Kaposi's sarcoma (KS), an acquired immunodeficiency syndrome (AIDS)-associated cancer, is more common in male patients with AIDS than in women with this disease. Results showing that the growth of KS-derived cell lines was inhibited in vitro and in vivo by a human pregnancy hormone (hCG) spurred clinical trials in which administration of hCG to patients with KS yielded some promising but variable results. Following the reported association of anti-KS activity with a human hCG-associated ribonuclease (RNase), i.e., eosinophil-derived neurotoxin (EDN), a unique form of hEDN genetically engineered and the cytotoxic effects of the recombinant protein were evaluated on KS Y-1 cells and on cells of other cancer types. The amino-terminus of hEDN was extended by four amino acid residues corresponding to the hEDN signal peptide. The cytotoxic activity of this hEDN variant, (-4)rhEDN, was tested on KS Y-1 cells and human glioma, melanoma, breast carcinoma, and renal carcinoma cells. Although rhEDN protein displayed little cytotoxicity against KS Y-1 cells (IC50 [50 % inhibition concentration] >100 mg/mL), (-4)rhEDN markedly inhibited cell viability (IC50= 6 mg/mL). Neither version of rhEDN inhibited the viability of other tested human cancer cell types. We have now solved the structure of (-4)rhEDN with synchrotron data extending to 1.0 Å resolution, using orthorhombic crystals in the space group P2_12_1_2_1, a = 42.14 Å, b = 52.56 Å, c = 56.63 Å. The refinement with SHELXL utilized anisotropic temperature factors and resulted in a model with R = 14.4%, R_free = 18.5%. A comparison of the previously available structure of EDN with this new structure of (-4)rhEDN sheds some light on the interactions of the extended N terminus of the molecule with the active site, and thus may help in the interpretation of the anti-cancer properties of this cytotoxic RNase.