TREATMENT STRATEGIES
ONCOLOGY

Volume 5 Issue 1

- Intratumoural Heterogeneity
- Metastatic Soft Tissue Sarcomas
- Pineal Parenchymal Tumours
- Renal Cell Cancer
- Treatment of Meningiomas
- Tumour Proliferation

Includes a Review of the 50th ASCO Congress 2014 - Chicago

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TREATMENT STRATEGIES ONCOLOGY

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Welcome... to the latest edition of *Treatment Strategies - Oncology*.

This edition will address the key topical areas in the oncology field and features an exciting collection of papers from esteemed oncologists.

Treatment Strategies - Oncology includes papers on topics such as

- Intratumoural Heterogeneity
- Metastatic Soft Tissue Sarcomas
- Pineal Parenchymal Tumours
- Renal Cell Cancer
- Treatment of Meningiomas
- Tumour Proliferation

We hope that this publication will provide you with a comprehensive review of the latest updates and technological advances in medicine.

Following on from a successful visit to Chicago, we have also included a review of the latest news and developments from this year's ASCO meeting.

So far, 2014 is proving to be a fantastic year for The Cambridge Research Centre, with some exciting changes including Treatment Strategies TV, where you can find footage from the most important scientific conferences, meetings and congresses, 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. Have you liked our new Facebook page? Here you can find all of the latest news about new projects and upcoming releases, and the Treatment Strategies' team are also all active on Twitter and LinkedIn.
See you in Chicago for ASCO 2015.

Nigel Lloyd, Managing Director

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

The International Liver Cancer Association Announces its 9th Annual Conference

ILCA 2015

4 – 6 September 2015
Paris, France

ILCA
International Liver Cancer Association

Conference Highlights:

State-of-the-Art Lectures

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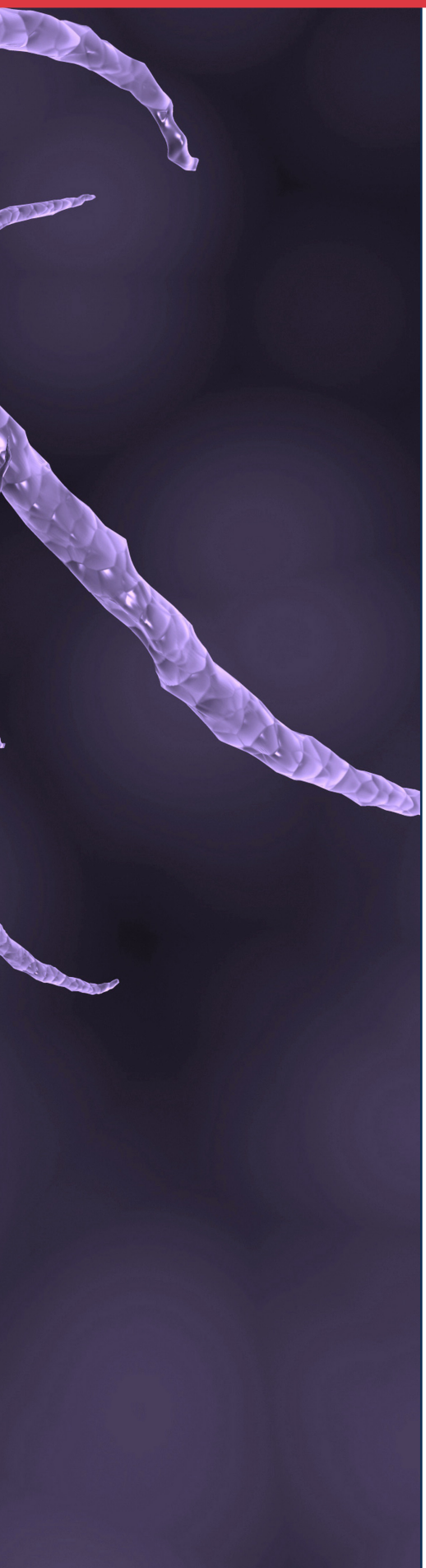
www.ilca2015.org



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Synergy among Breast Units

A project of

European School of Oncology
Learning to care

Need to quickly contact a breast expert colleague?

Is your Breast Unit organised according to state-of-the-art international standards?

Don't miss the opportunity
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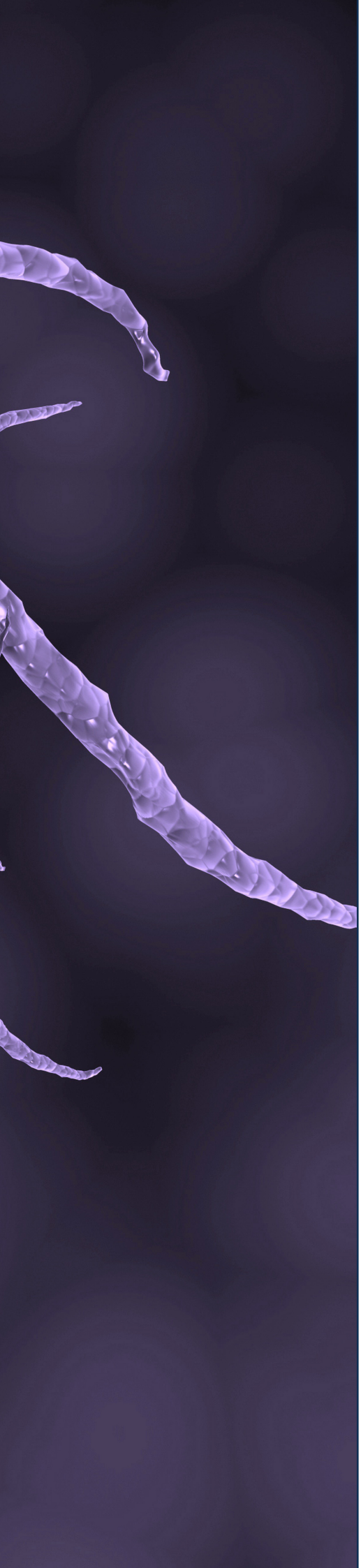
Breast Centres Network is the first international network of clinical centres exclusively dedicated to the diagnosis and treatment of breast cancer. It is a project of ESO (European School of Oncology) with the aim to promote and improve breast cancer care in Europe and throughout the world.

Our network includes Breast Units (Multidisciplinary Breast Centres) that fulfill minimum requirements (see Eligibility Gate online) to be considered referral centres. Organisation of Multidisciplinary Breast Units is recommended by EUSOMA, Europa Donna (European Breast Cancer Coalition) and the European Parliament.

We offer an online Breast Unit Directory that provides detailed information at a glance about our members in an attempt to broadcast the state-of-the-art international standards for multidisciplinary breast cancer care.



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Pancreatic Cancer UK run a confidential Support Line for anyone affected by pancreatic cancer. Our pancreatic cancer specialist nurses can provide tailored specialist information about pancreatic cancer, treatment options and managing symptoms and side effects. We can also listen to your concerns and provide support.

FREEPHONE SUPPORT LINE: 0808 801 0707 SUPPORT@PANCREATICCANCER.ORG.UK

The service is available Monday to Friday from 10am-4pm (the service is closed on Bank Holidays). Once you have contacted us one of the nurses will be in touch within 24 hours (or 48 hours if your enquiry is received over the weekend when the office is closed).

www.pancreaticcancer.org.uk/support

THE PANCREATIC CANCER RESEARCH CHALLENGE

One of our contributions to tackling the issue of underfunding in pancreatic cancer research is in the form of the Research Innovation Fund (RIF).

The Fund aims to spur creative and cutting edge ideas and approaches in pancreatic cancer research, including those successful in other areas of cancer research that have justifiable promise for pancreatic cancer. We are committed to investing in research and making it a priority and as such we are very proud to have awarded nearly £1million to researchers around the UK so far as part of this fund.

Our RIF grants are split into three areas of research: Early diagnosis projects, personalised treatment and improving the chances of treatment success.

CONTACT US 020 35 35 7090 RESEARCH@PANCREATICCANCER.ORG.UK

Find out more about specific projects in each area by visiting
www.pancreaticcancer.org.uk/rif

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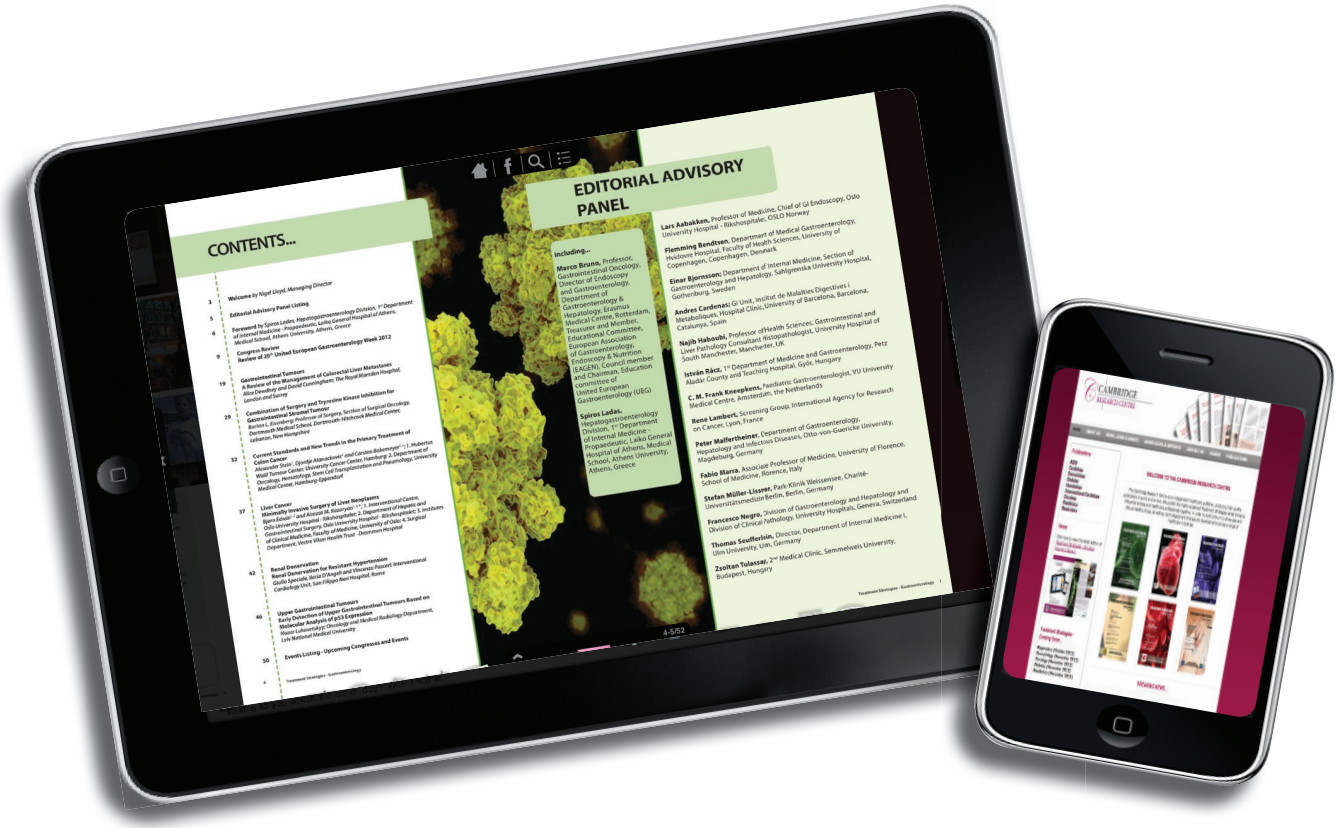

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50th ASCO Annual Meeting

30th May - 3rd June 2014 - Chicago

50th American Society of Clinical Oncology Annual Meeting

The Congress

News from ASCO 2014

The American Society of Clinical Oncology (ASCO) celebrated the 50th anniversary of its founding at its Annual Meeting this year. The Annual Meeting began on 30th May and ran through to 3rd June 2014 in the McCormick Place convention facility, Chicago.

Oncology professionals from around the world gathered to learn about, debate, and discuss exciting breakthroughs and advances in oncology. Attendees of the 2014 Annual Meeting heard clinical and scientific results that promise to broaden and accelerate global progress against cancer.

ASCO was founded in 1964 and is the world's leading professional organisation representing physicians who care for people with cancer. With nearly 35,000 members, ASCO is committed to improving cancer care through scientific meetings, educational programmes and peer-reviewed journals. ASCO is supported by its affiliate organisation, the Conquer Cancer Foundation, which funds ground-breaking research and programmes that make a tangible difference in the lives of people with cancer.

The Annual Meeting provides the opportunity for clinicians to get together, see old friends, and discuss varied interpretations of new data and most importantly identify better practices in improving patient care through the dissemination of better information.

Every year ASCO's Annual Meeting brings together in one place the largest number

of leading clinicians, clinical investigators and translational scientists along with a growing number of cancer care providers, all of whom share a drive to improve the lives of patients with cancer. Moreover, every year from this collection of dedicated, focused, and truly remarkable people emerges new insight, new ideas, new concepts and new opportunities.

The speed and efficiency of face-to-face communications and the collective wisdom found in a room of experts who are hearing and discussing new data for the first time is what makes this meeting significant in cancer advancement.

In addition, electronic tools were used to maximise the message from ASCO 2014, and there were Twitter feeds and disease-specific hashtags in addition to #ASCO14.

The 2013-2014 ASCO President Clifford A. Hudis, MD, FACP, of Memorial Sloan Kettering Cancer Centre, chose the theme for this year's Annual Meeting. The theme for ASCO's 50th Annual Meeting was "Science and Society" and focused on opportunities for the community of clinicians and researchers to lead the society in the quest for knowledge and insight. The meeting highlighted the unique role that clinicians who treat cancer can play in closing knowledge gaps that can develop between those who work in science and those who govern and lead society. As the depth of scientific understanding increases and the number of effective therapeutic options multiplies, there will be a growing need to communicate clinically important advances with precision and to convey the benefits of societal investment in science. Even within the increasingly specialised medical professional community, there is a growing need for on-going and efficient communications so that everyone can keep up with advances in many areas of cancer prevention and treatment.

The theme, "Science and Society" echoes and supports the fact that one cannot exist without the other, that each has obligations and responsibilities for the other, and that each is critical to the improvement of the lives of everyone with or worried about cancer.

ASCO's Education Programme reflected the concerns, priorities, and issues that affect every oncology professional. There were multidisciplinary sessions that emphasised collaborative care in the management of different cancers, topics relevant to daily practice, tools for delivering high quality care, global health challenges in oncology, and understanding molecular pathways and genomics.

Several themes emerged organically from the Education Programme, which reflected the prevailing interests and concerns in the contemporary practice of oncology. Attendees found discussions on cost of care and value integrated into many sessions; ample coverage of hot-topic issues, including genomics, global practice and research, environmental and behavioural contributors to cancer (including obesity, vitamins, tobacco, and inflammation); and a look ahead to new scientific horizons and the future of cancer care.

A record 5,530 abstracts were submitted this year, with more than 2,900 selected for presentation in Oral Abstract Sessions, Clinical Science Symposia, or Poster Sessions - a testament to the robustness of clinical cancer research and the exciting advances occurring in labs and practices across the globe. In

addition, more than 2,200 abstracts were selected for online publication.

The Plenary Session, where the most clinically significant abstracts are presented and discussed, took place on Sunday and was broadcast live on ASCO Live.

Four abstracts were selected for presentation which examined combined treatment strategies across three common disease sites: breast cancer (hormone manipulation and HER2 blockade), colorectal cancer and prostate cancer.

Three Post-Plenary Discussion Sessions, one for each disease site, were held directly following the Plenary Session to allow for more discussion with presenters and speakers on the presented abstracts. The discussions included; Genitourinary Cancer, Gastrointestinal Cancer and Breast Cancer.

In today's climate of escalating healthcare costs and multiple therapeutic options, it's more important than ever to focus on providing high-quality, high-value care for all patients with cancer. ASCO's commitment to helping oncology providers and their patients understand the relative value of treatment options is reflected in this year's Programme, and attendees heard and took part in conversations about value led by discussants in numerous Oral Abstract Sessions. Discussants with expertise in value in cancer care will participate in two Highlights of the Day Sessions and the three Post-Plenary Discussion Sessions, where they will provide context for the findings related to cost of treatment, adverse events, and outcomes, as appropriate.

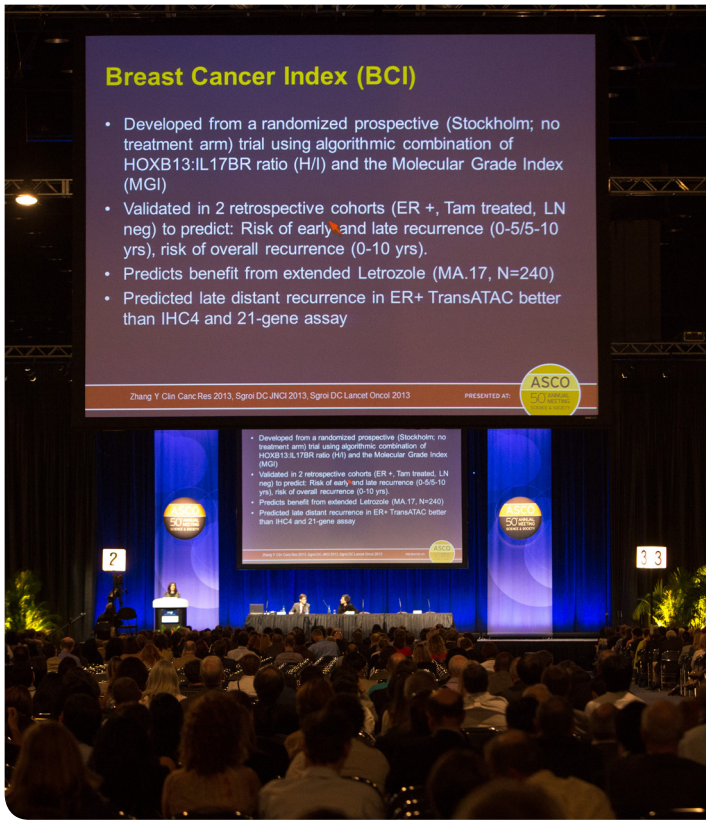
The Annual Meeting reflects a year-round effort on the part of ASCO staff, leadership and, most importantly, volunteers, who are working to make sure it reflects the accomplishments of ASCO's first 50 years.

ASCO's Annual Meeting aims to showcase the understanding of cancer and provides the opportunity to transform these insights into meaningful clinical benefits. Challenging the progress in cancer treatment is time, money, and imagination, which are being addressed where possible.

ASCO's CancerLinQ™ programme was highlighted at the meeting and will be promoted throughout the remainder of the year. Clinicians need to gain back time lost to paperwork and documentation to devote to research and the CancerLinQ promises to accelerate learning, provide useful clinical support, and return meaningful data using various electronic record systems. It offers the possibility of more return on the investment of time we all make in patient care.

Attendees had the opportunity to help build the future of cancer care by supporting the Conquer Cancer Foundation. The foundation aimed to raise $50,000 over the course of the meeting. The funds raised will help to support the Foundation's Mission Endowment, providing lasting support for some of ASCO's most critical priorities; Research; Professional education; Patient education and information International outreach and Quality of and access to care.

Delegates were also encouraged to note areas where they thought there would be opportunity for improvement so that next year's Meeting can be improved.



Chicago
USA

Chicago is the third most populous city in the United States and is the most populous city in both the U.S. state of Illinois and the American Midwest.

Its metropolitan area, sometimes called Chicagoland, is home to 9.5 million people and is the third-largest in the United States.

Chicago was incorporated as a city in 1837, near a portage between the Great Lakes and the Mississippi River watershed. The Chicago of today is an international hub for finance, commerce, industry, technology, telecommunications, and transportation, with O'Hare International Airport being the busiest airport in the world.

In 2012, Chicago was listed as an alpha global city by the Globalisation and World Cities Research Network, and ranks seventh in the world in the 2014 Global Cities Index

Chicago's culture includes contributions to the visual arts, novels, film, theatre, especially improvisational comedy, and music, particularly jazz, blues, soul, and the creation of house music. The city has many nicknames, which reflect the impressions and opinions about historical and contemporary Chicago. The best-known include the "Windy City" and "Second City."

Chicago has professional sports teams in each of the major professional leagues.

Data on the Treatment of Metastasised Renal Cell Carcinoma

Immunicum presented phase I/II data including data on their clinical candidate, INTUVAX, in patients with metastasised renal cell carcinoma (mRCC), during a general poster session.

In addition to demonstrating a favourable safety profile, INTUVAX, as a single agent, has shown clear signs of tumour specific immune activation and encouraging survival data for patients with poor prognosis. Furthermore, preliminary data indicate a synergistic effect between INTUVAX and subsequent treatment with tyrosine kinase inhibitors (TKIs).

Nine out of 11 evaluated patients exhibited an increased number of tumour specific and IFN-gamma producing lymphocytes (ELISPOT-assay including addition of autologous tumour material) when comparing pre-values with values obtained 1 week after the second vaccination.

A massive infiltration of CD8+ T cells was found in 5 out of 12 removed kidney tumours which, to the best of Immunicum's knowledge, is the most intensive and general intratumoural infiltration of CD8+ T cells ever reported in any human solid tumour. An additional two patients also showed a strong intratumoural infiltration of CD8+ T cells.

No initial objective tumour regression (according to so-called RECIST-criteria) was observed in any patient. However, three of the four patients who have so far received subsequent therapy with TKIs (3, 4, 9, and 17 months after vaccination), show an on going partial tumour regression. One of these responding patients (Heng/MSKCC poor prognosis) exhibited an extensive sarcomatoid transformation of the resected primary tumour. Notably, another responding patient with MSKCC poor prognosis, and who developed 4 brain metastases 4 months after INTUVAX treatment, has responded with a complete disappearance of two lesions and prominent shrinkage (>60%) of the other two lesions 6 months after initiation of sunitinib treatment. These two cases of objective response upon subsequent sunitinib treatment is surprising since recent data indicate that brain metastases as well as RCC with extensive sarcomatoid transformation are highly resistant to sunitinib.

Two patients exhibiting a late ongoing clinical response without add-on therapy, despite initial slow progress. One patient exhibits an ongoing stable disease for more than 6 months after previous slow tumour progression for 15 months. Remarkably, yet another patient exhibited an ongoing late objective partial (>40 %) tumour regression, without add-on therapy with TKIs that started after 16 months of very slow progression.

One year survival rate for the whole study group is currently at 63% (8 of 11 patients up for efficacy evaluation are still alive) which is comparable with historical data for newly diagnosed poor + intermediate prognosis patients on sunitinib or sunitinib + autologous DC-based cancer vaccination.

Median overall survival (mOS) for the whole patient population, or for different prognosis groups (poor and intermediate), is still not reached but has currently already surpassed recently reported mOS for newly diagnosed mRCC patients with MSKCC poor prognosis receiving upfront sunitinib before nephrectomy or newly diagnosed mRCC patients with Heng poor prognosis receiving an autologous DC-based cancer vaccine + sunitinib (12.7 vs 9.0 and 13.4 vs 9.1 months, respectively).

Median OS (from diagnosis) for the patient group with poor prognosis (Heng criteria) and concomitant extensive sarcomatoid differentiation (n=3, one received sunitinib 3 months after vaccination) was 7.5 months, which compares favourably with recent published data on mOS (from diagnosis), which was 3.0 months in this subgroup with very poor prognosis.

No clear-cut correlation between the numbers of injected vaccine cells, degree of HLA-incompatibility between vaccine cells and patient tissue or intratumoural infiltration of CD8+ T cells and OS has been observed. However, in patients with sarcomatoid differentiation (n=6) a tendency to prolonged survival is found in those with massive intratumoural infiltration of CD8+ T cells; OS for 2 patients with moderate CD8+ T cell infiltration was 3.8 and 7.5 months respectively and OS for 4 patients with massive infiltration was 7.0 months for one patient, while 3 patients are still alive at 10.0, 14.2 and 21 months after diagnosis.

Immunicum's findings indicate that intratumoural injection of pre-activated allogeneic DCs is safe and induces a systemic CTL-mediated anti-tumour response that may prolong survival in mRCC-patients. Moreover, data on patients who have received additional treatment with TKIs indicate a synergistic effect between intratumoural INTUVAX-vaccination and subsequent treatment with TKIs. A fully financed phase II study is currently in the final phase of planning.

For more information, please visit
www.immunicum.com

Data on Investigational Anti-cancer Agent

Eisai Co., announced a series of abstracts highlighting new study results on Halaven® (generic name: eribulin mesylate; non-taxane microtubule dynamics inhibitor, "eribulin") and lenvatinib (generic name; selective inhibitor of receptor tyrosine kinases (RTKs) with a novel binding mode) were presented during the 50th Annual Meeting of the American Society of Clinical Oncology.

The main presentations for this year's ASCO meeting included oral presentations highlighting the results of a Phase III study (the SELECT (Study of E7080 lenvatinib in differentiated Cancer of the Thyroid) study, Study 303) with lenvatinib, an investigational agent being evaluated as a potential treatment for radioiodine-refractory differentiated thyroid cancer (RR-DTC), given on Monday, June 2nd.

In addition, these findings were chosen by ASCO and featured in a press conference as part of the ASCO Annual Meeting press program on Saturday, May 31st.

New data on eribulin from the pooled analysis of two Phase III trials (Study 301 and the EMBRACE trial) in patients with metastatic breast cancer was also presented.

Major Eisai abstracts accepted for presentation at this year's ASCO meeting include:

- A phase III, multicentre, double-blind, placebo-controlled trial of lenvatinib (E7080) in patients with 131I-refractory differentiated thyroid cancer (SELECT).
- Prognostic and predictive role of circulating angiopoietin-2 in multiple solid tumours: An analysis of approximately 500 patients treated with lenvatinib across tumour types.
- A multicentre, open-label, phase III trial to compare the efficacy and safety of lenvatinib (E7080) versus sorafenib in first-line treatment of subjects with unresectable hepatocellular carcinoma.
- E7080 (lenvatinib) in addition to best supportive care (BSC) versus BSC alone in third-line or greater nonsquamous, non-small cell lung cancer (NSCLC).
- Efficacy of eribulin in patients (pts) with metastatic breast cancer (MBC): A pooled analysis by HER2 and ER status.
- Clinical effects of prior anthracycline or taxane use on eribulin as first-line treatment for HER+/- locally recurrent or metastatic breast cancer (BC): Results from two phase II, multicentre, single-arm studies.
- Clinical effects of prior trastuzumab on combination eribulin mesylate plus trastuzumab as first-line treatment for HER2+ locally recurrent or metastatic breast cancer (MBC): Results from a phase II, single-arm, multicentre study.
- Phase II feasibility study of dose-dense doxorubicin and cyclophosphamide (AC) followed by eribulin mesylate with or without prophylactic growth factor (GF) for adjuvant treatment of early-stage breast cancer (EBC).
- Phase II study of eribulin mesylate in patients (pts) with advanced soft tissue sarcoma (STS).
- Pharmacokinetics (PK) of eribulin mesylate in cancer patients (pts) with normal and impaired renal function.

For more information, please visit
www.eisai.com

High Disease Control Rate with Acelarin

NuCana presented impressive clinical data for their first-in-class anti-cancer agent, Acelarin.

NuCana is a clinical stage biopharmaceutical company developing and commercialising a range of exciting, new anti-cancer medicines. With its next generation of anti-cancer agents (nucleotide analogues), NuCana is setting new benchmarks for innovative therapeutic treatments. The state-of-the-art ProTide technology transforms existing therapies into better and safer medicines that overcome key cancer resistance mechanisms.

Patients with advanced, solid tumours relapsed or refractory to standard therapies were treated with Acelarin in a Phase I/II study (ProGem1) and an 88% disease control rate was achieved. The study has reached its primary objective, having established the recommended Phase II dose (RP2D) with a favourable safety profile.

The very positive clinical results with Acelarin were selected for oral discussion at ASCO's Poster Highlight Session. Of the twenty five evaluable patients that received two or more cycles of Acelarin, 20% achieved a Partial Response and 68% Stable Disease. This equates to an 88% disease control rate, which in the majority of cases was durable.

Acelarin is the first of a new class of agents in cancer, ProTides. These medicines are specifically designed to bypass the key resistance mechanisms that block the action of nucleoside analogues, which are widely used in cancer therapy.

In addition to the high disease control rate, Acelarin was well tolerated, with no unexpected adverse events (AEs). The most common AEs Grade 1 or 2 were anaemia; fatigue; transaminitis and thrombocytopaenia. Two dose limiting toxicities were observed, Grade 3 ALT and Grade 4 thrombocytopaenia.

The key to the successful clinical outcomes with Acelarin is found in its pharmacokinetic profile. Acelarin generates over 12 times higher intracellular levels of the active nucleotide analogue, dFdCTP compared with gemcitabine, and rapidly reached its Cmax, 30 minutes from end of infusion.

The ProGem1 study has completed its primary objective and has now entered an expansion stage at the RP2D to further assess the efficacy and safety profile of Acelarin in selected tumour types. Registration studies are being planned for pancreatic, biliary, ovarian and non-small cell lung cancers.

For more information, please visit
www.nucana.com

Data from Clinical Trial of Antibody-drug

Seattle Genetics presented interim phase 1 clinical data from SGN-CD19A, an antibody-drug conjugate (ADC) in development for the treatment of B-cell malignancies. SGN-CD19A is an ADC targeting CD19, a protein expressed on B-cell malignancies.

With over 16 years of experience and knowledge in ADC innovation, Seattle Genetics is the leader in developing ADCs, a technology designed to harness the targeting ability of antibodies to deliver cell-killing agents directly to cancer cells.

Of the more than 30 ADC candidates in clinical development, greater than 20 utilise Seattle Genetics' proprietary ADC technology. Seattle Genetics and its collaborators, including Genentech, AbbVie and Progenics, have nine data presentations at ASCO that highlight the widespread evaluation of its ADC technology to potentially impact the way cancer is treated.

Interim analysis of a phase 1, open-label, dose-escalation study of SGN-CD19A in patients with relapsed or refractory B-lineage non-Hodgkin lymphoma (Abstract #8505, oral presentation Sunday, June 1st at 9:48 a.m. Central Time)

Data was reported from 37 patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma (NHL), including 32 patients with diffuse large B-cell lymphoma (DLBCL), four patients with mantle cell lymphoma (MCL) and one patient with Grade 3 follicular lymphoma. The median age of patients was 65 years and the median number of prior systemic therapies was two, with 10 patients (27 per cent) having received a prior autologous stem cell transplant. Among enrolled patients, eight per cent were primary refractory, 54 per cent were refractory to their last treatment and 38 per cent had relapsed following a response to their last treatment.

The primary endpoints of the on-going clinical trial are to estimate the maximum tolerated dose and to evaluate the safety of SGN-CD19A. In addition, the trial is evaluating antitumour activity, pharmacokinetics, progression-free survival and overall survival. In this dose-escalation study, patients receive a single dose of SGN-CD19A on an every 3-week basis. Key findings included:

No dose limiting toxicity was observed in the first cycle for any patients. Adverse events were observed in the 6 milligrams per kilogram (mg/kg) dosing regimen after the first cycle, therefore enrollment was discontinued. The 3, 4 and 5 mg/kg cohorts are being expanded, and the trial continues to enroll.

At the time of data analysis, of the 37 patients treated across all dose levels, the objective response rate observed was 30 per cent (11 patients). Six patients (16 per cent) achieved a complete remission, five (14 per cent) achieved a partial remission, 13 (35 per cent) had stable disease and 13 (35 per cent) had progressive disease as best response. The clinical trial is on-going with nine of the 37 patients (24 per cent) remaining on treatment and new patients continuing to be enrolled.

The most common adverse events of any grade occurring in more than 30 per cent of patients were blurred vision (51 per cent), fatigue (38 per cent), dry eye (35 per cent), constipation (30 per cent) and keratopathy (30 per cent). Grade 3 or higher adverse events observed in two or more patients included blurred vision (six patients), keratopathy (three patients), low platelet count (three patients) and anaemia (three patients).

For more information please visit
www.seattlegenetics.com

Cabozantinib and Cobimetinib Featured in Ten Presentations

Cabozantinib and Cobimetinib were the subject of ten presentations at ASCO 2014 by Exelixis.

Exelixis is a biopharmaceutical company committed to developing small molecule therapies for the treatment of cancer. Exelixis is focusing its development and commercialisation efforts primarily on COMETRIQ® (cabozantinib), its wholly owned inhibitor of multiple receptor tyrosine kinases. Another Exelixis discovered compound, cobimetinib is a highly selective inhibitor of MEK, is being evaluated by Roche and Genentech in a broad development program under collaboration with Exelixis.

Cabozantinib inhibits the activity of tyrosine kinases including MET, VEGFRs and RET. These receptor tyrosine kinases are involved in both normal cellular function and in pathologic processes such as oncogenesis, metastasis, tumour angiogenesis, and maintenance of the tumour microenvironment. COMETRIQ® (cabozantinib) is currently approved by the U.S. Food and Drug Administration for the treatment of progressive, metastatic medullary thyroid cancer (MTC).

Cobimetinib is an inhibitor of MEK, a serine/threonine kinase that is a component of the RAS/RAF/MEK/ERK pathway. This pathway mediates signalling downstream of growth factor receptors, and is prominently activated in a wide variety of human tumours. In preclinical studies, oral dosing of cobimetinib resulted in sustained inhibition of MEK in RAS or BRAF mutant tumour models. Cobimetinib is being developed by Roche and Genentech, a member of the Roche Group, under collaboration with Exelixis.

Presentation included:

- Effect of cabozantinib on immunosuppressive subsets in metastatic urothelial carcinoma
- Phase 1 dose finding study of cabozantinib (cabo) + abiraterone (abi) combination therapy in castration resistant prostate cancer (CRPC): An investigator-sponsored study
- Phase II trial of XL184 (cabozantinib) plus erlotinib in patients (pts) with advanced EGFR-mutant non-small cell lung cancer (NSCLC) with progressive disease (PD) on epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy: a California Cancer Consortium phase II trial (NCI 9303)
- Phase 3 randomised, double-blind, controlled study of cabozantinib (XL184) versus placebo in subjects with hepatocellular carcinoma who have received prior sorafenib (CELESTIAL; NCT01908426)
- A phase II trial of cabozantinib in patients with carcinoid and pancreatic neuroendocrine tumours
- Phase II study of XL184 (Cabozantinib) in recurrent or metastatic endometrial cancer: A trial of the PMH, Chicago and California Phase II Consortia.
- A phase I study of Cabozantinib (XL184) in children and adolescents with recurrent or refractory solid tumours, including CNS tumours: A Children's Oncology Group phase I consortium trial
- Phase 3 randomised study of cabozantinib (XL184) versus everolimus in subjects with clear cell renal cell carcinoma (METEOR)
- A safety study of cabozantinib (C) plus docetaxel (D) and prednisone (P) in metastatic castrate-resistant prostate cancer (mCRPC)
- Metabolic tumour burden for prediction of overall survival following combined BRAF/MEK inhibition in patients with advanced BRAF mutant melanoma

For more information, please visit
www.exelixis.com

Data Presented on 27 Different Medicines

Roche presented new data on approved medicines, investigational-targeted combinations and the emerging pipeline.

Data in more than 19 tumour types was presented, including new results from the investigational cancer immunotherapy MPDL3280A (anti-PDL1) in advanced bladder cancer and the Bcl-2 inhibitor GDC-0199/ABT-199 in haematology.

Roche presented new data on nine approved and 18 investigational medicines during the Meeting. Of the more than 320 abstracts on Roche medicines, more than 40 were accepted for oral presentation during the ASCO Annual Meeting.

The data presented at ASCO shows the depth and strength of Roche's oncology pipeline and include the following highlights:

Cancer Immunotherapy: A phase 1 study of anti-PDL1 in advanced bladder cancer was presented in an oral session on Saturday 31st May. The presentation featured important updates including; overall response rate, biomarker and safety information. As part of Roche's global development plan to explore the potential of multiple immunotherapy targets in oncology, anti-PDL1 represents Roche's most advanced investigational cancer immunotherapy in development.

Haematology: In addition to data from Roche's anti-CD20 medicines MabThera/Rituxan (rituximab) and Gazyva (obinutuzumab), new data from two investigational medicines were presented for the first time at ASCO. The data included interim results of a phase 1b study of the Bcl-2 inhibitor GDC-0199/ABT-199 in combination with rituximab in patients with relapsed/refractory chronic lymphocytic leukemia and results of a phase 2 study of polatuzumab vedotin, an anti-CD79b antibody drug conjugate in relapsed/refractory non-Hodgkin lymphoma.

For more information please visit
www.roche.com

Investigational Patient-specific Immunotherapy

NeoStem, a leader in the emerging cellular therapy industry, announced results of a pooled analysis indicating that Melapuldencel-T, an investigational patient-specific immunotherapy for metastatic melanoma, may increase survival rates significantly for patients at the most advanced stages of the disease.

Melapuldencel-T, developed by California Stem Cell, Inc. and now NeoStem's most advanced product candidate and foundation for its Targeted Immunotherapy Program in oncology, is a late stage novel proprietary cancer cell therapy.

Melapuldencel-T has been approved to enter this trial with a Special Protocol Assessment ("SPA") from the Food and Drug Administration ("FDA") and has received Fast Track designation for metastatic melanoma, as well as Orphan Drug designation. The pooled results may not be predicative of our future Phase 3 results, in part because all patients will be treated using current day standards of care, and the Phase 3 study design will not include any uncontrolled data or cross-study comparisons, allow patients to be excluded from the analysis after data are collected, or permit pooling of different studies. Initially directed at patients with metastatic melanoma, Melapuldencel-T uses the patient's isolated and purified tumour stem cells to train the immune system to identify and eliminate cancer stem cells, the root cause of tumour formation and the key drivers of tumour escape, tumour genesis, self-renewal and recurrence in a broad spectrum of solid tumour cancers. The platform on which Melapuldencel-T is created, in which autologous dendritic cells are pulsed with irradiated tumour cells (DC/TC), is also being investigated for other indications including hepatocellular carcinoma and other immune responsive tumour types.

Robert O. Dillman, MD, study author and Vice-President, NeoStem Oncology presented the findings on Sunday, June 1st in a poster. The analysis presented included a subset of pooled data from three melanoma clinical trials, conducted successively from 1990-2011. Two of these trials (one of which was controlled and one of which was not) studied Melapuldencel-T. The new pooled analysis indicates significantly better five-year overall survival rates in patients treated with Melapuldencel-T than those treated with the comparator therapy (autologous tumour cells that had been irradiated to render them inactive) for the subset of patients who still had evidence of disease after prior treatment with one or more standard therapies.

Melapuldencel-T is an autologous immunotherapy intended to eliminate cancer-initiating (stem) cells capable of causing disease recurrence. The therapy employs the patient's own tumour cells and dendritic cells (a type of immune cell), along with granulocyte-macrophage colony stimulating factor (GM-CSF, a natural growth factor that stimulates white blood cells in the body). The patient's dendritic cells are mixed with the patient's tumour cells to create the therapeutic agent, which is then suspended in GM-CSF for injection into the patient.

Melapuldencel-T was developed by California Stem Cell, Inc., which was acquired by NeoStem in May 2014.

NeoStem is initiating a Phase 3 study of Melapuldencel-T later this year under a Special Protocol Assessment agreement with the U.S. FDA and the therapy has been granted fast-track designation by the agency as well.

The poster was based on further analysis of previously published data from 170 patients enrolled in three studies: a single-arm Phase 2 trial of irradiated, proliferating, autologous tumour cells, a single-arm Phase 2 trial of Melapuldencel-T, and a randomised trial directly comparing the two treatments. Twenty-seven comparator-treated patients were excluded to decrease interpatient differences associated with poor survival. Remaining patients were classified as NED or non-NED.

The analysis described addressed whether better survival was also associated with Melapuldencel-T in the non-NED patients (n=73). Survival curves were generated for 39 patients treated with Melapuldencel-T and 34 patients treated with the comparator, and compared by log-rank test. Five-year overall survival for all 73 non-NED patients was 27 per cent (median 25.5 months).

For more information please visit
www.neostem.com

Update on ADAPT Phase 3 Trial for AGS-003

Argos Therapeutics announced updated results from a completed phase 2 study of its Arcelis™ technology platform.

Argos Therapeutics is a biopharmaceutical company focused on the development and commercialisation of fully personalised immunotherapies for the treatment of cancer and infectious diseases using its Arcelis™ technology platform.

Arcelis is a fully personalised immunotherapy technology that captures mutated and variant antigens that are specific to each patient's disease. It is designed to overcome immunosuppression by producing a durable memory T cell response without adjuvants that may be associated with toxicity.

The results of the study highlighted the long-term survival observed in patients treated with sunitinib combined with AGS-003, the company's investigational fully personalised immunotherapy for cancer.

Argos' most advanced product candidate, AGS-003, is being evaluated in the pivotal ADAPT Phase 3 clinical trial for the treatment of metastatic renal cell carcinoma (mRCC). The company also plans to report data from its Phase 2b trial of AGS-004 for the treatment of HIV in mid-2014.

The results were presented in a poster presentation at the ASCO Annual Meeting on Friday, May 30th, 2014.

According to the results of the study treatment with AGS-003 in combination with sunitinib in an unfavourable risk mRCC patient population, resulted in median progression free survival (PFS) of 11.2 months and median overall survival (OS) of 30.2 months. Based upon recently published findings from the International mRCC Database Consortium, similar risk mRCC patients with a time from diagnosis to treatment of less than one year risk factor (DxTx < 1yr) have an expected median PFS of 5.7 months and median OS of 14.7 months.

In addition, 33 per cent of patients survived for greater than 4.5 years and 23% for more than five years, with two patients remaining in long-term remission for longer than five years following continued dosing with AGS-003. Adverse events (AEs) associated with the use of AGS-003 were minor with no grade 3 or 4 AEs and no evidence of autoimmunity.

AGS-003 is a fully personalised immunotherapy comprised of autologous tumour RNA-loaded dendritic cells. To create AGS-003, ribonucleic acid (RNA) is isolated from a small tumour sample taken from the patient in a standard tumour removal procedure s dendritic cells are obtained from a single leukapheresis procedure.

The tumour RNA is used to program optimised dendritic cells with the entire disease-antigen repertoire from the patient's tumour to trigger an immune-specific cancer. The antigen-loaded dendritic cells are then formulated into an intradermal injection for administration to the patient.

On Monday, June 2nd, 2014, Argos presented an update on progress in the on going ADAPT Phase 3 clinical trial for AGS-003 in a separate poster presentation at ASCO. The poster, entitled "Enrollment insights in the synchronous mRCC population: An update from the ongoing ADAPT Phase 3 study experience", was presented by Robert A. Figlin, MD, FACP

The ADAPT study is a randomised international Phase 3 trial comparing standard targeted therapy plus AGS-003 to standard therapy alone in the treatment of mRCC. More than 120 sites in North America and select other countries have been activated and > 400 patients have been consented for the tumour collection phase of the study.

For more information visit:
www.argostherapeutics.com

Phase 2 Clinical Data on Galeterone

Tokai Pharmaceuticals is a biopharmaceutical company focused on developing new treatments for prostate cancer and other hormonally driven diseases. The company's lead drug candidate, galeterone (TOK-001), is a first-in-class, multi-targeted, oral small molecule drug being developed for the treatment of patients with castration-resistant prostate cancer (CRPC). Based in Cambridge, Massachusetts, Tokai is backed by Apple Tree Partners, Novartis Venture Fund and the Satter Foundation.

Tokai Pharmaceuticals, Inc., announced updated results from its on going ARMOR2 Phase 2 study of its lead drug candidate, galeterone (TOK-001), in patients with castration-resistant prostate cancer (CRPC) was presented.

Galeterone (TOK-001) is a highly selective, multi-targeted, oral small molecule drug being developed for the treatment of castration-resistant prostate cancer (CRPC) that disrupts androgen receptor (AR) signaling, the key driver of CRPC, via multiple mechanisms of action. Galeterone combines the mechanisms of action of CYP17 inhibition and androgen receptor antagonism with that of androgen receptor degradation.

Tokai Pharmaceuticals is a biopharmaceutical company focused on developing new treatments for prostate cancer and other hormonally driven cancers.

The poster was presented by Bruce Montgomery, M.D., associate professor of medical oncology at the University of Washington School of Medicine, and co-principal investigator of ARMOR2 gave the first poster presentation on Saturday, May 31st, 2014.

This was titled 'Galeterone in men with CRPC: Results in four distinct patient populations from the ARMOR2 study'.

For more information visit:
www.tokaipharma.com

Data For Novel Antibody Therapeutic Programs

Merrimack Pharmaceuticals is a biopharmaceutical company discovering, developing and preparing to commercialise innovative medicines paired with companion diagnostics for the treatment of cancer. Merrimack seeks to gain a deeper understanding of underlying cancer biology through its systems biology-based approach and develop new insights, therapeutics and diagnostics to improve outcomes for cancer patients. Merrimack currently has six oncology therapeutics in clinical development and three additional candidates in late stage preclinical development.

At ASCO 2014 Merrimack presented Phase 1 clinical data from studies of MM-151, MM-141, MM-111 and MM-121. Data from these studies support the clinical advancement of Merrimack's novel antibody therapeutics.

Preliminary results from a Phase 1 study of MM-151, a novel oligoclonal anti-EGFR antibody combination, in patients with refractory solid tumours suggested clinical activity in colorectal cancer with an acceptable safety profile consistent with EGFR inhibition. Planning is underway for a Phase 2 study testing MM-151 in colorectal cancer.

Merrimack's MM-141, a tetravalent bi-specific antibody designed to block tumour survival signals by targeting receptor complexes containing IGF-1R and ErbB3, has completed the monotherapy arm in a Phase 1 study and reports no dose limiting toxicities. The next step for MM-141 is anticipated to be a Phase 2 study testing MM-141 in front line pancreatic cancer.

Merrimack also presented a Phase 1 multi-arm study of MM-111 in combination with standard of care regimens in multiple tumour types as well as a Phase 1 study of MM-121 in combination with cetuximab and irinotecan in patients with advanced solid cancers.

Preliminary Results from a Phase 1 Trial of MM-151 in Patients with Refractory Solid Tumours.

MM-151 is a novel oligoclonal anti-EGFR antibody combination designed to target EGFR-driven tumour growth. Preliminary data from a Phase 1 study in patients with refractory solid tumours show that MM-151 has an acceptable safety profile and preliminary signs of clinical activity in colorectal cancer.

- A total of 69 patients have been enrolled at escalating dose levels, with the most common tumour types including colorectal cancer (28 [41%]), non-small cell lung cancer (9 [13%]), head and neck cancers (5 [7%]), and pancreatic cancer (6 [9%]).
- The most common adverse event seen thus far was infusion related reaction (47 [68.1%]), which was managed with premedication and an optimised

infusion schedule.
- Partial responses (PR) were observed in two colorectal cancer patients and a total of eight (29% of mCRC) patients had stable disease (SD) for greater than four months
- Planning is underway for a Phase 2 trial to evaluate MM-151 in colorectal cancer.

Results from the Completed Monotherapy Arm of a Phase 1 Study of MM-141 in Patients with Advanced Solid Tumours

A Phase 1 dose-escalation study in patients with advanced solid tumours tested the tolerability and safety of MM-141, a novel tetravalent bispecific antibody inhibitor that targets both IGF-1R and ErbB3. MM-141 blocks and degrades complexes containing IGF-1R and ErbB3 receptors, leading to the downstream inhibition of tumour pro-survival signalling. Preclinical studies have shown that MM-141 has higher activity compared to a mixture of separate anti-IGF-1R and ErbB3 antibodies.
- This clinical study enrolled three arms: MM-141 as a monotherapy, MM-141 in combination with everolimus and MM-141 in combination with nab-paclitaxel and gemcitabine. Data presented detailed the completion of the monotherapy arm.
- There were no dose-limiting toxicities observed in the monotherapy arm at any dose level. The most common adverse events that were not deemed related to MM-141 monotherapy were vomiting, nausea, fatigue, abdominal pain and dyspnea.
- MM-141 monotherapy showed preliminary activity with disease stabilisation observed in patients with Ewing's Sarcoma and parotid gland carcinoma.
- Planning is underway for a Phase 2 study of MM-141 in combination with nab-paclitaxel and gemcitabine in front line pancreatic cancer.

Results from a Phase 1, Multi-arm Study of MM-111 in Combination with Standard of Care Regimens in Multiple Tumour Types

MM-111 is a bi-specific antibody designed to inhibit HER3 (ErbB3) signalling in HER2-positive tumours. Preclinical research has shown that MM-111 restores sensitivity to chemotherapy and HER2-targeted treatment. MM-111 was tested in a Phase 1 study in combination with a variety of standard of care HER2-targeted regimens, namely: 1) capecitabine, cisplatin and trastuzumab; 2) lapatinib with or without trastuzumab; 3) paclitaxel and trastuzumab; 4) lapatinib, paclitaxel and trastuzumab; and 5) docetaxel and trastuzumab. The study enrolled patients with multiple HER2 positive tumour types, including breast, bladder, colorectal, gastric, esophageal and ovarian cancers. Each arm in the study was designed to run as a separate Phase 1 trial to address safety and tolerability of MM-111, and utilised a "3+3" design with standard dosing of the standard of care regimen.
- A total of 86 patients with advanced HER2+ cancers were enrolled in the study.
- The combination of MM-111 with standard HER2-directed therapy was generally feasible with standard doses for the HER2 directed therapies. Only Arm 1 required a reduction in the dose of capecitabine to 800 mg/m2 as a result of dose limiting toxicity.
- Adverse events reported for MM-111 in combination with the standard of care HER2-targeted regimens were similar to adverse events reported for the regimens alone, which included diarrhoea, fatigue, decreased appetite, neutropaenia and hypokalaemia.
- Across all dosing regimens, the overall clinical benefit rate, defined as complete response, PR and SD for at least four months, was 55% in 86 evaluable patients.
- The combination of MM-111 and standard of care HER2 directed regimens showed clinical activity across a variety of advanced solid tumours with objective responses being observed in multiple HER2-positive tumour types.
- MM-111 is currently in a biomarker stratified Phase 2 study testing MM-111 in combination with trastuzumab and paclitaxel in patients with advanced gastric, oesophageal and gastroesophageal junction cancers.

Results from a Phase 1 Study of MM-121 in Combination with Cetuximab and Irinotecan in Patients with Advanced Cancers

This Phase 1 trial assessed the safety, tolerability and pharmacokinetic properties of MM-121 in combination with cetuximab or with cetuximab and irinotecan in patients with advanced solid cancers. MM-121 is a fully human monoclonal antibody that targets ErbB3, a cell surface receptor that is activated by the ligand heregulin.
- Patients were dosed in a standard "3+3" design with escalating doses of MM-121 and cetuximab in two groups without (n=34) or with biweekly irinotecan (n=14).
- The most common adverse events from across the entire study included fatigue, hypomagnesemia, diarrhea and hypokalaemia.
- Across all dosing regimens, 18/48 (37.5%) of patients achieved a best overall response of SD or PR, 14/48 (29.2%) had SD, 4/48 (8.3%) had a PR. Of the four patients who had PR, two had KRAS wild-type colorectal cancer, one had cholangiocarcinoma and one had NSCLC.
- One colorectal cancer patient previously treated with cetuximab and irinotecan achieved a PR on the MM-121/cetuximab/irinotecan combination. One head and neck cancer patient who previously received cetuximab achieved a durable response of SD on the MM-121/cetuximab combination.
- Phase 2 doses were established for the combination of MM-121 and cetuximab and MM-121, cetuximab and irinotecan.
- Further studies with these combinations are being evaluated.

For more information visit:
www.merrimackpharma.com

Key Advances in Cancer Presented by Novartis

Novartis presented key advances in cancer research at ASCO from four new pivotal studies in lung, blood and skin cancers.

Novartis showcased the results of research to target disease pathways with more than 150 abstracts. This included updated data in ALK+ non-small cell lung cancer and the first-ever presentations of key data in polycythemia vera, multiple myeloma (blood) and locally advanced or metastatic basal cell carcinoma (skin).

Clinical data featured at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO; May 30th-June 3rd, Chicago) included Zykadia™ (ceritinib), Jakavi®* (ruxolitinib), Tasigna® (nilotinib), Afinitor® (everolimus) and Exjade® (deferasirox), as well as pipeline compounds LBH589 (panobinostat), LDE225 (sonidegib) and others.

Data highlights included:
Key pivotal data across four oncology compounds

- Ceritinib: Ceritinib in advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC): Results of the ASCEND-1 trial Ruxolitinib: Results of a prospective, randomised, open-label Phase III study of ruxolitinib in polycythemia vera patients resistant to or intolerant of hydroxyurea: the RESPONSE trial
- Panobinostat: PANORAMA 1: A randomised, double-blind, Phase III study of panobinostat or placebo plus bortezomib and dexamethasone in relapsed or relapsed and refractory multiple myeloma
- Sonidegib: Randomised, double-blind study of sonidegib (LDE225) in patients with locally advanced or metastatic basal cell carcinoma

Emerging data on key Novartis marketed treatments, early combination studies and innovative clinical trial designs

- Everolimus: Meta-analysis of stomatitis incidence in everolimus clinical studies and its relationship with efficacy
- Everolimus: Prevention of stomatitis in patients with hormone receptor-positive advanced breast cancer treated with everolimus plus exemestane: A Phase II study of a steroid-based mouthwash
- Everolimus: Identification and validation of predictive biomarkers for everolimus in metastatic renal cell carcinoma: Analysis of 442 patients on RECORD-3
- Nilotinib: Treatment-free remission following nilotinib in patients with chronic myeloid leukemia in chronic phase: ENESTfreedom, ENESTop, ENESTgoal, and ENESTpath

- Nilotinib: ENESTnd 5-year update: Long-term outcomes of patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib vs imatinib
- Nilotinib: Effect of continued imatinib in patients with detectable BCR-ABL after ≥ 2 years on study on deep molecular responses (MR): 36-month update from ENESTcmr
- Ruxolitinib: Phase Ib, dose-finding study of ruxolitinib plus panobinostat in patients with myelofibrosis
- Deferasirox: Deferasirox–deferoxamine combination therapy reduces cardiac iron with rapid liver iron removal after 24 months in patients with severe transfusional iron overload (HYPERION)
- The signature program, a series of tissue-agnostic, mutation-specific signal finding trials

New findings from combination studies across oncology pipeline and presentations on CAR T cell therapy

- INC280: Safety and efficacy of INC280 in combination with gefitinib in patients with EGFR-mutated, MET-positive NSCLC: A single-arm Phase Ib/II study
- LEE011: Phase Ib/II study of LEE011, everolimus, and exemestane in postmenopausal women with ER+/HER2- metastatic breast cancer
- LEE011: Phase Ib study of LEE011 and BYL719 in combination with letrozole in estrogen receptor-positive, HER2-negative breast cancer
- CTL019: Genetically Engineered T Cells and Beyond: Immune Modulation Therapy in Chronic Lymphocytic Leukemia
- CTL019: Future Directions in Immune Targeting

Throughout ASCO, Novartis Oncology hosted a dedicated webpage (http://www.novartisoncology.com/asco-2014.jsp) that provided unique insights and perspectives into emerging areas of cancer care and research.

For more information please visit
www.novartis.com

Oncolytic Vaccine Enadenotucirev in Cancer Patients

PsiOxus Therapeutics is a privately held Oxford, UK-based clinical stage biotechnology company using non-traditional approaches to develop novel therapeutics that address cancer and other clinically unmet diseases.

PsiOxus Therapeutics announced the results of two of its on going phase I studies of the oncolytic vaccine enadenotucirev (previously known as ColoAd1).

Enadenotucirev is an oncolytic vaccine for the systemic treatment of metastatic cancer, which has demonstrated exceptional anti-cancer properties in late pre-clinical development and is now in phase I/II clinical development for multiple solid cancers including colorectal and ovarian cancer. MT-102 is a dual action Anabolic Catabolic Transforming Agent (ACTA) clinical development for the treatment of cachexia and sarcopaenia and which has demonstrated positive effects on lean muscle mass and muscle function in a phase II clinical trial in late stage colorectal and non-small cell lung cancer. The Company is also developing an adjuvant and immunotherapeutic platform PolyMAP, which combines polymers with synthetic adjuvants to significantly enhance the effectiveness of vaccines.

The EVOLVE (EValuating OncoLytic Vaccine Efficacy) trial is a phase I/II trial of intravenous administration of enadenotucirev to patients with epithelial cancers and the MoA (Mechanism of Action) trial is a phase I "window of opportunity" trial evaluating intravenous and intra- tumoural administration of enadenotucirev to patients with colon cancer. Enadenotucirev is an oncolytic Ad11/Ad3 chimeric group B adenovirus that has previously been shown to selectively destroy metastatic solid tumours at low concentrations in pre-clinical models.

To date a combined total of 46 cancer patients have been dosed with up to four cycles (12 doses) of enadenotucirev. An independent Data Safety Monitoring Committee has approved the proposed dose to be taken into phase 2 clinical trials for both single cycle and repeat cycle administration. This safety data was presented at the ASCO meeting.

Intra-tumoural delivery of oncolytic viruses to superficial tumour sites has been shown to be clinically successful in phase III clinical trials but systemic delivery of viruses to metastatic tumour sites via intravenous delivery has been more elusive. In the two PsiOxus studies, the ability to selectively deliver the live replicating virus to tumour cells has been examined by a number of techniques including positron emission tomography scans; immunohistochemistry; quantitative polymerase chain reaction assays; and viral plaque assays.

- Dr Emiliano Calvo presented 'A First in Human Phase I study of enadenotucirev, an oncolytic Ad11/Ad3 chimeric group B adenovirus, administered intravenously in patients with metastatic epithelial tumours'.
- Dr Rocio Garcia Carbonero presented 'Phase 1 Mechanism of Action Study of Intra-tumoural or Intravenous Administration of enadenotucirev, an Oncolytic Ad11/Ad3 Chimeric group B Adenovirus in Colon Cancer Patients Undergoing Resection of Primary Tumour'.

For more information please visit **www.psioxus.com**

2015 ASCO Annual Meeting

29th May-2nd June,2015

McCormick Place Chicago, Illinois

The 2015 ASCO Annual Meeting will be hosted at Chicago's McCormick Place, one of the nation's largest and most impressive convention and meeting centres. Located along the shore of Lake Michigan, McCormick Place's state-of-the-art facilities and fantastic location are sure to enhance any Annual Meeting experience.

Attendees of the 2015 Annual Meeting will find cutting-edge scientific presentations and comprehensive educational content.

The ASCO Annual Meeting brings together more than 25,000 oncology professionals from a broad range of specialties, making it an excellent venue for exploring the theme of the Meeting—"Illumination and Innovation."

Please visit: http://am.asco.org/visitors-guide-chicago

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HILTON ROSEMONT/CHICAGO O'HARE

HILTON ORRINGTON/EVANSTON

ASCO 2015...

The 51st ASCO Annual Meeting takes place in Chicago between 29th May - 2nd June, 2015.

Treatment Strategies takes a look at a number of the finest hotels Chicago has to offer...

HILTON ROSEMONT/ CHICAGO O'HARE
Location - 5550 N. RIVER ROAD, ROSEMONT, ILLINOIS, 60018, USA

The Hilton Rosemont/ Chicago O'Hare hotel is easily accessible from I-294 and I-90 expressways and is minutes from Chicago O'Hare International Airport.

The hotel provides a complimentary hotel airport shuttle service to and from each terminal.

The hotel is connected via covered sky bridge to the Donald E. Stephens Convention Center and is an ideal venue to hold your next business meeting or event with Rosemont meeting incentives. This Rosemont hotel offers more than 22,000 sq. ft. of versatile meeting and banquet space including a Grand Ballroom and Executive Conference Center.

Guests can start or end the day with a workout at the fully equipped 24-hour Life Fitness© fitness centre and unwind in the heated indoor pool featuring panoramic views of downtown Chicago skyline.

Liberty Tavern offers the best of Rosemont restaurant dining, featuring all-American favourites. Sip a refreshing cocktail at Liberty Tavern Lounge or indulge in 24-hour room service. If you're in a hurry, try Lobby Café proudly serving Starbucks Coffee and breakfast pastries, snacks and sandwiches to go at this hotel near Chicago O'Hare International.

HILTON ORRINGTON/ EVANSTON
Location - 1710 ORRINGTON AVENUE, EVANSTON, ILLINOIS, 60201, USA

The sophisticated Hilton Orrington/Evanston hotel is centrally located in the heart of downtown Evanston, Illinois.

Just 20 minutes from downtown Chicago, beside Lake Michigan, this Evanston, IL hotel is 30 minutes from O'Hare International Airport, 40 minutes from Chicago Midway Airport and close to corporate offices like Kraft Foods and Chase Bank.

McCormick Convention Center is 18 miles away. Northwestern University, boutique shops, restaurants, the subway into Chicago and a multiplex movie

theatre are all within walking distance of this downtown hotel.

Ease and convenience define the tastefully decorated hotel in Evanston, with comfortable accommodations and wireless internet access throughout the hotel. Hold business events in the 18,505 sq. ft. of flexible meeting and banquet facilities for 2-400, including the latest AV equipment and support from professional staff. An impressive 15,000 square feet.

Executive Conference Center is IACC certified. Use the 24-hour business centre for all your business necessities. Celebrate your wedding in style under the spectacular chandeliers of the historic Grand Ballroom.

Guest room amenities include European-style bathrooms with power showerheads. The large Executive Suite features a king guest room with separate parlor area and queen-sized sofa bed.

HILTON CHICAGO

Location - 720 SOUTH MICHIGAN AVENUE, CHICAGO, ILLINOIS, 60605, USA

Hilton Chicago combines a contemporary design and exciting atmosphere within this iconic Chicago hotel. The downtown Chicago hotel is located within walking distance to many Chicago attractions.

Guests can step outside the front door and walk through Grant Park to Chicago's Lakefront, Field Museum, Shedd Aquarium, Adler Planetarium or Soldier Field. Millennium Park and theatre and financial district events are only steps from the South Loop location. Navy Pier and Chicago Children's Museum are also nearby.

The Chicago hotel rooms and suites are decorated in a sophisticated style, feature HDTVs, in-room concierge computers and high-speed internet access. Newly designed business class rooms offer complimentary WiFi, health club access and refrigerator.

Guests can enhance their stay to the Executive Level which offers complimentary continental breakfast, non-alcoholic beverages and evening appetizers with an honor bar at the Executive Lounge.

The Hilton Chicago hotel is located near McCormick Place provides 234,000 sq. ft. of Chicago event space with 50 meeting rooms, three ballrooms and four exhibit halls.

Guests have the option of taking advantage of Hilton Chicago's Athletic Club, boasting a variety of fitness equipment, free weights, indoor running track, full-length heated indoor pool, whirlpool and sauna with seasonal sundeck.

Kitty O'Sheas is an Irish pub with live entertainment. The 720 South Bar & Grill offers a menu inspired by fresh, local ingredients. Enjoy signature foods, locally crafted beers, cocktails and wine.

For more information please visit **www3.hilton.com**

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Clinical Management and Molecular Features of Low to Intermediate-grade Pineal Parenchymal Tumours

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Introduction

The pineal body is a small endocrine gland adjacent to the vertebrate thalamus that produces melatonin to modulate circadian rhythms.[1,2] Tumours affecting the pineal gland account for approximately 0.5% of all intracranial malignancies and primary pineal parenchymal tumours are even less frequent.[3,4] The pineal gland can give rise to a heterogeneous group of neoplasms including pineal parenchymal tumours, germ cell tumours, astrocytomas, ependymomas and papillary pineal tumours.[5-7] The World Health Organization classifies pineal parenchymal tumours into pineocytomas (grade I), pineal parenchymal tumours of intermediate differentiation (PPTID; grade II and grade III), and malignant grade IV lesions known as pineoblastomas.[8,9] Pineocytomas and pineoblastomas each account for approximately 45% of pineal parenchymal tumours, while PPTID makes up the remaining 10%.[1,10] Classically, pineoblastomas arise in pediatric patients and young adults, whereas low-grade pineocytomas typically occur later in life.[11,12] Unlike glial tumours, which have been extensively documented to progress from low- to high-grade lesions, data for histologic progression of pineal tumours is limited to two case reports of tumour recurrence and transformation to pineoblastoma after surgical resection.[13-16]

Along the spectrum of pineal parenchymal tumours, pineocytomas are associated with the most favorable prognosis and rarely disseminate to the leptomeninges.[17,18] As such, 5-year survival exceeds 90% following gross total resection of pineocytoma.[17,19] Surgery is essential for all pineal region tumours, not only to obtain a tissue diagnosis, but also for symptomatic alleviation and restoration of cerebrospinal fluid flow through the third ventricle.[20] Early experience with open surgical treatment was associated with a 30-70% combined risk of morbidity and mortality, and has therefore given way to endoscopic third ventriculostomy.[21,22] Although pineoblastoma also requires tissue biopsy for diagnosis, the high propensity for recurrence and neuraxial spread mandates aggressive adjuvant craniospinal irradiation and multi-drug chemotherapy.

With histologic features that are characteristic of both pineocytoma and pineoblastoma, PPTID is a morphologically heterogeneous lesion. Retrospective data suggest that pineocytoma is more indolent than grade II PPTID, which is in turn less aggressive than grade III PPTID or pineoblastoma. However, treatment strategies and the prognosis of intermediate-grade pineal parenchymal tumours remain controversial. Given the intrinsic morbidities of craniospinal irradiation and chemotherapy, escalation of therapy for pineal region tumours is not without significant risk, and should only be undertaken when absolutely necessary. Here we review the literature pertaining to low- and intermediate-grade pineal parenchymal tumours in an effort to characterise the clinical and molecular features that necessitate the addition of adjuvant therapy to surgical resection.

Presentation and Diagnosis

The initial clinical manifestations of pineal tumours are heterogeneous and dependent on the extent of disease.

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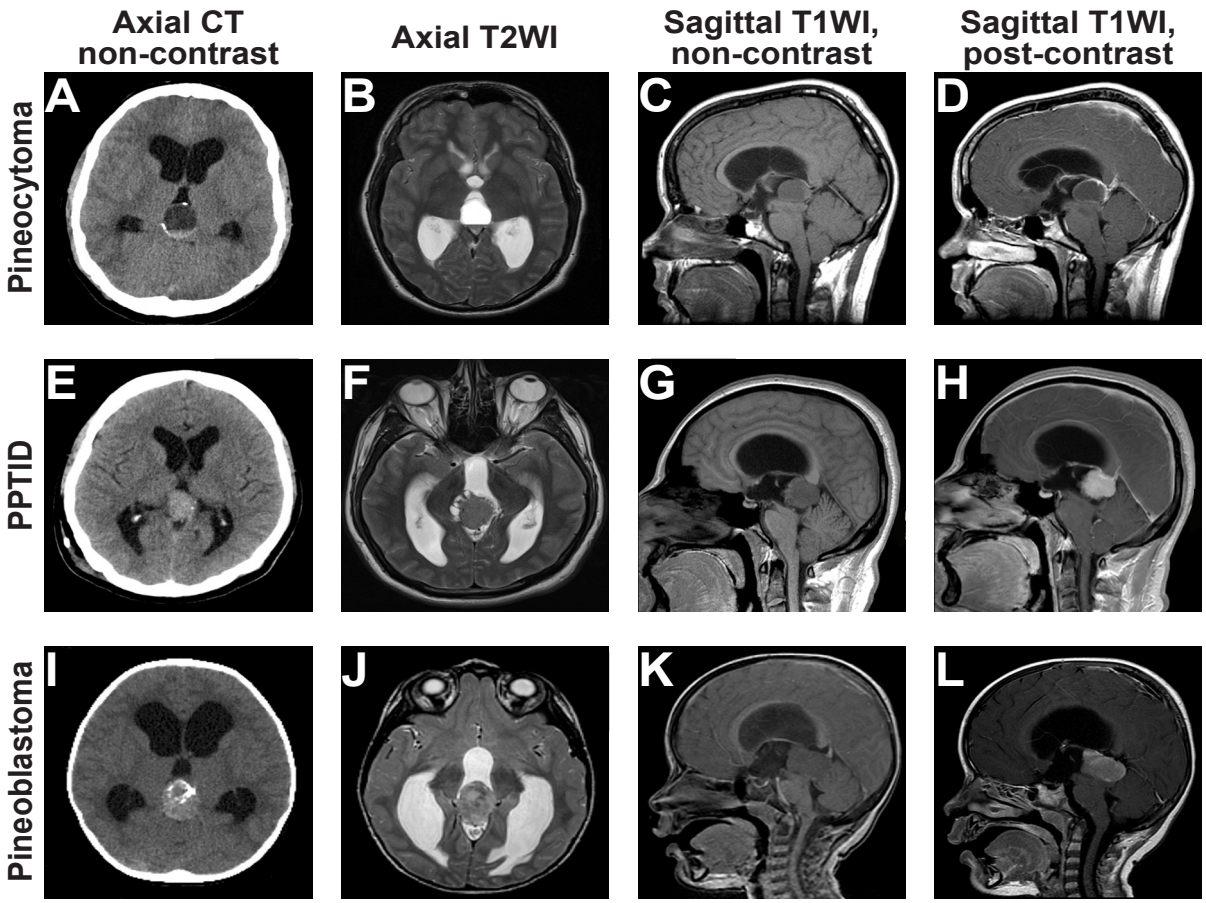

Figure 1. Radiographic characteristics of pineal parenchymal tumours. Computer tomography (CT) and magnetic resonance images (MRI) of pineocytoma (A-D), pineal parenchymal tumour of intermediate differentiation (PPTID, E-H), and pineoblastoma (I-L). Low-grade lesions are typically well circumscribed (C, D), while high-grade lesions may show evidence of local invasion (K, L). Although radiographic characteristics are non-specific for tumour grade, notable findings include cystic foci (B), peripheral "exploding" calcifications (I, E), and heterogeneous enhancement after injection of contrast (H, L).

Neurological dysfunction typically occurs as a result of increased intracranial pressure (ICP) due to interruption of cerebrospinal fluid (CSF) flow through the third ventricle. The most common presenting symptoms of pineal region tumours include headache (73%), ophthalmologic disturbance (47%), nausea/vomiting (40%), and gait disturbances (37%).[23] Clinical signs include papilledema (60%), ataxia (50%), upward gaze palsy (30%), tremor (20%), and altered pupillary reflexes (17%). Parinaud's syndrome, characterised by simultaneous vertical gaze abnormalities, nystagmus, and impaired convergence, may result from tectal compression.[24] Pineal tumours affecting suprasellar structures generally have an indolent course, with symptoms developing over months to years.[25-28]

All patients suspected of having pineal region tumours should receive a baseline ophthalmologic exam and CSF cytology via lumbar puncture after the risk of increased ICP is assessed. Although primary pineal parenchymal tumours are not associated with any specific biomarkers, the levels of beta human chorionic gonadotropin (β-hCG), alpha-fetoprotein (AFP), alkaline phosphatase, and lactate dehydrogenase may help differentiate between other pineal region malignancies. Increased levels of β-hCG and AFP are characteristic of embryonal carcinoma, whereas an isolated increase in AFP is common with endodermal sinus tumour, and isolated β-hCG elevation is found in choriocarcinoma. Germinomas may present with modest elevations of β-hCG, along with increased placental alkaline phosphatase and/or lactate dehydrogenase.[25] Finally, β-hCG >50 IU/L and/or an AFP >25 ng/ml in the presence of a midline mass is indicative of nongerminomatous germ cell tumour.[29] Patients with pineal region tumours may also show decreased variation in 24-hour melatonin levels.[30] Post-operatively, serum melatonin levels can be used to assess the extent of resection, with residual melatonin suggesting subtotal pinealectomy.[31] Finally, exogenous administration of melatonin may help to prevent disruption of sleep-wake cycles and the onset of post-pinealectomy syndrome.[32,33]

Initial workup of suspected pineal tumours should include a contrast-enhanced magnetic resonance image (MRI) of the brain and spine. Although there are no radiographic findings that are pathognomonic for pineal parenchymal tumours, low- and high-grade lesions are usually distinct. Pineocytomas typically appear

as small well-circumscribed lesions (see Figure 1A-D), whereas pineoblastomas are more frequently found to have internal hemorrhage, necrosis, local invasion, and neuraxial dissemination (see Figure 1I-L). On the other hand, differentiating PPTID from pineoblastoma is much more difficult at imaging. On computed tomography (CT), PPTID often appears as a hyperdense pineal mass with peripheral "exploding calcifications" that can be found in all grades of pineal parenchymal tumours (see Figure 1E, 1I).[34] Much like pineoblastomas, PPTID is heterogeneously iso- and hypointense on magnetic resonance (MR) T1 weighted images, and isointense on T2 sequences with cystic foci and heterogeneous enhancement (see Figure 1F-H). Attempts at discerning PPTID from pineoblastoma rely on assessing the number and degree of aggressive features, which can be quite subjective at times. Treatment decisions should therefore not be made without a tissue diagnosis.

Prognosis

Given the relative rarity of pineal parenchymal tumours, clinical outcome data are entirely limited to retrospective case series. One of the largest reports stratified by contemporary pathologic criteria compiled data from 12 European centers from 1972 to 1997 and demonstrated 5-year survival of 91%, 74%, 39%, and 10% for grade I through IV tumours, respectively.[19] Regarding patterns of relapse, 26%, 56% and 73% of grade II through IV tumours, respectively, recurred either locally or within the craniospinal axis, while no pineocytomas recurred. Mean time to progression after initial treatment was 5 years, 1.3 years, and 0.7 years for grade II though IV lesions, respectively, and the majority of patients with grade III and IV lesions recurred outside of the pineal gland. When accounting for all 76 patients retrospectively analyzed (19 patients with pineocytoma, 28 with PPTID, and 29 with pineoblastoma), tumour diameter less than 2.5 cm and low-grade histology were independent predictors of positive outcomes. Perhaps due to the pediatric predominance of pineoblastoma, age less than 20 was associated with a negative outcome on univariate analysis. With respect to the impact of the extent of surgery, resection reduces the rate of progression relative to biopsy alone, and a systematic review of the literature including 168 pineocytoma patients from 64 studies demonstrated that 5-year overall survival decreased precipitously in those receiving subtotal resection followed by radiotherapy (17%) versus gross total resection (88%).[35,36]

Outcomes data are even more limited for PPTID, which was first classified as a distinct entity by the WHO in 2007. A number of small, retrospective case series specifically focusing on PPTID have been published, but many of these consist of less than 10 subjects.[37,38] Some patients in those reports presented with localised disease, while others were found to have neuraxial dissemination. As such, PPTID patients are typically treated with surgery variably followed by adjuvant chemotherapy and/or radiation. The extent of radiotherapy in these patients ranges from stereotactic radiosurgery for residual local disease, to treatment of the entire craniospinal axis. With optimal management, 5-year overall survival from PPTID can approach 80%.[39] A retrospective, multi-institutional review including 37 patients with PPTID identified extent of disease, histologic differentiation, and response to adjuvant treatment as independent prognostic factors specific to intermediate- and high-grade pineal parenchymal tumours. In particular, residual primary tumour size after treatment was found to significantly influence median survival, and control of neuraxial metastases was more successful in patients with PPTID than in those with pineoblastoma. As is the case with low-grade pineal parenchymal tumours, local control for intermediate- and high-grade lesions is improved in older patients, but the age threshold is approximately 32-36 years.[39,40]

Molecular and Genetic Characteristics

Histologically, pineocytomas are composed of cells that closely resemble mature pineocytes. Consistently, chromosomal changes are rare in low-grade pineal parenchymal tumours, which typically show extensive neuronal differentiation.[41-43] MIB-1 labeling index correlates with histologic grade of pineal parenchymal tumours, although the prognostic significance p53 and neuronal markers expression, including neurofilament protein (NF), neuronal nuclear antigen (NeuN), and synaptophysin, is controversial.[12,42,44-47]

Microarray analysis demonstrates that pineocytomas are enriched in transcripts important for photo-transduction and melatonin synthesis, none of which are known to have oncogenic properties.[48] Although intermediate- and high-grade lesions have more chromosomal changes than pineocytomas, potentially leading to aberrant expression of growth factor receptors and transcription factors, there have been no unbiased analyses for differential genomic or molecular characteristics among pineal parenchymal tumours.[42,49] An individual patient data meta-analysis of DNA copy number in 15 pineal-region primitive neuroectodermal tumours (PNETs) demonstrated variable chromosomal gains and losses in low-grade tumours.[50] Interestingly, the pattern of genomic imbalances in pineoblastoma was unrelated to changes observed in low-grade tumours, and multivariate analysis demonstrated that tumour histology, age, and minimal copy number complexity were all favorable prognostic factors. In sum, the molecular and/or genetic mediators of pineal parenchymal tumours remain elusive, and the prognostic significance of immunohistochemical markers other than MIB-1 remains in debate.

Chemotherapy

Systemic therapy is often employed for disseminated or relapsed pineal parenchymal tumours, but there is no consensus regimen

for either PPTID or pineoblastoma. Rather, the majority of chemotherapy agents employed for unfavorable intermediate- and high-grade pineal parenchymal tumours are known to have efficacy in children with diverse central nervous system PNETs and low-grade gliomas.[51-53] Due to the relative rarity of pineal parenchymal tumours, patients in need of systemic therapy are often incorporated into broad central nervous systemic malignancy trials. However, the performance of specific individuals with pineal region tumours in these studies has been reported, and can inform therapeutic decisions.[54] Chemotherapeutic regimens employed in these studies included either ifosfamide, etoposid, high-dose methotrexate, cisplatin, and cytarabin, or vincristine, lomustine, and carboplatin, both of which were combined with craniospinal irradiation. Risk-adapted dose-reduction of craniospinal irradiation followed by high-dose chemotherapy and stem cell rescue has also been explored, and has demonstrated promising preliminary results.[55]

Radiotherapy and Radiosurgery

Fractionated radiotherapy is used to treat pineal parenchymal tumours (i) when the extent of residual local disease exceeds the volume threshold for radiosurgery; (ii) if there is evidence of dissemination along the craniospinal axis; (iii) or as a prophylactic measure for unfavorable intermediate- or high-grade tumours.[56] The pineal region with a minimal margin is often treated to a total dose of 50.4-54 Gy in 28-30 fractions for residual local disease, and total dose >50 Gy is associated with improved survival in pineoblastoma patients.[57] Furthermore, whole brain or whole ventricular radiation may be combined with treatment of the entire spinal cord up to 23.4-36 Gy in 13-20 fractions if there is evidence of neuraxial spread.

Although aggregate data from the literature may indicate otherwise, numerous retrospective case series have shown near-universal control of subtotally-resected low-grade pineal parenchymal tumours treated with adjuvant radiosurgery.[35,58-62] These series employed a range of prescriptions to treat tumours of a variety of sizes, but the body of evidence suggests that a median marginal dose of 14-20 Gy prescribed to the 50% isodose line is sufficient for long-term tumour control. Specifically, 5-year local control and overall survival from pineocytoma after radiosurgery is 85-100% and >90%, respectively.[63] Radiosurgery has similarly been associated with high rates of local control for intermediate- and high-grade pineal parenchymal tumour patients, but does not appear to lessen the propensity of these lesions to fail distantly within the neuraxis.[59-63] Finally, stereotactic implantation of 125I has been employed as both a primary and salvage treatment for pineal parenchymal tumour with excellent results, but this technique is less common than either radiosurgery or fractionated radiotherapy.[64]

References

1. Leemans CR, Braakhuis BJM, Brakenhoff RH: The molecular biology of head and neck cancer. Nat Rev Cancer 2011, 11:9–22.
2. Macchi MM, Bruce JN: Human pineal physiology and functional significance of melatonin. Front Neuroendocrinol 2004, 25:177–195.
3. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML: Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. N Engl J Med 2010, 363:24–35.
4. Surawicz TS, McCarthy BJ, Kupelian V, Jukich PJ, Bruner JM, Davis FG: Descriptive epidemiology of primary brain and CNS tumors: results from the Central Brain Tumor Registry of the United States, 1990-1994. Neuro-oncology 1999, 1:14–25.
5. Adelstein DJ, Li Y, Adams GL, Wagner H, Kish JA, Ensley JF, Schuller DE, Forastiere AA: An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003, 21:92–98.
6. Han SJ, Clark AJ, Ivan ME, Parsa AT, Perry A: Pathology of pineal parenchymal tumors. Neurosurg Clin N Am 2011, 22:335–40– vii.
7. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Calais G: Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004, 22:69–76.
8. Braakhuis BJM, Snijders PJF, Keune W-JH, Meijer CJLM, Ruijter-Schippers HJ, Leemans CR, Brakenhoff RH: Genetic patterns in head and neck cancers that contain or lack transcriptionally active human papillomavirus. J Natl Cancer Inst 2004, 96:998–1006.
9. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P: The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007, 114:97–109.
10. Hirato J, Nakazato Y: Pathology of pineal region tumors. J Neurooncol 2001, 54:239–249.
11. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, Jones CU, Sur R, Raben D, Jassem J, Ove R, Kies MS, Baselga J, Youssoufian H, Amellal N, Rowinsky EK, Ang KK: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006, 354:567–578.
12. Mena H, Rushing EJ, Ribas JL, Delahunt B, McCarthy WF: Tumors of pineal parenchymal cells: a correlation of histological features, including nucleolar organizer regions, with survival in 35 cases. Hum Pathol 1995, 26:20–30.
13. Kalyankrishna S, Grandis JR: Epidermal growth factor receptor biology in head and neck cancer. Journal of Clinical Oncology 2006, 24:2666–2672.
14. Howard BM, Hofstetter C, Wagner PL, Muskin ET, Lavi E, Boockvar JA: Transformation of a low-grade pineal parenchymal tumour to secondary pineoblastoma. Neuropathol Appl Neurobiol 2009, 35:214–217.
15. Ang KK, Berkey BA, Tu X, Zhang H-Z, Katz R, Hammond EH, Fu KK, Milas L: Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res 2002, 62:7350–7356.
16. Kim BS, Kim DK, Park S-H: Pineal parenchymal tumor of intermediate differentiation showing malignant progression at relapse. Neuropathology 2009, 29:602–608.
17. Schramek D, Sendoel A, Segal JP, Beronja S, Heller E, Oristian D, Reva B, Fuchs E: Direct in vivo RNAi screen unveils myosin IIa as a tumor suppressor of squamous cell carcinomas. Science 2014, 343:309–313.
18. Gomez C, Wu J, Pope W, Vinters H, Desalles A, Selch M: Pineocytoma with diffuse dissemination to the leptomeninges. Rare Tumors 2011, 3:e53.
19. Fauchon F, Jouvet A, Paquis P, Saint-Pierre G, Mottolese C, Ben Hassel M, Chauveinc L, Sichez JP, Philippon J, Schlienger M, Bouffet E: Parenchymal pineal tumors: a clinicopathological study of 76 cases. Radiation Oncology Biology 2000, 46:959–968.
20. Deshmukh VR, Smith KA, Rekate HL, Coons S, Spetzler RF: Diagnosis and management of pineocytomas. Neurosurgery 2004, 55:349–55– discussion 355–7.
21. Pecker J, Scarabin JM, Vallee B, Brucher JM: Treatment in tumours of the pineal region: value of sterotaxic biopsy. Surg Neurol 1979, 12:341–348.
22. Poppen JL, Marino R: Pinealomas and tumors of the posterior portion of the third ventricle. J Neurosurg 1968, 28:357–364.
23. Chang CG, Kageyama N, Kobayashi T, Yoshida J, Negoro M: Pineal Tumors: clinical diagnosis, with special emphasis on the significance of pineal calcification. Neurosurgery 1981, 8:656–668.
24. Lee AG, Brazis PW: Clinical Pathways in Neuro-Ophthalmology: an Evidence-Based Approach. New York: Thieme; 1998.
25. Allen JC: Management of primary intracranial germ cell tumors of childhood. Pediatr Neurosci 1987, 13:152–157.
26. Allen JC, Bruce J, Kun LE, Langford LA: Pineal Region Tumors. In Pineal Region Tumors. Edited by Levin VA. New York: Churchill-Livingstone; 1996:171–185.
27. Franzese A, Buongiovanni C, Belfiore G, Moggio G, Valerio G, Ciccarelli NP, Di Maio S: Pineal cyst in a girl with central precocious puberty. Clinical pediatrics 1997, 36:543–545.
28. Dickerman RD, Stevens QE, Steide JA, Schneider SJ: Precocious puberty associated with a pineal cyst: is it disinhibition of the hypothalamic-pituitary axis? Neuro endocrinology letters 2004, 25:173–175.
29. Calaminus G, Andreussi L, Garrè ML, Kortmann RD, Schober R, Gobel U: Secreting germ cell tumors of the central nervous system (CNS). First results of the cooperative German/Italian pilot study (CNS sGCT). Klinische Padiatrie 1997, 209:222–227.
30. Leston J, Mottolese C, Champier J, Jouvet A, Brun J, Sindou M, Chazot G, Claustrat B, Fèvre Montange M: Contribution of the daily melatonin profile to diagnosis of tumors of the pineal region. J Neurooncol 2009, 93:387–394.
31. Vorkapic P, Waldhauser F, Bruckner R, Biegelmayer C, Schmidbauer M, Pendl G: Serum melatonin levels: a new neurodiagnostic tool in pineal region tumors? Neurosurgery 1987, 21:817–824.
32. Kocher L, Brun J, Borson-Chazot F, Gonnaud PM, Claustrat B: Increased REM sleep associated with melatonin deficiency after pinealectomy: a case study. Chronobiology international 2006, 23:889–901.
33. Chazot G, Claustrat B, Broussolle E, Lapras C: Headache and Depression: Recurrent Symptoms in Adult Pinealectomized Patient. In Headache and Depression. Edited by G N, G B, G S, E M, G M. New York: Raven Press; 1991:229–303.
34. Komakula S, Warmuth-Metz M, Hildenbrand P, Loevner L, Hewlett R, Salzman K, Couldwell W, Lin C-T, Osborn A: Pineal parenchymal tumor of intermediate differentiation: imaging spectrum of an unusual tumor in 11 cases. Neuroradiology 2011, 53:577–584.
35. Clark AJ, Sughrue ME, Ivan ME, Aranda D, Rutkowski MJ, Kane AJ, Chang S, Parsa AT: Factors influencing overall survival rates for patients with pineocytoma. J Neurooncol 2010, 100:255–260.
36. Clark AJ, Sughrue ME, Aranda D, Parsa AT: Contemporary management of pineocytoma. Neurosurg Clin N Am 2011, 22:403–7– ix.
37. Ito T, Kanno H, Sato K-I, Oikawa M, Ozaki Y, Nakamura H, Terasaka S, Kobayashi H, Houkin K, Hatanaka K, Murata J-I, Tanaka S: Clinicopathologic Study of Pineal Parenchymal Tumors of Intermediate Differentiation. World Neurosurg 2014, 81:783–789.
38. Watanabe T, Mizowaki T, Arakawa Y, Iizuka Y, Ogura K, Sakanaka K, Miyamoto S, Hiraoka M: Pineal parenchymal tumor of intermediate differentiation: Treatment outcomes of five cases. Mol Clin Oncol 2014, 2:197–202.
39. Lutterbach J, Fauchon F, Schild SE, Chang SM, Pagenstecher A, Volk B, Ostertag C, Momm F, Jouvet A: Malignant pineal parenchymal tumors in adult patients: patterns of care and prognostic factors. Neurosurgery 2002, 51:44–55– discussion 55–6.
40. Villa S, Miller RC, Krengli M, Abusaris H, Baumert BG, Servagi-Vernat S, Igdem S, Lucas A, Boluda S, Mirimanoff RO: Primary pineal tumors: outcome and prognostic factors--a study from the Rare Cancer Network (RCN). Clin Transl Oncol 2012, 14:827–834.
41. Fevre-Montange M, Szathmari A, Champier J, Mokhtari K, Chrétien F, Coulon A, Figarella-Branger D, Polivka M, Varlet P, Uro-Coste E, Fauchon F, Jouvet A: Pineocytoma and pineal parenchymal tumors of intermediate differentiation presenting cytologic pleomorphism: a multicenter study. Brain Pathol 2008, 18:354–359.
42. Rickert CH, Simon R, Bergmann M, Dockhorn-Dworniczak B, Paulus W: Comparative genomic hybridization in pineal parenchymal tumors. Genes Chromosomes Cancer 2001, 30:99–104.
43. Jouvet A, Fèvre Montange M, Besançon R, Derrington E, Saint-Pierre G, Belin MF, Pialat J, Lapras C: Structural and ultrastructural characteristics of human pineal gland, and pineal parenchymal tumors. Acta Neuropathol 1994, 88:334–348.
44. Kanno H, Nishihara H, Oikawa M, Ozaki Y, Murata J, Sawamura Y, Kato M, Kubota K, Tanino M, Kimura T, Nagashima K, Itoh T, Tanaka S: Expression of O^6-methylguanine DNA methyltransferase (MGMT) and immunohistochemical analysis of 12 pineal parenchymal tumors. Neuropathology 2012, 32:647–653.
45. Numoto RT: Pineal parenchymal tumors: cell differentiation and prognosis. J Cancer Res Clin Oncol 1994, 120:683–690.
46. Tsumanuma I, Tanaka R, Washiyama K: Clinicopathological study of pineal parenchymal tumors: correlation between histopathological features, proliferative potential, and prognosis. Brain Tumor Pathol 1999, 16:61–68.
47. Tsumanuma I, Sato M, Okazaki H, Tanaka R, Washiyama K, Kawasaki T, Kumanishi T: The analysis of p53 tumor suppressor gene in pineal parenchymal tumors. Noshuyo Byori 1995, 12:39–43.
48. Fevre-Montange M, Champier J, Szathmari A, Wierinckx A, Mottolese C, Guyotat J, Figarella-Branger D, Jouvet A, Lachuer J: Microarray analysis reveals differential gene expression patterns in tumors of the pineal region. J Neuropathol Exp Neurol 2006, 65:675–684.
49. Li G, Mitra S, Karamchandani J, Edwards MSB, Wong AJ: Pineal parenchymal tumor of intermediate differentiation: clinicopathological

report and analysis of epidermal growth factor receptor variant III expression. Neurosurgery 2010, 66:963–8– discussion 968.
50. Bueren von AO, Gerss J, Hagel C, Cai H, Remke M, Hasselblatt M, Feuerstein BG, Pernet S, Delattre O, Korshunov A, Rutkowski S, Pfister SM, Baudis M: DNA copy number alterations in central primitive neuroectodermal tumors and tumors of the pineal region: an international individual patient data meta-analysis. J Neurooncol 2012, 109:415–423.
51. Packer RJ, Lange B, Ater J, Nicholson HS, Allen J, Walker R, Prados M, Jakacki R, Reaman G, Needles MN: Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. J Clin Oncol 1993, 11:850–856.
52. Packer RJ, Sutton LN, Elterman R, Lange B, Goldwein J, Nicholson HS, Mulne L, Boyett J, D'Angio G, Wechsler-Jentzsch K: Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. J Neurosurg 1994, 81:690–698.
53. Kurisaka M, Arisawa M, Mori T, Sakamoto T, Seike M, Mori K, Okada T, Wakiguchi H, Kurashige T: Combination chemotherapy (cisplatin, vinblastin) and low-dose irradiation in the treatment of pineal parenchymal cell tumors. Childs Nerv Syst 1998, 14:564–569.
54. Hinkes BG, Hoff von K, Deinlein F, Warmuth-Metz M, Soerensen N, Timmermann B, Mittler U, Urban C, Bode U, Pietsch T, Schlegel PG, Kortmann RD, Kuehl J, Rutkowski S: Childhood pineoblastoma: experiences from the prospective multicenter trials HIT-SKK87, HIT-SKK92 and HIT91. J Neurooncol 2007, 81:217–223.
55. Chintagumpala M, Hassall T, Palmer S, Ashley D, Wallace D, Kasow K, Merchant TE, Krasin MJ, Dauser R, Boop F, Krance R, Woo S, Cheuk R, Lau C, Gilbertson R, Gajjar A: A pilot study of risk-adapted radiotherapy and chemotherapy in patients with supratentorial PNET. Neuro-oncology 2009, 11:33–40.
56. Stoiber EM, Schaible B, Herfarth K, Schulz-Ertner D, Huber PE, Debus J, Oertel S: Long term outcome of adolescent and adult patients with pineal parenchymal tumors treated with fractionated radiotherapy between 1982 and 2003--a single institution's experience. Radiat Oncol 2010, 5:122.
57. Schild SE, Scheithauer BW, Haddock MG, Wong WW, Lyons MK, Marks LB, Norman MG, Burger PC: Histologically confirmed pineal tumors and other germ cell tumors of the brain. Cancer 1996, 78:2564–2571.
58. Wilson DA, Awad A-W, Brachman D, Coons SW, McBride H, Youssef E, Nakaji P, Shetter AG, Smith KA, Spetzler RF, Sanai N: Long-term radiosurgical control of subtotally resected adult pineocytomas. J Neurosurg 2012, 117:212–217.
59. Reyns N, Hayashi M, Chinot O, Manera L, Péragut J-C, Blond S, Régis J: The role of Gamma Knife radiosurgery in the treatment of pineal parenchymal tumours. Acta Neurochir (Wien) 2006, 148:5–11– discussion 11.
60. Hasegawa T, McInerney J, Kondziolka D, Lee JYK, Flickinger JC, Lunsford LD: Long-term results after stereotactic radiosurgery for patients with cavernous malformations. Neurosurgery 2002, 50:1190–7– discussion 1197–8.
61. Mori Y, Kobayashi T, Hasegawa T, Yoshida K, Kida Y: Stereotactic radiosurgery for pineal and related tumors. Prog Neurol Surg 2009, 23:106–118.
62. Kano H, Niranjan A, Kondziolka D, Flickinger JC, Lunsford D: Role of stereotactic radiosurgery in the management of pineal parenchymal tumors. Prog Neurol Surg 2009, 23:44–58.
63. Hanft SJ, Isaacson SR, Bruce JN: Stereotactic radiosurgery for pineal region tumors. Neurosurg Clin N Am 2011, 22:413–20– ix.
64. Maarouf M, Majdoub El F, Bührle C, Voges J, Lehrke R, Kocher M, Hunsche S, Treuer H, Sturm V: Pineal parenchymal tumors. Management with interstitial iodine-125 radiosurgery. Strahlenther Onkol 2010, 186:127–134.

Trovax in Renal Cell Cancer

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Renal Cell Cancer

Renal cell cancer (RCC) presents a therapeutic challenge to oncologists.[1] The treatment of metastatic RCC centers around molecular targeted agents such as monoclonal antibodies (e.g., bevacizumab), tyrosine kinase inhibitors (e.g., sunitinib, sorafenib, pazopanib, and axitnib), and mammalian target of rapamycin (e.g., temsirolimus and everolimus). The immunogenic nature of this tumour type was established by the development of interleukin (IL)–2 and interferon (IFN)–α as active agents, in addition to the occurrence of spontaneous regression following primary nephrectomy.[2] Despite these advances, there is still a need to identify new therapeutic agents that may be combined with current treatments to improve overall survival.

5T4 Oncofetal Antigen

5T4, an identified tumour-associated antigen, is an attractive therapeutic target in renal and other adenocarcinomas. In RCC, a study demonstrated that 5T4 was expressed at high levels and, importantly, was retained in metastatic tissue, validating 5T4 as a target for immunotherapeutic intervention.[2] The attenuated vaccinia virus modified vaccinia Ankara has been engineered to deliver the tumor antigen 5T4 (MVA-5 T4; Trovax®).[1,2] Importantly, 5T4 is expressed on the cell surface, which makes it a potential target for both T cell– and antibody-mediated effector responses.

Trovax® Vaccine

Trovax® has been evaluated in multiple phase 1, 2, and 3 studies in colorectal, prostate, and RCC patients. We will review the role of Trovax® in RCC.

Trovax® Clinical Trials

Phase 1 Trials

Phase 1/2 trials in RCC, prostate cancer, and colorectal cancer demonstrated that MVA-5T4 is safe.[3] Higher 5T4-specific antibody levels were higher at baseline than in healthy control subjects, and these levels increased further after treatment with MVA-5T4.[4] An early, robust antibody response to 5T4 after Trovax® therapy was associated with enhanced survival, although the result was not statistically significant in patients with RCC.[4]

Phase 2 Trials

In the phase 2 trial of Trovax® plus IFN-α, 13 received Trovax® alone and 15 patients received the combination. Nearly all (22/23) patients mounted 5T4-specific immune responses, with slightly higher (but statistically nonsignificant) responses in those receiving Trovax® plus IFN-α. One patient (who received the combination) had a partial response lasting >7 months. Another 14 patients (7 in each group) had disease stabilisation, and greater immune responses were associated with longer survival (P=0.01 for overall survival but nonsignificant for progression-free survival).[5]

A phase 2 study reported on Trovax® coadministered with low-dose IL-2 (250,000 U/kg or 125,000 U/kg). Most patients (21/25) mounted 5T4-specific immune responses, including all 11 patients who received ≥4 doses of Trovax®. This study found a survival benefit associated with the combination: 3 patients had objective tumour responses (2 complete and 1 partial), and 6 patients had stable disease lasting at least 6 months. Moreover, patients mounting the highest antibody titers had longer progression-free and overall survival than patients with lower antibody titers.[6]

In a study of high-dose IL-2 (600,000 U/kg) with Trovax® given to 25 patients with metastatic RCC, all patients developed 5T4-specific antibodies, and half of them had increased 5T4-specific T cell responses. Most of the patients with elevated T cell responses were those who had stable (not progressive) disease. However, despite these encouraging immune indicators, there was no improvement in objective response rates.[7]

TRIST Study

Given the results of these studies, the phase 3 Trovax® Renal Immunotherapy Survival Trial (TRIST) was conducted in which

Trovax® was added to standard-of-care therapy for RCC.[8] In this multi-institutional trial, 733 patients received standard of care therapy with sunitinib, IL-2, or IFN-α, of which 365 patients received one of these therapies plus Trovax® added to their regimen. Overall, no difference was found in overall survival between the groups. Because no survival benefit was seen after 6 months, the trial was stopped, but patient follow-up continued. This extended follow-up suggested that a small number of patients had a positive response to Trovax®. This prompted the investigators to conduct an exploratory multivariate analysis, in which they found (similar to the previous studies)[6,7]that patients with the highest antibody titers had slightly improved (though not statistically significant) survival.[8] However, the multivariate analysis also uncovered a drawback of the study: more patients with a favorable prognosis were in the placebo arm than in the Trovax® arm.

Prognostic Factors Associated with Outcomes in Trovax® Therapy

The clinical responses associated with higher immune responses in some patients prompted several studies to identify the prognostic markers associated with increased benefit. The investigators of the phase 3 trial[9] conducted an analysis of their data. They constructed an index composed of pre-treatment 5T4 antibody levels, hemoglobin, and hematocrit and applied this index to the phase 3 data. They found that this index was a significant predictor of treatment benefit – a higher value was associated with longer survival.[9,10] Additional analysis of the same data set found a number of factors associated with deriving a benefit from treatment with Trovax®: smaller tumor burden and normal hemoglobin concentration.[11] Hemoglobin concentration in particular was associated with not only benefit in terms of survival but also with tumor shrinkage among this set of patients.[11]

This correlation prompted the researchers of the phase 2 studies to examine their data for prognostic markers. From univariate and multivariate analyses, they constructed a model that stratified RCC patients into three risk groups: favorable, intermediate, and poor, according to the number of risk factors each patient had. Risk factors included neutrophils, bone metastases, ECOG performance status, lactate dehydrogenase levels, prior therapy with tyrosine kinase inhibitors plus immunotherapy, Fuhrman grade, and 5T4-specific antibody response. Patients with favorable risk (those with 0 risk factors) had significantly longer overall and progression-free survival than those with intermediate (1-2 risk factors) or poor (>3 risk factors) risk. Median OS was censored by cutoff in patients in the favorable risk group; it was 13.7 months in those with intermediate risk and 4.0 months in those with poor risk.[12] This prognostic model indicates that patient selection may be critical in fully utilising the potential of Trovax® for RCC.

Summary

Although overall responses are less impressive, Trovax® shows strong, durable responses in a subset of patients. Patient selection should include lower tumor burden associated with favorable prognostic factors. Recent advances in the understanding of tumor immunology and the development of agents such as the checkpoint inhibitors PD-1 and CTL4 could increase the therapeutic benefit of Trovax®.

References

1. Elkord E, Shablak A, Stern PL, Hawkins RE. 5T4 as a target for immunotherapy in renal cell carcinoma. Exp Rev Anticancer Ther 2009;9:1705-1709
2. Griffiths RW, Gilham DE, Dangoor A, Ramani V, Clarke NW, Stern, PL, Hawkins RE. Expression of the 5T4 oncofoetal antigen in renal cell carcinoma: a potential target for T-cell-based immunotherapy. Br J Cancer 2005;93:670-677
3. Amato RJ. 5T4-modified vaccinia Ankara: progress in tumor-associated antigen-based immunotherapy. Exp Opin Drug Eval 2010;10:281-287
4. Harrop R, Shingler W, Kelleher M, de Belin J, Treasure P. Cross-trial analysis of immunologic and clinical data resulting from phase I and II trials of MVA-5T4 (TroVax) in colorectal, renal, and prostate cancer patients. J Immunother 2010;33:999-1005
5. Hawkins RE, Macdermott C, Shablak A, Hamer C, Thistlethwaite F, Drury NL, Chikoti P, Shingler W, Naylor S, Harrop R. Vaccination of patients with metastatic renal cancer with modified vaccinia Ankara encoding the tumor antigen 5T4 (TroVax) given alongside interferon-alpha. J Immunother 2009;32(4):424-429
6. Amato RJ, Shingler W, Naylor S, Jac J, Willis J, Saxena S, Hernandez-McClain J, Harrop R. Vaccination of renal cell cancer patients with modified vaccinia Ankara delivering the tumor antigen 5T4 (TroVax) alone or administered in combination with interleukin 2: a phase 2 trial. Clin Cancer Res 2008;14:7504-7510
7. Kaufman HL, Taback B, Sherman W, Kim DW, Shingler WH, Moroziewicz D, DeRaffele G, Mitcham J, Carroll MW, Harrop R, Naylor S, Kim-Schulze S. Phase II trial of modified vaccinia Ankara (MVA) virus expression 5T4 and high dose interleukin-2 (IL-2) in patients with metastatic renal cell carcinoma. J Transl Med 2009;7:2
8. Amato RJ, Hawkins RE, Kaufman HL, Thompson JA, Tomczak P, Szczylik C, McDonald M, Eastty S, Shingler WH, de Belin J, Goonewardena M, Naylor S, Harrop R. Vaccination of metastatic renal cancer patients with MVA-5T4: a randomized, double-blind, placebo-controlled phase III study. Cancer Ther 2010;16(22):5539-5547
9. Harrop R, Shingler WH, McDonald M, Treasure P, Amato RJ, Hawkins RE, Kaufman HL, de Belin J, Kelleher M, Goonewardena M, Naylor S. MVA-5T4-induced immune responses are an early marker of efficacy in renal cancer patients. Cancer Immunol Immunother 2011;60:829-837
10. Harrop R, Treasure P, de Belin J, Kelleher M, Bolton G, Naylor S, Shingler WH. Analysis of pre-treatment markers predictive of treatment benefit for the therapeutic cancer vaccine MVA-5T4 (TroVax). Cancer Immunol Immunother 2012;;61(12):2283-2294
11. Amato RJ, Xiong Y, Peng H, Mohlere V. Clinical outcomes model in renal cell cancer patients treated with modified vaccinia Ankara plus tumor-associated antigen 5T4. Int J Biol Markers 2014; in press

Gap Junctions, Proliferation, Invasion and Cancer

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Cancer is still among the most often causes of death with increasing incidence. Hanahan and Weinberg[1] formulated 6 "hallmarks" of cancer, which describe cancer cell biology: (1) self-sufficiency in growth signals; (2) unlimited replication; (3) insensitivity to anti-growth signals, (4) insensibility to apoptosis; (5) tumour-induced angiogenesis; and (6) tissue invasion/metastasis. Although much research has been carried out and the mechanisms leading to malignant transformation of cells are better understood, the mechanisms of invasion regarding the primary tumour and the metastases are still a matter of debate. In most normal cell culture systems cells stop growing when reaching confluence, which is called "contact inhibition". Similarly, in normal tissue cells do not proliferate over the borders of the organ, and mostly cell growth is limited to the frontiers of the functional unit they belong to. In malignant growth this behaviour seems to be disturbed and cells grow without respecting tissue borders. Thus, the "contact inhibition" seems to be lost, which could be among the first steps into invasive growth. This contact inhibition requires that cells recognise the neighboured cell and can exchange informations regarding growth, cell type etc. This means that the cells need to communicate. Information exchange can be achieved in various ways: (I) cells may secrete mediators which affect the neighboured cells; (II) cells may bear receptors on their surface (cell-cell recognition molecules; cadherins like E-cadherin) which allow to bind to respective receptors on the neighboured cell, and cells can interact with the extracellular matrix via integrines. These are surface receptors intracellularly linked to a broad signal transduction machinery, which comprises the focal adhesion kinase (FAK), paxillin, and talin, and moreover is also linked via vinculin and actin to the cytoskeleton. This complex is also involved in the formation of lamellipodia during migration; (III) as a third interaction mode, cells may communicate directly via gap junctions. Gap junction channels are low ohmic cell-to-cell channels connecting the two cytoplasms. These channels can be opened and closed via a variety of mechanisms including protein kinases (e.g. PKC), mitogen-activated protein kinases (MAPK), tyrosine kinases etc.[2] A gap junction channel consists of two hemichannels (connexons) provided by either of the two neighboured cells. Each connexon is a hexamer of connexin proteins, so that the complete channel comprises 12 connexins. A connexin is a 4 transmembrane protein with an intracellular N-terminal and and intracellular carboxy tail. This carboxy tail is the most variant part of the molecule. By the variation in length the molecular weight of the molecule varies. 21 isoforms in humans are presently known, which are named by their molecular weight. Thus, connexin 43 (Cx43), the most abundant connexin, is a connexin with 43 kDa. The connexon (hexamer) can be formed by only one isoform (homomeric) or can consist different isoforms (heteromeric). Moreover, the gap junction channel can be built from 2 identical connexons (homotypic) or different connexons (heterotypic). At least, gap junction channels can connect cells of the same type (homocellular coupling), or can also connect cells of various types (e.g. cardiomyocytes and fibroblasts) (heterocellular coupling). The connexins are synthetised in the

Franziska Schlegel graduated with a specialisation in biology and began her doctoral thesis in Leipzig at the Research Lab for Cardiothoracic surgery, Heart Centre Leipzig, Germany. Under the direction of Professor Stefan Dhein she investigated the engineered heart tissue technology in an in vivo model of heart failure in rats. Her work was honoured with the Award of ProCordis as "best publication" in 2013. In 2014 Franziska Schlegel received a scholarship of Federal Ministry of Education and Research pointed in translational medicine. She published 5 articles, over 30 abstracts and presented her work of national and international conferences.

Stefan Dhein started in 2001 as the head of the Research Lab at Clinic for Cardiothoracic surgery, Heart Centre Leipzig, Germany, and worked previously at the universities of Cologne and Halle. He and his work as specialist in Pharmacology and Toxicology and in Clinical Pharmacology are recognised throughout the world. Recently, the "Sebastian-Kneipp-Stifung" honoured his work with the Sebastian-Kneipp Award standing for his scientific publication providing new research contributions to phytopharmacological therapy in 2011. He published more than 180 full articles in international peer review journals, more than 25 atricles in books and textbooks. He is author of four books, e.g. "Cardiac Gap Junctions", Karger, Verlag, Basel, 1998.

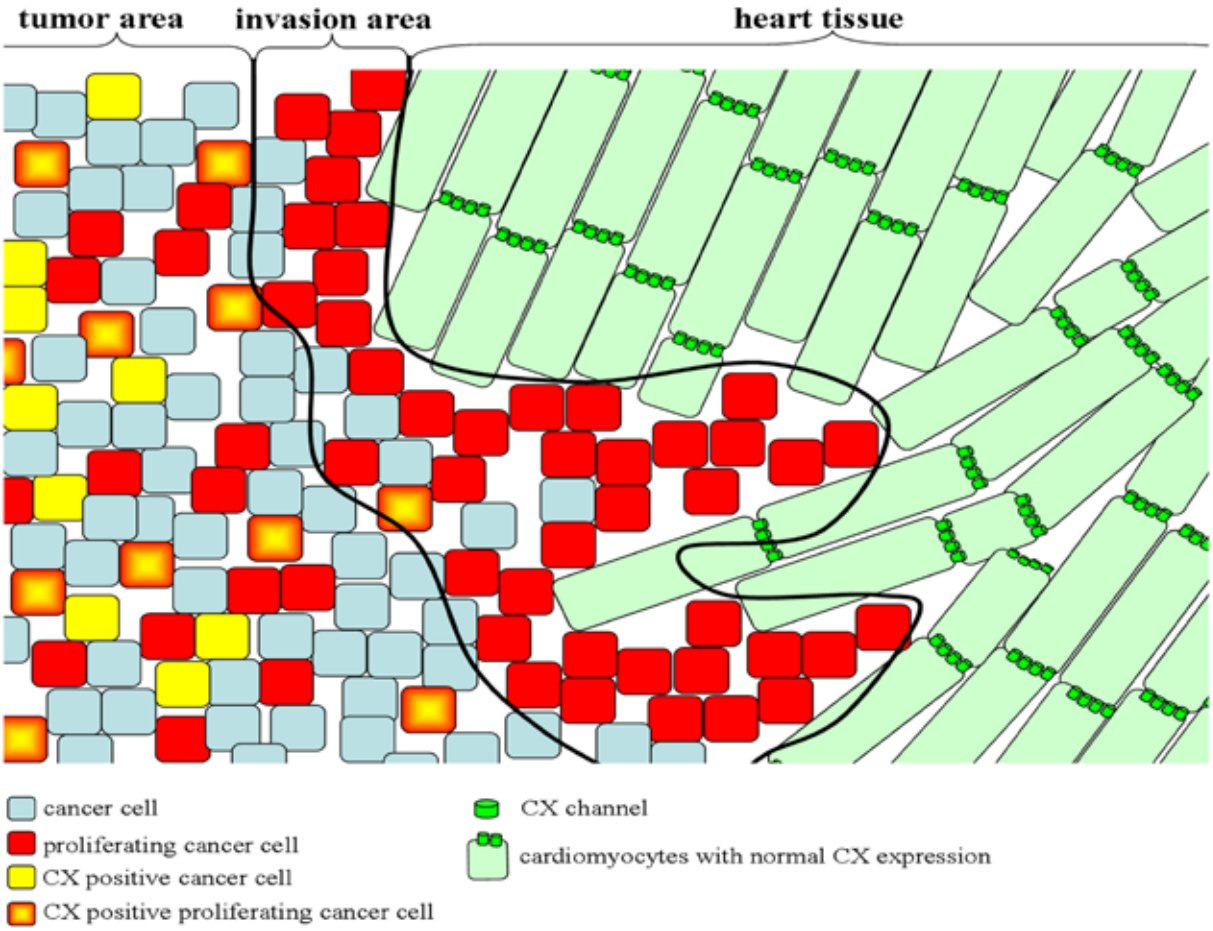

Figure 1. Schematic depiction of negative correlation between proliferating (ki-67 positive) and communicating (Cx positive) tumour cells in the invasion area, close to the heart tissue. In the invasion area we found malignant proliferating cells with nearly no Cx- expression that indicated a lost of communication in invasively growing tumour cells [according to reference 20] .

rough endoplasmic reticulum, transferred to the Golgi-apparatus where they are oligomerised to connexons, and then transported (probably via the tubulin apparatus) to the plasma membrane. There, they are thought to drift on lipid rafts, until they get contact to a gap junction plaque, where they form gap jucntion channels with the connexons of the neighboured cells under the help of cadherins and calcium. This channel then establishes a cytoplasma-to-cytoplasma low ohmic connection allowing electrical current to flow and enabling the exchange of small molecules (<1000 Da). The closure and opening of the channels, the incorporation into the membrane, and the degradation are regulated by phosphorylation processes mainly at the carboxy tail by a plethora of kinases.

Another aspect in the process of cancer is the formation of metastasis; in this process tumour cells must migrate from the tumour through the extracellular matrix, must break through a vessel wall and invade the vessel (intravasation). Then they circulate with the blood stream until they dock at a certain location again to the endothelium, trespass the vessel wall (extravasation), and finally form a new colony (colonisation). This process also requires communication between the cancer cells and at least the cells of the vessel wall.

Thus, the question arises which is the role of inter-cellular communication in the process of invasive growth and formation of metastasis. According to the considerations above, invasive growth could be associated with a loss of communication while the process of intra- and extravasation seems to require communication between the tumour cell and vascular wall cells, e.g. the vascular endothelium. In addition, a cancer cell must express and secrete proteases like metalloproteinases in order to be able to trespass the connective tissue. During migration a complex interplay and communication with the fibroblasts is required for further propagation. Moreover, a transition of the cell biology from a stationary cell to a migrating cell separated from the primary tumour (detachment) with all the changes in the cytoskeleton are required. In epithelial tumours this is typically called epithelial-to-mesenchymal-transition (EMT).[3] In the past these changes have been linked to the expression or non-expression of gap junction proteins. Unfortunately, the issue is rather complex, so that the role of the various connexin isoforms

in the cancer process are different and in some cases contrary.

During tissue invasion, cells typically express lower levels of cadherins so that the inter-cellular adhesion is lost. These cadherins are essential proteins of the adherens junctions. Intracellularly these cadherins are linked to catenins and thereby interact with the regulation of the cytoskeleton. Cadherin expression is positively associated with gap junction intercellular communication (GJIC). In epithelial tumours a cadherin switch from E-cadherin to N-cadherin during EMT has been described and seems associated with the loss of (detergent-resistant) gap junctional connexin-43, which is internalised by a endocytotic process.

Whether cell-matrix interactions via integrins can affect GJIC is still unclear. In keratinocytes, binding of α3β1 integrin to laminin-5 can enhance GJIC via involvement of Rho.[4] The interaction between integrins, GJIC and invasion however are incompletely understood. While in breast cancer cells Cx26 over-expression can reduce the invasive growth,[5] in prostate cancer cells Cx26 is associated with invasion.[6]

Moreover, gap junction proteins seem to be involved in the proteolytic activity of invading tumour cells: the urokinase-type plasminogen activator (uPA) system typically is induced by hypoxia-induced factor HIF1-α. Hypoxia is typical for the central parts of a tumour, and this mechanism would enable cells to migrate. Moreover, HIF1-α is involved in the VEGF expression and thereby contributes to tumour angiogenesis. Interestingly, this uPA activation can be inhibited by Cx32 over-expression in renal carcinoma cells.[7] Metalloproteinases also seem to be partially regulated via connexins: thus, elevated expression levels of Cx43 have been linked to enhanced MMP-activity,[8] while, in contrast, Cx26 seems to down-regulate MMP-9 activity and enhances TIMP-1.[5]

If cancer cells invade a tissue, it has been observed that they can form heterocellular gap junctions with stromal cells, mostly communicating with local fibroblasts or with astroglia.[9] In these cases high levels of connexin expression are associated with the invasive growth.[10] In other tumour cells Cx32 expression suppresses the invasive behaviour.[7] However, other mechanisms to activate stromal cells also seem to exist. Thus, different modes exist how cancer cells interact with stromal cells and how they invade tissue. This probably is dependent on (I) the type of the tumour cell, (II) the type of the stromal cell and the tissue type, (III) the connexin isoforms, and (IV) the phase of tumour progression (detachment of cells from the primary tumour; trespassing connective tissue; intravasation; extravasation; colonisation). Enhanced, but also reduced GJIC can contribute to the cancerogenic process. The latter was among the first ideas how GJIC may be involved in cancer, when Werner Loewenstein proposed that reduced gap junction inter-cellular communication may account for loss of growth inhibition.[11,12] Following this idea several groups showed that in malignant cells connexins can be down-regulated and that oncogenes or cancerogenic drugs (e.g. phorbol esters, hexachlorobenzene, cisplatin) often impair gap junction channel function or diminish connexin expression.[2,11,13-17] Connexins probably interact with the cancerogenic or metastatic process not only via GJIC but also via intracellular actions of the connexins: thus, the carboxy tail of Cx43 (Cx43-ct) seems to be important for invasion and the formation of the leading edge of the invasive tumour by augmenting p38 MAPK mediated cell migration independent from GJIC.[18,19]

In the line of the early view of Loewenstein,[11,12] we could demonstrate recently, that a sarcoma originating from engineered tissue made from bone-marrow derived stem cells did not express cardio-typic connexins in the invading edges of the tumour, while in the mid region of the sarcoma abundant expression of Cx43 was found.[20] The situation in this study, however, is direct invasion of the tumour into the heart and not single invading cells with amoeboid behaviour. This difference seems to be important in the light of the discussion above. Interestingly, we found that proliferative activity, determined by ki-67 positivity, which was highest in the protruding edges of the tumour was negatively correlated with the Cx43 expression (see figure 1). This is in support of Lowenstein´s theory that proliferating malignant cells do not communicate with their surrounding and thus do not sense the neighbouring cells (loss of contact inhibition). Interestingly, Trosko *et al*.[21] added another "hallmark of cancer" to the existing (see above), which is the down-regulation of GJIC thereby preventing the cell from a terminal differentiation and "mortalisation". These ideas are in good accordance to our observations,[20] but probably can not be generalised to all kinds of cancer/tumour. However, the considerations above indicate that modulation of GJIC may be an interesting approach to prevent invasive growth, malignancy or metastasis. Depending on the phase of the cancerogenic process, the type of connexin, the type of tissue enhancement or reduction of GJIC may inhibit the further progression.

References

1. Hanahan D, Weinberg RA.,„The hallmarks of cancer.", Cell (2000), 100: pp.57–70.
2. Salameh A, Dhein S.,„Pharmacology of gap junctions. New pharmacological targets for treatment of arrhythmia, seizure and cancer?", Biochim Biophys Acta. (2005), 1719(1-2): pp. 36-58.
3. Defamie N, Chepied A, Mesnil M.„Connexins, gap junctions and tissue invasion.", FEBS Lett. (2014), 588(8): pp. 1331-1338.
4. Lampe PD, Nguyen BP, Gil S, Usui M, Olerud J, Takada Y, Carter WG.,„Cellular interaction of integrin alpha3beta1 with laminin 5 promotes gap junctional communication.", J Cell Biol. (1998), 143(6): pp. 1735-1747.
5. Kalra J, Shao Q, Qin H, Thomas T, Alaoui-Jamali MA, Laird DW.,„Cx26 inhibits breast MDA-MB-435 cell tumorigenic properties by a gap junctional intercellular communication-independent mechanism.", Carcinogenesis (2006), 27(12): pp. 2528-2537.
6. Tate AW, Lung T, Radhakrishnan A, Lim SD, Lin X, Edlund M.,„Changes in gap junctional connexin isoforms during prostate cancer progression.", Prostate (2006), 66(1): pp. 19-31.
7. Hagiwara H, Sato H, Shirai S, Kobayashi S, Fukumoto K, Ishida T, Seki T, Ariga T, Yano T., „Connexin 32 down-regulates the fibrinolytic factors in metastatic renal cell carcinoma cells.", Life Sci. (2006), 78(19): pp. 2249-2254.
8. Zhang W, Nwagwu C, Le DM, Yong VW, Song H, Couldwell WT.,„Increased invasive capacity of connexin43-overexpressing malignant glioma cells.", J Neurosurg (2003), 99(6): pp. 1039-1046.
9. Oliveira R, Christov C, Guillamo JS, de Boüard S, Palfi S, Venance L, Tardy M, Peschanski M., „Contribution of gap junctional communication between tumor cells and astroglia to the invasion of the brain parenchyma by human glioblastomas.", BMC Cell Biol (2005), 6(1): pp. 7-8.
10. Miekus K, Czernik M, Sroka J, Czyz J, Madeja Z., „Contact stimulation of prostate cancer cell migration: the role of gap junctional coupling and migration stimulated by heterotypic cell-to-cell contacts in determination of the metastatic phenotype of Dunning rat prostate cancer cells.", Biol Cell (2005), 97(12): pp. 893-903.
11. Loewenstein WR, Kanno Y.,„Intercellular communication and the control of tissue growth: lack of communication between cancer cells.", Nature (1966), 209: pp. 1248-1249.
12. Loewenstein WR., "Junctional cell-to-cell communication and growth control.", Ann N Y Acad Sci (1980), 339: pp. 39-45.
13. Mesnil M, Crespin S, Avanzo JL, Zaidan-Dagli ML., "Defective gap junctional intercellular communication in the carcinogenic process.", Biochim Biophys Acta (2005), 1719: pp. 125-145.
14. Cronier L, Crespin S, Strale PO, Defamie N, Mesnil M., "Gap junctions and cancer: new functions for an old story.", Antioxid Redox Signal (2009), 11: pp. 323-338.
15. Laird DW, Fistouris P, Batist G, Alpert L, Huynh HT, Carystinos GD, Alaoui-Jamali MA., "Deficiency of connexin43 gap junctions is an independent marker for breast tumors.", Cancer Res (1999), 59: pp. 4104-4110.
16. Lampe PD.,„Analyzing phorbol ester effects on gap junctional communication: a dramatic inhibition of assembly.", J Cell Biol. (1994), 127: pp. 1895-1905.
17. Trosko JE, Chang CC, Madhukar BV, Klaunig JE., "Chemical, oncogene and growth factor inhibition gap junctional intercellular communication: an integrative hypothesis of carcinogenesis.", Pathobiology (1990); 58: pp. 265-278.
18. Bates DC, Sin WC, Aftab Q, Naus CC.,„Connexin43 enhances glioma invasion by a mechanism involving the carboxy terminus.", Glia. (2007), 55(15): pp. 1554-1564.
19. Behrens J, Kameritsch P, Wallner S, Pohl U, Pogoda K.,„The carboxyl tail of Cx43 augments p38 mediated cell migration in a gap junction-independent manner.", Eur J Cell Biol. (2010), 89(11): pp. 828-838.
20. Spath C, Schlegel F, Leontyev S, Mohr FW, Dhein S.,„Inverse Relationship between Tumor Proliferation Markers and Connexin Expression in a Malignant Cardiac Tumor Originating from Mesenchymal Stem Cell Engineered Tissue in a Rat in vivo Model.", Front Pharmacol. (2013), 4: pp. 42, doi: 10.3389/fphar.2013.00042. eCollection 2013.
21. Trosko JE, Chang CC, Upham BL, Tai MH., "Ignored hallmarks of carcinogenesis: stem cells and cell-cell communication.", Ann NY Acad Sci (2004), 1028: pp. 192-201.

Decision Making in Systemic Treatment Options for Advanced and/or Metastatic Soft Tissue Sarcomas

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Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of tumours arising mainly from the embryonic mesoderm and can be localised anywhere in the body. They comprise more than 50 different histological tumour entities exhibiting great differences in terms of clinical behaviour, pathogenesis and genetic alterations.[1] STS are rare with about 10.000 cases diagnosed each year in the United States. More than 40% are diagnosed in patients older than 55 years, although all age groups may be affected. If diagnosed at an early stage and complete surgical removal of all tumour manifestations can be achieved, the prognosis is favourable. However, in up to 50% of patients distant metastases will occur.[2] The median overall survival for advanced patients is approximately twelve months and has remained substantially unchanged during the last 20 years. Long-term survival occurs only in a small percentage of metastatic patients[3] clearly underpinning the need for new therapeutic strategies.

As effective targeted treatments are scarce for most advanced and/or metastatic STS doxorubicin and ifosfamide - which have been used for more than 30 years - still remain the backbone of systemic chemotherapy. In most cases, patients with advanced STS have a poor prognosis and the primary goal of treatment is disease control and palliation. Trabectedin and pazopanib have been introduced beyond first line therapy and have enriched the therapeutic armamentarium significantly (see Figure 1). For certain histological subtypes, specific chemotherapies may be used such as taxanes for angiosarcomas or gemcitabine alone or in combination with docetaxel for leiomyosarcomas. Recently, innovative therapeutic concepts have been studied more intensively; one of these approaches is to target angiogenesis which is one of the crucial drivers for the growth and dissemination of malignancies. A candidate for this approach is pazopanib, an orally available angiogenesis inhibitor that targets vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3 and platelet-derived growth factor receptor (PDGFR)-α and -β and c-kit.[4] In 2009, pazopanib was approved in the United States for the treatment of advanced and metastatic renal cell carcinoma.[5] The European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) performed a phase II study (EORTC 62043)[6] and a phase III study (EORTC 62072, PALETTE)[7] evaluating the activity and safety of pazopanib in STS patients in collaboration with GSK, finally leading to approval of pazopanib for advanced and metastatic in Europe, USA and Japan. Interestingly, a considerable number of patients showed a significantly longer progression-free and overall survival in these pivotal trials which has been analysed in a recently published paper.[8] However, there is no standardised therapeutic algorithm for advanced STS patients. Decision making in systemic treatment options for advanced STS patients has to take several factors into account such as patient and tumour characteristics, efficacy and side effects of the planned treatment as well as the primary treatment goal.

Bernd Kasper studied Medicine at the University of Heidelberg. In 2001, he finalised his thesis at the German Cancer Research Centre (DKFZ) dealing with new treatment strategies for chronic myelogenous leukaemia patients using the tyrosine kinase inhibitor imatinib. To deepen his training, he stayed at the Imperial College School of Medicine in London and the Jules Bordet Institute in Brussels. He specialised in Internal Medicine and Medical Haematology/Oncology at the University of Heidelberg. Currently, he works at the Sarcoma Unit at the Interdisciplinary Tumor Center Mannheim (ITM), Mannheim University Medical Center. Since 2011, he is Leading Physician and coordinator of the ITM. Dr. Kasper's research interest lies in the treatment of patients with bone and soft tissue sarcomas. He is head of the study center of the German Interdisciplinary Sarcoma Group (GISG) and is active in many national and international phase I, II and III trials.

First Line Therapy

According to the European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment and follow-up of STS doxorubicin monotherapy remains the standard in first line therapy for patients with advanced and/or metastatic STS.[9]

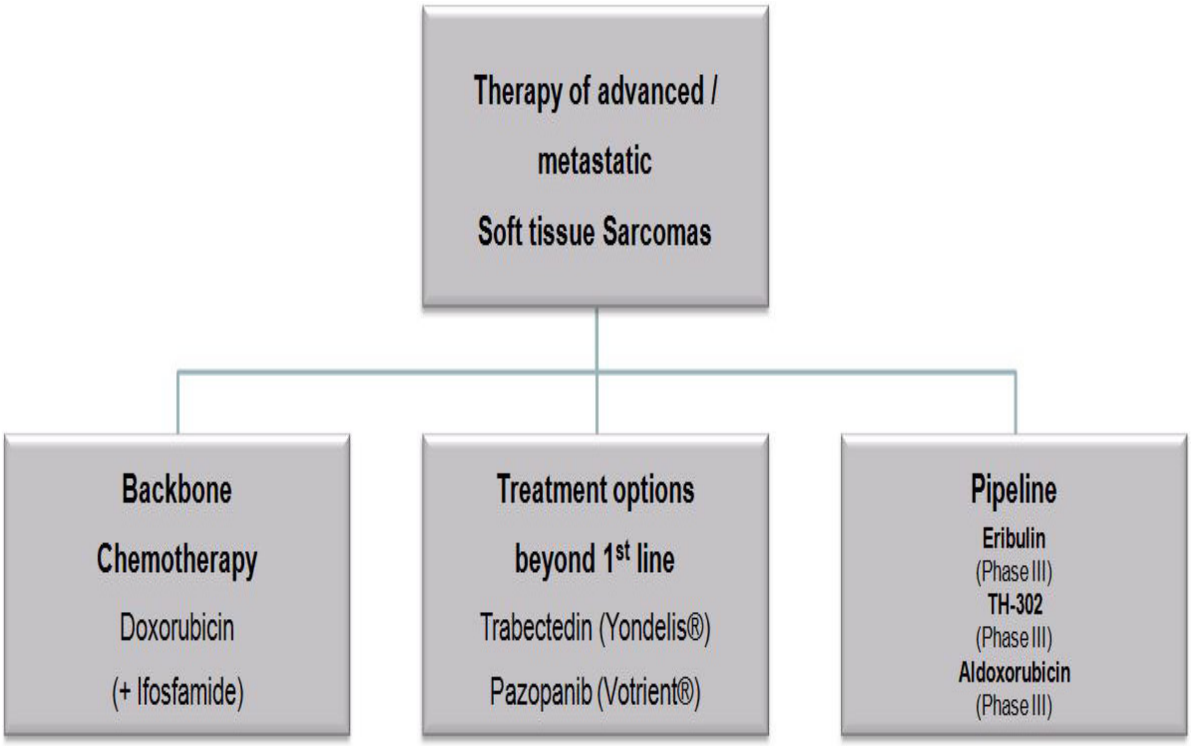


Figure 1. Current treatment options for advanced and/or metastatic STS.

The question whether doxorubicin alone or the combination of doxorubicin and ifosfamide should be used routinely in the first line setting has been always discussed controversially. Until now, all existing published literature - randomised trials and even meta-analyses - were not able to demonstrate any improvement in overall survival by combination therapies or dose intensification.[10,11,12,13] Most recently, the EORTC STBSG published data on the 62012 phase III trial addressing this question.[14] In this study, doxorubicin 75 mg/m^2 was either given as single-agent or intensified doxorubicin (75 mg/m^2; 25 mg/m^2 per day, days 1-3) plus ifosfamide (10 g/m^2 over 4 days) was administered as first line treatment. Hence, both doxorubicin and ifosfamide doses were higher than those reported in previous trials. However, the EORTC trial also failed to show an improvement in overall survival (12.8 months versus 14.3 months; $p = 0.076$), but could demonstrate a nearly doubled response rate (14% versus 26%; $p < 0.0006$) and a prolonged progression-free survival for the combination. The decision in favour of monotherapy or polychemotherapy should be clearly guided by the goal of the treatment in the unique patient's situation. If the primary goal of therapy is disease control and palliation, doxorubicin mono remains standard of care and an appropriate treatment option with less toxicity. Conversely, combination treatment would be justified if tumour shrinkage is important, e.g. to relieve acute symptoms or in a neoadjuvant intention before surgery or radiotherapy. The final decision, of course, is usually discussed within a multidisciplinary team in a tumour conference.

Second Line Therapy

There is no established second line therapy for advanced and/or metastatic STS patients.[15] In this setting, trabectedin has in several phase II studies as a promising therapeutic option.[16,17,18] In 2007, trabectedin was approved in Europe for the treatment of locally advanced and/or metastatic STS after failure of anthracycline and/or ifosfamide treatment. Trabectedin is the first compound of a new class of antitumour agents. It has been isolated from a marine tunicate, Ecteinascidia turbinata, acting as a minor groove binder through DNA destabilisation, inhibition of DNA repair mechanisms and modification of the anti-inflammatory and pro-angiogenic profile of the microenvironment.[19,20,21] Therefore, trabectedin's mode of action can be described as a "multi-target" agent.[22] Trabectedin demonstrated activity especially in the subgroups of (myxoid) liposarcoma, leiomyosarcoma and synovial sarcoma, however, its approval covers all subtypes of STS[23] and was based on the results of a phase II study in 270 patients with advanced leiomyosarcomas and liposarcomas favouring the 24h-infusion:[24] the primary endpoint, the median time to progression, was significant longer (3.7 vs. 2.3 months; $p = 0.03$) than for the 3h-infusion as well as the progression-free survival (3.3 vs. 2.3 months, $p = 0.04$). Due to the missing cumulative toxicity, trabectedin could be administered over multiple cycles and long time periods; 15-20% of the patients in the phase II registration trial received between 20 and 30 consecutive therapy cycles. Trabectedin is administered in a dose of 1.5 mg/m^2 as a 24h-infusion. Premedication consists of standard antiemetic medication plus 20 mg dexamethasone 30 min. before infusion start. Typical side effects include nausea,

fatigue, neutropenia, thrombocytopenia and a reversible, transient transaminases elevation in about 30-40% of patients. The advantages of trabectedin comprise its administration on an outpatient basis, the missing cumulative toxicity and organ specific toxicity (such as neuro- or cardiotoxicity), a long progression-free interval and, therefore, possible treatment durations of up to several years. The response rate is 15% for untreated and 8% for pre-treated patients; however, a high response rate is not the primary goal of treatment for many patients with advanced STS. In contrast, progression arrest using well tolerated and easily applicable compounds is often the primary treatment goal for this patient population.

The second approval for patients with advanced and/or metastatic STS was pazopanib in 2012 based on the EORTC phase III study (PALETTE). 369 patients progressive on prior lines of standard chemotherapy (for advanced metastatic disease) were randomly assigned to receive either pazopanib (n = 246) or placebo (n = 123). The study demonstrated a significant advantage in progression-free survival of three months in favour of the pazopanib arm (4.6 vs. 1.6 months; HR = 0.31, 95% CI: 0.24 - 0.40, $p < 0.0001$). The commonest side effects observed under treatment with pazopanib were nausea, fatigue, diarrhoea, weight loss and hypertension. The objective response rate in the PALETTE trial was 6% for the pazopanib arm and 0% for placebo (67% stable diseases in the pazopanib arm versus 38% in the placebo arm). Median progression-free survival for patients treated with pazopanib in the PALETTE trial was 4.6 months, median overall survival was 12.5 months, respectively. Therefore, PALETTE was the first global study performed in STS that scientifically demonstrated antitumour efficacy of an antiangiogenic compound targeting VEGFR. On the basis of these data pazopanib was approved in Europe, USA and Japan for the treatment of advanced and/or metastatic STS after failure of anthracycline and/or ifosfamide therapy excluding the subtype of liposarcomas. Therefore, pazopanib is a new, oral compound that has significantly enriched the therapeutic armamentarium for STS patients. One of the main advantages of pazopanib is its oral way of administration cutting down the number of necessary hospital consultations for the patients. Interestingly, a considerable number of patients from the phase II and III trials showed a significantly longer progression-free and overall survival which has been analysed within the EORTC database [8]. Pooling data from these two trials investigating patients treated orally with pazopanib (n = 344), it could be demonstrated that 36% (n = 124) and 34% (n = 116) of STS patients had a progression-free survival ≥ 6 months and were defined as long-term responders, or demonstrated an overall survival ≥ 18 months defined as long-term survivors, respectively. 76 patients (22.1%) were both long-term responders and survivors. The descriptive as well as the multivariate analysis confirmed the importance of prognostic factors such as performance status and tumour grade. A normal hemoglobin level at baseline was also found to be of prognostic relevance for progression-free and overall survival. Taken together, good performance status, low / intermediate grade of the primary tumour and a normal hemoglobin level at baseline were advantageous for long-term outcome. Twelve patients (3.5%) demonstrated a clinical benefit even beyond two years with a median time on pazopanib treatment of 2.4 years and the longest duration of 3.7 years. As expected, these patients were mainly young, female, with a good performance status and had more low or intermediate grade tumours at time of initial diagnosis and all of them had pulmonary metastases.[8]

Treatment Decision Making

There is more and more data showing different treatment responses in certain STS subtypes for different chemotherapeutic agents. On the basis of these data, an individualised and histology driven treatment approach seems possible. For example, synovial sarcomas, leiomyosarcomas and myxoid liposarcomas do respond well to chemotherapies. In contrast, alveolar STS, extraskeletal myxoid chondrosarcomas and clear cell sarcomas are more or less resistant to conventional chemotherapy. In addition, different aspects have to be taken into consideration for the decision making in systemic treatment options for advanced STS: (1) The patient himself plays a major role in decision making; his/her age, performance status and possible comorbidities influence the choice of the planned treatment significantly, e.g. combination versus monotherapy in first line treatment. (2) The tumour itself plays a role regarding histological subtype, localisation and grading; e.g. low / intermediate tumours benefit more from pazopanib than high grade tumours as described above. (3) The treatment itself has to be evaluated carefully in regard to efficacy, side effects, route of administration and availability in different countries. (4) The inclusion in open clinical studies has always to be taken into consideration and (5) - most importantly - the patient's wish and patient's preference has to be considered and discussed sensitively together with the patient.

Landscape of Clinical Studies

The landscape of clinical studies in Europe has traditionally been dominated by the EORTC STBSG (www.eortc.be). Recently, efficacy and safety of Eribulin and TH-302 have been evaluated in large international, multicenter phase III trials; results are awaited (see Figure 1). Phase II data for Palbociclib and Aldoxorubicin have been presented; a phase III trial has already been initiated for the later. In Europe, a lot of national sarcoma study groups have been founded such as the Italian Sarcoma Group (ISG), the French Sarcoma Group (FSG), the Spanish Group for Sarcoma Research (GEIS), the Sarcoma Platform Austria (S.P.A.) and the Scandinavian Sarcoma Group (SSG) developing own study protocols. In Germany, the German Interdisciplinary Sarcoma Group (GISG) was founded in 2008 and focuses on early phase I and II clinical trials with mainly academic and interdisciplinary questions and acts as a global

partner in international study collaborations (www.gisg.de).

Summary

• The treatment of patients with STS should be restricted to centres or professional networks with a specific expertise in this disease.

• The standard in first line therapy for patients with advanced and/or metastatic STS remains doxorubicin monotherapy. However, for younger patients in a good performance status without relevant comorbidities combination therapy with ifosfamide can be evaluated if tumour shrinkage, relieve of symptoms or another intervention after response are anticipated.

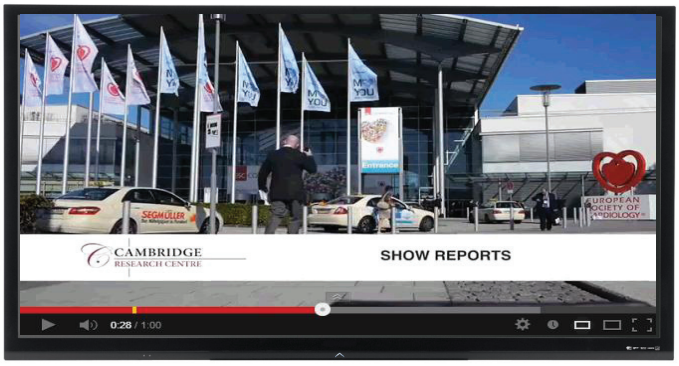
• Trabectedin and pazopanib evolved as two effective and well tolerated compounds in the second and third line treatment for advanced STS patients.

• Decision making in systemic treatment options for these patients has to consider multiple factors such as patient and tumour characteristics, therapy pros and cons, available studies and patients' preferences and should be individualised for each patient.

• New agents and therapy concepts are evaluated in clinical trials. Therefore, whenever possible, patients should be recruited to a clinical study protocol.

References

1. Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F, "WHO Classification of Tumours of Soft Tissue and Bone (IARC WHO Classification of Tumours)" (2013), 4th edition.
2. Kasper B, Hohenberger P, "Pazopanib: A promising new agent in the treatment of soft tissue sarcomas", Future. Oncol. (2011), 7: pp. 1373-1383.
3. Blay JY, van Glabbeke M, Verweij J, et al., "Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy", Eur. J. Cancer. (2003), 39: pp. 64-69.
4. Harris PA, Boloor A, Cheung M, et al., "Discovery of 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2 pyrimidinyl]amino] 2 methylbenzenesulfonamide (pazopanib), a novel and potent vascular endothelial growth factor receptor inhibitor", J. Med. Chem. (2008), 51: pp. 4632-4640.
5. Keisner SV, Shah SR, "Pazopanib - the newest tyrosine kinase inhibitor for the treatment of advanced or metastatic renal cell carcinoma", Drugs. (2011), 71: pp. 443-454.
6. Sleijfer S, Ray-Coquard I, Papai Z, et al., "Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European Organisation for Research and Treatment of Cancer - Soft Tissue and Bone Sarcoma Group (EORTC Study 62043)", J. Clin. Oncol. (2009), 27: pp. 3126-3132.
7. Van der Graaf WTA, Blay JY, Chawla SP, et al., "Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial", Lancet. (2012), 379: pp. 1879-1886.
8. Kasper B, Sleijfer S, Litière S, et al., "Long-term responders and survivors on pazopanib for advanced soft tissue sarcomas: subanalysis of two European Organisation for Research and Treatment of Cancer (EORTC) clinical trials 62043 and 62072", Ann. Oncol. (2014), 25: pp. 719-724.
9. ESMO/European Sarcoma Network Working Group, "Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up", Ann. Oncol.
10. Santoro A, Tursz T, Mouridsen H, et al., "Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group", J. Clin. Oncol. (1995), 13: pp. 1537-1545.
11. Antman K, Crowley J, Balcerzak SP, et al., "An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas", J. Clin. Oncol. (1993), 11: pp. 1276-1285.
12. Le Cesne A, Judson I, Crother D, et al., "Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: A trial of the European Organization for Research and Treatment of Cancer/ Soft Tissue and Bone Sarcoma Group", J. Clin. Oncol. (2000), 18: pp. 2676-2684.
13. Verma S, Younus J, Stys-Norman D, Haynes AE, Blackstein, and the Sarcoma Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care, "Dose-intensive chemotherapy with growth factor or autologous bone marrow/stem cell transplant support in first-line treatment of advanced or metastatic soft tissue sarcoma: a systemic review", Cancer. (2008), 112: pp. 1197-1205.
14. Judson I, Verweij J, Gelderblom H, et al., "Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial", Lancet. Oncol. (2014), 15: pp. 415-423.
15. Penel N, Van Glabbeke M, Marreaud S, et al., "Testing new regimens in patients with advanced soft tissue sarcoma: analysis of publications from the last 10 years", Ann. Oncol. (2011), 22: pp. 1266-1272.
16. Garcia-Carbonero R, Supko JG, Manola J, et al., "Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy", J. Clin. Oncol. (2004), 22: pp. 1480-1490.
17. Le Cesne A, Blay JY, Judson I, et al., "Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial", J. Clin. Oncol. (2005), 23: pp. 576-584.
18. Yovine A, Riofrio M, Blay JY, et al., "Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients", J. Clin. Oncol. (2004), 22: pp. 890-899.
19. Zewail-Foote M, Hurley LH, "Ecteinascidin-743: a minor groove alkylator that bends DNA toward the major groove", J. Med. Chem. (1999), 42: pp. 2493-2497.
20. Zewail-Foote M, Li VS, Kohn H, et al., "The inefficiency of incisions of ecteinascidin 743-DNA adducts by the UvrABC nuclease and the unique structural feature of the DNA adducts can be used to explain the repair-dependent toxicities of this antitumor agent", Chem. Biol. (2001), 8: pp. 1033-1049.
21. Herrero AB, Martín-Castellanos C, Marco E, Gago F, Moreno S, "Cross-talk between nucleotide excision and homologous recombination DNA repair pathways in the mechanism of action of antitumor trabectedin", Cancer. Res. (2006), 66: pp. 8155-8162.
22. Von Mehren M, "Trabectedin - a targeted chemotherapy?", Lancet. Oncol. (2007), 8: pp. 565-567.
23. Garcia-Carbonero R, Supko JG, Maki RG, et al., "Ecteinascidin-743 (ET-743) for chemotherapy-naive patients with advanced soft tissue sarcomas: multicenter phase II and pharmacokinetic study", J. Clin. Oncol. (2005), 3: pp. 5484-5492.
24. Demetri GD, Chawla SP, von Mehren M, et al., "Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules", J. Clin. Oncol. (2009), 27: pp. 4188-4196.



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Intratumoural Heterogeneity in Cancer: Lessons from Molecularly Targeted Agents for the Future Cancer Therapies

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Cancer is one of the most urgent health issues of today. Despite four decades of the intense research effort skyrocketed after the declaration of the global War on Cancer in 1971,[1] the ultimate goal of developing effective therapies for cancer still remains unmet. According to the latest data from WHO on cancer trends worldwide, the burden of cancer increases at an alarming pace with the number of cancer cases expected to grow from 14 million cases annually in 2012 to 22 million within the next two decades.[2] From the viewpoint of the socio-economic impact, fiscal burden of cancer remains disproportionately high relative to the clinical outcome of current cancer therapies. In 2010, the annual medial cost of cancer treatment was assumed to be US$ 163 billion and it is anticipated that this trend will continue.[2] A disproportionate relationship between the costs and clinical benefits of cancer treatments can be exemplified by current combination therapy used to treat gliomas.

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumour in adults (median age at presentation 64 years). 45.6% of malignant primary brain and CNS Tumours are Glioblastoma WHO°IV with an incidence is approximately 3-4 per 100,000 person-years.[3] The prognosis of GBM remains poor despite new therapy approaches in the past decade.[4] Currently, treatment of GBM consists of surgery and cytotoxic therapy. In 2005, the so-called Stupp regimen (named by the lead investigator) has become a standard for GBM treatment consisting of ionising radiation followed by a DNA methylating agent temozolomide.[5] In the clinical trial setting, temozolomide confers a modest but significant therapeutic benefit (overall survival of 14.6 months for patients treated with radiotherapy plus temozolomide compared to 12.1 months for patients treated with radiotherapy alone.[5] In a real-life setting, therapeutic effects conferred by temozolomide seem to be less profound and disproportionate to fiscal distress caused by a substantial increase in medical costs due to addition of temozolomide as adjuvant treatment for GBM ($184,107 in patients receiving both temozolomide and radiation compared to $88,827 for patients without adjuvant therapy).[6] It has been recognised that the so-called "financial toxicity" is an important criteria that contributes to the overall adverse effects and, consequently, might influence the outcome of cancer treatment.[7,8,9,10,11] The impact of financial distress caused by medical costs of cancer treatment is even mode dramatic in developing countries that bear more than 60% of the world's total cases of cancer.[2] In the face of growing cancer burden and global economic slowdown, the need in new effective treatments that would be affordable for the majority of cancer patients is pressing as never before.

We live in the era of molecularly targeted approaches to cancer treatment. The underlying principle of molecular-guided therapy that is targeting of tumour-associated antigens/markers (by drugs of humanised antibodies) to increase the precision and rate of tumour cells killing while sparing normal cells derives from the concept of a "magic bullet" formulated by Paul Erlich

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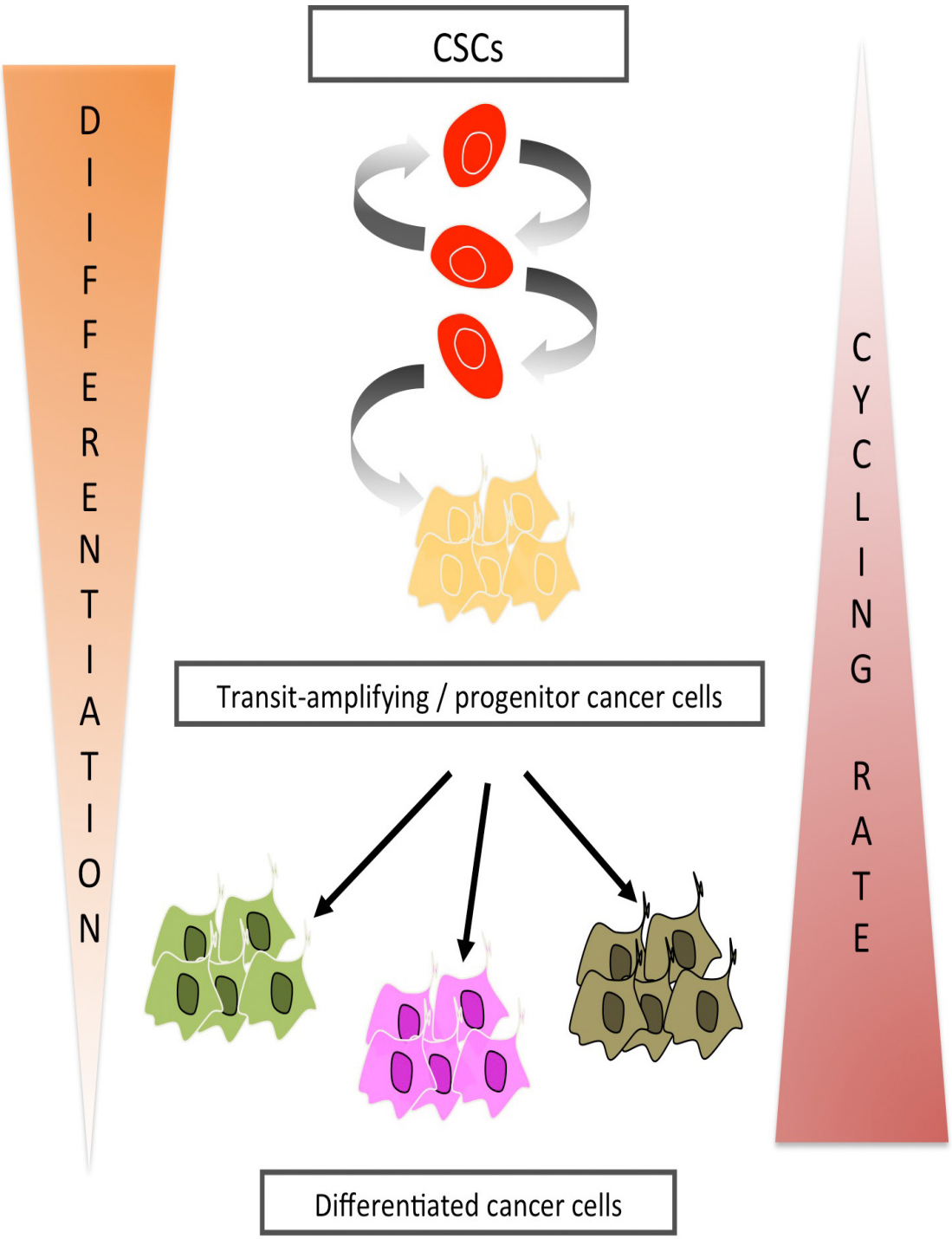

Figure 1. The hierarchical model of cancer. The tumour-propagating potential is distributed unequally among different types of cells comprising a heterogeneous tumour. Cancer stem cells (CSCs) are slowly cycling cells capable of tumour maintenance due to their dual propensity to self-renew and differentiate. Transit-amplifying/progenitor cancer cells may also re-acquire self-renewal potential through de-differentiation. Differentiated tumour cells comprising the tumour bulk are incapable of re-populating the tumour due to their limited proliferative potential.

more than 100 years ago.[12,13,14] Since the mid 90s, when first clinical trials using monoclonal antibodies have provided proof-of-principal for targeted therapy, great progress has been made in the understanding of processes underlying success and failure of molecularly informed approaches to treating cancer. Drastic improvement in the management of chronic myeloid leukaemia (CML) due to introduction of the first tyrosine kinase inhibitor imatinib[15] provides a striking example of the success of targeted therapy and its importance for treating cancers that are driven by a single genetic abnormality.[16] On the other hand, molecularly targeted therapies have proven less effective in treating genetically heterogeneous cancers with multiple aberrations in different genes/pathways that often have overlapping or compensatory functions. Diverse bypass mechanisms underlying resistance to targeted therapy have been identified. Feedback activation of signalling pathways with redundant functions,[17] co-occurrence

of mutations in other genes involved in synergistic interactions with the target gene[18] or emergence of subclones with secondary mutations coding for resistant versions of drug targets[19] can all contribute to tumour escape from targeted therapy. The emergence of therapy-resistant clones that express an altered version of the target molecule or carry compensatory mutations in other genes is one major hurdle in achieving durable effect of targeted therapy. Transient response to BRAF inhibitors in melanomas serves as an illustrative example of resistance through the selection of pre-existing minor clones lacking mutation in the target gene and/or re-activation of alternative pathways with compensatory functions.[20] The development of secondary mutations in the target gene in conjunction with re-activation of alternative pathways with compensatory functions is the underlying reason of resistance to anti-EGFR therapy in lung cancer.[21]

GBMs provide a further illustration of the relationship between the level of genetic complexity and therapy resistance. Genomic studies revealed that GBMs rely on the synergistic impact of multiple mutations and that deregulation of pRB, p53 and RTK/RAS/PI3K pathways is an obligatory event in GBMs.[22] The multiplicity and functional redundancy of genomic aberrations in GBMs is likely to be the primary reason for the low efficacy of cytotoxic therapy and failure of targeted monotherapies that have so far been tested in GBMs. Phase III trials testing the effects of anti-Vascular Endothelial Growth Factor (VEGF) therapy in first diagnosed GBMs provide most recent examples of GBMs resistance to monotargeted therapy. GBMs are characterised by extensive vascularisation and abnormal expression of VEGF, a key mediator of angiogenesis in gliomas. Anti-VEGF treatments lead to regression of existing microvessels, normalisation of surviving mature vasculature, and inhibition of vessel growth and neovascularisation. Bevacizumab is a humanised monoclonal immunoglobulin G antibody that neutralises the ability of VEGF to bind to the VEGF receptor (VEGFR). Maintaining the VEGF ligand inhibition may prevent tumour growth and may result in tumour shrinkage with time.[23,24,25] Indeed, phase II studies showed that addition of anti-VEGF therapy improves clinical outcome in recurrent and newly diagnosed GBMs.[26,27] Despite these encouraging results, two independent phase III trials failed to confirm therapeutic benefits of anti-VEGF therapy for newly diagnosed GBMs. Although there was an improvement in progression free survival, both studies showed that addition of Bevacizumab to Stupp regimen does not increase overall survival in patients with GBM.[28,29]

It has been recognised that intratumoural heterogeneity is one of the major mechanisms of tumour escape from targeted therapy. Term "Intratumoural heterogeneity" encompasses (epi) genetic, phenotypic and gene expression patterns diversity within the tumour. It has been well documented as a characteristic feature of malignant neoplasms including breast cancer,[30] renal carcinomas,[31,32] melanoma,[33] leukaemia,[34] pancreatic cancer,[35,36] oesophageal adenocarcinoma,[37] non-small cell lung cancer[38] and glioblastomas.[39] Intratumoural heterogeneity can be promoted by different mechanisms that can be roughly divided into mutational and non-mutational. Genomic instability defined as progressive mutagenic process accompanying neoplastic growth is the major mechanism of generating new mutations. According to the clonal evolution model, persistent changes in tumour genomes generate genetically and functionally distinct clones that may occupy different geographic territories within the tumour. There are several lines of evidences for the spatial patterns of intratumoural heterogeneity in advanced cancers. In GBMs, distinct patterns of genomic alterations and gene expression signatures can be found in different regions within the same tumour.[39] Similarly, more than 60% of all somatic mutations identified through a multi-region genetic analysis in renal carcinoma were found spatially separated within the same tumour and not detectable in every tumour region analyzed.[31] These findings indicate that different sampling strategies can strongly impact the interpretation of molecular profiling data obtained with single tumour samples and emphasise the need in suitable methodologies that would take into account the spatiotemporal patterns of intratumoural heterogeneity.

Intratumoural phenotypic heterogeneity can also be generated by the so-called cancer stem cells (CSCs). Owing to their propensity to divide by symmetric and asymmetric modes, CSCs are capable of maintaining their own pool but at the same time generate phenotypically diverse progeny with a more differentiated phenotype (see Figure 1). The CSC concept postulates that CSC and progenitor cancer cells are the only type of tumour cells (in CSC-derived tumours) capable of propagating tumour growth due to their infinite proliferative capacity (Garvalov *et al*. Magee *et al*.). Yet, CSCs comprise only minor population within the tumour most of which (tumour bulk) is comprised by differentiated cancer cells with limited tumour-propagating capacity. There is an emerging realisation that in CSC-driven cancers CSCs are primarily responsible for tumour relapse and represent a major limiting factor to improving the efficacy of current treatments. (see Figure 2). In GBMs, ionising radiation not only spares glioma stem cells but promotes their expansion.[40,41] Furthermore, there is also evidence that CSCs can survive the effects of molecularly targeted drugs despite expressing the target molecule: It has been shown that CML stem cells expressing BCR-ABL are capable to survive a sustained inhibition of the BCR-ABL kinase activity by the tyrosine kinase inhibitor imatinib, which effectively kills BCR-ABL expressing non-stem leukemic cells.[42] There is an emerging consensus that overcoming therapy resistance, either intrinsic

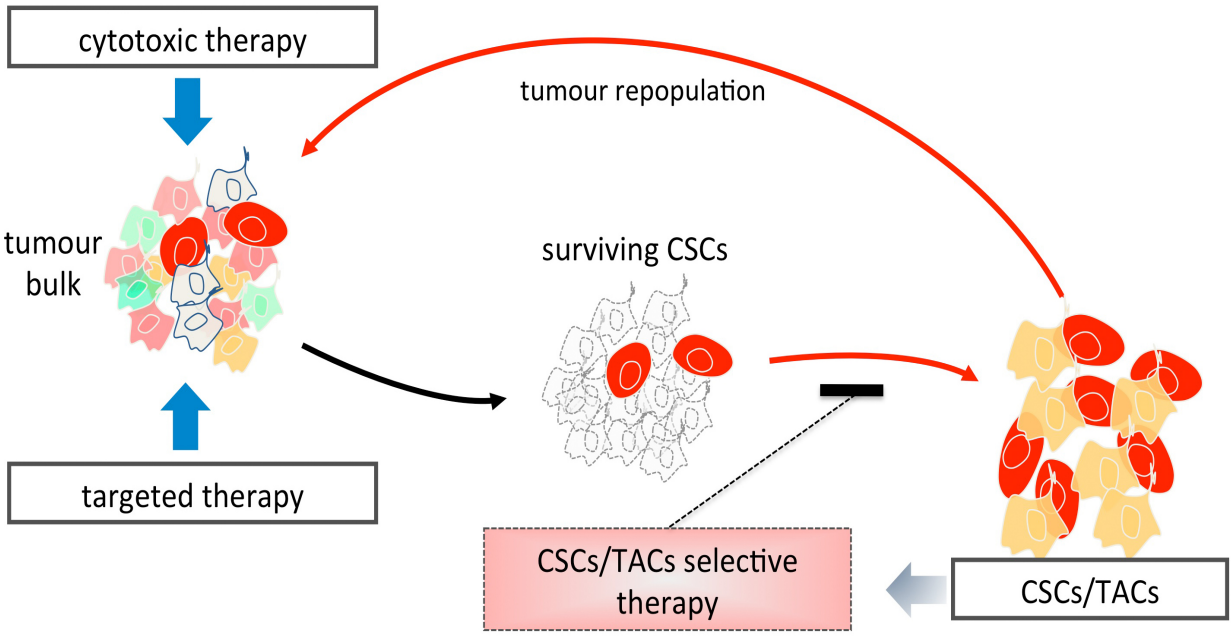

Figure 2. The CSC model of tumour recurrence. CSCs and their transit-amplifying progeny cells (TACs) are resistant to cytotoxic and targeted therapies and primarily responsible for tumour recurrence. Selective targeting of CSCs/TACs is required to prevent tumour re-growth after conventional therapy.

or acquired, would require to eliminate CSCs and that selective targeting of CSCs is a prerequisite for inhibiting tumour recurrence (rev. in reference 43). To accomplish this goal, the elucidation of mechanisms underlying CSCs responses to the cytotoxic stress is of pivotal importance. Currently, the identification of cellular pathways involved in the maintenance of stemness is an intensely explored area of research. The minority of CSCs, lack of definitive phenotypic markers for CSCs and heterogeneity within the CSC compartment render the task of selective targeting of CSCs challenging. Having said that, however, selective targeting of CSCs seems to be possible and there have been some encouraging results suggesting that inhibition of cellular pathways involved in the maintenance of stemness leads to the reduction of CSCs tumourigenicity and sensitises them to ionising radiation at least under laboratory conditions.[44,45,46,47]

In conclusion, intratumoural heterogeneity either mutation-driven or resulting from phenotypic changes in CSCs or their progeny is the underlying basis of tumour escape from targeted therapies. The elucidation of mechanisms that promote the expansion of resistant clones is critical to improve existing therapies and develop new strategies to overcome tumour recurrence. Commonly used cancer cell lines derive from pre-treated tumours and may thus be poorly representative of recurrent tumours. Experimental models for a recurrent cancer should help elucidate the mechanisms of tumour re-growth after therapy.

References

1. The National Cancer Act. The War on Cancer. Public Law. 1971:P.L. 92–218.
2. Stewart BM WC. World Cancer Report 2014. Lyon, France: International Agency for Research on Cancer. 2014.
3. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. World Health Organization Classification of Tumours of the Central Nervous System. IARC, Lyon. 2007.
4. Kohler BA, Ward E, McCarthy BJ, Schymura MJ, Ries LA, Eheman C, Jemal A, Anderson RN, Ajani UA, Edwards BK. Annual report to the nation on the status of cancer, 1975-2007, featuring tumours of the brain and other nervous system. J Natl Cancer Inst. 2011;103(9):714-36.
5. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 10;352(10):987-96. 2005;352(10):987-96.
6. Ray S, Bonafede MM, Mohile NA Treatment Patterns, Survival, and Healthcare Costs of Patients with Malignant Gliomas in a Large US Commercially Insured Population. Am Health Drug Benefits 2014;7(3):140-9.
7. Khera N. Reporting and grading financial toxicity. J Clin Oncol 2014;32(29):3337-8.
8. Zafar SY, Peppercorn JM, Schrag D, *et al*. The financial toxicity of cancer treatment: A pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. Oncologist 2013;18:381-390.
9. Shankaran V, Jolly S, Blough D, *et al*. Risk factors for financial hardship in patients receiving adjuvant chemotherapy for colon cancer: A population-based exploratory analysis. J Clin Oncol 2012;30:1608-1614.
10. Jagsi R, Pottow JA, Griffith KA, *et al*. Long-term financial burden of breast cancer: Experiences of a diverse cohort of survivors identified through population-based registries. J Clin Oncol. 2014; 32:1269-1276.
11. Khera N, Chang YH, Hashmi S, *et al*: Financial burden in recipients of allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2014;20:1375-1381.
12. Ehrlich P. Über moderne Chemotherapie. Beträge zur experimentellen Pathologie und Chemotherapie. 1909:165-202.
13. Ehrlich P. Die Grundlagen der experimentellen Chemotherapie. Zeitschrift fuer angewandte Chemie und Zentralblatt fuer technische Chemie. 1910;23:2-8.
14. Strebhardt K, Ullrich A. Paul Ehrlich's magic bullet concept: 100 years of progress. Nat Rev Cancer. 2008;8(6):473-80.
15. Kantarjian H, O'Brien S, Jabbour E, Garcia-Manero G, Quintas-Cardama A, Shan J, Rios MB, Ravandi F, Faderl S, Kadia T, Borthakur G, Huang X, Champlin R, Talpaz M, Cortes J. Improved survival in chronic myeloid leukemia since the introduction of imatinib therapy: a single-institution historical experience. Blood. 2012;119(9):1981-7.
16. Nowell PC, Hungerford D. A minute chromosome in human chronic granulocytic leukemia. Science. 1960;132:1487-501.
17. Prahallad A, Sun C, Huang S, Di Nicolantonio F, Salazar R, *et al*. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. Nature. 2012;483:100-3.
18. Mao M, Tian F, Mariadason JM, Tsao CC, Lemos R Jr., *et al*. Resistance to BRAF inhibition in BRAF-mutant colon cancer can be overcome with PI3K inhibition or demethylating agents. Clin Cancer Res. 2013(19):657-67.
19. Sakai W, Swisher EM, Karlan BY, Agarwal MK, Higgins J, *et al*. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. . Nature. 2008;451:1116-20.
20. Villanueva J, Vultur A, Herlyn M. Resistance to BRAF inhibitors: unraveling mechanisms and future treatment options. Cancer Res. 2011;71(23):7137-40.
21. Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. Nat Rev Cancer 2010;10(11):760-74.
22. Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008;455(7216):1061-8.
23. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev. 2004;25(4):581-611.
24. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol 2005;23(5):1101-27.
25. Shih T, Lindley C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. Clin Ther. 2006;28(11):1779-802.
26. Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, Garren N, Mackey M, Butman JA, Camphausen K, Park J, Albert PS, Fine HA.Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol. 2009;27(5):740-5.
27. Vredenburgh JJ, Desjardins A, Reardon DA, Peters KB, Herndon JE 2nd, Marcello J, Kirkpatrick JP, Sampson JH, Bailey L, Threatt S, Friedman AH, Bigner DD, Friedman HS. The addition of bevacizumab to standard radiation therapy and temozolomide followed by bevacizumab, temozolomide, and irinotecan for newly diagnosed glioblastoma. Clin Cancer Res. 2011;17(12):4119-24.
28. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, Carpentier AF, Hoang-Xuan K, Kavan P, Cernea D, Brandes AA, Hilton M, Abrey L, Cloughesy T.Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med. 2014;370(8):709-22.
29. Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, Colman H, Chakravarti A, Pugh S, Won M, Jeraj R, Brown PD, Jaeckle KA, Schiff D, Stieber VW, Brachman DG, Werner-Wasik M, Tremont-Lukats IW, Sulman EP, Aldape KD, Curran WJ Jr, Mehta MP. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014;370(8):699-708.
30. Russnes HG, Navin N, Hicks J, Borresen-Dale AL. Insight into the heterogeneity of breast cancer through next-generation sequencing. J Clin Invest. 2011;121:3810-8.
31. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, Martinez P, Matthews N, Stewart A, Tarpey P, Varela I, Phillimore B, Begum S, McDonald NQ, Butler A, Jones D, Raine K, Latimer C, Santos CR, Nohadani M, Eklund AC, Spencer-Dene B, Clark G, Pickering L, Stamp G, Gore M, Szallasi Z, Downward J, Futreal PA, Swanton C. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012 Mar 8;366(10):883-92
32. Martinez P, Birkbak NJ, Gerlinger M, McGranahan N, Burrell RA, Rowan AJ, Joshi T, Fisher R, Larkin J, Szallasi Z, Swanton C. Parallel evolution of tumour subclones mimics diversity between tumours. J Pathol 2013;230:356-64.
33. Anaka M, Hudson C, Lo PH, Do H, Caballero OL, Davis ID, Dobrovic A, Cebon J, Behren A. Intratumoral genetic heterogeneity in metastatic melanoma is accompanied by variation in malignant behaviors. BMC Med Genomics 2013 Oct 11;6:40 doi: 2013;6:40.
34. Anderson K, Lutz C, van Delft FW, Bateman CM, Guo Y, Colman SM, Kempski H, Moorman AV, Titley I, Swansbury J, Kearney L, Enver T, Greaves M. Genetic variegation of clonal architecture and propagating cells in leukaemia. Nature. 2011;469(7330):356-61.
35. Yachida S, Jones S, Bozic I, Antal T, Leary R, Fu B, Kamiyama M, Hruban RH, Eshleman JR, Nowak MA, Velculescu VE, Kinzler KW, Vogelstein B, Iacobuzio-Donahue CA. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature 2010;467(7319):1114-7.
36. Lou E, Subramanian S, Steer CJ.Pancreatic cancer: modulation of KRAS, MicroRNAs, and intercellular communication in the setting of tumor heterogeneity. Pancreas. 2013;42(8):1218-26.
37. Maley CC, Galipeau PC, Finley JC, Wongsurawat VJ, Li X, Sanchez CA, Paulson TG, Blount PL, Risques RA, Rabinovitch PS, Reid BJ.Genetic clonal diversity predicts progression to esophageal adenocarcinoma. Nat Genet. 2006;38(4):468-73.
38. Grob TJ, Hoenig T, Clauditz TS, Atanackovic D, Koenig AM, Vashist YK, Klose H, Simon R, Pantel K, Izbicki JR, Bokemeyer C, Sauter G, Wilczak W.Frequent intratumoral heterogeneity of EGFR gene copy gain in non-small cell lung cancer. Lung Cancer. 2013;79(3):221-7.
39. Sottoriva A, Spiteri I, Piccirillo SG, Touloumis A, Collins VP, Marioni JC, Curtis C, Watts C, Tavaré S.Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. Proc Natl Acad Sci U S A. 2013;110:4009-14.
40. Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, Dewhirst MW, Bigner DD, Rich JN.Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature 2006;444(7120):756-60.
41. Gilbertson RJ, Rich JN. Making a tumour's bed: glioblastoma stem cells and the vascular niche. Nat Rev Cancer. 2007;7(10):733-6.
42. Corbin AS, Agarwal A, Loriaux M, Cortes J, Deininger MW, Druker BJ. Human chronic myeloid leukemia stem cells are insensitive to imatinib despite inhibition of BCR-ABL activity. J Clin Invest. 2011;121(1):396-409.
43. Visvader JE, Lindeman GJ. Cancer stem cells: current status and evolving complexities. Cell stem cell. 2012;10(6):717-28.
44. Merchant AA, Matsui W. Targeting Hedgehog--a cancer stem cell pathway. Clin Cancer Res. 2010;16(12):3130-40.
45. Wang J, Wakeman TP, Lathia JD, Hjelmeland AB, Wang XF, White RR, Rich JN, Sullenger BA.Notch promotes radioresistance of glioma stem cells. Stem Cells. 2010;28(1):17-28.
46. Vermeulen L, De Sousa E Melo F, van der Heijden M, Cameron K, de Jong JH, Borovski T, Tuynman JB, Todaro M, Merz C, Rodermond H, Sprick MR, Kemper K, Richel DJ, Stassi G, Medema JP.Wnt activity defines colon cancer stem cells and is regulated by the microenvironment. Nat Cell Biol. 2010;12(5):468-76.
47. Zhang M, Atkinson RL, Rosen JM.Selective targeting of radiation-resistant tumor-initiating cells. Proc Natl Acad Sci U S A. 2010;107(8):3522-7.

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Current Challenges in the Treatment of Meningiomas: What Genomics has to Say

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Introduction

Meningiomas are the most frequent central nervous system (CNS) primary neoplasms. According to the Central Brain Tumor Registry of the US (CBTRUS) meningiomas represented 36% of all primary intracranial tumours reported during 2006-2010.[1] The World Health Organization (WHO) classifies meningiomas in 15 histological types and in three different grades. Nine of such types are considered WHO Grade I meningiomas, three are considered WHO Grade II (namely chordoid, clear cell and atypical meningiomas) and other three form part of WHO Grade III (namely papillary, rhabdoid and anaplastic meningiomas).[2] Anaplastic meningiomas represent 1-3% of the cases[3] and along with papillary and rhabdoid meningiomas they have the worst survival rate, with a mean overall survival (OS) and recurrence-free survival (RFS) time estimated in 3.3 years and 2.7 years, respectively.[4] Atypical meningiomas account for up to 15% of the cases,[3] and along with the other WHO Grade II meningioma types they have a significantly increased risk of death when compared to age and sex-matched controls.[5] OS and RFS in WHO Grade II meningiomas are estimated in 12.12 and 11.54 years, respectively; but choroid and clear cell meningiomas tend to behave more aggressively.[4,5] Finally, classic meningiomas represent about 81% of the cases and although they are considered benign,[6] they have varying rates of progression towards higher stages and some subclasses reach recurrence rates of 20%.[5] Notably, even benign meningiomas are associated with a significantly reduced long-term survival and increased recurrence rate.[7]

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Etiology

The etiology of meningioma is complex. The most clearly associated condition is Type 2 Neurofibromatosis (NF2), caused by germline mutations in the NF2 gene, since these patients develop meningiomas earlier in life.[5] Body mass and hormone replacement therapy in premenopausal women are positively associated with meningioma risk.[8,9] Gender is a well-characterized non-modifiable risk factor for meningioma. Its incidence is almost three times higher among women than among men.[1] Breast-feeding for at least 6 months is a protective factor.[8] Association of meningioma with breast cancer risk is controversial. Various studies have reported a positive and significant relationship in women but not in men,[10,11] whilst a more recent retrospective analysis observed no link between both conditions.[12] Ionizing radiation exposure is the principal modifiable risk factor.[5] No association could be detected between meningioma risk and regular mobile or cordless phone use.[13] However, heavy mobile phone users (>896 cumulative hours) are significantly associated with increased risk (Odds Ratio=2.57).[14] The effect of smoking is unclear, with positive, negative a neutral associations reported.[8,15,16] Finally, meningioma risk is also related to various immune processes. An inverse relationship with allergy and IgE serum levels has been described,[17-19] and a genomic approach identified seven innate immunity genes associated with meningioma risk.[20]

Current Therapeutic Approaches

The best treatment for meningiomas currently is surgery, with good results in low grade meningiomas and when complete resection can be achieved (Simpson Grade I-II). Recurrence is a frequent post-operative complication in meningiomas that is associated with increased mortality.[21] Recurrence risk increases with tumour grading and with conservative resections (Simpson Grade III-IV).[21,22] For example, anaplastic meningiomas have a recurrence rate of 20-40% one decade after complete resection and of 40-60% after subtotal resection.[23] Nevertheless, aggressive attempts to achieve

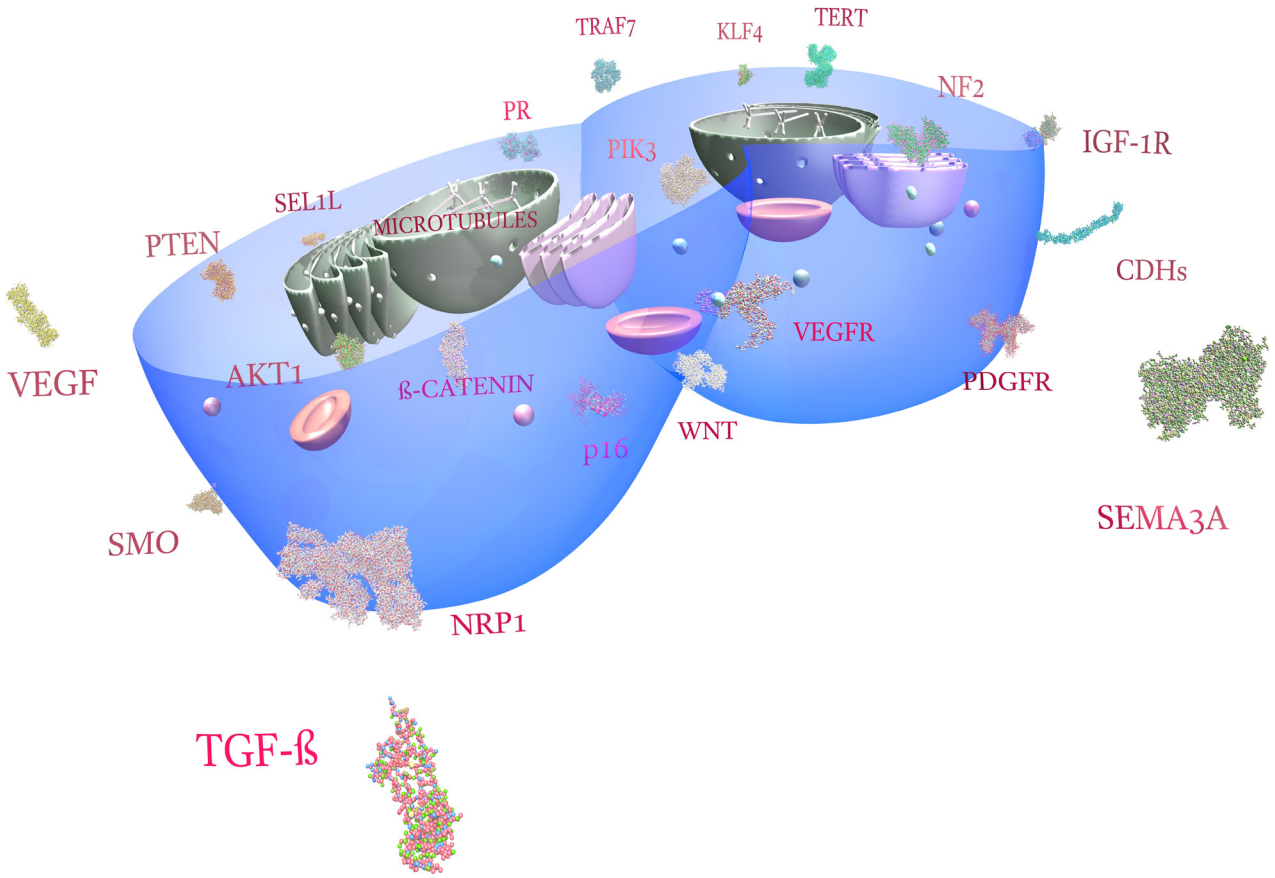

Figure 1. 3D representation of a dividing cell along with the proteins representing the main pathways involved in meningioma biology, progression and malignancy. Note that "CDHs" means "Cadherins" and that "p16" is the same as "CDKN2A". The rest of the proteins are labelled according to the text. Less studied pathways in meningioma, such as calcium channel activiy, HOX genes and lipid metabolism are not represented for the sake of brevity.

complete resection and repeated operations can be associated with considerable neurological morbidity and reduced OS than patients treated with near-total resection.[24] Radiotherapy is frequently used as adjuvant treatment, since it is associated with significantly better Progression Free Survival (PFS) rates.[25] Primary radiotherapy is recommended for inaccessible meningiomas, but controversy exists about the benefits of different techniques, radiation doses and target volume definition.[26]

Tumour progression following surgery and radiotherapy has little therapeutic options. The National Comprehensive Cancer Network (NCCN) recommends three drugs for these cases, namely hydroxyurea (HU), interferon-α (INFα) and octeotride.[27] A retrospective analysis of 35 patients with recurrent high-grade meningioma treated with HU did not show radiographic response in any patient and 57% of them manifested progressive disease,[28] whilst a long-term follow up of 13 patients with recurrent WHO grade I and II meningiomas did not show any complete or partial response.[29] INFα was tested in a group of 35 patients that had previously undergone surgery, radiotherapy and chemotherapy. No complete or partial response was observed, and although most patients remained stable after 3 cycles, the median survival was 8 months.[30] Since meningiomas intensely express somatostatin receptors, octeotride was tested in 16 patients with recurrent meningioma with promising results[31] but a more recent Phase II trial on 9 patients with WHO grade II and III meningiomas observed progressive disease in all patients at 10 months follow-up.[32] Moreover, Phase II clinical trials with either imatinib and HU[33] or erlotinib/gefitinib[34] observed modest and null effects in progressive and recurrent meningiomas, respectively. A meta-analysis of 47 publications about surgery and radiation-resistant meningiomas that were treated with a variety of chemotherapeutic agents revealed that the weighed average PFS at 6 months for WHO I meningiomas was 29%, whilst for WHO II and III it was 26%.[35] Such poor outcomes indicate that more effort needs to be made for the treatment of advanced and relapsing meningiomas.

Advances in Meningioma Genomics

Genomics has shed light on the mechanisms driving tumourigenesis and malignant progression in meningiomas during the last years. The most common findings are deletions on the 22q12.2 locus involving the NF2 gene.[36] Another common deletion is that of the CDKN2A/p16 locus, which tends to accumulate in high grade tumours and correlates with survival.[37]

Along with NF2, deletion of CDKN2AB locus (which encodes the ARF, CDKN2A/p16 and CDKN2B/p15 genes) promote meningioma development and malignant progression in mice.[38] A Genome-Wide Association Study (GWAS) found a susceptibility locus at 10p12.31 near the MLLT10 gene.[39] Other studies identified Single Nucleotide Polymorphisms (SNPs) associated to meningioma risk in Ki-RAS, ERCC2, ERCC4, SOD3, GSTT1, CASP8, MUTYH and PCNA.[5] More recently, frequent somatic mutations in TRAF7, KLF4, AKT1 and SMO were reported by various studies.[40,41] Interestingly, TRAF7 mutations were totally exclusive of NF2 mutations.[40] AKT1 and SMO mutations are mostly present in wild-type NF2 tumours.[40,41] These studies revealed that non NF2-tumours tend to be benign, to originate from the medial skull base and to show genomic stability,[40] whilst NF2-related meningiomas have increased chromosomal instability, tend to be atypical and are mostly located in the cerebral or cerebellar hemispheres.[40,42] A focused analysis of the main genes in the Epidermal Growth Factor Receptor (EGFR) pathway only revealed mutations in PIK3CA in less than 4% of the cases, and especially in Grade II and III tumours. No significant numbers of mutations were observed in EGFR, KRAS or BRAF.[43,44] PTEN, which is a PIK3 inhibitor and tumour suppressor gene, is mutated in a similar proportion of Grade II and Grade III meningiomas.[45] A recent study reported TERT promoter mutations associated with TERT expression changes in 28% of meningiomas undergoing malignant histological progression.[46]

Progesterone Receptor (PR) gene is overexpressed in Grade I meningiomas compared to Grade II and III meningiomas,[47] and it is strongly and inversely correlated with Ki-67, a marker of proliferation.[48] Abnormal splice forms of the Estrogen Receptor (ER) gene have been observed in meningiomas too.[49] Despite its weak expression, ER levels predominate in Grade I meningiomas.[50] Platelet-derived Growth Factor Receptor (PDGFR) blockade with micromolar concentrations of sunitinib has strong cytostatic and anti-migratory effects on meningioma cells *in vitro*,[51] and a clinical trial is undergoing to evaluate its effect on patients with relapsing or inoperable meningiomas.[52] Sunitinib also targets Vascular Endothelial Growth Factor Receptors (VEGFRs).[53] The expression of VEGF is positively correlated with mean microvascular density in meningiomas,[54] but a retrospective analysis of 15 patients with NF2-related meningiomas treated with bevacizumab only detected short duration responses. This suggests that the VEGF pathway is not the main driver of angiogenesis in meningiomas.[55] Nevertheless, a clinical trial is undergoing to evaluate the combination of bevacizumab and everolimus in the treatment of refractory and progressive meningiomas (56). Considering this, it seems reasonable that targeting other angiogenic factors may be a more reasonable approach. For example, Endothelin 1 (END1) is overexpressed in meningiomas and correlates with microvessel density.[57] Insulin-like Growth Factors (IGFs) and their receptors are involved in angiogenesis too.[58] Particularly, IGF1R has a recognized role as promoter of cell migration, tumour growth and angiogenesis in cancer.[59] We have recently described that a SNP in IGF1R is substantially associated to a co-expression network of genes deeply correlated with meningioma grade.[60] A study on NF2-deficient schwannomas discovered that increased proliferation in these tumours depends on the strong activation of PDGFR-β and ErbB2/3 on the one side, and on the over-expression and self-activation of IGF-1R on the other side.[61] Curiously, both pathways converged in PIK3, which is known to be mutated in advanced meningiomas.[43,44] Interestingly, a clinical case reported the reduction of a Grade I meningioma after treatment with an IGF-1R inhibitor for her lung adenocarcinoma.[62] Another important angiogenesis regulator, Neuropilin 1 (NRP1), probably has a important role in meningioma development. NRP1 acts as co-receptor of extracellular ligands such as VEGF-A, Semaphorin 3A (SEMA3A) and Transforming Growth Factor β (TGF-β).[63] NRP1 can promote or block angiogenesis depending on local conditions.[64] SEMA3A competes with VEGF for binding to NRP1, establishing a balance for normal vasculature development. VEGF/SEMA3A ratios positively correlate with meningioma grade and recurrence rate.[65] Moreover, NRP1 also has affinity for TGF-β receptors and increases TBF-β signalling,[66] which can further promote cancer progression.[67] NRP1 activity can partially explain the non-sustained responses to bevacizumab known so far in meningioma. Indeed, we have observed that SNPs in the NRP1 gene are significantly associated with patterns of gene expression associated with WHO Grade.[60] Blocking NRP1 and its interactions with VEGFR1 and VEGFR2 is an active field of basic and clinical research[68,69] and is a promising candidate for meningioma therapy.

Cadherins are a family of adhesion molecules that mediate cell-cell interactions[70] and whose role in meningioma is becoming increasingly important. E-cadherin is the most studied component due to its involvement in epithelial-to-mesenchimal transition, a hallmark of invasive cancers, including meningiomas.[71] Cadherin and Wnt/β-catenin pathways are intimately associated,[72] and not surprisingly deregulation of the Wnt pathway plays important roles in meningioma progression and recurrence.[73] We have recently described associations of genomic markers in four Cadherin genes (namely CDH8, CDH9, CDH12 and CDH13) with a co-expression network of transcripts associated with meningioma malignancy.[60] Other genes associated with calcium channel activity, HOX genes and lipid metabolism also ranked high in the results, which is consistent with some research results.[74-76] The most important components of this co-expression network were deeply enriched in microtubule-associated pathways and in the M-phase checkpoint.[60] In this same study, we also reported a group of SNPs significantly associated with meningioma stage in a region proximal to SEL1L, which encodes an unfolded protein response protein that fosters cell adaptation to an increased

proliferating rate.[60,77] Taken together, these findings suggest that the aforementioned pathways are great candidates for therapeutic modulation and they collectively merit further investigation.

Conclusion

Meningiomas are associated with increased morbidity and mortality rates in all their stages. Current treatment strategies are focused on surgery and radiotherapy, which are very effective for benign and resectable meningiomas. However, relapsing and high grade meningiomas do not benefit substantially from these approaches. Although some chemotherapeutic drugs are recommended in these cases, research has shown little beneficial effects. The advances in meningioma biology have identified various genes and pathways candidate for directed therapies (see Figure 1). The combined modulation of these targets is a promising area of research and should be evaluated in the near future.

References

1. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, Stroup NE, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. Neuro Oncol 2013; Suppl 2:ii1-56. doi: 10.1093/neuonc/not151.
2. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007; 114(2):97-109.
3. Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM. Meningioma grading: an analysis of histologic parameters. Am J Surg Pathol. 1997; 21(12):1455-65.
4. Yang SY, Park CK, Park SH, Kim DG, Chung YS, Jung HW. Atypical and anaplastic meningiomas: prognostic implications of clinicopathological features. J Neurol Neurosurg Psychiatry 2008; 79(5):574-80.
5. Santosh S, McCarthy BJ, Villano JL. Update on meningiomas.Oncologist 2011; 16:1604–13. doi:10.1634/theoncologist.2011-0193
6. Perry A, Scheithauer BW, Stafford SL, Lohse CM, Wollan PC. "Malignancy" in meningiomas: a clinicopathologic study of 116 patients, with grading implications. Cancer. 1999; 85(9):2046-56.
7. van Alkemade H, de Leau M, Dieleman EM, Kardaun JW, van Os R, Vandertop WP, van Furth WR, Stalpers LJ. Impaired survival and long-term neurological problems in benign meningioma. Neuro Oncol 2012; 14(5):658-66. doi: 10.1093/neuonc/nos013.
8. Claus EB, Calvocoressi L, Bondy ML, Wrensch M, Wiemels JL, Schildkraut JM. Exogenous hormone use, reproductive factors, and risk of intracranial meningioma in females. J Neurosurg 2013; 118(3):649-56. doi: 10.3171/2012.9.JNS12811.
9. Schildkraut JM, Calvocoressi L, Wang F, Wrensch M, Bondy ML, Wiemels JL, Claus EB. Endogenous and exogenous hormone exposure and the risk of meningioma in men. J Neurosurg 2014; 120(4):820-6. doi: 10.3171/2013.12.JNS131170.
10. Custer BS, Koepsell TD, Mueller BA. The association between breast carcinoma and meningioma in women. Cancer 2002; 94(6):1626-35.
11. Rao G, Giordano SH, Liu J, McCutcheon IE. The association of breast cancer and meningioma in men and women. Neurosurgery 2009; 65(3):483-9; discussion 489. doi: 10.1227/01.NEU.0000350876.91495.E0.
12. Criscitiello C, Disalvatore D, Santangelo M, Rotmensz N, Bazolli B, Maisonneuve P, Goldhirsch A, Curigliano G. No link between breast cancer and meningioma: results from a large monoinstitutional retrospective analysis. Cancer Epidemiol Biomarkers Prev 2014; 23(1):215-7. doi: 10.1158/1055-9965.EPI-13-1041.
13. Carlberg M, Söderqvist F, Hansson Mild K, Hardell L. Meningioma patients diagnosed 2007-2009 and the association with use of mobile and cordless phones: a case-control study. Environ Health 2013; 12(1):60. doi: 10.1186/1476-069X-12-60.
14. Coureau G, Bouvier G, Lebailly P, Fabbro-Peray P, Gruber A, Leffondre K, Guillamo JS, Loiseau H, Mathoulin-Pélissier S, Salamon R, Baldi I. Mobile phone use and brain tumours in the CERENAT case-control study. Occup Environ Med 2014; 71(7):514-22. doi: 10.1136/oemed-2013-101754.
15. Fan Z, Ji T, Wan S, Wu Y, Zhu Y, Xiao F, Zhan R. Smoking and risk of meningioma: a meta-analysis. Cancer Epidemiol 2013; 37(1):39-45. doi: 10.1016/j.canep.2012.09.004.
16. Claus EB, Walsh KM, Calvocoressi L, Bondy ML, Schildkraut JM, Wrensch M, Wiemels JL. Cigarette smoking and risk of meningioma: the effect of gender. Cancer Epidemiol Biomarkers Prev 2012; 21(6):943-50. doi: 10.1158/1055-9965.EPI-11-1059.
17. Turner MC, Krewski D, Armstrong BK, Chetrit A, Giles GG, Hours M, McBride ML, Parent MÉ, Sadetzki S, Siemiatycki J, Woodward A, Cardis E. Allergy and brain tumors in the INTERPHONE study: pooled results from Australia, Canada, France, Israel, and New Zealand. Cancer Causes Control 2013; 24(5):949-60. doi: 10.1007/s10552-013-0171-7.
18. Wiemels JL, Wrensch M, Sison JD, Zhou M, Bondy M, Calvocoressi L, Black PM, Yu H, Schildkraut JM, Claus EB. Reduced allergy and immunoglobulin E among adults with intracranial meningioma compared to controls. Int J Cancer 2011; 129(8):1932-9. doi: 10.1002/ijc.25858.
19. Wang M, Chen C, Qu J, Xu T, Lu Y, Chen J, Wu S. Inverse association between eczema and meningioma: a meta-analysis. Cancer Causes Control 2011; 22(10):1355-63. doi: 10.1007/s10552-011-9808-6.
20. Rajaraman P, Brenner AV, Neta G, Pfeiffer R, Wang SS, Yeager M, Thomas G, Fine HA, Linet MS, Rothman N, Chanock SJ, Inskip PD. Risk of meningioma and common variation in genes related to innate immunity. Cancer Epidemiol Biomarkers Prev 2010; 19(5):1356-61. doi: 10.1158/1055-9965.EPI-09-1151.
21. Bumrungrachpukdee P, Pruphetkaew N, Phukaoloun M, Pheunpathom N. Recurrence of intracranial meningioma after surgery: analysis of influencing factors and outcome. J Med Assoc Thai 2014; 97(4):399-406.
22. Hammouche S, Clark S, Wong AH, Eldridge P, Farah JO. Long-term survival analysis of atypical meningiomas: survival rates, prognostic factors, operative and radiotherapy treatment. Acta Neurochir (Wien) 2014; 156(8):1475-81. doi: 10.1007/s00701-014-2156-z.
23. Palma L, Celli P, Franco C, Cervoni L, Cantore G. Long-term prognosis for atypical and malignant meningiomas: a study of 71 surgical cases. J Neurosurg 1997; 86(5):793-800.
24. Sughrue ME, Sanai N, Shangari G, Parsa AT, Berger MS, McDermott MW. Outcome and survival following primary and repeat surgery for World Health Organization Grade III meningiomas. J Neurosurg 2010; 113(2):202-9. doi: 10.3171/2010.1.JNS091114.
25. Kaul D, Budach V, Wurm R, Gruen A, Graaf L, Habbel P, Badakhshi H. Linac-based stereotactic radiotherapy and radiosurgery in patients with meningioma. Radiat Oncol 2014; 9:78. doi: 10.1186/1748-717X-9-78.
26. Maclean J, Fersht N, Short S. Controversies in radiotherapy for meningioma. Clin Oncol (R Coll Radiol) 2014; 26(1):51-64. doi: 10.1016/j.clon.2013.10.001.
27. Brem SS, Bierman PJ, Brem H, Butowski N, Chamberlain MC, ChioccaEA, *et al*.: Central nervous system cancers. J Natl Compr Canc Netw 2011; 9:352–400
28. Chamberlain MC. Hydroxyurea for recurrent surgery and radiation refractory high-grade meningioma. J Neurooncol 2012; 107(2):315-21. doi: 10.1007/s11060-011-0741-z.
29. Kim MS, Yu DW, Jung YJ, Kim SW, Chang CH, Kim OL. Long-term follow-up result of hydroxyurea chemotherapy for recurrent meningiomas. J Korean Neurosurg Soc 2012; 52(6):517-22. doi: 10.3340/jkns.2012.52.6.517.
30. Chamberlain MC, Glantz MJ. Interferon-alpha for recurrent World Health Organization grade 1 intracranial meningiomas. Cancer 2008; 113(8):2146-51. doi: 10.1002/cncr.23803.
31. Chamberlain MC, Glantz MJ, Fadul CE. Recurrent meningioma: salvage therapy with long-acting somatostatin analogue. Neurology 2007; 69(10):969-73.
32. Simó M, Argyriou AA, Macià M, Plans G, Majós C, Vidal N, Gil M, Bruna J. Recurrent high-grade meningioma: a phase II trial with somatostatin analogue therapy. Cancer Chemother Pharmacol 2014; 73(5):919-23. doi: 10.1007/s00280-014-2422-z.
33. Reardon DA, Norden AD, Desjardins A, Vredenburgh JJ, Herndon JE 2nd, Coan A, Sampson JH, Gururangan S, Peters KB, McLendon RE, Norfleet JA, Lipp ES, Drappatz J, Wen PY, Friedman HS. Phase II study of Gleevec® plus hydroxyurea (HU) in adults with progressive or recurrent meningioma. J Neurooncol 2012; 106(2):409-15. doi: 10.1007/s11060-011-0687-1.
34. Norden AD, Raizer JJ, Abrey LE, Lamborn KR, Lassman AB, Chang SM, Yung WK, Gilbert MR, Fine HA, Mehta M, Deangelis LM, Cloughesy TF, Robins HI, Aldape K, Dancey J, Prados MD, Lieberman F, Wen PY. Phase II trials of erlotinib or gefitinib in patients with recurrent meningioma. J Neurooncol 2010; 96(2):211-7. doi: 10.1007/s11060-009-9948-7.
35. Kaley T, Barani I, Chamberlain M, McDermott M, Panageas K, Raizer J, Rogers L, Schiff D, Vogelbaum M, Weber D, Wen P. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review. Neuro Oncol 2014; 16(6):829-40. doi: 10.1093/neuonc/not330.
36. Choy W, Kim W, Nagasawa D, Stramotas S, Yew A, Gopen Q, Parsa AT, Yang I. The molecular genetics and tumor pathogenesis of meningiomas and the future directions of meningioma treatments. Neurosurg Focus; 30(5):E6. doi: 10.3171/2011.2.FOCUS1116.
37. Perry A, Banerjee R, Lohse CM, Kleinschmidt-DeMasters BK, Scheithauer BW. A role for chromosome 9p21 deletions in the malignant progression of meningiomas and the prognosis of anaplastic meningiomas. Brain Pathol 2002; 12(2):183-90.
38. Peyre M, Stemmer-Rachamimov A, Clermont-Taranchon E, Quentin S, El-Taraya N, Walczak C, Volk A, Niwa-Kawakita M, Karboul N, Giovannini M, Kalamarides M. Meningioma progression in mice triggered by Nf2 and Cdkn2ab inactivation. Oncogene 2013; 32(36):4264-72. doi: 10.1038/onc.2012.436.
39. Dobbins SE, Broderick P, Melin B, Feychting M, Johansen C, Andersson U, Brännström T, Schramm J, Olver B, Lloyd A, Ma YP, Hosking FJ, Lönn S, Ahlbom A, Henriksson R, Schoemaker MJ, Hepworth SJ, Hoffmann P, Mühleisen TW, Nöthen MM, Moebus S, Eisele L, Kosteljanetz M, Muir K, Swerdlow A, Simon M, Houlston RS. Common variation at 10p12.31 near MLLT10 influences meningioma risk. Nat Genet 2011; 43(9):825-7. doi: 10.1038/ng.879.
40. Clark VE, Erson-Omay EZ, Serin A, Yin J, Cotney J, Ozduman K, Avşar T, Li J, Murray PB, Henegariu O, Yilmaz S, Günel JM, Carrión-Grant G, Yilmaz B, Grady C, Tanrikulu B, Bakircioğlu M, Kaymakçalan H, Caglayan AO, Sencar L, Ceyhun E, Atik AF, Bayri Y, Bai H, Kolb LE, Hebert RM, Omay SB, Mishra-Gorur K, Choi M, Overton JD, Holland EC, Mane S, State MW, Bilgüvar K, Baehring JM, Gutin PH, Piepmeier JM, Vortmeyer A, Brennan CW, Pamir MN, Kiliç T, Lifton RP, Noonan JP, Yasuno K, Günel M. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science 2013; 339(6123):1077-80. doi: 10.1126/science.1233009.
41. Brastianos PK, Horowitz PM, Santagata S, Jones RT, McKenna A, Getz G, Ligon KL, Palescandolo E, Van Hummelen P, Ducar MD, Raza A, Sunkavalli A, Macconaill LE, Stemmer-Rachamimov AO, Louis DN, Hahn WC, Dunn IF, Beroukhim R. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. Nat Genet 2013; 45(3):285-9. doi: 10.1038/ng.2526.
42. Goutagny S, Bah AB, Henin D, Parfait B, Grayeli AB, Sterkers O, Kalamarides M. Long-term follow-up of 287 meningiomas in neurofibromatosis type

2 patients: clinical, radiological, and molecular features. Neuro Oncol 2012; 14(8):1090-6. doi: 10.1093/neuonc/nos129.
43. Bujko M, Kober P, Tysarowski A, Matyja E, Mandat T, Bonicki W, Siedlecki JA. EGFR, PIK3CA, KRAS and BRAF mutations in meningiomas. Oncol Lett 2014; 7(6):2019-2022.
44. Pang JC, Chung NY, Chan NH, Poon WS, Thomas T, Ng HK. Rare mutation of PIK3CA in meningiomas. Acta Neuropathol 2006; 111(3):284-5.
45. Peters N, Wellenreuther R, Rollbrocker B, Hayashi Y, Meyer-Puttlitz B, Duerr EM, Lenartz D, Marsh DJ, Schramm J, Wiestler OD, Parsons R, Eng C, von Deimling A. Analysis of the PTEN gene in human meningiomas. Neuropathol Appl Neurobiol 1998; 24(1):3-8.
46. Goutagny S, Nault JC, Mallet M, Henin D, Rossi JZ, Kalamarides M. High Incidence of Activating TERT Promoter Mutations in Meningiomas Undergoing Malignant Progression. Brain Pathol 2014; 24(2):184-9. doi: 10.1111/bpa.12110.
47. Roser F, Nakamura M, Bellinzona M, Rosahl SK, Ostertag H, Samii M. The prognostic value of progesterone receptor status in meningiomas. J Clin Pathol 2004; 57(10):1033-7.
48. Mukherjee S, Ghosh SN, Chatterjee U, Chatterjee S. Detection of progesterone receptor and the correlation with Ki-67 labeling index in meningiomas. Neurol India 2011; 59(6):817-22. doi: 10.4103/0028-3886.91357.
49. Sluyser M. Mutations in the estrogen receptor gene. Hum Mutat 1995; 6(2):97-103.
50. Fakhrjou A, Meshkini A, Shadrvan S. Status of Ki-67, estrogen and progesterone receptors in various subtypes of intracranial meningiomas. Pak J Biol Sci 2012; 15(11):530-5.
51. Andrae N, Kirches E, Hartig R, Haase D, Keilhoff G, Kalinski T, Mawrin C. Sunitinib targets PDGF-receptor and Flt3 and reduces survival and migration of human meningioma cells. Eur J Cancer 2012; 48(12):1831-41. doi: 10.1016/j.ejca.2012.01.032.
52. Memorial Sloan-Kettering Cancer Center. Phase II Trial of Sunitinib (SU011248) in Patients With Recurrent or Inoperable Meningioma In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2014 Mar 03]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT00589784 NLM Identifier: NCT00589784.
53. Beltran H, Kaur G, de España CG, Tagawa ST. Exploring the role of anti-angiogenic therapies in prostate cancer: results from the phase 3 trial of sunitinib. Asian J Androl 2014; 16(4):568-9. doi: 10.4103/1008-682X.127822.
54. Dharmalingam P, Roopesh Kumar VR, Verma SK. Vascular endothelial growth factor expression and angiogenesis in various grades and subtypes of meningioma. Indian J Pathol Microbiol 2013; 56(4):349-54. doi: 10.4103/0377-4929.125286.
55. Nunes FP, Merker VL, Jennings D, Caruso PA, di Tomaso E, Muzikansky A, Barker FG 2nd, Stemmer-Rachamimov A, Plotkin SR. Bevacizumab treatment for meningiomas in NF2: a retrospective analysis of 15 patients. PLoS One 2013; 8(3):e59941. doi: 10.1371/journal.pone.0059941.
56. SCRI Development Innovations, LLC. A Phase II Trial of the Combination of Bevacizumab and Everolimus in Patients With Refractory, Progressive Intracranial MeningiomaIn: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2014 Mar 03]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT00972335 NLM Identifier: NCT00972335.
57. Boldrini L, Pistolesi S, Gisfredi S, Ursino S, Alì G, Pieracci N, Basolo F, Parenti G, Fontanini G. Expression of endothelin 1 and its angiogenic role in meningiomas. Virchows Arch 2006; 449(5):546-53.
58. Werner H, Leroith D. Insulin and insulin-like growth factor receptors in the brain: Physiological and pathological aspects. Eur Neuropsychopharmacol 2014; pii: S0924-977X(14)00041-8. doi: 10.1016/j.euroneuro.2014.01.020.
59. Heidegger I, Kern J, Ofer P, Klocker H, Massoner P. Oncogenic functions of IGF1R and INSR in prostate cancer include enhanced tumor growth, cell migration and angiogenesis. Oncotarget 2014; 5(9):2723-35.
60. Iglesias Gómez JC, Mosquera Orgueira A. An integrative analysis of meningioma tumors reveals the determinant genes and pathways of malignant transformation. Front Oncol 2014; 4:147. doi: 10.3389/fonc.2014.00147.
61. Ammoun S, Schmid MC, Ristic N, Zhou L, Hilton D, Ercolano E, Carroll C, Hanemann CO. The role of insulin-like growth factors signaling in merlin-deficient human schwannomas. Glia 2012; 60(11):1721-33. doi: 10.1002/glia.22391.
62. Collins IM, Beddy P, O'Byrne KJ. Radiological response in an incidental meningioma in a patient treated with chemotherapy combined with CP-751,871, an IGF-1R inhibitor. Acta Oncol 2010; 49(6):872-4. doi: 10.3109/02841861003752408.
63. Chaudhary B, Khaled YS, Ammori BJ, Elkord E. Neuropilin 1: function and therapeutic potential in cancer. Cancer Immunol Immunother 2014; 63(2):81-99. doi: 10.1007/s00262-013-1500-0.
64. Koch S, van Meeteren LA, Morin E, Testini C, Weström S, Björkelund H, Le Jan S, Adler J, Berger P, Claesson-Welsh L. NRP1 presented in trans to the endothelium arrests VEGFR2 endocytosis, preventing angiogenic signaling and tumor initiation. Dev Cell 2014; 28(6):633-46. doi: 10.1016/j.devcel.2014.02.010.
65. Barresi V, Tuccari G. Increased ratio of vascular endothelial growth factor to semaphorin3A is a negative prognostic factor in human meningiomas. Neuropathology 2010 Mar 10. [Epub ahead of print]
66. Glinka Y, Stoilova S, Mohammed N, Prud'homme GJ. Neuropilin-1 exerts co-receptor function for TGF-beta-1 on the membrane of cancer cells and enhances responses to both latent and active TGF-beta. Carcinogenesis 2011; 32(4):613-21. doi: 10.1093/carcin/bgq281.
67. Zhang Q, Yu N, Lee C. Mysteries of TGF-β Paradox in Benign and Malignant Cells. Front Oncol 2014; 4:94. doi: 10.3389/fonc.2014.00094.
68. Patnaik A, LoRusso PM, Messersmith WA, Papadopoulos KP, Gore L, Beeram M, Ramakrishnan V, Kim AH, Beyer JC, Mason Shih L, Darbonne WC, Xin Y, Yu R, Xiang H, Brachmann RK, Weekes CD.A Phase Ib study evaluating MNRP1685A, a fully human anti-NRP1 monoclonal antibody, in combination with bevacizumab and paclitaxel in patients with advanced solid tumors. Cancer Chemother Pharmacol 2014; 73(5):951-60. doi: 10.1007/s00280-014-2426-8.
69. Starzec A, Miteva MA, Ladam P, Villoutreix BO, Perret GY. Discovery of novel inhibitors of vascular endothelial growth factor-A-Neuropilin-1 interaction by structure-based virtual screening. Bioorg Med Chem 2014; 22(15):4042-8. doi: 10.1016/j.bmc.2014.05.068.
70. van Roy F. Beyond E-cadherin: roles of other cadherin superfamily members in cancer. Nat Rev Cancer 2014; 14(2):121-34. doi: 10.1038/nrc3647.
71. Pecina-Slaus N, Cicvara-Pecina T, Kafka A. Epithelial-to-mesenchymal transition: possible role in meningiomas. Front Biosci (Elite Ed) 2012; 4:889-96.
72. Nelson WJ, Nusse R. Convergence of Wnt, beta-catenin, and cadherin pathways. Science 2004; 303(5663):1483-7.
73. Pham MH, Zada G, Mosich GM, Chen TC, Giannotta SL, Wang K, Mack WJ. Molecular genetics of meningiomas: a systematic review of the current literature and potential basis for future treatment paradigms. Neurosurg Focus 2011; 30(5):E7. doi: 10.3171/2011.2.FOCUS1117.
74. Ragel BT, Couldwell WT, Wurster RD, Jensen RL. Chronic suppressive therapy with calcium channel antagonists for refractory meningiomas. Neurosurg Focus 2007; 23(4):E10.
75. Di Vinci A, Brigati C, Casciano I, Banelli B, Borzì L, Forlani A, Ravetti GL, Allemanni G, Melloni I, Zona G, Spaziante R, Merlo DF, Romani M.HOXA7, 9, and 10 are methylation targets associated with aggressive behavior in meningiomas.Transl Res 2012; 160(5):355-62. doi: 10.1016/j.trsl.2012.05.007.
76. Rudling MJ, Angelin B, Peterson CO, Collins VP. Low density lipoprotein receptor activity in human intracranial tumors and its relation to the cholesterol requirement. Cancer Res 1990; 50(3):483-7.
77. Cattaneo M, Baronchelli S, Schiffer D, Mellai M, Caldera V, Saccani GJ, Dalpra L, Daga A, Orlandi R, DeBlasio P, Biunno I. Down-modulation of SEL1L, an unfolded protein response and endoplasmic reticulum-associated degradation protein, sensitizes glioma stem cells to the cytotoxic effect of valproic acid. J Biol Chem 2014; 289(5):2826-38. doi: 10.1074/jbc.M113.527754.

Upcoming Congresses and Meetings

EMBO | EMBL Symposium - Frontiers in Stem Cells and Cancer

29th - 31st March, 2015

Heidelberg, Germany

This conference aims to establish an interactive forum for stem cell- and molecular biologists that study pluripotency and its impact on cancer. Major emphases are cancer growth- and stem cell self-renewal mechanisms, their regulation by epigenetic means and non-coding RNAs. As such, the meeting is designed to connect scientists working in some of the most-intensely studied areas of research, not usually interacting in a concise conference setting.

www.embo-embl-symposia.org/symposia/2015/EES15-01/index.html

Gordon Research Conference — Cancer Genetics and Epigenetics 2015

12th - 7th April, 2015

Lucca, Italy

The causative links between genomic and genetic variations and cancer are well documented and have provided a greater understanding of tumour genesis and cancer progression. Molecular genetic information has been used to derive new therapeutic regimens and has accelerated the development and application of "personalised cancer medicine".

There are also an increasing appreciation that epigenetic aberrations that are often directly caused by genetic defects resulting in loss- or gain-of-function of epigenetic-regulators also contribute significantly to cancer onset and progression. Indeed, parallel integration of our knowledge of the cancer genome and epigenome using sophisticated "omics-based" technologies and high throughput functional screening techniques are providing even more tangible links between genetic/genomic aberrations, epigenetic/epigenomic dysregulation and tumour genesis. This information is being functionally validated using experimental models that accurately reflect the underlying genetic and epigenetic alterations observed in human tumour samples.

Moreover, the information is being translated into clinical use through the development of genetic and epigenetic biomarkers of cancer development, evolution, heterogeneity and response to therapeutic intervention.

This GRC series focuses on the advances in discovering and validating "driver" mutations in cancer genes, understanding the downstream consequences of these genetic changes on the epigenome and how this information is being best utilised to advance cancer detection, monitoring and therapy.

www.grc.org/programs.aspx?id=12552

3rd ESTRO Forum

24th - 28th April, 2015

Barcelona, Spain

The 3rd ESTRO Forum will provide a wonderful platform in which to explore innovations and the latest advances in radiation oncology.

www.estro.org

Controlling Cancer Summit

12th - 14th April, 2015

London, UK

With plenty of opportunity for networking and debate, this informal international meeting will bring you up to date with current research and thinking regarding cancer screening, prevention and treatment. Presenters will include Clinicians, Academics and members of the Pharmaceutical industry and we encourage presentations from the wide spectrum of cancer research, development and healthcare professionals.

www.regonline.co.uk/cancer2015

International Cancer Screening Network (ICSN) Meeting 2015

2nd - 4th June, 2015

Rotterdam, Netherlands

The International Cancer Screening Network (ICSN) Meeting focuses on collaborative research that is aimed at identifying and fostering efficient and effective approaches to cancer control through population-based screening. Meeting topics will include: - Individualised screening - Implementation and lessons learned from organised programs in middle-to-high-resource countries -

Optimising benefits and minimising harms; evidence on screening effectiveness - Screening in low-resource countries and populations - Informed decision making in cancer screening .

The ICSN is a voluntary consortium of countries that have active population-based cancer screening programs. The consortium was established in December 1988 as the International Breast Cancer Screening Database Project during an international workshop involving representatives from 11 countries. The consortium has since grown to encompass more than 30 countries and now addresses colorectal, cervical, and other types of cancer screening. The ICSN is dedicated to collaborative research aimed at identifying and fostering efficient and effective approaches to cancer control worldwide through population-based screening. It does not address efficacy or use clinical trials data.

www.scgcorp.com/ICSN2015/

8th International Symposium on "Focal Therapy and Imaging in Prostate and Kidney Cancer"

21st - 23rd June, 2015

Noordwijk, Netherlands

During our three day event, which aims to incorporate real-time imaging into the diagnostic and treatment strategy for prostate and kidney cancer, delegates will have the opportunity to get valuable insights by attending to an exciting and interactive scientific program with state-of-the-art presentation, video demonstrations and hands- on workshops, delivered by a World-class faculty. Participants will also have the opportunity to networking with our faculty and exchange opinions and experiences.

www.focaltherapy.org/

Annual Meeting on Supportive Care in Cancer

25th - 27th June, 2015

Copenhagen, Denmark

MASCC/ISOO 2015 Annual Meeting will focus on new developments, evidence-based supportive care, challenges and modern technology in supportive cancer care. 2015 will feature an early acceptance/rejection for abstract submission, state-of-the art program and expert faculty.

http://mascc2015.kenes.com

Oncologic Imaging Course

25th - 27th June, 2015

Dubrovnik, Croatia

www.oncoic.org

World Conference on Lung Cancer

6th -10th September, 2015

Denver, Colorado, USA

www.iaslc.org

International Meeting of the European Society of Gynaecological Oncology

24th - 27th October, 2015

Nice, France

Join over 2500 colleagues in the beautiful city of Nice for ESGO 2015; a unique educational experience where you will benefit and learn about the newest developments, innovative techniques and advanced practices in gynaecological oncology.

http://www.bad.org.uk/

Advanced Breast Cancer Third International Consensus Conference (ABC3)

5th - 7th November, 2015

Lisbon, Portugal

ABC Consensus Conferences have the ambitious goal of improving outcomes for all patients with advanced breast cancer. We believe that, backed by strong political advocacy, ABC guidelines will raise standards of care, improve awareness about how best to meet the needs of this underserved group of patients, and help identify research priorities so that clinical research is focused on the most important areas of unmet need.

http://esgo2015.esgo.org

AACR Annual Meeting

16th - 23rd April, 2016

Louisiana, USA

http://www.aacr.org

American Society of Clinical Oncology 2016 Annual Meeting

3rd - 7th June 2016

Chicago, USA

Attendees of the 2016 Annual Meeting will find cutting-edge scientific presentations and comprehensive educational content. The ASCO Annual Meeting brings together more than 25,000 oncology professionals from a broad range of specialties, making it an excellent venue for exploring the theme of the Meeting — "Science and Society." Prospective attendees can familiarise themselves with some basic information, including: The various session types that will take place at the Annual Meeting, The Cancer Education and Scientific Program Committees.

http://am.asco.org/

17th World Conference on Lung Cancer 2016

4th - 7th December 2016

Vienna, Austria

The World Conference on Lung Cancer (WCLC) is the world's largest meeting dedicated to lung cancer and other thoracic malignancies. More than 7,000 delegates come from more than 100 countries to discuss the latest developments in thoracic malignancy research. Attendees include surgeons, medical oncologists, radiation oncologists, pulmonologists, radiologists, pathologists, epidemiologists, basic research scientists, nurses and allied health professionals and patients.

www.iaslc.org/events/17th-world-conference-lung-cancer

For a more extensive list of upcoming events please visit : www.cambridgeresearchcentre.co.uk

The International Liver Cancer Association Announces its 9th Annual Conference

ILCA 2015

4 – 6 September 2015
Paris, France

ILCA
International Liver Cancer Association

Conference Highlights:

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www.ilca2015.org

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