Background Epigenetic targeting agents with immunotherapy represents an ongoing combinatorial approach in non-small cell lung cancer (NSCLC). Preclinical studies have shown that histone deacetylase (HDAC) and/or DNA methyltransferase (DNMT) inhibition can induce susceptibility to immune checkpoint inhibition (ICI), likely via an increase in tumor cell major histocompatibility complex I expression, reduction of tumor-associated myeloid-derived suppressor cells, and Th1 type chemokine facilitated CD8+ T cell tumor infiltration. Herein, we present the results of a multi-institution, randomized phase II study of epigenetic priming therapy, followed by nivolumab, compared to nivolumab alone.

Methods Patients with immune checkpoint naïve, previously treated advanced NSCLC and ECOG PS 0–1, stratified by histology, were initially randomized to receive azacitidine (40 mg/m2 subcutaneous days 1–5, 8–10) and entinostat (4 mg by mouth days 1 and 10) for 2 cycles followed by nivolumab (Arm A), or CC-486 (300 mg by mouth days 1–21) for 2 cycles followed by nivolumab monotherapy (3 mg/kg IV days 1 and 15) (Arm B) or to nivolumab alone (3 mg/kg Q2W) (Arm C) (NCT01928576). The primary endpoint was 32-week progression-free survival (PFS). Secondary endpoints included safety and tolerability, overall response rate (ORR), PFS, and overall survival (OS). Whole exome sequencing and bulk RNA sequencing of baseline and post-epigenetic priming tumor samples was performed, followed by computational deconvolution.

Results Between November 2013 and August 2018, 60 patients enrolled in the trial in Arm A (n=32), Arm B (n=7) and Arm C. (n=21) respectively. Arm B enrollment was terminated due to drug development discontinuation. Clinical outcomes, by arm, are reported here (table 1). Responding tumors harbored a higher content of mutations in aneuploid regions, higher HLA class I diversity and an enrichment of smoking- and DNA damage repair-related mutational signatures. Responses were noted in tumors harboring unfavorable co-mutations, such as KRAS/KEAP1. Gene set enrichment analyses revealed induction of antigen presentation and interferon-γ responses post epigenetic priming in responding tumors. Interferon-a, cancer testis antigens, and interferon-γ gene sets were significantly enriched post-epigenetic priming in patients with a longer PFS.

Conclusions Sequential therapy with epigenetic priming prior to ICI was safe and led to an expansion of the trial to include concurrent epigenetic therapy with nivolumab and patients who previously received ICI. While limited clinical efficacy was observed, in-depth genomic and transcriptomic analyses captured the biologic effect of epigenetic priming in re-shaping the tumor microenvironment and identified patients attaining benefit from epigenetic therapy and ICI.