

# Trends in the approval of cancer therapies by the FDA in the twenty-first century

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## Abstract

The cancer treatment landscape has changed dramatically since the turn of the century, resulting in substantial improvements in outcomes for patients. This Review summarizes trends in the approval of oncology therapeutic products by the United States Food and Drug Administration (FDA) from January 2000 to October 2022, based on a categorization of these products by their mechanism of action and primary target. Notably, the rate of oncology indication approvals has increased in this time, driven by approvals for targeted therapies, as has the rate of introduction of new therapeutic approaches. Kinase inhibitors are the dominant product class by number of approved products and indications, yet immune checkpoint inhibitors have the second most approvals despite not entering the market until 2011. Other trends include a slight increase in the share of approvals for biomarker-defined populations and the emergence of tumour-site-agnostic approvals. Finally, we consider the implications of the trends for the future of oncology therapeutic product development, including the impact of novel therapeutic approaches and technologies.

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## Introduction

Investigation into therapeutic products for cancer dates to the early 1900s, when the term ‘chemotherapy’ was coined<sup>1</sup>. Initial experiments showed promise, but the first widely used chemotherapy products were discovered in studies with chemical poisons during World War II<sup>1</sup>. The 1946 publication of results using nitrogen mustards for the treatment of lymphomas ushered in the field of oncology therapeutic product development<sup>1</sup>, and the first FDA approval of a chemotherapy for cancer was granted in 1949 for the nitrogen mustard mechlorethamine hydrochloride<sup>2</sup>.

For decades, therapeutic products for cancer were limited to systemic cytotoxic agents that affect rapidly dividing cells, including both cancer cells and healthy tissue, typically with substantial toxicity. The landscape of cancer treatment changed drastically in the late 1990s and early 2000s with the emergence of targeted therapies designed to take advantage of genetic susceptibilities in cancer cells, leading to selective killing of these cells<sup>3</sup>. The approvals of trastuzumab (an anti-HER2 antibody) for breast cancer in 1998 and imatinib (a small-molecule BCR-ABL inhibitor) for chronic myeloid leukaemia in 2001 are credited with ushering in the era of precision oncology<sup>3–5</sup>.

The advances in therapeutic product development in the twenty-first century have resulted in additional improvements in outcomes for patients with cancer. From 1995 to 1999, the age-adjusted US mortality from all cancer sites was 206 per 100,000 (ref. 6); this decreased to 155.5 per 100,000 in 2014–2018 (the latest available data)<sup>7</sup>. From 2016 to 2017, the largest single-year drop in overall cancer mortality so far – 2.2% – was reported, spurred by rapid declines in lung cancer mortality that have been partially attributed to the approval of immune checkpoint inhibitors (ICIs) and other new targeted therapies<sup>8</sup>.

In this Review, we discuss how the field of oncology has changed in the twenty-first century based on trends in the products approved for the treatment of cancer by the FDA from 2000 to 2022. We explore trends by mechanisms of action and examine how the type and pace of development have changed and advanced since 2000. We then discuss how these trends can be used to envision the future of therapeutic product development in oncology.

## Overall trends in oncology approvals

All FDA approvals of oncology therapeutic products from 1 January 2000 to 31 October 2022 were compiled as described in Box 1. A three-level classification system based on product mechanisms of action was devised to enable examination of approval trends by product groups and classes (Box 1, Fig. 1 and Supplementary Table 1). Distinct products were assigned to one of 99 subclasses that were aggregated into 31 classes (Fig. 1, outer ring), and these were in turn assembled into three groups (cytotoxic drugs, targeted drugs and targeted biologics; Fig. 1, inner ring).

Overall, there were 573 oncology indication approvals (referred to hereafter as approvals) granted for 206 distinct oncology products during the analysis period, of which 50 approvals were for cytotoxic drugs, 277 were for targeted drugs and 246 were for targeted biologics (Fig. 2a).

## Rate of approvals

The rate of approvals increased dramatically in the analysis period; mean annual approvals assessed in a 5-year period increased from 7.4 per year for 2000–2004 to 56 per year for November 2017–October 2022 (a 757% increase). Since 2009, this trend has been driven exclusively by the increased annual approval rate for targeted drugs and

biologics, whereas the rate of cytotoxic drug approvals was considerably lower and decreased slightly over the analysis period (Fig. 2b). The approval rate for targeted drugs was slightly higher than that of targeted biologics from 2000 to 2019, but the rate for targeted biologics surpassed targeted drugs in 2020–2022.

The mean annual number of new distinct products increased less sharply during the analysis period (Supplementary Fig. 1a), from 3.4 per year for 2000–2004 to 15.2 per year for November 2017–October 2022 (a 447% increase). Also, the mean number of approvals per distinct product was relatively steady across the analysis period, with means of 1.4–2.1 approvals per distinct product in year bins. However, the maximum number of approvals per product markedly increased in 2015–2022 (Supplementary Fig. 1b), as did the standard deviations for year bins, which ranged from 1.96 to 2.87 for 2015–2022, compared with 0.77–1.30 for 2000–2014. Accordingly, there were more outliers in the number of approvals per distinct product in 2015–2022 ( $n = 17$ ) than in 2000–2014 ( $n = 5$ ) (Supplementary Fig. 1b).

Overall, these data demonstrate that the increased approval rate in oncology in the analysis period can be attributed to both an increase in the annual number of new distinct products and an increase in the variation of the number of approvals per distinct product, with a greater number of products receiving exceptionally high numbers of approvals in more recent years.

The coronavirus disease 2019 (COVID-19) pandemic did not negatively affect the annual oncology therapeutic product approval rate: 73 approvals were granted from March 2020 to February 2021, compared with 42 approvals in the previous year. In contrast, the pandemic had a significant impact on oncology clinical trial conduct; a recent analysis of SWOG Cancer Research Network trials found that actual enrolments were 77% of expected enrolments in the first year of the pandemic (March 2020 to February 2021), although cancer control and prevention trials were more affected than therapeutic trials<sup>9</sup>. It remains to be seen whether the period of decreased clinical trial enrolment could have a delayed effect on future product approval rates owing to longer clinical development timelines.

## Approval trends by disease site

Therapeutic product approvals varied in number and timing by disease site over the analysis period (Fig. 2c). New approvals for breast cancer, leukaemia and lymphoma occurred throughout the analysis period, although the general increase in approval rates since 2014 is also evident for these diseases. For brain and head and neck cancers, approvals were sparse throughout the analysis period, whereas for skin and thyroid cancers, there were marked increases in the annual number of approvals in recent years after no new product approvals from 2000 to 2010. Since 2015, the most approvals have been granted for lung cancers, lymphoma, genitourinary cancers, breast cancer and leukaemia, each of which had  $\geq 35$  approvals in the past 8 years.

The first site-agnostic approval was granted in 2017 for pembrolizumab, an anti-PD1 antibody, for the treatment of certain patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumours. There are now eight site-agnostic approvals for seven distinct products, all of which are for solid tumours.

## Trends for therapeutic product classes

The three product groups in the classification system are made up of 31 classes based on general mechanisms of action. This enabled examination of trends for product classes over time (Fig. 3).

## Box 1

### Data collection and analysis

The analysis dataset includes all oncology therapeutic products granted regular and accelerated approvals by the FDA Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) from 1 January 2000 to 31 October 2022 (listed in Supplementary Table 3). The dataset includes original applications for new molecular entities or original biologics and efficacy supplements that provided new or modified indications, curated from publicly available approval letters, approved product lists and prescribing information<sup>54</sup>, and publicly available FDA websites<sup>55–57</sup>, along with the internal FDA document archiving, reporting and regulatory tracking system. Data on the nature of the approvals and approved products were collected in the analysis dataset. Details on the pivotal clinical trials that were the basis of these approvals, such as clinical trial design, outcomes and safety, were not collected.

The following were excluded from the analysis dataset: any approval that did not provide new or modified indications; non-oncology indications (for example, non-neoplastic haematology, palliative treatment, cancer prevention and supportive care); approvals for haematopoietic stem cell transplantation and its complications; supplemental approvals that converted an indication from accelerated to regular approval (without any modifications to the indication); supplemental approvals that only added or modified 'Limitation of Use' statements; supplemental approvals only related to companion diagnostics; and co-packaged combinations where the same indication was already approved on at least one of the distinct product applications. Applications and indications that were initially granted approval and later withdrawn were included in the analysis dataset. A single approval action (new drug application (NDA), biologics license application (BLA), or supplement) with multiple indications (for example, multiple lines of therapy) in one disease site (listed in Supplementary Table 2) was counted as one approval; a single approval action with indications across multiple disease sites was counted for each disease site. Approvals were included for combination indications that were approved on the application for each distinct product (that is, cross-labelled).

The novel hierarchical classification system presented here was developed by evaluating the entirety of the analysis dataset and designing three hierarchical levels: therapeutic product groups, classes and subclasses, which organize products by primary mechanism of action in respectively more specific categories (Supplementary Table 1). Sources to evaluate class names, classification system organization and distinct product characteristics included product labels<sup>54</sup>, FDA reviews<sup>54</sup>, the WHO Anatomical Therapeutic Chemical (WHO-ATC) classification system<sup>58</sup> and the NCI thesaurus<sup>59</sup>. These sources were consulted for development of the novel classification system but were insufficient for this analysis because they lacked mechanistic specificity and/or hierarchical organization. For example, the terms used in this system do not represent the FDA established pharmacologic class, which can be less specific than the classifications used here and does not have a hierarchical organization.

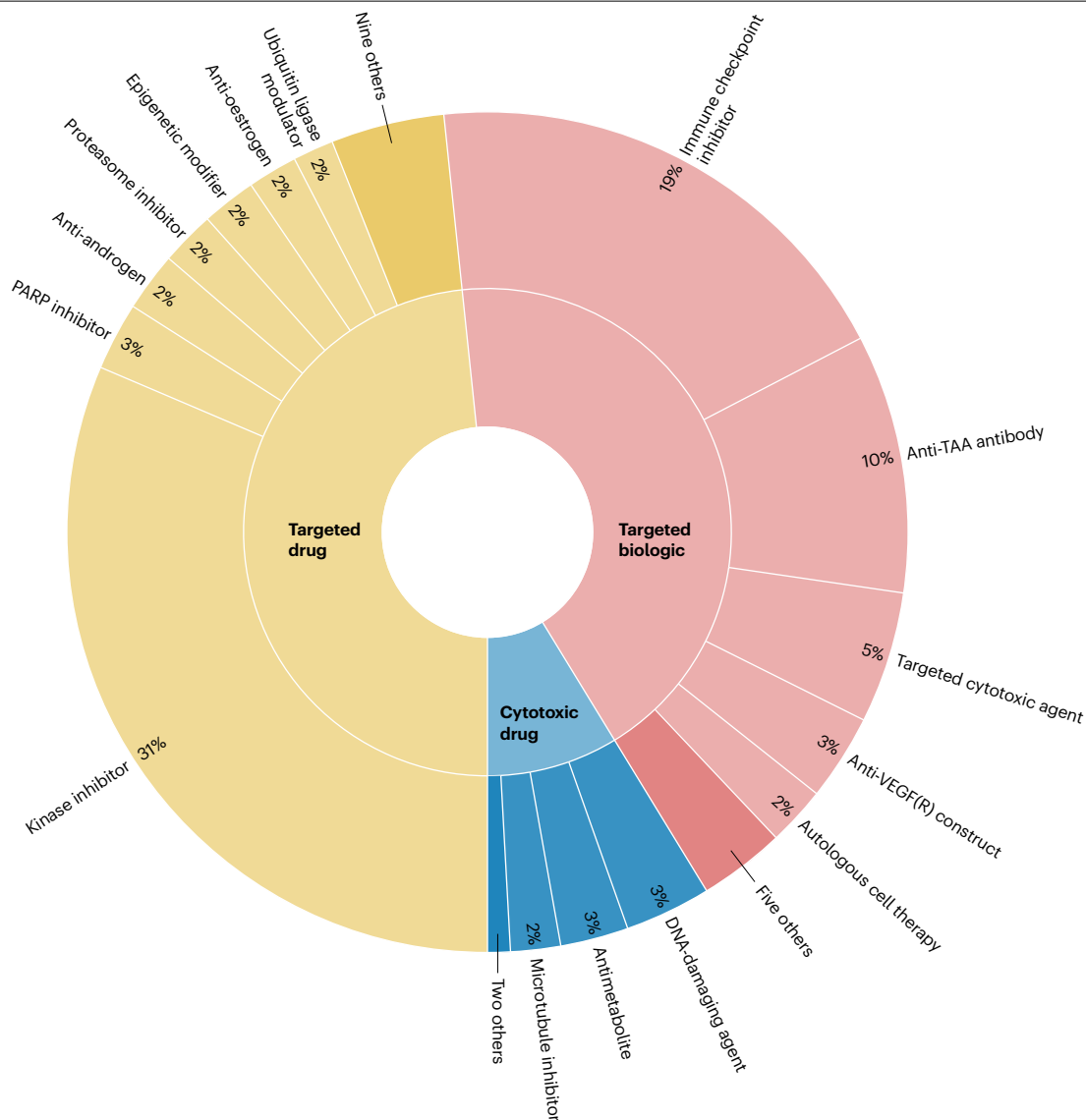
Distinct products were identified by product name; each distinct product may have multiple formulations and dosages. This is not related to FDA classification of products as new molecular entities for the purposes of FDA review, which is based on active ingredient as opposed to product name<sup>60</sup>. The primary molecular target for each product was identified through examination of section 12.1 of the prescribing information. In cases in which additional information was required to determine the primary molecular target, the FDA review for the product was consulted for further information on mechanism of action. The primary molecular target is that which is listed first or emphasized as the mechanism of action. For bispecific products, the primary target was the target on the tumour cell, or for the one product targeting two tumour cell proteins, the target listed first in the FDA established pharmacologic class (for simplicity). For targeted cytotoxic agents, the primary target was defined as the target of the antibody or protein linked to a cytotoxic substance. For products that harness the ubiquitin–proteasome system resulting in the degradation of one or more proteins via an induced proximity mechanism, the primary target was defined as the ubiquitin ligase (cereblon), consistent with the product labels. Secondary molecular targets were not included in analyses.

To assess the impact of individual product classes on the landscape of available oncology therapeutics, we juxtaposed the number of distinct products per class with the total number of approvals per class in the analysis period (Fig. 3a and Supplementary Fig. 2). Kinase inhibitors, a type of targeted drug, had the highest number of distinct products and highest number of approvals compared with all other classes. Kinase inhibitors had new approvals throughout the analysis period and remain a dominant class; the first-in-class drug (imatinib) was initially approved in 2001, and kinase inhibitors were tied for the most approvals per class in 2022.

The class with the second highest number of approvals was ICIs, a class of targeted biologic, despite only having first entered the market in 2011 and having the fifth-highest number of distinct products. Kinase inhibitors and ICIs had the same number of approvals in 2022

(nine) and had a similar number of approvals in the 5 years before that (91 and 82, respectively). Together, these results demonstrate the considerable impact that ICIs have had in the 11 years since their first-in-class approval, while also showing the continued importance of kinase inhibitors in the overall oncology therapeutic product landscape.

Five distinct products have received 12 or more approvals each since 2000 (Fig. 3b): three ICIs (pembrolizumab, nivolumab and atezolizumab), one anti-vascular endothelial growth factor (receptor) (VEGF(R)) construct (bevacizumab) and one kinase inhibitor (imatinib). These products are all targeted drugs or biologics, with no cytotoxic drugs having more than six approvals in the analysis period. We also examined products that were outliers for the number of approvals per distinct product in year bins (Supplementary Fig. 1b). Similarly, these outliers were all targeted biologics (13) or drugs (nine), with no distinct



**Fig. 1 | Overview of oncology therapeutic products approved by the FDA since 2000 by mechanism of action.** In the novel hierarchical product classification system developed for this analysis (Box 1), the 206 distinct oncology therapeutic products with approvals granted by the FDA from 1 January 2000 to 31 October 2022 were assigned to 99 subclasses (not shown), which were then aggregated into the 31 classes shown in the outer ring of the Krona plot<sup>52</sup>. These classes were assembled into three groups, shown in the inner ring of the plot. The wedge size and percentage reflect the number of approvals per class. Cytotoxic drug classes in the 'Two others' wedge: cytotoxic combination and protein synthesis

inhibitor. Targeted drug classes in the 'Nine others' wedge: apoptosis restorer; differentiation therapy; hedgehog pathway inhibitor; nuclear export inhibitor; radiotherapeutic drug; RAS inhibitor; retinoid; somatostatin receptor agonist; transcription factor inhibitor. Targeted biologic classes in the 'Five others' wedge: asparagine depleter; bispecific construct; immunostimulant; oncolytic viral therapy; radiotherapeutic antibody. PARP, poly(ADP-ribose) polymerase; TAA, tumour-associated antigen; VEGF(R), vascular endothelial growth factor (receptor).

cytotoxic drugs. The only product classes with more than two outliers were ICIs (eight) and kinase inhibitors (six). ICIs were responsible for 58% (89 of 154) of the approvals for outlier products, most of which were for the individual products pembrolizumab (39) and nivolumab (28); in contrast, kinase inhibitors were responsible for only 19% (29 of 154) of the approvals for outlier products, most of which were for the individual product imatinib (11). These analyses further demonstrate the impact of ICIs on the landscape of oncology approvals, especially

since the introduction of anti-PD1 antibodies (such as nivolumab and pembrolizumab) and anti-PDL1 antibodies (such as atezolizumab) in 2014 and 2016, respectively.

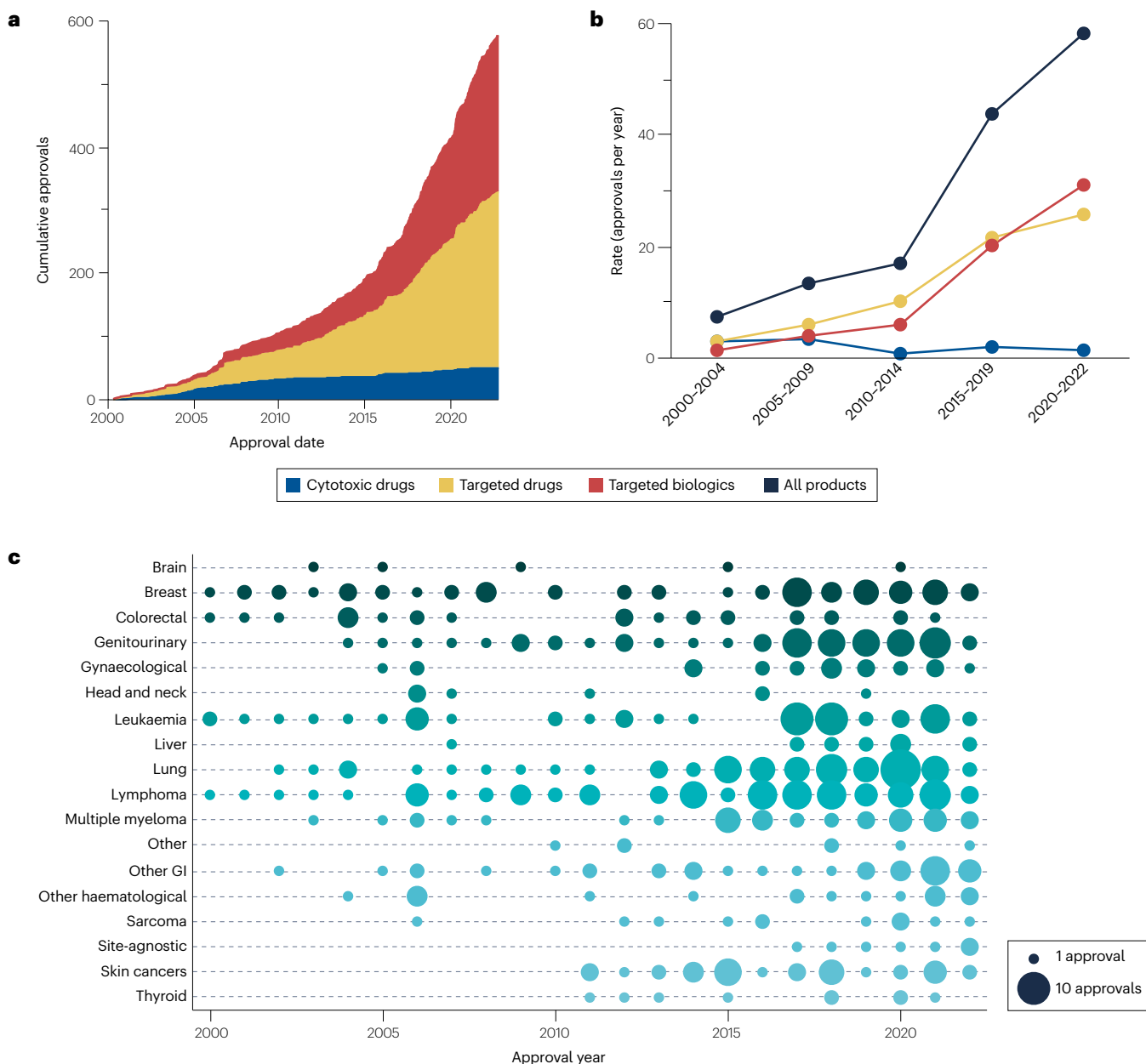
There are 29 product classes other than kinase inhibitors and ICIs that also contributed to the approved oncology product landscape. Anti-tumour-associated antigen (TAA) antibodies had the second most distinct products and third most approvals, and similar to kinase inhibitors, these approvals occurred throughout

# Review article

most of the analysis period (2001–2021). Most product classes had somewhat similar ranks in number of distinct products and number of approvals (Supplementary Fig. 2). The only class with a greater than ten-point difference between approval rank and distinct products rank was anti-VEGF(R) constructs, which had the fifth-highest number of approvals ( $n = 19$ ) and the 16th highest number of distinct products ( $n = 3$ ).

The early dominance of cytotoxic drugs and later emergence of targeted drugs and biologics is also evident. Many cytotoxic drug

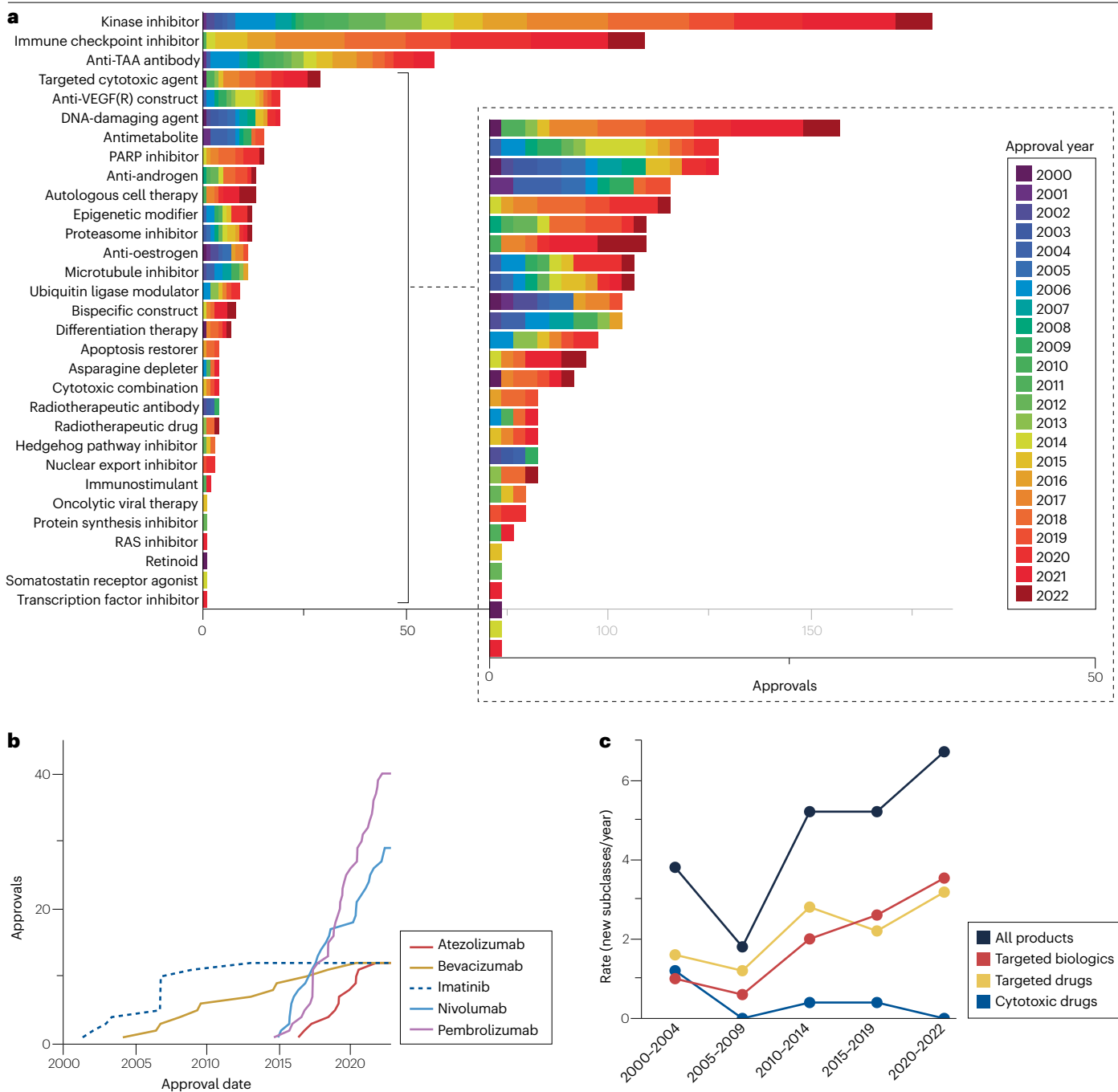
product classes, such as DNA-damaging agents, antimetabolites and microtubule inhibitors, had most of their approvals before 2010 (Fig. 3a). However, there were 53 indications for targeted drugs or biologics in combination with cytotoxic drugs approved after 2010 (see the section ‘Trends in single-agent and combination approvals’ below for more information). Together, although kinase inhibitors and ICIs have the most approvals, numerous other product classes made meaningful contributions to the approved product landscape.



**Fig. 2 | Trends in oncology therapeutic indication approvals since 2000.** **a**, Cumulative oncology approvals for the three product groups analysed: cytotoxic drugs, targeted drugs and targeted biologics. **b**, Rate of approvals (mean number of indication approvals per year) in the year bins shown, by

product group and overall. **c**, Bubble plot of the number of annual approvals by disease site. Bubble size corresponds to number of annual approvals. Disease sites encompass multiple specific diseases; see Supplementary Table 2 for a detailed list. GI, gastrointestinal.

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**Fig. 3 | Trends in approvals across product classes. a**, Total number of approvals per class coloured by approval year. **b**, Cumulative approvals for the five distinct products with the most approvals. Solid line, targeted biologic; dashed line, targeted drug. **c**, Mean rate of introduction of new subclasses in

year bins by product group and overall. PARP, poly(ADP-ribose) polymerase; TAA, tumour-associated antigen; VEGF(R), vascular endothelial growth factor (receptor).

## Product class trends by disease site

As described above, there have been numerous approvals for skin and thyroid cancers since 2010, after no approvals in the previous decade. Most of the 37 approvals in skin cancers were for ICIs (59%; 22 of 37), but other classes also contributed to increased therapeutic options

in this disease area. Kinase inhibitors targeting either BRAF or MEK accounted for 27% (10 of 37) of approvals for skin cancers and the remaining 14% (5 of 37) of approvals were from bispecific construct, hedgehog pathway inhibitor, immunostimulant and oncolytic viral therapy product classes. In contrast, all nine of the approvals in thyroid



cancer were for kinase inhibitors, including multi-kinase inhibitors and inhibitors of BRAF, MEK, RET and VEGFR1 (also known as FLT1) proteins. These examples demonstrate the important impact of both ICIs and kinase inhibitors, not only for cancer types with consistent therapeutic product development throughout the early twenty-first century, but also for cancer types with more recent advances.

There were also recent examples of the first therapeutic approvals for specific rare diseases. For example, selumetinib, a kinase inhibitor (a MEK inhibitor), was approved in 2020 as the first treatment for neurofibromatosis type 1 (NF1), a rare autosomal dominant disorder that is caused by germline mutations in the tumour suppressor gene *NF1* (ref. 10). The first treatment for light chain (AL) amyloidosis – a subcutaneous formulation of the anti-TAA antibody daratumumab (an anti-CD38 antibody) – was approved in 2021 (ref. 11), and the kinase inhibitor crizotinib (an ALK inhibitor) became the first approved therapy for inflammatory myofibroblastic tumour, a rare subtype of soft tissue sarcoma, in 2022 (ref. 12). Each of these examples is a targeted therapy, although these products followed different development paths. For instance, the selumetinib approval was an original product approval, whereas the daratumumab and crizotinib approvals were supplementary approvals.

The seven products with site-agnostic approvals noted above are kinase inhibitors (a BRAF inhibitor, a MEK inhibitor, two TRK inhibitors and a RET inhibitor) or ICIs (two anti-PD1 antibodies). Although not specifically for rare diseases, these approvals provide therapeutic options for both patients with rare molecular subsets of common diseases and patients with rare tumours harbouring the specific targeted mutations or genomic features<sup>13</sup>. Together, these examples demonstrate how advances in cancer genomics have enabled the identification of patient subsets who may benefit from targeted therapies.

## Product subclass trends

The 31 product classes were further subdivided into 99 subclasses that capture specific therapeutic targets and mechanisms (Supplementary Table 1). There were ten subclasses of cytotoxic drugs, 48 subclasses of targeted drugs and 41 subclasses of targeted biologics. On average, classes of targeted biologics contained more subclasses (mean 4.1 subclasses per class) than either targeted or cytotoxic drugs (means 3.0 and 2.0, respectively).

The kinase inhibitor class had the most subclasses (21), followed by the targeted cytotoxic agent class (12) and the anti-TAA antibody class (11), which is indicative of the many different molecular targets of products in these classes. The anti-PD1 antibody subclass, a type of ICI, had the most approvals (75), nearly three times that of the subclass with the second most approvals, BCR–ABL kinase inhibitors (27 approvals). There are 19 subclasses that had at least ten approvals: nine of these subclasses are part of the kinase inhibitor class, four are part of the anti-TAA antibody class and three are part of the ICI class. The remaining three subclasses are part of the anti-VEGF(R) construct, autologous cell therapy and PARP inhibitor classes, respectively.

The ICI class had the highest mean number of approvals per subclass (27.3; median 16.5). Although many kinase inhibitor subclasses had greater than ten approvals, they had an average of 8.6 approvals per subclass (median 7.0). Taken together, these observations illustrate that the impact of kinase inhibitors was primarily due to a wide variety of targeted kinases, which together resulted in large numbers of approved oncology indications, whereas the impact of ICIs stemmed from fewer subclasses of products that had more approvals across diseases. The wide variation in the number of approvals at the subclass

level could reflect the therapeutic approaches: some products are indicated for patients with mutation or expression of the molecular target protein or tumour types with activation of a certain signalling pathway, and thus are limited by the number of tumour types in which that molecular target protein or signalling pathway is altered; other products target the tumour microenvironment and may not be limited by the genomic landscape of different tumour types.

The introduction of new subclasses over time is one way to assess the pace of therapeutic product development and successful translation of novel cancer treatment approaches. The rate of new subclass introduction has increased from a mean of 3.8 new subclasses in 2000–2004 to 6.7 in 2020–2022 (Fig. 3c). Almost all of this innovation was due to new subclasses of targeted drugs and biologics, with only four new subclasses of cytotoxic drugs introduced since 2004. Targeted drugs had the highest rate of new subclass introduction from 2000 to 2014, but targeted biologics had a higher mean rate since 2015. The introduction of new subclasses of targeted biologics has followed a near-linear trend since 2005; it will be interesting to see whether innovation in therapeutic approaches for targeted biologics continues to outpace that for targeted drugs.

Overall, this analysis of trends in product approvals highlights the major impact that several product classes and subclasses have had on the oncology treatment landscape and the increased pace of innovation in the field. However, as it assesses only product approvals, it cannot illuminate trends for emerging therapeutic approaches for which products have not yet progressed from clinical trials to regulatory approval.

## Trends for molecular targets and pathways

Most approvals (97.4%) in the analysis dataset were for products that bind to or otherwise affect certain molecular targets; the remaining approvals do not have a known molecular target (2.6%). For the purposes of this analysis, we considered the gene encoding the primary molecular target protein not only for targeted drugs and biologics, but also cytotoxic drugs; secondary target proteins were not included.

There were 83 molecular targets for the 206 products with approvals for oncology indications in the analysis period. Most of the targets are proteins encoded by a single gene ( $n = 73$ ); other targets include two fusion proteins, two protein complexes, two protein families, an amino acid, a glycolipid, a peptide and DNA. Each molecular target was the primary target of 1–12 distinct products; EGFR, DNA, CD19 and HER2 (also known as ERBB2) were targeted by the highest number of distinct products (Supplementary Fig. 3a). The molecular targets with the most approvals were PD1 (also known as PDCD1), EGFR and the BCR–ABL1 fusion protein (Supplementary Fig. 3b), and PD1 had more than twice as many approvals (76) as EGFR (30). PD1 is targeted exclusively by ICIs, EGFR is targeted by multiple product classes (kinase inhibitors, anti-TAA antibodies and a bispecific construct) and BCR–ABL1 is targeted only by kinase inhibitors. So, ICIs and kinase inhibitors have made their impact on the oncology therapeutic product landscape in part through high numbers of approvals for a few target proteins.

The 73 single-gene-encoded molecular targets were analysed for additional insights into protein location and function. By subcellular location<sup>14</sup>, most (52%) are plasma membrane proteins, but the molecular targets also include cytoplasmic (22%), nuclear (21%) and extracellular (5%) proteins. The target proteins belong to 12 different protein classes<sup>15</sup>, the most frequent of which are transmembrane signal receptor, metabolite interconversion enzyme and protein-modifying enzyme (Supplementary Fig. 3c). The 73 target proteins are involved in 46 different pathways in the Panther Pathways database<sup>16</sup>; the pathways

with the most target proteins are angiogenesis (12 target proteins), B cell activation (ten) and the PDGF signalling pathway (nine); 31 target proteins are not involved in any pathways in the database. These results offer some insights into the cellular characteristics of the molecular target proteins and some of the pathways that are important targets for cancer therapeutics.

Ninety per cent of molecular target proteins (75 of 83) were targeted only by products in one class; however, CD19 was targeted by products in four different product classes (anti-TAA antibody, autologous cell therapy, bispecific construct and targeted cytotoxic agent), and EGFR, HER2 and BCMA (also known as TNFRSF17) were each targeted by products in three different classes. These proteins are all located on the plasma membrane. The physical accessibility of proteins on the cell surface could facilitate targeting by numerous product classes. Of the eight proteins targeted by more than one product class, seven are located in the plasma membrane and one is located in the nucleus. There are 31 other molecular target proteins located in the plasma membrane that are currently only targeted by one product class, so some of these may also be amenable to targeting with multiple product classes in the future. However, certain molecular target proteins with subcellular locations other than the plasma membrane may also be amenable to targeting by multiple product classes; for example, many targeted cytotoxic agents have intracellular secondary molecular target proteins that were not considered in this analysis but are also targeted by products in other classes.

## Interconnectedness of target proteins

Although the proteins targeted by oncology products belonged to 12 different protein classes, the molecular target proteins are highly interconnected in molecular pathways. Ingenuity Pathway Analysis (IPA)<sup>14</sup> revealed that the 73 targeted gene products belonged to 383 canonical pathways in the Ingenuity Knowledge Base, which consists of curated metabolic and cell signalling pathways. The 383 pathways contain a mean of 4.8 target genes per pathway (median 4; range 1–18); 303 of these pathways contain at least two target proteins, and 41 pathways contain at least ten target proteins. Each target gene belongs to a mean of 24.9 pathways (median 7; range 0–204); 11 target genes (15%) are not in any IPA canonical pathways. Altogether, these analyses demonstrate that molecular target proteins participate in many signalling pathways and are interconnected.

The implications of the interconnected nature of the molecular targets of oncology therapeutic products are especially important for the use of products in combination. Oncology products are indicated to be used either alone as single agents or in combination with other products as part of a multi-product therapeutic regimen. There were 187 approvals for combination indications, 80 of which were for two or more products with different identified gene targets; of these, 63.8% (51 of 80) were for two products with molecular protein targets in at least one of the same IPA canonical pathways. Therefore, most oncology combination indications for products with identified gene targets approved so far in the twenty-first century were for two products that influence the same pathway. The pathways most frequently targeted by two products in combination indications were the T cell exhaustion signalling pathway (23 indications, 16 of which are for the combination of nivolumab and the anti-CTLA4 antibody ipilimumab) and the tumour microenvironment pathway (19 indications, 13 of which are for the combination of BRAF and MEK inhibitors).

There are many possible effects on pharmacodynamics that can occur based on whether therapeutic product targets are in the same,

related or cross-talking pathways, as well as other factors, and these effects can be synergistic, additive or antagonistic<sup>17</sup>. Mapping out these effects and elucidating their mechanisms, as was done in 2009 for a set of combination indications<sup>17</sup>, was outside the scope of this analysis. Additionally, future investigation could support a deeper understanding of whether certain combination approaches affect the emergence of resistance<sup>18</sup>.

## Trends in biomarker-defined populations

Advances in sequencing technology and the exploration of the genomic landscape of cancer have facilitated the subclassification of cancer types by molecular alterations, enabled the development of therapies that take advantage of susceptibilities of cancer cells and ushered in the era of precision medicine<sup>3</sup>. Biomarkers based on the presence or absence of certain genetic alterations or expressed proteins are used to identify cancer subtypes and may be used to identify patients likely to derive benefit from specific therapies (that is, biomarker-defined populations).

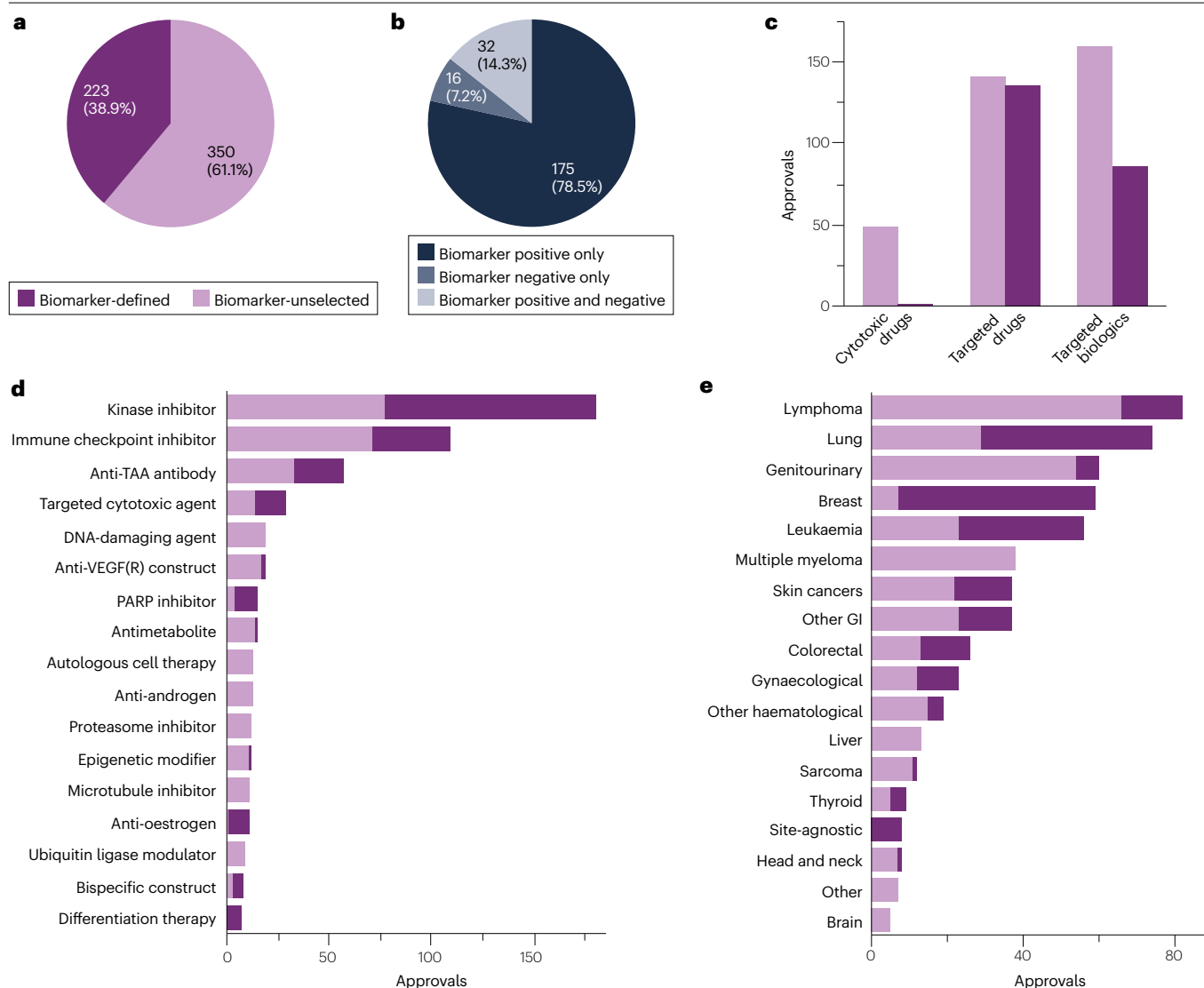
Although most oncology approvals (61.1%) were for biomarker-unselected populations, 38.9% (223 of 573) of oncology approvals were for biomarker-defined populations (Fig. 4a). There were seven approvals (1.2%) that granted both biomarker-defined and biomarker-unselected indications; in this analysis, we considered these approvals for biomarker-defined populations. Companion diagnostics are medical devices that are approved to provide information that is essential for use of a corresponding product, including for detection of biomarkers in oncology<sup>19</sup>; however, this Review is focused on therapeutic indications and does not discuss the development or approval of companion diagnostics.

## Prominent biomarkers

The biomarkers designated in the most approvals were HER2, EGFR, BRAF, HR (hormone receptor: oestrogen receptor (ER) and/or progesterone receptor (PR)) and the Philadelphia chromosome (the translocation that produces the BCR-ABL protein; Supplementary Fig. 4a). Biomarkers overlapped with the molecular target proteins of the indicated product in 132 approvals (59.2% of approvals using biomarkers). The most frequent biomarkers that were also the molecular target of the therapeutic product were HER2, the Philadelphia chromosome and EGFR. Fourteen (6.3%) of the remaining approvals used biomarkers that overlapped with a known molecular target of one of the indicated combination products. The remaining 77 approvals (34.5%) used biomarkers that were not a known molecular target of the indicated or combination product; the most frequent biomarkers for these approvals were HER2, PDL1 (also known as CD274) and dMMR. In these situations, biomarkers might instead define a molecular subtype of cancer (for example, HER2-negative breast cancer or dMMR colorectal cancer) or participate in the same signalling pathway as the molecular target protein (for example, PDL1 for anti-PD1 antibodies).

Most approvals in biomarker-defined populations were for biomarker-positive tumours only (78.5%); however, 32 approvals (14.3%) required tumours to be both positive for some biomarkers and negative for others (Fig. 4b). Sixteen approvals (7.2%) in biomarker-defined populations were only for tumours negative for biomarkers; of these, 13 were for targeted biologics, two were for targeted drugs and one was for a cytotoxic drug. Biomarker-negative-only approvals mostly designated well-defined molecular subtypes of disease and included five approvals for EGFR and ALK-negative lung cancer, three approvals for triple-negative breast cancer (ER, PR and HER2-negative), two approvals for BRAF(V600) wild-type melanoma, and two





**Fig. 4 | Trends in approvals for biomarker-defined populations. a**, Number (percentage) of approvals in biomarker-unselected and biomarker-defined populations. **b**, For approvals in biomarker-defined populations, number (percentage) of approvals for biomarker-positive tumours only, biomarker-negative tumours only or biomarker-positive and biomarker-negative tumours. **c–e**, Total number of approvals in biomarker-unselected and biomarker-defined populations by product group (**c**), product class (**d**) and disease site (**e**).

The dataset included seven approvals that contained indications for both biomarker-defined and biomarker-unselected populations, which were counted as biomarker-defined approvals. Product classes with fewer than five approvals were not included in panel **d**. GI, gastrointestinal; PARP, poly(ADP-ribose) polymerase; TAA, tumour-associated antigen; VEGF(R), vascular endothelial growth factor (receptor).

approvals for KRAS wild-type colorectal cancer; there was one approval each for tumours negative for HER2, MSI-H and dMMR, KIT(D816V) and the Philadelphia chromosome. Altogether, these analyses show that the most common use of biomarkers was for identifying tumours positive for the molecular target protein of an indicated product, although biomarkers are also used to define specific genomic contexts, including the absence of a biomarker.

## Trends in use of biomarkers

The use of biomarkers in oncology indication approvals increased slightly over the analysis period (Supplementary Fig. 4b). Biomarkers

were used in 32% of approvals in 2000–2004 and 30% in 2005–2009, then steadily increased to 43% in 2020–2022. The relatively small magnitude of this overall change (+11% from 2000 to 2022) is surprising given the increased adoption of next-generation sequencing and tumour profiling in recent years.

Biomarkers were used most frequently in approvals for targeted drugs (49% of approvals), whereas they were used in only 35% of approvals for targeted biologics. There was only one approval for a cytotoxic drug in a biomarker-defined population, and this was in combination with a targeted biologic for biomarker-negative tumours (the 2019 approval of pemetrexed in combination with pembrolizumab and

platinum chemotherapy for initial treatment of patients with metastatic non-squamous non-small-cell lung cancer (NSCLC) without EGFR or ALK aberrations). However, biomarkers were used in approvals for only 48% of product classes (Fig. 4d). Biomarkers were used for all approvals in two product classes (differentiation therapy and RAS inhibitor). Other classes that used biomarkers frequently were anti-oestrogens (91% of approvals), PARP inhibitors (73%) and bispecific constructs (63%). Product classes without approvals in biomarker-defined populations include 80% of cytotoxic drug classes (4 of 5), 50% of targeted drug classes (8 of 16) and 40% of targeted biologic classes (4 of 10). Kinase inhibitors alone were responsible for most (76%) of the targeted drug approvals in which biomarkers were used.

Biomarkers were used in approvals for 13 of the specific disease sites analysed, but there are currently no approvals using biomarkers in three disease sites (brain, liver and multiple myeloma) (Fig. 4e). All site-agnostic approvals were for biomarker-positive-only tumours, as the presence of a biomarker is crucial to identify molecularly defined disease subtypes in the absence of histological specification. For specific disease sites, biomarkers were used most frequently in breast cancer (88% of approvals) and lung cancer (61%). Molecular alterations have been used to define specific subtypes of breast cancer for many years, whereas lung cancer has only begun to be subdivided by molecular alterations more recently.

## Biomarkers in site-agnostic approvals

The biomarkers used in the eight site-agnostic approvals are *BRAF*<sup>V600E</sup> mutations, *NTRK* fusions, *RET* fusions, tumour mutation burden (TMB) high (>10 mutations per megabase), MSI-H or dMMR and dMMR alone. Three of these biomarkers are specific genes; the remaining biomarkers are based on other tumour genomic features such as mutation burden or DNA repair status. Two of the biomarkers – *NTRK* fusions and TMB high – did not have any site-specific approvals, whereas the other biomarkers had both site-agnostic and site-specific approvals. The development path for these products and biomarker-defined indications consisted of an initial site-agnostic approval followed by site-specific approval in some cases, and initial site-specific approval followed by site-agnostic approval in other cases.

## Trends in single-agent and combination approvals

Single-agent indications have accounted for around two-thirds (364 of 551) of oncology product approvals since 2000, and approximately one-third (187 of 551) of approvals were for combination indications (Fig. 5a). Approvals that included indications for both combination and single-agent use ( $n = 10$ ), approvals with indications for combinations followed by single-agent use ( $n = 4$ ) and approvals for fixed combination formulations ( $n = 8$ ) were not counted in this analysis. Cytotoxic drugs were used in combination most frequently (52% of approvals), followed by targeted biologics (43%); targeted drugs were used in combination less frequently, and combination indications accounted for only 23% of approvals in this group (Fig. 5b).

Certain product classes were used more frequently in combination than as single agents (Supplementary Fig. 5a), including asparagine depleters (100% combination use), microtubule inhibitors (80%), anti-VEGF(R) constructs (76%), anti-TAA antibodies (75%), nuclear export inhibitors (67%), DNA-damaging agents (53%) and radiotherapeutic antibodies (50%). Single-agent indications were more common than combinations for all other product classes. Numerous classes had approvals only for single-agent indications, including autologous cell therapies, bispecific constructs and eight classes with fewer than five approvals each.

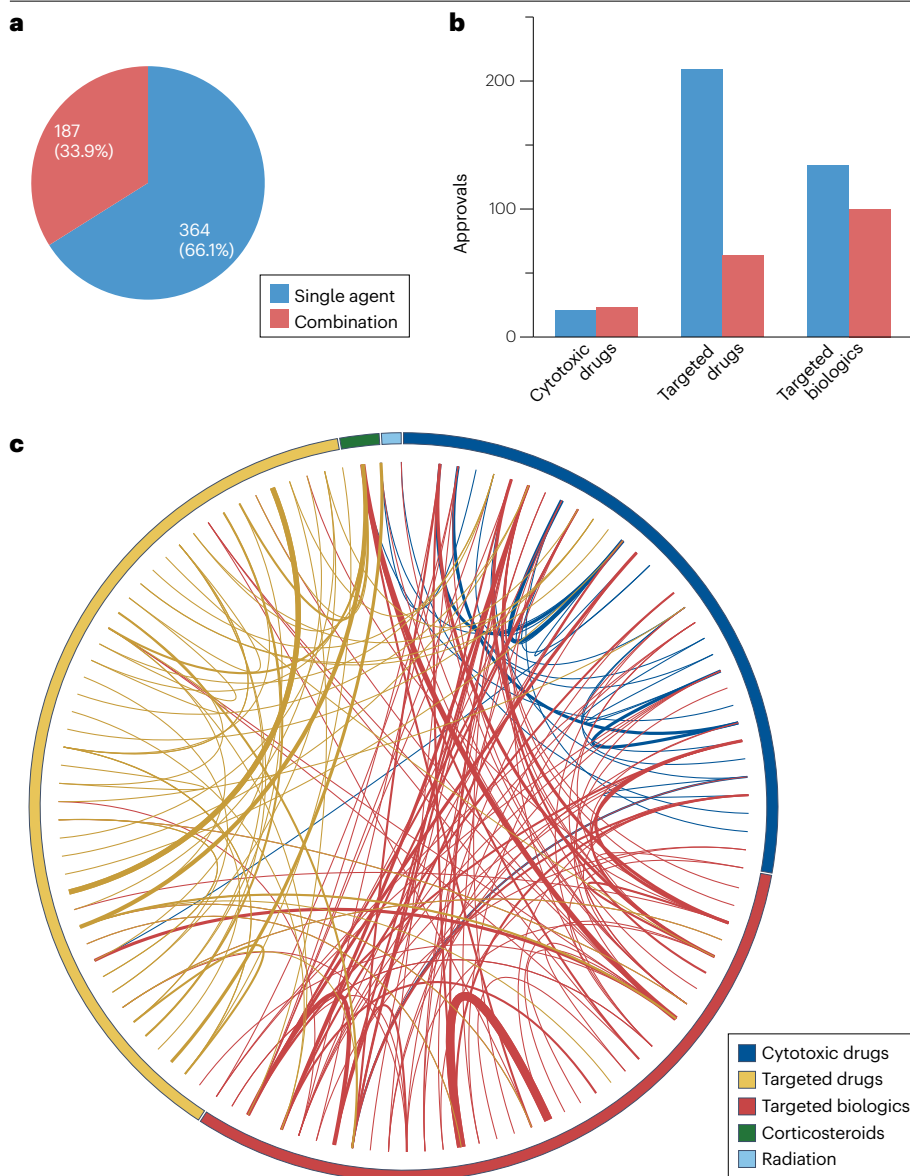
Combination indications were also more common than single-agent indications for some disease sites (Supplementary Fig. 5b). Disease sites with more than 50% approvals for combination indications included multiple myeloma (66% combination use), colorectal (65%), breast (63%), brain (60%) and head and neck (57%) cancers; single-agent indications were more common than combinations for all other disease sites. All approvals in the broad disease sites of other cancers ( $n = 7$ ) and other haematological neoplasms ( $n = 17$ ) were for single-agent indications.

## Combined product groups and classes

The 187 approvals for combination indications were examined further to explore the ways in which therapeutic product groups and classes were used together (Fig. 5c and Table 1). Cytotoxic drugs, when used in combination, were most frequently used in intragroup combinations with other cytotoxic drugs (78% of combination approvals); however, approvals of cytotoxic drug combination indications primarily occurred early in the analysis period (median approval year 2006), so this may simply reflect the products available at that time. Targeted drugs were also most frequently used in intragroup combinations, which accounted for 58% of combination approvals; the remaining combination approvals were with corticosteroids (20%), targeted biologics (19%) and cytotoxic drugs (17%). In contrast, targeted biologics were most frequently used in intergroup combinations with cytotoxic drugs (58% of combination approvals), and intragroup combinations were less frequent (33%).

Kinase inhibitors, ICIs and anti-TAA antibodies had the highest number of approved combination indications (41, 40 and 38, respectively). Kinase inhibitors were used in combination in 23% of approvals, and the most frequent combination classes were other kinase inhibitors and anti-oestrogens (each accounted for 34% of combination indications). ICIs were used in combination in 38% of approvals; 45% of combination indications were intraclass with other ICIs, all of which were for the combination of anti-CTLA4 antibodies and anti-PD1 or PDL1 antibodies (two indications also include a cytotoxic drug); ICIs were also used in combination with antimetabolites, chemotherapy, DNA-damaging agents, kinase inhibitors, microtubule inhibitors, anti-TAA antibodies and anti-VEGF(R) constructs. For anti-TAA antibodies, 68% of combination indications were for use in combination with two or more products; they were most frequently combined with DNA-damaging agents and corticosteroids. Similar to kinase inhibitors and ICIs, 11% of anti-TAA antibody combination indications were intraclass combinations with other anti-TAA antibodies. Of note, the only other class with intraclass combinations was DNA-damaging agents; all other approved combination indications were for interclass combinations. Overall, intraclass combinations accounted for only 20% of approved combination indications, and interclass combinations were generally much more common, even for groups with high percentages of intragroup combinations.

Sixty-five per cent of combination indications were for combination with one other product; if approvals indicated two or more combination products, those products were most often in the same group (18% of combination indications). However, there were 32 approvals that indicated two or more combination products across multiple groups; 53% of these (17 of 32) were in multiple myeloma, owing to the frequent combinations with corticosteroids and ubiquitin ligase modulators or proteasome inhibitors. Multiple myeloma indications also accounted for 81% (21 of 26) of combinations with corticosteroids; the remaining five instances were in prostate cancer. There were only



**Fig. 5 | Trends for single-agent and combination approvals.** **a**, Number (percentage) of approvals for single-agent indications and combination indications. **b**, Total number of approvals for single-agent and combination indications by product group. **c**, Circos plot<sup>33</sup> illustrating all 187 approvals for combination indications. Each line represents one product–combination product pairing. Line colour denotes the group of the approved product. Line ending location denotes the group of the combination product. Line width represents the number of approvals. For indications with combination products in two or more groups, one line is shown per group. The dataset had ten approvals with indications for both combination and single-agent use, four approvals with indications for combinations followed by single-agent use and eight approvals for fixed combination formulations, all of which ( $n = 22$ ; 3.8%) were not included in this figure.

two examples of approvals for combination indications that included products across all three product groups: the 2018 approval of daratumumab, an anti-TAA antibody, in combination with bortezomib, melphalan and prednisone in certain patients with multiple myeloma, and the 2020 approval of tucatinib, a kinase inhibitor, in combination with trastuzumab and capecitabine in certain patients with HER2-positive breast cancers. However, these cases were the exception, and combination indications were usually with only one other product or products in only one group.

### Product development paths

The percentages of initial product approvals for single agents compared with combination use were relatively steady across the analysis period; the share of initial approvals for combination use by year bin ranged from 15% to 28% (Supplementary Fig. 6a). Products initially

approved before 2000 ( $n = 15$ ), products initially approved for both single-agent and combination use ( $n = 5$ ), fixed combination products ( $n = 5$ ) and products initially approved for combination use and later approved for combination use followed by single-agent use ( $n = 1$ ) were excluded from these analyses.

Eighty-one per cent of products were approved for only one type of indication (146 of 180); of these, most were approved for single-agent use only (114 of 146). A total of 34 products were approved for multiple types of indications; 85% of these were initially approved for single-agent use, followed by combination use or approvals that included indications for both combination and single-agent use; only five products were initially approved for combination use and later granted single-agent indications (Supplementary Fig. 6b). The mean time between initial and second approval type was similar for products initially approved for single-agent or combination use (mean of

**Table 1 | Product and combination groups for combination indications**

Product group	Combination group	Percentage of combination indications <sup>a</sup>
Cytotoxic drugs	Cytotoxic drugs	78.3
	Targeted drugs	4.3
	Targeted biologics	8.7
	Corticosteroids	13.0
	Radiation	4.3
Targeted drugs	Cytotoxic drugs	17.2
	Targeted drugs	57.8
	Targeted biologics	18.8
	Corticosteroids	20.3
	Radiation	0.0
Targeted biologics	Cytotoxic drugs	58.0
	Targeted drugs	20.0
	Targeted biologics	33.0
	Corticosteroids	10.0
	Radiation	1.0

<sup>a</sup>Instances of an indication including two or more combination products across different groups were counted once per combination group; therefore, the total percentage of combination indications is greater than 100% per group; 9–21% of indications were in combination with two or more products across different groups.

4.59 and 4.53 years, respectively). However, the mean and spread of the time interval between approval types decreased throughout the analysis period; the mean time to second approval type was 7.28 years in 2000–2004, and this decreased to 2.73 years in 2015–2019 (Supplementary Fig. 6c). However, these statistics may be skewed by the limited follow-up time for products approved later in the analysis period.

## Trends in regulatory pathways

The accelerated approval (AA) pathway is an alternative product approval pathway to traditional approval that was introduced in 1992 and was initially focused on expediting product development during the HIV/AIDS crisis. This pathway is an expedited programme for products that treat serious or life-threatening conditions, including oncological diseases, and is based on improvement in an end point reasonably likely to predict clinical benefit, with confirmation of benefit demonstrated in a subsequent trial or trials<sup>20</sup>. AA addresses uncertainty and can allow for transformative products to be approved years earlier. However, should clinical benefit not be confirmed, a product or indication may be withdrawn from marketing.

As described in Box 1, this analysis included oncology approvals that have since been withdrawn, including 18 AAs (as of 31 October 2022)<sup>21</sup>. The withdrawn approvals included in this analysis were for products in seven different classes, all of which were targeted drugs or biologics; classes with more than one withdrawn AA were ICIs ( $n = 7$ ), kinase inhibitors ( $n = 5$ ) and epigenetic modifiers ( $n = 2$ ).

During the analysis period, 71% (407 of 573) of oncology approvals used the regular approval (RA) pathway, and 29% (166 of 573) used the AA pathway. Although the total number of AAs has increased in recent years (Supplementary Fig. 7), this was reflective of the overall increase in therapeutic product approval rate in the analysis period (Fig. 2b)

rather than an increased percentage of AA use in oncology. Examination of oncology AA use overall in year bins showed minor fluctuations in the annual percentage of approvals using the AA pathway; however, use of AA was relatively steady across the analysis period (Fig. 6a). The overall mean annual percentage of AAs from 2000–2022 was 30.6% (median 29.4%; range 10–71.4%). In the past five years, the mean annual percentage of AAs was 28.4% (median 27.3%; range 24.6–34.4%). Overall, use of the AA pathway has decreased slightly in the past five years and stabilized, with less variability between years than in the early 2000s.

AA was used most frequently for targeted biologics (31% AAs), slightly less frequently for targeted drugs (29%) and most infrequently for cytotoxic drugs (20%) (Fig. 6b). AA and RA were used even more variably across therapeutic product classes (Fig. 6c). Twelve product classes did not have any AAs; these were mostly classes with fewer than five approvals during the analysis period, along with three classes with more than five approvals (anti-androgens, microtubule inhibitors and differentiation therapies). Two classes had only AAs and no RAs (protein synthesis inhibitors and RAS inhibitors). Of classes with at least ten approvals, the highest use of AAs was in epigenetic modifiers (42% AAs), targeted cytotoxic agents (41%), antimetabolites (40%) and ICIs (39%). Although kinase inhibitors had the highest overall number of AAs (58), AA only accounted for 32% of approvals in this class.

AA and RA were used somewhat differently across disease sites (Fig. 6d). In contrast to the highly variable use of AA between classes, there were some products with AAs for all disease sites analysed. RA was used most frequently for 16 of 18 disease sites; the exceptions were two heterogeneous disease site groups: site-agnostic (100% AAs) and other cancers (57% AAs). Beyond these, AAs were used most often for lymphoma (40%), brain cancers (40%) and leukaemia (34%). AAs were used least frequently for other haematological neoplasms (11%), head and neck cancer (13%) and breast cancer (19%).

## Looking forwards

This analysis of oncology product approvals in the twenty-first century so far can also inform discussion of questions about what the next few decades in oncology product development will bring<sup>22</sup>.

## How will novel approaches impact the field?

This analysis revealed that innovation in oncology therapeutic approaches (quantified by the rate of introduction of new subclasses of products) has increased since 2004, driven almost solely by new types of targeted drugs and biologics. We have previously voiced concerns that the burgeoning development of ICIs, especially in the anti-PD1/PDL1 space, has resulted in duplicative product development efforts that deplete resources away from the exploration of alternative treatment approaches<sup>23</sup>. Despite this, development of new therapeutic approaches in oncology appears to be continuing steadily. This trend will be worthwhile to re-evaluate in the future, to see whether this continues or if ‘me too’ development is more incentivized.

There are numerous promising novel therapeutic approaches under development. Autologous cell therapies have emerged in the past 6 years as a novel and transformative therapeutic approach. There were 13 approvals in this class, including four in 2022 alone; 12 were chimeric antigen receptor (CAR)-T cell therapies, all of which were approved since 2017. These therapies reprogramme a patient’s T cells with transgenes encoding CARs, resulting in the activation of T cells and subsequent targeting of cancer cells. Although CAR-T cell therapies still make up most cell therapies under development (from preclinical

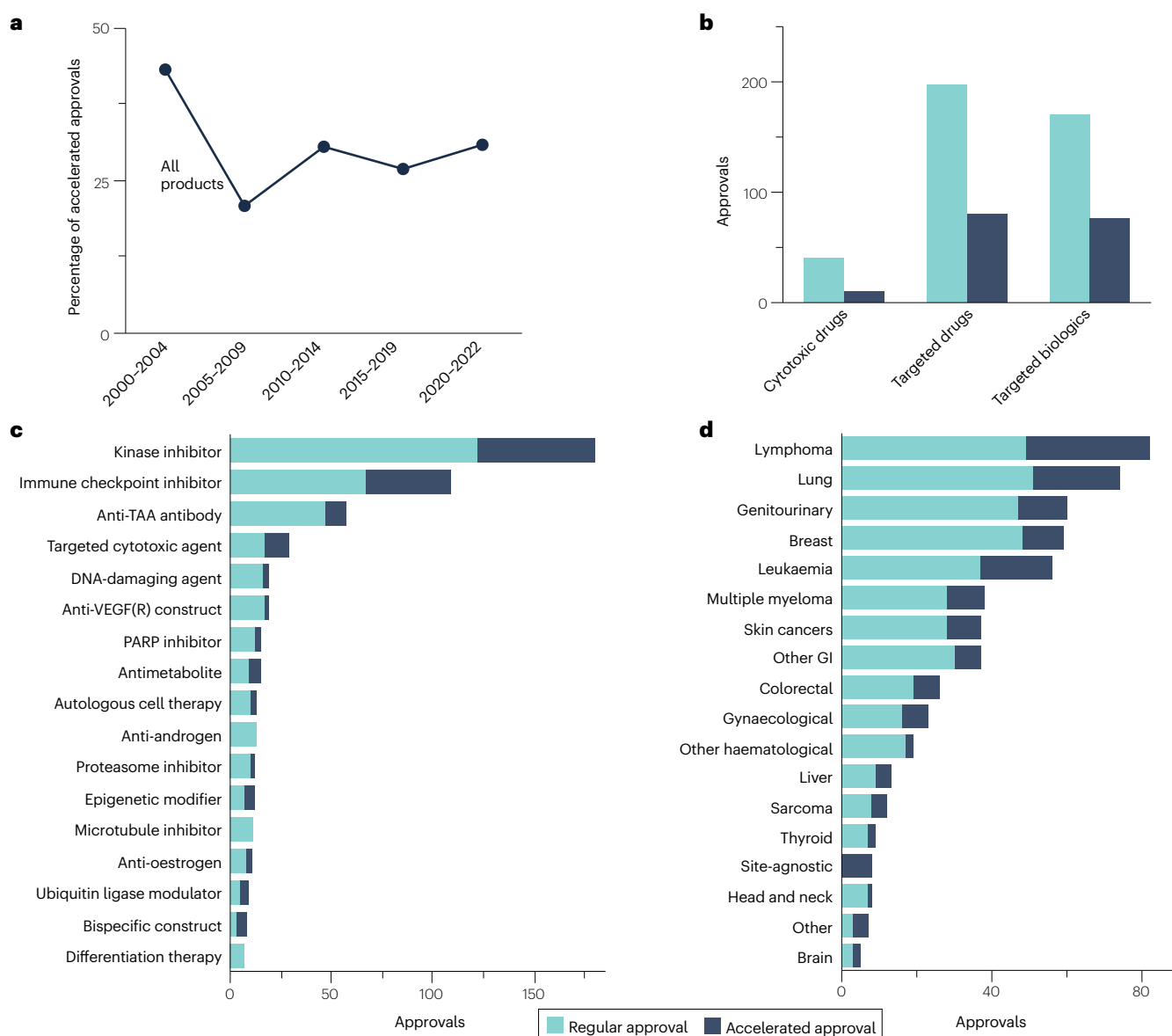


# Review article

to post-marketing studies), there is also considerable development ongoing with other types of cell therapy, including both autologous and allogeneic-based products<sup>24</sup>. The approved CAR-T cell therapies all target either CD19 or BCMA; however, many products with additional targets are under development, including CD20 (also known as MS4A1), CD22 and CD123 in haematological malignancies and TAAs, HER2 and GD2 in solid tumours<sup>24</sup>.

The targeting of neoantigens – tumour-specific antigens derived from somatic variants – has also emerged as a new approach. As neoantigens are tumour specific and not present in normal cells, these therapies have the potential for decreased off-target toxicities. Neoantigens can either be public (present in many individuals) or private

(identified in one individual). Public neoantigens, also known as shared neoantigens, offer the advantage of facilitating the development of off-the-shelf therapeutics that could potentially benefit large proportions of patients<sup>25</sup>. However, considerable development is ongoing to target private neoantigens with therapeutic products that are individually designed for a single patient<sup>26</sup>. The identification of both public and personalized neoantigens is based on sequencing DNA and/or RNA from tumour and normal samples and using bioinformatics tools to predict neoantigens that would be good therapeutic targets<sup>26</sup>. There are numerous general approaches under development to specifically target neoantigens, such as vaccines, cellular therapies (including the CAR-T cell therapies discussed above) and antibodies<sup>26</sup>.



**Fig. 6 | Trends in regulatory pathways for oncology approvals. a**, Percentage of accelerated approvals (AAs/total approvals) in year bins. **b**, Total number of approvals that used AA and regular approval (RA) pathways by product group. **c,d**, Total number of approvals that used AA and RA by product class (c) and

disease site (d). Product classes with fewer than five approvals were not included in panel c. GI, gastrointestinal; PARP, poly(ADP-ribose) polymerase; TAA, tumour-associated antigen; VEGF(R), vascular endothelial growth factor (receptor).



## Glossary

### Cytotoxic drugs

Small-molecule drugs with the primary mode of action of inducing cellular toxicity, generally by interacting with DNA or components of the cell cycle. They affect rapidly dividing cells and are usually genotoxic.

### Indication

The approved indication for a given product. This includes the use (for example, for treatment) and disease or condition for which the product is approved, as well as additional information, when applicable, such as use in conjunction with a primary mode of therapy (for example, in combination with another product(s)), the indicated population (for example, by age or biomarkers), and use in specific situations (for example, for use in previously treated patients).

### Targeted biologics

Biological products, including monoclonal antibodies, other antibody constructs and conjugates, cellular therapies, enzymes, fusion proteins and viral therapies. They typically recognize specific peptide sequences in proteins present on the surface of cancer cells and have high target specificity.

### Targeted drugs

Drugs that inhibit or interfere with defined molecular targets in cancer cells (such as kinases, receptors and other molecules) that are involved in intercellular or intracellular signalling pathways. They are primarily small-molecule drugs, but also include short peptides and radioactive agents without an antibody moiety.

Another area of interest is the application of novel approaches to targeting so-called ‘undruggable’ targets, which have characteristics that make them challenging to target, such as transcription factors, primary functionality through protein–protein interactions and 3D molecular structures that make binding sites difficult to reach<sup>27</sup>. Some targets that were previously considered undruggable, such as KRAS and BCL-2 (ref. 27), have been successfully targeted by recently approved products, and products are currently in development for others, such as MYC and p53 (ref. 28). There are many other novel approaches being applied to development of biologics and small molecules against undruggable targets, including molecular glue approaches that induce proximity of two molecules, proteomics-based approaches such as new covalent screening methods using mass spectrometry, and the targeting or modulation of RNA<sup>29</sup>. Bispecific constructs, which are engineered to target two proteins or epitopes, enable the targeting of cell–cell and protein–protein interactions, and have various potential applications, including targeting traditionally undruggable targets. Additionally, proteins that are challenging to target may be unintentionally targeted by products for which the full mechanisms of action have not been elucidated; for example, decades after their initial approval, ubiquitin ligase modulators such as lenalidomide were found to use a proximity induction approach, resulting in degradation of the transcription factors IKZF1 and IKZF3 (refs. 30,31).

Novel therapeutic approaches are also being applied to improve the delivery of therapeutics to brain tumours and metastases, which pose another important challenge in oncology therapeutic product development. The blood–brain barrier and the blood–tumour barrier are physical barriers that can be challenging for oncology therapeutics to cross<sup>32</sup>. There are numerous approaches in development to improve therapeutic delivery across these barriers, including cell-based approaches, molecular approaches to hijack or bypass the barriers, and physical and chemical disruption of the barriers<sup>32</sup>.

## How will site-agnostic development expand?

The first site-agnostic approval in oncology was in 2017. Approvals in this unique biomarker-defined disease setting continued steadily at a rate of one per year until 2022, when there were three approvals. The 2022 site-agnostic approvals are notable because they were all for biomarkers for specific gene alterations (*BRAF*<sup>V600E</sup> mutations and *RET* fusions) that also have approved site-specific indications. These suggest that development of site-agnostic indications is starting to expand for biomarkers of specific gene alterations already used in indications for specific disease sites. As we previously discussed, there are numerous considerations when evaluating whether a given biomarker is appropriate for a site-agnostic indication, such as variations in the specific mutations or landscape of resistance mutations across tumour types<sup>13,33</sup>. Additionally, qualification of a biomarker also relies on the evidence supporting the circumstances in which the genomic biomarker may have utility as a diagnostic, predictive, prognostic or other indicator<sup>34</sup>.

There has been considerable interest in site-agnostic product development, which is especially promising for the development of therapeutic products for rare tumours or rare subsets of common tumours in which disease-specific clinical trials are not feasible owing to small patient numbers. For example, a recent analysis of more than 100,000 cases in the AACR Project GENIE database of real-world genomic data annotated genetic alterations for potential clinical actionability and found that 16.5% of cases had tumours that lacked potentially actionable alterations with evidence in the same cancer type but harboured potentially actionable alterations targeted by a standard therapy in a different cancer type; this group represents a subset of patients that could potentially benefit from site-agnostic product development<sup>35</sup>. This indicates that continued development of site-agnostic approvals could help to increase patient access to therapies in the future.

## How will new technologies advance oncology?

Numerous recent technological advances are being explored for application to cancer therapeutic product development. Artificial intelligence and machine learning are promising approaches that are being studied in almost every aspect of oncology. This includes early-phase therapeutic product development, such as molecule design<sup>36</sup>, in silico screening and prediction of protein–protein interactions<sup>36</sup>, prediction of cancer neoantigens<sup>37</sup> and therapeutic product repurposing<sup>38</sup>. Machine learning is being used in later phases of therapeutic product development in oncology, including early cancer detection<sup>39</sup>, disease subclassification<sup>40</sup> and prediction of response to therapy<sup>41</sup>. Artificial intelligence approaches use multiple types of data for these purposes, including chemical, imaging, clinical and multi-omic data, much of which is stored in large-scale publicly available data repositories. The availability of big data is expected to continue to increase in the future, providing more opportunities to use these approaches to investigate complex questions.

Another new technology with many possible applications in oncology therapeutic product development is CRISPR-based genome engineering, which can be used to edit the genome and epigenome with high specificity<sup>42</sup>. The potential applications of this technology are numerous; in early translational cancer biology research, CRISPR systems can be used to model tumour genomic and epigenomic alterations to elucidate mechanisms and identify cancer-related genes by high-throughput screens<sup>42</sup>; there is also ongoing research that applies CRISPR technology ex vivo and in vivo for cancer therapeutics,

although more work is needed in this area before translation to clinical practice<sup>43</sup>.

The isolation, detection and analysis of circulating tumour DNA (ctDNA), also known as 'liquid biopsy', is another area with considerable potential to improve the practice of precision oncology and facilitate therapeutic product development. ctDNA is cell-free DNA from tumours that circulates in the bloodstream. In addition to being less invasive than traditional biopsies, ctDNA has the benefit of providing information on the total heterogeneous tumour<sup>44</sup>. Numerous oncology applications using ctDNA are currently being explored, including in therapeutic product development<sup>45</sup>, early detection<sup>46</sup>, genomic profiling<sup>46</sup>, biomarker detection by liquid biopsy companion diagnostics<sup>47</sup>, monitoring disease burden and cancer evolution<sup>44</sup>, early prediction of response to therapy<sup>48</sup>, and early identification of the emergence of therapeutic resistance<sup>49</sup>. The analysis of ctDNA can also be conducted using artificial intelligence-based approaches, such as in early detection<sup>39</sup>. Although many of these approaches are in their infancy and will require extensive further development before clinical translation or use for regulatory purposes, they hold the promise to improve therapeutic product development and patient outcomes.

## Conclusions

Since 2000, the rate of therapeutic product development in oncology has increased. There was rapid expansion of targeted drugs and biologics, whereas the pace of development of cytotoxic drugs slowed. Innovation in oncology therapeutic approaches, as gauged by the rate of introduction of new product subclasses, has increased. Kinase inhibitors have remained the dominant product class, but ICIs have had considerable impact since the first such product, ipilimumab, was approved in 2011. This is particularly evident from the number of approved indications for anti-PD1 antibodies compared with all other product subclasses.

Biomarker use in oncology indications has steadily increased since 2009, although the rate was slower than might be expected given the expansion of precision medicine in recent years. Biomarkers were used variably for product classes and disease sites but were necessary for defining indicated populations for all site-agnostic approvals in the absence of traditional histological specification. Single-agent indications were most frequent, but combination indications accounted for 34% of approvals in oncology, and the ways in which products were combined differ by product classification. Although there have been more approvals using the expedited AA pathway in recent years, this was reflective of the overall increase in oncology product development, and the rate of AA use in oncology remained relatively steady throughout the analysis period at an average of 31%.

It is important to note that these analyses were restricted to approvals within the USA, so these conclusions may not represent trends in available oncology therapeutics in other countries. It was previously found that the FDA often received oncology applications before other countries<sup>50</sup>. The FDA launched Project Orbis in 2019, a collaborative programme that provides a framework for concurrent submission and review of oncology products among international regulatory health authorities and thereby aims to facilitate faster global patient access to cancer treatments<sup>50,51</sup>. The first year of this programme demonstrated reductions in delays in oncology application submissions and approvals in partner countries<sup>51</sup>, and it will be interesting to see the impacts of this programme in the future.

Overall, the twenty-first century so far has seen increased pace and innovation in oncology therapeutic product development. With

numerous promising approaches and areas for further innovation, these trends may continue, resulting in further improvements in oncology therapies and outcomes for patients with cancer.

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## Author contributions

E.C.S., A.C.B., Y.G., R.M., G.E.P., H.S., A.S., M.D.T., W.X. and J.A.B. researched data for the article. E.C.S., R.P., V.A.R., J.S. and J.A.B. contributed substantially to discussion of content. E.C.S. and J.A.B. contributed to writing the manuscript. All authors except Y.G. and A.S. reviewed and edited the manuscript.

## Competing interests

Y.G., A.S. and J.A.B. completed work on this publication while employees at the FDA. At the time of publishing, Y.G. is an employee and shareholder at BeiGene, A.S. is an employee at the U.S. Department of Health and Human Services, and J.A.B. is an employee and shareholder at Treeline Biosciences. The other authors declare no competing interests.

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