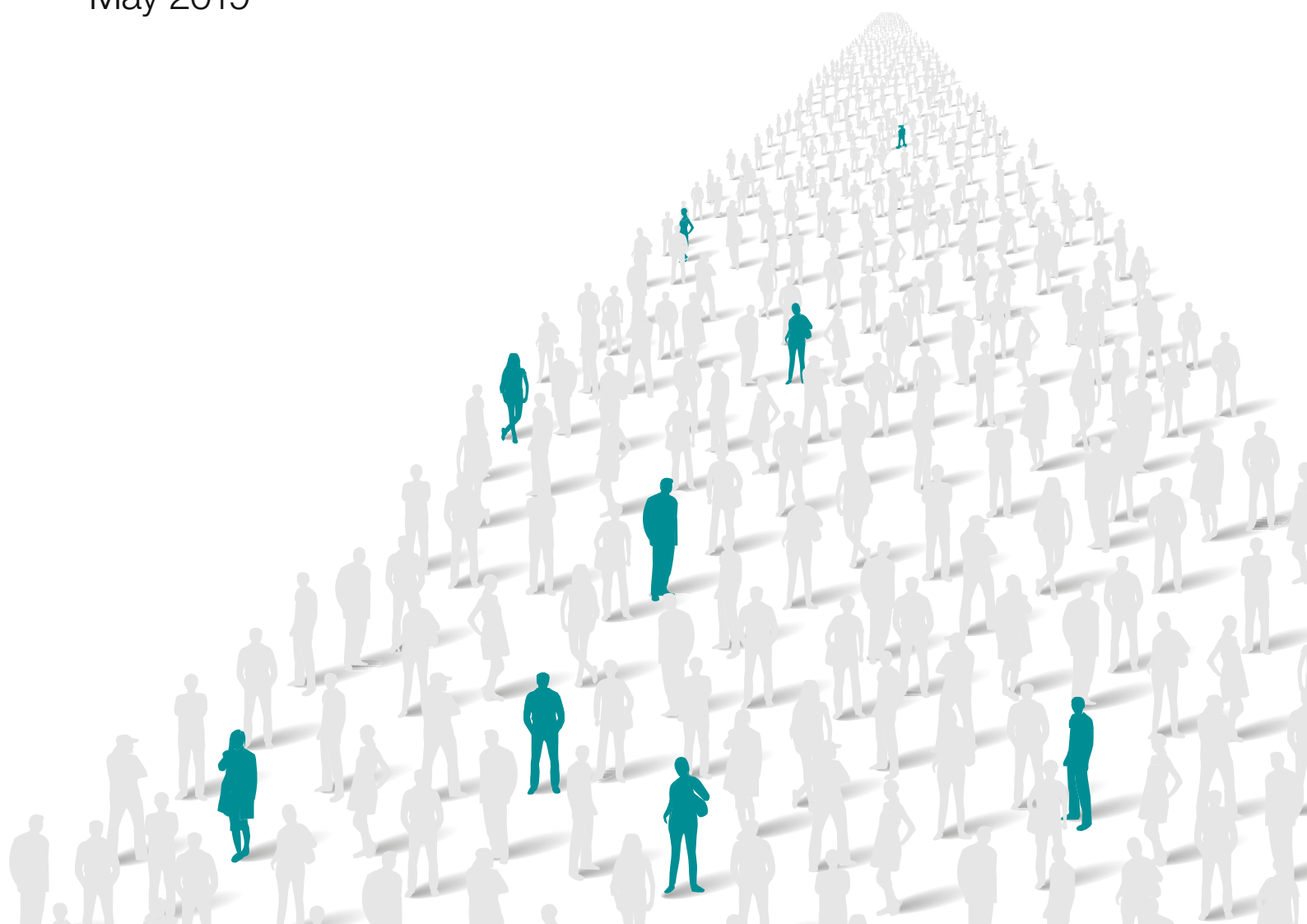
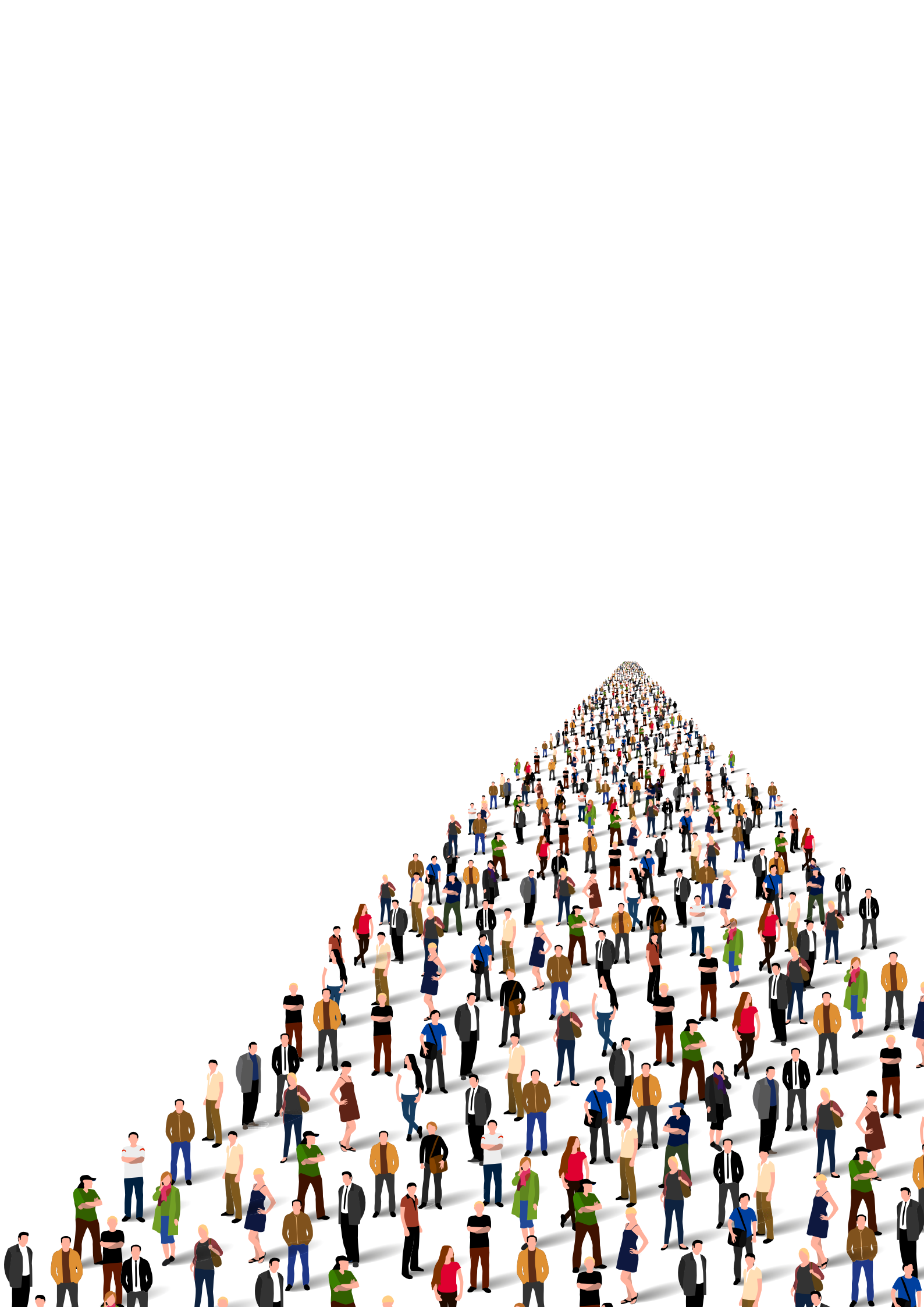


CAR-T: A Revolution That Favours The Few?

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The introduction of immunotherapy has transformed the treatment of cancer. Most notably, immune-checkpoint inhibitors targeting programmed cell death-1 protein (PD-1) or programmed death-ligand 1 (PD-L1) have demonstrated long-term efficacy benefits across multiple cancer types.¹⁻⁶ The success of immune checkpoint inhibitors has raised expectations for other types of immunotherapy in the treatment of cancer, which exploit different immune pathways and alternative protein targets to induce the patient's own immune response to destroy cancer cells.

Chimeric Antigen Receptor (CAR) T-cell therapy is a type of immunotherapy, involving extracting and genetically modifying a patient's own T-cells to express a CAR, which will target a specific tumour antigen. There are two broad classes of tumour antigens; tumour-specific antigens (TSA), which are found on tumour cells only, and tumour-associated antigens (TAA), which can also be found on some normal cells.⁷ The modified CAR-expressing T-cells are expanded ex vivo and subsequently infused back into the patient where they direct an immune response against tumour cells expressing the targeted tumour antigen.

CAR T-cell therapy has demonstrated promising outcomes in haematological malignancies, through targeting multiple different TAAs, such as **CD19**, **CD20**, and **CD30**⁸, although CD19 has garnered the most attention from industry. As of May 1, 2019, there were 66 registered Phase II or III active, industry-sponsored clinical trials evaluating CAR-T therapy in multiple cancer types⁹, highlighting the drive and high industry interest in this novel immune approach to treat cancer.

In a landmark decision in August 2018, the European Commission approved the first (and currently only) CAR-T therapies in Europe; Novartis's Kymriah (tisagenlecleucel) and Gilead's Yescarta (axicabtagene ciloleucel), both of which target CD19. As typically the case for oncology drug approvals, Europe has lagged behind the United States for CAR-T therapies, with FDA-approval for Kymriah coming almost one year earlier than that by the European Commission.

Based on tumour response data from the global JULIET and ELIANA trials ^{10, 11}, **Kymriah's** European approval is for both acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL), but within very specific patient types. Approval in ALL is specifically for paediatric and young adult patients up to 25 years of age with B-cell acute ALL, that is refractory, in relapse post-transplant, or in second or later relapse. Approval in DLBCL is specifically for adults with relapsed or refractory (R/R) status after two or more lines of systemic therapy.

Yescarta's European approval is for adults with R/R DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy, based on tumour response data from the Phase II ZUMA-1 trial. ¹²

Despite the unprecedented durable tumour responses produced by CAR-T therapies in patients with relapsed and refractory B cell malignancies, there are noteworthy barriers specific to this drug class that will likely restrict uptake. These include concerns over cost, logistics of integrating CAR T-cell production into clinical practice, disease control during CAR T-cell production, and identifying patients likely to respond to treatment. Another key concern for physicians regarding the use of CAR-T cell therapy is safety. Cytokine release syndrome (CRS), a profound systemic inflammatory response resulting from rapid immune activation, is a significant and potentially fatal CAR-T treatment-related toxicity. ¹³

Considering the challenges faced by CAR-T therapies, will their potential of revolutionising treatment for patients with relapsed and refractory B cell malignancies be realised?

Findings

To look into the uptake of CAR-T therapies, the Ipsos team turned to the Ipsos Global Oncology Monitor, a source of data where physicians are asked to report on their next drug-treated cancer patients seen in consultation during the time of the research. The Global Oncology Monitor captures patient record forms of all cancer patients (solid tumours and haematological malignancies). To gain insight into CAR-T therapies specifically, we focused on patient records collected for DLBCL patients.¹⁴

Interestingly, of the **139 DLBCL** patients for whom records were collected between January 1 and February 28, 2019, only 14 (10%) of this sample were considered suitable candidates for CAR-T therapy, according to our sampled physicians. Of the 14 patients considered suitable for CAR-T, our sampled physicians indicated that only 2 were currently receiving CAR-T therapy at the time of patient record completion. For the remaining 12 patients considered suitable, 7 were not approved for CAR-T treatment and 5 were unable to receive CAR-T therapy despite being approved for this treatment. Deteriorating condition, patient refusal and logistical challenges were among the reasons given by our sampled physicians for the 5 DLBCL patients approved for CAR-T therapy but unable to receive treatment.

Among the **125 DLBCL** patients who were *not* considered suitable for CAR-T therapy, the majority (68%) were receiving treatment in the first-line setting, where neither Kymriah nor Yescarta are indicated. Indeed, when focusing on our sample physician-stated reasons why their DLBCL patient was not considered suitable for CAR-T therapy, physicians for 58% of cases indicated it was because the 'treatment is not indicated for this patient' and in 24% of cases, the reason given was 'clinically ineligible'. However, other important reasons were stated by our sampled physicians for their DLBCL patient not being considered suitable for this type of therapy, including limited/unproven efficacy, safety concerns, accessibility, and preference for conventional treatment.

In addition to the low prevalence in our sample of CAR-T-eligible and CAR-T-receiving patients, of the 139 DLBCL reported patients only 4% specifically asked about CAR-T therapy. This might be potentially linked to limited patient awareness of this new class of agents as a new treatment.

Conclusion

Whilst CAR-T therapy holds the promise of revolutionising treatment for B-cell malignancies, our data indicate that there are several factors that could potentially impede uptake. A lack of eligible patients is one core issue and, although samples of these patients are small, early signs suggest this problem could be further compounded by the possibility that not all eligible patients will go on to receive this therapy. Such few patients receiving CAR-T could subsequently hinder the growth of physician comfort using these novel treatments. Indeed, increasing familiarity with CAR-T therapies will be critical for physicians to overcome concerns over safety and efficacy as they become more confident in recognising and managing any signs of toxicity associated with this drug class, in addition to seeing patients' response to treatment first-hand.

Novartis and Gilead have successfully brought a novel immunotherapy drug class to the European market, however, despite the positive media attention and high interest surrounding immunotherapy and the CAR-T drug class specifically, this article indicates a limited impact of CAR-T therapies in this early launch period of Kymriah and Yescarta, with only a restricted patient population benefiting from CAR-T treatment. Identifying suitable patients for CAR-T treatment appears to be the primary barrier to uptake, however Pharma will need to address issues around the logistics of treatment, safety concerns, and confidence in efficacy to maximise uptake.

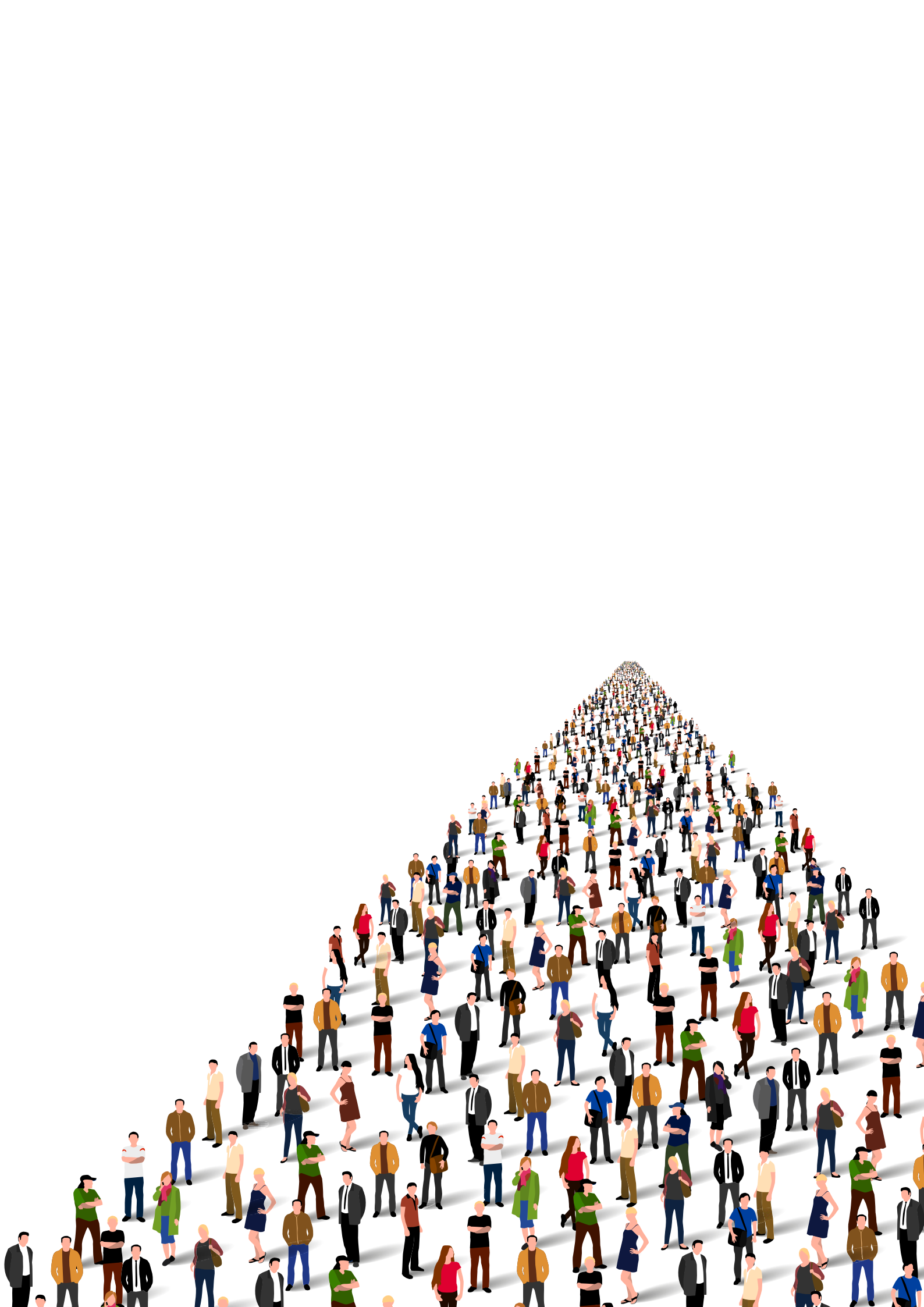
In an oncology era dominated by continuously and rapidly evolving treatment landscapes, will CAR-T therapies be able to gain a strong foothold in the market? Could the slow uptake of CAR-T treatments result in CAR-T therapies being replaced by yet more novel treatments? With two CAR-T therapies currently on the market and more in the pipeline, how will physicians decide which CAR-T treatment to use? These are just some of the questions that the Ipsos team is looking to answer with new studies in development, combining Real World Evidence with patients', physicians' and key opinion leaders' perceptions.

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*About the Research

Drug treatment patterns were investigated using EU5 data from the Ipsos Global Oncology Monitors, which are proprietary syndicated patient record databases. Specifically, doctors reported on drug-treated patients seen in consultation during the study period. Dates and sample sizes are given below, and all research was conducted online. All results cited were tested for significance using Pearson's chi-squared test; all results were significant at a threshold level of $p < 0.05$. Data are © Ipsos, all rights reserved.



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