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Abstract #: 8517 Rapid Oral Abstract Session

Prophylactic peptide vaccine targeting resistance mutations in advanced ALK-positive lung cancer: Primary analysis from the ARCHER trial.

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Background:

Acquired resistance to targeted therapy remains a major challenge in ALK-positive NSCLC and is often mediated by mutations in the ALK kinase domain. Prophylactic immune targeting of common ALK resistance mutations represents a novel strategy to delay or prevent the emergence of ALK inhibitor resistance.

Methods:

We conducted a first-in-human phase 1b clinical trial of a prophylactic peptide vaccine (ALK-Vac) in advanced ALK-positive NSCLC patients without progression on standard-of-care tyrosine kinase inhibitor (TKI) therapy. Patients continued their ALK TKI and received ALK-Vac, consisting of synthetic long peptides targeting seven common ALK resistance mutations (I1171T, I1171N, I1171S, L1196M, G1202R, D1203N, E1210K) plus poly-ICLC adjuvant. ALK-Vac was administered subcutaneously on days 1, 4, 8, 15, and 22 (priming) and weeks 12 and 20 (boost). Primary objectives were safety and vaccine-specific T cell responses assessed by IFN-γ ELISpot. Exploratory objectives included molecular and immune-phenotype dynamics assessed by ultrasensitive cell-free DNA (cfDNA) duplex sequencing and CyTOF mass cytometry.

Results:
Fifteen patients were enrolled and all completed the planned ALK-Vac regimen. Most patients (13/15, 87%) were receiving first-line TKI therapy. Concomitant TKIs included alectinib (7/15, 47%), lorlatinib (5/15, 33%), and brigatinib (3/15, 20%). At enrollment, median TKI duration was 43.7 months (range 4.6-74.2) and 67% of patients had no measurable disease. Treatment-related adverse events (TRAEs) were primarily grade 1 (93% of patients); most commonly injection site reactions (93%), fatigue (60%), and flu-like symptoms (40%). No grade ≥ 3 TRAEs were observed. T cell responses (≥2-fold increase in SFU) were detected in 71% (10/14) of evaluable patients, with a median 11.9-fold increase. Responses were observed to G1202R, L1196M, and D1203N (each 10/14, 71%), E1210K (9/14, 64%), and I1171N/S/T (each 7/14, 50%). With a median follow-up of 11.5 months, the disease control rate was 93% (14/15). One patient who achieved robust immune response against multiple resistance mutations developed oligoprogression on alectinib 8.5 months after starting ALK-Vac; molecular profiling of this lesion identified an emergent KRAS G12D mutation without detectable ALK resistance mutation.

Conclusions:
ALK-Vac was well-tolerated and induced vaccine-specific T cell responses in a minimal residual disease setting, demonstrating feasibility of prophylactic targeting of ALK resistance mutations as an adjunct to TKI therapy and supporting a broader immune-interception framework potentially applicable to other oncogene-driven NSCLC. Comprehensive cfDNA and immune-phenotyping analyses will be reported.

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Lung Cancer—Non-Small Cell Metastatic

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NCT05950139

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