738 What Is the Most Cost-Effective Strategy for Treating Newly Diagnosed Chronic Phase Chronic Myeloid Leukaemia (CML) after Imatinib Loses Patent Exclusivity?

https://ash.confex.com/ash/2014/webprogram/Paper71699.html

We analysed and compared the cost-effectiveness of 2 strategies for treating CML patients -- using imatinib first in all (altering therapy as needed in a stepwise approach) or by physician's choice, starting either imatinib or one of the approved second-generation tyrosine kinase inhibitors (TKIs) dasatinib or nilotinib. Currently, each TKI is patent-protected and commands about one-third of front-line CML treatment. Life-long treatment is recommended. Imatinib is losing patent exclusivity and facing generic competition presently in the US (in early 2016) and in EU member countries; its price is expected to drop 70-90% within two years following generic entry. …..

We conclude that when imatinib loses patent protection in 2016 in the US and its price declines, it will be the cost-effective initial treatment strategy for chronic phase CML compared to dasatinib and nilotinib. Our model and results demonstrate that system-level cost-effectiveness can be estimated based on country-specific (1) CML incidence and prevalence, (2) CML treatment patterns and associated costs across all medical inputs, including drugs, (3) expected date for loss of patent exclusivity, and (4) pricing policies for generic drugs and formulary placement decisions. Comparative cost-effectiveness data for the US, UK, and other selected EU countries will be presented.

1794 Updating Long-Term Outcome of Intermittent Imatinib (INTERIM) Treatment in Elderly Patients with Ph+-CML

https://ash.confex.com/ash/2014/webprogram/Paper67602.html

BACKGROUND: The INTERIM study (ClinicalTrials.gov NCT 00858806) showed that in elderly (> 65 years) Ph+ CML patients selected for a stable complete cytogenetic response (CCgR) lasting > 2 years, the policy of intermittent imatinib treatment (one month on/one month off) may affect the markers of residual disease (CCgR and major molecular response, MMR or $MR^{3.0}$), but not the clinical outcomes (overall survival and progression-free survival) *(Russo D et al, Blood 2013; 121(26):5138-44)*.

AIMS: To update the results of the INTERIM Study, with a follow up ≥ 5 years.

METHODS: After 4 years of follow up, patients continuing INTERIM treatment were monitored with peripheral blood RT-Q-PCR every 3 months according to the ELN-2013 guidelines.

RESULTS: At 48^{th}month, out of 76 patients enrolled in the INTERIM study, 13 (17%) had lost CCgR and MMR, 14 (18%) had lost MMR only and 50 patients (75%) continued INTERIM. The patients who had lost CCgR and/or MMR resumed imatinib continuously and all of them regained the CCgR and the MMR, within 3 to12 months. No patient progressed to accelerated or blastic phase, or developed clonal chromosomal abnormalities in Ph+ cells, or BCR-ABL mutations. No patient complained of new or more severe side effects during the months “on”.

After a follow up ≥ 5 years, 45/76 (59%) enrolled patients are on INTERIM, with a probability of maintaining intermittent administration of 59% (95% CI: 46-69). No patient lost the CCgR and only 9 additional patients lost the MMR while on intermittent treatment. All these patients

resumed continuous imatinib treatment and regained the MMR. Thus, at ≥ 5 years, the probability of maintaining CCgR is 80% (95% CI 68-87) and the probability of maintaining the MMR is 61% (95% CI: 48-71). From start of INTERIM, 6 patients died but no deaths were related to CML progression (3 cases of other non-haematological neoplasms, 1 stroke, 1 myocardial infarction, 1 chronic obstructive pulmonary disease).The PFS at ≥ 5 years is 94% (95% CI: 89-100)
CONCLUSIONS: In summary, with a follow up ≥ 5 years, intermittent imatinib administration (INTERIM) confirmed to be safe, to produce a reversible increase of residual molecular disease in about one third of patients, but not to affect the long-term outcome.

156 Comparing the Prognostic Significance of Early Predictors of Survival in Chronic Myeloid Leukaemia (CML) Treated with Imatinib - an Analysis of the Randomized CML-Study IV

https://ash.confex.com/ash/2014/webprogram/Paper70540.html

Introduction: Early prediction of outcome using response-related predictive landmarks has become a major paradigm in the clinical management of chronic myeloid leukemia (CML). Several studies have shown the predictive impact of 10% BCR-ABL^{IS} at 3 and 6 months for different tyrosine kinase inhibitors. The question, which landmark should define treatment failure and determine treatment intervention has been discussed vividly. However, an objective analysis of quality criteria for different early prognostic landmarks is lacking up to now. Here we compare sensitivity, specificity and the proportion of later disease progressions predicted by 3-month and 6-month landmarks in imatinib-treated patients of the CML-study IV.
Methods: A total of 1,303 newly diagnosed patients were assigned to an imatinib-based treatment arm of CML-Study IV by April 2010. Median follow-up was 7.1 years……
Results: Comparing the 10% BCR-ABL^{IS} landmark at 3 and 6 months, 8-year OS and PFS rates are equal or comparable (table). In contrast, sensitivity and specificity differ substantially with an advantage in favor of sensitivity for the 3-month landmark and in favor of specificity for the 6-month landmark. This difference is paralleled by a smaller proportion of high-risk patients and less progressions identified by the 6-month landmark. From a clinical point of view the 6-month landmark is not only less than half as sensitive, moreover a treatment intervention at 6 months might also prevent less progressions due to the delay of 3 months. The half-log reduction landmark at 3 months is as sensitive as 10% BCR-ABL^{IS} at the same time. However, it shows improved specificity and defines the smallest proportion of high-risk patients.
Conclusion: The 10% BCR-ABL^{IS} landmark, which is currently defining treatment failure at 6 months according to European LeukemiaNet (ELN) criteria, fails to detect the majority of patients with later disease progression. Less than a half-log reduction of individual baseline BCR-ABL transcript levels at 3 months on treatment identifies patients with later progressions as sensitive but with higher specificity as compared to 10% BCR-ABL^{IS}.

812 Early Disease Relapse after Tyrosine Kinase Inhibitor Treatment Discontinuation in CML Is Related both to Low Number and Impaired Function of NK-Cells

https://ash.confex.com/ash/2014/webprogram/Paper66989.html

Background: Recent reports suggest that approximately 40% of CML patients who have achieved sustained complete molecular remission are able to stop TKI treatment without disease relapse. However, there are no predictive markers for successful therapy discontinuation. Therefore, we set up an immunological sub-study in the ongoing pan-European EURO-SKI stopping study. Our aim was to identify predictive biomarkers for relapse/non-relapse and to understand more on the mechanisms of immune surveillance in CML.
Methods: The EURO-SKI study started in 2012, and patients included were at least three years on TKI and at least one year in MR4 or deeper before the study entry. Basic lymphocyte immunophenotyping (the number of NK-, T- and B-cells) was performed at the time of therapy discontinuation and 1, 6, and 12 months after the TKI stop and in case of relapse (defined as loss of MMR, *BCR-ABL1*>0.1% IS). In addition, from a proportion of patients more detailed immunophenotypic and functional analyses (cytotoxicity of NK-cells and secretion of Th1 type of cytokines IFN-γ/TNF-α) were done at the same times.
Results: Thus far 119 Nordic patients (imatinib n=105, dasatinib n=12, nilotinib n=2) who have discontinued TKI treatment within the EURO-SKI study have been included in the lymphocyte subclass analysis (results are presented from patients who have reached 6 months follow-up). Immunophenotyping analysis demonstrates that imatinib treated patients who were able to maintain remission for 6 months (n=36) had increased NK-cell counts (0.26 vs. 0.15x10^9cells/L, p=0.01, NK-cell proportion 18.9% vs. 11%, p=0.005) at the time of drug discontinuation compared to patients who relapsed early (before 5 months n=22).
Furthermore, the phenotype of NK-cells was more cytotoxic (more CD57+ and CD16+cells and less CD62L+cells), and also their IFN-γ/TNF-α secretion was enhanced (19.2% vs. 13%, p=0.02). Surprisingly, patients who relapsed more slowly (after 5 months, n=16) had similar baseline NK-cell counts (0.37x10^9cells/L), NK-cell proportion (21.2%), and phenotype and function as patients, who were able to stay in remission. No differences in the NK-cell counts were observed between patients who had detectable or undetectable *BCR-ABL1* transcripts at the baseline (0.22 x10^9cells/L vs. 0.31 x10^9cells/L, p=0.61). Interestingly, NK-cell count was higher in patients with low Sokal risk score than in patients with intermediate risk (0.33 x10^9cells/L vs. 0.20 x10^9cells/L, p=0.04). Furthermore, there was a trend that male patients had a higher proportion of NK-cells than females (21.6% vs. 15.7%, p=0.06). Pre-treatment with IFN-α or the duration of imatinib treatment did not have an effect on NK-cell count or proportion. In comparison to the imatinib group, dasatinib treated patients had higher NK-cell counts at the baseline (median 0.52x10^9cells/L vs. 0.26x10^9cells/L, p=0.02), and also the proportion of CD27 (median 50% vs. 16%, p=0.01) and CD57 expressing (median 79% vs. 74%, p=0.05) NK-cells was higher. The follow-up time of dasatinib treated patients is not yet long enough to correlate the NK-cell counts with the success of the treatment discontinuation.
The absolute number of T-cells or their function did not differ significantly between relapsing and non-relapsing patients at the time of treatment discontinuation. However, both CD4+ and CD8+ T-cells tended to be more mature in patients who stayed in remission compared to patients who relapsed early (CD4+CD57+CD62L- median 5.7% vs. 2.4%, p=0.06,

CD8+CD62L+CD45RA+ 13% vs. 26.7%, p=0.05). The analysis of follow-up samples showed that in patients who stayed in remission the Th1 type cytokine (IFN-γ/TNF-α) secretion of CD8+T-cells increased at 6 months compared to baseline (23.6 vs. 18.5%, p=0.07). Same phenomenon was observed in the late relapsing group at relapse compared to baseline (37.9 vs. 13.5%, p=0.03). No similar increase was observed in the early relapsing group.
Conclusions: Low NK-cell numbers and poor cytokine secretion may predict early disease relapse after TKI discontinuation. However, patients who relapse later have high numbers of normally functioning NK-cells. Further research (detailed phenotypic analysis of NK- and T-cells including activating and inhibitory receptors and immune checkpoint molecules) and correlation of biomarker data with clinical parameters are ongoing to understand the ultimate determining factors of relapse.

512 Cooperative Targeting of Bcl-2 Family Proteins by ABT-199 (GDC-0199) and Tyrosine Kinase Inhibitors to Eradicate Blast Crisis CML and CML Stem/Progenitor Cells

https://ash.confex.com/ash/2014/webprogram/Paper72972.html

Bcr-Abl tyrosine kinase supports CML cell survival in part by regulating anti-apoptotic Bcl-2 proteins such as Bcl-xL and Mcl-1. Tyrosine kinase inhibition, the front-line therapy for patients with chronic phase CML, is less effective in blast crisis (BC) patients and inactive against quiescent CML stem/progenitor cells. We reported that ABT-737, a dual Bcl-2/Bcl-xL inhibitor, induces apoptosis in BC CML cells including $CD34^+$quiescent CML cells. ABT-199, a potent Bcl-2 specific inhibitor, has entered clinical trials for various haematological malignancies. We hypothesized that cooperative targeting of anti-apoptotic Bcl-2 proteins using a combination of ABT-199 and tyrosine kinase inhibitors (TKIs) would exert enhanced activity against BC CML and CML stem/progenitor cells.
Cells from patients (n=4) with TKI-resistant BC CML were treated with ABT-199, TKIs, and combinations. Although exerting low activity by itself, ABT-199 in combination with TKIs synergistically induced apoptosis (CI<0.1) in bulk and $CD34^+38^-$cells from these patients regardless of their previous clinical responses to TKIs. The combinations had minimal activity against normal $CD34^+$cells (n=3). Mechanistic studies demonstrated that nilotinib inhibited the expression of Bcl-xL and Mcl-1 mRNA and protein, even in cells from TKI (including nilotinib) resistant patients. Individual inhibition of Bcl-xL or Mcl-1, and even more so inhibition of both, by siRNAs increased the sensitivity of cells to ABT-199, suggesting that cooperative inhibition of Bcl-2 by ABT-199 and Bcl-xL/Mcl-1 by TKIs contributes to the synergy…….
The *in vivo* experiments are ongoing.
Conclusions: ABT-199 and TKIs cooperatively target anti-apoptotic Bcl-2 family proteins. This combination is highly effective in killing bulk and $CD34^+38^-$ CML cells and quiescent $CD34^+$ CML stem/progenitor cells from BC CML patients *in vitro* and in suppressing leukaemia and leukaemia stem cells *in vivo*. This strategy has the potential to eradicate BC CML cells and CML stem/progenitor cells, neither of which are effectively targeted by TKIs alone.

1802 Propensity Score Matched Comparison of Dasatinib and Nilotinib As a Frontline Therapy in Newly Diagnosed CML with Chronic Phase

https://ash.confex.com/ash/2014/webprogram/Paper75039.html

Background: Dasatinib (DAS) and nilotinib (NIL) are standard frontline therapy for chronic myeloid leukaemia, chronic phase (CML-CP) based on randomized trials compared to imatinib. However, DAS and NIL have not been compared directly. The purpose of this study is to analyse efficacy, long-term outcome and toxicity of DAS and NIL as a front line therapy in newly diagnosed CML-CP. …..
Conclusion: In PS matched cohort of newly diagnosed CML-CP pts, the outcome observed with both treatment options (DAS and NIL) is excellent with no clear difference in response or long-term survival endpoints. Incidence of clinically significant AEs was similar between DAS and NIL.

4565 Phase II Clinical Trial Results of Dasatinib for Frontline Therapy in Patients with Chronic Myeloid Leukaemia (CML) in Chronic Phase (CP)

https://ash.confex.com/ash/2014/webprogram/Paper76030.html

Background: Dasatinib is approximately 300 times more potent than imatinib (IM) in vitro and has significant activity in patients (pts) with CML-CP resistant to or intolerant of IM. In 2005, we initiated a phase II trial to study the efficacy and safety of dasatinib in pts with previously untreated CML-CP.
Objective: To determine the long-term outcome of pts with CML-CP treated with front-line dasatinib. The primary endpoint was achievement of major molecular response (MMR) at 12 months (mos).
Methods: Pts with previously untreated CML-CP within 6 mos from diagnosis were eligible and received dasatinib 100 mg/day, randomized to either 50 mg twice daily (BID) or 100 mg once daily (QD). After 66 pts were accrued, the BID arm was closed and all subsequent pts were treated with 100 mg QD. No prior therapy was allowed except for IM for <1 month, or Hydroxyurea.
Results: From November 2005 to August 2014, a total of 155 pts have been enrolled. For this analysis, we included only those pts with a minimum of 12 mos follow-up: 107 pts (77 QD, 30 BID). Median age was 48 years (yrs) (range 16–83 yrs). Median baseline counts: WBC 26.4 K/uL, peripheral blood blasts 0%, bone marrow blasts 2%, and platelets 333 K/uL. Twenty-seven pts (25%) had brief prior exposure to IM. Sokal score by distribution: Low (76%), Intermediate (21%), High (4%). Median follow-up is 62.9 mos (11.7 - 104.1 mos). Of the 99 evaluable pts who were not in CHR at the start of therapy, 99 (100%) achieved CHR. Of 105 evaluable pts (i.e., followed for at least 3 mos), 105 (100%) achieved complete cytogenetic response (CCyR). MMR has been achieved in 94 pts (90%), including 59 pts (56%) with complete molecular response (CMR; minimum 100,000 ABL copies). BCR-ABL/ABL <10% at 3 mos occurred in 100/106 evaluable (94%) and at 6 mos in 98/104 evaluable (94%). At 6 mos, 93/102 evaluable (91%) pts had achieved a CCyR and 69/101 evaluable (68%) an MMR; corresponding figures at 12 mos are 92/97 pts evaluable (95%) and 73/95 pts evaluable (77%), respectively. Fifty-eight pts (54%) have required at least one dose reduction (most common reasons: 22 pts had dose reductions due to pleural effusions, 8 due to neurologic/headaches, 4 due to thrombocytopenia). The

actual median daily dose for all pts was 80mg (20–140mg). Five pts lost CCyR: (2/5 of these pts who lost CCyR ultimately progressed to accelerated phase (CML-AP)). The 3-yr and 5-yr overall survival (OS), event-free survival (EFS), transformation-free survival (TFS), and failure-free survival (FFS) are shown in the **Table**. There have been two deaths on study (1 pt: 74 yr-old woman with sepsis/infection; 1 pt: 53 yr-old man with morbid obesity and hypertension who died of unknown causes). Twenty-six (24%) pts have discontinued therapy: 11 due to toxicity (most commonly due to pleural effusion in 7 pts), 5 pt choice, 5 lost CCyR, 2 died on study, 2 pt non-adherence, 1 due to development of T315I mutation.

Conclusion: Rapid CCyR occurs in nearly all pts, and MMR was achieved in 90% of pts with previously untreated CML-CP treated with frontline dasatinib therapy with a favourable toxicity profile. Deep responses occur early. Only two patients experienced transformation to CML-AP, and only one patient developed T315I mutation. These results confirm the sustained efficacy of dasatinib as initial therapy for CML-CP.

Table: Outcomes at 3-year and 5-year time points in patients with CML treated with frontline dasatinib

	Total	Events	3-Year	5-Year
OS	107	5	98%	95%
EFS	107	8	95%	92%
TFS	107	4	99%	95%
FFS	107	24	84%	76%

***Definitions:** **EFS**: includes, at any time on study: International Randomized Study of Interferon and STI571 trial (IRIS)-defined events, which includes loss of major cytogenetic response, loss of complete hematologic response, transformation to accelerated or blast phase, death from any cause while on study. **FFS:** includes loss of complete cytogenetic response, failure to achieve response at set times as defined by European Leukaemia Net, treatment intolerance, or treatment discontinuation for any reason while on study. **TFS:** measured from start of therapy to date of transformation to accelerated or blast phases while on therapy or to date of last follow-up.

4532 Deep Molecular Response to Nilotinib As First-Line Treatment of BCR-ABL+ CML in Early Chronic Phase: A Phase 3b Multicentre Study of the Gimema CML Working Party

https://ash.confex.com/ash/2014/webprogram/Paper72851.html

Background: In the ENESTnd trial, nilotinib (NIL) showed a superior efficacy to imatinib (IM) with higher response rates and less frequent progression to advanced phases (ABP). Based on these results, NIL has been approved for frontline treatment of chronic myeloid leukaemia (CML). The treatment-free remission (TFR) is actually considered one of the most important treatment goals in CML and a sustained deep molecular response (DMR, MR4 or better) is a pre-requisite to achieve TFR. The 5-year update from the ENESTnd trial showed a superiority of NIL over IM in terms of both MR4 and MR4.5, but differences concerning the stability of DMR have not been reported. Moreover, a significant improvement in the long-term outcome has not been demonstrated yet. Despite the efficacy, cost and safety concerns may limit the NIL use as first line treatment in CML. Independent studies are extremely relevant to confirm or to extend the results of company-sponsored trials.

Aims and Methods: To assess the efficacy of NIL frontline in terms of DMR, a phase 3b study was conducted by the GIMEMA CML WP (CML0811; NCT01535391). The primary endpoint was the rate of MR4 at 24 months. Key secondary objectives: evaluation of the kinetics of molecular response, assessment of the safety profile, analysis of the outcome. The starting NIL dose was 300 mg BID, with dose escalation to 400 mg BID in case of suboptimal response or failure according to ELN 2009 criteria, with the exception of progression to ABP and in absence of safety issues or BCR-ABL mutations insensitive to NIL. The molecular response was assessed in GIMEMA standardized molecular laboratories (LabNet network) and the results were expressed according to the International Scale. The MR4 was defined as either detectable disease ≤ 0.01% BCR-ABL or undetectable disease with ≥ 10.000 ABL copies; the MR4.5 was defined as either detectable disease ≤ 0.0032% BCR-ABL or undetectable disease with ≥ 32.000 ABL copies. Sustained MR4 or MR4.5: MR4 or MR4.5 for at least 1 year a, with at least 3 evaluable analysis. Adverse events were recorded continuously. A prospective evaluation of glucose metabolism and serum lipids was planned. All the analyses were performed according to the ITT principle.

Results: 130 CML patients in early chronic phase have been enrolled in 32 Italian haematologic centres; median age, 50 years (range 18-85); high risk patients, 22%, 6% and 8% according to Sokal, Euro and EUTOS scores, respectively; clonal chromosomal abnormalities in Ph+ cells at baseline, 5%; e13a2 BCR-ABL transcript, 34%. The median follow-up is actually 21 months (all patients had at least 18 months observation; a minimum observation of 24 months will be reached by October 2014). Data with at least 24 months follow-up will be presented on site. At the last contact, the patients still on treatment with NIL were 110/130, 85% (74% with 600 mg, 7% with 300 mg or less, 4% with 800 mg daily), while 20/130 patients, 15%, permanently interrupted the study drug for the following reasons: 3% progression to ABP, 2% failure or suboptimal response (dose escalation not feasible), 1% allogeneic stem cell transplantation, 5% toxicity, 4% other reasons (including consent withdrawal and pregnancy). The complete cytogenetic response rate and the major molecular response rate at 12 months were 76% and 53%, respectively. The rates of MR4 at 3, 6, 12 and 18 months were 2%, 12%, 27% and 29%, respectively. Fifty-four patients achieved a MR4 at least once; the patients with a sustained MR4 were 18/54 (33%, or 14% of the total). The rates of MR4.5 at 3, 6, 12 and 18 months were 0, 3%, 10% and 13%, respectively. Only 3 patients achieved a sustained MR4.5. A significant increase of glycosylated haemoglobin was not observed. The total cholesterol, and both LDL and HDL cholesterol fractions significantly increased during treatment. Triglyceride concentrations had not significant variations. Six patients (5%) had a cardiovascular event, including myocardial infarction and arterial thrombosis. All the patients are still alive.

Conclusions: The molecular response rates seem to be superior to the historical data of IM. NIL 300 mg BID as frontline treatment of BCR-ABL+ CML, with dose optimization in case of non-optimal response, may improve the proportion of patients able to discontinue TKI treatment. Due to the metabolic effects, a baseline selection is crucial to maximize the therapeutic benefit and to minimize the cardiovascular risks.

3136 Hyperhomocysteinemia and High Doses of Nilotinib Favour Cardio-Vascular Events in Chronic Phase Chronic Myelogenous Leukaemia (CML) Patients

https://ash.confex.com/ash/2014/webprogram/Paper70145.html

Despite its high efficacy on CML, long-term exposure to nilotinib, a second generation tyrosine kinase inhibitor (TKI2), has been reported to increase the onset of arterial cardiovascular events (CVE) in chronic phase (CP) CML patients (pts), especially in pts with cardiovascular risk factors. However, some pts without any cardiovascular risk factors may experience arterial thrombotic events and the pathogenesis of this phenomenon remains obscure. Homocysteine (HC) is a key sulphured amino-acid derived from methionine, independently associated with increased frequencies of thrombo-embolic events, early arteriosclerosis and increased cardiovascular mortality (Nygard NEJM 1997). In addition, *in vitro*, this amino-acid induces the proliferation of smooth muscle cells, endothelial cell dysfunction, increased collagen synthesis and exerts pro-inflammatory rearrangements within the arterial wall.
In the present study, we wanted to determine if hyperhomocysteinemia might influence the onset of cardio-vascular events in a series of 114 CP CML pts on nilotinib……
In conclusion, nilotinib seems to favour CVE in the long-term in CP CML pts, especially in patients with CV risk factors, and these CVE are specifically linked to higher doses of nilotinib and high levels of homocysteinemia. This marker could represent a useful tool to detect pts at risk of arterial CVE on nilotinib. Whether hyperhomocysteinemia is one of the causes of CVE of a consequence of nilotinib treatment remains to be determined.

811 Dasatinib or Nilotinib Discontinuation in Chronic Phase (CP)-Chronic Myeloid Leukaemia (CML) Patients (pts) with Durably Undetectable *BCR-ABL* Transcripts: Interim Analysis of the STOP 2G-TKI Study with a Minimum Follow-up of 12 Months – on Behalf of the French CML Group Filmc

https://ash.confex.com/ash/2014/webprogram/Paper72021.html

Background: Tyrosine kinase inhibitors (TKIs) targeting BCR-ABL have revolutionized the prognosis of pts suffering from CML but these drugs are considered as non-definitively curative and current recommendation is to treat pts during their entire lifespan. However, prospective trials such as STIM, TWISTER and EUROSKI suggest that imatinib may be successfully stopped in pts with deep and sustained molecular responses. Here, we report on the feasibility of second generation TKIs discontinuation in the setting of the French STOP 2G-TKI study.

Conclusions: 2G-TKI could be safely and successfully discontinued in CP-CML pts with long-lasting undetectable *BCR-ABL* transcripts, especially in those without prior history of suboptimal response or resistance. Most of molecular relapses had an early onset and all were sensitive to

2G-TKI resumption. The recurrence of low levels of detectable residual disease below MMR after 2G-TKI withdrawal did not automatically herald CML relapse and did not preclude the possibility to remain treatment-free.

1321 Prospective Analysis of the Quality of Life of Chronic Phase CML Patients on Second Generation Tyrosine Kinase Inhibitors after Imatinib Failure. an Observational Study

https://ash.confex.com/ash/2014/webprogram/Paper70966.html

Imatinib (IM) failure in chronic phase CML patients is a peculiar situation where the quality of life (QoL) of patients has rarely been appreciated and assessed. A majority of patients is rescued by second generation tyrosine kinase inhibitors (TKI2) licensed in this setting. In the retrospective and prospective national observational POSTIM study we have already reported the value of the Hammersmith score in this population of patients. In the same population, we have also have prospectively analysed the QoL and the compliance of these IM-resistant or intolerant patients, on TKI2 (i. e. Nilotinib and Dasatinib) as a secondary objective, using a series of scores currently used to assess such characteristics (Morisky score, Functional Assessment of Cancer Therapy (FACT) subdivided in Physical Well Being (PWB), Social/Family Well Being (SWB), Emotional Well Being (EWB), Functional Well Being (FWB), Social/Family Well Being (SAC), (FACT+SAC=FACT-total), and FACT-Leu) calculated at 6 months and 12 months following first TKI2 initiation. These scores have been correlated to general characteristics of the patients, cytogenetic and molecular responses to TKI2 at one year of TKI2, and to survival.
Among the 174 patients enrolled in the POSTIM study, 76 patients have been enrolled in this QoL study in 16 university and non-university academic institutions between 2009 and 2012, and their data collected after informed consent. There were 36 males (47%) and 40 females with a median age at enrolment of 62 (25-86) years and a median duration of CML of 6.5 (3-18) years. Sokal score was low for 37%, intermediate for 28% and high for 35 % (6 pts unknown). IM was stopped because of IM-resistance in 41% (n=29) of the patients, IM-intolerance in 40% (n=28), IM-intolerance + resistance in 19% (n=13) of the patients (6 patients unknown). None of the patients had been allotransplanted previously. Eleven % (n=6) of the patients had a high Hammersmith score (HS), 20% (n=11) an intermediate HS, and 69% (n=37) a low HS of evaluable patients (22 patients non evaluable). Sixty-one percent of the patients (n=46) had Dasatinib and 39% (n=30) had nilotinib as a first TKI2. The first TKI2 has been stopped for first TKI2 resistance (7 patients), intolerance (13 patients) and for resistance and intolerance (3 patients). Eleven patients went from Dasatinib to Nilotinib and 18 from Nilotinib to Dasatinib. The median follow-up after initiation of the first TKI2 is 4.5 (2.5-7) years. There was no difference in PWB, SWB, EWB, FWB, and FACT between Dasatinib and Nilotinib groups (p=0.56, 0.36, 0.53, 0.70, 0.66 respectively). Only one patient died, therefore the overall survival analysis was not relevant. Thirty-four patients (45%) failed the TKI2 treatment. We went on analysing the failure free survival [(FFS), failure defined as no hematologic or cytogenetic response, CHR, CCyR, PCyR MMR or MR4.5 loss, death, progression to AP/BC, definitive TKI2 cessation for resistance or intolerance, allogeneic stem cell transplantation]. Cox model analysis demonstrated that FFS was significantly longer in patients with a high FACT score since TKI2 initiation (median not reached for high FACT versus 28 months for low FACT score, p=0.02, see figure 1) and since CML diagnosis (median 161 months for high FACT versus 66 months for low FACT score, p=0.002; median 162 months for high FACT-total versus 87.5 months for low FACT-total score, p=0.012). In addition, the FFS since diagnosis was significantly better for patients with a high PWB score

(median 161 months for high PWB versus 66 months for low PWB score, p=0.032). No difference in cytogenetic and molecular responses to TKI2 observed at 1 year have been influenced by any of the scores individually, or grouped (= FACT, FACT-total), neither the Morisky score.
In conclusion, this prospective analysis performed on a large population of patients failing imatinib, on TKI2, demonstrated that maintaining a good QoL for these patients evaluated through the FACT scores, can effectively improve failure-free survival on these drugs, and this needs to be a matter of concern for improving the long-term follow-up and the compliance to treatments of such patients.

3160 **Baseline Characteristics of CML Patients Across Europe - Comparing Real-World Patients with Patient Collectives Included in Clinical Trials**

https://ash.confex.com/ash/2014/webprogram/Paper75404.html

Introduction:
Most of the knowledge about treatments and outcome of CML patients originates from clinical studies. To get new and unbiased insights in the epidemiology, treatment and outcome of CML, the EUTOS population-based registry of newly diagnosed CML patients was established, - as part of the European Treatment and Outcome Study (EUTOS) for CML.
The aim was to collect the data of all adults with newly diagnosed CML, irrespective of treatment and of enrolment in studies.
Patients and Methods:
The EUTOS population-based registry collected data of newly diagnosed CML patients, 18 years or older, over a specified period of time from 2008 till 2012 living in defined regions. The data were collected by 22 study groups in 20 European countries. Data were gathered via a web-based CRF-system.
For comparison we used the already published data from five Company-sponsored registration studies IRIS (O'Brien et al, NEJM, 2003), TOPS (Cortes et al, JCO, 2009) ENESTnd (Saglio et al, NEJM, 2010), DASISION (Kantarjian et al, NEJM, 2010) and BELA (Cortes et al, JCO, 2012), from three Investigator-sponsored studies GIMEMA (Castagnetti et al, JCO, 2010 and Gugliotta et al, Blood, 2011), French SPIRIT (Preudhomme et al, NEJM, 2010) and German CML IV (Hehlmann et al, JCO, 2011) and from two single referral centres HAMMERSMITH (De Lavallade et al, JCO, 2008) and MDA (Jain et al, Blood, 2013).
Results:
Till 15.05.2014 2978 patients were registered in the EUTOS Population-based registry. 94.3% of the patients were diagnosed in chronic phase (CP), 3.6% in accelerated phase (AP), and 2.2% in blastic phase (BP). For the calculation of the prognostic scores 361 patients had to be excluded because they were pre-treated. For the comparison we used 2350 patients in Chronic Phase with laboratory values before any treatment.
54% of the patients in the EUTOS Population-based registry were male, less than in all studies (56.6 - 60.6%). The median age at diagnosis was 56 years, higher than in all studies (46 - 55). In EUTOS the proportion of patients more than 60 years and more than 65 years old was 40.4 % and 21.9 % respectively. Similar data were rarely reported in all other studies. Median value of the spleen size below costal margin was 0. 46.1% of the patients had a palpable spleen and 15.2% had a spleen size ≥ 10 (spleen size is always reported in cm under costal margin in this abstract). The % of palpable spleen is only reported by IRIS, 25.0% and by the FRENCH Spirit group, 49.8%. The median spleen is only reported by GIMEMA, 2.0. Spleen size ≥ 10 is reported

by IRIS, 6.0%, ENESTnd, 12.4% and HAMMERSMITH 25.5%. While the median values for Platelets and Haemoglobin show no big differences, the median WBC in EUTOS is 83.9 $x10^9$/l and in the Company-sponsored registration studies: IRIS 18-20 $x10^9$/l , in ENESTnd 23-26 $x10^9$/l, in DASISION 23-25 $x10^9$/l , and in BELA 22-23 $x10^9$/l, in the Investigator-sponsored studies: GIMEMA 55 $x10^9$/l , in the FRENCH SPIRIT 83-104 $x10^9$/l , in the GERMAN CML IV 75-91 $x10^9$/l , and in the single referral centre study HAMMERSMITH 140 $x10^9$/l, clearly indicating that in company-sponsored, registration studies, the reported values of the WBC were not recorded prior to any treatment. The median values for Blasts, Basophils and Eosinophils show also not so big differences. The % of Sokal low risk patients is in EUTOS with 34.5% lower than in all studies (35.2 - 60%) with the exception of HAMMERSMITH 28.9%.

Discussion:

The EUTOS Population-based registry provides the first European wide real-world series of patients with newly diagnosed Ph+, BCR-ABL+ CML. The age and sex distribution and some baseline characteristics such as Sokal Score as well as median WBC count in the EUTOS population-based registry are different from many prospective studies. This should be taken in due consideration before extrapolating the results of treatment studies to real life. Spleen size, which is known as an important value for prediction, is only very rarely reported in clinical studies. With further follow-up, this registry will provide a population-based insight on treatment, survival, and causes of death.

3138 A Two-Fold Rise of BCR-ABL Transcript Levels Advises BCR-ABL Mutation Analysis in Imatinib-Treated Chronic Myeloid Leukemia (CML) - an Analysis of the Randomized CML-Study IV

https://ash.confex.com/ash/2014/webprogram/Paper69474.html

Introduction: The clonal selection of a mutant BCR-ABL positive clone can be observed in about one of two patients with imatinib-resistant chronic myeloid leukaemia (CML). The early detection of BCR-ABL kinase domain mutations is crucial, since it allows to change the tyrosine kinase inhibitor (TKI) regimen in a timely manner and may therefore prevent disease progression and the accumulation of further genetic lesions. European LeukemiaNet (ELN) recommendations suggest a mutation analysis if optimal response criteria are not achieved at 3, 6, 12 or 18 months, or whenever a loss of optimal response occurs (Soverini et al., Blood 2011).
Conclusion: BCR-ABL kinase domain mutations occur already in a substantial proportion of patients with a doubling of BCR-ABL transcript levels, which should determine mutation analysis.

813 The Risk of Relapse in CML Patients Who Discontinued imatinib Can Be Predicted Based on Patients Age and the Results of dPCR Analysis

https://ash.confex.com/ash/2014/webprogram/Paper68085.html

Introduction. Chronic myeloid leukaemia (CML) patients (pts) treated with imatinib first line achieve complete cytogenetic response (CCyR) in > 70% of cases and major molecular response (MMR) in 18-58%. These pts have a life expectancy similar to the general population. However even undetectable BCR-ABL may not equate to eradication of the disease because of the sensitivity of Q-RT-PCR. A new diagnostic method, the digital-PCR (dPCR), able to detect 1 BCR-

ABL+ cell out of 10^7 cells, has been recently developed (Goh HG et al., 2011). dPCR corresponds to a 100 fold increase in sensitivity as compared to Q-RT-PCR. Therefore, dPCR by assessing the presence of minimal residual disease with higher sensitivity could potentially identify pts in whom CML has been eradicated.

Aims. The Imatinib Suspension And Validation (ISAV) study is aimed at validating the capability of dPCR to predict relapses after imatinib discontinuation in CML pts with negative Q-RT-PCR results**.**

Methods. This study involves 15 sites, 10 in Italy and 1 in each of the following countries: Germany, Spain, The Netherlands, Canada and Israel. CML pts (Chronic or Accelerated Phase) under imatinib therapy since more than 2 years and in complete molecular remission (CMR) were eligible for this study. Patients had to be in CMR for at least 18 months (mts), with a minimum of 3 Q-RT-PCR performed at their own sites. After signing the informed consent, blood samples are obtained for dPCR and the pts discontinue imatinib therapy. Standard Q-RT-PCR is performed monthly (mts 1-6) and then bimonthly for 36 mts to assess the maintenance of the molecular remission. The loss of molecular remission is defined as two consecutive positive Q-RT-PCR tests with at least one BCR-ABL/ABL value above 0.1%. Patients losing molecular remission resume imatinib treatment at the same dosage used before interruption. Patients' quality of life during imatinib discontinuation/resumption is evaluated through the EORTC – C30 Quality of Life questionnaire.

Results. The enrolment in ISAV began in November 2011 and ended in July 2013. The study enrolled 112 pts: Italy 69.6%, Germany 21.4%, Canada 5.3%, Spain 2.6% and Israel 0.9%. Among the 112 pts, 59.3% were male and 37.0% were aged 65 or older; median duration of imatinib treatment was 103.1 mts with median duration of CMR Of 25.8 mts before imatinib discontinuation. To date, the median follow-up (FUP) time is 16.6 mts [95% CI: 14.9-18.2]. Forty-seven pts (43.5%, 95% CI: 34.0-53.4) of the 108 eligible pts relapsed and resumed imatinib; 38/47 (80.9%) of them relapsed in the first 9 mts and the last relapse occurred 19.6 mts after imatinib discontinuation. A loss of CCyR occurred in 11 pts (23.4%): 10/11 CCyR losses were recovered; 1 patient withdrew the consent shortly after obtaining a partial cytogenetic response. No case of CML progression was observed. After the resumption of imatinib the median time to either MMR or CMR was 1.9 [95% CI: 1.2-2.4] mts. Of the 61 not-relapsed pts, 43 (39.8% of the total) regained Q-RT-PCR positivity but never lost MMR. The median time to Q-RT-PCR positivity was 3.6 mts [95% CI: 3.0-4.8] and the range of duration of Q-RT-PCR positivity (below 0.1%) was between 5.7 and 29.2 mts. No significant correlation between relapse and previous duration of imatinib treatment, use of interferon, time to CCyR or duration of CMR was identified. An inverse relationship between pts age and risk of relapse is evident: 90% of pts < 45 years relapsed vs 37.5% in the class ≥ 45 - < 65 years and 27.5% of pts ≥ 65 years, $p(\chi^2)<0.0001$. dPCR results showed that 23.4% of pts were positive and 76.6% negative, with a dPCR Negative Predictive Value (NPV) of 63.4% (Tab.1) and a significant NPV ratio (dPCR/Q-RT-PCR) of 1.131 [95% CI: 1.032-1.239]. Age and dPCR results predicted the risk of relapse: pts with less than 45 years and with a positive dPCR had the highest risk of relapse (100%) as opposed to pts ≥ 45 years and with negative dPCR (30.6%; Fig.1).

Conclusion. After 32 mts from the beginning of the study, with a median FUP of 16.6 mts, 43.5% of pts relapsed; the majority of relapses developed in the first 9 months after imatinib discontinuation. Age < 45 years and dPCR positivity are significantly associated with relapses.

3145 Incidence of CML in Europe - a Comparison of 19 European Countries with US SEER Data

https://ash.confex.com/ash/2014/webprogram/Paper72220.html

Introduction

As there are only few data available about the incidence, the stage of disease at diagnosis, the treatment and the outcome of chronic myeloid leukaemia (CML) in Europe the European Treatment and Outcome Study (EUTOS) for CML collected such data in 27 European countries. The population-based registry was set up by EUTOS to further explore the epidemiology, characteristics, treatment and outcomes of CML in Europe. The present work focused on the estimation of incidence of CML in Europe, in the single countries participating in the registry and the comparison to existing incidence estimations from the US.

3141 Five-Year Outcome of 215 Newly Diagnosed Chronic Myeloid Leukaemia Patients Treated Frontline with Nilotinib-Based Regimens: A Gimema CML Working Party Analysis

https://ash.confex.com/ash/2014/webprogram/Paper72569.html

Background. Nilotinib (NIL) is a potent and selective BCR-ABL inhibitor approved for the frontline treatment of chronic myeloid leukaemia (CML) based on the results of the ENESTnd study. The sustained superiority of NIL vs. imatinib (IM) was confirmed after 5 years of follow-up (Hughes et al, abs. 677, EHA 2014). However, few data are available on patients (pts) treated frontline with NIL outside of Company-initiated trials.

Results. The cumulative rates of CCyR and MMR were 93% and 88%, respectively. At 3 mos, 82% of the pts were in Partial Cytogenetic Response and 90% had a BCR-ABL/ABL (IS) < 10%; at 6 mos, 86% were in CCyR and 83% had a BCR-ABL/ABL (IS) < 1%; at 12 mos, 72% were in MMR; all these pts were optimal responders according to ELN 2013 recommendations. Overall, 80 (37%) pts permanently discontinued NIL: 45 (21%) for adverse events or intolerance; 25 (12%) for failures; 7 (3%) while in stable MR^4; 3 (1%) for other reasons. Cardiovascular adverse events (CVAE) were cause of permanent NIL discontinuation, after a median time of 37 mos, in 13 (6%) pts, and included 4 peripheral arterial occlusive diseases and 3 ischemic coronary diseases; only one pt died for CVAE. Nine (4.1%) pts progressed to AP/BP, 8/9 during the 1st year of therapy and one after 25 mos; all pts subsequently died (after a median of 13 mos, range 1-34 mos). NIL-resistant mutations were identified in 6 of these pts (4 T315I; 1 Y253H; 1 F359V); 7/9 progressions occurred in patients receiving NIL-IM. In addition, 6 pts were classified as failures at 3,6, or 12 mos according to ELN 2013 recommendations; afterwards, 10 pts developed a secondary resistance (3 loss of CHR, 3 loss of CCyR, and 4 confirmed loss of MMR). Overall, 17 (8%) pts died, in 7 cases for reasons unrelated to CML progression. The estimated 6-year OS, PFS, FFS, and EFS were 91%, 91%, 83%, and 59%, respectively.

Conclusion. Our National experience showed that most pts treated frontline with NIL-based regimens were optimal responders according to ELN recommendations and that 91% of the patients were estimated to be alive and progression-free at 6 years. In particular, NIL alone was highly effective in the prevention of AP/BP. Considering that AP/BP had in most cases an early onset and an extremely poor prognosis, its prevention should be the priority of CML treatment, especially in the firsts 2-3 years. However, afterwards, the relatively high number of CVAE

observed, suggests to focus, at least in selected patients, on strategies aimed at the prevention of CVAE (NIL dose reduction? switch to IM?).

1806 Gimema Registry of Conception/Pregnancy in Adult Patients Diagnosed with Chronic Myeloid Leukaemia (CML) Treated with Tyrosine Kinase Inhibitors (TKIs)

https://ash.confex.com/ash/2014/webprogram/Paper72576.html

The management of patients with chronic myeloid leukaemia (CML) during pregnancy is a matter of continuous debate. The introduction of the tyrosine kinase inhibitors (TKIs) in clinical practice has dramatically changed the prognosis of CML patients. Patients diagnosed in chronic phase can expect an excellent disease control and a normal lifespan. Issues relating to fertility and pregnancy must be introduced at diagnosis. Different reports were published in patients conceiving/getting pregnant during Imatinib treatment, while there are only sporadic data about other TKIs. The GIMEMA CML working party has started a retrospective and prospective study to describe all female pregnancies/male conception outcomes in the CML population from January 2013 until 2015.
Inclusion criteria were age>18, CML in any phase of the disease, conception/pregnancy while diagnosed with CML, treatment with TKIs (before, during or after pregnancy), and signed written informed consent IRB approved.
Sixty-three patients have been enrolled so far in the study. Male to female ratio was 43/20, mother age at pregnancy (female patients or female partners of male patients) varies from 22 to 37 years. ……..
Data on female patients population, regarding the status of CML at pregnancy, the CML therapy since conception and throughout pregnancy, particularly regarding the organogenesis period (between 5-12 weeks), the status of the illness during pregnancy (any MR4.5, MR4 and major molecular response, complete cytogenetic response, hematologic response losses, and progressions), the outcome of pregnancy, breast feeding, baby growth and development (walk, speech, behaviour), will be detailed. The same will be for female partners of male patients treated with TKIs other than Imatinib.
Acquiring detailed information about how a pregnancy/conception is managed will increase our knowledge in order to establish a consensus on patients with CML receiving TKIs who wants to father a child or become/are pregnant.

521 The Experience of the International Registry for Chronic Myeloid Leukaemia (CML) in Children and Adolescents (I-CML-Ped Study): Prognostic Consideration

https://ash.confex.com/ash/2014/webprogram/Paper67622.html

Aims: An international registry (I-CML-Ped Study) was established to assess epidemiology, management and outcome of CML in the paediatric population.
Methods: All national paediatric study groups were invited to include newly diagnosed children and adolescents less than 18 years with CML diagnosed later than January 2000.
Results: Since January 2011, 351 patients from 12 countries have been registered. Clinical and biological data at initial diagnosis are available in 278 patients. There was a male preponderance

(57%). The median age at diagnosis was 12.4 years (range, 9 months -17.5 years); 6% of the patients were younger than 4 years. At time of diagnosis 92% of the children were in chronic phase, 8% in accelerated phase and 1% in blastic phase according to the European Leukaemia Net criteria. The Sokal risk group distribution was: 18% low, 31% intermediate and 51% high risk. The majority of the patients showed a Lansky score of 100 (59%) or 90 (21%). Splenomegaly was present in 76% of patients. The median of the spleen size below the costal margin was 11 cm (range: 1 to 25 cm). The median of the leukocyte count was $235x10^9$/L (range: 5 to 1038). Additional chromosomal abnormalities in Ph-positive cells were observed in 6 % of the patients. The BCR-ABL transcript type was available in 227 patients: b3a2 54%, b2a2 38%, b3a2-b2a2 6% and b2a3 2%**.** The median follow-up time is 39 months (range, 0.5-161). Eight deaths were recorded. The estimated overall survival rate at 60 months is 95% (95%CI 89-97). Irrespective of treatment and follow-up, 124 (73%) of 169 assessable patients for cytogenetic response achieved complete cytogenetic response (CCyR). Exploratory analyses were performed in newly diagnosed patients regarding clinical and biological factors influencing the achievement of CCyR 12 months after starting imatinib. In univariate analyses, the Eutos score, the spleen size, the haematocrit level, the lymphocyte count and immature cells in peripheral blood, the percentage of granulocytes and monocytes in the marrow were identified as potential prognostic factors. However, only the percentage of the granulocytes in the marrow was identified as independent factor of achievement of CCyR at 12 months in multivariate analysis. Data collection and quality control regarding molecular assessment are ongoing.

Conclusion: The data indicates that children and adolescents with CML presented with clinical and biological differences compared to adult patients with CML. Identification of prognostic factors is needed to optimize the strategy in the paediatric population.