Trial watch: STING agonists in cancer therapy

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ABSTRACT
Stimulator of interferon response cGAMP interactor 1 (STING1, best known as STING) is an endoplasmic reticulum-sessile protein that serves as a signaling hub, receiving input from several pattern recognition receptors, most of which sense ectopic DNA species in the cytosol. In particular, STING ensures the production of type I interferon (IFN) in response to invading DNA viruses, bacterial pathogens, as well as DNA leaking from mitochondria or the nucleus (e.g., in cells exposed to chemotherapy or radiotherapy). As a type I IFN is critical for the initiation of anticancer immune responses, the pharmaceutical industry has generated molecules that directly activate STING for use in oncological indications. Such STING agonists are being tested in clinical trials with the rationale of activating STING in tumor cells or tumor-infiltrating immune cells (including dendritic cells) to elicit immunostimulatory effects, alone or in combination with a range of established chemotherapeutic and immunotherapeutic regimens. In this Trial Watch, we discuss preclinical evidence and accumulating clinical experience shaping the design of Phase I and Phase II trials that evaluate the safety and preliminary efficacy of STING agonists in cancer patients.

Introduction
Stimulator of interferon response cGAMP interactor 1 (STING1, best known as STING) was first described in 2008 as a transmembrane component of the endoplasmic reticulum (ER) that senses cytosolic double-stranded DNA (dsDNA).\textsuperscript{1–4} This key adaptor protein in innate immune signaling\textsuperscript{5–8} can be activated by several cytoplasmic DNA sensors\textsuperscript{9–11} including cyclic GMP-AMP synthase (CGAS),\textsuperscript{12–15} Z-DNA binding protein 1 (ZBP1, best known as DAI), DEAD-box helicase 41 (DDX41), interferon-gamma-inducible protein 16 (IFI16),\textsuperscript{16–18} and perhaps protein kinase, DNA-activated, catalytic subunit (PRKDC, best known as DNA-PK).\textsuperscript{19,20} Among these sensors, CGAS has been studied in an extensive fashion. Mechanically, the accumulation of ectopic dsDNA in the cytosol activates the enzymatic function of CGAS to generate cyclic GMP-AMP (cGAMP),\textsuperscript{15,24} as well as other cyclic dinucleotides (CDNs)\textsuperscript{25,26} bind to and activate STING, triggering a signal transduction pathway that culminates in the initiation of interferon regulatory factor 3 (IRF3)- or NF-κB-dependent transcriptional programs.\textsuperscript{27–30} Notably, CDN-bound STING also stimulates autophagy, an evolutionarily conserved mechanism for the preservation of cellular and organismal homeostasis,\textsuperscript{31–33} and such a function appears to be more ancient than the initiation of IRF3 and NF-κB transcriptional activity.\textsuperscript{34}

STING is particularly prone to activation in the context of viral or bacterial infection, at least in part reflecting (1) the elevated sensitivity of CGAS for histone-free DNA,\textsuperscript{35,36} and (2) the direct contribution of bacterial CDNs to STING.\textsuperscript{25,26} However, STING can also be triggered by the cytosolic accumulation of endogenous DNA of both nuclear\textsuperscript{37–39} and mitochondrial\textsuperscript{40–44} origin. Thus, cancer cells undergoing DNA damage and mitochondrial outer membrane permeabilization (MOMP)\textsuperscript{45} in response to chemotherapy or radiation therapy are likely to secrete type I interferon (IFN) and other STING-dependent cytokines,\textsuperscript{46–48} although the MOMP-driven activation of apoptotic caspases considerably inhibits the process.\textsuperscript{49–54} Moreover, dying cancer cells appear to deliver STING-activatory DNA species to dendritic cells (DCs),\textsuperscript{55–57} which are the key initiators of anticancer immune responses,\textsuperscript{58–62} at least in some cases via exosome release\textsuperscript{63} or GAP junctions.\textsuperscript{64,65}

In summary, STING occupies a central role in the activation of tumor-targeting immune responses,\textsuperscript{5,66,67} which generated considerable attention around the possibility to develop chemical STING agonists for use in oncological indications.\textsuperscript{68} In
STING signaling in preclinical tumor models

Accumulating preclinical evidence documents the relevance of STING signaling in malignant cells and innate immune effectors of the tumor microenvironment for the initiation of anticancer immunity. Initially, it has been proposed that the engulfment of dying cancer cells by tumor-infiltrating CD8α+ DCs would trigger STING signaling in the latter, culminating in the abundant secretion of type I IFN and consequent activation of autocrine and paracrine pathways supporting the cross-priming of tumor-specific CD8+ cytotoxic T lymphocytes (CTLs). Consistent with this model, Sting1−/− mice are unable to mount efficient T cell immunity against syngeneic melanomas and gliomas, correlating with deficient type I IFN production. Similarly, Goldenticket mice – which harbor a single nucleotide polymorphism in Sting1 (T596A) that mimics the effects of a loss-of-function mutation – cannot establish efficient IFN-dependent immune responses against Listeria monocytogenes. Subsequent works, however, suggested that STING signaling in neoplastic cells, responding to some chemotherapeutics and radiotherapy, when delivered according to optimal doses and fractionation schedules, also contributes to anticancer immunity, at least in some settings. In line with this model, the short-hairpin RNA-mediated depletion of CGAS or STING in mouse mammary carcinoma cells exposed to hypofractionated radiation abolishes their ability to establish a tumor-specific immune response with systemic outreach (so-called ‘abscopal response’) in the presence of an immunostimulatory agent. Moreover, recent data suggest that STING signaling in DCs may also be initiated by CGAS-activatory or STING-activatory molecules that accumulate in cancer cells responding to treatment and are
transferred to DCs via exosomes or GAP junctions. Thus, STING activation in both malignant and immune components of the tumor microenvironment has been linked to superior anticancer immunity in a variety of preclinical tumor models.

Over the past few years, these observations prompted an intense wave of investigation aimed at the identification and development of pharmacological STING agonists for use in cancer patients. Historically, flavone acetic acid (FAA) has been the first of such molecules to be investigated for its anticancer properties, although FAA was not known to trigger STING activation at that time. Indeed, FAA was originally characterized as a vascular-disrupting agent that showed some antitumoral activity against murine colon tumors. Although these results encouraged further testing, FAA failed to display robust anticancer activity in murine tumor models and in Phase I clinical trials. In an attempt to improve efficacy, various modifications were introduced into the molecular structure of FAA, resulting in a battery of derivatives including 5,6-dimethylxanthene-4-acetic acid (DMXAA, also known as ASA404 or vadimezan). Well before the identification of STING, intratumoral or systemic DMXAA administration was shown to exhibit IFN- and tumor necrosis factor (TNF)-dependent anticancer activity against multiple mouse and rat carcinomas, especially (but not exclusively) when tumors were grown in immunocompetent, syngeneic hosts (de facto suggesting to a mode of action not limited to vascular disruption). Moreover, DMXAA turned out to efficiently synergize with various other anticancer regimens in vivo, including (but not limited to): radiotherapy, thermoradiotherapy, radioimmunotherapy, chemotherapy (with a particular emphasis on taxanes), immuno-modulatory drugs such as thalidomide and immunotherapy.

Corroborating initial findings, the intratumoral or systemic administration of DMXAA or other STING agonists, alone or combined with other therapeutic agents, have ultimately been attributed pronounced therapeutic effects in numerous murine models of fibrosarcoma, glioma, melanoma, as well as breast, colorectal and prostate carcinoma. Moreover, various CDNs have been shown to boost the therapeutic activity of anticancer vaccines in a variety of tumor models, including (1) mouse 4T1 triple-negative mammary carcinomas treated with a Listeria monocytogenes-based vaccine; (2) mouse B16 melanomas treated with the TRIVAX vaccine, which consists of synthetic peptides, the Toll-like receptor 3 (TLR3) agonist polyinosinic-polycytidylic acid (poly(I:C)) and co-stimulatory antibodies targeting CD40, or the STINGVAX vaccine, a cellular vaccine engineered to secrete colony-stimulating factor 2 (CSF2, best known as GM-CSF), plus an immune checkpoint blocker targeting programmed cell death 1 (PDCD1, best known as PD-1), and (3) mouse CT26 colorectal carcinoma treated with the STINGVAX vaccine plus a PD-1 blocker.

However, natural CDNs are rapidly degraded by circulating and cell-bound enzymes, including ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), calling for the development of molecules with improved stability for clinical applications. Novel STING agonists developed to circumvent the limited half-life of natural CDNs include both CDN derivatives (e.g., GSK 532 and CDN-unrelated agents (e.g., TTI-10001, CRD5500 and amidobenzimidazole derivatives)). In vitro, GSK 532 can induce cytokine responses in human peripheral blood mononuclear cells (PBMCs) bearing various STING haplotypes, which is not the case of DMXAA and all natural CDNs. Intratumoral administration of GSK 532 mediated robust anticancer effects against CT26 colorectal carcinomas growing in immunocompetent syngeneic mice, culminating with the eradication of existing lesions and the establishment of protective immunity against rechallenge with the same cancer cell line. Such an antitumor effect was largely compromised after CD8 T cell depletion, further corroborating the ability of GSK 532 to initiate adaptive anticancer immunity. Intratumoral TTI-10001 administration induced the expression of various pro-inflammatory cytokines along with T cell activation in mice bearing MC38 colorectal carcinomas or A20 B-cell lymphoma, culminating with disease eradication in a significant fraction of animals. CRD5500 (also called LB-061) administered intratumorally or systemically induced tumor regression in BALB/c mice bearing syngeneic CT26 colorectal tumors engineered to express human STING, a therapeutic effect that was further increased when mice concomitantly received an immune checkpoint blocker. Finally, intravenous administration of an amidobenzimidazole (ABZI)-based compound to immuno-competent mice bearing syngeneic colorectal cancers resulted in complete and long-lasting disease control.

Additional lines of evidence supported the potential benefit of (re)activating STING for cancer therapy. For instance, the tumor suppressor MUS81 structure-specific endonuclease subunit (MUS81) has been shown to promote cytosolic DNA accumulation in prostate cancer cells, ultimately activating a STING-dependent program for cancer immunosurveillance. Along similar lines, the oncogene E7 from human papillomavirus (HPV) and E1A from adenovirus inhibit CGAS-STING signaling to subvert antiviral immunity in the host, which eventually facilitate malignant transformation. Finally, STING and/or CGAS expression is silenced by epigenetic mechanisms in various cancer types including colorectal tumors, further supporting the advantage obtained by developing neoplasms as a consequence of STING inactivation. Taken together, these preclinical findings provide robust grounds for testing STING agonists in cancer patients.

**STING agonists as cancer therapeutics**

**DMXAA**

Arguably, DMXAA is the best characterized of all STING agonists, largely reflecting its capacity to induce apoptosis in endothelial cells and hence the initial development of DMXAA as a STING-unrelated vascular-disrupting agent. When this Trial Watch was being redacted (April 2020), official sources listed only 18 clinical trials that investigate the safety and therapeutic profile of DMXAA in cancer patients (source [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (Table 1)).

DMXAA has preferentially been tested in patients with solid tumors, mainly in cohorts of individuals with advanced or
chemorefractory neoplasms. The Phase I trial NCT00863733, aiming to evaluate pharmacodynamics, pharmacokinetics, toxicity and preliminary antitumor efficacy of DMXAA, demonstrated a good safety profile and tolerability over a large range of doses.\textsuperscript{144} Notably, neither this study nor another Phase I clinical trial conducted in the United Kingdom documented significant degrees of myelosuppression in patients receiving DMXAA intravenously,\textsuperscript{145} pointing to DMXAA as to a good combinatorial partner for conventional chemotherapy. Nevertheless, additional investigations were required to elucidate the therapeutic potential of the compound.

Two other Phase I clinical trials (NCT00856336 and NCT00003697) tested intravenous DMXAA as a single agent in patients with various solid tumors, demonstrating some benefits only at doses higher than the ones generally tested in the clinic.\textsuperscript{146} Moreover, these studies confirmed that DMXAA perturbed retinal function, consistent with the inhibition of phosphodiesterases.\textsuperscript{146,147} Alongside, the tolerability, safety, efficacy and pharmacokinetics of DMXAA, combined with the microtubular poison docetaxel\textsuperscript{148,149} have been tested in Japanese patients affected by advanced or recurrent solid tumors.\textsuperscript{150,151} This Phase I clinical study (NCT01285453) proved that DMXAA plus docetaxel are generally well tolerated, documenting only Grade 1–2 adverse events including constipation, decreased appetite, alopecia, fatigue and neutropenia.\textsuperscript{150} These results led to the design of a Phase III clinical study (ATTRACT-2)\textsuperscript{145} testing DMXAA plus docetaxel as a second-line therapy for advanced non-small cell lung carcinoma (NSCLC).\textsuperscript{143} Unfortunately, the ATTRACT-2 trial has been prematurely terminated for undisclosed reasons probably linked to preliminary efficacy.\textsuperscript{152,153} A similar Phase II study was conducted in 70 patients affected by hormone-refractory metastatic prostate cancer (NCT00111618), demonstrating good safety and some degree of clinical activity.\textsuperscript{154} In the context of NSCLC, an additional Phase I trial (NCT00674102) aimed at investigating the safety and efficacy of DMXAA combined with carboplatin and paclitaxel in patients affected by squamous or non-squamous NSCLC.\textsuperscript{155} Despite some limitations, such as the restricted number of patients, DMXAA was associated with comparable safety and efficacy independent from the tumor histology, thus allowing for the inclusion of all patients in a Phase II expansion assay (NCT00832494). Additionally, this combinatorial chemotherapeutical regimen has been tested as first-line chemotherapy in a Phase II trial (NCT01057342) enrolling patients affected by

| Agonist                  | Indications            | Status       | Phase    | Route | Co-therapy                                      | NCT Number                                      |
|--------------------------|------------------------|--------------|----------|-------|-----------------------------------------------|------------------------------------------------|
| ADU-S100                 | Advanced solid tumors  | Active not   | I        | i.t.  | Combined with anti-CTLA4 mAb                  | NCT02675439                                    |
|                         | Lymphoma               | recruiting   |          |       | Combined with anti-PD1 mAb                    | NCT03172936                                    |
| BMS-986301               | Advanced solid tumors  | Recruiting   | II       | i.t.  | Combined with pembrolizumab                   | NCT00397141                                    |
| DMXAA                    | Advanced urothelial carcinoma | Withdrawn | II     | i.v.  | Combined with docetaxel                       | NCT01071928                                    |
|                         | Advanced solid tumors  | Completed    | I        | n.s.  | Combined with docetaxel                       | NCT01285453                                    |
|                         |                        | Terminated   | I        | i.v.  | As single agent                               | NCT00299701                                    |
|                         |                        |              |          |       | Combined with carboplatin + paclitaxel or docetaxel | NCT001240642                                    |
| Advanced tumors          | Terminated             | I            | n.s.    |       | Combined with taxane-based chemotherapy       | NCT01290380                                    |
| NSCLC                    | Completed              | I            | i.v.    |       | Combined with carboplatin and paclitaxel      | NCT00674102                                    |
| Prostate cancer          | Terminated             | III          | i.v.    |       | Combined with carboplatin and paclitaxel      | NCT00738387                                    |
| Refractory solid tumors  | Completed              | I            | i.v.    |       | Combined with carboplatin and paclitaxel      | NCT00662597                                    |
| SCLC                     | Completed              | II           | i.v.    |       | Combined with carboplatin and paclitaxel      | NCT00111618                                    |
| Solid tumors             | Completed              | I            | i.v.    |       | Combined with carboplatin, cetuximab and paclitaxel | NCT01031212                                    |
| E7766                    | Advanced solid tumors  | Recruiting   | I        | i.t.  | As single agent                               | NCT04144140                                    |
|                         | Bladder cancer         | Not yet      | I        | i.v.  | As single agent                               | NCT04109002                                    |
| GSK3745417               | Advanced solid tumors  | Recruiting   | I        | i.v.  | As single agent or combined with pembrolizumab | NCT03843359                                    |
| MK-1454                  | Advanced solid tumors  | Recruiting   | I        | i.t.  | As single agent                               | NCT03010176                                    |
|                         | Lymphoma               | Recruiting   | I        | i.t.  | As single agent or combined with pembrolizumab | NCT04238666                                    |
|                         | HNSCC                   | Recruiting   | II       | i.t.  | As single agent                               | NCT03249792                                    |
|                         |                        |              |          |       | Combined with pembrolizum and paclitaxel      | NCT00003697                                    |
| MK-2118                  | Advanced solid tumors  | Recruiting   | I        | i.t.  | As single agent                               | NCT03249792                                    |
|                         | Lymphoma               | Recruiting   | I        | i.t.  | As single agent                               | NCT00063733                                    |
| SB11285                  | Advanced solid tumors  | Recruiting   | I        | i.t.  | As single agent                               | NCT04096638                                    |

Abbreviations: HNSCC, head and neck squamous cell carcinoma; i.t., intratumorally; i.v., intravenously; mAb, monoclonal antibody; n.s., not specified, NSCLC, non-small cell lung carcinoma; s.c., subcutaneously; SCLC, small cell lung carcinoma.

Table 1. Clinical trials testing STING agonists in oncological indications.
advanced squamous small cell lung carcinoma (SCLC). This study was prematurely stopped due to lack of efficacy based on progression-free survival.

Thus, the addition of DMXAA to conventional chemotherapeutic agents with immunostimulatory effects has been consistently associated with poor preliminary efficacy or an increased rate of adverse reactions, as demonstrated by the consistent failure of prematurely terminated clinical trials (8 out of 18). In most such cases, DMXAA was combined with taxanes (docetaxel or paclitaxel) alone (NCT01290380 and NCT00738387) or in the context of carboplatin-based chemotherapy (NCT01240642, NCT00674102, NCT00662597 and NCT01299415), in patients with non-selected, advanced or chemorefractory solid tumors (NCT01285453, NCT01299701, NCT01278849, NCT01240642, NCT01290380, NCT01278758, NCT00856336, NCT01031212), or in a restricted oncological indication such as NSCLC (NCT00738387 and NCT00662597) or SCLC (NCT01057342). Two additional clinical assays testing DMXAA in cancer patients are currently listed as “withdrawn” (source www.clinicaltrials.gov). The first of such trials intended to test intravenous DMXAA as second-line chemotherapy in combination with docetaxel in patients affected by advanced urothelial carcinoma (NCT01071928). The second of such studies aimed to test DMXAA plus carboplatin, paclitaxel and the endothelial growth factor receptor (EGFR)-targeting agent cetuximab in patients with chemorefractory solid tumors (NCT01031212). Importantly, recent structure-function studies of mouse and human STING demonstrated that DMXAA does not bind to human STING, but only to its mouse counterparts,161,162 likely explaining the limited activity documented in clinical testing. That said, DMXAA appears to potently inhibit phosphodiesterases, which has been invoked to explain its vascular-disrupting properties.146,147 As phosphodiesterase inhibition is expected to favor the accumulation of endogenous CDNs, at least to some extent, whether the (limited) therapeutic effects of DMXAA are entirely STING-independent remains to be elucidated.

**Other STING agonists in clinical evaluation**

At least 15 different STING agonists other than DMXAA have been developed to circumvent the limited efficacy of the latter. E7766, belonging to a novel class of macrocyclic-bridged STING agonists (MBSAs) is the only STING agonist currently being tested in cancer patients as a standalone intravenous intervention. In particular, the tolerability, safety and preliminary activity of this molecule have been investigated in patients with advanced solid tumors or lymphomas (NCT04144140) as well as in individuals affected by non-muscle invasive bladder cancer (NCT04109902). Both these Phase I clinical studies forecast one dose-escalation part and a second dose-expansion phase. GSX3745176 is currently being tested as monotherapy or combined with the PD-1 blocking antibody pembrolizumab,165 in patients with advanced, refractory/relapsed solid tumors (NCT03843359, NCT03010176) or lymphomas (NCT03010176). Preliminary results suggest that this combinatorial regimen is safe and mediates some clinical activity.166 MK-1454 is being tested in patients with metastatic or unresectable, recurrent head and neck squamous cell carcinoma (HNSCC) (NCT04220866), while MK-2118 administered i.t. or s.c. (together with pembrolizumab) is being investigated in individuals affected by advanced/metastatic solid tumor or lymphomas (NCT03249792). ADU-S100 (also known as MIW815) is currently being tested in combination with pembrolizumab for CD274 (PD-L1)-positive recurrent or metastatic HNSCC patients (NCT03937141), as well in individuals with advanced solid tumors concomitantly receiving a PD-1 blocker other than pembrolizumab (NCT03172936) or the cytotoxic T-lymphocyte associated protein 4 (CTLA4) blocker ipilimumab (NCT02675439). Preliminary results from NCT03172936 suggest that the combination of ADU-S100 plus the PD-1 blocker spartalizumab is well tolerated and mediates some clinical activity in patients with solid tumors, particularly PD-1-naive triple-negative breast cancer168 and PD-1-relapsed/refractory melanoma.167,169,170 The success of this regimen might have a particular positive impact on melanoma patients refractory to PD-1 blockers.171-173 The PD-1 blocker nivolumab is also being tested in combination with the STING agonist SB11285 in subjects with advanced solid tumors (NCT04096638). Only one clinical trial, enrolling patients with advanced solid tumors (NCT03956680), evaluated the safety and preliminary efficacy of ipilimumab and nivolumab together,175-178 co-administered with the STING agonist BMS-986301.

**Indirect STING activation by cancer therapies**

Accumulating preclinical and clinical evidence demonstrates that numerous anticancer agents currently employed in the clinical practice or under clinical development can activate CGAS-STING signaling downstream of the accumulation of endogenous DNA in the cytosol, which may potentially provide an underestimated contribution to therapeutic efficacy. Among others, these agents include (1) radiation therapy, at least when administered according to optimal dose and fractionation schedules that do not favor the upregulation of the dsDNA-degrading enzyme three prime repair exonuclease 1 (TREX1),146,55,63,179-181 (2) molecules that cause DNA damage, such as cisplatin and topoisomerase inhibitors like etoposide, or compromise the DNA damage response, including the clinically employed poly(ADP)-ribose polymerase 1 (PARP) inhibitor olaparib, as well as experimental inhibitors of ATR serine/threonine kinase (ATR),191 or cause mitotic disturbances, such as paclitaxel and other taxanes.

Taken together, these observations suggest that several commonly used anticancer agents trigger STING-dependent cytokine responses. Besides contributing to therapeutic efficacy (at least to some degree), such responses may be actionable therapeutically, and hence need to be taken under attention consideration when combinatorial regimens are conceived.

**Concluding remarks**

Mounting preclinical and clinical evidence suggests that carefully designed agonists of human STING (as well as molecules that trigger STING signaling in an indirect fashion) activate therapeutically relevant type I IFN-dependent responses in cancer or immune cells, in particular DCs. Although to the
best of our knowledge no Phase III registration studies have yet been launched, several completed and ongoing Phase II studies have detected signs of clinical activity for STING agonists, though at the cost of non-negligible side effects. It will be interesting to learn whether mechanism-linked undesired effects can be minimized by favoring intratumoral over systemic delivery routes and whether this procedure would induce clinically exploitable systemic responses. If so, STING agonists may have a bright future.

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