BYON4228 is a pan-allelic blocking SIRPα antibody that potentiates killing of antibody-opsonized tumor cells and lacks binding to T cells

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BACKGROUND

A broad panel of tumor-targeting antibodies provides standard of care in clinical practice. For most antibodies immunological effector functions, including antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), critically contribute to their efficacy. In preclinical models, the CD47-SIRPα axis has been firmly established as an immune checkpoint that inhibits myeloid-derived ADC and ADCP, and therefore limits efficacy of anti-tumor antibodies. Different CD47-targeting molecules are currently in clinical development. However, the ubiquitously expressed CD47 not only binds SIRPα, but mediates functional interactions with other ligands as well, which may also be affected by these agents. Targeting of the primarily myeloid cell-restricted inhibitory immunoreceptor SIRPα may therefore represent a better strategy. However, SIRPα-targeting antibodies in clinical development either lack binding to both polymorphic SIRPα variants that are present in the human population, or they also block the related SIRPγ. Since SIRPγ is pivotal for optimal T cell responses, SIRPγ inhibition might curtail durable anti-tumor immunity. We therefore set out to develop a novel and unique SIRPα-blocking antibody, BYON4228, and report its preclinical characterization.

IN VITRO BINDING

BYON4228 is a potently pan-allelic SIRPα binder

IN VITRO FUNCTIONAL ACTIVITIES

BYON4228-induced ADCC and ADCD enhancement is Fc-tail independent

CONCLUSIONS

• Pan-allelic: BYON4228 recognizes both allelic variants SIRPα and SIRPγ, No binding to T cell-expressed SIRPγ
• No binding to T cell-expressed SIRPγ: leaving T cell activation and migration unimpaired49
• Blocking of the CD47-SIRPα axis: BYON4228’s epitope overlaps with the CD47-binding site
• Enhancement of immune cell effector functions: induced by therapeutic anti-tumor antibodies
• Broad potential clinical applicability: cellular effector functions enhancement of all tested therapeutic antibodies, incl. trastuzumab, rituximab, daratumumab and cetuximab
• Clinical studies: planned to start in 2022

REFERENCES/ OTHER

1. Toffoli et al. (2018) EMBO J 37:444

1. Byondis BV; Copyright (2020) Byondis BV
2. BYON4228 is a potent pan-allelic blocking SIRPα antibody that potentiates killing of antibody-opsonized tumor cells and lacks binding to T cells

Figure 1. Binding of BYON4228, trastuzumab (A,B) or cetuximab (C, D) to SIRPα- or SIRPγ-expressing B-cells (A, C) and SIRPγ-expressing 4T1 cells (B, D), respectively, in GADGET® transduced A431 cells expressing SIRPα.

Figure 2. Binding of BYON4228 to the CD47-binding site on SIRPα.

Figure 3. Neutrophil-induced antibody-dependent cellular cytotoxicity (ADCC) towards trastuzumab (A,B) or cetuximab (C,D), respectively, in the presence of a dose-response curve of indicated antibodies. (A,C) Results from representative donors. (B,D) BYON4228 OPC summary and ADCD ratios of all donors (N=11).

Figure 4. ADCC and ADCD enhancement is Fc-tail independent.

Figure 5. ADCC and ADCD enhancement is Fc-tail independent.

Figure 6. Antibody-dependent cellular phagocytosis (ADCP) of rituximab-opsonized Raji cells, in presence of indicated antibodies, by macrophages from a representative donor (A) and the ADCD EC50 (B) and ADCP PI ratios (C) of all donors (N=18). Phagocytosis index (PI) = number of phagocytosed tumor cells/total number of macrophages * 100.

Figure 7. ADCP of daratumumab (A,C) or rituximab (E) opsonized Daudi or Raji cells, respectively, in presence of indicated antibodies BYON4228 (IgG1-122A4/135A5), H11B (IgG1-52Z23B/4459B) or respective isotype controls, by macrophages from representative donors with different SIRPα epitope genotypes (A) or the ADCD EC50s (B) and ADCD PI ratios of all donors (C,E) (N=12-18).

Figure 8. Antibody-dependent cellular cytotoxicity (ADCC) towards trastuzumab (A,B) or cetuximab (C,D), respectively, in the presence of a dose-response curve of indicated antibodies. (A,C) Results from representative donors. (B,D) BYON4228 OPC summary and ADCD ratios of all donors (N=11).