DKN-01, a Therapeutic DKK1 Neutralizing Antibody, Has Immune Modulatory Activity in Nonclinical Tumor Models


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Abstract

Wnt signaling is a fundamental pathway that is dysregulated in oncology. The Wnt signaling modulator DKK1 is expressed in a variety of tumor types and elevated levels frequently correlate with poor survival. DKK1 promotes tumor growth by stimulating proliferation, metastasis, angiogenesis, and immunosuppression. DKN-01 is a humanized monoclonal therapeutic antibody that binds DKK1 with high affinity and selectivity. It is currently being evaluated clinically as a monotherapy and in combination with pembrolizumab in a variety of solid tumors. Here we describe further characterization of the mechanism of action of DKN-01 and demonstrate immune-mediated antitumor activity in nonclinical models. A murine version of DKN-01 (mDKN-01) has efficacy in a syngeneic melanoma B16 tumor model. mDKN-01 is unable to impede B16 tumor growth in NSG immunodeficient mice, indicating that a functioning immune system is required for antitumor activity. Furthermore, preliminary data suggest that mDKN-01 is targeting a myeloid-derived suppressor cell population in the tumor microenvironment and as such may work in combination with a checkpoint inhibitor. These data support an immune-mediated mechanism of action of DKN-01 and provide a rationale for clinical development in combination with immunotherapy agents.

Introduction

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Table 1: DKN-01 Binds Multiple Species of DKK1 with High Affinity

Table 2: DKN-01 is Specific for DKK1

Results

Figure 1: DKN-01 Neutralizes DKK1 in Cell Based Assays

Figure 2: Murine DKN-01 Activity Requires a Functioning Immune System

Figure 3: Murine DKN-01 Alters the Immune Infiltrate in the Tumor Microenvironment

Figure 4: Murine DKN-01 Induces Immune Gene Expression Changes

Figure 5: Murine DKN-01 Induces Cxcr7f0 But Not Cxcr3 Expression

Figure 6: Murine DKN-01 Has Additive Activity With an anti-PD-1 Antibody

Preliminary Results of Clinical Study Evaluating DKN-01 with KEYTRUDA® (pembrolizumab) in Patients with Advanced Gastroesophageal Adenocarcinoma (GEA)

Conclusions

- mDKN-01 has immune modulatory activity and is additive with anti-PD-1 in nonclinical models.
- Preliminary results from the clinical study of DKN-01 + pembrolizumab demonstrated that the combination was well tolerated and may have activity in patients less likely to respond to anti-PD-1 therapy alone.
- Clinical study ongoing NCT02013154

DKN-01 is a neutralizing antibody that binds DKK1 with high affinity and selectivity. It is being evaluated clinically as a monotherapy and in combination with pembrolizumab. Preliminary data suggest that mDKN-01 is targeting a myeloid-derived suppressor cell population in the tumor microenvironment, indicating that a functioning immune system is required for antitumor activity. Future studies will evaluate the clinical potential of DKN-01 in combination with immunotherapy agents.

Table 1: DKN-01 Binds Multiple Species of DKK1 with High Affinity

DKN-01 has immune modulatory activity in nonclinical tumor models, contributing to an immune suppressive tumor microenvironment. DKN-01 has been shown to have activity in a variety of tumor types, including melanoma and esophageal adenocarcinoma. It is currently being evaluated in clinical trials as a monotherapy and in combination with pembrolizumab.