Background Anti-PD1/PD-L1 immunotherapy is the standard of care for metastatic NSCLC but many tumors develop resistance. We hypothesize based on existing preclinical and clinical data that combining a T-cell agonist such as varlilumab (anti-CD27 antibody) with checkpoint inhibition may be synergistic and this synergy may be potentiated further by using targeted radiation (RT).1 2 RT improves antigen presentation and immune infiltration, and this combination may help overcoming resistance to PD-1/PD-L1 immunotherapy.

Methods We conducted an open-label, single-center, Phase I trial (NCT04081688) to determine the safety and clinical benefit of the PD-L1 inhibitor atezolizumab and anti-CD27 antibody, varlilumab in combination with palliative RT in patients with advanced or metastatic NSCLC with progression on prior PD-1/PD-L1 therapy. On Day 1 of each 21-day cycle, patients received varlilumab (10 mg/kg cycle 1; 3 mg/kg cycle 2 onwards, IV) followed by atezolizumab (1200 mg, IV) on day 2; figure 1. Palliative RT to a lung lesion was administered between cycle 1 and cycle 2 (50 Gy in 5 fractions or 40 Gy in 4–10 fractions). Pre- and post-treatment PBMC samples were collected for immunophenotyping by multiparameter flow cytometry.

Results Between 9/2019 and 4/2021, 15 patients were enrolled (1 patient did not receive treatment due to prior AE, 14 evaluable for safety). Median age was 64 years (range 35 to 73); 10 patients were female; 9 had received one prior line of therapy for metastatic NSCLC and 5 had received ≥2 prior lines (range 2 to 6). The median number of cycles received was 3 (range 1 to 9). The most common treatment-related AEs (all grades) were liver transaminitis (2; 14%) and hyperthyroidism (2; 14%). Three patients (21%) had at least one ≥ grade 3 treatment-related AE (colitis, fatigue, lung infection); there were no treatment-related deaths. There was only one grade 3 irAE requiring steroids (1 diarrhea/colitis). Of the 12 patients evaluable for efficacy, there were no PRs, 3 patients had SD (2 with SD > 4 months) and clinical benefit rate (CBR) was 25%. Median PFS was 2.0 months (95% CI 1.6 to 3.5) and median OS was 6.4 months (95% CI 2.1 to 16.9).

Conclusions Varlilumab in combination with atezolizumab and RT was safe and well tolerated; no additional signal was identified for toxicity. Clinical activity for the trial combination was modest with 25% of patients with stable disease as the best response. Correlative biomarker analyses to guide further research will be presented.

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Trial Registration Trial registered at clinicaltrials.gov as NCT04081688

REFERENCES
