Association of STK11/LKB1 genomic alterations with lack of benefit from the addition of pembrolizumab to platinum doublet chemotherapy in non-squamous non-small cell lung cancer.

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Abstract Disclosures

Background: Addition of pembrolizumab (P) to platinum-doublet chemotherapy [carboplatin (or cisplatin) and pemetrexed (CP)] prolongs overall survival and is a standard of care (SOC) for the 1st line treatment of metastatic EGFR/ALK-wild-type (wt) non-squamous non-small cell lung cancer (mnsNSCLC). Despite widespread adoption of the CPP regimen, molecular determinants of clinical benefit from the addition of P to CP remain poorly defined. We previously identified genomic alterations in STK11/LKB1 as a major driver of primary resistance to PD-1/PD-L1 blockade in mnsNSCLC. Here, we examine the impact of STK11/LKB1 alterations on clinical outcomes with CPP chemo-immunotherapy.

Methods: 497 pts with mnsNSCLC and tumor genomic profiling encompassing STK11/LKB1 from 17 academic institutions in the US and Europe were included in this study. Clinical outcomes were collected for two distinct patient cohorts: a) 377 pts treated with first-line CPP (or > 1st line following FDA-approved TKIs) that were alive for 14 days thereafter and b) 120 STK11/LKB1-mt pts that received CP prior to regulatory approval of CPP.

Results: Among 377 CPP-treated pts, STK11/LKB1 genomic alterations (N = 102) were associated with significantly shorter PFS (mPFS 4.8m vs 7.2m, HR 1.5, 95% CI 1.1 to 2.0; P = 0.0063) and shorter OS (mOS 10.6m vs 16.7m, HR 1.58, 95% CI 1.09 to 2.27; P = 0.0083) compared with STK11/LKB1-wt tumors (N = 275). ORR also differed significantly between the two groups (32.6% vs 44.7%, P = 0.049). Similar results were obtained.
when limiting the analysis to \textit{EGFR} and \textit{ALK}-wt tumors (N = 333). Importantly, in pts with \textit{STK11/LKB1}-mt mnsNSCLC, addition of pembrolizumab to CP did not improve PFS (mPFS 4.8m vs 4.3m, HR 1.13, 95% CI 0.83 to 1.54, \(P = 0.75\)) or OS (mOS 10.6m vs 10.3m, HR 1.03, 95% CI 0.71 to 1.49, \(P = 0.79\)) compared to CP alone.

**Conclusions:** In mnsNSCLC, \textit{STK11/LKB1} alterations define a subgroup of pts with inferior clinical outcomes with CPP and lack of benefit from the addition of pembrolizumab to CP chemotherapy. Novel therapeutic strategies are required to establish effective antitumor immunity in \textit{STK11/LKB1}-mutant NSCLC.

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