A PHASE I TRIAL OF ATEZOLIZUMAB AND VARLILUMAB IN COMBINATION WITH RADIATION IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

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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). 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