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A novel HER2/4-1BB bispecific antibody, YH32367 (ABL105) shows potent anti-tumor effect through tumor-directed T cell activation

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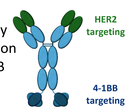
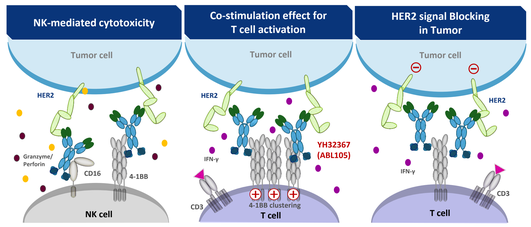
Background

YH32367 (ABL105), Anti-HER2/4-1BB bispecific antibody

Candidate	• Tumor-directed HER2/4-1BB bispecific antibody engineered to amplify tumor-localized activation while limiting super-agonistic activity of 4-1BB • IgG1 bispecific antibody 
Function	• Induction of T cell activation and survival through 4-1BB stimulation • Growth signal blocking via HER2 receptor binding in tumor • NK cell-mediated ADCC effect
Indication	• Potential applications in a variety of HER2$^+$ solid cancers
Development stage	• Preclinical • Lead candidate identified

Mechanism of action : Stimulation of T cells in tumor



*Anti-tumor effect via **NK** mediated cytotoxicity* | *Anti-tumor effect by **Tumor** specific T cells activation* | *Anti-tumor effect via **HER2 signal** blocking in tumor cells*

Materials and Methods

- **Anti-4-1BB Ab :** Strong agonistic anti-4-1BB monoclonal antibody (Benchmark), in-house production
- ***Target binding affinities*** were measured by SPR assay and cell binding assay. 4-1BB expressing Jurkat cells and HCC1954 cells were used in cell binding assay for 4-1BB and HER2, respectively.
- ***4-1BB activity*** was evaluated by 4-1BB bioassay in HER2 expressing cells. Normalized HER2 expression was calculated based on HER2 expression of SK-BR-3.
- ***In vitro efficacy on IFN-γ secretion and tumor cell survival*** was measured in hPBMC and HCC1954 co-culture system.
- ***In vivo efficacy studies*** were conducted in HCC1954 bearing hPBMC engrafted mouse model and hHER2/MC38 bearing h4-1BB knock in mouse model. HER2 expression of hHER2/MC38 tumor was evaluated by immunohistochemistry (IHC). MDA-MD-231 tumor tissue (HER2$^-$ tumor) and HCC1954 tumor tissue (HER2$^+$ tumor) were used as control of HER2 immunohistochemical stains.
- ***Tumor infiltrated immune cells*** were evaluated by IHC in tumors and livers.
- ***Number of CD45$^+$ cells in blood*** was analyzed using FACS analysis.
- ***Statistics***
- All data were presented as the mean ± SEM and analyzed using one-way ANOVA followed by Dunnett's multiple comparison tests in GraphPad Prism®.
  $^{***}p < 0.001$, $^{**}p < 0.01$ and $^{*}p < 0.05$ compared to Control group (G1).

Results

IN VITRO

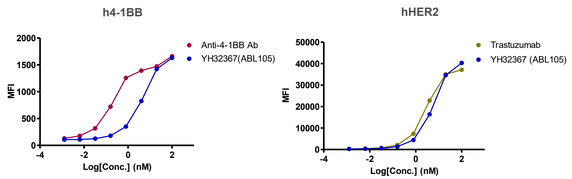
YH32367 exhibited potent binding efficacy to targets

Fig. 1. The binding affinities to targets

SPR assay

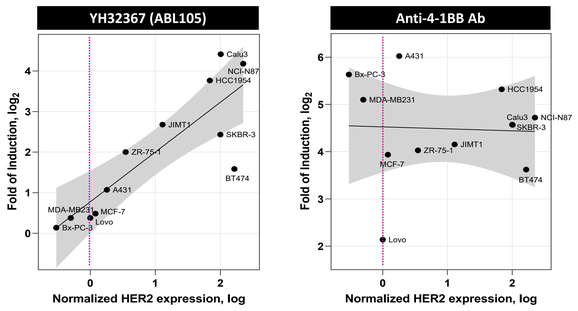
	K_D (nM)		
	YH32367(ABL105)	Anti-4-1BB Ab	Trastuzumab
h4-1BB	3.36	1.78	N/A
hHER2	0.48	N/A	0.58

Cell binding assay



YH32367 exhibited 4-1BB activation is dependent on HER2 expression

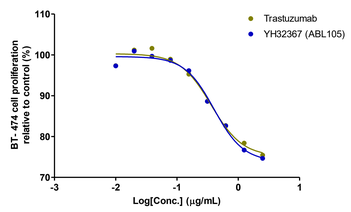
Fig. 2. HER2-dependent 4-1BB activation



✓Magenta dotted line : HER2 expression level of LoVo cell

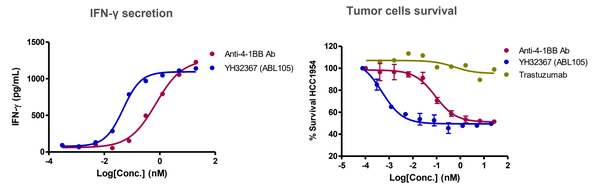
YH32367 was comparable to Trastuzumab in cancer cell growth inhibition

Fig. 3. *In vitro* efficacy on cell proliferation



YH32367 enhanced the cytotoxic effect of immune cells via 4-1BB activation in vitro

Fig. 4. *In vitro* efficacy on IFN-γ secretion and tumor cell survival

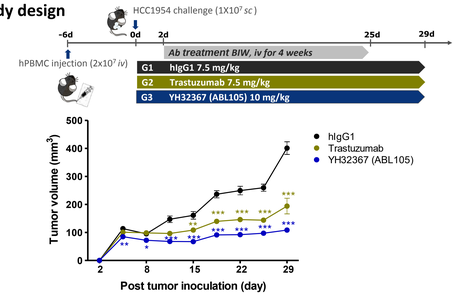


IN VIVO

YH32367 exhibited potent anti-tumor effect in humanized mouse model

Fig. 5. *In vivo* efficacy in HCC1954 bearing hPBMC engrafted mouse model

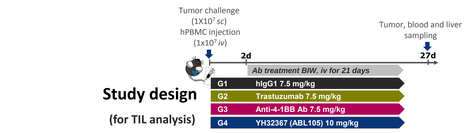
Study design



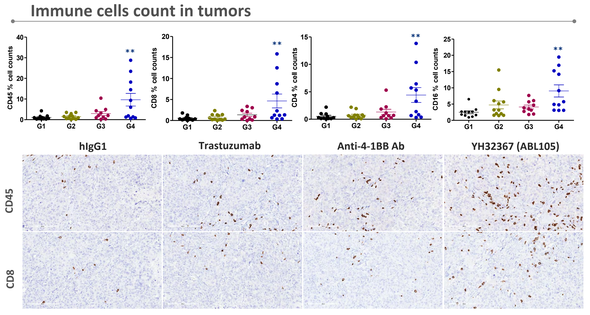
YH32367 enhanced immune cell infiltration into tumors

Fig. 6. Immune cell profile in HCC1954 bearing hPBMC engrafted mouse model

Study design (for TIL analysis)

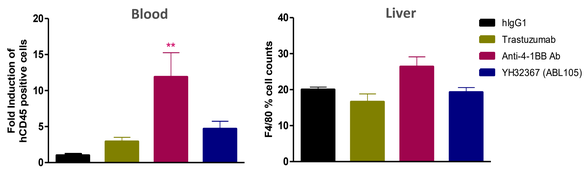


Immune cells count in tumors



YH32367 minimized undesirable immune response in peripheral blood and liver

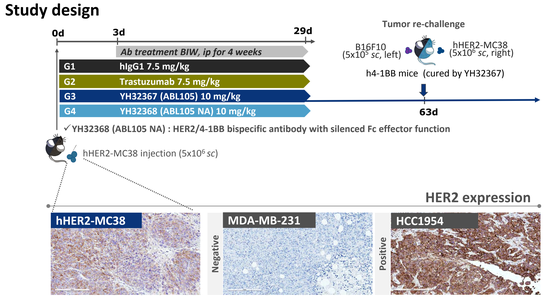
Fig. 7. Immune cell analysis in blood and liver of HCC1954 bearing hPBMC engrafted mouse model

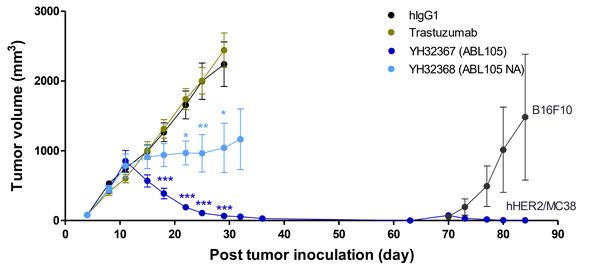


YH32367 exhibited prolonged anti-tumor effect via tumor specific memory T cells

Fig. 8. Anti-tumor effect in 4-1BB KI mouse model

Study design





Conclusion

YH32367 (ABL105) exhibited

- ***Tumor localized 4-1BB activation,*** which depends on cross-linking with HER2
- ***Strong tumor growth inhibition*** in hPBMC engrafted model and h4-1BB Knock-In model
- ***Prolonged anti-tumor effect*** via tumor specific memory T cells
- ***Minimized undesirable immune response*** compared to 4-1BB agonist antibodies

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