**16th International Lunenburg Lymphoma Biomarkers Consortium**
**Stanford University**
**April 6th – 7th 2018**

**Presence:** Delphine, Eva Kimby, David Scott, Eva Hoster, Laurie Sehn, Gilles Salles, Ton Hagenbeek (chair), Marie Jose Kersten (minutes), Ranjana Advani, John Raemaekers, Maria Calaminici, Wendy Stevens, Daphne de Jong, Birgitta Sander, Yaso Natkunam, Andreas Rosenwald

Absent with notification:

Welcome – Beverly Mitchell

Welcome – George Sledge

Welcome – Ranjana, Yaso

LLBC Chair – Ton Hagenbeek
Silent minute to honor Michael Pfreunschuh

**Andreas, Delphine, Laurie: DLBCL MYC study**
- see presentation for details
- huge amount of work (clinical databases, queries, statistical analysis by Delphine and her team)
- there is now a clean dataset and genetic dataset
- introduction to the literature
Important starting point:
1. which aggressive B-NHL are we studying: within the WHO 2016 we studied DLBCL (DLBCL –NOS and HGBL-DH). So DH/TH lymphomas should have DLBCL morphology. So not aggressive lymphomas with high grade morphology (eg Burkitt-like). German, Stanford, UK, Vancouver, French and Dutch cases do not contain Burkitt-Burkitt like cases since they were excluded either upfront or after revision (German cases).
- MYC translocation: in the literature 10% of DLBCL cases (high grade B 50%)
2. DH/TH: MYC tl + BCL2 and/or BCL6 (MYC is required)
3. Double expressors – MYC and BCL2 IHC (different cutoffs are used 40 and 50%). Not a separate entity in the WHO2016

- clinical implications of MYC rearrangements: usually inferior clinical outcome
- DH/TH lymphomas: reports in the literature often contain both DLBCL morphology and BCLU/high grade morphology. BCLU/HG inferior outcome compared to DLBCL morphology. However, these studies are biased (DLBCL only FISH in case of eg high Ki67)

- clinical significance of MYC single vs DH/TH: conflicting data, often low number of cases

- clinical
dual expressors do worse (30% of DLBCL, 50% of ABC)

Swsques & Johnson, Blood 2017: different cutoff, different percentages of cases called positive

Genetic vs protein double hit: do they have the same clinical significance?
More DE than DH cases. DE less inferior prognosis than DH?

Does the MYC translocation partner matter? Copie-Bergman Blood 2015
MYC-Ig significantly worse than MYC-non-Ig; MYC-non-Ig actually not worse than non-MYC

HGBL-DH/TH with DLBCL morphology: a GCB phenomenon (Scott Blood 2018)
MYC SH actually occur both in GCB and ABC; DH MYC/BCL2 and TH almost exclusively in GCB, DH MYC/BCL6 again in both GCB and ABC

**What can LLBC contribute: compare PFS/OS for:**
- DLBCL with and without MYC tl
- MYC-Ig (Igh, kappa, lambda) vs MYC-non-G
- MYC- vs MYC SH vs DH/TH
- double expressors vs the rest: how important/robust are the data? Some hesitation on the usefullness of this approach. OS/PFS curves can be produced with different cutoffs (10% increments).

A large NCI study is actually going forward lumping DE/DH together RCHOP/DA-EPOCH-R +/- venetoclax (Leonard/Abramson)

Technical
- everybody used the same Vysis probes
- Ig vs non-Ig: same fusion probes were used (kappa, lambda mostly done by Reiner Siebert in Ulm)

Delphine

5636 cases, 4459 registry, rest trials
5117 patients evaluable: clinical data available. For 2678 cases no MYC tl data are available, for 2166 (MYC-) +273 (MYC+) data available on MYC tl
Ig vs non-Ig n=203
DTH vs SH: n=220
DH BCL2: n=220
DH BCL6: n=220
TH n= 220

**Survival curves**
- per site/clinical trial vs registry/population based/single institution
- pts in clinical trials do better (cave: lead time bias, comorbidities, too sick to go an a trial, no high risk clinical trials in our cohort)
- no EFS/DSS data available
Should all be discussed.

**Methods:**

- description, selection of pts with MYC results.
- KM and log0rank
- adjusted Cox models: MYC, IPI, COO, stratification on type of data (cohort vs trial)
- diagnoses of proportional hazard
- interaction MYC variables and adjustment

MYC selection for cases for which translocation data are available
- 38% in cohort available vs 74% in trial
- cohort more needle biopsies --> less translocation analysis done? In the cohort data patients with translocation analysis done do better

MYC translocation data available: 12% MYC+ n=222, MYC- n=1694
- MYC+ higher IPI, stage, ECOG, extranodal, LDH
- older patients have higher % of MYC+?
- MYC+ predicts inferior OS/PFS
- MYC+ cases: if relapsing, early relapse (<12/24 months), difficult to salvage?
- mortality hazard is time dependent: large diference in the first 2 years, after that there is no excess mortality (already published) --> time dependent hazard ratio with a cutoff of 24 months.
With a time dependent HR: HR 2.4, after 2 yr no effect. With a classical proportional HR you would find a smaller effect
Trial patients have less chance of dying early if MYC+ than cohort patients.

Characteristics of dead MYC translocated patients: huge differences between the 78 pts who die within 24 months vs the pts who die after 24 months (stage, ECOG, IPI, etc
NB different strategies between the groups: eg Stanford has excluded cases with DLBLC and low grade lymphoma in the bone marrow, other groups have not.

MYC+ predicts inferior OS and PFS both in trials and in cohorts. HR non adjusted 1.661, time dependent 2.217 (<24 mo), 0.863 (>24 mo)
IPI high also remains prognostic (HR 2.397 for OS and 2.204 for PFS). From a methodological point of view it might be better to look at the different IPI variables in stead of dichotomized IPI high/not high.
MYC predicts inferior OS in high stage, but not low stage patients
MYC predicts inferio OS in both GCB and nonGCB

MYC Ig vs non-IG: data available for 165 cases: n= 92 Ig, n=73 non Ig
MYC Ig is a strong negative predictor of OS/PFS (MYC negative vs MYC-Ig). Ig vs non-I only significant for OS, not PFS

Cox adjusted:
MYC-Ig before 24 mo HR 2.672 vs 1.02 after 24 mo

What is the biological significance of Ig vs non-Ig? Ig-MYC universally higher expression of MYC. Non-Ig: some have no MYC-expression at all, some have also high expression level. This is sometimes a technical issue (polymorphism leads to no binding of the antibody). Also whether or not the lymphomas are DH/TH will be important. Non-Ig SH may not be prognostically important.
Conclusion:

**ACTION POINT:** study the MYC-Ig and non-Ig cases more in detail (look at MYC expression levels in these cases at the protein level and at the mRNA level; use a different MYC antibody; look at mutations, location of breakpoint in MYC).
- Go back to the material and retrieve the MYC+ cases – is material still available (Delphine and Andreas will identify the cases and forward a list to the 7 contributing groups)?
- depending on the number of cases for which material is still available decide on whether or not to pursue this additional study

Subgroups IPI: MYC Ig is a negative predictor of OS/PFS in IPI high patients and in high stage patients

MYC SH vs DTH
- clincial variables: SH patients are older but have lower IPI and lower LDH
- OS SH between negative and DTH. However in cohort more close to MYC negative and in trial more close to DTH?
- cohort vs trial (104 vs 72 pts): different results, also different proportions of SH vs DH/TH
- MYC DTH is a negative predictor of OS/PFS in IPI high and in high stage pts
- no difference between MYC/BCL2 DH and MYC/BCL6 DH in OS/PFS.
- adjusted HR for MYC dhBCL6 is 0.917 vs MYC dhBCL2

Conclusions/summary
- MYC tl status is a strong predictor of negative OS/PFS in DLBCL
- MYC/BCL2 and MYC/BCL6 DH and TH are strong predictors of negative OS/PFS
- no difference in OS/PFS between MYC/BCL2 and MYC/BCL6
- MYC SH different effect in trial vs cohort?
- MYC nonIg: moderate effect --> large nr of patients needed to reach adequate power
- to do: look at SH MYC-Ig vs non-Ig in the non-DH/TH patients?

Can we make any recommendations for clinical practice?
There are huge differences in testing in daily practice

Forest plot – multivariate models --> add to the report

**Still to be done for the main paper:**
- SH vs DH
- Ig vs non Ig in relation to MYC expression
- what to do with the TH (26 cases): describe separately and lump together with DH. One problem of lumping together is the fact that all the TH are GCB and eg MYC/BCL6 are non-GCB
- try to dissect PFS (progression or death as an event) and OS

**Next projects:**
- explore other cutoffs for MYC and BCL2 IHC (e.g. 20% and 70%)
- look at NCCN IPI?
- look at true primary refractory patients (progress under therapy/within 6 months) --> do NGS (exome sequencing) in those patients. Use a control group? Or use existing data from the literature

- are any data available on salvage? Delphine will check
- Ig vs non Ig in relation to MYC mRNA and protein level
- analysis of mutations in MYC

**Publication strategy:**
- submit abstract for ASH
- one paper with the FISH data and IHC (with some data on different cutoffs 40/50%): aim for JCO (2nd option Blood)
- additional paper Ig/non-Ig icw MYC expression levels (protein, mRNA) and different antibodies

**Philippe Gaulard, Daphne de Jong: T-NHL**

- which population: nodal PTCL.
- research question:
- biologic prognostic markers: less is already known, so it will be more discovery than validation
- molecular classification
Clinical unmet need
- heterogeneous
- 1/3 primary refractory, 1/3 relapse (very poor survival), 1/3 long term survivor

which biomarkers
- environment signature in AITL Iqbal
- DUSP22 rearr in ALK neg ALCL
- DDX3X mut in NK/T cell lymphoma

diagnostic issues not fully resolved
- PTCL-NOS
- AITL vs PTCL-NOS vs PTCL-TFH
- ALK neg ALCL vs PTCL-NOS

Large series: ITCL project, COMPLETE (Hsi), Lymphopath (Laurent JCO 2017)

ALCL (Gaulard Blood 2016, Pederson Blood 2017)

Issues we could address
- diagnostic – epidemiology PTCL, NOS vs PTCL THF
- heterogeneity of ALK neg ALCL, prognostic relevance of genetic subgroups (DUSP22)
- hterogeneityof te PTCL NOS category
- specific small entities, bi-ALCL< MEITC

Possibilities for TPCL:
- single center cohorts
- limited clinical trials (ACT1/2, ATT, ECHELON-2)
- large registries ITCL, Leeds, COMPLETE, LYSA/TENOMIC, T cell lymphoma project (Federico, 1602 cases registered, a part with tissue material (500 cases?))
- population based: Netherlands, Leeds, Sweden

which biomarkers & tools:
- morphology, IHC
- RT-MLPA --> may be a robust method for classification
- nanostring
- NGS panel or RNA seq/exome sequencing (600-1000 per sample)

Clinical questions:
Do an end of spectrum approach
- long term survivors (>5 yr) vs refractory and/or relapse < 1 year

Variation in treatment: CHOP, CHOEP, autologous SCT in first line

Go to defined subtypes
- AITL
- nodal PTCL vs TFH
- ALKneg ALCL

2 step approach

Action 1
Action 2

1 page outline proposal

France
Leeds
NL (Palga, NKR+)
Stanford
Federico
Germany (study patients?)
Barts

**Hodgkin lymphoma (Yaso, Ranjana)**
- based on availability of cases it does not seem feasible to do a HL project within LLBC.
Multifactorial:
- for clinical trials often no pathology specimens were collected
- for trials that have collected material this is already committed