1 – **Educational session** – salient points. Tim Hughes, Vivian Oehler and Rick Van Etten. Tim - Imatinib is a less toxic drug than what we are seeing with both Nilotinib and Dasatinib. Nilotinib for the cardio vascular side effects and Dasatinib for the pulmonary hypertension. The overall goal and pre-requisites (captured in the brackets) of CML Tx is: Normal Life Span (avoid progressions and avoid damage to organs), Normal Quality of Life (avoid organ damage, minimize toxicity) Treatment Free remission (sustained deep molecular response, immune mediated MRD). He then measured Imatinib, Nilotinib and Dasatinib against these goals and prerequisites and noted that although the 2nd generation TKI do a better job of helping patients achieve deeper response rates quicker, they are more toxic and can potentially damage organs, etc. he reminded everyone to see the poster by Delphine Rhea et al from Paris France titled '**Identification Of Patients (pts) With Chronic Myeloid Leukemia (CML) At High Risk Of Artery Occlusive Events (AOE) During Treatment With The 2nd Generation Tyrosine Kinase Inhibitor (TKI) Nilotinib, Using Risk Stratification For Cardiovascular Diseases (CVD) -** Conclusions: In our retrospective study, CVD risk estimation according to the 2012 ESC classification reveals that pts who belong to the H/VH risk group at baseline are at very high risk of AOE during nilotinib therapy. These findings now need to be validated in a prospective fashion. Nevertheless, we readily recommend that assessment of CVD risk should be performed in all pts considered for nilotinib therapy. Alternative TKI may be chosen whenever possible in pts at H/VH risk of CVD. In those treated with nilotinib, CVD risk should be reassessed throughout therapy and risk factors should be tightly controlled according to current guidelines.

Furthermore he stated that a significant proportion of patients had an increase in cholesterol requiring medical treatment, and 4 out of 31 patients had Arterial Occlusive Disease, and 35% of patients had to be started on statins. He spoke about Pulmonary Arterial Hypertension with Dasatinib and referred everyone to poster titled '**Pulmonary Hypertension (PHT) and Pleural Effusion During Dasatinib Therapy For CML Frequently Lead To Drug Withdrawal -** Conclusion: The current model of TKIs use in CML requires life-long therapy, which demands durable tolerability and safety. We found clinically relevant pulmonary complications of DAS therapy to be more frequent than previously reported, perhaps due to non-specific symptoms and low levels of awareness. We now recommend obtaining baseline chest X-ray and TTE prior to DAS therapy. Any new pulmonary signs or symptoms warrant early investigation, including repeat TTE for assessment of pulmonary arterial pressures. Moreover, the patient's capacity to tolerate PHT or pleural effusions, although difficult to predict, should be considered in choice of TKI agent. He then spoke about the STIM study and the TWISTER (STOPPING TRIAL IN AUSTRALIA) and remarked how both trials complement each other and show the same results making it even more feasible to talk about stopping as well as mentioning that TKI's are causing harm to patients so we need to see about getting more patients safely off therapy not to mention the cost savings. Given this he thinks that imatinib first line is always a good choice as long as the patient does not have a high SOKAL score or isn't at a high risk for

transformation, close monitoring and then switching to one of the newer TKI's if needed and the choice needs to take into consideration the patients risk profile as far as the aforementioned cardio vascular and pulmonary problems of both Nilotinib and dasatinib. He also talked about the toxicity of Ponatinib (Ariad) and showed a few slides showing the risk associated with cardiovascular, cerebovascular and peripheral vascular diseases. Patients need to be carefully assessed for known risk factors and once on TKI therapy they must be closely monitored. (my personal opinion is that it is very difficult to enforce this as many CML clinicians have accrued large CML patient populations. This presents an opportunity for CML patients to be educated, aware and informed so they can be their own advocates. Tim was asked if the FDA was to harsh on Ariad (Ponatinib) and he said he couldn't comment on the FDA but feels that Ponatinib is a very important drug, has not stopped any of his patients from taking Ponatinib and understands that patients need to be carefully monitored on this drug.

Vivian: Remarked that all of a sudden the 'uncommon' (CML prevalence) has become the common – CML patients are going to represent a high proportion of the clinicians patient base. Clearly patients with high SOKAL score and poor early response were at a high risk of transformation. CML patients do not die of CML; they die of 'co morbidity'.

Rick discussed mechanisms of resistance (nothing really new) and raised attention to the important new work being done to look at the immune system to determine what role it plays in allowing patients to go on a stop trial and remain treatment free – more on this in later sessions.

ORAL SESSIONS:

5 Year update on ENESTnd trial: Dr. G. Saglio presented the data from the trial, which compares Nilotinib to Imatinib. The dose for Nilotinib is 2 X 300 mg. Results are still tracking very well. Overall survival is 96.5% for Nilotinib and 94.7% for Imatinib. While some patients in both arms of the trial have dropped out for various reasons, there remains 62% of Nilotinib patients and 51% of Imatinib patients on the original trail regimen. At 5 years, 77% of the Nilotinib patients and 60% of the imatinib patients have achieved MMR (BCR is = than 0.1%), while 54% of the Nilotinib patients and 31% of the imatinib patients have achieved MR 4.5% (BCR – ABL <0.0032%, 4.5 log reduction or better).

While some patients on treatment did progress to more advanced phases of CML, the common denominator for those patients is that they failed to reach the milestones of >10% BCR ABL at the 3 month milestone. This shows how important monitoring early response is for determining and helping patients to achieve better outcomes.

Cardiovascular events were higher for patients in the Nilotinib treatment arm than for the imatinib arm. However, it is important to point out that most patients (85%) who had a cardiovascular event had at least one risk factor and had not been properly managed with regards to their hyperglycemia and hypercholesterolemia. This is very important for CML patients to be aware of the role they play in helping their healthcare teams stay on track with ensuring that proper patient management can significantly reduce the risk of suffering a cardiovascular event during treatment. This is very important that when we consider that more than half the

patients on Nilotinib achieved MR 4.5% (BCR – ABL <0.0032%, 4.5 log reduction or better) which makes them eligible for the drug stopping trials. Good health management becomes a very important factor to overall success with treatment and outcomes.

4 Year Update on dasatinib trial DASISION:

Dr. Jorge Cortes presented the results for the 4 years which continue to show very good overall survival for both arms, 93% for Dasatinib versus 92% for Imatinib. Similar to the results noted in the above Nilotinib trial, 74% of the patients on Dasatinib versus 60% of the patients on Imatinib reached MMR (BCR is = than 0.1%), and the rates of MR 4 or better were 47% for dasatinib versus 30% for imatinib. While side effects were tracked for both treatment arms of the trial, it is important to note that 22% of the patients on the dasatinib treatment arm experienced pleural effusions.

ENESTcmr trial:

Dr. Brian Leber, Canadian (Hamilton, Ontario) presented the results so far of the ENESTcmr trial. This trial looked to study the question if switching regimens helps patients reach deeper molecular responses. Patients accrued into this trial had received 2 years of prior imatinib therapy achieving a Complete Molecular response (what we now call MR 4.5 or better) but whose BCR ABL was still detectable. Half of the patients were switched to Nilotinib while the other half remained on imatinib, but the half that remained on imatinib could be switched to Nilotinib if after one year there was no improvement in their BCR ABL. The trial started with 207 patients, 62 patients had to drop out, 35 were due to adverse events, the rest for various other reasons. 106 patients still remain on Nilotinib treatment and 37 on imatinib.

It is important to highlight switching did not appear to have any affect to disease progression as no disease progression was reported for this trial. Additionally, switching increased the number of adverse events for patients and may have contributed for the high trial drop out rate. None-the-less, switching a patient to a second generation TKI may be beneficial for some patients to help them achieve deeper molecular responses and perhaps allow them to participate in future drug-stopping trials.

Stopping Trials:

There was a good round up of the various European stopping trials presented at ASH.

STIM1:

Dr. F. Mahon presented the results of the STIM1 trial (patients who had achieved 2 years undetectable BCR ABL were eligible for the trial). Patients PCR were taken once a month for the first year and once every two months for the preceding years. Treatment was restarted if patients showed a loss of 1 log on two consecutive PCR or loss of MMR at anytime. 100 patients were enrolled in the trial. Interestingly only SOKAL risk scores provided any prognostic indication of the risk for recurrence of BCR ABL detectability. No other factors such as, prior IFN therapy, time to BCR ABL undetectability, duration of imatinib treatment. 39% of patients remain undetectable 60 months out. The estimated savings of drug costs because od this trial is about 4.5 million (Euro's). It is important to note that patients should only consider stopping drugs as part of a clinical trial.

A-STIM (According to STIM trial) eligibility similar to STIM1 trial however, loss of MMR (BCR ABL => 0.1%) was the trigger for re-starting treatment. The overarching idea of this trial was to see if patients BCR ABL levels would move around, but in how many cases would it be a true case of disease relapse (recurrence or increased activity of the disease). And in fact, the Treatment Free Remission (TFR) rate is 60% for patients on this trial versus only 40% for patients on the STIM1 trial. We find this intriguing and, when co morbidities and adverse events are factored in, there may be an increasing logic of providing this type of treatment plan for more patients. Strict and very close monitoring is very important and patients should not attempt stopping treatment unless they are in a supervised trial.

STIM2 trial:

There were 127 patients accrued into this trial and more than half (75%) remain undetectable. Of the patients who relapsed (n=52), 48 of the relapses happened before the first four months and four occurred after 9 months. This trial shows that while patients PCR results may fluctuate it does not necessarily mean disease relapse or progression as long as the PCR fluctuations are at a very low level. This has lead to the researchers for this study to question whether stem cell eradication may be really necessary as a goal for curing the disease.

Disease Relapse After TKI Discontinuation In CML Is Related Both To Low Number and Impaired Function Of NK-Cells:Data From Euro-SKI

The Nordic group look at analyzing the data from the EURO-SKI trial by looking at the immunology profile of the patients who relapsed while in the trial. Their initial data shows that a higher of percentage of patients who relapsed seemed to have a lower count of NK (Natural Killer) Cells with impaired function as well. It suggests

that there can be an opportunity into continued research in this area and possibly identify targets for future drug treatments.