Received: 8 November 2024 | Revised: 1 April 2025 | Accepted: 12 May 2025

DOI: 10.1002/cncr.35939

ORIGINAL ARTICLE

First-in-human phase 1 study of KHK2455 monotherapy and in combination with mogamulizumab in patients with advanced solid tumors

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Abstract

Background: Indoleamine 2,3-dioxygenase 1 (IDO1) is a heme-containing enzyme that degrades tryptophan (Trp) to kynurenine (Kyn), which suppresses effector T cells and reduces antitumor activity. KHK2455 is a long-acting selective IDO1 inhibitor that blocks the heme component of the IDO holoenzyme. Mogamulizumab is a humanized immunoglobulin G1 monoclonal antibody targeting CCR4. KHK2455 + mogamulizumab demonstrated enhanced antitumor activity in preclinical studies, which led to a first-in-human, two-part, multicenter, open-label, phase 1, dose-escalation, cohort-expansion trial (ClinicalTrials.gov identifier NCT02867007) evaluating the safety/tolerability, pharmacokinetics, and IDO1 activity of KHK2455 alone and in combination with mogamulizumab in patients with treatment-refractory advanced solid tumors.

Methods: Patients received oral KHK2455 at fixed doses of 0.3, 1, 3, 10, 30, and 100 mg once daily as run-in monotherapy for 28 days (cycle 0), and then in combination with 1 mg/kg intravenous mogamulizumab given weekly for cycle 1 and every 2 weeks from cycle 2 onward.

Results: Thirty-six patients were enrolled. One patient with an initial diagnosis of lower esophageal cancer (100-mg cohort) experienced grade 3 gastrointestinal necrosis, and did not receive mogamulizumab. Overall, KHK2455 + mogamulizumab

The first two authors contributed equally to this article.

This study was presented in part at the Annual Meeting of the Society for Immunotherapy of Cancer; November 9–14, 2020; virtual.

This study was presented in part at the Annual Meeting of the American Association for Cancer Research; April 10–15 and May 17–21, 2021; Philadelphia, Pennsylvania.

This trial was registered at ClinicalTrials.gov (NCT02867007).

was well tolerated, with manageable adverse events at all doses. KHK2455 + mogamulizumab demonstrated dose-dependent plasma concentration increases and suppression of IDO1 activity. One patient with advanced bevacizumab-resistant glioblastoma demonstrated a durable confirmed Response Evaluation Criteria in Solid Tumors, version 1.1, partial response, and nine patients achieved a durable disease stabilization of ≥6 months. On the basis of the preliminary antitumor response, the cohort expansion was not initiated.

Conclusions: KHK2455 + mogamulizumab was safe and well tolerated with manageable toxicities, and resulted in dose-dependent suppression of IDO1 activity; signals of antitumor activity were observed.

KEYWORDS
indoleamine 2,3-dioxygenase 1 (IDO1) protein, mogamulizumab, pharmacodynamics, pharmacokinetics, phase 1 clinical trial, preclinical drug evaluation

INTRODUCTION

Indoleamine 2,3-dioxygenase 1 (IDO1) is a heme-containing enzyme that degrades tryptophan (Trp) to kynurenine (Kyn), which may suppress effector T cells and activate T-regulatory cells (T_{reg}s), and thus reduce antitumor immune responses.[1,2] High-IDO1 expression in tumors may create a barrier, and prevent penetration of active effector T cells.[3] Thus, IDO1 inhibition may cause antigen-presenting cell activation, effector T-cell tumor penetration, and antitumor immune response activation.[4]

IDO1 inhibitor monotherapy results have not shown convincing antitumor activity but preclinical studies of these inhibitors in combination with other immunotherapeutics in multiple cancers have shown promise. The first IDO1 inhibitor was indoximod, which demonstrated antitumor activity when combined with pembrolizumab in a single-arm, phase 2 trial of patients with advanced melanoma.[5] Epacadostat, an IDO1 inhibitor that forms a tertiary IDO1–heme–inhibitor complex, enhanced immunotherapeutics in a phase 1 study[6]; however, efficacy was not confirmed in phase 2/3 studies.[4] Epacadostat plus pembrolizumab, a programmed cell death protein 1 inhibitor, demonstrated objective tumor responses in a phase 1/2 study of patients with advanced solid tumors but did not improve progression-free survival (PFS) or overall survival (OS) in a phase 3 study of unresectable or metastatic melanoma.[7,8]

Novel IDO1 inhibitors linrodostat and KHK2455 differ from epacadostat by competing with heme for apoenzyme binding, and thereby prevent apo-IDO1 from forming an active complex and resulting in durable inhibition.[9] KHK2455 is a long-acting, potent, and selective IDO1 inhibitor that may enhance immunotherapeutic agents, such as mogamulizumab.[10]

Mogamulizumab is a recombinant, humanized monoclonal antibody of immunoglobulin G1-κ targeting CCR4.[11] CCR4 is expressed on some T-cell malignancies, T_{reg}s, and a subset of type 2 helper T cells.[12] Therefore, using mogamulizumab to reduce T_{reg}s may alleviate immunosuppression of the tumor microenvironment and improve antitumor response.[11,13] Mogamulizumab was approved by the Food and Drug Administration and the European Medicines Authority in cutaneous T-cell lymphoma (CTCL), and by Japan's Ministry of Health, Labor, and Welfare in adult T-cell lymphoma, peripheral T-cell lymphoma, and CTCL. To our knowledge, there are currently no clinical trials of other anti-CCR4 antibody therapies. Combining KHK2455 with mogamulizumab may target T_{reg}s, and thereby result in enhanced T–effector cell proliferation and IFN-γ secretion greater than KHK2455 alone.

On the basis of the preclinical in vitro and in vivo data, the KHK2455 + mogamulizumab combination was evaluated in this first-in-human, phase 1, modified 3 + 3 dose-escalation, cohort-expansion study in patients with locally advanced or metastatic solid tumors to characterize the safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of oral KHK2455 + mogamulizumab.

MATERIALS AND METHODS

Preclinical study methods

Supplementary Material S1 contain the preclinical study methods.

Clinical study and design

This was a first-in-human, open-label, phase 1, two-part, modified 3 + 3 dose-escalation, cohort-expansion study of KHK2455 monotherapy followed by combination therapy with mogamulizumab in patients with advanced solid tumors conducted at four sites in the United States and European Union (ClinicalTrials.gov identifier NCT02867007). In part 1, patients received oral KHK2455 at fixed doses of 0.3, 1, 3, 10, 30, and 100 mg once daily as run-in monotherapy for 28 days (cycle 0), followed by KHK2455 in combination

with intravenously administered mogamulizumab 1 mg/kg once weekly for cycle 1 and then every 2 weeks for cycle 2 and beyond. KHK2455 dose selection was based on nonclinical data in mice and cynomolgus monkeys (Kyowa Kirin, data on file). Doses were escalated with a modified 3 + 3 design on the basis of results from the first three dose-limiting toxicity (DLT)–evaluable patients in each dosing cohort. Part 2 of this trial was a planned cohort-expansion phase in which patients would be enrolled in cohorts on the basis of their specific tumor type, and treated with the KHK2455 dose established in part 1 in combination with mogamulizumab. After a detailed review of part 1, the sponsor determined that KHK2455 + mogamulizumab was safe and tolerable. However, after assessing the preliminary data from part 1 for potential approval in the future, the study did not proceed to part 2 of the trial, and was terminated after the completion of part 1.

Institutional review board (IRB) approval was received from the Advarra IRB (formerly Chesapeake IRB), Western IRB, University of Texas MD Anderson Cancer Center, and Comité de Protection des Personne Tours–Région Centre–Ouest 1 (study reference 2017T1-14), and the research was performed in accordance with the current version of the Declaration of Helsinki. All patients provided written informed consent before the study.

Patient population

Patients eligible for treatment included those aged ≥18 years with locally advanced or metastatic solid tumors who had failed available therapy for their respective cancer and had histological or cytological evidence of solid malignancy with measurable neoplastic disease (Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST 1.1]). Exclusion criteria included the following: previous treatment with an anti-CCR4 antibody or IDO1 inhibitor, known active central nervous system metastasis (excluding primary brain tumors), immunosuppressive medications taken within 14 days of the first study dose, autoimmune disease history (excluding vitiligo, endocrinopathies, and alopecia), or a history of organ or allogenic bone marrow transplant.

Outcomes and assessments

The primary objective of this study was to characterize the safety and tolerability and establish the MTD of KHK2455 administered orally in combination with mogamulizumab, as assessed by adverse events (AEs), ophthalmic examination, immunogenicity, 12-lead electrocardiogram readings, and clinical laboratory evaluations. Secondary objectives for KHK2455 administered alone or in combination with mogamulizumab were to characterize the pharmacokinetic (PK) profile, assess the effect of treatment on IDO inhibition, and evaluate the preliminary antitumor activity of this combination. Exploratory objectives included an evaluation of the effect of KHK2455, administered alone or in combination with mogamulizumab, on pharmacodynamic (PD) markers; an evaluation of immunogenicity; an exploration of the PK/PD relationships with antitumor responses, PD markers, and safety; and an evaluation of the effect of KHK2455 on serum concentrations of mogamulizumab.

Safety analysis

AEs were encoded according to MedDRA (version 19.0) by system organ class and preferred term. The intensity of AEs was assessed and graded with the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03). The MTD was defined as the highest dose evaluated at which no more than one patient in a cohort of six experienced a DLT during the 56-day observation period. DLTs were defined as the occurrence of any of the following toxicities considered related to either KHK2455 or mogamulizumab that had an onset during the first 56 days of treatment: grade 4 AEs, including immune-related AEs (excluding grade 4 neutropenia of <5 days and grade 4 lymphopenia of <14 days); grade ≥3 colitis, skin rash, or eye disorder that did not improve to grade ≤1 within 14 days of supportive care; grade ≥3 pneumonitis or neurotoxicity; liver transaminase elevation of >5× the upper limit of normal or total bilirubin of >3× the upper limit of normal that did not downgrade to grade <1 or baseline within 14 days; or any other grade ≥3 AE that did not improve to grade ≤1 within 14 days of supportive care, with the exception of grade 3 fatigue or thrombocytopenia.

PK analysis

Samples were collected to quantify the plasma concentrations of KHK2455 as follows. During cycle 1, extensive PK samples were collected at predose on day 1 and at predose and through 12 h postdose on day 15. During cycle 2 and beyond, predose PK samples were collected on days 1 and 15. Samples were analyzed for KHK2455 plasma concentrations with a high-performance liquid chromatography method with a triple-quadrupole mass spectrometer equipped with an atmospheric pressure chemical ionization source. PK parameters were estimated with KHK2455 plasma concentrations via noncompartmental methods. Estimated parameters included C_{max}, C_{trough}, t_{max}, and AUC_{0-24} for days 1 and 15 of cycle 1.

PD analysis

The PD effects on IDO inhibition after KHK2455 alone or in combination with mogamulizumab were assessed via patient plasma sampling and ex vivo stimulated peripheral blood mononuclear cells (PBMCs) with liquid chromatography–mass spectrometry. Circulating $CCR4^+$ T_{reg}s, activated T cells, and other immune cell populations were assessed by flow cytometry. Expression of tumor biomarkers, such as IDO, CCR4, CD8, and FoxP3, in tumor biopsy samples before and after KHK2455 + mogamulizumab was evaluated by immunohistochemistry. Plasma Kyn, Trp, and 3-hydroxyl-Kyn concentrations

were determined in plasma samples collected after KHK2455 alone or in combination with mogamulizumab.

PK/PD analysis

To understand the potential relationships between KHK2455 plasma concentrations and plasma Kyn/Trp (K/T) inhibition, the K/T ratio as a percentage of baseline was plotted against the observed time-matched KHK2455 plasma concentrations.

Efficacy analysis

Response was determined by radiographic evaluation of disease. Tumor assessments were performed at screening, every 8 weeks (±5 days) in year 1, and then every 16 weeks (±5 days) thereafter or as clinically indicated, until disease progression or study withdrawal. The proportion of patients in the efficacy analysis set who achieved a best response of confirmed complete response (CR) or partial response (PR) was assessed via RECIST 1.1. The duration of disease response was measured from time of first reported stable disease (SD) or better until time of disease progression.

Statistical analysis

The sample size for the dose-escalation phase was based on a modified 3 + 3 dose-finding design, and depended on toxicity. Up to six patients could be enrolled per cohort to characterize the safety profile. Six cohorts were planned (~36 patients). All efficacy analyses were based on the efficacy analysis set, which included all patients in the dose-escalation phase of the study who completed the first cycle of combination therapy and who had a baseline and at least one post-baseline on-study assessment of response. Objective response rate and disease control rate (DCR) were calculated with the Clopper–Pearson method with 95% CIs. Time-to-event variables (OS, PFS, and duration of disease response) were estimated with the Kaplan–Meier method. All safety analyses were based on the safety analysis set, which included all patients who received at least one dose of KHK2455, mogamulizumab, or both. Safety analysis results were summarized with frequency and percentage for categorical data, and statistics based on actual and change from baseline values for continuous variables. Missing values were not estimated but treated as missing in the statistical evaluation. All statistical analyses were conducted with SAS, version 9.4.

RESULTS

Preclinical study results

KHK2455 potently inhibited IDO1 with an half-maximal inhibitory concentration (IC_{50}) value of 14 nmol/L but did not inhibit indoleamine 2,3-dioxygenase 2 and tryptophan 2,3-dioxygenase activities up to 10,000 nmol/L (Table S1). These results indicated that KHK2455 selectively inhibited IDO1. Preclinical in vitro and in vivo studies were conducted to assess KHK2455 + mogamulizumab. In a coculture of human PBMCs and IDO1-expressing KATO-III tumor cells, KHK2455 + mogamulizumab showed an enhancement in T-cell proliferation and an increase in IFN-γ levels over KHK2455 alone (Figure S1). Anti–CTLA-4 antibody was used as a surrogate antibody for mogamulizumab in the mouse in vivo studies because this agent has been shown to deplete T_{reg}s in mice. Compared to anti–CTLA-4 antibody alone, the combination of KHK2455 and anti–CTLA-4 antibody exhibited an enhanced antitumor effect in mice bearing B16-F10-Luc tumors (Figure S2).

Patient baseline characteristics

Overall, 36 patients were enrolled across all cohorts (Figure S3). Baseline demographics, tumor types, disease characteristics, and representativeness of the study participants are shown in Table 1. Median patient age was 57 years (range, 27–74 years). Most patients had an Eastern Cooperative Oncology Group performance status of 1 (64%), and were metastatic (81%) at baseline. The most common tumor types were head and neck (19%), glioblastoma (17%), and ovarian (11%). All but one patient received prior systemic therapy, and all patients had prior surgery. Patients were mainly female (20; 56%), White (30; 83%), and non-Hispanic or Latino (26; 72%). Demographic considerations in patients with advanced solid tumors are available in Table 2.

Safety

In the safety analysis ($N = 36$), KHK2455 + mogamulizumab was well tolerated overall with manageable AEs at all doses, and the MTD was not reached. Treatment-emergent adverse events (TEAEs) occurring in any cycle by dose are shown in Table 3. Commonly reported TEAEs included drug eruption (56%), infusion-related reactions (IRRs; 39%), nausea (39%), fatigue (33%), headache (33%), and vomiting (31%) (Table S2). Among all TEAEs that occurred during any cycle, 75% and 81% of patients experienced at least one TEAE determined by investigators to be related (TRAE) to KHK2455 or mogamulizumab, respectively. Drug eruption (47% and 50%), IRRs (11% and 39%), and nausea (17% and 14%) were the most common TRAEs for KHK2455 and mogamulizumab, respectively. All TRAEs attributed to KHK2455 or mogamulizumab were grade ≤3. Overall, five patients experienced KHK2455- or one patient experienced two mogamulizumab-related TEAEs resulting in discontinuation of KHK2455 and/or mogamulizumab. The TRAEs that were attributed to KHK2455 or mogamulizumab and led to discontinuation were drug eruption ($n = 3$), aspartate aminotransferase (AST) increase ($n = 1$), fatigue ($n = 1$), and ejection fraction (EF) decrease due to myocarditis ($n = 1$). Before hospitalization, the patient who experienced myocarditis had an echocardiogram showing a nonserious grade 3 EF decrease. At the

TABLE 1 Baseline characteristics and demographics according to KHK2455 dose levels in combination with mogamulizumab.

	Mogamulizumab 1 mg/kg + KHK2455 dose						
Characteristic	**0.3 mg**	**1 mg**	**3 mg**	**10 mg**	**30 mg**	**100 mg**	**Total**
Enrolled, No.	5	7	4	5	6	9	36
Age, median (range), years	55 (53–72)	57 (32–73)	54 (45–74)	59 (43–67)	67 (42–72)	52 (27–64)	57 (27–74)
Male, No. (%)	2 (40)	3 (43)	2 (50)	0	2 (33)	7 (78)	16 (44)
Race, No. (%)							
White	5 (100)	6 (86)	3 (75)	5 (100)	6 (100)	5 (56)	30 (83)
Asian	0	1 (14)	0	0	0	0	1 (3)
NR	0	0	1 (25)	0	0	4 (44)	5 (14)
Ethnicity, No. (%)							
Hispanic or Latino	0	1 (14)	1 (25)	1 (20)	1 (17)	1 (11)	5 (14)
Not Hispanic or Latino	5 (100)	5 (71)	3 (75)	4 (80)	5 (83)	4 (44)	26 (72)
NR	0	0	0	0	0	4 (44)	4 (11)
Unknown	0	1 (14)	0	0	0	0	1 (3)
ECOG PS, No. (%)							
0	1 (20)	3 (43)	1 (25)	0	1 (17)	7 (78)	13 (36)
1	4 (80)	4 (57)	3 (75)	5 (100)	5 (83)	2 (22)	23 (64)
Primary tumor type, No. (%)							
Head and neck	2 (40)	1 (14)	2 (50)	0	2 (33)	0	7 (19)
Glioblastoma	0	0	0	1 (20)	1 (17)	4 (44)	6 (17)
Ovarian	2 (40)	1 (14)	0	0	0	1 (11)	4 (11)
Gastric	0	2 (9)	0	0	0	1 (11)	3 (8)
Sarcoma	0	1 (14)	1 (25)	1 (20)	0	0	3 (8)
Anal	0	0	0	1 (20)	0	0	1 (3)
Colorectal	0	0	1 (25)	0	0	0	1 (3)
Esophageal	0	0	0	0	0	1 (11)	1 (3)
Melanoma	0	0	0	0	1 (17)	0	1 (3)
Pancreatic	1 (20)	0	0	0	0	0	1 (3)
Prostate	0	0	0	0	1 (17)	0	1 (3)
Renal cell	0	0	0	1 (20)	0	0	1 (3)
Other	0	2 (29)	0	1 (20)	1 (17)	2 (22)	6 (17)
Stage at enrollment, No. (%)							
Locally advanced	0	1 (14)	0	1 (20)	1 (17)	4 (44)	7 (19)
Metastatic	5 (100)	6 (86)	4 (100)	4 (80)	5 (83)	1 (11)	29 (81)
Prior therapy, No. (%)							
Cancer surgery	5 (100)	7 (100)	4 (100)	4 (100)	6 (100)	9 (100)	36 (100)
Radiation therapy	4 (80)	3 (43)	4 (100)	3 (60)	5 (83)	7 (78)	26 (72)
Systemic therapy	5 (100)	6 (86)	4 (100)	5 (100)	6 (100)	9 (100)	35 (97)
Prior cancer regimens, median (range), No.	4 (3–8)	2 (0–8)	4 (3–8)	5 (3–9)	4 (1–5)	2 (1–5)	4 (0–9)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reported.

TABLE 2 Representativeness of study participants.

Cancer type	Advanced solid tumors
Considerations related to	
Sex	In 2017–2019 in the United States, the lifetime probability of being diagnosed with invasive cancer was slightly higher for men (40.9%) than for women (39.1%).
Age	The probability of developing an invasive cancer increases with age. In 2017–2019 in the United States, the percent probability of developing an invasive cancer was ~6% in adult males aged 50–59 years compared to ~34% in adult males aged 70 years and older. Similarly, the percent probability of developing an invasive cancer was ~6% in adult females aged 50–59 years compared to ~27% in adult females aged 70 years and older.
Race/ethnicity	In the United States from 2015 to 2020, overall cancer incidence (rate per 100,000 population) was highest among White people (466.6), followed by American Indian/Alaskan Native people (456.8) and Black people (453.7). Hispanic/Latino people had an incidence of 352.2.
Geography	In 2023, it is estimated that there were 1,958,310 new cancer cases in the United States, with most cases being female breast cancer (297,790), prostate (288,300), lung and bronchus (238,340), and colon and rectum (153,020). The states of California (192,770), Florida (162,410), Texas (139,100), and New York (123,810) have the highest number of estimated new cases of cancer of all types.
Other considerations	Differences in cancer risk vary by age. For example, the rates of new cancer cases in the United States among individuals aged 20–49 years were 80% higher in females than in males, whereas among those aged 75 years and older, they were nearly 50% higher in men.
Overall representativeness of this study	In this small study of 36 patients, there was a slightly higher percentage of women versus men enrolled (56% vs. 44%, respectively), which differs somewhat from the overall US population, which has a slightly higher percentage of men versus women diagnosed with advanced cancer. The median age in our study was 57 years, and ranged from 27 to 74 years. This age profile was slightly younger than the expected age profile for new cases of cancer in the United States. Most patients in our study were White (83%), followed by not reported (14%) and Asian (3%). Our study was limited to three locations in the United States and one in France, and evaluated a wide range of advanced solid tumors.

screening visit, EF was 58%. They were evaluated by a cardio-oncologist, underwent cardiac magnetic resonance imaging, and were diagnosed with nonserious grade 2 myocarditis. Both study drugs were permanently discontinued because of EF decrease and myocarditis. The patient discontinued from the study because of possible cardiac toxicity, as recommended by their physician. The investigator assessed the nonserious AEs of grade 3 EF decrease and grade 2 myocarditis as being related to KHK2455 + mogamulizumab.

One patient experienced a DLT during study treatment. This patient had an initial diagnosis of metastatic esophageal cancer, and experienced a DLT of grade 3 gastrointestinal necrosis after receiving treatment with KHK2455 100 mg, and the patient did not move on to mogamulizumab combination therapy. This DLT was determined by investigators to be related to KHK2455. Two patients experienced serious AEs (SAEs) with fatal outcomes (respiratory failure and general physical health deterioration) but neither was assessed by the investigator to be related to KHK2455 or mogamulizumab. Twelve additional patients experienced treatment-emergent SAEs: drug eruption was reported in three patients, and nausea and vomiting were reported in two patients each; all other SAEs occurred in one patient each.

No patients exhibited ophthalmic or multifocal electroretinography findings after receiving KHK2455 monotherapy or KHK2455 + mogamulizumab. There also were no meaningful relationships observed between plasma KHK2455 concentrations and change from baseline in QTc interval as assessed by 12-lead electrocardiography.

Eight patients experienced increased AST, and six patients had raised alanine aminotransferase (ALT). One patient experienced grade 3 AEs of increased AST and ALT. This patient also had a grade 3 AE of increased bilirubin, which led to discontinuation of the study drug combination.

Pharmacokinetics

Mean plasma KHK2455 concentration–time profiles after multiple oral doses in cycle 0 are shown in Figure 1. In cycle 0, plasma KHK2455 concentrations demonstrated dose-dependent increases before reaching steady state by day 8, which resulted in $R_{a,AUC0-\tau}$ values that ranged from 1.8 to 2.8 and $R_{a,Ctrough}$ values that ranged from 1.7 to 3.0 (Table S3). Multiple peaks in plasma concentrations were observed, and median t_{max} ranged from 1.0 to 5.9 h. C_{max} and

TABLE 3 Incidence of TEAEs occurring in any cycle by KHK2455 dose in combination with mogamulizumab.

	Mogamulizumab 1 mg/kg + KHK2455 dose						
Event	**0.3 mg**	**1 mg**	**3 mg**	**10 mg**	**30 mg**	**100 mg**	**Total**
Any TEAE, No. (%)	5 (100)	7 (100)	4 (100)	5 (100)	6 (100)	9 (100)	36 (100)
KHK2455 related	2 (40)	6 (86)	2 (50)	5 (100)	4 (67)	8 (89)	27 (75)
Mogamulizumab related	4 (80)	5 (71)	3 (75)	5 (100)	4 (67)	8 (89)	29 (81)
Any grade ≥3 TEAE, No. (%)	4 (80)	5 (71)	1 (25)	3 (60)	4 (67)	5 (56)	22 (61)
KHK2455 related	1 (20)	1 (14)	0	1 (20)	1 (17)	4 (44)	8 (22)
Mogamulizumab related	3 (60)	1 (14)	0	0	1 (17)	4 (44)	9 (25)
Any serious TEAE, No. (%)	3 (60)	3 (43)	0	2 (40)	1 (17)	5 (56)	14 (39)
KHK2455 related	0	0	0	1 (20)	0	2 (22)	3 (8)
Mogamulizumab related	1 (20)	1 (14)	0	1 (20)	0	2 (22)	5 (14)
D/C due to TEAE, No. (%)	3 (60)	2 (29)	0	1 (20)	1 (17)	2 (22)	9 (25)
TEAE led to KHK2455 D/C	3 (60)	2 (29)	0	1 (20)	1 (17)	2 (22)	9 (25)
TEAE led to mogamulizumab D/C	3 (60)	2 (29)	0	1 (20)	1 (17)	1 (11)	8 (22)
D/C due to related TEAE, No. (%)	2 (40)	0	0	1 (20)	1 (17)	1 (11)	5 (14)
KHK2455 related	1 (20)	0	0	1 (20)	1 (17)	1 (11)	4 (11)
Mogamulizumab related	2 (40)	0	0	1 (20)	1 (17)	1 (11)	5 (14)
Any TEAE with fatal outcome, No. (%)	1 (20)	0	0	0	0	1 (11)	2 (6)
KHK2455 related	0	0	0	0	0	0	0
Mogamulizumab related	0	0	0	0	0	0	0

Abbreviations: D/C, discontinuation; TEAE, treatment-emergent adverse event.

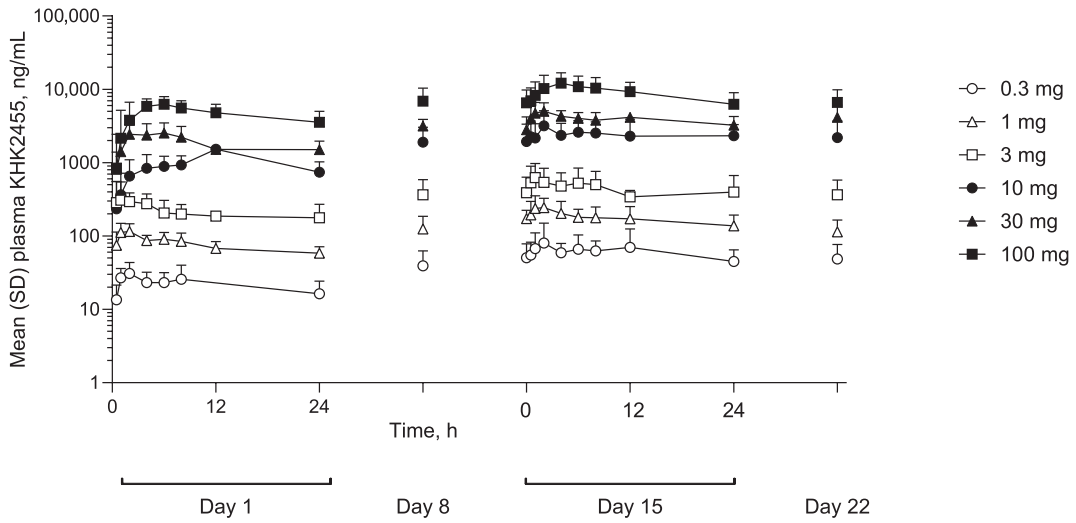

FIGURE 1 Mean plasma KHK2455 concentration–time profiles (cycle 0). SD indicates standard deviation and is represented by error bars.

$AUC_{0-\tau}$ demonstrated dose-dependent increases, although statistical analyses were not completed. The PK results of oral KHK2455 were similar in the monotherapy run-in phase and in the combination phase with mogamulizumab. There were no differences in PK parameters in cycle 0 compared to cycle 1.

Pharmacodynamics

KHK2455 + mogamulizumab demonstrated consistent and dose-dependent suppression of IDO1 activity as determined by plasma Kyn and K/T ratio decreases (Figure 2). Near-complete IDO inhibition

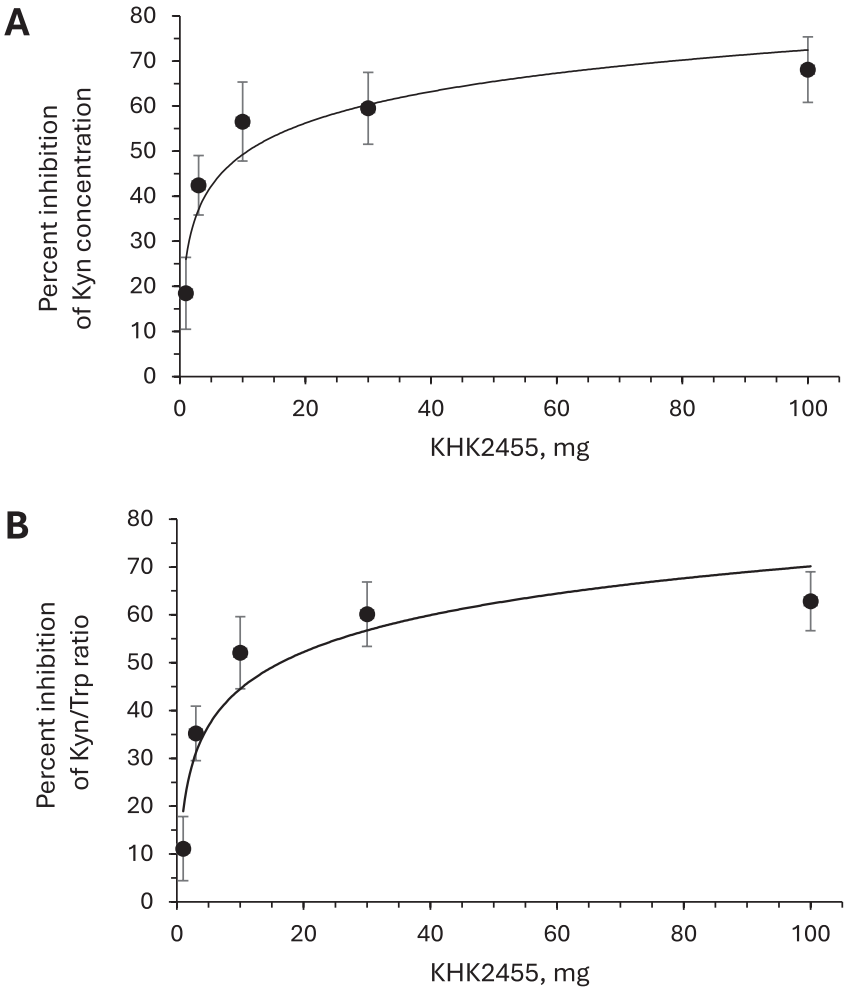

FIGURE 2 Dose-dependent inhibitory effect of KHK2455 on plasma Kyn production at day 15. Mean percent inhibition of plasma Kyn concentration (A) and Kyn/Trp ratio (B). Data present the mean percent inhibition ± standard error of each dosing group (n = 5, 7, 4, 6, and 9 for 1, 3, 10, 30, and 100 mg, respectively, in the KHK2455 monotherapy phase, day 15). Data for KHK2455 0.3 mg are not shown in the graphs (values < 0). Kyn indicates kynurenine; Trp, tryptophan.

of Kyn production was also observed in ex vivo stimulated PBMCs. Mogamulizumab combination therapy led to a reduction in $CCR4^+$ effector T_{reg}s and $CCR4^+$ nonsuppressive T_{reg}s, whereas $CCR4^+$-naive T_{reg}s remained stable.

Pharmacokinetics/pharmacodynamics

Consistent with the dose response, with increasing KHK2455 plasma concentrations the ratio of plasma K/T decreased in a nonlinear manner. The reduction plateaued at approximately 20% of baseline, with concentrations in the range of 5–10 μg/mL and greater (Figure S4).

Efficacy

Of the 35 evaluable patients, nine (26%) achieved durable SD (≥6 months, as per RECIST 1.1; Table 4): 0.3-mg cohort (n = 2): salivary gland carcinoma and squamous cell carcinoma (head and neck involving the left tonsil); 1-mg cohort (n = 2): adrenal and ovarian carcinoma; 3-mg cohort (n = 1): adenoid cystic carcinoma; 10-mg cohort (n = 1): renal cell carcinoma; and 100-mg cohort (n = 3): ovarian, glioblastoma, and anterior mediastinal adenocarcinoma. No patients experienced a RECIST 1.1 CR, and one patient with bevacizumab-resistant glioblastoma in the 10-mg cohort demonstrated a confirmed RECIST 1.1 PR (44% tumor reduction over a 2-year observation period), which yielded a DCR (CR + PR + SD) of 29% (95% CI, 14.6%–46.3%) in 10 of the 35 evaluable patients. The patient experiencing the RECIST 1.1 PR had not progressed at the time of database lock, and therefore the duration of disease response was censored at approximately 17.5 months.

DISCUSSION

KHK2455 is a selective IDO1 inhibitor with a novel mechanism that inhibited Kyn production in preclinical studies and exhibited synergistic inhibition of tumor growth in combination with anti–CTLA-4 antibody. Preclinical studies also showed that the combination of

TABLE 4 Summary of best overall response by RECIST 1.1.

	Mogamulizumab 1 mg/kg + KHK2455 dose						
	0.3 mg (n = 5)	1 mg (n = 7)	3 mg (n = 4)	10 mg (n = 5)	30 mg (n = 5)	100 mg (n = 9)	Total (N = 35)
SD, No. (%)	2 (40)	2 (29)	1 (25)	1 (20)	0	3 (33)	9 (26)
PD, No. (%)	3 (60)	5 (71)	3 (75)	3 (60)	4 (80)	6 (67)	24 (69)
NE, No. (%)	0	0	0	0	1 (20)	0	1 (3)
CR or PR, No. (%)[a]	0	0	0	1 (20)	0	0	1 (3) 95% CI, 0.1–14.9
CR, PR, or SD, No. (%)[a]	2 (40)	2 (29)	1 (25)	2 (40)	0	3 (33)	10 (29) 95% CI, 14.6–46.3

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease.

[a]Exact two-sided 95% CIs with the Clopper–Pearson method.

KHK2455 plus the anti-CCR4 antibody mogamulizumab resulted in increased T-cell activation. KHK2455 + mogamulizumab was found to be generally safe and well tolerated in this first-in-human, phase 1 trial, with mostly manageable toxicities. KHK2455 + mogamulizumab demonstrated dose-dependent PK plasma concentration increases and PD suppression of IDO1 activity. The total DCR, including one PR and nine SDs, was 29%.

Among the most common TEAEs reported with KHK2455 + mogamulizumab were IRRs and drug eruptions. In the phase 3 MAVORIC study, which included 184 mogamulizumab-treated patients with mycosis fungoides or Sézary syndrome (SS), IRRs and drug eruptions were reported in 33% and 24% of patients, respectively.[11] A post hoc analysis of the MAVORIC study revealed that drug eruptions associated with mogamulizumab were associated with a favorable response in patients with SS, and that long-term responders (60%) experienced drug eruptions.[14] In this study, TEAEs of drug eruption and IRRs considered to be related to mogamulizumab occurred at rates of 56% and 39% (N = 36), respectively. Because of KHK2455 + mogamulizumab potentially being T_{reg}-depleting therapeutics, cutaneous AEs may develop; however, attributing causality for drug eruption is challenging.[15]

KHK2455 100 mg/kg in combination with high-ultraviolet light was shown to cause retinal lesions in a nonclinical study in mice. Importantly, detailed ophthalmic and multifocal electroretinogram (ERG) examinations conducted in this study found no evidence of postbaseline ophthalmic or multifocal ERG findings after oral KHK2455 administration at any dose.

After reviewing part 1 and assessing the preliminary data of KHK2455 + mogamulizumab for potential approval in the future, the study did not proceed to part 2 and was terminated after completion of part 1, despite adequate safety and tolerability at all doses. However, oral KHK2455 administration produced plasma Kyn and K/T ratio decreases and nearly complete IDO inhibition of Kyn production, which suggested potent dose- and concentration-dependent IDO inhibition compared to that achieved with other IDO inhibitors. The inhibitory effect shown by these results warrants future evaluation of KHK2455 in combination with alternative immunotherapeutic agents.

In the phase 1 ECHO-202 study of epacadostat plus pembrolizumab, AST and ALT increases occurred in six and four patients, respectively, with one patient experiencing a grade 3/4 AST increase.[7] In the phase 3 ECHO-301 study, nine patients experienced grade 3/4 ALT increases, and seven patients experienced grade 3/4 AST increases.[8] For patients receiving KHK2455 at any dose, increases in AST and ALT occurred in eight and six patients, respectively, with only one patient experiencing grade 3 increases in both AST and ALT, which indicates a lack of liver toxicity in patients receiving KHK2455. This patient was hospitalized with increased alkaline phosphatase, increased AST, increased ALT, hypophosphatemia, and increased blood bilirubin, and presented with jaundiced eyes. They were diagnosed with grade 3 cholestatic jaundice due to a hepatic mass. After treatment, the SAE of grade 3 cholestatic jaundice resolved, and the patient was discharged.

These results of KHK2455 + mogamulizumab showing dose-dependent suppression of IDO1 activity by K/T ratio decreases are consistent with findings from a phase 1 study of epacadostat.[16] Dose-dependent decreases in Kyn were also observed in a phase 1/2 study of linrodostat plus nivolumab, although these changes did not correlate with tumor responses.[17] No analysis was completed in this study to correlate K/T ratio decreases and tumor responses.

Inferences regarding the efficacy of KHK2455 + mogamulizumab are limited by several factors. The small number of included participants precluded statistical testing of the preliminary antitumor activity of this combination. In addition, the lack of a comparator arm made it difficult to determine the absolute benefit of combination therapy versus monotherapy with KHK2455 or mogamulizumab.

However, the majority of participants in this study were aged 55 years or older with relapsed/refractory and heavily pretreated solid tumors, and therefore represent a population with traditionally worse survival outcomes. Even so, nine patients experienced SD out of 35 evaluable participants, and the median OS was more than 12 months with KHK2455 + mogamulizumab. In addition, the included participants had a wide variety of locally advanced or metastatic solid tumors, which suggests the potentially broad generalizability of this therapeutic strategy.

In conclusion, KHK2455 + mogamulizumab was well tolerated overall at all tested doses, and demonstrated selective inhibition of IDO1 while also suppressing Kyn production in a dose-dependent and sustained manner, which thereby indicates signs of preliminary antitumor activity in this study. Although the cohort expansion was not initiated for this combination, these results support the further exploration of IDO1 inhibitors in combination with other immunotherapeutic agents. Although combination therapy with KHK2455 + mogamulizumab is no longer being studied, KHK2455 was also evaluated in a phase 1 study in combination with avelumab, the programmed death ligand 1–blocking antibody, in patients with locally advanced or metastatic urothelial carcinoma (NCT03915405, KHK2455-002).

AUTHOR CONTRIBUTIONS

Timothy A. Yap: Conceptualization, formal analysis, investigation, writing–original draft, and writing–review and editing. **Olivier Rixe**: Conceptualization, formal analysis, investigation, writing–original draft, and writing–review and editing. **Capucine Baldini**: Investigation and writing–review and editing. **Ursa Brown-Glaberman**: Investigation and writing–review and editing. **Sergey Efuni**: Conceptualization, formal analysis, funding acquisition, investigation, methodology, data curation, validation, and writing–review and editing. **David S. Hong**: Investigation and writing–review and editing. **Christophe Massard**: Investigation and writing–review and editing. **Jameel Muzaffar**: Investigation and writing–review and editing. **Andreea Varga**: Investigation and writing–review and editing. **Emrullah Yilmaz**: Investigation and writing–review and editing. **Yuta Ikawa**: Conceptualization, formal analysis, funding acquisition, investigation, methodology, data curation, validation, writing–original draft, and writing–review and editing. **Lisa H. Shiue**: Writing–review and editing. **Yi Liu**: Conceptualization, formal analysis, funding acquisition, investigation, methodology, data curation, validation, writing–original draft, and writing–review and editing. **Matthew W. Hruska**: Conceptualization, formal analysis, funding acquisition, investigation, methodology, data curation, validation, writing–original draft, and writing–review and editing. **Henry Zhao**: Conceptualization, formal analysis, funding acquisition, investigation, methodology, data curation, validation, writing–original draft, and writing–review and editing. **Akihiro Tokunaga**: Conceptualization, formal analysis, investigation, methodology, data curation, validation, and writing–review and editing. **Solmaz Sahebjam**: Conceptualization, formal analysis, investigation, writing–original draft, and writing–review and editing.

ACKNOWLEDGMENTS

The authors thank all the investigators for their contributions to this study. We thank Dr. T. Murakami (Saitama Medical University, Saitama, Japan) for providing the B16-F10-Luc cell line; S. Nagata and R. Ebihara (Kyowa Kirin Co, Ltd, Shizuoka, Japan) for supporting the animal studies; and Kana Kunieda, Shoko Koshiba, Toshihiko Ishii, and Motoya Mie for contributing to the preclinical studies. This study was funded by Kyowa Kirin Inc. The authors thank Jonathan Mitchell PharmD, Rebecca D. Miles PhD, and Anthony DiLauro PhD of MedVal Scientific Information Services LLC for medical writing and editorial assistance, which were funded by Kyowa Kirin Inc. This manuscript was prepared according to "Good Publication Practice Guidelines for Company-Sponsored Biomedical Research: GPP 2022" of the International Society for Medical Publication Professionals. Timothy A. Yap is designated as the guarantor.

CONFLICT OF INTEREST STATEMENT

Timothy A. Yap is an employee of the University of Texas MD Anderson Cancer Center and vice president and head of Clinical Development in the Therapeutics Discovery Division, which has a commercial interest in DNA damage response and other inhibitors; has received funding paid to their institution from 858 Therapeutics, Accent Therapeutics, Acrivon, Aprea Therapeutics, Artios, AstraZeneca, Bayer, BeiGene, BioNTech, Blueprint, Boundless Bio, Bristol-Myers Squibb (BMS), Clovis, Constellation, Cyteir, Eisbach Bio, Eli Lilly, EMD Serono, Exelixis, Forbius, F-Star, Genentech, Gilead Foundation, GlaxoSmithKline (GSK), Golfers Against Cancer, Haihe, ImmuneSensor, Insilico Medicine, Ionis, Ipsen, Jounce, Karyopharm, KSQ, Kyowa Kirin, Loxo, Merck, Mirati, Novartis, Pfizer, Regeneron, Repare, Ribon, Rubius, Sanofi, Scholar Rock, Seattle Genetics, SpringWorks, Tesaro, Vivace, Zenith, and Zentalis Pharmaceuticals; has received consultancy funding from 858 Therapeutics, AbbVie, Acrivon, Adagene, Aduro, Aeneid Therapeutics, Almac, Alterome Therapeutics, Amgen, Amphista, Artios, Astex, AstraZeneca, Atavistik, Athena, Atrin, Avenzo, Avoro, Axiom, Baptist Health Systems, Bayer, BeiGene, Bicycle, BioCity Pharma, Bloom Burton, Bluestar Bio, BMS, Boxer, BridGene Biosciences, C4 Therapeutics, Calithera, Cancer Research Horizons, Cancer Research UK, Carrick Therapeutics, Circle Pharma, Clasp, Clovis, Cybrexa, Daiichi Sankyo, DAiNA, Dark Blue Therapeutics, Dawn Manco, Debiopharm, Diffusion, Duke Street Bio, EcoR1 Capital, Eikon, Ellipses Pharma, EMD Serono, Entos, Flagship Pioneering, Forbion, FoRx Therapeutics, F-Star, Genesis Therapeutics, Genmab, Glenmark, GLG, Globe Life Sciences, Grey Wolf Therapeutics, GSK, Guardant Health, Guidepoint, Ideaya Biosciences, Idience, Ignyta, I-Mab, ImmuneSensor, Impact Therapeutics, Institut Gustave Roussy, Intellisphere, Janssen, Jazz Pharmaceuticals, Kyn, Lumanity Commercial BioConsulting, MEI Pharma, Merck, Mereo, Merit Medical Systems, Monte Rosa Therapeutics, Natera, Nested Therapeutics, Nexys, Nimbus, Novocure, Odyssey, OHSU, OncoSec, Ono Pharma, Onxeo, PanAngium Therapeutics, Pegascy, PER, Pfizer, Piper Sandler, Plexium, Pliant Therapeutics, Prelude Therapeutics, ProLynx, Protai Bio, PSIM, Radiopharma Theranostics, Repare, resTORbio, Roche, Ryvu Therapeutics, SAKK,

Schrodinger, Servier Pharmaceuticals, Stablix, Synnovation, Synthis, Tango, TCG Crossover, TD2, Techspert, Terns Pharmaceuticals, Terremoto Biosciences, Tessellate Bio, Theragnostics, Thryv Therapeutics, Tolremo, Tome, Trevarx Biomedical, Varian, Veeva, Versant, Vibliome, Voronoi, XinThera, Zai Labs, and ZielBio; and is a stockholder in Seagen. Olivier Rixe has received research grant funding from Kyowa Kirin, and is an employee of and holds stock in Daiichi Sankyo. Capucine Baldini has received funding paid to their institution from AstraZeneca, BMS, Boehringer Ingelheim, GSK, INCA, Janssen-Cilag, Merck, Pfizer, Roche, and Sanofi; has received consultancy funding from the 4.UNCAN.eu Consensus Meeting, Bicycle, Guidepoint, and Rising Tide Foundation; has received honoraria and travel accommodations from Amgen, AstraZeneca, BMS, GSK, Merck Sharp & Dohme (MSD), and Sanofi; and has received nonfinancial support (drug supplied) from AstraZeneca, BMS, Boehringer Ingelheim, GSK, Medimmune, Merck, NH TherAguix, Pfizer, and Roche; as part of the Drug Development Department, she has served as a principal/subinvestigator of clinical trials for AbbVie, Adaptimmune, Adlai Nortye, Aduro, Agios, Amgen, Astex, AstraZeneca, Aveo, Basilea, Bayer Healthcare, BBB Technologies, BeiGene, Bicycle, Blueprint, BMS, Boehringer Ingelheim, Boston Pharmaceuticals, CASI, Celgene, CellCentric, Chugai, Cullinan Apollo, CureVac, Daiichi Sankyo, Debiopharm, Eisai, Eli Lilly, Exelixis, Faron, Forma, GamaMabs, Genentech, GSK, H3 Biomedicine, Imcheck, Incyte, Innate Pharma, Institut de Recherche Pierre Fabre, International Research Institute Servier, iTeos Belgium, Janssen-Cilag, Janssen R&D, Janssen Research Foundation, Kura Oncology, Kyowa Kirin Pharmaceutical Development, Lilly France, Loxo, Medimmune, Menarini, Merrimack, Merus, Molecular Partners, MSD-Chibret, Nanobiotix, Nektar, Novartis, OCTIMET, OncoEthix, Oncopeptides, Orion Genomics, OSE Immunotherapeutics, Pfizer, PharmaMar, Pierre Fabre Medicament, Relay, Roche, Sanofi Aventis, Seattle Genetics, SOTIO, Syros, Taiho, Tesaro, Transgene, Turning Point, and Xencor. Ursa Brown-Glaberman has received consultancy funding from Gilead, Pfizer, Sanofi, and Stemline, and has participated in speakers' bureaus for Gilead, Novartis, and Seattle Genetics. Sergey Efuni is a past employee of Kyowa Kirin; is a current employee of OncoC4; and is a stockholder in Dianthus Therapeutics and Magenta Therapeutics. David S. Hong has received research grant funding paid to their institution from 280Bio, AbbVie, Adaptimmune, Adlai Nortye, Amgen, Astellas Pharma, AstraZeneca, Bayer, BeiGene, BioBridges, Biomea Fusion, BMS, Daiichi Sankyo, Deciphera, Eisai, Eli Lilly, Endeavor, E.R. Squibb & Sons, Erasca, Exelixis, Fate Therapeutics, Genentech, Genmab, ImmunoGenesis, Incyte, Infinity, Janssen, Kyowa Kirin, Merck, Mirati, Navier, NCI-CTEP, Novartis, Numab, Pfizer, Pyramid Bio, Quanta, Revolution Medicines, Roche, Sanofi, Seagen, STCube, Takeda, TCR2, Turning Point Therapeutics, VM Oncology, and Yiling; has received support for travel, accommodations, and expenses from AACR, ASCO, CLCC, Bayer, BeiGene, Genmab, Medscape, Pfizer, SITC, and Telperian; has received consultancy funding from 280Bio, AbbVie, Acuta, Adaptimmune, Affini-T, Alkermes, Alpha Insights, Amgen, Astellas, AUM Biosciences, Axiom, Baxter, Bayer, Boxer Capital, BridgeBio, CARsgen, CLCC, COG, COR2ed, Cowen, EcoR1 Capital, EDDC, Erasca, Exelixis, Fate Therapeutics, Genentech, Gennao Bio, Gilead, GLG, Group H, Guidepoint, HCW Precision Oncology, ImmunoGenesis, Incyte, InduPro, Inhibrx, Janssen, Jounce, Kestrel Therapeutics, Liberium, MEDACorp, Medscape, Novartis, Numab, Oncologia Brasil, ORI Capital, Pfizer, Pharma Intelligence, POET Congress, Prime Oncology, Projects in Knowledge, Quanta, RAIN, Revolution Medicines, Ridgeline, Roche, Seagen, Stanford, STCube, Takeda, Tavistock, T-knife Therapeutics, Trieza, Turning Point Therapeutics, WebMD, Yiling, and Ziopharm; and has other ownership interests in CrossBridge Bio (advisor), Molecular Match (advisor), OncoResponse (founder and advisor), and Telperian (founder and advisor). Christophe Massard has received consultant/advisory fees from Amgen, Astellas, AstraZeneca, Bayer, BeiGene, BMS, Celgene, Debiopharm, Eli Lilly, Genentech, Ipsen, Janssen, MedImmune, MSD, Novartis, Pfizer, Roche, Sanofi, and Orion, and has served as a principal/subinvestigator of clinical trials for AbbVie, Aduro, Agios, Amgen, Argen-X, Astex, AstraZeneca, Aveo, Bayer, BeiGene, Blueprint, BMS, Boehringer Ingelheim, Celgene, Chugai, Clovis, Daiichi Sankyo, Debiopharm, Eisai, Eli Lilly, Eos, Exelixis, Forma, GamaMabs, Genentech, GORTEC, GSK, H3 Biomedicine, Incyte, Innate Pharma, Janssen, Kura Oncology, Kyowa Kirin, Loxo, LYSARC, Lytix Biopharma, Medimmune, Menarini, Merus, MSD, Nanobiotix, Nektar, Novartis, OCTIMET, OncoEthix, Oncopeptides, Orion, Pfizer, PharmaMar, Pierre Fabre, Roche, Sanofi, Servier, Sierra Oncology, Taiho, Takeda, Tesaro, and Xencor. Jameel Muzaffar reports professional activities for Exelixis, MSD, RAPT Therapeutics, and Seagen. 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DATA AVAILABILITY STATEMENT

The data generated in this study are available on reasonable request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Yap TA, Rixe O, Baldini C, et al. First-in-human phase 1 study of KHK2455 monotherapy and in combination with mogamulizumab in patients with advanced solid tumors. *Cancer*. 2025;e35939. doi:10.1002/cncr.35939