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Original Research

# Updated efficacy and safety of KEYNOTE-224: a phase II study of pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib

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**KEYWORDS**
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Long-term treatment

**Abstract** ***Objective:*** Pembrolizumab, a PD-1 inhibitor, demonstrated anti-tumour activity and tolerability in patients treated with sorafenib and with advanced hepatocellular carcinoma in KEYNOTE-224. Longer-term efficacy and safety after ~2.5 years of additional follow-up are reported.
***Patients and methods:*** Adults with confirmed hepatocellular carcinoma who experienced progression after or intolerance to sorafenib treatment received pembrolizumab 200 mg every 3 weeks for ≤35 cycles or until confirmed progression, unacceptable toxicity, withdrawal of consent or investigator decision. The primary end-point was objective response rate assessed by blinded independent central review per Response Evaluation Criteria in Solid Tumours v1.1. The secondary end-points included duration of response, disease control rate, time to progression, progression-free survival, overall survival and adverse events.
***Results:*** Efficacy and safety were assessed in 104 patients. The median time from first dose to data cutoff was 45.1 months (range, 41.3–49.3). Objective response rate was 18.3% (95% CI: 11.4–27.1), and median duration of response was 21.0 months (range, 3.1 to 39.5+). Disease control rate was 61.5%, and median time to progression was 4.8 months (95% CI: 3.9–7.0). Median progression-free survival was 4.9 months (95% CI: 3.5–6.7) and median overall survival was 13.2 months (95% CI: 9.7–15.3). Of 104 patients, 76 (73.1%) patients reported treatment-related adverse events; most were low grade in severity (grade 3–4, n = 26 [25.0%]; grade 5, n = 1 [1.0%]). Immune-mediated hepatitis occurred in 3 patients (all grade 3). No viral-induced hepatitis flares occurred.
***Conclusions:*** After ~2.5 years of additional follow-up, pembrolizumab continued to provide durable anti-tumour activity and no new safety concerns were identified.
***ClinicalTrials.gov identifier:*** NCT02702414.


## 1. Introduction

Liver cancer is one of the most frequently diagnosed malignancies, with hepatocellular carcinoma (HCC) accounting for ≥75% of cases [1]. Globally, HCC is a leading cause of cancer-related mortality [1,2]. Over time, advances in therapy have improved outcomes for some patients with HCC. Systemic treatment options in the first-line treatment setting for patients with advanced-stage HCC now include sorafenib [3], lenvatinib [4], and most recently bevacizumab plus atezolizumab [5]. For patients whose disease progresses on or who are unable to tolerate first-line treatment, second-line treatment options include regorafenib [6], cabozantinib [7], ramucirumab (in patients with an alpha fetoprotein level of ≥400 ng/mL) [8], and in the United States pembrolizumab [9,10], nivolumab [11], and nivolumab and ipilimumab [12].

Pembrolizumab, a programmed death-1 (PD-1) inhibitor, has shown clinical activity in patients with advanced HCC previously treated with sorafenib in the KEYNOTE-224 and KEYNOTE-240 studies [9,10]. In the phase II KEYNOTE-224 (NCT02702414) study, a substantial proportion of patients achieved an objective response (17%; 18/104) with pembrolizumab [9]. The safety profile of pembrolizumab was manageable, with most treatment-related adverse events (TRAEs) being grade 1–3. Similar findings were observed in the phase III KEYNOTE-240 (NCT02702401) study, despite the study not meeting pre-specified statistical criteria for the dual primary end-points of overall survival (OS) and progression-free survival (PFS) [10]. Here, we report efficacy and safety data for KEYNOTE-224 with ~2.5 years of additional follow-up, including outcomes for patients receiving a second course of pembrolizumab following disease progression after the first course of pembrolizumab.

## 2. Materials and methods

### 2.1. Study design and patients

KEYNOTE-224 (NCT02702414) was a non-randomised, multicentre, open-label phase II study [9]; results are presented for the second-line treatment setting (cohort 1).

Details of the study design, inclusion and exclusion criteria and primary results have been published [9]. In brief, eligible adults had a histologically or cytologically confirmed diagnosis of HCC, experienced documented progression after stopping treatment with sorafenib or experienced intolerance to sorafenib, and had Barcelona Clinic Liver Cancer stage C or B not amenable to or refractory to locoregional therapy and were not amenable to a curative treatment (Supplementary Materials). Patients with past or ongoing hepatitis C virus (HCV) or controlled hepatitis B virus (HBV) infection were eligible if protocol-defined criteria were met. HBV-positive was defined as HBsAg positive and/or HBV DNA detectable or anti-HBc positive, HBsAg negative and HBV DNA not detectable. HCV-positive was defined as either HCV RNA detectable and/or anti-HCV-positive.

Patients received pembrolizumab 200 mg intravenous infusion once every 3 weeks for ≤35 cycles or until confirmed progression/unacceptable toxicity, patient withdrawal of consent or investigator decision (Supplementary Materials).

The study protocol and all amendments were approved by the relevant ethics committee or institutional review board at each participating centre, and the study was conducted in accordance with standards of Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent.

### 2.2. Assessments and end-points

Response was assessed once every 9 weeks, measured according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) and assessed based on blinded independent central review (BICR) and investigators. The primary end-point was objective response rate (ORR) assessed by BICR per RECIST v1.1. The secondary end-points included duration of response (DOR), disease control rate (DCR), time to progression (TTP) and PFS all assessed by BICR per RECIST v1.1, OS, safety and tolerability (Supplementary Materials).

### 2.3. Statistical analysis

ORR and DCR (point estimates and 95% confidence intervals [CIs]) were evaluated by the binomial exact test. DOR, TTP, PFS and OS were estimated by the Kaplan–Meier method. An exploratory post hoc landmark analysis of OS after the first scan on treatment was performed to compare responders with non-responders at first scan.

## 3. Results

### 3.1. Patients

In KEYNOTE-224, 104 patients received ≥1 dose of pembrolizumab at the final analysis [9]. Baseline demographics and clinical characteristics were previously published [9]. The aetiology of HCC according to investigator assessment among patients uninfected with HBV or HCV was non-alcoholic steatohepatitis in 4 patients, diabetes mellitus in 28 patients and alcoholic liver disease in 4 patients, though patients may have had overlapping aetiologies. Among the treated patients, 10 patients completed treatment (Supplementary Fig. 1). The remaining 94 patients discontinued therapy. The primary reasons for discontinuation were PD in 61 patients and AEs in 24 patients. Four patients received a second course of pembrolizumab.

### 3.2. Response

At data cutoff (31st July 2020), the median time from the first dose to data cutoff was 45.1 months (range, 41.3–49.3) and the median duration of exposure was 4.2 months (range, 0.0–38.4). An objective response by BICR per RECIST v1.1 was recorded in 19 of 104 patients (18.3%; 95% CI: 11.4–27.1; Table 1). Overall, 3.8% (n = 4) of patients achieved a BOR of CR, 14.4% (n = 15) achieved a PR, 43.3% (n = 45) had stable disease (SD), and 32.7% (n = 34) had PD. DCR by BICR per RECIST v1.1 was 61.5% (95% CI: 51.5–70.9). At follow-up, the ORR by BICR per mRECIST was 16.3% (17/104), 18.3% (19/104) by BICR per irRECIST, and 13.5% (14/104) by investigator assessment per RECIST v1.1 (Table 1). The median time to response by BICR per RECIST v1.1 among responders was 2.1 months (range, 1.5–18.4). The response duration of ≥24 months as estimated by BICR per RECIST v1.1 was observed in 5 patients. Among those who achieved a response, DOR is shown in Fig. 1a. At data cutoff, 2 of the 19 responses were ongoing (both PR) and the longest response was 39.5+ months. Median DOR by BICR per RECIST v1.1 was 21.0 months (range, 3.1 to 39.5+; Table 1, Fig. 1b), and the Kaplan–Meier estimate for patients with a DOR of ≥12 months was 77.0% (Table 1).

Generally similar proportions of patients achieved confirmed ORR in pre-specified subgroups based on baseline demographics and clinical characteristics, including risk factors for poor prognosis (Fig. 2). Reductions from baseline in target lesion size were observed in 51 (49%) patients treated with pembrolizumab (Supplementary Fig. 2). Among the 60 patients who were uninfected with HBV or HCV, 32 (53%) patients had reductions from baseline in target lesion size, and among those infected with HCV (n = 25) or HBV (n = 21), 10 (40%) patients and 12 (57%) patients, respectively, had reductions from baseline in tumour target lesion size. After discontinuation of pembrolizumab, 43 patients (41.3%) received anti-cancer therapy (Supplementary Table 1).

Table 1
Response to pembrolizumab (N = 104).

| | BICR (RECIST v1.1) | BICR (mRECIST) | BICR (irRECIST) | Investigator (RECIST v1.1) |
|---|---|---|---|---|
| ORR (CR + PR), n (%; 95% CI) | 19 (18.3; 11.4–27.1) | 17 (16.3; 9.8–24.9) | 19 (18.3; 11.4–27.1) | 14 (13.5; 7.6–21.6) |
| BOR, n (%) [a] | | | | |
| CR | 4 (3.8) | 6 (5.8) | 4 (3.8) | 1 (1.0) |
| PR | 15 (14.4) | 11 (10.6) | 15 (14.4) | 13 (12.5) |
| SD | 45 (43.3) | 35 (33.7) | 53 (51.0) | 38 (36.5) |
| PD | 34 (32.7) | 47 (45.2) | 26 (25.0) | 47 (45.2) |
| Non-evaluable | 1 (1.0) | – | 1 (1.0) | – |
| No assessment [b] | 5 (4.8) | 5 (4.8) | 5 (4.8) | 5 (4.8) |
| DCR (CR + PR + SD), n (%; 95% CI) [c] | 64 (61.5; 51.5–70.9) | 52 (50.0; 40.0–60.0) | 72 (69.2; 59.4–77.9) | 52 (50.0; 40.0–60.0) |
| Median time to response, months (range) [d] | 2.1 (1.5–18.4) | 2.1 (1.5–18.6) | 2.1 (1.5–18.4) | 3.0 (2.0–6.2) |
| Median DOR, months (range)[d,e,f] | 21.0 (3.1–39.5+) | 25.8 (3.1–39.4+) | 26.0 (3.1–39.5+) | 28.1 (3.1–39.0+) |
| DOR ≥12 months, n (%)[d,e] | 13 (77.0) | 11 (69.7) | 13 (77.0) | 9 (71.4) |

BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; irRECIST, immune-related Response Evaluation Criteria in Solid Tumours; mRECIST, modified Response Evaluation Criteria in Solid Tumours for HCC; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease.
[a] Confirmed best response by BICR per RECIST v1.1.
[b] Patients without post-baseline assessment on the data cutoff date were considered not assessable for BOR.
[c] DCR includes CR, PR, and SD.
[d] Assessed in patients who had a BOR as confirmed CR or PR.
[e] From product-limit (Kaplan–Meier) method for censored data.
[f] "+" indicates that there is no progressive disease by the time of the last disease assessment.

### 3.3. PFS and OS

With extended follow-up, 95 of the 104 (91.3%) patients had died or had disease progression per BICR. The median PFS by BICR per RECIST v1.1 was 4.9 months (95% CI: 3.5–6.7; Fig. 3a). At 24 months, the PFS rate was 11.3% (95% CI: 6.0–18.5). The median TTP by BICR per RECIST v1.1 was 4.8 months (95% CI: 3.9–7.0; Fig. 3b). The estimated 24-month TTP rate was 21.8% (95% CI: 12.0–33.5). The median PFS by BICR per mRECIST was 3.1 months (95% CI: 2.2–4.1) and 6.7 months (95% CI, 4.9–8.0) by BICR per irRECIST; the 24-month PFS rate was 12.5% (95% CI: 6.9–19.7) and 14.3% (95% CI: 8.2–21.9), respectively. The median PFS by investigator assessment per RECIST v1.1 was 3.1 months (95% CI: 2.1–4.2); the 24-month PFS rate was 10.6% (95% CI: 5.6–17.3). The median TTP by BICR per mRECIST, by BICR per irRECIST and investigator assessment per RECIST v1.1 as well as 12- and 24-month TTP rates are shown in Supplementary Table 2.

As of the data cutoff, 86 of the 104 (82.7%) patients in the study had died; the median OS was 13.2 months (95% CI: 9.7–15.3; Fig. 4). The 24-month OS rate was 30.8% (95% CI: 22.2–39.7). In a landmark analysis for OS after the first scan on treatment for responders versus non-responders at first scan (from first scan falling between days 40 and 77), the median OS was not reached (95% CI: 10.7–not reached) among responders and was 10.3 months in non-responders (95% CI: 7.3–12.5; Supplementary Fig. 3). The hazard ratio was 0.28 (95% CI: 0.11–0.69).

### 3.4. Efficacy by second course

Four patients received a second course of pembrolizumab; 1 achieved a CR and 3 achieved a PR as the BOR on the first course of therapy. The DOR in the first course of therapy was 26.0 months for the patient who achieved a CR and 5.9 months, 16.6 months and 18.6 months for the 3 patients who achieved a PR. All patients had PD by BICR and/or investigator assessment. The interval from the last dose in the first course to the first dose in the second course was 19.2 months for the patient who achieved a CR in the first course, and 1.6 months, 9.5 months and 6.7 months for the 3 patients who achieved PR in first course. The BOR on the second course of therapy was PR (investigator assessment per irRECIST v1.1 [n = 1]), SD (investigator assessment per RECIST v1.1 [n = 1]; investigator assessment per irRECIST v1.1 [n = 1]) and PD (investigator assessment per RECIST v1.1 [n = 1]). In the second course of therapy, scans are not routinely centrally read; thus, based on investigator assessment, the DOR for the patient with a PR was 10.4 months, the TTP for the 2 patients with SD was 10.4 months and 4.1 months, and the TTP for the 1 patient with PD was 1.9 months.

### 3.5. Safety

Of the 104 patients, 76 (73.1%) patients reported TRAEs of any grade, with most being of low grade in severity (grade 3–4, n = 26 [25.0%]; grade 5, n = 1 [1.0%];

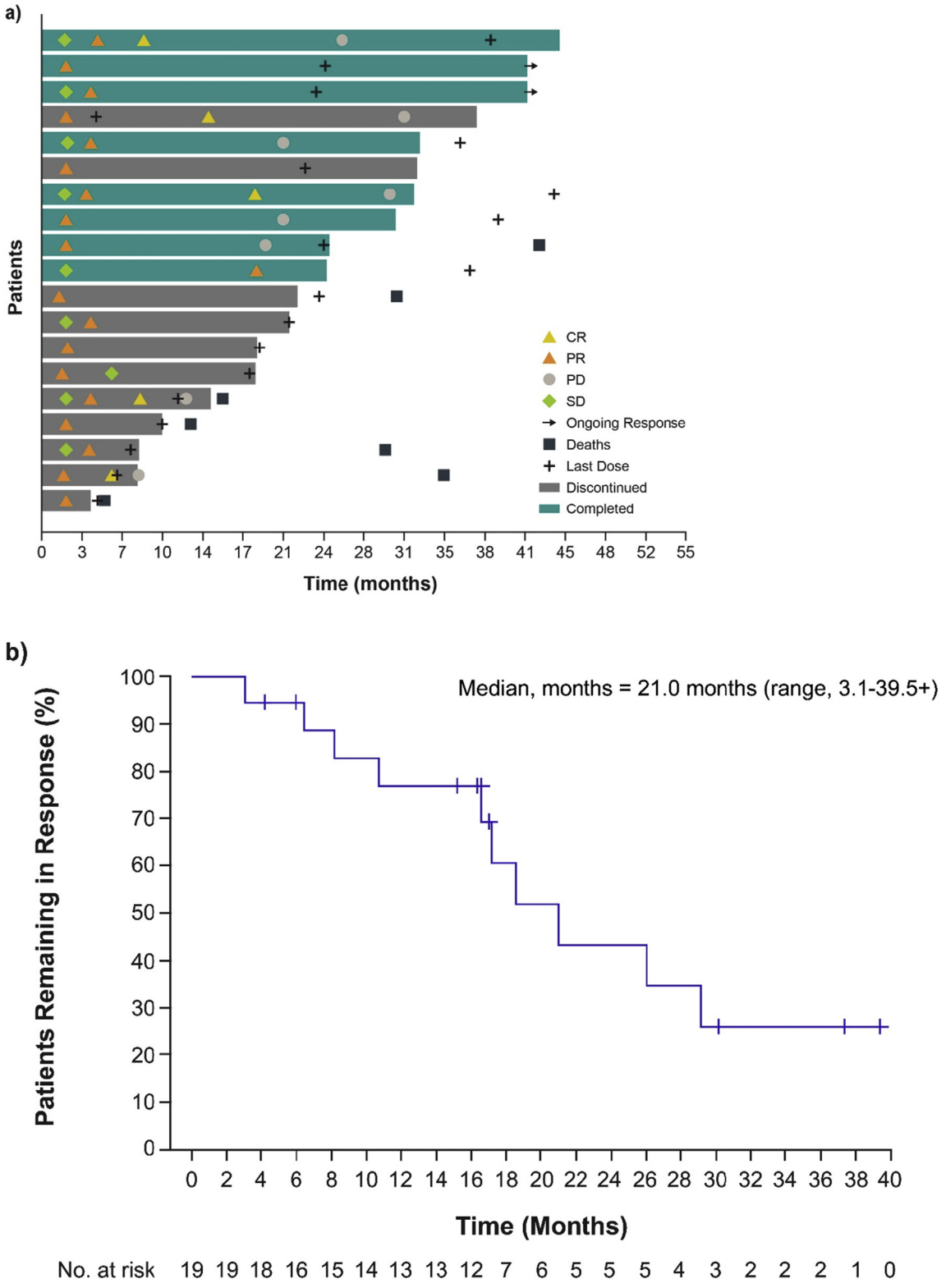


Fig. 1. Tumour response assessed by BICR per RECIST v1.1. (**a**) Response and duration for the 19 responders with a BOR of confirmed CR or PR only. Symbols for CRs, PRs and PD are the time each response was first reported (not BOR). Each bar represents an individual patient, and the length of each bar represents the time from the start of treatment to the last radiographic assessment. 'Completed' refers to completion of study medication. (**b**) Duration of response in the 19 patients who had a BOR of confirmed CR or PR estimated by the Kaplan–Meier method for censored data. '+' indicates no PD at the time of the last disease assessment. BICR, blinded independent central review; BOR, best overall response; CR, complete response; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease.

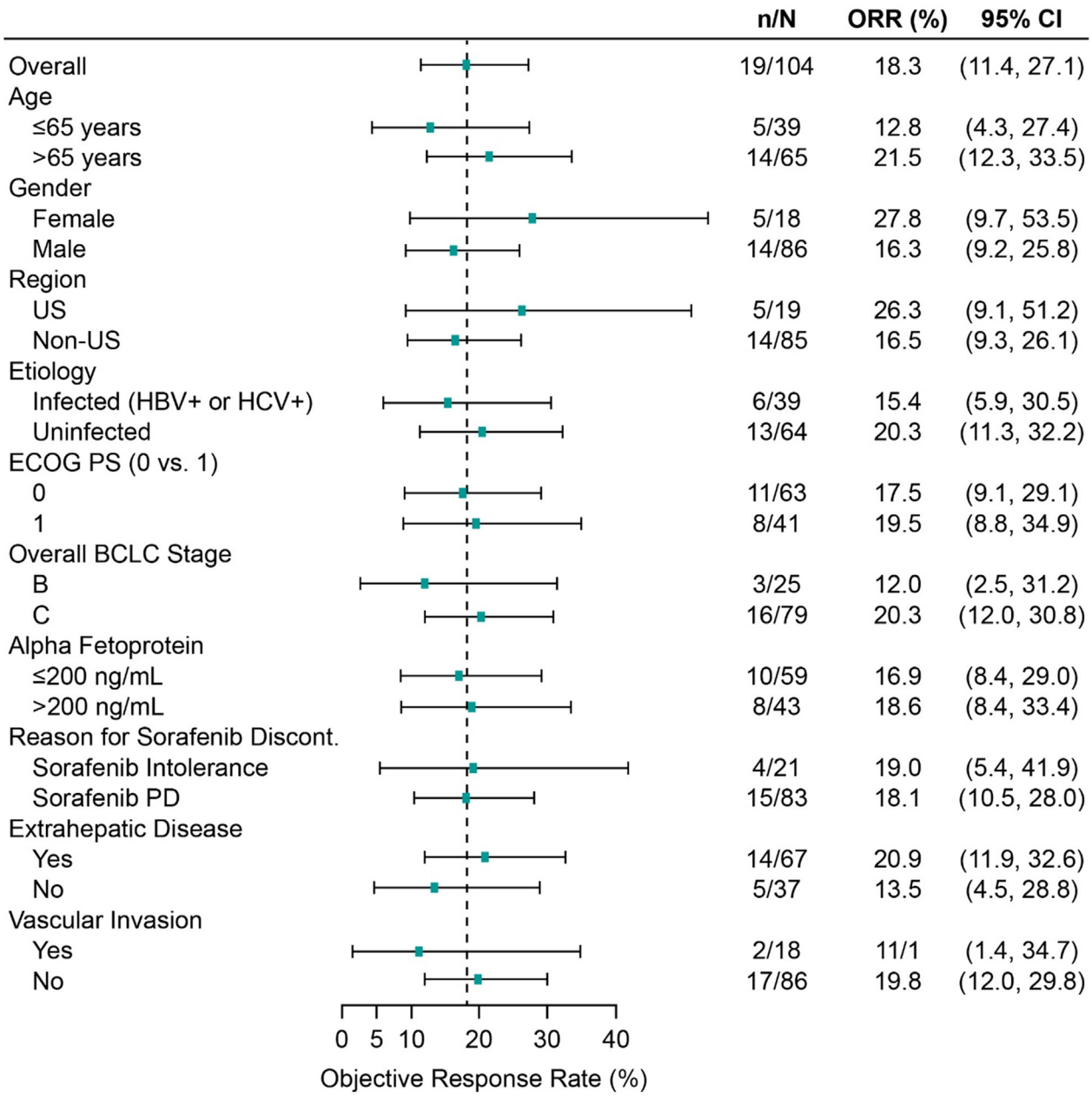


Fig. 2. Subgroup analysis of ORRs. Data are for all patients (N = 104) in the as-treated population assessed by BICR per RECIST v1.1. BCLC, Barcelona Clinic Liver Cancer; BICR, blinded independent central review; CI, confidence interval; discont., discontinued; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV+, hepatitis B virus–positive; HCV+, hepatitis C virus–positive; ORR, objective response rate; PD, progressive disease; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1.

Table 2). The most common AEs were fatigue (n = 31 [29.8%]), increased aspartate aminotransferase level (n = 26 [25.0%]), pruritus (n = 24 [23.1%]) and nausea (n = 21 [20.2%]). One death (bleeding attributed to esophagitis) was considered possibly due to a TRAE by the investigator. Sponsor-assessed immune-mediated hepatitis occurred in 3 (2.9%) patients, and all were grade 3 in severity. No viral hepatitis flare events were reported. A total of 5 (4.8%) patients discontinued due to TRAEs. TRAEs leading to discontinuation included adrenal insufficiency (n = 1, grade 3), gastroesophageal reflux disease (n = 1, grade 5), cholestatic jaundice (n = 1, grade 3), increased alanine aminotransferase level (n = 1, grade 3), increased aspartate aminotransferase level (n = 1, grade 3) and increased blood bilirubin (n = 1, grade 2).

## 4. Discussion

After ~2.5 years of additional follow-up in the KEYNOTE-224 study, pembrolizumab continued to provide durable anti-tumour activity and improvement

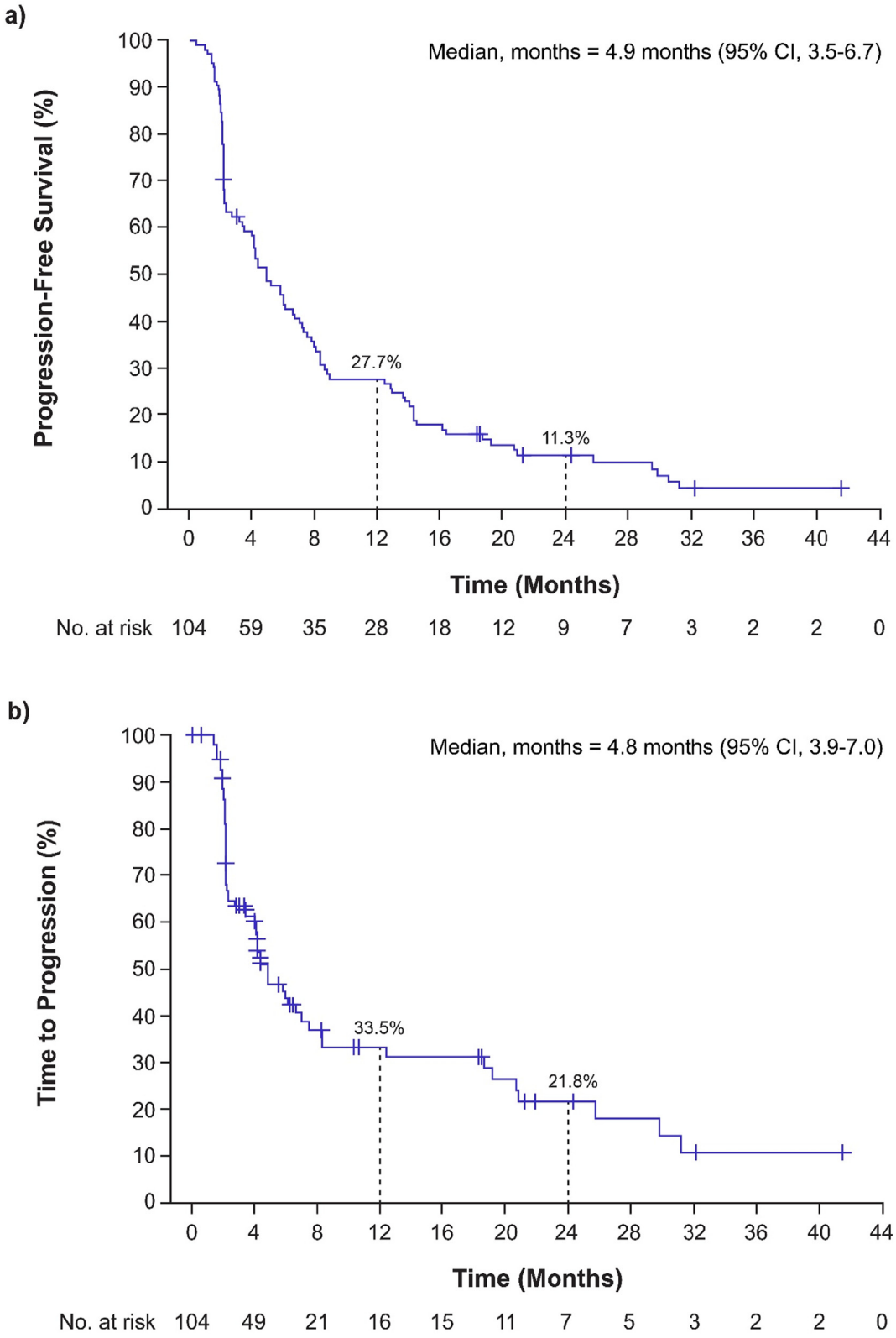


Fig. 3. Progression-free survival (PFS) and time to progression. (**a**) PFS in the all-patients-as-treated population by the Kaplan–Meier method per RECIST v1.1 by BICR. (**b**) TTP in the all-patients-as-treated population by the Kaplan–Meier method, per RECIST v1.1 by BICR, where TTP is defined as time from first dose to the first disease progression. BICR, blinded independent central review; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TTP, time to progression.

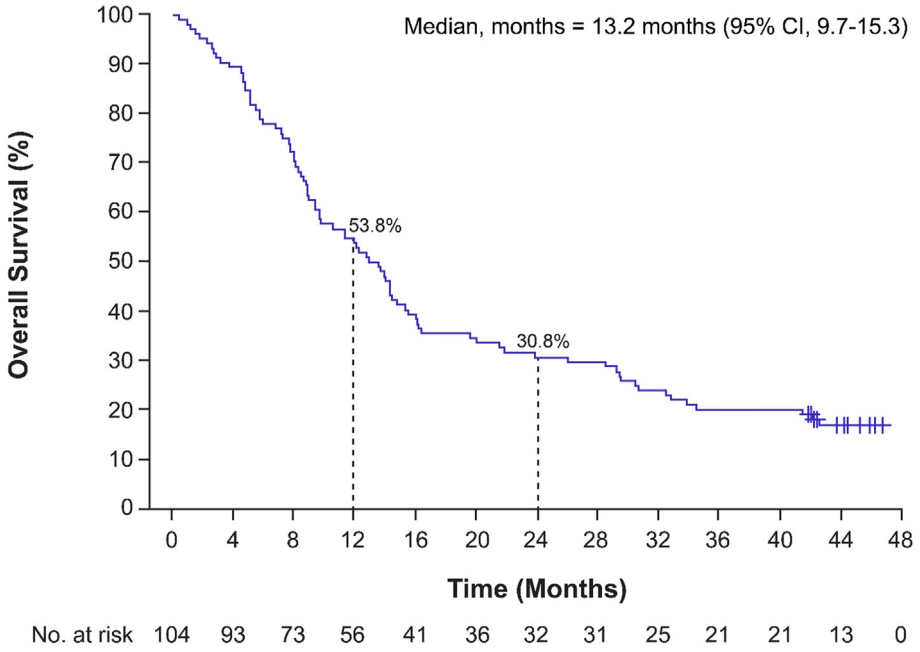


Fig. 4. Estimates of overall survival in the all-patients-as-treated population by the Kaplan–Meier method.

in BOR in patients with advanced HCC previously treated with sorafenib. The proportion of patients who achieved a CR increased compared with the primary analysis (3.8% versus 1.0%) [9]. The median DOR was 21 months, and 77% of patients had response lasting ≥12 months by Kaplan–Meier analysis. The exploratory end-points ORR, DOR, DCR, TTP and PFS assessed by BICR per irRECIST, investigator per RECIST v1.1 and by BICR per mRECIST were generally similar to those observed when assessed by BICR per RECIST v1.1. The estimated 24-month OS rate was 30.8%. In a landmark analysis, OS after the first on-treatment imaging assessment was substantially longer among those who achieved a response at the first assessment than those who did not. OS by BOR category was not evaluated because of the inherent bias associated with such an analysis; however, the analysis indicates that objective response in patients treated with pembrolizumab is associated with longer survival. Overall, pembrolizumab was well tolerated. The safety profile was consistent with the primary analysis with no change in frequency of sponsor-assessed immune-mediated hepatitis events in the period following final analysis. In addition, no cases of hepatitis B or C viral flare were observed.

These results are comparable to the magnitude of benefit observed in the double-blind, randomised phase III KEYNOTE-240 study, which evaluated a similar population of patients [10]. KEYNOTE-240 evaluated pembrolizumab plus best supportive care (BSC) compared with placebo plus BSC in patients with advanced HCC who experienced progression during or after treatment with sorafenib or were intolerant to sorafenib [10]. After a median follow-up (defined as time from randomisation to death or data cutoff, whichever is earlier) of 14 months, the ORR was 18.3% for pembrolizumab plus BSC, which is consistent with the current analysis (18.3%). In KEYNOTE-240, median OS was 13.9 months and median PFS was 3.0 months for pembrolizumab plus BSC; these results are similar to the median OS (13.2 months) and median PFS (4.9 months) observed here. The difference in PFS between KEYNOTE-240 and the current study may be partially attributed to a lower scan frequency (every 6 versus 9 weeks, respectively) [13]. The safety profile of pembrolizumab plus BSC was also comparable between KEYNOTE-240 and the current analysis. Most TRAEs were of low grade (grade ≥3: KEYNOTE-240, 19%; current analysis, 26%) and generally similar to those of pembrolizumab in other tumour types [14]. This is the first report of longer-term efficacy and safety for pembrolizumab in patients with advanced HCC previously treated with sorafenib, and the results suggest that pembrolizumab efficacy is durable and safety does not worsen with additional follow-up.

The results presented here are similar to those observed in the dose expansion cohort of the CheckMate 040 study for nivolumab monotherapy, which yielded an ORR of 14% with 32% of responders demonstrating response duration of ≥24 months [15]. At a minimum follow-up of 44 months in a separate cohort of the CheckMate 040 study examining nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) combination therapy, the ORR was 32%, which is slightly higher than the ORR reported here for pembrolizumab (18.3%) [12,16]. Median DOR with nivolumab (1 mg/kg) plus ipilimumab

Table 2
Adverse events (AEs; N = 104).

| AE, n (%) | Any | Grade 3 | Grade 4 |
|---|---|---|---|
| Treatment-related[a] | | | |
| ≥1 AE | 76 (73.1) | 25 (24.0) | 1 (1.0) |
| Occurring in ≥5% of patients (any attribution) | | | |
| Fatigue | 31 (29.8) | 6 (5.8) | 0 |
| Increased aspartate aminotransferase level | 26 (25.0) | 14 (13.5) | 1 (1.0) |
| Pruritus | 24 (23.1) | 0 | 0 |
| Nausea | 21 (20.2) | 1 (1.0) | 0 |
| Cough | 20 (19.2) | 0 | 0 |
| Peripheral oedema | 20 (19.2) | 1 (1.0) | 0 |
| Arthralgia | 18 (17.3) | 0 | 0 |
| Constipation | 18 (17.3) | 1 (1.0) | 0 |
| Diarrhoea | 17 (16.3) | 1 (1.0) | 0 |
| Abdominal pain | 16 (15.4) | 3 (2.9) | 0 |
| Asthenia | 16 (15.4) | 4 (3.8) | 0 |
| Ascites | 16 (15.4) | 9 (8.7) | 0 |
| Decreased appetite | 16 (15.4) | 3 (2.9) | 0 |
| Increased alanine aminotransferase level | 15 (14.4) | 7 (6.7) | 0 |
| Rash | 14 (13.5) | 1 (1.0) | 0 |
| Anaemia | 13 (12.5) | 5 (4.8) | 1 (1.0) |
| Dyspnoea | 12 (11.5) | 2 (1.9) | 0 |
| Upper abdominal pain | 10 (9.6) | 0 | 0 |
| Increased blood bilirubin | 10 (9.6) | 4 (3.8) | 1 (1.0) |
| Vomiting | 9 (8.7) | 1 (1.0) | 0 |
| Back pain | 8 (7.7) | 2 (1.9) | 0 |
| Hypothyroidism | 8 (7.7) | 0 | 0 |
| Myalgia | 8 (7.7) | 1 (1.0) | 0 |
| Headache | 7 (6.7) | 0 | 0 |
| Hyperkalaemia | 7 (6.7) | 3 (2.9) | 1 (1.0) |
| Insomnia | 7 (6.7) | 0 | 0 |
| Increased blood alkaline phosphatase level | 6 (5.8) | 0 | 0 |
| Muscle spasms | 6 (5.8) | 0 | 0 |
| Night sweats | 6 (5.8) | 0 | 0 |
| Productive cough | 6 (5.8) | 0 | 0 |
| Decreased weight | 6 (5.8) | 0 | 0 |
| AE of special interest, immune-mediated (any attribution)[b] | | | |
| Hypothyroidism | 8 (7.7) | 0 | 0 |
| Adrenal insufficiency | 3 (2.9) | 2 (1.9) | 0 |
| Thyroiditis | 2 (1.9) | 0 | 0 |
| Colitis | 2 (1.9) | 0 | 0 |
| Severe skin reaction | 1 (1.0) | 1 (1.0) | 0 |
| Hyperthyroidism | 1 (1.0) | 0 | 0 |
| Type 1 diabetes mellitus | 1 (1.0) | 1 (1.0) | 0 |
| Hepatic[c] | | | |
| Immune-mediated | 3 (2.9) | 3 (2.9) | 0 |
| Viral flare | 0 | 0 | 0 |

Patients are counted a single time for each applicable specific AE and may have >1 TRAE. AEs are listed in decreasing frequency.
[a] AEs attributed to treatment by investigator.
[b] AEs based on presumed immunological mechanism of action.
[c] Based on sponsor assessment; includes 3 AEs initially reported as increased aspartate and alanine aminotransferase levels, determined to be immune-mediated hepatitis by sponsor.

(3 mg/kg) combination therapy was also similar to that reported here for pembrolizumab (18 months versus 21 months, respectively) [16]. The rates of grade 3–5 TRAEs were lower with pembrolizumab monotherapy (26%) than nivolumab plus ipilimumab (53%) [16]. These data further support the benefit-risk ratio for pembrolizumab as second-line treatment for HCC.

Although KEYNOTE-224 confirms the durable antitumour activity and tolerability of pembrolizumab, the results are limited by the phase II, open-label and single-arm design. Ongoing phase III studies are evaluating pembrolizumab in patients with HCC in the adjuvant treatment setting (KEYNOTE-937; NCT03867084); first-line treatment setting in combination with lenvatinib (LEAP-002; NCT03713593); second-line treatment setting, specifically in the Asia Pacific region (KEYNOTE-394; NCT03062358) and in combination with lenvatinib and transarterial chemoembolization (LEAP-012; NCT04246177). Recently, the KEYNOTE-394 study met its primary end-point showing statistically significant and clinically meaningful improvement in OS with pembrolizumab plus BSC compared with placebo plus BSC as a second-line therapy for patients from Asia with advanced HCC [17]. After a median follow-up of 34 months, median (95% CI) OS was 15 (13–18) months for pembrolizumab versus 13 (11–15) months for placebo (hazard ratio, 0.79; 95% CI: 0.63–0.99; $p = 0.0180$). Significant improvement in the secondary end-points PFS and ORR was also observed. Median PFS was 2.6 months for pembrolizumab versus 2.3 months for placebo (hazard ratio, 0.74; 95% CI: 0.60–0.92; $p = 0.0032$) and ORR was 12.7% versus 1.3%, respectively ($p < 0.0001$). AEs were consistent with previous reports. These results expand on previous findings from KEYNOTE-240 [10], a globally conducted study of similar design, inclusion/exclusion criteria, and end-points and support the favourable benefit-to-risk profile of pembrolizumab in patients with previously treated advanced HCC.

## 5. Conclusion

Extended follow-up from KEYNOTE-224 demonstrated that pembrolizumab provides robust and durable efficacy in patients with advanced HCC who were previously treated with sorafenib. Taken together with the consistent safety profile for pembrolizumab, this report confirms the favourable benefit-risk of pembrolizumab in this population.

## Role of the funding source

The study sponsor, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, funded the study. Additionally, the study sponsor

designed the study protocol in collaboration with the Steering Advisory Committee.

## Prior presentation

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## Data availability and materials

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymised data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

## Author contributions

**M. Kudo** substantially contributed to the acquisition of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content; **R. S. Finn** substantially contributed to the conception, design, or planning of the study, analysis of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content; **J. Edeline** substantially contributed to the acquisition of the data and critically reviewing or revising the manuscript for important intellectual content; **S. Cattan** substantially contributed to the interpretation of the results and critically reviewing or revising the manuscript for important intellectual content; **S. Ogasawara** substantially contributed to acquisition of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content; **D. Palmer** substantially contributed to the interpretation of the results and critically reviewing or revising the manuscript for important intellectual content; **C. Verslype** substantially contributed to the acquisition of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content; **V. Zagonel** substantially contributed to the acquisition of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content; **L. Fartoux** substantially contributed to the interpretation of the results and critically reviewing or revising the manuscript for important intellectual content;**A. Vogel** substantially contributed to the acquisition of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content; **D. Sarker** substantially contributed to the analysis of the data, acquisition of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content; **G. Verset** substantially contributed to the acquisition of data and critically reviewing or revising the manuscript for important intellectual content; **S.L. Chan** substantially contributed to the acquisition of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content; **J. Knox** substantially contributed to the conception, design, or planning of the study, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content; **B. Daniele** substantially contributed to the interpretation of the results and critically reviewing or revising the manuscript for important intellectual content; **T. Yau** substantially contributed to analysis of the data, acquisition of the data, and critically reviewing or revising the manuscript for important intellectual content; **E.B. Gurary** substantially contributed to the analysis of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content; **A.B. Siegel** substantially contributed to conception, design, or planning of the study, analysis of the data, interpretation of the results, drafting the manuscript, and critically reviewing or revising the manuscript for important intellectual content; **A. Wang** substantially contributed to the analysis of the data, drafting of the manuscript, and

critically reviewing or revising the manuscript for important intellectual content; **A-L Cheng** substantially contributed to the conception, design, or planning of the study, acquisition of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content; **A.X. Zhu** substantially contributed to the conception, design, or planning of the study, acquisition of the data, interpretation of the results, and critically reviewing or revising the manuscript for important intellectual content.

## Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **M. Kudo** has received a grant and fees from Eisai, and Bristol Myers Squibb; has received fees from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and Eli Lilly; has served a consultant for Bayer, Eisai, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Roche, Bristol Myers Squibb, and Ono; and has received a grant from Otsuka, Taiho, EA Pharma, Takeda, Gilead, AbbVie, and Sumitomo Dainippon Pharma; **R.S. Finn** has received fees and a grant to his institution from Merck, Bayer, Eli Lilly, Bristol Myers Squibb, Eisai, Pfizer, Roche/Genentech; and has received fees from AstraZeneca and CStone; **J. Edeline** has received personal fees from Bayer, Bristol Myers Squibb, AstraZeneca, Eisai, Ipsen, Boston Scientific, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; and has received grants from Bristol Myers Squibb, BeiGene, and Boston Scientific; **S. Cattan** has nothing to disclose; **S. Ogasawara** has received a grant and fees from Bayer, Eisai, Eli Lilly; and has received fees from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, AstraZeneca, and Chugai; **D. Palmer** has received a grant and fees from Bristol Myers Squibb, NuCana Inc, and Sirtex; has received a grant from AstraZeneca; and has received fees from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Roche, and Eisai; **C. Verslype** has received a grant from Baye and Ipsen and has served as a consultant for Bayer, Ipsen, and Roche; **V. Zagonel** has served in an advisory capacity or as a consultant for Bristol Myers Squibb and Merck; has served as a speaker for Bayer, Roche, Bristol Myers Squibb, Astellas Pharma, SERVIER, AstraZeneca, Eli Lilly; and has received travel, accommodations, and expenses from Bayer, Roche, and SERVIER; **L. Fartoux** has no conflicts of interest to report. **A. Vogel** has received fees for serving in an advisory capacity/consultant, has received speaking fees, has received fees for expert testimony, and has received honoraria from AstraZeneca, Bayer, Bristol Myers Squibb, BTG, Eli Lilly, Incyte Corporation, Ipsen, Janssen, Merck, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Novartis, Pierre Fabre, Roche, Sanofi, and Servier; **D. Sarker** has received fees from Eisai, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, AstraZeneca, Bayer, and Surface Oncology; has received fees and non-financial support from Ipsen; has received non-financial support from MiNA Therapeutics; and has received a grant from Roche; **G. Verset** has received a grant from Terumo; has served as a consultant for Terumo and BTG; has served in an advisory capacity for Bayer, Eisai, and Roche; and has received travel expenses for attending congresses from Bayer, Bristol Myers Squibb, and Ipsen; **S.L. Chan** has participated as an advisor for AstraZeneca; **J. Knox** has received a grant for an investigator-initiated study from Merck; and has received fees for consulting from Merck, Ipsen, and Roche; **B. Daniele** has received fees from Ipsen, Eisai, Eli Lilly, AstraZeneca, Sanofi, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Bayer, Roche, and Amgen; and has received non-financial support from Ipsen, Bristol Myers Squibb; **T. Yau** has received fees for serving in an advisory capacity or as a consultant and has received honoraria from Bristol Myers Squibb, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Exelixis, Ipsen, Eisai, AstraZeneca, Bayer, Novartis, EMD Serono, AbbVie, Pfizer, Eli Lilly, Sirtex, SillaJen, Taiho, OrigiMed, New Beta Innovation, Sirtex, and H3 Biomedicine; **E.B. Gurary** and **A. B. Siegel** are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; **A. Wang** is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and has stock in Merck & Co., Inc., Kenilworth, NJ, USA; **A-L Cheng** has received fees for consulting from AstraZeneca, Bristol Myers Squibb, Eisai, Merck Serono, Novartis, Ono Pharmaceutical, Exelixis, Nucleix, Ipsen Innovation, Bayer Healthcare, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Roche/Genentech, BeiGene, CSR Pharma Group, F Hoffmann-La Roche, and IQVIA; has received travel support from Roche/Genentech, IQVIA, and Bayer Yakuhin; and has received speaker fees from Eisai, Novartis, Ono Pharmaceutical, Bayer Yakuhin, and Amgen Taiwan; **A.X. Zhu** has received fees for consulting from Merck, Eli Lilly, Bayer, Sanofi, Eisai, Exelixis, and Roche.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.02.009.

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