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Review Article

T cell Immunoglobulin and Mucin Domain Containing Protein 3 (TIM-3) Inhibitors in Oncology Clinical Trials: A Review

Benjamin Duong,[1] Pratyush Banskota,[1] Gerald S. Falchook[1]

[1]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA

Address correspondence to Gerald S. Falchook (gerald.falchook@sarahcannon.com).

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ABSTRACT

T cell immunoglobulin and mucin domain containing protein 3 (TIM-3) is a receptor found on a multitude of immune cells and is commonly overexpressed in patients with cancer. Due to its selective expression in immune cells and its preliminary efficacy in preclinical models, TIM-3 is a promising target as a treatment for cancer. Both monotherapy and combination regimens are being developed and are currently under investigation. This clinical review seeks to summarize and compile past, present, and future TIM-3 inhibitors in clinical trials.

Keywords: TIM-3 inhibitor, clinical trials, cancer, review

INTRODUCTION

T cell immunoglobulin and mucin domain containing protein 3 (TIM-3) is a receptor found on a multitude of immune cells, most predominantly on interferon-gamma producing CD4+ T cells (Th1) and CD8+ cytotoxic T cells (Tc1), as well as on regulatory T cells and innate immune cells.[1,2] Common ligands that bind to TIM-3 to induce inhibitory effects are galectin-9, phosphatidylserine (PtdSer), high-mobility group protein B1 (HMGB1), and CEACAM-1.[3] Upon activation of TIM-3 in normal cells, TIM-3 suppresses Th1 and Tc1 through reduced cytokine production or decreased proliferation responses to antigens.[4] In addition, this effect can be seen on other immune cells. Regulation of T cells via TIM-3 receptor in cancer is illustrated in Figure 1.

In patients with chronic viral infections or cancer, overexpression of TIM-3 is common. Overexpression of TIM-3 leads to T cell exhaustion, which is the primary mechanism of immune suppression associated with this receptor.[4] This phenomenon leads to the gradual loss of T cell function mostly in chronic viral infections or tumorigenesis.[2,5,6] TIM-3 overexpression can also affect the function and numbers of other various immune cells.[2] High TIM-3 expression correlates with immune suppression in tumors.[4] Regulation of T cells via TIM-3 receptor in cancer is illustrated in Figure 1.[7]

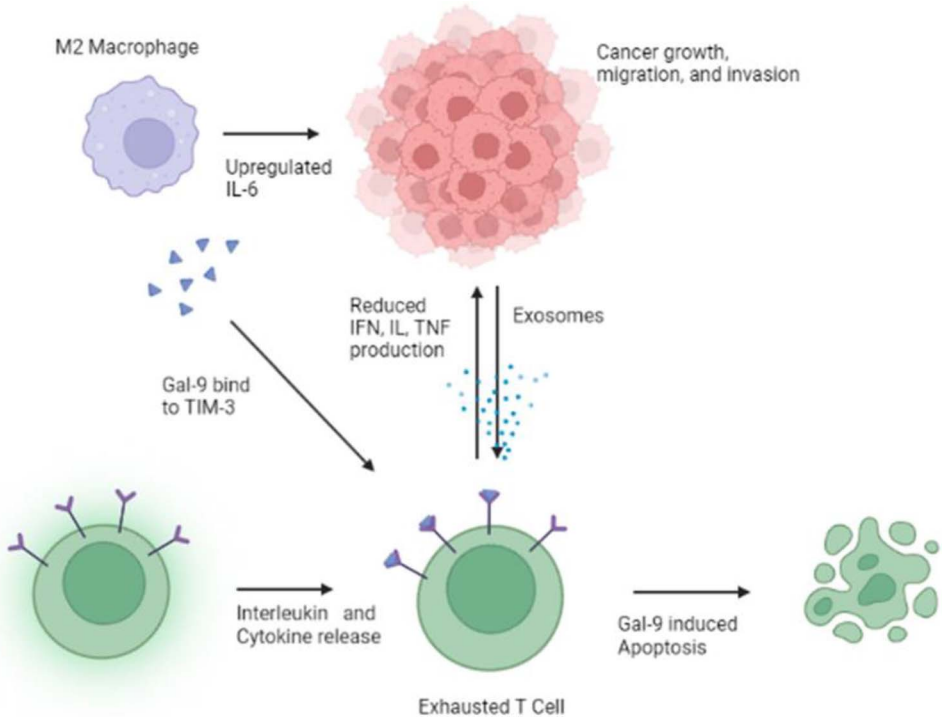

Figure 1. Regulation of T cells via TIM-3 receptor in cancer. Cytokine expression reduction, cancer exosome, and galectin-9 (Gal-9) binding to TIM-3 reduces overall T cell activity through an exhaustion phenotype. Increased binding of galectin-9 induces T cell apoptosis. Decreased interleukin (IL), interferon (IFN), and tumor necrosis factor (TNF) causes reduced antitumor response, allowing for cancer growth, invasion, and migration. Content based on Liu et al.[7]

TIM-3 has multiple different roles. Expression of TIM-3 may result in exhaustion of CD4+ T cells.[3,4] Within various myeloid cells, TIM-3 was shown to regulate innate immune responses and inhibitory responses, suggesting its role is specific to location and type of cell.[3] In monocytes and macrophages, TIM-3 antibodies were observed to increase activation and also aggravated autoimmune diseases.[3,4] TIM-3 antibodies also inhibited inflammatory cytokine production in vivo.[4]

Targeting of TIM-3 inhibitory receptors in patients with cancer may be a promising cancer treatment strategy. Administration of TIM-3 monoclonal antibodies (mAbs) was shown to have proliferative effects in antigen specific T cells, suggesting that expression of TIM-3 limited tumor infiltrating leukocytes.[4] Higher levels of TIM-3 expression on these cells correlated with poor patient survival.[4] However, preclinical mouse models involving TIM-3 mAbs administration found variable antitumor effects.[4,5] One study found no inhibition in tumor growth when tested on a CT26 colon adenocarcinoma model.[4,5] When administered in combination with a PD-1/PD-L1 or a CTLA4 mAb, these combinations slowed tumor progression and had much greater antitumor effects.[5] Thus, due to its selective expression in immune cells and its preliminary efficacy in preclinical models, TIM-3 is a promising target as a treatment for cancer. Both monotherapy and combination regimens are being developed and are currently under investigation.[4]

This clinical review aims to provide a concise compilation of the currently available results of clinical trials of TIM-3 inhibitors currently in development (Tables 1 and 2). The information in this review was collected from publicly available abstracts presented at oncology conferences, published manuscripts, and clinical trials registered on ClinicalTrials.gov. Search terms on ClinicalTrials.gov included "TIM-3," "TIM-3 inhibitors," and "T cell immunoglobulin and mucin domain containing protein 3." Filters used were "interventional." With trials that were completed, additional searches for associated articles were completed on Google to find published data if available. This search was performed between approximately June 1, 2022, and February 1, 2023.

TIM-3 INHIBITORS CURRENTLY IN CLINICAL DEVELOPMENT WITH PUBLISHED RESULTS

LY3321367

LY3321367 (Eli Lilly and Co., Indianapolis, IN, USA) is an anti-TIM-3 mAb, for which two trials have been initiated. The first trial is a phase Ia/b trial to determine the recommended dose of LY3321367 as monotherapy or in combination with LY3300054 (anti-PD-L1 inhibitor) in patients with solid tumors. The most common cancer treated was non–small-cell lung cancer. In dose escalation, LY3321367 was given as flat doses every 2 or 3 weeks starting at 3 mg intravenously (IV). In combination

Table 1. Clinical trials of TIM-3 inhibitors with published results

Drug Name	Trial Phase	Tumor Type	MTD/RP2D	Dose-limiting Toxicities	Terminal Half-life	*N*	Antitumor Activity	Biomarkers Examined
LY3321367	I	Advanced solid tumors	RP2D: 1200mg Q2W for four doses with 600 mg Q2W IV	Not provided	21 days	275	ORR was 4%; DCR was 48%	100% target engagement at doses > 600 mg, CD8 infiltration increased in half the patients
	I	MSI-H/dMMR tumors	Not provided	Not provided	Not provided	82	ORR was 45.0%; DCR was 70.0%	Not provided
LY3415244	I	Advanced solid tumors	MTD: 70 mg IV, no RP2D provided	No DLTs	Not provided	12	Not provided	Not provided
MBG453	I/II	Advanced solid tumor	RP2D: 800 mg sabatolimab Q4W in combination with 400 mg spartalizumab Q4W	Not provided	Not provided	252	Not provided	Three patients had >10% TIM-3 positive staining
	I	AML or MDS or CMML	Not provided	Not provided	Not provided	99	AML ORR 41.2%, MDS ORR 6.2%, CMML ORR 63.6%	Not provided
Sym023	I	Advanced solid tumors or lymphomas	MTD: 20 mg/kg Q2W IV	Not provided	4.37-8.49 days	24	Not provided	Not provided
TSR-022	I	Advanced solid tumors	RP2d: cobolimab 300 mg with dostarlimab 200 mg IV Q3W	3% of patients in 1A, 40% of patients in 1B, 0% of patients in 1C	9.5-12.3 days	369	ORR 42.9% in 1B, 7.7% in 1C; DCR 21% in 1A, 42.9% in 1B, 45% in 1C	The normalized free-to-total TIM-3 ratio decreased with increasing cobolimab dose and PK exposure, as expected.

AML: acute myelogenous leukemia; CMML: chronic myelomonocytic leukemia; DCR: disease control rate; DLT: dose limiting toxicity; dMMR: deficient DNA mismatch repair; IV: intravenous; MDS: myelodysplastic syndrome; MSI-H: micro-satellite instability-high; MTD: maximum tolerated dose; ORR: overall response rate; Q2W: every 2 weeks; Q3W: every 3 weeks; Q4W: every 4 weeks; RP2D: recommended phase 2 dose; TIM-3: T cell immunoglobulin and mucin domain containing protein 3.

Table 2. Ongoing clinical trials of TIM-3 inhibitors

TIM-3 Inhibitor	Monotherapy/Combination	Trial Phase	Tumor Type	Trial NCT Identifier	Study Start Date	Estimated Study Completion Date
AZD7789[20]	Monotherapy	Phase I/II	Advanced Solid Tumors	NCT04931654	9/28/2021	6/30/2025
AZD7789[21]	Monotherapy	Phase I/II	R/R cHL	NCT05216835	3/18/2022	2/16/2026
BGB-A425[22]	Combination (Tislelizumab, LBL-007)	Phase I/II	Advanced Solid Tumors	NCT03744468	11/13/2018	12/29/2027
BMS-986258[23]	Monotherapy/Combination (Nivolumab)	Phase II	Advanced Solid Tumors	NCT05201066	3/8/2018	3/20/2023
INCAGN02390[24]	Monotherapy	Phase I	Select Advanced Malignancies	NCT036652077	9/24/2018	8/18/2021
INCAGN02390[25]	Combination (INCMGA00012, INCAGN02385)	Phase I/II	Select Advanced Malignancies	NCT04370704	7/21/2023	8/4/2025
INCAGN02390[26]	Combination (INCAGN02385)	Phase II	Squamous Cell Carcinoma of Head and Neck	NCT05287113	11/14/2022	9/15/2024
INCAGN02390[27]	Combination (retifanlimab, epacadostat, INCAGN02385)	Phase II	Urothelial Carcinoma	NCT04586244	1/14/2022	6/1/2024
MGB453[28]	Combination (Decitabine, PDR001, Azacitidine)	Phase I	AML, MDS	NCT03066648	7/6/2017	9/8/2023
MGB453[29]	Combination (HDM201, Venetoclax)	Phase I	AML, MDS	NCT03940352	6/24/2019	12/1/2023
MGB453[30]	Monotherapy	Phase I	GBM	NCT03961971	2/18/2020	9/1/2024
MGB453[31]	Combination (Azacitidine)	Phase I/II	AML	NCT04623216	9/14/2021	3/3/2027
MGB453[32]	Combination (NIS793, canakinumab)	Phase I	MDS	NCT04810611	6/18/2021	9/12/2024
MGB453[33]	Combination (Magrolimab, Azacitidine)	Phase II	AML, MDS	NCT04812548	12/20/2024	10/26/2029
MGB453[34]	Combination (Ruxolitinib, Siremadlin, Crizanlizumab, rineterkib, NIS793)	Phase II	Myelofibrosis	NCT04150029	9/26/2019	3/15/2024
MGB453[35]	Combination (Azacitidine, Venetoclax)	Phase II	MDS	NCT048788432	5/31/2021	5/8/2023
MGB453[36]	Combination (Azacitidine, Venetoclax)	Phase II	MDS	NCT03946670	9/1/2020	3/13/2026
MGB453[37]	Combination (Decitabine, Azitacidine, Decitabine+Cedazuridine)	Phase II	MDS	NCT04878432	3/17/2022	3/31/2025
MBG453[38]	Combination (Azacitidne, Decitabine)	Phase II	MDS	NCT03946670	6/4/2019	8/10/2024
RO7121661[39]	Monotherapy (RO7121661)	Phase I	Advanced Solid Tumors	NCT03708328	10/15/2018	8/31/2023
RO7121662[40]	Combination (RO7121662, tobemstomig)	Phase II	Squamous Cell Carcinoma of the Esophagus	NCT04785820	6/25/2021	6/30/2025
Sym 023[41]	Combination (Sym 021, Sym 022)	Phase I	Solid Tumors, Lymphomas	NCT03311412	11/10/2017	3/23/2022
TSR-022[42]	Combination (TSR-042)	Phase II	Advanced Solid Tumors	NCT03680508	12/19/2019	10/1/2025
TSR-022[43]	Combination (TSR-042)	Phase II	Melanoma	NCT04139902	6/12/2020	10/31/2027

AML: acute myelogenous leukemia; GBM: glioblastoma; MDS: myelodysplastic syndrome.

with LY3300054, patients received increasing doses of LY3321367 starting at 70 mg together with 200, 700, or 1400 mg of LY3300054 in 2- or 3-week intervals. The recommended phase II dose of LY3321367 monotherapy was determined to be 1200 mg biweekly for four doses followed by 600 mg every 2 weeks. There were no dose-limiting toxicities in either monotherapy ($n = 30$) or combination cohorts ($n = 28$). Common adverse events included pruritus, rash, fatigue, anorexia, and infusion-related reactions. The half-life of LY3321367 as monotherapy was 21 days. Pharmacodynamic and pharmacokinetic modeling suggested 100% target cell engagement at doses $\geq$600 mg. In the monotherapy dose-expansion cohort, anti-PD-1/L1 refractory patients ($n = 23$) were observed to have an overall response rate (ORR) of 0%, disease control rate (DCR) of 35%, and a progression-free survival (PFS) of 1.9 months. Previous anti-PD-1/L1 responders ($n = 14$) had an ORR 7%, DCR 50%, and PFS 7.3 months. Combination expansion cohorts ($n = 91$) had ORR of 4% and DCR of 42%. LY3321367 was found to have modest antitumor activity but with favorable safety, pharmacodynamic, and pharmacokinetic profiles.[8]

The second study was a phase 1b trial as monotherapy or combination with LY3300054 (anti-PD-L1 inhibitor), for patients with micro-satellite instability-high/deficient DNA mismatch repair (MSI-H/dMMR) tumors. Eighty-two patients were enrolled, including monotherapy ($n = 40$), combination ($n = 20$), or combination for PD-1/PD-L1 inhibitor refractory patients ($n = 22$). Colorectal ($n = 39$, 47.6%) and endometrial ($n = 14$, 17.1%) cancers were the most common tumors enrolled. Adverse events occurred in 65.0% ($n = 13$) of combination therapy patients. The most common adverse event associated with combination therapy was pruritis ($n = 5$, 25%). Combination treatment patients who were PD-1/PD-L1 inhibitor naïve saw ORR of 45.0%, DCR of 70.0%. Median PFS was 7.6 months. In PD-1/PD-L1 inhibitor resistant cancers, 54.5% of patients had PD as the best response. In anti-PD-1/L1 inhibitor resistant or MSI-H/dMMR tumors, limited clinical efficacy was observed.[9]

LY3415244

LY3415244 (Eli Lilly and Co, Indianapolis, IN, USA) is a bispecific antibody targeting TIM-3 and PD-L1. The trial was intended to find the safety of LY3415244 as a monotherapy, given as IV in flat doses ranging from 3 to 70 mg IV every 2 weeks. Twelve patients enrolled, of whom two patients experienced anaphylactic shock as infusion-related adverse events. All patients developed antidrug antibodies. The antidrug antibody epitope specificity was determined to be directed against both the TIM-3 and PD-L1 arms of the bispecific antibody. The potential benefit:risk ratio was not ideal with further evaluation, and the study was terminated early.[10]

MBG453 (Sabatolimab)

MBG453 (Novartis, Cambridge, MA, USA) is a TIM-3 monoclonal antibody. To date, there have been 16 trials involving MBG453. The first-in-human study of MBG453 evaluated safety and determined a recommended phase II dose for future studies. MBG453 was administered as monotherapy or in combination with spartalizumab (PD1 inhibitor) in patients with advanced solid tumors. MBG453 was administered IV, 20 to 1200 mg every 2 or 4 weeks. Spartalizumab was administered IV, 80 to 400 mg every 2 or 4 weeks. A total of 219 patients enrolled, including 133 who received monotherapy and 68 who received the combination. The maximum tolerated dose was not reached. The most common adverse event was fatigue (9% MBG453; 15% combination). No objective responses were observed with the MBG453 monotherapy. Five patients treated with the combination achieved partial responses, lasting 12 to 27 months, including colorectal cancer ($n = 2$), non–small-cell lung cancer ($n = 1$), perianal melanoma ($n = 1$), and small-cell lung cancer ($n = 1$). The recommended phase 2 dose for MBG453 was determined to be 800 mg every 4 weeks either as monotherapy or in combination with 400 mg spartalizumab every 4 weeks.[11,12]

A phase 1b open-label, multicenter, dose-escalation study evaluated MBG453 in combination with hypomethylating agents (HMA) decitabine or azacitidine. Forty-eight patients with acute myelogenous leukemia (AML), 39 patients with myelodysplastic syndrome (MDS), and 12 patients with chronic myelomonocytic leukemia (CMML) received MBG453 combined with an HMA. The doses were 240 or 400 mg MBG453 or 800 mg MBG453 combined with decitabine (20 mg/m^2; IV days 1–5) or azacitidine (75 mg/m^2; IV/subcutaneously days 1–7) per 28-day cycle. The median duration of MBG453 exposure was 4.5 months for AML and 4.1 for MDS. The most common adverse events in patients with AML and MDS, respectively, were thrombocytopenia (with 45.8% and 51.2%), neutropenia (with 50.0% and 46.1%), febrile neutropenia (with 29.2%, 41.0%), anemia (with 27.1% and 28.2%), and pneumonia (with 10.4% and 5.1%). Discontinuation due to adverse events was rare among patients with AML, with 3 of 48 patients discontinuing (one each) for reasons of fatigue, febrile neutropenia, and possible hemophagocytic lymphohistiocytosis (HLH). No discontinuation occurred among patients with MDS. There was one dose-limiting toxicity that occurred with MBG453 240 mg every 2 weeks + decitabine. The maximum tolerated dose was not reached with either combination. Among the 34 evaluated patients with AML, the ORR was 41.2%. The median time to response (TTR) was 2.1 months, and the estimated 6-month duration of response (DOR) rate was 85.1%. The estimated 12-month PFS rate was 44%. Among 35 evaluated patients with MDS, the ORR was 6.2%, TTR was 2.0 months, 6-month DOR was 90%, and the estimated 12-month PFS rate was 58.1%. Twelve patients were evaluated with

CMML, and the ORR was 63.6%. The authors concluded that the combination of MBG453 with HMA is tolerable in patients with AML and MDS and showed promising antileukemic activity and durability.[13]

A phase II study evaluated MBG453 in combination with spartalizumab in patients with melanoma and non–small-cell lung cancer (NSCLC) pretreated with anti-PD-1/L1 therapy. The trial enrolled 33 patients including 16 with melanoma and 17 with NSCLC: 18.8% ($n = 3$) of patients with melanoma and 41.1% ($n = 7$) of patients with NSCLC had stable disease for $\gtrsim 6$ months. Common adverse events were fatigue, nausea, and pruritus. Baseline tumor PD-L1 was higher in patients with SD versus PD. A trend of an inverse association between tumor reduction and CD163 tumor expression was observed. The authors concluded that treatment was tolerated well but with limited efficacy in patients with melanoma or NSCLC.[14]

Sym023

Sym023 (Symphogen A/S, Ballerup, Denmark) is a recombinant, fully human, anti-TIM-3 mAb with two completed and one currently ongoing clinical trial. The first of the completed trials was the first-in-human trial of Sym023. This phase 1, open-label trial investigated the safety, tolerability, and antitumor activity of Sym023 as monotherapy in patients with advanced solid tumor malignancies, metastatic cancers, and lymphomas to find the maximum tolerated dose and the recommended phase 2 dose. Sym023 was administered IV in escalating doses ranging from 0.03 mg/kg to 20 mg/kg, given every 2 weeks. Twenty-four patients were enrolled in the trial. Treatment-related adverse events included anemia ($n = 1$, 4.2%) and fatigue ($n = 1$, 4.2%). The observed half-life was in the range of 105.10 hours for the 0.1 mg/kg cohort and 203.7 hours in 20 mg/kg cohorts. Of the 24 patients, none exhibited any response.[15]

An ongoing, open-label phase 1b trial has been initiated to evaluate safety and efficacy of Sym021 (anti-PD1 mAb) in various combinations in patients with recurrent advanced selected solid tumors. The trial included three substudies to evaluate safety, tolerability, and efficacy. Substudy 1 enrolled patients with biliary tract carcinoma onto either a combination of Sym021 (PD-1 mAb) and Sym022 (LAG-3 mAb) (Arm A) or a combination of Sym021 (PD-1 mAb) and Sym023 (Arm B). Sub-study 2 also enrolled patients with biliary tract carcinoma, who were treated on a combination regimen of Sym021, Sym023, and irinotecan. Sub-study 3 evaluated the combination of Sym021, Sym023, and irinotecan in patients with esophageal squamous cell carcinoma. After an interim analysis, the trial discontinued further enrollment into Sub-study 1 Arm A as of August 2021. Enrollment continues to Sub-study 1 Arm B and Sub-study 2.The 24 patients who were administered Sym-023 monotherapy experienced no partial responses with adverse events being primarily immune-mediated arthritis ($n = 1$, 4.2%) and fatigue ($n = 1$, 4.2%). Seventeen patients were administered the Sym021 and Sym023 combination therapy. Adverse events included ALT elevation ($n = 1$, 5.9%), lymphopenia ($n = 1$, 5.9%), fatigue ($n = 1$, 5.9%), cough ($n = 1$, 5.9%), and rash ($n = 1$, 5.9%). The combinations were all well tolerated. Antitumor activity has not yet been observed.[16,17]

TSR-022

TSR-022 (cobolimab; Tesaro, Waltham, MA) is an mAb against TIM-3. The first-in-human phase 1 study had two parts, with part one as dose escalation and part two as expansion. The doses evaluated include the following: (1A) cobolimab monotherapy at seven doses (six weight-based from 0.03 to 10 mg/kg and one flat dose of 1200 mg; (1B) cobolimab (1 mg/kg) with nivolumab (3 mg/kg) every 2 weeks; (1C) cobolimab (100, 300, or 900 mg) with dostarlimab (500 mg) every 3 weeks. A total of 104 patients were treated, including 46 patients in 1A, seven patients in 1B, and 55 patients in 1C. Four patients crossed over from 1A to 1C. The most common cancers were NSCLC and melanoma in 1A, NSCLC in 1B, and NSCLC, melanoma, and mesothelioma in 1C. Treatment-related treatment-emergent adverse effects (TR-TEAE) occurred in 67.4% of patients in 1A, 85.7% of patients in 1B, and 67.3% of patients in 1C. The most common adverse events were fatigue (13%) and nausea (8.7%) in 1A; diarrhea (57.1%) and nausea and vomiting (42.9%) in 1B; fatigue (20%) and rash (14.5%) in 1C. TR-TEAEs led to discontinuation in 1.1% of patients in 1A, 28.6% of patients in 1B, and 9.0% of patients in 1C. Dose-limiting toxicities occurred in 3% of patients in 1A, 40% of patients in 1B, and 0% of patients in 1C. The ORR was 0% in 1A, 42.9% in 1B (PRs in cervical cancer and NSCLC), and 16.4% in 1C (PRs in melanoma, neuroendocrine carcinoma, and mesothelioma). The recommended phase 2 dose was determined to be cobolimab 300 mg with dostarlimab 500 mg IV every 3 weeks. The terminal half-life of TSR-022 was 9.5 to 12.3 days for 1C. Part 2 results have not yet been presented.[18,19]

DISCUSSION

To date, at least 10 TIM-3 inhibitors have entered clinical trials for patients with solid tumor cancers, as well as MDS, AML, and CMML. Among the wide variety of malignancies treated with TIM-3 inhibitors in clinical trials, preliminary evidence of antitumor efficacy has been observed, including in AML, cervical cancer, NSCLC, melanoma, neuroendocrine carcinoma, and mesothelioma. Sabatolimab, cobolimab, and LY3321367 have each shown promising early efficacy. A phase I trial of sabatolimab with 34 patients with AML demonstrated an ORR of 41.2%. In the same trial, among 12 evaluable patients with CMML, an ORR of 63.6% was observed. The phase 1 trial of cobolimab demonstrated an ORR of 42.9%

among seven patients in the 1B flat dosing combination cohort with nivolumab and ORR of 16.4% among 55 patients in the 1C RP2D combination cohort with dostarlimab. Early clinical trials of LY3321367 showed an ORR of 7% as monotherapy among 14 patients who were previous anti-PD-1/L1 responders, as well as an ORR of 4% in combination with PD-1 inhibition but an ORR of 45% among combination treatment patients who were PD-1/PD-L1 inhibitor naïve.

TIM-3 inhibitors that have entered clinical trials to date have all been administered IV. The pharmacokinetic profiles of these agents have varied considerably, with half-lives as short as 4.37 to 8.49 days for sym023 and as long as 21 days for LY3321367. Accordingly, the dosing schedules of these agents have also varied but have usually been IV infusions every 2 to 4 weeks.

In general, TIM-3 inhibitors have been well-tolerated as monotherapy. Common toxicities have included fatigue, rash, and nausea, all of which were treatable with supportive medication and which did not usually require permanent discontinuation of treatment. Very few dose-limiting toxicities have been reported as monotherapy, including one patient with grade 3 lipase elevation in the monotherapy escalation portion of the phase 1 trial of cobolimab. Excellent tolerance as monotherapy suggested that TIM-3 inhibitors may be suitable partners for combination strategies.

Infusion-related reactions (IRRs) have been observed in multiple TIM-3 inhibitors and have the potential to disrupt further development of this drug class. On the clinical trial of LY3415244 (bispecific antibody targeting TIM-3 and PD-L1), two patients experienced anaphylaxis, resulting in early termination of the trial. In another example, on the clinical trial of LY3321367 (TIM-3 monoclonal antibody), IRRs were less severe, all grade 1 or 2, resolved with supportive measures, and did not prevent retreatment of patients. Notably, five of the six patients who experienced IRRs had been treated on the PD1 inhibitor combination arms of the trial.

Combination regimens of TIM-3 inhibitors with PD-1 inhibitors have generally been well tolerated to date. In addition to IRRs described herein, another notable exception is the combination of cobolimab with nivolumab, in which two of five treated patients experienced dose-limiting toxicities, including one patient with grade 3 diarrhea and one patient with grade 3 aspartate aminotransferase and alanine aminotransferase elevation. This exception is especially notable because in contrast, cobolimab was safely combined with a different PD-1 inhibitor, dostarlimab, with no dose-limiting toxicities observed among 55 patients treated with the combination.

CONCLUSION

In summary, TIM-3 inhibitors are a promising class of drug that has shown early antitumor activity in both solid tumor cancers and hematological malignancy. Additional studies are ongoing to further investigate safety and efficacy in various tumor types, as monotherapy and in combination with other agents.

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