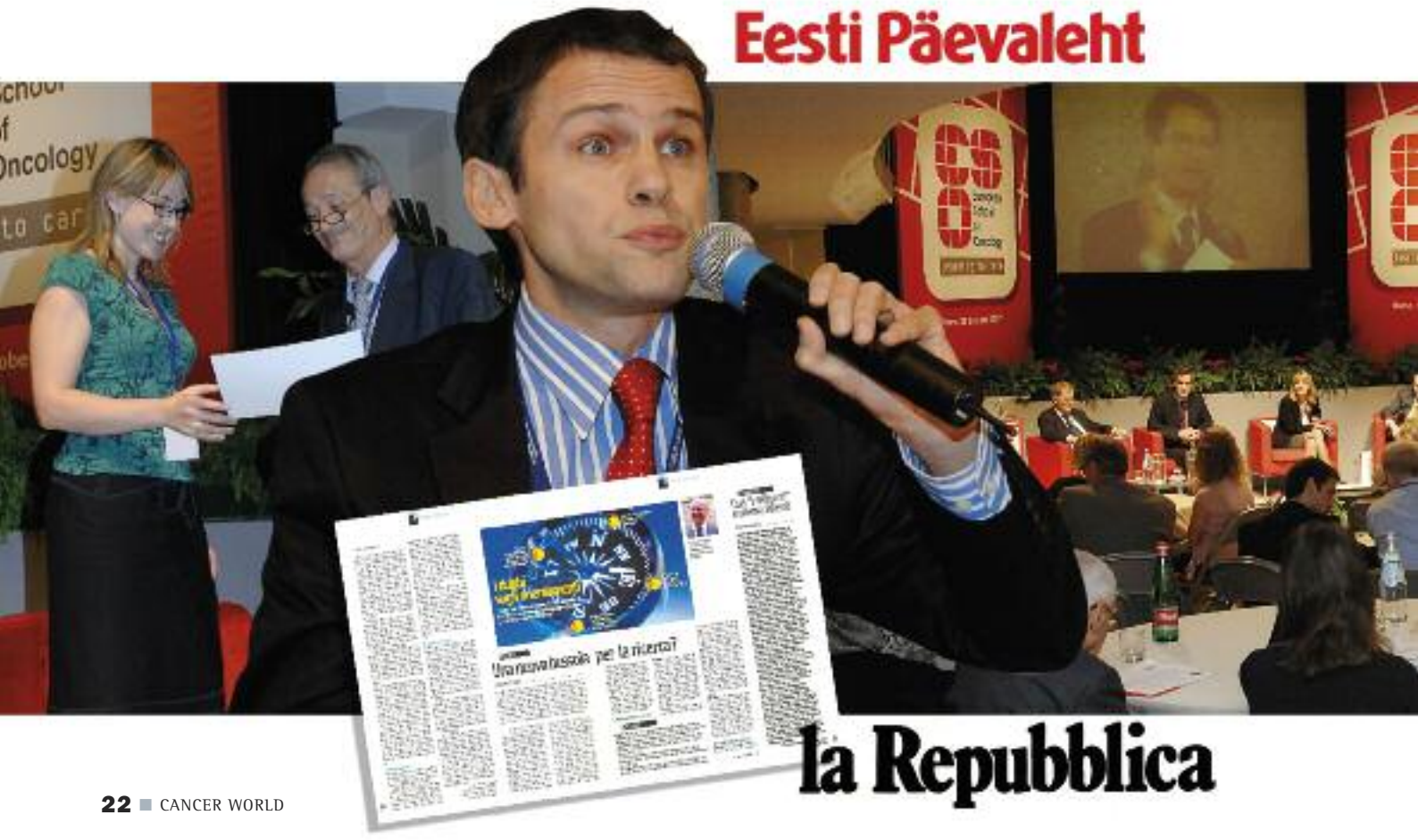
Our responsibility, our choices

ESO invites the media to a reality check on cancer

➜ Anna Wagstaff

The European School of Oncology marked the end of its 25th anniversary year by inviting a top-level line up of experts to debate, in front of the media, how effectively we are tackling cancer and whether a change of direction is needed.



With one in three of us destined to develop cancer and no cure in sight, many doctors and researchers are bemused and frustrated at the apparent public apathy about efforts to control the disease. Perhaps it's not surprising. Cancer is still regarded by the public with a sense of fatalism, and decades of media hype alternating between cancer scares and breakthrough drugs has only obscured the reality that research and better delivery of care is making slow and steady progress – and could make more if it were organised and funded better.

In an effort to promote informed and critical debate about the best way to tackle the rising tide of cancer, the European School of Oncology invited journalists from across Europe to Rome to question leading players drawn from academic research, industry, cancer charities, patient advocacy and regulatory authorities.

The event, held under the title "*Cancer: time for a reality check*" to mark ESO's 25th anniversary, was attended by thirty journalists from newspapers, magazines, TV, radio and new media from 13 European countries, with a further 700 people from across Europe and the US accessing the discussion via a live webcast.

Debates were moderated by four experienced journalists – Jonathon Alter, senior reporter for Newsweek magazine and NBC news in the US, Sarah Boseley, health editor for the UK daily *The Guardian*, Istvan Palugyai, editor of the leading Hungarian daily paper *Népszabadsag* and Paul Benkimoun, health reporter for the French daily *Le Monde*.

Losing the plot?

Cancer researchers have come under fire for focusing on pushing forward the frontiers of basic biology while neglecting innovative ways to tackle cancer – hence the opening session's title, *Quest for a cure: have we lost the plot?* Scott Lippman, professor in medicine and cancer prevention at the MD Anderson Cancer Center, Texas, and Bob Pinedo, director of the Vrije Universiteit medical centre in Amsterdam, looked at the evidence about survival rates over 40 years to draw conclusions about whether we need to refocus research efforts.

Engaging the public. The debate offered valuable background and context to journalists who cover cancer from scientific, health and social standpoints. It was covered in a variety of media, including some of Europe's national press and the *Economist*, which posted a link to the webcast of the debate on its Internet site

Lippman said that the current strategy is now beginning to pay off – understanding the 'sevenless' mutant fruit fly (missing the seventh light receptor normally present in a fruit fly's eye) had contributed directly to knowledge needed to develop targeted medicines. However, the real benefit will only be seen, he stressed, if there is a concerted effort to find out which drugs are effective in which type of patient.

Bob Pinedo: Early detection is the only reasonable and fast solution

Lippman, a lung cancer specialist, highlighted the use of the EGFR inhibitor erlotinib to treat patients with non-small-cell lung cancer. Although the drug offers a median extra survival of only around two months, 10–20% patients respond so dramatically that the treatment could keep them alive for years. Thanks to a huge translational research effort, comparing the tumour gene profiles of good responders with poor responders, we now know that most patients whose tumours shrink dramatically have a specific point mutation.

Scott Lippman: Find the right patients for the right drugs

For this subgroup of patients at least, argues Lippman, targeted therapies have delivered, and we need to give this strategy the best chance to succeed for other patient groups. Lab-based scientists have discovered a host of potentially 'druggable' targets that might be blocked to inhibit the cancer or stimulated to enhance the patient's own resistance. "We must now link the many promising targets/biomarkers to clinical trials designed to identify the right patient for the right drugs. That is personalised medicine. We are getting there."

Pinedo doesn't quibble with the science but worries about the timescale. Even in breast cancer, where the greatest advances have been made in identifying gene signatures, "we have still not seen prognostic selection of patients based on those genes" – let alone selection of personalised treatment. Finding relevant gene signatures is further complicated by the tendency of cancers to mutate, which could mean that the genetic profile of a tumour will change "every six months or even every month".

If we do succeed in matching patients to treatments, said Pinedo, we then have the prospect of turning advanced cancer into a chronic disease, keeping patients alive for longer and longer using combined therapies – an expensive and unsatisfactory solution. For patients with advanced colorectal cancer, for example, "Even excluding palliative treatment like stent, surgical debulking and radioablation of metastases, the cost of treating one patient equals more than 1,000 colonoscopies – this doesn't even include the psychological effects and the social cost."

Pinedo argues that the only "reasonable and fast solution" is to detect the disease early, when it is still curable. He has developed a way of testing stools for aberrant methylation, as an early sign of colorectal cancer. The test picks up 86% of stage I, II and III colorectal cancers, and has a false-positive rate of only 4%. The strategy now is to find a way in which people can use this test in the privacy of their own homes – cheaper and easier than population screening with colonoscopy, and with the potential for a far higher uptake. Pinedo points out that because colorectal cancer is easy to cure when caught early, an effective test would make a huge and immediate impact on what will soon be the major cancer killer in Europe.

Personalised therapies and focusing on early detection are clearly not counterposed – but the question of whether cancer research has the right balance between these approaches was a key theme of the day.

Personalised medicine

Whether the strategy of matching the right patients to the right drugs will be able to deliver on its promises was the subject of another session: *Can tumour gene profiling live up to expectations?* Lex Eggermont, who as former president of the EORTC played a major role in building Europe's capacity to carry out coordinated quality translational research, gave a cautiously optimistic answer: "In time it probably will, because it is solid biologic research."

Gene profiling is a way of capturing the biology of a tumour by analysing the expression of up to 30,000 genes in the tumour tissue. Researchers look for patterns that can help distinguish between different types of cancer, and try to find patterns that predict prognosis or response to various treatments (the key to personalised therapies) by making comparisons between the tissue of patients who survived longer (or responded better), and those who died earlier or failed to respond.

Lex Eggermont: Don't expect too much too soon

Before they can be used for clinical decision making, these 'candidate signatures' have to be validated by testing them in randomised clinical trials

– an operation that requires close cooperation between the labs and companies that do the gene analysis, the clinical team treating the patient, everyone involved in harvesting, transporting and storing the tissue… and the patients, who have to agree to the hassle and discomfort involved in giving biopsy specimens, blood and whatever other samples may be required.

John Ioannidis: We can't afford to underfund this research

Although no gene profile is yet being used to make clinical decisions, Eggermont says that things are already changing. For example, an EORTC trial has validated a gene signature with strong powers to predict which breast cancer patients respond best to taxane- and non-taxane-based chemotherapy. He cautions, however, against expecting too much too soon. Gene profiles change with time and in response to treatments, and it is simply not practical to subject patients to constant biopsies. "You cannot pressure the system," warns Eggermont, "[Gene profiling] will not yield the results everyone expects in three years. Come back in 10 years..."

John Ioannidis, of the University of Ioannina in Greece and Tufts University in Boston, stressed that research into personalised medicine will only deliver if it is done properly – which is often not the case. Looking for gene signatures is a trendy area of research, he said, and with 30,000 genes to choose from, anyone looking for a significant pattern is quite likely to find one. "How do we decide which ones are worth taking to the next step, really trying to make a difference with patients?"

Getting it right will be crucial, he said, as there is a limited amount of good-quality banked tissue with linked clinical histories available for researchers to study. Validating candidate signatures in clinical trials is a major logistical exercise, and patients have the right to expect the samples they donate not to be wasted on research that has little chance of helping future generations.

Ioannidis concludes that this will require more coordination and cooperation, in large and robust clinical trials, and investment in the research infrastructure. He answered the question: "Can we afford to fund such research?" by saying, "If you think that type of research is expensive, then try bad, fragmented uncoordinated research."

The spiralling cost of care

Expense was again a central issue in the session on *Spiralling costs: is rationing expensive cancer drugs the answer?* This offered a rare opportunity for discussion by the main stakeholders, with contributions from the UK's national director of cancer care Mike Richards, AstraZeneca's head of oncology Brent Vose, oncologist and former president of ASCO Larry Norton, pharmacologist and member of the European drug regulatory authority Silvio Garattini and patient advocate Lynn Faulds Wood.

Garattini said the regulatory authorities should insist on better evidence of how a drug works and who benefits before allowing new and expensive therapies onto the market. Most of the cancer drugs approved in the last 10 years, he said, had not been through phase III trials, and had been tested in very late disease, often with no controls or comparator arms. "Let's have better knowledge of the drug at the time of approval."

Silvio Garattini: We know too little about the drugs coming on to the market

From the funder's perspective, Richards argued that it is not possible to continue paying five-figure sums for each course of targeted drugs when only a small minority of patients substantially benefits. "We need new approaches to pricing. We need to look at value-based pricing and risk-sharing opportunities… We need to look at ways, when the industry has done its work, of how to get [the drug] into use in a way that society can bear, and at the same time learn more about them after they've come into use."

Mike Richards: We need to look at value-based pricing and risk-sharing opportunities

Norton, however, warned that rationing expensive drugs risked playing with the lives of patients who could benefit. "It is very hard to look at a patient and say you will only get two weeks so you are not going to get the drug, when that patient may get 20 years." He said that society was reaping the results of having ceded the task of drug development entirely to private industry. "Pharma has a job to do and that is to develop products that sell, so their shareholders can make a profit. As a society we shouldn't fault them for doing what they are supposed to do. The problem is the rest of society is not taking responsibility for curing cancer."

Vose, speaking from the industry, argued strongly against rationing as a solution. "I don't think it's all about pricing. I do think it's about targeting patients who can benefit,

avoiding those who can't, and avoiding those who will get serious side-effects." AstraZeneca, he said, reviews every drug to see if there is a way to select the patients who will benefit, but it is not always easy. "Look at Iressa [gefitinib]. It has been incredibly difficult to find those 10–20% of patients who really get that benefit, and we still don't know. The question is: how long do you want to wait?"

While risk sharing and post-licensing studies could be appropriate, he stressed that each drug is different and the answer lies in working in partnership to find solutions on a case-by-case basis. "I'm concerned that you drive down the road to a single solution that could actually delay the appearance of a drug like Iressa for five years or more while we try to fathom out what this gene profile has to be. That means, with a 10% response rate, you are probably talking about 30,000 patients a year not benefiting in a dramatic way. There has to be a meeting of minds as to how we as a society can take this forward."

Norton: Society is not taking responsibility for curing cancer

While this debate focused almost entirely on the cost of drugs, Richards – echoing the earlier debate on research strategies – argued that there are still big savings to be made by reducing the number of patients who progress to metastatic disease. "We need to invest more in prevention and early diagnosis. In the UK poor survival rates are largely due to later diagnosis. And let's concentrate on surgery. Surgery cures more cancers than any other treatment, and good quality surgery cures more than poor quality. A small investment in training would yield results."

Brent Vose: Each drug is different. We must work in partnership on a case-by-case basis

The point received strong support from Faulds Wood. "We've got the balance wrong. At the moment we're putting all the effort into the drugs, because that's where the money is. But we need to look more to prevention, and we need to look more at screening. Society has to decide at what happens… because in another 16 years all our bud-gets will be bust if we don't sort this."

Lynn Faulds Wood: We should stop focusing exclusively on drugs

Incentives and penalties

Decisions that affect how society organises cancer research receive far less media attention than rationing and reimbursement of expensive drugs. But these decision affect how quickly we make progress against cancer. This was the focus of the session *Are we rewarding mediocrity while penalising real innovation?* Debating this question were: Umberto Veronesi, scientific director of the European Institute of Oncology, Milan and one of the great innovators in breast cancer surgery; Lex Eggermont, former head of EORTC; Dinesh Purundare, GSK's European head of oncology; Harpal Kumar, head of Cancer Research UK and Cliff Leaf, a leading critic of the way cancer research is organised in the US (see also the Cover Story, p 6).

Eggermont talked of the need to foster greater public confidence in science, scientists and doctors. The problem behind the European Clinical Trials Directive, he said, was that it looked at clinical research purely as a potential threat to patients, without any acknowledgement of the huge benefits it is bringing. As a result Europe's clinical research effort has slowed and young researchers feel shackled and demoralised. "We do not mean to reward mediocrity, but we are inhibiting excellence by throwing up all these barriers."

However, Eggermont believes that Europe is also doing many things right. While president of EORTC he helped to organise leading institutions from many countries into a network capable of cooperating on translational research to find new targets and biomarkers and find out what works in which patients. "[This effort] must be multinational and share tissue and information, and have a consortium agreement on how to deal with new inventions. We need to create shared access to these tissues, and to have some of the royalties going back into the system. If you do not create that type of energy behind the system it will fail, and you will have to deal with intellectual property lawyers."

Kumar argued that bodies like Cancer Research UK that are independent of government and shareholders, provide the ideal setting for fostering innovative research. "We can't say what will be important, but we can create environments for creativity and innovation." That includes being able to take risks on innovative ideas with no guarantee of a return. It also means acting in a cooperative manner with the wider cancer research effort. "In CRUK every new tissue collection is required to be made completely available, and we are setting up a portal so we can make clearly identifiable every

tissue everywhere in the country. Every publication has to be put on open access within six months."

Umberto Veronesi is less upbeat about the current thrust of cancer research, arguing that it is focused on areas least likely to generate effective solutions. Western countries, he pointed out, spend 5% of research funding on prevention, 10% on early detection and 85% on treatment, of which 10% goes towards surgery and radiotherapy, and 90% towards medical treatment. "We should reverse this."

Harpal Kumar: The key is to create environments for innovation and creativity

He also spoke up for the primary importance of ideas. Veronesi himself led the early trials into breast conservation, which has saved tens of thousands of women from mastectomy. He also invented and trialled the sentinel node biopsy which allows most breast cancer patients to preserve their axillary lymph node and muscle function. But these trials received minimal funding.

"Everyone agrees on network of core institutions. But trials are becoming larger and longer. Sometimes it takes 5,000 people to discover a 3% difference. This is not innovation. Innovation is totally different. How many people 30–40 years ago believed cancer was a viral disease? Probably only 20 or 30. What is missing are new ideas. We don't have enough new revolutionary ideas."

Lack of innovative ideas is a concern also for Leaf, who argues that the research agenda has been hijacked by an academic system driven by the need to publish in leading scientific and medical journals, to advance careers and to attract grants. Instead of focusing their intelligence and enthusiasm on real innovative approaches to controlling cancer, young researchers are forced to focus research proposals around questions most likely to generate "interesting" results. This explains, says Leaf, why the hundreds of thousands of articles and studies on cancer in past decades have made so little impact, "the age-adjusted death rate from cancer is currently what it was in 1970 and in 1950. ...We have to rethink the mechanisms for rewarding young researchers," he concluded.

Umberto Veronesi: What is missing are revolutionary new ideas

But, as Norton pointed out, most treatment-focused research, in drugs at least, takes place in the private sector where profit, not publication, is the major driver. Here the problem is a competitive environment that is poor at sharing research and tissue, poor at cooperating, and where there are disincentives to narrowing down the patient population that will respond to the drugs.

Purundare from GSK stressed, however, that "the customer is the government" and he called on governments to "send proper signals for rewarding innovative research and development". We need, he added "a shared understanding of what innovation means," for example, how much value is attached to finding ways to deliver drugs orally rather than intravenously.

His point underlined earlier messages about the need for government, industry and the regulators to agree on what constitutes value and how to introduce new drugs in a way that works for industry and society. But it also highlighted the potential for governments to influence the research agenda in both the private and public sector by sending out the correct signals – which is what will have to happen if the research agenda is to shift substantially, for example, in favour of prevention and early detection.

Towards a public debate

In the end, there was no simple take-home message. But then this was never the idea. The 'reality check' was intended to help journalists stimulate public debate about what the priorities for cancer research should be, and how that research should be organised and funded. Comments from the journalists indicated that it went some way towards achieving this. They valued, in particular, the opportunity to hear criticism as well as praise for current research efforts, the diversity of speakers with strong opinions and experience, an opportunity for one-to-one interviews, and the concentrated presentation of so many current debates.

Dinesh Purundare: We need a shared understanding of what innovation means

The speakers also appreciated the chance to engage with the media. "We need more sessions like this where we are all talking together and these kinds of messages, even if there are disagreements, get aired in public," said Norton. "I've made outrageous statements in the US press and they get totally ignored because they are made once only. People have a very short attention span. We have to make this a continuous issue; something that is always discussed."

A webcast of the entire debate can be seen at http://esomediaforum.webcasting.it/