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Conference report

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CONFERENCE REPORT ESMO 2017

More than 23.000 people attended the European Society for Medical Oncology (ESMO) Annual Meeting, the most important oncology congress in Europe, which was held in Madrid. Melanoma, breast cancer and lung cancer were among the main types of tumour discussed at ESMO. However, a lot of important topics for myeloma patient advocates were discussed within the congress, such as patient outcomes, pricing, access to cancer treatments or the role of patient advocates in clinical research.

Ana Vallejo, Myeloma Patients Europe

1. SCIENCE AND PATIENTS

This supplement highlights the key developments in myeloma research presented at ASCO and EHA in 2017.

1.1. Why should patients care about science?

Science is something traditionally reserved for doctors and researchers. Statistics, dose-response curves, progression-free survival and lots of incomprehensible concepts patients struggle with. But in the last few years, the role of patient advocates and patient organisations has changed to become part of the drug development process and clinical research.

Defining the right outcomes and selecting the most important goals for patients are among the most relevant roles that advocates have in clinical research. 85 per cent of research is wasted, amounting to more than $85 billion per year, according to data shared by Jan Geissler, former director of the European Patients Academy on Therapeutic Innovation (EUPATI), in the session *'Science and advocacy: Why care about science'. "There are a lot of reasons why science doesn't address the most important goals for clinicians and patients. They are not thinking in the right outcomes since the beginning,"* said Geissler.

Eric Low, Amyloidosis Research Consortium and former vice-president of Myeloma Patients Europe (MPE) agreed with Geissler in his talk 'Integrating science into oncology for a better patient outcome'. *"Academia is doing a lot of research that doesn't matter. If national health systems are going to pay money, they need to be sure what they are paying for and their benefits. There is an innovation gap and we need to close it. We need the right data for regulators and to get that we have to change the way we collect evidence. The role of research charities and patient organisations has evolved from a primary emphasis on grant funding to a driving force that is advancing scientific development and leading cutting edge patient-centred research."*

Patient organisation operates on three different levels - patient support, health policy and research. The last one is probably the most difficult part for patients to be active in, but patient inputs could be very valuable in the design of clinical trials and therefore to have research that really address patient needs. *"We should prove our hypothesis with data. We are transforming patient advocacy into evidence-based patient advocacy. There are two ways to do successful advocacy: convince others to do good and relevant science or do research ourselves,"* commented Geissler.

But how do we know which trials are patient-centred and which aren't? For example, one of the most used drugs in oncology is dexamethasone. Regarding myeloma, this drug is included in every combination treatment but it has a lot of side effects. *"Having a combination dexamethasone free will be completely patient-centred research. All stakeholders should be involved in this kind of research because only through collaboration will we be successful"*, explained Low.

Oncologists also highlighted the benefit of defining the right goals from the outset, but also the need of public funding for their research. *"The pharmaceutical industry doesn't address patient needs. There are a lot of interesting studies that don't have any support. For example, one of the most important studies presented at ESMO shows that reducing adjuvant chemotherapy after surgery from 6 to 3 months*

in patients with colorectal cancer has the same efficacy. This is very important for patients because they have a shorter treatment and less side effects, but these kinds of studies are not interesting for pharmaceutical companies", explained Dr Miguel Martín, ESMO 2017 Local Officer and President of the Spanish Society of Medical Oncology (SEOM).

1.2. Clinical trial methodology

The involvement of patient advocates in science will not only have benefits in developing research that addresses patient needs, but also could have some benefit in the participation patients have in clinical trials through customised intervention to improve understanding and informed trial participation.

Clinical trials are fundamental to the development of new treatments for cancer, yet the annual accrual to cancer clinical trials worldwide is low, estimated at three to five per cent. A nationwide study in Ireland, presented at ESMO 2017, shows that although most oncology patients consider it important to have clinical trials available, many struggle with the central concepts that underpin trial methodology.

"As a medical oncologist, I have experienced situations where patients have declined clinical trial options because of misconceptions about them," said study author **Dr Catherine Kelly from Mater Misericordiae University Hospital in Dublin, Ireland.** *"To improve participation in clinical trials, we need to understand the factors influencing patients' decisions about taking part."*

In the course of the study, 1,090 adult patients with a diagnosed malignancy and being treated at one of 14 participating oncology centres across Ireland filled out anonymised

Jan Geissler

questionnaires in which they were asked to evaluate statements about clinical trials and research.

"Consistent with previous studies, the concepts of chance and randomisation posed difficulties to a significant proportion of patients. Over half of previous medical trial participants and 73 per cent of those who had never been on a cancer clinical trial did not understand that in a randomised trial, the treatment given was decided by chance," Kelly reported.

"We also found that most patients did not understand clinical equipoise: the fact that no one knows which treatment is best. Surprisingly, this was more marked in previous clinical trial participants, 60 per cent of whom believed that their doctor would know which study arm was best," she said.

"To provide informed consent when participating in a trial, patients need to understand these key concepts – and doctors explaining them well is essential to alleviating any fears that might prevent patients from participating. For example, many didn't realise that clinical trials are not just an option for when standard treatment has failed," she observed.

Eric Low

"Doctors have a responsibility to properly inform their patients in this regard, because they are the ones patients trust the most," Kelly said. *"As we analyse the data further, we will be able to offer physicians a more detailed picture of the questions patients need answered and the factors that influence their decision-making according to age group, cancer type, educational background and other demographics."*

Dr Bettina Ryll, Chair of the ESMO Patient Advocates Working Group (PAWG), commented: *"The question of whether patients understand clinical trial methodology is a very valid one, and what makes this study so interesting is that more than a quarter of the patients questioned had actually been on clinical trials before,"* she said.

"However, I was surprised at the median age of the cohort: 60 years. It would be interesting to compare the data collected here with younger patient groups, who access information in a very different way," Ryll observed. *"I would also expect to see differences across tumour groups: among breast cancer patients, for instance, who make up almost a third of the study cohort, and for most of whom there is a well-established standard of care, clinical trials are likely to be of less interest than among lung cancer patients, for whom the standard treatment is less effective."*

Ryll further cautioned: *"When we talk about understanding, it is important to consider that patients and physicians approach clinical trials from different perspectives: For example, the concept of randomisation is one that many patients question from a moral standpoint. Equipoise, by contrast, may be a laudable moral concept, but it is difficult to uphold if the results of earlier trials are already known: finding out whether a treatment is, say, 51 per cent better or only 49 per cent, may matter to a Health Technology Assessment (HTA) assessor – but not to a patient. This undermines the conclusion that patients simply do not understand equipoise."*

2. PATIENT OUTCOMES

2.1. Impact of chemotherapy in patients

Chemotherapy is one of the most used treatments in cancer. It is used in several types of cancer with high efficacy but also with severe adverse effects and with a high impact in the patient's quality of life. This is something well known by doctors, patients and carers, but once again, the patient perspective and the clinician perspective do not coincide (see section 1.1. Why should patients care about science?).

The preliminary results of a study presented at the ESMO 2017 Congress show that socio-psychological factors have become more significant for patients today than physical side effects such as nausea and vomiting, which were among the top concerns in similar studies carried out previously. *"The results show that there might be a gap between what doctors think is important or disturbing for patients, and what patients really think. Physical, psychological, social and spiritual support is needed at every stage of the disease,"* said **Karin Jordan, Chair of the ESMO Faculty Group on Palliative and Supportive Care and senior leading physician at the University of Heidelberg's Department of Medicine.**

The side effects of chemotherapy seriously impact cancer patients' daily lives, and managing them is a long time concern for doctors. Patient assessments on the subject have been carried out regularly since 1983. The new study presented at ESMO 2017 showed that perceptions of chemotherapy side effects in breast and ovarian cancer patients change not only over time, but also throughout the course of treatment.

"With the most recent analysis dating back to 2002, we felt it was time to collect new data and update the interview format," said study auth**or Dr Beyhan Ataseven from Kliniken Essen Mitte Evang, Huyssens-Stiftung in Essen, Germany.** *"Living conditions have changed, and so have the accompanying therapies linked to chemotherapy. As doctors, we want to know what our patients care about."*

Unlike previous studies, the team led by Ataseven focused exclusively on breast and ovarian cancer patients and added a longitudinal analysis by carrying out three separate interviews before, during and at the end of their chemotherapy.

At each interview, 141 patients scheduled for or undergoing chemotherapy were presented with two groups of cards respectively featuring physical and non-physical side effects. The patients selected their five most burdensome symptoms in each group and ranked them by importance. Out of these 10 main side effects, they were then asked to select the five most significant ones from both groups and to rank these as well.

"What we found is that, on the one hand, side effects like nausea and vomiting are no longer a major problem for patients – this can be explained by the fact that modern medication against these symptoms is very effective. On the other hand, hair loss is still a persistent, unsolved issue that particularly affects patients at the start of their treatment," said Ataseven. *"As time passes and patients get used to this, however, their concerns evolve and other side effects become more significant."*

"Looking at patients' perceptions over the entire course of their chemotherapy, the most difficult side effects they deal with are sleep disorders – which become increasingly important over time – and anxiety about the effects of their illness on their partner or family, which remains a top issue throughout," Ataseven explained.

"*As doctors, these findings might lead us to consi-*

der possible improvements to the accompanying therapies we offer our patients: For instance, sleeping tablets were not until now a part of the routine regimen. There is also a clear case for providing stronger psychological support to address patients' social anxieties and family-related concerns," she said.

Table 1
Ranking of side effects

	1983 (Coates et al.)	1993 (Griffin et al.)	2002 (Carelle et al.)	2016 Current study
1	Vomiting	Nausea	Affects my family or partner	Difficulty sleeping
2	Nausea	Constantly tired	Loss of hair	Affects my family or partner
3	Loss of hair	Loss of hair	Constantly tired	Loss of hair
4	Thought of coming for treatment	Thought of coming for treatment	Affects my work, home duties	Numbness in limbs
5	Length of time treatment takes at clinic	Vomiting	Affects my social activities	Shortness of breath

Table 2
Ranking

	T1 (before initiation of chemotherapy)	T2 (after 12+/-3 weeks of chemotherapy start)	T3 (end of chemotherapy +/- 2 weeks)
1	Affects my family or partner	Difficulty sleeping	Difficulty sleeping
2	Feeling of not coping with treatment	Affects my family or partner	Affects my family or partner
3	Loss of hair	Numbness in limbs	Numbness in limbs
4	Nausea	Loss of hair	Affects my work, home duties
5	Difficulty sleeping	Shortness of breath	Pins and needles in limbs (fingers, toes)

In total, 141 patients (95 BC and 45 OC) were recruited. All three interviews were completed in 113 patients. The most severe CSE reported was "difficulty sleeping" compared to "vomiting" in 1983, "nausea" in 1993, and "affects my family/partner" in 2002 (table 1). "Loss of hair" remained a top concern over all studies. Over the complete observation period "affects my family/partner" and "difficulty sleeping" were among the top five severe side effects. "Feeling of not coping" and "nausea" were ranked only at T1, but not at T2/T3. "Loss of hair" was ranked at T1/T2, but no longer at T3. In contrast, "numbness in limbs" became relevant in T2/T3 (table 2).

2.2. Triggers: a new tool to assess cancer patients' palliative needs

One of the most difficult phases that a patient and their relatives can cope with is the end of life phase. Palliative cares offer specialised care for those patients who can benefit from individual attention. However, defining when the referral should be done is not easy. The so-called "Triggers" tool, developed by the London Cancer Alliance to help clinicians in the UK recognise patients who need an early referral to specialist palliative care, has been successfully piloted at The Royal Marsden NHS Foundation, one of ESMO's Designated Centres of Integrated Oncology and Palliative Care. The preliminary results of the service evaluation presented at ESMO 2017 prove the usability of this tool by primary care teams and point to the feasibility of establishing an integrated service between oncology and palliative care teams on a wider scale.

Palliative care has traditionally been associated with optimising the quality of life (QoL) at the very end of life. However, research has shown that giving patients early access to specialist palliative care can have many benefits, including improving their prognosis.

The Triggers tool allows oncologists to assess their patients' needs in this respect at a much earlier stage, and to potentially refer them for specialist palliative care alongside active treatment. In its pilot phase the tool was introduced for new patients at The Royal Marsden's lung oncology outpatient clinic: in the first four months of the service, 84 per cent of eligible patients were reviewed within two months of their first clinic attendance.

"We found that 75 per cent of the patients reviewed triggered positive on one or more of the tool items. Of the 'Trigger positive' cohort, whose needs were then assessed by a palliative care team, 97 per cent were identified as having at least a moderate need for specialist palliative care – even though 81 per cent of them were still functioning well, ranking in the top two scores on the scale used to assess how a disease affects a patient's daily living abilities," said **Dr Jayne Wood from The Royal Marsden NHS Foundation Trust,** who led the evaluation.

"This tells us that we are addressing a real need, and that the tool is picking up a group of patients who have a real potential to benefit from referral to specialist palliative care. The goal is for the tool to become standard and easy for anyone on a patient's primary care team to use – for us, the next step will be to expand into other tumour groups," said Wood.

A lung cancer patient who was referred to The Royal Marsden after being diagnosed in April 2017 benefited from an early needs assessment via the Triggers tool: *"I was referred to the palliative care team around a fortnight after arriving at The Royal Marsden. They have helped me with medication, which has given me more energy, visited me at home, and have been able to advise me about different symptoms. I definitely feel that I can call them if I need them,"* she said.

ESMO Press conference

3. ACCESS AND NEW DRUGS

3.1. ESMO Magnitude of Benefit Scale and orphan drugs

The European Society for Medical Oncology (ESMO) has developed a validated and reproducible scale, ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) to assess the magnitude of clinical benefit for cancer medicines. This scale uses a rational, structured and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from anti-cancer treatments. This scale can be used as a tool to define which drugs have to be available for all patients in Europe and also help to price these drugs accordingly.

According to research presented at ESMO 2017, ESMO-MCBS is a valid tool for grading orphan drugs and determining how orphan and non-orphan drugs performed according to its established threshold for meaningful benefit.

The study included 63 drugs approved by the US Food and Drug Administration (FDA) between 2006 and 2016 for 118 solid tumour indications, of which 54 (46 per cent) were given orphan designation. Compared to non-orphan drugs, trials supporting orphan drug approval included fewer patients, were less often randomised, were more likely to assess intermediate endpoints rather than overall survival, and were less likely to evaluate experimental cytotoxic chemotherapy or endocrine therapy than targeted therapy.

The ESMO-MCBS could be applied to 70 per cent of trials supporting orphan designations. Less than half (48 per cent) met the ESMO-MCBS clinically meaningful benefit threshold compared to 41 per cent with non-orphan status. The difference was not statistically significant.

"Orphan drug designation did not influence the odds of meeting the ESMO-MCBS clinically meaningful benefit threshold," said lead author **Ms Consolación Molto Valiente, a researcher in the Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.**

"The ESMO-MCBS is applicable in most situations where randomised controlled trials are available, including those supporting approval for drugs granted orphan designation," she said. "However, the practicability of applying the ESMO-MCBS is more limited for orphan drugs as in over a quarter of cases drug approval is supported by single-arm studies."

Commenting on the results, **ESMO President-Elect Professor Josep Tabernero,** Director of the Vall d´Hebron Institute of Oncology (VHIO), Barcelona, Spain, observed: *"There were no major differences in the ability of the ESMO-MCBS to rank orphan and non-orphan drugs. This study used version 1.0 of the scale. Version 1.1 is now available and enables the scoring of single-arm studies in orphan diseases and for others with high unmet need. This will go even further to meet ESMO's goal of sustainable cancer care."*

Disparities in clinical added value between the ESMO-MCBS and the Health Technology Assessment (HTA) body in France was discussed in another study presented during the same session. *"The aims and scope of the ESMO-MCBS differ from those of an HTA body,"* said Tabernero.

"Some value-based assessment tools do not currently factor in considerations such as disease frequency or orphan designation," he continued. *"The ESMO-MCBS incorporates these criteria and many other important*

Josep Tabernero

aspects. Collaboration between the ESMO-MCBS, HTAs and other major frameworks will help to further improve and fine-tune our respective evaluation platforms.

"The ESMO-MCBS is a crucial component of ESMO's sustainable cancer care agenda, which is centred on advocating for access to quality treatment and for cancer prevention," concluded Tabernero.

3.2. DNA sequencing: new indications for existing drugs in rare cancers

One of the main problems in rare cancer treatments is the lack of new drugs to treat them while common cancers have a lot more treatments and resources to face them. However, imagine that a myeloma patient with no treatment options had the same genetic mutation as other breast cancer patients. Would it be possible to administrate breast cancer drugs in a myeloma patient? Something similar is what researchers from the Centre for Personalised Cancer Treatment (CPCT), a network of more than 40 hospitals in the Netherlands, are trying to achieve. So far adult patients with solid tumours, glioblastoma, lymphoma or myeloma with no standard treatment options were enrolled in the study in multiple parallel cohorts according to tumour type and trial drug.

Thanks to DNA sequencing, patients with rare cancers for which no standard treatment is available could receive existing therapies that work in patients treated for different cancers, but who carry the same genetic mutations. The first results of a multi-drug and multi-tumour clinical trial, presented at the ESMO 2017 Congress, show that this kind of precision oncology trial is not only feasible, but also has the potential to identify patient subgroups who could benefit from existing drugs outside of their registered indication.

The CPCT systematically collects biopsies from metastatic cancer patients, which are then analysed by Whole Genome Sequencing (WGS) in order to create a database that now comprises about 2,000 individuals treated for all types of cancer.

"By sequencing the whole genome in so many patients, we found commonalities between tumours and DNA mistakes. For example, the ERBB2 gene is mainly screened for in breast cancer patients, but we know that it is also present in patients with other tumour types," said principal study investigator **Prof. Emile Voest, from the Netherlands Cancer Institute in Amsterdam,** who led the trial on behalf of the CPCT.

"Now that we are able to identify these patients, the question is: How can we get them to benefit from existing, potentially active drugs? That is the basis for our Drug Rediscovery Protocol, which currently includes 19 different drugs from 10 pharmaceutical companies," Voest reported.

Since the trial was launched in late 2016, over 250 cases have been submitted for review: of these, about 70 patients have so far been found eligible and started treatment.

"We have preclinical evidence and case reports suggesting that certain drugs, which patients with a given genetic aberration and a certain type of cancer are sensitive to, could equally be active in patients with the same mutation in other tumour groups. However, we also know that the tissue background is extremely important: That's why we create study cohorts not just according to

genetic mutation, but also according to the specific tumour type," Voest explained.

The efficacy of the treatment for each cohort is analysed in a two-stage process: *"If in stage one, the first group of eight patients with the same tumour type and genetic mutation responds to the treatment, we expand the cohort to 24 patients in stage two to get a stronger indication of the clinical benefit,"* said Voest. *"Clinical benefit, in this case, is defined as either a complete remission, a partial response, where the tumour shrinks by more than 50 per cent, or disease stability for at least 16 weeks."*

To date, a clinical benefit has been observed in 37 per cent of trial participants, and six of the 20 study cohorts have graduated to stage two. *"We've seen real success with several anticancer drugs, including immunotherapy, a PARP inhibitor and an antibody combination,"* Voest reported.

"Our team is quite excited about these results, because everybody knows that developing new drugs is very expensive. With this study, we are providing a platform for expanding the indications of existing drugs and utilising them to their full potential," he said. *"Using drugs that are already available based on DNA sequencing is a truly novel approach to personalising medicine, and we are talking to regulatory authorities to see how new findings in this area can be translated to the clinic as quickly as possible for these rare subsets of patients."*

Dr Richard Marais, from the Cancer Research UK Manchester Institute, commented on the study: *"What makes this trial so exciting is that it could change the way we stratify patients for treatment, that is to say match their genetic profile with a treatment option. The team looks for mutations, some of which will have drugs to target them. If they find them, the patients are treated based on their genetics, rather than their indication: This is incredibly powerful. Beyond identifying new indications for existing drugs, this study is about finding treatments for patients for whom there is currently no standard of care,"* he said.

"Gene sequencing is starting to become standard practice in cancer care: For example, we know that about half of all melanoma patients have a so-called BRAF mutation, so we look for it and give the relevant individuals a BRAF drug. However, for these rare types of cancer or rare mutations, we need to sequence hundreds of genes to find the specific mutations that therapies can target. The CPCT has the ability to find those targets because it sequences the entire genome," Marais explained.

"This is very expensive, so the trial needs to show that it can be cost-effective and work for patients. Stratifying even 10 per cent of trial participants could make the process cost-neutral: for health systems around the world, this would mean that despite a high upfront investment, the downstream benefits to patients and potential reduction of the cost of treating them would be enormous," he said. *"In this context, the numbers presented are very impressive. They have definitely shown a proof of principle."*

» Licensing and reimbursement discrepancies

Discrepancies between licensing and reimbursement decisions have an impact on patient access to cancer treatment, according to research presented at the ESMO 2017 Congress.

The study evaluated decisions by authorities in 11 European countries and Canada on anti-cancer medicines approved by the European Medicines Agency and Health Canada between 2006 and 2016 for six tumour types. It found that 34 per cent of assessments led to complete or partial restrictions in access to medicines, potentially impacting more than 200,000 patients. Differences between countries on the number of drugs with restricted

access were independent of gross domestic product (GDP).

The researchers said that licensing and reimbursement decisions appear to be fragmented, resulting in varying restrictions that impede the use of effective medicines among clinically eligible patients and result in substantial loss of life years.

"There are potentially 200,000 patients in 12 countries who by licence should have access to drugs but are not getting them because of the reimbursement decision," said lead author Mrs Jan McKendrick, senior director, PRMA Consulting Ltd, Fleet, UK.

"The findings were independent of GDP so this was not purely down to a country's financial situation," she added. *"In some countries the reasons were clear – for example Canada only reimburses the trial population and the UK conducts a cost-effectiveness assessment – but many countries don't publish the rationale."*

» The role of biosimilars in the sustainability of healthcare systems and the access to medicines

Many things have been said about biosimilar drugs -similar versions of the originator biologic drugs- in the last few years. Biologic treatments such as monoclocan antibodies (moAbs) have had very good results in oncology. According to a position paper of ESMO, with the majority of moAbs coming off patent by 2020, the oncology landscape will be facing a lot of changes. The introduction of biosimilars, existence of their reference products (originator biologics) and creation of improved versions of existing biologics (biobetters), among others will constitute a challenging environment for all key stakeholders: prescribers, pharmacists, nurses, patients, reimbursing bodies and manufacturers.

The European Union (EU) has been a pioneer in approving biosimilars, with the approval of 23 biosimilars up to 2016. Prior to the introduction of biosimilars for monoclonal antibodies (moAbs), biosimilars only existed for low molecular weight compounds. In 2013, the European Medicines Agency (EMA) approved two biosimilars for infliximab, a monoclonal antibody (moAb), a large and complex molecule that is widely prescribed for patients in several disease areas, including oncology.

Although biological treatments are crucial to treating life-threatening conditions in all disease areas, *"With the anticancer medicines market set to surpass the 140 billion euros mark by 2020, healthcare decision makers are facing considerable challenges: tackling the issue of sustainability of healthcare systems and improving access to medicines for patients. Biological medicinal products, or those whose active substance is made by a living organism, will represent 19-20 per cent of the total global share of pharmaceutical sales by 2017, and thus form an essential part of the anticancer medicines offering"*, said the ESMO position paper.

"Biosimilar drugs can contribute to the sustainability of healthcare systems as they are cheaper than the original drugs. However, automatic substitution, which might be practice for generics, should therefore be avoided in the field of biosimilars. The substitution should be a decision taken by the doctor and only if the physician is well-informed about the product", said ESMO President-Elect Dr Josep Tabernero during the press conference held at ESMO 2017.

According the ESMO position paper about biosimilars, *"Interchangeability and switching should only be permitted if: the physician is well-informed about the products; the patient is fully briefed by the physician and a nurse is closely monitoring the changes and tracking any adverse events."*

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