EVT801: A differentiating anti-tumor approach

Targeting tumor angiogenesis with the selective VEGFR-3 inhibitor EVT801 in combination with cancer immunotherapy


1. Inhibition of tumor escape & metastasis
   - Stabilization of tumor vasculature
   - Inhibition of lymphangiogenesis
   - Reduction of tumor hypoxia

2. Enhanced anti-tumor immunity
   - No impact on T-cell viability
   - Decrease in immunosuppressive cells
   - Enhanced effector cell infiltration

3. Tumor killing
   - Direct effect on VEGFR-3+ tumor cells from endothelial origin

Vascular endothelial growth factor receptor 3 (VEGFR-3) is a membrane-bound receptor tyrosine kinase that is expressed on the surface of lymphatic endothelial cells. It plays a crucial role in the development of lymphatic vessels, which are involved in the transport of lymphatic fluids and immune cells throughout the body. The overexpression of VEGFR-3 has been observed in various solid tumors, including kidney cancer (MKC) and soft tissue sarcomas (STS).

Expression of vascular marker CD34, lymphatic marker D2-40 and VEGFR-3 in primary kidney tumors.

Consecutive slices of the same tumor were stained for VEGFR-3, CD34 and D2-40. VEGFR-3 was observed in CD34-positive vessels in the tumor and in the normal adjacent tissue, whereas D2-40 staining was mainly observed in normal adjacent tissue. Black arrows indicate lymphatic vessels.

VEGFR-3 expression in kidney cancer cohorts

A. Level of VEGFR-3 expression in 29 primary kidney cancer (PKC) samples and 23 metastatic kidney cancer (MKC) samples.
B. Representative IHC image of VEGFR-3 expression in PKC.
C. Representative IHC image of VEGFR-3 expression in PKC and normal adjacent tissue.
D. Representative IHC image of VEGFR-3 expression in liver metastasis of kidney tumor.
E. Representative IHC image of VEGFR-3 expression in bone metastasis after treatment with sunitinib.
F. Representative IHC image of VEGFR-3 expression in primary Kaposi's sarcoma

VEGFR3 expression has been validated in multiple indications including non small cell lung cancer, hepatocarcinoma and colorectal cancer.

VEGFR3 expression is defined as the expression level of VEGFR-3 on the surface of endothelial cells. High VEGFR-3 expression is associated with increased angiogenesis and tumor progression. By targeting VEGFR-3, EVT801 can inhibit tumor growth and metastasis.

Conclusion

EVT801 presents a more selective and less toxic profile than two major approved inhibitors of VEGFR3 (i.e., sorafenib and pazopanib). In monotherapy, EVT801 showed a potent antitumor effect in tumors with VEGFR3- positive microenvironment in preclinical models.

EVT801 will be evaluated as single agent in patients with kidney cancer and soft tissue sarcomas. Combination with cancer immunotherapies would come next.