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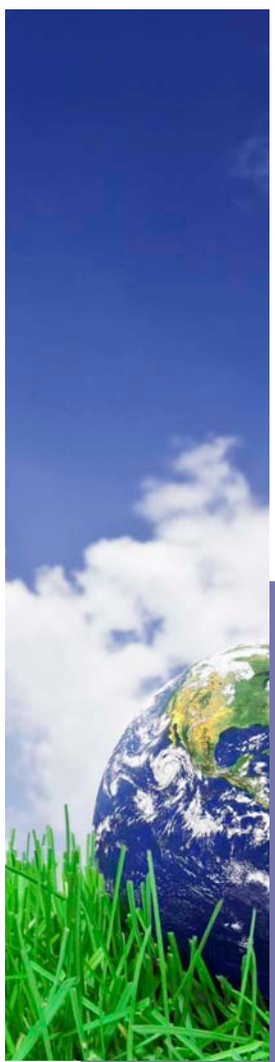

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Proceedings of the Workshop 'Rare cancers: the added value of closer cooperation'

Brussels, 12 July 2011

ENVI

EN Executive summary: DE/FR 2011

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ENVIRONMENT, PUBLIC HEALTH AND FOOD SAFETY

Workshop
'Rare Cancers:
The added value of closer cooperation'

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Proceedings

Abstract
In 2003, the EU established a 'cap & trade' emissions trading system (EU ETS) for greenhouse gas emissions of large industrial sources such as power plants and steel works. Covered installations need a tradable allowance for each tonne of their emissions. To ensure a reduction the cap is constantly reduced. The workshop discussed the basic functioning of the EU ETS and how emission reduction projects outside the EU, so called Flexible Mechanisms, can be used for compliance.

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This workshop was requested by the European Parliament's Committee on Environment, Public Health and Food Safety.

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EXECUTIVE SUMMARY

This report summarises the presentations and discussions at the Workshop on “Rare Cancers: The added value of closer cooperation” (Brussels, Tuesday 12 July 2011). The workshop was held by the Committee on Environment, Public Health and Food Safety (ENVI) of the European Parliament, and it was hosted by Ms Glenis WILLMOTT (MEP) and Mr Alojz PETERLE (MEP), co-chairs of the ENVI Committee’s Working Group on Health. The aim of the workshop was to gain a better understanding of the problem of rare cancers in Europe from the epidemiological, clinical, research and human stand points. Speakers included European Commission officials, academic experts, representatives from industry as well as patient organisations, and patients who have survived rare cancers.

A number of Members of the European Parliament (MEPs) were in attendance, including Mr Paolo BARTOLOZZI, Mr Michael CASHMAN, Ms Nessa CHILDERS, Ms Sidonia Elżbieta JĘDRZEJEWSKA, Ms Linda McAVAN, Dr Miroslav MIKOLÁŠIK, and Ms Christel SCHALDEMOSE.

Although each rare cancer strikes a relatively small number of people (the threshold for rare diseases is less then 5 cases per 100,000 year), these diseases in total account for an estimated 20% of cancer cases in Europe, and affect over half a million Europeans each year, including about 15,000 children and adolescents.

The first part of the workshop was dedicated to the Importance of Special Recognition for Rare (Orphan) Cancers in the context of the foreseen revision of the EU Clinical Trials Directive. In her opening remarks, Ms Glenis WILLMOTT (MEP) said that: ‘When we talk about added values of cooperation in Europe on rare cancers, the EU Clinical Trials Directive is probably one of the most important pieces of legislations to look at”. The Clinical Trials Directive aims at improving how the trials are conducted, including donations to tissue banks, which some Member States do not allow. Ms WILLMOTT underlined that "the Clinical Trials Directive needs improvement” in order to address rare cancers more effectively.

In the first presentation, Dr Andrzej Rys, Director of Health Systems and products at DG SANCO, acknowledged that the EU Clinical Trials Directive is not working properly, and the European Commission is preparing a proposal for its revision. One goal of the revision is to ensure that rules are clear and uniform across EU Member States.

Professor Paolo CASALI from the European Society for Medical Oncology (ESMO) discussed problems in developing treatments for rare cancers, and also noted that varying interpretations of the Directive across Member States were among the difficulties.

Dr Ruth LADENSTEIN, President of the European Society for Paediatric Oncology (SIOPE)/ European Network for Cancer Research in Children and Adolescents (ENCCA), highlighted the importance of differentiating between adult and child cancer treatment. Children are still “pharmaceutical orphans”, she said, and when they lack alternatives, doctors often prescribe them treatments used for adults as research is still needed on proper drugs and doses for children.

Professor Françoise MEUNIER, Director General of the European Organization for the Research and Treatment of Cancer (EORTC), noted that the Clinical Trials Directive needs to be “streamlined, simplified and harmonized” across countries to find out how to treat specific rare cancers more effectively.

Jan GEISSLER, Director of the Chronic Myelogenous Leukemia (CML) Network and a former sufferer of CML, presented his concerns over the Clinical Trials Directive, which he said had reduced participation rates in drug trials for rare cancers and increased costs and administrative requirements.

Paediatric oncology specialist Professor David WALKER from the University of Nottingham (UK) and his former patient, 14-year old Sam WHITE, who survived a rare brain cancer, discussed Sam’s treatment through an interactive dialog amongst them. A presentation by another former cancer patient (Peter WILKINSON, age 25) highlighted the human importance of the topic. He told the workshop about his treatment for pinealoblastoma, also a rare brain cancer. Peter WILKINSON then presented moving video footage from jimmyteens.tv (a website for young cancer sufferers to express themselves creatively) where he now works. The video was by and about a 15-year old girl regular contributor to the site who lost her battle with cancer in 2008.

The second part of the workshop, on Improving Radiation Therapies and Drug Development for Rare Cancers, looked at actions to treat rare cancers.

Dr Maria-José VIDAL-RAGOUT, Head of the Medical Research Unit at DG Research and Innovation, reviewed current activities funded by the EU’s 7th Framework Programme for Research to address rare cancers, as well as future prospects.

Professor Gilles VASSAL from the *Institut Gustave Roussy* (France) and President of the European Network for Innovative Therapies for Children with Cancer, said that children's needs are not being met in Europe, as the development of new treatments focuses on adults. He called for further public investment in research, public/private partnerships and improvements in the Paediatric Medicine Regulation.

Dr Pamela COHEN of Sanofi described research to identify new drug treatments for rare cancers. She explained that research into common cancers has identified important molecular sub-types, some of which could be recognised as rare cancers as they affect only a small share of the population. This new understanding helps to focus research on specific treatments for each sub-type.

Dr Stephanie COMBS from the EU-funded Union of Light Ion Centres in Europe (ULICE) presented new cancer treatment techniques involving proton and carbon ion radiation. She strengthened the high precision of ion beam therapy for moving targets. She added that proton radiotherapy in Paediatrics provides a great margin of benefit.

In his closing remarks, Mr Alojz PETERLE (MEP), recalled a slide presented at the workshop by one of the speakers that stated “20% more patients would be alive if...”. Our task, he said, is to address that “if”. He added that there are “no holidays in the fight against cancer... there are many rare cancers’’. He said that as a result of this Workshop, “We know more, we wish to know more and we wish to do more.’’

1. INTRODUCTION

Around four million people in the European Union are affected by rare cancers. Despite the rarity of each of the 186 rare cancers, they represent in total about 22% of all cancer cases, including all cancers in children, diagnosed in the EU27 each year. Rare cancers are a subset of rare diseases, which are defined as affecting no more than 5 per 10,000 persons.[1] Because of the scarcity of expertise, rare cancers and other rare diseases are often diagnosed late or misdiagnosed, resulting in additional suffering for the patients. Moreover, fewer treatments have developed for rare diseases than for common ones. For these reasons, rare diseases are an important policy concern for public health in Europe.

Access to appropriate health care for rare cancers differs significantly among Member States. There is therefore considerable scope for action at the EU level, both in promoting research and in sharing the scarce available knowledge on rare cancers. European cooperation can help ensure that knowledge can be shared and resources combined as efficiently as possible, in order to tackle rare diseases effectively across the EU as a whole.[2]

The European Clinical Trials Directive 2001/20/EC (EUCTD) was introduced to establish standardisation of research activity in clinical trials throughout the European Community. In its Communication of 10 December 2008 on "Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector", the Commission announced that an assessment would be made of the application of the Clinical Trials Directive. This assessment will consider various options for improving the functioning of the Clinical Trials Directive with a view to making legislative proposals, if appropriate, while taking the global dimension of clinical trials into account.[3]

To ensure greater harmonisation, the Commission is considering replacing the Directive with a Regulation, or a new Directive and a Regulation, which would cover different parts of the existing Directive.[4] Special recognition would be given to rare cancers within this new legislative framework.

Section 2 of this report includes a brief review of the policy background to the workshop. Section 3 then provides an overview of the workshop proceedings: summaries of all the presentations are included, as well as reports of subsequent question and answer sessions. Short biographies of the experts are provided in section 4. Annex I provides the Workshop Programme. The slides provided by the experts are presented in Annex II.

[1] "Useful Information on Rare Diseases from an EU Perspective". European Commission. http://ec.europa.eu/health/ph_information/documents/ev20040705_rd05_en.pdf

[2] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Committee of the Regions on Rare Diseases: Europe's challenges {SEC(2008)2713}{SEC(2008)2712} http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

[3] http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm

[4] Cancer Research UK: Policy Statement ,EU Clinical Trials Directive, September 2010 http://info.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@pol/documents/generalcontent/cr_070475.pdf

2. POLICY BACKGROUND

The EU has taken several important steps to address the issues relating to rare diseases, through legislation, research funding and also through policy strategies.

The Orphan Medicinal Product Regulation[5] seeks to encourage the research, development and marketing of medicines to treat, prevent or diagnose rare diseases. This regulation also set up the criteria for orphan designation in the EU and identifies incentives (e.g. 10-year market exclusivity, protocol assistance, access to the Centralised Procedure for Marketing Authorisation).[6]

As the first EU effort in this area, specific attention in the action plan was given to improving knowledge and facilitating access to information about these diseases. Within this action plan and the subsequent Programme of the Community Action in the field of public health[7] (2003-2008), numerous projects have been supported, including Orphanet, the European database of rare diseases and 'orphan' drugs (drugs for treatment of rare diseases).

The EU Clinical Trials Directive (Directive 2001/20/EC) has the aim of simplifying and harmonising the administrative requirements for clinical trials across the EU, whilst ensuring the safety of clinical trial participants, the ethical soundness of trials and the reliability and robustness of data generated.[8] Subsequently, legislation governing the development and authorisation of medicines for use in children (i.e. aged 0-17 years) was introduced in the European Union in January 2007. The new piece of legislation - Regulation (EC) No 1901/2006, as amended (the 'Paediatric Regulation') - changed the regulatory environment for paediatric medicines to better protect the health of children in the EU. The Paediatric Regulation brought new tasks and responsibilities for the European Medicines Agency, chief of which is the creation and operation of a Paediatric Committee within the Agency to provide objective scientific opinions on any development plan for medicines for use in children.[9]

The EU also supports research on rare cancers. In the current Seventh Framework Programme for Research and Technological Development (FP7 2007-2013), the Health Theme of the "Cooperation" Specific Programme finances multinational collaborative research in different forms. The main focus of the Health theme in the rare diseases area are Europe-wide studies of natural history, pathophysiology, and the development of preventive, diagnostic and therapeutic interventions.

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[5] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

[6] In order for a medicinal product to be granted orphan drug status , the medicine must fulfill a series of criteria:
1- prevalence of fewer than 5 disease cases out of a population of 10,000 people, or an expected return of investment that is insufficient to cover the cost of development;
2-the disease must be either life threatening, seriously debilitating or chronic and serious, and
3- it must be assumed to represent a clinically significant advantage to or a major contribution to patient care compared to existing treatments, if satisfactory methods exist.
These decisions are made by the European Medicine Agency's Committee for Orphan Medicinal Products (COMP).

[7] Decision No 1786/2002/EC of the European Parliament and of the Council of 23 September 2002 adopting a programme of Community action in the field of public health (2003-2008)

[8] NHS Confederation: Clinical Trials Directive
http://www.nhsconfed.org/NATIONALANDINTERNATIONAL/NHSEUROPEANOFFICE/OURWORK/CLINICAL-TRIALS/Pages/Clinical_trials_directive.aspx

[9] European Medicines Agency, Paediatric Medicine Development:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cd&jsenabled=true

The EU Health Strategy "Together for Health: A Strategic Approach for the EU 2008-2013"[10] identified rare diseases as one of the priorities for EU action.

The Commission's 2008 Communication on Rare diseases - Europe's challenges[11], sets the scope for further policy initiatives in this area. It aims to set out an overall strategy for rare diseases, and focuses on the areas of improving recognition and visibility on rare diseases, supporting policies on rare diseases in the Member States and developing European cooperation, coordination and regulation for rare diseases. The Communication strives to give direction to present and future Community activities in the field of rare diseases in order to further improve the access and equity to prevention, diagnosis and treatment for patients suffering from a rare disease throughout the European Union.

In response to this Communication from the Commission, the Council issued a Recommendation in 2009 on a European action in the field of rare diseases[12] which recommends that Member States put in place strategies at national level to implement the EU action (e.g. National Plans for Rare Diseases). This addresses several issues, including the development and marketing of medicines for treatment of rare diseases.

[10] White Paper Together for Health: A Strategic Approach for the EU 2008-2013 (COM(2007) 630 final) of 23 October 2007
[11] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases - Europe's challenges (COM(2008)679final) Welcome Package on Public Health
[12] Council Recommendation of 8 June 2009 on the action in the field of rare diseases (2009/C 151/02)

3. PROCEEDINGS OF THE WORKSHOP

3.1. Part 1: On the importance of special recognition for rare cancers in the revision of the EU Clinical Trials Directive

3.1.1. Welcome and opening – Glenis WILLMOTT and Alojz PETERLE (MEPs): Co-chairs, Working Group on Health

In opening the workshop, Ms WILLMOTT stressed that the Clinical Trials Directive is one of the most important pieces of legislation to look at when addressing rare cancers. She gave a special welcome to two young members of her East Midlands constituency at the workshop who survived rare cancers (Sam WHITE and Peter WILKINSON).

Mr PETERLE noted the importance of cooperation in the fight against rare cancers. He highlighted the need to conduct clinical trials in different countries to find the best way to treat rare cancers. Cross-border trials are difficult and very expensive, and the European Parliament aims to improve the Clinical Trials Directive and adopt the responses to it by 2012.

3.1.2. Andrzej RYS – Director of Health Systems and Products, European Commission, Directorate General for Health and Consumer Policy (DG SANCO)

Dr. RYS provided insights into the upcoming revision of the Clinical Trials Directive. He highlighted the EU's policy on rare diseases, noting that Europe is a global leader in this field. Dr Rys also emphasised the role of the EU in pharmaceutical regulation, and he mentioned the public consultation to assess the functioning of the Clinical Trials Directive (2001/20/EC), which was held between 9 October 2009 and 8 January 2010 and which received close to 140 responses. He underlined the value of this consultation and stated that DG SANCO hoped to publish the results soon. He also noted that a revision of the Directive is under preparation, and he hoped that the Commission could present it by the second quarter of 2012.

Dr. RYS said that fast and efficient approval process is needed for the revision, because the number of Clinical Trials in the EU is decreasing. The aim of the Directive should be to make the process better and safer for patients, researchers and industry, so that more Clinical Trials can occur.

Dr. RYS stressed the need for cooperation among research communities in Member States. Here, he said, there is a need to simplify rules and make them more adaptable. He emphasized that public research money should be used to subsidise research networks: this should be discussed in the context of the next framework programme, and both commercial and non-commercial organisations should be able to participate.

The Clinical Trials Directive is about how trials should be conducted. The system needs to be operational with multinational trials working in the benefit of patients. Dr. RYS reported that in March 2011, the European Commission launched a public register of all clinical trials underway within the European Union, with the aim of making medical research on drugs more transparent for patients, and this tool can be used to understand what is going on in Europe today.

3.1.3. Paolo CASALI – Executive board of European Action against Rare Cancers, European Society for Medical Oncology (ESMO)

Professor CASALI first referred to the European Society for Medical Oncology (ESMO) slogan: "Rare Cancers: More common than you think!" to explain that cancers are rare individually, but not on a collective level. Depending on the definition of 'rare', rare tumours represent in total approximately 20% of all cancer types, including all childhood cancers. Tackling rare cancers is a multi-stakeholder action process, and increased collaboration is needed. The conference on "Rare Cancers in Europe: Policy Challenges and Solutions", held by ESMO in conjunction with the pharmaceutical industry in November 2008, reached consensus on 39 recommendations to improve patient access to clinical trials: topics include regulatory approaches and organizational challenges.

Professor CASALI stated that rare cancer patients face a disadvantage because of problems in the regulation of treatments for orphan diseases. Because of the small number of patients who can participate in trials, a higher degree of uncertainty should be accepted for clinical decision making and regulators, if not, cancer patients are discriminated against. Another problem is related to the reimbursement of drugs. He warned that the gap between drug approval and reimbursement approval is widening. He called for a regulator at EU level instead of different regulations in 27 Member States.

He told the workshop that in February 2012 there will be a stakeholder event in Brussels to see if new methodologies for clinical trials are practicable and effective. More evidence needs to be gathered to see what works for patients and what new rules are needed. In particular, small clinical trials are needed for specific rare cancers, as there are only a small number of patients, and this presents an economic challenge. Professor Casali suggested that funding approaches might change and the pharmaceutical industry need not provide full funding for such trials.

Professor CASALI also spoke of the urgent need for a European Framework to tackle rare cancers as there are only a limited number of centres of excellence across Europe involved in this work. He stressed that FP7 clinical trials projects and EU-wide reference networks of clinical excellence carrying out these trials need infrastructure and facilities should be shared in order to reduce costs.

Professor CASALI highlighted that the way the Clinical Trials Directive is interpreted in 27 countries is also important. For example, there can be difficulties to obtain tissue samples in EU-wide trials, as some Member States interpret the Directive, in particular data protection and privacy rights, in non-homogenous ways. He stressed the need for an improved quality of data and quality of treatment, and concluded that a balance between privacy rights and research needs is required so that more lives can be saved.

Professor CASALI's presentation on "The problem of rare cancers'' can be found in Annex II.

3.1.4. Ruth LADENSTEIN- President of the European organisation for promoting optimal standards of care for children and young people with cancer (SIOPE); Coordinator of FP7 funded project ENCCA (European Network for Cancer Research in Children and Adolescents)

Dr. LADENSTEIN stated that for the purposes of research, children are often considered as miniature adults, which is a mistake as they are different in many aspects. She noted that 20% of the population in Europe is under 18 years of age and that there are 15,000 new cases of rare cancers in children and adolescents. She told the workshop that 3,000 children die each year; moreover, approximately 500,000 Europeans could be alive if they had access to the support available today. She also mentioned that survival rates in paediatric cancer 30 years ago ranged from 0 to 10%, and are closer to 80% today due to advances in research. However, to reach 90% survival rates in the coming years requires help from all of the policy makers, industry and scientific communities.

The critical issue, she said, is that children are still so to speak 'pharmaceutical orphans', despite the 2006 Paediatric Regulation. Dr LADENSTEIN explained that over the last 30 years there has been a lack of drugs for children, and there are currently major challenges in using off-label drugs.

Dr. LADENSTEIN noted that ENCCA is a network of excellence funded by the EU FP7 Framework Programme for research and technological development. For 2011-2014, its activities include the implementation of a European strategy for paediatric and adolescent oncology research, as well as training and education to harmonise multi-national trials across Europe. She added that bureaucracy and insurance are obstacles. She called for a refined risk differentiation and low regulatory burden and welcomed the idea of Member States covering insurance risk in Clinical Trials. Finally, she concluded that more attention to children, to the same level as that for adults, is needed- especially in rare disease orphan cases.

Dr LADENSTEIN's presentation on the "Needs of Children and Adolescents with Cancer'' can be found in Annex II.

3.1.5. Jan GEISSLER- Founder of the Chronic Myelogenous Leukemia (CML) Network

Mr GEISSLER started by welcoming the time allocated for patients' voices in the Workshop. He explained that he was a rare cancer patient during 10 years and was part of a Clinical Trial.

Mr GEISSLER said strong inequalities exist between groups of cancer patients: some have seen much stronger advances in survival rates than others. He outlined the specific challenges faced by rare cancer patients, which include: late or incorrect diagnosis, lack of access to therapies and clinical expertise, slow pace of research results, and lack of interest in funding rare cancer patient groups. He explained that during his treatment, he was forced to travel 800 km per week to participate in a clinical trial. He also stated that patients face stigma and discrimination at work as people haven't heard about their cancers before. Raising public awareness and identifying funding is very difficult, he said.
Mr GEISSLER explained how there are 6,000-8,000 rare diseases, and that approximately 250 of these are rare cancers (out of a total of 280 cancers).

He stressed that the policy challenge is to unite, not divide, groups working on rare diseases and those working on cancers.

He pointed out that when the Clinical Trial Directive was established in 2001, its main rationales included the safety of participants and the harmonisation of methods across the EU, as well as the reliability and robustness of trial data. In his view, however, implementation did not serve the interests of the patients, nor of researchers, clinicians or industry. Moreover, the paperwork related to patient trials has become onerous.

As a result of the Directive, the number of rare cancer patients taking part in clinical trials is decreasing, and trials are taking longer to complete due to the approval process, Mr GEISSLER stated. He also mentioned that patients with co-morbidities or older patients are more often excluded from clinical trials.

Mr. GEISSLER also stressed that the patient community is keen to be involved in the process to improve the Directive. He put forward suggestions for reforming the Clinical Trials Directive from a rare cancer patient perspective. He emphasised the need to strengthen academic research in Europe and reverse the trend of industry-led cancer research. Moreover, he stressed the need to put patients first, consider risk-adapted regulations, using Phase IV trials rather than Phase I and II trials for drugs not previously tested on humans. He also called for increased transparency of public information about trials and a re-assessment of cost/benefits especially with regard to new insurance requirements. Mr GEISSLER concluded by saying that this is a huge task, but more and more international organisations are willing to work together, including the International Brain Tumour Alliance (IBTA), Sarcoma Patients Euronet (SPAEN), CML Advocates Network, and many others.

Mr GEISSLER's presentation on "Rare Cancers and the Clinical Trials Directive: Patient Perspective'' can be found in Annex II.

3.1.6. Françoise MEUNIER- Director General of the European Organization for the Research and Treatment of Cancer (EORTC)

Professor MEUNIER began with announcing that March 2012 will be the 50 year anniversary of EORTC. She explained that approximately 6,000 patients join trials that are legally sponsored by EORTC each year. EORTC achievements in rare diseases are seen in areas such as larynx cancer (extending the time patients are able to speak) due to academic trial results. Survival rates of children with leukaemia have also improved over the past 30 years through clinical trial results.

Professor MEUNIER clarified that because there are so many different types of cancer they will not be cured so quickly. She also noted that patients shouldn't be put into the same cancer group either. In breast cancer, for example, it is necessary to screen 2,000 patients to determine the 200 with a specific molecular structure. This is even more important for treatment of rare cancers, which need multiple targets. Therefore, there is a strong need to develop robust methodology requiring tissues in order to prevent duplication and increased cooperation for Clinical Trials.

One impact of the Clinical Trials Directive is that although 70% of European patients are in multi-country Clinical Trials, the total number of trials are decreasing. For rare cancer patients, only 36% are involved in Investigator-Driven Clinical Trials. Although important to research, multicentre trials are very complex compared to single site clinical trials. Therefore, as previous speakers have mentioned, administrative requirements such as submissions to ethics committees as well as the conducting and reporting need to be streamlined, simplified and harmonized. A risk-based approach is very important, together with a harmonisation of insurance requirements across countries. The definition of Investigational Medicinal Products (IMP) also needs to be addressed. In cancer, multidisciplinary treatments, e.g. combining surgery and radiotherapy, are needed, and this leads to additional complexity in launching clinical trials.

Professor MEUNIER also noted the challenge of motivating clinical investigators to work in this field; this is difficult in terms of money; it is also time consuming to educate them. She concluded that it is very hard for universities or non-profit organisations to develop drugs for rare cancers. She recommended that new partnership models for industry and academia are needed, and an Investigator-Driven Clinical Trials (IDCT) international Clinical Trial fund should be created for more European research into rare cancers.

Professor MEUNIER's presentation can be found in Annex II.

3.1.7. David WALKER (Professor of Paediatric Oncology, University of Nottingham; Co-Director of the Children's Brain Tumour Research Centre) and his former patient Sam WHITE, Nottingham, UK.

Professor WALKER asked Sam WHITE about the journey that Sam has been on since diagnosis of his cancer. Sam, who is now 14 years old, does not remember the first time that he met Professor WALKER. Sam recollected what happened on the day he was admitted to hospital: it was a normal day but he had a severe headache, after school he went to bed and hours later he had a fit and was rushed to hospital. His cancerous brain tumour had imploded, causing him to become unconscious. Sam was kept in the intensive care unit on a ventilator (breathing machine), and had a major operation to stabilise the tumour. He was in hospital for more than a month. He then had chemotherapy; the first drug he was given (lomustine-CCNU) did not have a Phase I Clinical Trial in children, so consultants did not know how much to administer officially. He was treated with a new drug called Temozolomide because Professor WALKER was involved in a Phase I trial on brain tumour drugs, the results of which were published in 1998, so he knew how much dose to give children with high grade gliomas. Professor WALKER stressed that as children are not miniature adults in the biological sense, clinical trials like these are essential.

Radiotherapy treatment was next. Sam mentioned his fear of the MRI scan, which he overcame with the help of a hospital psychologist. Professor Walker noted that Professor Mansfield, the Nobel prize winner who helped to develop the MRI scanner (now in his 70s), is now trying to make the machine quieter to help patients.

Sam's therapy has successfully ended. He has returned to some sports now, but teaches hockey instead of playing it, and has started archery instead of playing football. He has recently received a Duke of Edinburgh award for walking 20 miles (32 km). Professor WALKER asked Sam what the best thing was that has happened since his recovery. Sam replied that he was pleased about regaining his confidence.

Finally, Professor WALKER asked Sam what he is most proud of. Sam's memory was affected by therapy, but it is improving now. He is proud of catching up at school and he is looking forward to being a "normal kid'' again.

Professor WALKER's abstract "Cancers in Children: Rare Tumours in a Minority Group of the Population" can be found in Annex II.

3.1.8. Peter WILKINSON, former patient, Sheffield, UK

Peter WILKINSON, now 25 years old, described surviving a rare cancer. When he was 21 years old in January 2007, Peter had frequent headaches and suffered from vision loss, changes in taste and personality, as well as back pain. Three times he visited his GP (general practitioner) and hospital Accident & Emergency services to find out what his symptoms meant, but to no avail. He thought that he needed glasses, so he went to the optician. After discussing his symptoms, the optician suggested Peter to go to the Royal Hallamshire Hospital in Sheffield, Yorkshire. In May 2007, he had a MRI scan which showed that he had a brain tumour. Because of this late diagnosis it had spread down his spine, hence the back pain. Peter described his surprise that all of his symptoms were missed by so many health professionals – this, he said, proves the need for more awareness for brain tumours and rare cancers.

At the time of diagnosis, Peter had three biopsies and bleeding on the brain. After several operations, he was shocked to be diagnosed with grade 4 pinealoblastoma, which is an extremely rare inoperable terminal tumour (only 10 people over the age of 3 years of age are diagnosed with this per year). Because of the lack of awareness about this specific type of cancer in health professionals, the oncology consultants gave him as many treatments as possible. This involved a lot of steroids, causing him to gain a large amount of weight in two months. His mood swings increased, and he did not want to talk to anybody about his cancer. Peter was more distressed about his appearance than his cancer, but as he lost weight in the next phase of treatment, the previous weight gain actually helped him to survive. Following that, he had six weeks of radiotherapy, which was very difficult to cope with. Although an MRI scan showed that the tumour was shrinking, he then had Packer-chemotherapy treatment13 for a further nine months.

During his treatment, the UK Teenage Cancer Trust helped him cope. The Trust helps cancer sufferers aged 13-25 years old. Peter was placed in a unit for 18-25 year olds, which he said was like a home away from home, and he was able to develop what he called his "tumour humour''. His attitude changed once there, which made his cancer bearable.

After one year, in May 2008, although Peter still had a brain tumour, there was no more cancer. In January 2009 the tumour disappeared, so today he is both cancer and tumour free. Peter described how he now has survivorship guilt because 6 friends have passed away due to cancer. Although he has late effects, including fatigue, neuropathy (foot nerve damage) and peripheral vision damage which prevents him from driving, Scheuermann's disease (arthritis in spine due to radiotheraphy), memory loss and will have endocrinological problems in the future, he sees his cancer as a positive experience.

[13] Packer Chemotheraphy is an adjuvant chemotherapy for meduloblastoma applied to patients treated with surgery and radiation that includes cisplatin, lomustine, and vincristine, which improves durable responses over those achieved with radiation alone.

Research can make things better, he said, especially for brain tumours. Now, he attends a "Late effects clinic" in Sheffield for young people and has all of his scans and blood tests in one centre. Peter believes that such centres should be available for everybody.

Peter was introduced to jimmyteens.tv by Mark Wilkinson, who made a short film about a young cancer patient. Peter was asked to contribute to jimmyteens.tv as video therapy had been a useful tool for other patients. In April 2009 Peter became video editor of jimmyteens.tv.
Now he has friends, a wife and a job, but realises that not everybody is as lucky as him. A moving jimmyteens.tv video by 15-year old Alice was then shown to explain what jimmyteens.tv is about.

Mr WILKINSON's presentation "Surviving a Rare Cancer'' can be found in Annex II.

3.1.9. Discussion

Question - Michael CASHMAN (MEP, West Midlands).

Mr CASHMAN noted what a remarkable insight this workshop had provided into the challenges for the review of the Clinical Trials Directive. He congratulated both Sam White and Peter Wilkinson on sharing experiences and their positive approach to life. He said that: "cancer is an amazing teacher, but it's not a teacher that you want to have too many lessons with. But having learnt the lessons, your life changes dramatically, and you two are a personification of that''. Mr CASHMAN asked about the review of the Clinical Trials Directive, because it was preventing the kind of measures discussed at the workshop.

Response-Dr Andrzej RYS

Dr RYS said that the Consultation process proved the need to change the legislation. He mentioned that the revision could propose a Regulation rather than a Directive as the legal instrument. He added that research networks and funding from the EU is needed if Europe wants to be a leader. He added that an impact assessment is underway, covering issues such as tissue banks. He also said that patients have to be a part of the approach.

Response-Prof Paolo CASALI:

Professor CASALI responded by saying that, regarding data protection, there are trade-offs to make in times of crisis. He added that rare cancer treatment is not always affordable, and that centres of excellence throughout Europe are suffering financially due to the economic crisis.

Response-Dr Ruth LADENSTEIN:

Dr LADENSTEIN remarked that we know from the history of clinical trials that if patients are treated in an average way, rather than the close attention under clinical trials, they have 20% lower survival rates. She warned that where clinical trials cannot be run any longer due to data protection issues, 20% more people die.

Response-Prof David WALKER:

Professor Walker noted that in a meeting that he had chaired the previous day at a hospital in Lincoln, UK, the hospital administration asked about the costs for clinical trials, as money was needed in other areas as well. He stated that the attitude of hospital boards needs to change, so that they focus more on research objectives, and collaboration is needed in order for this to happen.

3.2. Part 2: On improving Radiation Therapies and Drug Development for Rare Cancers

This section was introduced by Mr PETERLE.

3.2.1. Maria-José VIDAL-RAGOUT - Head of Medical Research Unit, DG Research and Innovation, European Commission.

Dr VIDAL explained that the health theme under the FP7 programme is an important means to support the objectives of the Europe 2020 strategy. These included collaborative research and improving public-private partnerships. She recommended the transfer of knowledge on best practices in cancer research via collaborative research, and policy initiatives. She noted that the FP7 budget for basic, clinical public health research is about 355 million Euros for 2007-2013; and about one-third of this amount is devoted to research of rare cancers. Dr Vidal added that 150-200 million Euro has been devoted to clinical trials in 2011, and examples of collaborative research were given, including ENCCA research into long-term side effects of current and future treatments in children. She also described support for infrastructures, such as the ULICE network of light-ion centres (described by Stephanie COMBS later in the workshop). She also noted that the Innovation Union is one of the seven flagships under the Europe 2010 Strategy, and it will include Partnerships that address major societal changes. These initiatives will provide further support for research funding.

Dr VIDAL's presentation "Health Strategy for the Europe 2020: Together for Health'' can be found in Annex II.

3.2.2. Gilles VASSAL - Head of Translational Research at Institute Gustave Roussy; SIOPE President-Elect

Professor VASSAL started by explain that rare cancer is a major public health issue as approximately 500,000 EU citizens will be diagnosed with a rare cancer, including 15,000 children. However, rare cancer is not a priority for the pharmaceutical industry. So what are the patient rights regarding drug development, Professor VASSAL asked?

He listed four pillars needed to improve drug development: Networking among academic institutions for research and expertise (already addressed through FP6 and FP7, with very positive results); public funding; establishing incentives for and obligations towards the pharmaceutical industry; and creating partnerships with patients and parents.

In the last 10 years there have been two major EU initiatives for rare cancer drug development: the Orphan Medicinal Product Regulation (Regulation (EC) No 141/2000) and the *Paediatric Regulation* (Regulation (EC) No 1901/2006) for medicinal products). But today, many rare cancers are still orphaned. Because there has not been an increase in number of paediatric cancer drugs in Europe (unlike the situation in the USA), off-knowledge drugs –those without research results for children– have to be prescribed instead. Therefore, there is an increased safety concern as the needs of EU children are not addressed.

Public investment is needed as funding and sustainability are the key issues for the research networks. Professor VASSAL concluded that Investigator-Driven clinical research in academia needs to be facilitated; and that public and private partnership, commitment and funding all help with rare cancer treatment.

Professor VASSAL's presentation "Improving Drug Developments for Rare Cancers'' can be found in Annex II.

3.2.3. Pamela COHEN - Associate Vice-President, Oncology Clinical Research, Sanofi

Dr COHEN noted that although she was the only pharmaceutical industry representative present, she is a paediatric oncologist by training.

Dr COHEN explained that recent research has re-defined several common tumour types, identifying a range of sub-types, some of which could be seen as rare or orphan cancers. She explained that cancers have traditionally been characterised through the microscope and histopathologically, i.e. their location, such as breast, colon and other organs, but now more diseases have been molecularly defined. Even rare cancers can be subdivided further based on discrete phenotyping; this has been the case, for example, for breast cancers.

She then gave two examples of progress in inhibitors in the treatment of cancer which act as molecular targeted agents (results first presented in May 2011):
1- Crizotinib, an anaplastic lymphoma kinase (ALK) inhibitor. ALK mutations account for about 3-5% of non-small cell lung cancers. In a Phase III clinical trial, 82 patients reported a 61% positive response to the drug (versus 8% response rate in those with the normal standard of care) and had a very significant 6 month survival rate of 90%.
2- Vemurafenib, a B-RAF inhibitor. Mutations in the BRAF gene have been only recognised in the last five years as a factor in some types of melanoma. In this Phase III trial with 550 patients, there was an 84% overall survival rate at around the 6 month stage (compared with a 64% survival rate in those treated with the chemotherapy drug dacarbazine, which requires more intensive treatment).

Dr COHEN asked whether molecularly characterised tumour subtypes should each be considered as separate diseases in order to carry out effective Clinical Trials. In many cases, this would classify them as rare (orphan) diseases.

At the same time, molecular characterisation offers promise of new treatments. Dr Cohen mentioned that she is currently working on a JAK2 inhibitor project for the rare tumour Myelofibrosis. The first trial had significant results (49% efficacy), and half the group is still alive after 3 years and have improved symptoms. This, Dr COHEN stated, is what we should expect in the future.

Like Professor CASALI before her, she concluded that treatment of rare diseases needs a higher degree of flexibility in the application of clinical trials rules in order to reach the level of people accepted for such trials. Ethical issues also need to be considered, to see if patients need to be randomised in these types of Clinical Trials at all or not.

Dr COHEN's presentation on "Drug Development of Rare Cancer treatments'' can be found in Annex II.

3.2.4. Stephanie COMBS – Radio-oncologist, University Hospital Heidelberg, ULICE (Union of Light Ion Centres in Europe, FP7 EC funded project)

Dr COMBS discussed the use of new techniques for radiation oncology being introduced in Europe. She explained that radiology is part of more than 50% of cancer treatment protocols. However, traditional radiation oncology faces several challenges, including toxicity risks and side effects, especially in paediatric patients.

New methods, using for example protons or carbon ions, can focus much better on tumours and have fewer side effects. An example of treating Paraspinal alveolar rhabdomyosarcoma (RMS) was given to demonstrate this.

Dr COMBS explained that several centres use protons in radiotherapy for clinical operations in Japan and the US, as well as in Heidelberg in Germany. She noted, however, that further research is needed, in particular to understand biological differences in tumours. Dr Combs explained that the EU funded ULICE project has added biology as the 5th dimension (5D) for cancer patient treatment. She described the Heidelberg Ion Therapy (HIT) Centre, which cost 130 million Euros to build. Recruitment is currently being conducted for trials on the treatment in rare tumours in skull base (which is a radio-resistant area), so more advanced techniques are needed in its treatment.

Dr COMB's presentation on "Improving Radiation Therapies and Drug Development for Rare Cancers: Modern Radiation Oncology'' can be found in Annex II.

3.2.5. Conclusions and closing statements*:*

In his concluding remarks, Mr PETERLE said he was encouraged to hear about the new treatments available, but noted that challenges still remain. He recalled the slide that said, "many people could be alive if...". He stated that as politicians, they need to turn the "could be's" into "should be's". He added that there are "no holidays in the fight against cancer..." and that "there are many rare cancers''.

Mr PETERLE said that as a result of this Workshop, "We know more, we wish to know more and we wish to do more.'' Mr PETERLE concluded that if this Workshop were a plenary session, the politicians would adopt at least two decisions: that the EU legislation should be strengthened, and that the efficacy of knowledge transfer should be increased.

The final word of the Workshop was from Ms WILLMOTT who said that we now know what we have to do in order to improve the Clinical Trials Directive. She reminded the audience that they had also heard about capacity building for cancer research, and that a better system is needed to deal with treatment of rare cancers, especially for children who need to be assessed differently. She concluded that it was good to hear from rare cancer patients because they matter: this helps those working in policy, industry, and research to focus on the right issues regarding treatment.

ANNEX I: PROGRAMME

Policy Department A-Economy & Science
for the
Committee on the Environment, Public Health and Food Safety (ENVI)

Workshop on 'Rare Cancers: The added value of closer cooperation'
Tuesday, 12 July 2011 from 16.30 to 19.00 hrs
European Parliament, Room ASP A5G-3, Brussels

AGENDA

16.30 - 16.35 Welcome and opening by Co-chairs of the Working Group on Health **Glenis WILLMOTT** and **Alojz PETERLE**

Part 1: On the importance of special recognition for rare cancers in the revision of the EU Clinical Trials Directive

16.35-16.40 **Andrzej RYS**, Director of Health Systems and Products, DG SANCO, European Commission

16.40-16.50 **Paolo CASALI,** European Action against Rare Cancers, European Society for Medical Oncology (ESMO)

16.50-17.00 Ruth LADENSTEIN, **SIOPE** (European organisation promoting optimal standards of care for children and young people with cancer) **President;** Coordinator of FP7 funded project ENCCA (European Network for Cancer Research in Children and Adolescents)

17.00-17.10 **Jan GEISSLER**, Chronic myelogenous leukemia (CML) Network

7.10-17-20 **Françoise MEUNIER**, Director General, European Organisation for the Research and Treatment of Cancer (EORTC)

17.20-17.30 **David WALKER**, University of Nottingham, UK with his former patient **Sam WHITE,** Nottingham, UK – Question and Answer session

17.30-17.45 **Peter WILKINSON,** patient, Nottingham introduced by **Glenis WILLMOTT**

Video on the struggles and challenges of a patient with a rare form of cancer

17.45- 18.05 Question Time

Part 2: On Improving Radiation Therapies and Drug Development for Rare Cancers

18.05-18.10 **Maria- José VIDAL-RAGOUT, Head of Unit Medical Research, DG Research and Innovation,** European Commission

18.10-18.20 **Gilles VASSAL,** SIOPE and Head of Translational Research at Institut Gustave Roussy

18.20-18.30 **Pamela COHEN**, Associate Vice-President, Oncology Clinical Research. Sanofi-Aventis

18.30- 18.40 **Stephanie COMBS,** University Hospital Heidelberg, ULICE (Union of Light Ion Centres in Europe, FP7 EC funded project)

18.40- 18.55 **Question time**

18.55-19.00 **Conclusions**

19.00 CLOSING

ANNEX II: SHORT BIOGRAPHIES OF EXPERTS

Andrzej RYS
Director of Health Systems and Products, SANCO, European Commission

Dr Ryś is a medical doctor graduated from Jagiellonian University, Krakow, Poland. He specialized in radiology and public health. In 1991 he established School of Public Health (SPH) at the Jagiellonian University and he was the SPH's director till 1997. From 1997-1999 he took up the post of director of Krakow's city health department. In 1995 –1999 he was the Polish director of the "Harvard-Jagiellonian Consortium for Health" – a project focusing on local governments' role in health care. In 1999 – 2002 he became the deputy Minister of Health in Poland and developed a new system of emergency medicine and new education system for nurses. He was a member of the Polish accession negotiators team. In 2003 he established and is Director of the Center for Innovation and Technology Transfer at Jagiellonian University, Krakow, Poland. He was also director for development of Diagnostic Ltd., executive director of the Polish Association of Private Health Care Employers and chief editor of the Journal "Health and Management". He joined the European Commission in June 2006.

Paolo CASALI
European Action against Rare Cancers, European Society for Medical Oncology (ESMO)

Dr Casali, MD, medical oncologist, is head of the Adult Mesenchymal Tumour Medical Oncology Unit, Istituto Nazionale Tumori, Milan, Italy. He also serves as Secretary of the Ethics Committee of this institution.

His clinical and research activities focus on rare tumors, especially adult sarcomas, including gastrointestinal stromal tumors (GIST), and uncommon histological types. He is the Secretary of the Italian Sarcoma Group, a national cooperative group for clinical and translational research on soft tissue and bone sarcomas, and is a member of the EORTC Soft Tissue & Bone Sarcoma Group. He chairs the Italian Network on Rare Tumors, a collaborative effort among Italian cancer centers, which tries to exploit distant patient sharing in order to improve quality of care and diminish health migration for rare solid cancers. He acts as an Editor of START ("State-of-the-Art Oncology in Europe"), an Italian-based, European state-of-the-art instrument on cancer treatment. He is a member of the Executive Board of ESMO (European Society for Medical Oncology) as chair of the Public Policy/European Affairs Committee, and is Faculty Coordinator for Sarcoma. He is a member of the Policy Committee of ECCO (European Cancer Organization).

He received his medical degree in 1984 in Milan, and trained at the Istituto Nazionale Tumori. He is certified in Clinical Oncology and Haematology, and has the ESMO Certificate in Medical Oncology. He teaches Medical Therapy of Rare Cancers at the Milan University postgraduate school in Oncology.

Ruth LADENSTEIN
President of SIOPE, European organisation promoting optimal standards of care for children and young people with cancer

Associate Professor Ruth Ladenstein (MD, MBA, cPM) is President of SIOP EUROPE (board member since September 2006). She is also an Advisory Board member of SIOPEN (SIOP Europe Neuroblastoma Group), and was President from May 2007-2011. Dr LADENSTEIN is also Associate Professor of Paediatrics to the University of Vienna Paediatric Department. Dr Ladenstein has been Head of S^2IRP Studies and Statistics on Integrated Research and Projects/Children's Cancer Research Institute (CCRI), Vienna since 1996, and Head of the department for paediatric solid tumours St. Anna Children's Hospital, Vienna since 1998.

Dr. Ladenstein has a Diploma in Oncology- 'DISC' (*diplôme interuniversitaire de spécialité complementaire de cancerologie*) from University Claude Bernard, Lyon, France. She is involved in the project coordination of 2 EU projects: FP5 SIOPEN-R-NET project [EC grant QLRI-CT-2002-01768], and FP7 ENCCA [European network for Cancer Research in Children and Adolescents, HEALTH 2010.2.4.1-3, no 261474].

Jan GEISSLER
Chronic myelogenous leukemia (CML) Network

Jan Geissler studied business at the University of Regensburg (Germany) and Aston University (Birmingham, UK), graduating with a university diploma in Business Administration. He then worked for more than 4 years for the media company Bertelsmann (Germany), co-founding and heading the product management, business development and marketing for their in-house startup BeMobile.

In July 2001, at the age of 28 years, Jan received his diagnosis of a rare cancer: Chronic Myeloid Leukemia (CML). He joined a phase I/II clinical trial and started to translate and publish medical publications into German lay language. In 2002, he founded the online patient community *Leukämie-Online/LeukaNET*, which is one of the most frequented online platforms for leukemia patients in the German speaking internet today.
In 2003, he co-founded the European Cancer Patient Coalition (ECPC) to represent the views of cancer patient organisations in European healthcare, as well as to provide a forum for European patients to share best practice on patient advocacy. His activities included connecting 315 ECPC member organisations from 42 countries, speaking on behalf of cancer patients at conferences, and working with various stakeholders to make information about clinical research more available to patients. He has participated in a number of consortia of FP7-funded projects, e.g. RARECARE.
In 2007, Jan co-founded the CML Advocates Network which today connects 55 leukaemia patient groups from all continents, sharing best practice in cancer patient advocacy and running joint campaigns. In 2008, Jan left his job leading multinational and multicultural innovation projects at Vodafone Group R&D (Germany) to turn his volunteer work for cancer patients into his profession. He became the first full time Director of the Coalition from 2008-10.

Today, Jan is Founder and Executive Director of Patvocates, taking forward a number of leading initiatives in the triangle of cancer policy, patient advocacy and social media. He is also a Board Member of the European Forum for Good Clinical Practice (EFGCP), Communications Manager of the International CML Foundation (iCMLf), and contributes in various advisory committees. He also acts as independent EU expert for reviews of FP7 projects, and is a patient representative in the EU Commission's Committee of Experts on Rare Diseases (EUCERD).

Françoise MEUNIER
Director General, European Organisation for the Research and Treatment of Cancer (EORTC)

Baroness Professor Meunier received her medical degree from the Université Libre de Bruxelles (ULB) and completed her research fellowship at the Memorial Sloan-Kettering Cancer Center in New York in 1977-1978 (Fulbright award). Both her Master's Degree in Medical Oncology and Internal Medicine, and PhD, are from the ULB. She is also certified as a Pharmaceutical Medicine specialist by the Faculty of Pharmaceutical Medicine in the UK as well as in Belgium, and has been a Fellow of the UK Royal College of Physicians since 1994.

Professor Meunier was Head of the Infectious Disease Department at the Institut Jules Bordet in Brussels, Belgium and her personal area of research included mainly Invasive Fungal Infections in Cancer Patients. She has over 150 peer-reviewed published articles and is a member of numerous international oncology scientific societies. The EORTC is a unique pan-European academic clinical research organization operating as a non-profit association under Belgian law. Professor Meunier has led the coordination and administration of all EORTC activities since 1991 with the mandate to promote the EORTC as a major European organization in the field of oncology with a network of 2500 oncologists in over 300 universities and a Headquarters staff of 160 representing 17 different nationalities. As Director General, she is responsible for the organization of scientific activities, public relations and medium-term EORTC strategy as defined by the EORTC Board.

Professor Meunier was awarded the Belgian Laureate "*Prix Femmes d'Europe 2004-2005*". She has been a member of the Belgian Royal Academy of Medicine (Académie Royale de Médecine de Belgique) since 2006. In 2007, she was conferred the honorary title of Baroness by His Royal Majesty King Albert II of Belgium. In 2009 she received the Pezcoller Foundation-ECCO award as recognition for her unique contribution to oncology and for the dedication of her professional life to the improvement of cancer treatment, care and research.

David WALKER
Professor of Paediatric Oncology, University of Nottingham, and co-director of the Children's Brain Tumour Research Centre

Professor Walker is Professor of Paediatric Oncology at the University of Nottingham and co-director of the Children's Brain Tumour Research Centre (CBTRC). He led the development of the clinical service for children with cancer in Nottingham as part of the Mid-Trent region from 1990 to 2006. The Nottingham Centre is part of the East Midlands Children and Young People's Integrated Cancer Service (CYPICS), lead centre for the Trent Health region with a population of six million people. He has participated in NHS management in a variety of roles including Clinical Director for Children's Services, lead clinician for Cancer Services, and is now lead clinician for Mid-Trent Cancer Research Network.

His research interests have a broad spectrum within paediatric oncology with a particular interest in brain tumours, health outcomes, functional imaging, drug delivery, clinical trials and adolescent medicine. Since the late nineties he has been the co-director of the CBTRC. This Research Centre has brought together over sixty clinical and scientific researchers across the University interested in research related to childhood brain tumours.

The current flagship project, Brain Pathways and its "Headsmart – Be brain tumour aware" campaign, is aiming to raise awareness across the UK of the relative risk of brain tumours in children and young people as one of the differential diagnoses of a broad spectrum of children's symptoms. Headsmart was launched in June 2011, supported by an evidence-based age-stratified health messages decision-support website and an evaluation programme, and is the product of a collaboration between the Children's CBTRC, Samantha Dickson Brain Tumour Trust, Royal College of Paediatrics and Child Health, and funded by The Health Foundation.

Professor Walker has participated in the All Party Parliamentary Group concerned with brain tumours since its inception in the last Parliament in the UK, and now sits on the Steering Group of the revised All Party Parliamentary Group. He advises on academic matters and matters related to brain tumours occurring in early life during childhood, adolescence and early adulthood. He is also an elected member of the Societe Internationale d'Oncologie Pediatrique Europe (SIOPE) Board. He contributes to undergraduate teaching through a regular seminar programme and the supervision of BMedSci Honours projects, as well as leadership within the Faculty of teaching committees.

Sam WHITE
Patient, Nottingham, UK

Sam is a young teenager from Newark, England. 14-year-old Sam was given just an hour to live by the doctors who diagnosed his rare brain tumour. Now, 18 months following treatment at the Children's Brain Tumour Research Centre (CBTRC), Sam has defied both the experts and the odds. Although the brain tumour has left him with some lasting effects, such as memory loss, Sam is back to school and studies in his own year-group with the help of a little extra educational support.

He faces everyday challenges with a mix of pragmatism and positive-thinking. Following his illness and rehabilitation, Sam has highlighted the effects of cancer in teenagers, which are not always addressed in the treatment of cancer sufferers. He recently spoke at the annual National Union of Teachers conference in England to tell teachers, learning mentors and teaching assistants just how hard it was for him to return to education, the support he received and also importantly the support he didn't receive.

Peter WILKINSON
Patient, Sheffield, UK

Peter Wilkinson is 25yrs old and from Barnsley, South Yorkshire, England. He was diagnosed with a cancerous brain tumour (pineal Blastoma grade 4) aged 21, which had spread down the spine due to a late diagnosis.

Following 6 weeks of radiotherapy treatment, he was transferred to a cancer unit in Sheffield for 18 -25 yr olds. Whilst having a 9-month PACKER chemotherapy regime, he was introduced to the www.jimmyteens.tv project, which gives young cancer patients the opportunity to express themselves creatively. Peter discovered his 'tumour humour' – a light hearted look towards his cancer- and become editor of the website. He now also presents his own monthly show. Although it has left him with disabilities including neuropathy (nerve damage), spinal arthritis, fatigue, and peripheral vision, Peter believes that cancer has been a positive in his life.

Maria- José VIDAL-RAGOUT
Head of Medical Research Unit, DG Research and Innovation Directorate General, European Commission

Maria Vidal is an MD, PhD in pharmacology. She heads the Unit of Medical Research within the Health Directorate of the Research and Innovation Directorate General at the European Commission.

Gilles VASSAL
SIOPE and Head of Translational Research at Institut Gustave Roussy

Professor Vassal trained as a Pediatric Oncologist, and has a PhD in Pharmacology. He is Professor of Oncology in University Paris-Sud, France and is currently head of Clinical Research at Institut Gustave Roussy, Villejuif, a large comprehensive cancer centre with 11000 new patients annually. For the last 20 years, he has focussed his research, clinical and training activity on the development of new drugs for children with cancer. This activity is now integrated in the development of personalized medicine for children and adolescents with cancer.

He founded, and is currently President of, the European Network for Innovative Therapies for Children with Cancer (ITCC) (www.itcc-consortium.org) that runs a comprehensive biology, preclinical and clinical research programme on new anticancer drugs in 6 EU member states. He coordinates two European projects: one exploring kinases in pediatric malignancies (KidsCancerKinome), the other developing Oral Off-patent Oncology drugs for Kids (O3K). He is vice-chair of the ENCCA (European Network for Cancer research in Children and Adolescents) network of excellence, and has recently launched in the FP7 program. Professor Vassal is Member of several Scientific Councils, including the European Academy for Cancer Sciences; and is an Expert at both the French Drug Agency (AFSSAPS) and European Medicines Agency (EMA). He is author and co-author of more than 150 publications in peer-reviewed journals.

Pamela COHEN
Associate Vice-President, Oncology Clinical Research at Sanofi-Aventis

Dr Cohen received her undergraduate degree from Barnard College and her medical degree from the Mount Sinai School of Medicine. She has recently joined Sanofi Oncology as Associate Vice President of Clinical Research. During her 12 years in the pharmaceutical industry she has held multiple senior positions in large pharmacology, biotechnology and diagnostics companies. Most recently, she was Chief Medical Officer at Kosan Biosciences, a biotech company focused exclusively on novel oncology therapeutics. Previously, she was the Global Oncology Therapeutic Area Head at GE Healthcare Medical Diagnostics, and was responsible for strategic development, clinical trial implementation and registration of novel molecularly targeted imaging diagnostics. She also held multiple positions at Novartis Oncology, most senior being Executive Director. At Novartis, besides being an early advocate for translational oncology and companion diagnostics, she was also responsible for late stage development through Phase III.

Dr Cohen has also held academic positions in pediatric hematology/oncology at Cornell and University of California at Los Angeles, and did her postgraduate hematology/oncology training at the National Cancer Institute and Stanford University. She has authored over 30 publications in the area of the molecular biology of pediatric and medical oncology, clinical development of targeted oncology therapeutics and the development of biomarkers, and molecularly targeted imaging agents for use in oncology drug development.

Stephanie COMBS

Radio-oncologist, University Hospital of Heidelberg. Partner of FP7 funded project ULICE (Union of Light Ion Centres in Europe)

Dr COMBS obtained her MD from Ruprecht-Karls-University in Heidelberg in 2003. She is a board-certified radiation oncologist with special focus in novel radiation techniques, including precision photon radiotherapy, image guided radiotherapy (IGRT) and particle therapy.

Dr COMBS has published numerous scientific articles in high-ranged peer-reviewed medical journals including Journal of Clinical Oncology, Cancer, International Journal of Radiation Oncology Biology Physics and Radiotherapy & Oncology. Her special interest is the improvement of multimodal treatment concept in patients with brain tumours, paediatric tumour patients, as well as gastrointestinal tumours, especially primary liver cancer and pancreatic cancer.

She is involved in over 20 clinical trials, and is the principal investigator and coordinating force for numerous trials in radiation oncology. Dr. Combs shows a special expertise I particle therapy and was in involved in the coordination of the clinical service at the Heidelberg Ion Therapy Centre (HIT). In that setting, she coordinated quality assurance and discussion with German National Authorities on Radiation Protection, designed several clinical trials for particle therapy, and is the coordinator of EU-Funded projects (ULICE and PARTNER) at the Heidelberg centre.

ANNEX III: PRESENTATIONS

European Action Against Rare Cancers

EU Clinical Trial Directive

The problem of rare cancers

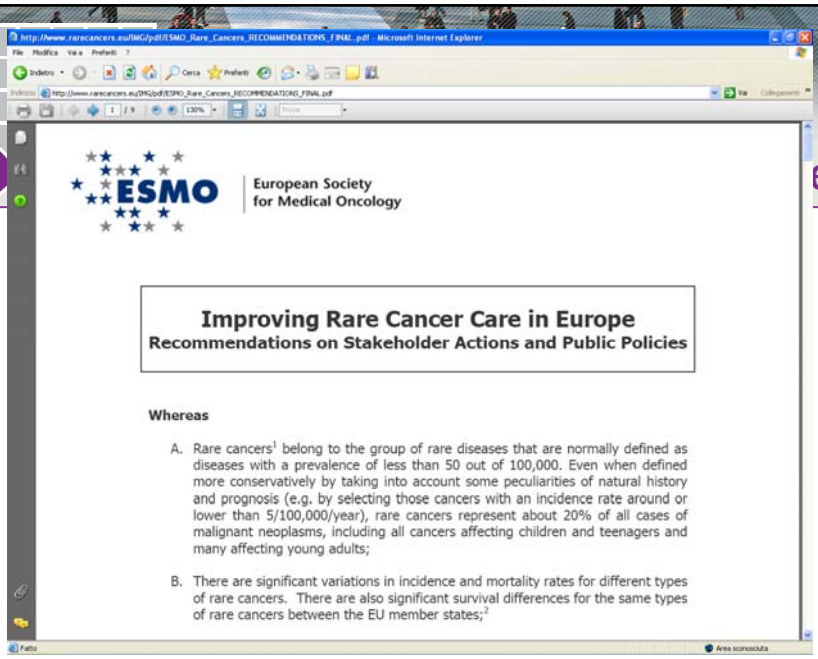
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

Paolo G. Casali
paolo.casali@istitutotumori.mi.it

European Action Against Rare Cancers


European Action Against Rare Cancers
ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE
European Society for Medical Oncology
EURORDIS
Rare Diseases Europe
IBTA
INTERNATIONAL BRAIN TUMOUR ALLIANCE
EUROPEAN CANCER PATIENT COALITION
Conticanet
EuroBoNeT
EORTC
European Organisation for Research and Treatment of Cancer
ECL
Association of European Cancer Leagues
SIOPE
SIOP Europe
CML AdvocatesNetwork
European Society of Pathology
cmlsupport
IEO
European Institute of Oncology
Fondazione IRCCS Istituto Nazionale dei Tumori
NOVARTIS
ONCOLOGY
Pfizer Oncology
orphanet
sanofi aventis


ESMO
Rare Tumours in Europe
CHALLENGES AND SOLUTIONS
6 November 2008 - Brussels
11.15 –13:15 PARALLEL BREAKOUT SESSIONS INCLUDING WORKING LUNCH
Workshop I
Rare tumours: Methodological and Regulatory Challenges
Chair: Paolo Casali, ESMO - Co-Chair: Jan Liliemark, Swedish Medicines Agency
The orphan drugs approval process - Filippo De Braud, European Institute of Oncology
Current guidelines on efficacy assessment in the EU - Iordanis Gravanis, EMEA
Strategies for rare tumours in medical statistics - Paolo Bruzzi, National Institute for Cancer Research of Genoa
A parliamentary perspective - Jolanta Dickute, MEP
Discussion
Workshop II
Rare tumours: Organisational Challenges
Chair: Jean-Yves Blay, Conticanet - Co-Chair: Bertram Wiedenman, Charité University Hospital Berlin
The challenge of rare tumours treatment in the EU - Peter Hohenberger, University of Heidelberg
The role of patient advocacy groups - Jan Geissler, European Cancer Patient Coalition
Developing networks in hematology - Rüdiger Hehlmann, Leukemia Network
Examples of overcoming the barriers - Thor Alvegard, Scandinavian Sarcoma Group & Markus Wartenberg, Sarcoma Patients EuroNet
Discussion
Workshop III
Rare tumours: Patient Access Challenges
Chair: Kathy Redmond, Cancer World - Co-Chair: Flaminia Macchia, Eurordis
Challenges and barriers: An overview - Yann Le Cam, Eurordis
Living with a rare tumour: a patient story - Ella Pybus, Meningioma UK
Discussion



European Society
for Medical Oncology

Improving Rare Cancer Care in Europe
Recommendations on Stakeholder Actions and Public Policies

Whereas

A. Rare cancers[1] belong to the group of rare diseases that are normally defined as diseases with a prevalence of less than 50 out of 100,000. Even when defined more conservatively by taking into account some peculiarities of natural history and prognosis (e.g. by selecting those cancers with an incidence rate around or lower than 5/100,000/year), rare cancers represent about 20% of all cases of malignant neoplasms, including all cancers affecting children and teenagers and many affecting young adults;

B. There are significant variations in incidence and mortality rates for different types of rare cancers. There are also significant survival differences for the same types of rare cancers between the EU member states;[2]

Rare Tumours in Europe

CHALLENGES AND SOLUTIONS

6 November 2008 - Brussels

We acknowledge that while the process for establishing the efficacy of new medicines is in principle the same for all cancers, the strength of the evidence – intended as level and quality of evidence and statistical precision – that is achievable in common cancers is difficult to achieve in rare conditions and, therefore, **a higher degree of uncertainty should be accepted** for regulatory as well as clinically informed decision-making

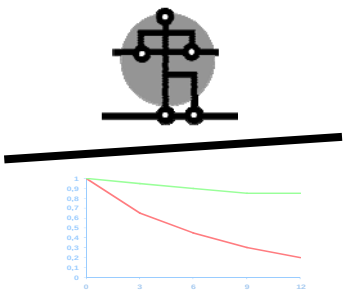
Orphan drug regulations

European Action Against Rare Cancers

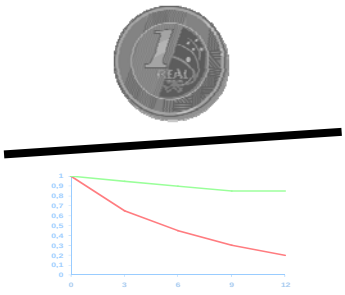
- *10-year marketing exclusivity*
- *fee reductions and exemptions*
- *protocol assistance*
- *national incentives*
- *EU-funded research*

European Action Against Rare Cancers

EU regulator



National regulator



Methodology of research

European Action Against Rare Cancers

- new study designs
- surrogate end points
- methods to combine evidence
- organization of studies

Brussels, 9-10 February 2012

Rare Tumours in Europe

CHALLENGES AND SOLUTIONS

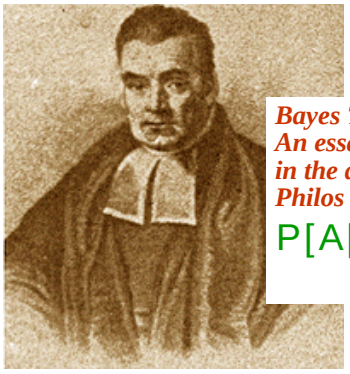
6 November 2008 - Brussels

7.

Call upon the research community to consider using a **Bayesian approach for the design of clinical trials** whenever well-powered randomised trials are not feasible due to the low incidence of the cancer entity and granted that sufficient information is available on the specific disease entity to empower such statistics (e.g. other clinical studies, biological evidence, analogies with more frequent diseases, the natural history of the disease, etc.). A mechanism for consensus development for definition of prior probability distributions should be devised.

Bayesian statistics

European Action Against Rare Cancers



Bayes T.
An essay towards solving a problem in the doctrine of chances.
Philos Trans R Soc Lond 1763; 53: 370-418

$$P[A|B] = P[A] \times \frac{P[B|A]}{P[B]}$$

The preclinical rationale

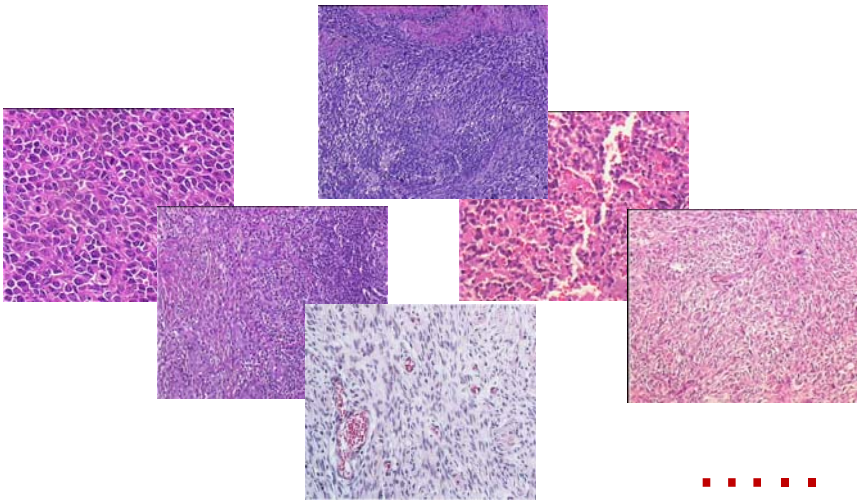
European Action Against Rare Cancers

The prior probability

European Action Against Rare Cancers

Small clinical studies for specific rare cancers

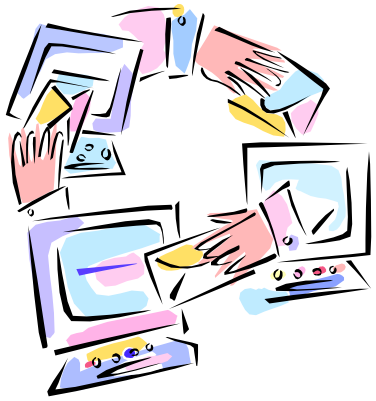
European Action Against Rare Cancers



. . . . .

A European framework for small clinical studies

European Action Against Rare Cancers



Clinical Trial Directive

European Action Against Rare Cancers

L 121/34 EN Official Journal of the European Communities 1.5.2001

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 4 April 2001

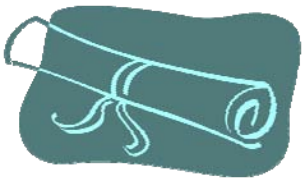
on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

European Action Against Rare Cancers

P. Bruegel - 1563

Quality of treatment

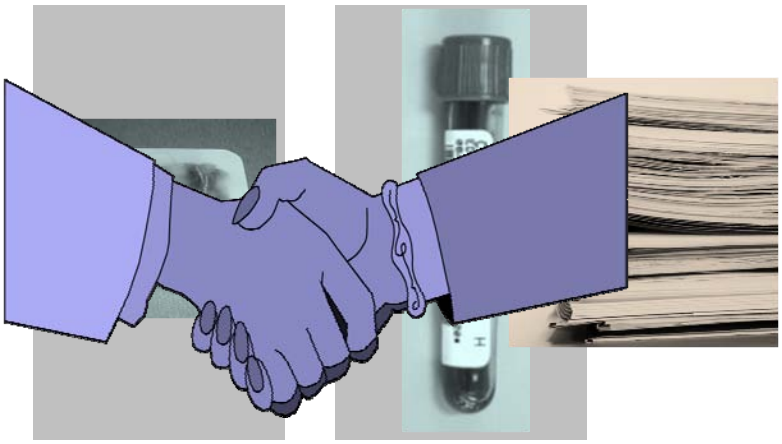
European Action Against Rare Cancers



VS

Tissue banks

European Action Against Rare Cancers



Data Protection Directive

European Action Against Rare Cancers

31.7.2002 EN Official Journal of the European Communities L 201/37

DIRECTIVE 2002/58/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 12 July 2002

concerning the processing of personal data and the protection of privacy in the electronic communications sector (Directive on privacy and electronic communications)

European Action Against Rare Cancers

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

European Society for Medical Oncology

Paolo G. Casali
paolo.casali@istitutotumori.mi.it

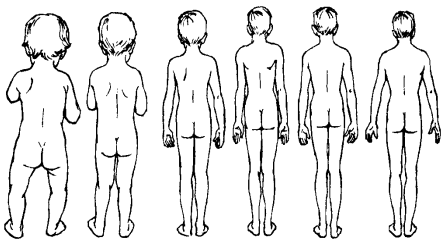
Needs of Children and Adolescents with Cancer

Ruth Ladenstein
SIOPE President
SIOPE Brussels, Belgium

ENCCA Project Coordinator
St. Anna Children's Hospital and Research Institute (Vienna, Austria)

Are Children Different ?

„ Children are not miniature adults"
...from a clinical trial
operational point of view neither



Heterogeneous in many aspects!

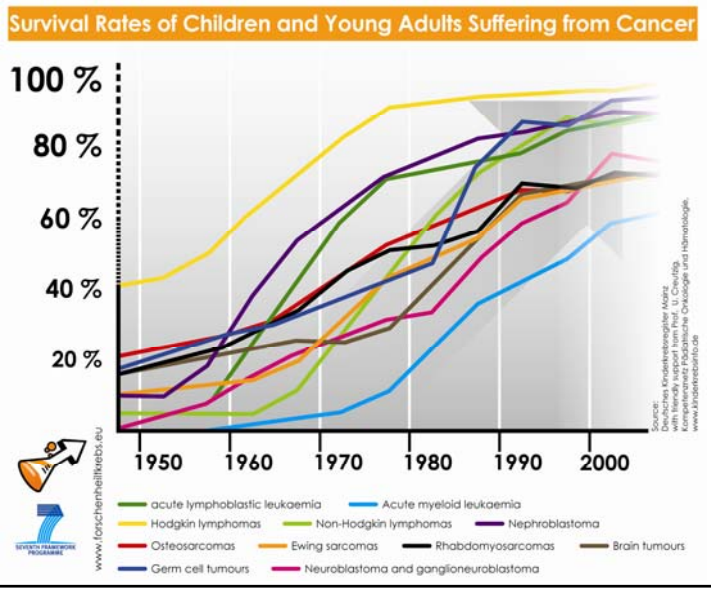
20% of the European Population
100 Millions < 18 Years !

Cancer in Children & Adolescents
A Rare Disease

- **15 000 new cases each year in Europe!**
- **> 60 different diseases from newborns to teenagers (even more when biomarkers are considered)**
- **80% can be cured with today's "Multidisciplinary Treatment Concepts" based on academic trials over the last 30 years**
- **BUT 3000 will die each year**
- **500.000 could be alive today if equal access to standard treatments were possible**
- **1 out of 1000 adults aged 18 to 40 is a paediatric cancer survivor**

…but a significant Public Health Issue

Survival Rates in Paediatric Cancer
A Major Academic Achievement!



>90% 2015 !?

80% today

<10% < 1960

Children are still „Pharmaceutical Orphans “ in spite of the Paediatric Regulation

The need is high BUT …..

80 % of drugs in use for children with cancer are licenced, but still are „off–label“ for

- **Age**
- **Indication**

- **Need to STOP daily experiments of drug use in children!**
- **Need to foster drug development according to children’s real needs !**
- **Bread crumbs off the table of adult drug development is not enough!**
- **Support needed from Policy-makers and Pharma**

Major Challenges and Limitations for Paediatric Oncology in Europe

- **Struggling to run investigator-driven clinical trials within the 2001 Clinical Trials Directive**
  - **Drug Definitions (“off lable”) in trials: Investigational medicinal products? = 1 or 5 to 20?**
  - **Currently no risk-based adjustment for paediatric academic trials**
  - **All qualify for highest bureaucracy and highest insurance needs and thus highest costs!**
- **Extremely poor access to new drugs despite the 2007 Paediatric Medicine Regulation**
- **Unequal access to standard therapies**
- **Lack of sustained & sufficient funding**

SIOPE SIOP Europe

encca

A Network of Excellence Structuring Clinical Research in Paediatric and Adolescent Oncology in Europe

HEALTH.2010.2.2.1-3

- **To improve both cure and quality of cure of children and adolescents suffering of cancer**

ENCCA Bridging Actions 2011- 2014

- **Policy activities to implement a European Strategy for pediatric and adolescent oncology research**
- Integration, harmonization and optimization

  (clinical trials /European CT templates & contracts/informed consent, trials methodology, tumor banking, biology)
- To foster and facilitate access to innovative therapies and tailored medicines and standard care across Europe
- Run a limited number of clinical and translational studies as examples
- Facilitate sharing and partnerships in the chain of all stakeholders

  (academia, parents and patients organizations, charities, pharmaceutical companies, regulatory bodies, governmental bodies,)
- Training and education
- Harmonize ethical definitions and solutions

ENCCA is a Beginning

- to meet rare disease needs
- to spread across Europe
- harmonize trials across Europe

➢ **BUT bureaucracy and insurance are still major constraints!**

Risks and Needs of Young People with Cancer

➢**The major risk is dying from cancer !**

➢**Multinational clinical trials remain vital for children with cancer**

➢**Regulatory complexity and associated high cost (management, controlling, insurance) have slowed progress and number of trials significantly in Europe**.

➢**Refinement of risk differentiation** of the therapeutic strategies within the next CTD for childhood cancer

- should consider current survival success rates !
- should allow solutions to **lower regulatory burden for estaböished standard treatments arms in spite the ongoing need of off-label drug use**
- should include an **obligation for MS to cover insurance risk** for all clinical negligence including research practice for public/common good in rare orphan diseases

➢**The CTD revision is a major opportunity to help to overcome current inequalities in Europe!**

Thank You for Considering Our Young Cancer Patients in Future Policy Decisions!

SIOP Europe

Please give attention to minorities with problems side lined over the last 30 years!

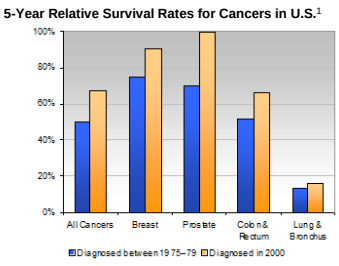
Rare Cancers and the CTD: Patient Perspective

Jan Geissler

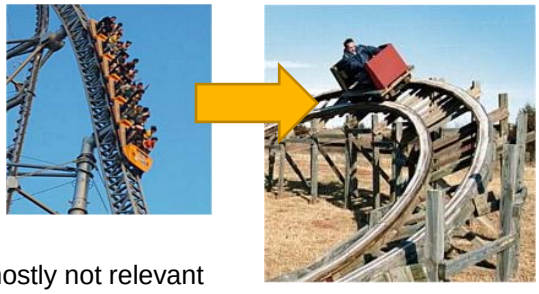
Co-founder, CML Advocates Network
Chair, LeukaNET
Secretary, European Forum For Good Clinical Practice
Member, EU Committee of Experts for Rare Diseases (EUCERD)

The rollercoaster patient journey of cancer

- **1 in 3 Europeans will get cancer in their lifetime**
- About 1/3 of them will have a rare cancer
- Depending on the cancer, strong inequalities exist
  - research has turned a deadly into a chronic disease
  - or there has been little progress and there is poor survival



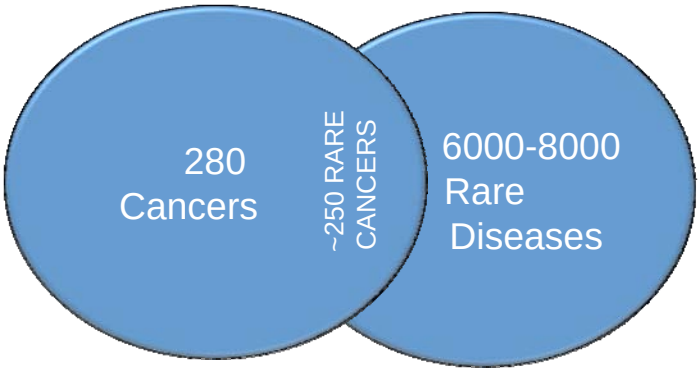
Patients with rare cancers face specific challenges



1. **Prevention/screening** mostly not relevant
2. **Late or incorrect diagnosis** common in many rare cancers
3. **Experienced doctor** not available locally
4. **Lack of access** to therapies and clinical expertise
5. **Slowness of research** (lack of trials & commercial interest),
6. **Facing stigma and inequity** (lack of public understanding)
7. **Lack of interest in funding rare cancer patient groups**

Rare diseases and rare cancers – is there a difference?

- Rare Cancers are often lost between common cancers and rare diseases
- Policy challenge: Unite, not divide



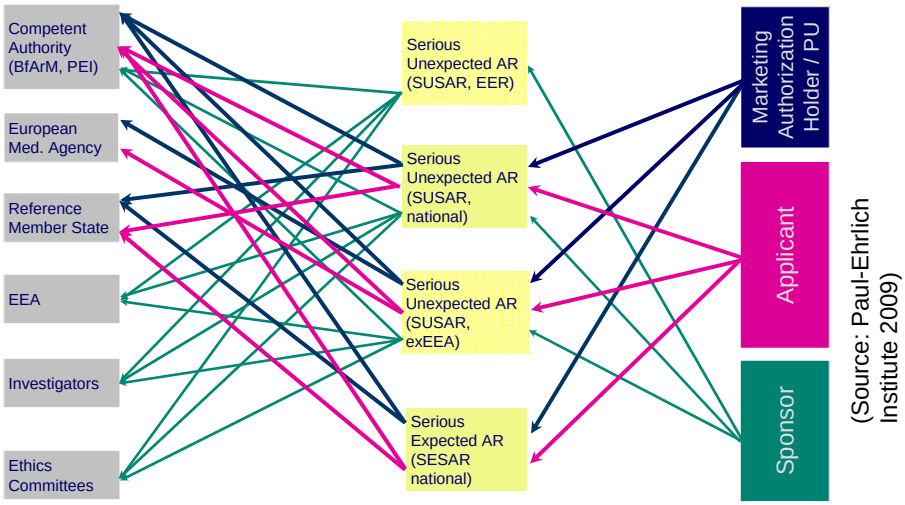
EU Regulation of Clinical Trials (CTD)

- Clinical Trial Directives 2001/20/EC and 2005/28/EC **introduced to protect us:**
  - **Ensure safety** of participants
  - **Guarantee rights** of participants
  - Harmonization of trial procedures across the EU
  - Increase reliability and robustness of trial data

- Implementation **did not serve the interests of patients** (nor researchers, clinicians or industry)

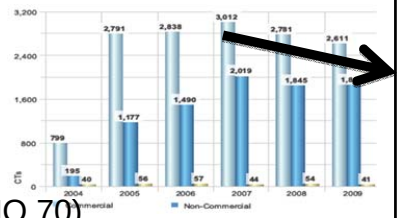
Example Trial Safety Reporting

Obligatory reporting of unexpected adverse events, based on German implementation of CTD in medicines law (§63b AMG) and Good Clinical Practice act (§13 GCP)



(Source: Paul-Ehrlich Institute 2009)

Some examples on CTD impact in rare cancers



(Source: ICREL Report 2008)

- Adult and pediatric trials: CTD has reduced participation rates significantly
- Low grade lymphoma (2007, OSHO 70) - protocol approval process took **4x longer and 10x costs for trial approval**
- German Hodgkin Study Group: **100,000 copied pages** submitted for a single clinical trial in 280 clinics, 65 ethics committees

- **Patients with co-morbidities or older patients** more often excluded from clinical trials

Added value of cooperation: what the patient community has done about the CTD

- **Worked with clinicians to understand CTD's impact on investigator-led research** (ELN, Networks of excellence)
- **Shared positions** with professional associations (EHA, EFGCP, ELN, …)
- **Worked with the EU Commission and EU Parliament** (e.g. consultations, petition)
- **Patients' voice at conferences (DIA, EFGCP)** to increase public pressure
- **Collaborated** e.g. with EAARC…

European Action Against Rare Cancers

Suggestions for modification of CTD: Perspective from rare cancer patients

- **Strengthen academic research in Europe:**
  Reverse the trend to industry-led cancer research
- **Return to a research-friendly framework** in Europe
  - **Put patients first!** (not industry, regulators, budgets)
  - **Consider risk-adapted regulation** (e.g. trials with approved drugs)
  - **Adjust safety reporting** to real need
  - **Increase transparency** of **public information about trials**
  - **Re-assessment of cost/benefit**, e.g. of new insurance requirements
- **Patients are the only true representatives of patients:**
  Inclusion when 'needs for protection' are discussed.

Internationally operating Rare Cancer Advocacy Organisations

- International Brain Tumour Alliance (IBTA) - http://www.theibta.org
- Sarcoma Patients Euronet (SPAEN) - http://www.sarcoma-patients.eu
- CML Advocates Network - http://www.cmladvocates.net
- International Kidney Cancer Coalition (IKCC) - http://www.ikcc.org
- European Cancer Patient Coalition (ECPC) – http://www.ecpc-online.org
- European Rare Disease Organisation (EURORDIS) - http://www.eurordis.org
- European Waldenström Network (EWMNetwork) - http://www.ewmnetwork.eu/
- European Myeloma Platform (EMP) - http://www.emp-myeloma.eu
- Myeloma Euronet - http://www.myeloma-euronet.org
- Lymphoma Coalition - http://www.lymphomacoalition.org
- Myelodysplastic Syndromes Foundation - www.mds-foundation.org
- Carcinoid & Neuroendocrine Tumor Society - http://www.cnets.org
- International Confederation Of Childhood Cancer Parent Organizations (ICCCPO) - http://icccpo.org/
- …

Rare Cancer patients need concerted action now!

Jan Geissler

- jan@leuka.net
- Twitter @jangeissler

- http://www.leukaemie-online.de
- http://www.cmladvocates.net

Workshop
"Rare Cancers:
The added value of closer cooperation"

12 July 2011
European Parliament

FRANCOISE MEUNIER, MD, PhD, FRCP
Director General
EORTC

Plan

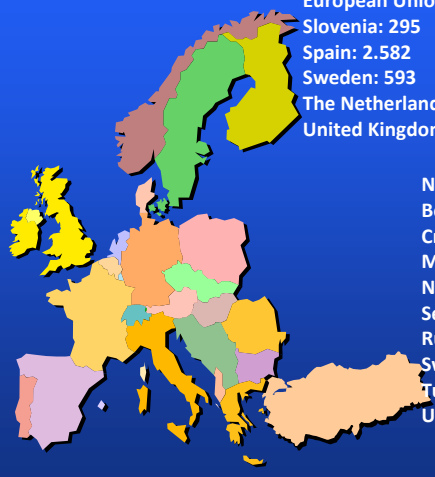
- About EORTC
- Clinical trials in rare cancers
- Impact of the Clinical Trial Directive
- Revision of the Clinical Trial Directive
- Additional proposals

About EORTC

- Created in 1962 to improve the standard of cancer treatment in Europe through:
  - Independent evaluation of innovative agents.
  - Test more effective therapeutic strategies (surgery, radiotherapy).
- Multinational network (300 institutions from 29 countries).
- Multidisciplinary:+/- 2,900 collaborators (clinicians, surgeons, radiotherapists, imagers, pathologists,....).
- 6,000 patients entered into EORTC trials/year.
- 30 clinical trials open to patient entry.
- Database of more than 180,000 patients.
- Headquarters in Brussels with 180 staff members.

Accrual of patients in EORTC clinical studies in 2000 - 2010: 67,003 patients

European Union:
Austria: 800
Belgium: 6,904
Bulgaria: 49
Cyprus: 73
Czech Republic: 153
Denmark: 502
Estonia: 7
Finland: 33
France: 13,312
Germany: 5,501
Greece: 48
Hungary: 192
Italy: 6.203
Latvia: 34
Luxemburg: 9
Malta: 20
Poland: 1.074
Portugal: 632
Republic of Ireland: 90
Romania: 20
Slovak Republic: 446



European Union (Cont.):
Slovenia: 295
Spain: 2.582
Sweden: 593
The Netherlands: 14,286
United Kingdom: 6,307

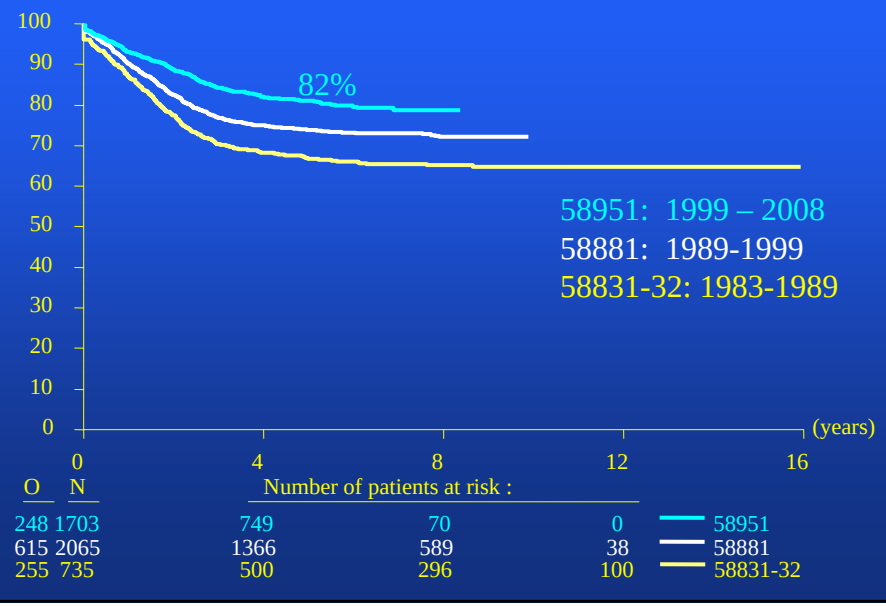
Non-EU Countries:
Bosnia: 8
Croatia: 346
Macedonia: 6
Norway: 454
Serbia : 261
Russia: 141
Switzerland: 1,336
Turkey: 631
Ukraine: 4

Rest of the World = 3,651 patients

EORTC ACHIEVEMENTS IN RARE DISEASES

- **Soft Tissue Sarcoma :**
  - **Gist Trial record breaking**
- **Melanoma :**
  - **Largest adjuvant trials in shortest time frame**
- **Brain Tumors : Adjuvant TMZ/XRT trial in GBM**
- **Haemato-oncology**
  - **Leukemia - trials / unique database**
  - **Lymphoma - trials / unique database**
  - **Children Leukemia - trials / unique database**
- **Head and Neck Cancer: Larynx preservation**

EORTC CHILDREN LEUKEMIA GROUP EVENT-FREE SURVIVAL OF ALL PATIENTS



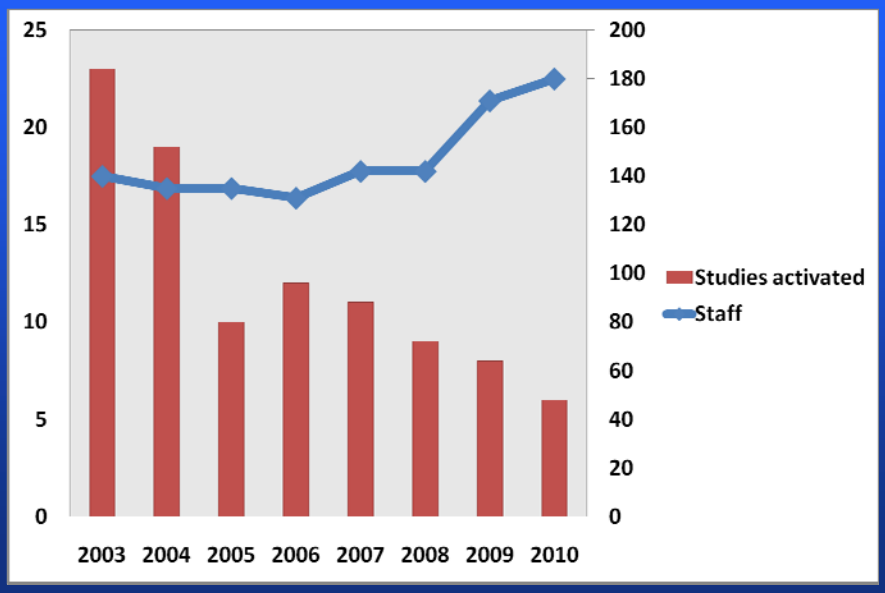
RARE CANCERS REQUIRE SPECIAL EFFORTS

- Adequate definition (the list is increasing with molecular classification of tumors).
- Smart but robust study methodology (tumor molecular characteristics and validated design).
- Discourage national/small sized trials (inconclusive, unethical and concomitantly conducted in several countries). PROMOTE COLLABORATION for timely accrual.
- Public funding of independent clinical trials (lack of market perspective for pharma).
- Harmonization of EU legal environment.

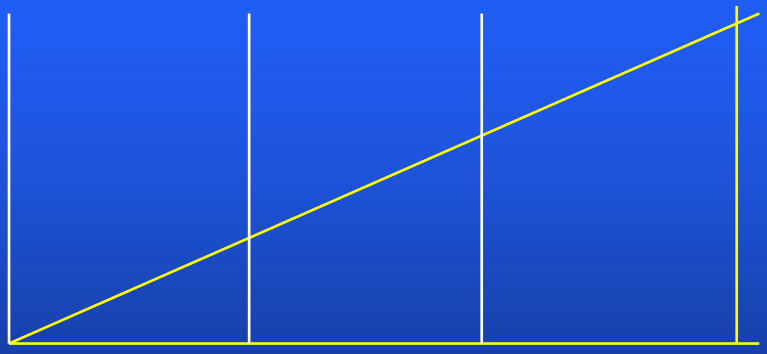
IMPACTS OF THE CLINICAL TRIAL DIRECTIVE 2001/20/EC

- Resources: increase of workload and costs
- Timeline: increase the delay before entry of the 1st patient and amendment implementation.
- Drop in EudraCT trial numbers
  2008= 9,334
  2009= 6,441
  2010= 5,914
  - 21 % of Multi-state trials
  - 70 % of patients in Multi-state trials
- Pharma versus IDCT
  - 36 % of IDTC (Investigators Driven Clinical Trials)
  - 64 % of Industry driven

IMPACTS OF THE CLINICAL TRIAL DIRECTIVE (EORTC data)



COMPLEXITY OF INVESTIGATOR DRIVEN CLINICAL TRIALS



Single site investigator-driven

Multicenter single network national trials

Multicenter single network EEA trials

Multicenter multi-network trials national /international or transcontinental

Small exploratory trials → Large phase III with sub-studies and TR

REVISION OF THE EU CLINICAL TRIALS DIRECTIVE (1)

Streamline-Simplify-Harmonize:

- **Procedures for authorizing clinical trials and the submission of amendments:**
  - **Single submission using electronic portal and English.**
  - **National competent authorities: Coordinated Assessment Procedure (like VHP) and mutual recognition. Opt-out option.**
  - **Mandatory for international trials.**
- **Achieve the single opinion in national ethical review.**
- **Safety reporting process. SUSAR management simplification. Clarification of the roles of CAs and ECs.**

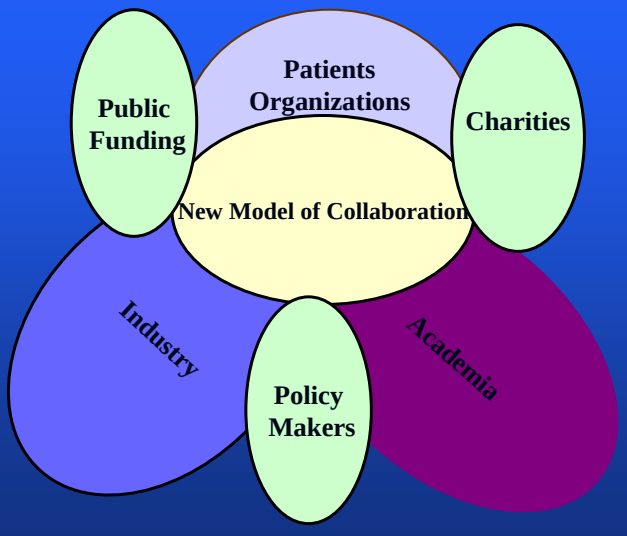
REVISION OF THE EU CLINICAL TRIALS DIRECTIVE (2)

- **Risk based approach (regulatory, pharmacovigilance, monitoring, insurance) applicable to all clinical trials:**
  - **Harmonize insurance requirement according countries.**
  - **Risk to be assessed first by the sponsor and approved by the regulatory bodies.**
- **IMP definition should exclude non-modified comparators available on the market, concomitant and background medication used in accordance with standard medical practice.**

ADDITIONAL PROPOSALS

- Education and career tracks for clinical investigators. How to motivate the young generation of MDs?
- Increase and promote patients' awareness and involvement
- Encourage partnership with pharma while preserving academics independency.
- European IDCT:
  - a Fund should be created
  - Mission: to fund every year a significant number of international IDCT
  - In all disease areas
  - Competitive process targeting scientific excellence and public health added value

CANCER CLINICAL TRIALS IN THE 21th CENTURY




EORTC
THANK YOU FOR YOUR ATTENTION

ABSTRACT by Professor David Walker, Children's Brain Tumour Research Centre, University of Nottingham, UK

Cancers in Children: Rare Tumours in a Minority Group of the Population

- *As a parent would you want your ill child treated with drugs, which are licensed or unlicensed for their use?*

- *As a parent would you want your ill child's doctor to select treatments based upon good quality research evidence or based upon his personal opinion and experience within his / her local health system?*

These two questions will be discussed at the Workshop.
As Children's Cancer Doctors we work with inspiring children and young people suffering from cancer on a daily basis. Whilst we are inspired by them to do our best, we are challenged by the problem identified by the two questions posed above.

Over the past 30 years we have been very successful in curing more children and adolescents by introducing new treatments within national and international clinical trials of new, predominantly combination drug treatments, which form the basis for patients' initial treatment. This partnership between doctors doing clinical research and their young patients and families means that we are driven to promote as comprehensive a programme of clinical trials as is possible.

In our cancer practice, most of our drugs are unlicensed for children, despite recent changes in legislation and the efforts of the European Medicines Agency (EMA) to try and catch up with licensing of previously used, but unlicensed drugs as well as the new drugs that are coming onto the market.

The evidence we use to select a patient's treatment is generated by including as many patients as possible within clinical trials of modern therapies as part of their initial therapy, frequently building upon complex, previously established recipes of treatments, thereby seeking to constantly improve outcomes.

Testing of entirely new drugs in children is becoming an increasing need as the range of new, highly effective molecules generated by scientific research is challenging the pharmaceutical industry and academic investigators to conduct trials in personalised disease groups. Children and young people frequently present special requirements for such personalised medicine by unique biology not only of their tumours but also state of growth and development of their normal tissues.

Our practice is limited by a number of key factors:

- The statistical challenge for researchers wishing to study the many different tumour types within the minority childhood population.

- The low priority for children's diseases as a focus for pharmaceutical-led drug development because of the challenge of their commercial justification, the over-emphasised perception of the ethical challenges of childhood research and their orphan status.

- Children in Europe have been denied access to innovative anticancer therapies while in the meantime many truly innovative medicines have been developed for the treatment of adult cancers. Despite the welcomed EU Paediatric Regulation, there are significant delays in the initiation of studies with new drugs in Europe and children are denied access to new potentially effective drugs (as compared to the US where many new drugs are studied in a timely fashion)

- Inequality of access to sufficient resources between the Member States to support the conduct of clinical trials with current legislative burden as well as the cost of insurance required by clinical trial sponsors.

This variation in research capacity limits the number of children across the Member States eligible for inclusion in trials of new therapy from which they, and others, benefit through the process of constantly exploring new treatments in children and young people.
In seeking to overcome these challenges we are aware of significant advances, which we celebrate:

- The EMA is strongly supporting the process of drug licensing for children although their task for children is overwhelming;

- The pharmaceutical industry is increasingly recognising that personalised medicine means that planned drug markets are no longer population-based but focussed upon patient groups identified by sophisticated biological screening;

- The EU FP7-funded European Network for Cancer research in Children and Adolescents (ENCCA) project provides an opportunity to support and further develop clinical trial networks of excellence.

- And finally the review of the EU Clinical Trials Directive provides a major opportunity to make changes that meet the needs of patients with rare cancers as a priority group, within which children and young people present a particular challenge because of their "minor" status and unique state of growth and development.

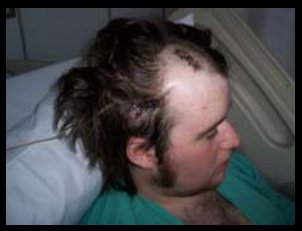
We wish to seek the participant's involvement and opinion on how they think that the current review of EU Clinical Trials Legislation could be best designed to meet the needs of people with rare cancers, where children and young people constitute an unique and predominant sub group.

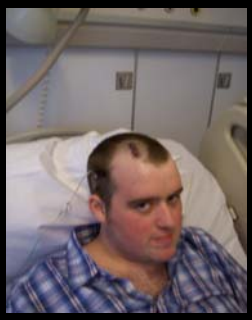
Professor David Walker in conjunction with Associate Professor Ruth Ladenstein and Professor Gilles Vassal of the SIOP Europe, the European Society for Paediatric Oncology (SIOPE) Board
Prof. David Walker, Children's Brain Tumour Research Centre, University of Nottingham, UK (David.Walker@nottingham.ac.uk)
Associate Professor Ruth Ladenstein, Children's Cancer Research Institute, Austria (ruth.ladenstein@ccri.at)
Prof. Gilles Vassal, Institut Gustave Roussy (gilles.vassal@igr.fr)

Surviving A Rare Cancer

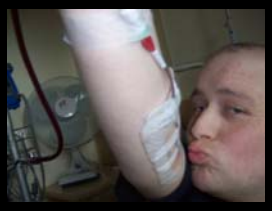
Peter Wilkinson

Diagnosis - Pineal Blastoma
Grade 4





Treatment



Coping With Cancer

All Clear - Back to normality?

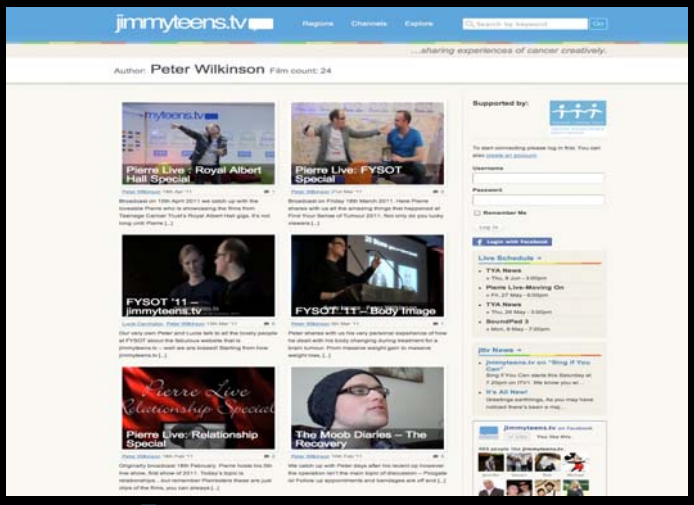
Young Peoples services in Sheffield...

jimmyteens.tv

TEENAGE CANCER TRUST
HELPING YOUNG PEOPLE FIGHT CANCER

AWARDS 2010
Pfizer
EXCELLENCE IN ONCOLOGY

www.jimmyteens.tv



jimmyteens.tv
sharing experiences of cancer creatively

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Health Strategy for the Europe 2020: Together for Health

Maria Vidal MD, PhD
Head of Unit
Medical Research
Health Directorate
DG Research and Innovation
European Commission

Rare Cancers: The value of closer cooperation Workshop 12 July 2011

COOPERATION

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Overview

- **The 7th Framework Programme for Research and its Health theme**
- **Rare cancers research in FP7: why, how and what?**
- **The future: what is next?**

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FP7 Health Programme

Main policy drivers:

- Improving health of European citizens
- Increasing competitiveness of European health-related industries and businesses
- Addressing global health issues
- Supporting the aims of Europe 2020: the 'Innovation Union'
  - ▶Collaborative research: FP7 projects
  - ▶Coordinating national research programmes: ERA-net
  - ▶Public-private partnerships: Innovative Medicines Initiative
  - ▶Joint Programming: Pilot Joint Programming Initiative on neurodegenerative diseases, in particular Alzheimer's
  - ▶European Partnership for Action Against Cancer
  - ▶European Partnership on Active and Healthy Ageing

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FP7 - EU cancer research

- **translate knowledge**
- **Reinforce basic-clinical links**
- **Reinforce investigator-industry links**
- **Continue to build critical mass**

Collaborative Research

-via small- and large-scale collaborative research projects

- **Reinforce coordination of research activities between member states**

Policy Initiatives

-via Support/Coordination/Joint Actions, Networks of Excellence, ERA-NET

Not legally binding

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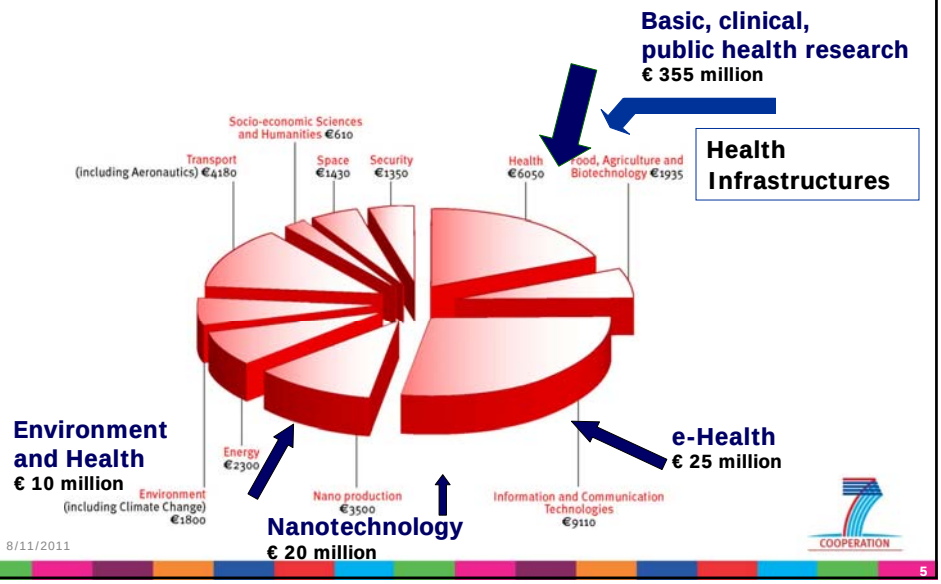
FP7 Cooperation programme: Support to translational cancer research



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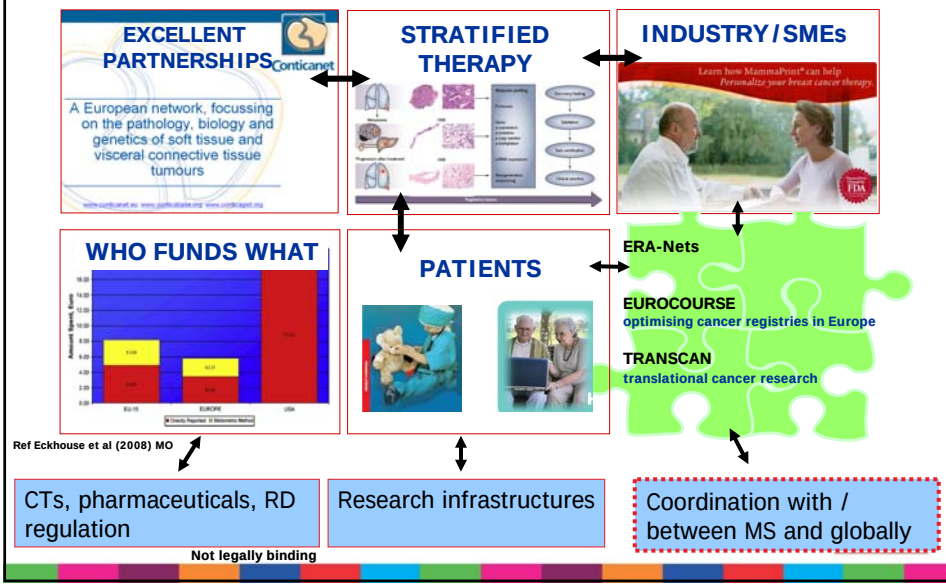
European Cancer Research Area: challenges



Ref Eckhouse et al (2008) MO

CTs, pharmaceuticals, RD regulation

Research infrastructures

Coordination with / between MS and globally

Not legally binding

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How?

- **Pulling of complementary research capacities and research institutions in collaborative projects**
  - **Facilitating the constitution of a critical mass of data and resources (e.g. data collection, clinical trials, comparative studies)**
  - **Establishing "proof of concept" for new methods and approaches**
  - **Steering exchange of best practices and development of evidence-based strategies for better diagnosis, treatment, care provision and delivery**
- **Capacity building by steering European knowledge, training and education schemes**

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Why?

- Very multidisciplinary area
- Essential to achieve critical mass, practical challenges to research
- Reduce knowledge fragmentation and enhance collaboration and management of effective clinical research in Europe
- Need to exchange best practices and provide research-based evidence of the effectiveness of approaches

What areas and questions have been addressed?

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FP7 - Overview and coverage

1st Call		2nd Call		4th Call		5th Call	
Non-coding RNA	CP	Multimodal radiation-based clinical trials	CP-IP	Translational cancer research	ERA-NET	Investigator-driven clinical trials in rare cancers	CP-IP
Clinical 'omics'-technology biomarkers	CP	Inflammation	CP-IP	Translational research between cancer research centres	NoE	Poor-prognosis cancers	CP-IP
Genomic instability	CP	Epidemiology of gene-environment interactions	CP-IP	Clinical research paediatric and adolescent oncology	NoE	Cancer aetiology in India	CP
Cancer screening biomarkers and/or methods	CP	Hypoxia	CP-IP	Infectious agents and cancer in Africa	CP		
End-of-life care	CP	Cancer registries	ERA-NET	Clinical research rare cancers in adults	CP-2		
Metastasis	CP	Cancer aetiology in Latin America - SICA	CP	Poor-prognosis cancers	CP-2		
Targeted drug delivery	CP			Long-term side effects	CP-2		
High-throughput bioassays and models	CP			Predicting individual response and resistance to therapy	CP-2		
				(Chemo)radiotherapy and/or surgery	CP-2		

3rd Call

No cancer topics

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Facilitating the constitution of a critical mass of data and resources (e.g. data collection, clinical trials, comparative studies)

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Collaborative research on rare cancers

TCAC in Cancer

association between defects in the tricarboxylic acid cycle (TCAC) and cancer - characterising the natural history and prevalence of TCAC-deficient cancers, unravelling the molecular mechanisms driving TCAC-associated tumourigenesis.

European MCL Network

innovative therapeutic strategies and molecular mechanisms of malignant transformation in mantle cell lymphoma; investigator initiated phase I/II studies to optimise therapeutic regimes

PROTHEIS

prognostic markers and new therapeutic targets in the Ewing's sarcoma family of tumours

childhope

Immunotherapy for paediatric tumours: acute B-lineage lymphoblastic leukaemia, non-Hodgkin B-lineage lymphoma and acute myeloid leukaemia.

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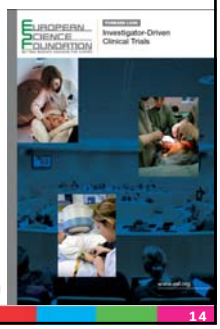
Investigator-driven cancer clinical trials (IDCTs)

For example due to:

- Stratification of cancer patients in subgroups
- Importance of shortening accrual times
- Better opportunities to address for example (very) rare cancers

Increasing complexity

- Industry has the resources to deal with the complexity of international clinical trials
- Dealing with the complexity is a challenge for **investigator-driven** clinical trials



European Clinical Research ECRIN Infrastructures Network

ICREL Impact on Clinical Research of European Legislation

Not legally binding

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Clinical Trials in FP7

Focus on clinical trials in the 2011 WP (currently under negotiations)

to bring discoveries into clinical testing,
to advance development of new approaches
and to compare treatments

- Most topics are for investigator-driven clinical trials (IDCTs), complementing development of new drugs by industry
- Phase I, II, III, IV (comparative effectiveness) trials
- Eight topics, with several projects to be funded in each topic including:
  - ***Investigator-driven treatment trials for rare cancers***
  - ***Investigator-driven clinical trials on off-patent medicines for children*** (oncology products in infants a priority)
- => Total EC contribution to Clinical Trials topics: **€150-200m**

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Clinical trials in rare cancers (under negotiations)

- **EUROSARC -** European Clinical trials in Rare Sarcomas within an integrated translational trial network
- **IMMOMEC -** IMmune MOdulating strategies for treatment of MErkel cell Carcinoma
- **IntReALL -** International study for treatment of childhood relapsed ALL 2010 with standard therapy, systematic integration of new agents, and establishment of standardized diagnostic and research

€ 17 million

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Involvement of patients in clinical trials

Patient Partner

PATIENT-PARTNER - identifying the patients' needs for partnership in the clinical trials context, sustainable communication platform, guidelines

Value+ project coordinated by the European Patient Forum - overview and analysis of current practice and trends regarding patient involvement in EU health supported projects

PREDICT - Increasing the Participation of the Elderly in Clinical Trials
To investigate reasons for the exclusion of the elderly in clinical trials and to provide solutions for this problem

RESPECT –
Relating Expectations and needs to the Participation and Empowerment of children in Clinical Trials
Identifying the needs of children who have participated or who might participate in clinical trials for new drugs, empowering children participating in clinical trials research.

Patient involvement encouraged in topics currently open

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Establishing "proof of concept" for new methods and approaches

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Trials to obtain a paediatric-use marketing authorisation (PUMA)

Recurrent topic in FP7 Health work programmes*

LoullaPhilla	Development of 6-mercaptopurine and methotrexate oral liquid formulations for the maintenance treatment of acute lymphoblastic leukemia in children
EPOC	Doxorubicin pharmacokinetics in the treatment of paediatric cancers.
O3K	Development of oral liquid formulations of Cyclophosphamide and Temozolomide for the treatment of childhood cancers.

*Donnelly F (2010) Pharmaceutical Policy and Law 12, 77-80.

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Steering exchange of best practices and development of evidence-based strategies for better diagnosis, treatment, care provision and delivery

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Integrating research in EU – Networks of Excellence

Conticanet

Improve understanding, diagnosis and management of connective tissue cancers.

EuroBoNeT

Increase and disseminate knowledge of primary bone tumours at the molecular level for development of new tools for patient care and cure and technology;.

ELN European LeukemiaNet

Integrate the leading leukaemia trial groups across Europe for advancements in leukaemia-related research and health care

encca

Improve the quality-of-life of children and adolescents with cancer, in particular the long-term side-effects of current and future treatments

EurocanPlatform

EUROCANPLATFORM - Structuring translational cancer research between cancer research centres in Europe

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Capacity building for cancer research

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Infrastructures

SPIRIT: Support of public and industrial research using ion beam technology
€7 million

IA CTs on rare diseases

ULICE: Union of Light-Ion Centres in Europe
€4.8 million

East-NMR: Enhancing Access and Services to East European users towards an efficient and coordinated Pan-European pool of NMR capacities to enable global collaborative research & boost technological advancements
€3.5 million

ELISA: European Light Sources Activities – Synchrotrons and Free Electron Lasers
€10 million

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Cancer registries

Surveillance of Rare Cancers in Europe RARECARE

- To provide an operational definition of "rare cancers", and a list of cancers that meet this definition, to estimate the burden of rare cancers in Europe (incidence, survival, prevalence and mortality), to improve the quality of data on rare cancers
- To disseminate the knowledge among stakeholders, including clinicians, patients and health planners

EUROCOURSE

to link and integrate national/regional programmes aimed at supporting cancer registries and research carried out using registry data. At the same time EUROCOURSE is seeking to optimize the use of cancer registration data for the amelioration of cancer control and the strengthening of population-based cancer research in Europe.

HAEMACARE
Cancer Registry based Project on Haematologic Malignancies

PanCare

EUROCARE

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Commission Communication "Action Against Cancer: European Partnership"

Four ambitious goals:

- Health promotion and early detection
- Applying best healthcare approaches in practice - identification and dissemination of good practice
- **Cooperation and coordination in cancer research**
  => to coordinate one third of research efforts funded by all sources in Europe by 2013
- Benchmarking process – providing the comparable information necessary for policy and action
- Implemented through a Joint Action supported by both the Commission and the Member States

European Partnership Action Against Cancer

-launched 29 September 2009
-duration: 2011-2013
-http://www.epaac.eu/home

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Stimulating innovation through coordination of Member States research activities

Mapping the state-of-the-art
Identifying common needs

Implementing joint actions

Eurocan Plus

Improving Coordination of Cancer Research in Europe

FP6

ERA-NETs

- **CoCanCPG - Coordination of Cancer Clinical Practice Guidelines in Europe (FP6)**
- **EUROCOURSE - Europe against Cancer: optimisation of the use of registries for scientific excellence in research (FP7)**
- **TRANSCAN – Translational cancer research in Europe (FP7)**

Networks of Excellence

- **EUROCANPLATFORM - Structuring translational cancer research between cancer research centres in Europe (FP7)**
- **ENCCA - Structuring clinical research in paediatric and adolescent oncology in Europe (FP7)**

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Drivers for FP7 from Innovation Union policy

- **Innovation-driven approach**
  - **Focus on SMEs** through genuine academia-industry collaborations
- **Challenge-driven approach**, focus on key challenges
- **Support implementation of European Innovation Partnerships**, such as **"Active and healthy ageing"**
- Stronger **socio-economic impact** - innovation dimension
  - with more attention to **exploitation phase**
- **Balance** upstream research and activities closer to market in order to achieve short and medium-term impact

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The Innovation Union

Innovation Union

One of the seven "flagship" initiatives of the Europe 2020 strategy

Key objective: to focus European research and innovation efforts on the main societal challenges faced by Europe

Two challenges: ageing of the European population, and growing needs related to health and access to medicines and health care

- Improving framework conditions for businesses to innovate, improving access to finance.
- Creating **'European Innovation Partnerships'** between the EU and national levels to speed up the development and deployment of the technologies needed to meet the challenges identified.
- Increasing focus of research funding effort on support to innovative, high-tech SME, fund high-impact and demonstration-type projects.

➡ Adoption of Communication 6 October 2010

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Innovation Union: the European Innovation Partnerships

Among a range of actions in various fields relevant to innovation, the Innovation Union foresees the launch of a series of **"European Innovation Partnerships" on themes linked to major societal challenges** that are shared across the EU.

- they will be **challenge-driven**
- they will act **across the whole research and innovation chain**
- they will serve as **overall frameworks** helping the EU and the Member states to address in a coordinated and efficient way research and innovation issues in the fields concerned.

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European Innovation Partnership on Active and Healthy Ageing

- The first pilot project of Innovation Partnerships has been launched in this field**. It should, by 2020, enable citizens to live longer independently in good health by increasing the average number of healthy life years by 2.**
- **Is** not a new instrument, **but a** coordinated framework **for definition and monitoring of actions**
- **Seeking to** optimise and streamline the use of existing tools**, under a single, coherent and integrated framework**
- **Bringing together actors at all levels and sectors to** mobilise available resources and expertise and define a **common vision**
- It will improve the sustainability and efficiency of our social and healthcare systems and contribute to create an EU and global market for innovative products and services.

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Green Paper on a Common Strategic Framework for future EU Research and Innovation Funding

A "Common Strategic Framework" to improve the efficiency of research and innovation funding at national and EU levels.

- **Giving the EU a world-beating science base; boosting competitiveness and tackling grand challenges such as health and an ageing population**
- **Making EU funding easier to access for participants through a streamlined set of funding instruments**
- **Establishing simpler and more consistent procedures for accounting for the use of the funds received**

Consultation on EU research and innovation funding

THANK YOU FOR YOUR ATTENTION !

http://ec.europa.eu/research/health

Improving Drug Development for Rare Cancers

Pr Gilles Vassal
Institut Gustave Roussy, Villejuif, France

ENVI workshop on Rare Cancers:
Tuesday, 12 July 2011
Brussels

Rare Cancers : numbers yearly

- 2.5 millions of EU citizens diagnosed with cancer*
  – 1 230 000 die of cancer
- ~20% have rare cancers
  – EU definition = prevalence <5 in 10,000
- ~500,000 citizens with a rare cancer including
- ALL 15,000 children and adolescents

A major Public Health Issue

*http://eu-cancer.iarc.fr/2-cancer-fact-sheets.html,en

Rare Cancers: the ISSUES

- More than 1000 malignant diseases in all organs complex to diagnose and treat
- Not a market for efficient Return on Investment: not a priority for Pharma

The patients needs/rights:

- Equal access across Europe to expertise and standard care
- Access to innovative therapies in due time

Improving Drug Development in Rare cancers: the 4 Pillars

1. Networking of academic institutions for expertise, care and research (quality, accreditation)
2. Public funding of research to understand the diseases mechanisms (system biology)
3. Incitives/Obligations towards Pharma to develop oncology drugs for rare cancers
4. Partnership with patients and parents

2 Major EU Initiatives for Drug Development in Rare Cancers

Official Journal of the European Union

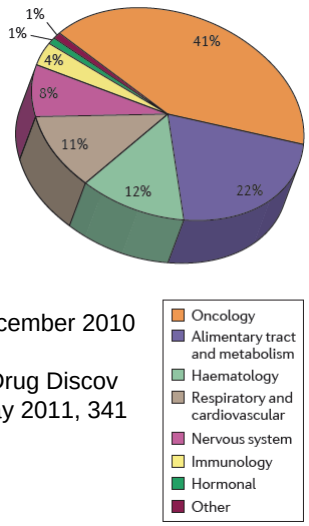
December 1999: Orphan Medicinal Products

REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 16 December 1999
on orphan medicinal products

December 2006: Medicinal Products for paediatric use

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 12 December 2006
on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004
(Text with EEA relevance)

Orphan DRUGS – 10 years of EU regulation*



*As of December 2010

Nat Rev Drug Discov
Vol10, May 2011, 341

- 850 orphan designations
- 63 approved drugs
  - 41% in oncology
  - Many hematological malignancies
  - Few solid tumors: kidney, GIST,Adrenal Glands
  - Many rare cancers remain ORPHAN

Eu Pediatric Medicine Regulation at year 4

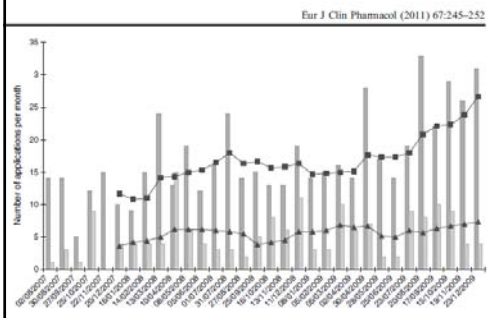


Fig. 1 Number of applications per month for Paediatric Investigation Plans (PIPs, *dark-grey bars*) and full waivers (*light-grey bars*) received by the European Medicines Agency (EMA) since the introduction of the Paediatric Regulation in 2007, including 6-month moving averages (*filled rectangles* PIPs, *filled triangles* full waivers)

- >1000 PIP applications
- 500 PIP approved
  - 13.4% endocrinology
  - 11% oncology
  - 10.8% infectious diseases
- But Initiation of PIP studies is deferred for 90% of new drugs

PIP = Pediatric Investigations Plan

EU Pediatic Medicine Regulation and Cancer in Children: a Major CONCERN

- Major needs in children are not addressed
  - because the pediatric development is driven by the Adult indication
- No increase in the number of new drugs studied in Europe (as opposed to the US)
- Consequences:
  - The urgency of proposing new treatments for children with not curable diseases is denied (ethical concern)
  - Pediatric oncologists prescribe new drugs off-knowledge for individual patients (safety concern)
  - Parents are tempted to go to the US to allow their child to participate to a clinical research (societal concern)

Improving drug development for rare cancers: CONCLUSION

- NEED for public investment – Europe AND member states
  - Funding research (basic, translational AND clinical)
  - AND networks (SUSTAINABILITY) in the FP8
- MAKE the PEdiatric Medicine REgulation a success for children and adolescents with cancer
- FACILITATE investigator-driven clinical research
- This is a Heath issue to be addressed through Public AND Private partnership, committment and funding

- **ITCC**
  Network for Innovative Therapies for Children with Cancer
  Running early phase trials and biology research for new anticancer agents in Europe since 2003
  http://www. itcc-consortium.org

- **ENCCA**
  the European Network for Cancer research in Children and Adolescents
  a FP7 Network of excellence to structure clinical research
  launched on Janduary 1st, 2011

Drug Development of Rare Cancer treatments

Pamela S. Cohen, MD
Sanofi Oncology
Cambridge, Massachussets, US
pamela.cohen@sanofi-aventis.com

SANOFI ONCOLOGY

Issues for discussion

1. Recent drug approvals in orphan cancers
2. Defining common tumor types by molecular phenotyping – creating orphan (rare) cancers out of common cancers?
3. SAR302503 : an example of orphan drug development
4. Challenges for drug development in orphan diseases.

SANOFI ONCOLOGY

PS Cohen
12 July 2011

Definition of rare (orphan) disease in EU

In the EU, a rare disease (including rare cancers) is one which affects fewer than 5 people per 10 000. The number of sufferers may still be high, however, as there are some 7 000 known rare diseases.

SANOFI ONCOLOGY

PS Cohen
12 July 2011

Multiple drugs approved in Orphan indications

Table 1. New Drug and Biologic Agents Approved to Treat Cancer, 2004-2010

Agents	Year Approved	Original Indication(s)	Drug Class (Other Similar Drugs)[a]	Alternative Therapies Available at Time of Approval[a]	Clinical Testing Duration (IND to NDA), y
		Orphan Drugs			
Pemetrexed	2004	Malignant pleural mesothelioma	Antifolate (methotrexate)	None approved for this indication	11.2
Azacitidine	2004	Myelodysplastic syndrome of certain F-A-B subtypes	DNA methylation inhibitor (none)	Supportive care, HSCT	3.5
Clofarabine	2004	Pediatric patients with ALL after at least 2 prior treatments	Purine antagonist (fludarabine, cladribine)	Numerous	5.3
Nelarabine	2005	Adult patients with T-cell lymphoblastic lymphoma and ALL after at least 2 prior treatments; pediatric patients with same conditions	Purine antagonist (fludarabine, cladribine)	None approved for this indication	10.9
Sorafenib	2005	Advanced renal cell carcinoma	Multiple tyrosine kinase inhibitor (none)	Interleukin 2	5.1
Lenalidomide	2005	Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a 5q deletion cytogenetic abnormality	Immunomodulator (thalidomide)	Azacitidine	4.9
Decitabine	2006	Myelodysplastic syndrome previously treated and untreated, de novo and secondary, of all F-A-B subtypes	DNA methylation inhibitor (azacitidine)	Azacitidine	7.3
Dasatinib	2006	Chronic-phase, accelerated-phase, or myeloid or lymphoid blast-phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib; Philadelphia chromosome–positive ALL with resistance or intolerance to prior therapy	BCR-ABL tyrosine kinase inhibitor (imatinib)	None approved for this indication	2.7
Vorinostat	2006	Cutaneous T-cell lymphoma on or following 2 systemic therapies	Histone deacetylase inhibitor (none)	None approved for this indication	6.2
Temsirolimus	2007	Advanced renal cell carcinoma	mTOR kinase inhibitor (sirolimus)	Sorafenib, sunitinib, interleukin 2	4.9
Nilotinib	2007	Philadelphia chromosome–positive chronic myelogenous leukemia in chronic phase and accelerated phase in adults resistant or intolerant to prior therapy that included imatinib	BCR-ABL tyrosine kinase inhibitor (imatinib, dasatinib)	Dasatinib	2.4
Bendamustine	2008	Chronic lymphocytic leukemia	Alkylating agent (carmustine, others)	Chlorambucil, rituximab, fludarabine	4.2
Pralatrexate	2009	Relapsed or refractory peripheral T-cell lymphoma	Antifolate (methotrexate)	None approved for this indication	12.1
Ofatumumab	2009	Chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab	CD20 monoclonal antibody (rituximab)	Chlorambucil, bendamustine, cyclophosphamide	4.7
Romidepsin	2009	Cutaneous T-cell lymphoma after ≥1 prior systemic therapy	Histone deacetylase inhibitor (vorinostat)	Bexarotene, vorinostat	6.6

Kesselheim et. al., JAMA 2011

Classification of Cancer Indications

Cancers have been traditionally characterized histopathologically

- e.g. breast, pancreas, colon cancer

More recently molecular characterization of tumors has revealed that most histopathologically characterized tumor types can be further subdivided based on molecular phenotyping (DNA mutations, RNA expression, etc)

- e.g. breast cancer can be divided into ER+, PR+, HER2+, or triple-negative
- Treatments targeting these subtypes (e.g. tamoxifen (ER+), herceptin (HER2+) offer significantly improved efficacy compared to previous approaches

Molecularly targeted populations treated with molecularly targeted agents are extremely effective compared to the standard of care

- **Crizotinib: an ALK kinase inhibitor**
  - **ALK mutations : 3-5% of non-small cell lung cancer**
  - **Incidence (EU) ~18,000 new cases/year or ~ 0.5/10,000**
  - **Phase III: extremely high efficacy in ALK-mutated population (N=82)**
    - 61% response rate (compared to 8% SOC).
    - PFS 10 months (compared to 2.6 months SOC)
    - 6-month OS estimated at 90% (compared to 25% for SOC)
- **Vemurafenib: a B-RAF inhibitor**
  - **Incidence of melanoma (EU): 35,000/year (**
  - **B-RAF V600E mutations: ~55 % of melanoma or ~0.5/10,000**
  - **Phase III: extremely high efficacy in B-RAF mutated population (N=550)**
    - Response rate: 48% (vs. 6% dacarbazine)
    - PFS 5.3 months, HR 0.37 (vs 1.3 months dacarbazine)
    - OS @ 6 months: 84% (vs 64% dacarbazine)
- **Other targeted drugs with high effectiveness in molecular targeted populations:**
  - **Gleevec, Nilotinib, Dasatinib: in bcr-abl mutated CML**
  - **Tarceva: in EGFR-mutated Lung cancer (10% of NSCLC ~ 1/10,000**

SHOULD molecularly characterized tumor subtypes, particularly subtypes with mutations in genes targeted by a targeted drug, be considered as separate indications, and if so, be offered the opportunity to be considered as orphan diseases?

Targeting the JAK2 pathway in Myelofibrosis – an example of drug development in an orphan indication

What is Myelofibrosis?

- Myelofibrosis is a life-threatening myeloproliferative neoplasm usually managed by hematologists and hem/oncs.
- Characterized by abnormal blood cell production and fibrosis (scarring) within the bone marrow
- MF occurs in two forms: primary and secondary
- Median survival is ~ 6 years; Death due to bleeding, infection and leukemia
- The 10 year risk of leukemic transformation may be ~ 20%
- No approved therapies

Most patients have enlarged spleens and constitutional symptoms

- •Fatigue
- •Abdominal Pain
- •Night Sweats
- •Weight Loss/Cachexia
- •Severe pruritis/itching

Incidence of MF in the EU

Table 5: Annual incidence of primary myelofibrosis in Europe (age standardized)

Country	Incidence per 10,000	Number of Cases	Period	Reference
France	**0.05**[2]	81	1980-2007	Girodon 2009
Sweden	**0.03**	20	1983-1992	Ridell 2000
	0.03	34	1983-1999	Johansson 2004
United Kingdom	**0.04**	61	1999-2000	Phekoo 2006

Prevalence of PMF is ~ 0.3 per 10,000, well below the EU definition of the orphan indication of 5 per 10,000

Significance of JAK2V617 Mutations in MF, PV and ET

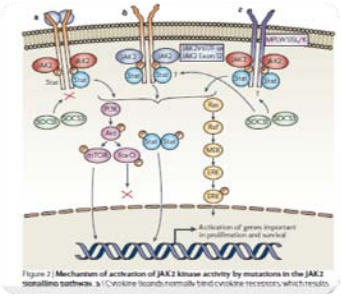


Table 1 | **Frequency of the *JAK2V617F* allele in myeloid disorders**

Disease	Frequency
Polycythaemia vera	81–99%
Essential thombocytosis	41–72%
Primary myelofibrosis	39–57%
Chronic myelomonocytic leukaemia	3–9%
Myelodysplasia*	3–5%
Acute myeloid leukaemia‡	<5%

*Most common in patients with refractory anaemia with ringed sideroblasts and thombocytosis, a clinically distinct subtype of myelodysplastic syndromes. ‡Most common in patients with a previous history of polycythaemia vera, essential thrombocytopaenia and primary myelofibrosis.

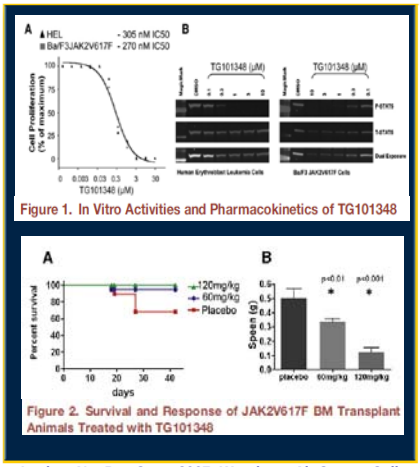


Figure 1. In Vitro Activities and Pharmacokinetics of TG101348

Figure 2. Survival and Response of JAK2V617F BM Transplant Animals Treated with TG101348

Levine. *Nat Rev Canc*. 2007; Wernig et. Al. *Cancer Cell*. 2008.

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12 July 2011

SAR302503/TG 101348 – A Highly Potent and Selective JAK-2 Inhibitor

JAK Selectivity Profile

	JAK-1	JAK-2	JAK-3	TYK2
SAR302503	46	1.3	96	171
INCB 18424	2.7	4.5	322	19
SB 1518	1280	23	533	Not reported
CYT 387	11	18	155	17

Molecular characteristics

- **Orally available**
- **Highly potent and selective against JAK-2 kinase**
- **Minimal JAK-1 and JAK-3 kinase inhibition reduces potential for off-target side effects**
- **Phase I data suggests good efficacy and safety`in Intermediate-2 and High-Risk MF patients**

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SAR302503 Phase I/II: Study design and results

- **Study design:**
  - **Ph I dose escalation (N=28); Ph II expansion (N=31) @ MTD 680 mg/day**
  - **Population: Int-2 and High Risk (IWG-MRT) Myelofibrosis patients with/without JAK2 mutation**
- **Safety:**
  - **asymptomatic hyperamylasemia (DLT), diarrhea, anemia,**
  - **680 mg/day probably too toxic due to anemia, and emergence of transfusion dependence on chronic administration**
- **Efficacy:**
  - **Best response at 6 months was Clinical Improvement (IWG-MRT criteria), based on reduction of splenomegaly by palpation**
    - MTD cohort RR= 49%
    - Overall RR = 42%
    - Duration: 63% of patients remain on drug for median 25 months (all doses).
  - **Significant improvement in constitutional symptoms (fatigue, cachexia, early satiety, night sweats**
  - **Significant decrease in JAK2 V617F mutant allele burden**
  - **Responses seen regardless of presence of JAK2 mutation**

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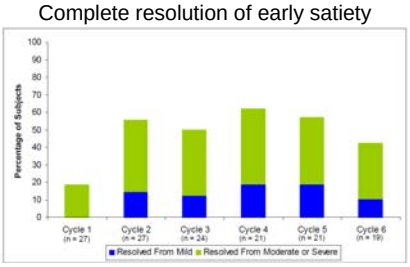
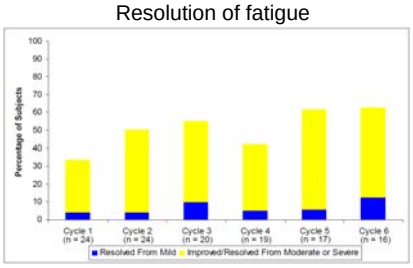
Improvement in Symptoms:
>50% of patients had improved or complete resolution of constitutional symptoms

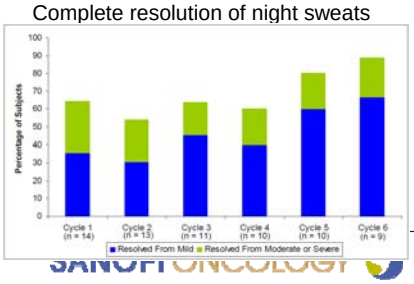
Complete resolution of early satiety



Resolution of fatigue



Complete resolution of night sweats



Symptom	N (%)	Improvement	Complete resolution
Cough	13(37%)	75%	67%
Pruritis	8 (23%)	75%	50%

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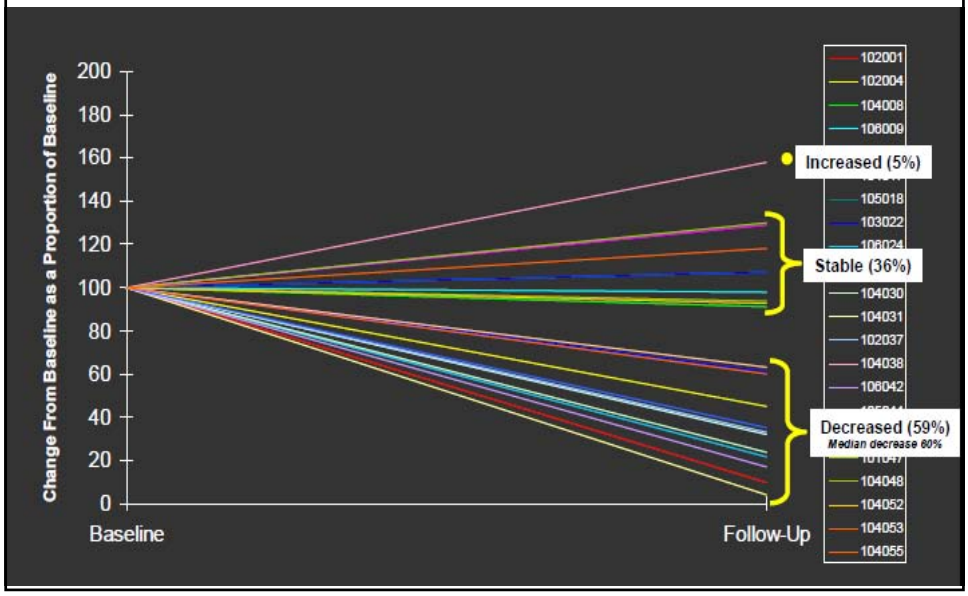
SAR302503 Effect on V617F Allele Burden in subjects with Baseline >20% (N=22)



Challenges to development of treatments for orphan oncology diseases

Registration strategy of orphan oncology diseases:

1. **Is there a need for a randomized, controlled Phase III in diseases where there is substantial efficacy seen in Phase I or II studies?**
   - **e.g. ALK, B-RAF inhibitors, Gleevec**

2. **Is it ethical to put patients on a control arm (placebo or best available care) ethical in situations where the control arm has very minimal efficacy in the face of substantial efficacy of the experimental drug??**
   - **e.g. B-RAF inhibitor in Phase III melanoma trial**

3. **Can surrogate endpoints e.g. response rate be used as an accelerated approval endpoint in orphan disease randomized Phase III trials**

Strategies for Health Authorities to encourage multiple competitor agents in rare diseases

1. **Once an agent gets accelerated approval, accrual to trials with competitor agents becomes difficult due to availability of 1st in class drug**
2. **EAP programs prior to approval also make competitor trial accrual challenging.**

Characteristics of Pivotal Trials in Orphan Diseases differ from those of Non-orphan Diseases in Oncology

Table 2. Characteristics of Pivotal Preapproval Trials of Orphan and Nonorphan Cancer Drugs

Characteristics	No. (%)[a] Orphan Drug Pivotal Trials (n = 23)	Nonorphan Drug Pivotal Trials (n = 15)	*P* Value
Enrollees, median (interquartile range)	96 (66-152)	290 (185-394)	<.001
Randomized, multigroup	7 (30)	12 (80)	.007
Comparator			
Active	4 (17)	7 (47)	.007
Supportive care	2 (9)	1 (7)	
Placebo	1 (4)	4 (27)	
None	16 (70)	3 (20)	
Blinding			
Double-blind	1 (4)	5 (33)	.04
Single-blind	1 (4)	0	
Open-label	21 (91)	10 (67)	
Primary trial end point reported[b]			
Disease response[c]	17 (68)	4 (27)	.04
Disease progression[d]	4 (16)	6 (40)	
Overall survival	2 (8)	4 (27)	
Other	2 (8)	1 (7)	

Kesselheim et. al., JAMA 2011

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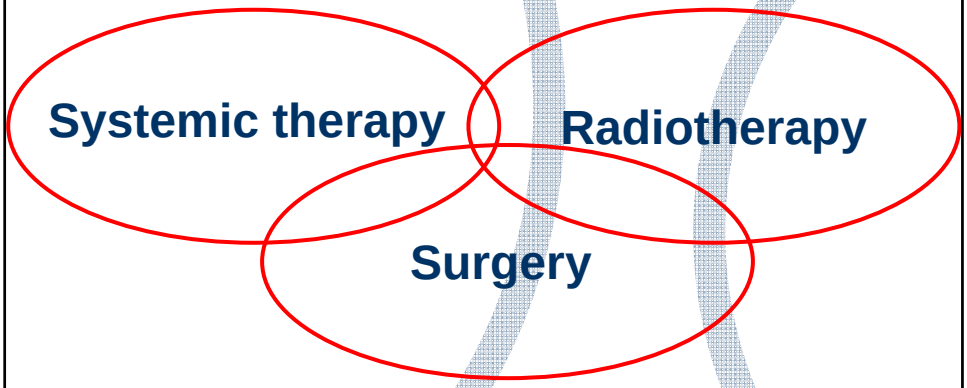
Improving Radiation Therapies and Drug Development for Rare Cancers: Modern Radiation Oncology

Priv.-Doz. Dr. med. Stephanie E. Combs
Department of Radiation Oncology

Multimodal Treatment Concepts In Oncology



Radiotherapy is included in more than 50% of all cancer treatment protocols.

Challenges in Radiation Oncology

- main goal: achievement of local and distant tumor control
- complex target/tumor volumes
- close vicinity to organs at risk
  - i.e. optic nerves, chiasm, brain stem, spinal cord
  - i.e. epiphyseal plates

-high risk for treatment related side effects
- -xerostomia
- -impairment of vision, blindness
- -growth and muscolosceletal abnormalities
- -endocrine and fertility dysfunctions
- -neuropsychological/neurobehavioral deficits
- -secondary malignancies

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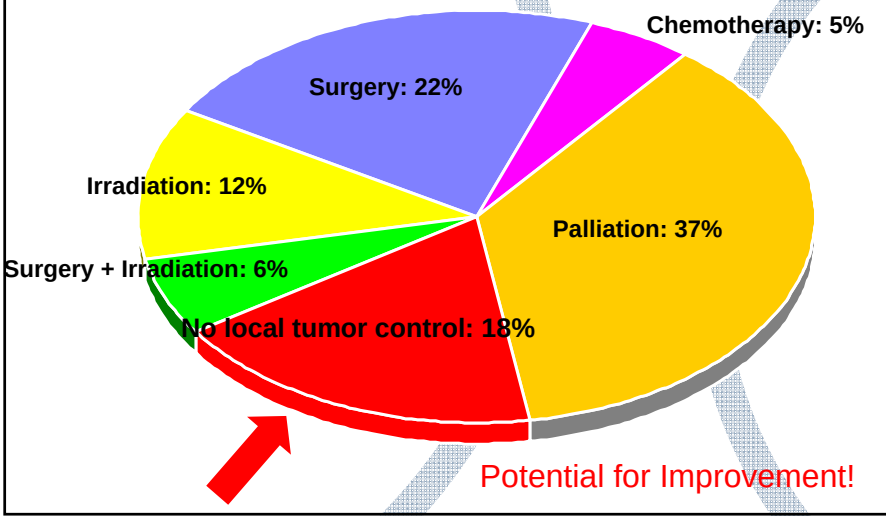
Current Status of Cancer Treatment

Localized Tumors: 58% **Metastasized Tumors: 42%**



Potential for Improvement!

Optimizing your focus…

Stereotactic Radiosurgery (SRS)

- Dose application in one fraction
- Short treatment times

Fractionated Stereotactic Radiotherapy (FSRT)

- Dose application in multiple fractions
- Lower risk for side effects – radiobiological benefit of fractionation (recovery)
- For smaller and larger target volumes

Intensity Modulated Radiotherapy (IMRT)

- Treatment of complex target volumes
- e.g. skull base tumors, tumors of the head-and-neck region, temporal glioblastomas

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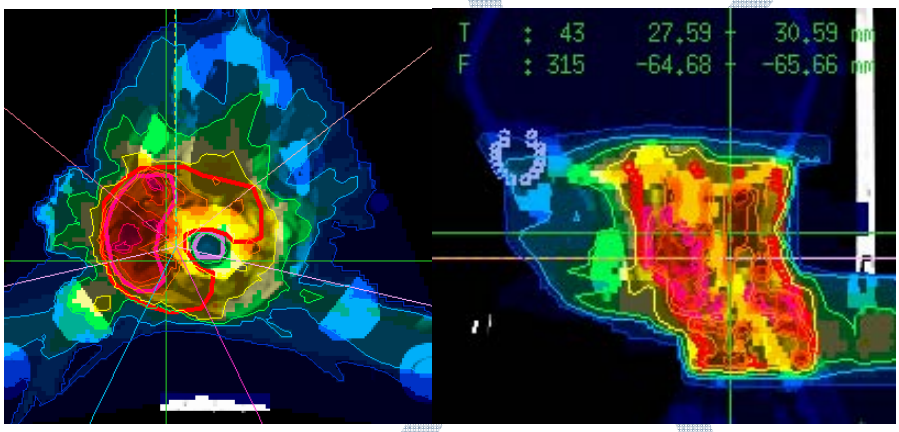
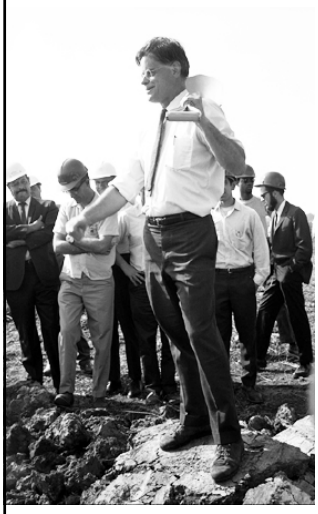
Paraspinal RMS: Complex Target Volume



Robert R. Wilson (1914-2000)
Radiotherapy using charged particles



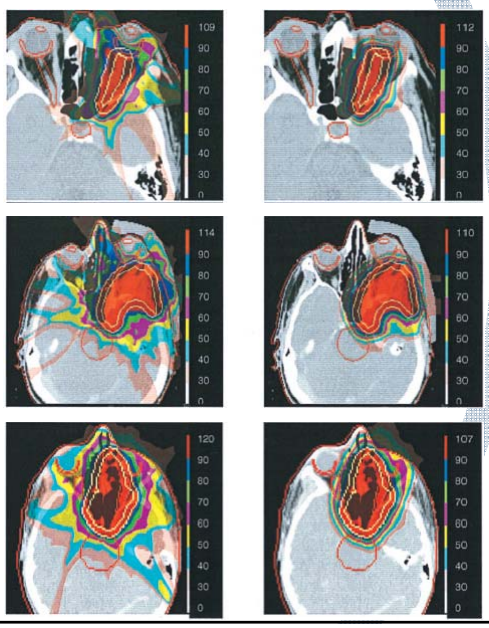
1946	Iontherapy for deep seeted tumors
1954	Lawrence Berkeley Laboratory, USA starts protontherapy
1957	Uppsala starts proton treatment
1975	Lawrence Berkeley Laboratory, USA starts using heavy charged particle
1990	Opening of the Proton Therapy Center in Loma Linda (USA)
1993	Start of Carbon Ion Therapy in Chiba (Japan)
1997	Protonentherapy starts in in Villingen/Schweiz
1997:	Carbon ion Radiotherapy starts at the University Hospital of Heidelberg, Germany at GSI in Darmstadt
Today	**Various clinical centers for particle therapy**

Fundamental Research

Clinical Research

Clinical Application

IMRT IMPT



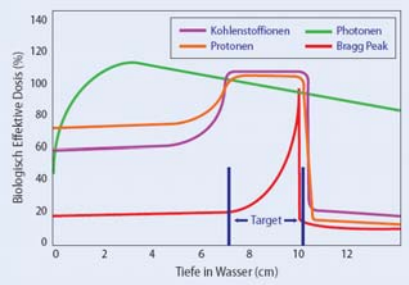
Optic Nerve Sheath Meningioma

Meningioma

Rhabdomyosarcoma

Miralbell et al., IJROBP 2000

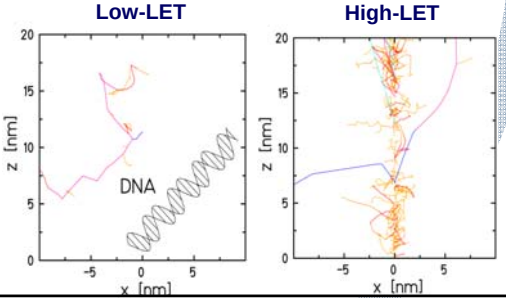
Physical and biological Benefit of Ion Beams



- inverse dose profile
- high local dose deposition in „Bragg Peak“
- sparing of normal tissue

Combs SE et al. Chirurg, 2007

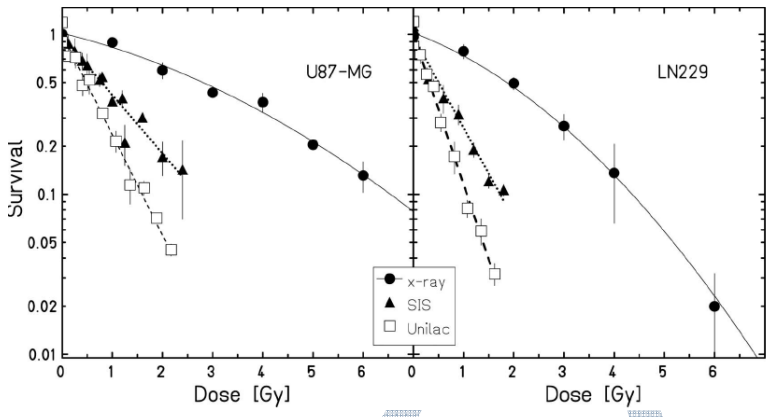
Low-LET **High-LET**



- carbon ions: higher relative biological effectiveness (RBE)
- difficult to repair radiation damage, i.e. double strand breaks
- correlation with repair proteins, e.g. p21

M. Scholz et al. Rad. Res. 2001

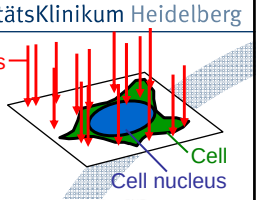
Radiobiological evaluation and correlation with the local effect model (LEM) of carbon ion radiation therapy and temozolomide in glioblastoma cell lines

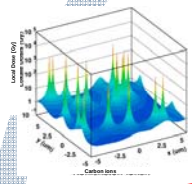


Combs SE et al. Int J Radiat Biol, 2009

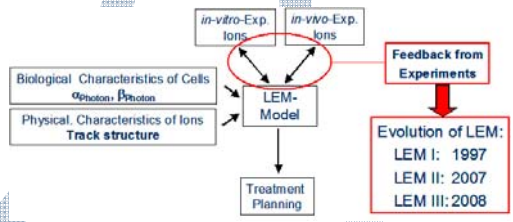
Variability of the RBE…..

- RBE decreases with dose
- RBE depends on the depth
- RBE depends on „effect“ or endpoint
- RBE depends on cell type
- RBE depends on .....





Treatment planning for carbon ions....



Courtesy of M.Scholz, GSI Darmstadt

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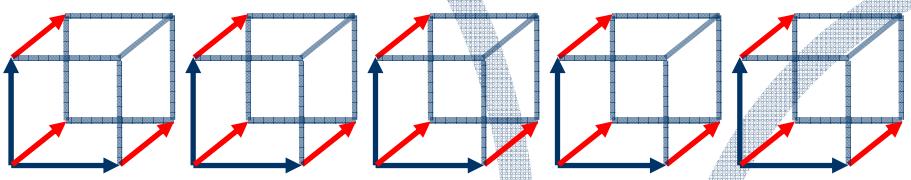


Space

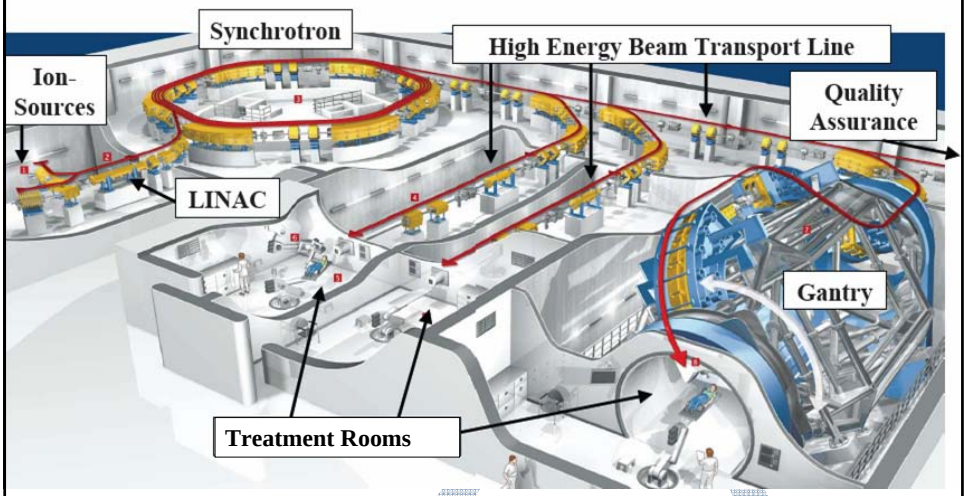
Time

Biology 5D

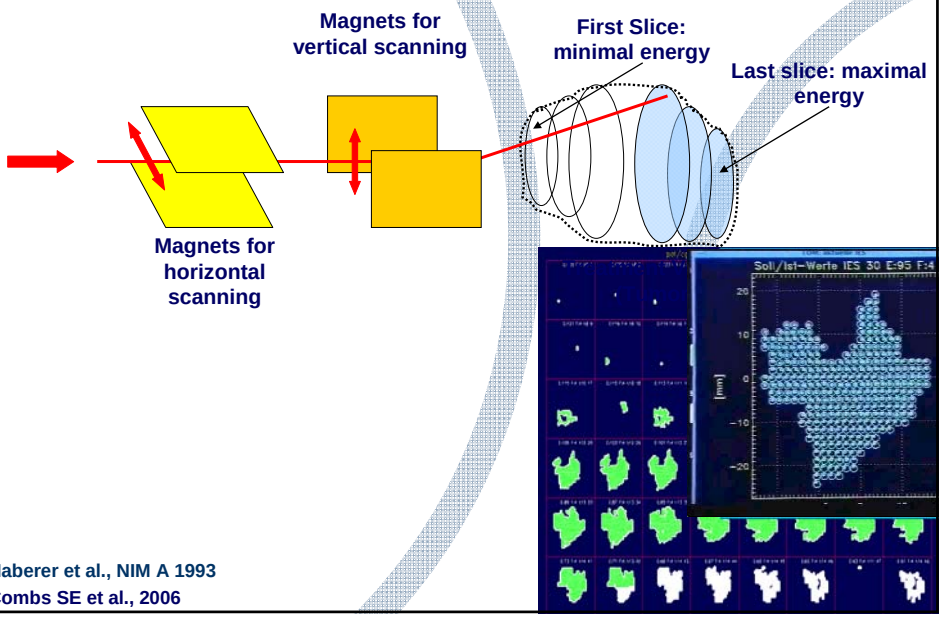
Heidelberg Ion Therapy Center (HIT)

UniversitätsKlinikum Heidelberg

Heidelberg Ion Therapy Center (HIT)



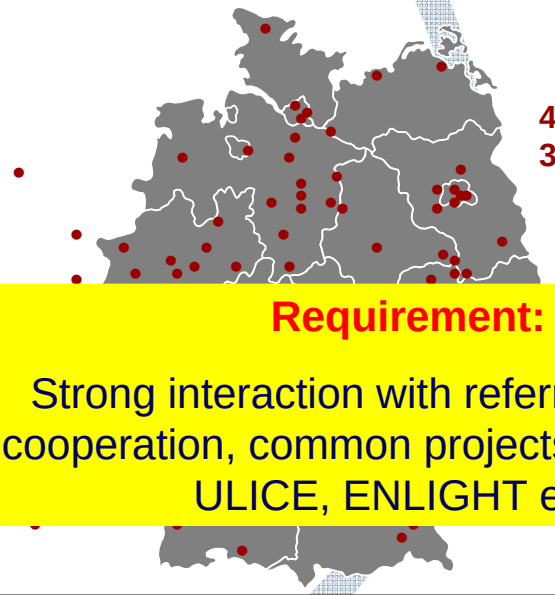
Intensity Modulated Raster Scanning



Haberer et al., NIM A 1993
Combs SE et al., 2006

Delivery of the first Carbon Ion Gantry

Patient Referall for Carbon Ion Radiotherapy



450 Patients at GSI
300 Patients at HIT
since 11/2009

Requirement:

Strong interaction with referring centers, cooperation, common projects (PARTNER, ULICE, ENLIGHT etc.)

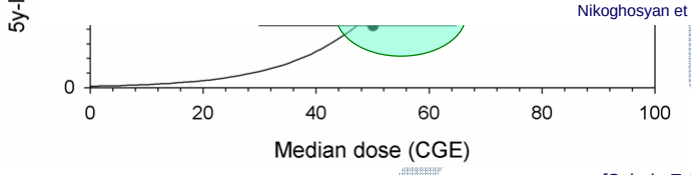
Motivation: Dose Response Relationship Radiotherapy of Skull Base Chordomas

2 Phase III Randomized Studies @ HIT:

Skull Base Chondrocarcoma:
Comparison of Proton and Carbon ion Radiotherapy

Skull Base Chordoma:
Comparison of Proton and Carbon ion Radiotherapy

Nikoghosyan et al., BMC Cancer 2010 a, b



[Schulz-Ertner, IJROBP 2007]

FSRT / IMRT vs. FSRT / IMRT + C12
locally advanced adenoidcystic carcinoma

- malignant salivary gland tumor
- skull base invation in advanced tumors
- complete surgical resection often not possible – macroscopic tumor
- radioresistant – high doses of RT needed

high-precision RT with photons
+
carbon ion boost
to the macroscopic tumor

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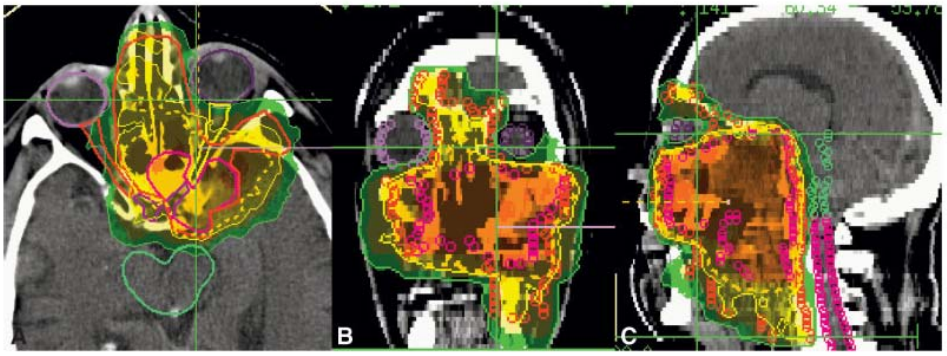
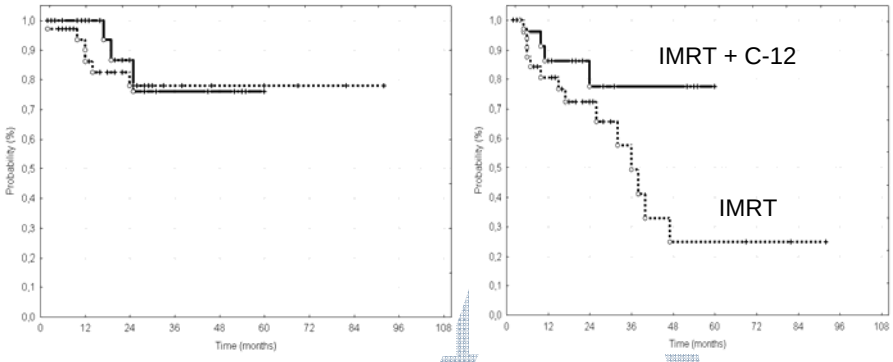
FSRT / IMRT vs. FSRT / IMRT + C12
locally advanced adenoidcystic carcinoma



Schulz-Ertner et al., 2005.

FSRT / IMRT vs. FSRT / IMRT + C12
locally advanced adenoidcystic carcinoma



- **no dose limiting acute toxicity**
- **late toxicity > CTC grade 2 < 5%**

Schulz-Ertner, Cancer. 2005 Jul 15;104(2):338-44

Adult Life after Radiation Therapy in Childhood

Chronic Health Conditions in Adult
Survivors of Childhood Cancer: The Childhood Cancer Survivor Study
Oeffinger et al. (MSKCC). NEJM 355(15):1572-82, 2006

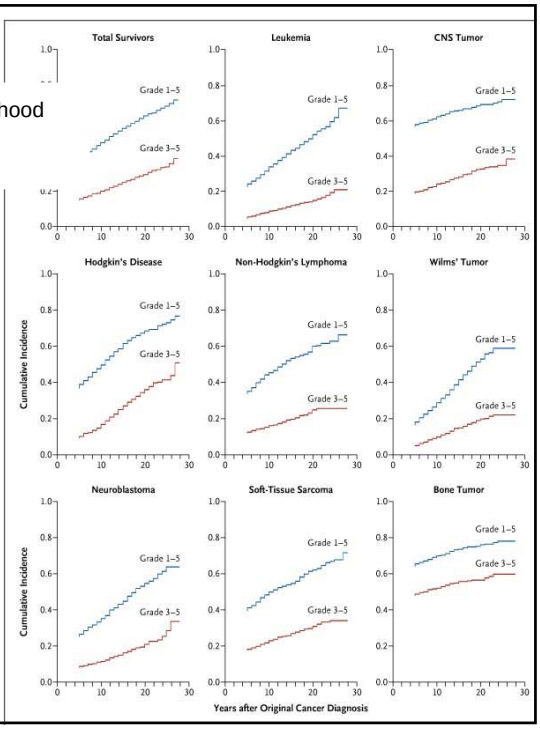
Method:

- Pooled data from 25 Pediatric Oncolgy Centers
- Diagnosis and Treatment of Childhood Cancer between 1970-1986

- 10,397 Survivors, > 3000 matched siblings
- Minimal survival time 5 years (up to 31 years):

Chronic Health Conditions in Adult Survivors of Childhood Cancer: The Childhood Cancer Survivor Study

Oeffinger et al. (MSKCC).
NEJM 355(15):1572-82, 2006



Cumulative Incidence of Chronic Health Conditions among 10,397 Adult Survivors of Pediatric Cancer, Severity of subsequent health conditions was scored according to the Common Terminology Criteria for Adverse Events (version 3) as:

mild (grade 1),
moderate (grade 2),
severe (grade 3),
life-threatening or disabling (grade 4),
or fatal (grade 5).

Chronic Health Conditions in Adult Survivors of Childhood Cancer: The Childhood Cancer Survivor Study

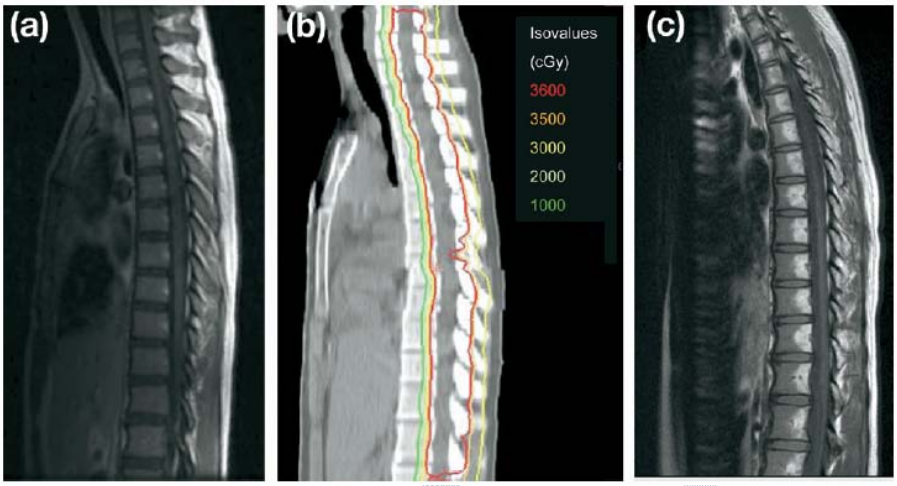
Oeffinger et al. (MSKCC). NEJM 355(15):1572-82, 2006

Results:

- 62% at least one chronic condition
- 1/4 severe or life-threatening condition
- 1/4 had 3 or more chronic health problems

Proton Radiation Therapy in Pediatrics:

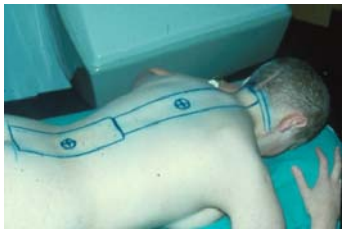
The greatest margin of benefit!



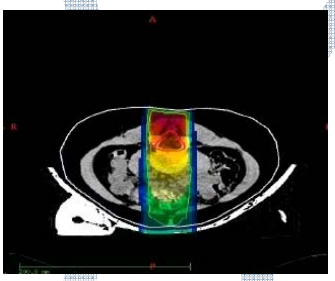
Krejcarek et al., IJROBP, 2007

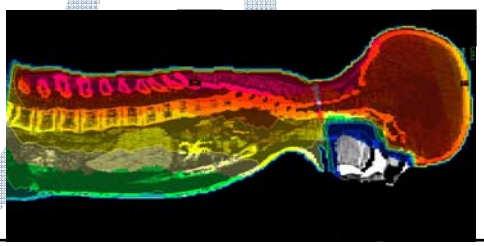
Craniospinal Irradiation: Conventional

Patient positioning



Dose: 32 Gy

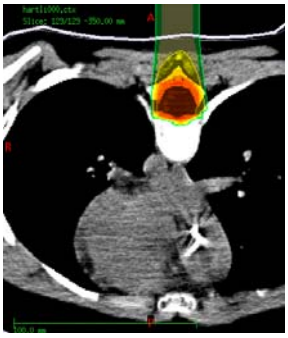


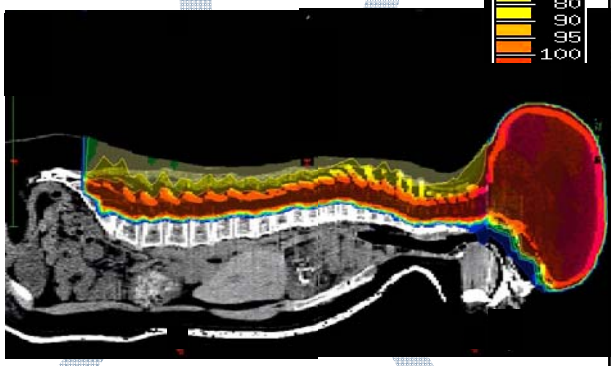


Organ Dose

Bone Marrow:	22 Gy
Hears:	18 Gy
Intestine:	20 Gy

Craniospinal Irradiation: Ion Therapy





Dose: 32 Gy

Organ Dose

Bone Marrow:	< 1 Gy
Hears:	< 0.5 Gy
Intestine:	< 0.5 Gy

The first 80 patients @ HIT

Indication	Number of patients n (%)
Skull Base	
Chordoma	9 (11%)
Chondrosarcoma	18 (22%)
Malignant Salivary Gland Tumors	29 (36%)
Astrocytoma	10 (13%)
pilocytic astrocytoma	1
WHO Grade II astrocytoma	2
anaplastic astrocytoma	1
primary glioblastoma	3
recurrent glioblastoma	3
Osteosarcoma	3 (4%)
skull and skull base	2
sacrum	1
Sacral Chordoma	5 (6%)
Other	6 (8%)
recurrent rectal cancer	2
nasopharyngeal cancer	1
rhabdomyosarcoma of the skull base	1
malignant melanoma of the paranasal sinus	1
chondrosarcoma of the left heel	1

Combs SE et al., Acta Oncologica 2010

The first 100 patients @ HIT

- center directly connected with the existing department of radiation oncology
- specialized clinics for primary contact and for follow-up
- outpatient treatment or inpatient on 3 wards
- individual positioning devices: head masks etc.
- target volume definition on CT, MRI, PET-CT
- ICRU-criteria: GTV, CTV, PTV...
- Siemens Dosimetrist/Oncologist for target volume definition
- Siemens PT Planning, Siemens, Erlangen, Germany for treatment planning
- patient positioning prior to each treatment with orthogonal X-rays focussing on bony landmarks

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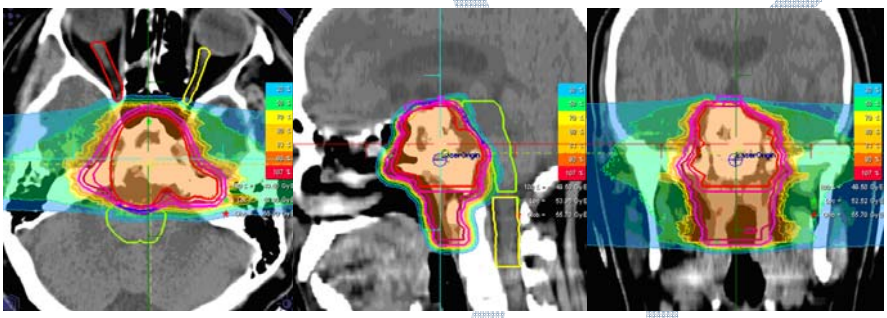
The first 80 patients @ HIT



Typical treatment plan for a patient with a skull base chordoma treated up to a total dose of 66 Gy E with carbon ion radiotherapy.

Combs SE et al., Acta Oncologica in press

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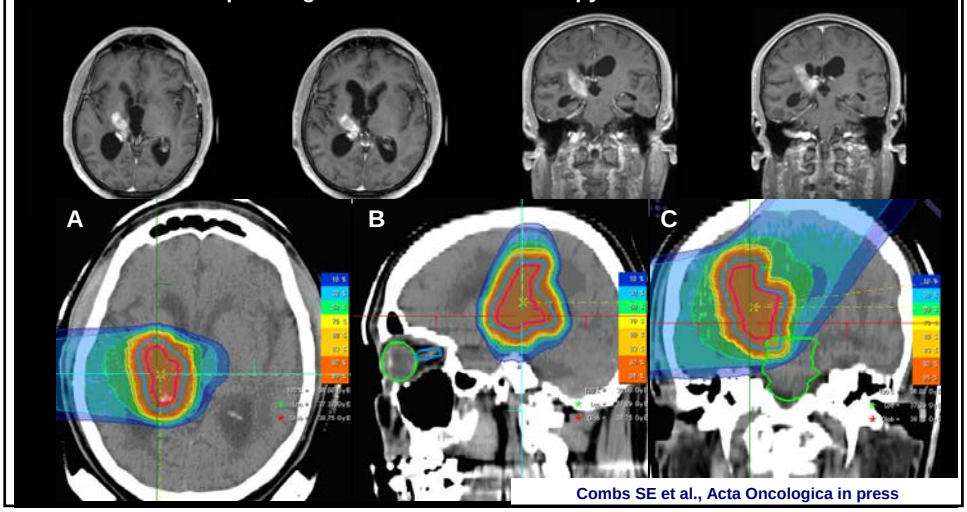
Carbon ion Radiation Therapy – Recurrent Glioblastoma

50 yrs. old male patient, primary diagnosis of glioblastoma 05/2007, neurosurgical resection and radiochemotherapy with temozolomide, 2008 temozolomide and cilengitide for recurrence; 01/2010 Carbon ion radiotherapy @ HIT for tumor progression

01/2010 – treatment planning for carbon ion radiotherapy



Combs SE et al., Acta Oncologica in press

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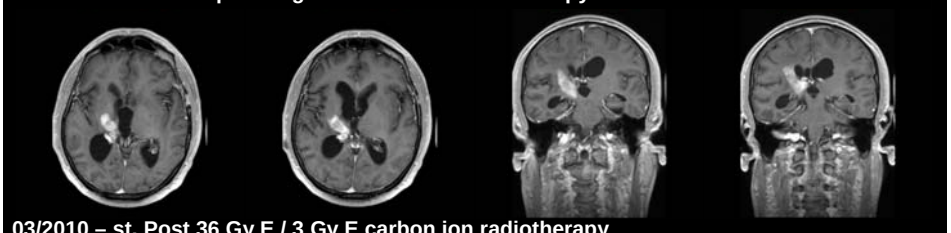

03/2010 – st. Post 36 Gy E / 3 Gy E carbon ion radiotherapy

Requirement:

Clinical Trials

Combs SE et al., Acta Oncologica in press

Future:

- New treatment facilities for carbon and proton treatment are in planning or under construction
- Innovative strategies for high-patient throughput to achieve cost-effective treatment
- First results of clinical phase I and II trials performed at NIRS support the assumption that carbon ions provide an enhanced biological effectiveness in adenoid cystic carcinomas, H/N melanomas, lung and liver tumors, large soft tissue sarcomas, chordomas / chondrosarcomas and prostate cancer
- Randomized trials proving the superiority of particles in comparison to photon IMRT and protons required
- Radiobiologic research will enable better exploitation of the advantages of carbon ion RT in future trials
- High Precision Treatment of Moving Targets

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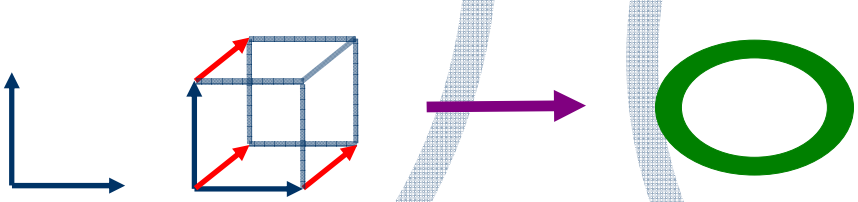
5D – the next dimension!

- new radiation qualities offer biological modulation of radiation response
- distinct radiobiological mechanisms can be used for long-term tumor control
- increased relative biological effectiveness (RBE) may translate into increased tumor control and survival
- targeted application, i.e. macroscopic tumor areas, hypoxic regions, radioresistant regions



dkfz. GSI HIT RadioOnkologie Behandeln Forschen Lehren

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