



EHA ANNUAL CONGRESS 2016

THE BELLA CENTER,
COPENHAGEN, DENMARK
9TH-12TH JUNE 2016

Welcome to the *European Medical Journal* review of the 21st Congress of the European Hematology Association

The city of Copenhagen has been voted the go-to place for holiday makers in Denmark, and from the 9th of June and the 4 days that followed, it was without a doubt the go-to place for haematologists around the world as the 21st Congress of the European Hematology Association (EHA) 2016 took place there. The beautiful city of Copenhagen is a cultural hub with international appeal, providing the perfect environment to meet and discuss all things haematology.

The EHA congress last appeared in Copenhagen back in 2008, welcoming around 6,500 people in attendance. After its 8-year break from the city, EHA 2016 is now able to boast well over 10,000 attendees. In light of the event's popularity, the President of the EHA, Prof Tony Green, Haematology Department, University of Cambridge, Cambridge, UK, took the opportunity to express in the opening ceremony address: "We feel confident there is something for everyone." This year's congress included a record number of 2,435 submitted abstracts and 84 submitted late breaking abstracts, all highlighting the latest innovations from a vibrant community of basic, translational, and clinical researchers within the field of haematology.

Each year, the EHA recognises important contributions made by leading haematology researchers with the José Carreras Award. This year the award was bestowed upon Prof Eva Hellström Lindberg, Sweden, in recognition of her contributions to translational and clinical research into the pathogenesis and treatment of myelodysplastic syndromes. Established in 2008, the Jean Bernard Lifetime Achievement Award honours the lifetime contributions of outstanding physicians and scientists to the advancement of haematology medicine. This year's award went to Prof Clara Camaschella, Italy, for her outstanding portfolio of work concerning the pathophysiology of inherited disorders of iron metabolism including hereditary haemochromatosis, genetic iron deficiency, and iron-loading anaemias.

Several EHA research fellowships were allocated to support researchers just beginning their careers and the winners were as follows: The John Goldman Clinical Research Fellowship: H. Poeck (Germany); the Clinical Research Fellowship:

G. Jansen (Netherlands); the Non-Clinical Junior Research Fellowship: D. Passaro (UK); the José Carreras Non-Clinical Research Fellowship: A. Nai (Italy); the Non-Clinical Advanced Research Fellowship: E. Laurenti (UK); and M. Crisan (UK). EHA President Prof Green emphasised the commitment of the organisation to the development of junior and early career researchers with the announcement of the launch of the new Clinical Research Training in Hematology programme. "This is a programme that will run throughout the coming year and is specifically targeted at young haematologists with the aim of providing them with a way of becoming specialised in the area of clinical trials," Prof Green said during the opening ceremony address.

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EHA 2016 was an excellent event that brought everyone up to speed with the latest innovations and developments through its comprehensive scientific and educational programme. It brought to the forefront many of the pressing issues and promising results that have emerged from recent haematology research and practice. This includes topics such as whether leukaemia patients can ever move on from life-long tyrosine kinase inhibitor therapy, and the promising results of the high remission rates for leukaemia patients receiving the antibody drug conjugate vadastuximab talirine in a Phase I trial. These are just two amongst the many stories reported in this year's journal which reflect a brilliant year for the advancement of haematological medicine, and we are already looking forward to next year's congress, which is set to take place in the Spanish capital, Madrid.



Congress Highlights



SGN-CD33A Antibody Drug Conjugate Causing High Remissions Rates for Leukaemia Patients

SGN-CD33A (also known as vadastuximab talirine) combined with hypomethylating therapy has shown promising results for the treatment of acute myeloid leukaemia (AML) in older patients.

This is according to a EHA press release dated 11th June 2016. It reports on data from an ongoing Phase I trial evaluating the antibody drug conjugate vadastuximab talirine in concert with standard therapies (azacitidine, decitabine) in older AML patients who have declined intensive frontline therapy.

AML is an aggressive form of blood cancer which is difficult to treat in older patients because intensive chemotherapy can cause adverse effects and response rates from standard therapies are modest. SGN-CD33A is targeted to CD33, which is expressed on leukaemic blasts in nearly all AML patients, with expression remaining relatively consistent across the range of ages, risk factors, and disease characteristics. The SGN-CD33A drug conjugate is comprised of a novel antibody system stably linked to a highly potent cell-killing agent.

As of 11th June 2016, 53 AML patients with an average age of 75 years old have been treated with SGN-CD33A combined with either the azacitidine or the decitabine methylating agent. Efficacy evaluation was available in 49 of the patients who had received this treatment. A composite complete remission rate of 73% was measured in the group. The mortality rates were 2% at 30 days and 8% at 60 days. Grade III, or severe adverse events, occurred in at least 20% of the patients who experienced febrile neutropenia, thrombocytopenia, anaemia, and neutropenia. The combination of treatment was found to be well-tolerated by patients and yielded encouraging response rates in older AML patients, which are favourable to other hypomethylating agents in this population.



84 submitted late breaking abstracts



Results of Ongoing Gene Therapy Study for Haemophilia B Reported

RESULTS of an ongoing study have been reported evaluating the safety and tolerability of a single intravenous infusion designed to facilitate production of the Factor IX (FIX) protein, according to a EHA press release dated 11th June 2016.

Haemophilia B is a genetic bleeding disorder caused by insufficient or defective blood clotting protein FIX, which affects roughly 80,000 males worldwide. Normal clotting factor activity levels range from >40-150%. Individuals with haemophilia B have FIX activity levels of <1%. This can result in recurrent joint, muscle, and tissue bleeding, as well as life-threatening bleeding in closed spaces such as the brain.

Prophylactic FIX protein replacement has been found to be effective in patients who fully adhere to the treatment. In spite of this, the burden of once or twice weekly intravenous infusions has meant that the treatment is not yet approved for widespread use. Researchers have provided updates on an ongoing Phase I/II study which is evaluating safety and tolerability of a single intravenous infusion of the gene transfer product SPK-9001. This product has been designed to allow the body to produce its own FIX protein by transferring a functioning FIX gene into the body of the patient.

...patients showed FIX activity levels of 32%, 39%, 25%, and 27%, respectively. These levels are above the threshold of 12% required to reduce the risk of bleeding.

As of 11th June 2016 four participants have been followed for 7-26 weeks after a single intravenous infusion with 5x10¹¹ vector genomes/kg of SPK-9001 without the need for immunosuppression. No serious adverse effects related to the product or procedure have been reported, including immune responses, and no patients have required steroids or other medications to suppress the immune system.

As of 22nd May 2016 patients showed FIX activity levels of 32%, 39%, 25%, and 27%, respectively. These levels are above the threshold of 12% required to reduce the risk of bleeding. The participants are no longer infusing FIX protein products and all are free from bleeding with the exception of a suspected ankle bleed in one patient 2 days after the gene transfer.

New Oral Anticoagulants Studied as Treatment for Major Bleeding

NEW oral anticoagulants (NOACs) used to treat major bleeding (MB) have been the focus of an international prospective cohort study presented at this year's EHA Congress

in Copenhagen, Denmark, according to a EHA press release dated 10th June 2016.

Death at 30 days was found to be significantly lower in patients treated with NOACs when compared with vitamin K antagonist (VKA) treatment. NOACs are presently used in clinical practice for prophylaxis of venous thromboembolism, along with prevention of stroke and systemic embolism in nonvalvular atrial fibrillation. They are associated with a favourable safety profile in Phase III randomised control trials, having lower incidences of MB compared with VKAs.

The multicentre study was performed to gauge the efficacy of NOACs against VKAs in real-life, comparing clinical presentation, management, and outcome of bleeding. The research incorporated an Italian cohort of nine hospitals and a German cohort from the Dresden NOAC registry, with a primary study outcome of in-hospital death at 30 days. Of the 874 patients hospitalised for MB, 76% of participants were treated with VKAs and 24% treated with NOACs. Incidents of MB included intracranial haemorrhage in 52% and 22% of patients on VKAs or NOACs, respectively; and gastrointestinal bleeding in 25% and 46%, respectively. Thirty-day mortality occurred in 136 patients: 17% of VKAs patients and 10% of NOAC patients.

“ The great advantage of NOACs is the reduced risk of intracranial haemorrhage, so we show that the lower mortality rate is due, not to an intrinsic capacity to reduce death between NOAC as compared with VKA patients, but to a different pattern of bleeding sites. ”

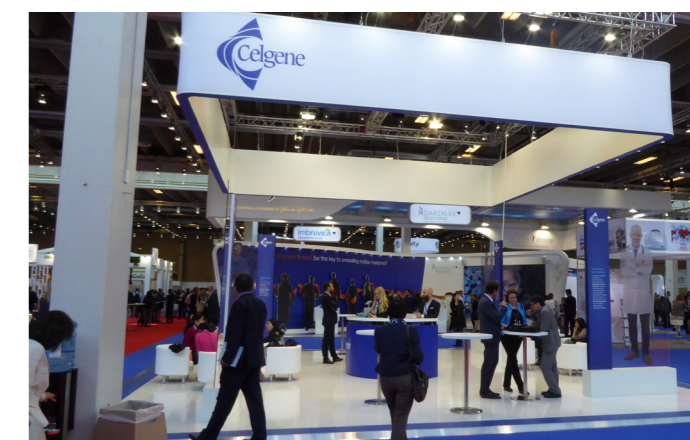
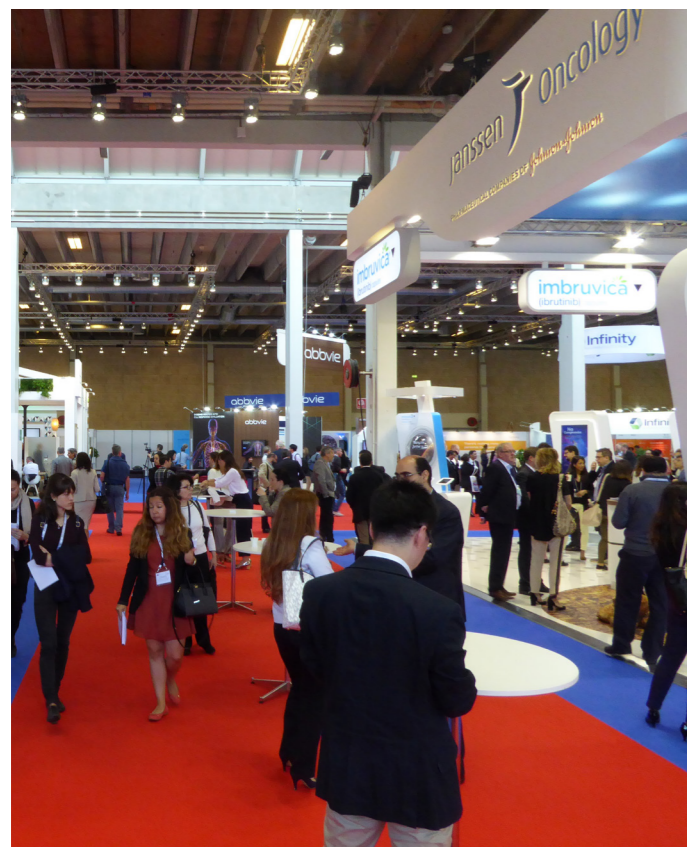
Leader of the study Dr Laura Franco, Stroke Unit, Vascular and Emergency Medicine, University of Perugia, Perugia, Italy, explained that while NOAC patients have a higher rate of gastrointestinal bleeding and lower rate of intracranial haemorrhage than VKA patients, these rates differ across bleeding sites. She commented: “The great advantage of NOACs is the reduced risk of intracranial haemorrhage, so we show that the lower mortality rate is due, not to an intrinsic

capacity to reduce death between NOAC as compared with VKA patients, but to a different pattern of bleeding sites.”

New Form of Invisible Inherited Thrombocytopenia Discovered

MUTATIONS in the *ETV6* gene can cause the development of a newly discovered form of inherited thrombocytopenia (IT), a EHA press release dated 10th June 2016 reported. The disorder, named ETV6-related thrombocytopenia (ETV6-RT), is characterised by a deficiency of platelets and puts patients at risk of a number of conditions.

The results of a study presented at this year's EHA congress in Copenhagen, Denmark, which identified this particular form of IT, suggest that ETV6-RT could present in roughly 5% of patients who have been diagnosed with IT. The disorder is passed on to children if one parent possesses the faulty gene, and is particularly dangerous as its characteristics differ greatly from the recognised warning signs of IT. Firstly, it is one of a very small number of IT variants which do not cause large platelet sizes; and secondly, there is a greatly reduced occurrence of bleeding (often a mild tendency but sometimes none at all).



The risk of blood cancer is a particular concern for paediatric patients with ETV6-RT.

The risk of blood cancer is a particular concern for paediatric patients with ETV6-RT. The authors of the study noted that, together with the difficulty of diagnosis due to the aforementioned characteristics, the increased risks of developing haematological malignancies, and particularly the risk of childhood B cell acute lymphoblastic leukaemia, should not be underestimated. The authors recommend devoting more attention to detecting blood cancer than the potential bleeding complications associated with the disorder, due to the infrequency of such events, which rarely affect quality of life for patients. Their recommendation is to run genetic screening for the *ETV6* mutation in any patient who displays platelets of a normal size but who has been diagnosed with IT.

Pre-leukaemic Stem Cells may be Key to Relapse in Acute Myeloid Leukaemia

PERSISTENCE of pre-leukaemic cells after chemotherapy is associated with recurrence of acute myeloid leukaemia (AML), according to a EHA press release dated 10th June 2016. AML is an aggressive cancer; intensive chemotherapy can induce remission, however recurrence is common especially amongst older patients.

The origin of AML in some patients is a mutation in a pre-leukaemic stem cell clone, this is a stem cell with somatic mutations which can develop into cells with additional mutations or into completely normal cells. Cells with additional mutations can progress to overt AML. Although chemotherapy can induce remission from leukaemia cells, pre-leukaemic cells can remain. This research aimed to divulge whether the persistence of these pre-leukaemic stem cells after chemotherapy changes outcomes and, ultimately, whether it affects survival.

The go-to place for haematologists



The cohort for this trial consisted of 107 patients who had entered remission during a German multicentre trial. Within these patients, 68 genes with their associated mutations were analysed at diagnosis and following treatment to see if they were cleared by chemotherapy. Remission specimens showed that, in 36% of patients, gene mutations found in leukaemia were still present, indicating the persistence of a pre-leukaemic clone. The genes found included a specific subset including: *DNMT3A*, *TET2*, *ASXL1*, and *SRSF2*. The presence of these mutations was more common in older patients.

The most important finding from this research is the fact that these persisting mutations resulted in an increased risk of disease recurrence after chemotherapy, compared with those without persisting mutations. This is a step toward understanding why so many patients relapse and how we may soon be treating them beyond the initial chemotherapy.

“ One thing that we plan to follow-up on this study, is to look at relapses in these patients and to track how often these really come from the pre-leukaemic clone. ”

Dr Klaus Metzeler, University Hospital, Ludwig-Maximilians-University, München, Germany, said: “One thing that we plan to follow-up on this study, is to look at relapses in these patients and to track how often these really come from the pre-leukaemic clone. That would give us further arguments to actually treat patients who have a pre-leukaemic clone after their standard induction chemotherapy.”



Potential Alternative for Relapsed and Refractory Myeloma Patients

MYELOMA patients who have relapsed or become refractory to treatment could have access to an effective alternative following the success of the daratumumab antibody in a Phase III study.

The results of an ongoing, open-label, randomised Phase III study conducted in 18 countries and involving 569 patients have been reported in a EHA press release dated 10th June 2016. The study evaluated daratumumab, a monoclonal antibody that binds to a novel target on myeloma cells, in combination with lenalidomide and dexamethasone. This therapy was compared to a control group who received only the lenalidomide and dexamethasone. All patients involved in the study had relapsed or refractory multiple myeloma and had received at least one prior line of therapy.

Following an interim analysis, researchers found an unparalleled 63% reduction in the risk of progression or death in the group receiving daratumumab when compared to the control group. This led to an early unblinding of the study. Overall responses ($p < 0.0001$) were experienced by 93% of the daratumumab group and 76% by the control group. The extent of treatment response was found to be much higher in those taking daratumumab with 76% patients experiencing a very good partial response or better ($p < 0.0001$) in comparison to 44% of control patients. With regards to a complete response, more than double the number of daratumumab patients (43% versus 19%) experienced a complete response or better ($p < 0.0001$).



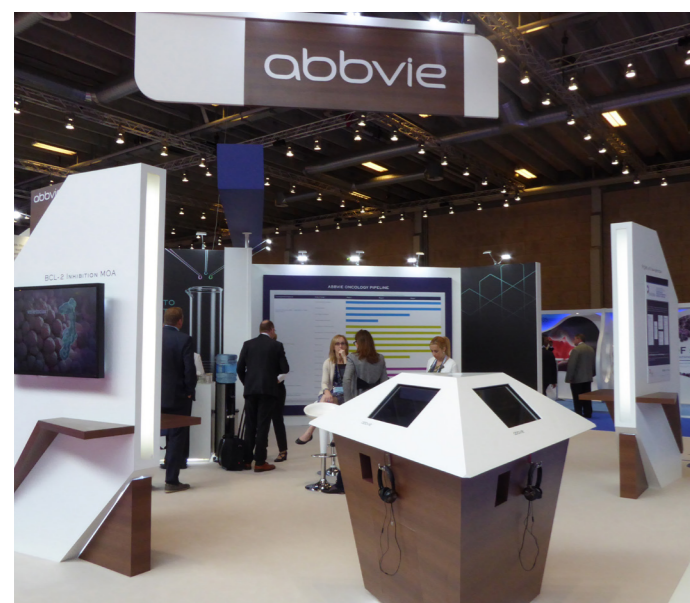
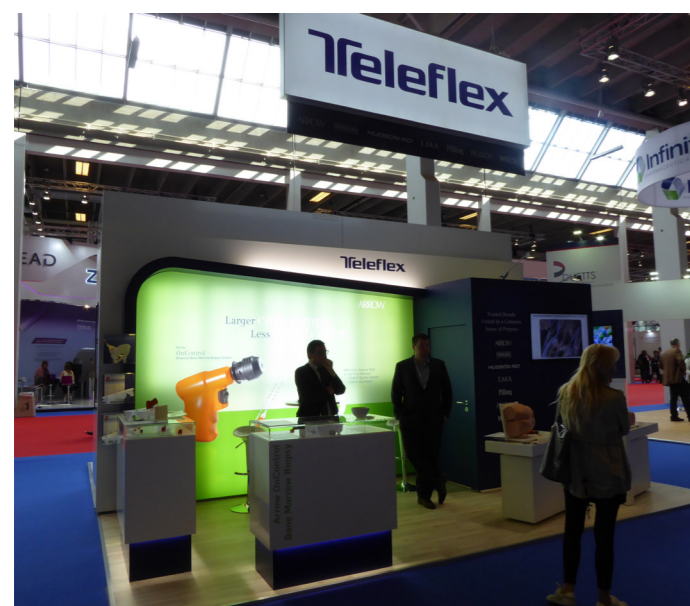
...the study has established a positive benefit/risk profile for daratumumab with lenalidomide and dexamethasone in multiple myeloma patients who have received at least one prior line of therapy.

The research suggests that this combination could be an effective alternative for refractory and relapsed patients as treatment was considered to be well-tolerated by the daratumumab group with the occurrence of adverse events among patients consistent with the known profiles of these drugs. Furthermore, the study has established a positive benefit/risk profile for daratumumab with lenalidomide and dexamethasone in multiple myeloma patients who have received at least one prior line of therapy.

Immunotherapy Offers Life-Saving Approach to Leukaemia Patients

RELAPSED or refractory (r/r) patients with acute lymphoblastic leukaemia (ALL) may soon have access to a life-saving alternative treatment in the form of an immunotherapy agent. The rate of adults with ALL who achieve disease control with intense chemotherapy is as high as 90%, although only half of those responsive to the treatment will be cured. For those who are unresponsive and r/r after chemotherapy, the resulting outcome is poor, regardless of further chemotherapy or treatment such as allogeneic haematopoietic stem cell transplantation. Immunotherapy,

however, offers a new treatment alternative for r/r patients by delivering antibody constructs that engage with a patient's T cells to fight ALL.



According to a EHA press release dated 10th June 2016, the results of previous Phase II trials have shown that blinatumomab, a bispecific T cell engager antibody construct, caused 43% of r/r patients with ALL to achieve disease control. It also reported on a more recent Phase III clinical trial which tested whether blinatumomab could achieve an increased survival benefit in r/r ALL patients compared to standard chemotherapy. The study involved 405 r/r ALL patients from Europe, North America, Asia, and Australia who were randomised in a 2:1 ratio to receive either blinatumomab (n=271) or a standard chemotherapy regimen (n=134). The results showed an improved overall survival of patients receiving blinatumomab.

The results of the trial indicate that blinatumomab is the first immunotherapy agent proven to extend the life of a patient with r/r ALL when compared with chemotherapy.

The Phase II trial was stopped prematurely as the antibody treatment almost doubled the overall survival rate when compared to chemotherapy. This was witnessed in each subgroup of patients, including those who had relapsed after an allogeneic haematopoietic stem cell transplantation, multiple different chemotherapy regimens, or both combined. No more severe side effects were seen after treatment with blinatumomab than chemotherapy. The results of the trial indicate that blinatumomab is the first immunotherapy agent proven to extend the life of a patient with r/r ALL when compared with chemotherapy.

Researchers Explore Effects of Leukaemia Patients Ending Life-Long Treatment

THE PROPORTION of chronic myeloid leukaemia patients maintaining a therapeutic response after stopping tyrosine kinase inhibitor (TKI) therapy has been examined in a study spanning across Europe. The study was conducted as an attempt to determine clinical and biological factors that would enable the successful ending of TKI therapy.

TKIs have significantly improved the survival rates of patients in the early chronic stages of chronic myeloid leukaemia yet this form of treatment continues for a period that spans across the lifetime of the patient. Previous research has explored the potential for patients to stop TKI therapy, revealing that 40-60% have been able to do so with a good therapy response.



According to a EHA press release dated 10th June 2016, 868 patients in 11 European countries were registered in the Phase III European Stop Tyrosine Kinase Inhibitor (EURO-SKI) study. The requirements of the study meant patients had to have at least 3 years of TKI therapy and to have had a very good response to therapy for at least 1 year prior to study entry. Patients were also required to have not failed previous TKI treatment in order to be included.

TKIs have significantly improved the survival rates of patients in the early chronic stages of chronic myeloid leukaemia yet this form of treatment continues for a period that spans across the lifetime of the patient.

The results of the study showed that 62% of the patients continued to maintain a therapeutic response 6 months after stopping the therapy. After 12 months of the therapy ending, 56% of patients continued a positive therapeutic response. The researchers also found that duration of TKI therapy as well as an encouraging treatment response prior to the end of the therapy was a predictor of whether stopping would be successful. The likelihood of a patient successfully stopping TKI therapy in relation to a patient's gender, age, or risk score was not determined by the study.

Nivolumab Benefits Patients with Relapsed Hodgkin's Lymphoma

A STUDY has been undertaken to examine the efficacy and safety of the drug nivolumab for patients with classical Hodgkin's lymphoma (cHL), according to a EHA press release dated 10th June 2016. The disease typically affects young men and women in their 30s and it is one of the most treatable types of cancer using a combination of chemotherapy and radiotherapy.





Despite this, cHL should still be a high priority, as approximately 20% of patients experience some form of relapse and will not be cured with first or second-line treatments. It has taken over three decades for a second drug to be introduced, nivolumab, as an effective treatment for the relapse of Hodgkin's lymphoma. A few years ago, brentuximab vedotin was the first drug to be approved by the US Food and Drug Administration (FDA) for the treatment of Hodgkin's lymphoma and nivolumab is due to be the second.

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Checkmate 205, the registrational trial for the Phase II evaluation of nivolumab with cHL showed positive results. Patients with cHL, after failure of both autologous stem cell transplantation and brentuximab vedotin treatment, were treated with nivolumab. The primary endpoint of objective response rate (ORR) per an independent radiologic review committee was 66.3% and 73% by investigator response (secondary endpoint). The median response time was 2.1 months, and time of remission was 7.8 months, (95% confidence interval: 6.6 to not evaluable). At the time of analysis, 62.3% of responses were ongoing. Forty-three patients who had exhibited no response when receiving brentuximab vedotin had an impressive 72% ORR with the newer drug. The results of the study also found no significant risks of using nivolumab, as the safety profile was consistent with previously reported data of this tumour type.

Ibrutinib Performs Well in Aggressive Leukaemia Trials

POSITIVE outcomes have been observed from an integrated analysis of chronic lymphocytic leukaemia (CLL) patients treated with ibrutinib, reports a EHA press release dated 10th June 2016. CLL patients with deletion of chromosome 17p (del17p) often present with an aggressive disease and characteristically poor outcomes; survival rarely exceeds 2-3 years in patients initially treated with chemotherapy.

The European Union (EU) and USA have nuanced regulations for use of the first-in-class Bruton's tyrosine kinase inhibitor, ibrutinib, although both have approved its use for those with del17p CLL. Aiming to examine the safety and efficacy outcomes of ibrutinib in this patient population, a cross-study of three clinical trials analysed 243 individuals with del17p CLL treated with once daily ibrutinib 420 mg (n=232) or 840 mg (n=11) to the primary endpoints of progressive disease or 'unacceptable toxicity'. The median time in study was 28 months at which point overall response rate was consistent across all three trials at 84%.

Over 10,000 attendees

With promising survival outcomes and a relatively low rate of discontinuation from adverse events the continued study of this patient group will have great significance...

At a 30-month follow-up, ~55% of the participants were progression-free and 67% had survived, figures exceeding the treatment outcomes of trials investigating alternative del17p CLL therapeutic strategies. Furthermore, adverse events Grade 3 or more leading to treatment discontinuation occurred in 15% of patients (n=36). This study is ongoing, with 45% of the cohort continuing on study treatment, however it is clear from the integrated results of these clinical trials presented at EHA 2016 that ibrutinib is a potential treatment candidate for difficult-to-treat CLL populations. With promising survival outcomes and a relatively low rate of discontinuation from adverse events the continued study of this patient group will have great significance, and further clinical trials of the safety and efficacy of ibrutinib are vital.

Genome Sequencing Used by Scientists to Tackle Blood Disease

RESEARCHERS around the world are currently in the process of sequencing the whole genomes of thousands of patients to identify the genetic causes of blood disorders as well as to gain insights into already known causes of some blood disorders.



Approximately three million people have a rare bleeding disorder or a disease of the platelets. Despite significant progress made in identifying the causes of many such diseases and disorders, many still remain unknown to scientists. The opportunity to generate large amounts of information to aid in future discoveries of the genetic causes of blood disorders and diseases could be a great benefit to millions of patients who experience these common life-threatening events.

According to a EHA press release dated the 11th June 2016, researchers and collaborators across the world supported by the National Institute Health Research (NIHR) BioResource for Rare Diseases in the UK are sequencing the whole genomes of thousands of patients without a genetic diagnosis. By collating the information collected from the sequencing into a research database and running computational analysis, common genetic changes can be identified, which may contribute to the disease.

Already the innovative approach has proved a success. The team have reported on the discovery of a genetic link between large platelets and deafness; a genetic change in a well-known cancer gene responsible for fragile bones; a link between scarring of bone marrow and a low platelet count; and an association between large platelets and heart rhythm problems. The team also explained that these discoveries and others have been able to benefit patients through accessible genetic testing available in the UK and elsewhere provided by thrombogenomics.org.uk.





Klaus-Michael Debatin

Chairman, Department of Paediatrics and Adolescent Medicine, University Medical Center Ulm, Ulm, Germany.

Q: You are a specialist in both haematology and paediatrics. How much does haematological practice differ between adult and paediatric populations?

A: The spectrum of diseases is obviously different in the different age groups. Leukaemia and solid tumours have a high prevalence in the advanced age group while the frequency is low in children and adolescents, with a peak in leukaemia in early childhood. The different spectrum of disease entities is seen in leukaemia wherein childhood and adolescence acute lymphoblastic leukaemia is the most prevalent malignancy followed by Hodgkin's lymphoma and acute myeloid leukaemia. Chronic myelocytic leukaemia is rare in the young age group, while in adults, chronic myeloid leukaemia, chronic lymphatic leukaemia, and acute myeloid leukaemia are the predominant diseases in addition to a broad spectrum of different lymphomas, mostly of mature lymphoid cells. The different disease spectrum may reflect different roots of origin such as genetic susceptibility, genetic driver lesions, etc. In general, malignant disorders in childhood are highly aggressive and are unequivocally rapidly fatal in course. In addition, paediatric haematology also deals with a large variety of, in part, very rare genetic disorders with a broad spectrum of clinical phenotypes, ranging from severe combined immunodeficiency due to defects in genes of lymphoid development, to defects in immunoregulation, to bone marrow failure syndromes, and genetic causes of anaemia. The different spectrum provides an extreme challenge for individualised therapy.

“ My own area of research over the past almost 30 years has laid the basis for the development of novel therapeutic strategies... ”

The enormous progress in genetic medicine provides a clear basis for understanding the diseases and developing of gene/pathway-directed therapies, both in malignant and non-malignant haematological diseases.

Q: What have been the main changes that you have witnessed since your career began in this area of medicine?

A: Over the past 30 years, the progress, especially in the treatment of childhood leukaemia has been enormous. With therapy protocols which started on the basis of trial and error, and empirical observations associated with a high burden of treatment related mortality, significant cure rates were achieved in the 1970s. Since then, treatment of childhood leukaemia and malignancies in childhood and adolescence in general has developed into one of the most significant success stories in oncology. To witness these developments directly, not only on the bedside of patients, but also on the bench of research has always been a privilege for me. The development of risk-adapted therapy protocols, where 'risk' is defined as outcome under a given therapeutic umbrella with a more and more refined risk-stratification strategy, has been the basis for this development. The identification of 'risk factors', starting from biological parameters such as age and gender, to immunophenotyping, to genotyping, to pathway-oriented translation of molecular genetic knowledge, is currently still the basis for clinical protocols that use a large extent of cytotoxic drugs that had been developed in the past without exact knowledge of their mechanism of action. Historically paediatric haematology/oncology has been concerned, in the early days, mainly with partially frustrating attempts to cure the diseases, whereas now we are more concerned

about the long-term sequelae of our patients on the background of an 80% success rate and long-term survival.

Q: What issues are currently affecting haematologists, especially those who focus on paediatric populations? What do you think could be done to address these problems?

A: In the area of malignant haematology we are particularly concerned with the long-term consequences of our successful therapies with the attempt to reduce therapy where possible and to sharpen therapeutic strategies. This includes pathway-directed approaches in areas where a cure is still not on the horizon. Genetic diseases on the other hand, to a large extent, will soon have the problem that we still cannot offer a true gene-oriented therapy, despite detailed knowledge of the genetic causes of the disease. Here, we clearly need more research on gene-correcting therapies, specifically with the knowledge that traditional approaches of gene therapy, using viral vector systems, led to a significant number of leukaemias in diseases, where haematopoietic stem cells have been gene-corrected.

Q: Your research focusses on apoptosis and tumour development. What are the latest developments in this field? Were there any particularly exciting presentations at this year's European Hematology Association (EHA) congress on current research in this area?

A: My own area of research over the past almost 30 years has laid the basis for the development of novel therapeutic strategies and novel compounds that specifically address cell death and survival pathways, both in tumour development as well as in therapy. These approaches include targeting anti-apoptotic *Bcl-2* family members by BH3 mimetics and the development of strategies to counteract apoptosis inhibitors. Also, *p53* is coming back into the focus as a therapeutic target by novel compounds that enable or restore deficient *p53* function. Such approaches have also been discussed in EHA meetings in the past 2 years.

Q: You have worked in Germany and the USA. How do the healthcare and research environments differ in terms of haematology between these countries?

A: I do not think that there are many differences with respect to patient treatment and outcome between Germany and the USA. As an example, Berlin-Frankfurt-Munster (BFM) protocols for treating acute lymphoblastic leukaemia developed in Germany have been, and still are, worldwide among the most successful treatment protocols and we are in good connection with our USA colleagues in balancing different treatment strategies and crossing over treatment elements that have shown superior outcome in either of these protocols. However, the difference between Germany (and Europe) and the USA is certainly in the research environment. While this is in part simply a financial issue, research budgets in the USA at comparable institutions are several fold up to 20-fold higher compared to budgets at German institutions. It is also a question of culture. Thus, the clinical researcher in the USA, although in many statements has been referred to as 'in danger' for the last few decades, is still active and many programmes at universities have a specific focus on the clinician scientist as a specific model for patient-oriented research. With the increasing knowledge in basic research related to clinical medicine, this translator position becomes even more important. Most universities in Germany have just started or built up clinical scientist programmes. In the past, like in my own career, becoming a clinical scientist has more been chance, opportunity, and individual initiative in the context of specific academic institutions or institutions funding researchers (Deutsche Forschungsgemeinschaft), than specific planning.

Q: How much progress has been made in cancer therapies in the last 10 years? What developments have had the most influence on this progress?

A: Over the past 10 years the speed of development in the -omics technologies and the discovery of genes causing specific diseases has certainly had the greatest impact on



our understanding of the nature of diseases. Incorporation of this knowledge into pathway-oriented therapies and in a deeper understanding of cell biology provide a basis for further development. However, in paediatric haematology such as in the treatment of acute lymphoblastic leukaemia, we have reached a very high level of cure rates with conventional therapy. Despite our increasing knowledge in basic research, this knowledge has not yet really translated into highly significant progress in further increasing this level. This may be partly due to the fact that identification of single-genetic lesions and single-pathway targeting by specific compounds will not solve the problem of heterogeneity of leukaemia cells and of the sheer number of deregulated pathways that occur in tumour cells. Thus, leukaemia, with rare exceptions, such as *BCR-ABL* targeting by imatinib (Glivec®) as the driver lesion, malignancies apparently need more than a driver to exhibit their malignant phenotype.

Q: How do congresses such as EHA benefit your clinical and research practice?

A: Over the years, EHA has become a central European and worldwide forum comparable (and sometimes even better) to American Society of Hematology (ASH) in discussing latest results in research and clinical practice. The quality of EHA meetings has improved greatly and the number of participants has now reached an astonishingly high level when compared to the starting years.

Q: Are there any areas in haematology which you feel are under-researched?

A: The focus on malignant haematology over the past years, has slightly put aside areas of non-malignant haematology in research and clinics, such as anaemia. However, at the moment, with a deeper understanding of the genetic causes of these diseases, the balance will swing back.

“ **Anti-cancer and anti-leukaemia therapy may in fact induce cell death and this cell death is a regulated phenomenon.** ”

Q: What have you been most proud of in your career to date?

A: This is a really tough question. I would not say that I am proud of, but I am very glad and satisfied having had the privilege to follow a specific area of research from the very beginning over the past 30 years. When we discovered one of the key apoptosis systems, the CD95 system, we could not even spell the word ‘apoptosis’ and did not have the slightest idea that cell death is a regulated phenomenon similar to cell proliferation. At this time, in the mid-to-late 1980s, the prevailing concept in oncology was that the main characteristic of tumours is their unlimited proliferation potential. Consequently, all therapies were aimed and considered to target cell proliferation. Anti-cancer and anti-leukaemia therapy may in fact induce cell death and this cell death is a regulated phenomenon. Sensitivity or resistance of cancer and leukaemia cells may depend on their susceptibility and intactness to undergo programmed cell death or apoptosis. This was neglected because there was no concept to talk about. The focus on translation from deciphering one of the important cell death systems, to defining sensitivity and resistance of tumour cells, and more recently the development of preclinical models for leukaemia and solid tumours, is certainly what I consider my contribution to the field to be. I was always privileged to work in an area of constant development and to be part of this, both in research as well as in clinical application. This is a great satisfaction to me.

Q: Do you have advice for anyone who wishes to follow a similar career path to yours?

A: Seek and use the opportunities in research and clinical practice! Be hungry to get as much knowledge as possible on the diseases that you treat! Stay in the clinic and focus on your patients! Return to the lab and focus on your specific research and then go back to the patient! I consider this back and forth between the bench and bedside that I experienced and performed throughout my career as the most important contribution to my career path.

Ruben Mesa

Professor of Medicine, Consultant Hematologist, Chairman of the Division of Hematology and Medical Oncology, and Deputy Director, Mayo Clinic Cancer Center, Scottsdale, Arizona, USA.

Q: What attracted you to the field of haematology and oncology, and more specifically, to researching myeloproliferative neoplasms (MPNs)?

A: The tremendous unmet needs in the field of cancer is really what drew me to focus on cancer; unmet needs scientifically, in terms of understanding, in terms of new therapies, and how to best help patients. I had the opportunity to interact with patients with MPNs even in my first year of medical school at the Mayo Medical School in Rochester, Minnesota, a long-time centre of excellence for these disorders. This significant lack of understanding, unmet needs, and lack of cohesion in the MPN community attracted me greatly.

Q: How far has our understanding and treatment of MPNs improved since you first began working in this area?

A: Our understanding of MPNs has grown exponentially since I began working in this arena in 1991. Our knowledge of the molecular pathogenesis had a watershed moment with the discovery of the *JAK2 V617F* mutation in 2005. Additionally, the development of agents specifically tested for MPNs has been transformational in that in the past we would largely only be able to test agents being looked at for other disorders. Finally, we have a much greater understanding of the unmet challenges of symptom burden in these patients.

Q: What have you found to be the greatest clinical challenge facing patients with MPNs?

A: As we have done direct surveys of patients with MPNs, they feel that their greatest unmet need is the issue of progressive disease and the question surrounding it: how can our medical therapies in particular, which have greatly improved in

their impact in preventing thrombosis, reducing splenomegaly, and improving symptoms, lead us to more definitive and longer periods of control of the disease and even disease eradication?

Q: Can you tell us more about the important role of personalised medicine in the treatment of these disorders?

A: Indeed, personalised medicine is incredibly important in heterogeneous disorders such as MPNs, which necessitate medicines to be personalised not only in terms of a very heterogeneous group of mutation profiles that may lead to alternative prognoses but also regarding how the disease affects the patient and their individual disease-related complications, symptom burden, and risk of progression.

Q: You have also highlighted the importance of allogeneic stem cell transplantation as a unique treatment for patients with a serious bone marrow disorder, myelofibrosis. As this treatment can have life-threatening side effects and is not applicable to many patients, can you speak on the future alternatives you anticipate will emerge to cure myelofibrosis?

A: I predict that the progress in myelofibrosis will be along two lines: continued improved safety of transplantation, and expansion of this potentially life-saving therapy that relies on graft versus leukaemia effect into a safer and more viable option for a greater number of patients. In parallel, I hope that further medical therapy will continue to either: 1) Control the disease indefinitely, which although not a cure would certainly be a step forward; or 2) Be able to further diminish the burden of disease for the individual so that other corresponding approaches would help eradicate the disease, whether they be based on the immune system or otherwise.



Q: What experimental treatments are you currently researching and do you expect any of these to enter clinical practice in the near future? Does it have a significant impact on the treatment of MPNs?

A: Many important therapies are in development: 1) Janus kinase inhibitors may have a more favourable impact on cytopenias, including pacritinib and momelitinib, which each have benefits in patients with thrombocytopenia and/or anaemia. I envision a situation where both of these agents would hopefully be available in the future and complement the significant benefits we have seen from ruxolitinib, in improving splenomegaly symptoms and survival; 2) PRM-151 is a particularly intriguing agent working against the fibrosing process that we hope will delay disease progression; and 3) Imetelstat is a telomerase inhibitor which has shown significant activity in early studies. Results of ongoing studies are anticipated with great interest.

Q: Have you been involved in research which has identified the impact of MPNs and sexuality and quality of life? How has this research affected patient care and do you anticipate it will affect the direction of future research in the field?

A: We currently have data on over 5,000 MPN patients from 40 countries and 15 different languages. With this cumulative information it is clear that intimacy is a major concern for patients with MPNs across the globe. Intimacy challenges include: 1) Physical limitations with intimacy, such as impotence or other issues; and 2) Intimacy challenges, which I think can be a tremendous strain for quality of life, as patients feel poorly, have pain, night sweats, and discomfort from splenomegaly. This puts a tremendous strain on intimacy as well as relationships. I am hopeful that, having identified this important need, we will be able to bring in further psychosocial support for patients with MPNs in addition to purely medical therapies, in order to better address these needs and view their care in a holistic manner.

“ Working in haematology and oncology is incredibly rewarding; it gives us the opportunity to learn from our patients and their loved ones as they go through an incredibly difficult journey. ”

Q: What efforts are being made to raise awareness for these disorders? Could anything be improved to help patients recognise warning signs or symptoms?

A: The era of the *JAK2* mutation in particular has greatly increased the awareness about testing for MPNs amongst primary care providers, internal medicine physicians, and many others outside of the realm of haematology. I do think this has been impactful in identifying earlier cases. The disorders as a whole are uncommon enough that increasing overall awareness in the general population in regards to the signs or symptoms of MPNs would probably not be ideal, in that some of the symptoms individually can overlap with other medical disorders such as fatigue, weight loss, and night sweats. But I think it is particularly important to build awareness amongst primary care physicians and other providers who are on the frontlines of caring for patients so that when a patient has signs, symptoms, or abnormal haematologic values potentially indicative of an MPN, there is not an excess delay in their diagnosis.

Q: What advice do you have for practitioners and trainees working within the field of haematology and oncology?

A: Working in haematology and oncology is incredibly rewarding; it gives us the opportunity to learn from our patients and their loved ones as they go through an incredibly difficult journey. In parallel it is a very rewarding scientific experience in a period of tremendous advances and success. It is an emotional field for those involved and has both high points and low points that never really become easier, for example losing patients to the diseases that we have battled against together. It is important, I think, to recognise that the role of the haematologist and medical oncologist is to help patients along a difficult journey and that we hopefully leave each interaction rewarded. In some individuals we may be able to eradicate disease, in others we may not, but hopefully all patients benefit from the care that we provide.

Q: What has been the proudest achievement of your career to date? Can you tell us about your professional goals for 2016?

A: I would say the proudest achievement of my career, having been involved with many clinical trials, getting medicines registered, and caring for many patients, has been our efforts to build greater awareness regarding the burden and suffering that patients with MPNs can have as a chronic disease. Also in helping physicians around

the world to be a bit more sensitive to a holistic approach and how to care for their patients. My professional goals for 2016 include trying to translate many of the efforts that we have been involved with in the clinical trial setting in ways that both become practical and helpful for individual haematology and medical oncology practices, which can be of use for the care of patients receiving standard therapies each and every day.

Emanuele Angelucci

Chairman, Hematology and Transplant Center, Ospedale Oncologico di Riferimento Regionale “Armando Businco”, Cagliari, Italy.

Q: Biological therapy is proving useful in many areas of medicine; how are such therapies being implemented for patients with haematological conditions?

A: This is a difficult question. I think that biological therapy has definitely improved and treatment outcomes will further improve in many areas of medicine. In order to do this, a specific approach looking at each disease individually is necessary.

Q: In what ways has the global effort to increase the availability of treatments for haematological diseases been affected by the development of new technologies? Is the trajectory promising?

A: At the moment many of the new technologies are not widely used. However, the trajectory is promising. Special effort should be made to extend new technologies to allow patients better access. A particularly important issue is drug access in non-industrialised countries.

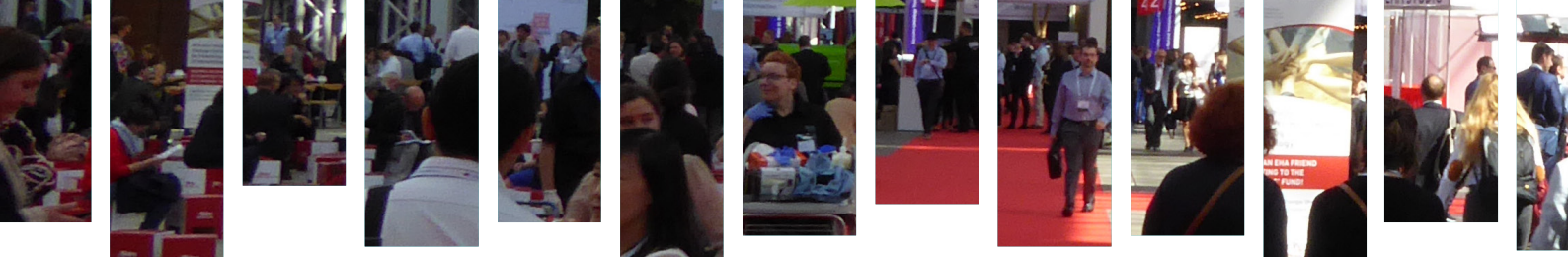
“ Genetic diseases such as thalassaemia are usually, but not always, chronic diseases which permit prolonged survival with traditional forms of treatment. ”

Q: Have there been any exciting developments in gene therapy in relation to your current research areas? How long before such approaches become part of daily practice?

A: Yes, indeed. Finally, after many years, gene therapy in thalassaemia seems to be close to being practical, approachable, and clinically applicable. However, two major problems still remain. Firstly, from a clinical point of view, there can be incomplete haemoglobin production after gene transfer. Secondly, there is the very high cost of the therapy itself. At the moment, the large majority of thalassaemia patients cannot approach gene therapy because of this.

Q: What are the crucial differences between genetic and acquired haematological diseases, from the point of view of the physician?

A: There are several differences that should be discussed depending on the disease. Genetic diseases such as thalassaemia are usually, but not always, chronic diseases which permit prolonged survival with traditional forms of treatment. On the other hand, acquired haematological diseases are usually, but not always, malignant diseases, mostly requiring a curative approach. Haematopoietic stem cell transplantation has changed the approach



to treating thalassaemia, introducing the idea of a cure. Gene therapy will also further change the approach.

Q: What efforts are being made to raise awareness of haematological conditions? Could anything else be done to help patients recognise warning signs or symptoms?

A: Patient associations are growing. For example, the Italian Association against Leukaemia-Lymphoma and Myeloma (AIL) is a very important association that has initiatives for raising patient awareness.

Q: In terms of the Italian healthcare system, have there been any recent developments to reduce treatment costs and improve opportunities for physicians?

A: Yes. Payment by result, cost sharing, and reimbursements have been recently introduced. The major costs in the Italian healthcare system are not the medications, as they account for no more 15% of the national healthcare system's budget.

The simplification of procedures and fight against excessive bureaucracy would help reduce the cost of the healthcare system.

Q: If you could suggest one way to increase the cure rate for elderly acute leukaemia patients, what would it be?

A: At the moment I believe that the best way to treat elderly patients with acute leukaemia is to enrol patients in well designed controlled clinical trials.

Q: Are there any areas of the field of haematology that you believe are under-researched? Why is this, and how would additional research in this area benefit the field as a whole?

A: Yes there are, rare diseases and non-malignant haematology.

Q: What do you foresee as being the 'next big thing' in haematology?

A: Hopefully, to make all therapies available for any patient with a stringent clinical indication.

“ I think that biological therapy has definitely improved and treatment outcomes will further improve in many areas of medicine. ”