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Characterization of accelerated approval status, trial endpoints and results, and recommendations in guidelines for oncology drug treatments from the National Comprehensive Cancer Network: cross sectional study

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ABSTRACT

OBJECTIVES To evaluate National Comprehensive Cancer Network (NCCN) guideline recommendations for oncology drug treatments that have been granted accelerated approval, and to determine whether recommendations are updated based on the results of confirmatory trials after approval and based on status updates from the US Food and Drug Administration (FDA).

DESIGN Cross sectional study.

SETTING US FDA and NCCN guidelines.

POPULATION Oncology therapeutic indications (ie, specific oncological conditions for which the drug is recommended) that have been granted accelerated approval in 2009-18.

MAIN OUTCOME MEASURES NCCN guideline reporting of accelerated approval status and postapproval confirmatory trials, and guideline recommendation alignment with postapproval confirmatory trial results and FDA status updates.

RESULTS 39 oncology drug treatments were granted accelerated approval for 62 oncological indications. Although all indications were recommended in NCCN guidelines, accelerated approval status was reported for 10 (16%) indications. At least one postapproval confirmatory trial was identified for all 62 indications, 33 (53%) of which confirmed benefit; among these indications, NCCN guidelines maintained the previous recommendation or strengthened the category of evidence for 27 (82%). Postapproval confirmatory trials failed to confirm benefit for 12 (19%) indications; among these indications, NCCN guidelines removed the previous recommendation or weakened the category of evidence for five (42%). NCCN guidelines reflected the FDA's decision to convert 30 (83%) of 36 indications from accelerated to traditional approval, of which 20 (67%) had guideline updates before the FDA's conversion decision. NCCN guidelines reflected the FDA's decision to withdraw seven (58%) of 12 indications from the market, of which four (57%) had guidelines updates before the FDA's withdrawal decision.

CONCLUSIONS NCCN guidelines always recommend drug treatments that have been granted accelerated approval for oncological indications, but do not provide information about their accelerated approval status, including surrogate endpoint use and status of postapproval confirmatory trials. NCCN guidelines consistently provide information on postapproval trial results confirming clinical benefit, but not on postapproval trials failing to confirm clinical benefit. NCCN guidelines more frequently update recommendation for indications converted to traditional approval than for those approvals that were withdrawn.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Oncology drug treatments are frequently granted accelerated approval by the Food and Drug Administration based on pivotal trials using surrogate markers, requiring sponsors to complete confirmatory trials after approval
⇒ Guidelines from the National Comprehensive Cancer Network (NCCN) inform patient care and guide coverage determinations by the Centres for Medicare and Medicaid Services
⇒ NCCN guidelines sometimes recommend drug indications with negative confirmatory trials, despite the withdrawal of approval

WHAT THIS STUDY ADDS

⇒ NCCN guidelines always recommend drug treatments granted accelerated approval for oncological indications but do not provide information about their accelerated approval status, including surrogate endpoint use and postapproval confirmatory trial status
⇒ NCCN guidelines consistently provided information on postapproval confirmatory trial results confirming clinical benefit, but not on postapproval trials that did not confirm clinical benefit; guidelines more frequently updated their recommendation for indications converted to traditional approval compared with those that were withdrawn
⇒ Most NCCN guideline recommendations are updated before the FDA's official decisions and are likely based on postapproval confirmatory trial results

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Opportunities exist for NCCN guidelines to explicitly state the FDA approval pathway, whether confirmation of clinical benefit is still pending, and the type of endpoints used in pivotal and postapproval confirmatory trials in a more standardized format
⇒ NCCN guidelines could be enhanced by including further rationale for recommending drug treatments when there is discordance between the guideline recommendations and evidence generated by postapproval confirmatory trials or FDA decisions
⇒ NCCN guidelines could be updated in response to comprehensive review and regulatory decision making by the FDA, rather than to the availability of the results of postapproval trials not yet reviewed by the agency

Introduction

Under the US Food and Drug Administration's (FDA) accelerated approval pathway, drug treatments that treat serious or life threatening diseases can receive approval based on pivotal trials using surrogate

markers as primary endpoints that are "reasonably likely to predict clinical benefit."[1] After accelerated approval, sponsors are required to complete confirmatory trials demonstrating the anticipated clinical benefit.[2] Based on the results of these postapproval trials, the FDA can convert the accelerated approval to traditional approval or withdraw market authorization.[2] Therapeutic drugs used for malignant haematological and oncological indications (ie, specific oncological conditions for which a drug is recommended) comprise most approvals via this pathway,[3] and particularly for these treatments, many surrogate markers used to support accelerated approval have been found to be poor predictors of long term clinical benefit.[4–6] Moreover, postapproval confirmatory trials, which are often delayed for years after approval,[7–9] do not consistently evaluate clinical outcomes as primary endpoints.[10] Therefore, there is often uncertainty about the true clinical benefit of drug treatments receiving accelerated approval even after the completion of postapproval confirmatory trials, and concerns have been raised that key evidentiary gaps might not be consistently communicated to patients, physicians, and healthcare payers.[11 12]

In oncology, the guidelines from the National Comprehensive Cancer Network (NCCN) are one of the three compendiums used to inform patient care and guide coverage determination by the Centres for Medicare and Medicaid Services.[13] However, these guidelines do not always reflect key information regarding drug treatments granted accelerated approval. For instance, drug treatments for oncological indications that have been granted accelerated approval often continued to be recommended for use by the NCCN guidelines despite postapproval confirmatory trials failing to demonstrate improvement in the primary endpoint.[14] Evidence also suggests that over a quarter of patients with oncology related indications could receive accelerated approval drugs that lack confirmed benefit and are subsequently withdrawn.[15] Moreover, beyond the evaluation of recommendation changes, little is known about how often NCCN guidelines describe other key characteristics of evidence given before and after approval (including the endpoint types and approval pathway) for oncological therapeutic indications granted accelerated approval that could affect the decisions made by patients, physicians, and payers.

Accordingly, for all oncology drug treatments granted accelerated approval between 2009 and 2018, we evaluated how often NCCN guidelines disclosed that therapeutics were approved under the accelerated approval pathway, described the primary endpoint supporting accelerated approval as a surrogate marker, provided information regarding the endpoints and status of postapproval confirmatory trials, and updated their recommendations according to the results of postapproval confirmatory trials or FDA approval status (ie, converted from accelerated approval to traditional approval or withdrawal from market).

Methods

This study followed the STROBE reporting guideline and used public, non-identifiable data that did not constitute human participants research (45 Code of Federal Regulations §46.102) and was not submitted for institutional review board review.[16]

Identifying drug treatments granted accelerated approval

Using the Drugs@FDA database,[17] we identified all drug treatments granted FDA accelerated approval from 1 January 2009 to 31 December 2018. We then limited our sample to drug treatments granted a malignant hematological or oncological indication, based on the World Health Organization's (WHO) Anatomical Therapeutic Chemical Classification system.[18] The 2018 cut-off allowed at least four years for postapproval confirmatory trials to be completed and for the evidence to be incorporated into NCCN guidelines. We excluded drug treatments targeting pediatric indications, and since NCCN guidelines are published by cancer type, we excluded drug treatments targeting tumor-agnostic indications (online supplemental figure).

Therapeutic indication and confirmatory trial characteristics

For each drug treatment, we used the Drugs@FDA database to identify the brand and generic names; therapeutic type (small molecule or biologic); accelerated approval indication, date, and required postapproval confirmatory trials; whether the original indication received orphan drug designation; and FDA status (no change to accelerated approval status, withdrawn, converted from accelerated to traditional approval) as of 31 December 2022. Market withdrawal could be initiated by the manufacturer or the FDA. Next, we identified the dates of conversion from accelerated approval to traditional approval or market withdrawal for each therapeutic indication, if available.

Using a previously described approach,[19] we identified ClinicalTrials.gov registrations and corresponding publications for each postapproval confirmatory trial (as of 31 December 2022). The postapproval confirmatory trials that the FDA required (that is, postmarketing requirements) were identified from the approval letters hyperlinked in the Drugs@FDA database. These letters often include a brief description of the study type, endpoints, and population for the postmarketing requirements. Then, for all new prospective cohort studies, registries, and clinical trials and all requirements that call for the completion and submission of the results from

ongoing prospective cohort studies and trials, we determined study registration and results reporting on ClinicalTrials.gov.

For postapproval confirmatory trials that were the extension of previous pivotal trials, we specifically searched for publications or ClinicalTrial.gov registrations for long term results. For each trial, we recorded the date of the first online publication reporting on its primary efficacy endpoint or, if no publication was located, the date of first results reported on ClinicalTrials.gov. We considered publications with interim results if the reported endpoint matched the trial's primary objective. For drug treatments with multiple postapproval confirmatory trials, we considered the date of the earliest publication. For each trial, we recorded the primary efficacy endpoints and categorized them as surrogate markers or clinical outcomes.[20] The results for the primary endpoint were then classified as positive if they favored the oncology drug treatment ($P<0.05$), and as negative for all other results. For single arm studies, we evaluated the authors' interpretation of benefit in the abstract of the publication (eg, a conclusion that a drug provides a durable benefit was considered a positive trial outcome). Indications were classified as having positive trials if either all trials were positive or if at least one trial was positive, and the remaining trials did not have results. Similarly, indications were classified as having negative trials if either all trials were negative or if at least one trial was negative, and the remaining trials did not have results.

Identification and review of NCCN clinical guidelines

We obtained all NCCN guidelines for the cancer types of interest published before 31 December 2022. The most recent version of each guideline was downloaded, and any previous versions were requested through the NCCN's permission request form (online supplemental table 1).[21] Next, we reviewed the full text of each guideline and recorded whether recommendations regarding the management of the therapeutic indications granted accelerated approval were included. We excluded drug treatments for which the results of postapproval confirmatory trials were available before the first available guideline and excluded drug treatments converted to traditional approval or withdrawn from the market before the first available guideline.

Identification of NCCN descriptions of accelerated approval and pivotal trial endpoints

For all indications recommended in an NCCN guideline before an FDA status update, we determined whether the corresponding guidelines stated that the drug treatment was approved via the accelerated approval pathway (or that confirmation of clinical benefit was still pending at the time the guideline was written) and that the approval was based on trials with surrogate markers as primary endpoints.

Identification of NCCN descriptions of postapproval confirmatory trials and FDA status changes

For each therapeutic indication, we determined whether any postapproval confirmatory trials were mentioned in their corresponding NCCN guidelines. For indications with at least one positive and at least one negative postapproval confirmatory trial, we determined whether both the positive and negative trials were referenced. For indications with postapproval confirmatory trials with surrogate markers as primary endpoints, we recorded whether the guidelines disclosed that the evidence was supported by surrogate endpoints.

For each therapeutic indication, we then determined whether and when NCCN recommendations were updated in relation to the postapproval confirmatory trial results. We further determined whether the indication or category of evidence and consensus were changed according to the postapproval confirmatory trial results: category 1 (based on high level evidence with uniform NCCN consensus), category 2A (based on lower level evidence with uniform NCCN consensus), category 2B (based on lower level of evidence with NCCN consensus), and category 3 (based on any level of evidence with major NCCN disagreement).[22] For indications with positive postapproval confirmatory trials, we recorded whether guidelines referenced the trials and either maintained the previous recommendation or strengthened the category of evidence. For indications with negative postapproval confirmatory trials, we determined whether guidelines referenced the trials and decreased the strength of evidence or removed the indication from their recommendations.

We then evaluated whether NCCN recommendations were updated in relation to FDA status changes and recorded the dates of the updates. For therapeutic indications that were converted from accelerated to traditional approval, we considered the guideline recommendations to reflect the FDA's decisions if the category of evidence was strengthened or if the indication was expanded according to the new approval. For indications that were withdrawn from the market, we considered the guidelines to reflect the FDA's decision if the indication was removed from guidelines' recommendations.

Statistical analysis

We summarized the characteristics of oncology drug treatments that were granted FDA accelerated approval, the corresponding confirmatory trials, and the associated NCCN guideline recommendations and references, using descriptive statistics. We examined the median (interquartile range (IQR)) duration from FDA status updates to NCCN guideline updates,

if applicable. Analyses were conducted using Excel (Microsoft).

Patient and public involvement

Patients and the public were not involved in the planning, design, and implementation of the study, because this study used secondary data. No patients were asked to advise on interpretation or writing up of the manuscript.

Results

Characteristics of oncology therapeutic indications granted accelerated approval

Between 2009 and 2018, the FDA granted accelerated approval to 45 drug treatments for 71 oncological or hematological malignancy indications that met our inclusion criteria. Of these indications, five (7%) had postapproval confirmatory trials with published results before the first available guideline, and four (6%) were converted from accelerated approval to traditional approval before the first available guideline.

Among the remaining 39 drug treatments that received accelerated approval for 62 unique and eligible indications, all had at least one postapproval confirmatory trial (median one trial per indication (IQR 1-2)). The most frequently represented treatment area was for hematological cancers (25 (40%); table 1). As of 31 December 2022, 36 (58%) indications were converted from accelerated to traditional approval, 12 (19%) were withdrawn from the market (all voluntarily initiated by the sponsors), and 14 (23%) had no change to their accelerated approval status.

Table 1 | Characteristics of oncological therapeutic indications with FDA accelerated approval in 2009-18

Characteristics of therapeutic indications	No (%)
Total No	62
Year of accelerated approval	
2009-12	9 (15)
2013-16	18 (29)
2017-18	35 (56)
Therapeutic type	
Biologic	34 (55)
Small molecule cytotoxic	3 (5)
Small molecule targeted	25 (40)
Orphan designation	
Yes	46 (74)
No	16 (26)
Cancer type or NCCN guideline *	
Hematological cancers	25 (40)
Gastrointestinal and hepatobiliary cancers	9 (15)
Lung cancer	9 (15)
Skin and soft tissue cancer	8 (13)
Gynecological and genitourinary cancer	6 (10)
Others	5 (8)
FDA approval status as of 31 December 2022	
Traditional approval	36 (58)
Accelerated approval	14 (23)
Withdrawn from market	12 (19)

Oncological therapeutic indications refer to the specific oncological condition for which the drug is recommended.

*NCCN guidelines were categorized as follows: hematological cancer: acute lymphoblastic leukemia, acute myeloid leukemia, B cell lymphoma, chronic lymphocytic leukemia, chronic myeloid leukemia, Hodgkin's lymphoma, multiple myeloma, and T cell lymphoma; gastrointestinal and hepatobiliary cancer: colon cancer, gastric cancer, and hepatobiliary cancer; lung cancer: small cell lung cancer and non-small cell lung cancer; skin and soft tissue cancer: melanoma, Merkel cell carcinoma, and soft tissue sarcoma; gynecological and genitourinary cancer: bladder cancer, cervical cancer, and ovarian cancer; others: breast cancer, central nervous system cancer, head and neck cancer.

FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network.

NCCN guideline descriptions of indications granted accelerated approval

All 62 accelerated approval indications were included in NCCN guideline recommendations. Among these, 10 (16%) had NCCN guidelines explaining that the drug treatment had been approved via the accelerated approval pathway or that confirmation of clinical benefit was still pending at the time the guideline was written. These guidelines included all guidelines for central nervous system cancer, colon cancer, gastric cancer, and hepatobiliary cancer (online supplemental table 2). All guidelines identified the specific primary endpoint supporting accelerated approval, but none characterized the primary endpoint as a surrogate marker.

NCCN guideline descriptions of postapproval confirmatory trials

Among the 62 indications, 26 (42%) had NCCN guidelines mentioning at least one postapproval confirmatory trial before FDA status conversion from accelerated approval to traditional approval or market withdrawal (table 2). Among the 34 indications with postapproval confirmatory trials evaluating only surrogate markers as the primary endpoints, 17 (50%) had NCCN guidelines that named the specific surrogate endpoints when describing the postapproval confirmatory trial results; none characterized the endpoints as a surrogate marker.

NCCN guideline recommendation alignment with FDA status updates

Among the 36 indications converted from accelerated to traditional approval, 30 (83%) had NCCN guidelines that reflected the FDA's conversion decision (ie, the category of evidence was strengthened, or the indication was expanded to be consistent with the new approval; table 3, figure 1). Of these 30 indications, 20 (67%) had NCCN guidelines that were updated before FDA's conversion from accelerated to traditional approval (by a median of 3.8 months (IQR

Table 2 | Results of postapproval confirmatory trials for oncology therapeutic indications with FDA accelerated approval

	Therapeutic indications with postapproval confirmatory trials with at least one primary clinical endpoint		Therapeutic indications with postapproval confirmatory trials with only surrogate markers as primary endpoints*		
Postapproval confirmatory trial results *	Total No (%)	No (%) of guidelines referencing postapproval confirmatory trial before FDA status update	Total No (%)	No (%) of guidelines referencing postapproval confirmatory trial before FDA status update	No (%) of guidelines mention or describe that postapproval confirmatory trials used only surrogate markers as primary endpoints
Positive (n=33)	13 (39)	5 (38)	20 (61)	12 (60)	0
Mixed positive and negative (n=4)	3 (75)	2 (67)	1 (25)	0	0
Negative (n=12)	11 (92)	7 (64)	1 (8)	0	0
Pending† (n=6)	0	—	6 (100)	0	0
Terminated (n=5)	1 (20)	0	4 (80)	0	0

*Postapproval confirmatory trials for two therapeutic indications (belinostat for the treatment of multiple myeloma, and panobinostat for the treatment of peripheral T cell lymphoma) were not located; both trials had surrogate endpoints.

†All postapproval confirmatory trials were pending without any reported results.

FDA, US Food and Drug Administration.

1.7-11.8)) and 10 (33%) had NCCN guidelines that were updated after FDA's conversion from accelerated to traditional approval (by a median of 2.6 months (0.5-4.7); figure 2).

Among the 12 indications withdrawn from the market, seven (58%) had NCCN guidelines that reflected the FDA's withdrawal decision (the indication was removed from guidelines' recommendations). Of these indications, four (57%) had NCCN guidelines that were updated before the FDA's withdrawal decision (by a median of 4.7 months (IQR 2.6-7.7)) and three (43%) had a guideline that was updated after the FDA's withdrawal decision (by a median of 0.6 months (0.5-1.5)). Five (42%) had NCCN guidelines that continued to recommend the drug despite FDA withdrawal.

NCCN guideline recommendation alignment with results of postapproval confirmatory trials

Among the 62 indications, 11 (18%) did not have any postapproval confirmatory trials with reported results, including six (10%) with pending trials and five (8%) with terminated trials. Among the 49 (79%) indications with postapproval confirmatory trials with available results, 33 (53%) had positive trials, 12 (19%) had negative trials, and four (6%) had trials with both positive and negative results. Of two (3%) indications with postapproval

Table 3 | Consistency of NCCN guideline recommendations with postapproval confirmatory trial results and FDA status changes for oncology therapeutic indications with FDA accelerated approval

	No (%) of indications with results available for at least one post approval confirmatory trial (n=49)							
	Positive trial results (n=33)†		Negative trial results (n=12)			Mixed positive and negative results (n=4)		
FDA status*	No change to accelerated approval status (n=3)	Converted to traditional approval (n=30)	No change to accelerated approval status (n=2)	Converted to traditional approval (n=3)	Withdrawn from market (n=7)	No change to accelerated approval status (n=0)	Converted to traditional approval (n=3)	Withdrawn from market (n=1)
Indications with guidelines reflecting trial results regardless of FDA's updated decision	2 (67)	25 (83)	1 (50)	1 (33)	3 (43)	NA	1 (33)	0
Indications with guidelines reflecting FDA's updated decision	NA	25 (83)	NA	3 (100)	4 (57)	NA	2 (67)	0

*As of 31 December 2022.

†No indications with positive trial results were withdrawn from the market.

FDA, US Food and Drug Administration; NA, not applicable; NCCN, National Comprehensive Cancer Network.

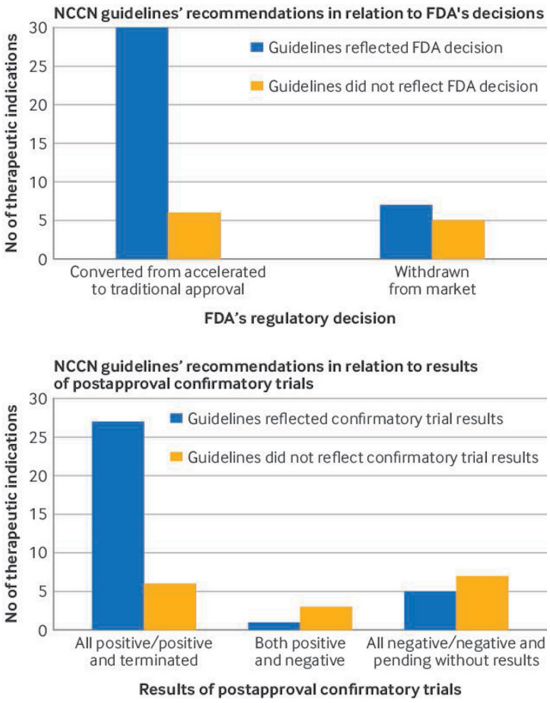

Figure 1 | NCCN guidelines' recommendations in relation to FDA's decisions and results of postapproval confirmatory trials. NCCN=National Comprehensive Cancer Network; FDA=US Food and Drug Administration

confirmatory trials that could not be located, one had no change to its accelerated approval status, and the other was withdrawn from the market and the corresponding guideline reflected the withdrawal.

Among the 33 indications with positive postapproval confirmatory trials, 27 (82%) had NCCN guidelines that referenced the postapproval confirmatory trials and either maintained the previous recommendation or strengthened the category of evidence (figure 1). Among the 12 indications with negative postapproval confirmatory trials, five (42%) had NCCN guidelines that referenced the postapproval trial results and decreased the strength of evidence or removed the indication from their recommendations. Among the four indications with postapproval confirmatory trials with both positive and negative results, one (25%) had an NCCN guideline that referenced both trial results.

Discussion

Principal findings

In this cross sectional study of 62 oncological therapeutic indications that received accelerated approval by the FDA from 2009 to 2018, we found that while all indications were included in NCCN guideline recommendations, indications that were withdrawn from the market or had failed their postapproval confirmatory trials often continued to be recommended for use. Some of these indications have been previously described as "dangling approvals."[23] Moreover, NCCN guidelines rarely acknowledged whether a drug treatment was approved under the accelerated approval pathway or provided information about the uncertainty around clinical benefit at the time of approval. Given that NCCN guidelines inform prescriber decision making,[13] these findings highlight the need for greater alignment between NCCN guidelines and FDA regulatory decisions as well as postapproval confirmatory trial results to inform clinical practice more accurately. Moreover, such greater alignment would also better inform federal coverage on oncology drug treatments approved through the accelerated approval pathway as the Centres for Medicare and Medicaid Services recognizes the NCCN guidelines as a mandated resource when making coverage policy decisions.[24]

We found that NCCN guidelines consistently provided information on positive postapproval confirmatory trial results, but when postapproval trial results failed to confirm benefit, the guideline recommendations were often not aligned with these results and continued to recommend the indicated drug regardless. These findings are consistent with a previous evaluation focused exclusively on oncology accelerated approval drugs with negative postapproval trials.[14] Such discordance causes additional challenges for physicians when making treatment recommendations and could lead to the prescription of ineffective treatments, which could create trade-offs for patients by limiting their ability to receive other treatments that are potentially more effective and might lead payers to cover drug treatments with limited or uncertain benefits.[25] NCCN guidelines could be enhanced by including further rationale for recommending drug treatments, particularly when discordance exists between the guideline recommendations and evidence generated by postapproval confirmatory trials or FDA decisions.

Our study suggests that most NCCN guideline recommendations are updated before the FDA's official decisions and are likely based on postapproval confirmatory trial results. While NCCN guidelines should communicate postapproval trial results as soon as they are available, NCCN might not have access to the more comprehensive patient level data that are reviewed by the FDA; relying solely on the trial results might offer a limited assessment of the evidence, potentially leading to inadequate consideration of the overall risk-benefit profile of therapeutic indications. NCCN guidelines might instead be updated in response to such comprehensive review and regulatory decision making by the FDA, rather than the availability of the results of postapproval trials not yet reviewed by the agency.

We found that most NCCN guidelines do not specify whether drug treatments are approved via the accelerated approval pathway or do not describe the uncertainty around clinical benefit at the time of

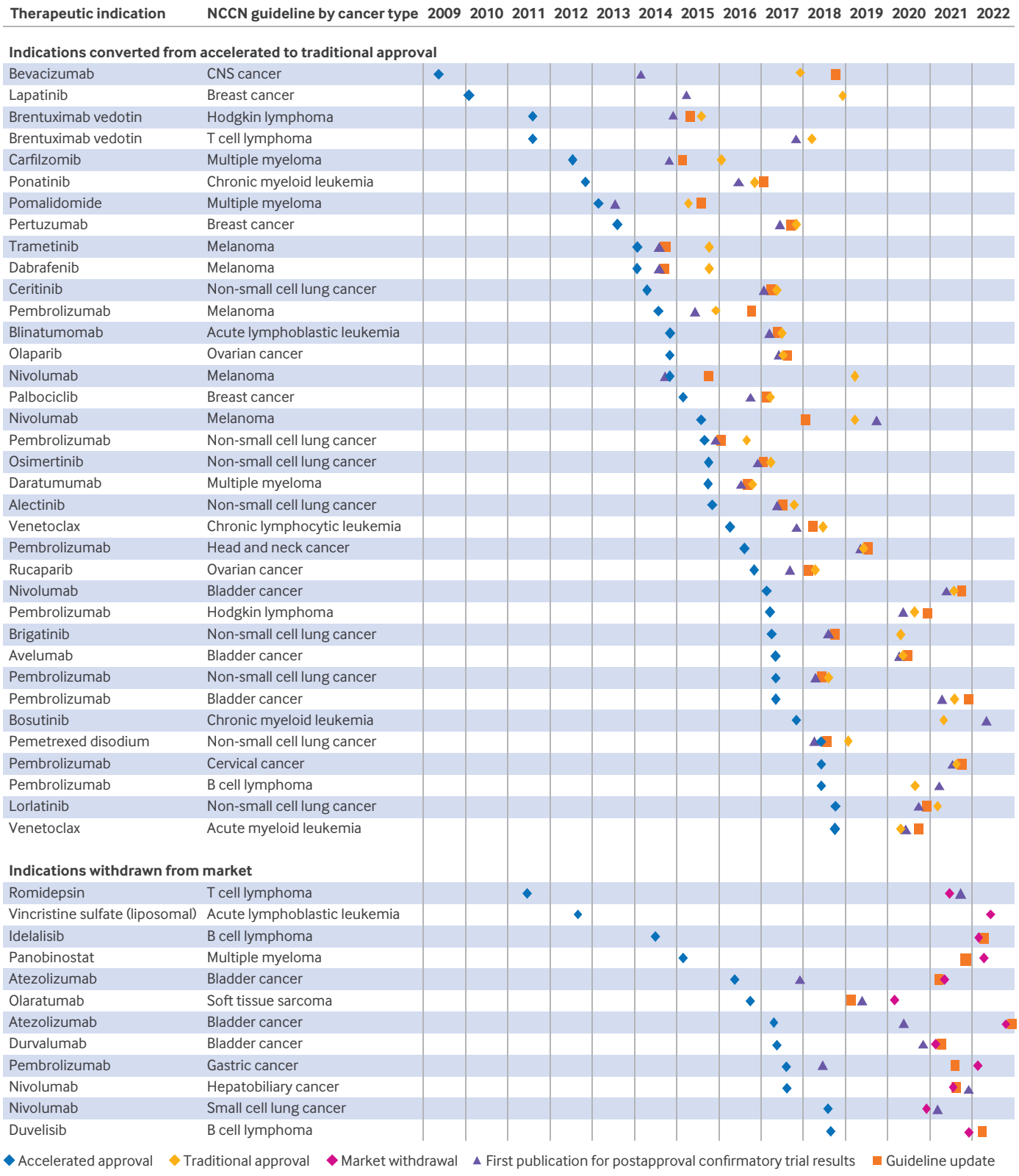

Figure 2 | Timing (by year) of FDA accelerated approval status of oncology therapeutic indications, results of postapproval confirmatory trial availability as publications, conversion to traditional approval or market withdrawal, and NCCN guideline updates. There were no duplicate indications; several drug treatments were granted accelerated approval for the same cancer types but for different indications or subtypes

approval, owing to the use of surrogate endpoints to support accelerated approval. There have been concerns that physicians might overestimate the evidence of new drug treatments' efficacy and, therefore, might not be fully aware of residual uncertainty that results from approvals based on clinical trials

using surrogate markers as primary endpoints.[11 26] While the NCCN guidelines name the specific surrogate endpoints used in pivotal and postapproval confirmatory trials, opportunities exist for NCCN guidelines to consistently and more comprehensively inform physician and payer decisions by explicitly stating the FDA approval pathway (ie, traditional or accelerated), whether confirmation of clinical benefit is still pending, and the type of endpoints (ie, clinical, surrogate, or composite) used in pivotal and postapproval confirmatory trials in a more standardized format.

Limitations of the study

This study had several limitations. First, we examined NCCN guideline updates only in relation to the results of postapproval confirmatory trials and FDA's decisions, whereas NCCN panels might rely on additional factors when making decisions, including potential confidential communication between manufacturers and guideline authors, the results of other clinical trials, and, in the case of label expanding indications, clinical experience from off-label use. These factors might account for guideline updates made ahead of FDA's regulatory decisions after postapproval confirmatory trial results became available.

Second, we used the brief postmarketing requirement descriptions in FDA's approval letters to identify corresponding trial registrations on ClinicalTrials.gov. Although this method has been used in previous studies,[19] two trials could not be located. Third, we allowed for at least six months for guidelines to reflect any withdrawal decisions by the FDA. Only one therapeutic indication (atezolizumab for the treatment of urothelial carcinoma) was withdrawn by the FDA in the second half of 2022, and the corresponding guideline acknowledged the withdrawal decisions by the FDA but continued to recommend the therapeutic indication.

Conclusion

In this cross sectional study, we found that although NCCN guidelines always recommend drug treatments granted accelerated approval for oncological indications, they do not provide information about their accelerated approval status, including surrogate endpoint use and postapproval confirmatory trial status. Moreover, NCCN guidelines often continue to recommend indications with postapproval trials failing to confirm clinical benefit or indications that were withdrawn from the market. Given the importance of NCCN guidelines in oncology practice and in coverage decisions made by the Centres for Medicare and Medicaid Services, opportunities exist to improve transparency regarding the evidence supporting FDA approvals and better align guideline recommendations with regulatory decisions to ensure that clinicians and payers can make informed prescribing and coverage decisions.

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dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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