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REVIEW

# Tumor necrosis factor superfamily signaling: life and death in cancer

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## Abstract

Immune checkpoint inhibitors have shaped the landscape of cancer treatment. However, many patients either do not respond or suffer from later progression. Numerous proteins can control immune system activity, including multiple tumor necrosis factor (TNF) superfamily (TNFSF) and TNF receptor superfamily (TNFRSF) members; these proteins play a complex role in regulating cell survival and death, cellular differentiation, and immune system activity. Notably, TNFSF/TNFRSF molecules may display either pro-tumoral or anti-tumoral activity, or even both, depending on tumor type. Therefore, TNF is a prototype of an enigmatic two-faced mediator in oncogenesis. To date, multiple anti-TNF agents have been approved and/or included in guidelines for treating autoimmune disorders and immune-related toxicities after immune checkpoint blockade for cancer. A confirmed role for the TNFSF/TNFRSF members in treating cancer has proven more elusive. In this review, we highlight the cancer-relevant TNFSF/TNFRSF family members, focusing on the death domain-containing and co-stimulation members and their signaling pathways, as well as their complicated role in the life and death of cancer cells.

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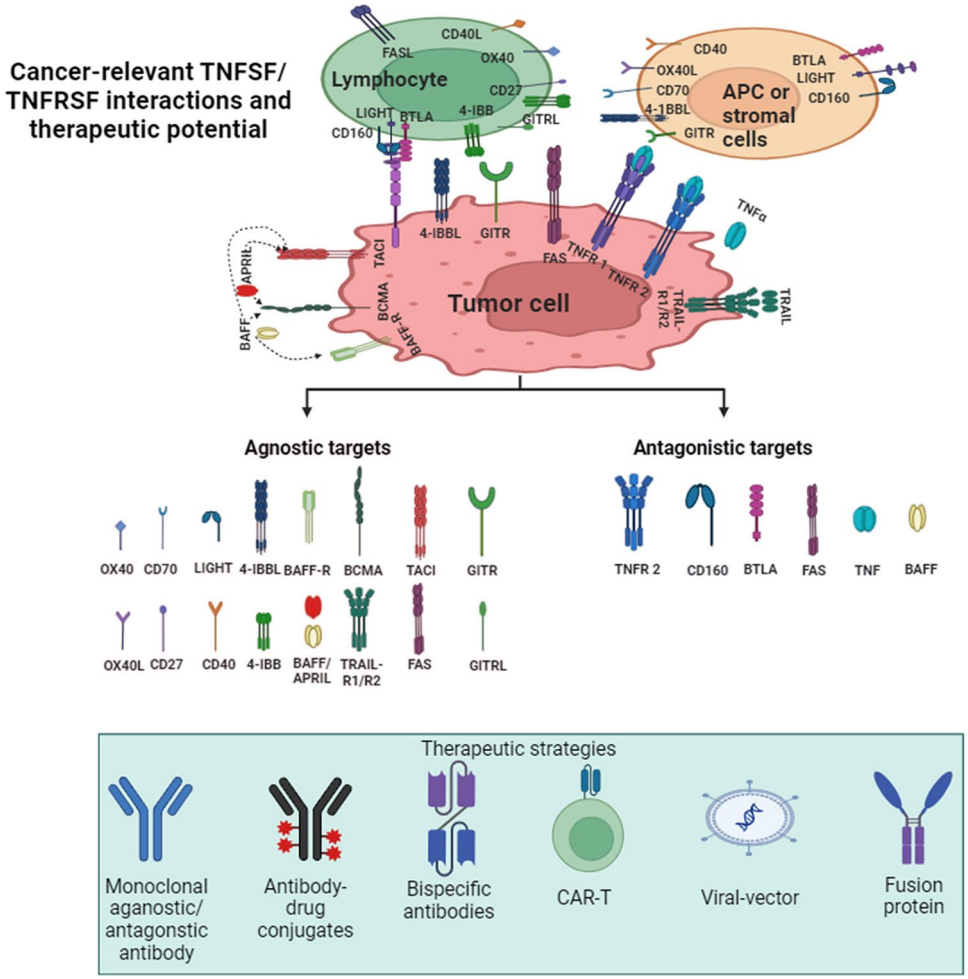
**Graphical Abstract**




**Keywords** TNFSF · TNFRSF · Immunotherapy · Novel immunotherapy targets · Personalized oncology · Tumor necrosis factor · Cancer

## 1 Introduction

The clinical development of immune checkpoint inhibitors (ICIs), mainly anti-PD1 or anti-CTLA4 agents, has been a game changer for the therapy of several types of cancer. However, ICIs are not a one-size-fit-all treatment and many patients do not respond or develop resistance to them [1]. Thus, other strategies are being explored, including blocking co-inhibitory checkpoints such as LAG-3, enhancing the activities of immune co-stimulatory receptors, and tumor microenvironment modifications [2–4]. In this regard, the tumor necrosis factor (TNF) protein family members are of enormous importance in cancer research due to their diverse biological and oncogenic activity and as potential targets for treatment [5].

The TNF proteins are divided into two superfamilies: the TNF receptor superfamily (TNFRSF) and the TNF superfamily (TNFSF) (Table 1) [6–18]. TNFSF is a group of soluble or membrane-bound proteins that bind to TNFRSF on target cells. There are at least 19 TNFSF ligands and they bind to at least 29 TNFRSFs [19]. Some of the best-known TNFSF ligands include the FAS ligand (FASL) and TNFSF10 (TRAIL). Upon ligand binding, TNFRSF induces intracellular signaling pathways of different TNF receptor-associated factor (TRAF) subtypes, which in turn regulates key cellular biologic processes. These interactions play a crucial role in the orchestration of cell survival, inflammation, proliferation, differentiation, and apoptosis.

In this review, we provide a succinct overview of the TNF pathway, including TNFSF/TFNRSF members, their

**Table 1** Examples of cancer-relevant members of TNFSF and TNFRSF and selected biologic activities

| TNF superfamily gene name | Protein name | TNF receptor superfamily gene name | TNF receptor superfamily protein name | Typical downstream action and comments | References |
|---|---|---|---|---|---|
| TNF | TNF-alpha | TNFRSF1A | TNFR1, TNFR2 | Induces apoptosis, inflammation, and immune response. Plays an important role in cachexia | [6] |
| TNFSF4 | OX40L | TNFRSF4 | OX40 (CD134) | Enhances T cell survival and proliferation | [7] |
| TNFSF5 | CD40L | TNFRSF5 | CD40 | Activates B cells, immunoglobulin production and enhances immune response | [8] |
| TNFSF6 | FasL (CD95L/CD178) | FAS | FAS (CD95) | Triggers apoptosis and immune system regulation | [9] |
| TNFSF7 | CD70 | TNFRSF7 | CD27 | Enhances T cell activation and survival | [10] |
| TNFSF8 | CD30L | TNFRSF8 | CD30 | Modulates cell survival and immune response | [11] |
| TNFSF9 | 4-1BB ligand (CD137L) | TNFRSF9 | 4-1BB (CD137) | Enhances T cell proliferation and survival | [12] |
| TNFSF10 | TRAIL (CD253) | TNFRSF10A, TNFRSF10B, TNFRSF10C, TNFRSF10D | DR4 (CD261), DR5 (CD262), DcR1 (CD263), DcR2 (CD264) | Induces apoptosis and immune system regulation | [13] |
| TNFSF12 | TWEAK | TNFRSF12A | Fn14 (CD266) | Modulates cell survival, proliferation, and inflammation | [14] |
| TNFSF13 | APRIL (CD256) | TNFRSF13B, TNFRSF17 | TACI (CD267), BCMA (CD257) | Regulates B-cell survival and antibody production | [15] |
| TNFSF13B | BAFF (CD257) | TNFRSF13C, TNFRSF17 | BAFF-R (CD268), BCMA (CD269) | Promotes B cell survival, and maturation proliferation | [15] |
| TNFSF14 | LIGHT (CD258) | TNFRSF3, TNFRSF14 | LTBR (CD18), HVEM (CD270), DcR3 | Regulates immune response and inflammation and lymphoid tissue development. Uniquely, HVEM can also bind to two non-TNFSF members of the Ig superfamily, BTLA and CD160 | [16] |
| TNFSF15 | TL1A | TNFRSF25 | DR3 | Modulates T cell activation and inflammation in mucosal tissue. Stimulates natural killer cells | [17] |
| TNFSF18 | GITRL | TNFRSF18 | GITR (CD357) | Modulates T cell activation and immune response | [18] |

Abbreviations: *APRIL* a proliferation-inducing ligand, *BAFF* B-cell activating factor, *BAFF-R* BAFF receptor, *BCMA* B-cell maturation antigen, *CD40L* CD40 ligand, *CD70* CD70 molecule, *DcR1* decoy receptor 1, *DcR2* decoy receptor 2, *DcR3* decoy receptor 3, *DR3* death receptor 3, *DR4* death receptor 4, *DR5* death receptor 5, *FasL* Fas ligand, *Fn14* fibroblast growth factor-inducible 14, *GITR* glucocorticoid-induced TNFR-related protein, *GITRL* glucocorticoid-induced TNFR-related protein ligand, *HVEM* herpesvirus entry mediator, *LIGHT* lymphotoxin-like, exhibits inducible expression, and competes with HSV glycoprotein D for HVEM, a receptor expressed by T lymphocytes, *LTBR* lymphotoxin beta receptor, *OX40L* OX40 ligand, *TACI* transmembrane activator and calcium modulator and cyclophilin ligand interactor, *TL1A* TNF-like ligand 1A, *TNF-alpha* tumor necrosis factor-alpha, *TNFR1* tumor necrosis factor receptor 1, *TNFR2* tumor necrosis factor receptor 2, *TNFRSF* tumor necrosis factor receptor superfamily, *TNFSF* tumor necrosis factor superfamily, *TRAIL* TNF-related apoptosis-inducing ligand

signaling cascades, current and ongoing clinical trials, and the role of anti-TNF in managing immune-related adverse events.

## 2 TNF pathways in cancer

In the cancer realm, TNF signaling reflects a two-faced family of molecules. On one hand, TNF family members can function as tumor promoters, because they can stimulate malignant cell proliferation, invasion and metastasis, and tumor angiogenesis. On the other hand, TNF family members can induce cancer cell apoptosis via death domains and other properties. TNFSF and TNFRSF play critical roles in controlling the balance of inflammation [20]. Figure 1 shows some of the interactions between TNFSF and TNFRSF in the tumor microenvironment (TME).

### 2.1 Death domain-containing members

A number of TNFRSF molecules can induce programmed cell death—apoptosis—as they contain a death domain. These different proteins share similar downstream signaling after their activation. They often stimulate Fas-associated protein with death domain (FADD) and death-inducing signaling complex (DISC) formation, and they recruit different caspases, mainly caspase 3, 8, and 10 [21].

#### 2.1.1 TNFR1, TNFR2, and TNF

TNF-α has diverse roles in carcinogenesis. In 1975, Carswell et al. discovered a novel protein in the hemorrhagic necrosis of a mouse tumor model, leading to the name "tumor necrosis factor" [22]. TNF binds two receptors: TNFR1, which is expressed in most cells; and TNFR2 which is mainly expressed in hematopoietic and immune cells [23]. TNFR1 is activated by binding to soluble TNF found in blood and extracellular space, while TNFR2 binds to both the transmembrane and soluble form of TNF [24]. The transformation of transmembrane TNF to a soluble TNF is mediated by the metalloprotease TNFα-converting enzyme (TACE) [25].

TNF binding can result in two distinct responses dependent on the activated receptors. Only TNFR1 has a death domain, which enables it to activate the signaling that leads to apoptosis and promotes inflammation [26]. On the other hand, TNFR2 lacks a death domain and instead prompts TNFR-associated factor 2 (TRAF2) recruitment, which mainly promotes cell proliferation and survival, cell activation, and migration [6, 27]. In addition, TNFR2 is expressed by multiple tumor types such as renal cell carcinoma, breast cancer, lung cancer, ovarian cancer, multiple myeloma, and esophageal carcinoma [27–30]. The diverse and paradoxical actions of TNF may largely depend on the bound receptor. For instance, while mainly known as an anti-tumor factor (as indicated by its name—"tumor necrosis factor"), Kulbe et al. noticed that TNF secretion by ovarian cancer cells stimulated cytokine release, neo-angiogenesis, and peritoneum invasion, indicating a pro-tumor effect [31]. These findings led to different strategies for targeting TNF in cancer. Additionally, TNFR2 also has a role in carcinogenesis by promoting inflammation. CD8 + effector T cells use TNFR2 for activation and cytotoxicity during the early immune response [32]. TNFR2 can also promote apoptosis signals to terminate the immune response [33]. Moreover, TNFR2 can stimulate the suppressive effects of CD4 + Foxp3 + regulatory T cells (Tregs) and CD8 + Foxp3 + Tregs by inducing their proliferation and activation [34, 35]. Thus, we suspect that TNFR2 works at first to promote inflammation at early carcinogenesis and then it shifts toward a suppressed immune microenvironment to maintain cancer cell survival. He et al. demonstrated that the loss of the TNFR2 allele promotes the development of breast cancer in mice with a more aggressive phenotype and metastatic potential [36]. Such possible effects might be due to promoting autocrine production of TNFα and the preferential activation of the canonical NF-κB signaling pathway. In addition, TNFR2 activation expressed on myeloid-derived suppressor cells was found to promote liver metastasis in murine colon and lung cancer models [37]. Moreover, losing the TNFR2 gene led to decreased lung metastases and Treg infiltration in a melanoma mouse model [38].

Both TNF and anti-TNF molecules have been used in the clinic. For example, in part to attenuate systemic side effects, local infusion strategies utilizing TNF, such as isolated limb perfusion, have been studied. Isolated limb perfusion of TNF with melphalan had activity in metastatic melanoma and unresectable sarcomas [39, 40]. Elia et al. demonstrated that the use of combined modified TNF, ICI, and adoptive cell therapy achieved substantial tumor shrinkage and immune cell infiltration in melanoma and prostate cancer models [41]. On the other side of the camp, the TICI-MEL (NTC03293784) trial assessed the benefit of adding an anti-TNF to the standard of care combinational immunotherapy in advanced melanoma. The authors found that the use of concurrent nivolumab, ipilimumab, and a TNF blocker, either infliximab or certolizumab, had a good safety profile and showed activity [42, 43]. However, only a small number of patients were treated; 13 patients received ipilimumab/nivolumab/infliximab and 20 patients ipilimumab/nivolumab/certolizumab. The use of soluble TNF receptors also showed modest activity in cutaneous T-cell lymphomas [44]. Badran et al. reported that in patients with immune-related enterocolitis due to ICI, the use of concurrent ICI and immunosuppressive therapy was associated with a

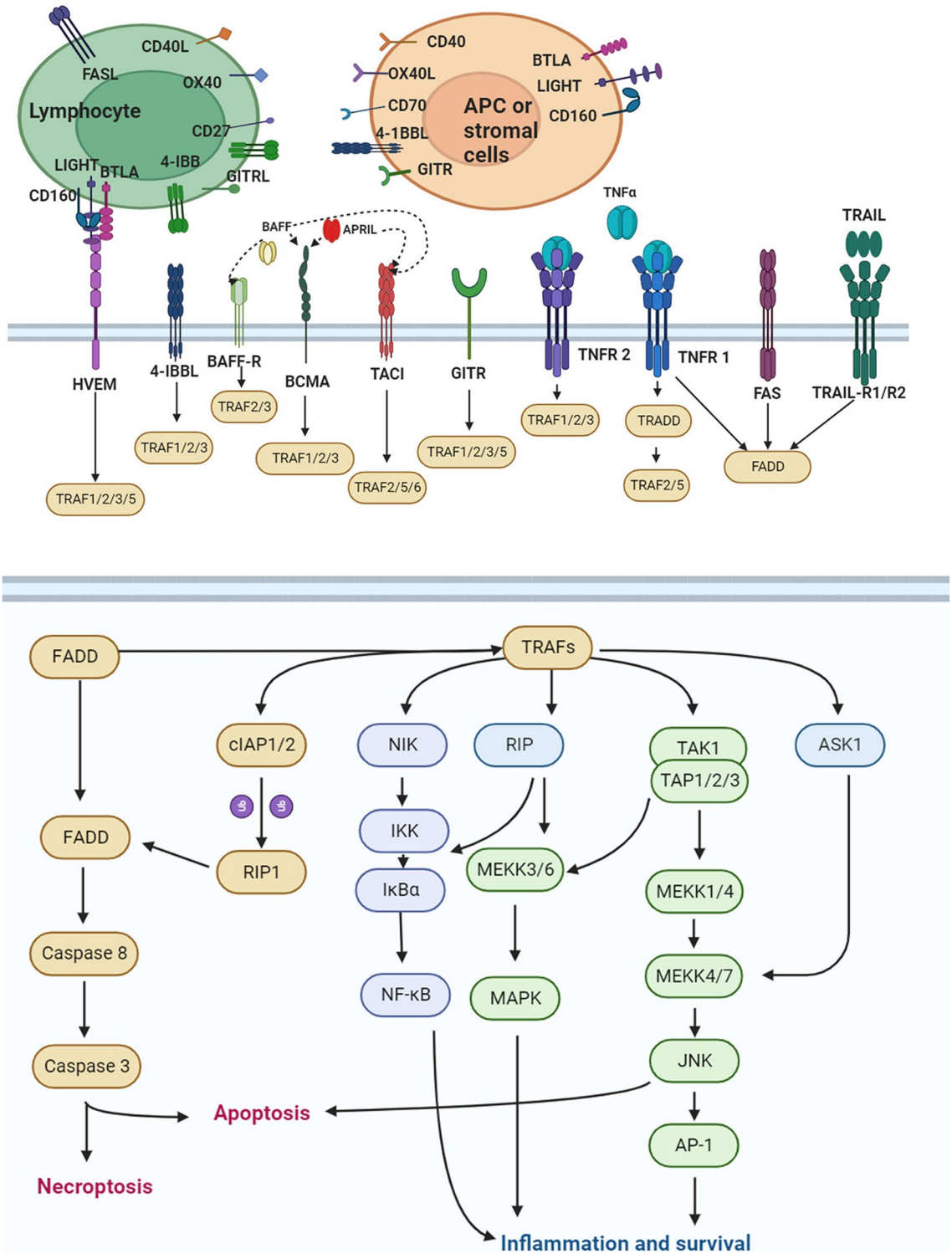



**Fig. 1** The interaction of TNFSF and TNFRSF and their downstream effectors. Upper panel: the interactions of TNFSF and TNFRSF members in tumor, lymphocytes, and stromal cells. The expression of some of these members results in multiple different effects. Lower panel: the downstream impact of the activation of TNFSF/TNFRSF leads to FADD or TRAF signals. The activation of FADD leads to subsequent cell death while the activation of TRAFs can lead to either cell survival or apoptosis, partially explaining the variability of the biologic impact of some TNFSF/TNFRSF members. Figure created with BioRender.com. Abbreviations: FADD, Fas-associated protein with death domain; TNFSF, tumor necrosis factor superfamily; TNFRSF, tumor necrosis factor receptor superfamily; TRAF, tumor necrosis factor (TNF) receptor-associated factor

**Table 2** Examples of treatment strategies targeting TNF-α in cancer clinical trials

| Strategies | Major results | Tumor types | References |
|---|---|---|---|
| Systemic recombinant TNF | Systemic single-agent recombinant TNF had low objective response rates | Advanced tumors | [46, 49] |
| TNF combined with IFNγ | Low objective response rate and significant toxicity | Multiple cancer types | [47] |
| Isolated limb infusion/perfusion | Objective response rates range between 49 to 90%. This approach is limited by the site of the tumor, the presence of metastases, local toxicity, and the need for specialized centers | Melanoma<br>Sarcoma | [39, 40] |
| TNFerade | TNFerade is an adenovector-based gene therapy activated by radiation to induce translation of the human TNF-α gene specifically in cancer cells<br>In a randomized phase III of locally advanced pancreatic cancer, TNFerade with the standard of care did not show a significant survival benefit compared to the standard of care alone | Advanced solid tumors<br>Pancreatic cancer | [48] |
| Anti-TNF drugs | TICIMEL explored adding anti-TNF agents' infliximab or certolizumab to nivolumab and ipilimumab in advanced melanoma. The ORR of the certolizumab and infliximab cohorts were 63% and 46%, respectively. Both combinations were safe with the certolizumab cohort having higher rates of adverse events compared to infliximab | Melanoma | [42, 43] |

Abbreviations: *IFN* interferon, *ORR* objective response rate, *TNF* tumor necrosis factor

possible decreased risk of enterocolitis recurrence and no treatment effect [45]. Although these studies are limited by their size and design, they offer new strategies to mitigate adverse events without compromising survival. Future studies are needed to investigate the validity of the TNF inhibitor approach and the potential underlying mechanisms. Table 2 summarizes examples of different TNF-α based therapies that reached the clinical trials stage [39, 40, 42, 46–49].

Targeting TNFR2 has also been explored. Several preclinical models showed the anti-tumor activity of anti-TNFR2 antibodies in acute myeloid leukemia, ovarian cancer, breast cancer, and colorectal cancer [50–53]. The mechanism behind this activity seems to revolve around selective depletion of T regulatory (Treg) cells while sparing T effector (Teff) cells. Thus, anti-TNFR2 could be a future tumor microenvironment (TME)-specific cancer therapy [6]. Clinical trials, such as NCT04752826 and NCT05238883, using anti-TNRF2 in solid tumors are ongoing.

#### 2.1.2 FAS and FAS ligand (FASL)

FASL is another death domain-containing member of the TNFSF family that plays a critical role in immune surveillance and elimination of damaged or infected cells [9]. FASL binds to the FAS receptor, leading to the formation of a death-inducing signaling complex (DISC) and subsequent activation of apoptotic pathways [54]. Dysregulation of the FAS-FASL pathway has been observed in various cancers, contributing to tumor immune escape and resistance to apoptosis [55]. A high FASL expression level was also closely associated with the development of gastric cancer, especially poorly differentiated gastric carcinoma [56]. In some cases, cancer cells can downregulate FAS expression or release soluble FASL, which can act as a decoy receptor and inhibit FAS-mediated apoptosis [57–59]. This evasion of cell death can promote tumor survival and progression. Interestingly, some studies suggested a "tumor counterattack" phenomenon where tumor cells expressing FASL can induce apoptosis of FAS-expressing tumor-infiltrating lymphocytes [60–62]. Although there is considerable evidence that this counterattack took place, its existence is still debatable [63]. In addition, FASL expressed on the tumor endothelium was found to reduce CD8 T-cell infiltration into the tumor [64]. Moreover, FAS is capable of the maintenance and survival of cancer stem cells (CSCs) and inducing the epithelial-to-mesenchymal transition (EMT) [65–68]. Thus, once cancer cells are unresponsive to FAS apoptotic signaling, they can exploit the FAS-mediated non-apoptotic oncogenic functions [9].

Several attempts have been made to develop FAS-agnostic molecules. The use of FAS agonist antibodies systemically administered led to severe hepatotoxicity in treated mice [69]. Another strategy was the use of FASL fusion proteins. ACRP30:FasL, also known as MegaFasL, is a fusion protein of the stalk region of adipocyte complement-related protein (ACRP30) and FasL [70]. CRP30:FasL was found to have an anti-tumor synergistic effect with imatinib in gastrointestinal stromal tumors [71]. NCT00437736 is the only phase I trial investigating MegaFasL in solid tumors. Although the study started in 2007, we could not find any online published report of the trial. CTLA4:FasL and CD40:FasL are other examples of fusion proteins. Orbach et al. showed that both CD40:FasL and CTLA4:FasL can induce cell pro-apoptotic

signal of malignant cells of lymphatic origin and inhibit anti-apoptotic proteins: cFLIP, caspase 8, caspase 9, and caspase 3 [72]. We are not aware of any current clinical trials of such strategies.

#### 2.1.3 TRAIL and its receptors

TRAIL, also known as Apo2L, is a member of the TNFSF that selectively induces apoptosis in cancer cells while sparing normal cells [73]. TRAIL binds to two groups of receptors: decoy receptors and death receptors. There are three decoy receptors, DcR1, DcR2, and OPG. DcR1 and DcR2 are surface proteins that block the transmission of the apoptotic signal, while OPG is a soluble secreted receptor that can also mitigate the apoptotic signals [13, 74, 75]. The death receptors DR4 (TRAIL-R1) and DR5 (TRAIL-R2) contain a death domain that leads to the activation of apoptotic signaling cascades upon binding [76]. Thus, TRAIL-mediated apoptosis is regulated by the balance between pro-apoptotic and anti-apoptotic proteins. Critically, naïve T cells are resistant to TRAIL-induced apoptosis [77]. However, T cells may become susceptible to TRAIL-induced apoptosis after repeated or prolonged activation [78]. In TRAIL knockout mice, there is an increased susceptibility to the development of different tumors such as lymphoma, fibrosarcoma breast cancer, and fibrosarcoma [79, 80]. In addition, the use of anti-TRAIL agents led to increased liver metastases in different TRAIL-sensitive cell lines, but this effect was not observed in NK-depleted and IFN-γ models, suggesting the need for both immune competency and TRAIL expression to prevent metastases [81].

Utilizing the TRAIL pathway for therapeutics started with developing TRAIL-receptor agonists (TRAs) as either recombinant TRAIL (rTRAIL) or death receptor agonistic antibodies [82]. Ashkenazi et al. were one of the first to describe the anti-tumor activity of recombinant TRAIL without evoking systematic toxicity *in vitro* and *in vivo* [83]. Moreover, other reports showed the efficacy of recombinant TRAIL [84, 85]. Herbst et al. conducted the first phase I, an open-label, dose-escalation, clinical trial of dulanermin, a rTRAIL, in patients with advanced cancer [86]. Although dulanermin was well tolerated, its anticancer activity was limited. Interestingly, two of five patients with chondrosarcoma achieved partial responses. One of the two patients was found to have high BCL-2, protein levels in resistance tissue (limited necrosis) compared to tumor necrotic tissue [87]. Also, dulanermin can bind to both decoy and death receptors, which may lead to diverging activity. In addition, resistance to dulanermin might be driven by alterations to TRAIL receptor 1 (DR4). Horak et al. found low DR4 expression driven by hypermethylation of the DR4 gene [88]. The authors also noted a short mean terminal phase half-life of dulanermin (0.56–1.02 h). Thus, combining dulanermin with other agents such as anti-BCL2 (e.g., venetoclax) and/or hypomethylating agents (such as decitabine and azacitidine) may alleviate resistance to rTRAIL and improve anti-tumor activity. Subsequently, DR5-targeted antibodies (TRAIL-R2 antibodies) were also under development. Lexatumumab (HGS-ETR2), a DR5-targeted antibody, was found to promote DR5 expression and induce apoptosis in renal cell carcinoma in a mice model [89]. In a phase I trial of lexatumumab in patients with advanced cancers, lexatumumab was safe and had a mean plasma half-life of more than 2 weeks at the recommended dose [90]. Overall, no patient achieved an objective response. Mapatumumab, a DR4-targeted antibody, was well tolerated, but no objective responses were observed in a phase I trial in patients with advanced solid tumors [91]. The results of three phase I trials of different DR5-targeted antibodies were reported in 2010: conatumumab, drozitumab, and tigatuzumab [92–94]. These trials shared similar safety profiles; however, none of these patients achieved an objective response. These results showed that although first-generation TRAIL receptor antibodies (TRAs) were safe, their clinical value was limited.

Many groups have tried to overcome the limitations of the first-generation TRA molecules, such as limited half-life, and weak agonistic activity for TRAIL-R1 and TRAIL-R2 [82]. A number of protein modifications of rTRAIL are being explored. Such modifications include adding amino acids to the N-terminal such as to the leucine zipper (LZ-TRAIL), isoleucine zipper (IZ-TRAIL), poly-histidine (His-TRAIL), or tenascin-C (TNC) oligomerization domain (TNC-TRAIL) [82]. SCB-313 is a human TRAIL-trimer fusion protein designed by in-frame fusion of the C-terminus of TRAIL and C-propeptide of α1collagen (Trimer-Tag) [95]. Liu et al. showed that TRAIL-trimer is 4–5 times superior compared to native TRAIL with pharmacokinetic and anti-tumor activity [96]. Currently, we are awaiting the results of three Chinese (NCT04051112, NCT04047771, NCT04123886) and two Australian (NCT03443674, NCT03869697) clinical trials assessing SCB-313 in malignant ascites, peritoneal carcinomatosis, malignant pleural effusions, and peritoneal malignancies. Mesenchymal stromal cells (MSCs) expressing TRIAL by a lentiviral (MSCTRAIL) is a new TRAIL-based approach for modulating TME. TACTICAL is an ongoing phase I/II trial to assess the safety and efficacy of MSCTRAIL in combination with first-line standard of care in patients with metastatic lung adenocarcinoma. For more potent signaling, TRAIL-R1/2 needs to trimerize after binding to TRAIL. Eftozanermin alfa (ABBV-621), a hexavalent agonistic fusion protein, is designed to increase receptor clustering independent of FcγR cross-linking [97]. It showed promising anti-tumor activity even in ABBV-621-resistant cells when combined with chemotherapeutics or BCL-XL inhibitors. In a phase I trial, de Jonge et al. showed that

Eftozanermin alfa in combination with venetoclax is safe but with potentially limited anti-tumor activity in acute myeloid leukemia and diffuse large B-cell lymphoma [98]. The same group found similar safety, and anti-tumor activity in solid tumors [99]. The baseline frequency of myeloblasts was higher in acute myeloid leukemia patients with progressive disease compared with the only patient who achieved a complete response. On the other hand, myelomonocytes were higher in the patient with complete response. This might be due to the high DR4 and DR5 expression on both myeloblasts and myelomonocytes. At baseline testing, DR4 and DR5 expression was found to be highest in the patient with complete response. Thus, future studies need to also evaluate the expression of TNFSF/TNFRSF genes in the tumor microenvironment in addition to tumor cells to better capture the prognostic ability of these proteins. TAS266 is an agonistic multivalent nanobody based on four high-affinity single variable domains (VHH) that target DR5 [100]. However, its phase I trial was terminated quickly due to severe unexpected hepatotoxicity [100]. The authors noted the presence of pre-existing anti-TAS266 antibodies in patients who developed hepatotoxicity. INBRX-109 is a next-generation agonistic multivalent nanobody that does not bind to anti-TAS266 antibodies found in the previous trial; the response rate was 40.7. None of the patients in the chondrosarcoma had severe transaminitis. These results led to the initiation of ChonDRAgon (NCT04950075) a phase II randomized trial for using INBRX-109 in conventional chondrosarcoma. Such recent advances highlight the potential of TRAIL-based drugs in cancer treatment.

## 2.2 Immune co-stimulation

During the generation of a successful adaptive immune response, many molecular signals are necessary. A primary signal is the binding of cognate antigens to T and B lymphocyte antigen receptors. Secondary signals include the engagement of co-stimulatory molecules expressed by T and B lymphocytes with their respective ligands. As outlined herein, several members of the TNF receptor family act and interact, after initial T cell activation, to sustain T cell responses.

### 2.2.1 CD-40 and CD-40L

CD40 (TNFRSF5) is a member of the TNFR superfamily that is expressed on a variety of immune cells such as dendritic cells (DC), B cells, and macrophages [8]. In addition, it is found in tumor cells, such as in multiple myeloma, Hodgkin lymphoma, non-Hodgkin lymphoma, renal cell carcinoma, urothelial carcinomas, and ovarian tumors [101, 102]. Its ligand, CD40L (TNFSF5), is expressed on the surface of T cells and natural killer (NK) cells [8]. This interaction induces a variety of immune responses, including the activation of APCs, the proliferation and differentiation of T cells, and the production of cytokines such as IL-12 and IFN-γ and chemokines [102]. This led to the development of agonistic anti-CD40 antibodies to mimic multimeric CD40L on CD40, promoting the recruitment of DCs, B-cell antibody production and T-cell differentiation, and cytotoxic activity [103–105].

As mentioned, CD40 expression is found on multiple tumors including bladder cancer, lung cancer, breast cancer, melanoma, colon cancer, acute lymphoblastic leukemia, and non-Hodgkin lymphoma [106]. The anti-tumor effect of CD40 agonism has been shown in many preclinical studies [107–109]. For a potent and effective activation of the CD40 pathway, two methods have been developed. Higher order crosslinking of the CD40 monoclonal antibody Fc region leads to the clustering of Fc-gamma receptors IIB (FcγRIIB) [107, 110]. ADC-1013, a fully human agonistic CD40 antibody, was the first to be tested as intra-tumoral therapy in advanced solid malignancies [111]. The trial showed ADC-1013 was safe with some good tumor response of superficial lesions. The second method is based on editing the IgG2 hinge region to provide activation with the need for FcγRIIB crosslinking [112]. Selicrelumab and CDX-1140 are examples of such antibodies [113]. Vonderheide et al. found that selicrelumab, a CD40 agonist monoclonal antibody, was safe but showed limited anti-tumor activity in advanced solid tumors [114]. The authors also noticed a transient yet significant drop in CD19 + B cells in all patients. CD40 and CD40L expression were not evaluated. The authors also did not report if selicrelumab was associated with higher CD8 + T cell infiltration. Increased CD8 + T cell infiltration and activation are expected after receiving CD40-based treatments [113]. In a phase I trial, the use of CDX-1140 with pembrolizumab for patients with PD-1/PD-L1-resistant solid tumors showed one patient with complete response [115]. Sotigalimab is a CD40 monoclonal antibody with an Fc-engineered segment to increase the interaction with FcγRIIB [116]. PRINCE is a randomized phase II trial evaluating the efficacy of sotigalimab and chemotherapy with and without nivolumab in first-line metastatic pancreatic cancer [117]. Surprisingly, the use of triple therapy was inferior in terms of survival compared to nivolumab and chemotherapy and sotigalimab with chemotherapy (1-year overall survival was 41.3%, 48.1%, and 57.7%, respectively). Recently, bi-specific antibodies targeting both CD40 and other tumor antigens have been under investigation. ABBV-428 is a mesothelin-CD40 bi-specific antibody that showed promising results in a preclinical mouse model [118]. Its anti-tumor effect was present in both mesothelin$^{+}$ and mesothelin$^{-}$ tumor cells. Luke et al. reported the safety and efficacy of ABBV-428 in advanced solid cancer patients.

Although safe, there were no objective responses [119]. In patients who had more than 90% CD40 receptor occupancy, no patients achieved objective responses. In addition, the baseline tumor expression of mesothelin did not correlate with progression-free survival. There was no clear pattern of CD8 + T cells, and PD-L1 expressing cell changes from baseline to after treatment. Importantly, no patient developed cytokine release syndrome with minimal changes in cytokines levels (IFN-γ, TNF-α, IL-6, IL-1β, IL-2, IL-8, IL-10, and IL-12p70) after ABBV-428 treatment. It should be noted that most patients in these trials have very advanced disease and/or are heavily pre-treated, which might drive the failure to anti-CD40. While the use of CD40-based immunotherapy has not achieved a clinical effect yet, we are still learning from previous pitfalls, improving on current strategies, and awaiting the results of ongoing trials.

#### 2.2.2 OX-40 and OX-40L

OX40, also known as TNFRSF4 (CD134), is transmembrane protein type I expressed on different T cells [120]. It is the sole receptor for OX40 ligand (OX40L). OX40L (TNFSF4) binding to OX40 leads to activating signals of T cells enhancing T-cell survival and pro-inflammatory cytokine production [121]. Similar to agonistic anti-CD40 antibodies, the use of agonistic OX40 antibodies can be theoretically of potential benefit in cancer treatment. Zhang et al. demonstrated that OX40 co-stimulation inhibits FOXP3 gene expression, a marker of Tregs, by increasing the expression of the transcription factors BATF and BATF3 and activating the mTOR pathway [122]. Agonistic OX40 antibodies have shown good anti-tumor responses either as monotherapy or as part of an immunotherapy combination in preclinical tumor models of immunologically active tumors [123–126]. It is worth noting that agonistic OX40 antibodies did not show similar results in tumors with poor immunogenicity [127].

Curti et al. conducted the first phase I clinical trial of agonistic OX40 antibodies. They treated 30 patients with metastatic tumors. They found that agonistic OX40 antibodies had an acceptable toxicity with lymphopenia being the most common adverse event and evidence of some nodular regression in 12 patients [128]. OX40 agonist antibodies also led to increased CD4 + FoxP3 − and CD8 + T cell proliferation with no changes to CD4 + FoxP3 − T cells. Davis et al. evaluated the safety and efficacy of INCAGN01949, an OX40 agonist [129]. INCAGN01949 had an acceptable safety profile but with a low disease control rate of 27.6%. In their trial, no predictors of progression were described although the authors noted higher OX40 receptor levels in the blood after receiving INCAGN01949. ENGAGE-1 is a phase I evaluation of the use of the OX40 agonist GSK3174998 with or without pembrolizumab in patients with advanced solid malignancies [130]. The authors found that GSK3174998 is well-tolerated with and without pembrolizumab but with unsatisfactory clinical activity. Notably, the greatest changes were observed for CD134 + cells, NK/NKT cells, and FOXP3 + Tregs. In addition, 39% of patients developed anti-GSK3174998 antibodies. This might partially explain the poor anti-tumor responses in these patients. However, GSK3174998's ability to modify the tumor microenvironment makes it a feasible candidate to be partnered with other immune checkpoint inhibitors in future studies. Although the aforementioned results did not show promising efficacy, we are still awaiting readouts from a number of trials.

#### 2.2.3 CD70 and CD27

CD27 (TNFRSF7) is constitutively expressed mostly in naive T cells. CD27 binds to CD70 (TNFSF7), which is transiently expressed on activated T cells, DC, and NK cells [10]. CD27 and CD70 binding results in immune cell survival, the expansion of T and B cells, and enhances cellular immunity [131]. CD70 is expressed in primary and metastatic tumor samples [132]. In addition, co-expression of CD27 and CD70 has been detected in different hematological malignancies such as acute myeloid leukemia, acute lymphoblastic leukemia, non-Hodgkin lymphoma, and multiple myeloma [133–136]. Subsequently, the role of this duo differs between solid and hematological malignancy. In hematological malignancies, the interaction promotes proliferation and stemness while leading to immune evasion in solid tumors [132]. In addition, the presence of CD27 on solid tumor cells and microenvironment is not essential in promoting the generation and maintenance of CSCs, metastasis, and heterogeneity [137, 138]. The CD27-CD70 interaction also increases the proliferation and reduces apoptosis of Tregs, via inducing CD4 + T cells to produce IL-2 [139]. Moreover, Liu et al. found that CD70 + breast cancer cells have self-renewal and differentiation ability and can metastasize to the lung [140]. Conversely, the loss of CD70 expression promoted cancer lung metastases in melanoma in vivo models [141]. Current treatment strategies revolve around either activating the CD70-CD27 axis of tumor-infiltrating lymphocytes or killing CD70-harboring cells [142].

Antibody–drug conjugates (ADCs) targeting CD70 have been studied in clinical settings. However, the first three ADCs investigated (MDX-1203, AMG 172, and SGN-75) were not well tolerated and no objective responses were seen [132, 143]. NCT04227847 is a phase I trial investigating the safety of SGN-CD70A in myeloid malignancies, a CD70 ADC. Cusatuzumab (ARGX-110) is an afucosylated glycoengineered CD70 antibody that activates both NK cells and complement systems to kill CD70-expressing cells via antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, respectively [144]. In a phase I trial,

cusatuzumab had a good safety profile but showed limited ant-tumor activity in advanced solid and hematological cancers [145]. There were no overall trends in blood and biochemical biomarkers data over time including CD70 RNA levels and soluble CD27 (sCD27) protein levels. Interestingly, patients with relapsed/refractory cutaneous T-cell lymphoma had a 23% objective response rate [146]. There was a drop in sCD27 levels in about 62% of partial responders in Sezary syndrome patients. Thus, sCD27 level changes might serve as biological biomarkers of response for CD70-based agents in some tumors.

Perhaps, the most exciting CD70-based therapy in early-phase clinical trials is CD70-based CAR-T cell therapy [147]. Other strategies targeting CD27 are also under investigation. In theory, CD27 is less promising due to its expression on non-tumor cells and lower expression on tumor cells compared to CD70 [148]. Varlilumab was the first CD27 agnostic monoclonal antibody to enter clinical trials. In the phase I trial conducted by Burris et al., varlilumab to 10 mg/kg was well tolerated without identification of a maximum tolerated dose. Varlilumab therapy resulted in one partial response in advanced solid tumors [149]. A follow-up phase I/II trial studied the use of varlilumab with nivolumab for advanced solid tumors [150]. The combination was well-tolerated, but the objective response rate for the whole cohort was 10%. A randomized phase II trial evaluating varlilumab combined with nivolumab versus nivolumab alone in B-cell non-Hodgkin lymphoma did not show additional response benefits compared to single-agent nivolumab [151].

#### 2.2.4 4-1BB and 4-1BBL

4-1BB (TNFRSF9; CD137) is expressed on activated T lymphocytes, monocytes, dendritic cells, and natural killer cells. It binds to 4-1BBL (TNFSF9) expressed on antigen-presenting cells (APCs) [12]. Binding can induce CD8 + T cell survival by increasing anti-apoptotic signals of Bcl-XL and Bfl-1 and decreasing the pro-apoptotic singles of Bim [152–154]. 4-1BB plays an important role in the anti-tumor activity of the tumor microenvironment [155]. Wilcox et al. found that IL-2 and IL-15 can induce 4-1BB-expressing NK cells which in turn can promote CD8 + T cells responsiveness to IL-2 and IFN-Y secretion [156]. Interestingly, 4-1BB can also lead to Treg proliferation and their differentiation to CD8 + or CD4 + T cells [157, 158]. Thus, 4-1BB agnostics have been an attractive idea for modulating the tumor microenvironment. Melero et al. were the first group to show the feasibility of using 4-1BB antibodies in mice sarcoma models [159]. Curran et al. found that the combination of anti-CTLA-4 and 4-1BB agonists led to an increase in CD8 + and CD4 + T cells in the B16 melanoma model [160]. Similarly, Chen et al. found that anti-PD1 and 4-1BB agonist combination led to tumor regression, IFN-Y and CD8 + T cells in the B16F10 melanoma model [161]. Interestingly, the authors compared that combination with an anti-PD-1 and anti-LAG-3 combination and found that the first had a more profound tumor regression effect compared to the latter. B16 melanoma is considered a poorly immunogenic model, which may suggest that an anti-PD1 and 4-1BB combination may enhance a tumor's "hotness."

Urelumab was the first anti-4-1BB agonist to start clinical trials. In the phase I trial reported by Sznol and colleagues, urelumab demonstrated dose-dependent neutropenia and 11% of the patients had grade 3/4 transaminitis [162]. Based on the phase I results, a phase II randomized trial was designed in patients with metastatic melanoma. However, the study was terminated due to grade 5 hepatotoxicity [163]. New clinical trials to combine a lower dose of urelumab with nivolumab, cetuximab, rituximab, and elotuzumab have been announced. However, hepatotoxicity was still present and the trials were halted for now. Utomilumab is another anti-4-1BB agonist with a presumably better safety profile. In the first phase I trial, there was no dose-limiting toxicity or transaminitis [164]. In another phase Ib trial, utomilumab was used in combination with pembrolizumab and showed a good safety profile and a 26.1% response rate [165]. Cohen et al. reported the results of utomilumab in combination with mogamulizumab. The combination was tolerable but with a low response rate of 4.2% [166]. In addition, 4-1BB is a part of the co-stimulatory endodomain in FDA-approved CAR-T cell therapies tisagenlecleucel and isocabtagene maraleucel for patients with B-cell acute lymphoblastic leukemia and large B-cell lymphoma [167]. Thus, 4-1BB has shown previous clinical significance and is potentially will be part of the next generation of immunotherapies.

#### 2.2.5 GITR and GITRL

GITR (TNFRSF18; CD357) is expressed on Tregs at a higher level while it can be found at lower levels on NK cells, B cells, and naïve and memory T cells [18, 168]. In addition, GITR expression rises 24–72 h after first activation on both Tregs and effector T cells [169, 170]. GITR binds to GITRL (TNFSF18) expressed on antigen-presenting cells [171]. As a result, GITR acts as a co-activating receptor and subsequent inflammatory response [172]. Coe et al. showed that the anti-tumor function of DTA-1, an agonistic GITR monoclonal antibody, is strongly associated with Treg depletion but not with their dysfunction [173]. Kim et al. found that tumor regression is mainly dependent on Treg depletion rather than on CD8 + activation [174]. Mitsui et al. studied combining anti-CTLA-4 with anti-GITR and showed further depletion of Treg and higher CD8 + in tumor sites in CMS5a (a murine fibrosarcoma cell line) and CT26 (a murine colon carcinoma cell line) [175]. Villarreal et al. reported the use of anti-PD-1, GITR monoclonal agonistic antibodies and a

peptide vaccine led to a significant regression of tumors in about half of the mice [176]. Leyland et al. concluded the GITRL fusion protein had a good anti-tumor effect which was enhanced by anti-OX40 and also when combined with PD-L1, PD-1, or CTLA-4 [177]. AMG228 was the first GITR monoclonal agonistic antibody to enter clinical trials. In the phase I trial, AMG228 was safe and well-tolerated but no biological nor anti-tumor activity was found [178]. Interestingly, in patients with available matched paired tumor biopsies, GITR expression was no longer detectable after AMG228 treatment compared to its presence in pretreatment samples. In addition, there was a decrease in Treg infiltration and GITR expression and increased CD8 + T cells in colorectal tumor samples after AMG228 treatment. No objective responses were seen in other GITR agonistic antibody trials such as those with BMS-986156, GWN323, and MK-4166 [165, 179–181]. MEDI1873, a GITRL agonistic antibody was safe but without objective responses in phase I trials of advanced solid tumors [182]. Although GITR-based strategies still did not show sufficient anti-tumor activity, they still demonstrated a level of tumor microenvironment modulation, indicating possible interactions with other immune checkpoint inhibitors.

#### 2.2.6 HVEM and LIGHT

HVEM, also known as TNFR superfamily 14 (TNFRSF14), was discovered for its role in the entry of Herpes Simplex Virus into cells and viral manipulation [183]. HVEM is expressed by many human tissue elements, including naïve T cells, APCs, endothelium, lung, kidney, and liver [16]. HVEM is a receptor for multiple ligands expressed in the immune system including the TNFSF members LIGHT (TNFSF14) and LTα and immunoglobulin superfamily members BTLA and CD160 [184]. Both LIGHT and LTα play a co-stimulatory role by binding to the cysteine-rich domain-2 (CRD2) and CRD3 of HVEM-activating NF-κB signals and subsequent activating lymphocytes. On the other hand, the binding of BTLA and CD160 to CRD1 of HVEM results in inhibiting antigen receptor stimulation in T cells and B cells. Furthermore, BTLA + dendritic cells promote Treg cell differentiation and the induction of peripheral Treg cell tolerance [185].

The expression of HVEM has been found to be upregulated in many tumors including melanoma, gastric cancer, colorectal carcinoma, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), and multiple myeloma [186, 187]. However, the expression of HVEM and BTLA were downregulated in follicular lymphoma. In 251 follicular lymphoma patients' samples, Cheung et al. found HVEM to be mutated in 18.3% [188]. The presence of HVEM mutation was associated with worse survival. On the other hand, activation of LTα promotes the formation of tertiary lymphoid structures and protects against lung cancer and melanoma development in mouse models [189]. Due to the dual action of HVEM in regulating the immune system, current therapeutic strategies are directed toward its ligands; LIGHT, BTLA, and CD160.

The expression of LIGHT mediates the remodeling of the TME by provoking IFNγ-mediated apoptosis and vasculature normalization and encouraging the generation of tertiary lymphoid structures [190]. LIGHT is expressed on activated T cells, tumor-sensing NK cells, and immature DC [191, 192]. Different therapeutic strategies are being studied to deliver or induce LIGHT in preclinical models. Yu et al. developed an adenovirus-expressing LIGHT (Ad-LIGHT) and showed its intra-tumoral administration to 4T1 tumor and $Ag104L^{d}$ fibrosarcoma model mouse model leads to CD8 + T cells tumor infiltration and killing of tumor cells in both the injection and metastatic sites [193]. A similar approach using Myxoma Virus Expressing LIGHT was found to be effective in pancreatic ductal adenocarcinoma and lung metastatic osteosarcoma models [194, 195]. Tang et al. developed a unique fusion protein by modifying fusing multiple monomers of LIGHT to an anti-EGFR monoclonal antibody (anti-EGFR-hmLIGHT) [196]. Anti-EGFR-hmLIGHT was effective in enhancing lymphocyte infiltration and tumor cell killing in Ag104Ld fibrosarcoma and MC38 colon adenocarcinoma mice models. In addition, the combination of anti-PD-L1 and anti-EGFR-hmLIGHT was associated with robust and deep anti-tumor activity in PD-L1-resistant models. However, the anti-tumor effect was less substantial in non-overexpressing EGFR cells. Although we are unaware of any early-phase clinical trials, we are predicting there will be some trials to be initiated soon due to the success of LIGHT-based therapy in preclinical models.

Other strategies include targeting either BTLA or CD160. Lasaro et al. showed that the BTLA/CD160-HVEM pathway blockade induces an anti-tumor effect on large tumors in a genetically modified mouse thyroid cancer model [197]. Sordo-Bahamonde et al. showed that the BTLA blockade increased NK cell-mediated cytotoxicity and depleted leukemic cell numbers in cocultured peripheral blood mononuclear cells from CLL patients [198]. Tifcemalimab, also known as icatolimab, is a first-in-class anti-BTLA monoclonal antibody. In a phase Ia dose escalation study by Schilder et al. (NCT04137900), 25 patients with advanced solid tumors were safely treated with no observed dose-limiting toxicity and with an ORR of 36.8% [199]. Importantly, the co-expression of CD8 and HVEM was associated with better response. Preliminary results of phase I/II trial (NCT05000684) (reported at the ASCO annual meeting in 2023) of tifcemalimab and toripalimab in patients with refractory extensive-stage small-cell lung cancer showed that a combination was well tolerated with an ORR of 26.3% [200]. The ORR was 40.0% in immunotherapy-naïve patients

and 8.3% in immunotherapy-treated patients. Preliminary results of a phase I trial of tifcemalimab with or without toripalimab (anti-PD1) in relapsed/refractory lymphomas (NCT04477772) reported a response rate of 42%. Notably, these patients were heavily pre-treated with 66.7% of the patients progressing upon prior anti-PD-1/L1 therapy [201]. Regarding CD160-based therapies, we are only aware of one phase I trial of an anti-CD160 in melanoma (NCT04477876) with no results published so far.

### 2.3 APRIL and BAFF systems

The B-cell activating factor (BAFF) (TNFSF13B; CD257) and a proliferation-inducing ligand (APRIL (TNFSF13)) are unique members of the TNFSF. Both proteins are type II transmembrane proteins with the latter being cleaved by proteases to be secreted in their soluble forms. Both signaling pathways are involved in B-cell survival, maturation, and differentiation [202]. BAFF can bind to BAFF-R, TACI, and weakly to BCMA. APRIL binds strongly to BCMA and moderately to TACI, whereas BAFF binds weakly to BCMA and strongly to TACI. The activation of these receptors on B and T cells enhances survival, co-stimulation of the adaptive immune system of cells, differentiation and maintenance of plasma cells, and proliferation linking it pathogenesis of different malignancies [15]. BAFF-BAFF-R interaction can also drive CD4 + T cells and Treg survival and proliferation via PI3K-Akt pathways [203].

BAFF, APRIL, and their receptors are overexpressed in different hematological malignancies [204]. The role of APRIL differs in solid malignancies as its presence in tumor microenvironment inhibits tumor cell apoptosis, and promotes metastasis [205]. APRIL was overexpressed in different solid tumors including breast cancer, glioma, cervical cancer, bladder cancer, and ovarian cancer [204, 206]. Moreover, the overexpression of APRIL, BCMA, and TACI participates in carcinogenesis in human non-small cell lung cancer and breast cancer by promoting survival signals of p38, ERK1/2, and JNK1/2 [205]. Targeting the BAFF and APRIL pathways and their receptors have been employed in different hematological malignancies. Different treatment strategies have been investigated such as anti-BAFF, anti-APRIL, anti-BAFF-R, and anti-BCMA antibodies, BAFF, APRIL, and BCMA CAR-T cell therapy, and bi-specific antibodies (reviewed in Ref. [207]). Belantamab mafodotin (anti-BCMA) is an antibody–drug conjugate that showed responses in about a third of multiple myeloma patients in phase II randomized, open-label trial, which led to its FDA approval [208]. In 2021, the FDA approved idecabtagene vicleucel, BCMA-based CAR-T therapy for relapsed/refractory multiple myeloma based on the results of the KarMMa trial [209]. In 2022, the FDA approved ciltacabtagene autoleucel, another BCMA-based CAR-T therapy based on the CARTITUDE-1 trial [202]. Ongoing trials of high interest of TNFSF/TNFRSF-based agents are summarized in Table 3.

## 3 Immunotherapy and treatment of side effects using TNF inhibitors

The frequency of immune-related adverse events (irAEs) varies, depending on the agents used, the number of cycles, and patients' genetic makeup [210]. Several guidelines were published to guide physicians on irAE management, including those provided by the American Society of Clinical Oncology (ASCO) [211], the European Society for Medical Oncology (ESMO) [212], the National Comprehensive Cancer Network (NCCN) [213], and the Society for Immunotherapy of Cancer (SITC) [214]. Corticosteroids are the first-line therapy against most irAEs. However, prolonged use of corticosteroids can result in a number of adverse effects such as hypertension, hyperglycemia, osteoporosis, and infections [215]. In addition, some patients may not respond to steroid treatment. Notably, the usual second-line option involves TNF inhibitors. Drugs such as infliximab, adalimumab, golimumab, etanercept, and certolizumab are all considered good options in cases of colitis, myocarditis, arthritis, and pneumonitis [216–218]. It is still largely unknown if using other TNFSF/TNFRSF inhibitors would result in clinically successful management of irAEs.

Verheijden et al. explored the outcome of patients with severe irAEs and found that the overall survival was lower in patients treated with TNF inhibitors compared to the corticosteroid-only group [219]. However, since this was not a prospective, randomized trial, it is unclear if the worse survival is due to the treatment with TNF inhibitors or due to patients with worse problems receiving the treatment. Wang et al. retrospectively compared the use of corticosteroids alone and corticosteroids with TNF inhibitors in patients with immune-related colitis and found no difference in outcome [220]. The difference between the two studies may be attributed to different follow-up times between patients who required a TNF inhibitor and those who did not as well as the fact that different cancer types were included and neither study was a randomized control trial [221]. Ogusu et al. showed that second-line immunosuppressants including infliximab for steroid-refractory irAEs in patients with lung cancer are effective in 72.2% of the cases [222]. Badran et al. reported patients who had immune-related enterocolitis, re-initiation of immunotherapy with concurrent selective immune inhibitors including anti-TNF agents is safe, reduces severe immune-related even recurrence, and has no negative impact on survival outcomes. [45]. Overall, these

**Table 3** Selected ongoing clinical trials targeting different TNFSF/TNFRSF members

| NCT ID | Drug of interest | Diagnosis | Target | Trial design | Setting | Rationale | No. of participants | Estimated completion year |
|---|---|---|---|---|---|---|---|---|
| NCT03298763 | MSCTRAIL | Non-small cell lung cancer | Mesenchymal stromal cells expressing TRAIL | Phase I/II multicenter, randomized double-blind placebo-controlled | Combination therapy (pemetrexed/cisplatin chemotherapy) | Delivering TRAIL-expressing cells to selectively induce apoptosis | 46 | 2025 |
| NCT04570631 | Eftozanermin alfa | Relapsed/refractory multiple myeloma | TRAIL receptor agonist | Phase I non-randomized trial | Combination with IV or subcutaneous (SC) bortezomib and oral dexamethasone tablet | Fusion protein based on TRAIL to selectively induce apoptosis | 40 | 2024 |
| NCT04950075 | INBRX-109 | Conventional chondrosarcoma | Death receptor 5 (DR5) antibody | Phase II randomized, blinded, placebo-controlled trial | Single-agent INBRX-109 | DR5 activation to induce cell death | 201 | 2024 |
| NCT04807972 | ABBV-927 | Pancreatic cancer | CD40 agonistic antibodies | Phase 1b/2, randomized, controlled, open-label study | ABBV-927 administered in combination with modified FOLFIRINOX (mFFX) with or without budigalimab | Promote immune responses using the CD40 axis | 40 | 2024 |
| NCT03502330 | APX005M | Melanoma, non-small cell lung cancer, and renal cell carcinoma | CD40 agonistic antibodies | A Phase I/Ib single-arm trial | APX005M in combination with nivolumab and cabiralizumab | Promote immune responses using the CD40 axis | 42 | 2027 |
| NCT03739931 | mRNA-2752 | Relapsed/refractory solid tumor malignancies or lymphoma | Lipid nanoparticle encapsulating mRNAs encoding human OX40L, IL-23, and IL-36γ | A Phase 1, open-label, multicenter, dose-escalation study | Intra-tumoral Injection alone and in combination with immune checkpoint blockade | OX40L, IL-23, and IL-36γ pro-inflammatory cytokines to promote immune responses | 264 | 2025 |
| NCT03092856 | PF-04518600 | Renal cell carcinoma | OX40 agonistic antibodies | Phase II randomized trial | Axitinib with or without anti-OX40 antibody | Promote immune responses using the OX40 axis | 62 | 2025 |
| NCT02830724 | Anti-hCD70 CAR transduced T cells | CD70-expressing cancers | Anti-CD70 CAR-T | Phase I/II non-randomized trial | Administering peripheral blood lymphocytes transduced with CD70-CAR-T cells | CD70-specific CAR-T to target CD-70-expressing cancer cells | 124 | 2028 |
| NCT04696731 | ALLO-316 | Renal cell carcinoma | Anti-CD70 CAR-T | Phase I single-arm trial | Lymphodepletion regimen of fludarabine, cyclophosphamide, and ALLO-647 followed by CD70 CAR-T therapy | CD70-specific CAR-T to target CD-70-expressing cancer cells | 120 | 2025 |
| NCT04903873 | EU101 | Advanced solid tumors | 4-1BB agonistic antibodies | Phase I/II single-arm trial | Single-agent EU101 | Promote immune responses using the 4-1BB axis | 110 | 2025 |

**Table 3** (continued)

| NCT ID | Drug of interest | Diagnosis | Target | Trial design | Setting | Rationale | No. of participants | Estimated completion year |
|---|---|---|---|---|---|---|---|---|
| NCT02845323 | Urelumab | Muscle-invasive urothelial carcinoma of the bladder | 4-1BB agonistic antibodies | Phase II randomized, blinded, controlled trial | Neoadjuvant nivolumab with or without urelumab (4-1BB agonistic antibodies) | Promote immune responses using the 4-1BB axis | 15 | 2024 |
| NCT05301764 | LVGN6051 | Soft tissue sarcoma | 4-1BB agonistic antibodies | Phase I/II single-arm trial | LVGN6051 combined with anlotinib | Promote immune responses using the 4-1BB axis | 65 | 2025 |
| NCT05117242 | Acasunlimab | Non-small cell lung cancer | 4-1BB agonistic antibodies | Phase II randomized, open-label, controlled trial | Acasunlimab with or without pembrolizumab | Promote immune responses using the 4-1BB axis | 160 | 2024 |
| NCT05192486 | GNC-038 | Diffuse large B-cell lymphoma | CD19xCD3 × 4-1BBxPD-L1 tetra-specific antibody | Phase Ib/II, open-label, multi-center study | Single-agent GNC-038 | Tetra-specific antibody to activate and enhance immune response and decrease immune system suppuration | 20 | 2024 |
| NCT04225039 | INCAGN01876 | Glioblastoma | GITR agonistic antibodies | Phase II non-randomized trial | Anti-GITR agonist INCAGN1876 and the PD-1 inhibitor INCMGA00012 in combination with stereotactic radiosurgery followed with/without surgery | Promote immune responses using the GITR axis | 39 | 2025 |
| NCT04021043 | BMS-986156 | Advanced solid tumors | GITR agonistic antibodies | Phase I/II non-randomized trial | Ipilimumab or nivolumab with BMS-986156 and hypofractionated stereotactic radiation therapy | Promote immune responses using the GITR axis | 68 | 2024 |
| NCT05891080 | JS004 | Non-small cell lung cancer | BTLA antagonist antibodies | Phase II randomized trial | Neoadjuvant toripalimab and JS004 combined with platinum-based doublet chemotherapy | Promote immune responses by inhibiting the BTLA axis | 124 | 2030 |
| NCT05427396 | JS004 | Advanced solid tumors | BTLA antagonist antibodies | Phase I single-arm trial | Recombinant humanized anti-btla monoclonal antibody (JS004) injection combined with toripalimab | Promote immune responses by inhibiting the BTLA axis | 198 | 2025 |

**Table 3** (continued)

| NCT ID | Drug of interest | Diagnosis | Target | Trial design | Setting | Rationale | No. of participants | Estimated completion year |
|---|---|---|---|---|---|---|---|---|
| NCT05664971 | JS004 | Non-small cell lung cancer | BTLA antagonist antibodies | Phase Ib/II single-arm trial | Recombinant humanized anti-BTLA monoclonal antibody (JS004) injection combined with toripalimab and with standard chemotherapy | Promote immune responses by inhibiting the BTLA axis | 240 | 2024 |
| NCT05069051 | Belimumab | Chronic lymphocytic leukemia | BAFF antagonist antibodies | Phase II randomized trial | Rituximab/venetoclax with or without belimumab | Promote sensitivity to rituximab/venetoclax by inhibiting the BTLA axis | 120 | 2027 |
| NCT05546723 | LMY-920 | Relapsed/refractory multiple myeloma | BAFF-based CAR-T | Phase I single-arm trial | Single-agent LMY-920 | BAFF-specific CAR-T to target BAFF receptors-expressing cancer cells | 30 | 2024 |
| NCT04879043 | HDP-101 | Relapsed/refractory multiple myeloma | BCMA antibody–drug conjugates | Phase I/II | Single-agent HDP-101 | Antibody–drug conjugates targeting BCMA-expressing cells with amanitin (RNA polymerase II inhibitor) as the payload | 78 | 2025 |

results suggest that TNF inhibitors are effective in managing irAEs and unlikely to affect overall survival, though the latter still remains incompletely adjudicated.

## 4 TNF-related molecules and their clinical impact beyond cancer

The TNFRSF and TNFSF play important roles in immune function and hence in autoimmune diseases, as well as in the body's response to a variety of infectious agents.

### 4.1 Autoimmune disease

The role of the TNFSF and TNFRSF molecules has been explored in autoimmune conditions [223]. The TNF-TNFR2 interaction induces T cell activation, expression of adhesion molecules on endothelial cells, and secretion of inflammatory cytokines such as IFNγ and IL-6 in inflammatory bowel disease [224]. TNF also plays a role in rheumatoid arthritis, psoriatic arthritis, and autoimmune uveitis [225]. Interestingly and similar to its double-edge role in cancer, TNF family members may also act to stabilize the disease [226]. However, anti-TNF drugs are still the mainstay of treatment of many autoimmune conditions due to their high efficacy and better safety profile compared to corticosteroids [227]. For example, infliximab is approved for the treatment of inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis, and psoriatic arthritis. Several TNF inhibitors are also authorized for skin autoimmune disorders such as psoriasis (infliximab, etanercept, and adalimumab) and for hidradenitis suppurativa (adalimumab), a severe long-term skin condition that produces skin abscesses and scarring [228]. Lastly, the FDA has authorized adalimumab, a TNFα inhibitor, as the sole systemic non-corticosteroid medication for the treatment of non-infectious uveitis [229]. These agents' FDA-approved indications in autoimmune diseases and their mechanisms of action are summarized in Table 4 [230].

In addition to TNF, OX40, 4-1BB, HVEM, LTβR, DcR3, BAFF, and GITR have been implicated in several autoimmune diseases (further reviewed in [231]). Activation of these co-stimulatory molecules can further recruit and activate lymphocytes and propagate the inflammatory effect of local tissues. Several preclinical and clinical studies have investigated targeting TNFSF/TNFRSF in autoimmune diseases [232]. Belimumab, a BAFF antagonist, was approved for the treatment of systemic lupus erythematosus in 2011 ending a 50-year drought of no new medications in that field [233]. The use of CD40L antagonists has been halted due to the increased risk of thromboembolic events [234]. Blocking GITR has been shown to be an effective strategy in a preclinical arthritis model, but we are not aware of any clinical trials of such agents [235]. Targeting 4-1BB in autoimmune diseases represents a unique situation as an unexpected finding is that 4-1BB agonism can shut off or limit autoimmune and other inflammatory reactions. [236]. This was partially attributed to its up-regulatory effect on Treg cells and subsequently less inflammation [237]. Still, no clinical trial results are currently available. Overall, the success of TNF inhibitors has not been replicated yet with other TNFSF/TNFRSF family members in autoimmune diseases, but ongoing investigations are being carried out to find the silver bullet.

### 4.2 Infectious diseases

There may be an increased risk of opportunistic infections such as tuberculosis and fungal infection in patients treated with TNF blockers, which may in turn be related to the role of TNF in both host defense and immune response [238]. Moreover, there may be an increased risk of herpes zoster in patients receiving TNF blockers for the treatment of rheumatological diseases [238]. HIV, varicella-zoster virus, Epstein–Barr virus, cytomegalovirus, and human

**Table 4** Examples of FDA-approved indications for commonly used anti-TNF drugs in managing immune-related conditions [230]

| Drug | Indications | Structure and target |
|---|---|---|
| Infliximab | Ankylosing spondylitis, Crohn's disease, psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis | Chimeric monoclonal antibody against TNF-α |
| Etanercept | Ankylosing spondylitis, psoriasis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, rheumatoid arthritis | A dimeric fusion protein of TNFR2 and a human IgG1 Fc domain |
| Adalimumab | Ankylosing spondylitis, Crohn's disease, hidradenitis suppurativa, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, and uveitis | Fully humanized monoclonal antibody against TNF-α |
| Golimumab | Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis | Fully humanized monoclonal antibody against TNF-α |
| Certolizumab pegol | Ankylosing spondylitis, Crohn's disease, psoriatic arthritis, rheumatoid arthritis | Fully humanized PEGylated anti-TNF-α monoclonal antibody |

papillomavirus may also occur in patients receiving TNF-blocking therapy for chronic inflammatory conditions [239].

Concerning COVID-19, TNF-α is among the early cytokines produced to mediate pro-inflammatory responses and enhance immune cell infiltration after SARS-CoV-2 infections. Yet, TNF-α-mediated inflammation can also cause detrimental tissue damage and promote lung fibrosis, which later results in pneumonia, pulmonary edema, and acute respiratory distress syndrome [240].

## 5 Conclusions and future directions

TNF-related molecules have a variety of paradoxical (inhibitory and stimulatory) effects on cancer cells [241]. The TNF proteins form a vast superfamily of receptors and ligands, which act as a communication module for cancer and immunity. These molecules exert a complex array of actions that affect oncogenesis as well as autoimmune diseases and infectious immunity. As a pro-inflammatory cytokine, TNF is secreted by inflammatory cells, which may be involved in inflammation-associated carcinogenesis. TNF exerts its biological functions through activating distinct signaling pathways such as NF-κB and JNK. NF-κB is a major cell survival signal that is anti-apoptotic, while sustained JNK activation contributes to cell death.

Regarding cancer, TNF is therefore two-faced. TNF can act as a tumor promoter because TNF stimulates cancer cells' growth, proliferation, invasion and metastasis, and tumor angiogenesis. TNF can also induce cancer cell death. The actions of the multiple TNFRSF and TNFSF molecules are similarly complex. This paradoxical effect might be driven by multiple mechanisms. First, the type of tumor may be important with a possible dichotomy between solid and hematological malignancies. The proliferation and activation of immune cells typically drive more anti-tumor activity in the first while, in hematological malignancies, there is exploitation of these mechanisms for the benefit of the malignant cells. Additionally, some TNFRSF members promote different activities. For example, HVEM promotes co-stimulatory signals when bound to LIGHT and LTα, while it promotes inhibitory signals when bound to CD160 and BTLA. Finally, whether the pro- or anti-tumor effect predominates also depends on the cell type involved, including tumor cells, CD8 + cells, CD4 + cells, Treg cells, and other tumor microenvironment cells.

Targeting immune checkpoints CTLA-4, PD-1, PD-L1, or LAG-3 has transformed cancer treatment. However, many tumors do not respond to targeting these checkpoints and patients may suffer from severe immune-related adverse events. In addition to exploring novel co-inhibitory targets, agonistic antibodies to stimulatory molecules such as TNF/TNF receptor family members may offer new treatment strategies for cancer patients. Most trials test next-generation immunotherapy in patients with very aggressive diseases and expected poor prognosis. Testing these drugs in earlier lines, fitter patients, and with ICI combination might be a feasible approach in future studies. Although many of the discussed approaches failed to demonstrate anti-tumor activity, they still showed a favorable TME modulation effect. Thus, it might be reasonable to use some of these drugs to mold the TME into a "hot" microenvironment followed by using ICI.

There is also a need to explore biomarkers for such novel treatments. We found that most trials failed to elucidate biomarker associations with response. As described previously, co-expression of CD8 and HVEM might predict anti-BTLA monoclonal antibody response and drop in sCD27 levels in Sezary syndrome [146], 199. Moreover, beyond the classically FDA-approved biomarkers (PD-L1 level, tumor mutational burden, and microsatellite stability), TNFSF and TNFRSF might be usable as predictive biomarkers for ICI response and survival[242]. Finally, combination approaches may theoretically have synergistic effects, improving the overall anti-tumor impact.

Targeting TNFSF/TNFRSF family members using both agonist and antagonist drugs is being explored in the clinic for patients with cancer. To date, anti-TNF agents have proven effective for treating multiple autoimmune disorders as well as for immune-related toxicities after checkpoint blockade for cancer. The use of specific TNF family member agonists and antagonists for cancer therapy has been less successful to date and may require biomarker selection of patients [243] as has been successfully applied in the precision genomics oncology field [244–248].

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## Declarations

**Competing interests** The authors declare no competing interests.

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