Industry Experience with PML:
Lessons Learned from TYSABRI® (natalizumab)

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Presentation Outline

- Risk Stratification with TYSABRI
- Case Definition for PML
- Benefit-Risk Communication

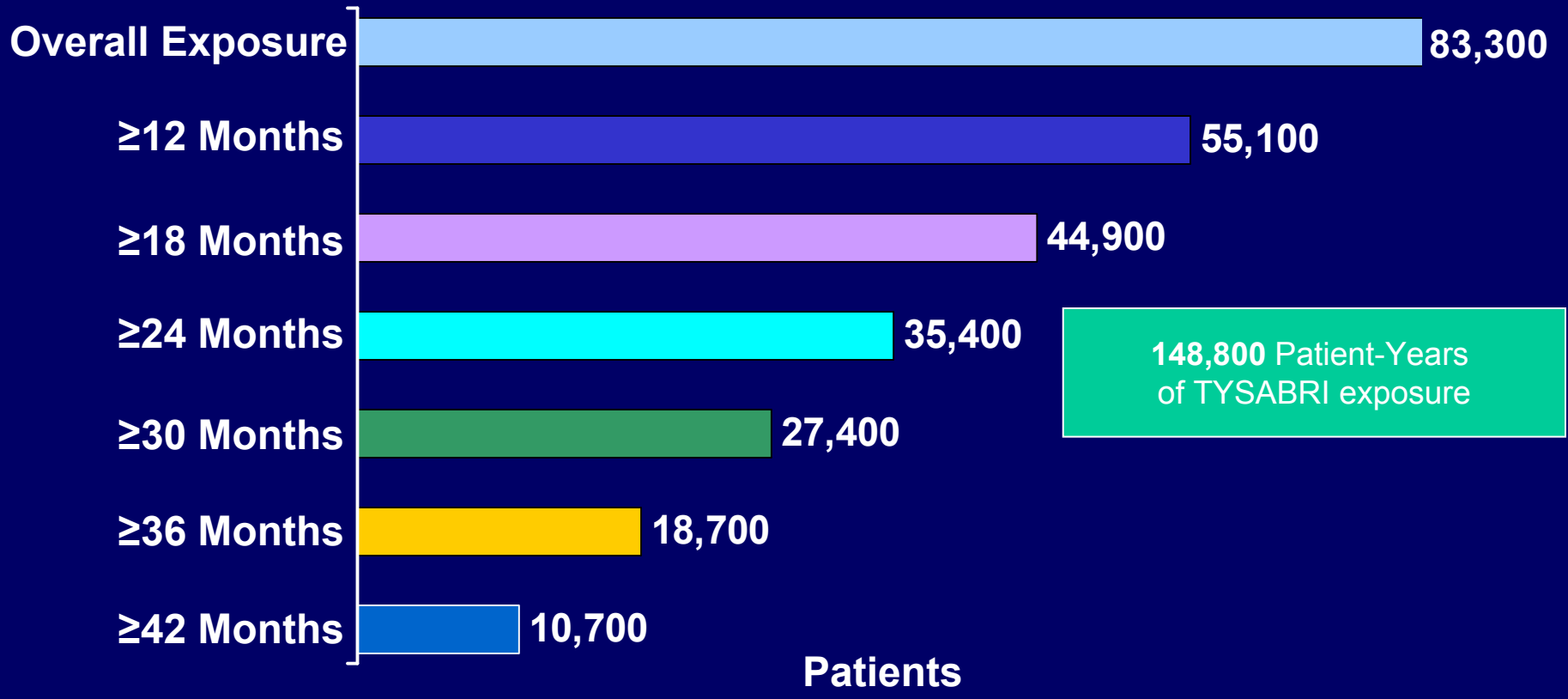
Risk Stratification with TYSABRI

TYSABRI® (Natalizumab) in the Treatment of Relapsing Multiple Sclerosis

- Monoclonal antibody against alpha-4 integrins
- Approved in >50 countries for relapsing multiple sclerosis
- Provides significant efficacy:
  - 68% reduction in annualized relapse rate
  - 42%-54% reduction in disability progression
- Due to risk of PML, global risk management programs implemented
  - US marketing approval in June 2006

Use of TYSABRI in the Post-Marketing Setting*

Worldwide post-marketing data from 23 November 2004 to 31 March 2011



*Post-marketing data includes patients exposed since 23 November 2004. This excludes a total of 4,700 patients exposed in clinical trials; 2,100 exposed for >12 months; 1,900 exposed for >18 months; 1,600 exposed for >24 months; 1,300 were exposed >30 months; 1,000 were exposed >36 months; and 700 were exposed >42 months. Exposure are estimates and may not fully reflect treatment interruptions that are used in certain patients.

PML Cases

- Of the 145 confirmed cases reported through July 5, 2011:
  - 57 are from the United States
  - 81 are from the European Economic Area
  - 7 are from the rest of the world

Biogen Idec Data on file.

PML Survival Outcomes

- 116 of 145 patients have survived (80% survival)
- Patients who survive have
  - Shorter duration of symptoms to diagnosis
  - More localized disease on brain MRI at presentation
  - Younger age and less disability prior to disease onset
- Improved survival likely due to:
  - earlier diagnosis
  - prompt cessation and active removal of TYSABRI
  - aggressive management of complications

*Data as of July 5, 2011

Functional Status in PML Survivors

Follow-up Time From PML Diagnosis	Number of Survivors at Follow-up Time with Karnofsky reported	Functional Status of Survivors		
		Mild Disability (Karnofsky = 80–100)	Moderate Disability (Karnofsky = 50–70)	Severe Disability (Karnofsky = 10–40)
≥ 6 months since PML diagnosis	47	6 (13%)	22 (47%)	19 (40%)*
≥ 9 months since PML diagnosis	18	3 (17%)	9 (50%)	6 (33%)

*Majority of patients with severe disability at ≥ 6 months from diagnosis (17/19, 89%) had Karnofsky scores of 40 which is at the interface between moderate and severe disability

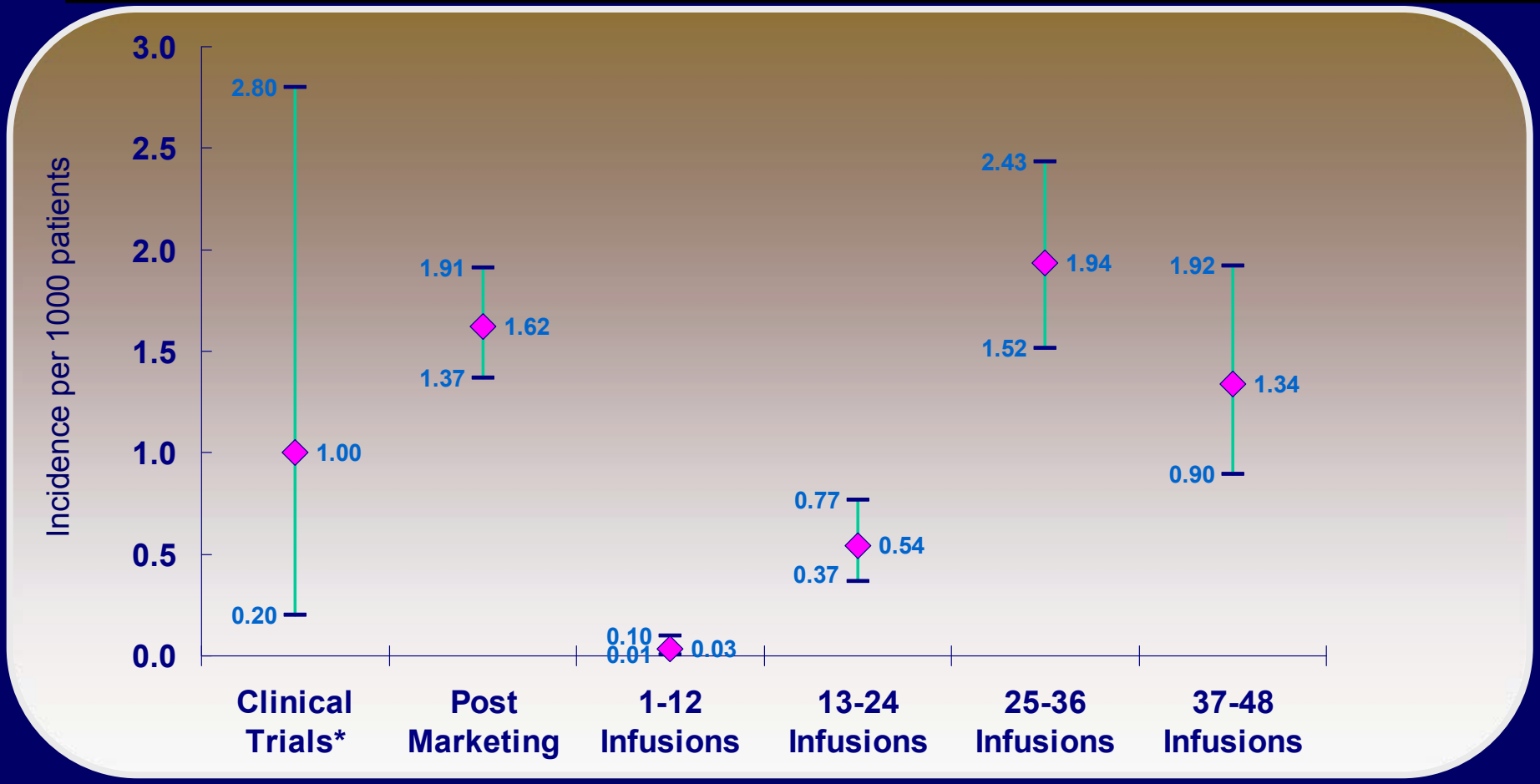
Based on data as of 01 June 2011 with 133 confirmed cases of PML and 109 survivors

Risk Factors for PML

- Each of the following risk factors is associated with an increased risk of PML in patients treated with TYSABRI:
  - Treatment duration, especially beyond 2 years.
  - Immunosuppressant use prior to receiving TYSABRI.
  - Presence of anti-JCV antibodies (Anti-JCV antibody positive status).

TYSABRI Summary of Product Characteristics June 2011

Incidence of PML by TYSABRI Treatment Duration



*Yousry TA, et al. *N Engl J Med.* 2006;354:924-933. Observed clinical trial rate in patients who received a mean of 17.9 monthly doses of natalizumab. T

he post-marketing rate is calculated as the number of PML cases since reintroduction in patients that have had at least 1 dose of natalizumab. Incidence estimates by treatment epoch are calculated based on TYSABRI exposure through June 30, 2011 and 145 confirmed cases as of July 5, 2011.

Prior Use of Immunosuppressants Increases the Risk of PML in TYSABRI-Treated Patients

- 42% of patients with PML had been treated with an immunosuppressant (IS) prior to receiving natalizumab
- Within the TYGRIS Observational Study, the proportion of all patients treated with natalizumab who had been treated with an IS prior to receiving natalizumab is 20.3%

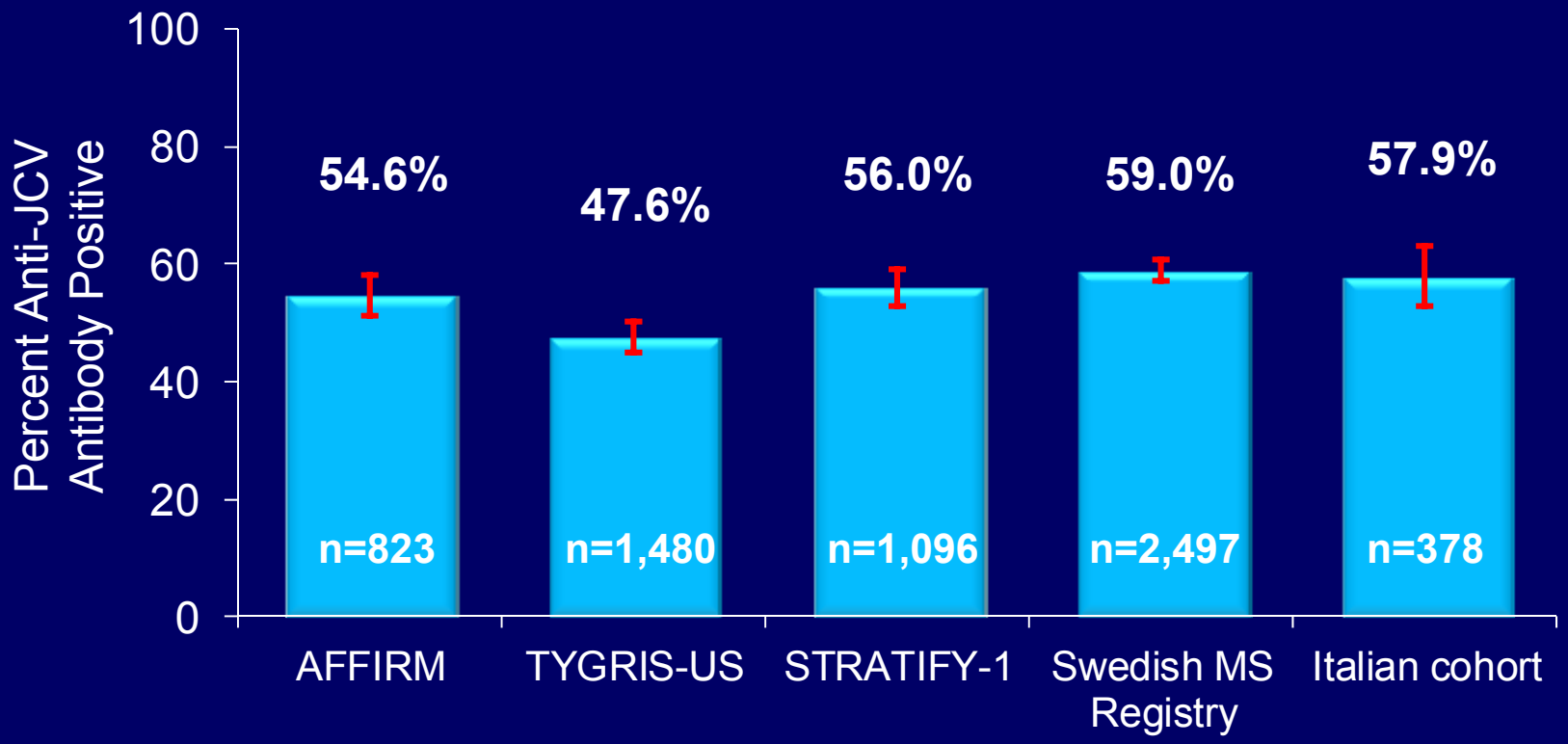
Based on PML cases as of 4 March 2011 and TYGRIS Observational Study data as of 23 November 2010. Biogen Idec, data on file.

Anti-JCV Antibody Assay

- JC virus infection is a key factor necessary for the development of PML
- The 2-step anti-JCV antibody assay (STRATIFY JCV) has been designed to identify patients exposed to the JC virus
- Prevalence of anti-JCV antibodies is ~50-60% in MS patients
- Prevalence not affected by TYSABRI treatment duration or prior immunosuppressant use
- Proportion of seropositive patients increases ~2-3% annually
- Low analytical false negative rate of ~3%

1. Gorelik et al. Ann Neurol 2010. 68: 295-303
2. Gorelik et al. Presented at: ECTRIMS; October 13-16, 2010; Gothenburg, Sweden. P873
3. Subramanyam et al. Presented at: ECTRIMS; October 13-16, 2010; Gothenburg, Sweden. Podium 138
4. Olsson et al. Presented at: ECTRIMS; October 13-16, 2010; Gothenburg, Sweden. P983
5. Biogen Idec Data on File.

Prevalence of Anti-JCV Antibodies Is Consistent Across Studies in MS Patients



Vertical bars represent 95% confidence intervals

1. Bozic et al. Presented at: AAN; April 9-16, 2011; Honolulu, Hawaii. P07.136
2. Sandrock et al. Presented at: AAN; April 9-16, 2011; Honolulu, Hawaii. P03.248
3. Moiola et al. Presented at: AAN; April 9-16, 2011; Honolulu, Hawaii. S30.007

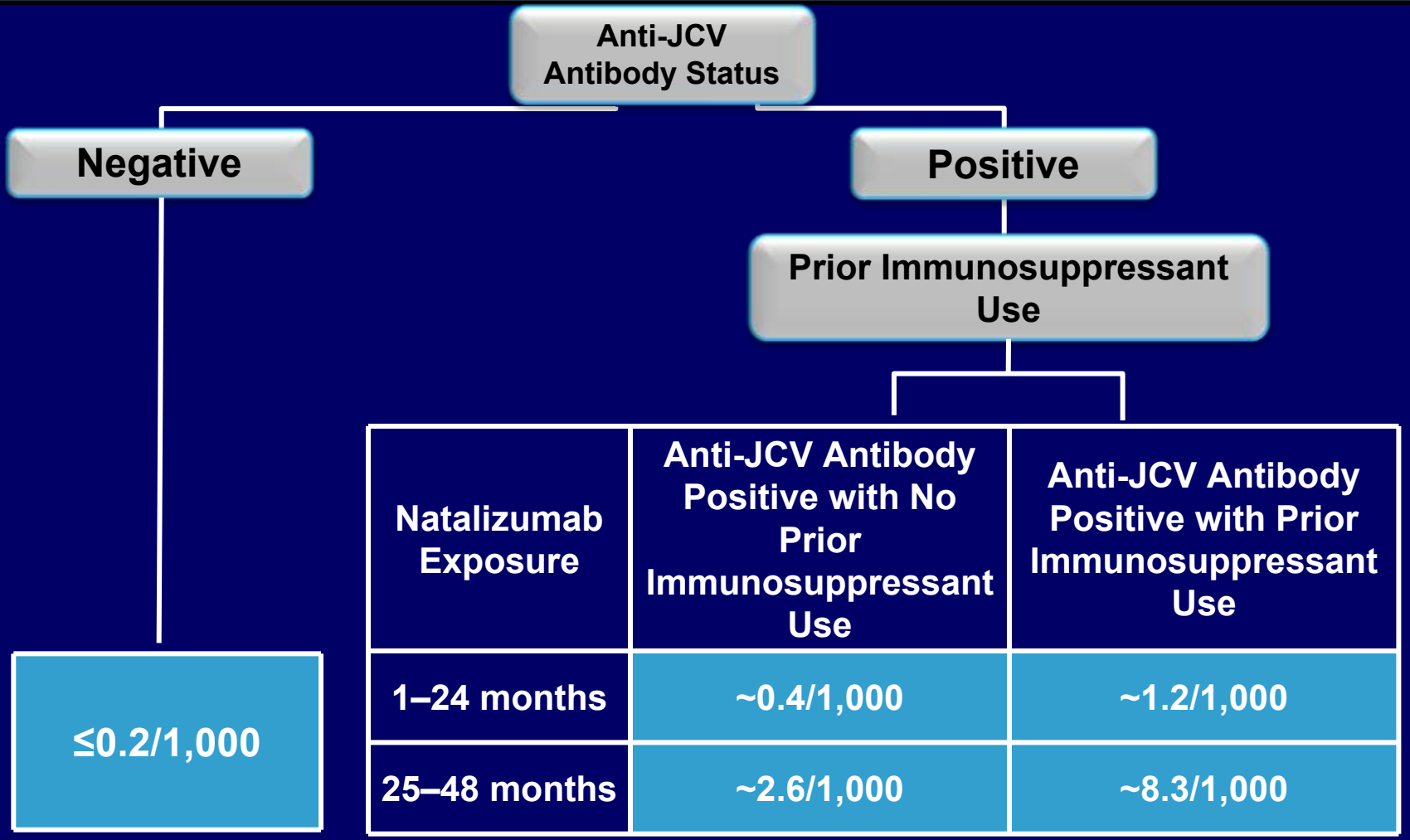
Anti-JCV Antibody Assay (Continued)

- As of 5 July 2011, anti-JCV antibodies were detected in all (n=30) TYSABRI-treated MS PML patients for whom serum samples were available 6-187 months prior to PML diagnosis

- The observed 30 out of 30 (100%) pre-PML cases is significantly different from the theoretically expected 15 out of 30 based on the 54% anti-JCV antibody positive rate observed in TYSABRI-treated MS population ($p<0.0001$).

Biogen Idec Data on File as of Juy 2011.

PML Risk Stratification Algorithm



Data beyond 4 years of TYSABRI exposure are limited.
Tysabri EU Prescribing Guidelines June 2011

PML Risk Stratification Including Anti-JCV Antibody Assay

- The clinical utility of anti-JCV antibodies to stratify patients at risk for PML development is being further evaluated in large studies.
- In December 2010, Biogen Idec and Elan filed with EU and US regulators to request approval to include anti-JCV antibody status in TYSABRI labeling.
- In June 2011, EC approved inclusion of anti-JCV antibody positive status as an additional risk factor for PML in the TYSABRI product label in EU.
- New era of personalized medicine: first biomarker in MS
- Risk stratification likely to be useful for individual benefit-risk treatment decisions regarding use of TYSABRI in MS patients

Biogen Idec Data on File as of Juy 2011.

Case Definition for PML

Evaluation of PML Reports

- Biogen Idec and Elan have several years of experience in evaluating reports of PML in patients treated with TYSABRI
- We are very diligent in evaluating any potential case of PML
- Definition for a confirmed case was developed in collaboration with PML experts:

Clinical and MRI findings consistent with PML and evidence of JCV DNA in CSF, preferably using an ultrasensitive, quantitative PCR assay

OR

Brain biopsy with evidence of JCV based on immunohistochemistry or in situ hybridization

Progressive multifocal leukoencephalopathy in HIV-1 infection

Paola Cinque, Igor J Koralnik, Simonetta Gerevini, Jose M Miro, Richard W Price

General Agreement on Criteria for Confirmed PML

***Panel:* Diagnostic criteria**

Definite (causative) diagnosis

- Cerebrospinal fluid confirmed progressive multifocal leukoencephalopathy: clinical and MRI findings consistent with the disease and evidence of JCV DNA in cerebrospinal fluid
- Tissue-confirmed progressive multifocal leukoencephalopathy: evidence of consistent neuropathology in brain tissues (biopsy or autopsy) with JCV DNA or protein detected by in situ techniques

Lancet Infect Dis 2009; 9: 625–36

Unique Challenges in Evaluation of PML Reports in TYSABRI-Treated MS Patients

- Due to education on PML by Biogen Idec and Elan, prescribers have high level of clinical vigilance for PML

  –Any patient with new neurological signs or symptoms should be evaluated for possible PML

- We highly encourage the reporting of possible PML to Biogen Idec

- Many of the reports of possible PML are early in their diagnostic work-up

Unique Challenges in Evaluation of PML Reports in TYSABRI-Treated MS Patients

- Cases detected early in clinical course (e.g. some patients are asymptomatic or have localized disease on MRI)
  - –Some cases may need repeated MRI and CSF over weeks or months to evaluate (e.g. MRI may be consistent with PML but CSF is negative)
- Use of various types of JCV DNA PCR assays with varying sensitivity and specificity
- Occasional difficulties in obtaining timely and detailed data from reporting physicians
- Differentiation between PML and MS can be challenging

PML Case Classification – Future Directions

- Biogen Idec and Elan support development of PML case assessment criteria using the Brighton Collaboration approach
- We believe there is general agreement regarding the definition for a confirmed case of PML
- Currently there are no established criteria for the definition of a “suspect case” of PML
  - Due to unique issues with TYSABRI and MS, may be difficult to establish universal criteria for “suspect cases”
- We look forward to further collaboration with regulators and PML experts in this area

Benefit-Risk Communication

Communication on PML

- Biogen Idec and Elan communicate extensively on PML risk
- Number of PML cases, incidence, risk factors, and other key information are updated on a monthly basis
- Data provided to physicians upon request
  - Through medical information web-sites and medical affairs personnel globally
- Feedback from prescribers has been favourable

Challenges in Communication of Emerging Safety Information

- Prescribers provide an abundance of information on their patients
- In return, prescribers expect to learn of new emerging safety information from the sponsor company
- Communications by a company to prescribers regarding emerging safety information may be viewed as a promotional activity by regulators in certain regions
- A pathway for companies to *proactively* communicate emerging safety information should be established

Challenges with Communicating Balanced Benefit-Risk Information

- Both risk and benefit information are essential to make an informed decision
- Current risk management activities communicate only risk, without any benefit information
- Leads to imbalance of benefit/risk information
- Unintended consequence may be that patients choose to forego appropriate treatment for their therapy
- We recommend adding benefit information to educational materials in the risk management plan

PML: Lessons Learned from TYSABRI

- Biogen Idec and Elan communicate extensively on PML risk
- There is general agreement regarding definition for confirmed PML
  - We look forward to further collaboration with regulators and PML experts on refinements to “suspect” PML definitions
- PML risk in TYSABRI patients is increasingly well characterized
  - Majority of patients alive (80%) with disability from mild to severe
  - Survival outcomes better than observed in other PML cohorts
  - Duration of TYSABRI treatment , prior immunosuppressant treatment and presence of anti-JCV antibody are risk factors for PML
  - Anti-JCV antibody assay results combined with other known PML risk factors can stratify the risk of PML
- New era of personalized medicine and individual benefit-risk treatment decisions for patients with MS