Clinical Pharmacology of Cytokine Release Syndrome with T-Cell–Engaging Bispecific Antibodies: Current Insights and Drug Development Strategies

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ABSTRACT

Cytokine release syndrome (CRS) is a common acute toxicity in T-cell therapies, including T-cell–engaging bispecific antibodies (T-BiSp). Effective CRS management and prevention are crucial in T-BiSp development. Required hospitalization for seven of the nine approved T-BiSp and the need for clinical intervention in severe cases highlight the importance of mitigation strategies to reduce health care burden and improve patient outcomes. In this review, we discuss the emerging evidence on CRS mitigation, management, and prediction. We cover different strategies for dose optimization, current and emerging (pre) treatment strategies, quantitative pharmacology tools used during drug development, and biomarkers and predictive factors. Insights are gleaned on step-up dosing and formulation effects on CRS and CRS relationships with cytokine dynamics and drug levels gathered through a review of T-BiSp licensing applications and emerging data from conferences and publications.

Introduction

Immune-targeting therapeutics have changed the cancer treatment landscape over the past three decades, the newest of which are T cell–engaging bispecific antibodies (T-BiSp). Since the first T-BiSp approval (blinatumomab) in 2014, seven additional T-BiSp have been approved by the FDA, all as monotherapy in metastatic or relapsed/refractory settings. The present T-BiSp landscape includes more than 100 T-BiSp in clinical development across various tumor targets, making T-BiSp poised to become major therapeutic modalities in oncology (1).

A major safety concern for T-BiSp is cytokine release syndrome (CRS; ref. 2). CRS is an on-target adverse response following T-cell activation or engagement, resulting in elevated systemic release of cytokines (2). Clinically, CRS presents as fever with or without hypotension, hypoxia, and organ dysfunction and is graded per the 2019 American Society of Transplantation and Cellular Therapy criteria (3, 4).

With growing interest and investment in T-BiSp as novel anticancer agents, dose regimen optimization to manage CRS risk is imperative. This review provides a snapshot of the rapidly evolving understanding of T-BiSp-induced CRS focused on clinical pharmacology and drug development aspects, including mitigation strategies, characterization, and prediction. Knowledge gaps and future research opportunities are highlighted.

Mitigating CRS through Dose and Regimen Optimization

Historically, the recommended phase II dose (RP2D), a key objective of phase I trials, for anticancer agents was determined by defining an MTD (5). For molecular targeted agents, however, the MTD is often not reached; i.e., maximal dose-dependent efficacy is below tolerability thresholds (5, 6). For immune agonists like T-BiSp, the optimal efficacious dose can be much lower than the MTD. The 2021 FDA-initiated Project Optimus placed greater emphasis on dose optimization during drug development and encouraged a robust evaluation of doses and schedules in order to optimize the benefit–risk profile of novel oncologic therapeutics (7).

Figure 1A shows the efficacy and CRS profiles of approved T-BiSp molecules. Recently authorized liquid tumor–targeting T-BiSp had 60% to 80% with overall response rates (ORR) of 39% to 79%. Tebentafusp, authorized for metastatic uveal melanoma, had a CRS occurrence of 89% (72% grade 2+) and 9% ORR, but further dose optimization was not requested by FDA (8). The acceptable CRS risk for T-BiSp molecules seems to vary depending on the disease setting and available therapeutic options.

Dose optimization requires considering the totality of evidence including safety, efficacy, patient burden, and treatment landscape for a disease. For T-BiSp molecules, optimization involves step-up dosing (SUD), target dose selection, dosing frequency, duration of treatment, and administration route, aimed at improving short- and long-term tolerability (including CRS risk) while maximizing efficacy. Below we discuss strategies and their outcomes for T-BiSp molecules approved and in development.

SUD

SUD involves the administration of small doses with submaximal efficacy prior to introducing the intended target dose. SUD attenuates the cascade of cytokine release and reduces overall CRS risk (2). This is explained by immune desensitization of cytokine release with repeated exposure (9, 10) and reduced T-cell activation following target depletion (11, 12). Importantly, SUD has facilitated decoupling of CRS risk and treatment activity such that

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similar CRS risk can be obtained following different target doses (**Table 1**).

All approved T-BiSp include SUD, and, consequently, CRS occurrence is low or minimal beyond the first targeted efficacious dose (**Fig. 1B**). Various dose-finding strategies are used during T-BiSp development, including increasing the number of steps with escalating target doses, varying SUD schedules for a single target dose, and split dosing, which involves splitting a step dose into two equal or unequal doses given closely together (**Table 1**). Two-step SUD schedules are most common among approved T-BiSp, administered 3 days apart for once weekly regimens and 7 days apart for every 3 weeks regimens (**Fig. 1B**).

In approved SUD schedules, CRS rates either increase with time, peaking at the first full dose (FD1), or decrease with time, peaking at the first step dose (SUD1; **Fig. 1B**). The prospective strategies used by investigators for dose selection are unknown. Retrospective evaluation shows that molecules with ascending CRS rates during SUD tend to have greater fold increases from SUD1 to FD1 (1 to 48–80 fold) compared with molecules with descending CRS rates (1 to 3.4–25 fold; Supplementary Table S1). This difference in CRS risk progression may reflect varying degrees of desensitization, which depends on target level and immune status. A mechanistic explanation of this phenomenon suggests that greater SUD1 amounts deplete the immune cell pool faster, reducing cytokine secretory capacity with future doses (10). Molecule, disease, and dosing interval factors may also play a role.

Routes of administration

Subcutaneous administration of T-BiSp was developed to improve safety and convenience for patients and caregivers (13, 14). Subcutaneous administration delays and reduces peak drug concentrations compared with intravenous administration, potentially lowering cytokine levels and CRS risk as found for alnuctamab (15, 16). A common development strategy is to develop subcutaneous administration in parallel with or after intravenous development, pivoting as early as phase I (**Table 1**). Epcoritamab is a unique example in which investigators initiated dosing in humans with a subcutaneous formulation (15, 17).

The extent of CRS risk mitigation by subcutaneous administration is not fully established and varies across T-BiSp molecules (18). Although investigators have alluded to better CRS profiles as the basis for pursuing subcutaneous dose expansion, external evaluation is difficult given differences in dose amounts and exposures of subcutaneous and intravenous arms. Without adjusting for exposure differences, a meta-analysis of B-cell maturation antigen–T-BiSp for multiple myeloma found subcutaneous formulations had higher grade ≤2 but lower grade 3+ CRS events than intravenous formulations (19). Preliminary phase II results with mosunetuzumab's subcutaneous formulation reported 20% CRS (6.6%, grade 2+) with the subcutaneous RP2D compared with 39% (17%, grade 2+) with the intravenous RP2D (20, 21). To our knowledge, this is the best exposure-equivalent intramolecule comparison of subcutaneous versus intravenous CRS risk available publicly; however, administration of the FD1 on day 8 with subcutaneous versus day 15 with intravenous may confound the comparison. Overall, the available evidence suggests that subcutaneous administration has promising potential to lower high-grade CRS risk.

Maintenance dose frequency

Evidence of the effect of maintenance dose frequency on CRS risk in T-BiSp therapy has not been extensively published. More frequent dosing leads to higher drug exposure and increases CRS risk, whereas longer intervals between doses may lead to loss of immune desensitization, potentially causing CRS resurgence. Therefore, minimizing CRS risk while keeping the disease controlled is a primary goal for maintenance dose regimen design. Dose-ranging was performed for every 2 weeks and once weekly teclistamab, but CRS by dosing schedule was not reported (14). Talquetamab is the only approved T-BiSp with two maintenance dose frequencies. Overall CRS and CRS following the full dose were similar between once weekly and every 2 weeks dosing (**Fig. 1**; ref. 22). Elranatamab is currently administered once weekly (23); a phase I/II study with grade 2+ CRS as the primary endpoint is evaluating every 2 weeks and monthly schedules and alternative SUD (24). This is supported by a prior mechanistic model demonstrating preserved effectiveness when transitioning from once weekly to every 2 weeks dosing (23).

Emerging Pretreatment Strategies for CRS

CRS is an immunologic cascade triggered by direct target cell lysis or therapeutic activation of T cells. These T cells produce cytokines like IFN-γ and TNFα, which activate innate immune cells such as macrophages and endothelial cells. These cells then release large amounts of proinflammatory cytokines like IL-6, perpetuating a cytokine storm through a positive feedback loop (2). Therapeutic interventions include blocking monocyte-released IL-6 (e.g., tocilizumab) and IL-1 (e.g., anakinra), blocking upstream T cell-released TNFα, and using JAK inhibitors, which prevent cytokine release without compromising T-cell cytotoxicity. Early implementation of prophylactic cytokine blockade is also recommended to reduce early-cycle cytokine release without impacting T-cell cytotoxicity (9). The field is rapidly evolving, with new agents and combinations being explored.

Pretreatment

All approved T-BiSp require pretreatment with corticosteroids, antipyretics (acetaminophen), prehydration, and antihistamines, typically through the first 1 to 2 full doses (Supplementary Table S2). Dexamethasone is the preferred corticosteroid for glofitamab and elranatamab, supported by lower CRS occurrence (23, 25). Administration of targeted antibodies to deplete peripheral B cells prior to T-BiSp administration in B cell lymphomas may also decrease CRS risk. Despite strong preclinical evidence, SUD was still required to reduce rates of grade 2+ CRS in obinutuzumab-pretreated patients receiving glofitamab (25–27). Emerging data suggests dexamethasone may offer more CRS protection compared with other corticosteroids, but the optimal role, context, and dosing schedule with or without other pretreatment agents remain unknown (28, 29).

Tocilizumab

Tocilizumab prophylaxis is predicted to block the IL-6 signaling pathway for 10 days after a single 8 mg/kg dose (30). When administered prophylactically 4 hours prior to the first or second teclistamab step dose, CRS occurrence reduced from 73% to ~30% (31, 32). When administered reactively as a CRS rescue agent, the dosing regimen of tocilizumab has been borrowed from CAR-T-induced CRS protocols and experience, which may not fully apply to T-BiSp cases (33). Modeling of mosunetuzumab and glofitamab data suggest that ≤2 tocilizumab doses per event, not exceeding three doses over 6 weeks, is sufficient to maintain tocilizumab activity and safe exposure (34), compared with up to four doses per event following CAR-T therapy (33). The pharmacologic rationale for administering multiple doses of tocilizumab in managing CRS is not strongly established, in general; it largely depends on clinician discretion and the resolution of CRS symptoms rather than a definitive pharmacologic necessity.

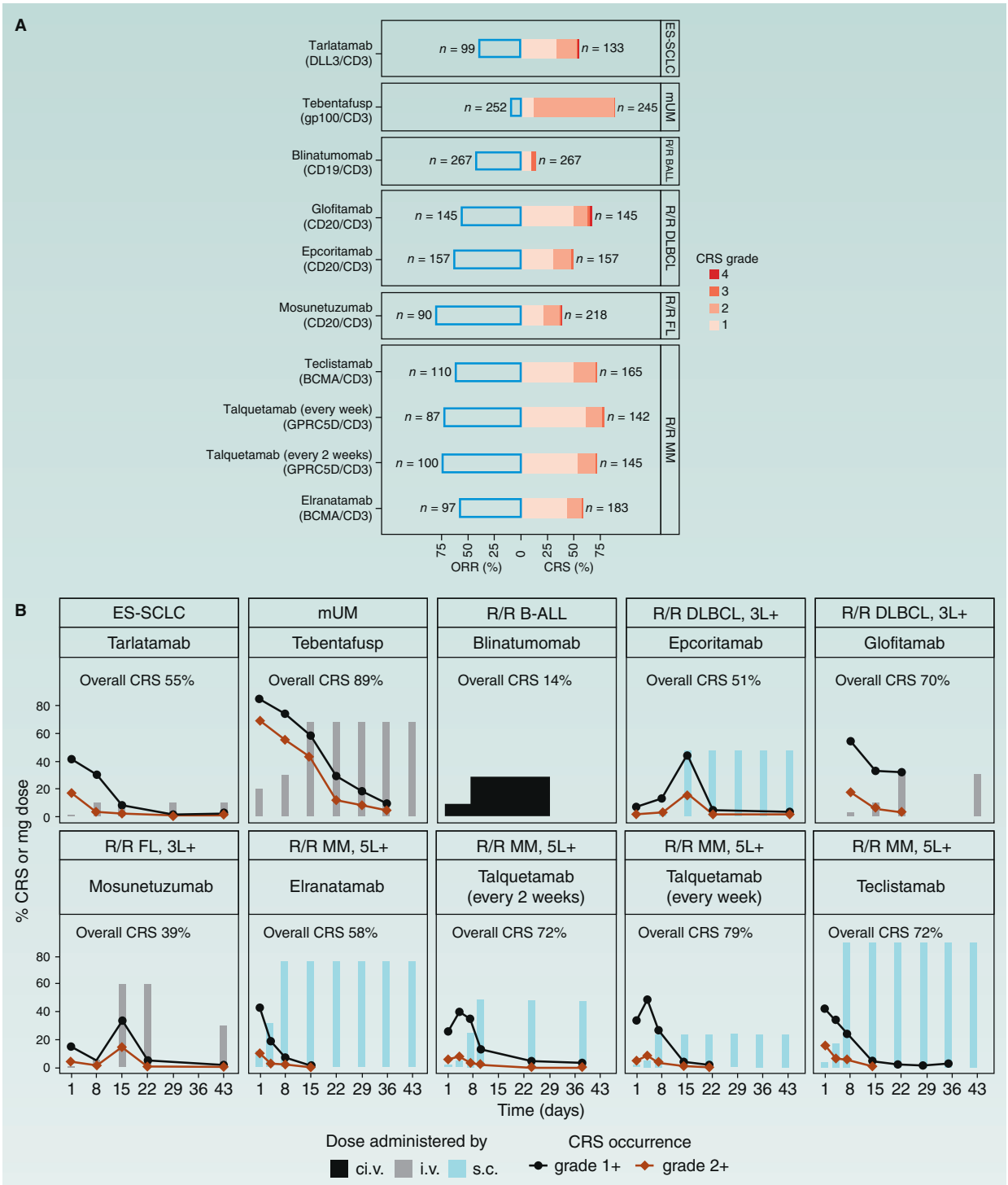

Figure 1.

Comparison of CRS across approved T-BiSp. **A,** Balance of efficacy vs. CRS. Molecule name (target) shown on the left axis and therapeutic indication on the right grouped axis. ORR was used as the efficacy endpoint for comparison across molecules. However, the primary endpoint was overall survival for tebentafusp and blinatumomab. The in-figure text values represent the number of patients contributing to CRS and efficacy assessments provided in the biologics licensing applications. **B,** CRS event rate per dose period (points, line) overlaid with dose amount (bars) for SUDs and target doses. Dose amounts in milligrams are depicted at scale, except that blinatumomab and tebentafusp are shown in micrograms. B-ALL, B precursor acute lymphoblastic leukemia; BCMA, B-cell maturation antigen; ci.v., continuous intravenous; DLBCL, diffuse large B-cell lymphoma; ES-SCLC, extensive-stage small cell lung cancer; FL, follicular lymphoma; MM, multiple myeloma; mUM, metastatic uveal melanoma; R/R, relapsed or refractory. Note: The unit for blinatumomab dose is micrograms.

Table 1. Examples of T-BiSp dose-finding strategies used related to CRS mitigation.

Category	Strategy, example
Step-up dose optimization	Increasing the number of steps with higher target dose levels during dose ranging: • Teclistamab dose escalation included one-step, two-step, and three-step regimens for intravenous and subcutaneous cohorts, in which more steps were initiated at higher target doses. A two-step subcutaneous once-weekly regimen and a three-step intravenous once-weekly regimen were selected for phase I dose expansion (14). • Epcoritamab dose-ranging trials used single-step at target doses <1.5 and double-step at target doses 1.5–60 mg (17) Testing multiple priming schedules per target dose: • Teclistamab dose ranging included different steps with the same target dose (0.02/0.8, 0.02/0.0576/0.8; mg/kg), the same steps with different target doses (0.01/0.06/0.18, 0.01/0.06/0.27; mg/kg), and the same steps with different maintenance dosing (2/6/30/150 once weekly and 2/6/30/300 every 2 weeks; mg; ref. 73). • Two SUD schedules for each epcoritamab target dose ≥6 mg were evaluated (e.g., 0.04/0.5/6 and 0.08/0.5/6), altering either SUD1 or SUD2 or both (17) Splitting step doses: • Elranatamab tested one priming dose (44 mg) in phase I. This single-step dose was converted to a double-step approach in a phase II trial by splitting the dose into 12 and 32 mg administered on days 1 and 4, respectively, and CRS was reduced by 8% (NCT04649359; NCT03269136; ref. 74). • Odronextamab split the administration of each of two step doses over 2 days (i.e., the SUD1 dose of 1 mg was administered as two 0.5 mg doses on separate days). They used split dosing after three escalations of SUD1 (1 mg+) and three escalations of SUD2 (20 mg+). Their selected RP2D regimen included a new SUD schedule with two untested SUDs and an additional third step (0.7/4/20), all administered as split doses (75) Flexible step-dose timing based on CRS: • Cevostamab evaluated a 0.3/3.3/160 regimen administered on day 1, days 2–4 (depending on the emergence and resolution of CRS), and day 8 (76) Single step for continuous infusion: • Initiating blinatumomab at 9 mcg/day (the lowest dose at which B-cell depletion was observed) for 1 week prior to escalating to the target dose (28 mcg/day) reduced CRS events occurring with the first dose [BLA 125557: Blincyto (blinatumomab)]
Target dose optimization	Changing the number of steps with a different maintenance dose regimen: • Talquetamab increased the maintenance dose from 0.4 mg/kg once weekly to 0.8 mg/kg every 2 weeks by adding a third step-up dose of 0.4 mg/kg. This every-2-week regimen had higher peak concentrations but similar average concentrations over the dose interval, maintaining efficacy without increasing CRS risk (BLA 761342: Talquetamab-tgvs) Keeping the same SUD with different target doses: • Linvoseltamab evaluated two RP2D cohorts in dose expansion with the same SUD: 5/25/50 and 5/25/200 mg. CRS occurrence was slightly lower in the 200 mg RP2D cohort (37%) than in the 50 mg one (53%), with similar CRS rates at the first target dose (77). • Odronextamab used the same SUD schedule (0.7/4/20) for different indication-specific target doses in the ELM-2 phase II trial (80 mg in FL and 160 mg in DLBCL, weekly); 55% CRS was observed in patients with DLBCL and FL treated at different target doses (78, 79)

(Continued on the following page)

Table 1. Examples of T-BiSp dose-finding strategies used related to CRS mitigation. (Cont'd)

Category	Strategy, example
Route of administration development	First filing in intravenous with parallel or sequential subcutaneous development: • Mosunetuzumab—subcutaneous dose escalation and expansion arms were added to the phase I/II trial in 2018, 4 years prior to intravenous filing (NCT02500407). • Glofitamab—a subcutaneous dose escalation trial was registered in 2021, 2 years prior to intravenous filing (ISRCTN17975931). • Blinatumomab—phase I/II study of subcutaneous blinatumomab in B-ALL began in 2020 (NCT04521231), 6 years after authorization of the continuous intravenous infusion formulation. Expansion to NHL indications began in 2017, evaluating both intravenous (phase II/III; NCT02910063) and subcutaneous (phase Ib; NCT02961881) First filing in intravenous with no planned subcutaneous development: • Tebentafusp—intravenous approval received in 2021. No trials of subcutaneous formulations are registered. • Tarlatamab—an intravenous infusion product for small cell lung cancer was recently approved by FDA in 2024. • Linvoseltamab—filing application with an intravenous product is under FDA and EMA in 2024 First filing in subcutaneous: • Teclistamab—conducted intravenous dose ranging, then subcutaneous dose ranging, and proceeded with subcutaneous dose expansion only (80). • Elranatamab—proceeded with subcutaneous dose expansion after concurrent intravenous and subcutaneous dose ranging (74). • Epcoritamab—only subcutaneous dose ranging and expansion were sought, which was supported by an *in vivo* study in cynomolgus monkeys demonstrating a similar degree of prolonged B-cell depletion with subcutaneous and intravenous administration (17) Parallel intravenous/subcutaneous development with unknown filing plan: • Alnuctamab—pivoted from intravenous to subcutaneous, reducing CRS from 76% to 56% (81, 82). A phase III trial is listed without formulation specification (NCT06232707). • Plamotamab—subcutaneous dose expansion was added after arms of intravenous dose ranging (NCT02924402). • ABBV-383—after completing intravenous dose ranging with three dose-expansion cohorts (NCT03933735; refs. 20, 40, 60), a new phase Ib study with a subcutaneous formulation was announced (NCT06223516)

B-ALL, B precursor acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FL, follicular lymphoma.

Kinase inhibitors

Kinase inhibitors have CRS mitigation potential by suppressing cytokine release downstream of TNFα signaling and offering antitumor activity (35, 36). *In vitro* assays revealed potent cytokine release inhibition while preserving T cell killing of PI3K, JAK, and mTOR inhibitors (36, 37). Itacitinib (JAK1 inhibitor) reduced overall CRS by 22% and grade 2+ CRS by 39% in a randomized placebo-controlled trial of axicabtagene ciloleucel in relapsed/refractory large B-cell lymphoma (38). POLB-001, a novel p38 MAPK inhibitor, significantly reduces cytokines and is in clinical development for inflammatory diseases and CRS, with plans for multiple myeloma (39).

CRS Biomarkers

Multiple cytokines including IL-6, IL-1, IL-2, IL-8, IL-10, IFN-γ, and TNFα are elevated in patients with CRS (**Fig. 2A**; ref. 40). IL-6, IL-10, and IFN-γ dynamics are included in most T-BiSp licensing applications and typically increase after step-up and target doses to varying degrees (Supplementary Fig. S1). Lower peaks are generally observed with subcutaneous administered T-BiSp.

IL-6 is highly elevated after dosing and has emerged as a key biomarker for the pharmacologic characterization of CRS (40). However, mean dose-period IL-6 peaks do not consistently trend with CRS rates for approved molecules (**Fig. 2B**). IL-6 trended with CRS for mosunetuzumab tebentafusp and tarlatamab, but IL-10 and IFN-γ better trended with CRS for glofitamab and elranatamab. Although post–step-dose IL-6 concentrations were not reported for epcoritamab recent cycle 1 dose optimization efforts have shown a reduction in CRS, which is associated with lower IL-6 levels (41). Tocilizumab administered prophylactically or for treatment increases IL-6 levels by saturating receptor-mediated IL-6 clearance and may alter the IL-6 to CRS relationship as found in teclistamab patients (30, 42, 43). Therefore, tocilizumab needs to be accounted for in IL-6 to CRS associations. TNFα peaks earlier than IL-6 and may be a better marker of CRS severity (44, 45). A multicytokine model including IL-6 and IL-8 as proinflammatory and IL-10 as anti-inflammatory effects may also aid CRS grade prediction (46).

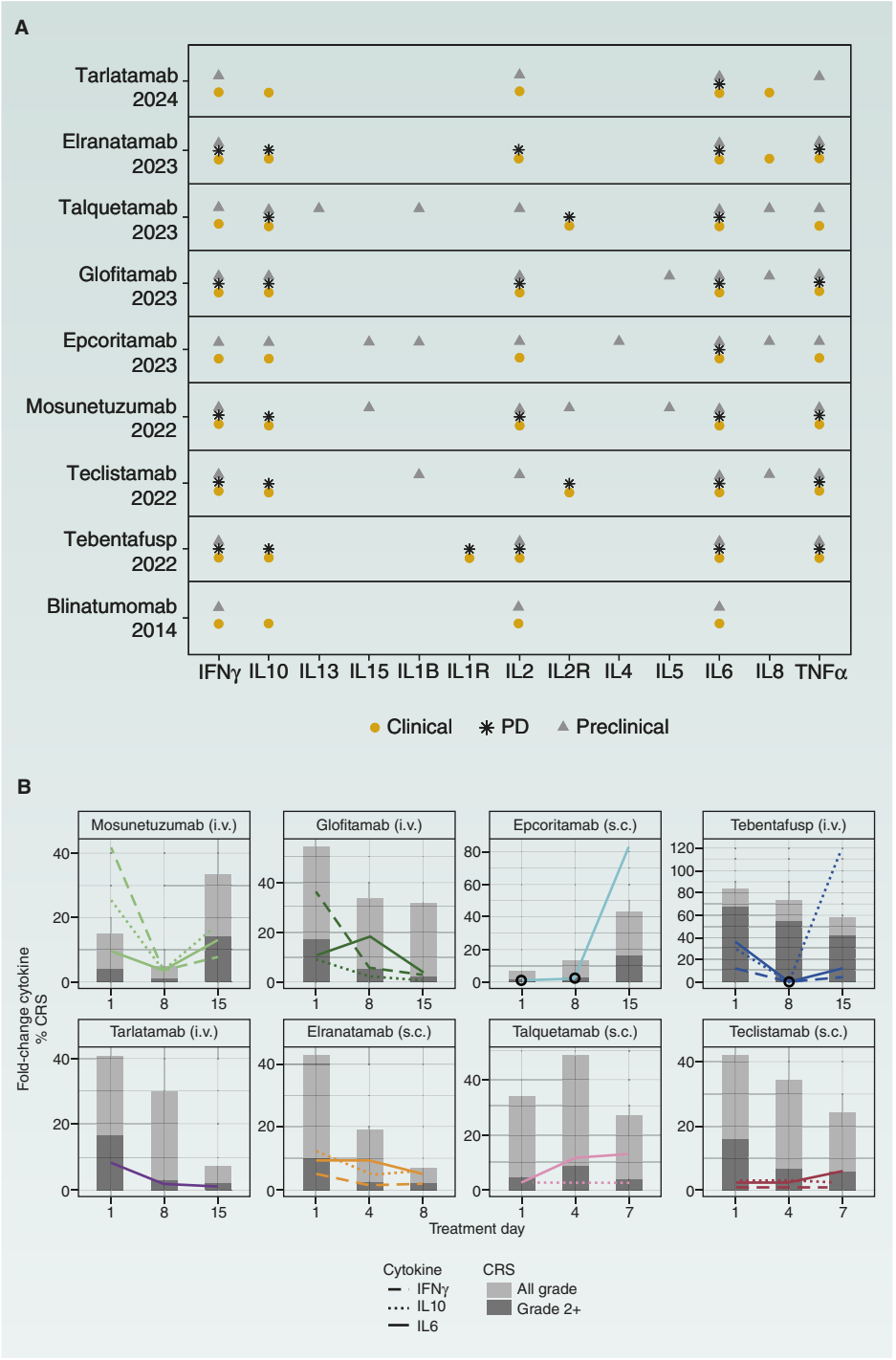

Figure 2.
Cytokine dynamics in approved T-BiSp. **A,** Cytokine biomarkers measured and reported in the nonclinical and clinical pharmacology sections of biological licensing applications (BLA). **B,** Mean cytokine peaks (lines), as fold change from baseline, overlaid with CRS rates (bars) postdose during the SUD phase. Cytokine levels were digitized from figures in molecule BLAs. Molecules that reported raw cytokine levels were converted to fold change using the mean baseline value. Open circles shown in epcoritamab and tebentafusp panels indicate when only predose cytokine levels were reported. i.v., intravenous; PD, pharmacodynamics (i.e., time-course profiles); s.c., subcutaneous.

Other biomarkers may aid CRS understanding and prediction. MCP-1, CXCL10, and MIP-1a(b) expression is induced by CD20/CD3 bispecifics (35). Clinical observations following CD19 chimeric antigen receptor T-cell (CAR-T) therapy and cell assays with CD3/carcinoembryonic antigen (CEA) bispecific suggest a role for angiopoietin-2 and von Willebrand factor in severe CRS (36, 47). Furthermore, the immune status for $CD4^+$, $CD8^+$, and regulatory T-cell populations may also affect individual CRS responses (48, 49).

Quantitative Clinical Pharmacology, Gaps, and Opportunities

Quantitative clinical pharmacology (qCP) approaches are powerful tools in drug development. They identify key contributors to clinical efficacy and safety, provide insights into untested clinical scenarios, and design safe and effective clinical trials with an increased probability of success. **Table 2** provides examples of qCP

approaches in drug development for CRS mitigation. Applying multiple methods synchronously in a parallel, sequential, or cross-talk manner is important to drive efficient and strategic decision-making during development (12, 48).

Mechanistic translational modeling (i.e., "bottom-up" approaches), such as quantitative systems pharmacology (QSP) and physiologically based pharmacokinetics (PBPK), is valuable when clinical experience is lacking or to leverage mechanistic insights. When linked with drug pharmacokinetics (PK) and trimer formation, QSP has been applied to predict cytokine and tumor dynamics under various SUD schedules to guide dose regimen optimization (10, 12, 50, 51). Additionally, it can be adapted to predict drug and disease interactions with combination regimens (52) and offer insights at the tissue level when combined with PBPK. Applications beyond SUD objectives include dose prediction in a new disease (11), formulation (53), and patient population (53). The future of T-BiSp drug development will likely focus on combination regimens to expand the therapeutic index and improve the benefit/risk profile, such as co-stimulatory agonistic bispecifics to enhance T-cell proliferation and cytotoxicity (54), agents to attenuate CRS response (36), and dual or triple T-BiSp therapy to diversify target engagement. Multitherapy QSP models will enable simultaneous prediction of efficacy and CRS risk with combination regimens, as applied for T-BiSp plus checkpoint inhibitors [e.g., anti-PD1/PDL1 (52, 55)], to streamline dose, regimen, and sequencing (56).

Empirical/statistical modeling of CRS (i.e., "top-down" approaches), such as logistic regression, is commonly applied to support dose selection in drug approvals. Investigators assess CRS endpoints using pharmacokinetic (PK) metrics [e.g., maximum concentration (Cmax) or derived receptor occupancy (RO)] at early dose periods, aligning with the CRS mechanism induced by T-BiSp. In contrast, efficacy endpoints have been described with early-cycle or steady-state PK metrics (i.e., cumulative AUC and average concentration) or trimer formation kinetics (Supplementary Fig. S2; refs. 10, 11). For most T-BiSp, there was a positive trend between Cmax/ROmax and the probability of CRS at SUDs and FD1 if enough CRS events were present (**Table 3**; Supplementary Fig. S2). No CRS E-R relationships were detected with talquetamab and epcoritamab levels (22, 57, 58) and may be due to a limited dose/concentration range and high response variability. Notably, glofitamab and mosunetuzumab used RO% instead of drug levels, resulting in a wider range of input exposure values given the interpatient variability in circulating anti-CD20 drugs (20, 25). Simulated trimer levels could be used to characterize CRS E-R as done for epcoritamab ORR E-R (57), but examples do not exist publicly. Postauthorization, time-to-CRS event modeling aided further optimization of epcoritamab SUD (59).

Multivariate predictive modeling could further inform risk-stratified patient monitoring or individualized dosing. Analyses for mosunetuzumab, glofitamab, teclistamab, and elranatamab reported various covariates associated with CRS including disease status and treatment history, target level, and effector cell status (**Table 3**). A CRS predictive model from 715 patients treated with T-BiSp identified ALL disease, prior infections, recent diagnosis, lower lactate dehydrogenase, and others associated with very high CRS risk (60). A risk stratification tool for grade 2+ CRS with the first glofitamab dose in aggressive non–Hodgkin lymphoma histologies excluding mantle cell lymphoma identified baseline lactate dehydrogenase, leukocyte count, age, cardiac morbidity, bone marrow and peripheral blood infiltration, Ann Arbor stage, and tumor burden as risk factors (61). The 5-parameter CRS risk prediction tool has been prospectively validated in aggressive non–Hodgkin lymphomas across several mono and combo glofitamab phase I trials with 94% true-positive prediction. The Cmax of the prior dose and tocilizumab use have also been shown to be important factors for predicting CRS in patients treated with teclistamab and elranatamab (43, 62). Other potential predictive factors include a proinflammatory tumor microenvironment (63), serum inorganic phosphate and magnesium level changes (64), and endothelial activation and stress index (EASIX) score (65), which have demonstrated predictive value in CRS post–CAR-T.

Platform modeling to further establish the link between drug exposure, trimer formation, biomarkers (e.g., IL-6), and CRS would aid RP2D optimization and translational predictions across different molecules. Hosseini and colleagues (12) developed a QSP model using preclinical mosunetuzumab data, calibrated to clinical blinatumomab data, to predict cytokine dynamics with untested mosunetuzumab dosing schedules. This could be extended to include an IL-6 to CRS relationship (59) to further predict CRS risk. A pan-molecule PK-cytokine-CRS model could thus inform discovery and clinical development by providing optimal PK targets and biomarker thresholds, enabling early decision-making.

Lastly, AI/ML methods are flexible in handling complex data, including correlated, nonlinear, and interdependent covariates thus could support CRS characterization and prediction. These methods can facilitate large-scale covariate searches and enable the identification of higher-dimensional relationships over time, which is challenging to achieve with traditional methods. Examples include time-to-event analysis (66), pharmacogenetic biomarker identification (67), survival prediction from tumor dynamics (68), and deep learning that conserves the time-dependent state (69). Such applications require large-scale clinical trial data, necessitating careful consideration for data handling (e.g., missing data) and practical judgment when interpreting data pooled from multiple clinical trials.

Discussion

Our review highlights that CRS remains a key safety concern for T-BiSp and integral to efficient drug development. Despite the recent availability of guidelines for assessing and managing CRS in T-BiSp therapies (70), it is acknowledged that creating high-level evidence-based guidelines is still premature. Balancing the benefit-risk ratio for this on-target adverse effect requires careful consideration. Clinical development goals aim to minimize CRS frequency and severity, thereby circumventing the need for intensive clinical interventions and hospitalization. SUD has effectively mitigated CRS with T-BiSp, limiting most events to grades 1 to 2. Despite early promising data, the effectiveness of subcutaneous administration alone in mitigating CRS is not yet proven. Pretreatment with steroids, tocilizumab, and potentially kinase inhibitors are additional tools, but the optimal dose and timing for CRS prevention requires further study of the pharmacologic interactions relevant to the dosing schedule, molecule, and disease contexts.

QCP has significantly influenced dose and regimen design to deliver safe and effective T-BiSp agents. Mechanistic-based approaches (i.e., QSP, PBPK, and mPKPD) have accelerated early clinical development, designed SUD schedules to mitigate CRS, selected first-in-human doses, and extrapolated intravenous to subcutaneous doses. CRS E-R has been successfully characterized with drug levels and RO. Creating a universal predictive algorithm for CRS is challenging because of its multifactorial nature. CRS occurrence and patterns are influenced by molecule design (e.g.,

Table 2. Quantitative clinical pharmacology strategies for CRS prediction during drug development.

Objective	Method	Example
Translation to first-in-human	Translational PKPD	Glofitamab nonlinear PK model in cynomolgus monkeys with indirect PD response of IL-6 cytokines translated to humans to propose estimated-in-human dose using predicted IL-6 threshold (25) First-in-human doses of odronextamab were informed by EC_{50} values of IFN-γ and IL-6 from *in vitro* cytokine release assays with whole blood from human donors. MTD was estimated from monkeys, in which IL-6 cytokine dynamics were assessed and found to correlate with Cmax. Retrospective analysis of phase I clinical data did not reveal a correlation between Cmax and peak IL-6, and the MTD was not reached (83)
Step dose exploration and optimization	Minimal PBPK/PD	Demonstrated mitigation of IL-6 release with a 5/15/60 stepwise regimen compared with flat dosing in patients with NHL using a minimally mechanistic PBPK/PD model built from reported preclinical and clinical blinatumomab data (11)
	Semimechanistic PK/PD	A "fit-for-purpose" semimechanistic PKPD model was established to characterize cytokine profiles postadministration after empirically observing that dose priming reduced CRS risk. Cytokine release was dependent on trimer formation and tumor kinetics. The structural model was intended to be parsimonious, so it could be adapted to hematologic or solid tumor–targeting bispecifics. They demonstrate good predictability of blinatumomab and P-cadherin LP DART cytokine profiles with different dosing schemes (84)
	QSP with digital twins	Using preclinical data for mosunetuzumab and blinatumomab and clinical data from blinatumomab clinical trials in ALL and NHL, a QSP model was developed and validated to predict B- and T-cell dynamics including systemic cytokines and tumor growth/regression for mosunetuzumab in patients with NHL. A virtual population was first used to predict the impact of step-dose regimens for mosunetuzumab on tumor and IL-6 dynamics. A later study updated this QSP model, calibrating with phase I/II data of mosunetuzumab. Using digital twins matching 140 clinical patients, they evaluated the impact of different dosing regimens on tumor burden and CRS risk (12, 51)
	QSP	A QSP model describing peripheral cytokine dynamics (IFN-γ, IL-6, IL-10, CXCL10, and CXCL11) following tebentafusp dosing was applied to inform the contribution of tumor and healthy tissue to cytokine release (an on-target effect because gp100 is expressed in both tissues). This model was calibrated to clinical data, and simulations were performed to determine the optimal number of step doses and dose amount to minimize CRS while maximizing treatment efficacy (10)
	Time to event	Epcoritamab PK were linked to the hazard of CRS events (all grade or grade 2+) and used to predict risk with regimens beyond the SUD tested in GCT3013-01 escalation (59)
Phase II dose selection	Semimechanistic PK/PD with exposure–CRS logistic regression	A cynomolgus monkey model was used to inform the structure of a mechanistic PK/PD of epcoritamab describing the biodistribution, trimer formation, and tumor response and calibrated with phase I/II clinical data. Response rate and trimer formation plateau were simulated for FL and DLBCL to select the target dose. Dose was confirmed with an exposure–CRS analysis from phase I dose escalation (57)

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Table 2. Quantitative clinical pharmacology strategies for CRS prediction during drug development. (Cont'd)

Objective	Method	Example
Indication/disease translation	Minimal PBPK/PD	Predicted blinatumomab starting dosing in patients with ALL based on data from patients with NHL by modifying disease-specific parameters of a minimally mechanistic PBPK/PD model. IL-6 and B-cell depletion were the predicted outputs (11)
Dose prediction with different routes of administration	PBPK (in tandem with mechanistic PD or E–R)	A PBPK framework including preclinical and clinical data was used to describe PK with intravenous administration of 8 CD3 T-cell engager modalities for solid and liquid tumors. Absorption parameters were added to extend the model for subcutaneous dosing. PK outputs could be linked to PD biomarkers or CRS risk using PKPD or E–R relationships (53)
	PK extrapolation	A PK model developed from intravenous dose escalation of teclistamab was used to predict an equivalent subcutaneous dose, assuming a 60% bioavailability and time of maximum concentration of 48–72 hours. Simulations showed 2–3-fold lower Cmax with subcutaneous than intravenous, which was associated with CRS events during intravenous administration, so comparable safety was anticipated (85)
Pediatric dose extrapolation	PBPK (in tandem with mechanistic PD or E–R)	A PBPK framework from adult intravenous was refined to predict pediatric (1 month to 17 years) PK using physiologic ontogeny data and validated with clinical pediatric PK data. Subcutaneous PK were predicted by adding ontogeny to absorption parameters. PK outputs could be linked to PD biomarkers or CRS risk using PKPD or E–R relationships (53)
Interaction prediction with combination treatment	QSP	A QSP platform that incorporated specific processes of immune–cancer cell interactions was used along with a virtual patient population to conduct *in silico* trials for combination therapy of a PDL1 checkpoint inhibitor and cibisatamab. Potential doses and administration for two drugs were compared to select the optimal combination therapy. Although this was applied to quantify the drug synergy in the context of efficacy, a similar platform could be used to predict interactions for CRS occurrence (52)
Patient risk stratification	Univariate and multivariate statistical models	A model with glofitamab data was developed to evaluate the association between baseline risk factors and the occurrence of grade ≥2 CRS. The predictive model enables the stratification of patients at high or low risk of CRS after the first dose of glofitamab. This type of predictive model could be applied in drug development to individualize treatment dosing and clinical CRS mitigation and monitoring (61)

Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, B precursor acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; E–R, exposure–response; FL, follicular lymphoma; NHL, non–Hodgkin lymphoma; PD, pharmacodynamics.

modality and affinity), disease context (e.g., target expression, microenvironment, and tissue distribution), patient population (e.g., tumor types), and clinical practices (e.g., prior treatments, dosing regimens, premedications, pretreatments, and rescue). These factors result in unique exposure–response and dose–response relationships. Developing a universal modeling platform that accounts for these variables could be valuable for future research. Future efforts using trimer formation may further integrate efficacy/risk predictions. AI/ML can expedite predictive modeling platforms, facilitate multivariate covariate searches, and enable large-scale use of longitudinal PK-biomarker-CRS data.

Solid tumor–targeting T-BiSp represent a large proportion of T-BiSp development (1). A key challenge is the broader target expression patterns and the mitigation of on-target off-tumor toxicities, including CRS (71). Preliminary data suggested higher CRS risk for some solid tumor T-BiSp. Mitigation strategies successful in liquid tumors may be applied to solid tumor development for further risk optimization (72). Tebentafusp, one of the earliest approved T-BiSp, was authorized with high-grade 2+ CRS occurrence (77%), yet the FDA deemed further dose optimization unnecessary (8). Newly authorized tarlatamab for small cell lung cancer reported 55% CRS (19%

Table 3. Pharmacokinetic exposure metrics for CRS E–R and efficacy E–R endpoints with T-BiSp administration.

Drug (dose schedule)	CRS E–R relationship	Efficacy E–R relationship	E–R other/notes
Tebentafusp/Kimmtrak (0.02/0.03/0.68 mg once weekly intravenous)	G1+ CRS events: vs. Cavg (SUD1), vs. Cavg (FD1), vs. Cmax (SUD1), vs. Cmax (FD1)	OS (KM): by Cmax,ss; by Cavg,ss; tumor CFBSL: by Cmax,ss; by Cavg,ss	No trend in IL-6 fold-change vs. Cavg (SUD1) or Cmax (SUD1); trend of lower Cavg and Cmax in patients with no CRS
Tarlatamab/Imdelltra (1/10/10 mg every 2 weeks intravenous)	P (G1+ CRS, G2+ CRS, and G3+ CRS): vs. Cavg (first cycle), vs. Cmax (first cycle), vs. Ctrough (first cycle)	PFS, OS, and DoR (KM): Cavg (first cycle); P (OR and DCR): vs. by Cavg (first cycle)	No clear trends in E–R relationships for G3+ CRS; a slight positive trend in E–R relationships for G1+ and G2+ CRS; however, the E-R may be confounded by the mitigation strategy of the 1 mg SUD
Epcoritamab/Epkinly (0.16/0.8/48 mg once weekly subcutaneous)	P (G1+ CRS, G2+ CRS, and CRS requiring tocilizumab): vs. AUC (CYC1), vs. SUD1, vs. SUD2, vs. FD1 vs. FD3	PFS and OS (KM): by AUC (CYC1) quartiles; P (CR and OR): vs. AUC (CYC1)	No CRS E–R relationships detected by logistic regression, including when evaluated by Cmax (57). Positive CRS E–R was observed for SUD1 and SUD2 using peak IL-6 as the driver (86)
Glofitamab/Columvi (2.5/10/30 mg every 3 weeks intravenous)	P (G2+ CRS): vs. ROavg (SUD1)	P (CR and OR): vs. AUC (CYC1–2)	Multivariate models for CRS identified ROavg (SUD1), baseline SPD, MCL histology, and Ann Arbor stage are significant covariates
Mosunetuzumab/Lunsumio (1/2/60/30 mg every 3 weeks intravenous)	P (G2+ CRS): vs. ROmax (D0–D42), vs. ROmax (SUD1), vs. ROmax (SUD2), vs. ROmax (SUD3)	P (CR and OR): vs. AUC (D0–D42), vs. ROavg (D0–D42)	Modest trend in IL-6 fold-change with increasing ROmax on day 1 but not following dosing days; multivariate model for CRS identified ROmax (day 0–day 42), baseline age >64 years, and MCL histology are significant covariates
Elranatamab/Elrexfio (12/32/76 mg once weekly intravenous)	P (G1+ CRS and G2+ CRS): vs. total Cmax (SUD1), vs. free Cmax (SUD1)	P (OR): vs. total Cmax (D0–D28), vs. free Cmax (D0–D28)	Multivariate model for CRS identified a lower likelihood of G1+ CRS with higher baseline sBCMA. Higher free and total Cmax (day 1) had a greater likelihood of G1+ and G2+ CRS
Talquetamab/Talvey (0.01/0.06/0.4 mg/kg once weekly subcutaneous)(0.01/0.06/0.4/0.8 mg/kg every 2 weeks subcutaneous)	G1+ and G2+ CRS events: by Cmax (SUD1), by Cmax (SUD2), by Cmax (SUD3) quartiles	P (OR): vs. Cavg (D0–D28), vs. Ctrough (FD1)	No CRS E–R relationships detected by quartile assessment, including when stratified by tocilizumab use
Teclistamab/Tecvalyi (0.06/0.3/1.5 mg/kg once weekly subcutaneous)	P (G1+ CRS): vs. Cmax (SUD1), vs. Cmax (SUD2)	P (OR): vs. Cavg (FD1), vs. Ctrough (FD4)	Multivariate models for CRS identified lower Cmax (SUD1), higher baseline sBCMA, and higher baseline age were less likely to experience CRS with SUD1. For SUD2, CRS decreased with higher Cmax (SUD1), higher Cmax (SUD2), females, lower ALP, and tocilizumab use

Abbreviations: BCMA, B-cell maturation antigen; Cavg, average concentration; CFBSL, change from baseline; Cmax, maximum concentration; CR, complete response; Ctrough, trough concentration; CYC1, cycle 1; D, dose; DCR, disease control rate; DoR, duration of response; E–R, exposure–response; FD, full dose; G1+, grade 1 plus; KM, Kaplan–Meier; MCL, mantle cell lymphoma; OR, objective response; OS, overall survival; P, probability; PFS, progression-free survival.

grade 2+), in line with CRS rates in liquid tumor T-BiSp (72). Clinical studies and QSP model simulations indicate that CRS in tebentafusp-treated patients is primarily driven by cytokine production in the skin rather than in tumor tissue, due to a larger immune cell pool in the skin (10). This complicates CRS prediction and management for solid tumor targets with broader expression patterns in both healthy and tumor tissues. Given that direct measurements of RO may not be feasible with solid tumors, QSP modeling offers a practical method for CRS prediction by incorporating tumor-associated antigen expression levels and simulating various dosing or intervention scenarios.

Regulatory policies will likely have a significant influence on CRS mitigation and management standards. Established frameworks like Project Optimus and the Model Informed Drug Development pilot foster productive engagement between drug developers and the FDA to address dose-related development questions and apply qCP for dose optimization. Because CRS is profoundly influenced by molecular properties and the specific disease, a comprehensive discussion around pharmacologic context is crucial. This can guide appropriate dose-finding strategies while maintaining a focus on the swift delivery of effective treatments to patients. Furthermore, real-world clinical infrastructure and CRS management guidelines are anticipated to evolve over the coming years. This underscores the need for collaboration between industry, regulatory bodies, and the healthcare community to ensure safe administration of T-BiSp for the benefit of the patients.

Authors' Disclosures

K.K. Radtke reports employment with Genentech/Roche and ownership of Genentech/Roche shares. B.C. Bender reports current employment with Roche and ownership of Roche stock. Mosunetuzumab, a Roche molecule, is highlighted in the review. D.C. Turner reports other support from Roche/Genentech during the conduct of the study. S. Roy reports other support from Roche/Genentech outside the submitted work. A. Belousov reports personal fees from Hoffmann-La Roche Ltd. during the conduct of the study, as well as a patent for P36683-US-1 issued to Hoffmann-La Roche. C.-C. Li reports current employment with and stock ownership in Genentech/Roche. No disclosures were reported by the other author.

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Note

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