INNOVATIVE THERAPIES IN CANCER (WP9)

Dr Muriel DAHAN
Head of the Clinical Guidelines and Medicines Direction
INCa in the health institutional environment

Ministry of health
DGS – DGOS – DSS - SGMAS

ARDS/OMEDIT
CRPV...

ARS/OMEDIT
CRPV...

ARS/OMEDIT
CRPV...

Other agencies
(SP, ANSES, ABM, ANAP, ASIP, ATIH, etc.)

HAS
Haut Autorité de Santé

MESR
Ministère de la Santé

CEPS
PR, Matignon, Other ministries

MINEFI
Ministre/ Cabinet

ORDRES
Ordres

ACADEMIES
Academies

COLLEGES
Colleges

LEARNED SOCIETIES
Learned societies

PARLEMENT
Parliament

SÉNAT

UNCAM
(CNAM, CCMSA, RSI)

L’ASSURANCE MALADIE

PF Anapath

PF Anapath

URPS

General practitioners, Healthcare facilities

nurses
Other healthcare professionals

Industries
GR

pharmacies
LBM
Radio...

Healthcare facilities

GHT

RRC

Muriel DAHAN – Directrice DRM INCa
**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)

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**New modalities for administrations:**
- PO, SC

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*Clinical application of genetically modified T cells in cancer therapy*

Michael H Kershaw, Jennifer A Westwood, Clare Y Slaney and Phillip K Darcy

**Anticorps bispécifique HER2-TDB**

- **TDB composé de deux brins distincts**
  - **Anticorps complet**

**Source INCa**

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Muriel DAHAN – Directrice DRM INCa
Immunotherapies and their associated biomarkers
INNOVATIVE IMMUNOTHERAPIES IN CANCER

• **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
BIOMARKERS ASSOCIATED WITH INNOVATIVE IMMUNOTHERAPIES

• **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) \( \geq 50\% \)
  • Pembrolizumab is approved by EMA as **second line** therapy only for adults whose tumours express PD-L1 with a **TPS \( \geq 1\% \)**

• **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
CHECKPOINT INHIBITORS

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

<table>
<thead>
<tr>
<th>Cancer types</th>
<th>anti-CTLA-4</th>
<th>anti-PD-1</th>
<th>anti-PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipilimumab</td>
<td>Nivolumab</td>
<td>Avelumab</td>
</tr>
<tr>
<td></td>
<td>(Yervoy®)</td>
<td>(Opdivo®)</td>
<td>(Bavencio®)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2011</td>
<td>June-15</td>
<td>Sept-17</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td></td>
<td>Oct-15</td>
<td></td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td></td>
<td>Aug-16</td>
<td></td>
</tr>
<tr>
<td>Classical Hodgkin's lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous head and neck cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td></td>
<td>May-17</td>
<td></td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
<td></td>
<td></td>
<td>Sept-17</td>
</tr>
</tbody>
</table>

- 4 new checkpoints inhibitors for 6 new localizations since 2015
CHALLENGES ASSOCIATED WITH CHECKPOINT INHIBITORS

• 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 length of treatment for anti-PD1/anti-PD-L1
**CAR-T CELLS**

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

<table>
<thead>
<tr>
<th>Molecule (Brand Name)</th>
<th>Localizations approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tisagenlecleucel</td>
<td>B-cell acute lymphoblastic leukaemia (ALL)</td>
</tr>
<tr>
<td>(Kymriah™)</td>
<td>diffuse large B-cell lymphoma (DLBCL)</td>
</tr>
<tr>
<td>Axicabtagene ciloleucel</td>
<td>diffuse large B-cell lymphoma (DLBCL)</td>
</tr>
<tr>
<td>(Yescarta™)</td>
<td>primary mediastinal large B-cell lymphoma (PMBCL)</td>
</tr>
</tbody>
</table>
CAR-T CELLS: A COMPLEX CIRCUIT

Stage 1: Sampling of patient's T cells by leukapheresis.

Stage 2: Testing of sample and storage of cells in cellular therapy unit.

Stage 3: Dispatch of cells to production site.

Stage 4: Ex vivo genetic modification by transduction or transfection.

Stage 5: Expression of specific receptor capable of detecting cancer cells.

Stage 6: Expansion of modified T cells.

Stage 7: Receipt of modified cells by pharmacy (innovative drug therapy).

Stage 8: CAR-T preparation.

Prior to CAR-T injection: Administration of lymphodepleting chemotherapy to enable expansion.

Injection

Monitoring of patient and short- and long-term adverse reaction management.
CHALLENGES ASSOCIATED WITH CAR-T CELLS

- 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
WP9 OBJECTIVES

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

iPAAC Stakeholder Forum, Brussels, 20 September 2018
## PARTICIPANTS WP9

<table>
<thead>
<tr>
<th>Associated partners</th>
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<tr>
<td><strong>Belgium</strong></td>
<td>Sciensano</td>
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<tr>
<td><strong>Italie</strong></td>
<td>CRO-Aviano</td>
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<td>(in collaboration with ISS)</td>
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<tr>
<td><strong>Lituanie</strong></td>
<td>National Centre of Pathology, Affiliate of Vilnius University Hospital Santaros Klinikos (VuHSK)</td>
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<tr>
<td><strong>Serbia</strong></td>
<td>Clinical Center of Kragujevac CCK</td>
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<td>(in collaboration with IPHS)</td>
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<tr>
<td><strong>Slovaquie</strong></td>
<td>Biomedical Research Center (BMC SAS)</td>
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<tr>
<td><strong>Spain</strong></td>
<td>INCLIVA</td>
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<td>CIBERONC</td>
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<tr>
<td><strong>Luxembourg</strong></td>
<td>National Cancer Institute</td>
</tr>
</tbody>
</table>

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)
**WP9 - GENERAL ORGANIZATION**

**02-03 July 2018**
Kick off meeting WP9 (Paris - INCa)

**16-17 April 2018**
Kick off meeting iPAAC (Luxembourg)

**Oct 2018**
WP9 meeting task 1 (M7 - Valencia)

**Feb 2019**
WP9 meeting tasks 2 & 3 (M11 - Brussels)

**Sept 2019**
WP9 meeting task 4 (M17 - Ljubljana)

**January 2021**
Workshop / presentation of results (M34 – INCa)

May 2019:
1st draft of the mapping of national guidelines

Nov. 2019:
1st draft biomarkers & Horizon scanning

April 2020:
1st draft real-life monitoring of immunotherapies

Jan 2021:
Final deliverable for Roadmap
TASK 9.1

CLINICAL PRACTICE GUIDELINES AND REFERENCE FRAMEWORK LINKED WITH THE IMMUNOTHERAPIES

Co-funded by the Health Programme of the European Union

iPAAC Stakeholder Forum, Brussels, 20 September 2018
TASK 9.1 - Guidelines and clinical practices reference framework

• **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
TASK 9.1 - SCOPE

• 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
TASK 9.1 - METHODOLOGY

**Literature review**

- Selection of key words and languages
- Definition of Inclusion & exclusion criteria
- Identification of guidelines and reference framework
- Brief presentation of each guideline (year of publication, authors, scope, key recommendations, 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
BIOMARKERS:
Predictive parameters for immunotherapies response and/or toxicity
TASK 9.2 - BIOMARKERS

• **Main goals:**
  
  • Analysis of biomarkers for innovative therapies as predictive parameters of response and/or side effects
    
    • 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
TASK 9.2 - METHODOLOGY

IDENTIFICATION OF BIOMARKERS USED IN CLINICAL ROUTINE

Similar method as for task 1
- Literature search
- Questionnaire
- Analysis of guidelines

+ Link with WP6

ANTICIPATION OF NEW BIOMARKERS

Similar method as for task 3
- Review of existing Horizon scanning systems
- Identification of specificities for biomarkers
TASK 9.3

HORIZON SCANNING :
A tool to anticipate innovative therapies
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 their impact on health, cost, society and the healthcare system; and to inform decision makers and research planners
GENERAL OBJECTIVES OF HORIZON SCANNING SYSTEMS

- 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
HORIZON SCANNING METHOD

Target of HS

Identification

Filtration

Prioritization

Analysis / Assessment report

Source: EuroScan, 2014: A toolkit for identification and assessment of new and emerging health technologies
TASK 9.3 – HORIZON SCANNING

• **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 example?)
    • Biomarkers

• **Deliverable:**
  • Horizon scanning in Europe: existing systems, new trends, implementation in Member states
  • April 2020
**TASK 9.3 - METHODOLOGY**

- Literature review
- Questionnaire

**Review of existing Horizon scanning systems and organizations**

- 
  - EuroScan
  - Benelux
  - Canadian Agency for Drugs and Technologies in Health

+ Pilot study for CAR-T cells?

**Highlight specific features needed for cell and gene therapies**

**Highlight specific features needed for biomarkers**
TASK 9.4
REAL LIFE MONITORING OF INNOVATIVE THERAPIES

Co-funded by the Health Programme of the European Union

iPAAC Stakeholder Forum, Brussels, 20 September 2018
 TASK 9.4 – REAL LIFE MONITORING OF INNOVATIVE THERAPIES

• **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

iPAAC Stakeholder Forum, Brussels, 20 September 2018
International literature review of system in place for real-life monitoring (with a focus of immunotherapies)
(CancerLink, 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
TASK 9.5

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

Co-funded by the Health Programme of the European Union

iPAAC Stakeholder Forum, Brussels, 20 September 2018
ROADMAP

Task 1
Guidelines

Task 2
Biomarkers

Task 3
Horizon Scanning

Task 4
Real Life monitoring

Task 5

Writing of the D 9.1: Roadmap on Implementation and Sustainability of Cancer Control Actions in the field of innovative cancer therapies

Coordination by WP4

ROADMAP Final deliverable

D 9.1: to be submitted to the European Commission

WP5
WP6
WP7
WP8
WP10
NEXT STEP

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

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THANK YOU FOR YOUR ATTENTION