**Background** Immune checkpoint blockers (ICBs) have revolutionized cancer treatment, but they are often associated with severe immune related adverse events (irAEs). These severe irAEs are more often seen in patients with obesity or concomitantly treated with cytotoxic therapies.

**Methods** We aimed to understand the mechanisms of ICB-induced irAEs, in the context of obesity [FD1] and ICB/chemotherapy combinations. We used a mouse model of cardiac irAEs, which is the most fatal type of irAE in ICB-treated cancer patients, with clinically relevant features: (i) an ICB-resistant cancer (pancreatic ductal adenocarcinoma or PDAC), (ii) obesity induced with high-fat diets, and (iii) a combination treatment of ICB (α-PD1 + α-CTLA4) and chemotherapy (FOLFIRINOX)[FD2]

**Results** Mice with orthotopic PDAC and obesity developed irAEs after treatment with ICB and chemotherapy as compared to [FD1] chow diet. These irAEs recapitulated those observed in patients with cancer and obesity, including cardiac dysfunction consistent with myocarditis, cardiac fibrosis, and increased circulating levels of interleukin-1 beta (IL-1b). IL-1b blockade prevented myocarditis and reduced cardiac fibrosis after immunotherapy. Importantly, IL-1b blockade also enhanced the anti-tumor effects of ICB + FOLFIRINOX combination therapy, and increased mouse survival.

**Conclusions** Using a translationally relevant mouse model, we discovered that IL-1b mediates ICB-induced cardiotoxicity, which is the most fatal type of irAE in ICB-treated cancer patients. In addition, we found that IL-1b blockers, which are already used in the clinic for other indications[FD1], may both reduce adverse events and enhance the antitumor effects triggered by immunotherapy.