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Supplementary information

Evolution of innovative drug R&D in China

In the format provided by the authors

Supplementary Box 1 | Data and analysis

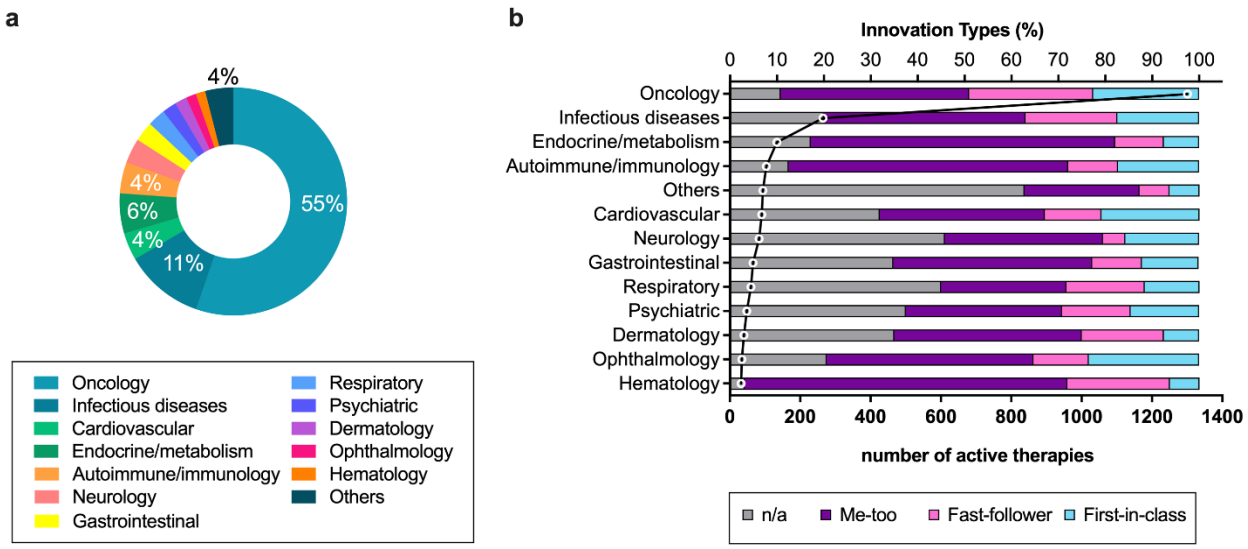
The data on China's domestic novel pipelines were collected from the Pharmcube database (one of the most authoritative platforms of drug information in China), curated from over 57 sources, including Chinese NMPA's Registration and Information Disclosure Platform for Drug Clinical Studies, Chinese Clinical Trial Register (ChiCTR), ClinicalTrials.gov clinical trial registries, scientific conferences, company press releases, published reports, investor presentations and other sources. Drugs were included in our analysis with the following eligibility criteria: investigational therapeutics and vaccines for treating any diseases, excluding generic drugs or biosimilars, that were discovered de novo in China or in-licensed by Chinese companies, and that entered clinical development but had not received marketing authorization in any country at the cut-off point of 1 July 2021. Drugs for which development no longer seems to be active were excluded. A total of 2,251 candidates were included in this analysis. Data were manually verified and further categorized by Tsinghua Clinical Research Institute (TCRI) and Pharmcube with parameters of drug target, drug type, innovation type, development stage in China and abroad, indications and location of origin. Some product information might not be publicly disclosed, which might skew the classification of individual products.

In terms of drug type, all investigational candidates were first classified as small molecules, monoclonal antibodies (mAbs), recombinant fusion proteins, vaccines (prophylactic and therapeutic), next-generation agents, Others (for agents which cannot be classified into the above categories) and N/A groups (for agents which were unamenable to classification owing to lack of adequate information). For next-generation agents, there were nine subgroups, including cell therapies, bispecific or multi-specific antibodies, antibody–drug conjugates (ADCs), gene therapies, oncolytic virus, nucleic acid-based, proteolysis-targeting chimeras (PROTACs), RNA/DNA-based vaccines and other next-generation drugs (for agents which cannot be classified into the above categories). The origins of drugs were divided into two major types: discovered in-house or in-licensed. There were also 19 agents that were not counted as either in-house nor in-licensed, given that the overseas companies that discovered the agents were acquired by Chinese biopharma companies. Indications were categorized into therapeutic areas, such as oncology (including haematologic cancers), infectious diseases, endocrine and metabolic diseases, autoimmune and immunologic diseases, cardiovascular diseases, neurologic diseases, gastrointestinal diseases, respiratory diseases, psychiatric diseases, dermatologic diseases, ophthalmologic diseases, haematologic diseases and others.

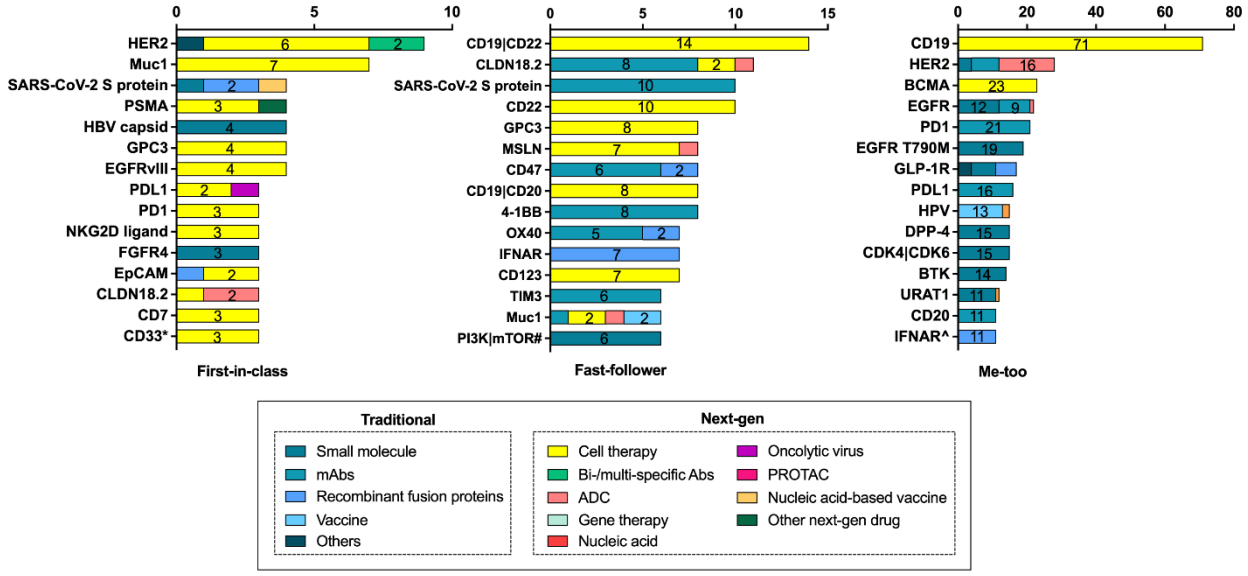
With regard to innovation type, all therapies were classified into three groups: first-in-class, fast-follower and me-too, according to their targets, mechanisms of action (MoA) and the most advanced development stages, in comparison to their global counterparts. Drugs with novel target(s) (targets for which there are not yet approved drugs in any drug classes) or novel MoAs that do, or do not, have class-leading clinical development status worldwide are defined as first-in-class or fast-follower, respectively. Those with the same targets and similar MoAs to already-approved drug classes are considered me-too.

To provide longitudinal analyses of the evolution of oncology drug landscape, we extracted therapeutic agents for treating patients with cancer in our current analysis and did a comprehensive comparison of landscapes between 1 January 2020 and 1 July 2021. Cancer therapies were classified into cytotoxic, targeted, immune-oncology (IO) therapies or N/A (targets and MoA that were not disclosed). Furthermore, IO therapies were sub-grouped into six categories as previously described[1]: 1) T cell-targeted immunomodulators, 2) other immunomodulators 3) cell therapies, 4) cancer vaccines, 5) oncolytic virus, 6) bispecific or multi-specific antibodies (T-cell-oriented).

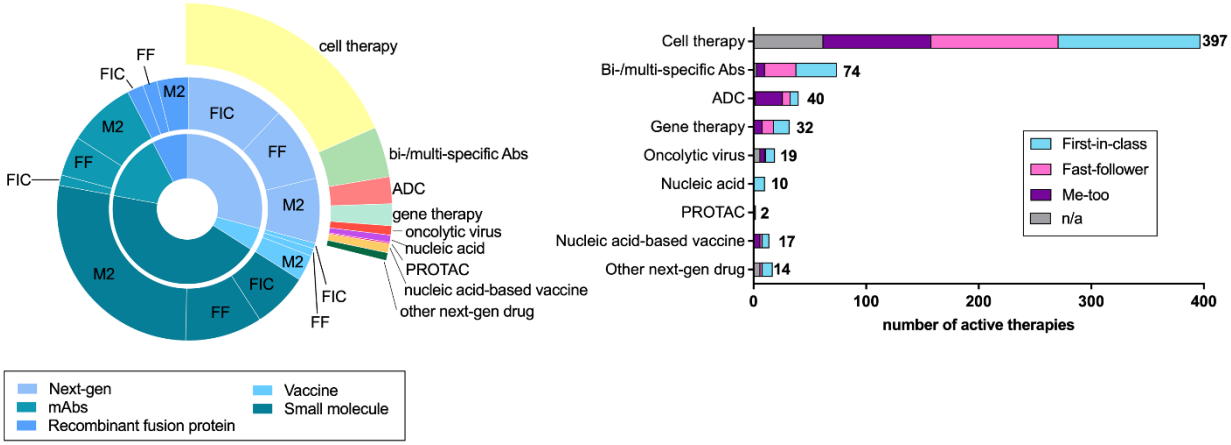
1. Tang, J., Shalabi, A. & Hubbard-Lucey, V. M. Comprehensive analysis of the clinical immuno-oncology landscape. *Ann Oncol* **29**, 84–91 (2018).



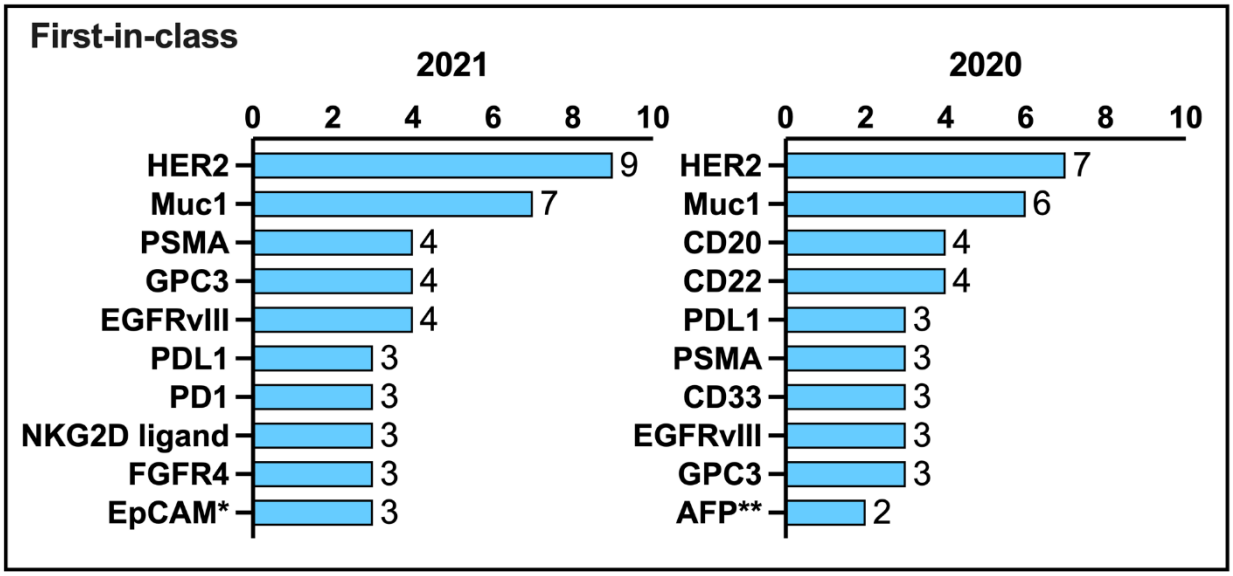
Supplementary Figure 1 | Overview of investigational agents by different therapeutic areas. a | The 2,251 agents were grouped by different therapeutic areas. Therapeutic areas with less than 20 products and products unamenable to classification owing to inadequate information or not fitting into the main therapeutic areas were included in an 'Others' group. **b |** The agents were classified into first-in-class, fast-follower and me-too therapies based on the mechanism of action. Products unamenable to classification owing to inadequate information were included in an 'n/a' group. Each white circle on the black line represents the number of active therapies of a specific therapeutic area.

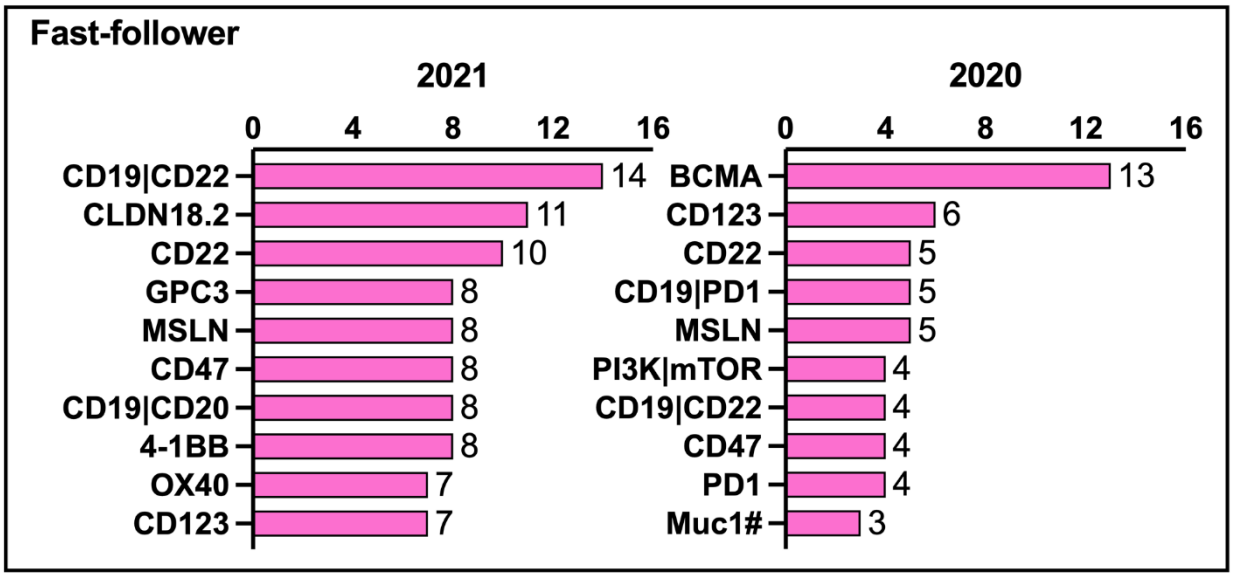


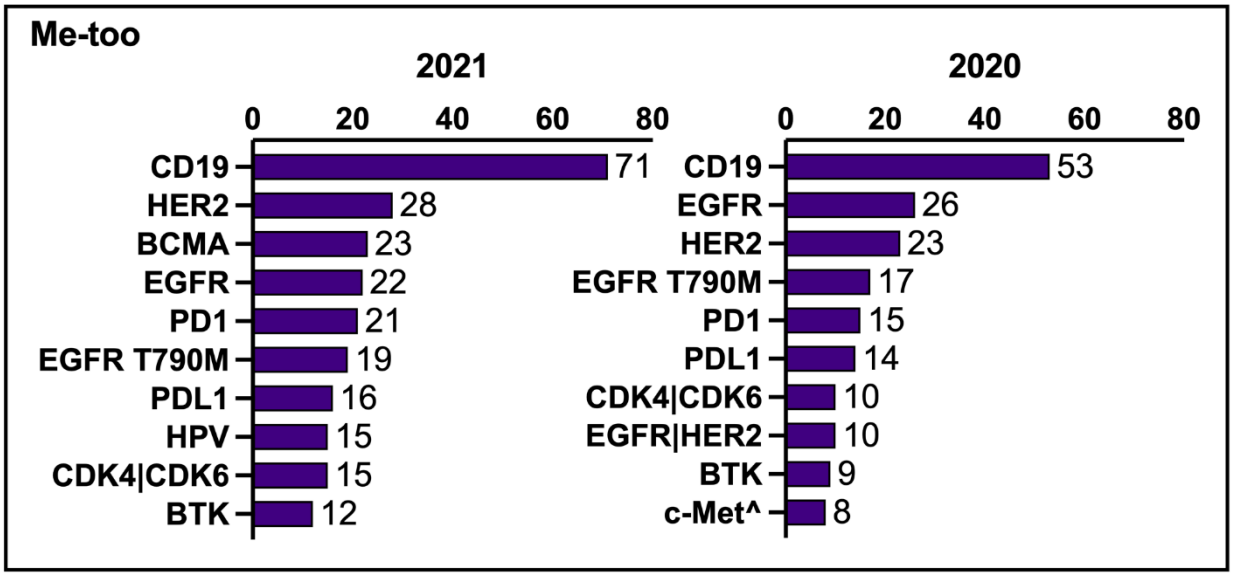
Supplementary Figure 2 | Top 15 targets of first-in-class, fast-follower and me-too agents. Drugs either engaged a single target (such as HER2) or multiple targets, indicated by a "|" symbol (such as CD19|CD22). *There were also three agents for CD276, CD22, and CD20. #There were also six agents for HBV capsid and LAG3. ^There were also eleven agents for EGFR|HER2. next-gen, next-generation; mAbs, monoclonal antibodies; ADC, antibody-drug conjugate; PROTAC, proteolysis-targeting chimeras.



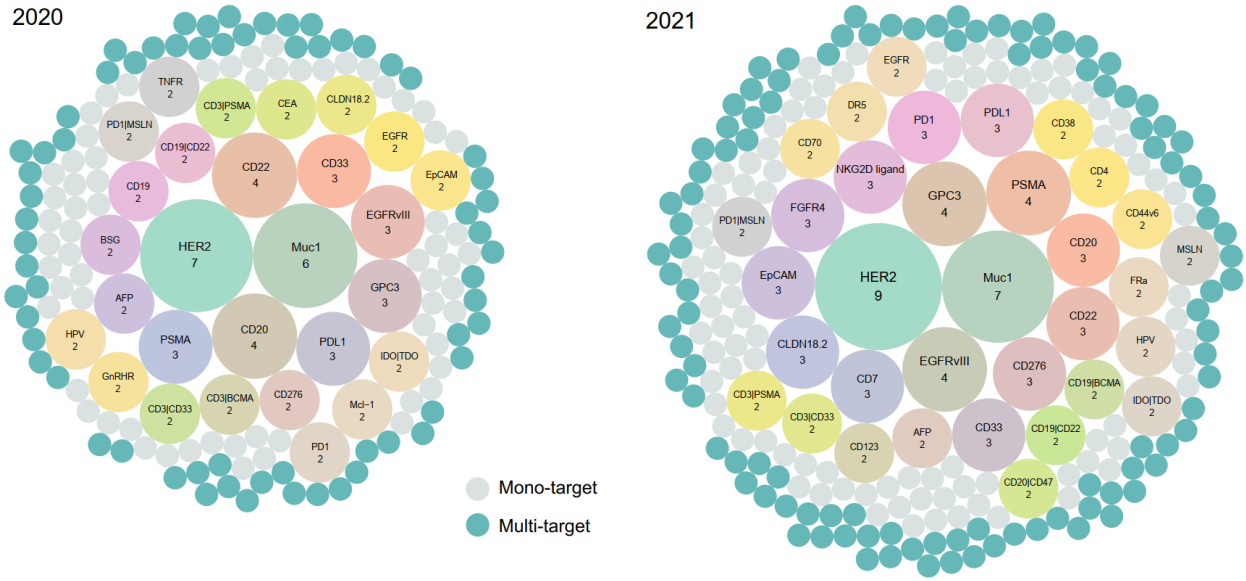
Supplementary Figure 3 | Overview of the five main groups of investigational agents. Products unamenable to classification owing to inadequate information and those not fitting into the five main groups were not shown in the donut charts. Next-generation (next-gen) agents were further classified as cell therapy, bi-/multi-specific antibodies (Abs), antibody–drug conjugate (ADC), gene therapy, oncolytic virus, nucleic acid, proteolysis-targeting chimera (PROTAC), nucleic acid-based vaccine and other next-gen drug (not fitting into the any of the next-gen groups). FIC, first-in-class; FF, fast-follower; M2, me-too; n/a, products unamenable to classification owing to inadequate information; mAbs, monoclonal antibodies.


First-in-class
2021
0 2 4 6 8 10
HER2 9
Muc1 7
PSMA 4
GPC3 4
EGFRvIII 4
PDL1 3
PD1 3
NKG2D ligand 3
FGFR4 3
EpCAM* 3
2020
0 2 4 6 8 10
HER2 7
Muc1 6
CD20 4
CD22 4
PDL1 3
PSMA 3
CD33 3
EGFRvIII 3
GPC3 3
AFP** 2

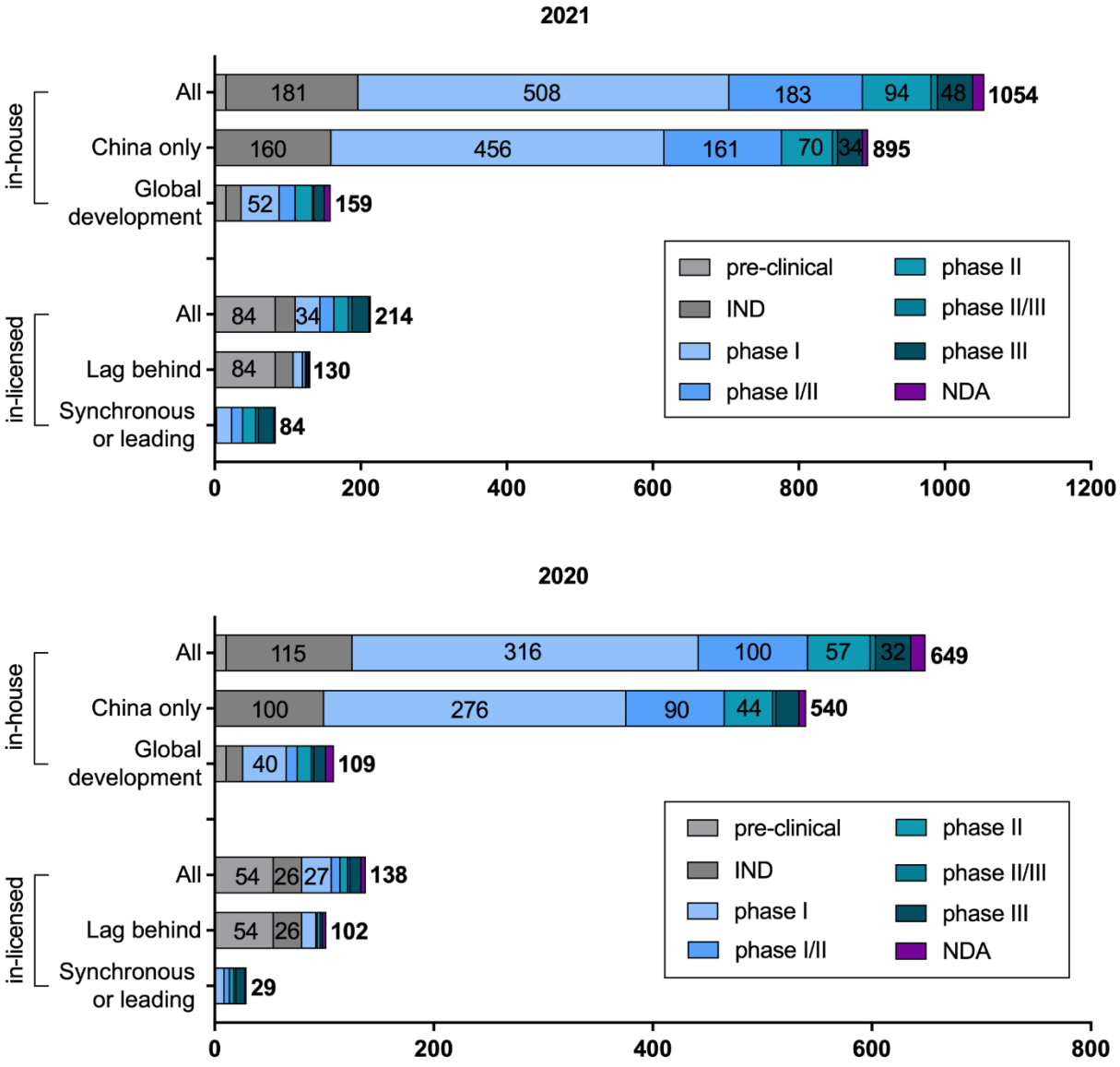

Fast-follower
2021
0 4 8 12 16
CD19|CD22 14
CLDN18.2 11
CD22 10
GPC3 8
MSLN 8
CD47 8
CD19|CD20 8
4-1BB 8
OX40 7
CD123 7
2020
0 4 8 12 16
BCMA 13
CD123 6
CD22 5
CD19|PD1 5
MSLN 5
PI3K|mTOR 4
CD19|CD22 4
CD47 4
PD1 4
Muc1# 3


Me-too
2021
0 20 40 60 80
CD19 71
HER2 28
BCMA 23
EGFR 22
PD1 21
EGFR T790M 19
PDL1 16
HPV 15
CDK4|CDK6 15
BTK 12
2020
0 20 40 60 80
CD19 53
EGFR 26
HER2 23
EGFR T790M 17
PD1 15
PDL1 14
CDK4|CDK6 10
EGFR|HER2 10
BTK 9
c-Met^ 8

Supplementary Figure 4 | Top 10 targets of anticancer drugs by different innovation types (2021 versus 2020). Drugs either engaged a single target (such as HER2) or multiple targets, indicated by a "|" symbol (such as CD19|CD20). *There were also three agents for CLDN18.2, CD7, CD33, CD276, CD22 and CD20; **There were also two agents for CD19, BSG, CD19|CD22, CD276, CD3|BCMA, CD3|CD33, CD3|PSMA, CEA, CLDN18.2, EGFR, EpCAM, HPV, IDO|TDO, Mcl-1, PD1 and PD1|MSLN; #There were also three agents for GPC3, Akt, CD30, ERK1|ERK, LAG3, NY-ESO-1, TIM3, and TRAIL; ^There were also eight agents for PARP, Top I and VEGFR2.



Supplementary Figure 5 | Overview of targets of first-in-class anticancer drugs (2021 versus 2020). The 228 targets in 2021 and 157 targets in 2020 are shown here. The number of agents of each target is indicated in the bubble. Those targets with only one agent are shown in grey (mono-target) and green (multi-target combinations) bubbles.



Supplementary Figure 6 | Most advanced development status in China and overseas for in-house and in-licensed oncology agents (2021 versus 2020). In-house products were classified into those developed only in China (China only) and those developed in China and other countries (global development). In-licensed drugs were grouped according to the latest development stage in China in comparison with that overseas — either lagging behind other countries or synchronously with/faster than other countries. Products lacking the global status or status in China were calculated in "All" group only.