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Original Research

Safety and efficacy of durvalumab in patients with head and neck squamous cell carcinoma: results from a phase I/II expansion cohort

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Abstract ***Introduction:*** Durvalumab selectively blocks programmed cell death ligand-1 (PD-L1) binding to programmed cell death-1. Encouraging clinical activity and manageable safety were reported in urothelial carcinoma, non–small-cell lung cancer (NSCLC), hepatocellular carcinoma (HC) and small-cell lung cancer (SCLC) in a multicenter phase I/II study. Safety and clinical activity in recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) were evaluated in the expansion phase.

Methods: Patients received 10 mg/kg of durvalumab intravenously every 2 weeks for 12 months or until confirmed progressive disease or unacceptable toxicity. The primary objective was safety; clinical activity was a secondary objective.

Results: Sixty-two patients were enrolled and evaluable (received first dose ≥24 weeks before data cutoff). Median age was 57 years; 40.3% were human papillomavirus (HPV)-positive; 32.3% had tumour cell PD-L1 expression ≥25%, and 62.9% were current/former smokers. They had a median of 2 prior systemic treatments (range, 1–13). All-causality adverse events (AEs) occurred in 98.4%; drug-related AEs occurred in 59.7% and were grade III–IV in 9.7%. There were no drug-related discontinuations or deaths. Objective response rate (blinded independent central review) was 6.5% (15.0% for PD-L1 ≥25%, 2.6% for <25%). Median time to response was 2.7 months (range, 1.2–5.5); median duration was 12.4 months (range, 3.5–20.5+). Median progression-free survival was 1.4 months; median overall survival (OS) was 8.4 months. OS rate was 62% at 6 months and 38% at 12 months (42% for PD-L1 ≥25%, 36% for <25%).

Conclusions: Durvalumab safety in HNSCC was manageable and consistent with other cohorts of the study. Early, durable responses in these heavily pretreated patients warrant further investigation; phase III monotherapy and combination therapy studies are ongoing.

Clinical trial registry: clinicaltrials.gov NCT01693562; MedImmune study 1108.

1. Introduction

Immunotherapeutic approaches have demonstrated clinical benefit in head and neck squamous cell carcinoma (HNSCC) [1–3]. High mutational burden due to tobacco usage or expression of human papillomavirus (HPV)–associated viral antigens may contribute to immunogenicity in HNSCC tumours [4–6]. However, HNSCC tumours are thought to inhibit immune activity by different mechanisms, including T-cell suppression and downregulation of molecules that promote antigen processing and T-cell recognition [7]. Programmed cell death-1 (PD-1) receptor is a key immune checkpoint receptor on activated T cells. Binding of PD-1 to programmed cell death ligand-1 (PD-L1) inhibits T-cell proliferation and activation [8]. PD-L1 binding to CD80 on T cells also downregulates activation and expansion [9]. Cancer cells can upregulate PD-L1 expression to protect themselves from tumour-specific T cells [8]. PD-1 expression is elevated in tumour infiltrating lymphocytes and PD-L1 expression is increased in HNSCC metastases compared with non-cancerous tissue, suggesting that the PD-1/PD-L1 axis is active in these tumours [10,11].

Durvalumab is a high-affinity human IgG1 monoclonal antibody that selectively blocks PD-L1 binding to PD-1 and CD-80/B7.1 [12]. Its safety, tolerability, pharmacokinetics, immunogenicity and antitumour activity in adults with advanced solid tumours were evaluated in a phase I/II global, multicenter, open-label, first-in-human dose-escalation and expansion study (NCT01693562). Encouraging clinical activity and manageable safety were observed in the urothelial carcinoma, non-small cell lung cancer, hepatocellular carcinoma and small-cell lung cancer cohorts [13–17]. Here, we report safety and efficacy in the HNSCC expansion cohort.

2. Methods

2.1. Study design and participants

Enrolment into the expansion phase began on 10th September 2013. Eligible patients were aged ≥18 years, had histologically or cytologically confirmed recurrent/metastatic HNSCC incurable with local therapy, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and ≥1 measurable lesion per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 criteria [18].

Archived unstained tumour tissue samples were required at the baseline for pharmacodynamic analyses; if unavailable, fresh tumour biopsies were performed. The samples were retrospectively analysed using the VENTANA BenchMark ULTRA PD-L1 (SP263) immunohistochemical assay [19]. PD-L1 expression by

tumour cells was determined by the percentage of cells with membranes staining positive for PD-L1 at any intensity. Samples were classified as PD-L1 ≥25% or <25% expression. The protocol required enrolment of at least 5–10 patients with PD-L1 expression ≥25%, which was achieved without needing to select patients.

Prior cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor therapy was permitted. Patients with active autoimmune disease, prior or persistent severe immune-related adverse events (AEs) or previous exposure to any anti–PD-1 or anti–PD-L1 antibody therapy were excluded.

The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council on Harmonization and Good Clinical Practice guidelines. The study protocol was reviewed and approved by the institutional review board/independent ethics committee of participating centres, and informed consent was obtained from all patients.

2.2. Study procedures and treatment

Patients received 10 mg/kg of durvalumab intravenously once every 2 weeks (q2w). Treatment continued for 12 months or until confirmed progressive disease (PD), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent or discontinuation for other reasons (Supplemental Fig. S1). Patients with confirmed PD could continue durvalumab in the absence of clinical deterioration and if investigators deemed that they might benefit from it. Antitumour activity was assessed by computed tomography or magnetic resonance imaging at the baseline and at 6, 12 and 16 weeks and every 8 weeks thereafter. Patients who achieved and maintained disease control (complete response [CR], partial response [PR], or stable disease [SD]) through the end of the 12-month treatment period entered follow-up.

Patients with PD after the initial 12-month treatment could resume durvalumab treatment, per original dosing guidelines, for up to 12 months. Patients with confirmed PD during the initial treatment or retreatment period who did not continue to receive durvalumab entered a follow-up for 90-day safety and survival assessments.

2.3. Study outcomes

The primary end-point of the dose-expansion phase was safety and tolerability, evaluated by AEs, serious AEs (SAEs) and other health parameters using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03 [20]. AEs of special interest (AESIs) were also assessed, defined as events of scientific and medical interest specific to the further understanding of durvalumab's safety profile and requiring close monitoring, and immune-mediated adverse events (imAEs), defined as AESIs requiring systemic steroids, endocrine therapy or other immunosuppressants, which are consistent with an immune-mediated mechanism and have no clear alternate aetiology.

The secondary study endpoints were antitumour activity, pharmacokinetics and immunogenicity. Assessment of antitumour activity included objective response rate (ORR), disease control rate (DCR24), duration of response (DoR) and progression-free survival (PFS) per blinded independent central review (BICR) as per the RECIST 1.1 criteria and overall survival (OS). ORR was defined as the proportion of patients with confirmed CR or PR. DCR24 was defined as the proportion of patients with CR, PR or SD ≥ 24 weeks. DoR was defined as the duration from the first documentation of objective response to the first documented PD or death due to any cause. Immunogenicity was summarized as the percentage of patients who developed detectable antibodies against durvalumab. The as-treated population included all patients who received any dose of durvalumab. The full analysis set (FAS) included treated patients with measurable disease at the baseline by BICR and an opportunity to be followed for ≥24 weeks before the data cutoff. Statistical analysis methods are summarized in the Supplemental Information.

3. Results

3.1. Patient disposition, baseline characteristics and treatment exposure

By the data cutoff (October 16, 2017), 62 patients were treated in the dose-expansion phase. Baseline demographics and disease characteristics are described in Table 1 (as-treated population) and Supplemental Table S1 (FAS population). Median age in the as-treated population was 57 years, 85.5% of patients were male, 61.3% had an ECOG performance status of 1, 40.3% were HPV positive (12/25 of whom were current/former smokers, including one with a history of using smokeless tobacco, and 13/25 were never smokers), 32.3% had tumour cell PD-L1 expression ≥25% and 62.9% were current/former smokers. Of those with PD-L1 expression ≥25%, 6/20 (30%) were HPV positive and 11/20 (55%) were HPV negative. They had a median of two prior systemic treatments (range, 1–13); few patients (n = 2 [3.2%] overall, both of whom were in the PD-L1 <25% group) had received prior immunotherapy.

Overall, 11.3% of patients completed 12 months of treatment. Treatment was not completed due to PD in 67.7%, death in 6.5%, patient request in 4.8%, withdrawal of consent in 3.2%, AE in 3.2% and investigator discretion in 3.2%. Patients received a median of six doses (range, 1–27). Median duration of the follow-up was 43.0 months (range, 1.4–49.2).

Table 1
Baseline demographics and disease characteristics (as-treated population).

Characteristic	Durvalumab (N = 62)
Median age, years (range)	57.0 (24–96)
Sex, n (%)	
Male	53 (85.5)
Female	9 (14.5)
TC PD-L1 expression, n (%)	
≥25%	20 (32.3)
<25%	39 (62.9)
Unknown[a]	3 (4.8)
HPV status, n (%)	
HPV positive	25 (40.3)
HPV negative	25 (40.1)
Unknown[b]	12 (19.4)
Tobacco use, n (%)	
Never smoked	23 (37.1)
Former/current smoker	39 (62.9)
ECOG PS, n (%)	
0	23 (37.1)
1	38 (61.3)
Prior systemic therapy regimens, n (%)	
1	16 (25.8)
2	17 (27.4)
3	15 (24.2)
≥4	14 (22.6)
Median (range)	2 (1–13)
Prior therapy with cetuximab, n (%)	26 (41.9)

ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papilloma virus; PD-L1, programmed cell death ligand-1:TC, tumour cell.
[a] PD-L1 status was not determined due to missing or non-evaluable tumour tissue samples.
[b] Documented HPV status was not available at baseline.

3.2. Safety and tolerability

All-causality AEs occurred in 98.4% of patients and were grade III–IV in 51.6%. All-causality AEs (hypotension and hypercalcaemia) led to discontinuation in 3.2% and death in 22.6%. There were no drug-related discontinuations or deaths. Drug-related AEs occurred in 59.7% and were grade III–IV in 9.7% (Table 2). The most common were fatigue (17.7%), diarrhoea (8.1%) and nausea (8.1%; Table 3). Drug-related pneumonitis was reported in two patients (3.2%); both cases were grade I in severity and both resolved. No drug-related colitis was observed. Drug-related AESIs occurred in 30.6% of patients, and one of these events (hypothyroidism) required endocrine therapy (levothyroxine). No other drug-related AESIs required steroid, endocrine or other immunosuppressive treatment. There were no SAEs of special interest. Drug-related imAEs were reported in 3.2% (the two grade I pneumonitis events described previously). Neither one required systemic steroids, endocrine therapy or other immunosuppression.

Table 2
Safety summary (as-treated population).

Events	Durvalumab (N = 62)
All events,[a] n (%)	
Any AE	61 (98.4)
Grade III–IV AEs	32 (51.6)
Serious AEs	30 (48.4)
Drug-related events[b] only, n (%)	
Any AE	37 (59.7)
Grade ≥3 AEs	6 (9.7)
Serious AEs	2 (3.2)
AEs leading to discontinuation	0 (0)
AEs leading to death	0 (0)

AE, adverse event; PD, progressive disease.
[a] Includes PD events.
[b] Causality assigned by investigator.

Table 3
Drug-related AEs occurring in ≥2% of patients (as-treated population).[a]

System organ class	Event	Durvalumab (N = 62) n (%)	
		All grades	Grade ≥III
Constitutional—general disorders	Fatigue	11 (17.7)	1 (1.6)
	Pyrexia	3 (4.8)	0
Endocrine	*Hypothyroidism*	2 (3.2)	0
Gastrointestinal	*Diarrhoea*	5 (8.1)	0
	Nausea	5 (8.1)	0
Laboratory investigations	*Increase in aspartate aminotransferase*	2 (3.2)	0
	Increase in blood alkaline phosphatase	2 (3.2)	0
	Increase in gamma-glutamyltransferase	3 (4.8)	2 (3.2)
Musculoskeletal	Arthralgia	2 (3.2)	0
Nervous system disorders	Dizziness	3 (4.8)	0
	Headache	2 (3.2)	0
Respiratory	Cough	2 (3.2)	0
	Dyspnoea	2 (3.2)	1 (1.6)
	Pneumonitis	2 (3.2)	0
Skin	*Pruritus*	4 (6.5)	0
	Rash	4 (6.5)	0
	Rash maculopapular	4 (6.5)	0
	Erythema	3 (4.8)	0
	Rash erythematous	2 (3.2)	1 (1.6)
	Dry skin	2 (3.2)	0

Note: AEs of special interest (which include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism) are italicized.
AE, adverse event.
[a] Causality assigned by investigator.

3.3. Clinical activity

All 62 patients had the opportunity for ≥24 weeks of follow-up. Confirmed objective responses were reported in 6.5% (95% confidence interval [CI], 1.8–15.7] of patients (4 PRs, 0 CRs; Table 4). DCR24 was 12.9%. ORR was numerically higher in the PD-L1 tumour cell (TC) ≥25% subgroup than in the PD-L1 TC <25% subgroup (15.0% vs 2.6%), as was DCR24 (20.0% vs. 7.7%). Responses occurred early and were durable. Median time to response was 2.7 months (range, 1.2–5.5), and

median duration of response was 12.4 months (range, 3.5–20.5+). ORR was 4.3% in patients who had received ≥2 prior systemic regimens.

Of the 62 patients in the as-treated population, seven did not have measurable disease at the baseline by BICR; the remaining 55 patients were included in the FAS. Objective responses are described in Supplemental Table S2.

ORR and DCR were numerically greater in HPV-negative patients than in HPV-positive patients, although two of the four responders had unknown HPV status. ORR and DCR were numerically greater in never smokers than in current/former smokers (Supplemental Fig. S2 and Supplemental Table S2).

Fig. 1 shows changes from the baseline in tumour size, stratified by PD-L1 status. Of the four patients who had a confirmed objective response, the best percentage decrease in tumour size ranged from 35.3% to 100%. The patient with the 100% shrinkage in target lesions maintained a non-CR/non-PD response in non-target lesions so was not considered a CR. Two of the four patients who achieved a response maintained it for >1 year. Twelve patients achieved SD, with a median duration of 5.2 months. Among the patients with progressive disease, one showed an atypical pattern and potential pseudo progression at the first on treatment assessment followed by PR. A new lesion was later detected at the eleventh assessment as portrayed in the spider plot (Fig. 1A).

Median OS in the overall population was 8.4 months (95% CI, 5.7–12.3). OS rate was 62.4% at 6 months (95% CI, 48.2–73.8) and 38.0% (95% CI, 24.5–51.4) at 12 months (Supplemental Fig. S3A). Median OS was numerically shorter in the PD-L1 TC <25% subgroup than in the PD-L1 TC ≥ 25% subgroup (7.4 vs. 8.4 months). OS rates were numerically higher in the PD-L1 <25% subgroup than in the ≥25% subgroup at 6 months (67% vs. 55%) but became more similar by 9 months (44% vs. 49%) and 12 months (36% vs. 42%).

Median PFS was 1.4 months (95% CI, 1.4–1.5) and was the same in never smokers, former smokers and current smokers (1.4 months). Median PFS was also similar for HPV-positive and HPV-negative patients (1.4 and 1.5 months, respectively). In the overall population, PFS rate was 11.9% at both 6 and 12 months (15.8% for PD-L1 ≥25%, 7.1% for PD-L1 <25%) (Supplemental Fig. S3B). Median PFS did not differ by PD-L1 TC expression.

Pharmacokinetic and immunogenicity results are summarized in the Supplemental Information.

4. Discussion

This dose-expansion study demonstrated the manageable safety profile and encouraging, durable antitumour activity of durvalumab in patients with HNSCC. Safety results were broadly comparable with those of other anti–PD-L1 and anti–PD-1 clinical studies in terms of frequency and types of drug-related AEs [21–26]. This included treatment-related grade III–IV AEs, reported in 9.7% of patients in the present study, compared with 9.0% with pembrolizumab in the phase Ib KEYNOTE-012 expansion cohort [27] and 13.1% with nivolumab in the phase II CheckMate 141 trial [28]. In our study, the incidence of drug-related pneumonitis was low (2 cases) and both events were grade I. No drug-related colitis was reported. There were no study drug-related discontinuations or deaths due to drug-related AEs.

The study population was more heavily pretreated than those of other checkpoint inhibitor studies in HNSCC (almost half the patients had received ≥3 prior systemic regimens, compared with 19.9% in CheckMate 141 [28]); however, evidence of antitumour activity was observed as early as 1.2 months, which is consistent with the early response timelines reported in other anti–PD-L1 trials in solid tumours, including HNSCC [22]. Durvalumab monotherapy showed similar antitumour activity in the phase II CONDOR and HAWK studies in patients whose HNSCC had progressed after one line of platinum-based therapy for recurrent/metastatic disease. In patients with PD-L1 <25%, ORR by BICR was 9.2% (all PRs) and median OS was 6.0 months in CONDOR [29]. In patients with PD-L1 ≥25%, ORR by BICR was 16.2% (including a CR in one patient [0.9%]

Table 4
Objective response rate and disease control rate overall and by PD-L1 status and HPV status per blinded independent central review in as-treated population.

Efficacy parameter	Overall	PD-L1 TC ≥25%	PD-L1 TC <25%	HPV positive[c]	HPV negative[c]
ORR[a], % (n/N)	6.5 (4/62)	15.0 (3/20)	2.6 (1/39)	0 (0/25)	8.0 (2/25)
95% CI	1.8–15.7	3.2–37.9	0.1–13.5	0.0–13.7	1.0–26.0
DCR24[a], % (n/N)	12.9[b] (8/62)	20.0 (4/20)	7.7 (3/39)	0 (0/25)	24.0 (6/25)
95% CI	5.7–23.9	5.7–43.7	1.6–20.9	0.0–13.7	9.4–45.1

CI, confidence interval; CR, complete response; DCR, disease control rate; HPV, human papillomavirus; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TC, tumour cell.

[a] ORR (confirmed CR and PR) and DCR24 (CR + PR + SD ≥ 24 weeks) are based on RECIST v1.1.

[b] Includes one patient with non-evaluable PD-L1 status with SD.

[c] There were two responders among the 12 patients with unknown HPV status.

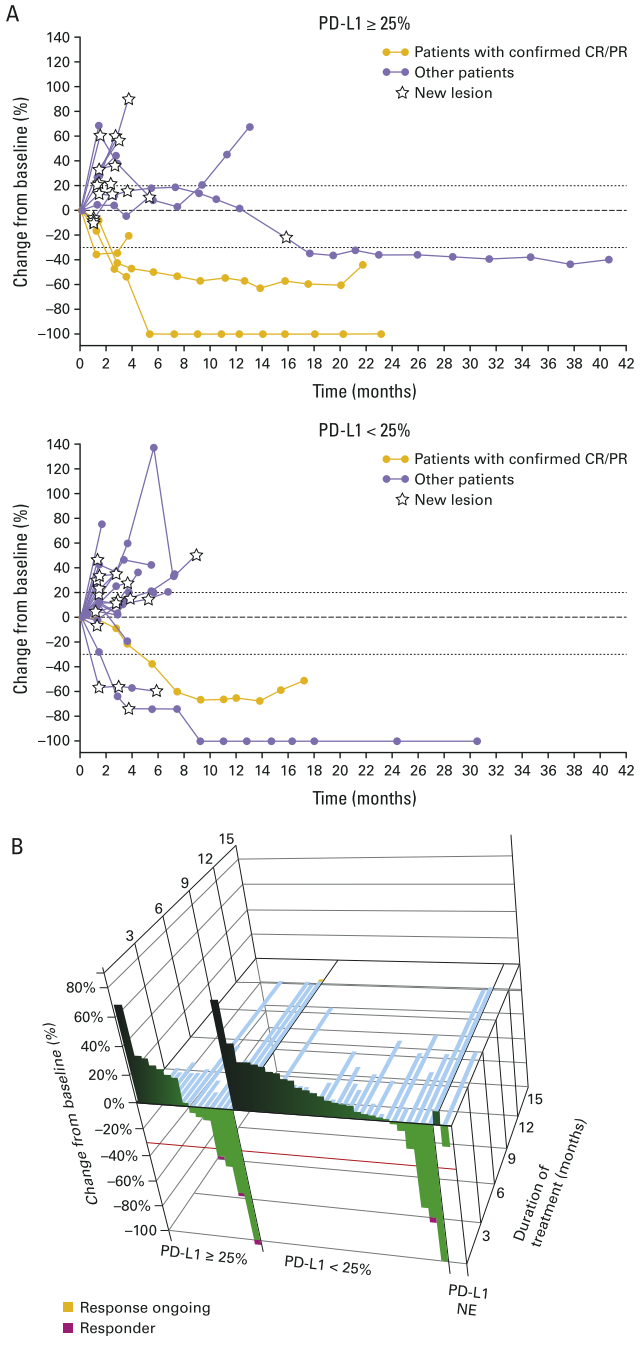

Fig. 1. Antitumour activity of durvalumab by PD-L1 status shown as (A) change in size of target lesions over time and (B) best change from the baseline in target lesion size. CR, complete response; NE, not evaluable; PD-L1, programmed cell death ligand-1; PR, partial response.

and PRs in 17 patients [15.3%]) and median OS was 7.1 months in HAWK [30].

Irrespective of PD-L1 expression levels, median OS data were similar for durvalumab in the present study (8.4 months), pembrolizumab (8.0 months) in the KEYNOTE-012 study [27] and nivolumab (7.5 months) in the CheckMate 141 trial [28]. The OS data were comparable even though the ORR for durvalumab in our study (6.5%) was numerically lower than those of the PD-1 inhibitors (18% for pembrolizumab [27] and 13.3% for nivolumab [28]). The durability of the responses (median, 12.4 months) may have contributed to the OS. Response rates may be imprecise predictors of OS. Moreover, cross-trial comparisons—particularly in smaller cohorts—can be limited because of differing patient populations and post-discontinuation therapies.

Our data and previous studies suggest that antitumour responses are more likely in patients with PD-L1 TC expression ≥25% than in those with PD-L1 TC expression <25% [10,11,22], although some durable responses were seen regardless of PD-L1 expression in this study. Tobacco-induced mutations and HPV-associated viral proteins are hypothesized to contribute to immunogenicity in HNSCC tumours [2,4,5]. A recent anti–PD-L1 study detected a trend of better responses in non-small cell lung cancer (NSCLC) patients who were smokers compared with non-smokers [22]. In contrast, median PFS did not differ by HPV status or smoking history in the current analysis, and all four responders had negative or unknown HPV status. This unexpected result may reflect the limited number of patients evaluated. Further study is needed to determine if smoking or HPV status is associated with the efficacy of durvalumab.

PD-1/PD-L1 blockade is associated with greater response rates in tumours expressing PD-L1 [1,22], but some patients may not respond to PD-L1 inhibition alone and could benefit from combination therapy, irrespective of PD-L1 status. Accordingly, durvalumab is being evaluated as monotherapy and in combination with the CTLA-4 inhibitor tremelimumab in phase III trials of HNSCC patients (EAGLE [NCT02369874] and KESTREL [NCT02551159]).

Author contributions

J.R.B., C.M., P.B.R., K.E.S. and X.S. contributed to study conception and design. N.H.S., S.-H.I.O., A.B., M.G.F., M.B., J.R.B., J.W., P.S., C.M., M.C.R., N.A., S.A. and S.N.K. collected and assembled the data. E.M., J.R.B., J.W., S.J.A., D.P.Z., F.X., M.C.R., P.B.R., M.B., N.A. and X.S. contributed in data analysis and interpretation. S.-H.I.O., M.G.F., E.M., J.W., P.S., C.M. and M.B. contributed in provision of study material or patients. N.H.S., S.-H.I.O., A.B., M.G.F., E.M., J.R.B., J.W., P.S., S.J.A., C.M., D.P.Z., F.X., M.C.R., K.E.S., P.B.R., N.A., X.S., S.A., M.B. and S.N.K. wrote the manuscript and approved the final manuscript.

Conflict of interest statement

N.H.S. served on the advisory boards of Roche/Genentech, Merck, Bristol-Myers Squibb, MedImmune/

AstraZeneca, Boehringer-Ingelheim, Pfizer, Pieris, PsiOxus, Synlogic, Aduro, Kyn Therapeutics, PureTechVentures, Horizon Pharma, EMD Serono, Gritstone Oncology, Chugai, TRM oncology and IFM therapeutics; and received research funding from Roche/Genentech, Pfizer, Merck, Bristol-Myers Squibb, MedImmune/AstraZeneca and Incyte. S.-H.I.O. received honoraria from Roche/Genentech, AstraZeneca, Pfizer and Takeda/Ariad; had a consulting or advisory role at Roche/Genentech, AstraZeneca, Pfizer and Takeda/Ariad; served on the speakers' bureaus of Roche/Genentech, AstraZeneca, Pfizer and Takeda/Ariad and received research funding from Roche/Genentech, AstraZeneca, Pfizer, Takeda/Ariad, Blueprint Medicines and TP Therapeutics. A.B. served on the speakers' bureaus of Bristol-Myers Squibb, Merck, AstraZeneca and Genentech. M.G.F. is an employee of Regeneron Pharmaceuticals; has stock ownership in Regeneron Pharmaceuticals; received patents, royalties and other intellectual property from Regeneron Pharmaceuticals and received travel, accommodations and expenses from Regeneron Pharmaceuticals. E.M. received honoraria from Genentech, AstraZeneca and Merck; had a consulting or advisory role at Genentech; served on the speakers' bureaus of AstraZeneca and Merck; received research funding from Genentech, AstraZeneca, Bristol-Myers Squibb, Pfizer, Tessa, GlaxoSmithKline and Merck and received reimbursement for travel, accommodations and expenses from Genentech, AstraZeneca and Merck. J.R.B. had a consulting or advisory role at Bristol-Myers Squibb (uncompensated), Amgen, Celgene, Eli Lilly and Merck; and received research funding from MedImmune/AstraZeneca, Bristol-Myers Squibb and Merck. 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Appendix A. Supplementary data

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