

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

### Whereas

- A. Rare cancers<sup>1</sup> 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;<sup>2</sup>
- 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. Sub-optimal 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 pathologic misdiagnosis. 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

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<sup>1</sup> This includes solid, liquid and paediatric tumours.

<sup>2</sup> Gatta G. Et al. Survival from rare cancer in adults: a population-based study. *Lancet Oncology*. 2006 Feb;7(2):132-40

- opinions within the public health system are not commonplace and many patients must travel long distances to access appropriate care;
- F. Exchange of experience, information and data on rare cancers is low;
  - G. Registries and tissue banks for rare cancers are lacking;
  - H. Clinical studies are more difficult to conduct in rare cancers due to the low number of patients. This makes it difficult to demonstrate the effectiveness of different therapeutic options and build a comprehensive evidence-base for practice. Therefore, medicines often have to be used off-label which creates reimbursement problems for patients, legal difficulties and extra bureaucracy for prescribers.<sup>3</sup> Moreover, it can be difficult to provide the level of data required to support the use of an unapproved drug on a compassionate use basis;
  - I. Since the EU Orphan Drug Regulation<sup>4</sup> entered into force, 20 of the 46 medical products that have been designated as orphan drugs have received marketing authorisation for a rare cancer indication<sup>5</sup>. However, despite the adoption of the EU Orphan Drugs Regulation, there are still a significant number of hurdles that discourage the development of new medicines to treat rare cancers;
  - J. We welcome the European Commission's recently adopted "Communication on Rare Diseases: Europe's Challenges"<sup>6</sup>;
  - K. We welcome the European Commission's Cancer Action Plan to be launched in 2009;
  - L. We welcome the European Commission's considerations on cross-border healthcare;
  - M. We welcome the High Level Pharmaceutical Forum's guiding principles on improving access to orphan drugs to all citizens in Europe<sup>7</sup>;
  - N. We welcome the European Commission's White Paper "Together for Health: A Strategic Approach for the EU 2008-2013"<sup>8</sup>;
  - O. We welcome the EU Research Framework Programme 2007-2013<sup>9</sup>;

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<sup>3</sup> ESMO Position Paper on off-label use of drugs in oncology:

<http://annonc.oxfordjournals.org/cgi/content/full/18/12/1923>

<sup>4</sup> Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Available at: [http://eur-](http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:EN:PDF)

[lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:EN:PDF](http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:EN:PDF)

<sup>5</sup> <http://ec.europa.eu/enterprise/pharmaceuticals/register/orphreg.htm> , accessed 4 December 2008

<sup>6</sup> Available at: [http://ec.europa.eu/health/ph\\_threats/non\\_com/docs/rare\\_com\\_en.pdf](http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf)

<sup>7</sup> Available at : [http://ec.europa.eu/pharmaforum/docs/final\\_conclusions\\_en.pdf](http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf)

<sup>8</sup> Available at: [http://ec.europa.eu/health/ph\\_overview/Documents/strategy\\_wp\\_en.pdf](http://ec.europa.eu/health/ph_overview/Documents/strategy_wp_en.pdf)

## **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.
2. Call upon regulatory bodies to properly value the use of non-frequentist (Bayesian<sup>10</sup>) statistical approaches and/or study designs where well-powered randomised clinical trials are not feasible due to the low incidence of the cancer entity.
3. Call for greater involvement of disease-oriented research communities, as well as patient groups and advocates, in the mechanisms by which regulatory bodies provide scientific advice to the pharmaceutical industry on the development of new agents for use in rare cancers.
4. Call upon regulatory bodies making decisions on the use of new agents in rare cancers to take into full consideration the whole treatment scenario of the disease in question and the potential of the new medicine within an overall treatment strategy.
5. Call upon Health Technology Assessment (HTA) agencies to include patients and their representatives as equal stakeholders in the assessment of treatments for rare cancers in order to ensure that HTA procedures are transparent, timely, and include in their cost-effectiveness model the wider social costs and benefits.
6. Call for HTA and pricing and reimbursement bodies to include specialist input from expert oncologists in rare cancers when making decisions about medicines for use in the treatment of rare cancers.
7. Call for changes to EU legislation that would enable the EMEA to carry out a common non-binding assessment of orphan drugs which would include input from member states and could be used by governments as a guide to facilitate national pricing and reimbursement for innovative medicines in rare cancers.

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<sup>9</sup> Seventh Research Framework Programme (FP7) website :  
[http://cordis.europa.eu/fp7/home\\_en.html](http://cordis.europa.eu/fp7/home_en.html)

<sup>10</sup> For more information on the Bayesian statistical approaches, please see Recommendation 13.

8. Call for optimal implementation of the EU Orphan Drugs Regulation<sup>11</sup> which aims to provide incentives for the development of Orphan Drugs.

<p style="text-align: center;"><b>Recommendations Addressing Methodological Barriers to Rare Cancer Care</b></p>
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We:

9. Call for more clinical trials in rare cancers.
10. Call upon the research community to consider the testing of new agents in rare cancer patients as an essential part of the clinical drug development process of new drugs. Among others, this could be achieved by establishing formal collaborations between centres of expertise aimed at increasing the participation of rare cancer patients in the early clinical research phase. It might also be achieved by establishing formal collaborations within the disease-oriented research communities, through cooperative groups and inter-group efforts, to explore the potential of new agents in specific rare cancers, soon after their Phase I development. It is understood that such an approach will require innovative clinical study designs.
11. Call on governments to promote funding for clinical studies in rare diseases, including rare cancers.
12. Encourage network-based clinical databases and tissue banks which would improve collection, harmonisation and provision of data on rare cancers, whether they are malignant or benign, and serve as sources of descriptive information, especially for very rare cancers, and as external controls for uncontrolled studies.
13. 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.). Bayesian approaches imply updating prior probability distributions of efficacy through new data in order to give rise to posterior probability distributions. A mechanism for consensus development for definition of these prior probability distributions should be devised.
14. Encourage clinicians and healthcare professionals to adopt into their current practice relationships based on the model of patients as equal partners in their

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<sup>11</sup> Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:EN:PDF>

own therapeutic journey and more widely, an acknowledgement of the informed patient as a valuable healthcare resource in the fight against cancer.

## **Recommendations Addressing the Need for Centres of Expertise and European Reference Networks**

We:

15. Call for EU consensus guidelines on multi-disciplinary treatment.
16. Call for an increase in the exchange of experience, information, data and best practices on rare cancers amongst all stakeholders, especially through 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<sup>12</sup>, 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.
18. Emphasise that a model for European reference networks could help to mitigate the high costs associated with rare cancer management.
19. Call for European harmonisation of the qualification criteria for centres and networks of expertise in rare cancers.
20. Call for appropriate and permanent funding for centres and networks of expertise, especially when such centres and networks are involved in European reference networks which maximise the spread of expertise.
21. Call for acknowledgement of the requirement for extra medical and institutional resources in order to manage patients in a collaborative manner and develop institutional multidisciplinary expertise, and for formal recognition that, in this particular clinical setting, healthcare and clinical research cannot be separated.
22. Call for treatment of rare cancers to be funded at the national level in addition to the regional/local levels.
23. Call for involvement of representatives of patients and caregivers as advisory members in the management of European reference networks on rare cancers.

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<sup>12</sup> Proposal for a Directive of the European Parliament and the Council on the application of patients' rights in cross-border healthcare, COM(2008)414. Available at: [http://ec.europa.eu/health/ph\\_overview/co\\_operation/healthcare/docs/COM\\_en.pdf](http://ec.europa.eu/health/ph_overview/co_operation/healthcare/docs/COM_en.pdf)

## **Recommendations Addressing Barriers to Patients' Access to Care**

We:

24. Draw attention to the fact that whilst programmes for prevention, screening and life-style changes might help tackle some of the more common cancers, these are often not relevant for most of the rare cancers. On this basis, it is crucial that a greater focus of attention is placed on research and high standards of medical care and support for patients.
25. Encourage the consideration of issues surrounding social justice, solidarity, equity and the interests of patients with rare cancers when setting public health priorities.
26. Call upon the EU member states and the pharmaceutical sector to commit to meaningful and transparent dialogue to ensure that treatments for rare cancers are made available in a timely manner to all patients who need them and reimbursed as long as they need them.
27. Call for proper implementation of the EU Transparency Directive<sup>13</sup>.
28. Encourage governments to shift from a risk averse to a risk management strategy when assessing new medicines for rare cancers. This strategy should recognise that patients with life threatening disease who have run out of treatment options are often more willing to accept a greater degree of risk attached to their treatments.
29. Urge the pharmaceutical industry to prioritise development of medicines for rare cancers.
30. Welcome the European Commission's considerations on patients' rights in cross-border healthcare. While recognising the economic burden associated with the provision of healthcare, we emphasise that geographic borders should not prevent patients from accessing best standards of care. Barriers may be reduced by making it easier for patients to cross borders as well as by fostering collaborative networks.
31. Encourage governments to address the barriers to appropriate care that patients with rare cancers face within their country, and specifically to implement

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<sup>13</sup> Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems. Available at:  
[http://ec.europa.eu/enterprise/phabiocom/docs/dir\\_1989\\_105/dir\\_1989\\_105\\_en.pdf](http://ec.europa.eu/enterprise/phabiocom/docs/dir_1989_105/dir_1989_105_en.pdf)

- measures that would facilitate reimbursement of patients who have received treatment from a centre of expertise or through a European reference network.
32. Call for mandatory and immediate referral of all suspected cases of rare cancers to centres of expertise, e.g. through collaborative networks.
  33. Call upon the EU, the member state governments and regulatory and reimbursement bodies to investigate the reasons for the wide use of off-label drugs in rare cancers, and take action to limit this by focusing on old agents whose patents have expired and by facilitating drug label extensions of new agents when appropriate. Special approval mechanisms should apply to reimbursement decisions for the range of off-label drugs that are currently used in the management of rare cancers.
  34. Call on the medical community, the pharmaceutical industry, and the regulatory bodies to ensure that potential conflicts of interests do not become a barrier to ensuring the best possible clinical decisions and advice to patients given the scarceness of expertise available on rare tumours.

### **Recommendations on Education of Healthcare Professionals**

We:

35. Call for improved education and on-going training for all healthcare professionals involved in the treatment and care of patients with rare cancers.
36. Encourage the development of innovative approaches to raising general practitioners' and pathologists' awareness about rare cancers, especially the symptoms and tumour characteristics that signal the need to refer the patient for specialist intervention or a second opinion.

### **Recommendations on Access to Information on Rare Cancers**

We:

37. Encourage the wide-spread dissemination, using different forms of communication tools, of easy-to-understand, comprehensive, balanced and high quality information about rare cancers and their treatments and the development of innovative strategies to support patients and to provide them with information about how to access expert treatment and care.



38. Call for the significant linguistic barriers that exist in Europe to be addressed by ensuring that information is made available in all the EU languages.
39. Welcome the publication by the European Commission of new guidelines that will help provide a constantly-updated, publicly-available list of rare cancer clinical trials in progress.

ENDS.



ESMO, the European Society for Medical Oncology, is a professional and scientific organisation which aims to create a large multidisciplinary community of professionals providing optimal care to all cancer patients.

The ESMO Political Recommendations are the result of the joint work of the research community, healthcare professionals, EU policy-makers and regulators, patients and industry representatives before, during and following the ESMO Conference on rare tumours on 6 November 2008 in Brussels. With this initiative ESMO is seeking to place the issue of rare cancers firmly on the European policy agenda. The aim of the Recommendations is to raise awareness about the issues surrounding rare cancer care and to suggest stakeholder action and public policies both at the EU and national levels as possible routes to solutions. The Recommendations have been developed on the basis of input from multiple stakeholders engaging at different levels.

**Steering Committee:**

Adamos Adamou, Member of the European Parliament  
José Baselga, President, European Society for Medical Oncology (ESMO)  
Jan Geissler, Director, European Cancer Patient Coalition (ECPC), President, Leukämie-Online  
Guido Guidi, Head of Region Europe, Novartis Oncology

**Organisational Committee:**

Ségolène Aymé, Orphanet  
Jean-Yves Blay, Conticanet  
Paolo Casali, ESMO  
Sandy Craine, the CML Support Group  
Filippo de Braud, European Institute of Oncology  
Aydin Dortok, Novartis Oncology  
Flaminia Macchia, Eurordis  
Kathy Oliver, International Brain Tumour Alliance  
Wendy Tse Yared, European Cancer League

**Partners:**

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