



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# EMA and Progressive Multifocal Leukoencephalopathy.

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Presented by: Henry Fitt  
Head of Coordination & Networking, Pharmacovigilance & Risk Management





# In my presentation...

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What is PML?

Why is EMA interested in PML?

What has EMA done regarding PML?

- PML research agenda
- Multi stakeholder workshop

How can EMA further help?

- Raising awareness
- Facilitate Funding?



# What is PML?

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- Progressive Multifocal Leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system caused by JC virus (JCV)
- Devastating course (progressive neurological disabilities, behavioural changes, dementia, death)
- Knowledge of JCV and PML are limited.
- Different medicines tested for the treatment of JCV and PML, none have yet demonstrated efficacy.



## What is PML?

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- PML is a severe adverse reaction of several drugs that affect immunological functions, in particular monoclonal antibodies (MAbs).
- Reports of PML related to the use of MAbs are growing and have occurred in patients with cancer, HIV/AIDS, transplantation patients, and patients with immune disorders such as rheumatoid arthritis or multiple sclerosis.



# Why is EMA interested in PML?

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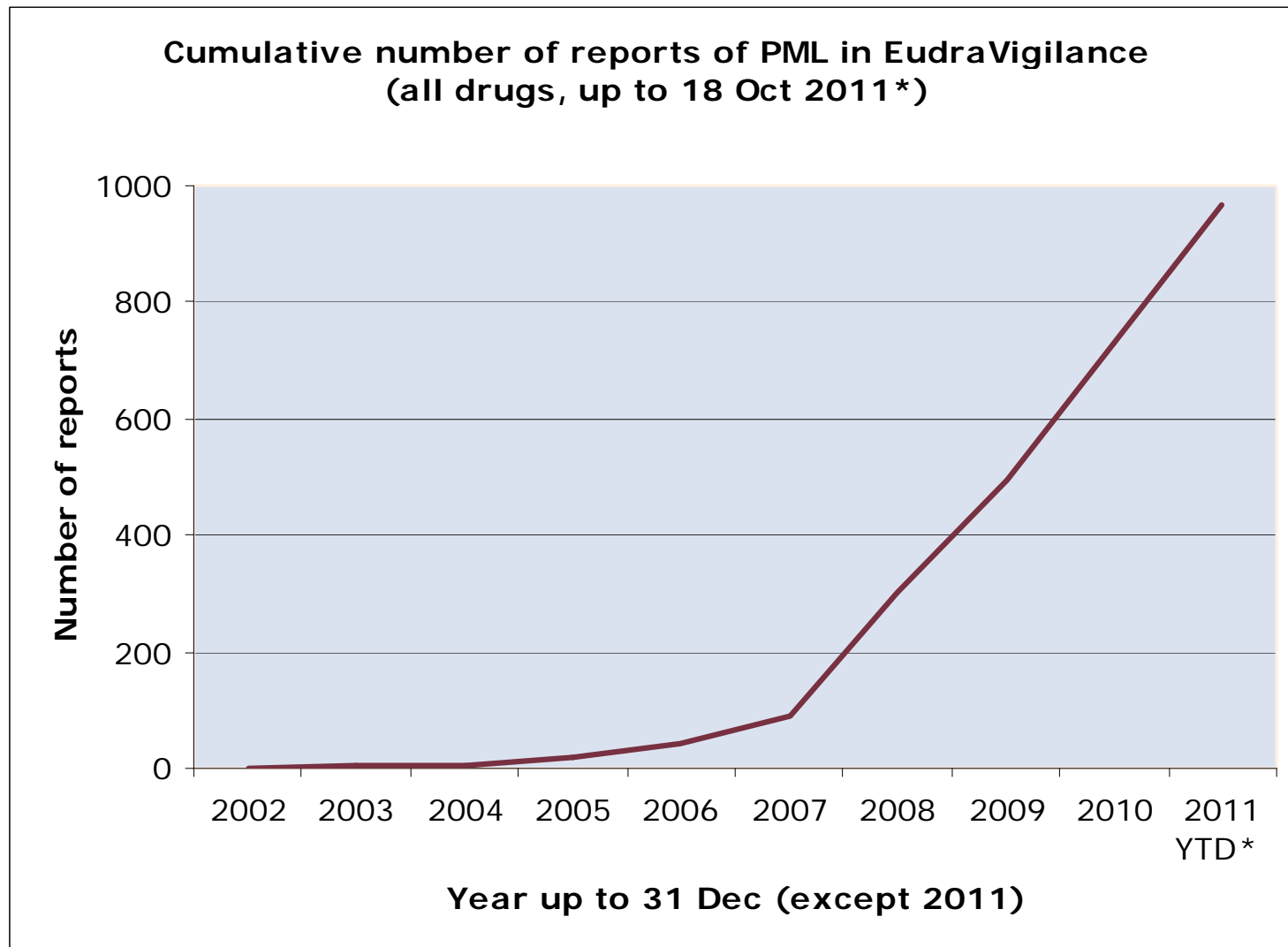
Confirmed cases of PML related to 4 EMA authorised MABs (from both clinical trials and post marketing).

- Tysabri (**natalizumab**), disease modifying therapy in highly active relapsing remitting multiple sclerosis
- Mabthera (**rituximab**), indicated in Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis
- Arzerra (**ofatumumab**) indicated for the treatment of chronic lymphocytic leukaemia (CLL)
- Raptiva (**efalizumab**) indicated for chronic plaque psoriasis (withdrawn)

Considering the mechanisms that link MABs and PML, more drugs from this class could be associated with PML.



# Why is EMA interested?





# Why is EMA interested in PML?

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From the public health protection perspective, considering

- PML is such a severe complication, and
- MAbs represent effective (or the only) treatment options for many serious diseases

it makes consideration of benefits and acceptable risks an issue of high interest.



## PML research agenda project

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- Different regulatory actions regarding drug-related PML (product specific) have been taken in recent years;
- Project to develop EMA “PML research agenda” (not product specific) since January 2010 in collaboration with FDA;
- An innovative approach to adverse events common to different medicines;
- Define researchable questions that would help regulatory agencies to protect public health;
- Endorsed by PhVWP and CHMP in June-July 2010.





# Transatlantic PML Workshop (July 2011)

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Brought together the experts and all the stakeholders on PML to a common purpose of reducing the burden of PML

## General objectives

1. Common understanding of research priorities;
2. Map ongoing research and identify gaps
3. Foster partnerships and funding to conduct research to fill knowledge and research gaps;
4. Agree a mechanism to ensure information sharing and regular stocktaking of research results, knowledge, knowledge gaps.



# Transatlantic PML workshop

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- Meeting very well attended and well received;
- Proceedings are published on EMA website:  
<https://docs.eudra.org/webtop/dr1/objectId/090142b281914a2c>
- Follow-up TC with key stakeholders on-going



# Scientific highlights I – What we know

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## The disease

- PML is a demyelinating disease, localised in the brain;
- It is rare, severe and can be lethal;
- Most frequently in immunosuppression;
- Diminished if trigger can be eliminated;
- PML can be induced by certain drugs.

## The virus

- Caused by JC virus (JCV);
- JCV infects only humans; no animal models exist; grows very slowly in vitro;
- JCV is common, present in around 50% of population;
- It has one serotype but several different genotypes are known;
- It can replicate in the urinary tract asymptotically.

## The PML patient

- Clinical presentation known;
- Less severe if: young patient, early diagnosis and intervention, unilobar;
- Malfunction of the immune system leads to higher risk;
- For drug-related PML, risk increases with duration of treatment (in first few years);
- The PML risk limits the use of some effective therapies.



# What we don't know

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## The disease:

- How to best ascertain the number of drug-induced PML cases;
- No universally accepted case definition exists;
- No specific prophylaxis or treatment exists;
- No animal model and no plaque assay;
- No predictive markers for PML;
- Limited data regarding the risk of drug-induced PML beyond 3 years of MAbs treatment;
- The long-term impact of IRIS therapies is unclear;

## The patient:

- How best to communicate the benefit/risk of drugs causing PML?
- Which patients should not be treated with a PML-inducing drug?
- Which biomarkers should be monitored for drug-induced PML?
- How often should MRIs and CSF assessments be conducted?
- What is the value of a drug holiday? • How can PML be distinguished from MS relapse?
- Which are the best type of information and communication tools to healthcare professionals and patients?



# Transatlantic PML workshop - **The Future**

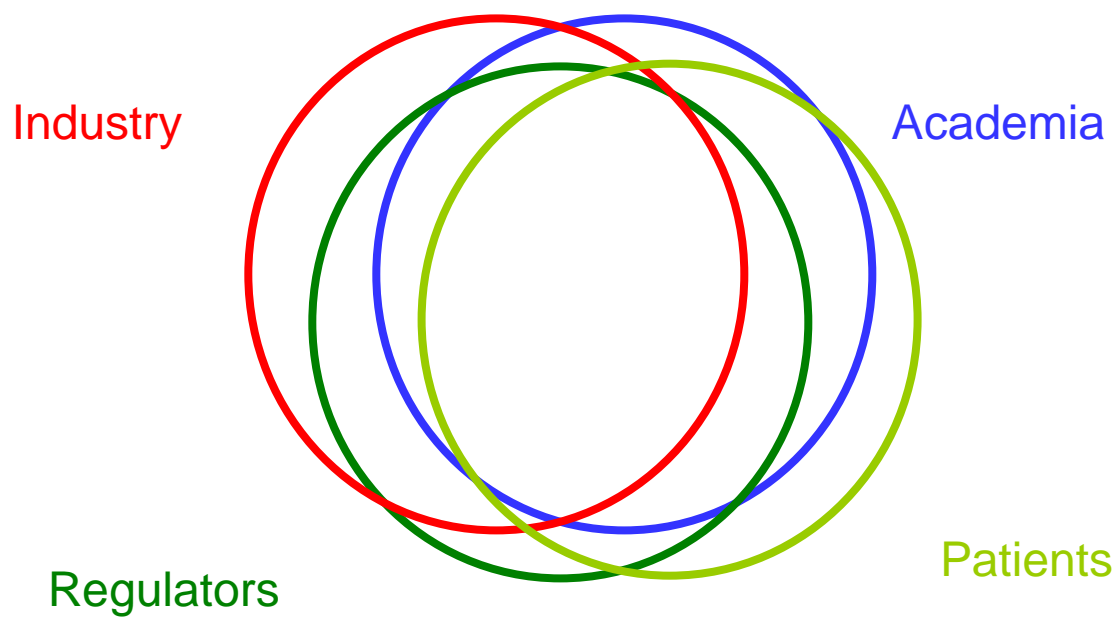
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- Benefit and risk should be presented together to inform decision making;
- PML challenges require collaboration on a global scale;
- Input from different disciplines/fields will benefit research progress;
- Sharing of information, best practice and resources between all stakeholders will produce results faster.



# Research Agendas I

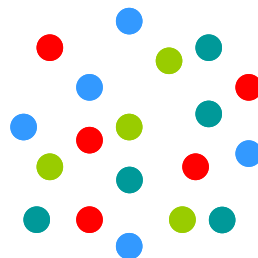
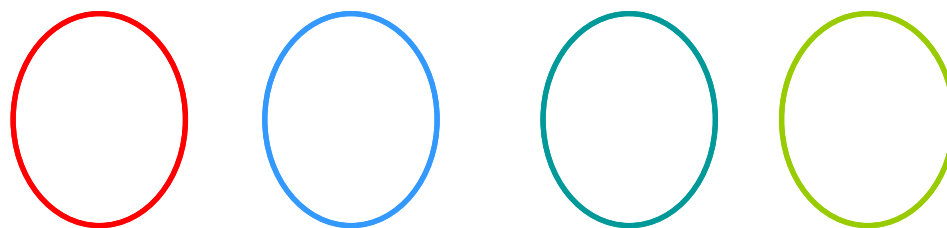
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# Research Agendas II

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# Revised Agenda Post-PML Workshop

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# JCV

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- Effective anti-viral therapy;
- Relevant animal model/cell culture model to test therapies;
- Viral gene regulation in specific cells;
- Develop small molecules to modulate viral growth and behaviour;
- Clinical studies for potential interventions;
- Investigate molecular genomics/proteomics (viral and host).



## Prediction and Prevention

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- How to identify populations at risk before treatment;
- Which patients should not be given specific drugs;
- Biomarkers;
- Anti-JCV antibodies as risks indicators;
- Risk of PML beyond 3 years;
- Develop vaccines, peptides and other prophylactic interventions;
- **Repository of samples.**



## Benefit/Risk

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- Which is the B/R ratio of PML-inducing drugs?
- Which patients should not take specific drugs?
- How to minimize the risk of PML?
- How to involve patients more in B/R methods and decisions?
- Which is the best way to evaluate effectiveness of risk minimization activities?
- Clinical validation of risk stratification assay.



# Therapy

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- How to treat PML?
- How to evaluate new therapies with risk of PML?
- Value of drug holidays;
- Best strategy for Immune Reconstitution Inflammatory syndrome (IRIS);
- Long-term value of plasma exchange/ immunoadsorption;
- Create a clinical database for research (demographics, clinical information, MRI images...).



# Communication

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- Improve pathways to collect information;
- Improve pathways to disseminate information (on disease, therapies, risks, safety, etc...);
- Improve communication between stakeholders;
- Establish collaborative research networks (PML Consortium).



# PML research agenda

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## **Drug-induced PML: A global agenda for a global challenge**

*Submitted for publication Nature's Clinical  
Pharmacology & Therapeutics*



# PML - Initiatives that may contribute

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- Industry PML Consortium (EMA observer in the Consortium Advisory Board)
- IMI
- EU (7<sup>th</sup>) Framework Programme
- NIH
- ENCePP
- Academic networks
- Registries
- Sentinel Initiative



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# THANK YOU