Abstract #355

Early analysis of activity in esophageal cancer during Phase 1 dose escalation of IKS014, a HER2-targeting antibody drug conjugate (ADC), in participants with advanced HER2+ and HER2 low solid tumors

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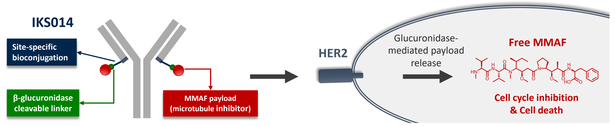
BACKGROUND

HER2 (c-erbB2, HER2/neu) overexpression, gene amplification and mutations are observed in a broad range of solid tumors, particularly breast, esophageal, cervical, ovarian, and gastric cancers where these HER2 alterations can contribute to disease progression. Despite recent advances in HER2-directed therapies and their integration into standard of care therapy across tumor types, most patients develop progressive disease with persistent HER2 expression and additional treatment options are needed for these patients.

IKS014 is an ADC targeting HER2 that comprises a humanized IgG1 antibody conjugated to the monomethyl auristatin F payload, via a novel β-glucuronidase-cleavable linker.

In the IKS014-01 Phase 1 study, anti-tumor activity, including objective responses, was observed at doses ≥ 40 mg/m². IKS014 (FS-1502) has been evaluated by a separate sponsor in trials conducted exclusively in China with activity noted at the equivalent dose level of ≥ 1.0 mg/kg [Li et al. 2024]. Here, preliminary safety and efficacy results are presented from dose escalation of the ongoing IKS014-01 trial conducted in Australia including efficacy in a subset of esophageal cancer patients.



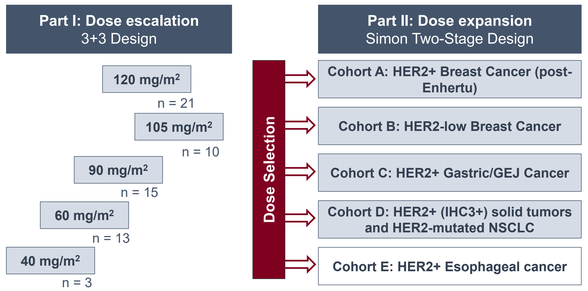
STUDY DESIGN AND ENROLLMENT

STUDY DESIGN: IKS014-01 is a non-randomized, open-label, multicenter trial of IKS014 in participants with locally advanced or metastatic solid tumors that express HER2 (NCT05872295). Part I, the dose-escalation portion (DE), was intended to establish the MTD and/or RP2D for IKS014 as monotherapy and to provide initial safety, tolerability, efficacy, PK, PD, and immunogenicity data. Participants in the DE portion must have HER2-expressing solid tumors with HER2+ (HER2-high) defined as IHC3+, IHC2+/ISH+ and HER2-low defined as IHC2+/ISH-, IHC2+/ISH unknown or IHC1+.

IKS014 was administered once every 3 weeks on Day 1 of each 21-day cycle. Participants were enrolled into cohorts of increasing dose levels using a standard 3+3 design and monitored for DLTs during Cycle 1. Tumor responses were assessed locally according to RECIST v1.1. Severity of Adverse Events (AEs) was graded according to CTCAE v5 with additional grading for ocular surface events. Part I enrichment cohorts could enroll up to 20 patients at selected dose levels to further characterize safety. Part II will include disease-specific Expansion Cohorts.

ENROLLMENT: A total of 62 patients were enrolled as of a 31-Jul-2025 data cut-off.

- Breast cancer (n=19, 6 HER2+ with 5 ER+ and/or PR+ and 13 HER2-low, with 9 ER+ and/or PR+).
- Esophageal cancer (n=10, all HER2+ and adenocarcinomas).
- Lung (n=6), ovarian (n=6), other solid tumors (n=21).
- Number of prior therapies ≥4: 71%. Median: 4



Clinical trial ID: NCT05872295; Study Start Date: 14 Sep 2023. **Sponsor:** Iksuda Therapeutics Ltd

EFFICACY

OVERALL ANTI-TUMOR ACTIVITY

- As of a 31-Jul-2025 data cut-off, 55 patients were evaluable for efficacy per RECIST.
- Median duration of follow-up was approximately 6.6 months.
- Encouraging anti-tumor activity was seen across all dose levels and in various tumor indications such as breast, esophageal, ovarian and gallbladder cancer and in patients with both HER2+ and HER2-low tumors.
- Responses were noted in 18 patients (13 PR, 4 uPR and 1 patient with non-measurable disease had complete regression).

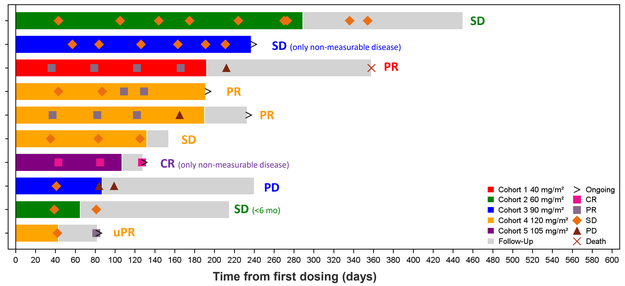
ANTI-TUMOR ACTIVITY in ESOPHAGEAL PATIENTS

- Of interest, 10 patients with HER2+ esophageal cancer, who had received prior therapy (median 3, range 1-6), were evaluable for efficacy in Part I.
- All patients had received prior HER2-targeting therapy with trastuzumab.
- Among these 10 patients, 5 achieved a response and 3 demonstrated stable disease > 6 months resulting in a clinical benefit rate (CBR) of 80% with IKS014.

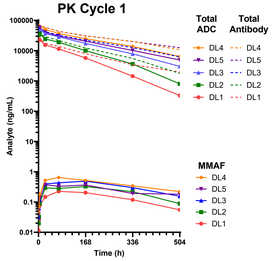
PHARMACOKINETICS:

- Novel linker design results in favorable ADC stability with low MMAF payload levels.
- ADC mean half-life of 3.3 to 6.6 days across cohorts.

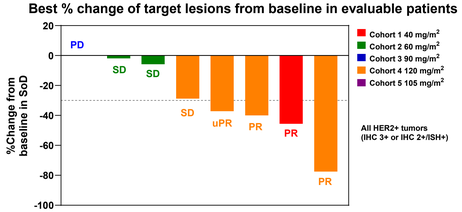
Time on treatment and best response in 10 HER2+ esophageal patients



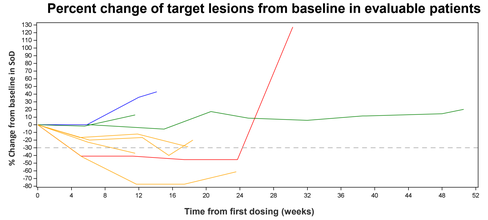
PK Cycle 1



Best % change of target lesions from baseline in evaluable patients



Percent change of target lesions from baseline in evaluable patients



Of 10 esophageal patients, only 8 patients with measurable disease and at least one evaluable post baseline assessment are presented. SoD = Sum of Diameters.

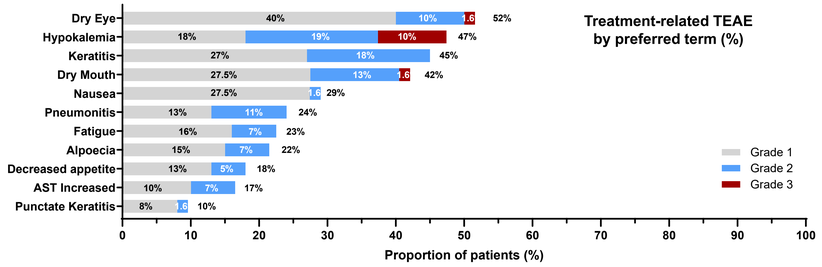
SAFETY

- The safety population included 62 patients who received at least one dose of study drug
- IKS014 was generally well-tolerated at doses up to 120 mg/m² (~3.2 mg/kg).
- Per protocol, the MTD was not reached and only one dose limiting toxicity of Gr 3 Infusion Related Reaction was seen.

Event	Pt n (%)
Any TEAE	**60 (96.8%)**
Any related TEAE	**58 (93.5%)**
Any Grade ≥ 3 TEAE	**26 (41.9%)**
Any related Grade ≥ 3 TEAE	**11 (17.7%)**
Related Grade ≥ 3 TEAEs excluding hypokalemia	**6 (9.7%)**
Any serious TEAE	**23 (37.1%)**
Any related serious TEAE	**5 (8.1%)**

- The safety profile was characterized by anticipated adverse effects including ocular surface AEs, pneumonitis and hypokalemia.
  - Ocular events were Gr 1/2 with only 1 pt, who did not receive any ocular prophylaxis, experiencing a Gr 3 event at the highest dose level. An ocular prophylaxis regimen has been advised through a protocol amendment late during the DE portion.
  - Pneumonitis was Gr 1/Gr 2 with no ≥Gr 3 events reported.
  - Hypokalemia was predominantly Gr 1/2 and addressed with oral K+ supplementation.

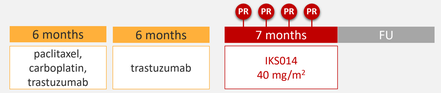
Treatment-related TEAE by preferred term (%)



CASE STUDIES

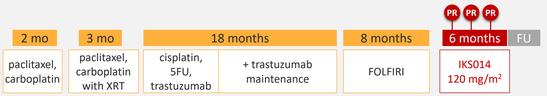
Durable partial response in trastuzumab-pretreated esophageal cancer

- 81y F, HER2+ (IHC3+) with two prior lines of therapies
- Received 10 cycles of IKS014 at 40 mg/m² with PR at EOC2, EOC4, EOC4 to EOC8
- Best RECIST response: PR with 45% reduction of target lesions



Partial response in heavily pretreated esophageal cancer

- 60y M, HER2+ (IHC2+/ISH+) with four prior lines of therapies
- Received 7 cycles of IKS014 at 120 mg/m² with PR at EOC2, EOC4, and EOC6
- Best RECIST response: PR with 77% reduction of target lesions



Durable complete response in trastuzumab-pretreated esophageal cancer

- 54y M, HER2+ (IHC3+) with two prior lines of therapies
- Received 8 cycles of IKS014 at 105 mg/m² with complete resolution of esophageal wall thickening
- On-going response for > 200 days
  - Updated as per Dec 2025

CONCLUSIONS

- Treatment with IKS014 was generally well-tolerated with anticipated adverse effects of ocular AEs, pneumonitis and hypokalemia, predominantly Gr 1 and Gr 2. No Gr 3 pneumonitis was reported.
- The novel linker design in IKS014 results in stable ADC PK with low levels of unconjugated MMAF payload in circulation.
- Anti-tumor activity has been observed across all dose levels and in various tumor indications.
- A dose of 105 mg/m² has been selected for further evaluation in the expansion cohorts.
- Among a subset of 10 pretreated patients with esophageal cancer, 5 achieved a response and 3 demonstrated stable disease > 6 months resulting in a clinical benefit rate of 80% with IKS014 warranting further exploration.
- The protocol will be amended to incorporate an additional expansion cohort specifically for patients with esophageal cancer who meet the following requirements:
  - Adenocarcinoma only.
  - HER2 status: IHC3+ or IHC2+/ISH+
  - Prior treatment with ≥ 1L of therapy which may have included a HER2-directed therapy.
- Activity was noted in other tumors as well:
  - Among 11 patients with breast cancer treated at doses ≥90 mg/m², 7 responses were seen with an ORR of 64%.
  - Among 4 patients with HER2+ breast cancer, 3 PRs/1 uPR were seen, including 3 patients who had received prior trastuzumab deruxtecan.
  - Among 7 patients with HER2-low breast cancer, 3 PRs (ORR 43%) were seen.
  - PRs/uPRs were also observed in pts with gall bladder, ovarian, endometrial and gastric cancers as well as NSCLC.

References: Li Q. et al, Nat. Commun. 15, 5158 (2024)

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