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CORRESPONDENCE

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Iparomlimab (QL1604) in patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) unresectable or metastatic solid tumors: a pivotal, single-arm, multicenter, phase II trial

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Abstract

Though several anti-PD-1/PD-L1 antibodies approved for monotherapy in microsatellite instability-high or mismatch repair-deficient unresectable/metastatic solid tumors, novel immunotherapy with better anti-tumor activity is needed in clinic. In this single-arm, multicenter, pivotal, phase II study, patients received iparomlimab (a novel humanized anti-PD-1 mAb, 200 mg or 3 mg/kg for patients with body weight < 40 kg, IV, Q3W) until disease progression, intolerable toxicities, withdrawal of consent, death, or up to 2 years. The primary endpoint was objective response rate (ORR) assessed by independent radiological review committee (IRRC). Totally, 120 patients were enrolled, of whom 60 patients failed from prior standard therapy, were enrolled in the full analysis set (FAS). As of Jan 20, 2024, the confirmed ORR per IRRC in FAS were 50.0% (30/60; 95% CI 36.8–63.2%) patients, including 4 (6.7%) complete response (CR) and 26 (43.3%) partial response (PR). In colorectal cancer (CRC) patients in FAS, the ORR reached 57.9% (22/38; 95% CI 40.8–73.7%) per IRRC, with 3 (7.9%) CR and 19 (50.0%) PR. Furtherly, the ORRs in liver metastatic or non-liver metastatic CRC patients were 52.9% (9/17, 95% CI 27.8–77.0%) vs 61.9% (13/21, 95% CI 38.4%–81.9%). The incidence of TRAE was 90.8% (any grade) and 20.8% (grade ≥ 3). Immune-related adverse events occurred in 33.3% (any grade) and 5.0% (grade ≥ 3) of patients. No iparomlimab-related death occurred. Iparomlimab presented encouraging antitumor activity with durable response and tolerable safety profile.

Trial registration ClinicalTrials.gov Identifier: NCT04326829.

Keywords Iparomlimab (QL1604), MSI-H/dMMR, PD-1, Solid tumors, Immunotherapy, Colorectal cancer, Liver metastasis

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To the Editor,

Microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR) solid tumors are highly sensitive to immunotherapy, however, only approximately 30–40% of MSI-H/dMMR solid tumors respond to programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) blockade, while about 30% of patients were primary resistance to immunotherapy [1–7]. Iparomlimab (QL1604) is a novel humanized anti-PD-1 mAb with favorable anti-tumor activity and good safety profile in patients with advanced or metastatic solid tumors in a phase I trial [8, 9]. This single-arm, multicenter, pivotal, phase II study assessed the efficacy and safety of iparomlimab in patients with MSI-H/dMMR unresectable or metastatic solid tumors (Additional file 1: method).

From Jun, 2020 to Jan, 2023, 120 eligible patients were enrolled and included in the intent to treat (ITT) group. Of them, 60 patients were included in the full analysis set (FAS) group. The patients with advanced colorectal cancer (CRC) should have failed from fluoropyrimidine, oxaliplatin, and irinotecan, patients with gastric cancer failed from ≥ two lines of standard of care, and other solid tumors failed from ≥ one prior treatment. Patient characteristics were summarized in Additional File 2: Table S1. The MSI-H/dMMR status was centrally identified in patients in FAS (Additional File 2: Table S2). As of Jan 20, 2024, the median treatment duration was 12.9 months (range, 0.7–26.4) (patient disposition shown in Additional File 2: Figs. S1, S2). In FAS, 55 out of 60 patients were evaluable. The confirmed objective response rate (ORR) per independent radiological review committee (IRRC) was 50.0% (30/60; 95% CI 36.8–63.2%), including 4 (6.7%) complete response (CR) and 26 (43.3%) partial response (PR) according to the Response Evaluation

Table 1 Efficacy of iparomlimab per RECIST v1.1 in FAS and ITT

Efficacy	Per IRRC		Per investigator	
	FAS (N = 60)	ITT (N = 120)	FAS (N = 60)	ITT (N = 60)
CR, n (%)	4 (6.7)	13 (10.8)	1 (1.7)	10 (8.3)
PR, n (%)	26 (43.3)	45 (37.5)	32 (53.3)	53 (44.2)
Non-CR/Non-PD	1 (1.7)	2 (1.7)	0	0
SD, n (%)	14 (23.3)	33 (27.5)	15 (25.0)	32 (26.7)
PD, n (%)	10 (16.7)	17 (14.2)	7 (11.7)	14 (11.7)
Not evaluable	0	1 (0.8)	0	2 (1.7)
Without efficacy assessment, n (%)	5 (8.3)	9 (7.5)	5 (8.3)	9 (7.5)
ORR, n (%, 95% CI)*	30 (50.0, 36.8–63.2)	58 (48.3, 39.1–57.6)	33 (55.0, 41.6–67.9)	63 (52.5, 43.2–61.7)
TMB > 30 Muts/Mb	11/21 (52.4, 29.8–74.3)	23/37 (62.2, 44.8–77.5)	14/21 (66.7, 43.0–85.4)	27/37 (75.7, 58.8–88.2)
TMB ≤ 30 Muts/Mb	11/22 (50.0, 28.2–71.8)	22/52 (42.3, 28.7–56.8)	11/22 (50.0, 28.2–71.8)	22/52 (42.3, 28.7–56.8)
DCR, n (%, 95% CI)	45 (75.0, 62.1–85.3)	93 (77.5, 69.0–84.6)	48 (80.0, 67.7–89.2)	95 (79.2, 70.8–86.0)
DOR, median (95% CI), months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (29.21, NE)
Range, months	1.4–32.0	1.4–39.1	1.4–32.0	1.4–37.7
6 month-DOR rate, % (95% CI)	100 (NE–NE)	100 (NE–NE)	93.5 (76.5–98.3)	96.7 (87.5–99.2)
12 month-DOR rate, % (95% CI)	95.8 (73.9–99.4)	98.0 (86.9–99.7)	88.6 (67.9–96.3)	94.5 (83.8–98.2)
24 month-DOR rate, % (95% CI)	95.8 (73.9–99.4)	95.3 (82.2–98.8)	88.6 (67.9–96.3)	88.5 (73.7–95.2)
PFS, median (95% CI), months	NE (16.36, NE)	NE (30.52, NE)	NE (12.39, NE)	NE (22.34, NE)
6 month-PFS, (%, 95% CI)	73.6 (60.1–83.2)	71.2 (61.9–78.6)	69.5 (55.6–79.8)	67.2 (57.6–75.0)
12 month-PFS, (%, 95% CI)	69.5 (55.5–79.9)	67.3 (57.8–75.1)	65.7 (51.6–76.6)	65.3 (55.7–73.3)
18 month-PFS, (%, 95% CI)	63.4 (48.1–75.3)	63.4 (53.4–71.8)	60.2 (45.3–72.3)	61.5 (51.5–70.1)
24 month-PFS, (%, 95% CI)	63.4 (48.1–75.3)	61.6 (51.3–70.4)	60.2 (45.3–72.3)	59.6 (49.2–68.6)
OS	FAS		ITT	
Median (95% CI), months	NE (NE, NE)		NE (NE, NE)	
12 month-OS, (%, 95% CI)	79.6 (66.8–87.9)		81.1 (72.7–87.1)	
18 month-OS, (%, 95% CI)	68.7 (54.2–79.5)		72.5 (62.9–80.0)	
24 month-OS, (%, 95% CI)	65.5 (50.1–77.1)		71.2 (61.3–78.9)	

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; FAS, full analysis set; ITT, intent to treat; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease. For ORR, DCR, and DoR, each CR and PR as the best overall response was confirmed 4 weeks later according to the RECIST Version 1.1. *Among the 60 and 120 patients in FAS and ITT, respectively

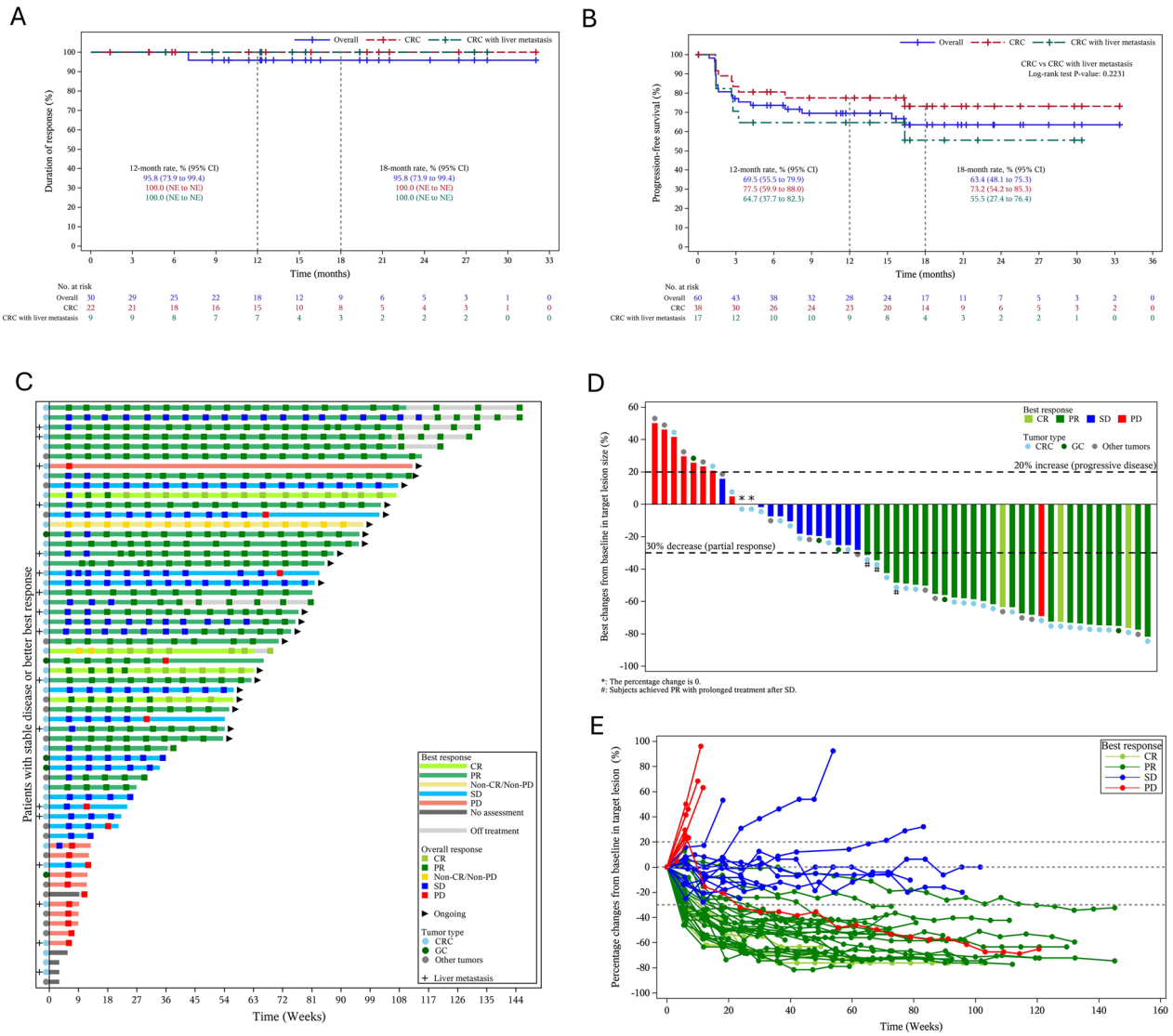

Fig. 1 Efficacy of iparomlimab in the full analysis set (FAS). The Kaplan–Meier estimates of duration of response (**A**) and progression-free survival (**B**) in overall, colorectal cancer (CRC), and liver metastatic CRC patients in the FAS. **C** Time to response and response duration in individual patients with best overall response of CR, PR, SD, and PD per IRRC assessment in FAS group. Bars length indicates the duration of treatment (dark) and time from last dose of study treatment to last imaging assessment (gray). **D** Waterfall plot depicting the best percentages change from baseline in target lesion size per IRRC in FAS group. Percentage change from baseline in the sum of the target lesions; lower dashed lines indicate a 30% decrease from baseline; upper dashed lines indicate a 20%increase from baseline. **E** Percentage changes from baseline in target lesion size over time per IRRC in FAS group. CR, complete response; PR, partial response; SD, steady disease; PD, progressive disease; FAS, full analysis set; IRRC, independent radiographic review committee

Criteria in Solid Tumors (RECIST) v1.1. With 14 (23.3%) stable disease (SD) and 1 (1.7%) non-CR/non-progressive disease (PD), the disease control rate (DCR) achieved 75.0% (95% CI 62.1–85.3%) in FAS. (Table 1, Fig. 1) The outcomes assessed by investigator were 80.0%, concordant with results assessed by IRRC ($p=0.9993$) in FAS (Table 1; Additional File 2: Table S3). The median duration of response (DOR), median progression-free survival (PFS), and median overall survival had not been reached in FAS (Table 1, Fig. 1A, B; Additional File 2: Fig. S3A). The response was durable, with the 12 month- and 24 month-DOR rates both being 95.8% (95% CI 73.9–99.4%) in FAS (Table 1, Fig. 1A). Besides, the efficacy per immune-related RECIST (iRECIST) was in consistency with the efficacy by IRRC per RECIST v1.1 (Additional File 2: Fig. S4). The efficacy of iparomlimab in ITT was similar with the efficacy in FAS (Table 1; Additional File 2: Figs. S5 and S3B).

Subgroup analyses for ORR in FAS and ITT populations were shown in Additional File 2: Fig. S6. Occurrence of immune-related adverse events (irAEs) was related with significant higher ORR (ORR: 65.0% (26/40, 95% CI 48.3–79.4%) vs. 40.0% (32/80, 95% CI 29.2–51.6%); $p=0.010$) compared with those without irAEs in the ITT population in post-hoc analysis. In CRC patients, the ORR reached 57.9% (38/60, 95% CI 40.8–73.7%) in FAS. Furtherly, the ORR in liver metastatic or non-liver metastatic CRC patients were 52.9% (9/17, 95% CI 27.8–77.0%) versus 61.9% (13/21, 95% CI 38.4–81.9%). (Additional File 2: Tables S4 and S5). Non-liver metastatic CRC (vs. liver metastatic CRC) and occurrence of irAEs (vs. no occurrence) might predict higher ORR and longer median PFS from iparomlimab treatment in CRC patients (Additional File 2: Tables S6 and S7). Besides, later response to iparomlimab might predict longer PFS (Additional File 2: Fig. S7). According to results of EQ-5D-5L and EORTC QLQ-C30 questionnaires, overall improvement was observed in most items and the time to definitive deterioration after iparomlimab treatment (Additional File 2: Figs. S8, S9 and S10). Adverse events, pharmacokinetics, and immunogenicity of iparomlimab were summarized in Additional File 2: Tables S8, S9 and S11. In safety set (120 patients), the incidence of TRAEs was 90.8% (any grade) and 20.8% (grade ≥ 3). The incidences of irAEs were 33.3% (any grade) and 5.0% (grade ≥ 3). Neither unexpected AEs nor treatment-related death occurred.

Iparomlimab presented encouraging antitumor activity with clinical meaningful durable response and tolerable safety, which supported the use of iparomlimab monotherapy in patients with MSI-H/dMMR solid tumors. The confirmative study trial with expanded sample size of ≥ 200 patients with MSI-H/dMMR solid tumors is recruiting.

Abbreviations

CRC	Colorectal cancer
CIs	Confidential intervals
CR	Complete response
DCR	Disease control rates
dMMR	Mismatch repair deficiency
DOR	Duration of response
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	5-Level 5-dimensional EuroQol instrument
FAS	Full analysis set
HRQoL	Health-related quality of life
irAEs	Immune-related adverse events
ITT	Intent-to-treat
MMR	Mismatch repair
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
Muts/Mb	Mutations per megabase
ORR	Objective response rate
OS	Overall survival
PD	Disease progression
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PR	Partial response
PFS	Progression-free survival
Q3W	Every 3 weeks
QLQ-C30	Quality of Life Questionnaire Core 30
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SD	Stable disease
TRAEs	Treatment-related adverse events

Supplementary Information

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Additional file 1.

Additional file 2.

Additional file 3.

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Author contributions
WG, FB, WF, LL, and XK were instrumental in the design of the trial and provided essential administrative support. WF, FB, JC, CJ, ZX, WY, YH, DY, MS, TW, XY, RZ, KK, KW, ZW, WL, ZZ, HZ, QG, XW, LH, XZ, WS, LZ, JY, MW, WH, and ZL played key roles in the collection of materials and patient data. WF and BZ were actively involved in both data collection and analysis. BZ conducted the data analysis. FB, LL, and WG contributed significantly to the interpretation of the data.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All patients gave their written informed consent. The study was approved by the Ethics Committee of the Fudan University Shanghai Cancer Center in Shanghai on March 31th, 2020 and the Ethics Committee of the West China School of Medicine/West China Hospital of Sichuan University in Chengdu on April 15th, 2020. Informed consent was taken from all patients before participating in any study-related procedure.

Consent for publication
Not applicable.

Competing interests
Wenlei Feng, Baihui Zhang, Lingyan Li, and Xiaoyan Kang were employees of the Qilu Pharmaceutical Co. Ltd. Their involvement did not influence the integrity and objectivity of the research findings presented in this study. The authors declare no competing interests.

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