FROM THE ANALYST'S COUCH

Trends in clinical development for PD-1/PD-L1 inhibitors

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PD-1/PD-L1-targeted monoclonal antibodies (mAbs) are now the standard of care for 16 different types of cancer and tissue-agnostic indication. Since our first PD-1/PD-L1 trial landscape survey conducted in September 2017 (*Ann. Oncol.* **24**, 84–89; 2019), 23 additional approvals have been granted to PD-1/PD-L1 mAbs by the FDA, and 4 new PD-1 mAbs have reached the market, bringing the total on the global market to 9. These achievements were powered by some of the largest clinical trial programmes ever in oncology. This report analyses the current landscape of clinical trials evaluating mAbs against PD-1/PD-L1.

PD-1/PD-L1 mAb clinical trial trends

Since 2006, 3,362 trials have been launched to test PD-1/PD-L1 mAbs alone or in combination with other agents, and 2,975 of them are still active as of September 2019, planning to recruit over 500,000 patients. Compared with our first survey conducted in September 2017, there are 1,469 more active clinical trials, which cover most cancer types, and span across all lines of therapies (FIG. 1).

At present, 76% of the active trials are testing combination regimens of PD-1/PD-L1 mAbs with other cancer therapies, such as immuno-oncology therapies, targeted therapies, chemotherapies or radiotherapies. The shift from monotherapy to combination therapy in the clinical trial space in recent years has resulted in 14 approvals of combination therapies by the FDA. Importantly, in the past two years, two new combination strategies received approval — the combination of a PD-1 mAb and targeted therapy for kidney cancer and endometrial cancer, and the combination of a PD-1 mAb, targeted therapy and chemotherapy for lung cancer.

We found that 295 other drug targets are being tested in combinations with PD-1/PD-L1 inhibitors, an increase of 136 targets in 2 years (Supplementary Fig. 1). The three most common combinations in the past 2 years are with chemotherapy (235 new trials), CTLA-4 mAbs (186 new trials) and therapies that target the vascular endothelial growth factor (VEGF) axis (114 new trials) (FIG. 2). This combination was the basis of four recent approvals by the FDA: two for kidney cancer (pembrolizumab plus axitinib, and avelumab plus axitinib), one for endometrial carcinoma (pembrolizumab plus lenvatinib) and one for non-small-cell lung cancer (atezolizumab, bevacizumab and chemotherapy), suggesting a potential broad utility of this combination strategy.

PD-1/PD-L1 trial size gets smaller

In terms of trial design, the average number of planned patient enrolments per trial has declined in the past 6 years from 429 patients

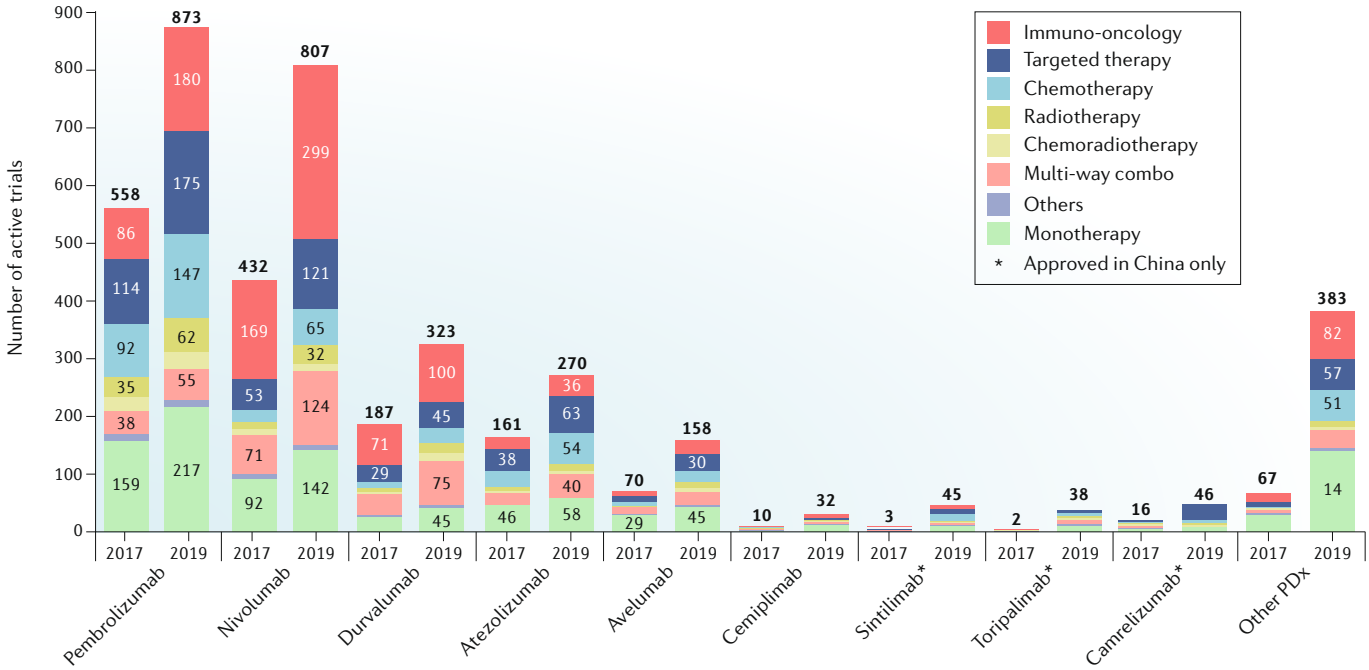

Fig. 1 | **The landscape of PD-1/PD-L1 inhibitor clinical trials in 2017 and 2019.** Four new PD-1 monoclonal antibodies (mAbs) have been approved in the past 2 years (cemiplimab, sintilimab, toripalimab and camrelizumab), adding to the five mAbs targeting PD-1 or PD-L1 already on the market. There were 2,975 active trials involving PD-1/PD-L1 mAbs in September 2019, compared with 1,506 in September 2017.

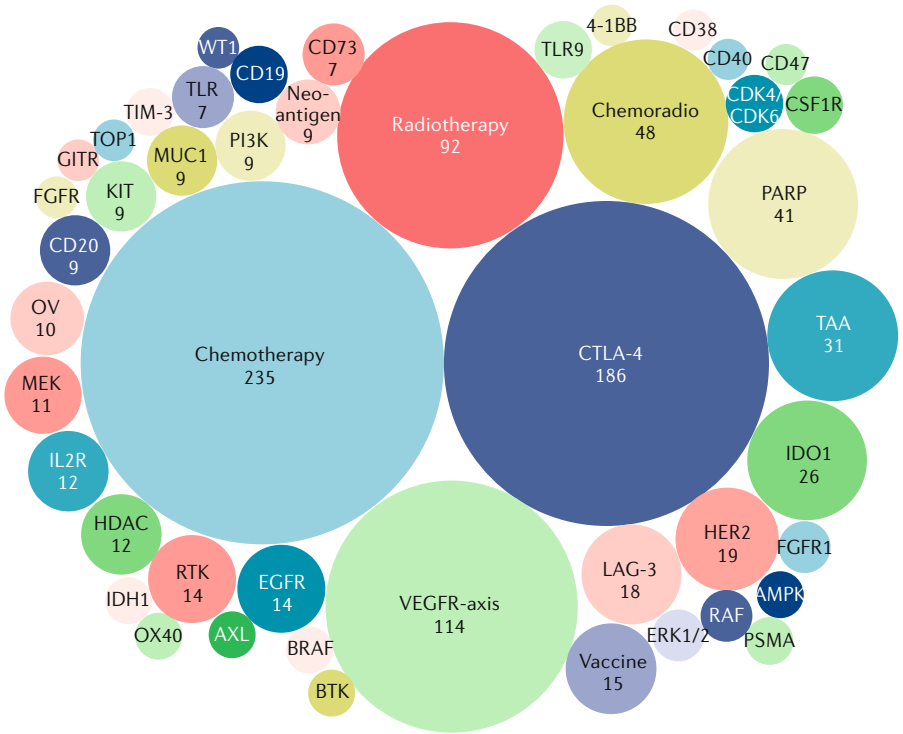

Fig. 2 | **Analysis of new combination trials with PD-1/PD-L1 inhibitors started in the past 2 years.** The number of clinical trials for the therapy types and targets with 7 or more trials is indicated in the labelled circles. The most popular combination is with chemotherapy, followed by CTLA-4 inhibitors, and then trials targeting either vascular endothelial growth factor (VEGF) or its receptor VEGFR. OV, oncolytic viruses; TAA, tumour-associated antigen.

per trial on average in 2014 to 129 patients per trial in 2019 (Supplementary Fig. 2). This decline in trial size is associated with a decrease in the number of new trials that target major cancer types such as melanoma, breast cancer and kidney cancer, as well as lung cancer. By contrast, more trials are targeting rare cancer types, which have a much smaller eligible patient population (Supplementary Fig. 3).

China has the highest recruitment rate

We calculated the median patient recruitment rate per clinical site in the USA, China, six other major markets (France, Germany, Italy, Japan, Spain and the UK), and the Asia-Pacific area (Australia, Hong Kong, Korea, New Zealand, Taiwan and Thailand) by using the patient recruitment rate of 629 clinical sites from 55 completed or ongoing PD-1/PD-L1 clinical trials managed by IQVIA. The USA has the lowest patient recruitment rate, probably owing to the highest penetration of PD-1/PD-L1 mAbs as standard of care. By contrast, the patient recruitment rate in China is almost six times higher for monotherapy trials and about four times higher for combination therapy than in the USA (FIG. 3). China has more than 4 million new cancer cases per year and most Chinese cancer patients do not receive PD-1/PD-L1 mAbs, which means the country has the largest number of patients who are eligible to join clinical trials.

Indeed, the clinical development of the three China-derived marketed PD-1 mAbs (sintilimab, toripalimab and camrelizumab) by Chinese companies was rapid (26–45 months) compared with the rest of the approved PD-1/PD-L1 mAbs, which was aided by the fast patient recruitment for these clinical trials. As China recently joined the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), data generated from trials in China may support market applications in other ICH member countries. The global PD-1/PD-L1 trial community should make use of this precious patient resource to accelerate clinical development.

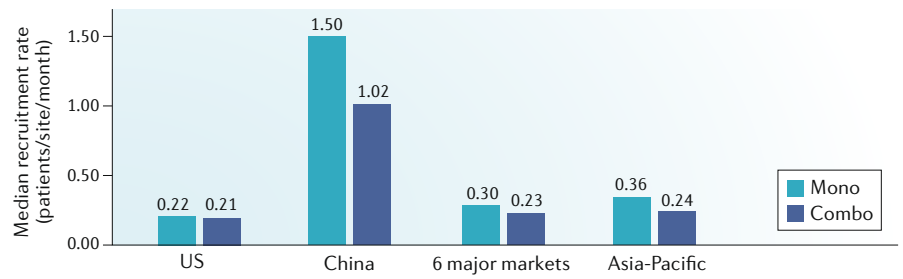

Fig. 3 | **The median patient recruitment rate for trials of PD-1/PD-L1 inhibitors in different countries or regions.** The six major markets are France, Germany, Italy, Japan, Spain and the UK. The Asia-Pacific area includes Australia, Hong Kong, Korea, New Zealand, Taiwan and Thailand.

Conclusion

The PD-1/PD-L1 mAb clinical trial landscape continues its growth by adding more trials, combination targets and cancer types. The convergence of innovation across various disciplines in this space has generated many practice-changing therapeutic regimens for patients. As the field is shifting to combination therapies, there is a need to develop an effective biomarker for each combination strategy to identify responding patients. In addition, as most patients treated with the approved PD-1/PD-L1 mAb regimens develop resistance or relapse, the field should pay more attention to the development of novel combinations that address PD-1/PD-L1 resistance. These novel biomarkers and therapies will need to be tested in clinical trials that require enrichment of sub-populations of patients. The large number of available patients in emerging markets could support faster enrolment in trials, which would ultimately bring more effective PD-1/PD-L1 therapies to more patients worldwide.

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Competing interests

V.M.H.-L. is an unpaid scientific advisor and holds equity in FX Biopharma. The other authors declare no competing interests.

Supplementary information

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