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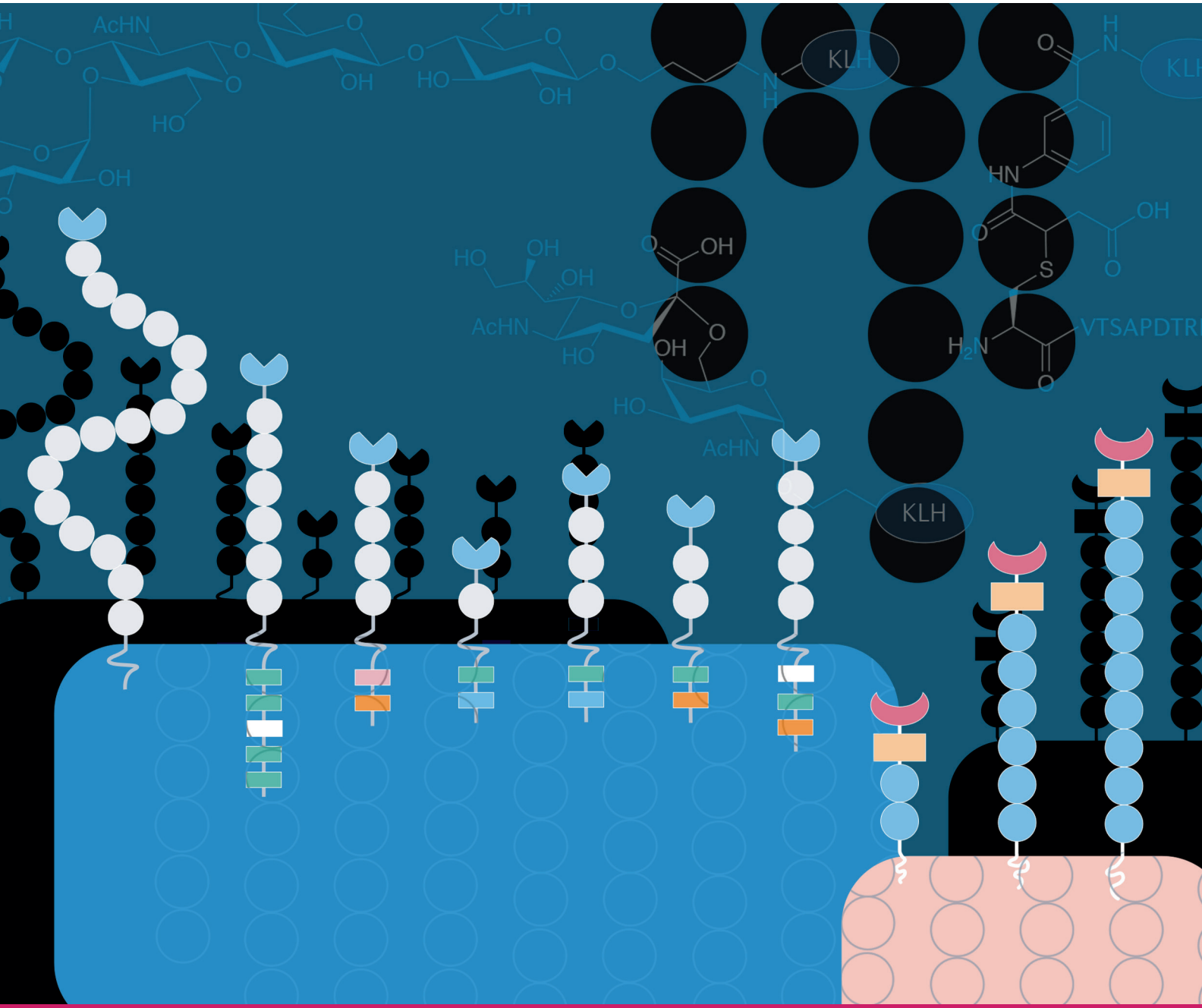

GLYCOBIOLOGY
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TRIAL WATCH

Combinations take centre stage in PD1/PDL1 inhibitor clinical trials

Targeting the PD1 and PDL1 immune checkpoint axis has paved the way for a new era of clinical care in cancer. Of the existing immuno-oncology (IO) agents in clinical development, anti-PD1 and anti-PDL1 monoclonal antibodies (mAbs) have achieved the most success. Indeed, there are ten approved anti-PD1/PDL1 mAbs in the global market, six of which are approved by the FDA. To date, these mAbs have garnered a total of 67 FDA approvals across 17 different cancer types and two tissue-agnostic conditions. This report summarizes the current landscape of anti-PD1/PDL1 mAb clinical trials and the challenges in patient recruitment.

Clinical trial growth doubled in 2020

As of our current update in September 2020, there are 4,400 clinical trials testing anti-PD1/PDL1 mAbs, 3,674 of which are active (FIG. 1). Compared with our first analysis conducted in September 2017, this represents a threefold increase in the total number of clinical trials testing anti-PD1/PDL1 mAbs. Remarkably, the growth in the past year, 2019–2020 (1,358 trials), has almost matched the 2-year growth between 2017 and 2019 (1,539 trials, Supplementary Fig. 1). Interestingly, the number of clinical trials assessing mAbs that are in clinical development but not yet FDA approved (Supplementary Fig. 1, Other PDx) shows the largest growth, notably in combination with other therapies, indicating a robust clinical development pipeline concentrated in anti-PD1/PDL1 combination treatment modalities. When we further analysed the landscape of anti-PD1/PDL1 therapies, we found that 2,949 out of the 3,674 active trials (80%) are testing combination regimens of anti-PD1/PDL1 mAbs with other cancer therapies, including IO therapies, targeted therapies, chemotherapies and radiotherapies. Therefore, the growth in the number of combination trials has outpaced the growth of trials assessing anti-PD1/PDL1 monotherapies in all stages of development.

Monotherapy trials are declining

To better understand the increased activity in anti-PD1/PDL1 mAb trials, we tracked the status changes in trials with a start date of 2014 or later (Supplementary Fig. 2). We found that the older trials have progressed to an 'active, not recruiting' phase, indicating finished recruitment or a completed study, whereas most trials starting from 2017 are in the 'not yet recruiting' or 'recruiting' phase. Notably, since 2017, the number of trials in these two phases is greater than the number of trials completed. This coincides with the peak of new monotherapy trials in 2017 (197), whereas combination trials continue to increase every year, comprising nearly 90% of all PD1/PDL1-targeted trials (FIG. 2). Accordingly, the average planned patient enrolment per monotherapy trial has declined more than 500% in the past 7 years from 854 in 2014 to 131 in 2020 (FIG. 2). By contrast, the average planned patient enrolment per combination trial has declined by only 40%, from 187 in 2014 to 111 in 2020. The overall decrease in planned enrolment may reflect a shift towards increased biomarker-based patient selection, which may slow recruitment and decrease trial size.

Global trends in patient recruitment

In our previous analyses, we calculated the median patient recruitment rate (RR) from clinical trial sites in the USA, China, and major markets in Europe and the Asia-Pacific area (*Nat. Rev. Drug Discov.* **19**, 163–164; 2020), and found that China had the highest RR in both monotherapy and combination anti-PD1/PDL1 mAb clinical trials. To update the previous analysis (2019) and ascertain the current RR globally, we acquired and analysed

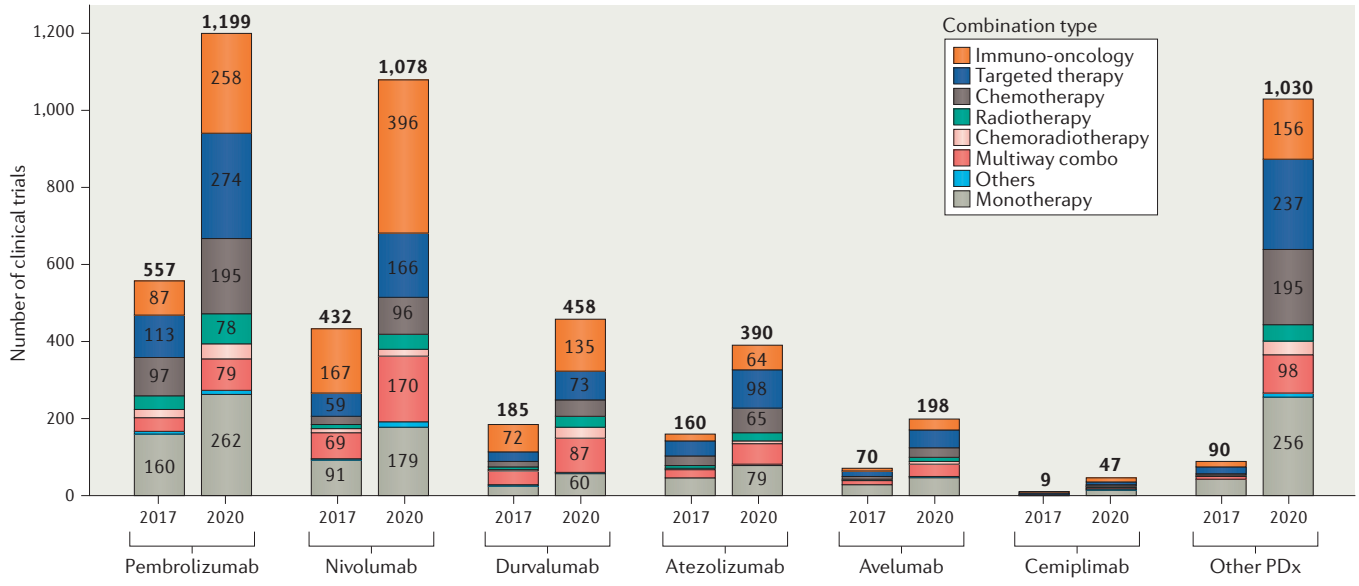

Fig. 1 | **The landscape of anti-PD1/PDL1 mAb clinical trials in 2017 and 2020.** As of September 2020, there are 4,400 clinical trials assessing anti-PD1/PDL1 mAbs, nearly tripling since September 2017. Other PDx includes any anti-PD1/PDL1 mAbs without FDA approvals.

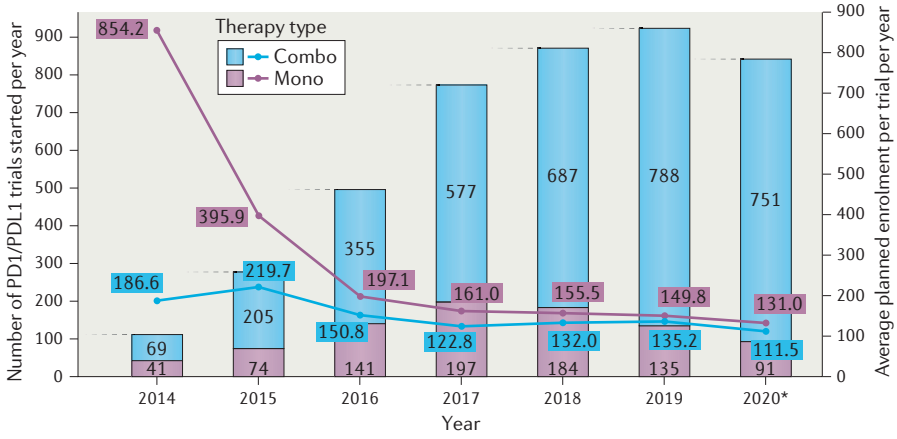

Fig. 2 | **Comparison of monotherapy and combination trials.** Most new trials since 2014 have been combination trials (bar graphs). The average planned patient enrolment (line graph) has decreased since 2014 for monotherapy trials more than for combination trials. *Only data from the first three quarters of 2020 were used to generate the analysis.

patient recruitment data from 200 additional unique clinical sites and 11 additional IQVIA-run clinical trials.

We found that, in the past year, RR in anti-PD1/PDL1 monotherapy trials decreased globally, with China showing the greatest drop (41%) (Supplementary Fig. 3). By contrast, RR in anti-PD1/PDL1 combination trials in China saw an increase of 18%, whereas RR largely decreased or stayed the same in all other regions. These RR trends are consistent with a shift from monotherapy trials to combination trials that may be more patient selective. Overall, China still maintains the highest RR in both monotherapy and combination trials, and the global RR drop in most trials could be a result of the timing of the COVID-19 pandemic.

New combination strategies

As the landscape of anti-PD1/PDL1 clinical trials moves towards combination strategies, which may be more efficacious, we examined the targets pursued by such modalities. Our analysis revealed that 253 drug target groups (excluding PD1/PDL1) are being tested, which represents an increase of 129 new target groups in the past 3 years (Supplementary Fig. 4). The trend in anti-PD1/PDL1 combination trials over the past decade showed VEGF/VEGFR-targeted therapy, chemotherapy and CTLA4-targeted therapy as top combination strategies, where the former two showed a continued steep upward trend in the number of trials started per year (FIG. 3). Indeed, a closer analysis of trials started in the first three quarters of 2020 revealed that combination of anti-PD1/PDL1 mAbs with VEGF/VEGFR-targeted therapies is the top combination treatment modality (154 new trials), surpassing chemotherapy (145 new trials) and anti-CTLA4 (64 new trials) (Supplementary Fig. 5). Based on the number of new trials started in the past year, emerging therapies of interest for the future may lie in combinations with approved therapies such as PARP inhibitors, as well as rising IO targets and agents such as TIGIT, TGFβ/TGFR, TLRs, oncolytic viruses and cancer vaccines.

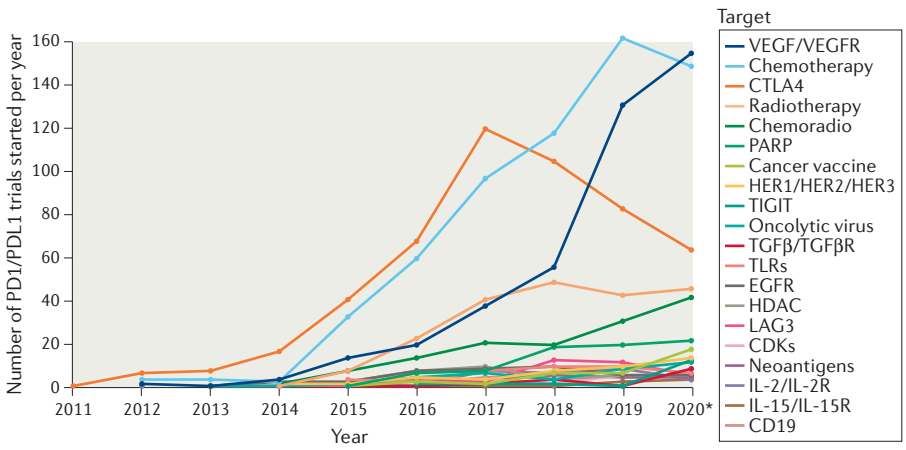

Fig. 3 | **Main targets assessed in combination with anti-PD1/PDL1 mAbs.** The graph shows the number of combination trials starting each year since 2011. The main 20 targets assessed in combination are shown in descending order according to the number of trials started in 2020. *Only data from the first three quarters of 2020 were used to generate the analysis.

Conclusions

Our analyses of the anti-PD1/PDL1 clinical trials landscape during the past 3 years have revealed a continued interest and increased growth beyond monotherapy trials to combination trials targeting more pathways. Development outside of FDA-approved agents has risen dramatically since our first report in 2017 and is quickly joining the hunt for promising new combinations. Consistent with findings from our previous analyses, combination trials have taken over new clinical development, and the field has shifted from using chemotherapy and anti-CTLA4 combinations to other targeted approaches such as angiogenesis-targeted agents and novel IO–IO combinations to bypass resistance mechanisms that prevent greater anti-PD1/PDL1 efficacy. Although our datasets indicate a robust growth in anti-PD1/PDL1 clinical trials, we did observe a fall in patient recruitment rates globally and a stall in the completion of enrolment for newer trials. The COVID-19 pandemic has touched virtually all aspects of life and its potential impact on the anti-PD1/PDL1 clinical pipeline is yet to be fully realized. As such, it is reasonable to believe that the pandemic could have played a part in the decreased patient enrolment and stalls in trials. Ongoing assessments of the landscape will be crucial to identify future new trends in the field and its effect on patients.

Samik Upadhaya[1], *Svetoslav T. Neftelino*[2], *Jeffrey P. Hodge*[2], *Cristina Oliva*[2], *Jay R. Campbell*[1] *and Jia Xin Yu*[1] ✉

[1]*Cancer Research Institute, New York, NY, USA.*

[2]*IQVIA, Durham, NC, USA.*

✉*e-mail: jyu@cancerresearch.org*

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Competing interests
The authors declare no competing interests.

Supplementary information
Supplementary information is available for this paper at https://doi.org/10.1038/d41573-020-00204-y.

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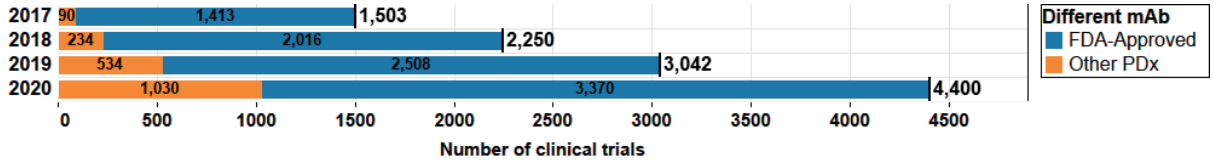
Supplementary information

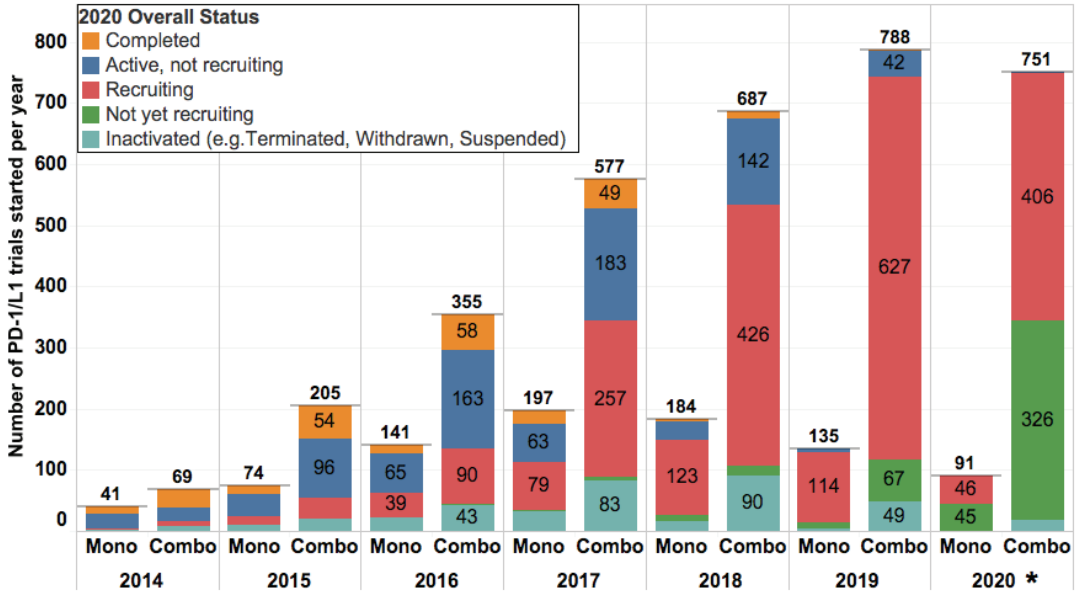
Combinations take centre stage in PD1/PDL1 inhibitor clinical trials

In the format provided by the authors

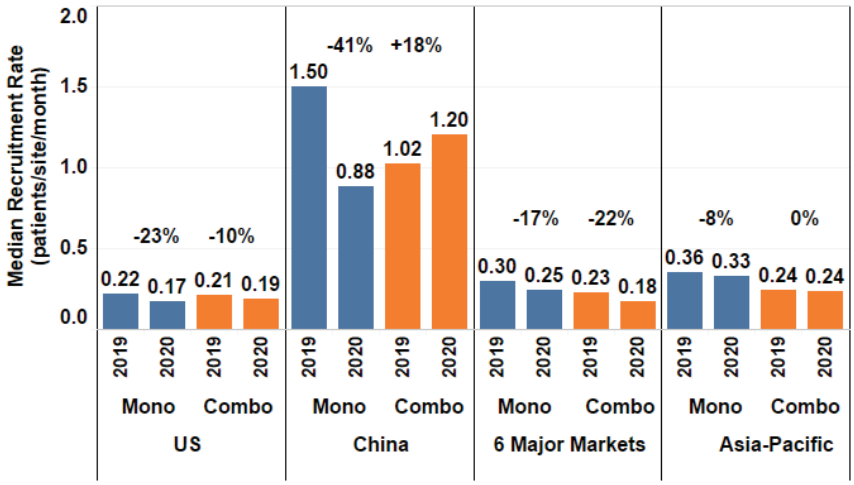
Supplementary Box 1 | Methods: The clinical trial information was collected in September 2020 from Clinicaltrials.gov. The classification of combination trial type and the identification of combination targets were based on CRI IO Analytics. The clinical trial recruitment information was collected from IQVIA internal database that tracks the real-time status of clinical trials managed by IQVIA. This patient recruitment analysis included information from 890 unique clinical trial sites from 66 clinical trials in 2020 and 690 unique clinical trials sites from 55 trials in 2019. These data only reflect a small fraction of the 4,400 anti-PD1/PDL1 clinical trials, and the results are therefore limited in reflecting the real actual patient recruitment rate of all ongoing PD1/PDL1 trials.



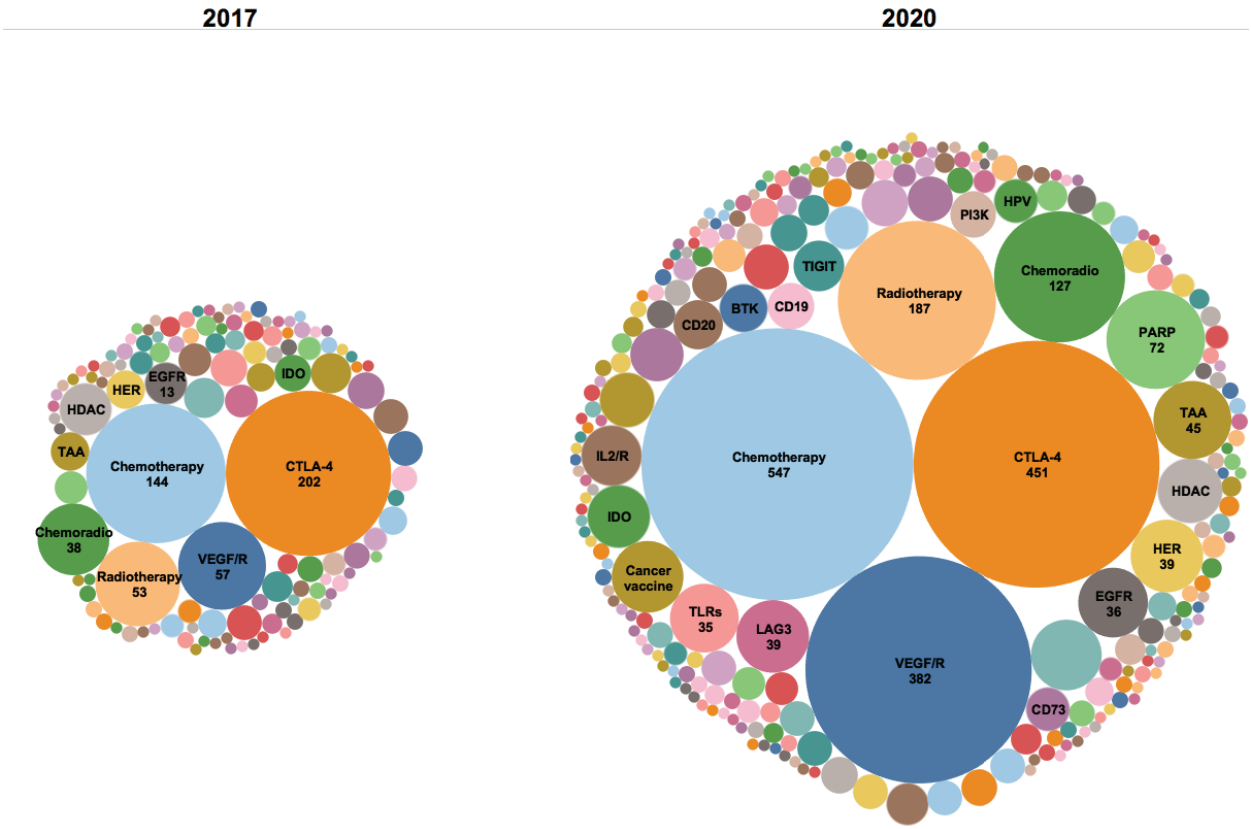
Supplementary Figure 1. The growth of landscape of PD1/L1 mAb clinical trials from 2017 to 2020. 4,400 clinical trials are in the current landscape as of September 2020, nearly tripling since in September 2017. FDA-approved mAbs include pembrolizumab, nivolumab, durvalumab, atezolizumab, avelumab, and cemiplimab. Other PDx include mAbs approved by regulatory agencies other than the FDA such as the EMA as well as those in clinical development and not yet approved.



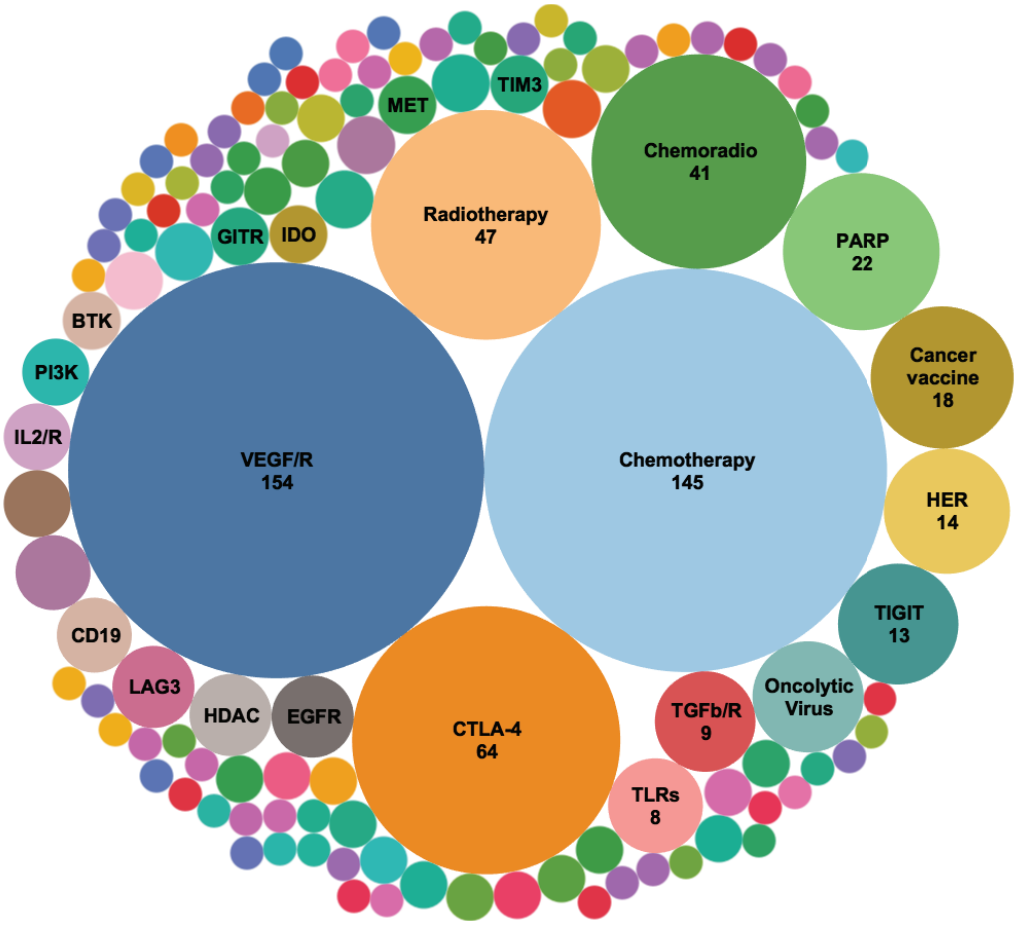
Supplementary Figure 2. Anti-PD1/PDL1 monotherapy and combination trials started from 2014 to 2020 (*only data from the first 3 quarters of 2020 were used to generate the analysis in the chart above.) The majority of trials started in past 4 years remain in recruitment phase, where the most recent trials have not started recruitment.



Supplementary Figure 3. Median patient recruitment rate in different countries or regions in 2019 compared to 2020 with changes in percentage between the years. Six major markets are France, Germany, Italy, Japan, Spain and United Kingdom. The Asia-Pacific (APAC) area includes Australia, Hong Kong, South Korea, New Zealand, Taiwan, and Thailand, excluding China and Japan. Mono and Combo denote monotherapy and combination therapy trials respectively.



Supplementary Figure 4. Target landscapes of combination trials in 2020 and 2017. The number of combination trials has more than tripled in the past three years (2,900 compared to 857), with an increase of 129 additional combination target groups from 124 target groups. Similar targets are grouped together to better identify trends in year to year analyses.



Supplementary Figure 5. Analysis of new combination trials (724 trials) starting in the year 2020*. When trials targeting VEGF and VEGFR were pooled together, this class of targets is the largest one tested in PD1/L1 combination trials opened in the past year, exceeding both chemotherapy and CTLA-4 combination trials. Immunomodulator targets represent many of the emerging targets. *Only first 3 quarters of 2020 are included in the analysis.

Cristina Oliva, *MD, Vice President, Head of Oncology Center of Excellence, IQVIA*

A board-certified medical oncologist licensed in UK and Italy, Cristina Oliva joined IQVIA in 2016 with nearly 20 years of global pharmaceutical drug development experience from first-in-human to Phase IV trials. In various oncology R&D roles in small to large biopharmaceutical companies, Dr. Oliva led development of cytotoxics, targeted small molecules and biologics. She has 12 years of clinical experience at major research institutes across Europe and more than 100 publications in oncology.

Jeffrey P. Hodge*, Vice President, Development Solutions, Oncology Center of Excellence, IQVIA*

Jeff Hodge has more than 25 years of oncology drug development experience, with a focus on early phase development. He joined IQVIA in 2010 after more than 15 years at GlaxoSmithKline where he was involved in 10 INDs and 5 NDAs. Jeff holds MS and BS degrees in Medical Microbiology and Bacteriology from Virginia Tech; he has published more than 90 abstracts and peer-reviewed papers and presents at international oncology meetings.

Svetoslav T. Neftelinov*, Associate Director, Global Feasibility, IQVIA*

Before joining IQVIA in 2008, Svetoslav Neftelinov earned a Doctor of Medicine degree from Medical University – Sofia, Bulgaria. With roles in country feasibility and then global feasibility, Dr. Neftelinov now manages the development of global clinical trial strategies, applying data and advanced analytics to target countries, sites and patients.