**Response and toxicity with immune checkpoint inhibition in older patients with non-small-cell lung cancer.**

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**Background:** Immune checkpoint inhibition (ICI) has rapidly become standard of care in advanced or metastatic non-small-cell lung cancer (NSCLC) treatment. Initial phase III clinical trials suggest ICI may have decreased efficacy in NSCLC patients ≥ 75 years old. The relationship between age-related immune system changes and ICI treatment is poorly understood.

**Methods:** The Johns Hopkins Upper Aerodigestive Diseases Immunotherapy Database was queried for all patients ≥ 75 years old treated with anti-PD-1/PD-L1 agents as part of a clinical trial or standard of care, from 2007 to 2018.

**Results:** Thirty-one patients ≥ 75 years old receiving anti-PD-1/PD-L1 agents for locally advanced or metastatic NSCLC were identified. Eleven patients were female, median age was 80.8 years (range: 75.1-90.6) with median ECOG PS=1 (range: 0-3). Twenty-seven patients received PD-1/PD-L1 monotherapy (nivolumab=16, pembrolizumab=10, atezolizumab=1) and 4 received combination (+chemotherapy=1, +ipilimumab=2, +additional ICI=1). Ten patients received ICI in the first-line setting (1L); 21 patients in the second-line or beyond (2L+). In 1L ICI monotherapy (n=8), median doses received was 5.5 (range: 2-19), median progression-free survival (mPFS) was 7.3m, and median overall survival (mOS) was 11.3m. In 2L+ patients, median dose administration was 4 (range: 1-24), mPFS was 7m and mOS was 7.6m. Across 1L and 2L+ ICI monotherapy patients, a rate of 81.5% all-grade toxicity was seen, of which 30% were high-grade (3+). All 1L and 2L+ ICI combination patients (n=4) experienced a toxicity, with 3 patients experiencing high-grade events. Across all patients, the most common low-grade toxicities were fatigue (n=8) and dyspnea (n=8). High-grade pneumonitis was seen in two 1L ICI monotherapy patients; 2L+ ICI monotherapy high-grade toxicities included dyspnea (n=4), hypoxia (n=1; Grade 5), pneumonitis (n=1), chest pain (n=1), delirium (n=1), aspiration (n=1), heart failure (n=1), lymphadenopathy (n=1) and pleural infection (n=1). Combination ICI high grade toxicities included pneumonitis (1L=1; 2L+=1) and rash (2L+=1). Across patients, reasons for treatment discontinuation included progressive disease (31%), with double the patients stopping for toxicity (62%) and treatment ongoing for 2 patients.

**Conclusions:** Our results indicate increased frequency and severity of toxicity in anti-PD1/PD-L1 treated older NSCLC patients, with decreased time to off treatment compared to landmark phase III studies. Survival data comparisons are limited in the setting of the current small sample size, but show interesting trends of decreased time on therapy and decreased overall survival. Further translational evaluation of senescent remodeling’s role in outcome and toxicity with ICI in older NSCLC patients is needed.