T-Cell Engaging Antibodies: Management of Cytokine Release Syndrome (CRS) and Immune Effector-Associated Neurotoxicity Syndrome (ICANS)

Clinical Practice Guideline

Authors: Andrea Crespo, Tom Kouroukis, Leta Forbes, Lauren Chun, Daniela Gallo-Hershberg, Cassandra McKay

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Introduction

Objective

Provincial guidance and standardization of the management of T-cell engaging antibody-associated cytokine release syndrome (CRS) and immune effector-associated neurotoxicity syndrome (ICANS) has been identified as a quality and safety gap in Ontario. The objective of this guideline is to provide clinicians with consensus-based evidence informed recommendations for the optimal prevention and management of CRS and ICANS in adult patients who are being treated with a T-cell engaging antibody.

Background

T-cell engaging antibodies are an emerging class of medication to treat cancer. They are unique in that they simultaneously bind to tumour cells and T-cells to elicit a tumour-directed immune response. The targeting of multiple signalling pathways to direct immune cells can enhance the destruction of cancer cells when compared to traditional monoclonal antibodies.[1] There are several T-cell engaging antibodies approved for use in Ontario for the treatment of various cancer types (hematologic cancers, lung cancer and uveal melanoma). Additionally, there are numerous T-cell engaging antibody clinical trials open in Ontario. It is anticipated that this class of medication will expand to treat many more types of cancers in the future.

In addition to killing cancer cells, T-cell engaging antibodies can cause early side effects through the activation of endogenous T-cells, including CRS and ICANS. CRS is the most common toxicity and is caused by cytokine release in the tumour microenvironment. This leads to a systemic reaction that often presents with mild flu-like symptoms (such as fever and chills) but can also become severe and life threatening quickly. The incidence, timing, and onset of CRS varies by disease site and subtype, antibody product, route of administration (intravenous [IV] vs subcutaneous), and dosing schedule.[2] CRS is related to treatment dose intensity and mostly occurs soon after the first few doses, during the ramp-up phase of treatment.[3,4]

ICANS occurs rarely and is a syndrome of neurotoxicity with symptoms ranging from mild attention deficits to lethal cerebral edema.[5] It typically occurs together with CRS, or soon after CRS has resolved.[6]

Optimal prevention and management of these side effects is necessary. These side effects are not seen with most systemic treatments for cancer, and many clinicians starting to treat patients with T-cell engagers currently have limited experience with their management.

There are published guidance documents for management of CRS and ICANS; however, they are largely based on the experience of managing these toxicities with other T-cell engaging therapies, such as chimeric antigen receptor (CAR) T-cell therapies, and are focused on specific hematologic disease sites.[2,4,6,7] The rates of CRS and ICANS, as well as severity, are lower with T-cell engaging antibodies than with CAR T-cell therapies.[8] This clinical guideline provides practical guidance that is

specific for T-cell engaging antibody-induced CRS and ICANS in adult patients receiving these medications in Ontario.

Methods

This clinical practice guideline was developed by a multidisciplinary Working Group (WG) consisting of physicians (oncologists, hematologists), pharmacists, nurses, and administrators who are knowledgeable in the areas of systemic treatment delivery, T-cell engaging antibodies, and the management of CRS and ICANS. The WG reviewed current relevant guidelines and available literature on CRS and ICANS, with an emphasis on the optimal management of these toxicities in adult patients receiving T-cell engaging antibodies.

The CADTH Health Technology review, "Anticytokine Therapy and Corticosteroids for Cytokine Release Syndrome and for Neurotoxicity Following T-Cell Engager or CAR-T Cell Therapy" was used as the foundation for recommendations on the use of supportive care medications for CRS and ICANS management.[6] Other guidelines were examined and discussed, including "Consensus recommendations on the management of toxicity associated with CD3×CD20 bispecific antibody therapy"[2] and "International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma".[7] New literature published since the CADTH Health Technology review were the focus of the literature search for the clinical topics related to the role of corticosteroids and anticytokine therapy. Other key clinical questions were identified by the WG and literature related to these specific questions were additional areas of focus. All content was approached with an Ontario-specific lens. An iterative consensus-building process was used to develop a comprehensive practical guideline. Final guideline content was validated by clinical experts.

Literature Search Strategy

A literature search was conducted using Ovid MEDLINE(R) and PeHUB Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to June 06, 2024> and Embase <1996 to 2024 Week 23> on June 7, 2024, with date limits of January 1, 2024 – June 6, 2024. A subsequent search using Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to June 10, 2024> and Embase <1996 to 2024 Week 24> was conducted on June 11, 2024 with the date limits of January 1, 2020 – June 10, 2024. No methodological filters were applied to limit retrieval by publication type. Duplicates were manually removed in Mendeley Reference Manager, version v1.19.8. Grey literature was located through a targeted internet search, as well as utilizing previously identified Canadian and international organizations and sources. The grey literature search ran between June 5, 2024 and June 7, 2024. Results were limited to documents published between January 1, 2020 to June 7, 2024. Appendix 4 outlines the detailed search strategies.

After preliminary review of the search results, additional searches were performed using PubMed, GoogleScholar, articles referenced within other studies, Ontario Health (Cancer Care Ontario) Drug Formulary documents, manufacturer published product monographs and organization-specific CRS and ICANS management algorithms. Publications that were new since the CADTH 2024 HTA were the primary focus of the searches.

Finally, abstract titles from the American Society of Hematology Annual Meeting and Exposition (December 2024) were scanned and abstracts identified as potentially relevant to this guideline were reviewed.

Prevention of CRS and ICANS

CRS and ICANS can first present with mild symptoms and quickly progress to life-threatening symptoms. For this reason, prophylactic strategies are used to try and prevent their occurrence. There are current mitigation strategies in routine use; however, they are largely based on experience in the CAR T-cell setting, and improvements in prevention could further reduce the incidence of these concerning toxicities in the setting of T-cell engaging antibodies.[2,6,9]

Clinical Question 1:

What mitigation strategies are effective at reducing the incidence of CRS and ICANS?

Recommendation 1:

The use of ramp-up dosing strategies, corticosteroid-based premedications, and close monitoring with supportive care (e.g., hydration) can help prevent the incidence and decrease the severity of CRS and ICANS. Treatment route may also be taken into consideration. Subcutaneous formulations may be less likely to cause CRS than IV formulations.

SUMMARY OF EVIDENCE & DISCUSSION

The exact mechanism of CRS and ICANS associated with T-cell engaging antibodies is not fully understood. It is likely that the simultaneous binding of the antibody to targets on plasma and effector cells triggers a systemic immune response leading to the production of inflammatory cytokines and chemokines such as interleukins (e.g. IL-6), or tumour necrosis factors (e.g. TNF-α) and interferons (e.g., IFN-γ).[2,6,9] Current measures to prevent severe CRS include the incorporation of a step-wise dosing strategy (ramp-up phase), and administration of corticosteroid-based premedications.[4] The product monographs of T-cell engaging antibodies outline specific recommended premedications, which are described in Appendix 3 below. The use of anticytokine therapy (such as tocilizumab) as CRS and ICANS prophylaxis is less clear and is not currently a standard routine practice.[6]

Soltantabar *et al* conducted a meta-analysis and systematic review of the impact of treatment modality and route on CRS in multiple myeloma. CRS profiles of B-cell maturation antigen (BCMA) -targeting T-cell therapies delivered by IV or subcutaneous (subcut) administration were compared. They found that the proportion of CRS grades ≥ 3 may be lower for agents administered via the subcut route compared with IV (subcut (3 studies, n = 311) vs. IV (5 studies, n = 338): 0.0% (95% CI: 0.0–1%) vs. 4% (95% CI: 0.0–10%), respectively (P value < 0.01)).[8] Additionally, the incidence of CRS reported in the Canadian product monograph of glofitamab (a CD-20 targeting T-cell engaging

antibody given IV) is higher than epcoritamab (a CD-20 targeting T-cell engaging antibody given subcutaneously) with rates of 61.8% and 49.7%, respectively.[10,11]

Clinical Question 1.1: Is there a role for tocilizumab prophylaxis?

Recommendation 1.1:

At this time there is insufficient evidence to recommend routine use of tocilizumab prophylaxis to prevent CRS and ICANS. Emerging data is promising; however, further prospective studies are needed to confirm the optimal approach.

SUMMARY OF EVIDENCE & DISCUSSION

The pathophysiology of CRS and ICANS is incompletely understood; however, both IL-1 and IL-6 have been determined to be key mediators. The IL-1 receptor antagonist, anakinra, and the IL-6 receptor-blocking antibody, tocilizumab, are commonly used to treat immune toxicities. In mice, prophylactic tocilizumab and anakinra prevented ICANS and CRS without reducing antileukemia CAR T-cell activity, which has led to the investigation of these drugs to prevent CRS and ICANS in patients with hematologic malignancies receiving immune-engaging therapies.[12]

The CADTH health technology review attempted to answer the question "What is the clinical effectiveness and safety of prophylactic or early use of anticytokine therapy, corticosteroids, or both for the prevention of cytokine release syndrome and neurotoxicity following T-cell engager therapy or CAR-T cell therapy?". They looked at 5 single institution studies: 3 retrospective chart review studies and 2 prospective cohort studies. The studies were all in the adult hematology setting, and there was a mix of CAR-T and T-cell engager therapies. Tocilizumab was used as prophylaxis or evaluated for the effect of early administration in the management setting compared to corticosteroids. One study evaluated anakinra as ICANS prophylaxis. Upon analysis of the data, the authors concluded that prophylactic or early use of tocilizumab resulted in either a lower incidence of CRS (mostly grade 1) or no major difference in the incidence or severity of CRS. They determined that there was no difference in incidence, grade, or duration of CRS with prophylactic anakinra and that there was no difference in all grades of ICANS with early use or prophylactic tocilizumab, corticosteroids or anakinra.[6]

Since the review, abstracts and a letter have been published on this topic. Van de Donk *et al* analysed follow-up data on the effects of prophylactic tocilizumab for the reduction of CRS in heavily pretreated multiple myeloma patients who received teclistamab in the MajesTEC-1 study. At a median follow-up of 8.1 months (range, 0.9-13.2), 24 patients received prophylactic tocilizumab. CRS occurred in 6 patients (25%; 2 grade 1, 4 grade 2, no grade ≥3) and 3 patients each had 1 recurrent CRS event. The median time to CRS onset was 2 days (range, 1–3), and the median duration was 2 days (range, 2–4). CRS was managed with additional tocilizumab in 5/6 pts and steroids in 1/6. All CRS events resolved and none led to teclistamab discontinuation. Five patients had a neurotoxicity event (grade 1 dizziness; grade 1 headache; grade 1 insomnia; grade 2 headache; grade 2 immune effector cell-associated neurotoxicity syndrome). The overall response rate (n=22) was 73% (59% very good partial response or better).[13,14]

Kowalski *et al* explored the use of prophylactic tocilizumab in relapsed/refractory multiple myeloma patients treated with teclistamab, elranatamab, and talquetamab (n=72) at a single centre. The published abstract outlines a low rate of CRS (14%; 95% CI: 7%-24%) and ICANS (8%; 95% CI: 3%-17%). Nine of ten CRS events were grade 1 (teclistamab, elranatamab and talquetamab) and 1 was grade 2 (elranatamab). Two of six ICANS events were grade 1; 2 were grade 2 (teclistamab and talquetamab) and 2 were grade 3 (talquetamab). The authors concluded that preventive tocilizumab may be an effective; however, larger randomized studies are needed to confirm the results.[15]

Updated results of a phase 2 single arm, multicentre prospective study of patients who received prophylactic tocilizumab prior to the first ramp-up dose of teclistamab in the outpatient setting (OPTec) was described by Rifkin *et al*. Eleven patients have completed the ramp-up phase so far and are included in the analysis. To date, no patients experienced CRS or ICANS or required hospitalization. The safety profile is similar to MajesTEC-1.[16]

Korst *et al* evaluated the efficacy of prophylactic tocilizumab (8 mg/kg IV, maximum dose of 800 mg) given 1 hour prior to the first step-up dose of teclistamab to prevent CRS (n=29). Other premedication included dexamethasone 16 mg, clemastine 2 mg, and acetaminophen 1000 mg. CRS occurred in 3 of the 29 patients (10.3%); one patient had grade 1 CRS after step-up dose 1, one patient had grade 2 CRS after step-up dose 1, and one patient with grade 1 CRS after step-up dose 2 and grade 2 CRS after the first full dose. All CRS events were resolved completely. Both patients who developed grade 2 CRS despite prophylactic tocilizumab had high tumour burden (70%–80% MM cells in bone marrow [BM] biopsy) and rapidly progressive disease. Tocilizumab prophylaxis had no negative impact on the activity of teclistamab with 24 of the 29 patients (82.8%) achieving a partial response or better with ≥VGPR in 75.9%. With a median follow-up of 8.7 months, the median progression free survival (PFS) was not reached (12-month PFS:63.5%). Overall survival at 12 months was 72.2%.[17]

The WG discussed the available data and determined that it is insufficient to make a recommendation to use tocilizumab prophylaxis routinely. Although the data is promising, more robust studies are needed.

Clinical Question 1.2: Are there standard premedications that can be used as prophylaxis across all T-cell engaging antibodies?

Recommendation 1.2:

For most T-cell engaging antibodies, give the following premedication for CRS and ICANS prophylaxis:

- a corticosteroid (dexamethasone 16-20 mg or equivalent)
  AND
- an antihistamine (diphenhydramine 50 mg PO/IV or equivalent*),
  with or without
- acetaminophen 650 to 1000 mg PO

Refer to individual product monographs and/or appendix 3 for drug-specific considerations. Individual patient factors should also be taken into consideration.[18–24]

* Central nervous system (CNS) effects of diphenhydramine may make it challenging to identify ICANS. Consider cetirizine, which has a lower incidence of CNS effects.

SUMMARY OF EVIDENCE & DISCUSSION

The WG reviewed the various premedication strategies recommended within individual product monographs. They discussed and agreed that most patients should receive prophylaxis with a corticosteroid, antihistamine, and, if recommended in the product monograph, acetaminophen. They concluded that a standard approach could be considered for all drugs within the class, and that individual patient risk factors should be taken into consideration.

Clinical Question 1.3: Are there factors that increase the risk of developing CRS or ICANS?

Recommendation 1.3:

Data is still emerging around risk factors for CRS and ICANS with T-cell engaging antibodies. It appears that high tumour burden and higher risk disease may increase the risk of CRS and ICANS. Most published information is in the setting of relapsed/refractory multiple myeloma with teclistamab and it is unclear if it is applicable to other disease sites and drugs. More studies are needed to identify a full list of risk factors for the development of CRS and ICANS with T-cell engaging antibodies. Existing neurological conditions should be taken into consideration when evaluating risk for ICANS.

SUMMARY OF EVIDENCE & DISCUSSION

Two retrospective real world evidence studies evaluating the use of teclistamab in heavily pretreated multiple myeloma patients with higher risk disease suggest that the overall incidence of ≥ grade 3 CRS and ICANS was low (3.5% and 4.6%, respectively (n=110); or rare (n=124)). Efficacy and safety were similar to that reported for MajesTEC-1, and there was an overall trend towards a higher risk of high grade CNS and ICANS with heavily pretreated higher risk disease as well as a trend toward poorer outcomes with higher risk disease (defined as high risk cytogenetics, extra-medullary disease (EMD), ISS of 3, and/or or ≥ 60% bone marrow infiltration).[25,26]

Hamadeh *et al* retrospectively analysed whether prior exposure to T-cell redirecting therapies had any impact on the incidence of CRS with teclistamab at Memorial Sloan Kettering (n=72; 27 had prior exposure). Overall CRS in the entire cohort was 63% (all Grade 1 or 2). CRS rates differed significantly between cohorts 1 (prior exposure) and 2 (37% vs 80%; P = .0004) – higher rates of grade 2 were reported in cohort 2 but it was not statistically significant. High-risk cytogenetic features and number of prior lines of therapy were also significantly associated with the risk of CRS in univariate logistic regression analysis. Cohort 1 had no ICANS and 2 patients in cohort 2 had ICANS (no statistical analysis). The authors concluded that there is a lower risk of CRS with teclistamab if patients have had prior T-cell directed BCMA treatment and that these patients are ideal candidates for outpatient ramp-up.[27]

Other studies have looked at predicting patient risk based on drug-specific factors.[28,29] A meta-analysis and systematic review analysed the efficacy and safety of BCMA-targeted compared to non-BCMA targeted antibodies in relapsed/refractory multiple myeloma. It included 14 studies and a total

of 1473 patients (829 BCMA, 644 non BCMA). They did not find significant differences in the risks of CRS between the two groups (CRS, any grade: 64% vs. 66%, P = 0.84; grade ≥ 3: 1% vs. 1%, P = 0.36). Non-BCMA-targeted drugs were associated with a higher risk of ICANS (ICANS, any grade: 11%vs. 2%, P < 0.01) and lower risks of fatigue (any grade: 14% vs. 30%, P < 0.01) and pyrexia (any grade: 14% vs. 29%, P < 0.01). Non-BCMA had higher overall response rate (ORR) (74% vs 54%, P < 0.01). The authors concluded that non-BCMA targeting T-cell engaging antibodies for multiple myeloma were associated with a higher incidence of developing ICANS.[28] A review article by Van de Vyner *et al* describes factors that may trigger CRS and increase the risk for CRS as reported *in vitro*, *in vivo*, and in clinics. They identified a strong dependency on tumour antigen affinity, CD3 affinity, tumour burden, and expression level, a moderate dependency on target accessibility, indication, and cell types. Overall, the authors concluded that further studies to develop risk assessment tools and models are needed.[29]

Some notable abstracts have been published which outline other risk factors for CRS and ICANS that are being evaluated. Real world evidence from 7 international multiple myeloma academic centres (n=103) demonstrated that creatinine clearance (CrCl) < 30 mL/min did not appear to alter the incidence or severity of CRS in heavily pretreated multiple myeloma patients (14 pts had CrCl <30mL/min with 2 on hemodialysis).[30]

Chen *et al* characterized exposure and efficacy/safety of tarlatamab in advanced small cell lung cancer (SCLC) patients (n=412) in phase 1 studies. They looked at the impact of patient factors (brain/liver metastases, smoking status, number of prior lines of treatment, prior immunotherapy, tumour size) and found no clinically meaningful changes in safety based on evaluated patient specific covariates.[31]

Dima *et al* evaluated the impact of older age and toxicity effects of teclistimab in patients with relapsed/refractory multiple myeloma. Retrospective data from 5 US academic centres (n=102) was evaluated; 33 (32%) were above the age of 70 years (older) with a median age of 75 (range 71-87) years, a median of 6 lines of therapy, 58% had high risk cytogenetics, and 39% EMD. In most cases, CRS was grade 1-2, and CRS rates were similar between the older and younger patient groups (67% vs 64%, p=0.7). Likewise, most ICANS events were grade 1-2, and rates were comparable between the two groups (21% vs 11%, p=0.17). High grade CRS and ICANS were infrequent but led to poor patient outcomes in the cohort.[32] Mian *et al* conducted a retrospective analysis utilizing the International Myeloma Foundation (IMF) immunotherapy database to understand the outcomes of older adults (age ≥70), including frail patients treated in the real-world with teclistamab (n=81). Frail older adults showed a trend towards higher rates of ≥ grade 2 CRS and ≥ grade 2 ICANS. They concluded that teclistamab can be safely utilized in older adults including frail older adults; however, additional proactive supportive care may be required to further optimize outcomes.[33]

Real world evaluation of relapsed/refractory multiple myeloma patients treated with teclistamab across 13 US academic centres (n=385) revealed comparable rates of CRS and ICANS relative to the MajesTEC-1 study, and most were limited to grade 1 or 2. Multivariable logistic regression models were fitted to estimate the effects of covariates on CRS and ICANS events, with a particular focus on grade ≥ 2 CRS, any-grade ICANS, and the combination of CRS grade ≥ 2 and/or any-grade ICANS. They found a significantly higher risk of CRS grade ≥ 2 and/or any-grade ICANS in patients with baseline platelets < 50 and/or ECOG ≥ 2 (which may reflect bone marrow disease burden).[34]

A retrospective single centre real world evidence trial of teclistamab in multiple myeloma patients (n=33) who were heavily pretreated, older, had a higher disease burden, organ dysfunction, and poor

performance status experienced a lower to similar incidence of CRS and similar incidence of ICANS compared to those in MajesTEC -1.[35]

Exploratory analysis of patients with large B-cell lymphoma with 2+ previous lines of treatment (median 3) who received glofitamab (n=154) looked at the association of total metabolic tumour volume (TMTV) and CRS. Higher TMTV was associated with an increased risk of Grade 2+ CRS. (first, second, third, and fourth TMTV quartiles was 2.8%, 11.1%, 16.7%, and 38.9%, respectively (Chi-square=16.273; degrees of freedom=1; $p<0.0001$)).[36]

The WG discussed the data and the fact that it is still emerging around risk factors for CRS and ICANS with T-cell engaging antibodies. Most of the published information is in the setting of relapsed/refractory multiple myeloma in patients treated with teclistamab. It is unclear at this time if findings are applicable to other disease sites and drugs.

Management of CRS

T-cell engaging antibodies actively treat many types of cancer. Unfortunately, they are also associated with toxicities related to immune activation, most commonly in the form of CRS.[2]

Incidence rates vary for approved T-cell engaging antibodies from 14 to 89%. The majority are grade 1-2 and most occur shortly after the ramp-up doses or first full doses (See Appendix 2). The American Society for Transplantation and Cellular Therapy (ASTCT) guidelines established a consensus grading system (grade 1 to 4) for both CRS and ICANS. The signs and symptoms of CRS can range from mild flu-like symptoms (e.g., fever, myalgia, headache, and fatigue) to life-threatening conditions (e.g., vasodilatory shock, capillary leak, hypoxia, and end-organ dysfunction). According to this grading, CRS severity is graded based on 3 clinical parameters, which are fever, hypotension, and hypoxia.[6]

Clinical Question 2:

What is the appropriate management of CRS based on grade?

Recommendation 2:

CRS should be managed according to the grade of severity. Table 1 summarizes consensus recommendations for management of CRS by grade.

Table 1: CRS Management by Grade[2,6,7]

CRS Grade and Definition*	Management
Grade 1 Fever ≥ 38◦C	Provide supportive care (e.g., hydration, acetaminophen 650-1000 mg PO q6-8h). Check blood pressure, pulse, temperature, and evaluate for any new symptoms such as weakness, confusion, hypoxia. Monitor vital signs q4h and prn. Assess for infection. Start dexamethasone 10 mg daily until resolved. Consider tocilizumab if no resolution after 48 hrs and negative blood cultures, especially in higher risk patients.
Grade 2 Fever with hypotension not requiring vasopressors and/or hypoxia requiring supplemental oxygen.	Urgent evaluation (in outpatient urgent care clinic or the emergency department, if patient coming from home). Inpatient management for most, unless outpatient urgent care clinic/infusion center is experienced in managing these patients and the patient has no hypoxia. Monitor vital signs at least q4h and prn. Supportive care: Acetaminophen 650-1000 mg PO q6-8h as needed. IV fluids/supplemental oxygen as appropriate. Dexamethasone 10 mg q12h until symptoms resolve. Evaluate for sepsis and consider empiric antibiotics. Tocilizumab 8 mg/kg IV (up to 800 mg) if symptoms persist despite corticosteroid. May repeat q8h for up to 3 doses.** Consider alternative agent (e.g., anakinra*** or siltuximab 11 mg/kg once) if persistent symptoms after 2 doses of tocilizumab.

*adapted from the ASTCT consensus grading[2,6]
**Maximum 3 doses within a 6-week period.
*** For patients with concurrent ICANS, there is a low threshold to switch to anakinra. Anakinra doses vary in the literature and based on the clinical scenario. Give a minimum of 100 mg per day. Doses up to 400 mg total per day have been reported. Reach out to centres with more experience for advice if needed.

CRS Grade and Definition*	Management
Grade 3 Fever with hypotension requiring a vasopressor and/or hypoxia requiring high-flow cannula, face mask, nonrebreather mask, or Venturi mask.	Admit to ICU or other monitored hospital setting for hemodynamic monitoring, IV fluids, oxygen therapy, and vasopressors. Supportive care: Acetaminophen 1000 mg PO q 6-8h, as needed. IV fluids/supplemental oxygen as appropriate. Dexamethasone 10-20 mg IV q6h until resolution to grade 1, followed by dexamethasone taper. If no rapid improvement (within 24 hours) switch to methylprednisolone IV up to 1 to 2 grams per day. Tocilizumab 8 mg/kg IV (up to 800 mg). May repeat q8h for up to 3 doses.** Evaluate for sepsis and consider empiric antibiotics. Consider alternative agent (e.g., anakinra*** or siltuximab 11 mg/kg once) if persistent symptoms after 2 doses of tocilizumab. If refractory hypotension/hypoxia and not in ICU, admit to ICU.

*adapted from the ASTCT consensus grading[2,6]

**Maximum 3 doses within a 6 week period.

*** For patients with concurrent ICANS, there is a low threshold to switch to anakinra. Anakinra doses vary in the literature and based on the clinical scenario. Give a minimum of 100 mg per day. Doses up to 400 mg total per day have been reported. Reach out to centres with more experience for advice if needed.

CRS Grade and Definition*	Management
Grade 4 Fever with hypotension requiring multiple vasopressors and/or hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, mechanical ventilation).	Admit to ICU for hemodynamic monitoring, IV fluids, oxygen therapy/positive pressure/mechanical ventilation, and vasopressors. Supportive care: Acetaminophen 1000 mg PO q6-8h as needed. IV fluids/supplemental oxygen, as appropriate. Dexamethasone 20 mg IV q6h until resolution to grade 1, followed by dexamethasone taper. If no rapid improvement (within 24 hours) switch to methylprednisolone IV up to 1 to 2 grams per day. Tocilizumab 8 mg/kg IV (up to 800 mg). May repeat in 8 hours.** Evaluate for sepsis and consider empiric antibiotics. Switch to alternative agent (e.g., anakinra*** or siltuximab 11 mg/kg once) if persistent grade 4 symptoms or rapid progression after 24h or2 doses of tocilizumab.

*adapted from the ASTCT consensus grading[2,6]
**Maximum 3 doses within a 6-week period.
*** For patients with concurrent ICANS, there is a low threshold to switch to anakinra. Anakinra doses vary in the literature and based on the clinical scenario. Give a minimum of 100 mg per day. Doses up to 400 mg total per day have been reported. Reach out to centres with more experience for advice if needed.

SUMMARY OF EVIDENCE & DISCUSSION

The WG discussed the published guidance around CRS management by grade, including the CADTH HTA (which summarized NCCN, ASCO, EBMT and JACIE, SITC), the ASH guidelines for the management of CD20 directed bispecific antibody toxicities and the International Myeloma Working Group's guideline on the optimal use of T-cell engaging bispecific antibodies in multiple myeloma.[2,6,7] Discussions focussed on confirming recommendations that are consistent among all of the references, determining the level of detail to include, current practices in Ontario, and developing consensus recommendations in areas where the references had differing information.

Management of ICANS

ICANS usually starts shortly after the onset of CRS, and higher grades of ICANS often occur concurrently with higher grade of CRS. ICANS can, however, occur in the absence of CRS. Symptoms of ICANS range from confusion, encephalopathy to seizures, and coma or death. Other potential symptoms include aphasia, facial paresis, myoclonus/tremors, and hemifacial spasms. In the ASTCT grading system, ICANS grade is determined by ICE (immune effector cell-associated encephalopathy) score (refer to Table 2), depressed level of consciousness, seizure, motor abilities, and elevated ICP (intracranial pressure/cerebral edema).[2,6]

Clinical Question 3:

What is the appropriate management of ICANS based on grade?

Recommendation 3:

ICANS should be managed according to the grade of severity. Table 3 summarizes consensus recommendations for management of ICANS by grade.

Table 2: ICE Scoring System to Assess Severity of Neurotoxicity[2,6]

ICE Scoring System	Score*
Orientation to year, month, city, hospital	4 points
Naming 3 objects	3 points
Following simple commands	1 point
Writing standard sentence	1 point
Attention to count backward from 100 by 10	1 point

*ICE score to be assessed twice daily and as clinically indicated during the ramp-up phase. Assess as clinically indicated thereafter.

Table 3: ICANS Management by Grade[2,6,7]

ICANS Grade and Definition*	Management
Grade 1 ICE score: 7 to 9 with no depressed level of consciousness.	Patients may be managed in the outpatient setting if appropriate resources are available (patients can be monitored closely in a setting with experienced staff); otherwise, admit to hospital (monitor vitals and ICE at least Q4-6h). Higher risk patients should be admitted upon presentation. Observe and provide supportive care (e.g., aspiration precautions, hold medications that cause CNS depression, etc.). Consider early administration of dexamethasone 10 mg IV × 1. Consider non sedating antiepileptic drugs for seizure prophylaxis (e.g., levetiracetam). If concurrent CRS, treat CRS aggressively according to grade and prioritize use of steroids and second line anakinra**. Admit to hospital in a monitored setting if ongoing CRS/ICANS symptoms.

*as defined by ASTCT consensus grading

**Tocilizumab is not recommended for ICANS in the absence of concurrent CRS. For patients with concurrent CRS, there is a low threshold to switch to anakinra. Anakinra doses vary in the literature and based on the clinical scenario. Give a minimum of 100 mg per day. Doses up to 400 mg total per day have been reported. Reach out to centres with more experience for advice if needed.

ICANS Grade and Definition*	Management
Grade 2 ICE score: 3 to 6; and/or mild somnolence awaking to voice.	Admit to hospital in a monitored setting to assess for ongoing CRS/ICANS symptoms (vitals and ICE at least q4h). Dexamethasone 10 mg IV q6h x 1 to 2 doses. If symptoms resolve, taper off or discontinue dexamethasone and continue to monitor. If continued or worsening symptoms at 12-24 hours, escalate to grade 3 management. Consider non sedating antiepileptic drugs for seizure prophylaxis (e.g. levetiracetam). If concurrent CRS, treat CRS aggressively according to grade and prioritize use of steroids and second line anakinra**. If no improvement within 48 hours, consider adding anakinra. EEG, CT, and/or MRI are recommended. Neurology consult, if available.
Grade 3 ICE score: 0 to 2; and/or depressed level of consciousness awakening only to tactile stimulus; and/or any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on electroencephalogram (EEG) that resolve with intervention; and/or focal or local edema on neuroimaging.	Admit to ICU. Neurology consult, if available. Start high dose corticosteroid (e.g., methylprednisolone IV up to 1-2 grams per day or dexamethasone 10-20 mg IV q6h), followed by taper if resolves to grade 1. Start non-sedating antiepileptic drugs for seizure prophylaxis (e.g. levetiracetam). Add anakinra** if no improvement (e.g., within 24 hours). EEG, CT, MRI, and CSF evaluation are recommended.

*as defined by ASTCT consensus grading

**Tocilizumab is not recommended for ICANS in the absence of concurrent CRS. For patients with concurrent CRS, there is a low threshold to switch to anakinra. Anakinra doses vary in the literature and based on the clinical scenario. Give a minimum of 100 mg per day. Doses up to 400 mg total per day have been reported. Reach out to centres with more experience for advice if needed.

ICANS Grade and Definition*	Management
Grade 4 ICE score: 0 (patient is unarousable and unable to perform ICE); and/or stupor or coma; and/or life-threatening prolonged seizure (> 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between; and/or diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilledema, sixth cranial nerve palsy, or papilledema; or Cushing triad.	Admit to ICU. Neurology consult. Start high dose corticosteroid (e.g., methylprednisolone IV up to 1-2 grams per day or dexamethasone 10-20 mg IV q6h), followed by taper if resolves to grade 1. Start non sedating antiepileptic drugs for seizure prophylaxis (e.g., levetiracetam). Add anakinra** if no improvement (e.g., within 24 hours). If symptoms persist, consider other agents (e.g., siltuximab 11 mg/kg). EEG, CT, MRI, and CSF evaluation are recommended.

*as defined by ASTCT consensus grading

**Tocilizumab is not recommended for ICANS in the absence of concurrent CRS. For patients with concurrent CRS, there is a low threshold to switch to anakinra. Anakinra doses vary in the literature and based on the clinical scenario. Give a minimum of 100 mg per day. Doses up to 400 mg total per day have been reported. Reach out to centres with more experience for advice if needed.

SUMMARY OF EVIDENCE & DISCUSSION

The WG discussed the published guidance around ICANS management by grade, including the CADTH HTA (which summarized NCCN, ASCO, EBMT and JACIE, SITC), the ASH guidelines for the Management of CD20 directed bispecific antibody toxicities and the International Myeloma Working Group's guideline on the optimal use of T-cell engaging bispecific antibodies in multiple myeloma.[2,6,7] Discussions focussed on confirming recommendations that are consistent among all of the references, determining the level of detail to include, current practices in Ontario, and developing consensus recommendations in areas where the references had differing information.

Outpatient Ramp-Up

CRS is most likely to occur during the ramp-up phase of T-cell engaging antibody administration. Most clinical trials and product monographs suggest inpatient admission for monitoring during this time. Outpatient management of patients receiving T-cell engaging antibodies, including during the ramp-up phase, could reduce resource utilization, improve access to treatment, and improve the patient experience.[37–39]

Clinical Question 4:

What factors need to be taken into consideration when determining who can receive ramp-up doses in the outpatient setting?

Recommendation 4:

Current data suggests that outpatient ramp-up may be done safely for many patients. Clinical and logistical factors should be taken into consideration when determining eligibility for outpatient ramp-up. Priority should be given to patients with:

- good performance status,
- lower disease burden,
- fewer comorbidities,
- the ability to stay close to a hospital that is able to treat CRS/ICANS and
- adequate home monitoring and caregiver support.

The WG recommends that centres develop local experience in managing T-cell engaging antibodies and comfort with CRS and ICANS in the inpatient setting. With local expertise, centres can look at transitioning to outpatient ramp-up in appropriate patients. Centres may want to consider developing a mentorship with centres who have experience in outpatient ramp-up.

SUMMARY OF EVIDENCE & DISCUSSION

Derman *et al.* (2024) conducted a panel interview of oncology practices with emergent experience of teclistamab in the real world (TecPIONEER Study). This consisted of panel interviews of oncology practices in the US (20 clinicians, 19 hospitals); all treating multiple myeloma patients receiving teclistamamb. Twelve centres (86%) provided inpatient ramp-up; 5 (26%) practiced outpatient/hybrid and 2 (11%) of the practices reported tocilizumab for CRS prophylaxis. Tocilizumab was uniformly used to treat grade 2+ CRS. Premedications were given as per the product monograph at all practice sites. Corticosteroids were the preferred treatment for neurotoxicity. Practices delivering outpatient ramp-up admitted patients if CRS occurred. No clinicians had any patient with grade 3+ CRS, and neurotoxicity was reported as rare and low grade. Clinicians indicated that for patients with higher disease burden, more comorbidities, and lack of caregiver support, they may prefer inpatient ramp-up even when the outpatient option is available.[38]

A French abstract described a monocentric experience of outpatient ramp-up dosing of teclistamab in relapsed and refractory multiple myeloma patients and outlined the eligibility for outpatient ramp-up dose administration (n=8) at their centre. It was based on clinical and logistical criteria: general condition maintained, no active infection, no high tumor burden or very rapidly progressing disease and the patient agreeing to stay within 30 minutes of the site for 48 hours after each ramp-up dose and after the first full dose. Home monitoring consisted of temperature, blood pressure and oxygen saturation by a homecare nurse twice a day for 15 days. Patients and caregivers were trained in self-monitoring for CRS and were provided with a blood pressure monitor and an oximeter. Patients were given a practical drug information sheet. Oral dexamethasone was available at home in case of emergency with 24-hour hospital contacts in the event of grade 2+ CRS or any other complication.[39]

A published abstract described the real-world treatment outcomes of teclistamab under an outpatient model for ramp-up dosing administration. It detailed characteristics, rates, and severity of CRS and ICANS in patients with multiple myeloma who received outpatient ramp-up at the Mayo Clinic (n=39). Eight (21%) had high-risk cytogenetics and 14 (36%) had prior exposure to other BCMA targeted therapies. Prevalent comorbidities included anemia (77%), hypertension (56%), lytic bone lesions (51%), neutropenia (49%), and hypogammaglobulinemia (41%). Renal impairment or failure was observed in 31%. The authors concluded that CRS rate and severity was comparable with other real-world evidence generated from various data sources and that outpatient ramp-up is safe and feasible.[37]

Appendix 1: Acknowledgements

T-cell Engaging Antibodies Implementation Working Group

Member	Affiliation(s)	Conflict of Interest Declarations
Dr. Leta Forbes, Co-chair	Provincial Head, Systemic Treatment Program, Ontario Health (Cancer Care Ontario) Co-chair	No relevant conflicts of interest to declare.
Dr. Tom Kouroukis Co-chair	Clinical Lead, Quality Care and Access, CMH & PDRP Hematology Cancer Lead, Ontario Health (Cancer Care Ontario)	No relevant conflicts of interest to declare.
Andrea Crespo Primary guideline author	Senior Pharmacist, Systemic Treatment Program, Ontario Health (Cancer Care Ontario)	No relevant conflicts of interest to declare.
Lauren Chun Project Lead	Lead, Specialized Services Oversight, Ontario Health (Cancer Care Ontario)	No relevant conflicts of interest to declare.
Daniela Gallo-Hershberg	Pharmacist, Group Manager, Systemic Treatment Program, Ontario Health (Cancer Care Ontario)	No relevant conflicts of interest to declare.
Cassandra McKay	Group Manager, Specialized Services Oversight, Ontario Health (Cancer Care Ontario)	No relevant conflicts of interest to declare.
Marina Bitton	Director, Cancer Care, Cardiology and Critical Care, North York General Hospital	No relevant conflicts of interest to declare.
Dr. Christine Chen	Medical Director, UHN-Princess Margaret	No relevant conflicts of interest to declare.
Dr. Sathish Gopalakrishnan	CMH Director, Health Sciences North	No relevant conflicts of interest to declare.
Dr. Rasna Gupta	Hematologist and oncologist, Windsor Regional Hospital	No relevant conflicts of interest to declare.
Dr. Lisa Hicks	Hematologist, Unity Health - St. Michael's Hospital	No relevant conflicts of interest to declare.
Laurie Ann Holmes	Nurse Educator, The Ottawa Hospital	No relevant conflicts of interest to declare.
Dr. Jai Jayakar	Hematologist, Southlake Regional Health Centre	No relevant conflicts of interest to declare.

Member	Affiliation(s)	Conflict of Interest Declarations
Dr. Shaqil Kassam	Medical Oncologist, Southlake Regional Health Centre	No relevant conflicts of interest to declare.
Dr. Philip Kuruvilla	Medical Oncologist, William Osler Health System	No relevant conflicts of interest to declare.
Dr. Nicole Laferriere	Hematologist, Regional Cancer Care, Thunder Bay Regional Health Sciences Centre	No relevant conflicts of interest to declare.
Linda Liu	Oncology Pharmacist, Michael Garron Hospital	No relevant conflicts of interest to declare.
Dr. Lee Mozessohn	Hematologist, Sunnybrook Odette Cancer Centre	No relevant conflicts of interest to declare.
Dr. Martha Louzada	Hematologist, London Health Sciences Centre	No relevant conflicts of interest to declare.
Dr. Farheen Manji	Hematologist, Trillium Health Partners	No relevant conflicts of interest to declare.
Margaret Mayer	Auto SCT Program Lead, Grand River Hospital	No relevant conflicts of interest to declare.
Laura Olmi	Advance Practice Nurse Educator, UHN – Princess Margaret Cancer Centre	No relevant conflicts of interest to declare.
Christine Piescic	Manager, Hematology Programs, Systemic Therapy & Oncology Satellite Sites, Royal Victoria Hospital	No relevant conflicts of interest to declare.
Devon Pilkington	Registered Nurse & Clinical Nurse Educator, London Health Sciences Centre	No relevant conflicts of interest to declare.
Tessa Senneker	Clinical Oncology Lead Pharmacist, Kingston Health Sciences Centre	No relevant conflicts of interest to declare.
Dr. Xinni Song	Medical Oncologist, The Ottawa Hospital	No relevant conflicts of interest to declare.
Lily Spasic	Manager, Oncology Pharmacy, Royal Victoria Hospital	No relevant conflicts of interest to declare.

Significant Contributors:

Kimberley Kerr, Specialist, Medical Librarian (Research Office), Ontario Health
Sylvia Rudnicki, Systemic Treatment Program, Ontario Health (Cancer Care Ontario)
Valerie Thompson and Sarah McBain, Health Literacy and Patient Education Team, Ontario Health (Cancer Care Ontario)

Appendix 2: T-Cell Engaging Antibodies and CRS[10,11,18–24]

Drug Name	Route	Indications	Target	CRS incidence	Mediatn time to CRS onset	CRS duration
Blinatumomab	IV	B-cell precursor acute lymphoblastic leukemia (ALL)	CD19	14%	2 days	-
Tebentafusp	IV	Metastatic uveal melanoma (HLA-A*02:01-postive)	gp100 peptide HLA-A*02:01	89%	0 days (day of infusion)	2 days
Teclistamab	Subcut	Multiple myeloma (after at least three prior lines of therapy)	B-cell maturation antigen (BCMA)	72% Grade 1: 50% Grade 2: 21% Grade 3: 0.6% Grade 4: 0%	2 days	2 days
Epcoritamab	Subcut	Diffuse large B-cell lymphoma (DLBCL) (after at least 2 lines of therapy)	CD20	49.7%	2 days	3 days
Glofitamab	IV	Diffuse large B-cell lymphoma (DLBCL) (after at least 2 lines of therapy)	CD20	61.8% Grade 1:45.4% Grade 2:12.5% Grade 3: 2.6% Grade 4: 1.3%	13.4 hours	40.8 hours
Elranatamab	Subcut	Multiple myeloma (after at least 3 prior lines of therapy)	B-cell maturation antigen (BCMA)	57.9% Grade 1:43.7% Grade 2:13.7% Grade 3: 0.5% Grade 4: 0%	2 days	2 days
Tarlatamab	IV	Extensive stage small cell lung cancer (ES-SCLC)	DLL3	55.1% Grade 1: 34.2% Grade 2: 19.3% Grade 3: 1.1% Grade 4: 0.5%	15.1 hours	-
Talquetamab	Subcut	Multiple myeloma (after at least 3 prior lines of therapy)	GPRC5D	76.7%	27 hours	17 hours
Mosunetuzumab	IV	Follicular lymphoma (after at least 2 prior lines of therapy)	CD20	39% Grade 1: 28% Grade 2: 15% Grade 3: 2% Grade 4: 0.5%	5 hours	3 days

Appendix 3: Premedications and Monitoring

10,11,18–24

Drug Name	Premedications	Doses	Recommended Monitoring
Blinatumomab	**MRD-positive ALL**: Prednisone 100 mg intravenously or equivalent (e.g., dexamethasone 16 mg)	1 hour prior to the first dose of each cycle.	**MRD-positive ALL** First 3 days of cycle 1 and the second 2 days of cycle 2. **Relapsed or Refractory ALL** First 9 days of cycle 1 and the second 2 days of cycle 2.
	Relapsed or Refractory ALL: Dexamethasone 20 mg intravenously	1 hour prior to the first dose of each cycle.	
Tebentafusp	**IV fluids** to minimize the risk of hypotension (associated with CRS).	Prior to infusion	16 hours after first three infusions
Teclistamab	**Corticosteroid** (oral or intravenous dexamethasone, 16 mg) **Antihistamine** (oral or intravenous diphenhydramine, 50 mg or equivalent) **Antipyretics** (oral or intravenous acetaminophen, 650 mg to 1000 mg or equivalent)	1 to 3 hours before each dose for first three doses	48 hours for all doses for first three doses
Epcoritamab	**Prednisolone** (100 mg oral or IV) or equivalent	30-120 minutes prior to each dose of cycle 1 AND for three consecutive days after each dose of cycle 1	24 hours for first full dose (day 15 of cycle 1)
	Diphenhydramine (50 mg oral or IV) or equivalent **Acetaminophen** (650 to 1000 mg oral)	30-120 minutes prior to first dose	
Glofitamab	**Obinutuzumab** – 1000 mg dose	On cycle 1 day 1 (7 days prior 1st dose)	10 hours after 1st dose.
	Intravenous glucocorticoid (20 mg dexamethasone or 100 mg prednisone/prednisolone or 80 mg methylprednisolone)	1 hour before infusion for cycle 1-3.	
	Oral analgesic/anti-pyretic (1000 mg acetaminophen/paracetamol)	At least 30 minutes before infusion for all cycles.	
	Anti-histamine (50 mg diphenhydramine (IV/PO)	At least 30 minutes before infusion for all cycles.	
Elranatamab	**Acetaminophen** (or equivalent) 650 mg orally **Dexamethasone** (or equivalent) 20 mg orally or intravenously **Diphenhydramine** (or equivalent) 25 mg orally	1 hour before first three doses.	48 hours after each ramp--up dose (or in proximity to healthcare facility)
Tarlatamab	**Dexamethasone** (or equivalent) 8 mg of intravenously	Within 1 hour prior to infusion on Day 1 and Day 8 (Cycle 1).	24 hours for Day 1 and Day 8 for Cycle 1
	1 litre of **normal saline** intravenously (over 4-5 hours)	Immediately after infusion on Day 1,8, and 15 (Cycle 1).	
Talquetamab	**Corticosteroid** (oral or intravenous dexamethasone, 16 mg or equivalent) **Antihistamine** (oral or intravenous diphenhydramine, 50 mg or equivalent)	1 to 3 hours before each dose.	48 hours after each ramp--up dose (or in proximity to healthcare facility)

	Antipyretics (oral or intravenous acetaminophen, 650 mg to 1000 mg or equivalent)		
Mosunetuzumab	**Corticosteroid** (Dexamethasone 20 mg intravenous or methylprednisolone 80 mg intravenous)	At least 1 hour prior to infusion for cycle 1 and 2.	-
	Antihistamine (Diphenhydramine hydrochloride 50 mg – 100 mg or equivalent oral or intravenous antihistamine)	At least 30 minutes prior to infusion for cycle 1 and 2.	
	Antipyretic (oral acetaminophen 500 mg to 1000mg)	At least 30 minutes prior to infusion for cycle 1 and 2.	

Appendix 4: Literature Search Strategy

Date Range: January 1, 2020 – June 11, 2024
Language: English
Database(s): Medline and Embase

Medline:
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to June 06, 2024>

1 Cytokine release syndrome/ or Cytotoxicity, Immunologic/ or Cytokines/ 219124
2 (CRS or Cytokine Release Syndrome).mp. 20116
3 neurotoxicity syndromes/ 7091
4 (ICANS or "Immune effector cell-associated neurotoxicity syndrome").mp. 568
5 (BsAbs or "bispecific T-cell engag*" or BTEs or BITE or BiTEs or "BiTEs gene" or "t cell engag*" or "T-cell" or "bispecific T-Cell engager therapy" or TCE).mp. 59526
6 (Chimeric antigen receptor or CAR-T).mp. 14291
7 ("anti-cytokine therap*" or "anticytokine therap*" or "anticytokine agent*" or "anti-cytokine agent*").mp. 710
8 adrenal cortex hormones/ 71505
9 corticosteroid*.mp. 128278
10 1 or 2 236335
11 3 or 4 7537
12 10 or 11 243280
13 5 or 6 73232
14 8 or 9 166485
15 7 or 14 167148
16 12 and 13 and 15 139
17 limit 16 to yr="2024" 13

Embase:
Ovid Embase <1996 to 2024 Week 23>

1 Cytokine release syndrome/ or Immunocytotoxicity/ or Cytokine/ 317,363
2 (CRS or Cytokine Release Syndrome).mp. 36,748
3 "toxicity and intoxication"/ 1,321
4 (ICANS or Immune effector cell-associated neurotoxicity syndrome).mp. 2,475
5 (T-cell engager* or TCE or Chimeric antigen receptor or CAR-T).mp. 45,620
6 T-cell therap*.mp. 19,296
7 (anti-cytokine therap* or anticytokine therap*or anticytokine agent* or anti-cytokine agent*).mp. 630
8 corticosteroid/ 307,581
9 corticosteroid*.mp. 407,318
10 1 or 2 or 3 or 4 343,525
11 5 or 6 or 7 50,317
12 8 or 9 407,318
13 10 and 11 and 12 1,035
14 limit 13 to yr=”2024” 59

Medline:

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to June 10, 2024>

1 exp antibodies, bispecific/ 4,458
2 ((bi-specific or bispecific) adj1 (antibod* or therap*)).ti,ab,kw. 4,533
3 ((bispecific or bi-specific or antibod*) adj2 t cell engag*).ti,ab,kw. 1,162
4 (BsAb* or BTEs or BiTEs gene).ti,ab,kw. 1,180
5 Pre-exposure prophylaxis/ or risk assessment/ or risk factors/ 1,234,472
6 ((prophyla* or prevent* or protect*) adj1 (therap* or treatment* or management or disease* or medicine*)).ti,ab,kw. 97,452
7 tocilizumab.ti,ab,kw. 7,011
8 (risk adj1 (stratification or assessment or evaluation or profile or predict* or increase* or calculator* or model or factor* or high or higher or intermedia* or low or lower or identification or status)).ti,ab,kw. 1,728,147
9 exp Neoplasms/ 4,045,648
10 (cancer or cancers or cancerous or neoplas* or tumor or tumors or tumour or tumours or leukemia or lymphoma or melanoma or carcinoma or cyst or neuroblastoma or malignan* or carcinoma* or adenoma or polyp or polyps or myeloma).ti,ab,kw. 4,660,319
11 exp cytokine release syndrome/ 2,546
12 (CRS or cytokine release syndrome).ti,ab,kw. 19,236
13 (ICANS or immune effector cell-associated neurotoxicity syndrome).ti,ab,kw,sh. 664
14 1 or 2 or 3 or 4 7,217
15 5 or 6 or 7 or 8 2,441,076
16 9 or 10 5,520,060
17 11 or 12 or 13 21,144
18 14 and 15 and 16 and 17 67
19 limit 18 to yr="2020-Current" 36

Embase:

Ovid Embase <1996 to 2024 Week 24>

1 exp antibodies, bispecific/ or bispecific T cell engager/ 7,480
2 ((bi-specific or bispecific) adj (antibod* or therap*)).ti,ab,kw,sh. 7,828
3 ((bispecific or bi-specific) adj2 t cell engag*).ti,ab,kw,sh. 2,354
4 (BsAb* or BTEs or BiTEs gene).ti,ab,kw. 1,630
5 Prophylaxis/ or risk assessment/ or risk factor/ 2,075,734
6 ((prophyla* or prevent* or protect*) adj1 (therap* or treatment* or management or disease* or medicine*)).ti,ab,kw. 123,760
7 tocilizumab.ti,ab,kw. 15,500
8 (risk adj1 (stratification or assessment or evaluation or profile or predict* or increase* or calculator* or model or factor* or high or higher or intermedia* or low or lower or identification or status)).ti,ab,kw. 2,467,326
9 exp Neoplasms/ 5,053,211
10 (cancer or cancers or cancerous or neoplas* or tumor or tumors or tumour or tumours or leukemia or lymphoma or melanoma or carcinoma or cyst or neuroblastoma or malignan* or carcinoma* or adenoma or polyp or polyps or myeloma).ti,ab,kw. 5,443,659
11 exp cytokine release syndrome/ or cytokine storm/ 23,391

12	(CRS or cytokine release syndrome).ti,ab,kw,tw,sh.	35,279
13	(ICANS or immune effector cell-associated neurotoxicity syndrome).ti,ab,kw,tw,sh.	2,433
14	1 or 2 or 3 or 4	11,316
15	5 or 6 or 7 or 8	3,487,493
16	9 or 10	6,286,586
17	11 or 12 or 13	47,797
18	14 and 15 and 16 and 17	419
19	limit 18 to yr="2020-Current"	230

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