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# New emerging targets in cancer immunotherapy: CD27 (TNFRSF7)

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## ABSTRACT

Cluster of differentiation 27 (CD27) is a member of the tumour necrosis factor receptor superfamily and plays a key role in T-cell activation by providing a costimulatory signal. Bound to its natural ligand CD70, CD27 signalling enhances T-cell proliferation and differentiation to effector and memory T cells and therefore has potential as an immune modulatory target in cancer treatment. The CD27 agonistic antibody varlilumab showed promising efficacy in haematological as well as solid cancers. Current studies investigate the combination of the CD27 agonistic antibody varlilumab in combination with the PD1 axis targeting immune checkpoint inhibitors like nivolumab or atezolizumab. Further, CD70 expression is used as a therapeutic target for ADCs, antibodies inducing ADCC, as well as the immunological target for chimeric antigen receptor gene-modified T cells and specific dendritic cell vaccination. In line with this, targeting the CD27 axis was shown to be feasible and safe in early clinical trials with the most commonly occurring side effects being thrombocytopenia, fatigue and nausea. In this mini review, we aimed to elucidate the immunobiology of CD27 and its potential as a target in cancer immunotherapy.

## PHYSIOLOGICAL FUNCTION OF CD27

Cluster of differentiation 27 (CD27, also TNFRSF7) is a transmembrane glycoprotein physiologically expressed on CD4+ and CD8+ T cells, natural killer (NK) cells and thymocytes, and is induced on B cells on priming.[1] CD27 belongs to the tumour necrosis factor receptor superfamily (TNFRSF) and plays a key role in T-cell and B-cell costimulation.[1 2] The natural ligand of CD27 is CD70 (CD27 ligand or CD27-L) which is quite restrictively and only transiently expressed on activated immune cells, including T cells, B cells, dendritic cells (DCs) and NK cells.[3 4]

Members of the TNFRSF like CD27 frequently present as key costimulatory T-cell receptors in order to generate a functional immune response.[5] The costimulatory T-cell signal via CD27 further enhances cell division and cell survival, as well as effector functions like cytokine production, especially IP-10, or cytotoxicity by activating different pathways like the nuclear factor-κB, phosphatidylinositol 3-kinase or protein kinase B.[6] Therefore, CD27/CD70 costimulation has the potential to boost the immunity by T-cell activation, increased clonal expansion and enhanced differentiation into antigen-specific cytotoxic and memory T cells.[7–12]

Further, CD27/CD70 also has the capability of influencing the innate immune system by inducing proliferation and cytotoxicity by increased interferon-gamma (IFN-γ) production of NK cells.[13] With regard to the B-cell lineage, in vitro studies showed that T cells that are expressing CD27 and CD70 play a key role in regulating B-cell activation and immunoglobulin synthesis.[14 15]

## CD27 SIGNALLING AND CD70 EXPRESSION IN CANCER

CD27 is a costimulatory T-cell receptor essential for optimal T-cell priming and memory differentiation. Especially in the activation of cytotoxic CD8+ T cells, CD27 signalling plays a central immunological role, potentially usable for antitumour therapy.[16] Tumour-infiltrating lymphocytes in the tumour microenvironment of solid tumours were shown to express CD27.[17] The CD27 ligand CD70 is restrictively expressed on activated immune cells and is usually absent in non-lymphoid normal tissue.[18] In various lymphoid malignancies like non-Hodgkin's lymphoma (NHL, 77%), diffuse large B-cell lymphoma (DLBCL, 71%) and mantle cell lymphoma (5%) a constitutive expression of CD70 has been described.[19–22] CD70 expression was frequently observed in several solid cancers including lung (10%), breast (2%), pancreatic (25%), ovarian (15%), colon (9%), renal cancer (87%), melanoma (16%) and glioblastoma (42%).[21 23 24] Furthermore, the importance of CD27/CD70 signalling for anticancer immunity is underscored by the observation that patients with germ line, somatic mutations or deletions in CD27 or CD70 more frequently develop Hodgkin lymphoma or DLBCL.[25] Therefore, targeting of the CD27/CD70 axis might be of therapeutic potential.

Targeting the CD27/CD70 axis with an agonistic CD27 antibody resulted in growth reduction of lung metastases and subcutaneous

tumours in a B16 melanoma model.[26] Anti-CD27 treatment also resulted in the maintenance of tumour-specific IFN-γ producing $CD8^+$ T cells within the tumour.[26] Efficacy of CD27/CD70 axis targeting antibodies was shown in preclinical models of lymphoma, renal cell carcinoma (RCC), breast cancer and sarcoma.[27–30] Growing evidence from preclinical studies further suggests a particular synergetic effect of agonistic CD27 antibodies with other immune-modulating agents, including OX40, CD40 and cytotoxic T-lymphocyte-associated protein 4 blockade.[5 31 32] Combinational approaches of agonistic CD27 antibodies and programmed cell death 1 (PD-1) blockade presented with the highest preclinical efficacy, successfully eradicating tumours in preclinical models.[32 33] Importantly, activation of the CD27/CD70 axis might also have protumoural immune suppressive effects driven by chronic stimulation and tumour-associated CD70 overexpression.[18] This effect is attributable to CD27 exploitation, enhanced survival signalling in natural regulatory T cells (Tregs) and induction of apoptosis of effector T cells.[18 34 35] Clinical data underlined this fact by showing that patients with follicular B-cell lymphoma with intratumoural CD70-expressing T cells presented with an exhausted phenotype with higher levels of PD-1 and T-cell immunoglobulin mucin domain-3.[36]

## CD27/CD70 TARGETING AGENTS UNDER DEVELOPMENT

Targeting the immunological functions of the CD27 axis can be approached by agonistic CD27 antibodies inducing increased antitumour immunity (table 1).

A human monoclonal antibody (mAb) directed at CD27 named varlilumab (also CDX-1127, 1F5) has entered clinical trials after showing preclinical efficacy.[37–39] A phase I study evaluated the safety and dosage in a total of n=56 patients with haematological cancers and advanced solid tumours, including metastatic melanoma, RCC, prostate cancer, ovarian cancer, colorectal cancer and non-small-cell lung cancer (NCT01460134). One of 15 patients with metastatic RCC achieved a partial response with 78% of tumour shrinkage and a progression-free survival (PFS) of 2.3 years, and 8/56 (14.29%) patients achieved stabilisation of disease (range of PFS 3.8–47.3 months).[40] One of 19 patients with heavily pretreated advanced B-cell lymphoma achieved a complete response (CR).[41] Varlilumab is further investigated in a phase I/II dose escalation and cohort expansion study (NCT02335918) in combination with nivolumab in different solid malignancies (n=175 patients).[42] So far, results are available only for colorectal and ovarian cancer showing that 5/49 (10%) of ovarian cancer patients achieved a partial response (PR) and 19/49 (39%) a stable disease (SD). Biopsies of ovarian cancer patients on treatment showed an increase in PD-1 and CD8+ T-cell expression profiles more prevalent in patients who had a better outcome.[42] In patients with colorectal cancer, 2/41 (5%) presented with a PR and 7/41 (17%) with a SD.[42] Investigation of biomarkers showed transient increases in serum chemokine levels and a decrease in circulating Tregs. Therefore, depletion of Tregs might also add to the antitumour immune-modulating activities of varlilumab, as well as to the risk of increased autoimmunity.[43] Further phase I trials with various combinations as well as phase II trials are still ongoing in RCC, squamous cell carcinoma of the head and neck, ovarian and colorectal cancers, and glioblastoma (table 2).

Furthermore, also CD70 targeting agents are tested in clinical trials with different compounds (table 1).[24 44 45] Here, CD70 is rather used as a specific target on the tumour cells.

Antibody drug conjugates (ADCs) use CD70 expression on tumour cells in a 'Trojan horse'-like function, allowing the linked cytotoxic agents to enter the tumour cells and induce cytotoxicity. CD70 expression on tumour cells can be targeted by specific antibodies in order to induce antibody-dependent cell-mediated cytotoxicity (ADCC). Chimeric antigen receptor gene-modified T (CAR-T) cells, as well as specific DC vaccinations targeting CD70 expression, were developed to use CD70 as a specific therapeutic target.

The CD70 targeting antibody ARGX-110, also named cusatuzumab, a glycoengineered mAb targeting CD70, was tested in various solid and haematological malignancies expressing CD70. The afucosylation of the anti-CD70 mAb is intended to improve its ability to induce the ADCC of CD70-expressing tumour cells. The best achieved overall response was SD in 14/26 (54%) patients.[46] Five patients (RCC, ovarian cancer, head and neck cancer, myoepithelial carcinoma and mesothelioma) had a PFS of >6 months.[46] One patient with T-cell lymphoma achieved a complete haematological response.[47]

A multicentric phase I study tested the ADC MDX-1203 (BMS-936561) consisting of a mAb targeting CD70 (MDX-1115) linked to a small drug molecule MED-2460.[48] In total, n=26 patients with advanced RCC or relapsed/refractory B-NHL were included. Preliminary efficacy assessment showed that 18/26 (69%) of patients achieved SD as best response. SGN-75, another CD70-blocking ADC, was tested in n=58 patients with relapsed or refractory CD70+ NHL or metastatic RCC.[21] Of the 58 patients, 1 achieved a CR, 2 patients had a PR and 20 (34.5%) had a SD. All three patients with objective responses had a 95% positively stained CD70 expression. SGN-CD70A was developed with a different cytotoxic agent, pyrrolobenzodiazepine, and investigated in n=18 CD70-positive RCC and n=20 patients with NHL in a phase I study (NCT02216890). One of 18 patients with RCC achieved a PR and 13/18 (72%) patients had a SD, resulting in a clinical benefit rate of 78%.[44] In patients with NHL, 1/20 patients achieved a CR and 3/20 a PR.[49] However, further development of this compound was stopped due to the high occurrence rate (94%) of treatment-related adverse events (AEs). Eighty-three per cent of patients in the early clinical development presented with at least one grade 3 treatment-related AE. The most frequently observed treatment-related AEs included thrombocytopenia

**Table 1** List of CD27/CD70 targeting antibodies tested in clinical trials

| Name of the compound | Mechanism of action | Tumour type | Phase of clinical trial development | Company | Clinical benefit rate= (CR+PR+SD)/ n (%) | Most common side effects | Reference/trial number |
|---|---|---|---|---|---|---|---|
| Varlilumab, CDX-1127 | Fully human IgG1 CD27 agonistic mAb | Haematological and solid cancers | Phase I, completed | Celldex Therapeutics | 9/56=16.1% | Fatigue (54%), nausea (30%), dyspnoea (25%) | Burris *et al*/NCT01460134[40] |
| SGN-75 | Humanised anti-CD70 IgG1 mAb linked to MMAF toxin | RCC, NHL | Phase I, completed | Seattle Genetics | 23/58=39.7% | Fatigue (40%), dry eye (32%), nausea (30%), thrombocytopenia (26%) | Tannir *et al*/NCT01015911[21] |
| SGN-75+everolimus | Humanised anti-CD70 IgG1 mAb linked to MMAF toxin+mTOR inhibitor | RCC | Phase I, terminated (reason: not available) | Seattle Genetics | n/a | n/a | NCT01677390 |
| SGN-CD70A | ADC directed against CD70 antigen with the cytotoxic component PBD | RCC, Mantle-Cell lymphoma, diffuse large B-cell lymphoma, grade 3 follicular lymphoma | Phase I, completed | Seattle Genetics | RCC: 14/18=77.8% Lymphoma: 4/20=20% | RCC: fatigue (67%), anaemia (61%), thrombocytopenia (56%) Lymphoma: thrombocytopenia (75%), nausea (55%), anaemia (50%), fatigue (50%) | Pal *et al*, Phillips *et al*/ NCT02216890[44 49] |
| AMG 172 | Humanised anti-CD27L IgG1 mAb linked to MCC-DM1 | RCC | Phase I, completed | Amgen | 8/37=21.6% | Thrombocytopenia (59%), nausea (54%), decreased appetite (49%), vomiting (46%), fatigue (35%) | Massard *et al*/NCT01497821[45] |
| ARGX-110 (Cusatuzumab) | Glycoengineered CD70 blocking mAb | Advanced cancers | Phase I, active, not recruiting | Argenx BVBA | 14/26=53.8% | Fatigue (65%), drug-related infusion-related reactions (38%), dyspnoea (31%), fever (31%) | Aftimos *et al*/ NCT01813539+NCT02759250[46] |
| MDX-1203, BMS-936561 | ADC of humanised CD70-mAb linked to MED-2460 | RCC, NHL | Phase I, completed | BMS | 18/26=69.2% | Fatigue (85%), nausea (54%), decreased appetite (39%) | Owonikoko *et al*/NCT00944905[48] |
| Varlilumab+ nivolumab | Fully human IgG1 CD27 agonistic mAb+fully human IgG4 mAb targeting PD-1 | SCCHN, ovarian cancer, colorectal cancer, RCC, glioblastoma | Phase I/II, completed | Celldex Therapeutics and BMS | OVA Ca: 24/49=49.0% CRC: 9/41=22.0% | OVA Ca: pruritus (18%), rash (18%), infusion reaction (17%) CRC: infusion reaction (31%), nausea (17%), lymphopenia (17%) | Sanborn *et al*/NCT02335918[42] |
| Varlilumab+ sunitinib | Fully human IgG1 CD27 agonistic mAb+small molecule inhibiting multiple receptor tyrosine kinases | RCC, urogenital neoplasms | Phase I, terminated (reason: portfolio reprioritisation) | Celldex Therapeutics | n/a | n/a | NCT02386111 |
| Varlilumab+ ipilimumab+CDX-1401 | Fully human IgG1 CD27 agonistic mAb+humanmAb blocking CTLA-4+immunomodulating vaccine made of fully human mAb linked to NY-ESO-1 in combination with poly-ICLC (Hiltonol) | Unresectable Stage III or stage IV melanoma | Phase I/II, terminated (reason: feasibility concerns due to changes in standard of care) | Celldex Therapeutics | n/a | n/a | NCT02413827 |
| Varlilumab+ ONT-10 | Fully human IgG1 CD27 agonistic mAb+liposomal synthetic glycopolypeptide vaccine MUC1 targeted antigen formulated with PET lipid A adjuvant | Breast cancer, ovarian cancer | Phase Ib, completed | Cascadian Therapeutics+ Celldex Therapeutics | n/a | n/a | NCT02270372 |

Continued

**Table 1** Continued

| Name of the compound | Mechanism of action | Tumour type | Phase of clinical trial development | Company | Clinical benefit rate= (CR+PR+SD)/ n (%) | Most common side effects | Reference/trial number |
|---|---|---|---|---|---|---|---|
| TriMix-DC+ TLR-DC | Autologous dendritic cell vaccine | Melanoma | Phase I/II, completed | Radboud University | 8/15=53.3% | Local skin injection site reactions: irritation, erythema, swelling (100%), flu-like symptoms (53%), chills (20%), fever (20%) | Wilgenhof *et al*/NCT01530698[50] |

ADC, antibody drug conjugate; CD27, cluster of differentiation 27; CD70, cluster of differentiation 70; CR, complete response; CRC, colorectal cancer; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, dentritic cell; mAb, monoclonal antibody; MCC-DM1, 4-[N-maleimidomethyl] cyclohexane-1-carboxylate + maytansine; MMAF, monomethyl auristatin F; mTor, mammalian target of rapamycin; MUC1, mucin 1; n/a, not available; NHL, non-Hodgkin's lymphoma; NY-ESO-1, New York esophageal squamous cell carcinoma-1; OVA Ca, ovarian cancer; PBD, pyrrolobenzodiazepine; PD-1, programmed cell death 1; poly-ICLC, polyinosinic-polycytidylic acid stabilised with polylysine and carboxymethyl cellulose; PR, partial response; RCC, renal cell carcinoma; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and nNeck; SD, stable disease; TLR, toll-like receptor.

(65%), neutropenia (30%) and anaemia (25%).[49] AMG 172 is another anti-CD70 ADC which was administered in n=37 patients with clear-cell RCC.[45] Two (5.4%) patients achieved a PR, 6 (16%) had a SD and 13 (35%) patients had a progressive disease.[45]

In another clinical trial, intradermal autologous TriMix-DC therapy that consists of monocyte-derived DCs targeting CD70, CD40L and constitutively active toll-like receptor four was tested in n=15 patients with stage IV melanoma (NCT01530698).[50] Of 15 patients, 2 achieved a CR, another 2 patients achieved a PR, and 4 patients a SD. TriMix-DC therapy was considered feasible, safe and immunogenic. In a preclinical study it could be shown that CD8+ T cells that were precultured with TriMix-DCs were partially protected against Tregs suppression.[51] Besides, Tregs have been shown to lose their suppressive capacity against effector T cells when cocultured with TriMix-DCs.[51]

Additionally, CD70 expression was used as the immunological target for CAR-T cells. Currently, two phase I/II trials, NCT02830724 and NCT03125577, are recruiting (table 2).

## TOLERABILITY OF CD27 AND CD70 TARGETING THERAPIES

Targeting CD27 induces increased antitumour immunity and therefore also presents with known immunological AEs. Here, varlilumab (fully human IgG1 CD27 agonistic mAb) was generally well tolerated, also in the maximum tested dosage of 10 mg/kg. Treatment-related side effects were of minor grade 1 or 2 severity with most commonly occurring fatigue (30%), rash (20%), nausea (16%) and diarrhoea (11%). Only 1/56 patient experienced a dose-limiting toxicity of grade 3, an asymptomatic hyponatraemia that resolved spontaneously.[40] Addition of varlilumab to nivolumab did not result in unexpected increased toxicity.[43]

CD70 expression is used as a therapeutic target by ADCs, antibodies inducing ADCC as well as CAR-T cells and specific DC vaccinations. Therefore, the side effect profile differs according to the applied therapeutic approach.

ARGX-110 (glycoengineered CD70 blocking mAb) showed a favourable safety profile without any dose-limiting toxicity and no immune-related AEs. Drug-related grade 3 AE (fatigue, anorexia and hypoxia) were observed in 2/26 patients.[46]

Further, several CD70 targeting ADCs were investigated. Safety reports did not conclude whether the major toxicity was derived from the payload or from targeting the CD70 axis. MDX-1203 (ADC of humanised CD70-mAb linked to MED-2460) targeting CD70 caused grade 3 hypersensitivity as a dose-limiting toxicity in 2/16 (13%) patients at the highest dosage of 15 mg/kg.[48] The other most frequently recorded AE were fatigue (85%), nausea (54%), decreased appetite (39%), anaemia and dyspnoea (35% each). Grade 3 and 4 AE attributed to the study drug occurred in 9/26 (35%) of patients including

**Table 2** List of CD27/CD70 targeting agents in ongoing clinical trials

| Name of the compound | Mechanism of action | Tumour type | Phase of clinical trial development | Company | Reference/trial number |
|---|---|---|---|---|---|
| Varlilumab+atezolizumab in combination with radiation therapy | Fully human IgG1 CD27 agonistic mAb+fully human IgG1 inhibitory mAb targeting PD-L1 | Stage III–IV NSCLC, metastatic NSCLC, unresectable NSCLC | Phase I, recruiting | Rutgers, The State University of New Jersey+NCI | NCT04081688 |
| Varlilumab+IMA950 vaccine+Poly ICLC (Hiltonol) | Fully human IgG1 CD27 agonistic mAb+multipeptide vaccine containing 11 tumour-associated peptides | Glioma, malignant glioma, astrocytoma grade II, oligodendroglioma, astrocytic oligoastrocytoma | Phase I, recruiting | Celldex Therapeutics | NCT02924038 |
| Anti-hCD70 CAR | Anti-hCD70 CAR transduced PBL targeting CD70 | Pancreatic cancer, RCC, breast cancer, melanoma, ovarian cancer | Phase I/II, recruiting | NCI | NCT02830724 |
| 4SCAR70 | Fourth-generation CAR-T cell targeting CD70 | B-cell malignancies | Phase I/II, recruiting | Shenzhen Geno-Immune Medical Institute | NCT03125577 |
| Varlilumab+nivolumab | Fully human IgG1 CD27 agonistic mAb+fully human IgG4 mAb targeting PD-1 | B-cell lymphoma | Phase II, recruiting | NCI | NCT03038672 |
| Varlilumab+DC vaccinations+standard of care RT and TMZ | Fully human IgG1 CD27 agonistic mAb+human pp65 CMV DCs+radiotherapy+alkylating agent | Glioblastoma | Phase II, suspended (reason: pending new testing requirements from the FDA) | Celldex Therapeutics | NCT03688178 |
| Varlilumab+rituximab | Fully human IgG1 CD27 agonistic mAb+mAb targeting CD20 | B-cell lymphoma | Phase IIa, recruiting | University Hospital Southampton NHS Foundation Trust+Celldex Therapeutics | NCT03307746 |
| Varlilumab+vaccination with 6MHP | Fully human IgG1 CD27 agonistic mAb+6 melanoma helper vaccine composed of 6 class II MHC-restricted helper peptides | Stage II–IV melanoma | Phase I/II, recruiting | Craig L Slingluff Jr+Celldex Therapeutics | NCT03617328 |
| Cusatuzumab+azacitidine | Glycoengineered CD70 blocking mAb+antimetabolite/demethylating agent | AML | Phase I+II, recruiting | Janssen Research & Development, LLV+Argenx BVBA | NCT04023526/ NCT04150887 |

AML, acute myeloid leukaemia; CAR-T cell, chimeric antigen receptor gene-modified T cell; CD27, cluster of differentiation 27; CD70, cluster of differentiation 70; DC, dentritic cell; FDA, Food and Drug Administration; mAb, monoclonal antibody; 6MHP, 6 melanoma helper vaccine comprised of 6 class II MHC-restricted helper peptides; NCI, National Cancer Institute; NSCLC, non-small-cell lung cancer; PBL, peripheral blood lymphocytes; PD-L1, programmed cell death 1 ligand 1; poly-ICLC, polyinosinic-polycytidylic acid stabilised with polylysine and carboxymethyl cellulose; RT, radiotherapy; TMZ, temozolomide.

pleural effusion (11.5%), face oedema (7.7%), thrombocytopenia (7.7%) and hypersensitivity (7.7%). Strikingly, delayed toxicities as in facial oedema and pleural or pericardial effusions occurred in 6/16 (38%) of patients and AE led to treatment continuation in 11/26 (42.3%) of patients who were treated at the highest dosage of 15 mg/kg.[48] Pharmacokinetic analyses revealed that an increased incidence of delayed hypersensitivity at the highest dosage was postulated to be related to the high total antibody load.[48]

The most commonly occurring AEs in patients treated with SGN-75 (humanised anti-CD70 IgG1 mAb linked to monomethyl auristatin F toxin) were fatigue (40%), dry eye (32%), nausea (30%) and thrombocytopenia (26%). Due to the occurrence of idiopathic thrombocytopenic purpura in two patients with NHL who were treated weekly, the dose escalation regimen in the weekly schedule was terminated.[21] Three patients had dose-limiting toxicities as in grade three nephrotic syndrome and Grade 4 neutropenia.[21] In the therapy with SGN-CD70, thrombocytopenia occurring in 56% presented as dose-limiting toxicity.[44] In the AMG 172 trial, the most common side effects were again thrombocytopenia (59%), nausea (54%), decreased appetite (49%), emesis (46%) and fatigue (35%).[45]

## CONCLUSIONS

In conclusion, the CD27/70 axis is a promising pathway for immunotherapies showing a potential clinical benefit in different haematological and solid tumours. Also combining agonistic costimulatory CD27 mAbs with already established immune checkpoint inhibitors like PD-1 targeting mAbs is foreseen to have a synergistic effect by different favourable effects on the tumour microenvironment. Further, CD70 targeting agents like CD70 directed ADCs bear the potential of effectively targeting CD70-expressing solid and haematological tumours. Further clinical trials are needed to investigate potential combinations of immune-modulating therapies, also at earlier stages of disease, to achieve the best possible outcome for patients with different cancers.

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