Phase I/Ib clinical trial of Sabatolimab, an Anti-TIM-3 Antibody, Alone and in Combination With Spartalizumab, an Anti-PD-1 Antibody, in Advanced Solid Tumors

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Abstract

Purpose: Sabatolimab (MBG453) and spartalizumab are monoclonal antibodies that bind T-cell immunoglobulin domain and mucin domain-3 (TIM-3) and programed death-1 (PD-1), respectively. This phase I/II study evaluated the safety and efficacy of sabatolimab, with or without spartalizumab, in patients with advanced solid tumors.

Methods: Primary objectives of the phase I/Ib part were to characterize the safety and estimate recommended doses for future studies (RP2Ds). Dose escalation was guided by a Bayesian (hierarchical) logistic regression model. Sabatolimab was administered intravenously, 20–1200 mg, every 2 or 4 weeks (Q2W, Q4W). Spartalizumab was administered intravenously, 80–400 mg, Q2W or Q4W.

Results: Enrolled patients (n=219) had a range of cancers, most commonly ovarian (17%) and colorectal cancer (7%); patients received sabatolimab (n=133) or sabatolimab plus spartalizumab (n=86). The maximum tolerated dose was not reached. The most common adverse event suspected to be treatment-related was fatigue (9%, sabatolimab; 15%, combination). No responses were seen with sabatolimab. Five patients receiving combination treatment had partial responses (6%; lasting 12–27 months), in colorectal cancer (n=2), non-small cell lung cancer (NSCLC), malignant perianal melanoma, and SCLC. Of the five, two patients had elevated expression of immune markers in baseline biopsies; another three had >10% TIM-3 positive staining, including one patient with NSCLC who received prior PD-1 therapy.

Conclusions: Sabatolimab plus spartalizumab was well tolerated and showed preliminary signs of antitumor activity. The RP2D for sabatolimab was selected as

800 mg Q4W (alternatively Q3W or Q2W schedules, based on modeling), with or without 400 mg spartalizumab Q4W.

Statement of translational relevance:

With many patients still failing to respond or progressing on immunotherapy, additional treatment options and new combination strategies are needed. In this first-in-human study in patients with advanced solid tumors, we establish sabatolimab as a novel immunotherapeutic agent which is well tolerated and showed preliminary signs of activity in combination with checkpoint inhibition. Although clinical activity was limited in this phase I study, the ongoing expansion phase will further determine the relevance of TIM-3 inhibition in solid tumors. With the RP2D now established, sabatolimab is also being investigated in a variety of hematologic malignancies where there is a strong rationale for TIM-3 inhibition.

Introduction

Immunotherapy is an important treatment strategy in cancer (1,2); however, many patients still fail to respond to checkpoint inhibitors or progress on treatment, highlighting a need for novel therapies and combinations (1,3).

TIM-3 is an inhibitory receptor with complex roles in the regulation of both innate and adaptive immune responses (4). It is broadly expressed on myeloid cells, natural killer cells, and dysfunctional T cells, often co-expressed with PD-1 (5-7). TIM-3 may also play a role in resistance to PD-1 blockade, with upregulation of TIM-3 reported both in mouse models and in patients progressing on, or exposed ex vivo to, anti-PD-1 (8,9). In animal models, dual blockade of TIM-3 and PD-1 restored T-cell function and suppressed tumor growth more effectively than targeting either pathway alone, supporting a rationale for combination therapy (7,10).

Sabatolimab (MBG453) is a humanized IgG4 (S228P; stabilized hinge mutation) monoclonal antibody (mAb) that binds TIM-3 with subnanomolar affinity and blocks interaction with its ligand, phosphatidylserine (PtdSer) and partially blocks the interaction of TIM-3 with Galectin-9 (11,12). Spartalizumab (PDR001) is a humanized IgG4 (S228P) mAb that binds PD-1 with subnanomolar activity and blocks interaction with programed death-ligand 1/2 (PD-L1/PD-L2) (13). Preliminary clinical activity has been seen with spartalizumab in patients with non-small cell lung cancer (NSCLC), melanoma, anaplastic thyroid cancer, and nasopharyngeal cancer (14-16). The safety profile is similar to other PD-1 mAbs (13,17,18).

This first-in-human phase I/II study was designed to investigate the safety and efficacy of sabatolimab, alone and in combination with spartalizumab, in patients with advanced solid tumors. Here, we describe the results from the phase I/Ib part.

Methods

Clinical Study Design and Oversight

This phase I/II, multi-center, open-label study (NCT02608268) included a phase I single-agent dose-escalation part, a phase Ib combination dose-escalation part, a dose-ranging part (DRP), and a phase II part. The DRP was dependent on preliminary efficacy (response or durable stable disease [SD] with tumor shrinkage, per Response Evaluation Criteria In Solid Tumors [RECIST] v1.1) during dose escalation. The DRP enrolled patients with advanced solid tumors, excluding melanoma, NSCLC, or renal cell carcinoma, and used doses deemed safe during dose escalation.

The study was sponsored by Novartis and was performed in compliance with Good Clinical Practice. The study protocol was approved by an Independent Ethics Committee or Institutional Review Board for each center and was conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from each patient. The first patient was enrolled on November 23, 2015; the data cut-off date was July 25, 2019.

Study Objectives

Primary objectives for the phase I/Ib part were to characterize the safety and tolerability of sabatolimab, with and without spartalizumab, and to estimate recommended doses for future studies. The primary objective for the DRP was to further investigate the safety and tolerability of sabatolimab. Secondary objectives included evaluation of preliminary antitumor activity, characterization of the

pharmacokinetic (PK) profile, and assessment of potential biomarkers of response to sabatolimab, with and without spartalizumab.

Patients

Patients eligible for the phase I/Ib part had advanced/metastatic solid tumors and had progressed on or were intolerant of standard therapy or had no standard therapy available. Patients were aged ≥18 years with adequate hematologic and organ function and an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. They were required to have measurable or non-measurable disease per RECIST v1.1, a tumor amenable to biopsy, and to give consent to biopsy at baseline.

Key exclusion criteria included history of hypersensitivity reactions to mAbs or drug-induced pneumonitis; active or history of autoimmune disease; current immunosuppressive medication; prior treatment with anti-CTLA-4 mAbs in combination with another checkpoint-targeting drug; prior participation in another investigational immunotherapy study; prior PD-1 or PD-L1 directed therapies were permitted if there was no incidence of associated toxicity leading to discontinuation of therapy.

In the phase II part of the study (not described here), patients eligible for combination treatment included those with melanoma, NSCLC, and renal cell carcinoma; patients eligible for sabatolimab treatment had advanced solid tumors, based on antitumor activity observed during phase I.

It was planned to enroll cohorts of 3–6 patients in the dose-escalation part, including at least 6 patients at the maximum tolerated dose/recommended phase II dose (RP2D) level. At least 21 and 15 patients were expected to be treated with single

agent and combination, respectively, for the model to have reasonable operating characteristics relating to maximum tolerated dose recommendation. A sample size of approximately 30–50 patients was to be treated in the DRP to gain more information about the overall safety and tolerability of sabatolimab.

Treatment Plan

The starting dose of single-agent sabatolimab was 80 mg, based on 5-week good laboratory practice toxicology studies in cynomolgus monkeys, or 20 mg when in combination with spartalizumab. The starting dose of spartalizumab was 80 mg. Both drugs were administered via intravenous infusion over 30 minutes, once every 2 or 4 weeks (Q2W, Q4W). Dose levels are detailed in **Supplementary Tables S1–2**. Dose-escalation decisions were guided by a Bayesian (hierarchical) logistic regression model (19) following the escalation with overdose control (EWOC) principle (20).

When given in combination, sabatolimab and spartalizumab were administered on the same day, with sabatolimab administered first. If the patient experienced an infusion reaction, appropriate premedication was permitted for subsequent doses. Treatment was administered until unacceptable toxicity, progressive disease as per immune-related response criteria (irRC), confirmed complete response (CR; per RECIST v1.1), or patient/physician decision. Treatment was discontinued if more than 2 consecutive doses of sabatolimab were missed due to toxicity, unless the patient was judged to be experiencing clinical benefit.

Dose-escalation decisions were based on all available safety, dose limiting toxicities (DLT), PK, and pharmacodynamic (PD) data, guided by a Bayesian (hierarchical)

logistic regression model (B[H]LRM) for sabatolimab in combination with spartalizumab and a BLRM for sabatolimab single agent. In both cases, the EWOC principle was applied. The BHLRM used in this study is an extension of the standard Bayesian hierarchical model (21,22). In the BHLRM, 2 strata were included for the 2 schedules tested in dose escalation. Additional strata allowed the incorporation of historical information on DLTs seen with single-agent spartalizumab. Within this structure the exchangeability, or otherwise, of dose/DLT information from the 2 tested schedules and the historical data were assessed in an ongoing fashion, allowing the model to adjust appropriately to differences in toxicity between the tested schedules or between those schedules and the historical data.

The dose-determining set for single-agent sabatolimab (Sab set) included patients who received all planned doses in cycle 1 (C1; each cycle is 28 days) and safety evaluations ≥28 days following the first dose, or who experienced a DLT during C1. The dose-determining set for combination treatment (Sab+Spart set) included patients who complete combination treatment in C1 (who also did not experience a DLT in C1) and received at least 1 dose of both sabatolimab and spartalizumab in C2 (and safety evaluations ≥28 days following the first dose of C2), or who experienced a DLT during C2.

A DLT was defined as an adverse event (AE) or abnormal laboratory value of grade 3 or above, assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications; exceptions are detailed in the study protocol.

Safety and Response Assessments

Regular safety assessments were performed based on physical examination, vital signs, ECOG performance status, laboratory parameters, and cardiac assessments. AEs, defined by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, were assessed at every visit.

Efficacy was evaluated by local investigator's assessment using RECIST v1.1 (23). Tumor assessments were performed at baseline by contrast-enhanced computed tomography with intravenous contrast of the brain, chest, abdomen, pelvis, and if there was evidence of disease, the neck. Subsequent assessments were performed on cycle 3 day 1 (C3D1), every 2 cycles until C11D1, then every 3 cycles until disease progression per irRC or patient withdrawal. Subsequent brain tumor assessments were performed only if disease was detected at baseline.

Pharmacokinetic Assessments

Serum samples were collected for PK profiling: pre-infusion and 1, 24, 168, 240, and 336 hours post-infusion during C1 and C3; pre-infusion during C4; pre-infusion and 1 hour post-infusion during C5–C6; and at the end of treatment. PK parameters included maximum concentration, exposure, and half-life. Samples were also analyzed for soluble TIM-3 (sTIM-3) using a validated ELISA. PK data were described using noncompartmental analysis, and together with sTIM-3 data, a PK/PD population model was developed.

Pharmacodynamic Assessments

Tumor biopsies were collected at screening. Expression of CD8 (Ventana, clone CD8/144B), PD-L1 (Dako, 22C3 pharmaDx), CD163 (Ventana, clone MRQ-26),

lymphocyte-activation gene 3 (LAG-3; Ventana, clone 17B4, R1231), and TIM-3 (Ventana, clone D5D5R, R1262) were evaluated by immunohistochemistry. Immunohistochemistry data are expressed as described in **Supplementary Table S3**.. Tumor biopsies were also analyzed using RNA sequencing (24,25); analyses focused on 28 genes and 7 gene signatures related to immune cell infiltration/function or pathways associated with TIM-3. The interferon gamma (IFNγ) (26), B-cell, cytotoxic cell, macrophage, and T-cell signatures (27) have been described; additional signatures were developed for neutrophils and regulatory T-cells (Tregs).

Statistical Methods

Data from the study were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and PD measurements using descriptive statistics (mean, standard deviation, median, minimum, and maximum), contingency tables (frequencies and percentages), and inferential analyses. Overall response rates (ORRs; CR or partial response [PR]) and disease control rates (DCRs; PR, CR, or SD) are summarized with accompanying 95% confidence intervals calculated using the exact Clopper–Pearson method.

Results

Patient Characteristics and Disposition

As of July 25, 2019, 219 patients had been treated in the phase I/Ib part of the study. Patients received single-agent sabatolimab (n=87) or sabatolimab plus

spartalizumab (n=86) Q2W or Q4W in the dose-escalation part, and single-agent sabatolimab (n=46) Q4W in the DRP. Sabatolimab was administered at doses 20–1200 mg and spartalizumab was administered at doses 80–400 mg.

Patient demographics and baseline characteristics are shown in **Table 1**. The median age was 59 years (range 23–86) and 95% of patients had an ECOG performance status of 0 or 1. Patients had a wide range of primary tumor types, most commonly ovarian cancer (n=37; 17%), colorectal cancer (CRC; n=15; 7%), mesothelioma, and pancreatic cancer (each n=12; 5%). A minority of patients were previously treated with PD-1/PD-L1 therapy (15%, prior PD-1; 2%, prior PD-L1). A total of 212 patients (97%) discontinued from study treatment, due to progressive disease (n=177; 81%), patient or physician decision (n=18; 8%), death (n=11; 5%), or AEs (n=6; 3%); the majority (96%) did not enter post-treatment follow-up.

DLTs, PK, RP2D

Of 151 patients included in the dose-determining set, 1 patient experienced a DLT: grade 4 myasthenia gravis, starting August 2017 (study day 21) and ending September 2017. The patient had a primary diagnosis of thymoma and received sabatolimab (240 mg Q4W) + spartalizumab (80 mg Q4W). The patient discontinued treatment and subsequently died due to disseminated intravascular coagulation over 30 days after the end of treatment.

PK parameters for sabatolimab and spartalizumab are shown in **Fig. 1** and **Supplementary Tables S1, S2, and S4**. Sabatolimab exposure was approximately dose-proportional from 240–1200 mg and sabatolimab exposures were comparable for single-agent and combination treatment. Accumulation of sabatolimab was low to

moderate and mean half-life in C1 ranged from 6 to 17 days. Levels of circulating sTIM-3 plateaued at doses above 800 mg Q4W and 240 mg Q2W (**Fig. 2**). A PK/PD population model was established to describe the dynamics of sTIM-3 and the simulation of target occupancy (11).

Based on PK, circulating sTIM-3 data, and the PK/PD model, the RP2D for sabatolimab was established at 800 mg Q4W, with alternative dosing schedules of 600 mg Q3W or 400 mg Q2W (based on modeling data), alone or in combination with spartalizumab at 400 mg Q4W. These doses were expected to maintain target occupancy greater than 90% in the tumor, in at least 90% of patients. As described below, sabatolimab with or without spartalizumab had a favorable safety profile at all dose levels, supporting these RP2Ds.

Safety and tolerability

Overall, 209 patients (95%) experienced at least one AE regardless of relationship to study treatment; 111 patients (51%) experienced grade 3/4 events (**Fig. 3**, **Supplementary Table S5**). There was no evidence that AE incidence was related to dose.

AEs considered by the investigator to be related to study treatment were experienced by 105 patients (48%; **Fig. 3**, **Supplementary Table S6**); incidence was higher in patients receiving combination treatment compared with single agent (58% vs 41%). The most frequent AE (≥5% of patients) reported with sabatolimab was fatigue (n=12; 9%), and most frequent AEs for combination treatment were fatigue (n=13; 15%), decreased appetite (n=7; 8%), diarrhea, rash (each n=6; 7%), elevated aspartate aminotransferase, and nausea (each n=5; 6%). Grade 3/4 AEs

suspected to be related to treatment were reported in 8 patients (9%) receiving combination treatment and 4 patients (3%) receiving single agent; the only grade 3/4 AE occurring in more than 1 patient was elevated lipase (n=2; 1%), in 2 patients receiving single-agent sabatolimab (80 mg Q4W; 1200 mg Q4W). Most suspected-related grade 3/4 AEs resolved without intervention (n=7); treatment was interrupted in 3 patients (anemia; hyperglycemia; gamma glutamyltransferase increase and hepatitis; all grade 3) and discontinued in 2 patients (grade 3 polyarthritis; grade 4 myasthenia gravis). An additional 7 patients discontinued treatment due to AEs, not suspected to be treatment related. Serious AEs (SAEs) suspected to be related to study treatment were reported for 5 patients (2%; 8 events), all in the combination group: grade 2 elevated blood alkaline phosphatase, grade 3 elevated gamma-glutamyltransferase, and grade 2 and 3 hepatitis in 1 patient (treatment interrupted); grade 2 nervous system disorder (acute neurologic syndrome associated with acute iatrogenic adrenal insufficiency; treatment interrupted); grade 2 pleural effusion (resolved without intervention); grade 4 myasthenia gravis (treatment discontinued); and grade 3 immune-related hepatitis (unknown). AEs of special interest, including potentially immune-related AEs, are summarized in **Supplementary Table S7**. There were 26 deaths on study: 23 (88%) from malignancy or disease progression, 1 from esophageal varices hemorrhage, 1 from pneumonia aspiration, and 1 unknown.

Efficacy

Median follow-up for efficacy was 5.7 months (0.2–39.6 months). Per RECIST v1.1, no responses were observed in patients receiving single-agent sabatolimab; SD was the best response reported for 34 patients (26%; **Supplementary Table S8**). Of these, 9 had SD lasting at least 6 months, in patients with mesothelioma, ovarian

cancer, small cell lung cancer (SCLC; each n=2), chordoma, NSCLC, and hemangiopericytoma (each n=1; **Fig. 4A**, **C**).

Five patients treated with sabatolimab plus spartalizumab had a PR (ORR = 6%; 95% CI, 2–13; **Supplementary Table S8**). Responses were seen in patients with CRC (n=2), NSCLC, malignant perianal melanoma, and SCLC (each n=1); of these, 1 patient with NSCLC had received prior PD-1 therapy. The duration of response for these 5 patients ranged from 12–27 months, with 3 PRs ongoing at the cut-off date (duration 20–27 months; **Fig. 4B**, **D**). A total of 33 patients (38%) receiving combination treatment had a best response of SD (DCR = 44%; 95% CI, 34–55), including 10 patients who received prior PD-1 therapy. Nine patients had SD lasting for at least 6 months (range 7–27 months), in patients with adenocarcinoma (unknown primary), CRC, endometrial cancer, liposarcoma, metastatic duodenal cancer, ovarian cancer, pheochromocytoma, and urothelial carcinoma (each n=1); the patient with liposarcoma had received prior PD-1 therapy.

One patient who experienced a PR was a 44-year-old female, former smoker, with poorly differentiated stage IV NSCLC (*EGFR*/*ROS*/*ALK* wild-type) with brain and lymph node metastases. Of note, this patient had SD as a best response to prior nivolumab therapy, followed by disease progression on nivolumab. In this study, she received sabatolimab 80 mg Q2W + spartalizumab 80 mg Q2W and had a PR, with a reduction of 69% in the sum of target lesion diameters; the response was ongoing at C29. Biomarkers analyses performed on a baseline tumor biopsy sample are described below (**Fig. 5**, **Supplementary Fig. S1**).

Biomarker analyses

Tumor biopsy samples obtained at baseline were analyzed by RNA sequencing, focusing on select genes and gene signatures related to immune cell infiltration and function in the tumor microenvironment, and pathways associated with TIM-3. Samples were also analyzed by immunohistochemistry. Biomarker data were plotted against best percentage change of the sum of the target lesion diameters (**Fig. 4**, **Supplementary Fig. S2**); there did not appear to be a relationship with any of the biomarkers analyzed.

For the responding patient with NSCLC, RNA sequencing revealed elevated expression of several genes at baseline, including FOXP3, LAG-3, PD-1, GZMB, PRF1, CCL4, and CXCL9, and immune signatures associated with IFNγ, cytotoxic T cells, Tregs, and macrophages. Immunohistochemistry analysis for this patient also revealed positive staining of TIM-3 (64%), CD8 (22%), LAG-3 (32%), CD163 (59%), and PD-L1 (80%; **Fig. 5**, S1). RNA sequencing of the screening biopsy from the responding patient with malignant perianal melanoma, who had a 39% reduction in the sum of target lesions, revealed elevated expression of a number of genes, including CD163, HAVCR2 (TIM-3), CCL3, and LGALS9, and immune signatures associated with cytotoxic T cells and macrophages. Both responding patients with CRC had >10% TIM-3 positive staining (12% and 15%) by immunohistochemistry but did not have elevated baseline levels of immune markers by RNA sequencing.

Discussion

Treatment with sabatolimab and spartalizumab was well tolerated across all doses tested. The incidence of grade 3/4 AEs suspected to be related to treatment was low, and toxicities in the combination group were consistent with those observed for

single-agent spartalizumab (13) and other αTIM-3/-PD-1 combination studies (28,29). The PK parameters for sabatolimab were not affected by addition of spartalizumab, nor was the RP2D, potentially facilitating other sabatolimab combination studies. The RP2D for sabatolimab was selected as 800 mg sabatolimab Q4W, alone or in combination with 400 mg spartalizumab Q4W. Two alternative sabatolimab dosing schedules of 600 mg Q3W or 400 mg Q2W were expected to achieve similar drug exposure and maintain 90% tumor target occupancy over the dose interval.

No responses were seen in patients receiving single-agent sabatolimab, consistent with preclinical observations that dual blockade of TIM-3 and PD-1 is more effective than targeting either pathway alone (7,10). Preliminary signs of antitumor activity were seen in patients receiving combination treatment; however, in the absence of a spartalizumab single-agent cohort, it was not possible to confirm additive or synergistic activity contributed by sabatolimab. In the combination group, 5 patients (6%) had a PR, and 9 patients had SD lasting for at least 6 months. Responses were seen in patients with NSCLC, malignant perianal melanoma, SCLC, and 2 patients with CRC: 1 microsatellite instability high and 1 microsatellite stable (investigator information, S. Hodi, March 2019; H. Gelderblom, January 2018). Clinical benefit was also seen in patients who had received prior treatment with PD-1 or PD-L1 therapy, including one PR in a patient with NSCLC who previously had durable clinical benefit followed by progression on nivolumab (last line of prior therapy). As this patient would not be expected to respond to PD-1 monotherapy, this observation supports the concept of synergistic activity. This patient had a tumor biopsy sample positive for PD-L1 and TIM-3 expression, consistent with the observation that TIM-3 upregulation has been seen following progression on PD-1 treatment (8). This

patient also had high levels of TIM-3 staining relative to CD8 staining, potentially reflecting myeloid TIM-3 detection. Overall, it was not possible to identify a relationship between potential biomarkers and response to treatment; however, 3 responding patients had >10% TIM-3–positive staining in biopsy samples. Patients were not selected based on biomarker expression and most patients receiving combination treatment had PD-L1–negative tumor biopsies. This may have limited the potential for efficacy, as PD-L1 positivity in tumors has been linked to response to PD-1 therapies (30).

These efficacy data are consistent with the preliminary data reported to date for other TIM-3–targeted agents. In a phase I study in patients with advanced relapsed/refractory solid tumors, one PR was reported in a patient with SCLC out of a cohort of 23 patients receiving the TIM-3 mAb, LY3321367 (29). In a phase I study in patients with NSCLC who had progressed on prior PD-1 therapy, 4 of 39 patients had a PR to treatment with TSR-022, a TIM-3 mAb, combined with TSR-042, a PD-1 mAb; all responding patients had PD-L1–positive tumors (28). Similar efficacy rates have also been reported for other early phase immunotherapy combination trials: 2 of 42 patients with advanced malignancies (both SCLC) and 7 of 68 patients with melanoma (prior immunotherapy) had a response to LAG-3 plus PD-1 mAb combinations (31,32). Additionally, preliminary clinical activity has been seen with sabatolimab plus HMA, decitabine, or azacitidine in patients with newly diagnosed unfit acute myeloid leukemia (AML) and higher-risk myelodysplastic syndrome (MDS) (33), where TIM-3 is expressed on leukemic stem cells and blasts but not normal hematopoietic stem cells (34-36); the safety profile was similar to that reported for HMA alone (37).

The phase II part of this study is ongoing in patients with melanoma or NSCLC resistant to PD-1/PD-L1 therapy. These data, along with the ongoing study in glioblastoma (NCT03961971), will further determine the relevance of TIM-3 inhibition in solid tumors. A comprehensive sabatolimab clinical development program is also ongoing in hematologic malignancies, based on the observation that TIM-3 is expressed on leukemic stem cells and blasts but not normal hematopoietic stem cells (34,35). This includes combinations with the HDM2-inhibitor, HDM201 (NCT03940352), venetoclax and azacitidine (NCT04150029), or hypomethylating agents (NCT03946670, NCT04266301) in patients with AML or high-risk MDS, and combination with ruxolitinib (NCT04097821) in patients with myelofibrosis.

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Table 1. Baseline patient demographics and characteristics, by treatment group.

	Dose-escalation part		Dose-ranging part	All patients
	Sabatolimab single agent n=87	Sabatolimab + spartalizumab n=86	Sabatolimab single agent n=46	(N=219)
Median age, years (range)	60.0 (23–84)	58.5 (25–86)	55.5 (31–83)	59.0 (23–86)
Sex, n (%)				
Female	45 (51.7)	39 (45.3)	37 (80.4)	121 (55.3)
Male	42 (48.3)	47 (54.7)	9 (19.6)	98 (44.7)
Race, n (%)				
Caucasian	58 (66.7)	59 (68.6)	41 (89.1)	158 (72.1)
Asian	27 (31.0)	24 (27.9)	2 (4.3)	53 (24.2)
Black	0	2 (2.3)	2 (4.3)	4 (1.8)
Other/unknown	2 (2.3)	1 (1.2)	1 (2.2)	4 (1.8)
ECOG performance status, n (%)				
0	35 (40.2)	28 (32.6)	18 (39.1)	81 (37.0)
1	47 (54.0)	53 (61.6)	26 (56.5)	126 (57.5)
2	5 (5.7)	5 (5.8)	2 (4.3)	12 (5.5)
Number of prior therapies, median (range)	3 (1–12)	3 (1–12)	3 (1–18)	3 (1–18)
Prior PD-1/PD-L1 therapy, n (%)				
Prior PD-1	11 (12.6)	21 (24.4)	0	32 (14.6)
Prior PD-L1	1 (1.1)	2 (2.3)	2 (4.3)	5 (2.3)
No prior PD-1/PD-L1	75 (86.2)	63 (73.3)	44 (95.7)	182 (83.1)
Disease diagnosis, n (%)				
Ovarian cancer	2 (2.3)	5 (5.8)	30 (65.2)	37 (16.9)
CRC	9 (10.3)	6 (7.0)	0	15 (6.8)
Mesothelioma	2 (2.3)	3 (3.5)	7 (15.2)	12 (5.5)
Pancreatic cancer	10 (11.5)	2 (2.3)	0	12 (5.5)
NSCLC	4 (4.6)	6 (7.0)	0	10 (4.6)
SCLC	0	3 (3.5)	6 (13.0)	9 (4.1)
Cholangiocarcinoma	5 (5.7)	2 (2.3)	0	7 (3.2)
Endometrial cancer	5 (5.7)	2 (2.3)	0	7 (3.2)
RCC	2 (2.3)	4 (4.7)	0	6 (2.7)
Sarcoma	4 (4.6)	2 (2.3)	0	6 (2.7)
Breast cancer	2 (2.3)	3 (3.5)	0	5 (2.3)

Cutaneous melanoma	2 (2.3)	3 (3.5)	0	5 (2.3)
Nasopharyngeal cancer	3 (3.4)	2 (2.3)	0	5 (2.3)
HCC	0	4 (4.7)	0	4 (1.8)
Merkel cell carcinoma	0	1 (1.2)	3 (6.5)	4 (1.8)
Cervical cancer	1 (1.1)	2 (2.3)	0	3 (1.4)
Esophageal cancer	0	3 (3.5)	0	3 (1.4)
Gastric cancer	2 (2.3)	1 (1.2)	0	3 (1.4)
Gastrointestinal stromal tumor	2 (2.3)	1 (1.2)	0	3 (1.4)
Glioblastoma	3 (3.4)	0	0	3 (1.4)
Head and neck cancer	2 (2.3)	1 (1.2)	0	3 (1.4)
Urothelial carcinoma	0	3 (3.5)	0	3 (1.4)
Uveal melanoma	0	3 (3.5)	0	3 (1.4)
Other[a]	27 (31.0)	24 (27.9)	0	51 (23.3)

[a]Includes indications reported in ≤2 patients.

Abbreviations: HCC, hepatocellular carcinoma; RCC, renal cell carcinoma.

Figures

Fig. 1. Sabatolimab median concentration–time profiles for sabatolimab ± spartalizumab, by treatment group. **A** Sabatolimab concentration–time profiles for patients receiving single-agent sabatolimab, by dosing schedule. **B** Sabatolimab concentration–time profiles for patients receiving sabatolimab in combination with spartalizumab, by dosing schedule. Sabatolimab single agent includes dose-escalation part and dose-ranging part.

Fig. 2. Circulating soluble TIM-3 in serum. Shaded regions correspond to 90% prediction interval from the PK/PD model. Includes data from dose-ranging part of the study.

Fig. 3. Adverse events of any grade, by treatment group. **A** AEs occurring in at least 5% of patients, regardless of relationship to study drug. **B** AEs occurring in at least 2% of patients, suspected to be related to study drug. Maximum grade is indicated. Sabatolimab single agent includes dose-escalation part and dose-ranging part.

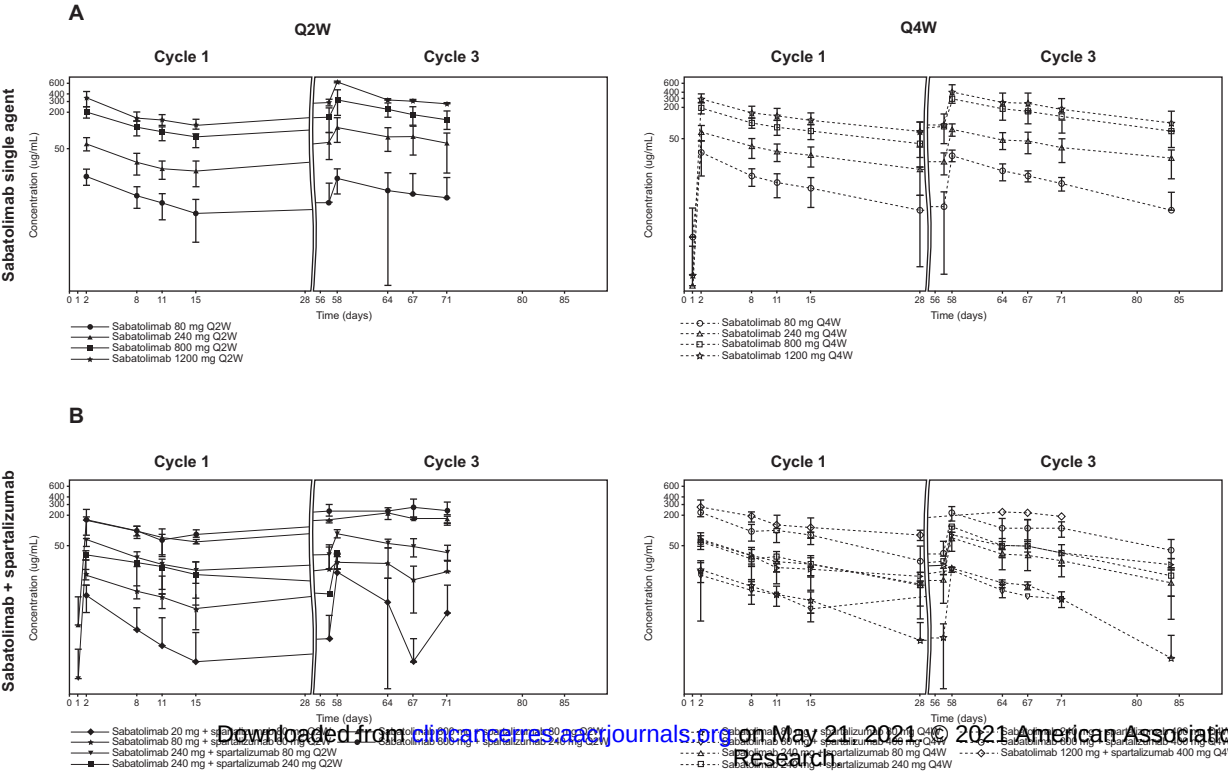
Fig. 4. Percentage change from baseline in target lesions over time and duration of exposure to sabatolimab ± spartalizumab, by treatment group. **A** Percentage change from baseline in target lesions over time in patients receiving single-agent

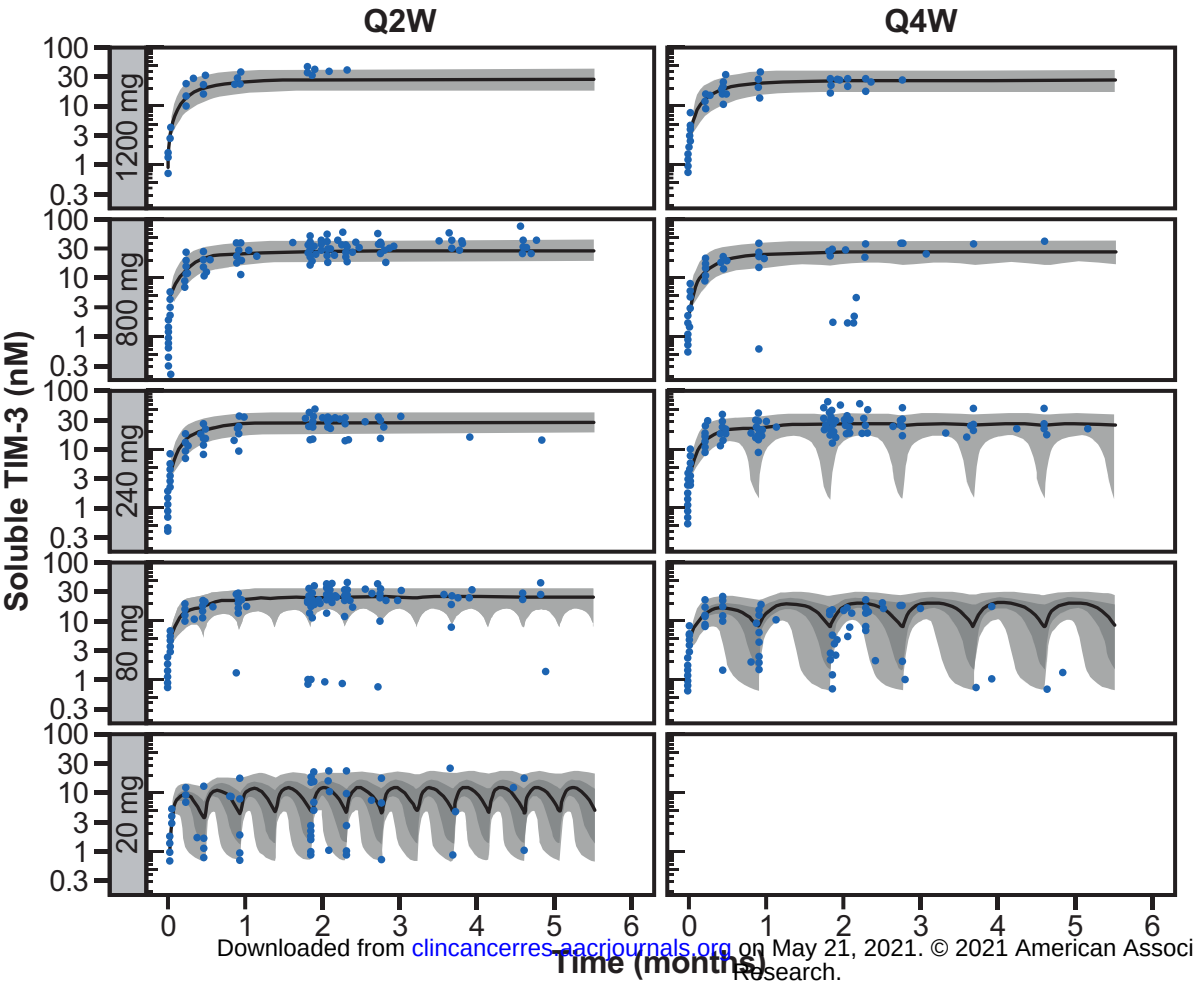
sabatolimab, by dose-escalation part and dose-ranging part. Best overall response is shown for each patient according to RECIST v1.1. **B** Percentage change from baseline in target lesions over time in patients receiving sabatolimab plus spartalizumab. Best overall response is shown for each patient according to RECIST v1.1. **C** Duration of exposure to single-agent sabatolimab, by indication, in patients with a best overall response of stable disease. Response assessments and prior PD-1/PD-L1 treatment are shown. **D** Duration of exposure to sabatolimab plus spartalizumab, by indication, in patients with a best overall response of stable disease or better. Response assessments and prior PD-1/PD-L1 treatment are shown. *One patient had decrease in the sum of diameters of target lesions more than 60%, though the patient had best overall response of progressive disease. This apparent discrepancy results from the fact that in this assessment, not all target lesions were evaluated.

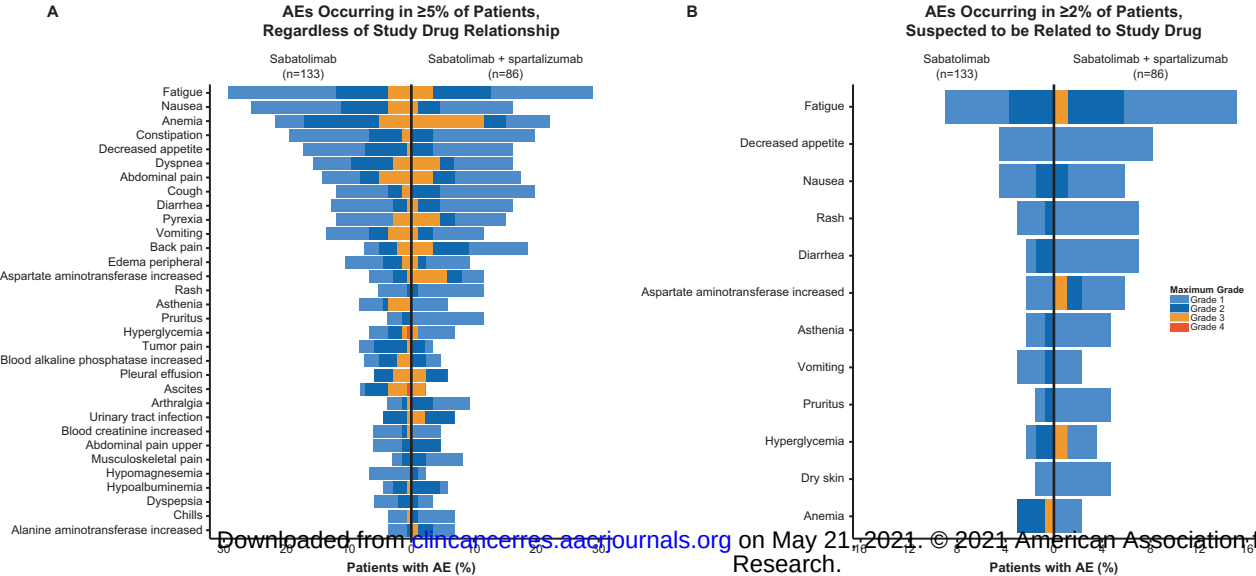
Sabatolimab single agent includes dose-escalation part and dose-ranging part. H&N, head and neck cancer; HCC, hepatocellular carcinoma; NPC, nasopharyngeal cancer; PD, progressive disease; RCC, renal cell carcinoma; UNK, unknown.

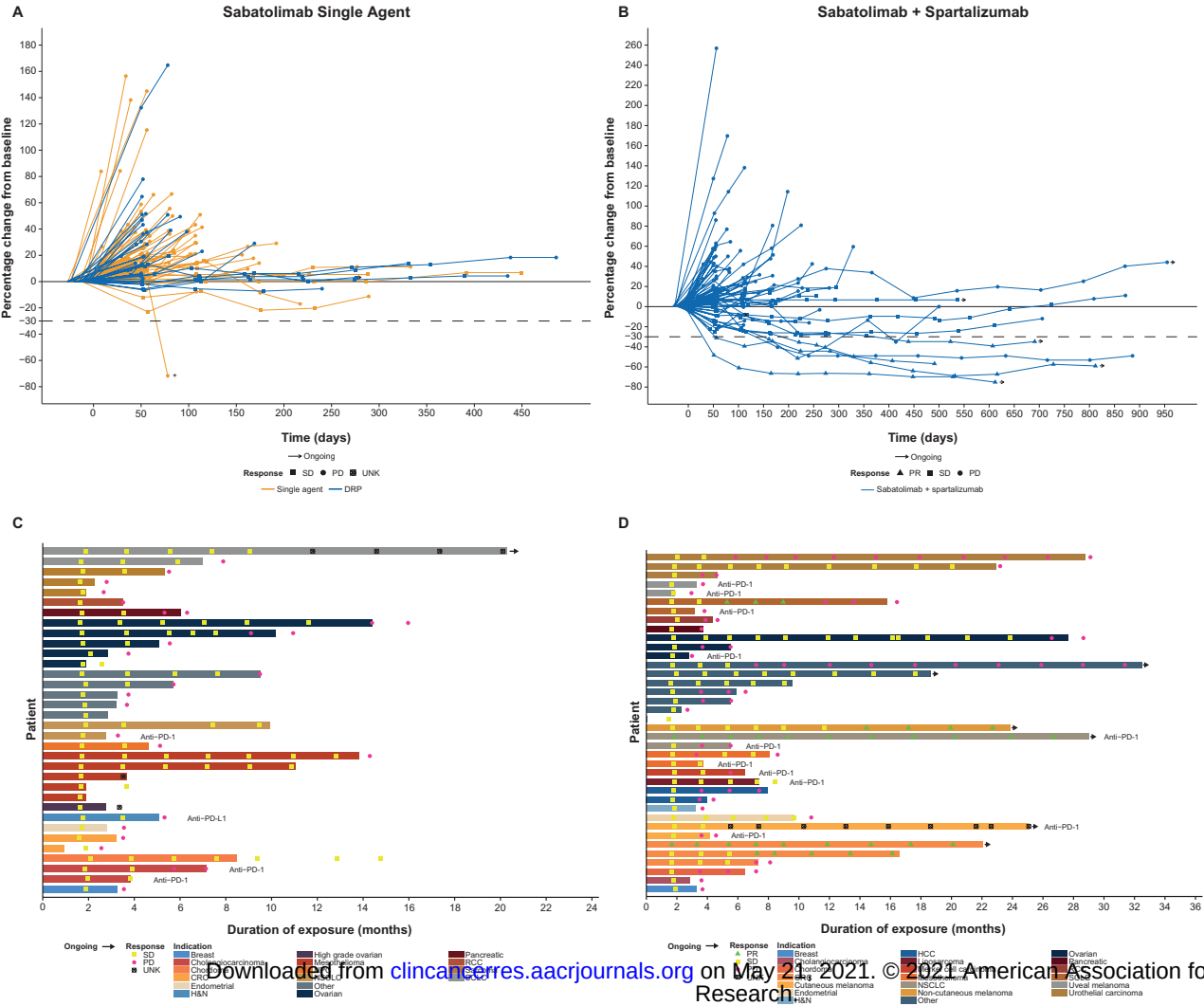
Fig. 5. Biomarker analysis in patients receiving sabatolimab + spartalizumab. Best percentage change from baseline and biomarker data were available for n=53 patients. **A** Best percentage change from baseline in target lesions over time in patients receiving sabatolimab + spartalizumab. Best overall response is shown for each patient according to RECIST v1.1. **B** Immune biomarker staining detected by immunohistochemistry in tumor biopsy samples obtained at baseline, see **Supplementary Table S3** for reportable area by analyte. **C** RNA sequencing in

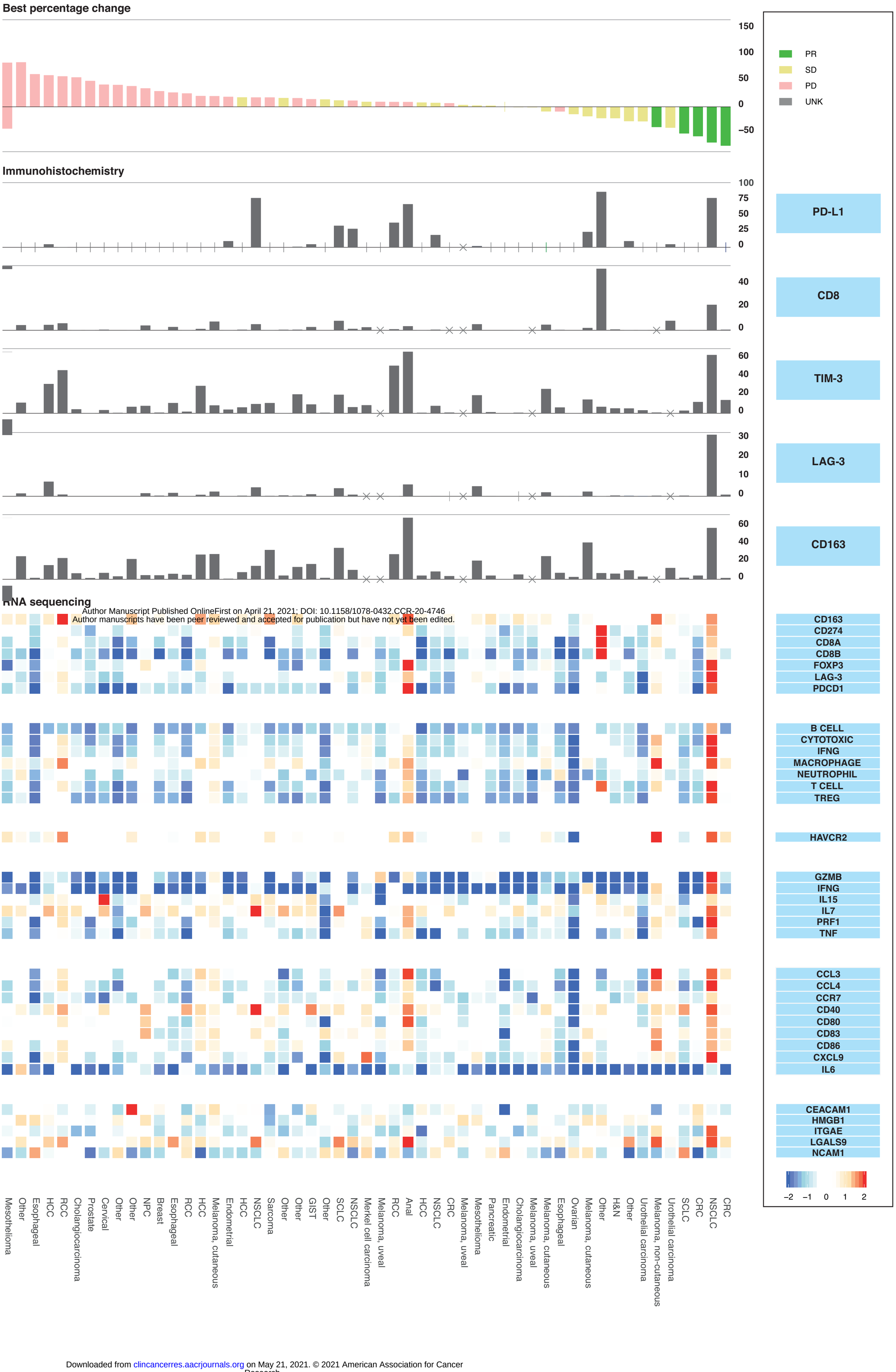
tumor biopsy samples obtained at baseline, reported as relative expression levels within the row per gene/signature. CD, cluster of differentiation; GIST, gastrointestinal stromal tumor; H&N, head and neck cancer; HCC, hepatocellular carcinoma; NA, not available; NPC, nasopharyngeal cancer; PD, progressive disease; RCC, renal cell carcinoma; UNK, unknown.











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Clinical Cancer Research

Phase I/Ib clinical trial of Sabatolimab, an Anti-TIM-3 Antibody, Alone and in Combination With Spartalizumab, an Anti-PD-1 Antibody, in Advanced Solid Tumors

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