Abstract: Agents that Alter Immune Tolerance: Effects on Development of Autoimmune Hepatitis

Autoimmune hepatitis can result from the treatment of patients with checkpoint inhibitory drugs that negate signals blocking lymphocyte activation, thereby generating immune responses with both intended (anti-tumor) and unintended (autoimmune disease) consequences. Thus, treatment of oncology patients with anti-CTLA4 mAb (ipilimumab) has induced autoimmune hepatitis in 7-19% of patients (1,2). Importantly, treatment of patients with ipilimumab together with dacarbazine, a drug known to have liver toxicity, induced immune mediated hepatitis (grade 3-4) in 31.6% as compared to only 2.4% in patients treated with dacarbazine alone (3) suggesting that autoimmunity, unleashed by check point inhibition, is strongly enhanced in the presence of tissue specific damage with release of autoantigens. Outcomes were generally favorable when treatment with such checkpoint blockers was stopped and, in many cases, patients were treated with corticosteroids or other immune suppressive agents (3). A second check point inhibitor, the PD-1 specific mAb nivolumab also induced hepatic toxicity in a significant cohort of melanoma patients (5-6%) with advanced disease (4). Synergy in development of liver toxicity was observed in combined PD-1 and CTLA-4 mAb therapy for patients with previously untreated advanced melanoma with an incidence of 18% overall and 8.3% of
grades 3-4 while that of PD-1 alone was 3.8/1.3 and CTLA-4 alone of 3.9/1.6 % (overall/grades3-4)(5). These adverse events were successfully managed with established guidelines regarding cessation of CP inhibitor therapy and, when needed, use of immune suppressants. Finally, treatment of patients with MS with a mAb to the IL-2R-a chain (CD25, Daclizumab) which is constitutively expressed at high levels on regulatory T cells (Tregs), precipitated autoimmune hepatitis in 0.3% of treated patients, and as well, caused ALT or AST elevations 5 times ULN in 4-6% of treated patients (6) suggesting that inhibition of Treg function by blocking the high affinity IL-2R complex may in some cases precipitate significant autoimmunity.