PUBLIC CONSULTATION
RARE DISEASES: EUROPE'S CHALLENGES
EUROPEAN COMMISSION
HEALTH AND CONSUMER PROTECTION DIRECTORATE GENERAL
HEALTH INFORMATION

ESMO COMMENTS

ESMO (European Society for Medical Oncology) is a highly qualified, professional, scientific and educational society.
With a worldwide membership since 1975, ESMO has continuously expanded its mission, aiming to create a wider community of professionals providing optimal care to all cancer patients.

ESMO strives to develop solutions, actions, initiatives that can help fighting against cancer and improving patients' quality of life.

ESMO participates to the improvement of the education of health professionals and the public. ESMO is not only a relevant place for health professionals but offers also a forum for a global community where patients and their families are significantly present.

ESMO would like to thank the European Commission for the opportunity given to contribute to the consultation process related to RARE DISEASES: EUROPE' S CHALLENGES.

The document includes an answer to the 14 specific questions identified in the text and mainly focuses on rare tumors where necessary.

Question 1: Is the current EU definition of a rare disease satisfactory?

As far as oncology is concerned, we believe that the definition is inappropriate. We advocate a definition based on incidence, not prevalence. In fact, contrary to rare non-neoplastic diseases (which are mainly genetic and chronic), prevalence does not render the actual frequency of a tumor, for the purposes that labeling a tumor as rare may have. In fact, everything in cancer happens once: definitive surgery is done once, first-line chemotherapy is done once, etc. Therefore, incidence is much more appropriate to estimate the number of patients having definitive surgery, first-line chemotherapy, etc. For example, the number of patients amenable to enter a clinical study is reflected by incidence. On the contrary, prevalence reflects both patients with active disease and those who are cured. As a matter of fact, some tumors with a high cure rate have a high prevalence, so that they may be considered frequent even if they are rare. Testicular cancer is an example. Other neoplasms with a low life expectancy have a low prevalence, and may be considered rare even if they are reasonably frequent. Small cell lung cancer is an example. There are strong reasons to use incidence, not prevalence, as a criterion for frequency of tumors.
In this context, ESMO is collaborating with an EU-funded project, RARECARE.

> This project is intended to help define indicators and collect and analyse relevant data on rare cancers, on a sustainable, long-term basis. It will generate both an operational definition of "rare cancers" and a list of cancers meeting that definition, with multidisciplinary and international agreement. The project will assess and, if required, adapt the validity of statistical methodology used for common cancers in estimating the burden of rare cancers. RARECARE will provide cancer burden indicators with data from population-based cancer registries and produce comparable information on rare cancers across Europe, taking into account the ECHI strategy and EUROSTAT standards for monitoring and surveillance. RARECARE will assess the quality and comparability of data on rare cancers across European countries. For selected rare cancers considered a high priority, an effort will be made to improve data quality by reviewing the information currently collected by cancer registries and disseminating the results, and linking it to other information resources via a specially designed website.

It has already held a consensus event in January 2008 on the definition of rare tumors. A list of rare tumors, based on a clinically sound definition, will be the outcome. A group of clinicians, mainly from the ESMO Faculty, agreed that incidence is a good criterion, and provisionally identified a threshold in the 3/100,000/year range under which a tumor might be reasonably considered as rare.

In any case, an important point is that rare tumors are fully considered within rare diseases. This is not always the case. Of course, the approach to tumors is essentially the same under the clinical methodology perspective, so that rare tumors may stand out from frequent ones less than a rare disease may do from other diseases. However, a rare tumor will pose exactly the same problems as rare non-neoplastic diseases, in regard to the feasibility of clinical trials, or the development of new drugs under selective indications.

Question 2: Do you agree that there is a pressing need to improve coding and classification in this area?

In the cancer field, neoplasms are very well codified. There is no difference in principle between rare and frequent neoplasms, as far as coding criteria are concerned. A list of rare tumors should follow existing classifications.

It is true that molecular biology may already split conventional nosographic entities into subgroups, some of which may be rare. However, this happens in the face of current classifications of tumors.

More in general, a difference should probably be made between tumor groups which are rare as such (e.g., sarcomas) and tumor entities which are rare within a group of frequent tumors (e.g., bronchioloalveolar lung carcinoma). Clearly, the expertise on the former may be found only in selected institutions, while the expertise on the latter is available wherever lung cancer is dealt with. So, referral to centers of excellence may apply only to the former, not to the latter. On the contrary, difficulties with patient enrollment in clinical trials are the same for both.

Question 3: Can a European inventory of rare diseases help your national/regional system to better deal with RD?

Yes, it would. In the cancer field, cancer population registries are able to provide reliable data on incidence. A list of rare tumors, according to an incidence-based criterion, is under development within the RARECARE project (see question 1). This may help find relevant numbers within cancer registries.

Question 4: Should the European Reference Networks privilege the transfer of knowledge? The mobility of patients? Both? How?

A major limitation of transfer of knowledge in rare diseases is the lack of reinforcement in the receiver. If a clinician learns a new notion on a rare disease, the notion is not reinforced, contrary to what happens with frequent diseases. This major limitation in knowledge spread is the reason why referral centers (centers of excellence, etc.) have proven useful for rare diseases. However, health migration is a consequence, along with waiting lists. Collaborative networks are a new option, by which patients are shared distantly. This may be particularly appropriate in oncology. Cancer treatment is conceptually uniform for all neoplasms, in a way. For example, chemotherapy may use similar drugs in frequent and rare neoplasms. However, the indication to one or chemotherapy may be a matter of knowledge. So, the knowledge may be shared over a network, while chemotherapy may be done even in a non-referral center. This keeps high quality of care, without inducing health migration. This is the reason why collaborative networks may be particularly useful in rare tumor oncology.

Question 5: Should on-line and electronic tools be implemented in this area?

Collaborative networks obviously benefit greatly from electronic tools.

Question 6: What can be done to further improve access to quality testing for RD?

Quality testing for diagnostic and predictive tools may be an issue in oncology.

Question 7: Do you see a major need in having an EU level assessment of potential population screening for RD?

The low prior probability of rare tumors generally rules out population screening as a concrete option.

Question 8: Do you envisage the solution to the orphan drugs accessibility problem on a national scale or on an EU scale?

The approval process for anticancer agents is centralized in the EU. So, methodological and regulatory problems need to be addressed at the EU level.

Question 9: Should the EU have an orphan regulation on medical devices and diagnostics?

With the new targeted drugs, identification of predictors may be essential. This may give rise to specific diagnostics, whose spread may encounter problems.

Question 10: What kind of specialised social and educational services for RD patients and their families should be recommended at EU level and at national level?

Information on proper referral is of major importance for patients with rare diseases, including rare tumors.

Question 11: What model of governance and of funding scheme would be appropriate for registries, databases and biobanks?

Biobanks may be particularly useful. Likewise, registries and clinical databases may provide useful information. Sometimes, even anecdotal information may have a great value. Unfortunately, medical journals currently disregard the value of case reports, or small series of cases, which on the contrary may be very helpful in the field of rare tumors.

Question 12: How do you see the role of partners (industry and charities) in an EU action on rare diseases? What model would be the most appropriate?

Rules on orphan drugs foresee incentives to pharmaceutical companies developing them. However, such incentives are enjoyed only if the drug is approved. Therefore, the non-approval risk remains a critical factor in the industry's decision-making process on whether to go on developing a new drug in a rare condition. A greater degree of certainty on the criteria for approval of orphan drugs would be helpful in order to actually encourage pharmaceutical companies develop orphan drugs. In particular, there is the open issue of whether the quality of evidence required to approve a drug in a rare tumor is the same as for a frequent tumor. If this is the case, the non-approval risk will continue to be high.

ESMO is embarking in 2008 in an initiative to study the methodological and regulatory implications of the approval of new drugs in rare tumors. This will be done in partnership with the industry, regulators and charities.
This initiative could generate a permanent structure in charge of preliminary global assessment (specificities of the issue, patients' needs, regulations…), potential recommendations at national and European level and continuous follow-up.

Question 13: Do you agree with the idea of having action plans? If yes should it be at national or regional level in your country?

Yes. What is important is that action plans may be fully consistent at all levels.

Question 14: Do you consider it necessary to establish a new European Agency on RD and to launch a feasibility study in 2009?

It would be a sign of political willingness in the field of rare diseases. But it is still as a preliminary necessity to consider if the existing structures and competences cannot provide an appropriate answer.

Brussels, 12 February 2008