TREATMENT STRATEGIES
ONCOLOGY

Volume 4 Issue 1

- Breast Cancer
- Castration-Resistant Prostate Cancer
- Colorectal Cancer
- Differentiated Thyroid Cancer
- Gastrointestinal Tumours
- Geriatric Oncology
- Head and Neck Cancer
- Sarcoma

Papers include...

Chemotherapy of the Recurrent/Metastatic Squamous Head and Neck Cancer – Past, Present and Future
Viktor Grünwald and Philipp Ivanyi

HER2 in Colorectal Cancer: One Marker Useful for Multiple Targeted Therapies
Milo Frattini, Vittoria Martin, Lorenza Landi, Jessica Salvini and Federico Cappuzzo

Primitive Synovial Sarcoma of the Kidney
Roberto Iacovelli, Valentina Orlando, Ilaria Attili, Simone Scagnoli, Martina Chirra and Enrico Cortesi

Recent Advances in the Treatment for Differentiated Thyroid Carcinoma
Romana T. Netea-Maier and Jan W. Smit

ECCO17
ESMO38
ESTRO32

Includes a review of the European Cancer Congress 2013

For men with metastatic prostate cancer, a major threat lives in their bones.

A SIGNIFICANT THREAT IN mCRPC

Bone metastases may be profoundly debilitating, leading to pain, pathological fractures, and spinal cord compression.[1] In fact, over 70% of patients with bone metastases experience bone pain.[1,2] In addition, treatment of skeletal-related events can also more than double medical costs.[3]

Bone metastases—and associated skeletal-related events—are associated with death in patients with mCRPC.[4]

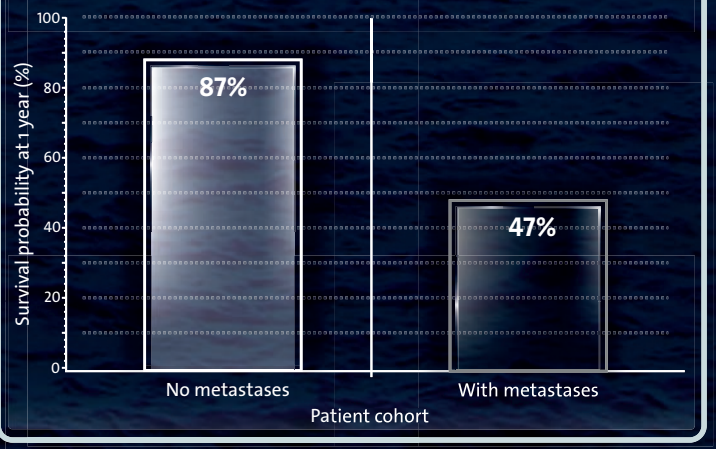
In a large cohort study of patients with an initial diagnosis of prostate cancer, mortality rate at year 1 in the subgroup of patients with bone metastases was more than 4 times the rate in the subgroup of patients with no bone metastases.[5]

- At year 1, survival fell from 87% in patients without bone metastases to just 47% in those with bone metastases[5]

Prostate cancer tumor cells are uniquely suited to proliferate within the bone microenvironment.[6] As a result, bone represents the earliest and most common site of prostate cancer metastasis.[7] In fact, 84% to 92% of patients with mCRPC show evidence of bone metastases.[8-11]

~90% OF PATIENTS WITH mCRPC SHOW EVIDENCE OF BONE METASTASES[8-11]

ONE-YEAR SURVIVAL OF PROSTATE CANCER PATIENTS[5a]



Adapted from Nørgaard et al.

[a]Of the 23,087 patients with initial diagnosis of prostate cancer, 22,404 had no bone metastases and 569 presented with bone metastases.

CONFRONTING THE THREAT

Extending survival in mCRPC patients remains a significant challenge. Recognizing the impact of bone metastases on mortality is an important step towards improving treatment of patients with mCRPC.[12]

For more information visit **www.crpcmets.com**

mCRPC: metastatic castration-resistant prostate cancer.

References: 1. Saad F, Gleason DM, Murray R, et al for the Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 2002;94(19):1458-1468. **2.** Saad F, Eastham J. Zoledronic acid improves clinical outcomes when administered before onset of bone pain in patients with prostate cancer. *Urology*. 2010;76(5):1175-1181. **3.** Groot MT, Boeken Kruger CGG, Pelger RCM, Uyl-de Groot CA. Costs of prostate cancer, metastatic to the bone, in the Netherlands. *Eur Urol*. 2003;43(3):226-232. **4.** Sathiakumar N, Delzell E, Morrisey MA, et al. Mortality following bone metastasis and skeletal-related events among men with prostate cancer: a population-based analysis of US Medicare beneficiaries, 1999-2006. *Prostate Cancer Prostatic Dis*. 2011;14(2):177-183. **5.** Nørgaard M, Jensen AØ, Jacobsen JB, Cetin K, Fryzek JP, Sørensen HT. Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007). *J Urol*. 2010;184(1):162-167. **6.** Efstathiou E, Logothetis CJ. A new therapy paradigm for prostate cancer founded on clinical observations. *Clin Cancer Res*. 2010;16(4):1100-1107. **7.** Bubendorf L, Schöpfer A, Wagner U, et al. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum Pathol*. 2000;31(5):578-583. **8.** Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy (supplemental appendix). *N Engl J Med*. 2012;367(13):1187-1197. http://www.nejm.org/doi/suppl/10.1056/NEJMoa1207506/suppl_file/nejmoa1207506_appendix.pdf. **9.** Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study [published correction appears in *Lancet Oncol*. 2012;13(11):e464]. *Lancet Oncol*. 2012;13(10):983-992. **10.** Tannock IF, de Wit R, Berry, WR, et al; TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512. **11.** Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004;351 (15):1513-1520. **12.** Aljumaily R, Mathew P. Optimal management of bone metastases in prostate cancer. *Curr Oncol Rep*. 2011;13(3):222-230.

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TREATMENT STRATEGIES - ONCOLOGY

TREATMENT STRATEGIES - ONCOLOGY - November 2013

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Published by The Cambridge Research Centre
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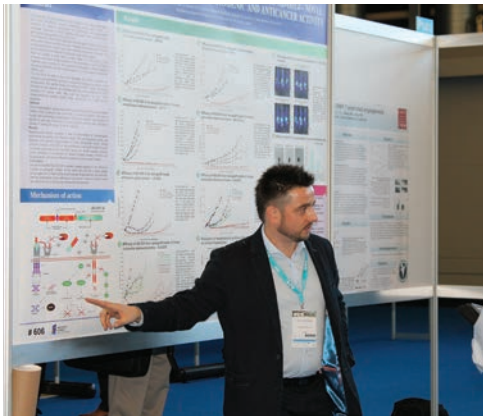
www.cambridgeresearchcentre.co.uk
T: +44 (0) 20 7953 8490

Printed by Printech (Europe) Limited



Welcome...

I am delighted to welcome you to the latest edition of *Treatment Strategies - Oncology*. In this edition we bring you a range of informative articles, as well as an in-depth review of The European Cancer Congress, which was held in Amsterdam this past September. The theme of this year's congress was 'Reinforcing Multidisciplinarity', and attendees were treated to a full and varied programme which promoted education and debate. Our review will provide you with the breaking news, research highlights and the best of the symposia, as well as a number of poster synopses. We really feel that this review will provide you with the highlights of the congress.

This edition also features a number of interesting and informative papers on subjects such as breast cancer, differentiated thyroid cancer, head and neck cancer and sarcoma. With these papers we aim to bring you new insights into the latest treatment strategies for a number of oncological conditions, and we hope that you enjoy the carefully chosen content.

2013 was a fantastic year for The Cambridge Research Centre, with some exciting changes including Treatment Strategies TV, where you can find footage from all of the most important scientific conferences, as well as interviews, symposia proceedings, roundtable events and much more. We also launched our range of interactive eBooks on iBooks, which is a great new way to read and download our content to your devices. We also launched our new Facebook page, where you can find all of the latest news about new projects and upcoming releases, and the team are also all active on Twitter and LinkedIn.

We hope that you enjoy this edition of *Treatment Strategies – Oncology*, and please do share your thoughts with us on this issue as well as what you would like to see in our next edition, which will feature a review of ESMO 2014.

Nigel Lloyd, Managing Director

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

8th World Research Congress of the European Association for Palliative Care

EAPC ONLUS

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to showcase and discuss cutting edge research within the field.

Will you join us?

Online registration for the congress is now open.
Early bird registration deadline: 1 March 2014.

www.eapcnet.eu/research2014

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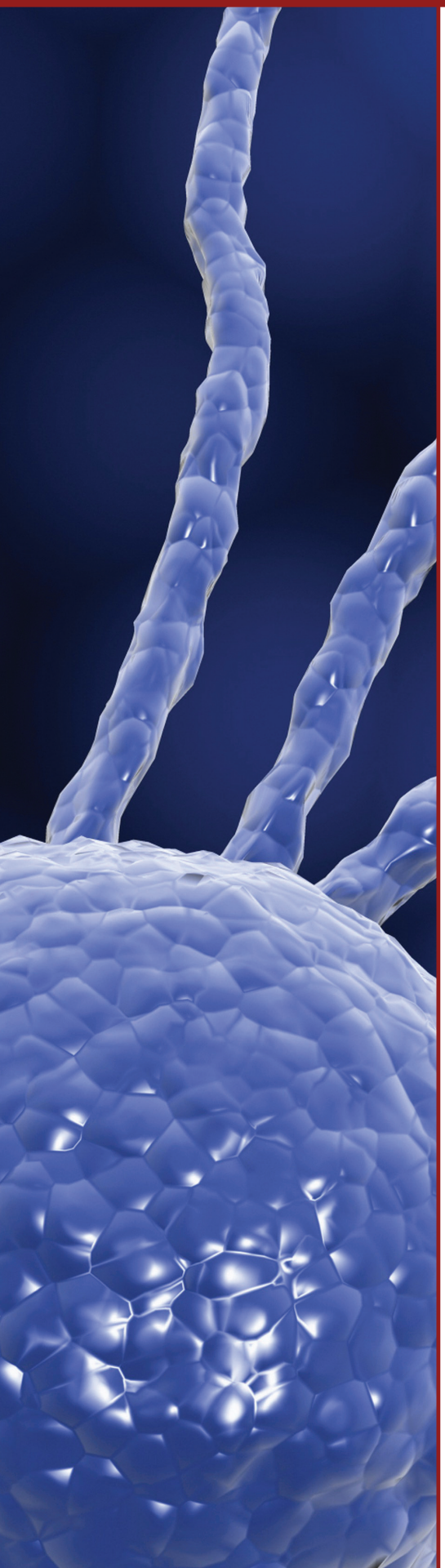

Some measure survival benefit in months.

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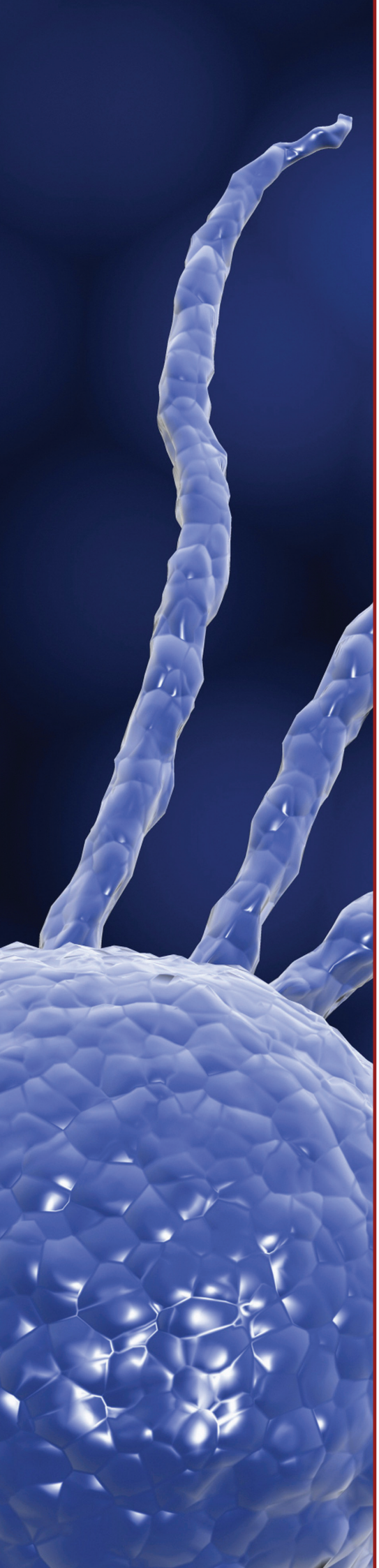

EDITORIAL ADVISORY PANEL - ONCOLOGY

Foreword

Ahmad Awada and **Philippe Aftimos**
Medical Oncology Clinic, Institut Jules Bordet – Université Libre de Bruxelles

Welcome to the latest issue of T*reatment Strategies – Oncology*. In this edition we will bring you an in-depth review of the European Cancer Congress, which includes all of the breaking news, awards, research and products, as well as news from important symposia proceedings and poster synopses. As oncology is such a vast and important area of medicine, the show provoked much discussion and debate, and we aim to bring you all of the highlights from the show.

Indeed, oncology is a rapidly moving field. In this edition of *Treatment Strategies – Oncology*, in addition to the review of ECC as detailed above, several interesting papers tackle a large spectrum of oncology topics, ranging from pathology to geriatric oncology and encompassing rare tumours. Histology is essential for the diagnosis of cancer and is also fundamental in determining prognostic and predictive markers. As an example, lobular breast cancer is less chemo-sensitive than the ductal subtype, and outcome is possibly better with upfront aromatase inhibitors in the early breast cancer setting. The expression and the quality assessment of predictive molecular markers are of the utmost importance for the therapeutic success of new biological agents (ALK translocation and the efficacy of crizotinib in NSCLC, HER-2 amplification and the efficacy of trastuzumab and T-DM1). In fact, the absence of HER-2/neu amplification in breast cancer is a marker of resistance to T-DM1 since trastuzumab cannot transport the cytotoxic component maytansine to cancer cells expression HER-2. If one predictive marker (K-RAS) could predict resistance to EGFR monoclonal antibodies in colorectal cancers, no predictive marker(s) has been able so far to predict full sensitivity to these agents. Consequently authors are looking into new molecular technologies such as gene and micro RNA signatures to answer this issue.

There are several solid tumours where only one line of chemotherapy (mainly based on platinum agents) is considered standard of care. Examples of such tumours are head & neck, oesophageal, gallbladder, bladder, cervix and anal cancers. There is an unmet need of further options based on new cytotoxics or biological agents. In this edition, temsirolimus seems to be active in refractory head and neck cancers. This group of tumours should be considered primarily for molecular screening programs of new anticancer agents.

The therapeutic management of rare tumours or histologies is challenging. Moreover, the incidence of this group of tumours is increasing with the ongoing cancer genes sequencing programmes subtyping common tumours into small groups of tumours with specific gene abnormalities. New cytotoxics and mainly new selective biological agents are considered the backbone of therapeutic strategies.

Geriatric oncology is advancing mainly in terms of evaluation tools. The current challenge is the introduction of these tools in the therapeutic management of older patients. Finally, improving the therapeutic index of therapies (increases in efficacy and/or decreases in side-effects) as well as improving the quality of life of patients are important topics in oncology. The development of subcutaneous formulation of trastuzumab is an example where the administration of an agent which is usually administered intravenously for a long period of time and is clearly facilitated.

We hope that you enjoy this edition of *Treatment Strategies - Oncology* and the content that has been included.

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Stivarga® is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine based chemotherapy, an anti VEGF therapy and an anti EGFR therapy

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- Reduced risk of disease progression[1,2]
- Increased disease control rate[1,2]

CORRECT data indicate that STIVARGA has a predictable toxicity profile. The majority of AEs were Grade 1 or 2. The most common Grade 3 or higher AEs were HFSR, fatigue, diarrhea, hypertension, and rash/desquamation[2]

References: 1. Bayer Pharma AG. STIVARGA (regorafenib) Summary of Product Characteristics 2013. 2. Grothey A, et al. Lancet. 2013;381(9863):303-12. ▼This medicinal product is subject to additional monitoring. **Stivarga 40 mg film-coated tablets** (Refer to full SmPC before prescribing.) **Composition:** *Active ingredient*: 40 mg regorafenib. *Excipients:* Cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone (K-25), silica (colloidal anhydrous), iron oxide red (E172), iron oxide yellow (E172), lecithin (derived from soya), macrogol 3350, polyvinyl alcohol (partly hydrolysed), talc, titanium dioxide (E171). **Indication:** Treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine based chemotherapy, an anti VEGF therapy and an anti EGFR therapy **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Warnings and Precautions:** It is recommended to perform liver function tests before initiation of treatment and monitor closely (at least every 2 weeks) during the first 2 months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome. Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment. Stivarga is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). When prescribing in patients with KRAS mutant tumours, physicians are recommended to carefully evaluate benefits and risks. Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding. Permanent discontinuation should be considered in the event of severe bleeding. Patients with a history of ischemic heart disease should be monitored for clinical signs and symptoms of myocardial ischemia. In patients who develop cardiac ischemia and/or infarction, interruption of Stivarga is recommended until resolution. The decision to restart Stivarga therapy should be based on careful consideration of the potential benefits/risks of the individual patient. Stivarga should be permanently discontinued if there is no resolution. In patients developing posterior reversible encephalopathy syndrome (PRES), discontinuation of Stivarga, along with control of hypertension and supportive medical management of other symptoms is recommended. Discontinuation of Stivarga is recommended in patients developing gastrointestinal perforation or fistula. Blood pressure should be controlled prior to initiation and during treatment and it is recommended to treat hypertension. In cases of severe or persistent hypertension despite adequate medical management, treatment should be temporarily interrupted and/or the dose reduced. In case of hypertensive crisis, treatment should be discontinued. For patients undergoing major surgical procedures it is recommended to interrupt treatment temporary for precautionary reasons, and to resume treatment based on clinical judgment of adequate wound healing. Management of hand-foot skin reaction (HFSR) may include the use of keratolytic creams and moisturizing creams for symptomatic relief. Dose reduction and/or temporary interruption, or, in severe or persistent cases, permanent discontinuation of Stivarga should be considered. It is recommended to monitor biochemical and metabolic parameters during treatment and to institute replacement therapy if required. Dose interruptions or reduction, or permanent discontinuation should be considered in case of persistent or recurrent significant abnormalities. 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European Cancer Congress (ECC) 2013

27 September - 1 October, Amsterdam

Annual Congress of the European Cancer Organisation

INSIDE...

The Congress

The Exhibition

Sara Taheri, *Treatment Strategies*, is delighted to bring you our review of the European Cancer Congress (ECC) 2013. The review features breaking news, awards, synopses of a series of posters presented at the event, together with symposia proceedings from the congress. The review is then followed by papers and articles which give a brief insight from a number of sessions highlighting findings that will have a direct impact upon clinical practice.

The European Society for Medical Oncology (ESMO) is the leading European professional organisation, committed to advancing the specialty of medical oncology and promoting a multidisciplinary approach to cancer treatment and care.

The 17th ECCO - 38th ESMO - 32nd European Cancer Congress ESTRO is organised in cooperation with ESSO 33, EACR, EONS and SIOPE. The European Cancer Congresses (ECC) are unique in Europe, offering an excellent multidisciplinary and multiprofessional educational opportunity in oncology and encouraging participation by all cancer specialities.

Held in the Amsterdam Congress Centre from the 27 September to 1 October, ECCO gathered the largest multi-disciplinary platform in Europe for cancer research, treatments and care geared toward patients' benefit.

The conference covered a wide spectrum of diagnostics, medicines and devices through the most advanced scientific programmes. So many professionals, experts in their fields, stakeholders and patients groups networked, interacted, and worked together to optimise cancer patients outcomes across Europe. The work and combined efforts of ECCO conferences present a unified voice for oncology professionals to the EU and ensure that oncology activities and funding remain at the top of EU agenda.

ECCO is a unique opportunity to hear directly from the leaders in the fields, discuss with papers for different specialities or countries, and share latest updates.

ECC 2013 was a truly multidisciplinary collaboration between 3 major groups — ECCO, ESMO and ESTRO. The meeting was held in Amsterdam from September 27 to October 1. Among the conference

WWW.ECCAMSTERDAM2013.ECCO-ORG.EU

highlights were presentations on:

- Turning advanced melanoma into a chronic disease with ipilimumab
- A new immunotherapeutic "game changer" in nonsmall-cell lung cancer
- The promise of genetic profiling for cancers of unknown origin
- Improving survival in advanced ovarian cancer with cediranib
- T-DM1 in heavily pretreated advanced breast cancer
- A State of Oncology report calling for radical solutions to address global disparities

The ECC 2013 Scientific Programme presented cutting-edge advances and expertise in scientific and clinical research, patient management, and practices through scientific and educational symposiums, special sessions, instructional conferences, workshops, discussions, etc.

"ECCO exists to uphold the right of all European cancer patients to the best possible treatment and care. That is why all those involved in ECCO are committed to connecting all stakeholders who share a vision toward advancing cancer research, prevention, treatment and care." says Professor Cornelius van de Velde, Chairman of ECCO.

In many ways, ECCO's forthcoming biennial congress in Amsterdam later this month is maintaining continuity with the success of the last meeting held in Stockholm two years ago. In Stockholm the bringing together of multidisciplinary teams on the panels of the meeting meant that experts in the entire field present had the opportunity to hear and understand the feedback and input from other experts in associated fields involved in patient treatment.

Before Stockholm there was concern as to whether bringing together such teams could really reflect what was happening on the ground for patients and care givers and benefit the treatment for patients by these multidisciplinary team. The success of Stockholm has emboldened ECCO's current President to enlarge and advance this approach. The congress in Amsterdam will therefore continue the theme and attempt to involve even more disciplines in these panels and processes.

Maybe we are seeing the first signs of a truly holistic approach to treating a patient that will naturally combine and blend with the growing emphasis on personalised medicine.

Amsterdam

This year, the congress was held in Amsterdam, the capital city of the Netherlands. Returning now in 2013 for the fifth time after 13 years following congresses in 1976, 1991, 1995 and 2000.

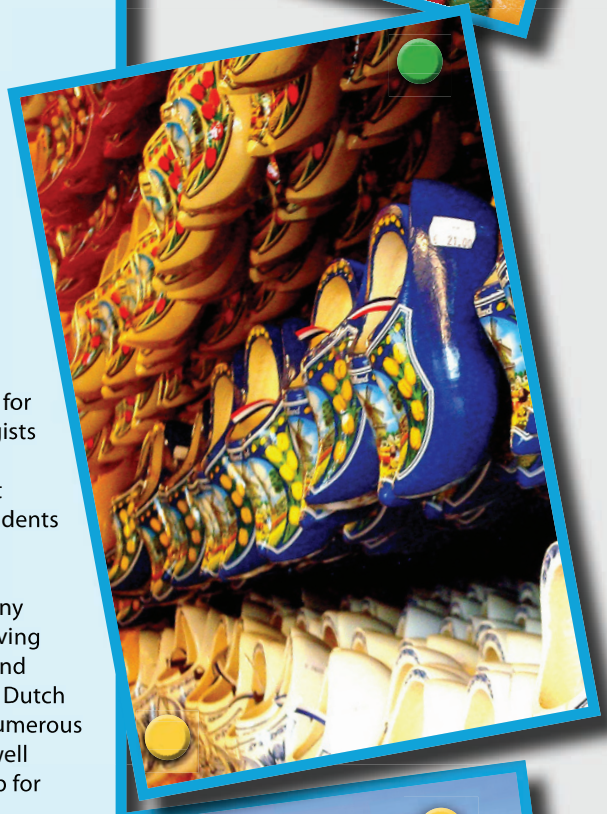
Amsterdam was an ideal location for this congress, with the huge airport of Schiphol close to the RAI congress centre, this venue was well placed to accommodate the 30,000 attendees.

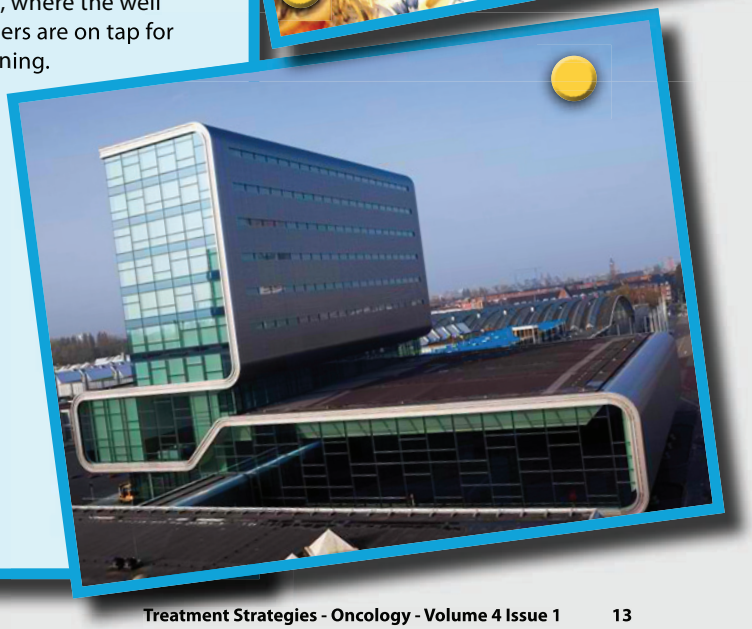
The congress centre is within easy reach of the city centre and its cultural and social attractions. The congress centre is just 5 kilometres away from the central Dam square with its Royal Palace.

Needless to say, Amsterdam has three world famous museums which have just reopened after extensive renovations: the Rijksmuseum, with its numerous paintings by the Dutch and flemish masters Rembrandt, Vermeer, hals and Rubens; the Stedelijk Museum for modern art; and the Van Gogh museum with the works of this Dutch impressionist exclusively.

For music, the Concertgebouw, one of the finest concert halls in the world and located in the museum quarter, sets the stage for a concert by 80 Dutch cardiologists Sunday 1 September at 20:00 in support of the CRASH project (Resuscitation Course for All Students in Holland).

Amsterdam's city centre has many small and larger restaurants serving typical Dutch food (often fish) and Asian products from the former Dutch colonies. Drinks are served in numerous Dutch brown pubs, where the well known national beers are on tap for drinks as well as dining.





Results of Lucanix® Phase III Therapeutic Vaccine Trial for Maintenance Therapy in Non-small Cell Lung Cancer

NovaRx Corporation presented the results from the randomised Phase III trial of Lucanix® (belagenpumatucel-L).

The primary endpoint of improving overall survival in 532 patients was not met. However, in the predefined subgroup of 305 stages IIIB/IV patients enrolled within 12 weeks of the completion of frontline chemotherapy, a median survival of 20.7 months was observed for Lucanix compared to 13.4 months for the control (HR 0.75). In a predefined subgroup of these patients with squamous cell carcinoma a median survival of 20.7 months was observed for Lucanix compared to 12.3 months for the control (HR 0.58). In another predefined subgroup of these patients who received radiation therapy prior to enrollment a median survival of 40.1 months was observed for Lucanix compared to 10.3 months for the control (HR 0.45). The endpoint was not met due to patients enrolled more than 12 weeks following the completion of chemotherapy.

Each year lung cancer causes approximately 160,000 deaths in the USA and close to two million deaths worldwide, more than the next four most lethal cancers combined.

Lucanix represents a new class of tumour vaccines designed to use allogeneic whole tumour cells to stimulate the patient's own immune system to attack the patient's tumour. The cells in Lucanix have been modified to block production of transforming growth factor beta (TGF-B), which is one of the primary methods cancers use to hide from the immune system. Blocking TGF-B allows the vaccine to initiate a strong immune response, resulting in long-term clinical benefit with minimal toxicity.

NovaRx is a private biotechnology company headquartered in San Diego. Using its TGF-B-blocking platform technology, NovaRx is also developing a universal tumour cell vaccine that targets all cancers and may be used therapeutically or prophylactically.

Nintedanib Data Shows Extended Overall Survival in Adenocarcinoma Patients

Boehringer Ingelhiem's oncology business continues to build up steam with new study data that demonstrates its investigational drug nintedanib is able to extend survival in a specific group of lung cancer patients.

Data from the LUME-Lung 1 study was presented at the European Cancer Congress in Amsterdam and showed that in patients who have advanced non-small cell lung cancer (NSCLC) with adenocarcinoma – cancer developed from the cells that produce mucus in the lining of the airways – nintedanib can help extend overall survival beyond one year after prior first-line chemotherapy. LUME-Lung 1 involved 1,314 patients NSCLC patients randomised to receive nintedanib and the chemotherapy docetaxel or placebo plus docetaxel.

Results demonstrated that the patients in the placebo arm had an increase in median overall survival of 10.3 months after patients failed first-line chemotherapy compared to the nintedanib arm, which saw an increase of 12.6 months.

In addition, the study showed that in adenocarcinoma patients who failed first-line chemotherapy within nine months, nintedanib had an even superior overall survival benefit compared to placebo. The results build on data presented by Boehringer at the American Society of Clinical Oncology (ASCO) meeting in Chicago in June 2013, which showed that nintedanib was unable to improve overall survival for the entire NSCLC population, but showed promise in those patients with adenocarcinoma.

The cancer is the most common of NSCLC – accounting for around 40 per cent of cases. Next is squamous cell carcinomas, which make up 25 to 30 per cent, while other types, including large cell carcinoma, make up the rest.

Boehringer is currently preparing regulatory submissions around the globe for nintedanib, putting it on course to be the company's second approved oncology drug.

The first was afatanib, a personalised treatment intended for patients with the epidermal growth factor receptor (EGFR) gene mutation. It was approved as a treatment for NSCLC in Europe earlier this month under the name Giotrif and in the US in July under the name Gilotrif.

Initial Phase 1 Clinical Data for TSR-011

TESARO, Inc., an oncology-focused biopharmaceutical company, presented initial data from a Phase 1 trial of TSR-011 today at the European Cancer Congress in Amsterdam. TSR-011 has been identified as a potent inhibitor of both anaplastic lymphoma kinase (ALK) and tropomyosin-related kinases (TRK). Preliminary clinical activity has been observed in this study in one papillary thyroid carcinoma patient and one pancreatic cancer patient without ALK expression, and in three patients with ALK-positive non-small cell lung cancer (NCSLC) who progressed following prior treatment with crizotinib.

Of the three ALK-positive NSCLC patients who progressed on prior crizotinib treatment, one achieved a RECIST partial response after four weeks of treatment with TSR-011; one, with disease not evaluable by RECIST criteria, achieved an investigator-assessed partial response; and one has stable disease. Each of these three patients remains on study today. In addition, one patient with papillary thyroid carcinoma and one patient with pancreatic cancer each have long term stable disease following several cycles of TSR-011 treatment. Preliminary results after eight weeks of treatment with TSR-011 demonstrated disease control (partial responses plus stable disease) in 11 of 17 (65%) evaluable patients treated with TSR-011.

"We are very pleased with the emerging profile of TSR-011, including the adverse event profile and early demonstration of clinical activity," said Dr. Mary Lynne Hedley, President of TESARO. "We remain on track to move into Phase 2a by the end of this year, which will allow us to further evaluate the benefit/risk profile of TSR-011 in patients with cancers that are ALK-positive or have TRK rearrangements."

Pharmacokinetic data demonstrated rapid absorption, predictable, dose proportional plasma concentrations following oral administration and an elimination half-life of 12 to 24 hours. TSR-011 was well tolerated at therapeutic dose levels, and no drug related Grade 4 or Grade 5 adverse events have been observed to date. The most frequently occurring dose limiting toxicities included ECG changes and dysaethesia, both of which were reversible.

Phase 2 Dose Selection and Cohort Expansion Into Patients With ALK-Positive or TRK-Mutated Tumours Anticipated to Occur by Year End.

Genentech Presents Late Breaking News

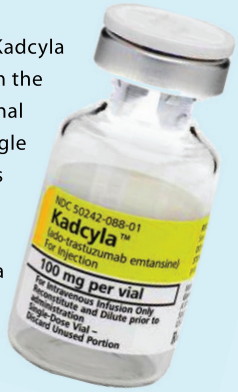
Genentech, announced that Kadcyla® (ado-trastuzumab emtansine) significantly extended the time people with advanced HER2-positive breast cancer (metastatic and unresectable locally advanced/recurrent) lived without their disease worsening (progression-free survival [PFS], a co-primary endpoint) compared to people who received a treatment of their physician's choice in an open-label Phase III study called TH3RESA. The data showed the risk of disease worsening or death was reduced by 47 percent for people who received Kadcyla (HR=0.528, p<0.0001). Data for overall survival, the other co-primary endpoint, are not yet mature. No new safety signals were observed with Kadcyla.

The study enrolled people with advanced HER2-positive breast cancer who had progressed despite prior treatment with at least two HER2-targeted medicines. It randomised people to receive either treatment with Kadcyla or a treatment of their physician's choice. Eighty percent of people treated with physician's choice received a regimen containing Herceptin® (trastuzumab).

"The TH3RESA study is the second large Phase III study in which Kadcyla has improved the amount of time patients with an advanced form of HER2-positive breast cancer lived without their tumour growing," said Hal Barron, M.D., chief medical officer and head, Global Product Development. "We are pleased that the data from multiple clinical trials reinforces Kadcyla's benefit for people with this aggressive disease."

The late-breaking TH3RESA data was presented at the European Cancer Congress (ECC), by Dr. Hans Wildiers, University Hospital Leuven, Gasthuisberg, Belgium and was also part of the official press program.

In February 2013, Kadcyla was approved by the U.S. Food and Drug Administration for the treatment of people with HER2-positive metastatic breast cancer who have received prior treatment with Herceptin and a taxane chemotherapy. Kadcyla recently received a positive opinion from the European Union's Committee for Medicinal Products for Human Use (CHMP) as a single agent for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received Herceptin and a taxane, separately or in combination. A European Commission decision on EU marketing approval is expected by the end of the year.



Phase 1b Trial of PEGPH20

Halozyme Therapeutics, Inc. announced mature patient progression free survival (PFS) and ongoing overall survival (OS) data from a Phase 1b trial of PEGPH20 (PEGylated Recombinant Human Hyaluronidase) in combination with gemcitabine for the treatment of patients with stage IV metastatic pancreatic cancer. In the trial, both PFS and OS data suggest a potential clinical benefit of using PEGPH20 with gemcitabine in patients with high levels of tumour-associated hyaluronan (HA). These results were presented in a poster session during the congress and early response rates from this trial were previously presented at the 2013 American Society of Clinical Oncology (ASCO) Annual meeting in June 2013.

The accumulation of HA, a protective matrix that surrounds many solid tumours, has been shown to be an indicator of poor patient prognosis and may accelerate disease progression. In this single arm study, all patients received PEGPH20 in combination with gemcitabine. The primary objective was to determine the recommended phase 2 dose. Exploratory analysis evaluated PFS and OS in a subset of patients with available biopsy samples and HA scores. In patients with high levels of tumour HA (n=6), PFS was 219 days compared to 108 days for patients with low levels of tumour HA (n=11), while OS in the high HA group was 529 days compared to 174 days for the low HA group. OS data is still not mature for the high HA group. With respect to the intent to treat population irrespective of HA status (n=24), PFS was 154 days and OS was 200 days.

"PEGPH20 has been shown in animal studies to deplete HA from tumours and improve perfusion and drug delivery to the tumour bed. The data from this trial suggest that similar processes may be occurring in patients as well and that patients with high levels of HA may derive the most treatment benefit from PEGPH20 combination therapy," stated Sunil R. Hingorani, M.D., Ph.D., Associate Member of the Clinical Research and Public Health Divisions at Fred Hutchinson Cancer Research Center and lead investigator for this study. "Pancreatic cancer is a devastating disease, and these data provide intriguing evidence for a new treatment paradigm. We look forward to the results for PEGPH20 in large randomised Phase 2 trials with the most active chemotherapy regimens available to definitively establish the potential benefit of this strategy and correlation with HA status."

Analysis of Long Term Survival with Ipilimumab

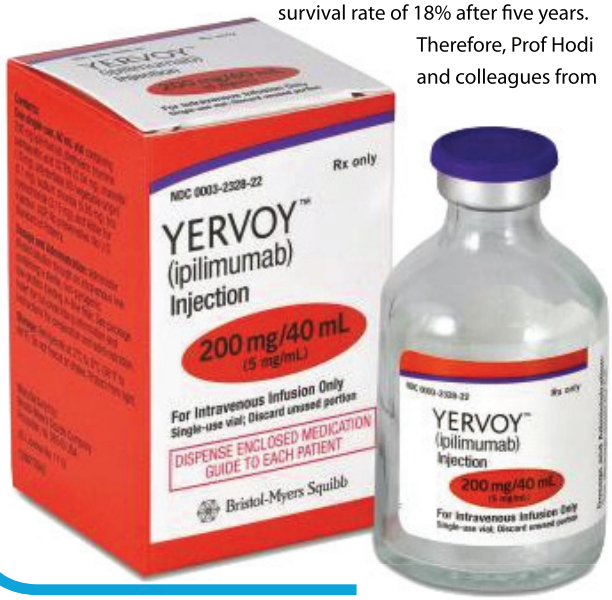
Patients with advanced melanoma, who have been treated with the monoclonal antibody, ipilimumab, can survive for up to ten years, according to the largest analysis of overall survival for these patients, presented at the 2013 ECC.

Professor Stephen Hodi (MD), Assistant Professor of Medicine at the Dana-Farber Cancer Institute (Boston, USA), told the congress: "Our findings demonstrate that there is a plateau in overall survival, which begins around the third year and extends through to the tenth year.

"These results are important to healthcare providers and patients with advanced melanoma since they provide a perspective on long-term survival for ipilimumab patients who are alive after three years of treatment. Our data, which represent the longest follow-up of the largest numbers of patients on any globally approved melanoma therapy, will provide a benchmark for future medicines for advanced melanoma."

Ipilimumab is a human monoclonal antibody that activates the immune system to fight melanoma skin cancer by targeting a protein receptor called Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4). In melanoma, CTLA-4 is inhibited from recognising and destroying cancer cells, but ipilimumab turns off the inhibitory mechanism, enabling CTLA-4 to continue killing the cancer cells.

It is already known that some patients treated with the drug survive for long periods, with one phase III clinical trial showing an overall survival rate of 18% after five years. Therefore, Prof Hodi and colleagues from Germany, France and the USA collected data on 1861 patients in 12 prospective and retrospective studies to provide a more precise estimate of ipilimumab's effect on long-term survival. In addition, they analysed data from a further 2985 patients who had been treated with the drug but were not part of any clinical trial, giving the researchers data on a total of 4846 patients.



The analysis of the 1861 patients showed that the median overall survival was 11.4 months (11.4 being the middle number separating the higher half of the patient survival time from the lower half). "Among these patients, 254 patients (22%) were still alive after three years. There were no deaths among patients who survived beyond seven years, at which time the overall survival rate was 17%. The longest overall survival follow-up in the database is 9.9 years," said Prof Hodi.

"The plateau, which started at three years and continued through to ten years, was observed regardless of dose (3 or 10 mg/kg), whether the patients had received previous treatment or not, and whether or not they had been kept on a maintenance dose of the drug. However, as this was not a randomised comparison, one cannot draw direct conclusions on differences between the doses or the populations."

When data from the total 4846 patients were analysed, the median overall survival was 9.5 months, with a plateau in overall survival starting around three years for 21% of the patients. "This slightly lower survival rate was because there were limited and incomplete data on overall survival, and patients given ipilimumab through the extended access programme tended to be more ill and with more advanced disease," explained Prof Hodi.

He concluded: "The limitation of this study is that it is a pooled analysis from phase II, phase III and observational data and not from a single randomised, controlled study. However, these results are consistent with our findings from randomised clinical trials and confirm the durability of the plateau in overall survival, previously shown to extend to at least five years but now shown to extend up to ten years."

Encouraging Patient Responses

In their presentation at the European Cancer Congress 2013, Roche announced encouraging patient responses in a trial for an experimental lung cancer drug. The Phase I clinical trial involves 85 patients, all former smokers, with locally advanced or metastatic non-small cell lung cancer; all of the patients had previously been treated, with more than half having received at least three prior systemic therapies.

The investigational medicine, known as anti-PDL1 antibody MPDL3280A, is designed to make cancer cells more vulnerable by interfering with a protein called PD-L1.

The protein called PD-L1 (Programmed Death-Ligand 1) is expressed in tumours. Scientists believe it plays a key role in allowing cancer to spread because it transmits an inhibitory signal to the immune system and so suppresses it. Scientists engineered MPDL3280A, which is a tumour immunotherapy drug, to target the ligand PD-L1 as a way to allow the immune system to effectively do its job. In general, tumour or cancer immunotherapy works by stimulating the immune system to recognise and attack the malignant cells.

"We hypothesised that smoking was associated with tumours that harbor more genetic mutations and, therefore, the immune systems of these patients might be more likely to respond and attack the tumours once PD-L1 had been blocked," Professor Jean-Charles Soria, director of the Site de Recherche Intégrée sur le Cancer (SIRIC) Socrate project at the Institut Gustave Roussy, France, explained in a press release.

To study MPDL3280A in ongoing international clinical trials, Soria and his colleagues have been enrolling patients with metastatic non-small cell lung cancer (NSCLC) who have failed to respond to chemotherapy. In some cases since Oct. 2012, the patients have been or are being treated with an intravenous infusion of MPDL3280A once every three weeks.

Among the findings presented, researchers discovered that MPDL3280A is generally well-tolerated, though about 13 percent of patients experienced some adverse event, such as fatigue (two percent), shortness of breath (0.7 percent), nausea (0.4 percent), or vomiting (0.4 percent). That said, the treatment often yielded rapid, durable responses. Analyzing the relationship between expression of PD-L1 (the number of cells expressing the protein) and benefit from the treatment, researchers discovered that response rates were most pronounced among those patients with the highest level of PD-L1 expression.

Presentation of SGI-110 AML Data

Astex Pharmaceuticals, a pharmaceutical company dedicated to the discovery and development of novel small molecule therapeutics, presented detailed clinical responses and biomarkers data of relapsed/refractory AML (r/r AML) patients treated in the Phase 1 part of the SGI-110-01 study.

The data were presented in the Oral Papers Session of Haematological Malignancies on Saturday, September 28, by Professor Jean-Pierre Issa, MD, Director, Fels Institute for Cancer and Molecular Biology, Temple University, Philadelphia, PA. The presentation title was: "Study of the correlation of baseline biomarkers and DNA demethylation to clinical responses in a Phase 1/2 randomised study of SGI-110, a novel subcutaneous hypomethylating agent, in the treatment of relapsed/refractory acute myeloid leukemia."

The presentation showed that of the 50 heavily pre-treated Phase 1 AML patients with LINE-1 DNA methylation data, there were 5 Complete Responses, or 10% (2 CRs, 1 CRp, and 2 CRi). There were no responders in the 31 patients (0%) who had LINE-1 DNA demethylation of less than 10% after treatment, while all 5 responders were in the 19 patients (26%) who had LINE-1 demethylation of at least 10% (0 vs. 26%, $p < 0.01$). The median duration of response was approximately 4 months (114 days), and two responders had complete responses for approximately 1 and 1.5 years (350, and 558 days respectively). Two of the 5 responders had prior hypomethylating agent treatment, and two patients had prior bone marrow transplants. Patients with low baseline DNMT-3b expression seemed to correlate with better LINE-1 demethylation and response. Other baseline biomarkers -- Cytidine deaminase (CDA), deoxycytidine kinase (dCK) and micro-RNA 29b -- did not seem to correlate with either LINE-1 demethylation or clinical response.

The first data from the Phase 2 AML patients in both r/r AML and treatment-naïve elderly AML were submitted for presentation at the upcoming 2013 American Society of Haematology Annual Meeting, December 7-10, New Orleans, LA. Top line data on the complete cohort of r/r AML patients, and 17 treatment-naïve elderly AML patients were released on August 28, 2013.

Studies Demonstrate Early Clinical Activity from AZD9291

AstraZeneca and its global biologics research and development arm, MedImmune, presented oncology data at the congress.

Data from a range of studies demonstrated early clinical activity from AZD9291, an irreversible inhibitor of epidermal growth factor receptor (EGFR) (Abstract #33 LBA); MEDI4736, a PD-L1 monoclonal antibody that is being studied in patients with advanced solid tumours (Abstract #802), and additional data supporting the company's accelerated development of olaparib, a poly ADP ribose polymerase (PARP) inhibitor (Abstract #846 in new tablet formulation in combination with carboplatin and paclitaxel; #801 in ovarian cancer patients with a germline BRCA1/2 mutation; #3002 in combination with chemotherapy, followed by maintenance monotherapy, in women with platinum-sensitive recurrent serous ovarian cancer). Additional Phase III data on AstraZeneca's cediranib, a vascular endothelial growth factor (VEGF) signalling inhibitor, in platinum-sensitive relapsed ovarian cancer will be presented by researchers from the UK Medical Research Council on 30 September (Abstract #10 LBA).

On 29 September, AstraZeneca presented Phase I data from a global open-label study of AZD9291 (Abstract #33 LBA), a third-generation oral, selective, irreversible inhibitor of EGFR-activating and resistance mutations in non-small-cell lung cancer (NSCLC). In the study, the compound was clinically active and tolerated as a monotherapy in patients with advanced EGFR mutation positive NSCLC whose tumours have progressed following prior therapy with an EGFR tyrosine kinase inhibitor (TKI).

"Cancer is one of our key therapeutic area priorities and we continue to make progress in our development pipeline," said Susan Galbraith, Head of Oncology Innovative Medicines Unit, AstraZeneca. "The encouraging results from the Phase I trial on AZD9291 in advanced non-small-cell lung cancer show it is active in patients for whom most therapeutic options have been exhausted. We look forward to seeing further results from this trial and although the compound is still at an early stage, we are now considering accelerating its development."

On 30 September, MedImmune presented pre-clinical and preliminary clinical data from the Phase I study of MEDI4736 in patients with advanced solid tumours (Abstract #802). Overall, MEDI4736 shows an encouraging level of clinical activity with a manageable safety profile relative to the small data set. In the dose escalation phase of the study, early tumour shrinkage was observed across a range of doses, including the lowest doses explored. The study is currently ongoing and the complete clinical and safety data will be presented at a future scientific meeting.

"MEDI4736 is off to a good start in the dose escalation Phase I study. The safety profile and observed activity at all doses studied are very encouraging at this early point," said Edward Bradley, Senior Vice President and Head of MedImmune's Oncology Innovative Medicines Unit. "MEDI4736 plays an important role in our growing portfolio of immune-mediated cancer therapies, which have the potential to become a cornerstone of future cancer therapy regimens, particularly in combination with other highly-active molecules."

AstraZeneca also presented data on olaparib (Abstracts #846, #801 and #3002), a PARP inhibitor that recently started Phase III development and that has been accepted for marketing authorisation by the European Medicines Agency (EMA) for the maintenance treatment of patients with platinum-sensitive relapsed serous ovarian cancer who have a BRCA mutation.

Key among these data was Study 24 (Abstract #801, 30 September) which confirmed 300 mg as the optimal dose for the tablet formulation of olaparib, which is the formulation and dose for the Phase III SOLO (Studies of OLaparib in Ovarian cancer) programme initiated on 4 September. The clinical trial programme will determine the benefit, by progression free survival (PFS), of olaparib as a maintenance monotherapy in ovarian cancer patients who have a BRCA mutation who are in complete or partial response following platinum-based chemotherapy in both the first line setting (SOLO 1), and in the relapsed setting (SOLO 2).

Synta Reception and Webcast

Synta hosted an Investor Reception and Webcast at the 2013 European Cancer Congress this year.

Synta Pharmaceuticals Corporation hosted an investor reception and webcast to discuss the development of its lead drug candidate, Ganetespib, for the treatment of lung and breast cancers at the 2013 European Cancer Congress (ECCO-ESMO-ESTRO).

Ganetespib, an investigational drug candidate, is a selective inhibitor of heat shock protein 90 (Hsp90), a molecular chaperone which controls the folding and activation of a number of client proteins that drive tumour development and progression.

Many solid and haematologic tumours are dependent on Hsp90 client proteins including proteins involved in "oncogene addiction" (ALK, HER2, mutant BRAF and EGFR, androgen receptor, estrogen receptor, JAK2); proteins involved in resistance to chemotherapy and radiation therapy (ATR, BCL2, BRCA1/2, CDK1/4, CHK1, survivin, and WEE1); proteins involved in angiogenesis (HIF-1alpha, VEGFR, PDFGR, and VEGF); and proteins involved in metastasis (MET, RAF, AKT, MMPs, HIF-1alpha, and IGF-1R).

In preclinical models, inhibition of Hsp90 by ganetespib results in the inactivation, destabilization, and eventual degradation of these cancer-promoting proteins. Ganetespib is being evaluated in trials in lung cancer, breast cancer, and other tumour types. The most common adverse event seen to date has been transient, mild or moderate diarrhea, which has been manageable with standard supportive care. Information on these trials can be found at www.clinicaltrials.gov.

Ganetespib has received Fast Track designation from FDA for second-line treatment of non-small cell lung adenocarcinoma in combination with docetaxel.

The reception webcast along with an accompanying slide presentation and can be viewed on the home page - www.syntapharma.com

SYNTA PHARMACEUTICALS®

TRANBERG^{CLS} Cancer Immunotherapy System

Clinical Laserthermia (CLS) attended the 17th European Cancer Congress (ECC) "Reinforcing multidisciplinarity" in Amsterdam 27 September -1 October, where the TRANBERGCLS - Cancer Immunotherapy System was pre-launched.

The new TRANBERGCLS - Cancer Immunotherapy System includes a laptop design mobile diode laser unit and disposable accessories specifically designed for safe and efficient performance of the imILTCLS cancer immunotherapy procedure.

The intended use of CLS's ILT system is to deliver laser energy in a way that gives controlled heating and destruction of cancer, including an anti-tumour immunologic effect against the treated cancer.

Erbitux Extends Survival in mCRC

Merck Serono, the biopharmaceutical division of Merck, announced that the German cooperative investigator group AIO (Arbeitsgemeinschaft Internistische Onkologie) reported new data from the Phase III head-to-head clinical trial FIRE-3, which show a clinically relevant improvement from Erbitux® (cetuximab) plus FOLFIRI versus bevacizumab plus FOLFIRI as 1st line treatment in metastatic colorectal cancer (mCRC) in patients with RAS wild-type tumours.[1]

The new data, from a preplanned exploratory analysis, were presented at the ECC 2013. The analysis shows a 7.5-month increase in median overall survival (OS) in mCRC patients with RAS wild-type tumours ((n=342); defined as having no mutations in exons 2, 3 and 4 of KRAS and NRAS), receiving 1st line Erbitux plus FOLFIRI compared with patients receiving bevacizumab plus FOLFIRI (OS: 33.1 months vs. 25.6 months, respectively; hazard ratio [HR]: 0.70; p=0.011). In a post hoc analysis of the patient group with any RAS mutations (n=178), patients who received Erbitux plus FOLFIRI 1st line reached an OS of 20.3 months vs. 20.6 months in the group that was treated with bevacizumab plus FOLFIRI (HR: 1.09; p=0.60).[1]

As previously presented at the annual meeting of ASCO 2013 and at the World Congress on Gastrointestinal Cancer 2013, the primary endpoint of the trial, objective response rate based on investigators' read in patients with KRAS exon 2 wild-type tumours, was not met.[2,3] In the patient group with KRAS exon 2 wild-type tumours, an expected and balanced cross-over or continuation beyond progression with regard to subsequent biologic treatments in 2nd line therapy (either EGFR antibody or bevacizumab) was observed. Also, no major imbalances were noted with regard to chemotherapies used in 2nd line treatment. It is important to note that this result is not fully mature (57% event rate in the "intent-to-treat" KRAS exon 2 wild-type population) and will be updated in due course.[2]

"These new data from the Phase III study FIRE-3 show a 7.5-month increase in median overall survival to 33.1 months when using 1st line Erbitux plus FOLFIRI as compared to using bevacizumab plus FOLFIRI in metastatic colorectal cancer. Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies," said Professor Volker Heinemann from the Ludwig-Maximilians University, Munich, and FIRE-3 principal investigator. "Together with insights from other recent relevant studies, these results suggest that 1st line treatment of RAS wild-type patients should include an anti-EGFR therapy."

"These results continue to reinforce the value of Erbitux as a 1st line treatment for metastatic colorectal cancer and show that RAS tumour status is likely to help to identify those patients who are most likely to benefit from Erbitux," said Dr. Annalisa Jenkins, Head of Global Drug Development and Medical for Merck Serono. "Additional biomarker analyses are being conducted on data from the pivotal Erbitux studies, CRYSTAL and OPUS to help shed additional light on the role of RAS mutations in these patients."

References

1. Heinemann V, et al. Oral presentation at the European Cancer Congress 2013, September 28. Abstract No:LBA17.
2. Heinemann V, et al. Oral presentation at the ASCO Annual Meeting 2013, June 1. Abstract No:LBA3506.
3. Modest D, et al. Oral presentation at the World Congress on Gastrointestinal Cancer 2013, July 6. Abstract No:O-0029.

Orbis Scalp Cooler

Omar Hussain and University of Huddersfield PhD Student, Wafaa Al Tameemi presented posters at the European Cancer Congress 2013.

Their ground-breaking studies in the cytoprotective role of cooling in chemo-induced alopecia will be showcased at this exciting European Congress with a global reach.

Paxman proudly showcased the Orbis model scalp cooler to the International audience at the European Cancer Congress, 2013.

Cancer chemotherapy affects rapidly dividing cells and at any given time, 90% of human hair follicles are in the actively dividing phase. Hair loss frequently occurs due to partial or total atrophy of the hair root bulb, causing constriction of the hair shaft, which then breaks off easily.

Scalp cooling works by lowering the temperature of the head and scalp immediately before, after and during the administration of chemotherapy. This in turn reduces the blood flow to the hair follicles, thus preventing or minimising the damage, meaning that hair loss is not inevitable.

Although successful scalp cooling depends on many factors, research and studies - several of which can be found in our downloads and resources centre – have shown that scalp cooling can be effective across a wide range of chemotherapy drugs such as; Epirubicin, Doxorubicin, Taxol and Taxotere.

Many patients experience great concern over the possibility of hair loss during what is already a distressing time and scalp cooling provides the only real alternative to hair loss with the use of many chemotherapy drugs.
It can result in a high level of retention or complete hair preservation which can improve patients' self confidence leading to positive attitudes towards treatment.

For more information visit the site here.
http://www.paxman-coolers.co.uk/how-it-works/

Synergies Between Cancer Vaccine and Chemotherapy

ISA Pharmaceuticals B.V., a clinical-stage biopharmaceutical company focusing on rationally designed therapeutic vaccines against cancer and persistent viral infections, announced that it had presented novel data on its lead compound ISA101 at this year's congress.

In a preclinical mouse model of cancer, chemotherapy with cisplatin increased the therapeutic response to subsequent vaccination with an HPV16 synthetic long peptide (SLP®). While cisplatin or HPV-SLP® treatment alone increased survival, long-term survival was only achieved by combining chemotherapy with the vaccine.

These findings are further supported by a Phase I toxicity / immunogenicity study in 18 women with advanced or recurrent cervical cancer eligible for chemotherapy. Concurrent with standard chemotherapy (including carboplatin and paclitaxel), 12 patients received ISA101, a therapeutic cancer vaccine consisting of 13 synthetic long peptides from the E6 and E7 oncoproteins of HPV16. The control group (n=6) did not receive vaccination. The study demonstrates that chemotherapy does not cause lymphodepletion or suppression of cellular immune responses in patients. Patients showed shifts in leukocyte composition associated with increased dendritic cell function and improved memory T cell responses to common recall antigens. Patients treated with chemotherapy and ISA101 exhibited robust and sustained HPV16-specific proliferative T cell responses.

"We are pleasantly surprised that standard chemotherapy for late-stage cervical cancer is not immunosuppressive for T cells, and that it permits robust proliferative T cell responses to ISA101," said Cornelis Melief, Chief Scientific Officer of ISA Pharmaceuticals. "Contrary to long-held beliefs, these results demonstrate that chemotherapy combines well with therapeutic cancer vaccines."

A New Indication for XGEVA

The U.S. Food and Drug Administration (FDA) approved XGEVA® (denosumab) for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone (GCTB). A new indication for XGEVA, this was approved following a priority review by the FDA, a designation reserved for drugs offering major advances in treatment, or provide a treatment where no adequate therapy exists.

GCTB typically affects individuals between the ages of 20 - 40. It is characterised by a bone destructive tumour that often results in fractures. When untreated, it often results in complete destruction of the affected bone, leading to bone fracture, joint dysfunction, deformity or amputation.

The approval of XGEVA is based on positive results from two open-label trials that enrolled patients with GCTB that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity. The overall objective response rate of the 187 patients evaluated was 25 percent. The estimated median time to response was three months. In the 47 patients with an objective response, 51 percent (24/47) had a duration of response lasting at least eight months. Three patients experienced disease progression following an objective response.

The safety profile of XGEVA in patients with GCTB was similar to that reported in studies of patients with bone metastases, and also appeared to be similar in skeletally mature adolescents and adults. Safety data was evaluated in 304 patients with GCTB who received at least one dose of XGEVA. Of these patients, 145 were treated for at least one year. The most common adverse reactions were arthralgia, headache, nausea, back pain, fatigue, and pain in the extremity. The most common serious adverse reactions were osteonecrosis of the jaw and osteomyelitis.

For patients with GCTB, XGEVA is administered as a subcutaneous injection (120 mg) every four weeks with additional 120 mg doses on days eight and 15 of the first month of therapy.

"With today's XGEVA FDA approval, Amgen can offer a much needed treatment option to patients who suffer from giant cell tumour of bone that cannot be adequately treated with surgery," said Dr Harper, executive vice president of Research and Development at Amgen. "Advances in our understanding of the underlying biology of this rare disorder have allowed Amgen to generate compelling clinical evidence to address the medical needs of patients and their healthcare providers."

HALAVEN® - Additional Analysis Findings Presented at ECC 2013

At the European Cancer Congress (ECC) 2013 Eisai Co., Ltd. President & CEO: Haruo Naito, announced that *post hoc* analysis findings regarding a Phase III trial (Study 301) of Halaven® (eribulin mesylate; below, "eribulin"), an anticancer agent being developed in-house, versus capecitabine in patients with metastatic breast cancer at were presented at the congress.

Improved progression-free survival (PFS) in patients receiving therapy for metastatic breast cancer often fails to translate into overall survival (OS) benefit. Previous results from Study 301 found no difference in PFS but demonstrated a trend for improved OS in patients who received eribulin ("Group E"), though not statistically significant, versus patients who received capecitabine ("Group C"). With the aim of investigating the discordance between OS and PFS, the post hoc analysis presented at the congress compared median OS in patient subsets by stratifying patients who had been confirmed with disease progression during the trial into two groups: patients with a newly detected metastasis (Group E: 271 patients, Group C: 285 patients) and patients who progressed with an increase in the size of pre-existing lesions (Group E: 147 patients, Group C: 129 patients). The analysis results showed that the median OS of these subsets was similar among patients who progressed with an increase in the size of pre-existing lesions (Group E: median OS of 17.4 months, Group C: median OS of 17.4 months; HR 1.13; 95% CI 0.87, 1.46; nominal p-value=0.35). In comparison, among patients confirmed to have a newly detected metastasis, Group E recorded a trend favoring extended OS, with a nominal p-value of 0.02 (Group E: median OS of 15.5 months, Group C: median OS of 12.9 months; HR 0.81; 95% CI 0.68, 0.97).

"These results suggest that the conventional PFS definition may not be adequate and that clinically meaningful differences may exist among different subsets of patients with metastatic breast cancer depending on how and where their disease progresses. The importance in this post hoc analysis of the emergence of 'new' metastases is intriguing and warrants further study" said Dr. Christopher Twelves, Professor of Clinical Cancer Pharmacology and Oncology, University of Leeds and St James' University Hospital and investigator for Study 301.

Furthermore, the *post hoc* analysis compared new metastasis-free survival (nMFS), which indicates the time until a new metastasis was first confirmed. This comparison showed an nMFS of 5.8 months in Group E (554 patients) and 5.2 months in Group C (548 patients), indicating a trend favoring extended nMFS in Group E by a difference of 0.6 months (HR 0.90; 95% CI 0.77, 1.05; nominal p-value=0.17).

Eisai will continue its efforts to translate in a clinical setting the main effect of eribulin as a non-taxane microtubule dynamics inhibitor as well as its experimental inhibitory effect on tumour metastasis as suggested in preclinical research findings to date. Through these endeavors, the company seeks to maximise the value of the agent in order to make further contributions to patients with cancer and their families.

Dendreon Presented PROVENGE®

Dendreon Corporation announced today the presentation of data from clinical studies featuring PROVENGE® (sipuleucel-T), an autologous cellular immunotherapy for metastatic castrate-resistant prostate cancer (mCRPC), at the 2013 European Cancer Congress in Amsterdam, September 27-October 1, 2013. Preliminary Phase II data surrounding DN24-02, an investigational autologous cellular immunotherapy for patients with surgically resected HER2+ urothelial cancer, will also be presented.

"These preliminary data are encouraging, and suggest that combining sipuleucel-T and abiraterone acetate plus prednisone is possible. It is not known if the potential for an immunostimulatory effect from low testosterone levels achieved with abiraterone may be offset by the potentially immunosuppressive effects of prednisone"

Preliminary data from a Phase II combination study demonstrated that PROVENGE product potency and immunological prime-boost responses are maintained when administered concurrently or sequentially with abiraterone acetate (AA) plus prednisone. Additionally, preliminary data from an ongoing open-label study of PROVENGE treatment in men with mCRPC who were previously treated with PROVENGE in the androgen dependent prostate cancer (ADPC) setting suggest long-lived immunological memory to PROVENGE years following initial treatment.

"The data presented at this Congress surrounding PROVENGE and DN24-02 further our understanding of the potential benefits of these personalised immunotherapies," said Mark Frohlich, M.D., executive vice president of research and development and chief medical officer at Dendreon. "The ability to sequence treatments such as PROVENGE with other therapies has the potential to transform the treatment of advanced prostate cancer, particularly in the current oncology landscape with the encouraging results from immunotherapy

Computed Tomography - Study Results and Demonstrations

The MEDIAN Technologies (ALMDT), a leading medical imaging software solutions developer and a service provider for image interpretation and management in oncology clinical trials, team were available at their booth to discuss the study results and to give demonstrations of MEDIAN's software solutions.

During the congress MEDIAN's scientists presented the results of a study on"Monitoring of Pulmonary Tumours in Computed Tomography: Thresholds for Volume-based Response Assessments and Target Lesions Selection".

Changes in lung tumour volume are emerging as a more sensitive imaging biomarker for disease evolution than uni-dimensional measurements of longest axial diameters. However, there are still missing scientific data to specify the magnitude of tumour volume changes that would allow classifying disease evolution and identifying if a patient responded to the therapy. This study proposes a solution for volume-based response assessments that provides thresholds for response, based on tumour volume, as well as a method for automatic identification of measurable lesions.

MEDIAN Technologies also coauthored a poster publication presented by Saga University, Japan: "Evaluation of a Cloud-based Local Read Paradigm for Imaging Evaluations in Oncology Clinical Trials".

The goal of the study is to evaluate a cloud-based paradigm implementing software solutions and services that standardise imaging evaluations among international investigator sites. The study was performed using MEDIAN's Lesion Management Solutions (LMS) and MEDIAN's Clinical Trial Imaging Services (CTIS).

Onapristone - An Oral, Anti-Progestin Hormone Blocker

Arno Therapeutics, Inc, a clinical stage biopharmaceutical company focused on the development of oncology therapeutics, announced data from two preclinical studies supporting its lead compound Onapristone. The data was presented during the Diagnostics/Biomarkers poster session.

The two separate preclinical studies further support the development of a diagnostic test to identify patients with activated progesterone receptor (APR) in tumour specimens as a potential biomarker of anti-progestin activity.

Onapristone is an oral, anti-progestin hormone blocker that has been shown to have considerable anti-tumour activity in breast cancer. Onapristone appears to have a unique ability to block the activated progesterone receptor (APR), which is believed to be a mechanism that may inhibit the growth of breast, endometrial and other tumours. The APR has the potential to function as a biomarker of anti-progestin activity.

"These findings are an expansion of the data set presented at the American Society of Clinical Oncology (ASCO) meeting earlier this year and further support the activated form of progesterone receptor as a target for treatment with an anti-progestin," said Alex Zukiwski, Chief Medical Officer of Arno Therapeutics and one of the authors for study abstract #1001. "With the development of a commercially-viable diagnostic test to recognise APR positive tumours, we will be able to identify the patients most likely to respond to treatment with Onapristone, which is moving toward a Phase I trial."

Clinical and pathological correlation of the activated form of the progesterone receptor (PR) in breast cancer (BC)
Abstract #1001; Poster #273.

The study evaluated 397 archived breast cancer samples to correlate the APR status (PR nuclear morphology) using immunohistochemistry (IHC) in BC biopsies to any clinical and/or pathological relationships. APR positive was defined as any tumour with more than 5 percent APR cells. The study found two distinct PR nuclear distribution patterns, an aggregated pattern (A) indicative of activated PR and a diffused, or finely granular pattern, (D) reflecting inactive PR.

The study concluded that although there was an association with higher tumour grade, the APR status was not clearly linked or associated with other prognostic variables such as clinical characteristics, markers for proliferation, estrogen receptor (ER), PR positivity or disease stage. This indicated that APR cannot be predicted by routine clinical data or pathological testing. Overall, the study established that further work on the APR is warranted, as the biomarker has the potential to determine which patients could benefit from anti-progestin treatment. Arno is currently developing a companion diagnostic to identify APR in solid tumours.

Clinical and pathological correlation of the activated form of the progesterone receptor (APR) in endometrial cancer (EC)
Abstract #1002; Poster #274.

The study evaluated 76 archived endometrial cancer samples using a standard IHC technique to determine the APR status in EC and to describe any clinical or pathological relationships with the ultimate goal of developing a companion diagnostic predicting the efficacy of anti-progestins in patients with EC.

The study suggests PR is constitutively active in a subset of endometrial tumours, but not in normal tissue. In such cases, investigation of anti-progestin treatment is warranted as it could inhibit tumour PR activity to disrupt any PR-driven proliferation. The study also concluded that detection of APR can be potentially performed in a routine clinical diagnostic setting, and that APR detection in endometrioid cancer is potentially valuable to identify patients who may benefit from anti-progestin treatment.

These findings support further evaluation of APR as a target for treatment with an anti-progestin, such as Onapristone.

"This data underscores the role of anti-progestins and supports using APR as a biomarker in solid tumours. We are moving forward in parallel the development of the diagnostic test and the clinical development of Onapristone," remarked Glenn Mattes, President and Chief Executive Officer of Arno Therapeutics.

Recently, Arno Therapeutics initiated a pharmacokinetic study in healthy volunteers and is moving toward its first Phase I trial with the submission of an Investigational Medicinal Product Dossier (IMPD) to the French Health Authority, L'Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), to request the clinical trial authorization of a Phase I dose escalation study evaluating Onapristone.

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Poster Synopsis

Effect of Impurities in Sample DNA on Multiplex Ligation-dependent Probe Amplification (MLPA)

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Introduction

MLPA® (Multiplex Ligation-dependent Probe Amplification) is a PCR-based technique that allows detection of copy number of up to 50 different genomic sequences, methylation status of promoter regions, as well as detection of selected point mutations simultaneously in one reaction [1, 2]. MLPA probes consist of left and right hybridising parts, which align next to each other on the genomic DNA and they all have universal PCR primer pair binding sites. MLPA is performed in four steps: 1) genomic DNA denaturation and hybridisation of left and right parts of probes; 2) ligation of the left and right parts of the probes; 3) PCR amplification of ligated probes by a single primer pair; 4) fragment separation by capillary electrophoresis and data analysis.

MLPA is routinely used in tumour diagnostics and in tumour characterisation. Molecular genetic analysis of tumour samples is a challenging task especially when scarce amounts of biospecimen are available (e.g. fine needle biopsies or archival FFPE tissue). In these cases MLPA is frequently the method of choice as it requires only 20-50 ng of DNA input. However, the quality of DNA from different samples may vary because of tissue source, fixation conditions and DNA extraction procedure and this can lead to less reliable MLPA results. Certain inhibitory substances can be co-purified with DNA and possibly affect MLPA at different steps. Sources of DNA sample contamination can be different, such as melanin from skin samples; calcium from bone marrow; EDTA and heparin as anticoagulants from blood; iron and haemoglobin as blood components, etc. We have studied the effect of several impurities by adding them to "pure" human gDNA samples with diploid gene copy number and confirmed that normal copy number status can be affected in the presence of impurities. We also discuss approaches for reducing these inhibitory effects.

Materials and Methods

MLPA was performed on 50 ng of human reference gDNA (Promega, G147A) dissolved in TE pH 8.5 with or without prior addition of various potentially inhibitory substances in the range of concentrations that affect MLPA: sodium chloride (40 mM – 200 mM), calcium (II) chloride (1.5 mM – 10 mM), EDTA (1.0 mM – 16.0 mM), iron (II) chloride (1.0 uM – 50 uM), iron (III) chloride (1.0 µM – 50 µM), haemoglobin (2 ng/ul – 5.0 µg/ul), heparin (0.02 U/ml – 0.14 U/ml) and melanin (2.0 ng – 4.0 ng).

To remove or to relieve the effect of sample impurities, the DNA samples were additionally purified with (I) ethanol precipitation, (II) phenol/chloroform purification or (III) by nucleospin gDNA Clean-up XS (Machery-Nagel) and (IV) by OneStep PCR Inhibitor removal Kit (Zymo Research). Moreover, reaction additives such as BSA (bovine serum albumin, NEB) or gp32 (T4 gene 32 protein, NEB) were used.

Results

MLPA probe signals exhibit variability in the presence of increasing concentrations of impurities. More than 10 % of probes show copy number ratios that fall outside of the 0.8-1.2 normal copy number ratio in the presence of increasing amounts of impurities starting from 80 mM NaCl, 2.5 mM CaCl2, 4 mM EDTA, 10 mM FeCl2, 25 mM FeCl3, 0.1 µg/µl haemoglobin, 0.04 U/ml heparin and 3.0 ng/µl melanin.

Sample impurities also affect the quality of an MLPA reaction. The poor quality of MLPA reaction can be seen from irregular peak pattern, high residual primer, probe signal sloping, deviations in Q-fragments and D-fragments.

Sample purification and reaction additives greatly improve the quality of MLPA reaction. Additional purification step on sample DNA as well as reaction additives eliminate the inhibitory effect of salts as well as of haemoglobin, heparin and melanin.

Conclusions and Recommendations

It is important to pay attention to the nature of bio specimen, as several tissue types contain substances such as iron, heparin and melanin, which can affect the MLPA procedure, if not removed during DNA purification. If necessary, an additional sample purification step such as an ethanol precipitation or purification column can be used to clean up samples. However, an essential recommendation is that similar sample treatment, extraction and possible purification step should be performed both on patient and reference DNA samples.

Lilit Atanesyan has obtained her MSc degree in Biophysics at Yerevan State University, Armenia. Following this, she completed her doctoral studies in Molecular Biology at the University of Zurich, Switzerland. Since 2011, she works at MRC-Holland developing products for genetic analyses of various human cancers.

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Poster Synopsis

Swedish Emesis Registry (SER) - A Web-based Quality Assurance Tool for Prevention and Treatment of Nausea and Vomiting Associated with Chemotherapy

Anki Delin Eriksson[1,2]

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More than half of the +50,000 people who get cancer every year in Sweden, receive chemotherapy at some time during the period of illness. Of these, at least 50% are affected by nausea or vomiting.

Chemotherapy-induced nausea and vomiting (CINV) is still a common side-effect of many cancer treatments. The symptoms have a major impact on patients' well-being and quality of life. Opportunities to prevent nausea and vomiting associated with chemotherapy have increased, but despite this, many patients still have problems especially with delayed nausea and vomiting from a few days up to several weeks after treatment.

Chemotherapy is usually given as an outpatient treatment, which means that the patient needs recommendations on how sickness can be prevented and treated after treatment. There are international consensus guidelines available for how nausea and vomiting should be treated, but they are difficult to follow in everyday clinical use. Also, individual risk-modifying risk factors are not always accounted for in the guidelines. Patients also react differently to the same chemotherapy.

The Swedish Emesis Registry (SER) is a web-based quality assurance tool for the prevention and treatment of nausea and vomiting associated with chemotherapy.

The aim of the Swedish Emesis registry is to offer patients' evidence-based antiemetic guidelines which take into account individual risk factors, and ensure the quality of antiemetic treatment by standardised monitoring. The goal is to minimise CINV and therefore improving patients' well-being and thus quality of life.

SER consists of evidence-based antiemetic guidelines for all common chemotherapy treatments. An assessment of the individual patient's risk for nausea is performed and the patient gets antiemetics according to the guidelines. A diary is printed from the register in which the patient may register degrees of nausea, vomiting and possible level of well-being morning and evening for 10 days after chemotherapy. The diary lists the recommended drugs for nausea for the patient to take home and take when required.

The responses from the patient diary are entered into the database and a new diary is given to the patient. If necessary, i.e if the patient had CINV despite antiemetics the antiemetics prescription is revised according to the guidelines Each participating clinic can produce graphs in real-time on how individual patients or groups of patients feel, which makes decisions on possible revisions to the guidelines. Each participating clinic can produce graphs in real-time over diary responses both for individual patients and groups of patients which makes reflections over necessary revisions to the guidelines possible. All participating clinics can also easily compare their own data with all participating clinics data.

In March 2013, there were 31771 diaries from 9403 patients entered into the register. Since 2012, the SER has been a national quality register, and there are currently fourteen oncology clinics in Sweden participating in the registry. The Swedish Antiemetic Group in Cancer Care have also produced a comprehensive course covering CINV, radiotherapy-induced nausea/vomiting and nausea/vomiting in the palliative care setting.

By providing evidence-based and individual guidelines for prevention and treatment of nausea and vomiting and following them up in a standardised way, the chances for an improved quality of life for patients increases. We anticipate that co-operation within the registry will lead to the establishment of national consensus guidelines, which would fully guarantee that all patients recieve an equal antiemetic treatment.

Anki Delin Eriksson is an RN with a masters degree in oncology nursing. She works at the Department of Oncology at Sahlgrenska University Hospital in Gothenburg, Sweden and at present, she works as a quality controller with quality and patient safety.

Poster Synopsis

MicroRNA-146a Controls Melanoma Via A Novel Pathway

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MicroRNAs (miRs) are small endogenous non-coding RNAs able to post-transcriptionally downregulate the expression of target genes via sequence-specific interactions with cognate messenger RNAs (mRNAs), triggering degradation or translation inhibition.[1] Given that an individual miR is able to inhibit multiple distinct mRNAs, they act as fundamental regulators of a variety of biological processes, including tumour establishment and progression.[2,3] As malignant melanoma is the most aggressive form of skin cancer, accounting for only 4% of cases but for as many as 74% of all skin cancer deaths at its metastatic stage, it is crucial to disclose its underlying molecular mechanisms.[4] By taking advantage of an in vivo-derived v-raf murine sarcoma viral oncogene homolog B1 (BRAF)-mutated melanoma progression model, composed of a parental non-metastatic cell line, A375P, and its derived highly aggressive cell line MA-2,[5] we identified a novel pathway controlled by miR-146a, whose expression enhances primary tumour growth while it impairs metastatisation.

Among many different dysregulated melano-miRs, miR-146a resulted of particular interest because we found it highly expressed in aggressive MA-2 versus non-aggressive A375P cells and, more relevantly, it resulted strongly upregulated in human melanoma invasive samples and metastases compared to in situ tumours. miR-146a's role in melanoma has been investigated by using miR-146a-modulated (up or down) cells in proliferation, anchorage-independent growth, migration and invasion assays in vitro as well as for tumour and metastasis formation experiments in vivo following subcutaneous or tail vein injections in nude mice. Interestingly, miR-146a transient or stable overexpression strongly enhanced MA-2 cell growth in vitro as well as primary tumour growth in vivo, while it impaired cell movement in vitro and metastatic colonization to the lung in vivo. On the other hand, miR-146a ablation completely reverted these phenotypes, thus emphasizing its importance in tumour formation and spreading.

To identify miR-146a targets we combined bioinformatics tools[6] with microarray analyses and found 55 genes downmodulated in miR-146a overexpressing MA-2 cells versus controls. Among them, two genes in the Notch pathway (the most predicted bioinformatically), Numb and lunatic fringe (LFNG), resulted highly depleted at the mRNA and protein level in miR-146a-enriched MA-2 cells. By employing reporter luciferase assays, we validated both genes as bona fide, strongly repressed direct targets. To assess if Numb and/or LFNG targeting was crucial in miR-146a-related phenotypes, we downmodulated their expression in MA-2 cells and observed that Numb or LFNG were able to reproduce some miR-146a-mediated phenotypes in vitro. In vivo experiments are ongoing.

Numb and LFNG have been described as negative regulators of Notch; Numb is an adaptor protein that triggers Notch1 degradation,[7,8] while LFNG is an N-acetylglucosaminyltransferase that modifies Notch receptors, enhancing Delta-mediated while inhibiting Serrate/Jagged-mediated signaling.[9] Notably, both genes are lost in different cancers, including breast.[10,11] We evaluated if Numb and LFNG knockdown could enhance Notch signaling in miR-146a-enriched cells and observed that miR-146a overexpression increases Notch1 protein expression and transcriptional activity. Furthermore, miR-146a induces Akt phosphorylation, as well as Hairy and Enhancer of Split 1 and 5 (HES-1 and HES-5) N-cadherin (CHD2) and cyclin d1 (CCND1) expression.

Taken together, our results suggest that miR-146a exerts a pleiotropic, dualistic role in cancer, promoting primary tumour growth while inhibiting metastatic colonization. Such duality is not unfrequent in the miR world and it may be explained considering that tumourigenesis and metastasis are distinct and independent processes. miR-146a-dependent Numb and LFNG knockdown and consequent Notch signaling alteration could at least partly account for these phenotypes, disclosing a novel pathway in melanoma establishment and progression.

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Monica Raimo graduated in Molecular Biology with *summa cum laude* in 2011 at the faculty of Mathematical, Physical and Natural Sciences of Turin University, Italy. She is currently a PhD student at the Molecular Biotechnology Center (MBC) in Prof. Taverna's lab, and is investigating the role of miR-146a in melanoma establishment and progression.

Poster Synopsis

Effects of Vitamin D Binding Protein-derived Macrophage Activating Factor (GcMAF) on Human Neuroblastoma Cells and Predicted Molecular Interaction with the Vitamin D Receptor

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Introduction

As of today, there are 57,821 published papers on the immunotherapy of cancer, with an exponential growth in the number of publications. According to a recent study, "immunotherapies require activation of macrophages to be effective"[1]. Since 1994, it has been demonstrated that macrophage activation requires vitamin D binding protein-derived Macrophage Activating Factor (GcMAF)[2]. Therefore, GcMAF has become a stronghold in the immunotherapy of cancer, and there are scores of studies on this subject including a very recent peer-reviewed report describing successful immunotherapy of patients with advanced cancer treated with GcMAF[3]. In this study we present data concerning the effect of GcMAF on human neuroblastoma cells.

Materials and Methods

Highly active purified GcMAF was obtained from Immuno Biotech Ltd, Guernsey, Channel Isles. GcMAF was purified according to the procedure described in Autism Insights[4]. Biological analysis demonstrated that this GcMAF had the highest activity in comparison with other preparations obtained from major researchers [5]. Human neuroblastoma cells SH-SY5Y were obtained from the Istituto Zooprofilattico Sperimentale, Brescia, Italy. SH-SY5Y cells originally derived from a metastatic bone tumour biopsy[6], and represent a model system to study the effects of anti-cancer therapies aimed at neuroblastoma[7]. However, since they are able to differentiate, they also represent a model system to study the neurobiology of neurodegenerative diseases[8]. Experiments, designed to study inhibition of cell proliferation, were conducted in the presence of 1% serum, whereas experiments designed to study differentiation were conducted in serum-free medium.

Results

GcMAF treatment of SH-SY5Y cells resulted in different effects depending on the proliferative activity of the cells. In actively proliferating cells, GcMAF inhibited cell proliferation in a dose-dependent manner and induced their apoptosis. In serum-starved, quiescent cells, GcMAF induced morphological changes indicating differentiation (Figure 1). The effects of GcMAF were mediated by cAMP production, possibly through cross-talk with the vitamin D receptor (VDR).

Discussion

Our results demonstrate that GcMAF inhibits actively proliferating human neuroblastoma cells, whereas it induces the differentiation of serum-starved (quiescent) human neuroblastoma cells. The concentration of GcMAF necessary to inhibit proliferation of actively proliferating cells was 10 fold higher than that required to induce differentiation of quiescent cells. The effect of GcMAF on actively proliferating human neuroblastoma cells was qualitatively superimposable to that observed when treating the same cell type with vitamin D3. In fact, GcMAF is a member of the so-called vitamin D axis since it derives from de-glycosylation of Vitamin D-Binding Protein or Gc protein. Consistent with this notion, we had previously demonstrated that polymorphisms of the VDR gene, known to be associated with the highest responses to VDR agonists, were associated also with the highest responses to GcMAF[9]. The interaction between GcMAF and VDR helps explaining the multiplicity of biological effects observed with GcMAF as well as the variety of clinical applications ranging from cancer to autism. Thus, VDR is expressed in a great number of cell types (including SH-SY5Ycells), and regulates a wide array of genes involved in the control of the major cell functions.

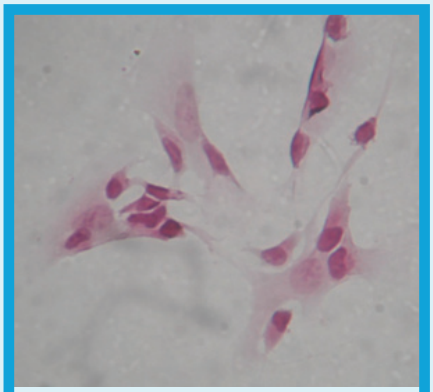

Figure 1. After 24 h stimulation with 8 pM GcMAF, serum-starved, quiescent cells showed a significant change in morphology that was consistent with the induction of differentiation. The cytoplasm was enlarged and several cytoplasmic elongations could be observed. The effect was dose- and time-dependent.

Marco Ruggiero holds a PhD in molecular biology, is a certified medical doctor specialised in clinical radiology, and is full professor of molecular biology at the Department of Experimental and Clinical Biomedical Sciences of the University of Firenze, Italy. He worked at Burroughs Wellcome Co. North Carolina, USA, where he published a seminal paper with Nobel Laureate Sir John Vane and, subsequently, at the National Cancer Institute of the NIH in Bethesda, working with Dr. Stuart A. Aaronson and Dr. Peter Duesberg. Since 1992 he has been Chair of Molecular Biology at the University of Firenze. He has published more than 150 peer-reviewed scientific papers on signal transduction in a variety of experimental and spontaneous pathologic system related with cancer, chronic kidney disease, chronic fatigue syndrome and neurological conditions. In the past 20 years he has worked on the vitamin D axis, a metabolic pathway that includes GcMAF. In the past 3 years he has published studies on the immunotherapeutic effects of GcMAF in cancer, chronic fatigue syndrome and neurological conditions.

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Patients' Self-assessed Knowledge about Cancer

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Background

Patients' need for information to manage everyday life is increasing. Studies show that patients, especially women, retrieve information related to disease and health on the Internet. In addition, this information influences the choices they subsequently make. This study distinguishes between examining the patient's desire for knowledge compared with the self-assessed current knowledge.

The purpose was to investigate:

- How much knowledge do cancer patients want to have about disease and treatment?
- How much knowledge do cancer patients currently have about disease and treatment?
- Is there a gender difference in the need of knowledge?

Methods

We used a questionnaire containing a VAS scale from 0-10 and questions such as "on a scale from 0 to 10 how much knowledge do you want to have about cancer?" Patients were asked to rank self-assessed wanted knowledge and current knowledge about disease and treatment. We randomly delivered the questionnaires to out-patients during a period of a few days in August 2012. Statistics were calculated with GraphPad Prism. Differences between wanted knowledge and current knowledge were tested with paired t tests. Differences between the two genders were tested with un-paired t tests. P-values < 0.05 were considered statistically significant. Reported p-values were two-sided.

Results

84 patients replied (100%) (38 men and 46 women) with a median age of 59 years (range 36-83). Women want to have knowledge about disease equivalent to 9.3 points, and men want to have knowledge equivalent to 9.2 points (p = 0.762). Women actually have knowledge about disease equivalent to 8.0 points, and men 7.2 points (p = 0.006). Figure 1.

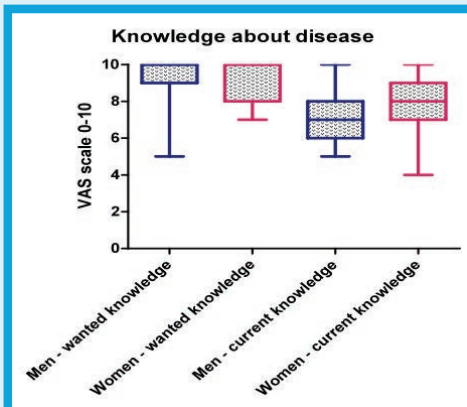

Figure 1.

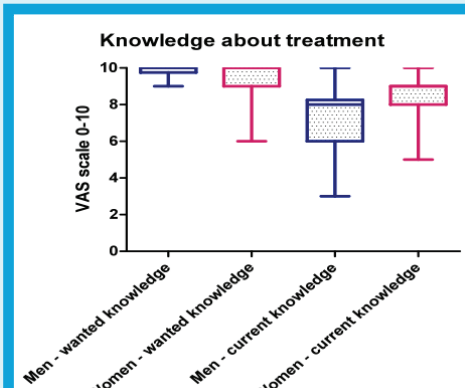

Figure 2.

Women want to have knowledge about treatment equivalent to 9.5 points, and men 9.8 points (p=.094). Women actually have knowledge about treatment equivalent to 8.4 points, and men 7.5 points (p=.002). Figure 2.

Discussion

It is well known that receiving a cancer diagnosis can be an overwhelming and frightening experience. A logical coping strategy is to seek out information, hoping to be empowered through knowledge. Studies show that cancer patients seek information and knowledge about their disease and treatment.[1,2] Different parameters affect their evaluation of the information[3].

Our study shows that men and women rate their knowledge differently. Another small study showed that there are differences in men´s and women´s salient beliefs about cancer[4]. Why these gender variations occur we do not know, but it may be important to understand the differences between men and women also in this context.

Conclusion

Both male and female patients want to have a high level of knowledge about their disease and the treatment. We could not demonstrate a significance difference between genders in their wishes. In this study, the female patients had a significantly higher self-assessed level of knowledge about both disease and treatment. It is relevant to study what this difference in level of knowledge causes and means.

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Lene Sigaard is clinical Head Nurse at the Department of Oncology, Odense University Hospital in Denmark. Her research and professional interests and responsibilities are cancer patients' responses to illness and treatment as well as written and oral communications.

Poster Synopsis

Loss of Epigenetic Control of Proto-oncogenic eEF1A2 as a Potential Way to Cancer Progression

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One of the current goals of cancer research is to identify every possible mechanism involved in cancer progression to develop low toxicity specific therapy for each individual case.

Thus, one of the proto-oncogenes that is deregulated in cancer is eukaryotic translation elongation factor 1A2 (eEF1A2).[1] It is tissue-specific protein, expression of which is restricted to terminally differentiated cells (cardiomyocytes, myocytes, and neurons). However, unusual appearance of eEF1A2 in non-specific tissues leads to cancer progression. The overexpression of eEF1A2 has been observed in numerous types of cancer.[2] Overexpression of oncogenes is frequently caused by multiplication or epigenetic changes in the corresponding oncogene loci. However, the overexpression of the eef1a2 gene was not related to genetic or epigenetic modifications in eef1a2 locus.[3] Thus, deregulation of the eEF1A2 expression can occur on the post-transcriptional level. We propose that eEF1A2 expression in cancer tissues may be controlled by microRNAs.

In silico analyses revealed miR-663 and miR-744 to be the most high-scoring target sites in the 3' untranslated region (3'UTR) of the EEF1A2. Both these miRNAs function preferentially as tumour suppressors, which directly inhibit the well-known oncogenes TGF-β, JunB and JunC. Intriguingly, the miR-663 promoter was earlier shown to be hypermethylated in breast cancer; thus was epigenetically inactivated in similar cancers where eEF1A2 overexpression was observed.[4]

To verify the inhibitory effect of miRNAs on eEF1A2 expression, a dual-luciferase assay was carried out. We showed that both miRNAs are able to inhibit reporter gene expression. Further experiments confirmed the inhibitory effects of miR-663 and miR-744 on the cellular eEF1A2 mRNA and protein levels.

Functional studies revealed that overexpression of both miR-663 and miR-744 inhibited the proliferation of the MCF7 breast cancer cell line. MiR-663 was shown to be upregulated during the resveratrol treatment, well known red wine component.5 Resveratrol also inhibited eEF1A2 expression in ovarian cancer cells.6 We observed upregulation of miR-663 and miR-744 with corresponding downregulation of eEF1A2 in resveratrol-treated MCF7 cells, suggesting that resveratrol may influence eEF1A2 expression through a miRNA-dependent pathway.

Thus, we have obtained additional evidence that regular red wine intake may be a good and enjoyable supplement to a diet which may lower cancer risk. Moreover, current data are in favour of a novel explanation for the abnormal occurrence of the eEF1A2 isoform in tumour tissues, indicating that it may be caused by the loss of microRNA-mediated post-transcriptional control.[7]

Andrii Vislovukh is a molecular biologist and has a MSc from Taras Shevchenko National University of Kyiv, Ukraine. Previously, after graduating *cum laude* Medical College he decided to devote his work to basic science. Currently, he is a doctoral student at the Institute of Molecular Biology and Genetics and is studying impairment of translational control during cancer development.

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Poster Synopsis

The Migration of Monocytes is Stimulated by Jagged-1 and DLL-4 via the Notch Pathway

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Introduction

Inflammation seems to play an important role in the development of pulmonary hypertension (PH).[1] Pulmonary vessels are thought to be influenced by inflammatory cells and chemokines they produce. These chemokines and cytokines regulate growth, migration and differentiation of inflammatory cells, which leads to vascular remodelling.[2]

The Notch signaling pathway is an evolutionarily conserved pathway in multicellular organisms. It is absolutely required for normal embryonic development, regulates cell-fate determination and the maintenance of stem cells in adults.[3-7]

The human Notch family includes four receptors (Notch 1-4) and five ligands (Jagged 1-2, Delta-like 1, 3, and 4).[8-10] All Notch receptors are single pass trans-membrane proteins composed of a functional extracellular, trans-membrane and an intracellular domain.

Material and Methods

Monocytes were isolated from EDTA-anticoagulated venous blood, taken from healthy donors with their informed consent followed by subpopulation specific MACS isolation protocols. For the chemotactic assays modified 48-well microchemotaxis chambers were used. For blocking experiments monocytes were pre-incubated with specific ligands for different durations. Migration depth of the cells in the filter was quantified microscopically by measuring the distance [µm] from the surface of the filters to the leading front of the cells.

The RNA of monocytes was isolated with RNA-BEE and transcribed into cDNA with Superscript III (Fa. Invitrogen). The quantification was done by real time PCR.

Results

All known Notch receptors (1 to 4) are expressed on human monocytes but to a different amount. The highest expression was observed for Notch 2 while the lowest expression was assessed for Notch 4. The two Notch ligands Jagged-1 and DLL-4 can induce chemotaxis of monocytes *in vitro*. Also priming of cells with both ligands induced a significant migratory response. As the ligands are expressed on cell surfaces we preincubated monocytes with these ligands for different time intervals to explore how long a cell-cell interaction might be necessary to elicit migration. Interestingly, at least a 30 min preincubation period was necessary to activate migration by Notch ligands. Specific blocking of ligand-induced migration was achieved by preincubation with the metalloprotease ADAM 17.

Conclusion

Jagged-1 and DLL-4 can stimulate direct migration of human monocytes. For this migratory response a cell-cell interaction of at least 30 minutes seems to be necessary. It can be suggested that Jagged-1 and DLL-4 are involved in attracting monocytes to inflammatory sites.

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Katherin Watzinger studied molecular biology at the University of Innsbruck, Austria. Since February 2012 she has been working on her PhD thesis "Role of the DSL-family on cell – cell interaction in pulmonary inflammation" at the pulmonary research lab at the Medical University of Innsbruck with the head ao. Univ.-Prof. Dr. Christian M. Kaehler.

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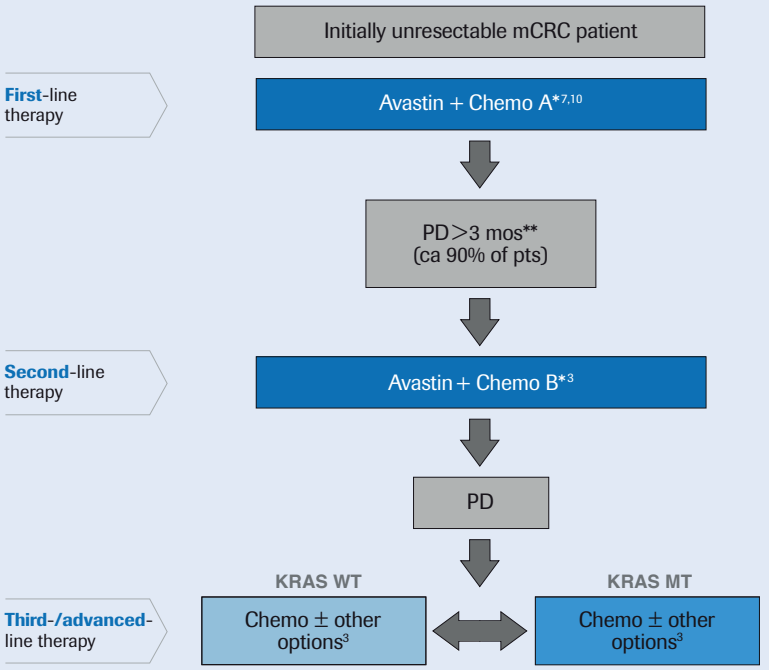

*Clinical evidence suggests oxaliplatin- or irinotecan-based chemotherapy followed by maintenance therapy to progression.[3,7,14]

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PRESCRIBING INFORMATION

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Dosage and Administration: Single use vials (25mg/ml bevacizumab) as 100mg/4ml or 400mg/16ml. Physicians experienced in antineoplastic medicines should supervise Avastin administration. *Recommended dose*: Continue until progression of underlying disease or until unacceptable toxicity. *Colorectal cancer*: either 5 mg/kg or 10 mg/kg every 2 weeks or 7.5 mg/kg or 15 mg/kg every 3 weeks. *Administration times; initial dose*: 90 minute IV infusion; *second dose*: 60 minute IV infusion if initial dose well tolerated; *subsequent dose*s: 30 minute IV infusion if second dose well tolerated. Do not administer as IV push or bolus or mix with glucose. Dose reduction for adverse events not recommended. If indicated, discontinue or temporarily suspend therapy. Not recommended in children or adolescents. No dose adjustment in the elderly.

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Pregnancy and Lactation: Contraindicated. No data on use in pregnancy; may inhibit foetal angiogenesis. Women of childbearing potential must use effective contraception during treatment and for 6 months after last dose. Discontinue breast-feeding during treatment and for 6 months after last dose.

Side-effects and Adverse Reactions: For full listings please refer to the Avastin SPC. *Serious reactions, very common*: Leucopenia, thrombocytopenia, neutropenia and febrile neutropenia. Peripheral sensory neuropathy. Hypertension. Diarrhoea, nausea, vomiting. Venous thromboembolic events. Asthenia, fatigue. *Serious reactions, common*: Anaemia. Sepsis, abscess, infection. Dehydration. Cerebrovascular accident, syncope, somnolence, headache. Supraventricular tachycardia, CHF. Arterial thromboembolism, deep vein thrombosis, haemorrhage, including pulmonary haemorrhage. Pulmonary embolism, dyspnoea, hypoxia, epistaxis. Ileus, intestinal perforation and obstruction, abdominal pain, GI disorder, stomatitis. Palmar-plantar erythrodysaesthesia syndrome. Muscular weakness, myalgia, arthralgia. Proteinuria, urinary tract infection. Pain, lethargy, mucosal inflammation. Dysphonia. *Serious reactions, uncommon/ rare/very rare*: Fistulae. PRES (with or without associated hypertension). Necrotising fasciitis. Hypertensive encephalopathy. *Serious reactions (frequency not known)*: pulmonary hypertension, nasal septum perforation, renal thrombotic microangiopathy which may clinically manifest as proteinuria with or without concomitant sunitinib use, gastrointestinal ulcer, hypersensitivity/infusion reactions with possible co-manifestations: dyspnoea/difficulty in breathing, flushing/redness/ rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting, ONJ, gall bladder perforation. *Other, very common*: Wound healing complications. Anorexia. Dysgeusia, dysarthria. Eye disorder, lacrimation increased, rhinitis. Rectal haemorrhage, constipation. Ovarian failure. Exfoliative dermatitis, dry skin, skin discolouration. Pyrexia. Any of the above may become serious. Elderly; increased risk of severe leucopenia and thrombocytopenia; neutropenia, nausea, headache, diarrhoea, fatigue, or arterial thromboembolic events. Laboratory abnormalities – refer to SPC. **Legal Category:** POM **Presentation and Basic NHS Cost:** Pack of one 100mg vial: £242.66. Pack of one 400mg vial: £924.40. Excluding VAT

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Treatment of HER-2 Positive Breast Cancer – Trastuzumab and Beyond

Magdolna Dank and **Tímea Tőkés**
Semmelweis University, Oncology Division of the 1st Department of Internal Medicine, Budapest, Hungary

Introduction

Individualised and personalised treatments are the most needed therapeutic pathways for both patients and treating physicians in daily oncological practice. The evolution of breast cancer treatment and drug development is one of the best examples of this new approach. The first successful targeted therapies were the anti-hormone medications for patients with hormone positive tumours (i.e. tamoxifen and aromatase inhibitors). The next step came with the recognition of new molecular pathological features: the realisation of the significance of the overexpression of HER-2 (human epidermal growth factor receptor type 2) on the surface of the tumour cells, resulting in an increased aggressiveness of the disease. Nowadays, therapeutic decisions inevitably depend on the results of the pathological evaluation of the breast tumours, especially on the biological behaviour and receptor structure of the tumour cells.

HER-2 is a member of the epidermal growth factor receptor (EGFR) family, which contains 4 transmembrane tyrosine kinase receptors. The HER-2 receptor has no natural ligands, and is overexpressed in approximately 20% of all breast cancers indicating poor prognosis.[1-5] HER receptors are naturally activated by homo- or heterodimerisation followed by tyrosine kinase pathway enhancement (PI3K and MAPK pathways) and proliferation stimulation. The HER2:HER3 heterodimers are the strongest and most stable and frequent dimers in breast cancer, and initiate highly excessive cell proliferation with the inhibition of apoptosis. Patients with overexpression of the HER-2 receptor usually suffer from more aggressive and extensive tumours with earlier occurrence of visceral metastases and poor overall survival.[6, 7] Before the appearance of anti HER-2 treatments, the mortality of these patients was much worse compared to HER-2 negative patients.[4, 8]

Magdolna Dank is an Associate Professor at the Semmelweis University, and Leader of the Oncology Division. She has degrees in internal medicine, clinical oncology, clinical pharmacology and is also a specialist of mental hygiene. The main theme of her PhD thesis was the predictive and prognostic factors in the treatment of breast cancer. As member of international and Hungarian oncology societies she is an active participant of the scientific community. Dr. Dank was and currently is principal investigator in phase II-IV studies in breast, colorectal, gastric and pancreatic cancers.

Tímea Tőkés has been working at the Oncology Division at Semmelweis University for 3 years; first as a medical student, and now as a PhD-student. Her research also focuses on breast cancer; Dr. Dank is her supervisor and project leader.

Trastuzumab

In 1998 the FDA (US Food and Drug Administration), and then in 2000 the EMA (European Medicines Agency) approved trastuzumab (Herceptin®), a monoclonal antibody for the treatment of metastatic HER-2 positive breast cancer.

Trastuzumab is a humanised monoclonal antibody against HER-2 which directly binds to the extracellular domain of the receptor inhibiting its functions through four known mechanisms. First trastuzumab stops the activation of the PI3K-MAPK pathways and causes cessation of the cell-proliferation signalisation.[9, 10] Secondly, trastuzumab inhibits VEGF (vascular endothelial growth factor) release and subsequent angiogenesis caused by HER2 overexpression.[11] Trastuzumab also prevents the formation of p95HER2, a truncated but independently active form of HER2.[12, 13] Finally, trastuzumab activates the immune response against the tumour due to the recognition of the trastuzumab-HER-2 complex by the immunocompetent-cells of the human body (antibody-dependent cytotoxicity, ADCC).[14, 15]

The most important and frequently investigated side-effect of trastuzumab is cardiotoxicity.[16] Therefore it is highly important to avoid co-administration of anthracyclines with trastuzumab, and the combination with taxanes is advantageous in this respect.[16-19] It is important to note that the cardiotoxicity of trastuzumab is reversible in most of the cases.[20-22]

Trastuzumab Against Metastatic Breast Cancer – The First Successful Applications

Trastuzumab was primarily registered for metastatic breast cancer treatment in combination with paclitaxel or docetaxel. The trastuzumab monotherapy was tolerable and safe, but not efficient enough by itself.[23-27] At first, Slamon *et al.* administered trastuzumab in combination

in their phase 3 study, where response rate increased by 18%, progression-free survival by 2.8 months and overall survival by 5 months in the trastuzumab-combination arms.[17] Gasparini *et al*. also found an outstanding 85% response rate with combination therapy (trastuzumab+docetaxel) against the 48% response rate with taxane monotherapy.[28] This obvious synergism between chemotherapy and trastuzumab led to further investigations[29, 30] that revealed that the most efficient combination therapies of trastuzumab were the ones with taxanes (paclitaxel- or docetaxel) or vinorelbin, not just in first-line, but also in second or third-line treatment, as well.[16]

Trastuzumab in the Adjuvant Setting – HERA, NSABP B31 and BCIRG Trials

Adjuvant administration was the next target for the researchers; randomised trials in adjuvant settings indicated that the addition of trastuzumab to chemotherapy significantly improved survival. The HERA trial[31] showed significantly increased progression-free and overall survival with 1 year of adjuvant trastuzumab treatment. The NSABP B31[32] trial showed a 12% difference in progression-free survival and a relative reduction in the risk of death by 33% for the benefit of adjuvant trastuzumab. The joint analysis of the NSABP B31 and the NCCTG N9831 trials found a statistically significant 39% reduction in death rate in favour of the trastuzumab-containing arms.[33] Safety results were also favourable; only 2% of the patients had symptomatic heart failure events and 75% of these were reversible.[34] The BCIRG 006 trial also showed better survival data with trastuzumab-containing regimens, and relapse risks were also much better compared to control arms.[35]

In conclusion, the addition of 1 year of adjuvant trastuzumab treatment to chemotherapy significantly improved disease-free and overall survival among women with HER2-positive breast cancer. Results of the randomised trials reasonably justified the inclusion of trastuzumab in the adjuvant protocols as well.[16, 36]

Neoadjuvant Trastuzumab Treatment - NOAH Trial and Beyond

Gianni *et al*. successfully applied trastuzumab in neoadjuvant setting in their phase 3 study. The NOAH trial applied 3 cycles of doxorubicin and paclitaxel followed by 4 cycles of paclitaxel and 3 cycles of CMF (cyclophosphamide + methotrexate + fluorouracil) therapy with or without concomitant trastuzumab treatment (completed for 1 year after surgery). The pCR rate was favourable on the trastuzumab arm (43% vs. 23%) and the response rate was 81% vs. 73%.[37] Buzdar *et al*. investigated the efficacy of 4 cycles of paclitaxel followed by 4 cycles of FEC (fluorouracil + epirubicin + cyclophosphamid) treatment ± weekly trastuzumab. The pCR rate was 65% vs. 26% in favour of trastuzumab.[38] According to these results, EMA approved trastuzumab in the neoadjuvant setting in 2011 for the treatment of 2 cm or larger tumours or inflammatory breast cancer in combination with chemotherapy, to be followed by adjuvant trastuzumab treatment.[16, 39]

Subcutaneous Administration of Trastuzumab – HannaH, PrefHER and SafeHER Studies

Trastuzumab is normally administered in every 3 weeks for HER-2 positive breast cancer patients by intravenous infusion. The goal of the new developments was to apply a new formulation of the drug subcutaneously, which could be cheaper, faster and more comfortable for the patients. Having the subcutaneous (SC) form, the need for an intravenous line is not necessary and patients could learn the injecting process by themselves. Moreover, the time-consuming administration of the drug could be shortened to approximately 5 minutes by the fixed dosed (600mg) SC form (compared to 30-90 minutes with the intravenous formulation).[40, 41]

The main limitation regarding this research was the fact that a restricted subcutaneous space must be used for drug administration. The minimal volume required for a SC trastuzumab injection was about 5 ml, but the volume of a painless SC injection cannot be more than approximately 1-2 ml.[40] Solution consisted of the addition of a novel excipient, hyaluronidase enzyme, that could rapidly catalyse the cleavage of the hyaluronan polymers, enhancing the available volume and the permeation of the co-administered agent, such as trastuzumab.[41] The recombinant human hyaluronidase (rHuPH20) allowed increased injection volume and enhanced the absorption of trastuzumab. Moreover, its effects were temporary and reversed completely within 24 hours.[40, 41]

Wynne *et al*. presented the results of their phase I/Ib study (NCT00800436) undertaken in patients with HER2-positive early breast cancer to identify the dose of SC trastuzumab that resulted in exposure comparable with the approved IV trastuzumab dose. A SC trastuzumab dose of 8 mg/kg was found to be comparable with the IV trastuzumab dose of 6 mg/kg. Besides, the SC formulation was well tolerated.[42] These results have further been used to select the fixed 600 mg dose for the SC administration, which was evaluated in the pivotal HannaH (enHANced treatment with NeoAdjuvant Herceptin) study.[41, 43]

The HannaH trial was designed to prove the non-inferiority of the fixed-dose SC formulation of trastuzumab compared to the IV formulation, based on co-primary endpoints of pharmacokinetics and efficacy. Patients with HER2-positive, operable, locally advanced or inflammatory breast cancer – so being eligible to primary systemic therapy – were randomised to receive 8 cycles of neoadjuvant chemotherapy. The regimen contained 4 cycles of docetaxel (75 mg/m^2) followed by 4 cycles of FEC (fluorouracil, epiadryamicin and cyclophosphamide) in the dosage of 500, 75 and 500 mg/m^2, respectively. Patients received trastuzumab concurrently in 3 weekly doses either intravenously (8 mg/kg, then 6 mg/kg) or subcutaneously in doses of 600 mg/5 ml. After surgery, patients continued the trastuzumab therapy – the same way as in the neoadjuvant setting – to complete 1 year of treatment. Safety has been monitored up to 24 months after the last trastuzumab dose, including cardiac monitoring.

Ismael *et al*. presented the results last year. 299 patients were randomised to the IV and 297 to the SC trastuzumab arm. Drug concentration in the blood measured just before surgery was at least as high for the SC as for the IV formulation – 69.0 and 51.8 µg/ml, respectively. As an efficacy endpoint, pCR (pathological complete remission) rate in patients treated in the SC arm was 45.4% vs. 40.7% with the IV formulation; the overall response rates were 87.2% vs. 88.8%, respectively. These results suggested non-inferiority of the efficacy and pharmacokinetic profiles of SC trastuzumab compared to standard IV administration.[43]

Safety and tolerability data from the HannaH study were further analysed by Jackisch *et al*.[44] The most common adverse events (AEs) (>25% in either arm) were alopecia, nausea, neutropenia, diarrhoea, asthenia, and fatigue, with similar incidence in the two arms. Incidence of severe AEs (≥ grade 3) occurred with a similar rate (52% in the intravenous and 51.9% in the subcutaneous arm); the most common of them being haematological (36.9% vs. 35.4%), gastrointestinal (6.4% vs. 5.7%) and infections (5.0% vs. 6.7%). Serious AEs (SAEs) were reported in 13.4% in IV vs. 21.9% in SC patients. The imbalance was largely driven by increased reporting of SAEs in the "infections" disease category in the SC arm vs. the IV arm (8.1% vs. 4.4%); however, no patients were withdrawn from treatment for this reason in the SC arm. The incidence of cardiac AEs was similar in both arms: 13.1% with IV and 12.8 % with SC administration.

In conclusion, the safety profile of the SC trastuzumab was comparable with the IV trastuzumab, and balanced between the two arms. There are no safety concerns with the use of a fixed 600 mg dose of SC trastuzumab compared with standard IV treatment.

Moreover there are two ongoing studies with SC trastuzumab, the PrefHER to investigate patient preference[45] and the SafeHER examining the safety of assisted and self-administered SC trastuzumab treatments.[46]

Trastuzumab-DM1

The trastuzumab-DM1 opened a new era in the development of anti-HER2-agents: researchers planned to bind a chemotherapeutic agent to the monoclonal antibody to enhance the cell destructive effects of trastuzumab. The T-DM1 (trastuzumab-emtansine) conjugate contains trastuzumab and a maytansine derivate, a cytotoxic agent from the Vinca-alkaloid family.

The phase II studies confirmed the efficacy of T-DM1 in patients with metastatic breast cancer that progressed after trastuzumab and/or lapatinib treatment. The response rate was 25.9%[47] and 34.5%,[48] respectively, and treatment was well tolerated. Perez *et al*. investigated the efficacy of T-DM1 compared to trastuzumab-docetaxel combination. Response rates were 64.2% on the T-DM1 arm and 58% on the trastuzumab-docetaxel arm. With T-DM1 registered side-effects and grade 3 toxicity were less, and the risk of cardiotoxicity was also lower. The overall survival was about the same in the two arms.[49]

There are two ongoing trials with T-DM1. The EMILIA study is investigating the efficacy and safety of T-DM1 monotherapy in second-line treatment vs. lapatinib+capecitabine combinations. The preliminary results suggested significantly prolonged progression-free (9.6 vs. 6.4 months) and overall survival (30.9 vs. 25.1 months – second interim analysis) with less toxicity on the T-DM1 arm compared to lapatinib+capecitabine (grade 3/4 adverse events: 41% vs. 57%).[50]

The MARIANNE trial is comparing the efficacy and safety of T-DM1 in monotherapy and in combinations (T-DM1+pertuzumab, T-DM1+placebo and trastuzumab+taxane arms) as first-line treatments for metastatic HER-2 positive breast cancer patients.[51]

New Agents

Additionally to TDM-1 there are new trastuzumab-related agents in phase I or II. The most promising drugs are – like T-DM1 – combinations of trastuzumab and a chemotherapeutic agent, such as MM-302, which is a conjugate of liposomal doxorubicin and trastuzumab.[52] Another interesting direction is the conjugation of differently functioning antibodies. Ertumaxomab is a hybrid, trifunctional antibody: it binds not just to HER-2, but to the CD3 antigen of the T-cells as well. The HER-2-ertumaxomab-CD3 complex increasingly activates phagocytosis and ADCC, and successfully enhances the anti-tumour immune response.[52]

Conclusion

In the treatment of breast cancer trastuzumab brought a new era and a life-changing option for patients with HER-2 positive breast cancer. New administration routes and new therapeutic agents are offering promising new perspectives in individualised oncotherapy. The resistance to trastuzumab is still an open question. However stronger suppression of HER2 signalisation by the addition of the HER2 dimerisation inhibitor pertuzumab to trastuzumab would be able – at least partly - to solve this problem. Investigations focusing on further signalisation pathways could offer multidirectional, individualised therapeutic strategies for HER-2 positive patients.

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Management of Castration-Resistant Prostate Cancer (CRPC)

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Introduction

Castration-resistant prostate cancer (CRPC) is the term given to the clinical state where prostate cancer progresses despite Androgen Depletion Therapy (ADT). Prostate cancer is the second most common cause of cancer death amongst men globally, according to the American Cancer Society. Prostate cancer deaths are typically due to metastatic CRPC (mCRPC). However, the introduction of novel treatments for mCRPC is resulting in improved survival times, according to recent studies.

CRPC is a catch-all term for a wide spectrum of disease. This can range from asymptomatic non-metastatic cancers, which are identified by rising PSA levels, to aggressive tumours with severe metastases. Around 90% of patients with mCRPC have bone metastases which can cause significant morbidity including pain, spinal chord compression, bone marrow failure and pathologic fractures.[1, 2, 3]

In this review we present an overview of the current management approaches of CRPC as well as outlining new novel treatments that have recently been approved and have shown promising outcomes in clinical trials. The approaches and treatments can be classified within four broad areas. The first is hormonal therapies that target the androgen receptor (AR) pathway. The second area is immunotherapy, which involves stimulating the immune system to reject cancer. The third area is systemic chemotherapy, while the fourth is bone-targeting therapies, which can help reduce bone fragility. The review will also look at the future treatments for CRPC including ongoing clinical trials designed to delay progression and address the morbidities and mordality associated with the condition.

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Hormonal Therapies

Secondary Hormonal Manipulation

As the AR remains active in virtually all patients with CRPC it is recommended that ADT should be continued in these patients. Secondary hormonal manipulation involves using combined androgen blockade (CAB), through adding an AR antagonist such as bicalutamide (for patients that have had an orchidectomy). Studies have shown that such an approach can cause prostate-specific antigen (PSA) reductions in 30% of patients.[4, 5, 6, 7, 8]

Systemic Corticosteroid Therapy

By treating patients with corticosteroid therapy with low-dose prednisone or dexamethasone, decreased levels of PSA can be realised in a third of patients with mCRPC. A number of studies have shown that prednisone therapy in mainly symptomatic CRPC patients can reduce PSA levels by 50% from baseline for those for whom the treatment is effective.[9, 10]

Abiraterone Acetate

Abiraterone acetate inhibits CYP17, an enzyme which is expressed in a number of cancers including prostate cancer. According to studies, CPY17 is critical for androgen production in the adrenal gland, as well as in prostate tumours.[11] In the COU-AA-301, multi-centre randomised, phase III clinical trial, abiraterone acetate plus prednisone increased medium survival by 4.6 months for patients with mCRPC, when compared to a placebo plus prednisone. In addition, all secondary end-points showed the superiority of abiraterone versus placebo. This includes medium time to PSA progression (1.9 month improvement), radiographic progression-free survival (2 month improvement), confirmed PSA response rate, as well as an increase in objective response as evaluated by Response

Evaluation Criteria in Solid Tumours (RECST).[12] As a result abiraterone acetate has been approved as a second-line treatment for CRPC by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Health Canada.

In 2012, the results of COU-AA-302 were announced. The phase III clinical trial evaluated abiraterone acetate plus prednisone versus placebo plus prednisone for patients with asymptomatic or mildly symptomatic mCRPC. In the abiraterone acetate plus prednisone arm of the trial, a 25% lower mortality was reported for men and so it was recommended that patients receiving the placebo switch to this group. In addition all end-points, such as time to opiate-use for cancer related pain, time to the start of chemotherapy and time to PSA progression favoured abiraterone acetate with prednisone.[13] As a result, the FDA and the EMA approved the treatment for chemotherapy-naïve mCRPC.

Enzalutamide

Enzalutamide is an AR antagonist drug. Enzalutamide has shown a five-fold increase in binding to the AR compared to bicalutamide. As opposed to other AR antagonists, enzaltumide does not have any agonistic activity. The drug can also reduce the size of LNCaP xenograft tumours, where as other AR antagonists can only restrict further growth. Enzalutamide was approved by the FDA in 2012. A phase III clinical trial demonstrated that enzalutamide increased medium overall survival times by 4.8 months compared to a placebo. [14]

Immunotherapy

In 2012, sipuleucel-T was the first immunotherapeutic agent approved by the FDA for the treatment of prostate cancer. The biotech drug is an autologous "vaccine". White blood cells are collected from the patient in order to harvest antigen-presenting cells (APCs). The APCs are then exposed to a prostatic acid phosphatase-granulocyte macrophage colony stimulating factor (PAP-GM-CSF) fusion protein. This is then reinfused into the patient's body. A double blind, multi-centre, placebo controlled phase III clinical trial demonstrated a 22% reduction in mortality in those in the sipuleucel-T arm of the trial compared with the placebo arm. Overall survival time was 25.8 months versus 21.7 months for the placebo.[15]

Other immunotherapeutic agents include investigational cancer vaccine PROSTVAC-V/F. The poxviral-based, PSA-targeted vaccine has demonstrated promising results in a phase II clinical trial. In a double-blind, randomised phase II study PROSTVAC-V/F was correlated with a 44% reduction in mortality rates and an 8.5 month increase in survival times in men with mCRPC versus the control. However, the primary end point of the trial was not overall survival difference but progression free survival (PFS), for which the drug showed no improvement versus control.[16,17] PROSTVAC-V/F is now in phase III clinical trials for overall survival both with and without adjuvant dose GM-CSF, versus a placebo.

Another therapy being developed is the human monoclonal antibody ipilimumab. According to preliminary results from early stage trials the use of ipilimumab on its own or in combination with GM-CSF or radiotherapy improved the anti-tumour immune response in prostate cancer patients.[18, 19, 20] Phase III trials are currently ongoing.[21, 22]

Systemic Chemotherapy

First-line Treatments

Since 2004, the standard treatment for men with detectable mCRPC has been docetaxel and prednisone. This is due to the results from two large-scale clinical trials - TA X327 and SWOG 9916 - which demonstrated the superiority of this treatment regime when compared to mitoxantrone and prednisone, which was the previous standard. In the TA X327 trial, 1,006 patients were randomly chosen to be given either docetaxel - with a dosage of 75 mg/m2 every 3 weeks or 30 mg/m2 every week - plus prednisone. On the other arm of the trial the patients received mitoxantrone - with a dosage of 12 mg/m2 every 3 weeks - plus prednisone. Men in the docetaxel group showed a 2.4 month improvement in survival compared to those in the mitoxantrone group. In addition 42% of those in the docetaxel arm saw a 50%+ reduction in serum PSA compared to 32% of those taking mitoxantrone plus prednisone. Also, docetaxel plus prednisone demonstrated a 13% increase in pain response and a 9% rise in a quality of life response.[23] As a result of these trials the recommended treatment for mCRPC - in order to improve overall survival as well as pain management and quality of life - is for the patient to receive 75 mg/m2 of docetaxel every three weeks plus 5mg of prednisone twice a day.

Second-line Treatments

Until a few years back there were no life-prolonging treatments available for those with docetaxel-resistant tumours or tumours in a post-docetaxel state. Up to 2010, mitoxantrone was the most commonly used second-line systemic chemotherapy, even though it has limited activity and increased toxicity and only demonstrated response rates of between 9-20%.[24,25,26]

A phase III randomised, placebo controlled clinical trial for the taxane agent cabazitaxel has recently been completed. In the trial, patients were randomly assigned to receive 10mg of prednisone daily with either 3-weekly doses of 25 mg/m2 of cabazitaxel or 12 mg/m2 mitoxantrone. A statistically significant increase in survival times emerged for those in the cabazitaxel arm of the trial, with median survival increasing to 15.1 months from 12.7 months for the mitoxantrone group. But both groups saw a high rate of grade 3–4 neutropenia, which was seen in 81.7% of those taking cabazitaxel and 58% of those taking mitoxantrone.[27] As a result of the trials, in 2010 the FDA approved cabazitaxel for treatment for patients with mCRPC previously treated with docetaxel. In 2011, Health Canada and the EMA also approved cabazitaxel.

Bone-targeted Therapy

One of the potential ramifications of prostate cancer can be bone loss, as well as other debilitating conditions such as bone pain, spinal chord compressions and pathologic fractures. Prostate cancer is a risk factor for both osteoporosis, as well as ADT-related bone loss.

Radiopharmaceuticals

Systemic radiopharmaceuticals allow the delivery of radiation to areas of high bone turnover. Two beta-emitting pharmaceuticals, strontium-89 and samarium-153, have been approved by the FDA for treating pain caused by bone metastases.[41] In a phase III clinical trial of radium-223 - an alpha emitting agent - there was a 2.8 month overall increase in survival for patients with mCRPC (14 months compared to 11.2 months). This translates to a 30% increase versus placebo. There was also a five month delay in time to first SRE[42, 43]. Radium-223 was approved by the FDA in May 2013 and the EMA In November 2013 as the first radiopharmaceutical that prolonged overall survival in this patient population.

Bisphosphonates

The most widely used bone targeting agents are bisphosphonates. These work by binding to calcium being integrated into the bone matrix. Multiple studies had demonstrated that bisphosphonates significantly reduce ADT-related bone loss for men with non-metastatic prostate cancer. However, no trials have yet to conclusively prove a reduction in bone fractures.[28, 29, 30, 31, 32, 33]

Zoledronic acid is a bisphosphonate that has been shown to reduce the risk of skeletal-related events (SRE's) in patients with bone metastases. A randomised, controlled, phase II clinical study showed that 4mg of zoledronic acid every three weeks resulted in a 48% reduction in annual incidence of SRE's. It also resulted in a five month delay in the medium time to first SRE as well as a 36% overall reduction in SRE's.[34, 35] Due to these results in 2002, the FDA and EMA approved zoledronic acid for preventing SREs in patients with mCRPC. However, there are some concerns over bisphosphonate-induced nephrotoxicity especially after intravenous administration, and so, the monitoring of serum creatinine before each treatment is recommended. Also, other side-effects have been noted such as self-limiting bone pain, flu-like symptoms, hypocalcaemia and osteonecrosis of the jaw (ONJ).[36]

Denosumab

The human monoclonal antibody denosumab (60mg every six months) has been shown to improve bone mass density and reduce new vertebral fractures for patients with nonmetastatic prostate cancer who are receiving ADT.[37] In a randomised, controlled trial denosumab (120mg every four weeks) was shown to be more effective than zoledronic acid for delaying the time to first SRE in men with mCRPC. Denosumab increased the time to first SRE from 17.1 months to 20.7 months.[38] Denosumab has not been shown to cause nephrotoxicity, although hypocalcaemia was seen more frequently with denosumab than with zoledronic acid and so it is suggested that vitamin D is appropriately repleted before therapy and calcium levels are continually monitored.[39] Meanwhile, in 2012, a clinical trial showed that denosumab delayed bone metastasis in patients with nonmetastatic CRPC (29.5 months compared to 25.2 months for a placebo). No difference in overall survival was found between denosumab and placebo groups.[40]

Conclusions

The therapeutic options for CRPC and mCRPC have increased markedly in the past ten years. Overall survival has been prolonged by hormone therapies such as abiraterone and enzalutamide. Sipuleucel-T is the first immunotherapeutic agent shown to be effective in treating prostate cancer while other immunotherapies such as ipilimumab and PROSTVAC-VF are currently being investigated. Regarding chemotherapy, docetaxel remains the main first-line treatment for mCRPC, while cabazitaxel is the standard second-line treatment. The risk of SRE's, meanwhile, can be reduced with the bisphosphonate zoledonic acid. Meanwhile, human monoclonal antibody denosumab has been shown to reduce time to first SRE in men with mCRPC and significantly delays bone metastasis in patients with nonmetastatic CRPC. With the current research being conducted into prostate cancer there is increased hope for patients. Men with CRPC are living longer, with improved quality of life although better treatments are still needed as the disease remains incurable.

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Time to First Symptomatic Skeletal Event (SSE) with Radium-223 Dichloride (Ra-223) in Patients with Castration-Resistant Prostate Cancer (CRPC) and Bone Metastases: ALSYMPCA Trial Stratification Factors Analysis

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Introduction

Bone metastases are highly prevalent in patients with advanced prostate cancer, occurring in > 90% of those with castration-resistant prostate cancer (CRPC).[1] Such patients are at an increased risk of skeletal events such as pathologic fractures, spinal cord compression, and the need for orthopaedic surgical intervention or radiation therapy to the bone.[2]

Radium-223 dichloride (Ra-223) is an alpha-emitting pharmaceutical that mimics calcium, thereby allowing it to form complexes with the bone mineral hydroxyapatite in areas where there is increased bone turnover, such as bone metastases. Ra-223 emits alpha-particles with ultrashort penetration (< 100 µm; 2-10 cell diameters), causing a highly localised antitumour effect on adjacent bone metastases while limiting damage to the surrounding normal tissue.[3-5]

Parameter	Radium-223 (n = 614)	Placebo (n = 307)
Age, mean, y	70.2	70.8
Race, Caucasian, n (%)	575 (94)	290 (95)
Baseline ECOG score, n (%)		
≤ 1	536 (87)	265 (87)
2	76 (12)	40 (13)
Extent of disease, n (%)		
< 6 metastases	100 (16)	38 (12)
6-20 metastases	262 (43)	147 (48)
> 20 metastases/superscan	249 (41)	121 (40)
Previous EBRT bone treatment, n (%)	306 (50)	149 (49)
EBRT within 12 wk of screening	99 (16)	48 (16)
Total ALP, U/L, median (range)	211 (32-6431)	223 (29-4805)
PSA, µg/L, median (range)	146 (3.8-6026)	173 (1.5-14500)
Prior docetaxel, yes (%)	352 (57)	174 (57)
Bisphosphonate at study entry, yes (%)	250 (41)	124 (40)

Table 1. Patient demographics and baseline characteristics (ALSYMPCA ITT population; N = 921). Alkaline phosphatase (ALP); external beam radiation therapy (EBRT); Eastern Cooperative Oncology Group (ECOG); prostate-specific antigen (PSA).

ALSYMPCA Trial

Based on phase 2 studies demonstrating that Ra-223 reduces pain and improves disease-related markers in patients with CRPC and bone metastases, the phase 3 Alpharadin in Symptomatic Prostate Cancer patients (ALSYMPCA) study was conducted to evaluate the efficacy and safety of Ra-223 in this population.[6] This study included 921 patients with confirmed, progressive CRPC with ≥ 2 bone metastases and receiving best standard of care; patients were randomised 2:1 to receive Ra-223 (at a dose of 50 kBq/kg IV) or matching placebo every 4 weeks for 6 doses (Figure 1).[6]

Results from the primary efficacy analysis indicated that Ra-223 significantly improved overall survival (primary end point; Figure 2) with

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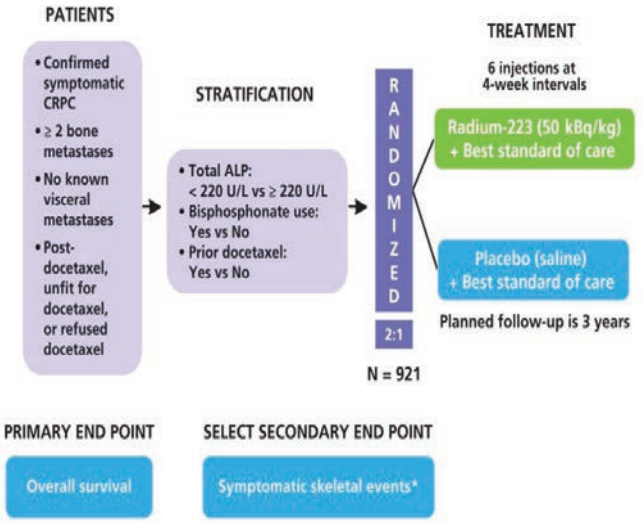

Figure 1. ALSYMPCA trial design. *Pathological bone fractures were required to be clinically relevent, not asymptomatic compression fractures.

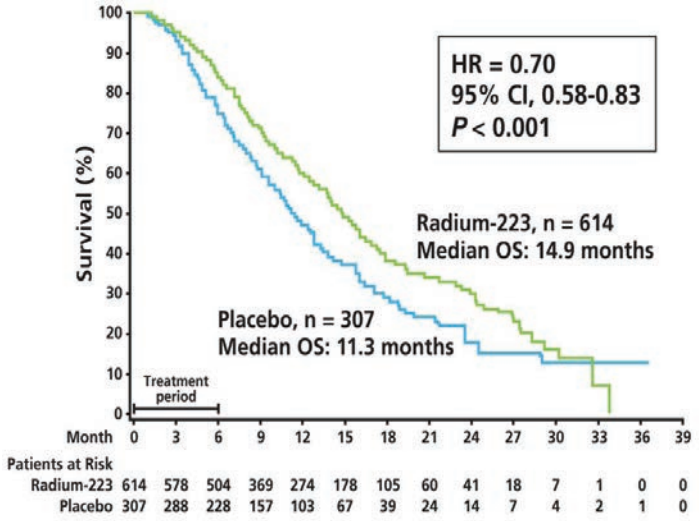

Figure 2. Overall survival in the overall intent-to-treat population in ALSYMPCA (N = 921). *P* value is for descriptive purpose only.

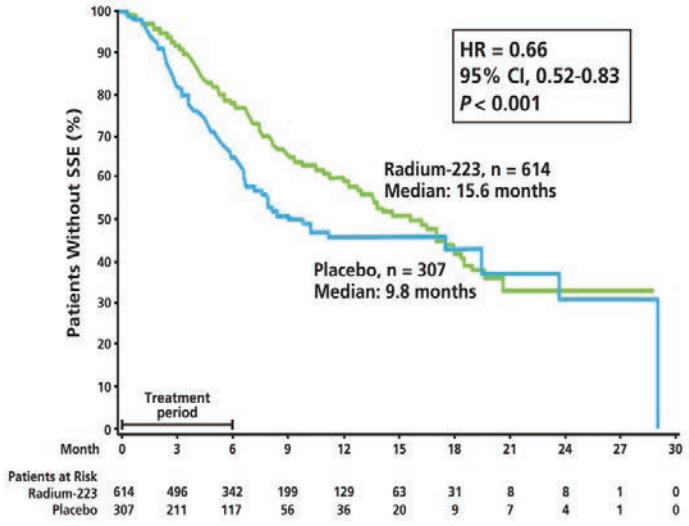

Figure 3. Time to first SSE in the overall intent-to-treat population in ALSYMPCA (N = 921). *P* value is for descriptive purpose only.

median overall survival durations of 14.9 and 11.3 months in the Ra-223 and placebo groups, respectively (hazard ratio, 0.70; 95% CI, 0.58-0.83; $P < 0.001$).[6] Ra-223 was also associated with a favourable safety profile with a low rate of haematologic adverse events.[6]

Stratification Analysis of the ALSYMPCA Trial

Rationale and Methods

An analysis of the effect of Ra-223 on the time for ALYSMPCA patients to first experience a new symptomatic skeletal event (SSE), according to baseline trial stratification factors, was performed and reported at the European Society for Medical Oncology (ESMO) 2013.[7] Unlike other studies that include asymptomatic fractures as a skeletal event, the reporting of SSEs in ALSYMPCA increases the clinical relevance of the results. SSEs were defined as (1) new symptomatic pathologic bone fractures, (2) use of external beam radiation therapy (EBRT) to relieve bone pain, (3) spinal cord compression, and (4) tumour-related orthopaedic surgical intervention. All skeletal events were required to be symptomatic on the basis of clinical evaluation and were not assessed by periodic radiologic review. The time to first SSE was assessed for the entire intent-to-treat (ITT) population (N = 921) and by the following baseline trial stratification factors:

- Current bisphosphonate use at study entry (yes/no)
- Prior docetaxel (yes/no)
- Alkaline phosphatase (ALP) levels (< 220 or ≥ 220 U/L)

Results

Patient demographics and baseline characteristics were similar between treatment groups (Table 1). Two hundred sixty-two of 614 patients receiving Ra-223 (43%) and 132/307 patients receiving placebo (43%) had concomitant use of a bone-targeted agent (bisphosphonate or denosumab) from the first injection to 12 weeks post last dose. Zoledronic acid was the most commonly used agent (87% and 86% of patients in the Ra-223 and placebo groups, respectively).

In the overall ITT population, Ra-223 significantly prolonged time to first SSE versus placebo (Figure 3). Ra-223 also prolonged time to first SSE regardless of the baseline stratification factors. As seen in Figure 4, treatment effect on time to first SSE favoured Ra-223 over placebo regardless of current bisphosphonate use. While the results suggested a greater effect on SSE in the subgroup who received a bisphosphonate than in the subgroup who did not, this interpretation should be made with caution, as the ALSYMPCA trial was not powered for subgroup analyses. Similarly, Ra-223 prolonged the time to first SSE versus placebo, regardless of prior docetaxel use (Figure 5) or baseline ALP level (Figure 6).

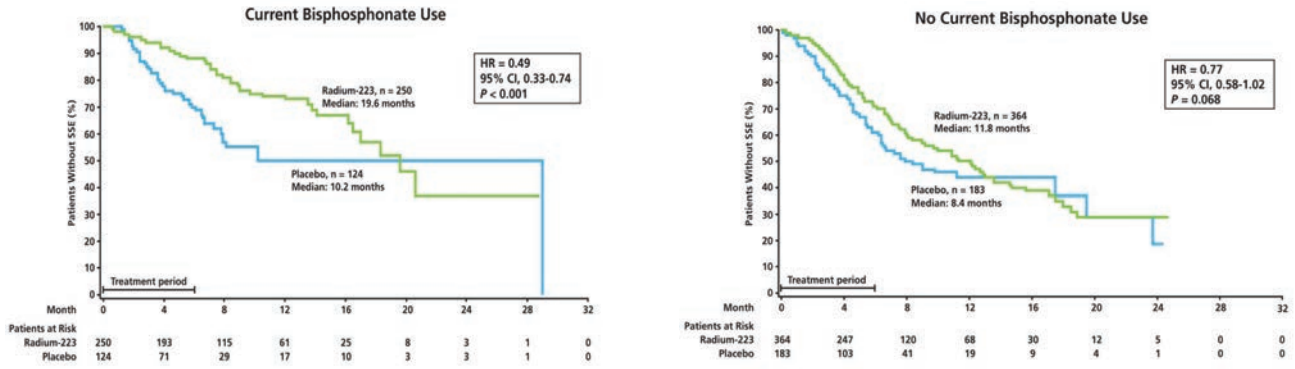

Figure 4. Time to first SSE stratified by bisphosphonate use at study entry (ITT population; N = 921). *P* value is for descriptive purpose only and not adjusted for multiplicity.

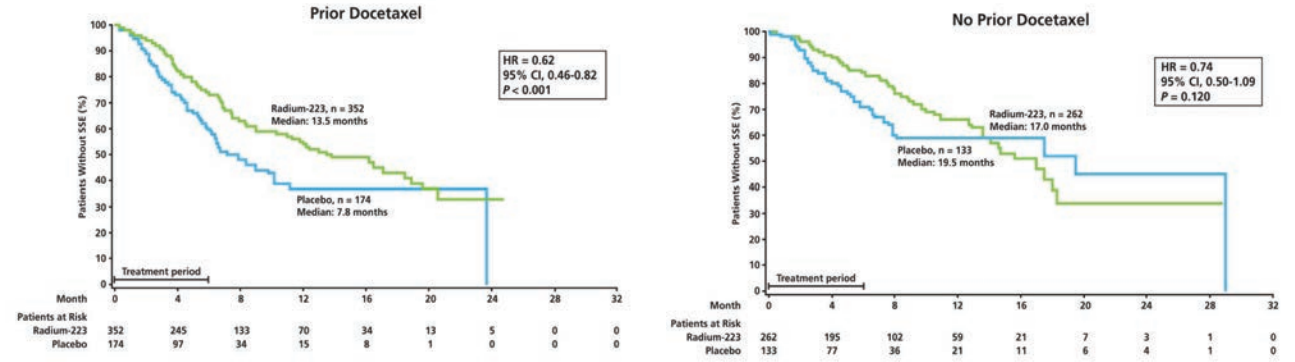

Figure 5. Time to first SSE stratified by prior docetaxel use (ITT population; N = 921). *P* value is for descriptive purpose only and not adjusted for multiplicity.

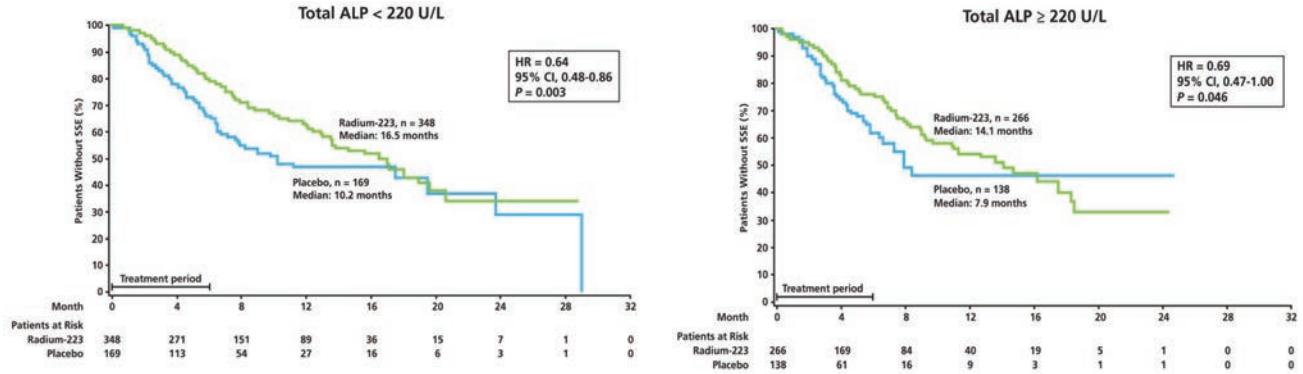

Figure 6. Time to first SSE stratified by baseline ALP levels (ITT population; N = 921). *P* value is for descriptive purpose only and not adjusted for multiplicity.

Conclusions

In addition to improving overall survival, Ra-223 prolonged the time to first SSE in patients with CRPC and bone metastases. The results of this analysis demonstrate that the beneficial effects of Ra-223 on skeletal morbidity occur regardless of baseline stratification factors. This observation, along with the clinical benefit of prolonging survival, makes Ra-223 an important treatment option for patients with CRPC and symptomatic bone metastases.

Disclaimers

Research support: supported by Bayer HealthCare, Whippany, New Jersey, USA, and Algeta ASA, Oslo, Norway.

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Castration-Resistant Prostate Cancer (CRPC) - Highlights from the European Cancer Congress 2013

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Reviewed by **Joe O'Sullivan,** Professor of Radiation Oncology, Centre for Cancer Research and Cell Biology, Queen's University Belfast

Summary

This review brings you our highlights of The European Cancer Congress (ECC) 2013, with a focus upon castration-resistant prostate cancer (CRPC).

The symposium presentations, from a satellite symposium session on Genitourinary Malignancies - Prostate Cancer, present the current treatment landscape in castration-resistant prostate cancer (CRPC) with bone metastases, the biology of bone metastases and rational for bone-targeted drug design, best practices for the early identification of patients at risk for bone metastases, and the future of bone-targets therapeutic options in the treatment of CRPC.

This review also summarises four key presentations and several posters on the treatment of CRPC. The presentations reviewed are as follows:

1. Early Identification of Bone Metastases: Prognosis and Future Directions by Fred Saad, Professor and Chairman of Urology, Director of Urologic Oncology, University of Montreal, Endowed Chair, University of Montreal Hospital Center, Montreal, Quebec, Canada.

2. Recent Progress in our Understanding of Bone Metastases, by Winald Gerritsen, Radboud University, Nijmegen, Netherlands.

3. The Present and Future of Bone-Targeted Therapy for CRPC, by Stéphane Oudard, Georges Pompidou, European Hospital, France.

4. Case report: A patient with metastatic Castration-Resistant Prostate Cancer (mCRPC) and bone metastases by Oliver Sartor, Loborde Professor for Cancer Research, Medical Director, Tulane Cancer Center, Tulane Medical School, New Orleans, Lousiana, USA.

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Summaries of four posters on genitourinary malignancies of the prostate also presented at the end of the review are as follows:

Abstract (2876): Time to first skeletal-related event (SRE) with radium-223 dichloride (Ra-223) in patients with CRPC and bone metastases: ALSYMPCA trial stratification factors analysis. R. Coleman, S. Fosså, A. Chodacki, S. Wedel, O. Bruland, K. Staudacher, J. Garcia-Vargas, O. Sartor.

Abstract (2878): Effects of Ra-223 on health-related quality of life (QoL) outcomes in the phase 3 ALSYMPCA study in patients with CRPC and bone metastases. C. Parker, D. Heinrich, D. Bottomley, P. Hoskin, L. Franzén, A. Solberg, V. Pawar J. Reuning-Scherer, C.G. O'Bryan-Tear, S. Nilsson.

Abstract (2883): Ra-223 efficacy and safety in patients with CRPC with bone metastases: Phase 3 ALSYMPCA study findings stratified by age group. P. Wiechno, S.I. Helle, J. Logue, S. Nilsson, O. Sartor, R.E. Coleman, J. Kliment, F. Fang, C. Parker.

Abstract (2877): Hematologic safety of Ra-223 in the phase 3 ALSYMPCA trial in CRPC patients with bone metastases: Baseline prognostic factor subgroup analysis. J. O'Sullivan, D.C. Johannessen, A. Widmark, I. Syndikus, N. James, M. Dall'Oglio, I. Haugen, A. Cross, J. Garcia-Vargas, N. Vogelzang.

Background

CRPC represents a spectrum of advanced prostate cancer ranging from a) patients with no metastases or symptoms and rise in serum prostate-specific antigen (PSA) levels despite androgen deprivation therapy (ADT), to b) patients with metastases and significant debilitation due to cancer symptoms. The prognosis of patients with mCRPC is determined by performance status, the presence of bone pain, the extent of disease (seen on bone scan) and serum alkaline phosphatase levels.[1]

Professor Fred Saad said that an increasing number of patients with CRPC present with no evidence of metastasis. There is no standard of care for this patient group.

Improved understanding of the molecular mechanisms that underlie CRPC and an expanded repertoire of therapeutic options have

resulted in an improvement in overall survival (OS) in patients with mCRPC. Patients with clinically asymptomatic mCRPC have an improved life expectancy of approximately 3 to 4 years as compared to the life expectancy of approximately 12 to 18 months in the past. Once these patients develop symptoms, their life expectancy falls to approximately 1 to 2 years.[2]

Highlighting the history of medical treatment of mCRPC, Saad noted that docetaxel (introduced in 2004) was the first therapy that improved OS in patients with mCRPC. Recently, the following new chemotherapeutic agent and three new advanced therapeutics have been shown to prolong OS in patients with mCRPC: cabazitaxel (2010); abiraterone acetate (2011), enzalutamide (2012) and radium-223 (2013). Table 1 below summarises Saad's review of combination chemotherapies currently used to treat mCRPC.

Combination Chemotherapy	Findings/Treatment Guidelines
Docetaxal-Prednisone	• Standard of care for the first-line treatment in mCRPC. • Approximately 25% improvement in OS as compared with mitoxantrone plus prednisone.[3, 4]
Cabazitaxel-Prednisone	• Second-line treatment for mCRPC in patients whose disease has progressed during, or after, docetaxel-based therapy. • Approximately 30% improvement in OS. • Approximately 25% in progression free survival (PFS) in mCRPC as compared with mitoxantrone-prednisone.[5]
Abiraterone-Prednisone	• Prolongs OS in patients with mCRPC whose disease has progressed following treatment with docetaxel. • Approximately 35% improvement in OS over the placebo-prednisone in phase 2 randomised study.[6] • Approved for treatment in docetaxel-naïve patients with mCRPC. • Patients treated with abiraterone-prednisone in a phase 2 study had a PFS of 16.5 months as compared to a PFS of 8.3 months seen in patients treated with prednisone alone; this represents a 45% improvement in PFS. [7]
Enzalutamide-Prednisone	• Improvement in OS of 4.8 months when compared with placebo; patients are therefore 37% less likely to die from mCRPC. [8]
Ra-223	• Improvement of 3.6 months when compared with placebo. • 30% reduction in risk of dying from mCRPC in patients treated with Ra-223.[9]

Table 1. Combination chemotherapy treatment in mCRPC.

Professor Saad said that until recently less 50% of patients with mCRPC received chemotherapy with docetaxel before dying of their disease.[10] Currently patients with mCRPC may receive hormone therapy, abiraterone-prednisone, or Ra-223 prior to treatment with docetaxel. For those patients whose disease has progressed after treatment with docetaxel, treatment options include cabazitaxel-prednisone, abiraterone-prednisone and Ra-223. Table 2 below presents promising new pipeline treatments currently in Phase 3 trials.

Dr Winald Gerritsen said normal bone remodelling relies on the balance and coordination between the activities of osteoblasts and osteoclasts; mCRPC interferes with normal bone homeostasis by interacting with the stromal cells, osteoblasts, osteoclasts, endothelial cells and extracellular matrix within the bone microenvironment.[11]

Prostate cancer cells secrete osteoblastic factors such as endothelin (ET-1), bone morphogenetic proteins (BMPs), insulin-like growth factor (IGFs), fibroblast growth factors (FGFs), plasmogen activator (uPA) and transforming growth factor-beta (TGF-β). These factors promote osteoblast proliferation, stimulate osteoblasts to produce factors that trigger the proliferation of prostate cancer cells, and promote the secretion of growth factors that trigger the deposition of immature (woven) bone matrix. The collagen fibres of woven bone matrix produced in this 'vicious cycle' of bone metastasis are arranged in irregular, random arrays and are therefore of suboptimal strength.[12, 13, 14]

Gerritsen said that targeting the altered microenvironment and the disordered bone matrix are key components of the treatment strategy in metastatic bone disease in CRPC.[15] Bisphosphonates, denosumab and radioisotopes are targeted therapies for treating bone metastases. These therapies work by a) interfering with deregulated signalling pathways to or from the bone, or b) targeting bone and actively killing prostate tumor cells. Figure 1 presents a graphical representation of the bone metastasis-targeted treatment strategies of bisphosphonates, denosumab, and radioisotope therapies in mCRPC.[16, 17, 18]

In summary, Dr Gerritsen highlighted the following key points.

- Bone is the most common site of prostate cancer metastasis; metastasis of the spinal column are common which can led to compression of the spine and subsequent decrease in QoL and increased medical cost.
- Bone metastases are associated with increased mortality, increased morbidity, decreased QoL and increased medical costs.
- The bone microenvironment provides an optimum location for tumour

Therapeutic approach	Specific pipeline therapies
Specific pipeline therapies	• Orteronel (a reversible inhibitor of 17,20-lyase which is a key enzyme in the production of androgenic hormones) • ARN- 509 (an AR antagonist)
Targeted therapies	• Custersin • Cabozantinib
Immunotherapies	• Ipilimumab • Prostvac

Table 2. Promising pipeline therapies in mCRPC.

survival and proliferation and represents an attractive therapeutic target.

• Denosumab and zoledronic acid delay SREs but do not provide a survival benefit.

• Ra-223 is FDA approved improves survival, delays SRE and relieves pain.[19]

Professor Saad identified bone pain, pathologic fracture, spinal cord compression and skeletal surgery as the main complications of bone metastases.[20, 21]

SREs

SREs are common in patients with mCRPC and are associated with significant cost and utilisation of health resource. Prostate cancer, Professor Saad said, has the highest risk of spinal cord compression among solid tumour cancers. Saad said that almost every bone-metastatic patient will experience bone complications before death.

Professor Saad said that:

• SREs reduce survival from mCRPC independent of any other factor. Similar results have been found for other metastatic cancers such as breast cancer and lung cancers affecting bone.

• Patients with 1 SRE are at higher risk of dying within a year of their SRE as compared with those patients with no SRE.[22]

• Extent of bone metastases is inversely correlated with survival.[23]

• Early diagnosis and early treatment improves survival rates.

• Patients with skeletal complication have a higher mortality risk of dying within one year than those that do not.

Saad noted that bone pain is a very important prognostic factor of patients with mCRPC; early intervention improves QoL, prognosis and OS in these patients. Patients who receive treatment for their disease before developing bone pain are 2 times less likely to develop skeletal complications from bone metastases.

Diagnosing Bone Metastases

The diagnosis of bone metastases remains a challenge. Approximately 30% of patients with normal bone scans were found to have metastasis on magnetic resonance imaging (MRI) scans; and MRI scanning revealed metastases in 47% of patients with equivocal bone scans.[24] Saad advised physicians to rely on MRI scanning for detecting bone metastases. Whole body MRI (WBMRI) with diffusion weighted imaging bone scan (DWIBS) is the most sensitive, specific and cost-effective approach for diagnosing and prognosis of bone metastases.[25]

Biomarkers and Bone Markers in mCRPC

Saad said that PSA remains the best biochemical marker for predicting when patients will develop metastases.

Key points:

• PSA doubling time allows physicians to stratify patients in terms of risk and determine how often patients should be scanned to properly track disease progression,

• Patients with PSA doubling time of less than 8 months risk of metastases increase exponentially.

• Patients with a stable PSA doubling time of approximately 10 months or greater can be followed on a yearly basis with bone imaging.[26]

There are 2 main categories or bone markers: markers of bone formation such as bone alkaline phosphatase (BALP), and markers of bone resorption (e.g. NTX, CTX, ICTP). Saad said that bone markers are extremely powerful prognostic indicators; these studies are also easy to conduct in clinical settings. In the absence of hepatic metastases, ALP is equivalent to BALP; NTX is the most commonly used marker for bone resorption.[27]

Key points:

• Bone markers predict the risk of bone complications and death more powerfully than PSA.[28]

• Patients with high elevation of ALP are 3 times more likely to die of the disease; they also have a high risk of developing complications as a result of bone metastases.

• NTX levels in the medium to high range have a significant risk of death and of complications from bone metastases compared with patients with normal levels of these bone markers.

• Normalising high bone marker levels of patients may result in a 38% reduction in the risk of bone complications and a 59% reduction in the risk of death as compared with the outcomes of patients whose bone marker levels remained elevated; this translates to a survival of 11 months in patients whose bone marker levels were consistently high as compared with 22 months in patients whose levels were normalised.

• Normalising bone markers may therefore be used as an indicator of the success of treatment.[29,30]

Professor Stéphane Oudard said that main drugs indicated for treatment

Treatments that Interfere with Deregulated Signalling Pathways to or from the Bone

Denosumab
- Human monoclonal antibody.
- Inhibits RANK ligand (RANKL).
- Prevents loss of osteoclast formation and survival.
- Palliative effects.
- No impact of overall survival.

Bisphosphonates
- Binds to bone mineral.
- Taken up by mature osteoclasts at bone resorption sites.
- Influences function of osteoclasts.
- Causes loss of bone resorption.
- Palliative effects.
- Reduces detrimental adverse effects of woven bone.
- No impact of overall survival.

Treatments that Target Bone and actively Kill Prostate Tumour Cells

External Beam Radiation Treatment
- Local Treatment.
- Effective in paniful bone metastases.
- Accurate calculation using image-guided radiotherapy.
- No improvement in overall survival.

Beta Emitting Radioisotopes
- Strontium-89 (Sr-89).
- Samarium-153 (Sam-153).
- Lead shield required.
- Highly effective for pain palliation.
- Effect on Stromal cells.
- Toxicity with Increased bone marrow exposure.
- No survival benefit.

Alpha Emitting Radioisotopes
- Ra-223.
- FDA approved.
- No lead shielding required.
- Can be administered in outpatient settings.
- Demonstrate improvement in overall survival.
- May preserve bone marrow health.

Figure 1. Graphical Representation of Bone Metastasis-targeted Treatment Strategies of Bisphosphonates, Denosumab, and Radioisotope Therapies in mCRPC.

of patients with mCRPC in the ESMO guidelines are: 1) intravenous (iv) zoledronic acid (FDA and EMA approved since 2002), and 2) subcutaneous (sc) denosumab (FDA and EMA approved since 2010); both improve pain palliation and delay SREs.

Although zoledronic acid significantly reduces the number of SREs in patients with mCRPC, denosumab performed better than zoledronic acid in preventing SREs; neither drug improves OS. Back pain, fatigue and osteonecrosis of the jaw are adverse effects (AEs) of these therapies. Patients also therefore additionally receive vitamin D and calcium to counteract AEs. Back pain occurs in 30% of patients on zoledronic acid and 32% of patients on denosumab; pain; fatigue occurs in 23% of patients on zoledronic acid and 27% of patients on denosumab. Approximately 1% to 2% of patients treated with these drugs develop osteonecrosis of the jaw.

Outlining the benefit of strontium-89 and samarium-153 for treating metastases-related bone pain, Oudard said that these treatments were also associated with leucopenia, thrombocytopenia, heamorrhage and infections. Patients should therefore receive post-radiotherapy platelets infusions to combat AEs.

Oudard reviewed results of the recent ALSYMPCA phase 3 trial of Ra-223.[31] Key findings of the study are as follows:

- Ra-223 delays SRE, SSE and death in mCRPC.
- Treatment with radium plus best standard of care (BoSC) improved OS regardless of prior chemotherapy treatments; there was an overall increase in OS of 3.6 months with a 4.6 months increase in docetaxel-naïve patients and 3.1 months increase in patients treated with docetaxel prior to Ra-223.
- Patients treated with Ra-223 + BSoC developed symptomatic SREs 5.8 months later than those treated with placebo + BSoC
- The AE profile of patients treated with Ra-223+ BSoC was similar to those treated with placebo + BSoC.

Reflecting on over 20 years in the field, Professor Sartor said that the introduction of docetaxel in 2004 changed the mindset of physicians treating mCRPC; Table 3 summarises the case of a 67-year-old patient with mCRPC diagnosed in 1999 prior to docetaxel, who was still alive in August 2013.

Sartor said that while there are many treatment options for mCRPC the disease remains fatal. Furthermore the post-docetaxel space is losing meaning, except to insurers and regulators; the post abiraterone space is increasingly more important. However, little is known about the implications of cross-interactions of abiraterone and other treatments for efficacy, prognosis and healthcare outcomes. Sartor also stressed the importance of a) early treatment in mCRPC, and b) respecting patients' preferences in treatment decisions.

Poster 2876 by Coleman and colleagues showed that Ra-223 prolonged time to first SRE in patients with mCRPC irrespective of baseline stratification factors.

Date	Case History
1999	Diagnosis: T2N0MO Gleason 7: Treated with radical prostatectomy
2000	Developed PSA recurrence: Treated with salvage radiation and LHRH analogue for 6 months
2004	A PSA rise was documented after ADR was stopped: treated with intermittent ADT
2010	mCRPC diagnosed (1 bone metastasis)
2011	Slow bone PSA rise observed: Treated with sipuleucel-T (switched to nilutamide)
2013	Pelvic pain and multiple lesions (on bone scan) + 2-cm soft-tissue para-aortic nodes (on CT scan)

Presentation at Medical Oncology Clinic of Professor Sartor in 2013

• Bone pain (worse in lower back); patient was taking ibuprofen and hydrocodone/acetaminophen PRN.

• Active lifestyle; patient did not want to be treated with chemotherapy.

• Laboratory results showed mild anaemia, normal WBC and platelets, elevated ALP, normal LDH, rising PSA, castrate level testosterone.

Table 3. mCRPC: Case study

Poster 2878 by Parker and colleagues showed that Ra-223 is a well-tolerated agent that improves survival, was associated with positive impact on QoL, and had a significantly longer time to deterioration in QoL in patients with mCRPC.

Poster 2883 by Wiechno and colleagues showed that regardless of age, Ra-223 prolonged survival regardless of patient age and showed consistent efficacy with a favourable safety profile in mCRPC

Poster 2877 by O'Sullivan and colleagues showed that treatment with Ra-223 is associated with a low incidence of myelosuppression.

Conclusion

Patients with advanced prostate cancer are at increased risk of bone metastases in their lifetime, early diagnosis with treatment of bone metastases has a positive impact on quality of life and survival. However much work remains to be done as the disease is still associated with significant morbidity and mortality rates.

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Current Treatment Strategies in Metastatic Colorectal Cancer

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Introduction

Colorectal cancer (CRC) is currently the third most common cancer worldwide, with up to 1 million new cases diagnosed each year.[1] Approximately 20–25% of patients already have metastases at the time of diagnosis and 20–25% of the remainder patients with CRC will develop metastases following the resection of the primary tumour.[2]

The prognosis of these patients has greatly improved over the past decades due to significant surgical and medical advances, but whenever the tumour progresses beyond surgical resectability, the disease is essentially incurable.[3]

Josep Tabernero is currently the Head of the Medical Oncology Department at the Vall d'Hebron University Hospital in Barcelona and the Director of the Vall d'Hebron Institute of Oncology. He is very actively involved in translational research and pharmacodynamic phase I studies with molecular targeted therapies. He is especially devoted to phase I and II studies with pharmacodynamic endpoints with novel agents directed to the membrane receptors, like the EGFR-family and IGF-1R, the PI3K and ERK signalling pathways, as well as downstream cytoplasmatic and intranucleous effectors like Mdm2/p53 and aurora kinase. He is a member of the European Society for Medical Oncology (ESMO), the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO), and different Editorial Boards including the Journal of Clinical Oncology, Clinical Cancer Research, Cancer Discovery, Clinical Colorectal Cancer and Annals of Oncology. He has (co) authored approximately 250 peer-reviewed papers. He has also been member of the Educational and Scientific Committees of the ESMO, ECCO, ASCO, AACR, AACR/NCI/EORTC, ASCO Gastrointestinal, and WCGIC meetings.

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For the majority of patients with metastatic CRC (mCRC), treatment is palliative rather than curative and median overall survival (OS) is about 2 years with best available systemic therapy.

The currently available systemic chemotherapeutic options for patients with mCRC consist essentially of fluoropyrimidine-based regimens alone or in combination with oxaliplatin (FOLFOX, CAPOX)[4,5] or irinotecan (FOLFIRI, CAPIRI).[6,7] The addition of the anti-vascular endothelial growth factor (VEGF) monoclonal antibody (MoAb) bevacizumab to the above-mentioned first- or second-line chemotherapies has demonstrated an improvement in OS and a delay in disease progression.[8,9] In patients carrying tumours with wild type (WT) RAS gene, the anti-epidermal growth factor receptor (EGFR) MoAbs cetuximab or panitumumab (in monotherapy or in combination with chemotherapy) can improve OS.[10-14]

Beyond these, two more drugs, aflibercept and regorafenib, have been recently approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in different settings for mCRC.

Nowadays efforts are underway to choose the most effective sequence of standard treatment and also to identify additional predictive biomarkers of response. Meanwhile, newer strategies targeting different pathways with recently developed drugs are underway.

Approved New Drugs in mCRC

Aflibercept

Aflibercept is a recombinant fusion protein with greater affinity than other MoAbs against VEGF-A. It also binds to VEGF-B and Placental growth factor (PlGF), ligands that also signal through the VEGFR pathway.[15-17]

Preclinical studies have demonstrated that aflibercept could substantially inhibit the growth and even cause regression of tumours implanted in mice, without increased toxicity.[18]

Phase I dose-escalation studies of aflibercept with both subcutaneous and intravenous administration, have shown a manageable safety profile with hints of antitumour activity in advanced solid tumours.[19-21]

The combination of aflibercept with FOLFIRI has demonstrated an advantage in OS (Hazard ratio (HR) 0.817; p= .0032) *versus* chemotherapy alone in a phase III study with patients with mCRC that had progressed after an oxaliplatin-based regimen, including patients who had received bevacizumab in the first-line treatment. The combination of aflibercept with chemotherapy also provides a statistically significant improvement in the other endpoints of efficacy like progression-free survival (PFS) (HR, 0.758; p<.0001) and response rate (RR) (19.8% vs 11.1%; p<.001). The safety profile of the combination of FOLFIRI plus aflibercept was manageable. Adverse events were reported in 99.2% and 97.9% of patients in the aflibercept arm and control arm respectively. Higher incidence of grade 3/4 adverse events in the experimental arm were reported for hypertension (19.3%) haemorrhage (2.8%), proteinuria (7.5%), arterial thromboembolic events (0.8%) and venous thromboembolic events (3.8%).[22]

This combination provides new therapeutic options for the treatment of patients with mCRC previously treated with oxaliplatin-based chemotherapy.

Regorafenib

Regorafenib (BAY 73-4506) is the first tyrosin-kinase inhibitor (TKI) approved for mCRC. This compound potently inhibits vascular endothelial growth factor receptor 1-3 (VEGFR 1-3), tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2), fibroblast growth factor receptor 1 (FGFR1) and platelet-derived growth factor receptor beta (PDGFR-b), but also KIT and RET, along with the intracellular signalling kinases c-RAF/RAF-1 and B-RAF.[23]

Regorafenib metabolites M2 and M5 have been shown to be pharmacologically active, with efficacies similar to the parent compound likely contributing to clinical activity.[24]

In patient-derived models of CRC regorafenib delayed time to tumour growth when administered alone and in combination with irinotecan, even bevacizumab-refractory models, suggesting that its wider antiangiogenic activity may be due to the inhibition of multiple RTKs.[25]

The clinical development of this drug has been extremely fast. Thirty-eight heavily pretreated mCRC patients were enrolled in a dose escalation and extension phase I study. Among the 27 evaluable patients, best responses included a confirmed partial response in one patient (4%) and stable disease in 19 patients (70%), giving a disease control rate of 74%.[26]

In a phase Ib study this drug has been tested in association with common chemotherapy schedules such as FOLFOX and FOLFIRI in patients with first-/second-line mCRC. Regorafenib had no significant effect on the pharmacokinetics of platinum and 5-FU, whereas exposure of SN-38 (the active metabolite of irinotecan) increased by 32%.[27]

The CORRECT trial is a double-blind, placebo-controlled study that randomised a total of 760 patients to receive either regorafenib plus best supportive care (BSC) or placebo plus BSC. The primary endpoint of OS was met at a preplanned interim analysis; data cut-off was on 21 July, 2011. Median OS was 6.4 months in the regorafenib group *versus* 5.0 months in the placebo group (HR 0.77, p=0.0052).[28] PFS was 1.9 months in the regorafenib group and 1.7 months in the placebo group (HR 0.49 p<0.0001, respectively). Even though the RR was not increased in the experimental arm, disease control was achieved in 41% of patients assigned to regorafenib arm and 15% in patients assigned to placebo arm (p<0.0001). Overall regorafenib was more toxic than BSC alone, with 54% grade 3 or 4 treatment-related adverse events in patients assigned regorafenib *versus* 14% in patients assigned placebo. The safety profile of this drug is consistent with other TKIs, being hand-foot skin reaction (47%), fatigue (47%), diarrhoea (34%), hypertension (28%), and rash or desquamation (26%) the most frequent regorafenib-related adverse events.

Even though the CORRECT trial has achieved its primary endpoint in a setting where there is no other effective treatment approved, markers of response are required in order to identify the subgroups of patients that could really benefit from this treatment, considering the safety profile and the modest survival benefit.

Upcoming Drugs in CRC

Main Pathways Altered in mCRC

In the past few years, the discovery of relatively common "druggable" genetic alterations, such as IGF2, IGFR, HER2, HER3, MEK, AKT, PI3K and mTOR,[29] has paved the way to newer treatment strategies in mCRC.

Dysregulation of the EGFR signalling pathway is a recognised mechanism of carcinogenesis. Since cetuximab and panitumumab have shown activity in randomised trials, the efforts in preclinical and clinical research have been focused in maximising the therapeutic index of these drugs and in understanding and overcoming the mechanisms of resistance. Newer agents targeting EGFR, with a more potent activity, are now under investigation.

Newer Anti EGFR Agents

SYM004 is novel mixture containing two antibodies (IgG1 992 and 1024) directed against distinct epitopes on the extracellular domain

of EGFR.[30] In preclinical models SYM004 has shown a superior anticancer efficacy compared with cetuximab and panitumumab. Due to its more pronounced EGFR internalisation, degradation and tumour growth inhibition, SYM004 can overcome acquired resistance to anti-EGFR MoAbs.[31,32] In the clinical setting, this mixture has been evaluated in 42 KRAS WT mCRC patients with prior clinical benefit to anti-EGFR MoAbs and subsequent progression during treatment or within 6 months after treatment cessation. About 30% of the patients experienced more than 10% tumour shrinkage, with a median PFS of 13.6 weeks. The toxicity profile is consistent with other anti-EGFR MoAb.[33]

A second example of a next-generation anti-EGFR agent is imgatuzumab (GA 201), a humanised and glycoengineered IgG1.[34] Due to the glicosilation of the Fc region, imgatuzumab has a great binding affinity for FcRIIIa on immune effector cells; this results in enhanced killing in antibody-dependent cell-mediated cytotoxicity (ADCC)-based assays, regardless of KRAS status.[35] In the expansion cohort phase I/II study, stable disease at 8 weeks occurred in 40% of pre-treated patients with KRAS-mutant advanced CRC.[36] Based on these data, imgatuzumab is being investigated in association with FOLFIRI *versus* FOLFIRI alone in KRAS-mutant CRC patients or *versus* FOLFIRI plus cetuximab in KRAS WT patients as second line treatment.[37]

Targeting other HER Members

A novel strategy that is currently being explored involves hitting other members of the HERB family, as a consequence of the high incidence of co-expression and heterodimerisation.

MEDH7945A is a dual-action IgG1 antibody binding to both HER3 and EGFR, intended to inhibit signalling from all major ligand-dependent HER dimers and to elicit ADCC. In the phase I expansion cohort, 4 out of 12 CRC patients previously treated with EGFR inhibitors, had a stable disease lasting more than 8 weeks. MEHD7945A is being evaluated in association with FOLFIRI *versus* cetuximab-FOLFIRI in second line in patients with KRAS WT mCRC (NCT01652482).[38]

Anti-HER-B2 therapy with trastuzumab has shown no efficacy in unselected CRC.[39,40] Therefore, HER2 amplification occurs in a small percentage (2%–5%) of genetically unselected cases. Preclinical data suggest that HER-B2 amplification could be an additional marker of resistance to EGFR-targeted therapy. In KRAS WT CRC patients that displayed de novo resistance to anti-EGFR, HER2 amplification rate seems to be higher.[41]

On this basis, the combination of trastuzumab in with lapatinib or pertuzumab is being explored in a phase II study in patients with HER2-positive, KRAS WT mCRC (EudraCT N. 2012-002128-33).

KRAS Mutations

Genetic alterations in the RAS–MAPK pathway are common in CRC and as we have already mentioned, KRAS and NRAS mutant tumours do not benefit from anti-EGFR treatment. Co-occurrence of alterations involving the RAS and PI3K pathways are found in one-third of tumours: also reported is compensatory activation of RAS downstream pathway, such as MEK, when the other pathway is inhibited. These results indicate that simultaneous inhibition of activated pathways may be required to achieve therapeutic benefit in RAS mutant patients.

However, patients treated in a phase I trial with PI3K and MEK inhibitors had no benefit from the combination therapy.[42]

On the other hand, preliminary data about KRAS mutant CRC patients treated in a phase I study with cetuximab and the MEK inhibitor selumetinib, show antitumour activity,[43] suggesting that the inhibition of MEK could restore sensitivity to anti-EGFR therapy even in the presence of a mutation of RAS. A similar study using panitumumab and MEK 162 (MEK inhibitor) is currently ongoing (NCT01927341).

BRAF Mutations and Sensitivity to BRAF Inhibitors

BRAF mutation has been recognised to be a strong negative prognostic factor; patients harboring a V600E mutation (8-9% of CRC cases) generally show a shorter PFS and an OS of about 15 months.[44,45] Agents that specifically target BRAF in mCRC have so far shown disappointing results.[46] This was explained by a rapid feedback activation of EGFR, supporting continued proliferation even in the presence of BRAF inhibition.[47] It seems therefore that the combined inhibition of BRAF and EGFR could overcome resistance to single agent anti-BRAF and this strategy is currently being explored in early development trials (NCT01791309. NCT01719380).

Immunotherapy in CRC

In recent years the field of immunotherapy in cancer is remarkably developing, especially for those types of cancer that have always shown a certain immune-sensitivity.

Whether this approach could elicit the endogenous antitumour immune response in CRC is still uncertain. Data retrieved from early development studies of anti-PD-L1 and anti-PD-1 blockade have shown no or occasional objective responses in CRC patients.[48-50]

The activation of the antitumour immune response by anti-PD-1/PD-L1 MoAbs seems to be driven by histologic features or oncogenic signalling pathways of the tumour or factors induced within the tumour microenvironment.

Therefore, upcoming clinical investigations of anti-PD-1/PD-L1 will select CRC patients for the expression of PD-L1 in tumour tissue or for the presence of microsatellite instability (MSI-H) (NCT02054806, NCT01876511, NCT02060188). In fact, MSI-H CRCs are histologically characterised by a strong local immune reaction with lymphocytic infiltration. In addition, frameshift mutations encountered in MSI-H CRC might lead to the generation of tumour-specific antigens.

Upcoming Non-targeted Drugs: TAS-102

TAS-102 is a novel antimetabolite composed by trifluridine (FTD) and the thymidine phosphorylase inhibitor 5-chloro-6-(2-iminopyrrolidin-1-yl) methyl-2,4 (1H,3H)-pyrimidinedione hydrochloride (TPI). This compound is thought to also have antiangiogenic properties. A phase II study conducted in Asia randomised 169 patients with refractory CRC to TAS-102 or placebo.[51] The experimental treatment resulted in a statistical significant difference in OS (HR for death 0.56) with a manageable safety profile. The confirmation of these results in the phase III trial RECOURSE (NCT01607957) is anticipated in the following months.

Conclusions

We have revised the current treatment strategy in mCRC, focusing on the last approved drugs and on the most innovative compounds that are being investigated in the clinical setting at the present time.

As we have described, research in mCRC cure involves very different strategies that have now reached different steps of development; MoAbs, TKIs, immunotherapy and cytotoxic agents. Researchers are sparing no effort in identifying predictive makers of response. This scenario seems promising but caution is needed; even though the identification of predictive markers may drive the treatment strategy, the correlation between a specific alteration in cancer and the treatment with a targeted agent does not always result in efficacy or clinical benefit for the patient. The complexity of the signalling pathways in an individual cancer, the intratumour heterogeneity and the safety profile of the drugs certainly play an important role.

In our opinion research is moving forward on a good path; we have seen the recent approval of newer drugs (aflibercept and regorafenib) and in the following years we might have newer standard treatment options among the latest compounds under development. Similarly, preclinical data currently being explored will be available for early development of new drugs.

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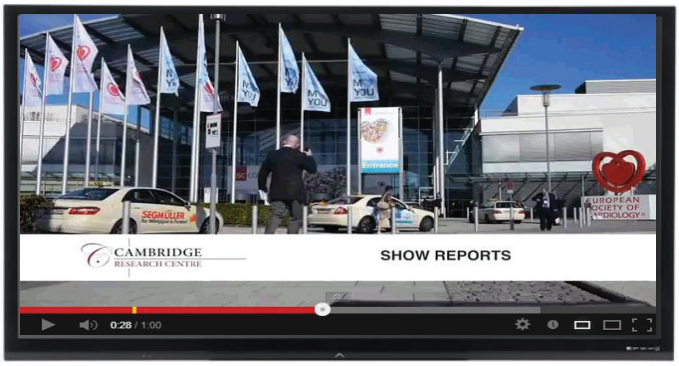

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HER2 in Colorectal Cancer: One Marker Useful for Multiple Targeted Therapies

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Targeted Therapies in Colorectal Cancer

Colorectal cancer (CRC) is a major health problem. Over one million new cases are discovered each year, and the disease-specific mortality rate, although constantly decreasing, is still 33% in Western countries.[1] The introduction of new biological treatments, especially if combined with standard chemotherapies (oxaliplatin and irinotecan), has led to a consistent benefit in patients with advanced stage disease.[2-4] Monoclonal antibodies against the Epidermal Growth Factor Receptor (EGFR), such as cetuximab and panitumumab, are effective only in a group of patients, accounting for about 30-40% of total cases and only in those showing a KRAS wild-type sequence. EGFR is a receptor tyrosine kinase (RTK) belonging to the HER/erbB family, and is able to activate two main downstream pathways: the KRAS-BRAF-MAP kinases pathway, mainly involved in cell duplication, and the PI3K-AKT-mTOR pathway, mainly involved in the regulation of apoptosis. Once activated, following different mechanisms (such as gene mutation or amplification, protein overexpression, ligands overexpression), EGFR is able to constitutively activate the two downstream pathways leading to an uncontrolled rate of cell proliferation.[5]

In addition to EGFR deregulation, EGFR downstream pathways can be constitutively activated in CRC following two different mechanisms: i) alterations directly occurring in the downstream pathways members, and ii) activation of other RTKs. The first mechanism of EGFR pathways deregulation is achieved when point mutations occur in the KRAS, BRAF or PIK3CA genes, and all of these alterations have been associated with resistance to EGFR-targeted therapies,[4, 6-9] although only KRAS mutational testing has been introduced into clinical practice after confirmation of its negative predictive role by several investigators in both retrospective and prospective studies.[10-11] Only a few studies have investigated BRAF and PIK3CA gene mutations as well as other alterations (NRAS gene mutations, PTEN protein loss of expression) and therefore, at the moment, these analyses have not been introduced in daily practice for the selection of patients before cetuximab/panitumumab administration. The second mechanism of EGFR pathways activation is related to the sharing of the KRAS-BRAF-MAP kinases and the PI3K-AKT-mTOR pathways with other RTKs, especially those belonging to the HER family. This group of RTKs includes EGFR, HER2, HER3 and HER4, and each member can easily heterodimerise with another monomer of the same family. In particular, HER2 is the main partner of EGFR in the heterodimerisation process, but deregulation occurring in HER2 itself can directly activate the EGFR downstream pathways independently from EGFR.[12]

HER2

The HER2 (Human Epidermal growth factor Receptor-2) gene, composed by 1256 nucleotides, is located on the long arm of chromosome 17 (17q11.2-q12), and encodes for a 185 kDa (p185) plasma membrane glycoprotein.[13] HER2 protein shares 50% of homology with EGFR.[14] At the moment, HER2 represents the unique HER family member without a specific extracellular ligand. HER2 is involved in the development of several neoplastic diseases, such as lung, colorectal and gastric cancer, but it is in breast cancer where HER2 plays a major and essential role. In breast cancer, HER2 has been studied for decades and specific guidelines have been recommended to investigate its status.[15] The two methods currently accepted to evaluate HER2 are represented by: immunohistochemistry (IHC), that allows to assess the protein expression; and fluorescent *in situ* hybridisation (FISH), to investigate the gene status. By IHC, patients classified as 3+ score are considered positive, whereas those evaluated as 0 or 1+ score are considered negative. Patients with a 2+ score are considered as borderline and another methodology (e.g.: FISH) should be used to reach the final conclusion. By FISH, HER2 gene amplification is defined in patients with a ratio (R) ≥ 2 between the HER2 gene and the centromere of chromosome 17 signal.[15]

Due to the relevant role of HER2 in the carcinogenetic process, several specific HER2 inhibitors have been developed, and trastuzumab represents the older and more widely used monoclonal antibody against this receptor. Trastuzumab in breast and gastric cancer is effective in patients with HER2 3+ score as detected by IHC or with gene amplification as detected by FISH.[16-17]

HER2 in Colorectal Cancer

In CRC, the rate of positive cases by IHC is still controversial, because some studies have included in this category not only cases with a positive

Author	#	Type of Tissue	Method	%
Kapitanovic[19]	221	Normal tissue Bening lesions CR ADC	IHC* IHC* IHC*	14%[a] 13,5 % 43,0%
Ooi[13]	224	CR ADC	IHC FISH	3% 3%
Al- Kuraya[20]	518	CR ADC	FISH	2,8%
Herreros-Villanueva[21]	118	CR ADC	FISH	26.3%[b]
Martin[28]	170[c]	CR ADC	FISH	4,0%

Table 1. HER2 Evaluation in CRC. NOTE: CR ADC : colorectal adenocarcinoma; * membrane and cytoplasm staining;[a] moderate/strongly immunostaining; [b] in KRAS/BRAF WT popultation; [c] only KRAS WT metastatic CRC patients.

membrane staining but also cases showing a positive cytoplasmic staining.[18] For example, Kapitanovic and co-workers also reported an immunohistochemical staining in normal colon mucosa, especially adjacent to adenoma and to carcinoma.[19] However, the majority of works reported a positive IHC rate in less than 10% of patients, and the few researchers who performed a comparison with FISH data demonstrated a complete overlapping between the two methodologies. Also by FISH, the rate of HER2 positive cases did not exceed 10%, with most of studies showing only up to 5% of positive cases.[13, 20] However, in specific subgroups of tumours (e.g.: those showing a concomitant KRAS and BRAF wild-type sequences), the rate of HER2 positive cases was significantly higher, up to 26%.[21] Details of studies evaluating HER2 in CRC are listed in Table 1.

Notwithstanding these differences in classifying HER2 CRC positive cases, especially at IHC level, there is a good consensus in considering HER2 deregulation in CRC as a negative clinical/histopathological prognostic marker. In fact, HER2 positive cases have been significantly associated with increased tumour size, lymph-node and/or liver metastasis, and advanced TNM stage. As regards to the impact on survival, Lu *et al*. found a positive association between HER2 deregulation and increased 5-year recurrence rate and decreased 5-year overall survival rate (in both univariate and multivariate analyses), whereas Li and colleagues, although confirming HER2 positivity as strictly associated with the presence of distant metastasis, failed to demonstrate a difference in terms of 5-year survival between HER2-positive and HER2-negative patients.[22, 23]

Interestingly, HER2 deregulation is absent in Familial Adenomatous Polyposis patients.[24]

The Role of HER2 in Targeted Therapies in Advanced Stage Disease

Due to the possibility of HER2 to dimerise with EGFR, it has been evaluated whether HER2 overexpression/gene deregulation could affect the efficacy of EGFR-targeted therapies. In 2008, Personeni and colleagues reported a case of HER2 amplification in a patient characterised by a concomitant amplification in the EGFR gene and absence of clinical benefit from cetuximab administration.[25] More recently, Yonesaka and co-workers started from a CRC cell line sensitive to cetuximab (GEO), serially treated with this drug until resistant clones appeared.[26] In the resistant clones, the activation of the MAP kinases pathway (evaluated as level of phosphorylation status of ERK 1/2 proteins) was not fully downregulated after cetuximab administration, while in the parental cell line these proteins were completely inhibited. The authors also demonstrated a presence of HER2 gene amplification by FISH, thus supporting the notion that HER2 gene amplification is one of the mechanisms able to bypass the block of the activation of the main EGFR downstream pathway (the MAP kinases pathway) after cetuximab administration, leading to resistance to EGFR-targeted therapies. The authors confirmed the role of HER2 by depleting HER2 expression with the use of HER2 specific short hairpin RNA, which restored both cetuximab efficacy and ERK 1/2 proteins complete downregulation. After performing the same experiments on cell lines from lung and head-and-neck squamous cell carcinomas, the authors obtained the same results, thus confirming HER2 gene amplification as a main mechanism of acquired resistance in cetuximab-treated cancers. In addition, the same study demonstrated that HER2 protein is able to activate the MAP kinases pathway directly, and not by interfering with cetuximab binding to EGFR nor with cetuximab mediated internalisation of EGFR. Finally, Yonesaka and colleagues evaluated tumour and blood specimens from 233 CRC patients treated with cetuximab alone or in combination with chemotherapy, and demonstrated that the median progression-free survival and the median overall survival were significantly longer (about double) for patients without HER2 gene amplification.[26]

Another study addressing the role played by HER2 in affecting the response to EGFR targeted therapies used a xenograft cohort from CRC-derived patients treated with cetuximab ("xenopatients").[27] The authors identified about 2% of cases with HER2 gene amplification, all characterised by strong receptor overexpression and all showing KRAS-BRAF wild-type sequences. Through the analysis of about 100 CRCs from different cohorts recruited for retrospective analyses, Bertotti and colleagues confirmed the association of HER2 gene amplification and absence of response to EGFR-targeted therapies, and observed a significant increase in the HER2 gene amplification rate in KRAS-BRAF wild-type patients with respect to the general population of advanced CRCs.[27]

Recently our group reported the results of an International consortium exploring the role of HER2 gene copy number in a large cohort on CRC patients from Italy, Switzerland and Greece treated with anti-EGFR therapies.[28] This study evaluated HER2 gene status by FISH in a cohort of 170 KRAS wild-type patients. By applying the guidelines valid for breast cancer patients and conventional cytogenetic criteria for interphasic FISH interpretation on solid tumours, the authors subdivided the cohort into different groups in relation to the type of HER2 deregulation and the quantity of cells involved. Among amplified patients (i.e., with R ≥ 2 in > 10% of cells), those showing HER2 gene amplification in all the tissue sample were identified and grouped apart ("HER2-all-A" patients). Among cases without HER2 gene amplification, patients with HER2 gene copy number gain (CNG) due to polysomy of Chromosome 17 and patients with a normal HER2 gene status were subdivided into different groups. The latest group was considered as carrying an HER2 FISH– profile, while patients with CNG and amplification in minor clones were grouped as HER2 FISH+*. By coupling the clinical response to these cytogenetic categories, the authors found two apparent opposite findings: patients characterised by CNG of HER2 gene or by HER2 gene amplification not in the totality of cells were characterised by a better survival and could benefit from EGFR-targeted therapies. On the contrary, patients with HER2 gene amplification in all the cells were resistant to anti-EGFR drugs. As an explanation, the authors suggested that HER2 is an essential driver in HER2-all-A cases, leading to MAP kinases and PI3K-mTOR pathways activation irrespectively of EGFR switching off after cetuximab administration. On the contrary, in HER2-FISH+* patients the carcinogenetic process is not due to HER2 but to a general karyotypic instability, also involving EGFR. In fact, the last group of patients is also characterised by a concomitant CNG of EGFR and, presumably, HER2 does not play an essential role in these cases.[28]

Conclusions

Although only few studies have included clinical data on the role of HER2 in patients with an advanced CRC treated with targeted therapies, it seems proven that HER2 deregulation, due to a massive protein expression and/or to gene amplification in the totality of cells, represents an independent predictive marker of resistance to EGFR-targeted therapies, possibly explaining why a group of cases with a proficient KRAS mutational profile does not benefit from these therapies. It is still to be demonstrated whether HER2 gene amplification also represents a mechanism of acquired resistance. The flip side of the coin is represented by the fact that HER2 deregulated patients can profit from HER2-targeted therapies, thus enlarging the number of therapies for advanced stages of CRC. This assumption is supported by preclinical data on cell lines and on xenopatients treated with a combination of cetuximab and anti-HER2 therapies.[26, 27] To deeply investigate this issue, several clinical trails are currently ongoing and the results are anxiously awaited.

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The Highlights of Colorectal Cancer at the European Cancer Congress 2013

Vanessa Lane
The Cambridge Research Centre

Introduction

This review brings you our highlights of The European Cancer Congress, with a focus upon Colorectal Cancer (CRC). This report brings together coverage of the symposium 'Integrated Novel Targeted Agents into mCRC and GIST to Optimize Patient Outcomes', with presentations by Dr. Heinz-Josef Lenz and Dr. Josep Tabernero, as well as the best of the posters highlighting CRC including research by Salvatore Siena, Alfredo Falcone, Jane Chang, and Robert Adams.

This symposium addressed how to integrate novel targeted agents into the management of patients with mCRC in order to optimise patient outcomes.

A presentation by Dr. Heinz-Josef Lenz focussed on the rationale for multikinase inhibition in mCRC.

Many growth factors and their associated receptors work in complementary, coordinated networks to regulate tumour growth. In addition, the tumour microenvironment is a critical partner in the development of cancer cell processes such as angiogenesis. This complexity provides the rationale for concurrent targeting of multiple growth factors and receptor pathways to optimally develop anticancer therapies.

The current standard of care for mCRC includes chemotherapy (fluoropyrimidines, oxaliplatin, irinotecan) and use of monoclonal antibodies (bevacizumab, cetuximab or panitumumab). However, no standard salvage therapy is available and there remains a high unmet clinical need for the treatment of mCRC. This has been highlighted by the emergence of KRAS mutations in almost half of all patients treated with epidermal growth factor receptor (EGFR) inhibitors.[1, 2]

Vanessa Lane has many years of experience within the field of medicine. She completed her studies at Queens University, Belfast, UK and the University of Cambridge, Cambridge, UK, and she has also held the position of Oncology Postdoctoral Research Associate at Cornell University Medical School, New York, USA. She has written extensively on the subject of oncology and congress proceedings.

Mutations in mCRC, whether driver or passenger, can be used as specific biomarkers to guide patient management.[3] This has been demonstrated for KRAS mutations, which have been shown to be strong predictors of survival, disease progression and treatment failure in mCRC patients treated with anti-EGFR antibodies.[4] Alterations in cell and stromal signalling occurring as acquired resistance to EGFR inhibitors have also illustrated the mode of action of multikinase inhibition.[5]

Regorafenib kinase selectivity profile is distinct and different from other multikinase inhibitors. It potently inhibits the angiogenic and stromal receptor tyrosine kinases VEGFR1, 2, and 3, TIE2 and PDGFR-β that promote tumour neovascularisation, vessel stabilisation and lymphatic vessel formation, and play an important role in the tumour microenvironment, all of which contribute to tumour development and metastasis formation.[6, 7] In preclinical models, regorafenib reduced microvessel area versus vehicle or no treatment,[6] and tumour-associated macrophage infiltration versus vehicle or DC101 (VEGFR-2 blocking monoclonal antibody).[8] In this latter study, inhibition of TIE2 resulted in a decrease in the accumulation of prometastatic and proangiogenic TIE2 expressing macrophages. This is particularly interesting, as one of the mechanisms described for the failure of antiangiogenic therapy and tumour evasion is the strong infiltration of tumour-associated macrophages, in particular of a subset that express the angiopoietin receptor tyrosine kinase with immunoglobulin and TIE2, which promote angiogenesis and tumour progression. Regorafenib was also shown to completely prevent the formation of liver metastases, whereas in DC101-treated animals, the metastatic rate was only reduced by 33% compared with the vehicle group.

Blockade of multiple growth factors and receptor pathways is needed to effectively treat mCRC,[6] and regorafenib leverages the genomic underpinnings of cancer pathogenesis. As a result, it exerts strong antiangiogenic, antitumorigenic and even antimetastatic effects on highly aggressive colon carcinomas and is a promising therapeutic advancement to address the unmet needs of patients with mCRC.[9]

In a second presentation, by Dr. Josep Tabernero, the topic of maximising patient outcomes in the mCRC care continuum was discussed.

Formal evaluation of the impact of regorafenib in the treatment of mCRC was conducted in the international randomised, placebo-controlled, Phase III CORRECT trial.[9] This large registration trial assessed regorafenib in patients with mCRC that had progressed after all approved standard therapies. The trial was conducted at 114 centres in 16 countries and included mCRC patients who had progressive disease during or within 3 months after the last standard therapy.

Patients were randomised to receive best supportive care plus oral regorafenib 160 mg or placebo once daily for the first 3 weeks of each 4 week cycle. The trial was designed to detect a 33% increase in overall survival (primary endpoint) with a hazard ratio of 0.75 and a power of 90%. A total of 760 patients were randomised to receive regorafenib (n=505) or placebo (n=255), and 753 patients initiated treatment (regorafenib n=500; placebo n=253; population for safety analyses).

The median overall survival was 6.4 months in the regorafenib group compared to 5.0 months in the placebo group (hazard ratio 0.77; 95% confidence interval [CI] 0.64-0.94; p=0.0052). This equated to a 25% decrease in the risk of death with regorafenib versus placebo.

Data from the standard therapies available for the treatment of mCRC show a consistent relative improvement in median overall survival, corresponding to an absolute benefit of approximately 1.4 months. Median progression free survival for regorafenib was found to be 1.9 months versus 1.7 months for placebo (hazard ratio 0.59; 95% CI 0.42-0.58; p<0.001). This equates to a 51% reduction in the risk of progression or death and 23% reduction in the risk of death alone.

The overall benefit was consistent regardless of patient subgroups, including time from first diagnosis, prior anticancer treatment and number of prior treatments. In addition, improvements in overall survival and progression free survival were seen in both KRAS wild type and KRAS mutant disease.[10]

A total of 41% of patients achieved disease control versus 14% for placebo patients (p<0.000001), with 42.8% patients having stable disease versus 14.5% for placebo patients.[11]

Treatment-related adverse events occurred in the majority of patients assigned to regorafenib (465, 93%).[9] However, the rate of adverse events was also relatively high for those assigned placebo (154, 61%). The most common adverse events of grade three or higher related to regorafenib were hand-foot skin reaction (83 patients, 17%), fatigue (48, 10%), diarrhoea (36, 7%), hypertension (36, 7%) and rash or desquamation (29, 6%). Drug-related adverse events that results in treatment discontinuation were reported in 8.2% of regorafenib-treated patients versus 1.2% of patients treated with placebo. In an additional analysis, common adverse events were found to occur early on during treatment and to stabilise over time.[12] The incidence of diarrhoea persisted at roughly 18-26% throughout treatment. No cumulative toxicity was observed. In addition, in this analysis, the mean daily dose was found to be largely stable after the first cycle, with the highest dose received in cycle 1 and decreasing over cycles 2 and 3 in order to manage adverse events.[12] The dose intensity remained relatively stabled between cycles 3-8, with an average dose of 120 mg daily; around 75% of the trial-mandated 160 mg dose.

It was concluded that regorafenib was a treatment that provided a significant increase in mCRC patient overall survival, progression-free survival and disease control rate versus placebo.[9]

In addition to the CORRECT trial leading to the approval of regorafenib, this study has been important for several reasons. It is the first trial to demonstrate a survival benefit with a tyrosine kinase inhibitor in mCRC. In addition, the trial has allayed the perception that drug approval cannot be achieved by testing agents in the refractory, last-line setting.

Additional data on the impact of regorafenib efficacy and tolerability on patient health-related quality of life (HRQoL) was presented in the poster sessions at ECC 2013.

Overall, changes in HRQoL (EORTC QLQ-C30, EQ-5D index and EQ-5D VAS) were found to be similar for both regorafenib and placebo.[13] An additional post-hoc analysis of the impact on HRQoL was presented. The benefit of regorafenib was examined by incorporating progression and survival into the HRQoL analysis to account for missing data from patient-reported outcomes due to worsening of health (as a result of disease progression or adverse events) by assuming that dropouts corresponded to a clinically meaningful deterioration in HRQoL.[14] The analysis found that, when deterioration was defined based on the earliest event of a minimal clinically important difference decrease in HRQoL, disease progression or death, patients in the regorafenib group had a reduced risk of deterioration compared with placebo. In addition, despite the occurrence of adverse events, regorafenib did not increase the risk of HRQoL deterioration compared with placebo.

In the CORRECT study, regorafenib was associated with a higher rate of adverse events, which were managed with protocol-specified dose interruptions or reductions. An analysis of these dose modifications was presented in a poster at ECC 2013.[15] Dose modifications were reported in 76% of regorafenib-treated patients and 38% of placebo recipients. Of these, 20% of regorafenib-treated patients and 3% of placebo recipients had dose reductions, with a mean duration of 7.5 days; 70% of regorafenib-treated patients and 38% of placebo recipients had dose interruptions, with a mean duration of 6 days. Despite the higher rate of adverse events requiring dose modifications in the regorafenib group, the proportion of patients discontinuing treatment due to adverse events was similar in the regorafenib and placebo groups, suggesting that timely dose modifications were effective for the management of treatment-emergent adverse events.

Regorafenib potently inhibits multiple protein kinases, including angiogenic, oncogenic and intracellular signalling kinases.[16, 17] In an analysis of patient-derived xenograft (PDX) CRC models, regorafenib was shown to inhibit tumour growth and delayed tumour progression independent of the mutational status of known oncogenes and tumour suppressor genes such as KRAS, BRAF, PI3K, and TP534. At ECC 2013, a new study which aimed to identify potential biomarkers that could be used to predict response to regorafenib was presented.[18] The investigators examined several PDX CRC animal models to identify regorafenib-insensitive models. For each model, the transcript profiles were analysed and characteristic gene expression signatures were identified. Silico prediction was used to expand this analysis to a larger set of regorafenib-unclassified models. Of six PDX models, five showed a response to regorafenib in terms of tumour growth inhibition. One regorafenib-insensitive model (Co8541) differed significantly from regorafenib-sensitive PDX models in terms of regorafenib-mediated tumour growth inhibition, histology and the immunohistochemical marker COX2. This model also showed significantly altered transcript profiles compared with regorafenib-sensitive models and most of the unclassified PDX CRC models. Four differentially expressed genes that may be involved in regorafenib responsiveness were identified (COX2, MUC2, IL8, and CFTR), most of which play a role in inflammatory processes and/or immune response pathways. Further analysis of transcript profiles identified additional tumour models classified as regorafenib-insensitive, but these need to be validated experimentally. Additional studies are ongoing.

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Recent Advances in the Treatment for Differentiated Thyroid Carcinoma

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Introduction

Thyroid carcinoma (TC) is the most common endocrine malignancy. During the last decades there has been a continuous increase in the incidence of TC worldwide.[1] Primary TC comprises tumours originating from the thyroid follicular epithelial cells (non-medullary TC, NMTC) or from the perifollicular calcitonine-producing cells (medullary TC, MTC). These two types of tumours differ from each other with respect to etiology, clinical course and treatment modalities. The NMTC are the most common, representing approximately 95% of all TCs. Among these, different histological subtypes can be differentiated: the papillary thyroid carcinoma (PTC)(80%), the follicular thyroid carcinoma (FTC) (10-15%) and the anaplastic thyroid carcinoma (ATC)(<5%). The prognosis of these types of TC is different, with a 10-year mortality rate of 5-10% for PTC and 15% for FTC in non-metastatic disease. However the 10-year mortality rate increases up to 90% for both types in the presence of distant metastases, which occur in approximately 15% of the patients.

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By contrast, the one-year mortality rate for ATC approaches 100%.[2] Because the PTC and the FTC are histologically well differentiated and share many biological characteristics and treatment modalities, they are often referred to together as differentiated TC (DTC). In this review we focus on the recent developments in the treatment of DTC.

The primary therapy of patients with DTC consists of (near-) total thyroidectomy followed by ablation of thyroid rests with radioactive iodine (I131, RAI). Locoregional recurrences are often amenable for repeated surgery and adjuvant treatment with RAI as long the tumours are able to concentrate RAI and rarely by external beam radiation therapy, complete remission being reported in 25-75% of the patients.[3] Occurrence of distant metastases significantly reduces the prognosis of patients with DTC, which is largely dependent on the sensitivity of the metastases to RAI. This is reflected by the 10-years survival rates in patients with metastatic disease, which are 60% in patients with RAI avid metastases, but only 10% in patients with RAI resistant tumours.[4] In these patients, although localised interventions such as surgery, external beam therapy or various catheter ablation techniques may result in symptom relief, even multimodality treatments seldom result in complete remission. Moreover, several small studies or case-reports showed very limited benefit of chemotherapy with either single agents, mostly doxorubicin, or combination regimens in patients with advanced and progressive DTC.[5]

Over the past decades, our understanding of thyroid (cancer) follicular cell biology and molecular genetics has advanced dramatically, leading to identification of specific oncogenic mutations as early genetic events in the TC tumourigenesis and of microenvironment signaling events involved in the progression of TC (Figure 1). This has resulted in the identification of potential targets for antitumoural agents that have subsequently been investigated in multi-centre clinical trials.

Molecular Bases of TC

Comparative tissue studies have shown that the molecular basis for different histological forms of DTC is different. The large majority of PTCs are characterised by the presence of mutually exclusive gene mutations in BRAF (in up to 70% of the PTCs), RAS (in 10-15% of the

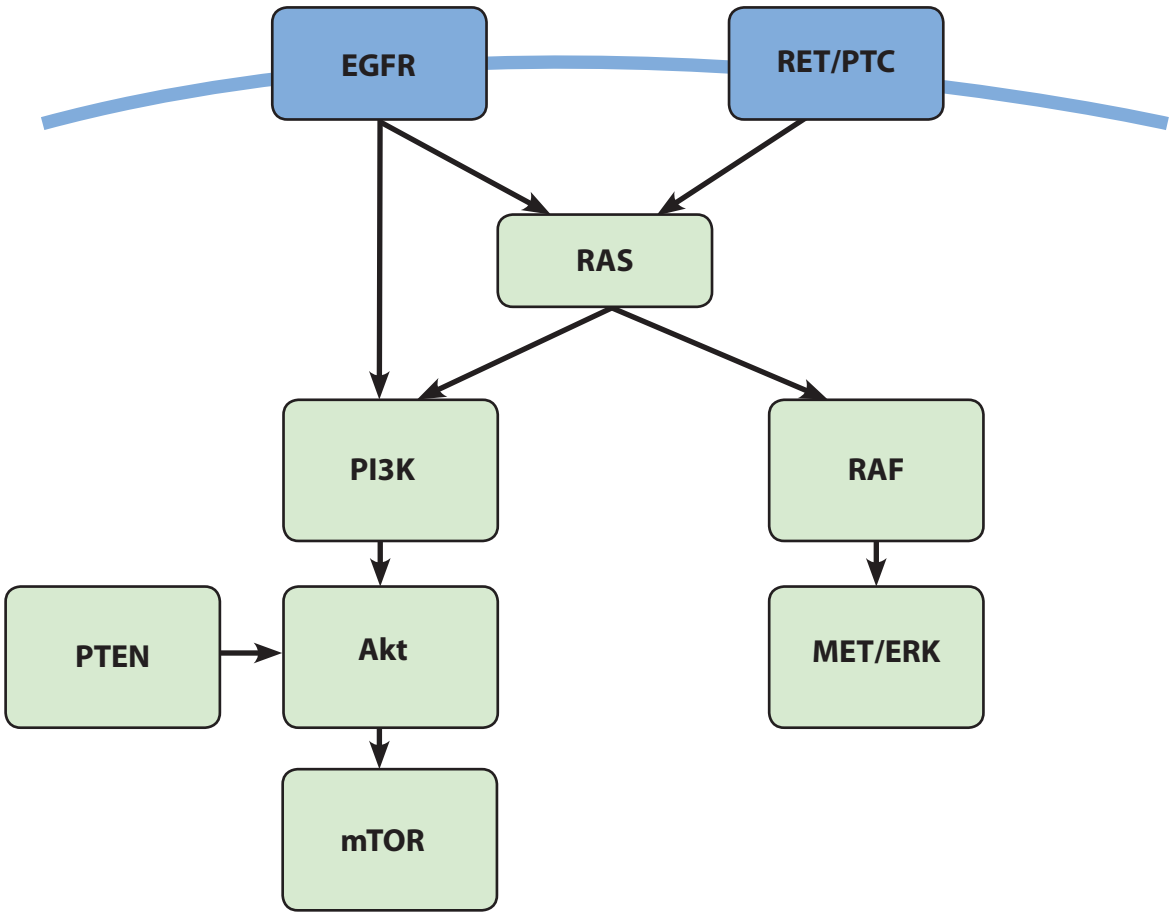

Figure 1. Signaling pathways involved in the pathogenesis of differentiated thyroid carcinoma.

PTCs) and RET rearrangements (in 10-15% of the PTCs) resulting in the activation of mitogen-activated protein kinase (MAPK) signaling, which is an important regulator of thyroid specific protein expression and proliferation.[6-10] The FTCs, on the other hand, have been found to harbour the PAX8-peroxisome proliferator-activated receptor (PPAR)-γ genetic rearrangement (30% of the FTCs) and RAS point mutations (10-15% of the FTCs).[11-13] Furthermore, several gene mutations have been found more often in tumours with more aggressive potential such as the poorly differentiated TC (PDTC) or the ATC, suggesting that some gene mutations may represent early initiating genetic events, leading to transformation of normal follicular cells in malignant cells, whereas others may represent late events resulting in a progression to more aggressive forms. An important player involved in this process is the Akt pathway,[14] which can be activated by mutations in the catalytic subunit of phosphatidyl-inositol-3-kinase (PI3K) (PIK3CA), which were found to be more common in ATC than in DTC[15] as well as in more aggressive tumours,[16, 17] sometimes in combination with BRAF or RAS mutations.[15] Also, inactivating mutations in the PTEN tumour suppressor gene, leading to activation of the PI3K-Akt pathways, have been found more often in advanced cancers.[18]

Apart from having a specific individual role in the pathogenesis of TC there is data in the literature suggesting that there is probably an important synergy between the consequences of these aberrant signaling pathways as well. One example is the observation that in the tumour cell lines harbouring BRAFV600E mutations that were resistant to treatment with a BRAF specific inhibitor, vemurafenib, the epidermal growth factor receptor (EGFR) was strongly activated.[19] Treatment with a combination of a specific BRAF inhibitor and an EGFR inhibitor *in vivo* resulted in decreased tumour growths.[20] This suggests that in advanced TC targeting multiple affected pathways may be more appropriate than targeting one specific pathway.

New Treatment Modalities for Advanced TC

Multiple trials have been carried out in the last decade using drugs targeting either multiple (multikinase inhibitors) or selectively one of the key kinases involved in the pathogenesis of TC (selective kinase inhibitors) (Table 1).

Multikinase Inhibitors (MKI)

The first MKIs targeted multiple VEGFRs that have been systematically studied in patients with TC: motesanib and axitinib followed by sunitinib and pazopanib. Motesanib (AMG 706), which targets the VEGFR, platelet–derived growth factor receptor (PDGFR), RET and c-KIT has first been investigated in a phase I trial in patients with advanced TC.[21] In this trial treatment with motesanib, it was associated with stable disease in

Drug	Targets	N (DTC)	RECIST*	SD (%)	PR (%)	PFS (mo)	Drug discontinued	Reference
Multikinase inhibitors								
Motesanib	VEGFR1-3, PDGFR, RET,c-Kit	93	Yes	35	14	9.3	13%	Sherman (2008)[22]
Axitinib	VEGFR1-3, PDGFR, c-Kit	45	No	42	31	18.1	13%	Cohen (2008)[24]
Sunitinib	VEGFR1-3, RET, RET/PTC	28	No	46	31	12.8	11%	Carr (2010)[25]
Pazopanib	VEGFR1-3, PDGFR, c–Kit	37	Yes	65	49	11.7	11%	Bible (2010)[26]
Sorafenib	BRAF, VEGFR1 and 2, RET, PDGFR	30 41 31 12	No No Yes No	53 56 34 78	23 15 26 18	19 15 14.5 >19	17% 26% 19% 6%	Gupta (2008)[27] Kloos (2009)[28] Hoftijzer (2009)[29] Ahmed (2011)[30]
Selective kinase inhibitors								
Gefitinib	EGFR	17	No	24	0	4	7%	Pennel (2008)[31]
Selumetinib	MEK1 and 2	39	No	54	3	8	15%	Hayes (2012)[32]

Table 1. Published phase II clinical trials with tyrosine kinase inhibitors in patients with DTC. (* progression according to RECIST required for inclusion; SD: stable disease; PR: Partial Remission; PFS: Progression Free Survival) .

50% of the patients and shrinkage of the tumour in 7% of the patients. Based on these findings a phase II trial has been performed including 93 patients with progressive DTC resulting in partial response (PR) in 14% and stable disease (SD) in 35% of the patients with a progression free survival (PFS) of 9.3 months.[22]

Axitinib (AG-013736) is another MKI that inhibits VEGFR, PDGFR and c-KIT that has been found in a phase I trial to induce some tumour shrinkage in one of the 5 patients with DTC.[23] Consequently a phase II trial was conducted by Cohen *et al*. including 45 patients with DTC of which 42% showed SD with a PFS of 18 months.[24] However in this study documentation of progressive disease according to the standard Response Evaluation Criteria in Solid Tumors (RECIST) was not required for inclusion.

Sunitinib (SU11248), a MKI directed against VEGFR1-3, RET, RET/PTC subtypes 1 and 3 has being investigated in patients with advanced TC. Carr *et al*. conducted a phase II study to assess the efficacy of sunitinib in patients with flurodeoxyglucose positron emission tomography (FDG-PET)-avid, iodine-refractory DTC and MTC and to investigate the usefulness of FDG_PET to assess early response.[25] In this study PR was achieved in 28% of (both DTC and MTC) patients and there was one (3%) complete remission. In addition, 46% of the patients had SD.

Treatment with Pazopanib (GW786034) that targets VEGFR1-3, PDGFR and c–Kit in a phase II trial in patients with DTC resulted in PR in 47% of the patients and PFI of 11.4 months.[26]

The most studied MKI for treatment of patients with advanced TC is Sorafenib (BAY 43-9006), which targets BRAF, VEGFR1 and 2 and RET and therefore might inhibit the growth of TC both through anti-proliferative and anti-angiogenic mechanisms. Four phase II trials have investigated the effects of sorafenib in patients with progressive or metastatic, mainly advanced TC.[27-30] Starting dosages of 400 mg sorafenib twice daily were used in these studies. The results of these studies are summarised in Table 1. The studies differed with respect to inclusion criteria and end-points. Although progressive disease according to RECIST was not required for inclusion in the study of Gupta *et al*., the authors state that all patients included had progressive disease. They found a PR of 23% and SD of 53% especially in the patients with advanced DTC.[27] The study of Kloos *et al*. focused on patients with metastatic PTC however progression documented by RECIST was not required for inclusion and a significant number of patients did not have progressive disease at the time of inclusion. Nonetheless in this study 6 (15%) of the 41 included patients had a PR and 23 (56%) had SD longer than 6 months.[28] Hoftijzer *et al*. investigated both the efficacy of sorafenib in 31 patients with with progressive metastatic or locally advanced RAI refractory DTC and the capacity of sorafenib to reinduce RAI uptake. In this study, at 26 weeks of sorafenib therapy, no reinduction of RAI uptake at metastatic sites was observed, but eight patients had a PR (26%) and 11 had SD (34%). Furthermore, sorafenib was significantly less effective in patients with bone metastases.[29] The study of Ahmed *et al*. included both patients with DTC (19) and MTC (15) showing either radiological (28 of the 34) or biochemical progression (6 of the 34). In patients with DTC the authors report a PR of 18% and SD of 78% after 12 months of treatment despite

dose reductions being required in 79% patients. The authors suggest therefore that sorafenib is better tolerable at low doses while still maintaining efficacy.[30] Based on these promising results a multi-centre, double-blind, randomised, placebo-controlled phase III study in 417 patients with locally advanced/metastatic RAI-refractory DTC (DECISION) has been carried out. This study, which was presented at ASCO 2013, showed that sorafenib extended median PFS by 5 months vs. placebo (10.8 months vs 5.8 months). Best response rates (CR+PR) were 12.2 vs 0.5%. The most frequent side-effects were hand-foot skin reaction, diarrhoea, alopecia, rash, fatigue and hypertension.

Selective Kinase Inhibitors (SKI)

Among the SKIs, gefitinib and selimetinib have shown moderate results in DTC. Gefitinib (ZD1839) is directed against EGFR. Its efficacy has been tested in a phase II trial in 17 patients with DTC. Although a PR could not be reached, in 4% of the patients a reduction in tumour size has been observed and 24% had SD for at least 24 weeks.[31]

Treatment with selumetinib (AZD6244), a selective allosteric MEK1 and MEK2 inhibitor, has been associated with SD lasting at least 5 months in 2 patients with advanced TC. A following phase II trial found a PR in 3% of the patients with advanced DTC and 66% with SD, with a PFI of 32 weeks.[32]

Interestingly, a phase II study with vemuravenib, which specifically targets the BRAFV600E mutation was recently presented at the ESMO 2013 convention. It was shown that median PFS was 15.6 months in treatment naive PTC patients and 6.8 months in PTC patients with prior TKI therapy.

In recent years, a number of studies have been performed to investigate the potential to induce redifferentiation of TC cells, with retinoic acid, lithium, histone modification agents.[33-38] However these treatments had only a modest clinical benefit. Pre-clinical studies showed that switching off the BRAF activation, either genetically or through inhibition of its downstream signaling molecules (MAPK), reduces the iodine uptake in the TC cells and that selective MAPK pathway antagonists increase the iodine uptake in these cells.[39] Based on these observations Ho *et al*. carried out a trial in 20 patients with advanced, RAI refractory DTC who underwent treatment with selumetinib for 4 months after which the RAI uptake was evaluated. The patients showing sufficient iodine uptake were subsequently treated with RAI. In this study, in 12 of the 20 included patients there has been an increase in iodine uptake after pretreatment with selumetinib and 8 of these patients were treated with RAI. Of these, 5 had confirmed PR and 3 had SD. Moreover enhanced iodine uptake has also been found in bone and nodal metastases, which in other studies have been more refractory for treatment with other TKI's.[40]

Concluding Remarks

Increasing our understanding of the TC carcinogenesis and progression has led to major advances in the treatment of patients with advanced and RAI refractory DTC. In particular, MKIs have shown significant activity in these patients. The activity of these agents has been consistently superior to conventional chemotherapy and associated with a favourable side-effect profile. All studies have found a PR in a variable percentage of the patients and stabilisation of the disease in the majority of the patients. However, some of afore mentioned studies are limited by the fact that documented progressive disease was not required for the inclusion. Furthermore even when the progressive disease was required at inclusion, it was differently defined as either radiological according to RECIST or biochemical, which cannot be used interchangeably. Moreover, all studies have used anatomical imaging to define response. Nevertheless, the use of anatomical imaging and the RECIST as end point have limitations, as they may not document changes in the tumour, such as necrosis as a result the treatment. Therefore, although the previous studies have attempted to include patients with more aggressive tumours, given the relatively indolent course of the DTC a report of SD is of limited value. For the same reason, one must bare in mind that even the reported PR responses do not necessarily correlate with overall survival and they have not yet been found to improve survival in these patients.

Furthermore, no complete remission has been reported in any study and most effects are temporary. Therefore, combination therapies of targeted compound will be of particular value. In addition, many patients included in the afore mentioned studies experienced adverse effects including fatigue, hypertension, diarrhoea, skin rash, weight loss and plantar-palmar erytrodysestesia, requiring dose reductions in more than 50% of the patients and discontinuation of the drug in 5-26% of the patients. This is particularly relevant for the patients with DTC who often have slowly progressive asymptomatic disease even in the presence of metastases. Therefore in the treatment decision the potential beneficial effects should be weight against the impact on the quality of life of these patients.

Treatment of patients with TC remains challenging. Advanced DTC are rare and therefore, to ensure optimal care and advance our understanding of tumour biology, progression and response to treatment it is highly recommended that these patients should be managed by multidisciplinary teams having extensive expertise in this field. Last but not least, given the many issues that remain to be addressed, participation in clinical trials should be considered once a decision to treat had been taken in these patients.

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The Highlights of Differentiated Thyroid Cancer at The European Cancer Congress 2013

Desirée Cox
The Cambridge Research Centre

Introduction

This review brings you our highlights of The European Cancer Congress, with a focus upon differentiated thyroid cancer (DTC). This report brings together coverage of the symposium 'Multikinase Inhibitors: Addressing Multiple Unmet Needs in Differentiated Thyroid Cancer', with presentations by Prof. Martin J. Schlumberger and Dr. Marcia Brose, as well as the best of the posters highlighting DTC at the event, including research by Dr. Jeanny Kwon.

Background

Up to 90% of all cancers involving the endocrine system are thyroid cancers. The vast majority of thyroid cancers are differentiated thyroid carcinomas (DTCs); 90% of thyroid cancers are DTCs.[1-3] For the most part, DTCs are indolent, highly curable malignancies. Between 80% and 90% of patients with DTCs survive for 10 or more years receiving their diagnosis.[4] However, some patients with metastatic DTC (advanced disease) develop disease that is refractory to conventional radioactive iodine 131 therapy (RAI-Refractory DTC). For these patients treatment options are limited and prognosis is poor.[5]

The advent of molecular therapies such as multikinase inhibitors (MKIs) targeting the vascular endothelial growth factor receptor (VEGFR) has dramatically changed the treatment landscape for patients with metastatic RAI-Refractory DTC.[6]

Given the current therapeutic landscape, key questions arising for clinicians treating and managing patients with DTCs are:

- Which patients with DTC should be treated with RAI therapy?
- What is the best treatment strategy for metastatic DTC?
- How should RAI-Refractory DTC be managed?
- What is the role of MKIs in the treatment of RAI-Refractory refractory disease?

This review presents highlights from ECC 2013, and explores new horizons in DTCs and the use of MKIs in the treatment of RAI-Refractory DTCs. It also addresses key issues for clinicians treating metastatic DTCs.

'Exploring Treatment Horizons With Multikinase Inhibitors in Differentiated Thyroid Cancer: Part 1'

Prof. Martin J. Schlumberger
(Nuclear Medicine and Endocrine Oncology, Institut Gustab Roussy and University of Paris-Sud, Villejuif, France)

The presentation given by Prof. Schlumberger identified key points in the epidemiology, diagnosis, treatment and management of DTC. Prof. Schlumberger focused on the use of radioactive iodine (RAI) treatment in DTC, and concluded by discussing the limitations in the treatment and management of metastatic DTC with RAI, and the definition of metastatic RAI-Refractory disease.

Recent publications have highlighted the rapid increase in incidence in thyroid cancer over the past 30 years.

Prof. Schlumberger emphasised that the increase in the incidence of thyroid cancer is due to improved screening and pathological techniques, and more efficient diagnostic tools for detecting thyroid cancers (such as ultrasonography (US) and fine needle aspiration biopsy (FNAB)) rather than an overall increase in all thyroid cancers.[7]

Prof. Schlumberger further noted that improved diagnostic detection tools have led to an increased incidence of micropapillary thyroid cancers less than 2 cm in diameter, which are curable with surgery and post-operative RAI therapy. Indeed, most of these patients will not see a recurrence of the disease.[8] The incidence of a) small thyroid carcinomas, b) large T3 and T4 thyroid tumours, and c) distant metastases has remained stable over time.[9]

Desirée Cox is an accomplished Medical Doctor, who completed her studies at both the University of Oxford, Oxford, UK and at the University of Cambridge, Cambridge, UK. Her clinical background encompasses practice, education and clinical studies, and her experience extends to many areas within medicine including gastrointestinal medicine and surgery and paediatric medicine. Dr. Cox also has extensive medical consulting experience and is the author of a number of books and peer-reviewed articles. She has also been a guest speaker at a number of universities including the University of Oxford, UK, INSERM, France and Rutgers University, USA.

In his presentation of the epidemiology of thyroid cancer, Prof. Schlumberger noted that there are approximately 7000 new cases of thyroid cancer in France per year; the incidence of thyroid cancer in France is similar to that of incidence in most European countries. Approximately 10% of all new cases of thyroid cancer are large T3 and T4 tumours; and, approximately 350 of new incidences of thyroid cancer will be refractory disease. Of the 350 cases of refractory disease, 200 are DTC, 50 are medullary thyroid carcinoma (MTC) and 100 are aggressive anaplastic tumours.[10]

Key Points in the Diagnosis of DTC

DTCs arise from the thyroid epithelial cells and are comprised of the following carcinomas subtypes: Papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and Hurthle cell carcinomas (HCC). Thyroid epithelial cells may also give rise to a lethal form of thyroid cancer known as anaplastic thyroid cancers (ATC), but this type of cancer is rare.[11] Poorly differentiated thyroid carcinomas (PDTC), may also be considered under the umbrella of DTCs, and represents a bridge between well-differentiated malignancies of thyrocytes and undifferentiated (anaplastic) thyroid carcinomas.[12]

Prof. Schlumberger pointed out that metastatic DTC represents the most common cause of death from thyroid cancers. Less than 10% of patients diagnosed with DTC will have distant metastases: 40% of these patients with metastatic disease have a primary PTC, 15% have a primary FTC, and 45% have a primary PDTC.[13]

The vast majority of patients with metastatic DTC will have distant metastases in bone and lung; 25% of patients have bone metastases, 50% have lung metastases, 20% have bone and lung metastases, and 5% have metastases at other sites.[14]

For 1 in 2 patients with metastatic disease, distant metastases will be detected at the point of diagnosis. Of the remaining patients whose metastatic DTC approximately 80% will have their metastases diagnosed within the first 5 years of follow-up.[15]

Treatment of Metastatic Disease in DTC: Therapeutic Tools

There are 3 approaches to treating patients with metastatic DTC. These are:

- TSH suppression
- Local treatments
- Systemic treatments

TSH Suppression

The growth of thyroid tumours may be suppressed by TSH suppressor agents such as levothyroxine; thyrotropin increases tumour growth and thyroxine (in the form of levothyroxine) inhibits and thyrotropin.

Prof. Schlumberger emphasised that TSH suppression greatly improves the overall survival (OS) of patients with metastatic DTC. TSH suppression also reduces the likelihood of disease recurring.[16, 17] TSH suppression therapy levothyroxine therapy should therefore be considered in all patients with DTC regardless of the extent of thyroid surgery or other treatments for the disease.[18]

Local Treatments

The primary goal of local treatments is to reduce tumour volume and symptom control: reducing the volume of cancer cells improves treatment outcome and disease prognosis.
Local treatment modalities include:

- Surgery of primary tumour and/lymph nodes.[19]
- External beam radiation therapy (EBRT) using high-energy radiation to destroy cancer cells or slow their growth.[20]
- Selective Embolisation of Thyroid Arteries (SETA).[21]
- Radiofrequency thermal ablation (RFTA) or cryoablation at tumour site or site of metastases.[22]
- High Intensity Focused Ultrasound (HIFU) of thyroid nodes.[23]
- Bone cement (or percutaneous osteoplasty), in which bone cement is injected into a painful bone metastatic lesion refractory to conventional therapy.[24]

Prof. Schlumberger pointed out that surgical treatment with RFTA is extremely effective in DTC. In cases where several distant metastases are present, surgical treatment along with TSH suppression greatly improves OS; the efficacy of TSH suppression in such cases is equivalent to surgical resection of metastases.

Systematic Treatments

RAI therapy has been mainstay of systematic treatment of metastatic DTC for the past 6 decades. Patients with metastatic DTC whose distant metastases have a high RAI uptake may be successfully treated with RAI therapy. These patients tend to have a good outcome and complete remission of the disease.[25]

RAI Therapy in the Clinic: Current Management

Prof. Schlumberger identified the 3 main stages of RAI therapy:[26]

1. The preparatory stage (approximately 1 week) involves withdrawing T4 from patients, thereby increasing TSH and stimulating uptake of RAI by distant metastases;
2. The RAI treatment stage (approximately 5 weeks) involves administering the treatment dose of RAI (3.7 GBq (100 mCi));
3. The Post-therapy stage where patients receive repeat doses of thyroxine suppression treatment 6 months after RAI treatment; then every 6 months for up to 2 years, and once a year thereafter until remission or cure.

What is the Outcome of RAI Therapy in Patients with Metastatic DTC?

RAI therapy is highly effective for many patients with metastatic DTC.

Over 45% of patients with DTC and distant metastases experienced complete remission with no further recurrence of their disease.

At the Institute Gustave-Roussy (Villejuif, France) where Prof. Schlumberger is based, a cumulative study of RAI therapy in 444 patients with metastatic DTC conducted over 4 decades (1953-1994) showed that:

• 295 of the 444 patients treated with RAI (66%) had initial RAI uptake;
• 127 of the 295 patients with RAI uptake (43%) had complete remission of the disease as evidence by normal x-rays taken after the treatment;
• Only 7% of patients who experienced complete remission saw recurrence of the disease;
• 92% of patients with complete remission had an overall survival of 10 years;
• There were only 4 deaths during the course of the study.[27]

Will RAI Therapy be Effective in your Patient?

Prof. Schlumberger advised physicians treating patients with metastatic DTC that the likelihood of the efficacy of RAI in individual patients may be assessed using the following parameters:

• Presence of serum thyroglobulin (Tg): Tg is a tumour marker for the disease.
• Quantitative measurement of the uptake of RAI: RAI uptake is essential for the efficacy of the RAI therapy.
• Measurement of target lesions using CT scan or MRI.
• Tumour response to RAI treatment determined by decrease in serum Tg.
• Decrease in RAI uptake and decrease in tumour size.
• Absence of tumour progression: RAI treatment should be discontinued in cases where anatomical imaging reveals tumour growth or progression.

How Long Should Patients be Treated with RAI? When is Enough, Enough?

RAI therapy has a cumulative effect in metastatic DTC. However, studies have shown that 96% of all remissions are observed with a cumulative activity of up to 22 GBq (600mCi): in other words, if DTC still persist after a cumulative radioactivity level of 22 GBq(600Ci) there is little chance that the patient will be cured with RAI.[28-30]

A retrospective analysis of 6841 patients treated with RAI showed that the risk of secondary solid tumour cancers and secondary leukaemias increases significantly with cumulative radioactive activity beyond 22 GBq (600Cmi).[31]

Drawing attention to a new biomarker for the detection and localisation of recurrent disease in DTC, namely 18F- fluoro-deoxy-glucose (FDG) PET, Prof. Schlumberger noted that FDG-PET may be used in the follow-up of patients with DTC to assess the limitations of RAI therapy in individual cases. In patients where there is high uptake of FDG there is little chance of the patient responding to RAI treatment.[32]

Recognising RAI-Refractory Disease: What should Clinicians Look For?

Finally Prof. Schlumberger defined RAI-Refractory metastatic DTC. Patients may be defined as having RAI-Refractory metastatic DTC if a) there is no detectable RAI uptake in one or more target lesions, and/or disease progression within 12 months of RAI treatment, and/or persistent disease after RAI treatment leading to cumulative RAI activity of 600mCi.

What to do once RAI-Refractory Disease has been Diagnosed?

Prof. Schlumberger's caution to physicians once RAI-Refractive metastatic DTC has been diagnosed is as follows:[33]

• RAI treatment should be stopped immediately after patients have been defined as having RAI-Refractory disease.
• TSH Suppression should be maintained in patients with RAI-Refractory DTC.
• Local treatment modalities should be used to reduce tumour burden and palliation in these patients.
• Disease progression should be assessed and considered for other systemic treatments in cases where the disease has progressed

Exploring Treatment Horizon With Multikinase Inhibitors in Differentiated Thyroid Cancer: Part 2

Dr. Marcia Brose
(Division of Hematology/Oncology Abramson Cancer Center University of Pennsylvania, Philadelphia, Pennsylvania, USA)

Dr. Brose's presentation picked up where Prof. Schlumberger left off by focusing on new possibilities for the use of the multi-kinase inhibitor (MKI) sorafenib in the treatment of RAI-Refractory DTC. Dr. Brose presented evidence for the efficacy of sorafenib in metastatic RAI-Refractory DTC from the first ever phase 3 randomised placebo controlled clinical trial (the DECISION trial) of sorafenib for RAI-Refractory DTC.

Dr. Brose noted that RAI-refractory DTC is a relatively rare condition which occurs in approximately 5% to 15% of patients with DTC, has a poor prognosis, and no standard therapy. Dr. Brose also noted that novel molecular target therapies such as sorafenib offer the possibility of improved prognosis in these patients.[34]

Sorafenib is a multikinase inhibitor (MKI) that targets the VEGF receptors VEGFR 1-3, as well as PDGFRs, BRAF, RET and cKit.[35]

The development of novel molecular targeted therapies over the past few decades has largely been due to recent advances in the understanding of the molecular mechanisms underlying tumour angiogenesis in general and the importance of vascular endothelial growth factor (VEGF) in influencing the microcellular environment and tumour behaviour.[36] VEGF tyrosine kinases activate tumour proliferation and metastasis by mediating various changing the vasculature and

promoting tumour growth. VEGF receptor TK inhibitors such as sorafenib inhibit VEGF signalling mechanism thereby reducing tumour growth.[37]

Sorafenib was originally approved for the treatment of advanced renal cell carcinoma (RCC) and hepatocellular carcinoma; its introduction in 2005 pioneered the concept of VEGF-targeted therapies in for the treatment of mRCC. Dr. Brose drew attention to a number of phase 2 trial studies of sorafenib that have shown that the drug has also been shown to have activity a monotherapy in refractory DTC.[38-40]
Promising phase 2 studies results led to the development of the first ever phase 3 randomised, double-blind, placebo-controlled trial (the DECISION trial) for determining the efficacy and safety of sorafenib in the treatment of RAI-Refractory DTC.[41]

Dr. Brose presented the results of the DECISION trial. The DECISION trial involved 417 patients with locally advanced or metastatic RAI-refractory DTC. Baseline disease characteristics including investigator-assessed histology, and lesion sites were well balanced between the study arms, as was median cumulative RAI exposure. The vast majority of patients in both groups had distant metastases.[42]

Dr. Brose noted that considerable attention was paid to inclusion criteria in the trial design. Patients included in the trial had progressive disease lasting for at least 14 months before being entered into the trial (as defined by the Response Evaluation Criteria In Solid Tumors (RECIST)). Patients who had undergone previous treatment with targeted therapy or chemotherapy were excluded. Patients were randomly assigned to 400 mg sorafenib orally twice daily or to placebo. Progression was assessed every 8 weeks. In cases where the disease had progressed during the course of the trial, progressed patients on placebo were allowed to cross over to the treatment group.

Dr. Brose highlighted the key findings of the DECISION trial. The trial results show that sorafenib is efficacious and safe in metastatic DTC and is a potentially new treatment option for patients with locally advanced or metastatic RAI-refractory DTC. The drug significantly improved progression-free survival (PFS) for patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC).

Sorafenib extended PFS in patients with DTC by 5 months compared with placebo. Sorafenib reduced target lesion size in 73% of patients, compared with 27% in the placebo arm. Of note, tumour shrinkage with sorafenib in symptomatic patients was often sufficient to alleviate symptoms.

Dr. Brose noted that PFS was the primary endpoint of the trial; overall survival (OS) was a secondary endpoint of the study. This secondary endpoint of the study was necessarily affected by the large proportion of patients in the placebo arm (71%) who have crossed over to treatment. Although no complete response was seen in the study, a partial response was seen in 12.2% of patients (over an average of 10.2 months) in the sorafenib arm as compared to 0.5% in the placebo arm. Benefit of treatment was seen in all pre-specified subgroups and across all regions (North America, Europe, and Asia) and age groups.

Finally Dr. Brose concluded that the DECISION trial results clearly show that sorafenib is a safe treatment for patients. AEs most often observed during the study included: hand and foot skin reactions, diarrhoea, alopecia, rash, fatigue, and hypertension. Most adverse events (AEs) experienced by the patients may be managed by dose reduction and with over-the-counter products. Only 18.8% of patients discontinued sorafenib due to AEs.

The most frequent serious AEs were secondary malignancies but these were observed in a small minority (4.3%) of patients treated with the sorafenib. Two deaths attributed to the study drug occurred; only one of these deaths occurred in a patient being treated with sorafenib.

Conclusions: Unmet Need

Sorafenib is novel, efficacious and safe MKI that is potentially new treatment option for patients with metastatic RAI-refractory DTC. However, there remains an unmet need for further knowledge of the process of tumour carcinogenesis of DTC which may in turn lead to new targeted drugs with different molecular targets and novel tools to optimise existing treatment regimens. There is also a need for further clinical trials on the outcome of existing targeted therapies.

Posters Presented at the European Cancer Congress 2013

BRAF Mutations / Differentiated Thyroid Cancer, Radioactive Iodine Refractory, Prognostic Factors /RAS Mutants / Sorafenib, for Radioactive Iodine-refractory Differentiated Thyroid Cancer

Marcia Brose, Christopher Nutting, Young Kee Shong, Steven Sherman, Jan Smit, June-Key Chung, Istvan Molnar, Michael Jeffers, Carol Pena, Martin Schlumberger

This first poster by Brose and colleagues provided a further analysis of DECISION trial with the view to determining whether genetic mutations associated with the etiology of DTC might be used as biomarkers to predict the efficacy of sorafenib in RAI-Refractory metastatic DTC.

Summary

The poster presented by Brose and colleagues reviewed the results of the phase III placebo controlled randomised controlled clinical trial – the DECISION trial – of sorafenib (400 mg bd) in patients with a14-month history of RAI-refractory DTC. Placebo group patients whose disease progressed were switched to the treatment group.

Tumour biopsies from 256 patients (61.4% of the study population) were also analysed for 238 mutations in 19 oncogenes in order to determine whether the BRAF and RAS genetic mutations could be used as biomarkers to predict efficacy of sorafenib in RAI-Refractory DTC.

BRAF and RAS mutations were detected in 30.1% treated with

sorafenib and 19.5% of patients treated with placebo. Other point mutations occurred in less than 5% of patients; 47.3% of patients had no detectable mutations.

The results of the DECISION trial showed that sorafenib reduced the risk of disease progression or death by 42% in patients as compared with those treated with placebo. The results also suggest that a) RAS and BRAF mutations were negative and positive prognostic factors, respectively, for progression free survival (PFS) in RAI-refractory DTC patients, and b) PFS in patients treated with sorafenib was prolonged regardless of BRAF and RAS mutation status of their tumours.

Role of Adjuvant Postoperative External Beam Radiotherapy for Well Differentiated Thyroid cancer

Jeanny Kwon, Hong-Gyun Wu, Yeo-Kyu Youn, Kyu Eun Lee, Kwang Hyun Kim, Do Joon Park

This final poster summary features a cumulative evaluation by Kwon and colleagues of the outcome of the use of adjuvant postoperative external beam radiotherapy (EBRT) in the treatment of well-differentiated thyroid cancer (WDTC).

Summary

Kwon and colleagues presented a cumulative evaluation of the outcome of 84 patients treated with adjuvant postoperative external beam radiotherapy (EBRT) for well-differentiated thyroid cancer (WDTC) over approximately 30 years. The majority of the patients had stage T3 or T4 disease. Ten patients (approximately 26%) had gross residual tumours, 5 patients (approximately 13%) had tumour cells at the margin. Thirty-nine of the patients (between ages 16 and 72 years) included in the study had received EBRT after initial radical surgery: 24 patients were females, 15 patients were males. Patients were followed for an average of 73 after EBRT.

The study showed that the five-year overall survival (OS) and locoregional recurrence free survival (LRFS) were 97.4% and 86.9%, respectively. Locoregional failures occurred in 5 and all failure sites were the neck node area. The study also showed that OS was significantly influenced by tumour invasion of the trachea or esophagus. LRFS was significantly decreased patients who a) were male, b) had gross residuum after resection, c) had close or positive tumour at surgical margin involvement, and d) whose tumour had invaded the trachea. No significant prognostic factors were identified and none of the patients experienced RTOG grade 3 or more toxicity.

The locoregional control rate of 87.2% obtained by Kwon and colleagues was comparable to historical controls with surgery alone despite the large proportion of patients with advanced diseased included in the study.

Overall, the study showed that EBRT is an effective and safe treatment option in patients with WDTC.

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Approaches to the Treatment of Minimal Residual Disease Following Adjuvant Chemotherapy

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Summary

Despite advances in the adjuvant treatment of surgically resected colon cancer, a significant proportion of patients suffer a relapse. Recurrence after therapy can be conceptualized as the result of minimal residual disease (MRD) escaping the cytotoxic effects of chemotherapy by achieving a condition of stasis or by concealment in a sanctuary site into which chemotherapy does not penetrate. There are several interventions which may provide improved survival and a reduction in the rate of relapse following completion of adjuvant therapy. These may work through direct cytotoxic effects on residual cancer cells or cancer stem cells or inhibition of release from dormancy. Here, the potential role and proposed mechanisms for various interventions, including diet modification, aspirin, statins, ACE inhibitors, metformin and physical activity are reviewed.

Introduction

Patients with high risk stage II and stage III colon cancer have a risk of recurrence within 5 years of up to 60% following surgery, with significant reduction in this risk following administration of fluorpyrimidine or fluorpyrimidine/oxaliplatin-based adjuvant therapies.[1] Even following administration of adjuvant chemotherapy however, 10-15% (stage II) to 35-40% (stage III) patients will eventually relapse with metastatic disease. The reduction in the frequency of relapse with chemotherapy is attributed to the eradication of micrometastatic minimal residual disease (MRD).

Most solid tumor malignancies are likely associated with disseminated disease that may persist as MRD after presumptively curative therapy. Recurrence after therapy can be conceptualized as the result of MRD escaping the cytotoxic effects of chemotherapy by achieving a condition of stasis or by concealment in a sanctuary site into which chemotherapy does not penetrate.[2] After a period of dormancy, residual cancer cells may reacquire tumor cell growth characteristics and present as a clinically-evident relapse. For colon and other cancers, survival of those cells that retain the capacity for self-renewal and multilineage differentiation potential, the cancer stem cells, may be the primary etiology of eventual recurrence.[3] Targeting these cancer stem cells, dormant or protected in a sanctuary site during adjuvant chemotherapy, has the potential to reduce relapse and extend survival, and may require non-traditional approaches and interventions.

Diet

Epidemiologic studies have established strong links between fiber (protective) and red/processed meat (deleterious) and the development of colorectal cancer.[4,5] More recently, the consumption of a more "Western" (or less "Eastern") diet has been associated with a three-fold higher rate of cancer recurrence in stage III colon cancer patients following adjuvant chemotherapy (comparison of highest quintile of Western pattern diet to lowest quintile).[6] It has been suggested that energy balance factors may influence recurrence as stage III colon cancer patients with higher dietary glycemic load and total carbohydrate intake have a significantly increased risk of recurrence and mortality.[7] Others have found that a high processed meat dietary pattern prior to diagnosis is significantly associated with a higher risk of tumor recurrence, metastases and death.[8]

Why would diet modification affect MRD and the propensity for relapse after surgery and chemotherapy? This may relate to systemic insulin levels as hyperinsulinemia has been linked to cancer recurrences and mortality in colorectal cancer survivors.[9,10] Diet may also modify the proliferative pathways stimulated by insulin-like growth factor, operating via the insulin-like growth factor (ILGF) receptor which has been strongly linked to cancer development.[11] Insulin and ILGF promote proliferation and inhibit apoptosis. The mechanism through which red meat may promote carcinogenesis is generally felt to relate to N-nitroso compounds which are known carcinogens[12] or high arginine content leading to excess polyamine production.[13]

Aspirin

Several epidemiological and randomized controlled trials have demonstrated a beneficial, protective effect of aspirin on the development of colorectal (CRC) cancers.[14-16] Aspirin also appears to improve survival after diagnosis and may inhibit the development

of metastases.[17, 18] Recently, Lioa and colleagues[19] showed that the positive effect of aspirin on survival after diagnosis of CRC is restricted to patients with PIK3CA mutated tumors. PIK3CA is mutated in about 20% of colorectal cancers and leads to increased synthesis of prostaglandin E2 via upregulation of cyclooxygenase-2 activity.[20] Regular use of aspirin after diagnosis, in patients with PIK3CA mutated tumors, had a significantly improved CRC-specific survival and overall survival. While aspirin has a multitude of cellular activities, it is felt that inhibition of cyclooxygenases COX1 and COX2 are its primary mechanism of action in CRC.[21]

Angiotensin converting enzyme inhibitors (ACEi)

ACEi are routinely utilized for the treatment of hypertension. Studies have suggested that the long term use of ACEi is associated with a lower likelihood of advanced neoplasia in a colonoscopy screening program for patients with heme-occult positive stool[22] and with a decreased incidence of advanced adenomatous colonic polyps.[23] A large cohort study in the UK confirmed a decreased risk of cancer in patients taking ACEi, although the predominant effect was for breast and prostate cancer and no statistically significant effect on colon cancer was found.[24] However, a more recent study[25] examined records of patients diagnosed with colon cancer and found that those taking ACEi, especially in combination with beta-blockers, had a decreased risk of tumor progression and an overall decreased mortality compared to unexposed individuals, even adjusting for stage at presentation. Given this, ACEi therapy in colon cancer patients not already receiving this medication, may prove beneficial in reducing relapse following adjuvant chemotherapy.

Angiotensin II mediates the induction of vascular endothelial growth factor (VEGF) and also promotes signaling through the PI3K-AKT, MAPK and STAT3 pathways.[26] ACEi may work through one or all of these mechanisms. Of interest, angiotensin II inhibition has also been shown to enhance the anti-tumor effect of COX2 inhibitors such as aspirin and other NSAIDs.[27]

Statins

Statins are inhibitors of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase commonly utilized to lower serum cholesterol and reduce mortality from cardiovascular disease. Their use has been linked to a modest but significant protective effect in colorectal cancer.[28] While the data regarding statins for adenoma prevention is complex and often contradictory, Siddiqui *et al.*[29] found that among patients already diagnosed with colon cancer, statin users had a 30% lower prevalence of metastases compared to non-statin users, suggesting that statins may impact outcomes by decreasing the invasiveness or metastatic properties of colorectal cancer cells. Another study found that statin use was strongly associated ($p<0.001$) with a lower likelihood of advanced neoplasia when undergoing screening colonoscopy.[22]

Statins exhibit numerous activities which may lead to a beneficial outcome for cancer patients. They have been shown to induce apoptosis (programmed cell death) through depletion of farnesylated or geranylgeranylated proteins.[30] Simvastatin has been shown to induce apoptosis in colorectal cancer cell lines *in vitro*.[31] Lovestatin induces apoptosis in human colon cancer cell lines via inhibition of cholesterol synthesis and can block proliferation through a G0/G1 arrest.[32]

Metformin

Metformin is a biguanide that is frequently used in the treatment of type II diabetes mellitus. Observational studies of patients with diabetes who are treated with metformin has shown a significantly lower risk of colon and rectal cancers (RR 0.63; $p<0.001$).[33] Low doses of metformin can reduce the number of aberrant crypt foci (felt to be a precursor lesion for CRC) and decrease the proliferative index of colonic epithelium in non-diabetic patients.[34]

Metformin has indirect effects through hepatic gluconeogenesis in reducing circulating insulin, ultimately decreasing cell growth and proliferation (see discussion under Diet, above). It also directly modulated mTOR signaling via activation of AMPK and inhibition of mTORC1.[35] This reduces protein synthesis and inhibits cell proliferation. The link to energy balance, and potential role following adjuvant chemotherapy for colon cancer patients, has led to the development of a phase II clinical trial in this patient population (NCT01340300).

Physical Activity

Increased physical activity following surgery and adjuvant chemotherapy in stage III colon cancer patients reduces the risk of cancer recurrence and mortality.[36] The hazard ratio for disease-free survival in this study was 0.51 for 18-27 MET-hours of activity per week and 0.55 for more than 27 MET-hours of activity per week, with statistical significance for both recurrence free and overall survival. This finding is consistent with data indicating reduced cancer recurrence post diagnosis in breast[37] and prostate[38] cancers. While the beneficial effect of physical activity following adjuvant chemotherapy is recently recognized, observational studies have long linked increased amounts of physical activity to a reduction in the incidence of colon cancer.[39]

Physical activity most likely works through similar mechanisms as diet and metformin, with modulation of energy balance and reduction in circulating levels of insulin and ILGF.[40] It has also been postulated to affect prostaglandin synthesis, bile acid secretion and gut flora.

Conclusions

The potential mechanisms of activity of the agents described above are summarized in Table 1. Their beneficial effects may be considered in three general categories: 1) direct anti-cancer

Agent/Intervention	Potential Mechanisms	Caveats
Diet	Reduced hyper-insulinemia; ILGF signaling; arginine	Dietary patterns both prior to diagnosis and following adjuvant chemotherapy appear to be important factors influencing recurrence
Aspirin	Cyclooxygenase inhibition	Activity only for tumors with PIK3CA mutations
ACEi	Inhibition of VEGF, PI3K-AKT, MAPK, STAT3	May be most effective in combination with beta-blockers or COX2 inhibitors
Statins	Apoptosis induction; induction of G0/G1 arrest	Decreased invasiveness or metastatic properties postulated
Metformin	Reduction of circulating insulin; direct inhibition of mTOR signaling	Observational studies in diabetics provide strong evidence for activity
Physical Activity	Reduction of circulating insulin and ILGF	Supports observational studies showing a reduced risk of colorectal cancer with increasing amounts of physical activity

Table 1. Potential interventions for minimal residual disease in colon cancer patients. ACEi = angiotensin converting enzyme inhibitor, ILGF – insulin-like growth factor, VEGF – vascular endothelial growth factor, COX2 – cyclooxygenase 2

properties, perhaps by affecting signaling pathways required for growth, 2) inhibition of release from dormancy, perhaps by affecting angiogenesis or other properties in the micrometastatic tumor microenvironment or 3) direct activity on cancer stem cells in sanctuary sites which are felt to be the etiology of many late recurrences following adjuvant chemotherapy. It is likely that lifestyle interventions such as diet and physical activity have indirect effects, possibly by modulating energy balance and acting through insulin and ILGF-associated mechanisms. Initial observations from epidemiologic studies have identified these interventions and many are now being incorporated into randomized controlled trials which will inform their future use for patients with colon cancer following adjuvant chemotherapy.

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Decision-making in Geriatric Oncology

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Introduction

In the coming decades, the ageing of society will result in a substantial increase in the number of elderly patients with cancer. Current oncology guidelines are primarily based on studies in younger and relatively fit patients, which cannot automatically be extrapolated to other patient groups. Incorporating expertise from the field of geriatric medicine can aid cancer specialists in the decision-making process for their elderly cancer patients.

Guideline Adherence

For decades, older age was an accepted contra-indication for cancer treatment and the issue of guideline adherence for the elderly was barely addressed in oncologic literature. In the last decades of the twentieth century, cancer specialists came to realise that this automatic exclusion of older patients did not do them justice.[1] In the wake of studies demonstrating that standard cancer treatment could be given successfully to selected elderly patients,[2] older patients not receiving standard care were stated to receive "substandard" or even "inappropriate" treatment.[1,3] However, for the elderly patient, discordance with standard practice or guideline-recommended treatment does not automatically imply that treatment is suboptimal, as valid reasons for a deviation from guidelines exist. Furthermore, although there is a general consensus that age should not be the primary reason for withholding treatment,[4,5] it would be unfair to say that age does not matter at all.[6] For instance, the process of ageing means that a person gradually loses a part of his or her physiological reserves, influencing their ability to tolerate treatment. In addition, much cancer treatment is aimed at preventing future cancer-related complications; as ageing limits the remaining life-expectancy of a patient, it may also limit the benefit of such treatment.

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Using the terms "substandard treatment" or "undertreatment" to describe non-standard treatment suggests that any tailoring of treatment to the patient's situation should be avoided. However, overtreatment of frail elderly patients may be as harmful as undertreatment. Therefore, tailor-made care should be the standard of care for older patients. The important questions that remain are what factors should guide such tailoring and how to reliably determine and balance potential benefit with potential harm in this patient population.

The Value of a Geriatric Assessment in Cancer Care

Hippocrates stated that it is more important to know what sort of person has a disease than what sort of disease a person has. This is an excellent starting point for the treatment of cancer in the heterogeneous elderly population. The speed at which physiological reserves decline will vary from person to person, and differences in genetic make-up and lifestyle will only become visible later in life. In addition, transient and chronic illnesses will leave their mark, as well as geriatric conditions such as dementia, depression, malnutrition, care dependence and decreased mobility. Previous studies have demonstrated that these geriatric conditions are easily overlooked,[7,8] particularly in the doctor's office, where patients tend to present themselves at their best and little time is reserved for a more in-depth examination of the patient's health status. Furthermore, even a patient that appears to be in good health may have lost much of his or her reserve capacity.

In oncology, the commonly used measure for a patient's vitality is the performance status.[9] However, in older patients, this measure may not be sufficiently sensitive to separate those patients that will be able to undergo standard cancer therapy from those who will require a tailoring of treatment. For this reason, oncologists are increasingly deferring to the geriatric concept of frailty to describe differences in vitality. Frailty is a physiological syndrome of decreased resistance to stressors, which results from the accumulation of decline in multiple organ systems.[10,11] It can be seen as the final common pathway of the ageing process. Because both cancer and cancer treatment represent significant stressors, it is thought that the frailty concept can be useful in oncology practice.[12] Another concept that has been adopted from geriatric medicine is the comprehensive geriatric assessment (CGA), which is a

method of detecting frailty by assessing the patient's physical, psychological, social and functional health status.[12]

Studies assessing the prevalence of geriatric comorbidity in patients aged 65 years and older admitted to the general medicine wards of three Dutch hospital demonstrated that over half of patients were suffering from malnutrition, mobility impairments and polypharmacy, while more that two-thirds of patients had mood disorders, pain and functional impairments.[13] In addition, almost half of the caregivers stated that they were overburdened. Detecting such geriatric issues could be a starting point for care interventions, aimed at improving overall health and quality of life. For example, one study found that older cancer patients receiving an in-patient geriatric consultation experienced less social limitation and pain at three months after discharge; the effect on pain was still significant one year later.[14]

In a systematic review of 37 studies on the predictive value of CGA in oncology, geriatric factors were found to be predictors of survival, toxicity of chemotherapy and surgical complications.[15] A patient's vulnerability to poor outcomes primarily appears to be determined by the accumulation of geriatric conditions; the nature of these conditions is of lesser importance. This was also demonstrated by the Dutch multicentre OMEGA study,[16] in which 78 patients with metastatic breast cancer received first-line single-agent palliative chemotherapy. The proportion of patients experiencing grade 3 and 4 chemotherapy-related toxicity was strongly associated with the number of geriatric conditions that were present at baseline: of patients without geriatric conditions, only 19% experienced such toxicity, compared to 56% of patients with two conditions and 80% of patients with three or more geriatric issues.[16] Of the individual geriatric conditions, only polypharmacy demonstrated an association with chemotherapy-related toxicity. In the same study, patients with one or more geriatric issues also demonstrated a poorer prognosis: median overall survival was 10.3 months for these patients compare to 19.9 months is patients without geriatric conditions.[16]

Screening Tools

Implementing a geriatric assessment into daily oncology practice has been demonstrated to be complicated. This is in part due to the fact that such assessments are laborious and time-consuming. For this reason, research has focused on identifying a frailty screening tool that can be used to separate fit oncologic patients who should be able to receive standard care, from those that are more vulnerable and would thus benefit from a more thorough geriatric assessment.[12] However, a recent systematic review has demonstrated that none of the screening instruments that are currently being used for this purpose have sufficient discriminative power.[17] Those instruments that have a good sensitivity, such as the Geriatric[8] or the triage risk screening tool, lack specificity; as a result, almost all patients are found to be vulnerable. Instruments with a good specificity, such as the Fried frailty criteria or the abbreviated comprehensive geriatric assessment, lack sensitivity and as result, a large proportion of frail patients are incorrectly identified as being fit. Even the most sensitive tools still had a negative predictive value of 60%.[17] Therefore, a two-stepped approach in which patients are first screened with a short screening instrument and are subsequently referred for further analysis in this screening is positive, but does not seem feasible with the currently available screening tools.

Another approach has been to develop tools which can be used for one aspect of the geriatric evaluation, for instance predicting toxicity of chemotherapy;[18, 19] although quick and useful for this particular purpose, such tools cannot replace the wealth of information provided by a full evaluation.

The Future of Geriatric Oncology

In the coming decades, the increasing ageing of the population and the explosive rises in the costs of healthcare will mean that the need for tailored cancer care for the elderly will also increase. However, a tailoring of care requires evidence on which to base treatment decisions; currently the knowledge on the impact of the various treatment options for the elderly patient is often lacking. More research specifically addressing the elderly population should therefore be a priority. Studies should incorporate baseline frailty data, allowing for a better comparison between the study population and the individual patient. Furthermore, these studies should not only focus on the commonly used oncologic outcome measures, such as disease-free survival or time-to-progression, but also include those outcome measures that are of particular importance to the elderly patient, such as care dependence, cognitive function and quality of life.

However, until these studies have been completed, the multidisciplinary cancer team will have to decide on the optimal treatment as best they can. The addition of a geriatric assessment or consulting a geriatric specialist appears to be of value: in addition to the prognostic value described earlier, European and American studies have demonstrated that the oncologic treatment plan is altered in 20-50% of elderly patients after a geriatric evaluation.[20-22] These studies reported both more and less intensive treatment, depending on the local treatment culture. In addition to an alteration in cancer treatment, over two-thirds of patients received non-oncologic interventions aimed at optimising the patient's overall condition prior to treatment and at improving their quality of life.

Conclusion

For older cancer patients, tailor-made care should be the standard of care, striking the golden mean between undertreatment and overtreatment and fully taking into account the heterogeneity of this population. A geriatric evaluation will provide invaluable information about the patient's overall health status, prognosis and ability to tolerate treatment, and can form a starting point for interventions aimed at improving overall health and quality of life. Its time-consuming nature may be an obstacle in the implementation of geriatric assessment in

daily oncology practice. However, in an age where the amount of time spent on staging and exploring disease characteristics is rapidly increasing, and more and more money is spent on increasingly sophisticated anti-cancer treatments, taking the time to explore whether or not a patient will be able to benefit from and tolerate cancer treatment should not be a matter of discussion.

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Chemotherapy of the Recurrent/Metastatic Squamous Head and Neck Cancer – Past, Present and Future

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Introduction

Treatment of the squamous cell cancer of the head and neck (SCCHN) is a multimodal challenge in the daily clinical routine.[1, 2] The aggressive nature of the SCCHN is emphasised by the fact that even in the absence of metastatic spread in localised stages, about 60% of patients will suffer from relapse, and or distant metastasis (R/M) within 2 years.[3, 4] R/M-SCCHN is associated with a median overall survival (OS) of 8-10 months, and curative treatment is not attainable.[3, 5-8] In this setting, palliative chemotherapy is the mainstay of therapy and is either applied as single-agent-, or combined chemotherapy, mostly with an EGFR inhibitor.[1-3, 9]

Often, the carcinogenesis of R/M-SCCHN relies on tobacco or alcohol abuse, which adds another layer of complexity to the choice of therapy, and may render combined therapies inappropriate for some patients.[1, 3, 8-10] Therefore, prognostic parameters were established, which may guide the chemotherapeutic choice and adaptation of treatment intensity with respect to patient's co-morbidities.[3, 8-11] Current discoveries in tumour biology in SCCHN have paved the way for novel therapeutic options, which may put the field beyond the scope of EGFR inhibition. Here, we discuss current and future perspectives on chemotherapy in R/M-SCCHN.

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First-line Therapy in R/M-SCCHN

The choice of first-line therapy varies among patients with R/M-SCCHN. For patients with no treatment limitations, a platin-based doublet remains the mainstay of chemotherapy, which is mainly combined with an EGFR inhibitor.[2, 3, 6, 7, 9] Combinations of three or more chemotherapeutics were explored in small series, but cannot be recommended for R/M-SCCHN patients outside of clinical trials.[3, 9, 12-19]

The most common regimen in R/M-SCCHN is cisplatin/5FU, which is superior in respect to objective response rate (ORR) when compared to single-agent therapy.[3, 9] In several phase III trials, cisplatin/5FU showed a response rate (RR) and progression-free survival (PFS) with a modest increase in toxicity in comparison to single-agent therapy, even though improvement of OS remained an unfulfilled goal.[5, 20, 21]

Paclitaxel or docetaxel were extensively tested in conjunction with cisplatin or carboplatin.[5, 22-33] The E1395 phase III trial compared cisplatin/paclitaxel versus (vs.) cisplatin/5FU. While ORR and OS remained virtually identical in the two arms, high-grade toxicities where somewhat lower for the paclitaxel arm.[5] Therefore, paclitaxel can be a proper alternative for 5FU, particularly if mucositis is of concern.[3, 5] However, no overall survival improvement was noticed in paclitaxel-based regimens.

The first improvement in OS for decades was catalysed by the anti-EGFR monoclonal-antibody cetuximab.[7] The EXTREME-study explored the role of platin/5FU with or without cetuximab in 1st line R/M-SCCHN patients, and illustrated a significant OS improvement from 7.4 to 10.1 month once cetuximab is added to a conventional two-drug platin/5FU-regimen.[7] Therefore, platinum/5FU in conjunction with cetuximab needs to be considered as the gold

standard in 1st line treatment.

The impact of 5FU within the concept of combined therapies was challenged when cetuximab was added to docetaxel and cisplatin in 1st line treatment, as in the recent phase II TPEx trial. Here, the outcome was encouraging, achieving an ORR of 54% and an OS of 15.3 months.[34] Therefore, hope for further improvement of the chemotherapeutic backbone in combination with an EGFR inhibitor is justified.

In medically unfit patients, single-agent 1st line therapy seems to be appropriate.[2] Numerous single-agents have been shown to exert anti-cancer activity (e.g. methotrexate, cisplatin, fluoropyrimidines, bleomycin, pemetrexed, vinorelbine, irinotecan, and taxanes).[3, 9, 25, 35-41] However, the lack of randomised controlled trials renders single-agent platin, taxanes, or methotrexate as possible options for these fragile patients.[3, 39-41]

Second-line Therapy in R/M-SCCHN

Inevitably, patients will acquire disease progression over time, and in principle, these patients are candidates for subsequent chemotherapy. Patients under evaluation for 2nd line therapy are often frail due to declining performance status, co-morbidities, or high tumour burden. Despite a plethora of agents that were tested in 2nd line, heterogeneity of patient cohorts, variation in definition of platin-failure, as well as the lack of sufficient randomised controlled trials render the interpretation of the current clinical standard difficult.[3, 9, 25, 35-37, 42-45] Among the available options in 2nd line, methotrexate or taxanes are the most common choices in the clinic.[3, 22, 25, 35, 36]

However, the clinical outcome remains poor in subsequent lines of therapies. A retrospective analysis revealed that 2nd line therapy was given to 43 of 151 patients only, achieving an ORR of 0%, and an median OS of 107 days, while the median OS of the complete cohort was 103 days.[46] Other trials supported these findings, with a median OS in the range of 3 to 7 months.[3, 9, 35, 46-50] Novel agents with a favourable toxicity profile are needed for these patients.

Targeted Treatment in R/M-SCCHN

Although cetuximab has improved the outcome of R/M-SCCHN patients for the first time for nearly 30 years, poor prognosis as well as therapy-associated toxicity still has to be considered as a major challenge in this disease. Targeted agents, thought to combine high potency with sparse toxicity, are considered to be valuable tools in SCCHN treatment. On the one hand, the anti-EGFR antibody cetuximab is an example of a successful transfer from molecular understanding to clinical improvement. On the other hand, the limited success of other molecular agents, also targeting alterations observed in SCCHN underlines the complexity of the pathophysiology of R/M-SCCHN. Therefore, additional strategies, which focus on EGFR resistance or SCCHN driving mutations are objectives of current clinical development.

The EGFR-signaling-axis

90% of SCCHN express the epidermal growth factor receptor (EGFR) protein and mRNA, which correlates with a poor clinical outcome.[51-54] EGFR, a transmembraneous receptor with a tyrosine-kinase domain (TK), and its ligand TGF-alpha are key elements in the carcinogenesis of SCCHN. This understanding renders it a prime target for drug inhibition as well as a possible pathway to overcome platin resistance.[52, 55, 56] In fact, the clinical success of cetuximab underlines the importance of the EGFR signaling-axis in SCCHN, even though further research is warranted to define the optimal algorithm of sequential chemotherapy in SCCHN. Today, cetuximab remains the only EGFR inhibitor, which showed sufficient efficacy in R/M-SCCHN in combination with chemotherapy.

Several anti-EGFR antibodies were tested in R/M-SCCHN: panitumumab, zalutumumab, nimotuzumab, and matuzumab.[49, 57] Zalutumumab improved the PFS in a phase III trial compared to best supportive care (BSC) with or without methotrexate in platin-refractory R/M-SCCHN, but failed to improve the OS.[49] The SPECTRUM trial showed promising activity of panitumumab in combination with chemotherapy, mirroring efficacy data from the EXTREME trial in 1st line therapy.[7, 57] Nimotuzumab is currently extensively investigated in different trials, while the development of matuzumab was stopped.[3, 58, 59] Overall, a large body of evidence supports the use of EGFR inhibitors in SCCHN.[3, 7, 60-62] To what extent an antibody-dependent mediated cellular cytotoxicity (ADCC) effect might catalyse the anti-tumour efficacy is a matter of debate, and distinct from effects seen with EGFR tyrosine-kinase inhibitors (TKI)[60, 63, 64] The next generation of EGFR antibodies may exert improvement in ADCC, which could further benefit clinical efficacy.

Clinical trials of EGFR-TKIs in R/M-SCCHN with erlotinib, as well as gefitinib in different settings and regimens surprisingly showed only modest activity of either agent (RR 1.4-15%).[44, 48, 61, 65-67] Phase III data led to disappointing results when gefitinib was compared with methotrexate in R/M-SCCHN patients.[48] More recently, the EGFR-TKI gefitinib and erlotinib have been explored in different settings in SCCHN. After failure of chemotherapy, the addition of gefitinib to docetaxel did not improve the OS or time to progression when compared to docetaxel in a randomised phase III trial.[66] Furthermore, the addition of erlotinib to radiochemotherapy in locally advanced SCCHN also failed to improve outcome in a randomised phase II protocol, suggesting that this generation of EGFR-TKI may not be key player in the treatment algorithm of SCCHN.[68]

A compensatory escape mechanism might result from crosstalk of the EGFR with other members of the ErbB/HER family-receptors.[69, 70] Reasonably, agents like the pan-HER inhibitors afatinib (BIBW2992), or PF00299804 are under investigation. Afatinib, a specific inhibitor for EGFR, HER2, and HER4 showed promising activity in a phase II study. A head-to-head comparison to cetuximab afatinib showed a PFS of 16 weeks vs. 10 weeks, respectively.[71] Afatinib was explicitly active after cetuximab failure, indicating that EGFR crosstalk may represent a late

event of cetuximab resistance. The current phase III trial LUX-H&N1 addresses the role of afatinib as single-agent in comparison with methotrexate in R/M-SCCHN (NCT01345682). Similar data was shown for the pan-HER TKI PF00299804 in R/M-SCCHN. A phase II trial in chemo naïve SCCHN patients detected a PFS and OS of 2.8 and 7.6 months respectively, and paved the way for further clinical development in SCCHN.[72]

Heterodimerisation of EGFR has been shown to modulate the cellular signaling. HER3-EGFR heterodimers activate the PI3K-AKT survival-pathway, which is another putative signaling-axis for EGFR resistance.[73-76] Clinically, the membranous HER3 expression is associated with worse prognosis; therefore humanised dual-specific antibodies binding EGFR and HER3 are under clinical investigations (NCT01207323, NCT00734305).

VEGF-inhibition and Multi-target-tyrosine-kinase-inhibitors

Similar to other cancers, the expression of vascular endothelial growth factor (VEGF) was found to be associated with poor prognosis in SCCHN.[77] EGFR up-regulates VEGF, and has also been considered as a mechanism of EGFR resistance.[78, 79] Reasonably, a phase-I/II trial targeting both pathways was performed. Here, the anti-VEGF antibody bevacizumab in conjunction with erlotinib showed meaningful clinical activity, illustrated by 4 complete responses (CR) in 48 patients. However, bleeding events were concerning.[80] In addition, bevacizumab in combination with cetuximab or pemetrexed achieved encouraging OS of 7.5, and 11.3 months respectively in a single arm phase II studies in 1st line treatment of R/M-SCCHN.[81, 82] Bleeding events occurred in both studies, but are common complications by the tumour recurrence at that stage of the disease. Therefore, the result of a recruiting phase III trial comparing doublets of platin/docetaxel or platin/5FU each with or without bevacizumab might define the role of VEGF inhibition in SCCHN (NCT00588770).

Additional clinical evidence supports the use of inhibitors of angiogenesis in R/M-SCCHN. The VEGFR inhibitor sunitinib has been explored in early clinical trials in SCCHN, and was either found to be inactive or only modest active.[83-85] However, tumour shrinkage was detected in both studies, and the treatment was well tolerated in patients with performance status 2 - indicating a possible role of this class of agents in R/M-SCCHN. The largest study enrolled 38 patients. Here, bleeding complications and tumour fistula were considered as drug-related and have cautioned the development of VEGFR inhibitors in SCCHN.[84] In conclusion, targeting the VEGF signaling-axis already proved to be a promising therapeutic approach and needs further validating studies.

The PI3K/AKT/mTOR Axis and Other Signaling Pathways

The PI3K/AKT/mTOR axis has been found to be unleashed in a significant number of tumours, and may predict clinical outcome of mTOR inhibitors.[86-88]

In SCCHN cells, inhibition of AKT induces apoptosis.[89] Clinically, the PI3K/AKT/mTOR pathway is activated in the majority of SCCHN.[90, 91] Activation may occur through mutation of PI3KCA in 11-17% of SCCHN patients, which has been suggested to occur later in carcinogenesis of SCCHN.[92, 93] Loss of PTEN expression with AKT activation is another mechanism by which mTOR is activated in SCCHN and has been associated with worse clinical outcome in squamous cell carcinoma of the tongue.[90] Mutation of PTEN or loss of heterozygosity (LOH) of the tuberous sclerosis tumour suppressor gene (TSC) has also been reported to occur in 23-39% of SCCHN.[94, 95] Whether or not the PI3K/AKT/mTOR axis relates to the HPV status remains elusive. A small series suggests an association between HPV negative SCCHN and PI3K/AKT/mTOR activation, even though it is too small to define a correlation.[96, 97] In conclusion, these studies underline the relevance of the PI3K/AKT/mTOR signaling pathway in SCCHN, and renders this pathway as a promising clinical target.[91, 98]

Clinical evidence for the putative role of mTOR inhibitors in SCCHN has recently been observed. We recently conducted a phase II trial, which explored temsirolimus after failure of platin and cetuximab treatment.[99] Clinical efficacy and good tolerability was found with disease stabilisation in 56% of the patients as best response, as well as a median PFS and OS of 56 and 152 days, respectively.[99] Another clinical trial explored temsirolimus 15 mg weekly i.v. in combination with erlotinib 150 mg OD in platin-refractory R/M-SCCHN patients.[100] After 12 treated patients, the trial was discontinued due to excessive toxicity. The incidence of activating pathway mutations was low and associated with a PFS and OS of 1.9 and 4 months, respectively.

The role of mTOR inhibition is further supported by the phase I/II CAPRA trial, which tested the combination of weekly carboplatin, paclitaxel, and everolimus as induction therapy in unresectable locally advanced SCCHN.[101] An encouraging ORR of 81% was reported and included one CR (4.8%). Pre- and post-treatment biopsies showed a significant decrease of S6-phosphorylation, a surrogate marker of mTOR inhibition. Based on this data, additional studies are warranted in SCCHN, which may define the clinical role of mTOR inhibitors in SCCHN.

Other signaling factors may also contribute to acquired EGFR resistance, such as G- protein coupled receptors, platelet derived growth factor receptor (PDGFR), Insulin like growth factor receptor 1 (IGF1R), or heterodimerisation of IGF1R and EGFR.[102] Identification of the targets´ role in drug resistance may help to define additional novel approaches in R/M-SCCHN. However, identifying the right target is not an easy process. In a preclinical xenograft SCCHN model, an additive antitumour effect was detected in tumours overexpressing IGF1R when dual inhibition of the IGF1R and EGFR was employed.[102] However, the IGF1R inhibitor figitumumab failed to achieve clinical activity in a recent phase II trial, rendering clinical applicability of IGF1R inhibition questionable.[103] A similar process was reported for SRC kinases. While preclinical studies suggested a role of SRC kinases in SCCHN, a phase II trial with dasatinib did not identify promising activity.[104]

Summary and Future Challenges

Platin-based chemotherapy regimens are the backbone of palliative chemotherapy for R/M-SCCHN patients. Cetuximab combined with platin-based chemotherapy has improved OS in R/M-SCCHN and is the gold standard for palliation. Certainly, many SCCHN patients may not qualify for this combination therapy and, hence, may require a more individual approach to select the most appropriate chemotherapy regimen, which may consist of a doublet or single-agent.

In 2nd line therapy, single-agent taxanes or methotrexate represent a reasonable approach. However, clinical activity remains poor in this scenario and novel agents are desperately needed to improve outcome of these patients.

With the increasing knowledge of molecular carcinogenesis and treatment resistance, novel therapies have emerged. In addition to novel EGFR inhibitors, agents which interfere with angiogenesis or mTOR are the most advanced in the field. Certainly, activating mutations of the PI3K/AKT/mTOR pathway are frequently found in SCCHN, but little is known about the predictive nature of these genetic alterations. Molecular analyses from current clinical trials with mTOR inhibitors are awaited. Expectations are high to define a molecular group of SCCHN, which may trigger the next generation of molecular defined clinical trials instead of a one-size fits all approach. The interaction of these molecular markers with HPV status - a key prognostic player in SCCHN - remains largely undefined. Untangling this tight network of tumour signaling and defining driving mutations is a premise for additional advance in the field of SCCHN.

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New Developments in Medical Innovation

Tom Gentile
President and CEO, GE Healthcare Systems

Introduction

In the summer of 2009, Cliona Draper went for her 10th annual mammogram. She had just turned 50, was busy raising her nine-year-old daughter, and was looking forward to adopting a second child from China.

An unusual "ripple" or "dimple" in her breast tissue appeared on the digital screen. Draper immediately underwent an ultrasound. The same day, she spoke to the radiologist and was examined by a surgeon. A biopsy was scheduled, and within 20 days, Draper learned that she had lobular invasive carcinoma.

Three weeks later, Draper was in surgery, and opted for a mastectomy. Fortunately, the cancer had not spread. Six months after surgery, Draper and her husband traveled to China and returned home with their new daughter in tow.

The "ripple" found by the screening is something Draper says she never would have felt on her own; her type of cancer is not easy to detect and can hide in dense breast tissue. But advanced technology detected it at an early stage, enabling Draper and her doctors to take quick action. The result is more years of life for Draper, who says she sometimes experiences a "profound sense of joy" simply at being alive.

Proven Impact

Outcomes like Draper's inspire researchers, clinicians and investors around the world and they inspire us at GE Healthcare to move innovation forward. Improved outcomes are within the reach of the global medical community because of its commitment and passion to scientific discovery. GE Healthcare's medical imaging technology is born from a commitment to design better-performing products, to increase access for more patients around the world and to optimise care quality in a way which is much more personalised for each patient in order to improve their outcome. GE Healthcare aims to do this in the most economical way possible.

Our strategy is to innovate in the right way, and for the right reasons. With GE Healthcare Systems spending $800 million annually on research and development in order to introduce between 50 to 60 new products every year, our portfolio is constantly evolving to meet clinical needs. Innovation is absolutely critical to the future of our business.

Data show that an innovation strategy can make a measurable impact in real healthcare settings. Continued innovation in imaging technology demonstrates a positive impact in quality, cost and access. Increased use of CT imaging has saved tens of thousands of patients from undergoing invasive and often risky exploratory surgical procedures in the chest and abdomen, while also saving billions of dollars in hospital charges. GE's study with St. Luke's Neuroscience Institute in Kansas City, Missouri, found that ready access to state-of-the-art CT imaging, in order to more accurately diagnose stroke patients (as part of a comprehensive coordinated care process) enabled six times as many patients to receive a key treatment sooner after the onset of symptoms. Patient stroke severity and negative outcomes were significantly reduced as compared to national averages. There are a wealth of similar examples that demonstrate the value of innovation in imaging technology and its role in improving the patient experience.

A System for Innovation

Medical imaging technologies carry the potential to reduce the burden of unnecessary and invasive procedures, and to improve patient outcomes by offering early detection and better informing treatment

Tom Gentile was appointed President and CEO of GE Healthcare's Healthcare Systems division in May 2011. He has worked for GE for 13 years and most recently spent three years as President and CEO of GE Aviation's Services division, transforming the services business into a global $7 billion platform. Before Aviation, he held a series of leadership roles within GE Capital's businesses in the US, France and Australia, and before joining the company he held leadership and strategy roles with McKinsey & Company, American broadcaster CBS, and General Motors. Tom also serves as the Chairman of the Board for Care Innovations, a home health JV between GE and Intel, and Chairman of the Board of InSightec, a global leader of MR guided focused ultrasound based in Israel. Additionally, Tom leads GE Healthcare's Volunteers Network.

Figure 1. The Continuum of Care.

options. Developing a way to operationalise this innovation is essential. Focusing on solutions to clinical issues - rather than simply innovating for innovation's sake - is facilitated through a specific product development process that quantifies the potential impact of new products in the critical areas of quality, cost and access. Once again, data plays a pivotal role. Rigorous evaluation starts with a proven and well-defined problem related to quality, affordability and/or access, and the evidence of a product's potential as a solution. At GE Healthcare, we look at the proposed value to each and every stakeholder involved, and gather evidence to support these claims. It is a way of asking: Are we about to significantly improve upon patient care, which is of course the ultimate goal, and is that improvement in balance with costs, distribution, and predicted application? Do customers need it, want it and will they use it to the extent that evidence of positive impact can be quantified? We also analyse the potential barriers to this value creation.

An important aspect of our process is validation through rigorous objective analysis that helps us step outside of internal bias and achieve better clarity about an innovation's true potential. Finally, as prudent investors, we carefully consider the market and technological/performance risks of any new innovation that we may add to our portfolio.

Continuous Collaboration

While we have devised an effective internal process to focus innovation, we know we don't have all of the ideas or answers. We collaborate constantly - with industry leaders, top research institutions, and even wide-reaching organisations with a major stake in what we have to offer. Our latest partnership with the National Football League is a $60 million research and innovation initiative aiming to develop faster and more accurate concussion-detecting imaging technology not only for athletes, but also military personnel and the general population. Professionals from Dartmouth to Ohio State to Seattle Children's Hospital are our research partners. This exciting initiative also includes an open innovation challenge to generate ideas for better protective equipment to prevent head trauma.

We continually seek partnership opportunities with such institutions, tapping their rich academic knowledge base to advance innovation in our key markets. A recent research agreement with the University of Wisconsin at Madison, for example, will drive innovation across all of our diagnostic imaging modalities.

If warranted, GE and our partners create entirely new organisations to commercialise innovation, dedicated to finding the best solutions around a particular healthcare issue. In a joint venture with Intel Corp., GE has created Intel-GE Care Innovations, an organisation that creates patient-driven technology solutions for home healthcare that support independent living in a more affordable way. As chairman of the board of this organisation, I see firsthand how our combined expertise and history of innovation and problem-solving is touching people's lives through proactive solutions that keep patients connected with providers from the comfort of their own homes.

Across all initiatives to catalyse, operationalise and commercialise innovation at GE Healthcare, our goal remains constant: find ways to deliver better care to more people around the globe at a lower cost. As a global leader with the reach, resources and expertise to truly shape the future of this field, we are realising exciting, large-scale and game-changing results in all of our specialty areas. While that kind of impact is a powerful motivator, we also find inspiration in individual stories of health sustained, or of health restored -- stories that celebrate the "profound joy" of being alive and well.

Driving Medical Innovation through the Care Continuum

Data, both scientific and economic, is at the front end of any solid innovation strategy. We leverage it to assess industry trends, identify the most significant customer and patient needs, understand the limitations of today's technology and explore the factors that lead to unwanted variance in care quality. We evaluate it to make smart decisions about where to innovate next, or how to leverage our broad resources and capabilities to advance innovation for a more powerful impact (Figure 1).

We have done just that with our late 2012 acquisition of U-Systems, with its breakthrough ultrasound technology for breast cancer screening. This technology has been proven to increase cancer detection by 35.7 percent in women with dense breasts and no prior breast interventions over mammography screening alone. While mammography is the standard of care for breast cancer screening in the U.S. and many other markets, we need to understand its limitations as an x-ray modality that can't always see through dense breast tissue. Modalities such as ultrasound can help us find cancers that mammography might miss,

while offering additional advantages (non-ionising radiation technology, clinical capability, affordability) that make it a modality to watch for the foreseeable future.

Public policy that influences market demand can play a key role in smart innovation. Current legislative momentum underscores the clinical value of what U-Systems brings to the field, as five U.S. states now require healthcare providers to let women know if they have dense breast tissue, and more than 40 percent of women in the U.S. do. Beyond the U.S., GE's global reach can help accelerate the technology's introduction on a much broader scale, to help increase early detection in more women around the world.

The U-Systems acquisition is also critical as part of GE's investment in providing integrated solutions that help each patient through his or her individual journey, which depends on their unique physiology, risk factors and disease type. For many disease states, including breast cancer, liver cancer, cardiovascular disease and Alzheimer's disease, GE offers the broadest product portfolio in our industry, with hardware, software, wetware and service solutions designed to address patient needs across the entire continuum of care, from diagnosis through treatment and monitoring.

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Varian Introduces RapidPlan™ to Increase Quality and Efficiency of Radiotherapy Treatment Planning

Neil Madle
Director, Corporate Communications/Investor Relations, Europe

Varian Medical Systems is introducing a new knowledge-based software tool designed to expedite the creation of complex intensity-modulated radiotherapy (IMRT) treatment plans.

RapidPlan™ software provides clinicians with standard of care models to use as a baseline for developing new IMRT treatment plans for their patients. IMRT is a type of radiotherapy that focuses precisely on the tumour while minimising exposure of surrounding healthy tissues.

"RapidPlan™ improves the quality and efficiency of treatment planning, much like our RapidArc technology enhanced treatment delivery," says Chris Toth, Vice President of Marketing for Varian's Oncology Systems business. "The RapidPlan™ software changes treatment planning by providing users with access to a knowledge base with standard-of-care models developed by leading practitioners. The goal is to help increase treatment plan quality and reduce variability without adding time to the planning process."

RapidPlan™ is a comprehensive tool within Varian's Eclipse treatment planning system that may be used to plan virtually every type of external beam radiotherapy, including intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), RapidArc radiotherapy, stereotactic body radiotherapy (SBRT), and stereotactic ablative radiotherapy (SABR). It is seamlessly integrated with Varian's Eclipse treatment planning software.

"RapidPlan™ is designed to be a 'learning system,'" says Corey Zankowski, Vice President of Product management. "Clinicians can select their 'best' treatment plans to include in a training set that can be used to create new and improved practice models in the future. In doing so, sites can customise RapidPlan™ to reflect their own practices. The models can also be shared among colleagues within a care network to create a practice standard. Eventually, as local knowledge bases expand and improve, organisations will be able to share best practices between institutions."

"RapidPlan™ helps automate an important part of the treatment planning process, in much the same way as our Smart Segmentation knowledge-based tool, introduced in 2011, which automates contouring of organs within diagnostic images," says Toth. "Both tools are designed to allow clinicians to access an extensive body of clinical experience while expediting cumbersome, time-consuming processes."

"We're excited to introduce RapidPlan™, and look forward to developing many more tools designed to improve the quality and cost effectiveness of care," says Kolleen Kennedy, President of Varian's Oncology Systems business. "We have launched an initiative that is focused on creating knowledge-driven solutions for the entire oncology continuum from diagnosis through survivorship. A new team within our organisation is working to leverage advanced informatics to unlock the power of collective knowledge."

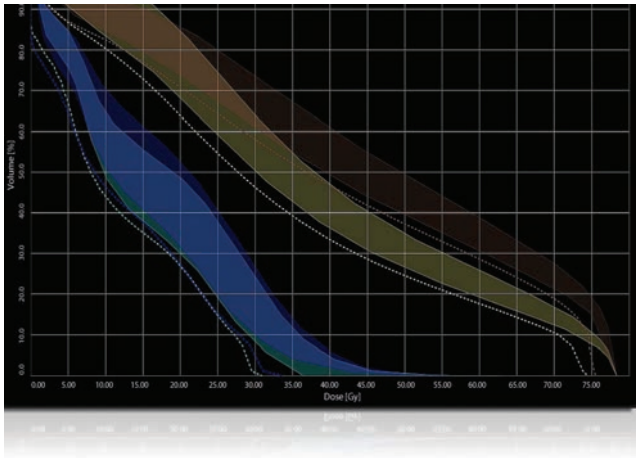

Figure 1. Using a knowledge base prior to treatment plans, RapidPlan may improve efficiency. The DVH chart above displays an estimated dose (blue and brown shading) for a prostate case.

Primitive Synovial Sarcoma of the Kidney

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Introduction

The term synovial sarcoma (SS) describes tumours arising near tendon sheaths and joint capsules. Despite its name, SS does not appear to arise from synovial membrane, but rather from as yet unknown multipotent stem cells that are capable of differentiating into mesenchymal and/or epithelial structures and lack the synovial characteristics.[1-3]

In general, the SS accounts for 7 to 8% of all malignant soft-tissue sarcomas, representing the most common mesenchymal tumour in children after the rhabdomyosarcoma.[4] SS usually occurs near to the joints of the arm, neck or leg, but considering its origin, other sites of tumour were described such as heart, lung, salivary glands, thyroid and finally in the kidney.

Primary synovial sarcoma of the kidney is a very rare entity in renal neoplasm: it was first described in 2000 by Argani *et al*., who distinguish it from a subset of embryonal sarcoma of the kidney.[5] Since its description, few cases have been published in medical literature as case reports or case series; this review aims to describe the main characteristic of this renal sarcoma from the molecular to the clinical aspects.

Genetic and Molecular Aspects

Renal SS is a well-defined disease characterised by a specific translocation t(X:18) which replaces the 8 C-terminal amino acids of SYT gene on chromosome 18 by the 78 C-terminal amino acids of SSX1, 2 or 4 on chromosome X.[6]

The products of SSX gene may function as transcriptional repressors. They are also capable of eliciting spontaneously humoral and cellular immune responses in cancer patients. In contrast to SSX, which is thought to act as a transcriptional regulator because of its sequence homology to other transcription repressors, SYT does not share a homologous region or conserved domain with other human proteins.[7] The encoded hybrid proteins are probably responsible for transforming activity.

Embryological studies reported that SYT participated in the regulation of actin fiber and cell motility and that Syt-/- was incompatible with embryos survival.[8] Micro-array analysis confirms that SYT-SSX1 mainly affects the focal adhesion pathway. In fact, when the gene is silenced, it enhances adhesion to the extracellular matrix through the induction of expression of myosin light-chain kinase and inhibits anchorage-independent growth *in vitro*.[9] Moreover, transformation activity of SYT–SSX fusion protein may be sustained by other factors such as IGF2, EPHRINS, and BCL2.[10]

Recently, it has been reported as the expression of the SS18/SSX fusion proteins in T-REx-293 cells was associated with increased p-(Tyr416)-SRC levels, linked with an induction of the insulin-like growth factor pathway. Treatment of synovial sarcoma cells with dasatinib led to apoptosis and inhibition of cellular proliferation, associated with reduced phosphorylation of FAK (PTK2), STAT3, IGF-IR, and AKT; moreover, the concurrent exposure of cells to dasatinib and chemotherapeutic agents resulted in additive effects.[11] These effects have also confirmed *in vivo* using nude mice with xenograft synovial sarcoma cells or treated with dasatinib or human SS cells treated with another Src inhibitor (SU6656).[11, 12]

Pathological Features

Argani *et al*. described this tumour as tan and rubbery. The presence of haemorrhage and necrosis was frequent and imparted a variegated appearance. The majority of tumours distorted the kidney so greatly that an epicenter could not be determined. Most tumours exhibited grossly identifiable smooth-walled cysts that were distinct from the pseudocysts resulting from degenerative changes.[5]

A major part of tumours has a local extension at diagnosis of 10 cm and even if the overall survival was found to be longer in patients with tumour extension fewer the 10 cm (48.0 vs. 24.0 months) the difference was not significant (p=0.23).[13] Only 8% of cases of renal SSs were found to be metastatic at diagnosis and one-third of patients developed metastasis after nephrectomy. The sites of metastasis suggest a haematological dissemination with lung (42%) and abdominal lymph-nodes and local relapse (each 29%) as the main sites followed by liver (24%) and bone (6%).[13]

Morphological description of the microscopic features recognises three different subgroups of SSs: (i) biphasic SS (BSS) with both epithelial cells

Patients Histology	Immunohistochemical expression (%) Immunohistochemical expression (%)					
	Vimentine	EMA	Bcl2	CD99	SMA	CK
MSS	100	67	100	43	47	62
BSS	100	100	100	100	0	100
PDSS	50	66	100	100	0	0

Table 1. Expression of some immunohistochemical markers by histological sub-type. MSS = monophasic synovial sarcoma; BSS = biphasic synovial sarcoma; PDSS = poorly differentiated synovial sarcoma.

and spindle cells of mesenchymal origin, (ii) monophasic SS (MSS) consisting only of the spindle cell component, and (iii) poorly differentiated SS (PDSS).[5]

The incidence of each histologic subtype in renal SS was found to be MSS in 76% of cases, BSS in 16% of cases and PDSS in 8% of cases. Interestingly, an inverse correlation was found between histologic features and tumour extension at diagnosis, with MSS characterised by greater tumours and PDSS by smaller tumours at diagnosis.[13]

Several immune-histochimical markers have been studied in renal-SS, as reported in Table 1. These may facilitate diagnosis among different subtypes: in fact, cytokeratins were highly expressed in BSS (100%), moderately in MSS (62% of cases) but not in PDSS ($p = 0.015$). The same was for the vimentin: highly expressed in MSS and BSS (both 100%) and moderately in PDSS (50%; $\chi 2$ test: $p=0.003$).[13]

Generally, the SYT-SSX1 and SYT-SSX2 have been reported to affect the microscopic feature of tumour, with the first closely related to BSS and the latter to MSS ($p = 0.003$), and characterised by a better prognosis.[14]

In renal-SS a SYT-SSX gene fusion was found in all cases analysed. The SYT-SSX2 translocation was the most frequent: it was found in 47% of cases compared to 26% of SYT-SSX1, and translocation t(X:22) has been reported in 27% of cases.[13] A possible relationship between genetic characteristic and pathological and clinical features was also hypothesised. In fact, comparative analyses revealed different expression of cytokeratin in SYT-SSX1 and SYT-SSX2 tumours (100% vs. 44%; $\chi 2$ test: $p = 0.038$) and a longer survival in metastatic patients with SYT-SSX2 tumours compared to SYT-SSX1(8.0 vs. 3.5 months) even if the difference was not significant ($p = 0.5$).[13]

Radiological Features

A preoperative radiological diagnosis of SS can be made on CT scan as a result of analysing the tumour's growth pattern: the tumour appears as a large, well-defined, soft-tissue mass that may extend into the renal pelvis or perinephric region. In addition, primary renal SS shows heterogeneous enhancement, haemorrhagic areas, calcifications, air-fluid levels and septations. On MRI, this tumour is T1 isointense to paraspinal muscles and shows heterogeneous T2 hyperintensity. Merged areas of low, intermediate and high signal intensity impart the so-called "triple sign", representing areas of haemorrhage, calcification, and air-fluid level.[15]

Clinical Features

Recently, we reviewed the medical literature for all cases reports published from 2000 to 2011, and we are able to describe the clinical and pathological characteristics of this disease.[13] Our systematic search found 64 cases in which no difference on incidence was found based on sex and confirms the younger age at diagnosis with a median value of 36.5 years. Furthermore, a number of patients had clinical symptoms at diagnosis such as pain (67%), haematuria (38%) and renal mass (25%).

The median survival was reported to be 4 years, but the clinical stage of tumours at diagnosis is the main prognostic factor, with metastatic patients characterised by an increased risk greater than 300% (HR: 343.9, 95%CI, 2.8 – 42,000; $p = 0.017$). Patients without metastases at diagnosis have a median disease-free survival of 33 months, but if they develop metastases, the prognosis was very poor, with a median overall survival of 6 months.[13]

Medical Treatment

Among the soft-tissue sarcomas, synovial sarcoma is reported to be one of the more responsive to systemic chemotherapy.[16, 17] The sub-analysis of the SS patients treated within the phase III study by the Eastern Cooperative Oncology Group (ECOG) supports this idea, reporting a significant difference in terms of objective regression rate in patients treated with ifosfamide and doxorubicin as compared with doxorubicin alone (88% vs. 20%; $p=0.02$).[18] Based on this evidence the ECOG designs a two-stage phase II trial to test the activity of the chemotherapy combination in this group. Patients were treated with ifosfamide 7.5 gm/m^2 plus doxorubicin 60 mg/m^2 given intravenously over two consecutive days every 3 weeks with G-CSF support. Even if chemotherapy was able to give a median survival of 11 months and 42% of partial response the study was prematurely closed due to the low accrual and to the toxicity with a high grade of neutropenia reported in all patients and a treatment-related death.[19]

The rarity of renal SS did not consent to draw a more specific trial even if the results from our analysis seem to confirm the activity of chemotherapy, reporting an increase in overall survival for patients treated with chemotherapy compared to who did not (15 vs. 6 months).[13] Unfortunately, the difference was not significant and several factors such as the retrospective nature of the analysis, the patient's performance status and the extension of disease may influence any definitive conclusion.

Another important issue in treatment of sarcomas is the use of chemotherapy in the adjuvant setting with the intent to delay tumour relapse and improve overall survival. About SS, a retrospective analysis of 76 cases of stage IIB/III synovial sarcoma has been published. In this study, all patients were treated by surgical resection and 51 received chemotherapy based on mesna, adriamycin, ifosfamide and deticene (MAID) or adriamycin, ifosfamide and mesna (AIM). The study reported a longer 5-years disease specific survival (73 vs. 31%; p=0.001) and a metastasis-free survival (P==0.008) in patient treated with adjuvant chemotherapy compared who did not; this might suggest a possible role of adjuvant chemotherapy and confirms the higher sensitivity of this neoplasia to chemotherapy.[21]

Conclusions

Finally, renal SS is a rare disease with a well-defined genetic background, and is clinically characterised by a dismal prognosis in metastatic patients and by a high recurrence-rate in non-metastatic patients. Considering the higher response rate, chemotherapy has a central role for the treatment of advanced disease and might be useful to delay tumour relapse in non-metastatic patients. The better knowledge of driver molecular pathways may improve treatment strategies to a targeted therapy in a next future.

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8th World Research Congress of the European Association for Palliative Care

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Upcoming Congresses and Meetings

11th APOS Annual Conference

13 – 15 February 2014

Tampa, USA

The theme of the 11th APOS (American Psycosocial Onology Society) Annual Conference is 'Implementing Quality Care Standards for Psychosocial Oncology and Supportive Care, and the impressive progrmme will feature a wealth of sessions, including preconference workshops on subjects such as Acute Cancer-Related Cognitive Therapy and Meaning-Centered Psychotherapy for Cancer Patients. The Conference will also feature Philip A Pizzo, Former Dean and Professor of Pediatrics and of Microbiology and Immunology, Stanford University School of Medicine and Carolyn D. Runowicz, Associate Dean for Academic Affairs Professor of Obstetrics and Gynecology, Florida International University, Herbert Wetheim College of Medicine as keynote speakers.

ECR 2014

06 – 10 March 2014

Vienna, Austria

The ECR is the Annual Meeting of the European Society of Radiology, and is known as one of the most innovative meetings within the scientific community, which is both trend-setting and dynamic. With over 20,000 participants attending from over 100 countries, the ECR Annual Meeting is a real global hub of scientific learning and discussion. Over the 5 day event, 343 session will take place, including state of the art symposia, professional challenges sessions, referesher courses, workshops and special focus sessions amongst others. This year's meeting looks set to be the most impressive yet, and is not to be missed.

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.

12th ERS Lung Science Conference

21 - 23 March 2014

Estoril, Portugal

The theme for the 12th ERS Lung Science Conference is 'Lung inflammation and immunity', and the scientific programme will provide up-to-date sessions on topics including new trends in immunology and asthma, immune responses in chronic lung diseases and the genesis of allergy and asthma. The Conference will also feature poster sessions and oral presentations, as well as debates and a Young Invesigator session, where the Willian MacNee award will be given.

Genes & Cancer Annual Meeting 2013

24 - 26 March 2014

Cambridge, 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.

4th European Lung Cancer Conference (ELCC)

26 – 29 March 2014

Geneva, Switzerland

The ELCC has been jointly organised by the European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC), where attendees will benefit from updates from thoracic oncology specialists and clinical practise in the field of lung cancer. Key topics will include molecular testing in advanced non-small cell lung cancer, mesothelioma and oncogenic-driven diseases. Meet-the-expert sessions, interactive workshops and in-depth lectures make this the thoracic conference of 2014. The meeting also encourages interaction and debate between participants and speakers.

ESTRO 33

04 - 08 April 2014

Vienna, Austria

ESTRO 33 is the leading European event in radiation oncology, and will focus pn new and emerging developments in the field. Through a range of different session types, the scientific programme will cover a number of different scientific topics, including new approaches to adaptive radiotherapy, the physical and biological optimization of radiation therapy

and new developments in radiation oncology. The event aims to move The European Society for Radiotherapy and Oncology's vision of access through a multidisciplinary approach forward, and prepare attendees for the challenges of the future.

IMPAKT 2014 Breast Cancer Conference

08 – 10 May 2014

Brussels, Belgium

The IMPAKT 2014 breast cancer conference will bring together a wide range of healthcare professionals with an aim of facilitating the advancement of a personalized approach to breast cancer management. The conference will explore a number of different themes, including metastatic dormancy, liquid biopsy and mathematical modeling. These themes will be expanded upon by key opinion leaders and top names within the field of breast cancer, and will be a conference not to be missed.

8th World Research Congress of the European Association for Palliative Care (EAPC)

05 – 07 June 2014

Ileida, Spain

The EAPC was established in 1988 with the aim to promote palliative care in Europe, and the organisation now represents thousands of members all over Europe, both as individuals and as a collective. The EAPC world research congresses began back in 2000 and have steadily grown larger, both in terms of participants and submitted abstracts, and it is now the most important meeting place for palliative care researchers. Through a variety of sessions, including symposia, Meet the Experts sessions, oral and poster presentations and plenary lectures, subjects such as palliative care in older people, trial design and clinical research challenges will be covered.

ESMO 16th World Congress on Gastrointestinal Cancer

25 – 28 June 2014

Barcelona, Spain

The ESMO 16th World Congress on Gastrointestinal Cancer will provide important clinical updates, new findings, new techniques and updates on the latest research within the field of gastrointestinal cancer. The congress will feature a number of different sessions on topics such as gastric cancer, rare tumours, multimodality therapy and imaging. Highlights will include meet the expert sessions, satelight symposia and discussion sessions. The congress will also have a focus upon young medical oncologists, and will feature a range of sessions which will identify their interests and clinical needs.

23rd Biennial Congress of the European Association for Cancer Research (EACR)

05 – 08 July 2014

Munich, Germany

The Biennial EACR Congress has a reputation for a high quality programme and inspirational speakers, and the 2014 event will be no different in this respect. The congress has grown rapidly in recent years, and it is expected that almost 2,000 scientists working in all fields of cancer research will come together to discuss the latest developments in this area. The theme of the 23rd congress is 'From Basic Research to Personalised Cancer Treatment', and the programme will offer exceptional plenary lectures and symposia, which will feature plenty of time for debate and discussion, as well as scientific symposia, workshops and oral and poster presentations.

ESMO 2014 Congress

26 – 30 September 2014

Madrid, Spain

The theme for ESMO 2014 is 'Precision Medicine in Cancer Care' and, whether you are a medical or surgical oncologist, radiotherapist, immunologist or pathologist, the congress will offer you the tools to improve patient outcomes. This is the ultimate goal of ESMO 2014. Delegates will experience a detailed exploration of the practical, political and financial issues that stand between the ideals and reality of implementing optimal care for every patient suffering with cancer.

The SIOG 2014 Annual Meeting

23 – 25 October 2014

Lisbon, Portugal

The SIOG Annual Meeting is the leading meeting for experts in the field of geriatric oncology. This event provides a unique platform for researchers, clinical practitioners in oncology, geriatricians, radiologists, psychologists, nutritionists, nurses, senior cancer survivors advocates to learn, interact and share results and best practice. It also allows for important improvements in the understanding and the practice of this multidisciplinary approach when treating senior adults with cancer. The conference features speakers from among the world's leading experts in the fields, and provides the opportunity for participants to learn from experienced peers and network with leaders from across the globe.

34th ESSO Congress in Partnership with BASO 2014

29 – 31 October 2014

Liverpool, UK

ESSO 34 – BASO 2014 is a unique event and held in joint partnership to mark the historical relationship between ESSO and BASO. The theme of the 2014 is 'quality outcome, global perspective' and the new format will include four tracks: breast, colorectal, upper GI-HPB and miscellaneous (head & neck, sarcoma/ melanoma, pelvic cancer). The high quality programme includes a panel of speakers who will be presenting the very latest developments and treands within the field. The 2014 event will see the return of the 'meet the Expert' and breakfast sessions, as well as the plenary debate sessions. A number of joint Society Sessions, which involve experts in different disciplines will also be included. The congress will also provide participants with additional educational opportunities, and an excellent platform for networking with colleagues from all over the globe.

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