ABSTRACT

Objectives The non-randomised, open-label, phase IIIb/IV multicohort CheckMate 920 trial explored the safety and efficacy of first-line nivolumab plus ipilimumab alternating with nivolumab monotherapy in patients with advanced renal cell carcinoma: the non-randomised, open-label, phase IIIb/IV CheckMate 920 trial. BMJ Open 2022;12:e058396. doi:10.1136/bmjopen-2021-058396

Setting Patients were enrolled from 48 largely community-based sites in the USA.

Participants 106 patients with previously untreated, predominantly clear cell aRCC received treatment.

Interventions Patients received NIVO 6 mg/kg plus IPI 1 mg/kg on day 1 of the first week of each 8-week cycle; the combination alternated with NIVO 480 mg monotherapy on day 1 of the fifth week of each 8-week cycle. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent or study end. The maximum treatment duration was 2 years. The primary endpoint was the incidence of high-grade (grade 3/4 and grade 5) immune-mediated adverse events (IMAEs) within 100 days of the last dose. Select secondary endpoints included time to onset and resolution of high-grade IMAEs, progression-free survival (PFS) and objective response rate (ORR). The incidence of treatment-related adverse events and the overall survival (OS) were the exploratory endpoints.

Results The most common grade 3/4 IMAEs were diarrhoea/colitis (7.5%) and rash (6.6%) and no grade 5 IMAEs occurred, with a minimum follow-up of 28.5 months. The median PFS was 4.8 (95% CI 3.0 to 8.3) months, the ORR in evaluable patients (n=96) was 34.4% (95% CI 25.0 to 44.8), and the median OS was not reached (95% CI 24.8 months to not estimable).

Conclusions While no new safety signals were reported with less frequent, but continual nivolumab plus ipilimumab dosing regimen, the modified regimen was not associated with clinical benefits relative to the approved NIVO+IPI dose. These results support the continued use of the currently approved NIVO+IPI combination dosing schedule for patients with aRCC.

Trial registration number NCT02982954.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The non-randomised, open-label, phase IIIb/IV multicohort trial explored the safety and efficacy with a less frequent, but continual nivolumab plus ipilimumab dosing regimen to determine whether this modification could potentially retain the efficacy benefits while further improving on the manageable safety profile previously observed with this combination in patients with advanced renal cell carcinoma (aRCC), helping to answer an important clinical question.

⇒ The trial was purposely conducted in a large community-based setting in order to better understand the tolerability of this alternative dosing regimen in a real-world context.

⇒ Direct cross-trial comparisons are not possible as there are a number of notable differences in the study design and research setting in this trial versus randomised clinical trials.

BACKGROUNDSafety and efficacy of first-line nivolumab plus ipilimumab alternating with nivolumab monotherapy in patients with advanced renal cell carcinoma: the non-randomised, open-label, phase IIIb/IV CheckMate 920 trial

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Received 19 October 2021
Accepted 14 June 2022

BMJ Open. First published as 10.1136/bmjopen-2021-058396 on 14 September 2022. Downloaded from http://bmjopen.bmj.com/ on September 23, 2023 by guest. Protected by copyright.
III CheckMate 214 trial. Patients in CheckMate 214 received NIVO (3 mg/kg) plus IPI (1 mg/kg) every 3 weeks for four doses followed by NIVO monotherapy (3 mg/kg) every 2 weeks (later modified to 240 mg every 2 weeks or 480 mg every 4 weeks per protocol amendment). The combination dosing schedule approved by the US Food Drug Administration (FDA) and the European Medicines Agency (EMA) is NIVO (3 mg/kg) plus IPI (1 mg/kg) every 3 weeks for four doses followed by NIVO monotherapy (either 240 mg every 2 weeks or 480 mg every 4 weeks). Overall survival (OS) and objective response rate (ORR) benefits were observed with NIVO+IPI versus sunitinib (SUN) in both IMDC intermediate-risk/poor-risk and intent-to-treat (ITT) patients. Treatment-related adverse events (AEs) occurred in 93% of patients in the NIVO-IPI arm and 97% in the SUN arm; grade 3 or 4 events occurred in 46% and 63% of patients, respectively. Looking at safety events by 6-month interval with extended follow-up in CheckMate 214, the incidence of both treatment-related AEs and treatment-related select (potentially immune-mediated) AEs was highest within the first 6 months of treatment with NIVO+IPI before decreasing substantially over time.

The phase IIIb/IV CheckMate 920 trial (NCT029982954) explored the safety and efficacy outcomes with a less frequent, but continual NIVO+IPI dosing regimen to determine if this modification could potentially retain the efficacy benefits while further improving on the manageable safety profile previously observed with this combination in patients with aRCC.

**METHODS**

CheckMate 920 is a largely community-based, multicohort, open-label, phase IIIb/IV trial. Phase IIIb/IV trials typically are conducted at or after the time of approval, and are intended to increase patient exposure and are driven by the needs of the industry (ie, evaluation of new indications, new comparators, different efficacy endpoints or different patient subpopulations). Modified NIVO+IPI dosing was evaluated in cohort 1 and is reported here (figure 1). Outcomes with standard NIVO+IPI dosing in patients with aRCC with clinical features mostly excluded from phase III studies were assessed in cohorts 2, 3 and 4 (data not reported here). Adults with previously untreated predominantly clear cell aRCC (advanced: not amenable to curative surgery or radiation therapy; or metastatic; American Joint Committee on Cancer stage IV disease) were included in cohort 1. Patients had histologically confirmed and measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST V.1.1) and Karnofsky performance status of at least 70%, and any IMDC risk score was permitted.

Patients were treated with NIVO 6 mg/kg plus IPI 1 mg/kg on day 1 of the first week of each 8-week cycle; the combination alternated with NIVO 480 mg monotherapy on day 1 of the fifth week of each 8-week cycle. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent or end of study. The maximum treatment duration was 2 years. Patients were permitted to continue treatment beyond RECIST v.1.1-defined progression under protocol-defined circumstances. No dose modifications were allowed for either NIVO or IPI. Patients who discontinued treatment due to an AE were eligible to receive NIVO monotherapy (480 mg every 4 weeks), contingent on medical monitor approval.

The primary objective for cohort 1 was to assess the incidence of high-grade (grade 3/4 and grade 5; National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.0) immune-mediated adverse events (IMAEs) in all treated patients. The secondary safety objective was to characterise the outcome of high-grade IMAEs (endpoints included median time to onset and median time to resolution of IMAEs, and high-grade IMAE management inclusive of the percentage of patients who received immune-modulating medication). Select secondary efficacy objectives included progression-free survival (PFS), ORR (complete response [CR] +

Figure 1 CheckMate 920 study design. One prior adjuvant or neoadjuvant therapy for completely resectable RCC was allowed if it did not include checkpoint inhibitors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy. ccRCC, clear cell renal cell carcinoma; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IPI, ipilimumab; KPS, Karnofsky performance status; nccRCC, non-clear cell carcinoma; NIVO, nivolumab; OS, overall survival; Q3W, every 3 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.
Table 1  Select baseline characteristics

| Baseline characteristics       | All treated patients (n=106) |
|-------------------------------|------------------------------|
| Median age (range), years     | 64.5 (40–84)                 |
| Sex, n (%)                    |                              |
| Male                          | 86 (81.1)                    |
| Female                        | 20 (18.9)                    |
| IMDC risk group, n (%)        |                              |
| Favourable                    | 21 (19.8)                    |
| Intermediate                  | 65 (61.3)                    |
| Poor                          | 20 (18.9)                    |
| Race, n (%)                   |                              |
| White                         | 104 (98.1)                   |
| Black or African American     | 1 (0.9)                      |
| Other                         | 1 (0.9)                      |
| KPS, n (%)                    |                              |
| 100                           | 36 (34.0)                    |
| 90                            | 45 (42.5)                    |
| 80                            | 24 (22.6)                    |
| 70                            | 1 (0.9)                      |
| Sarcomatoid features, n (%)   |                              |
| Yes                           | 12 (11.3)                    |
| No                            | 93 (87.7)                    |
| Not reported                  | 1 (0.9)                      |
| Disease stage at study entry, n (%) |                       |
| III                           | 2 (1.9)                      |
| IV                            | 104 (98.1)                   |
| Number of disease sites, n (%)|                              |
| 1                             | 5 (4.7)                      |
| ≥2                            | 101 (95.3)                   |
| Most common sites of disease, n (%) |                   |
| Visceral lung                 | 56 (52.8)                    |
| Lymph node                    | 43 (40.6)                    |
| Kidney                        | 41 (38.7)                    |
| Visceral liver                | 26 (24.5)                    |
| Visceral adrenal              | 16 (15.1)                    |
| Quantifiable tumour PD-L1 expression, n (%) |            |
| <1%                           | 83 (86.5)                    |
| ≥1%                           | 13 (13.5)                    |

Information shown in the table is based on data collected using electronic case report forms. *Patients may have more than one site.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance status; PD-L1, programmed death ligand 1.

The planned sample size was determined largely by the feasibility concern and based on the incidence of high-grade IMAEs with NIVO+IPI from other trials in patients with aRCC and non-small cell lung cancer. Given the values reported in the selected trials of combination treatment of approximately 40%–60% high-grade IMAEs, the estimated half-width of the 95% CI of high-grade IMAE rates between 9.3% and 9.8% for 100 participants was considered to be within an acceptable degree of precision.14 15

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George DJ, et al. BMJ Open 2022;12:e058396. doi:10.1136/bmjopen-2021-058396

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Results

Overall, 124 patients were enrolled in cohort 1, and 106 patients with predominantly clear cell aRCC received treatment. The enrolment period lasted from January 2017 to March 2018, and the last patient was enrolled on 9 February 2018; the results presented here are based on a cut-off date of 3 March 2020, with a minimum follow-up for OS of 28.5 months. The median age was 64.5 (range, 40–84) years, 81.1% of patients were male, 98.1% were white, 98.1% had stage IV disease at study entry, 11.3% had sarcomatoid features, and 19.8% had IMDC favourable-risk, 61.3% had intermediate-risk and 18.9% had poor-risk disease (table 1).

No patients continued treatment as of the cut-off date; the most common reasons for discontinuation were disease progression (58.5%) and study drug toxicity (18.9%). The median (range) duration of treatment was 5.1 (0–26.1) months for NIVO and 4.0 (0–25.7) months for IPI; overall, patients received a median (range) of 6.0 (1–26) doses of NIVO and 3.0 (1–13) doses of IPI. Unlike the approved dosing for NIVO+IPI in first-line aRCC, IPI was not limited to four doses in this trial and 40.6% of patients received more than four doses of IPI (online supplemental table S1).

The incidence of grade 3/4 IMAEs was low for each organ category and no grade 5 IMAEs were reported (table 2).

The most common grade 3/4 IMAEs reported in at least 5% of patients were diarrhoea/colitis (7.5%)
and rash (6.6%). Time to onset and time to resolution of IMAEs are summarised in Table 3. Overall, 33.0% of patients received corticosteroid treatment (≥40 mg prednisone or equivalent) to manage IMAEs; 21.7% of patients were treated for ≥14 days and 6.6% of patients were treated for ≥30 days. The median duration of corticosteroid treatment (≥40 mg prednisone or equivalent) to manage IMAEs was 3.0 weeks. Non-endocrine IMAEs that required the use of corticosteroid treatment (≥40 mg prednisone or equivalent) included pneumonitis in 2 patients, diarrhoea/colitis in 14 patients, hepatitis in 7 patients, nephritis/renal dysfunction in 2 patients, hyper-sensitivity in 4 patients and rash in 15 patients. Endocrine IMAEs that required corticosteroid treatment (≥40 mg prednisone or equivalent) for management included adrenal insufficiency in five patients, thyroiditis in one patient and hypophysitis in three patients.

Most of the any-grade IMAEs reported were treatment-related, non-serious, and did not result in discontinuation of NIVO+IPI. Treatment-related AEs of any grade occurred in 94 patients (88.7%); grade 3/4 treatment-related AEs occurred in 46 patients (43.3%; table 2). Fatigue (46.2%) was the most frequently reported any-grade treatment-related event. Treatment-related AEs of any grade leading to discontinuation were reported in 30 patients (28.3%; table 2).

A total of 44 patients (41.5%) died, of whom 4 (3.8%) died within 30 days after the last dose. The most common cause of death was disease progression, and one patient died from study drug toxicity (myasthenia gravis was cited as the cause of death; complete heart block and refractory hypotension were cited as potential causes).

PFS probabilities in all treated patients (n=106) were 28.7% (95% CI 20.0 to 37.9) at 12 months and 15.9% (95% CI 9.2 to 24.2) at 24 months, and the median PFS was 4.8 (95% CI 3.0 to 8.3) months (figure 2A). The ORR was 34.4% (95% CI 25.0 to 44.8) and the CR rate was 5.2% in evaluable patients (n=96; figure 2B); the clinical benefit rate was 63.5% (95% CI 53.1 to 73.1). The median TTR was 2.9 (range, 2.5–36.9) months, the median DOR was 9.2 (95% CI 6.0 to 22.9) months, and 14 of 33 responders (42.4%) had an ongoing response. The median OS was

| IMAE by category | Median (range) time to onset, weeks | Median (range) time to resolution, weeks |
|------------------|------------------------------------|----------------------------------------|
|                  | Any grade                          | Grade 3/4                              | Any grade                          | Grade 3/4                              |
| Rash             | n=27                               | 5.3 (0.3–80.4)                         | n=17                               | 12.6 (1.9–156.1)                      |
|                  |                                     | 4.0 (1.1–80.4)                         | n=2                                | NR (5.3–126.9+)                       |
| Hypothyroidism and thyroiditis† | n=21                 | 12.1 (2.3–25.1)                        | n=0                                | –                                   |
|                  |                                     | 21.4 (1.9–115.7)                       | n=5                                | NR (3.7–156.7+)                       |
| Adrenal insufficiency† | n=9                           | 33.9 (16.1–54.0)                      | n=4                                | NR (0.4–130.6+)                       |
|                  |                                     | 51.4 (21.0–54.0)                       | n=2                                | 0.7 (0.4–89.0+)                       |
| Hyperthyroidism† | n=8                                | 6.3 (4.0–39.1)                         | n=0                                | –                                   |
|                  |                                     | 8.4 (2.0–82.1)                         | n=8                                | 12.1 (5.1–134.7+)                     |
|                  |                                     | 3.0 (NC)                               | n=1                                | 3.0 (NC)                             |
| Diabetes mellitus† | n=6                          | 29.1 (4.3–58.6)                        | n=4                                | NR (0.4–141.3+)                       |
|                  |                                     | 13.6 (4.3–39.1)                        | n=2                                | NR (0.4–141.3+)                       |
| Hypersensitivity | n=6                                | 4.8 (4.0–8.1)                          | n=0                                | –                                   |
|                  |                                     | 0.1 (0.1–0.1)                          | n=6                                | –                                   |
| Pneumonitis       | n=3                                | 12.7 (11.1–64.0)                      | n=1                                | 14.9 (0.9–17.3)                      |
|                  |                                     | 12.7 (NC)                              | n=1                                | 0.9 (NC)                             |
| Hypophysitis†    | n=3                                | 33.9 (25.9–52.7)                      | n=0                                | –                                   |
|                  |                                     | 16.4 (3.7–29.1)                        | n=2                                | –                                   |
| Nephritis and renal dysfunction | n=2          | 6.0 (4.7–7.3)                          | n=0                                | –                                   |

*Includes events reported between the first dose and 100 days after last dose of study therapy. Time to onset was calculated from the first dosing date to the IMAE event onset date. Time to resolution was calculated from the IMAE onset date to IMAE end date. Events without a stop date or with a stop date equal to the date of death were considered unresolved. For each patient, the longest duration of IMAEs where immune-modulating medication was initiated is considered.
†Considered endocrine IMAEs.
+ Censored value; IMAE, immune-mediated adverse event; NC, not calculated; NR, not reached.
not reached (95% CI 24.8 months to not evaluable) in all treated patients (n=106), and OS probabilities were 78.1% (95% CI 68.9 to 84.9) at 12 months and 62.2% (95% CI 52.1 to 70.8) at 24 months (figure 2C).

DISCUSSION
A modified, continual, less frequent NIVO+IPI dosing regimen was explored in CheckMate 920 cohort 1 to describe the safety and efficacy outcomes relative to the approved NIVO+IPI dosing regimen established in CheckMate 214 to determine whether this modification could potentially retain the efficacy benefits while further improving on the manageable safety profile previously observed with this combination. The modified NIVO dosing regimen (6mg/kg every 8 weeks, alternating with a 480mg dose every 8 weeks, staggered by 4 weeks) was anticipated to provide a similar average steady-state plasma concentration exposure compared with the NIVO dose (3mg/kg every 2 weeks) administered in CheckMate 214. The modified IPI dosing regimen (1mg/kg every 8 weeks) was administered with prolonged intervals to allow for a lower probability of cumulative safety events versus the IPI schedule in CheckMate 214 (1mg/kg every 3 weeks). Patients received a maximum of four doses of IPI in CheckMate 214, whereas patients were able to continue IPI beyond four doses, as tolerated, in CheckMate 920. Finally, patients who discontinued IPI due to an AE were permitted to continue NIVO treatment as a monotherapy in CheckMate 920, unlike CheckMate 214.

The modified NIVO+IPI regimen was similarly tolerable to the standard regimen. Grade 3/4 IMAEs were infrequent (0%–7.5% for each category) and were manageable in the present study using established guidelines. Any-grade treatment-related AEs were reported in 89% of patients in the present study; 43% had grade 3/4 treatment-related AEs and 28% discontinued due to treatment-related AEs. For reference, any-grade treatment-related AEs were reported in 94% of patients in the NIVO+IPI arm; 47% had grade 3/4 treatment-related AEs and 22% discontinued due to treatment-related AEs after a comparable 30-month minimum follow-up in CheckMate 214. Overall, the modified regimen was not associated with safety benefits relative to the approved NIVO+IPI dose based on the safety profile observed in the CheckMate 214 trial.

In regard to efficacy, we observed a median PFS of 4.8 months (24-month PFS probability was 16%) with the modified NIVO+IPI regimen, ORR was 34% (5% achieved CR) and the median OS was not reached (24-month OS probability was 62%). For context, in CheckMate 214, the median PFS was 9.7 months (24-month PFS probability was 31%), ORR was 41% (11% achieved CR) and the median OS was not reached (24-month OS probability was 71%) with NIVO+IPI inITT patients after a comparable 30-month minimum follow-up.

Cross-trial comparisons should be made with caution and there are some inherent limitations associated with the CheckMate 920 study design and research setting versus randomised clinical trials. Unlike CheckMate 214, CheckMate 920 was purposely conducted in a large community-based setting in order to better understand the tolerability of this alternative dosing regimen in a real-world context. This distinction cannot be overstated as we have seen a wide disparity in outcomes associated with vascular endothelial growth factor receptor tyrosine kinase inhibitor use in prospective real-world settings compared with historical clinical trial data. Additional differences between this trial and CheckMate 214 include the study phase (IIIb/IV vs III), randomisation (no vs yes), arm (single vs comparative) and population size (106 vs 550).

There are currently several other ongoing phase II trials of NIVO+IPI in renal cell carcinoma (RCC) that are evaluating alternative dosing regimens. The phase II response-adaptive trial, Optimized Management of Nivolumab and Ipilimumab in Advanced Renal Cell Carcinoma (OMNIVORE) (NCT03203473), enrolled patients...
with metastatic RCC with no prior checkpoint inhibitor exposure (n=83). All patients received NIVO alone with subsequent arm allocation based on response, and either discontinued NIVO and were observed or received two doses of IPI. This study found that NIVO followed by two doses of IPI in patients without an objective response to NIVO monotherapy results in no complete responses and a low response conversion rate. The data did not support a response-adaptive strategy for checkpoint blockade in aRCC, and upfront dual checkpoint blockade was still recommended in patients eligible to receive this treatment. Another ongoing, prospective, single-stage, single-arm, multicentre phase II trial (NCT03297593) is evaluating the outcomes associated with reducing IPI in the combination treatment of metastatic RCC (mRCC). Patients begin treatment with NIVO (240mg every 2 weeks until week 20, then 480mg every 4 weeks thereafter). After 2 weeks, IPI 1mg/kg every 6 weeks is initiated. As soon as a radiographic CR or PR is observed, IPI is discontinued and NIVO is continued for a maximum of 2 years. Preliminary data suggest that this approach is non-inferior to the regimen evaluated in CheckMate 214. An additional phase II randomised study is evaluating multiple administration regimens for NIVO+IPI in patients with aRCC (CheckMate 800; NCT03029780). Patients are treated with either NIVO+IPI combination therapy or NIVO and IPI sequentially. Results have not yet been published.

Overall, the modified NIVO+IPI regimen evaluated in CheckMate 920 cohort 1 was associated with a similar safety profile relative to the approved dosing schedule, with a clinical benefit rate of 63.5%, suggesting that NIVO+IPI can benefit a broad selection of patients in real-world settings. Taken together, these results support the continued use of the NIVO+IPI standard dosing schedule approved by the FDA and EMA for patients with aRCC based on the CheckMate 214 trial results.

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Acknowledgements
The authors would like to acknowledge the patients and families who made this study possible; the clinical study teams who participated in the study; Dako, an Agilent Technologies company, for collaborative development of the PD-L1 immunohistochemistry 28-8 pharmDx assay (Santa Clara, California, USA); Bristol Myers Squibb (Princeton, New Jersey, USA) and Ono Pharmaceutical Company (Osaka, Japan); and the contributions of Nicole Thompson as protocol manager. Writing and editorial assistance was provided by Jen Tyson, PhD, of Parexel.

Contributors
All authors contributed to the data analysis and interpretation, drafting and reviewing of the manuscript, and provided final approval to submit the manuscript for publication. DJG, ARK, TEH: conceptualisation, investigation, writing - original draft, writing - review and editing. DLS, LNG, STK, AMM, JY, HM, NT, SST: investigation, writing - original draft, writing - review and editing. JZ: conceptualisation, data curation, writing - original draft, writing - review and editing. MA: data curation, formal analysis, writing - original draft, writing - review and editing. JLJ: conceptualisation, methodology, writing - original draft, writing - review and editing. DJG - guarantor.

Funding
This work was supported by Bristol Myers Squibb. Writing and editorial assistance was provided by Jen Tyson, PhD, of Parexel, funded by Bristol Myers Squibb.

Competing interests
DJG reports consulting or advisory roles from Bayer, Exelixis, Pfizer, Sanofi, Astellas Pharma, Innocin Pharma, Bristol Myers Squibb (BMS), Genentech, Janssen, Merck Sharp & Dohme, Myovant Sciences, AstraZeneca, Michael J Hennessy Associates, Vizuri and Constellation Pharmaceuticals; leadership from Capio Biosciences; speakers bureau from Sanofi, Bayer and Exelixis; travel, accommodations and expenses from Bayer, Exelixis, Merck, Pfizer, Sanofi, Janssen Oncology and UroToday; honoraria from Sanofi, Bayer, Exelixis, EMD Serono, OnLive, Pfizer, UroToday, Acceleron Pharma, American Association for Cancer Research, Axxess Oncology, Janssen Oncology and Millennium Medical Publishing; and research funding (all institution) from Exelixis, Janssen Oncology, Novartis, Pfizer, Astellas Pharma, BMS, Acerta Pharma, Bayer, Dendreon, Innocin Pharma, Calithera Biosciences and Sanofi/Aventis. DRS reports consulting or advisory roles (all institution) from Amgen, AstraZeneca, BMS, Curio Science, EMD Serono, Evidera, Exelixis, GlaxoSmithKline, Intellisphere, Ipsen Biopharmaceuticals, Janssen, Jazz Pharmaceuticals, Lilly, Mirati Therapeutics, Molecular Templates, Novartis, Novocure, Pfizer, Puma Biotechnology, Regeneron Pharmaceuticals, Roche/Genentech and Sanofi/Aventis; and research funding (all institution) from Avegia BioTherapeutics, Agios, Apollonics, Arcus, Arrys Therapeutics, Astellas, AstraZeneca, Bayer, BeGene, BIND Therapeutics, BioNTech RNA Pharmaceuticals, Blueprint Medicine, Boehringer Ingelheim, BMS, Calithera, Celgene, Celldex, Clovis, Cyteir Therapeutics, Daiichi Sankyo, Denovo Biopharma, Eisai, Elevation Oncology, EMD Serono, Evelope Biosciences, G1 Therapeutics, Roche/Genentech, GlaxoSmithKline, GPRAL, Hutchison MediPharma, ImClone Systems, Incyte, ImmunoGen, Ipsen, Janssen, Kronos Bio, Lilly, Loxo Oncology, MacroGenics, MedImmune, Merck, Molecular Partners, Molecular Template, Nektar, Neon Therapeutics, Novartis, Novocure, Oncology, Pfizer, PTC Therapeutics, PureTech Health, Razor Genomics, Repare Therapeutics, Rgenix, Takeda, Tesaro, Tizona Therapeutics, Transgene, UT Southwestern and Versartem. LNG reports employment from Florida Medical Clinic; leadership from Florida Cancer Specialists; honoraria from Ameris Pharma; consulting or advisory role from Janssen Oncology; and speakers bureau from Myriad Genetics. STK has no conflicts of interests to disclose. AMM reports consulting or advisory roles (all institution) from Ameris Pharma; consulting or advisory role from Janssen Oncology; and honoraria from the American Society of Clinical Oncology. JY reports consulting or advisory roles from BMS, Janssen and Lanthus. ARK reports remuneration for a consulting or advisory roles from Exelixis, AstraZeneca, Bayer, Pfizer, Novartis, Genentech, BMS and EMD Serono; speakers bureau from Janssen, Astellas Mediation, Pfizer, Novartis, Sanofi, Genentech/Roche, Eisai, AstraZeneca, BMS, Amgen, Exelixis, EMD Serono, Merck and Seattle Genetics/Astellas; travel, accommodations and expenses from Genentech, Promethius, Astellas Mediation, Janssen, Eisai, Bayer, Pfizer, Novartis, Exelixis and AstraZeneca; stock ownership from ECDM Medical; and research funding (all institution) from Genentech, Exelixis, Janssen, AstraZeneca, Bayer, BMS, Eisai, MacroGenics, Astellas Pharma, BeyondSpring Pharmaceuticals, BioCin Therapeutics, Clovis Oncology, Bavarian Nordic, Seattle Genetics, Immunomedics and Epizyme. HM has no conflicts of interests to disclose. NT reports consulting or advisory roles from Agen, InsiMed and Foundation Medicine. SST reports consulting or advisory roles from Merck, Intellisphere, Natera, BMS and Exelixis; patent pending (institution); and research.
funding (all institution) from Genentech, BMS, Merck, Calithera Biosciences, Pfizer, Jounce Therapeutics, Nektar, Exelixis and Clingen Group. JZ reports employment and stock ownership from BMS. MA reports employment from BMS. JLI reports employment and stock ownership from BMS. TEH reports employment from Texas Oncology; consulting or advisory roles from Bayer/Onyx, Pfizer, Novartis, Astellas Pharma, Johnson & Johnson, BMS, Eisai and Exelixis; speakers bureau from Pfizer, Johnson & Johnson, Eisai, Exelixis, Astellas Pharma and BMS; honoraria from Pfizer, Astellas Pharma, BMS, Exelixis, Eisai, Novartis, Johnson & Johnson and Bayer/Onyx; and research funding (all institution) from Pfizer, Johnson & Johnson, Exelixis, Eisai and BMS.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was conducted in accordance with Good Clinical Practice (GCP), as defined by the International Council for Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21 CFR 50). This trial was approved by the independent ethics committees and/or institutional review boards at each site. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Bristol Myers Squibb’s policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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