Background: The efficacy of natalizumab (Tysabri) in reducing new or newly enlarging T2 magnetic resonance imaging (MRI) lesions and improving Expanded Disability Status Scale (EDSS) score has been demonstrated in relapsing-remitting multiple sclerosis (RRMS) patients who are naive to disease-modifying therapies (DMTs). However, most patients currently receiving natalizumab have not responded to first-line DMTs. Objectives: To describe the MRI and EDSS progression of the patient cohort with RRMS that had initiated natalizumab after not responding to other therapies. Methods: In a retrospective chart review, 39 RRMS patients were followed for a minimum of 6 and a maximum of 24 months. Patients had a neurologic examination (EDSS) and MRI repeated every 6 months. Descriptive statistics and difference scores compared with baseline are reported for EDSS, T2-hyperintense (T2) lesions, gadolinium-enhancing (Gd+) lesions, and T1-hypointense lesions (black holes). Results: Of the 39 patients, 11 were previously treated with glatiramer acetate (Copaxone), 16 with interferon beta-1b (IFNβ-1b; Betaseron), 11 patients with IFNβ-1a (Avonex: 3 patients; Rebif: 8 patients), and 1 with azathioprine (Imuran). Patients may have received concomitant steroidal treatment or other agents not mentioned above, such as mitoxantrone. The median EDSS score was 3.0, and median counts for T2 lesions and black holes were 18 and 4, respectively. Gd+ lesions could not be significantly studied because only one new Gd+ lesion presented throughout the treatment course. No statistically significant changes in EDSS or MRI measures were observed at any of the examinations at 6, 12, 18, and 24 months. Through month 18, EDSS score appeared slightly worse (41% of patients worse, 32% the same, and 27% improved compared with month 0). This change was reversed at month 24, but only 13 patients completed treatment up to this point. Conversely, T2 lesion counts stayed the same or improved through month 24 (54% of patients stayed the same, 38% improved, and 8% were worse compared with month 0). The majority of patients had no change in black holes. Conclusions: At 18 months and up to 24 months of natalizumab treatment, 87% of RRMS patients previously treated with DMTs showed stable to improved MRI scans. Disability scores as measured by the EDSS were stable or improved in 59% of patients. Supported by: Consortium of Multiple Sclerosis Centers Disclosure: S.S. Kirzinger: Bayer Healthcare (consulting fee); Biogen Idec, Bayer Healthcare, EMD Serono, Pfizer, Teva Neuroscience, Questcor (honoraria). M. Ettensohn, J. Jones: Nothing to disclose. Keywords: disease-modifying treatment in MS, imaging and MS.