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PHASE I STUDIES

A phase 1a/1b trial of CSF-1R inhibitor LY3022855 in combination with durvalumab or tremelimumab in patients with advanced solid tumors

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Summary

Background LY3022855 is a recombinant, immunoglobulin, human monoclonal antibody targeting the colony-stimulating factor-1 receptor. This phase 1 trial determined the safety, pharmacokinetics, and antitumor activity of LY3022855 in combination with durvalumab or tremelimumab in patients with advanced solid cancers who had received standard anti-cancer treatments. *Methods* In Part A (dose-escalation), patients received intravenous (IV) LY3022855 25/50/75/100 mg once weekly (QW) combined with durvalumab 750 mg once every two weeks (Q2W) IV or LY3022855 50 or 100 mg QW IV with tremelimumab 75/225/750 mg once every four weeks. In Part B (dose-expansion), patients with non-small cell lung cancer (NSCLC) or ovarian cancer (OC) received recommended phase 2 dose (RP2D) of LY3022855 from Part A and durvalumab 750 mg Q2W. *Results* Seventy-two patients were enrolled (median age 61 years): Part A = 33, Part B = 39. In Part A, maximum tolerated dose was not reached, and LY3022855 100 mg QW and durvalumab 750 mg Q2W was the RP2D. Four dose-limiting equivalent toxicities occurred in two patients from OC cohort. In Part A, maximum concentration, area under the concentration-time curve, and serum concentration showed dose-dependent increase over two cycles of therapy. Overall rates of complete response, partial response, and disease control were 1.4%, 2.8%, and 33.3%. Treatment-emergent anti-drug antibodies were observed in 21.2% of patients. *Conclusions* LY3022855 combined with durvalumab or tremelimumab in patients with advanced NSCLC or OC had limited clinical activity, was well tolerated. The RP2D was LY3022855 100 mg QW with durvalumab 750 mg Q2W. ClinicalTrials.gov ID: NCT02718911 (Registration Date: May 3, 2011).

Keywords Advanced solid cancer · CSF-1 · CSF-1R inhibitor · LY3022855 · NSCLC · Ovarian cancer

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Introduction

Cancer cells can enhance tumor growth by activating immunosuppressive mechanisms within the tumor microenvironment (TME), which limits T cell function [1, 2]. Inhibitors of programmed cell death-1 protein (PD-1)/programmed cell death ligand 1 (PD-L1) and cytotoxic T lymphocyte associated protein 4 (CTLA-4) have resulted in improving survival in patients with multiple tumor types, resulting in approvals by the United States Food and Drug Administration [3, 4]. However, many cancers, such as ovarian cancer (OC), fail to respond frequently to immune checkpoint blockade, while a significant proportion of patients with non-small cell lung cancer (NSCLC) fail to respond or develop resistance to treatment [5].

Tumor-associated macrophages (TAMs), regulated by binding of colony-stimulating factor-1 (CSF-1)/macrophage colony-stimulating factor, contribute to tumor growth by different mechanisms, including the support for accumulation of regulatory T-cells. The accumulation of these regulatory T-cells suppresses the cytotoxic natural killer and $CD8^+$ T-cells, in turn increasing angiogenesis and tumor metastasis [6]. It has been reported that high infiltration of TAMs is an indicator of worse prognosis in different solid tumors [7]; therefore, disruption of the immunosuppressive effects of innate immune cells expressing CSF-1 via the CSF-1 receptor (CSF-1R) may be a promising treatment strategy, as observed in multiple preclinical studies determining the effect of CSF-1R blockade via CSF-1 in solid tumors [8–11]. In addition to CSF-1, interleukin (IL)-34 is a ligand for CSF-1R which has a different structure but has similar functions as that of CSF-1 [12].

LY3022855 is a novel, recombinant, immunoglobulin G sub-class1, human monoclonal antibody (mAb) which prevents binding of CSF-1 and IL-34 to CSF-1R, and inhibits CSF-1R activation for tumor regulation and growth [13, 14]. Preclinical studies suggested that CSF-1R blockade with LY3022855 modulates the TME in mouse cancer models [15]. A previous phase 1 study of LY3022855 monotherapy in patients with metastatic breast cancer (MBC) demonstrated good tolerability and target engagement activity, with two patients achieving stable disease (SD) for over nine months [14]. Blockade of PD-1/PD-L1 and CTLA-4 has shown anti-tumor activity in solid tumors [16], which includes promising anti-tumor activity of PD-1/PD-L1 in a subset of patients with NSCLC [17, 18], and limited anti-tumor activity of PD-1/PD-L1 alone or in combination with other checkpoint inhibitors in OC in preclinical setting [19]. To further investigate the dual blockade strategies of CSF-1R/PD-L1 or CSF-1R/CTLA-4, a phase 1a/1b trial of LY3022855 was conducted, where its safety and activity in combination with durvalumab (MEDI4736, anti-PD-L1 mAb) or tremelimumab (anti-CTLA-4 mAb) were determined in patients with advanced solid cancers in Part A and advanced NSCLC or OC in Part B.

Patients and methods

Study design

This trial was a multicenter, open-label, phase 1a/1b study of LY3022855 in combination with durvalumab or tremelimumab in patients with advanced solid tumors not amenable to curative therapy (Clinicaltrials.gov ID: NCT02718911). The study was conducted in two parts to characterize the safety profile, tolerability, pharmacodynamics, pharmacokinetics (PK), antitumor activity, and immunogenicity of LY3022855 and durvalumab or tremelimumab combination. Part A of the study was a dose-finding/dose-escalation phase to determine the optimal dose for LY3022855 in combination with durvalumab or tremelimumab. Part B was a dose-expansion phase of LY3022855 combined with durvalumab. The schema for the study design is presented in Fig. 1.

The study was performed in accordance with the International Conference on Harmonization guidelines and Declaration of Helsinki. The Institutional Review Board of each study site approved the study protocol, information brochure, and the informed consent form before study initiation.

Patient population

Adult patients with histologically or cytologically confirmed solid tumors, measurable and/or non-measurable disease, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1, who had recovered from the acute effects of previous treatments for cancer, and had a life expectancy of ≥12 weeks were included in the study. In Part A, patients with all solid tumor resistant to curative therapy were included, whereas in Part B, only patients with NSCLC or OC were included. Patients with NSCLC were refractory to immune checkpoint inhibitor (ICI) or had relapse after ICI therapy, and had received at least three lines of therapy. Patients with OC who had progressed after no more than three lines of therapy (with or without platinum) prior to inclusion were included in Part B.

Patients were excluded from the study if they had previously undergone surgery, or received LY3022855, mAbs, immunosuppressants within 28 days before enrollment; or had received small molecule therapy, radiation therapy within before 14 days of enrollment. Patients with presence of a second primary malignancy, serious preexisting medical conditions, malignancy or metastasis in the central nervous system, and

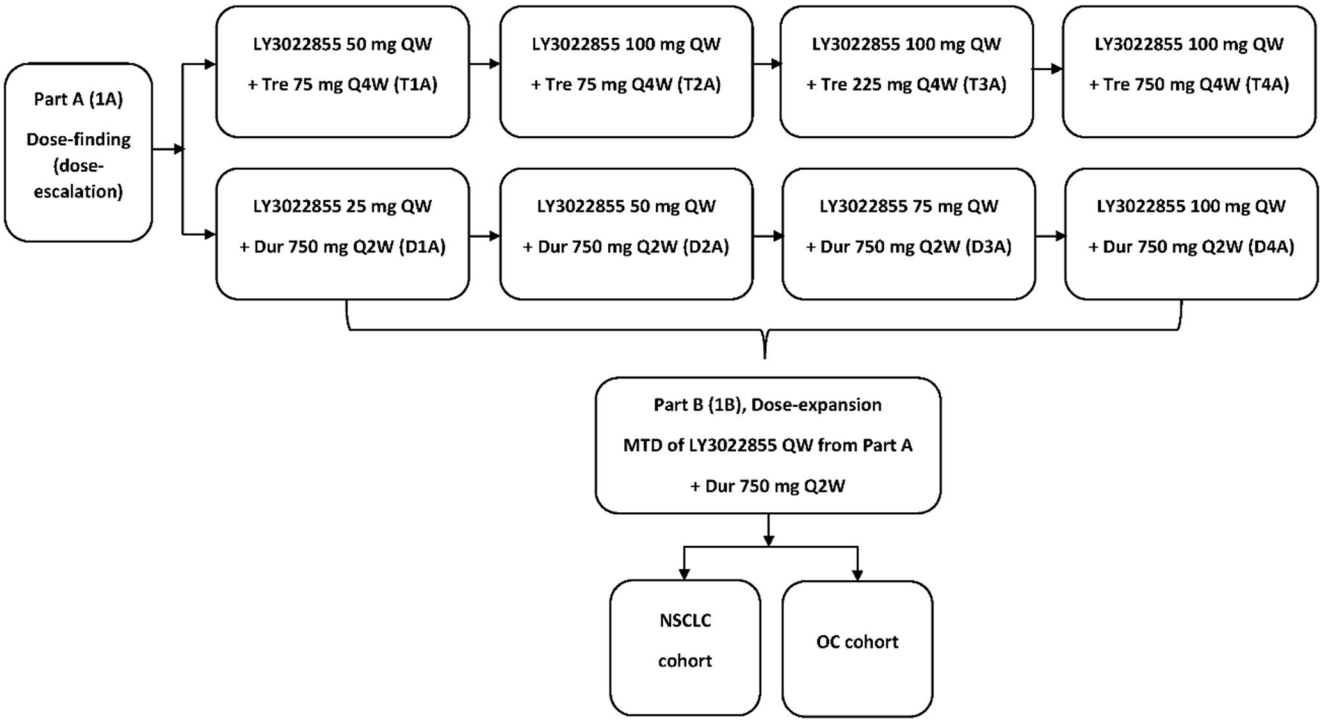

Fig. 1 Study Design. Dur, durvalumab; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; OC, ovarian cancer; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; Tre, tremelimumab. Note for Part A: Only LY3022855 (in both combinations) and tremelimumab, but not durvalumab, are dose escalated

known hypersensitivity to LY3022855, durvalumab, or tremelimumab were also excluded.

Treatment schedule

In Part A (dose-expansion/escalation), patients were divided into eight cohorts using a 3 + 3 study design: four cohorts each of LY3022855 in combination with durvalumab or tremelimumab.

The LY3022855 and durvalumab cohorts were administered intravenous LY3022855 doses of 25, 50, 75, or 100 mg once weekly (QW) in combination with durvalumab 750 mg once every two weeks (Q2W) (cohorts D1A, D2A, D3A, and D4A). The LY3022855 and tremelimumab combination was administered as: LY3022855 50 mg QW with tremelimumab 75 mg once every four weeks (Q4W) (T1A), LY3022855 100 mg QW with tremelimumab 75 mg Q4W (T2A), LY3022855 100 mg QW with tremelimumab 225 mg Q4W (T3A), and LY3022855 100 mg QW with tremelimumab 750 mg Q4W (T4A) (Supplementary Table S1). After receiving six doses of tremelimumab Q4W, the frequency of subsequent doses of tremelimumab was reduced to once every 12 weeks until discontinuation.

In Part B (disease-specific expansion), patients with NSCLC (B1) or OC (B2) were treated with LY3022855 and durvalumab at the maximum tolerated dose (MTD) identified in Part A.

Objectives and assessments

The primary objective was to characterize the safety profile and tolerability of the LY3022855 combinations used in this study. In addition, the study determined a recommended Phase 2 dose (RP2D) for LY3022855 with durvalumab combination in Part A. Secondary objectives included assessment of antitumor activity, development of immunogenicity/treatment-emergent anti-drug antibodies (TE ADAs), and characterization of PK of LY3022855 with durvalumab. The combination of LY3022855 with tremelimumab was deprioritized during the study and therefore, not reported in this disclosure.

In this study, MTD was defined as the highest tested dose that had less than 33% probability of causing a dose-limiting toxicity (DLT). Safety evaluation was performed using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 [20], and included adverse events (AEs), their severity, DLTs with each dose, association between study drug and AE, and dose adjustments due to AEs. A DLT was defined as a possible drug-related AE (Grade 3 and above) occurring during Cycle 1 (the DLT-evaluation period), which did not improve to the NCI-CTCAE Grade ≤ 2 despite medical management. Grade 2 pneumonitis that did not resolve to Grade ≤ 1 within three days of best supportive care were also included as DLTs. Adverse

events which met the DLT criteria after Cycle 1 were defined as dose-limiting equivalent toxicities (DLETs).

Serum sampling for PK analysis is presented in Supplementary Table S2. The samples were collected at regular intervals through the first four cycles of treatment. Serum samples were analyzed for LY3022855 (Covance Laboratories Inc., Chantilly, Virginia, USA), durvalumab, or tremelimumab using a validated enzyme-linked immunosorbent assay method. Pharmacokinetic parameter estimates for LY3022855 and durvalumab were determined by standard noncompartmental methods of analysis using Phoenix WinNonlin® 8.0 (Certara, L.P.; Princeton, New Jersey, USA).

Tumor measurements were performed using computed tomography or magnetic resonance imaging, with antitumor activity assessed in terms of tumor response data (RECIST version 1.1) [21] and time-to-event variables. The best overall response (BOR) was defined as response recorded from the "start of the study treatment until the end of treatment" [21]. The BOR to treatment included overall response rate (ORR) and disease control rate (DCR). Patients were considered to have a tumor response if they achieve a confirmed complete response (CR) or partial response (PR).

Immunogenicity data were summarized and assessed, as appropriate. The measures analyzed included presence of anti-drug antibodies (ADAs) at baseline, TE ADA, and ADA titer levels.

Statistical analysis

The estimated sample size for this study was 118 (78 patients in Part A and 40 patients in Part B). In Part A, sample size was determined primarily by the incidence of DLTs prior to establishing MTD. Planned enrollment was approximately 12 to 36 patients in the LY3022855 plus durvalumab combination, and approximately 12 to 42 patients in the LY3022855 plus tremelimumab combination. Every cohort in Part B had planned to enroll 20 patients, which was based on estimation of providing adequate precision for the estimated incidence rate of the patients having a specified AE or patients showing CR or PR to treatment.

The endpoints were described using descriptive analysis and no hypothesis testing was performed. Data were presented by cohort and treatment, wherever appropriate. Continuous variables were summarized using number of patients, percentages, mean (standard deviation), and median (minimum and maximum). Categorical endpoints were summarized using number of patients and percentages. Missing data were not imputed.

Results

Patient characteristics

A total of 72 patients (median age 61 years [range 29–84], 62.5% females) were enrolled in this study: 33 in Part A (LY3022855 + durvalumab = 15; LY3022855 + tremelimumab = 18) and 39 in Part B. The majority of the population (59.7%) was <65 years of age and Caucasian (97.1%). All patients had received at least one prior therapy and had history of undergoing surgery, radiotherapy, or systemic therapy. The patients were non-randomly assigned to 10 cohorts among Part A (eight cohorts) and Part B (two cohorts). All patients were off treatment at the time of analysis and were followed-up post-discontinuation (Table 1). The dose intensity in each cohort is presented in Supplementary Table S3.

Safety, toxicity, and recommended phase 2 dose of LY3022855

No DLT was observed in any of the cohorts; however, four DLETs were observed in two patients with OC (LY3022855 100 mg QW + durvalumab 750 mg Q2W cohort), including one patient with increased blood creatine phosphokinase in Cycle 4 and one patient with increased amylase, increased lipase, and autoimmune colitis in Cycle 2. All the reported DLETs were Grade 3. The DLETs of creatine phosphokinase elevation and autoimmune colitis were resolved with supportive treatment. MTD was not reached. The highest dose of LY3022855 and durvalumab combination investigated in Part A (LY3022855 100 mg QW + durvalumab 750 mg Q2W) was determined to be the RP2D, which was then administered in Part B.

Nineteen deaths (26.4%) occurred during the study (Part A: 12; Part B: seven). There were six deaths each in LY3022855 plus durvalumab (40%) and LY3022855 plus tremelimumab (33.3%) cohorts from Part A, and seven deaths in Part B (four in NSCLC cohort and three in the OC cohort). Nine deaths (12.5%) occurred during therapy or within 30 days of discontinuation of therapy: one was due to arterial hemorrhage within 30 days of discontinuation of treatment and eight were due to progressive disease. Among the 10 deaths that occurred 30 days after the discontinuation of therapy, one was due to *Clostridium difficile* infection and nine were due to PD. None of the deaths were considered related to the study treatment.

Serious adverse events (SAEs) occurred in 26 patients (36.1%); nine in Part A and 17 in Part B (Table 2). Table 3 presents SAEs in each cohort. No SAE was reported in LY3022855 25 mg, 50 mg, and 75 mg + durvalumab, and LY3022855 50 mg + tremelimumab 75 mg cohorts. Serious AEs of anemia (Grades 2 and 3), pyrexia (Grades 1 and 2), peritonitis bacterial (Grade 3), respiratory tract infection (Grades 1 and 2), and confusional state (Grades 1 and 3) were

Table 1 Patient disposition, demographic and baseline characteristics - by Cohort

Demographic Parameter	Part A								Part B		Overall
	LY 25 mg + Dur[a] (D1A, *n* =4)	LY 50 mg + Dur[a] (D2A, *n* =3)	LY 75 mg + Dur[a] (D3A, n=3)	LY 100 mg + Dur[a] (D4A, *n* = 5)	LY 50 mg+ Tre 75 mg (T1A, n=3)	LY 100 mg+ Tre 75 mg (T2A, n=5)	LY 100 mg+ Tre 225 mg (T3A, n=5)	LY 100 mg + Tre 750 mg (T4A, n=5)	LY + Dur[b] (B1, *n* = 19)	LY + Dur[b] (B2, *n* = 20)	Part A+Part B
Age	65.5 (59–73)	63 (59–84)	56 (50–71)	53 (51–66)	58 (53–67)	46 (34–83)	65 (43–72)	62 (45–71)	62 (49–80)	58 (29–75)	61 (29–84)
Gender											
Females	1 (25.0)	1 (33.3)	3 (100.0)	3 (60.0)	2 (66.7)	2 (40.0)	3 (60.0)	2 (40.0)	8 (42.1)	20 (100.0)	45 (62.5)
Males	3 (75.0)	2 (66.7)	0 (0.0)	2 (40.0)	1 (33.3)	3 (60.0)	2 (40.0)	3 (60.0)	11 (57.9)	0 (0.0)	27 (37.5)
Race											
African American	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	2 (2.9)
Caucasian	4 (100.0)	2 (66.7)	3 (100.0)	4[c] (100.0)	3 (100.0)	5 (100.0)	3[c] (100.0)	3[c] (75.0)	19 (100.0)	20 (100.0)	66 (97.1)[c]
Country											
USA	4 (100.0)	3 (100.0)	3 (100.0)	4 (80.0)	1 (33.3)	2 (40.0)	3 (60.0)	4 (80.0)	5 (26.3)	4 (20.0)	33 (45.8)
Israel	0 (0.0)	0 (0.0)	0 (0.0)	1 (20)	2 (66.7)	3 (60)	2 (40)	1 (20)	5 (26.3)	5 (25)	19 (26.4)
Belgium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (42.1)	11 (55)	19 (26.4)
Czech Rep.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.4)
Patients with≥1 concomitant therapy	4 (100.0)	3 (100.0)	3 (100.0)	5 (100.0)	3 (100.0)	5 (100.0)	5 (100.0)	5 (75.0)	19 (100.0)	20 (100.0)	72 (100.0)
Prior anti-cancer therapy											
Surgery	4 (100.0)	3 (100.0)	2 (66.7)	5 (100.0)	1 (33.3)	5 (100.0)	4 (80.0)	4 (80.0)	10 (52.6)	19 (95)	57 (79.2)
Radiotherapy	3 (75.0)	2 (66.7)	2 (66.7)	4 (80.0)	0 (0.0)	1 (20.0)	1 (20.0)	0 (0.0.0)	12 (63.3)	3 (15.0)	28 (38.9)
Systemic	4 (100.0)	3 (100.0)	3 (100.0)	4 (80.0)	3 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	19 (100.0)	20 (100.0)	71 (98.6)
Surgery											
Palliative	3 (75.0)	2 (66.7)	1 (33.3)	1 (20.0)	0 (0.0)	4 (80.0)	2 (40.0)	0 (0.0)	5 (26.3)	8 (40.0)	26 (36.1)
Curative	1 (25.0)	1 (33.33)	1 (33.3)	4 (80.0)	1 (33.3)	3 (60.0)	3 (60.0)	4 (80.0)	5 (26.3)	14 (70.0)	37 (51.4)
Radiotherapy											
Adjuvant	0 (0.0)	0 (0.0)	1 (33.3)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	0 (0.0)	6 (8.3)
Advanced/metastatic	3 (75.0)	3 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	0 (0.0)	9 (47.4)	3 (15.0)	20 (27.8)
Neoadjuvant	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	0 (0.0)	3 (4.2)
Patients off-treatment	4 (100.0)	3 (100.0)	3 (100.0)	5 (100.0)	3 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	19 (100.0)	20 (100.0)	72 (100.0)
Reason for discontinuation											
AE	0 (0.0)	1 (33.3)	0 (0.0)	2 (40.0)	0 (0.0)	1 (20.0)	1 (20.0)	0 (0.0)	4 (21.1)	2 (10.0)	11 (15.3)
Death	1 (25.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	4 (5.6)
Physician decision	0 (0.0)	0 (0.0)	1 (33.3)	1 (20.0)	1 (33.3)	0 (0.0)	0 (0.0)	2 (40.0)	1 (5.3)	4 (20.0)	10 (13.9)
Progressive disease	3 (75.0)	2 (66.7)	1 (33.3)	2 (40.0)	2 (66.7)	3 (60.0)	3 (60.0)	3 (60.0)	9 (47.4)	10 (50.0)	38 (52.8)

Table 1 (continued)

Demographic Parameter	Part A							Part B		Overall
	LY 25 mg + Dur[a] (D1A, $n = 4$)	LY 50 mg + Dur[a] (D2A, $n = 3$)	LY 75 mg + Dur[a] (D3A, n = 3)	LY 100 mg + Dur[a] (D4A, $n = 5$)	LY 50 mg + Tre 75 mg (T1A, n = 3)	LY 100 mg + Tre 75 mg (T2A, n = 5)	LY 100 mg + Tre 225 mg (T3A, n = 5)	LY 100 mg + Tre 750 mg (T4A, n = 5)	LY + Dur[b] (B1, $n = 19$)	LY + Dur[b] (B2, $n = 20$)	Part A + Part B
Withdrawal by subject	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	4 (21.1)	4 (20.0)	9 (12.5)
Off-treatment follow-up	3 (75.0)	3 (100.0)	1 (33.3)	5 (100.0)	3 (100.0)	4 (80.0)	3 (60.0)	4 (80.0)	15 (78.9)	11 (55.0)	52 (72.2)

All data are presented as n (%), unless specified

AE adverse event, *Dur* durvalumab, *LY* LY3022855, *QW* once weekly, *Q2W* once every 2 weeks, *Tre* tremelimumab

[a] Part A: All cohorts were administered durvalumab dose of 750 mg Q2W

[b] Part B: LY 100 mg QW + durvalumab 750 mg Q2W

[c] Population analyzed less than the population of the group

reported in two patients (2.8%) each in the overall population (Table 3). Drug-related SAEs were observed in five patients (6.9%; three in Part A and two in Part B) and included anemia (one patient), stress cardiomyopathy (one patient), hypothyroidism (one patient), autoimmune colitis (one patient), hypersensitivity (one patient), amylase increased and blood creatine phosphokinase increased (two patients), hyponatremia (one patient), and rash and rash maculo-papular (two patients). All treated patients experienced at least one treatment-emergent adverse event (TEAE) during the study.

Of the total patients, 84.7% had at least one drug-related TEAEs, with Grade 3 TEAEs being the most common among all the grades of TEAEs (69.4%, Table 2). Table 4 presents the most common all-cause TEAEs by grade in each cohort. Common Grade 3 drug-related TEAEs with ≥5% incidence rate included anemia (13.9%), increase in blood creatine phosphokinase (11.1%), hyponatremia (9.7%), increase in aspartate aminotransferase (8.3%), fatigue (6.9%,), hypertension (6.9%), increase in lipase (5.6%), and lymphopenia (5.6%). The frequency of drug-related TEAEs by maximum CTCAE grade are presented in Supplementary Table S4. Face edema was a notable drug-related TEAE observed in 26.4% patients. Common Grade 3 drug-related TEAEs included increase in blood creatine phosphokinase (11.1%), increase in aspartate aminotransferase (5.6%), increase in lipase (5.6%), fatigue (4.2%), maculo-papular rash (4.2%), anemia (2. 8%), increase in amylase (2.8%), hypertension (2.8%), and pruritus (2.8%).

Pharmacokinetics of LY3022855 and Durvalumab

All patients administered at least one dose of LY3022855 in combination with either durvalumab or tremelimumab were included in the PK dataset. LY3022855 exhibited dose-dependent increases across all metrics of PK exposure over two cycles of therapy, including maximum concentration, trough concentration (collected at 168 h), and area under the concentration-time curve (AUC) (Table 5). Concentrations of durvalumab were consistent across the PK collection period from Cycle 1 to Cycle 4 (Cycle 1: 122 [49]; Cycle 2: 131 [59]; Cycle 3 Week 1: 118 [47]; Cycle 3 Week 3: 121 [50]; and Cycle 4; 147 [57] ([geometric mean, (percentage of coefficient of variation)])).

Efficacy assessment and best overall response

The median progression-free survival (PFS) was 1.87 months (95% confidence interval [CI] 1.71, 3.22) in the overall population. Median PFS in cohorts D1A, D2A, and D3A were 4.26 months (95% CI 1.87, 19.17), 1.71 months (95% CI 1.35, 8.51), and 11.93 months (95% CI 1.41, 11.93), respectively. Median PFS was not reached in cohort D4A, as three of five patients were censored. For cohorts T1A to T4A, the median PFS was 1.71 months (95% CI 1.64, not available

Table 2 Safety summary by Cohort

Events	Part A								Part B		Overall
	LY 25 mg + Dur[a] (D1A, n=4)	LY 50 mg + Dur[a] (D2A, n=3)	LY 75 mg + Dur[a] (D3A, n=3)	LY 100 mg + Dur[a] (D4A, *n* = 5)	LY 50 mg+Tre 75 mg (T1A, n=3)	LY 100 mg+Tre 75 mg (T2A, *n* =5)	LY 100 mg+Tre 225 mg (T3A, n=5)	LY 100 mg + Tre 750 mg (T4A, n=5)	LY + Dur[b] (B1, *n* = 19)	LY + Dur[b] (B2, *n* = 20)	Part A+Part B
Patients with≥1 AE	4 (100.0)	3 (100.0)	3 (100.0)	5 (100.0)	3 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	19 (100.0)	20 (100.0)	72 (100.0)
Patients with≥1 SAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	2 (40)	3 (60)	3 (60)	12 (63.2)	5 (25.0)	26 (36.1)
Patients with≥1 TEAE											
1	1 (25.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	4 (5.6)
2	1 (25.0)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (20.0)	0 (0.0)	1 (5.3)	3 (15.0)	9 (12.5)
3	2 (50.0)	1 (33.3)	3 (100.0)	1 (20.0)	2 (66.7)	4 (80.0)	3 (60.0)	5 (100.0)	13 (68.4)	16 (80.0)	50 (69.4)
4	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	4 (21.1)	0 (0.0)	8 (11.1)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.4)
Any grade	4 (100.0)	3 (100.0)	3 (100.0)	5 (100.0)	3 (100.0)	5 (100.0)	5 (100.0)	5 (100.0)	19 (100.0)	20 (100.0)	72 (100.0)
Patients with≥1 drug-related TEAE											
1	2 (50.0)	1 (33.3)	0 (0.0)	1 (20.0)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	3 (15.0)	10 (13.9)
2	0 (0.0)	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	4 (80.0)	4 (80.0)	1 (20.0)	9 (47.4)	4 (20.0)	24 (33.3)
3	1 (25.0)	1 (33.3)	2 (66.7)	1 (20.0)	1 (33.3)	1 (20.0)	0 (0.0)	3 (60.0)	4 (21.1)	10 (50.0)	24 (33.3)
4	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.2)
Any grade	3 (75)	2 (66.7)	3 (100.0)	5 (100.0)	3 (100.0)	5 (100.0)	5 (100.0)	4 (80)	14 (73.7)	17 (85)	61 (84.7)

AE adverse event, *Dur* durvalumab, *LY* LY3022855, *QW* once weekly, *Q2W* once every 2 weeks, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event, *Tre* tremelimumab

All data are presented as n (%), unless specified

[a] Part A: All cohorts were administered durvalumab dose of 750 mg Q2W

[b] Part B: LY 100 mg QW + durvalumab 750 mg Q2W

Table 3 Summary of serious adverse events by Cohort

Part A				Part A	
LY 100 mg + Dur[a] (D4A, n = 5)	LY 100mg + Tre 75 mg (T2A, n = 5)	LY 100mg + Tre 225 mg (T3A, n = 5)	LY 100 mg + Tre 750 mg (T4A, n = 5)	LY + Dur[b] (B1, n = 19)	LY + Dur[b] (B2, n = 20)
				Febrile neutropenia (5.3)	
				Pericardial effusion (5.3)	
				Right ventricular dysfunction (5.3)	Anemia (5.0)
				Abdominal pain (5.3)	Stress cardiomyopathy (5.0)
				Dysphagia (5.3)	Autoimmune colitis (5.0)
	Abdominal discomfort (20.0)		Anemia (20.0)	Stomatitis (5.3)	Duodenal obstruction (5.0)
Hypothyroidism (20.0)	Nausea (20.0)	Pleural effusion (20.0)	Peritonitis bacterial (20.0)	Pyrexia (5.3)	Intestinal obstruction (5.0)
			Delirium (40.0)	Respiratory tract infection (5.3)	Pyrexia (5.0)
				Atypical pneumonia (5.3)	Eczema (5.0)
				Clostridium difficile infection (5.3)	Peritonitis bacterial (5.3)
				Diverticulitis (5.3)	Respiratory tract infection (5.0)
				Septic shock (5.3)	Upper respiratory tract infection (5.0)
				Dyspnea (5.3)	Pulmonary embolism (5.0)
				Pneumonia aspiration (5.3)	
				Pneumothorax (5.3)	

All data are presented as (%), unless specified

Dur durvalumab, *LY* LY3022855, *QW* once weekly, *Q2W* once every 2 weeks, *SAE* serious adverse event, *Tre* tremelimumab

[a] Part A: All cohorts were administered durvalumab dose of 750 mg Q2W

[b] Part B: LY 100 mg QW + durvalumab 750 mg Q2W

[NA]), 3.22 months (95% CI, 1.64, 9.01), 1.18 months (95% CI 0.72, NA), and 2.76 months (95% CI 1.71, 6.18), respectively. Median PFS was 1.68 months (95% CI 1.45, 3.19) and 1.87 months (95% CI 1.58, 6.48) for the NSCLC and OC cohorts, respectively.

Rates of PR, SD, and DCR were 2.8%, 29.2%, and 33.3% in the overall population, respectively. One patient in the OC cohort from Part B (5%) achieved a CR. Patients who achieved PR were from the LY3022855 + durvalumab cohort D4A (Fig. 2). The ORR in the overall population was 4.2% (two patients from cohort D4A and one patient from cohort B2). All three patients who achieved a response had received LY3022855 100 mg combined with durvalumab 750 mg. Figure 2 presents the response to treatment for the overall population and by parts.

Immunogenicity

Overall TE ADA rate was 21.2% and varied by cohort: 13.3% for LY3022855 + durvalumab cohorts, 23.5% for LY3022855 + tremelimumab cohorts, 5.9% for NSCLC cohort, and 41.2% for OC cohort. Maximum ADA titers of TE ADA-positive participants ranged from 1:20 to 1:1280 (median of 1:60).

Discussion

This is the first study to evaluate dose escalation of LY3022855 in combination with durvalumab or tremelimumab in patients with solid cancers. LY3022855 showed acceptable tolerability and safety in both the combinations. The MTD for LY3022855 and durvalumab was not reached and the dose of LY3022855 100 mg QW and durvalumab 750 mg Q2W was selected as the RP2D, which was administered to patients with NSCLC and OC in the disease-expansion phase. The overall findings from Part A and Part B suggested limited clinical activity in this heavily pre-treated population, with reported median PFS at 1.87 months, PR achieved in two (2.8%) patients, and SD

Table 4 Summary of all-cause treatment-emergent adverse events by grade

TEAEs							
Common TEAEs[a]	n (%)	Grade 3 TEAEs[b]	n (%)	Grade 4 TEAEs	n (%)	Grade 5 TEAE	n (%)
Fatigue	41 (56.9)	Anemia	10 (13.9)	Blood creatine phosphokinase increased	3 (4.2)	Arterial hemorrhage	1 (1.4)
Blood creatine phosphokinase increased	27 (37.5)	Blood creatine phosphokinase increased	8 (11.1)	Pericardial effusion	1 (1.4)		
Decreased appetite	26 (36.1)	Hyponatremia	7 (9.7)	Sepsis	1 (1.4)		
Nausea	25 (34.7)	Aspartate aminotransferase increased	6 (8.3)	Platelet count decreased	1 (1.4)		
Aspartate aminotransferase increased	24 (33.3)	Fatigue	5 (6.9)	Hypertriglyceridemia	1 (1.4)		
Abdominal pain	21 (29.2)	Hypertension	5 (6.9)	Hyponatremia	1 (1.4)		
Diarrhea	19 (26.4)	Lipase increased	4 (5.6)				
Anemia	19 (26.4)	Lymphocyte count decreased	4 (5.6)				
Face edema	19 (26.4)	Abdominal pain	3 (4.2)				
Pruritus	19 (26.4)	Edema peripheral	3 (4.2)				
Edema peripheral	18 (25.0)	Blood alkaline phosphatase increased	3 (4.2)				
Pyrexia	17 (23.6)	Rash maculo-papular	3 (4.2)				
Dyspnea	17 (23.6)	Diarrhea	2 (2.8)				
Rash maculo-papular	17 (23.6)	Peritonitis	2 (2.8)				
Cough	6 (22.2)	Gamma-glutamyltransferase increased	2 (2.8)				
Periorbital edema	16 (22.2)	Neutrophil count decreased	2 (2.8)				
Alanine aminotransferase increased	16 (22.2)	Alanine aminotransferase increased	2 (2.8)				
Vomiting	15 (20.8)	Amylase increased	2 (2.8)				
Hypertension	14 (19.4)	Hypercalcemia	2 (2.8)				
Myalgia	12 (16.7)	Hypokalemia	2 (2.8)				
Back pain	11 (15.3)	Hyperkalemia	2 (2.8)				
Hyponatremia	11 (15.3)	Back pain	2 (2.8)				
Headache	11 (15.3)	Confusional state	2 (2.8)				
Constipation	10 (13.9)	Pruritus	2 (2.8)				
Blood creatinine increased	9 (12.5)						
Abdominal distension	8 (11.1)						
Chills	8 (11.1)						
Dizziness	8 (11.1)						
Hypalbuminemia	8 (11.1)						
Amylase increased	8 (11.1)						

TEAE treatment-emergent adverse event

$N = 72$, number of patients in the safety population. All data are presented as n (%), unless specified

[a.] Includes TEAEs reported in 10% or patients

achieved in 21 (29.2%) patients. In addition to the present study, other CSF-1R inhibitors have also been investigated [22]. For solid tumors, CSF-1R inhibitors have been either evaluated as monotherapy [6, 23, 24] or in combination with chemotherapy [24, 25] or ICIs [26–28].

In this study, treatment with LY3022855 in combination with durvalumab or tremelimumab yielded acceptable safety results. With no DLTs in Part A and four DLETs in Part B, LY3022855 100 mg QW and durvalumab 750 mg Q2W was confirmed as the RP2D. Overall, 26 (36%) patients developed SAEs and five (6.9%) patients had drug-related SAEs; however, the proportion of drug-related TEAEs was 87.4%. All the deaths in the study (26.4%) occurred after discontinuation of treatment and did not have a causal relationship with treatment. Previous phase 1 studies of LY3022855 and other CSF-1R inhibitors demonstrated a similar safety profile [6, 23–25].

Table 5 Noncompartmental PK Analysis of LY3022855 100 mg QW and Durvalumab 750 mg Q2W in Part A

	LY3022855		Durvalumab
Cycle	1	2	1
N	44	29	38
Cmax (mg/mL)	32.9 (28)	43.1 (38)	251 (32)
tmax[a] (h)	2.06 (0.48–21.82)	1.83 (0.97–27.75)	1.58 (1–24.28)
t1/2[b] (h)	63.4[c] (36.4–104)	116[d] (42.1–316)	–
C168h (mg/mL)	5.00[e] (69)	13.4[f] (84)	–
Cav,τ (mg/mL)	14.9[g] (33)	27.1[h] (32)	–
AUC(0-∞) (h·mg/mL)	5250[c] (49)	7490[d] (56)	–
AUC(0-τ)[i] (h·mg/mL)	2500[g] (33)	4560[h] (32)	31900[j] (55)
CL (L/h)	0.0401[g] (33)	0.0219[h] (43)	–
Vss (L)	9.31[c] (63)	3.69[d] (35)	–
RA[k]	–	1.93[d] (32)	–

$AUC_{(0-\tau)}$ area under the concentration versus time curve from time zero to τ, $AUC_{(0-\infty)}$ area under the concentration versus time curve from time zero to ∞, C_{168h} serum concentration collected 168 h after the start of infusion, $C_{av,\tau}$ average serum concentration over dosing interval calculated using $AUC_{(0-\tau)}$, *CL* total body clearance, C_{max} maximum serum concentration, *h* hours, *N* number of patients in the analysis population, *QW* once a week, *Q2W* once every 2 week, R_A intrapatient accumulation ratio, $t_{1/2}$ terminal elimination half-life, t_{max} time of maximum serum concentration, V_{ss} volume of distribution at steady state

[a] Median (minimum, maximum)

[b] Geometric mean (minimum, maximum)

[c] N = 30 patients

[d] = 21 patients

[e] N = 31 patients

[f] N = 24 patients

[g] N = 35 patients

[h] N = 22 patients

[i] τ = 168 h for LY3022855; 336 h for durvalumab

[j] N = 6 patients

[k] RA = AUC(0-τ) Cycle 1/AUC(0-τ) Cycle 2

Combination of CSF-1R inhibitor, pexidartinib, with durvalumab showed a similar safety profile as other studies of CSF-1R monotherapy in patients with advanced pancreatic ductal carcinoma and colorectal cancer. Two DLTs of increased aspartate aminotransferase/increased alanine aminotransferase were reported [28]. Based on these findings, the safety and tolerability in our study were consistent with the observations in Phase 1 studies evaluating CSF-1R inhibitor monotherapy or its combinations with other therapies. As observed in Phase 1 studies for other CSF-1R inhibitors [6, 23–25], MTD was not reached for LY3022855 + durvalumab combination and the highest administered dose was confirmed as the RP2D. The safety profile of LY3022855 in this study was similar to the safety profile observed in another phase I trial of LY3022855 in patients with MBC or metastatic castration-resistant prostate cancer (MCRPC), in which the most frequent TEAEs of any grade included fatigue (38.2%), decrease in appetite (26.5%), and nausea (26.5%). Increases in lipase (23.5%) and creatine phosphokinase (20.6%) were also reported [14]. Occurrence of face edema (26.4%) in our study, a class effect of CSF-1R inhibitors, was consistent as observed with other CSF-1R inhibitors. However, the occurrence of face edema was lower than that observed with other CSF-1R mAbs [22].

LY3022855 exhibited a dose-dependent increase in exposure and slow elimination [29]. Exposures of LY3022855 in combination with durvalumab or tremelimumab are comparable to those observed in monotherapy studies [14, 29]. Similarly, combination with LY3022855 did not appear to affect durvalumab PK, with exposures which were consistent with monotherapy PK, as reported by Baverel et al. in patients with urothelial carcinoma and NSCLC [30]. The linear increase in PK parameters for LY3022855 was in alignment with other CSF-1R inhibitors [6, 24, 25]. Pharmacokinetics of AMG820, a CSF-1R inhibitor, was non-linear in the dose range of 1.5 mg/kg to 6 mg/kg due to small cohort size; however, AUC and maximum serum concentration increased with dose in the 1.5 mg/kg to 20 mg/kg dose ranges [6].

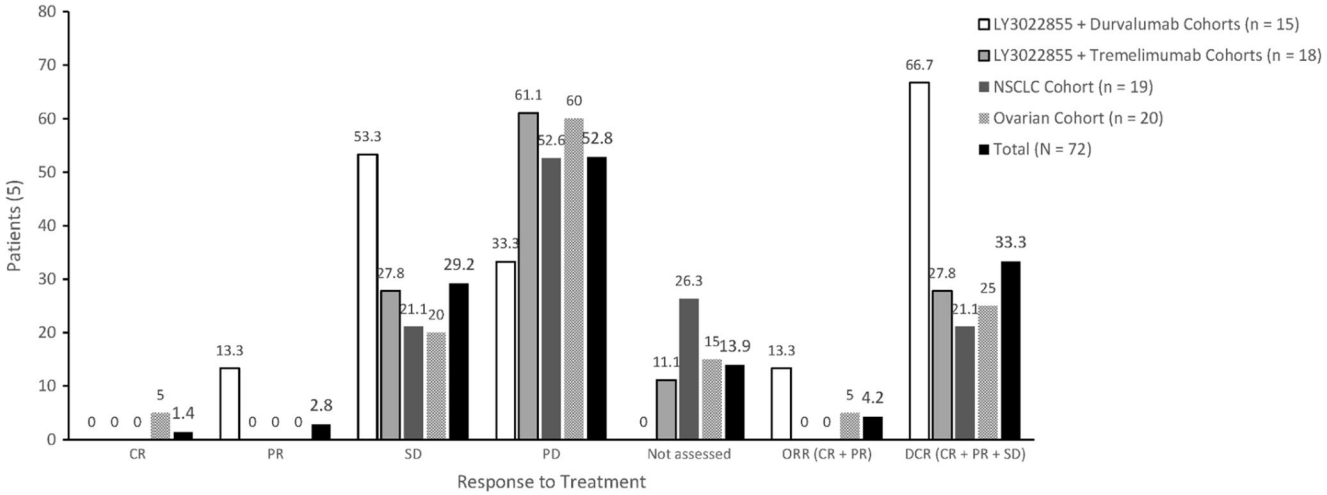

Fig. 2 Best Overall Response to Treatment – By Parts. CR, complete response; DCR, disease control rate; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. Part A: LY3022855 + durvalumab and LY3022855 + tremelimumab cohorts
Part B: NSCLC and ovarian cancer cohort.

Pexidartinib followed linear PK up to a dose of 1200 mg [25], whereas emactuzumab followed linear PK above dose of 900 mg [24]. Overall, the PK of LY3022855 was consistent with typical IgG1 mAb PK [31].

The overall response to treatment and improvement in median PFS with LY3022855 combination with durvalumab or tremelimumab were limited. With the RP2D of LY3022855 100 mg QW + durvalumab 750 mg Q2W, a BOR of SD and PR was achieved in 40% patients across Parts A and B. During the interim analysis of this study, one patient (2.8%) achieved SD from the 35 evaluated patients [29]. Compared with LY3022855, the rate of SD was 13% with emactuzumab monotherapy and 43% with emactuzumab and paclitaxel combination therapy [24]. In the MEDIPLEX study, 21% of patients achieved SD after pexidartinib and durvalumab combination [28]. LY3022855 also showed limited clinical activity in patients with MBC or MCRPC, with no patient achieving CR or PR. The rate of SD was 22.7% in patients with MBC and 42.8% in patients with MCRPC [14]. Because TME modulation may be a critical factor for efficacy, the combination of a CSF-1R inhibitor with other immunotherapy agents was hypothesized to be a promising strategy. The limited clinical benefit observed from our study and other studies may be attributed to unexplored or unknown resistance mechanisms [22]. In addition, the limited clinical response of ICIs (inhibitors of CSF-1R, PD-L1, and CTLA-4) in patients with advanced solid cancers, including NSCLC and OC, suggested that the population in the presented study was difficult to treat and hence had limited clinical activity [17–19, 22].

The overall low TE ADA rate of 21.2% for LY3022855, with low ADA titers, suggests low risk for any potential impact on exposure or efficacy. More importantly, no safety events related to ADA were detected. The overall low ADA titers in TE ADA-positive participants suggest low risk for ADA impact on exposure or efficacy. The proportion of TE ADA-positive patients in our study was higher than the proportion of healthy subjects developing ADAs to lacnotozumab in a phase 1 study (7.7%) [32]. Because no data have been reported on the ADAs for other CSF-1Rs [6, 23–25, 28], comparison with other CSF-1Rs with respect to ADA development could not be done.

This study has several limitations. First, the limited efficacy could have been due to the difficult-to-treat patient population enrolled in this study. Second, determining the duration of SD was not part of the planned analysis. Third, exploratory analysis on the pharmacodynamic effects of LY3022855 and durvalumab or tremelimumab combinations was not performed due to low sample size and lack of data. Despite these limitations, investigation of the safety of these combinations may be important for future research.

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Data availability Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request six months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once they are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment for up to two years per proposal. For details on submitting a request, see the instructions provided at www.clinicalstudydatarequest.com.

Code availability Not applicable.

Declarations

Ethics approval The study was performed in accordance with the International Conference on Harmonization guidelines and Declaration of Helsinki 1964 and its amendments. The Institutional Review Board of each study site approved the study protocol, information brochure, and the informed consent form before study initiation.

Consent to participate Informed consent was obtained from all individual participants included in the study.

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