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First-in-Human Phase 1/2 Study of Cafelkibart, an Anti-CCR8 Monoclonal Antibody, as Monotherapy or in Combination with PD-1 Inhibition in Solid Tumors

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Abstract

Cafelkibart, a novel Fc-enhanced anti–C-C motif chemokine receptor 8 (CCR8) monoclonal antibody, selectively depletes regulatory T cells in the tumor microenvironment. We present results from three non-randomized phase 1/2 clinical trials in Australia, China and the United States in patients with advanced, treatment-refractory solid tumors who received cafelkibart as monotherapy or with a programmed cell death protein 1 (PD-1) inhibitor. Endpoints included safety, pharmacokinetics, and efficacy. Among 446 patients overall, 85 received cafelkibart monotherapy and 361 combination therapy. No dose-limiting toxicities were observed. In patients receiving combination therapy, pooled objective response rates (ORR) were 24.4% (95% CI, 15.6–35.1) in gastric/gastroesophageal junction adenocarcinoma (GC/GEJC) and 19.2% (95% CI 10.9–30.1) in pancreatic ductal adenocarcinoma. In second-line GC/GEJC, pooled median progression-free survival and overall survival (mOS) were 4.3 months and 22.6 months. The manageable safety profile and encouraging antitumor activity of cafelkibart plus PD-1 inhibition supports further investigation.

ClinicalTrials.gov registration:

LM108-01-101: NCT05199753; LM108-01-102: NCT05255484; LM108-01-103: NCT05518045

INTRODUCTION

Although immunotherapy with immune checkpoint inhibitors (ICIs) has significantly improved cancer treatment,[1,2] primary and acquired resistance remain prevalent in solid tumors, particularly in gastrointestinal malignancies such as gastric/gastroesophageal junction adenocarcinoma (GC/GEJC) and pancreatic ductal adenocarcinoma (PDAC).[2–4] Response rates to ICIs in many cancers remain low and survival outcomes are poor.[2,4]

A key mechanism contributing to resistance involves tumor-infiltrating regulatory T cells (Tregs), which suppress antitumor immunity by inhibiting cytotoxic $CD8^+$ T-cell activity within the tumor microenvironment (TME).[5,6] Systemic Treg depletion strategies (e.g., with anti-cytotoxic T-lymphocyte antigen-4 therapy) can enhance immune response but often causes immune-related toxicities due to systemic Treg loss.[7,8] In contrast, the C-C motif chemokine receptor 8 (CCR8) is selectively overexpressed on tumor-infiltrating Tregs, with limited expression in peripheral Tregs and normal tissues, making it a promising target for localized Treg depletion with reduced systemic toxicity.[9–11] Preclinical studies have shown that anti-CCR8 antibodies preferentially deplete intratumoral Tregs, remodel the TME, and synergize with anti–programmed cell death protein 1 (PD-1) therapies to restore effective antitumor immune responses.[11–13]

Cafelkibart is a fully human anti-CCR8 immunoglobulin G1 monoclonal antibody engineered with an Fc-enhancing point mutation to boost antibody-dependent cellular cytotoxicity, enabling effective Treg depletion. Preclinical studies have demonstrated its robust antitumor activity in combination with PD-1 inhibitors.[14] Early clinical data also suggest encouraging antitumor activity when combined with PD-1 inhibitors in patients with advanced gastric and pancreatic cancers.[15,16]

We report results from three multicenter, phase 1/2 trials evaluating cafelkibart monotherapy or in combination with PD-1 blockade in patients with treatment-refractory solid tumors. Study-specific findings are reported, along with a pooled post hoc analysis of the three studies to provide an integrated assessment of safety, pharmacokinetics, and preliminary antitumor activity. Because of the limited numbers of patients with GC/GEJC and PDAC in the individual studies, efficacy analyses were pooled across the three studies to enable a more robust assessment within these tumor-specific populations. Pooled exploratory analysis using CCR8 levels was also conducted to evaluate associations with cafelkibart anti-tumor activity.

RESULTS

Patients

Across the three studies, 446 patients (Australia, LM108-01-101, n = 55; the United States, LM108-01-102, n = 24; and China, LM108-01-103, n = 367; Fig. 1) with advanced solid tumors were enrolled and treated between April 30, 2022, and December 12, 2024, with follow-up through September 23, 2025. In total, 85 received cafelkibart monotherapy (26 in LM108-01-101, 21 in LM108-01-102 and 38 in LM108-01-103, **Supplementary Table S1, S2**) and 361 in combination with a PD-1 inhibitor (29 in LM108-01-101, 3 in LM108-01-102 and 329 in LM108-01-103, Table 1, **Supplementary Table S3, Supplementary Fig. S1)**.

Table 1

Baseline characteristics of patients treated with cafelkibart and a PD-1 inhibitor.

	LM108-01-101			LM108-01-102			LM108-01-103		
	Total (n = 29)	**GC (n = 2)**	**PDAC (n = 6)**	**Total (n = 3)**	**GC (n = 1)**	**PDAC (n = 0)**	**Total (n = 329)**	**GC (n = 86)**	**PDAC (n = 74)**
Gender, n (%)									
Male	20 (69.0)	2 (100)	2 (33.3)	2 (66.7)	1 (100)	0	218 (66.3)	59 (68.6)	45 (60.8)
Female	9 (31.0)	0	4 (66.7)	1 (33.3)	0	0	111 (33.7)	27 (31.4)	29 (39.2)
Race, n (%)*									
Asian	1 (3.4)	1 (50.0)	0	0	0	0	329 (100)	86 (100)	74 (100)
White	24 (82.8)	1 (50.0)	6 (100)	3 (100)	1 (100)	0	0	0	0
Age (years)									
Median (min, max)	67 (40, 86)	72.5 (67, 78)	65.5 (57, 80)	43 (43, 58)	58 (58, 58)	-	60 (32, 80)	61 (34, 80)	63 (33, 76)
ECOG performance status, n (%)									
0	20 (69.0)	2 (100)	2 (33.3)	1 (33.3)	1 (100)	0	46 (14.0)	14 (16.3)	18 (24.3)
1	9 (31.0)	0	4 (66.7)	2 (66.7)	0	0	283 (86.0)	72 (83.7)	56 (75.7)
Prior treatment line, n (%)									
≤ 2	25 (86.2)	2 (100)	5 (83.3)	2 (66.7)	0	0	275 (83.6)	78 (90.7)	63 (85.1)
≥ 3	4 (13.8)	0	1 (16.7)	1 (33.3)	1 (100)	0	54 (16.4)	8 (9.3)	11 (14.9)
Disease diagnosis, n (%)†									
GC	2 (6.9)	2 (100)	0	1 (33.3)	1 (100)	0	86 (26.1)	86 (100)	0
PDAC	6 (20.7)	0	6 (100)	0	0	0	74 (22.5)	0	74 (100)
Other	21 (72.4)	0	0	2 (66.7)	0	0	169 (51.4)	0	0
Number of metastasis sites, n (%)									
0–2	21 (72.4)	2 (100)	5 (83.3)	0	0	0	221 (67.2)	67 (77.9)	47 (63.5)
≥ 3 sites	7 (24.1)	0	0	3 (100)	1 (100)	0	93 (28.3)	19 (22.1)	24 (32.4)
Missing	1 (3.4)	0	1 (16.7)	0	0	0	15 (4.6)	0	3 (4.1)
Prior radical resection of tumor, n (%)									
Yes	12 (41.4)	1 (50.0)	2 (33.3)	1 (33.3)	0	0	163 (49.5)	51 (59.3)	32 (43.2)
No	17 (58.6)	1 (50.0)	4 (66.7)	2 (66.7)	1 (100)	0	166 (50.5)	35 (40.7)	42 (56.8)
Histopathological type, n (%)									
Adenocarcinoma	12 (41.4)	2 (100)	6 (100)	3 (100)	1 (100)	0	168 (51.1)	63 (73.3)	66 (89.2)
Squamous cell carcinoma	2 (6.9)	0	0	0	0	0	21 (6.4)	0	0
Others	15 (51.7)	0	0	0	0	0	140 (42.6)	23 (26.7)	8 (10.8)
MSI/MMR status, n (%)									
MSI-H/dMMR	0	0	0	0	0	0	38 (11.6)	20 (23.3)	2 (2.7)
Unknown	29 (100)	2 (100)	6 (100)	3 (100)	1 (100)	0	291 (88.4)	66 (76.7)	72 (97.3)
Previous systemic therapies, n (%)									

* One patient (0.3%) identified as Native Hawaiian or Other Pacific Islander; 3 patients (0.8%) identified as having "Other" race.

† One patient had each of the following: adenoid cystic carcinoma, adrenocortical adenocarcinoma, breast cancer, biliary tract cancer, duodenal adenocarcinoma, endometrial carcinoma, endometrial stromal sarcoma, esophageal neuroendocrine carcinoma, gastrointestinal stromal tumor, mesothelioma, renal cell carcinoma, spindle epithelial tumor with thymus-like differentiation, small intestine cancer, and urothelial carcinoma.

dMMR, mismatch repair–deficient; ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability–high; PD-1, programmed cell death protein-1; PDAC, pancreatic ductal adenocarcinoma.

	LM108-01-101			LM108-01-102			LM108-01-103		
	Total (n = 29)	GC (n = 2)	PDAC (n = 6)	Total (n = 3)	GC (n = 1)	PDAC (n = 0)	Total (n = 329)	GC (n = 86)	PDAC (n = 74)
Gender, n (%)									
Fluorouracil	10 (34.5)	2 (100)	4 (66.7)	2 (66.7)	1 (100)	0	187 (56.8)	82 (95.3)	51 (68.9)
Taxanes	4 (13.8)	0	1 (16.7)	2 (66.7)	1 (100)	0	197 (59.9)	37 (43.0)	60 (81.1)
Platinum	10 (34.5)	1 (50.0)	3 (50.0)	3 (100)	1 (100)	0	247 (75.1)	82 (95.3)	27 (36.5)
Immunotherapy	16 (55.2)	2 (100)	1 (16.7)	2 (66.7)	1 (100)	0	180 (54.7)	74 (86.0)	10 (13.5)

* One patient (0.3%) identified as Native Hawaiian or Other Pacific Islander; 3 patients (0.8%) identified as having "Other" race.

† One patient had each of the following: adenoid cystic carcinoma, adrenocortical adenocarcinoma, breast cancer, biliary tract cancer, duodenal adenocarcinoma, endometrial carcinoma, endometrial stromal sarcoma, esophageal neuroendocrine carcinoma, gastrointestinal stromal tumor, mesothelioma, renal cell carcinoma, spindle epithelial tumor with thymus-like differentiation, small intestine cancer, and urothelial carcinoma.

dMMR, mismatch repair–deficient; ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability–high; PD-1, programmed cell death protein-1; PDAC, pancreatic ductal adenocarcinoma.

Baseline characteristics in the combination therapy cohort by study are summarized in Table 1. Across the three studies, median age was 60 years (range, 32–86) and the majority of patients (330/361, 91.4%) were Asian, largely reflecting the LM108-01-103 population. Most had received ≤ 2 prior lines of treatment before enrollment (302/361, 83.7%); 54.8% (198/361) had previously received immunotherapy, including 86.5% (77/89) of patients with GC/GEJC **(Supplementary Table S3)**.

Safety

Monotherapy

Safety data include patients with all solid tumors. Across the three studies, dose-limiting toxicities (DLTs) were not observed at any dose level across both monotherapy and combination therapy cohorts, and no maximum tolerated dose was defined.

Overall, 7/85 patients (8.2%) receiving monotherapy discontinued treatment owing to treatment-emergent adverse events (TEAEs **[Supplementary Table S4A]**; 3/26 [11.5%] from LM108-01-101, 4/21 [19.0%] from LM108-01-102, and none from LM108-01-103). Grade ≥ 3 TEAEs related to cafelkibart occurred in 14 patients overall (16.5% **[Supplementary Table S4B]**, and 4/26 [15.4%], 3/21 [14.3%], and 7/38 [18.4%] patients from the respective cohorts **[Supplementary Table S4C]**). In LM108-01-101, the most frequently reported TEAEs related to cafelkibart were fatigue and rash (5/26, 19.2% each); in LM108-01-102, they were rash maculo-papular (4/21, 19.0%) and diarrhea (3/21, 14.3%); and in LM108-01-103, they were proteinuria (11/38, 28.9%), anemia, and increased alanine and aspartate aminotransferases (10/38, 26.3% each). Across the studies, there was no apparent association between the incidence of grade 3 or higher TEAEs or immune-related adverse events (irAEs) and the administered dose (**Supplementary Tables S4A, B, D)**.

Combination therapy

In patients receiving combination therapy, any TEAEs occurred in 355/361 (98.3%) patients **(**Table 2, **Supplementary Table S5A)**. Fifty-one patients (51/361, 14.1%) discontinued treatment due to TEAEs (11/29 [37.9%] from LM108-01-101, 2/3 [66.7%] from LM108-01-102, 38/329 [11.6%] from LM108-01-103). The most common TEAEs related to any study drug reported with combination therapy in each study are shown in Table 2. Overall, treatment-related adverse events (TRAEs) related to any study drug were reported in 334/361 (92.5%). Grade 3 or higher TRAEs occurred in 175/361 patients (48.5% **[**Table 2, **Supplementary Table S5A]**; 20/29 [69.0%], 1/3 [33.3%] and 154/329 [46.8%] patients from the respective cohorts); laboratory abnormalities accounted for 79/175 (45%) of Grade ≥ 3 TRAEs, predominantly asymptomatic enzyme elevations. Serious TEAEs occurred in 185 (51.2%). Overall, 7/361 patients (1.9%) died from TRAEs (none in LM108-01-101 and LM108-01-102; 7/329 [2.1%] in LM108-01-103).

Table 2
Safety summary and TEAEs by system organ class preferred term with cafelkibart plus a PD-1 inhibitor (≥ 10%).

System Organ Class Preferred Term	LM108-01-101 (n = 29)		LM108-01-102 (n = 3)		LM108-01-103 (n = 329)		Pooled (N = 361)	
	All Grade	≥Grade 3	All Grade	≥Grade 3	All Grade	≥Grade 3	All Grade	≥Grade 3
Any TEAEs	29 (100)	25 (86.2)	3 (100)	2 (66.7)	323 (98.2)	190 (57.8)	355 (98.3)	217 (60.1)
Any TRAEs related to any study drug	28 (96.6)	20 (68.9)	2 (66.7)	1 (33.3)	304 (92.4)	154 (46.8)	334 (92.5)	175 (48.5)
Serious TEAEs	22 (75.9)		2 (66.7)		161 (48.9)		185 (51.2)	
Serious TRAEs related to any study drug	17 (58.6)		1 (33.3)		118 (35.9)		136 (37.7)	
irAEs	22 (75.9)	14 (48.3)	2 (66.7)	0	191 (58.1)	93 (28.3)	215 (59.6)	107 (29.6)
TEAE leading to any study drug dose interruption	18 (62.1)		2 (66.7)		172 (52.3)		192 (53.2)	
TEAEs leading to any study drug dose discontinuation	11 (37.9)		2 (66.7)		38 (11.6)		51 (14.1)	
TEAEs leading to death	1 (3.4)		0		7 (2.1)		7 (1.9)	
Investigations	19 (65.5)	11 (37.9)	0	0	286 (86.9)	85 (25.8)	305 (84.5)	96 (26.6)
Alanine aminotransferase increased	6 (20.7)	4 (13.8)	0	0	98 (29.8)	17 (5.2)	104 (28.8)	21 (5.8)
Aspartate aminotransferase increased	5 (17.2)	1 (3.4)	0	0	97 (29.5)	13 (4.0)	102 (28.3)	14 (3.9)
Lipase increased	10 (34.5)	4 (13.8)	0	0	88 (26.7)	35 (10.6)	98 (27.1)	39 (10.8)
Weight decreased	2 (6.9)	0	0	0	83 (25.2)	0	85 (23.5)	0
White blood cell count decreased	0	0	0	0	80 (24.3)	8 (2.4)	80 (22.2)	8 (2.2)
Platelet count decreased	0	0	0	0	77 (23.4)	6 (1.8)	77 (21.3)	6 (1.7)
Amylase increased	8 (27.6)	3 (10.3)	0	0	59 (17.9)	12 (3.6)	67 (18.6)	15 (4.2)
Blood bilirubin increased	0	0	0	0	58 (17.6)	8 (2.4)	58 (16.1)	8 (2.2)
Neutrophil count decreased	0	0	0	0	57 (17.3)	5 (1.5)	57 (15.8)	5 (1.4)
Bilirubin conjugated increased	0	0	0	0	50 (15.2)	9 (2.7)	50 (13.9)	9 (2.5)
Activated partial thromboplastin time prolonged	0	0	0	0	48 (14.6)	0	48 (13.3)	0
Metabolism and nutrition disorders	10 (34.5)	1 (3.4)	2 (66.7)	1 (33.3)	221 (67.2)	44 (13.4)	233 (64.5)	46 (12.7)
Hypoalbuminemia	0	0	0	0	100 (30.4)	1 (0.3)	100 (27.7)	1 (0.3)
Hyponatremia	0	0	2 (66.7)	1 (33.3)	96 (29.2)	1 (0.3)	98 (27.1)	2 (0.6)
Hypokalemia	2 (6.9)	0	1 (33.3)	0	79 (24.0)	25 (7.6)	82 (22.7)	25 (6.9)
Decreased appetite	3 (10.3)	0	0	0	71 (21.6)	5 (1.5)	74 (20.5)	5 (1.4)
Gastrointestinal disorders	23 (79.3)	15 (51.7)	2 (66.7)	1 (33.3)	176 (53.5)	57 (17.3)	201 (55.7)	73 (20.2)
Diarrhea	10 (34.5)	4 (13.8)	2 (66.7)	0	51 (15.5)	7 (2.1)	63 (17.5)	11 (3.0)
Nausea	10 (34.5)	2 (6.9)	0	0	44 (13.4)	4 (1.2)	54 (15.0)	6 (1.7)
Vomiting	5 (17.2)	1 (3.4)	1 (33.3)	0	32 (9.7)	5 (1.5)	38 (10.5)	6 (1.7)
General disorders and administration site conditions	16 (55.2)	1 (3.4)	3 (100)	0	167 (50.8)	15 (4.6)	186 (51.5)	16 (4.4)
Pyrexia	6 (20.7)	1 (3.4)	0	0	103 (31.3)	5 (1.5)	109 (30.2)	6 (1.7)
Asthenia	0	0	0	0	80 (24.3)	4 (1.2)	80 (22.2)	4 (1.1)
Blood and lymphatic system disorders	3 (10.3)	2 (6.9)	0	0	175 (53.2)	40 (12.2)	178 (49.3)	42 (11.6)
Anemia	1 (3.4)	0	0	0	172 (52.3)	34 (10.3)	173 (47.9)	34 (9.4)
Skin and subcutaneous tissue disorders	16 (55.2)	5 (17.2)	2 (66.7)	0	151 (45.9)	27 (8.2)	169 (46.8)	32 (8.9)

TEAEs considered related to any study drug and occurring in ≥ 10% of patients in the pooled population are shown.

irAE, immune-related adverse event; PD-1, programmed cell death protein 1; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

System Organ Class Preferred Term	LM108-01-101 (n = 29)		LM108-01-102 (n = 3)		LM108-01-103 (n = 329)		Pooled (N = 361)	
	All Grade	≥Grade 3	All Grade	≥Grade 3	All Grade	≥Grade 3	All Grade	≥Grade 3
Rash	9 (31.0)	1 (3.4)	0	0	94 (28.6)	15 (4.6)	103 (28.5)	16 (4.4)
Respiratory, thoracic and mediastinal disorders	12 (41.4)	3 (10.3)	3 (100)	0	103 (31.3)	20 (6.1)	118 (32.7)	23 (6.4)
Cough	7 (24.1)	0	1 (33.3)	0	57 (17.3)	0	65 (18.0)	0
Infections and infestations	17 (58.6)	5 (17.2)	1 (33.3)	0	95 (28.9)	38 (11.6)	113 (31.3)	43 (11.9)
Renal and urinary disorders	2 (6.9)	1 (3.4)	0	0	84 (25.5)	4 (1.2)	86 (23.8)	5 (1.4)
Proteinuria	0	0	0	0	68 (20.7)	1 (0.3)	68 (18.8)	1 (0.3)
Endocrine disorders	3 (10.3)	1 (3.4)	1 (33.3)	0	53 (16.1)	1 (0.3)	57 (15.8)	2 (0.6)
Hypothyroidism	2 (6.9)	1 (3.4)	0	0	39 (11.9)	0	41 (11.4)	1 (0.3)
Musculoskeletal and connective tissue disorders	7 (24.1)	1 (3.4)	1 (33.3)	0	45 (13.7)	4 (1.2)	53 (14.7)	5 (1.4)
Cardiac disorders	4 (13.8)	2 (6.9)	0	0	45 (13.7)	8 (2.4)	49 (13.6)	10 (2.8)
Hepatobiliary disorders	5 (17.2)	3 (10.3)	0	0	43 (13.1)	24 (7.3)	48 (13.3)	27 (7.5)

TEAEs considered related to any study drug and occurring in ≥ 10% of patients in the pooled population are shown.

irAE, immune-related adverse event; PD-1, programmed cell death protein 1; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

The most common TEAEs related to any study drug in LM108-01-101 were diarrhea (10/29 [34.5%; grade ≥ 3, 4/29 [13.8%]), nausea (10/29 [34.5%; grade ≥ 3, 2/29 [6.9%]), increased lipase (10/29 [34.5%]; grade ≥ 3, 4/29 [13.8%]), and rash (9/29 [31.0%]; grade ≥ 3, 1/29 [3.4%]). In LM108-01-102, these were hyponatremia (2/3, 66.7%; one grade 1 and one grade ≥ 3), diarrhea (2/3, 66.7%; both grade 1–2), and one case each (33.3%) of grade ≥ 3 colitis and gastritis. In LM108-01-103, these were anemia (172/329 [52.3%]; grade ≥ 3, 34/329 [10.3%]), pyrexia (103/329 [31.3%]; grade ≥ 3, 5/329 [1.5%]), hypoalbuminemia (100/329 [30.4%]; grade ≥ 3, 1/329 [0.3%]), hyponatremia (96/329 [29.2%]; grade ≥ 3, 1/329 [0.3%]), and rash (94/329 [28.6%]; grade ≥ 3, 15/329 [4.6%]) (Table 2).

Grade 3 or higher irAEs occurred in 14/29 (48.3%) of patients in LM108-01-101, none in LM108-01-102, and 93/329 (28.3%) of patients in LM108-01-103 (Table 2). Pooled data on the most frequent cafelkibart-related TEAEs are available in **Extended Data** Table 1; data on irAEs, and TEAEs leading to death are shown in **Supplementary Tables S5B and S5C**.

Pharmacokinetics

PK data were collected from 163 patients: LM108-01-101 (n = 55), LM108-01-102 (n = 23), and LM108-01-103 (n = 85). Systemic exposure to cafelkibart, based on maximum observed serum concentration (C_{max}) and area under the concentration-time curve (AUC) in patients with advanced solid tumors increased in a roughly dose proportional manner across doses ranging from 0.3 to 20 mg/kg after a single dose, and from 0.3 to 10 mg/kg following multiple Q3W doses. Following a single dose, the PK parameters ranged as follows: C_{max}, 8.6 to 604 μg/mL, AUC from time 0 to the last timepoint of measurable concentration, 33.4 to 2907 day*μg/mL, and half-life, 5.5 to 11.9 days. At steady state (Cycle 4), similar trends were observed, with mean accumulation ratios for AUC and C_{max} ranging from 0.8 to 2.4, indicating weak to moderate accumulation after multiple doses, particularly in the 10 to 20 mg/kg every two weeks (Q2W) cohorts (**Supplementary Tables S6 and S7**).

Efficacy

Monotherapy

Of the patients receiving monotherapy, 80 patients across the three studies were evaluable for efficacy (LM108-01-101, n = 24; LM108-01-102, n = 19; LM108-01-103, n = 37). The ORR ranged from 0%–12.5%. Partial response (PR) was seen in 0%–8.3% of patients, while complete response (CR) was observed in one patient in the LM108-01-101 study. Disease control rate (DCR) ranged from 33.3%–57.9%. The pooled ORR was 5.0% (4/80, 95% CI, 1.4 to 12.3), PR was 3.8%, and DCR was 40.0% (32/80, 95% CI, 29.2 to 51.6; **Supplementary Table S8**).

Clinical benefit—defined as CR, PR or stable disease without tumor increase—was observed in 31.3% (25/80) of patients, largely with intermediate (10 mg/kg Q3W) and high doses (10 mg/kg Q2W, 20 mg/kg Q2W/Q3W). No added efficacy was seen with higher doses. Safety outcomes in patients receiving monotherapy favored the intermediate dose: compared with 10 mg/kg Q3W, the 20 mg/kg Q3W group had higher rates of TEAEs (100% vs. 94.1%), serious AEs (57.1% vs. 32.4%), and discontinuations (28.6% vs. 0%; **Supplementary Table S4A**). Based on the integrated efficacy and safety profile, 10 mg/kg Q3W was selected as the recommended phase 2 dose for cafelkibart monotherapy.

Combination therapy in patients with GC/GEJC

In patients receiving combination therapy, 82 patients with GC/GEJC across the three studies were evaluable (2 from LM108-01-101, 1 from LM108-01-102, 79 from LM108-01-103). ORR was 100% (2/2; 95% CI, 15.8, 100.0) in LM108-01-101, 0% in LM108-01-102, and 22.8% (18/79; 95% CI, 14.1, 33.6) in LM108-01-103. DCR was 100% (2/2) in LM108-01-101, 100% (1/1) in LM108-01-102, and 69.6% (55/79; 95% CI, 58.2, 79.5) in LM108-01-103 (Fig. 2A). The median DOR was NE in all three studies. Median PFS was not evaluable (NE; 95% CI, 4.0 to NE) in LM108-01-101, 6.5 months (95% CI, NE) in LM108-01-102, and 4.2 months (95% CI, 2.8 to 5.5) in LM108-01-103. Median OS was NE (95% CI, NE), 6.5 (95% CI, NE), and 15.3 (95% CI, 11.1 to 22.6), respectively (Fig. 3A).

The pooled ORR was 24.4% (20/82; 95% CI, 15.6 to 35.1), and DCR was 70.7% (58/82; 95% CI, 59.6 to 80.3). The median DOR was 9.1 months (95% CI, 4.4 to NE). Median PFS was 4.3 months (95% CI, 2.8 to 5.6), and median OS was 15.8 months (95% CI, 11.2 to 22.6). Among 51 patients receiving second-line treatment in the three cohorts, the pooled ORR was 31.4% (16/51; 95% CI, 19.1 to 45.9), DCR was 66.7% (34/51; 95% CI, 52.1 to 79.2), median PFS was 4.3 months (95% CI, 1.9 to 5.7), and median OS was 22.6 months (95% CI, 10.8 to NE; Table 3).

Table 3
Efficacy of cafelkibart plus a PD-1 inhibitor in GC and PDAC (pooled data).

	All GC (n = 82)	2L GC			All PDAC (n = 73)	2L PDAC		
		Total (n = 51)	CCR8 ≥ 1* (n = 34)	CCR8 < 1* (n = 16)		Total (n = 46)	CCR8 ≥ 1* (n = 23)	CCR8 < 1* (n = 15)
Best overall response, n (%)								
CR	2 (2.4)	2 (3.9)	2 (5.9)	0	0	0	0	0
PR	18 (22.0)	14 (27.5)	10 (29.4)	4 (25.0)	14 (19.2)	11 (23.9)	6 (26.1)	3 (20.0)
SD	38 (46.3)	18 (35.3)	12 (35.3)	5 (31.3)	31 (42.5)	20 (43.5)	9 (39.1)	8 (53.3)
PD	24 (29.3)	17 (33.3)	10 (29.4)	7 (43.8)	28 (38.4)	15 (32.6)	8 (34.8)	4 (26.7)
Objective response rate (CR + PR)	20 (24.4)	16 (31.4)	12 (35.3)	4 (25.0)	14 (19.2)	11 (23.9)	6 (26.1)	3 (20.0)
95% CI†	(15.6, 35.1)	(19.1, 45.9)	(19.7, 53.5)	(7.3, 52.4)	(10.9, 30.1)	(12.6, 38.8)	(10.2, 48.4)	(4.3, 48.1)
Disease control rate (CR + PR+SD)	58 (70.7)	34 (66.7)	24 (70.6)	9 (56.3)	45 (61.6)	31 (67.4)	15 (65.2)	11 (73.3)
95% CI†	(59.6, 80.3)	(52.1, 79.2)	(52.5, 84.9)	(29.9, 80.2)	(49.5, 72.8)	(52.0, 80.5)	(42.7, 83.6)	(44.9, 92.2)
Duration of response (months)‡								
Median (95% CI)	9.1 (4.4, NE)	9.1 (2.8, NE)	NE (4.4, NE)	2.8 (2.3, NE)	5.6 (3.5, 11.6)	6.9 (3.0, NE)	5.5 (3.02, NE)	NE (6.93, NE)
Q1, Q3	6.4, NE	4.4, NE	6.4, NE	2.3, NE	4.4, 11.6	5.5, 11.6	3.5, 8.9	6.93, NE
Min, max	1.2+, 24.8+	1.2+, 24.8+	1.5+, 24.8+	1.2+, 4.1+	2.0+, 20.4+	2.04+, 20.4+	3.0, 20.4+	2.0+, 9.7+
Progression-free survival (months)‡								
Median (95% CI)	4.3 (2.8, 5.6)	4.3 (1.9, 5.7)	5.3 (1.9, 9.7)	2.8 (1.3, 5.4)	3.4 (1.6, 5.3)	4.9 (2.3, 6.7)	4.9 (1.4, 6.9)	5.5 (1.4, 8.1)
Q1, Q3	1.4, 9.9	1.3, 9.9	1.3, 13.2	1.4, 5.4	1.3, 8.1	1.4, 8.3	1.4, 8.3	1.4, 8.1
Min, max	0.3, 27.6+	0.7, 27.6+	0.7, 27.6+	0.7, 17.7	0.5, 21.8+	0.5, 21.8+	0.5, 21.8+	1.3+, 13.8
Overall survival (months)‡								
Median (95% CI)	15.8 (11.2, 22.6)	22.6 (10.8, NE)	22.6 (9.7, NE)	11.1 (8.1, NE)	8.3 (6.6, 11.8)	10.0 (6.7, 17.9)	8.8 (4.1, 18.9)	14.7 (5.3, NE)
Q1, Q3	8.0, NE	8.1, NE	7.8, NE	8.1, NE	4.1, 17.9	5.3, NE	4.0, 18.9	6.0, NE
Min, max	0.8, 27.6+	1.9, 27.6+	1.9, 27.6+	3.6, 21.2+	1.4, 26.2+	1.5, 26.2+	1.5, 26.2+	2.2+, 18.2+
Duration of survival follow-up (months)	17.1 (14.7, 20.1)	15.2 (12.0, 18.2)	15.2 (11.9, 19.2)	18.2 (9.7, NE)	18.2 (14.5, 22.1)	17.5 (13.3, 23.6)	24.3 (8.3, NE)	14.5 (6.7, NE)

	All GC (n = 82)	2L GC			All PDAC (n = 73)	2L PDAC		
		Total (n = 51)	CCR8 ≥ 1* (n = 34)	CCR8 < 1* (n = 16)		Total (n = 46)	CCR8 ≥ 1* (n = 23)	CCR8 < 1* (n = 15)
Best overall response, n (%)								

* CCR8 data were available for 50/51 patients with 2L GC and 38/46 patients with 2L PDAC; therefore, CCR8 subgroup totals do not sum to the respective overall population totals. ✝ Based on Clopper-Pearson method. ‡ Based on Kaplan–Meier estimates. + Indicates that the minimum or maximum value corresponds to a censored observation.

2L, second line; CCR8, C-C motif chemokine receptor 8; CI, confidence interval; CR, complete response; GC, gastric cancer; NE, not evaluable; PD, progressive disease; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; Q, quartile; SD, stable disease.

PD-1, programmed cell death protein 1.

[a] Efficacy outcomes for 10 mg/kg Q3W + anti-PD-1 Q3W.

2L, second line; BOR, best overall response; CCR8, C-C motif chemokine receptor 8; CR, complete response; DCR, disease control rate; GC, gastric cancer; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; SD stable disease.

[a] Efficacy outcomes for 10 mg/kg Q3W + anti-PD-1 Q3W.

2L, second line; CI, confidence interval; CR, complete response; DOR, duration of response; GC, gastric cancer; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein-1; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; SD stable disease.

Combination therapy in patients with PDAC

Among patients with PDAC receiving combination therapy, 73 were evaluable (5 from LM108-01-101, none from LM108-01-102, 68 from LM108-01-103). ORR was 40.0% (2/5; 95% CI, 5.3 to 85.3) in LM108-01-101 and 17.6% (12/68; 95% CI, 9.5 to 28.8) in LM108-01-103. DCR was 100% (5/5; 95% CI, 47.8 to 100) and 58.8% (40/68; 95% CI, 46.2 to 70.6; Fig. 2C), with median DOR 4.3 months (95% CI, 3.0 to NE) and 6.9 months (95% CI, 3.5 to 11.6), respectively. Median PFS was 5.8 months (95% CI, 2.7 to NE) and 3.3 months (95% CI, 1.4 to 4.9), and median OS was 11.6 months (95% CI, 4.0 to NE) and 8.1 months (95% CI, 6.4 to 11.8), respectively (Fig. 3C).

The pooled ORR was 19.2% (14/73; 95% CI, 10.9 to 30.1), and DCR was 61.6% (45/73; 95% CI, 49.5 to 72.8). The median DOR was 5.6 months (95% CI, 3.5 to 11.6). Median PFS was 3.4 months (95% CI, 1.6 to 5.3), and median OS was 8.3 months (95% CI, 6.6 to 11.8). Among 46 patients receiving second-line therapy, the pooled ORR was 23.9% (11/46; 95% CI, 12.6 to 38.8), DCR was 67.4% (31/46; 95% CI, 52.0 to 80.5), median PFS was 4.9 months (95% CI, 2.3 to 6.7), and median OS was 10.0 months (95% CI, 6.7 to 17.9; Table 3 **and Supplementary Fig. S2**).

Biomarker analyses

Due to the small number of patients in LM108-01-101 and LM108-01-102 with GC/GEJC and PDAC, exploratory biomarker analyses were performed on pooled data. Among second-line patients with GC/GEJC receiving combination therapy, biomarker data were available for 50 of 51 patients with at least one tumor assessment. Thirty-four patients had CCR8 expression levels ≥ 1; the ORR was 35.3% (12/34; 95% CI, 19.7 to 53.5), and DCR was 70.6% (24/34; 95% CI, 52.5 to 84.9; Fig. 2B). The median PFS was 5.3 months (95% CI, 1.9 to 9.7), and median OS was 22.6 months (95% CI, 9.7 to NE). Among 16 patients with CCR8 expression levels < 1, the ORR was 25.0% (4/16; 95% CI, 7.3 to 52.4), and DCR was 56.3% (9/16; 95% CI, 29.9 to 80.2; Fig. 2B). The median PFS was 2.8 months (95% CI, 1.3 to 5.4), and median OS was 11.1 months (95% CI, 8.1 to NE; Table 3, Fig. 3B, **and Supplementary Fig. S2, 2B**).

Among 38 patients with PDAC with biomarker data, 23 had CCR8 ≥ 1; the ORR was 26.1% (6/23; 95% CI, 10.2 to 48.4), and DCR was 65.2% (15/23; 95% CI, 42.7 to 83.6; Fig. 2D). The median PFS was 4.9 months (95% CI, 1.4 to 6.9), and median OS was 8.8 months (95% CI, 4.1 to 18.9). Among 15 patients with CCR8 < 1, the ORR was 20.0% (3/15; 95% CI, 4.3 to 48.1), and DCR was 73.3% (11/15; 95% CI, 44.9 to 92.2; Fig. 2D). The median PFS was 5.5 months (95% CI, 1.4 to 8.1), and median OS was 14.7 months (95% CI, 5.3 to NE; Table 3, Fig. 3D, **and Supplementary Fig. S2C, 2D**). **Supplementary Table S9** shows responses by clinical subgroups in second-line PDAC, while **Supplementary Fig. S3** shows individual tumor responses according to CCR8 expression in patients with PDAC receiving cafelkibart monotherapy.

Supplementary Fig. S4 illustrates representative immunohistochemistry samples demonstrating high and low CCR8 expression levels in GC/GEJC and PDAC tissues.

DISCUSSION

This analysis of phase 1/2 studies conducted across Australia, China and the United States, showed that cafelkibart, an Fc-enhanced anti-CCR8 monoclonal antibody, combined with a PD-1 inhibitor, was associated with promising antitumor activity and a manageable safety profile in advanced GC/GEJC and PDAC. Among patients receiving second-line treatment, the ORR ranged from 20.5%–100% in individual studies; ORR across all studies was 31.4% (16/51) in GC/GEJC and 23.9% (11/46) in PDAC tumor types, which are typically refractory to checkpoint inhibition.[2,3] These results compare favorably with historical ORRs of < 10% for anti-PD-1 monotherapy in similar settings.[17,18] Responses were durable in both GC/GEJC and PDAC. Subgroup analysis by CCR8

expression showed a trend towards greater response in second-line therapy for GC/GEJC, similar to findings in other solid tumor types, including pancreatic cancer.[15,16]

Cafelkibart was generally well tolerated both as monotherapy and in combination with PD-1 blockade. Although grade 3 or higher TRAEs were more frequent with combination therapy, they were consistent with known ICI toxicities. Dermatological adverse events (AEs) were common, but manageable. Grade 3 or higher irAEs occurred in approximately 30% of patients receiving combination therapy, without evidence of excess autoimmune toxicity, and consistent with known ICI-class events. Importantly, no DLTs were observed at any cafelkibart dose level, further supporting its overall tolerability.

Cafelkibart is the first CCR8-targeted therapeutic to demonstrate safety and clinical efficacy in solid tumors. CCR8 is preferentially expressed on highly suppressive intratumoral Tregs, with minimal peripheral expression.[19] By depleting these Tregs, cafelkibart reduces local immunosuppression and promotes infiltration and activation of CD8 + T cells, and other effector cells, restoring anti-tumor immunity.[14] When administered with PD-1 inhibitors, cafelkibart may reduce immune exclusion and support reinvigoration of exhausted T cells, while PD-1 blockade releases checkpoint-mediated suppression.[20] This complementary mechanism of action may overcome PD-1 inhibition resistance and improve antitumor immune responses.

CCR8 expression has been associated with poorer prognosis in GC/GEJC, providing a biological rationale for targeting CCR8.[13,21] In this context, a key finding is the association between intratumoral CCR8-expressing Tregs and clinical benefit in patients with GC/GEJC. In patients receiving second-line treatment, ORR was higher (12/34, 35.3%) in those with CCR8 expression levels ≥ 1 versus those with CCR8 < 1 (4/16, 25.0%), accompanied by numerically longer median PFS and a trend toward improved early OS in the CCR8 ≥ 1 subgroup. Taken together, these findings suggest that targeting CCR8 may be particularly relevant in patients with GC/GEJC who have adverse prognostic features.

In contrast, the role of tumor-level CCR8 expression in PDAC remains incompletely defined in the context of a highly heterogeneous immune microenvironment.[22] In our cohort, ORRs were similar for PDAC overall and the CCR8 ≥ 1 subgroup, with longer median PFS and a trend toward improved early OS in CCR8 < 1. Outcomes may have been influenced by underlying clinical characteristics; outcomes were more favorable in immunotherapy treatment–naïve patients and those without liver metastases. Taken together, these findings suggest that CCR8 expression may have potential as a predictive biomarker for cafelkibart-based therapy, although further studies are needed to understand its association with treatment efficacy and OS durability.

Several limitations should be noted. These were non-randomized, open-label studies, and comparisons with historical controls should be interpreted cautiously. Sample sizes were determined by safety, dose exploration, and cohort expansion instead of statistical considerations, as is typical for early-phase studies. In addition, the numbers of patients with GC/GEJC and PDAC enrolled in LM108-01-101 and LM108-01-102 were limited, restricting interpretation of efficacy within individual studies. Consequently, pooled analyses across the three studies were performed to enable a more robust assessment of efficacy and biomarker-response associations within these tumor-specific populations. PD-1 backbones varied, which may have influenced safety and efficacy outcomes. The CCR8 immunohistochemistry assay was non-standardized and requires further validation. Although CCR8 expression correlated with response, its modulation during therapy raises questions about optimal timing for assessment and patient selection. Longer follow-up is needed to determine the durability of responses and OS benefit.

The encouraging activity of cafelkibart plus PD-1 inhibition across different tumor types supports expansion into phase 2/3 trials targeting PD-1–refractory or immune-excluded cancers. Biomarker-enriched designs incorporating CCR8 expression may enhance therapeutic precision. As a first-in-class Fc-enhanced anti-CCR8 antibody with emerging clinical proof of concept, cafelkibart represents a novel strategy for modulating the immunosuppressive TME and overcoming resistance to immune checkpoint blockade.

Cafelkibart plus PD-1 inhibition demonstrated a favorable therapeutic index and manageable safety profile, supporting continued development of CCR8 as a promising immuno-oncology target and paving the way for biomarker-driven phase 3 studies in treatment-resistant cancers.

ONLINE METHODS

Study design

Three phase 1/2 clinical trials of cafelkibart were conducted in Australia (LM108-01-101; n = 55), the United States (LM108-01-102; n = 24), and China (LM108-01-103; n = 367). The studies consisted of a dose escalation phase and a dose expansion phase recruiting participants with solid tumors, including GC/GEJC and PDAC. Data cutoffs were December 31, 2024; October 17, 2023; and September 23, 2025, respectively. Baseline characteristics and safety analyses included patients who received at least one dose of cafelkibart. The pooled analysis (N = 446) included the full study population from the three trials.

Cafelkibart was administered intravenously on day 1 every 2 weeks (1 cycle: 14 days) or every 3 weeks (1 cycle: 21 days) either alone or in combination with a PD-1 inhibitor.

In the phase 1 dose-escalation stage, five prespecified dose levels of cafelkibart were explored. The initial two doses (0.3 mg/kg and 1 mg/kg) were evaluated using an accelerated titration design, followed by a traditional 3 + 3 design at subsequent dose levels (3 mg/kg, 10 mg/kg, and 20 mg/kg). Dose escalation proceeded after completion of the safety evaluation period without DLTs. One or more dose levels were selected for expansion to determine the recommended phase 2 dose.

In phase 2, LM108-01-101 and LM108-01-102 evaluated cafelkibart combined with pembrolizumab (200 mg every 3 weeks or 400 mg every 6 weeks), while LM108-01-103 assessed cafelkibart combined with toripalimab (240 mg every 3 weeks). Detailed study protocols are available in the **Supplementary Information**.

Study oversight

This study was sponsored by LaNova Medicines. The protocol was approved by the institutional review board and ethics committee at each participating center and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Trial conduct and safety were overseen by a safety monitoring committee composed of participating international investigators and sponsor representatives. All patients provided written informed consent prior to enrollment.

Patients

Eligible patients were ≥ 18 years of age, with histologically or cytologically confirmed recurrent or refractory advanced solid tumors after progression on, intolerance of, or ineligibility for standard therapy. Additional inclusion criteria included a life expectancy of ≥ 12 weeks, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ and marrow function. Patients enrolled in the expansion stage were required to have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Key exclusion criteria included central nervous system or meningeal metastasis, autoimmune or immunodeficiency disease, and active infections.

Endpoints

In phase 1, primary endpoints were DLTs and AEs, investigator-assessed per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Secondary endpoints included PK, immunogenicity, and preliminary antitumor activity (ORR, DCR, DOR, PFS, and OS).

In phase 2, the primary endpoint was ORR. Secondary endpoints included DCR, DOR, PFS, OS, AEs, PK, immunogenicity, and exploratory biomarker analyses.

Tumor assessments were performed at baseline and every 6 weeks. Responses were evaluated per RECIST version 1.1.

Biomarker analysis for CCR8 and PD-L1

The CCR8 and PD-L1 immunohistochemistry assays were developed and validated at CellCarta (Lake Forest, CA, USA). The CCR8 positive score, representing immune cell expression, was calculated as the percentage of CCR8-positive immune cells relative to the total number of cells.

Pharmacokinetics

PK assessments were performed in patients who received at least one dose of cafelkibart and had at least one evaluable PK parameter. PK parameters included drug exposure, elimination, and distribution (the volume of distribution at steady state).

Statistical analysis

Due to the exploratory nature of these early phase studies, the sample sizes of the three studies were not determined based on formal statistical considerations. Patients who received at least one dose of cafelkibart and provided at least one tumor assessment were included in the efficacy analysis set; those who received at least one dose of cafelkibart were included in the safety set. AEs were coded using MedDRA 26.1 and 27.1 and graded according to CTCAE version 5.0. The Clopper–Pearson method was used to calculate 95% CIs for ORR and DCR. The Kaplan–Meier method was utilized to estimate time-to-event endpoints (DOR, PFS, and OS); two-sided 95% CIs for medians were calculated using the Brookmeyer–Crowley method and for rates using Greenwood's formula. No formal interim analyses were planned; however, as LM108-01-103 is still ongoing, the results reported for this study are based on the data cutoff (September 23, 2025). Pooled post hoc analysis was conducted across the three studies to provide an integrated assessment of safety, pharmacokinetics, preliminary antitumor activity, and exploratory biomarker analysis. Statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA).

Declarations

DATA AVAILABILITY

The data supporting the findings of this study are available in the paper and the **Supplementary Information**. Reasonable requests for additional data sharing should be directed to the corresponding author.

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AUTHOR CONTRIBUTIONS

CL, JG and LS contributed to the conceptualization and design of the clinical development program and provided overall scientific and clinical leadership.

CL, JG, JZ, JY, MA, YJ, LZ, JD, CZ, DJ, JC, XY, JLX, BYW, YPZ, BM, LL, QL, YC, AS, YX, YS, RZ, MO, ARN, JW, JIX, YK, RB, AZ, BZW, YNZ, ZZ, HW, BQW, MB, GR, YIZ and LS contributed to the investigation, patient recruitment and/or acquisition of clinical data.

HL, YL, DF, XQ and CQ contributed to study design and conduct, data analysis and interpretation, and overall study oversight.

HL and XQ contributed substantially to data verification and quality review.

All authors contributed to the interpretation of the results and to drafting or critically reviewing the manuscript, approved the final version for publication, and agree to be accountable for the work.

FUNDING

This study was sponsored by LaNova Medicines. Medical writing support was also funded by LaNova Medicines. The sponsor was involved in the study design, data collection, analysis and interpretation of the data, and preparation of the manuscript.

COMPETING INTERESTS

LZ: Invited speaker: Astra Zeneca, MSD, Akesobio, Biokin Pharmaceutical, Kelun-Biotech; Research grant: Astra Zeneca, MSD, Novartis, BMS, Pierre-Fabre, Pifzer, Akesobio, Henrui Pharm, China Shiyao Pharm, QiLu pharm, Kelun-Biotech, Biokin Pharmaceutical, Innovent Biologics, Hansoh Pharmaceutical, Alphamab Oncology; Advisory board member: Astra Zeneca, MSD, Novartis, Abbvie, Kelun-Biotech, Biokin Pharmaceutical.

MO: Research funding: LaNova Medicines Ltd, ImmuneOnco Biopharmaceuticals, Werewolf Therapeutics Inc., Ikena Oncology, Immune-Onc Therapeutics, Monte Rosa Therapeutics Inc., ABM Therapeutics Corporation, PMV Pharmaceuticals Inc., Ideaya Biosciences, Krystal Biotech, Alphageneron Pharmaceuticals, BridgeBio Oncology Therapeutics.

ARN: Funding to institution for trials he is PI on: Loxo@Lilly, Surface Oncology, ADC Therapeutics, IGM Biosciences, EMD Serono, Aravive, Nikang Therapeutics, Inspirna, Exelexis, Revolution Medicine, Jacobio, Pionyr, Jazz Pharmaceuticals, NGM Biopharmaceuticals, Immunocore, Phanes Therapeutics, Kymera Therapeutics, Dren Bio, Marengo Therapeutics; Consultant Editor compensation: JCO Precision Oncology; Travel compensation: SITC, AACR, Conquer Cancer Foundation, BinayTara Foundation, Foundation Medicine, Caris Life Sciences, ASCO, Jazz Pharmaceuticals, Ideology Health, IASLC; Consultant or advisory board: Foundation Medicine, Astellas, NGM Biosciences; Natera, Regeneron, GE Health, Ideology Health, Takeda; Educational content or professional meeting honoraria: BinayTara Foundation, Foundation Medicine, Medlive, Precisca, Ideology Health; Grant Support: SWOG Hope Foundation; Conquer Cancer.

HL, YL, DF, XQ and CQ are employees of LaNova Medicines Ltd.

All other authors declare no competing or conflicting interests relevant to this work.

ETHICS APPROVAL AND INFORMED CONSENT

LM108-01-101 was approved by the Bellberry Human Research Ethics Committee, Australia; approval/reference number: 2021-11-1357 and The Alfred Hospital Ethics Committee, Australia; approval certificate number: HREC/82257/Alfred-2022; LM108-01-102 was approved by Advarra IRB, USA; approval/reference number: Pro00060689; and LM108-01-103 was approved by the respective committees listed in the table below. All three studies were conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and applicable local regulatory requirements. All patients provided written informed consent before enrollment and before undergoing any study-specific procedures.

Study Centre No.	Ethics Committee Name	Initial Ethics Approval No.
1	Beijing Cancer Hospital	2022YW89
2	Zhejiang Cancer Hospital	IRB-2022-1255 (Note)
3	Cancer Hospital of Shandong First Medical University	SDZLEC2022-260-01
4	Shanghai Pulmonary Hospital	22227ZL
6	Obstetrics and Gynecology Hospital of Fudan University	Gynecology Ethics Review 2023-09
7	Xuzhou Central Hospital	XZXY-LY-20230601-023
8	General Hospital of Xuzhou Mining Group	[2023] 021501
9	Shanghai East Hospital	[2023] Clinical Review No. 003
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11	The First Affiliated Hospital of Henan University of Science and Technology	2023-0032
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13	Sun Yat-sen University Cancer Center	A023-004-01
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28	Liaocheng People's Hospital	2023026; 2024047
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Figures

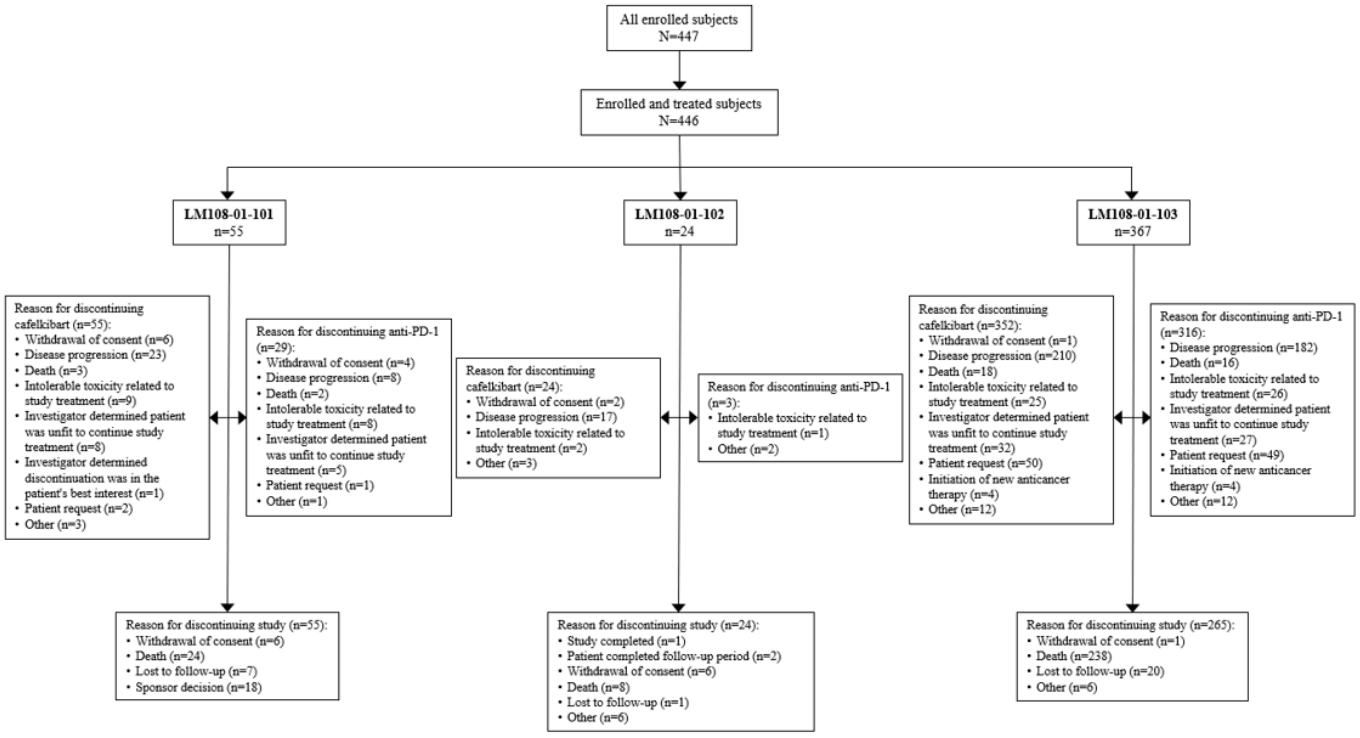


Figure 1

Patient disposition (CONSORT diagram).

PD-1, programmed cell death protein 1.

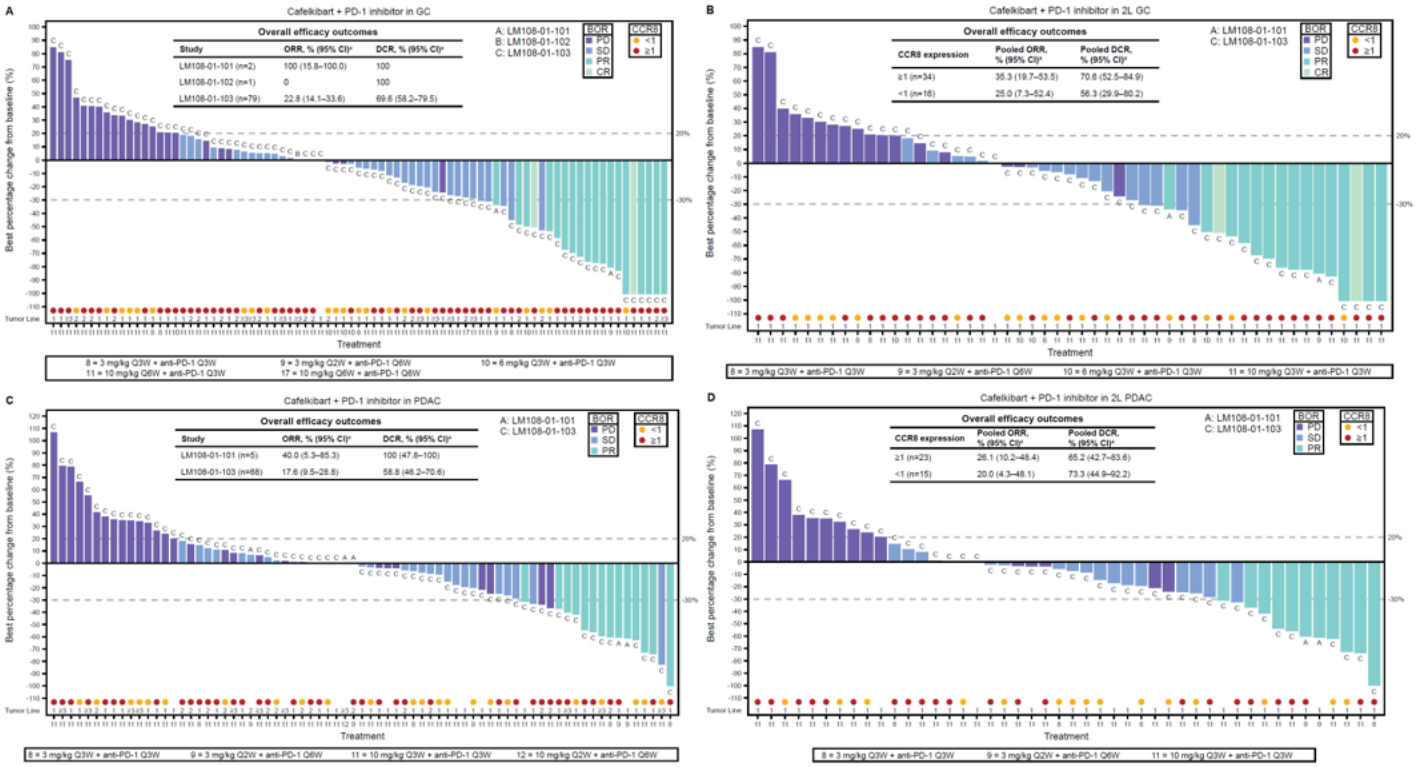


Figure 2

Waterfall plots of cafelkibart plus a PD-1 inhibitor in GC and PDAC; all treatment lines (left) and second-line treatment (right).

[a] Efficacy outcomes for 10 mg/kg Q3W + anti-PD-1 Q3W.

2L, second line; BOR, best overall response; CCR8, C-C motif chemokine receptor 8; CR, complete response; DCR, disease control rate; GC, gastric cancer; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; SD stable disease.

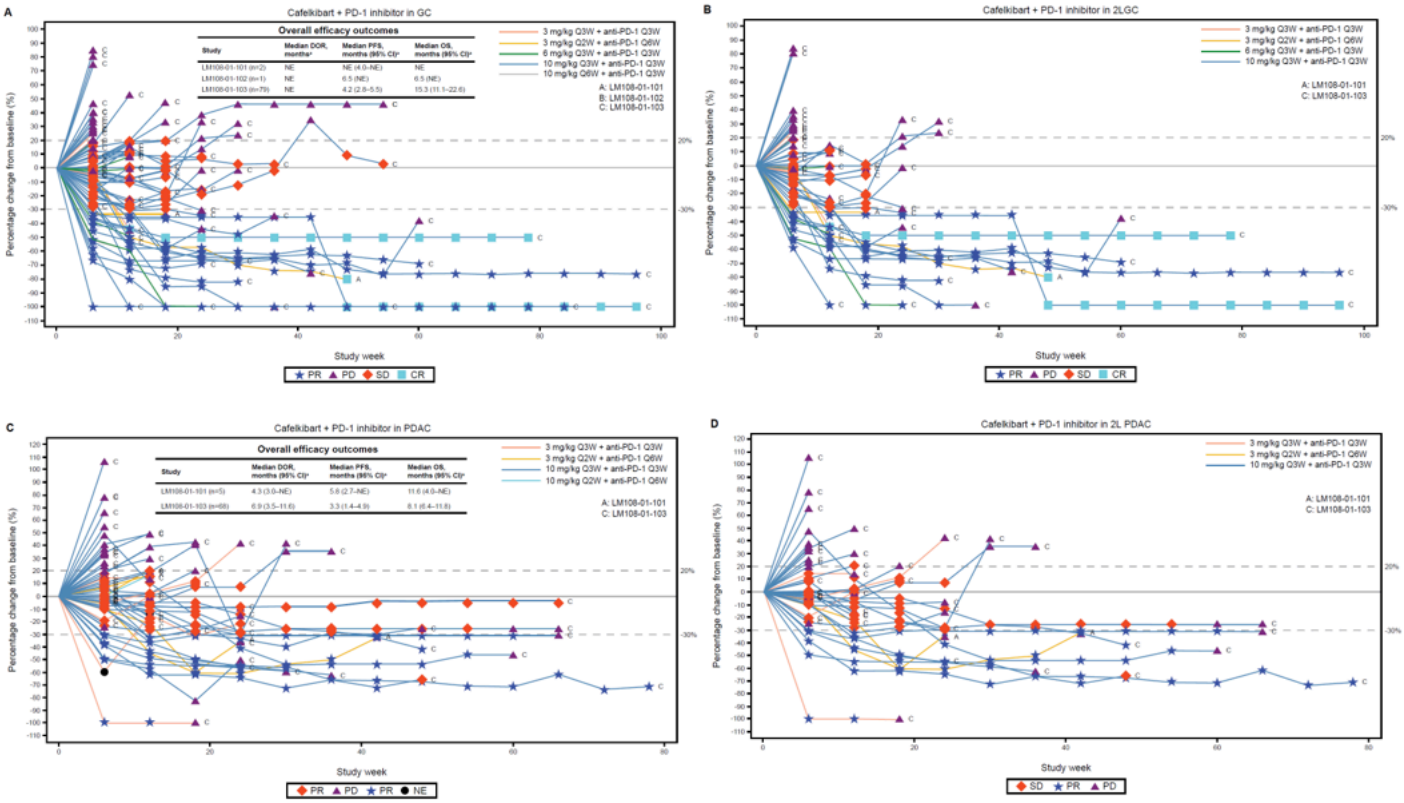


Figure 3

Spider plots for cafelkibart plus a PD-1 inhibitor in GC and PDAC; all treatment lines (left) and second-line treatment (right).

[a] Efficacy outcomes for 10 mg/kg Q3W + anti-PD-1 Q3W.

2L, second line; CI, confidence interval; CR, complete response; DOR, duration of response; GC, gastric cancer; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein-1; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; SD stable disease.

Supplementary Files

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- SupplementaryappendixRestructuredV3clean.docx