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Developments from the Cancer Medicines Forum and impact across cancer field:

Is the continuum from development into healthcare becoming a reality?

Denis Lacombe, MD, MSc
EORTC, CEO
Brussels, Belgium

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original reports

Standard Anthracycline Based Versus Docetaxel-Capecitabine in Early High Clinical and/or Genomic Risk Breast Cancer in the EORTC 10041/BIG 3-04 MINDACT Phase III Trial

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THE LANCET
Oncology

Estimation of Distant Metastasis–free Survival in Trials of Adjuvant Therapy for Melanoma

TO THE EDITOR: Recently, trials of adjuvant therapy for melanoma in which therapies that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death 1 (PD-1), or BRAF and MEK are assessed have reported positive results in terms of relapse-free survival and distant metastasis–free survival.[1-4] The European Organization for Research and Treatment of Cancer (EORTC) 18071 trial[1] compared ipilimumab with placebo in patients with resected stage III melanoma; the CheckMate 238 trial[2] compared nivolumab with ipilimumab in patients with resected stage IIIB, IIIC, or IV melanoma; and the COMBI-AD trial (Nov. 9, 2017, issue)[3,4] compared dabrafenib plus trametinib with placebo in patients with stage III melanoma with *BRAF* mutations.

The trials defined relapse-free survival as the time from randomization until first recurrence (local, regional, or distant metastasis) or death (or second primary cancer in the COMBI-AD

N ENGL J MED 380;14 NEJM.ORG APRIL 4, 2019

FAST TRACK — ARTICLES | VOLUME 6, ISSUE 12, P937-944, DECEMBER 01, 2005

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Health-related quality of life in patients with glioblastoma: a randomised controlled trial

Dr Martin JB Taphoorn, MD • Roger Stupp, MD • Corneel Coens, MSC • David Osoba, MD • Rolf Kortmann, MD • Martin J van den Bent, MD • et al. Show all authors

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VOLUME 35 · NUMBER 15 · MAY 20, 2017
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Ten-Year Progression-Free and Overall Survival in Patients With Unresectable or Metastatic GI Stromal Tumors: Long-Term Analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels

Paolo G. Casali, John Zalcberg, Axel Le Cesne, Peter Reichardt, Jean-Yves Blay, Lars H. Lindner, Ian R. Judson, Patrick Schöffski, Serge Leyvraz, Antoine Italiano, Viktor Grünwald, Antonio Lopez Pousa, Dusan Kotasek, Stefan Sleijfer, Jan M. Kerst, Piotr Rutkowski, Elena Fumagalli, Pancras Hogendoorn, Saskia Litière, Sandrine Marreaud, Winette van der Graaf, Alessandro Gronchi, and Jaap Verweij on behalf of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group

European Journal of Cancer 119 (2019) 1–10
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Original Research

Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial

Alexander M.M. Eggermont [a,*], Vanna Chiarion-Sileni [b], Jean-Jacques Grob [c], Reinhard Dummer [d], Jedd D. Wolchok [e], Henrik Schmidt [f], Omid Hamid [g], Caroline Robert [h], Paolo Antonio Ascierto [i], Jon M. Richards [j], Celeste Lebbe [k], Virginia Ferraresi [l], Michael Smylie [m], Jeffrey S. Weber [n], Michela Maio [o], Fareeda Hosein [p], Veer Alessandro Testori [s,1]

The NEW ENGLAND JOURNAL of MEDICINE

Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial

Mila Donker, Geertjan van Tienhoven, Marieke E Straver, Philip Meijnen, Cornelis J H van de Velde, Robert E Mansel, Luigi Cataliotti, A Helen Westenberg, Jean H G Klinkenbijl, Lorenzo Orzalesi, Willem H Bouma, Huub C J van der Mijle, Grard A P Nieuwenhuijzen, Sanne C Veltkamp, Leen Slaets, Nicole J Duez, Peter W de Graaf, Thijs van Dalen, Andreas Marinelli, Herman Rijna, Marko Snoj, Nigel J Bundred, Jos W S Merkus, Yazid Belkacemi, Patrick Petignat, Dominic A X Schinagl, Corneel Coens, Carlo G M Messina, Jan Bogaerts, Emiel J T Rutgers

Summary

Background If treatment of the axilla is indicated in patients with breast cancer who have a positive sentinel node, axillary lymph node dissection is the present standard. Although axillary lymph node dissection provides excellent regional control, it is associated with harmful side-effects. We aimed to assess whether axillary radiotherapy provides comparable regional control with fewer side-effects.

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EORTC Clinical Trial in Perspective

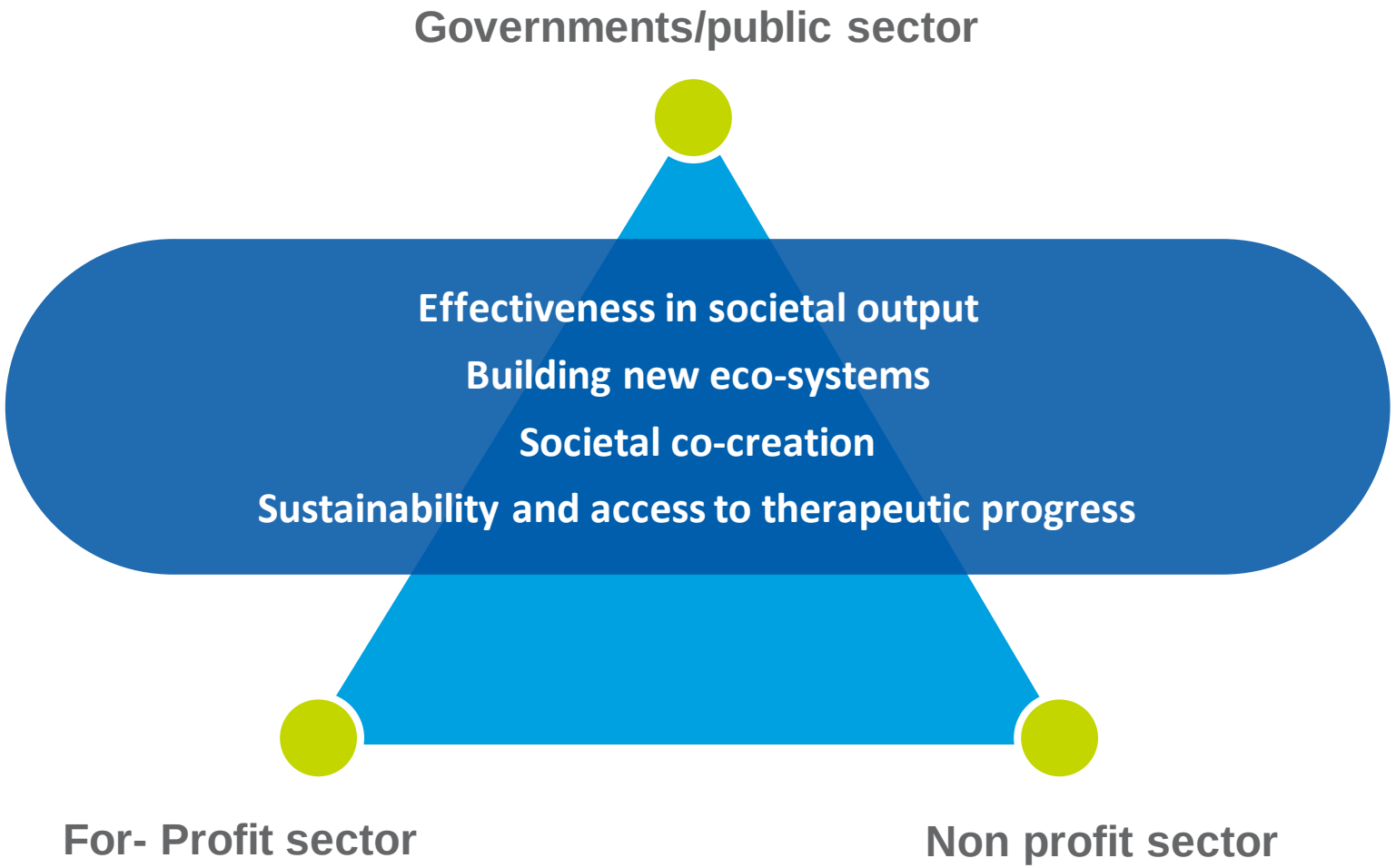
A multinational, multi-tumour basket study in very rare cancer types: The European Organization for Research and Treatment of Cancer phase II 90101 'CREATE' trial

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

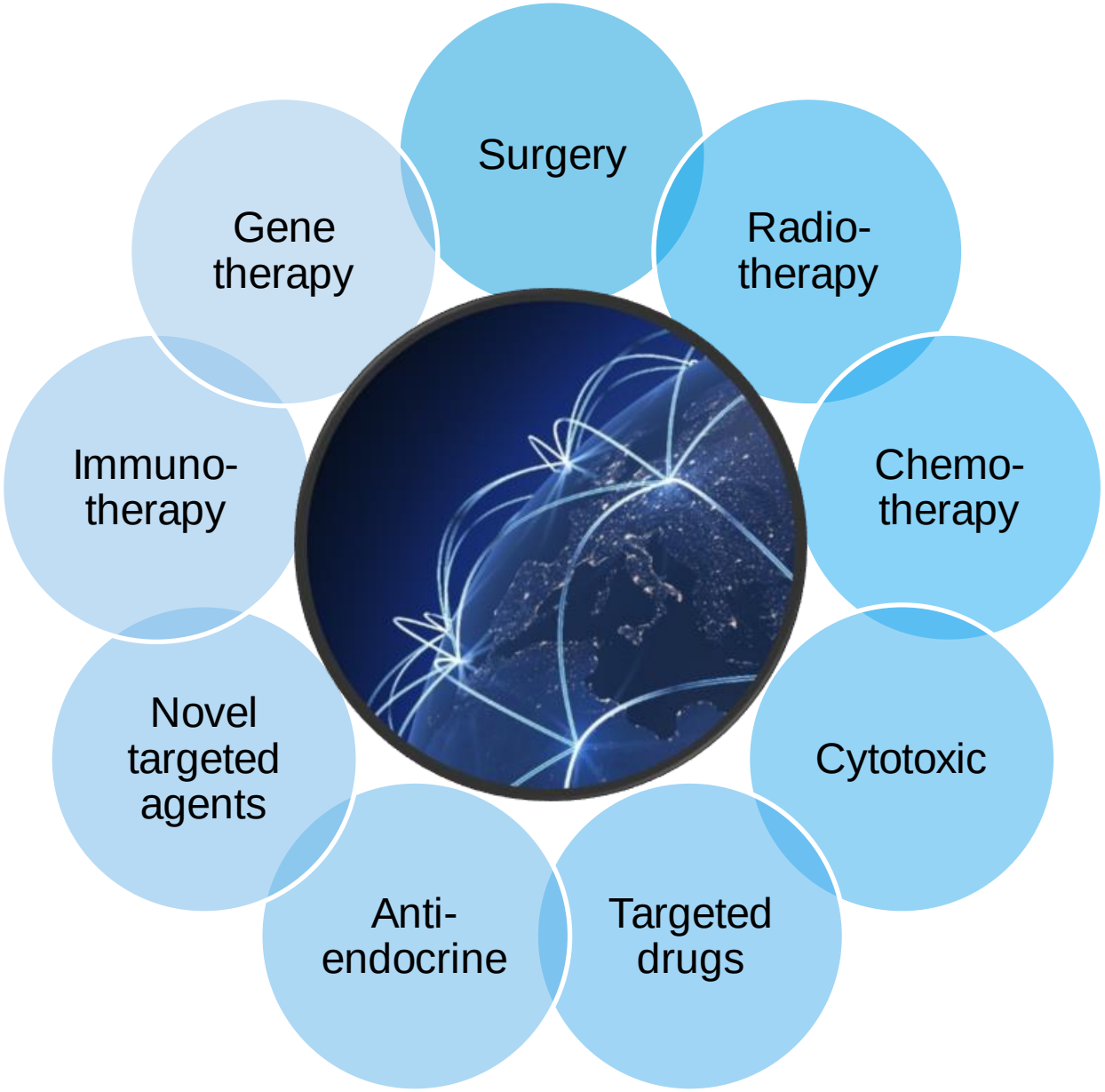
The eco-system….a societal balance?

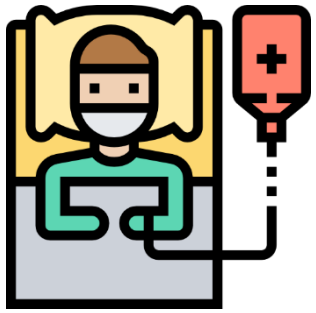


The Future is Combinatorial

Multidimensional data

Authorisation





Access

Optimal access

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The concept of treatment Optimisation

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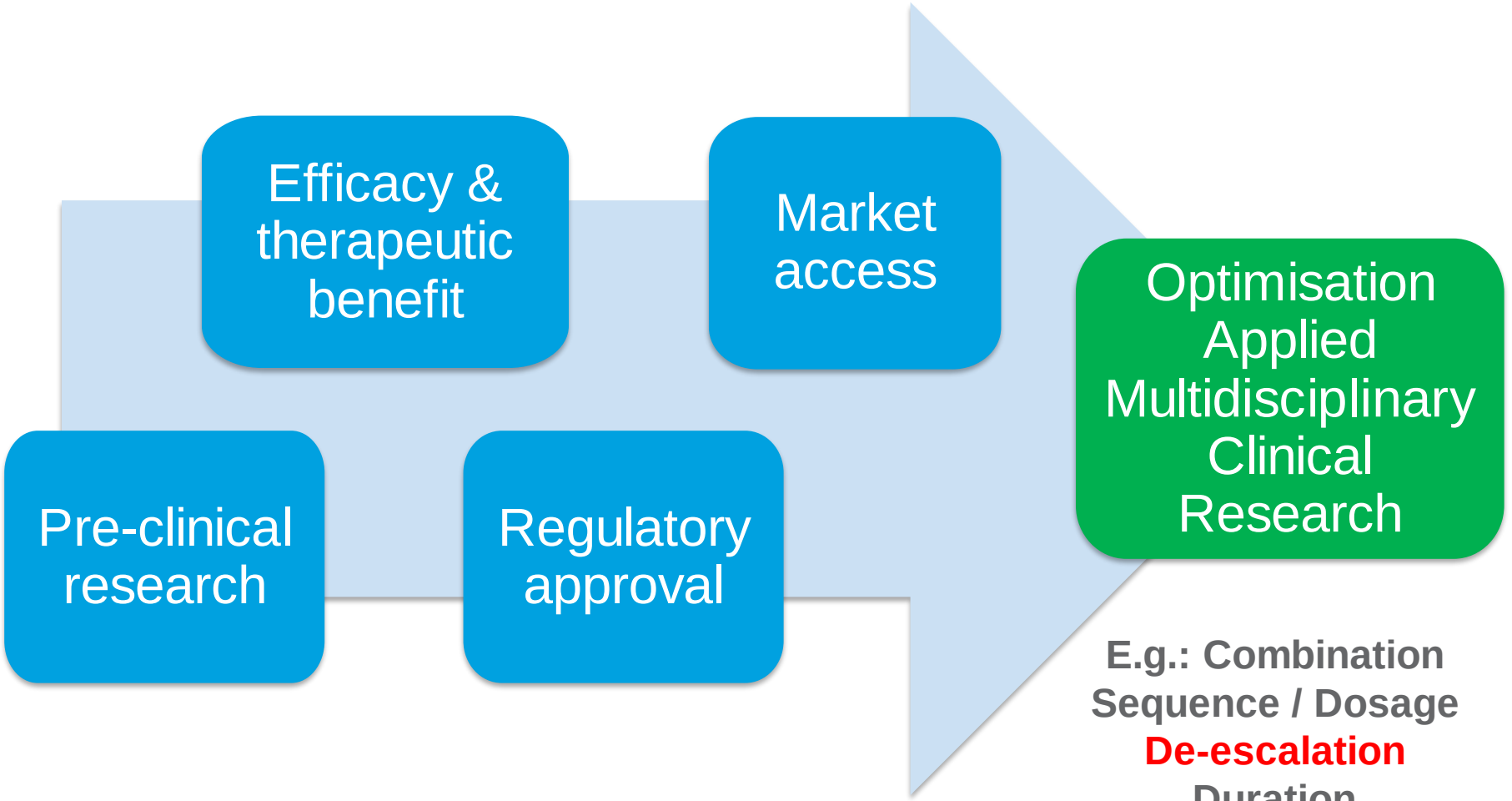
The work starts when a technology reaches the market.



Health System Optimisation

Health Services & Implementation Research

Access / costs
Guidelines
Cancer control plans

Clinically relevant endpoints for patients

Impact of registration of 4 new hormones in newly diagnosed metastatic prostate cancer

Agent	Study	n	HR (95%CI)	p
Abiraterone /P	LATITUDE	1199	0.62 (0.51 - 0.76)	<0.001
	STAMPEDE ITT	1917	0.63 (0.52 - 0.76)	<0.001
	STAMPEDE M1	1002	0.61 (0.49 - 0.75)	<0.001
	PEACE 1 ITT	1172	0.82 (0.69-0.98)	0.030
	PEACE 1 Docetaxel	710	0.75 (0.59-0.95)	0.017
Apalutamide	Titan	1052	0.65 (0.53 - 0.79)	<0.001
Enzalutamide	ENZAMET	1125	0.67 (0.52 - 0.86)	0.002
	ARCHES	1150	0.66 (0.53-0.81)	<0.0001
Radiotherapy	STAMPEDE RT	2061	0.92 (0.80 – 1.06)	0.266

- 7 trials
- 7 used continuous administration, 0 intermittent regimen.
- 20-30% long-term Grade 3-4 TEAE
- Cost increased 15k to 150k per patients
- No study so far looking a de-escalation, intermittent setting.

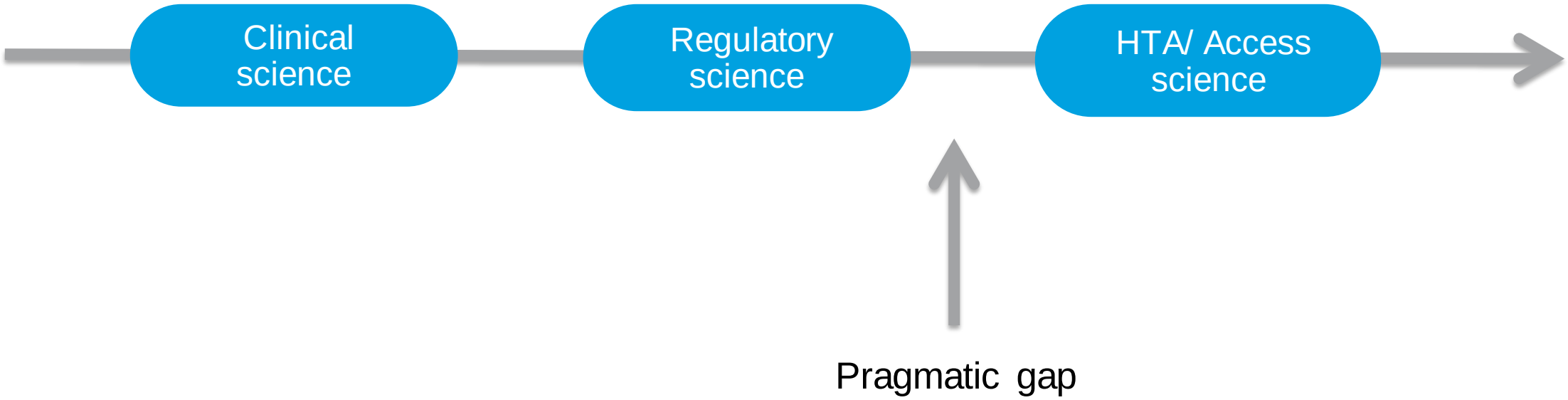
An example from surgical oncology: Effect of a Randomized Controlled Trial on Surgery for Cervical Cancer

- Minimally invasive (robotic or laparoscopic) surgery (MIS) had been adopted for cervical cancer despite lack of evidence
- RCT comparing MIS vs. open hysterectomy for early stage cervical cancer favoured open surgery: the principle of **medical reversal**

  Ramirez et al. J. Med. 2018;379:1895-904
- 2021: Effect of the **practice-changing RCT**, with variability among providers

  PJ Lewicki et al. N Engl J Med 2021;384:1669-1671D

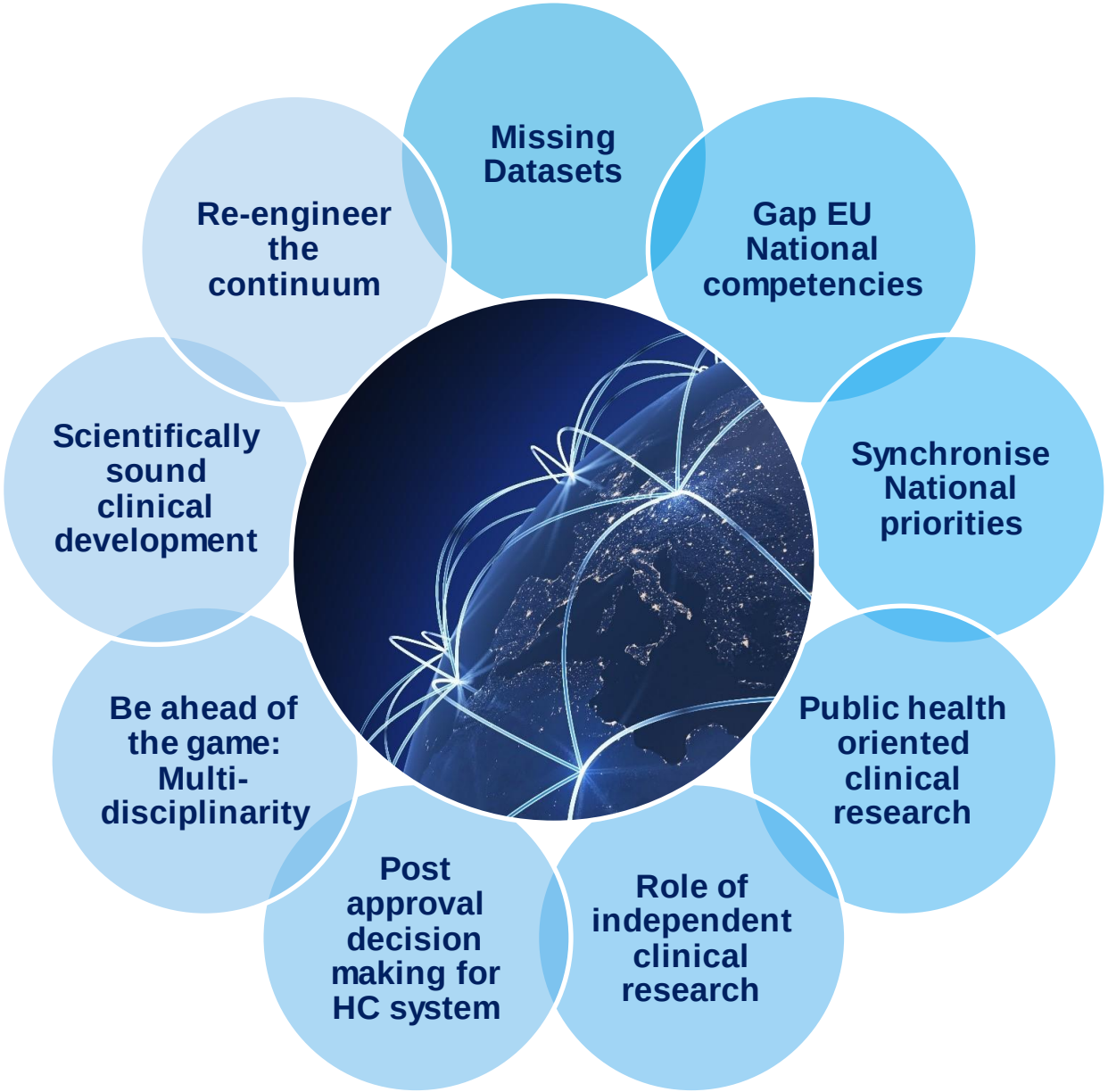
A new continuum to be set up ….Re-engineer….



Key questions we are addressing to policy makers

- How to recognise and structure the independent agenda in this continuum?
- How to address the gap supra-national versus national competences?
- If treatment optimisation is to be structured in the process: when, how and who?
- How do we re-engineer the sequence of relevant questions from drug development into access?
- How do we priortise questions and select the most appropriate methodology?
- How do we finance a multidisciplinary independent agenda at the European level?

Need for strategic intelligence approaches



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The Cancer Medicine Forum

The future of cancer therapy

Objectives of the Cancer Medicines Forum

To serve as a direct and official communication channel with the academic community in oncology

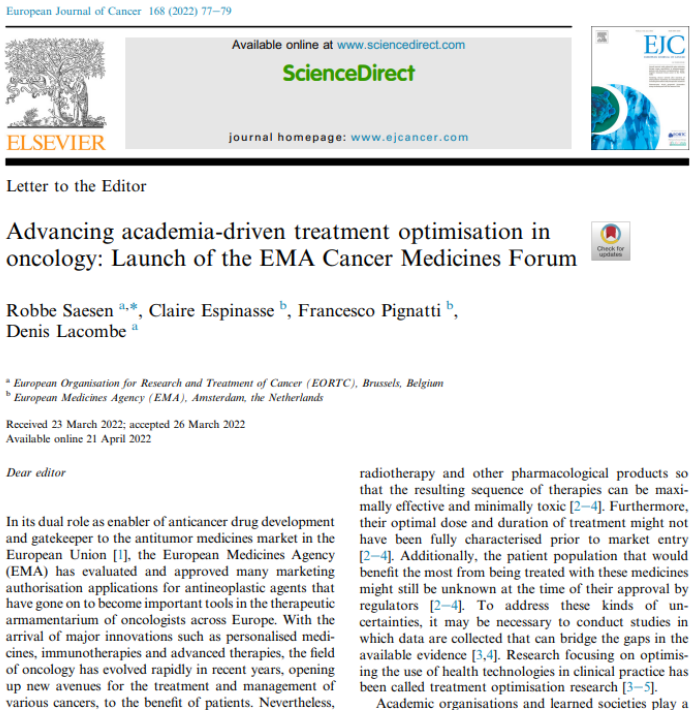
To identify key research questions and best methodological approach to improve the clinical use of cancer medicines

To discuss the uptake of academic work in the wider context of regulatory decision-making in oncology

Treatment optimisation

Launch of the Cancer Medicines Forum

- 1st CMF meeting held on 31st March 2022
- 2nd meeting held on 28th June 2022
- 3rd meeting held on 20th December 2022
- Chaired by EORTC- Denis Lacombe and EMA-Francesco Pignatti



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Letter to the Editor

Advancing academia-driven treatment optimisation in oncology: Launch of the EMA Cancer Medicines Forum

Robbe Saesen [a,*], Claire Espinasse [b], Francesco Pignatti [b], Denis Lacombe [a]

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Dear editor

In its dual role as enabler of anticancer drug development and gatekeeper to the antitumor medicines market in the European Union [1], the European Medicines Agency (EMA) has evaluated and approved many marketing authorisation applications for antineoplastic agents that have gone on to become important tools in the therapeutic armamentarium of oncologists across Europe. With the arrival of major innovations such as personalised medicines, immunotherapies and advanced therapies, the field of oncology has evolved rapidly in recent years, opening up new avenues for the treatment and management of various cancers, to the benefit of patients. Nevertheless, radiotherapy and other pharmacological products so that the resulting sequence of therapies can be maximally effective and minimally toxic [2–4]. Furthermore, their optimal dose and duration of treatment might not have been fully characterised prior to market entry [2–4]. Additionally, the patient population that would benefit the most from being treated with these medicines might still be unknown at the time of their approval by regulators [2–4]. To address these kinds of uncertainties, it may be necessary to conduct studies in which data are collected that can bridge the gaps in the available evidence [3,4]. Research focusing on optimising the use of health technologies in clinical practice has been called treatment optimisation research [3–5].

Academic organisations and learned societies play a

Cancer Medicines Forum: kick-off meeting

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- Event summary

Date: 31/03/2022
Location: Online, 08:30 - 12:30 Amsterdam time (CEST)

Event summary

This first meeting of EMA's Cancer Medicines Forum looked at challenges around research into optimising cancer treatments. These included dose-optimisation and similar approaches tailored to the characteristics of the patient and the disease.

The CMF aims to explore how EMA can contribute towards addressing remaining uncertainties about the use of cancer medicines in clinical practice.

The forum brings together representatives of **academic organisations** from EMA's Healthcare Professionals Working Party and the European medicines regulatory network.

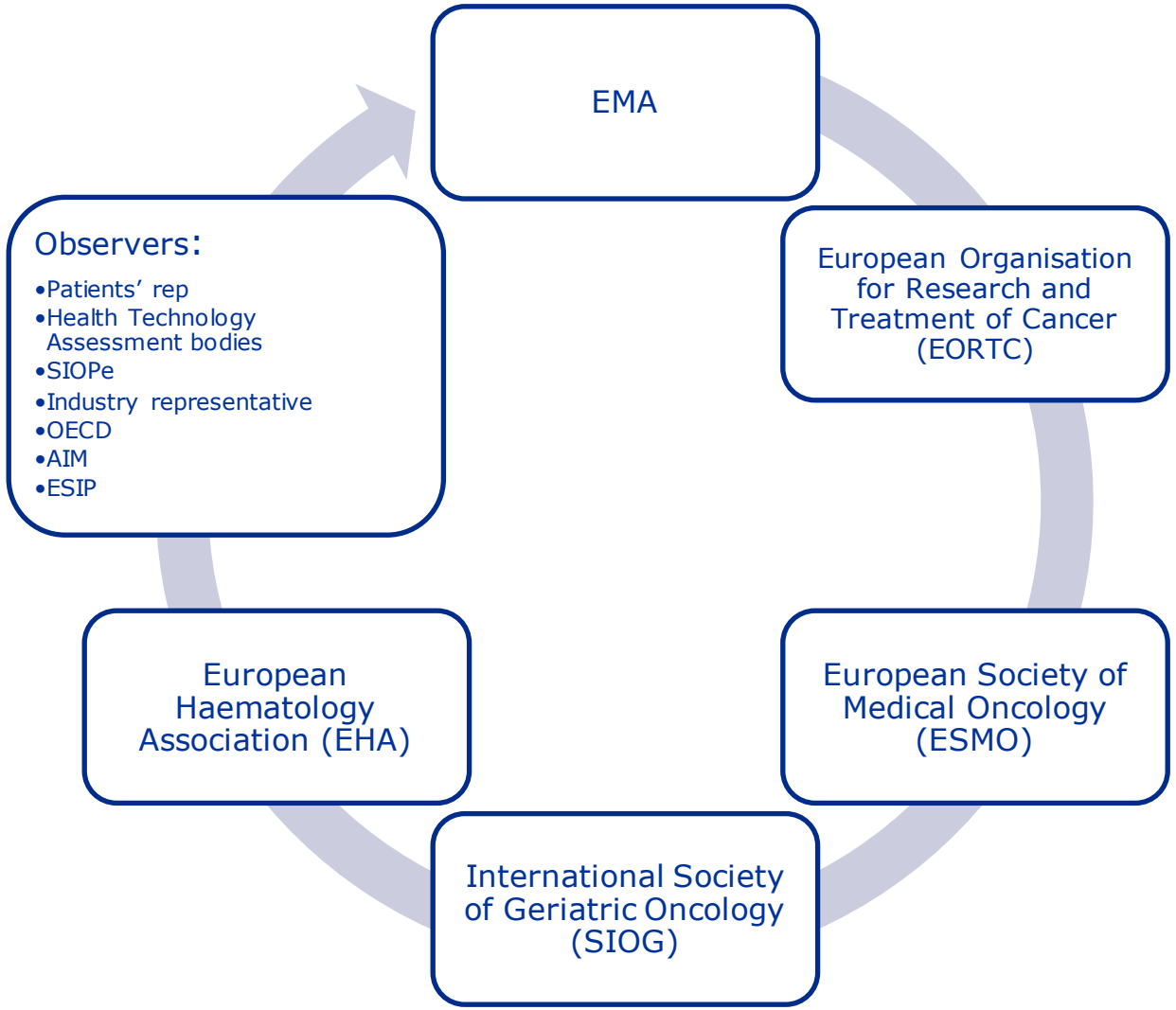
The results of discussions will support the prioritisation of actions to fight cancer in EMA's Regulatory Science Strategy to 2025 and Academia Collaboration Matrix Action Plan.

The meetings of the forum are by invitation only.

EMA launched the CMF together with the European Organisation for Research and Treatment of Cancer (EORTC) in March 2022.

EMA will review the composition and procedures of the forum after a one-year pilot phase.

Focus on academia with other stakeholders



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Key issues to be addressed by the CMF

Identification and labelling of TO questions	No structural approach to address the key critical questions for integrating a new drug into treatment strategies.	Set up a "mechanism" where field (patient-doctor- access) priorities are identified and agreed upon
Methodology	Which optimal methodology/design for which questions	Bridge the relevant questions and the methodology to apply Early access to innovation while mandating relevant TO agenda of studies Educate stakeholders to accept large simple pragmatic programs (few eligibility criteria)
Who	Currently nobody is in charge for TO resulting in absence of datasets	Analyze what falls in the remit of the commercial sector or not Build on independent solutions and infrastructure for access decisions into the healthcare systems
How	National: reach and impact not large enough International: organisational challenges	Bring evidence to healthcare systems decisional bodies that patient-centric and society-centric research can go together Ensure collegial endorsement for free access to agents which are already available in the health systems
When	Structuring TO questions in the process around marketing application: the earlier, the better	Explore what can be done pre-marketing (i.e. EMA scientific advice) Ensure expedited processes to run TO optimization trials when components of the trials are already available in the healthcare systems. Control efficiently the window of opportunities
Recruitment	Competition with industry-sponsored trials of novel agents if conducted as separate studies Loss of (perceived) equipoise in the post-approval setting	Structure the process of drug development versus TO trials Pragmatic studies with broad inclusion of participants, more attractive to oncologists Educate stakeholders to understand remaining uncertainty and value of additional trials to optimise patient treatment
Regulatory and legal aspects	High regulatory burden due to lack of separate provision for academic trials in Clinical Trials Regulation High regulatory burden due to the IMP status of the investigational drugs if used outside of the label Adherence to multiple different country-level laws and regulations if conducted as an international study	Legislative changes, e.g. separate provision for academic trials, change in definition of IMP Exemptions from existing laws and regulations Granting free access to IMPs which are already in the healthcare system for a given indication (independent of the stage of the disease independent) Cut red tape of undue bureaucracy
Datasets and reporting	Regulatory and access datasets are complementary Access datasets are not delivered efficiently or at all. Reporting to HTA/payers is not systematically in place	Ensure an appropriate continuum of regulatory into access science with complementarity of stakeholders Deliver efficient TO datasets limited to the key variables of relevance Sponsorship by independent, non-commercial parties to ensure public availability and accessibility of the data generated by TO/access studies
Funding	Lack of industry support due to lack of incentives No reimbursement of the investigational drugs since they are used outside of the label Country-level funding sources difficult to combine and coordinate for international studies Wasted resources in the healthcare systems due to lack of information on TO	New partnership with industry to conduct studies in the post-approval setting, as feasible and relevant Access to the investigational drugs through legislative changes or exemptions (doing a de-escalation study by itself cuts costs of the health care systems) Gain-sharing programs to reward countries that provide funding Public funding of TO trials through the savings by de-escalation of treatments.

Vision

Treatment optimization: research driven by academia, that should deliver the critically missing information needed for clinical practice and society.

It positions strategically, free of commercial of interest, in complement to the deliverables of the commercial sector and delivers sharable datasets with public health stakeholders

It is structured in the continuum of treatment development into access. The forms and the methods to achieve it take into account the interests and the needs of all stakeholders

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A European Imbalance

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World Health Organization

SEVENTY-FIFTH WORLD HEALTH ASSEMBLY
Agenda item 16.2

WHA75.8
27 May 2022

Strengthening clinical trials[1] to provide high-quality evidence on health interventions and to improve research quality and coordination

The Seventy-fifth World Health Assembly,