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Challenges and opportunities in the PD1/PDL1 inhibitor clinical trial landscape

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Challenges and opportunities in the PD1/PDL1 inhibitor clinical trial landscape

Last year marked a decade since the first checkpoint inhibitor, a monoclonal antibody (mAb) against CTLA4, was approved by the FDA to treat melanoma. This approval revolutionized cancer treatment and paved the way for clinical advances with immune checkpoint inhibitors and other immuno-oncology (IO) therapies. To date, the FDA has approved seven immune checkpoint inhibitors for the PD1/PDL1 pathway: four anti-PD1 and three anti-PDL1 mAbs, including the anti-PD1 mAb dostarlimab, approved in April 2021. This report provides an updated landscape of PD1/PDL1 clinical trials, including use of approved therapies in the clinic and a summary of emerging modalities.

Clinical trials continue to grow

There are currently 5,683 clinical trials testing anti-PD1/PDL1 mAbs — as monotherapy or in combination with other treatments — 4,897 of which are active (FIG. 1). Compared with the analysis we conducted in 2017, this represents a 278% increase in the total number of clinical trials in the past 5 years. Although the total number of clinical trials continues to increase every year, our observations across these years indicate that there has been a slow decline in the year-over-year increase. There was a 29% increase in the total number of clinical trials assessing anti-PD1/PDL1 mAbs in the past year, compared with a 50% increase from 2017 to 2018 (Supplementary Fig. 1). Looking at the trial landscape across FDA-approved versus other anti-PD1/PDL1 mAbs, the number of clinical trials assessing mAbs that are in clinical development but not yet approved by the FDA (Supplementary Fig. 1, 'Other PDx') continues to show robust activity, comprising 29% of all trials.

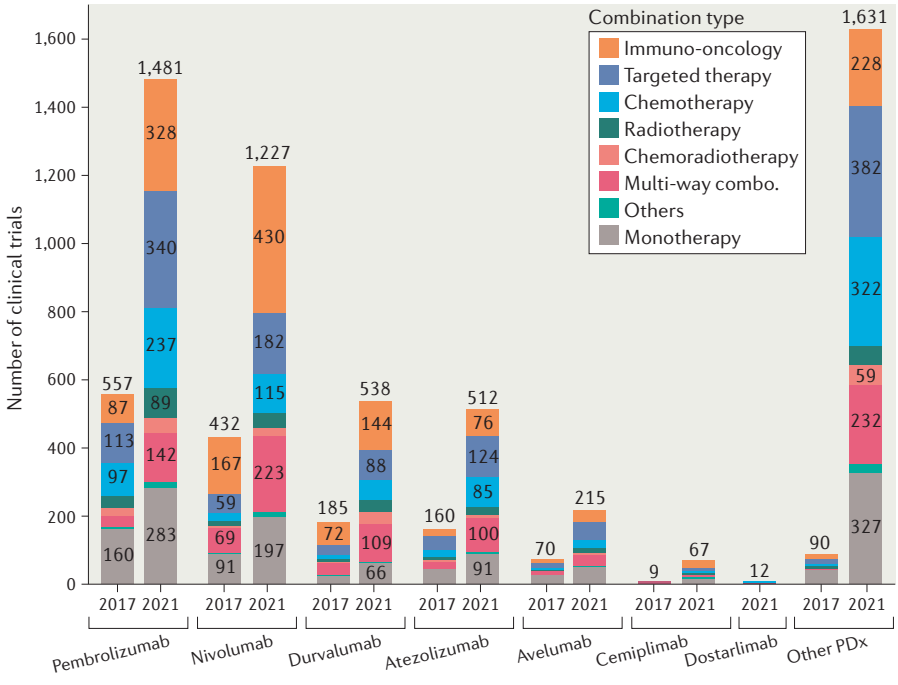

Fig. 1 | **The landscape of anti-PD1/PDL1 mAb clinical trials in 2017 and 2021.** As of December 2021, there are 5,683 clinical trials assessing anti-PD1/PDL1 mAbs. 'Other PDx' includes any anti-PD1/PDL1 mAbs without FDA approvals.

Combination approaches lead the field

Our analysis revealed that 4,062 out of 4,897 active trials (83%) are testing PD1/PDL1 combination regimens with other IO therapies, targeted therapies, chemotherapies and radiotherapies. Of these combination modalities, IO therapies lead the space with 1,058 active trials, and targeted therapies closely follow with 1,008 trials. Monotherapy trials continue to decrease, with 17% of active trials using monotherapies against PD1/PDL1, a trend consistent with previous updates. We compared average planned patient enrolment in monotherapy trials with that in combination trials. The data show that the average planned patient enrolment per monotherapy trial has been falling sharply over the years, resulting in a nearly 7-fold decrease compared to 2014, the year with the highest patient enrolment numbers in monotherapy trials (FIG. 2). Conversely, the average planned patient enrolment per combination trial has decreased more modestly, with a near 2-fold drop compared to its peak in 2015.

As anti-PD1/PDL1 clinical trials continue to move towards combination strategies, we updated our analyses of the targets pursued by such modalities. Excluding PD1/PDL1, there are nearly 300 targets and pathways being tested, 18% more since our last update (Supplementary Fig. 2). VEGF/VEGFR-targeted therapy, chemotherapy and CTLA4 inhibitors continue to be the top combination strategies, although VEGF/VEGFR-targeted combination trials seem to show less of a steep increase since 2020 (FIG. 3). By contrast, chemotherapy and CTLA4 combination trials show a decline.

Patient recruitment and anti-PD1/PDL1 usage

As per our previous analyses, China has led the field in patient recruitment rate (RR) in anti-PD1/PDL1 clinical trials in both monotherapy and combination settings. To obtain a real sense of the RR status globally, we gleaned information from 147 IQVIA-managed anti-PD1/PDL1 clinical trials across 960 unique sites. In line with our previous findings, RR in monotherapy trials continues to decline in the USA and China, albeit at a much lower rate in China (Supplementary Fig. 3). Interestingly, Asia-Pacific countries (Australia, New Zealand, South Korea, Hong Kong or Thailand) have seen an increase in RR in both monotherapy and combination trials. This spike could be a result of increasing clinical trial activity with

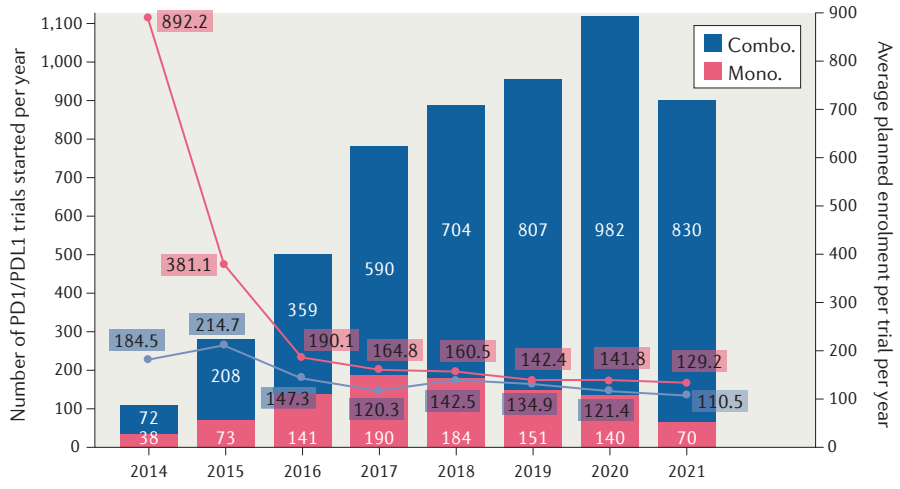

Fig. 2 | **Comparison of monotherapy and combination trials.** Most new trials since 2014 have been combination trials (bar graph). The average planned patient enrolment (line graph) has decreased since 2014 for monotherapy trials more than for combination trials.

new anti-PD1/PDL1 agents ('Other PDx'). Monitoring across these regions will yield meaningful insights into global trends for patient RR.

To further explore real-world data on anti-PD1/PDL1 usage, we used MIDAS, an IQVIA proprietary database containing global prescription by diagnosis and sales data for all currently marketed drugs. Our analyses on use of three generations of anti-PD1/PDL1 agents showed that the market size of the anti-PD1/PDL1 agents is intensively growing in terms of usage on the country level and in country spread (Supplementary Fig. 4). This trend is observed across all generations of anti-PD1/PDL1 agents. Typically, the sales of an anti-PD1/PDL1 agent (such as pembrolizumab, atezolizumab or nivolumab) start in the USA and a few big-market countries, such as France and Germany, and then quickly spread globally. Considering the high price of the drugs, high-income countries show highest per capita use.

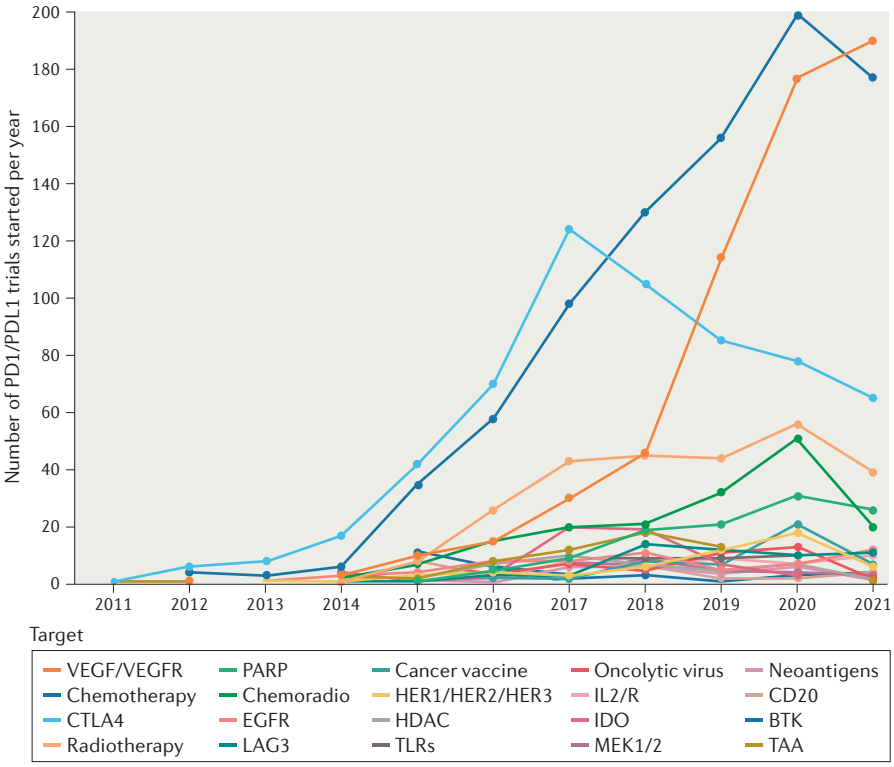

Fig. 3 | **Main targets assessed in combination with anti-PD1/PDL1 mAbs.** The graph shows the number of combination trials starting each year since 2011. The top 20 targets assessed in combination are shown in descending order according to the number of trials started in 2021.

New anti-PD1/PDL1 treatment modalities

We also explored new treatment avenues in the PD1/PDL1 landscape. There are currently 93 bispecific antibodies targeting PD1/PDL1 in development, four of which are targeting both PD1 and PDL1. Regarding stage of development, 62% are in preclinical development, 23% in phase I, 11% in phase II and 4% in phase III. Cumulatively, these bispecific antibodies are exploiting 28 different targets/mechanisms including other immune checkpoint pathways, such as CTLA4 and LAG3, which are already in phase III development (Supplementary Fig. 5). In addition, our analysis also revealed approximately 15 small-molecule PD1/PDL1 inhibitors, most of which are in early phase (preclinical and phase I) and are being developed for oral delivery (data not shown). Both bispecific and small-molecule oral PD1/PDL1 inhibitors represent newer developments in the landscape, which will likely continue to facilitate use of these agents in combination approaches.

Conclusion

Emerging combination strategies are promising and innovation remains with the development of bispecific antibodies and novel delivery platforms for PD1/PDL1 treatment modalities. Competition for patients continues globally for anti-PD1/PDL1 studies. In view of this, the FDA has expressed the need for optimizing drug development in this area including collaboration amongst sponsors on PD1/PDL1 combination strategies and encouragement of head-to-head randomized studies of PD1/PDL1 inhibitors to demonstrate differentiation (*N. Engl. J. Med.* https://doi.org/gn2gw7; 2021). We expect these challenges to persist in the near future. As the PD1/PDL1 drugs and clinical trials landscape continues to evolve, it will be important to monitor both the challenges and the opportunities in the field.

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Competing interests
The authors declare no competing interests.

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