Welcome from Rare Cancers Europe

Paolo G. Casali
paolo.casali@istitutotumori.mi.it
Rare Cancers Europe is a joint initiative based on a partnership between the European Society for Medical Oncology (ESMO), the European Organisation for Rare Diseases (EURORDIS), the European Cancer Patient Coalition (ECPC), the European Organisation for Research and Treatment of Cancer (EORTC), Conticanet, EuroBoNet, the World Sarcoma Network (WSN), the Association of European Cancer Leagues (ECL), the Chronic Myeloid Leukaemia Support Group, the International Brain Tumour Alliance (IBTA), Orphanet, the Chronic Myeloid Leukaemia Advocates Network, the Sarcoma Patients EuroNet Association (SPAEN), GIST Support UK & PAWS-GIST, Cancer 52, the International Kidney Cancer Coalition (iKCC), the Chordoma Foundation, the Fondazione IRCCS Istituto Nazionale dei Tumori, the European Institute of Oncology (IEO), the European Society for Paediatric Oncology (SIOP Europe), the European Society of Surgical Oncology (ESSO), the Grupo Español de Tumores Huérnicos e Infrecuentes (GETHI), the European School of Oncology (ESO), the European Oncology Nursing Society (EONS), ecancer, the European Society of Pathology (ESP), the European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB), Novartis Oncology (initiating sponsor and industry partner), Pfizer Oncology (industry partner), and Sanofi (industry partner). The campaign is moreover supported by additional corporate supporters, including Amgen (silver industry supporter) and Takeda Pharmaceuticals Europe (silver industry supporter).
Rare cancers are not so rare: The rare cancer burden in Europe

Gemma Gatta a, Jan Maarten van der Zwan b, Paolo G. Casali c, Sabine Siesling b, Angelo Paolo Dei Tos d, Ian Kunkler e, Renée Otter b, Lisa Licitra f, Sandra Mallone g, Andrea Tavilla g, Annalisa Trama a, Riccardo Capocaccia g, The RARECARE working group
## Soft Tissue Sarcoma

### Incidence

<table>
<thead>
<tr>
<th>Count</th>
<th>Rate</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>12345</td>
<td>4.75</td>
<td>4.50</td>
<td>4.90</td>
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</table>

### Prevalence

<table>
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<tr>
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<th>Rate</th>
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<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>12345</td>
<td>4.75</td>
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<td>4.90</td>
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</table>

### Mortality

<table>
<thead>
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<th>Lower CI</th>
<th>Upper CI</th>
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<tbody>
<tr>
<td>12345</td>
<td>4.75</td>
<td>4.50</td>
<td>4.90</td>
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</tbody>
</table>

### Age

<table>
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<th>Lower CI</th>
<th>Upper CI</th>
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<tr>
<td>&lt;64</td>
<td>4.75</td>
<td>4.50</td>
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### Gender

<table>
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<tbody>
<tr>
<td>Men</td>
<td>4.75</td>
<td>4.50</td>
<td>4.90</td>
</tr>
<tr>
<td>Women</td>
<td>4.75</td>
<td>4.50</td>
<td>4.90</td>
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### Region

<table>
<thead>
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<th>Rate</th>
<th>Lower CI</th>
<th>Upper CI</th>
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</thead>
<tbody>
<tr>
<td>Europe</td>
<td>4.75</td>
<td>4.50</td>
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### Socioeconomic Factors

<table>
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<th>Factor</th>
<th>Rate</th>
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<th>Upper CI</th>
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<tr>
<td>GDP</td>
<td>4.75</td>
<td>4.50</td>
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### Survival Rates

<table>
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<tr>
<th>Cohort</th>
<th>1988-93</th>
<th>2008-2013</th>
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<tbody>
<tr>
<td>Survival</td>
<td>5.69</td>
<td>7.89</td>
</tr>
<tr>
<td>Relative</td>
<td>5.69</td>
<td>7.89</td>
</tr>
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</table>

### Relative Survival by EU Region

<table>
<thead>
<tr>
<th>Region</th>
<th>5 yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Europe</td>
<td>56.0</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>54.4</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>55.5</td>
</tr>
<tr>
<td>Central Europe</td>
<td>55.5</td>
</tr>
<tr>
<td>EU Average</td>
<td>56.0</td>
</tr>
</tbody>
</table>

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1. The statistic could not be calculated.

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www.rarecare.eu
“Rare” cancers

incidence $\leq 6/100,000/\text{year}$
Casali PG et al, 2015, to be submitted
rare diseases

rare cancers
cancer
rare cancers
Rare cancers...

childhood
Rare cancers...

hematological

childhood
Rare cancers...

- Childhood
- Hematological
- Adult solid tumors
«Families» of rare cancers

1. SKIN/rare & non cutaneous MELANOMA
2. THORACIC/rare
3. MALE UROGENITAL/rare
4. FEMALE GENITAL/rare
5. DIGESTIVE/rare
6. NEUROENDOCRINE
7. ENDOCRINE ORGAN
8. CNS
9. SARCOMAS
10. HEAD & NECK
11. HEMATOLOGICAL/rare
12. PEDIATRIC
Rare Cancers Europe is a joint initiative based on a partnership between the European Society for Medical Oncology (ESMO), the European Organisation for Rare Diseases (EURORDIS), the European Cancer Patient Coalition (ECPC), the European Organisation for Research and Treatment of Cancer (EORTC), Conticanet, EuroBoNet, the World Sarcoma Network (WSN), the Association of European Cancer Leagues (ECL), the Chronic Myeloid Leukaemia Support Group, the International Brain Tumour Alliance (IBTA), Orphanet, the Chronic Myeloid Leukaemia Advocates Network, the Sarcoma Patients EuroNet Association (SPAEN), GIST Support UK & PAWS-GIST, Cancer 52, the International Kidney Cancer Coalition (IkCC), the Chordoma Foundation, the Fondazione IRCCS Istituto Nazionale dei Tumori, the European Institute of Oncology (IEO), the European Society for Paediatric Oncology (SIOP Europe), the European Society of Surgical Oncology (ESSO), the Grupo Español de Tumores Huérfanos e Infrecuentes (GETHI), the European School of Oncology (ESO), the European Oncology Nursing Society (EONS), ecancer, the European Society of Pathology (ESP), the European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB), Novartis Oncology (initiating sponsor and industry partner), Pfizer Oncology (industry partner), and Sanofi (industry partner). The campaign is moreover supported by additional corporate supporters, including Amgen (silver industry supporter) and Takeda Pharmaceuticals Europe (silver industry supporter).
Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper

P. G. Casali1, P. Bruzzi2, J. Bogaerts3 & J.-Y. Blay4 on behalf of the Rare Cancers Europe (RCE) Consensus Panel

1Adult Mesenchymal Tumour Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan; 2Clinical Epidemiology Unit, National Institute for Cancer Research, Genova, Italy; 3European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium; 4Department of Medical Oncology, Centre Léon Bérard, Centre de Recherche en Cancérologie, Université de Lyon, Lyon, France

Received 29 July 2014; revised 18 September 2014; accepted 19 September 2014

While they account for one-fifth of new cancer cases, rare cancers are difficult to study. A higher than average degree of uncertainty should be accommodated for clinical as well as for population-based decision making. Rules of rational decision making in conditions of uncertainty should be rigorously followed and would need widely informative clinical trials. In principle, any piece of new evidence would need to be exploited in rare cancers. Methodologies to explicitly weigh and combine all the available evidence should be refined, and the Bayesian logic can be instrumental to this end. Likewise, Bayesian-design trials may help optimize the low number of patients liable to be enrolled in clinical studies on rare cancers, as well as adaptive trials in general, with their inherent potential of flexibility when properly applied. While clinical studies are the mainstay to test hypotheses, the potential of electronic patient records should be exploited to generate new hypotheses, to create external controls for future studies (when internal controls are impractical), to study effectiveness of new treatments in real conditions. Framework study protocols in specific rare cancers to sequentially test sets of new agents, as from the early post-phase I development stage, should be encouraged. Also the compassionate and the off-label settings should be exploited to generate new evidence, and flexible regulatory innovations such as adaptive licensing could convey new agents early to rare cancer patients, while generating evidence. Though validation of surrogate endpoints is problematic in rare cancers, the use of an updated notion of tumor response may be of great value in the single patient to optimize the use of therapies, all the more the new ones. Disease-based communities, involving clinicians and patients, should be regularly consulted by regulatory bodies when setting their policies on drug approval and reimbursement in specific rare cancers.

Key words: rare cancers, clinical trials, research methodology

Ann Oncol. 2015 Feb;26(2):300
Political Recommendations on Rare Cancers

The catastrophe is a rare event. It is based on a set of Political Recommendations developed in 2003 by the European Commission.

The Political Recommendations address the challenges in rare cancer care and the need to promote a number of stakeholder actions and public policies at both EU and national levels.

The political recommendations were the outcome of the conference "Rare Cancers in the European Union". This Conference, held in November 2003 in Brussels, was hosted by the European Society for Medical Oncology (ESMO) and organised with the other co-organising partners. It brought together 123 participants representing a multitude of stakeholder from across Europe. The key findings and conclusions of the conference were then summarised by the conference chairs and shared with the audience.

The Political Recommendations were developed and made public at a press event, hosted by Esmo. They were presented to the European Parliament in December 2003.

ESMO European Society for Medical Oncology

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

Introduction

Rare cancers belong to a group of rare diseases that are normally defined as diseases with a prevalence of less than 50 per 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 of fewer than 50 per 100,000 per year), rare cancers represent about 20% of all cases of malignant neoplasms, including all cancers affecting children and teenagers and many affecting young adults.

A. Rare cancers belong to the group of rare diseases that are normally defined as diseases with a prevalence of less than 50 per 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 of fewer than 50 per 100,000 per 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.

C. Patients' access to treatments for rare cancers varies across and within the EU member states. Information about rare cancers, their treatment options and where to obtain appropriate treatment is in many cases not readily available to patients.

D. Suboptimal treatment outcomes are common for rare cancers due to a lack of medical expertise in the management of rare cancers, poor referral rates from general practitioners and pathologists misdiagnoses. Outcomes for a diverse range of rare cancers could be improved through the establishment of reference networks or centres of expertise. However, few reference networks or centres of expertise exist across the EU and funding is not available to cover the increased costs associated with the organisation of these networks.

E. Overall health and social costs can be far higher for patients with rare cancers, because effective treatments are not always reimbursed, referrals for second
European Action Against Rare Cancers

Recommendations Addressing
Regulatory Barriers in Rare Cancer Care

We:

1. 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.
Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper

P.G. Casali, F. Bruzzi, J. Bogunski & J.-Y. Belin on behalf of the Rare Cancers Europe RCE Consortium

While it is acknowledged to be difficult to conduct clinical research on rare cancers, the need to develop new treatments and therapies remains urgent.

- Clinical decision-making
- Methods to combine evidence
- New study designs
- Surrogate end points
- Organization of studies

Exploring ways to improve clinical research on rare cancers

Date: 01 Mar 2012

Organised by the European Society for Medical Oncology (ESMO) and Rare Cancers Europe, the Rare Cancers Conference held on 10 February 2012 in Brussels, provided a multi-stakeholder platform for rare cancer and rare disease experts from across Europe to exchange views and share insights into what can be done to improve the methodology of clinical research on rare cancers.

The first two conference sessions offered an overview of rare cancers and associated challenges for clinical research and drug development and also presented a variety of potential solutions as well as best practice examples. Where traditional frequent clinical research approaches are not possible, due to the small numbers of patients, it is particularly challenging to make sure that rare cancer patients are not being left without appropriate clinical research and therapeutic progress.

The third session of the conference therefore also highlighted the need for reaching a broad multi-stakeholder consensus on a set of recommendations on improving the methodology of clinical research on rare cancers. These recommendations will be the product of an ongoing multidisciplinary and multi-stakeholder online consensus discussion promoted by Rare Cancers Europe. They will focus on best methods including innovative ones for clinical research on rare cancers, and rare subgroups of frequent cancers, with the goal of encouraging:

- Clinical researchers to exploit innovative solutions for the design and analysis of clinical studies;
- clinicians to exploit innovative solutions for the combination of available knowledge;
- regulators to accept evidence built through these solutions;
- clinical trials and patients’ communities to exploit all forms of collaboration to put together as large series as possible for prospective and retrospective clinical and translational research;
- methodologists to advance research into new methodological solutions better fitting the needs of studies on small series.

All interested stakeholder groups are encouraged to actively participate in this open discussion, the result of which will be a consensus paper to be publicly presented in autumn 2012. This paper would then be used for related advocacy efforts. All parties interested in joining this discussion are invited to contact Rare Cancers Europe.
Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper

P. G. Casali*1, J. H. Bruzzi†, J. Bogert1 & J. Y. Bley* on behalf of the Rare Cancers Europe (RCE) Consensus Panel

1Aix Marseille Université, UMR 7280 BioSciences du Cancer, UMR 7020 CanCure, INSERM U1069 and Institut Curie, Marseille, France. 2Department of Biostatistics and Epidemiology, Statistics Center, Boston, MA, USA. 3Department of Biostatistics and Epidemiology, Statistics Center, Boston, MA, USA. 4Department of Biostatistics and Epidemiology, Statistics Center, Boston, MA, USA.

Received 23 July 2013, revised 31 August 2013, accepted 9 September 2013.

While less attention is paid to rare cancer patients, rare cancers are difficult to study. A higher than average degree of uncertainty should be accommodated for clinical trials as well as the population-based decision making. ‘Ratios of statistical power to clinical trial cost’ and clinical trial cost are key elements in ensuring the validity and effectiveness of clinical trials in rare cancers. Methodologies to adapt trial designs and to combine all the available evidence should be refined, and the Bayesian logic can be instrumental in this regard. However, Bayesian designs may help clinical trialists to get a higher number of patients with a high event rate into clinical studies. Rare cancers, as well as clinical trials in general, will have an increased potential for bias when properly applied. While clinical studies are the backbone of clinical hypotheses, the potential limitations of patient recruitment should be explored to generate new hypotheses. A comprehensive approach for future studies (neither intensive nor unbroken) to study effective and new treatment guidelines is needed. Framework studies to identify and assess rare cancers in sequence as well as rare agents, as from the early post-phase I development stage, should be considered. Also, the compassionate and the orphan status would be required to generate new evidence, and the need for regulatory innovations such as adaptive clinical trials could allow new agents early entry to rare cancer patients, while generating evidence. Though validation of surrogates and prognosis is problematic in rare cancers, the use of age- and disease-adjusted cut-off for tumor response may help in the development of strategies. The aim of this paper is to provide a comprehensive overview of the rare cancer patients, and their treatment and patients, should be harmonized with regulatory bodies when writing their policies on drug approval and reimbursement in specific rare cancers.

Key words: rare cancers, diagnostics, research methodology.
Josh Sommer
@sommerjo

Today at EMA regulators, clinicians, @ChordomaFDN agreed to work together on guidance for chordoma trials. Progress!
pic.twitter.com/ShR3SA8KXZ

30/04/2015 19:47:22
Pharma

Researchers
Pharma

Researchers
Patients

Regulators
Josh Sommer
@summerjo

Today at EMA regulators, clinicians, @ChordomaFDN agreed to work together on guidance for chordoma trials. Progress!
pic.twitter.com/ShR3SA8KXZ

30/04/2015 19:47:22
<table>
<thead>
<tr>
<th>Tweets on new published papers on rare adult solid cancers for health professionals by Italian Rare Cancer Network (see names on website)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy · retetumorirari.accmed.org</td>
<td></td>
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<tr>
<td><strong>Rare solid cancers</strong> @ReteTumoriRari</td>
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<tr>
<td>STS. Choi criteria not only in GIST: they may help with trabectedin as well: <a href="https://pubmed.gov/25499439">pubmed.gov/25499439</a></td>
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<tr>
<td><strong>Rare solid cancers</strong> @ReteTumoriRari</td>
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<tr>
<td>RARE CANCERS. A European consensus attempt to advance methodology of clinical studies: <a href="https://pubmed.gov/25274516">pubmed.gov/25274516</a></td>
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<tr>
<td><strong>Rare solid cancers</strong> @ReteTumoriRari</td>
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<tr>
<td>STS. Continuous infusion HD-ifosfamide is active in WD/DD-liposarcoma, even in some pts who received AI: <a href="https://pubmed.gov/25628856">pubmed.gov/25628856</a></td>
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<td>GIST. Further evidence for surgery of advanced responding disease, but again retrospective, thus only suggestive: <a href="https://pubmed.gov/25608759">pubmed.gov/25608759</a></td>
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<td>CHORDOMA. An effort by the whole disease community to build a global consensus on an ultrarare cancer: <a href="https://ncbi.nlm.nih.gov/pubmed/25638683">ncbi.nlm.nih.gov/pubmed/25638683</a></td>
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</table>
Referral to expert rare cancer pathologists is crucial for appropriateness

Networks are the best tool for proper referral

Multidisciplinarity is the best environment for rare cancer patient healthcare
Rare Cancers Consensus Meeting: Pathology in Rare Cancers

10 – 11 February 2014, Brussels

Conference Objective: Consensus Statement on Improving Pathological Diagnosis of Rare Cancers

Recommendations stemming from this consensus statement will be crucial in making sure that the Cross-Border Healthcare Directive has the right impact on the lives of patients suffering from rare cancers, through effective use of European Reference Networks.
17.

Call for increased integration of local, national and European centres of expertise into European reference networks, based on specific criteria as set out in the Commission’s proposed Directive on the application of patients’ rights in cross-border healthcare, in order to provide the necessary sound organisational structures for more efficient clinical research and early transfer of research data into clinical practice, thus improving the clinical management of rare cancers.
DIRECTIVES

DIRECTIVE 2011/24/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 9 March 2011
on the application of patients' rights in cross-border healthcare
“will provide highly specialised healthcare for rare or low prevalence complex diseases or conditions”
- promote good quality and safe care to patients by fostering proper diagnosis, treatment, follow-up and management of patients across the Network
- empower and involve patients
- offer and promote multi-disciplinary advice for complex cases
- develop and implement clinical guidelines and cross-border patient pathways
- exchange, gather and disseminate knowledge evidence and expertise within and outside the Network
- promote collaborative research within the Network
- reinforce research and epidemiological surveillance, through setting up of shared registries
- exchange and disseminate knowledge and best practices, in particular by supporting national centres and networks
RARE CANCERS

1. Pediatric cancers
2. Haematologic rare neoplasms
3. Sarcomas
4. Rare thoracic cancers
5. Neuroendocrine tumours
6. Head & neck cancers
7. Central nervous system tumours
8. Rare female genital cancers
9. Rare urological and male genital tumours
10. Endocrine gland tumours
11. Digestive rare cancers
12. Rare skin cancers & non-cutaneous melanoma
Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Ann Oncol. 2014 Sep;25 Suppl 3

http://www.esmo.org
Joint Action on Rare Cancers...