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Combinatorial chemo/immunotherapy for soft tissue sarcoma

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Background: Trabectedin has direct cytotoxic activity in tumor cells and has been shown to deplete pro-tumor macrophages in the tumor microenvironment. Nivolumab inhibits the immune checkpoint molecule, PD-1, which restores anti-tumor activity in tumor-infiltrating T cells.

Purpose: To assess the safety/toxicity and efficacy of sequential administration of trabectedin and nivolumab in patients with advanced soft tissue sarcoma (STS).

Methodology: 14 patients with metastatic STS were evaluated. Each patient received one dose of single-agent trabectedin (1.5 mg/m² continuous intravenous infusion, CIV, for 24 hours), followed by trabectedin CIV every 3 weeks, and nivolumab 3 mg/kg IV every 2 weeks. Safety/toxicity was analyzed using the NIH/NCI CTCAE v4.03. Tumor responses were assessed by RECIST v1.1 and immune-related response criteria (irRECIST).

Findings: Histologic subtypes include undifferentiated pleomorphic sarcoma, leiomyosarcoma, synovial sarcoma, myxoid liposarcoma and chondrosarcoma. All patients had metastatic disease and a median of 4 lines of prior chemotherapy.

Safety Analysis: Grade 3 treatment emergent adverse events include anemia, fatigue, decreased platelet count, decreased granulocyte count and increased creatine kinase.

Efficacy Analysis: 13 patients received at least 2 cycles of sequential chemo-/immuno-therapy, had follow-up CT scan/MRI, and were evaluated for objective response (OR), best overall response rate (BORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). There were 3 partial responses, 7 stable disease and 3 progressive disease, with BORR of 23.1%, DCR of 76.9%, median PFS >7.8 months (range: 3.5->10.4 months), median OS >8.4 months (3.6->10.4 months), 6 month PFS rate, 69.2%, and 6 month OS rate, 92%. Six-month OS rate for all 14 patients was 86%. In a phase 3 study, the median PFS was 4.2 months using trabectedin alone.

Conclusion: Taken together, the data suggest that paired administration of trabectedin and nivolumab is safe, and that this chemo-/immuno-therapy approach has synergistic activity.

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