Cancer Medicines Forum (CMF) – a way forward for treatment optimisation

REPORT OF THE WORKSHOP

5 April 2024

In-person and Virtual meeting / EMA, Amsterdam

AGENDA

Chairs: **Denis Lacombe (EORTC) and Francesco Pignatti (EMA)**

13:00 Welcome and opening speech

Presentation
Emer Cooke, Executive Director, EMA

Welcome (video)
Frank Vandenbroucke, Deputy Prime Minister and Minister of Health and Social Affairs

13:15 Session 1: Setting principles and rationale for treatment optimisation

Cancer Medicines Forum: rationale and achievements
Denis Lacombe, Chief Executive Officer, EORTC

Examples of drug development and optimisation questions/trials
Iphigenie Korakis, Department of Medical Oncology, Institut Universitaire du Cancer de Toulouse-Oncopole (IUCT-O), Toulouse, France
Bertrand Tombal, department of Surgery and Urology UCL, Brussels BE
Martin Kaiser, European Haematology Association

How could EU policies benefit of the work of the CMF?
Richard Sullivan, Kings college London, UK

Cancer Medicines Forum treatment optimisation framework
Caroline Voltz-Girolt, advanced therapy and haematological diseases office, EMA

14:40 Q&A

14:50 Session 2: Developing a new regulatory dimension for treatment optimisation

Cancer Drug Development as a Public Health Issue
Chris Booth, Queen's University Cancer Research Institute, Canada
The global Challenges of Post-market Optimisation Research

Daniel Goldstein, Tel-Aviv University

FDA Oncology centre of excellence: project PRAGMATICA
Donna Rivera, Associate Director of Pharmacoepidemiology, Real World Data and Real World Evidence, FDA

How does treatment optimisation apply to other fields of medicine?
Guy Brusselle, Ghent University Hospital, Belgium

15:55 Q&A

16:00 Coffee break

16:30 Panel Discussion

Regulator's perspective: *Pierre Demolis, ANSM, EMA*
HTA's perspective: *Beate Wieseler: Head of Department Drug Assessment, IQWIG*
Patient's perspective*: Ana Amariutei, European Patient Advocacy Institute*
Clinician's perspective*: Rosa Giuliani, HealthCare Professional Working Party*
Industry's perspective: *Michael Zaiac, Daiichi Sankyo*
Head of Medicines Agency's perspective: *Momir Radulovic, Agency for Medicinal Products and Medical Devices of the Republic of Slovenia*
Payer's perspective: *Ackbar Ketwaru, the Ministry of Health, Welfare and Sport, The Netherlands*
WHO Perspective: *Raffaella Casolino, World Health Organization*

18:00 Closing remarks

Wrap up: recommendations to the CMF and EU Policy makers Wrap up
Denis Lacombe (EORTC) and Francesco Pignatti (EMA)

REPORT

Introduction

EMA Executive Director Emer Cooke opened the workshop by highlighting the importance of treatment optimisation studies in finding ways to treat patients better. These studies have a key role in addressing critical questions regarding cancer medicines, but they come with their own set of challenges. Stakeholders and decision-makers involved often approach the question from different perspectives. While treatment optimisation studies are voluntary for marketing authorisation holders under the current legal framework, the EMA and EORTC established the CMF to address these complexities and find a way forward. Open dialogue within the CMF can promote collaboration among all stakeholders not just within the European Union but worldwide ultimately leading to a future where patients receive safe and effective treatment based on benefit-risk, cost-effectiveness assessments, and optimisation research.

Frank Vandenbroucke, Belgian Deputy Prime Minister and Minister of Health and Social Affairs, emphasised that the optimal use of newly emerged medicines often remains poorly documented, leaving patients' questions and societal concerns unanswered. Therefore, there is the need to bridge the gap between the evidence needed for regulatory approval of a new treatment and that required for clinical decision-making. Regulators and health systems prioritize fast access to treatments that appear promising but where the clinical data are often limited. Is it right that uncertainty about the best use of new drugs should be accepted in order to access them sooner? More data are needed, and the gap between evidence for approval and that for optimal use of drugs needs to be bridged, ideally both in the pre- and post-approval settings, and encouraging independent clinical research and multistakeholder collaboration, that is focused on patients' needs.

Session 1: Setting principles and rationale for treatment optimisation

EORTC CEO Denis Lacombe presented the rationale and achievements of the CMF. The story started in the late 2000s, when the development of personalised medicine meant that it became evident that the clinical trials conducted to inform regulatory decision-making and aimed at identifying and testing new cancer agents were not sufficient to inform healthcare systems. Instead, population wide research involving real-world data, health economics, pragmatic trials, and other divergences from the standard randomised controlled trial (RCT) for drug licensing were becoming more and more necessary, relevant, and important for patient care. But these new trials are not without challenges; the clinical research environment needs to be adapted, and stakeholders educated. There are also ethical issues involved, particularly in de-escalation trials, which seek to decrease toxicity to the patient while maintaining the best survival options.

Treatment optimisation is a spectrum and, in the continuum 'clinical science - regulatory science -HTA/access science', the pragmatic gap between the last two needs to be filled. What is required there is a checkpoint, possibly optimally done by independent networks, where clinical research meets epidemiology and healthcare technology assessment to ensure that the interests of healthcare systems as well as patients are taken into account. To achieve better outcomes for all, we need to further refine the pyramid of evidence-based medicine to make sure that new drugs are optimised at the post-licensing stage.

As treatment optimisation research is missing in the current framework, the CMF aims to serve as a direct and official communication with the oncology academic community, identifying the key research questions and methodological approaches, and discussing the uptake of academic work in the context of regulatory decision making. The members of the CMF are EMA, EORTC, ESMO, EHA and SIOG, being also constituted by observers, like HTA bodies, patients' representatives, SIOPe, industry, OECD, AIM and ESIP.

Iphigénie Korakis P.I, Clinical Research Unit-Early Phase Trials, IUCT-Oncopole Toulouse, France, said that immunotherapy has taken the world by storm, but it still lacks the strong and robust biomarkers needed to select the patients who will benefit the most from it. It also has an unpredictable toxicity profile at patient level, and this causes cost and organisational burdens for cancer centres. In some Phase III trials of immunotherapy, the dose selected was very much higher than the recognized lowest effective dose, which is leading to additional and potentially avoidable side effects. So, this raises the question of what should be the dose and the duration of treatment for patients.

In the MOIO randomised multicentre Phase III study, researchers are investigating the effect of using the standard dose intensity of immunotherapy over a reduced dose intensity in patients with metastatic cancers. The primary endpoint is progression-free survival, but they will also examine quality of life, cost-effectiveness, the treatment's safety profile and other secondary endpoints. The accrual duration as well as the follow-up period are planned to be 36 months, while treatment shall be continued until disease progression, unacceptable toxicity, death, or patient's/investigator's choice. Trials investigating different immunotherapy administration schedules are important, she said, because of all the unknowns: the dose, the duration, and the interval of administration. Avoiding overtreatment and unnecessary toxicities are also under scrutiny, as well as the high financial burden of the treatment, and a better prediction of its effectiveness.

Bertrand Tombal, from the Department of Surgery and Urology at UCL Brussels, Belgium, said that, despite intensive screening for prostate cancer, many patients do not present until they are at the metastatic stage, and that the usual treatment, while increasing overall survival, does not come without toxicity. This means that the patient pays a very high price, with chronic and serious side effects. Optimisation trials over the past 20 years have shown that there is often no need to treat the patient continuously until progression, which is easy to measure with a blood sample. The treatment can therefore be suspended without any detriment for the patient and a significant increase in quality of life. This is called intermittent androgen deprivation (IAD) therapy.

IAD was therefore the standard of care until new androgen receptor pathway inhibitors reached the market, and the concept was lost. However, the new treatments significantly increase the percentage of patients with a profound response, and hence the proportion that would be candidates for the intermittent approach. The DE-ESCALATE trial will validate the benefits of giving IAD treatment in metastatic hormone-naïve patients, attempting to minimise the use of drugs while maintaining patients' quality of life and survival. However, there is no industry support (the trial is funded under the EU Horizon scheme), and the trial is only feasible in a pragmatic, low-intervention outline. And because it compares two historical standards of care and, in the experimental arm, the medicine is not delivered exactly as per the summary of the product characteristics (SmPC), regulators see it as interventional, thus killing the pragmatism. So, there are still many hurdles to overcome in doing this type of trials.

Martin Kaiser spoke next, on behalf of the European Haematology Organisation. Haematologic cancers are complex, diverse, and often uncommon, he said. They make up about 10% of all oncological entities but are still subdivided into many different classes with a majority being systemic. While there has been substantive progress in the treatment of previous intractable haematologic cancers leading to increases in survival, there is a huge amount of tumour heterogeneity involved.

Additionally, inter-patient tumour heterogeneity ranges greatly. Patients with a potential for de-escalation have slow-growing tumours, are more predictable, and are still responding to existent medicines at relapse. But those with more aggressive biology – fast-growing tumours, less predictable, and no response at relapse, have a persistent unmet need. Identifying and stratifying these patients requires complex, specialist diagnostics. The default situation is that every patient receives the same kind of treatment, and physicians face the challenge of not knowing whether they are over or under-treating a particular patient.

With specialist diagnostics for minimum measurable disease, patients who can stop treatment can be identified, and trials such as GAIA/CLL13 in chronic lymphocytic leukaemia (CLL) have shown that stopping treatment is safe. In multiple myeloma, which is more aggressive than CLL, a whole set of tests is needed to identify patients with more aggressive biology, and different drug combinations are being used to address the aggressivity of the disease.

Currently, the specialised diagnostics needed for treatment optimisation in haematologic cancers face many challenges. They are neither part of the standard licensing evaluation process, nor of the standard reimbursement evaluation process, and they face difficulties relating to the IVD Regulation. They are outside the core expertise of most drug manufacturers and relatively underfunded, with a limited incentive for commercialisation, and the funding of diagnostic services is detached from drug budgets. So, although specialist diagnostics can reduce uncertainty for regulators, payers, and industry, and improve treatment for patients, there is still a long way to go. This is a confounding factor to identify subsets of patients who can benefit or not based on the biology of their disease.

Richard Sullivan, from the Institute of Cancer Policy, Kings College, London, said that over the past 25 years there had been extraordinary changes in European science policy and politics, but that policy had struggled to keep up with the pace of innovation, and also with clinical practice. The idea of value has taken on a far greater importance; 25 years ago, value-based healthcare was practically never mentioned. But how to define value when it spans so many different areas? It is not difficult to show that treatment optimisation provides value in most areas, apart from the potential problem of convincing patients and the public that doing less does not mean inferior quality care.

The relentless increase in drug development and authorisation in the 21st century means that more and more biopharmaceuticals are coming into clinical practice, often with a high level of uncertainty about their long-term efficacy, tolerability, and toxicity. And then there is the question of affordability. Unlike other types of industries, in healthcare, technology increases costs. This applies not only to medicines, but also to radiotherapy and surgery. So further research on all these technologies is needed to optimise their use and

inform clinical decisions, but obtaining funding for this is only one of the difficulties involved. Others include a missing methodological framework, insufficient reliable real-world datasets, industry reluctance to participate, ethical and legal issues, and a potential delay in patient access to new therapies if performed before approval whilst there may be recruitment issues if they are performed after. Consistent policy and political changes will be key to making progress in this area, he concluded.

The next speaker, Caroline Voltz-Girolt, from the EMA's Advanced Therapies and Haematological Diseases Office, said that currently the EMA has limited responsibilities with regard to treatment optimisation as per the current legal framework. But, in her personal view, there is a pathway to the inclusion of a treatment optimisation guideline following the agency's regulatory procedures, and this is currently under discussion, alongside the revision of the EU pharmaceutical legislation. For instance, in the pre-approval setting and specifically at the scientific advice and protocol assistance stage, EMA could prompt the applicant to ask specific questions around treatment optimisation, namely optimal dose.

Treatment optimisation could be integrated in existing EMA procedures, she said. In clinical evidence generation, for example, the initiation of disease specific workshops/webinars could help to understand current challenges with existing treatments, clinical practice, and identify areas of unmet needs. Treatment optimisation questions and planning could be systematically included in drug development and scientific advice, in collaboration with relevant stakeholders, such as HTA bodies, learned societies and patients. In post-marketing, EMA could ask in scientific assessment reports for treatment optimisation questions to be answered, and that these should be regularly and publicly updated. A real-life use monitoring system could be instigated, and results published in order to inform the research community.

In the end, the EMA should stimulate clinical study designs not only addressing the needs of the agency, but also downstream actors which is also very important because this is something that can therefore be more visible for all stakeholders to identify which research gaps are needed to be taken by industry or by academia. It will be important to listen to all stakeholders when taking this forward, she concluded.

Session 2: Developing a new regulatory dimension for treatment optimisation

Christopher Booth, from Queen's University, Kingston, Canada, opened by describing the cancer medicine paradox – the substantial overuse in many health systems of very toxic treatments that may have very small benefits, particularly towards the end of life. At the same time, those treatments with very large benefits are unavailable to large numbers of patients globally. In reality, there are three kinds of cancer treatment, he said. There are those that are transformative and really improve patients' lives; those that are not transformative, but still really good; and those where the levels of evidence are still uncertain. Many new medicines fall into this third group, where the benefits are quite small and need to be balanced against the real toxicities to which patients are exposed. Although oncologists are aware of this situation, the public, policymakers, and the media are, in the majority, are not.

In Ontario, research has shown that while non-cancer health spending is increasing by about 5% per year, in cancer the increase is 15%. Looking at it further, two-thirds of the cancer medicine budget was spent on treatments that had been shown in trials to improve survival by more than six months, but the other third had smaller benefits, and this included some that had no proven evidence of gain in survival. Not only was there no association between how well the medicine works and its price but, if anything, it was an inverse relationship where the drugs with the smallest benefit cost the most. Moreover, he reflected on the increasing use of very precarious endpoints in clinical trials and decision-making processes, such as progression-free survival, that is definitely not a surrogate for survival and quality of life in most settings.

He concluded by referring to the Common-Sense Oncology Group's proposals for tackling the current situation, which is unsatisfactory for patients, for clinicians, and for healthcare payers. The group argues that oncology needs a recalibrated approach that is more patient centred and prioritizes equitable cancer care. While they will welcome well-conducted trials and promote effective treatments, they will also challenge interventions that might cause more harm than good. Cancer medicines should help patients live longer and better lives, and this is underlined by the fact that oncologists are treating people rather than tumours. The current economic model for cancer medicine delivery and research is broken, and patients and health systems deserve better.

Daniel Goldstein, from Tel Aviv University, Israel, described work on treatment optimisation as a Sisyphean task, that needed involvement from all stakeholders to push the rock up the hill. After pre-market research, which is mostly industry-funded, it goes to the regulators and HTA agencies, the next steps being registration and reimbursement and then, potentially, post-market/optimisation research. But the funding for that is uncertain and, even if there is a little, it tends to fade away later. And yet such research is really important; when drugs get approved, the optimal dose is not always known, and neither is the duration of treatment. These gaps in knowledge have not only physical but also financial toxicity. So, the clinical and research community have work to do in order to tackle these aspects.

He cited the SONIA trial, a Dutch study of CDK4/6 inhibitors in first- or second-line metastatic breast cancer. The results showed that giving the treatment only second line had equivalent effectiveness with massively reduced costs and toxicity because the duration of treatment was so much shorter. So why is it so difficult to run such trials? It is not just a question of funding, but also of recruitment; patients may be reluctant to enter a trial, and clinicians may ask why a study is necessary simply in order to give a reduced dose. However, the Dutch have managed to convince their government that if it funds the studies, the health care system will save money. Such savings should turn into a revolving fund for the creation of new studies, which will all be self-funding. This is the way forward to maximising the potential of optimisation research, he concluded.

Donna Rivera, from the FDA (USA), said that the current clinical trial system was complex, restrictive, and resource intensive. It was burdensome for patients as well as providers. The FDA's Oncology Centre of Excellence has therefore launched Project Pragmatica, which is focused on advancing evidence generation for approved medical oncology products by exploring innovative patient-centred trial design approaches.

The project will look at ways in which different data sources and study designs could be integrated to be most effective for patient-centric evidence generation, she said. There should be no dichotomy in the different types of clinical trial data, but rather a continuum. For example, randomised controlled trials for drug authorisation are prospective, interventional, often with strict eligibility criteria, and with complex protocol-based assessment. But as researchers start to move across the continuum, they can think about ways of introducing other assessments and create the flexibility that allows the potential for selective monitoring. And then they can also start to think about the inclusion of real-world data, how it can be embedded in clinical care and clinical assessments. Further, this will enable researchers to enhance generalisability in clinical trials and thus reflect routine clinical practice by bringing trials closer to patients.

The FDA will be launching a new effort, Project Five and Five. In collaboration with the oncology community, it will identify five clinically relevant questions that can be answered in pragmatic trials over the next five years. The project's goal is to build a learning healthcare system that can support evidence for regulatory, clinical, and patient decision-making in a collaborative fashion, she concluded.

In the context of the EU, it was felt of relevance to address if and how the concept of treatment optimisation would also apply to other field of medicine. Guy Brusselle, a respiratory disease specialist from Ghent University, Belgium, cited asthma as another disease where there is a huge need for treatment optimisation, and where patient-centred applied clinical research was needed to investigate the real-life effectiveness and cost of medicines and also other treatments. Phase 2 and 3 clinical trials for drug development focus on short-

term safety and, while these are clearly important, it is insufficient to guide clinical practice. For this, we need clinical studies that include pragmatic randomised designs to study the effectiveness and long-term safety of a drug and compare it with other active treatments.

Over the last decade, the EMA and US Food and Drug Administration (FDA) have approved six biological therapies for the treatment of severe asthma, but we have no evidence allowing us to choose between them for an individual patient, he said. Although these drugs are major breakthroughs, there is no evidence on their optimal use in clinical practice. There are no head-to-head comparisons, no biomarkers for predicting potential response, and no evidence on real-life effectiveness and long-term safety, particularly in specific populations – pregnant women, the elderly, and children, for example. Nor is there evidence as to the duration of treatment.

What is needed to fill the research and evidence gap between the pre-approval development of medicines and their post-approval use in real life and clinical practice? Here there is an opportunity for the European Union and the EMA to co-ordinate international treatment optimisation studies, and especially pragmatic trials to evaluate the comparative teal-life effectiveness of drugs and other treatments in patients with non-communicable diseases in the EU. The era of precision medicine demands evidence of response at an individual rather than at group level, he concluded.

Discussions – questions/answers and panellists

Many suggestions for optimising cancer treatment were made, and there was general agreement that this should be done through an international, preferably European, effort. Speakers emphasised the need for personalised approaches and better data ownership. They also discussed the challenges of drug development, including the need for treatment optimisation, the need for/place of biomarkers, and a multistakeholder approach. There was agreement on the importance of collaboration, innovation, and careful consideration of optimisation in drug development, and the need for clearer aims and incentives to encourage such collaboration in optimisation research.

Among the many important points raised were the following:

- **Regulation**: Treatment optimisation evidence should be generated across the development process, both in pre- and post-authorisation settings, including for instance as a mandatory condition for marketing authorisation approval. Representatives from national and European regulatory authorities should work together to incorporate this requirement into authorisation policies. Additionally, the legal and regulatory frameworks should be adapted, facilitating the conduct of these studies, that are of reduced risk and, therefore, should have less regulatory requirements. Lastly, the stakeholders should address other important challenges in this context, namely the implementation of the results of these studies in clinical practice and whether label changes shall apply.

- **Collaboration**: Co-ordination will be needed between regulators, HTA bodies, healthcare providers and payers, research funding bodies, patient organisations, and industry. Opportunities for collaboration between stakeholders need to be considered, working towards the feasibility of these studies. The WHO's clinical trials initiative which have given rise to the set-up of a forum for discussing global clinical trials is a unique opportunity for partnership, specifically addressing pragmatic trials. Also building on the WHO WHA75.8 resolution, WHO has demonstrated willingness to expand collaborative activities with the cancer team in the future to address many of the aspects discussed during the workshop.

- **Patient-centricity**: Patient preferences in different age groups and disease types need to be taken into account so that optimisation studies can address priorities cross all patient populations. Treatment optimisation research, properly framed and carried out focusing on patient-centric outcomes, should accelerate patient access rather than delay it. A key question to be answered is not which disease a patient has, but which patient has a disease.

- **Funding**: Funding for optimisation research is extremely limited at present. Consideration needs to be given to the role of healthcare systems and payers in providing funding.

- **Study protocols**: Major questions to be answered at the treatment optimisation stage are 1) who not to treat? 2) When to treat? 3) When treating, how to improve the therapeutic index (reduced toxicity, both for patients and for payers) and improve effectiveness? The trade-off of activity and toxicity should not be seen as a secondary metric, and neither should quality of life.

Conclusion

Concluding the workshop, Francesco Pignatti (EMA) said that there was still far too little understanding of the optimal use of cancer drugs, even older ones. But there are also instances where the effects of drugs are so marginal that there will not be much to optimise; a better drug is needed. And how much time and money to spend on optimisation? These things need to be thought through carefully on a multi-stakeholder basis.

Funding is one of the key problems. Payer funding has been successful in a number of cases, notably in The Netherlands. But to be truly successful, international research is needed, and therefore international funding required. There is a role for EU funding bodies as well as other international bodies here.

Lastly, regulators have an important role to play, even if in the beginning this is simply limited to communicating what is known and what is not known about the optimal use of a treatment, and then listening to advice on what, ideally, clinicians and patients should have and would like to have. So, communication on all these aspects is very important.

The information available on real world data in drug use should be leveraged and communicated internationally. This will not substitute for randomised trials where the question being asked deserves that type of evidence but will help significantly in the quest to find the best treatment for individual patients.

In short, optimisation questions should become more systematic, when to address them, pre vs post licensing, the role of stakeholders, including independent research. Ensuring a visible link between post-authorisation optimisation and regulatory frameworks is of critical importance and for this developing international mechanisms at the level of healthcare systems to facilitate and finance independent clinical trials must be explored. New routes for public health /pragmatic clinical trials are to be developed.

Disclaimer

This report should not be understood as the official views of The EMA or its scientific committees.