Phase I Clinical Trial of Sipuleucel-T Combined with Escalating Doses of Ipilimumab (SIPIPI) in Progressive Metastatic Castrate-Resistant Prostate Cancer

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Abstract

Background: Sipuleucel–T (SIP-T), which functions by stimulating cancer-specific dendritic cells, prolongs survival in men with prostate cancer. Ipilimumab (IPI) enhances immune function by blocking CTLA-4. In a randomized, prospective trial, IPI achieved a borderline survival advantage in in advanced metastatic castration-resistant prostate cancer (mCRPC)r. SIP-T and IPI are potentially synergistic.
Methods: Nine men with progressive mCRPC were treated prospectively with SIP-T followed immediately by IPI with one of the following doses of IPI: 1 mg/kg 1 week after SIP-T, 1 mg/kg 1 and 4 weeks after SIP-T, or 1 mg/kg 1, 4 and 7 weeks after SIP-T. Three patients were evaluated at each level. Cancer-specific immunoglobulins directed at the GM-CSF/PAP (PA2024) fusion protein and at prostatic acid phosphatase (PAP) were measured prior to SIP-T, after SIP-T, 1 and 5 weeks after IPI, and subsequently every two months for 4 months, and every 3 months for an additional 12 months.
Results: Side effects from SIP-T were consistent with previous reports. IPI only caused a transient grade 1 rash in one patient. Median age, Gleason score, and number of previous hormonal interventions were 77 yrs., 8, and 3 respectively. 8 men had bone metastases; 1 was lymph node only. Statistically significant increases in serum IgG and IgG-IgM specific for PA2024 and PAP occurred after SIP-T. An additional statistically significant increase in these same immunoglobulins—above the levels achieved by SIP-T—occurred after IPI. Median clinical follow up is 36 months (range 26-40). Three patients died from progressive disease after 9, 18 and 20 months. Six patients are alive; only one has required chemotherapy. Out of the other five remaining patients, further treatments have included abiraterone acetate, enzalutamide, radium-223 dichloride, and spot radiation. One patient has an undetectable PSA without any other treatment except spot radiation. Median PSA at last follow up for the surviving patients is 3.8 (range .06-7.47).
Conclusions: In this small trial, the addition of IPI to SIP-T was well-tolerated. IPI increased immunoglobulins specific for the PA2024 protein and PAP above the level achieved with SIP-T alone. Five of the nine patients who entered the trial have still not required chemotherapy after a median of three years.

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CONFLICT OF INTEREST

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