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feature

From patent to patient: analysing access to innovative cancer drugs

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Analysis of cancer drugs licensed through the European Medicines Agency (EMA) in 2000–2016 shows that the number of authorisations increased over that timeframe. The median number of licensed drugs each year rose from six for 2000–2008 to 13.5 for 2009–2016. Over 2000–2016, there were 64 drug authorisations for haematological, 15 for breast, and 12 for skin cancer, but none for oesophageal, brain, bladder, or uterine cancer. Only 6% of authorisations included a paediatric indication. The average time for a drug to progress from patent priority date to availability on the National Health Service (NHS) increased from 12.8 years for drugs licensed in 2000–2008 to 14.0 years for those approved in 2009–2016. There was evidence that the most innovative drugs were not being prioritised for EMA licensing and NICE approval.

Introduction

Over the past two decades, we have seen a range of new targeted drugs and immunotherapies developed for cancer, enabled by our greatly enhanced understanding of the genomics and biology of human malignancies [1,2]. However, although there have been dramatic improvements in survival for some cancer types, progress against others has been much more modest. Many new targeted cancer treatments are initially highly effective, only for cancers to adapt, evolve, and become resistant [3,4]. Thus, there is an urgent need for innovative new treatments with novel mechanisms of action, so that we can treat cancers in new ways, often involving the use of rationally selected novel drug combinations, to avoid or overcome drug resistance [3,5].

There is now growing scrutiny of the whole ecosystem for cancer therapeutics, and whether it is sufficiently supporting the discovery and development of innovative new treatments, especially for those cancers of highest unmet need for which outcomes remain poor [6]. Cancer specialists and patients in many countries are concerned about how to ensure that healthcare systems can deliver rapid access to the latest effective treatments, especially given the high prices of many new drugs [7]. In England and Wales, new drugs must not only pass through clinical trials and authorisation, but also be judged by the UK National Institute for Health and Care Excellence (NICE) as cost-effective for use on the NHS [8]. This has sometimes been perceived as an additional barrier for patients in accessing the most innovative treatments.

The Institute of Cancer Research, London, is a global leader in academic cancer drug discovery, development, and commercialisation, and collaborates extensively with industry. We have a keen interest in understanding the extent to which current policy, regulation, and economic frameworks are supporting and rewarding the rapid development of innovative cancer drugs. In this report, we retrospectively analyse all cancer drugs newly licensed by the European Medicines Agency (EMA) between 2000 and 2016, with the aim of exploring the following questions: (i) what drugs have come through the pipeline and for which types of cancer?; (ii) how long did it take these to reach patients on the NHS? And (iii) is the system encouraging radical innovation?

Methodology

For consistency, we used the following terms throughout this report: (i) licensing: the evaluation undertaken by the EMA leading to a drug receiving an authorisation; (ii) authorisation: a licence from the EMA for use of a drug for a specific cancer indication; (iii) indication: a specific licensed use of a

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drug. One drug can receive multiple EMA authorisations for different indications, such as for different cancers; (iv) appraisal: the evaluation process undertaken by NICE to decide whether a drug should be made available on the NHS; and (v) approval: indicates when a drug has received a positive appraisal from NICE. This term can also be used to mean drug authorisation but, to avoid confusion, we have avoided doing so in this report.

We identified all cancer drugs first authorised by the EMA and listed on its database after 1 January 2000 and before 31 December 2016. We also recorded the total number of authorised cancer indications for each drug. We defined cancer drugs as those belonging to code L, which covers antineoplastic and immunomodulating agents within the WHO Anatomical Therapeutic Chemical Classification System. We looked at the number of EMA authorisations each year and also split the data into two time periods, from 2000 to 2008, and from 2009 to 2016, and carried out comparative analyses.

We examined how quickly drugs moved along the development pipeline from the patent priority date, through to the registration of the initial Phase I clinical trial, the award of the EMA authorisation licence, and, where applicable, the publication by NICE of its final appraisal determination evaluating the drug for use on the NHS. We chose these milestones because it was possible to collect data on them in a consistent, standardised manner, which was not always feasible for other events, such as the initial publication describing a drug or the reporting of data from the registration trial.

We also adapted published methodology [9] to assign a level of innovation to each drug, and to explore what implications this had for development and approval. We considered a drug highly innovative if it acted against a new molecular target or via a novel mechanism, represented a novel class of compound in an area of high unmet need, was novel in its application, or offered improved targeting through use of a biomarker. Within this category, we identified a subgroup we classed as representing the very highest level of innovation: drugs acting against novel targets or with a new mechanism of action. Moderately innovative drugs were those representing a novel class of compounds outside areas of high unmet need, or with reduced adverse effects or interactions, or having improved delivery or pharmacokinetics. Low innovation drugs were those with novel structures but within an existing class of compounds, or with improved production.

We aimed to assess how effectively the cancer therapeutics ecosystem is delivering drugs for patients, especially agents with high innovation; how long it is taking; and what improvements could be made. Our study focuses on drugs that had received regulatory authorisation from the EMA. It does not investigate the cancer drug ecosystem more widely, for example by looking at drugs that progressed through trials but were never licensed by the EMA, or that were still passing through clinical trials at the point of analysis. Detailed data are provided in the Supplemental information online.

Our statistical analysis is primarily descriptive. To assess the trend for EMA drug authorisations from 2000 to 2016, we display scatter plots both for the overall number and by innovation category. Smooth trends with 95% confidence intervals (CI) were fitted by means of generalised additive models (GAM) with thin plate regression splines, via automatic smoothness estimation [10]. Violin plots with embedded boxplots are used to visualise the underlying data distribution of continuous measures. For continuous variables, summary statistics of mean (standard deviation) and median (lower and upper quartiles) are displayed for normal data and skewed data, respectively. To assess differences between two independent groups, a two-sided two-sample t-test or Mann–Whitney test was used for normal and skewed data, respectively, with point estimates of the effect size and 95% CI. Statistical analyses were performed using R version 3.6.0 with R package ggplot2 [11].

Drugs authorised through the EMA

The number of cancer drugs authorised by the EMA increased substantially over the study period (Fig. 1a, Fig. S1A in the Supplemental information online). In total, the EMA authorised 97 cancer drugs across 177 cancer indications from 2000 to 2016. The rate of authorisations doubled over that time period, with a median of six per year (range 0–14) from 2000 to 2008, and 13.5 per year (range 8–28) from 2009 to 2016. In 2000, there were eight drugs licensed; in 2016, there were 28 (Fig. 1a). The increase in EMA authorisations over time was considerably greater for high and moderate innovation drugs than it was for low innovation drugs (Fig. S1b in the Supplemental information online).

Of the 97 cancer drugs authorised by the EMA, 50 (51%) were classed as highly innovative, although only 30 (31%) were within the subgroup showing the very highest level of innovation: acting on a new molecular target or via a new mechanism of action. Examples include the CDK4/6 inhibitor, palbociclib, and the immune checkpoint inhibitor, nivolumab. The proportion of drugs with this very highest degree of innovation increased only slightly over time: from eight of the 30 drugs (27%) authorised by the EMA from 2000 to 2008, to 22 of the 67 drugs (33%) from 2009 to 2016 (Fig. 1a).

Despite the increase in EMA authorisations overall, the number of drugs being licensed for cancer by the EMA varied markedly by tumour type. There were large numbers of authorisations for some cancer types, such as haematological, skin, and breast cancers, but very few for others, including several cancers of very high unmet need (Table 1).

Of note, over one-third (37%) of all of EMA authorisations were for the treatment of haematological cancers, including five for the tyrosine kinase inhibitor imatinib, one of the first generation of genetically targeted drugs (Table 1). There was a steep increase in the number of drug authorisations for skin cancers, rising from one approval from 2000 to 2008, to 11 from 2009 to 2016. A total of 15 drugs were authorised by the EMA for breast cancer: six between 2000 and 2008, and nine between 2009 and 2016. Authorisations for the treatment of lung cancer increased sharply, with four between 2000 and 2008, rising to 19 between 2009 and 2016.

By contrast, there were no EMA drug authorisations at all from 2000 to 2016 for some cancer types, including brain and oesophageal cancer, both malignancies of very high unmet need with 10-year survival rates of 13.5% and 12% respectively, as well as uterine and bladder cancer. Two further cancers of very high unmet need, liver and pancreatic cancer, had only one and four EMA authorisations, respectively, over this time period (Table 1).

Children are seeing far slower progress in gaining access to new treatments than adults. Only eight of the cancer drugs (8%) were authorised by the EMA for use in children. Across the 177 drug authorisations by the EMA, only ten (6%) included a paediatric indication (Fig. 1b). Six drugs had authorisations for childhood leukaemias, the most common group of childhood cancers. Only two drugs were licensed by the EMA for childhood cancers other than leukaemias, and there were no drugs with EMA authorisations for lymphomas or brain tumours, the second and third most common groups of cancers in children, respectively (Fig. 1c).

We analysed the drugs by British National Formulary (BNF) category (Table 2). The largest category was the protein kinase inhibitors, accounting for 32 of the 97 drugs (33%), followed by monoclonal antibodies, of which there were 21 (22%). There were 11 drugs within a broad

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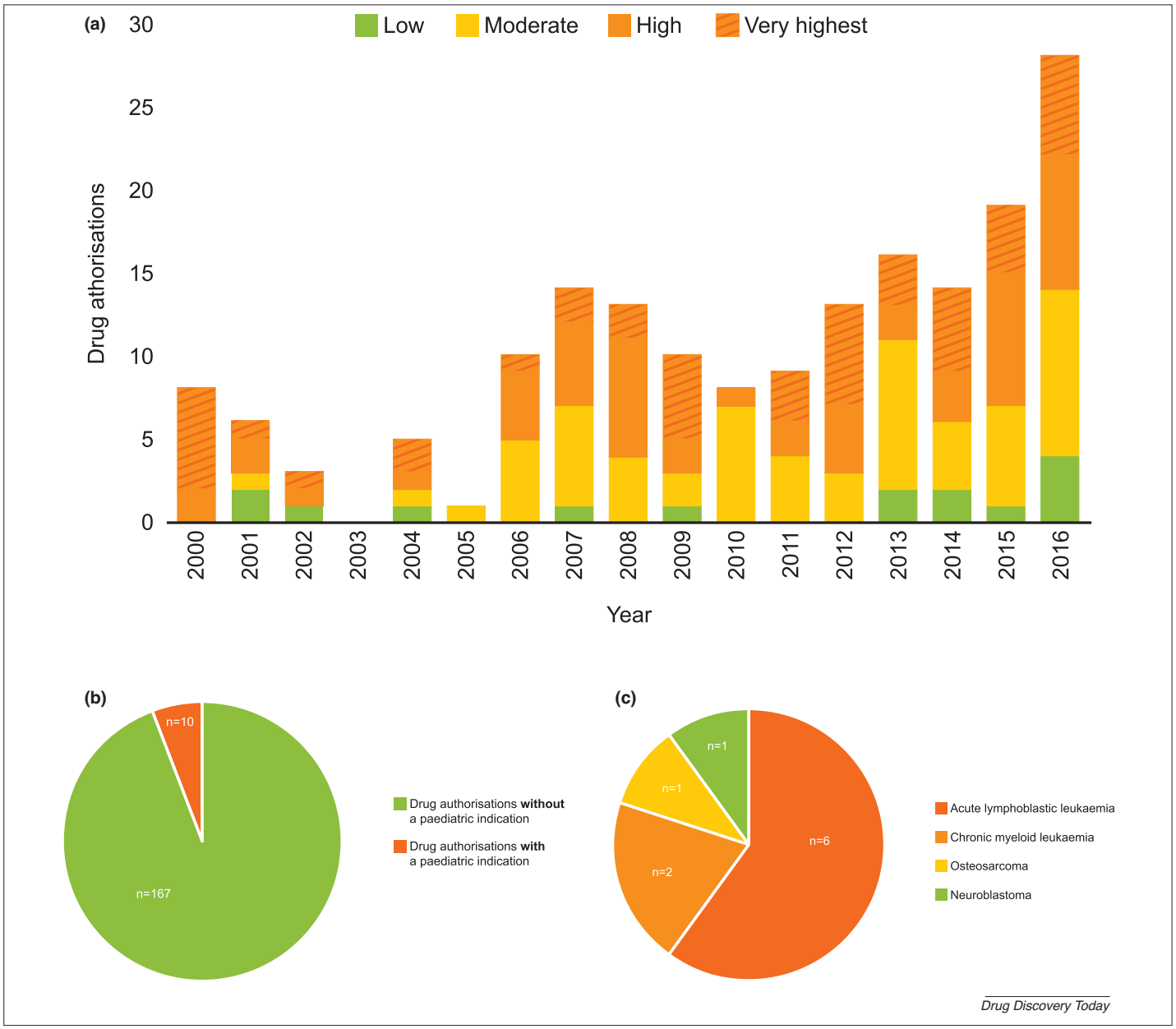

FIGURE 1

Analysis of cancer drugs authorised by the European Medicines Agency (EMA) between 2000 and 2016. (a) Number of EMA drug authorisations for cancer indications from 2000 to 2016, categorised by degree of innovation. (b) EMA authorisations for drugs with paediatric cancer indications from 2000 to 2016 (10), shown as a fraction of the total (177). (c) EMA paediatric cancer drug authorisations between 2000 and 2016 by cancer type.

BNF category of 'antineoplastics', while ten were antimetabolites. We also grouped together five drugs within a non-BNF category of immuno-oncology products: monoclonal antibodies acting as T cell checkpoint inhibitors (ipilimumab, nivolumab, and pembrolizumab), the viral immunotherapy talimogene laherparepvec, or T-VEC, and an HPV vaccine.

Length of time from patent to patient

We found that the time it takes to evaluate drugs in clinical trials and make them available for patients on the NHS has increased. The mean time from patent priority date through to a final appraisal determination by NICE did not shorten, but instead increased by 1.2 years (95% CI, –0.71 to 3.16), from 12.8 years for drugs first authorised by the EMA between 2000 and 2008, up to 14.0 years for drugs licensed between 2009 and 2016 (Table 3).

We examined each stage in the drug development timeline to understand better why it was taking longer to get drugs from the patent stage through to NICE approval and availability to patients on the NHS. The time taken to progress drugs from patent priority date through to registration of the Phase I trial increased from a median of 2 years for drugs first authorised by the EMA from 2000 to 2008 to 3 years for those licensed from 2009 to 2016, a difference of 1 year (95% CI, 0 to 2). The average time from the registration of the initial Phase I trial through to EMA authorisation also increased significantly by 1.3 years (95% CI, 0.18 to 2.5), rising from a mean of 7.7 years for drugs first licensed by the EMA from 2000 to 2008, to 9.0 years for those authorised from 2009 to 2016 (Table 3).

Figures S2a–c in the Supplemental information online display violin plots with embedded

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TABLE 1

Number of EMA cancer drug authorisations from 2000 to 2016, categorised by cancer type

Cancer type	Authorisations (2000–2008)	Authorisations (2009–2016)	Authorisations total (2000–2016)	% Authorisations (2000–2016)
Haematological	26	38	64	37%
Lung	4	19	23	13%
Breast	6	9	15	9%
Skin	1	11	12	7%
Bowel	6	5	11	6%
Kidney	4	6	10	6%
Stomach	3	5	8	5%
Prostate	0	6	6	3%
Sarcoma	1	4	5	3%
Thyroid	0	4	4	2%
Pancreatic	2	2	4	2%
Ovarian	0	3	3	2%
Head and neck	3	0	3	2%
Neuroendocrine	1	1	2	1%
Cervical	0	1	1	0.5%
Neuroblastoma (children)	0	1	1	0.5%
Liver	1	0	1	0.5%
Mesothelioma	1	0	1	0.5%
Urinary tract	0	1	1	0.5%
Brain	0	0	0	0%
Womb	0	0	0	0%
Bladder	0	0	0	0%
Oesophageal	0	0	0	0%
Testicular	0	0	0	0%

TABLE 2

Number of EMA cancer drug authorisations from 2000 to 2016, categorised by drug classes listed in the British National Formulary

Class of drug	No. of drugs	Example
Protein kinase inhibitors	32	Vermurafenib
Monoclonal antibodies	21	Ofatumumab
Antineoplastics	11	Panobinostat
Antimetabolites	10	Clofarabine
Immuno-oncology[a]	5	Pembrolizumab
Proteasome inhibitors	3	Bortezomib
Thalidomide and related analogues	3	Lenolidomide
Antiandrogens	2	Abiraterone
Taxanes	2	Cabazitaxel
Alkylating drugs	1	Chlormethine
Anthracyclines and related drugs	1	Pixantrone
Anti-gonadotrophin-releasing hormones	1	Degerelix
Anti-oestrogens	1	Fulvestrant
Immunostimulants	1	Mifamurtide
Interferons	1	Interferon alpha-2b
Photosensitisers	1	Temoporfin
Plant alkaloids	1	Trabectedin
Retinoid and related drugs	1	Bexarotene
Topoisomerase inhibitors	1	Irinotecan
Vinca alkaloids	1	Vinflunine
Viral vaccine	1	HPV vaccine

[a]Not a BNF category: includes ipilimumab, nivolumab, and pembrolizumab, which are monoclonal antibodies that act as immune checkpoint inhibitors; T-VEC, which is classed as an antineoplastic; and the HPV vaccine, which is a viral vaccine.

boxplots to visualise the distribution of the time taken for patent priority date to registration of the initial Phase I clinical trial, Phase I registration to EMA authorisation, and patent priority date to NICE final appraisal determination, respectively.

We found that the more highly innovative drugs did not progress faster through development (Table 4, Fig. S3 in the Supplemental information online). In fact, we observed that the higher the level of innovation assigned to a drug, the longer on average it took to move from patent priority date to NICE final appraisal determination. Highly innovative drugs took a mean of 14.3 years to progress from the patent priority date to availability on the NHS, compared with 11.1 years for low innovation drugs, which was 3.2 years longer (95% CI, 0.20 to 6.17). Moderate innovation drugs took a mean of 13.5 years, which was 2.4 years longer (95% CI, –0.72 to 5.49) than low innovation drugs. Highly innovative drugs also took 2.1 years longer

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TABLE 3

Analysis of how long it takes for drugs to be made available for patients across two time periods: 2000–2008 and 2009–2016[a]

Measurement phase	EMA drug authorisations from 2000 to 2008 Mean (sd) or Median[b] [LQ, UQ] time (in years)	EMA drug authorisations from 2009 to 2016 Mean (sd) or Median[b] [LQ, UQ] time (in years)	Average different of (2009 to 2016) – (2000 to 2008) (95% CI)
Patent to Phase I trial registration	2 [0,4][b]	3 [2,5][b]	1 (0 to 2)
Phase I trial registration to EMA authorisation	7.72 (3.11)	9.04 (3.81)	1.32 (0.18 to 2.45)
Patent to NICE final appraisal determination	12.8 (4.54)	14.0 (4.61)	1.23 (–0.71 to 3.16)

[a]The table shows mean (sd) or median [LQ, UQ][b] time in years, average difference in years between the time periods 2000 to 2008, and 2009 to 2016, and 95% CI. Data were analysed by t test or Mann–Whitney test[b] depending on data distribution.
Abbreviations: sd, standard deviation; LQ, 25th percentile; UQ, 75th percentile.

TABLE 4

Analysis of how long it takes for drugs to be made available for patients, by level of drug innovation[b]

Measurement phase	Low innovation Mean (sd) or Median [LQ, UQ][b] time (in years)	Moderate innovation Mean (sd) or Median [LQ, UQ][b] time (in years)	High innovation Mean (sd) or Median [LQ, UQ][b] time (in years)
Patent to Phase I trial registration	1 [0, 4.5][b]	3 [1.75, 5][b]	3 [1,4][b]
Phase I trial registration to EMA authorisation	6.77 (2.62)	8.68 (3.12)	8.85 (4.02)
Patent to NICE Final Appraisal Determination	11.09 (4.64)	13.47 (4.42)	14.28 (4.61)

[a]Abbreviations: LQ, 25th percentile; sd, standard deviation; UQ, 75th percentile.

(95% CI, –0.04 to 4.21) than low innovation drugs to progress from initial Phase I trial registration through to EMA authorisation (8.9 versus 6.8 years). Moderate innovation drugs took 1.9 years longer (95% CI, –0.29 to 4.11) than low innovation drugs (8.7 versus 6.8 years).

Figure S4 in the Supplemental information online shows violin plots that display the number of years from patent priority date to NICE final appraisal determination by innovation category over the two time periods. We observe an interesting feature, whereby the median time taken for the moderate innovation category increased substantially for Phase I to EMA authorisation (4 years, 95% CI, 2 to 6) and patent priority date to NICE approval (4 years, 95% CI, 0 to 8). For highly innovative drugs, there was a slight increase from patent priority date to Phase I, whereas the time taken for Phase I to EMA authorisation and patent priority date to NICE approval were fairly similar across the two time periods.

We found that NICE has successfully reduced the lag time between EMA authorisation and the start of its technology appraisals, from a mean of 21 months for drugs first licensed between 2000 and 2008, down to 6.5 months for drugs licensed between 2009 and 2016. However, NICE was no faster at carrying out its appraisals, which took 16.7 months from 2000 to 2008, and 16.0 months from 2009 to 2016.

Taken together, our findings suggest that cancer drugs have been reaching patients more slowly because of an increase in the time it takes for them to move through clinical trials and licensing, rather than because of delays in gaining approval from NICE. In addition, the more highly innovative drugs are progressing less rapidly than low innovation drugs.

Impact of degree of innovation on NICE approval

NICE has a key role in ensuring that public resources are spent on treatments that are good value for money for the NHS, because drugs might be licensed by the EMA with only modest contributions to patient benefit. We wanted to examine whether NICE was prioritising the most innovative drugs with the greatest potential for patient benefit for appraisal and approval.

Of concern, in view of the need for drugs that work in new ways, our findings suggest that the system for NICE appraisal has not given priority to approving the most innovative cancer medicines. Among the 97 cancer drugs first licensed between 2000 and 2016, we found that NICE recommended for use on the NHS around two-thirds (66%) of all those that it appraised. This proportion has remained consistent over the analysis period, at 67% for drugs licensed between 2000 and 2008, and 66% for those between 2009 and 2016. However, drugs authorised between 2000 and 2016 and classified as highly innovative were less likely to have been approved by NICE than lower innovation medicines (Fig. 2a). Thus, only 38% of highly innovative cancer drugs had received a positive recommendation from NICE at the time of our analysis, compared with 53% of drugs classed as moderately innovative and 40% of low innovation drugs.

Once NICE evaluates a drug, the chances that it will say yes are essentially the same regardless of whether it is a highly innovative treatment. NICE approved 69% of highly innovative drugs, compared with 63% of moderately innovative drugs and 67% of low innovation drugs. However, NICE was less likely to have appraised highly innovative drugs than lower innovation medicines. Only 68% of authorisations for highly innovative drugs had been appraised by NICE, compared with 73% of moderately innovative drugs and 87% of low innovation drugs (Fig. 2B). Our evidence indicates that highly innovative drugs were not being prioritised by NICE for appraisal during the study period.

NICE pledged in 2016 to evaluate all new cancer drugs in future, giving it the opportunity to address the discrepancy in appraisal rates for drugs in different innovation categories. Since then, the number of cancer drugs that NICE has appraised has increased; thus, it published 35 technology appraisals in 2016–2017, 45 in 2017–2018, and 42 in 2018–2019, compared with an average of 12.8 in the five years previously [12]. Since NICE took over the Cancer Drugs Fund in April 2016, the proportion of cancer drug appraisals that have been positive has also increased, to 76% from 59% previously.

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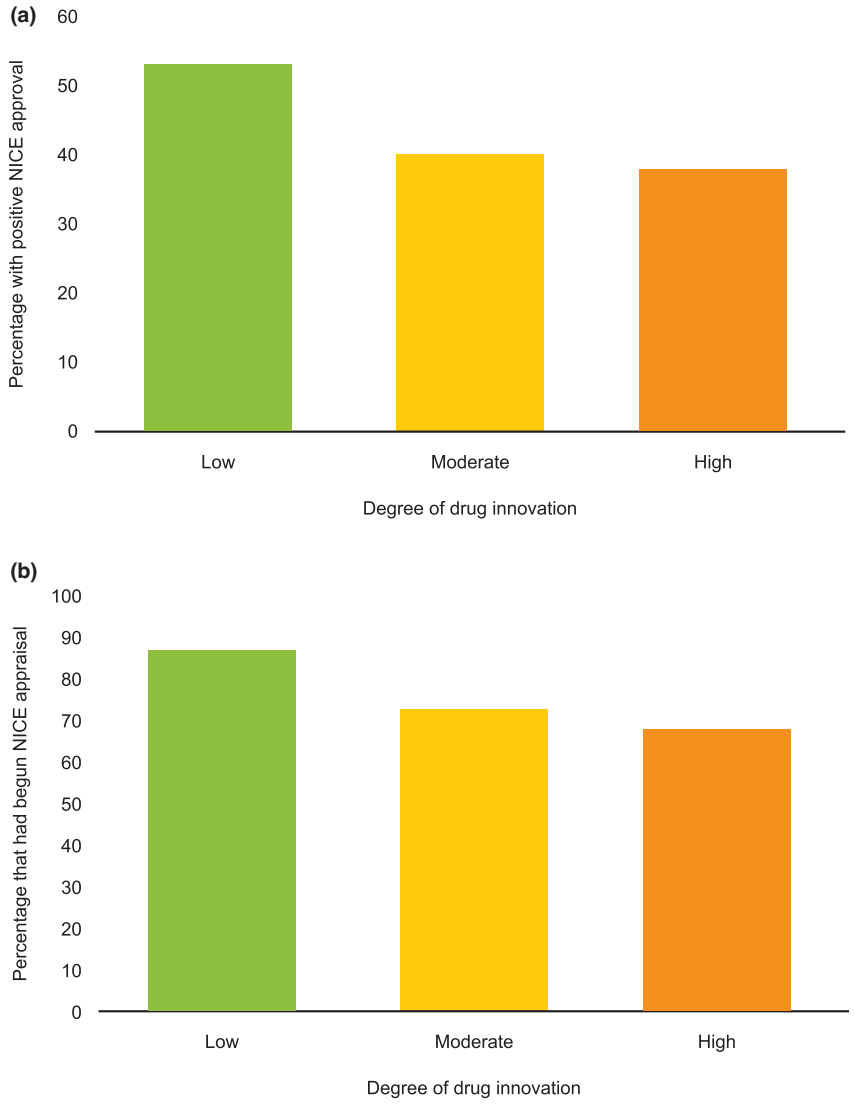

FIGURE 2

Analysis of National Institute of Health and Care Excellence (NICE) approvals of cancer drugs. (a) Percentage of 177 drug authorisations from 2000 to 2016 that had received a positive recommendation from NICE, categorised by their degree of innovation. (b) Percentage of 177 drug authorisations from 2000 to 2016 that had started a NICE appraisal at the time of our analysis, categorised by their degree of innovation.

Discussion

The factors influencing access to innovative drugs are wide-ranging and complex and not all are addressed in the present report. The number of drugs available for a given cancer indication depends on not only regulatory approvals, but also how many drugs are discovered preclinically, start early-phase trials in specific cancer indications, and then show therapeutic activity. Here, we focused deliberately and specifically on drugs that received EMA authorisation (between 2000 and 2016) and analysed their progress from patent priority date through EMA licensing and on to NICE approval, which is required for patient access on the NHS in England and Wales.

In addition, we acknowledge that what is required is not simply access to drugs, but rather availability of treatments that make a real difference to the lives of patients with cancer. Thus, it is to be expected that NICE (and other health technology assessment organisations) might reject some drugs that are approved by the EMA (or other equivalent regulators) but make only modest contributions to patient benefit, especially given the need to prioritise which treatments should be funded by a public healthcare system with limited resources [13].

Our analysis highlights the progress that is being made in developing innovative new cancer medicines. It also draws attention to the key policy challenges that will need to be overcome to ensure that patients can benefit from these advances as quickly as possible.

We found that, as scientific understanding of cancer has expanded, there has been an increase in the number of new cancer treatments developed and licensed. Targeted drugs, such as the CDK4/6 inhibitor palbociclib in oestrogen receptor-positive, HER2-negative metastatic breast cancers and the PARP inhibitor olaparib for BRCA-mutant ovarian cancers, together with immunotherapies, such as the immune checkpoint inhibitor nivolumab for melanoma and several other cancers, are highly innovative and are giving patients with advanced cancer new treatment options that are not only extending survival, but also greatly improving quality of life.

However, survival remains poor for many cancer types, and our analysis finds that cancers of very high unmet need are missing out on the rapid advances seen in other tumour types. We need to discover and develop new drugs for these diseases and to ensure that patients with

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the poorest outcomes are able to benefit from the same kind of concerted research efforts that have delivered great progress in other cancer types, such as breast, skin, and blood cancers.

In paediatric cancers, few targeted drugs are coming through to the clinic [14,15] and there is an urgent need to ensure that children with cancer are able to benefit from advances in research in the same way that patients with many adult cancers already are. We need stronger incentives for pharmaceutical companies to develop new treatments specifically for children, and regulations need to be tightened up to require that adult cancer drugs are evaluated in paediatric clinical trials wherever their mechanism of action is relevant for children [16], as will be strongly encouraged from 2020 when new legislation comes into force in the USA [17].

It is important to ensure that innovative cancer medicines reach patients more quickly. We found that the average time between the patent covering the drug being filed and it becoming available on the NHS had increased over the analysis period, with it taking longer in particular to progress from registration of Phase I trials to authorisation by the EMA. It is possible that drug development might have been slowed down by the EU Clinical Trials Directive, which has been widely regarded as excessively onerous [18,19]. The Directive is due to be replaced by the EU Clinical Trials Regulation once preparatory work is completed, and it will be important to closely monitor the effect that this has on the time it takes to set up and progress cancer trials.

A range of initiatives have been introduced over the past five years to try to ensure that drugs are licensed more quickly, including the UK's Early Access to Medicines Scheme [20] and recent Accelerated Access pathway for innovative treatments [21], and also the European Union (EU)'s Priority Medicines scheme, PRIME [22], which provides early dialogue between companies and the EMA. In addition, the EMA is able to give conditional market authorisation as one way of speeding up access to new medicines, with 17 cancer drugs authorised through this route during a 10-year period between July 2006 and June 2016 [23]. Further research is required to understand the impact of these various schemes.

If we are to overcome the major clinical challenge of the ability of cancer to adapt, evolve, and become drug resistant, we need drugs with new mechanisms of action that can deliver step changes in cancer outcomes, and can be combined in novel, rationally selected combinations [3,4]. We believe that more needs to be done to encourage the pharmaceutical industry to pursue radical innovation in drug discovery and development. Pharmaceutical companies can often be risk averse in taking on new targets. Many pursue the same small number of clinically validated targets, some of which can be subject to more than 20 commercial programmes, leading to duplication and opportunity cost [24]. Although there is a welcome increase in willingness to introduce more innovation in clinical trial design, with encouragement from the EMA and the US Food and Drug Administration (FDA), there is still some reluctance to embrace the use of innovative and streamlined study methodologies, such as stratified, basket, and adaptive trials [25].

Governments can play a part in stimulating interactions between universities and industry, and academic researchers can take a stronger role in championing more innovative approaches to drug discovery and development [7]. Our policies, regulatory systems, and economic frameworks must also do more to encourage the pharmaceutical industry to embrace the kind of creative risk taking that is needed for real innovation. We welcome the fact that substantial numbers of innovative cancer drugs with novel mechanisms of action are being approved and made available for patients, but it is a concern to see so many companies working on the same targets [22], while other promising treatment opportunities based on highly novel targets are being neglected [26]. Companies and their academic partners should have greater confidence that innovation in drug discovery and development will be supported and rewarded, through more flexible approaches to the evaluation of trial data, and by ensuring that the most innovative treatments are made available for patients as quickly as possible.

We believe that the EMA could learn from best practice elsewhere in the world in taking a faster, more flexible approach to assessing evidence during drug authorisation. Studies have shown that the EMA is slower than the FDA at evaluating new drugs, and tends to receive submissions for licensing later [27,28]. We recognise that the EMA has made some progress in evolving its approaches to evaluating evidence [20], but we believe that further changes are needed to speed up access to markets for the most innovative treatments. For instance, the EMA could assess more drugs based on Phase II trial data, or using endpoints such as progression-free survival or quality of life improvement rather than overall survival, with later evaluation of benefit through assessment of additional real-life data and follow-up action. Recent data from 2018 show that the FDA approved certain oncology drugs based on novel endpoints, namely metastasis-free survival and minimal residual disease response rate [29].

We encourage NICE to fast track appraisals of the most mechanistically innovative cancer drugs and to take into account their degree of innovation in deciding whether they should be approved for patients on the NHS. Worryingly, our analysis found that highly innovative drugs were less likely to receive a positive appraisal from NICE than low innovation medicines. We believe that NICE's definition of innovation, based primarily on effectiveness in areas of unmet need, is too restrictive and does not do enough to recognise mechanistic innovation. We would like to see NICE's evaluation processes take greater account of whether a cancer drug is novel in its drug target or mechanism of action, unique in a rare disease, or innovative in the way it is used or delivered. The coming review of NICE appraisal processes is an opportunity to improve the way that innovative drugs are assessed.

It is particularly important to prioritise and accelerate drugs acting on novel targets and with novel mechanisms of action, because it is combinations of such mechanistically innovative agents that are most likely to have an impact on overcoming cancer evolution and drug resistance, the major clinical problem we currently face in cancer treatment.

The low number of drugs coming through for several tumours with poor clinical outcomes and for children is of concern. This is likely to be multifactorial, potentially involving different, more challenging, or unexplored biology, lower levels of funding for preclinical academic research on these cancers, and less interest from pharmaceutical companies, related, for example, to a lack of previously successful precedents in a given cancer, market size, prior failures, and, hence, the calculation or perception of high risk.

We believe that the progress needed to deliver big improvements in cancer survival is eminently achievable, but it will rely on creative risk taking in drug discovery and development. We need to find ways of encouraging radical innovation, and ensuring that the advances produced reach patients as quickly as possible, so that more patients with cancer can live longer, healthier lives.

Conflict of interest

The ICR works with a range of commercial partners on drug discovery and development, and, in some cases, benefits from collaboration

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and invention income. P.W. is a consultant for Astex Pharmaceuticals, CV6 Therapeutics, Nextechinvest, and Storm Therapeutics, and holds equity in Nextechinvest, Storm Therapeutics, and Chroma Therapeutics. C.Y. received honoraria from Celgene and is a statistical consultant for Faron Pharmaceuticals. The ICR also has a Rewards to Inventors scheme.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.drudis.2020.01.004.

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