A common case definition for PML

Transatlantic workshop:
Drug-related Progressive Multifocal Leukoencephalopathy (PML)
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Introduction

- up to 14.07.2011 a total of 146 confirmed PML cases have been reported from post-marketing experience
- 3 PML cases (2MS, 1 CD) have been reported from clinical trials
- first post-marketing PML case was diagnosed in 07/2008
- continuous increased reporting of PML cases triggered an Art. 20 procedure in November 2009 (29 PML cases)
- implementation of warning statement, that duration of more than 24 months of Tysabri treatment is increasing the risk of PML in MS
- CHMP opinion on favourable benefit/ risk balance in April 2011 with further identification of additional risk factors for PML (IS and JCV serology)

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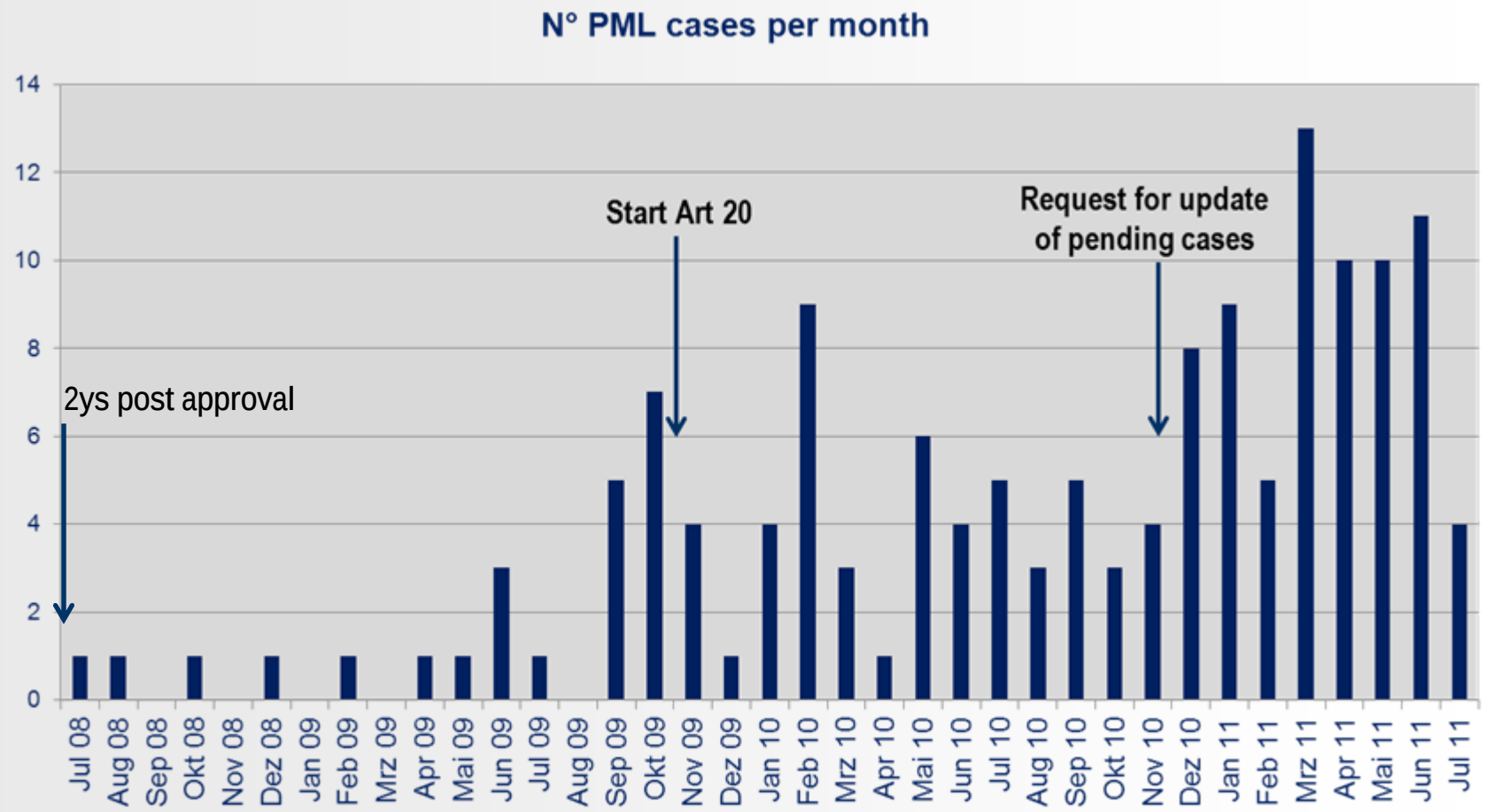
Post-marketing reports of PML cases



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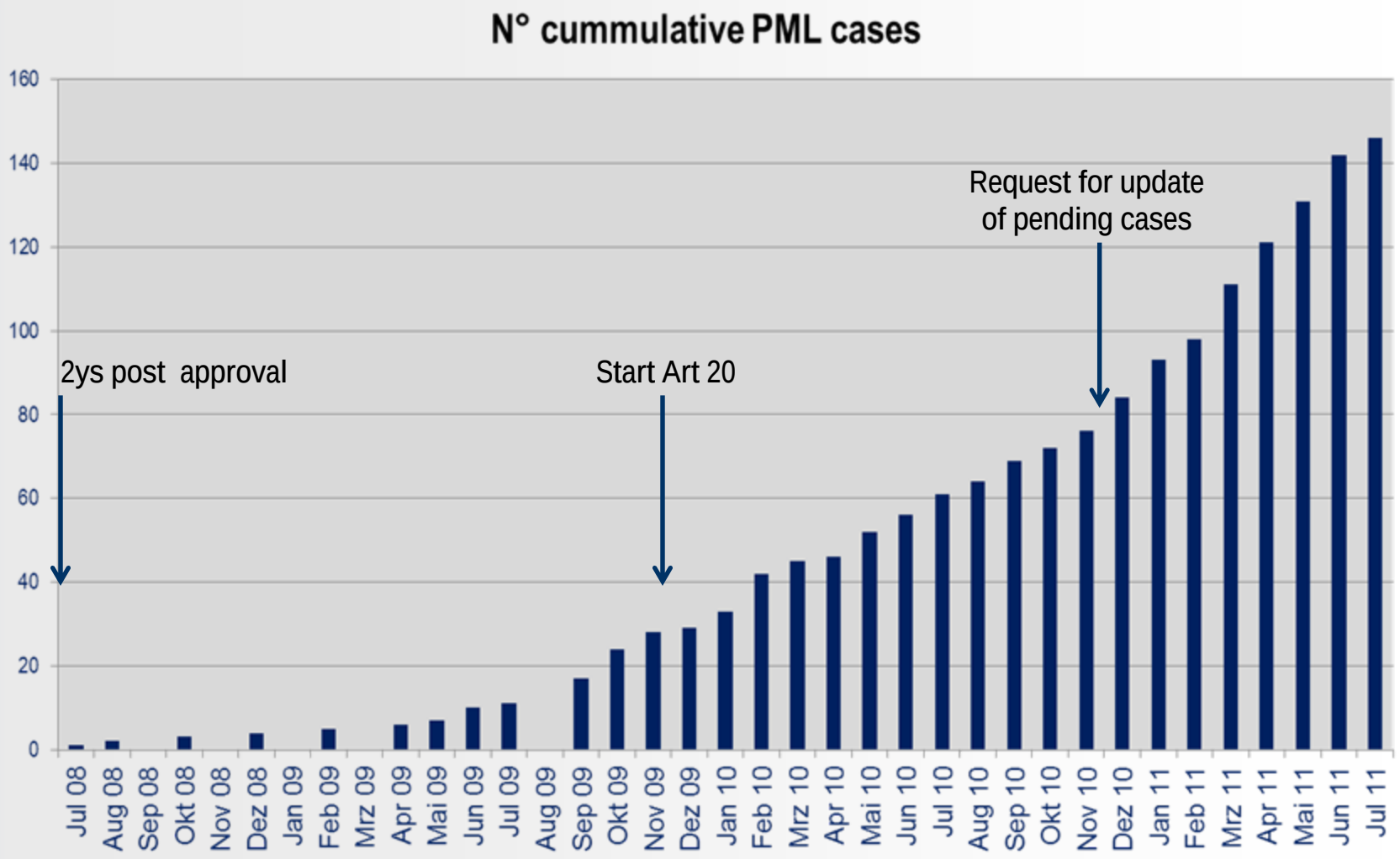
Post-marketing reports of PML cases



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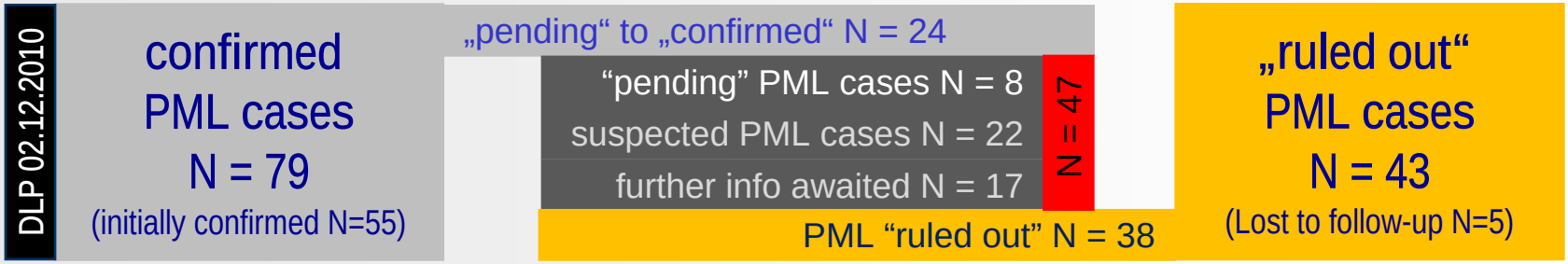
Why applying a common case definition for PML?



Request for a case definition to judge on reported PM suspected PML cases

confirmation of a suspected case of PML requires the presence of JCV DNA in the CSF, but the presence of JCV DNA in isolation, without clinical symptoms and MRI features consistent with the diagnosis, is insufficient to confirm a case of PML.

=> Confirmation of PML if clinical symptoms, MRI pathology and JCV DNA is positive in CSF and confirmed in reference Lab.

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Proposal – level 1 of diagnostic certainty

Clinical symptoms consistent with PML

Presence of focal neurological deficits, including new deficits, that may be subacute in onset, or worsening of deficits; symptoms may include e.g.

recent changes in behaviour or personality, cognitive dysfunction, hemiparesis, language disturbance, retrochiasmal visual deficits,new onset of seizures (one symptom may be sufficient to raise the suspicion of a PML).

AND

Evidence of PML from a brain biopsy

Histopathological evidence from brain biopsy (demyelination, enlarged oligodendroglial cells, bizarre astrocytes) in addition to immunohistochemical (JCV large T Ag and JCV VP1 capsid protein) or electron microscopic (JCV virions) evidence.

OR

Clinical Symptoms Consistent with PML (see above)

AND

Characteristic PML findings on MRI as described in a radiological report OR based on expert review of MRI.

AND

PCR for JC Virus DNA in CSF positive (obtained by a laboratory with specific virological expertise and a validated assay).

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Proposal – level 2 of diagnostic certainty

Clinical Symptoms Consistent with PML

Presence of focal neurological deficits, including new deficits, that may be subacute in onset, or worsening of deficits; symptoms may include e.g.

recent changes in behaviour or personality, cognitive dysfunction, hemiparesis, language disturbance, retrochiasmal visual deficits,new onset of seizures (one symptom may be sufficient to raise the suspicion of a PML).

AND

PCR for JC Virus DNA in CSF positive (obtained by a laboratory with specific virological expertise and a validated assay).

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Proposal – level 3 of diagnostic certainty

a) Clinical Symptoms Consistent with PML (see above)
AND
Brain MRI Characteristic of PML (see above)
AND
PCR for JC Virus DNA in CSF or brain biopsy are NOT available OR PCR assay for JCV DNA in CSF was obtained by a laboratory with unknown validation status of assay

b) Clinical symptoms somewhat unclear or not reported
AND
Brain MRI Characteristic of PML (see above)
AND
PCR for JC Virus DNA in CSF positive (obtained by reference laboratory)

c) Clinical symptoms somewhat unclear or not reported, MRI not available or unspecific (may also be consistent with MS relapse)
AND
PCR for JC Virus DNA in CSF positive (obtained by reference laboratory)
AND
IRIS reported after suspension of Tysabri and/or initiation of PML treatment (e.g. PLEX)

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Proposal – level 4 and 5 of diagnostic certainty

4) Cases not fulfilling level 1 to level 3 of diagnostic certainty (e.g. because of missing information) AND not meeting the exclusion criteria (category 5).

5) Neurological clinical assessment lead to alternative diagnosis (e.g. stroke, MS relapse)
AND
Absence of characteristic features of PML on brain MRI/ not characteristic for PML
AND
PCR for JC Virus DNA in CSF negative OR brain biopsy negative for PML (reference lab)

OR

Neurological clinical assessment lead to alternative diagnosis (e.g. stroke, MS relapse)
AND
Absence of characteristic features of PML on brain MRI/ not characteristic for PML

OR

Neurological clinical assessment lead to alternative diagnosis (e.g. stroke, MS relapse)
AND
PCR for JC Virus DNA in CSF negative OR brain biopsy negative for PML (reference lab)

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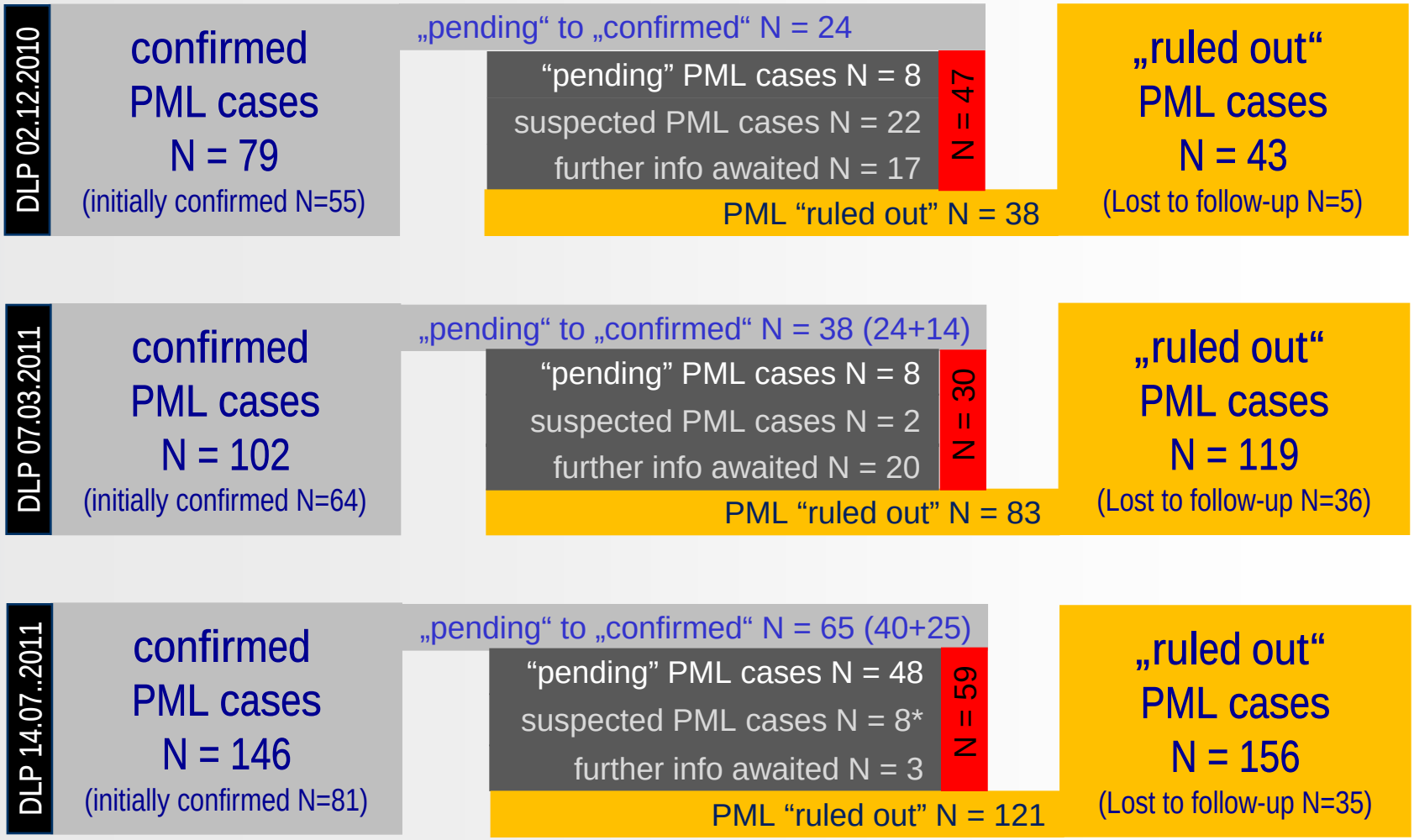
Summary



*Including 2 „intermediate PML cases