

Scientific Abstract

Soft tissue sarcoma is an uncommon neoplasm with only about 6,000 cases diagnosed in adults each year in the United States^[1]. Approximately 10-20% of these patients with soft tissue sarcoma of the extremity are destined for amputation or severely debilitating surgery. The prognosis for patients with soft tissue sarcoma is poor for those over 60 years of age with tumors greater than 5 cm or with high-grade histology. Currently, a multidisciplinary treatment approach, including surgery, chemotherapy and radiation therapy is recommended. While soft tissue sarcomas can arise almost anywhere on the body, about 65 percent occur in the arms, hands, legs or feet. The major types soft tissue sarcomas found in the extremities include fibrosarcoma, liposarcoma, rhabdomyosarcoma, leiomyosarcoma, lymphangiosarcoma, synovial sarcoma, neurofibrosarcoma and chondrosarcoma.

TNFerade™ biologic (Ad_{Gv}EGR.TNF.11D) is an E1-, partial E3-, E4-, replication deficient, adenovirus serotype 5, gene transfer vector. The transgene in this vector is the cDNA for human tumor necrosis factor- α (TNF- α). Elements of the radiation inducible early growth response (Egr-1) promoter are ligated upstream from the transgene to allow for maximum expression of TNF- α only in the presence of ionizing radiation.

TNF- α is a human cytokine well known for its anti-tumor effects, and its ability to act synergistically with radiation therapy. It has been approved for use in Europe via isolated limb perfusion for the treatment of soft tissue sarcoma. Its wider use as an anti-cancer agent, however, has been limited by severe systemic side effects. It is proposed that this locally delivered gene transfer approach using the TNF- α gene would capitalize on the anti-tumor effects of TNF- α while eliminating the need to use isolated limb perfusion, which is a very cumbersome procedure, and is associated with significant morbidity and mortality.

Studies of TNFerade™ biologic have demonstrated efficacy and tolerability in a variety of animal models. Furthermore, these studies show a synergistic effect of combined treatment with TNFerade™ biologic and radiation resulting in a greater tumor response than seen with each individual treatment modality.

Intratumoral administration of TNFerade™ Biologic combined with radiation therapy provides a convenient means of delivering TNF- α locally, with the potential for an improved tumor response rate over radiation alone. To evaluate this in adult subjects with soft tissue sarcoma, this study is designed as dose escalating with 3-6 subjects at each dose level. A total of 18 to 30 subjects are expected to be enrolled. TNFerade™ Biologic will be injected twice during week 1 and once a week for the next four weeks. Radiation therapy will be started during week 1 and continue for up to 5 weeks at the discretion of the treating radiation oncologist. The primary objectives of this investigation are: (1) to assess the safety, tolerability and feasibility of direct intratumoral injection of TNFerade™ biologic in soft tissue sarcoma as adjunct to surgery or for palliation and (2) to identify the maximum tolerated dose (MTD) of TNFerade™ biologic and radiation.

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