needs to be defined, and this technology is still not fully incorporated into the routine work-up of our patients.
In summary, molecular analyses have become technically feasible in virtually all patients with haematological neoplasms. They may help to define "molecular entities" as a starting point to find new more specific therapies. They often provide prognostic information which although easily publishable, has limited practical importance as such (a personal statement that will predictably yield some controversy from the audience). Predictive markers useful to select individualised treatment are welcome, but still not applicable in the majority of cases seen in our clinics. To refer to the title, molecular biologists are encouraged to continue to improve our understanding of the "gene pathology" of these cancers, but should seek links with clinicians, who in turn need to speak their language for an improved mutual understanding.

## 8
## Acute myeloid leukemia

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The treatment of acute myeloid leukemia (AML) in spite of a steady progress is still associated with considerable failure rates. This applies to patients with AML of any age. The majority of patients with AML are 60 years of age or older, in whom treatment disease outcome has remained most unsatisfactory. When treated with chemotherapy, this age group has an estimated survival of approximately 10–20% at 5 years. There has been an intense interest in the introduction of new modalities and exploring new ways of using conventional approaches. In this respect particularly the use of high-dose daunorubicin chemotherapy in patients with AML has raised recent interest.
From a biologic and clinical viewpoint acute myeloid leukemia is an extraordinarily heterogeneous disease. The molecular heterogeneity of the leukemia is the key determinant of treatment failure. Today, cytogenetics are commonly used in clinical practice for the assessment of individual prognosis. The recently postulated monosomal karyotype appears to provide better predictability of adverse outcome than the classical complex karyotype. Modern high-throughput approaches provide powerful tools for the discovery genetic biomarkers and the evaluation of their clinical relevance. Numerous, widely diverse genetic abnormalities (gene mutations, expression abnormalities) have been discovered. Examples of clinically relevant gene aberrations involve CEBP-alpha, RAS, nucleophosmin-1, FLT-3, WT1, EVI-1, MN-1, ERG, TET-2, IDH1 but there are many more to come.
The remarkable genomic heterogeneity is a reflection of the underlying somatic genetic abnormalities in transformed hematopoietic stem cells that as successive events over years accumulate in the neoplastic clone of a patient's leukemia during the evolution of the disease. As these genetic changes perturb diverse cellular pathways and functions, they often confer a profound impact upon the clinical phenotype of the disease at presentation and treatment response. Knowledge about the somatic mutations and genetic alterations driving these phenotypic variations in the leukemia will establish novel defined diagnostic subtypes of AML with diverse prognosis (diagnosis). The identification of biomarkers with prognostic significance using genome-wide approaches and large numbers of well defined cohorts will construct an informative background for risk adapted treatment decisions according disease risk (prognosis and treatment choice). For instance, allogeneic hematopoietic stem cell transplantation (alloSCT) furnishes the most effective antileukemic postremission modality available today but the advantage in terms of antileukemic activity has to be cautiously balanced against the increased risk of death and morbidity that is typically connected with alloSCT. The increasing insight into the remarkably diverse genetics of AML provides a backgound for a decision algorithm of alloSCT in AML according the estimated individual relapse risks of patients with AML. Finally, these insights will most likely furnish leads to potential therapeutic targets for drug development (treatment). Thus therapeutic and diagnostic developments emerging at the interface of laboratory and clinical research create a perspective of personalized therapeutics in AML.

## 9
## Chronic lymphocytic leukaemia

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Rapid progress has been achieved recently in the management of chronic lymphocytic leukemia (CLL). New insights into the molecular pathology of CLL have generated a plethora of biological markers that predict the prognosis and influence therapeutic decisions. Moreover, fludarabine, bendamustine, and two monoclonal antibodies, alemtuzumab and rituximab, have been approved by European and/or American regulatory agencies. Additional monoclonal antibodies targeting CD20, CD23, CD37, CD38 or CD40, as well as drugs designed to interfere with proteins regulating the cell cycle, the apoptotic machinery, or the leukemic microenvironment (e.g. flavopiridol, oblimersen, ABT-263, or lenalidomide) are currently tested in clinical trials. An increased experience with reduced-intensity allogeneic progenitor cell transplantation allows offering this option to physically fit patients. In my presentation, I will review and summarize the current use of these different modalities in CLL therapy.

## 10
## Myeloproliferative neoplasms Ph- negative

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Polycythemia Vera (PV), Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF) are included in the group of classical Ph-negative Myeloproliferative Neoplasms (MPNs) Understanding of the pathophysiology of these disorders dramatically improved following the description, in the last five years, of recurrent molecular abnormalities represented by: (1) the V617F mutation in *JAK2* exon 14, that is the most frequent and involves >95% of PV and ~60–70% of ET patients; (2) a number of molecular alterations located in *JAK2* exon 12, that have been described in 50–80% of the *JAK2*-wild type PV patients; (3) mutations in *MPL*, mostly represented by the W515L or W515K allele, that are presented by ~7% of ET patients; (4) mutations of the TET2 (ten-eleven translocation (2) gene reported in 20% of MDS and MPN/MDS and 8–15% of MPNs. Genotyping for such molecular abnormalities has already become a standard tool in the diagnostic work-up of patients suspected to have a MPN and constitutes a major criterion for diagnosis, according to the new WHO classification of myeloid neoplasms. As a consequence of an early diagnosis, it is very likely that the frequency and clinical presentation of these disorders will change in the next future. Currently, there is no therapy able to eradicate the molecular hallmark leading to these malignant diseases. Thus, therapy is aimed at preventing the major clinical relevant complications such as thrombosis in PV and ET and to alleviate anemia and splenomegaly in PMF.
*Polycythemia Vera and Essential Thrombocythemia* Major causes of morbidity and mortality in polycythemia vera (PV) and essential thrombocythemia (ET) are represented by

thrombosis and bleeding, progression to myelofibrosis and transformation to acute leukemia. Myelosuppressive therapy, preferentially with hydroxyurea, can reduce the rate of vascular complications, but there is some concern about an increased rate of leukemic transformation with this agent. Therefore, management of these disorders poses a significant challenge, and a risk-oriented therapeutic approach should be followed to avoid inappropriate exposure to cytotoxic drugs on one side or suboptimal treatment on the other. Established risk factors for cardiovascular events are represented by older age and previous thrombosis, while impact of novel biological factors, including leukocytosis and JAK2V617F mutational status and/or mutational burden, is under active investigation. Low-risk PV patients should be managed only with phlebotomy and aspirin, while high-risk patients should also receive cytotoxic therapy. Regarding the management of ET, there is no clear indication for intervention in low-risk patients, while high-risk patients should be managed with chemotherapy. Other therapeutic options, such as interferon alpha or anagrelide, may find place in selected patients including those who are resistant/intolerant to hydroxyurea.

*Primary Myelofibrosis* PMF is a clonal disorder arising from an early stem cell and the stromal bone marrow reaction is due to fibrogenic and angiogenic cytokines derived from clonal megakaryocytes. Managing patients with myelofibrosis (MF) is a difficult task. Patients suffer from a variable, but severe range of disease manifestations including massive splenomegaly, cytopenias, significant constitutional symptoms, possible transformation to blast phase and premature death. Clinical trials with new nonspecific-targeted therapies have confirmed that their use in PMF is of modest clinical activity. Cure is achievable through allogeneic stem cell transplantation.

There is a great expectation for novel drugs targeting the constitutively active JAK2/STAT pathway. Over a dozen JAK2 inhibitors are in development, with some leading compounds showing promising early results particularly for control of disease associated splenomegaly and symptoms. Parallel trials with immunomodulatory therapy for MF associated anemia and stromal manifestations of the disease are continuing. The future may well see the approval of a range of agents for MPN patients, with differing mechanisms of action, efficacy and toxicity profiles.

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## Lymphomas and myeloma

### 11
### New biological determinants in lymphoma

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Prognostication for lymphoma patients has always been a challenge, given the heterogeneity of histology, clinical presentation, and underlying biological mechanisms driving the aggressiveness of the disease. They help to provide information towards the patient, to choose the optimal therapeutic approach, to compare clinical trials, and may also lead to identify patient's groups eligible for targeted therapies. From immunohistochemical markers to gene expression profile, a number of approaches have been developed in the last 20 years, providing new tools and indexes. Most of these biomarkers were rationally based on our improved understanding of lymphoid differentiation and malignant lymphoma biology. Few have however spread in clinical practice for multiple reasons, including their accessibility or their cost, their reproducibility and robustness, but also their lack of validation in large cohorts.

In order to gain a better knowledge of the power of IHC biomarkers to help prognosticate diffuse large B-cell (DLBCL) lymphoma patients, Lunenburg Lymphoma Biomarker Consortium (LLBC) evaluated a large international patients cohort in order to investigate a new clinicobiological prognostic index. Clinical data and pathological samples were retrieved from 12 clinical studies from Europe and North-America, with patients treated before (e-CHOP group) or after the rituximab era. Using tissue microarrays from 1514 of these 2451 patients, IHC for BCL2, BCL6, CD5, CD10, MUM1, Ki67 and HLA-DR was performed and scored according to previously validated protocols. Optimal cut points were then determined and the prognostic value for overall survival of individual markers, their interrelation and interaction with the International Prognostic Index (IPI) were assessed to investigate a combined index.

This presentation will include the description of objective cut-points identified, newly recognized correlations between