Background The phase 3 IMpower150 trial showed significantly improved progression-free survival (PFS) and overall survival (OS) with atezolizumab plus bevacizumab plus carboplatin-paclitaxel (ABCP) versus bevacizumab plus carboplatin-paclitaxel (BCP) in chemotherapy-naive patients with non-squamous metastatic NSCLC, regardless of tumor PD-L1 status. Based on these findings, ABCP became an approved first-line treatment for metastatic non-squamous NSCLC. No clinical benefit was seen with atezolizumab plus carboplatin-paclitaxel (ACP) versus BCP in the intent-to-treat population. Our objectives were to characterize the molecular subtypes of non-squamous NSCLC and to explore the relationship between molecular subtype, PD-L1 status and clinical outcomes with ABCP, ACP and BCP.

Methods RNA sequencing of 564 primary pre-treatment non-squamous NSCLC tumor samples from IMpower150 was analyzed in the ACBP (n=195), ACP (n=178) and BCP (n=185) treatment arms; 6 samples were from patients who were not treated. Non-negative matrix factorization (NMF) was applied to variably expressed genes to define non-squamous molecular subtypes. Tumor PD-L1 levels for each subtype were determined by SP263 immunohistochemistry (Ventana). OS and PFS in each treatment arm were analyzed by NMF subtype.

Results Four molecular subtypes were identified. NMF1 (n=103) had high enrichment of endothelial cells, neutrophils and basal/squamous-like cells. NMF2 (n=184) had enrichment of mature dendritic cells, macrophages, monocytes and proliferation. NMF3 (n=158) had the highest enrichment of adenocarcinoma and the lowest levels of squamous and CD8+ T-cells, monocytes and alveolar macrophages. NMF4 (n=119) had the most lymphocyte-inflamed transcriptomic profile, with high enrichment of epithelial-to-mesenchymal transition and B, dendritic, stromal and T cells. PD-L1 expression was significantly higher in NMF2 and NMF4 than in NMF1 and NMF3 (P=7.34e-10). Patients with NMF1 and NMF4 had significantly longer PFS with ABCP than ACP or BCP (P=0.009 and P<0.0001, respectively; table 1). Those with NMF2 and NMF3 showed no differences in PFS between treatments. Patients with NMF1 showed significantly longer OS with ABCP than other treatments (HR for ABCP vs BCP: 0.51 [95% CI, 0.29–0.90]; P=0.019). In patients with NMF4, median OS was 35.4, 17.6 and 21.7 months with ABCP, ACP and BCP, respectively (HR for ABCP vs BCP: 0.59 [95% CI: 0.34, 1.03]; P=0.059).

Conclusions Four molecular subtypes of treatment-naïve, non-squamous, metastatic NSCLC with different immune-cell and tumor microenvironmental features were characterized. Two subtypes had high tumor PD-L1 expression but different immune-cell profiles and clinical outcomes with ABCP. NMF4 may identify a subset of patients with advanced non-squamous NSCLC who benefit uniquely from 1L ACBP treatment. Further investigation is required.