CML AdvocatesNetwork

EUROPEAN HEMATOLOGY ASSOCIATION
23RD CONGRESS

SATURDAY, JUNE 16. CLINICAL. ORAL.

Abstract: S809

FINAL RESULTS OF THE DESTINY STUDY OF DE-ESCALATION AND STOPPING TREATMENT IN CHRONIC MYELOID LEUKAEMIA

Richard Clark

11:30 AM-11:45 AM

Location: Room A2

Aims

TKI treatment was de-escalated to 50% of the standard dose (imatinib 200mg daily, dasatinib 50mg daily or nilotinib 200mg twice daily) for 12 months, then stopped altogether for a further 24 months. Centralised PCR monitoring was carried out 1-2 monthly, expressed according to International Scale. Molecular recurrence was defined as the first of 2 consecutive samples >0.1%; this required recommencement of the relevant TKI at full dose.

Conclusion

The present finding of minimal (only 5) recurrences in the second stopping year, thus sustaining the excellent previously reported RFS out to 24 months of stopping, suggests that initial de-escalation is not simply delaying recurrence, though the mechanism of its benefit is not yet clear. Possibilities include gradual mobilisation of leukaemic stem cells into cycle and/or gradual improvement in the anti-leukaemic immune response at a time when TKI is still present. These require further study.

SATURDAY, JUNE 16. CLINICAL. ORAL.

Abstract: S810

CHOICES: A RANDOMIZED PHASE II TRIAL FOR IMATINIB VS HYDROXYCHLOROQUINE PLUS IM FOR PATIENTS WITH CML IN MCYR WITH RESIDUAL DISEASE DETECTABLE BY Q-PCR

Dr. Gillian Horne

11:45 AM-12:00 PM

Location: Room A2

Aims
The primary study end-point was the proportion of treatment 'successes', defined as patients who had >0.5 log reduction in their 12-month (mth) qPCR level from baseline. The secondary study end-points were the proportion of treatment 'successes' at 24 mth, molecular response and progression at 12 and 24 mth, comparison of IM levels between study arms, and the proportion of patients who achieved whole blood HCQ levels >2000ng/ml.

Conclusion
We confirm that IM+HCQ is a tolerable combination in CP-CML, with significant improvement in overall qPCR levels and MMR at 24 mth. This suggests that there may be a potential long-term benefit of combined therapy on qPCR levels and achievement of deep molecular response. Longer follow-up will be required to confirm this.

SATURDAY, JUNE 16. CLINICAL. ORAL.

Abstract: S811

THE EUTOS LONG-TERM SURVIVAL (ELTS) SCORE IS SUPERIOR TO THE SOKAL SCORE FOR PROGNOSIS OF SURVIVAL PROBABILITIES OF PATIENTS WITH CHRONIC-PHASE CHRONIC MYELOID LEUKAEMIA

Markus Pfirrmann

12:00 PM-12:15 PM

Location: Room A2

Aims
The Sokal score had allocated 23% of patients to the high-risk group, the ELTS score 12%. Long-term outcome of TKIs suggests that allocating >20% CP CML patients into a high-risk group is too pessimistic. The aim of this analysis was to compare risk group allocations and prognosis between the two scoring systems.

Conclusion
The Sokal score allocated 13% (n=671) more patients to the high-risk group than the ELTS score. As these patients had significantly and clinically relevant lower CIPs of death and higher OS probabilities, the allocation of the Sokal score was not appropriate. OS probabilities but not the CIPs of 1,200 patients assessed as low-risk by the ELTS and non-low-risk by the Sokal score were different from the probabilities of 1,837 assessed as low-risk patients by both scores. For prediction of long-term survival, the use of the ELTS score is recommended.

SUNDAY, JUNE 17. BIOLOGY AND TRANSLATIONAL RESEARCH. ORAL.

Abstract: S1550

THE TUMOR SUPPRESSOR MIR-300 PRESERVES CANCER STEM CELLS AND INHIBITS NK CELL ANTICANCER IMMUNITY.

Dr. Danilo PERROTTI

08:00 AM-08:15 AM

Location: Room A2

Aims
miR-300 interconnects CSCs, microenvironment and immune cells.

Conclusion
In Summary, loss of miR-300 expression is essential for survival/proliferation of leukemic progenitors and, therefore, increased miR-300 expression is necessary for reduced NK cell number/activity and maintenance of the LSC reservoir. Induction of TUG1 may occur to preserve LSC survival after migration into the BM endosteal niche where quiescence is induced by MSCs and low O_2 levels through marked induction of intracellular miR-300 levels. Thus, disrupting the miR-300/TUG1 balance may represent a potential therapeutic approach for treatment/eradication of LSC-derived leukemias and restoration of innate immunity.

SUNDAY, JUNE 17. BIOLOGY AND TRANSLATIONAL RESEARCH. ORAL.

Abstract: S1551

JAK1-STAT3 SIGNALING AXIS SUPPORTS LEUKEMIC STEM CELL PERSISTENCE IN CML

Mirle Schemionek

08:15 AM-08:30 AM

Location: Room A2

Aims

In this study, we first analyzed STAT3 activation in TKI treated leukemic cells, and how it is influenced by the BM microenvironment. Subsequently, we aimed to identify the mechanism allowing for TKI-persisting STAT3 activation and evaluated the therapeutic potential of combined Bcr-Abl and JAK1 inhibition using human cell lines, primary murine cells, as well as primary CML $CD34^{+}$ cells.

Conclusion

In the presence of BM microenvironment-derived CM, STAT3 is upregulated in Bcr-Abl leukemic cells upon oncogene inhibition. Here, we identified JAK1 as the STAT3-activating kinase in CML cells. JAK1 inhibition by TKIs decreases $pSTAT3^{Y705}$ levels, blocks proliferation and reduces the CFU capacity. Upon Bcr-Abl and JAK1 inhibition, apoptosis is strongly induced compared to IM treatment alone in quiescent LCS. Our data demonstrate that persistent STAT3 activation is observed under IM treatment and supported by the microenvironment via JAK1 thus promoting LSC survival. As a consequence, JAK1 emerges as a potential therapeutic target for curative CML therapies.

SUNDAY, JUNE 17. BIOLOGY AND TRANSLATIONAL RESEARCH. ORAL.

Abstract: S1552

MS4A3 REGULATES CELL SURFACE CYTOKINE RECEPTOR EXPRESSION, DIFFERENTIATION, AND DRUG RESISTANCE IN CHRONIC MYELOID LEUKEMIA

Anna Eiring

08:30 AM-08:45 AM

Location: Room A2

Aims

The aim of this study was to identify the functional consequence of reduced MS4A3 expression in TKI resistance and blastic transformation of CML.

Conclusion

Altogether, these data suggest that MS4A3 plays a key role in 1) BCR-ABL1 kinase-independent resistance, 2) progression of CML from the chronic to the blastic phase of disease, and 3) in primitive CML stem cells versus progenitors.

SUNDAY, JUNE 17. BIOLOGY AND TRANSLATIONAL RESEARCH. ORAL.

Abstract: S1553

THE COMBINATION OF THE MDM2 ANTAGONIST, IDASANUTLIN WITH NILOTINIB TARGETS PRIMITIVE CHRONIC MYELOID LEUKEMIA (CML) CELLS IN VITRO AND IN VIVO.

Mary Scott

08:45 AM-09:00 AM

Location: Room A2

Aims

As our ultimate aim is to introduce novel therapies into the clinic that eliminate CML LSC, we examined the effect the MDM2 antagonist, idasanutlin ('Idasa') has in combination with nilotinib ('Nil') on leukemia cell numbers and LSC *in vitro* and *in vivo*.

Conclusion

Overall these data show that pharmacological modulation of p53 in combination with TKI can target the most primitive CML cells, potentially in a synergistic manner. Moreover, recovery data from our PDX model suggests that this combination may abrogate the stem cell expansion which is seen with TKI alone following drug withdrawal, giving hope for treatment-free survival in patients. A planned clinical trial will test the efficacy of idasanutlin in combination with TKI.