Abstract ID# 2206545

SUSTAINED RESPONSES/DISEASE CONTROL USING AUTOLOGOUS ENHANCED NATURAL KILLER CELLS PLUS AN IMMUNE CHECKPOINT INHIBITOR AS TREATMENT FOR RARE CHEMOTHERAPY-RESISTANT ADVANCED SOFT TISSUE SARCOMAS

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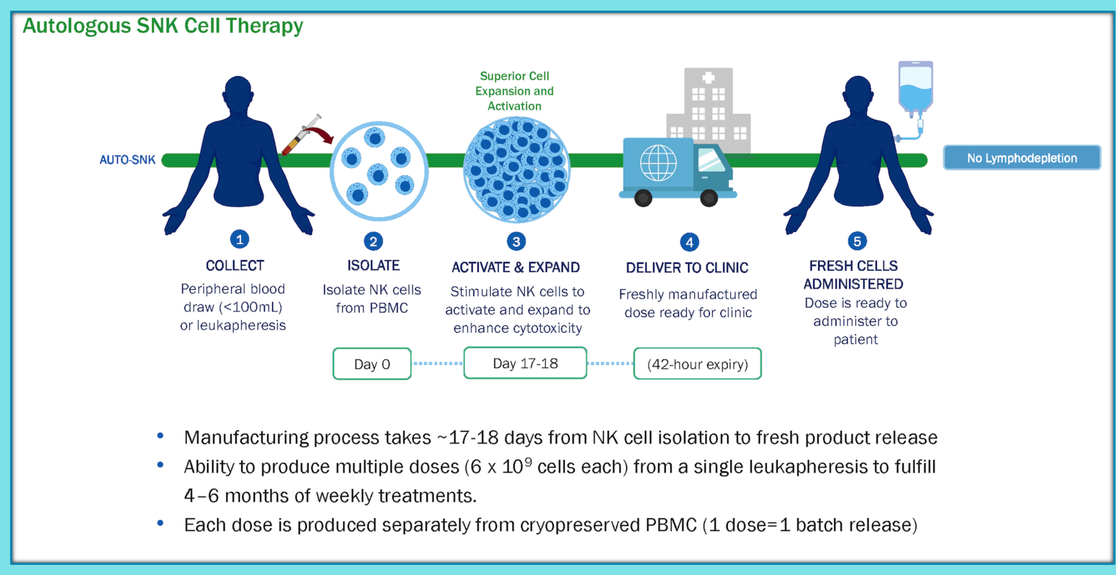
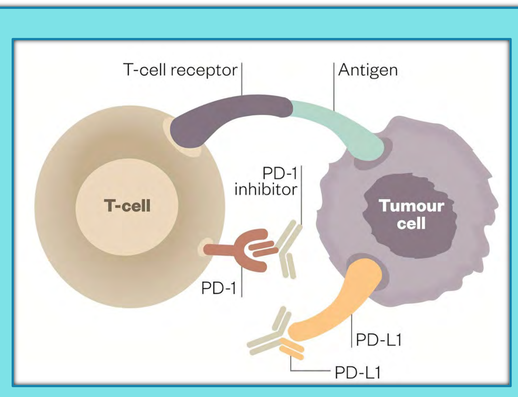
ABSTRACT

Background and Rationale: Advanced or metastatic sarcoma is associated with an invariably fatal outcome. SNK01 is a first-in-kind, autologous non-genetically modified natural killer cell therapy with highly enhanced cytotoxicity and over 90% activating receptor expression which can be consistently produced from chemotherapy-treated patients. **Objective:** To report three unique cases of chemotherapy-resistant advanced soft tissue sarcoma (STS) who achieved durable partial responses and disease control with SNK01 plus an immune checkpoint inhibitor. **Methods:** Three patients with chemotherapy-resistant soft tissue sarcoma participated in FDA authorized and WIRB approved protocols. Cases #1 and 2 received autologous enhanced NK cells (SNK01) 2 x 10^9 cells i.v. q 2 weeks and pembrolizumab 200 mg i.v. q 3 weeks. Case #3 was enrolled in the SK01-US01 study and received SNK01 4 x 10^9 cells i.v. q 2 weeks and avelumab 800 mg i.v. q 2 weeks. The histologic subtypes include desmoplastic small round cell tumor (DSRCT), radiation-induced chondrosarcoma (RIC) and undifferentiated spindle cell sarcoma. **Results:** Case #1(DSCRT): The tumors gradually decreased in size over one year to a 47% response. Patient then underwent a surgical debulking procedure followed by whole abdominal radiation and intraperitoneal chemotherapy, after which he resumed SNK01 and pembrolizumab regimen. His last scan showed sustained complete remission (Figure). He has now received 32 cycles of SNK01 + pembrolizumab over 28 months and has an Eastern Cooperative Oncology Group score of 0 (fully active, able to carry on all pre-disease performance without restriction. The reported median overall survival for advanced STS is 8-13 months. Case #2 (RIC): Patient had a 38% partial response after four months of treatment, underwent debulking surgery but died of post-surgical infection. The patient had received 18 cycles of SNK01 + pembrolizumab and survived 12 additional months. Case #3 (Undifferentiated spindle cell sarcoma): Patient had durable disease control (stable disease) during the 12-month treatment period. The reported median progression free survival for advanced STS is 4.1 months. Grade 3 or greater adverse events hypothyroidism (n=1), increased ALT (n=1), increased alkaline phosphatase (n=1) and increased GGT (n=1). **Conclusion:** These unique case studies clearly demonstrate the potential of SNK01 in controlling tumor growth in conjunction with an immune checkpoint inhibitor with manageable toxicity. Phase 2 studies are being planned to confirm these promising results.

MECHANISM OF ACTION





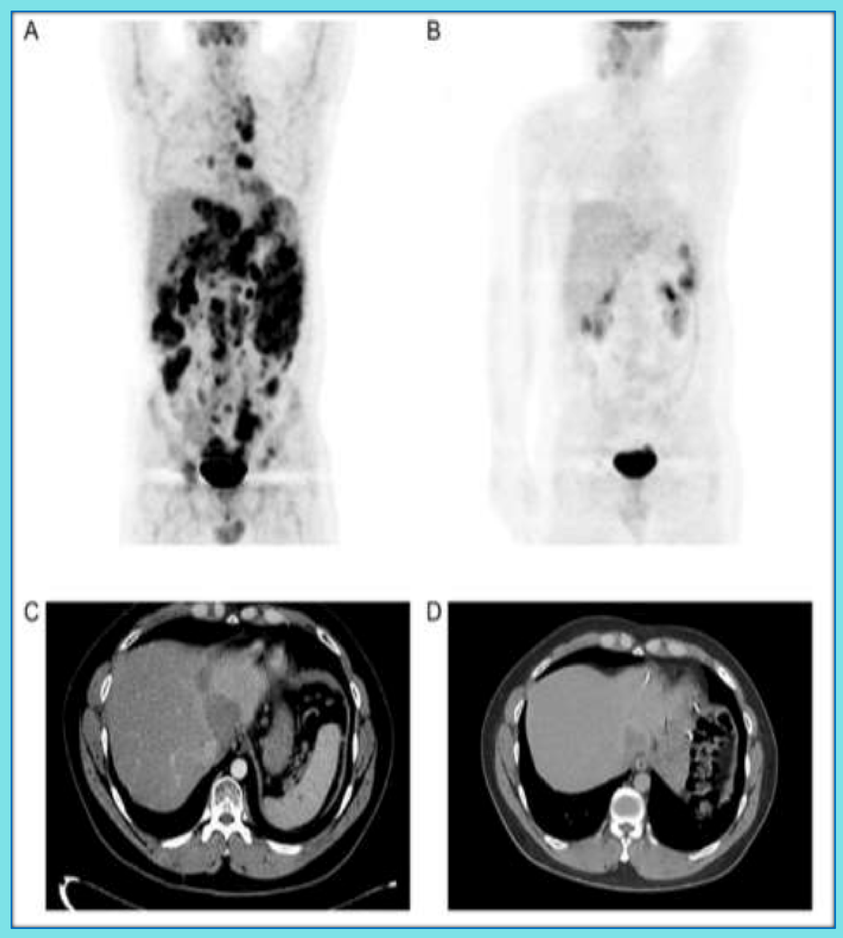
Legend. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

PATIENTS & RESULTS

Case #1(DSCRT): The tumors gradually decreased in size over one year to a 47% partial response. Patient then underwent a surgical debulking procedure followed by whole abdominal radiation and intraperitoneal chemotherapy, after which he resumed SNK01 and pembrolizumab regimen. His last scan showed sustained complete surgical remission. Figure (right) shows a dramatic reduction in in FDG avidity by PET scan and the size of tumors after combination therapy with SNK01 and pembrolizumab (A) PET scan before treatment; (B) PET scan after SNK01 plus pembrolizumab treatment followed by debulking procedure; (C) Abdominal CT scan before treatment; (D) Abdominal CT scan after SNK01 plus pembrolizumab treatment followed by debulking procedure. Grade 2 treatment-related adverse events included hypothyroidism, fatigue, rash, and pruritus, with no Grade 3 adverse events.

Case #2 (RIC): Patient had a 38% partial response after four months of treatment, underwent debulking surgery but died of post-surgical infection. The patient had received 18 cycles of SNK01 + pembrolizumab and survived 12 additional months. Grade 3 include hypothyroidism, increased ALT, increased alkaline phosphatase and increased GGT.

Case #3 (Undifferentiated spindle cell sarcoma): Patient had durable disease control (stable disease) during the 12-month treatment period. There were no treatment-related Grade 3 or greater adverse events.



CONCLUSIONS

Taken together, the data suggests that:

- SNK01 plus pembrolizumab may be a viable salvage therapy regimen for chemotherapy-resistant advanced sarcoma with manageable toxicity, and
- SNKo1 natural killer cells mediate a favorable response to immune checkpoint inhibitor therapy while reducing immune-related adverse events.
- Phase 2 studies are in planning to confirm these encouraging results and biologic insights.

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