IKSUDA THERAPEUTICS

Abstract #1753

IKS014, a HER2-targeting antibody drug conjugate incorporating novel bioconjugation and tumor-selective linker technology with improved in vivo efficacy and tolerability

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Background

HER2 has long been a target of high interest for antibody and antibody drug conjugate (ADC) therapeutics due to its well-documented overexpression in breast, gastric and lung cancer. While trastuzumab and ado-trastuzumab emtansine (T-DM1) have become an integral part of treatment paradigms for HER2-positive cancer, the more recent approvals of the fam-trastuzumab deruxtecan (DS-8201) ADC and the Fc-engineered margetuximab antibody have highlighted the potential for continued improvement over existing HER2-targeting therapies.

IKS014 is a HER2-directed ADC that incorporates site-directed conjugation and tumor-selective glucuronide-trigger linker technology to reduce systemic off-target toxicity while maximizing efficient intracellular lysosomal payload release, thus holding the promise of a wider therapeutic index. IKS014 is comprised of a HER2 targeting antibody conjugated to the microtubule agent MMAF via a proprietary beta-glucuronide linker. Site-specific conjugation results in a homogeneous ADC with a defined drug-to-antibody ratio (DAR) 2 and good physio-chemical properties.

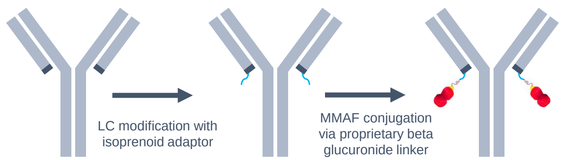
In vitro, IKS014 demonstrated dose dependent specific cytotoxicity against Her2-positive cell lines. In vivo activity was evaluated in HER2-positive preclinical models with varying HER2 expression levels in comparison to benchmark ADCs. In JIMT-1 breast cancer xenografts with moderate HER2-expression (HER2 IHC 2+), IKS014 causes complete regressions at a single dose of 5 mg/kg and partial regressions at 1 mg/kg, while T-DM1 results in only tumor growth inhibition even at 15 mg/kg. Anti-tumor efficacy of IKS014 in NCI-N87 (HER2 3+) gastric xenografts is comparable to DS-8201 but superior to T-DM1 at equivalent single doses ranging from 1 to 5 mg/kg. In a HER2-positive patient-derived gastric cancer model (HER2 2+), IKS014 was highly active at 5 mg/kg Q2W x2, while T-DM1 was inactive at the same dosing schedule.

IKS014 demonstrated stable PK in rat and monkey, and DAR 2 was maintained for up to 4 weeks. In cynomolgus monkeys, IKS014 was tolerated at 12 mg/kg single dose and 5 mg/kg repeat dose without ocular or lung toxicity findings.

IKS014 was highly efficacious against HER2-positive tumor xenografts in vivo, including models with moderate target expression, and compared favorably to clinically validated benchmark ADCs. This improved preclinical efficacy combined with stable PK and good tolerability profile warrants further development of this novel ADC for HER2-positive cancers.

ADC Generation

IKS014 was generated by site-specific conjugation of the tubulin inhibitor MMAF at an engineered Cysteine on the antibody light chain C-terminus via a proprietary beta-glucuronide linker.



- Manufacturing and purification yields a homogeneous ADC with drug to antibody ratio (DAR) of 2
- Minimal aggregate formation observed by SEC-HPLC
- Conjugation has no impact on binding affinity of the antibody
- Optimized chemistry results in superior linker and ADC stability in plasma

In vitro and in vivo Pharmacology

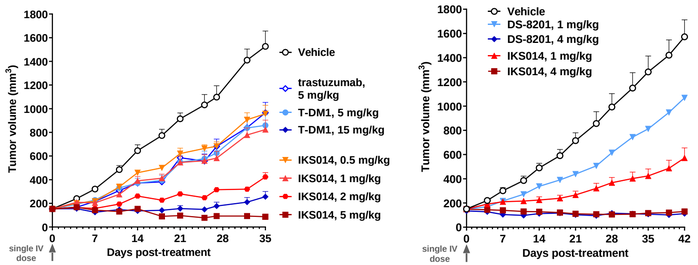
IKS014 demonstrates potent in vitro activity in cell lines with varying HER2 expression

Cell Line	SK-BR3	BT-474	NCI-N87	HCC-1954	SK-OV-3	Calu-3	JIMT-1
HER2 IHC	3+	3+	3+	3+	3+	2+	2+
IKS014 (DAR 2)	**0.16**	**0.34**	**0.51**	**0.21**	**0.36**	**0.48**	**0.39**
T-DM1 (DAR 3.5)	**0.48**	**1.61**	**0.86**	**0.86**	**0.69**	>30	>30
Herceptin	**0.45**	**1.22**	>30	>30	>30	>30	>30
Paclitaxel	5.90	10.4	5.99	9.23	12.8	18.6	4.72

- IKS014 shows dose-dependent cell killing in vitro with sub-nanomolar EC50 in HER2 high and moderate expressing cell lines
- Unlike IKS014, T-DM1 was not active in Calu-3 and JIMT-1 cells

In vitro cytotoxicity assays were conducted in HER2-positive cell lines following 3-day incubation using Cell-Titre Glo (Promega). EC50 given in nM ADC.

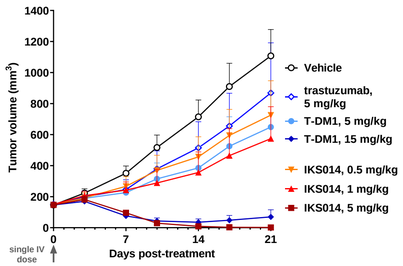
In vivo anti-tumor efficacy in NCI-N87 (HER2 3+) gastric xenograft is comparable to DS-8201 and superior to T-DM1



- IKS014 results in complete tumor growth inhibition following a single IV dose of 4 or 5 mg/kg in a HER2 high gastric cancer xenograft with >3 fold greater activity than T-DM1 (DAR 3.5) and comparable activity to DS-8201 (right)

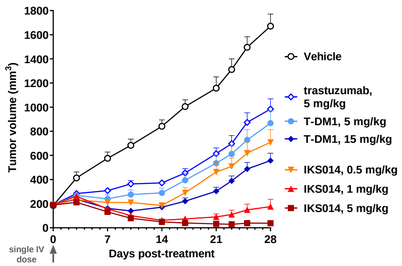
In vivo efficacy was evaluated in female BALB/c nude mice for BT474 and NCI-N87 or SCID Beige mice for JIMT-1 subcutaneous xenografts. Treatment was initiated when tumor volume reached 150-200 mm³ with n=5 per group.

IKS014 in vivo anti-tumor activity in BT-474 (HER2 3+) breast cancer xenograft model is superior to trastuzumab and T-DM1



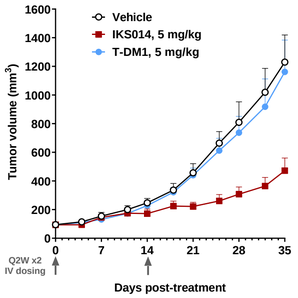
- IKS014 results in complete tumor regression following a single dose IV of 5 mg/kg in HER2 high breast cancer cell-line (IHC: HER2 3+)
- Trastuzumab has marginal activity and T-DM1 only modestly inhibits tumor growth at a dose 3-fold higher

In vivo efficacy in T-DM1-resistant JIMT-1 (HER2 2+) breast cancer xenograft model



- IKS014 causes complete regressions at a single dose of 5 mg/kg and partial regressions at 1 mg/kg in JIMT-1 with moderate HER2-expression
- Trastuzumab emtansine (T-DM1) only results in tumor growth inhibition at 15 mg/kg single dose
- DS-8201 shows only marginal tumor regression at 10 mg/kg Q7d x 2 in this model[1]

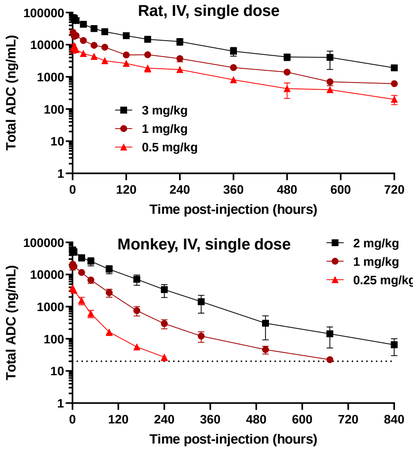
IKS014 is more efficacious than T-DM1 in a gastric cancer PDX model (HER2 2+)



- IKS014 demonstrates strong in vivo efficacy against a patient-derived gastric cancer xenograft model at 5mg/kg Q2W x2
- In comparison, Trastuzumab emtansine (T-DM1) showed limited to no activity at the same dosing schedule

PK and Safety Assessment

IKS014 demonstrates stable ADC PK profile in vivo



Total ADC levels in plasma were determined by ELISA following single dose IV injection.
Total Ab concentrations were comparable (data not shown).
Free MMAF <LLOQ in rat and maximum of ~30 pg/mL in monkey plasma.

Safety assessment

- GLP-compliant single dose and repeat dose studies in cynomolgus monkeys yielded an HNSTD of 12 mg/kg for single dose; and 5 mg/kg Q3W x4 for repeat dose administration of IKS014 ADC
- Safety findings were limited to hematologic changes and serum chemistry including increase in liver function tests
- No ocular findings were noted

Conclusions

- IKS014 is a HER2-targeting ADC with an MMAF prodrug design incorporating a beta-glucuronidase cleavable linker that requires lysosomal activation
- Novel site-directed bioconjugation results in a homogeneous ADC with defined DAR and good physio-chemical properties
- In vitro, IKS014 results in dose dependent specific cytotoxicity against HER2-positive cell lines with a range of HER2 expression
- Potent in vivo activity in breast and gastric cancer xenograft models with HER2 3+ and 2+ expression levels at single doses of 1-5 mg/kg was comparable to or superior to clinical benchmark anti-HER2 ADCs
- IKS014 demonstrates stable ADC PK profile in rat and cynomolgus monkey
- Prodrug design incorporated into IKS014 results in favorable in vivo tolerability with an HNSTD of 12 mg/kg in cynomolgus monkeys
- Potential for expanded therapeutic index supports further development[2]

References

1. Ogitani Y, et al., Clin Cancer Res. 2016 Oct 15;22(20):5097-5108
2. Phase 1 study of FS-1502 in patients with HER2 expressing advanced solid tumors and breast cancer (NCT03944499)

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