Personalised treatments from regulatory perspective

CDDF multi-stakeholder workshop

New modalities in cancer drug development

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Outline

1. Personalised medicine and regulatory framework in EU
2. Biomarkers as means of personalisation in oncology and non-oncology therapeutic areas
3. Biomarkers and biomarker assays/tests in the context of medicinal products development and assessment
4. Relevant guidance
5. Key messages

Personalised medicine (PM)

Definition of European Council (2015)

- There is no commonly agreed definition of the term “personalised medicine”.
- It is widely understood that PM refers to a **medical model using characterisation of individuals’ phenotypes and genotypes** (e.g. molecular profiling, medical imaging, lifestyle data):
    - for **tailoring** the **right therapeutic strategy** for the **right person** at the **right time;**
    - and/or to determine the **predisposition** to disease and/or to deliver timely and targeted **prevention**.

https://health.ec.europa.eu/medicinal-products/personalised-medicine_en

Personalised medicine (PM)

Definition of European Council (2015)

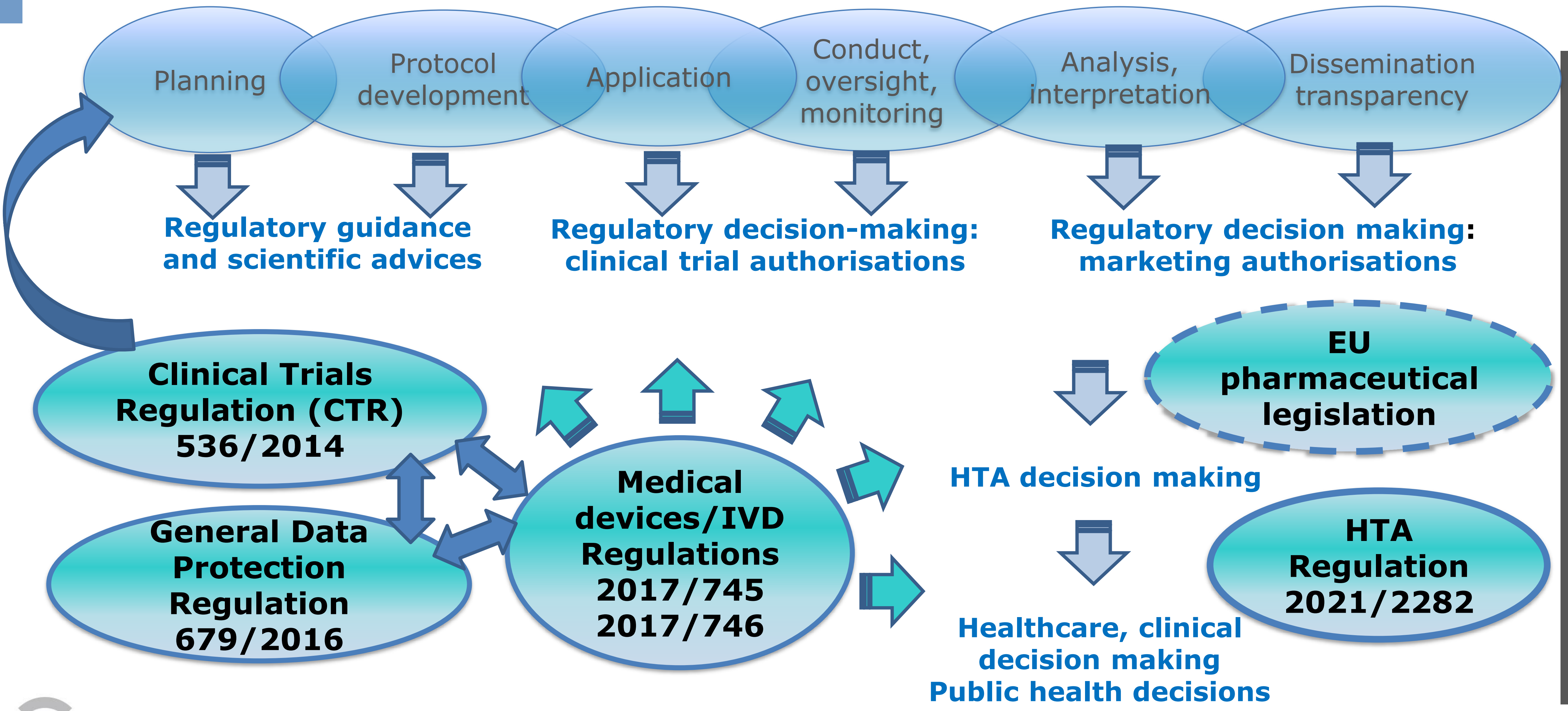
- PM relates to the broader concept of **patient-centred care**, which takes into account that, in general, healthcare systems need to better respond to patient needs.

- Individuals and health systems face new challenges with the development of PM, including **balancing its risks and benefits** while also considering its **ethical, financial, social and legal implications**, particularly regarding pricing and reimbursement, data protection and public interest in processing personal data.

- The development and implementation of PM goes hand in hand with the development of relevant **diagnostics**.

https://health.ec.europa.eu/medicinal-products/personalised-medicine_en

Evolving regulatory framework in EU



Biomarkers in the context of medicinal product life cycle

Biomarker

is commonly defined as a characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions.

Predictive role: ability to identify and select patients that are more likely to experience a certain clinical outcome to a specific therapy

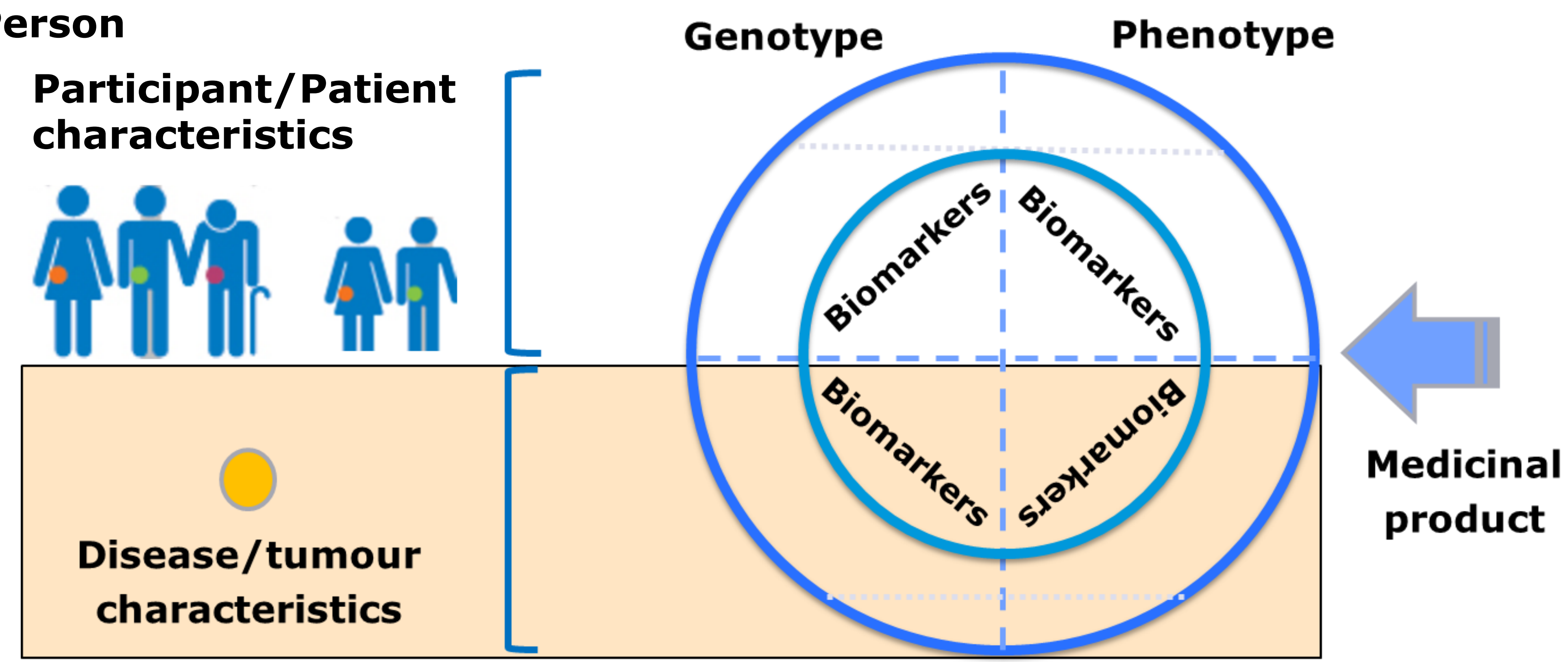
(such as efficacy- or safety-related outcome)

Prognostic role: ability to identify and select patients that are more likely to experience a certain outcome, regardless of treatment

Diagnostic role: ability to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease

https://www.ema.europa.eu/en/evaluation-anticancer-medicinal-products-scientific-guideline

Biomarkers (BMs) in oncology and non-oncology therapeutic areas



Exposure

Comedications
Socio-economic factors
Environmental exposure

Combinations with non-pharmacological treatment

Disease-related

- Diagnostic
- Prognostic
- Susceptibility/risk
- Monitoring

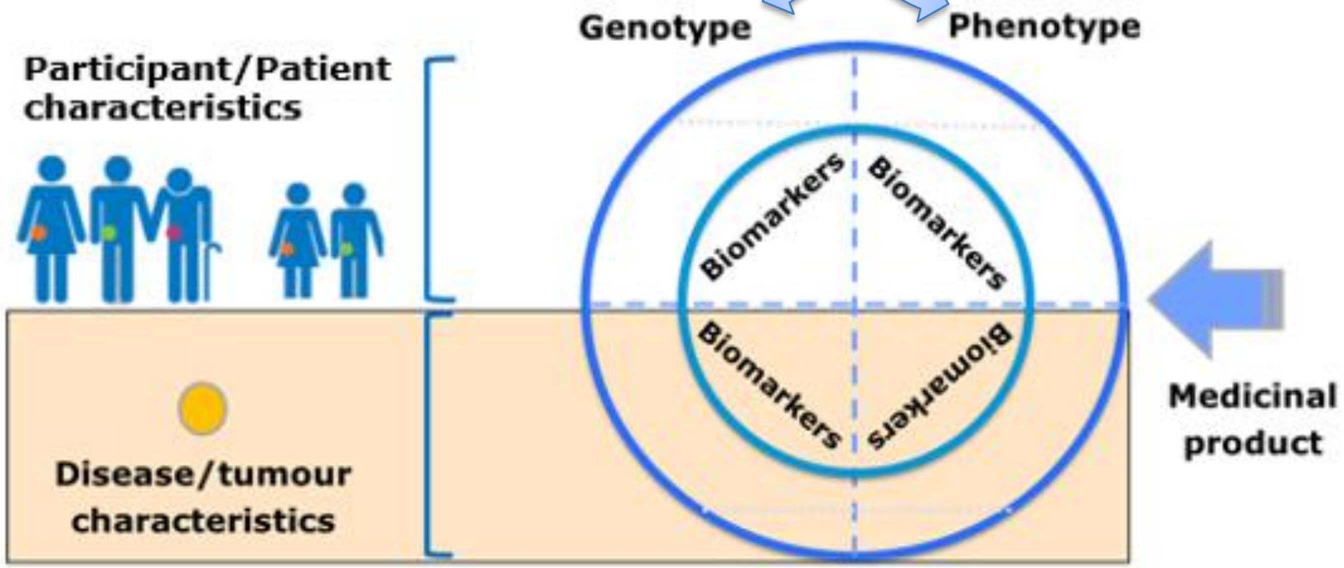
Treatment - related

-Predictive
-Safety
-Pharmacodynamic

Biomarkers and biomarker assays in oncology: examples

Genetic polymorphisms e.g. in cytochrome P450, germline mutations predisposing to cancer

Phenotypic characteristics of patients measures by biomarker assays



Mono- (poly-) genic biomarkers and assays (e.g. NGS, ctDNA etc)

Other molecular biomarkers and assays (epigenetic, proteomic, multi-omics etc.)

Biomarkers (one or multiple) and assays (one or multiple, multiplex) used for treatment with medicinal products (one or multiple) in certain indications (one or multiple)

Context of biomarkers use in medicinal product (MP) development

Context of use:

Biomarker role/category + **intended use** in medicinal product development, e.g.

Diagnostic biomarker **used to** define eligibility criteria in clinical trials (inclusion/exclusion)

Prognostic biomarker **used to** - stratify patients in a randomised clinical trial
- enrich patient population for enrolment in clinical trial (e.g. patients with higher risk of relapse)

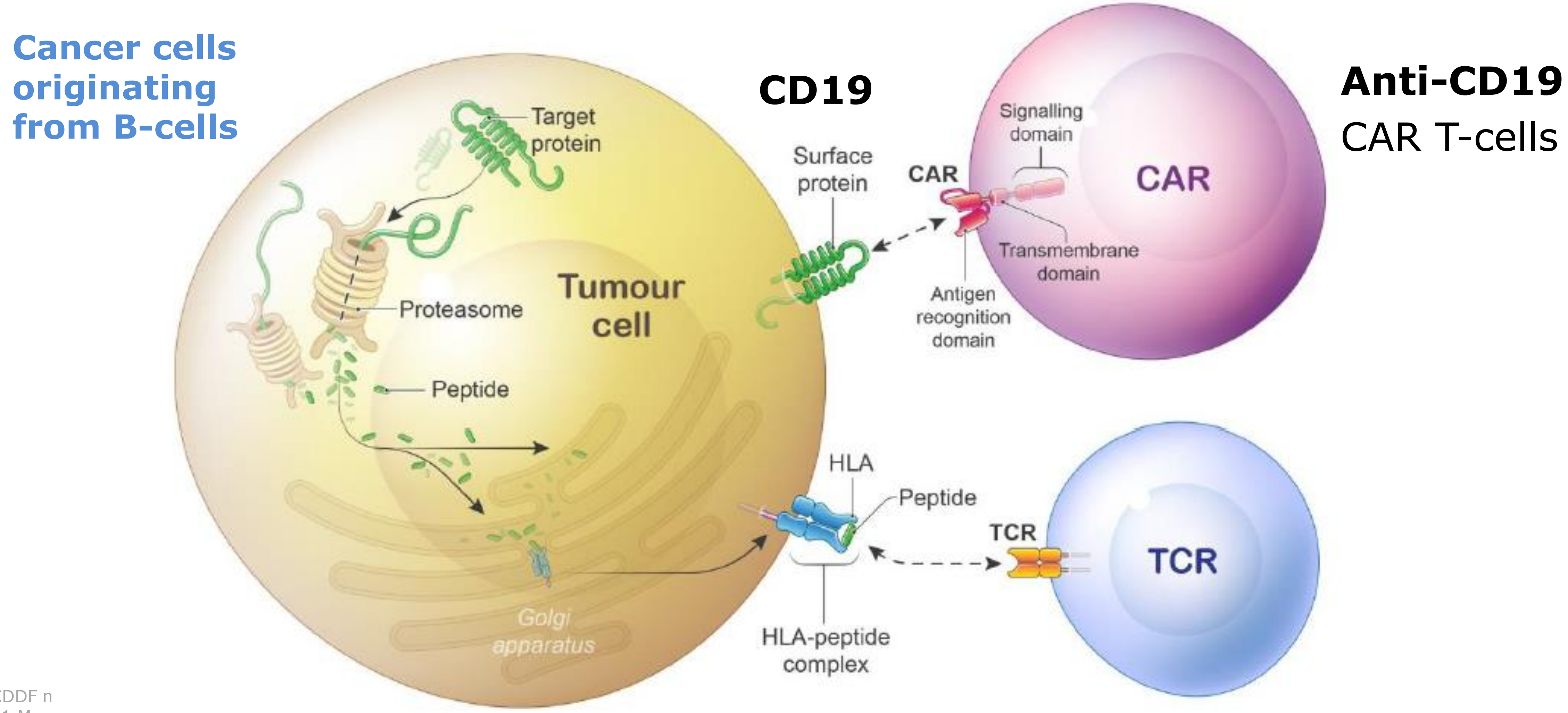
Predictive biomarker **used to** - identify patients on basis of effect from an intervention
- enrich patient population for enrolment in clinical trial (e.g. patients who are more likely to respond)

Monitoring biomarker **used to** detect change in the degree or extent of a disease

Pharmacodynamic biomarker **used to** show a biological response related to an intervention

Chimeric antigen receptor T cells and CD19 as biomarker

- **Mechanism of action**



Context of biomarkers use in MP development: example of CD19

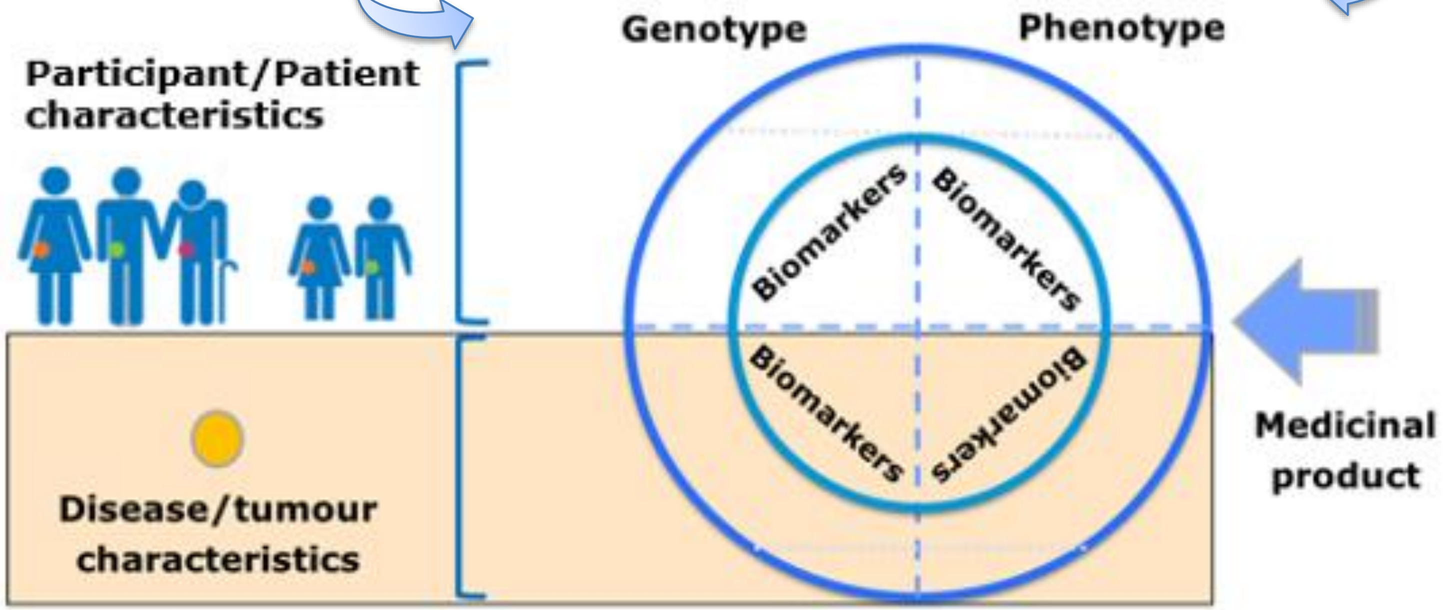
-diagnostic biomarker to define eligibility criteria in clinical trials

-predictive biomarker to enrich patient population for enrolment in clinical trial (e.g. patients who are more likely to respond)

-monitoring biomarker to detect change in the extent of a disease

-pharmacodynamic biomarker to show a biological response related to an intervention

CD19 **gene** encodes a transmembrane **protein** of importance to B-cells function

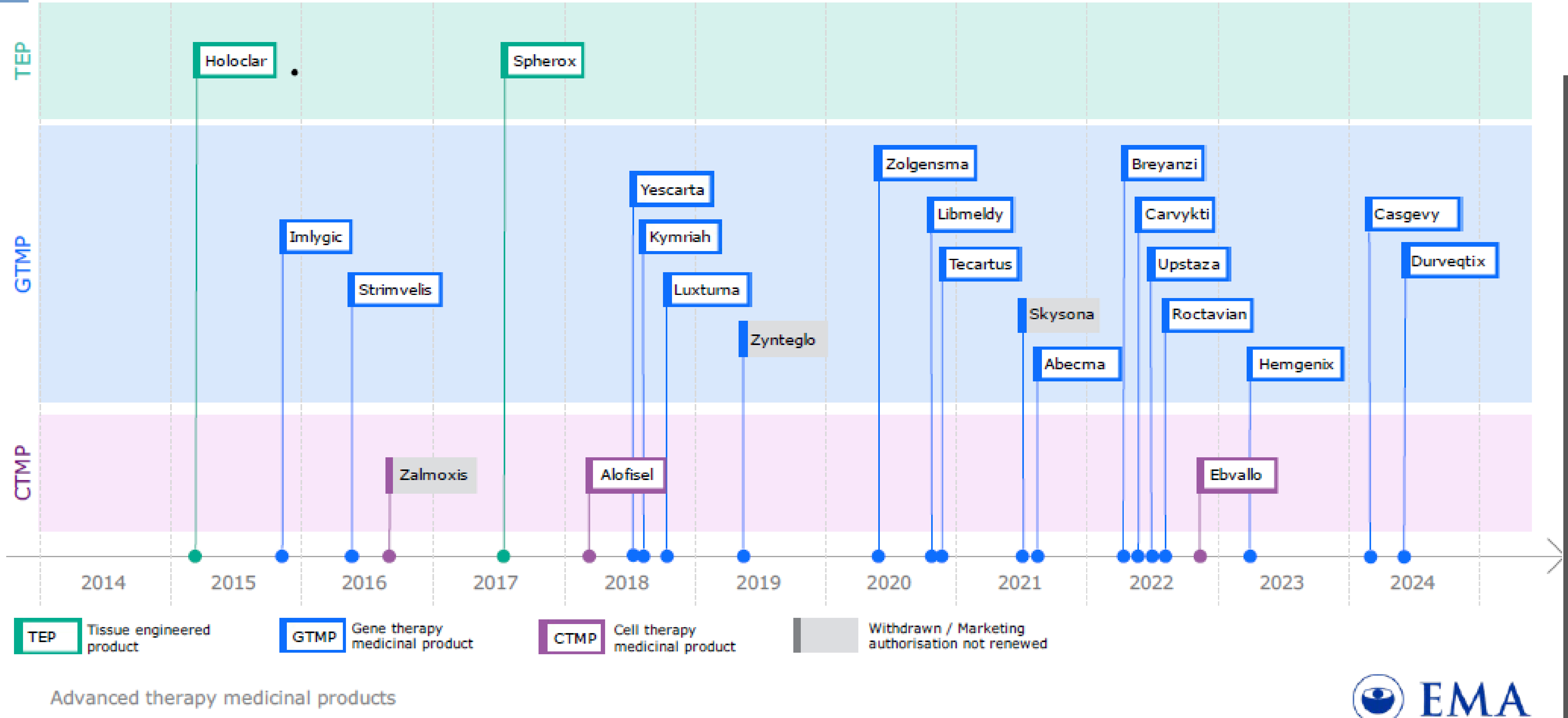


CD19 **gene** in cells of B-cell origin

CD19 antigens on the surface of **cancer cells originating from B-cells**

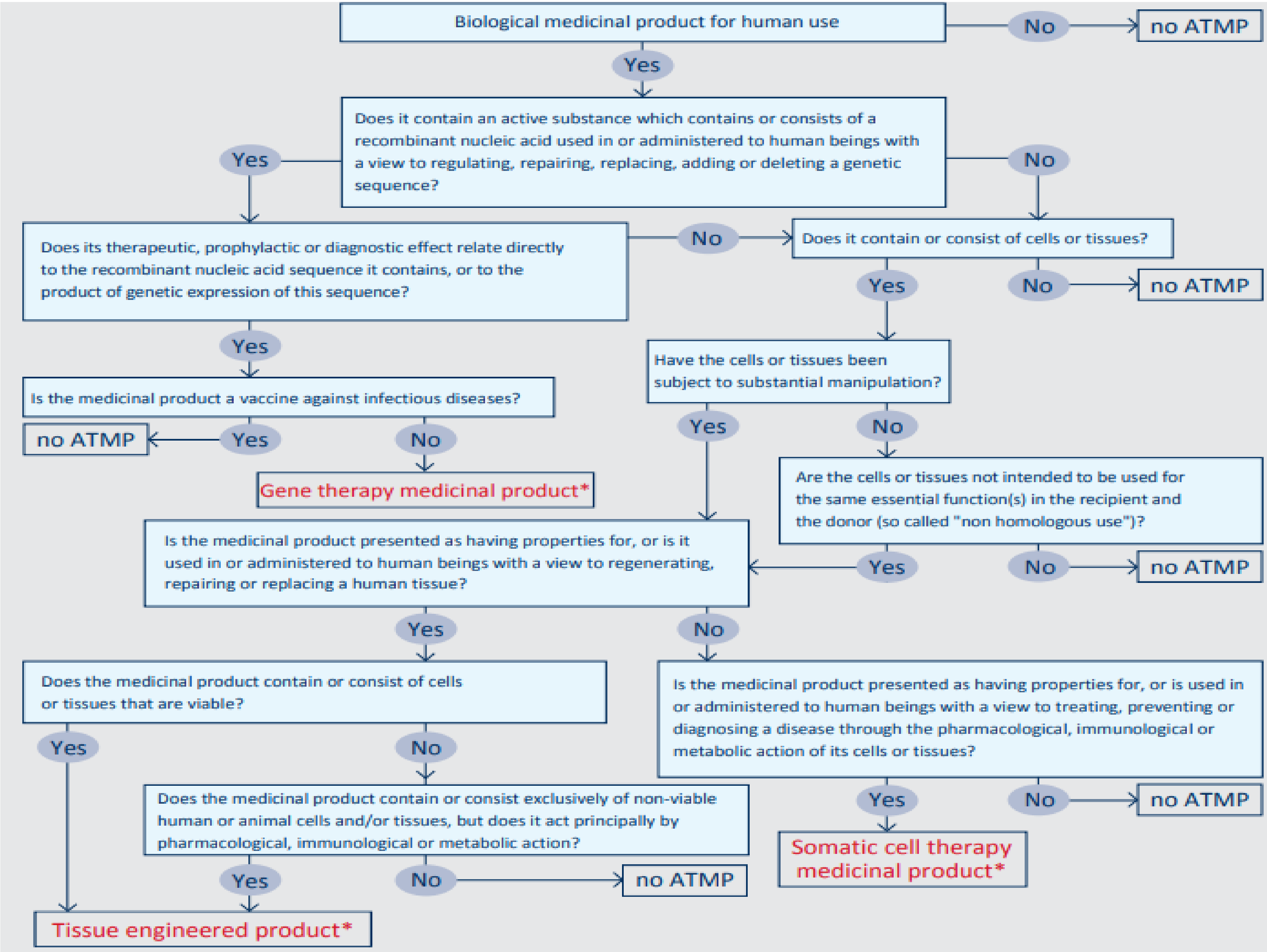
CD19 antigens on the surface of **pathogenic B-cells (autoimmune diseases)**

Advanced therapy Medicinal Products (ATMPs) authorised in EU



From "CAT quarterly highlights and approved ATMPs February 2025"
https://www.ema.europa.eu/en/committees/cat/cat-agendas-minutes-reports

ATMPs classification: decision tree



https://www.pei.de/SharedDocs/Downloads/EN/regulation-en/advice/inno-decision-tree-atmp.pdf?__blob=publicationFile&v=2

Classification of CAR T-cell therapies as ATMPs (GTMPs)

Gene therapy medicinal product means a biological medicinal product which has the both of following characteristics **(a) and (b)**:

(a) it contains an **active substance** which contains or consists of a **recombinant nucleic acid** used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting **a genetic sequence**;

(b) its therapeutic, prophylactic or diagnostic **effect relates directly to the recombinant nucleic acid sequence** it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

Directive 2001/83/EC, Annex I, Part IV, as modified by Commission Directive 2009/120/EC; Article 2(1)(d) of Regulation (EC) No. 1394/2007; https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en.pdf-0

Scientific recommendations on classification of ATMPs: examples

The list of medicines that the CAT has assessed and recommended classifying as ATMPs or not since March 2019 is available. EMA updates the list on a quarterly basis.

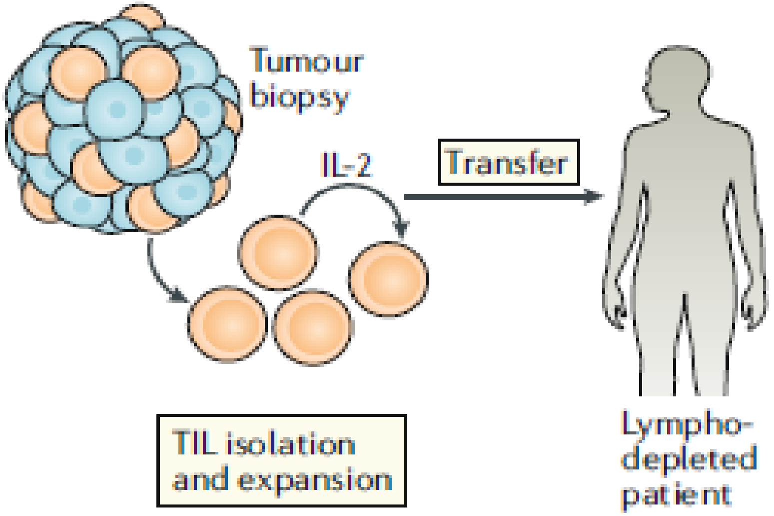
Public descripion of Active substance	Indication (public)	Classification conclusion	Outcome of classification
Autologous anti-CD19 chimeric antigen receptor T-cells	Treatment of CD19-expressing B-cell malignancies	On the basis that the product: •contains an active substance which contains a recombinant nucleic acid administered to human beings with a view to adding a genetic sequence; •its therapeutic effect relates directly to the product of genetic expression of this sequence The EMA/CAT considers that the Product falls within the definition of a gene therapy medicinal product	GTMP

Usually based on the principle of hierarchy of classification (most stringent should be chosen): gene therapy is primary over cell therapy classification (e.g. for genetically modified cell product)

https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/advanced-therapies-marketing-authorisation/scientific-recommendations-classification-advanced-therapy-medicinal-products

Some other ATMPs with autologous source of cells

Autologous
tumour-infiltrating lymphocytes



Public description of Active substance	Indication (public)	Classification conclusion	Outcome of classification
Autologous tumour-infiltrating lymphocytes	Treatment of adult subjects with advanced melanoma	On the basis that: • the product contains cells that have been subject to substantial manipulation; • Its therapeutic effect relates to a view to treating patients with solid tumours through the immunological action of the cells, the EMA/CAT considers that the Product falls within the definition of a of a **somatic cell therapy medicinal product.**	sCTMP

https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/advanced-therapies-marketing-authorisation/scientific-recommendations-classification-advanced-therapy-medicinal-products

Development of other immunotherapies against cancer: use of dendritic cells

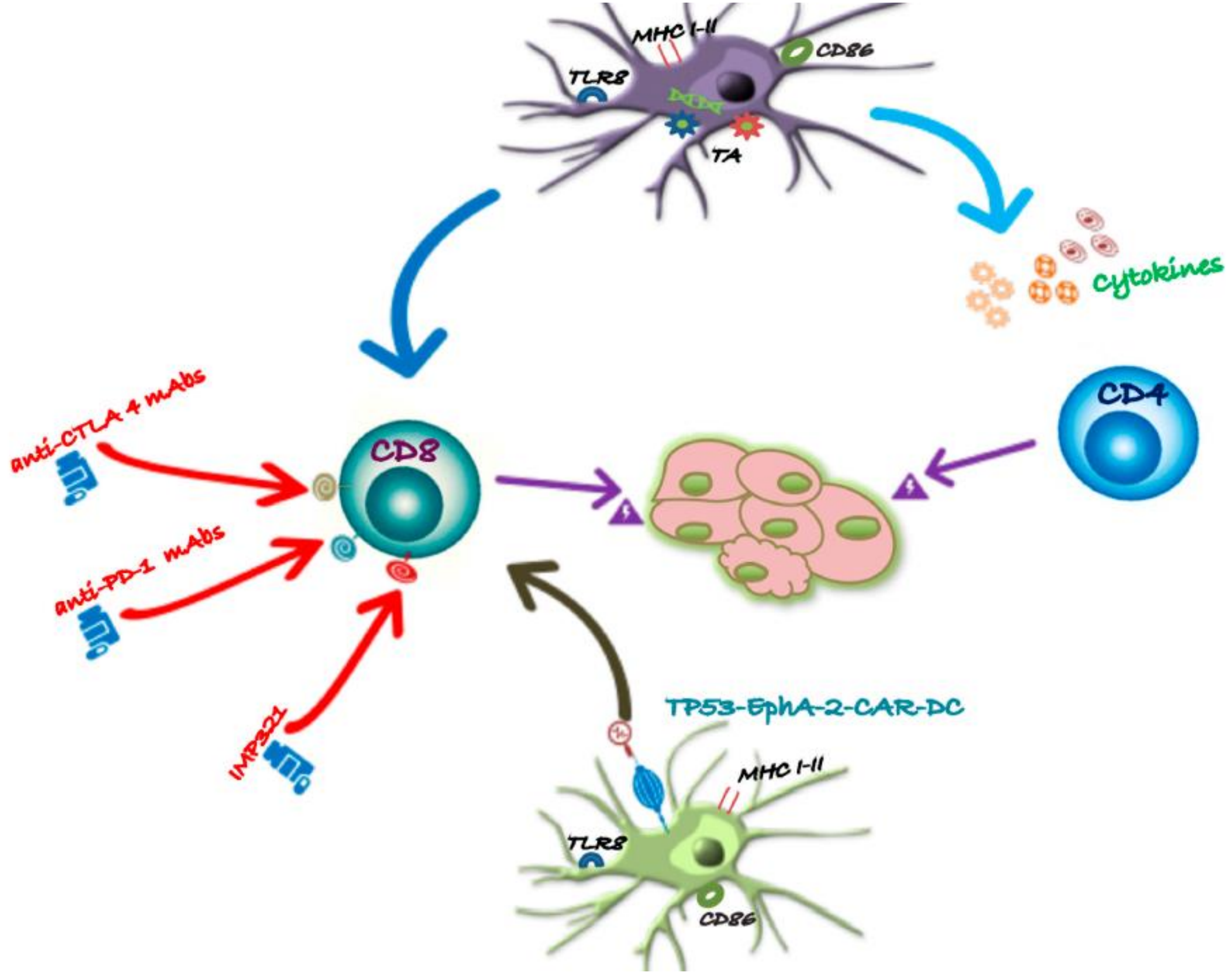


Image modified from: Zanotta et el, 2024 Enhancing Dendritic Cell Cancer Vaccination: The Synergy of Immune Checkpoint Inhibitors in Combined Therapies, https:// doi.org/10.3390/ijms25147509

ATMPs as immunotherapies vs vaccines

Regulation ATMPs:
"Gene therapy medicinal products shall not include vaccines against infectious diseases".

ATMPs classification guidance: *"For classification purposes, vaccines are expected to have prophylactic mode of action, i.e. prevention of an infectious disease in humans"*

Definition of **vaccines** in the European Pharmacopoeia (not in Regulation):

"Vaccines for human use are preparations containing antigens capable of ***inducing a specific and active immunity*** *in man against an* ***infecting agent or the toxin or antigen*** *elaborated by it."*

From the definition above – the mode of action of vaccines is primarily prophylactic, to be used for prevention of infectious diseases rather than for treatment (any diseases).

https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en.pdf-0

ATMPs with non-viral delivery of messenger RNA (mRNA)

Nanoparticles containing mRNA of human papilloma viruses (E6 or E7 antigens) involved in pathogenesis of cancer (used for treatment rather than for prevention)

Target – cancers expressing human papilloma viruses (not viral infectious condition)

Public descripion of Active substance	Indication (public)	Classification conclusion	Outcome of classification
Lipid nanoparticles composed of E6 or E7 mRNA with added TriMix adjuvant.	Treatment of recurrent/metastatic HPV16-positive carcinoma	On the basis that: the active substance contains recombinant nucleic acids the product is to be administered to human beings with a view to adding a genetic sequence its therapeutic effect relates directly to the to the product of genetic expression of this sequence the EMA/CAT considers that the Product falls within the definition of a **gene therapy medicinal product**.	GTMP

Classified as gene therapies based on the principle of hierarchy of classification (most stringent)

https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/advanced-therapies-marketing-authorisation/scientific-recommendations-classification-advanced-therapy-medicinal-products

Immunotherapies targeting cancer neoantigens

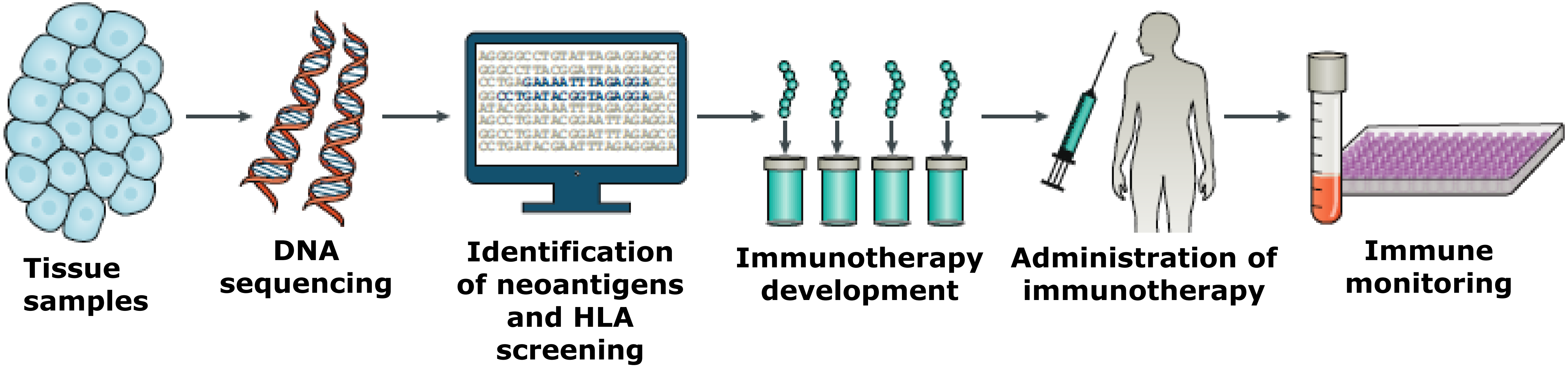


Image modified from: Waldman et el, 2020 A guide to cancer immunotherapy: from T cell basic science to clinical practice, https://doi.org/10.1038/s41577-020-0306-5

Paul-Ehrlich-Institut

Key aspects of an assessment

Overview of pipeline
- Description of steps, inputs and outputs

Risk assessment
- Risk of false predictions
- Risk of tools used

Validation
- Analytical validation as part of risk assessment
- Published, purchased, in-house or synthetic data

Risk management
- Accept, avoid, transfer, reduce
- Verification, filtering

Change control
- Identify possible changes
- Low/medium/high risk changes

https://www.ema.europa.eu/en/events/hma-ema-multi-stakeholder-workshop-artificial-intelligence-ai-enabling-safe-responsible-use-ai, "Assessing the use of AI in neo-antigen prediction pipelines", Liam Childs (PEI)

Gene-edited medicinal products as example

- **Casgevy**

Casgevy (exagamglogene autotemcel) is a genetically modified autologous CD34+ cell enriched population that contains haematopoietic stem and progenitor cells (HSPCs) edited ex vivo by CRISPR/Cas9 at the erythroid-specific enhancer region of the BCL11A gene.

β-thalassemia

Casgevy is indicated for the treatment of transfusion-dependent β-thalassemia (TDT) in patients 12 years of age and older for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Sickle cell disease

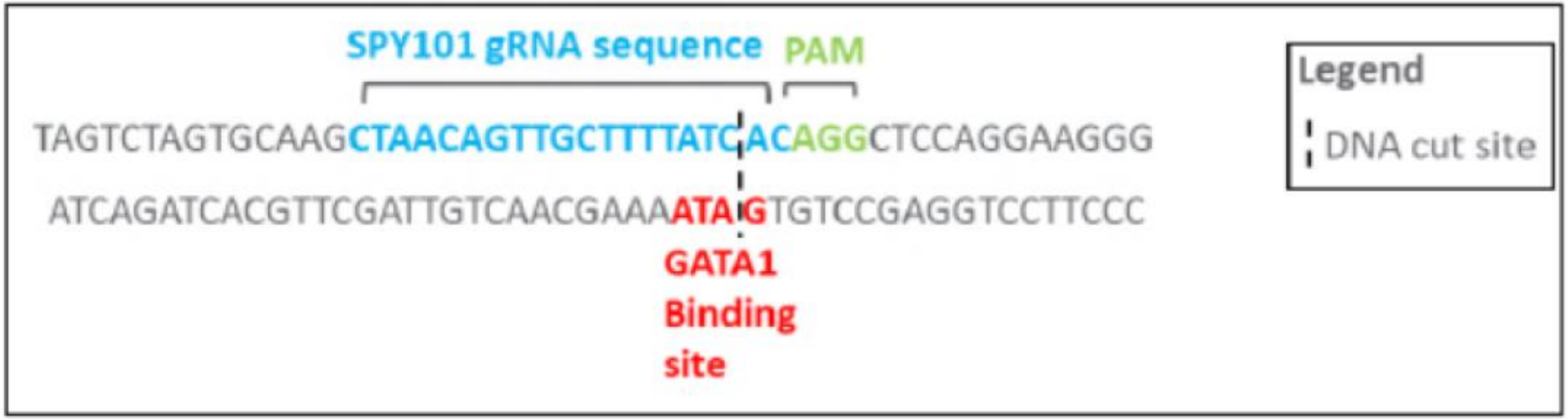
Casgevy is indicated for the treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Gene-edited medicinal products as example

- **Mechanism of action (MoA)**

Casgevy is a cell therapy consisting of autologous CD34+ HSPCs ex vivo edited by **CRISPR/Cas9-technology**.

The highly specific guide RNA enables CRISPR/Cas9 to make a precise DNA double-strand break at the critical transcription factor binding site (GATA1) in the erythroid specific enhancer region of the BCL11A gene.



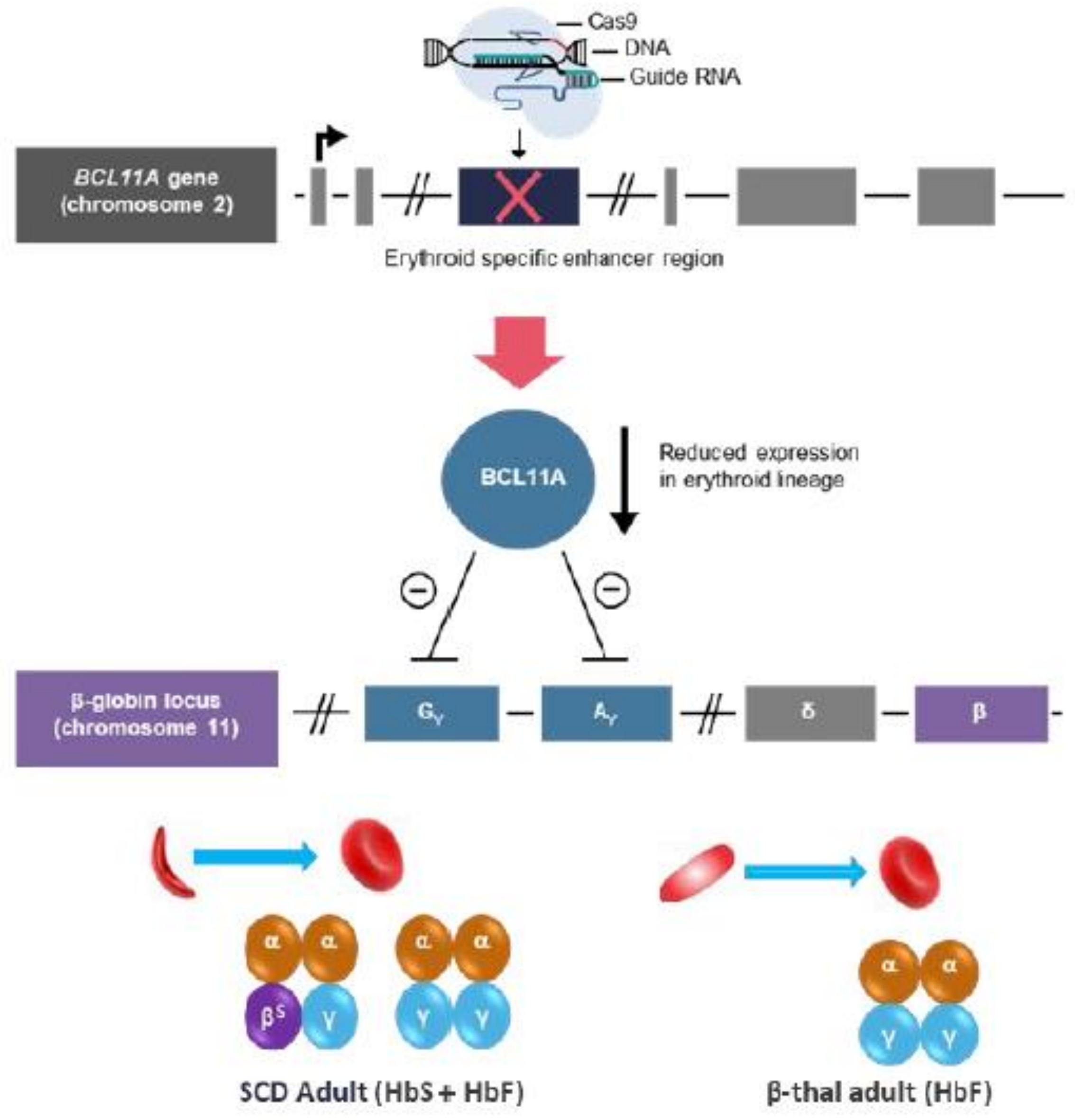
Casgevy MoA

GATA1 binding is irreversibly disrupted and BCL11A expression reduced.

Result: an increase in γ-globin expression and foetal haemoglobin (HbF) protein production in erythroid cells, addressing the absent globin in transfusion-dependent β-thalassemia (TDT) and the aberrant globin in sickle cell disease (SCD).

In patients with TDT, γ-globin production is expected to correct the α-globin to non-α-globin imbalance, thereby reducing ineffective erythropoiesis and haemolysis and increasing total haemoglobin levels.

In patients with severe SCD, HbF expression is expected to reduce intracellular HbS concentration, preventing the red blood cells from sickling.



Source: Modified from Canver and Orkin, 2016

Current guidance of relevance

General (in development):

Biomarkers and Diagnostics

- Guideline on predictive biomarker assay development
- Revision of Good pharmacogenomic practice guideline
- Radiopharmaceutical diagnostics guideline

Specific to oncology:

- Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6.) – section 5 Biomarkers

ATMPs

- Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials (EMA/CAT/22473/2025)

https://www.ema.europa.eu/en/documents/other/consolidated-3-year-rolling-work-plan-methodology-working-party-2025-2027_en.pdf
https://www.ema.europa.eu/en/human-regulatory-overview/advanced-therapy-medicinal-products-overview/guidelines-relevant-advanced-therapy-medicinal-products

Key messages

- Personalisation is an integral part of the medicinal products life cycle

- Biomarkers and biomarker assays/tests are increasingly used in the context of medicinal products life cycle as one of the means of personalisation

- ATMPs are types of biological medicinal products with increasing use of biomarkers and other means of personalisation (e.g. use of autologous cells vs allogeneic cells, specific genotypic an/or phenotypic characteristics of patients and diseases such as tumours)

- General regulatory guidance and requirements are applicable, with specific considerations for medicinal product types and their mechanism of action

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