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REVIEW

Novel strategies for the mitigation of cytokine release syndrome induced by T cell engaging therapies with a focus on the use of kinase inhibitors

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ABSTRACT

T cell engaging therapies, like CAR-T cells and T cell engagers, redirect T cells toward tumor cells, facilitating the formation of a cytotoxic synapse and resulting in subsequent tumor cell killing. T cell receptor or CAR-T downstream signaling triggers a release of pro-inflammatory cytokines, which can induce a Cytokine Release Syndrome (CRS). The incidence of CRS is still hardly predictable among individuals and remains one of the major dose-limiting safety liabilities associated with on-target activity of T cell engaging therapies. This emphasizes the need to elaborate mitigation strategies, which reduce cytokine release while retaining efficacy. Here, we review pre-clinical and clinical approaches applied for the management of CRS symptoms in the context of T cell engaging therapies, highlighting the use of tyrosine kinase inhibitors as an emerging mitigation strategy. In particular, we focus on the effects of Bruton's tyrosine kinase (BTK), Src family including Lck, mammalian target of rapamycin (mTOR) and Janus tyrosine kinase (JAK) inhibitors on T cell functionality and cytokine release, to provide a rationale for their use as mitigation strategies against CRS in the context of T cell engaging therapies.

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1. Introduction

In the field of cancer immunotherapy, redirecting T cell cytotoxicity toward tumor cells is a promising approach for the treatment of various types of cancer. For this purpose, two main strategies are currently developed; one involving T cell genetic modification with chimeric antigen receptors (CAR) and the other one using T cell engaging bispecific antibodies linking the CD3ε chain of the T cell receptor (TCR) to the targeted tumor antigen.[1–6] The CD19 bispecific T cell engager (BiTE) blinatumomab and the TCR-based gp100-peptide MHC specific T cell engaging ImmTAC tebentafusp are approved for the treatment of acute lymphocytic leukemia (ALL) and metastatic uveal melanoma, respectively.[7,8] We have previously described several T cell bispecific antibodies (TCBs) including CEA-TCB (cibisatamab) directed against CEA positive solid tumors, CD20-TCB (glofitamab) indicated for B cell malignancies, WT1-TCB, a TCR-like TCB that recognizes a WT1 derived peptide presented by HLA-A02 on AML cells, and BCMA-TCB for the treatment of multiple myeloma.[1–3,9–12] In the field of CAR-T cells several CD19-targeted CAR-T cell products Kymriah (tisagenlecleucel); Yescarta, (axicabtagene ciloleucel); Tecartus (brexucabtagene autoleucel), Breyanzi (lisocabtagene maraleucel) are approved for ALL and/or B cell malignancies.[13,14] The BCMA-targeted CAR-T cell products Abecma (idecabtagene vicleucel) and Carvykti (ciltacabtagene autoleucel) are also approved for the treatment of multiple myeloma.[15,16] Both T cell engagers and CAR-T cells are showing remarkable clinical efficacy, particularly to cure hematological tumors, opening an avenue for approval of other T cell engaging therapies.[17,18] Consequently, various CAR-T cell products and T cell engagers against a wide spectrum of solid tumors and hematological tumors are under development and hold a great promise.[19,20]

As part of their natural mechanism of action, on-target activity of T cell engaging therapies can lead to strong release of pro-inflammatory cytokines that can potentially induce a Cytokine Release Syndrome (CRS).[21–24] CRS may also occur after viral infection including COVID-19 or after treatment with other classes of immunotherapies including the super agonist anti-CD28 antibody TGN1412.[25,26] The hallmark of CRS is a cytokine storm associated with an over-activation of the immune system which can cause symptoms including fever, hypotension and respiratory deficiency and, in the worst case, multi-organ failure.[25,27,28] In the context of T cell engaging therapies, the cytokine release cascade is initiated by T cell activation and then amplified by myeloid and T cell-derived cytokines.[28–33] This may further mediate endothelial cell activation and vascular leakage in various tissues and organs, manifesting symptoms including hypotension and hypoxia.[28,34,35]

The ASTCT classifies CRS into different grades based on clinical symptoms (fever, hypotension, and hypoxia). The management of grade 2 and higher grade CRS requires patient hospitalization and the use of vasopressors, oxygen flow, high-dose glucocorticoids, and/or IL-6 R blockade to alleviate symptoms.[27] To improve patient well-being, and reduce the

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cost associated to hospitalization, there is a need to anticipate the occurrence of grade 2 or higher grade CRS by implementing early interventions.[36] In the specific case of T cell engagers, step-up or fractionated dosing schedules are used in the clinic to lower the risk of first-infusion cytokine storm that may be observed after flat-dose administration.[37] Nevertheless, CRS still remains a frequent dose-limiting safety liability associated with on-target activity of T cell engagers.

The severity and onset of CRS are likely to vary across the types and formats of the T cell engaging therapies (e.g. CAR-T cell vs. T cell engagers, costimulatory domain, binder affinity), and to differ between hematological and solid tumor indications.[3,45,24,32,38] Whereas CRS incidence was lower for first-generation CAR-T cells, CRS is more commonly reported with second-generation CAR-T cells, which include a co-stimulatory domain.[39] Even though T cell activation is the common trigger of cytokine release, the onset of CRS comes later for CAR-T cells than for T cell engagers as a consequence of the slower kinetics of cytokine release.[35] For CAR-T cells, the peak of cytokine release typically occurs a few days after infusion and is associated with CAR-T cell proliferation and activation.[24,38] For T cell engagers, the peak of cytokine release can occur within hours after the first infusion depending on the affinity of the CD3 and tumor antigen binder, and is reduced after repeated treatments.[40,41] For CAR-T cells, CRS management may be more challenging than for T cell engagers, as their activity cannot be stopped by simple dose-interruption. Regarding the variability between cancer indications, circulating cytokines may possibly be found at high levels during the treatment of hematological tumors with T cell engaging therapies, due to unrestricted on-target activity on peripheral B cells and in lymphoid organs. In solid tumor indications, cytokine release is rather expected to occur locally in the tumor microenvironment, unless the targeted tumor antigen is also expressed in healthy tissues. Additionally, the tumor load may also contribute the severity of CRS.[42] Altogether, this supports the need to establish CRS mitigation strategies specific to each different class of T cell engaging therapies and indications.

In this review, we will first discuss the current management of CRS with glucocorticoids and/or tocilizumab and the development of novel targeted approaches toward specific cytokine pathways. We will then dive into the promising use of tyrosine kinase inhibitors targeting Src family, BTK, JAK, and mTOR kinases downstream of TCR activation to prevent T-cell derived cytokine release while retaining T cell engaging therapy efficacy.

2. Glucocorticoids

Glucocorticoids like methylprednisolone or dexamethasone are the most commonly used agents for the mitigation of CRS induced by T cell engaging therapies (Figure 1). They suppress inflammatory reactions and are effective in reducing CRS symptoms.[4,27,28,43–45] In preclinical models, they were shown to retain the efficacy of a GPC3 TRAB T cell engager.[4] In the clinic, the transient use of high-dose glucocorticoids for the management or prophylaxis of CRS was reported not to interfere with complete response rate after treatment with BiTE antibodies [46] or CAR-T cells.[47] In addition to preventing CRS, glucocorticoids can also cross the blood–brain barrier (BBB) and could mitigate neurotoxicity risks associated with T cell engaging therapies against hematological targets.[48] However, it is still controversial whether longer term exposure to glucocorticoids might have an inhibitory effect on treatment efficacy. Indeed, they are known to suppress T cell function and T cell

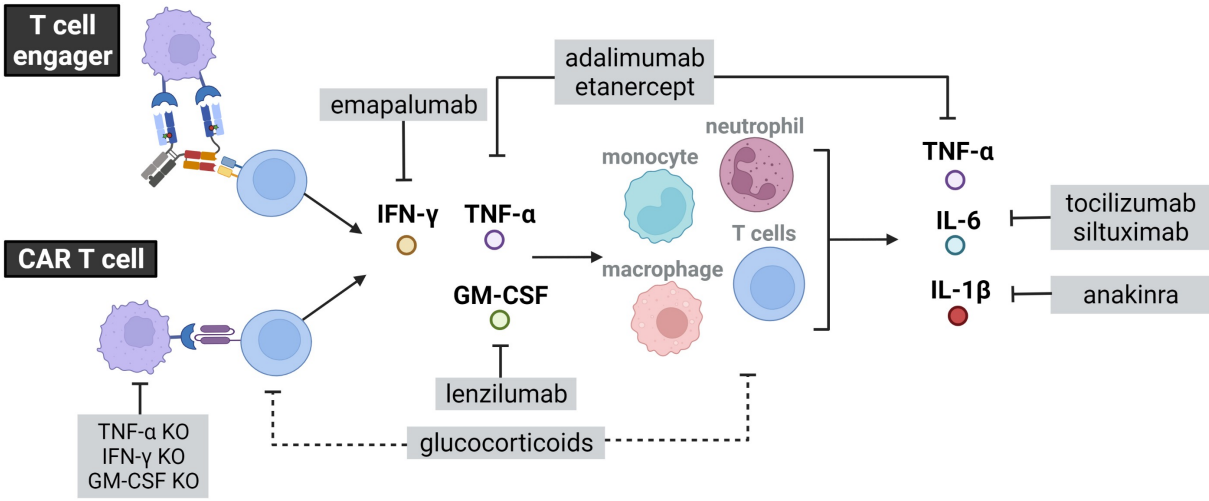

Figure 1. Schematic representation of glucocorticoids and cytokine targeted approaches used for the mitigation of cytokine release induced by T cell engaging therapies. Glucocorticoids and tocilizumab are the most commonly used interventions for CRS. Unlike tocilizumab, which blocks IL-6 R, siltuximab blocks IL-6 and may prevent neurotoxicity in addition to CRS by stopping IL-6 from crossing the blood–brain barrier. Besides, In vitro and in vivo studies have suggested novel cytokine targeted approaches for the mitigation of CRS. Those are directed against pro-inflammatory cytokines including IL-1β (anakinra), TNF-α (Adalimumab/etanercept), IFN-γ (emapulamab), or GM-CSF (lenzimumab). Along those lines, TNF-α, IFN-γ and GM-CSF knock-out can be engineered in CAR-T cells to prevent CRS. Pre-treatment with targeted antibodies depleting and/or masking the tumor. Created with BioRender.com

infiltration in solid tumors, especially when used at high dose for the mitigation of CRS.[49,50] Besides, some patients are refractory to glucocorticoids, emphasizing the need to explore alternative approaches.[4]

3. Cytokine targeted approaches

3.1 Blockade of myeloid-derived cytokines – IL-6, IL-6 R, IL-1 R blockade

After treatment with T cell engagers, IL-6 and IL-1β are released by myeloid cells, downstream of T cell derived cytokines and are described as key cytokines involved in the pathophysiology of CRS[30,32,33,51] (Figure 1). IL-6 levels were reported to correlate with the severity of CRS, highlighting the role of IL-6 in mediating CRS symptoms.[24] Tocilizumab is a monoclonal antibody that competitively prevents the binding of IL-6 to its receptor IL-6 R. It was first approved for the treatment of rheumatoid arthritis before being successfully used in the clinic to mitigate CRS symptoms induced by CAR-T cells (BLA 125276/S-114).[27] Based on these data, tocilizumab has been approved for the treatment of CAR T cell-induced cytokine release syndrome. Norelli *et al.* and Giavridis *et al.* developed mouse models mimicking CAR-T cell-induced CRS and showed that IL-1 R and IL-6 R blockade prevented CD19 CAR-T cells induced-CRS but that only IL-1 R blockade protected the mice from neurological adverse events.[29,31] The IL-1 blocking fusion protein anakinra was shown to be an efficient drug for the mitigation of both CRS and neurotoxicity.[50,52] Siltuximab is a monoclonal antibody that binds IL-6 with a higher affinity than tocilizumab for IL-6 R. One advantage of siltuximab over tocilizumab may be that it prevents IL-6 to cross the BBB, and therefore could mitigate CAR-T cell-induced neurotoxicity. Nevertheless, this hypothesis remains to be proven.[48]

3.2 Blockade of T- cell derived cytokines – TNF-α, GM-CSF, and IFN-γ blockade

As the cascade of cytokines mediated by T cell engaging therapies is initiated by on-target T cell activation and cytokine release, there is a rationale to block upstream T cell-derived cytokines for the mitigation of CRS (Figure 1).

The prophylactic blockade of TNF-α resulted in a significant decrease in IL-6 and IL-1β release after treatment with HER2-T cell dependent bispecific antibody (TDB), both in *in vitro* co-culture of PBMCs and HER2-expressing cells and in immunocompetent MMTV-HER2 transgenic mice.[32] These findings were confirmed *in vitro* for other T cell bispecific antibodies (Tyrp1-TCB, CEA-TCB, and FolR-TCB).[33] The prophylactic blockade of TNF-α appears as promising strategy to control the activation of myeloid cells and the release of IL-6 and IL-1β.[30,32,33] Etanercept was used to mitigate CRS in a patient treated with BCMA CAR-T cells who had elevated serum TNF-α levels.[53] However, TNF-α is also known to induce upregulation of ICAM and VCAM, favoring T cell infiltration in the tumors and its blockade may interfere with anti-tumor efficacy of T cell engaging therapies targeted against solid tumors.[3]

Similarly, the blockade of CAR-T cell-derived GM-SCF prevented cytokine release in co-culture of CD19 CAR-T cells with tumor cells. *In vivo*, GM-CSF CRISPR/Cas9-knockout in CD19 CAR-T cells or the combination of CD19 CAR-T cells with anti-GM-CSF antibody (lenzilumab) prevented cytokine release and neurotoxicity in mice engrafted with acute lymphoblastic leukemia (ALL) patient-derived xenograft, while retaining CAR-T cell efficacy.[54,55]

The blockade of IFN-γ with emapalumab or the IFN-γ knock-out in CAR-T cells prevented the activation of pro-inflammatory macrophages together with the associated cytokine release.[51,56,57] While these studies did not show a negative impact on the efficacy of IFN-γ KO CAR-T cells, other studies showed that IFN-γ blockade decreased the accumulation of $CD8^+$ T cells within tumors after treatment with an anti-HER2xCD3 TDB. In particular, the blockade of IFN-γ prevented the release of essential chemokines involved in T cell recruitment. Therefore, IFN-γ blockade may ultimately negatively affect anti-tumor efficacy when combined with T cell engaging therapies, especially when targeted against solid tumors where T cell infiltration plays a major role in response.[58]

On-target activity of T-cell engaging therapies results in T cell activation and cytokine release, which initiate the cytokine storm. Therefore, a strategy to reduce strong release of pro-inflammatory cytokines on first infusion consists in covering the targeted antigen with a masking antibody (Figure 2). The pre-treatment with anti-CAIX monoclonal antibody competed with CAIX CAR-T cells, reducing on-target CAR-T cell activity and cytokine release.[59] Another example is the pre-treatment with obinutzumab (Gazyva) to avoid CRS occurrence in patients with hematological malignancies treated with the CD20xCD3 TCB glofitamab. By de-bulking peripheral B cells and competing with glofitamab for CD20 binding, the pre-treatment with obinutuzumab decreases on-target cytokine release while retaining a profound anti-tumor efficacy.[3,11,37,60] Pre-treatment with obinutuzumab or other anti-CD20 antibodies may also reduce CRS induced by CD19-targeted CAR-T cells or CD3 bispecific antibodies. However, it was not yet evaluated more broadly, for example, in patients with large peripheral tumor load like in chronic lymphocytic leukemia (CLL).

4. Engineering of T cell engager format

The therapeutic index of T cell engagers can also be improved by engineering lower affinity CD3 binders that trigger less cytokine release while retaining efficient in vivo anti-tumor efficacy.[61–64] *In vitro*, lower CD3 binder affinity is associated with reduced tumor cell killing and reduced cytokine release.[61,62] *In vivo*, a low-affinity CD3 binder retains efficacy while reducing cytokine release and ensuring optimal bio-distribution and accumulation in the tumor.[65] Additionally, Dang *et al.* described that a lower affinity CD3 binder does not trigger activation and proliferation of immunosuppressive Tregs, preventing their infiltration in tumor tissues.[40] Altogether, CD3 engagement on TCR appears more sensitive to trigger signaling pathways involved in T cell cytotoxicity than cytokine release. Consequently, fine-tuning of CD3 binder affinity is an approach

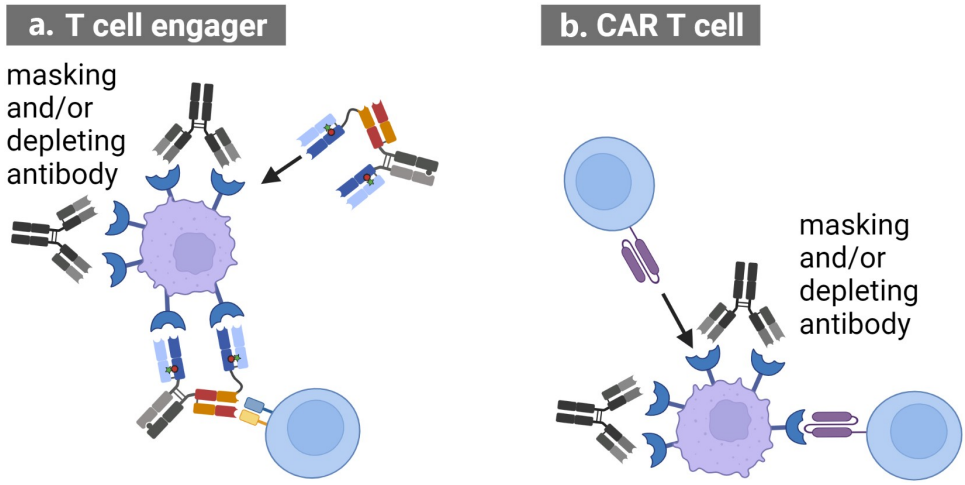

Figure 2. Pre-treatment with antibodies depleting tumor cells and competing for target binding with A. T cell engager or B. CAR T cells can be used to mitigate CRS. When used prior to treatment with T cell engaging therapies, these masking and/or depleting antibodies reduce on-target T cell activation resulting in a lower release of cytokines on first infusion. Created with BioRender.com

to lower CRS occurrence while retaining T cell-mediated cytotoxicity. In this context, new formats of TCBs are currently being engineered and evaluated in an attempt to increase their tolerability by avoiding off-tumor activity. One approach relies on protease-activated TCBs where masking of the anti-CD3 Fab fragment with an anti-idiotypic mask was proven to enhance selectivity and safety of TCBs, as the mask needs to be cleaved by tumor-specific proteases to activate the TCB.[66] Another approach relies on pH-dependent TCBs engineered with the conditionally active biologic (CAB) technology, where the CD3 binder is only active under acidic intra-tumoral pH and remains inactive in healthy tissues.[67,68]

5. Modular CAR-T cells and safety switches

For CAR-T cell therapies, CRS and safety management is more challenging than for T cell engagers, as their activity cannot be stopped by simple dose-interruption. The use of modular CAR-T cells and their respective adaptor molecules may allow to control CAR-T cell activity by dose titration of the CAR adaptor molecule. Depending on the exposure of the CAR adaptor, dose interruption of the molecule may not result in a prompt switch-off of CAR-T cell activity.[69] To achieve a faster switch-off, counter-CAR adaptors can be applied to neutralize the adaptor molecule. Further safety switches have been developed to stop the activity and proliferation of CAR-T cells in rare cases of severe toxicity. One example is the development of STOP-CAR -T cells where the administration of a small-molecule drug can inactivate their functions.[70] Along those lines, Zheng *et al.* reviewed the use of small molecule-based safety switches that aim to provide pharmacological control over CAR-T cell activity.[71] Jan *et al.* engineered lenalidomide OFF switch degradable CAR-T cells and lenalidomide ON switch split CAR-T cells. Those chemical genetic switches in CAR-T cells rapidly and reversibly control CAR T cell activity and degradation to mitigate toxicities associated with CAR-T cell treatment. Recently, SNIP CAR-T cells were engineered with a protease-based platform to control CAR-T cell activity with an FDA approved small molecule, allowing to switch-off CAR activity by dose interruption of the drug.[72] This novel design also circumvents on-target off-tumor activity and rapid T cell exhaustion, which may be observed with classical CAR-T cells.

By interacting with downstream signaling pathways of CAR activation, kinase inhibitors may represent attractive approaches to switch-off CAR-T cell activity.

6. The use of kinase inhibitors for CRS mitigation

Recent screening of kinase inhibitors identified compounds able to enhance or suppress functionality of CAR-T cells or T cells following stimulation with CD3 bispecific antibodies.[73–76] Here, we will attempt to decipher the effects of the main FDA-approved tyrosine kinase inhibitors including Bruton's tyrosine kinase (BTK), BCR-Abl, mammalian target of rapamycin (mTOR) and JAK/STAT inhibitors, on T cell functionality and cytokine release, to provide a rationale for their use as mitigation strategy against CRS (Figure 3). The clinical interventions using tyrosine kinase inhibitors for the mitigation of CRS in the context of CAR-T cell or CD3 bispecific antibody therapies are summarized in Table 1.

6.1 BTK inhibitors

Ruella *et al.* showed that the combination of ibrutinib and CD19 CAR-T cells enhanced the killing of Mantle Cell Lymphoma (MCL) cells *in vitro* and led to profound and durable responses in NSG mice engrafted with MCL xenograft.[79] In addition, ibrutinib co-treatment with CD19 CAR-T cells reduced cytokine release in the serum of these mice (IL-6, IFN-γ, TNF-α, IL-2, and GM-CSF).[80] *In vitro*, escalating concentrations of ibrutinib (10 nmol/L, 100 nmol/L, and 1000 nmol/L) in the assay medium did not significantly reduce CD19-CAR T cell-derived cytokine release and functionality (grzB, Fas ligand, IFN-γ, perforin, and TRAIL). However, treatment of MCL cells with ibrutinib decreased cytokine levels in the cell culture supernatants, reflecting its cytotoxic activity toward cancer B cells.[79]

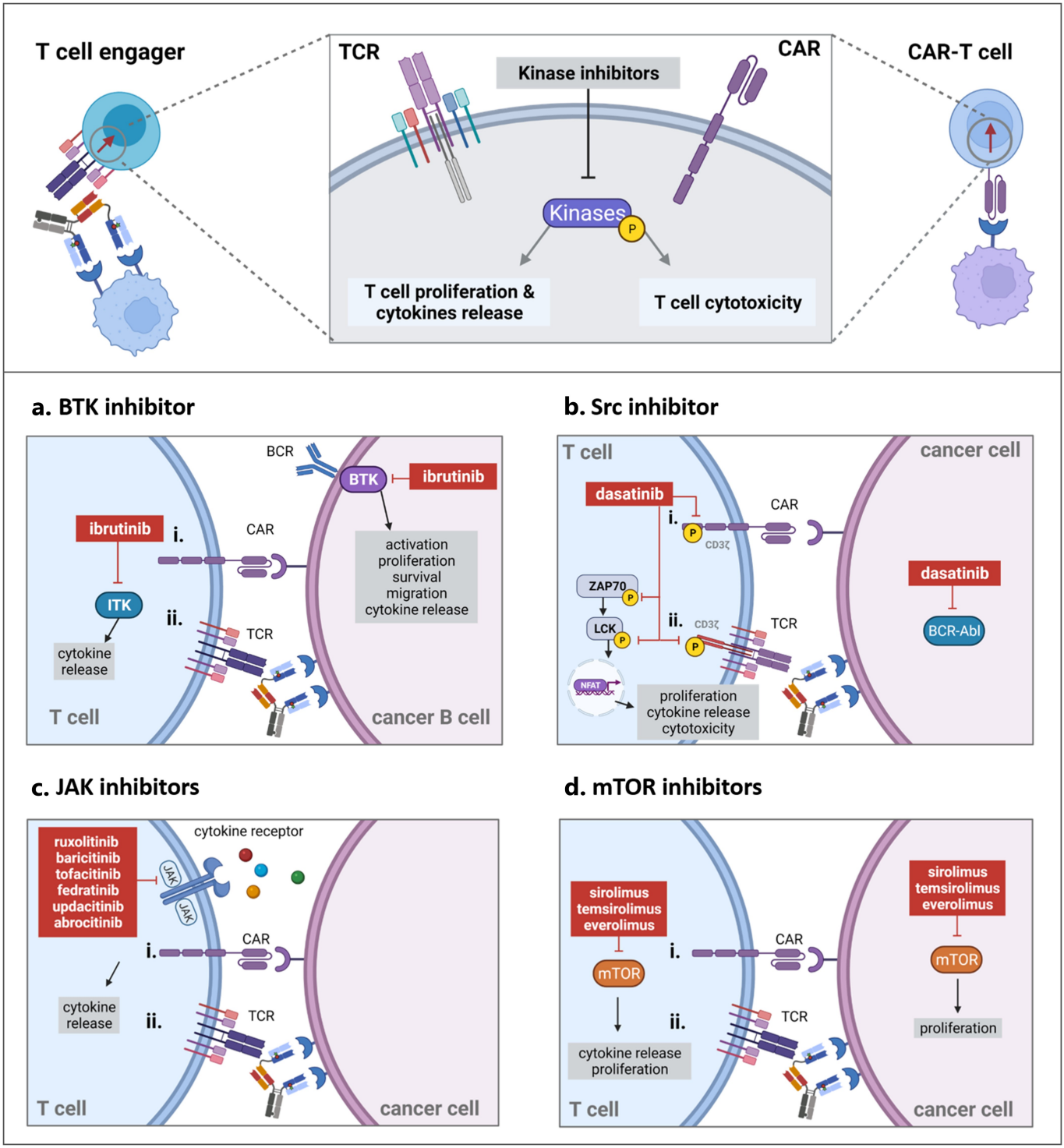

Figure 3. Kinase inhibitors target kinase-signaling pathways involved downstream of TCR or CAR activation and interfere with T cell proliferation, T cell cytokine release and/or T cell-mediated cytotoxicity. **Panel A**. The BTK inhibitor ibrutinib prevents phosphorylation of ITK kinases downstream of CAR (i) or TCR activation (ii) and of BTK kinases in tumor cells resulting in a reduction of cytokine release. The combination of ibrutinib with T cell engaging therapies directed against hematological tumors may increase treatment efficacy while preventing the risk of CRS. **Panel B**. Dasatinib blocks CD3ξ, ZAP70 and Lck kinases phosphorylation and NFAT-mediated gene transcription resulting in a reversible switch-off of T cell functionality for CAR-T cell (i) and T cell engagers (ii). BCR-Abl expressed in leukemia cells is a target of dasatinib. Dasatinib may be combined with T cell engaging therapies directed against acute lymphoblastic leukemia to decrease incidence of CRS. **Panel C**. JAK inhibitors prevent JAK phosphorylation downstream of various cytokine receptors and can reduce CAR T cell (i) or CD3 bispecific antibody-induced cytokine release (ii). They prevent cytokine release while retaining the efficacy of T cell engaging therapy. **Panel D**. mTOR inhibitors prevent mTOR signaling downstream of CAR (i) or TCR activation (ii) as well as mTOR signaling in tumor cells resulting in a reduction of cytokine release and cell proliferation. mTOR inhibitors retain cytotoxic properties of T cells and may be combined with T cell engaging therapies in indications where they exert direct anti-tumor efficacy. Created with BioRender.com

To investigate the mode of action of ibrutinib, Godwin *et al.* compared the effect of ibrutinib to the more specific BTK inhibitor acalabrutinib and to other IL-2-inducible kinase (ITK) and Src inhibitors using *in vitro* co-cultures of acute lymphoblastic leukemia (ALL) cell lines or acute myeloid leukemia (AML) cell lines with T cells in the presence of CD19/

Table 1. Summary of the clinical interventions with kinase inhibitors for the mitigation or prevention of CRS induced by T cell engaging therapies.

Study	Therapy	Disease	Results/comments
Gauthier *et al*., 2020 NCT01865617	CD19 CAR-T cells (CD28 and 4–1BB) + ibrutinib	CLL	Ibrutinib reduced CRS severity while retaining efficacy. • Con-ibrutinib cohort: 14/19 patients experienced CRS, among which 0/19 were grade ≥3 CRS • No-ibrutinib cohort: 18/19 patients experienced CRS, among which 2/19 were grade ≥3 CRS.
Uy *et al*., 2019 NCT02152956	flotetuzumab + ruxolitinib	AML	Prophylaxis ruxolitinib modified the cytokine profile but did not resolve CRS symptoms induced by flotetuzumab. • Con-ruxolitinib cohort: 9/10 patients experienced CRS, among which 4/10 were grade 1 CRS, 5/10 were grade 2 CRS and 0/10 were grade ≥3 CRS. • No-ruxolitinib cohort: 23/23 patients experienced CRS, among which 17/23 were grade 1 CRS, 5/23 were grade 2 CRS and 1/23 were grade ≥3 CRS.
Wei *et al*., 2020 Chi CTR1900025419	CD22/CD19 CAR-T cells + ruxolitinib	Ph+ ALL	Ruxolitinib was used to treat glucocorticoid-refractory CRS. After dexamethasone treatment, ruxolitinib resolved CRS symptoms. This was associated with a reduction of cytokines, ferritin and CRP levels and no apparent effect on the CAR-T cell anti-leukemic activity.
Zi *et al*., 2021 NCT04303520	CD22/ CD19 CAR-T cells + ruxolitinib	Ph+ ALL	Ruxolitinib was used to treat glucocorticoid and tocilizumab-refractory CRS. After tocilizumab and methylprednisolone treatment, ruxolitinib resolved CRS symptoms. This was associated with a reduction of cytokines, ferritin and CRP levels and no apparent effect on the CAR-T cell anti-leukemic activity.
ChiCTR190002531 (patient 1) ISRCTN19144142 (Patient 2).	CD7 CAR-T cells + ruxolitinib and etanercept	T ALL	Concomitant use of ruxolitinib and etanercept induced a change in cytokine profile but did not fully resolve CRS symptoms (administration of noradrenaline was sustained to mitigate CRS grade 3 in both patients)
Park *et al*., 2021 NCT04071366	CD19 CAR-T cells + itacitinib (JAK1 inhibitor)	r/r B cell malignancies	Ongoing study
Assi *et al*., 2017 [77]	Ponatinib, bosutinib or dasatinib + blinatumomab	ALL	Two cases of grade 2 CRS (resolved with glucocorticoids and tocilizumab). One case was observed with dasatinib and the other with ponatinib.
King *et al*., 2019 [78]	Ponatinib, imatinib, nilotinib or dasatinib + blinatumomab	ALL	Blinatumomab was used to eliminate remaining ALL cells in patients with MRD and spare toxicity associated to chemotherapy. CRS (grade 1–2) was observed in 3/11 patients
Foà *et al*., 2020 NCT0244768	Dasatinib + blinatumomab	Ph+ALL	Concomitant use of blinatumomab and dasatinib was safe and efficacious.

CD33xCD3 bispecific antibodies.[81] Their results suggest that the mechanisms by which ibrutinib inhibits T cell cytotoxicity is unlikely to be mediated via BTK inhibition, but rather triggered by ITK inhibition downstream of TCR activation[82] (Figure 3A).

At clinically relevant doses, the reduction in cytokine release observed with ibrutinib is probably mediated by a synergistic effect on tumor cell-derived cytokine release and on CD19 CAR-T cell-derived cytokine release. In addition, ibrutinib polarizes the different T-cell populations toward effector cells and reduces their exhaustion marker expression. This may enable a better functionality of CAR-T cells or T cells following stimulation with T cell engagers.[83,84]

In the clinic, Gauthier *et al.* reported that the combination of CD19 CAR-T cells with ibrutinib to treat CLL patients after ibrutinib failure was well tolerated and associated with lower CRS-associated cytokines in the serum and lower CRS severity.[85] In terms of efficacy, the combination of CD19 CAR-T cells with ibrutinib lead to comparable response rates than achieved with CD19 CAR-T cell monotherapy.[86] Additionally, ibrutinib reduced obinutuzumab-infusion-related reaction (IRR) in CLL patients, suggesting that it may reduce cytokine release associated with other classes of immunotherapies.[87,88]

6.2. BCR-Abl/Src family inhibitors

Weber *et al.* and Mestermann *et al.* described the use of the FDA-approved kinase inhibitor dasatinib as a rapid and reversible pharmacological ON/OFF switch for CAR-T cells.[89,90] By inhibiting phosphorylation of CD3ξ, Lck and ZAP70 kinases downstream of the CAR construct, dasatinib can prevent CAR-T cell functionality and cytokine release (Figure 3B). The inhibitory effects of dasatinib being reversible, a temporary switch-off of activated CAR-T cells with dasatinib could prevent lethal CRS in a mouse model reproducing high-grade CRS, while maintaining long-term efficacy.[89,90] Weber *et al.* also demonstrated that transient ON/OFF switches with dasatinib could prevent rapid CAR-T cell exhaustion and restore T cell functionality.[91] Dasatinib was also shown to reversibly switch-off cytotoxicity and cytokine release from PBMCs that were pre-stimulated with HLA-A2 WT1-TCB or CEA-TCB.[92] Furthermore, dasatinib stopped CD19-TCB-mediated B cell depletion and cytokine release in vivo in humanized NSG mice (Figure 3B).[92,93] Based on these findings, the use of dasatinib was developed as a safety switch for HLA-A2 WT1-TCB, a TCR-like TCB, associated with the potential unpredictable recognition of WT1-similar peptides presented by MHC class-I on healthy cells. Another use of dasatinib could be to stop TCB activity in rare cases of life-threatening CRS where glucocorticoids may not be sufficient.[92,93] Along those lines, the multi-pharmacologically targeted kinase inhibitor midostaurin was shown to switch-off T cell proliferation and cytokine release following stimulation with CD33-directed uniCAR and CD33 T cell engager at clinically relevant doses.[94] The authors report that the inhibitory effects of midostaurin are likely driven through off-target inhibition of Lck and ZAP70 kinases, similarly to dasatinib.

In a lymphoma patient-derived xenograft model in huNSG mice, transient interventions with dasatinib on the first infusion with CD19-TCB strongly reduced cytokine release while minimally interfering with long-term anti-tumor efficacy.[76] This supports the transient prophylactic use of dasatinib to prevent CRS after the first infusion with CD3 bispecific antibodies.

In the clinic, Foà *et al.* used dasatinib as induction therapy for 85 days in patients with acute lymphoblastic leukemia (ALL) followed by a consolidation therapy with concomitant treatment of blinatumomab and dasatinib.[95,96] This approach was successful with an overall survival of 95% and a disease-free survival of 88% at a median follow-up of 18 months. Importantly, it was associated with few toxic effects. The combination of blinatumomab and dasatinib was associated with a safe and efficacious response. In the study described by Foà *et al.*, the de-bulking of tumor cells using the BCR-Abl inhibitor dasatinib in the induction phase considerably reduced the tumor load. Therefore, the risk of CRS was reduced in the consolidation phase combining blinatumomab and dasatinib. Although the *in vitro* continuous exposure of dasatinib was shown to suppress blinatumomab-mediated T cell activity,[97] it is likely that the *in vivo* PK/PD properties of dasatinib inducing rapid ON/OFF switches during the consolidation phase may explain the safety and efficacy profile of blinatumomab treatment. It can also be hypothesized that the transient ON/OFF switches with dasatinib may have even prevented rapid T cell exhaustion thereby prolonging T cell functionality, as recently described by Weber *et al.* in the field of CAR T cells.[91] The trial reported by Foà *et al.* likely benefited from both the direct anti-tumor effect of dasatinib in the induction phase and its effect on cytokine release during the consolidation phase, making the treatment with blinatumomab well tolerated.

6.3. JAK inhibitors

Since many cytokines involved in cytokine release syndrome signal through the JAK/STAT pathways, the use of FDA-approved JAK inhibitors for the mitigation of CRS induced by T cell engaging therapies was investigated (Figure 3C).[98–100]

Kenderian *et al.* have shown that ruxolitinib may prevent CRS after CD123 CAR-T cell therapy using an acute myeloid leukemia xenograft mouse model. Mice treated with CD123 CAR-T cells in combination with ruxolitinib exhibited less severe weight loss and attenuated cytokine release. In this model, ruxolitinib retained treatment efficacy providing long-term survival.[101] Additionally, the combination of ruxolitinib with CD19 CAR-T cells reduced *in vitro* proliferation and *in vivo* expansion while maintaining their therapeutic efficacy and decreasing cytokine release.[102] Itacitinib, a JAK1 inhibitor, was also shown to prevent IL-6, IFN-γ, IL-2, and IL-8 release in co-culture of $CD19^+$ lymphoma cells with CD19 CAR-T cells.[103] Co-treatment with itacitinib did not impair CD19 CAR-T cell anti-tumor activity in immune-deficient NSG mice inoculated with $CD19^+$ expressing Nalm6 lymphoma cells. Furthermore, itacitinib was shown to prevent release of IL-6 from macrophages after *in vitro* and *in vivo* LPS stimulation, showing that JAK1 inhibition directly affects myeloid-derived cytokine release.[103]

In the field of T cell engagers, the combination of FDA-approved JAK inhibitors (ruxolitinib, baricitinib, fedratinib, and tofacitinib) strongly reduced CEA-TCB and CD19-TCB-induced cytokine release while retaining *in vitro* activity at pharmacologically active doses.[76] *In vivo*, ruxolitinib reduced CD19-TCB-mediated cytokine release in non-tumor bearing humanized NSG mice (huNSG).[76] In a lymphoma patient-derived xenograft (PDX) model in huNSG mice, ruxolitinib prophylaxis minimally interfered with CD19-TCB anti-tumor efficacy.[76] Altogether, these preclinical findings suggest that JAK inhibitors efficiently modulate the cytokine profile after T cell engaging therapies.

In the clinic, ruxolitinib was used for CRS management in a patient being refractory to glucocorticoids after treatment with CD22/CD19 CAR-T cell.[104] Ruxolitinib was given after dexamethasone and reduced the body temperature, cytokine levels (IL-6, IL-8, IL-10, and TNF-α), ferritin and CRP levels while not influencing CAR-T cell anti-leukemic activity. In line with this, ruxolitinib combined to etanercept (anti-TNF-α) was used for the mitigation of grade 3 CRS developed in two patients after treatment with CD7 targeted universal CAR-T cells.[105] Ruxolitinib reduced cytokine levels in the serum of the two patients. Nevertheless, noradrenaline treatment was continued, making it complicated to conclude on the effects of ruxolitinib in preventing CRS symptoms. In another study, Uy *et al.* reported that prophylactic treatment with ruxolitinib decreased cytokine secretion, but did not lead to discernable improvement in clinical severity of CRS in patients receiving flotetuzumab, emphasizing that the pan-JAK inhibitor ruxolitinib alone may not be sufficient to mitigate CRS.[106] Itacitinib, a more selective JAK1 inhibitor, is currently being explored for the prevention of CD19 CAR-T cell induced CRS in patients with hematological malignancies.[103,107] Additionally, the combination of ruxolitinib with other mitigating agents including tocilizumab or low-dose glucocorticoids might be beneficial to improve CRS symptoms management and remains to be explored pre-clinically.

6.4 mTOR inhibitors

A recent screening of 52 FDA-approved kinase inhibitors revealed that mTOR inhibitors reduced T cell proliferation and cytokine release following TCR activation via CD3 stimulation.[76] In a co-culture of PBMCs and tumor cells, the FDA-approved mTOR inhibitors sirolimus, temsirolimus, and everolimus prevented T-cell mediated cytokine release while retaining tumor cell killing following treatment with CEA-TCB and CD19-TCB at pharmacologically active doses-[76] (Figure 3D). When compared side by side to JAK, Src inhibitors, and glucocorticoids, mTOR inhibitors appear to be the most potent kinase inhibitors, which strongly reduce *in vitro* cytokine release while preserving T cell killing.[76] *In vivo*, sirolimus favorably prevented first infusion cytokine release and retained B cell depletion in non-tumor bearing huNSG treated with CD19-TCB.[76] In a lymphoma patient-derived xenograft model in huNSG mice, transient treatment with sirolimus on first infusion with CD19-TCB retained long-term anti-tumor efficacy comparably to JAK, Src inhibitors and dexamethasone.[76] Altogether, these data suggests that mTOR inhibitors may be the preferred candidates for prophylaxis of CRS. Since mTOR inhibitors are used as anti-tumor agents in various solid cancers, a combination with a solid-tumor targeted TCB may be of particular interest to prevent CRS while maintaining efficacy in such indications.[108,109] Indeed, mTOR signaling is frequently dysregulated in various cancers, such as breast, prostate, lung, liver, and renal cell carcinomas. It was reported that the upregulation of mTOR signaling may promote growth factor receptor signaling, angiogenesis, glycolytic activity, lipid metabolism, cancer cell migration, and suppression of autophagy, resulting in tumor growth and progression.[110,111] Esfahani *et al.* showed that sirolimus promoted allograft tolerance while retaining pembrolizumab-mediated anti-tumor activity in a melanoma patient undergoing kidney allograft rejection resulting from pembrolizumab treatment.[112] This further supports targeting the mTOR pathway to mitigate inflammation-driven adverse events related to treatment with immunotherapies while retaining their efficacy.

7. Summary

There is a need of developing prophylactic mitigation strategies that would prevent the occurrence of grade 1 or higher grade CRS after treatment with T cell engaging therapies, thereby improving patient well-being and reducing treatment costs associated to hospitalization for symptoms management.

The idea of using targeted approaches using single anti-cytokine antibodies might be a way to retain other cytokines essential for anti-tumor efficacy of T cell engaging therapies, especially those targeting solid tumors. In such indications, various cytokines and chemokines are required for effective T cell infiltration. However, these targeted approaches may not be sufficient to prevent the rapid and massive cytokine storm caused by constructs engineered with high avidity binders toward the tumor-associated antigen and/or toward the CD3ε of the TCR.[41] In such circumstances, the transient inhibition of the broad spectrum of cytokines and chemokines might more efficiently resolve CRS symptoms, as observed with glucocorticoids.

This sheds light on novel broader approaches, including the use of tyrosine kinase inhibitors, which interfere with signaling pathways downstream of TCR or CAR activation resulting in reduction of T cell-derived cytokine release.[73,76,89,90,92] The BTK inhibitor ibrutinib is of particular interest for the mitigation of CRS associated with T cell engaging therapies against B cell malignancies like CLL or MCL, where BTK inhibition is pharmacologically active.[86] When combined with CAR-T cells or T cell engagers, ibrutinib does not only prevent cytokine release but also exerts anti-tumor activity and related debulking effect, resulting in a safer and more efficacious treatment of CLL or MCL.[79,81]

The kinase inhibitor dasatinib was shown to suppress both cytokine release and T cell-mediated cytotoxicity following CAR or TCR activation.[89,92] Therefore, it represents an attractive safety switch for the mitigation of severe CRS or other adverse events where glucocorticoids would not be sufficient to rapidly switch-off T cell functionality. In the clinical trial described by Foà *et al.*, the BCR-Abl inhibitor dasatinib pre-depleted ALL tumor cells therefore reducing

the risk of on-target CRS in the consolidation phase, where the combination of blinatumomab and dasatinib eliminated the residual tumor cells with few CRS events.[95] During this step, dasatinib targeted Src and Lck kinases downstream of TCR activation by blinatumomab, preventing cytokine release and T cell-mediated cytotoxicity.[97] Since the inhibitory properties of dasatinib are reversible, it most likely induced rapid ON/OFF switches that did not fully suppress blinatumomab activity and may have even hindered rapid T cell exhaustion.[91]

In contrast, the mTOR and JAK inhibitors were shown to suppress cytokine release while retaining T cell cytotoxicity after stimulation with CD3 bispecific antibodies.[76] In the clinic, the JAK1/2 inhibitor ruxolitinib induced a change in cytokine profile, which was not sufficient to prevent CRS clinical signs, unless combined with glucocorticoids or other cytokine neutralizing antibodies.[106] The side-by-side *in vitro* comparison of JAK and mTOR inhibitors reveals that the blockade of the mTOR pathway more broadly reduces cytokine release. Consequently, mTOR inhibitors represent attractive candidates for the mitigation of CRS. Nevertheless, this remains to be clinically tested.[76]

In the specific case of CD3 bispecific antibodies, these kinase inhibitors may be used as premedication on the first infusion for constructs at high risk for CRS. These compounds may not or only transiently interfere with treatment efficacy, benefiting from the combination of long PK/PD properties of large molecules with short PK/PD of small molecules. Another important feature of kinase inhibitors is their potential antitumor activity, which makes them ideal combination partners with T cell engaging therapies in the same cancer indications.

In addition to reducing cytokine release, these compounds may also induce epigenetic reprogramming of T cells, by interfering with signaling pathways downstream of TCR or CAR activation. One example is the use of dasatinib to prevent antigen-dependent T cell differentiation during the manufacturing of GRP78 CAR-T cells, by blocking CAR signaling post activation. As a result, GRP78 CAR-T cells effector functions were improved.[113] Along those lines, the addition of PI3K inhibitor duvelisib during the manufacturing of CD19 CAR-T cells reprogrammed stem-cell like properties in the terminally differentiated T cells with exhausted phenotypes of CLL patients.[114,115] An interesting aspect of kinase inhibitors to be further explored is their potential to reprogram T cells toward more functional phenotypes following CAR or TCR activation.

Article highlights

- The use of cytokine/cytokine receptor targeted antibodies for the mitigation of CRS
- The use of target cell pre-depletion approaches and/or target cell masking antibodies
- The engineering of CD3 binders of T cell engagers to reduce first infusion cytokine release
- The emerging use of FDA-approved kinase inhibitors to prevent cytokine release following treatment with T cell engaging therapies

Disclosure statement

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Data availability statement

Data are available on request.

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