REVIEW

Effectiveness of chimeric antigen receptor-T therapy on prostate cancer: A preclinical and clinical systematic review

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ABSTRACT

Chimeric antigen receptor-T (CAR-T) therapy has been an effective treatment for leukemia and lymphoma. Unlike hematological cancers, solid tumors like prostate cancer utilize a dynamic microenvironment to evade the host immune defenses. We aimed to systematically review preclinical and clinical studies to evaluate how CAR-T therapies in prostate cancer modify the tumor microenvironment and influence patient outcomes. PubMed, Embase, and Scopus were screened for published, peer–reviewed preclinical and clinical studies in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The CAR-T antigen, tumor eradication rates, change in prostate–specific antigen (PSA) expression, and tumor tissue infiltration were compared across studies. Nineteen preclinical trials examining xenograft mice models and 3 phase I clinical trials with 32 total patients were included in this review. Tumor eradication rates in mice treated with armored CAR-T therapy were significantly greater than that of mice treated with unarmored CAR-T cells (p–value < .05). Ten of 32 clinical trial patients had a minimum of 30% PSA decline. Patients receiving higher doses of lymphocyte depletion (LD) therapy had higher peaks of CAR-T expansion, and those receiving LD therapy before CAR-T infusion experienced reduced dose–limiting toxicities. Immunohistochemistry staining of biopsied tumor tissue suggests CAR-T increased T cell proliferation markers and upregulated cytokines. CAR-T cells can modify the tumor microenvironment when armored or paired with LD therapy. Future studies should include expanded clinical investigations, particularly using armored CAR-T cells with LD regimens, to determine its safety and efficacy profiles in prostate cancer.

Key Words: Chimeric antigen receptor-T, Chimeric antigen receptor-T therapy, Prostate cancer, Solid tumors

1. INTRODUCTION

Prostate cancer is the most prevalent malignancy and second most common cause of cancer related deaths in men.[1] Incidence rates have increased 3% annually for the last decade, with a projected 299,010 new cases and 35,250 deaths in 2024.[1] While localized tumors can be treated with surgery and radiation, a diagnosis of metastatic prostate cancer indicates more complex treatments such as androgen deprivation therapy and/or docetaxel chemotherapy.[2] Furthermore, metastatic prostate cancer can become unresponsive to androgen deprivation therapy, transforming into metastatic castration-resistant prostate cancer (mCRPC), which is incurable.[3,4]

Chimeric antigen receptor-T (CAR-T) cell therapy is a promising option involving the use of genetically engineered T-cells to target cancer cells and subsequently eliminate

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them via T cell activity. The phenomenal success of CAR-T cell therapy in treating hematological malignancies such as leukemia and lymphoma has invigorated the field of oncology, leading the community to consider its use for solid tumors.[5] There are currently several limitations in treating solid malignancies with CAR-T cells such as the immunosuppressive tumor microenvironment, tumor antigen heterogeneity, and T cell extravasation and proliferation within the tumor.[6]

Several studies have emerged in recent years investigating the application of CAR-T therapy in treating advanced prostate cancer. Many of these studies involve targeting prostate-specific membrane antigen (PSMA), which is expressed on the surface of prostate cancer cells. PSMA is a promising target for CAR-T therapy because it is present in all tumor stages and expression is increased in metastatic stages of disease refractory to androgen deprivation therapy.[7] Other studies involve targeting CEACAM5, STEAP1, and NKG2D: all antigens with increased expression in prostate cancer cells and thus promising targets for T cell trafficking.[8–10] Recent studies have investigated the co-expression of interleukin molecules on the surface of CAR-T cells to heighten the therapy response, producing a new generation of armored CAR-T cells that may be more promising in tackling solid tumors.[11–13] Clinically, CAR-T is preceded with a lymphocyte depletion (LD) regimen as a bridging therapy, which can also enhance CAR-T proliferation rates.[14]

In this systematic review, we aim to elucidate the effectiveness of CAR-T therapy on the outcomes of prostate cancer in preclinical xenograft mouse models and published clinical trial data. Measures of outcomes include tumor eradication rates, percent change of prostate–specific antigen (PSA) expression, and tumor tissue infiltration. Because one of the main challenges in utilizing CAR-T cells for prostate cancer is tissue infiltration, factors that allow CAR-T treatment to overcome the tumor microenvironment, like armoring and LD regimens, will also be investigated.

2. METHODS

2.1 Study search and selection

Utilizing recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), studies across PubMed, Embase, and Scopus were collected for study selection under the Boolean search phrase "[(chimeric antigen receptor T) OR (CAR-T)] AND [prostate]." No additional restrictions were set to the search. Studies were included if they were peer-reviewed articles reporting CAR-T therapy outcomes, including prostate tumor regression. Exclusion criteria included case reports, review articles, conference abstracts, articles not in English, expert opinions, letters to editors, and preclinical studies in which in vivo results were not specified or those that tested CAR-T therapy in combination with chemotherapy. This review is registered with PROSPERO under ID: CRD42024558434. Two independent reviewers (HC and AG) assessed studies according to the inclusion criteria from the preliminary database search. A third senior author resolved disputes in article selection.

2.2 Data collection

Study variables extracted from preclinical studies included antigen targets of CAR-T therapy, in vitro CAR-T cytotoxicity and proliferation, in vivo tumor regression and infiltration, and response phenotype. Study variables extracted from clinical trials included patient age, prior patient therapy, patient length of follow–up, patient indication for CAR-T, toxicities and side effects, CAR-T expansion and persistence, anti-tumor efficacy, tumor trafficking, and tumor microenvironment profile. Data was extracted and assembled using Microsoft Excel (Microsoft Office 2011; Microsoft, Redmond, WA).

2.3 Quality and risk of bias assessment

Clinical study quality was judged with the Methodological Index for Non-Randomized Studies (MINORS) criteria. Each checklist item receives 0 (not reported), 1 (reported inadequately), or 2 (reported adequately), for a maximum of 16 points in non-comparative studies (8 items) and 24 points in comparative studies (12 items).

The quality of preclinical studies was assessed using a modified version of the MINORS criteria, known as the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE)'s Risk of Bias tool.[15] Each of the ten criteria are scored with either low bias, high bias, or an unclear bias. The overal percentage for low bias was totaled for each article. Two reviewers scored every paper independently, then reconciled any differences through joint re-review until both reviewers reached full agreement.

3. RESULTS

3.1 Study selection

An initial search of Scopus, Embase, and PubMed yielded 1,050 studies. After removing 199 duplicates, 851 records remained for title and abstract screening. Of these, 820 were excluded based on our predetermined exclusion criteria, leaving 31 articles for full-text review. Nine studies were further excluded for not meeting inclusion criteria, resulting in 22 studies included in the final analysis—19 preclinical and 3 clinical. The PRISMA flow diagram outlining the search and selection process is shown in Figure 1.

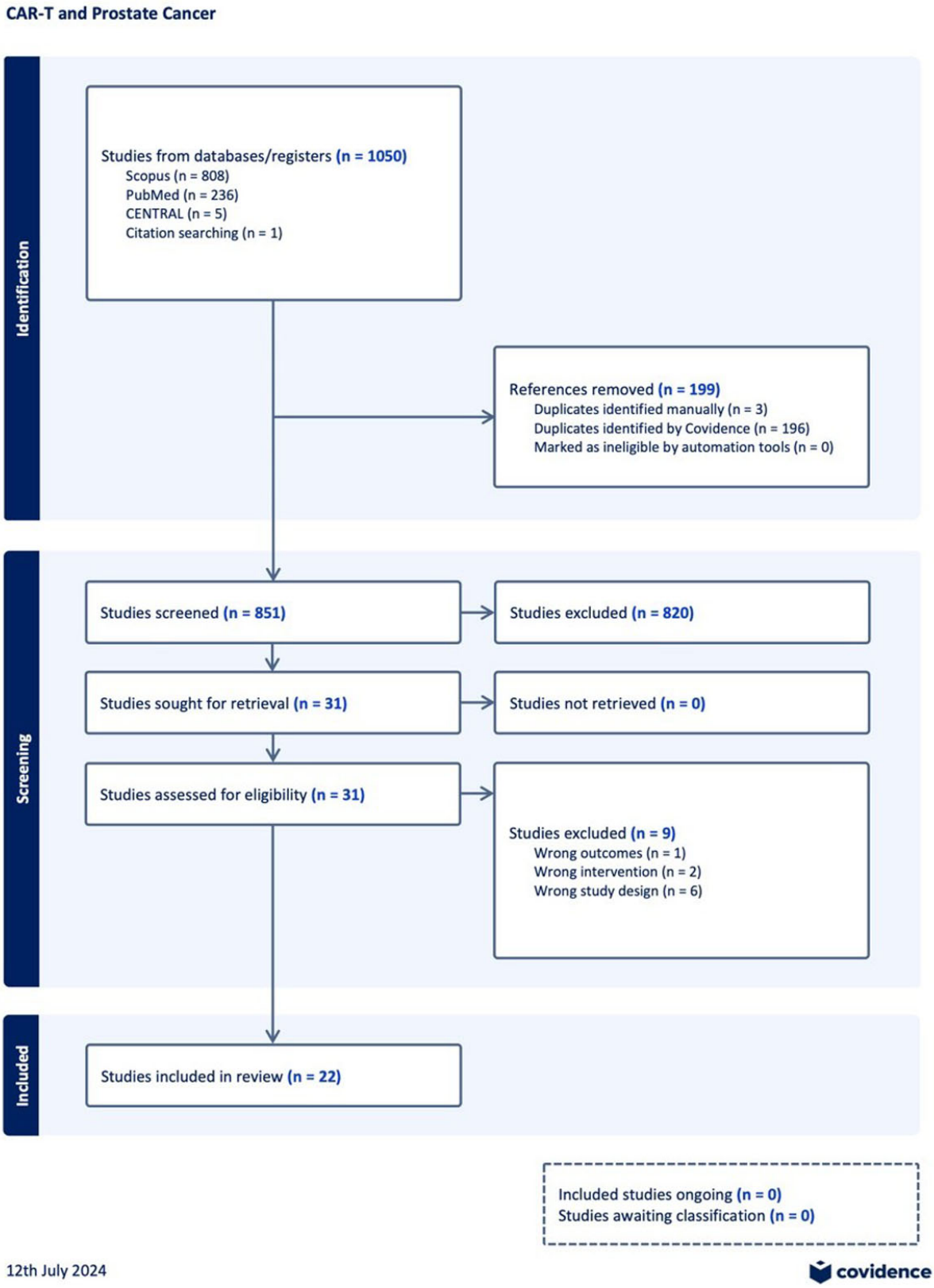

Figure 1. Studies screen according to PRISMA

Depicts the methodology in study selection, including sources of screen studies, number of studies screened, and the inclusion and exclusion criteria

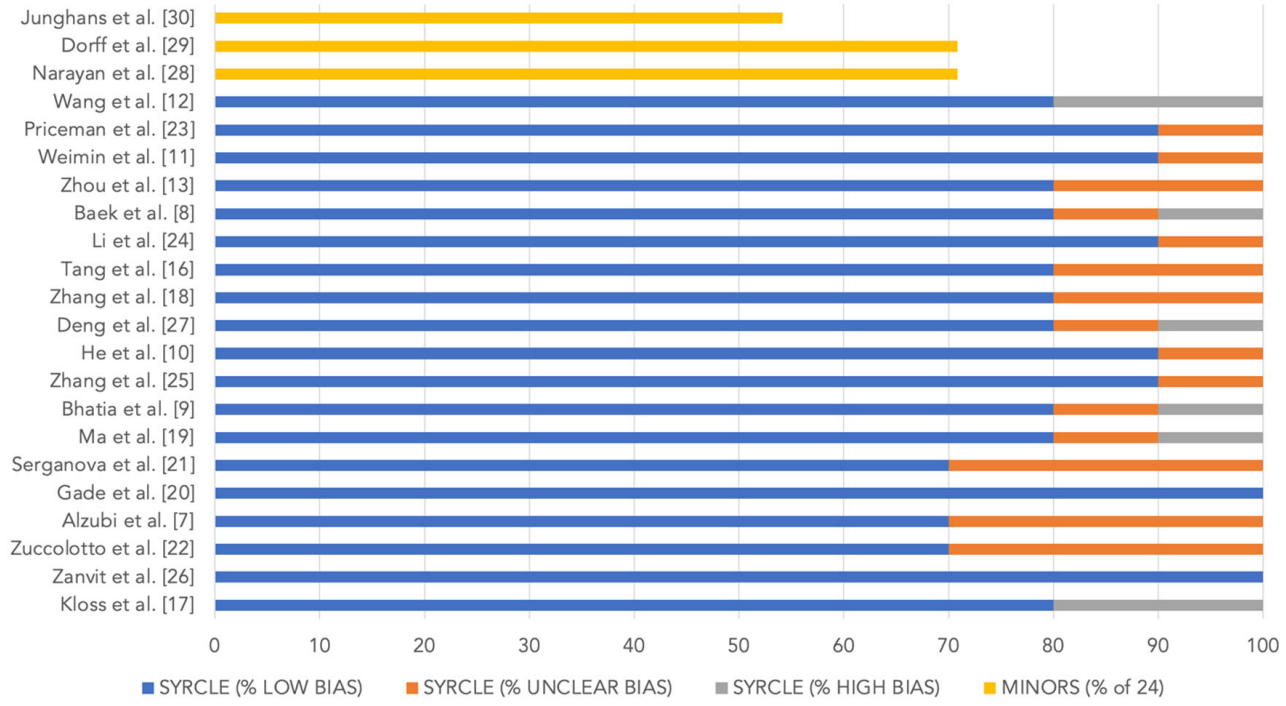

Figure 2. Selected studies bias assessment

Summarizes the total MINORS score as a percentage of 24 for three clinical studies and the SYRCLE scores for 19 preclinical studies

3.2 Methodological index and risk of bias assessment

The mean ± standard deviation (range) of the MINORS score for 3 comparative studies observing clinical outcomes of various CAR-T doses and combination lymphocyte depletion (LD) regimens was 15.67 ± 2.31, indicating low bias. For preclinical studies, the proportion of criteria met with low bias, high bias, or unclear bias was determined for each study. The MINORS and SYRCLE scores are reported as percentages for each study in Figure 2.

3.3 Preclinical studies: CAR-T target antigens and methods

The 19 preclinical studies[7–13, 16–27] included in this review were published between 2005-2023. Eight studies focused on PSMA as the target antigen for CAR-T cell therapy, two studies evaluated human PSMA (hPMSA), two studies analyzed prostate stem cell antigen (PSCA), and two studies used B7-H3. Additional CAR-T therapy target antigens include STEAP1, STEAP2, NKG2D, CEACAM5, and EpCAM. Of the 19 studies, 12 studies compared a traditional CAR-T therapy with an armored CAR-T cell, which includes a modified immunological receptor in addition to the CAR in order to heighten the response.[7, 8, 10–13, 16–19, 23, 26] Table 1 summarizes the author of each study, CAR-T target antigen, any investigated armored CAR-T therapy, and CAR-T tumor infiltration.

For in vitro CAR-T cytotoxicity and proliferation analysis, all studies used one or more prostate tumor cell lines, including PC3, LNCaP, and DU145.[7–13, 16–27] For in vivo tumor regression, all studies used a xenograft mice model or patient–derived xenograft mice model (PDX) using highly immunodeficient NOD/SCID/IL2rγnull (NSG) mice.[7–13, 16–27] Mice were inoculated with prostate tumor cells, derived from cell lines or patient samples, and treated with adoptive T cell therapy at a designated day or until the tumor reached a specific volume.[7–13, 16–27] The one exception was Ma et al.,[19] in which the sample mice received γ-irradiation at 5,000 cGy and inoculated with PC3-PSMA+ prostate tumor cell line and adoptive T cell therapy the same day. The number of mice in each experimental group, control or treatment, ranged from 3 to 20. Tumor volume was recorded using manual measurement with calipers or imaging using bioluminescence(BIL)–tagged prostate tumor cells upon initial inoculation within mice.[7–13, 16–27] Tumor infiltration of CAR-T cells and immunological markers were recorded in select studies using immunohistochemistry staining on sacrificed mice tissue, of which results are included in Table 1.[9–11, 18, 21, 23, 24, 26]

3.4 Preclinical studies: CAR-T in vitro and in vivo efficacy against prostate tumors

All in vitro studies demonstrated that the CAR-T therapy elicited an antigen–specific cytotoxicity, except Gade et al.[20] demonstrated antigen–specific cytotoxicity in vivo.

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Nine out of 12 studies comparing armored CAR-T and unarmored CAR-T found an observable or statistically significant increase in armored CAR-T cell proliferation or cytotoxicity compared to unarmored CAR-T in vitro.[7, 8, 10–13, 16–19, 23, 26]

In studies that examined the efficacy of armored CAR-T cells, results indicated that armored CAR-T cells reduced tumor burden or significantly decreased tumor volume compared to unarmored CAR-T treatment controls.[7, 8, 10–13, 16–19, 23, 26] One study examining the efficacy of unarmored anti-PSMA CAR-T demonstrated that 6/11 mice experienced significant tumor regression, and 11/16 experienced a partial or complete response but relapsed.[19] Both studies examining armored anti-PSCA CAR-T therapy not only indicated a decrease in tumor burden, but Priceman et al.[23] also indicate complete tumor eradication of all mice treated with anti-PSCA CAR-T armored with CD28 costimulatory domain.

Studies examining other CAR-T antigens, including B7-H3, STEAP1, STEAP2, NKG2D, also demonstrated significant reduction in tumor burden or tumor volume in treated mice.[9, 10, 24–26] While anti-CEAMCAM5 CAR-T and anti-EpCAM CAR-T both reduced tumor volume, studies indicated the treatment significantly prolonged survival in mice compared to control non-CAR T cells.[8, 27] Preclinical studies that reported tumor eradication rates, or a tumor volume of 0 mm^3 after CAR-T treatment, is summarized in Figure 3. There is a statistically significant increase in tumor eradication rates of mice treated with armored CAR-T therapy compared to mice treated with unarmored CAR-T cells (see Figure 3).

Table 1. Preclinical selected studies characteristics, armored CAR-T therapy, and tumor infiltration

Study	CAR-T Therapy Target	Armored CAR-T Receptor	CAR-T Tumor Infiltration
Tang et al. [16]	anti-PSMA CAR-T	anti-dnTGF-βRII-trTIM3-PSMA CAR-T	NR
Alzubi et al. [7]	anti-PSMA CAR-T	D7 CAR28-T	NR
Wang et al. [12]	anti-PSMA CAR-T	anti-IL23mAB-T2A-PSMA CAR-T	NR
Weimin et al. [11]	anti-PSMA CAR-T	anti-PSMA-ICR CAR-T	Armored CAR-T cells had higher rates of infiltration
Kloss et al. [17]	anti-PSMA CAR-T	anti-dnTGF-βRII-T2A-PSMA CAR-T	NR
Zhang et al. [18]	anti-PSMA CAR-T	anti-dnTGF-βRII-PSMA CAR-T)	***Armored CAR-T cells had higher rates of infiltration and apoptosis
Ma et al. [19]	anti-PSMA CAR-T	IgCD28TCR	NR
Gade et al. [20]	anti-PSMA CAR-T	NS	NR
Serganova et al. [21]	anti-hPSMA CAR-T	NS	CAR-T cells infiltrated lung metastasis tumor microenvironment
Zuccolotto et al. [22]	anti-hPSMA CAR-T	NS	NR
Zhou et al. [13]	anti-PSCA CAR-T	ΔPD-1-anti-PSCA CAR-T	NR
Priceman et al. [23]	anti-PSCA CAR-T	anti-PSCA-CD28 CAR-T anti-PSCA-4-1BB CAR-T	Armored CAR-T cells had higher rates of infiltration
Li et al. [24]	anti-B7-H3 CAR-T	NS	CAR-T cells infiltrated tumor tissue
Zhang et al. [25]	anti-B7-H3 CAR-T (target prostate cancer stem cells)	NS	NR
Bhatia et al. [9]	anti-STEAP1 CAR-T	NS	CAR-T cells infiltrated tumor tissue
Zanvit et al. [26]	anti-STEAP2 CAR-T	anti-dnTGF-βRII-T2A-40A3 CAR-T	Armored CAR-T cells had higher rates of infiltration in bone metastasis
He et al. [10]	anti-NKG2D CAR-T	anti-NKG2D-IL-7 CAR-T	Armored CAR-T cells had higher rates of infiltration
Baek et al. [8]	anti-CEACAM5 CAR-T	anti-CEACAM5 CAR-T 3rd generation	NR
Deng et al. [27]	anti-EpCAM CAR-T	NS	NR

Note. Summarizes the selected preclinical CAR-T therapy, studied armored CAR-T therapy, and tumor infiltration responses. $^{***}p < .001$, NS = Not studies; NR = Not reported

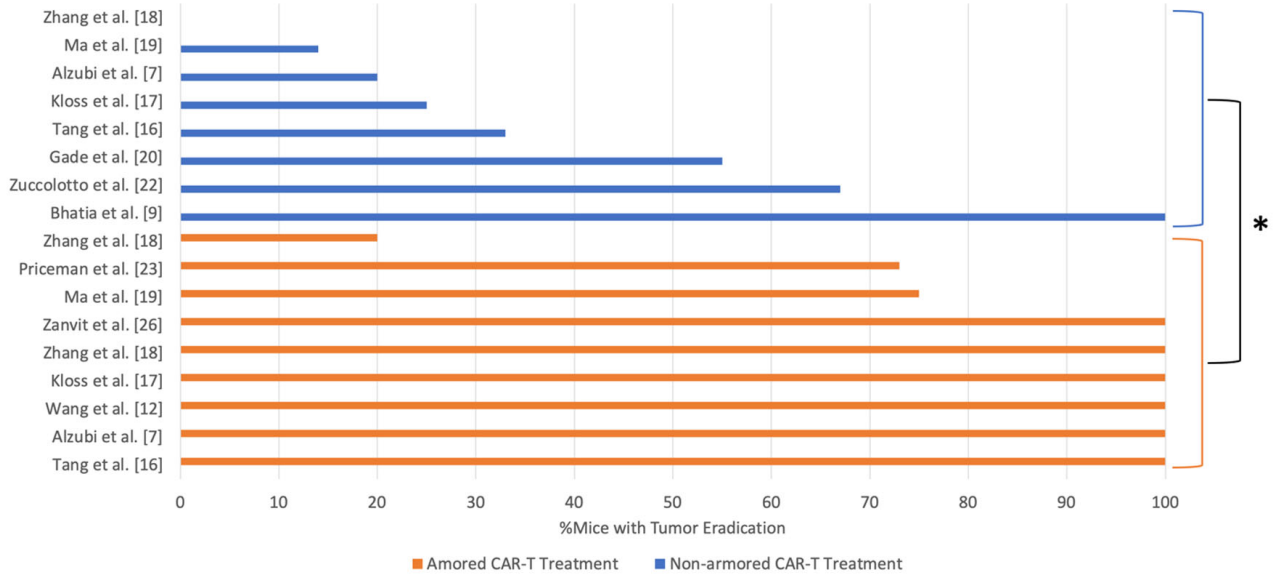

Figure 3. Preclinical mice tumor eradication rates

*Compares the tumor eradication rates in mice xenograft models, specifically from preclinical studies that reported rates of mice with 0 mm^3 tumor volume after treatment, either armored CAR-T therapy or unarmored CAR-T therapy. *p < .05*

Table 2. Preclinical armored CAR-T investigations, T cell response phenotype, and cytokine response phenotype

Study	CAR-T Therapy Target	Armored CAR-T Receptor	Enhanced T Cell Response Phenotype by Armored CAR-T	Enhanced Cytokine Response Phenotype by Armored CAR-T
Tang et al. [16]	anti-PSMA CAR-T	anti-dnTGF-βRII-trTIM3-PSMA CAR-T	Similar to unarmored CAR-T	*IFN-γ
Alzubi et al. [7]	anti-PSMA CAR-T	D7 CAR28-T	Effector memory T cells, terminally effector T cells	NR
Wang et al. [12]	anti-PSMA CAR-T	anti-IL23mAB-T2A-PSMA CAR-T	*Memory CD8+, effector and memory CD4+	*IL-4, IL-5, IL-13, TNF-α and GM-CSF
Weimin et al. [11]	anti-PSMA CAR-T	anti-PSMA-ICR CAR-T	NR	*IFN-γ and TNF-α
Kloss et al. [17]	anti-PSMA CAR-T	anti-dnTGF-βRII-T2A-PSMA CAR-T	**Memory CD8+	IL-4, IL-5, IL-13, IP-10, MIPI-α, MIPI-β
Zhang et al. [18]	anti-PSMA CAR-T	anti-dnTGF-βRII-PSMA CAR-T	*Memory CD8+	***IFN-γ and IL-12
Ma et al. [19]	anti-PSMA CAR-T	IgCD28TCR	NR	IFN-γ and IL-2
Zhou et al. [13]	anti-PSCA CAR-T	ΔPD-1-anti-PSCA CAR-T	CD4+, CD8+	IFN-γ and IL-2
Priceman et al. [23]	anti-PSCA CAR-T	anti-PSCA-CD28 CAR-T anti-PSCA-4-1BB CAR-T	Similar between both Armored CAR-T	*anti-PSCA-CD28 CAR-T cells produced more IFN-γ than anti-PSCA-4-1BB CAR-T
Zanvit et al. [26]	anti-STEAP2 CAR-T	anti-dnTGF-βRII-T2A-40A3 CAR-T	NR	NR
He et al. [10]	anti-NKG2D CAR-T	anti-NKG2D-IL-7 CAR-T	*CD8+/CD4+ ratio	IL-7
Baek et al. [8]	anti-CEACAM5 CAR-T	anti-CEACAM5 CAR-T 3rd generation	Similar to unarmored CAR-T	IL-4 and GM-CSF

Note. Summarizes the selected preclinical studies that investigated CAR-T therapies, with treatment T cell and cytokine response phenotypes compared to unarmored CAR-T counterpart therapies. *p < .05; **p < 0.01; ***p < .001; NR = Not reported

All five studies examining armored CAR-T therapy infiltration in tumor tissue demonstrated that armored CAR-T therapy was more effective at infiltration compared to unarmored CAR-T, due to increased CAR-T or inflammatory cells.[10,11,18,23,26] Twelve studies determined that CAR-T therapy, both armored and unarmored, can mount T cell responses involving effector, memory, CD4+, and CD8+ cells.[7–10,12,13,16–18,20,23,25] Armored CAR-T therapies either induced a response with greater or equal quantities of T cells compared to unarmored CAR-T therapies. Interestingly, Wang et al.[12] and Kloss et al.[17] found that anti-IL23mAB-T2A-PSMA CAR-T and anti-dnTGF-βRII-T2A-PSMA CAR-T, respectively, mount a Th2 response with supplementary IL-4, IL-5, and IL-13 cytokines. Table 2 summarizes preclinical studies that investigated armored CAR-T therapies, and the phenotype of T cell and cytokine responses enhanced by armored CAR-T therapy.

3.5 Clinical trials: Study characteristics and patient demographic information

The 3 clinical trials[28–30] included in this review were published between 2016-2024. All 3 studies had a prospective design.[28–30] The level of evidence was 2 in all three clinical trials. Across all 3 included studies, a total of 32 patients (100% male) were identified with mean ages ranging from 51 to 75 years. Clinically tested CAR-T therapy includes armored anti-dnTGFβR-PSMA CAR-T,[28] anti-PSCA CAR-T,[29] and anti-PSMA CAR-T.[30] Table 3 summarizes the author of each study, median age, CAR-T target antigen, previous patient therapies, prostate–specific antigen (PSA) change, cytokine responses, and survival rates. All patients were diagnosed with mCRPC, which received prior treatment with androgen receptor signaling inhibitor (100%), docetaxel chemotherapy (56.25%), and cabazitaxel chemotherapy (25%).[28–30] Enrollment criteria for Narayan et al.[28] included $\geq$ 10% of tumor cells with PSMA expression,[29] while enrollment criteria for Dorff et al.[29] included $\geq$ 30% of tumor cells with PSCA expression.[30] All three studies pre–treated their patients with a lymphocyte depletion (LD) regimen consisting of cyclophosphamide and fludarabine; Narayan et al.[28] and Dorff et al.[29] included control groups in which patients were not given LD and only provided with CAR-T therapy. Table 4 includes details regarding patient diagnosis, baseline PSA levels, previous therapies, LD regimen, and cohort treatment regimen.

3.6 Clinical trials: Therapy response, outcomes, tissue infiltration, and dose–limiting toxicities

Treatment with a LD regimen enhanced CAR-T expansion;[28,29] however, the peak of CAR-T expansion was not greatly impacted by reduced doses of LD therapy.[29] Narayan et al.[28] stated that Patient 9, member of Cohort 3 receiving higher doses of LD therapy, had the earliest and greatest peak of CAR-T expansion at day 9, and was followed by a subsequent peak at day 27. Patients 11 and 12, who both received LD therapy, exhibited a longer–lasting response, as CAR-T levels maintained elevated over 200 days after the initial infusion.[28]

Table 3. Clinical selected studies characteristics, PSA change, and responses

Study	Number of Total Patients (Male)	Median Age with Range	CAR-T Therapy	PSA % Change Pre to Post Treatment	Elevated Cytokines	Survival Rates
Narayan et al. [28]	13 (100%)	70 (57-72)	anti-dnTGFβR-PSMA CAR-T	Minimum -30% PSA in 4/13 patients	GM-CSF, IFN-γ, IL-10, IL-2R, IL-6, IL-8 (patients with Grade 2+ CRS)	Median Survival: 15.9 Months
Dorff et al. [29]	14 (100%)	Cohort DL1 62 (59-69) Cohort DL2 70 (42-73) Cohort DL3 69 (62-72)	anti-PSCA CAR-T	Minimum –30% PSA in 4/14 patients	* IFN-γ, IL-10, IL-2R, IL-6, and IP-10 (patients with Grade 1 or 2 CRS)	Six Month Survival: 33% Six Month Survival: 67% Six Month Survival: 40%
Junghans et al. [30]	5 (100%)	61 (51-75)	anti-PSMA CAR-T	–50% PSA in Patient 1 –70% PSA in Patient 2	** Increase in IL-2 levels in patients with lower engraftment CAR-T dosages	NR

Note. Summarizes the selected clinical study characteristic, PSA change, and responses. PSA = Prostate-specific antigen, $^{*}p < 0.05$; $^{**}p < 0.01$; NR = Not reported

Table 4. Clinical selected studies patient diagnosis, patient previous therapy, LD regimen, and cohort data

Study	Diagnosis (Stage [Number of Patients])	Baseline PSA (ng/mL) with Median and Range	Previous Therapy (Number of Patients)	Lymphocyte Depletion Regimen	Cohort Data (cohort size)
Narayan et al. [28]	mCRPC (Stage 4 [8], Stage 3 [4], Stage 2 [1])	36.6 (5.2–1,683)	Androgen receptor signaling inhibitor (13), Docetaxel chemotherapy (6)	3 daily doses of Cyc 300 mg/m^2 and Flu 30 mg/m^2	Cohort 1: 1-3E7 CAR-T (3) Cohort 2: 1-3E8 CAR-T (3) Cohort 3: 1-3 E8 CAR-T with Cyc/Flu (1) Cohort 3: 1-3 E7 CAR-T with Cyc/Flu (6)
Dorff et al. [29]	mCRPC (NR)	Cohort 1: 16.5 (10.7–20.4) Cohort 2: 88 (11.7–590.2) Cohort 3: 235.3 (1.79–3,260)	Androgen receptor signaling inhibitor (14), Docetaxel chemotherapy (12), Cabazitaxel (8), Docetaxel and Cabazitaxel (8)	Cyc 500 mg/m^2 daily from day 5 to 3 Flu 30 mg/m^2 daily from day 5 to 3	Cohort 1: 1E8 CAR-T (3) Cohort 2: 1E8 CAR-T with Cyc/Flu (6) Cohort 3: 1E8 CAR-T with Cyc (300 mg)/Flu (5)
Junghans et al. [30]	mCRPC (NR)	NR	Androgen blockage (6), LHRH analogue (6), External Radiotherapy (6), Ketoconazole (3), Chemotherapy (3), Radical Prostatectomy (3)	Cyc 60 mg/kg daily from day 8 to 7 Flu 25mg/m^2 daily from day 6 to 2	Patients 1, 2, 3: 1E9 CAR-T with Cyc/Flu (3) Patients 4, 5: 1E10 CAR-T with Cyc/Flu (2)

Note. Summarizes the selected clinical study patient diagnosis, previous patient therapy, lymphocyte depletion regimens, and cohort treatment therapies. mCRPC = Metastatic castration-resistant prostate cancer; CYC = Cyclophosphamide; FLU = Fludarabine; NR = Not reported

Out of 32 patients in this review, 10 patients had a minimum of 30% PSA decline. Narayan et al.[28] observed a minimum decrease of 30% PSA antigen expression in 4 out 13 patients, with a median of PSA decline of 22.35%. Similarly, Dorff et al.[29] observed a minimum decrease of 30% PSA antigen expression in 4 out 14 patients; one of which maintained a PSA decline of greater than 30% for over 28 days.[29] Junghans et al.[30] stated that Patient 1 and 2 experienced a PSA decline of 50% and 70%, respectively, and exhibited a partial response. On the other hand, Patients 3, 4, and 5 had a minor response or no response at all.[30] Plasma IL-2 levels of Patients 1 and 2 peaked at quantities greater than 2000 pg/mL, while Patients 3 and 4 had lower plasma IL-2 levels peaks ranging from 100 to 200 pg/mL.[30] Consequently, Junghans et al.[30] concluded that lowering the anti-PSMA CAR-T dosage can enhance PSA decline and increase IL-2 immune response. Therefore, the trial was terminated prematurely as anti-PSMA CAR-T therapy would require IL-2 supplementation for effective response.[30]

Narayan et al.[28] performed follow–up every 3 months for up to 2 years with long term follow-up with 15 years, while Dorff et al.[29] performed follow–up until the last patient's death at 33 months. The median survival of patients in Narayan et al.'s[28] study was 477 days, or 15.9 months, with a median disease progression–free survival of 132 days, or 4.4 months. The three cohorts studied by Dorff et al.[29] had a median 6 month survival of 33%, 67%, and 40%, while the rates of stable disease progression were 0%, 67%, and 60%, respectively. Therapy responses and treatment outcomes are summarized in Table 3.

When analyzing CAR-T infiltration within tumor tissue, Narayan et al.[28] observed some infiltration that was not consistent across all patients. More specifically, biopsy analysis before and after anti-dnTGFβR-PSMA CAR-T therapy revealed increased Ki-67, OX40L, and granzyme expression, indicating increased T-cell proliferation and activation.[28] In T-cell rich stromal tissue, there was a significant upregulation of PSMA, Ki-67, CD44, CD14 and CD40, associated with PSA decline.[28] Supporting these findings, Dorff et al.[29] found that bone biopsies after CAR-T treatment had reduced PSMA+ and Ki-67 expression with increased infiltration of CD3+ and CD8+ cells. Additionally, there was elevated CD8+ central memory and effector memory response 28 days after infusion, while PD-1 levels increased 21 days after infusion as an exhaustion phenotype.[29]

With regards to dose-limiting toxicities, the most common was cytokine release syndrome (CRS), which affected a total of 9 patients, followed by anemia, neutropenia, neutropenia fever, and maculopapular rash, which affected 5, 5, 5, and 4 patients, respectively.[28–30] Patient 9 from Narayan et al.'s[28] investigation had successful CAR-T expansion and rapid PSA decline of > 98%; however, Patient 9 experienced fatal toxicities including grade 4 CRS, hypoxic respiratory failure, capillary leak syndrome, and vasopressor–dependent hypotension. Therefore, the CAR-T dosage was adjusted to a lower amount for patients in Cohort-3.[28] Total frequency of dose–limiting toxicities across all three clinical trials are summarized in Figure 4.

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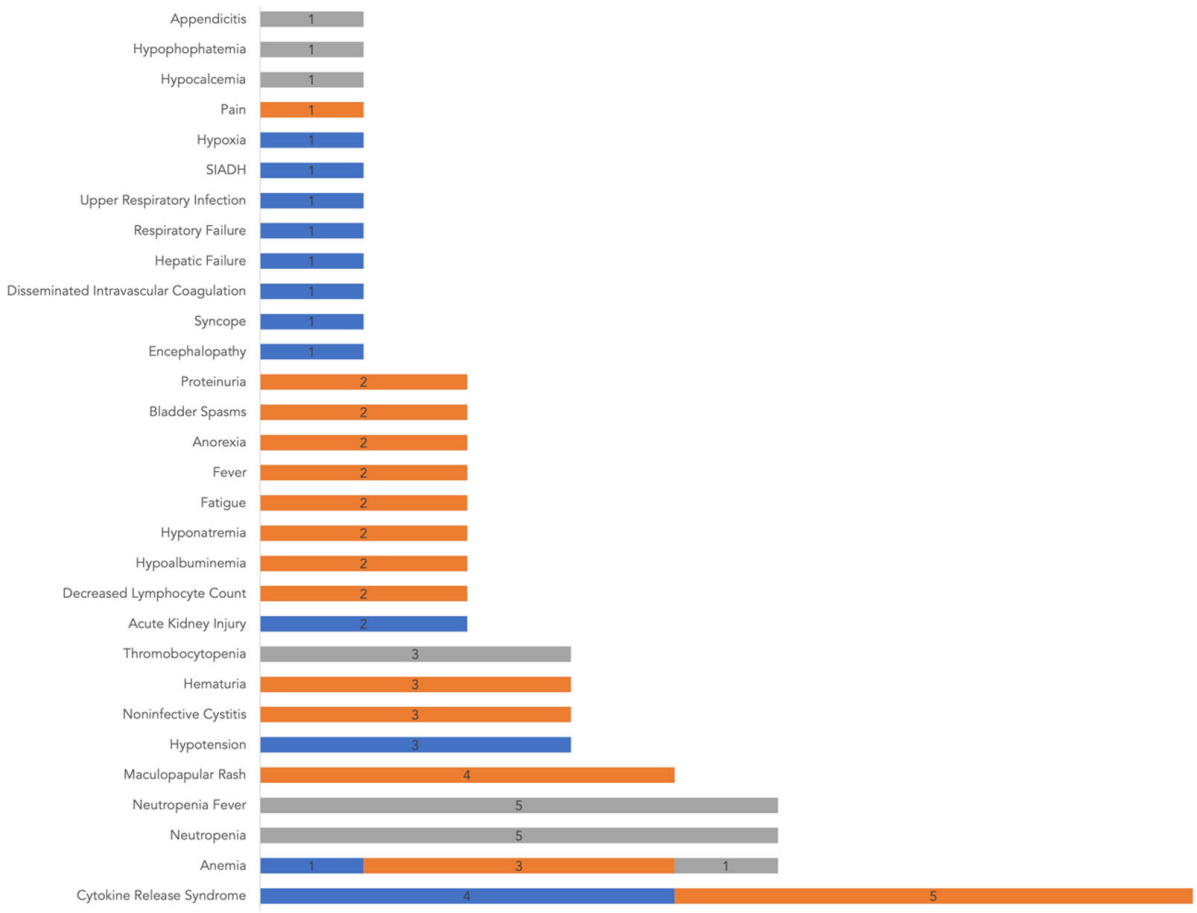

Figure 4. Frequency of dose–limiting toxicities in selected clinical trials
Reports the total incidences of DLTs across selected clinical trials

4. Discussion

CAR-T therapy is a form of personalized, immunological therapy that is currently under clinical investigation for treatment of solid tumors like prostate cancer. This review summarizes the preclinical efficacy CAR-T therapy in prostate cancer xenograft mice models and the findings of currently published clinical trials. Preclinical data indicates that CAR-T therapy is effective in tumor regression and eliciting immune responses; armored CAR-T therapy was even more effective in doing so. CAR-T therapy with a LD regimen is effective in infiltrating tumor tissue and modifying the tumor microenvironment, showing promise to clinically reduce PSA expression in patient tissue and improve outcomes in combination with other therapies. Based on the clinical results, dose–limiting toxicities (DLTs) can be reduced by adjusting the CAR-T doses and LD regimen timing, therefore maximizing CAR-T expansion after lymphocyte depletion.[28]

Currently, the challenges CAR-T therapy must overcome is the immunosuppression within the tumor microenvironment, anatomical infiltration, and viable antigen targets.[6,31] Preclinically, armored CAR-T cells not only effectively reduced tumor burden,[7,10–13,16–19,21,26] but also prolonged survival compared to their unarmored CAR-T cell counterparts.[8,13] Additionally, armored CAR-T demonstrated the capacity to infiltrate prostate tumor tissue,[10,11,18,23,26] elicit an inflammatory response,[12,17] and induce significantly higher rates of apoptosis in antigen–specific tissue.[18] Interestingly, there is strong clinical evidence to support that unarmored anti-PSMA CAR-T has high antitumor rates and strong T cell expansion with stem cell memory T cell subtype.[32] However, armored CAR-T cells are critical in eliminating solid tumors due to their ability to target the tumor microenvironment and enhance the therapy immune response.[33] A clinical trial testing anti-PSCA armored with Rimiducid, a lipid–permeable tacrolimus analogue, has shown to induce effective T-cell expansion and response persistence without any incidences of DLTs, neurotoxicity, or CRS.[34]

Clinical findings support the efficacy of CAR-T therapy with a LD regimen in modifying the tumor microenvironment. Junghans et al clinical trial testing the efficacy of a first generation anti-PSMA CAR-T demonstrated greater PSA%

declines in patients with lower CAR-T doses and higher subsequent IL-2 levels, suggesting that immune response of the microenvironment plays a critical role in tumor eradication.[30] After anti-dnTGFβR-PSMA CAR-T infusion and LD Regimen, T-cell rich stroma within the tumor microenvironment had elevated levels of T cell proliferation markers and increased PSMA levels, which were both associated with a decline in PSA levels.[28] Additionally, analysis of peripheral blood CAR-T cells 28 days after anti-PSCA CAR-T infusion with LD regimen had elevated CX3CR1 levels, which mimics the response to a PD-1 blockade therapy.[29] Therefore, the LD regimen plays a keystone role in modifying the tumor microenvironment to enhance the antitumor effects of CAR-T cells.[29] Carboplatin has been shown to modify the tumor microenvironment to augment anti-Lewis Y antigen CAR-T therapy response in prostate cancer mice models.[35] Docetaxel has also been shown to corroborate anti-PSMA CAR-T activity in xenograft models by reducing immunosuppressive markers in tumor tissue and enhancing T cell proliferation.[36]

Therefore, clinical evidence supports the efficacy and safety of CAR-T therapy for treatment of prostate cancer tumors.[28–30, 32, 34, 37] Patient 9's results of > 98% PSA decline from Narayan et al.[28] demonstrate the true capacity of CAR-T therapy in conjunction with LD Regimen, yet the treatment was aggressive and induced a myriad of DLTs. While Narayan et al.[28] delivered anti-dnTGFβR-PSMA CAR-T simultaneously with the LD regimen, Dorff et al.[29] prescribed the LD regimen during the days prior to unarmored anti-PSCA CAR-T infusion to ensure lymphocyte depletion occurs before maximum CAR-T expansion. Compared to other clinical trials,[28, 32, 38] Dorff et al.[29] suspects the reason that cohort members did not experience any high-grade neurologic toxicity or macrophage activation syndrome was due to the timing of the LD regimen or PSCA antigen target. Therefore, providing a low dose LD regimen followed by armored CAR-T therapy is a promising regimen to maximize CAR-T expansion and minimize DLTs when targeting solid prostate cancer. The LD regimen is suspected to be the reason for DLTs,[29] and the appropriate LD dosage and intervention to maximize CAR-T efficacy and minimize DLTs is a critical objective for ongoing and future clinical trials.

There are many clinical trials currently collecting data on the efficacy of CAR-T therapy on prostate cancer tumors; however, only few clinical trials have completed their investigation and published their data as peer reviewed journal articles. Therefore, little information was available on the long–term outcomes as most clinical data was from phase I trials. This review examined the efficacy of CAR-T therapy in treating prostate cancer tumors; however, it must be noted that comparisons were drawn between studies targeting different CAR-T antigens. Consequently, differences in outcomes between selected studies may be due to differences in the therapy itself.

This review supports that CAR-T therapy is an effective and safe treatment for prostate cancer tumors. Armored CAR-T cells and CAR-T therapy in conjunction with LD regimen have a strong potential for tumor eradication due to their ability to modify the tumor microenvironment. Future clinical trials may investigate the appropriate dosage of CAR-T infusions and combinational therapies to minimize DLTs.

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AUTHORS CONTRIBUTIONS

Amidala Geetaumesh conceptualized and designed the study. Amidala Geetaumesh, Sarah Swerdlow, and Hannah Chang wrote the first draft of the manuscript. Amidala Geetaumesh completed data acquisition and statistical analysis with Sarah Swerdlow. Priya Manhas Yun assisted in data collection and completed manuscript editing. Priya Manhas Yun and Dr. Eldo E Frezza reviewed and edited the manuscript. Each co-author contributed to either the delivery of the study or helped to devise the protocol. All authors have given final approval for the current version to be published.

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