From the analyst's couch

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Immuno-oncology clinical trials take a turn beyond PD1/PDL1 inhibitors

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For more than a decade now, the global landscape of immuno-oncology (IO) clinical trials has been dominated by studies testing PD1 and PDL1 inhibitors, whether as monotherapy or in combinations. However, in 2022 that trend started to change. In this analysis, the Cancer Research Institute (CRI) provides its latest assessment on the global IO landscape, including year-by-year comparisons on therapy modalities, targets, and indications addressed in trials starting between 2018 and 2022.

IO clinical trials take a new direction

CRI's database contains 17,558 global IO clinical trials (testing at least one immunotherapeutic agent) that started, or were planned to start, any time between 1986 and 2025 (Supplementary Fig. 1). To obtain a more accurate view on the current trends in the IO trials landscape, we focused the present analysis on those trials with start dates between 2018 and 2022 (9,007 trials), and calculated year-over-year changes.

Number of new phase II IO trials decreased in 2022. Our analysis shows a reduction in the number of new IO trials in 2022, in contrast with the previous years, which showed a trend of an increasing number of new trials (Fig. 1a). Although this recess is minor (−2.9%), and both phase I and III trials continued to increase in 2022 (by 8.8% and 6.6%, respectively), we observe a reduction in the number of phase II trials (1,188 in 2022 versus 1,269 in 2021 — a 6.4% decrease). This trend may point towards augmented caution from sponsors in advancing assets from phase I to phase II, rather than a generalized deceleration.

To get further granularity into this decrease, we investigated aspects of clinical trials such as indications, modalities and targets. Our analysis revealed that the number of trials starting decreased in 2022 for head and neck cancers (−31.0%), respiratory and/or thoracic malignancies (−24.7%), skin cancers (−9.8%), and digestive and/or gastrointestinal cancers (−8.3%). The year 2022 was the second in a row registering a decrease of new trials in skin cancer, with 2021 already showing a 7.9% decrease with respect to 2020. IO clinical trials in other malignancies continued to increase in 2022 relative to 2021, such as for mixed types of solid tumours (20.2%), haematological cancers (4.7%), gynaecological tumours (3.7%) and genitourinary cancers (1.7%) (Supplementary Fig. 2a). Of note, the sharp increase in trials exploring mixed types of solid tumours in 2022 may be explained, in part, by the increase observed in phase I trials and decrease in phase II trials, as earlier phase trials generally address a range of tumour types that cannot be fitted within more organ- or system-specific categories. A breakdown by indication and trial phase is also provided in Supplementary Fig. 2b.

Number of IO trials using anti-PD1/PDL1 monoclonal antibodies decreased in 2022. To understand how usage of different IO therapeutic modalities has changed in the past 5 years, we investigated the number of clinical trials incorporating each IO drug modality and organized them by clinical trial start date. Our results show that the number of trials using T-cell-targeted immunomodulators (TIMs) decreased by 6.0% in 2022, a noteworthy change as this is the first observation of a decline after continuous year-over-year increases since 2018. By contrast, we observe a steady year-over-year growth of cell therapies since 2018, as well as an increase in the use of non-TIMs ('other immunomodulators', OIMs) and cancer vaccines since 2020 (Fig. 1b). A breakdown by trial phase for this analysis is included in Supplementary Fig. 3.

Further analyses of the subcategories within each therapeutic modality indicates that, within the TIM modality, T-cell-targeted monoclonal antibodies (TIM mAbs) is the only category that registers a decreased usage in oncology clinical trials in 2022, with a 9.5% reduction relative to 2021 (Supplementary Fig. 4a).

TIM mAbs is a modality largely dominated by anti-PD1/PDL1 mAbs. Side-by-side comparison between 2020, 2021 and 2022 confirms that the number of trials using PD1/PDL1-targeted mAbs decreased by 10.3% in 2022 relative to 2021. Similarly, we notice a reduction of 5.6% in the number of trials using anti-TIGIT mAbs. By contrast, trials using mAbs targeting CTLA4 and LAG3 have increased by 17.9% and 36.8%, respectively (Supplementary Fig. 4b). When analysing phase II trials only, we observe an association between the reduction of phase II trials and PD1/PDL1 mAbs usage, with a drop of 8.9% in phase II trials incorporating this drug type (Supplementary Fig. 4c).

Moving beyond PD1/PDL1 mAbs

Other interesting insights can be extracted from a closer look at the rest of IO therapeutic modalities. Within TIM, the usage of bispecific/multispecific antibodies has grown every year since 2018, with a 9.0% increase in 2022, like T cell engagers, of which usage has grown by 13.3% in 2022 (Supplementary Fig. 4a). Haematological cancer targets, such as CD20 and CD19, continue to be the most popular targets among T cell engagers. CD20 has followed CD19 very closely in the past years and has finally surpassed it as the most frequent T cell engager target in trials started in 2022 (Supplementary Fig. 5a). Targets of other TIM bispecific and multispecific antibodies can be seen in Supplementary Fig. 5b.

Within cell therapies, trials using chimeric antigen receptor (CAR)-T cells dominate the space, representing more than half of the cell therapy assets used across IO trials between 2018 and 2022. CAR-T cell usage has grown by 5.6% between 2021 and 2022. However, we see a more accelerated increase in the usage of other cell therapies during the same time, such as other T cells (24.2%), NK cells (7.7%) and bacterial assets (28.6%) (Supplementary Fig. 6a). Targets of cell therapies used in oncology clinical trials between 2020 and 2022 can be seen in Supplementary Fig 6b. Consistent with our recent cell therapy landscape analysis (*Nat. Rev. Drug Discov.* **9**, 631–632; 2022), we observe that there are now almost as many clinical trials in solid tumours as there are trials in haematological malignancies, with the former accounting for 47.1% of all new 2022 IO trials for which cell therapies are being tested, a 14.2% increase over 2021 (Supplementary Fig. 7).

The use of OIMs in IO clinical trials also increased in 2021 and 2022. Of note, although the use of mAbs in this modality decreased

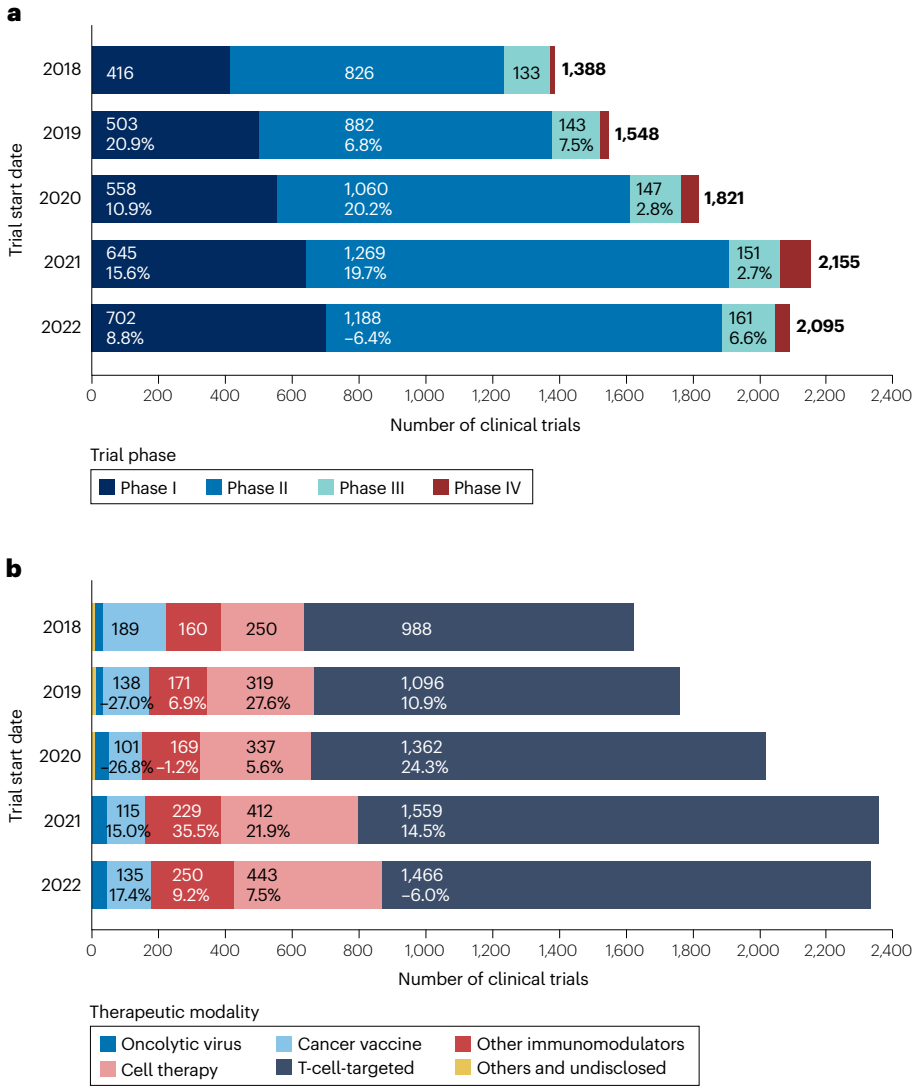

Fig. 1 | The number of phase II trials decreased in 2022, together with usage of T-cell-targeted immunomodulators. a, Number of immuno-oncology (IO) clinical trials, by trial phase and starting year. **b**, Number of IO clinical trials according to type of IO drug, by clinical trial start date. The total number of trials in panel **b** does not correspond to the number of unique trials (those trials assessing more than one modality are counted once for each different IO modality used). In both panels, % indicates year-over-year growth.

over the past year (10.4% decrease from 2021 to 2022), the use of other OIM modalities has increased, including recombinant and/or fusion proteins — currently the most popular modality within OIMs, use of which grew by 8.0% last year — as well as small molecules, nucleotides and bispecific/multispecific antibodies engaging immune cells other than T cells (Supplementary Fig. 8a). Among targets of this modality, interleukins, particularly IL-2, or their receptors, dominate the space, in addition to other targets such as CD47 and different toll-like receptors, such as TLR3 (Supplementary Fig. 8b).

In general, the diversity of targets across IO modalities has expanded over the past years, with 146 different targets in trials started in 2020, 160 in 2021 and 195 in 2022 (Supplementary Fig. 9).

Conclusions and future directions

Our current analysis of global IO clinical trials shows that the field took a turn in 2022 with respect to previous years. After more than a decade of an upward trajectory, we notice a decrease in new clinical trials, a shift driven largely by the reduction in phase II studies using anti-PD1/PDL1 mAbs. We interpret this as a sign that sponsors are being more selective when prioritizing assets and IO combinations for further development in the clinical pipeline. This situation is also likely precipitated, in part, by the fact that many anti-PD1/PDL1 mAbs are reaching patent expiration in the coming years.

Concomitant to these downward trends, there is an increase in the number of phase I trials, as well as a rise in the usage of newer therapeutic modalities (such as different types of engineered cell therapies and bispecific antibodies), and a continued growth in the number of proteins being targeted by IO assets. All of these are healthy signs of innovation in the IO space, which is increasingly exploring novel drug modalities and mechanisms of action for immune stimulation and reprogramming beyond PD1/PDL1 mAbs, which have been the mainstay combo partner for new IO agents advancing in clinical development beyond phase I. Continued longitudinal analyses in the coming years will be necessary to monitor and understand evolution of these trends.

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Competing interests

The authors declare no competing interests.

Additional information

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