Clinical value of guideline recommended molecular targets and genome targeted cancer therapies: cross sectional study

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ABSTRACT

OBJECTIVE

To assess the clinical benefit and actionability of molecular targets for genome targeted cancer drugs recommended for clinical practice by the National Comprehensive Cancer Network (NCCN).

DESIGN

Cross sectional study.

PARTICIPANTS/SETTING

Genome targeted cancer drugs recommended by NCCN guidelines in the advanced setting.

MAIN OUTCOME MEASURES

Molecular target actionability was assessed using the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT). Clinical benefit of genome targeted oncology therapies was evaluated using the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS). Molecular targets at ESCAT category level I associated with studies showing substantial clinical benefit by ESMO-MCBS (grades 4-5) were designated as high benefit, and those linked to studies achieving an ESMO-MCBS grade of 3 were categorized as being of promising but unproven benefit.

RESULTS

411 recommendations related to 74 genome targeted drugs targeting 50 driver alterations were examined. Most recommendations (346/411; 84%) were associated with clinical trials of various phases, but 16% (65/411) relied on only case reports or pre-clinical studies. However, clinical trials mostly comprised phase I or phase II (271/346; 78%), single arm (262/346; 76%) studies. The primary endpoint assessed in most trials was overall response rate (271/346; 78%) rather than survival. ESCAT tier I targetability encompassed 60% (246/411) of target recommendations, 35% (142/411) were classified as tier II or III, and 6% (23/411) had their relevance yet to be determined (tiers IV to X). When ESMO-MCBS was applied to 267 scorable trials, only 12% (32/267) showed substantial clinical benefit (grades 4-5) and 45% (121/267) were grade 3. When both frameworks were combined, 12% (32/267) of trials supported a determination of high benefit and 33% (88/267) indicated promising but unproven benefit. Of the 118 interventions endorsed by NCCN authors as preferred, 62 (53%) applied to treatments with high or promising but unproven benefit.

CONCLUSION

According to the ESCAT and ESMO-MCBS frameworks, about one eighth of genome based treatments for solid cancer were rated as likely to offer a high benefit to patients, whereas around a third were identified as offering a promising but unproven substantial benefit. Ensuring that NCCN recommendations are aligned with expected clinical benefits is crucial for promoting informed, evidence based, genomic guided treatment decisions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Precision oncology is transforming cancer care, particularly for advanced, treatment resistant cases, but the clinical importance of many genetic alterations remains uncertain

The evidence base underlying National Comprehensive Cancer Network (NCCN) recommendations can vary widely across different cancers

Frameworks from the European Society for Medical Oncology (ESMO) can help patients and physicians to assess the molecular targetability and expected clinical benefit of cancer drugs

WHAT THIS STUDY ADDS

About an eighth of genome targeted cancer therapies in NCCN guidelines for metastatic cancer were rated as offering a high likelihood of benefit

Another third of therapies were rated as being of promising but unproven benefit according to the ESMO frameworks.

Better alignment between NCCN recommendations and ESMO frameworks could help to guide stakeholders in selecting cancer therapy supported by the highest quality evidence

Introduction

Advances in molecular characterization of tumors and the development of targeted treatments hold promise for improving patients' survival and quality of life. Groundbreaking examples include trastuzumab-pertuzumab for HER2 expressing breast cancer and osimertinib for EGFR mutated non-small cell lung cancer.[1 2] Although these therapies are now considered standards in cancer care, genome targeted treatments offer limited benefit for most patients with metastatic cancer owing to the small subset of potential responders and challenges of drug resistance and cancer progression.[3 4]

The increasing importance of genomic testing in cancer care is accompanied by advances in next generation sequencing. With a growing number of genome targeted cancer drugs being approved or under investigation, the opportunities for precision cancer medicine have broadened, particularly for patients facing advanced treatment resistant disease. In May 2024 the website MyCancerGenome.org provided a catalog of 18 271 genetic biomarkers and 5519 genome targeted cancer therapies available.[5] However, despite the widespread implementation of this technology, the clinical relevance of many genomic alterations is unknown, risking overestimation of the benefits of tailored therapies.[6 7]

In response to these challenges, the European Society for Medical Oncology (ESMO) developed a

grading system for molecular targets—the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT).[8] ESCAT aims to prioritize actionable genomic alterations as markers for selecting patients for targeted therapies. By categorizing genomic alterations into 10 tiers of decreasing evidence for benefit (tiers I to X), this framework prioritizes targets on the basis of levels of evidence, considering clinical trial design as well as specific treatment contexts and indications (supplementary table A). For example, germline BRCA1/BRCA2 mutations as targets for rucaparib are classified as tier I-A in ovarian cancer,[9] tier I-B in prostate cancer,[10] tier II-B in pancreatic cancer,[11] and tier III-A in lung cancer.[12]

Concern is growing about the increasing use of surrogate measures in pivotal trials of cancer drugs leading to regulatory approval, without evidence for overall survival or quality of life benefits.[13 14] This concern is intensified by the high costs of these new treatments. To assist physicians, patients, and regulators in choosing therapies, ESMO created the Magnitude of Clinical Benefit Scale (ESMO-MCBS[15]) to evaluate the clinical benefit associated with new drug therapies for cancer on the basis of treatment effectiveness, adverse events, and quality of life (supplementary table B).

Limited data are available to guide application of precision oncology in clinical decisions about cancer treatment.[16-18] In the case of genome targeted cancer therapies approved by the US Food and Drug Administration (FDA) from 2015 to 2022, fewer than a third showed meaningful added benefits for patients at the time of approval, as indicated by the ESMO-MCBS and ESCAT frameworks.[19] The National Comprehensive Cancer Network (NCCN) guidelines are cancer specific recommendations extensively used in clinical practice worldwide.[20] NCCN guidelines cover more than 97% of US patients with cancer. Additionally, 47% of registered users accessing these guidelines are from outside the US, and downloads of guidelines span more than 180 countries.[21] US public and private insurers rely on the NCCN for decisions on coverage.[22-24] We therefore evaluated the validity of the targets and the value of the outcomes used in the clinical trials supporting genome targeted cancer drugs recommended in advanced cancer by the NCCN guidelines.

Methods

Search strategy

We obtained the most recent versions of the NCCN guidelines for solid cancers on 1 May 2023.[20] Data were extracted between May 2023 and August 2023. We first extracted genome targeted oncology therapies and their genomic alteration targets for advanced cancer recommendations. We defined genome targeted drugs as those approved on the basis of a genomic test whereby the drug was designed to target a specific genomic alteration. We excluded drugs related to cytotoxic chemotherapy or hormonal therapy and non-genome targeted drugs. We then extracted the references to the publications supporting those drug recommendations. We classified the evidence supporting NCCN recommendations as no evidence provided, case report or series, observational study, review article, phase I trial, phase I-II trial, phase II trial, or phase III trial. Where the NCCN did not provide a specific reference, we did searches on PubMed and Google Scholar to collect supporting evidence. Our search terms included the name of the genome targeted therapy, the specific genomic alteration targeted, the type of cancer, and the setting of the recommendation. We then extracted the characteristics and outcomes of the trials from the publications, including sample size, trial design (randomized versus single arm), blinding (blinded versus open label), phase of clinical trial, primary efficacy endpoints supporting the approval (overall survival versus an intermediate measure (for example, progression-free survival, overall response rate, or duration of response)), and information about quality of life and toxicity when available. If multiple or overlapping studies covered the same recommendation, we prioritized the most robust, preferring phase III trials to phase II/I trials and preferring endpoints such as overall survival to intermediate endpoints. If multiple references from the same study supported the same recommendation, we gave preference to those with the most up-to-date data. For studies that did not provide information on quality of life, we searched the following criteria in PubMed: quality of life, patient reported outcomes, the name of the drug, the name of the trial, and the ClinicalTrials.gov identification number. We also collected data for the treatment setting (first line or subsequent line(s)), NCCN levels of evidence (1, 2A, or other), and NCCN preference categories ("preferred regimen," "other recommended regimens," or "useful in certain circumstances") (supplementary table C).

Finally, we searched Drugs@FDA[25] to identify all new and supplemental indications for genome targeted drugs approved for the treatment of solid tumors up to August 2023, following the methods previously reported.[26] We then categorized recommendations into FDA approved and non-approved (off label) indications.

Data synthesis and scoring

To assess the clinical evidence level supporting specific genomic alterations as targets for the drugs in our study, we used the ESCAT framework.[8] ESCAT tier I genomic alterations are clinically relevant on the basis of a clinical trial showing improved outcomes for the genomic alteration-therapy combination. The distinction between tier I-A, I-B, and I-C is based on the level of evidence, determined by the design of the clinical trial analyzing the biomarker (I-A: prospective, randomized; I-B: prospective, single arm; I-C: basket trial). For tissue agnostic drug approvals, defined as drugs approved on the basis of genome targets irrespective of organ site or histology, we maintained the tier assignment as tissue agnostic drug group, even if data on objective response rate were unavailable or no responses were observed for specific subtypes.

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ESCAT tier II alterations are those that hold potential clinical relevance, on the basis of evidence from retrospective clinical trials (II-A) or prospective trials that do not show survival benefits (II-B). Tier III targets are predicted targets linked to an expected improvement in outcome on the basis of clinical trial data from other tumor types. Tier IV targets are those that show potential in pre-clinical studies but lack more rigorous evidence of efficacy in a given cancer. Tier V targets are genomic alterations linked to responses to a targeted drug match that might serve as suitable targets for combination therapy strategies. Tier X alterations lack evidence as therapeutic targets and should not be considered in clinical decision making.[8] See supplementary table A for more detail on ESCAT tiers and examples.

To assess clinical benefit, we applied the ESMO-MCBS framework to each study. We used publicly available forms,[27] and for studies supporting FDA approvals we cross checked the results with the ESMO website.[28] We defined substantial clinical benefit as grade 4 or 5 for studies of non-curative intent.[15] Supplementary table B shows the different available forms, levels of evidence, and examples.

Initially, the ESCAT framework was designed as a clinical benefit centered system, ranking genomic alterations deemed ready for routine use (ESCAT evidence class I-A and I-B) as targets for precision medicine in cancer with substantial improvements as defined by the ESMO-MCBS v1.1 (grade 4 or 5 for non-curative intent).[8] However, in our view, this definition has two major limitations. Firstly, previous studies have indicated that ESMO-MCBS scores of ≥3 correlate with positive health technology assessments, suggesting that new therapies with these scores deliver meaningful benefits that justify reimbursement.[29] Secondly, more cancer drugs have recently received regulatory approval on the basis of high levels of early efficacy in smaller biomarker defined populations, including agnostic drug approvals, through the increased use of overall response rate evaluated in single arm trials.[30] However, these trials must show not only substantial efficacy but also improvements in quality of life or be supported by data from confirmatory post-marketing studies to meet the high clinical benefit thresholds with the ESMO-MCBS framework. These criteria are often difficult to meet at the time of approval.[26]

To overcome these limitations, we expanded our study to include a broader definition of high benefit genome based cancer treatments and added a second group for drugs indicating moderate benefit. We rated molecular targets associated with substantial clinical benefit (ESMO-MCBS grade 4 or 5) and qualifying for ESCAT category levels I-A, I-B, and I-C as high benefit genome based cancer treatments. We classified molecular targets with a grade 3 on ESMO-MCBS and ESCAT tiers I-A, I-B, and I-C as having promising but unproven benefits.

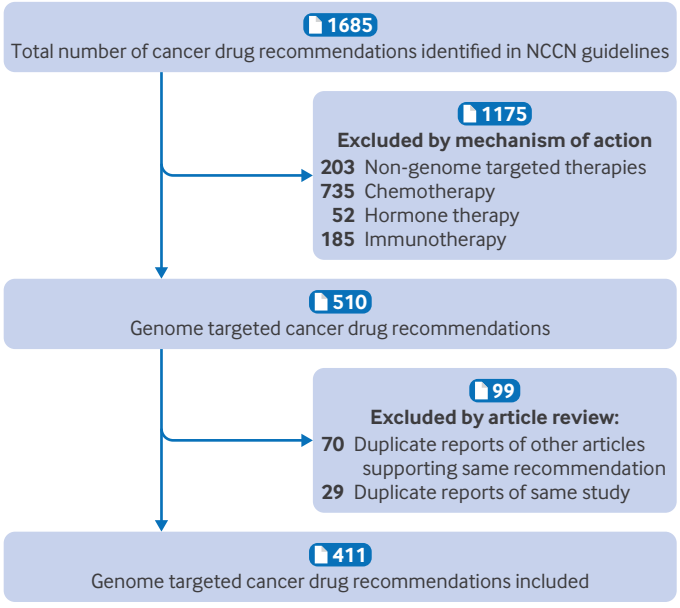

Fig 1 | Identification and selection of cancer drug recommendations identified in National Comprehensive Cancer Network (NCCN) guidelines. One recommendation can be supported by one or more articles. Guidelines included biliary tract cancers, bladder cancer, breast cancer, central nervous system cancers, cervical cancer, colorectal cancer, endometrial cancer, gastric cancer, gastrointestinal stromal tumor, head and neck - salivary gland tumors, hepatocellular carcinoma, melanoma, non-small cell lung cancer, neuroendocrine and adrenal tumors, ovarian cancer, soft tissue sarcoma, pancreatic adenocarcinoma, prostate cancer, testicular cancer, thyroid carcinoma, uterine cancer, and vulvar cancer

Statistical analysis

We used Fisher's exact test to compare genome based cancer therapies with high benefit and promising but unproven benefit versus those with low benefit. We explored associations between recommendations approved with and without FDA approval and the characteristics of recommendations by using the Fisher's exact test for categorical data and the Mann-Whitney U test for non-parametric data. All analyses were univariate, as multivariable analysis was not feasible owing to the limited number of off label recommendations. All P values resulted from two sided tests, and significance was determined at $P<0.05$ (BM SPSS, version 26.0 for Windows). We applied no corrections for multiple significance testing. This research adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cross sectional studies.

Patient and public involvement

Patients were not involved in the formulation of the research question or the establishment of outcome measures or in developing plans for the design or implementation of the study. No patients were consulted for insights on interpreting or writing up results. The study was initiated before patient and public involvement was common. However, results will be disseminated via conference presentations, publications in lay media, and interactive online tools.

Results

Of a total of 515 NCCN recommendations, 411 met our inclusion criteria (fig 1) and covered 74 genome

Table 1 | Characteristics of NCCN cancer recommendations for genome targeted drug indications in advanced cancer

Characteristics	No (%) recommendations (n=411)
Drugs:	
FDA approved	246 (60)
Off label use	165 (40)
Drug class:	
Small molecule inhibitors	286 (70)
Immunotherapy	66 (16)
Antibody	37 (9)
Antibody-drug conjugate	14 (3)
No specific drug recommended*	8 (2)
Disease site:	
Non-small cell lung cancer	83 (20)
Breast cancer	49 (12)
Colorectal cancer	17 (4)
Prostate cancer	5 (1)
Other tumors†	257 (63)
Line of therapy:	
First line	106 (26)
Second/subsequent line	305 (74)
Source of recommendation:	
Clinical trials or studies	346 (84)
Pre-clinical data or case reports	16 (4)
Extrapolation from other tumor types	42 (10)
No references cited‡	7 (2)
NCCN categories of evidence:	
1	33 (8)
2A	322 (78)
2B and 3	56 (14)
NCCN categories of preference§:	
Preferred intervention	113/395 (29)
Other recommended intervention	84/395 (21)
Useful in certain circumstances	198/395 (50)
None reported	16

FDA=Food and Drug Administration; NCCN=National Comprehensive Cancer Network.
* For certain genomic alterations, NCCN authors suggest offering targeted drugs without specifically endorsing any particular options.
† Other reviewed guidelines: biliary tract cancers, bladder cancer, central nervous system cancers, cervical cancer, endometrial cancer, gastric cancer, gastrointestinal stromal tumor, head and neck - salivary gland tumors, hepatocellular carcinoma, melanoma, neuroendocrine and adrenal tumors, ovarian cancer, soft tissue sarcoma, pancreatic adenocarcinoma, testicular cancer, thyroid carcinoma, uterine cancer, vulvar cancer.
‡ Alterations for which no evidence suggesting actionable targeting was reported in NCCN guideline and no evidence was found through searches on PubMed and Google Scholar. These targets were classified as ESCAT tier X.
§ NCCN authors did not endorse any NCCN preference category for 16 recommendations.

targeted drugs targeting 50 driver alterations. Of these, 346 (84%) recommendations were associated with evidence of varying quality from clinical trials or studies and 65 (16%) relied on pre-clinical studies and/or case reports (16; 4%), extrapolation from other tumor types (42; 10%), or evidence that could not be identified (7; 2%) (table 1). Of the 411 recommendations, 49 (12%) lacked citations. We identified supporting literature for 42 of these, leaving seven (2%) cases in which the underlying evidence could not be identified.

Characteristics of NCCN recommendations and supporting trials

Of 411 NCCN recommendations, 246 (60%) were for FDA approved indications (table 1). Most NCCN recommended treatment options were judged by the NCCN as having category 2A evidence (322; 78%) and 33 (8%) were assigned category 1. Of the 395 recommendations with NCCN preference categories endorsed by NCCN authors (16 recommendations lacked NCCN author endorsements for any preference category), 198 (50%) were rated as "useful in certain circumstances" and 113 (29%) were classified as "preferred."

We included 346 studies (table 2). The median sample size was 26 (range 0-991) patients. Among 104 tissue agnostic drug trials, 32% (n=33) did not include patients of that specific subtype and 73% (n=76) had fewer than 10 patients within a subtype. Seventy eight per cent (271/346) of NCCN recommendations were supported by only phase I or phase II trials, 76% (262/346) were supported by single arm studies, and 93% (323/346) were supported by open label studies. The most common primary endpoint in 271 (78%) studies was "objective response rate." Within this subgroup, the median objective response rate was 46% and the median duration of response was 9.4 months. For 57 (21%) of these studies, the median duration of response was not reached. However, 77 (28%) studies did not report the objective response rate for the specific tumor type analyzed, and 129 (48%) lacked available data on duration of response.

Ratings for molecular targets and clinical benefit

Among the 411 NCCN target recommendations eligible for scoring with ESCAT, 60% (246/411) were categorized as clinically significant (tier I: I-A 18% (72/411); I-B 17% (70/411); I-C 25% (104/411)), whereas one third (24%; 100/411) were categorized as potentially relevant (tier II (II-A 6% (23/411); II-B 19% (77/411)) or tier III (10%; 42/411)). Fewer than a 10th had a relevance yet to be determined (tiers IV to X). These included 2% (10/411) supported by pre-clinical studies (tier IV), 1% (6/411) using a co-targeting strategy (tier V), and 2% (7/411) that did not have any supporting evidence (tier X) (fig 2).

When we applied the ESMO-MCBS evaluation framework to the 267 trials supporting genome targeted recommendations that were scorable, only 32 (12%) were grades 4 or 5, representing a finding of substantial clinical benefit. Among the 235 that did not meet this threshold, 121 (51%) were grade 3, 73 (31%) were grade 2, 29 were grade 1 (12%), and 12 (5%) were grade 0. ESMO-MCBS could not be applied to the remaining 144 (35%) of 411 recommendations. In 65 instances, the recommendations were derived from case reports, pre-clinical studies, or extrapolation from other tumor types or lacked identifiable references. In 77 cases, the primary endpoints of single arm studies were unsuitable for assessment owing to unreported objective response rate. The remaining two trials could not be scored using the ESMO-MCBS, because the outcomes did not achieve statistical significance.

Molecular targets from ESCAT category level I that were associated with substantial clinical benefit according to ESMO-MCBS accounted for 12% (32/267) of the trials and were designated as high benefit genome based cancer treatments. Molecular targets within ESCAT category level I linked to a grade 3 in ESMO-MCBS constituted 33% (88/267) of the trials and were categorized as treatments with promising but unproven benefit (fig 3). The NCCN guidelines

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Table 2 | Characteristics of clinical trials supporting National Comprehensive Cancer Network recommendations for genome targeted drug indications in advanced cancer

Characteristics	No (%) trials (n=346)
Study design:	
Randomized	82 (24)
Single arm	262 (76)
Observational study	1 (<1)
Systematic review	1 (<1)
Blinding:	
Open label	323 (93)
Double blind	23 (7)
Phase of study:	
I	36 (10)
I/II	81 (23)
II	154 (45)
III	72 (21)
III or IV	2 (<1)
Observational	1 (<1)
Sample size:	
Median	26
Mean	99
Range	0-991*
Primary endpoint:	
Overall survival	12 (3)
Intermediate endpoint	334 (97)
Overall response rate	271
Progression-free survival	63
Basis of decision:	
Subgroup analysis	247 (71)
Entire study population	99 (29)

* 33 recommendations for tissue agnostic drug approvals, defined as those approved on basis of genome targets irrespective of organ site or histology, had no patients of this subtype included in trial supporting recommendation.

were more likely to assign genome targeted drugs with high and promising but unproven clinical benefits into category 1 (23% v 3%; P<0.001) or the preferred category (53% v 25%; P<0.001), in contrast to less beneficial therapy options (table 3).

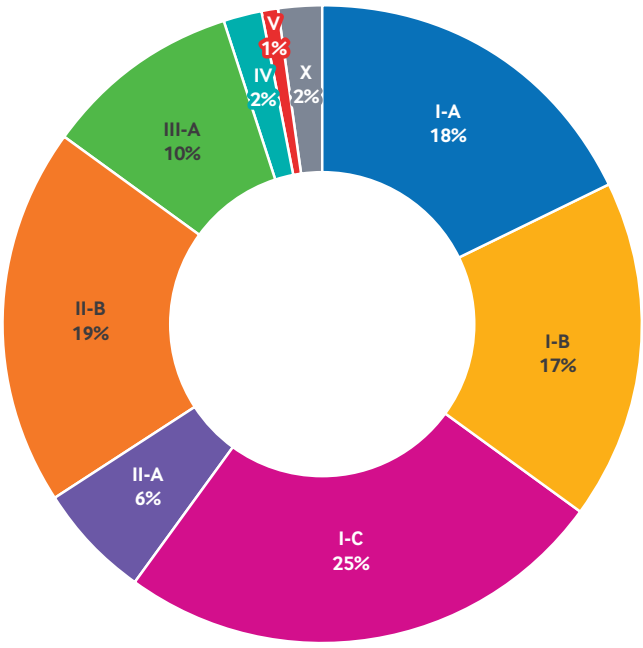

Fig 2 | European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT) levels of evidence for molecular targets. Figure shows proportions of molecular targets falling into different ESCAT levels of evidence among genome targeted drugs recommended by National Comprehensive Cancer Network guidelines

Characteristics of NCCN recommendations for genome targeted treatments with and without FDA approval

As shown in table 4, of the 118 preferred interventions endorsed by NCCN guidelines, 62 (53%) were categorized as "recommendations with high or promising but unproven benefit." In addition, genome based cancer treatments with high and promising but unproven benefit were more likely to be approved by the FDA (61% *v* 16%; P<0.001). Recommendations for off label uses were less frequently based on randomized trials (18% *v* 26%; P=0.03), phase III trials (11% *v* 25%; P=0.009), or studies with blinding (0% *v* 9%, P=0.001).

Discussion

Among more than 400 NCCN recommendations extracted from 22 guidelines, only about an eighth of genome based treatments for solid cancer were rated as highly likely to provide clinical benefit, whereas around a third were identified as having a promising but unproven substantial benefit, according to the ESCAT and ESMO-MCBS frameworks. Given the pivotal role of the NCCN in guiding global oncology practice and determining insurance coverage of cancer drugs in the US, these findings have broad implications for clinical decision making and reimbursement policies.

Challenges and implications of genome targeted therapies in oncology practice

Although personalized therapy may yield survival or quality of life benefits for some patients, certain targets lack proven efficacy and some might even be suboptimal choices. Among targets in the lower ESCAT tiers III to X (representing a third of our cohort), offering a patient enrolment in a clinical trial could be a similarly valid alternative approach, if one is available.

Roughly 10% of NCCN recommendations were classified by ESCAT as tier III-A on the basis of clinical benefit in other tumor entities, including ALK inhibitors in biliary tract cancers, uterine sarcoma, thyroid carcinoma, or melanoma. Although a rationale supports targeted therapy such as ALK inhibitors in certain cancers, clinical evidence for their efficacy outside of ALK rearranged non-small cell lung cancer and inflammatory myofibroblastic tumor is limited or absent.[31 32] Genetic alterations in cancer are commonly distributed across diverse disease types, but the predictive accuracy of these alterations varies depending on the specific cancer type. For example, in the case of HER2 amplification, the effectiveness of treatments can vary substantially among different cancer types. Use of pertuzumab (with trastuzumab and chemotherapy) has shown an overall survival advantage of more than 15 months for patients with HER2 positive metastatic breast cancer compared with trastuzumab and chemotherapy alone.[1] Conversely, in HER2 positive metastatic biliary tract cancer and salivary gland tumors—for which trastuzumab and pertuzumab do not hold FDA approval but were included in NCCN guidelines—the observed "objective

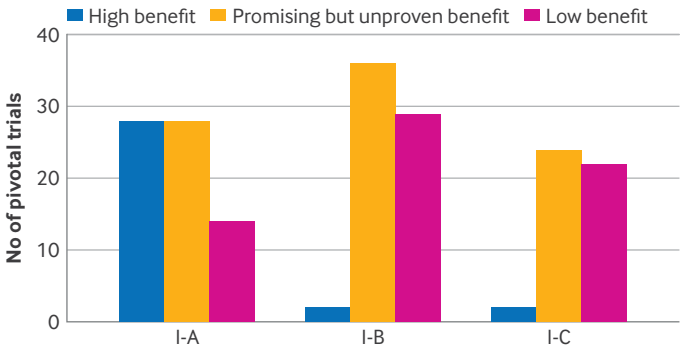

Fig 3 | Value of molecular targets recommended by National Comprehensive Cancer Network (NCCN) guidelines. Molecular targets associated with substantial clinical benefit by European Society for Medical Oncology - Magnitude of Clinical Benefit Scale (ESMO-MCBS) (grade 4 or 5 for those of non-curative intent) and qualifying for ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) tiers I-A, I-B, and I-C, were rated as high benefit genome based cancer treatments. Molecular targets achieving a grade 3 on ESMO-MCBS and qualifying for ESCAT tiers I-A, I-B, and I-C were classified as being of promising but unproven benefit

response rate" ranged from 23% to 60% without survival endpoint data.[33 34]

Decisions regarding treatment based on comprehensive genome profiling in routine oncology practice remain challenging. Practice guidelines play a crucial role in standardizing cancer care and promoting equal access to adequate treatments, as well as guiding decisions about resource allocation. In recent years, clinical guidelines such as those of the NCCN have increasingly endorsed genomic testing in cancer care. In 2017 NCCN guidelines urged profiling for non-small cell lung cancer targeting ALK, ROS1, and EGFR alterations.[35] In our 2023 review, endorsements spanned BRCA1/2, BRAF, FGFR, homologous recombination deficient, KIT, KRAS, MSI-H, dMMR, MET, NTRK, PALB2, PIK3CA, RET, and TMB and encompassed around 50 specific genomic alterations. However, prospective evidence to support non-selective molecularly guided treatment decisions is limited. Multiple single arm studies have shown objective response rates ranging from 1% to 30% in patients with tumors containing actionable alterations.[17 36-39] An initial randomized study evaluating personalized medicine for cancer showed no meaningful difference in outcomes with the use of multigene sequencing for patients with metastatic cancers refractory to standard of care compared with unmatched therapies.[16] In this context, the ESCAT framework can be useful for patients and prescribers to identify actionable genomic alterations in patients with cancer and assist clinicians in prioritizing the use of genome targeted therapies.

Extensive research and validation have confirmed the applicability of ESMO-MCBS and ESCAT frameworks.[40-45] For example, pooled data from the SAFIR02-BREAST and SAFIR-PI3K trials showed progression-free survival benefit in patients with HER2 non-overexpressing breast cancer receiving matched treatments classified as level I/II according to ESCAT (9.1 months versus 2.8 months with chemotherapy; hazard ratio 0.41, 95% confidence interval (CI) 0.27 to 0.61; P<0.001) compared with chemotherapy.[43] By contrast, no benefit was shown in the intention-to-treat population (5.5 months versus 2.9 months; hazard ratio 0.77, 95% CI 0.56 to 1.06; P=0.11) or the ESCAT beyond level II subgroup (2.8 months versus 3.1 months; 1.15, 0.76 to 1.75; P=0.49). Our study and these findings reinforce the importance of molecularly guided treatment decisions supported by evidence. Further research and dissemination of decisions aids such as the ESCAT and ESMO-MCBS frameworks can assist in clinical decision making around these treatments, which are also invariably expensive.

Contemporary oncologic care frequently incorporates the use of drugs off label, with approximately 30% of prescriptions falling into this category.[23 46] Off label prescriptions represent a substantial part of annual healthcare costs in the US, potentially accounting for half of all oncologic drug use.[47] A study examining 10 commonly prescribed cancer drugs found that about 30% of their use was off label, leading to an annual cost of $4.5 bn (£3.5 bn; €4.2 bn).[46] Such use may be evidence based even in the absence of a formal FDA

Table 3 | NCCN categories of evidence and preference for genome targeted therapies rated by ESCAT and ESMO-MBCS as high or promising but unproven benefit versus low benefit. Values are numbers (percentages) unless stated otherwise

	All recommendations	Recommendations with high or promising but unproven benefit*	Recommendations with low benefit	P value†
NCCN categories of evidence (n=267)‡				
1	33 (12)	28 (23)	5 (3)	<0.001
2	206 (77)	84 (70)	122 (83)	
2B and 3	28 (10)	8 (7)	20 (14)	
NCCN categories of preference (n=263)§				
Preferred intervention	98 (37)	62 (53)	36 (25)	<0.001
Other recommended intervention	65 (25)	26 (22)	39 (27)	
Useful in certain circumstances	100 (38)	30 (25)	70 (48)	

ESCAT=European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets; ESMO-MCBS=European Society for Medical Oncology Magnitude of Clinical Benefit Grading Scale; NCCN=National Comprehensive Cancer Network.
* Molecular targets associated with substantial clinical benefit by ESMO-MCBS (grade 4 or 5 for those of non-curative intent) and qualifying for ESCAT category level I were rated as high benefit genome based cancer treatments, and those with grade 3 by ESMO-MCBS and qualifying for ESCAT category level I were rated as promising but unproven benefit genome based cancer treatments.
† Calculated by Fisher's exact test.
‡ NCCN authors did not endorse any NCCN preference category for 16/411 recommendations.
§ NCCN authors did not endorse any NCCN preference category for four genomic alterations that are scorable with ESCAT and ESMO-MCBS.

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Table 4 | Characteristics of NCCN recommendations for genome targeted therapies with versus without FDA approval. Values are numbers (percentages) unless stated otherwise

Characteristics	All recommendations	Recommendations with FDA approval	Recommendations without FDA approval	P value*
Median sample size	26	22	25	0.31
Study design†:	346 (100)			
Randomized controlled trial	82 (24)	63 (26)	19 (18)	0.03
Single arm trial	262 (76)	179 (74)	83 (80)	
Others	2 (<1)	0	2 (2)	
Blinding†:				
Open label	323 (93)	219 (91)	104 (100)	0.001
Double blind	23 (7)	23 (9)	0 (0)	
Study phase†:				
Phase I and II	271 (78)	179 (74)	92 (88)	0.009
Phase III	72 (21)	61 (25)	11 (11)	
Phase IIIb/IV	3 (1)	2 (1)	1 (1)	
High and promising but unproven benefit genomic based cancer treatments‡:	267 (100)§			
Yes		105 (61)	15 (16)	<0.001
No		67 (39)	80 (84)	

FDA=Food and Drug Administration; NCCN=National Comprehensive Cancer Network.
* P values calculated by Pearson x^2 test (categorical data) or Mann-Whitney U test (continuous data).
† Among 411 NCCN recommendations, 346 (84%) were supported by evidence from clinical trials or studies.
‡ Molecular targets associated with substantial clinical benefit by European Society for Medical Oncology Magnitude of Clinical Benefit Grading Scale (ESMO-MCBS) (grade 4 or 5 for those of non-curative intent) and qualifying for European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets (ESCAT) category level I were rated as high benefit genomic based cancer treatments, and those with grade 3 by ESMO-MCBS and qualifying for ESCAT category level I were rated as moderate benefit genomic based cancer treatments.
§ 267 trials supporting genome targeted recommendations were assessable using both ESMO-MCBS and ESCAT frameworks.

indication, but this is often not the case. Off label use has not diminished for genome targeted drugs; enhanced access to comprehensive genomic profiling facilitates the detection of targetable tumor alterations, even for drugs that lack a formal indication. In our study, 40% of the recommendations for genome targeted therapies were off label. Compared with FDA approved indications, NCCN off label recommendations were less likely to be supported by phase III, blinded, randomized trials or to have overall survival as the primary endpoint.

Policy implications of findings

Our study identifies several areas of potential improvement in guideline driven cancer care. Firstly, we found that only 25% of NCCN recommendations were supported by evidence from randomized controlled trials. Among the 84 indications supporting cancer drugs approved by the FDA from 2015 to 2022, fewer than half (46%) were backed by evidence from randomized trials.[48] When evaluating the clinical evidence supporting NCCN recommendations, most trials had one or more of the following characteristics: single arm studies; reliance on "objective response rate" as the primary endpoint; based on subgroup analyses; and recommendations based on limited sample sizes, uncertainty about the benefits of those drugs,[14] and potentially greater risk of post-marketing safety related problems.[49 50] When recommendations were based on objective response rate results, data were missing for one third of therapies and half lacked duration of response data, primarily owing to a limited number of patients with a specific target. These examples highlight the importance of ongoing data collection, ideally integrated into clinical studies and registries, to comprehensively evaluate the risks and benefits of molecular targeted therapies in a continuous manner.[51] Examples of this model include DRUP (NCT02925234), TAPUR (NCT02693535), and MoST (ACTRN12616000908437).

Our findings also emphasize the need to refine the NCCN's recommendation algorithm to better consider the levels of evidence for predictive biomarkers in specific cancers. The approval of new treatments for specific and narrow patient populations defined by genomic markers presents a challenge in implementing precision medicine in clinical practice. The rarity of many therapeutic targets means that clinical practice guidelines play a pivotal role, particularly in treatment stratification for genome targeted drug recommendations. Several approaches could enhance the clarity of the NCCN guidelines. Firstly, adherence to the RIGHT (Reporting Items for Practice Guidelines in Healthcare) statement and AGREE-II (Appraisal of Guidelines for Research and Evaluation II) instrument, which could enhance the transparency and methodological quality of guidelines.[52] Secondly, highlighting the hierarchy among different treatment options, incorporating the highest level of scientific evidence supporting each recommendation and the most current updates available. Finally, integrating the ESMO-MCBS scale and the ESCAT scale into the guidelines, similarly to their use in the ESMO guidelines; this would enable physicians to interpret genomic data more effectively and empower patients to participate more fully in shared decision making.

Strengths and limitations of study

We did an extensive review of 22 solid cancer guidelines, covering more than 400 NCCN recommendations. Additionally, in cases in which references were not

provided or lacked information about targetability, we did independent research to find supporting evidence for recommendations beyond the references provided by the NCCN.

This study has limitations. Firstly, data on drugs can evolve over time after their market release and may have changed since our analysis. Secondly, some NCCN recommended uses may lack FDA approval because pharmaceutical companies chose not to register the new indication—for example, in the case of a less profitable drug. Thirdly, we did not apply corrections for multiple significance testing, which could affect the interpretation of borderline P values as hypothesis generating. Finally, 76% of trials in our cohort had a single arm design; as a result, only a minority of these single arm studies met the criteria for substantial clinical benefit as defined in ESMO-MCBS version 1.1. To overcome this limitation, we broadened our study to include an additional cohort comprising drugs that achieved an ESMO-MCBS grade of 3 and ESCAT tier I, indicating moderate benefit.

Conclusions

Decisions about treatment based on comprehensive genome profiling in oncology practice remain challenging. Patients who have not responded to standard therapies have limited treatment options, which adds to the complexity of selecting the most appropriate therapy. Genetic profiling offers the potential to identify additional treatment possibilities in such cases, but the abundance of data requires a systematic approach to navigate the results. Benefit frameworks such as ESMO-MCBS and ESCAT can assist patients, prescribers, and payers in discerning which genome targeted therapies are supported by the highest quality evidence. The NCCN guidelines play a crucial role in real world clinical practice. Efforts should be focused on improving NCCN recommendations to enable evidence based treatment selection based on next generation sequencing results. Such measures could assist patients, prescribers, and payers in discerning which uses of drugs are supported by the highest quality evidence.

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Ethical approval: Not needed, as this was a study of publicly available data and the study did not involve human participants.

Data Sharing: Data are publicly available.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The authors plan to disseminate the study and study results to research institutions, medical associations, and patient communities. The article has been presented at ASCO 2024 as a poster presentation.

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1 Swain SM, Miles D, Kim SB, et al,CLEOPATRA study group. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2020;21:519-30. doi:10.1016/S1470-2045(19)30863-0
2 Ramalingam SS, Vansteenkiste J, Planchard D, et al,FLAURA Investigators. Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC. *N Engl J Med* 2020;382:41-50. doi:10.1056/NEJMoa1913662
3 Marquart J, Chen EY, Prasad V. Estimation of the Percentage of US Patients With Cancer Who Benefit From Genome-Driven Oncology. *JAMA Oncol* 2018;4:1093-8. doi:10.1001/jamaoncol.2018.1660
4 Bhang HE, Ruddy DA, Krishnamurthy Radhakrishna V, et al. Studying clonal dynamics in response to cancer therapy using high-complexity barcoding. *Nat Med* 2015;21:440-8. doi:10.1038/nm.3841
5 My Cancer Genome. Biomarkers. https://www.mycancergenome.org/content/biomarkers/#biomarker_type=Genetic%20Biomarkers.
6 Tannock IF, Hickman JA. Limits to Personalized Cancer Medicine. *N Engl J Med* 2016;375:1289-94. doi:10.1056/NEJMsb1607705
7 Marketing personalized cancer treatments requires careful language. *Nature* 2018;558:5-6. doi:10.1038/d41586-018-05323-6
8 Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol* 2018;29:1895-902. doi:10.1093/annonc/mdy263
9 Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2017;18:75-87.
10 Abida W, Patnaik A, Campbell D, et al,TRITON2 investigators. Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration. *J Clin Oncol* 2020;38:3763-72. doi:10.1200/JCO.20.01035
11 Reiss KA, Mick R, O'Hara MH, et al. Phase II Study of Maintenance Rucaparib in Patients With Platinum-Sensitive Advanced Pancreatic Cancer and a Pathogenic Germline or Somatic Variant in *BRCA1*, *BRCA2*, or *PALB2*. *J Clin Oncol* 2021;39:2497-505. doi:10.1200/JCO.21.00003
12 Pérez-Peiró M, Valentí-Serra P, León-González B, et al. Attenuation of Tumor Burden in Response to Rucaparib in Lung Adenocarcinoma: The Contribution of Oxidative Stress, Apoptosis, and DNA Damage. *Int J Mol Sci* 2023;24:2580. doi:10.3390/ijms24032580
13 Mitra-Majumdar M, Gunter SJ, Kesselheim AS, et al. Analysis of Supportive Evidence for US Food and Drug Administration Approvals of Novel Drugs in 2020. *JAMA Netw Open* 2022;5:e2212454. doi:10.1001/jamanetworkopen.2022.12454
14 Del Paggio JC, Berry JS, Hopman WM, et al. Evolution of the Randomized Clinical Trial in the Era of Precision Oncology. *JAMA Oncol* 2021;7:728-34. doi:10.1001/jamaoncol.2021.0379
15 Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Ann Oncol* 2017;28:2340-66. doi:10.1093/annonc/mdx310
16 Le Tourneau C, Delord JP, Gonçalves A, et al,SHIVA investigators. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol* 2015;16:1324-34. doi:10.1016/S1470-2045(15)00188-6

17 André F, Bachelot T, Commo F, et al. Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER). *Lancet Oncol* 2014;15:267-74. doi:10.1016/S1470-2045(13)70611-9
18 Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA* 2014;311:1998-2006. doi:10.1001/jama.2014.3741
19 Tibau A, Hwang TJ, Molto C, Avorn J, Kesselheim AS. Clinical Value of Molecular Targets and FDA-Approved Genome-Targeted Cancer Therapies. *JAMA Oncol* 2024;10:634-41. doi:10.1001/jamaoncol.2024.0194
20 National Comprehensive Cancer Network. NCCN guidelines. www.nccn.org/professionals/physician_gls/f_guidelines.asp.
21 National Comprehensive Cancer Network. Home page. 2023. https://www.nccn.org/.
22 National Comprehensive Cancer Network. NCCN Drugs & Biologics Compendium. 2023. https://www.nccn.org/professionals/drug_compendium/default.aspx.
23 Wagner J, Marquart J, Ruby J, et al. Frequency and level of evidence used in recommendations by the National Comprehensive Cancer Network guidelines beyond approvals of the US Food and Drug Administration: retrospective observational study. *BMJ* 2018;360:k668. doi:10.1136/bmj.k668
24 Gyawali B, Rome BN, Kesselheim AS. Regulatory and clinical consequences of negative confirmatory trials of accelerated approval cancer drugs: retrospective observational study. *BMJ* 2021;374:n1959. doi:10.1136/bmj.n1959
25 Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/.
26 Tibau A, Molto C, Borrell M, et al. Magnitude of Clinical Benefit of Cancer Drugs Approved by the US Food and Drug Administration Based on Single-Arm Trials. *JAMA Oncol* 2018;4:1610-1. doi:10.1001/jamaoncol.2018.4300
27 European Society for Medical Oncology. ESMO-MCBS Evaluation Forms. https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms.
28 European Society for Medical Oncology. ESMO-MCBS Scorecards. https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards.
29 Hammerman A, Greenberg-Dotan S, Feldhamer I, Birnbaum Y, Cherny NI. The ESMO-Magnitude of Clinical Benefit Scale for novel oncology drugs: correspondence with three years of reimbursement decisions in Israel. *Expert Rev Pharmacoecon Outcomes Res* 2018;18:119-22. doi:10.1080/14737167.2017.1343146
30 Agrawal S, Arora S, Amiri-Kordestani L, et al. Use of Single-Arm Trials for US Food and Drug Administration Drug Approval in Oncology, 2002-2021. *JAMA Oncol* 2023;9:266-72. doi:10.1001/jamaoncol.2022.5985
31 Peters S, Camidge DR, Shaw AT, et al,ALEX Trial Investigators. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2017;377:829-38. doi:10.1056/NEJMoa1704795
32 Butrynski JE, D'Adamo DR, Hornick JL, et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. *N Engl J Med* 2010;363:1727-33. doi:10.1056/NEJMoa1007056
33 Javle M, Borad MJ, Azad NS, et al. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol* 2021;22:1290-300. doi:10.1016/S1470-2045(21)00336-3
34 Kurzrock R, Bowles DW, Kang H, et al. Targeted therapy for advanced salivary gland carcinoma based on molecular profiling: results from MyPathway, a phase IIa multiple basket study. *Ann Oncol* 2020;31:412-21. doi:10.1016/j.annonc.2019.11.018
35 Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017;15:504-35. doi:10.6004/jnccn.2017.0050
36 Massard C, Michiels S, Ferté C, et al. High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: Results of the MOSCATO 01 Trial. *Cancer Discov* 2017;7:586-95. doi:10.1158/2159-8290.CD-16-1396
37 Tsimberidou AM, Wen S, Hong DS, et al. Personalized medicine for patients with advanced cancer in the phase I program at MD Anderson: validation and landmark analyses. *Clin Cancer Res* 2014;20:4827-36. doi:10.1158/1078-0432.CCR-14-0603
38 Priestley P, Baber J, Lolkema MP, et al. Pan-cancer whole-genome analyses of metastatic solid tumours. *Nature* 2019;575:210-6. doi:10.1038/s41586-019-1689-y
39 Trédan O, Wang Q, Pissaloux D, et al,ProfiLER investigators. Molecular screening program to select molecular-based recommended therapies for metastatic cancer patients: analysis from the ProfiLER trial. *Ann Oncol* 2019;30:757-65. doi:10.1093/annonc/mdz080
40 Vokinger KN, Hwang TJ, Grischott T, et al. Prices and clinical benefit of cancer drugs in the USA and Europe: a cost-benefit analysis. *Lancet Oncol* 2020;21:664-70. doi:10.1016/S1470-2045(20)30139-X
41 Tibau A, Molto C, Ocana A, et al. Magnitude of Clinical Benefit of Cancer Drugs Approved by the US Food and Drug Administration. *J Natl Cancer Inst* 2018;110:486-92. doi:10.1093/jnci/djx232
42 Grössmann N, Del Paggio JC, Wolf S, et al. Five years of EMA-approved systemic cancer therapies for solid tumours-a comparison of two thresholds for meaningful clinical benefit. *Eur J Cancer* 2017;82:66-71. doi:10.1016/j.ejca.2017.05.029
43 Andre F, Filleron T, Kamal M, et al. Genomics to select treatment for patients with metastatic breast cancer. *Nature* 2022;610:343-8. doi:10.1038/s41586-022-05068-3
44 Filetti S, Durante C, Hartl D, et al,ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019;30:1856-83. doi:10.1093/annonc/mdz400
45 Gennari A, André F, Barrios CH, et al,ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* 2021;32:1475-95. doi:10.1016/j.annonc.2021.09.019
46 Conti RM, Bernstein AC, Villaflor VM, Schilsky RL, Rosenthal MB, Bach PB. Prevalence of off-label use and spending in 2010 among patent-protected chemotherapies in a population-based cohort of medical oncologists. *J Clin Oncol* 2013;31:1134-9. doi:10.1200/JCO.2012.42.7252
47 Demonaco HJ, Ali A, Hippel Ev. The major role of clinicians in the discovery of off-label drug therapies. *Pharmacotherapy* 2006;26:323-32. doi:10.1592/phco.26.3.323
48 Tibau A, Hwang TJ, Molto C, Avorn J, Kesselheim AS. Clinical Value of Molecular Targets and FDA-Approved Genome-Targeted Cancer Therapies. *JAMA Oncol* 2024;10:634-41. doi:10.1001/jamaoncol.2024.0194
49 Downing NS, Shah ND, Aminawung JA, et al. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *JAMA* 2017;317:1854-63. doi:10.1001/jama.2017.5150
50 Shepshelovich D, Tibau A, Goldvaser H, et al. Postmarketing Modifications of Drug Labels for Cancer Drugs Approved by the US Food and Drug Administration Between 2006 and 2016 With and Without Supporting Randomized Controlled Trials. *J Clin Oncol* 2018;36:1798-804. doi:10.1200/JCO.2017.77.5593
51 Mateo J, Steuten L, Aftimos P, et al. Delivering precision oncology to patients with cancer. *Nat Med* 2022;28:658-65. doi:10.1038/s41591-022-01717-2
52 Wayant C, Cooper C, Turner D, Vassar M. Evaluation of the NCCN guidelines using the RIGHT Statement and AGREE-II instrument: a cross-sectional review. *BMJ Evid Based Med* 2019;24:219-26. doi:10.1136/bmjebm-2018-111153
53 Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2015;372:30-9. doi:10.1056/NEJMoa1412690
54 Drilon A, Siena S, Dziadziuszko R, et al,trial investigators. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 2020;21:261-70. doi:10.1016/S1470-2045(19)30690-4
55 Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med* 2018;378:731-9. doi:10.1056/NEJMoa1714448
56 Howell SJ, Casbard A, Carucci M, et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive, HER2-negative breast cancer (FAKTION): overall survival, updated progression-free survival, and expanded biomarker analysis from a randomised, phase 2 trial. *Lancet Oncol* 2022;23:851-64. doi:10.1016/S1470-2045(22)00284-4
57 de Salins V, Loganadane G, Joly C, et al. Complete response in anaplastic lymphoma kinase-rearranged oncocytic thyroid cancer: A case report and review of literature. *World J Clin Oncol* 2020;11:495-503. doi:10.5306/wjco.v11.i7.495
58 Bidard FC, Ng CK, Cottu P, et al. Response to dual HER2 blockade in a patient with HER3-mutant metastatic breast cancer. *Ann Oncol* 2015;26:1704-9. doi:10.1093/annonc/mdv217
59 Zhang J, Chen B, Li H, et al,Ka Fai To. Cancer-associated fibroblasts potentiate colorectal cancer progression by crosstalk of the IGF2-IGF1R and Hippo-YAP1 signaling pathways. *J Pathol* 2023;259:205-19. doi:10.1002/path.6033
60 Liu J, Guzman MA, Pezanowski D, et al. FOXO1-FGFR1 fusion and amplification in a solid variant of alveolar rhabdomyosarcoma. *Mod Pathol* 2011;24:1327-35. doi:10.1038/modpathol.2011.98
61 Renovanz M, Kurz SC, Rieger J, et al. Clinical outcome of biomarker-guided therapies in adult patients with tumors of the nervous system. *Neurooncol Adv* 2023;5:vdad012. doi:10.1093/noajnl/vdad012

62 Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015;16:25-35. doi:10.1016/S1470-2045(14)71159-3
63 Mok TS, Wu YL, Ahn MJ, et al,AURA3 Investigators. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. *N Engl J Med* 2017;376:629-40. doi:10.1056/NEJMoa1612674
64 Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol* 2022;23:1261-73. doi:10.1016/S1470-2045(22)00541-1

Web appendix: Supplementary tables