preclinical models »?

Combination of new agents: strong rational with blockade of different pathways. Drugs not yet approved. Competition between drugs

No clear choice but two agents are nowadays fashionable for non GCB:
Ibrutinib, lenalidomide

What to do with refractory GCB? And double hit lymphoma

from physical/morphological description and empiric therapies to molecular characterization and rational targeted therapies
Acknowledgments
All investigators and pathologists

- All patients
- All contributing EBMT centres
- EBMT LWP
  - Peter Dreger
  - Chara Kyriakou
  - Herve Finel
  - Anna Sureda
  - Harry Schouten
EFKARISTO POLI