BNC420 is a novel VEGFR3 selective inhibitor, which unlike the pan-VEGFR inhibitor Sunitinib, suppresses lymphatic metastasis in a model of metastatic melanoma

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**Background**

Cancer metastasis is the primary cause of cancer-related deaths with dissemination of cancer cells from the primary tumor occurring via the blood stream and lymphatic vessels to the draining lymph nodes. Metastatic melanoma spreads through local lymphatic invasion and dissemination to regional lymph nodes. Intra-tumoral and peritumoral lymphatics represent a prognostic indicator for metastasis and overall patient survival (Karaman et al 2014). Induction of tumor associated lymphatic vessel growth through expression of VEGFC and signaling through the vascular endothelial growth factor receptor VEGF3R are key molecular elements underpinning the formation of tumor lymphatics. Targeting VEGF3/VEGF3R inhibits lymphatic mediated metastasis. Several tyrosine kinase inhibitors of the VEGF family receptors have been approved for use in a number of cancer indications (e.g. Sunitinib). Despite the demonstrated therapeutic benefit gained by such agents, there have been reports of undesirable increased metastasis occurring as a consequence of inhibiting the function of VEGF2. It has been previously reported that inhibition of VEGF2 in preclinical models augments metastasis through increased hypoxia within the tumor microenvironment (Pàez-Ribes et al 2009). Furthermore, clinical evidence has demonstrated that VEGF2 inhibition can induce a more invasive metastatic disease (Ebos et al 2009). We have discovered BNC420 (Abstract #4029, AACR 2014), a tyrosine kinase inhibitor that potently inhibits VEGF3 while displaying selectivity over VEGF2 and VEGFR1. BNC420 is very effective in suppressing lymphatic metastasis in a preclinical model of melanoma.

**BNC420 is a potent inhibitor of VEGFR3 and displays selectivity over VEGFR2**

![Figure 1](image)

**Melanoma in Transit**

![In-transit lesions tracking down ear towards draining lymph node](image)

Vehicle | BNC420
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![Figure 2](image)

BNC420 is a potent inhibitor of VEGFR3 and displays selectivity over VEGFR2.

![Figure 3](image)

**BNc420 suppressed the development of lymph node metastasis and in-transit lesions**

![Figure 4](image)

![Figure 5](image)

![Figure 6](image)

![Figure 7](image)

**Conclusions**

- BNC420 selectively inhibits VEGFR3 phosphorylation and displays significant selectivity over VEGFR2 and VEGFR1
- In a murine model of melanoma, BNC420 suppressed the development of peri-tumoral lymphatics, the growth of in-transit metastatic lesions and the spread of metastasis to the draining lymph nodes
- The pan-VEGFR inhibitor Sunitinib failed to suppress lymph node metastasis and appeared to enhance formation of in-transit metastatic lesions. These data are consistent with previous report showing that pan-VEGFR inhibitors augment metastasis through increased hypoxia within the tumor microenvironment (Pàez-Ribes et al 2009)
- Unlike pan-VEGFR inhibitors, BNC420 suppresses metastasis - this is potentially due to its selectivity for VEGFR3 over VEGFR2

**References**