CD24 expression profile

CD24 is a small glycosylphosphatidylinositol (GPI)-anchored glycoprotein overexpressed on multiple types of cancers including lymphoma, breast cancer, ovarian cancer, where it reportedly regulates cell migration, invasion, proliferation and immune escape. Apart from being viewed as a tumor-associated antigen (TAA), CD24 was recently found to suppress tumor phagocytosis by delivering a “don’t-eat-me” signal via binding to Siglec10 expressed on tumor-associated macrophages. We hypothesize that selective tumor targeting of the CD24-Siglec10 pathway by anti-CD24 mAb may represent a novel therapeutic approach to enhance anti-cancer immunity while avoiding potential on-target off-tumor toxicity.

Binding profile of NXA01 with CD24

NXA01 is a novel, humanized anti-CD24 IgG1 derived from hybridoma. The affinity of NXA01 binding with CD24 was measured by SPR with Kd of 1.5 nM. The complex structure of NXA01 (Fab) bound with CD24 was determined by crystallography at 2.5 Å. The detailed interactions between NXA01 and CD24 were well resolved (purple, amino acids in the CDRs that interact with the mature recombinant CD24).

Effective CD24-Siglec10 blocking and ADC/ADCP

NXA01 blocked hCD24 Siglec10 interaction with an IC50 of 8.2 nM and could also mediate direct killing of MDA-MB-468 cells through both ADC and ADCP at EC50 lower than 10 nM which is comparable with a lead competitor.

Best-in-class tumor selectivity in vitro

NXA01 bound to hCD24 on tumor cells such as NALM6 but NOT to normal human B cells or activated T cell or granulocytes while other competitors had detectable binding to normal cells. This tumor selectivity was related to preferential binding of NXA01 to aglycosylated or hypoglycosylated hCD24 as an enzymatic deglycosylation of normal cells restored binding. Overall, NXA01 may exhibit a better safety profile than some of the lead competitors.

Conclusions

- NXA01, a potential best-in-class CD24 blocking antibody with selective tumor binding and strong anti-tumor activity in vitro and in vivo.
- Dual mechanism of ADCD and macrophage checkpoint blockade.
- High titer clone selected with good product quality and stability, along with high yield downstream process.
- Well-tolerated in repeated-dose GLP toxicity study.
- US IND filing by the end of 2023 for phase 1 dose escalation study planned for next year.

Discovery of NXA01, a novel CD24 antibody with tumor selectivity and potent anti-tumor activity
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Enhanced ADCP through Blockade of “don’t eat me” signal

NXA01-Fab enhanced robust ADCP activity of tafasitamab analog (anti-CD19).

Potent antitumor efficacy in multiple analogs

NXA01 exhibited strong antitumor efficacy in colon cancer CDX model (MC38-hCD24), leukemia CDX model (NALM6) and triple negative breast cancer CDX model (MDA-MB-468) with maximal inhibition of 104%, 105% and 51%, respectively.