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Special Article

Clinical Practice Recommendations for the Use of Next-Generation Sequencing in Patients with Solid Cancer: A Joint Report from KSMO and KSP

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In recent years, next-generation sequencing (NGS)–based genetic testing has become crucial in cancer care. While its primary objective is to identify actionable genetic alterations to guide treatment decisions, its scope has broadened to encompass aiding in pathological diagnosis and exploring resistance mechanisms. With the ongoing expansion in NGS application and reliance, a compelling necessity arises for expert consensus on its application in solid cancers. To address this demand, the forthcoming recommendations not only provide pragmatic guidance for the clinical use of NGS but also systematically classify actionable genes based on specific cancer types. Additionally, these recommendations will incorporate expert perspectives on crucial biomarkers, ensuring informed decisions regarding circulating tumor DNA panel testing.

Key words Next-generation sequencing, Solid cancer, Precision medicine, Korea

Introduction

Over the past few years, next-generation sequencing (NGS)–based genetic testing has emerged as a crucial aspect of cancer patient care, with the number of tests performed rapidly increasing since its reimbursement by the national health insurance in Korea in 2017. However, as the use of NGS-based genetic testing continues to expand, there is an increasing need for maximizing benefits for patients while also considering cost-effectiveness.

The primary objective of NGS-based genetic testing is to identify targetable actionable genes that can guide treatment selection. However, its application has expanded to include diagnosis and exploration of resistance mechanisms, enabling more personalized treatment options. Moreover, biomarkers like homologous recombination deficiency (HRD), microsatellite instability–high (MSI-H)/mismatch repair deficiency (MMR-D), and high tumor mutational burden (TMB-H) have gained increasing significance. Consequently, NGS-based testing is now widely used to analyze these biomarkers and make well-informed treatment decisions.

With the expanding application of NGS-based genetic testing, there is a need for expert consensus on best practices and guidelines for its use. This recommendation aims to (1) provide guidance on the practical application of NGS in daily clinical practice and (2) classify actionable gene lists by cancer type, based on a comprehensive review of the literature and the consensus of experts. Furthermore, the recommendation will present expert opinions, based on existing evidence, regarding biomarkers including HRD, MSI-H/MMR-D, TMB, and circulating tumor DNA (ctDNA) panel testing.

Materials and Methods

The Korean Society of Medical Oncology (KSMO) and the Korean Society of Pathologists (KSP) have collaborated to develop subsequent clinical practice recommendations. These focus on key questions not addressed in the previous guidelines for NGS-based genetic testing and the molecular tumor board from the KSMO and Korean Cancer Study Group (KCSG) Precision Medicine Networking Group [1]. In March and April of 2022, the Steering Committee and Writing Committee were reestablished. They were comprised

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of medical oncologists, pathologists, and bioinformaticians convened by KSMO, KCSG, and KSP. Two main issues were addressed: the proper recommendations for NGS-based genetic testing in solid cancers, and the classification level determination of genes applicable in Korea. The committees initially conducted a survey to assess the appropriateness of key questions, achieving consensus through feedback from all committee members, to confirm the final selection of key questions. Subsequently, recommendations for these questions were drafted by the Steering Committee and further refined through extensive discussions with all committee members during a comprehensive workshop in September 2022. These modified recommendations were then finalized through a final survey in November 2022. Additionally, the Writing Committee classified actionable genes by cancer type using the Korean Precision Medicine Networking Group (KPMNG) scale for clinical actionability of molecular targets (Table 1). The references for determining the actionability of target genes include case series and clinical trials from all phases (phase I, II, III) published up to August 31, 2023. Studies that were part of basket trials were also considered for inclusion. Furthermore, significant abstracts from clinical trials presented at the American Society of Clinical Oncology Annual Meeting and the European Society for Medical Oncology (ESMO) Congress were incorporated. Subsequently, these gene lists, along with their corresponding references, were shared with disease-specific divisions within KCSG and KSP, where feedback and input from these committees were incorporated to further refine the rankings. The lists underwent one final review and confirmation by the entire committee. The finalized recommendations were presented at the 2023 KSMO annual meeting and announced at the 2023 KSP annual meeting. These recommendations have received endorsements from both KSMO and KSP.

Key Questions and Recommendations

1. Question 1. What are the appropriate recommendations for NGS-based genetic testing in solid cancers?

Recommendation 1. NGS-based genetic testing is recommended for patients with advanced or metastatic solid cancers who are eligible for systemic treatments.

There is mounting evidence that NGS-based matched treatments enhance outcomes in patients with advanced or metastatic cancers [2-6]. Even in tumor types like breast cancer, where the role of NGS has traditionally been less defined, a recent study has shown improved treatment outcomes when patients were matched to appropriate therapies through comprehensive genomic analysis, including NGS [7].

Genomic testing should be conducted in patients with advanced or metastatic solid cancers if there are approved treatments matching genomic biomarkers by a regulatory authority. For instance, several genetic tests, including those for *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *KRAS*, *ERBB2*, and *RET*, should be conducted in patients with non-squamous non–small cell lung cancer (NSCLC). In cases where multiple gene tests are required, NGS can efficiently utilize tumor tissue compared to testing individual genes. The National Comprehensive Cancer Network guideline for NSCLC also recommends panel-based genomic testing by NGS [8]. The use of a multi-gene panel by NGS is also recommended for tumors like ovarian cancer, prostate cancer, and pancreatic cancer. Testing for homologous recombination repair (HRR) related genes is required for these types of cancers to inform the use of poly(ADP-ribose) polymerase (PARP) inhibitors. Even for

Table 1. KPMNG scale of clinical actionability of molecular target (K-CAT) [1]

Level	Clinical implication	Required level of evidence
1	Treatment should be considered standard of care	MFDS, FDA, EMA or equivalent-approved drug OR Prospective, randomized, phase III trials showing the benefit of survival endpoints
2	Treatment would be considered	Prospective phase I/II trials show clinical benefit[a)]
3	Clinical trials to be discussed with patients	A: Retrospective study or case series show potential clinical benefit in a specific tumor type
		B: Clinical studies show potential clinical benefit in other indications
4	Preclinical data only, lack of clinical data	Preclinical evidence suggests the potential benefit
G	Suspicious germline variant on tumor tissue NGS	Suggestive actionable germline variant on tumor tissue testing
R	Predictive biomarker of resistance	FDA-recognized predictive biomarker of resistance

EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; K-CAT, KPMNG scale of Clinical Actionability of molecular Targets; KPMNG, Korean Precision Medicine Networking Group; MFDS, Ministry of Food and Drug Safety; NGS, next-generation sequencing. [a)]Prospective phase I/II trials supporting level 2 targets include clinical trials across tumor types such as basket trials. In this case, the clinical benefit needs to be judged by expert consensus.

patients with cancers in which actionable genetic alterations are rarely found, NGS is recommended, taking into account tumor-agnostic biomarkers. MSI-H/MMR-D, TMB-H, *BRAF* V600E, *RET* fusion, and *NTRK* fusions have been approved by the U.S. Food and Drug Administration (FDA) as tumor-agnostic biomarkers [9-20]. In Korea, matched treatments for tumors with MSI-H/MMR-D and *NTRK* fusions have been approved.

If a biomarker-matched treatment showing clinical benefit has not yet received regulatory approval, we strongly encourage patients to participate in clinical trials based on molecular profiles from NGS. Our goal is to provide maximum treatment options for individual patients with advanced or metastatic cancer. The probability of detecting actionable genetic alterations using NGS varies based on the cancer type [2]. Given that the potential benefits of NGS may vary among individuals, it is essential to discuss its aims and limitations with the patient. Furthermore, NGS is not recommended when systemic treatment is unfeasible due to factors including the patient's performance status, comorbidities, and socioeconomic conditions.

Recommendation 2. NGS-based genetic testing can be recommended for the pathological diagnosis of solid cancers.

Precise pathological diagnosis is a fundamental component of precision oncology and in predicting prognosis for patients with solid cancer. Notably, in the recently published classification of tumors by the World Health Organization (WHO), the diagnosis of tumors defined by genetic alterations is gradually expanding. Consequently, there are increasing cases in which a final pathological diagnosis is made based on NGS results. In addition, OncoKB [21], which is widely referred to in the interpretation of genetic alterations, provides information about diagnosis of hematologic malignancy by classifying the genetic alterations into 'Diagnostic' Level Dx1 (required for diagnosis), Dx2 (supports diagnosis), and Dx3 (investigational diagnosis). It is anticipated that this trend will soon be reflected in the diagnosis of solid cancers. We will briefly discuss the application of NGS in the diagnosis of bone and soft tissue sarcoma, renal cell carcinoma, and central nervous system tumors, using these as representatives.

1) Bone and soft tissue sarcomas

As more than half of soft tissue tumors and approximately a quarter of bone tumors harbor recurrent genetic alterations [22], molecular analysis is a strong diagnostic tool for the evaluation of bone and soft tissue sarcomas. There are several advantages of using NGS: simultaneous examination of multiple genomic regions, low-level tumor sample requirement and intuitive visualization of results [23]. NGS panels designed for sarcoma diagnosis utilize primers for the detection of fusions, amplifications, deletions and point mutations, which broadly cover genetic alterations in various sarcoma types. In daily practice, pathologists often encounter cases in which NGS provides the precise diagnosis by confirming or excluding differential diagnoses. Some cases can be even diagnosed toward unsuspected entities on the microscopic examination after NGS analysis [24].

NGS analysis may be applied for differential diagnosis of bone and soft tissue sarcomas as follows: (1) low-grade central osteosarcoma (*MDM2*) vs. fibrous dysplasia (*GNAS*); (2) chondroblastic osteosarcoma (chromosomal instability) vs. chondrosarcoma (*IDH1/2*); (3) malignant peripheral nerve sheath tumor (*CDKN2A*) vs. atypical neurofibroma; (4) liposarcoma (*MDM2*) vs. atypical pleomorphic lipomatous tumor (*RB1*); (5) alveolar rhabdomyosarcoma (*PAX3/7::FOXO1*) vs. embryonal rhabdomyosarcoma (mutations in *RAS-MAPK* pathway); (6) tumors of uncertain differentiation (Ewing sarcoma, round cell sarcoma with *EWSR1*-non-ETS fusions, *CIC*-rearranged sarcoma, sarcoma with *BCOR* genetic alterations, synovial sarcoma, alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma, clear cell sarcoma of soft tissue, etc.).

2) Renal cell carcinoma

NGS-based genetic panel test can be recommended for the pathological diagnosis of molecularly defined renal cell carcinoma (RCC), which includes fumarate hydratase (*FH*)–deficient RCC, succinate dehydrogenase (SDH)–deficient RCC, *TFE3*-rearranged RCC, *TFEB*-rearranged or *TFEB*-amplified RCC, *ELOC* (formerly *TCEB1*)-mutated RCC, *SMARCB1* (INI1)-deficient RCC, and *ALK*-rearranged RCC according to the recent 2022 WHO classification [25]. The molecular alterations of these renal tumors are as follows: biallelic *FH* mutation/inactivation in *FH*-deficient RCC; inactivating mutations of one of SDH genes, most commonly *SDHB*, followed by *SDHA* and *SDHC*, and rarely *SDHD* in SDH-deficient RCC; translocations involving *TFE3* in *TFE3*-rearranged RCC; translocations involving *TFEB* in *TFEB*-rearranged RCC; *TFEB* amplification in *TFEB*-amplified RCC; inactivating mutations exclusively at *TCEB1* Y79 in *ELOC* (formerly *TCEB1*)-mutated RCC; translocations or deletions involving 22q11.23 in *SMARCB1* (INI1)-deficient RCC; translocations involving *ALK* in *ALK*-rearranged RCC. In addition, NGS-based genetic panel test may also be recommended for morphologically defined renal tumors with characteristic molecular alteration. Clear cell RCC is characterized by the loss of chromosome 3p accompanied by the inactivation mutation or methylation of the remaining *VHL* gene. Papillary RCC commonly shows gains of chromosomes 7 and 17, and loss of the Y chromosome with *MET*

alterations in the low-grade tumor. Chromophobe RCC has losses of multiple chromosomes including 1, 2, 6, 10, 13, 17, 21, and Y. Eosinophilic solid and cystic RCC can show *TSC* gene mutations or biallelic losses.

3) Central nervous system tumor

With the development of research techniques such as NGS, our understanding of the molecular and clinicopathological characteristics of brain tumors has advanced greatly. Based on these changes, following the 2016 Central Nervous System (CNS) WHO classification revised 4th edition [26] and cIMPACT-NOW [27], the 2021 CNS WHO classification 5th edition [28] fully included the molecular genetic characteristics of tumors in the WHO classification of brain tumors. In the 2021 CNS WHO classification, several molecular genetic characteristics such as gliomas, glioneuronal tumors, ependymomas, embryonic tumors (medulloblastoma, etc.), and meningiomas were introduced into the diagnostic criteria. Molecular genetic characteristics included in the diagnostic criteria range from those that can be identified with a single test (sequencing, fluorescence in situ hybridization, etc.) to those that require integrated identification of various genes involved in a specific pathway, as well as those that identify chromosomal arm-level copy number alterations. To cover all of these, NGS testing is essential. In addition, these molecular classifications determine the diagnosis of the tumor and further determine the WHO grade, which is a basic brain tumor grading system that determines the treatment strategy. The use of traditional histopathological morphological classification alone without NGS testing can mislead patients' treatment strategies.

Recommendation 3. NGS-based genetic testing can be repeated in patients with solid cancer in case of disease recurrence or development of drug resistance.

Acquired resistance inevitably occurs with the growing use of targeted agents targeting various driver oncogenes. Representatively, we have seen the successful development of osimertinib, the third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) during the last decade [29]. At the time of drug development, osimertinib was developed for the patients who revealed the acquired *EGFR* threonine to methionine at codon 790 (T790M) mutation at the time of treatment failure with first- or second-generation EGFR TKI [30]. Therefore, the detection of *EGFR* T790M has been crucial for making treatment decisions in patients who experienced treatment failure with first- or second-generation EGFR TKIs [8]. Apart from *EGFR* T790M, other types of acquired resistance mechanisms were revealed by NGS, such as *ERBB2* amplification or *MET* amplification [31]. Given the recent memorial imprint of resistance mechanism discovery, we have started using repeated NGS to detect acquired resistance in on-treatment tumor tissue, as well as in liquid biopsy samples.

Generally, acquired resistance can be classified into two categories: (1) target-dependent, such as target gene mutations, and (2) target-independent, such as gene aberrations in bypass pathways [32]. Beyond the *EGFR* T790M mutation, the *EGFR* C797S mutation is one of the most common *EGFR*-dependent resistance mechanisms against osimertinib [33]. *MET* amplification is another type of bypass pathway resistance mechanism across oncogene-driven subsets of NSCLC [34]. The *EML4::ALK* fusion, occurring in 3%-7% of all NSCLC cases, is currently treated with alectinib or brigatinib, the second-generation ALK TKIs, which are the standard treatments for treatment-naïve ALK-positive NSCLC patients [35-37]. *ALK* G1202R, solvent front mutation affecting drug binding to active site, is the most common target-dependent mutation [38]. Detecting the *ALK* G1202R mutation through NGS enables the prediction of a notable response with subsequent lorlatinib. *NTRK* fusion is a tumor agonistic driver oncogene, detected in less than 1% of solid cancers. With introduction of larotrectinib and entrectinib in clinic, several target-dependent point mutations were noted, which can be found by NGS [19,20]. Repotrectinib (TPX-0005) has demonstrated anti-tumor efficacy in patients previously treated with NTRK-targeting TKIs and who harbor target-dependent *TRK* mutations [39].

Since the 2000s, the clinical use of NGS has expanded beyond the detection of driver oncogenes. It has paved the way for the discovery of novel targets associated with acquired resistance and provided valuable insights into potential targets for the next generation of targeted therapeutics. However, it's important to acknowledge certain limitations associated with the repetition of NGS testing. Challenges include the increased cost, difficulties in obtaining repeated tumor biopsies, and associated risks. Additionally, the likelihood of identifying actionable targets at the point of resistance can vary depending on the specific cancer type and drugs, with potential restrictions in drug availability. Nonetheless, it remains evident that NGS can play a crucial role in helping inform subsequent treatment decisions for certain patients who have experienced treatment failure with targeted therapy.

2. Question 2. How can we determine the classification level of genes applicable in Korea?

Advancements in NGS technologies have facilitated the identification of driver mutations in cancer, prompting a shift from a histology-based to a molecular-based approach in cancer treatment. Simultaneously, the advent of targeted therapies has allowed for treatments based on genetic altera-

Table 2. List of genetic alterations with tumor agnostic indications by FDA

Gene/Alteration	Matched treatment	K-CAT	Reference
NTRK fusion	Entrectinib Larotrectinib	1	[19,20]
BRAF V600E	Dabrafenib+trametinib (except colorectal cancer)	1	[11-17]
RET fusion	Selpercatinib	1	[18]
Microsatellite instability–high/Mismatch repair deficiency	Pembrolizumab	1	[9,40]
High tumor mutation burden	Pembrolizumab	1	[10]

FDA, U.S. Food and Drug Administration; K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets.

Table 3. List of genomic alterations level 1/2/3A according to K-CAT in advanced NSCLC

Gene	Alteration	Prevalence (%)	K-CAT	Reference
EGFR	Exon 19 in-frame deletions, L858R, G719X, L861Q, S761I	30-46	1	[41-45]
	T790M	50 of treated *EGFR* mutant NSCLC	1, R	[29,46,47]
	Exon 20 in-frame insertion	3	1	[48,49]
BRAF	V600E	2-4	1	[12,13,50]
ALK	Rearrangement/Fusions	3-5	1	[36,37,51,52]
KRAS	G12C	13	1	[53,54]
MET	Exon 14 in-frame deletions, Exon 14 splice mutations	3-4	1	[55,56]
	Amplification	3-5	2	[56]
RET	Rearrangement/Fusions	1.7	1	[57,58]
ROS1	Rearrangement/Fusions	2.6	1	[59,60]
ERBB2	Exon 20 in-frame insertion	2.3	1	[61-64]
	Amplification	2.4-38	2	[65,66]

K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets; NSCLC, non–small cell lung cancer.

tions irrespective of the tumor's origin. This concept, known as tissue-agnostic indication, has demonstrated promising results in recent studies and has become a crucial element in the standard care for cancer. Currently, the tissue-agnostic indications approved by the FDA are listed in Table 2 [9-20, 40].

Taking into account both the evidence level of clinical research and clinical benefit, the committee members classified actionable genes for each type of cancer based on their level using KPMNG scale of Clinical Actionability of molecular Targets (K-CAT). We also included certain genes, such as *POLE* in endometrial cancer, that are clinically significant and thus necessitate testing. The actionable gene lists for NSCLC, breast cancer, esophageal cancer, stomach cancer, colorectal cancer, head and neck cancer, pancreatic cancer, biliary tract cancer, endometrial cancer, urothelial cancer, and kidney cancer are provided in Tables 3-17 [11-15,29,36,37,41-190]. Each table included genes corresponding to levels 1 through 3A.

3. Additional topics

1) Homologous recombination deficiency

Genomic instability is one of the most frequent underlying features of carcinogenesis, and defective DNA repair has been described as a cancer hallmark [191]. HRR is a series of interrelated pathways that function in the repair of DNA double-strand breaks and interstrand crosslinks [192]. Important genes involved in the HRR process include *BRCA1*, *BRCA2*, *RAD51*, *RAD51C*, *RAD51D*, *ATM*, *ATR*, *PALB2*, *MRE11*, *NBS1*, *BARD1*, *CHEK1*, and *CHEK2* [193,194]. However, it is essential to note that the list of genes known to be related to the HRR process is continually evolving through ongoing research. A defect in the HRR pathway has been linked to several cancers, including breast, ovarian, prostate

Table 4. List of genomic alterations level 1/2/3A according to K-CAT in advanced breast cancer

Gene	Alteration	Prevalence (%)	K-CAT	Reference
ERBB2	Amplifications	15-20	1	[67-71]
	Oncogenic mutations	4	2	[72,73]
PIK3CA[a)]	Oncogenic mutations	30-40	1	[74,75]
BRCA1/2	Germline oncogenic mutations	4	1	[76,77]
BRCA1/2[b)]	Somatic oncogenic mutations[c)]	3	2	[78-80]
PTEN	Oncogenic mutations	7	2	[81,82]
ESR1	Oncogenic mutations (mechanism of resistance)	10	R	[83]
AKT1	E17K	5	2	[82,84]
PALB2[d)]	Germline oncogenic mutations	0.5-1	2	[79,85]

HRD, homologous recombination deficiency; K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets; PARP, poly(adenosine diphosphate [ADP]–ribose) polymerase. [a)]This applies only to breast cancer that is hormone receptor-positive/HER2-negative and has mutations including E542K, E545A, H1047R, H1047Y, Q546E, H1047L, Q546R, E545G, E545D, E545K, C420R. Other oncogenic mutations not included in this category, caution is needed, since it is unknown whether other mutations are associated with response to phosphoinositide 3-kinase inhibitor therapy, [b)]Phase III trials of PARP inhibitors have been conducted in patients with germline *BRCA* mutations, and their therapeutic effects have been confirmed. In some studies, the effects of PARP inhibitors have also been reported in patients with somatic *BRCA* mutations, and somatic tumor sequencing can identify many germline *BRCA* mutations, [c)]In addition to *BRCA 1/2*, there are several other genes associated with homologous recombination deficiency, including *ATRX*, *BLM*, *BRIP1*, *CHEK2*, *FANCA/C/D2/E/F/G/L*, *MRE11A*, *NBN*, *PALB2*, and *RAD50*. Although the discovery frequency of each gene is very low, they are collectively found in approximately 8% of all breast cancers, [d)]There are multiple germline mutations associated with HRD in breast cancer patients, but this table only includes the two most frequent ones.

Table 5. List of genomic alterations level 1/2/3A according to K-CAT in advanced esophageal cancer

Gene	Alteration	Prevalence (%)	K-CAT	Reference
ERBB2	Amplification	3.9-10	2	[86]

K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets.

Table 6. List of genomic alterations level 1/2/3A according to K-CAT in advanced stomach cancer

Gene	Alteration	Prevalence (%)	K-CAT	Reference
ERBB2	Amplification	15	1	[87-89]
FGFR2[a)]	Amplification	5	2	[90]
MET	Amplification	2-5	2	[91]
EGFR	Amplification	5-10	3A	[92]

ctDNA, circulating tumor DNA; K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets.
[a)]FGFR2b overexpression or *FGFR2* amplification by ctDNA analysis.

and pancreatic cancer [117,142,153,195], and HRD can make tumors more sensitive to platinum-based chemotherapy and PARP inhibitors [196,197]. Thus, it is critical to develop methods for determining the HRD status in order to maximize clinical benefit from these drugs.

There are three main categories of available tests for HRD analyzing (1) the etiology of HRD (mutation/methylation sequencing), (2) the current homologous recombination status (functional assays), and (3) prior HRD exposure (genomic scars). Each type of cancer (ovarian, breast, pancreatic and prostate) requires different tests. The germline *BRCA* 1/2 mutation test is useful for predicting response to PARP inhibitors in ovarian and breast cancer [76,143-146,198]. In ovarian cancer, tumor (incorporating germline and somatic) as well as somatic *BRCA* 1/2 mutation testing exhibit good clinical validity by reliably identifying the subset of patients who benefit from PARP inhibitor therapy [146-148]. Evidence regarding the benefit of mutation tests for each non-

Table 7. List of genomic alterations level 1/2/3A according to K-CAT in advanced colorectal cancer

Gene	Alteration	Prevalence (%)	K-CAT	Reference
KRAS	Oncogenic mutations	40	R	[93,94]
NRAS	Oncogenic mutations	3-5	R	[95,96]
BRAF	V600E	5-10	1	[96-98]
Mismatch repair deficiency	MSI-H/MMR-D	4-5	1	[99,100]
ERBB2	Amplification	4-5	1	[101]
KRAS	G12C	3	2	[102,103]
POLE	Exonuclease domain mutations	1-3	2	[104-106]

K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets; MSI-H, microsatellite instability–high; MMR-D, mismatch repair deficiency.

Table 8. List of genomic alterations level 1/2/3A according to K-CAT in advanced head and neck cancer

Gene	Alteration	Prevalence (%)[a]	K-CAT	Reference
NOTCH1, 2, 3	Oncogenic mutations	10-12	2	[107,108]
ERRB2	Amplification	30-40	2	[109-111]
FGFR1, 3	Amplification/Oncogenic mutations	1-7	2	[112-114]
MET	Amplification	1	3A	[115,116]

K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets. [a]The above prevalence is about the representative subtype among various subtypes of head and neck cancer.

Table 9. List of genomic alterations level 1/2/3A according to K-CAT in advanced pancreatic cancer

Gene	Alteration	Prevalence (%)	K-CAT	Reference
BRCA 1/2	Germline oncogenic mutations	1-4	1	[117,118]
PALB2	Oncogenic mutations	0.6	2	[118]
KRAS	G12C	2-3	2	[119,120]
PIK3CA	Oncogenic mutations	3	3A	[121]
ERBB2	Amplifications/Oncogenic mutations	1-2	3A	[72,122]
ALK	Rearrangement/Fusions	< 1	3A	[123]
NRG1	Rearrangement/Fusions	1	3A	[124]
ROS1	Rearrangement/Fusions	< 1	3A	[125]

K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets.

Table 10. List of genomic alterations level 1/2/3A according to K-CAT in advanced biliary tract cancer

Gene	Alteration	Prevalence (%)	K-CAT	Reference
IDH1	Oncogenic mutations	10-23	1	[126,127]
FGFR2	Rearrangement/Fusions	8-14	1	[128-130]
BRAF	V600E	5	1	[14,15]
ERBB2	Amplification	10	2	[131-133]

K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets.

Table 11. List of genomic alterations level 1/2/3A according to K-CAT in advanced endometrial cancer

Gene	Alteration	Prevalence (%)	K-CAT	Reference
ERBB2	Amplification	30 of uterine serous carcinoma	2	[134]
AKT1	E17K	2	2	[84]
POLE[a]	Oncogenic mutations	5-15	NA	[135,136]
TP53[a),b)]	Oncogenic mutations	5-15	NA	[135]

IHC, immunohistochemistry; K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets; MMR, mismatch repair; NGS, next-generation sequencing; TCGA, The Cancer Genome Atlas. [a]Adjuvant treatment of endometrial cancer based on molecular classification, [b]Considering the coverage limitations of NGS for detecting p53 loss, a combined IHC approach is recommended. The TCGA approach results in the molecular stratification of endometrial cancer (EC) into four distinct molecular groups [137]; (1) ultramutated [> 100 mut/Mb)] with pathogenic variations in the exonuclease domain of DNA polymerase epsilon (*POLE*)-ultramutated (*POLE*mut), (2) hypermutated (10-100 mut/Mb), microsatellite-unstable, (3) somatic copy number-high with frequent pathogenic variants in TP53, and (4) an MMR-proficient, low somatic copy number aberration subgroup with a low mutational burden. Extensive research on these surrogate markers has revealed a strong correlation with clinical outcome, thus proving their prognostic value [138-140]. *POLE*mut EC had generally has an excellent clinical outcome, while p53-abn EC has the worst, regardless of risk category, type of adjuvant treatment, tumor type, or grade. Adjuvant chemotherapy is beneficial in for patients with p53mut EC, while treatment de-escalation is being explored in patients with *POLE*mut EC [139], which exhibits a favorable outcome [141]. Consequently, all EC pathology specimens should undergo molecular classification, independent of histological type, using well-established IHC staining for p53 and MMR proteins (MLH1, PMS2, MSH2, MSH6), in conjunction with targeted tumor sequencing (*POLE* hotspot analysis). While *POLE* hotspot analysis is currently unavailable in Korea, and most NGS panels include the *POLE* gene, it has been incorporated into the recommendations. Moreover, since IHC plays a well-established role in identifying p53 mutations and NGS target sequencing of *TP53* is insufficient to identify all loss of P53 function, IHC confirmation of p53 is recommended over NGS testing as a priority.

Table 12. List of genomic alterations level 1/2/3A according to K-CAT in advanced ovarian cancer

Gene	Alteration	Prevalence (%)	K-CAT	Reference
BRCA 1/2	Oncogenic mutations	5-15	1	[142-149]
HRD score	GIS, LOH	50	1	[142-144,146,148]
AKT1	E17K	2	2	[84]

GIS, genomic instability scores; HRD, homologous recombination deficiency; K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets; LOH, loss of heterozygosity.

Table 13. List of genomic alterations level 1/2/3A according to K-CAT in advanced urothelial cancer

Gene	Alteration	Prevalence (%)	K-CAT	Reference
FGFR3	Oncogenic mutations Rearrangement/Fusions	13-15	1	[150]
FGFR2	Rearrangement/Fusions	Unknown	1	[150]
ERCC2	Oncogenic mutations	9-12	3A	[151,152]

K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets.

BRCA HRR gene for predicting responses to PARP inhibitors remains insufficient in ovarian cancer. HRD tests using genomic instability scores (GIS) or loss of heterozygosity (LOH) scores are useful for predicting the responses to PARP inhibitors in ovarian cancer patients without *BRCA* 1/2 mutation [142,144,146]. The GIS from myChoice CDx (Myriad Genetics) represents the sum of LOH, large-scale transitions, and telomeric allelic imbalance and a GIS of 42 has been established as the threshold to determine HRD positivity [199,200]. To date, GIS is the only genomic scar assay that has been evaluated in first-line randomized controlled trials for ovarian cancer [142,143]. The LOH test (FoundationOne CDx, Foundation Medicine) uses NGS to determine the percentage of genomic LOH and LOH-high is defined with a cut-off of 16% or higher, referencing The Cancer Genome Atlas data [201]. In metastatic pancreatic cancer, a germline *BRCA*

Table 14. List of genomic alterations level 1/2/3A according to K-CAT in advanced prostate cancer

Gene	Alteration	Prevalence (%)	K-CAT	Reference
BRCA2	Germline and/or somatic oncogenic mutations	3-13	1	[153,154]
BRCA1	Germline and/or somatic oncogenic mutations	1	1	[153,154]
ATM	Oncogenic mutations	6-7	1	[153,154]
BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L	Oncogenic mutations	< 1-5	1	[153,154]

K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets.

Table 15. List of genomic alterations level 1/2/3A according to K-CAT in advanced kidney cancer

Gene	Alteration	Prevalence (%)	K-CAT	Reference
VHL	Germline oncogenic mutations	0.2	1	[155]
FH	Germline oncogenic mutations	0.5	3A	[156,157]
ALK	Rearrangement/Fusions	0.3-0.5	3A	[158]

K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets.

Table 16. List of genomic alterations level 1/2/3A according to K-CAT in advanced melanoma

Gene	Alteration	Prevalence (%)	K-CAT	Reference
BRAF	V600E/K	35-50	1	[11,159-162]
	V600 (excluding V600E/K)	~5	1	[163]
KIT	D579del and 12 other oncogenic mutations	1-7	2	[164,165]
NRAS	Oncogenic mutations	~20	2	[166,167]
BRAF	Rearrangement/Fusions	3-7	3A	[168,169]
	K601, L597	< 1	3A	[170-173]

K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets.

1/2 mutation test is recommended to evaluate the potential benefits of PARP inhibitors as maintenance treatment for patients whose tumors have not progressed after first-line platinum-based chemotherapy [117]. In castration-resistant prostate cancer, it is recommended to assess by sequencing for *BRCA* 1/2 mutations, at a minimum, using germline and/or somatic tumor DNA [153,202]. To date, insufficient evidence is available regarding the benefit of performing a HRD functional assays to predict response to PARP inhibitor; however, the potential for using functional assays in conjunction with HRR gene tests and genomic tests should be evaluated. While there have been multiple NGS assays to evaluate HRD status, only a limited number of tests are clinically accepted, and their technical details including evaluation criteria are unclear. Many methodological approaches have been proposed to measure HRD status using NGS data of various types, including whole genome sequencing (WGS), whole exome sequencing (WES) and targeted sequencing [203,204]. However, the absence of congruent measure remains a challenge to validate their reliability and consistency. Although WGS has not yet been approved for the diagnosis of HRD, it might become a promising diagnostic tool for HRD in the near future.

2) Microsatellite instability-high/mismatch repair deficiency

MSI-H/MMR-D has become an important biomarker of eligibility for immune checkpoint inhibitor (ICI) therapy as

Table 17. List of genomic alterations level 1/2/3A according to K-CAT in advanced sarcoma

Gene	Alteration	Prevalence (%)	K-CAT	Reference
KIT	Oncogenic mutations	~75-80 in GIST	1	[174,175]
PDGFRA	Oncogenic mutations	~8-10 in GIST	1	[175-177]
PDGFB	Rearrangement/Fusions mostly *COL1A1::PDGFB*	~90 in DFSP	1	[178-179]
ALK	Rearrangement/Fusions	~50 in IMT	1	[180-182]
SMARCB1	Deletion	~83 in ES	2	[183]
IDH1	Oncogenic mutations	~65 in chondrosarcoma	2	[184]
TSC2	Oncogenic mutations	~30 in PEComa	2	[185,186]
MDM2	Amplification	~90 in WDLPS/DDLPS; frequent in IS, low grade OSA	2	[187,188]
CDK4	Amplification	~90 in WDLPS/DDLPS; frequent in IS, low grade OSA	2	[187,189]
MET	Oncogenic mutations, Rearrangement/Fusions, Amplification	< 1	2	[190]

DFSP, dermatofibrosarcoma protuberans; ES, epithelioid sarcoma; GIST, gastrointestinal stromal tumor; IMT, inflammatory myofibroblastic tumor; IS, intimal sarcoma; K-CAT, Korean Precision Medicine Networking Group scale of Clinical Actionability of molecular Targets; OSA, osteosarcoma; WDLPS/DDLPS, well-differentiated/de-differentiated liposarcoma.

the FDA has approved ICIs for patients with unresectable or metastatic MSI-H/MMR-D solid cancers regardless of tumor types [9,40,205]. The polymerase chain reaction (PCR)–based assessment of selected microsatellite loci in a patient's tumor and matched non-neoplastic tissue had been accepted as the gold standard method before the era of NGS. Nevertheless, the PCR-based MSI test can be misleading in certain cases because the selected microsatellite loci (typically, 5 to 8 loci) may not cover all affected microsatellite regions [206]. Alternatively, MMR-D can be inferred through immunohistochemistry (IHC) of MMR proteins, such as MLH1, MSH2, MSH6, and PMS2, since most MMR-deficient tumors exhibit a loss of MMR protein expression. However, there are limitations to detecting MMR-D by the IHC method. Certain tumors harboring pathogenic missense or in-frame insertion/deletion mutations of MMR genes may still show intact MMR protein expressions, and interpretation errors may occur when the staining quality is poor.

Since NGS is now widely used in clinical practice, it has been investigated whether NGS can be used to detect MSI-H/MMR-D in clinical setting. Numerous validation studies have demonstrated that NGS can accurately detect pathogenic or likely pathogenic mutations affecting MMR genes and can determine MMR-D reliably. Thus, there is a consensus that NGS can replace the standard PCR-based MSI test. NGS can detect MSI-H/MMR-D in various ways [207]. Several computational tools for detection of MSI-H/MMR-D using NGS data are available: mSINGS [208], MSIsensor [209], MANTIS [210], and MOSAIC [211]. Furthermore, NGS can detect MSI-H/MMR-D even in the absence of the patient's matched normal tissue [212,213]. Furthermore, pathogenic or likely pathogenic MMR gene mutations detected by NGS testing may select candidates of germline genetic testing for Lynch syndrome. Finally, NGS-based MSI-H/MMR-D testing may provide information about eligibility for immunotherapy in tumor types where MMR IHC and/or PCR-based MSI tests have not been done during routine clinical practice.

3) Analysis of TMB by NGS panel

ICIs can enhance a durable anti-tumor immune response and prolong overall survival [214]. However, only a subset of the patients showed a dramatic response to immunotherapy, and the identification of predictive biomarkers was essential to identify responders to immunotherapy, such as programmed death-ligand 1 expression, MSI-H/MMR-D and TMB-H [215-217]. TMB is defined as the number of somatic mutations (mut) per megabase (Mb) of genomic sequence [217]. TMB is a surrogate marker for making immunogenic neopeptides shown on the surface of tumor cells by major histocompatibility complexes, which affect the anti-tumor immune response to ICIs [218,219].

In June 2020, the FDA authorized pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic TMB-H (≥ 10 mut/Mb) solid tumors, as determined by FoundationOneCDx assay, that have progressed following prior treatment and who have no satisfactory alternative treatment options [220]. Therefore, determining the TMB value and identifying TMB-H tumors are among

the most critical aspects in the clinical NGS analysis.

Although the TMB calculation can vary according to the test assays, the gold standard method for TMB estimation is WES with tumor tissues and matched normal samples. However, since WES has limitations in terms of time and costs to apply in clinical use, analytic methods and algorithms have been developed for calculating TMB from clinical targeted NGS panel tests [221,222]. Targeted NGS panel tests usually cover only a small limited size (about 1 to 2 Mb) of exonic regions, so sophisticated bioinformatic algorithms and statistical methods must be applied to filter out noise variants and artifacts caused by formalin-fixed tissues. For tumor-only sequencing, which is currently conducted in most targeted gene panels in Korea, germline variants are filtered out using genomic information from public databases or data on allele frequency in normal populations to avoid TMB overestimation. In several studies, the evaluated TMB from targeted NGS panel testing showed a high correlation with the TMB calculated by WES using analytic techniques [221,222].

Since the targeted gene panels currently used in the clinic have different analysis pipelines for variant calling and apply various filtering criteria to select variants used in TMB calculation, TMB values vary among the tests, and the criteria for TMB-H are diverse [223]. Also, the distribution of TMB values and criteria for TMB-H are different by tumor type, even when calculating TMB with the same panel. In general, more than TMB of 10 mut/Mb has been used for the definition of TMB-H tumors, but the reliable value of TMB-H can be different among the test panels and requires caution in interpreting the estimated TMB value. In some studies, the TMB of 17-20 mut/Mb is considered TMB-H and a candidate for immunotherapy conservatively [224]. Therefore, standardization of TMB analysis among test panels, validation of TMB-H tumors with different assays, and establishing reliable criteria for TMB-H will be needed for the further precise application of TMB analysis with the clinical tumor NGS panels.

4) Clinical utility and limitations of ctDNA-based genetic panel tests using blood sample

As the growing number of druggable oncogenic drivers has been identified in solid cancer [225], ctDNA-based approach can be used as an alternative approach for facilitating the identification of tumor tissue genotype. However, ctDNA can be influenced by multiple preanalytical factors and the methodology of analysis [226]. Since the ctDNA detection rate is highly related to tumor burden and is affected by various factors such as plasma levels of ctDNA, assay sensitivity, and tumor biology, a negative result from the ctDNA test may not necessarily indicate a true negative. In particular, low analytical sensitivity may occur because ctDNA assay are performed solely on DNA derived from tumor cells [227]. Recent studies have reported that gene fusions and splice variants have higher detection rates when sequencing is performed with RNA transcripts [228,229]. In addition, in the case of copy number variations (CNVs), determining the presence of CNVs remains challenging due to its dependence on ctDNA fractions [230,231]. Hence, ctDNA-based test reports should include essential elements, including pre-analytical elements, sequencing results, potential factors related to the germline variants, and limitations of assays to assist the interpretation of the report to the clinician [232].

ctDNA-based genotyping can be used as either complementary to tissue genotyping or as the first choice in certain circumstances. ctDNA-based genotyping has advantages over tissue-based genotyping in a short turnaround time, invasiveness, and feasibility in serial assessment [233-235]. Due to the limitation of tissue-based genotyping, which can be affected by tissue accessibility or tumor purity, ctDNA-based genotyping can be conducted as initial genotyping in the rapidly growing aggressive tumor when challenges or delays in sample acquisition are anticipated. In addition, the ctDNA-based genotyping first approach can be preferred for the evaluation of emerged resistance mechanism [236]. ctDNA-based genotyping can also be used as a complementary method, either concurrently or sequentially with tissue-based genotyping in case of incomplete tumor genotyping or foreseen inadequate results due to uncertain adequacy of tissue [237].

Before genotyping ctDNA sequences, the concentration of cell-free DNA in plasma can be used as a prognostic biomarker [238,239]. The sensitivity of ctDNA assay varies among the primary sites and tumor types and should be considered at applying ctDNA test in clinical use [240]. Similarly, the metastatic site of the tumor affects the ctDNA detection and should be taken into account for using ctDNA assay [241]. Additionally, MSI-H/MMR-D and TMB-H, as determined by ctDNA assay, have been widely studied [242-244]. Improving the accuracy of the MSI detection and TMB calculation from ctDNA and defining reliable criteria for MSI-H/MMR-D and TMB-H in the ctDNA assay is anticipated to broaden the use of ctDNA tests.

Conclusion

NGS-based genetic testing has become an essential tool in treating patients with advanced solid cancers. This report provides clinical recommendations for the application of NGS in such patients, offering expert opinions on its diagnostic uses, and gene classification in accordance with K-CAT, while taking the domestic Korean context into consideration.

As cancer genomics advances and new therapies emerge, the current gene classification is subject to dynamic changes, and the application of NGS is anticipated to continuously evolve. Consequently, healthcare providers and researchers are encouraged to stay abreast of the latest advancements in the field of precision oncology to ensure optimal patient care and further cancer research.

Author Contributions

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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References

1. Yoon S, Kim M, Hong YS, Kim HS, Kim ST, Kim J, et al. Recommendations for the use of next-generation sequencing and the molecular tumor board for patients with advanced cancer: a report from KSMO and KCSG Precision Medicine Networking Group. Cancer Res Treat. 2022;54:1-9.
2. Zehir A, Benayed R, Shah RH, Syed A, Middha S, Kim HR, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med. 2017;23:703-13.
3. Tsimberidou AM, Hong DS, Ye Y, Cartwright C, Wheler JJ, Falchook GS, et al. Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT): an MD Anderson precision medicine study. JCO Precis Oncol. 2017;2017:PO.17.00002.
4. Massard C, Michiels S, Ferte C, Le Deley MC, Lacroix L, Hollebecque A, 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.
5. Cousin S, Grellety T, Toulmonde M, Auzanneau C, Khalifa E, Laizet Y, et al. Clinical impact of extensive molecular profiling in advanced cancer patients. J Hematol Oncol. 2017;10:45.
6. Tsimberidou AM, Wen S, Hong DS, Wheler JJ, Falchook GS, Fu S, 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.
7. Andre F, Filleron T, Kamal M, Mosele F, Arnedos M, Dalenc F, et al. Genomics to select treatment for patients with metastatic breast cancer. Nature. 2022;610:343-8.
8. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. Non-small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2022;20:497-530.
9. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol. 2020;38:1-10.
10. Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020;21:1353-65.
11. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372:30-9.
12. Planchard D, Besse B, Groen HJ, Souquet PJ, Quoix E, Baik CS, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol. 2016;17:984-93.
13. Planchard D, Smit EF, Groen HJ, Mazieres J, Besse B, Helland A, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol. 2017;18:1307-16.
14. Subbiah V, Lassen U, Elez E, Italiano A, Curigliano G, Javle M, et al. Dabrafenib plus trametinib in patients with BRAF(V600E)-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. Lancet Oncol. 2020;21:1234-43.
15. Salama AK, Li S, Macrae ER, Park JI, Mitchell EP, Zwiebel JA, et al. Dabrafenib and trametinib in patients with tumors with BRAF(V600E) mutations: results of the NCI-MATCH trial subprotocol H. J Clin Oncol. 2020;38:3895-904.
16. Wen PY, Stein A, van den Bent M, De Greve J, Wick A, de Vos F, et al. Dabrafenib plus trametinib in patients with BRAF(V600E)-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. Lancet Oncol. 2022;23:53-64.
17. Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JHM, Soria JC, et al. Dabrafenib plus trametinib in patients with BRAF V600E-mutant anaplastic thyroid cancer: updated analysis from the phase II ROAR basket study. Ann Oncol. 2022;33:406-15.
18. Subbiah V, Wolf J, Konda B, Kang H, Spira A, Weiss J, 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.
19. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378:731-9.
20. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020;21:271-82.
21. Chakravarty D, Gao J, Phillips SM, Kundra R, Zhang H, Wang J, et al. OncoKB: a precision oncology knowledge base. JCO Precis Oncol. 2017;2017:PO.17.00011.
22. McConnell L, Houghton O, Stewart P, Gazdova J, Srivastava S, Kim C, et al. A novel next generation sequencing approach to improve sarcoma diagnosis. Mod Pathol. 2020;33:1350-9.
23. Szurian K, Kashofer K, Liegl-Atzwanger B. Role of next-generation sequencing as a diagnostic tool for the evaluation of bone and soft-tissue tumors. Pathobiology. 2017;84:323-38.
24. Gounder MM, Agaram NP, Trabucco SE, Robinson V, Ferraro RA, Millis SZ, et al. Clinical genomic profiling in the management of patients with soft tissue and bone sarcoma. Nat Commun. 2022;13:3406.
25. Moch H, Amin MB, Berney DM, Comperat EM, Gill AJ, Hartmann A, et al. The 2022 World Health Organization classification of tumours of the urinary system and male genital organs-part A: renal, penile, and testicular tumours. Eur Urol. 2022;82:458-68.
26. Louis DN, Perry A, Reifenberger G, von Deimling A, Fig-

arella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131:803-20.
27. Louis DN, Aldape K, Brat DJ, Capper D, Ellison DW, Hawkins C, et al. Announcing cIMPACT-NOW: the consortium to inform molecular and practical approaches to CNS tumor taxonomy. Acta Neuropathol. 2017;133:1-3.
28. WHO classification of tumours of the central nervous system tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2021.
29. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. 2017;376:629-40.
30. Janne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med. 2015;372:1689-99.
31. Westover D, Zugazagoitia J, Cho BC, Lovly CM, Paz-Ares L. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. Ann Oncol. 2018; 29:i10-9.
32. Wang Z, Xing Y, Li B, Li X, Liu B, Wang Y. Molecular pathways, resistance mechanisms and targeted interventions in non-small-cell lung cancer. Mol Biomed. 2022;3:42.
33. He J, Zhou Z, Sun X, Yang Z, Zheng P, Xu S, et al. The new opportunities in medicinal chemistry of fourth-generation EGFR inhibitors to overcome C797S mutation. Eur J Med Chem. 2021;210:112995.
34. Coleman N, Hong L, Zhang J, Heymach J, Hong D, Le X. Beyond epidermal growth factor receptor: MET amplification as a general resistance driver to targeted therapy in oncogene-driven non-small-cell lung cancer. ESMO Open. 2021;6:100319.
35. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. 2007; 448:561-6.
36. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2017;377:829-38.
37. Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N Engl J Med. 2018;379:2027-39.
38. Shiba-Ishii A, Johnson TW, Dagogo-Jack I, Mino-Kenudson M, Johnson TR, Wei P, et al. Analysis of lorlatinib analogs reveals a roadmap for targeting diverse compound resistance mutations in ALK-positive lung cancer. Nat Cancer. 2022;3 :710-22.
39. Yun MR, Kim DH, Kim SY, Joo HS, Lee YW, Choi HM, et al. Repotrectinib exhibits potent antitumor activity in treatment-naive and solvent-front-mutant ROS1-rearranged non-small cell lung cancer. Clin Cancer Res. 2020;26:3287-95.
40. Le DT, Kim TW, Van Cutsem E, Geva R, Jager D, Hara H, et al. Phase II open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: KEYNOTE-164. J Clin Oncol. 2020;38:11-9.
41. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947-57.
42. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13:239-46.
43. Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18:1454-66.
44. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018;378:113-25.
45. Cho BC, Han JY, Kim SW, Lee KH, Cho EK, Lee YG, et al. A phase 1/2 study of lazertinib 240 mg in patients with advanced EGFR T790M-positive NSCLC after previous EGFR tyrosine kinase inhibitors. J Thorac Oncol. 2022;17:558-67.
46. Yun CH, Mengwasser KE, Toms AV, Woo MS, Greulich H, Wong KK, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc Natl Acad Sci U S A. 2008;105:2070-5.
47. Cross DA, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov. 2014;4:1046-61.
48. Zhou C, Ramalingam SS, Kim TM, Kim SW, Yang JC, Riely GJ, et al. Treatment outcomes and safety of mobocertinib in platinum-pretreated patients with EGFR exon 20 insertion-positive metastatic non-small cell lung cancer: a phase 1/2 open-label nonrandomized clinical trial. JAMA Oncol. 2021; 7:e214761.
49. Park K, Haura EB, Leighl NB, Mitchell P, Shu CA, Girard N, et al. Amivantamab in EGFR exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: initial results from the CHRYSALIS phase I study. J Clin Oncol. 2021;39:3391-402.
50. Planchard D, Kim TM, Mazieres J, Quoix E, Riely G, Barlesi F, et al. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016;17:642-50.
51. Soria JC, Tan DS, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017;389:917-29.
52. Shaw AT, Bauer TM, de Marinis F, Felip E, Goto Y, Liu G, et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. N Engl J Med. 2020;383:2018-29.
53. Janne PA, Riely GJ, Gadgeel SM, Heist RS, Ou SI, Pacheco JM, et al. Adagrasib in non-small-cell lung cancer harboring a

KRAS(G12C) mutation. N Engl J Med. 2022;387:120-31.
54. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. N Engl J Med. 2021;384:2371-81.
55. Paik PK, Felip E, Veillon R, Sakai H, Cortot AB, Garassino MC, et al. Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. N Engl J Med. 2020;383:931-43.
56. Wolf J, Seto T, Han JY, Reguart N, Garon EB, Groen HJ, et al. Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. N Engl J Med. 2020;383:944-57.
57. Drilon A, Oxnard GR, Tan DS, Loong HH, Johnson M, Gainor J, et al. Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med. 2020;383:813-24.
58. Gainor JF, Curigliano G, Kim DW, Lee DH, Besse B, Baik CS, et al. Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. Lancet Oncol. 2021;22:959-69.
59. Shaw AT, Riely GJ, Bang YJ, Kim DW, Camidge DR, Solomon BJ, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. Ann Oncol. 2019;30:1121-6.
60. Drilon A, Siena S, Dziadziuszko R, Barlesi F, Krebs MG, Shaw AT, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020;21:261-70.
61. Mazieres J, Lafitte C, Ricordel C, Greillier L, Negre E, Zalcman G, et al. Combination of trastuzumab, pertuzumab, and docetaxel in patients with advanced non-small-cell lung cancer harboring HER2 mutations: results from the IFCT-1703 R2D2 trial. J Clin Oncol. 2022;40:719-28.
62. Li BT, Smit EF, Goto Y, Nakagawa K, Udagawa H, Mazieres J, et al. Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. N Engl J Med. 2022;386:241-51.
63. Le X, Cornelissen R, Garassino M, Clarke JM, Tchekmedyian N, Goldman JW, et al. Poziotinib in non-small-cell lung cancer harboring HER2 exon 20 insertion mutations after prior therapies: ZENITH20-2 trial. J Clin Oncol. 2022;40:710-8.
64. Iwama E, Zenke Y, Sugawara S, Daga H, Morise M, Yanagitani N, et al. Trastuzumab emtansine for patients with non-small cell lung cancer positive for human epidermal growth factor receptor 2 exon-20 insertion mutations. Eur J Cancer. 2022;162:99-106.
65. Peters S, Stahel R, Bubendorf L, Bonomi P, Villegas A, Kowalski DM, et al. Trastuzumab emtansine (T-DM1) in patients with previously treated HER2-overexpressing metastatic non-small cell lung cancer: efficacy, safety, and biomarkers. Clin Cancer Res. 2019;25:64-72.
66. Yang G, Xu H, Yang Y, Zhang S, Xu F, Hao X, et al. Pyrotinib combined with apatinib for targeting metastatic non-small cell lung cancer with HER2 alterations: a prospective, open-label, single-arm phase 2 study (PATHER2). BMC Med. 2022;20:277.
67. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783-92.
68. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783-91.
69. Krop IE, Kim SB, Gonzalez-Martin A, LoRusso PM, Ferrero JM, Smitt M, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15:689-99.
70. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372:724-34.
71. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med. 2020;382:597-609.
72. Hyman DM, Piha-Paul SA, Won H, Rodon J, Saura C, Shapiro GI, et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. Nature. 2018;554:189-94.
73. Smyth LM, Piha-Paul SA, Won HH, Schram AM, Saura C, Loi S, et al. Efficacy and determinants of response to HER kinase inhibition in HER2-mutant metastatic breast cancer. Cancer Discov. 2020;10:198-213.
74. Andre F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med. 2019;380:1929-40.
75. Rugo HS, Lerebours F, Ciruelos E, Drullinsky P, Ruiz-Borrego M, Neven P, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. Lancet Oncol. 2021;22:489-98.
76. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017;377:523-33.
77. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Goncalves A, Lee KH, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med. 2018;379:753-63.
78. Balasubramaniam S, Beaver JA, Horton S, Fernandes LL, Tang S, Horne HN, et al. FDA approval summary: rucaparib for the treatment of patients with deleterious BRCA mutation-associated advanced ovarian cancer. Clin Cancer Res. 2017;23:7165-70.
79. Tung NM, Robson ME, Ventz S, Santa-Maria CA, Nanda R, Marcom PK, et al. TBCRC 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. J Clin Oncol. 2020;38:4274-82.
80. Gennari A, Andre F, Barrios CH, Cortes J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32:1475-95.
81. Schmid P, Abraham J, Chan S, Wheatley D, Brunt AM, Nemsadze G, et al. Capivasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-neg-

ative breast cancer: the PAKT trial. J Clin Oncol. 2020;38:423-33.
82. Howell SJ, Casbard A, Carucci M, Ingarfield K, Butler R, Morgan S, 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.
83. Bidard FC, Kaklamani VG, Neven P, Streich G, Montero AJ, Forget F, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. J Clin Oncol. 2022;40:3246-56.
84. Hyman DM, Smyth LM, Donoghue MT, Westin SN, Bedard PL, Dean EJ, et al. AKT inhibition in solid tumors with AKT1 mutations. J Clin Oncol. 2017;35:2251-9.
85. Kuemmel S, Harrach H, Schmutzler RK, Kostara A, Ziegler-Lohr K, Dyson MH, et al. Olaparib for metastatic breast cancer in a patient with a germline PALB2 variant. NPJ Breast Cancer. 2020;6:31.
86. Janjigian YY, Maron SB, Chatila WK, Millang B, Chavan SS, Alterman C, et al. First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial. Lancet Oncol. 2020;21:821-31.
87. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687-97.
88. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382:2419-30.
89. Chung HC, Bang YJ, Fuchs CS, Qin SK, Satoh T, Shitara K, et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811. Future Oncol. 2021;17:491-501.
90. Wainberg ZA, Enzinger PC, Kang YK, Qin S, Yamaguchi K, Kim IH, et al. Bemarituzumab in patients with FGFR2b-selected gastric or gastro-oesophageal junction adenocarcinoma (FIGHT): a randomised, double-blind, placebo-controlled, phase 2 study. Lancet Oncol. 2022;23:1430-40.
91. Lee J, Kim ST, Kim K, Lee H, Kozarewa I, Mortimer PG, et al. Tumor genomic profiling guides patients with metastatic gastric cancer to targeted treatment: the VIKTORY Umbrella trial. Cancer Discov. 2019;9:1388-405.
92. Maron SB, Moya S, Morano F, Emmett MJ, Chou JF, Sabwa S, et al. Epidermal growth factor receptor inhibition in epidermal growth factor receptor-amplified gastroesophageal cancer: retrospective global experience. J Clin Oncol. 2022; 40:2458-67.
93. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008; 359:1757-65.
94. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360:1408-17.
95. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med. 2013;369:1023-34.
96. Van Cutsem E, Lenz HJ, Kohne CH, Heinemann V, Tejpar S, Melezinek I, et al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. J Clin Oncol. 2015;33:692-700.
97. Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. N Engl J Med. 2019;381: 1632-43.
98. Kopetz S, Guthrie KA, Morris VK, Lenz HJ, Magliocco AM, Maru D, et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406). J Clin Oncol. 2021;39:285-94.
99. Overman MJ, Lonardi S, Wong KY, Lenz HJ, Gelsomino F, Aglietta M, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol. 2018;36:773-9.
100. Andre T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med. 2020;383:2207-18.
101. Strickler JH, Cercek A, Siena S, Andre T, Ng K, Van Cutsem E, et al. Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, RAS wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study. Lancet Oncol. 2023;24:496-508.
102. Fakih MG, Kopetz S, Kuboki Y, Kim TW, Munster PN, Krauss JC, et al. Sotorasib for previously treated colorectal cancers with KRAS(G12C) mutation (CodeBreaK100): a prespecified analysis of a single-arm, phase 2 trial. Lancet Oncol. 2022; 23:115-24.
103. Yaeger R, Weiss J, Pelster MS, Spira AI, Barve M, Ou SI, et al. Adagrasib with or without cetuximab in colorectal cancer with mutated KRAS G12C. N Engl J Med. 2023;388:44-54.
104. Garmezy B, Gheeya J, Lin HY, Huang Y, Kim T, Jiang X, et al. Clinical and molecular characterization of POLE mutations as predictive biomarkers of response to immune checkpoint inhibitors in advanced cancers. JCO Precis Oncol. 2022;6: e2100267.
105. Rousseau B, Bieche I, Pasmant E, Hamzaoui N, Leulliot N, Michon L, et al. PD-1 blockade in solid tumors with defects in polymerase epsilon. Cancer Discov. 2022;12:1435-48.
106. Wang F, Zhao Q, Wang YN, Jin Y, He MM, Liu ZX, et al. Evaluation of POLE and POLD1 mutations as biomarkers for immunotherapy outcomes across multiple cancer types. JAMA Oncol. 2019;5:1504-6.

107. Ferrarotto R, Eckhardt G, Patnaik A, LoRusso P, Faoro L, Heymach JV, et al. A phase I dose-escalation and dose-expansion study of brontictuzumab in subjects with selected solid tumors. Ann Oncol. 2018;29:1561-8.
108. Ferrarotto R, Mitani Y, Diao L, Guijarro I, Wang J, Zweidler-McKay P, et al. Activating NOTCH1 mutations define a distinct subgroup of patients with adenoid cystic carcinoma who have poor prognosis, propensity to bone and liver metastasis, and potential responsiveness to Notch1 inhibitors. J Clin Oncol. 2017;35:352-60.
109. Jhaveri KL, Wang XV, Makker V, Luoh SW, Mitchell EP, Zwiebel JA, et al. Ado-trastuzumab emtansine (T-DM1) in patients with HER2-amplified tumors excluding breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas: results from the NCI-MATCH trial (EAY131) subprotocol Q. Ann Oncol. 2019;30:1821-30.
110. Kurzrock R, Bowles DW, Kang H, Meric-Bernstam F, Hainsworth J, Spigel DR, 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.
111. Takahashi H, Tada Y, Saotome T, Akazawa K, Ojiri H, Fushimi C, et al. Phase II trial of trastuzumab and docetaxel in patients with human epidermal growth factor receptor 2-positive salivary duct carcinoma. J Clin Oncol. 2019;37:125-34.
112. Tabernero J, Bahleda R, Dienstmann R, Infante JR, Mita A, Italiano A, et al. Phase I dose-escalation study of JNJ-42756493, an oral pan-fibroblast growth factor receptor inhibitor, in patients with advanced solid tumors. J Clin Oncol. 2015;33:3401-8.
113. Nogova L, Sequist LV, Perez Garcia JM, Andre F, Delord JP, Hidalgo M, et al. Evaluation of BGJ398, a fibroblast growth factor receptor 1-3 kinase inhibitor, in patients with advanced solid tumors harboring genetic alterations in fibroblast growth factor receptors: results of a global phase I, dose-escalation and dose-expansion study. J Clin Oncol. 2017;35:157-65.
114. Goke F, Franzen A, Hinz TK, Marek LA, Yoon P, Sharma R, et al. FGFR1 expression levels predict BGJ398 sensitivity of FGFR1-dependent head and neck squamous cell cancers. Clin Cancer Res. 2015;21:4356-64.
115. Kochanny SE, Worden FP, Adkins DR, Lim DW, Bauman JE, Wagner SA, et al. A randomized phase 2 network trial of tivantinib plus cetuximab versus cetuximab in patients with recurrent/metastatic head and neck squamous cell carcinoma. Cancer. 2020;126:2146-52.
116. Rothenberger NJ, Stabile LP. Hepatocyte growth factor/c-Met signaling in head and neck cancer and implications for treatment. Cancers (Basel). 2017;9:39.
117. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381:317-27.
118. Reiss KA, Mick R, O'Hara MH, Teitelbaum U, Karasic TB, Schneider C, 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.
119. Strickler JH, Satake H, George TJ, Yaeger R, Hollebecque A, Garrido-Laguna I, et al. Sotorasib in KRAS p.G12C-mutated advanced pancreatic cancer. N Engl J Med. 2023;388:33-43.
120. Bekaii-Saab TS, Yaeger R, Spira AI, Pelster MS, Sabari JK, Hafez N, et al. Adagrasib in advanced solid tumors harboring a KRAS(G12C) mutation. J Clin Oncol. 2023;41:4097-106.
121. Payne SN, Maher ME, Tran NH, Van De Hey DR, Foley TM, Yueh AE, et al. PIK3CA mutations can initiate pancreatic tumorigenesis and are targetable with PI3K inhibitors. Oncogenesis. 2015;4:e169.
122. Harder J, Ihorst G, Heinemann V, Hofheinz R, Moehler M, Buechler P, et al. Multicentre phase II trial of trastuzumab and capecitabine in patients with HER2 overexpressing metastatic pancreatic cancer. Br J Cancer. 2012;106:1033-8.
123. Singhi AD, Ali SM, Lacy J, Hendifar A, Nguyen K, Koo J, et al. Identification of targetable ALK rearrangements in pancreatic ductal adenocarcinoma. J Natl Compr Canc Netw. 2017;15:555-62.
124. Schram AM, O'Reilly EM, O'Kane GM, Goto K, Kim DW, Neuzillet C, et al. Efficacy and safety of zenocutuzumab in advanced pancreas cancer and other solid tumors harboring NRG1 fusions. J Clin Oncol. 2021;39(15 Suppl):3003.
125. Pishvaian MJ, Garrido-Laguna I, Liu SV, Multani PS, Chow-Maneval E, Rolfo C. Entrectinib in TRK and ROS1 fusion-positive metastatic pancreatic cancer. JCO Precis Oncol. 2018;2:1-7.
126. Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21:796-807.
127. Zhu AX, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the phase 3 randomized clinical ClarIDHy trial. JAMA Oncol. 2021;7:1669-77.
128. Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol. 2020;21:671-84.
129. Javle M, Roychowdhury S, Kelley RK, Sadeghi S, Macarulla T, Weiss KH, et al. Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. Lancet Gastroenterol Hepatol. 2021;6:803-15.
130. Goyal L, Meric-Bernstam F, Hollebecque A, Valle JW, Morizane C, Karasic TB, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. N Engl J Med. 2023;388:228-39.
131. Javle M, Borad MJ, Azad NS, Kurzrock R, Abou-Alfa GK, George B, 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.
132. Lee CK, Chon HJ, Cheon J, Lee MA, Im HS, Jang JS, et al. Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19-14). Lancet Gastroenterol Hepatol. 2023;8:56-65.
133. Ohba A, Morizane C, Ueno M, Kobayashi S, Kawamoto Y, Komatsu Y, et al. Multicenter phase II trial of trastuzumab deruxtecan for HER2-positive unresectable or recurrent biliary tract cancer: HERB trial. Future Oncol. 2022;18:2351-60.
134. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, et al. Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. J Clin Oncol. 2018;36:2044-51.
135. Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33:860-77.
136. Leon-Castillo A, Britton H, McConechy MK, McAlpine JN, Nout R, Kommoss S, et al. Interpretation of somatic POLE mutations in endometrial carcinoma. J Pathol. 2020;250:323-35.
137. Rios-Doria E, Momeni-Boroujeni A, Friedman CF, Selenica P, Zhou Q, Wu M, et al. Integration of clinical sequencing and immunohistochemistry for the molecular classification of endometrial carcinoma. Gynecol Oncol. 2023;174:262-72.
138. Talhouk A, McConechy MK, Leung S, Li-Chang HH, Kwon JS, Melnyk N, et al. A clinically applicable molecular-based classification for endometrial cancers. Br J Cancer. 2015;113:299-310.
139. Leon-Castillo A, de Boer SM, Powell ME, Mileshkin LR, Mackay HJ, Leary A, et al. Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy. J Clin Oncol. 2020;38:3388-97.
140. Kommoss S, McConechy MK, Kommoss F, Leung S, Bunz A, Magrill J, et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Ann Oncol. 2018;29:1180-8.
141. van den Heerik A, Horeweg N, Nout RA, Lutgens L, van der Steen-Banasik EM, Westerveld GH, et al. PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer. Int J Gynecol Cancer. 2020;30:2002-7.
142. Gonzalez-Martin A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019;381:2391-402.
143. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med. 2019;381:2403-15.
144. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375:2154-64.
145. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379:2495-505.
146. Ray-Coquard I, Pautier P, Pignata S, Perol D, Gonzalez-Martin A, Berger R, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med. 2019;381:2416-28.
147. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 2014;15:852-61.
148. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390:1949-61.
149. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18:1274-84.
150. Loriot Y, Necchi A, Park SH, Garcia-Donas J, Huddart R, Burgess E, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med. 2019;381:338-48.
151. Van Allen EM, Mouw KW, Kim P, Iyer G, Wagle N, Al-Ahmadie H, et al. Somatic ERCC2 mutations correlate with cisplatin sensitivity in muscle-invasive urothelial carcinoma. Cancer Discov. 2014;4:1140-53.
152. Liu D, Plimack ER, Hoffman-Censits J, Garraway LA, Bellmunt J, Van Allen E, et al. Clinical validation of chemotherapy response biomarker ERCC2 in muscle-invasive urothelial bladder carcinoma. JAMA Oncol. 2016;2:1094-6.
153. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med. 2020;382:2091-102.
154. Hussain M, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med. 2020;383:2345-57.
155. Jonasch E, Donskov F, Iliopoulos O, Rathmell WK, Narayan VK, Maughan BL, et al. Belzutifan for renal cell carcinoma in von Hippel-Lindau disease. N Engl J Med. 2021;385:2036-46.
156. Choi Y, Keam B, Kim M, Yoon S, Kim D, Choi JG, et al. Bevacizumab plus erlotinib combination therapy for advanced hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma: a multicenter retrospective analysis in Korean patients. Cancer Res Treat. 2019;51:1549-56.
157. Srinivasan R, Gurram S, Harthy MA, Singer EA, Sidana A, Shuch BM, et al. Results from a phase II study of bevacizumab and erlotinib in subjects with advanced hereditary leiomyomatosis and renal cell cancer (HLRCC) or sporadic papillary renal cell cancer. J Clin Oncol. 2020;38(15 Suppl):5004.

158. Iannantuono GM, Riondino S, Sganga S, Roselli M, Torino F. Activity of ALK inhibitors in renal cancer with ALK clterations: a systematic review. Int J Mol Sci. 2022;23:3995.
159. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19:603-15.
160. Larkin J, Ascierto PA, Dreno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014;371:1867-76.
161. Long GV, Hauschild A, Santinami M, Atkinson V, Mandala M, Chiarion-Sileni V, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med. 2017;377:1813-23.
162. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014; 371:1877-88.
163. Gutzmer R, Stroyakovskiy D, Gogas H, Robert C, Lewis K, Protsenko S, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAF (V600) mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020;395:1835-44.
164. Carvajal RD, Antonescu CR, Wolchok JD, Chapman PB, Roman RA, Teitcher J, et al. KIT as a therapeutic target in metastatic melanoma. JAMA. 2011;305:2327-34.
165. Hodi FS, Corless CL, Giobbie-Hurder A, Fletcher JA, Zhu M, Marino-Enriquez A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol. 2013;31:3182-90.
166. Dummer R, Schadendorf D, Ascierto PA, Arance A, Dutriaux C, Di Giacomo AM, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18:435-45.
167. Shin SJ, Lee J, Kim TM, Kim JS, Kim YJ, Hong YS, et al. A phase Ib trial of belvarafenib in combination with cobimetinib in patients with advanced solid tumors: interim results of dose-escalation and patients with NRAS-mutant melanoma of dose-expansion. J Clin Oncol. 2021;39(15 Suppl):3007.
168. Menzies AM, Yeh I, Botton T, Bastian BC, Scolyer RA, Long GV. Clinical activity of the MEK inhibitor trametinib in metastatic melanoma containing BRAF kinase fusion. Pigment Cell Melanoma Res. 2015;28:607-10.
169. Hutchinson KE, Lipson D, Stephens PJ, Otto G, Lehmann BD, Lyle PL, et al. BRAF fusions define a distinct molecular subset of melanomas with potential sensitivity to MEK inhibition. Clin Cancer Res. 2013;19:6696-702.
170. Bowyer SE, Rao AD, Lyle M, Sandhu S, Long GV, McArthur GA, et al. Activity of trametinib in K601E and L597Q BRAF mutation-positive metastatic melanoma. Melanoma Res. 2014;24:504-8.
171. Dankner M, Lajoie M, Moldoveanu D, Nguyen TT, Savage P, Rajkumar S, et al. Dual MAPK inhibition is an effective therapeutic strategy for a subset of class II BRAF mutant melanomas. Clin Cancer Res. 2018;24:6483-94.
172. Kim KB, Kefford R, Pavlick AC, Infante JR, Ribas A, Sosman JA, et al. Phase II study of the MEK1/MEK2 inhibitor trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. J Clin Oncol. 2013;31:482-9.
173. Marconcini R, Galli L, Antonuzzo A, Bursi S, Roncella C, Fontanini G, et al. Metastatic BRAF K601E-mutated melanoma reaches complete response to MEK inhibitor trametinib administered for over 36 months. Exp Hematol Oncol. 2017; 6:6.
174. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368:1329-38.
175. Heinrich MC, Rankin C, Blanke CD, Demetri GD, Borden EC, Ryan CW, et al. Correlation of long-term results of imatinib in advanced gastrointestinal stromal tumors with next-generation sequencing results: analysis of phase 3 SWOG Intergroup Trial S0033. JAMA Oncol. 2017;3:944-52.
176. Cassier PA, Fumagalli E, Rutkowski P, Schoffski P, Van Glabbeke M, Debiec-Rychter M, et al. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. Clin Cancer Res. 2012;18:4458-64.
177. Heinrich MC, Jones RL, von Mehren M, Schoffski P, Serrano C, Kang YK, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. Lancet Oncol. 2020;21:935-46.
178. McArthur GA, Demetri GD, van Oosterom A, Heinrich MC, Debiec-Rychter M, Corless CL, et al. Molecular and clinical analysis of locally advanced dermatofibrosarcoma protuberans treated with imatinib: Imatinib Target Exploration Consortium Study B2225. J Clin Oncol. 2005;23:866-73.
179. Navarrete-Dechent C, Mori S, Barker CA, Dickson MA, Nehal KS. Imatinib treatment for locally advanced or metastatic dermatofibrosarcoma protuberans: a systematic review. JAMA Dermatol. 2019;155:361-9.
180. Butrynski JE, D'Adamo DR, Hornick JL, Dal Cin P, Antonescu CR, Jhanwar SC, et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med. 2010;363:1727-33.
181. Nishio M, Murakami H, Horiike A, Takahashi T, Hirai F, Suenaga N, et al. Phase I study of ceritinib (LDK378) in Japanese patients with advanced, anaplastic lymphoma kinase-rearranged non-small-cell lung cancer or other tumors. J Thorac Oncol. 2015;10:1058-66.
182. Gettinger SN, Bazhenova LA, Langer CJ, Salgia R, Gold KA, Rosell R, et al. Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. Lancet Oncol. 2016;17:1683-96.

183. Gounder M, Schoffski P, Jones RL, Agulnik M, Cote GM, Villalobos VM, et al. Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study. Lancet Oncol. 2020;21:1423-32.
184. Tap WD, Villalobos VM, Cote GM, Burris H, Janku F, Mir O, et al. Phase I study of the mutant IDH1 inhibitor ivosidenib: safety and clinical activity in patients with advanced chondrosarcoma. J Clin Oncol. 2020;38:1693-701.
185. Akumalla S, Madison R, Lin DI, Schrock AB, Yakirevich E, Rosenzweig M, et al. Characterization of clinical cases of malignant PEComa via comprehensive genomic profiling of DNA and RNA. Oncology. 2020;98:905-12.
186. Wagner AJ, Ravi V, Riedel RF, Ganjoo K, Van Tine BA, Chugh R, et al. nab-Sirolimus for patients with malignant perivascular epithelioid cell tumors. J Clin Oncol. 2021;39:3660-70.
187. Abdul Razak AR, Bauer S, Suarez C, Lin CC, Quek R, Hutter-Kronke ML, et al. Co-targeting of MDM2 and CDK4/6 with siremadlin and ribociclib for the treatment of patients with well-differentiated or dedifferentiated liposarcoma: results from a proof-of-concept, phase Ib study. Clin Cancer Res. 2022;28:1087-97.
188. LoRusso P, Yamamoto N, Patel MR, Laurie SA, Bauer TM, Geng J, et al. The MDM2-p53 antagonist brigimadlin (BI 907828) in patients with advanced or metastatic solid tumors: results of a phase Ia, first-in-human, dose-escalation study. Cancer Discov. 2023;13:1802-13.
189. Dickson MA, Schwartz GK, Keohan ML, D'Angelo SP, Gounder MM, Chi P, et al. Progression-free survival among patients with well-differentiated or dedifferentiated liposarcoma treated with CDK4 inhibitor palbociclib: a phase 2 clinical trial. JAMA Oncol. 2016;2:937-40.
190. Schoffski P, Wozniak A, Stacchiotti S, Rutkowski P, Blay JY, Lindner LH, et al. Activity and safety of crizotinib in patients with advanced clear-cell sarcoma with MET alterations: European Organization for Research and Treatment of Cancer phase II trial 90101 'CREATE'. Ann Oncol. 2017;28:3000-8.
191. Negrini S, Gorgoulis VG, Halazonetis TD. Genomic instability: an evolving hallmark of cancer. Nat Rev Mol Cell Biol. 2010;11:220-8.
192. Lord CJ, Ashworth A. The DNA damage response and cancer therapy. Nature. 2012;481:287-94.
193. Yamamoto H, Hirasawa A. Homologous recombination deficiencies and hereditary tumors. Int J Mol Sci. 2021;23:348.
194. Toh M, Ngeow J. Homologous recombination deficiency: cancer predispositions and treatment implications. Oncologist. 2021;26:e1526-37.
195. Robson ME, Tung N, Conte P, Im SA, Senkus E, Xu B, et al. OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol. 2019;30:558-66.
196. Norquist BM, Brady MF, Harrell MI, Walsh T, Lee MK, Gulsuner S, et al. Mutations in homologous recombination genes and outcomes in ovarian carcinoma patients in GOG 218: an NRG Oncology/Gynecologic Oncology Group Study. Clin Cancer Res. 2018;24:777-83.
197. Pennington KP, Walsh T, Harrell MI, Lee MK, Pennil CC, Rendi MH, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res. 2014;20:764-75.
198. Geyer CE Jr, Garber JE, Gelber RD, Yothers G, Taboada M, Ross L, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. Ann Oncol. 2022;33:1250-68.
199. Telli ML, Timms KM, Reid J, Hennessy B, Mills GB, Jensen KC, et al. Homologous recombination deficiency (HRD) score predicts response to platinum-containing neoadjuvant chemotherapy in patients with triple-negative breast cancer. Clin Cancer Res. 2016;22:3764-73.
200. Watkins JA, Irshad S, Grigoriadis A, Tutt AN. Genomic scars as biomarkers of homologous recombination deficiency and drug response in breast and ovarian cancers. Breast Cancer Res. 2014;16:211.
201. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474:609-15.
202. Lotan TL, Tomlins SA, Bismar TA, Van der Kwast TH, Grignon D, Egevad L, et al. Report From the International Society of Urological Pathology (ISUP) Consultation Conference on Molecular Pathology of Urogenital Cancers. I. Molecular Biomarkers in Prostate Cancer. Am J Surg Pathol. 2020;44:e15-29.
203. Sztupinszki Z, Diossy M, Krzystanek M, Reiniger L, Csabai I, Favero F, et al. Migrating the SNP array-based homologous recombination deficiency measures to next generation sequencing data of breast cancer. NPJ Breast Cancer. 2018;4:16.
204. Wang X, Xu Y, Zhang Y, Wang S, Zhang X, Yi X, et al. HRD-MILN: accurately estimate tumor homologous recombination deficiency status from targeted panel sequencing data. Front Genet. 2022;13:990244.
205. Lemery S, Keegan P, Pazdur R. First FDA approval agnostic of cancer site: when a biomarker defines the indication. N Engl J Med. 2017;377:1409-12.
206. Bonneville R, Krook MA, Chen HZ, Smith A, Samorodnitsky E, Wing MR, et al. Detection of microsatellite instability biomarkers via next-generation sequencing. Methods Mol Biol. 2020;2055:119-32.
207. Haraldsdottir S. Microsatellite instability testing using next-generation sequencing data and therapy implications. JCO Precis Oncol. 2017;1:1-4.
208. Salipante SJ, Scroggins SM, Hampel HL, Turner EH, Pritchard CC. Microsatellite instability detection by next generation sequencing. Clin Chem. 2014;60:1192-9.
209. Niu B, Ye K, Zhang Q, Lu C, Xie M, McLellan MD, et al. MSIsensor: microsatellite instability detection using paired tumor-normal sequence data. Bioinformatics. 2014;30:1015-6.
210. Kautto EA, Bonneville R, Miya J, Yu L, Krook MA, Reeser JW, et al. Performance evaluation for rapid detection of pan-cancer microsatellite instability with MANTIS. Oncotarget. 2017;8:7452-63.
211. Hause RJ, Pritchard CC, Shendure J, Salipante SJ. Classification and characterization of microsatellite instability across

18 cancer types. Nat Med. 2016;22:1342-50.
212. Kim JE, Chun SM, Hong YS, Kim KP, Kim SY, Kim J, et al. Mutation burden and I index for detection of microsatellite instability in colorectal cancer by targeted next-generation sequencing. J Mol Diagn. 2019;21:241-50.
213. Middha S, Zhang L, Nafa K, Jayakumaran G, Wong D, Kim HR, et al. Reliable Pan-cancer microsatellite instability assessment by using targeted next-generation sequencing data. JCO Precis Oncol. 2017;2017:PO.17.00084.
214. Sharma P, Siddiqui BA, Anandhan S, Yadav SS, Subudhi SK, Gao J, et al. The next decade of immune checkpoint therapy. Cancer Discov. 2021;11:838-57.
215. Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. Mol Cancer Ther. 2015; 14:847-56.
216. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357:409-13.
217. Sha D, Jin Z, Budczies J, Kluck K, Stenzinger A, Sinicrope FA. Tumor mutational burden as a predictive biomarker in solid tumors. Cancer Discov. 2020;10:1808-25.
218. Samstein RM, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet. 2019;51:202-6.
219. Jardim DL, Goodman A, de Melo Gagliato D, Kurzrock R. The challenges of tumor mutational burden as an immunotherapy biomarker. Cancer Cell. 2021;39:154-73.
220. Marcus L, Fashoyin-Aje LA, Donoghue M, Yuan M, Rodriguez L, Gallagher PS, et al. FDA approval summary: pembrolizumab for the treatment of tumor mutational burden-high solid tumors. Clin Cancer Res. 2021;27:4685-9.
221. Chalmers ZR, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med. 2017;9:34.
222. Buchhalter I, Rempel E, Endris V, Allgauer M, Neumann O, Volckmar AL, et al. Size matters: dissecting key parameters for panel-based tumor mutational burden analysis. Int J Cancer. 2019;144:848-58.
223. Fumet JD, Truntzer C, Yarchoan M, Ghiringhelli F. Tumour mutational burden as a biomarker for immunotherapy: Current data and emerging concepts. Eur J Cancer. 2020;131:40-50.
224. Luchini C, Bibeau F, Ligtenberg MJL, Singh N, Nottegar A, Bosse T, et al. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. Ann Oncol. 2019;30:1232-43.
225. Gambardella V, Tarazona N, Cejalvo JM, Lombardi P, Huerta M, Rosello S, et al. Personalized medicine: recent progress in cancer therapy. Cancers (Basel). 2020;12:1009.
226. Cescon DW, Bratman SV, Chan SM, Siu LL. Circulating tumor DNA and liquid biopsy in oncology. Nat Cancer. 2020; 1:276-90.
227. Sugimoto A, Matsumoto S, Udagawa H, Itotani R, Usui Y, Umemura S, et al. A large-scale prospective concordance study of plasma- and tissue-based next-generation targeted sequencing for advanced non-small cell lung cancer (LC-SCRUM-Liquid). Clin Cancer Res. 2023;29:1506-14.
228. Benayed R, Offin M, Mullaney K, Sukhadia P, Rios K, Desmeules P, et al. High yield of RNA sequencing for targetable kinase fusions in lung adenocarcinomas with no mitogenic driver alteration detected by DNA sequencing and low tumor mutation burden. Clin Cancer Res. 2019;25:4712-22.
229. Heydt C, Wolwer CB, Velazquez Camacho O, Wagener-Ryczek S, Pappesch R, Siemanowski J, et al. Detection of gene fusions using targeted next-generation sequencing: a comparative evaluation. BMC Med Genomics. 2021;14:62.
230. Wyatt AW, Annala M, Aggarwal R, Beja K, Feng F, Youngren J, et al. Concordance of circulating tumor DNA and matched metastatic tissue biopsy in prostate cancer. J Natl Cancer Inst. 2017;109:djx118.
231. Kingston B, Cutts RJ, Bye H, Beaney M, Walsh-Crestani G, Hrebien S, et al. Genomic profile of advanced breast cancer in circulating tumour DNA. Nat Commun. 2021;12:2423.
232. Pascual J, Attard G, Bidard FC, Curigliano G, De Mattos-Arruda L, Diehn M, et al. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2022;33:750-68.
233. Pisapia P, Malapelle U, Troncone G. Liquid biopsy and lung cancer. Acta Cytol. 2019;63:489-96.
234. Kim H, Park KU. Clinical circulating tumor DNA testing for precision oncology. Cancer Res Treat. 2023;55:351-66.
235. Cha Y, Kim S, Han SW. Utilizing plasma circulating tumor DNA sequencing for precision medicine in the management of solid cancers. Cancer Res Treat. 2023;55:367-84.
236. Mack PC, Banks KC, Espenschied CR, Burich RA, Zill OA, Lee CE, et al. Spectrum of driver mutations and clinical impact of circulating tumor DNA analysis in non-small cell lung cancer: analysis of over 8000 cases. Cancer. 2020;126: 3219-28.
237. Leighl NB, Page RD, Raymond VM, Daniel DB, Divers SG, Reckamp KL, et al. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. Clin Cancer Res. 2019;25:4691-700.
238. Viller Tuxen I, Barlebo Ahlborn L, Mau-Soerensen M, Staal Rohrberg K, Cilius Nielsen F, Oestrup O, et al. Plasma total cell-free DNA is a prognostic biomarker of overall survival in metastatic solid tumour patients. Br J Cancer. 2019;121:125-30.
239. Mirtavoos-Mahyari H, Ghafouri-Fard S, Khosravi A, Motevaseli E, Esfahani-Monfared Z, Seifi S, et al. Circulating free DNA concentration as a marker of disease recurrence and metastatic potential in lung cancer. Clin Transl Med. 2019;8:14.
240. Zhang Y, Yao Y, Xu Y, Li L, Gong Y, Zhang K, et al. Pan-cancer circulating tumor DNA detection in over 10,000 Chinese patients. Nat Commun. 2021;12:11.

241. Kim S, Lim Y, Kang JK, Kim HP, Roh H, Kim SY, et al. Dynamic changes in longitudinal circulating tumour DNA profile during metastatic colorectal cancer treatment. Br J Cancer. 2022;127:898-907.
242. Cai Z, Wang Z, Liu C, Shi D, Li D, Zheng M, et al. Detection of microsatellite instability from circulating tumor DNA by targeted deep sequencing. J Mol Diagn. 2020;22:860-70.
243. Fridland S, Choi J, Nam M, Schellenberg SJ, Kim E, Lee G, et al. Assessing tumor heterogeneity: integrating tissue and circulating tumor DNA (ctDNA) analysis in the era of immunooncology - blood TMB is not the same as tissue TMB. J Immunother Cancer. 2021;9:e002551.
244. Gilson P, Merlin JL, Harle A. Detection of microsatellite instability: state of the art and future applications in circulating tumour DNA (ctDNA). Cancers (Basel). 2021;13:1491.