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REVIEW

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Trial watch: TLR3 agonists in cancer therapy

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ABSTRACT

Toll-like receptor 3 (TLR3) is a pattern recognition receptor that senses exogenous (viral) as well as endogenous (mammalian) double-stranded RNA in endosomes. On activation, TLR3 initiates a signal transduction pathway that culminates with the secretion of pro-inflammatory cytokines including type I interferon (IFN). The latter is essential not only for innate immune responses to infection but also for the initiation of antigen-specific immunity against viruses and malignant cells. These aspects of TLR3 biology have supported the development of various agonists for use as stand-alone agents or combined with other therapeutic modalities in cancer patients. Here, we review recent preclinical and clinical advances in the development of TLR3 agonists for oncological disorders.

Abbreviations: cDC, conventional dendritic cell; CMT, cytokine modulating treatment; CRC, colorectal carcinoma; CTL, cytotoxic T lymphocyte; DC, dendritic cell; dsRNA, double-stranded RNA; FLT3LG, fms-related receptor tyrosine kinase 3 ligand; HNSCC, head and neck squamous cell carcinoma; IFN, interferon; IL, interleukin; ISV, *in situ* vaccine; MUC1, mucin 1, cell surface associated; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; polyA:U, polyadenylic:polyuridylic acid; polyI:C, polyriboinosinic: polyribocytidylic acid; TLR, Toll-like receptor

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Introduction

Toll-like receptors (TLRs) are an evolutionarily conserved family of pattern recognition receptors (PRRs)[1–4] that detect conserved molecular motifs in microbial and endogenous products, which are generally referred to as microbe- or damage-associated molecular patterns (MAMPs or DAMPs), respectively.[5–11]

Since the initial discovery of Toll as a *Drosophila melanogaster* receptor with antifungal activity,[12–14] no less than 13TLRs have been characterized in mammalian organisms, 10 of which are also encoded by the human genome.[5,15] Mammalian TLRs localize either to the cell surface (TLR1, TLR2, TLR4, TLR6, TLR10) or within endosomal compartments (TLR3, TLR7, TLR8, TLR9).[5,16] Such endosomal TLRs are specialized in the recognition of potentially pathogenic nucleic acids, based on three general principles (1) availability (a function of initial concentration and degradation by endogenous nucleases), (2) localization (of both nucleic acids and TLRs) and (3) structural features (secondary nucleic acid conformations as well as chemical modifications).[17–19] On activation, nucleic acid-sensing TLRs initiate a signal transduction cascade that culminates with the secretion of numerous pro-inflammatory cytokines including type I interferon (IFN), which promote both innate and adaptive immune responses.[20–26]

Double-stranded RNA (dsRNA) molecules are the prototypic ligands of TLR3,[27] and activation occurs upon dsRNA binding to TLR3 leucine-rich repeats (LLR) domain.[28,29] Several mechanisms have been suggested to account for the accumulation of TLR3-activitory dsRNA molecules within endosomes, including clathrin-dependent endocytosis,[30,31] uptake of apoptotic bodies from infected cells,[32,33] autophagic uptake of dsRNA from the cytosol and trafficking to endosomes in the context of inhibited lysosomal degradation,[34–36] and formation of dsRNA complexes with cathelicidin antimicrobial peptide (CAMP).[37,38]

Upon ligand binding, the cytoplasmic Toll/IL-1 receptor (TIR) domain of TLR3[39,40] engages toll-like receptor adaptor molecule 1 (TIRAM1, best known as TRIF) and toll-like receptor adaptor molecule 2 (TIRAM2, best known as TRAM) to initiate a signal transduction cascade that culminates with the activation of TANK binding kinase 1 (TBK1)[41] and consequent derepression of interferon regulatory factor 3 (IRF3),[42] IRF7[43] and nuclear factor-kappa

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B (NF-κB).[44–46] Moreover, active TLR3 can signal via the mitogen-activated protein kinase (MAPK) system[5,47,48] to initiate transcriptional programs downstream of Jun proto-oncogene, AP-1 transcription factor subunit (JUN, best known as AP-1)[49] and cAMP responsive element binding protein 1 (CREB1).[50,51] Thus, TLR3 signaling favors the synthesis and secretion of a panoply of pro-inflammatory cytokines including not only type I IFN but also tumor necrosis factor (TNF), interleukin 6 (IL-6) and various chemokines such as C-C motif chemokine ligand 2 (CCL2) and C-X-C motif chemokine ligand 1 (CXCL1).[52–57] Of note, unlike other TLRs, TLR3 signaling appears to require tyrosine phosphorylation upon dsRNA recognition,[58] and operates exclusively via an MYD88 innate immune signal transduction adaptor (MYD88)-independent mechanism.[59,60]

Defective TLR3 activity contributes to numerous pathologies, including chronic inflammation, sepsis, autoimmune disorders and cancer.[61–66] Specifically, loss-of-function TLR3 polymorphisms have been associated with an increased risk for breast carcinoma,[67] cervical cancer,[68] oral squamous cell carcinoma,[69] hepatocellular carcinoma (HCC),[70] and colorectal carcinoma (CRC);[71] as well as with poor disease outcome in patients with CRC[72] and non-small cell lung carcinoma (NSCLC).[73] Moreover, high expression levels of TLR3 or TRIF have been shown to convey positive prognostic value in patients with HCC,[74,75] and neuroblastoma,[76] while TLR3 expression has attributed predictive value in a cohort of women with breast carcinoma treated with adjuvant radiotherapy plus a TLR3 agonist.[77,78] Finally, several studies have demonstrated that the emission of DAMPs by dying cancer cells, either spontaneously or following treatment, enables the initiation of an efficient and durable anticancer immune response through the activation of TLRs and other PRRs on immune cells of the host.[79–82] Thus, TLR3 stimulation stands out as a promising strategy to (re)instance cancer immunosurveillance[83] and demonstrated potential especially as an adjuvant to therapeutic tumor-targeting vaccines.[84–91] However, whereas TLRs located at the plasma membrane can be actioned with small molecules and antibodies, targeting nucleic-acid sensing TLRs, such as TLR3, require modified oligonucleotides.[87] Indeed, besides natural dsRNA molecules, TLR3 also recognizes synthetic dsRNA analogs,[48] such as polyriboinosinic:polyribocytidylic acid (polyI:C),[92] polyadenylic:polyuridylic acid (polyA:U),[93] polyriboinosinic-polyribocytidylic acid-polylysine carboxymethylcellulose (polyI:CLC, best known as Hiltonol™)[94] and polyI:C_{12}U (best known as Ampligen™ or rintatolimod),[95,96] all of which have been consistently used to induce TLR3 signaling *in vitro* and *in vivo*.[97–101]

Over the past few years, numerous studies have confirmed the ability of TLR3 agonists to support the activation of tumor-specific immune responses in mice and patients, especially when combined with other therapeutic modalities.[90,102-104] However, the clinical efficacy of this approach remains limited, potentially reflecting the existence of numerous, non-overlapping immunosuppressive pathways that must be simultaneously disabled to allow for therapeutically relevant tumor-targeting immune responses in patients.[83,105,105-107,109] Here, we discuss recent progress on the development of TLR3 agonists for cancer therapy.

Preclinical advances

In this section, we summarize the key preclinical studies on the ability of TLR3 agonists to (re)instate anticancer immunosurveillance, which have been released since the publication of the latest Trial Watch dealing with this topic.[90]

PolyI:C and polyA:U, dsRNA mimetics

PolyI:C was originally synthesized in the mid-1960s by Hilleman and colleagues.[108] This synthetic dsRNA consists of an RNA duplex composed of one inosinic acid polymer and one cytidylic acid polymer. The treatment of immature dendritic cells (DCs) with TLR3 induces their functional maturation, as demonstrated by a reduction in phagocytic/pinocytic capacity coupled to increased expression of co-stimulatory molecules (*e.g.*, CD80 and CD86), maturation markers (*e.g.*, CD83) and immunostimulatory cytokines (*e.g.*, IL-12).[109] Interestingly, TLR3 is highly expressed both by a subset of mouse ($CD8\alpha^+$)[110,112] and human ($CD141^+$)[113,114] DCs commonly known as type I conventional DCs (cDC1s).[86,115-117] This basic leucine zipper ATF-like transcription factor 3 (BATF3)-dependent DC lineage has been extensively studied for its ability to efficiently cross-prime $CD8^+$ cytotoxic T lymphocytes (CTLs).[118–120] In line with these observations, Kline et al. have recently demonstrated that intraperitoneal injection of polyI:C elicits robust anti-leukemia T cell immunity and considerably prolongs survival of leukemia-bearing mice upon the engagement of $CD8\alpha^+$ cDC1s.[121]

Several combinatorial regimens have been developed to increase the antineoplastic effects of polyI:C, some of which demonstrated pronounced therapeutic activity in preclinical models of melanoma[122,123] as well as CRC,[124,125] mammary,[124] and squamous carcinoma.[122] In particular, systemic administration of the DC growth factor fms-related receptor tyrosine kinase 3 ligand (FLT3 LG) followed by intratumoral polyI:C injections improved magnitude and duration of response to B-Raf proto-oncogene, serine/threonine kinase (BRAF) and CD274 (best known as PD-L1) blockade in mouse B16 melanomas, via a mechanism involving cDC1s.[123,126] Di and colleagues have recently evaluated the efficacy of polyI:C administered in combination with epithelial growth factor receptor (EGFR)vIII-targeted CAR-T cells,[127] both *in vitro* and in immunocompetent mice bearing subcutaneous CRC or orthotopic mammary cancer xenografts. In this setting, polyI:C significantly increased the levels of effector cytokines such as IL-2 and IFNγ, as well as the lytic activity of CAR-T cells while reducing the number and function of myeloid-derived suppressor cells (MDSC) in the peripheral blood and spleen.[124] Interestingly, Guinn and colleagues have recently reported that IFNγ synergizes with polyI:C in limiting the growth of mouse B16 melanoma and human UM-SCC1 squamous carcinoma cells *in vitro*, suggesting yet another mechanism through which polyI:C may mediate antineoplastic effects *in vivo*.[122] Along similar lines, polyI:C and the microtubular poison paclitaxel[128] have been reported to synergistically inhibit the growth of paclitaxel-resistant human CRC cells *in vitro* through a pathway that involves enhanced interferon beta 1 (IFNB1) expression downstream of TLR3.[125] These latter

findings suggest that the ability of polyI:C (and potentially other TLR3 agonists) to activate innate immune pathways in malignant cells may contribute to its therapeutic efficacy,[129] which is generally attributed to the engagement of the host immune system. Further supporting this possibility, TLR3 is known to promote apoptosis[98,130,131] as well as a non-apoptotic form of cancer cell death known as necroptosis,[132–134] which (at least in some settings) has therapeutic value.[135,136]

Several laboratories have recently focused their attention on the design of innovative delivery platforms for polyI:C. Thus, Aznar and collaborators have developed a nanoplexed formulation of polyI:C complexed with polyethylenimine (BO-112), which induces the apoptotic demise of cancer cells accompanied by features of immunogenic cell death (ICD).[137] Intratumoral injection of BO-112 to mouse MC38 CRCs, 4T1 mammary carcinomas and B16 melanomas promoted tumor infiltration by $CD8^+$ CTLs and established at least some degree of disease control dependent on IFNγ,[137] fostering clinical testing in patients with solid tumors (NCT02828098). Alongside, polyI:C has been delivered together with cancer cell lysates[138] with an injectable and self-assembled poly (*L*-valine) hydrogel. This vaccine formulation allowed for the recruitment, activation and maturation of DCs *in vivo* as it improved antigen persistence at the injection site and antigen drainage to lymph nodes.[139] Thus, subcutaneous administration of the hydrogel-based vaccine to melanoma-bearing mice mediated robust antineoplastic effects through a proficient CTL response.[139]

Similar to polyI:C, polyA:U was synthesized by the Hilleman's laboratory in the mid-1960s.[110] This double-stranded polyribonucleotide, composed of equimolar polyadenylic acid and polyuridylic acid, was extensively investigated in the 1980s[140-142] as the first clinical trials investigating the safety and preliminary activity of polyI:C documented side effects including fever, nausea and hypotension on systemic administration.[142,143] Even though polyI:C is more potent than polyA:U,[93,99,144] the latter is still used in several studies, at least in part because of its reduced toxicity. Supporting the ability of polyA:U to enhance anticancer immune responses, adjuvant polyA:U administration has been associated with a significant reduction in the risk for metastatic relapse amongst breast cancer patients with TLR3-expressing tumors.[77] Recently, Roselli et *al.* have reported that the intratumoral administration of naked polyA:U delays the growth of B16 melanomas *in vivo*, and significantly prolongs the survival of tumor-bearing mice.[112] This effect appears to be orchestrated by multiple changes within the lymphoid compartment of the tumor microenvironment, encompassing an increased abundance of $CD8^+$ CTLs expressing the effector molecule granzyme B (GZMB),[145] a reduction in the relative amount of tumor-infiltrating $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cells[105] (with respect to $CD8^+$ cells), an improved proliferation of tumor-antigen specific $CD8^+$ CTLs, as well as an enhanced expression of programmed cell death 1 (PDCD1, best known as PD-1)[146] and its main ligand CD274. These findings suggest that, similar to numerous chemotherapeutic agents that promote PD-L1 expression,[147,148] polyA:U might be advantageously combined with immunotherapies blocking the PD-1/PD-L1 axis.[112,149,150]

Ampligen™, an analogue of polyI:C

Ampligen™ (also known polyI:C_{12} U, AMP-516 or rintatolimod) was synthesized in the 1970 s by William A. Carter by adding unpaired uracil and guanine bases to the classical polyI:C structure.[151] Ampligen™, which drives type I IFN production and IFNB1-dependent type I helper (T_H1) responses with reduced toxicity as compared to polyI:C,[151] was originally intended for the treatment of chronic fatigue syndrome (CFS), a complex disorder characterized by extreme fatigue,[152,153] and only later it was used as a TLR3 agonist for other indications including cancer.[151] Recently, Tomasicchio *et al.* haver recruited 12 women with stage 1 to 3 breast carcinoma for *ex vivo* studies on their DC compartment, ultimately demonstrating that optimal DC maturation required a combinatorial treatment including Ampligen™, an autologous tumor cell lysate, the TLR7/8 agonist resiquimod,[154,155] and a cytokine cocktail encompassing IFNγ, IFNα, IL-1β and CD40 ligand (CD40 L). DCs matured *ex vivo* under these conditions produced high levels of IL-12 and could enhance antigen-specific $CD8^+$ CTL responses against erb-B2 receptor tyrosine kinase (ERBB2, better known as HER-2)[156] and mucin 1, cell surface associated (MUC1)[157] leading to the destruction of autologous breast cancer cells *in vitro*.[158]

Riboxxol, a dsRNA duplex

Riboxxol (also known as RGIC®50) is a synthetic dsRNA containing cytosines, inosines and guanosines that potently stimulates the secretion of several pro-inflammatory cytokines and improves the ability of mouse and human cDC1s to stimulate T cell proliferation.[159] Schau and colleagues have recently designed a targeted delivery system consisting of neutravidin (a deglycosylated version of avidin)[160,161] conjugated to monobiotinylated Riboxxol and a humanized anti-prostate stem cell antigen (PSCA) single-chain antibody derivative. These nanoparticle-like immunoconjugates, which were called "rapid inducer of cellular inflammation and apoptosis" (RICIA) were able to specifically deliver Riboxxol to PSCA-expressing tumor cells and induce a type I IFN response coupled to apoptotic cell death.[162]

ARNAX, a double-stranded RNA mimic

ARNAX is a TLR3 agonist originally developed by Matsumoto and collaborators that consists of a phosphorothioate oligodeoxynucleotide (ODN)-guided dsRNA.[163] Unlike polyI:C, this chimeric molecule does not activate intracellular RNA sensors other than TLR3[164,165] such as DExD/H-box helicase 58 (DDX58 best known as RIG-I) and interferon induced with helicase C domain 1 (IFIH1, best known as MDA5) and hence presents reduced toxicity *in vitro* and *in vivo*.[166–168] Takeda and collaborators have recently demonstrated that ARNAX synergizes with a model peptide vaccine and a CD274 (best known as PD-L1) blockers in the eradication of various mouse tumors established in immunocompetent hosts.[169]

Translational and clinical progress

Results from a number of translational and clinical studies addressing the safety and therapeutic potential of TLR3

agonists have been reported in the peer-reviewed literature since the publication of the latest Trial Watch on this topic (October 2018).[90] Here, we discuss some of these studies with a focus on findings and concepts that recapitulate the current state-of-the-art.

Translational studies

Recent immunohistochemical studies demonstrate that high TLR3 expression by tumor cells correlates with favorable disease outcome in a cohort of 194 patients with early-stage NSCLC, whereas TLR3 expression on immune cells, infiltrating the tumor bed, is associated with poor overall survival.[170] At least in part, these observations appear to reflect the ability of TLR3 activation to drive apoptotic cell death in cancer cells, as demonstrated *in vitro* as well as by the immunohistochemical quantification of active caspase 3 (CASP3), a key mediator of apoptosis,[171–173] in tumor biopsies. Tan and colleagues have recently reported that nasopharyngeal carcinoma (NPC) biopsies exhibit increased *TLR3* mRNA levels as compared to healthy nasopharyngeal tissues,[54] which appears to constitute an actionable therapeutic target. Indeed, Hiltonol™ synergized with the endothelial growth factor receptor (EGFR)-specific antibody cetuximab in (1) maturation of DCs, (2) activation of natural killer (NK) cell-dependent antibody-dependent cellular cytotoxicity (ADCC) and cytotoxicity, and tumor infiltration by EGFR-specific CTLs.[54] None of these effects was affected by TLR3 polymorphisms (e.g., L412F or C829T), pleading in favor of a broad use of Hiltonol™ against NPC.[54] Finally, Hammerich et al. developed an *in situ* vaccine (ISV) approach, combining recombinant human FLT3LG, local radiotherapy, and Hiltonol™ that robustly activated an anticancer immune response amenable to boosting with PD-1 blockers in lymphoma bearing mice.[174] These results prompted the initiation of a hitherto ongoing clinical trial (NCT01976585) enrolling patients with advanced stage indolent non-Hodgkin's lymphoma (iNHL).

Clinical studies

Preliminary results for the aforementioned NCT01976585 clinical trial (testing a Hiltonol™-based ISV approach in patients with iNHL) suggested that both responders and non-responders to the ISV develop (at least some degree of) anticancer immunity, based on analysis of peripheral blood mononuclear cells (PBMCs) for maturation and exhaustion markers in DCs and CTLs.[174] However, it seems that a population of PD-1$^+$CD8$^+$ T lymphocytes emerges in non-responders, potentially explaining why of 11 patients included in this preliminary analysis, no less than 8 experienced partial or complete lymphoma regression in the presence of a PD-1 blocker.[174] Conversely, only six patients showed stable disease or minor regression (lasting 3 to 18 months) at distant untreated tumors whereas two patients progressed. Altogether, these findings suggest that iNHL patients might benefit from a Hiltonol™-based ISV approach combined with PD-1 blockers.

Weed et al. reported preliminary results from a Phase I clinical assay testing the safety and immunological efficacy of a MUC1-targeting peptide vaccine admixed with Hiltonol™ and combined with a phosphodiesterase type 5 (PDE5) inhibitor (tadalafil)[175] in subjects with head and neck squamous cell carcinoma (HNSCC) (NCT02544880).[176] While no severe side effects and treatment-limiting toxicities were documented, this regimen increased the amount of activated tumor-infiltrating lymphocytes (TIL) and reduced the levels of PD-L1$^+$ macrophages at the tumor edge,[176] suggesting that the addition of a PD-1- or PD-L1-taregting immune checkpoint blockers may be useful also in this setting. Alongside, a pilot study on patients with metastatic HNSCC and melanoma who received intratumoral or intramuscular Hiltonol™ reported clinical benefits for at least one of the 8 individuals enrolled in this trial, coupled to moderate side effects (such as inflammation at the injection site and fatigue) as well as increased levels of CD4, CD8, PD-1, and PD-L1 in tumors, confirming the activation of systemic immunity.[177]

Keskin and colleagues reported the results of a Phase Ib clinical trial in which newly diagnosed glioblastoma patients with unmethylated methylguanine methyltransferase (*MGMT*) received a personalized neoantigen vaccine, previously administered to melanoma patients,[178–180] admixed with Hiltonol™.[181] This regimen generated strong intratumoral T-cell responses even though glioblastoma is generally viewed as an immunological 'desert',[182] suggesting that robustly adjuvanted neoepitope-targeting vaccines may constitute a valid approach for the treatment of glioblastoma, especially in combination with immune checkpoint blockers.[183] Apparently at odds with this notion, Boydell and colleagues reported that a multipeptide vaccine (IMA950) admixed with Hiltonol™, administered prior to the vascular endothelial growth factor A (VEGFA)-targeting antibody bevacizumab,[184,185] failed to improve the therapeutic activity of the latter in high-grade glioma patients, as assessed by progression-free and overall survival (NCT01920191).[186]

Melssen *et al.* investigated the safety, immunogenicity and preliminary efficacy of a multipeptide vaccine[187,188] admixed with (1) Hiltonol™ and/or incomplete Freund's adjuvant (IFA), or (2) the mixed TLR2/TLR4 agonist lipopolysaccharide (LPS)[189,190] and/or IFA in melanoma patients (NCT01585350).[191] Preliminary findings from this study indicate that Hiltonol™ plus IFA can induce durable peptide-specific CD8$^+$ T cell responses in the absence of considerable side effects (dose-limiting toxicities were documented in only 11% of the subjects). Finally, one Phase I study evaluated the therapeutic effect of TLR3 agonists in pediatric cancers (NCT01188096).[192] Of note, all six patients affected by type I neurofibromatosis (among the 23 enrolled in the trial) tolerated Hiltonol™ as a stand-alone intervention (mild side effects included fever, pain at site of injection, erythema and myalgias),[192] supporting the planification of a Phase II study for this specific oncological indication.

Overall, this translational and clinical literature supports the notion that TLR3 agonists may favor the ability of therapeutic vaccines to (re)activate immunosurveillance in (at least some) patients affected by solid tumors, although efficacy in the absence of immune checkpoint blockers remains limited.

Recently initiated clinical trials

Since the submission of the latest Trial Watch dealing with this topic (October 2018),[90] only 8 clinical studies encompassing

the administration of TLR3 agonists to cancer patients have been initiated (source http://clinicaltrials.gov/), all of which involved either Hiltonol™ (4 studies),[193–195] or Ampligen™ (4 studies)[151] (Table 1).

In particular, NCT04119830 aims at evaluating the toxicity of Ampligen™ in combination with the PD-1 blocker pembrolizumab,[196,197] as well as the impact of this regimen on progression-free and overall survival in patients affected by metastatic, refractory or unresectable CRC.[198] Patients with CRC-derived liver metastases[199] are also being enrolled in NCT03403634, Phase II study involving the administration of a recombinant IFNα-2b (rIFNα-2b)- and Ampligen™-based cytokine modulating treatment (CMT)[200] plus the nonsteroidal anti-inflammatory drug celecoxib.[201] In this study, the impact of treatment on the immune microenvironment is evaluated by the immunohistochemical assessment of CTL/T_{REG} cell ratio.[202–204]

In an analogous manner, HLA-A2$^+$ individuals with primary PD-1-resistant or refractory melanoma are being enrolled in NCT04093323, a Phase II study combining the aforementioned CMT (rIFNα-2b, Ampligen™, and celecoxib) with a vaccine in which cDC1s are loaded with tumor blood vessel-derived antigenic peptides. Twelve weeks after treatment initiation, patients with progressive disease may receive the cytotoxic T-lymphocyte associated protein 4 (CTLA4) blocker ipilimumab[205-209] with or without a PD-1/PD-L1 inhibitor. Patients experiencing complete responses or stable disease may receive PD-1/PD-L1 inhibitors or an appropriate alternative care. A modified variant of the rIFNα-2b-based CMT that involves aspirin[210,212] instead of celecoxib is also being tested in prostate cancer patients scheduled for radical prostatectomy (NCT03899987). The objectives of this window-of-opportunity study aim at assessing safety, antitumor activity, and immunomodulatory effects.

Hiltonol™ is being tested as a stand-alone intervention only in a Phase I clinical assay involving the intravenous administration of the drug to patients affected by malignant pleural mesothelioma prior to surgical resection (NCT04345705). All the other clinical trials recently initiated to test Hiltonol™ in patients with cancer co-involve indeed either a PD-1 blocker[197,213] (NCT03789097 and NCT03835533) or an agonist for the co-stimulatory T cell receptor CD27 (varlilumab, also known as CDX-1127)[214,215] (NCT03617328).

In particular, Hiltonol™ is being administered in combination with radiotherapy and rhFLT3LG as *in situ* vaccine supported by systemic pembrolizumab[216] to patients affected by metastatic breast cancer, HNSCC and NHL in the context of a Phase I/II assay (NCT03789097). This combinatorial regimen includes three therapies directed against a "target site": (1) rhFLT3LG, known also by the name of CDX-301,[217,218] that specifically recruits and expands DCs, (2) radiation therapy to the tumor and the draining lymph node (administered at a 10–20 times lower dose compared to the standard for patients with this specific type of neoplasm),[78] and (3) Hiltonol™, which should activate the immune cells recruited into the tumor by rhFLT3LG and radiation. Of note, pembrolizumab is already approved by the U.S. Food and Drug Administration (FDA) for the treatment of several neoplasms including HNSCC, but is not effective against metastatic breast carcinomas and NHL.[219,220]

Along similar lines, Hiltonol™ is currently being tested in individuals with metastatic castration-resistant prostate cancer[221-224] simultaneously receiving the PD-1 blocker nivolumab,[225] rhFLT3LG and stereotactic body radiation therapy (SBRT)[226] (NCT03835533). The principal purpose of this study is to monitor the safety and efficacy of different immunotherapy-based combinatorial regimens: one arm (cohort B) receives the aforementioned Hiltonol™-based regimen; a second arm (cohort A) receives nivolumab together with NKTR-214, an IL-2 agonist targeting interleukin 2 receptor subunit beta (IL2RB, also known as CD122)[227–229]; and (3) a third arm (cohort C) receives nivolumab together with rhFLT3LG and INO-5151, a combined formulation of INO-5150 – a DNA vector expressing kallikrein-related peptidase 3 (KLK3, best known as PSA)[230] and folate hydrolase 1 (FOLH1, best known as PSMA)[231] – and INO-9012 – a DNA vector expressing IL-12.[232]

Finally, the Phase I/II clinical study NCT03617328 evaluates the safety, efficacy and immunogenicity of a peptide vaccine comprised six class II MHC-restricted peptides (6MHP) in patients with melanoma. In this trial, vaccination is adjuvanted with Hiltonol™ and montanide ISA-51,[233] as well as with varlilumab.[234–236]

Table 1. Clinical trials currently testing TLR3 agonists in oncological indications.

Agonist	Indication(s)	Phase(s)	Route	Recruitment	Interventions	Ref
Ampligen	Colorectal cancer	II	*i.v.*	Not yet recruiting	Combined with pembrolizumab	NCT04119830
				Recruiting	Combined with celecoxib and rIFNα-2b	NCT03403634
	Melanoma	II	*i.v.*	Not yet recruiting	Combined with DC vaccination, celecoxib, PD-1/PD-L1 inhibitors and rIFNα-2b	NCT04093323
	Prostate cancer	II	*i.v.*	Recruiting	Combined with aspirin ± rIFNα-2b	NCT03899987
Hiltonol	Breast cancer HNSCC NHL	I/II	*i.t.*	Recruiting	Combined with pembrolizumab, radiotherapy and rhFLT3LG	NCT03789097
	Melanoma	I/II	*i.d. s.c.*	Recruiting	Combined with multipeptide vaccine, montanide ISA-51 ± varlilumab	NCT03617328
	Mesothelioma	I	*i.t.*	Not yet recruiting	As single agent	NCT04345705
	Prostate cancer	I	*i.m.*	Recruiting	Combined with nivolumab, rhFLT3LG and SBRT	NCT03835533

Abbreviations: HNSCC, head and neck squamous cell carcinoma; *i.d.*, intra derma; *i.m.*, intra musculum; *i.t.*, intra tumorem; *i.v.*, intra venam; NHL, non-Hodgkin's lymphoma; rhFLT3LG, recombinant human fms-like tyrosine kinase 3 ligand; rIFNα-2b, recombinant interferon α-2b; SBRT, stereotactic body radiation therapy; *s.c.*, sub cutem.

The status of the following clinical trials discussed in our previous Trial Watches dealing with TLR3 agonists[90] has changed during the past 19 months: NCT02334735, NCT02544880, NCT02721043, NCT02826434, NCT02873819, NCT02897765, NCT03162562, NCT03358719, NCT03380871 and NCT03597282 which are now listed as "Active, not recruiting"; NCT02886065, which is listed as "Recruiting"; NCT02134925 which is currently listed as "Active, not recruiting with results"; NCT02149225, which is listed as "Completed"; NCT03206047 and NCT03300817, which have been "Suspended"; NCT02061449 which has been "Terminated"; as well as NCT02754362, which has been "Withdrawn" (source http://clinicaltrials.gov/).

NCT02134925 is a randomized Phase II study evaluating a MUC1-targeting peptide vaccine admixed with Hiltonol™ *versus* placebo in patients with newly diagnosed advanced colon polyps. Preliminary results from 110 patients enrolled in the study suggest that vaccination induces superior levels of circulating MUC1-specific IgG, and some degree of reduction in adenoma recurrence rate (56.3% versus 66.0%) (source http://clinicaltrials.gov/). To the best of our knowledge, the results of NCT02149225 (a Phase I study investigating the safety and preliminary efficacy of a Hiltonol™-adjuvanted vaccine in glioblastoma patients) have not been disseminated yet. NCT03206047 (a Phase I/II trial testing Hiltonol™-adjuvanted DC-targeting vaccine in women with recurrent ovarian, fallopian tube, or primary peritoneal cancer) and NCT03300817 (a Phase I study testing a Hiltonol™-adjuvanted, MUC1-targeting vaccine to prevent lung cancer in former and current smokers) have been suspended for undisclosed reasons or to ensure patient safety during the Covid19 epidemics,[237–239] respectively (source http://clinicaltrials.gov/). NCT02061449 (a Phase I study investigating Hiltonol™ plus radiation in patients with advanced cutaneous T cell lymphoma) has been terminated because of poor accrual. Finally, NCT02754362 (a Phase II trial testing Hiltonol™ and montanide ISA-51 in support of a multipeptide vaccine administered prior to bevacizumab in glioblastoma patients) has been withdrawn due to personnel changes (source http://clinicaltrials.gov/).

Concluding remarks

The blockade of co-inhibitory T cell receptors or their ligands, as achieved with immune checkpoint inhibitors targeting CTLA4, PD-1 and PD-L1, has been a major success in the treatment of patients with various tumors. However, at this stage, immunotherapies only provide long-term clinical benefits to a minority of patients, calling for a drastic amelioration of standard of care. In this context, numerous studies have been launched to identify additional immunosuppressive or immunostimulatory circuitries that can be drugged. As discussed in the present Trial Watch, TLR3 stands out as a promising target for the (re)elicitation of anticancer immunosurveillance. However, the existence of numerous immunosuppressive circuitries that enable tumor progression and resistance to conventional therapies considerably limits the efficacy of TLR3 agonists employed as stand-alone agents, as well as of vaccines adjuvanted with TLR3 agonists, to mediate clinically relevant effects. We surmise that the development of properly scheduled combinatorial regimens involving multiple immunotherapeutic agents (notably, immune checkpoint blockers and agents that recruit and expand DCs) will be required for harnessing the full antineoplastic potential of TLR3 agonists.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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