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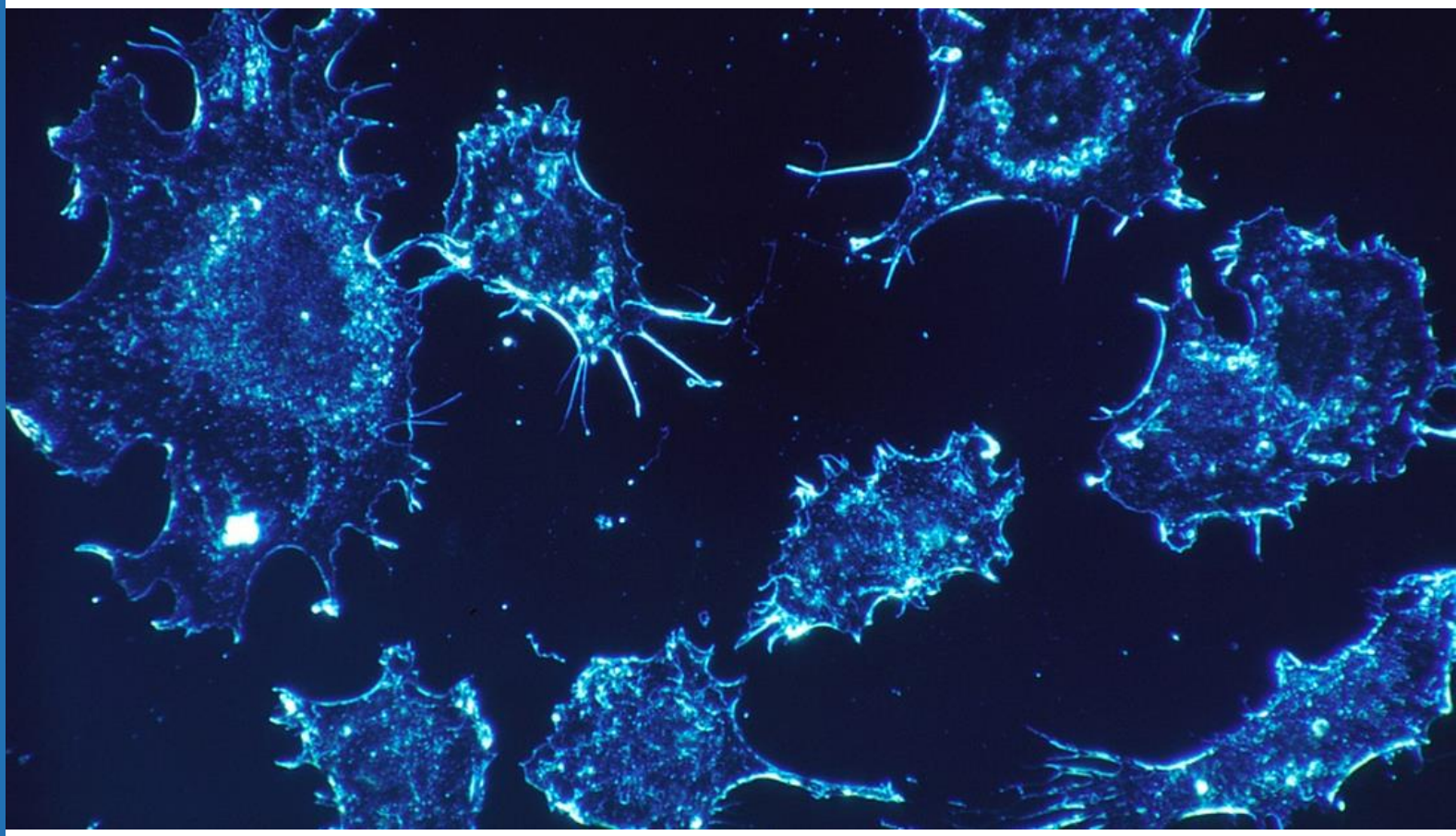

Cancer & Immunotherapy: greatest challenges and novel therapies inspiring European citizens

Annual Lecture - Summary report

17 November 2020

Online event

About FEAM, The Federation of European Academies of Medicine (www.feam.eu)

FEAM is the European platform of national Academies of Medicine, Medical Sections of Academies of Sciences, Academies of Veterinary Sciences and of Pharmacy in Europe. Its mission is to promote cooperation among them; to provide them with a platform to formulate their collective voice on matters concerning human and animal medicine, biomedical research, education, and health with a European dimension; and to extend to the European authorities the advisory role that they exercise in their own countries on these matters.

About the FEAM European Biomedical Policy Forum

The FEAM European Biomedical Policy Forum provides a platform for discussion on key policy issues for the biomedical community. The Forum is an initiative from the Federation of European Academies of Medicine (FEAM). It aims to bring together representatives from academia, research charities, industry, European and national trade associations and professional bodies, regulators, public health bodies, and patient and consumers groups. If you would like further information on the FEAM European Biomedical Policy Forum or becoming a partner, please contact info@feam.eu

Disclaimer

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Federation of European Academies of Medicine (FEAM) and its Member Academies, or the FEAM European Biomedical Policy Forum partners.

Acknowledgments

FEAM warmly thanks the speakers for their contribution to the webinar, Cancer Research UK (CRUK) for its support, Catherine Collins from Science Unscrambled SRL for moderating the event and Elisa Corritore, Forum Scientific Policy Officer, for preparing its summary report.

The overall discussion highlighted the need for multidisciplinary collaboration between public and private health sectors. Key messages delivered include:

- Promotion by Governments of initiatives that drive citizens towards healthy lifestyles at individual and societal level should be supported as 47% of cancer cases are preventable in this manner.

- Collaboration between citizens, patients, clinicians, academics, private companies, policy makers and stakeholders should be strengthened to identify research priorities collectively. Partnerships between academic institutions and private companies should be implemented to translate proof of principle in effective treatments.

- Digital transformation, artificial intelligence and data sharing represent the base of the future healthcare system and a big data plan for cancer is needed.

- Support for research and discovery of new biomarkers for cancer is needed eventually to transform cancer patient care by fulfilling the vision of Precision Medicine. A screening of the population should be implemented to identify causes of variability between individuals responding differently to treatments.

- Childhood cancer is not included in the list of top priorities for private companies as it is considered a rare disease. Most drugs currently available on the market have been developed for adult cancers. There is a need to support the implementation of new technologies for childhood cancer by developing private-public initiatives. More research and collaboration are necessary to produce CAR-T cells for different types of cancers.

- Regulatory and authorization procedures should be simplified and accelerated to promote translational research. In the EU some new drugs for cancer have not been approved yet, while they are already accepted in the US.

- The price of new therapies is often very expansive. Pharmaceutical companies are currently identifying new models to determine the right renumeration for such expansive treatments. Partnership with academies, clinicians, patients and policymakers should be strengthened to collectively identify models that provide fair renumeration based on the "real value" of a drug.

- The establishment of a comprehensive cancer infrastructure should be developed, a physical platform where European representatives across sectors could meet to discuss and find solutions to common issues by strengthening the health system capacity.

- Cancer research and screening should continue in future pandemics. The entire ecosystem of clinical trials should be more resilient in view of future pandemics.

Report of the event

Introduction

On July 2019, the EU Commissioner for Research, Science and Innovation - Carlos Moedas - officially launched the work on five major European research and innovation missions that will be part of Horizon Europe (cancer, climate change and sustainability, water and fisheries, food and agriculture, smart-cities). These European R&I missions aim to deliver solutions to some of the greatest challenges facing our world. Cancer research is one of the areas identified as a EU mission because of its pressing challenge on the current society. The number of cancer diagnosis in Europe is increasing annually; currently about 2.7 million new cases are counted in the EU-27, a number which is expected to increase of 25% by 2035 under the current trend. Data become even more alarming when taking in consideration the impact of this disease worldwide. About 25% of all cancer cases occur in Europe, while Europe represents only 10% of the world's population. In the last few decades, immunotherapy brought great promises for treating cancer, with new drugs and procedures being discovered at a very fast pace. On 17 November 2020, the FEAM European Biomedical Policy Forum convened its annual lecture to discuss - with regulators, health care professionals, researchers and patients - challenges and opportunities provided by this new emerging treatment to better control and eradicate cancer.

European policy perspective – The Cancer Mission

At the opening of the Forum annual lecture, *Walter Ricciardi* - Chair of the Horizon Europe Cancer Mission - presented the very ambitious goal that the European Commission has planned to conquer cancer. The strategic mission aims to save three million lives from cancer by 2030. Horizon 2020 was a major success for supporting cancer research, however European citizens have not been sufficiently sensitized about the effort placed by the Commission to tackle this issue. Learning from the past, the objective of the Cancer Mission - to provide directions to European research & innovation institutes - will be achieved by involving citizens, patients and stakeholders in setting research priorities and by planning, managing and evaluating projects in a collaborative way. Europe requires more coordination and better healthcare programmes for diagnosis to increase patients' quality of life. The report of the Mission Board for Cancer, handed over to the European Commission in September 2020, showed evidence that by 2030, more than three million lives can be saved, helping people living longer and better by acting on different intervention areas:

1. Understanding and supporting research from basic science to clinical and translational research. The European initiative UNCAN.eu will develop an EU-wide research programme to advance and implement personalised medicine. A genome sequencing tool – screening over 5,000 citizens across the EU - will be investigated with the potential to predict cancer.
2. Development and implementation of EU policy programmes for early diagnosis. This action aims to improve quality of life for cancer patients, survivors and citizens. 47% of cancer cases are preventable by changing lifestyle habits. Governments should promote initiatives that drive citizens towards healthy lifestyles at individual and societal level.
3. Equity of access to healthcare in all European countries. Disparities exist within and between Member States. This issue leads to inequalities in outcomes, cancer research and screening. Solidarity between countries is vital.
4. A European Cancer Disease Center will be created to centralize and share common findings. Digital transformation and data sharing represent the base for the future healthcare system.
5. Supporting implementation of new technologies in childhood cancer with the development of private-public initiatives.

The Cancer Mission will interact with the programme of the other EU Missions as common values and objectives are connected. For instance, 20% of cancer cases are indeed provoked by environmental pollution. All these initiatives will be implemented in the next seven years to conquer cancer.

Lecture

Following the intervention from the chair of the Cancer Mission, *Pierre Coulie* - Professor at the Duve Institute (UCL – Brussels) and Past President of the Belgian Royal Academy of Medicine (ARMB) – delivered his presentation describing the latest scientific developments in cancer immunotherapy and the elements that should be further investigated. Cancer immunotherapy uses the capabilities of our immune system to reject tumors or prevent their recurrence. Cytolytic T-lymphocytes (CTL) are the main effectors of our immune system for killing tumor cells. This happens with exquisite specificity. CTL can be tumor-specific, recognizing a wide array of antigens. An immune attack against the tumor can be developed spontaneously in cancer patients. Specificity and memory confer to antitumor T cells a unique therapeutic profile, with a long-lasting, tumor-specific activity. Following the activation by antigens, a T-cell response can be modulated by stimulatory or inhibitory coreceptors. By administrating agonist or blocking

antibodies, this T-cell activity can be modulated. For example, the CTL-4 and PD-1 receptors inhibit T-cell activation to avoid dramatic proliferation in physiological conditions. By blocking those receptors with specific antibodies, T-cell activity and proliferation last longer. This is the property exploited for cancer immunotherapy.

Nowadays, the use of anti-CTLA-4 (ipilimumab), anti-PD-1 (nivolumab, pembrolizumab) and anti-PD-L1 (avelumab, atezolizumab, durvalumab) antibodies is the most used cancer immunotherapy. By administrating anti-CTLA-4 (ipilimumab), about 20% of patients with advanced melanoma can survive at least 10 years following the treatment, whereas a combination of therapies with anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab, pembrolizumab) raises up to 50% the survival after 5 years. Another alternative to treat cancer patients is immunization. With active immunization, tumoral antigens are directly transferred to patients, whereas with passive immunization, antitumoral T cells are transferred to patients. These T-cells can be unmodified or genetically modified, for example the Chimeric Antigen Receptor - T cells or CAR-T cells that provided spectacular results in patients with CD19+ B cell leukemias. Despite promising results observed so far, immunotherapies are not equally efficient in all types of cancers and not all patients respond positively to treatments. One of the major challenges resides on the level of toxicity. CTLA-4 or PD-1 blockades can be followed by serious immune-related side effects. After transfusion, anti-CD19 CAR T-cells eliminate all B cells in the recipient, both normal and tumoral ones. In some cases, they can induce neurotoxicity due to the presence of rare CD19+ cells in the brain. Another issue is resistance to immunotherapy, either following lower expression of antigens or due to the promotion of local immunosuppression. Currently, many combinations of PD1-blockade and various means to alleviate immunoresistance are being explored in preclinical and clinical settings.

Panel discussion

Following the keynote lecture, a panel discussion was initiated to gather views from experts across sectors. *Bart Neyns*, Head of the Department of Medical Oncology at Universitair Ziekenhuis Brussel and clinical professor of the Faculty of Medicine at Vrije Universiteit Brussel (VUB), provided the clinical perspective on the benefits that immunotherapy can bring to patients. A large heterogeneity between patients exists in the way they respond to immunotherapies. An important requirement to reach successful therapies is given by the level of immunogenicity of targeted tumors. If the tumor is sufficiently immunogenic, the chances to obtain successful results are much higher. However, despite the knowledge acquired over the last years, it is not possible yet to predict which

patient will respond better compared to others. Some patients have been cured, some of them are still living after 15 years from the first treatment with checkpoint inhibitory drugs, others are in complete remission. A large-scale screening of the population should be conducted to identify the cause of such variability between individuals.

Denis Lacombe - Director-General of the European Organization for Research and Treatment of Cancer - also highlighted the importance to select suitable patients and the need to find a good balance between efficiency and toxicity for a certain therapy. Over the past years, clinical research has completely changed and new approaches will emerge. A better understanding and an optimization of the procedures used to administer such drugs is needed. The issue of encountering high-level toxicity during treatments is an important challenge to be addressed.

In line with the comment of Denise Lacombe, Pierre Coulie highlighted the need for a supportive regulatory process for research and discovery of new biomarkers. Complex authorization papers are often required for simple procedures. This complexity represents an obstacle for translational research. In the EU some drugs for cancer have not been approved yet, while they are already accepted in the US.

Michael Zaiac, Head of the Oncology Global Drug Development at Novartis, addressed the question of pricing. Pharmaceutical companies are in the process of identifying the right strategy to reimburse fairly such expansive treatments. A model for single-shot treatments is not available yet. Partnership with academics, clinicians, patients and policymakers should be strengthened to identify collectively models that provide adequate reimbursement based on the "real value" of a drug.

Franco Locatelli, Head of the Department of Pediatric Haematology and Oncology at the IRCCS Bambino Gesù Children's Hospital, and Full Professor of Pediatrics at the Sapienza University of Rome, noted that the best results had been obtained by using immune checkpoint inhibitory therapies for Hodgkin lymphoma. In pediatric cancers, the same approach showed more limitations. By contrast, using either CAR-T cells or Bi-specific T-cell engagers (BiTEs), greater results - with longer-term persistency - had been observed in childhood malignancies compared to adulthood. More research and collaboration are necessary to produce CAR-T cells for other types of pediatric cancers. Privileged partnerships, alliances between academic institutions and private companies should be strengthened to translate proof of principle in effective treatments and to tackle unmet medical needs. Novel platforms should be employed for CAR-T therapies to have quick access to off-of-the-shelf drugs from allogeneic donors.

Pam Kearns, Senior Clinical Advisor for Cancer Research UK (CRUK), explained that data for childhood cancers cannot be extrapolated directly from trials conducted on adults. B-cell malignancies are the most common childhood types of cancer targeted by immunotherapy. However, drug development is still proceeding with some difficulties for different reasons:

1. The biology of a childhood cancer is different from the one observed in adulthood. The innate immune system is different as well as the levels of antigens.
2. Childhood cancer is not included in the top list of priorities for private companies as it is considered a rare disease. Most of the drugs currently available on the market have been developed for adult cancer only.
3. Partnerships between industry, academia and patient groups are needed. Complex issues linked to immunotherapy, such as the evaluation of toxicity effects, can be tackled by engaging with patients and families. The establishment of a consortium of multi-stakeholders could provide opportunities to discuss new drug developments.

Ralf Herold, Senior Scientific Officer for the European Medicines Agency (EMA), commented on the issue of delayed approvals for drugs comparing to the US regulatory system. The EMA is working with EU national competent authorities to improve regulating new cancer treatments and to tailor safety investigations. In 2017, the International Council for Harmonisation (ICH) started the ongoing review of the Good Clinical Practice (GCP) guidelines to better support regulation for clinical trials, which is an opportunity to engage for high-quality clinical trials and to make them more patient-centred. The requirements for authorization procedures are equivalent for all types of originator drugs, and similar even in regions in which the regulatory framework is different. Indeed, some products are authorized in Europe later than in the US. This is a situation that should be addressed in Europe by collaboration.

Lieve Wierinck, former MEP and member of the board of DiCE (Digestive Cancers Europe), provided her opinion on the current policy context for cancer research in Europe. Today, the EU is finally considering cancer as a priority issue. An initiative as the Horizon Europe Cancer Mission covering research and prevention as well as prevention and screening is a first. There are issues that must still be addressed, such as the need to find new biomarkers, the implementation of personalized medicine and the need to make immunotherapies affordable for all citizens. Collaboration between public and private institutions at EU and national levels is

fundamental to share experience and good practices. For instance, the Erasmus system should be available not only for students but also for specialists and professionals. In connection with this comment, Denis Lacombe also raised the issue of improving collaboration between institutions by creating physical infrastructures and virtual platforms where European representatives from across the sectors could easily meet to discuss common issues.

Fabrizio Sestini, Senior Expert in Digital Social Innovation at DG CONNECT - European Commission, provided an important opinion from a patient's perspective. Today, European citizens know more about treatments than causes of cancer and this issue should be addressed. Citizens should be better informed about lifestyle habits to adopt to prevent cancer. Common platforms and digital tools for sharing data should be created as they could significantly contribute to the progress in research and personalized treatments. Fabrizio Sestini also wondered what regulatory changes could be brought in to tackle the issue of high costs for immunotherapy treatments.

The impact of COVID-19 on cancer research

According to Bart Neyns, healthcare professionals were reallocated to different departments during the COVID-19 pandemic. Clinical research was severely affected as recruitment processes for clinical trials were suspended by hospitals and institutions. George Griffin - President of FEAM - explained that in the UK cancer screening was negatively affected by the pandemics. Early diagnosis and prevention are crucial. From an industry perspective, Michael Zaiac highlighted that the supply of innovative medicines - unrelated to COVID-19 - was not affected given the sufficient emergency stocks in place. However, companies encountered a high demand of generic drugs. Important collaborations with Governments were established to distribute free medicines for COVID-19. Franco Locatelli noted that the pandemic negatively impacted basic and translational research in his own institution by prolonging timelines of experimental projects. For clinical trials, the impact was limited and a new way to enroll patients for clinical trials was implemented. Nevertheless, the major cancer pediatric associations expressed their concerns during the pandemics by reporting cases in which delays in diagnosis and treatments led to dramatic consequences that compromised the chance of survival in young patients. Pamela Kearns raised the issue of how the pandemic heavily impacted financial support for cancer research. Funds for CRUK research programmes were drastically reduced from an overall annual baseline of 400 million to 250 million pounds. The *Cancer Grand Challenges* initiative, a global funding platform, was recently launched by the CRUK and the National Cancer

Institute to support research, innovation, and prevention by promoting international collaborations.

Additional material available:

1. Programme of the event
2. Recording of the event

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