A novel HER2/4-1BB bispecific antibody, YH32367 (ABL105) exerts significant anti-tumor effects through tumor-directed T cell activation

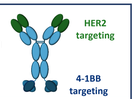
Eunjung Lee [1], Hyejin Chung[2], Yangsoon Lee[2], Eun-Jung Lee[1], Young Bong Park[1], Youngseok Kim[1], Ju Young Park[1], Sujin Ahn[1], Junhwan Kim[1], Kyoung Kyu Ahn[1], Kyeongsu Park[2], , Wonjun Son[2], Donghoon Yeom[2], Jaeho Jung[2], Jonghwa Won[2], Se-Woong Oh[1]

[1]Yuhan Corporation, Seoul, Republic of Korea , [2]ABL Bio Inc., Gyeonggi-do, Republic of Korea

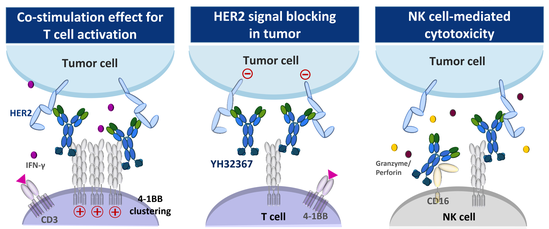
Background

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 • Humanized 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	• HER2 positive solid cancers: breast, gastric, biliary, bladder cancer *etc.*
Competitiveness	• Compared to HER2-mAb or ADC, YH32367 is expected to have - Long-term clinical efficacy due to tumor-specific immune-memory - Significantly lower toxicity compared to HER2-ADC - Potential treatment option for patients who have progressed after prior anti-HER2-based regimens
Development stage	• Preclinical GLP toxicity studies: ongoing • Clinical material manufacturing for first-in-human study: ongoing • First-in-human study planned in 2022



Mechanism of action: Tumor-targeted 4-1BB agonism



Methods

- ***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
- ***4-1BB activity*** was evaluated by 4-1BB bioassay in HER2 expressing cells and FcγR over-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-MB-231 tumor tissue (HER2$^-$ tumor) and HCC1954 tumor tissue (HER2$^+$ tumor) were used as control of HER2 immunohistochemical stains.
- ***Tumor infiltrated immune cells*** were measured by IHC in tumors and livers.
- ***Number of CD45$^+$ cells in blood*** was analyzed using FACS analysis.
- ***Number of F4/80$^+$ cells in liver*** was counted using IHC.
- **Benchmark Abs:** Strong agonistic anti-4-1BB monoclonal antibody and anti-4-1BB/HER2 targeting bsAb (In house preparation)
- ***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

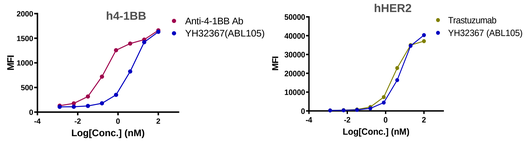
YH32367 exhibits potent binding affinities to targets

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 leads to 4-1BB activation through HER2 expression level-dependent binding and FcγRI-mediated crosslinking

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

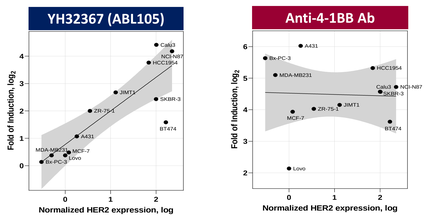
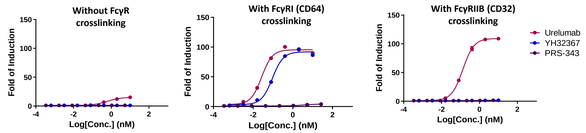
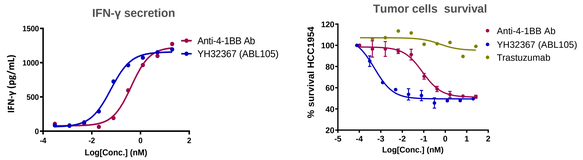


Fig. 3. FcγRI-mediated 4-1BB activation



YH32367 enhances 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

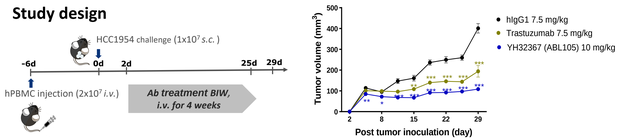


IN VIVO

YH32367 exhibits potent anti-tumor effect in humanized mice model

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

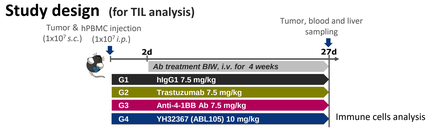
Study design



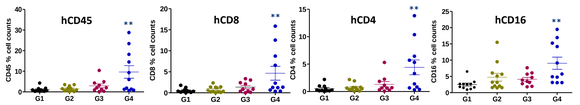
YH32367 enhances immune cell infiltration into tumors

Fig. 6. Immune cell profile in HCC1954 bearing hPBMC engrafted mice

Study design (for TIL analysis)

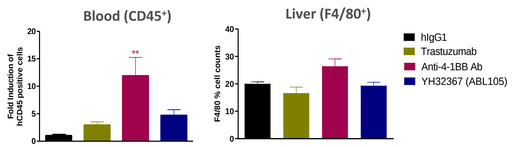


Immune cells count in tumors



YH32367 is designed to minimize undesirable immune response in peripheral blood and liver

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



YH32367 exhibits a significant anti-tumor effect to HER2+ tumor in h4-1BB KI mice model

Fig. 8. Significant tumor growth inhibition following single *i.v. treatment*

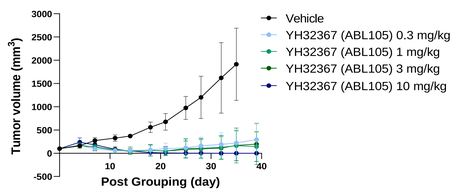
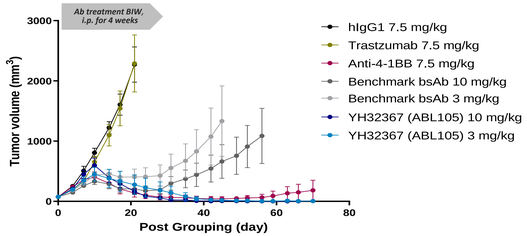
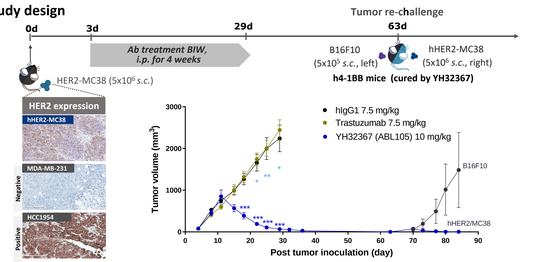


Fig. 9. Remarkable anti-tumor efficacy of YH32367



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

Fig. 10. Prolonged anti-tumor effect in h4-1BB KI mice



A favorable safety profile of YH32367 demonstrated in repeat-dose cynomolgus monkey toxicology study

- 4-week repeated dose monkey GLP toxicology study in progress
- During the in life phase, no notable changes in body weight/food consumption as well as no mortality

Table. 1. GLP-Toxicology study design

Group	Dose level (mg/kg)	No. of animals			
		Toxicity		Recovery	
		M	F	M	F
G1 control	0	3	3	2	2
G2 Low	10	3	3		
G3 Intermediate	30	3	3		
G4 high	100	3	3	2	2

Conclusion

YH32367 (ABL105) exhibited

- ***Tumor localized 4-1BB activation*** depending on crosslinking with HER2 and FcγRI
- ***Potent in vitro activity*** achieved by HER2 and 4-1BB binding
- ***Superior anti-tumor efficacy*** confirmed in hPBMC engraft and h4-1BB KI model
- ***Tumor specific memory T cells effect*** verified through prolonged anti-tumor effect
- ***Significantly low hepatotoxicity*** identified due to the conditional 4-1BB activation

For more information, please contact us at: hkkim@yuhan.co.kr, +82-2-828-0164, or visit www.yuhan.co.kr

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