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PROGRAMMED DEATH (PD)-1 AND PD-LIGAND-1 INHIBITORS IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER: A SYSTEMATIC REVIEW OF THEIR EFFICACY AND SAFETY

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Background Treatment advances have been made in non-small cell lung cancer (NSCLC) with the development and approval of programmed death (PD)-1 and PD-ligand 1 (PD-L1) inhibitors. PD-1 and PD-L1 inhibitors may be used as monotherapies or in combination with other agents and have been shown to improve NSCLC patient outcomes in clinical trials. We conducted a systematic search to compare the efficacy and safety of PD-1/PD-L1 inhibitors in the treatment of NSCLC.

Methods A systematic literature search of PubMed was conducted to identify phase III clinical trials in which the efficacy of PD-1/PD-L1 inhibitors in the treatment of NSCLC was evaluated. PD-1 inhibitors included nivolumab and pembrolizumab; PD-L1 inhibitors included atezolizumab, avelumab, and durvalumab. Patient characteristics and efficacy data were extracted.

Results Sixteen phase III clinical trials were identified (nivolumab=4; pembrolizumab=5; atezolizumab=5; avelumab=1; durvalumab=1). Across the 3 nivolumab monotherapy trials (n=638; median ages: 61–63 years), median progression-free survival (PFS) ranged 2.3–4.2 months; response rates ranged 19%–26%; grade 3/4 adverse events occurred in 7%–18% of patients. Nivolumab in combination with ipilimumab (n=583; median age: 64 years) had a median PFS of 5.1 months and response rate of 33%; grade 3/4 adverse events occurred in 33% of patients. Across the 3 pembrolizumab monotherapy trials (n=1,481; median ages: 63–64 years), median PFS ranged 3.9–10.3 months; response rates ranged 18%–45%; grade ≥ 3 adverse events occurred in 13%–27% of patients. In the 2 pembrolizumab combination therapy trials (n=688; median ages: 65 years), median PFS ranged 6.4–8.8 months; response rates ranged 48%–58%; grade ≥ 3 adverse events occurred in 67%–70% of patients. In the 4 atezolizumab combination therapy trials (n=1,486; median ages: 63–64 years), median PFS ranged 6.3–8.3 months; response rates ranged 47%–63.5%; grade 3/4 adverse events occurred in 54%–73% of patients. In the 3 monotherapy trials of atezolizumab (n=613; median age: 63 years), avelumab (n=396; median age: 64 years), and durvalumab (n=476; median age: 64 years), the median months of PFS were 2.7, 2.8, and 17.2, respectively; response rates were 14%, 15%, and 30%, respectively; grade ≥ 3 adverse events occurred in 15%, 10%, and 30.5% of patients, respectively.

Conclusions Although treatment responses varied, most of the evaluated PD-1/PD-L1 inhibitors were associated with a clinical benefit for NSCLC trial patients. Generally, treatment efficacy was greater with combination therapies, but adverse events occurred more frequently. Innovations in the targeting/personalization of PD-1/PD-L1 combination therapies will likely lead to improved NSCLC patient outcomes and further research is needed in this regard.

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FOSTRIECIN POTENTIATES GENOME INSTABILITY AND ANTI-TUMOR IMMUNITY IN OVARIAN CANCER

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Background Increased immune infiltration in ovarian tumors has been linked to improved patient outcome. Nonetheless, responses to checkpoint blockade therapies have been disappointing in ovarian cancer patients. This has been attributed to the low mutational burden present in ovarian tumors. However, many tumor antigens have been identified in ovarian cancer, which underscores the critical need to identify new treatment strategies that will trigger anti-tumor immunity in ovarian cancer. Recent studies have revealed that defects in DNA damage repair (DDR) pathways can contribute to improved responses to immune-directed therapies.^{1,2} We previously discovered that CT45 expression sensitizes ovarian cancer cells to chemotherapy via its interaction with the protein phosphatase 4 (PP4) complex.³ PP4 is known to play a key role in DDR pathways; however, its potential effects on anti-tumor immunity remain unknown.

Methods Using fostriecin, a commercially available inhibitor of PP4, we studied the effect of fostriecin on chemosensitivity using cell cycle analysis and cell viability assays. To study the effect of fostriecin on DNA damage, we performed comet assays and measured micronuclei along with FANCD2 foci formation. Furthermore, using western blot, qPCR, and T cell activation assays, we assessed the role of fostriecin in promoting an inflammatory response. We tested the efficacy of combining fostriecin with carboplatin and PD-1 inhibition in a syngeneic mouse model of ovarian cancer.

Results Our results show that fostriecin treatment combined with carboplatin leads to increased carboplatin sensitivity, DNA damage, and micronuclei formation. Using a panel of ovarian cancer cells, we show that fostriecin treatment triggers an anti-tumor immune response via STAT1 activation resulting in increased expression of pro-inflammatory cytokines. Furthermore, in a syngeneic mouse ID8 ovarian cancer cell line, we demonstrate that combination treatment of fostriecin and carboplatin significantly increased CD8 T cell activation over carboplatin treatment alone.

Conclusions Our work has identified a role for PP4 inhibition in promoting anti-tumor immunity. These findings form the groundwork for the rationale design of a clinical trial combining PP4 inhibitors with chemo-immunotherapy as a new approach in ovarian cancer treatment.

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