Background
Cancer cachexia exerts a negative clinical influence on advanced non-small-cell lung cancer (NSCLC) patients treated with immune checkpoint inhibitors (ICI). The prognostic impact of body weight change during ICI treatment remains unknown. The gut microbiota (GM) is a key contributor to ICI response in cancer. However, the association between cancer cachexia and GM and their association with ICI response remains unexplored.

Methods
In this observational prospective study, we included 113 Japanese patients with NSCLC treated with ICI monotherapy or chemoimmunotherapy. Fecal samples were collected prior to ICI initiation and 16S rRNA gene sequence was performed. Microbiota composition was analyzed based on patients' cancer cachexia status, change in weight after ICI initiation as well as PFS and OS. Cancer cachexia was defined as the following: (1) weight loss > 5% or (2) BMI < 20 kg/m2 and weight loss > 2%, over the past 6 months.

Results

Figure 1. Differential analysis of GM stratified according to presence of cancer cachexia at the baseline
(A) Alpha diversity analysis with the Shannon and FaithPD indices, (B) Ordination method-based nonmetric multidimensional scaling plots with Bray-Curtis distance, (C) Differential abundance analysis with LEfSe.

Figure 2A-C. (A) Best objective response and estimated survival curves for (B) PFS and (C) OS comparing patients with cancer cachexia (n = 57) against non-cachexia (n = 56) in the overall cohort. E, F, Differential analysis with LEfSe between the subgroups according to (E) PFS and (F) OS. G, H, Survival curves for PFS and OS comparing changes in the patients' longitudinal body weight during ICI therapy. (G) PFS and (H) OS comparing the "cachexia-reversible" and "reversible" groups against those without cachexia at baseline. "Cachexia-reversible" were those who experienced > 5% or >2% for BMI < 20 kg/m2) of weight gain compared with baseline during ICI therapy; we categorized the rest into the "cachexia irreversible" group.

Conclusions
We demonstrated that cachexia and longitudinal bodyweight change had prognostic impact on patients with NSCLC treated with ICI therapy. In addition, we observed different microbiota compositions between patients with and without cachexia. Targeted microbiota interventions may represent a new type of intervention to overcome cachexia in patients with NSCLC.