with a distinct clinical outcome, and may be predictive of refractoriness to most available drugs. For this subset of patients, a number of novel non-chemotherapeutic therapies have demonstrated an unprecedented efficacy with longer progression free survival in randomized trials. These new agents are all targeting signaling or prosurvival pathways that appear to be crucial for the onset and progression of CLL.

Decades of research have indeed proved the key role played by stimuli originating from the microenvironment, to fuel the expansion and accumulation of the neoplastic B lymphocytes. In particular, it is clear that CLL cells accumulate and expand in response to stimuli occurring through the B Cell Receptor (BCR), and indeed a number of specific inhibitors of key components downstream this receptor (including SYK, BTK and PI3K-delta) have now become targets exploited in ongoing clinical trials, opening the path for a novel class of therapeutic compounds in CLL, soon to be registered for clinical use.

Similarly, CLL cells are known to express high levels of antiapoptotic molecules including BCL2 that is now the target of another class of drug compounds showing impressive data in clinical trials leading to MRD negative remissions lone or when associated with anti-CD20 antibodies.

This is a very exciting and promising era for CLL treatment as a relevant number of novel therapeutics are now at reach, and it will be interesting in the near future to test how their combination could be helpful on the way to cure this yet incurable disease.

SP-024

CD19-SPECIFIC CHIMERIC ANTIGEN RECEPTOR-MODIFIED T CELLS FOR RELAPSED,REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

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Chimeric antigen receptors (CAR) are recombinant molecules that combine antigen recognition via an extracellular single chain antibody with intracellular signaling domains into a single protein and have been used mostly in T cells. At the University of Pennsylvania we have targeted CD19 in B cell malignancies since this molecule is exclusively expressed by B cells, and from very early to late differentiation stages of both normal and malignant B cells. We have treated 14 patients (12 men and 2 women; median age of 67 (range, 51–78); 4 prior therapies (range, 1–10); 6 patients with p53 mutations. All with active disease at time of infusion. Lymphodepleting chemotherapy was fludarabine/cyclophosphamide (3), pentostatin/cyclophosphamide (5), or bendamustine (6). Autologous T cells were collected via apheresis and transduced with a lentivirus carrying the CAR19 molecule and expanded using anti-CD3/CD28 beads. Patients enrolled in this trial had to have relapsed or have persistent disease after one (patients with p53 mutations) or at least two prior treatments and progressed at least within two years of their last treatment. After lymphodepleting chemotherapy patients received CTL019 cells on a split dose scheme: 10% on day 1, 30% on the next day, and 60% on day 3, unless patients developed fevers or other toxicities, which is when the doses were held. A median of 1.4×10^8(range, 0.14–5.9) CTL019 cells were infused over day 0, 1 and 2.

There were no infusional toxicities >grade 2 although 6 patients developed fevers within 24 hrs of infusion #1 (3) or #2 (3) and did not receive additional CTL019 cells. Median follow-up as of July 15, 2013 was 9.4 mo (4–35) for all patients and 16 mo (5–35) for the 8 responding patients. Three patients (21%) achieved a CR (follow-up 11, 34, and 35 mo), 5 (36%) achieved a PR (med follow up 11 mo, range 5–27 mo) and 6 (43%) had no response, for an overall major response rate of 57%. Two of 5 patients with a PR progressed 4 mo after infusion with CD19+ CLL, and no patient with a CR has relapsed.

Comparing responders to non-responders, there has been no association between response and patient age (66 vs 67 yrs), number of prior therapies (median 4 each), cell dose (7.5 vs 11.5×10^8 MNC), or p53 mutation (3/8 vs 3/6, $p>0.9$), implying that within the dose ranges studied, there is no obvious dose: response relationship.

All responding patients developed a delayed cytokine release syndrome (CRS), concurrent with peak T cell expansion, and was manifested by fever, and variable degrees of nausea, anorexia, myalgias, and transient hypotension and hypoxia. Detailed cytokine analysis showed marked increases from baseline values of IL-6, IFN-γ, and soluble IL-2 receptor, while no significant elevation in systemic levels of TNFα or IL-2 were observed. The CRS required intervention in 5 patients. Treatment was initiated for hemodynamic or respiratory instability and was rapidly reversed in all cases with corticosteroids in 1 patient and the IL6-receptor antagonist tocilizumab (4 patients); 3 of these 4 patients also received 1 or 2 doses of corticosteroids. Persistence of CTL019 cells has been detected by flow cytometry in all 6 patients with ongoing responses 5–35 months after infusion, and all patients have sustained B cell aplasia without any unusual infectious complications.

In conclusion we have demonstrated that CTL019 cells can undergo robust in-vivo expansion and persist for at least 3 years. CTL019 therapy is associated with a significant CRS that responds rapidly to anti-cytokine treatment. CTL019 cells can induce potent and sustained responses (8/14) for patients with advanced, relapsed and refractory CLL regardless of p53 mutation status.

SP-025

CML RESPONSE MONITORING IN 2014

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The advent of Tyrosine Kinase Inhibitors (TKIs) and progress in clinical outcome of Chronic Myeloid Leukemia (CML) has posed numerous questions regarding the choice of the TKI and more importantly, the response monitoring, the selection of appropriate TKI at an appropriate and specific time points. This has posed a dilemma of whether one TKI is better than the other if appropriate guidelines are followed strictly. Imatinib is effective for most of the CML patients who achieves a gold standard response of complete cytogenetic response (CCYR) and lately major molecular response (MMR). The important issues based on the current studies and follow up on randomized trials from IRIS as well as DASISION and ENEST indicate importance of earlier molecular response. Hence, selecting patients for early intermediate who do not have earlier molecular response ($\leq$10%) at 3 months may be appropriate as they tend to have a lower progression free survival (PFS). As there has been a dramatic decline in mortality in this targeted era, there are also emerging issues like resistance and tolerance to TKIs. The establishment of robust monitoring guidelines like NCCN or ELN has generated more clinical questions.

The presentation will focus on expanding role of molecular monitoring and its impact on clinical questions of sequencing and changing of TKIs in an integrated risk adapted approach.

SP-026

HOW I TREAT ESSENTIAL THROMBOCYTHEMIA

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Having contributed to the recommendations of the Czech Collaborative Group for Ph-Myeloproliferative Diseases (CZEMP) for diagnosis and treatment of *BCR/ABL*-negative myeloproliferative diseases (MPD), i.e. essential thrombocythemia (ET), polycythaemia vera (PV) and primary myelofibrosis (PMF) [1], I follow these recommendations also in treating patients with ET.

ET is a stable disease with a minimal risk (if any) of transition into myelofibrosis (the so-called post-ET myelofibrosis may be commonly a misdiagnosed PMF-0 from the beginning) or into secondary leukemia (the majority of these cases may result from genotoxic therapy). Thus, the major therapeutic goal is the prevent morbidity from complications, i.e. thrombosis, which may be invalidating, and bleeding, which is almost never life-threatening, and also to prevent some deleterious sequellae of the therapy itself (the principle of *non nocere*).

The rationale of formulation of the CZEMP treatment guidelines was an in-depth expert analysis (as vigorous evidence-based conclusions are still scarce) of the major risk factors of thrombosis. The Bergamo study [2]

identified age and previous thrombosis, later the *JAK2*^{V617F} mutation was shown to be thrombogenic [3] Even in our first version of the guidelines, we counted with the thrombophilic states, be it hereditable or acquired [4]. The ingenious metaanalysis of thrombotic and bleeding complications both being a function of the platelet count by J.J. Michiels *et al.* was a strong inspiration having many therapeutic implications [5]. We took into account that both antiaggregation and cytoreducing therapy may decrease the incidence of thrombotic events [6,7]. Finally, we counted with the fact that the cytostatic drugs may be genotoxic *in vitro* and *in vivo* – a growing body of evidence shows that even the relatively safe drug, such as hydroxyurea (HU), may be leukemogenic and carcinogenic in the long term [8–11].

The attitude to management of thrombocythemia in ET and other MPDs with thrombocythemia (MPD-T; i.e. the early stages of PMF and PV) according to CZEMP is identical [1] (but we admit it can differ in the near future). The patients are stratified by their thrombotic risk as described above. The prognostic impact of the majority of these risk factors have been now verified in analyses of the prospective Registry of anagrelide (ANG; Thromboreductin®)-treated patients in Czechia [12]. The majority of these risk factors (with the exception of the thrombophilic states) are taken into account by the recent IPSET risk criteria [13].

Only patients up to 65 years lacking the above mentioned risks with a platelet count $<1000\times10^9$/l are considered as low-risk and do not demand cytoreducing therapy. The others are high-risk ones and have an indication for thromboreduction. Although platelet counts at diagnosis are not regarded as a valid prothrombotic risk factor (based on the Italian studies [14]), the data from our Registry clearly show that platelet counts do matter: their median was much higher preceding the thrombotic events than at time points without any ensuing thrombosis (although we confirmed the inverse relationship of the platelet counts at diagnosis to thrombosis – this is most likely because patients with higher platelet counts receive more often cytoreducing therapy). This finding strongly point to the need of decreasing platelet counts to prevent thrombosis [12].

Only in patients older than 65 years, the potentially leukemogenic drug HU may be used in the long term to reduce the platelet counts. In the younger ones, the choice is between ANG and interferon-alpha (IFN). Although white blood cell (WBC) counts have not been included into the CZEMP risk stratification yet, it may be desirable to reduce them in case they are above normal (this implies using IFN in younger and HU in older individuals). However, elevated WBC is a more common finding in early PMF or PV rather than in ET. The treatment goal in high-risk patients is to maintain platelet counts below 400, and in low-risk ones (once thromboreducing therapy was started), below 600×10^9/l. Acetylsalicylic acid (ASA) is given to all patients with MPD-T with platelets $<1000\times10^9$/l (at higher counts, hemorrhage may be imminent, the risk being a function of the platelet count), unless a contraindication is present [1]. The only exception may be very young low-risk patients. In case of platelet count normalization, ASA may be withdrawn in cases of low-risk ET or PMF.

It should be clearly stated that the CZEMP (and the Central European Myeloproliferative Study Organization; CEMPO; not yet published) recommendations on one side differ largely from those proposed by other groups of experts, such as LeukemiaNet or the British guidelines [15,16]. The latter guidelines recommend HU as primary cytoreducing treatment for high risk patients (*nota bene*, even the risk stratification differs) without any age differentiation. In the CZEMP guidelines, HU cannot be recommended to younger patients on long-term as explained above.

The CZEMP strategy of MPD-T management transfers into low incidence of thrombotic complications, as emerges from the analyses from Registry of ANG-treated patients, first presented at ASH 2011 (the cohort comprised 839 patients) [12]. Currently, 1179 patients are registered. If we compare the incidence of thrombotic events in history (prior to Registry entry) and during follow-up on ANG ± ASA treatment (median: 39 months), we see that venous events were decreased 6.7-fold, arterial events 1.8-fold, microcirculatory events 1.7-fold, while the bleeding episodes (the vast majority being minor events) increased 2.0-fold. The incidence of thrombosis during follow-up was the following (events per 100 patient-years): all thrombotic events: 4.40, arterial events: 1.84, microcirculatory events: 1.03, and venous events: 0.63.

As ET is a stable disease, typically, treatment is continuous and seldom requires major changes (the more cautious we should be to follow the *non nocere* principle). In contrast, in early PMF patients, the cyto-/thromboreducing therapy has to decreased in the long term due to progressive bone marrow fibrotization.

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SP-027
HOW I TREAT PATIENTS WITH POLYCYTHEMIA VERA

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Polycythemia vera (PV) is characterized by symptoms such headache, visual disturbances, fatigue, vertigo, water induced itching (aquagenic pruritus) or erythromelalgia which can occur on a daily basis. Potentially life threatening complications are heart or brain infarction, deep vene thrombosis with pulmonary embolism or abdominal thromboses (e.g. Budd Chiari Syndrome). In some individuals also bleeding complications are observed.

Over time transformation into acute leukemia or myelofibrosis can occur. Hence, factors should be avoided which facilitate these transformations.

Treatment goals are two fold: to reduce the symptoms to improve quality of life and prevent thromboembolic complications to prolong life. Therapy is risk adapted meaning that other variables such as fitness, molecular thrombophilic risk factors, physical activity, nonsmoking or vascular conditions are integrated into the therapeutical strategy.

Gold standard is normalisation of the hematocrit. A recent prospective study separating PV patients in two groups (discrimination at 45%) underlines the importance of lowering the hematocrit in order to prevent thromboembolic complications. Additional intake of aspirin is advocated. Therapeutic options are phlebotomy (with the risk of causing symptoms of iron deficiency), hydroxyurea (with the risk of tumor and leukemia promotion) and interferon-alpha. In France, long term treatment with hydroxyurea (more than 10 years) has revealed a high transformation rate into leukemia. This has not been observed in patients from other countries which may be explained with genetic differences among individuals with different ethnic backgrounds.

Through the recent introduction of pegylated alpha-interferons into PV therapy the use of this agent has been increased due to its better tolerability than conventional interferon-alpha. For platelet lowering anagrelide is the treatment of choice.

More recently, JAK2 inhibitors are being investigated for their potential in PV: the completed response-trial has shown good efficacy and safety in comparison to best evaluable conventional therapy of ruxolitinib [2]. Moreover, the JAK1/JAK2 inhibitor momelotinib is currently under investigation.

A symptom often neglected by the physician but having a strong impact on quality of life of the PV patient is aquagenic pruritus. It can have various qualities, precede the diagnosis of PV by years and maybe difficult to treat [3].

All these issues are discussed in the presentation. Attendents are encouraged to bring their own case histories for discussion.

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SP-028
APPROACH IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA

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Despite the progress made in the first-line treatment of young and elderly patients with multiple myeloma (MM), disease relapse is the ultimate fate of the majority of patients. Before starting treatment, it is important to take some patient- and disease-related aspects into consideration. First of all, patients need to be screened at relapse for the presence of disease-related symptoms and signs (CRAB criteria). If there is only a biochemical relapse represented by an increase in, or a reappearance of, the M- protein in serum and/or urine without disease-related symptoms, a "watch and wait" policy with careful and frequent monitoring of the patient and the disease is justified. However, when there is a very rapid increase in M-spike and/or the emergence of myeloma-related symptoms or complications, treatment needs to be initiated. The therapeutic choice will depend on the previous treatment (response, response duration, side effects), patient-related factors, disease-related factors, and drug availability. If a previous treatment has resulted in a clinically meaningful response, or even more precisely in a response that averaged or superseded the median response duration, one can always consider to retreat with that particular regimen, on condition that there were no serious or irreversible toxicities. However, when the patient has not yet been exposed to the so call novel agents (thalidomide, lenalidomide, bortezomib), these drugs should be preferentially started. For patients already exposed to bortezomib and achieving a durable response, retreatment with a bortezomib-based regimen is to be considered. Similarly, a second autograft can be considered for patients with an initial response duration of at least 2 to 3 years after their first transplant, and who are still in good clinical condition. Of course, when a patient has not yet been exposed to lenalidomide, or in case of peripheral neuropathy, or insufficient response to bortezomib, lenalidomide plus dexamethasone can be considered as a regimen of choice. When later relapses occur, the disease will become more difficult to control and patients will more likely suffer from disease- or treatment-related complications. Therefore treatment of first relapse should aim for an optimal and durable response whilst maintaining quality of life of the patient.

Currently several "newer" drugs are becoming available for the treatment of relapsed myeloma patients. These include second generation proteasome inhibitors and the thalidomide-/lenalidomide analogue pomalidomide. Pomalidomide with weekly dexamethasone is currently registered in the EU for treatment of relapsed/refractory myeloma patients who are progressive on their last treatment, and who have received at least two treatment lines including bortezomib and lenalidomide. Second generation proteasome inhibitors like carfilzomib, ixazomib and oprozomib are in several phases of clinical development. Finally, monoclonal antibodies like daratumumab, elotuzumab, and other cell-cycle specific drugs will change the landscape of multiple myeloma treatment in the following years. The pivotal data of these compounds will be presented at the meeting.

SP-029
WHAT ARE THE NEW AGENTS IN THE MANAGEMENT OF PATIENTS WITH MULTIPLE MYELOMA?

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Although multiple myeloma is a rare disease and incurable it has been the envoy of researchers working on other disease with the plethora of agents being offered and developed to treat patients with this cancer. Great optimism is developing as many new agents attacking new pathways are explored.

Multiple myeloma is quite a heterogeneous disease and neoplastic plasma cells can use several metabolic pathways in order to take a growth advantage. In addition, several studies have shown that different neoplastic clones may emerge in different phases of disease and it is possible that each clone has a different profile of drug sensitivity. It is therefore possible that each of the drugs is effective only in a subgroup of patients and within this group only during a specific phase