EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Regulatory considerations in cancer immunotherapy product development

Perspectives of the European Medicines Agency

Presented by Patrick Celis, PhD on 4 November 2015
CAT secretariat

An agency of the European Union

# Presenter disclosure information and disclaimer

Patrick Celis

I have not relationships related to this presentation to disclose

Disclaimer:

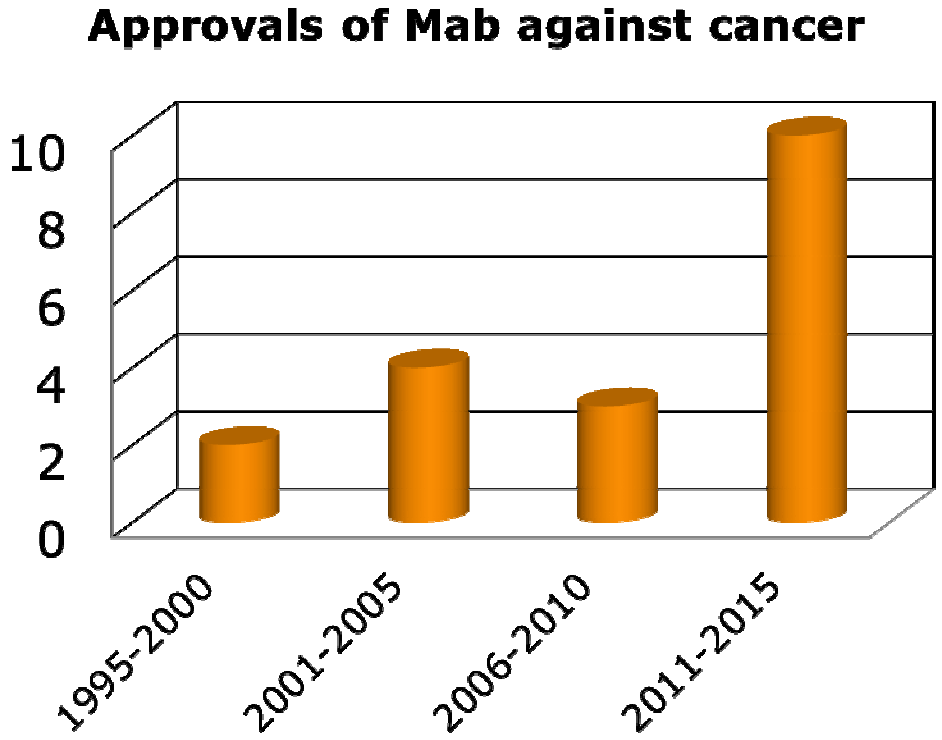
The view expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflection the position of the EMA or one of its Committees or working parties.

# Content

- Cancer immunotherapies: Approvals / experience at EMA
  - Monoclonal antibodies
  - Gene and cell-based immunotherapies
- Pipeline
  - Gene and cell-based cancer treatments in clinical trials and scientific advice
- How to get the best support for development of innovative medicines?

# Marketing authorisation applications for Cancer immunotherapies

- Monoclonal antibodies:
  - 18 products approved (4 in 2015), 1 refused, 1 withdrawn



# Marketing authorisation applications for Cancer immunotherapies: monoclonal AB

- PD-1 receptor blockers
  - Nivolumab (Nivolumab BMS/Opdivo) – NSCLC/melanoma (2015)
  - Pembrolizumab (Keytruda) – melanoma (2015)
- CTLA4 receptor blocker
  - Ipilumumab (Yervoy) – melanoma (2011)
- Targeting CD20 receptor (lymphocytes)
  - Ofatumumab (Arzerra) – CLL (2010)
  - Obinutuzumab (Gazyvaro) – CLL (2014)
  - Rituximab (MabThera) – Non Hodgkin lymphoma / CLL (1998)

# Marketing authorisation applications for Cancer immunotherapies: monoclonal AB

- VEGF receptor blockers
  - Bevacizumab (Avastin) – carcinoma of colon / rectum (2005) (additional indications approved: breast, lung, kidney, ovarian, fallopian tube, pertioneal, cervix cancer)
  - Ramucirumab (Cyramza) – gastric cancer / gastro-oesophageal junction adenocarcinoma (2014)
- Targetting EGFR
  - Cetuximab (Erbitux) – CLL (2004)
  - Panitumumab (Vectibix) – colorectal cancer (2007)
- Targetting HER-2
  - Trastuzumab (Herceptin) – breast cancer (2000)
  - Pertuzumab (Perjeta) – breast cancer (2013)

# Marketing authorisation applications for Cancer immunotherapies: monoclonal AB

- Combined actions
  - Brentuximab conjugated to monomethyl auristatis E: binds to CD30 on lymphocytes + cytotoxin (microtubular inhibitor) (Adcetris) – CD30+ Hodgkin Lymphoma (2012)
  - Trastuzumab conjugated to DM1: binds to HER2 + toxic effect on cell skeleton assemby (Kadcyla) – breast cancer (2013)
  - Ibritumomab + $^{90}Y$: binds to CD20 on B-lymphocytes + B cell destruction by radiolabel (Zevalin) – non Hodgkin lymphoma (2004)
- Other targets
  - EpCAM: catumaxomab (Removab) – EpCAM+ tumours (2009)
  - Ganglioside GD2: Dinutuximab (Unituxin) – neuroblastoma (2015)

# Marketing authorisation applications for Cancer immunotherapies

- Gene and cell-based products (4)
  - Cerepro (sitimagene ceradenovec) – High grade glioma: withdrawn (after neg opinion)
  - Advexin (contusugene ladenovec) – Li-Fraumeni cancer / Squamous cell carcinoma of head/neck: withdrawn (during review)
  - Provenge (sipuleucel-T) – Prostate cancer: approved (2013) / withdrawn (for commercial reasons)
  - Imlygic (talimogene laherparepvec) – melanoma: approved (2015)

# Gene/cell based cancer treatments products under development

- Clinical trials
  - 01/2009 → 12/2014: 167 / 503 trials (33.2 %) with indication oncology / haemato-oncology.

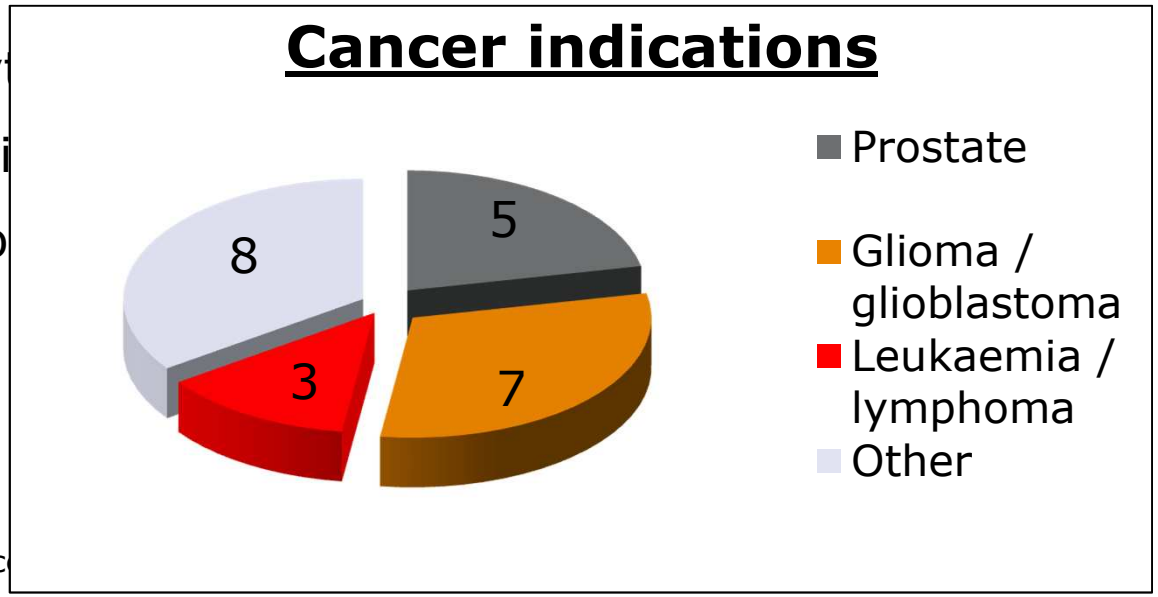
| Haemato-oncology/oncology | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | total |
| GT | 12 | 8 | 13 | 15 | 11 | 8 | 67 |
| CT | 22 | 13 | 19 | 13 | 18 | 15 | 100 |

- Scientific advice
  - 01/2009 → 12/2014: 23 different GT/CT oncology products
  - 11 GTMP / 12 CTMP

# Gene/cell based cancer treatment products in scientific advice (2009-2014)

- Cell therapy products (12)
  - Dendritic cells loaded with tumour antigens/peptides: 11
  - Other cell types: 1
- Gene therapy products (11)
  - Recombinant oncoly
  - Recombinant bacteri
  - Plasmids / non-onco
  - CAR-T cells: 2 *

(*: 2 additional CAR-T's in 2015)



# Gene/cell based cancer treatment products in scientific advice

- Clinical development programme

→ Generally, advice is requested on the (confirmatory) clinical trial protocol

  - Design / blinding / control
  - Endpoints (e.g. PFS or OS as 1° endpoint?)
  - Patient selection criteria
  - Statistical analysis plan
  - Is Ph1 + Ph2 trial sufficient for conditional license? (Ph3 post authorisation)

# Gene/cell based cancer treatment products in scientific advice

Non-clinical development programme

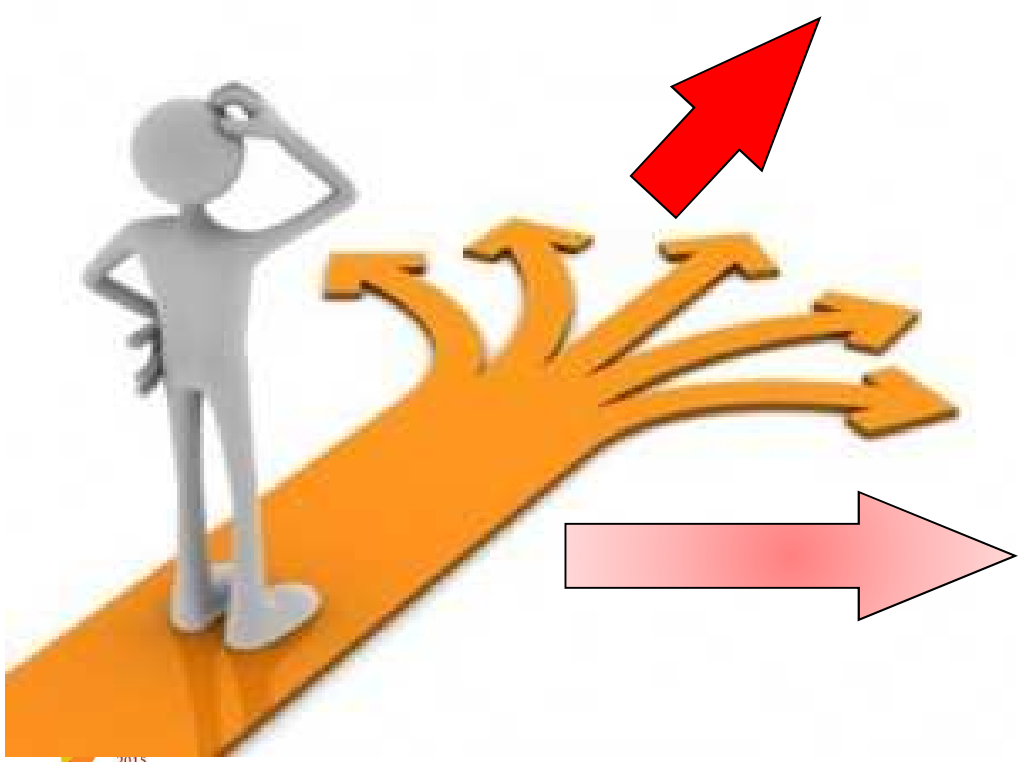
- Absence of a relevant animal model: in vitro study to demonstrate anti tumour effect?
- Long term toxicity / carcinogenicity study in animals with human cell product?
- Biodistribution/shedding/ERA (for GT)

Quality development

- Product specific
- Comparability, potency assays

# Looking for the best way forward to develop an innovative medicines / ATMP?

**Other EMA activities**



**Scientific advice** from CHMP and CAT at the EMA via SAWP

# Support to developers of medicines

## Scientific advice

**➔ Incentive: early – late / scientific certainty**

- Open to all applicants
- Scientific advice is given from the SAWP of the CHMP in collaboration with the CAT (+ other committees & working parties)
- Possibility for parallel SA with FDA
- EMA/HTA parallel scientific advice

# Support to developers of medicines

## Innovation task forces (ITF)

- Agency-wide coordination
- Briefing meetings: forum for early dialogue with drug developers

## Micro-, small- and medium-sized enterprise (SME) office

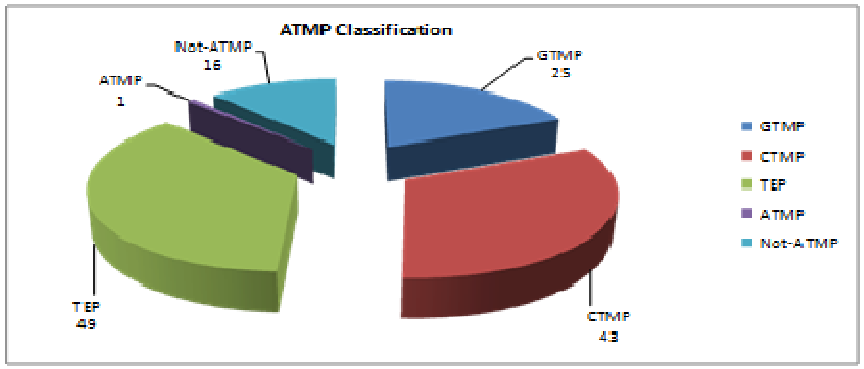
- EMA's SME office to promote innovation and the development of new medicines
- dedicated personnel support: responds to practical or procedural follow-up of product development
- SME specific incentives

# Support to developers of ATMPs

## ATMP classification procedure

**→ Incentive: Early / Regulatory certainty**

- Open to all applicants
- Free of charge
- Scientific recommendation from CAT on the regulatory classification of their ATMP
- Simple, 60-day procedure




(Status July 2015)

# Support to developers of ATMPs

## ATMP Certification procedure

**→ Incentive: early-late / scientific certainty**

- Only for SMEs
- Scientific evaluation by CAT of
  - (early) quality / development data (Module 3)
  - (early) non-clinical data (Module 4)
- 90 day procedure
- The applicant will always received the evaluation report and List of issue for future consideration
  - If positive evaluation: Certificate by EMA
- 6 Certification procedures finalised

# Early access mechanisms in EU

- Conditional marketing authorisation
  - MP for seriously debilitating/life-treatening diseases; for use in emergency situations; for orphan MP
  - Criteria: B/R positive + comprehensive data can be provided + unmet medical need + immediate availability outweighs risk due to missing data.

- Accelerated assessment
  - Medicinal products of major public health interest and in particular from the viewpoint of therapeutic innovation

# Early access mechanisms in EU

- Adaptive pathways
  - Scientific concept of development and data generation
  - Iterative development with use of real-life data
    - Extension of indication after initial approval
    - Conditional MA (eg on basis of surrogate endpoint) → full MA
  - Engagement with other heathcare-decision makers
    - Patients, prescribers, HTA

→ Pilot project since March 2014

# Early access mechanisms in EU


- PRIME (Priority Medicines)
  - To foster development of medicines with a high public health potential
    - Reinforced scientific and regulatory advice
    - Optimise development for robust data generation
    - Enable accelerated assessment
  - Eligibility to PRIME: justification of potential major public health benefit (criteria similar to those for accelerated assessment)
  - What does PRIME offer:
    - Early appointment of Rapporteur, tailored support, iterative SA at major development timepoints

# Lessons and Take home messages

- Key points
  - Many biological cancer immunotherapies (Mab) have been approved in EU
    - Often same products in EU and US
  - Gene/cell based cancer products
    - A substantial number are under development
    - Only 2 approved (in EU and US):
      - Provenge (DC-based) – prostate cancer
      - Imlygic (GM oncolytic virus) - melanoma

# Lessons and Take home messages

- Lessons learned
  - The regulatory system in EU is different from US but product development is global
  - Close and frequent interactions with EU regulatory authorities (national/EMA) is strongly advised, especially for gene / cell based products:
    - Scientific advice (on quality, non-clinical & clinical development)
    - Early access mechanisms
  - EMA and FDA talk to each other: Regular Oncology cluster and ATMP cluster telecons.

# Thank you for your attention. Any questions?

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- Information on ATMPs: follow 'Human Regulatory / Advanced Therapies'

- Information on PRIME:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/10/news_detail_002424.jsp&mid=WC0b01ac058004d5c1