TREATMENT STRATEGIES
ONCOLOGY

Volume 3 Issue 2

- **Breast Cancer**
- **Gynaecological Cancers**
- **Lung Cancer**
- **Melanoma**
- **Motion Management Technologies**
- **Multiple Myeloma**
- **Spinal Fractures**

Articles include:

Determining Optimal Treatment Regimens for Major Histological Subtypes of Breast Cancer

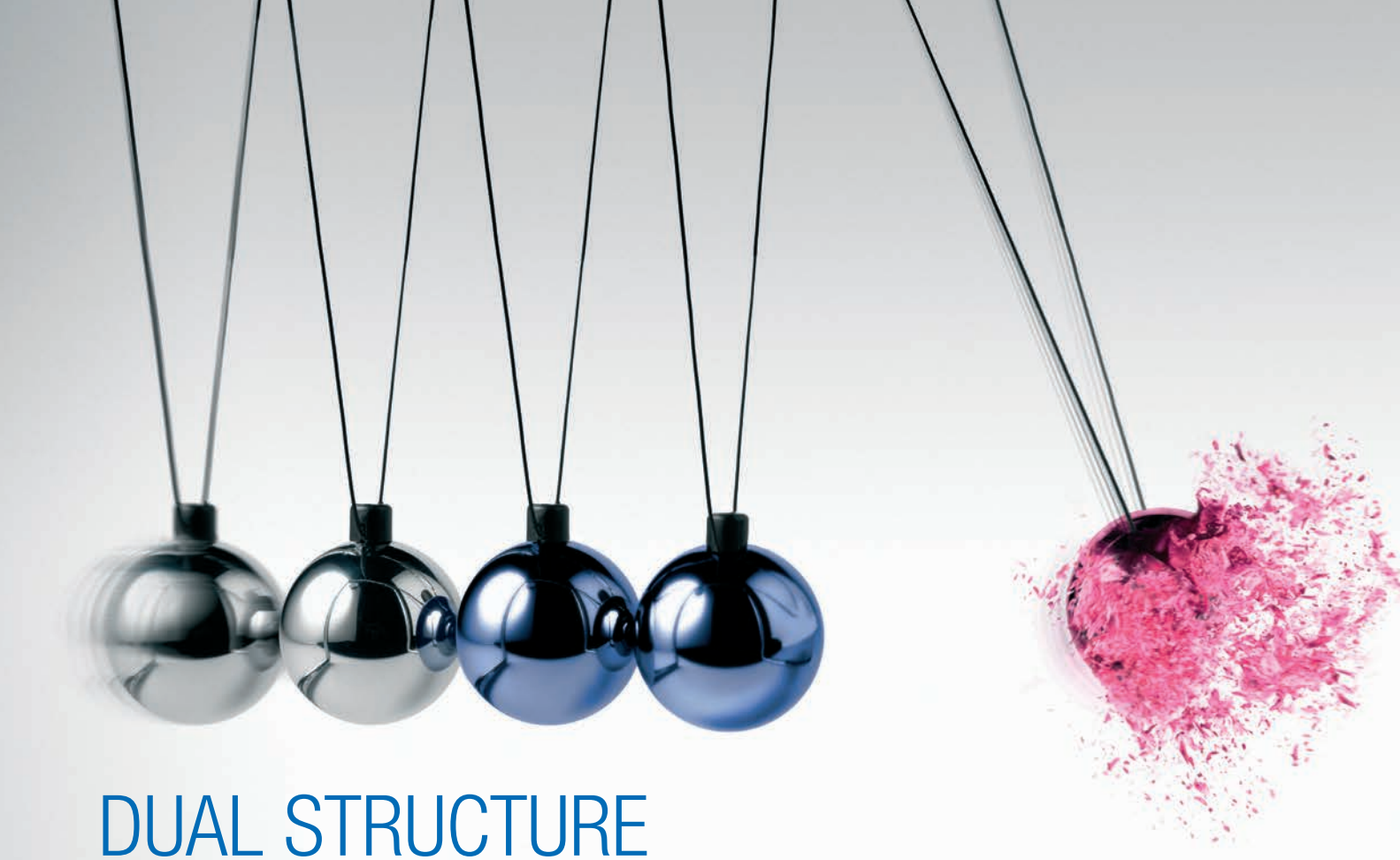
Efficiency in Breast Care

Image Guided Adaptive Brachytherapy in Locally Advanced Cervical Cancers: Preliminary Results and Perspectives

Key to the Success of Active Immunotherapy in Melanoma

Management of Painful Vertebral Compression Fractures in Cancer: Role of Balloon Kyphoplasty

Includes a review of the 2012 ESMO Congress



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CLL = chronic lymphocytic leukaemia; iNHL = indolent non-Hodgkin's lymphoma; MM = multiple myeloma

References: 1. *Levact®* Summary of Product Characteristics, Astellas Pharma GmbH. **2.** Leoni L *et al.* Clin Cancer Res 2008;309(14):309-317. **3.** Ozegowski W and Krebs D. Zbl Pharm 1971(10): 1013-1019. **4.** Knauf W *et al.* J Clin Oncol 2009;27(26):4378-4384. **5.** Cheson B *et al.* Poster presented at the 2009 Pan Pacific Lymphoma Conference; Hawaii, June 22-26, 2009. **6.** Knauf W *et al.* Abstract 2376 and related poster presented at ASH 2009. New Orleans, December 6, 2009. **7.** Friedberg J *et al.* J Clin Oncol 2008;26:204-210. **8.** Kahl B *et al.* Cancer 2010;106-114 doi: 10.1002/cncr.24714.

Levact®▼ 2.5 mg/ml, powder for concentrate for solution for infusion. Prescribing Information United Kingdom. Please read the Summary of Product Characteristics before prescribing. Presentation: Powder for concentrate for solution for infusion. White, microcrystalline powder. One 26 ml vial of powder contains 25 mg bendamustine hydrochloride. One 60 ml vial of powder contains 100 mg bendamustine hydrochloride. **Indications:** First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. Indolent non-Hodgkin's lymphomas as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen. Front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment. **Dosage and administration:** For i.v. infusion over 30-60 minutes. Monotherapy for CLL, 100 mg/m^2 on Days 1 & 2, every 4 weeks. Monotherapy for indolent NHL, 120 mg/m^2 on Days 1 & 2, every 3 weeks. MM, 120 – 150mg/m^2 on Days 1 & 2, 60 mg/m^2 prednisone i.v. or per os on day 1 to 4, every 4 weeks. For further details please refer to the SmPC. **Contra-indications:** Hypersensitivity to the active substance or excipients, during breast feeding, severe hepatic impairment, jaundice, severe bone marrow suppression and severe blood count alterations, major surgery (less than 30 days prior to start of treatment), infections, yellow fever vaccinations. **Precautions and warnings:** Myelosuppression, infections, skin reactions, patients with cardiac disorders, nausea, vomiting, tumour lysis syndrome, anaphylaxis, contraception, extravasation. **Interactions:** No *in vivo* interaction studies have been performed. Combined use with myelosuppressive agents may potentiate effects on bone marrow. Combination with cyclosporine or tacrolimus may result in excessive immunosuppression. Risk of infection following live virus vaccination which may be fatal. Potential for interaction with CYP1A2 inhibitors exists. **Pregnancy and lactation:** Not recommended. **Side-effects:** The most common adverse drug reactions are haematological reactions (leukopenia, neutropenia, thrombocytopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting), infection, tumour lysis syndrome, haemorrhage, anaemia, hypersensitivity, insomnia, cardiac dysfunction (such as palpitations, angina pectoris, arrhythmia), hypotension, hypertension, pulmonary dysfunction, diarrhoea, constipation, stomatitis, alopecia, skin disorders, amenorrhea, mucosal inflammation, fatigue, pyrexia, pain, chills, dehydration, anorexia, haemoglobin decrease, creatinine increase, urea increase, AST increase, ALT increase, alkaline phosphatase increase, bilirubin increase, and hypokalemia. Other side-effects that could be serious are sepsis, pneumonia primary atypical, haemolysis, anaphylaxis, somnolence, aphonia, paraesthesia, peripheral sensory neuropathy, anticholinergic syndrome, ataxia, encephalitis, pericardial effusion, tachycardia, myocardial infarction, cardiac failure, acute circulatory failure, pulmonary fibrosis, GI haemorrhage, hyperhidrosis, infertility, multi-organ failure, Stevens-Johnson syndrome, toxic epidermal necrolysis and encephalitis. Please refer to the SmPC for further details of other uncommon side-effects. **Legal category:** POM. **Package quantities and price:** 26 ml vials containing 25 mg bendamustine are supplied in packs of: 5 vials £347.26. 20 vials £1379.04 60. ml vials containing 100 mg bendamustine are supplied in packs of: 5 vials £1379.04. **Marketing Authorisation number:** PL 14427/0026. **Marketing Authorisation holder:** Astellas Pharma GmbH, Postfach 50 01 66, D-80971, Munchen, Germany, Phone: +49 (0) 89 45 44 01. **Distributed by:** Napp Pharmaceuticals Ltd, Cambridge Science Park, Milton Road, Cambridge CB4 0GW, UK. Tel: 01223 424444. For medical information enquiries, please contact oncologymedinfo@napp.co.uk **Date of preparation:** June 2010. ®*Levact* and the NAPP device are Registered Trade Marks.

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TREATMENT STRATEGIES - ONCOLOGY

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Welcome...

I am delighted to welcome you to the latest edition of *Treatment Strategies – Oncology*. This issue will address key topical areas in oncological medicine and features an exciting collection of articles from leading oncology specialists. After the success of the previous edition, we once again hope to provide you with a comprehensive review of the latest updates and advances from the oncological field.

This edition includes an independent review of the European Society of Medical Oncology (ESMO) 2012 Congress which this year took place in Vienna, Austria. Oncology professionals from across the globe gathered at the Austria Centre Vienna to discover the latest scientific advances, examine new technologies and connect with like-minded members on topics of interest.

The European Society for Medical Oncology (ESMO) is the leading European professional organisation in the field which is committed to advancing the speciality of medical oncology and promoting a multidisciplinary approach to cancer treatment and care. This advancement is achieved through the fostering and encouragement of good science, which leads to better medicine and determines best practise. The ESMO congress is an excellent forum wihere the most recent research, breakthroughs, treatments and products within the field of oncology can be shared. This year a record-breaking 16,394 delegates were in attendance and, over the five-day congress, 140 scientific and educational sessions were staged.

We hope that the information included in this edition will be useful for the readers and help serve as a forum in which to present the constantly evolving findings in the oncological field. Following the success of the first edition we aim to maintain the highest standards for the series. It would be much appreciated if you could provide us with your feedback; by working with your opinions we will ensure that *Treatment Strategies – Oncology* remains one of the most useful publications in the industry.

I am looking forward to joining you next year in Stokholm for the 17th ECCO – 38th ESMO – 32nd ESTRO European Cancer Conference!

Nigel Lloyd, Editorial Director

The Cambridge Research Centre wishes to thank the following societies for their assistance and involvement in this publication.

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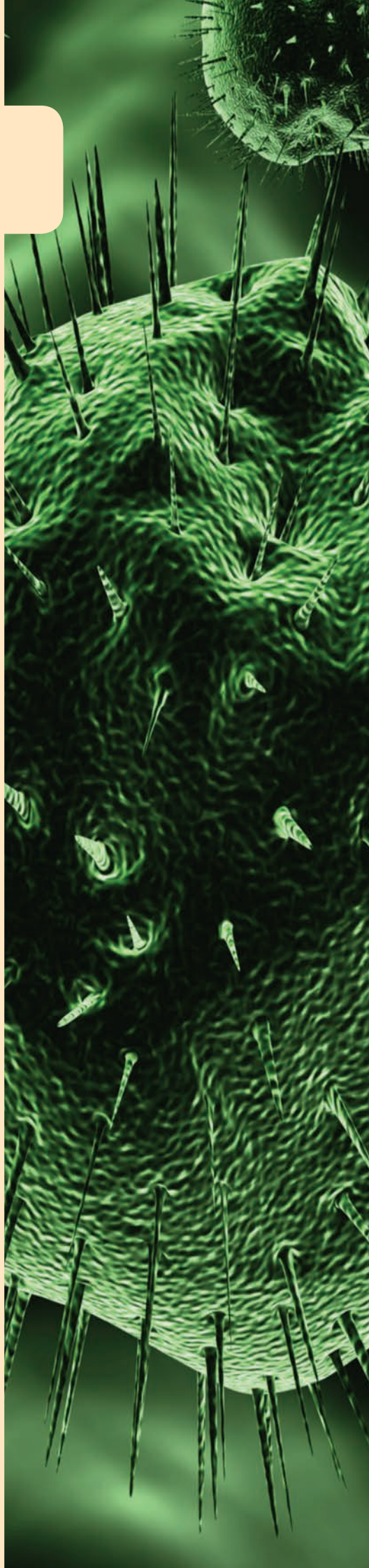

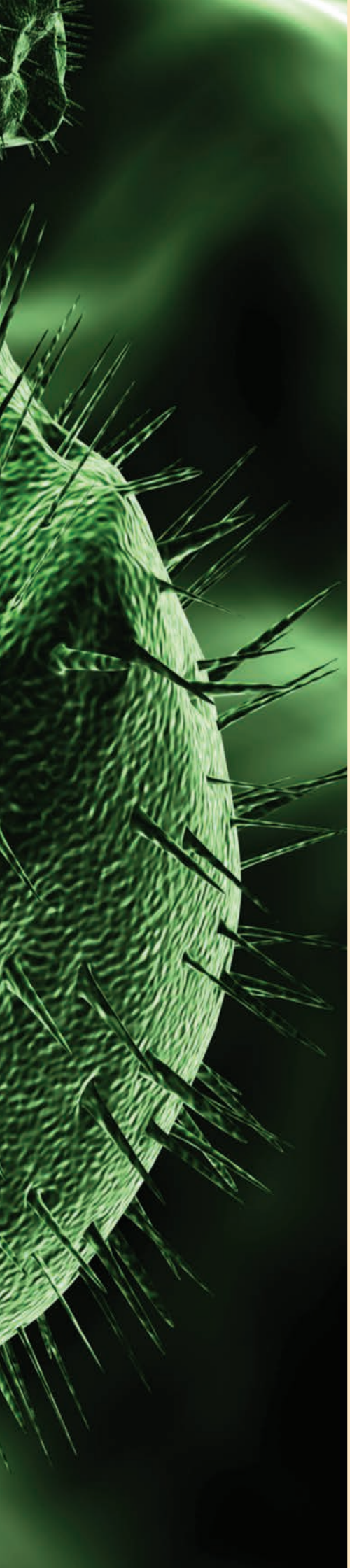

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Foreword

Hani Gabra
Professor of Medical Oncology and Head of the Molecular Therapeutics Section, Imperial College London

Welcome to the latest issue of T*reatment Strategies – Oncology*. We hope that this edition continues the resounding success of the last, and fulfils its aim of bringing healthcare professionals the latest updates and developments within the field of oncology.

My sense of oncology at the moment is that of an accelerating train, the engine is stoked up and is beginning to direct real power to the wheels, sending us faster every moment to our planned destination.

This stoked up engine of our molecular understanding of cancer, new molecular technologies and their implementation in translational and proof of concept clinical trials grows more powerful constantly. Our previous sense of lack of clinically-relevant engagement with the molecular revolution and the human genome project has given way to real wins as technology has improved and has become implemented in relevant molecular understanding in the clinic. The successes that are Glivec and Herceptin in CML, GIST and breast cancer continue to make headway using other targeted therapies in molecular subtypes of lung (EGFR tareting), renal (HIF targeting), gastric (HER2 targeting) cancer and melanoma (Braf). These successes have depended on the relevant molecular subtype representing a sufficiently large component of the clinical phenotype to give a strong signal in clinical trials.

The challenges now centre on development of predictive biomarkers to provide a "test" for every drug. These predictive biomarkers are challenging to develop sufficiently early in the drug development process to allow prospective evaluation in phase I/II and prospective validation/clinical evaluation in phase III trials. These approaches have at their heart not the old drug development rationale of killing a drug as quickly as possible, rather identifying a population of patients, perhaps across tumour sites that may actually benefit. Our understanding of cancer ontology has been further enhanced by the realisation that cancer heterogeneity is very real and not a theoretical phenomenon, with clear differences between tumour deposits at different sites within an individual, and also temporal/linear (as opposed to spatial) heterogeneity indicating tumour evolution through therapy. This linear heterogeneity represents an important current issue, the development of personalised medicines as tumours evolve over time and under the selective pressure of the cancer treatment itself. This sequential evaluation of tissue during the treatment of a patient is hopefully a way forward that has clinical utility. This edition of *Treatment Strategies - Oncology* incorporates these approaches in different scenarios of cancer therapy and treatment development and demonstrates these principles as they relate to different cancer types.

We hope that you enjoy the latest edition of *Treatment Strategies – Oncology* and the papers that have been included. Oncology is one of the most dynamic areas of medicine, in which new discoveries and developments are constantly being made. We hope that the publication gives an in-depth overview of some of the most important and interesting topics within the field today.

Hani Gabra is Professor of Medical Oncology and Head of the Molecular Therapeutics Section at Imperial College London. He is Director of the Ovarian Cancer Action Research Centre at the Hammersmith Campus of Imperial College and is Lead Cancer Clinician for the Gynaecological and Gastrointestinal cancer services at Imperial College Healthcare NHS Trust. Dr. Gabri attended medical school at Glasgow University and graduated in 1987. After completing his PhD and medical oncology specialist training at the MRC Human Genetics Unit and the Western General Hospital in Edinburgh, he took up the post of Clinical Scientist / Honorary Consultant in Medical Oncology at the ICRF/CR-UK Medical Oncology Unit in Edinburgh and was head of the CR-UK Ovarian Cancer Cell and Molecular Genetics Group from 1998-2003 when he moved to London to take up his present appointment. His basic research interests are in ovarian cancer tumour-suppressor genes, his group having identified the OPCML and the WWOX tumour-suppressor genes, and cancer multiplatform molecular profiling and integrative OMICS. He has translational research interests in the molecular basis of clinical platinum resistance as well as all phases of clinical research.

Between 2004-2009 Hani led the Scottish Gynaecological Cancer Trials Group (SCOTROC) Ovarian Cancer Section and was the Scottish Group's representative to the Gynaecological Cancer Intergroup (GCIG), and the NCRI's translational committee for gynaecological cancer. He currently sits on CTAAC, the CR-UK clinical trials national funding committee. He is a founder member and President of the European Translational Ovarian Cancer Network (EUTROC), and is a member of several international consortia of ovarian cancer molecular profiling and functional biology. He sits on the Editorial Board of *European Journal of Cancer* and several other journals, holds several visiting professorships and is a member of many international societies.

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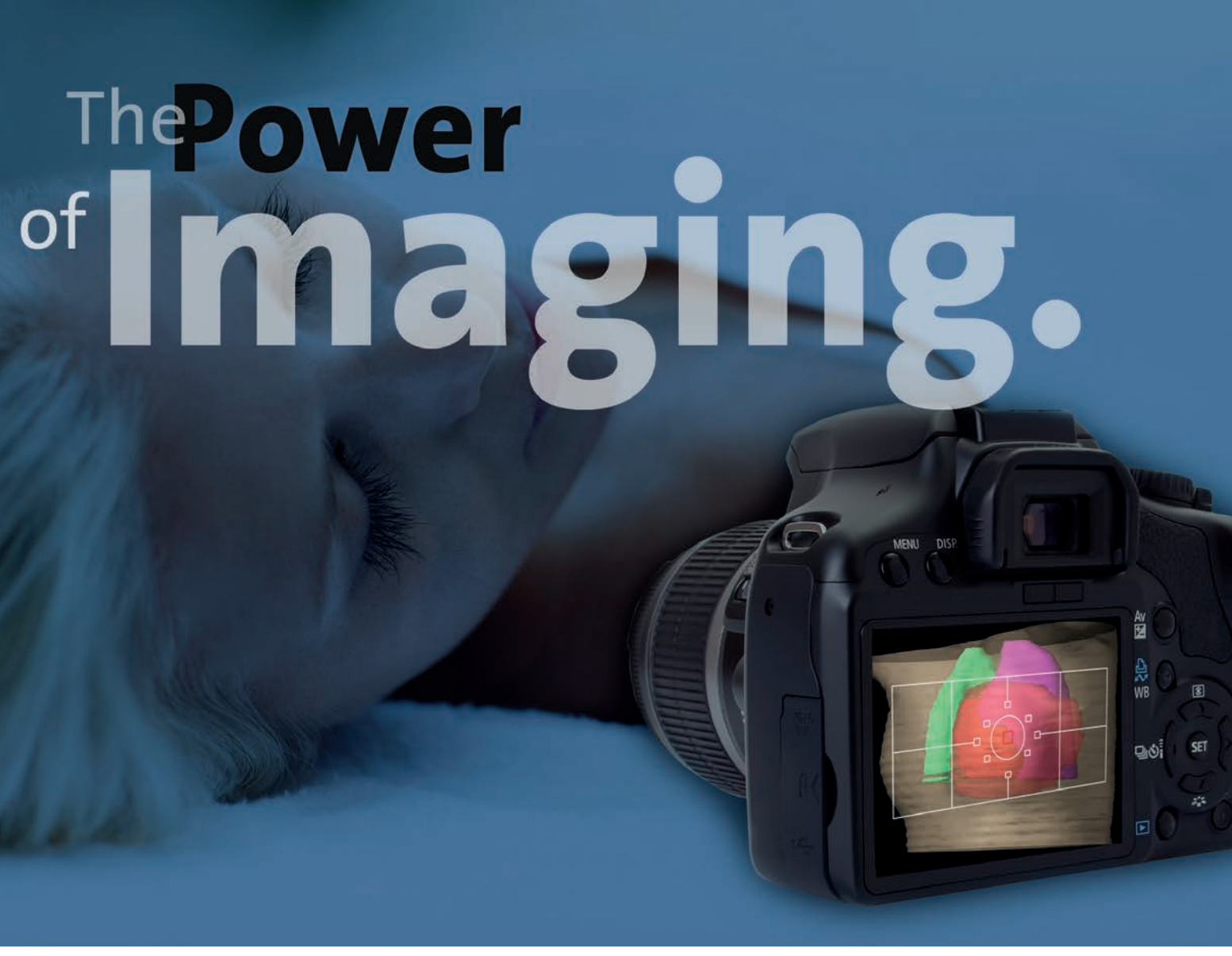

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ESMO 2012 Annual Congress Review

28 Sept - 02 Oct 2012 - Vienna

European Society for Medical Oncology Annual Congress — Review

INSIDE...

The Meeting

The Exhibition

Hannah Corby, *Treatment Strategies*, takes a look over a number of key sessions, as well as spotlighting several stands and products being demonstrated at the exhibition. We then follow with papers and reviews which give a brief insight from a number of sessions highlighting findings that will have direct repercussions on clinical practise that are still very much being discussed.

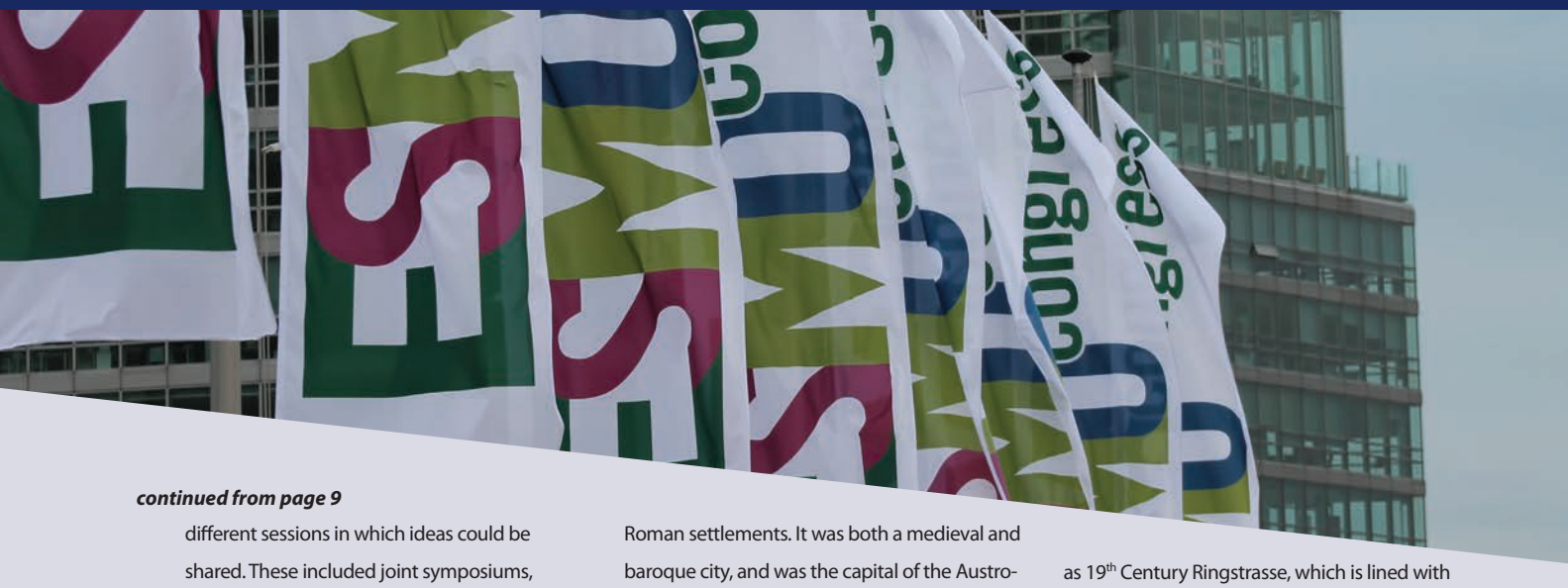
The European Society for Medical Oncology (ESMO) is the leading European professional organisation and is committed to advancing the speciality of medical oncology and promoting a multidisciplinary approach to cancer treatment and care. This advancement is achieved through the fostering and encouragement of good science, which leads to better medicine and determines best practise.

The ESMO congress is an excellent forum within which the most recent research, breakthroughs, treatments and products within the field of oncology can be shared. This year a record-breaking 16,394 delegates were in attendance, and over the five day congress, 140 scientific and educational sessions were staged. Additionally, 1,238 abstracts were selected for presentation, including 31 late breaking abstracts.

The congress featured a wide range of

Introduction *continues on page 10*

The congress was held in the Austria Centre Vienna.



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different sessions in which ideas could be shared. These included joint symposiums, which brought together the research of different organisations on topics such as Innovative Approaches to the Treatment of Brain Metastases and Imaging Biomarkers in the Era of Targeted Therapies, and Patient Cases sessions, which used previous cases in the discussion of the latest treatments and ideas within the field.

Additionally, special sessions and symposiums took place throughout the five-day congress, highlighting particularly important discoveries or areas within the field. These sessions covered topics such as cancer pain management and the new wave of genetic information. Keynote sessions also highlighted new information, and this year featured topics including Metabolic Pathways Supporting Tumour Progression.

Further sessions offered included Challenge the Experts, Young Oncologists Masterclass, Patient Seminars, Educational sessions and Poster presentations, which offered delegates the opportunity to discover the latest innovations in oncology at their leisure.

This year, ESMO was held in Vienna. Vienna is both the largest city and the capital of Austria, as well as one of the country's nine states. It is located in northeastern Austria, at the easternmost extension of the Alps in the Vienna Basin. It has a population of 1.731 million and it is the 9th largest city in the EU. The city is rich in history, and has its roots in early Celtic and Roman settlements. It was both a medieval and baroque city, and was the capital of the Austro-Hungarian Empire. In 2001, the city centre was designated a UNESCO World Heritage Site.

Vienna is also Austria's cultural, economic and political centre, as well as being the main centre of education. It is home to a large number of universities and professional colleges, including many international establishments. In 2012 it was ranked 2nd in a study of the world's most livable cities.

As home to the world's first psychoanalyst Sigmund Freud, the city is often described as the 'city of dreams', as well as the 'city of music' due to its long musical tradition. Vienna was the leading European music centre from the great age of Viennese classicism to the early part of 20th Century. It has been host to a range of influential composers such as Brahms, Bruckner, Mahler and Richard Strauss.

In addition, Vienna has a long tradition of art and culture, including theatre, opera, classical music and fine arts. Indeed, the Burgtheater is considered one of the best theatres in the German-speaking world. The city was ranked 1st globally for culture and innovation in both 2007 and 2008, and attracts around 5 million visitors annually. Major tourist attractions in Vienna include the imperial palaces of the Hofburg and Schönbrunn, which is also home to the world's oldest zoo, Tiergarten Schönbrunn, as well as the Riesenrad in the Prater. The historic centre of Vienna is rich in architectural ensembles including Baroque castles and gardens, as well as 19th Century Ringstrasse, which is lined with grand buildings, monument and parks.

Furthermore, Vienna is famous for its culinary creations, in particular the production of the finest cakes and desserts. These include hot apple strudel, sweet pancakes and Sachertorte. It is also one of the few remaining world cities which has its own vineyards, and the dry white wine Grüner Veltliner is the most widely cultivated wine in Austria. Beer is also of importance in Vienna. The city has a single large brewery, Ottakringer, and more than ten microbreweries. Viennese cafés also have a long and distinguished history in Vienna, which dates back centuries. In the 19th Century, many famous writers, artists, politicians and scientists were constant coffee house patrons.

The congress was held in the Austria Centre Vienna, which is located in the most modern part of Vienna. The conference centre has 17 halls and 190 additional rooms, as well as 9 foyer restaurants and modern conference equipment. It has a total of 22, 000 sqm of exhibition space, and so was the perfect location for the largest European oncology conference.

Following on from the last edition, we have once again commissioned a number of authors to discuss the various sessions that took place across the four-days, spotlighted findings and research that were presented, as well as bringing you a round-up of the stands found within the lively exhibition hall.

Leading Cancer Specialists From Europe and Beyond Recognised at ESMO 2012

The European Society for Medical Oncology (ESMO) has recognised two eminent cancer specialists and one European institution for their contribution to the advancement of medical oncology at the ESMO 2012 Congress. The awards were presented to Professors Ian Tannock and Jean Yves Blay and to the European Organisation for Research and Treatment of Cancer (EORTC) during the Opening Ceremony of the 37th ESMO Congress, 28th September – 2nd October, Vienna, Austria.

Professor Ian Tannock was bestowed with the 2012 ESMO Award for his work on clinical trials for men with metastatic prostate cancer and laboratory-based research on the microenvironment of solid tumours, their resistance to drugs and methods to overcome it.

"His notable efforts have undoubtedly impacted on cancer control and better outcomes for many patients," notes Dr. Josep Tabernero, Chair of the ESMO Fellowship and Award Committee. "More specifically, this award recognises his tremendous contributions in improving methodology for undertaking clinical trials with emphasis on endpoints of clinical benefit and, at a laboratory level, unmasking aspects of solid tumour biology as well as improving outcomes of treatment with chemotherapy."

Based at the University Of Toronto, Canada, where he is Professor of Medicine and Medical Biophysics, Prof. Tannock has led and helped to design trials that led to the identification of optimal chemotherapy for men with metastatic castration-resistant prostate cancer.

"ESMO is a truly international and intercontinental society but I am particularly honoured to be the first oncologist not based in Europe to receive this award" Professor Tannock comments. "If the ESMO award is in recognition of my career in oncology, part of it should be given to the many international fellows who have collaborated with me - their ideas and enthusiasm have sustained my career and my greatest reward is observing their success," he continues.

The recipient of the 2012 Hamilton Fairley Award was Professor Jean Yves Blay, for his contribution to translational cancer research. "His work has afforded increased visibility of his country, France, on the international map; the referral system developed by the French Sarcoma group, which he co-chairs, is also setting new standards," said Dr. Tabernero.

Jean-Yves Blay is Professor of Medicine in Medical Oncology and Head of the Medical Oncology Department and the Translational Research Pole at the Centre Léon Bérard of the Université Claude Bernard in Lyon, France. He is one of Europe's most published lead and co-authors, with more than 350 peer-reviewed papers, principally on sarcomas, GIST and immunotherapy. He writes and lectures on public health issues such as breast and prostate cancer screening programs. He is a president of the EORTC and serves as scientific committee member of 5 cancer centers in France. He has been a reviewer for the *Journal of Clinical Oncology*, *Blood*, *Cancer*, *Annals of Oncology*, and the *European Journal of Cancer*.

"His citation for the distinguished Hamilton Fairley Award – which was established in 1998 to commemorate one of the founding fathers of medical oncology in Europe – notes the international recognition he has achieved for his lifetime of work in cancer science and research," highlighted Dr. Tabernero. "It is an immense privilege to receive this award. The recognition by ESMO, an organisation I cherish particularly, is extremely important for me." Professor Blay stated.

"Translational research has been my focus overall these years, with the ups and downs of all research activities. So this is a major encouragement to continue. Even more importantly, I am certain that this award will help me to convince the young medical researchers --the next generation to focus on applied research. This is happening here and now!" he added.

The 2012 ESMO Lifetime Achievement Award was presented to the European Organisation for Research and Treatment of Cancer (EORTC) represented by Professor Françoise Meunier, who has been the EORTC Director General for

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over 20 years.

"This unique pan-European non-profit clinical cancer research organisation comprising over 300 hospitals and cancer centers in over 30 countries, including some 2,500 collaborators from all disciplines involved in cancer treatment and research has been and continues to be the largest organisation which carries out independent clinical studies at the European level in all types of cancer," Dr. Tabernero notes.

"EORTC is a truly unique organisation" Professor Meunier emphasised. It was built 50 years ago on a European spirit and its mission remains essential today: "Facing the increasing incidence of cancer, it is our role and responsibility to define optimal therapeutic strategies for all patients."

The ESMO Lifetime Achievement Award is presented to individuals or groups possessing an international reputation and demonstrated commitment to cancer treatment and research. "We would like to thank all the presidents for their unrestricted support, the Board members, the dedicated network and the committed staff who understood the vision and allowed EORTC to become a reference research institute in Europe and beyond."

"We are very honoured by this award, which is a tremendous recognition of EORTC's contribution to improve cancer care," she concluded.

Combining S-1 and Docetaxel Improves Survival in Advanced Gastric Cancer

Updated results of phase III START trial presented at ESMO 2012

An updated analysis of a Japanese phase III trial has shown that the combination of the oral fluoropyrimidine S-1 with docetaxel is beneficial for metastatic gastric cancer patients. S-1 is used as a standard treatment for advanced and recurrent gastric cancer in East Asia. The researchers reported updated results from this study at the ESMO 2012 Congress of the European Society for Medical Oncology in Vienna, which was reported initially in 2011.

The results had been reported through a planned analysis in 2011, however an independent biostatistician pointed out that a large number of censored cases led to an insufficient number of events for proper analysis. Now, Dr. Kazuhiro Yoshida and colleagues presented an updated analysis.

They found that among the 635 patients analysed, the median survival time was 12.48 months in the combination therapy group compared to 10.78 months in patients who received S-1 alone. Neutropenia was the most frequent adverse events in the docetaxel/S-1 arm with one death occurring from grade 4 thrombocytopenia. According to Dr Yoshida, this combination is much better than S-1 monotherapy which is regarded as one of the standard therapies for metastatic gastric cancer in Japan.

The earlier SPIRITS trial also showed that S-1 plus cisplatin is a standard therapy for gastric cancer in Asia, Dr Yoshida noted. However, data from this study in Japanese patients demonstrated more promising overall survival with a larger number of patients compared to the SPIRITS trial. These data will have an impact on daily practice for gastric cancer patients. Commenting on the study, Prof. Jean-Yves Douillard, ICO Centre Rene Gauducheau, France, Chair of the ESMO Educational Committee, not involved in the study, said that the START trial is a large study, meeting its primary end-point of improved survival showing a significant 17% reduction of the risk of death and a good median of 12.5 vs. 10.8 months in favor of the combination. Progression-free survival and overall response-rate were also significantly better in the combination arm.

The START study, with the combination of docetaxel and S-1, might represent an alternative to the platinum-containing regimens widely used in Europe, but would need first to be evaluated in Caucasian populations to assess feasibility and tolerance at doses of docetaxel usually used in Europe, and not at lower doses as routinely done in Japan.

Urgent Need for Integrated Oncology and Palliative Care

16 new ESMO Designated Centers of Integrated Oncology and Palliative Care

The European Society for Medical Oncology (ESMO) has awarded ESMO Designated Center of Integrated Oncology and Palliative Care accreditation to 16 new oncology centers. The centers received the acknowledgment at the ESMO 2012 Congress, which will also highlight two new Italian studies demonstrating how palliative care works in practice in Italy. The first study explores use of analgesics; the second looks at different models for organisation of the integration of palliative care with oncology.

First established in 2003, this ambitious ESMO project aims to improve the infrastructure for the provision of palliative care globally. The initiative came partly in response to the World Health Organisation (WHO) report "Cancer pain relief and palliative care".

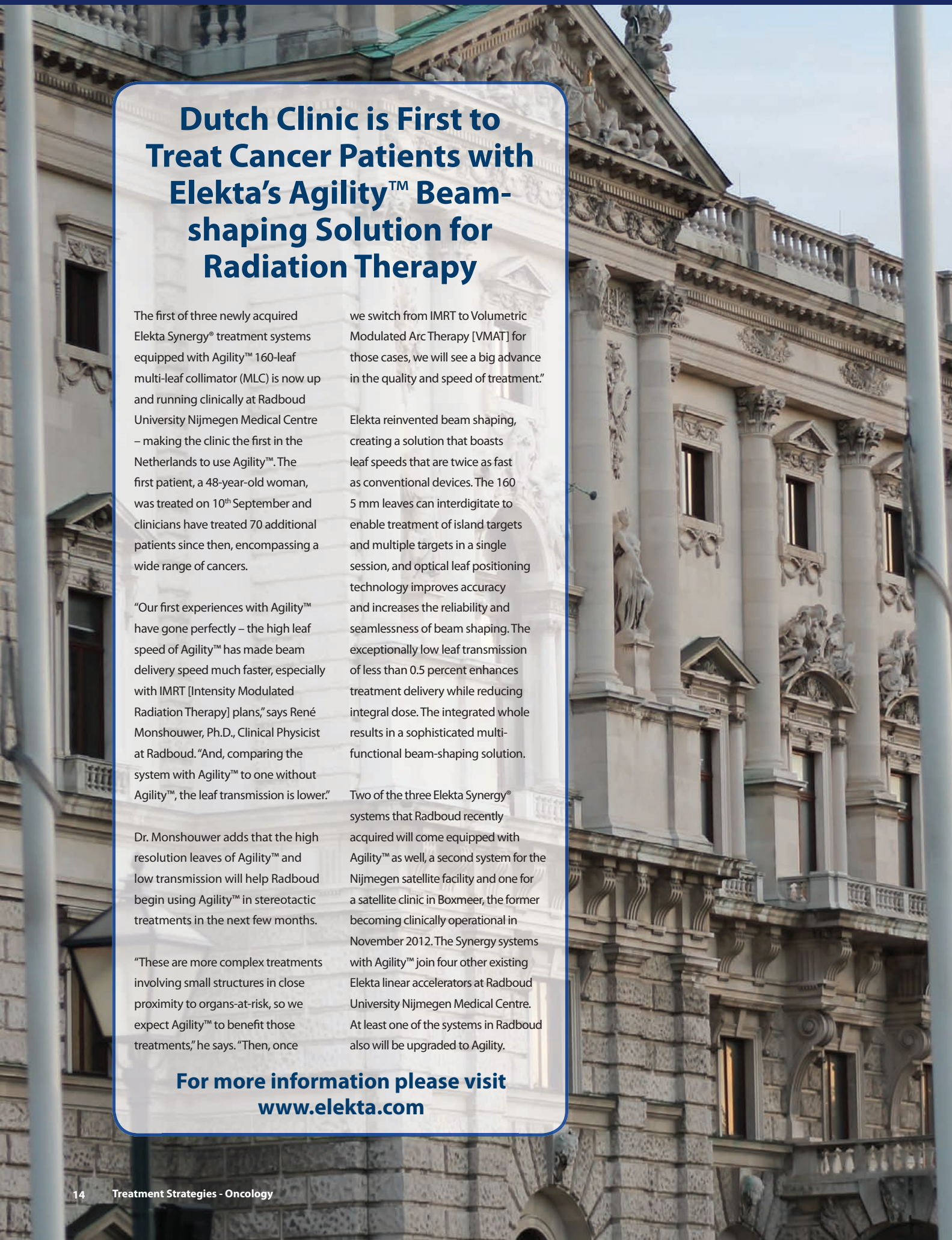
"This year's awardees -13 based in Europe, one in Egypt, one in Singapore and one in India - demonstrate the truly international scope of ESMO's work. It shows how ESMO wants to help humanity, not just European oncology patients," says Raphael Catane, one of the founding members of the ESMO Palliative Care Working Group.

"In addition to making efforts to prolong the life of oncology patients, ESMO felt that we needed to ensure that quality of life was good. We've made considerable efforts to change the mindset of doctors and patients that taking care of symptoms need not diminish efforts to prolong life. From the outset of diagnosis we wanted to integrate palliative care into the practice of medical oncology," said Dr Catane, from the Institute of Oncology, Sheba Medical Center, Israel.
The award, judged anonymously by ESMO Palliative Care Working Group members, assesses centers according to 13 rigorous criteria. Any oncology department or cancer centre can apply, with ESMO emphasising that size is not important, what matters most is the quality and extent of integration of services. The criteria have come to be regarded as a "roadmap" for how to build palliative care services. Unsuccessful applicants are invited to further develop their programs and reapply.

Receiving the certification allows centers to use the title "ESMO Designated Center of Integrated Oncology and Palliative Care" and also be eligible to receive fellows in palliative medicine, supported by ESMO grants. For successful applicants, however, there is no room for complacency, since awards need to be renewed every three years. Of the current 127 (including the 16 new centers) accredited centers, 50 have been reaccredited once (27 this year) and 21 twice (eight this year).

Undoubtedly, the much sought after accolade has contributed to increasing the profile of palliative care within oncology units across the world. "ESMO's initiative has certainly raised a lot of interest, as demonstrated by the growing list of centers that adhere to this program. It's one of many ways to encourage the development of truly multidisciplinary cancer centers which look at the patient's needs in all aspects of cancer treatment," said Dr Aapro, from the Clinique de Genolier, Switzerland.

"The work of the ESMO Palliative Care Working Group has undoubtedly enhanced the lives of thousands of cancer patients in Europe and beyond," said Dr. Catane.



Dutch Clinic is First to Treat Cancer Patients with Elekta's Agility™ Beam-shaping Solution for Radiation Therapy

The first of three newly acquired Elekta Synergy® treatment systems equipped with Agility™ 160-leaf multi-leaf collimator (MLC) is now up and running clinically at Radboud University Nijmegen Medical Centre – making the clinic the first in the Netherlands to use Agility™. The first patient, a 48-year-old woman, was treated on 10th September and clinicians have treated 70 additional patients since then, encompassing a wide range of cancers.

"Our first experiences with Agility™ have gone perfectly – the high leaf speed of Agility™ has made beam delivery speed much faster, especially with IMRT [Intensity Modulated Radiation Therapy] plans," says René Monshouwer, Ph.D., Clinical Physicist at Radboud. "And, comparing the system with Agility™ to one without Agility™, the leaf transmission is lower."

Dr. Monshouwer adds that the high resolution leaves of Agility™ and low transmission will help Radboud begin using Agility™ in stereotactic treatments in the next few months.

"These are more complex treatments involving small structures in close proximity to organs-at-risk, so we expect Agility™ to benefit those treatments," he says. "Then, once we switch from IMRT to Volumetric Modulated Arc Therapy [VMAT] for those cases, we will see a big advance in the quality and speed of treatment."

Elekta reinvented beam shaping, creating a solution that boasts leaf speeds that are twice as fast as conventional devices. The 160 5 mm leaves can interdigitate to enable treatment of island targets and multiple targets in a single session, and optical leaf positioning technology improves accuracy and increases the reliability and seamlessness of beam shaping. The exceptionally low leaf transmission of less than 0.5 percent enhances treatment delivery while reducing integral dose. The integrated whole results in a sophisticated multi-functional beam-shaping solution.

Two of the three Elekta Synergy® systems that Radboud recently acquired will come equipped with Agility™ as well, a second system for the Nijmegen satellite facility and one for a satellite clinic in Boxmeer, the former becoming clinically operational in November 2012. The Synergy systems with Agility™ join four other existing Elekta linear accelerators at Radboud University Nijmegen Medical Centre. At least one of the systems in Radboud also will be upgraded to Agility.

For more information please visit www.elekta.com

New Four- and Five-Year Survival Data for YERVOY® (ipilimumab) in Treatment-Naïve and Previously-Treated Metastatic Melanoma Presented at the ESMO 2012 Congress

· Long-Term Follow Up From Phase 3 Study (024) Demonstrated That 19.0 Percent of Treatment-Naïve Patients Who Received YERVOY® at Investigational Dose of 10 mg/kg Plus Dacarbazine (DTIC) Were Alive at Four Years vs. 9.6 Percent of Patients Treated with DTIC Alone

· Few New Immune-Related Adverse Events Occurred Beyond Two Years of Treatment in Study 024

· Five-Year Follow Up from Three Exploratory Phase 2 Trials Add to Growing Body of Survival Data for YERVOY in Metastatic Melanoma

· In Both Analyses, Updated Survival Rates Remained Relatively Stable

Bristol-Myers Squibb Company has announced four- and five-year survival rates based on long-term follow up from Phase 3 and Phase 2 YERVOY® (ipilimumab) clinical trials in patients with treatment-naïve and previously-treated metastatic melanoma. The data were presented at the ESMO 2012 Congress (European Society for Medical Oncology). (Abstract #1127 and 1116.)

In the Phase 3 trial (024), patients who had not previously received treatment for metastatic melanoma (n=502) were randomised to receive either the investigational dose of YERVOY® 10 mg/kg in combination with dacarbazine (DTIC, 850 mg/m^2) or DTIC alone. Long-term follow-up from this study demonstrated that treatment with YERVOY® plus DTIC resulted in a four-year survival rate of 19.0% compared to 9.6% for DTIC alone. Additionally, the overall survival data appeared relatively stable between years three and four for patients treated with YERVOY® plus DTIC (21.2% at three years and 19.0% at four years). The three and four-year survival rates for patients treated with placebo plus DTIC were 12.1% and 9.6%, respectively.

In three Phase 2 trials (007 [n=115], 008 [n=155] and 022 [n=217]) in which five-year follow-up data are available through a rollover study (025), patients received YERVOY® at 0.3 mg/kg, 3.0 mg/kg or 10 mg/kg. No comparator treatment arms were included in these studies. In treatment-naïve patients, the five-year estimated survival rates ranged from 38% to 49%, which was unchanged from the four-year rates. In previously-treated patients, the five-year estimated survival rates (12% to 28%) were relatively stable compared to the rates at four years (14% to 28%).

For patients who were alive after four years and who continue on therapy in study 024, few new immune-related adverse events occurred beyond two years of treatment. Overall safety data from these investigational studies have been previously presented. The types of adverse events (AEs) attributed to YERVOY® in these studies were generally mechanism (immune)- based. YERVOY® can result in severe and fatal immune-related adverse reactions due to T-cell activation and proliferation. Adverse events associated with YERVOY® were managed with protocol-specific guidelines, including the administration of systemic corticosteroids, dose interruption/discontinuation and/or other immunosuppressants.

"Metastatic melanoma is one of the most aggressive forms of cancer with a historical five-year survival rate of less than ten percent in patients with distant metastasis. Results from these investigational studies showed a prolonged survival benefit with YERVOY® at four and five years for some patients," said Celeste Lebbe, M.D., Professor of Dermatology, Hôpital Saint-Louis. "These results add to the growing body of long-term survival data seen in some patients treated with YERVOY® and further our understanding of the potential of this immunotherapy in the treatment of metastatic melanoma."

ESMO 2012: Roche Underscores Leadership in Oncology with New Data in HER2 Positive Breast Cancer and Skin Cancer

Roche has announced data on thirteen of its investigational and approved products at the European Society for Medical Oncology (ESMO) Congress taking place in Vienna, Austria on 28 September - 2 October 2012.

During the past 50 years, Roche has developed and secured approval for ten cancer medicines. The data presented at ESMO 2012 reflect not only the continuing role being played by Roche's early discoveries, but also the potential of the company's newer treatments. Highlights included data on personalised medicines from the company's HER2 and skin cancer franchises.

"Our mission is to develop therapies that transform medicine," said Hal Barron M.D., Chief Medical Officer and Head, Global Product Development. "The improvement in survival with trastuzumab emtansine (T-DM1) and other data presented at ESMO reflect our commitment to make a real difference for people living with cancer."

HER2-positive Breast Cancer

Since it was first licensed in 1998, Herceptin has become the foundation of care in HER2-positive breast cancer. Data presented at ESMO 2012 will reflect both the pivotal role Herceptin continues to play, but also highlights how decades of research into HER2-positive cancer is enabling Roche to lead the next wave of developments that may further improve the treatment and outcomes for women with this aggressive disease.

• Further results including overall survival data will be presented from the Phase III EMILIA study. The trial compared trastuzumab emtansine (T-DM1) to Xeloda plus lapatinib in patients with HER2-positive unresectable locally advanced or metastatic breast cancer who had previously been treated with Herceptin and a taxane chemotherapy.
• Roche and the Breast International Group (BIG) will present the final analysis of the 5,000 patient, Phase III HERA (HERceptin Adjuvant) study. The study assessed how adjuvant treatment with Herceptin has impacted the disease free survival (DFS; the time lived without return of the disease) of women with HER2-positive early breast cancer after completion of standard chemotherapy. Data will be presented comparing the DFS of women given Herceptin treatment for two years compared to those treated with Herceptin for one year. In addition, an update will be provided on Herceptin given for one year versus observation after eight years of follow-up.

Results from the PHARE study (run by the French National Cancer Institute), investigating six months versus one year of Herceptin treatment, were also be presented.

Skin Cancer

In the past, patients with metastatic melanoma could expect to live for as little as six to nine months after diagnosis. Today, treatments such as Zelboraf (vemurafenib) are helping to stall the growth or spread of the cancer and are enabling patients to survive longer, for the first time extending life expectancy beyond one year for many patients. Despite this progress, more still needs to be done to improve outcomes and to ensure that patients have treatment options at all stages of the disease:

• At ESMO 2012, results from a pilot study of 24 patients with BRAF V600 mutation-positive metastatic melanoma and symptomatic brain metastases who were treated with Zelboraf will be presented.

Roche is building on its extensive clinical experience with Zelboraf to investigate a number of combination approaches, which may in the future expand the treatment options available to patients with this incurable disease. At ESMO 2012 the first results from BRIM7, a Phase Ib dose ranging study assessing the potential of combining Zelboraf with the MEK inhibitor GDC-0973 will be presented.
• Roche will further study the combination of Zelboraf and the MEK inhibitor GDC-0973 in a Phase III clinical investigation.

About Herceptin

Herceptin (trastuzumab) is a humanised monoclonal antibody, designed to target and block the function of HER2, a protein produced by a specific gene with cancer-causing potential when it is overexpressed. The mode of action of Herceptin is unique in that it activates the body's immune system and suppresses HER2 signalling to target and destroy the tumour. Herceptin has demonstrated unprecedented efficacy in treating both early and advanced (metastatic) HER2-positive breast cancer. Given on its own

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as monotherapy as well as in combination with or following standard chemotherapy or following surgery, Herceptin has been shown to improve overall survival, response rates and disease-free survival while maintaining quality of life in women with HER2-positive breast cancer.

A subcutaneous (SC) formulation of Herceptin, administered as a five minute injection under the skin, is currently being investigated. An application for Herceptin SC (vial) formulation has been submitted to some Regulatory Authorities, including EMA and Swissmedic, and is currently under assessment. Herceptin has been used to treat more than 1.2 million people with HER2-positive breast cancer worldwide.

About Trastuzumab Emtansine

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate (ADC) being studied in HER2-positive cancers. It is comprised of the antibody trastuzumab and the chemotherapy agent DM1 attached together using a stable linker. Trastuzumab emtansine is designed to target and inhibit HER2 signalling, and to deliver the chemotherapy agent DM1 directly inside HER2-positive cancer cells. Trastuzumab emtansine binds to the HER2-positive cancer cells and is thought to block out-of-control signals that make the cancer grow while also calling on the body's immune system to attack the cancer cells. Once trastuzumab emtansine is absorbed into those cancer cells, it is designed to destroy them by releasing the DM1.

About Zelboraf®

Zelboraf is a personalised oral medicine designed to specifically inhibit the activity of the mutant BRAF protein. It is the first and only approved BRAF inhibitor and has been proven to help patients with BRAF V600 mutation-positive metastatic melanoma in two important ways; it stalls the growth or spread of the cancer (PFS) and helps patients survive longer (OS), for the first time extending life expectancy beyond one year for many patients. Clinical experience with Zelboraf is growing every day; it is already approved in 40 countries and has been used for the treatment of more than 7000 BRAF V600 mutation-positive metastatic melanoma patients worldwide.

To further enhance the potential treatment options available to patients at all stages of the disease, Roche is building on its extensive clinical experience with Zelboraf to investigate a number of combination approaches, including Zelboraf with the MEK inhibitor GDC-0973 and Zelboraf with immunotherapies.

GDC-0973 [XL518] is a potent, highly selective inhibitor of MEK, a serine/threonine kinase that is a component of the RAS/RAF/MEK/ERK pathway. GDC-0973 is being developed by Genentech, a member of the Roche Group, under a collaboration agreement with Exelixis.

Caris Life Sciences Launches Caris Target Now™ Select for NSCLC, Melanoma, and Cancers of the Breast, Colon, and Ovary

Enhanced Molecular Profiling Service Now Includes More Biomarker Analysis Options, Faster Turnaround Time, and Clinical Trial Matching

Caris Life Sciences®, a leading biosciences company focused on enabling precise and personalised healthcare through molecular profiling and blood-based diagnostic services, has announced the launch of Caris Target Now™ Select, an advanced, evidence-based molecular profiling service for patients with non-small cell lung cancer (NSCLC), melanoma, and cancers of the breast, colon and ovary. In addition, the company has enhanced the original Caris Target Now™ comprehensive molecular profiling service offering for all solid tumours.

"This latest effort by Caris is another significant step in what I call health improvement, while at the same time fulfilling on the promise of personalised medicine," said David D. Halbert, Chairman and CEO, Caris Life Sciences. "With these enhancements, we believe we can prolong the lives of patients and improve outcomes, while also lowering costs to the healthcare system."

Caris Target Now™ Select incorporates updated, evidence-based technology platforms to determine the genomic information unique to a patient's tumour based on the presence of relevant biomarkers. In addition to providing focused biomarker profiles designed for earlier-stage cancer patients, it offers the advantages of known "on-Compendium-only" drug associations, faster turnaround time, the capability to derive meaningful results from smaller tissue samples, up to 30 reported biomarkers per patient (depending on tumour type), and – for the first time – Clinical Trials Connector™, a service that enables biomarker-specific clinical trial matching.

"Caris Target Now™ Select is an important new tool to assist physicians in choosing among standard drug choices earlier in the course of treatment, where molecular profiling can have the largest benefit to patient care," said Tom Spalding, Oncology Senior Vice President and Group Head, Caris Life Sciences. "In addition, the new Clinical Trials Connector™ uncovers even more possibilities by linking patients to open and enrolling clinical trials based upon their individual biomarker status."

Using the strongest clinical evidence, Caris Target Now™ Select highlights known therapeutic associations with appropriate, tumour-specific treatments for the five target tumour types, as identified in the National Comprehensive Cancer Network Drug & Biologics Compendium™. In addition, the newly enhanced version of Caris' original molecular profiling service (now renamed Caris Target Now™ Comprehensive) provides both on- and off-Compendium therapeutic associations for all solid tumours, across a wide range of evidence.

"Caris Target Now™ Select is an evidence-based molecular profiling service that can help both earlier-stage and later-stage cancer patients, as it employs the most relevant biomarkers and technologies to help decode a patient's tumour," said Sandeep Reddy, MD, Clinical Professor of Medicine at the David Geffen School of Medicine at the University of California, Los Angeles (UCLA) and Senior Medical Director at Caris. "This service allows physicians to augment their years of experience with advanced

theranostic resources, further personalising cancer care based on the expression status of specific biomarkers."

Through analysis with multiple, highly integrated technology platforms such as immunohistochemistry (IHC), fluorescence *in situ* hybridisation (FISH), polymerase chain reaction (PCR), and DNA sequencing, both the Caris Target Now™ Select and Comprehensive services provide vital information that may be useful to oncologists in individualising therapeutic regimens for cancer patients. By utilising the most relevant, evidence-based molecular profiling technologies to determine the biomarkers unique to a patient's tumour, and performing an extensive review of clinical literature correlating biomarkers to drug response, Caris Target Now™ Select can help illuminate the benefit (or lack thereof) of specific agents, and may reveal appropriate treatments not previously considered.

For more information visit

www.caristargetnow.com

New Findings Highlight the Challenges of Managing Blood Clotting in Cancer Patients

New findings that highlight the challenges of managing thromboembolic events in patients being treated for cancer were released at the ESMO 2012 Congress of the European Society for Medical Oncology in Vienna.

"Venous thromboembolism causes symptoms in about 3 to 4% of cancer patients whose chemotherapy drugs are delivered via a central venous catheter", comments Dr. Fausto Roila, from Medical Oncology Department, Terni, Italy, Chair of the ESMO 2012 Supportive Care Track. "When asymptomatic patients are considered, these events affect about 12-18% of patients who have central venous catheters".

Efficacy of Anticoagulation for Cancer Patients Suggests Guidelines Should be Reconsidered

Anticoagulants are effective for preventing deep vein thrombosis in cancer patients who have a central venous catheter in place for the delivery of chemotherapy, the results of a new French study reveal.

The risk of deep vein thrombosis (DVT) is higher among cancer patients than among the general population. Furthermore, patients undergoing chemotherapy often have central venous access devices implanted. These devices are associated with deep vein thrombosis, which can lead to a pulmonary embolism and in some cases, death. But whether an anticoagulant prophylaxis is needed for patients with cancer with a central venous catheter is a controversial subject.

Dr Sandrine Lavau-Denes, from Centre Hospitalier Universitaire à Limoges, and colleagues performed a phase III prospective, randomised trial in 407 patients and found that anticoagulation significantly reduced the incidence of catheter-related DVT.

"The current guidelines of the American Society of Clinical Oncology, American College of Chest Physicians, and the French National Federation of the League of Centers against Cancer do not recommend prophylactic anticoagulant treatment for cancer outpatients," Dr Lavau-Denes says. "In recent studies and meta-analyses, results are still contradictory, perhaps because of the heterogeneity of the screened patients. We think that these new results should lead to a new reflection."

Dr Fausto Roila, who was not involved in the study, said: "The incidence of CVC-related thrombosis was significantly lower with the two anticoagulant drugs [8.1% (22/272) versus 14.8% (20//135), respectively]."

Dr. Roila noted however that the study has some limitations, including the fact that it is a single-centre study requiring 11 years to be completed. Therefore, "the results of this study should be confirmed by other double-blind, randomised clinical trials, before changing the actual recommendations".

NanoString Technologies Obtains CE Mark for PAM50-based Test for Breast Cancer

Testing Kit Available in Early 2013 Will Offer EU Patients Risk of Recurrence Score and Intrinsic Subtyping

NanoString Technologies, Inc., a privately held provider of life science tools for translational research and developer of molecular diagnostics, has announced that it has obtained the CE Mark for its PAM50-based gene expression test for breast cancer, clearing the company to sell its test in the European Union and other countries recognising the CE Mark.

NanoString's test provides a subtype classification based on the fundamental biology of an individual's breast tumour (referred to as intrinsic subtyping), as well as a prognostic score that predicts the probability of cancer recurrence over 10 years in post-menopausal women with hormone receptor-positive, early stage breast cancer (ESBC) who have been treated with hormonal therapy. Together with studies from the literature, this information has been shown to convey valuable information about a patient's prognosis that can inform critical decisions about the patient's course of therapy.

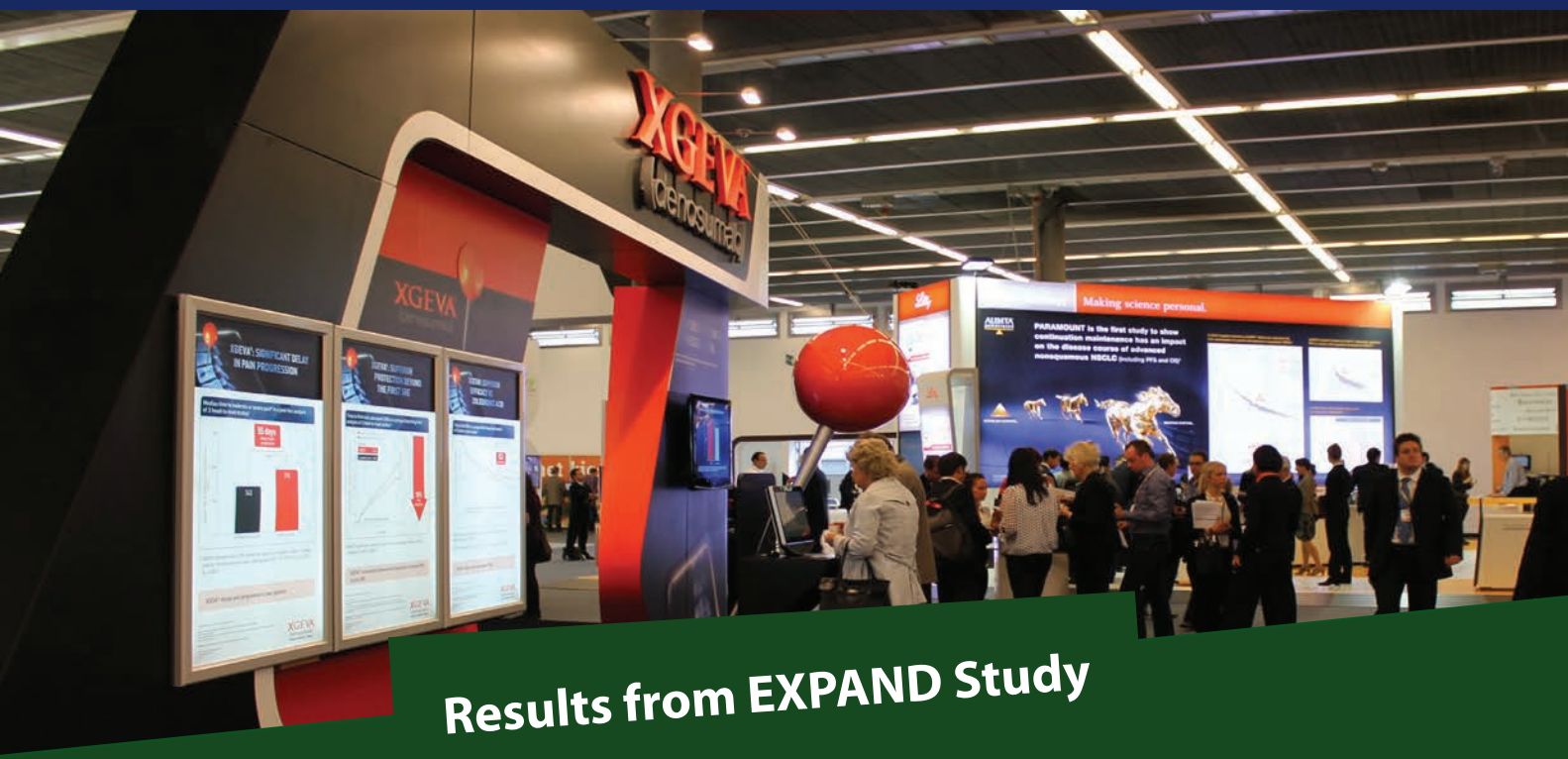
"We are delighted to complete our first regulatory filing for our PAM50-based gene expression diagnostic test for breast cancer less than two years after beginning our rigorous clinical development program," said Bruce Seeley, Senior Vice President & General Manager, Diagnostics at NanoString Technologies. "Women and their clinicians in countries that accept the CE Mark will soon have a new option for informing important treatment decisions, and for bringing more certainty to those decisions. This filing is right on the heels of the landmark study from The Cancer Genome Atlas that demonstrated the power of the PAM50 for subtyping breast cancer into four distinct diseases, and importantly the clinical use of intrinsic subtyping is already included in the St. Gallen International Breast Cancer Treatment Guidelines."

NanoString intends to begin marketing its breast cancer test in major markets that accept the CE Mark in early 2013. The company has a worldwide license for the PAM50 gene signature to develop *in vitro* diagnostic and research products for breast cancer on its nCounter® Analysis System. The clinical development program for NanoString's PAM50-based breast cancer test is designed to support both regulatory requirements for market-specific approval and its incorporation into worldwide breast cancer treatment guidelines.

"PAM50 on the nCounter® platform represents the next generation in genomic testing for breast cancer, providing a powerful new tool for reliable and accurate genomic testing that can be done in local laboratories in countries that recognise the CE Mark," said Brad Gray, President and Chief Executive Officer of NanoString Technologies. "This regulatory filing is an important milestone in NanoString's vision to support the global democratisation of genomic testing, and make high-impact gene-profiling tests widely available as *in vitro* diagnostic products. We extend heart-felt congratulations and gratitude to our collaborators who contributed to this achievement."

The CE Mark is based on positive results from NanoString's first clinical validation study, as well as a recently completed multi-site analytical validation study. The results of the clinical validation study, which included more than 1,000 samples from the TransATAC study of postmenopausal women with hormone receptor-positive early-stage breast cancer (ESBC), were presented by the study's independent investigators at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium. The results of the multi-site analytical validation study are expected to be presented at a major clinical meeting during 2013.

More information is available at www.nanostring.com



Results from EXPAND Study

EXPAND study shows no benefit from adding cetuximab to the first-line chemotherapy in advanced gastric cancer

EXPAND is a large open-label, randomised, controlled, phase III trial of cetuximab plus capecitabine and cisplatin in patients with advanced gastric cancer, which has a poor prognosis and no established standard treatment. The results from the study do not show a benefit from adding cetuximab. The study data were reported by Dr. Florian Lordick at the ESMO 2012 Congress in Vienna.

The current trial compared capecitabine and cisplatin with and without anti-EGFR agent cetuximab in patients with gastric and gastroesophageal junction cancer. The primary of the EXPAND study was progression-free survival, assessed by an independent review committee. The study protocol was amended due to lower progression-free survival observed. Between June 2008 and December 2010, 904 patients from 25 countries were enrolled and randomised; 455 patients received capecitabine and cisplatin plus cetuximab and 449 received only capecitabine and cisplatin. Overall, patients were 74% male and 83% had stomach cancer; 97% of the patients had metastatic disease. Patient outcome was similar between treatment groups and the primary and secondary endpoints were not met; progression-free survival was 4.4 versus 5.6 months and overall survival was 9.4 versus 10.7 months with cetuximab combination and control treatment, respectively. Overall response rates were 29% with cetuximab and 30% with control. Safety profiles were consistent with those known for each agent but more grades 3/4 and serious adverse events were reported in the cetuximab arm. Negative results of this trial can not be explained by toxicity. Tissue is available for biomarker analysis from 97% of included patients and the analysis is currently on-going.

Dr. Arnaud Roth, who discussed the abstract during the Presidential session, questioned if this is the right setting to learn more on anti-EGFR inhibition in gastric cancer. In his opinion the EXPAND study represents a great opportunity for translational research and multivariate analyses testing; it is also an opportunity to establish sub-groups of gastric cancer by genomic expression profiling. The advantage for such analyses is that the EXPAND was a large study in metastatic cancer, performed in homogeneous patient population; clinical database is of high quality, tumour material is already available and patients gave their consent for additional research. During the session he urged that academics get access to that material to help best scientific advances and to improve the outlook of gastric cancer patients.

In conclusion, no general benefit was seen from adding cetuximab to first-line capecitabine and cisplatin for treating patients with advanced gastric cancer and more study is needed to find effective treatments for these patients.

New Weapons in the Fight Against Cancer

Where are the most promising developments from first-in-human studies?

Several new first-in-man studies for drugs targeted against a range of cancers were released at the ESMO 2012 Congress of the European Society for Medical Oncology in Vienna.

"These studies represent our first glance at some of the drugs that may improve cancer treatment in coming years," said Prof. Ahmad Awada, head of the medical oncology clinic at Jules Bordet Institute, Brussels, Belgium, chair of the ESMO 2012 Developmental Therapeutics track. "Today's findings highlight the ways that clinical research is working on cancer therapies that target specific molecular pathways within tumour cells and their microenvironment. At ESMO 2012 this year, interesting early reports will be presented on MEK-, MET- and HSP90 inhibitors as well as studies on drugs targeting EGFR and PI3K and agents active in ALK-positive lung cancer resistant to crizotinib. In addition, new immunotherapeutic strategies and new generations of hormonal agents will be at the menu at this year's ESMO congress."

Key Selected Studies Include:

A Proof-of-concept Study of ODM-201 in Patients with Progressive Castration-resistant Prostate Cancer

In a dose-escalation trial, 87% of 15 patients who received a novel androgen receptor agonist called ODM-201 experienced a PSA decrease at 12 weeks. "These early results are very promising, and such are rarely seen in these early trials. ODM-201 might be a new hormonal treatment option, and its efficacy-safety profile seems to be very promising in prostate cancer patients," said study author Dr Christophe Massard from Institute Gustave Roussy. "Unlike other anti-androgens, according to non-clinical data, ODM-201 has minimal or no brain entrance, and thus no testosterone increase in animal models. Therefore ODM-201 could be a promising new drug option for patients with metastatic or non-metastatic prostate cancer. The results need to be confirmed in bigger patient population of course."

A Dose-escalation Study of Oral Selective c-Met Inhibitor EMD 1214063 in Patients with Advanced Solid Tumours

The cell surface receptor tyrosine kinase c-Met is an emerging target for cancer treatment. EMD 1214063 is a highly selective, reversible and ATP-competitive c-Met inhibitor that causes growth inhibition and regression of HGF-dependent and HGF-independent tumours in pre-clinical models. This dose-escalation study is ongoing, with some preliminary evidence of clinical response being seen.

Multicenter Study of the Investigational Drug TAK-733, an Oral MEK Inhibitor

Preliminary data of this trial in patients with advanced solid tumours indicate that TAK-733 is generally well tolerated and pharmacodynamically active with signs of anti-tumour activity in patients with advanced non-haematologic malignancies, say researchers.

Phase II Study of HSP90 Inhibitor AUY922 in Patients with ALK-rearranged or EGFR-mutated Advanced Lung Cancer

Among 121 patients with previously treated non-small cell lung cancer, activity was demonstrated in both ALK+ and EGFR-mutant patients, say investigators. Overall tumour response and progression-free survival rates observed warrant further studies, particularly among EGFR-mutant patients.

Results of a First-in-human Study of the ALK Inhibitor LDK378 in Advanced Solid Tumours

Investigators report striking activity in ALK+ non-small cell lung cancer patients treated at doses over 400mg who had previously progressed following crizotinib.

Dose-finding Study of the ALK/EGFR Inhibitor AP26113 in Patients with Advanced Malignancies

AP26113 was well tolerated with preliminary anti-cancer activity in ALK+ patients naive to, or failing, prior crizotinib, researchers say.

Leading Cancer Center Uses High Intensity Mode on Varian TrueBeam™ Device to Deliver Precise Brain Radiosurgery

Clinicians at one of the UK's largest radiotherapy departments have commenced brain radiosurgery treatments that enable patients to spend less time on the treatment table while aiding precision by minimising the chance of movement during treatment. Doctors at the Beatson West of Scotland Cancer Centre in Glasgow have begun delivering the pioneering treatments using a TrueBeam™ STx linear accelerator from Varian Medical Systems.

A 71-year-old female with breast cancer that metastasised to her brain received the first such pioneering radiosurgery treatment for two small brain metastases - just 5mm and 6mm in diameter – in a single treatment. "Reducing the time the patient spends on the treatment couch is not only easier on the patient but also reduces the opportunity for movement during the treatment, which helps enhance precision," said clinical oncologist Dr. Brian Clark. "Without the TrueBeam™ system's High Intensity Mode the patient would have received single-fraction fixed beam radiosurgery, taking 45-60 minutes to deliver, with all the inherent problems of potential movement."

In addition to the High Intensity Mode, the first treatment at Glasgow utilised Varian's RapidArc® technology for dose delivery, further expediting the treatment. RapidArc makes it possible to complete a precise treatment by delivering dose continuously during just one or two rotations of the machine around the patient. During a RapidArc treatment, the beam is continually shaped and reshaped to closely conform the dose to the size, shape, and location of the tumour and minimise the dose to surrounding healthy tissue. By using a two-arc approach and delivering the dose at 2400 monitor units per minute --- twice as fast as conventional linear accelerators --- doctors at Glasgow were able to deliver the full prescribed radiosurgery dose of 25 Gy within a single session, with a "beam on" time of five minutes.

"As soon as we installed the TrueBeam™ system we wanted to start utilising the High Intensity Mode together with RapidArc to deliver higher doses in a single treatment session," said Garry Currie, head of radiotherapy physics. "The RapidArc planning capability and superior imaging enable us to achieve very high precision, giving us the confidence to deliver such a high dose in a single session to carry out what is effectively a non-invasive technique on small brain metastases."

Garry Currie said following the success of early TrueBeam™ High Intensity Mode treatments, the technique will be utilised for all radiosurgical treatments at the hospital, including SABR stereotactic radiosurgery in the rest of the body.

The Beatson West of Scotland Cancer Centre treats more than 7,000 patients each year on 11 Varian medical linear accelerators. With a catchment area covering half the population of Scotland, the center has a history of pioneering advanced radiotherapy treatments.

Designed to advance the treatment of lung, breast, prostate, gynaecologic, liver, head and neck, and other types of cancer, TrueBeam™ features a multitude of technical innovations that dynamically synchronise imaging, patient positioning, motion management, and treatment delivery. The TrueBeam™ STx is a high-end model optimised for radiosurgical applications, where very large doses are delivered in a single treatment or only a few sessions.

Oral Palonosetron Shows Safe and Effective Control of Nausea and Vomiting Induced by Multiple Cycles of Chemotherapy

New data presented at the 2012 meeting of the European Society of Medical Oncology (ESMO) in Vienna show antiemetic efficacy maintained across the chemotherapy cycles and a positive safety profile

The oral formulation of palonosetron, the second generation 5-HT3 receptor antagonist (5-HT3 RA), is effective and safe in preventing chemotherapy-induced nausea and vomiting (CINV) over multiple cycles of moderate emetogenic chemotherapy (MEC), according to the data presented by Prof. Steven Grunberg, Professor of Medicine and Pharmacology, Division of Hematology and Oncology, University of Vermont, USA, at the ESMO (European Society of Medical Oncology) Vienna 2012 Congress.

"Palonosetron, a pharmacologically distinct 5-HT3 RA offers superior CINV prevention compared with other 5-HT3 RAs when administered as a single intra-venous dose", Prof. Grunberg said. Palonosetron is approved by the European Medicine Agency (EMA) and the US Food and Drug Administration (FDA) for the prevention of CINV in the intra-venous dosage of 0.25 mg and in the oral dosage of 0.50 mg, with a demonstrated comparable clinical effect of the two formulations. "In our multicenter, open-label study, patients received a single 0.75 mg dose of oral palonosetron to best evaluate the safety of the oral formulation of multiple cycles of chemotherapy", Prof. Grunberg explained.

217 patients, enrolled in 22 study centers in Europe, Mexico and the United States, received oral palonosetron with or without - at investigator discretion - concomitant administration of dexamethasone (8 mg on the first day of treatment) 1 hour prior to MEC for up to a maximum of 4 consecutive cycles. The total number of evaluated cycles was 654; on average 3 per patient, with about half of the patients receiving 4 cycles. Antiemetic efficacy was maintained across the chemotherapy cycles with overall complete response rates (i.e.: no emesis and no need for rescue medication) ranging from 55 to 60% of the patients over the 3-4 cycles.

"The majority of adverse effects were ofmild intensity, with headache the most common one. The few severe, serious adverse effects in the safety profile did not raise clinical concerns. In conclusion, we can say that oral palonosetron is well tolerated and effective in preventing CINV over multiple cycles in patients receiving MEC", Prof. Grunberg said.

Individualised Treatment Strategies to Maximise Survival in Metastatic Colorectal Cancer

Introduction

A summary of the presentations given by Cornelis Punt, Oncologist, Department of Medical Oncology, Academic Medical Centre, University of Amsterdam, The Netherlands; Thomas Gruenberger, Surgeon, Department of Surgery, Medical University of Vienna, Austria; and Axel Grothey, Oncologist, Medical Oncology, Mayo Clinic, Rochester, Minnesota, US, at the European Society for Medical Oncology, 28th September 2012.

Background

Approximately 50% of patients with colorectal cancer (CRC) will develop metastases, and 25% present with metastatic CRC (mCRC) at diagnosis.[1] Prognosis for mCRC is still poor, with five-year overall survival (OS) around 10%.[2-5] While a minority of patients may be eligible for curative surgery, long-term OS is the primary treatment goal for the majority of patients with mCRC. Only a minority of patients can be treated with surgery; for the vast majority, maintaining quality of life (QoL) is the main goal of therapy. New developments and treatment options that have become available in the last ten years have improved patient outcomes, but this means that making decisions on treatment strategies has become much more complex.

This article will examine treatment goals and management strategies for patients based on disease characteristics, and will present recent data demonstrating improved OS for patients continuing with bevacizumab, suggesting a new paradigm in the treatment of mCRC.

Individualised Treatment Strategies to Maximise Survival in Metastatic Colorectal Cancer
Roche Sponsored Satellite Symposium at the European Society for Medical Oncology (ESMO) Congress, Vienna, Amsterdam, 28th September 2012

Chair: Axel Grothey, Mayo Clinic, Rochester, Minnesota, US

Welcome by the Chair
Axel Grothey, Mayo Clinic, Rochester, Minnesota, US

Clinical Expert Panel Discussion: Bevacizumab Beyond Progression in Daily Clinical Practice
Cornelis Punt, Academic Medical Centre, University of Amsterdam, The Netherlands

Clinical Expert Panel Discussion: Defining the Treatment Goal to Optimise Patient Benefit
Thomas Gruenberger, Medical University of Vienna, Austria

Evidence Based Treatment Algorithm across the Continuum of Care
Axel Grothey, Mayo Clinic, Rochester, Minnesota, US

Bevacizumab Beyond Progression in Clinical Practice

Cornelis Punt
(Amsterdam, The Netherlands)

Background

Data from the Phase III ML18147 Treatment across Multiple Lines (TML) trial were first presented at the American Society of Clinical Oncology (ASCO) congress earlier in 2012.

Vascular endothelial growth factor (VEGF) is expressed throughout the tumour lifecycle; tumours continually require VEGF to recruit new vasculature[6] and VEGF continues to be expressed throughout tumour progression, even as secondary pathways emerge.[7-10] The clinical hypothesis in the TML trial was that, in the observational studies BRITE and ARIES, OS was significantly improved with bevacizumab beyond progression versus no bevacizumab beyond progression.[11, 12]

TML Study Design

In the TML trial, patients with unresectable, histologically confirmed mCRC who progressed within three months after discontinuation of first-line bevacizumab plus chemotherapy were randomised to receive second-line fluoropyrimidine-based chemotherapy plus bevacizumab (2.5 mg/kg/week equivalent). The choice of oxaliplatin- or irinotecan-based second-line chemotherapy was dependent on the regimen used in first-line therapy (crossover) and included as a stratification variable. The primary endpoint was OS; secondary endpoints included progression-free survival (PFS), response rate and safety.[13] Key eligibility criteria were at least three consecutive months of first-line bevacizumab-based therapy and progressive disease up to three months after the last bevacizumab administration.

Overall Survival and Progression-free Survival – Intention to Treat Population

Of 820 patients randomised from February 2006 to June 2010 (409 to bevacizumab plus chemotherapy and 411 to chemotherapy alone), baseline patient and disease characteristics were well balanced between arms.[13] The study met its primary endpoint; median OS was 11.2 months for bevacizumab plus chemotherapy and 9.8 months for chemotherapy (hazard ratio [HR]=0.81; 95% confidence interval [CI] 0.69–0.94; unstratified log-rank test, p=0.0062).[13]

Median PFS was 5.7 months for bevacizumab plus chemotherapy and 4.1 months for chemotherapy (HR=0.68; 95% CI 0.59–0.78; unstratified log-rank test, p<0.0001).[13] Subgroup analysis showed that this benefit was maintained across all subgroups except in female population, in whom the benefit was less clear.[13, 14]

Adverse Events of Special Interest to Bevacizumab – Safety Population

The adverse event profile was consistent with previously reported data for bevacizumab plus chemotherapy and there were no more unusual side effects than other first-line treatments. Severe toxicity was low and toxicity was manageable. Compared with historical data from bevacizumab treatment in first- or second-line mCRC, bevacizumab-related adverse events were not increased when continuing bevacizumab beyond progression.[13]

TML – Confirmation of Overall Survival Benefit

These results demonstrate that bevacizumab plus chemotherapy (crossed over from first-line regimen) continued beyond progression significantly prolongs OS and PFS in second-line mCRC.[13]

Other studies of chemotherapy with and without bevacizumab show a benefit of bevacizumab plus chemotherapy over chemotherapy alone and that bevacizumab has proven benefits in first-line, second-line and beyond progression.[15-18] In a 2004 study, for example, the median duration of survival was 20.3 months in a group given irinotecan, bolus fluorouracil, and leucovorin, plus bevacizumab, as compared with 15.6 months in a group given irinotecan, bolus fluorouracil, and leucovorin plus placebo, corresponding to a HR for death of 0.66 (p<0.001).[15]

Integration of TML into Clinical Practice

But the question is, how should the knowledge of bevacizumab's benefit be integrated into clinical practice? Several different strategies can be used. The first, which is the most widely used in the Netherlands, is to give the patient chemotherapy plus bevacizumab, then a different chemotherapy from progression, followed by an anti-epidermal growth factor receptor (anti-EGFR) after further progression. Some data show that a chemotherapy agent with an anti-EGFR may produce good results, when then switching to second-line chemotherapy plus bevacizumab, but there are limited data on using bevacizumab after an anti-EGFR. The TML data show that the optimal regimen is first-line bevacizumab, second-line bevacizumab, followed by other options in later lines.[13]

In summary, continuing bevacizumab through first- and second-line treatment significantly prolongs OS and PFS. Continuation of bevacizumab beyond progression is well tolerated with no new safety signals. Bevacizumab beyond progression represents a new treatment strategy to achieve long-term survival, and the TML trial is the only one in mCRC to demonstrate efficacy with continued biological therapy through first- and second-line treatment. The TML data show that bevacizumab can be given at every line of treatment, as this will provide significant benefit in terms of OS. The main question to be answered now, however, is which patients will receive the most benefit from this treatment strategy?

Defining the Treatment Goal to Optimise Patient Benefit

Thomas Gruenberger

(Vienna, Austria)

Hepatic Resection Improves Long-term Survival

A retrospective review of patients newly diagnosed with mCRC treated at two academic centres from 1990 through 2006 showed that hepatic resection improves long-term survival.[19] Five-year survival rate was higher in patients undergoing hepatic resection (55.2%) than in patients with unresected disease (19.5%).[19] This illustrates that surgery has some place in treating mCRC, but the right candidates for surgery need to be defined.

Criteria to Define Resectability in Metastatic Colorectal Cancer

Criteria used to define resectability in mCRC include upfront resectable cases (10%). These patients have sufficient remnant liver (30%) of healthy volume. Borderline resectable cases (20%) require tumour downsizing to achieve resectability, making them eligible for surgery; there may be invasion or contact of metastases with preservable vascular structures. Unresectable patients (70%) have multiple disease sites, with all liver segments infiltrated by metastases and poor patient performance status. Assessment of individual cases by multidisciplinary teams is critical to defining the patient's resectability.

Perioperative Chemotherapy in Patients with Resectable Liver Metastases

Surgical resection alone is regarded as the standard of care for patients with liver mCRC, but relapse is common. In a randomised trial, perioperative chemotherapy in patients with resectable liver metastases was compared to surgery alone (182 in perioperative chemotherapy group versus 182 in surgery group).[20, 21] Patients were centrally randomised by minimisation, adjusting for centre and risk score. The primary objective was to detect a HR of 0.71 or less for PFS. The absolute increase in rate of PFS at three years was 7.3% in patients undergoing

resection.[20] These results show that perioperative chemotherapy with FOLFOX4 is compatible with major liver surgery and reduces the risk of events of PFS in eligible and resected patients. However, further results presented at the ASCO congress in 2012 showed that there was no significant difference in OS between arms (HR=0.88, 95% CI 0.68-1.14, p=0.34) (all randomised);[21] perioperative chemotherapy with FOLFOX4 did not significantly improve OS over surgery alone.[21]

Summary of Studies of Bevacizumab in Patients with Liver-only Metastases

Looking specifically at trials which assessed patients with liver-limited disease, several studies of bevacizumab in patients with liver-only metastases have been performed. Response rates in these patients were higher than in the overall population.[22-26] Furthermore, resection rates were impressive when bevacizumab was added.[22-26] For the BOXER and GONO trials and in an Austrian study from 2008, the overall response rate was over 70%.[24-26] Therefore, the data do support the use of bevacizumab. However, a high proportion of patients experience disease recurrence and 80% of patients who have had surgical resection experience recurrence within three years.[27-30] Risk factors such as multiple tumours, lymph node involvements, involved resection margins and a tumour size greater than 5 cm must be kept in mind and discussed in multidisciplinary team meetings to decide on the aim of treatment for individual patients.[27-30]

Pathological Response: Bevacizumab Plus Chemotherapy

It is important to observe the pathological response of bevacizumab plus chemotherapy. Recent trials showed that bevacizumab plus chemotherapy significantly improves pathological response rate (38%) compared with chemotherapy alone (10%).[31-33]

In summary, it is crucial to discuss individual patients in multidisciplinary team meeting, as patients with mCRC have different disease characteristics and these influence treatment goals. A surgeon should be included in the multidisciplinary team meeting as there are currently no clear guidelines on resectability. (However, the results of a trial clearly defining resectability in multinational setting in 80 patients treated with FOLFOX plus bevacizumab will be presented at the next ASCO congress.)

Individual treatment strategies can be used to maximise survival in mCRC. And the data from several trials clearly indicate that bevacizumab is an effective therapy option in mCRC patients with upfront resectable, borderline resectable or unresectable disease. The majority of patients with mCRC require long-term disease control.

Evidence-based Treatment Algorithms Across the Continuum of Care

Axel Grothey
(Rochester, Minnesota)

Background

A high proportion (70%) of patients with mCRC have "never-resectable" disease and require effective disease control, long-term survival and maintenance of QoL.[34-40] The majority of patients have extrahepatic metastases that are unsuitable for resection.[41, 42] Even if resection of liver metastases is feasible, most patients relapse within two years.[28, 29, 43-46] OS is the most important treatment goal for the majority of patients with mCRC.[47, 48]

A high number of agents are available for the treatment of mCRC, from chemotherapy agents such as oxaplatin to more targeted agents such as bevacizumab and cetuximab. Data have shown that exposure to multiple chemotherapy agents is associated with prolonged OS, as demonstrated by analysis of data from 21 arms of 11 published Phase III trials with 5,768 patients with advanced CRC on exposure to fluorouracil/leucovorin, irinotecan, and oxaliplatin; median OS (months)=13.2+(% patients with three drugs × 0.1; p=0.0001, R2=0.85.[49]

Key Challenges in Unresectable Metastatic Colorectal Cancer

New treatment approaches are needed to maximise the benefit from the high number of biologics now available. Existing data can be used to derive sequence algorithms that utilise several biologics across multiple therapy lines and improved survival correlates with exposure to all available therapies.

Phase II/III Trials of First-line Bevacizumab

Real data should be used to determine the best treatment strategy. A lot is not yet clear, for example, there are no head-to-head comparisons between anti-EGFR and bevacizumab as first-line treatment. However, a lot can be determined from the existing data. In several trials, bevacizumab has proven OS and PFS benefit as first-line therapy.[15, 16, 50-56] For example, in a study by Saltz *et al*., a total of 1,401 patients were randomly assigned to XELOX versus FOLFOX-4, and then to bevacizumab versus placebo. Median PFS was 9.4 months in the bevacizumab group and 8.0 months in the placebo group (HR, 0.83; 97.5% CI, 0.72 to 0.95; p=0.0023).[16]

A significant improvement in both PFS and OS was shown in a 2004 study in which 813 patients with previously untreated mCRC were randomly assigned to receive irinotecan, bolus fluorouracil and leucovorin (IFL) plus bevacizumab or to receive IFL plus placebo.[15] The median OS was 20.3 months in the group given IFL plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a HR for death of 0.66 (p<0.001).[15] The median duration of PFS was 10.6 months in the group given IFL plus bevacizumab, as compared with 6.2 months in the group given IFL plus placebo (HR for disease progression, 0.54; p<0.001), demonstrating that the addition of bevacizumab to fluorouracil-based combination chemotherapy results in statistically significant and clinically meaningful improvement in survival among patients with mCRC.[15]

Phase III Trials of Bevacizumab: First-line, Second-line and Beyond Progression

As well as demonstrating benefit as first-line therapy, Phase III trials have shown that bevacizumab has proven OS benefit in second-line and beyond progression as well.[13, 15, 18] Recent data, presented at ASCO 2012 showed that the median OS was 11.2 months for bevacizumab plus chemotherapy and 9.8 months for chemotherapy (HR=0.81; 95% CI 0.69–0.94; unstratified log-rank test, p=0.0062).[13]

Progression-free/Disease-free Survival for Epidermal Growth Factor Receptor Inhibitors Improves Across Lines of Therapy in KRAS Wild-type Metastatic Colorectal Cancer

Data from several trials demonstrate that the use of cetuximab with adjuvant mFOLFOX6 compared with mFOLFOX6 alone did not result in improved disease-free survival,[57] nor did it add significant benefit to the Nordic FLOX (bolus fluorouracil/folinic acid and oxaliplatin) regimen in first-line treatment of mCRC.[58] There was also no confirmed a benefit of addition of cetuximab to oxaliplatin-based chemotherapy.[59] Data from a study by Douillard *et al*., however, showed that panitumumab-FOLFOX4 was well tolerated and significantly improved PFS in patients with wild-type (WT) KRAS tumours.[60] And in a separate study, the addition of cetuximab to FOLFIRI as first-line therapy improved survival in patients with KRAS wild-type mCRC.[61] The PICCOLO trial showed that panitumumab is effective in combination with irinotecan for chemoresistant advanced colorectal cancer.[62] A further study of panitumumab plus FOLFIRI revealed that it significantly improved PFS and was well-tolerated as second-line treatment in patients with WT KRAS mCRC,[63] and a study of panitumumab as monotherapy showed that its efficacy in mCRC is confined to patients with WT KRAS tumours.[64] Cetuximab was also shown to benefit patients with a tumour bearing WT KRAS.[65]

A Case of Unresectable Metastatic Colorectal Cancer: 2010

In a case study of unresectable mCRC from 2010, before the new treatments emerged, a 55-year-old male with unresectable liver-only metastases was given bevacizumab plus XELOX. A treatment break followed and then he was given FOLFIRI followed by an EGFR inhibitor plus irinotecan. This treatment sequence only utilises two biologics across three lines of treatment.

VELOUR: Phase III Trial of Second-line Aflibercept Plus FOLFIRI – Efficacy

New data from the VELOUR Phase III trial studying the effect of adding aflibercept to FOLFIRI in patients with mCRC previously treated with oxaliplatin, including patients who received prior bevacizumab, revealed a statistically significant survival benefit with FOLFIRI plus afilbercept over FOLFIRI combined with placebo.[66] Adding aflibercept to FOLFIRI significantly improved OS relative to placebo plus FOLFIRI (HR, 0.817; 95.34% CI, 0.713 to 0.937; p=0.0032) with median survival times of 13.50 versus 12.06 months, respectively.[66] Aflibercept also significantly improved PFS (PFS; HR, 0.758; 95% CI, 0.661 to 0.869; p< 0.0001), with median PFS times of 6.90 versus 4.67 months, respectively.[66] Improvement in OS and PFS with aflibercept appeared to be independent of prior treatment with bevacizumab.[66]

TML Phase III Trial of Bevacizumab Plus Chemotherapy Through First- and Second-line – Efficacy

The TML trial results showed that bevacizumab through first- and second-line significantly improved OS and PFS compared with chemotherapy alone (median OS 11.2 months for bevacizumab plus chemotherapy and 9.8 months for chemotherapy alone [HR=0.81; 95% CI 0.69–0.94; unstratified log-rank test, p=0.0062] and median PFS was 5.7 months for bevacizumab plus chemotherapy and 4.1 months for chemotherapy alone (HR=0.68; 95% CI 0.59–0.78; unstratified log-rank test, p<0.0001).[13]

CORRECT: Phase III Study of Regorafenib in the Salvage Treatment of Metastatic Colorectal Cancer – Efficacy

The CORRECT Phase III study of regorafenib in the salvage treatment of mCRC showed regorafenib significantly improved OS and PFS compared with placebo.[67] In the study, patients were randomised 2:1 to receive best supportive care plus either regorafenib (160 mg od po, three weeks on/one week off) or placebo. The results showed that OS and PFS were significantly improved in the regorafenib arm compared to the placebo arm: HR for OS was 0.77 (95% CI 0.64-0.94, 1-sided p=0.0052), median OS was 6.4 versus 5.0 months; HR for PFS 0.49 (95% CI 0.42-0.58, 1-sided p<0.000001), and median PFS 1.9 versus 1.7 months.

Based on the data from the CORRECT, TML and VELOUR trials, it is possible to determine optimised treatment strategies for individual patients with unresectable mCRC.

In summary, the majority of patients with mCRC have unresectable, non-curable disease. Extending the duration of life and maintaining QoL are therefore the principal treatment goals. To obtain these goals, treatment sequences have to be optimised. Bevacizumab is the only biologic proven to extend OS in first-line, second-line and now beyond progression, therefore, continuing bevacizumab through first and second lines of therapy while reserving other treatment options for later lines is an effective strategy to maximise long-term OS.

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Emerging treatment strategies

to improve overall survival in unresectable mCRC

For the vast majority of patients with incurable metastatic colorectal cancer (mCRC), the principle treatment goal is to extend their survival for as long as possible with minimal impact on their quality of life.

Fortunately, median survival rates have improved dramatically for these patients, from 4–5 months in 1970, up to 24 months and beyond in the most recent trials with the support of advanced surgical techniques, modern chemotherapy and novel targeted agents.[1]

Today, with the broad range of treatment options available in mCRC, the focus is not necessarily on which treatment to use but on when to use it. The emerging treatment strategy in mCRC is to determine the best treatment sequence to expose patients to the benefits of all possible treatment options.[2]

A sequencing approach to extend life

Sequencing therapies are needed to help extend the lives of patients with initially unresectable mCRC, where the majority of patients will never achieve cure.[3]

These mCRC patients should be exposed to all available biologic options at some point during their treatment journey.[2,4] Careful selection of the biologic treatment sequence from first line and beyond, into second and third line, can help to improve survival[4] and deliver the best outcomes for patients.

The right medicine, at the right time

In the absence of directly comparable clinical trials for biologics, selecting the optimal treatment sequence can be a challenge. A valid approach involves evaluation of available clinical trial data in each line of therapy,[4] with a focus on the magnitude of benefit achieved.

Consideration should also be given to the therapeutic targets of biologic treatments when determining their place in the treatment sequence. For example, treatment strategies that include VEGF inhibition should recognise that VEGF is present from the earliest stages of tumour development, whilst also acknowledging the persistent, continuous nature of VEGF expression.[5,6]

Finally, patients are now likely to receive multiple drugs in sequential therapy; therefore, the timing of drug toxicity exposure needs to be managed effectively to avoid compromising your patient's daily living, quality of life and their ability to receive further systemic and/or targeted therapies.[2]

Prescribing Information can be found opposite

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Conclusion

With the emergence of novel treatment strategies in mCRC, patients with incurable disease have a better chance to significantly extend their survival to two years or beyond. Adopting an upfront treatment strategy on how to effectively sequence the patient's biologic therapies will help to achieve the primary goal of extending survival for as long as possible with minimal impact on daily living.

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Turning Today's Challenge Into Tomorrow's Success for Hodgkin Lymphoma and Systemic Anaplastic Large Cell Lymphoma

Introduction

The satellite symposium titled, "Turning Today's Challenge into Tomorrow's Success for Hodgkin Lymphoma and Systemic Anaplastic Large Cell Lymphoma" was held during the European Society for Medical Oncology (ESMO) Congress on Saturday 29th September 2012 at the Austria Centre Vienna, Vienna, Austria. The meeting was chaired by Doctor Andreas Engert, University Hospital of Cologne, Köln, Germany.

Where Are We Today?

Pier Luigi Zinzani

(Italy)

In the last 50 years there has been a steady and significant improvement in disease specific and overall survival (OS) for Hodgkin lymphoma (HL).

In patients with early stage HL and a favourable prognosis, treatment with 2 cycles of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) followed by 20 Gy of involved field radiation therapy (IFRT) is as effective as, and less toxic than, 4 cycles of ABVD followed by 30 Gy of IFRT.[1] On the other hand, intensified chemotherapy with 2 cycles of bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine (also called Oncovin), procarbazine and prednisone (BEACOPP) escalated followed by 2 cycles of ABVD plus IFRT significantly improves tumour control in patients with early unfavourable HL.[2] In this setting, when compared with ABVD, BEACOPP has also been found to result in better initial tumour control in advanced disease, but the long term clinical outcome in terms of OS does not appear to differ significantly between the two regimens.[3]

This was shown when ABVD (8 cycles) was compared to BEACOPP (escalated 4 cycles ≥ baseline 4) in stage III/IV advanced HL patients.[4] The primary endpoint of event free survival was similar between treatment arms. However, more progressions/relapses were observed with ABVD. In addition, early discontinuations were more frequent with BEACOPP. This study showed that dose intensification in an advanced group of patients does not impact OS. Therefore, other considerations such as treatment burden and cost, fertility issues, long term relapses and immediate and late morbidity may guide physician/patient decisions toward use of ABVD or BEACOPP.

The role of FDG positron emission tomography (FDG-PET) in the management of HL is also a critical issue. In guiding the decision making process, PET imaging has emerged as the single most important tool for planning of risk adapted treatment in advanced HL.[5] The 2 year progression free survival (PFS) for 260 newly diagnosed patients with HL (190 with stages IIB through IVB and 70 with stage IIA plus adverse prognostic factors) with positive PET-2 (PET scan performed at baseline and after 2 cycles of ABVD) was 12.8%, and for patients with negative PET-2 results was 95.0% ($p<0.0001$).[5]

The importance of PET in guiding the need for additional therapy was confirmed in a prospective randomised clinical trial comparing different BEACOPP regimens.[6]

The management of HL in the elderly population (>60 years of

Turning Today's Challenge Into Tomorrow's Success for Hodgkin Lymphoma and Systemic Anaplastic Large Cell Lymphoma
Takeda Sponsored Satellite Symposium at the European Society for Medical Oncology (ESMO) Congress, Vienna, Amsterdam, 29th September 2012

Chair: Andreas Engert, University Hospital of Cologne, Köln, Germany

Welcome by the Chair
Andreas Engert, University Hospital of Cologne, Department of Internal Medicine I, Köln, Germany

Where are we Today?
Pier Luigi Zinzani, University of Bologna, Bologna, Italy

Agents for Change?
Ulrich Jäger, Medical University of Vienna, Austria

Where Could we be Tomorrow?
Tim Illidge, University of Manchester, Manchester, United Kingdom

60 Minutes in Clinic With...
Reda Bouabdallah, Sainte Marguerite, Marseille, France

Javier Briones Meijide, Santa Creu and Sant Pau Hospital, Barcelona, Spain

Martin Hutchings, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

age) remains suboptimal.[7] Elderly patients are under-represented in clinical trials and there is no standard treatment approach in this patient population. Outcomes are inferior to those seen in younger patients (elderly patients more often have mixed cellularity subtype, "B" symptoms, elevated erythrocyte sedimentation rate and poorer performance status). and are thought to be due to a number of factors. These include the different presentation of disease, the present of comorbidities that preclude appropriate treatment, inadequate treatment and treatment related toxicities (e.g. bleomycin induced lung toxicity).[8]

In patients with chemosensitive first relapse of HL, high dose carmustine, etoposide, cytarabine and melphalan (BEAM) and transplantation of haemopoietic stem cells (HSCT) has been shown to improve freedom from treatment failure irrespective of the length of initial remission, compared to dexamethasone-BEAM (Dexa-BEAM). Freedom from treatment failure at 3 years was significantly better for patients given BEAM-HSCT (55%) than for those on Dexa-BEAM (34%; difference -21%, 95% CI -39.87 to -2.13; p=0.019).

Even with the high rate of cure, there are still many HL patients that fail to respond to, or relapse following, initial treatment. There is currently no standard of care and the management of these patients continues to be a significant unmet medical need.

This problem has been emphasised by an analysis of OS in patients who relapsed following autologous stem cell transplantation (ASCT).[9] Patients with ASCT as their most recent treatment and relapsed showed the worst OS: 0.7 months for those who relapsed at 0-3 months after transplant versus 1 year for those who relapsed after 3-6 months. At the 1 year cut off, median survival was approximately 2 years. This analysis demonstrates that survival following relapse within the first year after transplantation is so poor that this time point should be considered as a stratification point for clinical trials.

Peripheral T cell lymphoma (PTCL) and natural killer/T cell lymphoma (NKTCL) are rare and heterogeneous forms of non-HL (NHL) that, in general, are associated with a poor clinical outcome.[10] The most common subtypes are PTCL not otherwise specified (NOS; 25.9%), angioimmunoblastic type (18.5%), NKTCL (10.4%) and adult T cell leukaemia/lymphoma (ATLL; 9.6%). Although, the WHO classification is useful for defining subtypes of PTCL and NKTCL, expert haematopathological review is important for accurate diagnosis. The clinical outcome for patients with most of these lymphoma subtypes is poor with standard therapies. The use of an anthracycline-containing regimen has not been found to be associated with an improved outcome in PTCL-NOS or the angioimmunoblastic type, but is associated with an improved outcome in ALK-positive anaplastic large cell lymphoma (ALK+ ALCL).

The features of ALK+ ALCL, ALK- ALCL and primary cutaneous ALCL have been described in the 2008 WHO classification.[11] The 5 year OS for each varies, with the best outcomes seen in primary cutaneous ALCL (>90% versus 65-90% and 30-40% for ALK+ and ALK-, respectively).[12, 13] In the German High-Grade Non-Hodgkin Lymphoma Study, the highest survival rates were found in patients with ALK+ ALCL.[14] Three-year event-free survival (EFS) and OS were 75.8% and 89.8% (ALK+ ALCL), 50.0% and 67.5% (AITL), 45.7% and 62.1% (ALK- ALCL), and 41.1% and 53.9% (PTCL), respectively.[14]

The NCCN induction therapy guidelines recommend that ALK+ ALCL should be treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) plus radiotherapy.[15] For ALK- ALCL stage I, II and low or low/intermediate international prognostic indicator (IPI), inclusion in a clinical trial or use of multi-agent chemotherapy (4-6 cycles) plus locoregional radiotherapy is recommended. The same schedule adjusted to 6-8 cycles of chemotherapy is recommended in ALK- ALCL stage I and II when the IPI is high or high-intermediate, or when stage III/IV disease is present.

In a 5 year follow up, the Nordic Lymphoma Group (NLG) assessed the efficacy of a dose dense approach consolidated by upfront high dose chemotherapy (HDT) and ASCT in previously untreated PTCL.[16] The treatment was well tolerated and led to long term PFS in 44% of treatment naïve patients with PTCL, which was an encouraging outcome, particularly considering the high median age (57 years) and adverse risk profile of the study population. When the results were analysed according to patient type, it was found that the best results were obtained in ALK- ALCL patients.

Remission rates in sALCL with combination chemotherapy are approximately 80%, but relapse after first line therapy is common.[17] Response rates to the new agent brentuximab vedotin in patients with relapsed/refractory ALK+ and ALK- ALCL have exceeded 80% with frequent complete responses and a median duration of response greater than 1 year.[17]

Relapsed/refractory HL and relapsed systemic ALCL (sALCL) can present a diagnostic challenge for the pathologist and clinician, and more data is needed to inform treatment decisions and improve outcomes.

Agents for Change?

Ulrich Jäger

(Austria)

There are still unmet needs in the treatment of HL and ALCL. These diseases, although distinct have some similarities in terms of cell signalling that could be utilised to develop new therapies. They both have a strong dependence on the microenvironment in terms of cross talk between tumour cells and supporting cells in both diseases, as well as a shared expression of some of the cellular molecules.

In HL, Hodgkin/Reed-Sternberg (H/RS) cells, as the malignant cell type,

have a major role in the orchestration of the microenvironment milieu associated with HL. They can directly induce the recruitment of several immune cell types from the peripheral circulation and also trigger the local expansion of diverse cellular subsets.[18, 19, 20] Several observations indicate that H/RS cells are dependent on survival signals received from immune/inflammatory cells. Included in the survival signals that are provided by inflammatory cells to the H/RS cells is the activation of CD30, a member of the tumour necrosis factor (TNF) family. CD30 is expressed abundantly on RS cells and is capable of promoting cell proliferation and survival as well as inducing antiproliferative responses and cell death. The CD30 molecule is an activation antigen. When it is inhibited, the activation pathway is blocked and cell apoptosis occurs.[19]

Therefore, there is the opportunity to modify the interaction between H/RS cells and the surrounding microenvironment. In HL, this could be achieved by blocking the signalling of the TNF family, which is mainly though nuclear factor-κB (NF-κB),[21] which is constitutively activated and serves as a survival factor of tumour cells.

In ALCL, regardless of the subtype, the disease is associated with the expression of CD30, and CD30 and ALK signalling have been found to be closely linked.[22]

CD30 is also expressed in non-malignant cells, including B and T cells, macrophages and mast cells, among others.[23, 24] CD30 expression is associated with T cell activation and the presence of Epstein Barr virus and human T lymphotropic virus.

High levels of CD30 are additionally expressed in primary cutaneous CD30+ disorders and PTCL, and CD30 expression is also seen at lower levels in other haematopoietic malignancies.[23, 25, 26, 27, 28]

A number of biomarkers have been identified in HL, including CD68 and CD20. Both of these molecules have been found to be good predictors of survival.[29, 30] Thymus and activation regulated chemokine (TARC) protein levels are high at the beginning of the disease and levels fall with treatment.[31]

CD30 in its soluble form can be of prognostic value, dependent on the type of therapy. Two prospective studies have found that soluble CD30 levels are related to future lymphoma risk in a concentration-dependent manner.[28, 32] A correlation between serum soluble CD30 and poor prognosis in CD30+ lymphomas (HL and ALCL) has also been observed. In addition, high CD30 levels correlate with disease burden. It is not yet known if CD30 is a good predictor of response to treatment.

There are a number of new strategies being investigated for the treatment of HL and ALCL. These include the development of brentuximab vedotin, which is an antibody drug conjugate (ADC) that targets CD30 expressing malignant cells.[33, 34, 35] It binds to CD30, and the subsequent complex is internalised in the tumour cell, where it leads to the release of the cytotoxic agent monomethyl auristatin E (MMAE). MMAE disrupts the microtubule network and leads to G2/M cell cycle arrest and cell apoptosis. Molecular characterisation of brentuximab vedotin has revealed that the anti-CD30 antibody portion of the conjugate acts to target the agent to CD30 positive cells.[36]

Preclinical studies have shown the anti-tumour activity of brentuximab vedotin when combined with chemotherapeutic agents in a murine xenograft model of HL.[37]

When developing new therapies for HL and ALCL, it is important to take into consideration the genetic background of the patient, the chromosomal aberrations and somatic mutations associated with the tumour type and the microenvironment of the tumour cells. A deeper understanding of the pathogenesis of HL and ALCL may provide more opportunities for the manipulation of these diseases.

Where Could we be Tomorrow?

Tim Illidge

(United Kingdom)

As previously mentioned, brentuximab vedotin (formerly SGN-35) is an ADC consisting of an anti-CD30 monoclonal antibody linked to MMAE.[38, 39] In July 2012, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion recommending to the European Commission conditional marketing authorisation for the following indications: (1) the treatment of adult patients with relapsed or refractory CD30 positive HL following ASCT or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option, and (2) for the treatment of adult patients with relapsed or refractory sALCL.[40]

The first clinical trial of brentuximab vedotin was a Phase I, open label, multicentre dose escalation study in patients with relapsed/refractory CD30+ haematological malignancies.[41] This study included 45 patients (42 with HL, two with sALCL and one with CD30+ angioimmunoblastic T cell lymphoma) with a median age of 36 years (range: 20-87). The patients were heavily pretreated and there was no restriction in the number of prior treatment regimens, although patients who had undergone allogeneic transplant were excluded.

Patients received brentuximab vedotin at doses ranging from 0.1-3.6 mg/kg of body weight every 3 weeks. The maximum tolerated dose was 1.8 mg/kg every 3 weeks. Objective responses were observed in 6 of 12 patients (50%) who received brentuximab vedotin at the maximally tolerated dose of 1.8 mg/kg, and the median duration of response was at least 9.7 months. Tumour regression was observed in 36 of 42 evaluable patients (86%).

A dose-limiting toxic (DLT) effect (grade 4 thrombocytopenia) occurred in 1 of 6 patients who received a dose of 1.8 mg/kg; unrelated grade 3 acute renal failure occurred in 1 of 6 patients who received a dose of 2.7 mg/kg. In the single patient who received a dose of 3.6 mg/kg, febrile

neutropenia and presumed sepsis developed, which both contributed to death 14 days after the first dose. At the 2.7 mg dose, two additional patients had three DLT effects (grade 3 hyperglycaemia in the first patient and grade 3 unrelated prostatitis and febrile neutropenia in the second patient) for a total of 3 of 12 patients with DLT effects at this dose level. On the basis of these observations, a dose of 2.7 mg/kg was associated with unacceptable toxic effects, and 1.8 mg/kg was considered the highest dose that did not cause unacceptable adverse effects. The most common adverse events (AEs), typically grade 1 or 2 in severity, were fatigue (16 patients, 36%), pyrexia (15 patients, 33%), and diarrhoea, nausea, neutropenia and peripheral neuropathy (10 patients, 22% each). A total of 27 serious AEs occurred in 14 patients (31%) during the study; of these events, 9 (33%) were considered by the investigators to be related to the study drug. A total of 12 patients (27%) had AEs other than progression that led to treatment withdrawal.

Based on the favourable results in the Phase I study, two pivotal Phase II trials were conducted. The first was in relapsed/refractory HL; the second was in relapsed/refractory sALCL.[38, 39, 42] These parallel trials used the same dosing schedule of brentuximab vedotin of 1.8 mg/kg administered every 3 weeks in an outpatient setting.

The Phase II study in HL enrolled 102 patients with relapsed/refractory HL who had failed a prior ASCT.[38] The median age was 31 years (range, 15-77) and patients had received a median of 3.5 prior regimens (range: 1-13). There was no limit to the number of prior treatment regimens. In this population of heavily pretreated patients, brentuximab vedotin was associated with an objective response rate (ORR) of 75%, including 34% complete remission (CR). The median duration of response was 6.7 months overall and 20.5 months among patients in CR. Tumour regression was observed in 94% of evaluated patients. Among patients who had received systemic therapy after ASCT before study enrolment, median PFS was higher with brentuximab vedotin than with the prior therapy.

Updated survival data from this trial have demonstrated that the median OS has not been reached after a 26.5 month median follow up.[43]

Brentuximab vedotin was generally well tolerated, with few grade 3/4 events reported.[38] The most common (≥10%) treatment related AEs were peripheral sensory neuropathy (42%), nausea (35%), fatigue (34%), neutropenia (19%), diarrhoea (18%), pyrexia (14%), vomiting (13%), arthralgia (12%), pruritus (12%), myalgia (11%), peripheral motor neuropathy (11%) and alopecia (10%). A total of 56 patients (55%) experienced AEs of grade 3 or higher. Besides peripheral sensory neuropathy (8%), the majority of grade 3 or higher AEs were laboratory abnormalities including neutropenia (20%), thrombocytopenia (8%), and anaemia (6%). No cases of febrile neutropenia were observed. There were no deaths within 30 days from the last drug administration, and no deaths were attributed to the study drug. Twenty patients had AEs that led to treatment discontinuation.

The Phase II trial of brentuximab vedotin in sALCL enrolled 58 patients with relapsed/refractory sALCL.[39] The ORR in this study was 86%, including 59% CR.[42] The median response duration was 13.2 months overall and was not reached after a median follow up of 15 months in patients in CR. The most common (≥20%) treatment emergent AEs of any grade, regardless of relationship to brentuximab vedotin, were peripheral sensory neuropathy (41%), nausea (40%), fatigue (38%), pyrexia (34%), diarrhoea (29%), rash (24%), constipation (22%) and neutropenia (21%). Adverse events of grade 3 or higher were experienced by 60% of patients. Among events of grade 3 or higher severity that occurred in the study, the most common were neutropenia (21%), thrombocytopenia (14%), peripheral sensory neuropathy (12%) and anaemia (7%).[39] Six deaths occurred within 30 days of the last administration of brentuximab vedotin; none of these deaths were attributed to study drug. Adverse events led to treatment discontinuation in 14 patients (24%); the only AE that resulted in treatment discontinuation in more than one patient was peripheral sensory neuropathy (six patients). Thus, the activity of brentuximab vedotin was similar in both disease states.

Ongoing and planned studies are evaluating other uses of brentuximab vedotin. Multiple studies are evaluating combination strategies in the frontline setting of HL, to assess whether response rates higher than the 75% observed in the relapsed/refractory setting can be achieved as well as the safety of combination use.

A Phase I study has been designed to evaluate brentuximab vedotin in combination with ABVD or adriamycin, vinblastine, and dacarbazine without bleomycin (AVD) in the first line treatment of HL. Interim results suggested positive activity of this approach, with all patients in the study attaining CR.[44] Adverse events were primarily related to the combination chemotherapy. The most common AEs included neutropenia (77%) and nausea (66%). Peripheral sensory neuropathy, fatigue, vomiting, and constipation also occurred. Sensory neuropathy was entirely grade 1/2. The combination of brentuximab vedotin and ABVD was associated with a significant risk of pulmonary toxicity, which was observed in 40% of patients. Pulmonary toxicity typically occurred during cycles 3-6 and was reversible in 9 of 10 patients; 7 of 10 patients discontinued bleomycin and were able to continue with the brentuximab vedotin plus AVD. No DLTs were observed.

Because of the pulmonary toxicity, the bleomycin was eliminated, and patients are continuing to receive brentuximab vedotin plus AVD. The FDA has added a contraindication for brentuximab vedotin, warning against the concomitant use of bleomycin, as well as dosing of brentuximab vedotin if progressive multifocal leukoencephalopathy (PML) is suspected and discontinuing brentuximab vedotin if a diagnosis of PML is confirmed. The omission of bleomycin should not present a major challenge, as bleomycin may be considered the weakest component of the ABVD regimen.

The investigators also conducted interim PET analyses of disease activity. The clinical significance of interim PET results in the context of novel combinations such as AVD plus brentuximab vedotin is unknown. However, the ABVD experience predicts that patients with detectable disease by PET scan at the interim analysis typically have poor outcomes and require additional therapy.

The ongoing AETHERA (Antibody Drug Conjugate Empowered Trial for Hodgkin to Evaluate Progression After ASCT) trial is a randomised, double blind, placebo controlled Phase III study comparing brentuximab vedotin and placebo in approximately 325 patients at high risk of residual HL following ASCT.[46] Patients in this high risk category include those with a history of refractory HL, those who relapsed or progressed within 1 year after receiving frontline chemotherapy and those who had disease outside of the lymph nodes at the time of relapse before ASCT. The primary endpoint of the AETHERA trial is PFS. Secondary endpoints include OS, safety and tolerability. Another strategy being evaluated in the pre-transplant setting is the addition of brentuximab vedotin to platinum based regimens such as ifosfamide, carboplatin and etoposide (ICE) or dexamethasone, high dose cytarabine and cisplatinum (DHAP). Trials are planned to evaluate whether brentuximab vedotin can increase the likelihood of attaining CR prior to ASCT and decrease the toxicity of these regimens.

Finally, there is also interest in evaluating brentuximab vedotin based combination strategies in patients with relapsed/refractory HL after ASCT, in an attempt to improve upon the 34% CR rate observed with single agent brentuximab vedotin.

Current studies indicate that brentuximab vedotin is an efficacious treatment option with anticipated manageable tolerability in heavily pretreated relapsing/remitting HL post ASCT and relapsing/remitting sALCL patients. In order to effectively manage potential side effects if brentuximab vedotin, patients should be monitored, and dose delay or reduction can be considered, if required.

60 Minutes in Clinic With…

Reda Bouabdallah (France); Javier Briones Meijide (Spain); Martin Hutchings (Denmark)

Case 1

A 19 year old male with relapsing nodular sclerosing classical HL. Biopsy revealed RS cells and positive staining for CD15 and CD30. The tumour was classified as stage IIA bulky and IPS of 1. First line treatment was 6xAVBD plus consolidation with IFRT (32 Gy over 4 weeks). A CR was seen. However, the patient relapsed 11 months after treatment, still at stage IIA. The first salvage treatment regimen was 3xDHAP (21 day cycles). A CR (PET-CT) was observed. The patient proceeded to ASCT. At 6 months post ASCT, the patient relapsed again with cervical and mediastinal nodes and B symptoms. A biopsy of the cervical node revealed nodular sclerosing HL. The tumour had progressed to stage IIB.

The audience was asked what treatment they would recommend at this stage, and 83% chose novel drug therapy (brentuximab vedotin, bendamustine, benalidomide), over salvage chemotherapy followed by allogeneic transplantation (10%), radiotherapy (5%) or salvage chemotherapy alone (2%).

The patient was given 4x novantrone, oncovin, velban and prednisone (NOVP) (21 day cycles) as a second salvage regimen, and a CR (PET) was seen. The third salvage regimen was an allogeneic transplantation with reduced intensity conditioning from a fully matched unrelated donor (MUD). After 13 months, the patient relapsed again (stage IIA).

The audience was again asked what treatment they would recommend at this stage, and 58% chose novel agents, 30% inclusion in a clinical trial, 9% donor lymphocyte infusion (DLI) and 3% palliative treatment.

The patient was given two DLI and had a CR. He continues to be in CR 4 years after the last DLI. He receives no medication.

Case 2

A 22 year old female with a localised nodular sclerosing classical HL, Stage IIB, with positive staining for CD15 and CD30. She received 4xABVD plus IFRT (36 Gy over 4 weeks) to mediastinum and cervical nodes and had a CR, but relapsed 11 months after treatment. The salvage treatment chosen was 4xMONE, 2xDHAP, 3xBEACOPP during a 7 month period. She had a partial response (PR). BEAM plus ASCT was performed in PR status. Two months after a second ASCT, the disease was considered progressive with B symptoms and axillary lymph node enlargement. Rather than consider palliative treatment, the patient was entered into a Phase II clinical trial with brentuximab vedotin. She had a CR after 2 cycles of treatment. She had a further 6 cycles of treatment. After 8 cycles of treatment, a new staging confirmed the continuous CR status. The patients is still alive and in continuous CR 32 months after the end of treatment.

Case 3

A 37 year old female with stage IIA HL. The patient initially received 3xABVD but had only a PR, with a biopsy confirming nodular sclerosing HL. The patients underwent HDT-ASCT. The PET-CT was still positive.

The audience were asked what their choice of treatment would be at this stage and 77% chose single drug novel agent therapy, 15% chose mediastinoscopy or thoracotomy, 6% chose a third line chemotherapy agent and 2% would have waited and performed a new PET-CT after 1-2 months.

The patient had a biopsy by open thoracotomy and PET-CT was repeated 1 and 3 months later. Disease progression appeared to be confirmed in the mediastinum and spleen, but with non-necrotic granulomatous infiltration on biopsy. There was an increase in pulmonary symptoms and pleural effusion and the patient

developed heart failure (NYHA class IV), which was treated with diuretics and ACE inhibitor. PET-CT was repeated 5 months later. Some structural regression and a clear decrease in FDG uptake was noted. The NYHA status had changed to class II. Four months later, PET-CT indicated a CR. Three months later the patient is still in CR.

Disclaimers

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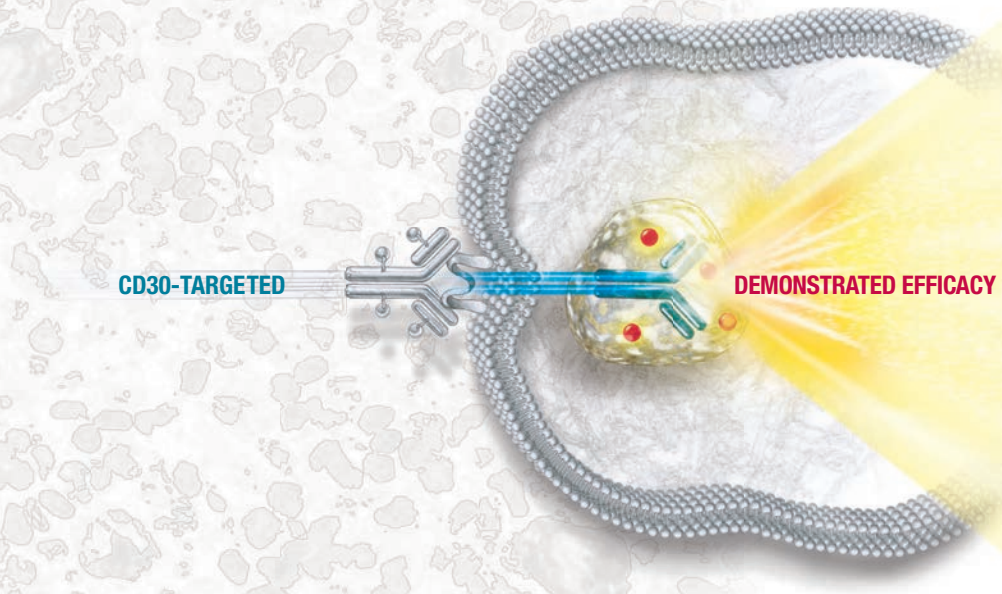
In relapsed or refractory CD30+ Hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma (sALCL) as demonstrated in two phase II, single-arm, open-label trials (n=102 for Hodgkin lymphoma and n=58 for sALCL), as well as in two phase I studies and a Named Patient Programme (NPP)[1-3]



In relapsed or refractory Hodgkin lymphoma with prior ASCT[1]

75% ORR | **33.3% CR**

In relapsed or refractory Hodgkin lymphoma without prior ASCT[1]

54% ORR | **22% CR**

In relapsed or refractory sALCL[1]

86% ORR | **58.6% CR**

ORR: overall response rate; CR: complete remission

In relapsed or refractory Hodgkin lymphoma with prior ASCT	In relapsed or refractory Hodgkin lymphoma without prior ASCT	In relapsed or refractory sALCL
'Complete remission' patients achieved a **21.7 month** median PFS[2]	Safety data were consistent with the safety profile of the pivotal clinical studies[1]	'Complete remission' patients achieved a **14.6 month** median PFS[3]

Adcetris was generally well tolerated in the clinical trials, with the most frequently observed adverse events being peripheral sensory neuropathy, fatigue, nausea, diarrhoea, neutropenia, vomiting, pyrexia, and upper respiratory tract infection. Peripheral neuropathy was generally reversible and manageable through dose modification.[1]

Recommended dosing schedule of 1.8 mg/kg* every three weeks. Treatment should be continued until disease progression or unacceptable toxicity. Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year)[1]

*If patient's weight is more than 100 kg, the dose calculation should use 100 kg. The maximum recommended dose is 180 mg.[1]

Adcetris, a novel CD30-targeted antibody-drug conjugate, provides antitumour efficacy for relapsed or refractory Hodgkin lymphoma and sALCL patients[1]

- Adcetris is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):[1]
  1. following autologous stem cell transplant (ASCT) or
  2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option
- Adcetris is indicated for the treatment of adult patients with relapsed or refractory sALCL[1]
- Adcetris is contraindicated for patients who are hypersensitive to the active substance or any of the excipients. Combined use of bleomycin and Adcetris causes pulmonary toxicity and is contraindicated.[1]

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brentuximab vedotin

Abbreviated Prescribing Information:
Adcetris (brentuximab vedotin)
(Refer to Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 50 mg powder for concentrate for solution for infusion. **Indication:** Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option; Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL). **Dosage & Administration:** Adcetris should be administered under the supervision of a physician experienced in the use of anti-cancer agents. Recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks (If the patient's weight is more than 100 kg, the dose calculation should use 100kg). Treatment should be continued until disease progression or unacceptable toxicity. Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles. Complete blood counts should be monitored prior to administration of each dose of this treatment. Patients should be monitored during and after infusion. For reconstitution and administration instructions please refer to SmPC section 6.6. **Dose Adjustments:** If neutropenia develops during treatment it should be managed by dose delays (see SmPC). If peripheral sensory or motor neuropathy emerges or worsens during treatment patients may require delay and dose reduction or discontinuation of Adcetris (see SmPC). *Renal or hepatic impairment:* No data available regarding use in renal or hepatic failure. *Elderly patients (≥65yrs):* No data available. *Paediatric patients (<18 yrs):* No data available. In nonclinical studies thymus depletion has been observed. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed. Combined use of bleomycin and Adcetris causes pulmonary toxicity. **Warnings and Precautions:** Progressive multifocal leukoencephalopathy (PML) has been reported in patients who received Adcetris after receiving multiple prior chemotherapy regimens; patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. Adcetris dosing should be held for any suspected case of PML and permanently discontinued if a diagnosis of PML is confirmed. Patients should be monitored during treatment for the emergence of possible serious and opportunistic infections. Immediate and delayed infusion-related reactions (IRR), as well as anaphylaxis, have been reported. Monitor patients during and after infusion. Adcetris should be immediately and permanently discontinued if anaphylaxis occurs. Infusion should be interrupted if infusion reaction occurs (see SmPC). Patients with rapidly proliferating tumour and high tumour burden are at risk of tumour lysis syndrome; these patients should be monitored and managed according to best medical practice. Adcetris may cause peripheral neuropathy which is reversible in most cases. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require delay and dose reduction or discontinuation of Adcetris (see SmPC). Grade 3 or 4 anaemia, thrombocytopenia and neutropenia can occur with Adcetris. Refer to SmPC for dose adjustments if neutropenia develops. Patients should be monitored for fever and managed according to best medical practice if febrile neutropenia develops. If Stevens-Johnson syndrome occurs, treatment with Adcetris should be discontinued and appropriate medical therapy administered. Any patient who experiences an event of hyperglycaemia should have their serum glucose monitored and managed appropriately. MMAE clearance might be affected by moderate and severe renal impairment, and by low serum albumin concentrations (see SmPC). Adcetris contains a maximum of 2.1 mmol (or 47 mg) of sodium per dose. *Pregnancy & lactation:* No data available. Studies in animals have shown reproductive toxicity. *Fertility:* In non-clinical studies, Adcetris treatment has resulted in testicular toxicity, and may alter male fertility. **Drug Interactions:** Co-administration of Adcetris with strong CYP3A4 and P-gp inhibitors, such as ketoconazole, may increase the incidence of neutropenia; with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to Adcetris however, it reduced exposure to MMAE; and midazolam, a CYP3A4 substrate, did not alter the metabolism of midazolam therefore, Adcetris is not expected to alter the exposure to medicines that are metabolized by CYP3A4 enzymes. **Adverse Effects:** *Very common (>10%):* Infection, neutropenia, peripheral sensory neuropathy, diarrhoea, nausea, vomiting, alopecia, pruritus, myalgia, fatigue, pyrexia, infusion-related reactions. *Common (≥1/100 to <1/10):* Upper respiratory tract infection, herpes zoster, pneumonia, anaemia, thrombocytopenia, hyperglycaemia, peripheral motor neuropathy, dizziness, demyelinating polyneuropathy, cough, dyspnoea, constipation, rash, arthralgia, back pain, chills. *Uncommon (≥1/1000 to <1/100):* Oral candidiasis, Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, Tumour lysis syndrome, Stevens-Johnson syndrome. *Serious adverse drug reactions were:* neutropenia, thrombocytopenia, constipation, diarrhoea, vomiting, pyrexia, peripheral motor neuropathy and peripheral sensory neuropathy, hyperglycaemia, demyelinating polyneuropathy, tumour lysis syndrome and Stevens-Johnson syndrome. **Pharmaceutical Precautions:** Store vial in a refrigerator (2°C-8°C), protected from light. After reconstitution/dilution, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C 8°C. **PI Date of Preparation:** October 2012 **PI approval code:** EU/ADC-010088 **Legal category:** POM Basic **NHS Price & Marketing Authorisation:** £2,500 for each Adcetris 50mg vial (EU/1/12/794/001) **Name & Address of Marketing Authorisation Holder:** Takeda Global Research and Development Centre (Europe) Ltd., 61 Aldwych, London, WC2B 4AE, UK **Further information is available from:** Takeda Pharmaceuticals Europe Ltd. Medical and Scientific Affairs. 61 Aldwych, London, WC2B 4AE, UK. +44 (0) 203 116 8879.

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Adcetris has received a conditional marketing authorisation in Europe. A conditional marketing authorisation is granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact additional data are still required. The European regulatory agency will review new information on Adcetris at least every year and the summary of product characteristics will be updated as necessary.

Please refer to the summary of product characteristics for details on the full side-effect profile and drug interactions of Adcetris. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Takeda

References: 1. Adcetris Summary of Product Characteristics 2012. **2.** Younes A, *et al. J Clin Oncol* 2012; 30: 2183-2189. **3.** Pro B, *et al. J Clin Oncol* 2012; 30: 2190-2196.

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Non-Hodgkin Lymphoma: Improving Outcomes in Rare Lymphomas

Introduction

The satellite symposium titled, "Non-Hodgkin Lymphoma (NHL): Improving Outcomes in Rare Lymphomas" was held during the 17th Congress of the European Hematology Association (EHA) on Thursday 14th June 2012 at the RAI Exhibition and Convention Centre, Amsterdam, The Netherlands. The meeting was chaired by Professor Martin Dreyling, Klinikum der Universitaet Muenchen-Grosshadern, Munich, Germany.

Prof. Dreyling opened the symposium by highlighting that the focus of the presentations was on unlicensed, experimental therapies for non-Hodgkin's Lymphoma (NHL). There is a plethora of clinical data supporting treatment for the two largest lymphoma groups: diffuse large B cell lymphoma (DLBCL), and follicular lymphoma (FL). None of the available treatments for lymphoma is specifically licensed to treat these rarer diseases, despite the rarer lymphomas comprising almost half of all cases.[1]

Treatment regimens for DLBCL and FL are based on robust clinical data. Survival data for DLBCL demonstrate the significant 10-year progression-free (PFS) and overall survival (OS) advantages of adding rituximab to standard CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin [vincristine], and prednisone) therapy; i.e., R-CHOP.[2] Similar benefits are seen with FL with the addition of rituximab to CHOP.[3] R-CHOP is the recognised international treatment standard, with no equipotent alternative.[4]

Currently, ongoing Phase III clinical trials generally focus on improving R-CHOP outcomes in both DLBCL and FL through the addition of molecular therapy approaches. However, the nature of rarer histologies, such as mantle cell, marginal zone B cell and lymphoplasmacytic lymphomas, makes Phase III studies cumbersome and lengthy. Nonetheless, there are a wealth of Phase II data focusing on these rarer lymphomas, which require interpretation, although most treatments are experimental and unlicensed.

Non-Hodgkin Lymphoma: Improving Outcomes in Rare Lymphomas
Mundipharma Sponsored Satellite Symposium at the European Hematology Association (EHA) Congress, Amsterdam, The Netherlands, June 14, 2012

Chair: Martin Dreyling, Klinikum der Universitaet Muenchen-Grosshadern, Munich, Germany

Welcome and Introduction
Martin Dreyling, Klinikum der Universitaet Muenchen-Grosshadern, Munich, Germany

Management of Waldenström's Macroglobulinaemia
Steven Treon, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, United States

Mantle Cell Lymphoma in the Elderly
Simon Rule, Derriford Hospital, Plymouth, United Kingdom

Marginal Zone Lymphoma – Novel Treatment Options
Antonio Salar, Hospital del Mar-IMAS, Spain

Final Questions and Conclusions
Martin Dreyling, Klinikum der Universitaet Muenchen-Grosshadern, Munich, Germany

Management of Waldenström's Macroglobulinaemia

Steven Treon
(Boston, United States)

The incidence of Waldenström's macroglobulinaemia (WM) has been drastically underestimated, both in Europe and the US. Underestimations may be based on the separation of cases into diagnoses of lymphoplasmacytic lymphomas and WM. Waldenström's macroglobulinaemia should be considered as an indolent lymphoma rather than a myelomatous disease, even though there are many similarities. In the US, there are approximately 3,000 new WM cases per year; analogous figures in Europe are expected.

WM has a strong familial relationship, with up to 25% of patients having a first or second degree relative with WM or other closely linked lymphoma; Ashkenazi Jews present with a significantly higher familial relationship.

WM usually presents in the bone marrow, and OS is related to symptomatic status at the time of diagnosis. Disease manifestations include reductions in hematocrit, white blood

cell and platelet counts, with presence of hyperviscosity syndrome; e.g., epistaxis and impaired vision. Adenopathy, splenomegaly, cryoglobulinaemia, cold agglutinaemia or fatigue may also be present.

Consensus recommendations for initiation of therapy include:
→Hemoglobin ≤10 g/dL
→Platelet count <100,000 mm^3 on basis of disease
→Symptomatic hyperviscosity (>4.0 cp)
→Moderate/severe peripheral neuropathy
→Immunoglobulin M (IgM), or paraprotein-related problems; e.g., symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, amyloidosis

Rituximab-based treatments are the primary therapy for WM, although IgM levels must be monitored before starting therapy. Initiation of rituximab in patients with elevated IgM levels may induce an IgM flare, resulting in hyperviscosity crisis. Patients with IgM flare are usually treated via chemotherapy without rituximab.

With the benefits of long term maintenance therapies, transplants are often only considered in patients with multiple relapses in a refractory disease. This usually involves treatment in end of therapy situations – although there is evidence that transplant may be more effective at an earlier stage.

Options for medical therapy generally include rituximab combinations. Although rituximab monotherapy presents a minor or partial response (rates of up to 45%)[6-8] combination therapies increase response rates towards 90%.[9-15] When used in combination with bortezomib or bendamustine, complete remissions (CR) occur in up to 30% of patients.[16-18]

Combinations with cyclophosphamide are used commonly and usually provide response rates of approximately 80%, with up to 3 years of remission. Whereas, nucleoside analogues have been quite problematic, mainly due to a high risk of disease transformation, the possible impact on stem cells and the decreased potential for autologous transplantation.

As peripheral neuropathy is a specific burden in younger patients, nucleoside analogues are generally avoided in this population. Immunomodulatory treatments, including thalidomide and lenalidomide, are used conservatively due to the associated side effects of peripheral neuropathy and abrupt hematocrit decreases, respectively.

Bortezomib is considered an important therapeutic option in combination with rituximab, especially when used with concomitant steroids, and demonstrates response rates as high as 90%.[16, 17] However, the neuropathic potential of any treatment is of specific concern in the WM population compared with analogous populations. Thus, clinical application of bortezomib is more frequently used on a once weekly basis at a higher dose (approximately 1.6 mg/m^2), rather than the conventional twice weekly dose.

When compared with CHOP-R as the first-line treatment in WM lymphoma patients, the combination of bendamustine and rituximab improves progression-free and complete response rates, (median PFS 54.8 months vs. 34.8 months (p=0.0002); CR rate 40.1% vs. 30.8%, p=0.0323, respectively), whilst showing a better tolerability profile, when compared with CHOP-R as first-line treatment in WM lymphoma patients.[18]

Once patients are treated and have achieved remission, the question of maintenance therapy must be addressed. Even though there are no prospective studies examining the outcomes of maintenance therapy, an observational study in 248 rituximab-naïve WM patients demonstrated a significant improvement in PFS and OS in those receiving a rituximab-based therapy, compared with observation alone (median PFS, 56.3 vs. 28.6 months, p=0.0001;[19] median OS, >120 vs. 116 months, p=0.0095[20]).

Overall, the focus of WM treatment should be to improve the symptomatic status of the patient, rather than treating the clinical laboratory numbers; over-treatment can rapidly compound the problems of side effects in this population.

In terms of novel directions, paired genomic sequencing of individuals' tumour and non-tumour cells show a mutation in chromosome 3p22.2 on the MYD88 gene in 91% of patients with WM, unlike patients with marginal zone lymphomas; separating these disease states has previously been problematic. Inhibiting MYD88 blocks receptor signalling and induces apoptosis of WM cells, representing a potential novel target for future treatments.

Mantle Cell Lymphoma in the Elderly

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Mantle Cell Lymphoma (MCL) is characteristically a disease of elderly males, with most patients aged 65 years and above, presenting with late-stage extranodal gastrointestinal involvement and is associated with a poor outcome.

In general, the standard treatment for MCL in younger patients is high dose arabinofuranosyl cytidine (ARA C) based therapy and a transplant; however, elderly patients, especially 'frail elderly', cannot tolerate high ARA C doses. In this non-transplant eligible population, treatment of asymptomatic patients does not appear to increase survival, whereas the 'watch and wait' approach has demonstrated significant survival advantages over early treatment (p=0.004).[21]

Although median OS has doubled during the past 30 years, reported improvements in historical OS data may be due to the availability of anthracycline-containing regimens and new treatment approaches, such as antilymphoma antibodies or stem cell transplantation.[22] Clinical studies of conventional chemotherapy in historical nonblastoid MCL populations (Lymphoma Study Group, 1975 to 1986; German Low Grade Lymphoma Study Group, 1996 to 2004) have not demonstrated significant survival advantages with any specific treatment regimen.

In a Phase II randomised UK registry study of fludarabine/cyclophosphamide combination treatment, with or without rituximab, there was a significant improvement in PFS in the rituximab-containing arm after a median follow-up of 47.6 months (median PFS 15.9 vs. 29.8 months; hazard ratio [HR] 0.54 [0.42, 0.69]; p<0.001).[23] This translated into a significant increase in OS of 8.3 months following rituximab (median OS 37.4 vs. 45.7 months for non-rituximab and rituximab-containing treatment, respectively; HR 0.73 [0.54, 0.97]; p=0.03).[23]

Further analyses demonstrated that rituximab-based therapy maintained an OS advantage across all subgroups studied, particularly in the elderly.[23] When age and survival were compared by treatment, elderly patients had significantly lower PFS and OS compared with their younger counterparts, regardless of treatment modality.[23]

When considering bendamustine, the recent StiL NHL1 study of 514 patients that included 93 patients with MCL, examined the survival benefits of bendamustine plus rituximab (B-R) vs. CHOP-R. Outcome data show that treatment with B-R had a significant PFS benefit in the MCL group compared with CHOP-R (median PFS 35.4 vs. 22.1 months, respectively; HR 0.50 [95% Confidence Interval (CI) 0.29-0.81]; p=0.0061), and offered a superior tolerability profile.[24]

New monoclonal antibodies are under investigation for the treatment of MCL. Initial results suggest that anti CD20 antibodies, including ofatumumab and GA101, demonstrate greater *in vitro* activity against MCL than rituximab, and show promising early *in vivo* results.[25]

Ibrutinib (PCI-32765) is an orally administered irreversible inhibitor of Bruton's tyrosine kinase (Btk). Preliminary Phase II results in both bortezomib-naïve and -exposed patients suggest that monotherapy induces a high objective response rate (58-75%) in previously treated elderly patients with relapsed or refractory MCL. Treatment was well tolerated, with transient Grade 1 or 2 diarrhoea, fatigue, and nausea reported most frequently; Grade 3 or 4 hematological adverse events (AEs) were experienced by ≤3% of patients. Phase III trials of ibrutinib in MCL as both a single and combination agent are planned.[26]

Overall, the chemotherapy options for MCL are becoming clearer, and should be selected on a per-patient basis, especially in the elderly. Non-chemotherapy options, such as antibody therapies and newer emerging therapies, will have a definite role in the future treatment of this disease.

Marginal Zone Lymphoma – Novel Treatment Options

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Marginal zone lymphomas are cell neoplasms arising from the marginal zone of the B cell, which can be found in the lymph node, spleen and mucosa-associated lymphoid tissue.

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) are a major neoplastic component originating from the B cells of the marginal zone compartment, and comprise morphologically heterogeneous small B cells and include marginal zone cells, small lymphocytes and scattered immunoblasts. MALT lymphomas comprise up to 10% of all lymphoid neoplasms,[27] and may arise at many sites; at least one-third are observed in the stomach.

Although MALT lymphoma has a specific immunophenotype, it has many non-specific morphological features, and is often difficult to diagnose. In addition, there is no specific marker for flow cytometry/immunohistochemistry, and biopsy volumes tend to be very low, even though dissemination to multiple mucosal sites is not uncommon.

Standard laboratory work-up should include a complete blood count, basic biochemistry (including LDH and β2-microglobulin), hepatitis B and C serology, bone marrow biopsy and CT scans. If identified as a Gastric MALT lymphoma, additional tests should include gastroscopy (with multiple biopsies), endoscopic ultrasound (for evaluation of the stoma and regional lymph node involvement) and *Helicobacter pylori* serology or a stool antigen test.

In non-gastric MALT lymphoma, a link between *Chlamydia psittaci* infection and lymphoma regression has been suggested.[28] Recent, Phase II study data demonstrate that eradication of C.psittaci significantly improves overall response rates in patients with ocular adnexa MALT lymphoma treated with doxycycline (100 mg bd, 3 weeks).[29]

Chemotherapy is usually reserved for patients with disseminated disease at diagnosis, or those with relapse following radiotherapy. Currently, there is no consensus regarding the best therapeutic option for patients.[30] Radiotherapy is mainly used in non-gastric MALT lymphoma, and this organ-preserving approach provides a low morbidity and mortality rate, but must be balanced against treatment-related toxicities, such as cataracts and xerophthalmia.[31-33]

When considering treatment with IMiDs, a Phase II study of lenalidomide (25 mg/day for six cycles) in MALT lymphoma patients (n=18) showed an overall response rate of 65% with an

acceptable tolerability profile.[34]

Radioimmunotherapy using 90Y-ibritumomab has been used predominantly in patients with follicular lymphoma. However, small patient studies in MALT lymphoma, both as first-line treatment and following rituximab, suggest response rates of at least 80% and CR rates of 67-83%, depending on disease loci. Hematological AEs were reported across all studies.[35-37]

The introduction of rituximab revolutionised the treatment of MALT lymphomas. In a multicenter, open-label, Phase II study of patients with either gastric (n=12) or extragastric (n=10) MALT lymphoma, treatment with rituximab (375 mg/m^2) and the purine analogue fludarabine (25 mg/m^2) demonstrated response rates of 100% after six treatment cycles, with 90% achieving a complete response. PFS at 2 years was 100% and 89%, in patients with gastric and extragastric MALT lymphoma, respectively.[30]

Bendamustine has demonstrated a low *in vitro* hematopoietic toxicity compared with the fludarabine,[38] and may also have benefits in the treatment of MALT lymphoma. In a prospective Phase II Spanish trial, bendamustine was combined with rituximab for the treatment of patients with MALT lymphoma.[39] After three treatment cycles (bendamustine, 90 mg/m^2 on Day 1 and 2; rituximab 375 mg/m^2 on Day 1), patients experiencing CR received an additional cycle, whilst patients with a partial response received an additional three cycles; patients with stable disease or disease progression were withdrawn from the study.[39]

Interim results suggest that all patients responded after three treatment cycles, with a CR rate of 85%. After completion of all scheduled treatment cycles (i.e., 4 or 6 cycles), the CR rate increased to 97%.[39] Analysis of the full data set analysis is ongoing and expected to be available at the next annual meeting of the American Society of Hematology.

"Only 15% of patients needed more than four cycles [of bendamustine-rituximab] to achieve complete remission."

Overall, excellent results have been achieved with radiotherapy in gastric MALT lymphoma. Medical chemotherapy comprising rituximab with bendamustine have also been highly effective in treating gastric and extragastric MALT lymphoma, combining high response and remission rates with an acceptable safety profile.

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Determining Optimal Treatment Regimens for Major Histological Subtypes of Breast Cancer

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Until recently, all early-stage breast cancer patients received adjuvant tamoxifen. Later studies, however, revealed that effectiveness was limited to those patients with hormone receptor (HR) positive disease.[1] Likewise, studies have shown variations in efficacy of adjuvant chemotherapy based on subtype and HR expression.[2-5] Personalised treatment of breast cancer is gaining recognition and is increasingly dependent on patient- and tumour-specific characteristics to determine an optimal treatment regimen. The most common types of breast cancer are invasive ductal (IDC) and invasive lobular cancer (ILC), and are found in 80% and 5-15% of all female breast cancer patients respectively.[6] Evidence is suggesting that the incidence of ILC is on the rise, especially in postmenopausal women, owing to the increased use of hormone replacement therapy.[6, 7] Although breast cancer treatment regimens are leaning towards a patient- and tumour-tailored approach, no distinction is made between breast cancer subtypes. Nevertheless, there is some evidence to suggest that a more directive approach may be desired. In this era of a growing trend towards tailor-made treatment regimens, it is important to investigate differences in efficacy of therapy based on variations in tumour characteristics in order to better treat our patients. Here, we provide a comprehensive review of the differences between the major histological subtypes of breast cancer and present opportunities for a more personalised approach to the treatment of ILC.

Tumour Biology

Several clinical and biological differences exist between ILC and IDC; ILC patients tend to be older, tumours are larger, and generally present with a lower histological grade.[7, 8] In addition, ILC is more frequently estrogen receptor (ER) and progesterone receptor (PR) positive, and HER2, p53, and epidermal growth factor receptor (EGFR) negative when compared to IDC.[7, 9] ILC tumour cells are distinguished by their typical morphological characteristics, consisting of small, round cells with little cytoplasm, that grow in a distinctive single-file pattern.[7] Furthermore, Berx *et al*. found that tumour growth in ILC is incohesive, primarily due to the inactivation of E-cadherin, a cell adhesion protein.[10] ILC is characterised by a multifocal diffuse infiltrative growth pattern and its margins are generally more difficult to detect, both by palpation and mammography, than IDC.[7, 11, 12] Tumour infiltration occurs in a manner that does not destroy underlying anatomical structures or activate a significant connective tissue reaction, and it has been implied that this is the reason for the difficulty in detecting ILC through mammography.[13, 14]

In addition to their multifocality, bilateral tumours are also more prevalent in ILC patients than IDC patients, with up to a third of patients with ILC being diagnosed with a bilateral tumour.[15, 16] With regard to disease progression, several studies have confirmed discrete patterns of metastatic spread between IDC and ILC. While IDC commonly spreads to the regional lymph nodes, lungs, liver and bone,[17] more common metastatic sites for ILC include the gastrointestinal tract, peritoneum, gynecologic organs, and meninges.[18-20] Following primary surgery, it is not uncommon that ILC patients present with tumour-positive resection margins and undergo more numerous mastectomies, owing to its diffuse growing character and typically multifocal disposition.[12, 21-27] Despite these findings, an increase in the number of locoregional relapses in ILC patients has not been demonstrated.[25] Furthermore, notwithstanding the biological and clinical dissimilarities between IDC and ILC, these have not been found to interfere with overall outcomes.[7, 28, 29]

Response to Systemic Therapy

Chemotherapy

There is a scarcity of data on the role of histological subtypes in the adjuvant setting. Farese *et al*. reviewed 39 randomised adjuvant trials and found that only in four of these the histological subtype of patients was mentioned in the baseline demographics. In none of these studies, analyses were performed based on histological subtypes.[30] Similarly, in the overview of randomised trials by the Early Breast Cancer Trialists' Collaborative Group, no data is provided on the benefit of adjuvant or hormonal treatment for ILC and IDC separately.[31] Truin *et al*. recently reported two retrospective studies based on data of postmenopausal women in regional and national Dutch cancer registries, in which survival after hormonal therapy combined with chemotherapy was compared with hormonal therapy alone.[32] In both

studies, patients with IDC benefited more from the combination therapy than from hormonal therapy alone, while patients with ILC seemed to have no benefit of additionally chemotherapy.

Neoadjuvant chemotherapy is on the rise in patients with breast cancer, and its effectiveness in downsizing and downstaging large tumours and axillary lymph nodes provides a suitable opportunity to observe response to adjuvant systemic treatment and improve surgical outcomes, as well as to predict patient prognosis and tailor further treatment.[27, 33-35] This has also come with the prospect of investigating tumour response specifically in different histological subtypes of breast cancer. To date, several non-randomised studies have reported pathological complete response (pCR) rates of IDC and ILC separately.[12, 22, 23, 26, 27, 36-39] Studies on neoadjuvant chemotherapy have repeatedly revealed differences in pCR rates between IDC and ILC. Although the definitions of pCR are not consistent amongst these studies, the results are quite conclusive. pCR rates varied between 0 and 3% for ILC and between 9 and 20% for IDC.[22, 26, 27] In randomised trials that reported on post-chemotherapy pathological response, pCR rates were also greater for IDC patients.[10-14] Furthermore, in a pooled analysis of 7 German neoadjuvant trials, non-lobular histology likewise appeared to be a better predictor of response (pCR 9% ILC vs. 23% IDC).[15] Cocquyt *et al*. and Mathieu *et al*. also found clinical response rates to be lower in patients with ILC.[12, 27] Of note, some of these studies reported better prognosis for ILC patients, despite the lower response rates.[12, 21, 26, 27]

Reasons are unclear for the differences in outcomes between ILC and IDC with respect to chemotherapy, it has been suggested that hormone receptor (HR) status plays a crucial role in determining chemosensitivity, in addition to hormonal sensitivity. Investigations of adjuvant chemotherapy have revealed differences in outcomes between HR negative and HR positive patients, and showed that adjuvant chemotherapy is more effective in patients with HR negative tumours than in patients with HR positive tumours.[2, 3, 33, 35] Previously, the St Gallen consensus guidelines acknowledged that response to chemotherapy decreased with increasing HR expression, while highly endocrine sensitive tumours are those with high expression of both estrogen receptor (ER) and progesterone receptor (PR).[40-42]

The aforementioned studies indicate that ILC is less sensitive to neoadjuvant chemotherapy, and hence less likely to result in pCR than IDC. This leads to the inclination to suggest that ILC patients may be better treated with (neo)adjuvant endocrine therapy, and that (neo)adjuvant chemotherapy may be further withheld in ILC patients insensitive to chemotherapy in the neoadjuvant setting.

Hormonal Therapy

Earlier studies established an association between hormone receptor expression and benefit of adjuvant endocrine therapy, with HR-negative patients having no additional advantage and HR-positive patients requiring at least five years of adjuvant treatment with tamoxifen, aromatase inhibitors, or a combination of the two.[43-47] In addition, several studies have endorsed the association between higher levels of ER expression and the improved efficacy of endocrine therapy.[40, 41, 48-51] In HR-positive patients, preferential treatment by quantitative HR expression is currently not widely applied, although the transATAC (Arimidex, Tamoxifen Alone or in Combination) trial found a significant benefit in time to relapse with respect to increasing ER expression in patients treated with anastrozole, but not for tamoxifen.[51] Similarly, recent results of an unplanned analysis of quantitative estrogen receptor expression and the treatment preference in the TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial were reported.[50] ER-rich patients had a significant advantage when treated with exemestane for five years upfront, while a sequential treatment regimen was preferred in patients with low ER expression. Although it is plausible to assume a greater benefit of endocrine therapy in ILC than IDC, as ILC frequently expresses HR more strongly than IDC, ILC was not found to have an advantage over IDC in the TEAM trial.[50]

Neoadjuvant endocrine therapy is gaining popularity, especially in older, postmenopausal HR positive breast cancer patients.[52, 57] However, evidence is sparse with regard to comparing efficacy of neoadjuvant endocrine therapy in ILC versus IDC patients. Older women more commonly have HR positive disease, and toxicities of adjuvant chemotherapy are significant. In this case, neoadjuvant chemotherapy may not be the optimal treatment for this subset of patients. Semiglazov compared primary endocrine therapy with chemotherapy in HR-positive breast cancer patients.[56] 121 patients were treated with anastrozole or exemestane for 3 months preoperatively, while 118 patients were assigned four 3-week cycles of neoadjuvant chemotherapy. Although there was no difference in pCR rates between the endocrine and chemotherapy groups, higher rates of BCS (33% vs. 24%, p=0.058) were reported. Furthermore, toxicity profiles were much better in the endocrine-treated group.[56] Studies have also looked at determining a preferred endocrine treatment regimen. Two studies did not establish a benefit of anastrozole over tamoxifen, both for a period of 12 weeks.[52, 57] However, the P024 trial studied four months of preoperative letrozole versus tamoxifen treatment. A significant benefit of letrozole over tamoxifen was ascertained, which implies that longer treatment duration is necessary to attain the true advantage of endocrine therapy.[55] However, no distinction was made between ILC and IDC seperately in these studies.

Although studies are still investigating optimal duration of therapy, at least six months of aromatase inhibitor therapy have been recommended, although one study by Dixon has gone up to 24 months of preoperative therapy with persistent downsizing.[58] Another small study evaluated tumour response to neoadjuvant

letrozole treatment in ER-positive ILC patients specifically. Sixty-one patients with large operable or locally advanced tumours were included. A notable mean caliper-measured reduction in clinical volume of more than two-thirds was observed at 3 months. The final rate of successful breast conservation was 81%. In 5 patients successful breast conservation was achieved only after a re-excision. The authors concluded that this breast conservation rate is acceptable, again because margin involvement is generally higher in ILC than in IDC.[54]

Tumour biological characteristics have helped pave the way towards a more personalised approach in the treatment of breast cancer. While histological subtype has helped predict benefit of (neo)adjuvant chemotherapy, HR expression, on the other hand, has been an invaluable predictor of endocrine treatment efficacy in hormone-sensitive breast cancer patients. Although no preferential treatment regimen has yet been established for ILC patients, the investigation by van de Water *et al*. confirms that endocrine therapy is at least as effective in IDC as ILC patients.[50] It seems, therefore, that these biomarkers of treatment efficacy need to be further investigated in order to establish whether a preferential treatment regimen is warranted for major histological subtypes of breast cancer, and which could be especially valuable in the neoadjuvant treatment setting. A new study proposal is underway within our study group, comparing efficacy of neoadjuvant chemotherapy with neoadjuvant endocrine therapy in lobular breast cancer patients. Until results of such a trial are available, ILC patients deserve careful attention in order to provide the best possible personalised treatment regimen.

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Efficiency in Breast Care

Vanessa Lane
Treatment Strategies

Summary

Breast cancer is the leading cause of cancer death in women worldwide. Rapid, early and accurate diagnosis are essential in order to improve treatment outcomes. Several new technologies are now available to support the screening and diagnosis of patients with suspected breast cancer. These can be used as part of a one stop shop breast cancer screening programme, which facilitates the streamlining of cancer care into a single location and shortens the time between diagnosis and treatment.

Breast Cancer Epidemiology and Survival

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women worldwide, with an estimated 1.4 million new breast cancer cases and 458,000 deaths in 2008.[1] Incidence and mortality rates vary internationally by more than 5-fold, with the highest rates seen in developed countries.[2] In contrast to the incidence trends, breast cancer mortality rates in many of these countries have been stable or decreasing during the past 25 years because of early detection through mammography and improved treatment.[2]

The likelihood of diagnosis increases with age, doubling about every 10 years until the menopause, when the rate of increase slows dramatically. The lifetime risk is almost 11% (1 in 9).[3]

In a single year, the average general practitioner (GP), with a patient list of 2,000, could expect to see one or two new cases of symptomatic breast cancer, but will see considerably more patients with benign breast problems.[4] A hospital responsible for a population of 300,000 will deal with perhaps 40 new GP referrals each week, plus maybe two women referred after screening mammography; breast cancer will be diagnosed in approximately 200 patients per year. As the majority of patients present with symptomatic breast cancer, there is a real unmet need to improve screening programmes and to provide rapid, efficient and accurate breast cancer diagnosis.

Evolution of Breast Cancer Care

In many regions, breast cancer diagnostic services have become increasingly streamlined in recent years, and patients are often seen by multidisciplinary teams (MDTs) in dedicated breast clinics.[5] However, there are still some underserved regions around the world where many women do not have easy access to breast screening clinics.

The standard diagnostic process is referred to as 'triple assessment', namely expert clinical breast examination, breast imaging and, when necessary, needle biopsy.[6]

Triple assessment carried out in an MDT setting is extremely safe with an overall diagnostic accuracy of 99.6%.[7] This means that, for every 1,000 patients seen and discharged, just over four will return and be diagnosed with breast cancer in the following 3 years. Of these, 1.3 will have been unequivocally missed at the initial presentation and a further 0.4 will have had a subtle imaging abnormality that was overlooked at the initial assessment. The 'missed' cancer rate overall is therefore 1.7 per 1,000 women discharged over a 3 year period.

Once a patient has been screened and diagnosed, there are a number of additional key stages in the breast cancer patient care pathway, including biopsy, staging and ultimately treatment.

New Technologies Available for Breast Cancer Screening and Diagnosis

Screening mammography is the standard of care and is aimed at detecting breast cancer in an early stage in women without breast symptoms. Though widely established as the only screening imaging modality that can reduce breast cancer mortality, mammography has some limitations, such as lesions masked by normal fibroglandular tissue, lesions seen on only one view and subtle architectural distortions.[8,9] Partly because of these limitations, mammography misses about 20% of invasive breast cancers.[10,11]

As a result of these limitations, imaging techniques have experienced a highly significant development in recent years. The morphological image, of great value, has evolved into a physiological and functional image, capable of providing additional and valuable information to better understand disease processes. The most important advance has been the introduction of digital mammography. Digital mammography

has now become the "gold standard" technique for the study of breast pathology and is used in screening of women aged between 40-50 years, depending on each country.[12]

Full Field Digital Mammography

Full field digital mammography (FFDM) enables high quality breast images with higher contrast resolution, improved dynamic range and rapid processing of data and images compared with screen film mammography. It has been shown to provide increased accuracy in screening pre- or perimenopausal women, women younger than 50 years of age and women with dense breasts.[13] Moreover, FFDM has offered the possibility of developing new and advanced applications for breast imaging.

Computer-aided detection with FFDM is effective in assisting radiologists with earlier detection of breast cancer.[14] It had been shown to have a high sensitivity in identifying cancers manifesting as calcifications and masses, which is maintained in cancers with lower mammographic sensitivity, including invasive lobular carcinomas and small neoplasms (1-20 mm).[14] In particular, this screening method results in enhanced earlier detection of breast cancer by showing 89% of tumours that are 1–10 mm in diameter.[14]

Senographe™

Senographe™ is a full field digital system designed to enable high quality and rapid digital mammograms and is the only system to use the same integrated image chain. It can be used for in office screening, diagnostics, interventions and mobile screenings, as it can capture images with a digital detector so the images are available for immediate display on a monitor at high resolution.[15] Senographe™ uses 3 megapixel quality for acquisition of images and 5 megapixels for reading and reviewing the images.

SenoBright™

SenoBright™ is performed as an adjunct to inconclusive mammography and ultrasound, and highlights areas of unusual blood flow patterns. It is based on a new contrast enhanced spectral mammography (CESM) technology and is a combination of digital mammography with an intravenous injection of iodine (contrast agent). The examination provides two images per view of both breasts, one which shows tissue morphology like a standard mammography image (tissue density), the second revealing an iodine-contrasted image with the background signal subtracted out, which may assist radiologists in localising a known or suspected lesion.

Digital Breast Tomosynthesis

Mammography continues to have certain limitations inherent to the principle of obtaining a two-dimensional (2D) image of a 3D compressed glandular parenchyma, causing lesions to be masked, sometimes due to the superimposition of glandular structures in the X-ray beam.[12] This structure superimposition can impede visualising a lesion (false negative) or identifying a lesion as suspicious that is actually a glandular accumulation (false positive).[12]

Digital breast tomosynthesis (DBT) is a recent innovation in X-ray breast imaging in which sequential tomographical images through the breast can be reconstructed from a limited number of projection images obtained at various angles.[16]

This 3D imaging technology uses a low dose short X-ray sweep around the compressed breast. The acquired projection images are processed electronically in order to reconstruct a 3D representation of the entire breast. This technique attempts to increase lesion conspicuity and highlight lesion morphology by minimising the superimposition of overlying breast tissue that occurs with 2D projection mammographical images.[16]

A number of features of this technology ensure a high quality image. These include the step and shoot tube motion that provides sharper lesion margins than the classical continuous tube motion, and an optimal angle aperture range. DBT measures the distance between consecutive planes and not the thickness, as it is done in CT acquisitions, so improving the visualisation of microcalcifications by reducing the distance between them. An iterative reconstruction algorithm yields images that are FFDM like, easy to interpret and with reconstruction times equivalent to transfer times. This reconstruction method has a mechanism that positively impacts microcalcification conspicuity versus the classic filtered back projection algorithm.

The resulting images are reconstructed at a cutting thickness between 0.5 mm, and they can be visualised at a workstation, with software specialised in tomosynthesis.[12] A compressed breast, 5 cm thick, will generate 100 tomosynthesis images, each 1 mm thick.[12]

The radiation dose of a 3D tomosynthesis and 2D mammography is within the standards accepted by the Mammography Quality Standards Act (MQSA).[17]

Quantitative Positron Emission Tomography in Treatment Monitoring

Increasing numbers of patients with newly diagnosed breast cancer receive primary systemic therapy followed by surgery.[18] Histopathology provides an accurate assessment of treatment efficacy on the basis of the extent of residual tumour and regressive changes within tumour tissue. However, only approximately 20% of breast cancer patients achieve a pathologic complete response, a fact that necessitates methods for monitoring therapeutic effectiveness early during therapy.[18] 18F-FDG PET and 18F-FDG PET/CT provide essential information regarding a response to primary chemotherapy. Patients with low tumour metabolic activity on pre-treatment 18F-FDG PET are not likely to achieve a histopathological response. The degree of changes in 18F-FDG uptake after the initiation of therapy is correlated with the

histopathological response after the completion of therapy. Thus, tumour metabolic changes assessed early during therapy predict therapeutic effectiveness in individual patients. Early identification of ineffective therapy might also be helpful in patients with metastatic breast cancer as many palliative treatment options are available.

Breast Cancer Screening Programme

An ideal breast cancer screening programme should be able to offer a one stop shop breast cancer clinic that allows clinicians to streamline cancer care into a single location. This increases the effectiveness of the patient care pathway while initiating more collaboration within the MDT. It also offers a number of advantages, such as alleviating patient anxiety, providing a more rapid diagnosis time and enabling clinicians to reduce the time between screening and the start of treatment.

The Healthymagination Initiative

GE has launched a new commitment to advancing cancer care through the Healthymagination initiative, aimed at accelerating cancer innovation and improving care for 10 million cancer patients around the world by 2020.

This health sustainability programme is an innovative, new and fully integrated care model that has been designed to reduce the cost of healthcare, improve the quality of care and increase care access.

The GE breast cancer screening programme is an integral component of this care model. It provides infrastructure, training, awareness and advocacy. The programme includes a number of key elements to improve screening and meet the needs of the medical community it has been designed to support. These include a dedicated call centre, deployment of mobile or fixed clinics to underserved areas, educational programmes and additional external staffing support and resources where needed.

A care pathway that can be tailored to regional needs has been developed to identify patients at risk and provide recommendations for screening and follow up. In addition, ongoing support is being provided for awareness campaigns and analysis of local breast cancer trends.

By delivering the best possible information, advice, treatment and care to patients with breast cancer it is hoped that this programme will improve patient outcomes and ultimately save lives affected by breast cancer.

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Image Guided Adaptive Brachytherapy in Locally Advanced Cervical Cancers: Preliminary Results and Perspectives

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Introduction

Radiation therapy (external beam radiotherapy, EBRT, followed by brachytherapy) is the cornerstone of the treatment of locally advanced cervical cancer.[1] Brachytherapy plays a fundamental role in the treatment of locally advanced cervical cancers. It permits delivery of high doses to the tumour while minimising the doses delivered to organs at risk (rectum, bladder, sigmoid colon and small bowel). In typical schedules, 40 to 50% of the total dose delivered to the high-risk clinical target volume (HR-CTV) is delivered by brachytherapy. Another advantage over external beam radiotherapy is to eliminate organ motion, as the radioactive sources follow the tumour.[2] In combination with radiotherapy it is a standard of care for tumours staged from IB2 to IVA according to the FIGO (Fédération Internationale de Gynécologie Obstértrique).

Over the past 15 years, two major advances have taken place in this strategy. The first was concomitant chemotherapy, which became standard in 1999, after the publication of 5 randomised studies showing its superiority over exclusive radiotherapy.[3-7] A recent meta-analysis revealed an improvement of 6% for loco-regional disease in locally advanced cervical carcinoma, which translated into a gain of 5% in overall survival.[8] Secondly, technical advances in the field of brachytherapy allowed the use of 3D modality images, such as MRI or CT. So far, conventional brachytherapy was based on geometrically constructed prescription points (A points) and on the use of orthogonal X-rays for planning. Standard prescriptions were used regardless of tumour size, shape, or response to EBRT. In the same way, doses delivered to OAR (bladder and rectum) were evaluated by calculating dose delivered to precise points.[9] It was shown that those two ICRU (International Commission for Radiation Units and Measurements) points are generally underestimating the maximal delivered dose compared to 3D evaluated dose assessment. Kang *et al*. studied the efficacy of such standard plannifing to point A by delineating gross tumour volume (GTV) on CT-scans. They showed that prescribing to point A overestimates the dose delivered to the tumour.[10] By generating dose volume histograms, they reported that the prescribed dose to point A encompassed 98.5%, 89.5%, 79.5 and 59.5% of the (GTV) on average, for staged IB1, IB2, IIB and IIIB lesions respectively, and therefore demonstrated the limitations of such a technique.

The integration of 3D images into treatment planning, allowed delineation of tumours and OAR, making the use of points obsolete. Wachter *et al*. showed that dose volume histograms generated from outer organ contouring were a good estimation of doses given to organ walls, when considering small volumes such as 0.1 cm^3 or 2 cm^3.[11]

The GEC-ESTRO group (Groupe Européen de Curiethérapie- European Society for Therapeutic Radiology and Oncology) published recommendations in 2005 and 2006, on tumour and OAR contouring, and on reporting dose volume parameters.[12, 13] They proposed an individual approach, by defining two target volumes at the time of brachytherapy: a high risk CTV encompassing the residual tumour after EBRT as well as grey zones and at least the whole cervix and an intermediate risk CTV (IR-CTV), taking into account the initial tumour volume as well as the residual volume at the time of brachytherapy. These recent concepts defined image guided adaptive brachytherapy, which implies therefore: 3D imaging and dose optimisation to target volumes.

Currently, dose constraints to the maximal 2 cm^3 of the OAR relies on the experience of conventional X rays based brachytherapy: 70-75 Gy (Eq D2, with a α/β of 3 for late morbidity and a repair half-time of 1.5 hours) for rectum, 85-80 Gy for bladder, and by analogy to rectum, at the lack of data, 70-75 Gy for sigmoid.[14] No reliable dose constraints could be established for small bowel or vagina.

Preliminary Results

Following its publication in 2005 and 2006, the GEC-ESTRO recommendations became a standard to guide and report brachytherapy. IGABT was rapidly implemented throughout Europe. In a descriptive survey, Guedea *et al*. reported an increase in the use of CT based dosimetry from centres around Europe, from 33% in 2001 to 61% in 2010.[15]

Several dosimetric studies show a clear advantage to using IGABT in the treatment of locally advanced cervical cancer over conventional 2D brachytherapy.[16, 17] Tanderup *et al*. reported comparisons of 2D standard plans to MRI based plans in 72 patients. For small tumours, HR CTV was well covered in 94% of the cases with standard plans, but OAR tolerance

thresholds were exceeded in 72% of the cases (maximal 2 cm^3 of bladder < 90 Gy and 2 cm3 of the rectum/sigmoid < 75 Gy.[18] Optimisation permitted to lower this rate to 6%. For larger tumours, standard plans were adequate in only 25% of the cases whereas full coverage could be obtained in 72% of the cases with optimisation. Zwahlen *et al*. reached the same conclusion with a smaller set of patients (20).[19]

Dimopoulos *et al*. showed that MRI enables accurate delineation for GTV, HR-CTV, IR-CTV and OAR. Therefore, MRI has been considered as the reference imaging for contouring GTV and CTVs. However, Viswanathan *et al*. compared MRI and to CT in a dosimetric study. In this publication, ten patients underwent both CT and MRI after brachytherapy. Contouring and planning was according to the GEC-ESTRO recommendations. They concluded that there was no difference in delineating OAR but CT systematically overestimated the tumour volumes for defining HR and IR CTVs.[20]

The first clinical series came from Potter *et al*. They reported the outcomes of 145 patients treated with high-dose rate brachytherapy among two periods: 1998-2000, during which MRI was used, but limited optimisation was performed and 2001-2003, during which they applied the GEC-ESTRO recommendations and the concepts of risk volumes (HR and IR-CTVs).[21] Outcomes were similar for small tumours, but authors showed an improvement of nearly 20% in local control (from 64 to 82%) in the group a tumours > 5 cm in width, and 30% in overall survival (from 28 to 58%) combined with a reduction of severe toxicities (from 10 to 2%). From the same series of patients, Dimopoulos *et al*. showed a dose effect relationship between dose to the HR-CTV and local control. Patients who achieved D90 (dose delivered to 90% of HR-CTV) > 87 Gy (2 Gy equivalent) had a local relapse rate of 4%, whereas those who had a D90 < 87 Gy had a 20% risk of local relapse.[22]

Recently, Schmid *et al*. reviewed the data of 265 patients treated from 1998 to 2010. They reported a correlation between dose coverage and local relapse. The D90 was 77 Gy for patient who experienced local relapse whereas it was 95 Gy for those with local control.[23] In 85% of the relapses, low dose regions (<87%) could be identified. In a recent update of the Vienna series, Potter *et al*. published an update of their series.[24] One hundred and fifty six consecutive patients treated from 2001 to 2008 were reported. Local control was 98% for tumours 2-5 cm width, and 95% for larger tumours. Late treatment induced toxicity was low, as only 11 grade 3-4 events were reported for the whole series. Georg *et al*. published correlations between DVH parameter and morbidity. They showed that the D2 cm^3 had a good predictive value for late rectal and bladder toxicities.[25] They failed to find correlation for sigmoid and bowel, possibly due to a lack of events.

In our institution, we published the first series on MRI based pulsed-dose rate brachytherapy, in 45 patients with no local recurrences after a median follow-up of 2 years.[26] We recently updated our database.[27] Local control was 92% in a series of 163 patients with a median follow-up of 37 months. According to the CTC 3.0, 7.4% of the patients experienced late grade 3-4 toxicity, but most of those had undergone post radiation hysterectomy: 14.8% versus 2.9% (p=0.005). At the beginning of our experience, post radiation hysterectomy was still part of the treatment for stage I and II lesions, but the efficacy of IGABT on local control led us to abandon this procedure which was shown to cause unacceptable morbidity, particularly when the rate of complete histological response to IGABT was taken into account.[28] In a smaller set of patients with advanced disease (mainly stage III and IV), Mahantshetty *et al*. reported promising results in a small cohort of 24 patients from which half had stage IIIB diseases. Only one local relapse was reported after 24 months of follow-up.[29]

Recently, a French multicentric prospective non randomised study comparing 2D versus 3D brachytherapy was published. Patients were divided into 3 groups: brachytherapy followed by surgery for IB1 lesions (group 1), chemoradiation followed by brachytherapy and surgery (group 2) or definitive radiation therapy (chemoradiation followed by brachytherapy, group 3) for locally advanced staged lesions.[30] In each group, patients were treated either with conventional 2D brachytherapy or 3D image guided brachytherapy following the GEC-ESTRO recommendations, according to availability of equipment and at the discretion of local investigator. Results showed significantly better outcomes in the patients treated with 3D brachytherapy in comparison to 2D brachytherapy in terms of local relapse free survival (78.5% versus 73.9% in group 3 and 93% versus 84.7%, in group 2, p=0,003). This was translated into a significant improvement by 4-5% of disease free survival in groups 2 and 3, without any significant impact on overall survival. Authors also showed an improvement of grade 2-4 toxicities: 42.4% versus 53.5% in group 3 and 29.4% versus 40.6% in group 2 (p=0.028). In a separate publication the investigators reported a correlation between D0.1 cm^3, D2 cm^3 of the rectum and D0.1 cm^3 and dose delivered to the ICRU point of the bladder and grade 2-4 toxicity.[31] It should be noted that 57% of the patients of the series had a post radiation hysterectomy.

Perspectives

Preliminary reports are encouraging, but the next step is to provide higher scientific evidence of the efficacy of IGABT. The GEC-ESTRO network is leading a prospective non randomised multicentric study, EMBRACE, on MRI based IGABT.[32] Twenty four centres around the world are attending the study. The aim is to include 1,000 patients. Accrual begun in 2008 and should close in late 2013. The principal objectives are local control and morbidity. One other major purpose of this study is to establish DVH correlations with outcome, both for CTVs and OAR. Dose constraints in both favourable and unfavourable cases would permit to stratify diseases and decide to escalate the dose or conversely to de-escalate the dose in good responders.

At the same time, the network created a wide database of patients treated before the launch of EMBRACE, named retroEMBRACE.[33]

Preliminary results presented in abstract form seem to confirm the promising results published by individual centres.[34]

Another poorly understood aspect of morbidity after treatment for cervical cancer is sexual morbidity. Most patients complain of dyspareunia which is multi factorial: post radiation vaginal sequelae, tumour related changes, psychological consequences, personal culture and treatment induced menopause. GEC-ESTRO has just launched an ancillary study of this subject in order to accurately report morbidity and quality of life, and to correlate doses delivered to different regions / points of the vagina with radiation induced vaginal toxicity.

Image guided adaptive brachytherapy appears highly effective, improving local control with acceptable morbidity. As a consequence, the pattern of relapse is changing, with the emerging significance of distant relapses. In our series, distant metastasis is the first site of relapse in more than 70% of the patients who relapse.[28] Furthermore, in half of the cases, distant metastasis is isolated. This clearly raises the question of more aggressive systemic treatment. Concomitant chemoradiation was shown to have little but significant impact on distant control. Other chemotherapies have been studied such as gemcitabine which is a powerful radiosensitiser, and seems to be effective in combination with cisplatinum.[35] In our institution, we are completing a phase I study on cidofovir, an anti-HPV drug which was showed to be a radiosensitiser, in combination with concomitant chemoradiation.[36] Notably, a phase III study, OUTBACK, has been launched in high risk patients (stage III or IV or lymph node positive), evaluating the role of adjuvant carboplatin-paclitaxel.[37]

Conclusion

Since the late 1990s, significant advances have been made in image guided adaptive brachytherapy for locally advanced cervical cancer. The GEC-ESTRO recommendations helped to standardise and disseminate the technique. Initial clinical results showed that local control in bulky tumours could be improved by 20%, with an acceptable morbidity. The international collaborative study EMBRACE is hoped to definitively establish MRI based brachytherapy as a treatment gold standard.

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Early Detection in Lung Cancer

Vanessa Lane
Treatment Strategies

Summary

Lung cancer continues to be an aggressive disease with a high mortality rate. Early detection of lung cancer is an important opportunity for decreasing mortality. Considerable interest has been shown in developing screening tools to detect early stage lung cancer. Low dose computed tomography (CT) has been shown to increase survival. However, further refinement of imaging technologies has now made it possible to substantially reduce the radiation dose typically associated with chest CT and its associated risks. These advanced imaging technologies, when used for lung cancer diagnosis, offer clinicians comparable or improved imaging to existing methods, but at much lower doses of radiation.

Epidemiology and Survival Rates in Lung Cancer

Lung cancer is an aggressive and heterogeneous disease with continuing low rates of long term survival despite advances in surgical, radiotherapeutic and chemotherapeutic approaches.[1, 2, 3] Worldwide, lung cancer continues to be the leading cause of cancer deaths in men and the second leading cause of cancer deaths in women. For 2008, the projected figures were around 1.6 million new lung cancer cases and 1.4 million deaths.[4, 5]

Evolution of Lung Cancer Care

The current National Comprehensive Cancer Network (NCCN) guidelines recommend screening for lung cancer in high risk populations (age 55-74 years and >30 pack year history of smoking and smoking cessation <15 years or age ≥50 years and 20 pack year history of smoking and one additional risk factor [other than second hand smoking]).[6] The goal of lung cancer screening is to detect disease at an early stage when cure or control may be possible, thereby decreasing disease specific deaths in the population.

Randomised trials of screening have shown that the use of chest radiography with or without cytological analysis of sputum specimens does not reduce lung cancer mortality.[7] This has lead to increased use of CT as a screening tool for many cancers, including lung cancer. Low dose CT has been used since the 1990s, and has enabled high resolution volumetric imaging in a single breath hold.[8] Low dose CT is the only early detection modality that has been shown to improve lung cancer survival rates.[9]

However, there are increasing concerns about the magnitude of the radiation dose delivered in CT and the potential increase in the incidence of radiation induced carcinogenesis.[10] This has lead to the search for lower dose techniques with sufficient diagnostic accuracy to detect lung cancer earlier .

Several dose reduction techniques have been successfully implemented and have been shown to reduce radiation exposure (e.g., tube current modulation, reduced tube voltage, use of a higher pitch and noise reduction filters). However, further reductions in radiation dose are hindered by increased image noise and degraded image quality, mainly as a result of limitations of the standard filtered back projection (FBP) reconstruction algorithm currently used on most CT systems.[11] Use of an iterative reconstruction (IR) algorithm is an alternative image reconstruction technique. Unlike conventional FBP, which is based on simpler mathematical assumptions of the tomographical imaging system, IR generates a set of synthesised projections by accurately modelling the data collection process in CT.

Implementing Advanced Imaging Technologies in Lung Cancer Early Detection and Diagnosis

Adaptive Statistical Iterative Reconstruction (ASiR™)

One of the first IR algorithms released for clinical use was the adaptive statistical iterative reconstruction (ASiR™) algorithm. Several clinical studies have shown that ASiR™ provides diagnostically acceptable images with a reduced image noise for low radiation dose CT.[12, 13, 14, 15] The combination of scanning in high definition mode and ASiR™ image reconstruction has allowed for a dose reduction of around 50% without significant loss of image quality.[16, 17, 18, 19]

In addition, low dose CT (LDCT, 0.2 mSv) using ASiR™ blending has been shown to have a high degree of sensitivity for small lung nodule (SN) detection.[20] In this study, for significant sized (≥ 3 mm) non-

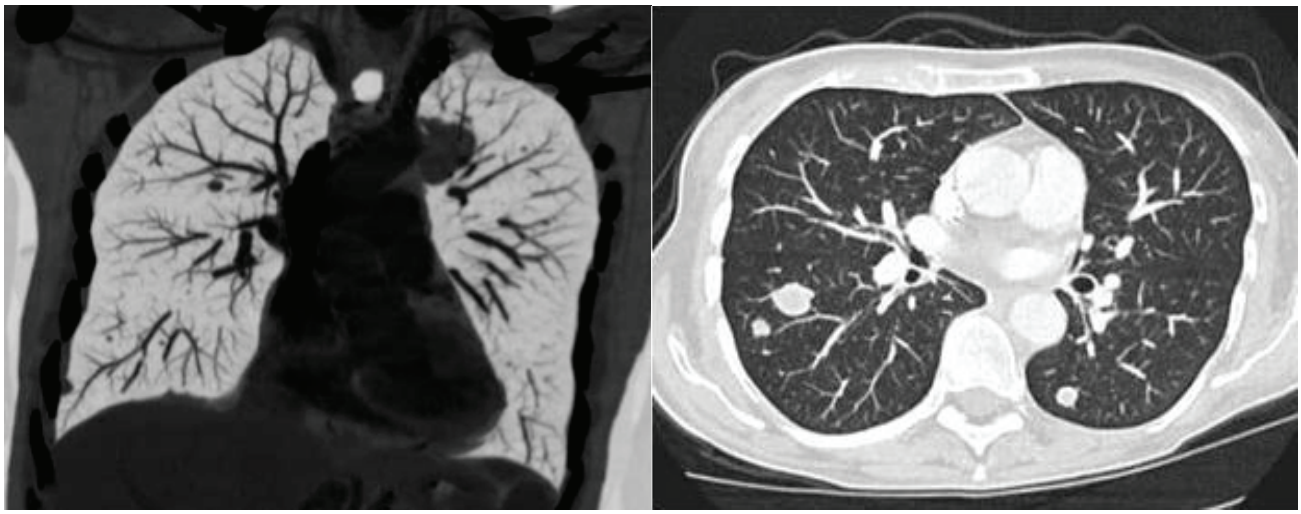

Figure 1. ASiR™ imaging of lung cancer (radiation dose 1.7 mSv).

calcified SN, sensitivities were superior on ASiR™ vs. FBP-driven images (78% vs. 60%, p<0.01). Furthermore, ASiR™ driven LDCT helped detect 84% of peripherally located SNs and 69% of ground glass opacity nodules. It was concluded by the study investigators that LDCT using ASiR™ was comparable to that of plain chest radiography and may offer a technique that could be used in lung cancer early detection with lower radiation risk.

Veo™ (Ultra Low Dose CT)

More recent developments, such as model based IR (MBIR), include an algorithm that accurately models the entire optical chain (real size of focal spot and detectors) and takes into account the noise of the system (photons statistics and electronic noise). As CT data sets reconstructed with an MBIR algorithm have a very low level of noise,[21] MBIR carries the potential for even more drastic reduction in dose for obtaining images of diagnostic quality.

Veo™ is the world's first MBIR product. It offers a significant enhancement in the key areas that define CT image quality. Spatial resolution is increased by up to 33% across the entire body, providing unmatched clarity and detail. Low contrast detectability is also improved by up to 40%, helping differentiate small structures and

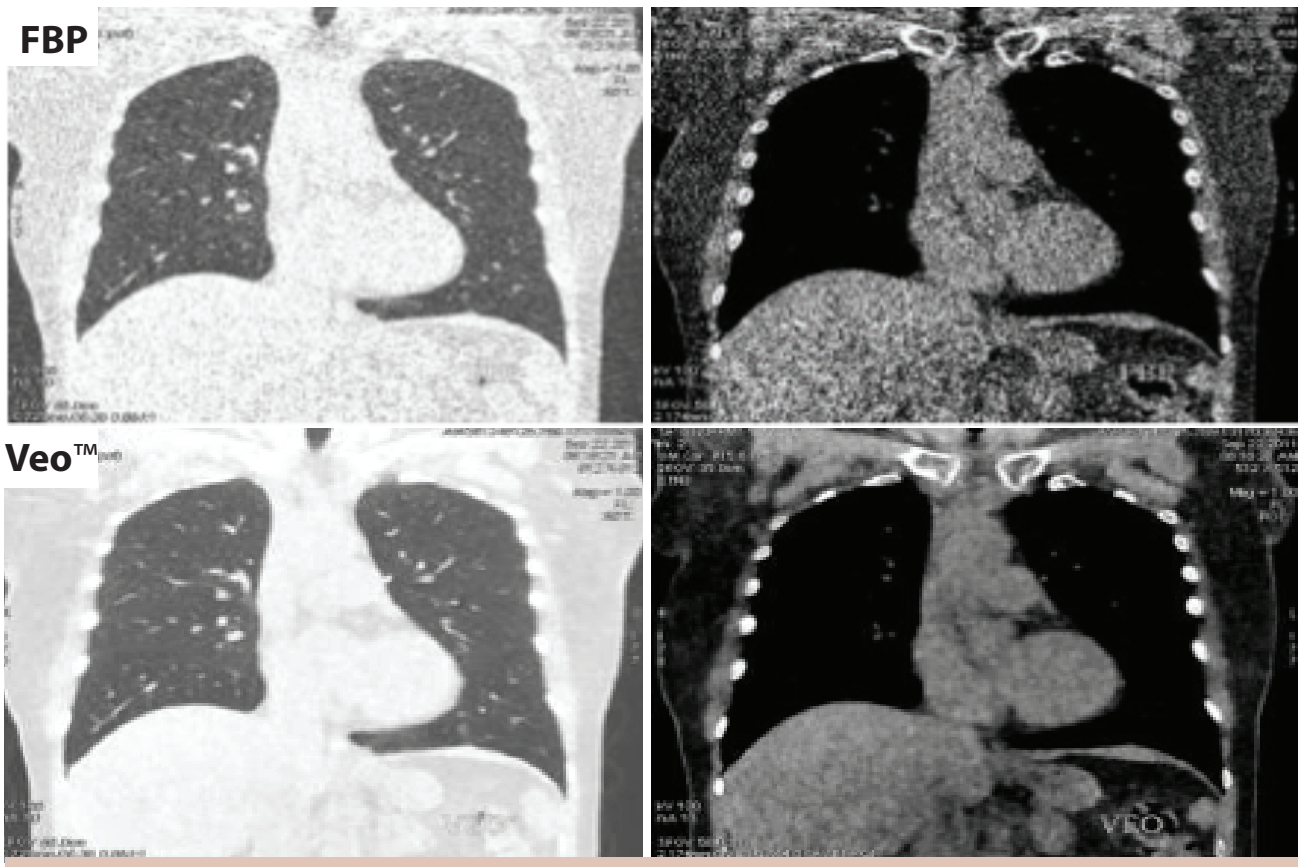

Figure 2. Veo™ ULDCT images of thorax (radiation dose 0.11 mSv) vs. FBP.

providing better clarity in soft tissue exams and challenging anatomies. In addition, Veo™ is able to subtract noise rather than merely masking it, significantly increasing image quality, and can minimise common artifacts such as beam hardening, calcium blooming and aliasing, revealing details that can be crucial for a diagnosis.

Current low dose CT lung cancer early detection protocol requires tube current of 50-160 mA with estimated mean effective dose of 1.5 mSv. However, ULDCT lung cancer early detection under 0.5 mSv has been found to be feasible by using a new MBIR algorithm,[22] thus substantially reducing radiation induced cancer risks associated with annual CT exams in smokers and former smokers. In fact, diagnostically acceptable chest CT images acquired with up to 80% less radiation have been attainable using MBIR,[11] and have been shown to be superior to ASiR™.[11, 23]

In addition ULDCT (Veo™) in conjunction with ASiR™ has been shown to detection pulmonary nodules, including non-calcified pulmonary nodules,[24, 25] with significantly increased image quality vs. FBP or ASiR™ ($p<0.001$).[26]

VolumeRAD™

VolumeRAD™ offers distinctive plane chest images to remove overlying structuring using 3D X-ray tomosynthesis. Digital tomosynthesis combines digital image capture and processing with simple tube/detector motion as used in conventional radiographical tomography.

Although there are some similarities to CT, it is a separate technique. This technology is performed with an X-ray system and provides volumetric data about the lung anatomy, enhancing the amount of information provided by the X-ray examination and can help to improve clinical diagnosis by removing overlying structures, enhancing local tissue separation and providing depth information about the lung.

Dr Bertolaccini and colleagues from the Thoracic Surgery Unit in Cuneo, Italy directed by Dr Terzi analysed data from over 1,500 patients with no previous evidence of cancer, who were screened using this technique. They identified abnormalities in the lungs of 268 subjects, of whom 16 (1.07%) were found to have lung cancer. The digital tomography took around 11 seconds, and the lung cancer detection rate using digital chest tomography was similar to the detection rate of previous studies using CT scanning. Compared to chest CT, patients who underwent digital chest tomography received a far lower radiation dose.

Conclusions

Advancement in imaging technology has lead to improvements in the early diagnosis and outcomes of patients with lung cancer. This has included a number of new technologies, including ASiR™, Veo™ and VolumeRAD™. These offer the ability to achieve comparable or better images to chest CT, while substantially reducing the radiation dose. In the case of VolumeRAD™, more detailed information can be gained in the form of 3D images. These tools have the potential to provide an integrated solution to help detect lung cancer earlier and save more patient lives.

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Key to the Success of Active Immunotherapy in Melanoma

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Introduction

The incidence of melanoma is increasing rapidly worldwide. marketing authorisation of ipilimumab (anti-CTLA-4 – cytotoxic T-lymphocyte antigen-4 - human monoclonal antibodies) and vemurafenib (BRAF inhibitor) in Europe and U.S is changing the standard of care of metastatic melanoma patients. In addition, awaited results of phase III trials evaluating combination of dabrafenib (BRAF inhibitor)[1] and trametinib (MEK inhibitor)[2] may further affect the standard of care. Earlier studies of the combination of BRAF and MEK inhibitors demonstrated that the addition of trametinib to dabrafenib may help to overcome the melanoma resistance to BRAF inhibitors used alone.[3] However, the clinical benefit of the above combination needs to be evaluated in ongoing phase III study.[4]

Lack of effective treatment of patients with resected high risk or metastatic melanoma forces clinicians to follow up the patients and apply the treatment only when metastases recure. However, two different forms of interferon (IFN): INF – alfa-2b and pegylated-IFN-alfa-2b are currently approved for adjuvant treatment in patients with resected high-risk melanoma (stage IIB and stage III). Although INFs use in the clinic is limited due to high toxicity and questionable effectiveness. Currently we are waiting for the results of two melanoma adjuvant phase III studies evaluating ipilimumab and MAGE-A3[5] ASCI vaccine.[6] Moreover, wemurafenib and combination of dabrafenib + trametinib are tested in melanoma adjuvant setting.[7] However, clinical benefits of ipilimumab and transient effects of BRAF inhibitors are still not satisfactory, thus development of other strategies is required.

Allogeneic Gene Modified Cellular Melanoma Vaccine (AGI-101H)

There are number of reasons why further development of active specific immunotherapy of melanoma such as melanoma vaccines is necessary, (i) melanoma belongs to immunogenic malignancies with 7-10 % sporadic spontaneous remissions of primary lesions, (ii) adoptive transfer of active immune effector cells has been shown to eradicate tumours,[8] (iii) targeting the immune-checkpoint proteins (CTLA-4, PD-1, PD-1L) have shown efficacy in some unselected melanoma patients.[9-13] In addition, small molecules targeted therapies as well as cytotoxic drugs are associated with activation of the immune system.[14] Thus, melanoma therapeutic vaccines if applied in the proper setting, especially as adjuvant treatment following surgery, carry potential as a key approach to treat melanoma patients.

We have developed therapeutic allogeneic gene modified cellular melanoma vaccine (AGI-101H) – at the moment the only one in the class – which generated significant fraction of long-term advanced melanoma survivals. AGI-101H consists of two melanoma cell lines virally-transduced with Hyper-IL-6 cDNA, encoding fusion protein comprising of interleukin 6 (IL-6) and its soluble receptor. The vaccine was evaluated in four single-arm phase II studies in patients with measurable metastases (trials 2 and 4 – data not published) and in patients with completely resected metastases in adjuvant setting (trials 3 and 5). The adjuvant studies enrolled 97 and 99 patients to trial 3 and 5, respectively. Patients treated with AGI-101H presented stage IIIB (n=71), IIIC (n=81) and IV (n=39) resected disease. The vaccine was administered 8 times every 2 weeks (induction phase) and afterwards every month (maintenance) until the patients death. At disease progression, maintenance was continued or induction was repeated and followed by maintenance. Re-induction was applied alone or in combination with surgical resection of metastases. Some patients with massive progression not responding to the re-induction were excluded from the study and enrolled to other melanoma clinical trials or qualified to chemotherapy. The median follow-up in trial 3 and 5 was 10,5 and 6,2 years respectively (as of January 1, 2011). In trial 3, 5-years survived 66.7%, 43.8% and 26.1% of patients in stage IIIB, IIIC and IV, respectively. While in trial 5, 5-years survived 56.3%, 39.8% and 41.2% of patients in stage IIIB, IIIC and IV, respectively.[15]

It has been observed that patients treated with AGI-101H presented extended disease free survival (DFS) and overall survival (OS) when compered to non-treated controls in large randomised melanoma studies. In the EORTC 18891 trial the 4-year survival in patients with

stage IIIB and IIIC receiving placebo was 52% and 33%, respectively.[16] In another phase III study evaluating vindesine conducted in patients with melanoma after complete metastasectomy of spread to regional sites, lymph nodes, and distant sites the 5-year survival probability in the control group was 22%.[17] Also in melanoma polyvalent, shed-antigen vaccine study the 3-year survival in patients with stage IIIB and IIIC resected melanoma receiving placebo was only 33%.[18]

Re-induction was performed in 67% (trial 3) and 55% (trial 5) of patients developing progression of the disease of those 51% (both trials) undergone surgical resection of metastases prior to re-induction. In patients without surgery, disease control (CR, PR, SD) was observed in 57% (trial3) and 37% (trial5). All patients with progression of the disease not receiving re-induction died, while 18% (trial 3) and 38% (trial 5) to the underlying re-induction survived at data cut-off. The re-induction reduced the risk of death. In a Cox model for the OS computed from initiation of vaccination the HR re-induction was 0.6 (trial 3) and 0.3 (trial 5). However the risk reduction (3-fold) was statistically significant only in trial 5 ($p<0.005$).[15]

Clinical Trial Design

Clinical trial designs originally developed for chemotherapeutic agents were, and still are, required by regulatory agencies for active immunotherapy approaches. However, biological therapies such as monoclonal antibodies or cancer vaccines significantly differ from cytotoxic drugs in terms of mode of action and toxicity. Moreover, poorly designed clinical trials may lead to overlooking the patient's benefit and a decline in marketing authorisation of effective therapeutic products. A number of studies of immunotherapy approaches have demonstrated high efficacy in early-phase clinical trials, but failed in randomised phase III studies.[19] Development of biological therapies of cancer brings new challenges for the design and execution of clinical trials. Many research groups[20-24] and clinical consortia[25, 26] have postulated modification and unification of the active immunotherapy clinical trial designs, including appropriate end-points.

Currently for the evaluation of drugs in phase III studies OS is a "gold standard" and primary end point of choice. However, OS might be affected by: subsequent therapies; *cross-over* of patients after disease progression from the control group to the study arm; requires time and large cohorts of patients. In efficacy, randomised phase II trials an adoptive component might be required. Acceptable surrogate primary end points used in adjuvant and measurable metastatic studies are DFS and progression free survival (PFS), respectively, which can reduce the time of randomised efficacy trials. However DFS and PFS might not be suitable for the evaluation of immunotherapeutics due to the necessary time for the patients immune system to develop tumour response. Classical definition of DFS or PFS in patients developing relapse or progression might exclude the patient from the study to early, while patients with disease progression may still benefit from the treatment.[27]

In phase II metastatic melanoma study evaluating AGI-101H clinical responses were usually observed after 3-4 months from the start of vaccination. Although in some patients tumour regression was noted after several months or even years following stabilisation of disease (SD).[28, 29] Furthermore, in many immunotherapy trials during the first clinical assessment of tumours, they tend to enlarge due to infiltration by inflammatory cells and then shrink later on.[30] Moreover, immunotherapeutics may not induce tumour volume reduction, but yet still be effective in slowing the kinetics of tumour progression and extending the patient's survival.[31] It has been proposed by the Cancer Vaccine Clinical Trial Working Group (CVCTWG) that confirmation of progression should be performed in second tumour assessment, while early progression should not be taken into consideration. In patients with early progression and subsequent response following second progression the time of DFS and PFS should be calculated from the start of drug administration to the occurrence of second progression.[26] Observations from ipilimumab studies conducted in metatstatic melanoma patients lead to the development of new guidelines (immune-related response criteria – irRC) for the evaluation of tumour response in these patients. According to irRC the first tumour assessment should be performed after 12 weeks from the start of ipilimumab treatment, where the median time to response development is slightly over 3 months. Furthermore, in some patients, responses after the initial increase in total tumour burden in the presence of new lesions were associated with favourable survival.[30]

A well-designed immunotherapy study is extremely important especially in immunogenic malignancies like melanoma or kidney cancer were these drugs can provide long term survival. This was observed in patients treated with IL-2 or ipilimumab. Atkins *et al*. conducted a study in 270 metastatic melanoma patients treated with IL-2. The objective response rate was 16% (6% - CR, 10% - PR). The median duration of CR was 59 months. Disease did not progress in any patient who developed response lasting more than 30 months[32, 33] Response rates in melanoma patients treated with ipilimumab in phase II and III studies were observed in the minority of patients (7-15%). Although 2 and 3-year OS is noted respectively in 21-30% (3 and 10 mg/kg ipilimumab) and 25% (10 mg/kg ipilimumab) of patents.[9, 34, 35, 36]

Combinational Therapy

Various approaches of melanoma treatment demonstrated clinical efficacy as single agents in phase II studies, but failed to show extended OS in phase III trials. However, gp100 peptide vaccine combined with IL-2 has shown clinical benefit in phase III study, indicating the necessity of developing multi-agent approaches.[37] Also the development of successful BRAF inhibitor/immune therapy-based (anti-CTLA4 or anti-PD1 therapy) combinations offers the real

possibility that very durable responses could be achieved. A phase I/II trial evaluating ipilimumab in combination with vemurafenib is currently ongoing.[38] Strategies consisting of immunomodulating agents and cancer vaccines might result in higher efficacy of the treatment, with decreased adverse events related to drugs modulating the immune system. In patients immunised with autologous tumour vaccine modified with GM-CSF gene prior to ipilimumab treatment, grade 3 and 4 irAE were not observed. These results indicate that ipilimumab immune related adverse events (irAE) might be minimised by melanoma specific immunisation, which in turn will narrow the array of CTL clones to be re-activated [39]. BMS-936558 (anti-PD1) a monoclonal antibody was tested recently with the combination of a multipeptide vaccine (consisting of MART-1/gp100/NY-ESO-1 peptides with adjuvant Montanide ISA 51) in an early phase study demonstrating a high response rate in patients with metastatic melanoma.[40]

Tumour microenvironment seems to be a very important target in the development of effective cancer immunotherapy. Hypoxia generated in the tumour microenvironment is responsible for the promotion of tumours growth due to the induction of angiogenesis.[41] Hypoxia also causes local and systemic immunosuppression which blocks effector immune cells.[42] Combination of specific immunotherapy with agents normalising tumour hypoxia may pave the way for novel approaches of melanoma treatment.

Conclusions

The potential of active immunotherapy has been evidenced by the approval of dendritic cell based prostate vaccine – Sipuleucel-T and immunomodulating monoclonal antibody – ipiliumumab in melanoma patients. Long-lasting survival of significant fraction of melanoma patients immunised with allogeneic genetically modified vaccine (AGI-101H) or combinational treatment strategies involving active immunotherapy further supports the break thoughts in the cancer treatment. Better understanding of tumour-related immunesuppression mechanisms and their braking, as well as proper clinical trial design, will lead to the further progress in the field of active cancer immunotherapy. Moreover, active immunotherapy needs to be combined with small molecules. Certainly without support of the immune system elimination of cancer may not be possible.

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Respiratory Gating, Triggered Imaging and Calypso® Transponders: Motion Management Technologies from Varian Medical Systems

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Today's radiotherapy and radiosurgery treatments utilise a number of advanced motion management tools. To enable high energy X-rays to be delivered as precisely as possible, it is vital to take account of both patient and tumour motion, and modern treatments systems must offer tools for clinicians to achieve this. When treating common cancers such as breast cancer and lung cancer, respiration is the greatest source of motion. Varian Medical Systems has pioneered multiple techniques which allow more precise treatment delivery by taking into account the impact of the patient's breathing on the position of the tumour, including gating and triggered imaging.

Gated RapidArc® radiotherapy, which is available on Varian's line of medical linear accelerators, makes it possible to monitor patient breathing and compensate for tumour motion while quickly delivering dose during a continuous rotation around the patient. This development enables the use of RapidArc® to target lung tumours with greater precision by "gating" the beam—turning it on and off—in response to tumour motion.

"With Gated RapidArc®, it is possible to deliver highly targeted treatments to many types of tumours, including lung tumours that are moving, in less time than would otherwise be required," said Dow Wilson, Varian's CEO. "According to the American Cancer Society, during the last decade, lung cancer became the leading cause of cancer death for both men and women in the United States. Gated RapidArc® should make an impact in the treatment of lung cancer."

A 51-year-old breast cancer patient from Switzerland became the first person in the world to be treated using Gated RapidArc® in 2010. The treatment took place at the Istituto Oncologico della Svizzera Italiana (IOSI) radiation oncology unit in Bellinzona, a public comprehensive cancer center serving 330,000 inhabitants in southern Switzerland, and part of Ente Ospedaliero Cantonale at San Giovanni Hospital.

Dr. Giorgia Nicolini, Medical Physicist at IOSI, said, "This is a very fast and straightforward procedure for the patient, who doesn't speak the local language, Italian, but in any case has found it very easy to follow instructions for gating. She has been fully co-operative and the part of the treatment time taken up by breathing management is decreasing after the first sessions. She also appreciates having to spend less time on the treatment couch."

The hospital had used breath-hold gating as part of the treatment procedure for all left breast cancer patients since 2005 to better spare the heart and lung from exposure during radiotherapy treatment. Prior to Gated RapidArc®, conventional seven-field gated IMRT treatments would have taken 15 minutes to deliver. Using two-arc Gated RapidArc®, the treatment takes place in around four minutes.

Dr. Nicolini said clinicians at IOSI compared RapidArc® and IMRT treatment plans for the patient and decided RapidArc® offered the better opportunity to spare nearby organs from exposure and target the tumour. "The use of two partial arcs enables us to shape a better dose distribution and do a better job of sparing the opposite breast," said Antonella Richetti, M.D., Head of the IOSI Radiation Oncology Department. In addition, RapidArc® enabled the dose to be delivered using fewer than half the dose monitor units needed for an equivalent conventional seven-field IMRT treatment.

"We are now using Gated RapidArc® to treat all left-sided breast cancer patients when there is a need to include the supraclavicolar and/or internal mammary chain lymph nodes, or when chest wall anatomy will affect the dose to organs we want to protect," said Dr. Nicolini.

Since that first treatment in Switzerland, many more patients globally have been treated using Gated RapidArc® to account for tumour motion.

Triggered Imaging

With intrafraction motion review (IMR), or "triggered imaging," the gating system also triggers the imager to generate a low-dose X-ray of the targeted tumour at a specific point in the patient's respiratory cycle.

Late last year, the University of Alabama (UAB) in the United States became the first medical centre in the world last week to utilise triggered imaging to continually monitor tumour location during

Figure 1. The TrueBeam™ system's linear accelrator enables a visual verification of a tumour's location and confirmation that it is being properly targeted.

radiosurgery for lung cancer. IMR, which is a unique capability of the TrueBeam™ linear accelerator, enables visual verification that a tumour is being properly targeted.

"With triggered imaging, clinicians use the imager on the TrueBeam™ system to observe the targeted tumour repeatedly, at a predetermined portion of the respiratory cycle, in order to check on the tumour's location and trajectory," said Chris Toth, VP of Oncology Systems marketing at Varian. "If the tumour is not where it is supposed to be, they can halt treatment and intervene to enhance the accuracy of the targeting."

Doctors at UAB use the IMR tool along with Gated RapidArc® radiosurgery to treat inoperable early-stage lung cancer.

"With IMR, we can now monitor the gating accuracy and ensure that the beam hits the tumour," said Richard Popple, Ph.D., associate Professor of Medical Physics at UAB. "It allows us to monitor tumour position in real time and intervene if a change in patient respiratory pattern causes a shift. The enhanced precision could potentially increase tumour control and decrease the amount of surrounding healthy lung tissues exposed to the beam."

"The IMR tool offers us a way of verifying that our gating strategy remains valid throughout an entire treatment," added Chris Dobelbower, M.D., Ph.D., radiation oncologist at UAB. "It also gives us the ability to hold the beam should the target wander from isocentre if the patient's breathing pattern were to change due to a cough or a sneeze, or other interference."

To utilise IMR during the treatment for lung cancer, Dr. Dobelbower collaborated with thoracic surgeon Douglas J. Minnich, M.D., assistant professor at UAB Healthcare, who placed a set of radio-opaque fiducial markers into the lung tumour using electromagnetic navigational bronchoscopy—an approach that employs three-dimensional CT imaging to guide the procedure. These markers made it possible to see the tumour's location within the surrounding healthy tissues using X-ray images generated during treatment.

"IMR makes it possible to complete lung cancer treatments with a high level of precision and confidence that you're treating the area you want to treat," Dr. Minnich said. "Rather than imaging at the beginning of treatment and then doing your best to account for respiratory motion, IMR allows you to actually watch the tumour and monitor targeting as the treatment proceeds."

According to Dr. Dobelbower, the ability to generate an image with every breath, identify when a targeted tumour has shifted, stop a treatment, and reposition the patient makes a new level of precision feasible. "This was previously only possible by a time-consuming and cumbersome process of interrupting treatment for additional imaging," he said.

GPS for the Body

Varian's advanced treatment systems have incorporated an interface for the Calypso® transponder system, sometimes referred to as 'GPS for the Body' for some time. Last year, Varian acquired Calypso® with a

Figure 2. The Varian TrueBeam™ System

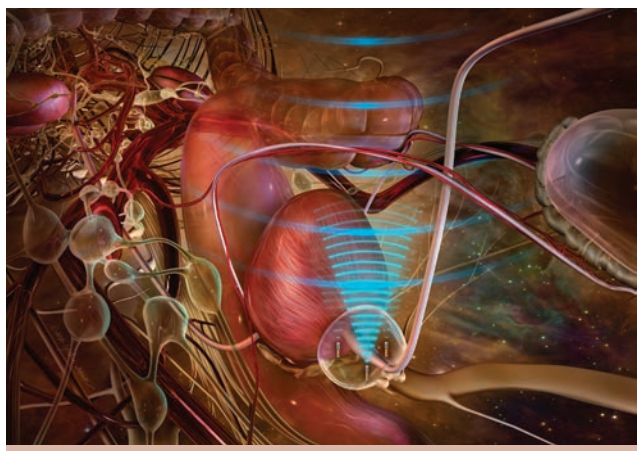

Figure 3. An image of the prostate. The Calypso® system enables clinicians to track the prostate in real time, in order to enhance treatment accuracy.

view to extending the cancer sites for which the use of Calypso® transponders is approved. Such approval currently exists for use in the prostate and on the surface of the patient, while Varian hopes to secure approval for use in the lung in 2013.

Just as a GPS tracking system in a car can pinpoint where the car is at all times in relation to its destination, Calypso® 'GPS for the body' provides continuous real-time information as to the precise location of the prostate. "The prostate is not a stationary target," says Corey Zankowski, Varian's VP of Oncology Systems product management. "It can shift by as much as several millimeters during a radiotherapy treatment session. The Calypso® system enables clinicians to track the prostate in real time during treatment, in order to enhance treatment accuracy."

A recent clinical study entitled, 'Assessing the Impact of Margin Reduction (AIM),' published in the medical journal *Urology*, demonstrated that the use of Calypso® real-time tracking during radiotherapy treatments for prostate cancer resulted in a significant reduction in serious treatment-related side effects.[1]

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Treatment of Relapsed Refractory Myeloma – Updates from EHA 2012

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Introduction

For the last ten years thalidomide, lenalidomide and bortezomib have been classed as the 'new' agents in myeloma treatment. These have rapidly become incorporated into standard practice, and have led to significant improvements in overall and progression free survival.[1] Almost all patients, however, eventually develop drug resistance and relapse. Once patients become resistant to these agents, prognosis is poor.[2] A number of novel agents are being developed to meet the need for subsequent treatment. These are going through clinical trials, and their efficacy at different stages in the disease course assessed. In order to standardise the reporting of clinical trial experience in these patients, the International Myeloma Working Group (IMWG) have recently introduced some definitions of the different stages of disease.[3] Patients are defined as 'primary refractory' if they have never achieved a response of at least minimal response (MR), 'relapsed refractory' if they have achieved at least MR to a prior therapy, but have not achieved MR on salvage therapy or relapsed within 60 days of salvage therapy, and 'relapsed' if they have had a period off therapy and have clinical disease progression requiring treatment.

Treating patients with relapsed or relapsed refractory disease is challenging, as they often have worsening symptoms resulting from their disease as well as residual side effects from previous lines of therapy, for example recurrent infections, peripheral neuropathy or low blood counts due to bone marrow insufficiency. Therefore, for drugs used at relapse or in the relapse refractory setting to become useful in clinical practice, it will be important that they are not only effective but also minimise the exacerbation of existing, or the development of new, treatment related side effects. These issues place limits on the type of treatment, combination and schedule that is appropriate. For example, patients with low blood counts may not be able to tolerate a drug that causes further marrow suppression, or might require very regular blood product transfusion and the use of growth factors, impacting their quality of life.

Here we present a summary of the most promising new drugs that are being trialled in the relapsed refractory setting, and also some that have progressed to trials looking at their role earlier in the disease course. The potential list is long, and so the focus is on the two new agents likely to become licensed first, pomalidomide and carfilzomib. We provide an update on the latest relevant trial data including data presented at the European Hematology Association (EHA) 17th Congress, June 14-17 2012.

Immunomodulatory Drugs (IMiDs)

The use of the IMiDs, thalidomide and lenalidomide, has changed the outcomes of myeloma patients significantly over the last 10 years.[1] Pomalidomide is a new IMiD with multiple mechanisms of action including direct cytotoxic effects, inhibition of cytokine secretion by the stroma, anti-angiogenic activity, immune modulatory effects and inhibition of the myeloma and bone marrow stromal cell interaction.[4, 5] It is structurally similar to lenalidomide and thalidomide, but differs functionally as well as in its side effect profile, the most common side effects being myelosuppression, fatigue and venous thromboembolism.

Phase I and II studies have shown promising results in both relapsed refractory patients and those treated earlier in their disease course. The initial phase I study in relapsed refractory disease showed 54% of patients achieved ≥PR, with 17% CR.[6] The maximum tolerated dose (MTD) in this study was 2mg daily. A further phase I/II study explored a different dosing schedule of pomalidomide given on days 1-21 of a 28 day cycle rather than continuously. The MTD was 4mg daily with response rate ≥PR of 22%.[7] Direct comparisons are difficult due to the different dosing schedules and the fact that patients were at different stages in their disease course. In addition, for patients in the higher dose study, dexamethasone was added if there was no response or disease progression after 4 cycles of treatment. However, both studies demonstrated promising activity in relapsed refractory patients.

In a phase II study of 60 patients treated with pomalidomide (2mg daily) with dexamethasone (40mg weekly) who had relapsed refractory disease and had received 1-3 prior regimes, the response rate was 63% (≥PR) with 3 patients achieving CR and 17 VGPR.[8] A subsequent study went on to confirm responses in patients refractory to lenalidomide. In this study, the majority of patients had also previously been treated with thalidomide (58%) and bortezomib (59%), and 70% had received 3 or more previous regimes. The response rate was slightly lower (34% ≥PR)

as would be expected in this heavily pre-treated group.[9]

As the initial studies had compared different dose schedules, in order to determine the optimum dose, a phase II study in patients relapsed and refractory to both bortezomib and lenalidomide compared pomalidomide 2mg daily to 4mg daily of a 28 day cycle (with dexamethasone 40mg weekly). It achieved response rates of 49% and 43% respectively (≥MR).[10] The most common toxicity observed was myelosuppression with haematologic toxicity grade 3 or 4 seen in 80-83% of patients. The most common non-haematologic toxicity was fatigue (88-91%). The overall survival at 6 months was 78% (2mg) and 62% (4mg) with progression free survival at 6 months of 56% (2mg) and 34% (4mg). The authors concluded no significant advantage to the 4mg dose over the 2mg dose.

In a further study to look at the issues around dose scheduling, IFM 2009-02, compared 4mg daily on days 1-21 of a 28 day cycle with 4mg daily on days 1-28 of a 28 day cycle. Patients included in the study were symptomatic and had progressive disease following at least two cycles of lenalidomide and two cycles of bortezomib (either separately or in combination).[11] Each group received dexamethasone 40mg weekly. The authors reported an overall response rate (≥PR) of 34.9% in the 21 day arm and 34.1% in the 28 day arm, including 4.7% and 7.3% VGPR respectively and a median PFS of 6.3 months in both arms. They concluded that there was no clear difference in the two dosing schedules. At the EHA, Dr Leleu[12] presented a subanalysis of data from this study. He compared the patients' response to pomalidomide plus dexamethasone with that to their last line of therapy. The data showed evidence that patients with disease refractory to their last line of therapy, including to lenalidomide, had a similar overall response and PFS to the entire study population, and that the time to progression improved in comparison to their last treatment. This data confirms the activity of pomalidomide in patients who have been exposed to, and are resistant to, multiple lines of therapy including IMiDs.

These promising results have led to the initiation of a number of studies looking at pomalidomide in combination with other anti-myeloma therapies. Dr Palumbo[13] presented the results of a phase I trial looking at the efficacy and safety of the new combination of pomalidomide (at four dose levels 1, 1.5, 2 and 2.5mg daily) with prednisolone (50mg every other day) and cyclophosphamide (50mg every other day) followed by pomalidomide and prednisolone as maintenance. Patients had received 1-3 prior lines of therapy and were relapsed and refractory to lenalidomide. The overall response rate of 29 evaluable patients was 72% including 7% CR and 21% VGPR. At 7.3 months of follow up, 82% of patients were free of disease progression and 93% were alive. Toxicities were limited but included grade 4 neutropenia (17%), thrombocytopenia (7%) and thromboembolism (3%), with 10% of patients discontinuing treatment due to their toxicity.

These studies provide further evidence that pomalidomide is effective in relapsed and relapsed refractory patients regardless of their prior resistance to therapy, and that novel combinations may improve the effectiveness further. Clearly it is important to determine that pomalidomide and dexamethasone is more efficacious than standard relapse refractory therapy, and to achieve this a phase III trial of pomalidomide plus low dose dexamethasone vs high dose dexamethasome alone is currently recruiting patients with relapsed disease refractory to both bortezomib and lenalidomide. For some relapsed refractory patients however, the myelosuppression seen may be a limitation to treatment, and may result in increased use of growth factors, blood product support and/or infections, and so further exploration of dosing schedules may be warrented.

Proteosome Inhibitors

Bortezomib, the first in class proteosome inhibitor, is now licensed for the treatment of both young, fit patients with myeloma, as well as older, less fit patients with the same disease, both as initial treatment and relapse. Carfilzomib is a new proteosome inhibitor which is structurally distinct from bortezomib and reputed to have a more favourable side effect profile. Its mechanism of action differs by having irreversible binding to the proteosome, whereas bortezomib binding is slowly reversible.[14] This leads to a more sustained inhibition and a resulting difference in dosing schedule. In addition, preclinical studies suggested minimal activity with off-target enzymes, which may help reduce side effects.

Several early phase studies support these preclinical findings. The most recently published showed that in relapsed, bortezomib naive patients treated with carfilzomib (Cohort 1: 20mg/m^2 on days 1, 2, 8, 9, 15 and 16 of a 28 day cycle. Cohort 2: 20mg/m^2 cycle 1 and 27mg/m^2 subsequent cycles) the overall response rate (≥PR) was 42.4% in cohort 1 and 52.2% in cohort.[2] The most common side effects were fatigue and nausea. Peripheral neuropathy was seen in 17% but only in one patient at grade 3 and none at grade 4. Median time to progression was 8.3 months for cohort 1 and not reached for the higher dose cohort.[15]

Disease activity has also been seen in bortezomib refractory patients. One phase II study demonstrated good responses to carfilzomib (20mg/m^2 cycle 1, 27mg/ m^2 cycle 2+) with an overall response rate of 24% and median overall survival of 15.5 months. This was maintained even in those patients with adverse cytogenetics.[16] These two studies confirmed disease activity in relapsed refractory patients, suggested that the 20mg/m^2 cycle 1, 27mg/m^2 cycle 2+ dosing schedule was appropriate to take forward and confirmed pre-clinical observations that peripheral neuropathy with carfilzomib is low.

Dr Martin[17] explored the data on peripheral neuropathy (PN) further at EHA, and presented data from across four phase II trials using carfilzomib, including a total of 526 patients. Clearly this issue is particularly important for myeloma patients as many have significant PN affecting their quality of life either due to the disease itself or to their previous treatments, and this often limits the ability to deliver effective

treatment. The analysis showed an incidence of PN of only 14% despite the fact that most patients had a medical history significant for PN. In total only 0.2% of patients discontinued medication due to PN, and only 0.8% required a dose reduction. These low rates of PN either as a new occurrence or exacerbation of existing symptoms enabled patients to remain on treatment for a longer duration.

From a similar cross-trial analysis, Dr Harvey[18] presented the results of cumulative renal adverse events with carfilzomib treatment. This is of particular concern in myeloma as patients are susceptible to renal injury both as part of their disease and from its treatment. The results showed that 13% of patients experienced significant worsening of renal function despite 71% having renal impairment at baseline. Only 50% of these required a change in carfilzomib therapy. Importantly, results from the trial focusing on patients with varying degrees of renal function showed no pharmacokinetic differences in the patients with a wide range of renal function. The group concluded that carfilzomib dose and schedule, like bortezomib, does not need to be adjusted in patients with baseline renal impairment, even in those on renal replacement therapy.

As would be expected, a number of recent studies have been presented looking at carfilzomib at different disease stages and in combination with other effective myeloma therapies. A phase II trial looked at carfilzomib combined with thalidomide and dexamethasone as induction treatment prior to high dose melphalan and autologous stem cell transplant.[19] Patients received 4 cycles prior to transplant of carfilzomib (20 mg/m^2 on days 1 and 2 followed by 27mg/m^2 on days 8, 9,15 and 16 of cycle 1 and on days 1, 2, 8, 9, 15 and 16 of all subsequent 28 day cycles), thalidomide (200 mg days 1-28) and dexamethasone (40 mg weekly). Following autograft they received consolidation therapy consisting of 4, 28 day cycles of carfilzomib (27 mg/m^2 days 1, 2, 8, 9, 15 and 16), thalidomide (50 mg days 1-28) and dexamethasone (20 mg weekly). Promising results were reported for the first 20 evaluable patients, with a response rate after induction of CR/sCR 21%, VGPR 47% and PR 16%. The most common grade 3 and 4 toxicities included metabolic disorders (n=4), cardiovascular including venous thromboembolism (n=5) and reversible renal failure (n=3). All patients successfully mobilised stem cells for autograft. This early data provides some promising evidence of efficacy in this setting, however longer follow up is required for major conclusions, although again it is interesting to note the low PN rate.

Dr Mikhael[20] presented data at EHA from a phase I/II trial of cyclophosphamide, carfilzomib, thalidomide and dexamethasone as induction treatment in patients with newly diagnosed myeloma. Patients received carfilzomib (20mg/m^2 cycle 1, 27mg/m^2 cycle 2+ IV on days 1, 2, 8, 9, 15, 16), thalidomide (100mg po daily), cyclophosphamide (300mg/m^2 po on days 1, 8, 15) and dexamethasone (40mg po days 1, 8, 15, 22) for 4 cycles to be followed by autologous stem cell transplant. The overall response rate prior to transplant was 100% (CR 32%, VGPR 47%, PR 21%). Neuropathy was not common and only at grade I where seen. 52% of patients experienced grade 3 toxicity and 19% grade 4 toxicity. The most common of which were fatigue, generalised muscle weakness, cytopenias and thromboembolism. However these toxicities appeared tolerable given the excellent response rates.

A further phase I/II study exploring a proteosome and IMiD based combination investigated the use of carfilzomib (20, 27 or 36 mg/m^2, days 1, 2, 8, 9, 15, 16 and 1, 2, 15, 16 after cycle 8) with weekly dexamethasone (40/20mg cycles 1-4/5+) and lenalidomide (25mg days 1-21) as induction treatment in 53 newly diagnosed patients. Patients received 4 cycles of treatment before, if eligible, proceeding to stem cell harvesting before recommencing treatment with the option of transplantation, either then or to be deferred. The responses seen were rapid and 62% of patients achieved at least a near CR after a median of 12 cycles and 98% achieved at least PR. In those who received at least 8 cycles this response improved to 78%. The PFS rate at 12 months was 97% and at 24 months 92%.[21] These studies provide further evidence of the efficacy of carfilzomib when used as induction treatment in addition to its use in the relapsed refractory setting.

However, in order for carfilzomib to become standard of care, further studies are required. In the relapsed refractory setting the Focus study is currently comparing the use of carfilzomib with best supportive care (corticosteroid: prednisolonse 30mg every second day or dexamethasone 6mg every second day, +/- cyclophosphamide 50mg daily, which may be added at investigator discretion). For use earlier in the disease course, a phase 3 trial (Aspire) of carfilzomib for relapsed patients who have received at least one, but no more than three, previous therapies has just reached its recruitment target and the results are awaited. This compared the addition of carfilzomib to lenalidomide and dexamethasone vs lenalidomide and dexamethasone alone. A further phase 3 trial (Endeavor) is currently recruiting in a similar disease group, relapsed patients, aimed at comparing proteosome inhibitor efficacy and tolerability, and will compare carfilzomib and dexamethasone to bortezomib and dexamethasone.

The success of bortezomib and carfilzomib has provided support for the development of other proteosome inhibitors in myeloma including marizomib, a non-peptide proteosome inhibitor, and MLN9708, an oral proteosome inhibitor, in which clinical trials are now underway. Dr Richardson[22] presented the results of two phase 1/2 trials at EHA on MLN9708 use in previously untreated patients combined with lenalidomide and dexamethasone. The two studies compared weekly or twice weekly dosing of MLN9708. Of 38 evaluable weekly dosed patients, 34 achieved ≥PR (7 CR, 5 VGPR, 22 PR), all 3 evaluable twice weekly dosed patients achieved ≥PR (2 VGPR, 1 CR). Toxicity was manageable with only one patient having ≥ grade 3 PN, and this was at a dose higher than the eventual MTD. This regime would have clear benefits to patients' quality of life by not requiring any IV therapies, reducing both the discomfort of the

Mechanisms of Action	Agent	Stage of Development
Proteosome inhibitor	Carfilzomib (intravenous)	Phase III
	NPI – 0052 (intravenous)	Phase I
	MLN 9708 (oral)	Phase III
Immunomodulation (IMiD)	Pomalidomide	Phase III
Monoclonal antibody	CNTO 328 (anti-IL6)	Phase II
	Daratumumab (anti-CD38)	Phase I/II
	Elotuzumab (anti-CS1)	Phase III
	BT062 (anti-CD138)	Phase I/II
	LY2127399 (anti-BAFF)	Phase III
Histone Deacetylase (HDAC) Inhibitor	Vorinostat	Phase III
	Panobinostat	Phase III
	CHR3996	Phase I
PI3K/AKT/mTOR inhibitors	Perifosine	Phase III
	Temsirolimus	Phase II
	INK 128	Phase I
JNK activator (anti-angiogenic)	Plitidepsin	Phase II
Aminopeptidase inhibitor	Tosedostat	Phase I
BRAF inhibitor	Vemurafinib	Phase II
Heat shock protein 90 (HSP90) inhibitor	KW-2478	Phase II
Cyclin dependent kinase inhibitor	AT7519	Phase II
	PD0332991	Phase II
	Dinaciclib	Phase I/II
Aurora Kinase inhibitor	MLN8237	Phase I
	ENMD-2076	Phase I
MEK inhibitor	AZD6244	Phase II
Kinesin spindle protein inhibitor	ARRY-520	Phase I/II
Hedgehog inhibitor	GDC-0449	Phase I

Table 1. New agents in development by mechanism of action.

administration process and visits to hospital, and so further data on its toxicity and efficacy profile are eagerly awaited.

Conclusions

New agents are needed to overcome resistance to the currently available therapies in myeloma in order to improve patient outcomes. Their development has been made possible thanks to an increased understanding of the molecular pathology of myeloma, enabling targeting of myeloma cells within the bone marrow microenvironment by a number of different pathways. Within this article we have concentrated on the two new drugs which are closest to licensing, carfilzomib and pomalidomide. These are demonstrating high response rates with tolerable side effect profiles. Encouragingly, responses have also been good in patients resistant to other therapies including those of the same class of drug. Survival data is, however, limited in some of these early studies due to short follow up times. The favourable side effect profiles are particularly encouraging for the relapsed refractory group of patients, as the focus of their care must necessarily be around quality of life as well as disease control. The results from randomised phase 3 trials will prove critical in the further evaluation of these new drugs and their move into mainstream clinical practice.

Excitingly, a number of other small molecules and antibodies with excellent preclinical activity are also being investigated in phase I, II and III clinical trials in myeloma. (Table 1) Demonstrating the efficacy of these drugs is going to be challenging, especially if, as traditionally has been the case, clinical trials are first initiated in relapsed refractory disease where patients are heavily pre-treated and resistant to both IMiDs and proteasome inhibitors. However, as many of these drugs target key signalling pathways in myeloma, it is hoped that early results will be positive and the anti-myeloma armamentarium will continue to expand.

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Management of Painful Vertebral Compression Fractures in Cancer: Role of Balloon Kyphoplasty

Vanessa Lane
Treatment Strategies

Vertebral compression fractures (VCF) can occur as a direct consequence of cancer or as an indirect result of cancer therapy. VCF are particularly prevalent in multiple myeloma (MM: 26-34% of patients),[1, 2] and are a common complication of several types of solid tumours, occurring in 20% of breast cancer patients, 6% of those with prostate cancer and 8% of patients with lung cancer that present bone metastasis.[3] In addition to being associated with symptoms of back pain, VCF further increase the deterioration in patient health and quality of life (QOL) while increasing the mortality rate.[4] A large retrospective analysis of metastatic breast cancer patients (n=1130) receiving chemotherapy or hormone therapy, found that a fracture significantly increased the risk of death compared to patients without a fracture (32%, p=0.003).[5] In severe cases, metastatic spinal cord compression (MSCC) can occur when there is pathological vertebral body collapse or direct tumour growth causing compression of the spinal cord or *cauda equina*. In the US, patients dying of cancer have an estimated 3.4% annual incidence of MSCC requiring hospitalisation.[6] In addition, post mortem evidence indicates that the incidence could be as high as 5-10% of patients with advanced cancer.[7] Irreversible neurological damage ensues with resulting paraplegia.

Surgical and nonsurgical managements are used to treat VCF. The goals of nonsurgical management are to reduce pain (with analgesics, bed rest and radiation therapy), improve functional status (with orthotic devices) and prevent future fractures (with antiresorptive therapy).[3] Conservative management is of limited benefit due to continued bone loss from tumour invasion, poor nutritional status, immobilisation, prolonged steroid use, gonadal ablation, chemotherapy and radiotherapy.[8]

In most cases, spinal tumour surgery is a treatment of last resort, i.e., other nonsurgical treatments, such as radiation and chemotherapy have already been tried and will often continue to be used in the patient's treatment regimen. The goal in spinal tumour surgery for metastatic cancer is to perform the minimum surgery necessary to provide the patient as rapid a recovery as possible. When the cancer is limited only to one portion of the spinal column, the goal of surgery is often to completely remove the cancer, if possible, with the hope of potentially curing the cancer.

If there are neurological symptoms, an open procedure is usually necessary. These open procedures usually require insertion of rods, screws and cement to reinforce the spinal column. Sometimes a more extensive approach is required, particularly when aiming for a cure in excising primary tumours of the spinal column or excising an isolated metastasis from the spinal column.

A preferred, earlier alternative in the patient's disease progression is vertebral augmentation.

Vertebral Augmentation

Vertebral augmentation is a generic term used to describe a number of minimally invasive spine treatments, including vertebroplasty and kyphoplasty, which deliver polymethylmethacrylate (PMMA) bone cement into the fractured vertebral body via percutaneous needles. A review of the literature has shown that vertebral augmentation is a rapid, safe, durable and effective palliative treatment for metastatic VCF.[9] The focus of this review is balloon kyphoplasty (BKP).

Balloon Kyphoplasty Procedure

BKP is a minimally invasive technique and has been shown to reduce pain caused by VCF, restore lost vertebral body height and improve function and QOL.[10, 11]

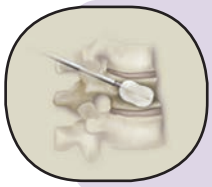
BKP differs from other surgical therapies for VCF such as vertebroplasty, as it is designed to stabilise the fracture by providing a controlled fill and distribution of bone cement while aiming at correcting vertebral body deformity.

During the minimally invasive BKP procedure, working tubes are inserted into the pedicle to create small pathways into the vertebral body, generally in a bilateral approach. Orthopaedic balloons are inserted and then inflated inside the vertebral body in an attempt to reduce the vertebral body height deformity. Inflation and removal of the balloons create a cavity in the vertebral body that is filled with viscous PMMA cement (Figure 1).

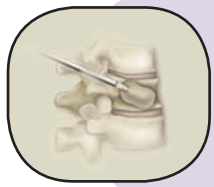
As patients can live longer with palliative therapy, there is a need to

1. 

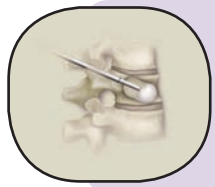
Cancer weakens your bones, which can cause the vertebrae in the spine to collapse. When this happens, it is called a spinal fracture or vertebral compression fracture (VCF).

2. 

Two small balloons are inserted and inflated in the fractured vertebra in an attempt to raise the collapsed bone and restore it back to its normal shape.

3. 

Balloons are then deflated and removed.

4. 

The cavities left by the balloons are filled with special cement to create an internal cast and stablise the fracture.

Figure 1. BKP procedure

effectively manage pain, disability and loss of health related QOL. There is a growing body of evidence that demonstrates the relative safety and effectiveness of BKP in the treatment of VCFs in patients with MM or spinal metastases from primary tumours.

Current Evidence for BKP for VCF in Patients With MM or Osteolytic Spinal Metastases

Current evidence for BKP for cancer related VCF includes one randomised controlled trial, two systematic reviews and at least 22 non-randomised clinical studies, which include more than 750 patients.

The CAFE Study

There has been one randomised clinical study comparing the safety and efficacy of BKP treatment with standard nonsurgical management in patients with cancer who have painful VCF.[11] The study, which included 134 patients with VCF who had various types of cancer such as breast, lung and prostate or MM, took place at 22 sites in the US, Europe, Australia and Canada. The patients were assessed for multiple outcomes relating to QOL, physical function and back pain, and the primary outcome was the change in back-specific function from baseline to 1 month between the groups, as measured by the RDQ score. All patients could receive analgesics, bed rest, bracing, physiotherapy, rehabilitation programmes, walking aids, radiation treatment, and other anti-tumour therapy at the discretion of treating physicians. Patients with concurrent osteoporosis or bone metastasis could also receive treatment with calcium, vitamin D supplements, and antiresorptive or anabolic agents as necessary.

There were statistically significant treatment differences across groups in the mean change from baseline scores in RDQ and PCS scores at months 1, 3 and 6 versus no statistically significant change for control patients. There were 81% of BKP patients that presented at least a two-point improvement in RDQ versus 28% of control patients (minimal clinically important difference or MCID; $p<0.0001$).

BKP patients experienced clinically and statistically significant improvement in back pain from baseline of -3.3 points ($p<0.0001$) at 1 month.

The BKP group also showed a clinically and statistically significant 8.4 point improvement ($p<0.0001$) in the SF-36 Physical Component Summary (measuring QOL weighted on physical abilities) at 1 month versus the control group. There was also a mean 11.1 point improvement ($p<0.0001$) in the SF-36 Mental Component Summary score (measuring QOL weighted on mental abilities) at 1 month versus control. These results are summarised in Table 1.

Medical adverse events were similar at 1 month between the two groups (26/70 for BKP versus 19/64 for the control). Most of these were back pain (4/70 for BKP and 5/64 for control) and symptomatic vertebral fracture (2/70 for BKP and 3/64 for control). One BKP patient had serious adverse events at 1 month (intraoperative non-Q-wave myocardial infarction with intermittent atrial fibrillation) related to anaesthesia that resolved. There was no difference in radiographical or clinical subsequent vertebral fractures between the two groups at 1 month. A subsequent vertebral fracture within 1 month of the index procedure observed in 1 BKP patient (with cement leakage to the adjacent disc) was a serious adverse event reported as related to the device.

A limitation of this study was that randomisation of treatment lasted for only 1 month. After the first month, patients were allowed to crossover from the control group to receive kyphoplasty, creating a non-randomised population for the long-term analysis. Of 134 randomised, 60 did not complete the entire 12 month study and many patients in the control group crossed over; however, almost 90% of patients completed the 1 month assessment. The number of dropouts was high but not unexpected for patients with cancer. In addition to the treatment effects observed up to 1 month, there were statistically significant treatment differences across groups in favour of BKP in terms of the mean change from baseline scores in RDQ and PCS scores at months 3 and 6. The improvement observed in functional status, quality of life and pain with BKP continued until the end of the study (12 months).

Outcomes	Measure	BKP	NSM (control)
Back pain	RDQ	Improved*†‡	No Change
QOL	Karnofsky		
	SF-36 PCS		
	SF-36 MCS	Improved*‡	
Activity	Activity days	Increased*‡	
	Bed rest days	Decreased*‡	
Pain	NRS	Decreased*†‡	
	Analgesic use	Decreased by 36%‡	Decreased by 12%

MCS=mental component; NRS=numeric rating scale; NSM=nonsurgical management; PCS= physical component; QOL=quality of life; RDQ = Roland Morris Disability Questionnaire.

*Statistically significant (p<0.001) improvement from baseline; †Clinically significant improvement from baseline (MCID); ‡Statistically significantly better than NSM.

Table 1. CAFE study outcomes at 1 month[11]

Given the limited improvement in the control group, this study indicated that BKP should be considered as an early treatment option for patients with cancer and symptomatic VCF.

Systematic Reviews

Two recent comprehensive systematic literature reviews have demonstrated the relative safety and effectiveness of BKP treatment in patients with cancer-related VCFs.[12, 13] These included electronic (PubMed, EMBASE, The Cochrane Library, Medtronic databases and websites for NIH and WHO) and manual (reference lists of existing reviews and meta-analyses) searches. There were no language restrictions and case studies that included 10 or more patients and retrospective and prospective studies were included.

Evidence on pain relief in patients undergoing BKP has been reported in a 2011 systematic review of 21 studies, including the CAFE study. Significant improvements for various pain measures (including back pain numeric rating score, visual analogue pain scale [VAS] and SF-36 bodily pain) were reported.[13]

Six studies reported impact on analgesic use. There was a significant reduction in the use of analgesics after BKP compared to baseline.

Function capacity (RDQ, Karnofsky performance status [KPS], SF-36, Oswestry Disability Index [ODI], Eastern Cooperative Oncology Group [ECOG] performance status and motion ability scores) was assessed in 14 studies and the initial rapid improvements with BKP were maintained during follow up (p<0.05 versus pre-operatively).

Quality of life was assessed in seven studies. The improved QOL following BKP was evident in the short term and was sustained in the longer term, up to 1 year follow up in patients with metastases from primary cancer and up to 5 years in patients with MM. These improvements were greater following BKP than when nonsurgical methods were used. An improved QOL and functioning prevents the functional and health risks of being bed ridden. In one study 68% of the patients were ambulatory at an average of 9 months after BKP.

Although height restoration and kyphotic correction are not the first priority in these patients, there was also significant height gain following BKP compared to pre-BKP values for posterior heights in two of 12 studies, as well as evidence that the vertebrae height gain was sustained up to 2 years after BKP.

BKP is minimally invasive and results in a shorter hospital stay than other more complex spinal surgeries, and can be performed in an outpatient setting. This was demonstrated by a maximum 4 days stay in hospital after BKP, with most patients released after 24 hours (71% of studies). Anaesthesia during BKP was general (13/17, 76%) or local plus sedation (4/17, 24%) and without complication.

In this review, BKP was found not to lead to increased mortality, and rates of major clinical complications were low. In seven studies, there were no procedure related deaths within 30 days of BKP reported, and in 18 of 20 studies (90%) no major complications were reported.

Cement leakage after BKP is a potential complication. The incidence of cement leakage varied in studies of patients with MM (0-26%), osteolytic metastases (0-18.6%) and in a mixed population (0-33%). Although cement leakage was reported in 20 out of 22 studies, in 16 of 20 studies, no cases of cement leakage with clinical implications occurred.

Overall, new vertebral fractures occurred in 0-47% of patients. In MM patients the range was 2-42%, and was believed to be likely related to disease progression rather than to surgical intervention. No new fractures occurred in one study, and only 8% were reported in a similar study of patients with bone metastases from primary tumour.

This supports earlier findings from a meta-analysis of non-randomised studies, where improvements with BKP in functional

Study	Patients (Level)	Multiple myeloma			
		VAS	SF-36	ODI	Follow up
		(pre-op; post-op)			
Astolfi 2009	30 (45)	8.65; 2.84*	-	-	5 years (p<0.005)
Dudeney 2002	18 (55)	-	23.2; 55.4*	-	7.4 months (p=0.0008)
Khanna 2008	56 (NR)	-	28.2; 48.0*	45.1-32.5 (last follow up)*	12.8 months (p<0.001)
Kose 2006	18 (22)	38.0; 12.1*	-	-	1 year (p<0.001)
Lane 2004	19 (46)	-	-	49.0; 32.6*	3 months (p<0.001)
Lieberman 2003	63 (264)	6.18; 2.84*	28.33; 47.56*	46.7; 30.33*	18 weeks (p<0.05)
Pflugmacher 2007	26 (59)	8.6; 2.4*	-	78.1; 37.3*	2 years (p<0.05)
Zou 2010	21 (43)	8.1; 3.6*	21.3; 44.7*	63.2; 37.1*	1 year (p<0.05)
Osteolytic metastasis					
Ashamalla 2009	26 (33)	8.6; 2.8*		-	1 day (p<0.0001)
Cardoso 2009	19 (24)	8.5; 2.6*		-	1 month (p<0.0001)
Eleraky 2011	14 (30)	79; 37*		-	1 year (p<0.001)
Gerszten 2009	11 (11)	8; 3 (last follow up)		-	7-44 months
Pflugmacher 2008	65 (99)	83; 33*		81; 39*	2 years (p<0.0001)
Qian 2011	48 (124)	7.4; 3.8*			2 years (p<0.001)
Sandri 2010	11 (11)	8.0; 1.8*		-	6 weeks (p<0.05)
Zhao 2008	33 (49)	8.1; 2.1*		--	6 months (p<0.01)
Mixed population					
Berenson 2011	134 (68)	7.3; 3.2*			1 month (p<0.05)
Dalbayrak 2010	31 (39)	7.2; 1.6*			Post-operative
Fourney 2003	22 (NR)	Improvement or Complete pain relief (80%), no change (7%)			4.5 months
Vrionis 2005	50 (128)	Improvement or Complete pain relief (96%)			9 months
*Reported as significant.					

Table 2. Systematic reviews: reported pain outcomes[11, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32]

capacity (ODI) from baseline were sustained for up to 2 years.[12] In addition, there were significant improvements in VAS postoperatively, which were sustained to the end of follow up at 1 or 2 years (three studies; standard mean difference [SMD]; 4.27, p<0.001). There was significant vertebral height gain following BKP compared to pre-BKP values for anterior and midline heights in two studies. In seven studies, no procedure-related deaths within 30 days of BKP were reported and the mean cement leakage rate was 5.8% (1.96-9.64).

Overall, these two systematic reviews demonstrated that BKP provided rapid and sustained pain relief, improved functional status, performance and QOL versus nonsurgical management.

Quality of evidence grading identified several gaps in the assessment of BKP for treatment of cancer related VCF.

Guidelines

A guideline system combining the Harrington's classification (neurological status and structural changes), Tokuhashi's prognostic scoring system, Tomita's spread of spinal metastasis and Kostuik's instability model has been developed for the management of metastatic spinal tumours.[33] Considerable and immediate relief of pain can be obtained by combining chemotherapy and a cement augmentation procedure (vertebroplasty or BKP). Augmentation is recommended for class II lytic lesions, all class III lesions, class IV lesions (Tokuhashi score <5) and class V lesions (Tokuhasi score >9 and Tomita M).

In addition, the International Myeloma Working Group (IMWG) published a consensus on the role of vertebral augmentation in multiple myeloma.[34] Primary indications for vertebral augmentation include: severe pain present (pain >7/10 on Visual Analogue Scale), collapse of one or more vertebra (VCF) and bone destruction (osteolytic/osteopenic) with high risk of collapse of one or more vertebra. Secondary indications are severe pain absent (pain ≤7/10 on VAS), significant loss of height and/or structural integrity or stability.

Conclusions

There is increasing evidence to support BKP for cancer related fractures of the spine, even in chronic malignant fractures. Provided that the pain is debilitating and correlates to clinical examination

Study	Patients (Level)	Multiple myeloma		
		ODI	SF-36	Follow up
		(pre-op; post-op)		
Astolfi 2009	30 (45)	87; 45*	23.0; 76.5*	5 years
Dudeney 2002	18 (55)	-	21.3; 50.6*	7.4 months (p=0.001)
Khanna 2006	56 (NR)	-	26.2; 44.2*	12.9 months
Lieberman 2003	63 (264)	-	24.5; 47.2*	1 year
Pflugmacher 2007	26 (59)	Significant functional improvement		2 years
Zou 2010	21 (43)	-	31.6; 47.2*	16 weeks
		Osteolytic metastasis		
		ECOG	**ODI**	**Follow up**
Ashamalla 2009	26 (33)	2.4; 2.0*	-	1 month (p<0.05)
Cardoso 2009	19 (24)	2.4; 2.0*	-	1 month (p<0.05)
Eleraky 2011	14 (30)	-	83; 33*	1 year (p<0.05)
Pflugmacher 2006	65 (99)	-	81; 35*	2 years (p<0.05)
Qian 2011	48 (124)	-	71.5; 31.7*	2 years (p<0.05)
		Mobility ability score		
Zhao 2008	33 (49)	3.4; 1.6*		6 months (p<0.05)
Mixed population				
		RDQ	**KPS**	**Follow up**
Berenson 2011	134 (68)	17.6; 9.1 (p<0.0001)	-8.4 vs. control*	1 month (p<0.05)
Vrionis 2005	50 (128)	65% of patients ambulatory		9 months (mean)
*Reported as significant.				

Table 3. Systematic reviews: functional capacity outcomes[11, 14, 15, 16, 19, 20, 21, 22, 23, 24, 26, 27, 29, 32]

and diagnostic work up, and that there is an absence of clinical spinal cord compression and overt instability. BKP in VCFs can provide rapid and sustained improvements in pain, functional status and overall QOL. The use of vertebral augmentation is recommended by guidelines in appropriate patients. However, more evidence is needed to confirm the results seen to date, to understand the role of vertebral augmentation in the prevention of spine related events, particularly delaying or avoiding neurological deterioration potentially leading to paralysis and to establish the impact on longer term functioning and offsetting of medical resources. In all cases, vertebral augmentation should only be carried out by experienced operators.

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Upcoming Congresses and Meetings

The 2012 Genes & Cancer Meeting

10 - 12 December 2012

Warwick, United Kingdom

The Genes and Cancer Series aims to highlight some of the year's most important themes in cancer biology, and the annual conference features an international line up of speakers, who will be covering a wide range of topics at the cutting edge of cancer research. There will be a particular focus upon the identification of the genetic lesions and signaling pathways/molecules that contribute to the ontogeny of cancer, and which are accessible to therapeutic intervention strategies.

2013 Society of Radiographers Annual Radiotherapy Conference

01 - 03 February 2013

Brighton, United Kingdom

The three-day Annual Radiotherapy Conference explores a wide range of areas within the field of radiotherapy, including safety in radiotherapy, radiotherapy trials and the national radiotherapy strategy. These topics are presented through plenary lectures, poster and oral presentations, student papers and question and answer sessions, which encourage debate and discussion.

4th International Conference on Innovative Approaches in Head and Neck Oncology

07 - 09 Feburary 2013

Barcelona, Spain

The European Society for Radiotherapy and Oncology (ESTRO), the European Head and Neck Society (EHNS) and the European Society for Medical Oncology (ESMO) have collaborated once again to host this biannual conference. The meeting will combine prestigious invited state of the art lectures on the latest innovative approaches, as well as proffered papers and poster presentations on new data in the field of head and neck oncology. The programme will also feature bypro and contra debates and interactive tumour board sessions, which will encourage audience participation. There will also be a special focus on the presentation of new data from practice changing randomised trials. Highlighted areas will include robotic and minimally invasive surgery, quality of life and supportive care and oncogenesis and HPV related cancers.

10th Anniversary of the APOS Annual Conference

14 - 16 February 2013

California, United States

The theme of the 10th APOS Annual Conference is 'From Psychosocial Oncology to Oncology Supportive Care Services: New Evidence, Standards and Models for Patient-centered Care.' It will feature a day of pre-conference workshops on subjects such as Body Image Changes and Disfigurement, Meaning-centered Psychotherapy in Cancer and Palliative Care, as well as plenary lectures, oral and poster sessions.

European Congress of Radiology

07 – 11 March 2013

Vienna, Austria

The ECR is the annual meeting of the European Society of Radiology (ESR). It is a trend-setting, dynamic and service-oriented congress, and is known as one of the most innovative meetings within the scientific community, embedded in a unique and inspiring ambience. Highlights include the new Horizons sessions, which aim to provide practitioners with an overview of new developments within cartilage imaging, imagining of the mind and MR/PET. Other sessions include state-of-the-art symposia on Haematological Malignancy and Imaging Impingement Syndromes, multidisciplinary sessions focused upon Carcinoma, workshops and special focus sessions on MRI and Imagining, as well as poster and oral presentations.

5th IMPAKT Breast Cancer Conference

02 - 04 May 2013

Brussels, Belgium

IMPAKT focuses specifically on translational research and new drug development, in an era where there is the potential to provide tailored treatment to biologically homogeneous groups of patients. IMPAKT provides the ideal environment to foster a dialogue between laboratory and clinical scientists, as well as representatives of the pharmaceutical industry. The congress is also important as it enables physicians to enhance their knowledge and improve their skills to use new technologies and integrate translational research components into clinical trials.

European Multidisciplinary Conference in Thoracic Oncology (EMCTO)

09 - 11 May 2013

Lugano, Switzerland

The European Multidisciplinary conference in Thoracic Oncology is organised in partnership between the European Society for Medical Oncology (ESMO), The European Society for Radiotherapy and Oncology (ESTRO),

the European Society of Thoracic Surgeons (ESTS) and the European Respiratory Society (ERS), and the European Thoracic Oncology Platfom (ETOP). These partners have created a programme that integrates perspectives from the different disciplines and demonstrates how the multidisciplinary team can combine knowledge for personalised treatment of the whole range of thoracic oncology tumours. In 2013 participants will find a mix of educational sessions and presentations on the latest scientific advances, as well as the opportunity to discuss the latest ideas and research from the field.

4th World Congress of the International Academy of Oral Oncology in 2013

15 - 18 May 2013

Rhodes Island, Greece

The International Academy of Oral Oncology brings together clinicians and scientists worldwide to combine their knowledge and expertise with regards to issues relating to etiopathogenesis, epidemiology, prevention and management of oral and perioral tumours and of oral disease in patients with malignancies. The theme of the 4th World Congress of the International Academy of Oral Oncology is 'From Genes to Clinical Care', and will feature symposiums, oral and poster presentations and panel discussions.

15th World Congress on Gastrointestinal Cancer

03 - 06 July 2013

Barcelona, Spain

The ESMO World Congress on Gastrointestinal Cancer is the world's leading forum for practicing clinicians and specialists in cancer research, and covers malignancies affecting every component of the gastrointestinal cancer, and the latest management options for common and uncommon tumours. The congress is built upon a multidisciplinary approach, which is provided in the presentation of cutting edge research by widely recognised experts, as well as presentations on selected controversial topics; meet the expert sessions, case discussions, and satellite symposia on specific topics. With a focus on personalised therapy, multidisciplinary management and unraveling molecular mechanisms, this event educates and updates the broad range of experts who participate in the treatment of gastrointestinal cancers, providing a clear overview for treatment.

45th Congress of the International Society of Pediatric Oncology (SIOP)

25 – 28 September 2013

Hong Kong, China

As the largest annual paediatric cancer meeting in the world, SIOP has developed into the premier forum to network and share knowledge on the research and treatment of all cancer types in children and young people. SIOP has over 800 members worldwide, including doctors, nurses, other healthcare professionals, scientist and researchers. Their aim is to improve and optimise cancer treatments throughout the world. The 45th Congress of the International Society of Paediatric Oncology is your opportunity to gain access to the latest research and advances in the field.

ECCO 17 - ESMO 38 - ESTRO 32 European Cancer Congress

27 September – 01 October 2013

Amsterdam, The Netherlands

The renowned biennial series of multidisciplinary European Cancer Congresses are recognised as the premier cancer meetings in Europe. 17th ECCO – 38th ESMO – 32nd ESTRO European Cancer Congress will continue positioning multidisciplinarity as the way to best improve the prevention, diagnosis, treatment and care of cancer patients. In addition to special joint symposia, which deal with topics that reflect the daily needs of oncology practitioners, leading experts in the field have been selected to share their latest research and provoke debate. The ECC 2013 promises to be an even stronger, pioneering programme for showcasing the latest developments in practise-changing studies of new and significant scientific importance.

33rd Congress of the European Society of Surgical Oncology

27 September - 01 October 2013

Amsterdam, The Netherlands

Esso 33 will take place at the European Cancer Congress in 2013, and will feature a very strong surgical oncological tract throughout the event's programme, which will highlight the pivotal role of surgery in the diagnosis, staging and curing of cancer. It will also reinforce the importance of a multidisciplinary approach to treatment and care in the 21st century. With nearly 18,000 oncology professionals in attendance, this event looks set to be one of the largest in Europe.

International Society of Geriatric Oncology Annual Meeting

24 – 26 October 2013

Copenhagen, Denmark

The SIOG Annual Meeting 2013 aims to address the ways in which the care of elderly patients with cancer can be improved around the world. Focusing on research, clinical practise, education and advocacy, the meeting will feature a range of different sessions including plenary lectures featuring key figures within the field, symposiums and poster and oral presentations.

9th European Breast Cancer Conference (EBCC-9)

19 – 21 March 2014

Glasgow, United Kingdom

Building on the successes of previous Conferences, the 9th European Breast Cancer Conference (EBCC-9) will draw an audience convening all stakeholders in the breast cancer field to contribute and engage in the must-have conversations and cross-talk. The exceptional standards which were set at EBCC-8 will be continued throughout the wide selection of keynote symposia, teaching lectures, clinical symposia and debate sessions. Additionally, a range of outstanding speakers will be presenting plenary lectures, and there will be the opportunity to talk to experts at a local and international level about breast cancer concerns.

EORTC EANO ESMO

Conference 2013

Trends in Central Nervous System Malignancies

22-23 MARCH 2013

PRAGUE, CZECH REPUBLIC

Third in the biennial series, the **EORTC-EANO-ESMO 2013** Conference is recognised as:

- Improving the neuro-oncology field
- Accelerating the translation of cutting edge discovery at the clinical level
- Advancing the management, treatment and care of patients with central nervous system tumours
- Further promoting international scientific cooperation, debate and exchange
- Providing a rigorous review of novel therapies, agents and combination strategies
- Revealing the very latest findings in basic and clinical research
- Adopting a multidisciplinary approach (neurosurgeons, neurologists, neuropathologists, medical oncologists, radiation oncologists)
- Facilitating interaction through a series of plenary sessions, workshops and breakout sessions

IMPORTANT DATES

Abstract submission opens: 11 December 2012

Deadline Abstract submission: 11 February 2013

Early Rate Registration closes: 11 January 2013

For further information and to view the Scientific Programme:
www.ecco-org.eu/EORTC_EANO_ESMO

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