

'You give me fever!': are health services ready for immune cell engager therapy in advanced solid malignancies?

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ABSTRACT

Immune cell engager therapeutic strategies using bioengineered molecules to redirect immune cells into tumor are starting to demonstrate promising clinical activity in multiple early phase trials across numerous targets and a range of solid tumor types. These therapies, however, carry the risk of exaggerated cytokine-mediated on-target off-tumor adverse events that require highly specialized inpatient facilities. We report here the Royal Marsden experience of treating patients with advanced solid tumors on early phase immune engager clinical trials in a dedicated inpatient facility, focusing specifically on patterns of cytokine-mediated toxicity seen and proposing a risk-mitigation algorithm for the safe, feasible and scalable delivery of these therapies.

MAIN TEXT

The field of cancer immunotherapy has recently grown to encompass a new class of specifically engineered antibodies, designed to redirect host immune cells to targeted tumor cells. Chimeric-antigen receptor T-cell adoptive immunotherapy (CAR-T) led the way by harvesting host T-cells and modifying them *ex vivo* to recognize cancer-specific targets before reintroducing them to the host; CAR-T has proved its potential with remarkable efficacy. But it is not without its drawbacks. The process is 'bespoke', with complex and lengthy manufacturing, and can be fatally toxic due to massive cytokine release and neurotoxicity,¹ thereby requiring specialist centers for delivery and currently only licensed for rare aggressive hematological malignancies.

Newer generations of bioengineered immune-cell engagers built on this strategy, using designer antibody fragments to *both* recognize and target antigens expressed on tumor cells, as well as recognize, bind, and activate immune cells (figure 1A,B). These soluble recombinant fusion proteins are engineered in multiple formats based on single chain variable fragments; typically one end binds to selected tumor associated

antigens (TAAs) or tumor-associated peptide-Major Histocompatibility Complex (MHC) complexes, while the other binds the constant part of the T-cell receptor (TCR) complex (CD3) on effector T-cells or CD16 on natural killer cells.² This leads to the formation of an immunological synapse, triggering activation and redirection of cytotoxic T-cells (BiTEs) or natural killer cells (BiKEs) toward predefined tumor targets³ (figure 1A,B). Critically, these redirection therapies can employ *all* available T-cell or natural killer cells and are not limited to tumor-specific immune cells, conferring a significant advantage compared with immune checkpoint-based therapies⁴ or CAR-T therapy.⁵

This enables *off-the-shelf availability*—potentially widening the scope of targets and tumor types that may be therapeutically targeted. Following the approval of the first 'off the shelf' T-cell engager blinatumomab, a bispecific antibody targeting CD19 on malignant B cells and CD3 on naïve T-cells in the rare hematological malignancy acute lymphoblastic leukemia in 2014,^{2,6} there have been more than 100 distinct clinical trials of this emerging class of immune cell redirecting antibodies against a range of targets (eg, the tumor-associated antigens CEA, PSMA, HER2, EGFR, Claudin6 and EpCAM, as well as cancer testis antigens NYESO1, MAGE, and PRAME)⁷ (figure 1C). The first of these to gain regulatory approval on the basis of an observed survival benefit in a large phase III trial is tebentafusp (Kimmtrak), an affinity-enhanced T-cell receptor fused to an anti-CD3 effector that can redirect T cells to target glycoprotein 100-positive cells in uveal melanoma.^{8,9} Encouraging preliminary data from numerous other agents in multiple solid tumor indications suggest that we may indeed be on the cusp of a transformative revolution in cancer immunotherapy for solid tumors.^{10–12}



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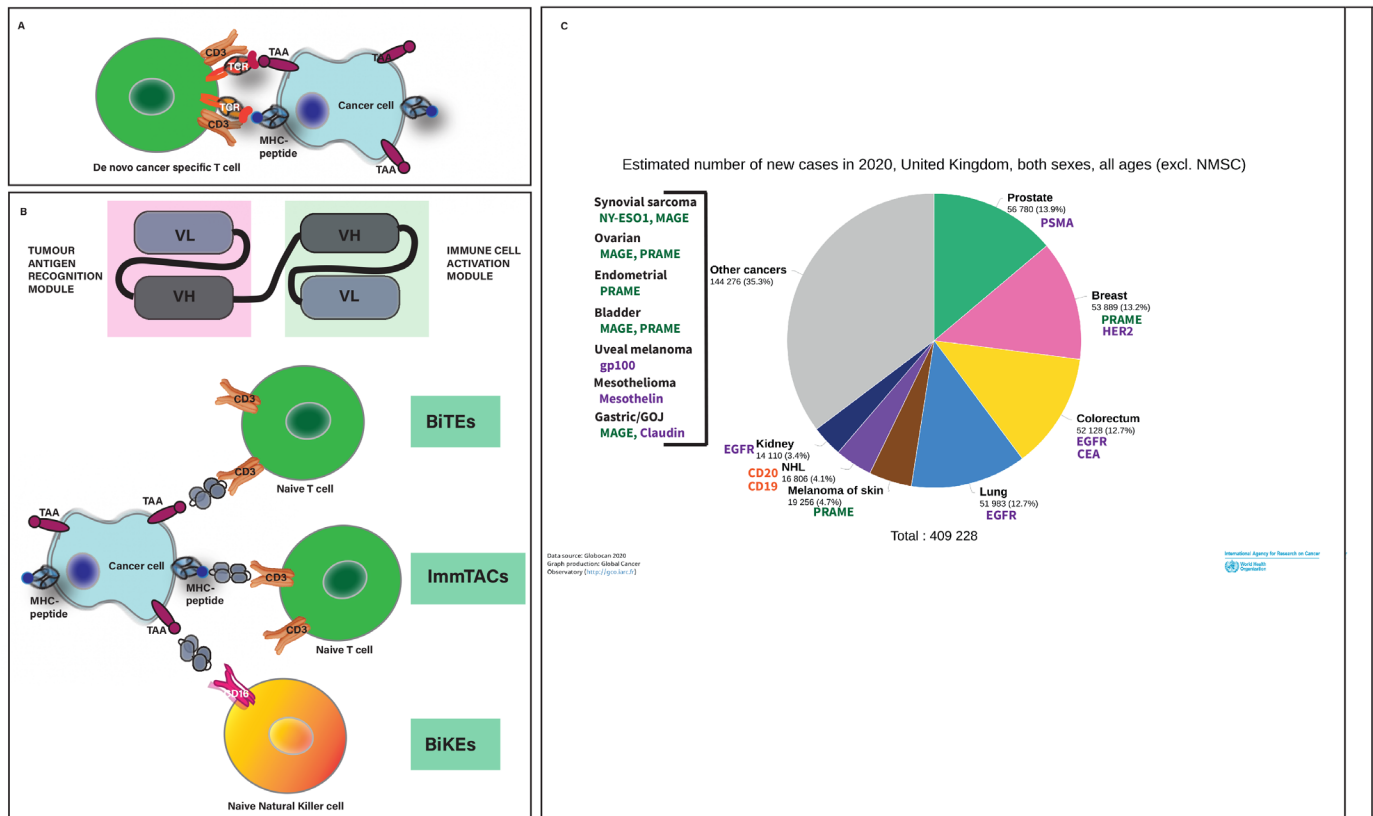


Figure 1 Cartoon illustration of the immunological synapse formed de novo (A) and on stimulation by bioengineered immune engagers (B). Figure 1A shows the interface between a de novo cancer-specific T-lymphocyte (left) and a cancer cell (right), cross-bridging its own multichain T-cell receptor/CD3 (TCR/CD3) complex and a tumor-associated antigen (TAA), either directly or via an major histocompatibility complex (MHC)-peptide. Figure 1B illustrates how bioengineered immune engagers (upper figure) consisting of tumor antigen recognition modules and immune cell activation modules *redirect* immune cells (*lower figure*) toward cancer cells by artificially bridging TAAs or MHC-presented antigens to surface-expressed CD3 (T cells) or other cell-surface receptors (eg, CD16a on natural killer cells). Immune cell engagers are constructed in a variety of designs most commonly utilizing two single chain variable fragments connected by flexible linkers, the most common illustrated here where (VH) variable fragment heavy chain and (VL) variable fragment light chain. (C) The potential utility of immune cell engagers across solid tumors. Current targets of immune-cell engagers currently being tested in clinical trials (green: cancer-testis antigens; purple: cancer-associated antigens; orange: lineage markers) superimposed on a pie chart depicting the estimated number of newly diagnosed UK patients per solid tumor type (excluding non-melanoma skin cancer) for 2020.¹⁴

Artificial activation of cytotoxic immune cells, however, comes with significant on-target off-tumor adverse effects due to the exaggerated release of cytokines. This is well described in the setting of CAR-T therapies, manifesting from asymptomatic transient fever, mild influenza-like symptoms to more severe uncontrolled systemic inflammatory response with vasopressor-requiring circulatory shock, vascular leakage, disseminated intravascular coagulation, and life-threatening multiorgan system failure with neurological sequelae requiring highly specialist inpatient care teams with the support of intensive care units.¹³ With bioengineered immune cell engagers, cytokine release syndrome is also frequently seen (eg, reported in 76% of patients treated on the pivotal phase III trial of tebentafusp⁹), accounting for nervousness about how the expanding use of these therapies will be scaled up across health services.

In this perspective piece, we reflect on our experience of managing the safety of patients with a range of

solid tumors treated on early phase engineered immune engager clinical trials in a dedicated phase I unit with a view of sharing lessons learned in anticipation of further development of these therapies and their widespread use.

Across the 33-month period between February 2019 and November 2021, 598 doses of immune cell engager investigational medicine products (IMPs) were administered to 48 patients enrolled onto eight distinct immune engager early phase clinical trials in the RMH/ICR Drug Development Unit (these only included patients treated with bispecific or trispecific immune engager antibodies, but excluding TCR or CAR-T therapies).

Our cohort included patients with heavily pretreated advanced solid malignancies from a variety of primary sites—prostate (33%), ovarian (17%), sarcoma (17%), colorectal (8%), melanoma (8%), lymphoma (4%), lung (6%), breast (2%), peritoneal pseudomyxoma (2%) and esophageal (2%). These patients were identified from the trials database and reviewed retrospectively. As per

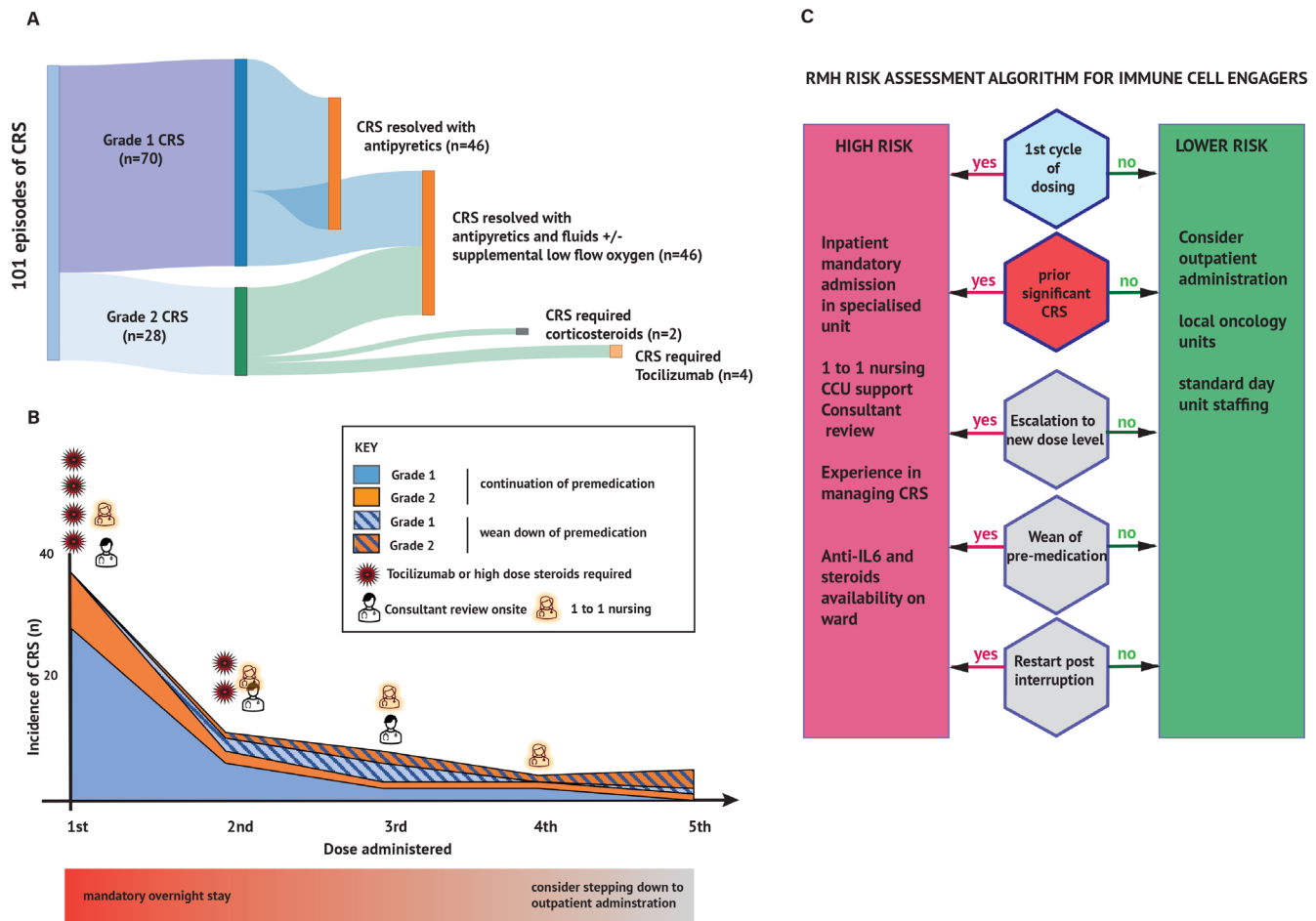


Figure 2 (A, B) Analysis of Cytokine Release Syndrome (CRS) events seen on immune cell engager therapy within the RMH/ICR Drug Development Unit. (A) Sankey diagram depicting 101 episodes of CRS seen in the RMH/ICR Drug Development Unit across the reporting period (598 treatments administered) illustrating the severity of each CRS episode and the treatments required with outcome. All grade 1 events resolved with a ward-based ceiling of care. Six episodes did not resolve with supportive measures and required the administration of steroids or tocilizumab. (B) Depicts the same data illustrated across time, with incidence of CRS at each administration of IMP at a particular dose level (eg, first dosing, second dosing at that dose level, third, etc). The number of episodes of CRS were highest at the first administration of any dose level and reduced with repeated dosing. More severe events requiring high dose steroids or tocilizumab were only seen at the first or second administration of immune cell engager (four events at first dosing, two further events at second dosing). CRS at later doses were only associated with wean of steroid premedication, or dose interruption. One-to-one nursing resource (orange icon) and senior consultant onsite review required (white icon) on the unit is shown, similarly focused on the initial few administrations of immune engager therapy. (C) Proposed algorithm for risk assessment and resource management of immune engager therapy delivery planning for scalability.

the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria¹³ for Cytokine Release Syndrome (CRS) grading, patients who fulfilled the criterion of fever $\geq 38^{\circ}\text{C}$ within 24 hours of receiving the investigational medicinal product were identified and selected for detailed analysis.

Of the administered IMP doses, 17% (n=101) resulted in an episode of CRS as defined by the American Society for Transplantation and Cellular Therapy (ASTCT) criterion. Of these, 67% were grade 1 and 33% were grade 2 (figure 2A). There were no grade 3 or above events. When CRS occurred, it was typically symptomatic and heralded by rigors/chills (experienced in 59% of cases) just prior to the development of fever. Other commonly experienced symptoms included nausea and/or vomiting

(29%), headaches (13%), pain flares (8%—either myalgia or around known sites of disease), diarrhea (7%) or respiratory symptoms (2%—one patient experienced dyspnea and one wheezing). Of the episodes of CRS, 18% were asymptomatic. Of the CRS events, 34% were defined by fever alone, but the majority of events included a transient tachycardia (53%). Hypotension and hypoxia were featured in 29% and 6% of events, respectively.

The majority of cases were managed with the administration of antipyretics (either paracetamol and/or ibuprofen), which were sufficient to resolve the episode in just under half of cases (47%). A further 47% of events were managed successfully with a combination of intravenous fluids and antipyretics. Despite only 29% of events featuring hypotension, intravenous fluid support was

given often (53%), usually prophylactically when patients were noted to have a high lactate on venous blood gas or gastrointestinal symptomatology (vomiting/diarrhea).

Across our cohort of patients with solid tumor, there were only six episodes (6%) of symptomatic CRS in which supportive measures were deemed insufficient, and steroids or tocilizumab were given. All six events in which steroids or tocilizumab were given were grade 2 and occurred in the planned acute (24–48 hour) hospitalization period following dosing (figure 2A). All patients who developed a grade 2 reaction had one-to-one nursing for intensive monitoring, received prompt senior review by a drug development consultant on call, and critical care outreach review. Importantly, these occurred most commonly on the first (67%) or second dosing (33%) (figure 2B) and fully resolved with supportive treatment. Of the six patients who experienced grade 2 CRS, four (67%) went on to be safely retreated.

The two most commonly adopted risk reduction strategies per trial protocols were use of ‘step dosing’ and steroid premedication. The risk of developing CRS was highest at the first dose of any dose level with tachyphylaxis seen with repeated dosing (figure 2B). By the fifth infusion at any dose level, the relative risk of any event of CRS was reduced by 56%, with the majority of these (80%) occurring in patients who had a wean of steroid premedication (figure 2B). Beyond this timeframe, CRS was only seen in patients who had continued to, and persistently reacted, or had a dose interruption (eg, due to a holiday) or a change in premedication.

Importantly, we did not observe any events of neurotoxicity or immune effector cell-associated neurotoxicity syndrome despite three patients having previously undiagnosed micro-metastatic brain metastases, or previously treated and stable brain metastases.

By mapping the totality of our experience so far, we propose the following considerations for operational readiness for scalability of immune engager therapy delivery for solid tumors in cancer centers both UK wide and across the world (figure 2C). A risk-mitigated approach would allow for the safe transition of patients from high-intensity care in specialized units to lower intensity day units and local centers. Patients would be treated in specialized units for their first cycle of treatments, where the risk of CRS is greatest. These units will be consultant-led with experienced teams and critical care support. Stepping down to an outpatient/local facility would only be considered for those patients who did not experience a prior reaction/and were tolerating their current dose/premedication regime. Patients who were being considered for a dose change/wean of steroids, or had an interruption of dosing would need to restart dosing in a specialized center to ensure tolerability.

This approach would also allow knowledge sharing between the specialized centers and the day units/local cancer centers, thereby training and building capacity for future scalability. As familiarity with immune engagers increases, and with establishment of a safe transition

approaches, it might be possible to introduce a more nuanced approach in the locoregional centers while ensuring safety of the patients. The future is on us, and with appropriate risk-mitigation strategies, we can be ready to rapidly roll out next-generation immune engager therapies safely for all patients with solid tumor.

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REFERENCES

- 1 Titov A, Petukhov A, Staliarova A, *et al*. The biological basis and clinical symptoms of CAR-T therapy-associated toxicities. *Cell Death Dis* 2018;9:897.
- 2 Labrijn AF, Janmaat ML, Reichert JM, *et al*. Bispecific antibodies: a mechanistic review of the pipeline. *Nat Rev Drug Discov* 2019;18:585–608.
- 3 Bromley SK, Burack WR, Johnson KG. The immunological synapse, 2001. Available: www.annualreviews.org
- 4 Slaney CY, Wang P, Darcy PK. Cars versus bites: a comparison between T Cell-Redirection strategies for cancer treatment. Available: www.aacrjournals.org [Accessed 26 Sep 2022].
- 5 Goebeler M-E, Bargou RC. T cell-engaging therapies - BiTEs and beyond. *Nat Rev Clin Oncol* 2020;17:418–34.
- 6 Przepiorka D, Ko C-W, Deisseroth A. Fda approval: Blinatumomab clinical cancer research 2015;21:4035–9.
- 7 Fucà G, Spagnoletti A, Ambrosini M, *et al*. Immune cell engagers in solid tumors: promises and challenges of the next generation immunotherapy. *ESMO Open* 2021;6:100046 <https://pubmed.ncbi.nlm.nih.gov/33508733/>
- 8 Project information. Tebentafusp for treating advanced (unresectable or metastatic) uveal melanoma [ID1441] | Guidance | NICE, 2022
- 9 Nathan P, Hassel JC, Rutkowski P, *et al*. Overall survival benefit with Tebentafusp in metastatic uveal melanoma. *N Engl J Med* 2021;385:1196–206.
- 10 Lopez J, Shinde R, Burgess M. Trial in progress: first-in-human study of a novel anti-NY-ESO-1-anti-CD3, TCR-based bispecific (IMCnyeso) as monotherapy in NY-ESO-1/LAGE-1A-posit | OncologyPRO, 2019. Available: <https://oncologypro.esmo.org/meeting-resources/esmo-2019-congress/trial-in-progress-first-in-human-study-of-a-novel-anti-ny-eso-1-anti-cd3-tcr-based-bispecific-imcnyeso-as-monotherapy-in-ny-eso-1-lage-1a-posit> [Accessed 26 Sep 2022].
- 11 Davar D, Sweis R, G BJ. Phase 1 dose escalation of IMC-C103C a CD3_MAGE-A4 T cell receptor (TCR) bispecific protein | OncologyPRO, 2021. Available: <https://oncologypro.esmo.org/meeting-resources/esmo-immuno-oncology-congress/phase-1-dose-escalation-of-imc-c103c-a-cd3-mage-a4-t-cell-receptor-tcr-bispecific-protein> [Accessed 26 Sep 2022].
- 12 Bendell JC, Fong L, Stein MN. First-In-Human phase I study of HPN424. a tri-specific half-life extended PSMA-targeting T-cell engager in patients with metastatic castration-resistant prostate cancer 2020;38:5552.

- 13 Lee DW, Santomaso BD, Locke FL, *et al.* ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant* 2019;25:625–38.
- 14 Sung H, Ferlay J, Siegel RL, *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.