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 recent approvals of the li-metastatic denuxamet (DS-8201) ADC and the Fc-engineered maratuzumab 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 cellular payload release, thus holding the promise of a wider therapeutic index. IKS014 is comprised of a HER2-targeting antibody conjugated to the microtubule-targeting agent MMAF via a proprietary beta-glucuronide linker. Site-specific conjugation results in a homogeneous ADC with a defined drug-to-antibody ratio (DAR) and good physicalchemical 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 gastric 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 HCC 8201 (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 QW x2, while T-DM1 was inactive at the dosing schedule.

IKS014 demonstrated stable PK in rat and monkey, and DAR 3 was maintained for up to 4 weeks. In cyclophosphamide, IKS014 was tolerated at 12 mg/kg single dose and 5 mg/kg repeat dose without oocytotoxicity or tumor 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.

Conclusions

IKS014 is a HER2-targeting ADC with an MMAF prodrug design incorporating a beta-glucuronidase cleavable linker that improves biostability and activity.

Site-directed bioconjugation results in a homogeneous ADC with defined DAR and good physiochemical 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 vivo.

PK and Safety Assessment

Safety assessment

- GLP-compliant single dose and repeat dose studies in cynomolgus monkeys yielded an INSDT of 12 mg/kg for single dose, and 5 mg/kg QW 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 oocytotoxic findings were noted.

References

2. Phase 1 study of FS-1502 in patients with HER2 expressing advanced solid tumors and breast cancer (NCT03944489)

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

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

IKS014 in vivo anti-tumor activity in BT-474 (HER2 3+) breast cancer xenograft model

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

IKS014 demonstrates stable ADC PK profile in vivo

IKS014 demonstrates complete tumor growth inhibition following a single IV dose of 4 mg 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)

IKS014 shows dose-dependent cell killing in vitro with sub-nanomolar EC50 in HER2 high and moderate expressing cell lines

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

In vivo efficacious in female BALB/c nude mice for BT474 and NC-87 or SCID Beige mice for JIMT-1 subcutaneous xenografts. Treatment was initiated when tumor volume reached 150-200 mm³ with half-pairs.

Tumor volume (mm³)

1 mg/kg

3 mg/kg

5 mg/kg

Vehicle

IKS014, 5 mg/kg

T-DM1, 5 mg/kg

Days post-treatment

0 7 14 21 28 35

0

200

400

600

800

1000

1200

1400

1600

1800

Days post-treatment

Time post-injection (hours)

Total ADC levels in plasma were determined following single dose IV injection.

PK profile and safety assessment

MMAF conjugation via proprietary beta-glucuronide linker

Drug conjugation and purification yields a homogeneous ADC with drug to antibody ratio (DAR) of 2

Manufacturing and purification yields a homogeneous ADC with drug to antibody ratio (DAR) of 2

Degradation products 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

LC-modification with desalted adaptor

MMAF conjugation via proprietary beta-glucuronide linker

Manufacturing and purification yields a homogeneous ADC with drug to antibody ratio (DAR) of 2

Degradation products 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

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.

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