A preclinical profile of VB6-845: a recombinant immunotoxin for targeting ovarian cancer

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ABSTRACT

Ovarian cancer is the fourth most common cause of cancer mortality in women. Most patients present with advanced disease due to non-distinctive symptoms. Advances in surgery and treatment modalities have improved survival, but prognosis remains poor with a five-year survival rate of about 30% signifying the lack of effective treatment. VB6-845 is a recombinant fusion protein consisting of a tumor-targeting Fab linked to de-immunized Bouganin. VB6-845 specifically targets the epithelial cell adhesion molecule (Ep-CAM) that is highly expressed on many epithelial carcinomas, including gynecological cancers. Examination of VB6-845 cross-reactivity in gynecological carcinomas was conducted using Immunohistochemistry (IHC) analysis that included various disease stages and grades. VB6-845 immunoreactivity against ovarian primary and metastatic carcinomas was >90%. For endometrial and cervical carcinomas the reactivity was 95% and 64% respectively. IHC also was used to assess the potential for VB6-845 cross-reactivity with normal human tissue. Positive binding was seen in some epithelial tissues whereas binding was not observed in non-epithelial tissues or stromal components. To evaluate safety of VB6-845, toxicology studies were conducted. An acute dose toxicology study was conducted in the Sprague-Dawley rat. The MTD was determined to be 200 mg/kg at which animals presented with odema of the paws and liver enzymes levels were elevated more than 10 fold above normal. A non-human primate toxicology study was conducted in Cynomolgus monkeys. Animals were I.V. dosed twice, one week apart, at 10, 30, 60, 90 mg/kg in a dose escalation study. There were no mortalities, changes in body weight, and few clinical signs attributed to VB6-845 dosing. Elevated liver enzyme levels correlated to microscopic changes in the liver of animals dosed at 60 and 90 mg/kg. Microscopic changes also were noted in the kidneys, spleen and lymph nodes. All VB6-845 related changes had resolved by the end of the recovery period and the NOAEL was 30 mg/kg. The pharmacokinetic profile indicated that there was dose proportionality of VB6-845 (a 9-fold dose increase resulted in a 9-fold C_{max} increase) to the mean peak exposure. The mean half-life ($T_{1/2}$) values of VB6-845 were similar between Days 1 and 8 (2.49 $\pm$ 0.13 and 2.40 $\pm$ 0.48 hours, respectively). The preclinical profile concerning specificity and safety indicate that VB6-845 was well tolerated and will be effective in directing its potent cytolytic effect against ovarian cancer.