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A Phase 1 Dose Escalation Trial of IKS014, a HER2-Targeting Antibody Drug Conjugate (ADC), in Participants with Advanced HER2+ Solid Tumors

M. Ameratunga[1], A. Nagrial[2], P. Lau[3], K.T. Bui[4], D. Sabanathan[5], D. Browning[6], J. Thirlway[6], R. Lutz[6], J. Deckert[6], J. O'Leary[6], V. Ganju[7]

[1]Department of Medical Oncology, Alfred Health, Melbourne, Australia, [2]Department of Medical Oncology, Westmead Hospital, Westmead, Australia, [3]Department of Medical Oncology, Linear Clinical Research, Nedlands, Australia, [4]Medical Oncology Department, Concord Cancer Centre, Concord West, Australia, [5]Faculty of Medicine, Health and Human Sciences, Macquarie University, Macquarie Park, Australia, [6]ADC Development, Iksuda Therapeutics Ltd, Newcastle-upon-Tyne, United Kingdom, [7]Oncology Department, Peninsula and Southeast Oncology Group, Frankston, Australia

Background

IKS014 is an Antibody Drug Conjugate (ADC) targeting HER2 that is comprised of a human IgG1 antibody conjugated at two engineered cysteines to the monomethyl auristatin F (MMAF) cytotoxic agent via a novel β-glucuronidase-cleavable linker.

HER2 (c-erbB2, HER2/neu) overexpression, gene amplification and mutations are observed in a broad range of solid tumors, particularly breast, cervical, ovarian, esophageal, 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 has been evaluated by a separate sponsor in trials conducted exclusively in China under the drug name FS-1502. Anti-tumor activity, including objective responses, was noted in patients treated at doses ≥ 1.0 mg/kg [Li et al. 2024], which is equivalent to the 40 mg/m^2 dose in this study.

Here, preliminary safety, efficacy and pharmacokinetic results are presented from the dose escalation portion of the IKS014-01 trial conducted in Australia.

Study Design

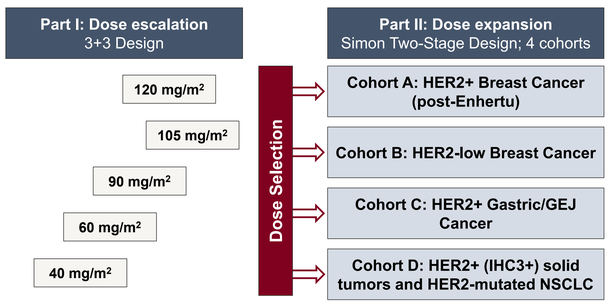
IKS014-01 is a non-randomized, open-label, multicenter trial of IKS014 in participants with locally advanced or metastatic solid tumors that express HER2 (NCT05872295), currently being conducted in Australia.

Part I, the dose-escalation portion (DE), is intended to establish the MTD and/or RP2D for IKS014 as monotherapy and to provide initial safety, tolerability, efficacy, PK, PD, and immunogenicity characteristics of IKS014. 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 that had been deemed safe and biologically active by the Safety Review Committee, to further characterize the safety of IKS014.

Part II will include 4 disease-specific Expansion Cohorts (EC).



Key Inclusion Criteria

- ≥ 18 years, ECOG 0-1.
- Part I: Pts with HER2 expressing locally advanced or metastatic solid tumors that that have failed standard therapy (including surgery, chemotherapy, radiation therapy or biotherapy) or for which there is no curative standard therapy available.
- Measurable or non-measurable disease.
- Part II: Disease specific with HER2 status per ASCO-CAP, where applicable. Measurable disease only.

Key Exclusion Criteria

- Clinically significant cardiovascular, hepatic, pulmonary disease.
- Current evidence of significant corneal disease or condition.
- Active CNS involvement.
- Active HIV, HBV or HCV infection.
- Unresolved Grade >1 toxicity from prior therapy, with exceptions.

Abbreviations: CNS, Central Nervous System; ECOG, Eastern Cooperative Oncology Group; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus

Enrollment and Efficacy

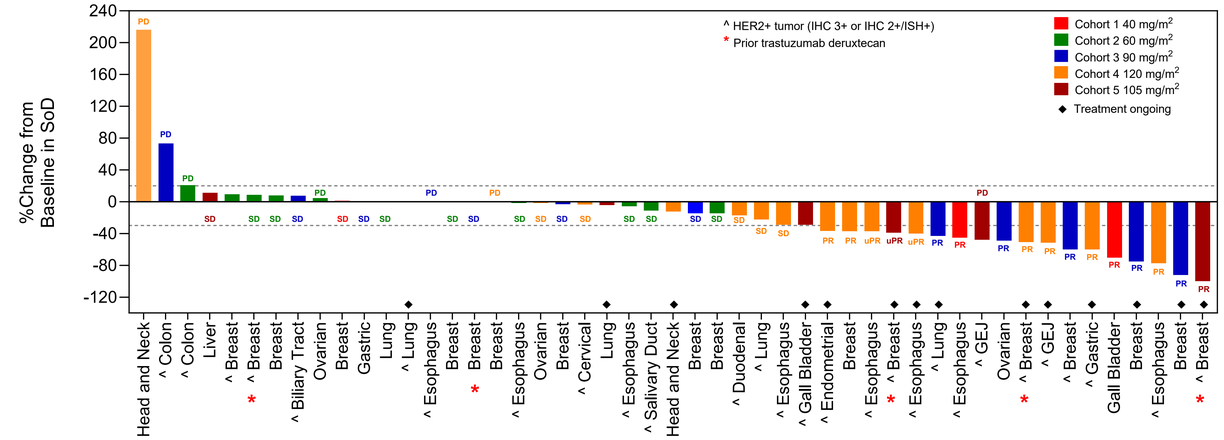
ENROLLMENT

- 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).
  - Median number of prior therapies was 4.

Cohort Number	IKS014 Dose Level (mg/m²)	Approximate IKS014 Dose in mg/kg	Patients in Dose Escalation Cohorts (n)	Patients in Enrichment Cohorts	Total Number of Patients
1	40	1.1	3	-	3
2	60	1.6	3	10	13
3	90	2.4	3	12	15
4	120	3.2	3	18	21
5	105	2.8	-	10	10

ANTI-TUMOR ACTIVITY

- At the data cutoff date, 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.
- Partial responses (PRs) and unconfirmed PRs (uPRs) have been observed in various tumor indications including breast, lung, esophageal, ovarian, gastric, gallbladder and GEJ cancers in both HER2+ and HER2-low tumors.
- Responses were noted in 18 patients (13 PR, 4 uPR and 1 pt with non-measurable disease had complete regression).
- Durable responses were noted across tumor indications and all dose levels.



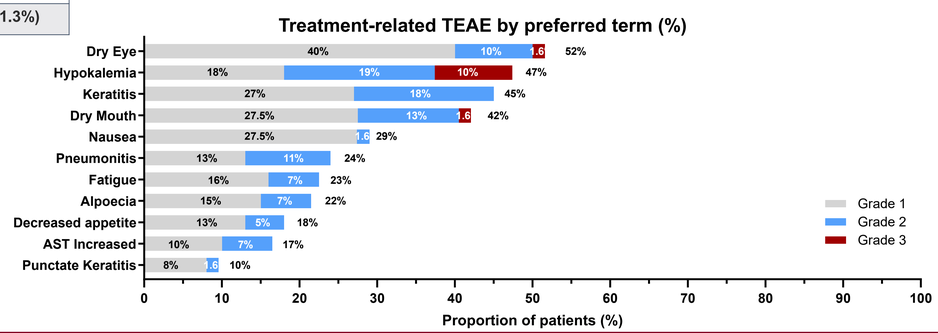
Safety

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%)**

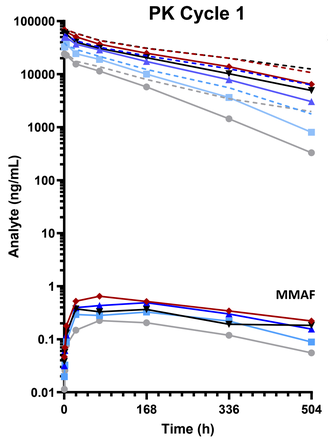
Event	Pt n (%)
Discontinuation	7 (11.3%)
Dose delay	31 (50.0%)
Dose reduction	7 (11.3%)

SUMMARY OF SAFETY

- The safety population includes 62 patients who received at least one dose of study drug.
- IKS014 was generally well-tolerated at doses up to 120 mg/m^2 (~3.2 mg/kg).
- The most common treatment-related adverse events (with incidence ≥ 15%) in order of decreasing frequency were dry eye, hypokalemia, keratitis, dry mouth, nausea, pneumonitis, fatigue, alopecia, decreased appetite, and aminotransferase increased.
- The safety profile was characterized by anticipated adverse effects which included 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.
- One dose limiting toxicity of Gr 3 Infusion Related Reaction was seen at the highest dose level.



Pharmacokinetics



- Novel linker design results in favorable ADC stability with low levels of unconjugated MMAF payload (< 1 ng/mL).
- Total ADC PK profile is similar to the antibody profile with a mean half-life of 3.3 to 6.6 days across dose levels in Cycle 1.
- Exposure to total ADC increased in a dose-proportional manner and half-life was ≥ 5 days at doses ≥ 90 mg/m^2, similar to the FS-1502 experience in China.
- Limited accumulation was observed between Cycle 1 and 3.

Cycle	Cohort	Dose Level (mg/m²)	C_{MAX} (ng/mL)	$AUC_{0\text{-}21d}$ (h*ng/mL)	ARAUC $_{0\text{-}21d}$	$T_{1/2}$ (d)	CL (mL/h*m²)
1	1	**40**	23,800	2,500,000		3.3	0.0158
	2	**60**	38,200	4,560,000		3.7	0.0128
	3	**90**	55,200	7,700,000		5.0	0.0109
	5	**105**	61,800	9,150,000		6.6	0.0103
	4	**120**	70,100	10,500,000		6.6	0.0101
3	1	**40**	23,400	4,660,000	1.87	3.8	
	2	**60**	39,500	6,590,000	1.42	4.6	
	3	**90**	59,700	11,600,000	1.41	5.4	
	5	**105**	60,100	11,800,000	1.36	5.1	
	4	**120**	78,000	16,500,000	1.48	7.1	

Total ADC, Antibody and unconjugated MMAF concentrations were determined by hybrid LC-MS/MS and PK parameters determined by non-compartmental analysis.

AR AUC: AUC Accumulation ratio, $T_{1/2}$: half-life, CL: clearance

Conclusions

- Treatment with IKS014 was generally well-tolerated with anticipated adverse effects of ocular AEs, pneumonitis and hypokalemia, predominantly Gr 1 and Gr 2.
- 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.
- Among 11 pts with breast cancer treated at doses ≥90 mg/m^2, 7 responses (ORR 64%) were seen:
  - Among 4 pts with HER2+ disease, 3 PRs/1 uPR were seen, including 3 pts who had received prior trastuzumab deruxtecan.
  - Among 7 pts with HER2-low disease, 3 PRs (ORR 43%) were seen.
- Among 10 pts with pre-treated, HER2+ esophageal cancer that were enrolled across all dose levels, 5 achieved a response including a complete regression in 1 pt with non-measurable disease only
- PRs/uPRs were also observed in pts with gall bladder, ovarian, endometrial, gastric, and GEJ cancers as well as NSCLC.
- An MTD was not reached per protocol. Dose selection for further evaluation in the expansion cohorts will be based on preliminary activity, safety, PK/PD and overall benefit-risk assessment from dose escalation.

Study Information and Disclosures

Clinical trial ID: NCT05872295; Study Start Date: 14 Sep 2023

Sponsor: Study sponsored by Iksuda Therapeutics Ltd

Dr. M. Ameratunga has no relevant conflicts of interest to declare

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

CONTACT: Iksuda Therapeutics Ltd, info@iksuda.com