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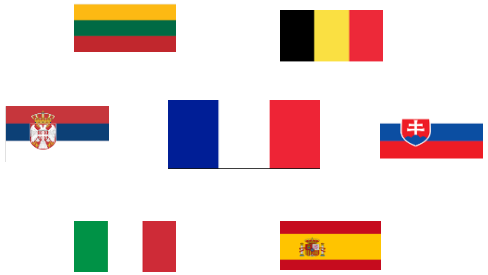

INNOVATIVE THERAPIES IN CANCER (WP9)

Dr Muriel DAHAN

Head of the Clinical Guidelines and Medicines Direction

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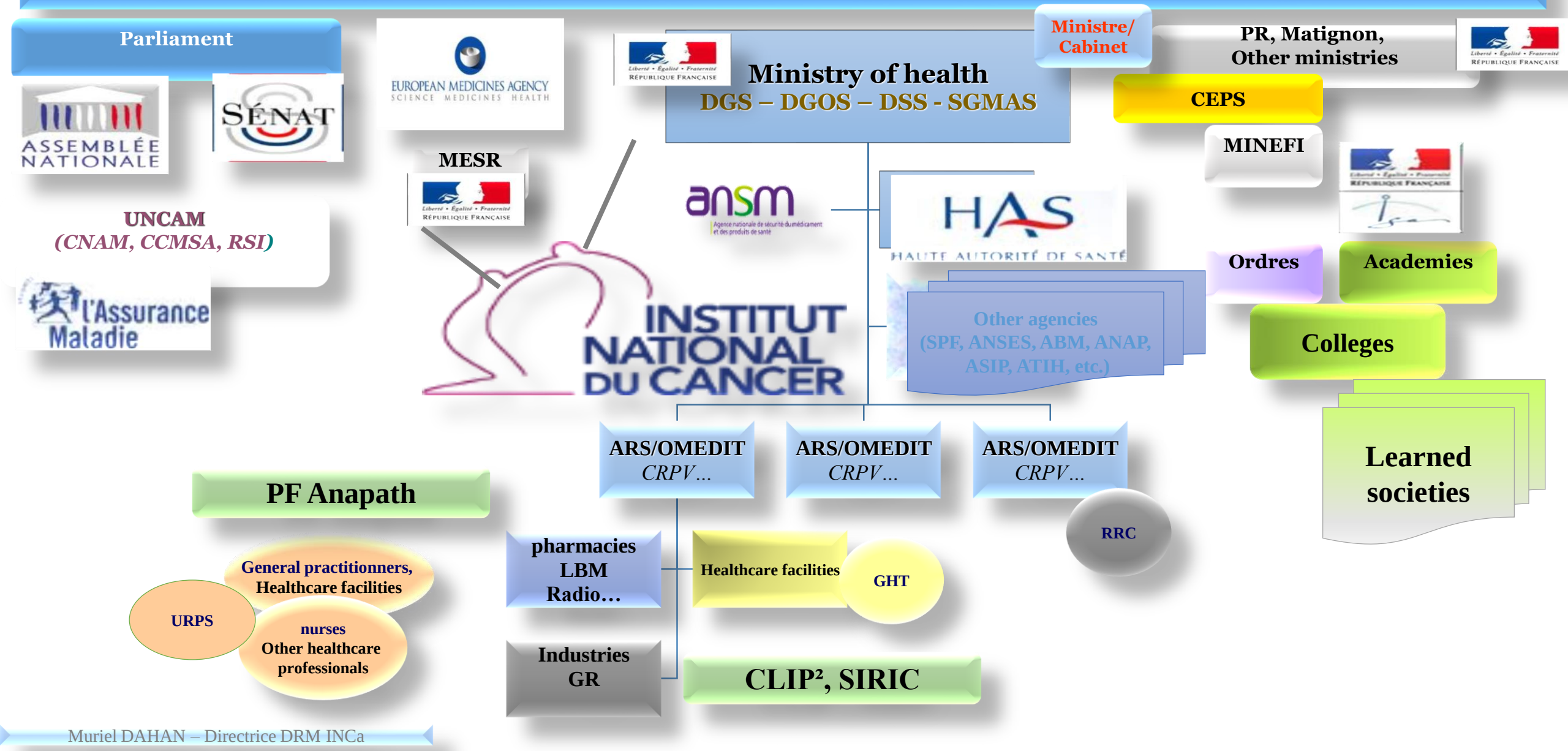
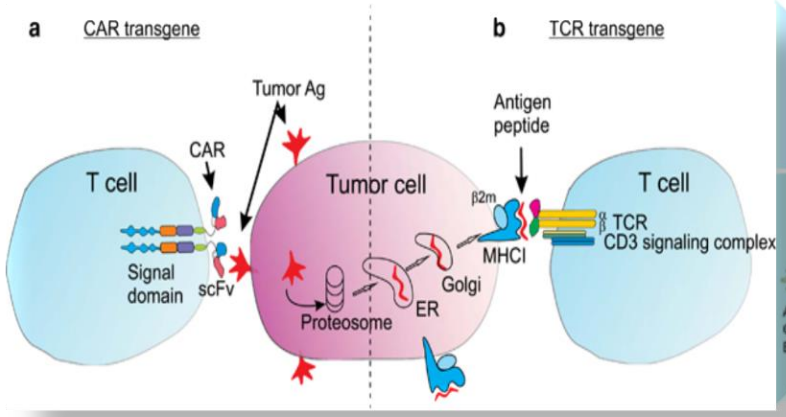
INCa in the health institutional environment



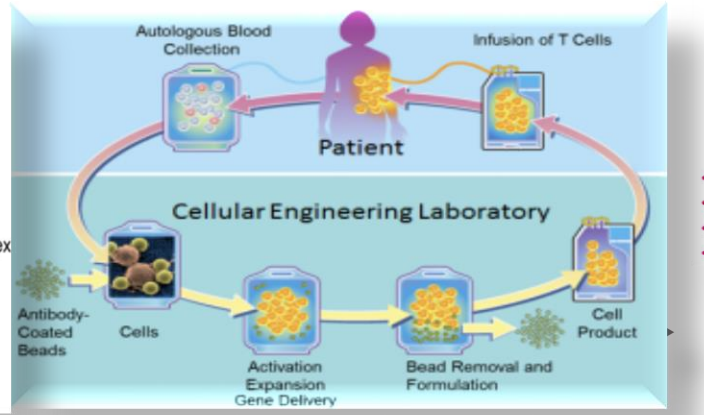
Oncology : Multiple innovation from various ranges

- **Breakthrough innovations:**
  - Targeted therapies (MEK, BRAF600…)
  - Specific immunotherapies (anti CTLA4, antiPD1, PDL-1)
  - Oncolytic viruses, vaccines
  - **CAR-T cells (chimeric antigen receptors) TCR-T – UCAR-T…**

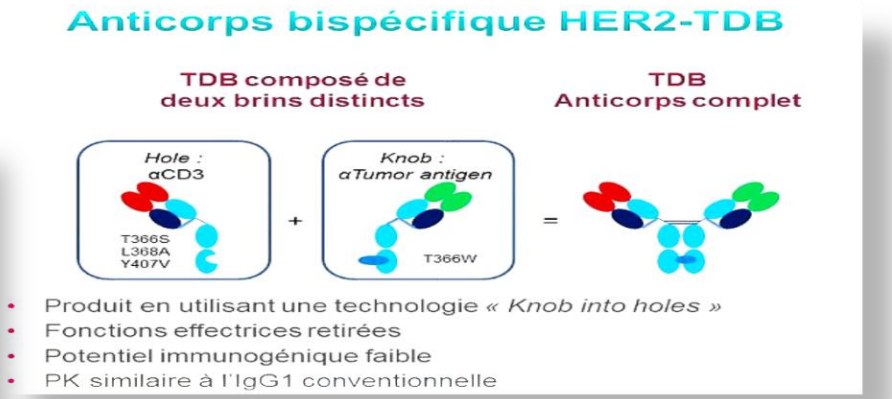
- **New types of medicines :**
  - Conjugated antibodies (trastu emtansine)
  - Fusion protein (aflibercept)
  - Binding nanoparticules (nab paclitaxel)
  - Bi-specific antibody (blinatumomab)



Clinical application of genetically modified T cells in cancer therapy
Michael H Kershaw, Jennifer A Westwood, Clare Y Slaney and Phillip K Darcy



Source INCa



New modalities for administrations:

- PO, SC

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Immunotherapies and their associated biomarkers

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INNOVATIVE IMMUNOTHERAPIES IN CANCER

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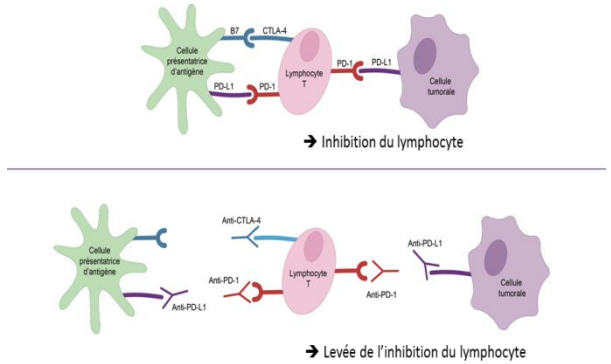
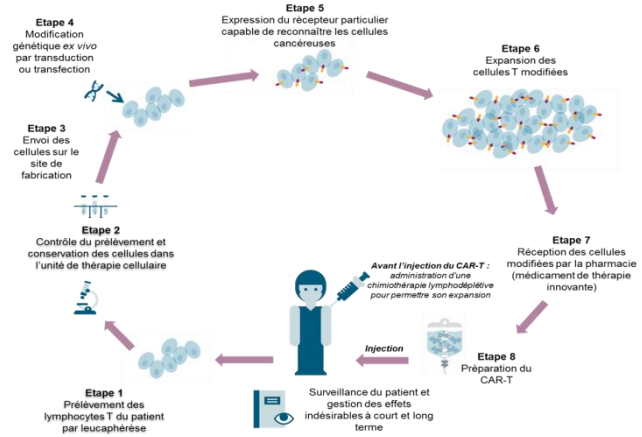
- **Focus on**
  - Checkpoint inhibitors
  - CAR-T cells

Task 1, 2 & 4



- **Potentiel other innovative immunotherapies**
  - New anti-cancer vaccines
  - Oncolytic viruses
  - Bi-specific antibodies (blinatumomab)
  - IDO, LAG 3
  - …

Task 2 & 3



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BIOMARKERS ASSOCIATED WITH INNOVATIVE IMMUNOTHERAPIES

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- **PD-L1 expression**

  Already used in clinical practices in Europe: examples with pembrolizumab for Lung Cancer (NSCLC)

  - Pembrolizumab is approved by the EMA as first line therapy only for adult whose tumours express PD-L1 with a tumour proportion score (TPS) ≥ 50%
  - Pembrolizumab is approved by EMA as second line therapy only for adults whose tumours express PD-L1 with a TPS ≥ 1%

- **Microsatellite instability and mismatch repair (MSI-H / dMMR)**

  Already used in clinical practices in the USA

  - Pembrolizumab is approved by the FDA for all histological types in patients carrying a DNA repair gene abnormality (dMMR) or exhibiting high microsatellite instability (MSI-H)
  - Nivolumab is approved by the FDA for the treatment of MSI-H metastatic colorectal cancer

- **Tumor mutational burden (TMB)**

  - Emerging biomarker in immuno-oncology
  - Recent clinical trials showed an interest to use this biomarker in NSCLC to better identify responders

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CHECKPOINT INHIBITORS

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- Overview of the types of cancers for which checkpoint inhibitors have (at least) one approved therapeutic indication in the European union:

	CHECKPOINT INHIBITORS				
	anti-CTLA-4	anti-PD-1		anti-PD-L1	
Cancer types*	Ipilimumab (Yervoy®)	Nivolumab (Opdivo®)	Pembrolizumab (Keytruda®)	Avelumab (Bavencio®)	Atezolizumab (Tecentriq®)
Melanoma	2011	June-15	July-15		
Non-small cell lung cancer		Oct-15	Aug-16		Sept-17
Renal cell carcinoma		Apr-16			
Classical Hodgkin's lymphoma		Nov-16	May-17		
Squamous head and neck cancer		Apr-17			
Urothelial carcinoma		June-17	Aug-17		Sept-17
Merkel cell carcinoma				Sept-17	

➔ 4 new checkpoints inhibitors for 6 new localizations since 2015

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CHALLENGES ASSOCIATED WITH CHECKPOINT INHIBITORS

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- **Clinical development still very rich**
  - Might lead to new indications, new associations (interest of the Horizon scanning activities – WP9 task 3)
- **Moving towards a more personalized medicine**
  - High impact of biomarkers on treatment prescription (WP9 – task 2)
- **Brutal disruption of therapeutic strategies: some parameters still need to be further assessed** (WP9 task 1 & 4)
  - Hard to define the best place in the treatment strategy (e.g. Diverging opinions for preferred first line treatment for BRAF mutated patients with metastatic melanoma (anti-BRAF/anti MEK versus anti-PD-L1)
  - No defined lenght of treatment for anti-PD1/anti-PD-L1

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CAR-T CELLS

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- CAR-T cells have been recently approved by the EMA (summer 2018): they should be available on the market very soon for hematologic tumors

Molecule (Brand Name)	Localizations approved
Tisagenlecleucel (Kymriah™)	B-cell acute lymphoblastic leukaemia (ALL)
	diffuse large B-cell lymphoma (DLBCL)
Axicabtagene ciloleucel (Yescarta™)	diffuse large B-cell lymphoma (DLBCL)
	primary mediastinal large B-cell lymphoma (PMBCL)

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CAR-T CELLS: A COMPLEX CIRCUIT

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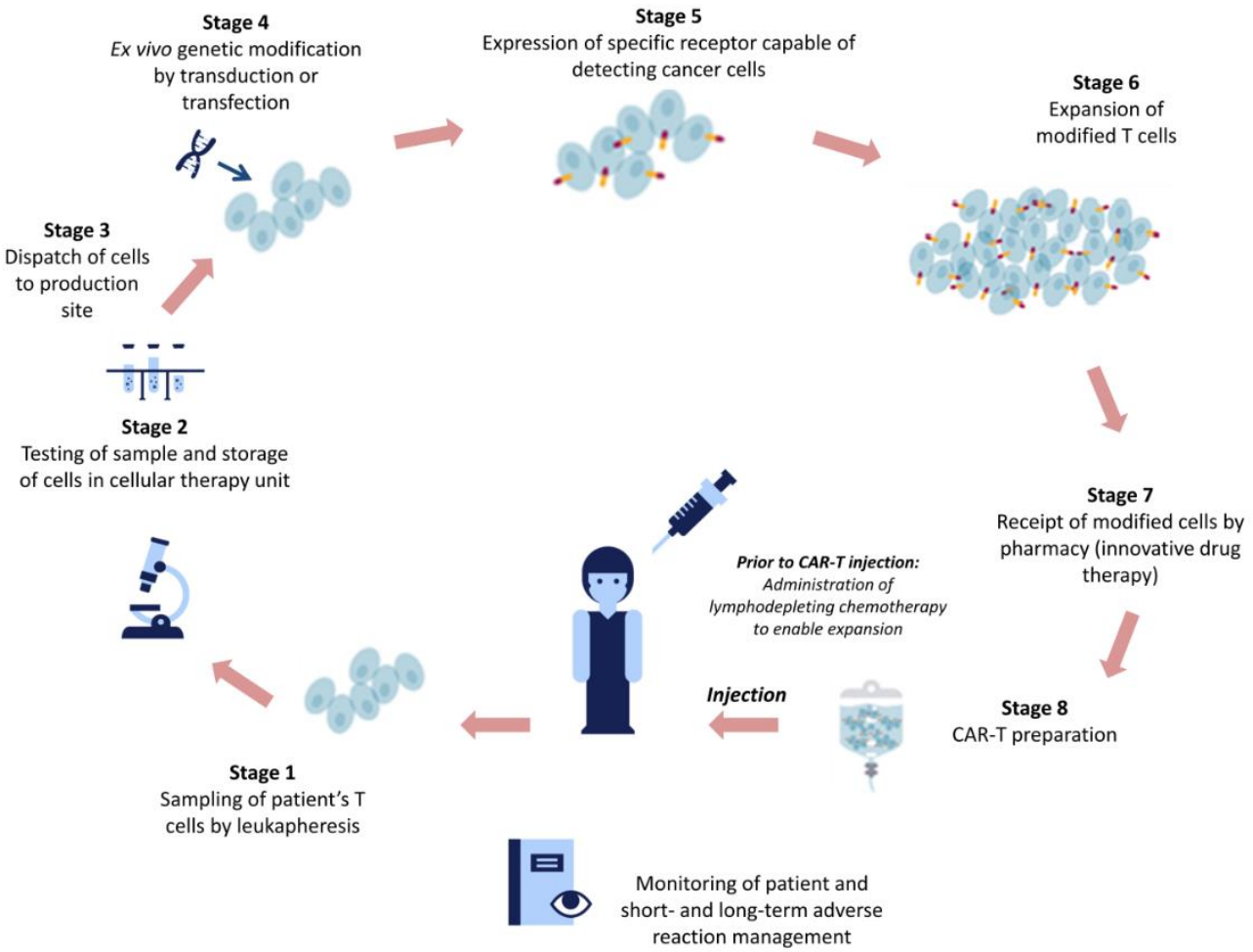

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CHALLENGES ASSOCIATED WITH CAR-T CELLS

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- **Complex product and pathway**
  ➔ Need for qualified centers
- **Life-threatening adverse reactions can occur**
  ➔ Require competent medical care (e.g. cytokine release syndrome, neurologic toxicity)
- **Large ongoing Clinical development, also in solid tumors**
  ➔ Might lead to new indications, new associations (WP9 task 3)
- **Economic challenge: very high prices** (320 000€ expected in Germany for Kymriah)
  ➔ Attention required to maintain equity of treatment access and sustainability of the health care systems to be evaluated

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iPAAC WP9

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WP9 OBJECTIVES

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INNOVATIVE THERAPIES IN CANCER - IMMUNOTHERAPIES

1) Map existing **guidelines** and reference frameworks regarding the use of immunotherapies in clinical practices and identify potential off-label use

➔ Promote the proper use of these innovative treatments

➔ Spur coordination across institutions, professionals and Member States

2) Identify and validate predictive **biomarkers** for response, resistance or toxicity

➔Better identify responders or non responders

3) Identify and predict impact of forthcoming innovative treatments (**horizon scanning** activities)

➔ Anticipation of new therapies, their associated costs and their place in the therapeutic strategy

4) Identify tools that could be implemented in Europe for **real-life monitoring** of innovative treatments

➔Provide guidance regarding the assessment of innovative therapies in real-life setting

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PARTICIPANTS WP9

Associated partners	
Belgium	Sciensano
Italie	CRO-Aviano (in collaboration with ISS)
Lituanie	National Centre of Pathology, Affiliate of Vilnius University Hospital Santaros Klinikos (VuHSK)
Serbia	Clinical Center of Kragujevac CCK (in collaboration with IPHS)
Slovaquie	Biomedical Research Center (BMC SAS)
Collaborative partners	
Spain	INCLIVA
	CIBERONC
Luxembourg	National Cancer Institute
	The European Society for Paediatric Oncology

And potential participation of experts from:

- European Medicine Agency (EMA)
- European Society for Medical Oncology (ESMO)
- European Network for Health Technology Assessment (EUnetHTA)
- National Institute for Health and Care Excellence (NICE)
- Paul Ehrlich Institute (PEI)

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WP9 - GENERAL ORGANIZATION

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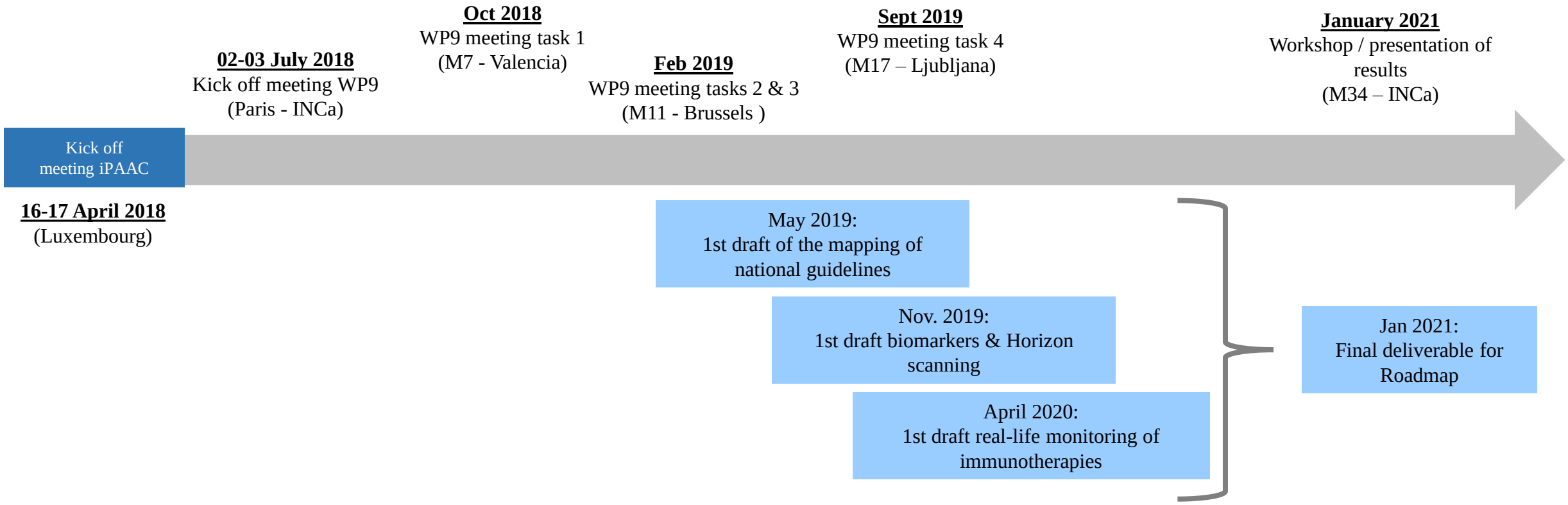

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TASK 9.1

INSTITUT NATIONAL DU CANCER

CLINICAL PRACTICE GUIDELINES AND REFERENCE FRAMEWORK LINKED WITH THE IMMUNOTHERAPIES

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TASK 9.1 - Guidelines and clinical practices reference framework

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- **Main goals:**
  - Provide current status regarding Clinical Practice Guidelines, and compare the place of innovative immunotherapies in cancer treatment strategies.
    - Off-label uses will be highlighted
  - Provide a mapping a reference frameworks linked with the use of innovative immunotherapies including
    - HTA agencies recommendations for the use of these innovative therapies and potential restrictions of use;
    - Health agencies opinions and existing reference frameworks for early market access and for off-label use of innovative immunotherapies.

- **Deliverables:**
  - Mapping of clinical practice guidelines and reference frameworks regarding the use of innovative therapies
  - Due date: September 2019

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TASK 9.1 - SCOPE

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- **Checkpoints inhibitors**
  - The arrival of these therapies has lead to a strong disruption of treatment strategies ➔ many guidelines have been or will be updated
  - High impact of biomarkers on treatment prescriptions
    - PD-L1 expression
    - Microsatellite instability (MSI) status
    - Tumor Mutational Burden

- **CAR-T cells**
  - Revolutionary gene and cell therapy

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TASK 9.1 - METHODOLOGY

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Literature review

Selection of key words and languages

↓

Definition of Inclusion & exlusion criteria

↓

Identification of guidelines and reference framework

↓

Brief presentation of each guideline
(year of publication, authors, scope, key recommandations, biomarkers, …)

Questionnaire

Development of relevant questions

↓

Identification of survey responders
(Stakeholders, Learned societies, National health authorities, public health institutions…)

↓

Survey dissemination
(online format)

Assessment of guidelines (including off label use) & reference frameworks

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TASK 9.2

INSTITUT NATIONAL DU CANCER

BIOMARKERS:

Predictive parameters for immunotherapies response and/or toxicity

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TASK 9.2 - BIOMARKERS

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- **Main goals:**
  - Analysis of biomarkers for innovative therapies as predictive parameters of response and/or side effets
    - Map existing guidelines in order to have an overview of the use of biomarkers for immunotherapies in clinical routine
    - Identify parameters specific to biomarkers to be included in a Horizon scanning to anticipate the use of predictive biomarkers in clinical routine
- **Deliverable:**
  - Mapping of existing national guidelines with biomarkers used in clinical routine
  - November 2019

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TASK 9.2 - METHODOLOGY

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IDENTIFICATION OF BIOMARKERS USED IN CLINICAL ROUTINE

Similar method as for task 1

- Literature search
- Questionnaire
- Analysis of guidelines

ANTICIPATION OF NEW BIOMARKERS

Similar method as for task 3

- Review of existing Horizon scanning systems
- Identification of specificities for biomarkers

+ Link with WP6

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TASK 9.3

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HORIZON SCANNING :

A tool to anticipate innovative therapies

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HORIZON SCANNING - DEFINITION

- Also called « Early awareness and alert systems »

- Euroscan definition: Horizon scanning aim to identify, filter, and prioritize new and emerging health technologies; to assess or predict ther impact on health, cost, society and the healthcare system; and to inform decision makers and research planners

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GENERAL OBJECTIVES OF HORIZON SCANNING SYSTEMS

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- Identify medicines before evidence has been generated
- Support early dialogue between evaluators and health services
- Help evaluators and health agencies
- Collaboration with countries which have developed horizon scanning process
  - Share competencies
  - Develop new tools in order to improve horizon scanning processes

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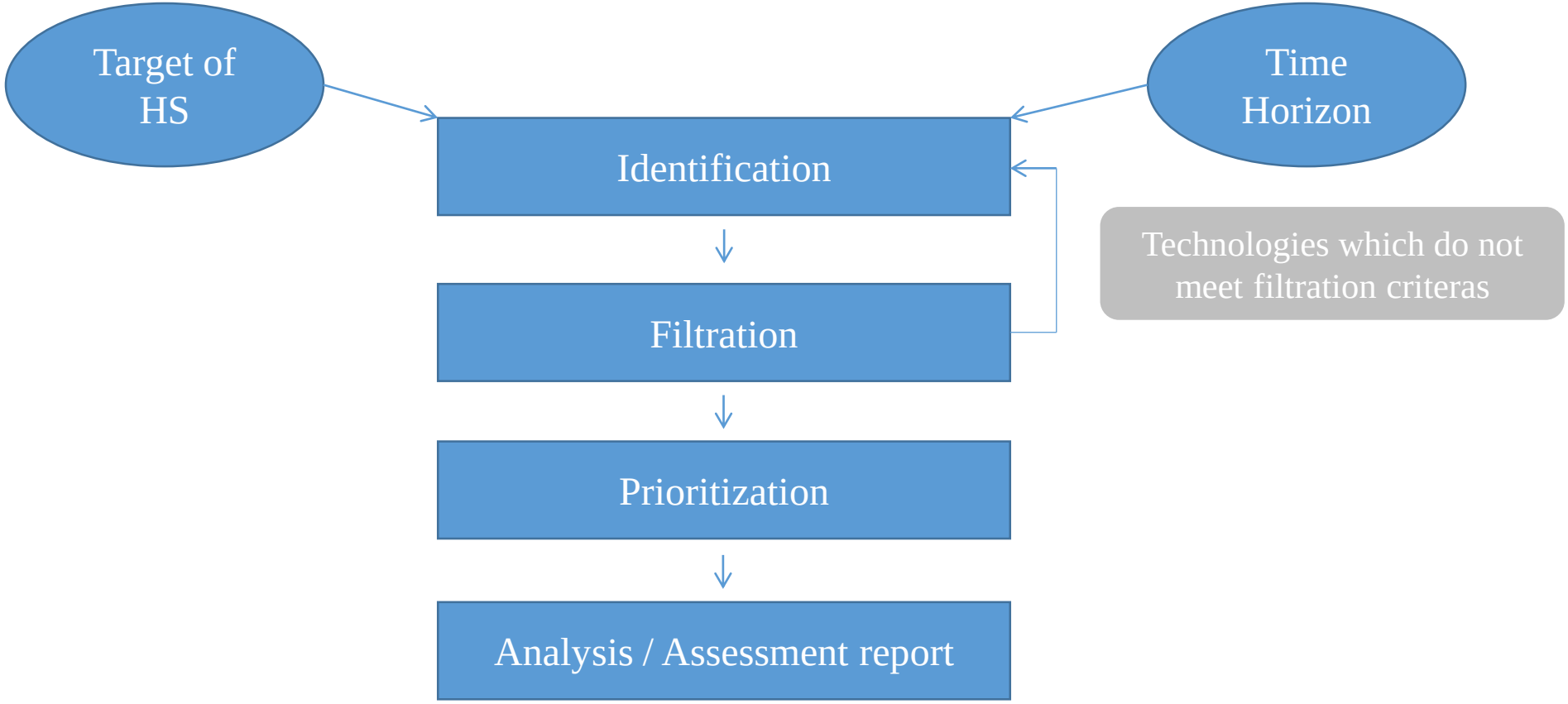
HORIZON SCANNING METHOD



Source : EuroScan , 2014 : A toolkit for identification and assessment of new and emerging health technologies

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TASK 9.3 – HORIZON SCANNING

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- **Main goals:**
  - Anticipation of market approval of incoming new therapies and rising costs
  - Identify uses and services provided by Horizon scanning systems
  - Identify special Horizon scanning features to be considered for:
    - Gene and cells therapies (CAR-T cells as an exemple?)
    - Biomarkers

- **Deliverable:**
  - Horizon scanning in Europe: existing systems, new trends, implementation in Member states
  - April 2020

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TASK 9.3 - METHODOLOGY

Literature review

Questionnaire

Review of existing Horizon scanning systems and organizations

+ pilot study for CAR-T cells ?

Highlight specific features needed for cell and gene therapies

Highlight specific features needed for biomarkers

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TASK 9.4

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REAL LIFE MONITORING OF INNOVATIVE THERAPIES

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TASK 9.4 – REAL LIFE MONITORING OF INNOVATIVE THERAPIES

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- **Main goals:**
  - Identify and compare the European initiatives for real-life monitoring of immunotherapies
  - Provide guidance and methodology for the assessment of innovative therapies in real-life settings
  - Help synergies between the existing initiatives (pairing of data)

- **Deliverable:**
  - European tools for real-life monitoring of selected immunotherapies
  - December 2020

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TASK 9.4 - METHODOLOGY

International literature review of system in place for real-life monitoring (with a focus of immunotherapies)
(CancerLinq, AIFA , ENCEPP, GPRD, …)

↓

From the literature review: classification of identified system according to the goal of each system /type of data collected

↓

Questionnaire to identify initiatives in EU in terms of systems in place for the real-life monitoring of immunotherapies

↓

Appraisal: strength and weakness of each system

↓

Provide recommendations for Member states for implementation of real-life monitoring systems

If possible, implementation of real-life pilot study post-authorization to help positioning medicines in real-life setting

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TASK 9.5

DRAFTING THE ROADMAP ON IMPLEMENTATION AND SUSTAINABILITY OF CANCER CONTROL ACTIONS IN THE FIELD OF INNOVATIVE CANCER THERAPIES

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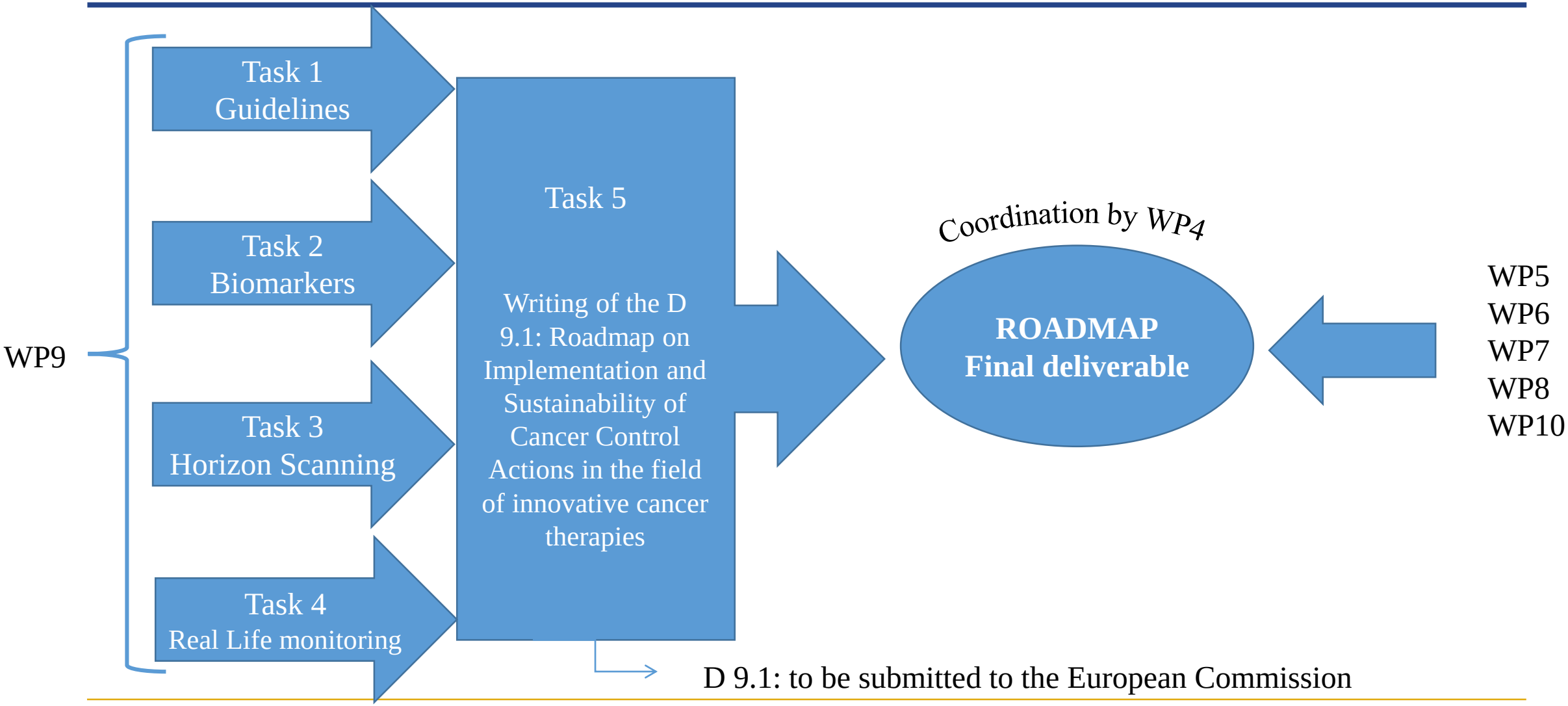
ROADMAP



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NEXT STEP

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- WP9 Task 1 meeting on 02 October in Valencia, Spain

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