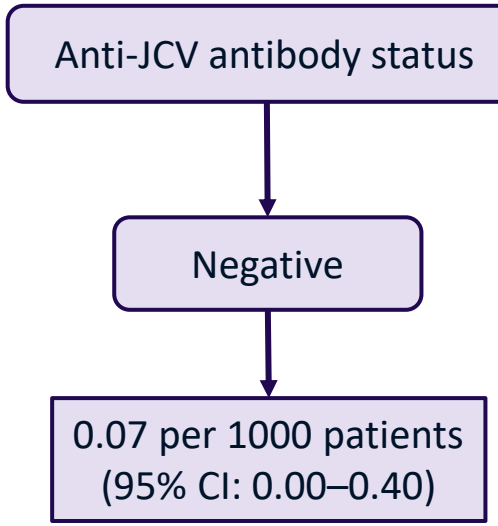
Natalizumab-Associated PML

Conditional probability of developing PML based on known risk factors
(latest published risk estimates)



Positive

Natalizumab exposure (months)	No previous IS use, per 1000 patients (95% CI)			Previous IS use, per 1000 patients (95% CI)
	Index ≤0.9	Index >0.9 to ≤1.5	Index >1.5	
1–12	0.01 (0.00–0.04)	0.1 (0.0–0.2)	0.2 (0.2–0.5)	0.4 (0.0–2.3)
13–24	0.06 (0.00–0.16)	0.3 (0.0–0.6)	1.0 (0.3–1.7)	0.5 (0.0–2.6)
25–36	0.2 (0.0–0.4)	0.8 (0.1–1.6)	2.8 (1.5–4.1)	3.9 (1.6–8.0)
37–48	0.4 (0.0–1.1)	2.1 (0.2–4.0)	7.1 (4.6–9.5)	8.8 (4.6–15.4)
49–60	0.5 (0.0–1.3)	2.4 (0.2–4.7)	8.2 (5.0–11.3)	8.8 (3.8–17.3)
61–72	0.6 (0.0–1.6)	3.0 (0.2–5.9)	10.2 (5.7–14.7)	5.6 (1.2–16.3)

PML, progressive multifocal leukoencephalopathy; JCV, John Cunningham virus; IS=immunosuppressant.

Ho PR et al. *Lancet Neurol*. 2017;16:925-933.

Strategies for Mitigating Risk of Natalizumab-Associated PML

Risk of PML if natalizumab is continued

Risk of increased/recurrent disease activity if natalizumab is discontinued

Monitoring[1]

- Clinical vigilance
- Screening every 3–4 months with an abbreviated MRI protocol
  - (ie, fluid-attenuated inversion recovery, T2-weighted, and diffusion-weighted imaging)

Extended-interval dosing[2,3]

- Real-world studies and the randomized NOVA study suggest dosing can be extended to every 6 weeks in most patients who are stable on 4-week dosing without clinically meaningful loss of efficacy[2]
- Analysis of data from the TOUCH program showed clinically and statistically significantly lower PML risk with extended-interval dosing[3]

Switching[4,5]

- Associated with greater risk if carry-over PML develops
- Washout periods longer than 4 weeks associated with higher reactivation of disease activity (relapse and/or MRI)
- Bridging options include intermittent methylprednisolone or an oral agent for 6–12 months before switching to another monoclonal antibody

PML, progressive multifocal leukoencephalopathy; TOUCH, Tysabri (natalizumab) Outreach: Unified Commitment to Health.

1. Wattjes MP et al. *Lancet Neurol.* 2021;20:653-6702; 2. Foley JF et al. *Lancet Neurol.* 2022;21:608-619; 3. Ryerson LZ et al. *Neurology*. 2019;93:e1452-e1462; 4. Giovannoni G et al. *Pract Neurol.* 2016;16:389-393; 5. Havla J et al. *Ther Clin Risk Manag*. 2013;9:361-369.