FROM THE ANALYST'S COUCH

Cancer cell therapies: the clinical trial landscape

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Cell therapies constitute the largest number of agents in development in immuno-oncology (*Nat. Rev. Drug Discov.* **18**, 899–900; 2019). Here, we provide an update on the pipeline and clinical trials of cancer cell therapies. We also compare the current landscape (with a March 2020 data cut-off point) with our previous update from March 2019 (*Nat. Rev. Drug Discov.* **18**, 821–822; 2019).

Cancer cell therapy pipeline

Pipeline trends. The current global cancer cell therapy pipeline includes 1,483 active agents, 472 more than last year. Among the different cell therapy types, the chimeric antigen receptor (CAR)-T cell class has the largest increase (290 agents this year versus 164 in 2019), whereas novel T cell approaches (such as CRISPR engineered T cells or γδT cells) and other cell therapies (such as macrophage-based therapies) have increased by 49 and 56 agents, respectively (FIG. 1).

To improve our understanding of the year-on-year developments, the active agents were reclassified based on their origin as autologous or allogeneic (off-the-shelf) (Supplementary Fig. 1). A majority of cellular immunotherapies (667) in development are autologous in nature. However, the greatest percentage increase from those reported last year comes from preclinical (73.8% increase) and phase I (90.9% increase) development of allogeneic therapies. For most therapies in phase II and beyond that are being developed in countries other than the United States, it has not been disclosed whether they are autologous or allogeneic (Supplementary Fig. 2). Of note, the previously marketed allogeneic agent nalotimagene carmaleucel was withdrawn from the EU markets by its manufacturer MolMed in October 2019 following its failure to improve disease-free survival in a phase III trial.

Top targets for blood and solid tumour indications. To better understand the targets of cell therapies for cancer, the top ten targets for blood and solid tumour indications are shown in FIG. 2a,b. CD19 is still the most dominant target for cell therapies against blood indications, but the number of active agents targeting B cell maturation antigen (BCMA) or CD22 have nearly doubled since last year. The largest category for solid tumours is made up of cell therapies for which the tumour-associated antigen (TAA) has not been disclosed, and the greatest change in the top ten targets is for glypican 3 (GPC3) and prostate-specific membrane antigen (PSMA). This increase may be due to the well-validated associations of increased expression of GPC3 in paediatric solid embryonal tumours and adult hepatocellular carcinoma (which is highly prevalent in China) and of PSMA in prostate cancer.

Clinical trial development. To gain a better understanding of the clinical development of cell therapies, information from GlobalData's clinical trials database was used to look at trials by therapy type and indication (Supplementary Fig. 3 and 4). Among the trials with published readouts, primary end points were met more frequently in phase I or II trials for solid and blood indications, with few reported negative readouts (FIG. 3). Interestingly, tumour-infiltrating lymphocyte (TIL) therapies or NK cell therapies have had positive readouts in solid tumours in phase I or phase II, whereas other cell therapies, such as cytokine-induced killer cells (an ex vivo-induced type of NKT cells), have had positive results in phase III or IV trials. Novel T cell technologies based on allogeneic transplantation have more positive results in early phases in blood cancers than in solid tumours.

Global development. The United States and China dominate the cancer cell therapy pipeline, and the number of agents in development in China is closing in on the number of agents in development in the United States (508 agents compared with 600) (Supplementary Fig. 5). Most cell therapies in the United States are being developed by the pharmaceutical industry. Although cell therapies in China have been traditionally developed by academic institutions, in the past year, cell therapies developed by industry

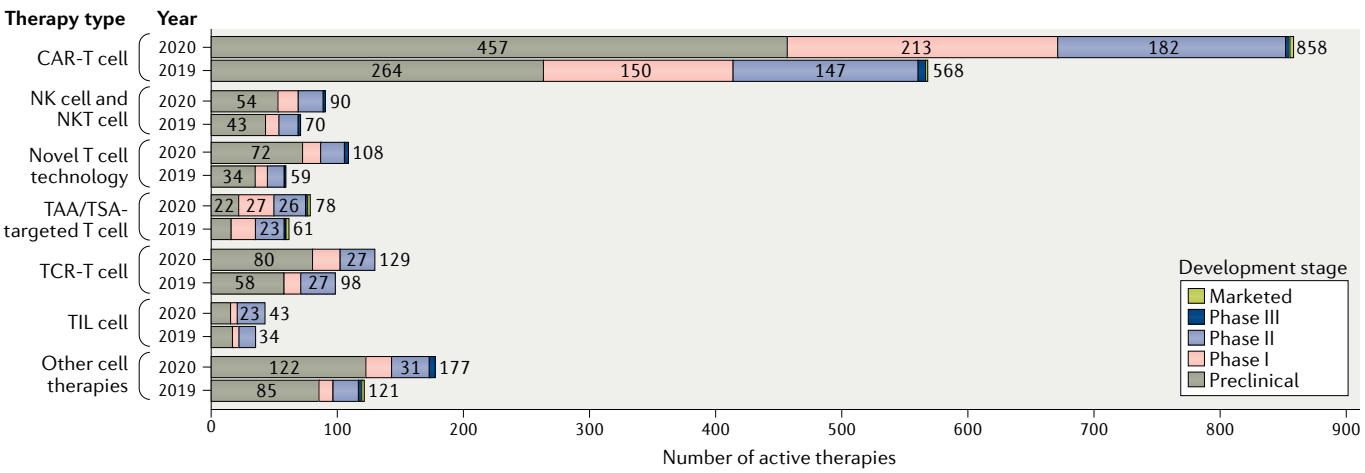

Fig. 1 | **Trends in the cancer cell therapy pipeline.** Comparison of the pipeline in March 2019 and March 2020 (data on analysis included in the Supplementary file). TAA, tumour-associated antigen; TCR, T cell receptor; TIL, tumour-infiltrating lymphocyte; TSA, tumour-specific antigen.

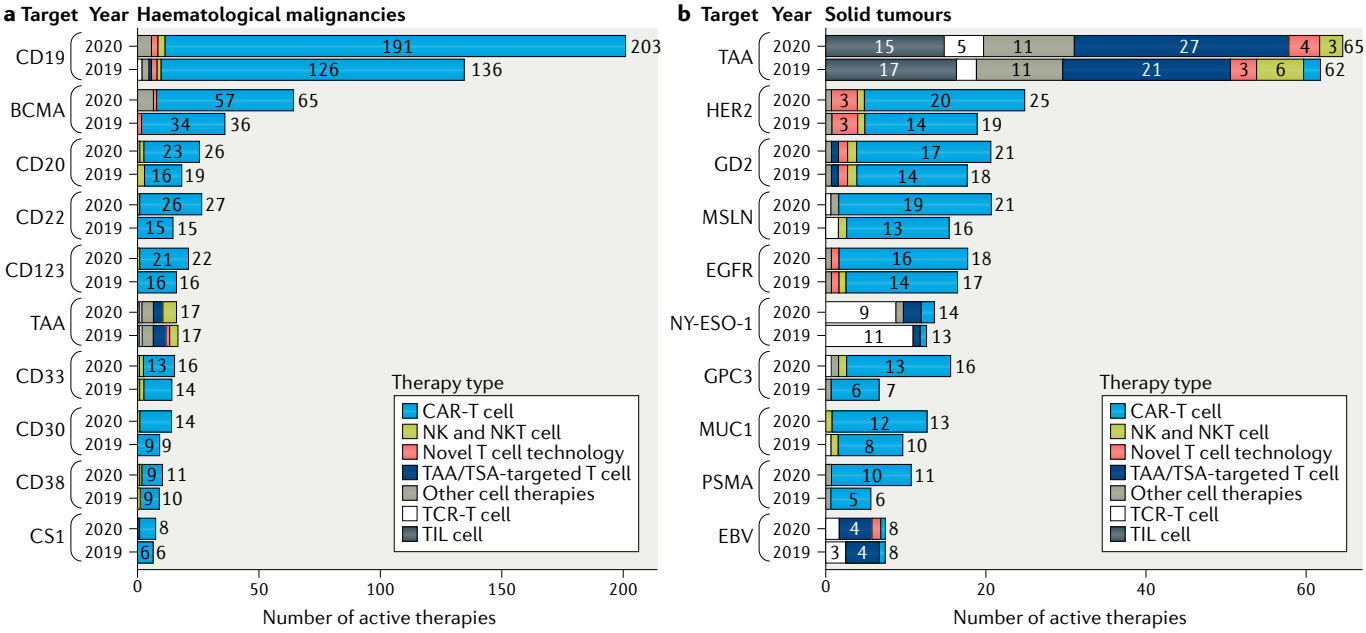

Fig. 2 | **Top targets of cell therapies for blood and solid tumours.** CD19 continues to be the top target for blood cancers, whereas the top category for solid tumours is agents for which the tumour-associated antigen (TAA) has not been disclosed.

in China have surpassed those developed by academia. The preclinical assets in China have nearly tripled in a year, increasing from 69 to 202, but how many of these assets will progress to the later stages of development remains to be seen (Supplementary Fig. 6). Phase I and phase II cancer cell therapy development in China has grown in proportion to the nearly 50% general increase year over year, similar to the growth ratio in the United States. The clinical trial landscape globally matches the target therapy development pipeline, in which the United States and China dominate the field. However, currently, China has more cell therapy trials (871) than the United States (718) (Supplementary Fig. 7).

Conclusion and outlook

The number of cell therapies in preclinical and clinical development continues to expand. The field is increasingly exploring off-the-shelf therapies as commercially viable options for wider patient populations. Such new therapies hold promise, but whether they match the effectiveness of autologous therapies remains to be seen, especially after the only authorized allogeneic, non-vaccine cell therapy was withdrawn from the EU markets owing to its lack of efficacy in phase III. So far, most allogeneic agents are in preclinical and early-phase clinical development, and it may be some time until these agents achieve widespread clinical validation. Data from both blood and solid cancer clinical trials using allogeneic and autologous cell therapies show positive outcomes, but these data are limited and mainly from early-phase trials investigating safety of the products. It is important to note that results from trials with negative outcomes may not be publicly disclosed, which may skew the end point status analysis towards positive outcomes.

China continues to develop new cell therapies, and the shift from academia to pharmaceutical industry development may increase its rigour. China has also seen an increase in preclinical development in the past year, becoming a leader in conducting cell therapy trials in oncology, followed by the United States. However, this momentum is very likely to be affected by the extensive disruption of clinical trials globally across all therapy areas due to the COVID-19 pandemic.

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Competing interests

V.M.H.-L. is a scientific advisor and has equity interest in Fx Biopharma. The other authors declare no competing interests.

Supplementary information

Supplementary information is available for this paper at https://doi.org/10.1038/d41573-020-00099-9.

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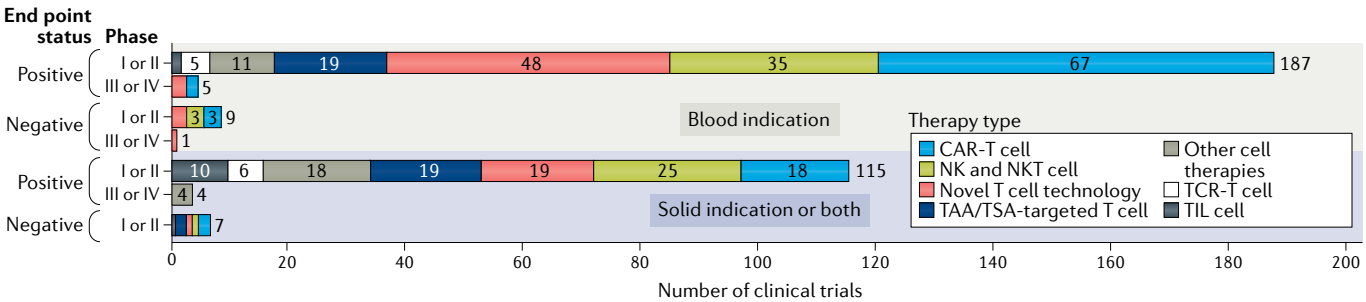

Fig. 3 | **Outcomes from clinical trials of cell therapies for cancer.** End point status of trials with published results by cancer type, therapy type and phase. 'Positive' indicates fully and partially met end points. 'Negative' indicates unmet end points. TAA, tumour-associated antigen; TCR, T cell receptor; TIL, tumour-infiltrating lymphocyte; TSA, tumour-specific antigen.