Title

Phase 1/2 study of monalizumab plus durvalumab in patients with advanced solid tumors.

Journal

Journal for ImmunoTherapy of Cancer, 12(2)

Authors

Patel, Sandip

Alonso-Gordoa, Teresa

Banerjee, Susana

et al.

Publication Date

2024-02-02

DOI

10.1136/jitc-2023-007340

Journal for ImmunoTherapy of Cancer

Phase 1/2 study of monalizumab plus durvalumab in patients with advanced solid tumors

Sandip P Patel ,[1] Teresa Alonso-Gordoa,[2] Susana Banerjee,[3] Ding Wang,[4] Jarushka Naidoo ,[5,6] Nathan E Standifer,[7] Doug C Palmer,[8] Lin-Yang Cheng,[8] Panagiotis Kourtesis,[8] Maria L Ascierto,[8] Mayukh Das,[8] Jennifer R Diamond,[9] Matthew D Hellmann,[10] Benedito A Carneiro[11]

To cite: Patel SP, Alonso-Gordoa T, Banerjee S, *et al*. Phase 1/2 study of monalizumab plus durvalumab in patients with advanced solid tumors. *Journal for ImmunoTherapy of Cancer* 2024;**12**:e007340. doi:10.1136/jitc-2023-007340

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jitc-2023-007340).

Accepted 16 November 2023

For numbered affiliations see end of article.

Correspondence to
Dr Sandip P Patel;
spatel@ucsd.edu

ABSTRACT

Background The combination of monalizumab (anti-NKG2A/CD94) and durvalumab (anti-programmed death ligand-1) may promote antitumor immunity by targeting innate and adaptive immunity. This phase 1/2 study of monalizumab and durvalumab evaluated safety, antitumor activity, and pharmacodynamics in patients with advanced solid tumors.

Main body Immunotherapy-naïve patients aged ≥18 years with advanced disease, Eastern Cooperative Oncology Group performance status of 0–1, and 1–3 prior lines of systemic therapy in the recurrent/metastatic setting were enrolled. In part 1 (dose escalation), patients received durvalumab 1500 mg every 4 weeks (Q4W) with increasing doses of monalizumab Q2W/Q4W (n=15). Dose expansion in part 1 included patients with cervical cancer (n=15; durvalumab 1500 mg Q4W and monalizumab 750 mg Q2W) or metastatic microsatellite stable (MSS)-colorectal cancer (CRC) (n=15; durvalumab 1500 mg Q4W and monalizumab 750 mg Q4W). In part 2 (dose expansion), patients with MSS-CRC (n=40), non-small cell lung cancer (NSCLC; n=20), MSS-endometrial cancer (n=40), or ovarian cancer (n=40) received durvalumab 1500 mg Q4W and monalizumab 750 mg Q2W. The primary endpoint was safety. Secondary endpoints included antitumor activity per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1). Exploratory analyses included assessment of T-cell and natural killer (NK) cell activation and proliferation in peripheral blood and the tumor microenvironment (TME). The study enrolled 185 patients (part 1, 45; part 2, 140). No dose-limiting toxicities were observed and the maximum tolerated dose was not reached. In part 2, the most common treatment-related adverse events were fatigue (12.1%), asthenia (9.3%), diarrhea (9.3%), pruritus (7.9%), and pyrexia (7.1%). In the expansion cohorts, response rates were 0% (cervical), 7.7% (MSS-CRC), 10% (NSCLC), 5.4% (ovarian), and 0% (MSS-endometrial). Sustained NK cell activation, $CD8^+$ T-cell proliferation, increased serum levels of CXCL10 (C-X-C motif chemokine ligand 10) and CXCL11, and increased tumor infiltration of $CD8^+$ and granzyme B^+ cells were observed.

Conclusions Although efficacy was modest, monalizumab plus durvalumab was well tolerated and encouraging immune activation was observed in the peripheral blood and TME.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Blockade of immune checkpoint pathways using monoclonal antibodies has substantially improved treatment outcomes for a range of malignancies.

⇒ In addition to T cells, natural killer (NK) cells are effector lymphocytes of innate immunity that can exert antitumor effector functions.

WHAT THIS STUDY ADDS

⇒ Highlights the potential clinical utility of combining therapies that block the non-redundant NK group-2 member-A/human leukocyte antigen E and programmed cell death protein 1/programmed death ligand-1 pathways to enhance the immune response of NK and $CD8^+$ T cells in the tumor microenvironment (TME).

⇒ Provides evidence for immune activation following combination treatment in the peripheral blood and the TME.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this study support the exploration of combinatorial treatment approaches that enhance both the innate and adaptive immune responses.

Trial registration number NCT02671435.

INTRODUCTION

Multiple signaling molecules that regulate innate and adaptive immunity play critical roles in maintaining an immunosuppressive state in the tumor microenvironment (TME).[1] A major mechanism for promoting the immunosuppressive state involves the upregulation of immune checkpoint pathways, such as cytotoxic T-lymphocyte-antigen 4 (CTLA-4) and programmed cell death (ligand)-1 (PD-(L)1).[2] A blockade of these pathways using monoclonal antibodies enables the release of effector T cells and has substantially improved treatment outcomes for a range of malignancies.[3 4] Treatment combinations with other modalities,

such as chemotherapy and targeted therapies, have further broadened the clinical benefit for many patients.[4] Progress has also been made in identifying predictive biomarkers to characterize patient subsets most likely to respond to specific therapies, allowing a more individualized and targeted approach to treatment.[3 5] However, only a small proportion of patients treated with checkpoint inhibitors develop long-term remission and disease control, highlighting the underlying complexity of the host immune response and TME.[6]

In addition to T cells, natural killer (NK) cells are effector lymphocytes of innate immunity that also exert antitumor effector functions but do not require immune priming.[7] A subset of NK cells expresses programmed cell death protein 1 (PD-1) and CTLA-4, as well as other immune checkpoint molecules such as NK group-2 member-A (NKG2A), killer cell immunoglobulin-like receptors, and leukocyte immunoglobulin-like receptors.[1 8 9] These molecular features of NK cells allow the opportunity for dual checkpoint pathway inhibition and the simultaneous targeting of innate and adaptive immunity via T cells and NK cells. Combinations of checkpoint blockades could be further augmented by modulating NK-specific immune checkpoints and enhancing antibody-dependent cellular cytotoxicity.[1 10 11] Preclinical studies have shown that NKG2A is often coexpressed with PD-1 on $CD8^+$ T cells.[12] In murine lymphoma models, the combined blockade of PD-1/PD-L1 and NKG2A/HLA class I histocompatibility antigen, alpha-chain E (HLA-E) pathways resulted in durable antitumor $CD8^+$ T-cell responses.[13] Therefore, combining inhibition of the NKG2A/HLA-E and PD-1/PD-L1 pathways may improve antitumor efficacy by enhancing activation of both NK and cytotoxic T lymphocytes (CTLs) in the TME via non-redundant complementary mechanisms (online supplemental figure 1). To test this hypothesis in a clinical setting, we evaluated the combination treatment with durvalumab, an approved anti-PD-L1 antibody, and monalizumab, an antibody that inhibits NKG2A.

Monalizumab is a humanized IgG4 antibody with a high affinity and specificity for the inhibitory checkpoint receptor NKG2A/CD94.[13] This receptor is expressed on cytotoxic lymphocytes present in the peripheral blood and the TME (NK cells, NK-T cells, and CTLs).[13] Elevated expression of NKG2A/CD94 by tumor-infiltrating NK cells is associated with decreased cytotoxic potential.[14–16] This decrease in cytotoxic potential is mediated by the binding of the NKG2A/CD94 ligand HLA-E, which is overexpressed in a variety of solid tumors, including colorectal cancer (CRC), non-small cell lung cancer (NSCLC), ovarian, cervical, endometrial, and prostate cancers.[17–21] Disruption of NKG2A/CD94 binding by monalizumab suppresses inhibitory signaling by tumors on both NK cells and T cells.[13] There are several ongoing clinical trials of monalizumab in combination with durvalumab (online supplemental table 1).

The study presented here is a first combination in human, phase 1/2 dose-escalation and dose-expansion study of monalizumab plus durvalumab in patients with advanced solid tumors. The study consisted of three parts: dose escalation and expansion in patients with advanced solid tumors (part 1); dose expansion in select advanced solid tumors (part 2); and dose exploration in combination with standard-of-care therapies in patients with microsatellite stable (MSS) CRC (part 3). This manuscript reports the safety and efficacy results of the dose-escalation and dose-expansion cohorts (part 1) and expansion cohorts (part 2) in patients with MSS-CRC, NSCLC, MSS-endometrial cancer, cervical cancer, and ovarian cancer. Patients with these malignancies were selected based on the high unmet clinical need and elevated HLA-E expression in these tumor types. The exploratory analysis of pharmacodynamic biomarker assessments in the peripheral blood and tumor tissue are also presented.

METHODS

Study design and treatment

This was a multicenter, open label, phase 1/2 study of monalizumab in combination with durvalumab that enrolled patients with advanced solid tumors between February 22, 2016 and April 26, 2019. Patients were enrolled across 60 study sites globally.

For part 1 (dose escalation), sequential cohorts of three patients received durvalumab (1500 mg every 4 weeks (Q4W)) in combination with monalizumab at one of four planned dose levels, via intravenous infusion over approximately 60 min (22.5 mg, 75 mg, 225 mg, 750 mg every 2 weeks (Q2W)) or an alternative treatment schedule of 750 mg Q4W. Additionally, for part 1 (dose expansion), 15 patients with cervical cancer received durvalumab 1500 mg Q4W and monalizumab 750 mg Q2W and 15 patients with MSS-CRC received durvalumab 1500 mg Q4W and monalizumab 750 mg Q4W (online supplemental figure 2). A modified toxicity probability interval algorithm using a simple beta-binomial Bayesian model[22] determined a target dose-limiting toxicity (DLT) rate of ≥33% and an equivalence interval of 25%–35% for dose-escalation/de-escalation decisions, as well as maximum tolerated dose (MTD) determination. A dose level was considered unsafe, with no additional patients enrolled, if it had an estimated 95% or greater probability of exceeding the target DLT rate of ≥33% with at least three patients treated at that dose level. The combination of monalizumab 750 mg Q2W and durvalumab 1500 mg Q4W was considered safe by the dose-escalation committee (comprising the sponsor medical monitor and all participating investigators who enrolled patients) and was used in the dose expansion.

For part 2 dose expansion, 40 patients were enrolled in each of the MSS-CRC, ovarian cancer, and MSS-endometrial cancer cohorts. Twenty patients were enrolled in the NSCLC cohort. On dosing days when both monalizumab and durvalumab were administered, durvalumab was administered first followed by

monalizumab starting 15–30 min after the completion of the durvalumab infusion.

Study treatment continued until unacceptable toxicity, documentation of confirmed progressive disease, or documentation of patient withdrawal for up to 3 years.

Patient and public involvement

Although patients made important contributions to this research as study participants, patients and members of the public were not involved with the research study design, recruitment, or conduct of the study presented in this manuscript. Further, they are not involved in the dissemination of study results.

Patients

Patients were eligible if they were aged ≥18 years and had histological documentation of advanced, recurrent, or metastatic MSS-CRC, NSCLC, MSS-endometrial cancer, high-grade serous epithelial ovarian cancer (including fallopian tubal carcinoma and peritoneal carcinoma), cervical cancer (adenocarcinoma or squamous cell carcinoma), castration-resistant prostate cancer, or pancreatic adenocarcinoma.

Patients with MSS-CRC were screened to confirm that their cancers did not have defective DNA mismatch repair/microsatellite instability, defined by changes in ≥2 panels of microsatellite markers (ie, BAT-25, BAT-26, NR-21, NR-24, or MONO-27) or immunohistochemistry demonstrating the absence of protein expression of any one or more of the following proteins: MLH1, MSH2, MSH6, or PMS2. Patients had received 1–2 prior lines (NSCLC, MSS-endometrial cancer, cervical cancer, castration resistant prostate cancer, or pancreatic adenocarcinoma) or 1–3 prior lines (ovarian cancer or MSS-CRC) of standard systemic therapy in the recurrent/metastatic setting. All patients were immunotherapy naïve. For all tumor types, there was to be no evidence of partial small bowel obstruction or small bowel obstruction within 4 weeks before the first scheduled dose of study treatment.

Patients were included if they had at least one measurable lesion by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1,[23] and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were excluded from the dose expansion if they were previously treated with anti-PD-1, anti-PD-L1, or anti-CTLA-4 immunotherapy. However, patients who received prior anti-PD-1, anti-PD-L1, or anti-CTLA-4 immunotherapy could be enrolled for dose escalation if they met the following criteria: they did not experience toxicity that led to discontinuation of checkpoint inhibitors; all adverse events (AEs) while receiving prior immunotherapy were completely resolved; they did not experience a ≥grade 3 immune-related AE or an any-grade immune-related neurological or ocular AE during prior immunotherapy; they did not require additional immunosuppression other than corticosteroids for the management of an AE; they did not experience recurrence of an AE if rechallenged; and they did not require maintenance doses of >10 mg prednisone or equivalent per day. Although patients who had received prior immunotherapy were allowed to be enrolled in the dose-escalation part of the study (if they satisfied additional eligibility criteria), all of the enrolled patients in part 1 and part 2 of this study were immunotherapy-naïve. Additional inclusion and exclusion criteria are included in online supplemental methods.

Study endpoints

The primary endpoint was safety. Secondary endpoints included antitumor activity (best overall response (BOR) per RECIST v1.1 by investigator), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and the assessment of response according to biomarkers (including PD-L1 and HLA-expression) in pretreatment tumor biopsies. Exploratory analysis included the assessment of T-cell and NK-cell activation and proliferation in the peripheral blood and TME, the number and activity of $CD8^+$ effector T cells and NK cells, expression of immunomodulatory proteins (PD-1) within tumor biopsies, and soluble immune mediators in serum and plasma (ie, CXCL9 (C-X-C motif chemokine ligand 9), CXCL10, CXCL11, and interferon-γ).

Assessments

Safety was assessed by the presence of AEs, serious adverse events (SAEs), DLTs, abnormal laboratory parameters, vital signs, and ECG results. AEs and DLTs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

The period for DLT evaluation was defined as the time from the start of the first dose of monalizumab and durvalumab until the planned administration of the second dose of durvalumab and the third dose of monalizumab (28 days after the first dose of durvalumab and monalizumab or 14 days after the second dose of monalizumab). A DLT was defined during dose escalation as any treatment-related grade 3 or higher toxicity that occurred during the DLT-evaluation period. Additional details regarding DLT classification can be found in online supplemental methods.

Objective response rate (ORR) was defined as the BOR of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST v1.1. Disease control rate (DCR) was defined as CR, PR, or stable disease (SD; for ≥8 weeks (±3 days)) based on RECIST v1.1. DoR was defined as the duration from the first documentation of objective response to the first documented disease progression or death due to any cause, whichever occurred first. PFS and OS were measured from the start of treatment or randomization with investigational product until the first documentation of disease progression or death due to any cause. Translational and pharmacokinetic analyses methods are presented in online supplemental methods.

Statistical analyses

Tabular summaries are presented by treatment group, categorical data are summarized by the number and percentage of patients in each category, and continuous variables are summarized by descriptive statistics.

For dose escalation (part 1), the number of patients enrolled was dependent on the observed toxicities. For the dose expansion (part 2), enrollment of approximately 40 patients was planned in each of the MSS-CRC, ovarian, NSCLC, and MSS-endometrial cohorts, with a potential futility stop after the first 20 patients at the discretion of the sponsor. The futility criteria for MSS-CRC, ovarian, and the MSS-endometrial expansion cohorts was 0 objective responses out of the initial 20 patients. The observed 0/20 response provided an upper limit of a one-sided 80% CI of approximately 8%, which means that a response rate >8% can be ruled out with 80% confidence, and enrollment would be stopped for lack of desirable response rate. The futility criteria for NSCLC expansion cohort was ≤1 objective response out of the initial 20 patients. Observing 1/20 response gives an upper limit of a one-sided 80% CI of approximately 14%, which means that a response rate >14% can be ruled out with 80% confidence and hence enrollment may be stopped for lack of desirable response rate.

ORR and DCR were estimated by the proportion of objective response and disease control (with 80% and 95% CIs), respectively, using exact binomial distribution. DoR was evaluated for the subgroup of patients with an OR using the Kaplan-Meier method. PFS (censored at last tumor assessment date) and OS (censored on last known date of survival) were estimated using the Kaplan-Meier method.

The as-treated population included patients who received any investigational products and was used to evaluate baseline characteristics and all safety/efficacy endpoints. The DLT-evaluable population included all patients enrolled in dose-escalation who received at least one dose of investigational products and completed the safety follow-up through the DLT-evaluation period or experienced any DLT during the DLT-evaluation period. The response-evaluable population included patients in the as-treated population who had at least one post-baseline disease assessment, who died from any cause, or who discontinued because of clinical progressive disease before any postbaseline tumor assessment. Statistical analyses were performed using SAS System V.9.4 or higher (SAS Institute, Cary, NC).

RESULTS

Patients

Between February 22, 2016 and April 26, 2019, 185 patients were enrolled. For the dose escalation (part 1), 15 patients were initially enrolled and treated with 1500 mg of durvalumab Q4W with increasing doses of monalizumab: 22.5 mg Q2W (n=3); 75 mg Q2W (n=3); 225 mg Q2W (n=3); 750 mg Q2W (n=3); and 750 mg Q4W (n=3). Part 1 (dose expansion) also included an additional 15 patients with cervical cancer treated with monalizumab (750 mg Q2W) and durvalumab (1500 mg Q4W), and an additional 15 patients with MSS-CRC treated with monalizumab (750 mg Q4W) and durvalumab (1500 mg Q4W). Therefore, 16 patients with cervical cancer (1 patient from dose escalation and 15 patients from dose expansion who received the same dose and treatment frequency) were evaluated as a separate expansion cohort in part 1. The tumor histologies in the cervical cancer cohort included squamous cell carcinoma (n=9), adenocarcinoma (n=5), and mucinous carcinoma (n=2). Two patients with cervical cancer had mixed histology tumors (two histological subtypes); each instance was counted once for each histological type. The histological subtype was unknown for one patient.

In part 1 (dose escalation and expansion), a total of 45 patients were enrolled (MSS-CRC, n=19; cervical cancer, n=17; MSS-endometrial cancer, n=3; pancreatic cancer, n=3; ovarian cancer, n=3). During part 2 (dose expansion), 140 patients were enrolled (MSS-CRC, n=40; ovarian cancer, n=40; MSS-endometrial cancer, n=40; NSCLC, n=20). All patients in part 2 were treated with durvalumab 1500 mg Q4W and monalizumab 750 mg Q2W. Dose selection for the dose-expansion part was based on the highest dose administered following a method described in the protocol in the absence of any observed DLTs and not reaching the MTD. Patient demographics and baseline disease characteristics are summarized in table 1.

All patients in both part 1 and part 2 of the study received at least one prior line of therapy (table 1). Baseline PD-L1 data were available for 36/45 (80%) patients in part 1 (dose escalation and expansion), 11/16 (68.8%) patients in part 1 (cervical expansion), and 125/140 (89.3%) patients in part 2 (table 1). In part 1 (dose escalation and expansion), three (6.6%) patients had a PD-L1 tumor proportion score (TPS) ≥25%. In part 1 (cervical expansion), two (12.5%) patients had a TPS of ≥25%. In part 2 (dose expansion), 14 (10%) patients had a TPS of ≥25%. PD-L1 expression data were missing or unknown for 9 (20%) patients in part 1 (dose escalation and expansion), 5 (31.3%) patients in part 1 (cervical expansion), and 31 (22%) patients in part 2 (table 1).

Overall, 157/185 (84.9%) patients discontinued treatment due to progressive disease, 5/185 (2.7%) patients discontinued because of AEs, 3/185 (1.6%) patients were lost to follow-up, and 4/185 (2.2%) died. As of the data cut-off date of October 30, 2020, the median (minimum, maximum) duration of follow-up was 36.5 months (0.30–53.9).

Safety

The median duration of treatment was 2.3 (range, 0.46–41.7) months for monalizumab and 2.8 (range, 0.62–41.7) months for durvalumab. There were no observed DLTs, and the MTD was not reached. The combination of monalizumab 750 mg Q2W and durvalumab

Table 1 Patient demographic and baseline disease characteristics, as-treated population

Parameter	Part 1 Monalizumab dose escalation/expansion+durvalumab* n=45						Part 2 Monalizumab dose expansion+durvalumab† n=140			
				750 mg (Q2W) n=18‡						
	22.5 mg (Q2W) n=3	75 mg (Q2W) n=3	225 mg (Q2W) n=3	750 mg (Q2W) n=18‡	Cervical (backfill) 750 mg (Q2W) n=16¶	750 mg (Q4W) n=18§	MSS-CRC n=40	Ovarian n=40	MSS-endometrial n=40	NSCLC n=20
Median age, years (range)	69 (33–72)	55 (38–74)	61 (43–73)	57 (32–79)	54.5 (32–79)	58 (37–79)	55 (23–79)	62.5 (42–75)	64 (45–79)	65.5 (44–74)
Male, n (%)	0	0	1 (33.3)	1 (5.6)	0	12 (66.7)	25 (62.5)	0	0	14 (70)
Race, n (%)										
White	3 (100)	3 (100)	3 (100)	15 (83.3)	14 (87.5)	15 (83.3)	36 (90)	35 (87.5)	30 (75)	16 (80)
Black	0	0	0	1 (5.6)	0	0	1 (2.5)	3 (7.5)	4 (10)	1 (5)
Asian	0	0	0	1 (5.6)	1 (6.3)	2 (11.1)	3 (7.5)	1 (2.5)	2 (5)	0
Baseline PD-L1**, n (%)										
<25%	3 (100)	3 (100)	3 (100)	11 (61.1)	9 (56.3)	13 (72.2)	29 (72.5)	32 (80)	31 (77.5)	10 (50)
≥25%	0	0	0	2 (11.1)	2 (12.5)	1 (5.6)	0	5 (12.5)	1 (2.5)	6 (30)
Unknown††	0	0	0	5 (27.8)	5 (31.3)	4 (22.2)	11 (27.5)	3 (7.5)	8 (20)	4 (20)
Most recent line of therapy for recurrent/metastatic disease, n (%)										
First line	1 (33.3)	1 (33.3)	2 (66.7)	13 (72.2)	12 (75)	5 (27.8)	6 (15)	10 (25)	21 (52.5)	19 (95)
Second line	1 (33.3)	2 (66.7)	0	5 (27.8)	4 (25)	8 (44.4)	11 (27.5)	12 (30)	16 (40)	1 (5)
≥ Third line	1 (33.3)	0	1 (33.3)	0	0	5 (27.8)	23 (57.5)	17 (42.5)	1 (2.5)	0
NA	0	0	0	0	0	0	0	1 (2.5)	2 (5)	0
Prior radiation therapy, n (%)	1 (33.3)	1 (33.3)	0	13 (72.2)	12 (75.0)	9 (50.0)	13 (32.5)	6 (15.0)	25 (62.5)	8 (40.0)
Prior surgery, n (%)	2 (66.7)	2 (66.7)	2 (66.7)	7 (38.9)	5 (31.3)	14 (77.8)	32 (80.0)	30 (75.0)	29 (72.5)	5 (25.0)

*Doses indicated for each escalation cohort are for monalizumab Q2W (except where noted); durvalumab was administered at 1500 mg Q4W for all cohorts.
†For the dose expansion (Part 2), monalizumab was administered at 750 mg Q2W and durvalumab was administered at 1500 mg Q4W for all cohorts.
‡Total includes 16 patients with cervical cancer, 1 patient with MSS-CRC, and 1 patient with pancreatic cancer.
§Total includes 15 patients with MSS-CRC, 1 patient with MSS-endometrial cancer, 1 patient with pancreatic cancer, and 1 patient with cervical cancer.
¶Total includes one patient with cervical cancer from the dose escalation treated at this dose level. An additional 15 patients with cervical cancer were enrolled to "backfill" the dose-escalation cohort in Part 1 and were included in the Part 1 dose expansion.
**Tumor proportion score.
††Unknown baseline PD-L1 indicates that biopsy samples were either not collected or not evaluable.
MSS, microsatellite stable; MSS-CRC, microsatellite-stable colorectal cancer; NA, not available; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

1500 mg Q4W was considered safe by the dose-escalation committee, and was selected for treatment in the dose expansion. Overall safety data are summarized in online supplemental table 3.

During part 1 (dose escalation and expansion, n=45), the most common treatment-related AEs were constipation (12/45; 26.7%), decreased appetite (11/45; 24.4%), diarrhea (11/45; 24.4%), nausea (11/45; 24.4%), and fatigue (9/45; 20.0%). In part 1 (cervical dose expansion, n=16), the most common treatment-related AEs were asthenia (3/16; 18.8%), arthralgia, decreased appetite, diarrhea, myalgia, and vomiting (each 2/16; 12.5%). Additionally, there was one patient with treatment-related AEs that led to discontinuation (myocarditis and pericarditis). There were 14 grade 3/4 AEs reported in 10/16 (62.5%) patients (hydronephrosis, n=2; anemia, blood creatine increased, constipation, dyspnea, hematuria, myocarditis, nausea, pulmonary embolism, pyelonephritis, subcapsular renal hematoma, urinary tract infection, and vomiting, n=1 each). In part 1 cervical expansion cohort, 1/16 (6.3%) patients had a grade 3/4 treatment-related AE of myocarditis, and 2/16 (12.5%) patients had at least one treatment-related SAE (myocarditis, pericarditis, and vomiting; all n=1). In part 1 MSS-CRC expansion cohort, 1/18 (5.6%) patients had a grade 3/4 treatment-related AE of asthenia.

In part 2 (dose expansion), the most common treatment-related AEs were fatigue (17/140; 12.1%), asthenia (13/140; 9.3%), diarrhea (13/140; 9.3%), pruritus (11/140; 7.9%), and pyrexia (10/140; 7.1%). Two patients in part 2 had treatment-related AEs that led to discontinuation (infusion-related reaction, MSS-endometrial cancer cohort, n=1; pneumonitis, NSCLC cohort, n=1). In part 2, 74/140 (52.9%) patients had grade 3/4 AEs, with the most frequent being anemia (11/140; 7.9%), abdominal pain (8/140; 5.7%), ascites (6/140; 4.3%), dyspnea (6/140; 4.3%), and hyponatremia (6/140; 4.3%). In total, 20 (14.3%) patients in part 2 experienced grade 3/4 treatment-related AEs, with the most common being alanine aminotransferase increased, anemia, colitis, and hypokalemia (each n=2; table 2). Of 140 patients, 9 (6.4%) had at least one treatment-related SAE: colitis (2/140; 1.4%), acute kidney injury, anaphylactic shock, diarrhea, encephalitis autoimmune, encephalomyelitis, hypocalcemia, hypomagnesemia, infusion-related reaction, nephritis, and pneumonitis (each 1/140; 1.4%).

During part 1 (dose escalation and expansion), there was one death—a patient with cervical cancer due to an

Table 2 Treatment-related grade 3/4 adverse events, dose expansion* (part 2), as-treated population

Preferred term	MSS-CRC n=40	Ovarian n=40	MSS-endometrial n=40	NSCLC n=20	Total N=140
Alanine aminotransferase increased	0	1 (2.5)	1 (2.5)	0	2 (1.4)
Aspartate aminotransferase increased	1 (2.5)	0	0	0	1 (0.7)
Anemia	0	0	2 (5.0)	0	2 (1.4)
Colitis	0	2 (5.0)	0	0	2 (1.4)
Hypokalemia	0	1 (2.5)	1 (2.5)	0	2 (1.4)
Anaphylactic shock	0	0	0	1 (5.0)	1 (0.7)
Arthralgia	0	1 (2.5)	0	0	1 (0.7)
Asthenia	0	1 (2.5)	0	0	1 (0.7)
Blood creatinine increased	0	0	1 (2.5)	0	1 (0.7)
Dyspnea	0	0	0	1 (5.0)	1 (0.7)
Encephalitis autoimmune	0	0	1 (2.5)	0	1 (0.7)
Encephalomyelitis	0	1 (2.5)	0	0	1 (0.7)
Hyperlipasemia/lipase increased	1 (2.5)	0	0	1 (5.0)	1 (0.7)
Hypermagnesemia	0	0	1 (2.5)	0	1 (0.7)
Hyperuricemia	0	0	1 (2.5)	0	1 (0.7)
Hypocalcemia	0	0	1 (2.5)	0	1 (0.7)
Hypomagnesemia	0	0	1 (2.5)	0	1 (0.7)
Hyponatremia	0	0	1 (2.5)	0	1 (0.7)
Infusion-related reaction	0	0	1 (2.5)	0	1 (0.7)
Pneumonitis	0	0	0	1 (5.0)	1 (0.7)
Myocarditis	0	0	0	0	1 (0.7)

Patients are counted once for each system organ class and preferred term, regardless of the number of events.
*Monalizumab was administered at 750 mg Q2W and durvalumab was administered at 1500 mg Q4W for all cohorts.
MSS, microsatellite stable; MSS-CRC, microsatellite-stable colorectal cancer; NSCLC, non-small cell lung cancer; Q#W, every # weeks.

AE that was unrelated to treatment (pneumonia; cervical expansion cohort). There were two deaths due to AEs in part 2 (MSS-endometrial cancer cohort, bipolar disorder, n=1; NSCLC cohort, lower respiratory tract infection, n=1). Both deaths were considered unrelated to study treatment.

Efficacy

Among all patients evaluable for response, one patient in the MSS-CRC cohort had a confirmed CR and six patients had confirmed PRs (MSS-CRC, n=2; NSCLC, n=2; and ovarian cancer, n=2). There were no responses observed in part 1 (online supplemental table 4). In part 2 expansion cohorts, the ORRs were: 10.0% in the NSCLC cohort; 7.7% in the MSS-CRC cohort; 5.4% in the ovarian cohort. There were no responses observed in the MSS-endometrial cohort (table 3). The median DoR ranged from 16.1 to 22.9 weeks (table 3). There were two patients with durable responses: MSS-CRC (CR; DoR ≥104 weeks) and ovarian cancer (PR; DoR ≥88 weeks) (table 3). The patient with MSS-CRC was in their 40s and had one prior line of therapy for metastatic disease with a BOR of PR. This patient had no history of bone marrow or stem cell transplantation or radiation treatment. The patient with ovarian cancer was in their 60s and had four prior lines of therapy and a BOR of CR to the most recent treatment prior to enrollment. One patient with ovarian cancer remained on treatment for ≥33 months. In part 1 cervical expansion cohort, median PFS was 2.0 (range, 1.7–3.4) months and median OS was 8.6 (range, 3.5–16.7) months. Median PFS ranged from 1.8 to 2.0 months, and median OS ranged from 8.6 to 16.7 months in part 2 expansion cohorts (table 3).

Overall change in tumor size from baseline for each patient in the MSS-CRC, ovarian cancer, MSS-endometrial cancer, NSCLC, and cervical cancer disease-specific expansion cohorts are shown in figure 1. Several patients reported >30% reduction in sum of target lesions; but did not meet RECIST v1.1 criteria for tumor response. The change in tumor size from baseline in all expansion cohorts is shown in online supplemental figure 3.

Exploratory translational analyses

In the peripheral blood, full and sustained NKG2A receptor occupancy was observed at the highest dose level of monalizumab (750 mg Q2W; online supplemental figure 4).

Table 3 Clinical activity in part 2 expansion cohorts, response-evaluable population*†

Parameter	MSS-CRC n=39	Ovarian n=37	Endometrial MSS n=39	NSCLC n=20
Best overall response, n (%)				
Complete response	1 (2.6)	0	0	0
Partial response	2 (5.1)	2 (5.4)	0	2 (10.0)
Stable disease	12 (30.8)	10 (27.0)	15 (38.5)	6 (30.0)
Unconfirmed partial response	0	1 (2.7)	0	1 (5.0)
Progressive disease	20 (51.3)	24 (64.9)	20 (51.3)	11 (55.0)
NE/NA‡	4 (10.3)	1 (2.7)	4 (10.3)	1 (5.0)
Objective response rate§, n (%)	3 (7.7)	2 (5.4)	0	2 (10.0)
95% CI	(1.7–21.4)	(0.7–18.7)	(0.0–9.5)	(1.2–31.7)
Median duration of response, weeks	16.1	NR	NA	22.9
(minimum, maximum)	(15.9–104.4)¶	(24.0–88.3)¶	(NA–NA)	(10.1–35.6)
Disease control rate at 16 weeks, n (%)	12 (30.8)	12 (32.4)	10 (25.6)	8 (40.0)
95% CI	(17.0–47.6)	(18.0–49.8)	(13.0–42.1)	(19.1–63.9)
Disease control rate at 24 weeks, n (%)	7 (17.9)	6 (16.2)	5 (12.8)	5 (25.0)
95% CI	(7.5–33.5)	(6.2–32.0)	(4.3–27.4)	(8.7–49.1)
Median OS**, months (95% CI)	10.6 (6.0–20.1)	16.7 (9.7–20.1)	10.7 (6.7–17.3)	8.8 (5.8–15.6)
Median PFS**, months (95% CI)	1.9 (1.8–3.6)	1.8 (1.7–1.9)	1.8 (1.7–3.3)	1.9 (1.7–3.7)

ORR=CR+PR; DCR16=CR+PR+SD ≥16 weeks; DCR24=CR+PR+SD ≥24 weeks.
*Response-evaluable population includes patients in the as-treated population who have at least one postbaseline disease assessment or discontinued due to death or disease progression before the first postbaseline disease assessment.
†Monalizumab was administered at 750 mg Q2W and durvalumab was administered at 1500 mg Q4W.
‡Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.
§Confirmed responses only.
¶Response was ongoing at last assessment.
**As-treated population (MM-CRC, n=40; ovarian cancer, n=40; MSS-endometrial, n=40; NSCLC, n=20; cervical cancer, n=16).
CR, complete response; DCR, disease control rate; MSS, microsatellite stable; MSS-CRC, microsatellite-stable colorectal cancer; NA, not available; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q#W, every # weeks; SD, stable disease.

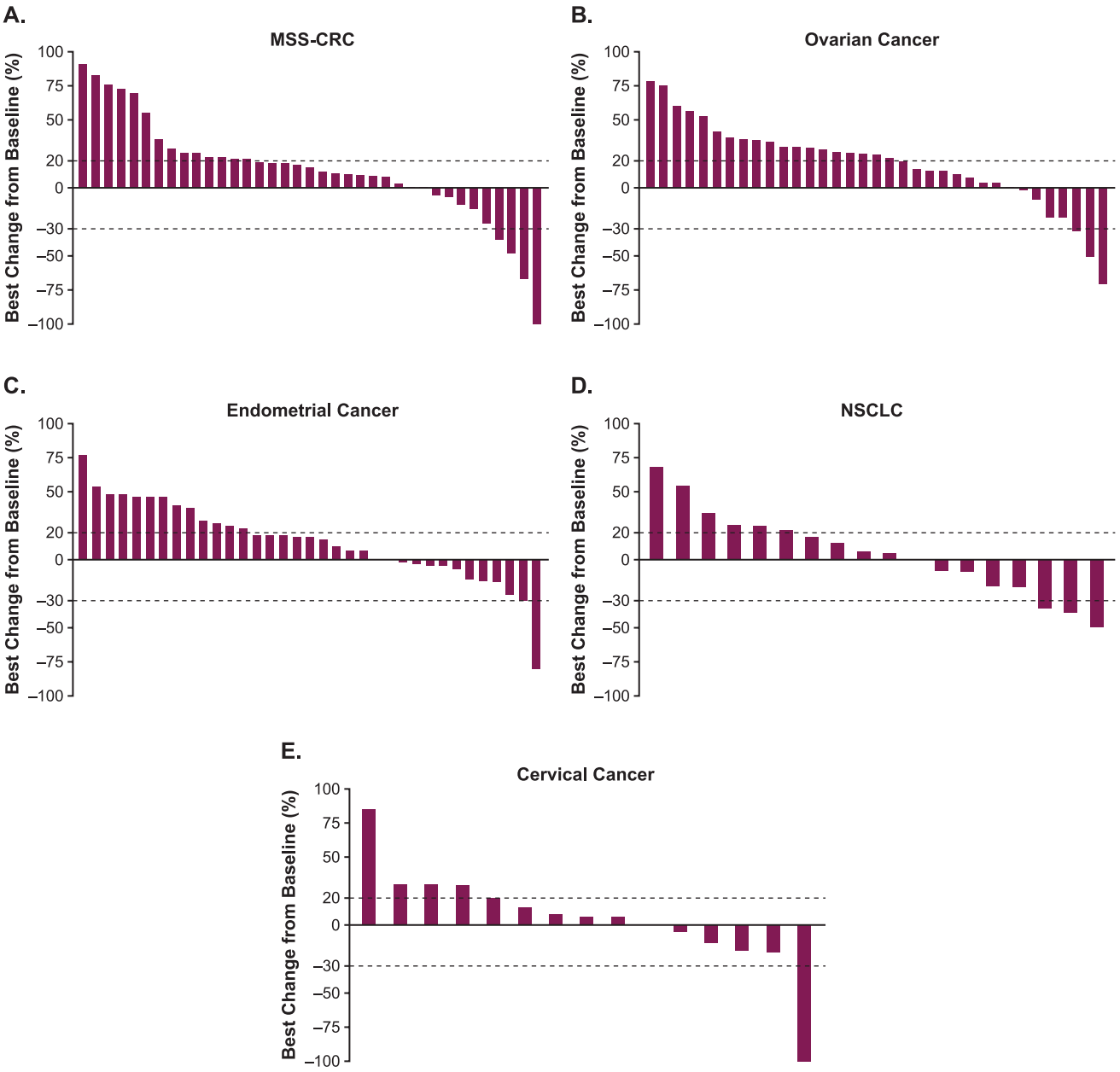

Figure 1 Change in tumor size from baseline for (A) MSS-CRC, (B) ovarian cancer, (C) MSS-endometrial cancer, (D) NSCLC, and (E) cervical cancer (part 1 and part 2 dose-expansion cohorts; response-evaluable population). (A) In the MSS-CRC cohort, there were 4 out of 37 patients with >30% reduction in sum of target lesions; however, 3 had disease response per RECIST v1.1. (B) In the ovarian cancer cohort, there were 2 out of 35 patients with >30% reduction in sum of target lesions and these 2 patients also had disease response per RECIST v1.1. (C) In the MSS-endometrial cancer cohort, there was 1 out of 35 patients with >30% reduction in sum of target lesions; however, there were no tumor responses per RECIST v1.1. (D) In the NSCLC cohort, there were 3 out of 18 patients with >30% reduction in sum of target lesions; however, 1 patient had disease response per RECIST v1.1. (E) In the cervical cancer cohort, there was 1 out of 15 patients with >30% reduction in sum of target lesions; however, there were no tumor responses per RECIST v1.1. MSS, microsatellite stable; MSS-CRC, microsatellite-stable colorectal cancer; NSCLC, non-small cell lung cancer; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

Treatment with monalizumab and durvalumab reduced the number of $CD56^{bright}$ NK cell subsets ($CD3^{-}$ $CD16^{-}CD56^{+}$) in the periphery, which are typically $NKG2A^{+}$ (figure 2A).[24] The $CD56^{dim}$ CD16+ population was also monitored; however, subpopulations did not pass assay validation. Monalizumab and durvalumab induced peripheral activation of NK cells, indicated by increased expression levels of the NK activation marker CD38 on $CD56^{bright}$ NK cells (figure 2B).[25] Peak increases in proliferating ($Ki67^{+}$) CD4 and CD8 T cells in the peripheral blood at levels 50% or greater versus baseline were observed in patients treated with the combination of monalizumab and durvalumab on day 8 post-treatment (figure 2C), consistent with levels observed for durvalumab monotherapy.[26 27] These pharmacodynamic effects were observed to varying degrees across all cohorts (online supplemental figure 5).

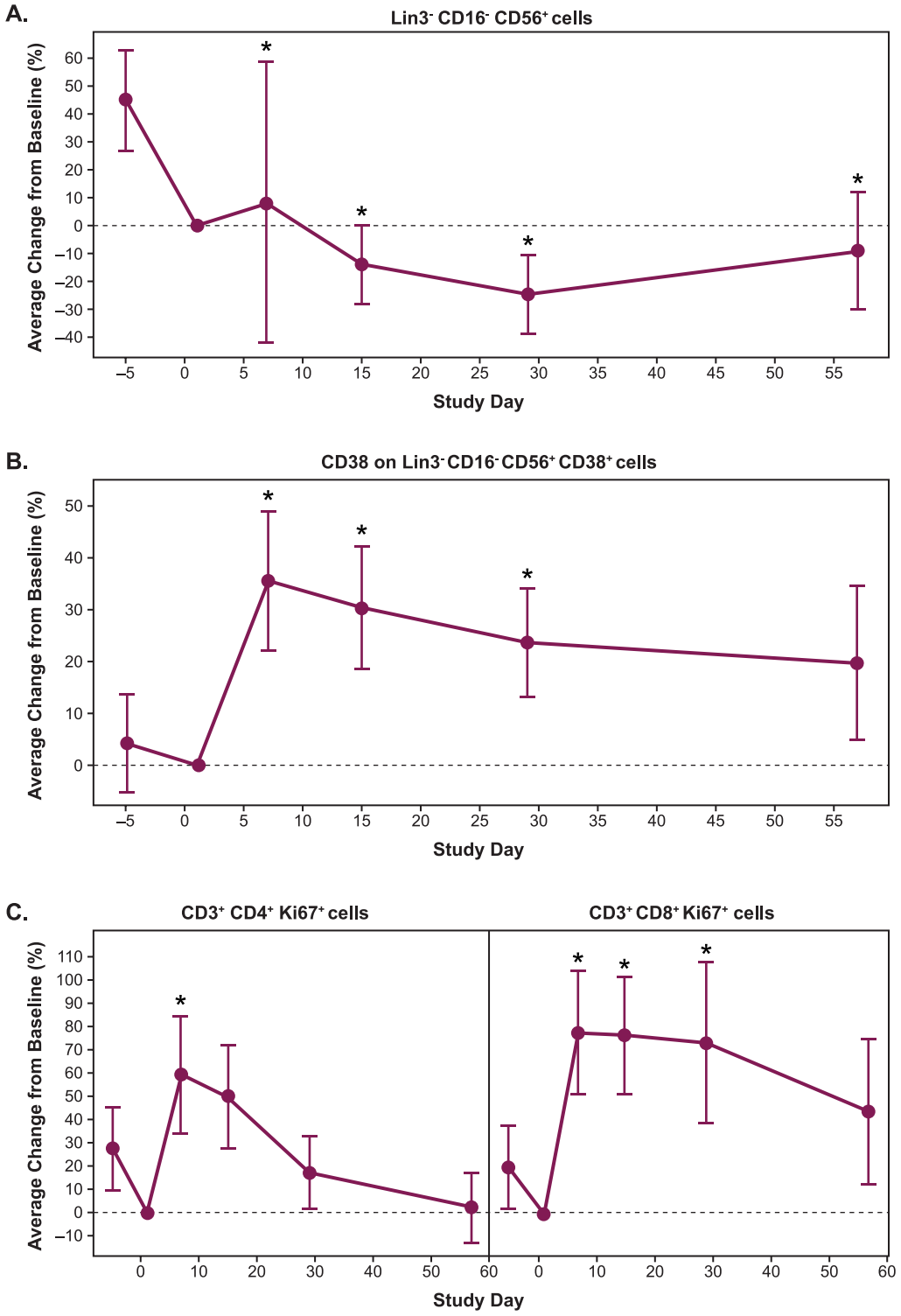

Figure 2 Change in lymphocyte subpopulations in the circulation before and after treatment with monalizumab and durvalumab (A) Lin3$^-$ CD16$^-$ CD56$^+$ NK, (B) CD38 relative expression on Lin3$^-$ CD16$^-$ CD56$^+$ CD38$^+$ NK, and (C) CD3$^+$ CD4$^+$ Ki67$^+$ or CD3$^+$ CD8$^+$ Ki67$^+$ T cells. Samples were from patients in the NSCLC, MSS-CRC, MSS-endometrial cancer, and ovarian cancer expansion cohorts. Error bars represent SE of the mean. Lin3$^-$, negative for expression of lineage markers for T and B cells and monocytes (CD3, CD14, CD19, and CD20). *P<0.01 versus change from baseline value on study day –5 using pairwise comparison by Wilcoxon method. MSS, microsatellite stable; MSS-CRC, microsatellite-stable colorectal cancer; NK, natural killer; NSCLC, non-small cell lung cancer.

Levels of immune activating cytokines CXCL10 and CXCL11 increased in the periphery 5 weeks after combination treatment (figure 3A,B). Intratumoral proliferation of CD3$^+$Ki67$^+$ cells, granzyme B$^+$ (GZMB$^+$) cells, and CD8$^+$ cells significantly increased at week 9 after combination treatment (p=0.02, p=0.002, and p=0.01, respectively;

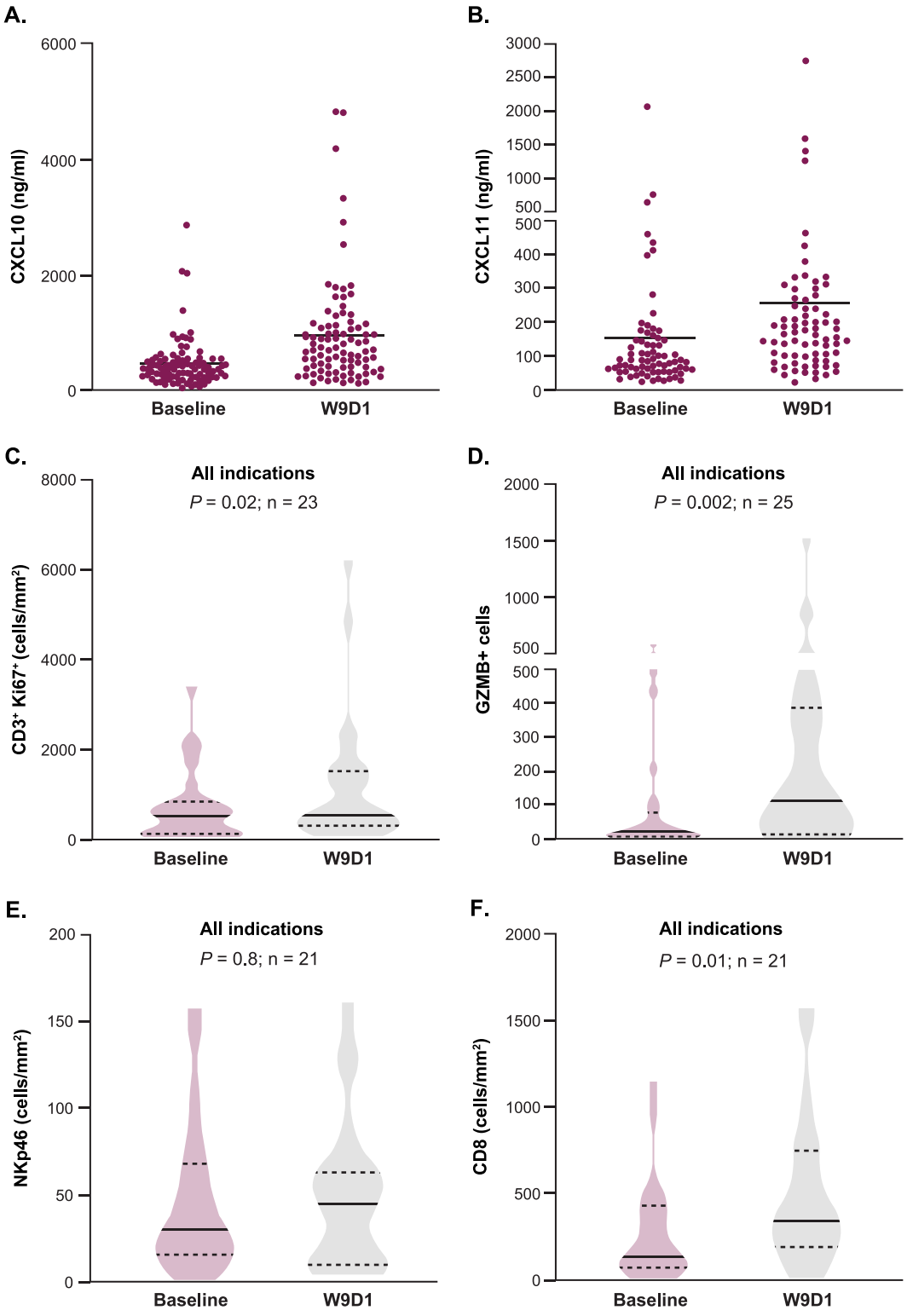

Figure 3 Immune activation in the periphery and tumor microenvironment. Levels of immune activating cytokines (A) CXCL10 and (B) CXCL11 at baseline and after monalizumab and durvalumab treatment. Intratumoral levels of (C) $CD3^{+}Ki67^{+}$, (D) GZMB, (E) NKp46, and (F) CD8 cells at baseline and after monalizumab and durvalumab treatment. Samples were obtained from patients treated with monalizumab and durvalumab in the NSCLC, CRC, MSS-endometrial cancer, and ovarian cancer expansion cohorts. CXCL-10, C-X-C motif chemokine ligand 10; CXCL11, C-X-C motif chemokine ligand 11; D, day; GZMB, Granzyme B; MSS, microsatellite stable; MSS-CRC, microsatellite-stable colorectal cancer; NSCLC, non-small cell lung cancer; W, week.

figure 3C,D,F). No significant increase in intratumoral NKp46$^+$ cells was observed (figure 3E).

Tumor-expression levels of PD-L1, HLA-E, NKp46, and CD8$^+$ cells before treatment were not associated with efficacy in the dose-escalation phase, and only minimal positive correlations between intratumoral HLA-E and PD-L1 expression levels were observed (R=0.17, p=0.13; online supplemental figure 6). A positive association between intratumoral quantities of NKp46$^+$ and CD8$^+$ T cells was observed at baseline (online supplemental figure 6A). An in vitro co-culture assay system was used to evaluate the contributions of durvalumab or monalizumab to the observed changes in circulating cell populations. An increase in the proliferation of NK cells and the expression of CD38 on CD56^{bright} NK cells was observed in the presence of monalizumab, but not durvalumab (online supplemental figure 7).

DISCUSSION

In this first combination study evaluating durvalumab plus monalizumab in patients with advanced recurrent or metastatic solid tumors, the dose escalation showed a manageable safety profile with no DLTs. Overall, ORRs were ≤10% among the five expansion cohorts of part 1 and part 2, with six PRs (MSS-CRC, n=2; ovarian, n=2; and NSCLC, n=2) and one CR (MSS-CRC). Notably, two patients (MSS-CRC and ovarian cancer) had durable responses (≥104 weeks and ≥88 weeks, respectively). Although only modest clinical activity was reported, responses were observed in patients with tumor types that previously had demonstrated limited activity with immunotherapy, such as MSS-CRC.[28]

Pharmacodynamic effects in the peripheral blood were consistent with the proposed mechanisms of action of monalizumab and durvalumab. Following treatment with monalizumab and durvalumab, immune activation was observed in the periphery, as indicated by increased expression of CD38 on CD56^{bright} NK cells. While CD38 is constitutively expressed on NK cells, increased expression has been reported in patients following vaccination or recent viral infection, suggesting that surface expression increases with cell activation.[29 30] The increase occurred predominantly in the CD56^{bright} NK cell subset, which expresses NKG2A.[24] This suggests that the effect was mediated by monalizumab treatment, particularly since complete receptor saturation was observed with the 750 mg dose Q2W. The results demonstrated increases in circulating quantities of CD8$^+$Ki67$^+$ T cells, consistent with the magnitudes observed in patients receiving durvalumab monotherapy, suggesting that monalizumab elicits a minimal effect on CD8$^+$ T cells. Based on these observations, it is likely that monalizumab and durvalumab exert non-overlapping activities on NK and T cells, respectively. Immune activation observed in the TME at week 9, as evidenced by increased proliferating total T cells, CD8$^+$ T cells, and granzyme B-expressing cells, suggests that the combination of monalizumab and durvalumab potentiates the immune response.

Though the safety profile of monalizumab combination therapy is clinically favorable and the translational data support immune activation, the overall efficacy signal in this relatively small cohort of patients with advanced disease was modest. Owing to the low number of responders and variability observed in the exploratory analyses of immunological profiles, potential correlations between clinical outcome and immune activation could not be identified. Possible reasons for a lack of robust activity may include host and tumor characteristics or suboptimal immune activation unable to overcome immune suppression. Notably, most patients had a high tumor volume and may have had complex molecular aberrations, as suggested by the advanced stage of disease. It is also currently recognized that most of the tumor types enrolled in this study are not responsive to checkpoint inhibitor monotherapy, except in specific patient populations, such as those with high PD-L1 expression or microsatellite instability status. Additionally, the general lack of efficacy of immune checkpoint inhibitors in heavily pretreated populations has been observed in several clinical trials.[31 32] In the context of advanced disease after multiple lines of prior therapy, this may be compounded by a lack of immune fitness and a downregulation of effector CD8$^+$ T cells. Despite the large sample size, subgroup analysis to evaluate host immune response was difficult due to the heterogeneous nature of the patient population (ie, multiple tumor types and differences in prior lines of therapies).

The therapeutic potential of targeting NK cell activation in solid tumors is evolving with a better understanding of positive and negative regulators of NK cell effector function.[1] Similar to CD8$^+$ T cells, the TME plays an important role in modulating the activity of NK cells. For instance, TME inhibitory signals reduce NK cell localization and lead to phenotypic modifications of NK cells in the peritumoral area.[8] However, the clinical impact of NKG2A inhibition has not been completely elucidated,[1] and combination strategies targeting other NK cell checkpoint molecules and immune activation pathways might be necessary to drive clinically meaningful therapeutic responses. Monalizumab could be combined with standard chemotherapy, targeted therapies that activate the immune system, or novel agents that promote antitumor immunity. Studying the effects in a homogeneous patient population within a limited stage disease setting known to be responsive to immune checkpoint inhibition therapy may provide additional insight. Based on the preliminary clinical activity observed in parts 1 and 2 of the current study, a dose-exploration part evaluated the combination of monalizumab and durvalumab with standard-of-care chemotherapy, with or without biological agents (bevacizumab or cetuximab), in patients with MSS-CRC who are receiving first-line or second-line treatment.

Monalizumab is being evaluated in clinical trials in combination with other therapies in several cancer types

including squamous cell carcinoma of the head and neck (HNSCC) and NSCLC (online supplemental table 1). In an ongoing phase 2 trial (NCT02643550) in patients with recurrent or metastatic HNSCC, the combination of monalizumab, cetuximab, and durvalumab was well-tolerated and demonstrated preliminary antitumor activity with confirmed PRs in 13/40 patients (ORR, 32.5%), including three CRs.[33] A randomized phase 3 trial, INTERLINK-1, evaluated the efficacy and safety of monalizumab and cetuximab in patients with recurrent or metastatic HNSCC with prior PD-(L)1 inhibitor treatment (NCT04590963); however, the study did not meet a predefined threshold for efficacy as per a planned futility interim analysis.[34] The combination of monalizumab and durvalumab is also being clinically evaluated. Interim results from the phase 2 COAST (NCT03822351) study demonstrated improved ORR and PFS with the combination, compared with durvalumab monotherapy in patients with unresectable, locally advanced, stage 3 NSCLC.[35] A phase 3 study (PACIFIC-9) of monalizumab and durvalumab following concurrent chemoradiation in patients with locally advanced, stage 3, unresectable NSCLC is recruiting patients (NCT05221840). Additional phase 2 studies are ongoing in patients with early-stage, resectable NSCLC to determine whether monalizumab and durvalumab can improve outcomes when combined with chemotherapy and followed by surgical resection. The neo-COAST study is evaluating monalizumab with durvalumab followed by surgical resection (NCT03794544). A major pathological response occurred in 30% of patients treated with durvalumab in combination with monalizumab.[36] Targeting NK cells in the field of immune oncotherapy continues to remain an important and promising therapeutic approach. In addition to the findings from the current study, results from ongoing clinical trials in this area will provide important data in guiding this developing area of clinical research.

The current study highlights the potential clinical utility of combining therapies that block the non-redundant NKG2A/HLA-E and PD-1/PD-L1 pathways to enhance the immune response of NK and $CD8^+$ T cells in the TME. The results of this study support the exploration of combinatorial treatment approaches that enhance both innate and adaptive immune responses.

Author affiliations
[1]University of California San Diego, Moores Cancer Center, San Diego, California, USA
[2]Hospital Universitario Ramón y Cajal, Madrid, Spain
[3]Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK
[4]Henry Ford Health System, Detroit, Michigan, USA
[5]Johns Hopkins Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, USA
[6]Johns Hopkins Medicine The Bloomberg~Kimmel Institute for Cancer Immunotherapy, Baltimore, Maryland, USA
[7]BioPharmaceuticals Research and Development, AstraZeneca, South San Francisco, California, USA
[8]Oncology Research and Development, AstraZeneca, Gaithersburg, Maryland, USA
[9]University of Colorado, Anschutz Medical Campus, Denver, Colorado, USA
[10]Memorial Sloan Kettering Cancer Center, New York, New York, USA
[11]Legorreta Cancer Center at Brown University, Lifespan Cancer Institute, Providence, Rhode Island, USA

Twitter Sandip P Patel @PatelOncology and Jarushka Naidoo @DrJNaidoo

Acknowledgements Medical writing assistance, conducted in accordance with Good Publication Practice Update 2022 (GPP 2022) and the International Committee of Medical Journal Editors (ICMJE) guidelines, was provided by Oxford PharmaGenesis, Newtown, PA, USA, and funded by AstraZeneca, Gaithersburg, MD, USA. Parts of this work were presented previously at ASCO 2018 (Segal NH, *et al*, Abstract 3540) and at ESMO 2018 (Diamond JR, *et al*, Abstract 1194-P).

Contributors SPP: data acquisition, analysis, interpretation, and preparation of manuscript. TA-G, DCP: data interpretation and manuscript review. SB, JRD, MDH, BAC: data acquisition, data interpretation, and manuscript review. DW, JN: data acquisition, data interpretation, and manuscript review. NES: design of translational methods (flow cytometry), translational data analysis, figure preparation, methods, results, and discussion sections. L-YC, PK, MD: clinical data evaluation and analysis, data interpretation, and manuscript review. MLA: design translational strategy; translational data evaluation and analysis, preparation of the figures, materials and methods, results, and discussion sections for the translational data reported herein. All authors reviewed all drafts and approved the final manuscript for submission. SPP is the guarantor for this work.

Funding This study was funded by AstraZeneca, Gaithersburg, MD, USA. Grant number is not applicable.

Competing interests SP: scientific advisory income from: Amgen, AstraZeneca, Bristol Myers Squibb, Certis, Eli Lilly, Genentech, Illumina, Merck, Pfizer, Rakuten, and Tempus; SP's university receives research funding from: Amgen, AstraZeneca/MedImmune, Bristol Myers Squibb, Eli Lilly, Fate Therapeutics, Iovance, Merck, Pfizer, Roche/Genentech, and SQZ Biotechnologies.TA-G has received research funding, honoraria, and non-financial or other support from IPSEN, Adacap, Pfizer, Sanofi, EISAI, Lilly, Bayer, Janssen, BMS, Astellas, Novartis, Roche, and Merck. SB: institutional grants: AstraZeneca and GlaxoSmithKline. Honoraria for Advisory boards: Amgen, AstraZeneca, Genmab, GlaxoSmithKline, Immunogen, Merck Sharp & Dohme, Merck Sereno, Mersana Therapeutics, OncXerna, Seagen, and Shattuck Labs; Honoraria for lectures: Amgen, AstraZeneca, Clovis, GlaxoSmithKline, Immunogen, Merck Sharp & Dohme, Mersana Therapeutics, Pfizer, and Roche. DW, JN, NES, DCP, L-YC, PK, MDH: employment by and stock ownership/options in AstraZeneca. MLA: former employment by and stock ownership/options in AstraZeneca. MD: employment by and stock ownership/options in AstraZeneca. JRD: institutional funds received from: AstraZeneca, Abbvie, Astellas, Gilead, Merck, Deciphera, Hutchison, BMS, Adlai Norte, Takeda, OnKure Therapeutics; Consulting: Gilead, OnKure Therapeutics; Equity Interest: OnKure Therapeutics. BAC: institutional research support: Astra Zeneca, Abbvie, Actuate Therapeutics, Astellas, Bayer, Dragonfly Therapeutics, Pfizer, Repare Therapeutics. Scientific advisory boards: Foundation Medicine, Tempus, Seattle Genetics, G1 therapeutics.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study was conducted in accordance with all local laws, International Conference on Harmonization and Good Clinical Practice guidelines, ethical principles outlined in the Declaration of Helsinki, and an Independent Ethics Committee review (online supplemental table 2). Participants gave informed consent to participate in the study before taking part. All patients provided written informed consent before study entry.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. AstraZeneca's data sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

ORCID iDs
Sandip P Patel http://orcid.org/0000-0002-8387-4840
Jarushka Naidoo http://orcid.org/0000-0002-3470-8686

REFERENCES

1 Poggi A, Zocchi MR. Natural killer cells and immune-Checkpoint inhibitor therapy: Current knowledge and new challenges. *Mol Ther Oncolytics* 2022;24:26–42.
2 Jiang X, Wang J, Deng X, *et al*. Role of the tumor Microenvironment in PD-L1/PD-1-mediated tumor immune escape. *Mol Cancer* 2019;18:10.
3 Ribas A, Wolchok JD. Cancer Immunotherapy using Checkpoint blockade. *Science* 2018;359:1350–5.
4 Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint blockade in cancer therapy. *J Clin Oncol* 2015;33:1974–82.
5 Cristescu R, Aurora-Garg D, Albright A, *et al*. Tumor mutational burden predicts the efficacy of Pembrolizumab monotherapy: a pan-tumor retrospective analysis of participants with advanced solid tumors. *J Immunother Cancer* 2022;10:e003091.
6 Russell BL, Sooklal SA, Malindisa ST, *et al*. The tumor Microenvironment factors that promote resistance to immune Checkpoint blockade therapy. *Front Oncol* 2021;11:641428.
7 Woan KV, Miller JS. Harnessing natural killer cell antitumor immunity: from the bench to bedside. *Cancer Immunol Res* 2019;7:1742–7.
8 Chen Z, Yang Y, Liu LL, *et al*. n.d. Strategies to augment natural killer (NK) cell activity against solid tumors. *Cancers*;11:1040.
9 Hsu J, Hodgins JJ, Marathe M, *et al*. Contribution of NK cells to Immunotherapy mediated by PD-1/PD-L1 blockade. *J Clin Invest* 2018;128:4654–68.
10 Park J-E, Kim S-E, Keam B, *et al*. Anti-tumor effects of NK cells and anti-PD-L1 antibody with antibody-dependent cellular cytotoxicity in PD-L1-positive cancer cell lines. *J Immunother Cancer* 2020;8:e000873.
11 Deguine J, Breart B, Lemaître F, *et al*. Cutting edge: tumor-targeting antibodies enhance Nkg2D-mediated NK cell cytotoxicity by stabilizing NK cell-tumor cell interactions. *J Immunol* 2012;189:5493–7.
12 Borst L, Sluijter M, Sturm G, *et al*. Nkg2A is a late immune Checkpoint on Cd8 T cells and marks repeated stimulation and cell division. *Int J Cancer* 2022;150:688–704.
13 André P, Denis C, Soulas C, *et al*. Anti-Nkg2A mAb is a Checkpoint inhibitor that promotes anti-tumor immunity by unleashing both T and NK cells. *Cell* 2018;175:1731–43.
14 Sheu B-C, Chiou S-H, Lin H-H, *et al*. Up-regulation of inhibitory natural killer receptors Cd94/Nkg2A with suppressed intracellular Perforin expression of tumor-infiltrating Cd8+ T lymphocytes in human Cervical carcinoma. *Cancer Res* 2005;65:2921–9.
15 Mamessier E, Sylvain A, Thibult M-L, *et al*. Human breast cancer cells enhance self tolerance by promoting evasion from NK cell antitumor immunity. *J Clin Invest* 2011;121:3609–22.
16 Platonova S, Cherfils-Vicini J, Damotte D, *et al*. Profound coordinated alterations of Intratumoral NK cell phenotype and function in lung carcinoma. *Cancer Res* 2011;71:5412–22.
17 Aparicio-Pagés MN, Verspaget HW, Peña AS, *et al*. Natural killer cell activity in patients with adenocarcinoma in the upper gastrointestinal tract. *J Clin Lab Immunol* 1991;35:27–32.
18 Gooden M, Lampen M, Jordanova ES, *et al*. HLA-E expression by gynecological cancers restrains tumor-infiltrating Cd8(+) T lymphocytes. *Proc Natl Acad Sci U S A* 2011;108:10656–61.
19 Pasero C, Gravis G, Granjeaud S, *et al*. Highly effective NK cells are associated with good prognosis in patients with metastatic prostate cancer. *Oncotarget* 2015;6:14360–73.
20 Zeestraten ECM, Reimers MS, Saadatmand S, *et al*. Combined analysis of HLA class I, HLA-E and HLA-G predicts prognosis in colon cancer patients. *Br J Cancer* 2014;110:459–68.
21 Versluis MAC, Marchal S, Plat A, *et al*. The Prognostic benefit of tumour-infiltrating natural killer cells in endometrial cancer is dependent on concurrent overexpression of human Leucocyte antigen-E in the tumour Microenvironment. *Eur J Cancer* 2017;86:285–95.
22 Ji Y, Liu P, Li Y, *et al*. A modified toxicity probability interval method for dose-finding trials. *Clin Trials* 2010;7:653–63.
23 Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
24 Voss SD, Daley J, Ritz J, *et al*. Participation of the Cd94 receptor complex in Costimulation of human natural killer cells. *J Immunol* 1998;160:1618–26.
25 Mallone R, Funaro A, Zubiaur M, *et al*. Signaling through Cd38 induces NK cell activation. *Int Immunol* 2001;13:397–409.
26 Naidus E, Bouquet J, Oh DY, *et al*. Early changes in the circulating T cells are associated with clinical outcomes after PD-L1 blockade by Durvalumab in advanced NSCLC patients. *Cancer Immunol Immunother* 2021;70:2095–102.
27 Kamphorst AO, Pillai RN, Yang S, *et al*. Proliferation of PD-1+ Cd8 T cells in peripheral blood after PD-1-targeted therapy in lung cancer patients. *Proc Natl Acad Sci U S A* 2017;114:4993–8.
28 Ooki A, Shinozaki E, Yamaguchi K. Immunotherapy in colorectal cancer: current and future strategies. *J Anus Rectum Colon* 2021;5:11–24.
29 Neves PC da C, Matos DC de S, Marcovistz R, *et al*. TLR expression and NK cell activation after human yellow fever vaccination. *Vaccine* 2009;27:5543–9.
30 Zhao J, Li Y, Jin L, *et al*. Natural killer cells are characterized by the Concomitantly increased interferon-gamma and cytotoxicity in acute resolved hepatitis B patients. *PLoS ONE* 2012;7:e49135.
31 Schoenfeld AJ, Hellmann MD. Acquired resistance to immune Checkpoint inhibitors. *Cancer Cell* 2020;37:443–55.
32 Gandini A, Puglisi S, Pirrone C, *et al*. The role of Immunotherapy in Microsatellites stable metastatic colorectal cancer: state of the art and future perspectives. *Front Oncol* 2023;13:1161048.
33 Colevas DA, Misiukiewicz K, Pearson AT, *et al*. Monalizumab, Cetuximab and Durvalumab in first line treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): a phase 2 trial. *Annals of Oncology* 2021;32:S1432.
34 pharma I. *Innate pharma provides update on Astrazeneca-sponsored INTERLINK-1 phase 3 study*. 2022.
35 Herbst RS, Majem M, Barlesi F, *et al*. COAST: an open-label, phase II, multidrug platform study of Durvalumab alone or in combination with Oleclumab or Monalizumab in patients with Unresectable, stage III non-small-cell lung cancer. *J Clin Oncol* 2022;40:3383–93.
36 Cascone T, García-Campelo R, Spicer J, *et al*. Neocoast: open-label, randomized, phase 2, multidrug platform study of Neoadjuvant Durvalumab alone or combined with novel agents in patients (Pts) with Resectable, early-stage non-small cell lung cancer (NSCLC). *Cancer Res* 2022;82(12_Supplement):CT011.