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New emerging targets in cancer immunotherapy: the role of VISTA

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ABSTRACT

The immune surveillance system is complex and regulated by different actors. Programmed death protein-ligand 1 (PD-L1), the only approved biomarker in clinical practice, has proven to be imperfect in selecting patients to immune checkpoint inhibitors treatment. Therefore, new biomarkers, and new therapeutic targets, are needed to maximise the efficacy of immunotherapy. V-domain Ig Suppressor of T-cell Activation (VISTA) is a programmed death protein-1 (PD-1) homolog expressed on T cells and on antigen-presenting cells, which regulates processes of activation and repression of the immune system with not yet completely clarified mechanisms. Its blockage has demonstrated in vitro and in vivo antitumour activity. The clinical research of VISTA antagonists is ongoing. Particularly, CA-170, an orally delivered dual inhibitor of VISTA and PD-L1, has shown to have clinical efficacy in phase I and II clinical trials in different advanced solid tumour types. Further data are needed to define whether this drug class can become a new therapeutic option for patients with VISTA expressing cancers.

BIOLOGICAL BACKGROUND

V-domain Ig Suppressor of T-cell Activation (VISTA) (also known as differentiation of embryonic stem cells 1, Gi24, B7-H5, SISP1, DD1α and programmed death protein-1 (PD-1) homolog (PD-1H)), is a 55 000 to 65 000 Da molecular weight type I immunoglobulin membrane protein, highly conserved across different species, especially in the cytoplasmatic domain.[1] VISTA is codified by *Vsir* gene, located within the intron of the *CDH23* gene on chromosome 10,[1] and is highly expressed on mature antigen-presenting cells (APCs) characterised by high CD11b and, to a lesser extent, on $CD8^+$, $CD4^+$ and regulatory T cells (Tregs) as well as on tumour-infiltrating lymphocytes (TILs).[2] VISTA is a co-inhibitory receptor on $CD4^+$ cells, while it acts as co-inhibitory ligand for T cells, as demonstrated by in vitro experiments where VISTA-immunoglobulin fusion protein inhibited their activation, proliferation and cytokines production during anti-CD3 activation.[3] This observation is strengthened by the evidence that $VISTA^{-/-}$ $CD4^+$ T cells had stronger antigen-specific proliferation and cytokine production as compared with wild-type ones.[4 5] Therefore, as a paradigm, it also acts as ligand when expressed on APCs (myeloid cells), conveying inhibitory signals extrinsically to T cells (figure 1).[6] Its counterpart has not been completely elucidated, but recent in vitro evidences discovered V-Set and Immunoglobulin domain containing 3 (VSIG-3), also known as Immunoglobulin Superfamily member 11 (IGSF11) and Brain-specific and Testis-specific Immunoglobulin Superfamily (BT-IgSF), as co-inhibitory ligand on tumour cells.[7] The extracellular domain of VISTA shares a structural similitude with programmed death protein-ligand 1 (PD-L1); however, VISTA is not associated with the CD28-B7 family as it does not cluster with, thus VISTA and PD-1 checkpoint pathways are independent.[2] Differently from other negative checkpoint regulators such as cytotoxic T-lymphocyte-associate protein 4 (CTLA-4), PD-1 and lymphocyte-activation gene 3 (LAG3), VISTA seems to be constitutively expressed on resting T cells, thus being a homeostatic regulator that actively normalises immune response at the earliest stages.[8] Indeed, experimental models showed that VISTA agonists could prevent acute graft-versus-host disease (GVHD) in mice, but only when treatment was initiated between 1 and 0 days before GVHD induction,[9] while VISTA antagonists lead to autoimmunity phenomena.[1] In addition, unlike VISTA, CTLA-4 is expressed on T-cell surface and blocks its activation at the priming stage, while PD-1 has an inhibitory function at the effector stage (figure 1).[10]

VISTA-deficient mice have been created to further explore its physiological role. A model characterised by exon 1 deletion showed higher frequency of activated T cells in the spleen that, after in vitro re-activation, produced more gamma interferon, tumour necrosis factor alpha and interleukin 17A; at the same time, mice were characterised by more myeloid cells in the spleen, higher plasma levels of chemokines and increased immune-infiltrates in the lung, liver and pancreas.[4 5] A second murine model, based on the backcrossing of VISTA heterozygous

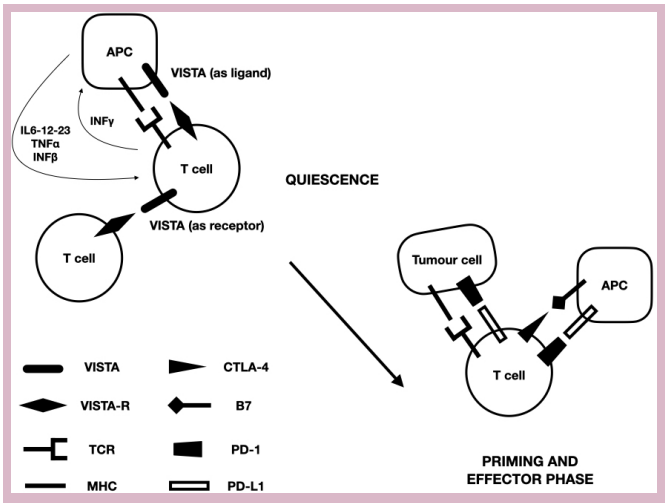

Figure 1 Expression of V-domain Ig Suppressor of T-cell Activation (VISTA) and its role in maintaining T-cell quiescence. VISTA acts as inhibitory receptor on T cells, and as ligand when expressed on APCs. VISTA normalises immune responses at the earliest stages of T-cell activation, while CTLA-4 and PD-1 have inhibitory functions at T cells priming and effector stages.
APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte-associate protein 4; IFN, interferon; IL, interleukin; PD-1, programmed death protein-1; PD-L1, programmed death protein-ligand 1; TNF, tumour necrosis factor.

mice, was characterised by overt autoimmunity, especially dermatitis as well as otitis, eye-related inflammation and seizures along with high autoantibody titres and renal immune complex deposition.[11] Mice models showed VISTA upregulation in the tumour microenvironment (TME), playing a critical role in antitumour immunity[3] through its contribution to the generation and stability of Tregs[12] and its expression on tumour-infiltrating myeloid cells. Indeed, a 10-fold increase of VISTA expression has been found in myeloid-derived suppressors cells (MDSCs) in the TME as compared with peripheral lymph nodes. Such differences might be explained by local factors such as hypoxia.[3] Despite its expression is consistently detected on immune cell infiltrates, human protein has also been shown in tumour cells with a cytoplasmatic pattern.[13–17] VISTA antagonism promotes tumour-specific effector T cells activation, reduces the induction and function of adaptive Tregs and enhances myeloid APCs-mediated inflammatory responses, thus involving both innate and adaptive immunity processes in vivo. Agents directed against VISTA reshape TME as well, by reducing MDSCs and tumour-specific Tregs and by increasing TILs proliferation and effector T cells function.[3 7 8] On the other side, overexpression of VISTA increased tumour growth in fibrosarcoma models thorough the ligand activity on suppressing T-cell immunity.[1] Some preclinical works suggest that blocking VISTA reduces growth of different neoplasms, regardless of their immunogenic status or origin (transplanted or induced). Notably, VISTA and PD-1 checkpoints do not seem to be redundant in antigen-specific responses and in chronic inflammation, paving the way to explore VISTA blockade both as single therapy and in combinations in tumours treatment.[18]

In cancer models, VISTA deficiency leads to resistance to GL261 glioma through $CD4^+$ T cells and some clones of anti-VISTA suppress different cancer cell lines.[3 4 18]

A hamster monoclonal VISTA-neutralising antibody (13F3 clone) suppressed tumour growth of murine melanoma B16-OVA model,[3] CT26 colon cancer, MB49 bladder carcinoma, B16BL6 melanoma.[19] In animal models, VISTA inhibition was observed to be effective regardless of its expression on tumour cells, and also of PD-L1 expression.[3] The synergic effect of dual VISTA/PD-L1 blockage was observed both in terms of immunological T cells response, in double VISTA/PD-L1 knockout mice, and of therapeutic efficacy, in murine model treated with specific monoclonal antibodies (mAbs).[18]

VISTA expression has been analysed in multiple tumour types, with contrasting results when assessing its potential prognostic and predictive role.[13–15 19–24] VISTA expression on tumour cells, but not on immune cells, was associated with prolonged progression-free survival (PFS) and overall survival (OS) in patients with high-grade serous ovarian cancer,[22] and when assessed by immunohistochemistry on TILs of oesophageal adenocarcinoma revealed a favourable outcome and particularly long-term survivors in the earlier stages of disease (T1/T2 tumours).[23] $VISTA^+$ and $CD8^+$ TILs subtype had a better OS in a cohort of hepatocellular carcinomas,[15] while a poorer OS has been found in oral squamous-cell carcinoma patient subgroup with VISTA high and CD8 low expression.[16] Moreover, VISTA expression was found to be an independent negative prognostic factor in cutaneous melanoma,[20] but it was not correlated with clinical outcomes among treatment-naïve patients with gastric cancer.[24]

Notably, a study evaluated VISTA expression prior to treatment and at the time of progression in 16 patients with advanced melanoma treated (and responding) with anti-PD-1 ± anti-CTLA-4 mAbs.[25] The authors reported significantly increased density of $VISTA^+$ lymphocytes at the time of progression, as well as increased tumour PD-L1 expression. Similar results were reported in prostate cancer following ipilimumab treatment.[26]

TARGETED AGENTS UNDER DEVELOPMENT AND CURRENT ONGOING CLINICAL TRIALS

The first anti-VISTA molecule ever developed was an intravenously delivered mAbs, called JNJ-61610588. It has been investigated in a first-in-human open-label phase I study (ClinicalTrials.gov Identifier NCT02671955), which enrolled patients with solid tumours, who had already received at least one line of therapy for advanced disease. The trial foresees an experimental dose escalation part, exploring the maximum tolerated dose (MTD); a biomarker evaluation part among patients with non-small cell lung cancer (NSCLC), treated at or

Table 1 Targeted agents under development

Name of the compound	Mechanism of action	Phase of clinical trial development	Company
JNJ-61610588	Human monoclonal antibody against VISTA	I	Janssen Research & Development (USA)
CA-170	Small molecule VISTA/PD-L1 antagonist	I/II	Curis (USA), Aurigene (India)

PD-L1, programmed death protein-ligand 1; VISTA, V-domain Ig Suppressor of T-cell Activation.

below the recommended phase II dose (RP2D) until disease progression (PD); two dose expansion parts, one among participants with NSCLC and one among patients with different solid cancers (small cell lung cancer, head and neck (HN), pancreatic, colorectal, cervical cancer) treated at the RP2D until PD. The enrolment is closed, and results are awaited.

VISTA is a PD-1H that participates in creating and maintaining an immune-suppressive TME, through the promotion of Tregs maturation and the prevention of T cells activation.[27] It shares many properties with PD-1, PD-L1 and other B7 family proteins, particularly being co-upregulated in TILs, but it differs for the pattern of expression. VISTA exerts its inhibitory role on APCs independently of PD-1, thus supporting the possible synergic effect if the two pathways were simultaneously blocked,[28] as shown in the aforementioned preclinical models.[11]

A study, presented at the Society for Immunotherapy of Cancer (SITC) Meeting in 2018, aimed at establishing VISTA expression on different tumour types by quantitative immunofluorescence of the corresponding protein on cancer tissue microarrays and by a genomic approach.[29] VISTA expressing tumours were found to be low-grade glioma, glioblastoma multiforme, clear cell renal cell carcinoma, HN squamous cell carcinoma, sarcomas and malignant pleural mesothelioma (MPM). Moreover, pathways associated with aberrant high or low VISTA expression were identified by RNA signature analysis from the Pan-Cancer Atlas dataset, among which were: *Arf6*, *VEGFR1*, Lissencephaly gene (*LIS1*), *Ras*, *FAS* (CD95), *EPHB*, *FOXA1* and *ErbB2/ErbB3*.[29]

In this setting, a first-in-class oral small-molecule selectively targeting and inhibiting both VISTA and PD-L1/PD-L2, called AUPM-170 or CA-170, was designed. This agent demonstrated in vitro immune-modulation activity, and in vivo antitumour efficacy in syngeneic cancer models. It did not exert specific immune function, with regard to other immune checkpoints like CTLA-4, TIM3, LAG3 or BTLA.[30 31] A phase I study enrolled patients with advanced solid tumours and lymphomas (ClinicalTrials.gov Identifier NCT02812875, CA-170–101), without symptomatic central nervous system involvement, for which standard therapies, including approved anti-PD-1/PD-L1, were no longer effective. The dose expansion phase Ib, planned to confirm safety and tolerability of oral CA-170 after having exploited the dose-limiting toxicities (DLTs), the MTD and RP2D, focused on solid tumours known to express VISTA only. Secondary and exploratory end points included pharmacokinetic, preliminary anticancer activity, biomarkers and pharmacodynamic effects.

Exploratory efficacy data from the first 50 enrolled patients, with at least one tumour response evaluation in the phase Ia CA-170–101 trial, were presented at SITC Meeting in 2018. Patients were treated with a dose up to 1200 mg twice daily in 21 days cycles. Overall, 33 patients, both immune checkpoint inhibitors (ICIs) naïve or pretreated, had a stable disease (SD) as best response according to response evaluation criteria in solid tumours (RECIST). No partial/complete responses (PR/CR) were observed. About 20% of patients remained on treatment for at least seven cycles. No DLTs were observed. The majority of treatment-related adverse events (TRAEs) were of grade 1–2, including fatigue, nausea, chills, pruritus, constipation, vomiting, fever, anorexia. TRAEs grade 3–4 occurred in five patients: lipase increase, amylase increase, blood bilirubin increase, fatigue, hypokalaemia, nausea and vomiting.[32]

Results from the mesothelioma cohort in the dose expansion phase Ib trial were presented at 2019 SITC Congress.[33] VISTA showed to be highly expressed in MPM (almost 90% expression on tumour and inflammatory cells), particularly in epithelioid subtype, rather than in biphasic and sarcomatoid. Its expression correlated with mesothelin expression and, contrary to what observed with PD-L1 expression, was associated with more favourable prognosis. No correlation with PD-1, PD-L1 or tumour mutational burden was found.[21] Twelve patients with pretreated MPM were treated with CA-170, and no responses were reported. Seven out of 11 patients evaluable for response (>1 postbaseline tumour assessment) had a SD as best response (two treated at 200 mg twice daily, five treated with escalated dose up to 1200 mg twice daily). One patient remained on study treatment for over 21 weeks with SD, and four patients for >12 weeks.[33]

The phase II trial is unfolding (Clinical Trials Registry-India CTRI/2017/12/011026) and started the enrolment on January 2018. It restricts the inclusion to patients affected by NSCLC, HN/oral cavity cancer, microsatellite instability-high or mismatch repair deficient positive cancers and Hodgkin's lymphoma (HL), who have already received from one up to three lines of therapy (ICIs excluded). It randomises patients to receive CA-170 400 vs 800 mg daily in continuous, until PD or intolerable toxicities, with an open-label design. The first activity results were presented at 2018 SITC Congress. Among 56 patients with at least one response evaluation, the

Table 2 Current ongoing clinical trials

Identifier number	Tumour type	Setting	Phase	Drug	Treatment arms	Status
ClinicalTrial.gov NCT02671955	Solid tumours	Advanced disease, >2nd line of treatment	I	JNJ-61610588	Single arm, open label	Recruitment terminated (12 patients enrolled)
ClinicalTrials.gov NCT02812875	Solid tumours and lymphomas	Advanced disease, >2nd line of treatment	I	CA-170	Single arm, open label	Active (estimated enrolment of 300 patients)
Clinical Trials Registry-India CTRI/2017/12/011026	NSCLC, HN/oral cavity, MSI-High or dMMR cancers, HL	Advanced disease, from 2nd to 4th line of treatment	II	CA-170	Randomised, parallel group, multiple arm, open label	Active (estimated enrolment of 130 patients)

dMMR, mismatch repair deficient; HL, Hodgkin's lymphoma; HN, head and neck; MSI, microsatellite instability; NSCLC, non-small cell lung cancer.

clinical benefit rate (CBR), defined as rate of SD/PR/CR by immune-related response criteria in solid tumours and by Lugano criterion for HL, was 52%. Better results have been observed at the lower dose, but curiously with higher toxicities. Immune-related adverse events were globally reported in 8 patients: hypothyroidism in five cases, two cases of skin rash and one case of grade 3 neutropenia and anaemia that led to treatment discontinuation.[34] An updated subanalysis restricted to 13 patients with non-squamous NSCLC, presented as poster at the European Society for Medical Oncology Congress 2019, reported a CBR >70%, but without objective responses, with a median PFS of 4.6 and 2.8 months with 400 or 800 mg, respectively.[35]

Tables 1 and 2 summarize main characteristics of anti-VISTA agents under development and current ongoing clinical trials.

CONCLUSIONS

VISTA is a critical immune checkpoint hampering the generation of antitumour immunity. Its blockage reduces adaptive Tregs, impairs their suppressive function and potentiates both tumour-specific T cells activation and APCs inflammatory response.[26] The molecular bases of such effects are not fully understood,[36] even if evidence supports both T-cell extrinsic and intrinsic role of VISTA, and putative ligands have recently been discovered.[6 7 37] The development of VISTA inhibitors, notably CA-170 that is the first small molecule targeting PD-1/PD-L1 axis entering the clinical research, retains some interesting aspects: the possibility of simultaneous multimolecules blockage, working at multiple levels on immune-surveillance mechanisms; the oral route of administration, which simplify patient's management and reduces risks related to infusion; the potential good activity in tumours with high VISTA expression, but low PD-L1 expression (eg, MPM).[33] The role of VISTA is under assessment, and currently available safety and efficacy data do not preclude further investigations. A better understanding of the molecular pathways involved and regulated by VISTA, together with the identification of its ligands in vivo, could be fundamental to define the role of this biomarker among the negative checkpoint regulators, and its proper value as a therapeutic target. Its function at the T cells quiescence state, upstream of the priming and effector phases, and its engagement within the TME rather than on cancer cells, provide a rationale to a combined blockage of VISTA, CTLA-4 and PD-1/PD-L1 axes.

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